SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIP OF ALLOSTERIC INHIBITORS OF THE AAA ATPASE P97

by

Celeste Alverez

B.S., Miami University, 2011

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This dissertation was presented

by

Celeste Alverez

It was defended on

November 21, 2019

and approved by

Barry Gold, Professor Emeritus, Department of Pharmaceutical Sciences

Donna M. Huryn, Professor, Department of Pharmaceutical Sciences

W. Seth Horne, Associate Professor, Department of Chemistry

Dissertation Advisor: Peter Wipf, Distinguished University Professor, Department of Chemistry

SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIP OF ALLOSTERIC INHIBITORS OF THE AAA ATPASE P97

Celeste Alverez, PhD

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This thesis describes the design and synthesis of allosteric, small molecule inhibitors targeting the cancer relevant p97. Due to its pivotal role of maintaining proteostasis, while both normal and cancerous cells need p97, cancerous cells become reliant on its activity to survive. Based on the initial success of proteosome inhibitors it was proposed that targeting p97, which functions upstream of the proteosome, will mitigate compensatory pathway activation observed with proteosome inhibition. In order to test this hypothesis, a campaign to identify small molecule inhibitors of p97 was initiated which identified three distinct chemotypes: two related chemotypes contained indole cores that were initially explored, and a third alkylsulfanyl-1,2,4-triazole based molecule that was found to be the most amenable to modification. The best compound reported in the initial publication, **NMS-873**, was shown to possess good potency, but poor solubility. Therefore, modification of this chemotype focused on incorporating solubilizing groups and reducing lipophilicity of the linear side chain of the molecule including various carbamate containing aliphatic heterocycles. Additional changes focused on improving potency while considering stability. To accomplish this, the thioether was replaced with an ether linker or oxidizing it to a sulfone. In addition, difluorination of the phenol side chain to reduce electron density of the ring was found to significantly improve potency. Through an iterative structure-activity relationship effort, five analogs with unique structural features were identified that maintained or improved activity relative to **NMS-873**.

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LIST OF ABBREVIATIONS

1,2-DCE 1,2-dichloroethane

AAA ..... ATPases associated with diverse cellular activities

Ac ..... acetyl

AcOH ..... acetic acid

ADME ..... absorption, distribution, metabolism, and excretion

ADP ..... adenosine diphosphate

ATP ..... adenosine triphosphate

ATPγS ..... adenosine 5'-(3-thiotriphosphate)

BI ..... Boehringer-Ingelheim

Bn ..... benzyl

Boc ..... *tert*-butyloxycarbonyl

Boc_2O ..... di-*tert*-butyl dicarbonate

Bu ..... butyl

Bz ..... benzoyl

cat. ..... catalytic

CBC ..... Chemical Biology Consortium

CD ..... circular dichroism spectroscopy

CDI ..... carbonyldiimidazole

CL ..... clearance

CL_{int}.....in vitro intrinsic clearance

cLogD .....calculated partition coefficient pH 7.4

CMT2Y .....Charcot-Marie-Tooth disease type 2Y

cryo-EM ..... cryogenic electron microscopy

CyJohnPhos..... (2-biphenyl)dicyclohexylphosphine

CYP450..... cytochrome P450

Da.....Daltons

DAST ..... (diethylamino)sulfur trifluoride

DBU .....1,8-diazabicyclo[5.4.0]undec-7-ene

dec. .....decomposed

DIAD.....diisopropyl azodicarboxylate

DIBAL .....diisobutylaluminium hydride

DiPEA .....*N*,*N*-diisopropylethylamine

DMA ..... *N*,*N*-dimethylacetamide

DMAP 4-dimethylaminopyridine

DMF .....*N*,*N*-dimethylformamide

DMP .....Dess-Martin periodinane

DMSO ..... dimethylsulfoxide

DNA ..... deoxyribonucleic acid

DPPA ..... diphenylphosphoryl azide

dppm .....bis(diphenylphosphino)methane

EDC.....1-ethyl-3(3-dimethylaminopropyl)carbodiimide

ee ..... enantiomeric excess

ELSD..... evaporative light scattering detector

equiv. (eq.) ..... equivalents

ER ..... endoplasmic reticulum

ERAD..... endoplasmic reticulum-associated degradation

ESI..... electrospray ionization

EtOAc ..... ethyl acetate

EWG ..... electron withdrawing group

FALS..... familial amyotrophic lateral sclerosis (ALS)

FDA..... US Food and Drug Administration

FMO..... flavin-containing monooxygenase

G..... gram(s)

GFP .....green fluorescent protein

h..... hour(s)

HATU ..... 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

HBA ..... hydrogen bond acceptor

HBD ..... hydrogen bond donor

HCT-116 ..... a human colorectal carcinoma

HFPO ..... hexafluoropropylene oxide

HLM..... human liver microsomes

HOBt..... 1-hydroxybenzotriazole

HPLC .....high performance liquid chromatography

Hrd1 ..... HMG-CoA reductase degradation 1

HRMS ..... high-resolution mass spectroscopy

Hsp ..... heat shock protein

HTS ..... high-throughput screen

hν ..... irradiated with light

IC_{50} ..... concentration resulting in 50% inhibition of activity

*i*Pr ..... isopropyl

IR ..... infrared spectroscopy

IκB ..... NFκB endogenous inhibitor

K_m ..... Michaelis constant, concentration of substrate where the reaction rate is 50%

LC3 ..... microtubule-associated 1A/1B-light chain 3

LCMS ..... liquid chromatography mass spectrometry

$LiAlD_4$ ..... lithium aluminum deuteride

MAD ..... mitochondria associated degradation

m-CPBA ..... 3-chloroperbenzoic acid

Me ..... methyl

MeCN ..... acetonitrile

mg ..... milligram(s)

min ..... minute(s)

MIP 1-methyl-1-methoxyethyl

mL ..... milliliter(s)

m.p. ..... melting point

Ms (mesyl) ..... methanesulfonyl

MSP1 ..... multisystem proteinopathy 1

µL ..... microliter(s)

µM ..... micromolar

NBS ..... N-bromosuccinimide

n-BuLi ..... *n*-butyllithium

NCI ..... National Cancer Institute

NFκB ..... nuclear factor kappa-light-chain-enhancer of activated B cells

nM ..... nanomolar

nm ..... nanometer(s)

NMP 1-methyl-2-pyrrolidinone

NMR ..... nuclear magnetic resonance

NSCLC ..... non-small cell lung carcinoma

ODD-Luc ..... HIF1α oxygen-dependent degradation domain fused to luciferase

PBS ..... phosphate buffered saline

Pd/C ..... palladium on carbon

$Pd_2(dba)_3$ ..... tris(dibenzylideneacetone)dipalladium(0)

PG ..... protecting group

Ph ..... phenyl

Piv ..... pivaloyl

PK ..... pharmacokinetic

PMA ..... phosphomolybdic acid

PNB ..... *p*-nitrobenzyl

PO ..... oral dosing (per os)

PPh_3 ..... triphenylphosphine

PPTS ..... pyridinium *p*-toluenesulfonate

PSA ..... polar surface area

p-TsOH ..... *p*-toluenesulfonic acid

$Rh_2(OAc)_4$ ..... rhodium(II) acetate dimer

RNAi ..... ribose nucleic acid (RNA) interference

$RuCl_2$(*p*-cymene)]$_2$ ..... dichloro(*p*-cymene)ruthenium(II) dimer

SAR ..... structure-activity relationship

SFC ..... supercritical fluid chromatography

siRNA ..... small interfering RNA

SPR ..... surface plasmon resonance

STAB ..... sodium triacetoxyborohydride

TBAF ..... tetrabutylammonium fluoride

TDP-43 ..... transactive response (TAR) DNA binding protein-43

TFA ..... trifluoroacetic acid

THF ..... tetrahydrofuran

THP tetrahydro-2*H*-pyran

TLC ..... thin layer chromatography

TMSCl ..... chlorotrimethylsilane

$TMSCF_3$ ..... (trifluoromethyl)trimethylsilane

TMSCN ..... cyanotrimethylsilane

Ts (tosyl) ..... toluenesulfonyl

Ub^{G76V}-GFP ..... ubiquitin, with glycine 76 mutated to valine, fused to GFP

UCLA ..... University of California, Los Angeles

Ufd1 ..... ubiquitin fusion degradation 1

UPR..... unfolded protein response

UPS ..... ubiquitin-proteasome system

UV..... ultraviolet

VCP.....Valosin-containing protein

V_{max} ..... maximum rate of enzyme reaction at saturating substrate concentration

V_{ss} ..... steady state volume of distribution

WT .....wild type

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late night mental health talks). I would also like to thank my friends and family that have always been there to support and encourage me no matter what. I would especially like to thank my mother, Janet Alverez, who though she is not here, has been my inspiration in pursuing medicinal chemistry from the start so that I may one day help others who face the same health difficulties as she did but not face the same fate. Lastly, I would like to thank my father, Marc Alverez, most of all for his endless support, love, and encouragement over the years.

1.0 INTRODUCTION

Cancer is a leading cause of death worldwide.[1] In 2018, an estimated 18.1 million new cases and 9.6 million cancer related deaths, across all cancer types, have been projected.[1] In addition, it is predicted that by 2040 an additional 29.5 million people worldwide will be diagnosed with cancer per year.[2] This makes the development of new cancer chemotherapeutics an increasingly important endeavor. An appealing target for the treatment of cancer has been protein homeostasis and the ubiquitin-proteasome system due to cellular reliance on this system for proliferation and survival. The US Food and Drug Administration (FDA) approved the first proteasome inhibitor, bortezomib, in 2003, attracting numerous laboratories to this field.[3] However, targeting the proteasome has had limited success thus far, with FDA approvals for only three drugs for the treatment of lymphoma and melanoma.[4, 5] A recently explored alternative target that plays a crucial role in protein homeostasis is p97. p97, also known as Valosin-containing protein (VCP) and Cdc48 in yeast, is a member of the AAA (ATPases associated with diverse cellular activities) ATPase superfamily. It has been found to be upregulated in many tumor types including non-small cell lung carcinoma (NSCLC), prostate cancer, breast cancer, and colorectal carcinoma, with its elevated expression level correlating to poor prognosis of patients, thus making it an appealing target for chemotherapeutic development.[4, 6-15]

1.1 BIOLOGICAL FEATURES OF P97

1.1.1 Biological function of p97

The chaperone p97, or a related homolog, can be found in nearly all branches of life. In mammalian cells, it is primarily found in the cytoplasm, however, a fraction is found at specific organelles such as the endoplasmic reticulum (ER), Golgi apparatus, and mitochondria, as well as within the nucleus.[16] p97 is abundant, comprising approximately 1% of the protein makeup of the cell.[17] This can likely be attributed to the numerous roles p97 has within the cell. Generally, it has three main roles that all functions can be related to: 1) protein homeostasis, 2) membrane trafficking, and 3) cell cycle and nucleic acid regulation.[16, 18] p97 is able to perform this varied array of functions via its various complexes formed with a large number of adaptor and cofactor proteins.[19]

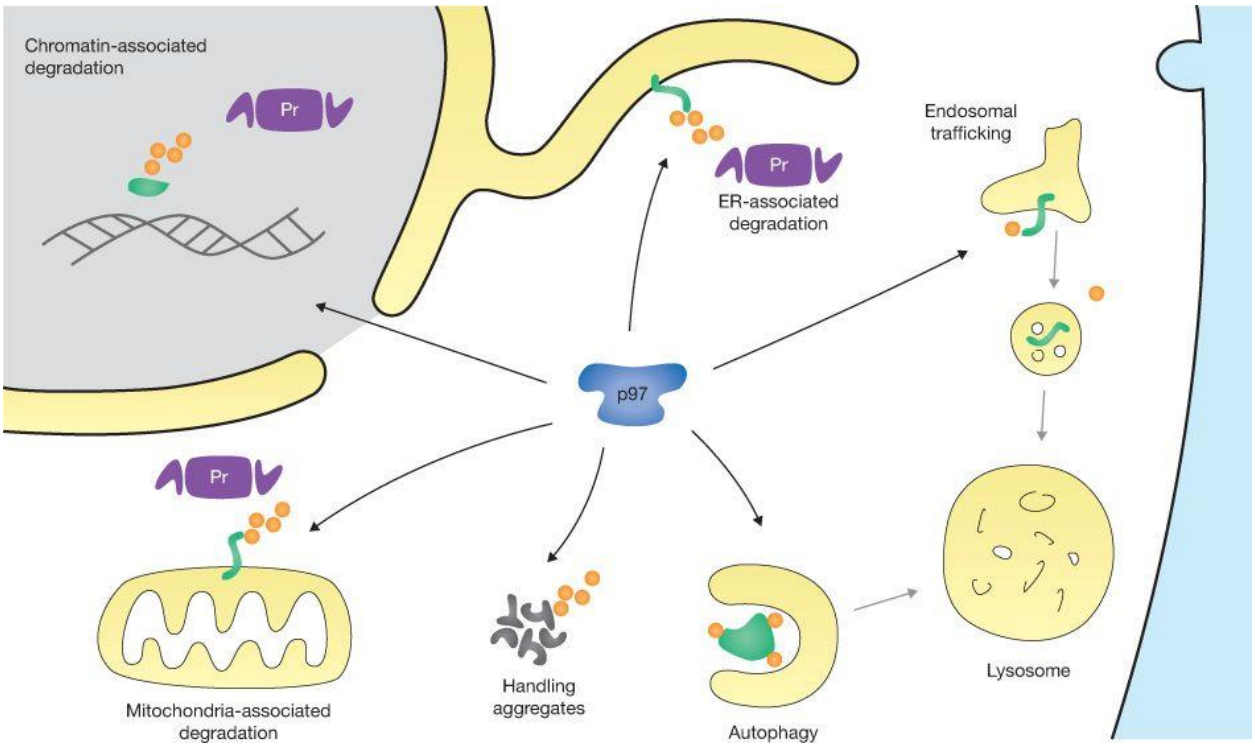

Figure 1-1. Cartoon illustrating select, fundamental roles p97 plays within the cell.[18]

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Amongst these functions, p97 plays an especially important role in protein homeostasis. It has major roles in ER-associated degradation (ERAD), mitochondria associated degradation (MAD), and degradation of protein aggregates and misfolded cytoplasmic proteins (Figure 1-1).[16, 18] The role of p97 in ERAD has been well studied. At the ER, p97 removes or retrotranslocates ubiquitinated protein substrates from the ER membrane into the cytoplasm where they can be identified and degraded by the proteasome (Figure 1-2). p97 is known to mediate the ERAD of a number of substrates, with the well-studied p97-Ufd1-Npl4 complex specifically having been found to play a role in this retrotranslocation event.[20] Ballar et al. showed that different members of this complex were required depending on whether the initial retrotranslocation event to remove luminal proteins was initiated by the E3 ligase Hrd1 or

gp78.[20] They showed that the Hrd1-initated pathway of ERAD activity was mediated by the full p97-Ufd1-Npl4 complex while the gp78-initated pathway required only a p97-Npl4 complex for retrotranslocation to the cytosol.[20] These cofactors allow p97 to remodel and retrotranslocate substrates from the ER. Since p97 primarily binds to ubiquitinated substrates through its many cofactors. When an ubiquitinated substrate is bound, ATP is hydrolyzed, resulting in a conformational change within the p97-cofactor complex and substrate remodeling.[16] After the remodeling event, the polyubiquitin chain of the substrate is trimmed by a deubiquitinase and the substrate is released to the cytoplasm for proteosome degradation.[18] Since p97 plays an essential role in ERAD, loss of p97 function can, at the ER specifically, result in ER-stress induced apoptosis via the unfolded protein response (UPR).[21]

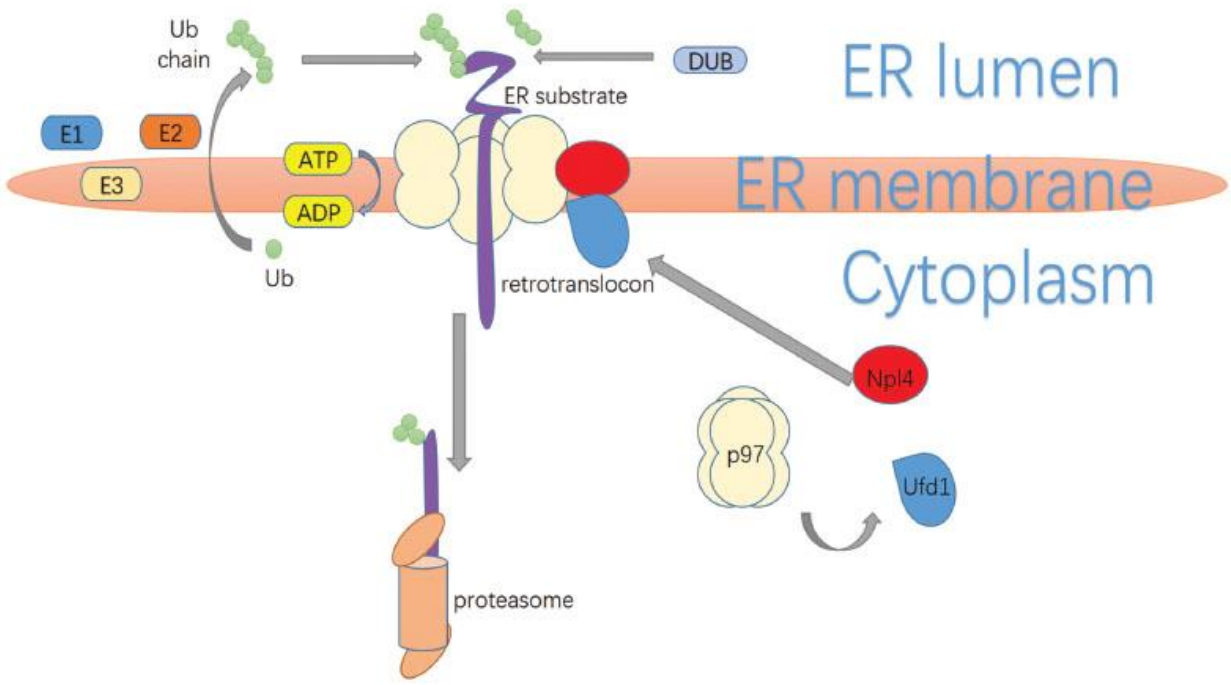

Figure 1-2. Diagram illustrating the role of p97 in ERAD.[22]

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Though a link between p97 activity and autophagy has been known for nearly a decade, the role p97 plays in regulating autophagy is still controversial, with conflicting reports suggesting that it is conversely an activator and a mediator, or inhibitor, of autophagy.[23-25] Both Chou et al. and Tresse et al. independently showed that p97 activity is required for autophagosome maturation of vesicles containing ubiquitinated substrates and therefore the degradation of these substrates. However, both studies showed that p97 is not required for the initiation of autophagy, but is ultimately responsible for the autophagic degradation of ubiquitinated materials.[23, 24] Separately, they were able to draw these conclusions by observing the microtubule-associated 1A/1B-light chain 3 (LC3). Both groups noted an accumulation of immature autophagosomes, observed as an increase of the autophagosome maturation marker, LC3-II, positive vesicles, upon RNAi treatment targeting p97.[23, 24] Conversely, when Anderson et al. explored the effects of their pre-clinical agent, CB-5083, they showed that treatment of cells with their p97 inhibitor lead to p62, an autophagy adaptor protein, and LC3 co-localized foci from the cells indicating the activation of autophagy.[25] This directly contradicts what Tresse observed which was an approximately 3.5-fold accumulation of p62 in p97 knockdown cells.[23] However, Anderson et al. go on to further support that their observations are in fact mediated by p97 by showing that siRNA knockdown of p97, in their hands, resulted in a decrease in the p62 levels within the cell.[25] In addition to the unclear role p97 plays in autophagy, the exact target of p97 which mediates this activity is also still unknown.[26]

The role of p97 and especially its yeast homolog, Cdc48, in cell cycle regulation has been well studied. Since cell cycle progression is determined by the turnover of cell cycle related proteins, p97 is instrumental in regulating this process.[27] The role of p97 in DNA replication and

chromatin dynamics appears to be fairly complex.[18] In combination with Udf-1 and Npl-4, p97 extracts Cdt-1 from chromatin to allow for DNA repair and replication at sites of UV damage.[27, 28] Once the cell progresses into mitosis, p97 performs several additional tasks to promote cell division. One of the first known roles of p97 in mitosis was the extraction of the kinase Aurora B from the chromatin in the last stages of mitosis to allow for chromatin decondensation and nuclear envelop formation.[29] However, more recent work by Dobrynin et al. indicates that p97 involvement begins as early as the prometaphase. They showed that in HeLa cells when Udf-1-Npl-4 was depleted there were increased levels of Aurora B present in chromosomes in both prometaphase and metaphase, resulting in misalignment and extended periods of time to coalesce into a metaphase plate. In addition, they observed that in anaphase the chromosome segregation was also defective, yielding lagging chromosomes and chromosome bridges which resulted in nuclear aberrations in the daughter cells.[30] Though the specific mechanism of how the p97-Udf-1-Npl-1 complex mediates these Aurora B-related effects is unknown, these data illustrate the important role that p97 plays in regulating the cell cycle.

1.1.2 Role of p97 in disease

A precise regulation of p97 is essential to normal cellular operation. Therefore, strict control of p97 activity needs to be maintained, otherwise disease can result. p97 has been both directly and indirectly linked to various neurodegenerative diseases including MSP1 (mucopolysaccharidosis type 1), FALS (familial amyotrophic lateral sclerosis), CMT2Y (autosomal dominant Charcot-Marie-Tooth disease type 2 due to p97 mutation), Alzheimer's disease, Huntington's disease, and Parkinson's disease.[4, 26] MSP1, formerly known as Inclusion Body Myopathy associated with Paget's disease of the bone and Frontotemporal Dementia or IBMPFD) was one of first

diseases linked to aberrant p97 activity, at least partially due to numerous p97 mutations.[31] MSP1 is a progressive, lethal autosomal dominant genetic disorder that primarily affects the muscles, bones, and/or the brain and can often be characterized by inclusions containing ubiquitin, TAR DNA binding protein-43 (TDP-43), and p97, especially in the muscles and brain.[26] A study by Ritson et al. in a *Drosophila melanogaster* model of MSP1/IBMPFD showed that disease causing mutations in p97 lead to redistribution of TDP-43 to the cytoplasm which lead to the neurodegenerative phenotype.[32] The commonality among these neurodegenerative diseases linked to p97 is the inability to clear protein aggregates and aberrant proteins, illustrating the importance of the role p97 plays in proteostasis.

p97 activity has also been linked to the cancer phenotype. In 2003, Yamamoto et al. reported the correlation between p97 expression levels and patient prognosis in several cancer types, including esophageal, thyroid, lung, liver, stomach, pancreatic, and colorectal cancer.[6-9, 11-14] Several pathways involving p97 constitute the molecular mechanisms by which its aberrations can lead to cancer (Figure 1-3). p97 facilitates the proteasomal degradation of p53 and the NFκB endogenous inhibitor, IκB. As a result, p97 overexpression allows for increased tumor growth, invasion, and metastasis.[6, 7, 11, 22] However, in the same study, the authors showed that p97 inhibition or knockdown suppressed cancer cell growth and migration, and increased apoptosis.[33] Through the use of a xenograft model, they also showed that chemotherapeutic intervention against p97 was able to significantly reduce NSCLC tumor growth.[33] This ability to stop growth and to kill cancer cells can potentially be attributed to cancer cells reliance or "addiction" to mechanisms of protein quality control, including p97.[34] Very recently, Parzych et al. determined that p97 plays a crucial role in cellular metabolism, especially under conditions of nutrient deprivation, specifically glutamine.[35] Under these starvation conditions, they observed p97

expression and elevated p97 protein levels, indicating that it might play a key role in the UPS starvation response.[35] Given the elevated requirement for nutrients, especially amino acids, by continuously and rapidly growing and replicating cancer cells, as well as the reliance on proliferation and survival promoting pathways, p97 represents a vital player in the cancer phenotype.

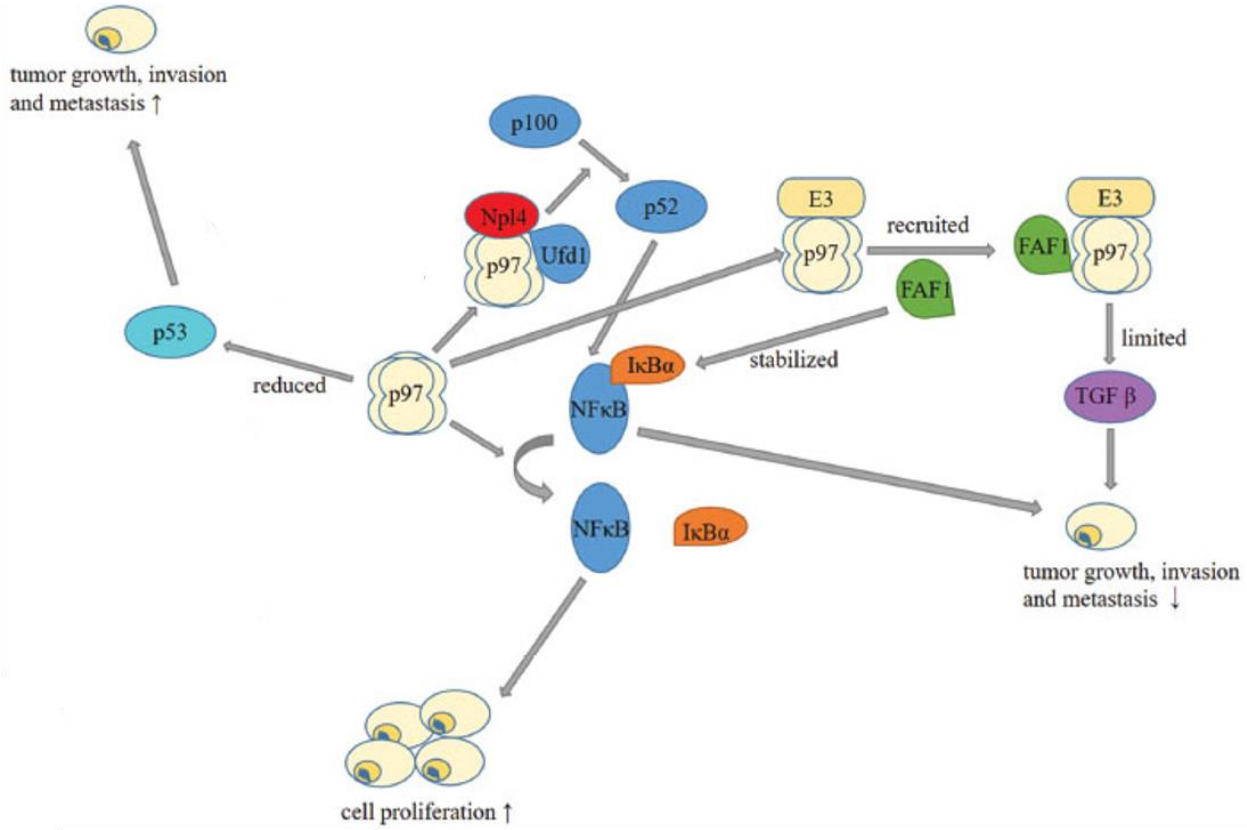

Figure 1-3. Schematic summary of cancer-relevant pathways with p97 involvement.[22]

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1.1.3 Structure of p97

p97 forms a homohexameric ring in which each monomer is composed of three domains, the N, D1, and D2 domains (Figure 1-4, **A**).[18] The D1 domain connects to the D2 domain by a short linker (D1-D2 linker) and the N domain sits on the outside of the D1 domains, again attached by a linker (D1-N linker), forming an additional circle around the top of the core of the hexamer (Figure 1-4, lower). The six monomers adjoin to form a pore or channel at their center (Figure 1-4, **B**). The D1 and D2 domains are the type II AAA ATPase domains containing the characteristic nucleotide binding sites which are located at the interfaces between each monomer (RecA-like domains). These binding sites contain Walker A and Walker B motifs for nucleotide binding and hydrolysis, respectively.[26] Despite the similarities between the two ATPase domains (approximately 40% sequence identity and approximately 60% overall similarity), their function is not equal in relation to substrate remodeling and extraction.[36] Specifically, the D1 domain is primarily responsible for mediating hexamer formation and N domain movement while the D2 domain is primarily responsible for the ATP hydrolysis utilized for protein remodeling and extraction.[18, 37, 38] The N domain, however, is the primary site of co-chaperone, adaptor, and substrate binding.[37] In addition to the differences in ATPase domain function, the structures of the two binding sites was recently shown to be different. Firstly, the D1 nucleotide binding site can be accessed from the top face or the side of the hexamer, while the D2 nucleotide binding site can be accessed only by the side of the hexamer with the D1-D2 linker determining the shape of the D2 site.[36] In addition, differences in the amino acid residue composition of the two sites were found during the course of studies intending to understand the molecular binding of the ATP-competitive inhibitor CB-5083. This was accomplished by obtaining and solving X-ray crystals of CB-5083 bound to a D1-D2 truncated protein and comparing this structure with that

of an ADP bound full length p97 (PDB: 3CF3), as well as looking at CB-5083 resistant mutants to confirm key residues.[36] A number of key residues for CB-5083 binding in the D2 binding site were identified and when compared to the D1 binding site were shown to not be conserved, however, in a separate earlier study by Hänzelmann *et al*., nucleotide binding residues were shown to be conserved.[36, 39] The key differences identified by Hänzelmann et al. between the D1 and D2 sites were much more subtle; the side chain of the arginine in the arginine finger (R359) of D1 was found to be much more flexible than the D2 equivalent (R635) preventing interaction with a hydrogen bonding network.[39] In addition, a proline (P) to phenylalanine (F) switch is made within the arginine fingers from D2 to D1, respectively, and this phenylalanine side chain changes conformations dependent on the type of nucleotide bound to the D1 binding site.[39] This phenylalanine plays a key role in determining the type of nucleotide bound and therefore has a significant impact on the ATPase activity of D1, shown by its mutation to alanine resulting in a 75% loss of ATPase activity compared to wild type.[39]

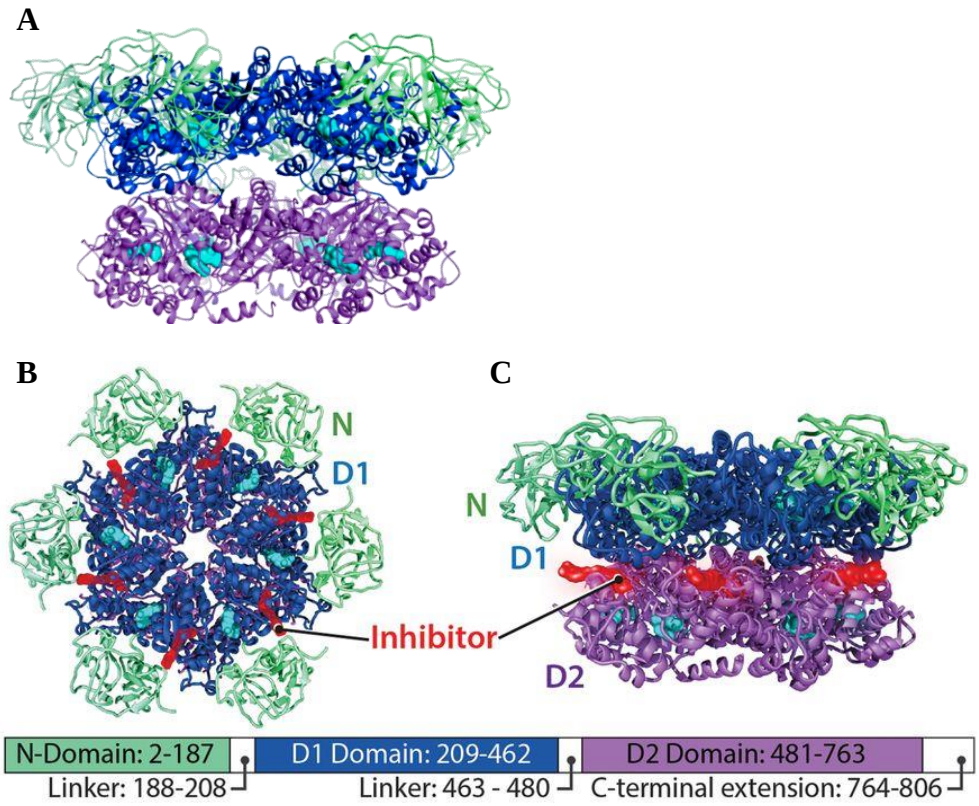

Figure 1-4. Ribbon diagrams derived from cryo-EM data at 2.4 Å of full length p97 highlighting the three structural domains as well as sites of nucleotide and inhibitor binding.

(A) Side view of the ribbon diagram showing the N domain (green), D1 domain (blue), and D2 domain (purple) bound to ADP (cyan). (B) Top view of the homohexameric ring structure of p97 with ADP (cyan) and an allosteric inhibitor bound (red). (Lower) Schematic of the p97 sequence showing the various regions of the structure color coded to match the ribbon structure above. (C) Side view of the structure with ADP and inhibitor bound.[37]

Over the last two decades, the conformational changes p97 undergoes within the cell have been reaffirmed. Recently, the first high resolution structures of the p97 homohexamer were solved to provide the strongest evidence thus far for the activation of p97 before this remodeling activity.[37] The proposed mechanism is comprised of two steps (Figure 1-5). The first step is p97 activation, by binding of ATP to the D2 domain, which results in the movement of

the D2 domain "down" (Figure 1-5, **B**). This also results in structural changes in the D1-D2 interface that "unlock" the N domain. Next, ATP binds at the D1 domain, which causes the N domain to move into the "up" position (~75° difference from the "down" position before second ATP binding event) which likely allows for effector protein binding (Figure 1-5, **C**). This movement of the N domain also results in movement of the N-D1 linker which significantly alters the D1 nucleotide binding domain. In addition, Banerjee et al. noted that as ATP bound to the D2 domain there was an approximately 6.8 Å contraction of the pore within the D2 ring while ATP binding to D1 did not result in any additional pore diameter changes in either the D1 or D2 rings.[37] It should be noted that all six protomers are not necessarily synchronized in their activation, or nucleotide binding, and that there can be numerous partially activated p97 states present at any given time.[26, 40] Though this mechanism of conformational change is well studied, the means by which p97 carries out its effects on other proteins is less clear. Two possible mechanisms by which p97 can extract substrates from the target structure (membrane, aggregate, or chromatin) have been proposed: 1) p97 conformational change while attached to the substrate can result in partial unfolding that disrupts the interactions between the substrate and the target structure, or 2) the substrate is threaded through the central pore of p97, resulting in unfolding.[26] Bodnar and Rapoport recently showed that in the case of polyubiquitinated model substrates, once the polyubiquitin chain interacted with the adaptors Udf-1 and Npl-4 of the p97-Udf-1-Npl-4 complex, ATP hydrolysis by the D2 domain lead to threading of the chain through the pore of p97 and unfolding of the substrate. Once the unfolding occurred, ATP hydrolysis in D1 as well as trimming of the polyubiquitin to an oligoubiquitin chain by a deubiquitinase, proposed to be YOD1 (Otu1 in yeast), lead to the release of the newly unfolded, shorter ubiquitin-tagged substrate from the p97 complex (Figure 1-6).[41]

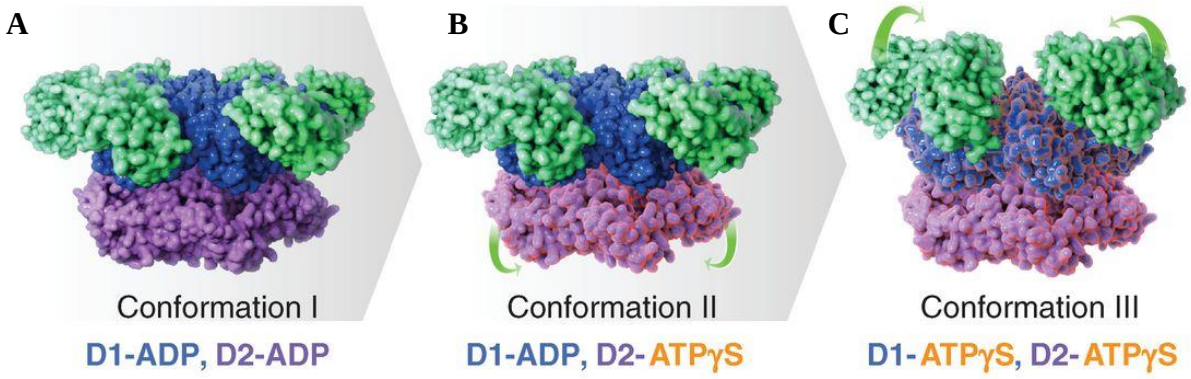

Figure 1-5. Cryo-EM surface model structures of the three conformations identified during the process of nucleotide binding, with arrows showing the conformational changes at each step.

(A) ~3.3 Å resolution structure of the completely ADP bound structure with domains color coded: N domain (green), D1 domain (blue), and D2 domain (purple). (B) ~3.2 Å resolution structure of the D1-ADP and D2-ATPγS bound structure. (C) ~3.3 Å resolution structure of the completely ATPγS bound structure.[37]

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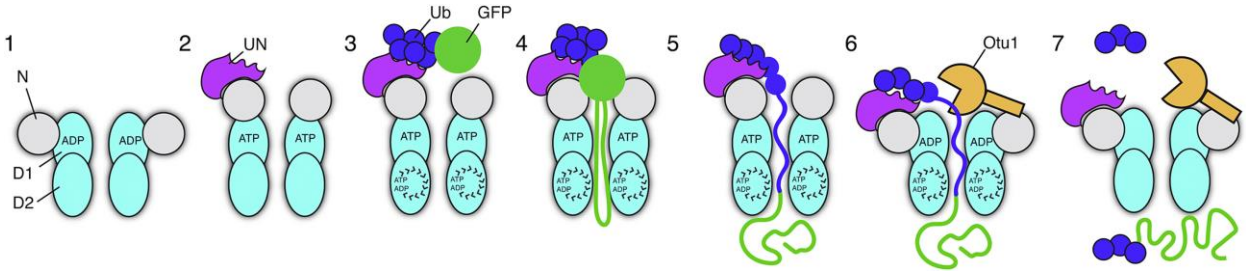

Figure 1-6. Schematic representation of the mechanism of p97 unfolding of polyubiquitinated substrates.

p97/Cdc48 D1 and D2 domains (cyan), p97/Cdc48 N domain (gray), Udf-1-Npl-4 complex (magenta), ubiquitin (blue), GFP/model substrate (green), deubiquitinase/Otu1/YOD1 (orange).[41]

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1.1.4 Targeting protein homeostasis for cancer treatment

After first being discovered in 1987, the proteasome has been well studied and characterized.[42-44] Once the importance of the proteasome was understood, the hypothesis that it could play a crucial role in the cancer phenotype and that it could be a viable chemotherapeutic target was proposed.[45, 46] The proteasome's main role within the cell is to degrade unnecessary or damaged proteins. Therefore, the proteasome plays an important role in cell cycle progression. In addition, the proteasome removes damaged and aberrant proteins. Both activities become very important in cancer cells due to their increased proliferation rate. Therefore, targeting the proteasome for cancer chemotherapy has been a popular strategy in the past.[3] This effort has led to the FDA approval of three proteasome inhibitors: bortezomib (Velcade®), carfilzomib (Kyprolis®), and ixazomib (Ninlaro®).[47] Bortezomib was the first FDA approved proteasome inhibitor in 2003, suggesting that targeting protein homeostasis was a viable method for treating cancer. Though the discovery and approval of bortezomib was a key step in the development of protein quality control targeting drugs, bortezomib still had many limitations. In clinical trials, it showed a 35% response rate (38% with partial and complete responses combined) which was as much as a 20% increase over the standard of care dexamethasone.[47] However, some patients do not respond to bortezomib treatment and a large population relapses after bortezomib treatment. Since bortezomib was first approved, only two additional proteasome drugs have been approved for the treatment of multiple myeloma and lymphoma, but no other tumor types.[47]

Though these proteasome targeting drugs lay the foundation for treating cancer via protein quality control, there is still room for improvement. It has been proposed that one of the imitations of the proteasome inhibitors is that upon proteasome inhibition compensatory pathways are activated and cause increased expression of proteasome proteins, allowing the cells

to recover.[34] Since p97 functions upstream of the proteasome and is only required for a fraction of the proteasome activity, it is theorized that especially in combination therapies the same compensatory pathways will not be activated and will lead to improved efficacy.[4, 48] In addition, p97 directly and indirectly regulates key tumor-related proteins (see Sections 1.1.1 and 1.1.2).[33, 34]

1.2 KNOWN INHIBITORS OF P97

Within the p97 literature, examples of competitive, uncompetitive, and non-competitive inhibitors have been reported and key examples of each type will be discussed below.

1.2.1 ATP competitive inhibitors

Competitive inhibitors are characterized by their ability to bind free enzyme. The binding with regard to substrate, ATP, is mutually exclusive, meaning that only the inhibitor or the nucleotide can be bound at any given time, typically because they have the same binding site. This results in an increase in the K_m of the enzyme while the V_{max} is unaffected.[49] One of the earliest small molecules identified to target p97 was called DBeQ (**1-1**), i.e. *N*^{2},*N*^{4}-dibenzylquinazoline-2,4-diamine (Figure 1-7).[24] DBeQ was shown to be a reversible and selective inhibitor of p97 with a biochemical IC_{50} of 1.5±0.4 μM and a cellular IC_{50} of 2.6±0.3 μM. The reversibility of the compound was supported by the retained activity against p97^{C522A}, a mutant where the reactive cysteine residue within the ATP binding site is replaced by alanine. The selectivity of DBeQ was demonstrated by comparing its IC_{50} for the p97-independent proteasome substrate ODD-Luc

versus the p97-dependent substrate Ub^{G76V}-GFP. In this assay format, DBeQ showed a greater than 10-fold loss of activity for ODD-Luc versus Ub^{G76V}-GFP. It was also tested against a panel of approximately 170 kinases and at 15 μM it did not show significant inhibition.[24] DBeQ was found to bind both the D1- and D2-domain active sites.[50] DBeQ affects the ERAD branch of p97 activity, resulting in accumulation of GFP fused T-cell receptor α-chain (TCRα-GFP) which is embedded into the ER when over expressed in non-T cells and degraded by the proteasome in a p97-dependent manner. Optimization of the diaminoquinazoline chemotype led to several lead compounds as well as one clinical candidate.[25, 51]

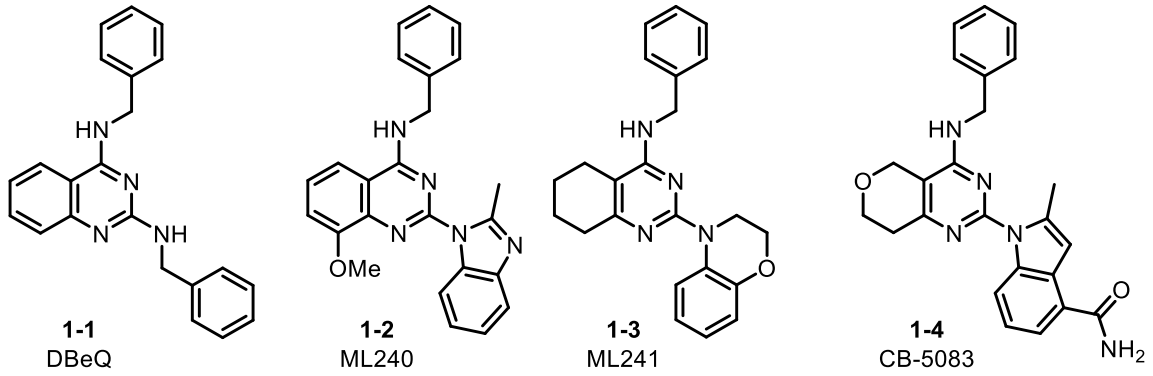


Figure 1-7. Structures of the diaminoquinazoline series.

The second generation diaminoquinazolines, ML240 (**1-2**) and ML241 (**1-3**), were reported two years later by the same groups (Figure 1-7).[51] Both compounds retained the pyrimidine-2,4-diamine core of DBeQ as well as the benzyl group at the 4-nitrogen. However, they differed in the ring fused to the pyrimidine as well as the heterocycle attached at the 2-nitrogen. Despite these differences, both compounds showed low-micromolar activity in a biochemical ATPase assay, however, in a cellular assay determining the degradation of Ub^{G76V}-GFP, there was a clear preference for compound **1-2** over **1-3** (0.9±0.1 μM versus 3.5±0.4 μM, respectively). Both compounds were shown to act via p97 inhibition and not by another p97-

independent pathway in an assay of the degradation of ODD-Luc.[51] Compound **1-2** was shown to rapidly activate apoptotic pathways as well as block autophagosome maturation; however, compound **1-3** did not accomplish this.[51] Both **1-2** and **1-3** were also shown to affect the ERAD activity of p97, albeit **1-3** to a weaker degree than **1-2**. Like DBeQ, **1-2** resulted in decreased autophagosome maturation as determined by LC3-II accumulation; in contrast, **1-3** did not show any such affects. Compound **1-2** was effective as an antiproliferative agent in a number of cell lines in the NCI60 panel, a panel of 60 human tumor cell lines used to identify compounds with anticancer activity.[51] Unlike DBeQ, the second generation analogs were found to only inhibit the D2 domain binding site.[50] Overall, the second generation compounds, **1-2** and **1-3**, showed improved potency and improved specificity relative to **1-1**.

Despite these significant improvements, ML240 (**1-2**) and ML241 (**1-3**) only had low micromolar cellular activity, and improvements were still required to produce a viable clinical candidate. The company that licensed the diaminoquinazoline intellectual property (IP), Cleave Biosciences Inc., generated a clinical candidate, CB-5083 (**1-4**), via a lead optimization strategy to improve potency, ADME, and physiochemical and pharmacokinetic properties (Figure 1-7).[52] They reaffirmed that the N^4-benzylpyrimidine-2,4-diamine was required for activity; however, they were able to modify the 2-amino heterocycle as well as the fused pyrimidine ring. Once again, they showed that the scaffold was ATP-competitive and only bound to the D2 domain. CB-5083 had a biochemical IC_{50} of 11 nM and a cellular IC_{50} in a CellTiter-Glo assay of 0.68 μM, which corresponded to a 74-fold (under the same assay conditions) and a nearly 5-fold improvement, respectively.[52] Treatment with CB-5083 also resulted in ERAD disruption as determined by accumulation of TCRα-GFP; however, unlike the previously reported analogs that inhibited autophagy, CB-5083 appeared to induce autophagy. This was shown by the rapid

clearance of p62- and LC3-II-positive foci in **1-4** treated cells.[25] In addition, Anderson et al. showed, both *in vitro* and *in vivo*, that CB-5083 was able to induce cancer cell death and decrease tumor growth after oral administration in tumor xenograft studies, including both hematological and solid tumor types.[25] Given these promising findings, CB-5083 was tested in two Phase I clinical trials for advanced solid tumors and multiple myeloma. Both trials were terminated, however, due to an off-target retinal toxicity due to PDE6 inhibition.[36]

1.2.2 ATP uncompetitive inhibitors

Uncompetitive inhibitors are characterized by an ability to only bind enzyme-substrate complexes, not free-unbound enzyme, resulting in a decreased enzyme K_m and V_{max}.[49] Thus far, the only uncompetitive p97 inhibitors published are from the collaborative effort of the p97 group within the Chemical Biology Consortium (CBC).[37, 53-58] The CBC team identified several weakly active inhibitor series in a high-throughput screen (HTS) of 246,000 compounds using a biochemical ADP-Glo™ assay (Figure 1-8).[54, 56] Though three chemotypes were classified as uncompetitive inhibitors, only two were studied extensively. The first series, characterized by an amide indole core, was reported in the literature.[54] The initial hit **1-5** was determined to bind at the D2 domain but not the D1 domain. This was demonstrated by an absence of inhibitory activity against the truncated form of p97 bearing only the N and D1 domains.[54] In addition, the amide indole chemotype was shown to be an uncompetitive binder with regard to ATP, given that **1-5** and analogs inhibited the ATP bound complex more potently than the ATP unbound state. This was demonstrated by the decrease in the IC_{50} of **1-5** as the concentration of ATP increased (IC_{50} = 11.5 ± 4.6 μM at 20 μM ATP versus IC_{50} = 2.5 ± 1.7 μM at 100 μM ATP).[54]

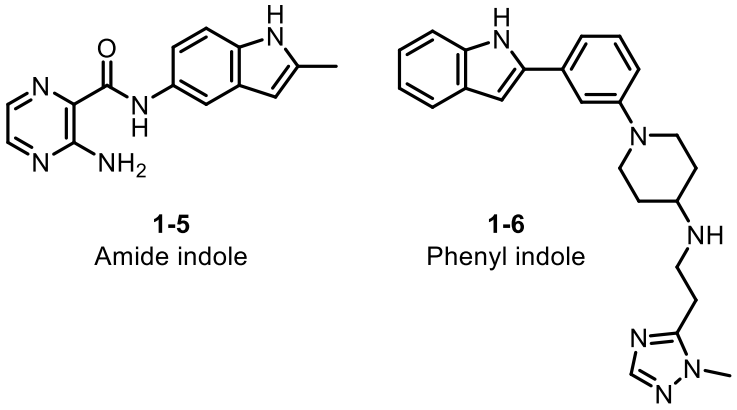


Figure 1-8. Structures of the two hits identified from the CBC HTS.[54, 56]

To explore the SAR of the amide indole chemotype, the structure was divided into four zones (Figure 1-9). The synthetic approach taken for the library was to disconnect the amide bond, allowing for a straightforward generation of analogs. This was accomplished by purchasing or synthesizing the desired amine and carboxylic acid building blocks and connect them via an amide coupling utilizing 1-[bis-(dimethylamino)-methylene]-1*H*-1,2,3-triazolo[4,5-b]-pyridinium 3-oxide hexafluorophosphate (HATU) and an amine base (Scheme 1-1).[54]

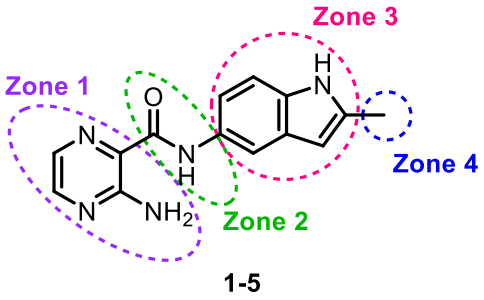
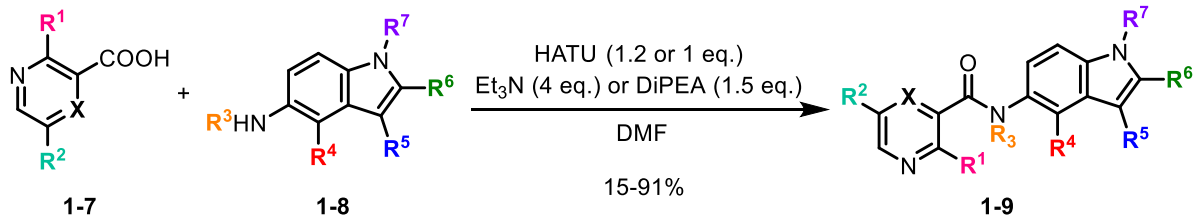


Figure 1-9. Zones of structural modification for the amide indole 1-5.



Scheme 1-1. General synthesis of amide indole analogs showing points of diversification.

All zones of **1-5** were explored to probe the binding pocket and establish the SAR of this initial hit.[54] Beginning with zone 1, additional aryl groups, particularly heterocyclic groups, were screened to determine whether the starting pyrazine was optimal. While nearly all replacements were found to be detrimental to activity, removal of the *N*-4 nitrogen yielding the 2-amino pyridine derivative (**1-10**, IC_{50} = 0.5 ± 0.2 μM).[54] The substitution pattern within zone 1 was also explored; these changes consisted of removing and replacing the 2-amino group, as well as adding substituents at the 5-position. Despite relatively conservative replacements being made at the 2-position (replacement with hydrogen, hydroxy, and *N*-methyl amino groups), only the unsubstituted amine was tolerated. At the 5-position, both smaller and larger groups, including cyano; ethyl; 4-pyridyl; and 2-methyl-1*H*-indol-5-yl, were prepared to probe the size of the pocket. While the smaller groups (cyano and ethyl) retained some activity (IC_{50} < 50 μM) they all resulted in significant losses in activity, indicating that the pocket surrounding zone 1 was relatively small and not amenable to larger groups (Figure 1-10).[54]

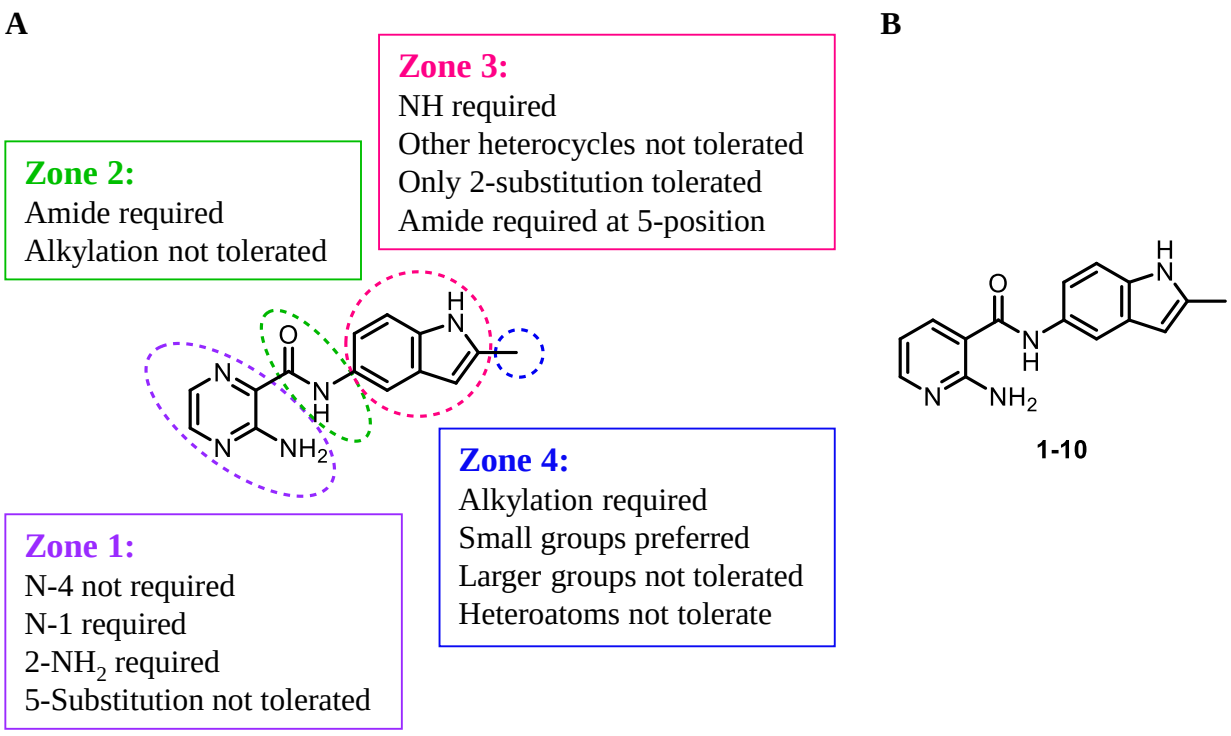


Figure 1-10. SAR summary and best analog derived from the amide indole series.

(A) SAR summary for amide indole derivatives of hit **1-5**. (B) Best amide indole analog discovered from SAR campaign.[54]

The SAR within the three remaining zones proved to be quite limited as well.[54] Zone 2 modifications included a reduction of the amide to the benzylic amine, which retained partial activity (IC_{50} = 10 ± 1.5 µM), while replacement with an ester linkage as well as alkylation on the nitrogen of the amide lead to complete loss of potency.[54] These finding suggested an important hydrogen bonding interaction which was very dependent on the pK_a of the hydrogen bond donor, the amine nitrogen, hence the significant loss of activity of the amine. Zone 3 was explored by replacement of the indole, such as with 2-methylquinoline, as well as the addition of substituents at various positions. Modifications of both types resulted in significant or total loss of activity. Once again showing that the binding pocket at the indole region was very specific to the 2-substituted indole. Finally, zone 4 modification focused on the removal and elongation of

the alkyl group. A small alkyl group (methyl or ethyl) was found to be required in the 2-position; however, larger chains were not tolerated, emphasizing the small volume of the binding site. The difficulty in modifying zones 3 and 4 was supported by NMR studies of **1-5** in the presence and absence of a truncated p97 D2 domain, which showed line broadening of the 2- and 3-positions of the indole in the presence of the D2 domain relative to the protein free spectra.[54] This data suggests that the indole, especially at the 2- and 3-positions, tightly interacts with the D2 domain.

A second series identified via HTS was characterized by a phenyl indole (**1-6**, Figure 1-8) with a flexible, basic side chain. Some SAR data, as well as a study of the substituent effects at the 5-position of the indole, have been reported.[53, 56] This series, like the amide indole series, was found to bind uncompetitively to p97.[56] Early experiments with **1-6** in a biochemical assay against p97 with varying concentrations of ATP (20 μM and 100 μM) showed that at the lower, 20 μM, concentration, **1-6** was approximately 2.5-fold less potent (IC_{50}= 2.4 μM) than in the presence of 100 μM ATP (IC_{50}= 0.99 μM).[56, 59] Given the appealing uncompetitive binding and generally favorable, within standard drug-like ranges, physical properties, a SAR campaign to explore the structure of **1-6** was carried out.[53, 55-57] The structure of **1-6** was broken into five zones for modification (Figure 1-11). The SAR was carried out in a systematic fashion to identify the preferable fragments in each zone and then a mix-and-match optimization was carried out to identify the overall best analogs.[53, 55-57] The synthetic approach taken to achieve this relied on a modular synthesis. First, the 2-phenyl indole core was synthesized in either two steps or one step via imine formation, followed by Fischer indole synthesis or C-H arylation, respectively (Scheme 1-2, **A** and **B**, respectively). The resulting *meta*-aryl bromide was then reacted with the piperidine ketal under Buchwald-Hartwig conditions. The ketal was deprotected under acidic conditions to reveal the ketone which was then carried into a titanium (IV)-mediated

reductive amination with the desired amine (see Section 3.3 for synthesis).[53, 56] In the later stages of the synthesis, once the preferable side chain fragments (zones 3-5) were identified, the Buchwald-Hartwig coupling could be carried out with the fully functionalized side chain fragment, followed by Boc deprotection to give the final analogs (see Chapter 3.3 for synthesis).[53, 56]

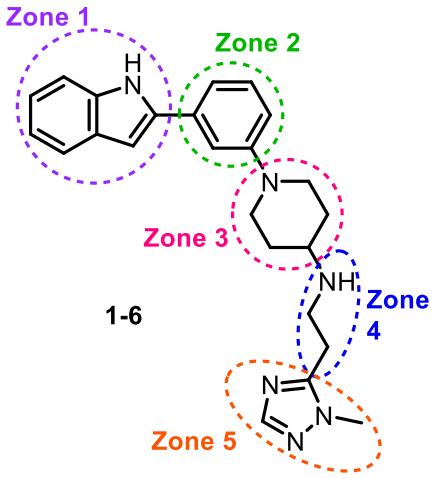
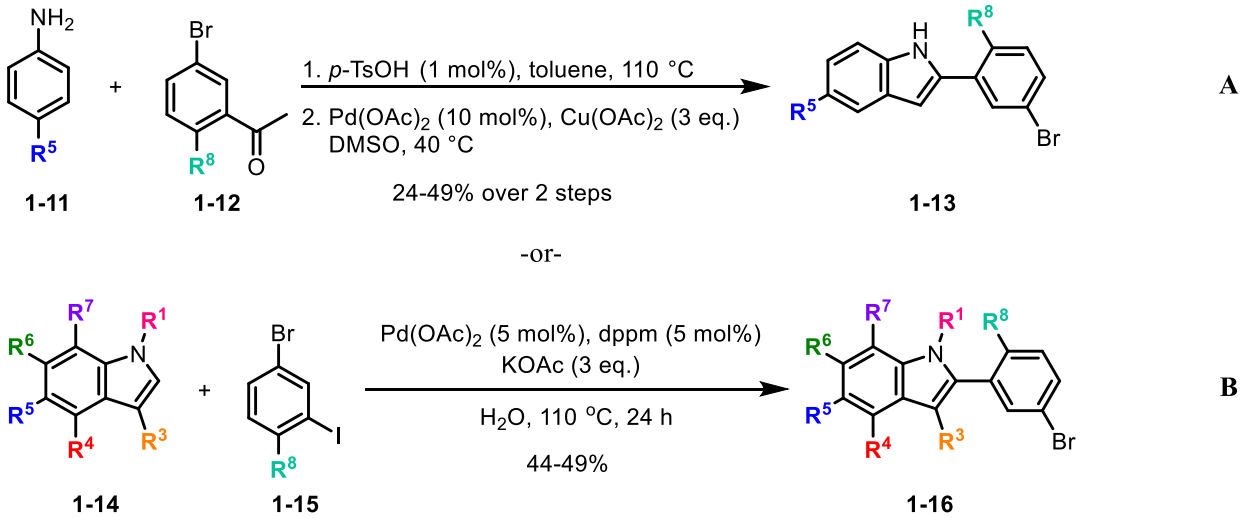


Figure 1-11. Zones of structural modification for the phenyl indole chemotype.



Scheme 1-2. General synthesis of phenyl indole core showing basic of diversification.

(A) Two-step synthesis (imine formation followed by indole cyclization) of phenyl indole core.[53] (B) One-step synthesis (C,H-arylation) of phenyl indole core.[53]

All five zones of **1-6** were explored while trying to maintain the drug-like physiochemical properties and improve the potency of the hit. The indole of zone 1 was found to be very sensitive to modification. Both the replacement of the indole with additional fused aryl systems, as well as substitution of the 5-position of the indole were carried out.[53, 55] All replacements of the indole were found to be inferior; however small groups at the 5-position were well tolerated with the 5-cyano, 5-fluoro, and 5-nitro performing the best (IC_{50} = 44 ± 45 nM, IC_{50} = 55 ± 87 nM, IC_{50} = 47 ± 40 nM, respectively).[53, 55] This showed that the binding pocket around the indole was small, preferred hydrogen bonding competent groups (especially hydrogen bond acceptors as evidenced by the top three compounds), and was very sensitive to electronic effects.[55] In addition to this, it was observed that small apolar and hydrophobic groups were moderately tolerated (most retaining submicromolar potencies) in the 5-position as well.[55] In zone 2, substitution at the 2-position with a methyl group was well tolerated (IC_{50}s < 100 nM), indicating that a part of the binding pocket was likely very hydrophobic.[55] However, conformationally restricting the molecule by tethering the phenyl to the indole by formation of a benzo[α]carbazole core resulted in a >2-fold loss of activity compared to the unsubstituted indole.[55] Zone 3 modification focused on removal of the nitrogen within the piperidine and testing of both the *cis* and *trans* cyclohexane analogs.[56] The piperidine was found to play an important role in binding, likely participating in a hydrogen bonding interaction, given that the cyclohexane analogs were >80-fold (*cis*) and >3-fold (*trans*) less active than their nitrogen-containing counterpart.[56] However, the drastic difference in the two cyclohexane analogs' potencies showed the large effect that the orientation of the side chain has on binding. The *cis*

analog was shown to move key hydrogen bonding interactions between the side chain and p97 out of range, while the *trans* analog was able to orient the amine side chain to maintain hydrogen bonding interactions.[56] Zone 4 modification focused on replacing the nitrogen within the linker, modifying the length of the linker, and adding additional substitution to the linker (See Chapter 3.3 for nitrogen linker replacements).[56, 57] The SAR within zone 4 was found to be less restrictive than many other regions of the chemotype. The linker tolerated both lengthening and shortening of the parent amino ethyl linker, with preference for two carbon or zero carbon linkers, as well as the addition of small cyclic rings (cyclobutyl and oxetanyl) at the C2 of the ethyl linker.[56] However, fused ring and spirocyclic systems which restricted the flexibility of the side chain were shown to be 16- to >200-fold less potent than their more flexible counterparts.[56] This finding emphasized the necessity of flexibility within the side chain to adopt a preferred conformation for binding. The final region of the chemotype, zone 5, was explored through the replacement of the 1-methyl-1,2,4-triazole with aryl and nitrogen containing alkyl groups. The synthesis of phenyl and pyridyl containing analogs showed the importance of heteroatoms within this tail group given the nearly 3-fold loss of activity of the phenyl versus the pyridyl and 1-methyl-1,2,4-triazole (**1-6**) compounds.[56] The replacement of the aryl nitrogen-containing systems with alkyl and basic nitrogen-containing groups, like piperazine and dimethylamine, lead to significant increases in potency with the piperazines being preferred.[56] This preference for the basic piperazine group suggested hydrogen bonding interactions, likely at both nitrogens given the increased potency of the piperazine over dimethylamine. This was later supported by molecular modeling which showed key hydrogen bonds between the *N*-1 with Gln494 and *N*-4 with Glu534.[56] The 4-position of the piperazine was also explored and it was found that the size of the alkyl group was not important and that both small (methyl) and large (*tert*-butyl) groups

were tolerated, with a slight preference for more lipophilic groups, *iso*-propyl being the most potent one.[56]

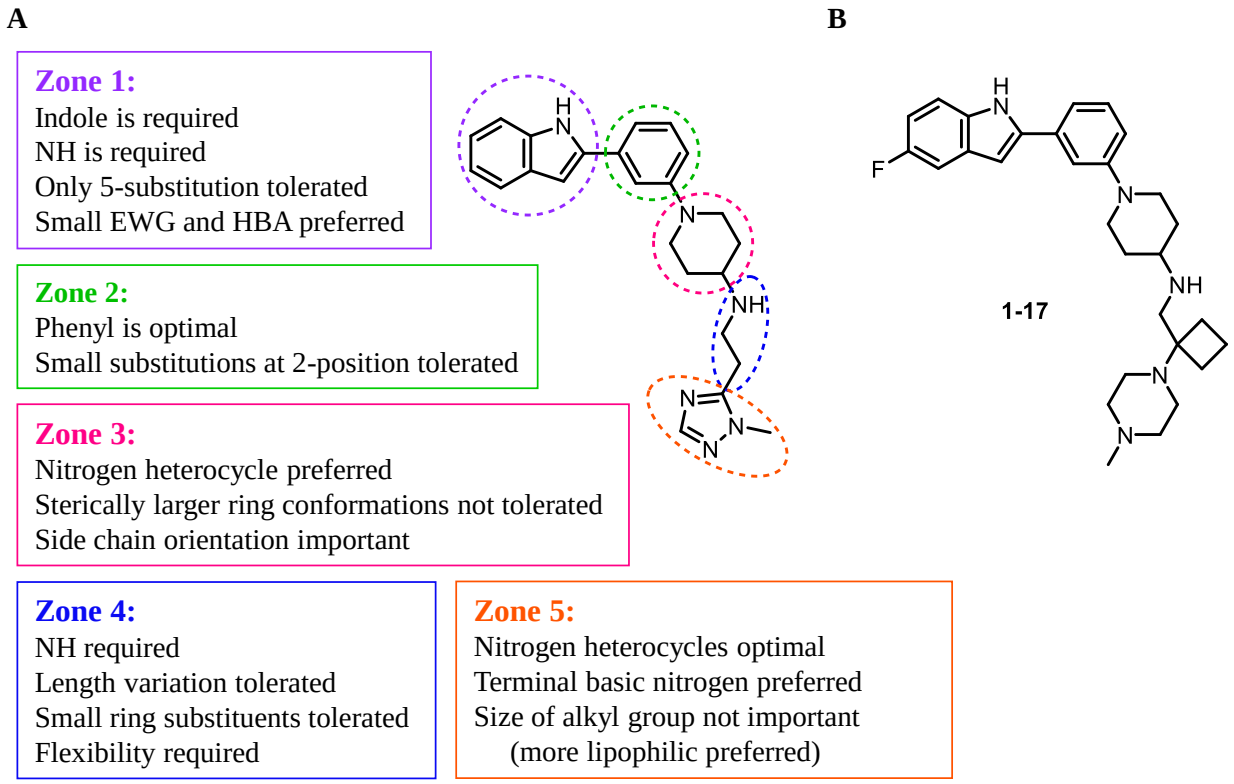


Figure 1-12. SAR summary and best analog derived from the phenyl indole series.

(A) SAR summary for phenyl indole derivatives of hit **1-6**. (B) Best phenyl indole analog discovered from SAR campaign.[53, 55, 56]

The location of the binding site of these inhibitors was determined to be the D2 domain, and ultimately this was confirmed by a cryo-EM structure of p97 bound to an advanced analog of **1-6** which showed the binding site to be an allosteric site within the D2 domain.[37, 55] A 2.3 Å structure showed that the specific location of the binding pocket was located near the protomer interface (Figure 1-13, **A** and **B** upper). The binding mode originally reported by Banerjee et al. showed the indole tucked deep into a hydrophobic pocket, with the 5-position fluorine engaged

in a hydrogen-fluorine type hydrogen bond with Ser511 (Figure 1-13, **B** lower). The phenyl ring was also tucked back into the pocket while the piperidine occupied a cleft just outside of this pocket (Figure 1-13, **B** lower). This supported the SAR that was observed for zones 1-3 and showed that the pocket around the phenyl indole was narrow, not allowing for larger groups or additional substituents around the core. The cryo-EM had difficulty identifying the orientation and position of the side chain due to low densities at zones 4 and 5 leading to questions about the interactions occurring with the side chain. In collaboration with Leidos Biomedical Research, Inc. and the Frederick National Laboratory for Cancer Research's Developmental Therapeutics Program, the authors were able to conduct computational studies on the cryo-EM structure, which showed additional interactions which better agreed with the experimental SAR.[55] First, they observed π-stacking between the indole and Phe618, hydrogen bonding of the indole NH with the backbone carbonyl of Val493, and two threonine residues that were found to move to accommodate small polar and non-polar groups at the 5-position (Figure 1-13, **C**). The phenyl ring was shown to sit in a hydrophobic pocket, while the piperidine nitrogen was engaged in a dipole-dipole interaction with the thiol of Cys535, supporting the reduced potency of the *trans* cyclohexane analog. With the use of the computational refinements, a reasonable orientation of the linker and terminal heterocycle was determined that agreed with the SAR. This showed hydrogen bonding interactions between the carboxylate of Glu498 and the linker nitrogen, the amide of Gln494 and *N*-1 of the piperazine, and the carboxylate of Glu534 and *N*-4 of the piperazine. Overall, the refined structure agreed with and supported the SAR that was published, and suggested the importance of the flexible nature of the molecules for adopting the necessary shape for binding to p97.

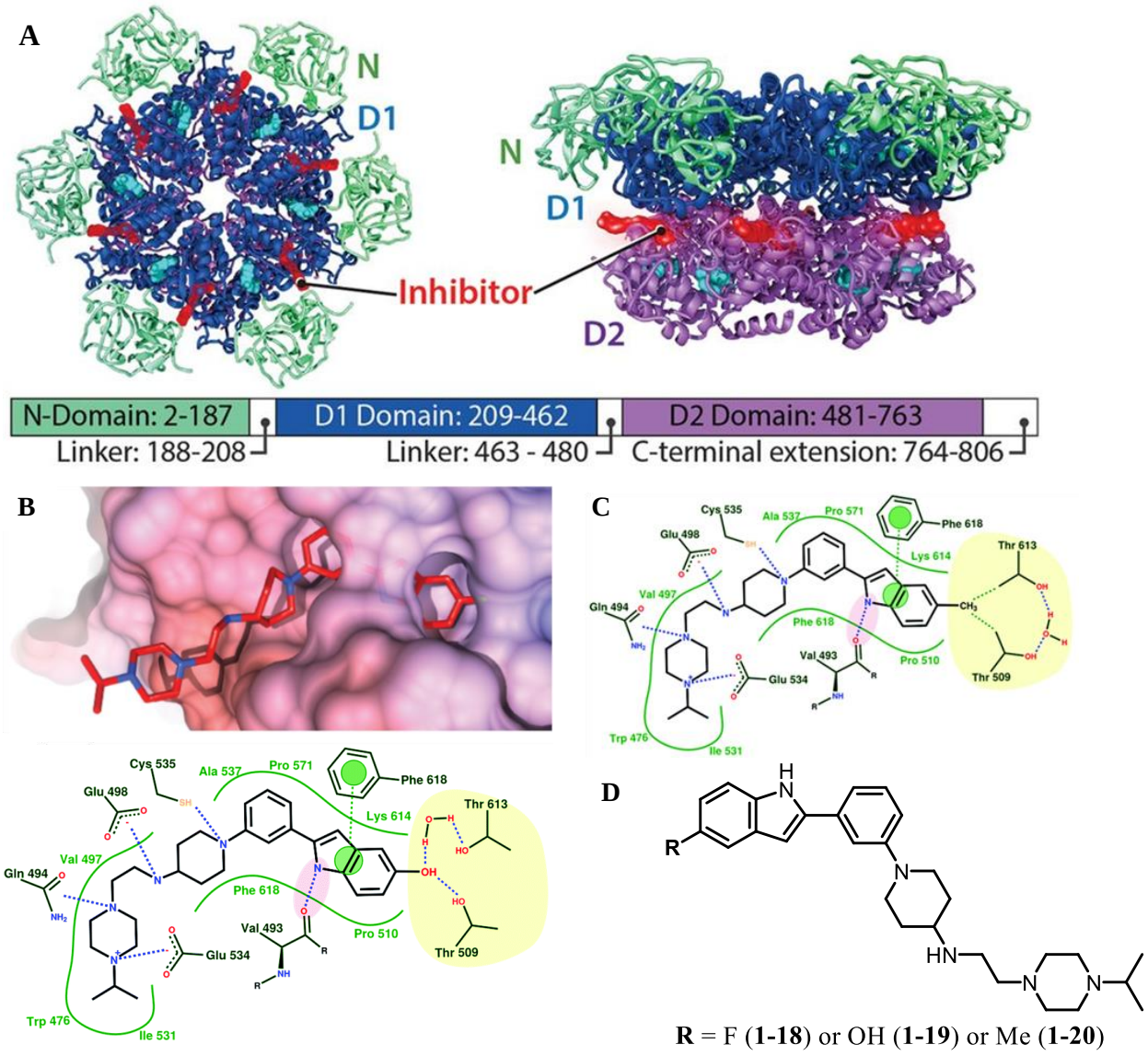


Figure 1-13. Cryo-EM and refined structures of advanced analogs bound to p97.

(A) Overview of the p97 hexamer with advanced analog (**1-18**, **D**) bound to each protomer. N-Domain (green), D1 domain (blue), D2 domain (purple), inhibitor (red), ADP (cyan).[37] (B) Upper: View of a single protomer showing the location of the bound inhibitor (**1-18**, red) relative to each domain and bound ADP (cyan).[37] Lower: 2D schematic representation of inhibitor (**1-19**, **D**) in the binding pocket showing the nearby residues and key interactions with the binding pocket residues for the refinement of the binding site identified by cryo-EM for **1-18**. H-bonding (blue dashed), hydrophobic interactions (green dashed), π-stacking (green circles).[55] (C) 2D schematic representation of inhibitor (**1-20**, **D**) in the binding pocket showing the nearby residues and key interactions with the binding pocket residues.[55] (D) Structures of inhibitors used in Cryo-EM and molecular modeling.[37, 55, 56]

The mechanism of action for the phenyl indole chemotype was also elucidated during the course of the cryo-EM studies. Three distinct conformations of p97 were observed while titrating ATPγS into the ADP bound, inactive p97. Those three conformations were found to be: D1-ADP and D2-ADP bound, D1-ADP and D2-ATPγS, and D1-ATPγS and D2-ATPγS (Figure 1-14, **A**) (described previously in Section 1.1.3). The cryo-EM structure showed that the specific binding site was located near the D1-D2 interface (Figure 1-14, **B**). It was suggested that the inhibitor binds to the ADP bound state preferentially, and upon this binding event, it prevents ATP binding to D2 due to steric clashes between the inhibitor and the observed D2-ATP bound configuration. This prevents the initiation of the conformational changes, and results in p97 deactivation (Figure 1-14, **B**).[37]

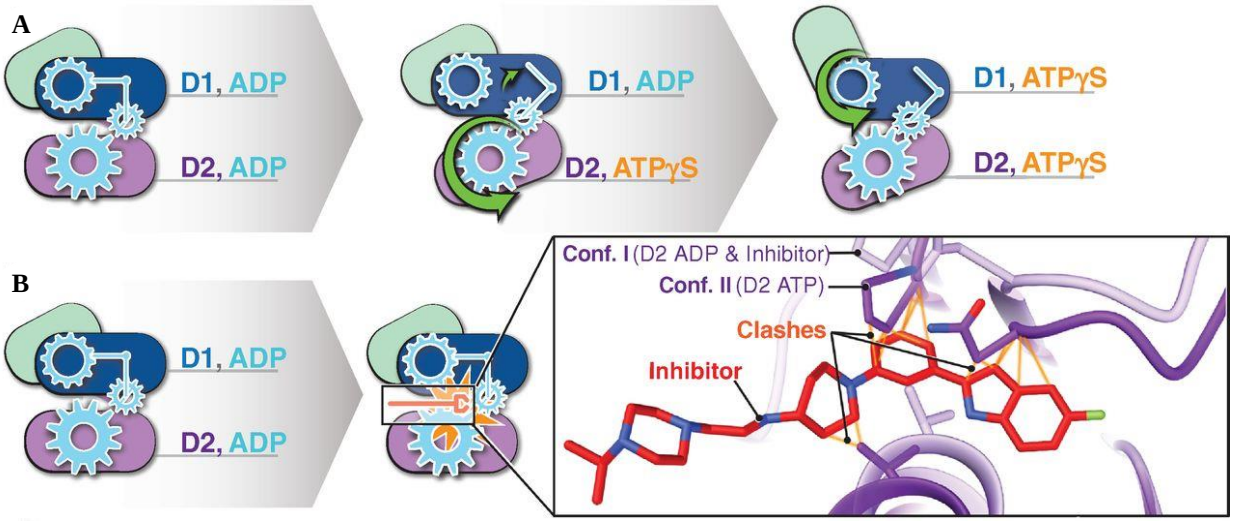


Figure 1-14. Mechanism of phenyl indole chemotype inhibition.

(A) Conformational changes p97 undergoes during the step-wise activation by the ATP surrogate ATPγS. (B) The phenyl indole inhibitor (**1-18**) binds to the D2-ADP complex and prevents ADP-ATP exchange, and works as a "wrench" in the p97 gears. Close up of the overlay between the D2-ADP, inhibitor bound structure (light purple) and the D2-ATP bound structure (dark purple) showing the steric clashes (orange) between the protein and inhibitor (red).[37]

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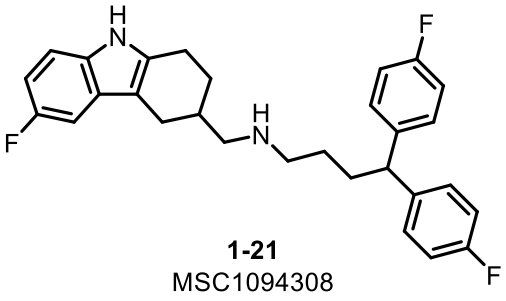
With the understanding of how the phenyl indole analogs inhibited p97 activity, the analogs were then evaluated for their cellular activity. The analogs were first tested in the standard ubiquitinated substrate (Ub^{G76V}-GFP) accumulation assay described in Section 1.2.1. When **1-17** was screened in this assay, it was shown to show modest inhibition at an early time point (15 µM at 1 h), but not at the final time point (6 h) at the highest tested concentration (40 µM).[56] As a potential reason for this very potent analog (IC_{50} = 10 nM in biochemical assay) showing little to no effect in the cellular assays, it was proposed that permeability could be limited; however, related analogs showed high intracellular concentrations, effectively discrediting permeability as the cause of inactivity.[56] Finally, it was proposed that the assay

format may have been reason for the lack of activity, meaning that the Ub^{G76V}-GFP accumulation assay may not assess all aspects of p97 activity and that the phenyl indole analogs disrupt only certain aspects of p97's cellular functions. Autophagy was then suggested as the specific mechanism of activity of the phenyl indole analogs.[56] The ability of these analogs to affect the biological function of p97 was further supported by their cell growth inhibition in several cell lines in the NCI60 panel.[56]

1.2.3 ATP non-competitive inhibitors

Non-competitive inhibitors are characterized by their ability to bind either free enzyme or substrate-bound enzyme. This results in two separate equilibrium constants, one for inhibitor binding to free enzyme and the second for inhibitor binding to the substrate-bound enzyme. Non-competitive inhibitors can partially favor binding to either state or can have equal affinity to both. Given their ability to bind to either substrate-bound or -unbound forms, these types of inhibitors typically bind at allosteric, or non-active, sites. The effects of non-competitive inhibitors on the Michaelis-Menten kinetics of its target enzyme are: no change in K_m and decrease in V_{max}.[49] Thus far, only two non-competitive inhibitors have been reported in the literature, the first by a collaboration between Nerviano Medical Sciences and Genentech and the second by a collaboration between University of Duisburg-Essen and Merck KGaA.[60, 61] Compound **1-21**, published by a partnership between academia and industry, was shown to have low micromolar activity (7.2±1.1 μM) against p97 (Figure 1-15). Given this low biochemical potency, the compound currently is not viable as a drug candidate; however, it proved to be a useful tool compound. Using photoaffinity cross-linking studies, the authors were able to show that it bound to a known allosteric site within the D2 domain of p97. They were able to support

this finding with inhibition studies using the Walker B mutant K251A, which disrupts nucleotide binding to the D1 domain, and K524A, which disrupts nucleotide binding to the D2 domain. The authors showed that when **1-21** was tested in $p97^{K251A}$, there was similar inhibition as with $p97^{WT}$, whereas in $p97^{K524A}$ there was decreased inhibition, therefore confirming the D2 binding site. Finally, in a single concentration cellular activity assay, **1-21** showed the ability to induce p97-mediated accumulation of Ub^{G76V}-GFP by Western blot.[61]



1-21
MSC1094308

Figure 1-15. Structure of the tool compound **MSC1094308**.[61]

The Nerviano and Genentech efforts began with an HTS that generated the initial hit **1-22** (Figure 1-16) which showed low micromolar biochemical activity (2.69 µM), but no activity within cells at concentrations as high as 20 µM.[60] They also proposed that this alkylsulfanyl-1,2,4-triazole chemotype was non-competitive in nature due to a lack of significant change in biochemical IC_{50} at 60 µM and 1 mM ATP concentrations. During the course of their SAR efforts, the authors were able to find that the 3-pyridine was preferred over phenyl in the *N*-1 position of the triazole, the cyclopentyl was the preferred alkyl group at the thioether, a bi-phenyl ether side chain was preferred over the mono-phenyl ether, and that the 5-methyl substituted phenol was preferred over the unsubstituted phenol of the side chain. These key findings lead to the discovery of **1-25,** also known as **NMS-873** (Figure 1-16).[60] The authors reconfirmed that

NMS-873 maintained the non-competitive binding of **1-22**. It also improved on the biochemical activity of **1-22** by greater than 100-fold, IC_{50} = 0.024 μM versus 2.69 μM for **1-22**, and achieved sub-micromolar cellular activity in HCT-116 cells, IC_{50} = 0.38 μM. **NMS-873** was also shown to be selective for p97 versus other AAA ATPases, Hsp90, and 50 kinases.[60] To better understand the binding of these alkylsulfanyl-1,2,4-triazoles, Magnaghi et al. carried out photo cross-linking studies of compounds **1-23** and **1-24** with WT p97 (Figure 1-16).[62] From the cross-linking study, the authors identified that **1-23** labeled Asn616 while **1-24** labeled the adjacent amino acid, Lys615. Given these separate, adjacent labeling events using two tool compounds with proximal reactive azido moieties, the authors were confident that a single binding site was indicated. They used this information along with publicly available crystal structures of p97 to develop a model that identified the binding site to be in a channel between the D1 and D2 domains between adjacent protomers leading from the outside to the interior pore of the hexamer (Figure 1-17). The authors demonstrated that **NMS-873** competently activated the UPR by increased levels of CHOP, a biomarker of p97 inhibition, decreased autophagy marked by increased levels of LC3-II, and increased apoptosis by cleavage of PARP-1 and caspase-3.[62] Given these positive markers of **NMS-873** activity as a cytotoxic agent for tumor cells, the authors carried out a mouse PK study to assess its potential use in further studies. After a single 1 mg/kg IV bolus, it was shown that **NMS-873** had good distribution throughout the body (V_{ss} = 5882±1298 mL/kg) but was cleared very quickly (CL = 115±31 mL/min/kg) resulting in low overall exposure (2.26±0.07 μM·h). This correlated well with the data obtained from a single oral dose (PO) of 10 mg/kg which showed only a 16.4% bioavailability.[60] The authors postulated that this could be a result of the low solubility of the compound (approx. 7 μM in ammonium acetate buffer, pH 7) or first pass metabolism ($t_{1/2\ IV}$ = 0.9 h). Given these results, the authors

conceded that to be a viable candidate for further studies, the solubility and metabolic stability of **NMS-873** needed to be improved.

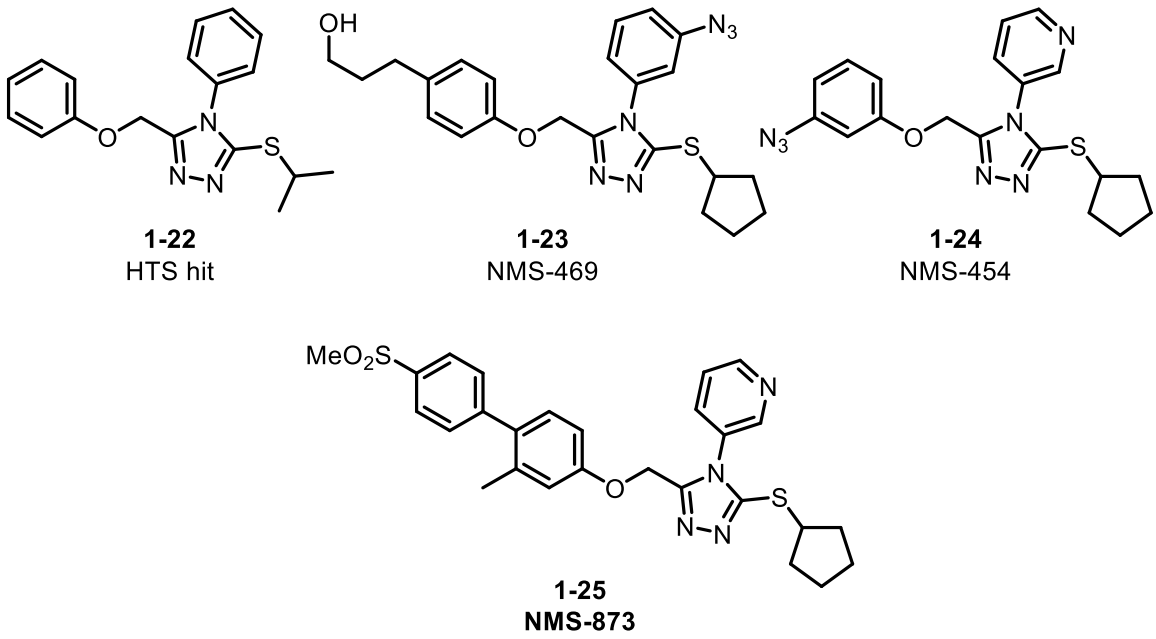


Figure 1-16. Structures of four alkylsulfanyl-1,2,4-triazoles.[60, 62]

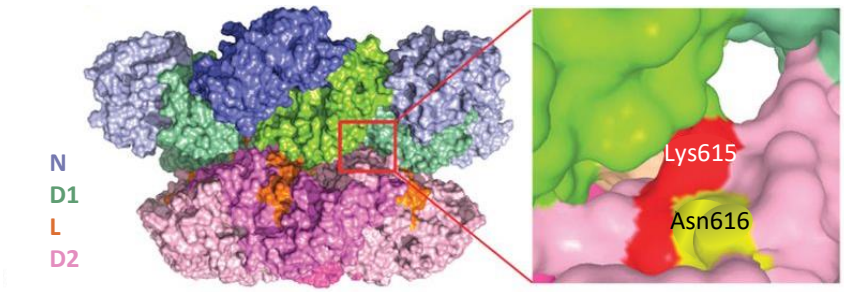


Figure 1-17. Location of alkylsulfanyl-1,2,4-triazole binding site in a 3D representation of the p97 hexamer as determined by cross-linked amino acid location.[62]

N domains (purple), D1 domains (green), D1/D2 linkers (orange), D2 domains (pink).[62]

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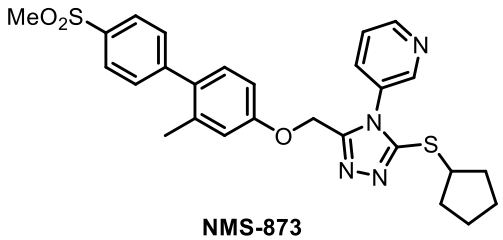
2.0 DESIGN AND SYNTHESIS OF TRIAZOLE ANALOGS

As discussed in Section 1.2.3, Nerviano Medical Sciences and Genentech Inc. reported analogs of the alkylsulfanyl-1,2,4-triazole scaffold, **NMS-873**, to be allosteric, non-competitive inhibitors of p97 binding to a pocket between the D2 of one protomer and the D1 of an adjacent protomer near the D1-D2 linker region (Figure 2-1).[60, 62] Polucci *et al*. reported that **NMS-873** showed good activity in both biochemical and cellular assays (IC_{50} = 0.024 μM and HCT-116 CellTiter-Glo® IC_{50} = 0.38 μM, respectively) and selectivity against related AAA ATPases, Hsp90, and 50 kinases up to 10 μM.[60] While they described select PK and ADME properties as being favorable, namely cell permeability (P_{app} = 21.6 x 10^{-6} cm/s in Caco-2 cells) and volume of distribution (V_{ss} = 5882 ± 1298 mL/kg), they showed that several properties were not favorable (Table 2-1).[60] Given the good potency of **NMS-873** and the less than desirable properties, we recognized the potential for improving the reported structure to optimize both the activity and properties. Consequently, a library was prepared to explore improvements of these features.[58, 63]



NMS-873

Figure 2-1. Structure of **NMS-873**.

Table 2-1. Physiochemical properties and literature values for PK properties of **NMS-873**.[60]

Property	Value
Molecular weight (MW)	520 Da
Hydrogen bond donors (HBD)	0
Hydrogen bond acceptors (HBA)	6
Polar surface area (PSA) [a]	87 $Å^2$
Lipophilicity at pH 7.4 (clogD) [a]	4.7
Solubility (S) [b]	7 μM
Cell permeability (P_{app}, Caco-2) [b]	21.6 x 10^{-6} cm/s
Highest concentration in blood (C_{max}) [b, c]	0.30 ± 0.08 μM
Clearance (CL) [b, c]	115 ± 31 mL/min/kg
Volume of distribution (V_{ss}) [b, c]	5882 ± 1298 mL/kg
Half-life ($t_{1/2}$) [b, c]	0.9 h
Highest concentration in blood (C_{max}) [b, d]	0.06 ± 0.02 μM
Time to highest concentration (t_{max}) [b, d]	0.8 h
Half-life ($t_{1/2}$) [b, d]	6.0 h
Bioavailability [b, d]	16.4%

[a] Calculated using Instant JChem [64]; [b] Literature values[60]; [c] iv dosing 1 mg/kg[60]; [d] po dosing 10 mg/kg[60]

2.1 EARLY TRIAZOLE ANALOGS

The medicinal chemistry efforts described below were carried out by a team of medicinal chemists working at the University of Pittsburgh Chemical Diversity Center (UPCDC) as a part of a larger team including Leidos within the Chemical Biology Consortium (CBC) of the National Cancer Institute Experimental Therapeutics (NExT) program. As a result, the sections discussing synthesis (Section 2.2) and structure-activity relationship (Section 2.3.1) of this thesis

will focus on the work I contributed to the project unless stated otherwise with the exception of the biological data which was generated by collaborators within the CBC team. Due to the nature of the team science that was conducted during this project, additional data that cannot be shown due to (a) being contributed to the project without my involvement and (b) confidentiality requirements by the CBC and Leidos was also collected and will only be taken into consideration in the discussion (Section 2.3.2) to provide a more complete understanding of the project as a whole. In addition, the SAR will be elaborated on in the discussion (Section 2.3.2) with conclusions based on additional analogs not discussed in the SAR section (Section 2.3.1) due to being prepared by others on the chemistry team.

Overall, the goals of the proposed modifications to the **NMS-873** scaffold were to improve the potency to match or surpass that of **CB-5083**, the most advanced p97 targeting small molecule to date, as well as to make modifications that would be predicted to have beneficial effects on the properties of the molecule. In the earliest stage of exploration of the **NMS-873** scaffold, zone 1 was explored. Modification began here due to the ease of synthesis of these derivatives and to determine whether activity could be improved by modifying or replacing the cyclopentane ring (Figure 2-2). In addition, this site was selected first due to the known metabolic liability of thioether (or sulfide) moieties, including the aryl-alkyl thioether present in **NMS-873**. Thioethers have been shown to undergo both enzymatic oxidation (by CYP450s and flavin-containing monooxygenases, FMO) and dealkylation (by CYP450s) which could potentially be a concern for the chemotype going forward.[65-68]

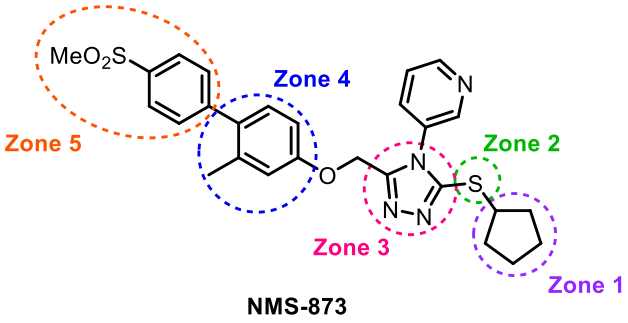
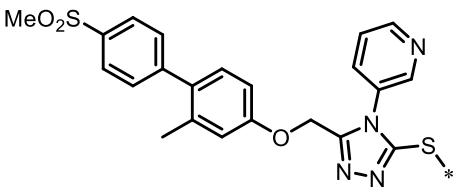


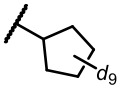
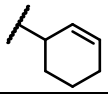
Figure 2-2. Zones of structural modification for the triazole-containing **NMS-873**.

During the course of zone 1 exploration, a number of analogs were prepared included changes that increased the steric bulk of the groups attached to the sulfur, as well as the incorporation of fluorine which would increase the steric hindrance and decrease electron density of this group.[69, 70] The mechanism of sulfide oxidation to either the sulfoxide or sulfone is a direct process hence increasing the steric bulk adjacent to the sulfur should limit access of the heme iron (CYP450s) or the reactive 4α-hydroperoxyflavin (FMOs), however, the mechanism of *S*-dealkylation is not direct.[71, 72] Sulfur dealkylation has been proposed to occur via the hydroxylation of an α-carbon of the thioether followed by cleavage of the oxidized α-carbon-sulfur bond.[68] Therefore, fluorination of the α-carbon can block the initial oxidation event, and given the preference for more lipophilic substrates by both CYP450s and FMOs, increasing the polarity could result in decreased affinity of the active site for the analogs. Though a number of analogs addressing these hypotheses were prepared, only two retained sufficient activity to justify further use (Table 2-2; see Chapter 3.4.2 for additional structures).[63] While no analogs incorporating fluorine or more sterically hindered thioethers were found to be as potent as the original cyclopentane, the perdeuterated cyclopentane (**2-1**) was found to be tolerated in the biochemical assay. With the incorporation of deuterium, **2-1** potentially decreased the role of α-hydroxylation at the tertiary carbon of the cyclopentane, and therefore dealkylation, due to the

kinetic isotope effect.[73] In addition to the discovery of **2-1**, the cyclohex-2-ene (**2-2**) was shown to retain biochemical activity. Although the cyclohex-2-ene group does not sterically crowd the sulfur or physically block hydroxylation, it was hypothesized to increase the polarizability of the zone 1 side chain which has been proposed to modulate polarity and solubility.[74-76]

Table 2-2. Zone 1 replacements and associated p97 inhibitory activity in biochemical assay.[i]



Entry	Compound	*	IC_{50} (μM) [a]
1	**NMS-873**		0.038[77]
2	**2-1**		≈ **NMS-873**
3	**2-2**		≈ **NMS-873**

[a] BIOMOL® Green biochemical assay at 200 μM ATP.[50]

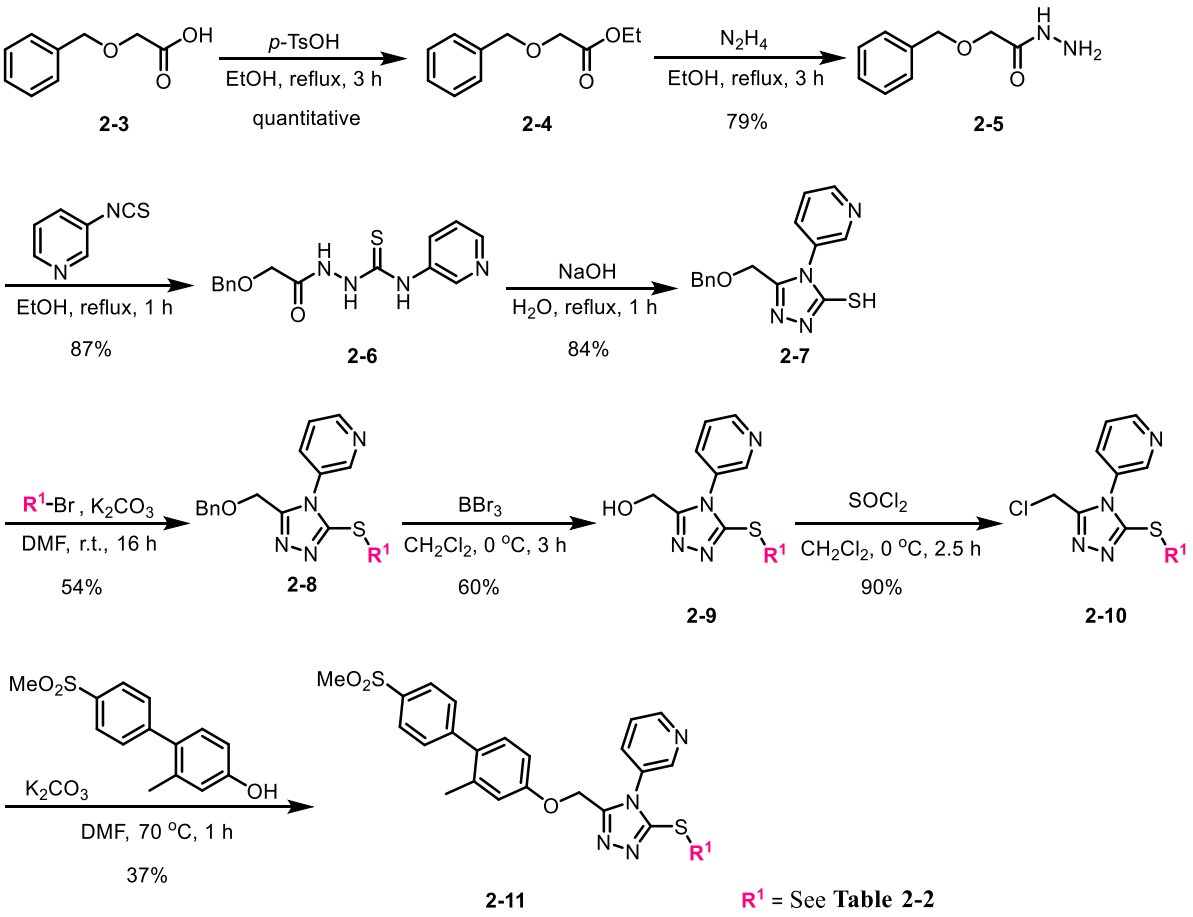
2.2 GENERAL SYNTHESIS OF TRIAZOLE ANALOGS

The strategy utilized to prepare analogs of **NMS-873** involved the synthesis of the core composed of zones 2 and 3 as well as the pyridine and methylene alcohol. Once the core was prepared, the thiol of zone 2 was alkylated with the desired group at zone 1 and then the phenol portion, comprised of zones 4 and 5, was added to the core. In the later stages of the SAR

[i] **2-1** synthesized by Dr. Matthew LaPorte; **2-2** synthesized by Eric Miller

exploration, zone 5 was further elaborated to give the final desired analogs. Like the syntheses of the phenyl indole analogs described in Chapter 1.2.2, the approach taken for the triazole series allowed for a modular design and synthesis.

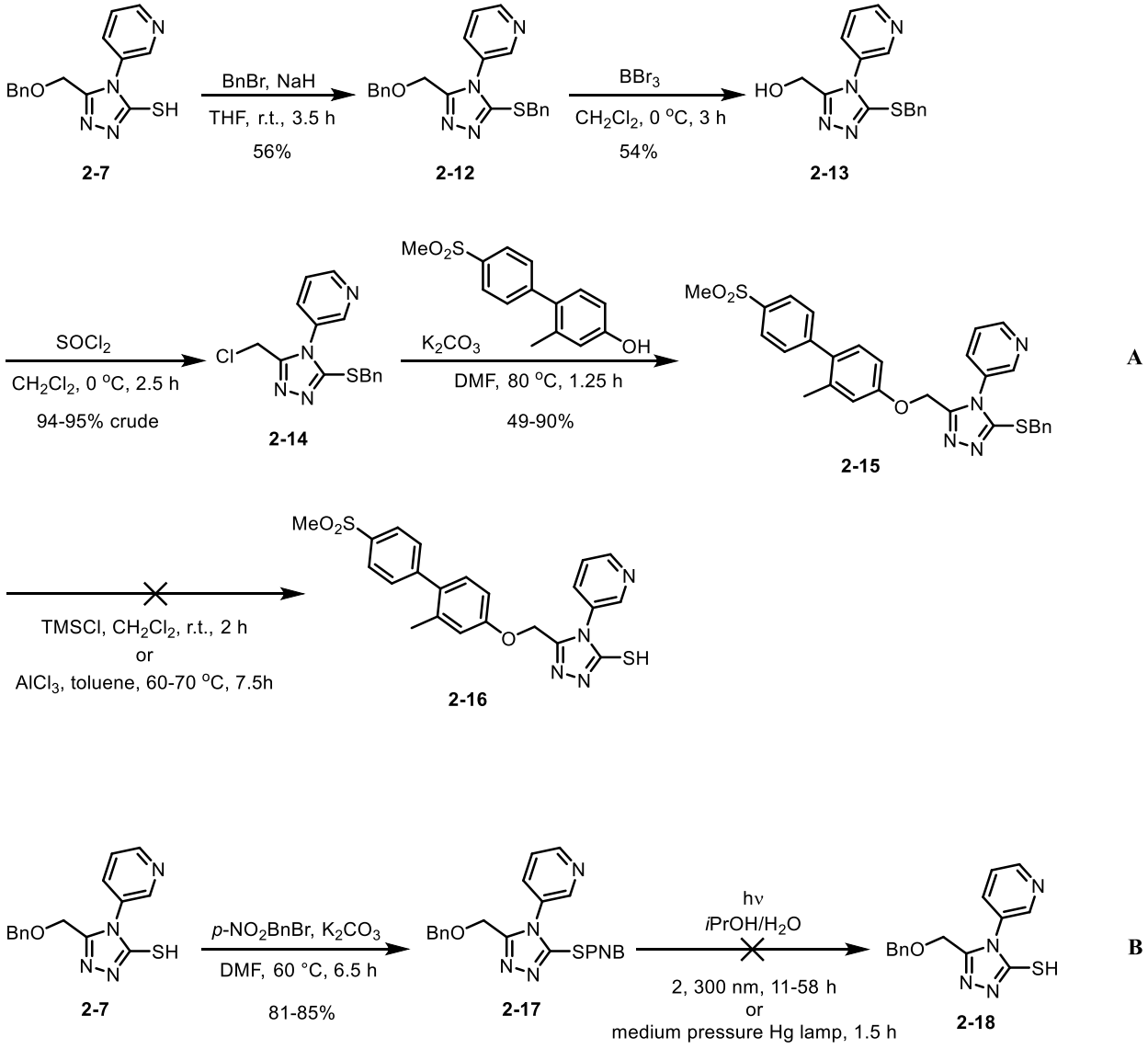
The general synthetic scheme followed that outlined by Polucci *et al*. (Scheme 2-1).[60] Though the synthesis through **2-7** was straightforward and high yielding, the use of boron tribromide (BBr_3) to remove the benzyl group severely limited the zone 1 groups that could be prepared. Only simple alkyl groups were tolerated due to the use of such a harsh reagent; therefore, a new protecting group strategy was explored to try to identify a more universally suitable synthetic route.



Scheme 2-1. Synthesis of triazole analogs utilizing a literature route.[60]

The first alternate routes explored aimed to install the zone 1 group last instead of early on to allow for a more convergent synthesis. Zone 1 could thus be readily diversified in the last step (Scheme 1-2). To accomplish this, the sulfur group was protected with either a benzyl Scheme 2-2, **A**) or *p*-nitrobenzyl (PNB) ether (Scheme 2-2, **B**). In the case of the benzyl route, the methylene alcohol was deprotected under the standard BBr_3 conditions, alkylated with the phenol chain, and then the sulfur was unmasked (Scheme 2-2, **A**). Unfortunately, the removal of the benzyl group proved to be difficult. In the presence of chlorotrimethylsilane (TMSCl) as the Lewis acid no reaction occurred. Aluminum (III) chloride ($AlCl_3$) was also attempted in the removal of the *S*-benzyl protecting group. However, in this case, while $AlCl_3$ did result in

consumption of **2-15**, only an unidentified product was formed and no desired **2-16** was found. Given the difficulty of deprotecting the *S*-benzyl group, the more activated PNB group was tried. While installation of the PNB on the sulfur went well (81-85% yield), it was again the removal that proved difficult. The advantage of the PNB versus the Bn group was that under irradiation (hν) the PNB ether (thioether) can be cleaved to give the alcohol (thiol) and *p*-nitrosobenzaldehyde.[78] However, despite utilizing two different light sources at different wavelengths (λ) and different wattages to try to tune the reactivity, neither condition was able to cleanly give **2-18**, at best a 1:1 ratio **2-17**:**2-18** was achieved with two 300 nm Hg-lamps after 58 h. Upon resubjection of the reaction mixture to light no further reaction occurred. Due to the difficulty of deprotecting **2-17**, a simplified test substrate, this approach was not further explored on the more complex desired system. Because of this, the sulfur protecting strategy was abandoned and an *O*-tetrahydro-2*H*-pyran (THP) protecting group was selected (Scheme 2-3).

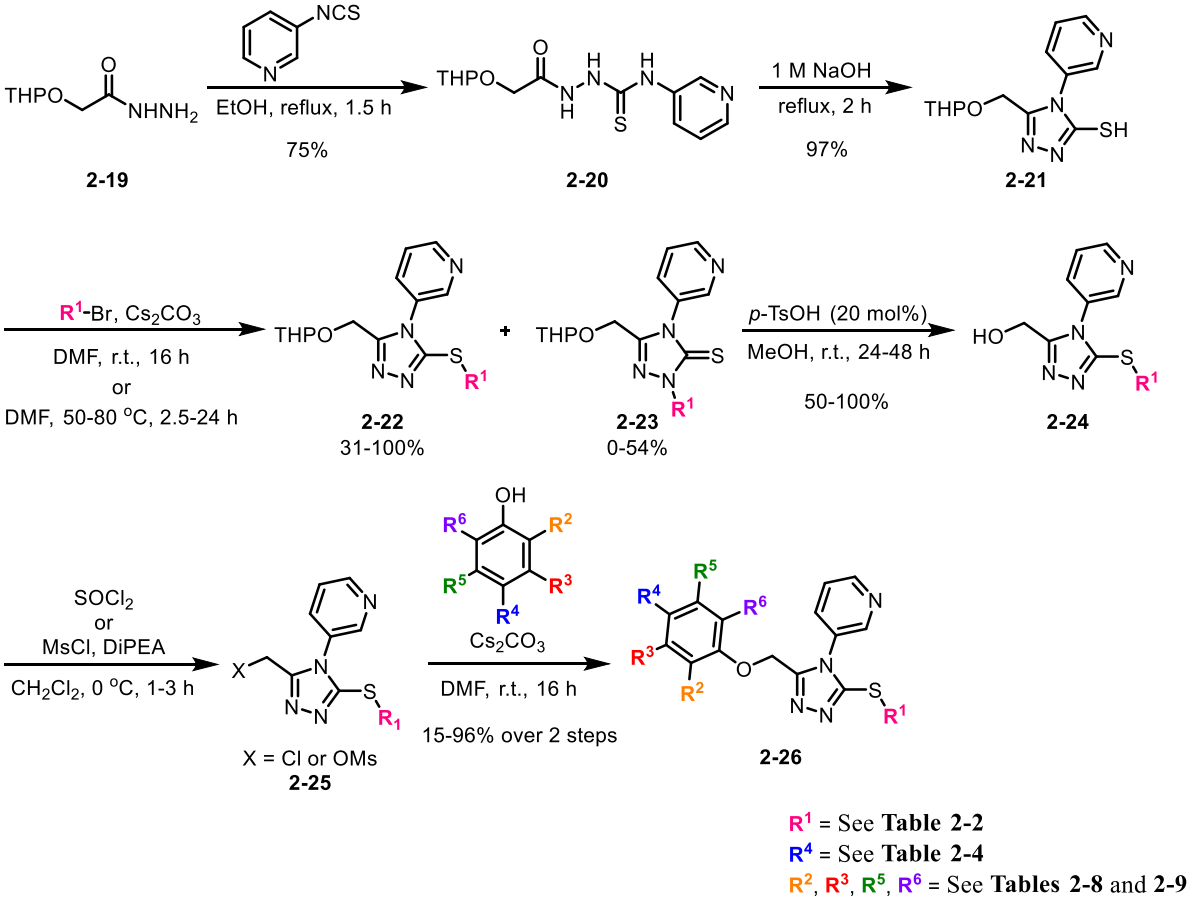


Scheme 2-2. Attempted alternate synthetic routes utilizing sulfur protecting groups.

(A) Modification of published route utilizing a benzyl (Bn) protecting group on the sulfur.[60] (B) The PNB group could not be successfully removed.

The synthesis of analogs via the improved protecting group strategy using an *O*-THP group maintained the original length of the synthesis (Scheme 2-3). Intermediate **2-19** was prepared in an analogous method to the literature[79] and from this hydrazide through the deprotection, the synthesis paralleled the original synthesis reported by Polucci et al.[60] Not only

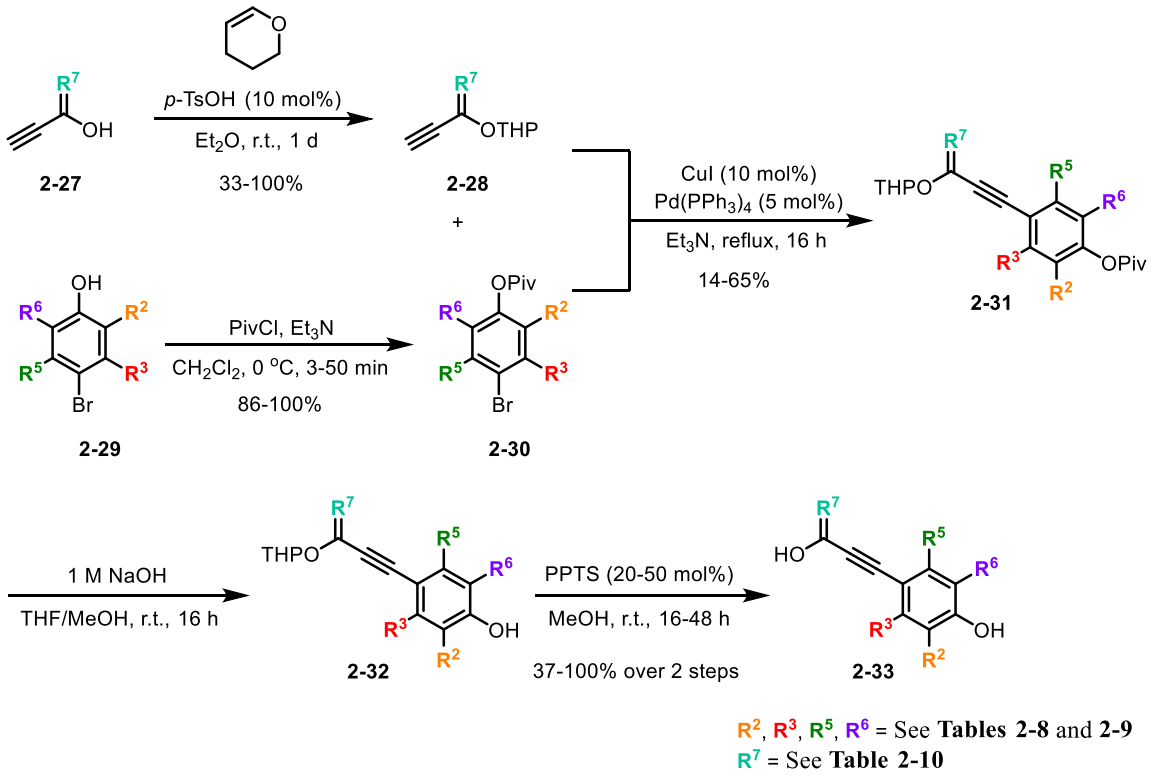
was the desired *S*-alkylated product (**2-22**) observed, but the *N*-alkylated product (**2-23**) was also found to varying degrees in most reactions. With the *O*-THP group, the deprotection required only catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH, 20 mol%), allowing for the installation of a variety of groups in zone 1, including acid labile groups. The activation of the benzyl alcohol, **2-24**, was carried out with either thionyl chloride ($SOCl_2$) or methanesulfonyl chloride (MsCl) and diisopropylethylamine (DiPEA) which was carried on after minimal workup to the nucleophilic substitution reaction to install the desired phenol side chain. Large variability was seen in the yields for this step due to varying degrees of stability of **2-25** while handling the product before the alkylation reaction.



Scheme 2-3. General synthesis of **NMS-873** analogs utilizing the preferred *O*-THP protecting group.[63]

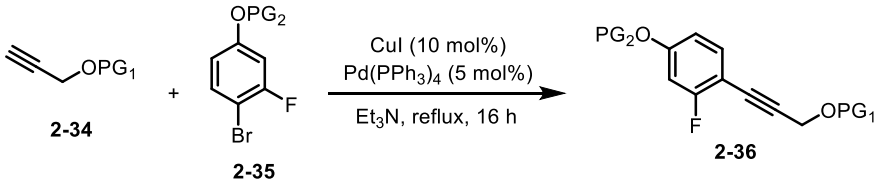
While exploring the SAR at zone 5, analogs were prepared as described above in Scheme 2-3; however, it was discovered that the alkyne was a useful bioisostere of the phenyl ring at the 4-position of the phenol. In order to maintain the presence of heteroatoms at the terminal portion of zone 5, substituted alkynes, i.e. propargyl alcohols and amines, were prepared (Scheme 2-4). The propargyl alcohol-containing side chain was prepared via a sequence that began with the *O*-THP protection of the desired propargyl alcohol and *O*-pivaloyl (Piv) protection of the desired *p*-bromo phenol (Scheme 2-4). The two protected building blocks were then coupled via a Sonogashira cross coupling to give the fully protected side chain fragment. Conditions were tested on 4-bromo-3-fluorophenol and propargyl alcohol in which the cross coupling was carried out on all permutations of the protecting scheme for the these building blocks (Table 2-2). Starting with both unprotected alcohols, none of the desired cross coupling product, **2-36,** was observed by liquid chromatography coupled mass spectrometry (LCMS). When the propargyl alcohol was protected as the *O*-THP ether but the phenol was unprotected, no product was observed either. In the opposite case, with the phenol protected as the *O*-Piv, and the propargyl alcohol unprotected, some product was observed by LCMS; however, the reaction was very messy and the amount was not quantifiable or isolatable. Useable quantities of product were only isolated when both alcohols were protected, resulting in a cleaner reaction profile and higher conversion of the starting material. In addition, it has been shown that phenols can undergo side reactions, including *O*-arylation, which could account for the significantly more messy LCMS profile observed with unprotected phenol.[80] The *O*-pivaloyl group was then removed with aqueous sodium hydroxide (NaOH) and the crude product, after workup and concentration, was treated with pyridinium *p*-toluenesulfonate (PPTS) to remove the *O*-THP group to give the fully

deprotected side chain (**2-33**). This fragment was then added to the core via an S_N2 reaction. Further elaboration of the propargyl alcohol will be discussed in section 2.3.1.



Scheme 2-4. General synthesis of propargyl side chain **NMS-873** analogs.

Table 2-3. Screening of protecting group strategy for Sonogashira cross coupling in the synthesis of the propargyl alcohol side chain fragment.



Entry	PG_1	PG_2	Yield
1	H	H	no desired pdt
2	THP	H	no desired pdt
3	H	Piv	messy, unable to isolate pdt
4	THP	Piv	25%

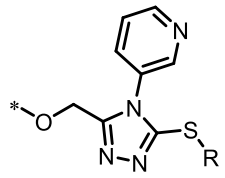
2.3 BIOLOGICAL SCREENING OF TRIAZOLE ANALOGS

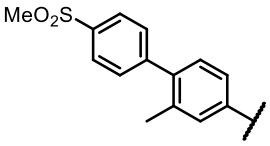
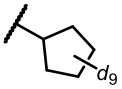
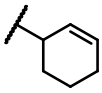
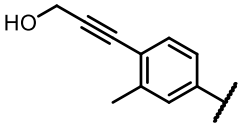
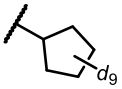
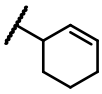
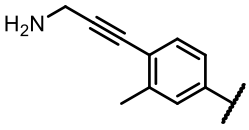
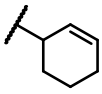
2.3.1 Structure-activity relationship

A library of analogs of **NMS-873** were prepared and screened against p97 for inhibition.[81] The inhibitory activities (IC_{50}) of selected analogs are summarized in Tables 2-4 through 2-11.[58, 63] Modification of the **NMS-873** chemotype began with zone 1 which was quickly shown to tolerate only minor adjustments to the size and composition of this group (see Section 2.1). Further exploration of the scaffold focused on continuing to improve the activity of the structure. Consideration was also given to modifications which would be proposed to impact stability and reduce lipophilicity, or cLogD, to address the key problems identified by Nerviano Medical Sciences and Genentech.[60]

Based on the limitations for structural modification identified in zone 1, zone 5 was explored next as a means of making significant impact on the activity and physical properties of the **NMS-873** scaffold (Table 2-4). To accomplish this, the 4-methylsulfonyl benzene group was replaced with either prop-2-yn-1-ol (or propargyl alcohol, **2-37**, **2-38**, **2-39**) or prop-2-yn-1-amine (propargyl amine, **2-40**) groups with the alkyne being proposed as an isostere of the phenyl group and the propargyl heteroatom possibly maintaining interactions originally made by the methanesulfonyl group. Alkynes can serve as *p*-substituted phenyl isosteres due to their ability to mimic the π-system of the phenyl ring as well as maintain the linear geometry of the two *para* substituents.[82] Fortunately, upon testing the analogs containing the propargyl groups, this hypothesis was supported by their biochemical potency (Table 2-4, entries 2 and 3). Not only do all four analogs maintain good biochemical potency (under 50 nM for 3 of the 4 alkyne-containing analogs), the replacement of the aryl group with the alkyne provided the benefit that all analogs decreased in cLogD. This decrease in lipophilicity could suggest an improvement in solubility versus the biphenyl containing compounds: **NMS-873**, **2-1**, and **2-2**. Also, given the retention of potency between the alkyne- and phenyl-containing analogs, the alkyne does serve not only as an isostere, in which the definition is primarily focused on the structural features of the replacement, but also as a bioisostere, in which the definition includes the impact the structural modification has on the activity of the resulting analog.

Table 2-4. Replacements of zone 5 to reduce size and improve solubility and associated p97 inhibitory activity.[ii]



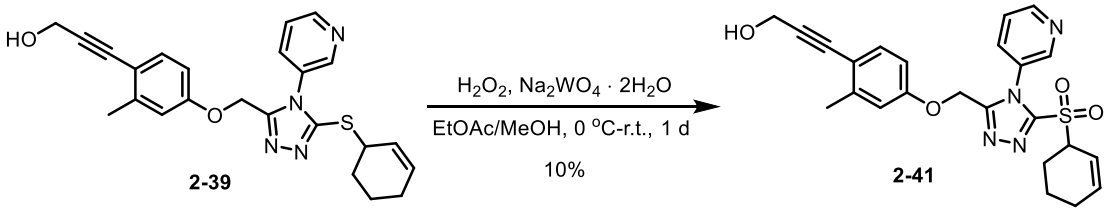
Entry	Compound	*	R	IC_{50} (μM) [a]	cLogD [b]
1	**NMS-873**			0.038[77]	4.7
	2-1			≈ **NMS-873**	4.7
	2-2			≈ **NMS-873**	4.9
2	**2-37**			0.093[58]	3.9
	2-38			0.048[58]	3.9
	2-39			0.037[58]	4.1
3	**2-40**			0.044[58]	2.8

[a] BIOMOL® Green biochemical assay at 200 μM ATP.[50] [b] Calculated using Instant JChem. [64]

After determining that incorporation of the propargyl alcohol into zone 5 maintained potency and reduced cLogD, the next consideration was for the potentially metabolically labile thioether in zone 2. Given that one major goal of the SAR exploration was to distinguish resulting analogs from **NMS-873**, the thioether in zone 2 was identified as an important group to explore. In addition, given that thioethers are known metabolic liabilities (as described in section 2.1) modifications which limit these metabolic pathways were the primary focus (Table 2-5).[83, 84]

[ii] **2-40** synthesized by Dr. Alexander Chatterley

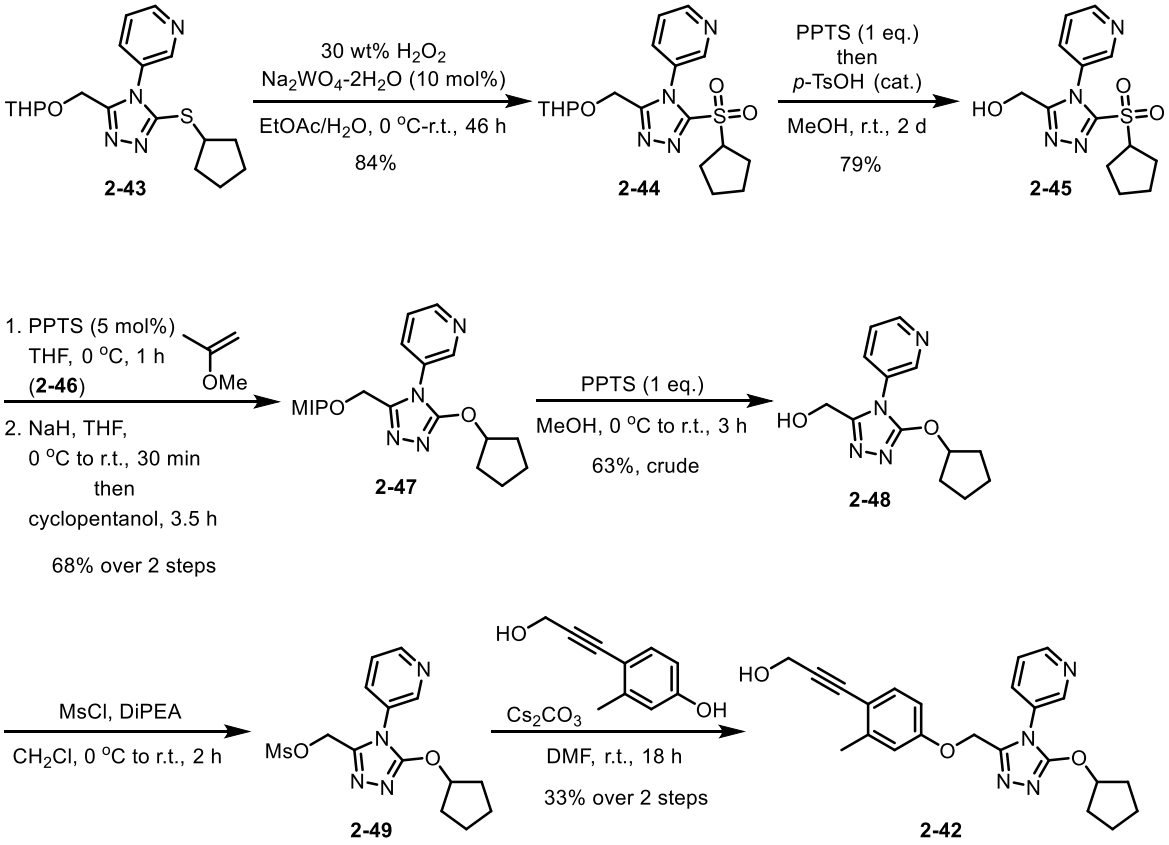
The sulfur atom of **2-39** was oxidized to the sulfone (**2-41**) to determine whether the potential metabolite would have any biological activity (Table 2-5, entry 3 versus 2). Compound **2-41** was prepared by treating **2-39** with hydrogen peroxide (H_2O_2) and sodium tungstate dihydrate ($NaWO_4 \cdot 2H_2O$) which gave **2-41** in 10% yield (Scheme 2-5). Sodium tungstate/hydrogen peroxide were selected for the oxidation in this case due to previous reports by Giam et al. that this system showed good selectivity for thioethers over pyridines.[85] Though no *N*-oxide and minimal sulfoxide (10%) were observed after 1 day, a significant loss of the cyclohexene ring was observed by LCMS, and **2-41** was isolated in low yield. Unfortunately, there was a significant loss of both biochemical activity (>100-fold) and cellular activity (>25-fold) for **2-41** compared to **2-39**. This clearly showed that the oxidation of the thioether was not tolerated.



Scheme 2-5. Synthesis of the sulfone **2-41**.[63]

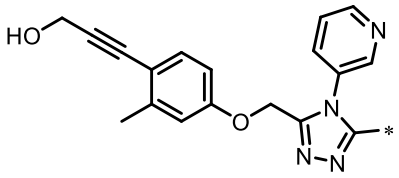
The corresponding ether at zone 2 was also prepared. While the ether would likely retain the dealkylation metabolic liability, the oxygen is not further oxidized which is an advantage over the sulfur atom. The synthesis of the oxygen replacement proceeded in an analogous manner to that described by Polucci et al.[60, 63] This synthesis began with the previously assembled cyclopentyl thioether, **2-43**, which was oxidized to the sulfone (**2-44**) using the same sodium tungstate catalyst/H_2O_2 oxidizing system used above for the synthesis of **2-41**. Before displacing the sulfone to give the ether, there were concerns about the ability to remove the *O*-THP protecting group in the presence of the zone 2 ether; therefore, the *O*-THP group was

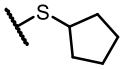
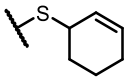
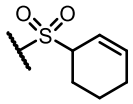
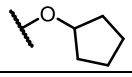
removed, at first, with stoichiometric PPTS. However, after one day the reaction had not gone to completion, and a catalytic amount of *p*-TsOH was added. The alcohol was then protected with the more labile 1-methyl-1-methoxyethyl (*O*-MIP) protecting group. The sulfone was displaced after deprotonation of cyclopentanol with 60 wt% sodium hydride (NaH) in an S_N2 reaction to give the di-ether compound, **2-47**. The *O*-MIP group was removed with one equivalent of PPTS at room temperature, giving a moderate yield of the desired deprotected alcohol. The final two steps of the sequence followed the general synthesis described previously with the preparation of the mesylate (**2-49**) from MsCl and DiPEA which was carried crude into the S_N2 reaction with the phenol side chain fragment and cesium carbonate (Cs_2CO_3) to give **2-42** in 33% yield over 2 steps (Scheme 2-6). However, **2-42** was found to have a weaker effect in both the biochemical and cellular assays by about 2.5 to 4-fold, respectively (Table 2-5, entry 4).



Scheme 2-6. Synthesis of **2-42**.[63]

Table 2-5. Zone 2 replacements to reduce potential metabolism and associated p97 inhibitory activity.



Entry	Compound	*	IC_{50} (μM) [a]
1	**2-37**		0.093[58]
2	**2-39**		0.037[58]
3	**2-41**		4.8[58]
4	**2-42**		0.18[58]

[a] BIOMOL® Green biochemical assay at 200 μM ATP.[50]

Based on the efforts to improve potency and reduce metabolic "hot-spots", the structure-activity relationship identified thus far is shown in Figure 2-3. Overall in zone 1, cyclic alkyl groups were found to be preferred with ring sizes of 5 and 6 being well tolerated. It was also observed that incorporation of deuterium in an attempt to improve stability was also well tolerated for activity, as was the addition of an alkene. In zone 2, it was seen that both a sulfur atom and an oxygen atom were tolerated, but the bulkier oxidation product of the thioether, the sulfone, was not tolerated within the binding pocket. In addition, initial replacement of the biphenyl side chain with a phenyl alkyne was well tolerated. Both the propargyl alcohol and propargyl amine were well tolerated biochemically and which could be used as a site for further structural modification.

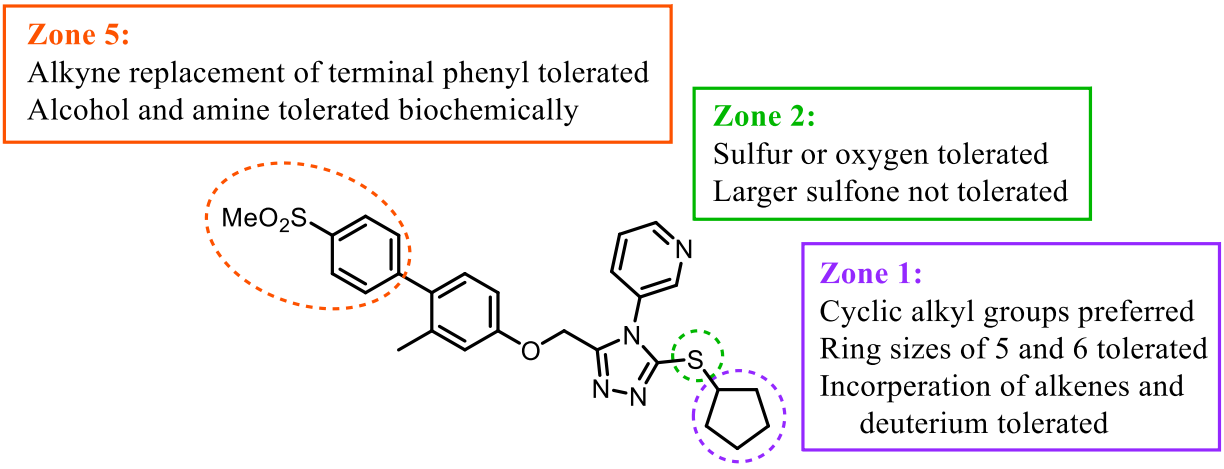


Figure 2-3. SAR summary for zones 1, 2, and phenyl replacement of zone 5.

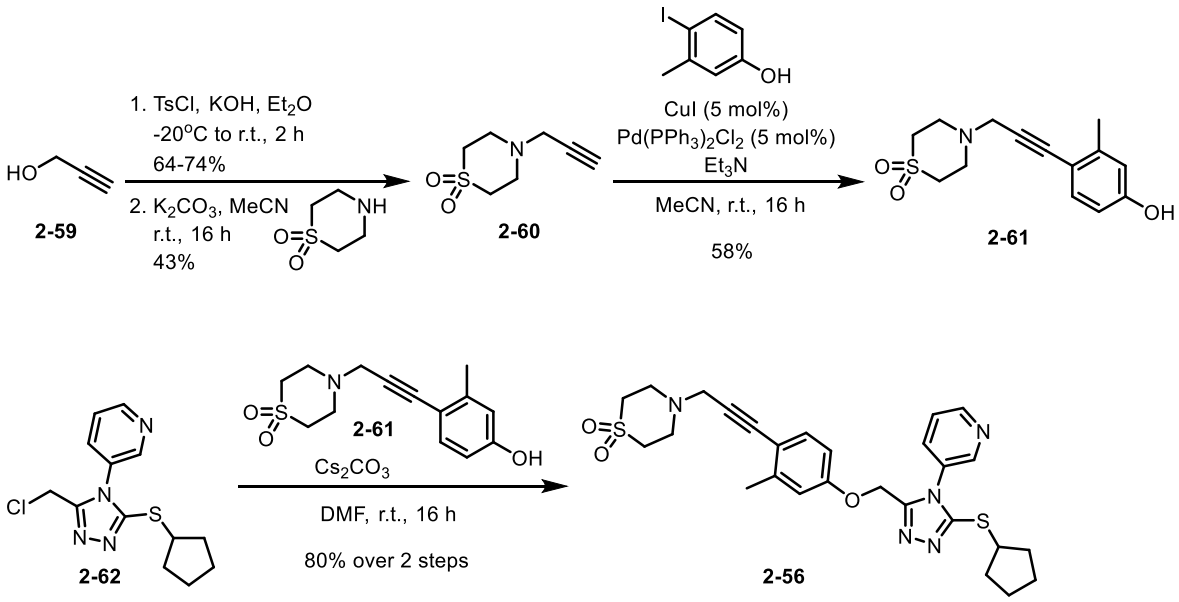
After determining that the thioether linkage was optimal in zone 2, the focus returned to zone 5, in particular the heteroatom of the propargyl group. Further exploration lead to optimizing the propargyl side chain by capping it with small alkyl groups as well as additional solubilizing groups (Table 2-6). The methyl ether (**2-50**) maintained efficacy within 2-fold

(versus **2-38**, IC_{50} = 0.069 vs. 0.048 μM, respectively) even without the hydrogen bond donor (HBD) that is present in **2-38**. Given this tolerance of the methyl ether, the larger 2-pyran analog (**2-51**) was prepared but resulted in a 3-fold loss of activity in the biochemical assay. Realizing that the SAR of these ethers was limited, carbamate derivatives were targeted next for synthesis with the goal to introduce additional hydrogen bonds as well as solubilizing moieties (Table 2-6, entry 5). Due to the good potency and high solubility of the corresponding phenyl indole analogs,[53, 55, 56] the ethyl *N*-isopropylpiperazine fragment (**2-52** and **2-53**) was incorporated (see Chapter 1.2.2). Though the addition of this fragment increases the molecular weight by 197 Daltons versus the alcohol, in the case of the deuterated analog (**2-52**), a 2-fold increase in biochemical potency was accomplished. In the case of the cyclohexenyl analog (**2-53**), a more modest improvement was observed (2-fold biochemical). This finding supports the hypothesis that outside of the hydrophobic channel that the phenyl-alkyne portion of the side chain resides in, there is a more hydrophilic or solvent-exposed region which has only been accessed by these larger carbamate analogs thus far.

Analogs of the propargyl amine were explored next to determine the effects of amino derivatives. First, secondary and tertiary amines were synthesized to determine if an HBD group was required. The *N*-methylpiperidine (**2-54**) represented a secondary amine that maintained an additional hydrogen bond acceptor (HBA), the heteroatom at the terminus, that was found to be beneficial in the carbamate analogs. Fortunately, the relatively smaller *N*-methylpiperidine showed good activity in the biochemical assay (IC_{50} = 0.036 μM), indicating that the larger ethyl *N*-isopropylpiperazine group may not be necessary for potent activity, and that a smaller basic group might convey similar potency. Next, tertiary amines including morpholino (**2-55**) and thiomorpholino 1,1-dioxide (**2-56** and **2-57**) were tested. Overall, all three analogs showed good

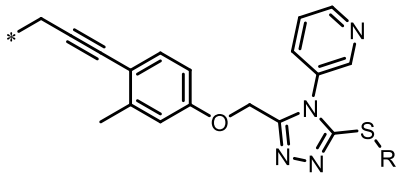
activity in the biochemical assay (<40 nM). This suggests that the binding site does not require the HBD of the secondary amines, however, the NH could be beneficial for solubility purposes. In addition to the amines, an amide analog (**2-58**) was also prepared. This ethyl amide was equipotent in the biochemical assay (Table 2-6, entry 9 versus 2). Overall, the similarities in biochemical activity of all analogs described in Table 2-6 suggests that the zone 5 terminal group does not have to be basic for potent inhibition. The tolerance for nearly all capping groups in the biochemical assay reinforces the hypothesis that the region of the binding site where this terminal zone 5 group resides is large and can accommodate groups of all sizes.

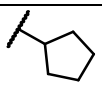
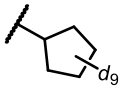
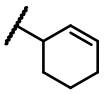
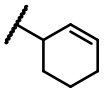
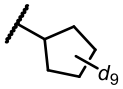
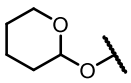
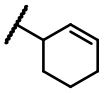
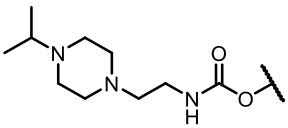
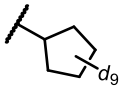
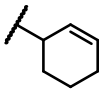
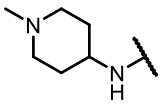
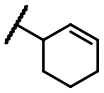
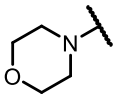
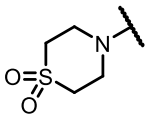
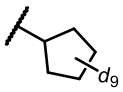
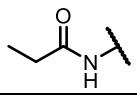
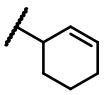
The secondary amine analogs, **2-55**, **2-56**, and **2-57**, were synthesized in an analogous method as described above; however, a new method was required for the synthesis of the side chain (Scheme 2-7). The propargyl alcohol was tosylated using 4-methylbenzenesulfonyl chloride (TsCl) and potassium hydroxide (KOH) at low temperature (-20 °C) and warmed to room temperature over 2 h. After aqueous workup, the intermediate was carried on to the S_N2 displacement with morpholine (**2-55**) or thiomorpholine 1,1-dioxide (**2-56** and **2-57**, Scheme 2-7). With the desired propargyl amines prepared, the last step of the side chain synthesis involved the Sonogashira coupling of the propargyl amine (**2-60**) and 4-iodo-3-methylphenol with bis(triphenylphosphine)palladium(II) dichloride [$Pd(PPh_3)_2Cl_2$] as the catalyst, copper (I) iodide (CuI) as the co-catalyst, and trimethylamine (Et_3N) as the base to give the completed side chain which could then be used in the alkylation of the core to give the final products.



Scheme 2-7. Representative synthesis of secondary amine zone 5 analogs.[63]

Table 2-6. Optimization of zone 5 capping group and associated p97 inhibitory activity.[iii]

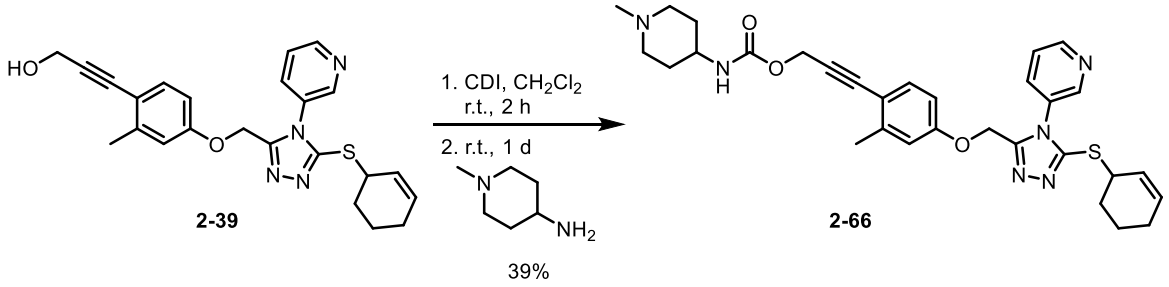


Entry	Compound	*	R	IC_{50} (μM) [a]	cLogD [b]
1	**2-37**			0.093[58]	3.9
	2-38			0.048[58]	3.9
	2-39			0.037[58]	4.1
2	**2-40**			0.044[58]	2.8
3	**2-50**			0.069[58]	4.5
4	**2-51**			0.11[58]	5.7
5	**2-52**			0.034[58]	3.9
	2-53			0.019[58]	4.1
6	**2-54**			0.036[58]	2.7
7	**2-55**			0.039[58]	4.4
8	**2-56**			0.18[58]	3.3
	2-57			0.16[58]	3.3
9	**2-58**			0.030[58]	4.5

[a] BIOMOL® Green biochemical assay at 200 μM ATP.[50] [b] Calculated using Instant JChem[64]

[iii] **2-54** synthesized by Dr. Alexander Chatterley; **2-58** synthesized by Dr. Chaemin Lim

The synthesis of all carbamate analogs was straightforward, requiring only two additional steps which were carried out in a one-pot sequence (Scheme 2-8). Starting with one of the propargyl alcohols (**2-38** or **2-39**) previously synthesized as described in Scheme 2-3, activation with carbonyldiimidazole (CDI) was monitored by LCMS. After the addition of the amine, the reaction mixture was stirred for at least 16 h. Occasionally, triethylamine was added in cases where amine salts were used, as well as sometimes an additional portion of the amine was required to drive the conversion to completion. Overall, the yield of the carbamate step ranged from low to high (16-96%), with the low yields typically from early analogs before the workup was optimized to utilize brine instead of just water. Due to the improved solubility of these compounds, a portion of the final product can partition into the aqueous layer, but the use of brine significantly reduced this loss.



Scheme 2-8. Representative synthesis of carbamate analogs.[63]

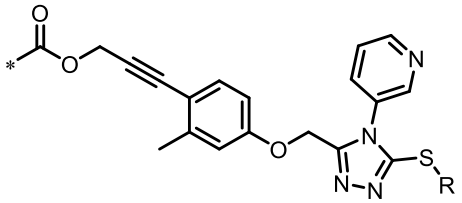
Carbamates, **2-52** and **2-53**, showed the best overall activities, as a result additional groups at the nitrogen of the carbamate were also explored (Table 2-7). While both larger and smaller groups were utilized, the goal was to determine if a smaller group containing fewer basic nitrogens would maintain potency. Therefore, the smaller trifluoroethyl amine containing carbamate (**2-63**) was prepared first (Table 2-7, entry 2). This replacement maintained the

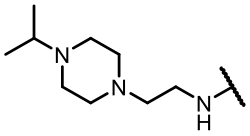
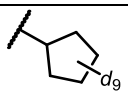
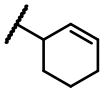
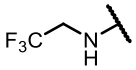
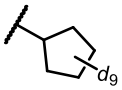
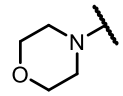
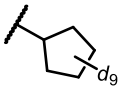
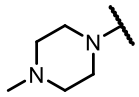
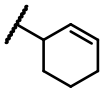
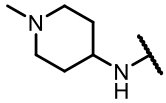
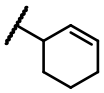
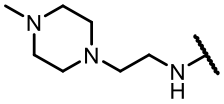
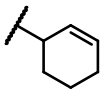
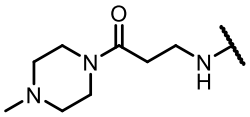
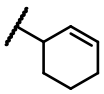
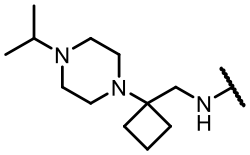
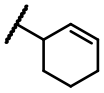
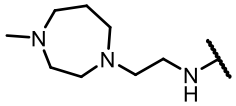
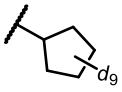
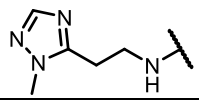
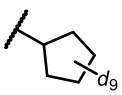
secondary amine of the previously tested carbamate, but removed two basic nitrogens, while still potentially allowing for additional hydrogen bonding interactions (fluorine hydrogen bond) that may have been present with the piperazine nitrogen.[86] In fact, **2-63** proved to be equipotent in the biochemical assay suggesting that it was able to maintain interactions that **2-52** made. Since, in the case of the amines, the secondary propargyl amine, **2-54**, was as potent as the tertiary propargyl amines, **2-55** to **2-57**, it stood to reason that the secondary amine would perform well at the nitrogen of the carbamate as well. To test this hypothesis, the tertiary amine, morpholine (**2-64**) and *N*-methyl-4-piperazine (**2-65**), containing carbamate analogs were prepared. In the biochemical assay, these two analogs were nearly the same and maintained the efficacy of their larger counterparts **2-52** and **2-53** (Table 2-7, entries 3 and 4 versus 1 and 2). This discrepancy in the activities between the very similar **2-64** and **2-65** cannot not be justified by the zone 1 groups because **2-52** and **2-53** which have the perdeuterated and cyclohex-2-ene groups are equipotent. This indicates that the difference is due to the presence of the basic nitrogen in the piperazine versus the oxygen in the morpholine. Given that the *N*-methyl-4-piperidine (**2-54**) was the most potent propargyl amine analog, this group was chosen to be incorporated onto the carbamate as well (**2-66**). Again, there was no change in the biochemical activity. The successful use of the *N*-methyl-4-piperidinyl carbamate group as well as the *N*-methyl-4-piperazine carbamate reaffirms that the HBD amine is not required for activity, however it does result in minor increases in potency.

Given that the inclusion of the side chain fragment from the phenyl indole chemotype (see Chapter 1.2.2) resulted in good biochemical activities for **2-52** and **2-53**, additional analogs containing some of the best side chain fragments from the phenyl indole series were prepared (Table 2-7, entries 6-10). The slightly smaller terminal alkyl group on **2-67** (*N*-methyl vs **2-53**'s

N-isopropyl) maintained activity relative to its slightly more lipophilic counterpart, **2-53**. The longer, amide-containing analog (**2-68**) and the bulkier, "kinked," cyclobutane-containing analog (**2-69**) also maintained the potency of **2-53**. The larger diazepane-containing **2-70** also showed good activity biochemically. The need for a basic nitrogen in the heterocycle was tested further with the 1-methyl-1*H*-1,2,4-triazole-containing **2-71**. Given that this heteroaryl analog is only weakly basic, it was useful to assess whether it was the basicity of the nitrogens in the previous heterocyclic compounds or the presence of the heteroatoms themselves that lead to good activity. This aryl heterocycle-containing analog resulted in a 2.5-fold loss in activity compared to **2-52** (Table 2-7, entry 10 versus 1). Overall, it appears that the large carbamate group of **2-52** and **2-53** is not required for potent activity and that a truncated version lacking the linker and with only a basic nitrogen containing heterocycle conveys the same potent inhibition. Given the poor physiochemical properties of **NMS-873**, it was encouraging to see that with the replacement of the biphenyl side chain with the propargyl carbamate side chains, the lipophilicity of **2-66** decreased by greater than one log unit (4.7 vs 3.4, respectively).

Table 2-7. Optimization of zone 5 carbamates and associated p97 inhibitory activity.



Entry	Compound	*	R	IC_{50} (μM) [a]	cLogD [b]
1	**2-52**			0.034[58]	3.9
	2-53			0.019[58]	4.1
2	**2-63**			0.034[58]	5.2
3	**2-64**			0.044[58]	4.2
4	**2-65**			0.030[58]	4.4
5	**2-66**			0.025[58]	3.4
6	**2-67**			0.025[58]	3.8
7	**2-68**			0.029[58]	3.5
8	**2-69**			0.011[58]	5.1
9	**2-70**			0.023[58]	3.0
10	**2-71**			0.052[58]	4.0

[a] BIOMOL® Green biochemical assay at 200 μM ATP.[50] [b] Calculated using Instant JChem.[64]

While exploring the various moieties that could be utilized as propargyl end groups, it became clear that many groups were tolerated in the zone 5 position (Figure 2-4). Nearly all amine derivatives were well tolerated biochemically. The simplest propargyl alcohol derivatives, ethers, were not well tolerated however. The slightly more complex propargyl alcohol derivative, the oxygen-linked carbamates, showed good potency. When the carbamate moiety was further explored a slight preference heterocycle-containing groups was seen, though all tested carbamates showed good activity in the biochemical assay. Also, carbamates that contained a secondary amine versus a tertiary amine performed slightly better. Despite this slight preference for secondary amines, there was no observable preference for the length of the linker connecting the secondary amine of the carbamate to the terminal heterocycle given that compounds with no linker (**2-66**) and a 3-carbon linker (**2-68**) performed essentially the same in both assays.

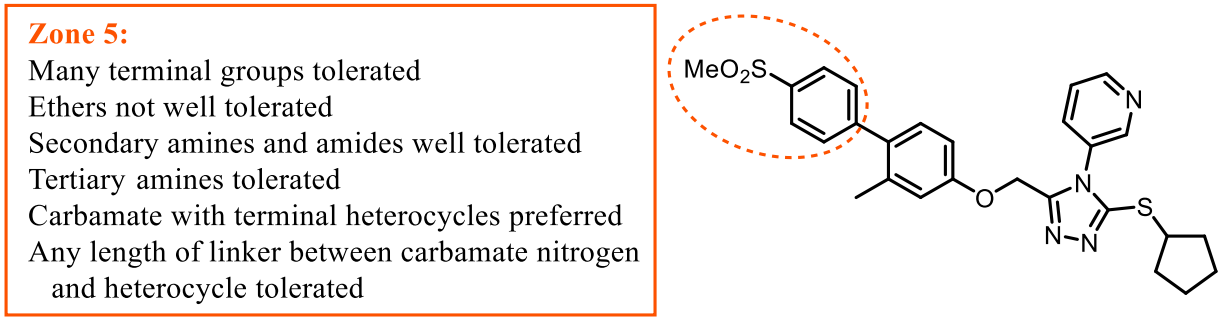


Figure 2-4. SAR summary for the zone 5 end groups.

After unsuccessful attempts to replace or modify the sulfur in zone 2, other proposed metabolically labile sites were taken into consideration as a way of mitigating potential stability liabilities. Especially important in zone 4 was to distinguish the current series from that of the originally reported **NMS-873**.[60] The electron rich phenol was modified with fluorine atoms, and, other electron withdrawing groups (EWG) to differentiate the phenol and to potentially modulate

metabolism.[87] Methyl group replacement with a fluorine atom (**2-72** and **2-73**) was well tolerated, in terms of binding, with equivalent IC_{50} for both the perdeuterated- (**2-72**) and cyclohex-2-ene- (**2-73**) containing analogs (Table 2-8, entry 2 versus 1). Since metabolism data indicating specific sites of oxidation were not available, predictions were based on literature reports.[88] Therefore, di-fluorinated analogs were prepared which aimed to maintain the beneficial 3-fluoro group, as well as block the potentially hydroxylated *ortho*-position of the phenol which is a known metabolite. These included the 2,3- and 2,5-difluoro analogs (Table 2-8, entries 4 and 5). The 2,5-difluoro analogs with the perdeuterated- (**2-74**) and the cyclohex-2-ene-cores (**2-75**) both showed 2-fold improvement in biochemical activity compared to **2-72** and **2-73**. The 2,3-difluoro analog (**2-75**) also maintained the biochemical activity of **2-39** and **2-73** (Table 2-8, entry 5 versus 1 and 2). Additional di-fluorination patterns were also explored to determine the optimal pattern (Table 2-9). The di-fluorinated analogs in conjunction with the two mono-fluorinated analogs demonstrate a preference for fluorination in the *meta*-position of the phenol ring. This observation is based on the at least 1.5-fold lower activity is observed if no *meta*-substitution is present.

These observations were explored further by replacing various fluorines with other substituents. Compound **2-77**, where a methoxy was added to the 2-position to give a 5-fluoro-2-methoxy substitution pattern, was moderately tolerated in the biochemical assay. The larger methoxy group could block the metabolic liabilities of the *ortho*-positions as well as ether cleavage of the phenol due to its steric bulk, however a slight preference for smaller, electron withdrawing 2-substituents appears to exist for optimal binding. To assess the requirements of the 3-position, two larger and more electron withdrawing analogs were prepared: 3-cyano (**2-78**) and 3-trifluoromethyl. The 3-cyano analog showed a 3-fold loss in biochemical activity relative

to **2-39** and nearly 5-fold relative to **2-73**. While the 3-methyl (**2-67**) and 3-fluoro (**2-79**) analogs with the ethyl *N*-methylpiperazine carbamate side chains showed similar potencies in the biochemical assay, replacement of the 3-substituent with a trifluoromethyl group, as in **2-80**, resulted in a 2-fold loss in potency in the biochemical assay. This suggests that for potent binding the electronics of the phenol ring are not the most important factor, given that both donating and withdrawing groups were tolerated.

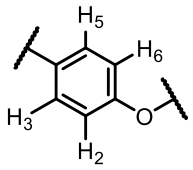
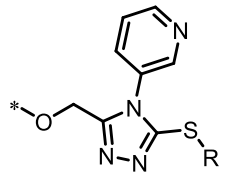
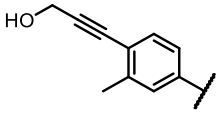
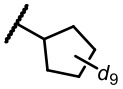
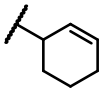
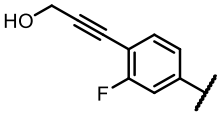
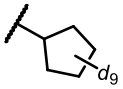
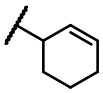
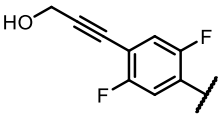
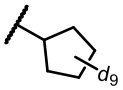
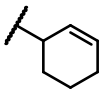
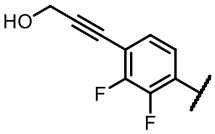
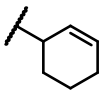
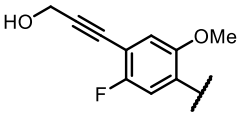
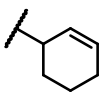
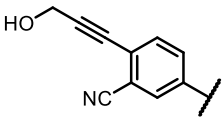
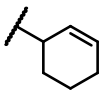
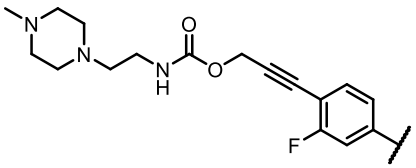
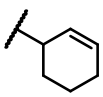
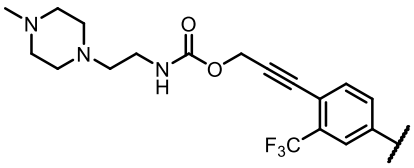
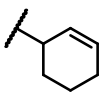


Figure 2-5. Numbering scheme for the substituted phenol side chain relative to the 3-methyl phenols **2-38** and **2-39**.

Table 2-8. Alternatively, substituted zone 4 phenols and associated p97 inhibitory activity.



Entry	Compound	*	R	IC_{50} (μM) [a]
1	**2-38**			0.048[58]
	2-39			0.037[58]
2	**2-72**			0.030[58]
	2-73			0.026[58]
4	**2-74**			0.021[58]
	2-75			0.020[58]
5	**2-76**			0.040[58]
8	**2-77**			0.040[58]
9	**2-78**			0.10[58]
10	**2-79**			0.020[58]
11	**2-80**			0.043[58]

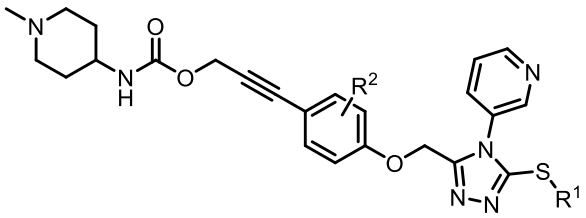
[a] BIOMOL® Green biochemical assay at 200 μM ATP.[50]

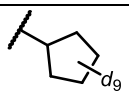
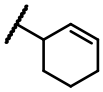
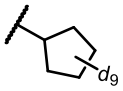
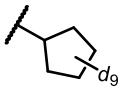
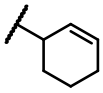
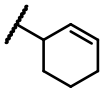
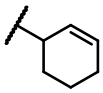
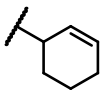
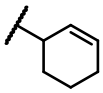
The optimal di-fluorination pattern was first evaluated with compounds containing the previously preferred *N*-methylpiperidine carbamate (Table 2-9). Further evaluation of *N*-methylpiperidine carbamate analogs began with the mono-fluorinated **2-82**. With the perdeuterated thioether in place, it showed equipotent inhibition in the biochemical assay as compared with **2-81**. Given that the difluoro analogs were shown to be efficacious with the propargyl alcohol side chain, their *N*-methylpiperidine carbamate counterparts were also synthesized in all di-fluorination combinations (Table 2-9, entries 4-7). Both the perdeuterated and cyclohex-2-ene thioether analogs were prepared with the 2,5-difluoro pattern (**2-83** and **2-84**, respectively), and the 2,3-difluoro (**2-85**) and 3,5-difluoro (**2-86**) were synthesized with the cyclohex-2-ene thioether. The 2,5-, 2,3-, and 3,5- analogs all showed < 20 nM activity in the biochemical assay (Table 2-9, entries 4 and 6). The 17 nM IC_{50} value of **2-85** was very nice to see given that **2-76** was the least active of the tested di-fluorination patterns for the propargyl alcohol side chain.

The substitution with non-fluorine groups was readdressed on the *N*-methylpiperidine carbamate system as well to see if the same preference for fluorination carried over with the more potent zone 5 group (Table 2-9, entries 8 and 9). The 5-fluoro-2-methoxy analog (**2-87**) nicely retained biochemical potency, indicating that the binding pocket around the phenol is spacious enough to accommodate larger groups in the 2-position. Further supporting this hypothesis is that the 3-cyano analog (**2-88**), though showing slightly weaker biochemical potency (30 nM), was able to maintain activity within 2-fold relative to **2-66** and **2-81**. This supports the observation that an electron deficient phenol ring is well tolerated, but larger and more electron withdrawing the groups result in a slightly diminished activity (Hammett constant, σ_{meta}, = 0.56 versus 0.34 for CN and F, respectively).[89] There does not appear to be a strong

correlation between the IC_{50} of these substituted phenol analogs and their cLogD, which is the same for all difluoro analogs, or their PSA, which shows only very subtle changes for each substitution pattern but cannot account for the SAR.

Table 2-9. Substituted zone 4 phenols (see Figure 2-5 for numbering scheme) with preferred *N*-methylpiperidine carbamate and associated p97 inhibitory activity.[iv]



Entry	Compound	R^2	R^1	IC_{50} (μM) [a]
1	**2-81**	3-Me		0.016[58]
	2-66			0.025[58]
2	**2-82**	3-F		0.016[58]
4	**2-83**	2,5-F		0.010[58]
	2-84			0.012[58]
5	**2-85**	2,3-F		0.017[58]
6	**2-86**	3,5-F		0.012[58]
8	**2-87**	5-F, 2-OMe		0.019[58]
9	**2-88**	3-CN		0.030[58]

[a] BIOMOL® Green biochemical assay at 200 μM ATP.[50]

[iv] **2-81** synthesized by Kaylan Kerrigan.

While exploring modification of the phenol ring, it was found that the 3-methyl group could readily be replaced which was important to distinguish from **NMS-873** (Figure 2-6). Replacement with groups that reduce the electron density of the ring and potentially impact its metabolism, such as the smaller fluorine atom was well tolerated. However, slightly larger groups such as the trifluoromethyl group or cyano were not quite as well tolerated. Further incorporation of an additional fluorine onto the ring was preferred over the mono-fluoro analog. While exploring all variations of the bis-fluorination pattern, it was shown that *meta* substitution is preferred for binding.

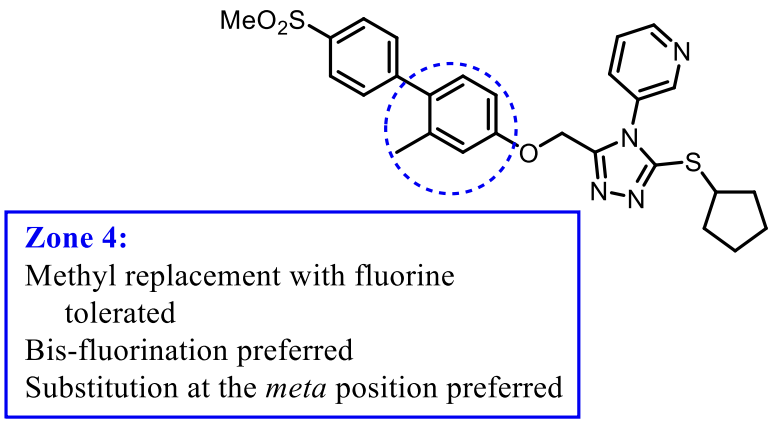


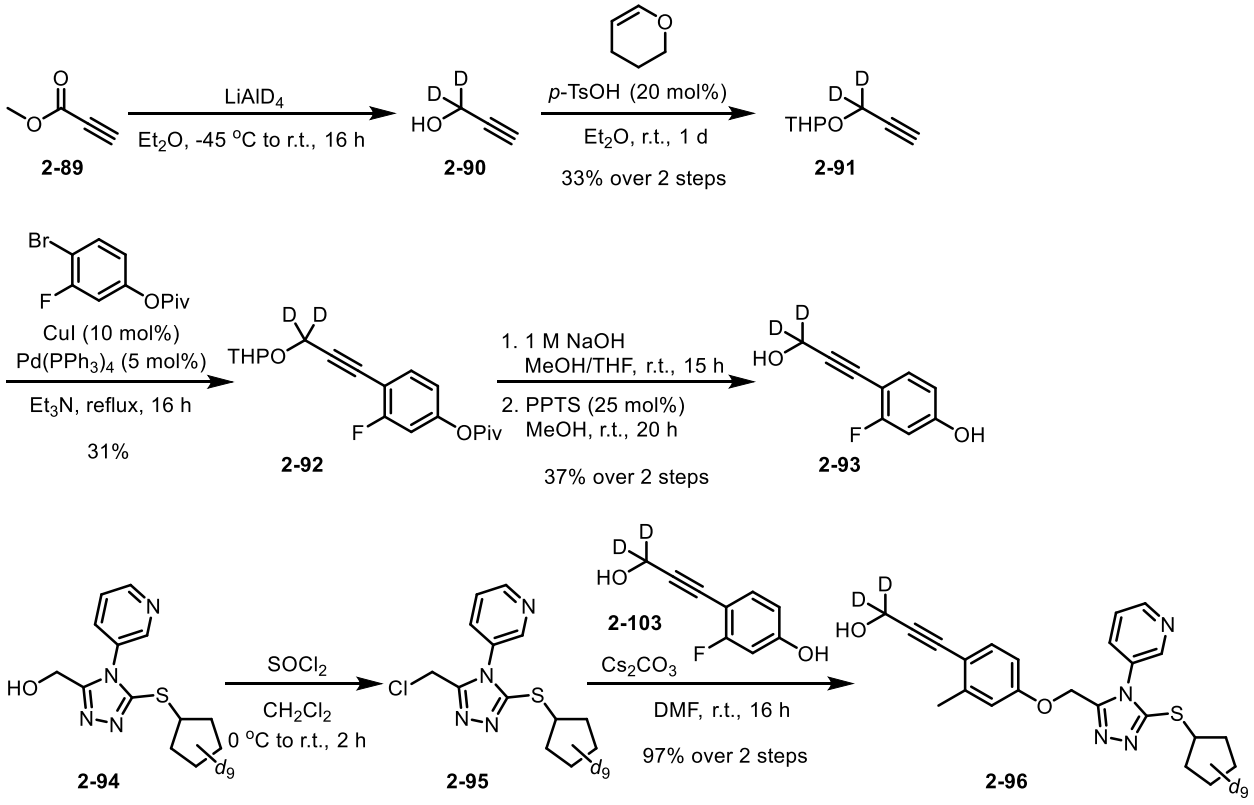
Figure 2-6. SAR summary for zone 4 substituents.

The propargyl methylene in zone 5 was also viewed as a further location to introduce substituents that could be used to distinguish the scaffold further from **NMS-873** as well as introduce groups that could affect metabolism. Alkylation was primarily used in these modifications; however, an isotope switch to the deuterated propargyl system was also made to take advantage of the kinetic isotope effect to reduce metabolism without significantly changing

the binding of the compound (Table 2-10). First the methylated analog (**2-97**) was prepared but this incorporation lead to a nearly 2-fold loss in the biochemical activity relative to **2-38**. However, given that a large number of additional propargyl groups were tested previously with varying degrees of success, it was clear that a selection of the previous moieties should be prepared (Table 2-10, entries 3-5). The methyl ether (**2-98**), morpholine (**2-99**), and ethyl *N*-isopropylpiperazine carbamate (**2-100**) were all tested and showed decreased potency of at least 2.5-fold and up to 4-fold, relative to **2-97**, in the biochemical assay. These IC_{50} values represent a more significant loss of activity versus their CH_2-containing counterparts (**2-50**, **2-55**, and **2-52**), indicating that the additional substituent likely does not fit into the binding pocket as well as the unsubstituted analogs. This reinforces the hypothesis that the alkyl portion of the side chain binds in a narrow hydrophobic channel which cannot accommodate larger substituents at the methylene position. This is further supported by the fact that all methylated analogs (Table 2-10, entries 2-5) showed a significant loss (2- to 7-fold) in the biochemical assay alone. To further assess the tolerance of the binding pocket for methylene substitution, analogs with additional substituents were prepared (Table 2-10, entries 6 and 7). The trifluoromethyl analog (**2-101**) showed a similar biochemical activity to **2-100** but a 7-fold loss of activity relative to **2-53**. Both the methylated and trifluoromethylated analogs were synthesized as racemic mixtures, and therefore it is unknown whether one of the enantiomers would bind better than the other. However, given that the addition of the previously good ethyl *N*-isopropylpiperazine carbamate did not significantly improve the biochemical potency of the two analogs and move their IC_{50} values closer to their unsubstituted counterparts (34 nM for **2-52**, and 19 nM for **2-53**), it stands to reason that resolution of the enantiomers would not lead to a single super-potent and a single inactive analog. To be thorough, the bulkier *gem*-dimethyl analog (**2-102**) was also prepared to

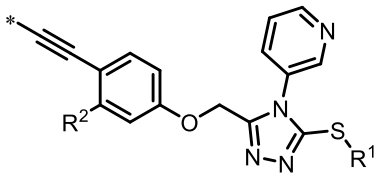
further support the claim that steric bulk is not well tolerated at the propargyl position. In principle, the steric bulk would mask the adjacent alcohol and physically block oxidation of the methylene group which could be advantageous for stability purposes as well.[90] However, the *gem*-dimethyl group resulted in a decrease of the IC_{50} by a factor of 2.5 relative to **2-39**. Finally, deuterium were incorporated which could further differentiate the side chain from that of **NMS-873** and replace the potentially labile hydrogens with this more stable isotope.[91-93] This CD_2-containing analog (**2-96**) maintained the activity of **2-72** in the biochemical assay, which when this data is taken together with the biochemical activities of the alkyl substituted analogs further supports the hypothesis that the binding region where the methylene resides is narrow.

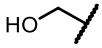
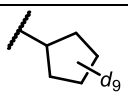
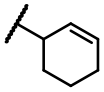
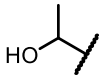
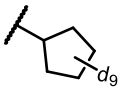
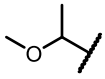
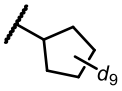
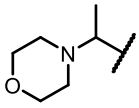
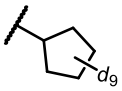
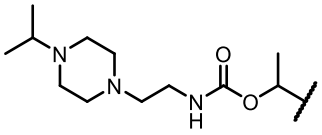
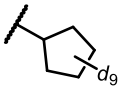
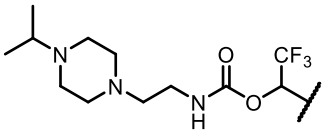
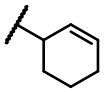
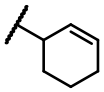
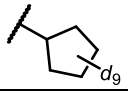
The synthesis of the deuterated propargyl analog was carried out as described in Scheme 2-9. First, methyl propiolate was reduced to the alcohol using lithium aluminum deuteride ($LiAlD_4$) in diethyl ether at -45 °C allowing it to warm to room temperature over 2 h and then stirring at room temperature overnight. Then the alcohol was protected as the tetrahydropyran (THP) ether giving the desired alkyne after Kugelrohr distillation at about 20 Torr and 80-90 °C. This protected alkyne and the protected 4-bromo-3-fluorophenol were then coupled in 31% yield to give the intact side chain. The two protecting groups were removed sequentially using NaOH to remove the *O*-Piv group and PPTS to remove the *O*-THP group, giving a 37% yield of the fully deprotected side chain (**2-93**) after two steps. After activation of the hydroxyl group with $SOCl_2$, the chloride was displaced with **2-93** to give **2-96** in 97% yield over two steps.



Scheme 2-9. Synthesis of the deuterated propargyl analog **2-96**.[63]

Table 2-10. Substitution of the propargyl methylene in zone 5 and associated p97 inhibitory activity.



Entry	Compound	*	R^2	R^1	IC_{50} (μM) [a]
1	**2-38**		Me		0.048[58]
	2-39		Me		0.037[58]
2	**2-97**		Me		0.068[58]
3	**2-98**		Me		0.16[58]
4	**2-99**		Me		0.17[58]
5	**2-100**		Me		0.13[58]
6	**2-101**		Me		0.11[58]
7	**2-102**		Me		0.096[58]
8	**2-96**		F		0.030[58]

[a] BIOMOL® Green biochemical assay at 200 μM ATP.[50]

While trying to modify the unsubstituted propargyl position, it was determined that significant alteration was not well tolerated biochemically (Figure 2-7). Even with the incorporation of end groups that typically benefited potency, the small methyl substituents were not tolerated. However, switching the hydrogens at this position with their metabolically more stable isotopes, deuterium, was tolerated.

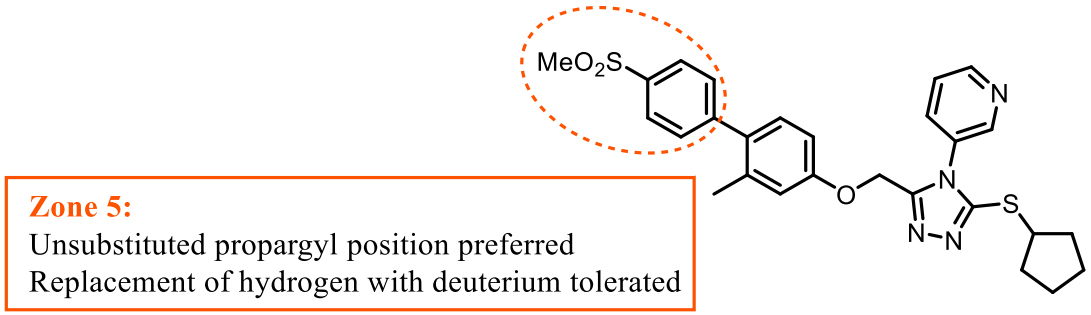
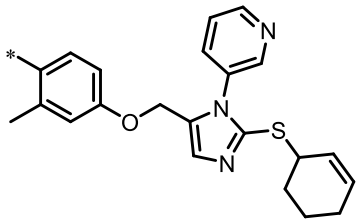


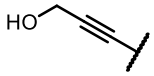
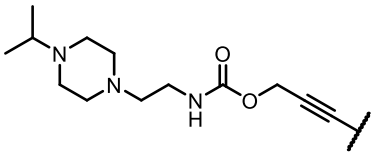
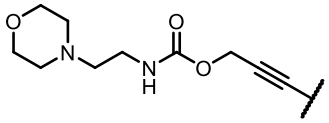
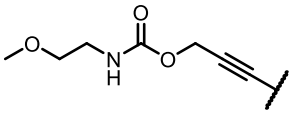
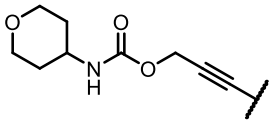
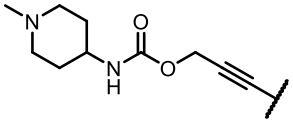
Figure 2-7. SAR summary for substitution at the propargyl position in zone 5.

The final zone for the **NMS-873** chemotype that remained unexplored was zone 3. In the original report no heterocycles other than the 3-mercapto-1,2,4-triazole were prepared. This region could therefore be a key means by which to distinguish the currently described endeavor. In addition, having not explored additional heterocycles, it is unknown whether all three nitrogens of the triazole are required for binding. In order to explore this question, the 2-mercapto-1*H*-imidazole core was evaluated as an alternative to the triazole. The removal of *N*-1 from the 3-mercapto-1,2,4-triazole core proved to be well tolerated biochemically (Table 2-11). Even with the unoptimized propargyl alcohol side chain (**2-103**), the biochemical activity was 37 nM. However, when carbamates were introduced the activity improved relative to **2-103**. Two new extended carbamates were prepared (ethyl morpholine: **2-105** and 2-methoxyethane: **2-106**) along with the 4-pyran (**2-107**) and *N*-methylpiperidine (**2-108**) carbamates (Table 2-11, entries 3-6). These carbamates were utilized to test whether the SAR for the triazole core extended to the imidazole core. Basic nitrogen containing heterocycles resulted in better activity, and the much larger carbamates were not necessary for potent activity. All biochemical assays for the three oxygen-containing carbamates gave IC_{50} values in the 30-40 nM range. Analyzing the efficacies for all carbamate analogs in the imidazole series indicates that the trend of a basic nitrogen-containing heterocycle being preferred for both core series. In addition, comparing the

activities of **2-104** and **2-108** shows that, again the trend of not requiring the larger carbamate for potent activity carries over between the two core types. **2-104** was found to inhibit p97 at 26 nM while **2-108** was significantly more potent in the biochemical assay (14 nM). This data suggests that the binding mode for the triazole and imidazole series' is likely the same given that some of the SAR trends observed for the triazoles were mirrored in the imidazoles. In addition, the activity of **2-108** is comparable to **2-66** (IC_{50} = 14 nM versus IC_{50} = 25 nM, respectively) indicating that the 2*N* of the 1,2,4-triazole, the nitrogen next to the side chain is not necessary for potent activity.

Table 2-11. Zone 3 imidazole replacement of triazole analogs and associated p97 inhibitory activity.[v]



Entry	Compound	*	IC_{50} (μM) [a]
1	**2-103**		0.037[58]
2	**2-104**		0.026[63]
3	**2-105**		0.036[63]
4	**2-106**		0.039[63]
5	**2-107**		0.034[63]
6	**2-108**		0.014[63]

[a] BIOMOL® Green biochemical assay at 200 μM ATP.[50]

The SAR for the sample of imidazole analogs described follows that of the triazole compounds (Figure 2-8). Carbamate analogs were preferred over the unsubstituted propargyl alcohol and carbamates with nitrogen-containing heterocycles were preferred over other carbamates. Again, any length of the linker connecting the carbamate and the terminal heterocycle was tolerated, but shorter lengths were slightly preferred. Given the overall

[v] **2-104** and **2-108** synthesized by Dr. Marina Kovaliov

similarities in the biochemical activities for the imidazole and triazole series, it was shown that the *N*-1 of the triazole was not necessary for binding.

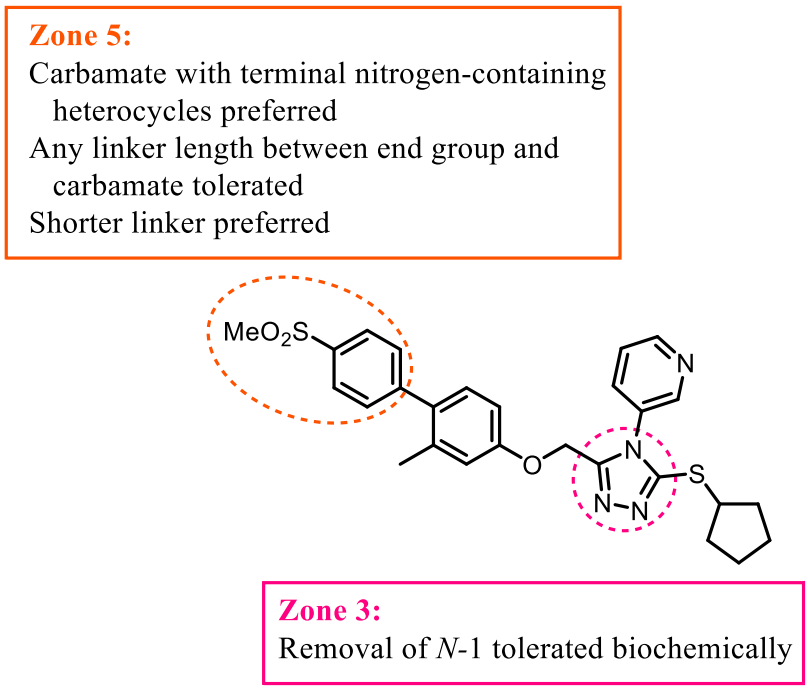
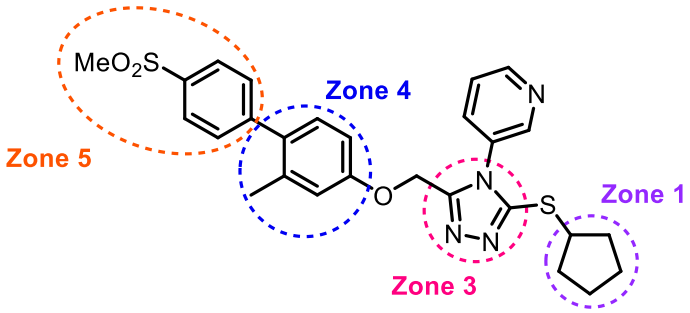


Figure 2-8. SAR summary for imidazole analogs.

Since only limited modification was tolerated in zone 2 there was no need for an extensive additional optimization effort. Therefore, the key preferred fragments necessary for potent inhibition are outlined in Figure 2-9. Five compounds were identified as the most potent overall over the course of this SAR development (Figure 2-10). The activity difference between these analogs is very small, which is not surprising given the similarity between these structures. Three contain the same triazole core (zones 1-3), one has the perdeuterated zone 1 cyclopentane, and only one has the imidazole in zone 3. In zone 4, the only difference is the di-fluorination pattern (2,5- or 3,5-difluoro) or 3-methyl phenol and within zone 5 only nitrogen heterocycle containing carbamates resulted in this high level of activity.

A



B

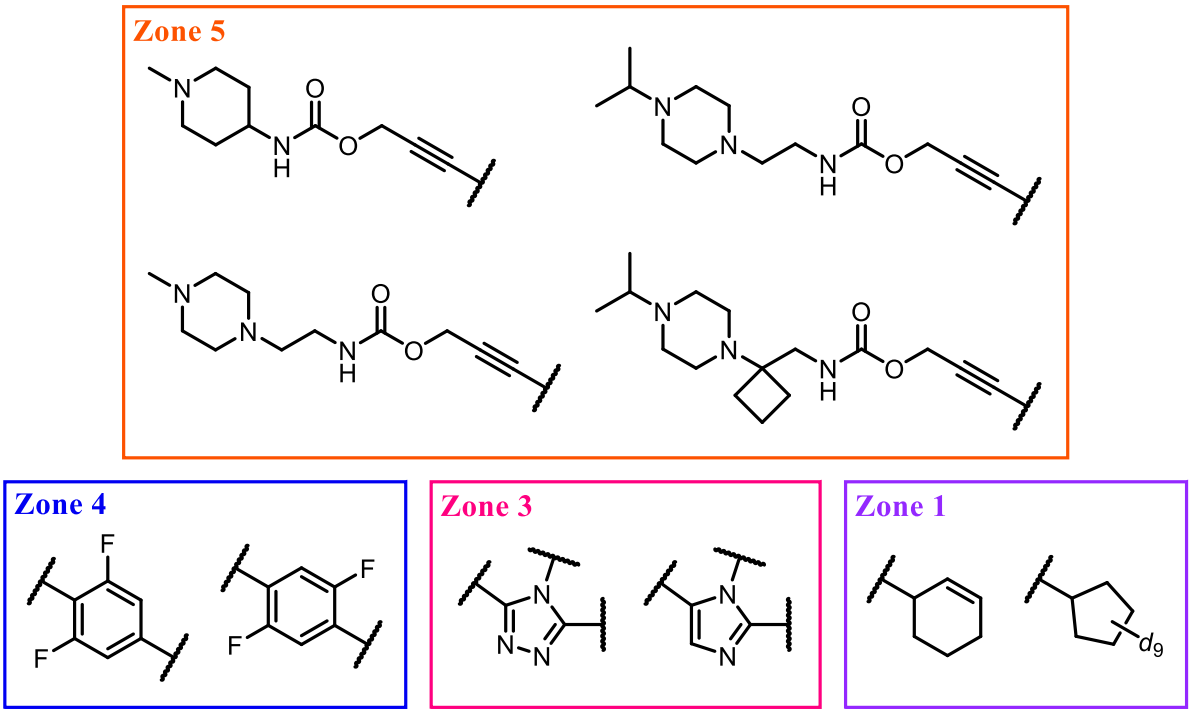


Figure 2-9. The structure of **NMS-873** with the preferred fragments identified at each zone from the SAR campaign.

(A) Structure of **NMS-873** showing the 5 zones of structural modification. (B) The preferred fragments for each zone. The preferred propargyl carbamates in zone 5 (orange); the preferred di-fluorinated phenols in zone 4 (blue); the triazole and 2-mercapto-1*H*-imidazole in zone 3 (pink); and the preferred cycles in zone 1 (purple).

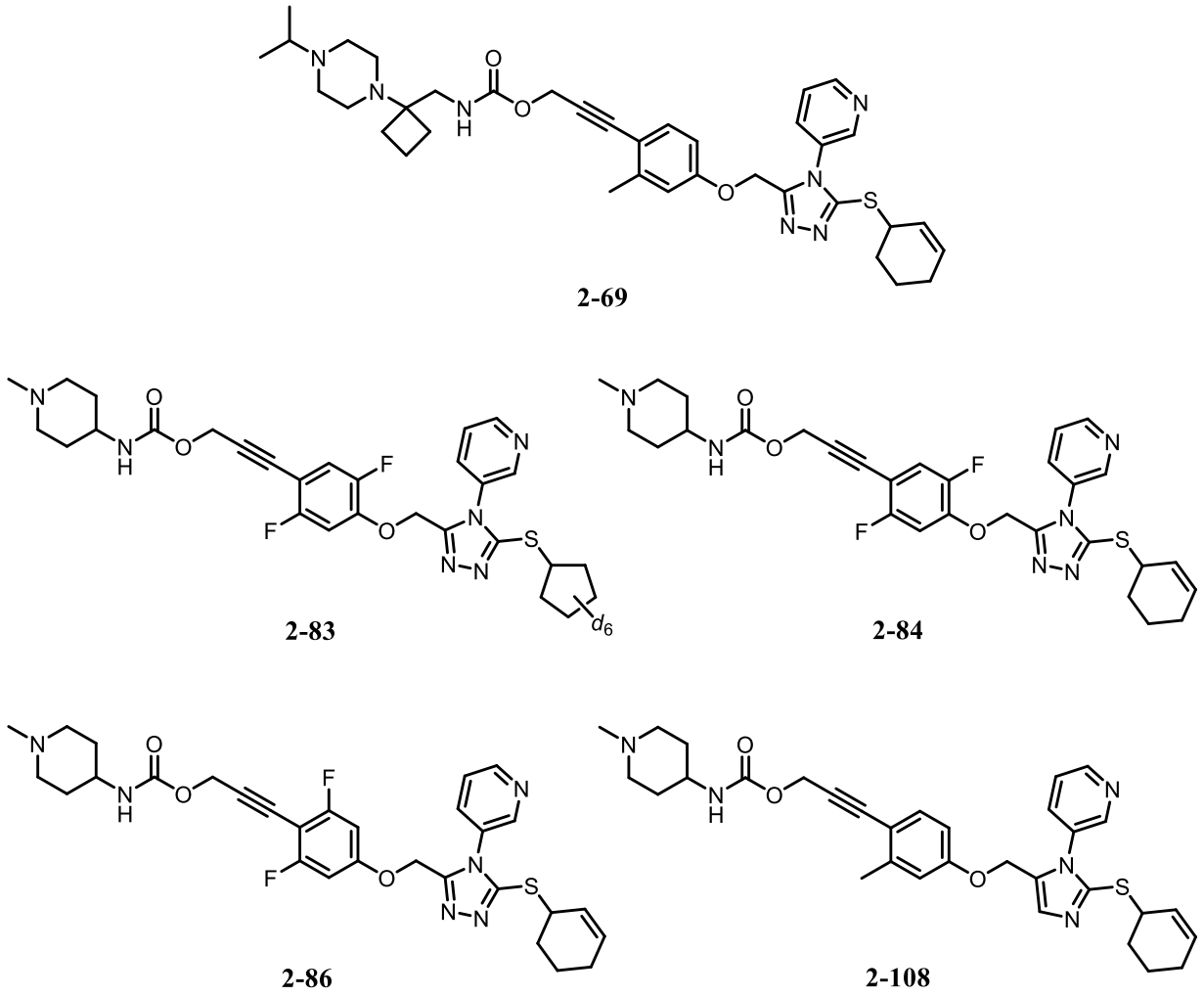


Figure 2-10. The five most potent analogs.

2.3.2 Discussion

Similar to the previously reported chemotypes (amide indole and phenyl indole), the SAR for the triazole series was fairly narrow (Figure 2-14). The core region of **NMS-873** (zones 1-3) was less tolerant to modification while the side chain (zones 4 and 5) showed flexibility in the functionality that could be accommodated. The successful replacement of the phenyl ring with the alkyne moiety indicates a region of the binding pocket that is likely narrow. This is supported

by the 5-fold loss of biochemical activity of the analogs with additional propargyl substituents; only the relatively small methylated analog (**2-97**) showed a small loss of activity (2-fold) and the deuterated analog (**2-96**) retained activity. In addition, the rigid conformation of the alkyne and its attached groups lead to a structure which has a limited range of conformations that it can adopt. This can allow for smaller entropic penalties for binding which can also help to explain the improved potency of the phenyl alkyne versus the biphenyl series.

The observed SAR for zone 5 paralleled that described in the literature for the side chain of the phenyl indole series where the terminal portion of zone 5 (beyond the propargyl methylene) was very tolerant to many groups in the biochemical assay. Nearly all terminal functional groups tested showed IC_{50} values between 50 and 10 nM. All groups were linked through a heteroatom due to the successful incorporation of the propargyl alcohol or amine. With respect to the propargyl heteroatom, there was no preference for the type of hydrogen bonding ability given that both the HBD/HBA **2-52** and the HBA **2-57** had very similar activities (IC_{50} ~ 20-30 nM). Regarding the class of terminal groups preferred, the binding pocket showed tolerance for amine, carbamate, and amide groups indicating that this portion of the molecule is not tightly bound and might be in a solvent exposed region of the binding site. Generally, groups that contained additional heteroatoms for participating hydrogen bonding interactions were favored which would support the hypothesis that these groups are solvent exposed or in a hydrophilic region.

The SAR at zone 4 shows a clear preference for *meta*-substitution relative to the phenol alcohol in the biochemical assay. *Ortho*-substitution is tolerated, but preferrably when combined with *meta*-substitution (**2-84**, **2-85**, and **2-86**). Given the similar sizes of hydrogen and fluorine (van der Waals radii = 1.2 and 1.47 Å, respectively) it can be assumed that the differences in

biochemical activity can be attributed to electronic features (Figure 2-11).[94] Analysis of the electrostatic potential maps for all zone 4 variations reveals several features that could contribute to potency. Groups larger than a methyl group at the 3-position lead to a slight decrease in potency; trifluoromethyl and cyano are both larger than the methyl (trifluoromethyl is overall bulkier and cyano extends further into the pocket) and their analogs were approximately 2- to 3-fold less potent than the comparable 3-methyl analogs. Groups only containing the smaller fluoro either retained or increased activity. The alkyne might participate in a π-π stacking interaction, and the lack of electron density in the case of a *ortho-ortho* (2,6-difluoro) substitution pattern could disrupt that interaction, resulting in decreased biochemical activity. This is further supported by the similar potencies of the 3-fluoro, 2,3-difluoro, 2-fluoro-5-methoxy, 2,5-difluoro, and 3,5-difluoro analogs which show very similar biochemical potencies as well as similar alkyne electron densities. In addition, there is an apparent preference for compounds with a relatively uniform phenyl π-system that is neither overly electron rich or electron poor (consistent green coloration in the electrostatic potential maps below).

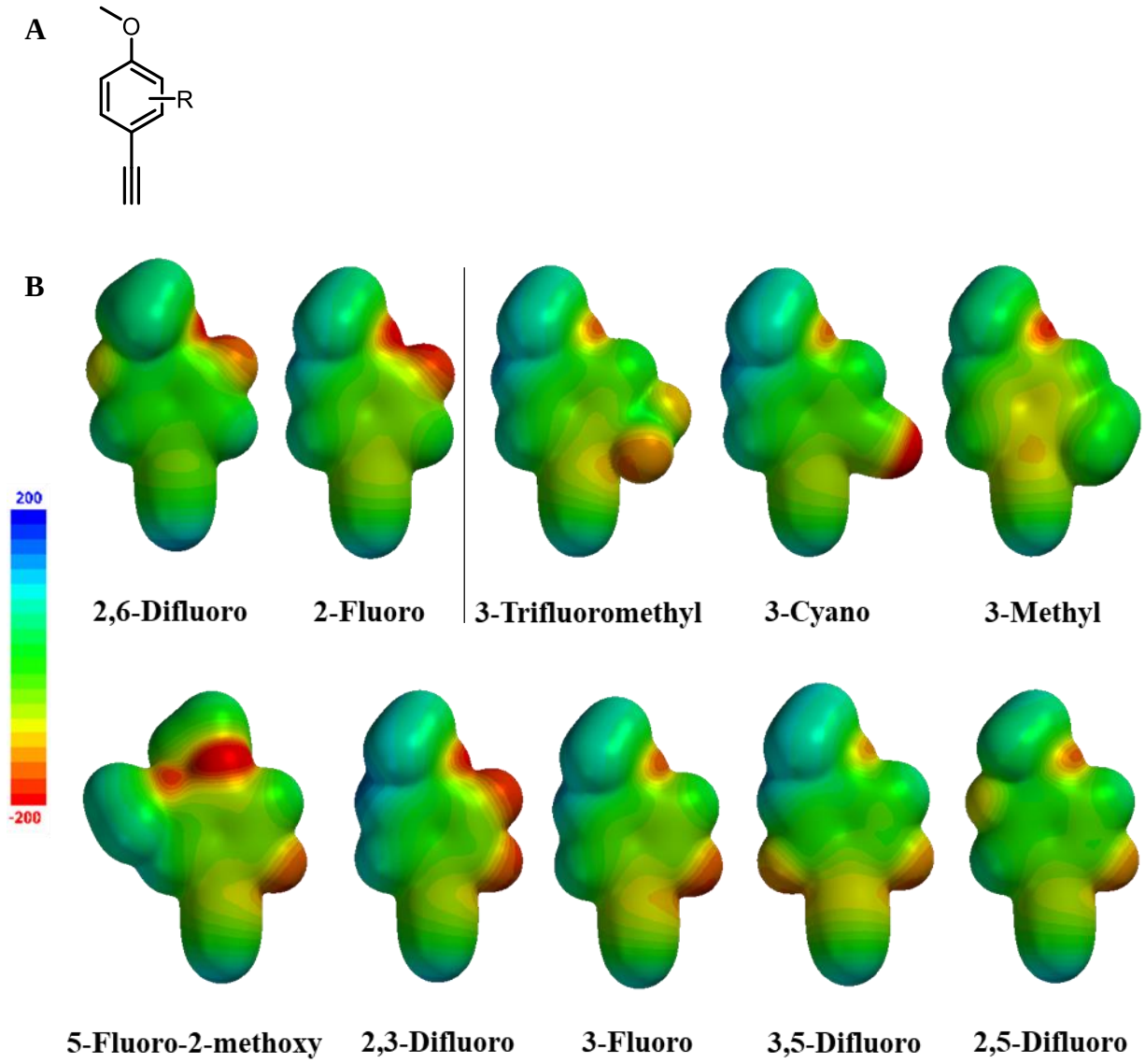


Figure 2-11. Electrostatic potential maps for the substituted phenylacetylenes in zone 4.[95]

(A) The structure used for the calculation. (B) Calculated with PM3 parametrization in water. The color coding (scale on the left) reflects the electrostatic potential experienced by a positive probe charge (red = attractive, blue = repulsive). Generated using Spartan Student (7.2.6).[96] Organized from least potent (beginning with the 3-trifluoromethyl, 2,6-difluoro and 2-fluoro calculated as *ortho*-substituted references) to most potent (left to right and top to bottom)

The core of the **NMS-873** scaffold (zones 1-3) showed a much lower tolerance for modification. In zone 3, a very similar imidazole core derivative which maintained the vectors of the original **NMS-873** was prepared (Figure 2-12); the 2-mercapto-1*H*-imidazole showed an improvement in biochemical activity in the case of the best carbamate zone 5 group, but overall it was equipotent in biochemical potency. While its biochemical activity was encouraging and showed that the *N*-1 was not required for binding. Sequential removal of the remaining two nitrogens is still desired to further probe the necessity of each. The IC_{50} values for **2-103** versus **2-39**, for instance (as well as for the other three analogs that were synthesized with the triazole and imidazole cores) suggests that there is either hydrogen bonding occurring with the *N*-2 or *N*-4 nitrogens that are not being affected by the removal of the *N*-1 or that there is π-stacking occurring that is not affected by the change in electronics when *N*-1 is removed.

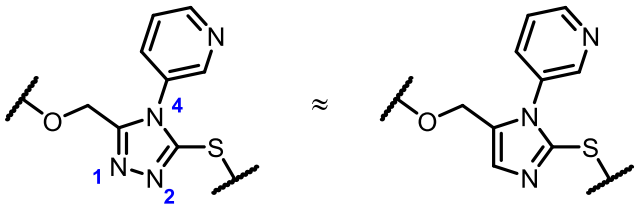


Figure 2-12. Relative activities of the tested **NMS-873** chemotype cores.

The SAR of zone 2 was also very tight. In the biochemical assay, only the replacement of the sulfur with oxygen retained the same potency. Both the sulfur and the oxygen can participate in hydrogen bonding which could explain that moderate tolerance for both. Sulfur is not a traditional hydrogen bonding atom, and when it is considered, it is thought of as a weak hydrogen bond acceptor.[97, 98] However, thioethers have been shown to be stronger HBA in the case of acyclic thioethers relative to acyclic ethers when the donor is an alcohol and shown to be

equally strong HBA when the donor is an amine.[97, 98] This supports the observation that both the sulfur and oxygen containing analogs are potent. The sulfone analog, however, showed the weakest activity likely due to its significantly increased size. In addition, the sulfone C-S-C bond angle has been predicted or shown to be from 98.5° to 103° while the thioether C-S-C bond angle was shown to be 105°.[99, 100] The reduced size of the angle in the case of the sulfone may be enough of a change to cause an unfavorable interaction or steric clash in the zone 1 binding region, especially given that the SAR at zone 1 indicates that the size of the pocket is relatively small. In addition to the thioether and ether linkages, carbon- and nitrogen-replacements of the sulfur were made either by other UPCDC members or by Polucci et al. Simply comparing the zone 2 modifications presented in the literature with an unsubstituted phenyl ring in zone 4 and cyclopentyl ring in zone 1, the thioether (IC_{50} = 0.72 μM) was at least twice as potent as the ether (IC_{50} = 2.25 μM), methylene (IC_{50} = 1.97 μM), or secondary amine (IC_{50} = 2.85 μM).[60] Though the amine derivative was not prepared with one of the improved zone 5 modifications, the carbon equivalent of **2-52** without deuteration of the cyclopental was reported to have an IC_{50} = 0.12 μM while **2-52** has an IC_{50} = 0.037 μM indicating that even with the improvements that were made in other areas of the molecule, the thioether was best zone 2 group based on the balance of activity and ease of preparation.[63]

As indicated above by the preference for the thioether, sulfur can hold a special place in medicinal chemistry. The bond angles of C-S-C in thioethers have been shown to be smaller than that of C-C-C in methylenes and of C-O-C in ethers.[101] In addition, the van der Waals radius of sulfur (R = 1.80-1.85 Å) is larger than that of either oxygen (R = 1.40-1.58 Å) or carbon (R = 1.68-1.77 Å) indicating that sulfur uniquely fills the space of that region of the binding pocket.[102] Further emphasizing its importance, sulfur and its related compounds have also been used

throughout history as treatments for various maladies since before it was known that sulfur was an element.[103, 104] As a result, when medicinal chemistry efforts have been employed for the development of new drugs, sulfur is one of the most common elements used. A 2014 study found that of the top 200 brand name drugs of 2011 (by either sale or prescription), sulfur was found in 22-25% percent of non-biological drugs.[103] Sulfur has been found in many forms in these drugs including in heterocycles, such as thiophenes; thiazoles; and β-lactams, and acyclic forms, such as sulfonamides, sulfones, and thioethers.[103, 105] Thioethers such as those studied in this triazole series comprise about 9% of the sulfur compounds currently found in sulfur containing drugs. A few of these thioether containing drugs include Singulair® and Brilinta®.[103, 105] Thioether containing compounds, such as pesticides, have been shown to have metabolic liability though, with oxidation to the sulfoxides and sulfones in human liver microsomes by CYP450's and FMO.[66]

Though many modifications were made within zone 1, only a few showed submicromolar IC_{50} values and within that, three were of interest, including the original cyclopentyl group. These three were structurally closely related given that all were carbocyclic groups with ring sizes of 5- or 6-carbons, and two were saturated and one was unsaturated. Given these minor differences and very specific requirements for activity, this indicates that the site where the zone 1 group resides is hydrophobic in nature and small in size. However, polarizability also appears to play an important role in binding. This is best shown in the case of the alkene containing cyclohex-2-ene versus the cyclohexane.[106] Though the cyclohexane analog was synthesized outside the scope of this thesis, to understand the importance of the alkene for potency, analogs differing only in the alkene showed a 2-fold difference in biochemical potency favoring the cyclohex-2-ene over the cyclohexane. Another possible benefit to the introduction of the double

bond in the cyclohex-2-ene analogs is the potential for π-π stacking between aromatic residues and the π system of the cyclohex-2-ene.[107] A π-π interaction within the binding site could explain why the 2-fluorocyclohex-2-ene analog resulted in a nearly 14-fold loss of activity in the biochemical assay.[63] Looking beyond the biochemical assay, the inclusion of a double bond can be beneficial due to the possibility of a reduction in lipophilicity and a reduction in entropy due to the limited number of conformations that can be adopted, both of these can subtly change the solubility of the molecule and affect the permeability as well.[74]

Deuteration within zone 1 was also well tolerated. Deuterium has been known to exist since the 1930's and has been incorporated into small molecules for decades primarily to study reaction mechanisms.[108] The use of deuterium in pharmaceuticals, however, dates back to the 1970's where its inclusion was said to improve PK properties and reduce toxicity.[109] The principle in which this proton to deuterium switch is made is based on the kinetic isotope effect (KIE). The KIE of deuterium is a mathematical calculation (DKIE = k_H/k_D) based on the theoretical rates of cleavage of the carbon-hydrogen and carbon-deuterium bond. This principle is based on the fact that the atomic mass of deuterium is higher than that of a hydrogen, and as a result, the vibrational energies calculated for carbon-deuterium bonds are lower than that for carbon-hydrogen bonds, and therefore, the zero-point energy (or lowest energy state) for carbon-deuterium bonds is lower than that for corresponding carbon-hydrogen bonds.[108] Consequently, carbon-deuterium bonds are theoretically harder to cleave due to higher activation energy and a slower reaction rate.[108] In the case of metabolism of small molecules, this principle is not always the most important driver when a hydrogen-deuterium switch is made to try to improve stability, and this is because in the complex system of metabolism of drug molecules by CYP450s, the resulting rate limiting step might not be at the site of this switch.[110] Despite these challenges in

predicting useful sites of deuterium incorporation, it has been a strategy that has been employed successfully in a number of clinical candidates and resulted in the first deuterated FDA approved drug entering the market. Deutetrabenazine or Austedo® was found by Teva Pharmaceuticals Industries Ltd. as a deuterated derivative of an older drug, tetrabenazine, in which the methoxy groups on the phenyl ring were replaced with trideuteromethoxy groups (Figure 2-13) as a treatment for the involuntary movement disorder chorea typically associated with Huntington's disease and tardive dyskinesia.[111] Deuteration in the case of deutetrabenazine was shown to successfully reduce the rate of metabolism and increase half-life, as well as reduce the C_{max} of its active metabolites allowing for a more favorable, lower dosing regimen in humans relative to tetrabenazine.[112] Based on the recent successful movement of a number of deuterated small molecules into the clinic and Austedo® into the market, it is likely that incorporation of deuterium is a trend that will likely continue in the field of medicinal chemistry.

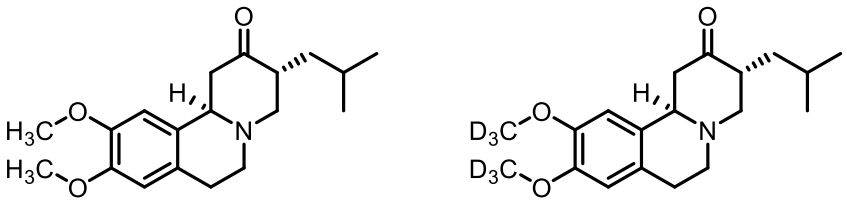


Figure 2-13. Structures of tetrabenazine and Austedo®.[111]

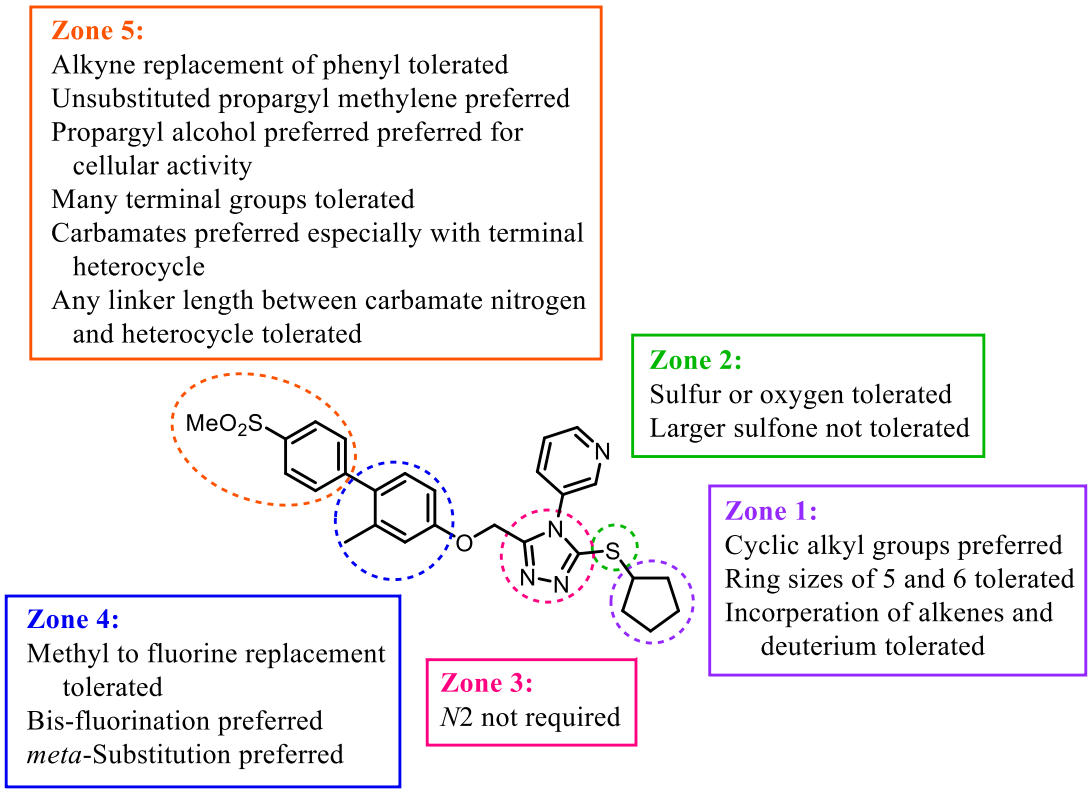


Figure 2-14. SAR summary for triazole derivatives of **NMS-873**.

Still necessary for the full understanding of the SAR of the triazole series is the determination of the binding mode within p97. Though Magnaghi et al. showed through photo cross-linking studies that very early analogs of the triazole bound in a tunnel between two adjacent D1 domains and a D2 domain of p97 (Figure 2-15), further studies need to be carried out on advanced analogs to verify that the newer and more complex compounds bind to the same region. Given that a large number of modifications were made to the tail region (zones 4 and 5) it stands to reason that these modifications that resulted in increased potency could direct the molecule into a new region of the binding pocket and potentially a new pocket altogether. Therefore, further efforts toward confirming this initial result need to be carried out to resolve the binding site of this series.

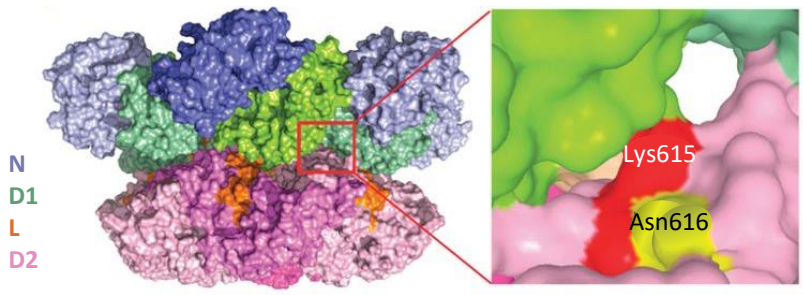


Figure 2-15. Location of the triazole binding site proposed by Magnaghi et al. [62]

Location of alkylsulfanyl-1,2,4-triazole binding site in a 3D representation of the p97 hexamer as determined by cross-linked amino acid location. N domains (purple), D1 domains (green), D1/D2 linkers (orange), D2 domains (pink).[62]

Overall, an extensive SAR effort was conducted to improve the biochemical activity of the **NMS-873** scaffold with consideration made for changes that would impact its physiochemical properties as well. Thanks to the development of a new synthetic route which allowed for incorporation of a wider range of moieties, a large library of analogs which explored nearly all regions of the original scaffold were prepared. While trying to distinguish the current triazole series from that published by Nerviano and Genentech, fragments previously beneficial in the phenyl indole SAR campaign were utilized to improve the activity of this triazole series. In addition, during further attempts to differentiate the phenol region and potentially remove metabolically labile sites, the preferred di-fluorophenols in zone 4 were serendipitously found to significantly improve activity. After the second stage optimization effort, five compounds were identified that showed significant and the best overall improvement in the biochemical potency relative to **NMS-873** (3- to 4-fold).

3.0 EXPERIMENTALS

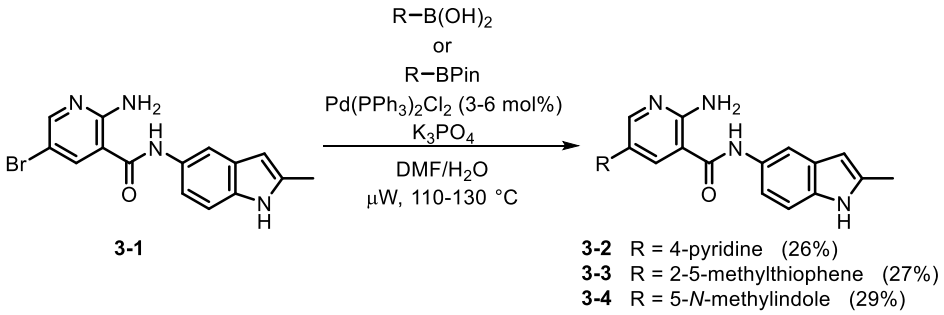
3.1 GENERAL EXPERIMENTAL

Reactions were carried out under nitrogen or argon unless stated otherwise. Glassware was dried in an oven at 130 °C for at least 30 minutes followed by flame drying prior to use. THF was distilled over sodium/benzophenone ketyl or purified using an alumina column filtration system, diethyl ether was distilled over sodium/benzophenone ketyl, CH_2Cl_2 was distilled over calcium hydride or purified using an alumina column filtration system, methanol, ethanol, *t*-butanol, and 1,4-dioxane were dried 4Å molecular sieves, DMF was dried using a neutral alumina column, ethyl acetate was dried by filtering through a SiO_2 column. Reagent grade Et_3N, DiPEA, acetone, DMAc, and MeCN were used without treatment. HPLC grade water was used without treatment. Solvents were used without degassing unless otherwise stated. Solvents and solutions that were deoxygenated were sparged with nitrogen or argon for at least 30 minutes before being transferred into the reaction unless stated otherwise. Reactions carried out at 0 °C or -5 °C used an ice bath, reactions at -78 °C used an acetone/dry ice bath, and reactions at -20 °C used a brine/ice bath. Microwave reactions were performed in glass microwave vials (sealed cap) with continuous magnetic stirring and an external surface temperature sensor in a Biotage Initiator microwave reactor. Reactions were monitored by TLC (on pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and were visualized by 254 nm UV light followed by staining with a

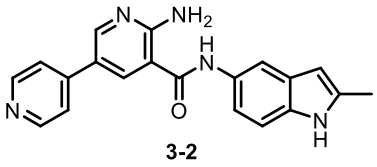
$KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution) or PMA solution (10 g of phosphomolybdic acid in 100 mL of absolute ethanol) unless otherwise stated. Reactions were used without purification unless stated otherwise. Reactions that were purified via chromatography were carried out on SiO_2 (SiliaFlash® F60, Silicycle) or using and ISCO-Rf chromatography system on prepacked SiO_2 columns (RediSep® Rf, 40-60 μm, Teledyne ISCO) or on reusable columns packed with SiO_2 (SiliaFlash® F60, Silicycle).

Melting points (uncorrected) were determined using a Mel-Temp instrument. Infrared spectra (IR) were collected on a Perkin Elmer ATR IR. ^1H NMR spectrum were obtained at 300, 400, 500, or 600 MHz on a Bruker Avance III 300MHz, 400MHz, 500MHz, or 600MHz, respectively, instrument using $CDCl_3$ unless stated otherwise. All experiments were run at room temperature, approximately 296 K. Chemical shifts are reported in parts per million (ppm) using the residual solvent peak as an internal standard. ^1H spectral details reported as chemical shift, multiplicity (s= singlet, d= doublet, t= triplet, q= quartet, quintet, sept= septet, m= multiplet, dd= doublet of doublets, ddd= doublet of doublet of doublets, dt= doublet of triplets, ddt= doublet of doublet of triplets, dtd= doublet of triplet of doublets, dq= doublet of quartets, bs= broad singlet, app= apparent), coupling constant, number of protons. ^{13}C NMR spectra were run at 100, 125, or 150 MHz and are reported as chemical shift, multiplicity, coupling constant where applicable. ^{19}F NMR spectra were run at 376 or 471 MHz (uncalibrated) and are reported as chemical shift, multiplicity, coupling constant. High-resolution mass spectra (HRMS or LCMS) analyses were completed on a Thermo Scientific Exactive Orbitrap mass spectrometer using electrospray (ESI) ionization with purities of final compounds were determined using an Agilent Technologies 385-ELSD using $MeCN/H_2O$ with 0.1% formic acid; purities of final products were >95%.

3.2 UNPUBLISHED AMIDE INDOLE EXPERIMENTALS

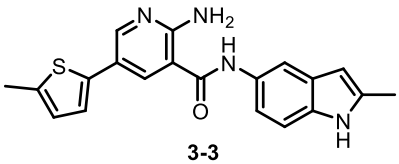


Scheme 3-1. Synthesis of amide indole analogs.



6-Amino-*N*-(2-methyl-1*H*-indol-5-yl)-[3,4'-bipyridine]-5-carboxamide (3-2).[54] To a solution of 2-amino-5-bromo-N-(2-methyl-1*H*-indol-5-yl)nicotinamide (0.10 g, 0.29 mmol) in deoxygenated DMF (2.7 mL) was added $Pd(PPh_3)_2Cl_2$ (0.01 g, 0.01 mmol) and pyridine-4-boronic acid (0.05 g, 0.43 mmol) followed by K_3PO_4 (0.12 g, 0.58 mmol) and deoxygenated water (0.68 mL). The reaction vial was sealed and heated in a Biotage Initiator microwave under argon at 120 °C for 1 h. The resulting mixture was diluted with EtOAc, washed with water, dried ($MgSO_4$), filtered, and concentrated with SiO_2. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). Product **3-2** was obtained as pale yellow solid (0.05 g, 53%): m.p. 185 °C (dec.); IR (neat) 3285, 3135, 1631, 1595, 1564, 1451, 1247, 1000, 796 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 9.99 (bs, 1 H), 9.54 (s, 1 H), 8.59 (d, *J* = 4.8 Hz, 3 H), 8.50 (s, 1 H), 7.88 (s, 1 H), 7.70 (d, *J* = 5.5 Hz, 2 H), 7.37 – 7.22 (m, 2 H), 7.09 (bs, 1 H), 6.15 (s, 1 H), 2.42 (d, *J* = 4.1 Hz, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.8, 160.5, 151.2,

150.6, 145.8, 137.3, 135.5, 134.9, 131.7, 130.1, 122.4, 120.9, 116.1, 116.0, 112.8, 111.9, 110.9, 100.7, 13.6; HRMS (ESI): *m/z* calculated for $C_{20}H_{18}ON_5$ (M+H) 344.1506, found 344.1504; ELS purity (100%).

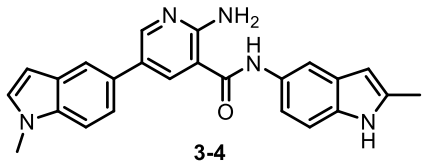


3-3

4,4,5,5-Tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane.[113] To a solution of 2-methylthiophene (0.25 mL, 2.50 mmol) in THF (12.5 mL) at -78 °C was added *n*-BuLi (2.22 mL, 2.99 mmol) dropwise. The reaction was then stirred at -78 °C for 1 h followed by 1 h at room temperature. The solution was cooled to -78 °C and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.14 mL, 5.49 mmol) was slowly added and then stirred for 1 h. The reaction was warmed to room temperature and stirred for 7 h. Water (7 mL) and diethyl ether (5 mL) were added and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude 4,4,5,5-tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane was obtained as a pale-yellow oil (0.41 g, 73%) and carried on without further purification or characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 3.3 Hz, 1 H), 6.84 (m, 1 H), 2.53 (d, *J* = 0.6 Hz, 3 H), 1.33 (s, 12 H).

2-Amino-*N*-(2-methyl-1*H*-indol-5-yl)-5-(5-methylthiophen-2-yl)nicotinamide (3-3).[54] To a solution of 2-amino-5-bromo-N-(2-methyl-1*H*-indol-5-yl)nicotinamide (0.10 g, 0.29 mmol) in deoxygenated DMF (2.7 mL) was added $Pd(PPh_3)_2Cl_2$ (6.0 mg, 0.01 mmol) and 4,4,5,5-tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane (0.13 g, 0.58 mmol) followed by K_3PO_4 (0.12 g, 0.58 mmol) and deoxygenated water (0.68 mL). The reaction vial was sealed and

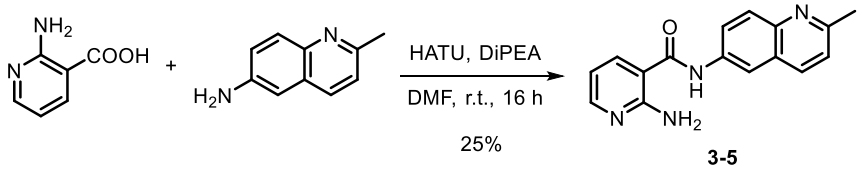
heated in a Biotage Initiator microwave under argon at 120 °C for 1 h. The resulting mixture was diluted with EtOAc, washed with water, dried ($MgSO_4$), filtered, and concentrated with SiO_2. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). Product **3-3** was obtained as a yellow solid (0.03 g, 27%): m.p. 202 °C (dec.); IR (neat) 3533, 3464, 3408, 3285, 3143, 1635, 1531, 1445, 1243, 917, 791 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 9.97 (bs, 1 H), 9.53 (s, 1 H), 8.35 (d, *J* = 2.6 Hz, 1 H), 8.22 (d, *J* = 2.5 Hz, 1 H), 7.89 (s, 1 H), 7.33 (d, *J* = 8.5 Hz, 1 H), 7.26 (d, *J* = 8.5 Hz, 1 H), 7.13 (t, *J* = 3.0 Hz, 1 H), 6.88 (s, 2 H), 6.76 (s, 1 H), 6.15 (s, 1 H), 2.48 (s, 3 H), 2.42 (d, *J* = 2.0 Hz, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.0, 158.3, 148.0, 138.6, 138.1, 136.4, 134.0, 133.1, 130.9, 129.2, 126.2, 122.2, 119.7, 115.2, 111.9, 111.0, 110.0, 99.8, 14.3, 12.8; HRMS (ESI): *m/z* calculated for $C_{20}H_{19}ON_4S$ (M+H) 363.1274, found 363.1278; ELS purity (100%).



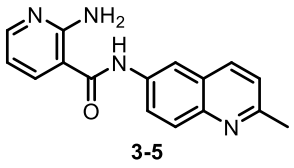
3-4

2-Amino-5-(1-methyl-1*H*-indol-5-yl)-*N*-(2-methyl-1*H*-indol-5-yl)nicotinamide (3-4). To a solution of 2-amino-5-bromo-N-(2-methyl-1*H*-indol-5-yl)nicotinamide (0.06 g, 0.17 mmol) in deoxygenated DMF (1.64 mL) was added $Pd(PPh_3)_2Cl_2$ (3.0 mg, 0.01 mmol) and *N*-methylindole-5-boronic acid (0.05 g, 0.26 mmol) followed by K_3PO_4 (0.07 g, 0.35 mmol) and deoxygenated water (0.41 mL). The reaction was microwaved under argon at 110 °C for 1 h. The resulting mixture was diluted with EtOAc, washed with water, dried ($MgSO_4$), filtered, and concentrated with SiO_2. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0) (2x). Product **3-4** was obtained as an off-white solid (0.01 g, 20%): m.p. 230°C (dec.); IR (neat) 3464, 3417, 3262, 3100, 1631, 1466, 1289, 1240, 1186, 858,

781, 725 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.97 (bs, 1 H), 9.54 (s, 1 H), 8.46 (d, *J* = 2.3 Hz, 1 H), 8.33 (d, *J* = 2.2 Hz, 1 H), 7.92 (d, *J* = 2.0 Hz, 1 H), 7.82 (d, *J* = 1.4 Hz, 1 H), 7.48 (d, *J* = 1.3 Hz, 2 H), 7.35 (dd, *J* = 8.6, 2.1 Hz, 1 H), 7.26 (dd, *J* = 5.9, 2.8 Hz, 2 H), 6.76 (bs, 2 H), 6.48 (d, *J* = 3.0 Hz, 1 H), 6.15 (s, 1 H), 3.87 (s, 3 H), 2.42 (s, 3 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 167.3, 150.3, 137.2, 135.4, 134.8, 132.0, 130.8, 130.2, 130.1, 127.6, 121.0, 118.9, 116.1, 112.8, 110.9, 110.7, 101.7, 100.7, 33.0, 13.6; HRMS (ESI): *m/z* calculated for $C_{24}H_{22}ON_5$ (M+H) 396.1819, found 396.1817; ELS purity (100%).



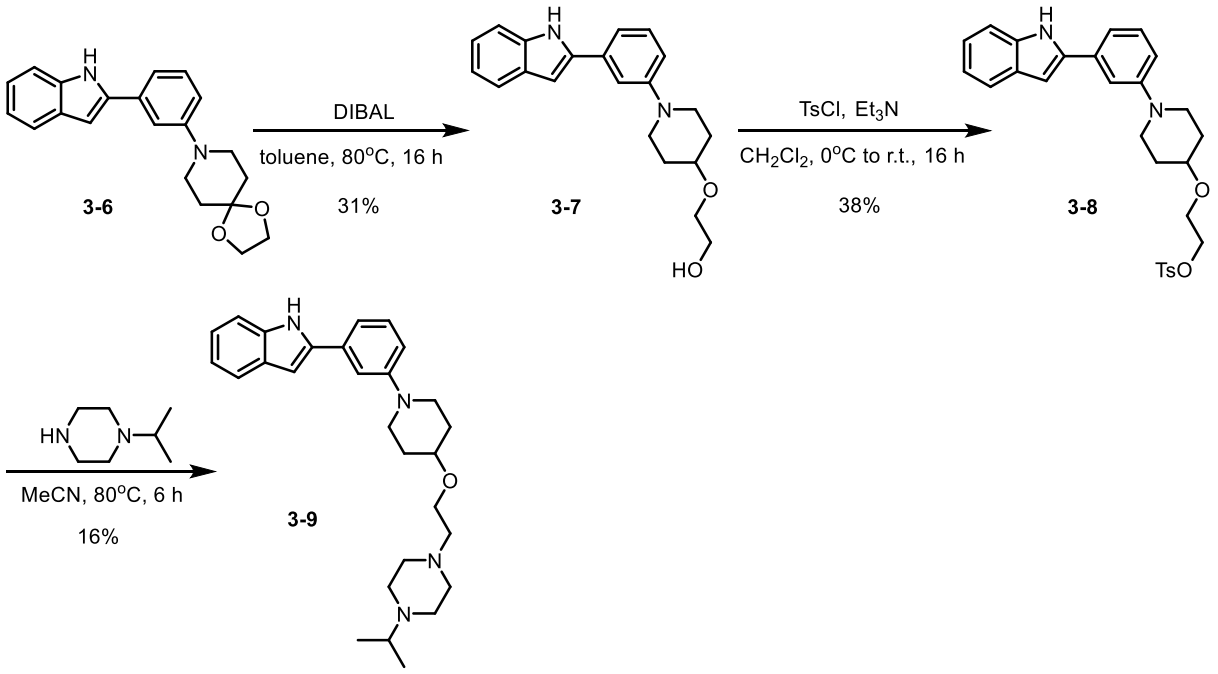
Scheme 3-2. Synthesis of 2-methylquinoline indole replacement.



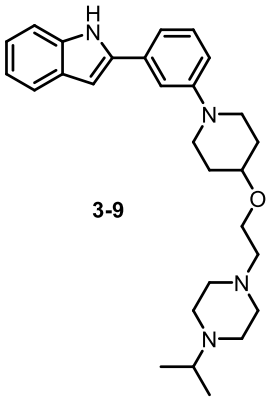
2-Amino-*N*-(2-methylquinolin-6-yl)nicotinamide (3-5).[54] To a solution of 2-aminonicotinic acid (0.04 g, 0.31 mmol) in DMF (1.25 mL) was added DiPEA (0.21 mL, 1.23 mmol) and HATU (0.14 g, 0.37 mmol) and stirred for 40 min under argon. 5-Amino-2-methylquinoline (0.05 g, 0.31 mmol) was added and the reaction stirred at room temperature 16 h. The reaction was diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The solid was washed with CH_2Cl_2 followed by purification by chromatography on SiO_2 (MeOH/CH_2Cl_2: 0/100 to 10/90) (2x) followed by chromatography on SiO_2 (ISCO, MeOH/ CH_2Cl_2: 0/100 to 5/95). The product was then precipitated from CH_2Cl_2 with cyclohexanes. The

solid was then triturated with distilled hexanes (5x). Product **3-5** was obtained as a pale yellow solid (0.02 g, 25%): m.p. 215-217 °C (dec.); IR (acetone) 3488, 3326, 3080, 2922, 1659, 1598, 1548, 1378, 1287, 1126, 822, 775 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.73 (bs, 1 H), 8.44 (d, *J* = 2.4 Hz, 1 H), 8.18 – 8.10 (m, 3 H), 7.96 (dd, *J* = 9.1, 2.4 Hz, 1 H), 7.91 (d, *J* = 9.0 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 1 H), 6.82 (bs, 3 H), 6.66 (dd, *J* = 7.7, 4.8 Hz, 1 H), 2.65 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.9, 159.4, 157.6, 152.0, 145.2, 136.5, 136.4, 135.6, 129.0, 126.8, 123.9, 122.3, 116.5, 111.7, 110.2, 24.3; HRMS (ESI): *m/z* calculated for $C_{16}H_{15}ON_4$ (M+H) 279.1239, found 279.1240; ELS purity (98.3%).

3.3 UNPUBLISHED PHENYL INDOLE EXPERIMENTALS



Scheme 3-3. Synthesis of oxygen linker replacement.

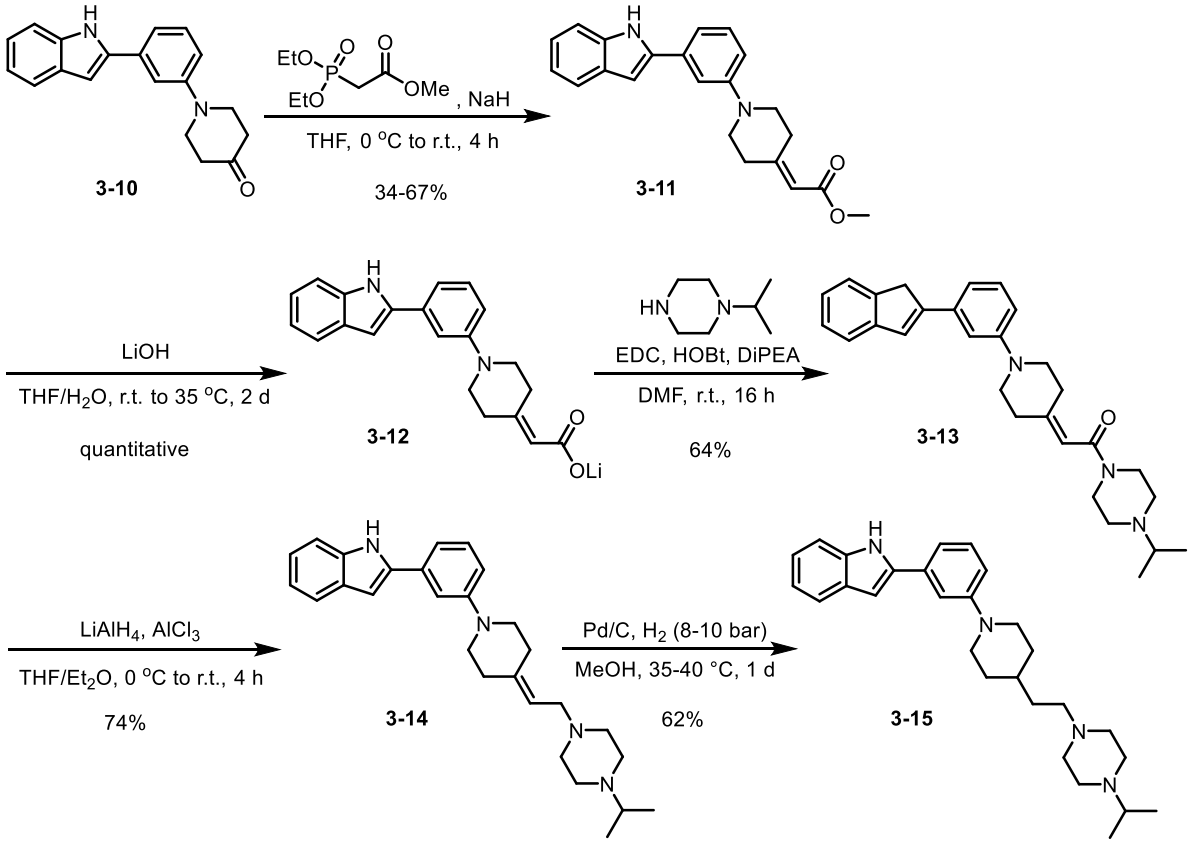


3-9

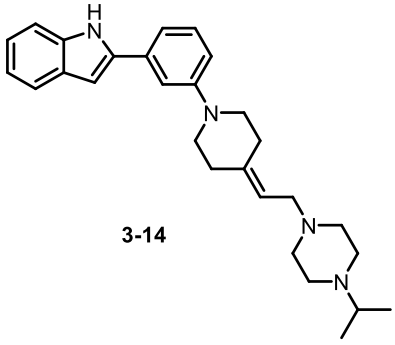
2-((1-(3-(1*H*-Indol-2-yl)phenyl)piperidin-4-yl)oxy)ethan-1-ol (3-7).[114] To a solution of 8-(3-(1*H*-indol-2-yl)phenyl)-1,4-dioxa-8-azaspiro[4.5]decane (0.50 g, 1.50 mmol) in toluene (4.5 mL) at 0 °C was added DIBAL (4.34 mL, 4.34 mmol, 1M). The reaction was stirred at 80 °C 16 h. The reaction was quenched with brine (4.3 mL) and the aqueous was extracted with EtOAc (3x). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The product was combined with a previous batch and purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 40/60 to 60/40). Indole **3-7** was obtained impure as a pink film (0.298 g, 52% combined) and carried on without further purification or characterization: HRMS (ESI): *m/z* calculated for $C_{21}H_{25}O_2N_2$ (M+H) 337.1911, found 337.1909.

2-((1-(3-(1*H*-Indol-2-yl)phenyl)piperidin-4-yl)oxy)ethyl 4-methylbenzenesulfonate (3-8).[115] To a solution of **3-2** (0.29 g, 0.85 mmol) in CH_2Cl_2 (8.8 mL) at 0 °C was added Et_3N (0.18 mL, 1.27 mmol) and DMAP (0.01 g, 0.08 mmol) followed by p-toluenesulfonyl chloride (0.16 g, 0.85 mmol). The reaction was warmed to room temperature and stirred 16 h. The reaction was quenched with ice water and organic layer was separated, washed with brine, dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 40/60). Indole **3-8** was obtained impure as a pink goo (0.26 g, 61%) and carried on without further purification or characterization: HRMS (ESI): *m/z* calculated for $C_{28}H_{31}O_4N_2S$ (M+H) 491.1999, found 491.2000.

2-(3-(4-(2-(4-Isopropylpiperazin-1-yl)ethoxy)piperidin-1-yl)phenyl)-1*H*-indole (3-9).[116] To a solution of **3-3** (0.13 g, 0.25 mmol) in MeCN (0.4 mL) was added 1-isopropylpiperazine (75 µL, 0.51 mmol) and the reaction stirred at 80 °C for 6 h. The reaction was then cooled to room temperature and quenched with brine. The aqueous was extracted with MeCN (3x), dried (Na_2SO_4), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). Product **3-9** was obtained as a light brown foam (0.019 g, 17%): IR (neat) 3245, 2925, 2823, 1601, 1454, 1219, 1175, 1120, 1010, 778, 726, 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1 H), 7.80 (d, *J* = 7.8 Hz, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.33 – 7.23 (m, 1 H), 7.21 – 7.03 (m, 3 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 6.78 (s, 1 H), 3.61 – 3.50 (m, 4 H), 3.44 (tt, *J* = 8.7, 4.1 Hz, 1 H), 2.97 (ddd, *J* = 12.7, 9.2, 3.2 Hz, 3 H), 2.79 (s, 9 H), 2.63 (t, *J* = 5.5 Hz, 2 H), 1.97 (t, *J* = 6.6 Hz, 3 H), 1.70 (dtd, *J* = 13.0, 9.1, 3.6 Hz, 2 H), 1.12 (d, *J* = 6.7 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 142.5, 140.0, 138.6, 136.9, 133.3, 129.6, 129.2, 128.9, 125.9, 122.0, 120.4, 119.9, 116.5, 115.8, 113.3, 111.3, 99.4, 65.0, 57.4, 56.3, 51.4, 47.8, 47.2, 21.4, 17.4; HRMS (ESI): *m/z* calculated for $C_{28}H_{39}ON_4$ (M+H) 447.3118, found 447.3116; ELS purity (98.8%).



Scheme 3-4. Synthesis of carbon linker replacement analogs.



1-(3-(1*H*-Indol-2-yl)phenyl)piperidin-4-one (3-10)[vi]**.** A solution of 8-(3-(1*H*-indol-2-yl)phenyl)-1,4-dioxa-8-azaspiro[4.5]decane (0.70 g, 2.09 mmol) in acetone (250 mL) and 3.6 N HCl (250 mL) was heated at reflux for 4 h. The reaction was then cooled to 0 °C, quenched with

[vi] Full characterization by Raffaele Colombo

K_2CO_3 (to pH 7), and extracted with EtOAc (3x). The combined organic layers were combined, concentrated, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The product was purified by chromatography on SiO_2 (EtOAc/Hexanes: 25/75). Indole **3-10** was obtained as a pale pink solid (0.45 g, 77%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (bs, 1 H), 7.64 (d, *J* = 7.8 Hz, 1 H), 7.38 (ABq, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 7.7 Hz, 2 H), 7.28-7.27 (m, 1 H), 7.23-7.10 (m, 3 H), 6.95 (dd, *J* = 8.1, 2.1 Hz, 1 H), 6.82 (d, *J* = 1.5 Hz, 1 H), 3.69 (t, *J* = 6 H, 4 H), 2.61 (t, *J* = 6.2 Hz, 4 H); HRMS (ESI): *m/z* calculated for $C_{19}H_{19}ON_2$ (M+H) 291.1492, found 291.1489.

Methyl 2-(1-(3-(1*H*-indol-2-yl)phenyl)piperidin-4-ylidene)acetate (3-11)[vii]**.** To a suspension of NaH (0.09 g, 2.30 mmol) in dry THF (5 mL) at 0 °C was added dropwise a solution of methyl diethylphosphonoacetate (0.44 mL, 2.30 mmol) in dry THF (5 mL) and the mixture was stirred for 1 h. A solution of **3-10** (0.45 g, 1.53 mmol) in dry THF (3 mL) was added dropwise at 0 °C. The reaction was warmed to room temperature and stirred for 3 h. The reaction was quenched with brine (50 mL), extracted with EtOAc (4x), washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 30/70). Indole **3-11** was obtained as a light tan foam (0.36 g, 67%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (bs, 1 H), 7.64 (d, *J* = 7.6 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.34 (t, *J* = 7.8 Hz, 1 H), 7.23-7.10 (m, 4 H), 6.92 (dd, *J* = 8.2, 2.2 Hz, 1 H), 6.81 (d, *J* = 1.2 Hz, 1 H), 5.76 (s, 1 H), 3.72 (s, 3 H), 3.42 (p, *J* = 5.6 Hz, 4 H), 3.15 (t, *J* = 5.6 Hz, 2 H), 2.49 (t, *J* = 5.4 Hz, 2 H); HRMS (ESI): *m/z* calculated for $C_{22}H_{23}O_2N_2$ (M+H) 347.1754, found 347.1753.

[vii] Full characterization by Zhizhou Yue

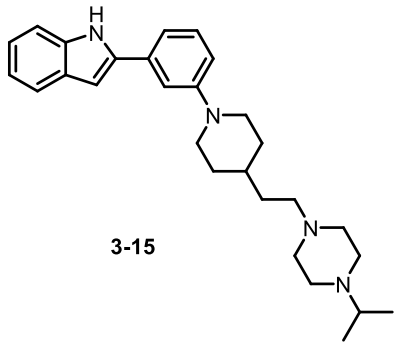
Lithium 2-(1-(3-(1H-indol-2-yl)phenyl)piperidin-4-ylidene)acetate (3-12)[viii]**.** To a mixture of **3-11** (0.35 g, 1.01 mmol) in THF (9.8 mL) and H_2O (4.9 mL) was added LiOH monohydrate (0.05 g, 2.02 mmol) in one portion. This yellow mixture was then stirred at room temperature 16 h. Additional LiOH monohydrate (0.012 g, 0.50 mmol) was added and the reaction was stirred at 35 °C 16 h. The reaction was concentrated to give **3-12** as a pale-yellow solid (0.35 g, + LiOH) and carried on without further characterization: HRMS (ESI): *m/z* calculated for $C_{21}H_{21}O_2N_2$ (M+H) 333.1598, found 333.1596.

2-(1-(3-(1*H*-Indol-2-yl)phenyl)piperidin-4-ylidene)-1-(4-isopropylpiperazin-1-yl)ethan-1-one (3-13)[ix]**.** To a solution of **3-12** (0.15 g, 0.44 mmol) in dry DMF (2.2 mL) was added *N*-isopropylpiperazine (65 µL, 0.49 mmol) followed by EDC (0.10 g, 0.53 mmol), HOBt (0.07 g, 0.53 mmol), and DiPEA (0.15 mL, 0.88 mmol) and reaction was stirred at room temperature 16 h. The reaction was then diluted with sat. $NaHCO_3$ (10 mL), extracted with EtOAc (3x), washed with brine, dried (Na_2SO_4), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 10/90) (x2). Indole **3-13** was obtained as an off-white solid (0.13 g, 64%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (bs, 1 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.41 (d, *J* = 8.4 Hz, 1 H), 7.33 (t, *J* = 7.8 Hz, 1 H), 7.23-7.09 (m, 4 H), 6.91 (app d, *J* = 6.6 Hz, 1 H), 6.80 (s, 1 H), 5.88 (s, 1 H), 3.68 (app bs, 2 H), 3.55 (app bs, 2 H), 3.40 (p, *J* = 5.5 Hz, 4 H), 2.72 (t, *J* = 5.3 Hz, 3 H), 2.48-2.44 (m, 6 H), 1.05 (d, *J* = 6.3 Hz, 6 H); HRMS (ESI): *m/z* calculated for $C_{28}H_{35}ON_4$ (M+H) 443.2805, found 443.2803.

[viii] Full characterization of the carboxylic acid by Zhizhou Yue

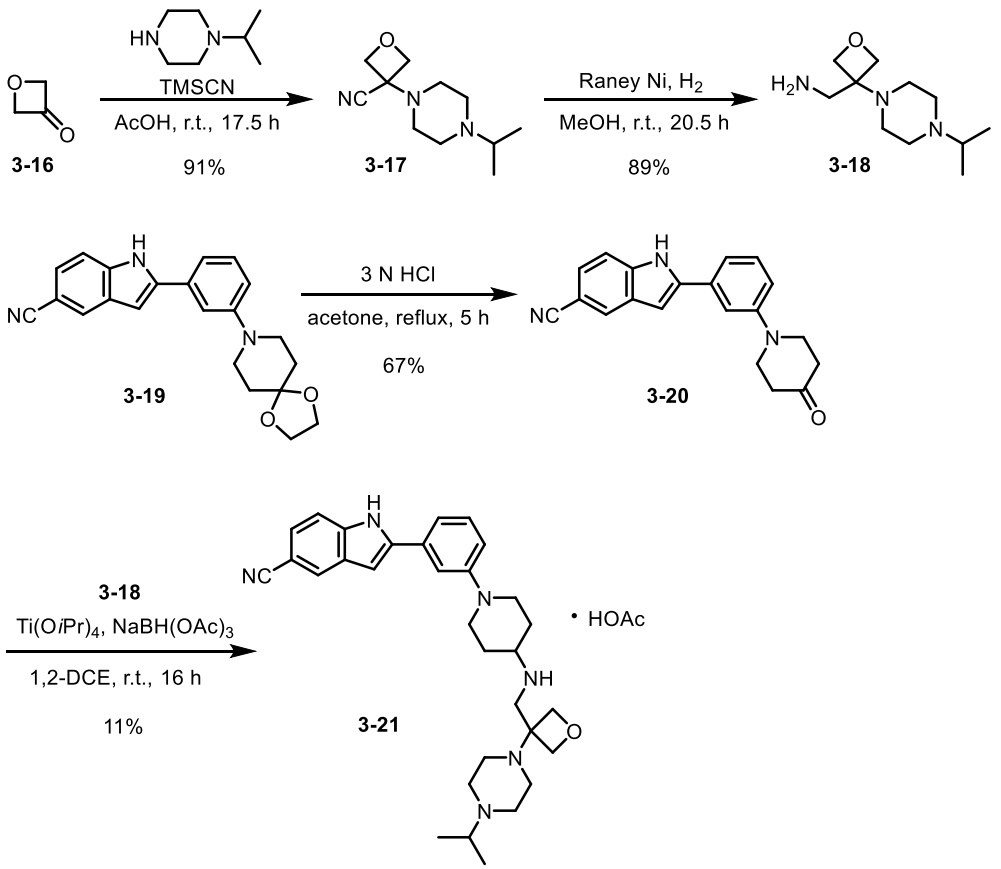
[ix] Full characterization of the 4-methyl piperazine analog by Zhizhou Yue

2-(3-(4-(2-(4-Isopropylpiperazin-1-yl)ethylidene)piperidin-1-yl)phenyl)-1*H*-indole (3-14). To a solution of $LiAlH_4$ (0.19 mL, 0.28 mmol, 1M) in diethyl ether (0.3 mL) at 0 °C was added $AlCl_3$ (0.04 g, 0.28 mmol) in diethyl ether (0.36 mL) and the suspension stirred for 45 min. A solution of **3-13** (0.08 g, 0.19 mmol) in THF (0.13 mL) was then added dropwise and the reaction stirred at room temperature for 2 h. The reaction was cooled to 0 °C and quenched with water (0.07 mL), NaOH (0.2 mL, 1 M), and water (0.21 mL). The aqueous was extracted with EtOAc, the combined organic layers dried (Na_2SO_4), filtered, and concentrated. The product was filtered through a plug of basic Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 5/95). Product **3-14** was obtained as an off-white foam (0.06 g, 74%): IR (neat) 3177, 3058, 2964, 2813, 1601, 1453, 1336, 1211, 1175, 1002, 776, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.42 – 7.36 (m, 1 H), 7.31 (t, *J* = 7.9 Hz, 1 H), 7.25 – 7.14 (m, 2 H), 7.16 – 7.07 (m, 2 H), 6.91 (dd, *J* = 8.3, 2.4 Hz, 1 H), 6.80 (dd, *J* = 2.0, 0.9 Hz, 1 H), 5.39 (t, *J* = 7.2 Hz, 1 H), 3.31 (dt, *J* = 11.5, 5.7 Hz, 4 H), 3.04 (d, *J* = 7.2 Hz, 2 H), 2.66 (p, *J* = 6.5 Hz, 1 H), 2.58 (s, 7 H), 2.45 (t, *J* = 5.8 Hz, 2 H), 2.39 (t, *J* = 5.5 Hz, 2 H), 1.06 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 139.1, 138.6, 136.7, 133.4, 129.8, 129.3, 122.2, 120.6, 120.2, 119.6, 116.4, 116.0, 113.4, 110.9, 100.0, 55.0, 54.4, 53.5, 51.5, 50.5, 48.7, 35.8, 28.4, 18.7; HRMS (ESI): *m/z* calculated for $C_{28}H_{37}N_4$ (M+H) 429.3013, found 429.3010; ELS purity (100%).

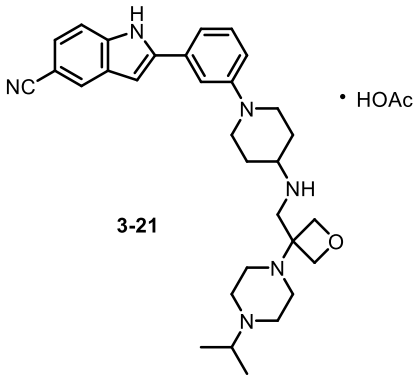


3-15

2-(3-(4-(2-(4-Isopropylpiperazin-1-yl)ethyl)piperidin-1-yl)phenyl)-1*H*-indole (3-15). To a solution of **3-14** (0.032 g, 0.075 mmol) in MeOH (1.7 mL) was added Pd/C (2.0 mg, 0.004 mmol). The reaction was stirred in the Parr hydrogenator under H_2 (8 bar) at 35 °C 16 h. Additional Pd/C (2.0 mg, 0.004 mmol) was added and the reaction was stirred under H_2 (10 bar) at 40 °C for 6 h. The reaction was filtered through Celite, washed with MeOH, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). Product **3-15** was obtained as a tan foam (0.020 g, 62%): IR (neat) 3194, 2923, 2810, 1600, 1453, 1359, 1299, 1176, 967, 775, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (bs, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.30 (t, *J* = 7.9 Hz, 1 H), 7.25 (d, *J* = 2.1 Hz, 1 H), 7.20 – 7.07 (m, 3 H), 6.89 (dd, *J* = 8.2, 2.5 Hz, 1 H), 6.79 (d, *J* = 1.9 Hz, 1 H), 3.73 (d, *J* = 11.6 Hz, 2 H), 2.84 – 2.53 (m, 11 H), 2.47 – 2.38 (m, 2 H), 1.78 (d, *J* = 9.7 Hz, 2 H), 1.53 – 1.33 (m, 5 H), 1.10 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 138.7, 136.8, 133.3, 129.6, 129.3, 122.1, 120.5, 120.1, 116.4, 116.0, 113.5, 111.0, 99.7, 55.9, 54.9, 52.6, 49.9, 48.1, 34.2, 33.2, 32.3, 18.2; HRMS (ESI): *m/z* calculated for $C_{28}H_{39}N_4$ (M+H) 431.3169, found 431.3170; ELS purity (100%).



Scheme 3-5. Synthesis of the oxetane-containing linker analog.



3-(4-Isopropylpiperazin-1-yl)oxetane-3-carbonitrile (3-17)[117]**.** To AcOH (3.2 mL) at 0 °C was added 1-isopropylpiperazine (1.49 mL, 10.1 mmol) followed by 3-oxetanone (133 µL, 2.02 mmol) and TMSCN (687 µL, 5.05 mmol). The reaction was warmed to room temperature and stirred 16 h. The reaction was diluted with CH_2Cl_2 (10 mL) and basified to pH 9 with NaOH (32% w/w). The aqueous was extracted with CH_2Cl_2 (2x) and the combined organic layers were

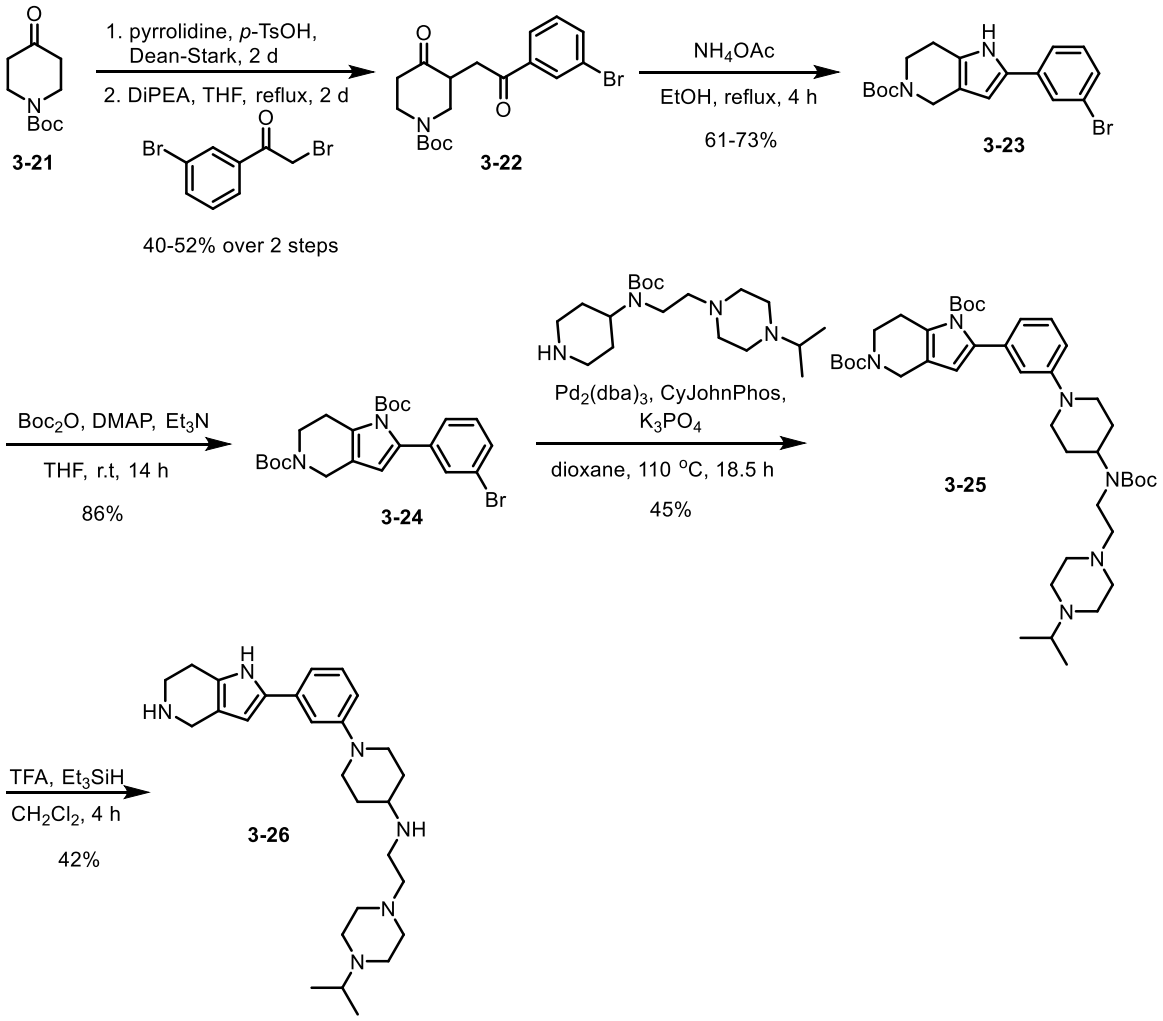
dried (Na_2SO_4), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). Oxetane **3-17** was obtained as a pale yellow crystalline solid (0.383g, 91%): m.p. 80-82 °C; IR (neat) 2960, 2884, 2824, 1453, 1365, 1273, 1226, 1178, 1146, 994, 983, 925, 787 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.79 (d, *J* = 6.4 Hz, 2 H), 4.65 (d, *J* = 6.4 Hz, 2 H), 2.71 (sept, *J* = 6.7 Hz, 1 H), 2.62 (bs, 4 H), 2.47 (t, *J* = 4.8 Hz, 4 H), 1.05 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.4, 59.0, 54.3, 47.7, 46.2, 18.4; HRMS (ESI): *m/z* calculated for $C_{11}H_{20}ON_3$ (M+H) 210.1601, found 210.1600.

(3-(4-Isopropylpiperazin-1-yl)oxetan-3-yl)methanamine (3-18)[118]**.** To a solution of **3-17** (0.150 g, 0.717 mmol) in MeOH (12.8 mL) was added a catalytic amount of Raney-Ni (15 drops). The reaction was sparged for 10 sec with H_2 and the reaction was stirred under an atmosphere of H_2 16 h. The reaction was filtered through a pad of Celite, washed with THF, and concentrated. Oxetane **3-18** was obtained as a yellow oil (0.136 g, 89%) and carried on without further purification or characterization: ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (d, *J* = 6.6 Hz, 2 H), 4.28 (d, *J* = 6.3 Hz, 2 H), 3.11 (s, 2 H), 2.67-2.56 (m, 9 H), 1.20 (bs, 2 H), 1.06 (d, *J* = 6.6 Hz, 6 H).

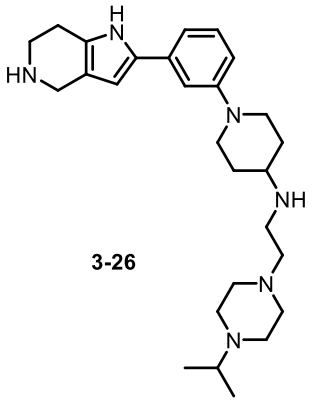
2-(3-(4-Oxopiperidin-1-yl)phenyl)-1*H*-indole-5-carbonitrile (3-20). To a solution of 2-(3-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)phenyl)-1*H*-indole-5-carbonitrile (0.150 g, 0.417 mmol) in acetone (53 mL) was added HCl (3 M, 53 mL) at room temperature and the reaction was heated to reflux. After 4.75 h, the solution was cooled to room temperature and allowed to stir at room temperature for 16 h. The reaction was cooled to 0 °C and neutralized with Na_2CO_3. The mixture was extracted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 50/50).

Indole **3-20** was obtained as a yellow solid (0.088 g, 67%) and carried on without further characterization: HRMS (ESI): *m/z* calculated for $C_{20}H_{18}ON_3$ (M+H) 316.1444, found 316.1442.

2-(3-(4-(((3-(4-Isopropylpiperazin-1-yl)oxetan-3-yl)methyl)amino)piperidin-1-yl)phenyl)-1*H*-indole-5-carbonitrile acetate (3-21). To a solution of **3-20** (0.050 g, 0.162 mmol), **3-18** (0.038 g, 0.178 mmol) in 1,2-DCE (1.6 mL) was added Ti(O*i*Pr)$_4$ (0.075 mL, 0.244 mmol) at room temperature. After 30 min, NaBH(OAc)$_3$ (0.025 g, 0.081 mmol) was added. After 1 h, additional NaBH(OAc)$_3$ (0.025 g, 0.081 mmol) was added and the solution was stirred at rooom temperature. After 8 h, additional NaBH(OAc)$_3$ (0.025 g, 0.081 mmol) was added. After 16 h, trace product by LCMS was seen. An additional 0.95 mL 1,2-DCE and 0.5 mL CH_2Cl_2 were added along with Ti(O*i*Pr)$_4$ (0.10 mL) and **3-18** (0.050 g) and stirred at room temperature. After 30 min, NaBH(OAc)$_3$ (0.025 g, 0.081 mmol) was added (3x). The reaction was filtered through a pad of Celite. The Celite was washed with CH_2Cl_2 and MeOH (collected separately). The MeOH wash was concentrated and washed with EtO_2 (3x). Product **3-21** was obtained as the acetate salt as a pale yellow solid (0.013 g, 10%): m.p. 220 °C (dec.); IR (neat) 2934, 2218, 1707, 1571, 1400, 1263, 1044, 974, 809, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/MeOD) δ 7.72 (d, *J* = 1.5 Hz, 1 H), 7.28 (d, *J* = 8.7 Hz, 1 H), 7.18 – 7.09 (m, 3 H), 7.08 – 7.04 (m, 1 H), 6.75 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.64 (s, 1 H), 4.55 (d, *J* = 6.7 Hz, 2 H), 4.20 (s, 4 H), 4.15 (d, *J* = 6.7 Hz, 2 H), 3.57 (d, *J* = 12.5 Hz, 2 H), 2.91 (s, 2 H), 2.72 – 2.60 (m, 4 H), 2.50 – 2.44 (m, 1 H), 1.85 (d, *J* = 12.8 Hz, 2 H), 1.79 (s, 4 H), 1.46 – 1.32 (m, 2 H), 0.95 (d, *J* = 6.6 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3 (AcOH), 151.7, 141.2, 139.1, 132.5, 129.7, 128.7, 125.6, 124.3, 121.1, 117.2, 116.6, 113.9, 112.0, 101.7, 99.2, 63.1, 55.8, 55.4, 44.4, 31.4, 22.0 (AcOH), 17.3; HRMS (ESI): *m/z* calculated for $C_{31}H_{41}ON_6$ (M+H) 513.3336, found 513.3336; ELS purity (98.6%).



Scheme 3-6. Synthesis of 4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine indole replacement.



3-26

***tert*-Butyl 4-oxopiperidine-1-carboxylate (3-21)**[119]**.** To at solution of 4-piperidone monohydrate hydrochloride (0.500 g, 3.22 mmol) in MeOH (7.4 mL) was added Et_3N (0.679 mL, 4.83 mmol) and the solution stirred for 5 min. Di-*tert*-butyl dicarbonate (0.896 mL, 4.19 mmol) was added slowly over 5 min followed by DMAP (tip of spatula). The reaction was stirred 16 h at room temperature. The solvent was removed in vacuo and the residue dissolved in CH_2Cl_2 (2.5 mL). The combined organic layers were washed with 2 N HCl (2x), sat. Na_2CO_3 (1.7 mL), and brine. Then dried (Na_2SO_4), filtered, and concentrated. Piperidine **3-21** was dried in vacuo and obtained as a white solid (0.619 g, 96%) and carried on without further purification or characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72 (t, *J* = 6.2 Hz, 4 H), 2.44 (t, *J* = 6.2 Hz, 4 H), 1.49 (s, 9 H).

***tert*-Butyl 3-(2-(3-bromophenyl)-2-oxoethyl)-4-oxopiperidine-1-carboxylate (3-22)**[120]**.** To a solution of **3-21** (1.00 g, 4.97 mmol) in toluene (13.4 mL) was added pyrrolidine (0.628 mL, 7.45 mmol) and *p*-TsOH (tip of spatula) and heated to 120 °C under Dean Stark conditions 16 h. The reaction was then concentrated in vacuo and crude *tert*-Butyl 4-(pyrrolidin-1-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**3-22 intermediate**) was obtained as a dark orange oil and carried on without further purification or characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (bs, 1 H), 3.95 (bs, 2 H), 3.71 (t, *J* = 6.3 Hz, 1 H), 3.02 (app t, *J* = 6.5 Hz, 4 H), 2.28 (t, *J* = 4.8 Hz, 2 H), 1.87-1.83 (m, 4 H), 1.46 (s, 9 H). To a solution of **3-22 intermediate** (1.25 g, 4.97 mmol) in THF (16 mL) was added 3-bromophenacyl bromide (1.14 g, 3.98 mmol) and DiPEA

(1.30 mL, 7.45 mmol). The reaction was stirred at reflux for 1 d. The reaction was concentrated and purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 40/60). Piperidine **3-22** was obtained as a red oil (1.03 g, 52%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (t, *J* = 1.7 Hz, 1 H), 7.89 (app d, *J* = 7.8, 1 H), 7.72-7.68 (app d, 1 H), 7.35 (t, *J* = 8.0 Hz, 1 H), 4.35 (bs, 2 H), 3.45 (dd, *J* = 18, 6.6 Hz, 1 H), 3.21 (td, *J* = 12, 5.2 Hz, 2 H), 2.94 (t, *J* = 12 Hz, 1 H), 2.78 (dd, *J* = 18, 5.3 Hz, 1 H), 2.67-2.56 (m, 1 H), 2.46 (dt, *J* = 14, 3.6 Hz, 1 H), 1.50 (s, 9 H).

***tert*-Butyl 2-(3-bromophenyl)-1,4,6,7-tetrahydro-5*H*-pyrrolo[3,2-*c*]pyridine-5-carboxylate (3-23)**[120]**.** To a solution of **3-22** (1.00 g, 2.52 mmol) in EtOH (18.2 mL) was added ammonium acetate (0.973 g, 12.6 mmol) and the reaction stirred at reflux for about 4 h. The reaction was cooled to room temperature and concentrated. The residue was taken up in CH_2Cl_2 (18 mL) and sat. $NaHCO_3$ (13 mL) was added. The aqueous was extracted with CH_2Cl_2 (3x), dried (Na_2SO_4), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 25/75). Pyrrolo[3,2-*c*]pyridine **3-23** was obtained as a tan solid (0.691 g, 73%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (bs, 1 H), 7.55 (t, *J* = 1.8 Hz, 1 H), 7.35-7.28 (m, 2 H), 7.20 (t, *J* = 7.8 Hz, 1 H), 6.30 (d, *J* = 2.0 Hz, 1 H), 4.43 (s, 2 H), 3.75 (bs, 2 H), 2.72 (bs, 2 H), 1.49 (s, 9 H); HRMS (ESI): *m/z* calculated for $C_{18}H_2O_2N_2Br$ (M+H) 37.0854, found 377.0856.

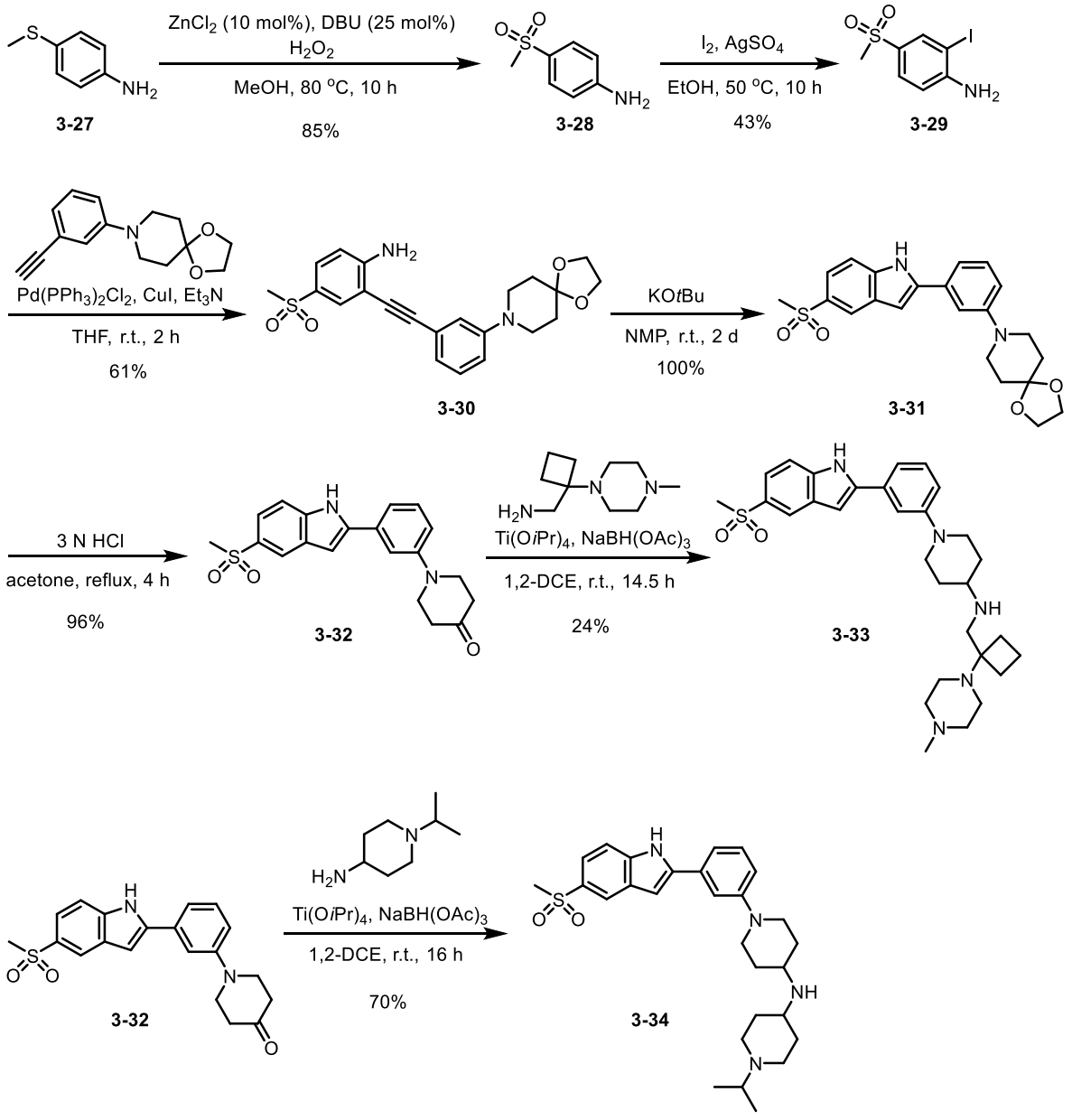
Di-*tert*-butyl 2-(3-bromophenyl)-6,7-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine-1,5(4*H*)-dicarboxylate (3-24)[121]**.** To a solution of **3-23** (0.220 g, 0.583 mmol) in THF (7.2 mL) was added Et_3N (0.164 mL, 1.17 mmol), DMAP (0.021 g, 0.175 mmol), and di-*tert*-butyl dicarbonate (0.229 g, 1.05 mmol). The reaction was stirred at room temperature 16 h. The reaction was quenched with H_2O, extracted with CH_2Cl_2 (3x), and washed with brine. The combined organic

layers were dried (Na_2SO_4), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). Pyrrolo[3,2-*c*]pyridine **3-24** was obtained as an off-white foam (0.240 g, 86%): IR (CH_2Cl_2) 2978, 2932, 1738, 1692, 1594, 1468, 1420, 1367, 1349, 1324, 1304, 1232, 1156, 1118, 1097, 1023, 924, 881, 848, 783, 732, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.39 (m, 2 H), 7.23-7.20 (m, 2 H), 6.02 (s, 1 H), 4.36 (s, 2 H), 3.70 (t, *J* = 5.3 Hz, 2 H), 2.96 (t, *J* = 5.9 Hz, 2 H), 1.49 (s, 9 H), 1.31 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 149.4, 136.9, 133.2, 131.7, 129.8, 129.3, 127.0, 121.6, 83.9, 79.8, 28.5, 27.5, 25.5; HRMS (ESI): *m/z* calculated for $C_{23}H_{30}O_4N_2Br$ (M+H) 477.1383, found 477.1378.

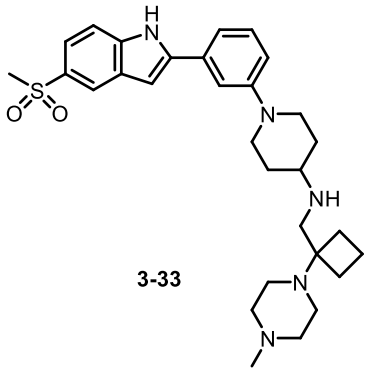
Di-*tert*-butyl 2-(3-(4-((*tert*-butoxycarbonyl)(2-(4-isopropylpiperazin-1-yl)ethyl)amino)piperidin-1-yl)phenyl)-6,7-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine-1,5(4*H*)-dicarboxylate (3-25). To a suspension of **3-24** (0.100 g, 0.209 mmol) in dry degassed dioxane (1.15 mL), *tert*-butyl (2-(4-isopropylpiperazin-1-yl)ethyl)(piperidin-4-yl)carbamate (0.089 g, 0.251 mmol), K_3PO_4 (0.068 g, 0.314 mmol), $Pd_2(dba)_3$ (4.0 mg, 0.004 mmol), and CyJohnPhos (6.0 mg, 0.017 mmol) was degassed for 5 minutes by bubbling nitrogen. The flask was sealed, and the reaction mixture was heated at 110 °C 16 h. The reaction mixture was diluted with sat. $NaHCO_3$ and extracted with EtOAc (3x). The combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). Pyrrolo[3,2-*c*]pyridine **3-25** was obtained as an orange-brown foam (0.071 g, 45%) and carried on without further characterization: ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 8.0 Hz, 1 H), 6.86-6.82 (m, 2 H), 6.75 (d, *J* = 7.2 Hz, 1 H), 5.99 (s, 1 H), 4.36 (s, 2 H), 3.73-3.69 (m, 4 H), 3.23 (bs, 2 H), 2.94 (s,

2 H), 2.75-2.44 (m, 14 H), 1.76 (s, 4 H), 1.45 (d, *J* = 6.0 Hz, 18 H), 1.27 (s, 9 H), 1.04 (d, *J* = 6.4 Hz, 6 H); HRMS (ESI): *m/z* calculated for $C_{42}H_{67}O_6N_6$ (M+H) 751.5117, found 751.5113.

***N*-(2-(4-Isopropylpiperazin-1-yl)ethyl)-1-(3-(4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)phenyl)piperidin-4-amine (3-26).** To a solution of **3-25** (0.030 g, 0.055 mmol) in CH_2Cl_2 (3.3 mL) was added Et_3SiH (36.5 µL, 0.226 mmol) and TFA (0.471 mL, 6.34 mmol). After 1 h, the solution was concentrated, diluted with CH_2Cl_2 and quenched with solid $NaHCO_3$ and 2 mL H_2O. The combined organic layers were removed and dried (Na_2SO_4), filtered, concentrated, and stored. The aqueous was concentrated and the residue taken up in EtOH and CH_2Cl_2. The combined organic layers were concentrated and take up in CH_2Cl_2 and the solid filtered off (2x). Product **3-26** was obtained from the aqueous layer as a yellow oil (0.017 g, 42%): IR (neat) 3177, 3059, 2931, 2813, 1676, 1593, 1462, 1381, 1344, 1273, 1177, 1117, 982, 774, 731, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (bs, 1 H), 7.19 (t, *J* = 7.9 Hz, 1 H), 7.00 (t, *J* = 2.0 Hz, 1 H), 6.88 (d, *J* = 7.6 Hz, 1 H), 6.75 (dd, *J* = 8.3, 2.5 Hz, 1 H), 6.19 (d, *J* = 2.2 Hz, 1 H), 3.84 (s, 2 H), 3.68 (dt, *J* = 12.7, 3.7 Hz, 2 H), 3.14 (q, *J* = 5.9 Hz, 2 H), 2.78 (dt, *J* = 12.3, 7.6 Hz, 4 H), 2.69 – 2.57 (m, 3 H), 2.57 – 2.43 (m, 11 H), 2.31 – 2.18 (m, 2 H), 2.02 – 1.93 (m, 2 H), 1.51 (qd, *J* = 11.9, 3.8 Hz, 2 H), 1.04 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 133.9, 131.3, 129.4, 126.1, 17.8, 115.1, 114.3, 112.1, 102.7, 58.0, 55.1, 54.5, 53.5, 48.8, 48.7, 43.6, 43.6, 43.4, 32.6, 23.9, 18.7; HRMS (ESI): *m/z* calculated for $C_{27}H_{43}N_6$ (M+H) 451.3544, found 451.3540; ELS purity (98.3%).



Scheme 3-7. Synthesis of 5-(methylsulfonyl)-1*H*-indole analogs.



3-33

4-(Methylsulfonyl)aniline (3-28)[122]**.** To a 250 mL sealed flask was added $ZnCl_2$ (0.048 g, 0.352 mmol), DBU (0.133 mL, 0.880 mmol), 4-(methylthio)aniline (0.447 mL, 3.52 mmol), and MeOH (7.05 mL). Hydrogen peroxide (1.44 mL, 14.1 mmol) was added last and the vessel sealed at heated to 80 °C behind a blast shield for 10 h. The reaction was cooled to room temperature and the reaction quenched with sat. Na_2SO_3 and the aqueous extracted with EtOAc (2x). The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Aniline **3-28** was obtained as a white solid (0.511 g, 85%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.67 (m, 2 H), 6.71-6.69 (m, 2 H), 4.22 (bs, 2 H), 3.00 (s, 3 H); HRMS (ESI): *m/z* calculated for $C_7H_{10}O_2NS$ (M+H) 172.0427, found 172.0427.

2-Iodo-4-(methylsulfonyl)aniline (3-29)[123]**.** To a solution of **3-28** (0.500 g, 2.90 mmol) in EtOH (27.5 mL) at 50° C was added a solution of I_2 (0.247 g, 0.973 mmol) and $AgSO_4$ (0.365 g, 1.75 mmol) in EtOH (7.5 mL). The reaction was stirred for 1 h and an additional solution of I_2 (0.247 g, 0.973 mmol) and $AgSO_4$ (0.365 g, 1.75 mmol) in EtOH (7.5 mL) was added (x2, after 1 h and 2 h). The reaction was then stirred at 50 °C 16 h. The hot reaction was filtered through Celite and the solvent concentrated. The residue was triturated with 50 °C EtOH (7.5 mL) for 45 min then cooled to 0 °C, the solid filtered, and dried in vacuo. Aniline **3-29** was obtained as a brown solid (0.374 g, 43%) and carried on without further purification or characterization: ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.17 (d, *J* = 2.0 Hz, 1 H), 7.67 (dd, *J* = 8.6, 2.2 Hz, 1 H), 6.77 (d, *J* = 8.4 Hz, 1 H), 3.02 (s, 3 H); HRMS (ESI): *m/z* calculated for $C_7H_9O_2NIS$ (M+H) 297.9393, found 297.9391.

2-((3-(1,4-Dioxa-8-azaspiro[4.5]decan-8-yl)phenyl)ethynyl)-4-(methylsulfonyl)aniline (3-30)[124]**.** To a solution of **3-29** (0.280 g, 0.939 mmol) in degassed THF (8.17 mL) was added 8-(3-ethynylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (0.597 g, 2.45 mmol), degassed Et_3N (0.689 mL, 4.91 mmol), $Pd(PPh_3)_2Cl_2$ (0.115 g, 0.164 mmol), and CuI (0.031 g, 0.164 mmol). The reaction was degassed by sparging with N_2 for an additional 5 min. The reaction was stirred at room temperature for 2 h. The reaction was diluted with EtOAc, washed with NH_4OH, the combined organic layers dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 10/90 to 80/20). Aniline **3-30** was obtained as a tan solid (0.237 g, 61%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 2.4 Hz, 1 H), 7.65 (dd, *J* = 8.7, 2.1 Hz, 1 H), 7.26-7.22 (m, 1 H), 7.10 (bs, 1 H), 6.99 (bs, 2 H), 6.78 (d, *J* = 8.4 Hz, 1 H), 4.81 (bs, 2 H), 4.00 (s, 4 H), 3.38 (t, *J* = 5.4 Hz, 4 H), 3.02 (s, 3 H), 1.86 (bs, 4 H); HRMS (ESI): *m/z* calculated for $C_{22}H_{25}O_2N_2S$ (M+H) 413.1530, found 413.1528.

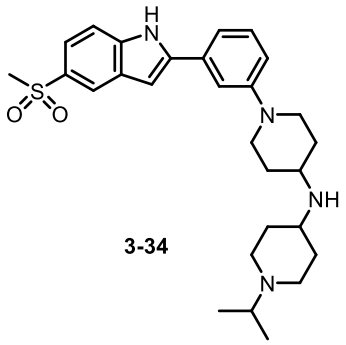
8-(3-(5-(Methylsulfonyl)-1*H*-indol-2-yl)phenyl)-1,4-dioxa-8-azaspiro[4.5]decane (3-31)[124]**.** To a solution of **3-30** (0.230 g, 0.558 mmol) in NMP (1.14 mL) was added KO*t*Bu (0.128 g, 1.12 mmol) and the reaction was stirred at room temperature for 2 d. The reaction was diluted with EtOAc, washed with half-saturated brine (5x), dried ($MgSO_4$), filtered, and concentrated. Indole **3-31** was obtained as a solid (0.229 g, 100%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1 H), 7.66 (d, *J* = 8.8 Hz, 1 H), 7.43 (d, *J* = 8.4 Hz, 1 H), 7.39-7.37 (m, 2 H), 6.80 (s, 1 H), 4.03 (s, 4 H), 3.60 (bs, 2 H), 3.38 (t, *J* = 7.0 Hz, 1 H), 3.09 (s, 3

H), 2.84 (s, 2 H), 2.37 (t, *J* = 8.2 Hz, 1 H), 2.06-1.98 (m, 2 H); HRMS (ESI): *m/z* calculated for $C_{22}H_{25}O_4N_2S$ (M+H) 413.1530, found 413.1531.

1-(3-(5-(Methylsulfonyl)-1*H*-indol-2-yl)phenyl)piperidin-4-one (3-32). To a solution of **3-31** (0.220 g, 0.533 mmol) in acetone (67.7 mL) was added HCl (3 M, 67.7 mL) at room temperature and the reaction was heated to reflux. After 4 h, the solution was cooled to room temperature and allowed to stir for 16 h. The reaction was cooled to 0 °C and neutralized with Na_2CO_3. The mixture was extracted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 50/50). Indole **3-32** was obtained as a pale yellow solid (0.189 g, 96%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (bs, 1 H), 8.25 (d, *J* = 1.6 Hz, 1 H), 7.72 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.52 (d, *J* = 8.4 Hz, 1 H), 7.42 (t, *J* = 8.0 Hz, 2 H), 7.07 (d, *J*= 8.0 Hz, 1 H), 6.92 (d, *J* = 1.6 Hz, 1 H), 3.74 (t, *J* = 6.0 Hz, 4 H), 3.10 (s, 3 H), 2.70 (bs, 4 H); HRMS (ESI): *m/z* calculated for $C_{20}H_{21}O_3N_2S$ (M+H) 369.1267, found 369.1266.

***N*-((1-(4-Methylpiperazin-1-yl)cyclobutyl)methyl)-1-(3-(5-(methylsulfonyl)-1*H*-indol-2-yl)phenyl)piperidin-4-amine (3-33).** To a solution of **3-32** (0.090 g, 0.244 mmol), (1-(4-methylpiperazin-1-yl)cyclobutyl)methanamine (0.049 g, 0.269 mmol) in 1,2-DCE (2.41 mL) was added Ti(O*i*Pr)$_4$ (0.082 mL, 0.269 mmol) at room temperature. After 30 min, $NaBH(OAc)_3$ (0.025 g, 0.114 mmol) was added. After 1 h, additional $NaBH(OAc)_3$ (0.025 g, 0.114 mmol) was added and the solution was stirred at room temperature. After 1 h, additional $NaBH(OAc)_3$ (0.025 g, 0.114 mmol) was added and the reaction allowed to stir 16 h. The solution was diluted with sat. $NaHCO_3$, extracted with EtOAc (2x), dried (Na_2SO_4), filtered, and concentrated. The product was purified by chromatography on Al_2O_3-neutral (MeOH/CH_2Cl_2 + 0.1% Et_3N: 0/100 to 8/92) followed by filtration through a plug of basic Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 5/95).

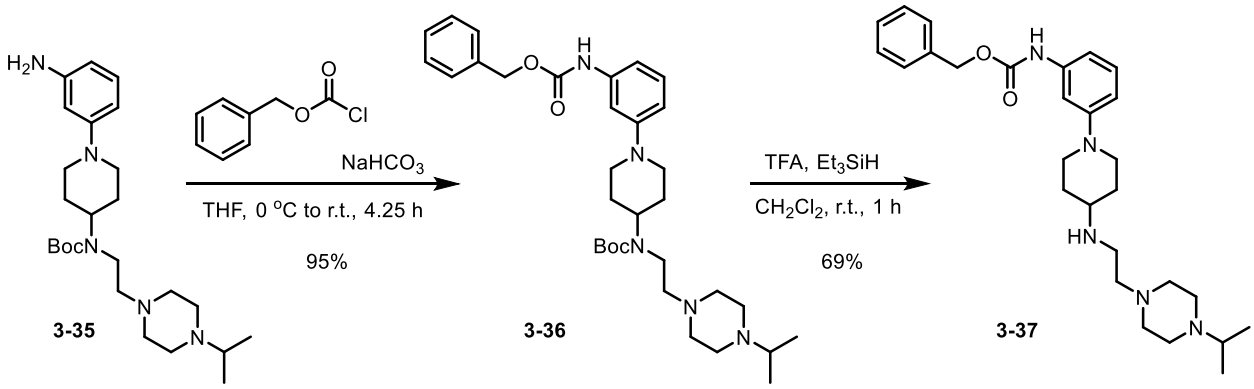
Product **3-33** was obtained as a tan foam (0.032 g, 24%): IR (CH_2Cl_2) 3542, 3128, 2931, 2804, 1604, 1585, 1486, 1449, 1285, 1220, 1139, 1124, 954, 804, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1 H), 8.21 (s, 1 H), 7.65 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.51 (d, *J* = 8.6 Hz, 1 H), 7.30 (t, *J* = 7.9 Hz, 1 H), 7.14 (d, *J* = 7.6 Hz, 1 H), 6.92 (dd, *J* = 8.2, 2.4 Hz, 1 H), 6.86 (s, 1 H), 3.71 (dt, *J* = 12.7, 3.9 Hz, 2 H), 3.08 (s, 3 H), 2.84 (d, *J* = 11.3 Hz, 2 H), 2.80 (s, 2 H), 2.61 – 2.50 (m, 10 H), 2.43 (bs, 1 H), 2.27 (s, 3 H), 2.19 – 2.07 (m, 2 H), 1.94 (dd, *J* = 13.0, 3.7 Hz, 2 H), 1.75 – 1.63 (m, 4 H), 1.49 (qd, *J* = 11.2, 3.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 141.7, 139.2, 132.3, 131.6, 129.8, 128.8, 121.1, 120.2, 116.5, 113.5, 111.7, 100.5, 62.6, 55.8, 55.3, 50.6, 48.4, 46.0, 45.3, 45.2, 32.4, 27.0, 13.9; HRMS (ESI): *m/z* calculated for $C_{30}H_{42}O_2N_5S$ (M+H) 536.3054, found 536.3052; ELS purity (100%).



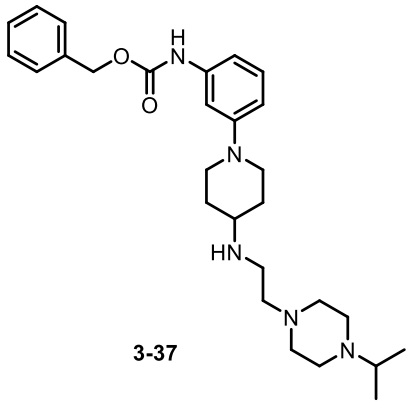
3-34

1-Isopropyl-*N*-(1-(3-(5-(methylsulfonyl)-1*H*-indol-2-yl)phenyl)piperidin-4-yl)piperidin-4-amine (3-34). To a solution of **3-32** (0.090 g, 0.244 mmol), 4-amino-1-isopropyl piperidine (0.045 mL, 0.267 mmol) in 1,2-DCE (2.41 mL) was added Ti(O*i*Pr)$_4$ (0.082 mL, 0.267 mmol) at room temperature. After 30 min, $NaBH(OAc)_3$ (0.025 g, 0.114 mmol) was added. After 1 h, additional $NaBH(OAc)_3$ (0.025 g, 0.114 mmol) was added and the solution was stirred at rooom temperature. After 1 h, additional $NaBH(OAc)_3$ (0.025 g, 0.114 mmol) was added and the reaction allowed to stir 16 h. The solution was diluted with sat. $NaHCO_3$, extracted with EtOAc

(2x), dried (Na_2SO_4), filtered, and concentrated. The product was purified by chromatography on Al_2O_3-neutral (MeOH/CH_2Cl_2 + 0.1% Et_3N: 0/100 to 5/95) followed by filtration through a plug of basic Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 5/95). Product **3-34** was obtained as a tan foam (0.085 g, 70%): IR (CH_2Cl_2) 3538, 3133, 2973, 2934, 2795, 2250, 1605, 1487, 1449, 1283, 1222, 1134, 1120, 1061, 954, 920, 773, 726, 693 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$/MeOD) δ 8.18 (q, *J* = 1.9 Hz, 1 H), 7.62 (dq, *J* = 8.2, 2.0 Hz, 1 H), 7.48 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.28 (dd, *J* = 8.0, 3.1 Hz, 1 H), 7.17 (d, *J* = 7.5 Hz, 1 H), 6.91 – 6.85 (m, 2 H), 6.84 (d, *J* = 2.6 Hz, 1 H), 3.72 – 3.67 (m, 2 H), 3.06 – 3.04 (m, 3 H), 2.85 – 2.81 (m, 2 H), 2.81 – 2.70 (m, 3 H), 2.70 – 2.64 (m, 1 H), 2.60 – 2.53 (m, 1 H), 2.17 – 2.10 (m, 2 H), 1.88 (t, *J* = 12.0 Hz, 4 H), 1.47 (tq, *J* = 12.0, 8.5, 6.0 Hz, 2 H), 1.37 – 1.27 (m, 2 H), 1.01 (dd, *J* = 6.7, 2.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$/MeOD) δ 151.7, 141.6, 139.4, 132.2, 130.8, 129.5, 128.5, 120.6, 119.6, 116.8, 116.3, 113.6, 111.7, 99.9, 54.3, 50.9, 50.7, 47.5, 45.0, 32.4, 32.2, 18.0; HRMS (ESI): *m/z* calculated for $C_{28}H_{39}O_2N_4S$ (M+H) 495.2788, found 495.2789; ELS purity (100%).



Scheme 3-8. Representative synthesis of carbamate indole replacements from chloroformates.

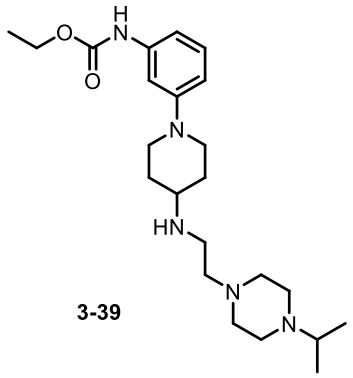


3-37

***tert*-Butyl (1-(3-(((benzyloxy)carbonyl)amino)phenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (3-36)**. To a solution of *tert*-butyl (1-(3-aminophenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (0.061 g, 0.137 mmol) in THF (0.35 mL) was added $NaHCO_3$ (0.046 g, 0.548 mmol). The suspension was cooled to 0 °C and benzyl chloroformate (46.2 µL, 0.137 mmol) was added and the reaction was allowed to warm to room temperature over 4.25 h. The reaction was filtered and the solid washed with THF. The combined organic layers were concentrated in the presence of MeOH. Crude carbamate **3-36** was obtained as a brown-orange foam (0.075 g, 95%) and carried on without further purification or characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.34 (m, 5 H), 7.15 (t, *J* = 8.0 Hz, 2 H), 6.69 (d, *J* = 8.0 Hz, 1 H), 6.62 (d, *J* = 6.4 Hz, 2 H), 5.19 (s, 2 H), 4.11 (bs, 1 H), 3.73 (d, *J* = 12 Hz, 2 H), 3.21 (bs, 3 H), 2.76-2.50 (m, 12 H), 2.17 (s, 1 H), 1.75 (bs, 4 H), 1.46 (s, 9 H), 1.06 (bs, 6 H); HRMS (ESI): *m/z* calculated for $C_{33}H_{50}O_4N_5$ (M+H) 580.3857, found 580.3796.

Benzyl (3-(4-((2-(4-isopropylpiperazin-1-yl)ethyl)amino)piperidin-1-yl)phenyl)carbamate (3-37). To a solution of **3-36** (0.070 g, 0.121 mmol) in CH_2Cl_2 (3.1 mL) was added Et_3SiH (48.6 µL, 0.302 mmol) and TFA (0.628 mL, 8.45 mmol). After 1 h, the solution was concentrated, diluted with sat. $NaHCO_3$, extracted with EtOAc (3x), washed with brine, dried (Na_2SO_4),

filtered, and concentrated. The product was purified by chromatography on SiO_2 (MeOH/CH_2Cl_2: 5/95 to 20/80) followed by filtering through a plug of basic Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 5/95). Product **3-37** was obtained as a yellow goo (0.040 g, 69%): IR (neat) 3302, 2932, 2810, 1728, 1608, 1591, 1547, 1497, 1447, 1293, 1218, 1177, 1052, 843, 765, 728, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5 H), 7.17 – 7.08 (m, 2 H), 7.01 (s, 1 H), 6.68 (d, *J* = 7.6 Hz, 1 H), 6.61 (dd, *J* = 8.3, 2.4 Hz, 1 H), 5.16 (s, 2 H), 3.67 – 3.59 (m, 2 H), 2.77 – 2.69 (m, 4 H), 2.63 (sept, *J* = 6.5 Hz, 1 H), 2.59 – 2.42 (m, 12 H), 1.96 – 1.89 (m, 2 H), 1.46 (tt, *J* = 12.0, 6.1 Hz, 2 H), 1.03 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 152.2, 138.7, 136.2, 129.4, 128.6, 128.3, 128.3, 111.5, 109.5, 106.7, 66.8, 58.0, 55.1, 54.4, 53.6, 48.8, 48.4, 43.4, 32.5, 28.5, 18.7. HRMS (ESI): *m/z* calculated for $C_{28}H_{42}O_2N_5$ (M+H) 480.3333, found 480.3275; ELS purity (99.8%).

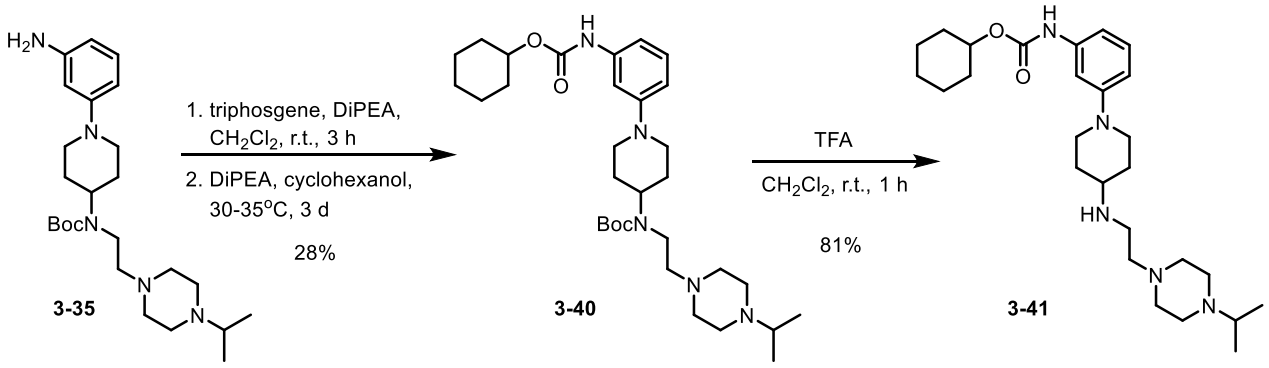


3-39

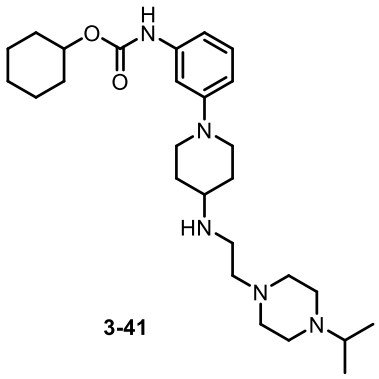
***tert*-Butyl (1-(3-((ethoxycarbonyl)amino)phenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (3-38)**. To a solution of *tert*-butyl (1-(3-aminophenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (0.050 g, 0.112 mmol) in THF (0.29 mL) was added $NaHCO_3$ (0.038 g, 0.449 mmol). The suspension was cooled to 0 °C and ethyl chloroformate (10.7 µL, 0.112 mmol) was added and the reaction warmed to room temperature over 4.25 h. The reaction was filtered and the solid washed with THF. The combined organic layers were

concentrated in the presence of MeOH. Crude carbamate **3-38** was obtained as a brown-orange foam (0.069 g) and carried on without further purification or characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, *J* = 8.1 Hz, 1 H), 6.68 (d, *J* = 8.1 Hz, 1 H), 6.62 (dd, *J* = 7.8, 2.1 Hz, 1 H), 6.52 (bs, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 3.77-3.72 (m, 2 H), 3.33 (d, *J* = 7.5 Hz, 2 H), 3.23-2.78 (m, 8 H), 2.57 (t, *J* = 7.2 Hz, 2 H), 1.87-1.83 (m, 1 H), 1.74 (bs, 3 H), 1.57 (bs, 4 H), 1.46-1.43 (m, 15 H), 1.31 (t, *J* = 7.1 Hz, 3 H); HRMS (ESI): *m/z* calculated for $C_{28}H_{48}O_4N_5$ (M+H) 518.3701, found 518.3702.

Ethyl (3-(4-((2-(4-isopropylpiperazin-1-yl)ethyl)amino)piperidin-1-yl)phenyl)carbamate (3-39). To a solution of **3-38** (0.060 g, 0.116 mmol) in CH_2Cl_2 (3 mL) was added Et_3SiH (46.7 µL, 0.290 mmol) and TFA (0.603 mL, 8.11 mmol). After 1 h, the solution was concentrated, diluted with sat. $NaHCO_3$, extracted with EtOAc (3x), washed with brine, dried (Na_2SO_4), filtered, and concentrated. The product was purified by chromatography on Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 5/95). Product **3-39** was obtained as a yellow foam (0.035 g, 72%): IR (CH_2Cl_2) 3302, 2930, 2810, 1727, 1608, 1548, 1497, 1447, 1382, 1294, 1223, 1177, 1068, 856, 767, 692 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (bs, 1 H), 7.11 (td, *J* = 8.1, 2.7 Hz, 1 H), 6.85 (s, 1 H), 6.66 (dd, *J* = 7.9, 1.9 Hz, 1 H), 6.60 (dd, *J* = 8.3, 2.5 Hz, 1 H), 4.18 (qd, *J* = 7.1, 2.4 Hz, 2 H), 3.68 – 3.60 (m, 2 H), 2.78 – 2.69 (m, 4 H), 2.62 (h, *J* = 6.6 Hz, 1 H), 2.58 – 2.42 (m, 12 H), 1.93 (d, *J* = 12.4 Hz, 2 H), 1.45 (qd, *J* = 12.4, 3.8 Hz, 2 H), 1.27 (td, *J* = 7.2, 2.4 Hz, 3 H), 1.03 (dd, *J* = 6.5, 2.2 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 152.2, 138.9, 129.4, 111.3, 109.4, 106.6, 61.0, 58.0, 55.1, 54.4, 53.5, 48.8, 48.4, 43.4, 32.5, 18.7, 14.6; HRMS (ESI): *m/z* calculated for $C_{23}H_{40}O_2N_5$ (M+H) 418.3177, found 418.3173; ELS purity (100%).

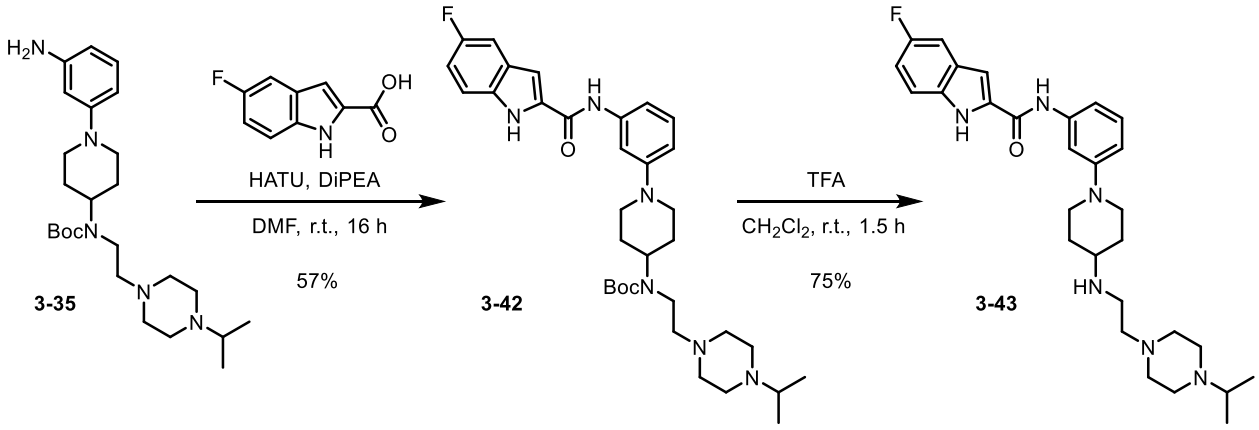


Scheme 3-9. Synthesis of cyclohexyl carbamate indole replacement.

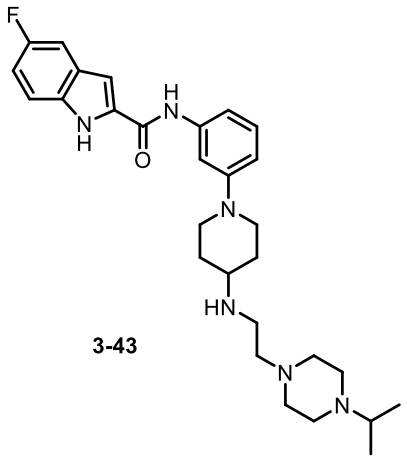


***tert*-Butyl (1-(3-(((cyclohexyloxy)carbonyl)amino)phenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (3-40)**[125]**.** To a solution of *tert*-butyl (1-(3-aminophenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (0.050 g, 0.112 mmol) in dry CH_2Cl_2 (0.5 mL) at 0 °C was added DiPEA (29.3 µL, 0.135 mmol) followed by triphosgene (0.033 g, 0.112 mmol). The reaction was warmed to room temperature over 3 h. Additional DiPEA (39.0 µL, 0.258 mmol) was added followed by cyclohexanol (0.120 mL, 0.114 mmol) and the reaction was stirred at 30-35 °C for 3 d. Sat. $NaHCO_3$ was added to quench and the aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). Carbamate **3-40** was obtained as a yellow film (0.018 g, 28%) and carried on without further characterization: HRMS (ESI): *m/z* calculated for $C_{32}H_{54}O_4N_5$ (M+H) 572.4170, found 572.4094.

Cyclohexyl (3-(4-((2-(4-isopropylpiperazin-1-yl)ethyl)amino)piperidin-1-yl)phenyl)carbamate (3-41). To a solution of **3-40** (0.017 g, 0.030 mmol) in CH_2Cl_2 (0.77 mL) was added TFA (0.155 mL, 2.08 mmol). After 1 h, the solution was concentrated, diluted with sat. $NaHCO_3$, extracted with EtOAc (3x), washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by chromatography on Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 2/98). Product **3-41** was obtained as an orange-brown foam (0.011 g, 81%): IR (CH_2Cl_2) 3309, 2934, 2811, 1720, 1607, 1548, 1497, 1448, 1221, 1177, 1059, 982, 767, 733, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (bs, 1 H), 7.12 (t, *J* = 8.0 Hz, 1 H), 6.65 (dd, *J* = 8.0, 1.5 Hz, 1 H), 6.61 (dd, *J* = 8.5, 2.0 Hz, 1 H), 6.58 (bs, 1 H), 4.72 (m, 1 H), 3.67 (d, *J* = 13 Hz, 2 H), 2.77-2.74 (m, 4 H), 2.64-2.49 (m, 12 H), 1.96-1.91 (m, 4 H), 1.73 (t, *J* = 4.3 Hz, 2 H), 1.49-1.36 (m, 8 H), 1.04 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 152.2, 139.0, 129.4, 111.2, 109.3, 106.5, 73.5, 58.1, 56.0, 55.1, 54.5, 53.5, 48.8, 48.4, 43.4, 32.6, 32.0, 30.9, 29.7, 25.4, 23.8, 18.7; HRMS (ESI): *m/z* calculated for $C_{27}H_{46}O_2N_5$ (M+H) 472.3646, found 472.3585; ELS purity (100%).



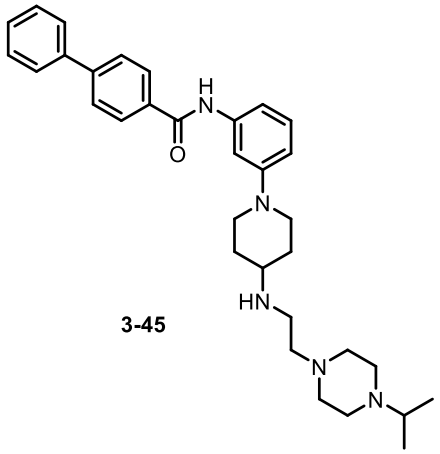
Scheme 3-10. Representative synthesis of amide indole replacements.



3-43

***tert*-Butyl (1-(3-(5-fluoro-1*H*-indole-2-carboxamido)phenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (3-42).** To a solution of 5-fluoroindole-2-carboxylic acid (0.023 g, 0.123 mmol) in DMF (0.3 mL) was added DiPEA (0.078 mL, 0.449 mmol) and HATU (0.051 g, 0.135 mmol) and stirred for 40 min under argon. *tert*-Butyl (1-(3-aminophenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (0.050 g, 0.112 mmol) in DMF (0.16 mL) was added and the reaction stirred 16 h. The reaction was diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The solid was washed with CH_2Cl_2 followed by purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 5/95) to give amide **3-42** (0.039 g, 57%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (bs, 1 H), 7.85 (bs, 1 H), 7.42 (d, *J* = 4.5 Hz, 1 H), 7.39 (d, *J* = 3.9 Hz, 1 H), 7.31 (dd, *J* = 9.6, 2.4 Hz, 1 H), 7.26-7.21 (m, 1 H), 7.07 (td, *J* = 9.0, 2.7 Hz, 1 H), 7.00-6.98 (m, 2 H), 6.72 (app d, *J* = 9.9 Hz, 1 H), 3.80 (d, *J* = 12 Hz, 2 H), 3.22 (bs, 2 H), 2.83-2.51 (m, 14 H), 1.75 (bs, 4 H), 1.47 (s, 9 H), 1.13 (d, *J* = 6.0 Hz, 6 H); HRMS (ESI): *m/z* calculated for $C_{34}H_{48}O_3N_6F$ (M+H) 607.3766, found 607.3767.

5-Fluoro-*N*-(3-(4-((2-(4-isopropylpiperazin-1-yl)ethyl)amino)piperidin-1-yl)phenyl)-1*H*-indole-2-carboxamide (3-43). To a solution of **3-42** (0.035 g, 0.058 mmol) in CH_2Cl_2 (1.48 mL) was added TFA (0.300 mL, 4.04 mmol). After about 1.5 h, the solution was concentrated, diluted with sat. $NaHCO_3$, extracted with EtOAc (3x), washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by chromatography on Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 5/95). Product **3-43** was obtained as a pale yellow foam (0.022 g, 75%): IR (CH_2Cl_2) 3274, 2945, 2815, 1645, 1606, 1544, 1493, 1445, 1328, 1216, 1176, 1112, 955, 855, 799, 769, 732, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.20 (bs, 1 H), 8.02 (s, 1 H), 7.37 (s, 1 H), 7.33 (dd, *J* = 4.5, 4.5 Hz, 1 H), 7.27-7.21 (m, 2 H), 7.04-6.99 (m, 2 H), 6.96 (s, 1 H), 6.74 (dd, *J* = 1.5 Hz, 1 H), 3.68 (d, *J* = 13 Hz, 2.80-2.73 (m, 4 H), 2.65-2.48 (m, 12 H), 1.93 (d, *J* = 12 Hz, 2 H), 1.47 (qd, *J* = 9.5, 3.5 Hz, 2 H), 1.04 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 158.2 (d, J_{CF} = 235 Hz), 152.3, 138.2, 133.5, 132.5, 129.6, 127.7 (d, J_{CF} =10 Hz), 113.8 (d, J_{CF} = 28 Hz), 113.1 (d, J_{CF} = 10 Hz), 112.9, 111.0, 106.2 (d, J_{CF} = 23 Hz), 102.6 (d, J_{CF} = 5 Hz), 58.0, 55.0, 54.5, 53.6, 48.8, 48.3, 43.4, 32.5, 18.7; ^{17}F NMR (470 MHz, $CDCl_3$) δ -122.9; HRMS (ESI): *m/z* calculated for $C_{29}H_{40}ON_6F$ (M+H) 507.3242, found 507.3241; ELS purity (100%).

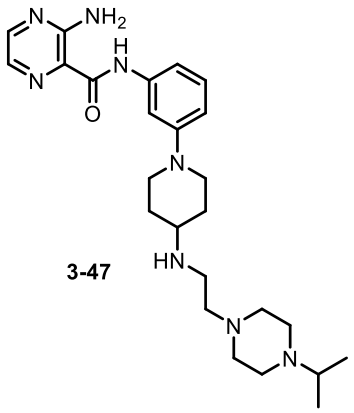


3-45

***tert*-Butyl (1-(3-([1,1'-biphenyl]-4-carboxamido)phenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (3-44).** To a solution of 4-biphenylcarboxylic acid (0.025 g, 0.123 mmol) in DMF (0.3 mL) was added DiPEA (0.078 mL, 0.449 mmol) and HATU (0.051 g, 0.135 mmol) and stirred for 40 min under argon. *tert*-Butyl (1-(3-aminophenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (0.054 g, 0.121 mmol) in DMF (0.16 mL) was added and the reaction stirred 16 h. The reaction was diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The solid was washed with CH_2Cl_2 followed by purification by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 5/95) to give amide **3-44** (0.035 g, 50%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2 H), 7.78 (bs, 1 H), 7.72 (d, *J* = 8.1 Hz, 2 H), 7.64 (d, *J* = 7.5 Hz, 2 H), 7.51-7.38 (m, 4 H), 7.26-7.21 (m, 1 H), 6.95 (d, *J* = 9.9 Hz, 1 H), 6.72 (app d, *J* = 7.8 Hz, 1 H), 3.81 (d, *J* = 12 Hz, 2 H), 3.24 (bs, 2 H), 2.82-2.50 (m, 12 H), 1.78-1.60 (m, 6 H), 1.47 (s, 9 H), 1.06 (bs, 6 H); HRMS (ESI): *m/z* calculated for $C_{38}H_{52}O_3N_5$ (M+H) 626.4065, found 626.4061.

***N*-(3-(4-((2-(4-isopropylpiperazin-1-yl)ethyl)amino)piperidin-1-yl)phenyl)-[1,1'-biphenyl]-4-carboxamide (3-45).** To a solution of **3-44** (0.033 g, 0.053 mmol) in CH_2Cl_2 (1.35 mL) was added TFA (0.274 mL, 3.69 mmol). After 1 h, the solution was concentrated, diluted with sat. $NaHCO_3$, extracted with EtOAc (3x), washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by chromatography on Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 2/98). Product **3-45** was obtained as a tan foam (0.026 g, 94%): IR (CH_2Cl_2) 3291, 3032, 2932, 2809, 1648, 1607, 1542, 1487, 1442, 1301, 1261, 1177, 1116, 983, 852, 743, 694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (bs, 1 H), 7.92 (d, *J* = 8.5 Hz, 2 H), 7.67 (d, *J* = 8.0 Hz, 2 H), 7.60 (d, *J* = 8.0 Hz, 2 H), 7.49 (bs, 1 H), 7.46 (t, *J* = 7.5 Hz, 2 H), 7.39 (t, *J* = 7.3 Hz, 1 H),

7.20 (t, *J* = 8.0 Hz, 1 H), 6.95 (dd, *J* = 8.0, 1.0 Hz, 1 H), 6.72 (dd, *J* = 8.5, 2.0 Hz, 1 H), 3.70 (d, *J* = 13 Hz, 2 H), 2.81-2.74 (m, 4 H), 2.66-2.49 (m, 12 H), 1.96 (d, *J* = 12 Hz, 2 H), 1.48 (qd, *J* = 12, 3.0 Hz, 2 H), 1.04 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 152.2, 144.5, 139.9, 138.9, 133.8, 129.5, 129.0, 128.1, 127.6, 127.4, 127.2, 112.6, 110.8, 108.2, 58.1, 55.1, 54.5, 53.6, 48.8, 48.4, 43.5, 32.6, 18.7; HRMS (ESI): *m/z* calculated for $C_{33}H_{44}ON_5$ (M+H) 526.3540, found 526.3537; ELS purity (100%).

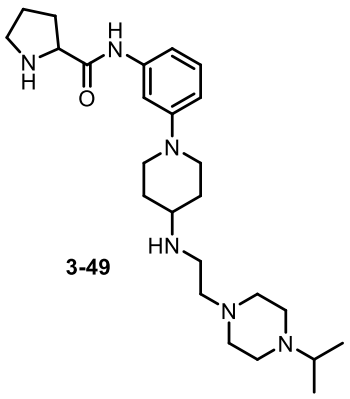


3-47

***tert*-Butyl (1-(3-(3-aminopyrazine-2-carboxamido)phenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (3-46).** To a solution of 3-amino-pyrazine-2-carboxylic acid (0.018 g, 0.123 mmol) in DMF (0.3 mL) was added DiPEA (0.078 mL, 0.449 mmol) and HATU (0.051 g, 0.135 mmol) and stirred for 40 min under argon. *tert*-Butyl (1-(3-aminophenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (0.052 g, 0.117 mmol) in DMF (0.16 mL) was added and the reaction stirred 16 h. The reaction was diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The solid was washed with CH_2Cl_2 followed by purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 5/95) to give amide **3-46** (0.045 g, 71%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1 H), 8.22 (d, *J* = 2.4 Hz, 1 H), 7.87 (d, *J* = 2.1 Hz, 1 H),

7.52 (bs, 1 H), 7.11 (bs, 1 H), 6.80 (bs, 1 H), 3.81 (d, *J* = 12 Hz, 2 H), 3.38-2.88 (m, 12 H), 2.61 (bs, 2 H), 1.89-1.84 (m, 6 H), 1.49-1.41 (m, 15 H); HRMS (ESI): *m/z* calculated for $C_{30}H_{47}O_3N_8$ (M+H) 567.3766, found 567.3765.

3-Amino-*N*-(3-(4-((2-(4-isopropylpiperazin-1-yl)ethyl)amino)piperidin-1-yl)phenyl)pyrazine-2-carboxamide (3-47). To a solution of **3-46** (0.043 g, 0.076 mmol) in CH_2Cl_2 (1.95 mL) was added TFA (0.395 mL, 5.31 mmol). After 1 h, the solution was concentrated, diluted with sat. $NaHCO_3$, extracted with EtOAc (3x), washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by chromatography on Al_2O_3 (MeOH/ CH_2Cl_2: 0/100 to 5/95). Product **3-47** was obtained as a yellow foam (0.025 g, 71%): IR (CH_2Cl_2) 3341, 2933, 2810, 1665, 1603, 1529, 1496, 1438, 1382, 1235, 1178, 1109, 983, 919, 810, 767, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.73 (s, 1 H), 8.17 (d, *J* = 2.5 Hz, 1 H), 7.83 (d, *J* = 2.5 Hz, 1 H), 7.38 (t, *J* = 2.0 Hz, 1 H), 7.21 (t, *J* = 8.3 Hz, 1 H), 7.05 (dd, *J* = 8.0, 1.3 Hz, 1 H), 6.71 (dd, *J* = 8.5, 2.0 Hz, 1 H), 3.70 (d, *J* = 13 Hz, 2 H), 2.82-2.74 (m, 4 H), 2.65-2.48 (m, 12 H), 1.97 (d, *J* = 11 Hz, 2 H), 1.49 (qd, *J* = 12, 3.4 Hz, 2 H), 1.03 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 155.4, 152.2, 147.0, 138.3, 131.5, 129.5, 126.4, 112.5, 110.6, 107.6, 58.3, 55.1, 54.4, 53.6, 48.7, 48.4, 43.5, 32.6, 18.7; HRMS (ESI): *m/z* calculated for $C_{25}H_{39}ON_8$ (M+H) 467.3241, found 467.3238; ELS purity (100%).

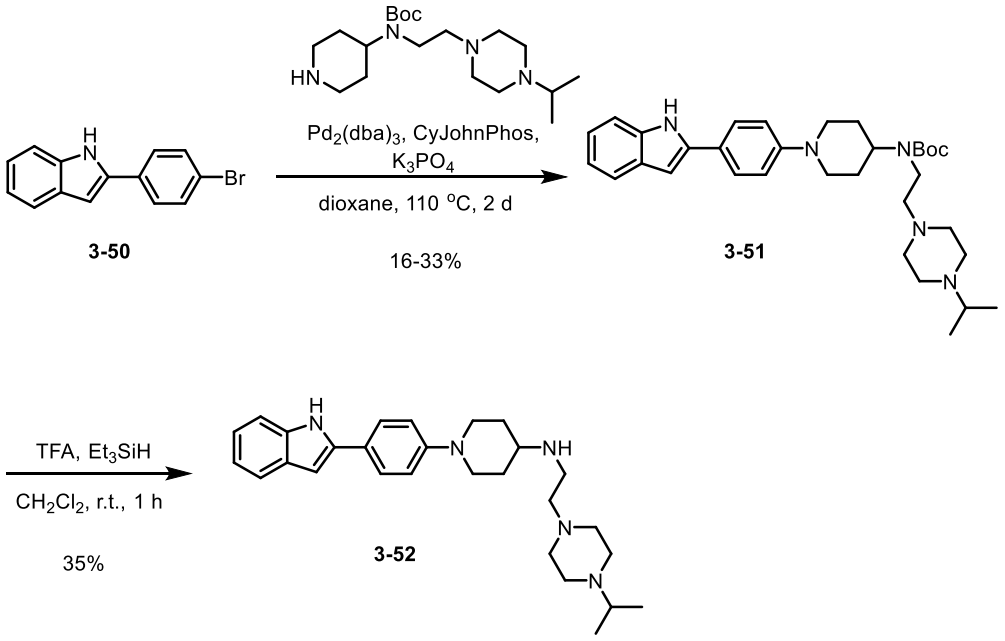


3-49

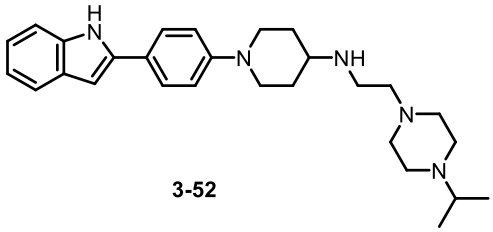
***tert*-Butyl 2-((3-(4-((*tert*-butoxycarbonyl)(2-(4-isopropylpiperazin-1-yl)ethyl)amino)piperidin-1-yl)phenyl)carbamoyl)pyrrolidine-1-carboxylate (3-48).** To a solution of *N*-Boc-proline (0.027 g, 0.123 mmol) in DMF (0.3 mL) was added DiPEA (0.078 mL, 0.449 mmol) and HATU (0.051 g, 0.135 mmol) and stirred for 40 min under argon. *tert*-Butyl (1-(3-aminophenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (0.056 g, 0.126 mmol) in DMF (0.16 mL) was added and the reaction stirred 16 h. The reaction was diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The solid was washed with CH_2Cl_2 followed by purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 5/95) to give amide **3-48** (0.039 g, 54%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (bs, 1 H), 7.14 (t, *J* = 8.1 Hz, 1 H), 6.79 (d, *J* = 7.2, 1 H), 6.63 (d, *J* = 7.2 Hz, 1 H), 4.42 (bs, 1 H), 3.74 (d, *J* = 12 Hz, 2 H), 3.43 (bs, 2 H), 3.22 (bs, 2 H), 2.78-2.44 (m, 15 H), 1.92-1.75 (m, 7 H), 1.47 (s, 9 H), 1.43 (s, 9 H), 1.05 (d, *J* = 6.6 Hz, 6 H).

***N*-(3-(4-((2-(4-isopropylpiperazin-1-yl)ethyl)amino)piperidin-1-yl)phenyl)pyrrolidine-2-carboxamide (3-49).** To a solution of **3-48** (0.039 g, 0.061 mmol) in CH_2Cl_2 (1.56 mL) was added TFA (0.315 mL, 4.25 mmol). After 1 h, the solution was concentrated, diluted with sat. $NaHCO_3$, extracted with EtOAc (3x), washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by chromatography on Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 5/95). Product **3-49** was obtained as a brown goo (0.012 g, 45%): $[\alpha]_D$ = -0.27 ° (c = 1.00, CH_2Cl_2); IR (CH_2Cl_2) 3274, 2933, 2811, 1676, 1603, 1524, 1496, 1447, 1382, 1294, 1177, 1114, 983, 863, 770, 732, 693 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (s, 1 H), 7.41 (t, *J* = 2.5 Hz, 1 H), 7.16 (t, *J* = 8.0 Hz, 1 H), 6.90 (dd, *J* = 7.8, 1.3 Hz, 1 H), 6.66 (dd, *J* = 8.0, 2.0 Hz, 1 H), 3.83 (dd, *J* = 5.5, 5.0 Hz, 1 H), 3.69 (d, *J* = 13 Hz, 2 H), 3.09-3.07 (m, 1 H), 2.99-2.96 (m, 1 H),

2.80-2.75 (m, 4 H), 2.65-2.50 (m, 12 H), 2.25-2.15 (m, 1 H), 2.05 (sext, *J* = 6.3 Hz, 1 H), 1.96 (d, *J* = 12 Hz, 2 H), 1.77-1.73 (m, 2 H), 1.48 (qd, *J* = 12, 3.0 Hz, 2 H), 1.05 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 152.2, 138.7, 129.3, 112.0, 110.0, 107.2, 61.1, 58.0, 55.1, 54.5, 53.5, 48.8, 48.5, 48.4, 47.4, 43.4, 32.6, 30.7, 26.3, 18.7; HRMS (ESI): *m/z* calculated for $C_{25}H_{43}ON_6$ (M+H) 443.3493, found 443.3491; ELS purity (97.3%).



Scheme 3-11. Synthesis of *para* substituted phenyl indole analog.

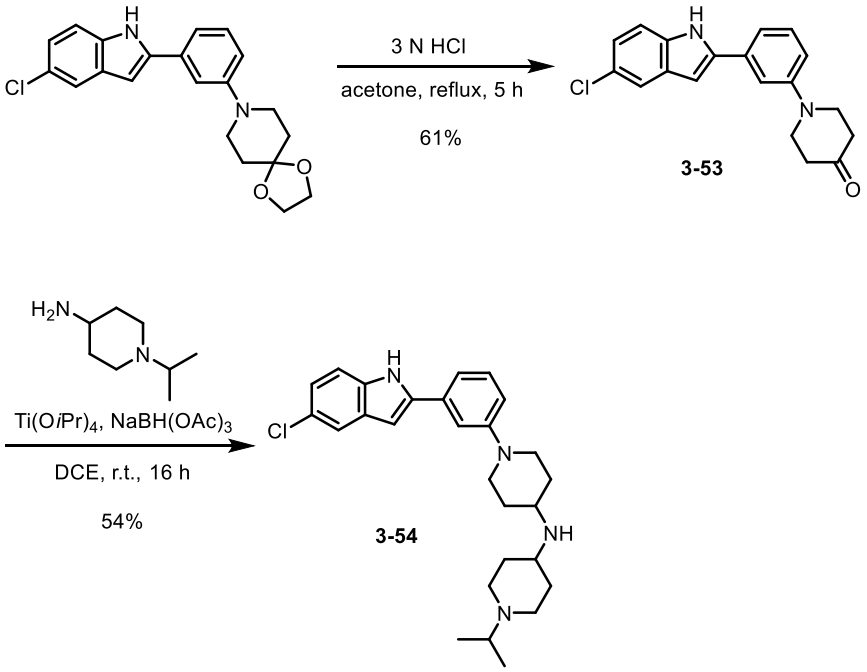


***tert*-Butyl (1-(4-(1*H*-indol-2-yl)phenyl)piperidin-4-yl)(2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (3-51).** To a suspension of 2-(4-bromophenyl)-1*H*-indole (0.100 g, 0.367 mmol) in dry degassed dioxane (1.0 mL), *tert*-butyl (2-(4-isopropylpiperazin-1-

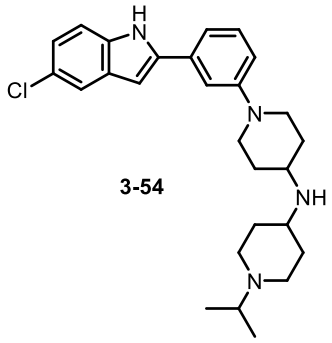
yl)ethyl)(piperidin-4-yl)carbamate (0.156 g, 0.441 mmol), K_3PO_4 (0.119 g, 0.551 mmol), $Pd_2(dba)_3$ (7.0 mg, 0.007 mmol), and CyJohnPhos (0.011 g, 0.029 mmol) was degassed for 5 minutes by bubbling nitrogen. The flask was sealed, and the reaction mixture was heated at 110 °C 16 h. The reaction mixture was diluted with sat. $NaHCO_3$ and extracted with EtOAc (3x). The combined organic phases were washed with brine (15 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (MeOH/CH_2Cl_2: 0/100 to 10/90). Indole **3-51** was obtained as a yellow-brown foam (0.066 g, 33%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (bs, 1 H), 7.59 (d, *J* = 7.6 Hz, 1 H), 7.54 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 7.17-7.08 (m, 2 H), 6.95 (d, *J* = 8.4 Hz, 6.69 (d, *J* = 1.6 Hz, 1 H), 4.14 (bs, 1 H), 3.79 (d, 12 Hz, 2 H), 3.24 (bs, 2 H), 2.84-2.77 (m, 2 H), 2.66-2.46 (m, 11 H), 1.78 (bs, 4 H), 1.48 (s, 9 H), 1.04 (d, *J* = 6.4 Hz, 6 H); HRMS (ESI): *m/z* calculated for $C_{33}H_{48}O_2N_5$ (M+H) 546.3803, found 546.3802.

1-(4-(1*H*-Indol-2-yl)phenyl)-*N*-(2-(4-isopropylpiperazin-1-yl)ethyl)piperidin-4-amine (3-52). To a solution of **3-51** (0.060 g, 0.110 mmol) in CH_2Cl_2 (2.8 mL) was added Et_3SiH (44.3 µL, 0.275 mmol) and TFA (0.572 mL, 7.70 mmol). After 1 h, the solution was concentrated, diluted with sat. $NaHCO_3$, extracted with EtOAc (3x), washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (MeOH/CH_2Cl_2: 5/95 to 100/0) followed by filtering through a plug of basic Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 5/95). Product **3-52** was obtained as a yellow solid (0.017 g, 35%): m.p. 197-198.6 °C; IR (neat) 3438, 2930, 2810, 1610, 1548, 1504, 1455, 1350, 1298, 1221, 1178, 1112, 984, 917, 824, 786, 749, 662 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.32 (bs, 1 H), 7.59 (d, *J* = 7.5 Hz, 1 H), 7.54 (d, *J* = 9.0 Hz, 2 H), 7.36 (d, *J* = 7.8 Hz, 1 H), 7.17-7.06 (m, 2 H), 6.98 (d, *J* = 9.0 Hz, 2 H), 6.68 (d, *J* = 1.2 Hz, 1 H), 3.74 (d, *J* = 13 Hz, 2 H), 2.88-2.76 (m, 5 H), 2.70-2.43 (m, 11 H), 1.99 (d, *J* = 11 Hz, 2 H),

1.52 (qd, *J* = 13, 11, 3.9, 2.4 Hz, 2 H), 1.06 (d, *J* = 6.3 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 138.4, 136.6, 129.6, 126.1, 123.1, 121.6, 120.2, 120.0, 116.3, 110.6, 98.2, 58.0, 55.0, 54.5, 53.5, 48.7, 48.1, 43.4, 32.4, 27.8, 18.7; HRMS (ESI): *m/z* calculated for $C_{28}H_{40}N_5$ (M+H) 446.3278, found 446.3278; ELS purity (97.9%).



Scheme 3-12. Synthesis of 5-chloroindole analog.

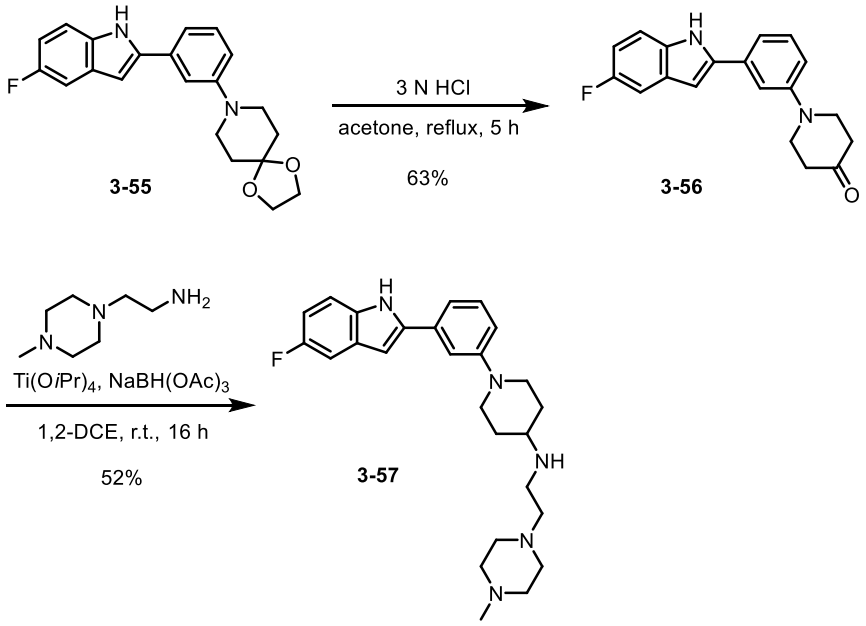


1-(3-(5-Chloro-1*H*-indol-2-yl)phenyl)piperidin-4-one (3-53). To a solution of 8-(3-(5-chloro-1*H*-indol-2-yl)phenyl)-1,4-dioxa-8-azaspiro[4.5]decane (0.100 g, 0.271 mmol) in acetone (35

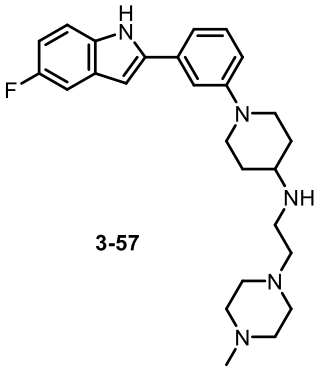
mL) was added HCl (3 M, 35 mL) at room temperature and the reaction was heated to reflux. After 3 h, the solution was cooled to room temperature and stirred at room temperature 16 h. The reaction was then cooled to 0 °C and neutralized with Na_2CO_3. The aqueous was extracted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 5/95 to 50/50). Indole **3-53** was obtained as an orange solid (0.053 g, 61%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 1.36 Hz, 1 H), 7.39 (t, *J* = 7.8 Hz, 1 H), 7.33-7.37 (m, 2 H), 7.20 (d, *J* = 6.8 Hz, 1 H), 7.15 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.01 (d, *J* = 8.0 Hz, 1 H), 6.75 (d, *J* = 1.6 Hz, 1 H), 3.70 (t, *J* = 6.0 Hz, 4 H), 2.66 (t, *J* = 5.4 Hz, 4 H).

1-(3-(5-Chloro-1*H*-indol-2-yl)phenyl)-*N*-(1-isopropylpiperidin-4-yl)piperidin-4-amine (3-54). To a solution of **3-53** (0.050 g, 0.154 mmol), 4-amino-1-isopropyl piperidine (0.028 mL, 0.169 mmol) in 1,2-DCE (1.52 mL) was added Ti(O*i*Pr)$_4$ (0.052 mL, 0.169 mmol) and stirred at room temperature. After 30 min, $NaBH(OAc)_3$ (0.016 g, 0.072 mmol) was added. After an additional 1 h, $NaBH(OAc)_3$ (0.016 g, 0.072 mmol) was added and the solution was stirred at rooom temperature 16 h. Additional $NaBH(OAc)_3$ (0.016 g, 0.072 mmol) was added and stirred for 4 h. The solution was diluted with sat. $NaHCO_3$, extracted with EtOAc (2x), dried (Na_2SO_4), filtered, and concentrated. The product was purified by chromatography on Al_2O_3-neutral (MeOH/CH_2Cl_2 + 0.1% Et_3N: 0/100 to 10/90) followed by filtration through a plug of basic Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 5/95). Product **3-54** was obtained as a pale tan foam (0.038 g, 54%): IR (CH_2Cl_2) 3140, 2932, 2817, 1603, 1577, 1447, 1314, 1173, 1122, 916, 855, 781, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (bs, 1 H), 7.56 (d, *J* = 2.0 Hz, 1 H), 7.28 (dd, *J* = 10.0, 8.2 Hz, 2 H), 7.18 (t, *J* = 2.1 Hz, 1 H), 7.11 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.06 (dt, *J* = 7.8, 1.1 Hz, 1 H), 6.89 (dd, *J* = 7.9, 1.9 Hz, 1 H), 6.72 – 6.67 (m, 1 H), 3.71 (dd, *J* = 12.7, 3.9 Hz, 2 H), 2.83

(ddd, *J* = 24.7, 11.7, 3.1 Hz, 5 H), 2.72 (dt, *J* = 13.1, 6.6 Hz, 1 H), 2.60 (tt, *J* = 10.5, 4.0 Hz, 1 H), 2.18 (td, *J* = 11.6, 2.4 Hz, 2 H), 1.92 (td, *J* = 14.0, 3.7 Hz, 5 H), 1.49 (qd, *J* = 11.9, 3.9 Hz, 2 H), 1.35 (qd, *J* = 11.1, 3.7 Hz, 2 H), 1.04 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 140.2, 135.1, 132.8, 130.3, 129.7, 125.7, 122.3, 119.9, 116.4, 116.2, 113.5, 111.9, 99.4, 54.5, 51.6, 51.1, 48.5, 47.8, 33.8, 33.0, 18.5; HRMS (ESI): *m/z* calculated for $C_{27}H_{36}N_4Cl$ (M+H) 451.2623, found 451.2619; ELS purity (100%).



Scheme 3-13. Synthesis of 5-fluoroindole analog with *N*-methylpiperazine terminal group.



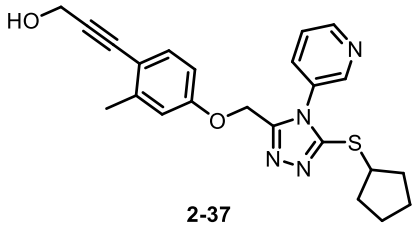
1-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)piperidin-4-one (3-56). To a solution of 8-(3-(5-fluoro-1*H*-indol-2-yl)phenyl)-1,4-dioxa-8-azaspiro[4.5]decane (0.300 g, 0.851 mmol) in acetone (110 mL) was added HCl (3 M, 110 mL) at room temperature then heated to reflux. After 5 h, the solution was cooled to room temperature and stirred 16 h. The reaction was then cooled to 0 °C and neutralized with Na_2CO_3. The mixture was extracted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 5/95 to 50/50). Indole **3-56** was obtained as an orange solid (0.166 g, 63%) and carried on without further characterization: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.35 (bs, 1 H), 7.23-7.40 (m, 4 H), 7.16 (d, *J* = 7.6 Hz, 1 H), 6.91-6.98 (m, 2 H), 6.77 (dd, *J* = 2.1, 0.7 Hz, 1 H), 3.68 (t, *J* = 6.1 Hz, 4 H) 2.60 (t, *J* = 6.1 Hz, 4 H).

1-(3-(5-Fluoro-1*H*-indol-2-yl)phenyl)-N-(2-(4-methylpiperazin-1-yl)ethyl)piperidin-4-amine (3-57). To a solution of **3-56** (0.15 g, 0.49 mmol), 2-(4-methylpiperazin-1-yl)ethan-1-amine (0.077 g, 0.54 mmol) in 1,2-DCE (4.8 mL) was added Ti(O*i*Pr)$_4$ (0.16 mL, 0.54 mmol) at room temperature. After 30 min, $NaBH(OAc)_3$ (0.060 g, 0.27 mmol) was added. After 1 h, additional $NaBH(OAc)_3$ (0.060 g, 0.27 mmol) was added and the solution was stirred at rooom temperature. After 8 h, additional $NaBH(OAc)_3$ (0.060 g, 0.27 mmol) was added. After 4 h, the solution was diluted with sat. $NaHCO_3$, extracted with EtOAc (2x), dried (Na_2SO_4), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2 + 0.1% Et_3N: 0/100 to 20/80) followed by Kugelrohr distillation (40-45 °C, 5 h) to remove Et_3N. Product **3-57** was obtained as a yellow solid (0.111 g, 52%): IR (neat) 3062, 2930, 2811, 1576, 1491, 1456, 1194, 1114, 959, 855, 781, 736 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ 10.80 (s, 1 H), 7.48 – 7.42 (m, 1 H), 7.38 (dd, *J* = 8.8, 4.5 Hz, 1 H), 7.31 – 7.19 (m, 3 H), 6.95 – 6.82 (m, 3 H), 3.76 (dt, *J* = 12.9, 4.1 Hz, 2 H), 3.56 (s, 2 H), 2.86 (td, *J* = 12.5, 11.9, 2.7 Hz, 2 H), 2.74 (t, *J* = 6.1 Hz,

2 H), 2.66 (tt, J = 10.0, 3.9 Hz, 1 H), 2.44 (t, J = 6.1 Hz, 2 H), 2.38 – 2.31 (m, 7 H), 2.17 (s, 3 H), 2.02 – 1.92 (m, 2 H), 1.57 – 1.38 (m, 2 H); ^{13}C NMR (acetone-d_6, 151 MHz) δ 158.7 (d, J_{CF} = 232.1 Hz), 153.1, 141.7, 134.8, 133.8, 130.5 (d, J_{CF} = 10.3 Hz), 130.3, 116.7, 116.4, 113.7, 112.8 (d, J_{CF} = 9.6 Hz), 110.3 (d, J_{CF} = 26.2 Hz), 105.3 (d, J_{CF} = 23.5 Hz), 99.8 (d, J_{CF} = 4.9 Hz), 58.6, 56.0, 55.6, 53.9, 48.7, 46.3, 44.2, 33.0; ^{19}F NMR (acetone-d_6, 565 MHz;) δ -126.4; HRMS (ESI$^+$): *m/z* calculated for $C_{26}H_{35}N_5F$ (M+H) 436.2871, found 436.2869; ELS purity (100%).

3.4 TRIAZOLE EXPERIMENTALS

3.4.1 Analogs of NMS-873 described in Chapter 2.3.12.0



2-37

2-(Prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran. To a solution of propargyl alcohol (0.52 mL, 8.7 mmol) in CH_2Cl_2 (20 mL) was added 3,4-dihydro-2*H*-pyran (0.97 mL, 10 mmol) and the reaction stirred at room temperature for 10 min. *p*-TsOH (0.16 g, 0.87 mmol) was added and the reaction stirred at room temperature 16 h. The reaction was then washed with water, NaOH (1 M), and brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The tetrahydro-2*H*-pyran was obtained as a colorless oil (1.3 g) and carried on without further purification or characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (t, J = 3.1 Hz, 1 H), 4.19-

4.33 (m, 2 H), 3.80-3.87 (m, 1 H), 3.50-3.55 (m, 1 H), 2.41 (t, *J* = 2.4 Hz, 1 H), 1.52-1.82 (m, 6 H).

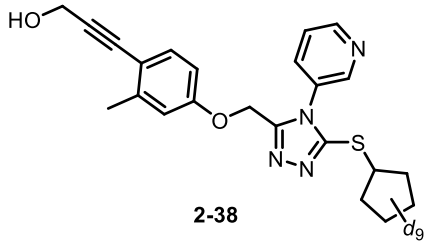
3-Methyl-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol [126]**.** To a solution of 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (0.30 g, 2.1 mmol) and 4-iodo-3-methylphenol (0.46 g, 1.9 mmol) in dry, deoxygenated MeCN (3.3 mL) was added $Pd(PPh_3)_2Cl_2$ (0.070 g, 0.097 mmol) and CuI (0.019 g, 0.097 mmol) followed by Et_3N (0.69 mL, 4.9 mmol). The reaction was stirred at room temperature 16 h. The reaction was diluted with EtOAc, washed with brine, filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 20/80 to 100/0). The tetrahydro-2*H*-pyran was obtained as a brown crystalline solid (0.27 g, 56%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.3 Hz, 1 H), 6.67 (d, *J* = 2.2 Hz, 1 H), 6.59 (dd, *J* = 8.3, 2.4 Hz, 1 H), 4.93 (t, *J* = 3.1 Hz, 1 H), 4.78 (s, 1 H), 4.57-4.46 (m, 2 H), 3.86-3.94 (m, 1 H), 3.53-3.60 (m, 1 H), 2.38 (s, 3 H), 1.57-1.92 (m, 6 H).

3-(3-(Cyclopentylthio)-5-((3-methyl-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenoxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine[60]**.** To a solution of crude 3-(3-(chloromethyl)-5-(cyclopentylthio)-4H-1,2,4-triazol-4-yl)pyridine (0.053 g, 0.18 mmol) in dry DMF (2.8 mL) was added 3-methyl-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol (0.053 g, 0.21 mmol) and Cs_2CO_3 (0.12 g, 0.36 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with EtOAc, and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The triazole was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The product was obtained as a yellow viscous oil (0.072 g, 79%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, *J*

= 4.8, 1.5 Hz, 1 H), 8.59 (dd, *J* = 2.5, 0.5 Hz, 1 H), 7.66 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.44 (ddd, *J* = 8.1, 4.8, 0.7 Hz, 1 H), 7.27 (d, *J* = 8.5 Hz, 1 H), 6.66 (d, *J* = 2.6 Hz, 1 H), 6.61 (dd, *J* = 8.5, 2.6 Hz, 1 H), 5.04 (s, 2 H), 4.88 (t, *J* = 3.4 Hz, 1 H), 4.52-4.43 (m, 2 H), 4.04-4.01 (m, 1 H), 3.86 (ddd, *J* = 11.4, 8.7, 2.9 Hz, 1 H), 3.56-3.50 (m, 1 H), 2.34 (s, 3 H), 2.22-2.14 (m, 2 H), 1.50-1.85 (m, 12 H); HRMS (ESI^+): *m/z* calculated for $C_{28}H_{33}O_3N_4S$ (M+H) 505.2268, found 505.2269.

3-(4-((5-(Cyclopentylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-ol (2-37)[x]**.** To a solution of 3-(3-(cyclopentylthio)-5-((3-methyl-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenoxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (0.072 g, 0.14 mmol) in MeOH (0.5 mL) was added PPTS (9.0 mg, 0.036 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with CH_2Cl_2 (2 mL) and extracted with sat. $NaHCO_3$ (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-37** was obtained as a pale yellow viscous oil (0.032 g, 54%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, *J* = 3.9 Hz, 1 H), 8.60 (s, 1 H), 7.67 (dt, *J* = 8.1, 1.7 Hz, 1 H), 7.45 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.21 (d, *J* = 8.4 Hz, 1 H), 6.63 (d, *J* = 1.7 Hz, 1 H), 6.57 (dd, *J* = 8.5, 2.0 Hz, 1 H), 5.03 (s, 2 H), 4.50 (s, 2 H), 4.07-3.98 (m, 1 H), 2.92 (bs, 1 H), 2.31 (s, 3 H), 2.19-2.15 (m, 2 H), 1.65-1.59 (m, 6 H); HRMS (ESI^+): *m/z* calculated for $C_{23}H_{25}O_2N_4S$ (M+H) 421.1693, found 421.1691.

[x] Full characterization by Marina Kovaliov, described batch not biologically tested



2-38

3-(3-((Cyclopentyl-*d*$_9$)thio)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine[60]. To a solution of 4-(pyridin-3-yl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazole-3-thiol (0.400 g, 1.37 mmol) in DMF (8 mL) was added cyclopentyl bromide-*d*$_9$ (0.123 mL, 1.78 mmol) and Cs_2CO_3 (0.892 g, 2.74 mmol). The reaction was stirred at room temperature for 15 h. The reaction was diluted with EtOAc (20 mL), washed with H_2O and brine (2x), dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The triazole was obtained as a colorless white foam (0.369 g, 73%) and carried on without further characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.64 (dd, *J* = 2.5, 0.4 Hz, 1 H), 7.72 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.49 (ddd, *J* = 8.1, 4.8, 0.7 Hz, 1 H), 4.66 (d, *J* = 12.6 Hz, 1 H), 4.56 (t, *J* = 2.9 Hz, 1 H), 4.49 (d, *J* = 12.6 Hz, 1 H), 3.45-3.39 (m, 2 H), 1.62-1.39 (m, 6 H); HRMS (ESI$^+$): *m/z* calculated for $C_{18}H_{16}{}^2H_9O_2N_4S$ (M+H) 370.2258, found 370.2255.

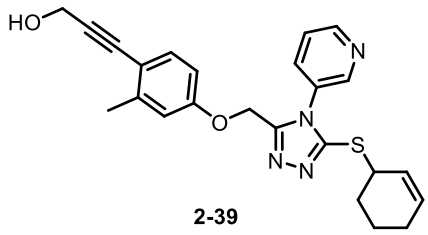
(5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methanol. To a solution of 3-(3-((cyclopentyl-*d*$_9$)thio)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (0.36 g, 0.97 mmol) in MeOH (4.5 mL) was added *p*-TsOH (0.037 g, 0.19 mmol) and the reaction stirred at room temperature for 1.5 d. The reaction was quenched by adding poly(4-vinylpyridine) and stirring for 30 min. The solid filtered off and the solvent concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). The triazole was obtained as a white solid (0.222 g, 80%) and carried on without further characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, *J* = 4.3 Hz, 1 H), 8.68 (d, *J* = 1.9 Hz, 1

H), 7.86 (ddd, *J* = 8.1, 2.4, 1.5 Hz, 1 H), 7.52 (dd, *J* = 8.1, 4.8 Hz, 1 H), 4.63 (s, 2 H), 2.71 (bs, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 153.7, 151.0, 147.9, 135.0, 130.1, 124.2, 54.4, 33.0-32.6 (m, CD), 23.5 (app s, CD).

3-(3-(Chloromethyl)-5-((cyclopentyl-*d*$_9$)thio)-4*H*-1,2,4-triazol-4-yl)pyridine. To a solution of (5-((cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methanol (0.216 g, 0.757 mmol) in dry CH_2Cl_2 (16.5 mL) at 0 °C was added thionyl chloride (82.8 µL, 1.14 mmol) and the reaction stirred at 0 °C for 2 h. The reaction was cooled to 0 °C and quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2 (3x), dried ($MgSO_4$), filtered, and concentrated. The triazole was obtained as a pale-yellow oil and carried on without further purification or characterization: HRMS (ESI^+): *m/z* calculated for $C_{13}H_7{}^2H_9N_4S$ (M+H) 304.1344, found 304.1342.

4-(3-Hydroxyprop-1-yn-1-yl)-3-methylphenol[127]**.** To a solution of 4-iodo-3-methylphenol (1.4 g, 6.2 mmol) and propargyl alcohol (0.41 mL, 7.1 mmol) in dry, deoxygenated MeCN (11.2 mL) was added CuI (0.082 g, 0.43 mmol) and $Pd(PPh_3)_2Cl_2$ (0.26 g, 0.37 mmol) followed by Et_3N (1.8 mL, 13 mmol). The reaction was stirred at room temperature 16 h. The reaction was concentrated and dissolved in H_2O (20 mL) and Et_2O (20 mL) then 1M HCl (2 mL) was added. The aqueous was extracted with Et_2O (2x) and the combined organic layers washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The phenol was obtained as an orange solid (0.667 g, 67%) and carried on without further characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.3 Hz, 1 H), 6.67 (d, *J* = 2.6 Hz, 1 H), 6.60 (ddd, *J* = 8.3, 2.6, 0.4 Hz, 1 H), 5.00 (s, 1 H), 4.52 (d, *J* = 6.1 Hz, 2 H), 2.38 (s, 3 H), 1.65 (t, *J* = 6.1 Hz, 1 H); HRMS (ESI^-): *m/z* calculated for $C_{10}H_9O_2$ (M-H) 161.0597, found 161.0600.

3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-ol (2-38)[xi]**.** To a solution of crude 3-(3-(chloromethyl)-5-((cyclopentyl-*d*$_9$)thio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.230 g, 0.757 mmol) in dry DMF (12.3 mL) was added 4-(3-hydroxyprop-1-yn-1-yl)-3-methylphenol (0.160 g, 0.984 mmol) and Cs_2CO_3 (0.370 g, 1.14 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-38** was obtained as a white foam (0.311 g, 96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.61 (d, *J* = 2.4 Hz, 1 H), 7.67 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.46 (ddd, *J* = 8.1, 4.8, 0.6 Hz, 1 H), 7.24 (d, *J* = 8.5 Hz, 1 H), 6.65 (d, *J* = 2.5 Hz, 1 H), 6.60 (dd, *J* = 8.5, 2.6 Hz, 1 H), 5.05 (s, 2 H), 4.50 (d, *J* = 5.7 Hz, 2 H), 2.43-2.39 (m, 1 H), 2.33 (s, 3 H); HRMS (ESI$^+$): *m/z* calculated for $C_{23}H_{16}{}^2H_9O_2N_4S$ (M+H) 430.2258, found 430.2256.



2-39

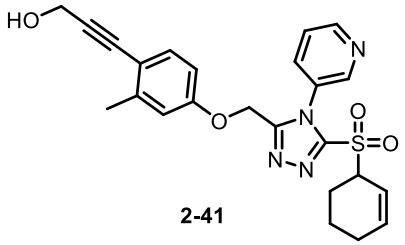
(5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and **3-(3-(chloromethyl)-5-(cyclohex-2-en-1-ylthio)-4*H*-1,2,4-triazol-4-yl)pyridine.** To a solution of (5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methanol (0.290 g, 1.01 mmol) and DiPEA (219 µL, 1.26 mmol) in CH_2Cl_2 (10.8 mL) at 0 °C was added MsCl

[xi] Full characterization by Marina Kovaliov, described batch not biologically tested

(85.6 µL, 1.11 mmol) dropwise. The reaction was stirred at 0 °C and slowly warmed to room temperature over 2.5 h. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$ and sat. NH_4Cl, dried ($MgSO_4$), filtered, and concentrated. The triazole was obtained a mixture of the mesylate and chloride and carried on without purification or characterization: HRMS (ESI^+) mesylate: *m/z* calculated for $C_{15}H_{19}O_3N_4S_2$ (M+H) 367.0893, found 367.0890; HRMS (ESI^+) chloride: *m/z* calculated for $C_{14}H_{16}N_4ClS$ (M+H) 307.0779, found 307.0776.

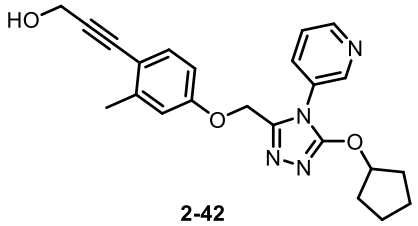
3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-ol (2-39)[xii]**.** To a solution of the mixture from above (0.369 g, 1.01 mmol) in dry DMF (14.8 mL) was added 4-(3-hydroxyprop-1-yn-1-yl)-3-methylphenol (0.180 g, 1.11 mmol) and Cs_2CO_3 (0.361 g, 1.11 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-39** was obtained as an off-white solid (0.365 g, 84%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.61 (d, *J* = 2.4 Hz, 1 H), 7.67 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.46 (ddd, *J* = 8.1, 4.8, 0.6 Hz, 1 H), 7.27 (d, *J* = 8.9 Hz, 1 H), 6.68 (d, *J* = 2.5 Hz, 1 H), 6.63 (dd, *J* = 8.5, 2.6 Hz, 1 H), 5.90-5.85 (m, 1 H), 5.77-5.72 (m, *J* = 1.9 Hz, 1 H), 5.10-5.03 (m, 2 H), 4.59-4.55 (m, 1 H), 4.51 (d, *J* = 5.9 Hz, 2 H), 2.36 (s, 3 H), 2.13-1.97 (m, 4 H), 1.84 (t, *J* = 6.1 Hz, 1 H), 1.78-1.65 (m, 2 H); HRMS (ESI^+): *m/z* calculated for $C_{24}H_{25}O_2N_4S$ (M+H) 433.1693, found 433.1690.

[xii] Full characterization by Michael Houghton; described batch not biologically tested



2-41

3-(4-((5-(Cyclohex-2-en-1-ylsulfonyl)-4-(pyridin-3-yl)-4H-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-ol (2-41)[85]**.** To a solution of **2-39** (0.055 g, 0.13 mmol) in EtOAc (0.4 mL) and H_2O (0.04 mL) was added Na_2WO_4-$2H_2O$ (4.8 mg, 0.014 mmol). The reaction was cooled to 0 °C and treated with H_2O_2 (0.039 mL, 30%). After 1 h, the reaction was warmed to room temperature and stirred 16 h. LCMS showed no reaction so MeOH (0.4 mL) was added to dissolve everything and the reaction stirred for 5 h. The reaction was diluted with satd. $NaHCO_3$, extracted with EtOAc, washed with brine, dried ($MgSO_4$), filtered and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). Product **2-41** was obtained as a pale yellow foam (6.0 mg, 10%): IR (neat) 3325, 2921, 2862, 2235, 2178, 1603, 1484, 1445, 1324, 1229, 1139, 1029, 913, 819, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.8, 1.2 Hz, 1 H), 8.68 (d, *J* = 2.5 Hz, 1 H), 7.77-7.81 (m, 1 H), 7.47 (dd, *J* = 8.2, 4.8 Hz, 1 H), 7.28 (d, *J* = 8.6 Hz, 1 H), 6.66-6.59 (m, 2 H), 6.23 (dq, *J* = 10.1, 3.0 Hz, 1 H), 5.75 (dq, *J* = 7.7, 2.5 Hz, 1 H), 5.15-5.06 (m, 2 H), 4.51-4.45 (m, 3 H), 2.36 (s, 3 H), 2.26-2.06 (m, 4 H), 1.93-1.79 (m, 2 H), 1.67-1.61 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 153.4, 152.9, 152.0, 147.8, 142.6, 137.8, 135.3, 133.7, 129.4, 123.9, 116.6, 116.1, 115.8, 112.0, 90.6, 84.0, 61.5, 59.5, 51.9, 24.5, 22.0, 21.0, 19.2; HRMS (ESI^+): *m/z* calculated for $C_{24}H_{25}O_4N_4S$ (M+H) 465.1591, found 465.1590; ELS purity (100%).



2-42

3-(3-(Cyclopentylsulfonyl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (2-44).[85] To a solution of **2-43** (0.54 g, 1.50 mmol) in EtOAc (4.8 mL) and H_2O (0.48 mL) was added Na_2WO_4-$2H_2O$ (0.057 g, 0.17 mmol). The reaction was cooled to 0 °C and treated with H_2O_2 (30 wt%, 0.046 mL, 4.50 mmol). After 1 h, the reaction was warmed to room temperature and stirred for 16 h. An additional 2 eq. of H_2O_2 (0.3 mL) was added and the reaction stirred for 8 h. LCMS still showed starting material so an additional 2 eq. H_2O_2 was added and the reaction stirred for 16 h. The reaction was diluted with sat. $NaHCO_3$, extracted with EtOAc, washed with brine, dried ($MgSO_4$), filtered and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Triazole **2-44** was obtained as a white solid (0.495 g, 84%): IR (neat) 2948, 2871, 1711, 1581, 1485, 1444, 1321, 1144, 1124, 1077, 1034, 901, 827, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.79 (d, *J* = 4.8 Hz, 1 H), 8.73 (d, *J* = 2.3 Hz, 1 H), 7.85 (ddd, *J* = 8.1, 2.1, 1.6 Hz, 1 H), 7.51 (dd, *J* = 8.1, 4.8 Hz, 1 H), 4.72 (d, *J* = 12.8 Hz, 1 H), 4.52-4.54 (m, 2 H), 4.19 (quintet, *J* = 7.9 Hz, 1 H), 3.35-3.42 (m, 2 H), 2.14 (q, *J* = 7.0 Hz, 4 H), 1.76-1.80 (m, 2 H), 1.67-1.72 (m, 2 H) 1.41-1.61 (m, 6 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.7, 153.3, 151.7, 148.1, 135.4, 129.6, 123.8, 98.7, 63.5, 61.8, 58.4, 30.0, 27.1, 26.1, 25.1, 18.7; HRMS (ESI^+): *m/z* calculated for $C_{18}H_{25}O_4N_4S$ (M+H) 393.1591, found 393.1589.

(5-(Cyclopentylsulfonyl)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methanol (2-45). To a solution of **2-44** (0.480 g, 1.22 mmol) in MeOH (5.6 mL) was added PPTS (0.307 g, 1.22 mmol) and the reaction stirred at room temperature for 22 h. TLC showed mainly starting material

remaining so *p*-TsOH (tip of spatula) was added and the reaction stirred for 1 d. The reaction was diluted with EtOAc and quenched with $NaHCO_3$. The aqueous was extracted with EtOAc (3x) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). Triazole **2-45** was obtained as a white solid (0.297 g, 79%): m.p. 179.0-180.6 °C; IR (neat) 3201, 3067, 2974, 2934, 2874, 1582, 1487, 1434, 1330, 1316, 1306, 1146, 1048, 1001, 829, 707 cm^{-1}; ^1H NMR ($CD_3OD/CDCl_3$, 600 MHz) δ 8.58 (dd, *J* = 4.8, 0.8 Hz, 1 H), 8.54 (d, *J* = 2.1 Hz, 1 H), 7.78 (ddd, *J* = 8.2, 2.5, 1.5 Hz, 1 H), 7.42 (dd, *J* = 8.1, 4.9 Hz, 1 H), 4.42 (s, 2 H), 4.14 (bs, 1 H), 3.90 (quintet, *J* = 7.9 Hz, 1 H), 1.90-1.93 (m, 4 H) 1.49-1.63 (m, 4 H); ^{13}C NMR ($CD_3OD/CDCl_3$, 150 MHz) δ 157.0, 152.5, 151.0, 147.3, 135.8, 129.5, 124.1, 63.5, 53.4, 26.6, 25.7; HRMS (ESI^+): *m/z* calculated for $C_{13}H_{17}O_3N_4S$ (M+H) 309.1016, found 309.1014.

3-(3-(Cyclopentylsulfonyl)-5-(((2-methoxypropan-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (2-46). To a solution of **2-45** (0.28 g, 0.91 mmol) in THF (6 mL) at 0 °C was added 2-methoxypropene (0.17 mL, 1.8 mmol) and PPTS (0.023 g, 0.091 mmol). The reaction was stirred at 0 °C for 1 h then diluted with CH_2Cl_2 and quenched with $NaHCO_3$. The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. Triazole **2-46** was obtained as a white solid (0.35 g) and carried on without further purification or characterization: ^1H NMR (300 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 4.8, 0.9 Hz, 1 H), 8.73 (d, *J* = 2.3 Hz, 1 H), 7.84 (dt, *J* = 8.2, 1.8 Hz, 1 H), 7.50 (dd, *J* = 8.1, 4.9 Hz, 1 H), 4.48 (s, 2 H), 4.20 (quintet, *J* = 7.9 Hz, 1 H), 2.98 (s, 3 H), 2.18-2.11 (m, 4 H), 1.86-1.65 (m, 4 H), 1.19 (s, 6 H).

3-(3-(Cyclopentyloxy)-5-(((2-methoxypropan-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (2-47). To a solution of cyclopentanol (0.11 mL, 1.2 mmol) in THF (1 mL) at 0 °C was added NaH (0.039 g, 0.99 mmol) and the reaction warmed to room temperature for 30 min.

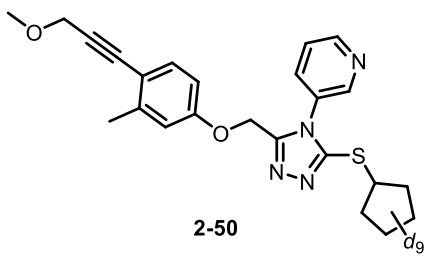
A solution of **2-46** (0.15 g, 0.39 mmol) in DMF (1.7 mL) was added and the reaction stirred at room temperature for 3.5 h. The reaction was cooled to room temperature, quenched with sat. NH_4Cl, and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and SiO_2 was added and stirred for 30 min. The solvent was removed, and the material dry loaded onto the column. Triazole **2-47** was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0; MeOH/CH_2Cl_2: 0/100 to 10/90; EtOAc: 100). The product was obtained as a colorless oil (0.089 g, 68%) and carried on without further characterization: HRMS (ESI^+): *m/z* calculated for $C_{17}H_{25}O_3N_4$ (M+H) 333.1921, found 333.1919.

(5-(Cyclopentyloxy)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methanol (2-48). To a solution of **2-47** (0.085 g, 0.26 mmol) in MeOH (0.5 mL) at 5 °C (ice bath) was added PPTS (tip of spatula). The reaction was stirred at this temperature for 2.75 h. The reaction was quenched with sat. $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Triazole **2-48** was obtained as a white foam (0.063 g, 63%) and carried on without further purification or characterization: ^1H NMR (500 MHz, $CDCl_3$) δ 8.71 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.69 (dd, *J* = 2.5, 0.6 Hz, 1 H), 7.86 (ddd, *J* = 8.2, 2.5, 1.5 Hz, 1 H), 7.49 (ddd, *J* = 8.2, 4.8, 0.8 Hz, 1 H), 5.43 (app septet, *J* = 2.8 Hz, 1 H), 4.58 (d, *J* = 5.1 Hz, 2 H), 3.64 (s, 1 H), 1.92-2.00 (m, 3 H), 1.91-1.84 (m, 3 H), 1.66-1.59 (m, 6 H); HRMS (ESI^+): *m/z* calculated for $C_{13}H_{17}O_2N_4$ (M+H) 261.1346, found 261.1344.

(5-(Cyclopentyloxy)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate (2-49). To a solution of **2-48** (0.062 g, 0.16 mmol) and DiPEA (0.056 mL, 0.32 mmol) in CH_2Cl_2 (3.2 mL) at 0 °C was added MsCl (0.022 mL, 0.28 mmol) dropwise. The reaction was stirred at 0 °C and slowly warmed to room temperature over about 2 h. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$ and sat. NH_4Cl, dried ($MgSO_4$), filtered, and concentrated. Triazole **2-**

49 was obtained as a brown oil and carried on without purification or characterization: HRMS (ESI^+): *m/z* calculated for $C_{14}H_{19}O_4N_4S$ (M+H) 339.1122, found 339.1118.

3-(4-((5-(Cyclopentyloxy)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-ol (2-42). To a solution of crude **2-49** (0.054 g, 0.16 mmol) in dry DMF (2.6 mL) was added 4-(3-hydroxyprop-1-yn-1-yl)-3-methylphenol (0.034 g, 0.21 mmol) and Cs_2CO_3 (0.078 g, 0.24 mmol) and the reaction stirred at room temperature for 18 h. The reaction was diluted with EtOAc, and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was combined with a crude batch and purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0) followed by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 5/95). Product **2-42** was obtained as a waxy off-white solid (0.047 g, 33% combined): m.p. 145.3-147.8 °C; IR (neat) 3237, 2961, 2856, 1561, 1489, 1460, 1301, 1233, 1029, 1014, 956, 812, 705 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.7 Hz, 1 H), 8.59 (d, *J* = 2.1 Hz, 1 H), 7.67 (dt, *J* = 8.2, 1.8 Hz, 1 H), 7.41 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.19 (s, 1 H), 6.62 (d, *J* = 2.2 Hz, 1 H), 6.56 (dd, *J* = 8.5, 2.4 Hz, 1 H), 5.41 (tt, *J* = 5.6, 2.7 Hz, 1 H), 4.95 (s, 2 H), 4.49 (s, 2 H), 3.75 (bs, 1 H), 2.28 (s, 3 H), 1.95-1.90 (m, 2 H), 1.84-1.81 (m, 2 H), 1.63-1.55 (m, 4 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.6, 150.3, 147.33, 147.28, 142.3, 134.0, 133.4, 129.4, 124.1, 116.2, 115.7, 111.9, 90.9, 85.2, 83.5, 60.3, 51.3, 32.8, 23.6, 20.9; HRMS (ESI^+): *m/z* calculated for $C_{23}H_{25}O_3N_4$ (M+H) 405.1921, found 405.1917; ELS purity (100%).



2-50

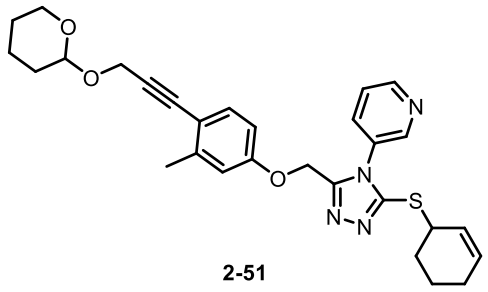
3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl methanesulfonate[128, 129]**.** To a solution of **2-38** (0.12 g, 0.28 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.079 mL, 0.56 mmol) and MsCl (0.026 mL, 0.34 mmol) and the reaction stirred at 0 °C for 3.5 h. The reaction was diluted with EtOAc and washed with sat. $NaHCO_3$, sat. NH_4Cl, and brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude triazole was obtained as a brown orange oil and carried on without further purification or characterization: HRMS (ESI^+): *m/z* calculated for $C_{24}H_{18}{}^2H_9O_4N_4S_2$ (M+H) 508.2026, found 508.2032.

3-(3-((Cyclopentyl-*d*$_9$)thio)-5-((4-(3-methoxyprop-1-yn-1-yl)-3-methylphenoxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (2-50). 3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl methanesulfonate (0.070 g, 0.14 mmol) was dissolved in MeOH (0.5 mL) and the reaction stirred 16 h at room temperature. The reaction was concentrated and loaded onto the column. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 10/90) followed by chromatography on C18-SiO_2 (RP-ISCO, MeCN/H_2O: 10/90 to 95/5). Product **2-50** was obtained as a colorless viscous oil (0.020 g, 33%)[130]

Alternatively:

To a solution of crude 3-(3-(chloromethyl)-5-((cyclopentyl-*d*$_9$)thio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.027 g, 0.088 mmol) in dry DMF (1.3 mL) was added 4-(3-methoxyprop-1-yn-1-yl)-3-methylphenol (0.016 g, 0.091 mmol) and Cs_2CO_3 (0.031 g, 0.096 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2

(ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-50** was obtained as white foam (0.019 g, 48%): IR (neat) 3047, 2928, 2223, 2110, 1603, 1484, 1445, 1290, 1230, 1167, 1094, 1021, 996, 817, 707 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (bs, 1 H), 8.61 (bs, 1 H), 7.67 (d, *J* = 8.2 Hz, 1 H), 7.46 (dd, *J* = 7.5, 4.8 Hz, 1 H), 7.28 (d, *J* = 8.5 Hz, 1 H), 6.68 (d, *J* = 2.1 Hz, 1 H), 6.63 (dd, *J* = 8.5, 2.4 Hz, 1 H), 5.05 (s, 2 H), 4.32 (s, 2 H), 3.43 (s, 3 H), 2.36 (s, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 157.3, 154.2, 151.36, 151.24, 148.2, 142.5, 134.8, 133.7, 130.3, 124.2, 115.9, 112.1, 88.0, 84.9, 60.6, 60.1, 57.6, 45.6 (t, J_{CD} = 23.8 Hz), 33.0 (dt, J_{CD} = 40.3, 20.4 Hz), 23.6 (t, J_{CD} = 20.1 Hz), 21.0; HRMS (ESI^+): *m/z* calculated for $C_{24}H_{18}{}^{2}H_9O_2N_4S$ (M+H) 444.2414, found 444.2407; ELS purity (100%).



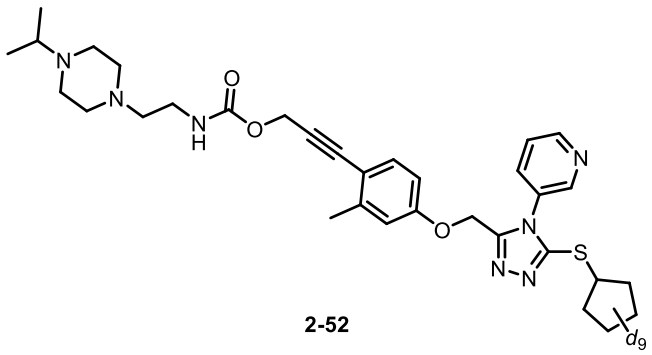
2-51

2-(Prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran. To a solution of propargyl alcohol (0.52 mL, 8.7 mmol) in CH_2Cl_2 (20 mL) was added 3,4-dihydro-2*H*-pyran (0.97 mL, 10 mmol) and the reaction stirred at room temperature for 10 min. *p*-TsOH (0.16 g, 0.87 mmol) was added and the reaction stirred at room temperature 16 h. The reaction was then washed with water, NaOH (1 M), and brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude tetrahydro-2*H*-pyran was obtained as a colorless oil (1.3 g, >100%) and carried on without further purification or characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (t, *J* = 3.1 Hz, 1 H), 4.33-4.19 (m, 2 H), 3.87-3.80 (m, 1 H), 3.55-3.50 (m, 1 H), 2.41 (t, *J* = 2.4 Hz, 1 H), 1.82-1.52 (m, 6 H).

3-Methyl-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol[126]**.** To a solution of 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (0.30 g, 2.1 mmol) and 4-iodo-3-methylphenol (0.46 g, 1.9 mmol) in dry, deoxygenated MeCN (3.3 mL) was added $Pd(PPh_3)_2Cl_2$ (0.070 g, 0.097 mmol) and CuI (0.019 g, 0.097 mmol) followed by Et_3N (0.69 mL, 4.9 mmol). The reaction was stirred at room temperature 16 h. The reaction was diluted with EtOAc, washed with brine, filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 20/80 to 100/0). The phenol was obtained as a brown crystalline solid (0.27 g, 56%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.3 Hz, 1 H), 6.67 (d, *J* = 2.2 Hz, 1 H), 6.59 (dd, *J* = 8.3, 2.4 Hz, 1 H), 4.93 (t, *J* = 3.1 Hz, 1 H), 4.78 (s, 1 H), 4.57-4.46 (m, 2 H), 3.94-3.86 (m, 1 H), 3.60-3.53 (m, 1 H), 2.38 (s, 3 H), 1.92-1.57 (m, 6 H).

3-(3-(Cyclohex-2-en-1-ylthio)-5-((3-methyl-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenoxy)methyl)-4H-1,2,4-triazol-4-yl)pyridine (2-51). To the crude mixture of (5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and 3-(3-(chloromethyl)-5-(cyclohex-2-en-1-ylthio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.063 g, 0.17 mmol) in dry DMF (2.7 mL) was added 3-methyl-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol (0.051 g, 0.21 mmol) and Cs_2CO_3 (0.11 g, 0.34 mmol) and the reaction stirred at room temperature 16 h. The reaction was cooled to room temperature, diluted with EtOAc, and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-51** was obtained as a pale yellow viscous oil (0.056 g, 64%): IR (neat) 3039, 2941, 2859, 1736, 1604, 1484, 1443, 1231, 1118, 1021, 869, 815, 732, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 3.9 Hz, 1 H), 8.59 (d, *J* = 2.0 Hz, 1 H), 7.66 (ddd, *J* = 8.1, 2.5, 1.5 Hz, 1 H), 7.44 (dd, *J* = 8.1, 4.8 Hz, 1 H),

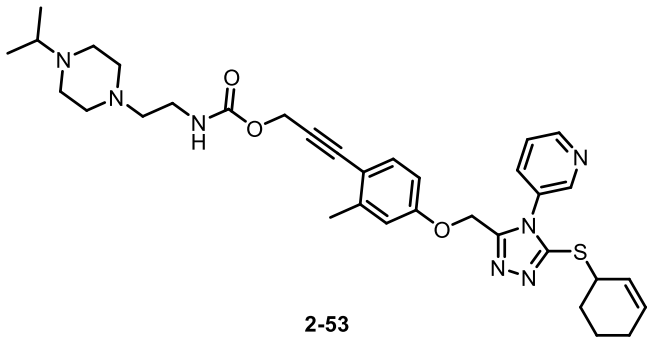
7.26 (d, *J* = 8.5 Hz, 1 H), 6.65 (d, *J* = 2.6 Hz, 1 H), 6.60 (dd, *J* = 8.5, 2.6 Hz, 1 H), 5.84 (ddq, *J* = 9.8, 3.8, 1.9 Hz, 1 H), 5.71 (ddt, *J* = 9.9, 3.9, 2.0 Hz, 1 H), 5.07-5.01 (m, 2 H), 4.88 (t, *J* = 3.4 Hz, 1 H), 4.54 (dd, *J* = 4.2, 1.8 Hz, 1 H), 4.52-4.42 (m, 2 H), 3.85 (ddd, *J* = 11.4, 8.7, 2.9 Hz, 1 H), 3.55-3.50 (m, 1 H), 2.33 (s, 3 H), 2.0-1.97 (m, 4 H), 1.73-1.50 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 153.5, 151.4, 151.2, 148.1, 142.5, 134.8, 133.6, 132.4, 130.03, 129.92, 125.4, 124.1, 116.2, 115.7, 111.9, 96.7, 88.0, 84.2, 62.1, 59.9, 54.9, 44.1, 30.4, 29.2, 25.4, 24.9, 21.0, 19.2; HRMS (ESI^+): *m/z* calculated for $C_{29}H_{33}O_3N_4S$ (M+H) 517.2268, found 517.2272; ELS purity (100%).



2-52

3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl (2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (2-52)[131]**.** To a solution of **2-38** (0.300 g, 0.698 mmol) in dry CH_2Cl_2 (10.3 mL) was added CDI (0.170 g, 1.05 mmol) and the reaction stirred at room temperature under argon for 2 h. 2-(4-Isopropylpiperazin-1-yl)ethan-1-amine (0.179 g, 1.05 mmol) was added and the reaction stirred at room temperature. After stirring for 15 h additional 2-(4-isopropylpiperazin-1-yl)ethan-1-amine (0.120 g, 0.698 mmol) was added and the reaction stirred for 1 d. The reaction was then diluted with CH_2Cl_2 and washed with water. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90).

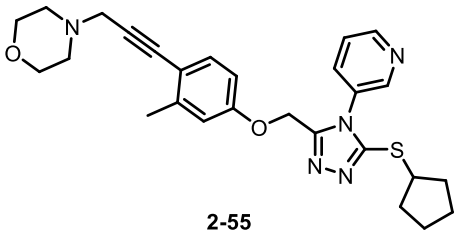
The concentrated fractions were taken up in CH_2Cl_2 and washed with water to remove residual imidazole. Product **2-52** was obtained as a sticky pale yellow foam (0.348 g, 76%): IR (neat) 3280, 2964, 2814, 2225, 1719, 1604, 1495, 1485, 1230, 1126, 1022, 816, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (dd, *J* = 4.8, 0.8 Hz, 1 H), 8.56 (d, *J* = 2.5 Hz, 1 H), 7.64 (dddd, *J* = 8.1, 2.3, 1.5, 0.7 Hz, 1 H), 7.41 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.23 (d, *J* = 8.5 Hz, 1 H), 6.63 (d, *J* = 2.4 Hz, 1 H), 6.58 (dd, *J* = 8.5, 2.6 Hz, 1 H), 5.45 (t, *J* = 4.3 Hz, 1 H), 5.01 (s, 2 H), 4.86 (s, 2 H), 3.25 (q, *J* = 5.7 Hz, 2 H), 2.61 (dquintet, *J* = 13.0, 6.5 Hz, 1 H), 2.54-2.32 (m, 10 H), 2.30 (s, 3 H), 0.99 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 157.3, 155.6, 154.0, 151.13, 151.12, 148.0, 142.6, 134.7, 133.7, 130.0, 124.0, 115.7, 111.9, 99.4, 86.5, 84.6, 59.8, 56.7, 54.4, 53.3, 53.0, 48.5, 37.5, 45.0-45.7 (m, CD), 32.3-33.2 (m, CD), 22.5-23.9 (m, CD), 20.9, 18.5; HRMS (ESI^+): *m/z* calculated for $C_{33}H_{35}{}^2H_9O_3N_7S$ (M+H) 627.3786, found 627.3783; ELS purity (100%).



2-53

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl (2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (2-53)[131]. To a solution of **2-39** (0.055 g, 0.13 mmol) in dry CH_2Cl_2 (1.5 mL) was added CDI (0.023 g, 0.14 mmol) and the reaction stirred at room temperature under argon for 2 h. A solution of 2-(4-isopropylpiperazin-1-yl)ethan-1-amine (0.033 g, 0.19 mmol) in dry CH_2Cl_2 (0.5 mL) was then

added and the reaction stirred for 2 d at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 20/80) followed by filtration through a plug of basic Al_2O_3 (MeOH/ CH_2Cl_2: 0/100 to 3/97). Product **2-53** was obtained as a white foam (0.058 g, 73%): IR (neat) 3303, 2936, 2815, 1719, 1485, 1445, 1230, 1127, 1023, 984, 707 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 8.74 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.71 (d, *J* = 2.5 Hz, 1 H), 7.98 (ddd, *J* = 8.1, 2.5, 1.5 Hz, 1 H), 7.62 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.27 (d, *J* = 8.5 Hz, 1 H), 6.82 (d, *J* = 2.5 Hz, 1 H), 6.75 (dd, *J* = 8.5, 2.6 Hz, 1 H), 6.27 (t, *J* = 4.1 Hz, 1 H), 5.86 (dtd, *J* = 9.8, 3.8, 1.6 Hz, 1 H), 5.72 (ddt, *J* = 9.9, 4.2, 2.1 Hz, 1 H), 5.22-5.17 (m, 2 H), 4.88 (s, 2 H), 4.41 (qd, *J* = 4.2, 2.0 Hz, 1 H), 3.25 (q, *J* = 6.1 Hz, 2 H), 2.58 (dquintet, *J* = 13.1, 6.5 Hz, 1 H), 2.50-2.35 (m, 10 H), 2.32 (s, 3 H), 2.04-1.99 (m, 3 H), 1.95 (ddt, *J* = 14.0, 6.9, 3.5 Hz, 1 H), 1.71 (ddtd, *J* = 13.8, 10.4, 7.0, 3.4 Hz, 1 H), 1.65-1.59 (m, 1 H), 0.96 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (150 MHz, acetone-d_6) δ 158.7, 156.3, 152.9, 152.5, 151.8, 149.0, 143.0, 136.0, 134.1, 132.6, 131.2, 126.5, 125.0, 116.7, 116.3, 113.1, 88.3, 84.6, 60.9, 58.2, 54.8, 54.4, 53.1, 49.2, 44.8, 38.9, 25.4, 20.8, 19.8, 18.8; HRMS (ESI^+): *m/z* calculated for $C_{34}H_{44}O_3N_7S$ (M+H) 630.3221, found 630.3221; ELS purity (100%).



2-55

Prop-2-yn-1-yl 4-methylbenzenesulfonate. To a solution of propargyl alcohol (0.52 mL, 8.7 mmol) and TsCl (1.7 g, 9.1 mmol) in Et_2O (17.3 mL) at -20 °C was added powdered KOH (3.4 g, 52 mmol). The reaction was stirred allowed to warm to 0 °C over 1 h and then stirred for an

additional 1 h. The reaction was then poured into water and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The tosylate was obtained as a pale brown oil (1.4 g, 74%) and carried on without further purification or characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.80 (m, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 4.70 (d, *J* = 2.5 Hz, 2 H), 2.47 (t, *J* = 2.5 Hz, 1 H), 2.45 (s, 3 H).

4-(Prop-2-yn-1-yl)morpholine[132, 133]**.** To a solution of prop-2-yn-1-yl 4-methylbenzenesulfonate (1.00 g, 4.76 mmol) in THF (4.6 mL) was added morpholine (0.832 mL, 9.51 mmol) and K_2CO_3 (1.31 g, 9.51 mmol). The reaction was stirred at room temperature 16 h and diluted with EtOAc (5 mL). The combined organic layers were washed with sat. NH_4Cl (5 mL) and brine, then the aqueous layers were extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The morpholine was purified by Kugelrohr distillation (250 Torr, 150 °C). The product was obtained as a colorless oil (0.533 g, 64%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (app t, *J* = 4.7 Hz, 4 H), 3.29 (d, *J* = 2.4 Hz, 2 H), 2.57 (app t, *J* = 4.7 Hz, 4 H), 2.26 (t, *J* = 2.4 Hz, 1 H).

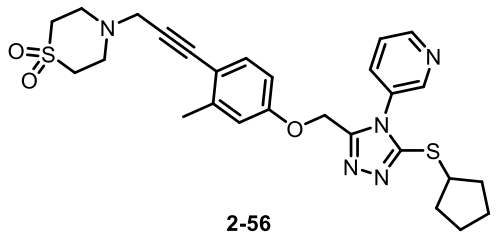
3-Methyl-4-(3-morpholinoprop-1-yn-1-yl)phenol[126]**.** To a solution of 4-(prop-2-yn-1-yl)morpholine (0.30 g, 1.7 mmol) and 4-iodo-3-methylphenol (0.44 g, 1.9 mmol) in dry, deoxygenated MeCN (4.6 mL) was added $Pd(PPh_3)_2Cl_2$ (0.061 g, 0.085 mmol) and CuI (0.017 g, 0.085 mmol) followed by Et_3N (0.60 mL, 4.3 mmol). The reaction was stirred at room temperature 16 h. The reaction was diluted with EtOAc, washed with brine, filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 20/80 to 100/0). The phenol was obtained as a brown crystalline solid (0.29 g, 73%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.3 Hz, 1 H), 6.84 (s, 1 H), 6.64 (d, *J* = 2.3 Hz, 1 H), 6.57 (dd, *J* = 8.3, 2.5 Hz, 1 H), 3.81 (app t, *J* = 4.7 Hz, 4 H),

3.56 (s, 2 H), 2.70 (app t, *J* = 4.7 Hz, 4 H), 2.30 (s, 3 H); HRMS (ESI^+): *m/z* calculated for $C_{14}H_{18}O_2N$ (M+H) 232.1332, found 232.1333.

(5-(Cyclopentylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and **3-(3-(chloromethyl)-5-(cyclopentylthio)-4*H*-1,2,4-triazol-4-yl)pyridine**. To a solution of (5-(cyclopentylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methanol (0.050 g, 0.18 mmol) and DiPEA (0.063 mL, 0.36 mmol) in CH_2Cl_2 (2.4 mL) at 0 °C was added MsCl (0.024 mL, 0.32 mmol) dropwise. The reaction was stirred at 0 ° C and slowly warmed to room temperature over about 2 h. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$ and sat. NH_4Cl, dried ($MgSO_4$), filtered, and concentrated. The triazole was obtained as a mixture of mesylate and chloride and carried on without purification or characterization: HRMS (ESI^+) chloride: *m/z* calculated for $C_{13}H_{16}N_4ClS$ (M+H) 295.0779, found 295.0776; HRMS (ESI^+) mesylate: *m/z* calculated for $C_{14}H_{19}O_3N_4S_2$ (M+H) 355.0893, found 355.0891.

4-(3-(4-((5-(Cyclopentylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl)morpholine (2-55). To a solution of the mixture from above (0.064 g, 0.18 mmol) in dry DMF (3 mL) was added 3-methyl-4-(3-morpholinoprop-1-yn-1-yl)phenol (0.054 g, 0.23 mmol) and Cs_2CO_3 (0.088 g, 0.27 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 10/00). Product **2-55** was obtained as a pale red foam (0.039 g, 44%): IR (neat) 3423, 3049, 2955, 2858, 1603, 1485, 1448, 1290, 1230, 1167, 1114, 1003, 861, 819, 707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.4 Hz, 1 H), 8.59 (d, *J* = 1.8 Hz, 1 H), 7.66 (d, *J* = 8.1 Hz, 1 H), 7.43 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.24 (d, *J* = 8.5 Hz, 1 H), 6.65 (d, *J* =

2.1 Hz, 1 H), 6.60 (dd, *J* = 8.5, 2.4 Hz, 1 H), 5.03 (s, 2 H), 4.01 (quintet, *J* = 6.6 Hz, 1 H), 3.73 (t, *J* = 4.5 Hz, 4 H), 3.50 (s, 2 H), 2.60 (t, *J* = 4.3 Hz, 4 H), 2.33 (s, 3 H), 2.19-2.15 (m, 2 H), 1.69-1.59 (m, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 157.0, 154.0, 151.29, 151.18, 148.1, 142.1, 134.8, 133.5, 130.1, 124.1, 116.6, 115.8, 112.0, 86.8, 84.0, 66.9, 59.9, 52.4, 48.2, 46.1, 33.9, 24.7, 21.2; HRMS (ESI^+): *m/z* calculated for $C_{27}H_{32}O_2N_5S$ (M+H) 490.2271, found 490.2270; ELS purity (100%).



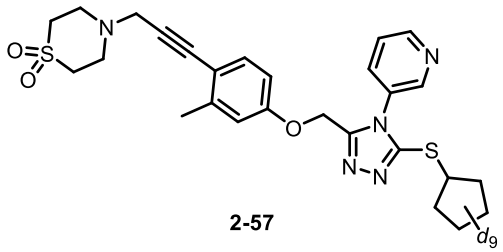
2-56

4-(Prop-2-yn-1-yl)thiomorpholine 1,1-dioxide[132, 133]**.** To a solution of thiomorpholine-1,1-dioxide (0.500 g, 2.85 mmol) and K_2CO_3 (1.18 g, 8.56 mmol) in MeCN (5.8 mL) was added prop-2-yn-1-yl 4-methylbenzenesulfonate (0.720 g, 3.43 mmol) . The reaction was stirred at room temperature 16 h then concentrated. The residue was resuspended in EtOAc, filtered, and loaded onto and ISCO cartridge. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). The thiomorpholine 1,1-dioxide was obtained as a white solid (0.212 g, 43%) and carried on without further characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.43 (d, *J* = 2.5 Hz, 2 H), 3.11-3.08 (m, 8 H), 2.33 (t, *J* = 2.4 Hz, 1 H); HRMS (ESI^+): *m/z* calculated for $C_7H_{12}O_2NS$ (M+H) 174.0583, found 174.0582.

4-(3-(4-Hydroxy-2-methylphenyl)prop-2-yn-1-yl)thiomorpholine 1,1-dioxide[126]**.** To a solution of 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (0.10 g, 0.58 mmol) and 4-iodo-3-methylphenol (0.15 g, 0.63 mmol) in dry, deoxygenated MeCN (1.1 mL) was added $Pd(PPh_3)_2Cl_2$ (0.021 g, 0.029 mmol) and CuI (5.6 mg, 0.029 mmol) followed by Et_3N (0.20 mL,

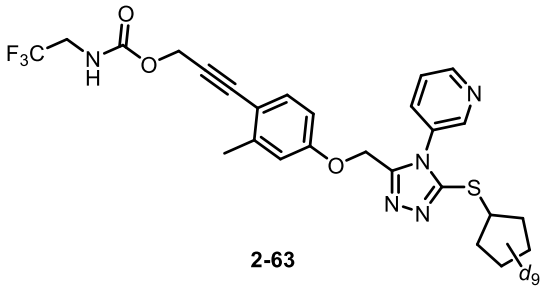
1.4 mmol). The reaction was stirred at room temperature 16 h. The reaction was diluted with EtOAc, washed with brine, filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 20/80 to 100/0). The phenol was obtained as a tan foam (0.094 g, 58%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 1 H), 6.65 (bs, 1 H), 6.58 (dd, *J* = 8.5, 1.5 Hz, 1 H), 3.65 (s, 2 H), 3.1-3.06 (m, 8 H), 2.35 (s, 3 H).

4-(3-(4-((5-(Cyclopentylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (2-56). To a solution of crude 3-(3-(chloromethyl)-5-(cyclopentylthio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.043 g, 0.15 mmol) in dry DMF (2.4 mL) was added 4-(3-(4-hydroxy-2-methylphenyl)prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (0.053 g, 0.19 mmol) and $CsCO_3$ (0.071 g, 0.22 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 10/00). Product **2-56** was obtained as a white foam (0.063 g, 80%): IR (neat) 2951, 2869, 2232, 1604, 1485, 1447, 1296, 1230, 1125, 1047, 907, 724, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.60 (d, *J* = 2.1 Hz, 1 H), 7.67 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.46 (ddd, *J* = 8.1, 4.8, 0.6 Hz, 1 H), 7.25 (d, *J* = 8.5 Hz, 1 H), 6.68 (d, *J* = 2.5 Hz, 1 H), 6.63 (dd, *J* = 8.5, 2.6 Hz, 1 H), 5.06 (s, 2 H), 4.00-4.07 (m, 1 H), 3.65 (s, 2 H), 3.15-3.08 (m, 8 H), 2.35 (s, 3 H), 2.22-2.15 (m, 2 H), 1.71-1.59 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 154.1, 151.22, 151.20, 148.0, 142.2, 134.8, 133.5, 130.1, 124.1, 115.96, 115.80, 112.0, 85.7, 84.7, 59.9, 51.5, 50.2, 47.7, 46.1, 33.8, 24.6, 21.2; HRMS (ESI^+): *m/z* calculated for $C_{27}H_{32}O_3N_5S_2$ (M+H) 538.1941, found 538.1943; ELS purity (100%).



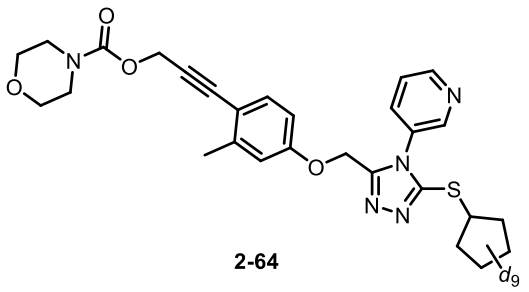
2-57

4-(3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (2-57). To a solution of crude 3-(3-(chloromethyl)-5-((cyclopentyl-*d*$_9$)thio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.028 g, 0.092 mmol) in dry DMF (1.5 mL) was added 4-(3-(4-hydroxy-2-methylphenyl)prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (0.033 g, 0.12 mmol) and Cs_2CO_3 (0.045 g, 0.14 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 10/00). Product **2-57** was obtained as a white foam (0.041 g, 81%): IR (neat) 3376, 2928, 2849, 2229, 1602, 1486, 1446, 1296, 1232, 1125, 1022, 951, 828, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.59 (d, *J* = 2.3 Hz, 1 H), 7.67 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.45 (ddd, *J* = 8.1, 4.8, 0.6 Hz, 1 H), 7.24 (d, *J* = 8.5 Hz, 1 H), 6.67 (d, *J* = 2.6 Hz, 1 H), 6.62 (dd, *J* = 8.5, 2.6 Hz, 1 H), 5.05 (s, 2 H), 3.64 (s, 2 H), 3.14-3.07 (m, 8 H), 2.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 154.1, 151.2, 148.1, 142.2, 134.8, 133.6, 130.1, 124.1, 115.99, 115.83, 112.0, 85.7, 84.7, 59.9, 51.6, 50.2, 47.7, 33.1-32.7 (m, CD), 24.0-23.1 (m, CD), 21.2; HRMS (ESI$^+$): *m/z* calculated for $C_{27}H_{23}{}^2H_9O_3N_5S_2$ (M+H) 547.2506, found 547.2501; ELS purity (100%).



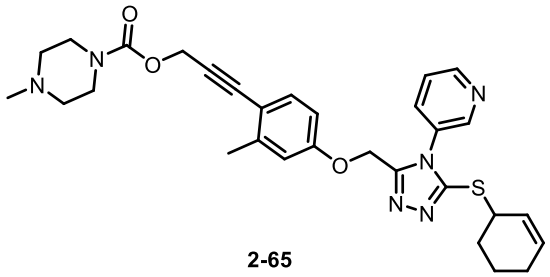
2-63

3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl (2,2,2-trifluoroethyl)carbamate (2-63)[131]**.** To a solution of **2-38** (0.055 g, 0.13 mmol) in dry CH_2Cl_2 (1.5 mL) was added CDI (0.023 g, 0.14 mmol) and the reaction stirred at room temperature under argon for 2 h. 2,2,2-Trifluoroethylamine (0.015 mL, 0.19 mmol) was then added and the reaction stirred 16 h at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-63** was obtained as a white foam (0.012 g, 16%): IR (neat) 3238, 3048, 2939, 2228, 1730, 1551, 1485, 1284, 1230, 1147, 1032, 829, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.61 (dd, *J* = 2.5, 0.3 Hz, 1 H), 7.67 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.46 (ddd, *J* = 8.1, 4.8, 0.6 Hz, 1 H), 7.28 (d, *J* = 8.5 Hz, 1 H), 6.68 (d, *J* = 2.6 Hz, 1 H), 6.63 (dd, *J* = 8.5, 2.6 Hz, 1 H), 5.26 (t, *J* = 5.4 Hz, 1 H), 5.06 (s, 2 H), 4.96 (s, 2 H), 3.84 (qd, *J* = 8.8, 6.9 Hz, 2 H), 2.35 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 155.5, 154.3, 151.31, 151.27, 148.1, 142.9, 134.9, 133.9, 130.2, 122.7-125.5 (m, CD), 124.2, 120.0, 115.9, 115.6, 112.0, 85.8, 85.4, 59.9, 54.5, 42.9 (q, J_{CF} = 35.0 Hz), 32.9 (app d, J_{CF} = 276.9 Hz) 23.6 (dt, J_{CD} = 38.7, 19.4 Hz), 21.0; HRMS (ESI^+): *m/z* calculated for $C_{26}H_{18}{}^2H_9O_3N_5F_3S$ (M+H) 555.2346, found 555.2343; ELS purity (100%).



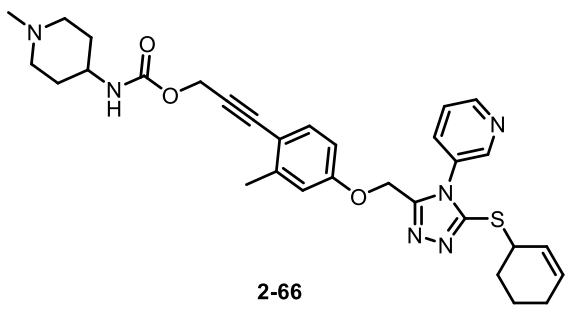
2-64

3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl morpholine-4-carboxylate (2-64). To a solution of **2-38** (0.055 g, 0.13 mmol) in dry CH_2Cl_2 (1.5 mL) was added CDI (0.023 g, 0.14 mmol) and the reaction stirred at room temperature under argon for 2 h. Morpholine (0.017 mL, 0.19 mmol) was then added and the reaction stirred 16 h at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0) followed by chromatography on C18-SiO_2 (RP-ISCO, MeCN/H_2O: 10/90 to 95/5). Product **2-64** was obtained as a white foam (0.054 g, 78%): IR (neat) 2920, 2858, 2225, 1701, 1603, 1431, 1278, 1231, 1115, 1022, 817, 728, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.58 (d, *J* = 2.5 Hz, 1 H), 7.66 (dddd, *J* = 8.2, 2.5, 1.6, 0.5 Hz, 1 H), 7.44 (ddt, *J* = 8.1, 4.8, 0.8 Hz, 1 H), 7.26 (d, *J* = 8.5 Hz, 1 H), 6.66 (d, *J* = 2.2 Hz, 1 H), 6.61 (dd, *J* = 8.5, 2.6 Hz, 1 H), 5.03 (s, 2 H), 4.92 (s, 2 H), 3.63 (bs, 4 H), 3.47 (t, *J* = 4.7 Hz, 4 H), 2.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 154.6, 154.1, 151.2, 148.0, 142.7, 134.7, 133.7, 130.1, 124.1, 115.74, 115.69, 111.9, 86.5, 84.8, 66.6, 59.9, 54.1, 44.3-44.0 (m, CD), 32.8 (dt, J_{CD} = 39.0, 19.1 Hz) 23.6 (dd, J_{CD} = 39.3, 19.7 Hz), 20.9; HRMS (ESI^+): *m/z* calculated for $C_{28}H_{23}{}^2H_9O_4N_5S$ (M+H) 543.2733, found 543.2734; ELS purity (100%).



2-65

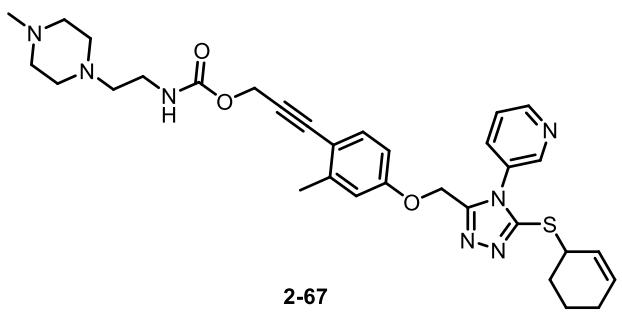
3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl 4-methylpiperazine-1-carboxylate (2-65). To a solution of **2-39** (0.050 g, 0.12 mmol) in dry CH_2Cl_2 (2 mL) was added CDI (0.028 g, 0.17 mmol) and the reaction stirred at room temperature under argon for 2 h. 1-Methylpiperazine (0.019 mL, 0.17 mmol) was added and the reaction stirred at room temperature 16 h. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 12.5/87.5) followed by chromatography on SiO_2 (ISCO, MeOH/ CH_2Cl_2: 0/100 to 8/92), the mixed fractions were re-purified by (ISCO, MeOH/ CH_2Cl_2: 0/100 to 10/90). Product **2-65** was obtained as a pale yellow oil (0.030 g, 46%): IR (neat) 2937, 2793, 2231, 1702, 1604, 1439, 1292, 1231, 1148, 1004, 820, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.7, 1.2 Hz, 1 H), 8.61 (d, *J* = 2.2 Hz, 1 H), 7.67 (dt, *J* = 8.1, 1.8 Hz, 1 H), 7.46 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.30 (d, *J* = 8.5 Hz, 1 H), 6.68 (d, *J* = 2.0 Hz, 1 H), 6.63 (dd, *J* = 8.5, 2.3 Hz, 1 H), 5.90-5.85 (m, 1 H), 5.75 (dt, *J* = 10.1, 1.9 Hz, 1 H), 5.07 (s, 2 H), 4.93 (s, 2 H), 4.57 (d, *J* = 2.0 Hz, 1 H), 3.53 (t, *J* = 5.0 Hz, 4 H), 2.36-2.39 (m, 6 H), 2.30 (s, 3 H), 2.17-2.01 (m, 5 H), 1.80-1.67 (m, 2 H); ^{13}C NMR ($CDCl_3$, 76 MHz) δ 157.4, 154.7, 153.5, 151.4, 151.2, 148.1, 142.8, 134.8, 133.8, 132.4, 130.1, 125.5, 124.1, 115.8, 112.0, 86.8, 84.7, 60.0, 54.8, 54.0, 46.2, 44.2, 43.9, 29.3, 24.9, 20.9, 19.3; HRMS (ESI^+): *m/z* calculated for $C_{30}H_{35}O_3N_6S$ (M+H) 559.2486, found 559.2486; ELS purity (100%).



2-66

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl (1-methylpiperidin-4-yl)carbamate (2-66). To a solution of **2-39** (0.050 g, 0.12 mmol) in dry CH_2Cl_2 (2 mL) was added CDI (0.028 g, 0.17 mmol) and the reaction stirred at room temperature under argon for 2 h. 4-Amino-1-methylpiperidine (0.022 mL, 0.17 mmol) was added and the reaction stirred 16 h at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 40/60) followed by chromatography on SiO_2 (ISCO, MeOH/ CH_2Cl_2: 0/100 to 20/80) and the mixed fractions were repurified by (ISCO, MeOH/ CH_2Cl_2: 0/100 to 12.5/87.5). Product **2-66** was obtained as a white foam (0.026 g, 39%): IR (neat) 3257, 2936, 1718, 1604, 1485, 1447, 1270, 1231, 1045, 868, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.72 (dd, *J* = 4.7, 0.8 Hz, 1 H), 8.59 (d, *J* = 2.2 Hz, 1 H), 7.65 (ddd, *J* = 8.1, 2.3, 1.6 Hz, 1 H), 7.43 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 6.66 (d, *J* = 2.0 Hz, 1 H), 6.60 (dd, *J* = 8.5, 2.3 Hz, 1 H), 5.87-5.82 (m, 1 H), 5.74-5.69 (m, 1 H), 5.09-5.00 (m, 2 H), 4.88 (s, 2 H), 4.54 (app d, *J* = 2.4 Hz, 1 H), 3.55-3.46 (m, 1 H), 2.73 (d, *J* = 11.5 Hz, 2 H), 2.33 (s, 3 H), 2.24 (s, 3 H), 2.06-1.99 (m, 9 H), 1.73-1.62 (m, 2 H), 1.46 (qd, *J* = 11.7, 3.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 76 MHz) δ 157.4, 155.0, 153.5, 151.4, 151.2, 148.1, 142.8, 134.8, 133.8, 132.4, 130.1, 125.5, 124.1, 115.8, 112.0, 86.6, 84.8, 60.0, 54.4, 53.4, 47.9, 46.2, 44.2, 32.5, 29.3, 24.9, 20.9, 19.3;

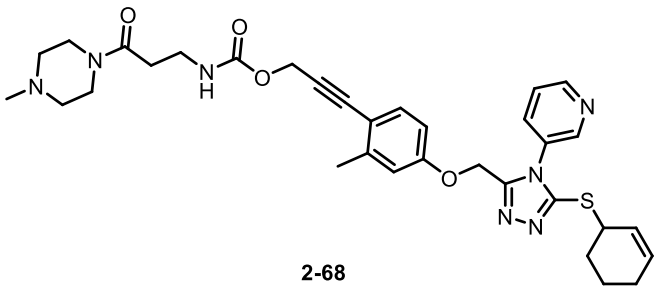
HRMS (ESI^+): *m/z* calculated for $C_{31}H_{37}O_3N_6S$ (M+H) 573.2642, found 573.2642; ELS purity (100%).



2-67

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl (2-(4-methylpiperazin-1-yl)ethyl)carbamate (2-67). To a solution of **2-39** (0.050 g, 0.12 mmol) in dry CH_2Cl_2 (1.5 mL) was added CDI (0.028 g, 0.17 mmol) and the reaction stirred at room temperature under argon for 2 h. A solution of 2-(4-isopropylpiperazin-1-yl)ethan-1-amine (0.025 g, 0.17 mmol) in dry CH_2Cl_2 (0.5 mL) was then added and the reaction stirred at room temperature for 3 d. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 40/60) followed by chromatography on SiO_2 (ISCO, MeOH/ CH_2Cl_2: 0/100 to 15/85). Product **2-67** was obtained as a white foam (0.020 g, 28%): IR (neat) 3282, 2935, 2796, 1717, 1604, 1485, 1444, 1230, 1165, 1012, 818, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.60 (d, *J* = 2.5 Hz, 1 H), 7.66 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.44 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.28 (d, *J* = 8.5 Hz, 1 H), 6.67 (d, *J* = 2.4 Hz, 1 H), 6.62 (dd, *J* = 8.5, 2.6 Hz, 1 H), 5.88-5.84 (m, 1 H), 5.73 (dt, *J* = 9.9, 2.1 Hz, 1 H), 5.37 (s, 1 H), 5.05 (s, 2 H), 4.91 (s, 2 H), 4.56 (dd, *J* = 3.8, 1.5 Hz, 1 H), 3.28 (q, *J* = 5.7 Hz, 2 H), 2.47 (t, *J* = 6.0 Hz, 8 H), 2.35 (s, 3 H), 2.26 (s, 3 H), 2.08-1.99 (m, 5 H), 1.73-1.64 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4,

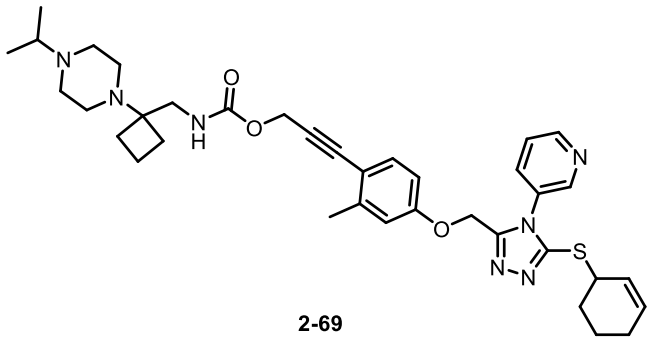
155.7, 153.6, 151.41, 151.27, 148.1, 142.8, 134.8, 133.9, 132.5, 130.1, 125.5, 124.1, 115.8, 112.0, 86.6, 84.8, 59.9, 56.8, 55.2, 53.5, 52.9, 46.1, 44.1, 37.7, 29.3, 24.9, 21.0, 19.2; HRMS (ESI^+): *m/z* calculated for $C_{32}H_{40}O_3N_7S$ (M+H) 602.2908, found 602.2907; ELS purity (100%).



2-68

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl (3-(4-methylpiperazin-1-yl)-3-oxopropyl)carbamate (2-68). To a solution of **2-39** (0.050 g, 0.12 mmol) in dry CH_2Cl_2 (1.5 mL) was added CDI (0.028 g, 0.17 mmol) and the reaction stirred at room temperature under argon for 2 h. A solution of 3-amino-1-(4-methylpiperazin-1-yl)propan-1-one (0.030 g, 0.17 mmol) in dry CH_2Cl_2 (0.5 mL) was then added and the reaction stirred 16 h at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 30/70) followed by chromatography on SiO_2 (ISCO, MeOH/ CH_2Cl_2: 0/100 to 10/90). Product **2-68** was obtained as a white foam (0.025 g, 34%): IR (neat) 3284, 2936, 2795, 1718, 1634, 1442, 1226, 1138, 1000, 817, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (dd, *J* = 4.8, 1.6 Hz, 1 H), 8.59 (d, *J* = 2.0 Hz, 1 H), 7.65 (ddd, *J* = 8.1, 2.5, 1.4 Hz, 1 H), 7.44 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.26 (dd, *J* = 8.6, 2.0 Hz, 1 H), 6.66 (d, *J* = 1.2 Hz, 1 H), 6.61 (dd, *J* = 8.6, 1.9 Hz, 1 H), 5.87-5.83 (m, 1 H), 5.74-5.70 (m, 1 H), 5.66 (t, *J* = 5.3 Hz, 1 H), 5.07-5.01 (m, 2 H), 4.87 (s, 2 H), 4.55-4.54 (m, 1 H), 3.60 (dd, *J* = 9.3, 5.2 Hz, 2 H), 3.50-3.45 (m, 2 H), 3.42-3.40 (m, 2 H),

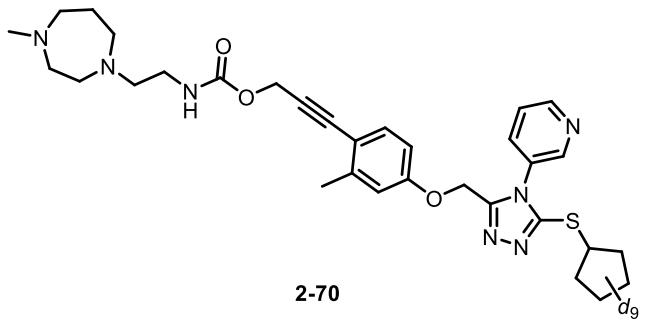
2.50 (t, *J* = 5.6 Hz, 2 H), 2.35-2.33 (m, 7 H), 2.27 (s, 3 H), 2.07-1.97 (m, 4 H), 1.73-1.62 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 157.4, 155.8, 153.5, 151.41, 151.25, 148.1, 142.7, 134.8, 133.8, 132.5, 130.1, 125.5, 124.1, 115.81, 115.76, 112.0, 86.6, 84.6, 59.9, 55.0, 54.7, 53.4, 46.1, 45.2, 44.1, 41.5, 36.9, 33.2, 29.3, 24.9, 21.0, 19.2; HRMS (ESI^+): *m/z* calculated for $C_{33}H_{404}N_7S$ (M+H) 630.2857, found 630.2858; ELS purity (100%).



2-69

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl ((1-(4-isopropylpiperazin-1-yl)cyclobutyl)methyl)carbamate (2-69). To a solution of **2-39** (0.050 g, 0.12 mmol) in dry CH_2Cl_2 (1.5 mL) was added CDI (0.028 g, 0.17 mmol) and the reaction stirred at room temperature under argon for 2 h. A solution of (1-(4-isopropylpiperazin-1-yl)cyclobutyl)methanamine (0.037 g, 0.17 mmol) in dry CH_2Cl_2 (0.5 mL) was then added and the reaction stirred for 2 d at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 10/90). Product **2-69** was obtained as a white foam (0.056 g, 73%): IR (neat) 3388, 2936, 2815, 1717, 1604, 1485, 1445, 1222, 1123, 1022, 984, 732, 706 cm^{-1}; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.74 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.71 (d, *J* = 2.5 Hz, 1 H), 7.98 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.62 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.27 (d, *J* = 8.5 Hz, 1 H),

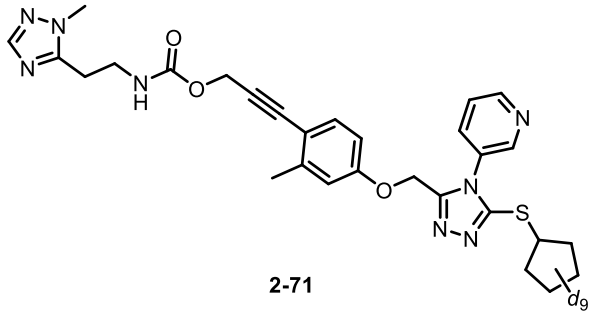
6.81 (d, *J* = 2.5 Hz, 1 H), 6.75 (dd, *J* = 8.5, 2.6 Hz, 1 H), 6.08 (t, *J* = 5.4 Hz, 1 H), 5.86 (dtd, *J* = 9.8, 3.8, 1.6 Hz, 1 H), 5.72 (ddt, *J* = 9.9, 4.1, 2.1 Hz, 1 H), 5.22-5.17 (m, 2 H), 4.89 (s, 2 H), 4.41 (dtt, *J* = 6.3, 4.2, 2.1 Hz, 1 H), 3.38 (d, *J* = 5.8 Hz, 2 H), 2.57 (tt, *J* = 13.1, 6.5 Hz, 1 H), 2.51 (bs, 4 H), 2.44 (bs, 4 H), 2.32 (s, 3 H), 2.10-1.93 (m, 6 H), 1.77-1.62 (m, 6 H), 0.96 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (150 MHz, acetone-d_6) δ 158.7, 156.7, 152.9, 152.5, 151.9, 149.0, 143.0, 136.0, 134.1, 132.7, 131.2, 126.5, 125.0, 116.7, 116.3, 113.1, 88.3, 84.7, 63.5, 60.9, 54.8, 53.3, 50.5, 49.9, 46.1, 44.8, 44.1, 27.8, 27.5, 25.4, 20.9, 19.8, 18.8, 13.9; HRMS (ESI$^+$): *m/z* calculated for $C_{37}H_{48}O_3N_7S$ (M+H) 670.3534, found 670.3534; ELS purity (100%).



2-70

3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl (2-(4-isopropyl-1,4-diazepan-1-yl)ethyl)carbamate (2-70). To a solution of **2-38** (0.055 g, 0.13 mmol) in dry CH_2Cl_2 (1.5 mL) was added CDI (0.031 g, 0.19 mmol) and the reaction stirred at room temperature under argon for 2 h. A solution of 2-(4-isopropyl-1,4-diazepan-1-yl)ethan-1-amine (0.036 g, 0.19 mmol) in dry CH_2Cl_2 (0.5 mL) was then added and the reaction stirred for 2 d at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 60/40) followed by filtration through basic Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 10/90). Product **2-70** was obtained as a colorless viscous oil/goo (0.041 g, 49%): IR (neat) 3314, 2931,

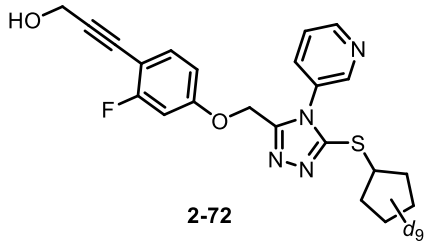
2819, 2224, 1719, 1604, 1485, 1230, 1122, 1023, 997, 818, 707 cm^{-1}; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.74 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.71 (dd, *J* = 2.5, 0.5 Hz, 1 H), 7.97 (ddd, *J* = 8.1, 2.6, 1.5 Hz, 1 H), 7.62 (ddd, *J* = 8.1, 4.8, 0.7 Hz, 1 H), 7.27 (d, *J* = 8.5 Hz, 1 H), 6.81 (d, *J* = 2.5 Hz, 1 H), 6.74 (dd, *J* = 8.5, 2.6 Hz, 1 H), 6.26 (t, *J* = 5.5 Hz, 1 H), 5.18 (s, 2 H), 4.88 (s, 2 H), 3.21 (q, *J* = 6.1 Hz, 2 H), 2.82 (dquintet, *J* = 13.2, 6.6 Hz, 1 H), 2.69-2.67 (m, 2 H), 2.64-2.62 (m, 4 H), 2.59 (dt, *J* = 6.3, 3.3 Hz, 4 H), 2.32 (s, 3 H), 1.69 (dt, *J* = 12.1, 6.0 Hz, 2 H), 0.94 (d, *J* = 6.6 Hz, 6 H); ^{13}C NMR (150 MHz, acetone-d_6) δ 158.7, 156.4, 153.5, 152.3, 151.9, 149.0, 143.0, 136.0, 134.1, 131.3, 125.1, 116.7, 116.3, 113.1, 88.3, 84.6, 60.9, 57.9, 57.7, 55.6, 54.5, 53.1, 51.5, 50.2, 46.2 (t, J_{CD} = 23.8 Hz), 39.8, 33.3 (t, J_{CD} = 19.7 Hz) 24.1 (dd, J_{CD} = 40.7, 19.8 Hz), 20.8, 18.6; HRMS (ESI^{+}): *m/z* calculated for $C_{34}H_{37}{}^{2}H_9O_3N_7S$ (M+H) 641.3942, found 641.3940; ELS purity (100%).



2-71

3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl (2-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate (2-71). To a solution of **2-38** (0.055 g, 0.13 mmol) in dry CH_2Cl_2 (1.5 mL) was added CDI (0.031 g, 0.19 mmol) and the reaction stirred at room temperature under argon for 2 h. A solution of 2-(1-methyl-1H-1,2,4-triazol-5-yl)ethan-1-amine (0.024 g, 0.19 mmol) in dry CH_2Cl_2 (0.5 mL) was then added and the reaction stirred for 2 d at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered,

and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 10/90). Product **2-71** was obtained as a yellow foam (0.065 g, 87%): IR (neat) 3264, 3049, 2949, 2224, 1711, 1485, 1445, 1222, 1124, 1021, 997, 819, 707 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 8.74 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.71 (t, *J* = 1.2 Hz, 1 H), 7.98 (ddt, *J* = 8.1, 2.6, 1.3 Hz, 1 H), 7.68 (bs, 1 H), 7.62 (ddd, *J* = 8.1, 4.8, 0.5 Hz, 1 H), 7.27 (d, *J* = 8.5 Hz, 1 H), 6.81 (d, *J* = 2.4 Hz, 1 H), 6.75 (dd, *J* = 8.5, 2.5 Hz, 1 H), 5.19 (s, 2 H), 4.89 (s, 2 H), 3.81 (s, 3 H), 3.57-3.53 (m, 2 H), 2.99 (t, *J* = 6.8 Hz, 2 H), 2.31 (s, 3 H); ^{13}C NMR (150 MHz, acetone-d_6) δ 158.7, 156.4, 154.1, 153.5, 152.3, 151.8, 150.6, 149.0, 143.0, 136.0, 134.1, 131.3, 125.1, 116.7, 116.2, 113.1, 88.1, 84.7, 60.9, 53.3, 46.3 (t, J_{CD} = 20.5 Hz), 39.5, 35.3, 33.4 (dd, J_{CD} = 40.1, 19.9 Hz), 26.6, 24.0 (quintet, J_{CD} = 20.9 Hz), 20.8; HRMS (ESI^+): *m/z* calculated for $C_{29}H_{24}{}^2H_9O_3N_8S$ (M+H) 582.2956, found 582.2955; ELS purity (100%).



2-72

4-Bromo-3-fluorophenyl pivalate[134]**.** To a solution of 4-bromo-3-fluorophenol (1.00 g, 5.24 mmol) and Et_3N (0.809 mL, 5.76 mmol) in CH_2Cl_2 (10.5 mL) at 0 °C was added PivCl (0.709 mL, 5.76 mmol). The reaction was stirred at 0 °C for 20 min then diluted with Et_2O (15 mL) and filtered. The filtrate was concentrated and taken up in Et_2O (15 mL), filtered, and concentrated. The product was obtained as a tan oil that solidified in the freezer (1.41 g, 98%) and the pivalate was carried on without further purification or characterization: ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.6, 7.9 Hz, 1 H), 6.92 (dd, *J* = 9.1, 2.6 Hz, 1 H), 6.79 (ddd, *J* = 8.7, 2.5, 1.2 Hz, 1 H), 1.35 (s, 9 H).

3-Fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl pivalate[135]**.** To a solution of 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (2.65 g, 18.9 mmol) and 4-bromo-3-fluorophenyl pivalate (4.00 g, 14.5 mmol) in deoxygenated Et_3N (11.2 mL) was added $Pd(PPh_3)_4$ (0.840 g, 0.727 mmol) and CuI (0.283 g, 1.45 mmol). The reaction was sparged with argon for 2 min then stirred at reflux 16 h. The reaction was concentrated, and the residue taken up in Et_2O, washed with sat. NH_4Cl and brine, filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 0/100 to 10/90). The pivalate was obtained as a yellow oil (2.95 g, 61%): IR (neat) 2942, 1756, 1615, 1578, 1501, 1365, 1257, 1143, 1109, 1096, 1023, 973, 899, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, *J* = 8.1 Hz, 1 H), 6.86-6.80 (m, 2 H), 4.88 (t, *J* = 3.4 Hz, 1 H), 4.53-4.44 (m, 2 H), 3.86 (ddd, *J* = 11.4, 8.9, 2.8 Hz, 1 H), 3.54 (dtd, *J* = 11.0, 4.3, 1.3 Hz, 1 H), 1.84-1.71 (m, 2 H), 1.66-1.51 (m, 4 H), 1.31 (s, 9 H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 176.3, 163.0 (d, J_{CF} = 253 Hz), 151.9 (d, J_{CF} = 10.3 Hz, 133.9 (d, J_{CF} = 2.0 Hz), 117.4 (d, J_{CF} = 3.4 Hz), 109.8 (d, J_{CF} = 24.1 Hz), 108.8 (d, J_{CF} = 16.1 Hz), 96.9, 90.5 (d, J_{CF} = 3.0 Hz), 78.6, 62.0, 54.7, 39.2, 30.3, 27.0, 25.4, 19.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.4; HRMS (ESI^+): *m/z* calculated for $C_{19}H_{24}O_4F$ (M+H) 335.1652, found 335.1652.

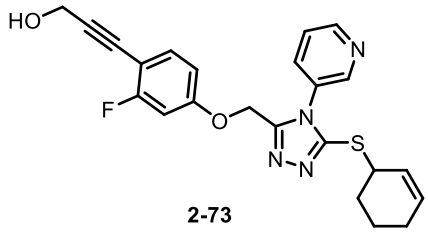
3-Fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol[136]**.** To a solution of 3-fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl pivalate (1.00 g, 2.99 mmol) in THF (44 mL) and MeOH (44 mL) was added a solution of NaOH (1 M, 32.9 mL) dropwise and the reaction was stirred at room temperature 16 h. The reaction was concentrated and diluted with CH_2Cl_2 (100 mL). The solution was then neutralized to pH 7 with 2 N HCl and the aqueous extracted with CH_2Cl_2 (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude phenol was obtained as a yellow oil (0.887 g, 119%) and carried on without further purification or characterization: ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, *J* = 8.4

Hz, 1 H), 6.65-6.60 (m, 2 H), 5.02 (t, *J* = 3.2 Hz, 1 H), 4.63-4.52 (m, 2 H), 3.98 (ddd, *J* = 11.3, 8.7, 2.9 Hz, 1 H), 3.70-3.64 (m, 1 H), 1.97-1.81 (m, 2 H), 1.77-1.60 (m, 4 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.4; HRMS (ESI^-): *m/z* calculated for $C_{14}H_{14}O_3F$ (M-H) 249.0921, found 249.0927.

3-Fluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol. To a solution of 3-fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol (0.408 g, 1.63 mmol) in MeOH (10 mL) was added PPTS (0.102 g, 0.408 mmol) and the reaction stirred at room temperature for 44.5 h. The reaction was diluted with CH_2Cl_2 and extracted with sat. $NaHCO_3$. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The phenol was obtained as a pale yellow solid (0.128 g, 47%): m.p. 101-102.8 °C; IR (neat) 3405, 3225, 2868, 2237, 1619, 1591, 1506, 1469, 1306, 1222, 1152, 1112, 1021, 947, 839, 804 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$/acetone-d_6) δ 6.99 (t, *J* = 8.4 Hz, 1 H), 6.40-6.35 (m, 2 H), 4.26 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$/acetone-d_6,) δ 163.5 (d, J_{CF} = 250.0 Hz), 158.7 (d, J_{CF} = 11.2 Hz), 133.9, 111.4 (d, J_{CF} = 2.4 Hz), 102.9 (d, J_{CF} = 8.1 Hz), 102.8 (d, J_{CF} = 8.0 Hz), 101.8 (d, J_{CF} = 16.2 Hz), 90.6 (d, J_{CF} = 2.9 Hz), 78.2, 50.7; ^{19}F NMR (470 MHz, $CDCl_3$/acetone-d_6,) δ -104.0; HRMS (ESI^-): *m/z* calculated for $C_9H_6O_2F$ (M-H) 165.0346, found 165.0352.

3-(4-((5-((Cyclopentyl-d_9)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-fluorophenyl)prop-2-yn-1-ol (2-72). To a solution of 3-(3-(chloromethyl)-5-((cyclopentyl-d_9)thio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.053 g, 0.17 mmol) in dry DMF (2.9 mL) was added 3-fluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol (0.032 g, 0.19 mmol) and Cs_2CO_3 (0.063 g, 0.19 mmol) and the reaction stirred at room temperature for 18 h. The reaction was diluted with EtOAc, and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The

combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-72** was obtained as an off-white solid (0.074 g, 98%): IR (neat) 3218, 2943, 2855, 2225, 1619, 1576, 1505, 1484, 1396, 1288, 1162, 1023, 836, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.60 (d, *J* = 2.3 Hz, 1 H), 7.67 (ddd, *J* = 8.1, 2.5, 1.5 Hz, 1 H), 7.47 (ddd, *J* = 8.1, 4.8, 0.6 Hz, 1 H), 7.22 (t, *J* = 8.4 Hz, 1 H), 6.60-6.51 (m, 2 H), 5.04 (s, 2 H), 4.48 (d, *J* = 5.5 Hz, 2 H), 3.32 (t, *J* = 5.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (d, J_{CF} = 252.0 Hz), 158.4 (d, J_{CF} = 10.4 Hz), 156.6, 154.4, 151.2, 150.7, 147.9, 134.8, 134.3 (d, J_{CF} = 2.9 Hz), 130.0, 124.2, 110.5 (d, *J* = 3.1 Hz), 104.7 (d, J_{CF} = 16.1 Hz), 102.7 (d, J_{CF} = 25.0 Hz), 92.1 (d, J_{CF} = 3.0 Hz), 78.1, 60.1, 51.3, 45.7-45.2 (m, CD), 33.2-32.4 (m, CD), 23.7-23.3 (m, CD); ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.1; HRMS (ESI^+): *m/z* calculated for $C_{22}H_{13}{}^2H_9O_2N_4FS$ (M+H) 434.2007, found 434.2003; ELS purity (100%).



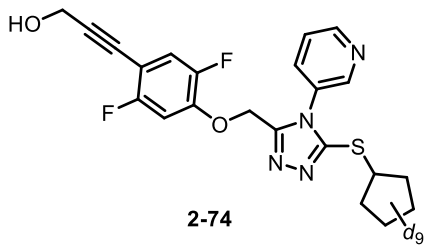
2-73

3-(3-(Cyclohex-2-en-1-ylthio)-5-((3-fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenoxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine. To the crude mixture of (5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and 3-(3-(chloromethyl)-5-(cyclohex-2-en-1-ylthio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.254 g, 0.693 mmol) in dry DMF (10.1 mL) was added 3-fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol (0.191 g, 0.762 mmol) and Cs_2CO_3 (0.248 g, 0.762 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with EtOAc, and organic layer washed with

water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 80/20). The triazole was obtained as an off-white solid (0.227 g, 63%): IR ($CDCl_3$) 3032, 2942, 2863, 2230, 1619, 1571, 1505, 1442, 1286, 1163, 1120, 1021, 902, 814, 726, 707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.60 (d, *J* = 2.4 Hz, 1 H), 7.66 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.48 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.30 (t, *J* = 8.3 Hz, 1 H), 6.61 (ddd, *J* = 17.4, 9.6, 2.5 Hz, 2 H), 5.87 (dtd, *J* = 9.7, 3.8, 1.3 Hz, 1 H), 5.74 (ddd, *J* = 9.9, 4.0, 1.9 Hz, 1 H), 5.09-5.04 (m, 2 H), 4.87 (t, *J* = 3.4 Hz, 1 H), 4.57 (dd, *J* = 3.9, 1.6 Hz, 1 H), 4.47 (q, *J* = 13.4 Hz, 2 H), 3.87 (ddd, *J* = 11.4, 8.9, 2.7 Hz, 1 H), 3.59-3.53 (m, 1 H), 2.12-1.52 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8 (d, J_{CF} = 253.0 Hz), 158.5 (d, J_{CF} = 10.6 Hz), 153.9, 151.4, 150.9, 148.1, 134.8, 134.6 (d, J_{CF} = 3.2 Hz), 132.6, 130.0, 125.5, 124.2, 110.5 (d, J_{CF} = 3.2 Hz), 105.0 (d, J_{CF} = 16.3 Hz), 102.9 (d, J_{CF} = 24.9 Hz), 97.0, 89.6 (d, J_{CF} = 2.9 Hz), 78.9, 62.2, 60.3, 54.9, 44.2, 30.4, 29.3, 25.5, 24.9, 19.26, 19.18; ^{19}F NMR (470 MHz, $CDCl_3$) δ -106.7; HRMS (ESI^+): *m/z* calculated for $C_{28}H_{30}O_3N_4FS$ (M+H) 521.2017, found 521.2014.

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-fluorophenyl)prop-2-yn-1-ol (2-73). To a solution of 3-(3-(cyclohex-2-en-1-ylthio)-5-((3-fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenoxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (0.20 g, 0.38 mmol) in MeOH (1.4 mL) was added PPTS (0.024 g, 0.096 mmol) and the reaction stirred at room temperature for 21 h. The reaction was diluted with CH_2Cl_2 (5 mL) and extracted with sat. $NaHCO_3$ (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-73** was obtained as a pale yellow solid (0.145 g, 87%): m.p. 167.9-

169.4 °C; IR (neat) 3231, 2931, 2854, 1619, 1575, 1504, 1450, 1394, 1318, 1227, 1168, 1121, 1102, 1028, 969, 834, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 4.2 Hz, 1 H), 8.65 (d, *J* = 1.9 Hz, 1 H), 7.74-7.71 (m, 1 H), 7.52 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.29 (d, *J* = 9.5 Hz, 1 H), 6.62 (ddd, *J* = 19.5, 9.6, 2.4 Hz, 2 H), 5.92-5.89 (m, 1 H), 5.77 (dt, *J* = 9.9, 2.0 Hz, 1 H), 5.13-5.07 (m, 2 H), 4.60 (d, *J* = 2.5 Hz, 1 H), 4.53 (s, 2 H), 3.09 (bs, 1 H), 2.12-2.01 (m, 4 H), 1.75-1.69 (m, *J* = 11.1, 7.8, 3.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 162.2, 158.5 (d, J_{CF} = 10.5 Hz), 153.9, 151.1 (d, J_{CF} = 42.3 Hz), 148.0, 134.9, 134.4, 132.6, 130.0, 125.4, 124.3, 110.6 (d, J_{CF} = 2.8 Hz), 104.8 (d, J_{CF} = 16.1 Hz), 102.8 (d, J_{CF} = 24.8 Hz), 92.1 (d, J_{CF} = 2.9 Hz), 78.3, 60.2, 51.5, 44.2, 29.3, 24.9, 19.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.9; HRMS (ESI^+): *m/z* calculated for $C_{23}H_{22}O_3N_4FS$ (M+H) 437.1442, found 437.1438; ELS purity (100%).



2-74

4-Bromo-2,5-difluorophenyl pivalate. To a solution of 4-bromo-2,5-difluorophenol (0.500 g, 2.39 mmol) and Et_3N (0.370 mL, 2.63 mmol) in CH_2Cl_2 (4.7 mL) at 0 °C was added PivCl (0.656 mL, 2.63 mmol). The reaction was stirred at 0 °C for 30 min then diluted with Et_2O (10 mL) and filtered. The filtrate was concentrated and taken up in Et_2O (10 mL), filtered, and concentrated. The product was obtained as a white solid (0.661 g, 94%) and the pivalate carried on without further purification: IR (neat) 3056, 2978, 1755, 1494, 1476, 1404, 1274, 1187, 1140, 1092, 1027, 1000, 905, 806, 738, 658 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 9.0, 6.2 Hz, 1 H), 6.97 (dd, *J* = 8.1, 6.5 Hz, 1 H), 1.36 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 155.1 (dd, J_{CF} = 245.5, 3.3 Hz), 150.5 (dd, J_{CF} = 249.8, 3.6 Hz), 138.4 (dd, J_{CF} = 14.6, 9.9 Hz),

120.8 (dd, J_{CF} = 23.7, 1.3 Hz), 112.2 (dd, J_{CF} = 26.5, 1.3 Hz), 105.4 (dd, J_{CF} = 23.5, 8.3 Hz), 39.4, 27.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ -110.5 (d, *J* = 13.6 Hz), -131.4 (d, *J* = 13.4 Hz); HRMS (ESI^+): *m/z* calculated for $C_{11}H_{12}O_2BrF_2$ (M+H) 292.9983, found 292.9995.

2,5-Difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl pivalate. To a solution of 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (0.31 g, 2.2 mmol) and 4-bromo-2,5-difluorophenyl pivalate (0.50 g, 1.7 mmol) in deoxygenated Et_3N (1.32 mL) was added $Pd(PPh_3)_4$ (0.099 g, 0.085 mmol) and CuI (0.032 g, 0.17 mmol). The reaction was sparged with argon for 2 min then stirred at reflux 18.5 h. The reaction was concentrated, and the residue taken up in Et_2O, washed with sat. NH_4Cl and brine, filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 0/100 to 10/90). The pivalate was obtained as a yellow oil (0.37 g, 62%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 9.8, 6.3 Hz, 1 H), 6.89 (dd, *J* = 8.8, 6.4 Hz, 1 H), 4.89 (t, *J* = 3.3 Hz, 1 H), 4.55-4.46 (m, 2 H), 3.88 (ddd, *J* = 11.4, 8.9, 2.9 Hz, 1 H), 3.60-3.54 (m, 1 H), 1.86-1.74 (m, 2 H), 1.69-1.53 (m, 4 H), 1.36 (s, 9 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.1 (d, *J* = 14.9 Hz), -133.4 (d, *J* = 14.8 Hz); HRMS (ESI^+): *m/z* calculated for $C_{19}H_{23}O_4F_2$ (M+H) 353.1559, found 353.1560.

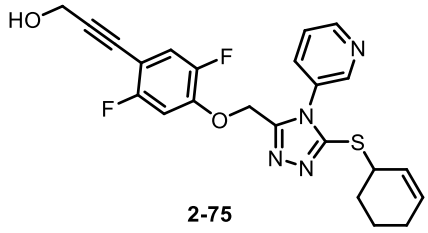
2,5-Difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol. To a solution of 2,5-difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl (0.36 g, 1.0 mmol) in THF (14.5 mL) and MeOH (14.5 mL) was added a solution of NaOH (1 M, 5.6 mL) dropwise and the reaction was stirred at room temperature 13.5 h. The reaction was concentrated and diluted with CH_2Cl_2. The solution was then neutralized to pH 7 with 2 N HCl and the aqueous extracted with CH_2Cl_2 (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude phenol was obtained as a yellow oil that solidified upon standing (0.29

g) and carried on without further purification or characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 10.4, 6.4 Hz, 1 H), 6.72 (dd, *J* = 9.6, 7.4 Hz, 1 H), 4.92 (t, *J* = 3.3 Hz, 1 H), 4.49 (q, *J* = 13.7 Hz, 2 H), 3.89 (ddd, *J* = 11.4, 9.1, 2.6 Hz, 1 H), 3.61-3.57 (m, 1 H), 1.89-1.74 (m, 2 H), 1.69-1.54 (m, 4 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -112.8 (d, *J* = 14.2 Hz), -145.0 (d, *J* = 14.3 Hz); HRMS (ESI^+): *m/z* calculated for $C_{14}H_{13}O_3F_2$ (M+H) 267.0827, found 267.0834.

2,5-Difluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol. To a solution of crude 2,5-difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol (0.274 g, 1.02 mmol) in MeOH (6.3 mL) was added PPTS (0.128 g, 0.511 mmol) and the reaction stirred at room temperature for 2 d. The reaction was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The phenol was obtained as an off-white solid (0.163 g, 86%): IR (acetone) 3381, 3088, 2232, 1692, 1632, 1512, 1433, 1261, 1222, 1170, 1012, 874, 817 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.10 (dd, *J* = 11.0, 6.7 Hz, 1 H), 6.75 (dd, *J* = 10.3, 7.4 Hz, 1 H), 4.46 (s, 2 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 160.0 (dd, J_{CF} = 246.1, 1.8 Hz), 148.1 (dd, J_{CF} = 237.8, 2.8 Hz), 147.4 (dd, J_{CF} = 15.3, 11.8 Hz), 120.1 (dd, J_{CF} = 21.7, 3.4 Hz), 105.8 (dd, J_{CF} = 26.2, 3.1 Hz), 102.4 (dd, J_{CF} = 18.6, 8.4 Hz), 92.9 (d, J_{CF} = 3.4 Hz), 77.6 (d, J_{CF} = 2.1 Hz), 51.0; ^{19}F NMR (470 MHz, acetone-d_6) δ -115.6 (d, *J* = 14.2 Hz), -142.8 (d, *J* = 13.9 Hz); HRMS (ESI^-): *m/z* calculated for $C_9H_5O_2F_2$ (M-H) 183.0252, found 183.0244.

3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-ol (2-74). To a solution of crude 3-(3-(chloromethyl)-5-((cyclopentyl-d_9)thio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.14 g, 0.46 mmol) in dry DMF (7.5 mL) was added 2,5-difluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol (0.092 g, 0.50 mmol) and Cs_2CO_3 (0.16 g, 0.50 mmol) and the reaction stirred at room temperature for 18 h. The reaction was

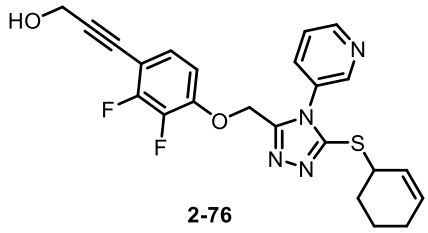
diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc and the combined organic layers dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-74** was obtained as a white foam (0.183 g, 89%): IR (neat) 3215, 2922, 2852, 2226, 1507, 1421, 1343, 1270, 1223, 1178, 1033, 1000, 848, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 8.74 (dd, *J* = 4.9, 1.3 Hz, 1 H), 8.64 (d, *J* = 2.3 Hz, 1 H), 7.89 (ddd, *J* = 8.2, 2.5, 1.5 Hz, 1 H), 7.60 (ddd, *J* = 8.2, 4.9, 0.4 Hz, 1 H), 7.07 (dd, *J* = 10.9, 6.5 Hz, 1 H), 6.92 (dd, *J* = 10.0, 7.0 Hz, 1 H), 5.16 (s, 2 H), 4.56 (s, 1 H), 4.41 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$) δ 158.6 (dd, J_{CF} = 249.1, 2.3 Hz), 154.4, 150.7, 150.3, 147.6 (dd, J_{CF} = 243.8, 3.3 Hz), 145.6 (dd, J_{CF} = 12.8, 10.0 Hz), 135.4, 129.5, 124.4, 119.3 (dd, J_{CF} = 21.3, 2.7 Hz), 104.1 (dd, J_{CF} = 18.5, 8.3 Hz), 103.1 (dd, J_{CF} = 27.2, 0.9 Hz), 92.7 (d, J_{CF} = 3.4 Hz), 76.1 (d, J_{CF} = 2.0 Hz), 60.6, 50.0, 45.5-45.0 (m, CD), 32.7-31.9 (m, CD), 23.4-22.5 (m, CD); ^{19}F NMR (376 MHz, $CDCl_3/CD_3OD$) δ -112.5 (d, *J* = 14.6 Hz), -139.2 (d, *J* = 14.5 Hz); HRMS (ESI^+): *m/z* calculated for $C_{22}H_{12}{}^2H_9O_2N_4F_2S$ (M+H) 452.1913, found 452.1905; ELS purity (100%).



2-75

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-ol (2-75). To the crude mixture of (5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and 3-(3-(chloromethyl)-5-(cyclohex-2-en-1-ylthio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.090 g, 0.25 mmol) in dry DMF (4 mL) was added 2,5-difluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol (0.050 g, 0.27 mmol) and

Cs_2CO_3 (0.088 g, 0.27 mmol) and the reaction stirred at room temperature for about 19.5 h. The reaction was diluted with EtOAc, and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-75** was obtained as an off-white solid (0.088 g, 79%): m.p. 172.9-175 °C; IR (neat) 3204, 2944, 2850, 1628, 1508, 1481, 1454, 1422, 1346, 1226, 1178, 1038, 997, 867, 848, 751, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3/CD_3OD$) δ 8.60 (d, *J* = 4.5 Hz, 1 H), 8.48 (d, *J* = 2.0 Hz, 1 H), 7.69 (d, *J* = 7.9 Hz, 1 H), 7.43 (dd, *J* = 8.0, 4.9 Hz, 1 H), 6.93 (dd, *J* = 10.8, 6.5 Hz, 1 H), 6.73 (dd, *J* = 9.7, 7.1 Hz, 1 H), 5.75-5.73 (m, 1 H), 5.57 (dt, *J* = 9.7, 1.7 Hz, 1 H), 5.02-4.96 (m, 2 H), 4.35 (d, *J* = 1.9 Hz, 1 H), 4.28 (s, 2 H), 3.92 (bs, 1 H), 1.95-1.81 (m, 4 H), 1.59-1.50 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3/CD_3OD$) δ 158.8 (dd, J_{CF} = 249.4, 2.0 Hz), 154.0, 151.0, 150.5, 147.9 (dd, J_{CF} = 243.9, 3.1 Hz), 147.5, 145.8 (dd, J_{CF} = 12.8, 9.9 Hz), 135.4, 132.5, 129.7, 124.8, 124.4, 119.6 (dd, J_{CF} = 21.6, 2.7 Hz), 104.5 (dd, J_{CF} = 18.3, 8.3 Hz), 103.4 (d, J_{CF} = 28.1 Hz), 93.0 (d, J_{CF} = 3.4 Hz), 76.4 (d, J_{CF} = 1.4 Hz), 60.9, 50.4, 44.1, 28.9, 24.6, 18.8; ^{19}F NMR (470 MHz, $CDCl_3/CD_3OD$) δ -112.2 (d, *J* = 14.6 Hz), -139.0 (d, *J* = 14.1 Hz); HRMS (ESI^+): *m/z* calculated for $C_{23}H_{21}O_2N_4F_2S$ (M+H) 455.1348, found 455.1348; ELS purity (100%).



2-76

4-Bromo-2,3-difluorophenyl pivalate. To a solution of 4-bromo-2,3-difluorophenol (0.500 g, 2.30 mmol) and Et_3N (0.355 mL, 2.53 mmol) in CH_2Cl_2 (4.7 mL) at 0 °C was added PivCl

(0.630 mL, 2.53 mmol). The reaction was stirred at 0 °C for 30 min then diluted with Et_2O (10 mL) and filtered. The filtrate was concentrated and taken up in Et_2O (10 mL), filtered, and concentrated. The product was obtained as an off-white solid (0.672 g, 100%) and the pivalate carried on without further purification: IR (neat) 2978, 1752, 1487, 1471, 1266, 1088, 1035, 1008, 879, 790 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (ddd, *J* = 9.0, 6.7, 2.4 Hz, 1 H), 6.83 (ddd, *J* = 9.0, 6.9, 2.2 Hz, 1 H), 1.37 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 148.9 (dd, J_{CF} = 249.8, 12.7 Hz), 144.0 (dd, J_{CF} = 255.1, 14.7 Hz), 139.5 (d, J_{CF} = 10.1 Hz), 126.9 (d, J_{CF} = 4.3 Hz), 119.4 (d, J_{CF} = 3.6 Hz), 107.1 (d, J_{CF} = 18.2 Hz), 39.4, 27.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ -127.2 (d, *J* = 20.9 Hz) -147.2 (d, *J* = 20.9 Hz); HRMS (ESI^+): *m/z* calculated for $C_{11}H_{12}O_2BrF_2$ (M+H) 292.9983, found 292.9996.

2,3-Difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl pivalate. To a solution of 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (0.31 g, 2.2 mmol) and 4-bromo-2,3-difluorophenyl pivalate (0.50 g, 1.7 mmol) in deoxygenated Et_3N (1.32 mL) was added $Pd(PPh_3)_4$ (0.099 g, 0.085 mmol) and CuI (0.032 g, 0.17 mmol). The reaction was sparged with argon for 2 min then stirred at reflux for 18.5 h. The reaction was concentrated, and the residue taken up in Et_2O, washed with sat. NH_4Cl and brine, filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 0/100 to 10/90). The pivalate was obtained as a yellow oil (0.36 g, 60%) and carried on without further characterization: ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (ddd, *J* = 8.8, 6.8, 2.1 Hz, 1 H), 6.84 (ddd, *J* = 8.7, 6.8, 1.9 Hz, 1 H), 4.89 (t, *J* = 3.3 Hz, 1 H), 4.56-4.47 (m, 2 H), 3.89 (ddd, *J* = 11.4, 8.9, 2.8 Hz, 1 H), 3.60-3.55 (m, 1 H), 1.86-1.74 (m, 2 H), 1.69-1.53 (m, 4 H), 1.37 (s, 9 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -132.2 (d, *J* = 20.5 Hz), -150.5 (d, *J* = 20.4 Hz); HRMS (ESI^+): *m/z* calculated for $C_{19}H_{23}O_4F_2$ (M+H) 353.1559, found 353.1557.

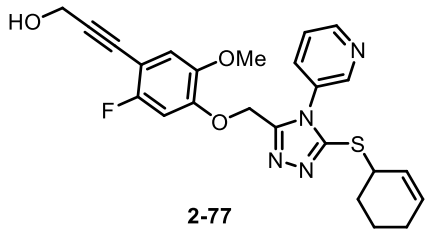
2,3-Difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol. To a solution of 2,3-difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl pivalate (0.35 g, 0.99 mmol) in THF (14.5 mL) and MeOH (14.5 mL) was added a solution of NaOH (1 M, 5.5 mL) dropwise and the reaction was stirred at room temperature for about 13.5 h. The reaction was concentrated and diluted with CH_2Cl_2. The solution was then neutralized to pH 7 with 2 N HCl and the aqueous extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude phenol was obtained as a pale brown oil that solidified upon standing (0.25 g, 95%) and carried on without further purification or characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08-7.03 (m, 1 H), 6.73-6.69 (m, *J* = 2.8 Hz, 1 H), 4.91 (t, *J* = 3.5 Hz, 1 H), 4.50 (app q, *J* = 13.1 Hz, 2 H), 3.92-3.87 (m, 1 H), 3.61-3.56 (m, 1 H), 1.77 (d, *J* = 0.9 Hz, 2 H), 1.69-1.55 (m, 4 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -133.4 (d, *J* = 20.5 Hz), -162.9 (d, *J* = 20.7 Hz); HRMS (ESI^+): *m/z* calculated for $C_{14}H_{13}O_3F_2$ (M+H) 267.0827, found 267.0837.

2,3-Difluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol. To a solution of crude 2,3-difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol (0.253 g, 0.944 mmol) in MeOH (5.8 mL) was added PPTS (0.119 g, 0.472 mmol) and the reaction stirred at room temperature for 2 d. The reaction was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The phenol was obtained as an off-white solid (0.146 g, 84%): IR (acetone) 3548, 3103, 2925, 2226, 1693, 1632, 1512, 1481, 1320, 1257, 1067, 1021, 997, 976, 808, 723, 656 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.07 (ddd, *J* = 8.7, 7.5, 2.3 Hz, 1 H), 6.80 (ddd, *J* = 8.7, 8.1, 1.9 Hz, 1 H), 4.43 (s, 2 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 151.8 (dd, *J* = 249.2, 11.1 Hz), 147.3 (dd, *J* = 9.9, 2.7 Hz), 140.2 (dd, *J* = 242.9, 13.9 Hz), 127.6 (dd, *J* = 3.9, 1.8 Hz), 113.0 (d, *J* = 2.4 Hz), 103.5 (d, *J* = 13.1 Hz), 92.9

(d, J = 3.6 Hz), 76.3 (d, J = 3.6 Hz), 50.1; ^{19}F NMR (470 MHz, acetone-d_6) δ -136.7 (d, J = 20.5 Hz); -162.5 (d, J = 19.1 Hz); HRMS (ESI$^-$): *m/z* calculated for $C_9H_5O_2F_2$ (M-H) 183.0252, found 183.0255.

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,3-difluorophenyl)prop-2-yn-1-ol (2-76). To the crude mixture of (5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4H-1,2,4-triazol-3-yl)methyl methanesulfonate and 3-(3-(chloromethyl)-5-(cyclohex-2-en-1-ylthio)-4H-1,2,4-triazol-4-yl)pyridine (0.090 g, 0.25 mmol) in dry DMF (4 mL) was added 2,3-difluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol (0.050 g, 0.27 mmol) and Cs_2CO_3 (0.088 g, 0.27 mmol) and the reaction stirred at room temperature for 18.5 h. The reaction was diluted with EtOAc, and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-76** was obtained as a yellow foam (0.081 g, 72%): IR (neat) 3196, 2917, 2851, 1631, 1507, 1483, 1451, 1394, 1305, 1186, 1089, 1053, 996, 804, 707 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD) δ 8.69 (d, J = 3.1 Hz, 1 H), 8.55 (s, 1 H), 7.72 (dd, J = 6.3, 1.8 Hz, 1 H), 7.48 (dd, J = 7.8, 5.0 Hz, 1 H), 7.04-6.98 (m, 1 H), 6.76 (td, J = 8.1, 1.4 Hz, 1 H), 5.83-5.80 (m, 1 H), 5.67-5.63 (m, 1 H), 5.08 (s, 2 H), 4.45 (d, J = 1.4 Hz, 1 H), 4.37 (s, 2 H), 3.20 (s, 1 H), 2.02-1.87 (m, 4 H), 1.67-1.61 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD) δ 154.0, 151.5 (dd, J_{CF} = 253.0, 11.0 Hz), 151.1, 150.6, 147.5, 146.5 (dd, J_{CF} = 8.2, 2.8 Hz), 141.1 (dd, J_{CF} = 249.2, 14.1 Hz), 135.5, 132.6, 129.7, 127.4 (d, J_{CF} = 4.2 Hz), 124.8, 124.5, 109.9 (d, J_{CF} = 3.5 Hz), 106.8 (d, J_{CF} = 12.9 Hz), 93.2 (d, J_{CF} = 3.5 Hz), 76.4 (d, J_{CF} = 3.9 Hz), 61.0, 50.4, 44.1, 28.9, 24.6, 18.8; ^{19}F NMR (470 MHz, $CDCl_3$/CD_3OD) δ -133.5 (d, J = 19.5 Hz), -157.8 (d, J =

19.4 Hz); HRMS (ESI$^+$): *m/z* calculated for $C_{23}H_{21}O_2N_4F_2S$ (M+H) 455.1348, found 455.1345; ELS purity (100%).



2-77

4-Bromo-5-fluoro-2-methoxyphenyl pivalate. To a solution of 4-bromo-5-fluoro-2-methoxyphenol (0.500 g, 2.26 mmol) and Et_3N (0.350 mL, 2.49 mmol) in CH_2Cl_2 (4.4 mL) at 0 °C was added PivCl (0.620 mL, 2.49 mmol). The reaction was stirred at 0 °C for 100 min then diluted with Et_2O (10 mL) and filtered. The filtrate was concentrated and taken up in Et_2O (10 mL), filtered, and concentrated. The product was obtained as a brown solid (0.662 g, 96%) and the pivalate carried on without further purification: IR (neat) 2968, 1746, 1504, 1396, 1270, 1206, 1137, 1103, 1027, 993, 901, 798, 760, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 6.3 Hz, 1 H), 6.86 (d, *J* = 8.2 Hz, 1 H), 3.75 (s, 3 H), 1.34 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 152.8 (d, J_{CF} = 241.4 Hz), 148.3 (d, J_{CF} = 3.0 Hz), 139.8 (d, J_{CF} = 9.5 Hz), 116.3, 111.6 (d, J_{CF} = 25.9 Hz), 104.9 (d, J_{CF} = 22.6 Hz), 56.6, 39.1, 27.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ -115.9; HRMS (ESI$^+$): *m/z* calculated for $C_{12}H_{15}O_3BrF$ (M+H) 305.0183, found 305.0202.

5-Fluoro-2-methoxy-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl pivalate. To a solution of 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (0.30 g, 2.1 mmol) and 4-bromo-5-fluoro-2-methoxyphenyl pivalate (0.50 g, 1.6 mmol) in deoxygenated Et_3N (1.27 mL) was added $Pd(PPh_3)_4$ (0.095 g, 0.082 mmol) and CuI (0.031 g, 0.16 mmol). The reaction was sparged with argon for 2 min then stirred at reflux for 16.5 h. The reaction was concentrated, and the residue

taken up in Et_2O, washed with sat. NH_4Cl and brine, filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 0/100 to 15/85). The pivalate was obtained as a yellow oil (0.31 g, 52%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 6.3 Hz, 1 H), 6.80 (d, *J* = 8.8 Hz, 1 H), 4.90 (t, *J* = 3.2 Hz, 1 H), 4.51 (q, *J* = 12.3 Hz, 2 H), 3.89 (ddd, *J* = 11.3, 9.1, 2.7 Hz, 1 H), 3.77 (s, 3 H), 3.57 (dt, *J* = 10.4, 4.7 Hz, 1 H), 1.88-1.50 (m, 6 H), 1.35 (s, 9 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.1; HRMS (ESI^+): *m/z* calculated for $C_{20}H_{26}O_5F$ (M+H) 365.1759, found 365.1759.

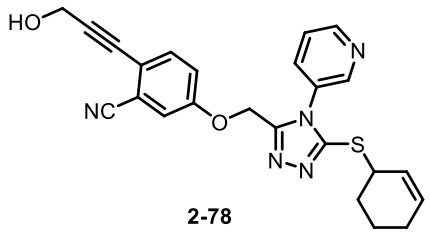
5-Fluoro-2-methoxy-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol. To a solution of 5-fluoro-2-methoxy-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl pivalate (0.30 g, 0.82 mmol) in THF (12 mL) and MeOH (12 mL) was added a solution of NaOH (1 M, 4.5 mL) dropwise and the reaction was stirred at room temperature for 14 h. The reaction was concentrated and diluted with CH_2Cl_2. The solution was then neutralized to pH 7 with 2 N HCl and the aqueous extracted with CH_2Cl_2 (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude phenol was obtained as a brown oil (0.25 g) and carried on without further purification or characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (d, *J* = 6.4 Hz, 1 H), 6.66 (d, *J* = 9.8 Hz, 1 H), 4.91 (t, *J* = 3.4 Hz, 1 H), 4.50 (q, *J* = 16.2 Hz, 2 H), 3.91-3.87 (m, 1 H), 3.86 (s, 3 H), 3.57 (dtd, *J* = 11.2, 4.4, 1.2 Hz, 1 H), 1.89-1.54 (m, 6 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -116.8; HRMS (ESI^-): *m/z* calculated for $C_{15}H_{16}O_4F$ (M-H) 279.1027, found 279.1033.

5-Fluoro-4-(3-hydroxyprop-1-yn-1-yl)-2-methoxyphenol. To a solution of crude 5-fluoro-2-methoxy-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol (0.231 g, 0.824 mmol) in MeOH (5.1 mL) was added PPTS (0.104 g, 0.412 mmol) and the reaction stirred at room temperature for 2 d. The reaction was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. The

combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The phenol was obtained as an off-white solid (0.121 g, 75%): IR (acetone) 3459, 3166, 2992, 2231, 1620, 1602, 1508, 1435, 1292, 1221, 1204, 1173, 1013, 865, 660 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.45 (bs, 1 H), 6.92 (d, J = 6.8 Hz, 1 H), 6.66 (d, J = 10.4 Hz, 1 H), 4.42 (s, 3 H), 3.83 (s, 3 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.7 (d, J_{CF} = 242.5 Hz), 149.4 (d, J_{CF} = 11.8 Hz), 144.8 (d, J_{CF} = 2.5 Hz), 115.8 (d, J_{CF} = 2.8 Hz), 103.8 (d, J_{CF} = 26.1 Hz), 101.6 (d, J_{CF} = 17.3 Hz), 92.6 (d, J_{CF} = 3.4 Hz), 78.6, 56.8, 51.1; ^{19}F NMR (470 MHz, acetone-d_6) δ -119.7; HRMS (ESI^-): *m/z* calculated for $C_{10}H_8O_3F$ (M-H) 195.0452, found 195.0456.

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-fluoro-5-methoxyphenyl)prop-2-yn-1-ol (2-77). To the crude mixture of (5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and 3-(3-(chloromethyl)-5-(cyclohex-2-en-1-ylthio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.085 g, 0.23 mmol) in dry DMF (3.8 mL) was added 5-fluoro-4-(3-hydroxyprop-1-yn-1-yl)-2-methoxyphenol (0.050 g, 0.25 mmol) and Cs_2CO_3 (0.083 g, 0.25 mmol) and the reaction stirred at room temperature for 20.5 h. The reaction was diluted with EtOAc, and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-77** was obtained as a yellow foam (0.088 g, 82%): IR (neat) 3288, 2930, 1615, 1505, 1445, 1220, 1206, 1133, 1025, 998, 867, 752, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.72 (dd, J = 4.8, 1.2 Hz, 1 H), 8.64 (d, J = 2.2 Hz, 1 H), 7.77 (ddd, J = 8.1, 2.4, 1.5 Hz, 1 H), 7.44 (dd, J = 8.0, 4.9 Hz, 1 H), 6.76 (d, J = 6.6 Hz, 1 H), 6.63 (d, J = 10.1 Hz, 1 H), 5.88-5.82 (m, 1 H), 5.71 (dt, J = 9.9, 2.0 Hz, 1 H), 5.10-5.01 (m, 2 H), 4.54 (app d, J = 2.4 Hz, 1

H), 4.48 (s, 2 H), 3.70 (s, 3 H), 3.49 (bs, 1 H), 2.12-1.94 (m, 4 H), 1.77-1.59 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0 (d, J_{CF} = 245.8 Hz), 153.7, 151.0, 151.0 (d, J_{CF} = 12.5 Hz), 150.9, 148.1, 147.5 (d, J_{CF} = 9.4 Hz), 145.5 (d, J_{CF} = 2.8 Hz), 135.2, 132.5, 129.8, 125.3, 124.1, 115.1 (d, J_{CF} = 2.4 Hz), 103.6 (d, J_{CF} = 16.8 Hz), 102.8 (d, J_{CF} = 26.8 Hz), 92.5 (d, J_{CF} = 3.6 Hz), 78.1, 61.0, 56.2, 51.1, 44.0, 29.2, 24.8, 19.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ -116.9; HRMS (ESI^+): *m/z* calculated for $C_{24}H_{24}O_3N_4FS$ (M+H) 467.1548, found 467.1546; ELS purity (100%).



2-78

4-Bromo-3-cyanophenyl pivalate. To a solution of 4-bromo-5-hydroxybenzonitrile (0.500 g, 2.53 mmol) and Et_3N (0.390 mL, 2.78 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added PivCl (0.692 mL, 2.78 mmol). The reaction was stirred at 0 °C for 50 min then diluted with Et_2O (10 mL) and filtered. The filtrate was concentrated and taken up in Et_2O (10 mL), filtered, and concentrated. The product was obtained as a brown oil (0.720 g, 101%) and the pivalate carried on without further purification: IR (neat) 2977, 2936, 2236, 1754, 1465, 1396, 1259, 1225, 1151, 1095, 1027, 902, 833 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.8 Hz, 1 H), 7.40 (d, *J* = 2.7 Hz, 1 H), 7.20 (dd, *J* = 8.8, 2.8 Hz, 1 H), 1.35 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 150.3, 134.2, 127.9, 127.5, 121.7, 116.8, 116.5, 39.4, 27.1; HRMS (ESI^+): *m/z* calculated for $C_{12}H_{13}O_2NBr$ (M+H) 282.0124, found 282.0123.

3-Cyano-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl. To a solution of 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (0.32 g, 2.3 mmol) and 4-bromo-3-cyanophenyl pivalate (0.50 g, 1.8 mmol) in deoxygenated Et_3N (1.37 mL) was added $Pd(PPh_3)_4$ (0.10 g, 0.089

mmol) and CuI (0.034 g, 0.18 mmol). The reaction was sparged with argon for 2 min then stirred at reflux for 13 h. The reaction was concentrated, and the residue taken up in Et_2O, washed with sat. NH_4Cl and brine, filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 0/100 to 10/90). The phenol was obtained as a yellow oil (0.40 g, 65%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.6 Hz, 1 H), 7.38 (d, *J* = 2.3 Hz, 1 H), 7.26 (dd, *J* = 8.6, 2.4 Hz, 1 H), 4.95 (t, *J* = 3.3 Hz, 1 H), 4.55 (s, 2 H), 3.89 (ddd, *J* = 11.4, 8.7, 2.9 Hz, 1 H), 3.61-3.56 (m, 1 H), 1.89-1.75 (m, 2 H), 1.69-1.51 (m, 4 H), 1.35 (s, 9 H); HRMS (ESI$^+$): *m/z* calculated for $C_{20}H_{23}O_4NNa$ (M+Na) 364.1519, found 364.1517.

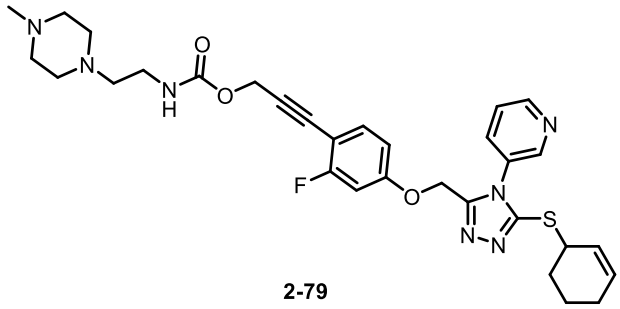
5-Hydroxy-2-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)benzonitrile. To a solution of 3-cyano-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl pivalate (0.38 g, 1.1 mmol) in THF (16.3 mL) and MeOH (16.3 mL) was added a solution of NaOH (1 M, 6.12 mL) dropwise and the reaction was stirred at room temperature for 14 h. The reaction was concentrated and diluted with CH_2Cl_2. The solution was then neutralized to pH 7 with 2 N HCl and the aqueous extracted with CH_2Cl_2 (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude phenol was obtained as a brown oil (0.31 g) and carried on without further purification or characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.6 Hz, 1 H), 7.07 (d, *J* = 2.6 Hz, 1 H), 6.99 (dd, *J* = 8.6, 2.6 Hz, 1 H), 5.00 (t, *J* = 3.2 Hz, 1 H), 4.58-4.50 (m, 2 H), 3.91 (ddd, *J* = 11.4, 8.7, 2.8 Hz, 1 H), 3.64-3.59 (m, 1 H), 1.90-1.76 (m, 2 H), 1.70-1.55 (m, 5 H); HRMS (ESI$^-$): *m/z* calculated for $C_{15}H_{14}O_3N$ (M-H) 256.0968, found 256.0973.

5-Hydroxy-2-(3-hydroxyprop-1-yn-1-yl)benzonitrile. To a solution of crude 5-hydroxy-2-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)benzonitrile (0.286 g, 1.11 mmol) in MeOH (6.8

mL) was added PPTS (0.140 g, 0.556 mmol) and the reaction stirred at room temperature for 2 d. The reaction was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The phenol was obtained as a tan solid (0.171 g, 89%): IR (acetone) 3368, 3166, 2922, 2237, 1693, 1601, 1503, 1440, 1308, 1245, 1010, 955, 856, 720 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.47 (bs, 1 H), 7.43 (d, J = 8.6 Hz, 1 H), 7.17 (d, J = 2.6 Hz, 1 H), 7.12 (dd, J = 8.6, 2.6 Hz, 1 H), 4.63 (bs, 1 H), 4.48 (s, 2 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 158.3, 135.1, 121.2, 119.8, 118.0, 117.8, 116.6, 93.3, 81.1, 50.9; HRMS (ESI^-): *m/z* calculated for $C_{10}H_6O_2N$ (M-H) 172.0393, found 172.0396.

5-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-(3-hydroxyprop-1-yn-1-yl)benzonitrile (2-78). To the crude mixture of (5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and 3-(3-(chloromethyl)-5-(cyclohex-2-en-1-ylthio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.096 g, 0.26 mmol) in dry DMF (4.3 mL) was added 5-hydroxy-2-(3-hydroxyprop-1-yn-1-yl)benzonitrile (0.050 g, 0.29 mmol) and Cs_2CO_3 (0.094 g, 0.29 mmol) and the reaction stirred at room temperature for 20.5 h. The reaction was diluted with EtOAc, and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-78** was obtained as a pale yellow foam (0.089 g, 77%): IR (neat) 3273, 3069, 2924, 2230, 1600, 1485, 1445, 1308, 1216, 1164, 1030, 827, 751, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, J = 4.6 Hz, 1 H), 8.58 (d, J = 1.8 Hz, 1 H), 7.70 (dt, J = 8.1, 1.8 Hz, 1 H), 7.50 (dd, J = 8.0, 4.9 Hz, 1 H), 7.35 (d, J = 9.3 Hz, 1 H), 7.07-7.05 (m, 2 H), 5.85-5.81 (m, 1 H), 5.67 (dt, J = 9.9, 2.0 Hz, 1 H), 5.11-5.05 (m, 2 H), 4.49 (d, J = 2.2 Hz, 1 H), 4.45

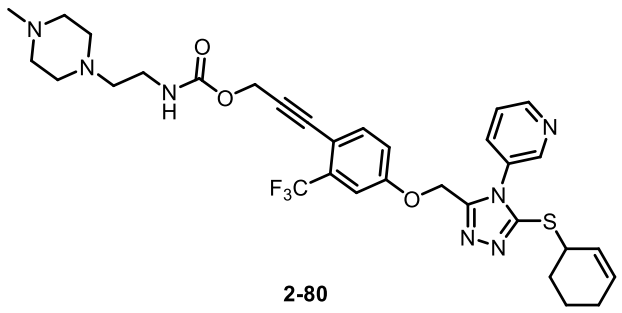
(s, 2 H), 2.47 (s, 1 H), 2.06-1.92 (m, 4 H), 1.71-1.59 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 154.0, 151.3, 150.6, 147.8, 135.0, 134.2, 132.6, 129.8, 125.2, 124.4, 120.3, 119.5, 118.4, 117.1, 116.2, 93.7, 80.4, 60.2, 50.8, 44.2, 29.2, 24.8, 19.1; HRMS (ESI^+): *m/z* calculated for $C_{24}H_{22}O_2N_5S$ (M+H) 444.1489, found 444.1487; ELS purity (100%).



2-79

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-fluorophenyl)prop-2-yn-1-yl (2-(4-methylpiperazin-1-yl)ethyl)carbamate (2-79)[131]**.** To a solution of **2-73** (0.060 g, 0.14 mmol) in dry CH_2Cl_2 (1.5 mL) was added CDI (0.033 g, 0.21 mmol) and the reaction stirred at room temperature under argon for 2 h. A solution of 2-(4-methylpiperazin-1-yl)ethan-1-amine (0.030 g, 0.21 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred 16 h at room temperature. An additional 1 eq. of 2-(4-methylpiperazin-1-yl)ethan-1-amine was added and the reaction stirred for 1 d. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 30/70) followed by filtration through a plug of basic Al_2O_3 (MeOH/$CDCl_3$: 0/100 to 5/95). Product **2-79** was obtained as a sticky white foam (0.075 g, 90%): IR (neat) 3261, 2940, 2803, 1714, 1620, 1505, 1446, 1255, 1163, 1011, 910, 726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.59-8.58 (m, 1 H), 7.68 (ddd, *J* = 8.1, 2.5, 1.5 Hz, 1 H), 7.47 (ddd, *J* = 8.1, 4.8, 0.7 Hz, 1 H), 7.29 (d, *J* = 7.7 Hz, 1 H), 6.64-6.58 (m, 2 H), 6.23 (s, 1 H), 5.87-

5.83 (m, J = 1.4 Hz, 1 H), 5.73-5.69 (m, 1 H), 5.57 (app t, J = 3.4 Hz, 1 H), 5.10-5.03 (m, 2 H), 4.87 (s, 2 H), 4.53 (dd, J = 4.0, 1.7 Hz, 1 H), 3.28 (q, J = 5.7 Hz, 2 H), 2.56-2.48 (m, 9 H), 2.34 (s, 3 H), 2.10-1.94 (m, 4 H), 1.59-1.75 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 162.3, 158.7 (d, J_{CF} = 10.7 Hz), 155.5, 153.6, 151.3, 150.8, 147.9, 134.7, 134.5 (d, J_{CF} = 2.6 Hz), 132.4, 129.8, 125.3, 124.1, 110.6 (d, J_{CF} = 2.7 Hz), 104.3 (d, J_{CF} = 24.1 Hz), 102.8 (d, J_{CF} = 28.7 Hz), 87.9 (d, J_{CF} = 2.8 Hz), 79.2, 60.2, 56.7, 54.6, 53.1, 52.0, 45.4, 44.0, 37.6, 29.2, 24.8, 19.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ -106.6; HRMS (ESI^+): *m/z* calculated for $C_{31}H_{37}O_3N_7FS$ (M+H) 606.2657, found 606.2655; ELS purity (100%).



2-80

4-Bromo-3-(trifluoromethyl)phenyl pivalate[134]**.** To a solution of 3-trifluoromethyl-4-bromophenol (1.00 g, 4.02 mmol) and Et_3N (0.622 mL, 4.43 mmol) in CH_2Cl_2 (8.1 mL) at 0 °C was added PivCl (0.545 mL, 4.43 mmol). The reaction was stirred at 0 °C for 30 min then diluted with Et_2O (10 mL) and filtered. The filtrate was concentrated and taken up in Et_2O (10 mL), filtered, and concentrated. The pivalate was obtained as an off-white solid (1.35 g) and carried on without further purification or characterization.

4-(3-((Tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)-3-(trifluoromethyl)phenyl pivalate[135]**.** To a solution of 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (1.40 g, 10.0 mmol) and 4-bromo-3-(trifluoromethyl)phenyl pivalate (2.50 g, 7.69 mmol) in deoxygenated Et_3N (5.94 mL) was added $Pd(PPh_3)_4$ (0.444 g, 0.384 mmol) and CuI (0.146 g, 0.769 mmol). The reaction was

sparged with argon for 2 min then stirred at reflux for 18.5 h. The reaction was concentrated, and the residue taken up in Et_2O, washed with sat. NH_4Cl and brine, filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 0/100 to 10/90). The pivalate was obtained as a yellow oil (0.849 g, 29%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.5 Hz, 1 H), 7.35 (d, *J* = 2.1 Hz, 1 H), 7.21 (dd, *J* = 8.4, 2.1 Hz, 1 H), 4.91 (t, *J* = 2.9 Hz, 1 H), 4.52 (s, 2 H), 3.89 (ddd, *J* = 11.1, 8.3, 3.0 Hz, 1 H), 3.56 (dt, *J* = 11.2, 4.1 Hz, 1 H), 1.87-1.57 (m, 6 H), 1.36 (s, 9 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6; HRMS (ESI^+): *m/z* calculated for $C_{20}H_{24}O_4F_3$ (M+H) 385.1621, found 385.1623.

4-(3-((Tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)-3-(trifluoromethyl)phenol. To a solution of 4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)-3-(trifluoromethyl)phenyl pivalate (0.84 g, 2.2 mmol) in THF (32 mL) and MeOH (32 mL) was added a solution of NaOH (1 M, 24.0 mL) dropwise and the reaction was stirred at room temperature 16 h. The reaction was concentrated and diluted with CH_2Cl_2 (100 mL). The solution was then neutralized to pH 7 with 2 N HCl and the aqueous extracted with CH_2Cl_2 (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude phenol was obtained as a yellow oil (0.67 g) and carried on without further purification: IR (neat) 3265, 2948, 2868, 2244, 1616, 1501, 1447, 1323, 1258, 1120, 1013, 902, 872, 807, 673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 1 H), 7.09 (d, *J* = 2.6 Hz, 1 H), 6.89 (dd, *J* = 8.4, 2.4 Hz, 1 H), 5.00 (dd, *J* = 4.0, 2.7 Hz, 1 H), 4.56-4.48 (m, 2 H), 3.94 (ddd, *J* = 11.4, 8.5, 3.1 Hz, 1 H), 3.65-3.60 (m, 1 H), 1.77-1.87 (m, 2 H), 1.69-1.56 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 135.9, 133.2 (q, J_{CF} = 30.5 Hz), 123.2 (q, J_{CF} = 273.6 Hz), 118.5, 113.6 (q, J_{CF} = 5.2 Hz), 112.0 (q, J_{CF} = 2.1 Hz), 97.1,

88.1 (app d, J_{CF} = 1.0 Hz), 82.5, 62.7, 55.1, 30.4, 25.4, 19.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6; HRMS (ESI^+): *m/z* calculated for $C_{15}H_{16}O_3F_3$ (M+H) 301.1046, found 301.1045.

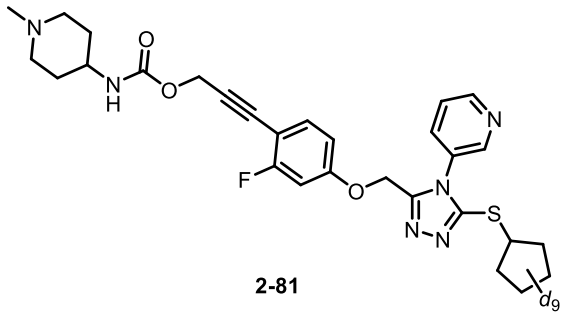
3-(3-(Cyclohex-2-en-1-ylthio)-5-((4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)-3-(trifluoromethyl)phenoxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine. To the crude mixture of (5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and 3-(3-(chloromethyl)-5-(cyclohex-2-en-1-ylthio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.254 g, 0.693 mmol) in dry DMF (9.8 mL) was added 4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)-3-(trifluoromethyl)phenol (0.229 g, 0.762 mmol) and Cs_2CO_3 (0.248 g, 0.762 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The triazole was obtained as an off-white solid (0.379 g, 96%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.63 (d, *J* = 2.1 Hz, 1 H), 7.68 (ddd, *J* = 8.0, 2.4, 1.4 Hz, 1 H), 7.51-7.40 (m, 2 H), 7.08-7.04 (m, 2 H), 5.91-5.87 (m, 1 H), 5.78-5.74 (m, 1 H), 5.12 (s, 2 H), 4.89 (t, *J* = 3.0 Hz, 1 H), 4.64-4.56 (m, 1 H), 4.49 (s, 2 H), 3.92-3.85 (m, 1 H), 3.57-3.52 (m, 1 H), 2.10-2.02 (m, 4 H), 1.90-1.56 (m, 8 H); HRMS (ESI^+): *m/z* calculated for $C_{29}H_{30}O_3N_4F_3S$ (M+H) 571.1985, found 571.1983.

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-(trifluoromethyl)phenyl)prop-2-yn-1-ol. To a solution of 3-(3-(cyclohex-2-en-1-ylthio)-5-((4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)-3-(trifluoromethyl)phenoxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (0.37 g, 0.65 mmol) in MeOH (2.4 mL) was added PPTS (0.041 g, 0.16 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with

CH_2Cl_2 (10 mL) and extracted with sat. $NaHCO_3$ (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The triazole was obtained as a pale yellow solid (0.182 g, 58%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.8, 1.2 Hz, 1 H), 8.62 (d, *J* = 2.5 Hz, 1 H), 7.68 (ddd, *J* = 8.1, 2.5, 1.5 Hz, 1 H), 7.51-7.45 (m, 2 H), 7.08-7.04 (m, 2 H), 5.91-5.86 (m, 1 H), 5.77-5.72 (m, 1 H), 5.12 (s, 2 H), 4.59 (dd, *J* = 4.0, 1.6 Hz, 1 H), 4.49 (s, 2 H), 2.00-2.10 (m, 3 H), 1.77-1.69 (m, 4 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6; HRMS (ESI^+): *m/z* calculated for $C_{24}H_{22}O_2N_4F_3S$ (M+H) 487.1410, found 487.1446.

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-(trifluoromethyl)phenyl)prop-2-yn-1-yl (2-(4-methylpiperazin-1-yl)ethyl)carbamate (2-80). To a solution of 3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-(trifluoromethyl)phenyl)prop-2-yn-1-ol (0.065 g, 0.13 mmol) in dry CH_2Cl_2 (1.5 mL) was added CDI (0.032 g, 0.20 mmol) and the reaction stirred at room temperature under argon for 2 h. A solution of 2-(4-methylpiperazin-1-yl)ethan-1-amine (0.029 g, 0.20 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred 16 h at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 30/70) followed by filtration through a plug of cotton. Product **2-80** was obtained as a white foam (0.051 g, 58%): IR (neat) 3315, 2940, 2803, 1719, 1612, 1498, 1438, 1312, 1134, 1011, 911, 825, 726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.8, 1.2 Hz, 1 H), 8.62 (d, *J* = 2.4 Hz, 1 H), 7.67 (dt, *J* = 8.1, 1.8 Hz, 1 H), 7.49 (td, *J* = 8.2, 4.5 Hz, 2 H), 7.08-7.05 (m, 2 H), 5.90-5.86 (m, 1 H), 5.75 (dt, *J* = 9.9, 2.0 Hz, 1 H), 5.37 (app s, 1

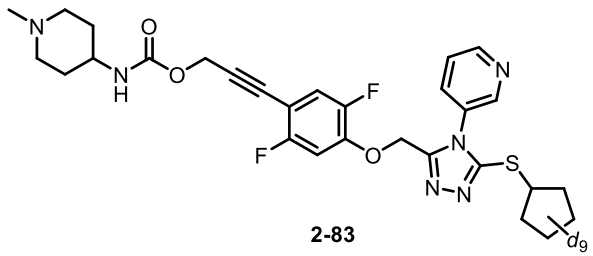
H), 5.15-5.09 (m, 2 H), 4.90 (s, 2 H), 4.59 (app d, J = 2.4 Hz, 1 H), 3.30 (q, J = 5.6 Hz, 2 H), 2.54-2.37 (m, 8 H), 2.28-2.25 (m, 4 H), 2.14-1.99- (m, 5 H), 1.78-1.67 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 157.0, 155.6, 153.8, 151.4, 150.7, 147.9, 136.1, 134.7, 133.4 (q, J_{CF} = 31.0 Hz), 125.3, 124.2, 122.9 (q, J_{CF} = 273.9 Hz), 132.5, 129.9, 117.1, 113.8 (app d, J_{CF} = 1.9 Hz), 113.2 (q, J_{CF} = 5.1 Hz), 88.3, 81.5, 60.2, 56.8, 54.9, 53.1, 52.7, 45.9, 44.1, 37.6, 29.2, 24.9, 22.3, 19.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6; HRMS (ESI^+): *m/z* calculated for $C_{32}H_{37}O_3N_7F_3S$ (M+H) 656.2625, found 656.2618; ELS purity (100%).



2-81

3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-fluorophenyl)prop-2-yn-1-yl (1-methylpiperidin-4-yl)carbamate (2-81). To a solution of **2-72** (0.070 g, 0.16 mmol) in dry CH_2Cl_2 (1.8 mL) was added CDI (0.039 g, 0.24 mmol) and the reaction stirred at room temperature under argon for 3 h. 4-Amino-1-methylpiperidine (0.061 mL, 0.48 mmol) was added and the reaction stirred at room temperature for 21 h. The reaction was diluted with CH_2Cl_2 and washed with water and brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 15/85). Product **2-81** was obtained as a white foam (0.083 g, 90%): IR (neat) 3238, 2940, 2787, 2227, 1714, 1620, 1505, 1447, 1270, 1226, 1162, 1044, 1017, 727, 707 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (dd, J = 4.8, 1.2 Hz, 1 H), 8.57 (d, J = 2.5 Hz, 1 H), 7.64 (dt, J = 8.1, 1.9 Hz, 1 H), 7.44 (dd, J = 8.1, 4.8 Hz, 1 H), 7.25 (t, J = 8.2 Hz, 1 H),

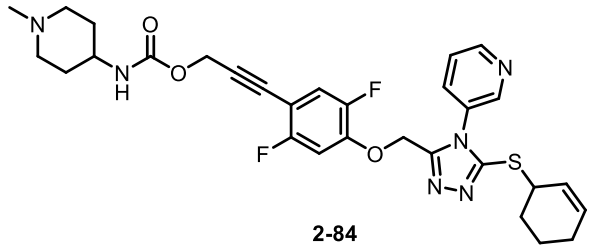
6.58 (ddd, *J* = 16.0, 9.7, 2.2 Hz, 2 H), 5.03 (s, 2 H), 5.01 (s, 1 H), 4.84 (s, 2 H), 3.47 (t, *J* = 3.6 Hz, 1 H), 2.70 (d, *J* = 10.4 Hz, 2 H), 2.21 (s, 3 H), 2.03 (t, *J* = 10.9 Hz, 2 H), 1.90 (dd, *J* = 12.9, 2.6 Hz, 2 H), 1.44 (qd, *J* = 11.7, 2.9 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5 (d, J_{CF} = 253.0 Hz), 158.7 (d, J_{CF} = 10.7 Hz), 154.8, 154.3, 151.3, 150.7, 147.9, 134.7, 134.5 (d, J_{CF} = 2.7 Hz), 130.0, 124.2, 110.5 (d, J_{CF} = 3.3 Hz), 104.4 (d, J_{CF} = 16.1 Hz), 102.8 (d, J_{CF} = 24.7 Hz), 87.9 (d, J_{CF} = 3.2 Hz), 79.2, 60.2, 54.4, 53.1, 47.9, 46.2, 45.7-45.3 (m, CD), 33.0-32.5 (m, CD), 32.5, 23.9-23.0 (m, CD); ^{19}F NMR (470 MHz, $CDCl_3$) δ -106.6; HRMS (ESI$^+$): *m/z* calculated for $C_{29}H_{25}{}^2H_9O_3N_6FS$ (M+H) 574.2957, found 574.2949; ELS purity (100%).



2-83

3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl (1-methylpiperidin-4-yl)carbamate (2-83). To a solution of **2-74** (0.090 g, 0.20 mmol) in dry CH_2Cl_2 (2.2 mL) was added CDI (0.048 g, 0.30 mmol) and the reaction stirred at room temperature for 3 h. 4-Amino-1-methylpiperidine (0.075 mL, 0.60 mmol) was added and the reaction stirred at room temperature for 20.5 h. The reaction was then diluted with CH_2Cl_2 and washed with water and brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 15/85). Product **2-83** was obtained as a white foam (0.098 g, 83%): IR (neat) 3235, 2940, 2790, 2226, 1714, 1629, 1507, 1447, 1271, 1224, 1044, 1003, 707 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (dd, *J* = 4.7, 1.0 Hz, 1 H), 8.57 (d, *J* = 2.3 Hz, 1 H), 7.70 (dt, *J* = 8.1, 1.8 Hz, 1 H), 7.44 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.01 (dd, *J* = 10.6, 6.5 Hz, 1 H),

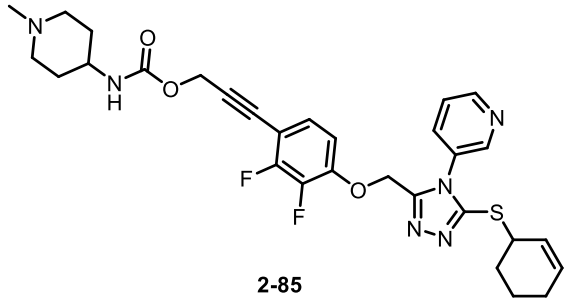
6.83 (dd, *J* = 9.6, 7.1 Hz, 1 H), 5.15 (d, *J* = 7.6 Hz, 1 H), 5.06 (s, 2 H), 4.81 (s, 2 H), 3.45 (s, 1 H), 2.71 (d, *J* = 9.7 Hz, 2 H), 2.20 (s, 3 H), 2.03 (t, *J* = 10.9 Hz, 2 H), 1.88 (d, *J* = 10.7 Hz, 2 H), 1.45 (qd, *J* = 11.6, 2.7 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2 (dd, J_{CF} = 250.4, 1.9 Hz), 159.2 (dd, J_{CF} = 250.4, 1.9 Hz), 148.0 (dd, J_{CF} = 244.3, 3.2 Hz), 146.4 (dd, J_{CF} = 12.7, 10.0 Hz), 119.9 (dd, J_{CF} = 21.5, 2.2 Hz), 103.8 (dd, J_{CF} = 18.4, 8.5 Hz), 103.6 (d, J_{CF} = 27.2 Hz), 88.8 (d, J_{CF} = 3.4 Hz), 78.1 (d, J_{CF} = 1.6 Hz), 45.4 (t, J_{CD} = 21.9 Hz), 32.8 (dt, J_{CD} = 40.1, 20.0 Hz), 23.5 (dt, J_{CD} = 39.7, 19.9 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -111.3 (d, *J* = 14.0 Hz), -138.6 (d, *J* = 14.0 Hz); HRMS (ESI^+): *m/z* calculated for $C_{29}H_{24}{}^2H_9O_3N_6F_2S$ (M+H) 592.2862, found 592.2858; ELS purity (100%).



2-84

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl (1-methylpiperidin-4-yl)carbamate (2-84). To a solution of **2-75** (0.060 g, 0.13 mmol) in dry CH_2Cl_2 (2 mL) was added CDI (0.032 g, 0.20 mmol) and the reaction stirred at room temperature under argon for 3 h. 4-Amino-1-methylpiperidine (0.050 mL, 0.40 mmol) was added and the reaction stirred at room temperature for 23 h. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 15/85). Product **2-84** was obtained as an off-white foam (0.069 g, 88%): IR (neat) 3254, 2937, 2788, 1713, 1629, 1506, 1446, 1271, 1224, 1179, 1044, 999, 725, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.59 (d, *J* = 2.1 Hz, 1

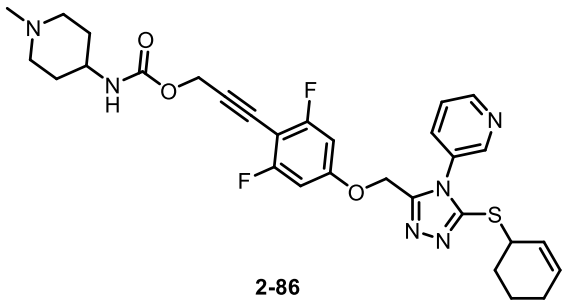
H), 7.71 (ddd, *J* = 8.2, 2.5, 1.5 Hz, 1 H), 7.45 (ddd, *J* = 8.1, 4.8, 0.6 Hz, 1 H), 7.03 (dd, *J* = 10.7, 6.5 Hz, 1 H), 6.84 (dd, *J* = 9.8, 7.0 Hz, 1 H), 5.85-5.81 (m, 1 H), 5.69 (ddt, *J* = 9.9, 4.0, 2.0 Hz, 1 H), 5.10 (d, *J* = 7.0 Hz, 1 H), 5.08 (s, 2 H), 4.83 (s, 2 H), 4.54-4.50 (m, 1 H), 3.51-3.44 (m, 1 H), 3.03 (s, 1 H), 2.73 (d, *J* = 11.3 Hz, 2 H), 2.22 (s, 3 H), 2.08-1.88 (m, 8 H), 1.73-1.57 (m, *J* = 7.3, 3.7 Hz, 2 H), 1.46 (qd, *J* = 11.8, 3.3 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (dd, J_{CF} = 246.5, 4.3 Hz), 154.7, 154.0, 151.4, 150.4, 148.0 (dd, J_{CF} = 244.2, 3.3 Hz), 147.9, 146.4 (dd, J_{CF} = 12.6, 9.9 Hz), 135.0, 132.5, 129.7, 125.3, 124.2, 119.9 (dd, J_{CF} = 21.2, 5.5 Hz), 103.9 (dd, J_{CF} = 18.1, 8.5 Hz), 103.6 (d, J_{CF} = 28.0 Hz), 88.8 (d, J_{CF} = 3.6 Hz), 78.2 (d, J_{CF} = 2.0 Hz), 61.2, 54.3, 52.9, 48.0, 46.1, 44.1, 32.3, 29.2, 24.8, 19.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.1 (d, *J* = 14.4 Hz), -138.5 (d, *J* = 14.5 Hz); HRMS (ESI^+): *m/z* calculated for $C_{30}H_{33}O_3N_6F_2S$ (M+H) 595.2297, found 595.2296; ELS purity (100%).



2-85

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,3-difluorophenyl)prop-2-yn-1-yl (1-methylpiperidin-4-yl)carbamate (2-85). To a solution of **2-76** (0.055 g, 0.12 mmol) in dry CH_2Cl_2 (1.8 mL) was added CDI (0.029 g, 0.18 mmol) and the reaction stirred at room temperature under argon for 3 h. 4-Amino-1-methylpiperidine (0.045 mL, 0.36 mmol) was added and the reaction stirred 16 h at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2

(ISCO, MeOH/CH_2Cl_2: 0/100 to 15/85). Product **2-85** was obtained as an off-white foam (0.049 g, 69%): 3235, 3031, 2935, 2787, 1716, 1506, 1484, 1446, 1271, 1233, 1094, 1041, 810, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.61 (d, *J* = 2.3 Hz, 1 H), 7.73 (ddd, *J* = 8.1, 2.4, 1.6 Hz, 1 H), 7.49 (dd, *J* = 8.2, 4.8 Hz, 1 H), 7.09 (td, *J* = 8.0, 2.1 Hz, 1 H), 6.88-6.82 (m, 1 H), 5.90-5.85 (m, 1 H), 5.73 (dt, *J* = 9.9, 2.0 Hz, 1 H), 5.18-5.10 (m, 2 H), 4.88 (s, 2 H), 4.83 (d, *J* = 6.4 Hz, 1 H), 4.57 (dd, *J* = 3.9, 1.8 Hz, 1 H), 3.57-3.48 (m, 1 H), 2.76 (d, *J* = 11.7 Hz, 2 H), 2.27 (s, 3 H), 2.18-1.92 (m, 9 H), 1.79-1.61 (m, 2 H), 1.49 (qd, *J* = 11.8, 3.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 154.1, 151.9 (dd, J_{CF} = 254.0, 11.2 Hz), 151.5, 150.6, 147.9, 147.2 (dd, J_{CF} = 8.4, 2.8 Hz), 141.3 (dd, J_{CF} = 249.6, 14.0 Hz), 135.1, 132.6, 129.8, 127.8 (d, J_{CF} = 4.3 Hz), 125.4, 124.3, 110.1 (d, J_{CF} = 3.5 Hz), 106.3 (d, J_{CF} = 13.0 Hz), 89.0 (d, J_{CF} = 3.5 Hz), 78.2 (d, J_{CF} = 3.7 Hz), 61.3, 54.3, 53.0, 47.9, 46.2, 44.1, 32.4, 29.3, 24.9, 19.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -132.4 (d, *J* = 20.2 Hz), -157.2 (d, *J* = 20.1 Hz); HRMS (ESI^+): *m/z* calculated for $C_{30}H_{33}O_3N_6F_2S$ (M+H) 595.2297, found 595.2298; ELS purity (99.9%).



2-86

4-Bromo-3,5-difluorophenyl pivalate. To a solution of 4-bromo-3,5-difluorophenol (0.500 g, 2.39 mmol) and Et_3N (0.370 mL, 2.63 mmol) in CH_2Cl_2 (4.7 mL) at 0 °C was added PivCl (0.656 mL, 2.63 mmol). The reaction was stirred at 0 °C for 35 min then diluted with Et_2O (10 mL) and filtered. The filtrate was concentrated and taken up in Et_2O (10 mL), filtered, and concentrated. The product was obtained as a white solid (0.601 g, 86%) and the pivalate carried

on without further purification: IR (neat) 2977, 1750, 1601, 1472, 1438, 1272, 1128, 1097, 1058, 1022, 896 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79-6.76 (m, 2 H), 1.34 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 159.8 (dd, J_{CF} = 248.9, 6.3 Hz), 151.1 (t, J_{CF} = 12.7 Hz), 106.5 (dd, J_{CF} = 26.0, 3.3 Hz), 94.8 (t, J_{CF} = 24.5 Hz), 39.2, 27.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ -103.9; HRMS (ESI^+): *m/z* calculated for $C_{11}H_{12}O_2BrF_2$ (M+H) 292.9983, found 292.9993.

3,5-Difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl pivalate. To a solution of 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (0.31 g, 2.2 mmol) and 4-bromo-3,5-difluorophenyl pivalate (0.50 g, 1.7 mmol) in deoxygenated Et_3N (1.32 mL) was added $Pd(PPh_3)_4$ (0.099 g, 0.085 mmol) and CuI (0.032 g, 0.17 mmol). The reaction was sparged with argon for 2 min then stirred at reflux for 13 h. The reaction was concentrated, and the residue taken up in Et_2O, washed with sat. NH_4Cl and brine, filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 0/100 to 10/90). The pivalate was obtained as a yellow oil (0.084 g, 14%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69-6.74 (m, 2 H), 4.92 (t, *J* = 3.3 Hz, 1 H), 4.58-4.50 (m, 2 H), 3.89 (ddd, *J* = 11.5, 8.9, 2.9 Hz, 1 H), 3.60-3.54 (m, 1 H), 1.87-1.73 (m, 2 H), 1.6-1.53 (m, 4 H), 1.33 (s, 9 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.1, HRMS (ESI^+): *m/z* calculated for $C_{19}H_{23}O_4F_2$ (M+H) 353.1559, found 353.1555.

3,5-Difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol. To a solution of 3,5-difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl pivalate (0.080 g, 0.23 mmol) in THF (3.3 mL) and MeOH (3.3 mL) was added a solution of NaOH (1 M, 1.2 mL) dropwise and the reaction was stirred at room temperature for 13.5 h. The reaction was concentrated and diluted with CH_2Cl_2. The solution was then neutralized to pH 7 with 2 N HCl and the aqueous extracted with CH_2Cl_2 (2x). The combined organic layers were dried ($MgSO_4$),

filtered, and concentrated. The crude phenol was obtained as a pale yellow oil (0.062 g) and carried on without further purification or characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40-6.36 (m, 2 H), 4.96 (t, *J* = 3.0 Hz, 1 H), 4.57-4.50 (m, 2 H), 3.93-3.89 (m, 1 H), 3.62-3.58 (m, 1 H), 1.90-1.75 (m, 2 H), 1.70-1.55 (m, 4 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -106.8; HRMS (ESI^-): *m/z* calculated for $C_{14}H_{13}O_3F_2$ (M-H) 267.0827, found 267.0834.

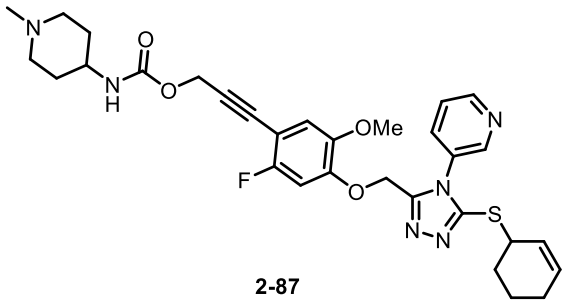
3,5-Difluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol. To a solution of crude 3,5-difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol (0.061 g, 0.23 mmol) in MeOH (1.4 mL) was added PPTS (0.029 g, 0.11 mmol) and the reaction stirred at room temperature for 2 d. The reaction was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The phenol was obtained as an off-white solid (0.042 g, 100%): IR (acetone) 3619, 3257, 3073, 2929, 2242, 1638, 1597, 1508, 1470, 1368, 1149, 1022, 836 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.64 (s, 1 H), 6.56-6.51 (m, 2 H), 4.44 (s, 2 H), 4.38 (bs, 1 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 164.7 (dd, *J* = 248.9, 9.1 Hz), 160.4 (t, *J* = 14.6 Hz), 100.2-100.0 (dd, *J* = 21.3, 5.9 Hz), 97.8 (t, *J* = 2.8 Hz), 93.5 (t, *J* = 20.5 Hz), 71.6, 51.1; ^{19}F NMR (470 MHz, acetone-d_6) δ -109.5; HRMS (ESI^-): *m/z* calculated for $C_9H_5O_2F_2$ (M-H) 183.0252, found 183.0256.

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,6-difluorophenyl)prop-2-yn-1-ol. To the crude mixture of (5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and 3-(3-(chloromethyl)-5-(cyclohex-2-en-1-ylthio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.063 g, 0.17 mmol) in dry DMF (2.8 mL) was added 3,5-difluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol (0.035 g, 0.19 mmol) and Cs_2CO_3 (0.062 g, 0.19 mmol) and the reaction stirred at room temperature for 19.5 h. The reaction was diluted

with EtOAc, and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0) followed by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 5/95). The triazole was obtained as a pale yellow solid (0.032 g, 41%) and carried on without further characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, *J* = 4.0 Hz, 1 H), 8.61 (d, *J* = 2.3 Hz, 1 H), 7.68 (ddd, *J* = 8.2, 2.3, 1.7 Hz, 1 H), 7.51 (dd, *J* = 8.1, 4.8 Hz, 1 H), 6.48-6.44 (m, 2 H), 5.90-5.86 (m, 1 H), 5.76-5.73 (m, 1 H), 5.08-5.03 (m, 2 H), 4.59 (d, *J* = 2.2 Hz, 1 H), 4.52 (d, *J* = 4.8 Hz, 2 H), 2.12-2.06 (m, 1 H), 2.03-1.99 (m, 3 H), 1.74-1.65 (m, 3 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -105.5 (d, *J* = 8.1 Hz); HRMS (ESI^+): *m/z* calculated for $C_{23}H_{21}O_2N_4F_2S$ (M+H) 455.1348, found 455.1346.

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,6-difluorophenyl)prop-2-yn-1-yl (1-methylpiperidin-4-yl)carbamate (2-86). To a solution of 3-(4-((5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,6-difluorophenyl)prop-2-yn-1-ol (0.032 g, 0.070 mmol) in dry CH_2Cl_2 (1 mL) was added CDI (0.017 g, 0.11 mmol) and the reaction stirred at room temperature under argon for 3 h. 4-Amino-1-methylpiperidine (0.027 mL, 0.21 mmol) was added and the reaction stirred at room temperature for 15.5 h. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 15/85). Product **2-86** was obtained as a white foam (0.034 g, 82%): IR (neat) 3236, 3033, 2936, 2788, 1715, 1635, 1574, 1504, 1445, 1271, 1234, 1147, 1042, 829, 708 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.58 (dd, *J* = 2.5, 0.5 Hz, 1 H), 7.66 (ddd, *J* = 8.1, 2.6, 1.6 Hz, 1 H), 7.48 (ddd, *J* = 8.1, 4.8, 0.7 Hz, 1 H), 6.49-6.44 (m, 2 H), 5.88-5.83 (m, 1 H), 5.74-5.70 (m, 1 H), 5.07-5.01

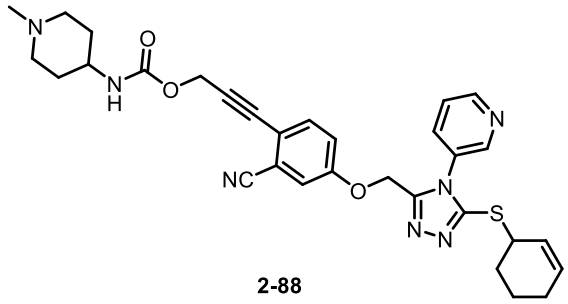
(m, 2 H), 4.98 (d, J = 7.8 Hz, 1 H), 4.88 (s, 2 H), 4.58-4.53 (m, 1 H), 3.51-3.48 (m, 1 H), 2.74 (d, J = 11.3 Hz, 2 H), 2.50 (s, 1 H), 2.24 (s, 3 H), 2.10-1.90 (m, 7 H), 1.75-1.62 (m, 2 H), 1.52-1.42 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (dd, J_{CF} = 253.7, 8.2 Hz), 158.6 (t, J_{CF} = 13.6 Hz), 154.8, 154.0, 151.5, 150.4, 147.9, 134.7, 132.6, 129.8, 125.3, 124.3, 98.9 (dd, J_{CF} = 27.1, 1.3 Hz), 95.1 (t, J_{CF} = 20.0 Hz), 92.5 (t, J_{CF} = 2.8 Hz), 73.0, 60.4, 54.4, 53.1, 47.9, 46.2, 44.1, 32.4, 29.3, 24.9, 19.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.1; HRMS (ESI^+): *m/z* calculated for $C_{30}H_{33}O_3N_6F_2S$ (M+H) 595.2297, found 595.2297; ELS purity (100%).



2-87

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-fluoro-5-methoxyphenyl)prop-2-yn-1-yl (1-methylpiperidin-4-yl)carbamate (2-87). To a solution of **2-77** (0.058 g, 0.12 mmol) in dry CH_2Cl_2 (1.4 mL) was added CDI (0.030 g, 0.19 mmol) and the reaction stirred at room temperature under argon for 3 h. 4-Amino-1-methylpiperidine (0.047 mL, 0.37 mmol) was added and the reaction stirred at room temperature for 13 h. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 15/85). Product **2-87** was obtained as an off-white foam (0.059 g, 78%): IR (neat) 3236, 2935, 2788, 2239, 1714, 1505, 1445, 1270, 1222, 1208, 1044, 1000, 854, 726, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, J = 4.8, 1.5 Hz, 1 H), 8.61 (d, J = 2.4 Hz, 1 H), 7.73 (ddd, J = 8.1, 2.5, 1.6 Hz, 1 H), 7.41 (ddd, J = 8.1, 4.8, 0.6 Hz, 1 H), 6.79 (d, J

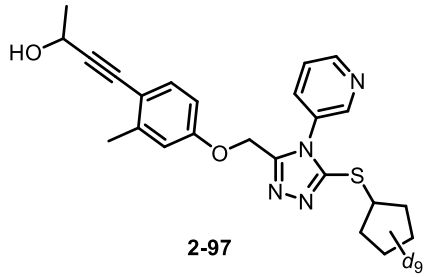
= 6.5 Hz, 1 H), 6.69 (d, *J* = 10.0 Hz, 1 H), 5.86-5.82 (m, 1 H), 5.74-5.69 (m, *J* = 1.9 Hz, 1 H), 5.09-5.03 (m, 2 H), 4.90 (s, 1 H), 4.87 (s, 2 H), 4.53 (dd, *J* = 4.1, 1.7 Hz, 1 H), 3.69 (s, 3 H), 3.51-3.48 (m, 1 H), 2.72 (dt, *J* = 12.0, 3.2 Hz, 2 H), 2.24 (s, 3 H), 1.90-2.10 (m, 8 H), 1.76-1.59 (m, 2 H), 1.76-1.43 (m, 5 H), 1.48 (qd, *J* = 11.8, 3.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8 (d, J_{CF} = 247.4 Hz), 154.9, 153.7, 151.2, 151.0, 148.3, 148.1 (d, J_{CF} = 9.5 Hz), 145.9 (d, J_{CF} = 2.8 Hz), 135.0, 132.3, 130.0, 125.6, 124.0, 115.7 (d, J_{CF} = 5.2 Hz), 103.6, 103.4 (d, J_{CF} = 8.8 Hz), 88.0 (d, J_{CF} = 3.7 Hz), 79.5, 61.4, 56.4, 54.3, 53.2, 48.0, 46.2, 44.2, 32.5, 29.4, 24.9, 19.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.2; HRMS (ESI^+): *m/z* calculated for $C_{31}H_{36}O_4N_6FS$ (M+H) 607.2497, found 607.2493; ELS purity (100%).



2-88

3-(2-Cyano-4-((5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)phenyl)prop-2-yn-1-yl (1-methylpiperidin-4-yl)carbamate (2-88). To a solution of **2-78** (0.056 g, 0.13 mmol) in dry CH_2Cl_2 (1.9 mL) was added CDI (0.031 g, 0.19 mmol) and the reaction stirred at room temperature under argon for 3 h. 4-Amino-1-methylpiperidine (0.048 mL, 0.38 mmol) was added and the reaction stirred at room temperature for 22 h. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/ CH_2Cl_2: 0/100 to 15/85). Product **2-88** was obtained as a tan foam (0.054 g, 74%): IR (neat) 3183, 2940, 2788, 2234, 1710, 1600, 1486, 1449, 1308, 1265, 1236, 1222, 1044,

1016, 830, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 4.7, 1.2 Hz, 1 H), 8.56 (d, *J* = 2.5 Hz, 1 H), 7.67 (ddd, *J* = 8.1, 2.4, 1.4 Hz, 1 H), 7.49 (dd, *J* = 8.1, 4.9 Hz, 1 H), 7.41-7.39 (m, 1 H), 7.07 (dd, *J* = 7.3, 2.6 Hz, 2 H), 5.85-5.82 (m, 1 H), 5.69-5.67 (m, 1 H), 5.11-5.04 (m, 2 H), 4.86 (s, 2 H), 4.50 (s, 1 H), 3.46 (s, 1 H), 2.83-2.73 (m, 3 H), 2.23 (s, 3 H), 2.06-1.87 (m, 8 H), 1.73-1.59 (m, 2 H), 1.50-1.41 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 155.1, 153.9, 151.2, 150.5, 147.6, 134.9, 134.3, 132.6, 129.7, 125.0, 124.4, 119.6, 119.3, 118.4, 116.61, 116.42, 89.2, 81.5, 60.0, 54.2, 52.7, 47.4, 45.8, 44.1, 31.6, 29.0, 24.7, 19.0; HRMS (ESI^+): *m/z* calculated for $C_{31}H_{34}O_3N_7S$ (M+H) 584.2438, found 584.2437; ELS purity (100%).

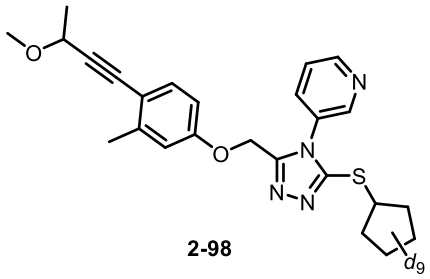


2-97

4-(3-Hydroxybut-1-yn-1-yl)-3-methylphenol[126]**.** To a solution of 3-butyn-2-ol (0.17 mL, 2.1 mmol) and 4-iodo-3-methylphenol (0.39 g, 1.6 mmol) in dry, deoxygenated MeCN (2.9 mL) was added $Pd(PPh_3)_2Cl_2$ (0.059 g, 0.082 mmol) and CuI (0.016 g, 0.082 mmol) followed by Et_3N (0.58 mL, 4.1 mmol). The reaction was stirred at room temperature 16 h. The reaction was diluted with EtOAc, washed with brine, filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 0/100 to 50/50). The phenol was obtained as a brown oil that solidifies upon standing (0.27 g, 94%) and carried on without further characterization: ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (app s, 1 H), 6.67 (d, *J* = 2.6 Hz, 1 H), 6.60 (dd, *J* = 8.3, 2.6 Hz, 1 H), 4.92 (bs, 1 H), 4.78 (q, *J* = 6.5 Hz, 1 H), 2.37 (s, 3 H), 1.89 (bs, 1 H),

1.56 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 155.8, 142.5, 133.7, 116.6, 114.9, 112.9, 93.6, 83.0, 59.3, 24.8, 20.8.

4-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)but-3-yn-2-ol (2-97). To a solution of crude 3-(3-(chloromethyl)-5-((cyclopentyl-d_9)thio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.16 g, 0.53 mmol) in dry DMF (8.5 mL) was added 4-(3-hydroxybut-1-yn-1-yl)-3-methylphenol (0.10 g, 0.58 mmol) and Cs_2CO_3 (0.19 g, 0.58 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with EtOAc, and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 80/20). Product **2-97** was obtained as a yellow foam (0.189 g, 81%): IR (neat) 3291, 2979, 2223, 1702, 1604, 1485, 1450, 1234, 1098, 1021, 811, 703 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.74 (dd, J = 4.8, 1.5 Hz, 1 H), 8.70 (d, J = 2.1 Hz, 1 H), 7.96 (ddd, J = 8.1, 2.6, 1.5 Hz, 1 H), 7.62 (ddd, J = 8.1, 4.8, 0.7 Hz, 1 H), 7.22 (d, J = 8.5 Hz, 1 H), 6.79 (d, J = 2.6 Hz, 1 H), 6.72 (dd, J = 8.5, 2.4 Hz, 1 H), 5.17 (s, 2 H), 4.73-4.65 (m, 1 H), 4.36 (d, J = 5.4 Hz, 1 H), 2.31 (s, 3 H), 1.45 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 158.3, 153.5, 152.4, 151.9, 149.0, 142.5, 136.0, 133.7, 131.4, 125.1, 117.1, 116.7, 113.0, 96.4, 81.6, 60.9, 58.5, 33.2 (d, J_{CD} = 21.1 Hz), 25.3, 24.0 (s, CD), 20.8; HRMS (ESI$^+$): *m/z* calculated for $C_{24}H_{18}{}^2H_9O_2N_4S$ (M+H) 444.2414, found 444.2415; ELS purity (100%).

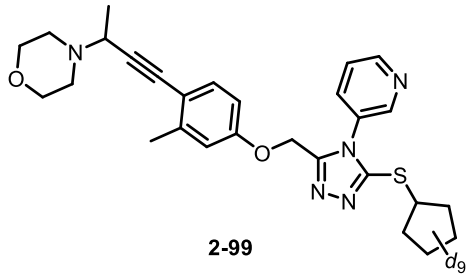


2-98

4-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)but-3-yn-2-yl methanesulfonate.[128, 129] To a solution of **2-97** (0.10 g, 0.23 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added Et_3N (0.063 mL, 0.45 mmol) and MsCl (0.021 mL, 0.27 mmol) and the reaction stirred at 0 °C for 2 h. The reaction was diluted with EtOAc and washed with sat. $NaHCO_3$, sat. NH_4Cl, and brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude triazole was obtained as a brown orange oil and carried on without further purification or characterization: HRMS (ESI^+) observed as methyl ether from LCMS conditions: *m/z* calculated for $C_{25}H_{20}{}^2H_9O_2N_4S$ (M+H) 458.2571, found 458.2568.

3-(3-((Cyclopentyl-*d*$_9$)thio)-5-((4-(3-methoxybut-1-yn-1-yl)-3-methylphenoxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (2-98). To a solution of MeOH (0.10 mL, 1.1 mmol) in THF (0.1 mL) at 0 °C was added NaH (0.051 g, 1.3 mmol) and stirred for 20 min. The suspension was then added dropwise to a solution of 4-(4-((5-((cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)but-3-yn-2-yl methanesulfonate (0.055 g, 0.11 mmol) in THF (0.12 mL) at 0 °C. The reaction was warmed to room temperature and stirred 16 h. The reaction was diluted with CH_2Cl_2 (1 mL) and quenched with water (1 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 10/90) followed by chromatography on C18-SiO_2 (RP-ISCO, MeCN/H_2O: 10/90 to 95/5). Product **2-98** was obtained as a yellow sticky

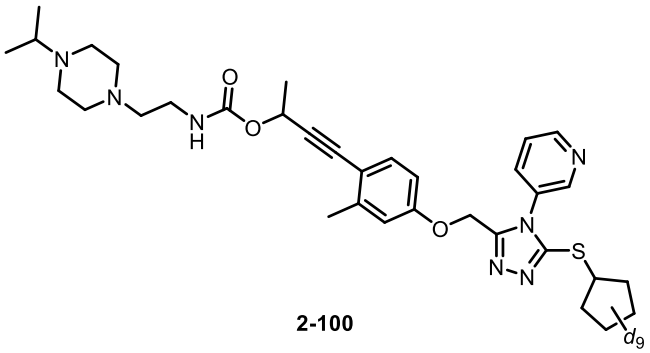
oil (8.0 mg, 17%): IR (neat) 2984, 2226, 1603, 1484, 1445, 1229, 1110, 1094, 1021, 820, 707 cm^{-1}; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.74 (d, *J* = 4.7 Hz, 1 H), 8.70 (d, *J* = 2.5 Hz, 1 H), 7.97 (d, *J* = 8.1 Hz, 1 H), 7.62 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.28 (d, *J* = 8.5 Hz, 1 H), 6.82 (d, *J* = 2.4 Hz, 1 H), 6.74 (dd, *J* = 8.5, 2.5 Hz, 1 H), 5.18 (s, 2 H), 4.32 (q, *J* = 6.6 Hz, 1 H), 3.38 (s, 3 H), 2.34 (s, 3 H), 1.43 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, acetone-d_6) δ 158.5, 153.5, 152.4, 151.9, 149.1, 142.6, 136.0, 134.0, 131.4, 125.1, 116.74, 116.71, 113.1, 93.0, 83.9, 67.9, 60.9, 56.2, 22.6, 20.9; HRMS (ESI^{+}): *m/z* calculated for $C_{25}H_{20}{}^{2}H_9O_2N_4S$ (M+H) 458.2571, found 458.2569; ELS purity (100%).



2-99

4-(4-(4-((5-(((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)but-3-yn-2-yl)morpholine (2-99).[137] To a solution of 4-(4-((5-((cyclopentyl-d_9)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)but-3-yn-2-yl methanesulfonate (0.055 g, 0.11 mmol) in MeCN (0.15 mL) was added morpholine (0.020 mL, 0.23 mmol) and the reaction stirred at room temperature 16 h. The reaction was concentrated and loaded onto the column. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0; MeOH/EtOAc: 0/100 to 10/90) followed by chromatography on C18-SiO_2 (RP-ISCO, MeCN/H_2O: 10/90 to 95/5). Product **2-99** was obtained as an orange sticky foam (0.015 g, 28%): IR (neat) 2955, 2854, 2227, 1701, 1604, 1485, 1446, 1290, 1228, 1115, 1029, 818, 708 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.78-8.68 (m, 2 H), 8.01-7.93 (m,

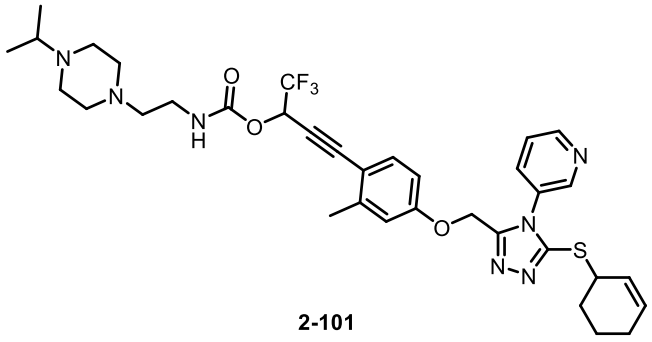
1 H), 7.62 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.27 (d, *J* = 8.5 Hz, 1 H), 6.81 (d, *J* = 2.7 Hz, 1 H), 6.73 (dd, *J* = 8.5, 2.7 Hz, 1 H), 5.17 (s, 2 H), 3.75-3.56 (m, 5 H), 2.72-2.63 (m, 2 H), 2.54-2.45 (m, 2 H), 2.35 (s, 3 H), 1.37 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (150 MHz, acetone-d_6) δ 206.1, 158.3, 153.5, 152.4, 151.9, 149.1, 142.3, 136.0, 134.0, 131.4, 125.1, 117.3, 116.7, 113.1, 91.8, 84.2, 67.6, 60.9, 53.3, 50.5-50.3 (m), 33.6-33.2 (m), 21.3, 19.8, 14.5; HRMS (ESI$^+$): *m/z* calculated for $C_{28}H_{25}{}^2H_9O_2N_5S$ (M+H) 513.2993, found 513.2989; ELS purity (100%).



2-100

4-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)but-3-yn-2-yl (2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (2-100). To a solution of **2-97** (0.055 g, 0.12 mmol) in dry CH_2Cl_2 (1.5 mL) was added CDI (0.030 g, 0.19 mmol) and the reaction stirred at room temperature under argon for 2 h. A solution of 2-(4-isopropylpiperazin-1-yl)ethan-1-amine (0.032 g, 0.19 mmol) in dry CH_2Cl_2 (0.5 mL) was then added and the reaction stirred for 2 d at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 20/80) followed by filtration through basic Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 5/95). Product **2-100** was obtained as a white foam (0.047 g, 59%): IR (neat) 3334, 2965, 2813, 2227, 1713, 1604, 1485, 1446, 1230, 1082, 1027, 817, 707 cm^{-1}; ^{1}H NMR (600 MHz, acetone-d_6) δ ,

8.74 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.70 (d, *J* = 2.5 Hz, 1 H), 7.98-7.96 (m, 1 H), 7.62 (ddd, *J* = 8.1, 4.8, 0.6 Hz, 1 H), 7.25 (d, *J* = 8.5 Hz, 1 H), 6.81 (d, *J* = 2.5 Hz, 1 H), 6.74 (dd, *J* = 8.5, 2.6 Hz, 1 H), 6.19 (q, *J* = 5.9 Hz, 1 H), 5.58 (q, *J* = 6.6 Hz, 1 H), 5.18 (s, 2 H), 3.24 (q, *J* = 6.2 Hz, 2 H), 2.58 (dt, *J* = 13.1, 6.5 Hz, 1 H), 2.43 (dd, *J* = 16.2, 9.7 Hz, 10 H), 2.32 (s, 3 H), 1.50 (d, *J* = 6.7 Hz, 3 H), 0.96 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR (150 MHz, acetone-d_6) δ 158.6, 156.1, 153.5, 152.3, 151.8, 149.0, 142.9, 136.0, 133.9, 131.3, 125.1, 116.7, 116.3, 113.1, 92.5, 83.1, 61.3, 60.9, 58.2, 54.8, 54.4, 49.2, 46.4-46.1 (m, CD), 38.8, 33.3 (t, J_{CD} = 20.2 Hz), 24.0 (t, J_{CD} = 19.8 Hz), 22.3, 20.8, 18.8; HRMS (ESI$^+$): *m/z* calculated for $C_{34}H_{37}{}^2H_9O_3N_7S$ (M+H) 641.3942, found 641.3940; ELS purity (100%).



2-101

4-(3-Hydroxyprop-1-yn-1-yl)-3-methylphenyl pivalate[138]**.** To a solution of 4-(3-hydroxyprop-1-yn-1-yl)-3-methylphenol (0.564 g, 3.48 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added Et_3N (0.538 mL, 3.83 mmol) followed by pivaloyl chloride (0.385 mL, 3.13 mmol) dropwise and the reaction was stirred at room temperature for 4 h. The reaction was diluted with CH_2Cl_2 (10 mL) and washed with sat. $NaHCO_3$, sat. NH_4Cl, and brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The pivalate was obtained as a pale brown oil that solidified upon standing (0.532 g, 62%) and carried on without further characterization: ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.3 Hz, 1 H), 6.91 (d, *J* = 2.2 Hz, 1 H), 6.85 (dd, *J* = 8.3, 2.4 Hz, 1 H), 4.53 (d, *J* = 5.6 Hz, 2 H), 2.42 (s, 3 H), 1.63 (t, *J* = 5.8 Hz, 1 H), 1.35 (s, 9 H).

3-Methyl-4-(3-oxoprop-1-yn-1-yl)phenyl pivalate[139]**.** To a solution of 4-(3-hydroxyprop-1-yn-1-yl)-3-methylphenyl pivalate (0.174 g, 0.706 mmol) in CH_2Cl_2 (2.6 mL) at 0 °C was added DMP (0.303 g, 0.706 mmol) and the reaction stirred at 0 °C for about 1 h. The reaction was poured into cold sat. $NaHCO_3$ (2 mL) and diluted with CH_2Cl_2 (2 mL). The combined organic layers were washed with sat. Na_2SO_3 (3x), water (2 mL), and brine (2 mL), dried ($MgSO_4$), filtered, and concentrated. The pivalate was obtained as a white solid (0.153 g, 89%) and carried on without further purification or characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.46 (s, 1 H), 7.58 (d, *J* = 8.4 Hz, 1 H), 7.00 (d, *J* = 2.1 Hz, 1 H), 6.94 (ddd, *J* = 8.4, 2.3, 0.3 Hz, 1 H), 2.50 (s, 3 H), 1.36 (s, 9 H).

3-Methyl-4-(4,4,4-trifluoro-3-hydroxybut-1-yn-1-yl)phenyl pivalate[140]**.** To a solution of 3-methyl-4-(3-oxoprop-1-yn-1-yl)phenyl pivalate (0.15 g, 0.61 mmol) in THF (0.8 mL) was added $TMSCF_3$ (0.12 mL, 0.80 mmol) then cooled to 0 °C and stirred under argon for 10 min. TBAF (2 drop) was then added and the reaction stirred for 10 min at 0 °C. The reaction was warmed to room temperature and stirred 16 h. The reaction was cooled to 0 °C, water (0.061 mL) followed by TBAF (0.061 mL) were added and the reaction warmed to room temperature and stirred for 3 h. The reaction was diluted with Et_2O (2 mL) and water (1 mL). The aqueous was extracted with Et_2O (2x) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 35/65). The still silylated intermediate was resubjected to the desilylation conditions: The mixture was dissolved in THF (0.8 mL) and treated with water (0.061 mL) and TBAF (0.061 mL) and stirred for 7 h. The reaction was diluted with Et_2O (2 mL) and water (1 mL). The aqueous was extracted

with Et_2O (2x) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 35/65). The pivalate was obtained as a yellow oil (0.102 g, 53%) and carried on without further characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 1 H), 6.93 (dd, *J* = 1.8, 0.4 Hz, 1 H), 6.87 (ddd, *J* = 8.3, 2.4, 0.5 Hz, 1 H), 4.91 (q, *J* = 5.6 Hz, 1 H), 2.91 (bs, 1 H), 2.41 (s, 3 H), 1.35 (s, 9 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -79.4; MS (ESI^-): M-H found 313.2.

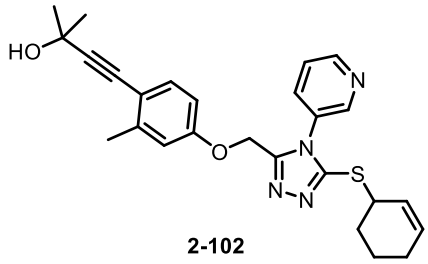
3-Methyl-4-(4,4,4-trifluoro-3-hydroxybut-1-yn-1-yl)phenol[141]**.** To a solution of 3-methyl-4-(4,4,4-trifluoro-3-hydroxybut-1-yn-1-yl)phenyl pivalate (0.045 g, 0.14 mmol) in EtOH (0.15 mL) was added Cs_2CO_3 (0.056 g, 0.17 mmol) and the reaction stirred at room temperature for 20 h. The reaction was concentrated, and the phenol obtained as a red-brown solid and carried on without further purification or characterization: HRMS (ESI^-): *m/z* calculated for $C_{11}H_8O_2F_3$ (M-H) 229.0471, found 229.0481.

4-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)-1,1,1-trifluorobut-3-yn-2-ol. To the crude mixture of (5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and 3-(3-(chloromethyl)-5-(cyclohex-2-en-1-ylthio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.045 g, 0.12 mmol) in dry DMF (1.8 mL) was added 3-methyl-4-(4,4,4-trifluoro-3-hydroxybut-1-yn-1-yl)phenol (0.049 g, 0.14 mmol) and Cs_2CO_3 (0.048 g, 0.15 mmol) and the reaction was stirred at room temperature 16 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The triazole was obtained impure as a yellow oil (~20 mg, ~30%) and carried on without further characterization: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (d, *J* = 3.4 Hz, 1 H), 8.60 (s,

1 H), 7.68 (d, *J* = 7.9 Hz, 1 H), 7.47 (dd, *J* = 7.7, 5.0 Hz, 1 H), 7.20 (dd, *J* = 8.3, 4.5 Hz, 1 H), 6.62 (s, 1 H), 6.54-6.57 (m, 1 H), 5.88-5.86 (m, 1 H), 5.73-5.72 (m, 1 H), 5.06-4.95 (m, 4 H), 4.56 (bs, 1 H), 2.29 (s, 2 H), 2.09-2.01 (m, 4 H), 1.67-1.66 (m, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.8, 153.8, 151.31, 151.18, 148.0, 143.2, 135.1, 133.8, 132.6, 130.1, 125.4, 124.3, 123.3 (q, J_{CF} = 284.5 Hz), 115.8, 114.7, 112.0, 86.0, 84.5, 77.2, 62.9 (q, J_{CF} = 36.0 Hz), 59.8, 56.1, 44.2, 29.3, 24.9, 22.8, 20.8, 19.2; ^{19}F NMR (565 MHz, $CDCl_3$) δ -79.2; HRMS (ESI^+): *m/z* calculated for $C_{25}H_{24}O_2N_4F_3S$ (M+H) 501.1567, found 501.1569.

4-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)-1,1,1-trifluorobut-3-yn-2-yl (2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (2-101). To a solution of 4-(4-((5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)-1,1,1-trifluorobut-3-yn-2-ol (0.026 g, 0.052 mmol) in dry CH_2Cl_2 (0.5 mL) was added CDI (0.013 g, 0.078 mmol) and the reaction stirred at room temperature under argon for 2 h. A solution of 2-(4-isopropylpiperazin-1-yl)ethan-1-amine (0.013 g, 0.078 mmol) in dry CH_2Cl_2 (0.5 mL) was then added and the reaction stirred for 4 d at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0; MeOH/EtOAc: 0/100 to 30/70) followed by filtration through a plug of basic Al_2O_3 (MeOH/$CDCl_3$: 0/100 to 2/98). Product **2-101** was obtained as a gooey white foam (0.012 g, 32%): IR (neat) 3246, 2935, 2815, 2234, 1737, 1604, 1485, 1445, 1232, 1181, 1140, 1036, 995, 707 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.60 (d, *J* = 2.4 Hz, 1 H), 7.66 (ddd, *J* = 8.1, 2.5, 1.5 Hz, 1 H), 7.46 (ddd, *J* = 8.1, 4.8, 0.3 Hz, 1 H), 7.33 (d, *J* = 8.5 Hz, 1 H), 6.70 (d, *J* = 2.4 Hz, 1 H), 6.65 (dd, *J* = 8.5, 2.6 Hz, 1 H), 6.08 (q, *J* = 5.8 Hz, 1 H), 5.87 (dtd, *J* = 9.8, 3.8, 1.4 Hz, 1 H),

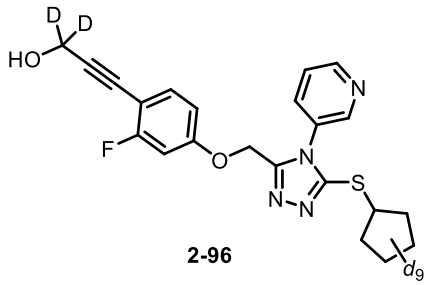
5.76-5.73 (m, 1 H), 5.54 (t, *J* = 4.7 Hz, 1 H), 5.10-5.05 (m, 2 H), 4.57 (dd, *J* = 3.9, 1.6 Hz, 1 H), 3.33 (dd, *J* = 11.6, 5.6 Hz, 2 H), 2.64 (dquintet, *J* = 13.0, 6.5 Hz, 1 H), 2.59-2.45 (m, 10 H), 2.36 (s, 3 H), 2.01-2.09 (m, 4 H), 1.75-1.65 (m, 2 H), 1.04 (d, *J* = 6.5 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.1, 153.74, 153.68, 151.3, 148.2, 143.6, 134.8, 134.2, 132.5, 130.1, 125.6, 124.2, 121.1 (q, J_{CF} = 281.1 Hz), 116.0, 114.5, 112.2, 86.7, 81.5, 62.9 (q, J_{CF} = 37.3 Hz), 60.0, 56.7, 54.6, 53.4, 48.7, 44.2, 38.0, 29.4, 25.0, 20.8, 19.3, 18.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.8; HRMS (ESI^+): *m/z* calculated for $C_{35}H_{43}O_3N_7F_3S$ (M+H) 698.3095, found 698.3096; ELS purity (100%).



2-102

4-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-methylphenyl)-2-methylbut-3-yn-2-ol (2-102). To the crude mixture of (5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and 3-(3-(chloromethyl)-5-(cyclohex-2-en-1-ylthio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.063 g, 0.17 mmol) in dry DMF (2.5 mL) was added 4-(3-hydroxy-3-methylbut-1-yn-1-yl)-3-methylphenol (0.052 g, 0.21 mmol) and Cs_2CO_3 (0.11 g, 0.34 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-102** was obtained as a tan foam (0.037 g, 47%): IR (neat) 3311, 2978, 2927, 1604,

1485, 1444, 1231, 1163, 1032, 816, 707 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.74 (dd, *J* = 4.8, 1.3 Hz, 1 H), 8.71 (d, *J* = 2.4 Hz, 1 H), 7.97 (ddd, *J* = 8.1, 2.4, 1.5 Hz, 1 H), 7.62 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.21 (d, *J* = 8.5 Hz, 1 H), 6.79 (d, *J* = 2.4 Hz, 1 H), 6.72 (dd, *J* = 8.5, 2.6 Hz, 1 H), 5.87 (dtd, *J* = 9.6, 3.8, 1.2 Hz, 1 H), 5.72 (ddt, *J* = 9.9, 3.9, 2.0 Hz, 1 H), 5.18 (s, 2 H), 4.41-4.40 (m, 1 H), 4.37 (s, 1 H), 2.31 (s, 3 H), 2.02-1.95 (m, 4 H), 1.72-1.64 (m, 2 H), 1.53 (s, 6 H); ^{13}C NMR (150 MHz, acetone-d_6) δ 158.2, 152.9, 152.5, 151.8, 149.0, 142.4, 136.0, 133.5, 132.7, 131.3, 129.3, 126.5, 125.1, 117.2, 116.6, 113.0, 99.2, 80.0, 65.2, 60.9, 44.8, 32.2, 25.4, 20.8, 19.7; HRMS (ESI^+): *m/z* calculated for $C_{26}H_{29}O_2N_4S$ (M+H) 461.2006, found 461.2007; ELS purity (100%).



2-((Prop-2-yn-1-yl-1,1-*d*$_2$)oxy)tetrahydro-2*H*-pyran[142]**.** To a suspension of $LiAlD_4$ (0.484 g, 11.3 mmol) in Et_2O (30.8 mL) at -40 to -50 °C was added methyl propiolate (1.06 mL, 11.5 mmol) in Et_2O (10.2 mL) over 10 min. The reaction was stirred at -30 °C for 1 h and slowly warmed to room temperature over 2 h. The reaction was stirred for an additional 11.5 h. The reaction was quenched with dropwise addition of water (0.5 mL), NaOH (0.5 mL), and water (1 mL). The solid was filtered off and washed with Et_2O (20 mL), the filtrate was dried ($MgSO_4$), filtered, and the volume reduced. Crude prop-2-yn-1,1-d_2-1-ol was obtained as a pale-yellow oil and carried on without further purification or characterization: ^1H NMR (500 MHz, $CDCl_3$) δ 3.68 (s, 1 H), 2.29 (s, 1 H).

To a solution of crude prop-2-yn-1,1-d_2-1-ol (0.669 mL, 11.5 mmol) in Et_2O was added 3,4-dihydro-2*H*-pyran (1.30 mL, 14.2 mmol) and the reaction stirred at room temperature for 10 min. *p*-TsOH (0.226 g, 1.19 mmol) was then added and the reaction stirred at room temperature for 23.5 h. The reaction was then washed with water, 1 M NaOH, and brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude material was distilled via Kugelrohr (~20 torr, 80-90 °C). The alkyne was obtained as a colorless oil (0.561 g, 34%) and carried on without further purification or characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.95 (dd, *J* = 4.6, 2.9 Hz, 1 H), 3.88-3.84 (m, 1 H), 3.80 (s, 1 H), 3.55-3.50 (m, 1 H), 1.79-1.50 (m, 6 H).

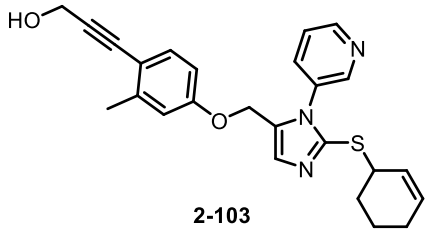
3-Fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl-3,3-d_2)phenyl pivalate. To a solution of 2-((prop-2-yn-1-yl-1,1-d_2)oxy)tetrahydro-2*H*-pyran (0.55 g, 3.9 mmol) and 4-bromo-3-fluorophenyl pivalate (0.89 g, 3.2 mmol) in deoxygenated Et_3N (2.5 mL, 18 mmol) was added $Pd(PPh_3)_4$ (0.19 g, 0.16 mmol) and CuI (0.061 g, 0.32 mmol). The reaction was sparged with argon for 2 min then stirred at reflux for 16 h. The reaction was concentrated, and the residue taken up in Et_2O, washed with sat. NH_4Cl and brine, filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 0/100 to 10/90). The pivalate was obtained as a yellow oil (0.337 g, 31%) and carried on without further characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (t, *J* = 8.1 Hz, 1 H), 6.86 (dd, *J* = 9.7, 2.1 Hz, 1 H), 6.83 (ddd, *J* = 8.4, 2.3, 0.7 Hz, 1 H), 4.90 (t, *J* = 3.4 Hz, 1 H), 3.91-3.87 (m, 1 H), 3.59-3.55 (m, 1 H), 1.91-1.81 (m, 1 H), 1.80-1.74 (m, 1 H), 1.68-1.53 (m, 4 H), 1.34 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 163.1 (d, J_{CF} = 253.0 Hz), 152.0 (d, J_{CF} = 10.6 Hz), 134.0 (d, J_{CF} = 2.6 Hz), 117.5 (d, J_{CF} = 3.6 Hz), 109.9 (d, J_{CF} = 24.4 Hz), 108.9 (d, J_{CF} = 16.3 Hz), 90.5, 78.7, 62.2, 39.3, 30.4, 27.2, 25.5, 19.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ -107.4.

3-Fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl-3,3-d_2)phenol. To a solution of 3-fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl-3,3-d_2)phenyl pivalate (0.332 g, 0.987 mmol) in THF (14.5 mL) and MeOH (14.5 mL) was added a solution of NaOH (1 M, 10.9 mL) dropwise and the reaction was stirred at room temperature for about 15 h. The reaction was concentrated and diluted with CH_2Cl_2 (30 mL). The solution was then neutralized to pH 7 with 2 N HCl and the aqueous extracted with CH_2Cl_2 (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude phenol was obtained as a yellow oil (0.261 g) and carried on without further purification or characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.1 Hz, 1 H), 6.59-6.55 (m, 2 H), 4.92 (t, *J* = 3.4 Hz, 1 H), 3.89 (ddd, *J* = 11.4, 8.8, 2.9 Hz, 1 H), 3.59-3.55 (m, 1 H), 1.88-1.73 (m, 2 H), 1.69-1.52 (m, 4 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.8.

3-Fluoro-4-(3-hydroxyprop-1-yn-1-yl-3,3-d_2)phenol. To a solution of 3-fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl-3,3-d_2)phenol (0.25 g, 0.99 mmol) in MeOH (6 mL) was added PPTS (0.062 g, 0.25 mmol) and the reaction stirred at room temperature for 19.5 h. The reaction was diluted with CH_2Cl_2 (20 mL) and extracted with sat. $NaHCO_3$. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 40/100). The phenol was obtained as an off-white solid (0.061 g, 37%): m.p. 99.8-102.1 °C; IR (neat) 3411, 3235, 2932, 2811, 2238, 1623, 1590, 1506, 1468, 1307, 1239, 1093, 965, 839, 780, 659 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/acetone-d_6) δ 7.15 (t, *J* = 8.1 Hz, 1 H), 6.56-6.50 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$/acetone-d_6) δ 163.2 (d, J_{CF} = 250.0 Hz), 158.6 (d, J_{CF} = 11.2 Hz), 133.8 (d, J_{CF} = 3.4 Hz), 111.3 (d, J_{CF} = 2.9 Hz), 102.7 (d, J_{CF} = 23.7 Hz), 101.7 (d, J_{CF} = 16.1 Hz), 90.5 (d, J_{CF} =

2.5 Hz), 78.1, 50.0 (t, J_{CD} = 22.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$/acetone-d_6) δ -109.3; HRMS (ESI^-): *m/z* calculated for $C_9H_4{}^2H_2O_2F$ (M-H) 167.0472, found 167.0470.

3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2-fluorophenyl)prop-2-yn-1,1-*d*$_2$-1-ol (2-96). To a solution of 3-(3-(chloromethyl)-5-((cyclopentyl-*d*$_9$)thio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.082 g, 0.27 mmol) in DMF (4.5 mL) was added 3-fluoro-4-(3-hydroxyprop-1-yn-1-yl-3,3-*d*$_2$)phenol (0.054 g, 0.32 mmol) and Cs_2CO_3 (0.11 g, 0.32 mmol) and the reaction stirred at room temperature for 16 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-96** was obtained as an off-white solid (0.11 g, 97%): m.p. 163-164 °C; IR (neat) 3209, 2791, 2225, 2097, 1618, 1575, 1504, 1454, 1395, 1288, 1162, 1092, 1018, 966, 807, 707 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.61 (d, *J* = 2.4 Hz, 1 H), 7.68 (ddd, *J* = 8.1, 2.4, 1.6 Hz, 1 H), 7.48 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.23 (t, *J* = 8.3 Hz, 1 H), 6.59 (dd, *J* = 8.6, 2.5 Hz, 1 H), 6.54 (dd, *J* = 10.7, 2.4 Hz, 1 H), 5.05 (s, 2 H), 3.11 (bs, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2 (d, J_{CF} = 252.3 Hz), 158.3 (d, J_{CF} = 10.6 Hz), 154.3, 151.2, 150.7, 147.8, 134.9, 134.2 (d, J_{CF} = 2.8 Hz), 129.9, 124.3, 110.5 (d, J_{CF} = 3.2 Hz), 104.7 (d, J_{CF} = 15.8 Hz), 102.6 (d, J_{CF} = 25.0 Hz), 92.4, 77.8, 60., 50.5 (t, J_{CD} = 22.3 Hz), 45.4 (t, J_{CF} = 24.2 Hz), 33.1-32.5 (m), 23.8-23.2 (m); ^{19}F NMR (470 MHz, $CDCl_3$) δ -107.1; HRMS (ESI^+): *m/z* calculated for $C_{22}H_{11}{}^2H_{11}O_2N_4FS$ (M+H) 436.2132, found 436.2129; ELS purity (100%).



2-103

Ethyl 2-(cyclohex-2-en-1-ylthio)-1-(pyridin-3-yl)-1*H*-imidazole-5-carboxylate. To a solution of ethyl 2-mercapto-1-(pyridin-3-yl)-1*H*-imidazole-5-carboxylate (0.200 g, 0.802 mmol) in DMF (4.1 mL) was added 3-bromocyclohexene (0.138 mL, 1.20 mmol) and Cs_2CO_3 (0.523, 1.60 mmol) the reaction mixture was stirred for 1 h at room temperature. Then the reaction was diluted with water (10 mL) and extracted with EtOAc (2x). The combined organics were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 50/50). The imidazole was obtained as a white foam (0.206 g, 78%): IR (neat) 3100, 2984, 2939, 1712, 1534, 1482, 1429, 1369, 1321, 1274, 1159, 1028, 997, 868, 816, 764, 750, 712 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.8 Hz, 1 H), 8.53 (d, *J* = 2.3 Hz, 1 H), 7.86 (s, 1 H), 7.64 (ddd, *J* = 8.1, 2.4, 1.4 Hz, 1 H), 7.45 (dd, *J* = 8.0, 4.8 Hz, 1 H), 5.87-5.84 (m, 1 H), 5.72 (ddt, *J* = 9.9, 4.2, 2.2 Hz, 1 H), 4.53-4.52 (m, 1 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 2.08-2.00 (m, 3 H), 1.93-1.89 (m, 1 H), 1.75-1.62 (m, 2 H), 1.19 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 150.8, 150.1, 148.4, 137.9, 135.3, 133.0, 132.0, 125.7, 125.6, 123.5, 60.6, 43.8, 29.2, 24.8, 19.2, 14.1; HRMS (ESI^+): *m/z* calculated for $C_{17}H_{20}O_2N_3S$ (M+H) 330.1271, found 330.1269.

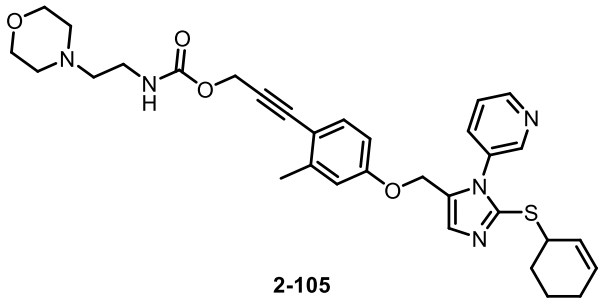
(2-(Cyclohex-2-en-1-ylthio)-1-(pyridin-3-yl)-1*H*-imidazol-5-yl)methanol[143]**.** To a solution of $LiAlH_4$ (0.28 mL, 4 M, 1.1 mmol) in dry Et_2O (4.9 mL) at -40 °C under nitrogen was added a solution of ethyl 2-(cyclohex-2-en-1-ylthio)-1-(pyridin-3-yl)-1*H*-imidazole-5-carboxylate (0.25 g, 0.76 mmol) in dry CH_2Cl_2 (4.9 mL) dropwise. The reaction was stirred for 10 min. The reaction was then quenched with water (0.31 mL), 1M NaOH (0.31 mL), and water (0.94 mL).

The suspension was diluted with CH_2Cl_2 (10 mL) and then dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (EtOAc/hexanes: 50/50 to MeOH/EtOAc: 5/95). The imidazole was obtained as a colorless oil (0.205 g, 94%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.63 (dd, *J* = 2.5, 0.6 Hz, 1 H), 7.76 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.47 (ddd, *J* = 8.1, 4.8, 0.8 Hz, 1 H), 7.20 (s, 1 H), 5.84-5.79 (m, 1 H), 5.70-5.65 (m, 1 H), 4.47-4.40 (m, 2 H), 4.30-4.26 (m, 1 H), 2.02-1.95 (m, 3 H), 1.88-1.81 (m, 1 H), 1.74-1.64 (m, 2 H); HRMS (ESI$^+$): *m/z* calculated for $C_{15}H_{18}ON_3S$ (M+H) 288.1165, found 288.1164.

3-(2-(Cyclohex-2-en-1-ylthio)-5-((3-methyl-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenoxy)methyl)-1*H*-imidazol-1-yl)pyridine. To a solution of (2-(cyclohex-2-en-1-ylthio)-1-(pyridin-3-yl)-1*H*-imidazol-5-yl)methanol (0.200 g, 0.696 mmol), PPh_3 (0.219 g, 0.835 mmol), and 3-methyl-4-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol (0.206 g, 0.835 mmol) in dry THF (2.9 mL) at 0 °C was added DIAD (0.164 mL, 0.835 mmol) dropwise. The reaction was stirred at room temperature 16 h. The reaction was poured into water (5 mL) and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The imidazole was obtained as a white foam (0.210 g, 58%) and carried on without further characterization: IR (neat) 2939, 2861, 2221, 1721, 1603, 1496, 1483, 1432, 1229, 1116, 1020, 813, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.63 (dd, *J* = 2.6, 0.5 Hz, 1 H), 7.71 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.41 (ddd, *J* = 8.1, 4.9, 0.7 Hz, 1 H), 7.32 (s, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 6.61 (d, *J* = 2.5 Hz, 1 H), 6.55 (dd, *J* = 8.4, 2.6 Hz, 1 H), 5.84-5.81 (m, 1 H), 5.71-5.67 (m, 1 H), 4.91 (t, *J* = 3.5 Hz, 1 H), 4.78-4.72 (m, 2 H), 4.50 (d, *J* = 5.1 Hz, 2 H), 4.36 (bs, 1 H), 3.89 (ddd, *J* = 11.5, 8.6, 3.1 Hz, 1 H),

3.58-3.53 (m, 1 H), 2.36 (s, 3 H), 2.36-1.97 (m, 3 H), 1.88-1.84 (m, 3 H), 1.76-1.55 (m, 6 H); HRMS (ESI^+): *m/z* calculated for $C_{30}H_{34}O_3N_3S$ (M+H) 516.2315, found 516.2316.

3-(4-((2-(Cyclohex-2-en-1-ylthio)-1-(pyridin-3-yl)-1*H*-imidazol-5-yl)methoxy)-2-methylphenyl)prop-2-yn-1-ol (2-103)[xiii]**.** To a solution of 3-(2-(cyclohex-2-en-1-ylthio)-5-((3-methyl-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenoxy)methyl)-1*H*-imidazol-1-yl)pyridine (0.110 g, 0.213 mmol) in MeOH (6 mL) was added PPTS (0.160 g, 0.640 mmol) and then stirred at 40-50 °C for 2 h. The reaction was then concentrated, and the residue dissolved in EtOAc, washed with satd. $NaHCO_3$, and brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **2-103** was obtained as an off-white foam (0.0637 g, 69%): HRMS (ESI^+): *m/z* calculated for $C_{25}H_{26}O_2N_3S$ (M+H) 432.1740, found 432.1736.

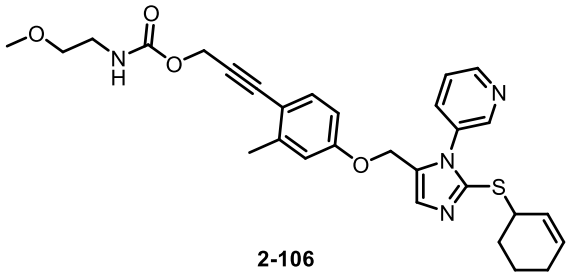


2-105

3-(4-((2-(Cyclohex-2-en-1-ylthio)-1-(pyridin-3-yl)-1H-imidazol-5-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl (2-morpholinoethyl)carbamate (2-105). To a solution of **2-103** (0.040 g, 0.93 mmol) in dry CH_2Cl_2 (1.5 mL) was added CDI (0.023 g, 0.14 mmol) and the reaction stirred at room temperature under argon 16 h. 4-(2-Aminoethyl)-morpholine (18 µL,

[xiii] Full characterization by Matthew LaPorte; described batch not biologically tested

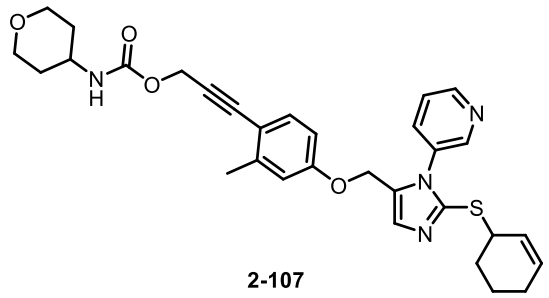
0.14 mmol) was added and the reaction stirred 16 h at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 5/95). Product **2-105** was obtained as a sticky white foam (0.035 g, 64%): IR (neat) 3312, 3031, 2933, 2856, 2220, 1718, 1603, 1495, 1432, 1291, 1228, 1140, 1115, 1028, 815, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.61 (d, *J* = 2.4 Hz, 1 H), 7.69 (ddd, *J* = 8.1, 2.4, 1.6 Hz, 1 H), 7.39 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.29 (s, 1 H), 7.27 (d, *J* = 8.8 Hz, 1 H), 6.60 (d, *J* = 2.4 Hz, 1 H), 6.54 (dd, *J* = 8.5, 2.5 Hz, 1 H), 5.83-5.78 (m, *J* = 1.4 Hz, 1 H), 5.70-5.65 (m, 1 H), 5.37-5.36 (m, 1 H), 4.91 (s, 2 H), 4.77-4.70 (m, 2 H), 4.32-4.31 (m, 1 H), 3.67 (t, *J* = 4.6 Hz, 4 H), 3.29 (q, *J* = 5.7 Hz, 2 H), 2.48-2.42 (m, 6 H), 2.34 (s, 3 H), 2.03-1.95 (m, 3 H), 1.90-1.83 (m, *J* = 3.5 Hz, 1 H), 1.74-1.55 (m, 2 H); ^{13}C NMR ($CD_3OD/CDCl_3$,) δ 157.9, 155.7, 150.4, 148.9, 145.7, 142.6, 135.6, 133.8, 132.2, 131.7, 131.5, 129.5, 126.0, 123.8, 115.8, 115.2, 112.0, 86.4, 85.0, 67.0, 59.4, 57.4, 53.56, 53.40, 44.5, 37.3, 29.3, 24.9, 21.0, 19.2; HRMS (ESI^+): *m/z* calculated for $C_{32}H_{38}O_4N_5S$ (M+H) 588.2639, found 588.2645; ELS purity (100%).



2-106

3-(4-((2-(Cyclohex-2-en-1-ylthio)-1-(pyridin-3-yl)-1*H*-imidazol-5-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl (2-methoxyethyl)carbamate (2-106). To a solution of **2-103** (0.031 g, 0.072 mmol) in dry CH_2Cl_2 (1 mL) was added CDI (0.017 g, 0.11 mmol) and the

reaction stirred at room temperature under argon 16 h. 2-Methoxyethylamine (9.4 µL, 0.11 mmol) was added and the reaction stirred 16 h at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 80/20). Product **2-106** was obtained as a sticky white foam (0.027 g, 70%): IR (neat) 3329, 3029, 2929, 2225, 1718, 1603, 1496, 1432, 1228, 1119, 1021, 910, 815, 728, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.61 (d, *J* = 2.5 Hz, 1 H), 7.69 (ddd, *J* = 8.1, 2.4, 1.6 Hz, 1 H), 7.39 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.29 (s, 1 H), 7.27 (d, *J* = 8.3 Hz, 1 H), 6.60 (d, *J* = 2.4 Hz, 1 H), 6.54 (dd, *J* = 8.5, 2.6 Hz, 1 H), 5.83-5.78 (m, 1 H), 5.68 (ddt, *J* = 9.9, 4.1, 2.0 Hz, 1 H), 5.22-5.20 (m, 1 H), 4.91 (s, 2 H), 4.77-4.70 (m, 2 H), 4.31 (dd, *J* = 4.0, 1.6 Hz, 1 H), 3.45 (t, *J* = 4.9 Hz, 2 H), 3.37 (q, *J* = 5.2 Hz, 2 H), 3.33 (s, 3 H), 2.34 (s, 3 H), 2.03-1.95 (m, 2 H), 1.92-1.87 (m, 2 H), 1.74-1.56 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 155.8, 150.4, 148.9, 145.7, 142.6, 135.6, 133.7, 132.2, 131.7, 131.5, 129.5, 126.0, 123.8, 115.8, 115.3, 112.0, 86.4, 84.9, 71.4, 59.5, 58.9, 53.6, 44.5, 41.0, 29.3, 24.9, 21.0, 19.2; HRMS (ESI^+): *m/z* calculated for $C_{29}H_{33}O_4N_4S$ (M+H) 533.2217, found 533.2220; ELS purity (100%).

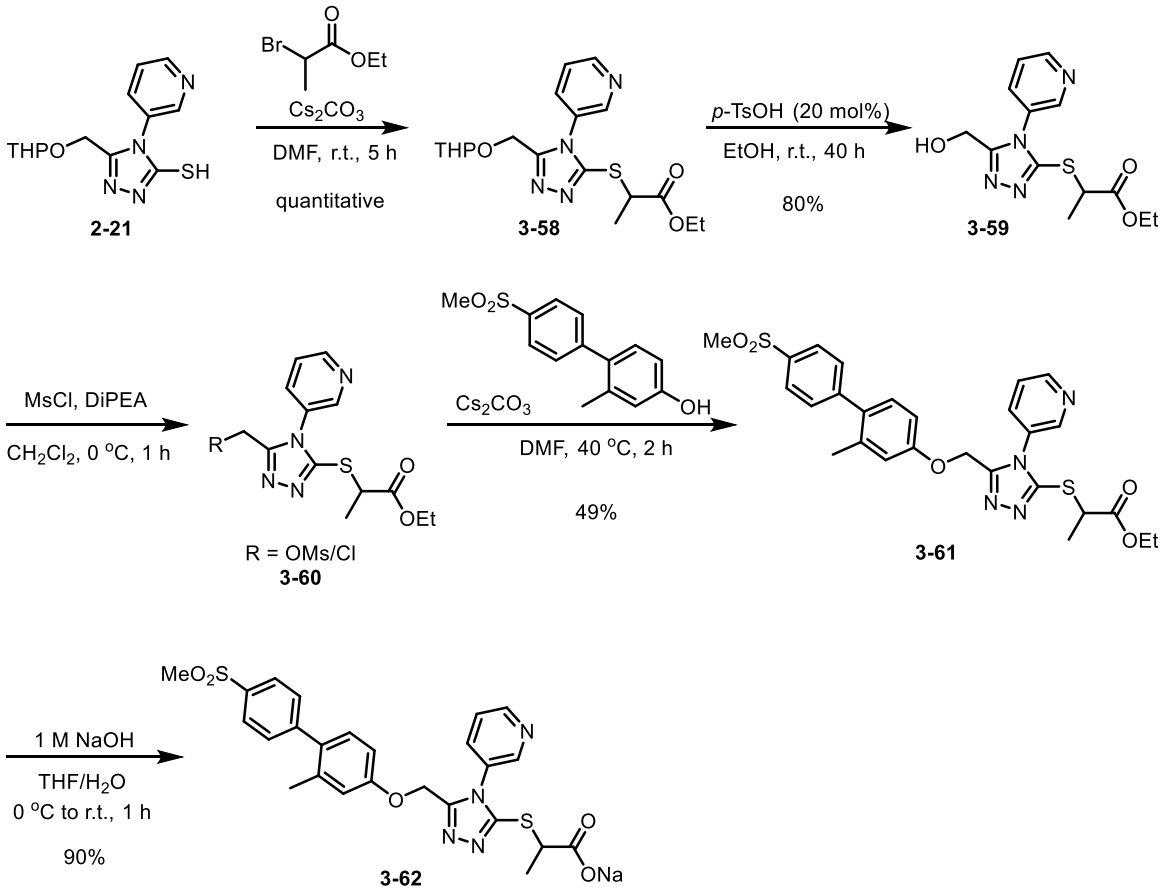


2-107

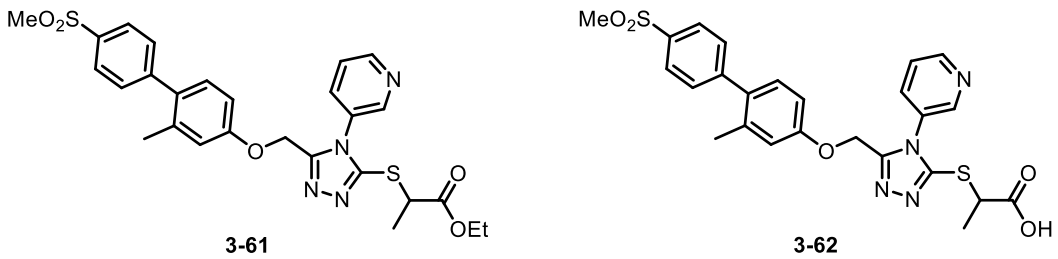
3-(4-((2-(Cyclohex-2-en-1-ylthio)-1-(pyridin-3-yl)-1H-imidazol-5-yl)methoxy)-2-methylphenyl)prop-2-yn-1-yl (tetrahydro-2H-pyran-4-yl)carbamate (2-107). To a solution of **2-103** (0.031 g, 0.72 mmol) in dry CH_2Cl_2 (1 mL) was added CDI (0.017 g, 0.11 mmol) and

the reaction stirred at room temperature under argon 16 h. 4-Aminotetrahydropyran (11 µL, 0.11 mmol) was added and the reaction stirred 16 h at room temperature. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 80/20). Product **2-107** was obtained as a white foam (0.028 g, 69%): IR (neat) 3321, 3033, 2938, 2852, 2223, 1713, 1603, 1496, 1432, 1228, 1042, 907, 815, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.61 (dd, *J* = 2.5, 0.5 Hz, 1 H), 7.69 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.38 (ddd, *J* = 8.1, 4.8, 0.6 Hz, 1 H), 7.29 (s, 1 H), 7.26 (d, *J* = 8.5 Hz, 1 H), 6.60 (d, *J* = 2.4 Hz, 1 H), 6.54 (dd, *J* = 8.5, 2.5 Hz, 1 H), 5.83-5.78 (m, *J* = 1.5 Hz, 1 H), 5.70-5.65 (m, *J* = 1.9 Hz, 1 H), 4.89 (s, 2 H), 4.76-4.70 (m, 2 H), 4.31 (dd, *J* = 4.2, 1.8 Hz, 1 H), 3.93 (dt, *J* = 11.6, 3.4 Hz, 2 H), 3.73-3.70 (m, 1 H), 3.44 (td, *J* = 11.6, 1.9 Hz, 2 H), 2.33 (s, 3 H), 2.03-1.83 (m, 7 H), 1.72-1.56 (m, 2 H), 1.51-1.41 (m, *J* = 4.1 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 154.9, 150.4, 148.9, 145.7, 142.6, 135.6, 133.7, 132.2, 131.7, 131.5, 129.5, 126.0, 123.8, 115.8, 115.2, 112.0, 86.3, 85.0, 66.7, 59.4, 53.5, 47.5, 44.5, 33.4, 29.3, 24.9, 21.0, 19.2; HRMS (ESI^+): *m/z* calculated for $C_{31}H_{35}O_4N_4S$ (M+H) 559.2374, found 559.2375; ELS purity (100%).

3.4.2 Additional, undescribed analogs of NMS-873



Scheme 3-14. Synthesis of branched ester and carboxylic acid zone 1 replacements.



Ethyl 2-((4-(pyridin-3-yl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-3-yl)thio)propanoate (3-58). To a solution of **2-21** (0.200 g, 0.684 mmol) in DMF (5.9 mL) was added Cs_2CO_3 (0.44 g, 1.37 mmol) and ethyl 2-bromopropionate (0.112 mL, 0.855 mmol). The reaction was stirred at room temperature for 4.5 h. The reaction was poured into water (10 mL) and the aqueous was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude was concentrated with heptane (3x) to remove residual DMF. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 3/97). Triazole **3-58** was obtained as a colorless oil (0.334 g, DMF present) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.67 (t, *J* = 2.4 Hz, 1 H), 7.75 (ddt, *J* = 8.1, 2.6, 1.5 Hz, 1 H), 7.50 (dd, *J* = 7.9, 4.8 Hz, 1 H), 4.68 (dd, *J* = 12.6, 8.0 Hz, 1 H), 4.58-4.56 (m, 1 H), 4.52-4.46 (m, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 3.44-3.41 (m, 2 H), 1.68 (s, 1 H), 1.62 (dd, *J* = 7.2, 0.6 Hz, 3 H), 1.60-1.40 (m, 5 H), 1.24 (t, *J* = 7.1 Hz, 3 H); HRMS (ESI$^+$): *m/z* calculated for $C_{18}H_{25}O_4N_4S$ (M+H) 393.1591, found 393.1591.

Ethyl 2-((5-(hydroxymethyl)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)propanoate (3-59). To a solution of **3-58** (0.250 g, 0.637 mmol) in EtOH (2.5 mL) was added *p*-TsOH (0.022 g, 0.127 mmol) and the reaction stirred at room temperature for about 40 h. The reaction was quenched by adding poly(4-vinylpyridine) and stirring for 30 min. The solid filtered off and the solvent concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 5/95). Triazole **3-59** was obtained as a pale yellow oil (0.158 g, 80%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, *J* = 4.4 Hz, 1 H), 8.69 (d, *J* = 1.9 Hz, 1 H), 7.82 (d, *J* = 8.6 Hz, 1 H), 7.52 (dd, *J* = 8.0, 4.9 Hz, 1 H), 4.64 (d, *J* = 6.4 Hz, 2 H), 4.45 (q, *J* = 7.3 Hz, 1 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 2.95 (t, *J* = 6.4 Hz, 1 H),

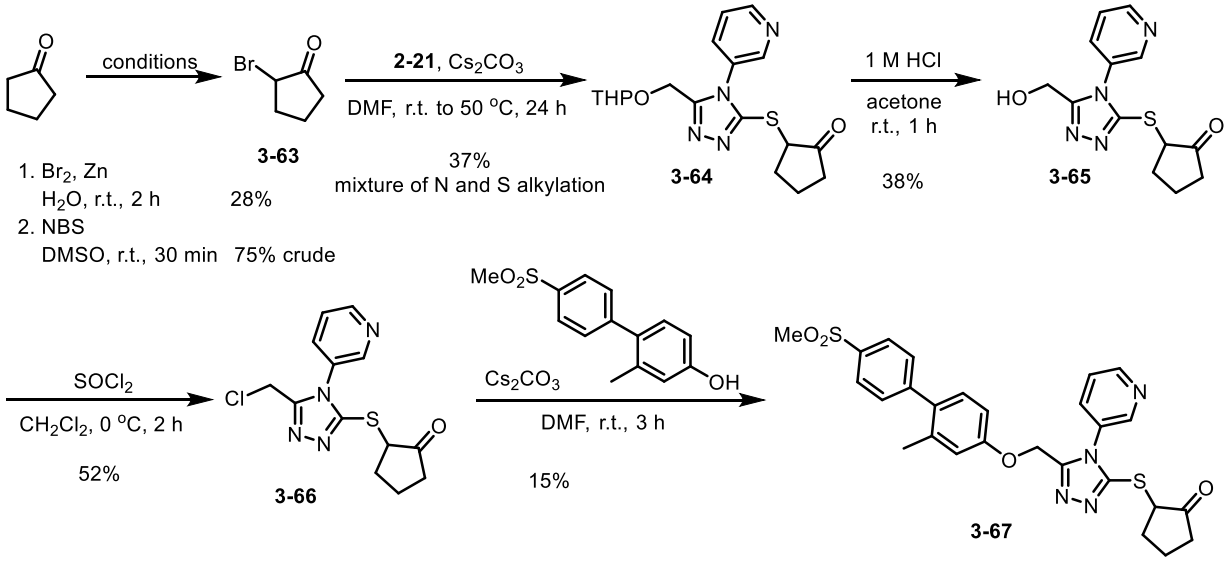
1.62 (d, *J* = 7.2 Hz, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H); HRMS (ESI^+): *m/z* calculated for $C_{13}H_{17}O_3N_4S$ (M+H) 309.1016, found 309.1014.

Ethyl 2-((5-(((methylsulfonyl)oxy)methyl)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)propanoate and **Ethyl 2-((5-(chloromethyl)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)propanoate (3-60).** To a solution of **3-59** (0.155 g, 0.503 mmol) and MsCl (0.039 mL, 0.503 mmol) in CH_2Cl_2 (6.6 mL) at 0 °C was added DiPEA (0.087 mL, 0.503 mmol) dropwise. The reaction was stirred at 0 °C for 1 h. The reaction was diluted with CH_2Cl_2, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. Triazole **3-60** was obtained as a mixture of mesylate and chloride (0.217 g) and carried on without purification or characterization: HRMS (ESI^+): *m/z* calculated for $C_{13}H_{16}O_2N_4ClS$ (M+H) 327.0677, found 327.0675; HRMS (ESI^+): *m/z* calculated for $C_{14}H_{19}O_5N_4S_2$ (M+H) 387.0791, found 387.0789.

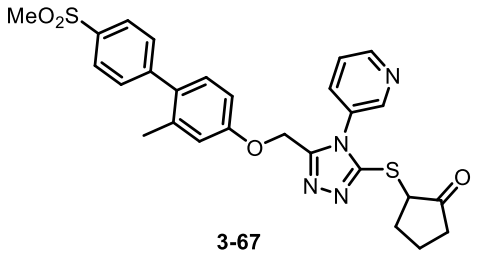
Ethyl 2-((5-(((2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)oxy)methyl)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)propanoate (3-61)[60]**.** To a solution of the mixture from above (**3-60**) (0.215 g, 0.556 mmol) in dry DMF (3.7 mL) was added 2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-ol (0.153 g, 0.584 mmol) and Cs_2CO_3 (0.363 g, 1.11 mmol) and the reaction heated at 40 °C for about 2 h. The reaction was poured into water (5 mL) and the aqueous extracted with EtOAc (2x). The combined organic layers were washed with brine, sat. LiCl, dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (EtOAc/Hexanes: 50/50 to 100/0). Product **3-61** was obtained as a white foam (0.152 g, 49%): IR (CH_2Cl_2) 3054, 2983, 2930, 1731, 1605, 1484, 1309, 1234, 1149, 1024, 957, 819, 778, 731, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.68 (d, *J* = 2.3 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 2 H), 7.77 (ddd, *J* = 8.1, 2.4, 1.6 Hz, 1 H), 7.51 (dd, *J* = 8.3, 4.6 Hz, 1 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 7.10-7.08 (m, 1 H), 6.81-6.79 (m, 2 H), 5.16-5.09 (m, 2 H), 4.52 (q, *J* =

7.3 Hz, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 3.10 (s, 3 H), 2.21 (s, 3 H), 1.65 (d, *J* = 7.3 Hz, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 157.1, 151.95, 151.79, 151.4, 148.1, 147.1, 138.8, 137.0, 134.9, 133.9, 130.9, 130.3, 129.9, 127.3, 124.2, 116.9, 112.3, 62.0, 60.0, 45.1, 44.6, 20.7, 18.2, 14.1; HRMS (ESI^+): *m/z* calculated for $C_{27}H_{29}O_5N_4S_2$ (M+H) 553.1574, found 553.1569; ELS purity (100%).

Sodium 2-((5-(((2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)oxy)methyl)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)propanoate (3-62)[144]. To a solution of **3-61** (0.125 g, 0.226 mmol) in THF (0.42 mL) at 0 °C was added NaOH (0.23 mL, 1 M). The reaction was warmed to room temperature and the reaction stirred for 1 h. The reaction was concentrated, and the residue was taken up in water, washed with chloroform, and the aqueous concentrated. Product **3-62** was obtained as an orange foam (0.111 g, 90%): IR (neat) 3385, 2928, 2465, 1594, 1485, 1390, 1295, 1227, 1147, 1003, 817, 779, 707 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (dd, *J* = 4.7, 0.9 Hz, 1 H), 8.68 (d, *J* = 2.3 Hz, 1 H), 7.99 (dt, *J* = 8.4, 1.7 Hz, 1 H), 7.94 (d, *J* = 8.3 Hz, 2 H), 7.63 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.57 (d, *J* = 8.3 Hz, 2 H), 7.12 (d, *J* = 8.3 Hz, 1 H), 6.83-6.79 (m, 2 H), 5.14 (s, 2 H), 3.92 (q, *J* = 6.9 Hz, 1 H), 3.26 (s, 3 H), 2.18 (s, 3 H), 1.45 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CD_3OD/CDCl_3$) δ 177.1, 156.9, 154.2, 151.5, 150.8, 147.7, 147.0, 138.4, 136.8, 135.4, 133.6, 130.6, 130.10, 129.95, 127.0, 124.3, 116.5, 111.9, 59.6, 44.2, 20.3, 18.9; HRMS (ESI^+): *m/z* calculated for $C_{25}H_{25}O_5N_4S_2$ (M+H) 525.1261, found 525.1261; ELS purity (100%).



Scheme 3-15. Synthesis of cyclopentanone zone 1 analog.



2-Bromocyclopentan-1-one (3-63). To a solution of cyclopentanone (1.02 mL, 11.9 mmol) in distilled H_2O (11.9 mL) was added zinc dust (0.389 g, 5.94 mmol) followed by bromine (0.914 mL, 17.8 mmol). The reaction was stirred at room temperature for 30 min. The solid was removed by filtration and washed with Et_2O. The aqueous was extracted with Et_2O (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was filtered through a pad of neutral Al_2O_3 followed by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 20/80). Cyclopentanone **3-63** was obtained as an orange oil (0.543 g, 28%).

Alternatively:

To a solution of cyclopentanone (1.05 mL, 11.9 mmol) in DMSO (11.9 mL) was added NBS (2.24 g, 12.5 mmol) in 3 portions. The reaction was stirred for 15 min. The reaction was diluted with sat. NH_4Cl then extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was taken up in CCl_4, the solid filtered off, washed (3x), and the filtrated concentrated. Cyclopentanone **3-63** was obtained as a yellow oil (1.46 g, 75%), data matches that reported in the literature: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32-4.24 (m, 1 H), 2.53-2.37 (m, 2 H), 2.31-2.19 (m, 3 H), 2.07-2.03 (m, 1 H).

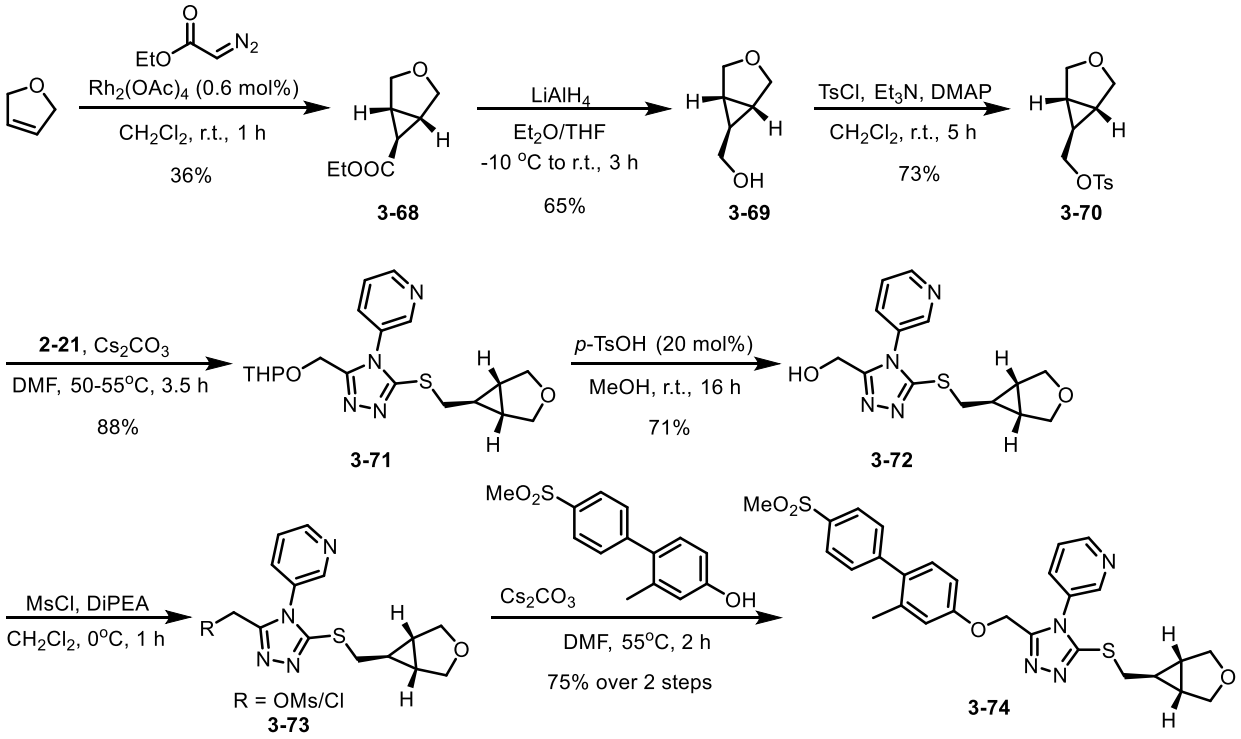
2-((4-(Pyridin-3-yl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-3-yl)thio)cyclopentan-1-one (3-64). To a solution of 4-(pyridin-3-yl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazole-3-thiol (0.500 g, 1.71 mmol) in DMF (14.8 mL) was added Cs_2CO_3 (1.11 g, 3.42 mmol) and **3-63** (0.335 g, 2.05 mmol). The reaction was stirred at room temperature 16 h. The reaction was poured into water (20 mL) and the aqueous was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude was concentrated with heptane (3x) to remove residual DMF. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). Triazole **3-64** was obtained as a colorless oil as an inseparable mixture of product and starting material (0.235 g, 18.5%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.8, 1.3 Hz, 1 H), 8.72-8.69 (m, 1 H), 7.87-7.79 (m, 1 H), 7.51 (ddd, *J* = 11.1, 8.0, 4.6 Hz, 1 H), 4.67 (dd, *J* = 12.6, 2.4 Hz, 1 H), 4.58-4.48 (m, 2 H), 4.06 (ddd, *J* = 9.8, 8.4, 1.4 Hz, 1 H), 3.48-3.40 (m, 2 H), 2.69-2.63 (m, 1 H), 2.40-2.37 (m, 1 H), 2.22-2.14 (m, 1 H), 1.98-1.90 (m, *J* = 6.3, 3.1 Hz, 1 H), 1.63-1.41 (m, 8 H); HRMS (ESI^+): *m/z* calculated for $C_{18}H_{23}O_3N_4S$ (M+H) 375.1485, found 375.1481.

2-((5-(Hydroxymethyl)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)cyclopentan-1-one (3-65). To a solution of **3-64** (0.230 g, 0.614 mmol) in acetone (3 mL) was added HCl (1 M, 1.2 mL) and the reaction stirred at room temperature for 1 h. The reaction was cooled to 0 °C and neutralized with solid K_2CO_3. The aqueous was extracted with EtOAc (3x) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 3/97 to 10/90). Triazole **3-65** was obtained as a colorless crystalline solid (0.068 g, 38%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, *J* = 4.0 Hz, 1 H), 8.71 (s, 1 H), 7.86 (dt, *J* = 8.2, 1.7 Hz, 1 H), 7.52 (dd, *J* = 8.1, 4.9 Hz, 1 H), 4.63 (s, 2 H), 4.03 (dd, *J* = 9.6, 8.3 Hz, 1 H), 2.65-2.59 (m, 1 H), 2.37 (dd, *J* = 9.0, 6.0 Hz, 2 H), 2.18-2.12 (m, 2 H), 1.95-1.91 (m, 2 H); HRMS (ESI^+): *m/z* calculated for $C_{13}H_{15}O_2N_4S$ (M+H) 291.0910, found 291.0908.

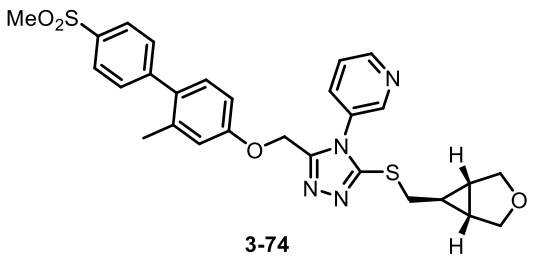
2-((5-(Chloromethyl)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)cyclopentan-1-one (3-66). To a solution of **3-65** (0.065 g, 0.224 mmol) in dry CH_2Cl_2 (4.9 mL) at 0 °C was added thionyl chloride (0.025 mL, 0.336 mmol) and the reaction stirred at 0 °C for about 2 h. The reaction was cooled to 0 °C and quenched with sat. $NaHCO_3$, extracted with EtOAc (3x), dried ($MgSO_4$), filtered, and concentrated. Triazole **3-66** was obtained as a pale orange oil (0.036 g, 52%) and carried on without further purification or characterization: HRMS (ESI^+): *m/z* calculated for $C_{13}H_{14}ON_4ClS$ (M+H) 309.0571, found 309.0570.

2-((5-(((2-Methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)oxy)methyl)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)cyclopentan-1-one (3-67). To a solution of crude **3-66** (0.036 g, 0.117 mmol) in dry DMF (1.9 mL) was added 2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-ol (0.046 g, 0.175 mmol) and Cs_2CO_3 (0.114 g, 0.350 mmol) and the reaction was stirred at room temperature 16 h. The reaction was poured into water (5 mL) and the aqueous extracted with

EtOAc (2x). The combined organic layers were washed with brine, sat. LiCl, dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 5/95). Product **3-67** was obtained as a pale yellow oil (0.010 g, 15%): IR (neat) 2925, 1737, 1605, 1484, 1447, 1300, 1233, 1147, 1090, 999, 956, 910, 816, 778, 727, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.70 (d, *J* = 2.2 Hz, 1 H), 7.97-7.95 (m, 2 H), 7.81 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.51 (ddd, *J* = 8.2, 4.8, 0.6 Hz, 1 H), 7.47-7.45 (m, 2 H), 7.10-7.08 (m, 1 H), 6.81-6.78 (m, 2 H), 5.11 (s, 2 H), 4.07 (dd, *J* = 10.1, 8.3 Hz, 1 H), 3.10 (s, 3 H), 2.69-2.66 (m, 1 H), 2.40 (dd, *J* = 9.3, 5.9 Hz, 2 H), 2.22-2.16 (m, 5 H), 1.99-1.93 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.6, 157.2, 152.0, 151.7, 151.5, 148.2, 147.2, 138.9, 137.1, 135.1, 133.9, 131.0, 130.4, 130.0, 127.4, 124.2, 116.9, 112.4, 60.0, 52.0, 44.7, 36.7, 30.8, 20.8; HRMS (ESI^+): *m/z* calculated for $C_{27}H_{27}O_4N_4S_2$ (M+H) 535.1468, found 535.1464; ELS purity (100%).



Scheme 3-16. Synthesis of oxabicyclo[3.1.0]hexane analog.



3-74

Ethyl (1α,5α,6α)-3-oxabicyclo[3.1.0]hexane-6-carboxylate (3-68).[145] In 4 separated flasks, a solution of 2,5-dihydrofuran (0.88 mL, 11 mmol) in CH_2Cl_2 (10 mL) at room temperature was added $Rh(OAc)_2$ dimer (0.030 g, 0.069 mmol) followed by ethyl diazoacetate (0.92 mL, 7.6 mmol) dropwise via syringe pump (0.17 mL/h). The reaction was stirred at room temperature for 1 h. The 4 reactions were combined, filtered through a pad of Celite, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 15/85). The *trans* (1α,5α,6α)-3-oxabicyclo[3.1.0]hexane **3-68** was obtained as colorless oil (1.89 g, 36%, 90% pure) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.1 Hz, 2 H), 3.92 (d, *J* = 8.7 Hz, 2 H), 3.75 (d, *J* = 8.6 Hz, 2 H), 2.16 (m, 2 H), 1.60 (t, *J* = 3.1 Hz, 1 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

((1α,5α,6α)-3-Oxabicyclo[3.1.0]hexan-6-yl)methanol (3-69). To a solution of **3-68** (0.500 g, 3.20 mmol) in Et_2O (18 mL) at -10 °C was added $LiAlH_4$ (0.96 mL, 3.84 mmol, 4 M) dropwise over 1 h. The reaction was stirred at -10 °C for 1 h then warmed to room temperature and stirred for 1 h. The reaction was cooled to -5 °C and quenched with aq. potassium sodium tartrate (8.5 mL) and stirred for 30 min. The aqueous was extracted with EtOAc (3x), dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 50/50). (1α,5α,6α)-3-Oxabicyclo[3.1.0]hexane **3-69** was obtained as a colorless oil (0.239 g, 56%) and carried on without further characterization: ^{1}H NMR (300 MHz,

$CDCl_3$) δ 3.87 (d, *J* = 8.2 Hz, 2 H), 3.69 (d, *J* = 8.0 Hz, 2 H), 3.53 (dd, *J* = 6.4, 5.7 Hz, 2 H), 1.55-1.54 (m, 2 H), 1.34 (t, *J* = 5.3 Hz, 1 H), 1.09 (tt, *J* = 7.0, 3.5 Hz, 1 H).

((1*α*,5*α*,6*α*)-3-Oxabicyclo[3.1.0]hexan-6-yl)methyl 4-methylbenzenesulfonate (3-70). To a solution of **3-69** (0.23 g, 2.0 mmol) and Et_3N (0.37 mL, 2.6 mmol) in CH_2Cl_2 (5.9 mL) was added a solution of TsCl (0.42 g, 2.2 mmol) in CH_2Cl_2 (2.2 mL) followed by DMAP (0.025 g, 0.20 mmol) in CH_2Cl_2 (0.81 mL). The reaction was stirred at room temperature for 4 h. The reaction was quenched with sat. NH_4Cl and the aqueous extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. (1α,5α,6α)-3-Oxabicyclo[3.1.0]hexane **3-70** was obtained as a pale yellow oil (0.505 g, 74%, 79% pure) and carried on without further purification or characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 3.96 (d, *J* = 7.5 Hz, 2 H), 3.77 (d, *J* = 8.5 Hz, 2 H), 3.62 (d, *J* = 8.3 Hz, 2 H), 2.45 (s, 3 H), 1.56-1.55 (m, 2 H), 1.08 (tt, *J* = 7.4, 3.6 Hz, 1 H).

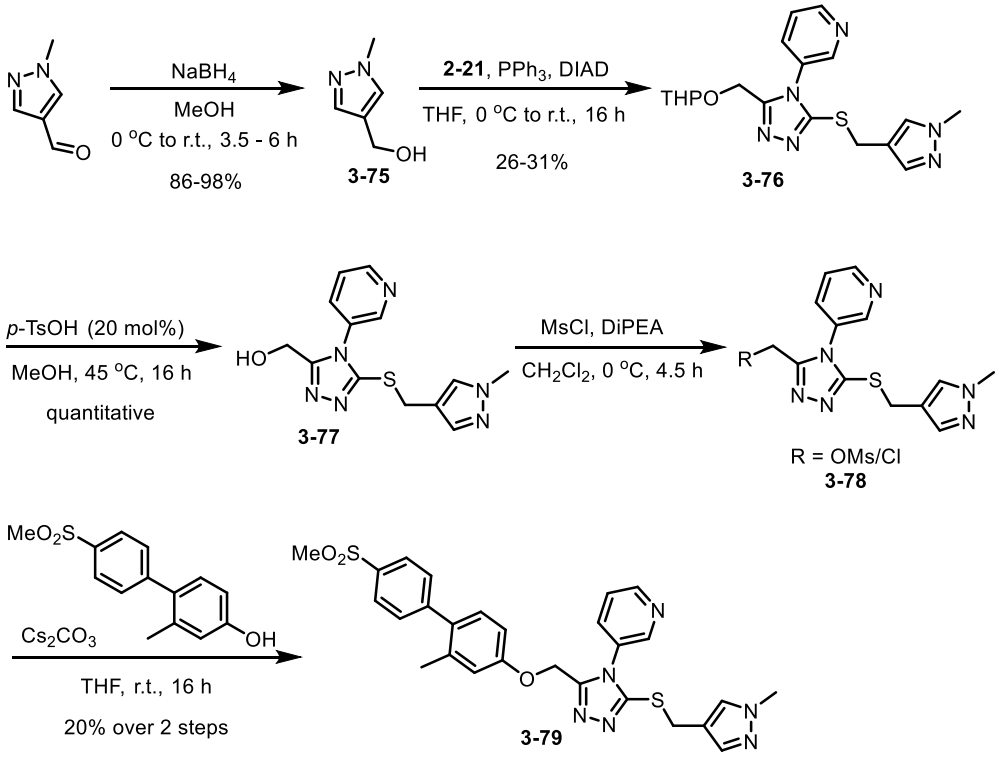
3-(3-((((1*α*,5*α*,6*α*)-3-Oxabicyclo[3.1.0]hexan-6-yl)methyl)thio)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (3-71). To a solution of 4-(pyridin-3-yl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazole-3-thiol (0.150 g, 0.513 mmol) in DMF (4.5 mL) was added Cs_2CO_3 (0.334 g, 1.03 mmol) and **3-70** (0.246 g, 0.770 mmol). The reaction was stirred at 50 °C for 3.5 h. The reaction was poured into water (5 mL) and the aqueous was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude was concentrated with heptane (3x) to remove residual DMF. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). Triazole **3-71** was obtained as a pale yellow oil (0.175 g, 88%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.66 (dd, *J* = 2.5, 0.5 Hz, 1 H), 7.73 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.50 (ddd, *J* =

8.1, 4.8, 0.7 Hz, 1 H), 4.67 (d, *J* = 12.6 Hz, 1 H), 4.57 (t, *J* = 3.0 Hz, 1 H), 4.50 (d, *J* = 12.6 Hz, 1 H), 3.83 (d, *J* = 8.4 Hz, 2 H), 3.64 (d, *J* = 8.3 Hz, 2 H), 3.46-3.40 (m, 2 H), 3.27 (d, *J* = 7.5 Hz, 2 H), 1.62-1.43 (m, 8 H), 1.12 (tt, *J* = 7.4, 3.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 153.1, 151.2, 148.4, 135.0, 130.4, 124.1, 98.4, 69.6, 61.8, 58.8, 35.3, 30.1, 25.30, 25.23, 19.6, 18.8; HRMS (ESI^+): *m/z* calculated for $C_{19}H_{25}O_3N_4S$ (M+H) 389.1642, found 389.1642.

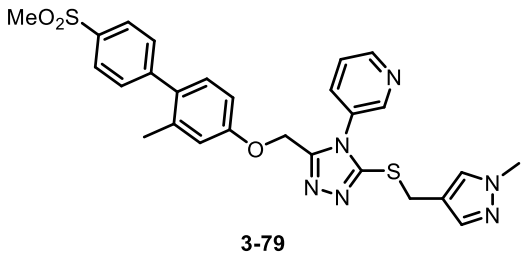
(5-((((1α,5α,6α)-3-Oxabicyclo[3.1.0]hexan-6-yl)methyl)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methanol (3-72). To a solution of **3-71** (0.17 g, 0.44 mmol) in MeOH (2 mL) was added *p*-TsOH (0.017 g, 0.088 mmol) and the reaction stirred at room temperature 16 h. The reaction was quenched by adding poly(4-vinylpyridine), the solid filtered off and the solvent concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). Triazole **3-72** was obtained as a pale-yellow oil (0.094 g, 71%) and carried on without further characterization: HRMS (ESI^+): *m/z* calculated for $C_{14}H_{17}O_2N_4S$ (M+H) 305.1067, found 305.1064.

(5-((((1α,5α,6α)-3-Oxabicyclo[3.1.0]hexan-6-yl)methyl)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and **3-(3-((((1α,5α,6α)-3-Oxabicyclo[3.1.0]hexan-6-yl)methyl)thio)-5-(chloromethyl)-4*H*-1,2,4-triazol-4-yl)pyridine (3-73).** To a solution of **3-72** (0.090 g, 0.30 mmol) and DiPEA (0.10 mL, 0.59 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added MsCl (0.040 mL, 0.52 mmol) dropwise. The reaction was stirred at 0 °C and slowly warmed to room temperature over about 1 h. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$ and sat. NH_4Cl, dried ($MgSO_4$), filtered, and concentrated. Triazole **3-73** was obtained as a mixture of mesylate and chloride and carried on without purification or characterization: HRMS (ESI^+): *m/z* calculated for $C_{14}H_{16}ON_4ClS$ (M+H) 323.0728, found 323.0727; HRMS (ESI^+): *m/z* calculated for $C_{15}H_{19}O_4N_4S_2$ (M+H) 383.0842, found 383.0842.

3-(3-((((1α,5α,6α)-3-Oxabicyclo[3.1.0]hexan-6-yl)methyl)thio)-5-(((2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (3-74). To a solution of the mixture from above (**3-73**) (0.110 g, 0.288 mmol) in dry DMF (5 mL) was added 2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-ol (0.113 g, 0.431 mmol) and Cs_2CO_3 (0.281 g, 0.863 mmol) and the reaction stirred at 55 °C for 2 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 10/90). Product **3-74** was obtained as a white foam (0.119 g, 75%): IR (neat) 3048, 2961, 2927, 2858, 1605, 1484, 1447, 1303, 1233, 1149, 1077, 1001, 956, 909, 847, 778, 728, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.8 Hz, 1 H), 8.61 (d, *J* = 2.2 Hz, 1 H), 7.89 (d, *J* = 8.2 Hz, 2 H), 7.73 (d, *J* = 8.1 Hz, 1 H), 7.48 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.40 (d, *J* = 8.2 Hz, 2 H), 7.04-7.02 (m, 1 H), 6.77-6.73 (m, 2 H), 5.07 (s, 2 H), 3.75 (d, *J* = 8.4 Hz, 2 H), 3.56 (d, *J* = 8.3 Hz, 2 H), 3.22 (d, *J* = 7.5 Hz, 2 H), 3.04 (s, 3 H), 2.16 (s, 3 H), 1.56 (app s, 2 H), 1.08 (tt, *J* = 7.3, 3.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 153.5, 151.6, 151.2, 147.9, 147.0, 138.7, 136.9, 134.7, 133.6, 130.8, 130.2, 129.9, 127.1, 124.1, 116.7, 112.2, 69.3, 59.8, 44.5, 35.2, 25.1, 20.6, 19.4; HRMS (ESI^+): *m/z* calculated for $C_{28}H_{29}O_4N_4S_2$ (M+H) 549.1625, found 549.1630; ELS purity (100%).



Scheme 3-17. Synthesis of pyrazole zone 1 analog.



(1-Methyl-1*H*-pyrazol-4-yl)methanol (3-75).[146] To a solution of 1-methyl-1*H*-pyrazole-4-carbaldehyde (0.25 g, 2.18 mmol) in MeOH (3.5 mL) at 0 °C was added $NaBH_4$ (0.18 g, 4.58 mmol) in portions. The reaction was warmed to room temperature and stirred for 2 h. An additional 0.5 equivalent $NaBH_4$ was added and the reaction stirred for 1.5 h. The reaction was cooled to 0 °C and neutralized with 2 N HCl. The solvent was reduced in vacuo and the aqueous extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Pyrazole **3-75** was obtained as a colorless oil (0.240 g, 98%) and carried on

without further purification or characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 1 H), 7.29 (s, 1 H), 4.40 (s, 2 H), 3.75 (s, 3 H), 3.72 (s, 1 H); HRMS (ESI^+): *m/z* calculated for $C_5H_9ON_2$ (M+H) 113.0709, found 113.0711.

3-(3-(((1-Methyl-1*H*-pyrazol-4-yl)methyl)thio)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (3-76). To a solution of 4-(pyridin-3-yl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazole-3-thiol (0.307 g, 1.05 mmol) in THF (14 mL) was added PPh_3 (0.278 g, 1.06 mmol) followed by **3-75** (0.200 g, 1.78 mmol). The reaction was cooled to 0 °C and DIAD (0.285 mL, 1.36 mmol) was added. The reaction was slowly warmed to room temperature and stirred for about 27 h. The solution was concentrated, and the product purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 3/97 to 10/90). Triazole **3-76** was obtained as a pale yellow oil (0.265 g, 26%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.54 (dd, *J* = 2.5, 0.5 Hz, 1 H), 7.61 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.45 (ddd, *J* = 8.1, 4.8, 0.7 Hz, 1 H), 7.39 (s, 1 H), 7.38 (s, 1 H), 4.66 (d, *J* = 12.6 Hz, 1 H), 4.58-4.54 (m, *J* = 6.6, 3.8 Hz, 1 H), 4.49 (d, *J* = 12.6 Hz, 1 H), 4.33 (s, 2 H), 3.82 (s, 3 H), 3.48-3.40 (m, 2 H), 1.60-1.39 (m, 6 H); HRMS (ESI^+): *m/z* calculated for $C_{18}H_{23}O_2N_6S$ (M+H) 387.1598, found 387.1594.

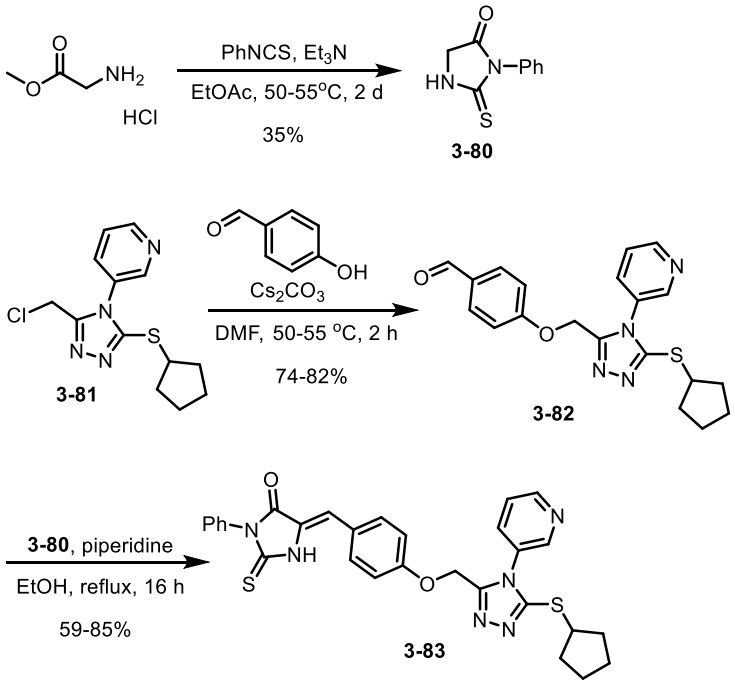
(5-(((1-Methyl-1*H*-pyrazol-4-yl)methyl)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methanol (3-77). To a solution of **3-76** (0.250 g, 0.346 mmol) in MeOH (2.6 mL) was added *p*-TsOH (0.134 g, 0.776 mmol) and the reaction stirred at room temperature for about 12.5 h. The reaction was quenched by adding poly(4-vinylpyridine) and stirring for 30 min. The solid filtered off and the solvent concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). Triazole **3-77** was obtained as a white gel (0.114 g, solvent present) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ

8.76 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.56 (dd, *J* = 2.5, 0.6 Hz, 1 H), 7.69 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.48 (ddd, *J* = 8.2, 4.8, 0.7 Hz, 1 H), 7.37 (d, *J* = 1.1 Hz, 2 H), 4.63 (d, *J* = 6.4 Hz, 2 H), 4.33 (s, 2 H), 3.83 (s, 3 H), 3.06 (t, *J* = 6.7 Hz, 1 H); HRMS (ESI^+): *m/z* calculated for $C_{13}H_{15}ON_6S$ (M+H) 303.1023, found 303.1021.

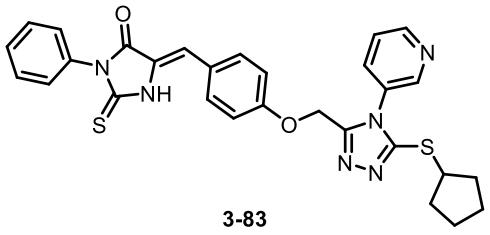
(5-(((1-Methyl-1*H*-pyrazol-4-yl)methyl)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and **3-(3-(Chloromethyl)-5-(((1-methyl-1*H*-pyrazol-4-yl)methyl)thio)-4*H*-1,2,4-triazol-4-yl)pyridine (3-78).** To a solution of **3-77** (0.060 g, 0.198 mmol) and MsCl (0.015 mL, 0.198 mmol) in CH_2Cl_2 (2.7 mL) at 0 °C was added DiPEA (0.035 mL, 0.198 mmol) dropwise. The reaction was stirred at 0 °C and slowly warmed to room temperature over about 3.5 h. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. Triazole **3-78** was obtained as a mixture of mesylate and chloride and carried on without purification or characterization: HRMS (ESI^+): *m/z* calculated for $C_{13}H_{14}N_6ClS$ (M+H) 321.0684, found 321.0682; HRMS (ESI^+): *m/z* calculated for $C_{14}H_{17}O_3N_6S_2$ (M+H) 381.0798, found 381.0796.

3-(3-(((1-Methyl-1*H*-pyrazol-4-yl)methyl)thio)-5-(((2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (3-79). To a solution of the mixture from above (**3-78**) (0.075 g, 0.197 mmol) in dry THF (3.5 mL) was added 2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-ol (0.078 g, 0.296 mmol) and Cs_2CO_3 (0.193 g, 0.591 mmol) and the reaction stirred at room temperature 16 h. The reaction was concentrated, and the product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0, MeOH/EtOAc: 5/95). Triazole **3-79** was obtained as a white foam (0.022 g, 20% over 2 steps): IR (CH_2Cl_2) 3392, 2927, 1594, 1485, 1448, 1390, 1299, 1233, 1147, 1003, 958, 817, 779, 707 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.76 (d, *J* = 4.6 Hz, 1 H), 8.55 (d, *J* = 2.0 Hz, 1 H), 7.96-

7.94 (m, 2 H), 7.63 (ddd, *J* = 8.1, 2.5, 1.5 Hz, 1 H), 7.48-7.44 (m, 3 H), 7.40 (d, *J* = 5.8 Hz, 2 H), 7.10-7.08 (m, 1 H), 6.81-6.79 (m, 2 H), 5.11 (s, 2 H), 4.36 (s, 2 H), 3.83 (s, 3 H), 3.10 (s, 3 H), 2.21 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.1, 153.4, 151.8, 151.4, 148.0, 147.2, 139.3, 138.8, 137.1, 135.1, 134.8, 133.9, 131.0, 130.34, 130.23, 129.9, 127.3, 124.2, 116.9, 116.3, 112.3, 59.9, 44.7, 39.1, 27.0, 20.7; HRMS (ESI^+): *m/z* calculated for $C_{27}H_{27}O_3N_6S_2$ (M+H) 547.1581, found 547.1578; ELS purity (99.6%).



Scheme 3-18. Synthesis of zone 5 hydantoin analog.



3-Phenyl-2-thioxoimidazolidin-4-one (3-80).[147] To a suspension of glycine methyl ester HCl (0.500 g, 3.94 mmol) in dry EtOAc (8 mL) was added Et_3N (0.554 mL, 3.94 mmol) and phenyl isothiocyanate (0.471 mL, 3.94 mmol) and the reaction was heated to 40 °C for 2 d. The reaction was cooled to room temperature and the solvent removed under vacuum. The residue was taken up in EtOAc (20 mL) and the solid was filtered off. The filtrate was dried ($MgSO_4$), filtered, and concentrated. Crude 3-phenyl-2-thioxoimidazolidin-4-one **3-80** was triturated with Et_2O and the product was obtained as a yellow-orange solid (0.266 g, 35%), data matches that reported in the literature: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.46 (m, 3 H), 7.34-7.31 (m, 2 H), 7.11 (bs, 1 H), 4.29 (s, 2 H); HRMS (ESI^+): *m/z* calculated for $C_9H_9ON_2S$ (M+H) 193.0430, found 193.0430.

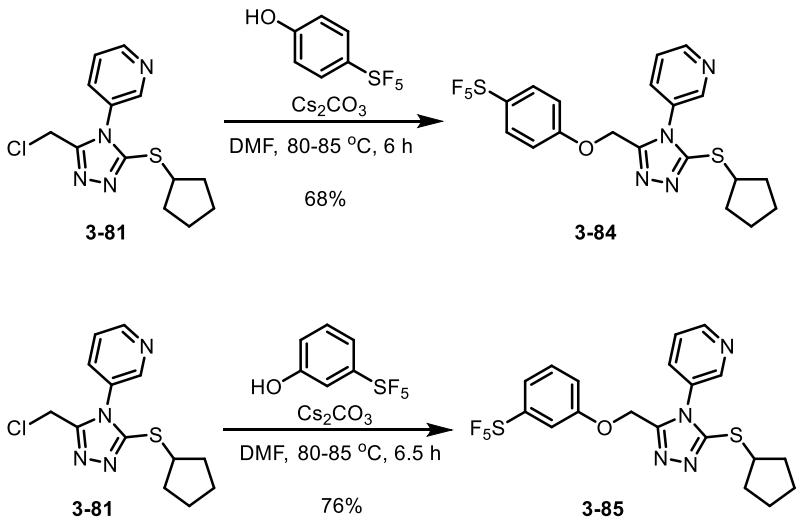
3-(3-(Chloromethyl)-5-(cyclopentylthio)-4H-1,2,4-triazol-4-yl)pyridine (3-81). To a solution of (5-(cyclopentylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methanol (0.040 g, 0.145 mmol) in dry CH_2Cl_2 (3.2 mL) at 0 °C was added thionyl chloride (16.0 µL, 0.217 mmol) and the reaction stirred at 0 °C for about 2 h. The reaction was cooled to 0 °C and quenched with sat. $NaHCO_3$, extracted with EtOAc (3x), dried ($MgSO_4$), filtered, and concentrated. Triazole **3-81** was obtained as a colorless oil (0.037 g, 87%) and carried on without further purification or characterization: HRMS (ESI^+): *m/z* calculated for $C_{13}H_{16}N_4ClS$ (M+H) 295.0779, found 295.0777.

4-((5-(Cyclopentylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)benzaldehyde (3-82). To a solution of crude (**3-81**) (0.097 g, 0.329 mmol) in dry DMF (8.6 mL) was added 4-hydroxybenzaldehyde (0.061 g, 0.494 mmol) and Cs_2CO_3 (0.322 g, 0.987 mmol) and the reaction stirred at 50 °C for 2 h. The reaction was cooled to room temperature, poured into water (5 mL) and the aqueous extracted with EtOAc (2x). The combined organic layers were washed with brine, sat. LiCl, dried ($MgSO_4$), filtered, and concentrated. The product was purified by

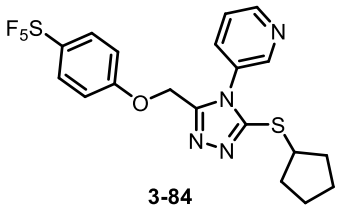
chromatography on SiO_2 (SiO_2, MeOH/CH_2Cl_2: 0/100 to 10/90). Triazole **3-82** was obtained as a pale yellow solid (0.93 g, 74%) and carried on without further characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (s, 1 H), 8.77 (dd, *J* = 4.8, 0.8 Hz, 1 H), 8.62 (d, *J* = 2.2 Hz, 1 H), 7.82-7.79 (m, 2 H), 7.68 (ddd, *J* = 8.1, 2.1, 1.2 Hz, 1 H), 7.48 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.02 (d, *J* = 8.6 Hz, 2 H), 5.17 (s, 2 H), 4.06 (quintet, *J* = 6.7 Hz, 1 H), 2.23-2.19 (m, 2 H), 1.73-1.61 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6, 162.0, 154.4, 151.3, 150.6, 148.0, 134.7, 132.0, 130.9, 130.0, 124.1, 115.0, 60.0, 46.1, 33.8, 24.6; HRMS (ESI$^+$): *m/z* calculated for $C_{20}H_{21}O_2N_4S$ (M+H) 381.1380, found 381.1377.

(*Z*)-5-(4-((5-(Cyclopentylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)benzylidene)-3-phenyl-2-thioxoimidazolidin-4-one (3-83)[147]**.** To a solution of **3-82** (0.070 g, 0.184 mmol) and **3-80** (0.046 g, 0.239 mmol) in EtOH (3 mL) was added piperidine (36.4 µL, 0.368 mmol). The reaction was sealed and stirred at reflux 16 h. The reaction was cooled to room temperature and concentrated. The residue was taken up in EtOAc (20 mL), washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90) followed by chromatography on Al_2O_3-neutral (MeOH/CH_2Cl_2: 0/100 to 5/95). Product **3-83** was obtained as a yellow glassy foam (0.060 g, 59%): IR (CH_2Cl_2) 3050, 2925, 2866, 1732, 1651, 1599, 1482, 1449, 1394, 1242, 1171, 1002, 824, 730, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (bs, 1 H), 8.78 (dd, *J* = 4.8, 1.3 Hz, 1 H), 8.54 (d, *J* = 2.3 Hz, 1 H), 7.70 (ddd, *J* = 8.1, 2.2, 1.6 Hz, 1 H), 7.54-7.43 (m, 7 H), 7.38-7.35 (m, 2 H), 6.95 (d, *J* = 8.7 Hz, 2 H), 6.75 (s, 1 H), 5.15 (s, 2 H), 4.07-4.03 (m, 1 H), 2.23-2.17 (m, 2 H), 1.72-1.60 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 163.6, 158.4, 154.5, 151.4, 151.1, 148.1, 135.0, 132.8, 131.3, 130.1, 129.39, 129.32, 128.3, 126.9, 125.6,

124.3, 116.1, 113.6, 60.2, 46.2, 34.0, 24.7; HRMS (ESI^+): *m/z* calculated for $C_{29}H_{27}O_2N_6S_2$ (M+H) 555.1631, found 555.1631; ELS purity (100%).

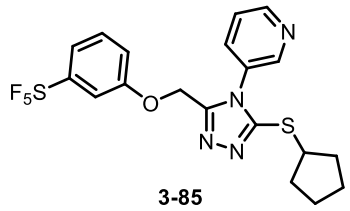


Scheme 3-19. Synthesis of zone 5 SF_5 replacements.



3-(3-(Cyclopentylthio)-5-((4-(pentafluoro-λ^6-sulfanyl)phenoxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (3-84). To a solution of crude **3-81** (0.037 g, 0.126 mmol) in dry DMF (3.4 mL) was added 4-(pentafluorothio)phenol (0.041 g, 0.188 mmol) and Cs_2CO_3 (0.123 g, 0.377 mmol) and the reaction stirred at 80 °C for 6 h. The reaction was cooled to room temperature, poured into water (5 mL) and the aqueous extracted with EtOAc (2x). The combined organic layers were washed with brine, sat. LiCl, dried ($MgSO_4$), filtered, and concentrated. The product was combined with a previous batch and purified by chromatography on SiO_2 (EtOAc/Hexanes: 0/100 to 100/0). Product **3-84** was obtained as a white foam (0.053 g, 68% combined): IR (neat)

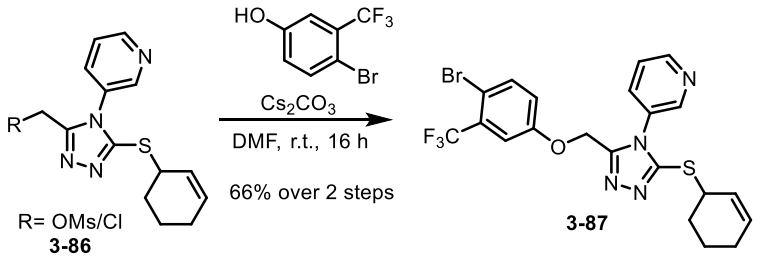
3064, 2959, 2869, 1586, 1497, 1485, 1454, 1402, 1308, 1254, 1189, 1098, 1014, 999, 848, 827, 801, 777, 707 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.8, 1.2 Hz, 1 H), 8.60 (d, *J* = 2.4 Hz, 1 H), 7.67 (ddd, *J* = 8.1, 2.0, 1.7 Hz, 1 H), 7.62 (app d, *J* = 9.2 Hz, 2 H), 7.47 (dd, *J* = 8.1, 4.8 Hz, 1 H), 6.93 (d, *J* = 9.0 Hz, 2 H), 5.12 (s, 2 H), 4.03 (quintet, *J* = 6.6 Hz, 1 H), 2.20-2.16 (m, 2 H), 1.73-1.68 (m, 2 H), 1.63-1.60 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 154.5, 151.4, 150.7, 148.0, 147.7 (app t, J_{CF} = 17.9 Hz), 134.7, 130.0, 127.9 (quintet, J_{CF} = 4.5 Hz), 124.2, 114.5, 60.2, 46.2, 33.9, 24.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ 85.4 (quintet, J_{FF} = 150 Hz), 64.0 (d, J_{FF} = 150 Hz); HRMS (ESI^+): *m/z* calculated for $C_{19}H_{20}ON_4F_5S_2$ (M+H) 479.0993, found 479.0989; ELS purity (100%).



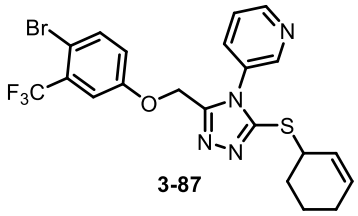
3-85

3-(3-(Cyclopentylthio)-5-((3-(pentafluoro-λ^6-sulfanyl)phenoxy)methyl)-4H-1,2,4-triazol-4-yl)pyridine (3-85). To a solution of crude **3-81** (0.059 g, 0.200 mmol) in dry DMF (5 mL) was added 3-(pentafluorothio)phenol (0.066 g, 0.300 mmol) and Cs_2CO_3 (0.196 g, 0.600 mmol) and the reaction stirred at 80 °C for 6 h. The reaction was cooled to room temperature, poured into water (5 mL) and the aqueous extracted with EtOAc (2x). The combined organic layers were washed with brine, sat. LiCl, dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (EtOAc/Hexanes: 0/100 to 100/0). Product **3-85** was obtained as a pale yellow solid (0.073 g, 76%): IR (neat) 2968, 2870, 1602, 1587, 1488, 1446, 1393, 1290, 1240, 1104, 1048, 898, 824, 811, 774, 712, 681 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.74 (app d, *J* = 4.7 Hz, 1 H), 8.61 (d, *J* = 2.1 Hz, 1 H), 7.68 (app d, *J* = 8.1 Hz, 1 H), 7.47 (dd,

J = 8.1, 4.8 Hz, 1 H), 7.32 (d, *J* = 4.5 Hz, 2 H), 7.16 (s, 1 H), 7.11-7.07 (m, 1 H), 5.10 (s, 2 H), 4.01 (quintet, *J* = 6.5 Hz, 1 H), 2.21-2.14 (m, 2 H), 1.72-1.58 (m, 6 H); ^{13}C NMR (76 MHz, $CDCl_3$): δ 157.1, 154.7 (app t, J_{CF} = 17.6 Hz), 154.3, 151.4, 150.7, 147.9, 134.7, 130.1, 129.8, 124.2, 119.5 (app t, J_{CF} = 4.8 Hz), 117.6, 113.6 (app t, J_{CF} = 4.8 Hz), 60.6, 46.2, 33.9, 24.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ 83.9 (quintet, J_{FF} = 150 Hz), 62.7 (d, J_{FF} = 150 Hz); HRMS (ESI$^+$): *m/z* calculated for $C_{19}H_{20}ON_4F_5S_2$ (M+H) 479.0993, found 479.0990; ELS purity (100%).

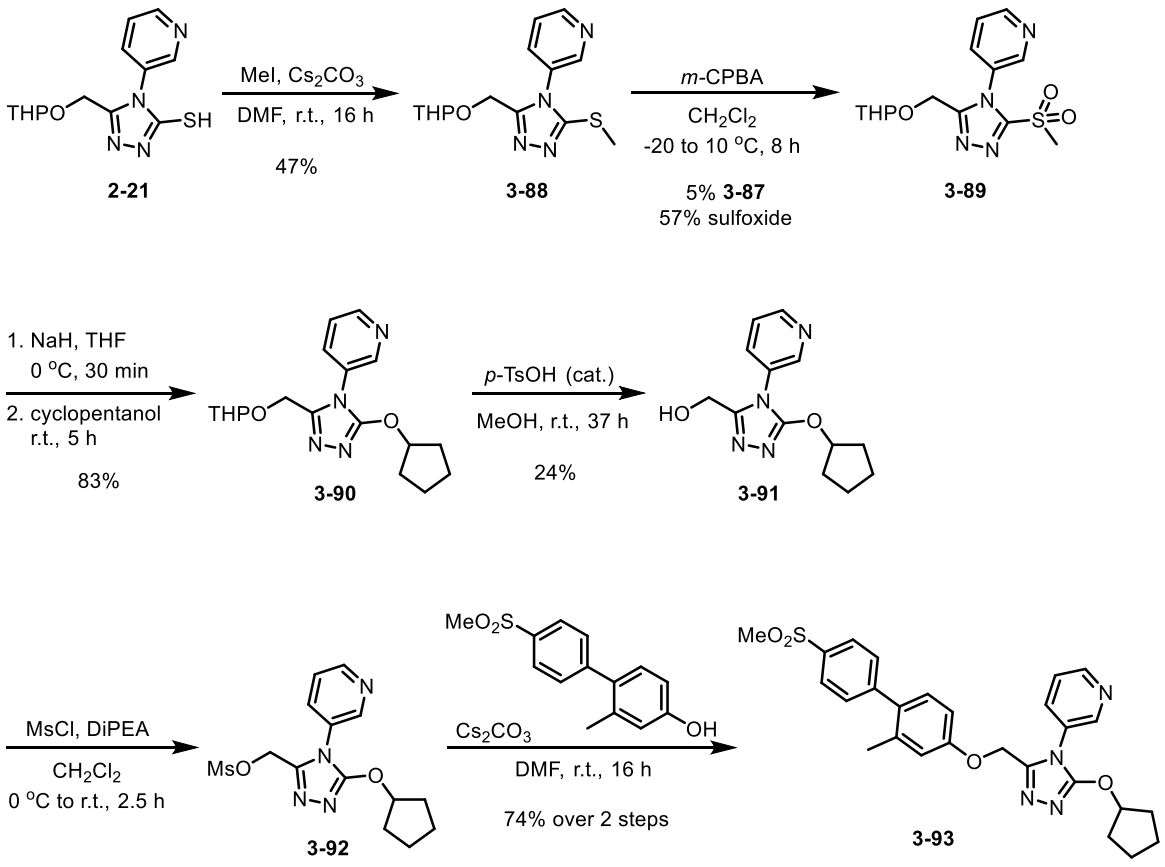


Scheme 3-20. Synthesis of zone 4 4-bromo-3-trifluoromethyl phenol analog.

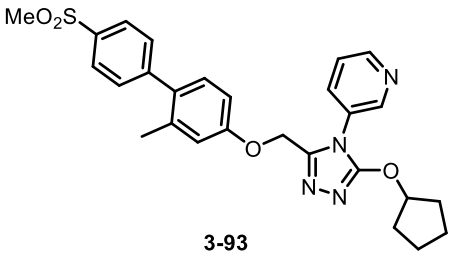


3-(3-((4-Bromo-3-(trifluoromethyl)phenoxy)methyl)-5-(cyclohex-2-en-1-ylthio)-4*H*-1,2,4-triazol-4-yl)pyridine (3-87). To a solution of crude **3-86** (0.095 g, 0.26 mmol) in dry DMF (3.8 mL) was added 3-trifluoromethyl-4-bromophenol (0.071 g, 0.29 mmol) and Cs_2CO_3 (0.093 g, 0.29 mmol) and the reaction stirred at room temperature overnight. The reaction was diluted with EtOAc, and organic layer washed with water. The aqueous was extracted with EtOAc (3 x 7 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0) followed by

chromatography on SiO_2 (ISCO, MeOH/ CH_2Cl_2: 0/100 to 4/96). Product **3-87** was obtained as a white solid (0.088 g, 66%): m.p. 123.5-125.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.62-8.63 (m, 1 H), 7.67-7.69 (m, 1 H), 7.56 (d, *J* = 8.8 Hz, 1 H), 7.51 (dd, *J* = 4.8, 0.6 Hz, 1 H), 7.15 (d, *J* = 3.0 Hz, 1 H), 7.01 (dd, *J* = 8.8, 3.0 Hz, 1 H), 5.86-5.91 (m, 1 H), 5.75 (dt, *J* = 9.6, 2.0 Hz, 1 H), 5.07-5.13 (m, 2 H), 4.59 (dd, *J* = 4.0, 1.6 Hz, 1 H), 2.01-2.14 (m, 4 H) 1.65-1.78 (m, *J* = 3.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.3, 153.7, 151.4, 150.7, 147.9, 136.0, 134.7, 132.5, 131.1 (q, J_{CF} = 31.6 Hz), 129.8, 125.3, 124.2, 122.4 (q, J_{CF} = 273.7 Hz), 118.9, 115.1 (q, J_{CF} = 5.6 Hz), 111.4 (app d, J_{CF} = 1.8 Hz), 60.3, 44.1, 29.2, 24.8, 19.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -63.0; HRMS (ESI^+): *m/z* calculated for $C_{21}H_{19}ON_4BrF_3S$ (M+H) 511.0410, found 511.0404; ELS purity (100%).



Scheme 3-21. Synthesis of zone 2 sulfur replacement with oxygen, with biphenyl side chain analog.



3-93

3-(3-(Methylthio)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (3-88). To a solution of 4-(pyridin-3-yl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazole-3-thiol (1.00 g, 3.42 mmol) in DMF (8 mL) was added MeI (2.28 mL, 5.13 mmol) followed by Cs_2CO_3 (2.25 g, 6.84 mmol). The reaction was stirred at room temperature 16 h. The reaction was diluted with EtOAc, washed with H_2O, brine, dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 50/50 to 100/0). Triazole **3-88** was obtained as a yellow oil (0.496 g, 47%) and carried on without further characterization: HRMS (ESI^+): *m/z* calculated for $C_{14}H_{19}O_2N_4S$ (M+H) 307.1223, found 307.1222.

3-(3-(Methylsulfonyl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (3-89). To a solution of **3-88** (0.100 g, 0.326 mmol) in CH_2Cl_2 (3 mL) was added *m*-CPBA (0.105 g, 0.424 mmol) at -20 °C. The reaction was stirred at -20 °C for 1 h then warmed to 10 °C for 7 h. The reaction was diluted with CH_2Cl_2, washed with $Na_2S_2O_3$, $NaHCO_3$, water, and brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 10/90). Sulfoxide **3-89** was obtained as a white solid (0.063 g, 57%) and the sulfone was obtained as a white solid (5.0 mg, 5%) and carried on without further characterization.

3-(3-(Cyclopentyloxy)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (3-90).[60] To a solution of cyclopentanol (0.14 g, 0.80 mmol) in dry THF (1.8 mL) at

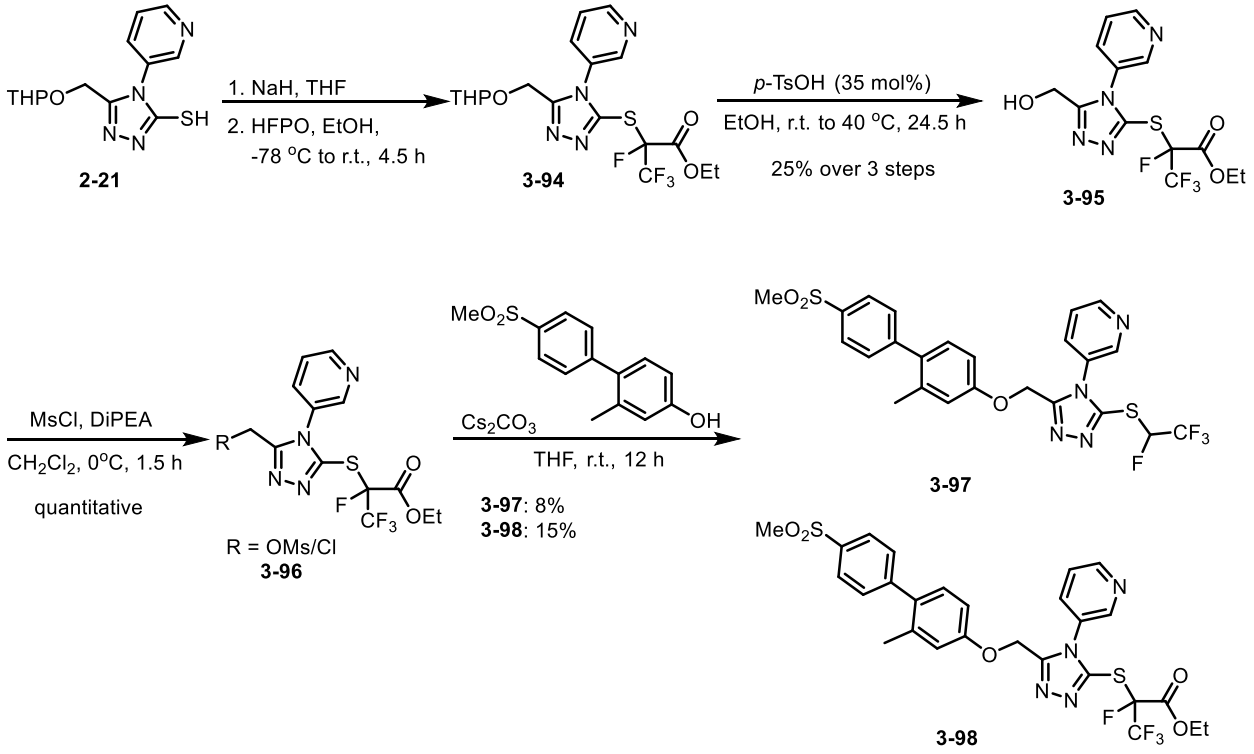
0 °C was added NaH (0.026 g, 0.66 mmol) and the reaction warmed to room temperature for 30 min. **3-89** (0.090 g, 0.27 mmol) was added in portions. The reaction was stirred at room temperature for 5 h. The reaction was diluted with H_2O and extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 0/100 to 100/0). Triazole **3-90** was obtained as a white solid (0.076 g, 83%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 4.8, 1.0 Hz, 1 H), 8.67 (d, *J* = 2.2 Hz, 1 H), 7.74 (dt, *J* = 8.2, 1.8 Hz, 1 H), 7.46 (dd, *J* = 8.1, 4.8 Hz, 1 H), 5.45 (tt, *J* = 5.6, 2.8 Hz, 1 H), 4.64-4.60 (m, 2 H), 4.45 (d, *J* = 12.6 Hz, 1 H), 3.58-3.52 (m, 1 H), 3.48-3.42 (m, 1 H), 1.98-1.85 (m, 4 H), 1.66-1.46 (m, *J* = 5.3 Hz, 10 H); HRMS (ESI^+): *m/z* calculated for $C_{18}H_{25}O_3N_4$ (M+H) 345.1921, found 345.1919.

(5-(Cyclopentyloxy)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methanol (3-91). To a solution of **3-90** (0.072 g, 0.21 mmol) in MeOH (1 mL) was added *p*-TsOH (tip of spatula) and the reaction stirred at room temperature 16 h. The reaction was quenched by adding poly(4-vinylpyridine) and stirring for 30 min. The solid filtered off and the solvent concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/ CH_2Cl_2: 0/100 to 10/90). Triazole **3-91** was obtained as a white solid (0.013 g, 24%) and carried on without further characterization: HRMS (ESI^+): *m/z* calculated for $C_{13}H_{17}O_2N_4$ (M+H) 261.1346, found 261.1345.

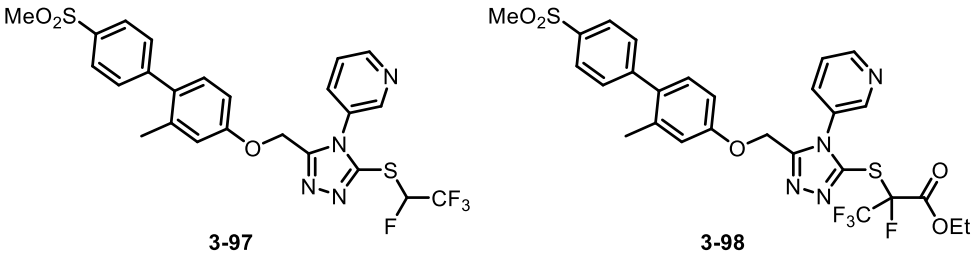
(5-(Cyclopentyloxy)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate (3-92). To a solution of **3-91** (0.013 g, 0.049 mmol) and DiPEA (0.017 mL, 0.098 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added MsCl (6.7 µL, 0.086 mmol) dropwise. The reaction was stirred at 0 °C and slowly warmed to room temperature over 2.5 h. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$ and sat. NH_4Cl, dried ($MgSO_4$), filtered, and concentrated. Triazole **3-**

92 was obtained as an orange oil and carried on without purification or characterization: HRMS (ESI^+): *m/z* calculated for $C_{14}H_{19}O_4N_4S$ (M+H) 339.1122, found 339.1119.

3-(3-(Cyclopentyloxy)-5-(((2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (3-93). To a solution of crude **3-92** (0.017 g, 0.050 mmol) in dry DMF (0.8 mL) was added 2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-ol (0.017 g, 0.065 mmol) and Cs_2CO_3 (0.025 g, 0.075 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/EtOAc: 0/100 to 10/00). Product **3-93** was obtained as a white foam (0.019 g, 74%): IR (neat) 2960, 2871, 1553, 1487, 1455, 1306, 1232, 1149, 1090, 1004, 955, 815, 778, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 4.3 Hz, 1 H), 8.67 (d, *J* = 1.1 Hz, 1 H), 7.96-7.93 (m, 2 H), 7.75 (ddd, *J* = 8.2, 2.4, 1.5 Hz, 1 H), 7.48-7.44 (m, 3 H), 7.10-7.08 (m, 1 H), 6.85-6.82 (m, 2 H), 5.46 (tt, *J* = 5.7, 2.8 Hz, 1 H), 5.04 (s, 2 H), 3.09 (s, 3 H), 2.21 (s, 3 H), 1.96-1.86 (m, 4 H), 1.66-1.60 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 157.3, 150.4, 147.55, 147.41, 147.27, 138.8, 137.1, 134.0, 133.8, 131.0, 130.4, 129.6, 127.3, 124.1, 117.0, 112.4, 85.2, 60.5, 44.7, 32.9, 23.6, 20.8; HRMS (ESI^+): *m/z* calculated for $C_{27}H_{29}O_4N_4S$ (M+H) 505.1904, found 505.1901; ELS purity (100%).



Scheme 3-22. Synthesis of zone 1 2,3,3,3-tetrafluoro analogs.



Ethyl 2,3,3,3-tetrafluoro-2-((4-(pyridin-3-yl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-3-yl)thio)propanoate (3-94).[148] To a solution of 4-(pyridin-3-yl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazole-3-thiol (0.500 g, 1.71 mmol) in THF (10.8 mL) was added NaH (0.075 g, 1.88 mmol) in portions at room temperature. The reaction was stirred at room temperature 16 h. The reaction was concentrated, and the residue suspended in hexanes. The solid was filtered and washed with distilled hexanes (3x). The product (sodium

4-(pyridin-3-yl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazole-3-thiolate) was obtained as a pale brown foam (0.538 g, 100%) and carried on without further purification.

To a solution of sodium 4-(pyridin-3-yl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazole-3-thiolate (0.535 g, 1.70 mmol) in EtOH (3.5 mL) at -78 °C was added hexafluoropropylene oxide (0.224 mL, 5 drops by dry ice condenser, 1.70 mmol). The reaction was warmed to room temperature and stirred for 4 h with dry ice condenser in place. The reaction was poured onto ice cooled sat. $NaHCO_3$. The aqueous was extracted with EtOAc (3x), dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 35/65 to 100/0) to give the crude triazole **3-94** (0.467 g, 16%, 27% pure by UV) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (dd, *J* = 4.7, 1.0 Hz, 1 H), 8.50 (d, *J* = 1.6 Hz, 1 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.41 (dd, *J* = 8.1, 4.9 Hz, 1 H), 4.56 (t, *J* = 12.5 Hz, 1 H), 4.42-4.36 (m, 2 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 3.26-3.20 (m, 2 H), 1.42-1.23 (m, 6 H), 1.13 (t, *J* = 7.1 Hz, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.0 (dd, J_{FF} = 10.4, 7.8 Hz), -144.1 (dq, J_{FF} = 20.8, 10.3 Hz); HRMS (ESI^+): *m/z* calculated for $C_{18}H_{21}O_4N_4F_4S$ (M+H) 465.1214, found 465.1213.

Ethyl 2,3,3,3-tetrafluoro-2-((5-(hydroxymethyl)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)propanoate (3-95). To a solution of **3-94** (0.467 g, 1.01 mmol) in EtOH (4 mL) was added *p*-TsOH (0.035 g, 0.201 mmol) and the reaction stirred at room temperature for 16 h. LCMS still showed starting material, the reaction was heated to 40 °C for 8 h. The reaction was quenched by adding poly(4-vinylpyridine) and stirring for 30 min. The solid filtered off and the solvent concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90) followed by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 3/97 to 10/90). Triazole **3-95** was obtained as a pale yellow oil (0.162 g, 85%; 25% over 3 steps)

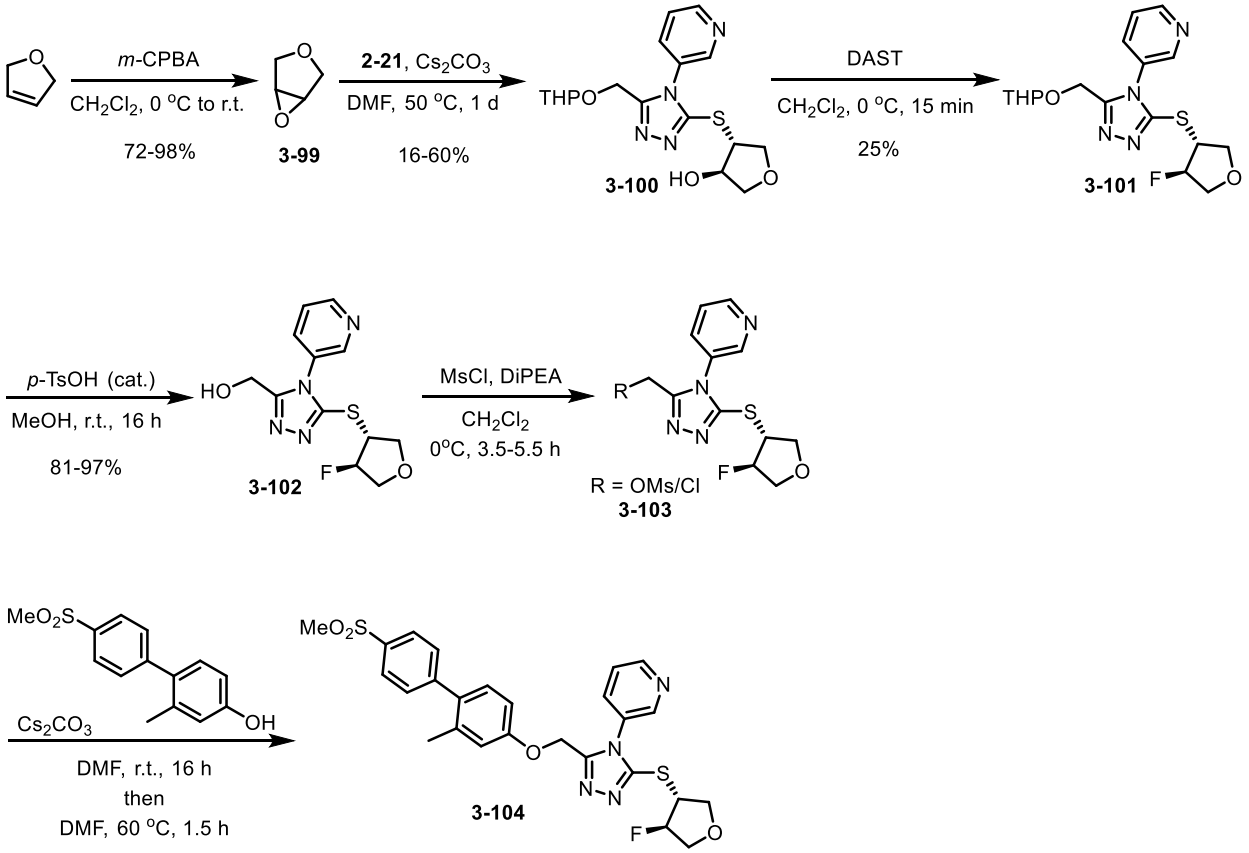
and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (dd, *J* = 4.8, 1.3 Hz, 1 H), 8.64 (d, *J* = 2.5 Hz, 1 H), 7.82 (dt, *J* = 8.3, 1.7 Hz, 1 H), 7.56 (dd, *J* = 8.2, 4.8 Hz, 1 H), 4.73-4.64 (m, 2 H), 4.33-4.28 (m, 2 H), 3.08 (t, *J* = 6.6 Hz, 1 H), 1.34 (t, *J* = 7.1 Hz, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$): -74.6 (d, J_{FF} = 10.7 Hz), -143.9 (q, J_{FF} = 10.6 Hz); HRMS (ESI^+): *m/z* calculated for $C_{13}H_{13}O_3N_4F_4S$ (M+H) 381.0639, found 381.0637.

Ethyl 2,3,3,3-tetrafluoro-2-((5-(((methylsulfonyl)oxy)methyl)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)propanoate and **Ethyl 2-((5-(chloromethyl)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)-2,3,3,3-tetrafluoropropanoate (3-96).** To a solution of **3-95** (0.155 g, 0.408 mmol) and MsCl (0.047 mL, 0.408 mmol) in CH_2Cl_2 (5.5 mL) at 0 °C was added DiPEA (0.106 mL, 0.408 mmol) dropwise. The reaction was stirred at 0 °C and slowly warmed to room temperature over about 1.3 h. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$ and sat. NH_4Cl, dried ($MgSO_4$), filtered, and concentrated. Triazole **3-96** was obtained as a mixture of mesylate and chloride and carried on without purification or characterization: HRMS (ESI^+): *m/z* calculated for $C_{13}H_{12}O_2N_4ClF_4S$ (M+H) 399.0300, found 399.0299; HRMS (ESI^+): *m/z* calculated for $C_{14}H_{15}O_5N_4F_4S$+2 (M+H) 459.0415, found 459.0412.

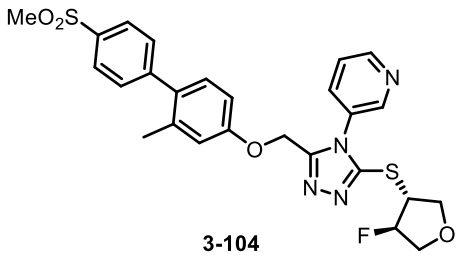
3-(3-(((2-Methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)oxy)methyl)-5-((1,2,2,2-tetrafluoroethyl)thio)-4*H*-1,2,4-triazol-4-yl)pyridine (3-97) and **Ethyl 2,3,3,3-tetrafluoro-2-((5-(((2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)oxy)methyl)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)propanoate (3-98).** To a solution of the mixture from above (**3-96**) (0.180 g, 0.393 mmol) in dry THF (7 mL) was added 2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-ol (0.155 g, 0.589 mmol) and Cs_2CO_3 (0.384 g, 1.18 mmol) and the reaction stirred at room temperature 16 h. The reaction was concentrated and washed with water. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 30/70 to 100/0) followed by

HPLC (C18-SiO_2, MeCN/H2O + 0.1% TFA: 25/75 to 75/25). The decarboxylated product (**3-97**) was obtained as a white foam (0.016 g, 8%) and the carboxylated product (**3-98**) was obtained as a white foam (0.036 g, 15%): **3-97**: IR (CH_2Cl_2) 3051, 2924, 1745, 1681, 1605, 1484, 1446, 1299, 1195, 1148, 1036, 1003, 956, 779, 733, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.91 (dd, *J* = 5.0, 1.2 Hz, 1 H), 8.81 (d, *J* = 2.3 Hz, 1 H), 8.00 (dt, *J* = 8.2, 1.2 Hz, 1 H), 7.96-7.94 (m, 2 H), 7.78 (dd, *J* = 8.1, 5.1 Hz, 1 H), 7.46-7.43 (m, 2 H), 7.09 (d, *J* = 8.1 Hz, 1 H), 6.78-6.68 (m, 3 H), 5.25 (s, 2 H), 3.10 (s, 3 H), 2.20 (s, 3 H); ^{13}C NMR (125 MHz $CDCl_3$) δ 159.9 (q, J_{CF} = 40.8 Hz), 156.6, 153.7, 150.0, 147.7, 147.1, 146.3, 138.9, 137.5 (d, J_{CF} = 5.6 Hz), 134.5, 131.1, 130.38, 130.20, 127.4, 125.7, 120.8 (app dd, J_{CF} = 281.6, 29.3 Hz), 116.7, 112.1, 94.0 (dq, J_{CF} = 239.7, 38.4 Hz), 59.7, 44.7, 20.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ -76.7 (d, J_{FF} = 14.6 Hz), -169.2 (q, J_{FF} = 14.4 Hz); HRMS (ESI^+): *m/z* calculated for $C_{24}H_{21}O_3N_4FS_2$ (M+H) 553.0986, found 553.0987; ELS purity (100%).

3-98: IR (neat) 3057, 2924, 1758, 1603, 1482, 1443, 1277, 1212, 1191, 1146, 1089, 1027, 1003, 954, 934, 816, 777, 733, 705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.86-8.85 (m, 1 H), 8.70 (s, 1 H), 7.94 (d, *J* = 8.3 Hz, 3 H), 7.66 (dd, *J* = 8.0, 4.9 Hz, 1 H), 7.44 (d, *J* = 8.3 Hz, 2 H), 7.07 (d, *J* = 8.8 Hz, 1 H), 6.74-6.72 (m, 2 H), 5.20 (s, 2 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 3.09 (s, 3 H), 2.19 (s, 3 H), 1.31 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1 (d, J_{CF} = 27.3 Hz), 156.7, 154.5, 150.4, 147.2, 146.9, 143.9, 138.8, 137.2, 137.0, 134.2, 130.9, 130.2, 127.2, 124.7, 121.2 (dq, J_{CF} = 286.5, 30.4 Hz), 116.8, 112.1, 98.8 (dq, J_{CF} = 251.8, 34.3 Hz), 64.9, 60.1, 44.5, 20.5, 13.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ -74.6 (d, J_{FF} = 10.5 Hz), -143.3 (app d, J_{FF} = 4.2 Hz); HRMS (ESI^+): *m/z* calculated for $C_{27}H_{25}O_5N_4F_4S_2$ (M+H) 625.1197, found 625.1195; ELS purity (100%).



Scheme 3-23. Synthesis of 4-fluoro THF analog.



3,6-Dioxabicyclo[3.1.0]hexane (3-99).[149] To a solution of 2,5-dihydrofuran (1.08 mL, 14.3 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added *m*-CPBA (4.58 g, 18.6 mmol). The reaction was warmed to room temperature and stirred for 3 d. The reaction was quenched with NaOH (1 M) and sat. $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. 3,6-Dioxabicyclo[3.1.0]hexane **3-99** was obtained as a pale-yellow oil (1.20 g, 98%) and carried on without further purification or characterization, data

matches that reported in the literature: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (dd, *J* = 10.5, 1.4 Hz, 2 H), 3.79 (s, 2 H), 3.65 (d, *J* = 10.7 Hz, 2 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 67.5, 56.0.

4-((4-(Pyridin-3-yl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-3-yl)thio)tetrahydrofuran-3-ol (3-100). To a solution of 4-(pyridin-3-yl)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazole-3-thiol (0.200 g, 0.684 mmol) in DMF (5.9 mL) was added Cs_2CO_3 (0.446 g, 1.37 mmol) and **3-99** (0.088 g, 1.03 mmol). The reaction was stirred at 50 °C 16 h. An additional 1 equivalent of 3,6-dioxabicyclo[3.1.0]hexane was added, and the reaction stirred at 50 °C for 9 h. The reaction was poured into water (10 mL) and the aqueous was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude was concentrated with heptane (3x) to remove residual DMF. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 3/97 to 10/90). The mixture of *trans* products was obtained as a colorless oil (0.090 g, 35%) and carried on without further characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 4.8, 1.3 Hz, 1 H), 8.68 (d, *J* = 2.3 Hz, 1 H), 7.76 (ddd, *J* = 8.1, 2.2, 1.7 Hz, 1 H), 7.52 (dd, *J* = 8.1, 4.8 Hz, 1 H), 5.30 (s, 1 H), 4.69 (t, *J* = 12.7 Hz, 1 H), 4.58 (t, *J* = 7.8 Hz, 2 H), 4.50 (t, *J* = 12.7 Hz, 1 H), 4.35-4.32 (m, 1 H), 4.14 (dd, *J* = 9.5, 6.4 Hz, 1 H), 4.00 (ddt, *J* = 7.6, 6.2, 3.2 Hz, 1 H), 3.79 (dd, *J* = 9.7, 4.8 Hz, 1 H), 3.61 (dd, *J* = 10.1, 6.1 Hz, 1 H), 3.49-3.43 (m, 2 H), 1.67-1.42 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 153.22, 153.19, 151.6, 148.2, 134.9, 134.8, 130.0, 124.3, 98.5, 80.1, 74.3, 70.9, 62.0, 61.9, 58.7, 58.6, 52.24, 52.21, 30.1, 25.2, 18.89, 18.85.

3-(3-((*trans*-4-Fluorotetrahydrofuran-3-yl)thio)-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (3-101).[150, 151] To a solution of **3-100** (0.085 g, 0.225 mmol) in CH_2Cl_2 (4.5 mL) at 0 °C was added DAST (0.125 mL, 0.898 mmol) dropwise. The reaction was stirred at 0 °C for 15 min. The reaction was quenched with sat. $NaHCO_3$. The

product was purified by chromatography on SiO_2 (MeOH/CH_2Cl_2: 0/100 to 10/90). Triazole **3-101** was obtained as a colorless oil (0.038 g, 25%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.66 (d, *J* = 2.5 Hz, 1 H), 7.73 (dddd, *J* = 8.1, 2.4, 1.6, 0.5 Hz, 1 H), 7.51 (ddd, *J* = 8.1, 4.8, 0.7 Hz, 1 H), 5.45-5.26 (m, 1 H), 4.70 (dd, *J* = 12.6, 1.9 Hz, 1 H), 4.58-4.56 (m, 1 H), 4.52 (dd, *J* = 12.6, 2.2 Hz, 1 H), 4.40-4.29 (m, 2 H), 4.13-4.10 (m, 1 H), 4.01-4.00 (m, 1 H), 3.84-3.79 (m, 1 H), 3.45-3.43 (m, 2 H), 1.62-1.43 (m, 6 H); HRMS (ESI$^+$): *m/z* calculated for $C_{17}H_{22}O_3N_4FS$ (M+H) 381.1391, found 381.1389.

(5-((*trans*-4-Fluorotetrahydrofuran-3-yl)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methanol (3-102). To a solution of **3-101** (0.035 g, 0.092 mmol) in MeOH (0.4 mL) was added *p*-TsOH (tip of spatula) and the reaction stirred at room temperature 16 h. The reaction was quenched by adding poly(4-vinylpyridine) and stirring for 30 min. The solid filtered off and the solvent concentrated. The product was purified by chromatography on Al_2O_3-neutral (MeOH/CH_2Cl_2: 0/100 to 5/95). Triazole **3-102** was obtained as a pale yellow film (0.026 g, 97%) and carried on without further characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.68 (d, *J* = 2.4 Hz, 1 H), 7.87 (ddd, *J* = 8.2, 2.5, 1.6 Hz, 1 H), 7.55 (dd, *J* = 8.1, 4.8 Hz, 1 H), 5.40-5.20 (m, 1 H), 4.65 (d, *J* = 5.0 Hz, 2 H), 4.57-4.53 (m, 1 H), 4.38-4.23 (m, 2 H), 4.14-4.08 (m, 1 H), 3.98 (d, *J* = 2.4 Hz, 1 H), 3.80-3.75 (m, 1 H); HRMS (ESI$^+$): *m/z* calculated for $C_{12}H_{14}O_2N_4FS$ (M+H) 297.0816, found 297.0814.

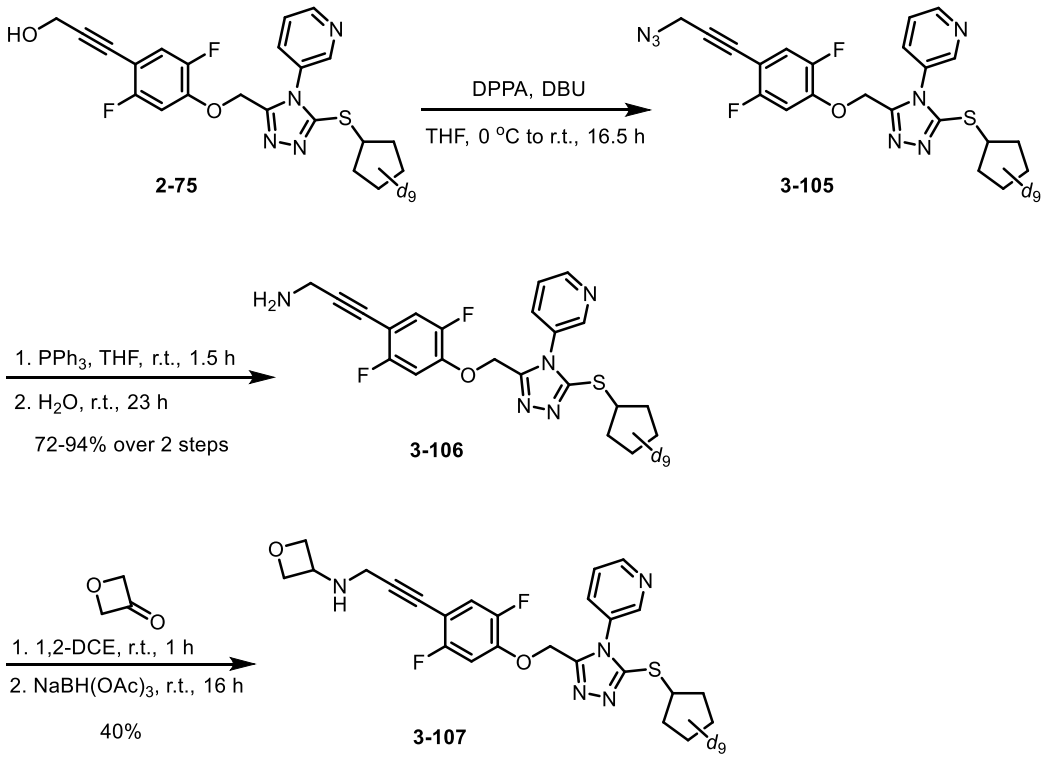
(5-((*trans*-4-Fluorotetrahydrofuran-3-yl)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and **3-(3-(Chloromethyl)-5-((4-fluorotetrahydrofuran-3-yl)thio)-4*H*-1,2,4-triazol-4-yl)pyridine (3-103)**. To a solution of **3-102** (0.026 g, 0.088 mmol) and MsCl (7.0 µL, 0.088 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C was added DiPEA (0.015 mL, 0.088 mmol) dropwise.

The reaction was stirred at 0 °C and slowly warmed to room temperature over about 3.5 h. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. Triazole **3-103** was obtained as a mixture of mesylate and chloride (0.060 g) and carried on without purification or characterization: HRMS (ESI^+): *m/z* calculated for $C_{12}H_{13}ON_4ClFS$ (M+H) 315.0477, found 315.0475; HRMS (ESI^+): *m/z* calculated for $C_{13}H_{16}O_4N_4FS_2$ (M+H) 375.0592, found 375.0589.

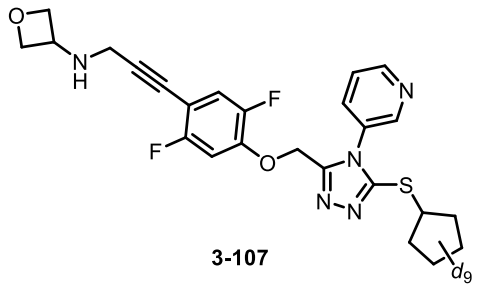
3-(3-((*trans*-4-Fluorotetrahydrofuran-3-yl)thio)-5-(((2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)oxy)methyl)-4*H*-1,2,4-triazol-4-yl)pyridine (3-104). To a solution of the mixture from above (**3-103**) (0.032 g, 0.085 mmol) in dry THF (1.5 mL) was added 2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-ol (0.034 g, 0.128 mmol) and Cs_2CO_3 (0.084 g, 0.256 mmol) and the reaction stirred at room temperature 16 h. LCMS showed trace product. The reaction was diluted with CH_2Cl_2, extraction with H_2O, sat. $NaHCO_3$, and sat. NH_4Cl. The combined organic layers dried ($MgSO_4$), filtered, and concentrated.

The clean material was resubjected as: To a solution of the mixture from above (0.032 g, 0.085 mmol) in dry DMF (1.5 mL) was added 2-methyl-4'-(methylsulfonyl)-[1,1'-biphenyl]-4-ol (0.034 g, 0.128 mmol) and Cs_2CO_3 (0.084 g, 0.256 mmol) and the reaction heated to 60 °C for about 1.5 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **3-104** was obtained as a white foam (0.031 g, 68%): IR (CH_2Cl_2) 3055, 2926, 2873, 1604, 1484, 1448, 1301, 1276, 1233, 1148, 1088, 956, 848, 818, 778, 731, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (dd, *J* = 4.8, 1.3 Hz, 1 H), 8.65 (d, *J* = 2.4 Hz, 1 H), 7.94 (d, *J* = 8.3 Hz, 2 H), 7.75 (ddd, *J* = 8.1, 2.4, 1.6 Hz, 1 H), 7.52 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.44 (d, *J* =

8.4 Hz, 2 H), 7.09-7.07 (m, 1 H), 6.80-6.78 (m, 2 H), 5.42-5.28 (m, 1 H), 5.13 (s, 2 H), 4.39-4.30 (m, 2 H), 4.12-3.97 (m, 2 H), 3.83-3.79 (m, 1 H), 3.09 (s, 3 H), 2.20 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 152.2, 151.7, 151.4, 147.9, 147.1, 138.8, 137.1, 134.7, 133.9, 131.0, 130.3, 129.7, 127.3, 124.4, 116.8, 112.3, 96.7 (d, J_{CF} = 187.9 Hz), 72.4 (d, J_{CF} = 23.5 Hz), 71.6, 59.8, 49.8 (d, J_{CF} = 25.6 Hz), 44.6, 20.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ -168.7; HRMS (ESI^+): *m/z* calculated for $C_{26}H_{26}O_4N_4FS_2$ (M+H) 541.1374, found 541.1373; ELS purity (100%).



Scheme 3-24. Synthesis of propargyl amine derivatives.



3-107

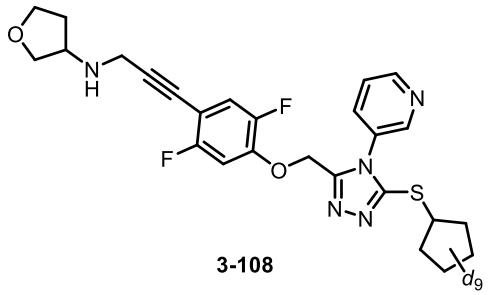
3-(3-((4-(3-Azidoprop-1-yn-1-yl)-2,5-difluorophenoxy)methyl)-5-((cyclopentyl-*d*$_9$)thio)-4*H*-1,2,4-triazol-4-yl)pyridine (**3-105**)[152]**.** To a solution of **2-75** (0.190 g, 0.421 mmol) in THF (3.2 mL) at 0 °C was added DPPA (102 µL, 0.505 mmol) followed by DBU (75.4 µL, 0.505 mmol) dropwise. The reaction was warmed to room temperature 16 h. The reaction was diluted with EtOAc then washed with sat. NH_4Cl and the aqueous was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The impure triazole **3-105** was obtained as a pale-yellow solid (0.180 g, 90%) and carried on without further purification or characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 4.8 Hz, 1 H), 8.64 (s, 1 H), 7.74 (d, *J* = 8.2 Hz, 1 H), 7.54-7.46 (m, 1 H), 7.12 (dd, *J* = 10.7, 6.4 Hz, 1 H), 6.95-6.86 (m, 1 H), 5.12 (s, 2 H), 4.14 (s, 2 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.9 (d, *J* = 14.3 Hz), -138.4 (d, *J* = 14.1 Hz)·; HRMS (ESI$^+$): *m/z* calculated for $C_{22}H_{11}{}^2H_9ON_7F_2S$ (M+H) 477.1978, found 477.1974.

3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-amine (**3-106**)[152]**.** To a solution of 3-(3-((4-(3-azidoprop-1-yn-1-yl)-2,5-difluorophenoxy)methyl)-5-((cyclopentyl-*d*$_9$)thio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.211 g, 0.443 mmol) in THF (4.2 mL) was added PPh_3 (0.174 g, 0.664 mmol) and the reaction stirred for 1.5 h. Water (0.32 mL) was added and the reaction stirred at room temperature for about 23 h. The reaction was concentrated, and the crude product was purified by chromatography on

SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90). The triazole **3-106** was obtained as an off-white solid (0.188 g, 94%) and carried on without further characterization: ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.71 (app d, *J* = 3.0 Hz, 1 H), 8.58 (app s, 1 H), 7.76 (ddd, *J* = 8.2, 2.5, 1.6 Hz, 1 H), 7.51 (ddd, *J* = 8.2, 4.9, 0.8 Hz, 1 H), 7.23 (q, *J* = 7.6 Hz, 1 H), 7.08 (ddd, *J* = 10.2, 6.7, 3.8 Hz, 1 H), 6.87 (dd, *J* = 9.6, 7.5 Hz, 1 H), 5.09 (s, 2 H), 3.60 (s, 2 H), 3.48 (s, 1 H), 3.30 (s, 1 H); ^{19}F NMR (CD_2Cl_2, 376 MHz) δ -113.2 (d, *J* = 14.3 Hz), -139.5 (d, *J* = 14.0 Hz); HRMS (ESI$^+$): *m/z* calculated for $C_{22}H_{13}{}^2H_9ON_5F_2S$ (M+H) 451.2073, found 451.2068.

***N*-(3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl)oxetan-3-amine (3-107).** To a solution of **3-106** (0.080 g, 0.18 mmol) in 1,2-DCE (4 mL) was added 3-oxetanone (11 μL, 0.18 mmol). After 3 h $NaBH(OAc)_3$ (0.095 g, 0.45 mmol) was added and the reaction stirred 16 h at room temperature. After 16 h a second portion of $NaBH(OAc)_3$ (0.095 g, 0.45 mmol) was added and the reaction stirred for 7 h. The reaction was diluted with CH_2Cl_2 and washed with water. The aqueous was extracted with CH_2Cl_2 (2x) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (MeOH/EtOAc: 0/100 to 4/96). Product **3-107** was obtained as a white foam (0.036 g, 40%): IR (neat) 3274, 3052, 2956, 2870, 2224, 1629, 1507, 1484, 1447, 1332, 1222, 1177, 1133, 998, 969, 851, 734, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.61 (d, *J* = 2.5 Hz, 1 H), 7.73 (ddd, *J* = 8.2, 2.6, 1.5 Hz, 1 H), 7.48 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.00 (dd, *J* = 10.8, 6.5 Hz, 1 H), 6.85 (dd, *J* = 9.9, 7.0 Hz, 1 H), 5.08 (s, 2 H), 4.84 (t, *J* = 6.9 Hz, 2 H), 4.52 (t, *J* = 6.4 Hz, 2 H), 4.08 (p, *J* = 6.6 Hz, 1 H), 3.61 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0 (dd, J_{CF} = 249.4, 2.1 Hz), 154.6, 151.4, 150.2, 148.1 (dd, J_{CF} = 244.3, 3.2 Hz), 147.9, 146.0 (dd, J_{CF} = 12.8, 9.8 Hz), 135.0, 129.8, 124.2, 119.6 (dd, J_{CF} = 21.4, 2.7 Hz), 104.5 (dd, J_{CF} = 18.3, 8.4 Hz), 103.7 (d, J_{CF} = 27.1 Hz), 92.7 (d,

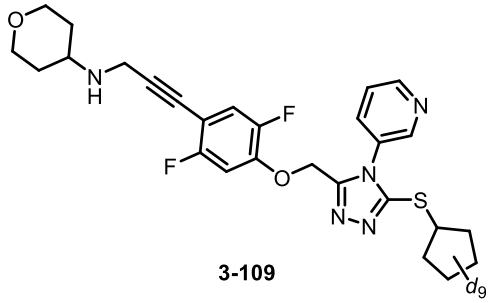
J_{CF} = 3.6 Hz), 79.9, 75.6 (d, J_{CF} = 2.1 Hz), 61.2, 53.6, 45.3 (d, J = 24.0 Hz), 37.6-36.8 (m, CD), 33.3-32.3 (m, CD), 23.5 (dt, J_{CD} = 40.2, 19.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.0 (d, J = 14.1 Hz), -138.6 (d, J = 14.2 Hz); HRMS (ESI^+): *m/z* calculated for $C_{25}H_{17}{}^2H_9O_2N_5F_2S$ (M+H) 507.2335, found 507.2329; ELS purity (100%).



3-108

***N*-(3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl)tetrahydrofuran-3-amine (3-108).** To a solution of **3-106** (0.080 g, 0.18 mmol) in 1,2-DCE (4 mL) and AcOH (2 drops) was added dihydrofuran-3-one (15 µL, 0.20 mmol). After 1 h $NaBH(OAc)_3$ (0.19 g, 0.89 mmol) was added and the reaction stirred 16 h at room temperature. The reaction was diluted with CH_2Cl_2 and washed with water. The aqueous was extracted with CH_2Cl_2 (2x) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 7/93) then chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0 to MeOH/CH_2Cl_2: 0/100 to 7/93) followed by filtration through a plug of basic Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 3/97). Product **3-108** was obtained as a yellow foam (0.029 g, 31%): IR (neat) 3305, 3054, 2918, 2849, 1627, 1524, 1509, 1485, 1446, 1399, 1352, 1324, 1278, 1219, 1174, 1131, 1053, 995, 945, 884, 842, 796, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, J = 4.9, 1.5 Hz, 1 H), 8.62 (d, J = 2.5 Hz, 1 H), 7.73 (ddd, J = 8.1, 2.6, 1.6 Hz, 1 H), 7.49 (dd, J = 8.1, 4.8 Hz, 1 H), 7.05 (dd, J = 10.8, 6.6 Hz, 1 H), 6.86 (dd, J = 9.9, 7.0 Hz, 1 H), 5.09 (s, 2 H),

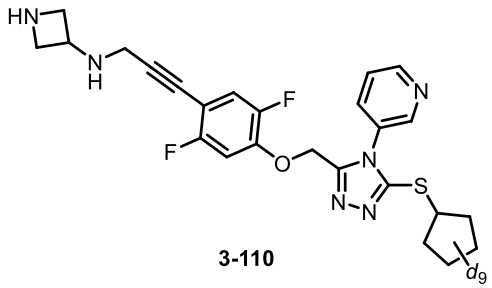
3.95-3.88 (m, 1 H), 3.88-3.82 (m, 1 H), 3.79 (td, J = 8.2, 5.6 Hz, 1 H), 3.64 (s, 2 H), 3.65-3.57 (m, 2 H), 2.18-2.05 (m, 1 H), 1.80-1.71 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0 (dd, J_{CF} = 249.3, 2.2 Hz), 154.7, 151.4, 150.2, 148.1 (dd, J = 244.0, 3.2 Hz), 147.9, 145.9 (dd, J_{CF} = 12.7, 10.0 Hz), 135.0, 129.8, 124.2, 119.8 (dd, J_{CF} = 21.3, 2.6 Hz), 104.8 (dd, J_{CF} = 18.4, 8.4 Hz), 103.6 (d, J_{CF} = 27.1 Hz), 92.7 (d, J_{CF} = 3.6 Hz), 75.6 (d, J_{CF} = 2.1 Hz), 73.2, 67.2, 61.2, 57.3, 45.7-45.1 (m, CF), 37.6, 33.0, 32.9-32.3 (m, CD), 29.7 (d, J_{CF} = 3.4 Hz), 23.8-23.0 (m, CD); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.9 (d, J = 14.3 Hz), -138.7 (d, J = 14.3 Hz); HRMS (ESI$^+$): *m/z* calculated for $C_{26}H_{19}{}^2H_9O_2N_5F_2S$ (M+H) 521.2491, found 521.2490; ELS purity (100%).



3-109

***N*-(3-(4-((5-((cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl)tetrahydro-2*H*-pyran-4-amine (3-109).** To a solution of **3-106** (0.070 g, 0.16 mmol) in 1,2-DCE (3.5 mL) and AcOH (2 drops) was added 4-oxotetrahydropyran (23 µL, 0.24 mmol). After 1 h $NaBH(OAc)_3$ (0.16 g, 0.78 mmol) was added and the reaction stirred at room temperature for 16 h. The reaction was diluted with CH_2Cl_2 and washed with water. The aqueous was extracted with CH_2Cl_2 (2x) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90) followed by filtration through a plug of basic Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 1/99). It was then purified again by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 7/93) followed by filtration through a plug of basic Al_2O_3

(MeOH/CH_2Cl_2: 0/100 to 2/98). Product **3-109** was obtained as a yellow foam (0.041 g, 50%): IR (neat) 3047, 2918, 2848, 2226, 1629, 1507, 1484, 1446, 1222, 1177, 1136, 997, 816, 733, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.8, 0.8 Hz, 1 H), 8.61 (d, *J* = 2.4 Hz, 1 H), 7.73 (dd, *J* = 8.1, 1.5 Hz, 1 H), 7.48 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.03 (dd, *J* = 10.8, 6.5 Hz, 1 H), 6.86 (dd, *J* = 9.8, 7.0 Hz, 1 H), 5.08 (s, 2 H), 3.96 (dt, *J* = 11.5, 3.1 Hz, 2 H), 3.67 (s, 2 H), 3.41 (td, *J* = 11.6, 1.7 Hz, 2 H), 2.93 (tt, *J* = 9.9, 4.7 Hz, 1 H), 1.81 (dd, *J* = 12.5, 1.5 Hz, 2 H), 1.42 (qd, *J* = 11.7, 4.1 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1 (dd, J_{CF} = 249.2, 2.1 Hz), 154.7, 151.5, 150.3, 148.2 (dd, J_{CF} = 243.9, 3.0 Hz), 148.0, 145.9 (dd, J_{CF} = 12.7, 10.0 Hz), 135.0, 129.9, 124.3, 119.8 (dd, J_{CF} = 21.6, 2.8 Hz), 105.0 (dd, J_{CF} = 18.3, 8.3 Hz), 103.8 (d, J_{CF} = 27.4 Hz), 93.0 (d, J_{CF} = 3.6 Hz), 75.5 (d, J_{CF} = 2.2 Hz), 66.7, 61.3, 52.4, 45.5 (t, J_{CD} = 23.0 Hz), 35.8, 33.3, 33.1-32.7 (m), 23.9-23.5 (m); ^{19}F NMR (470 MHz, $CDCl_3$) δ -112.0 (d, *J* = 14.2 Hz), -138.7 (d, *J* = 14.4 Hz); HRMS (ESI^+): *m/z* calculated for $C_{27}H_{21}{}^2H_9O_3N_5F_2S$ (M+H) 535.2648, found 535.2644; ELS purity (100%).



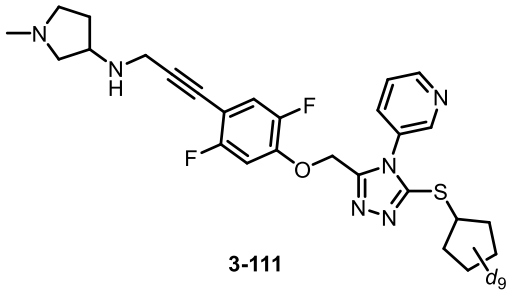
3-110

***tert*-Butyl 3-((3-(4-((5-((cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl)amino)azetidine-1-carboxylate.** To a solution of **3-106** (0.12 g, 0.26 mmol) in 1,2-DCE (5.75 mL) was added *tert*-butyl 3-oxoazetidine-1-carboxylate (0.044 g, 0.26 mmol) followed by AcOH (2 drops). After 3 h $NaBH(OAc)_3$ (0.13 g, 0.65 mmol) was added and the reaction stirred 16 h at room temperature. After stirring 16 h additional

$NaBH(OAc)_3$ (0.13 g, 0.65 mmol) and $Ti(OiPr)_4$ (76 µL, 0.25 mmol) were added and stirred for 12 h. The reaction was diluted with CH_2Cl_2 and washed with water. The aqueous was extracted with CH_2Cl_2 (2x) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (MeOH/EtOAc: 0/100 to 7/93). The triazole was obtained as an off-white foam (0.079 g, 51%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.64 (d, *J* = 2.6 Hz, 1 H), 7.78-7.71 (m, 1 H), 7.50 (dd, *J* = 8.2, 4.9 Hz, 1 H), 7.04 (dd, *J* = 10.8, 6.5 Hz, 1 H), 6.87 (dd, *J* = 9.9, 7.0 Hz, 1 H), 5.10 (s, 2 H), 4.18-4.09 (m, 2 H), 3.78-3.69 (m, 3 H), 3.63 (s, 2 H), 1.43 (s, 9 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.8 (d, *J* = 14.3 Hz), -138.6 (d, *J* = 14.2 Hz).

***N*-(3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl)azetidin-3-amine 2,2,2-trifluoroacetate (3-110).** To a solution of *tert*-butyl 3-((3-(4-((5-((cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl)amino)azetidine-1-carboxylate (0.078 g, 0.13 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C was added TFA (0.50 mL, 6.7 mmol) dropwise. The reaction was stirred at 0 °C for 2 h. The reaction was filtered through a plug of basic Al_2O_3 ($MeOH/CH_2Cl_2$: 0/100 and 10/100), and organic phase were concentrated onto C18-SiO_2. The product was purified by chromatography on C18-SiO_2 (RP-ISCO, $MeCN/H_2O$: 5/95 to 95/5). The mono TFA salt of **3-110** was obtained as a white foam (0.041 g, 52%): IR (neat) 3405, 3053, 2670, 2229, 1674, 1630, 1508, 1486, 1333, 1201, 1178, 1132, 1002, 832, 799, 721, 707 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (s, 1 H), 8.75 (d, *J* = 4.9 Hz, 1 H), 8.63-8.59 (m, 1 H), 7.74 (dt, *J* = 8.3, 1.9 Hz, 1 H), 7.49 (dd, *J* = 8.1, 4.8 Hz, 1 H), 6.97 (dd, *J* = 10.7, 6.5 Hz, 1 H), 6.85 (dd, *J* = 10.0, 6.9 Hz, 1 H), 5.09 (s, 2 H), 4.28 (t, *J* = 9.0 Hz, 2 H), 4.10-4.05 (m, 2 H), 4.00 (q, *J* = 7.1 Hz, 1 H), 3.64 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1 (dd, J_{CF} = 248.5, 2.0 Hz), 154.7, 151.5,

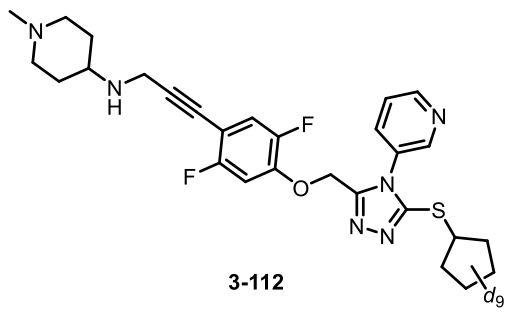
150.4, 148.1 (dd, J_{CF} = 244.2, 2.7 Hz), 147.9, 146.1 (dd, J_{CF} = 12.6, 10.3 Hz), 135.0, 129.7, 124.3, 119.5 (dd, J_{CF} = 21.3, 2.4 Hz), 104.2 (dd, J_{CF} = 18.2, 8.8 Hz), 103.8 (d, J_{CF} = 27.4 Hz), 92.1, 76.3, 61.2, 54.4, 50.7, 45.9-45.1 (m, CD), 37.2, 34.4-32.0 (m, CD), 24.7-22.4 (m, CD); ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.5, -112.4 (d, *J* = 13.9 Hz), -138.4 (d, *J* = 14.1 Hz); HRMS (ESI^+): *m/z* calculated for $C_{25}H_{18}ON_6F_2S$ (M+H) 506.2495, found 506.2491; ELS purity (100%).



3-111

***N*-(3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl)-1-methylpyrrolidin-3-amine (3-111).** To a solution of **3-106** (0.080 g, 0.16 mmol) in 1,2-DCE (4 mL) and AcOH (2 drops) was added 1-methyl-3-pyrrolidinone (20 µL, 0.20 mmol). After 1 h $NaBH(OAc)_3$ (0.19 g, 0.89 mmol) was added and the reaction stirred 16 h at room temperature. The reaction was diluted with CH_2Cl_2 and washed with water. The aqueous was extracted with CH_2Cl_2 (2x) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on basic Al_2O_3 (ISCO, MeOH/CH_2Cl_2: 0/100 to 5/95) followed by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 50/50) followed by filtration through a plug of basic Al_2O_3 (Al_2O_3, MeOH/CH_2Cl_2: 0/100 to 10/90). Product **3-111** was obtained as a yellow foam (0.026 g, 27%): IR (neat) 2938, 2778, 2225, 1629, 1507, 1484, 1446, 1331, 1222, 1177, 1131, 997, 875, 818, 729, 707 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.61 (dd, *J* = 2.5, 0.8 Hz, 1 H), 7.72 (ddd, *J* = 8.2, 2.6, 1.5 Hz, 1 H), 7.47 (ddd, *J* = 8.1, 4.8, 0.8 Hz, 1 H), 7.03 (dd,

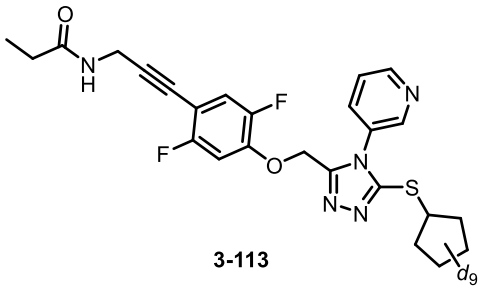
J = 10.9, 6.5 Hz, 1 H), 6.83 (dd, *J* = 9.8, 7.0 Hz, 1 H), 5.08 (s, 2 H), 3.63-3.56 (m, 2 H), 3.51 (ddt, *J* = 8.5, 6.3, 4.5 Hz, 1 H), 2.68 (dd, *J* = 9.5, 6.5 Hz, 1 H), 2.61 (td, *J* = 8.7, 5.8 Hz, 1 H), 2.49-2.41 (m, 1 H), 2.38 (dd, *J* = 9.5, 4.5 Hz, 1 H), 2.32 (s, 3 H), 2.14 (dtd, *J* = 12.9, 8.2, 5.7 Hz, 1 H), 1.63-1.53 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0 (dd, J_{CF} = 249.2, 2.2 Hz), 154.6, 151.4, 150.3, 148.1 (dd, J_{CF} = 244.0, 3.2 Hz), 147.9, 145.8 (dd, J_{CF} = 12.8, 9.9 Hz), 135.0, 129.8, 124.2, 119.8 (dd, J_{CF} = 21.4, 2.9 Hz), 105.0 (dd, J_{CF} = 18.3, 8.4 Hz), 103.7 (dd, J_{CF} = 27.4, 1.6 Hz), 93.0 (d, J_{CF} = 3.6 Hz), 75.3 (d, J_{CF} = 2.2 Hz), 62.7, 61.2, 56.8, 55.2, 42.2, 37.6, 32.9 (app d, J_{CD} = 20.2 Hz), 32.6, 23.9-23.2 (m, CD); ^{19}F NMR (470 MHz, $CDCl_3$) δ -112.0 (d, *J* = 14.4 Hz), -138.8 (d, *J* = 14.5 Hz); HRMS (ESI$^+$): *m/z* calculated for $C_{27}H_{22}{}^2H_9ON_6F_2S$ (M+H) 534.2808, found 534.2807; ELS purity (100%).



3-112

***N*-(3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl)-1-methylpiperidin-4-amine (3-112).** To a solution of **3-106** (0.070 g, 0.16 mmol) in 1,2-DCE (3.5 mL) and AcOH (1 drop) was added 1-methyl-4-piperididone (30 µL, 0.24 mmol). After 1 h $NaBH(OAc)_3$ (0.26 g, 1.2 mmol) was added and the reaction stirred at room temperature for 16.5 h. The reaction was diluted with CH_2Cl_2 and washed with water. The crude material was extracted into the aqueous layer which was concentrated. The residue was dissolved in MeOH/CH_2Cl_2 (5%) and washed with sat. $NaHCO_3$. The combined organic layers were filtered through basic Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 7/93).

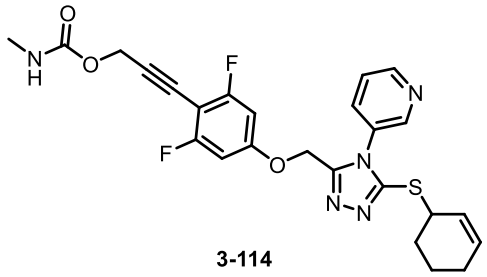
The product was concentrated then filtered through a plug of basic Al_2O_3 (0/100 to 5/95). Product **3-112** was obtained as an off-white foam (0.061 g, 45%): IR (neat) 3046, 2936, 2784, 2227, 1629, 1507, 1484, 1447, 1274, 1221, 1177, 1112, 997, 734, 707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.8, 1.6 Hz, 1 H), 8.61 (dd, *J* = 2.4, 0.6 Hz, 1 H), 7.73 (ddd, *J* = 8.1, 2.6, 1.5 Hz, 1 H), 7.48 (ddd, *J* = 8.1, 4.8, 0.8 Hz, 1 H), 7.03 (dd, *J* = 10.9, 6.6 Hz, 1 H), 6.85 (dd, *J* = 9.8, 7.0 Hz, 1 H), 5.08 (s, 2 H), 3.66 (s, 2 H), 2.80 (d, *J* = 11.6 Hz, 2 H), 2.70 (tt, *J* = 9.6, 4.5 Hz, 1 H), 2.25 (s, 3 H), 2.01 (t, *J* = 11.0 Hz, 2 H), 1.85 (dd, *J* = 12.6, 1.2 Hz, 2 H), 1.46-1.39 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0 (app d, J_{CF} = 248.9 Hz), 154.5, 151.4, 150.3, 148.1 (dd, J_{CF} = 243.8, 2.7 Hz), 147.9, 145.7 (dd, J_{CF} = 12.9, 9.9 Hz), 135.0, 129.8, 124.2, 119.7 (d, J_{CF} = 21.7 Hz), 105.0 (dd, J_{CF} = 18.5, 9.0 Hz), 103.7 (d, J_{CF} = 27.5 Hz), 93.2 (d, J_{CF} = 3.5 Hz), 75.3, 61.2, 54.3, 52.9, 46.2, 45.4 (t, J_{CD} = 22.3 Hz), 36.1, 33.2-32.7 (m), 32.3, 23.7-23.2 (m); ^{19}F NMR (470 MHz, $CDCl_3$) δ -112.1 (d, *J* = 14.1 Hz), -138.8 (d, *J* = 14.1 Hz); HRMS (ESI^+): *m/z* calculated for $C_{28}H_{24}{}^2H_9ON_6F_2S$ (M+H) 548.2964, found 548.2962; ELS purity (100%).



3-113

***N*-(3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl)propionamide (3-113).** To a solution of **3-106** (0.040 g, 0.080 mmol) in DMF (0.9 mL) was added propionic acid (6.6 µL, 0.088 mmol) and DiPEA (28 µL, 0.16 mmol) followed by HOBt (0.014 g, 0.10 mmol) and EDC (0.021 g, 0.10 mmol). The reaction was stirred at room temperature for 15.5 h. The reaction was diluted with CH_2Cl_2 and

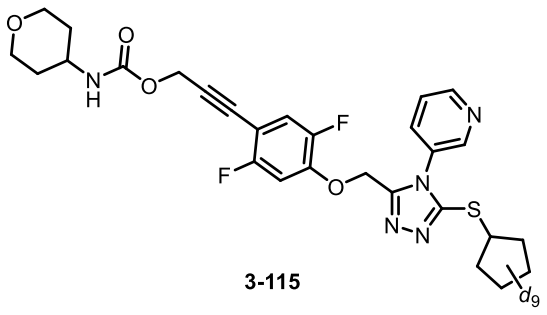
washed with water (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0) followed by filtration through a plug of basic Al_2O_3 (MeOH/$CDCl_3$: 0/100 to 3/97). Product **3-113** was obtained as a white solid (0.030 g, 74%): m.p. 122.9 - 131.2 °C; IR (neat) 3274, 3056, 2917, 2228, 1659, 1630, 1509, 1449, 1273, 1225, 1179, 999, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.63 (dd, *J* = 2.6, 0.5 Hz, 1 H), 7.74 (ddd, *J* = 8.2, 2.6, 1.5 Hz, 1 H), 7.49 (ddd, *J* = 8.1, 4.8, 0.7 Hz, 1 H), 7.05 (dd, *J* = 10.8, 6.5 Hz, 1 H), 6.86 (dd, *J* = 9.9, 7.0 Hz, 1 H), 5.81 (s, 1 H), 5.10 (s, 2 H), 4.28 (d, *J* = 5.2 Hz, 2 H), 2.25 (q, *J* = 7.6 Hz, 2 H), 1.17 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 159.1 (dd, *J* = 249.5, 2.1 Hz), 154.7, 151.5, 150.3, 148.1 (dd, *J* = 244.4, 3.4 Hz), 147.9, 146.2 (dd, *J* = 12.8, 9.9 Hz), 135.1, 129.8, 124.3, 119.9 (dd, *J* = 21.5, 2.9 Hz), 104.3 (dd, *J* = 18.3, 8.5 Hz), 103.6 (d, *J* = 28.5 Hz), 90.5 (d, *J* = 3.6 Hz), 75.2 (d, *J* = 1.9 Hz), 61.2, 45.5 (t, *J* = 21.9 Hz), 33.3-32.7 (m), 30.0, 29.5, 23.9-23.2 (m), 9.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ -111.8 (d, *J* = 14.2 Hz), -138.5 (d, *J* = 14.0 Hz); HRMS (ESI^+): *m/z* calculated for $C_{25}H_{17}{}^2H_9O_2N_5F_2S$ (M+H) 507.2335, found 507.2328; ELS purity (100%).



3-114

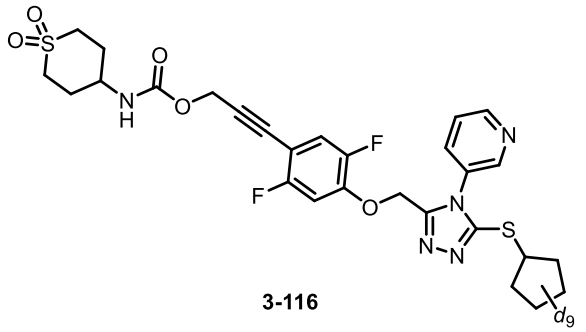
3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,6-difluorophenyl)prop-2-yn-1-yl methylcarbamate (3-114). To a solution of 3-(4-((5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,6-difluorophenyl)prop-2-yn-1-

ol (0.10 g, 0.22 mmol) in dry CH_2Cl_2 (2.5 mL) was added CDI (0.054 g, 0.33 mmol) was added and the mixture was stirred at room temperature for 4 h. Et_3N (0.14 mL, 0.97 mmol) was added followed by methylamine hydrochloride (0.065 g, 0.97 mmol) were added and the reaction was stirred 16 h at room temperature. The reaction solution was diluted with CH_2Cl_2 and extracted with water. The organic phase was dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **3-114** was obtained as a white foam (0.11 g, 95%): IR (neat) 3342, 3055, 2940, 1720, 1635, 1503, 1445, 1253, 1148, 1027, 997, 828, 752, 708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.71 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.55 (d, *J* = 2.6 Hz, 1 H), 7.66 (ddd, *J* = 8.1, 2.6, 1.5 Hz, 1 H), 7.46 (dd, *J* = 8.0, 4.8 Hz, 1 H), 6.44-6.40 (m, 2 H), 5.80 (dtd, *J* = 9.3, 3.7, 1.4 Hz, 1 H), 5.70-5.63 (m, 1 H), 5.25 (d, *J* = 4.8 Hz, 1 H), 5.05-5.00 (m, 2 H), 4.85 (s, 2 H), 4.49 (dd, *J* = 4.5, 2.1 Hz, 1 H), 2.74 (d, *J* = 4.9 Hz, 3 H), 2.05-1.89 (m, 4 H), 1.70-1.55 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8 (dd, J_{CF} = 253.4, 8.1 Hz), 158.6 (t, J_{CF} = 13.6 Hz), 156.2, 153.8, 151.4, 150.4, 147.9, 134.7, 132.4, 129.8, 125.3 (d, J_{CF} = 3.2 Hz), 124.2, 99.2-97.6 (m, CF), 95.0 (t, J_{CF} = 20.3 Hz), 92.7, 72.7, 60.5, 53.0, 44.1, 29.2, 27.6, 24.8, 19.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ -105.3; HRMS (ESI^+): *m/z* calculated for $C_{25}H_{24}O_3N_5F_2S$ (M+H) 512.1562, found 512.1563; ELS purity (100%).



3-115

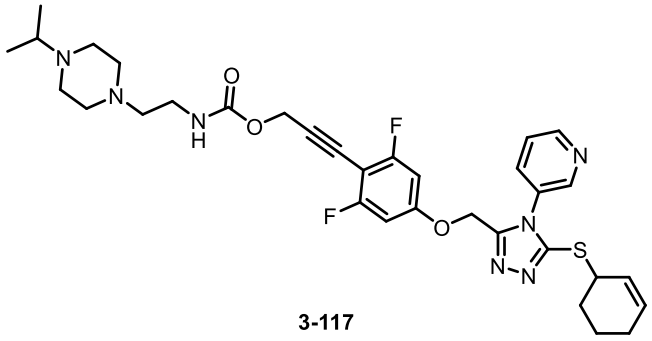
3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl (tetrahydro-2*H*-pyran-4-yl)carbamate (3-115). To a solution of **2-75** (0.070 g, 0.16 mmol) in dry CH_2Cl_2 (1.7 mL) was added CDI (0.038 g, 0.23 mmol) and the reaction stirred at room temperature under argon for 3 h. 4-Aminotetrahydropyran (0.048 mL, 0.47 mmol) was added and the reaction stirred at room temperature for about 22 h. The reaction was diluted with CH_2Cl_2 and washed with water and brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 10/90), then chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 5/95), then chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0), then chromatography on C18-SiO_2 (RP-ISCO, MeCN/H_2O: 5/95 to 95/5). Product **3-115** was obtained as a white foam (0.030 g, 33%): IR (neat) 3301, 2955, 2850, 1721, 1509, 1449, 1270, 1226, 1046, 1008, 709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.8, 1.3 Hz, 1 H), 8.62 (d, *J* = 2.3 Hz, 1 H), 7.73 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.49 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.07 (dd, *J* = 10.7, 6.5 Hz, 1 H), 6.88 (dd, *J* = 9.8, 7.0 Hz, 1 H), 5.10 (s, 2 H), 4.90-4.88 (m, 3 H), 3.93 (dt, *J* = 11.6, 3.4 Hz, 2 H), 3.74-3.68 (m, 1 H), 3.44 (td, *J* = 11.7, 2.0 Hz, 2 H), 1.91 (ddd, *J* = 12.5, 4.0, 1.8 Hz, 2 H), 1.52-1.42 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (d, J_{CF} = 250.6 Hz), 154.8, 154.7, 151.5, 150.2, 148.1 (dd, J_{CF} = 244.2, 3.3 Hz), 148.0, 146.6 (dd, J_{CF} = 12.7, 9.8 Hz), 135.1, 129.9, 124.3, 120.0 (dd, J_{CF} = 22.6, 1.7 Hz), 103.9 (dd, J_{CF} = 18.2, 8.4 Hz), 103.6 (dd, J_{CF} = 27.3, 1.5 Hz), 88.7 (d, J_{CF} = 3.4 Hz), 78.4 (d, J_{CF} = 2.0 Hz), 66.8, 61.2, 53.1, 47.6, 45.5 (t, J_{CD} = 21.7 Hz), 33.4, 33.1-32.7 (m), 23.8-23.2 (m); ^{19}F NMR (470 MHz, $CDCl_3$) δ -111.1 (d, *J* = 14.0 Hz), -138.5 (d, *J* = 14.0 Hz); HRMS (ESI$^+$): *m/z* calculated for $C_{28}H_{21}{}^2H_9O_4N_5F_2S$ (M+H) 579.2546, found 579.2544; ELS purity (100%).



3-116

3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl (1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)carbamate (3-116). To a solution of **2-75** (0.070 g, 0.16 mmol) in dry CH_2Cl_2 (1.7 mL) was added CDI (0.038 g, 0.23 mmol) and the reaction stirred at room temperature under argon for 3 h. 1,1-Dioxo-tetrahydrothiopyran-4-amine (0.069 g, 0.47 mmol) was added and the reaction stirred at room temperature for 17 h. LCMS showed mainly the acyl imidazole intermediate so Et_3N (1 eq., 22 µL, 0.15 mmol) was added and the reaction stirred at room temperature for 1 d. The reaction was diluted with CH_2Cl_2 and washed with water and brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0) then chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 5/95). Product **3-116** was obtained as a white foam (0.083 g, 85%): IR (neat) 3339, 3058, 2935, 2229, 1720, 1507, 1288, 1224, 1122, 1037, 1000, 849, 731, 705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.63 (dd, *J* = 2.5, 0.5 Hz, 1 H), 7.73 (ddd, *J* = 8.1, 2.6, 1.5 Hz, 1 H), 7.50 (ddd, *J* = 8.1, 4.8, 0.7 Hz, 1 H), 7.08 (dd, *J* = 10.7, 6.5 Hz, 1 H), 6.90 (dd, *J* = 9.8, 6.9 Hz, 1 H), 5.11 (s, 2 H), 4.90 (s, 3 H), 3.87-3.80 (m, *J* = 3.7 Hz, 1 H), 3.08 (t, *J* = 5.9 Hz, 4 H), 2.37-2.33 (m, 2 H), 2.19-2.11 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2 (dd, J_{CF} = 249.9, 2.1 Hz), 154.9, 154.7, 151.4, 150.2, 148.0 (dd, J_{CF} = 244.6, 3.1 Hz), 147.9, 146.6 (dd, J_{CF} = 12.7, 10.0 Hz), 135.0, 129.8, 124.3, 119.8 (dd, J_{CF} = 21.6, 2.4 Hz), 103.7 (d, J_{CF} = 26.4

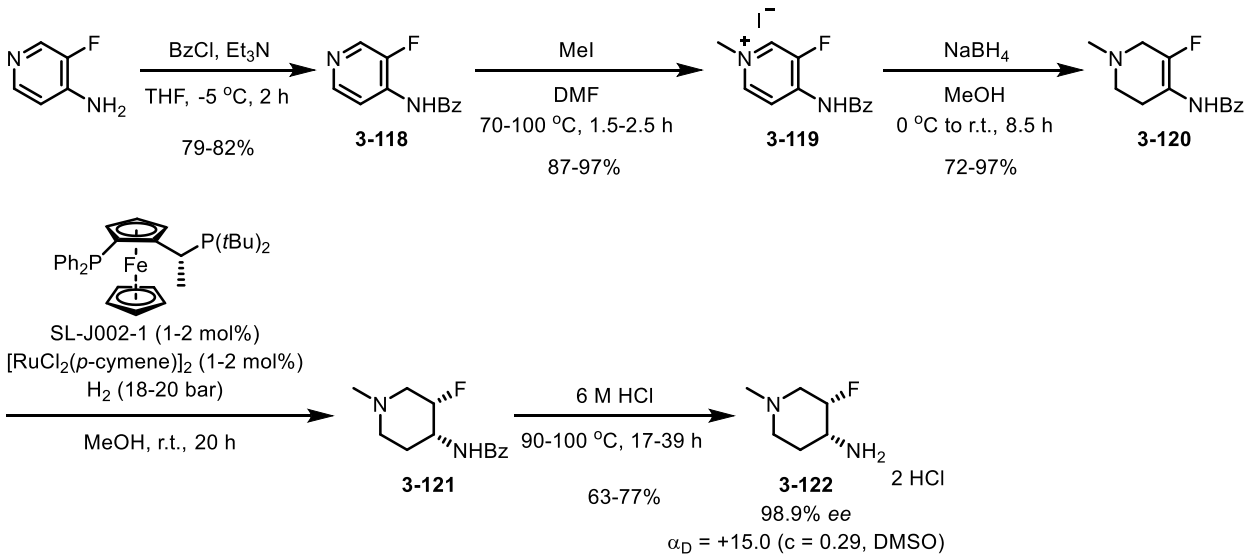
Hz), 103.6 (dd, J_{CF} = 17.9, 8.4 Hz), 88.5 (d, J_{CF} = 3.3 Hz), 78.5, 61.1, 53.3, 49.2, 46.8, 45.4 (t, J_{CD} = 22.6 Hz), 32.8 (app t, J_{CD} = 20.1 Hz), 29.7, 23.5 (app t, J_{CD} = 19.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -111.4 (d, *J* = 14.0 Hz), -138.3 (d, *J* = 14.2 Hz); HRMS (ESI^+): *m/z* calculated for $C_{28}H_{21}{}^2H_9O_5N_5F_2S_2$ (M+H) 627.2216, found 627.2216; ELS purity (100%).



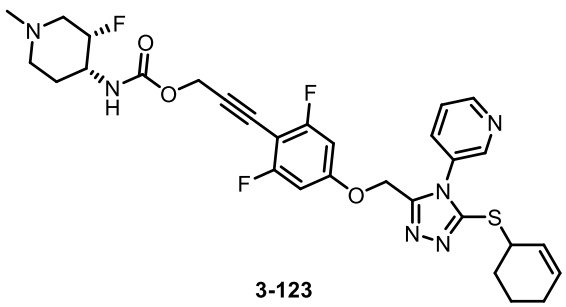
3-117

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,6-difluorophenyl)prop-2-yn-1-yl (2-(4-isopropylpiperazin-1-yl)ethyl)carbamate (3-117). To a solution of 3-(4-((5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4H-1,2,4-triazol-3-yl)methoxy)-2,6-difluorophenyl)prop-2-yn-1-ol (0.10 g, 0.22 mmol) in CH_2Cl_2 (2 mL) was added CDI (0.054 g, 0.33 mmol) and the reaction stirred at room temperature for 4 h. A solution of 2-(4-isopropylpiperazin-1-yl)ethan-1-amine (0.11 g, 0.66 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction stirred 16 h at room temperature. The reaction was diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated onto C18-SiO_2. The product was purified by chromatography on C18-SiO_2 (RP-ISCO, MeCN/H_2O: 5/95 to 96/5). Product **3-117** was obtained as a pale yellow foam (0.11 g, 74%): IR (neat) 3256, 2936, 2814, 1719, 1635, 1504, 1445, 1253, 1145, 1036, 829, 752, 708 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.9, 1.5 Hz, 1 H), 8.59 (d, *J* = 2.5 Hz, 1 H), 7.66 (dt, *J* = 8.2, 2.1 Hz, 1 H), 7.49 (dd, *J* = 8.1, 4.8 Hz, 1 H), 6.52-6.44 (m, 2 H), 5.87 (dtd, *J* = 9.5, 3.8, 1.3 Hz, 1 H), 5.74

(ddd, J = 10.0, 4.4, 2.2 Hz, 1 H), 5.41 (t, J = 5.3 Hz, 1 H), 5.08-5.01 (m, 2 H), 4.92 (s, 2 H), 4.58 (qd, J = 4.3, 3.0, 2.3 Hz, 1 H), 3.28 (q, J = 5.7 Hz, 2 H), 2.62 (p, J = 6.5 Hz, 1 H), 2.57-2.40 (m, 9 H), 2.14-1.91 (m, 5 H), 1.76-1.63 (m, 2 H), 1.03 (d, J = 6.4 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8 (dd, J_{CF} = 253.5, 8.1 Hz), 158.6 (t, J_{CF} = 13.6 Hz), 155.4, 153.8, 151.3, 150.4, 147.9, 134.6, 132.4, 129.8, 125.3, 124.1, 99.2-98.5 (m), 95.1 (t, J_{CF} = 20.0 Hz), 92.6, 77.4, 77.2, 76.9, 72.8, 60.4, 56.8, 54.3, 53.2, 53.0, 48.6, 44.1, 37.7, 29.2, 24.8, 19.1, 18.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ -105.2; HRMS (ESI^+): *m/z* calculated for $C_{33}H_{40}O_3N_7F_2S$ (M+H) 652.2876, found 652.2879; ELS purity (100%).



Scheme 3-25. Synthesis of (3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-amine building block.



3-123

***N*-(3-Fluoropyridin-4-yl)benzamide (3-118)**[153]**.** To a solution of 3-fluoro-4-aminopyridine (2.00 g, 17.8 mmol) in THF (22 mL) under N_2 at -5 °C was added Et_3N (5.01 mL, 35.7 mmol) followed by benzoyl chloride (2.38 mL, 20.5 mmol) dropwise. The reaction was stirred for 2 h and filtered. The filter was washed with THF and then the filtrated was concentrated. The residue was dissolved in boiling EtOAc (8 mL) and hexanes (2.6 mL) and cooled to 0 °C. The solid was filtered off and dried under vacuum. The pyridine **3-118** was obtained as an off-white solid (3.17 g, 82%), data matches that reported in the literature: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dd, *J* = 6.7, 5.4 Hz, 1 H), 8.46 (d, *J* = 2.4 Hz, 1 H), 8.39 (d, *J* = 5.4 Hz, 1 H), 8.28 (bs, 1 H), 7.89 (dd, *J* = 7.2, 1.7 Hz, 2 H), 7.66-7.57 (m, 1 H), 7.53 (dd, *J* = 8.4, 6.9 Hz, 2 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -147.0; HRMS (ESI^+): *m/z* calculated for $C_{12}H_{10}ON_2F$ (M+H) 217.0772, found 217.0769.

4-Benzamido-3-fluoro-1-methylpyridin-1-ium iodide (3-119)[153]**.** To a solution of *N*-(3-fluoropyridin-4-yl)benzamide (6.00 g, 27.8 mmol) in dry DMF (30.6 mL) at 70 °C. Iodomethane (1.90 mL, 30.5 mmol) was then added dropwise and the reaction heated to 100 °C for 2.25 h. The reaction was cooled to room temperature and poured into cold EtOAc (150 mL). After 1 h the precipitate was filtered and washed with EtOAc (3x). The solid was dried under vacuum 16 h and the pyridinium salt **3-119** was obtained as a pale yellow solid (9.50 g, 96%): IR (neat) 3210, 3155, 3126, 3020, 1695, 1598, 1519, 1475, 1331, 1309, 1264, 1149, 1087, 1074, 977, 905, 847, 717 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.32 (s, 1 H), 9.34 (dd, *J* = 6.2, 1.7 Hz, 1 H), 8.80 (d, *J* = 7.0 Hz, 1 H), 8.69 (t, *J* = 7.3 Hz, 1 H), 8.02-7.93 (m, 2 H), 7.74-7.66 (m, 1 H), 7.59 (t, *J* = 7.7 Hz, 2 H), 4.27 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 149.7 (d, J_{CF} = 252.0 Hz), 143.7, 141.8 (d, J_{CF} = 8.9 Hz), 135.5 (d, J_{CF} = 36.1 Hz), 133.7, 133.1, 129.3, 129.1 118.1 (d, J_{CF}

= 3.2 Hz), 47.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -125.3; HRMS (ESI^+): *m/z* calculated for $C_{13}H_{12}ON_2F$ (M+H) 231.0928, found 231.0928.

***N*-(5-Fluoro-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)benzamide** (**3-120**)[153]**.** To a solution of 4-benzamido-3-fluoro-1-methylpyridin-1-ium iodide (5.20 g, 14.5 mmol) in MeOH (33.5 mL) at 0 °C was added $NaBH_4$ (1.38 g, 36.3 mmol) portion-wise over 30 min. After stirring for 3 h, the remaining $NaBH_4$ (1.38 g, 36.3 mmol) was added and the reaction stirred for 5.5 h. The reaction was quenched with sat. NH_4Cl (8.4 mL) and stirred for 10 min. Sat. $NaHCO_3$ (10 mL) was added, stirred for 2 h, and the volume reduced. The aqueous was extracted with EtOAc (3x). The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The 1,2,3,6-tetrahydropyridine **3-120** was obtained as a pale yellow solid (3.29 g, 97%): IR (neat) 3438, 3260, 2792, 2385, 1741, 1653, 1529, 1491, 1293, 1084, 881, 799, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.74 (m, 2 H), 7.54-7.49 (m, 2 H), 7.46-7.41 (m, 2 H), 3.19 (app s, 3 H), 2.96-2.86 (m, 2 H), 2.66 (t, *J* = 5.7 Hz, 2 H), 2.43 (d, *J* = 0.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 144.4 (d, J_{CF} = 250.9 Hz), 134.4, 131.9, 128.7, 127.2, 113.9 (d, J_{CF} = 5.1 Hz), 52.6 (d, J_{CF} = 28.9 Hz), 51.7, 45.0, 25.4; HRMS (ESI^+): *m/z* calculated for $C_{13}H_{16}ON_2F$ (M+H) 235.1241, found 235.1240.

***N*-((3*S*,4*R*)-3-Fluoro-1-methylpiperidin-4-yl)benzamide** (**3-121**)[153]**.** Catalyst Preparation:

A dry 20 mL vial was charged with $[RuCl_2(p\text{-cymene})]_2$ (0.032 g, 0.053 mmol) and SL-J002-1 (0.32 g, 0.055 mmol) and the vial vacuum purged and flushed with argon (3x). The solid was dissolved in dry, deoxygenated MeOH (0.9 mL) and stirred at 40 °C for 45 min then cooled to room temperature.

Reaction:

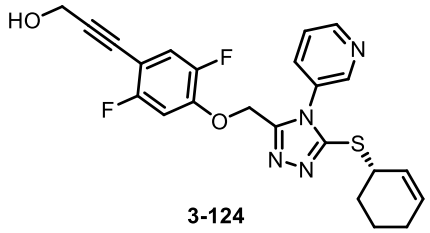
A solution of *N*-(5-fluoro-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)benzamide (0.62 g, 2.6 mmol) in dry deoxygenated MeOH (2.4 mL) was added to the catalyst mixture prepared above. The vial was then transferred into an argon purged Parr vessel and uncapped under nitrogen. The vessel was sealed and purged with argon (2x) and then H_2 (2x). The reaction was pressurized to 18 bar and stirred at room temperature for 20 h. The solution was sparged with N_2 for 10 min, filtered through SiO_2 gel layered over Celite (1:5 SiO_2:Celite), and the plug was washed with MeOH/CH_2Cl_2 (10%, 20 mL). The solvent was removed under vacuum and the piperidine **3-121** was obtained as a brown solid (0.65 g) and carried on without further purification or characterization: 98.9% *ee* (CHIRALPAK® AD-H, 10:90 *i*PrOH:Hexanes, 0.1% DEA, 1 mL/min); $[\alpha]_D$ crude = +6 (c = 0.38, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.1 Hz, 1 H), 7.51 (t, *J* = 7.4 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 1 H), 6.37 (d, *J* = 8.7 Hz, 1 H), 4.79 (d, *J* = 49.6 Hz, 1 H), 4.27-4.13 (m, 1 H), 3.23 (ddt, *J* = 13.2, 10.3, 2.8 Hz, 1 H), 2.94 (dt, *J* = 12.1, 2.5 Hz, 1 H), 2.33 (s, 3 H), 2.32-2.21 (m, 1 H), 2.21-2.12 (m, 1 H), 2.03-1.86 (m, 2 H); ^{19}F NMR (471 MHz, $CDCl_3$) δ -200.8; HRMS (ESI^+): *m/z* calculated for $C_{13}H_{18}ON_2F$ (M+H) 237.1398, found 237.1398.

(3*S*,4*R*)-3-Fluoro-1-methylpiperidin-4-amine dihydrochloride (**3-122**)[153]**.** Aqueous HCl (6 M, 1.0 mL) and *N*-((3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-yl)benzamide (0.10 g, 6.0 mmol) were added to a 5 mL round bottom, fitted with a condenser, and connected to a sodium hydroxide scrubber. The reaction was heated to 90 °C 16 h, LCMS showed remaining benzamide starting material, so the reaction was heated to reflux for 20 h then allowed to cool to room temperature. The reaction was filtered and the solid washed with water. The filtrate was concentrated and azeotroped with ethanol (3x). The product was recrystallized from hot ethanol and the crystals washed with cold ethanol and Et_2O. The piperidine **3-122** was obtained as a tan crystalline solid

(0.087 g, 63%): $[\alpha]_D$ = +15 (c = 0.29, DMSO); IR (neat) 3376, 2982, 2818, 2557, 2064, 1601, 1533, 1464, 1398, 1248, 1171, 1053, 978, 949, 879 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 5.23 (d, *J* = 47.2 Hz, 1 H), 3.98 (t, *J* = 12.4 Hz, 1 H), 3.71 (t, *J* = 8.7 Hz, 1 H), 3.62 (dd, *J* = 15.0, 10.0 Hz, 2 H), 3.50 (dd, *J* = 39.7, 14.7 Hz, 1 H), 3.27 (s, 1 H), 2.95 (s, 3 H), 2.23 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 85.6 (d, J_{CF} = 177.2 Hz), 54.2 (d, J_{CF} = 19.8 Hz), 51.6, 46.8 (d, J_{CF} = 18.2 Hz), 43.4, 22.4; ^{19}F NMR (470 MHz, CD_3OD) δ -205.4; HRMS (ESI^+): *m/z* calculated for $C_6H_{14}N_2F$ (M+H) 133.1136, found 133.1136.

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,6-difluorophenyl)prop-2-yn-1-yl ((3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-yl)carbamate (3-123). To a solution of 3-(4-((5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,6-difluorophenyl)prop-2-yn-1-ol (0.06 g, 0.13 mmol) in dry CH_2Cl_2 (2 mL) was added CDI (0.032 g, 0.20 mmol) and the mixture was stirred at room temperature for 4 h. Et_3N (0.12 mL, 0.86 mmol) followed by (3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-amine dihydrochloride (0.081 g, 0.40 mmol) were added and the reaction was stirred for about 2 d at room temperature. The reaction was concentrated directly onto C18-SiO_2 and the product was purified by chromatography on C18-SiO_2 (RP-ISCO, MeCN/H_2O: 5/95 to 95/5). Product **3-123** was obtained as a pale yellow foam (0.036 g, 44%): $[\alpha]_D$ = +20 (c = 0.5135, MeOH); IR (CH_2Cl_2) 3227, 2941, 2793, 2242, 1717, 1635, 1504, 1445, 1254, 1150, 1046, 1028, 910, 831, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.59 (d, *J* = 2.3 Hz, 1 H), 7.66 (ddd, *J* = 8.2, 2.6, 1.6 Hz, 1 H), 7.48 (dd, *J* = 8.1, 4.8 Hz, 1 H), 6.47 (d, *J* = 8.5 Hz, 2 H), 5.86 (ddt, *J* = 9.0, 3.7, 1.8 Hz, 1 H), 5.77-5.68 (m, 1 H), 5.29 (d, *J* = 9.0 Hz, 1 H), 5.05 (s, 2 H), 4.91 (d, *J* = 1.5 Hz, 2 H), 4.68 (d, *J* = 49.6 Hz, 1 H), 4.57 (dd, *J* = 4.3, 2.0 Hz, 1 H), 3.76-3.57 (m, 1 H), 3.20-3.08 (m, 1 H), 2.86 (dd, *J* = 11.4, 2.8 Hz, 1 H), 2.27 (s, 3 H), 2.17 (dd, *J* = 38.1, 13.2

Hz, 1 H), 2.14 – 1.94 (m, 5 H), 1.93-1.73 (m, 2 H), 1.77-1.58 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (dd, J_{CF} = 253.6, 8.1 Hz), 158.6 (t, J_{CF} = 13.6 Hz), 154.9, 153.9, 151.4, 150.3, 147.9, 134.7, 132.5, 129.8, 125.3, 124.2, 98.9 (d, J_{CF} = 27.3 Hz), 95.1 (t, J_{CF} = 20.1 Hz), 92.2, 88.4 (d, J_{CF} = 176.2 Hz), 73.1, 60.4, 58.0 (d, J_{CF} = 18.6 Hz), 53.9, 53.4, 49.9 (d, J_{CF} = 17.9 Hz), 45.8, 44.1, 29.2, 27.2, 24.8, 19.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ -105, -201; HRMS (ESI$^+$): *m/z* calculated for $C_{30}H_{32}O_3N_6F_3S$ (M+H) 613.2203, found 613.2204; ELS purity (100%).

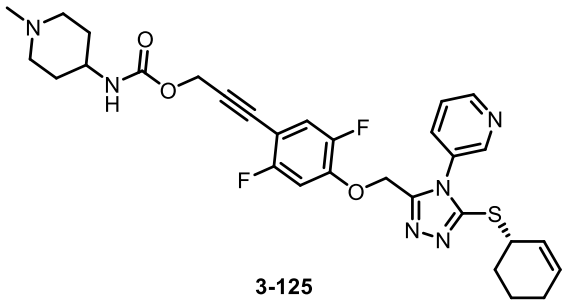


3-124

(*S*)-(-)-3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-ol (3-124)[xiv]**.** To the crude mixture of (*S*)-(5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and (*S*)-3-(3-(chloromethyl)-5-(cyclohex-2-en-1-ylthio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.13 g, 0.35 mmol) in DMF (5.5 mL) was added 2,5-difluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol (0.070 g, 0.38 mmol) and Cs_2CO_3 (0.12 g, 0.38 mmol) and the reaction stirred at room temperature for 13 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes:

[xiv] Enantiomerically pure (*S*)-(5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methanol was obtained from Albany Molecular Research Inc. (AMRI): $[\alpha]_D$ = -164 (c = 0.375, MeOH), which was converted to the mesylate and chloride mixture via the standard procedure used for the racemic compound.

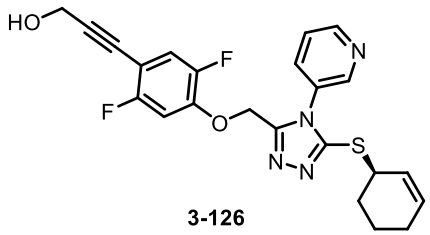
0/100 to 100/0). Product **3-124** was obtained as a white solid (0.150 g, 95%): $[\alpha]_D$ = -116 (c = 0.1975, CH_2Cl_2); m.p. 163-164 °C; IR (CH_2Cl_2) 3186, 2926, 2851, 1627, 1513, 1451, 1421, 1340, 1225, 1176, 1038, 1002, 847, 752, 708 cm^{-1}; ^1H NMR (400 MHz, $CD_3OD/CDCl_3$) δ 8.74 (dd, *J* = 4.8, 0.9 Hz, 1 H), 8.67 (d, *J* = 2.2 Hz, 1 H), 7.98 (ddd, *J* = 8.2, 2.3, 1.5 Hz, 1 H), 7.65 (dd, *J* = 8.2, 4.9 Hz, 1 H), 7.16 (dd, *J* = 11.0, 6.6 Hz, 1 H), 7.06 (dd, *J* = 10.3, 7.1 Hz, 1 H), 5.90 (dtd, *J* = 9.8, 3.9, 1.4 Hz, 1 H), 5.68 (ddt, *J* = 9.7, 4.2, 2.2 Hz, 1 H), 5.25 (s, 2 H), 4.38 (s, 2 H), 4.37-4.35 (m, 1 H), 2.09-2.00 (m, 3 H), 1.96-1.89 (m, *J* = 3.5 Hz, 1 H), 1.78-1.63 (m, 2 H); ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$) δ 160.1 (dd, J_{CF} = 246.6, 2.8 Hz), 154.8, 152.4, 152.0, 149.2 (dd, J_{CF} = 241.9, 3.3 Hz), 148.8, 147.3 (dd, J_{CF} = 13.1, 9.9 Hz), 137.1, 133.6, 131.2, 126.0, 125.8, 120.5 (dd, J_{CF} = 21.4, 2.9 Hz), 105.5 (dd, J_{CF} = 18.2, 7.9 Hz), 104.7 (d, J_{CF} = 1.8 Hz), 104.5 (d, J_{CF} = 1.7 Hz), 93.9 (d, J_{CF} = 3.2 Hz), 77.2 (d, J_{CF} = 2.0 Hz), 62.1, 51.0, 45.5, 30.1, 25.6, 19.8; ^{19}F NMR (376 MHz, $CD_3OD/CDCl_3$) δ -113.6 (d, *J* = 14.2 Hz), -140.2 (d, *J* = 14.7 Hz); HRMS (ESI^+): *m/z* calculated for $C_{23}H_{21}O_2N_4F_2S$ (M+H) 455.1348, found 455.1348; ELS purity (100%).



3-125

(*S*)-(-)-3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl (1-methylpiperidin-4-yl)carbamate (3-125). To a solution of **3-124** (0.13 g, 0.28 mmol) in CH_2Cl_2 (3.1 mL) was added (0.067 g, 0.41 mmol) and the reaction stirred at room temperature for 4 h. 4-Amino-1-methylpiperidine (0.10 mL, 0.83 mmol) was

added and the reaction stirred at room temperature for 1.5 d. The reaction was diluted with CH_2Cl_2 and washed with water and brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 15/85) followed by filtration through a plug of basic Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 5/95) (2x). Product **3-125** was obtained as a white foam (0.148 g, 90%): $[\alpha]_D$ = -87 (c = 0.2025, CH_2Cl_2); IR (neat) 3288, 2939, 2788, 1713, 1629, 1506, 1447, 1271, 1225, 1179, 1044, 1003, 727, 707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.56 (d, *J* = 2.3 Hz, 1 H), 7.69 (ddd, *J* = 8.1, 2.5, 1.6 Hz, 1 H), 7.42 (ddd, *J* = 8.1, 4.8, 0.5 Hz, 1 H), 6.98 (dd, *J* = 10.7, 6.4 Hz, 1 H), 6.81 (dd, *J* = 9.7, 7.0 Hz, 1 H), 5.79 (dtd, *J* = 9.7, 3.8, 1.3 Hz, 1 H), 5.67-5.64 (m, 1 H), 5.26 (d, *J* = 7.8 Hz, 1 H), 5.08-5.03 (m, 2 H), 4.79 (s, 2 H), 4.48 (dd, *J* = 3.9, 1.6 Hz, 1 H), 3.46-3.39 (m, 1 H), 2.68 (d, *J* = 10.3 Hz, 2 H), 2.17 (s, 3 H), 2.04-1.89 (m, 6 H), 1.86 (dd, *J* = 12.7, 3.0 Hz, 2 H), 1.68-1.55 (m, *J* = 7.9, 7.7, 7.3, 4.1 Hz, 2 H), 1.45-1.38 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1 (dd, J_{CF} = 250.2, 2.0 Hz), 154.7, 153.9, 151.3, 150.3, 147.9 (dd, J_{CF} = 244.3, 3.3 Hz), 147.8, 146.3 (dd, J_{CF} = 12.7, 10.0 Hz), 134.9, 132.4, 129.6, 125.2, 124.1, 119.8 (dd, J_{CF} = 21.5, 2.1 Hz), 103.8 (dd, J_{CF} = 18.2, 8.3 Hz), 103.5 (d, J_{CF} = 27.4 Hz), 88.8 (d, J_{CF} = 3.5 Hz), 78.0 (d, J_{CF} = 1.6 Hz), 61.1, 54.3, 52.8, 47.9, 46.1, 44.0, 32.3, 29.1, 24.7, 19.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ -111.3 (d, *J* = 14.0 Hz), -138.6 (d, *J* = 14.1 Hz); HRMS (ESI^+): *m/z* calculated for $C_{30}H_{33}O_3N_6F_2S$ (M+H) 595.2297, found 595.2298; ELS purity (100%).



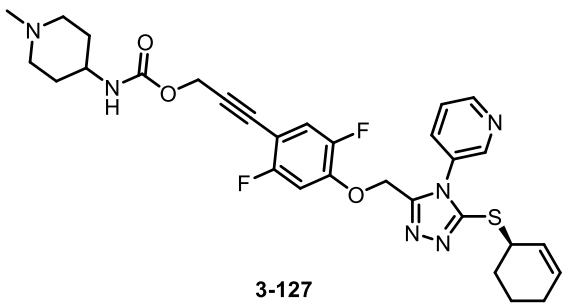
3-126

(*R*)-(5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate. To a solution of (*R*)-(5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methanol[xv] (0.14 g, 0.49 mmol) in CH_2Cl_2 (2.8 mL) at 0 °C was added DiPEA (0.16 mL, 0.94 mmol) and MsCl (63 µL, 0.82 mmol) dropwise. The reaction was stirred at 0 °C and slowly warmed to room temperature over 70 min. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, and sat. NH_4Cl, dried ($MgSO_4$), filtered, and concentrated. The crude triazole was carried on without purification or characterization: HRMS (ESI^+): *m/z* calculated for $C_{15}H_{19}O_3N_4S_2$ (M+H) 367.0893, found 367.0890.

(*R*)-3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-ol (3-126)[xvi]. To a solution of crude (*R*)-(5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate (0.718 g, 1096 mmol) in DMF (31 mL) was added 2,5-difluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol (0.433 g, 2.35 mmol) and Cs_2CO_3 (0.766 g, 2.35 mmol) and the reaction stirred for 20 h at room temperature. The reaction was then diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated. Product **3-126** was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The product was obtained as a pale-yellow solid (0.725 g, 81%): $[\alpha]_D$ = +117 (c = 0.63, CH_2Cl_2); HRMS (ESI^+): *m/z* calculated for $C_{23}H_{21}O_2N_4F_2S$ (M+H) 455.1348, found 455.1347.

[xv] Enantiomerically pure (*R*)-(5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methanol was obtained from Albany Molecular Research Inc. (AMRI).

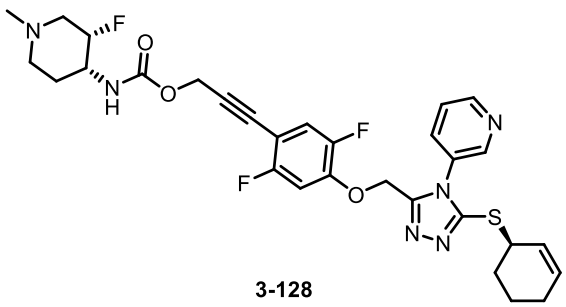
[xvi] Full characterization by Matthew LaPorte; described batch not biologically tested



3-127

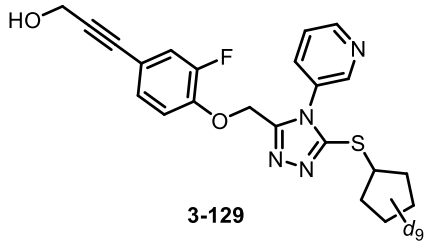
(*R*)-3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl (1-methylpiperidin-4-yl)carbamate (3-127) [xvii]**.** To a solution of **3-126** (0.62 g, 1.4 mmol) in dry CH_2Cl_2 (17.9 mL) was added CDI (0.33 g, 0.20 mmol) and the mixture was stirred at room temperature for 3 h. 4-Amino-1-methylpiperidine (0.51 mL, 4.1 mmol) was added and the reaction was stirred for 19 h at room temperature. The reaction solution was concentrated directly onto C18-SiO_2 and the product was purified by chromatography on C18-SiO_2 (RP-ISCO, MeCN/H_2O: 5/95 to 95/5). Product **3-127** was obtained as a white foam (0.50 g, 61%): $[\alpha]_D$ = +84 (c = 0.485, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.8, 1.5 Hz, 1 H), 8.63 (dd, *J* = 2.5, 0.7 Hz, 1 H), 7.73 (ddd, *J* = 8.2, 2.6, 1.5 Hz, 1 H), 7.49 (ddd, *J* = 8.2, 4.8, 0.8 Hz, 1 H), 7.09 (dd, *J* = 10.7, 6.4 Hz, 1 H), 6.87 (dd, *J* = 9.8, 6.9 Hz, 1 H), 5.88 (dtd, *J* = 8.9, 3.7, 1.4 Hz, 1 H), 5.75 (ddd, *J* = 10.2, 4.5, 2.2 Hz, 1 H), 5.14-5.07 (m, 2 H), 4.88 (s, 2 H), 4.73 (d, *J* = 7.9 Hz, 1 H), 4.62-4.57 (m, 1 H), 3.58-3.47 (m, 1 H), 2.75 (d, *J* = 10.3 Hz, 2 H), 2.27 (s, 3 H), 2.14-1.99 (m, 5 H), 1.99-1.92 (m, 2 H), 1.83 (bs, 1 H), 1.79-1.62 (m, 2 H), 1.48 (qd, *J* = 11.1, 3.8 Hz, 2 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -111.1 (d, J_{CF} = 14.0 Hz), -138.5 (d, J_{CF} = 14.0 Hz); HRMS (ESI^+): *m/z* calculated for $C_{30}H_{33}O_3N_6F_2S$ (M+H) 595.2297, found 595.2294; ELS purity (100%).

[xvii] Full characterization by Matthew LaPorte.



3-128

3-(4-((5-(((*R*)-Cyclohex-2-en-1-yl)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-2,5-difluorophenyl)prop-2-yn-1-yl ((3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-yl)carbamate (3-128). To a solution of **3-126** (0.050 g, 0.11 mmol) in dry CH_2Cl_2 (1.4 mL) was added CDI (0.027 g, 0.17 mmol) was added and the mixture was stirred at room temperature for 3 h. Et_3N (0.085 mL, 0.61 mmol) and (3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-amine dihydrochloride (0.056 g, 0.28 mmol) were added and the reaction was stirred for 19 h at room temperature. LCMS showed remaining starting material, additional Et_3N (0.017 mL, 0.12 mmol) and (3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-amine dihydrochloride (0.015 g, 0.074 mmol) were added and stirred for 28 h. The reaction solution was concentrated directly onto C18-SiO_2 and the product was purified by chromatography on C18-SiO_2 (RP-ISCO, MeCN/H_2O: 5/95 to 95/5). Product **3-128** was obtained as a pale yellow foam (0.047 g, 69%): $[\alpha]_D$ = +100 (c = 0.4075, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.9, 1.5 Hz, 1 H), 8.63 (d, *J* = 2.5 Hz, 1 H), 7.73 (ddd, *J* = 8.1, 2.6, 1.5 Hz, 1 H), 7.49 (dd, *J* = 8.1, 4.8 Hz, 1 H), 7.10 (dd, *J* = 10.7, 6.4 Hz, 1 H), 6.88 (dd, *J* = 9.8, 6.8 Hz, 1 H), 5.92-5.85 (m, 1 H), 5.75 (ddd, *J* = 9.8, 4.1, 2.1 Hz, 1 H), 5.15-5.07 (m, 3 H), 4.90 (s, 2 H), 4.70 (d, *J* = 49.4 Hz, 1 H), 4.62-4.58 (m, 1 H), 3.76-3.61 (m, 1 H), 3.16 (t, *J* = 11.7 Hz, 1 H), 2.88 (d, *J* = 11.7 Hz, 1 H), 2.30 (s, 3 H), 2.20 (dd, *J* = 38.2, 13.1 Hz, 1 H), 2.14-1.99 (m, 5 H), 1.93-1.79 (m, 2 H), 1.79-1.65 (m, 2 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -111.0 (d, J_{CF} = 14.1 Hz), -138.5 (d, J_{CF} = 14.0 Hz), -201.1; HRMS (ESI^+): *m/z* calculated for $C_{30}H_{32}O_3N_6F_3S$ (M+H) 613.2203, found 613.2202; ELS purity (100%).



3-129

4-Bromo-2-fluorophenyl pivalate. To a solution of 4-bromo-2-fluorophenol (0.500 g, 2.62 mmol) and Et_3N (0.405 mL, 2.88 mmol) in CH_2Cl_2 (5.1 mL) at 0 °C was added PivCl (0.354 mL, 2.88 mmol). The reaction was stirred at 0 °C for 50 min then diluted with Et_2O (10 mL) and filtered. The filtrate was concentrated and taken up in Et_2O (10 mL), filtered, and concentrated. The pivalate was obtained as a pink-brown oil (0.657 g, 91%) and carried on without further purification: IR ($CHCl_3$) 2976, 1761, 1595, 1493, 1481, 1261, 1187, 1092, 1064, 879, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, J = 9.5, 2.2 Hz, 1 H), 7.26 (ddd, J = 8.6, 2.2, 1.5 Hz, 1 H), 6.99 (t, J = 8.3 Hz, 1 H), 1.37 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 154.1 (d, J_{CF} = 253.8 Hz), 138.0 (d, J_{CF} = 12.9 Hz), 127.7 (d, J_{CF} = 3.7 Hz), 125.1 (d, J_{CF} = 1.3 Hz), 120.3 (d, J_{CF} = 21.9 Hz), 118.6 (d, J_{CF} = 8.5 Hz), 39.3, 27.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -125.5; HRMS (ESI^+): *m/z* calculated for $C_{11}H_{13}O_2BrF$ (M+H) 275.0078, found 275.0087.

2-Fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl pivalate. To a solution of 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (0.33 g, 2.4 mmol) and 4-bromo-2-fluorophenyl pivalate (0.50 g, 1.8 mmol) in deoxygenated Et_3N (1.4 mL) was added $Pd(PPh_3)_4$ (0.11 g, 0.091 mmol) and CuI (0.035 g, 0.18 mmol). The reaction was sparged with argon for 2 min then stirred at reflux for 18 h. The reaction was concentrated, and the residue taken up in Et_2O, washed with sat. NH_4Cl and brine, filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 0/100 to 10/90). The pivalate was obtained as a pale pink foam (0.32 g, 53%) and carried on without further characterization: ^1H NMR (500 MHz, $CDCl_3$) δ 7.25-7.21 (m, 2 H), 7.04 (t, J = 8.2 Hz, 1 H), 4.87 (t, J = 3.4 Hz, 1 H), 4.47 (q, J = 16.3 Hz, 2 H),

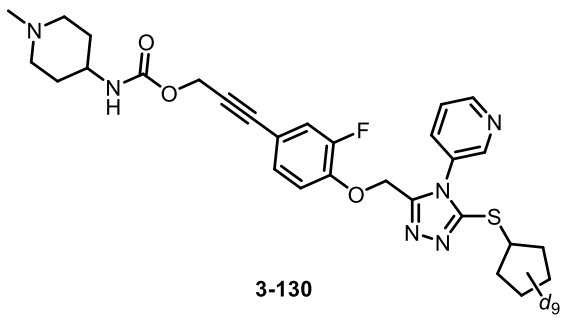
3.88 (ddd, *J* = 11.5, 9.0, 2.7 Hz, 1 H), 3.57 (dtd, *J* = 11.1, 4.3, 1.4 Hz, 1 H), 1.87-1.74 (m, 2 H), 1.69-1.53 (m, 4 H), 1.37 (s, 9 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -128.3; HRMS (ESI^+): *m/z* calculated for $C_{19}H_{24}O_4F$ (M+H) 335.1653, found 335.1671.

2-Fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol. To a solution of 2-fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl pivalate (0.320 g, 0.957 mmol) in THF (14 mL) and MeOH (14 mL) was added a solution of NaOH (1 M, 5.26 mL) dropwise and the reaction stirred at room temperature for 15 h. The reaction was concentrated and diluted with CH_2Cl_2. The solution was then neutralized to pH 7 with 2N HCl and the aqueous extracted with CH_2Cl_2 (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude phenol was obtained as a brown oil (0.253 g) and carried on without further purification or characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.12 (m, 2 H), 6.92 (t, *J* = 8.6 Hz, 1 H), 4.89 (bs, 1 H), 4.46 (q, *J* = 12.3 Hz, 2 H), 3.89 (app td, *J* = 10.0, 2.3 Hz, 1 H), 3.58 (app dt, *J* = 10.3, 4.7 Hz, 1 H), 1.87-1.54 (m, 7 H); HRMS (ESI^+): *m/z* calculated for $C_{14}H_{14}O_3F$ (M-H) 249.0921, found 249.0907.

2-Fluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol. To a solution of 2-fluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol (0.240 g, 0.957 mmol) in MeOH (5.9 mL) was added PPTS (0.120 g, 0.478 mmol) and the reaction stirred at room temperature for 2 d. The reaction was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The phenol was obtained as a pale pink-brown solid (0.0944 g, 59%): IR (acetone) 3477, 3301, 2930, 2225, 1619, 1593, 1516, 1383, 1297, 1246, 1112, 1009, 981, 865, 812, 781 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.14 (dd, *J* = 11.7, 1.9 Hz, 1 H), 7.08 (ddd, *J* = 8.3, 1.8, 0.9 Hz, 1 H), 6.97 (t, *J* = 8.7 Hz, 1 H), 4.39 (s, 2 H); ^{13}C NMR

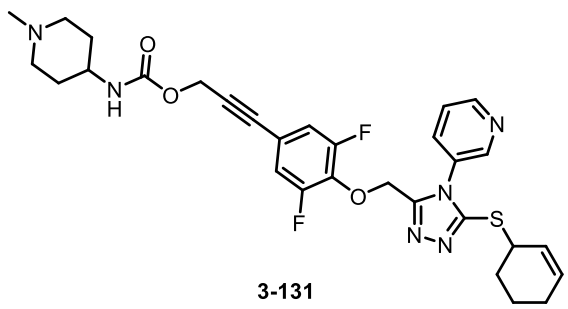
(125 MHz, acetone-d_6) δ 151.7 (d, J_{CF} = 241.5 Hz), 146.5 (d, J_{CF} = 12.8 Hz), 129.2 (d, J_{CF} = 2.9 Hz), 119.7 (d, J_{CF} = 19.9 Hz), 118.8 (d, J_{CF} = 3.3 Hz), 115.3 (d, J_{CF} = 7.7 Hz), 88.3, 83.8 (d, J_{CF} = 2.8 Hz), 51.0; ^{19}F NMR (470 MHz, acetone-d_6) δ -137.8; HRMS (ESI$^-$): *m/z* calculated for $C_9H_6O_2F$ (M-H) 165.0346, found 165.0339.

3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-3-fluorophenyl)prop-2-yn-1-ol (3-129). To a solution of crude 3-(3-(chloromethyl)-5-((cyclopentyl-d_9)thio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.069 g, 0.28 mmol) in dry DMF (3.6 mL) was added 2-fluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol (0.045 g, 0.27 mmol) and Cs_2CO_3 (0.089 g, 0.27 mmol) and the reaction stirred at room temperature for 14.5 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). Product **3-129** was obtained as a white foam (0.089 g, 90%): IR (neat) 3230, 2902, 2857, 2405, 2225, 1508, 1485, 1397, 1298, 1268, 1222, 1124, 1039, 999, 841, 710 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$/CD_3OD) δ 8.70 (dd, *J* = 4.9, 1.4 Hz, 1 H), 8.58 (d, *J* = 2.5 Hz, 1 H), 7.79 (ddd, *J* = 8.2, 2.5, 1.5 Hz, 1 H), 7.52 (ddd, *J* = 8.1, 4.9, 0.7 Hz, 1 H), 7.09-7.04 (m, 2 H), 6.95 (t, *J* = 8.5 Hz, 1 H), 5.08 (s, 2 H), 4.34 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD,) δ 153.9 (d, J_{CF} = 164.6 Hz), 151.1, 150.9, 150.6, 147.7, 145.3 (d, J_{CF} = 11.1 Hz), 135.6, 129.9, 128.3 (d, J_{CF} = 3.5 Hz), 124.6, 119.5 (d, J_{CF} = 19.5 Hz), 117.4 (d, J_{CF} = 8.2 Hz), 115.5 (d, J_{CF} = 1.3 Hz), 88.1, 83.0 (d, J_{CF} = 2.8 Hz), 60.9, 50.6, 45.5 (t, J_{CD} = 23.1 Hz), 33.2-32.4 (m, CD), 23.9-23.1 (m, CD); ^{19}F NMR (470 MHz, $CDCl_3$/CD_3OD) δ -133.3; HRMS (ESI$^+$): *m/z* calculated for $C_{22}H_{13}{}^2H_9O_2N_4FS$ (M+H) 434.2007, found 434.2004; ELS purity (100%).



3-130

3-(4-((5-((Cyclopentyl-*d*$_9$)thio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-3-fluorophenyl)prop-2-yn-1-yl (4-methylcyclohexyl)carbamate (3-130). To a solution of **3-129** (0.062 g, 0.14 mmol) in CH_2Cl_2 (1.6 mL) was added CDI (0.035 g, 0.21 mmol) and the reaction stirred at room temperature for 3 h. 4-Amino-1-methylpiperidine (53 µL, 0.43 mmol) was added and the reaction stirred at room temperature for about 2 d. The reaction was diluted with CH_2Cl_2 and washed with water and brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/CH_2Cl_2: 0/100 to 15/85) followed by filtration through a plug of basic Al_2O_3 (MeOH/CH_2Cl_2: 0/100 to 5/95). Product **3-130** was obtained as a white foam (0.070 g, 85%): IR (neat) 3258, 3052, 2941, 2788, 2227, 1714, 1511, 1447, 1300, 1268, 1220, 1044, 998, 733, 706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (t, *J* = 3.6 Hz, 1 H), 8.57 (t, *J* = 2.2 Hz, 1 H), 7.70 (dd, *J* = 8.1, 1.2 Hz, 1 H), 7.42 (dt, *J* = 7.8, 3.8 Hz, 1 H), 7.05-7.02 (m, 2 H), 6.96 (td, *J* = 8.4, 2.4 Hz, 1 H), 5.07 (d, *J* = 2.1 Hz, 3 H), 4.79 (s, 2 H), 3.45 (bs, 1 H), 2.69 (d, *J* = 9.6 Hz, 2 H), 2.19 (d, *J* = 3.1 Hz, 3 H), 2.01 (t, *J* = 10.8 Hz, 2 H), 1.88 (d, *J* = 12.4 Hz, 2 H), 1.43 (q, *J* = 11.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5 (d, J_{CF} = 43.7 Hz), 152.9, 151.2, 150.6, 150.5, 147.9, 145.8 (d, J_{CF} = 10.9 Hz), 135.0, 129.8, 128.5 (d, J_{CF} = 3.4 Hz), 124.1, 119.7 (d, J_{CF} = 19.8 Hz), 116.5 (d, J_{CF} = 8.4 Hz), 115.4 (d, J_{CF} = 1.3 Hz), 84.5, 83.7, 61.0, 54.3, 52.9, 47.9, 46.1, 45.4 (t, J_{CD} = 24.1 Hz), 33.0-32.4 (m, CD), 32.4, 23.7-23.3 (m, CD); ^{19}F NMR (376 MHz, $CDCl_3$) δ -133.2; HRMS (ESI$^+$): *m/z* calculated for $C_{29}H_{25}{}^2H_9O_3N_6FS$ (M+H) 574.2957, found 574.2952; ELS purity (100%).



3-131

4-Bromo-2,6-difluorophenyl pivalate. To a solution of 4-bromo-2,6-difluorophenol (1.00 g, 4.78 mmol) and Et_3N (0.740 mL, 5.26 mmol) in CH_2Cl_2 (9.4 mL) at 0 °C was added PivCl (1.31 mL, 5.26 mmol). The reaction was stirred at 0 °C for 35 min then diluted with Et_2O (20 mL) and filtered. The filtrate was concentrated and taken up in Et_2O (20 mL), filtered, and concentrated. The crude pivalate was obtained as a tan liquid (1.42 g) and carried on without further purification: IR (neat) 2977, 1774, 1605, 1499, 1428, 1309, 1207, 1084, 1074, 1043, 1027, 866, 839, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16-7.10 (m, 2 H), 1.37 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.3, 174.7, 155.3 (dd, J_{CF} = 254.2, 5.1 Hz), 127.2 (t, J_{CF} = 15.9 Hz), 117.7 (t, J_{CF} = 10.9 Hz), 116.1-115.8 (m), 77.4, 77.1, 76.8, 39.2, 38.5, 26.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -124.5; HRMS (ESI^+): *m/z* calculated for $C_{11}H_{12}O_2BrF_2$ (M+H) 292.9983, found 292.9993.

2,6-Difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl pivalate. To a solution of 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (0.44 g, 3.1 mmol) and 4-bromo-2,6-difluorophenyl pivalate (0.70 g, 2.4 mmol) in deoxygenated Et_3N (1.85 mL) was added $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol) and CuI (0.045 g, 0.24 mmol). The reaction was sparged with argon for 2 min then stirred at reflux 16 h. The reaction was filtered, concentrated, and the residue taken up in Et_2O. The combined organic layers were washed with sat. NH_4Cl and brine, filtered through a plug of SiO_2, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/hexanes: 0/100 to 10/90). The pivalate was obtained as a yellow oil (0.21

g, 25%) and carried on without further characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (dd, *J* = 7.7, 4.5 Hz, 2 H), 4.86 (t, *J* = 3.4 Hz, 1 H), 4.54-4.38 (m, 2 H), 3.88 (ddd, *J* = 11.5, 9.1, 3.2 Hz, 1 H), 3.62-3.52 (m, 1 H), 1.90-1.73 (m, 2 H), 1.70-1.49 (m, 4 H), 1.24 (s, 9 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.4; HRMS (ESI^+): *m/z* calculated for $C_{19}H_{23}O_4F_2$ (M+H) 353.1559, found 353.1554.

2,6-Difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol. To a solution of 2,6-difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenyl pivalate (0.20 g, 0.57 mmol) in THF (8.1 mL) and MeOH (8.1 mL) was added a solution of NaOH (1 M, 3.1 mL) dropwise and the reaction was stirred at room temperature 16 h. The reaction was concentrated and diluted with CH_2Cl_2. The solution was then neutralized to pH 7 with 2 N HCl and the aqueous extracted with CH_2Cl_2 (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude phenol was obtained as a yellow oil (0.18 g) and carried on without further purification or characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06-6.96 (m, 2 H), 4.86 (t, *J* = 3.4 Hz, 1 H), 4.51-4.38 (m, 2 H), 3.88 (ddd, *J* = 11.7, 9.2, 3.0 Hz, 1 H), 3.61-3.54 (m, 1 H), 1.91-1.72 (m, 1 H), 1.71-1.48 (m, 7 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -135.3; HRMS (ESI^-): *m/z* calculated for $C_{14}H_{13}O_3F_2$ (M-H) 267.0827, found 267.0821.

2,6-Difluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol. To a solution of crude 2,6-difluoro-4-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)phenol (0.15 g, 0.57 mmol) in MeOH (3.5 mL) was added PPTS (0.071 g, 0.28 mmol) and the reaction stirred at room temperature for 2 d. The reaction was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The phenol was obtained as an off-white solid (0.029 g, 27%, 37% BRSM): IR (neat) 3323, 3092, 2949, 1601, 1524, 1433, 1337, 1241, 1199,

1034, 1014, 977, 857, 777 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.08-6.98 (m, 2 H), 4.40 (s, 2 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 152.1 (dd, J_{CF} = 242.7, 7.6 Hz), 135.2 (t, J_{CF} = 16.2 Hz), 115.1-114.8 (m, CF), 113.2 (t, J_{CF} = 10.7 Hz), 88.6, 81.9 (t, J_{CF} = 3.5 Hz), 50.0; ^{19}F NMR (470 MHz, acetone-d_6) δ -134.4; HRMS (ESI^-): *m/z* calculated for $C_9H_5O_2F_2$ (M-H) 183.0252, found 183.0240.

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-3,5-difluorophenyl)prop-2-yn-1-ol. To the crude mixture of (5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methyl methanesulfonate and 3-(3-(chloromethyl)-5-(cyclohex-2-en-1-ylthio)-4*H*-1,2,4-triazol-4-yl)pyridine (0.045 g, 0.12 mmol) in DMF (2.1 mL) was added 2,6-difluoro-4-(3-hydroxyprop-1-yn-1-yl)phenol (0.025 g, 0.14 mmol) and Cs_2CO_3 (0.040 g, 0.12 mmol) and the reaction stirred at room temperature 16 h. The reaction was diluted with EtOAc and organic layer washed with water. The aqueous was extracted with EtOAc (3x) and the combined organic layers dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, EtOAc/Hexanes: 0/100 to 100/0). The triazole was obtained as a white solid (0.041 g, 75%) and carried on without further characterization: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 4.8, 1.6 Hz, 1 H), 8.71 (d, *J* = 2.6 Hz, 1 H), 7.84 (ddd, *J* = 8.1, 2.6, 1.5 Hz, 1 H), 7.52 (ddd, *J* = 8.1, 4.9, 0.8 Hz, 1 H), 6.96-6.90 (m, 2 H), 5.88 (ddt, *J* = 9.3, 3.9, 1.9 Hz, 1 H), 5.75 (ddd, *J* = 10.0, 4.4, 2.2 Hz, 1 H), 5.14-5.09 (m, 3 H), 4.56 (bs, 1 H), 4.46 (d, *J* = 6.0 Hz, 2 H), 2.12-1.95 (m, 4 H), 1.82 (t, *J* = 6.2 Hz, 1 H), 1.78-1.63 (m, 2 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -127.1; HRMS (ESI^+): *m/z* calculated for $C_{23}H_{21}O_2N_4F_2S$ (M+H) 455.1348, found 455.1346.

3-(4-((5-(Cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4H-1,2,4-triazol-3-yl)methoxy)-3,5-difluorophenyl)prop-2-yn-1-yl (1-methylpiperidin-4-yl)carbamate (3-131). To a solution of

3-(4-((5-(cyclohex-2-en-1-ylthio)-4-(pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)methoxy)-3,5-difluorophenyl)prop-2-yn-1-ol (0.042 g, 0.092 mmol) in dry CH_2Cl_2 (1.4 mL) was added CDI (0.022 g, 0.14 mmol) and the reaction stirred at room temperature under argon for 3 h. 4-Amino-1-methylpiperidine (0.035 mL, 0.28 mmol) was added and the reaction stirred for 24 h at room temperature. LCMS showed remaining starting material so additional 4-amino-1-methylpiperidine (0.035 mL, 0.28 mmol) was added and the reaction stirred for an additional 24 h. The reaction was then diluted with CH_2Cl_2 and washed with brine. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by chromatography on SiO_2 (ISCO, MeOH/ CH_2Cl_2: 0/100 to 15/85) then filtered through a plug of basic Al_2O_3 (MeOH/ CH_2Cl_2: 0/100 to 10/90). Product **3-131** was obtained as a tan foam (0. 0.044 g, 80%): IR (neat) 3258, 3034, 2939, 2791, 1714, 1509, 1485, 1447, 1428, 1351, 1271, 1234, 1212, 1045, 1035, 1000, 977, 858, 732, 707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.9, 1.5 Hz, 1 H), 8.68 (d, *J* = 2.5 Hz, 1 H), 7.82 (ddd, *J* = 8.2, 2.5, 1.5 Hz, 1 H), 7.50 (dd, *J* = 8.1, 4.8 Hz, 1 H), 6.96-6.88 (m, 2 H), 5.86 (dtd, *J* = 9.3, 3.7, 1.4 Hz, 1 H), 5.75-5.69 (m, 1 H), 5.10 (s, 2 H), 4.82 (s, 2 H), 4.56-4.50 (m, 1 H), 3.55-3.45 (m, 1 H), 2.73 (d, *J* = 11.6 Hz, 2 H), 2.24 (s, 3 H), 2.13-1.89 (m, 9 H), 1.72 (dddd, *J* = 13.7, 10.5, 7.0, 3.1 Hz, 1 H), 1.65 (dtd, *J* = 13.8, 5.7, 3.4 Hz, 1 H), 1.47 (qd, *J* = 11.0, 3.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4 (dd, J_{CF} = 249.4, 6.2 Hz), 154.7, 153.7, 151.2, 150.9, 148.0, 135.1, 134.4 (t, J_{CF} = 14.6 Hz), 132.4, 129.9, 125.4, 124.2, 118.6 (t, J_{CF} = 11.3 Hz), 116.3-115.8 (m, CF), 85.4, 83.6-83.2 (m, CF), 64.6, 54.3, 52.7, 47.9, 46.1, 44.2, 32.4, 29.2, 24.8, 19.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ -127.1; HRMS (ESI^+): *m/z* calculated for $C_{30}H_{33}O_3N_6F_2S$ (M+H) 595.2297, found 595.2296; ELS purity (100%).

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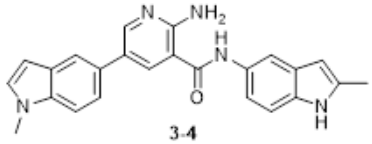
CNA-599-11, 1H, acetone, 400 MHz



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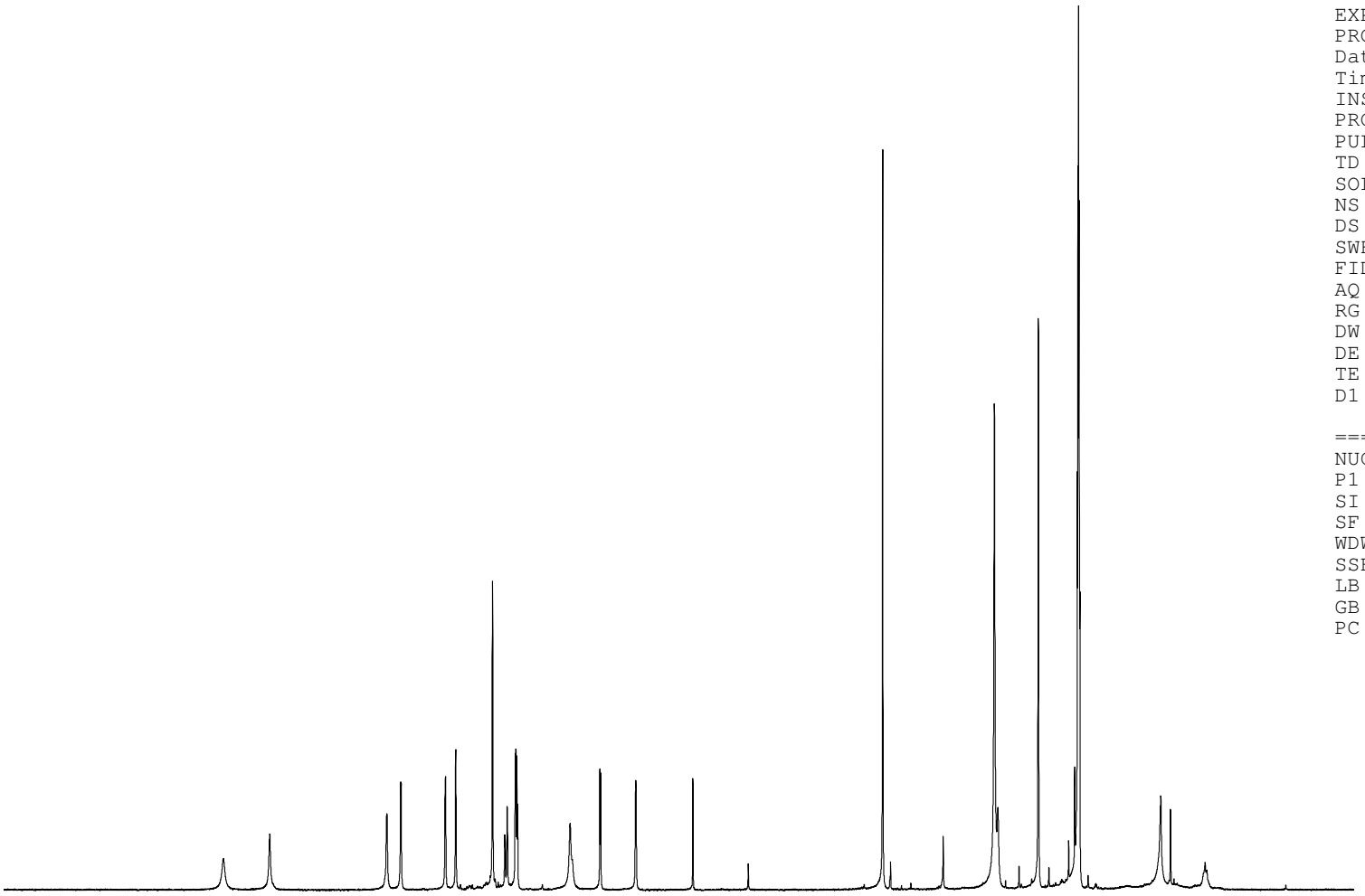
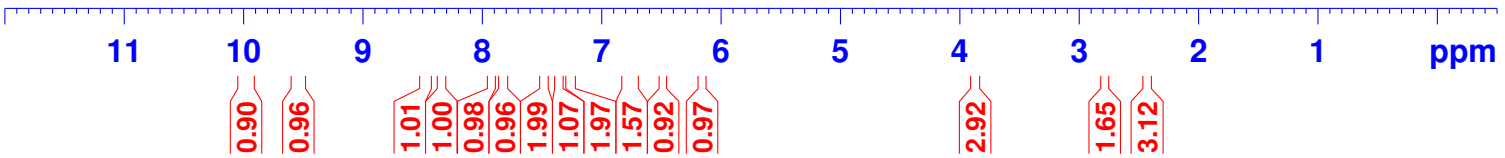
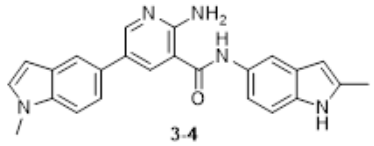


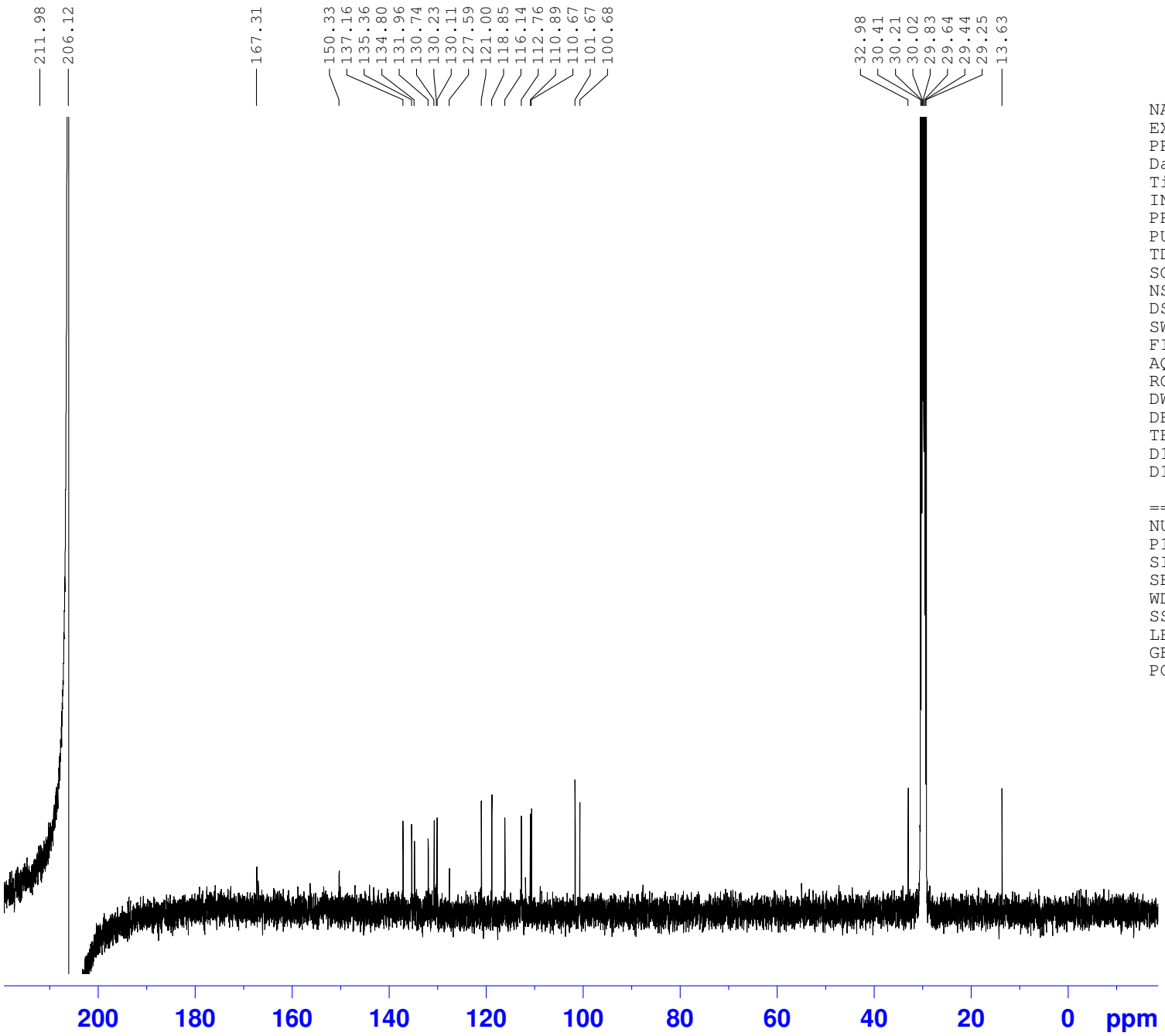


0.90 0.96 1.01 1.00 0.98 0.96 1.99 1.07 1.97 1.57 0.92 0.97 2.92 1.65 3.12

NAME	CNA-599-11
EXPNO	1
PROCNO	1
Date_	20140710
Time	3.13
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	144
DW	60.800 usec
DE	6.50 usec
TE	93.5 K
D1	1.00000000 sec
======== CHANNEL f1 ========	
NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300072 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

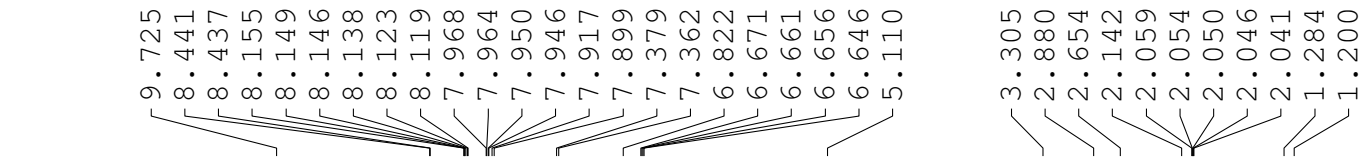
CNA-599-11, 13C, acetone, 400 MHz

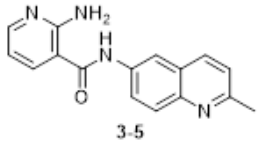




NAME	CNA-599-11
EXPNO	2
PROCNO	1
Date_	20140710
Time	6.10
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	Acetone
NS	3072
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	92.8 K
D1	2.00000000 sec
D11	0.03000000 sec
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
SI	32768
SF	100.6126784 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-599-31, 1H, acetone, 500 MHz





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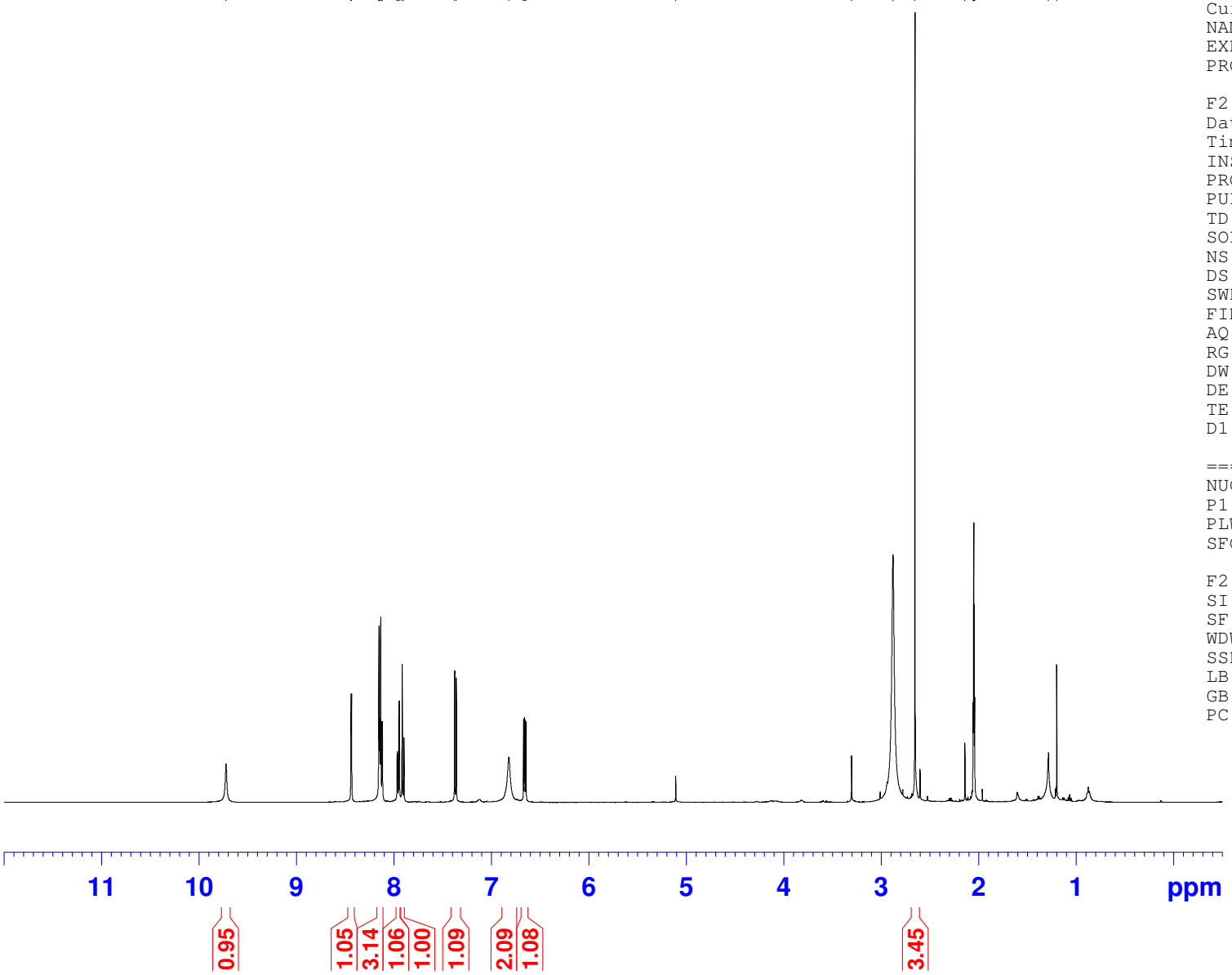
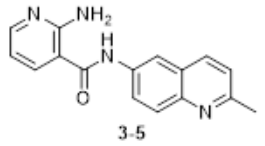
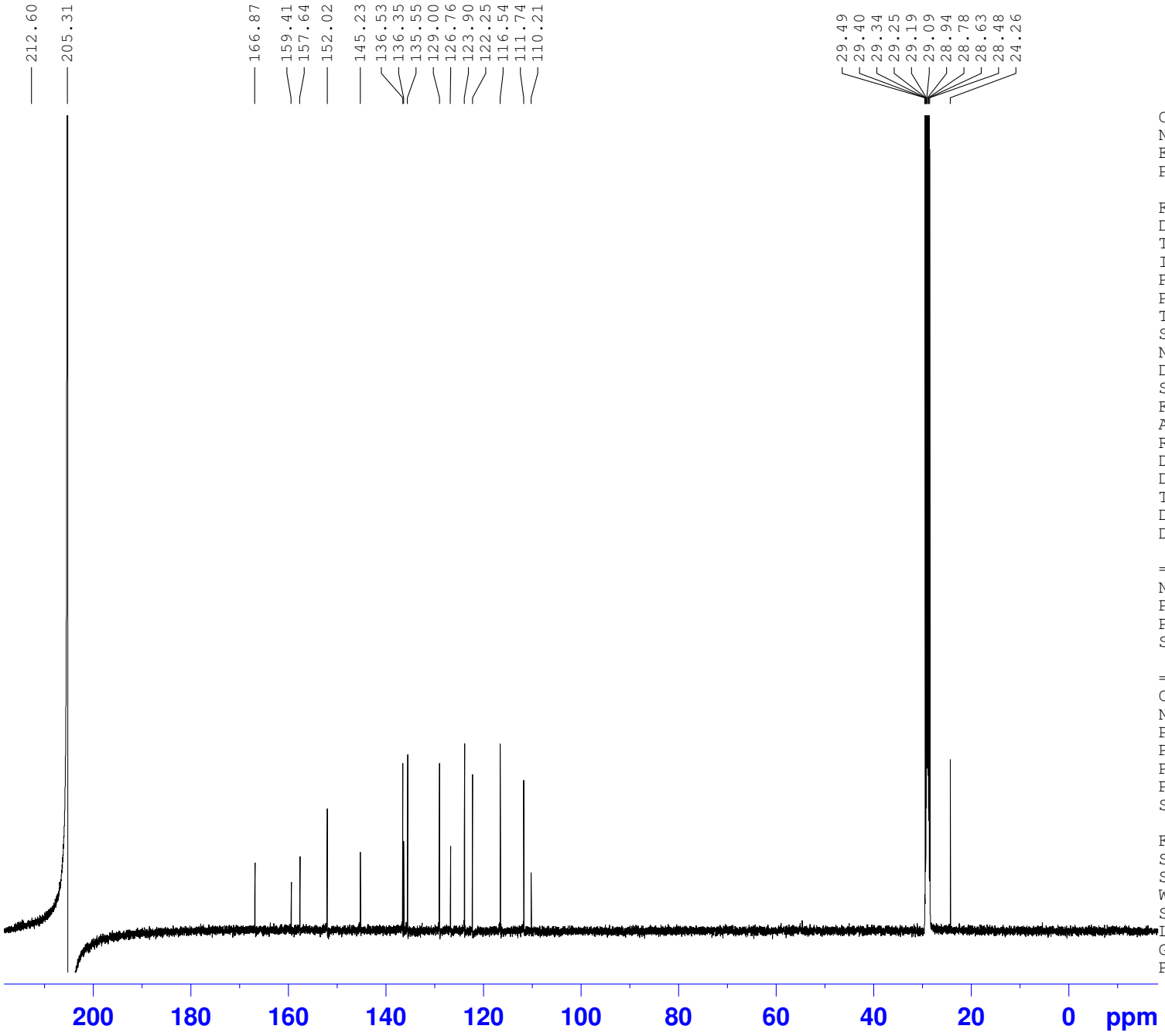



```
Current Data Parameters
NAME          CNA-599-31
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140722
Time               12.00
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT          Acetone
NS                    16
DS                     2
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1719923 sec
RG                 90.5
DW                48.400 usec
DE                 6.50 usec
TE                298.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                10.20 usec
PLW1        18.74300003 W
SFO1        500.1630887 MHz

F2 - Processing parameters
SI                 65536
SF          500.1600084 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-599-31, 13C, acetone, 500 MHz



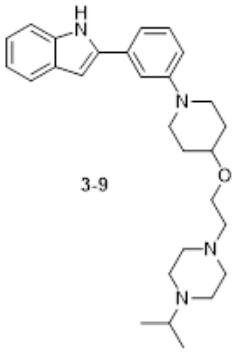
3-5




```
Current Data Parameters
NAME          CNA-599-31
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140722
Time               14.05
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT         Acetone
NS                 2300
DS                    4
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ            1.1010548 sec
RG                  203
DW                16.800 use
DE                 6.50 use
TE                298.0 K
D1           2.00000000 sec
D11          0.03000000 sec

======== CHANNEL f1 =======
NUC1                13C
P1                 8.80 use
PLW1       112.58000183 W
SFO1        125.7779080 MHz

======== CHANNEL f2 =======
CPDPRG2         waltz16
NUC2                1H
PCPD2            80.00 use
PLW2        18.74300003 W
PLW12        0.36736000 W
PLW13    0 W
SFO2         500.1620006 MHz

F2 - Processing parameters
SI                 32768
SF          125.7653320 MHz
WDW                  EM
SSB      0
LB                1.00 Hz
GB       0
PC                1.40
```

CNA-599-60, 1H, CDCl3, 400 MHz

7.802 7.604 7.585 7.447 7.427 7.320 7.299 7.279 7.267 7.260 7.199 7.184 7.166 7.143 7.123 7.098 7.080 7.061 7.037 6.871 6.852 6.790 3.586 3.549 3.445 3.436 3.004 2.976 2.951 2.794 2.654 2.642 2.630 2.347 1.960 1.742 1.720 1.709 1.697 1.262 1.138 1.122

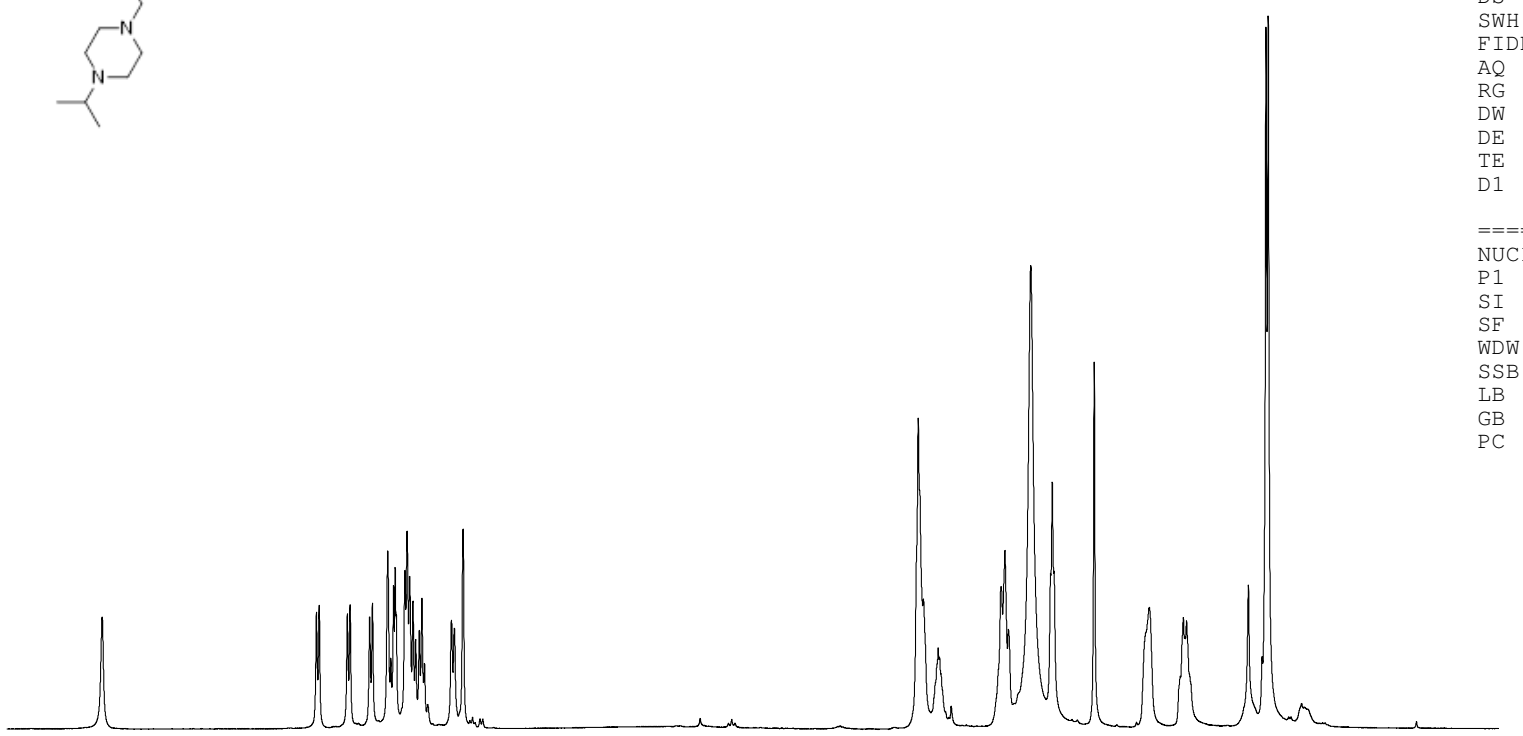


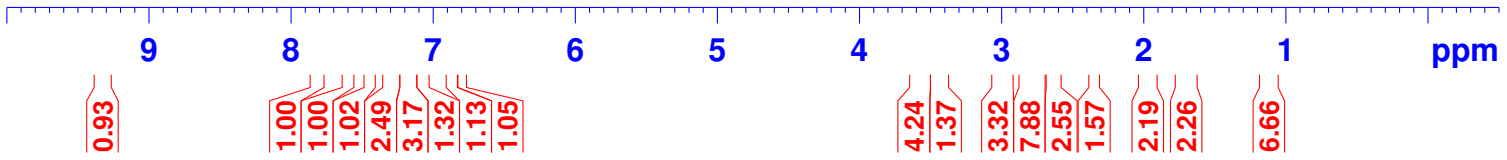
3-9

NAME	CNA-599-60
EXPNO	1
PROCNO	1
Date_	20140904
Time	12.34
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	50.8
DW	60.800 usec
DE	6.50 usec
TE	84.0 K
D1	1.00000000 sec

======== CHANNEL f1 ========

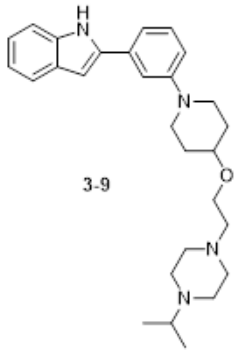
NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300078 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00





0.93 1.00 1.00 1.02 2.49 3.17 1.32 1.13 1.05 4.24 1.37 3.32 7.88 2.55 1.57 2.19 2.26 6.66

CNA-599-60, 13C, CDCl3, 400 MHz



3-9

151.84
142.50
140.03
138.55
136.94
133.32
129.63
129.15
128.85
125.94
121.96
120.37
119.94
116.53
115.83
113.26
111.28
99.40

77.39
77.07
76.75
75.12

65.01

57.42
56.25
51.40
47.78
47.17

30.86

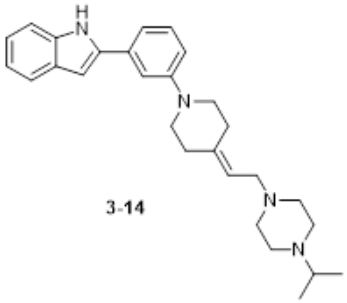
21.36
17.40

NAME	CNA-599-60
EXPNO	2
PROCNO	1
Date_	20140904
Time	12.50
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	256
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	82.6 K
D1	2.00000000 sec
D11	0.03000000 sec

======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
SI	32768
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-599-75, 1H, CDCl3, 400 MHz

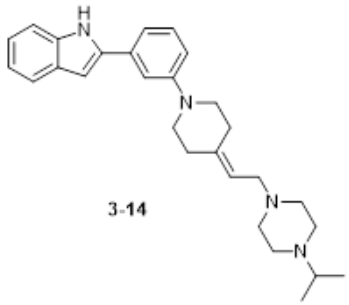
8.318 7.632 7.612 7.411 7.393 7.342 7.322 7.302 7.260 7.223 7.205 7.188 7.170 7.167 7.132 7.114 6.924 6.920 6.904 6.900 6.803 6.800 5.396 3.341 3.327 3.313 3.300 3.286 3.052 3.034 2.675 2.659 2.642 2.626 2.575 2.474 2.460 2.446 2.408 2.395 2.382 1.577 1.062 1.045



3-14

NAME	CNA-599-75
EXPNO	1
PROCNO	1
Date_	20140918
Time	12.14
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	161
DW	60.800 usec
DE	6.50 usec
TE	96.3 K
D1	1.00000000 sec
======== CHANNEL f1 ========	
NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300101 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-599-75, 13C, CDCl3, 400 MHz

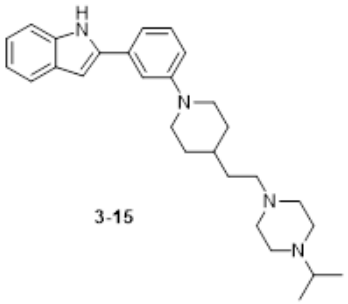


3-14

NAME	CNA-599-75
EXPNO	2
PROCNO	1
Date_	20140918
Time	12.51
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	803
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	57
DW	20.800 usec
DE	6.50 usec
TE	298.0 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-599-85, 1H, CDCl3, 400 MHz

8.757 7.621 7.602 7.419 7.399 7.316 7.296 7.276 7.260 7.249 7.170 7.153 7.149 7.127 7.121 7.119 7.101 6.901 6.896 6.881 6.876 6.791 6.788 3.742 3.712 2.783 2.767 2.738 2.709 2.669 2.631 2.607 2.446 2.427 2.407 1.796 1.772 1.500 1.488 1.482 1.407 1.397 1.105 1.089



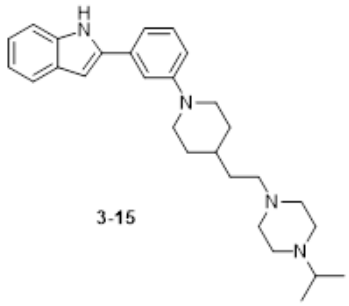
3-15

NAME	CNA-599-85
EXPNO	1
PROCNO	1
Date_	20141001
Time	22.03
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	71.8
DW	60.800 usec
DE	6.50 usec
TE	298.0 K
D1	2.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300123 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-599-85, 13C, CDCl3, 400 MHz

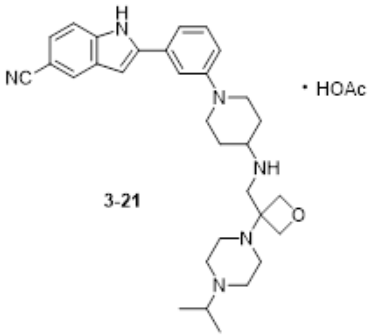


3-15

NAME	CNA-599-85
EXPNO	2
PROCNO	1
Date_	20141001
Time	23.00
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	700
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	80.6
DW	20.800 usec
DE	6.50 usec
TE	298.0 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

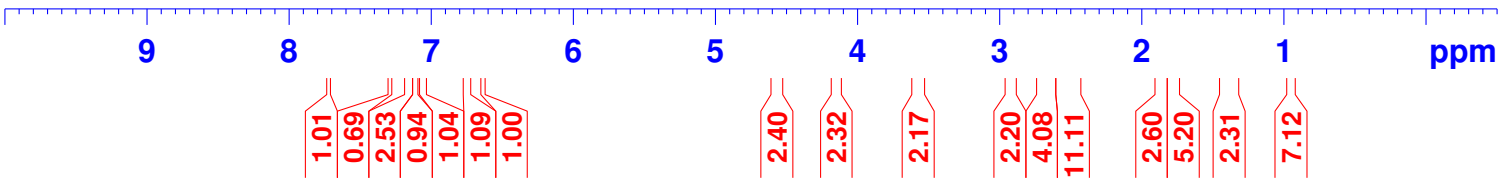
CNA-637-8, 1H, CDCl3/MeOD, 400 MHz

7.720 7.286 7.260 7.169 7.159 7.155 7.138 7.134 7.122 7.102 7.068 7.048 6.761 6.757 6.741 6.737 6.636 4.559 4.542 4.200 4.155 4.138 3.584 3.552 3.136 3.132 3.128 3.124 3.120 2.913 2.700 2.669 2.650 2.638 2.618 2.552 1.864 1.835 1.789 1.425 1.398 1.376 0.953 0.937

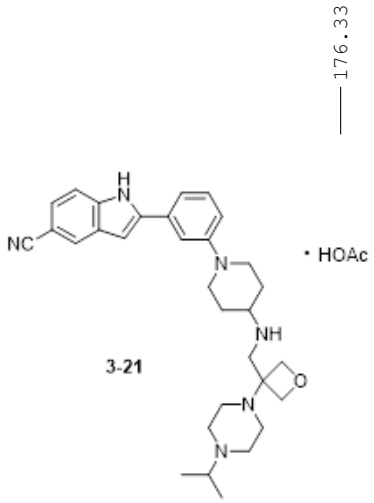


3-21

NAME	CNA-637-8
EXPNO	1
PROCNO	1
Date_	20150212
Time	11.26
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	MeOD
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	161
DW	60.800 usec
DE	6.50 usec
TE	95.6 K
D1	1.00000000 sec
======== CHANNEL f1 ========	
NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300809 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



CNA-637-8, 13C, CDCl3/MeOD, 400 MHz



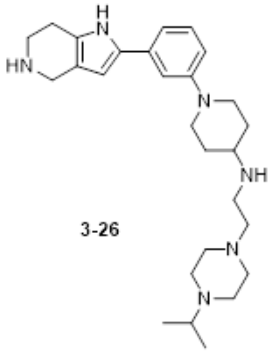
176.33
151.67
141.24
139.08
132.49
129.68
128.74
125.62
124.31
121.11
117.21
116.59
113.86
111.98
101.69
99.20
77.62
77.49
77.30
76.98
76.27
63.07
55.80
55.37
49.30
49.09
48.87
48.66
48.45
48.23
48.02
44.35
31.44
21.96
17.32

200 180 160 140 120 100 80 60 40 20 0 ppm

NAME	CNA-637-8
EXPNO	3
PROCNO	1
Date_	20150212
Time	4.58
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	MeOD
NS	3745
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	144
DW	20.800 usec
DE	6.50 usec
TE	296.0 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	15
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-617-71, 1H, CDCl3, 400 MHz

8.352 7.260 7.210 7.190 7.170 6.997 6.888 6.869 6.767 6.763 6.747 6.742 6.191 6.187 3.845 3.693 3.663 3.158 3.143 3.129 2.811 2.777 2.759 2.745 2.666 2.652 2.637 2.620 2.604 2.589 2.579 2.533 2.516 2.501 2.485 2.245 1.988 1.960 1.545 1.517 1.494 1.489 1.050 1.034

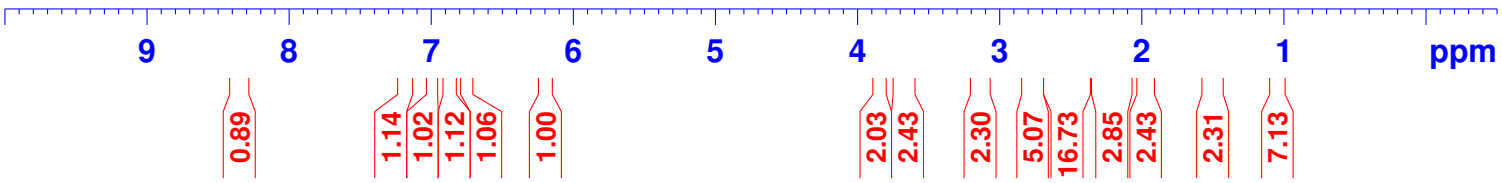


3-26

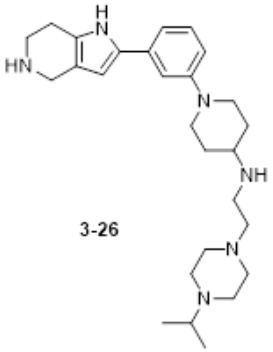
NAME	CNA-617-71
EXPNO	1
PROCNO	1
Date_	20150114
Time	20.32
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	64
DW	60.800 usec
DE	6.50 usec
TE	298.0 K
D1	2.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300123 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



CNA-617-71, 13C, CDCl3, 400 MHz



3-26

151.95
133.88
131.34
129.44
126.07
117.82
115.05
114.25
112.07
102.73
77.38
77.27
77.06
76.75
57.99
55.12
54.47
53.54
48.75
48.69
43.62
43.56
43.42
32.59
23.93
18.69

NAME	CNA-617-71
EXPNO	2
PROCNO	1
Date_	20150114
Time	20.46
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1170
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	71.8
DW	20.800 usec
DE	6.50 usec
TE	298.0 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-637-33, 1H, CDCl3, 400 MHz

9.757
8.209
7.666
7.663
7.644
7.641
7.519
7.498
7.315
7.295
7.275
7.260
7.147
7.128
6.928
6.925
6.908
6.856
3.724
3.694
2.858
2.829
2.802
2.557
2.410
2.268
2.147
2.132
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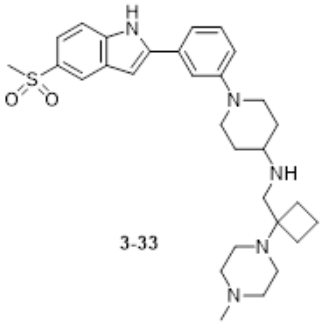
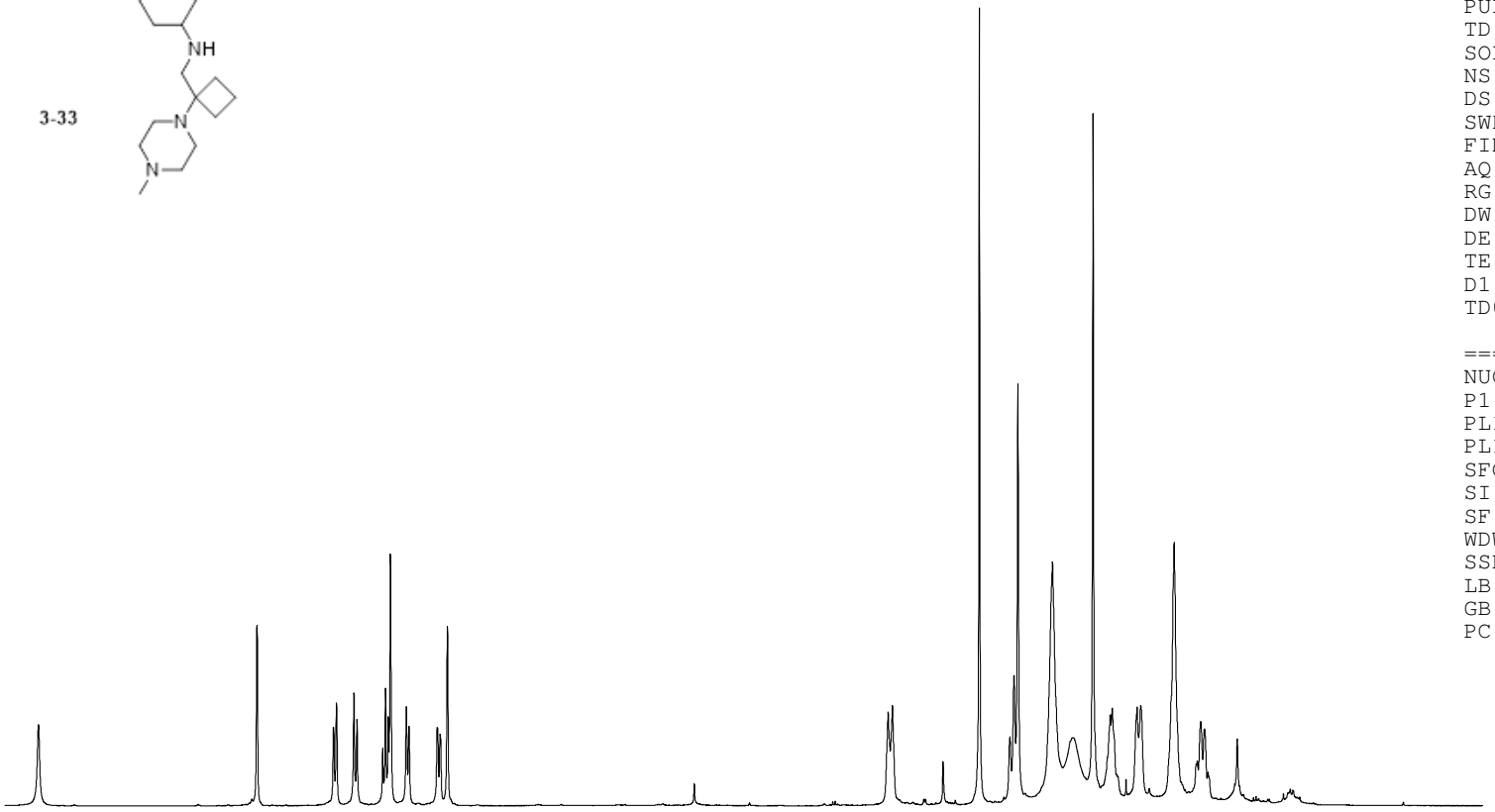
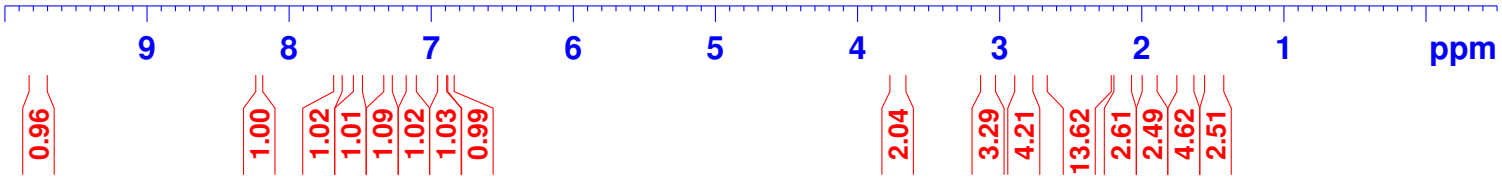
1.536
1.528
1.503
1.476
1.451
1.443



3-33

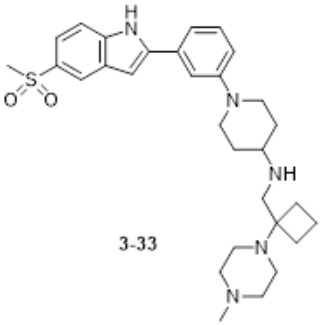




0.96 1.00 1.02 1.01 1.09 1.02 1.03 0.99 2.04 3.29 4.21 13.62 2.61 2.49 4.62 2.51

NAME	CNA-637-33
EXPNO	1
PROCNO	1
Date_	20150312
Time	0.25
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	50.8
DW	60.800 usec
DE	6.50 usec
TE	295.5 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300124 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-637-33, 13C, CDCl3, 400 MHz

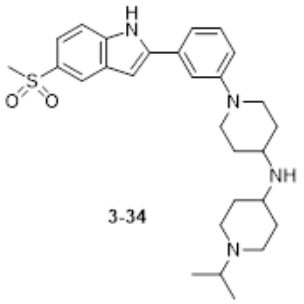


3-33

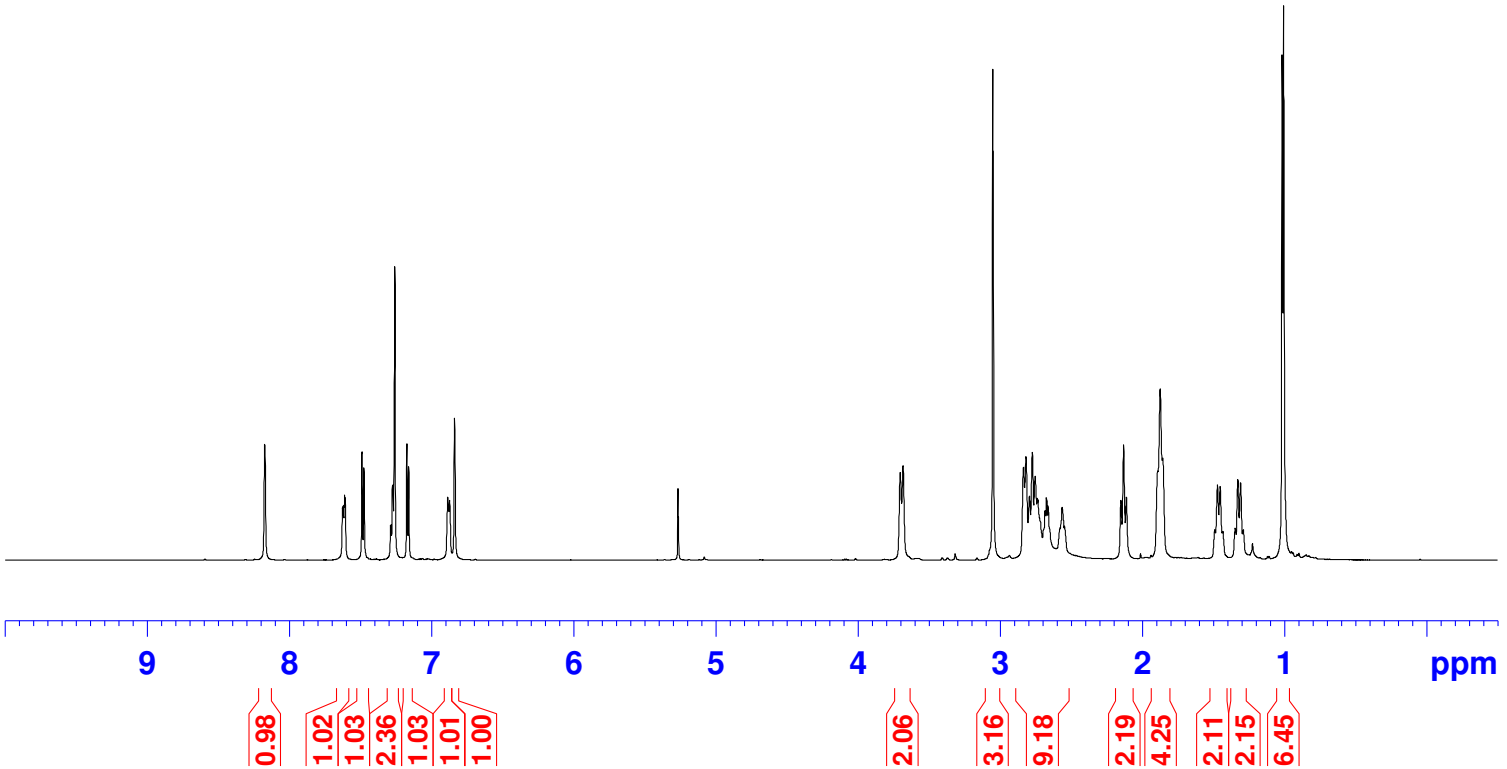
NAME	CNA-637-33
EXPNO	2
PROCNO	1
Date_	20150312
Time	0.43
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	513
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	101
DW	20.800 usec
DE	6.50 usec
TE	295.6 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-637-32, 1H, CDCl3/MeOD, 600 MHz

8.177 8.174 7.625 7.617 7.614 7.611 7.492 7.478 7.278 7.273 7.260 7.175 7.163 6.888 6.875 6.841 6.838 3.704 3.685 3.054 3.052 3.050 2.837 2.820 2.795 2.775 2.754 2.741 2.735 2.676 2.665 2.566 2.152 2.132 2.113 1.893 1.875 1.857 1.472 1.453 1.328 1.310 1.019 1.008



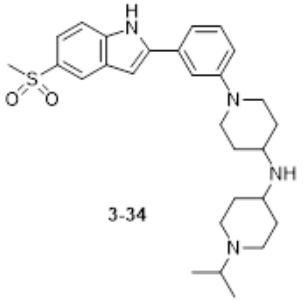
3-34



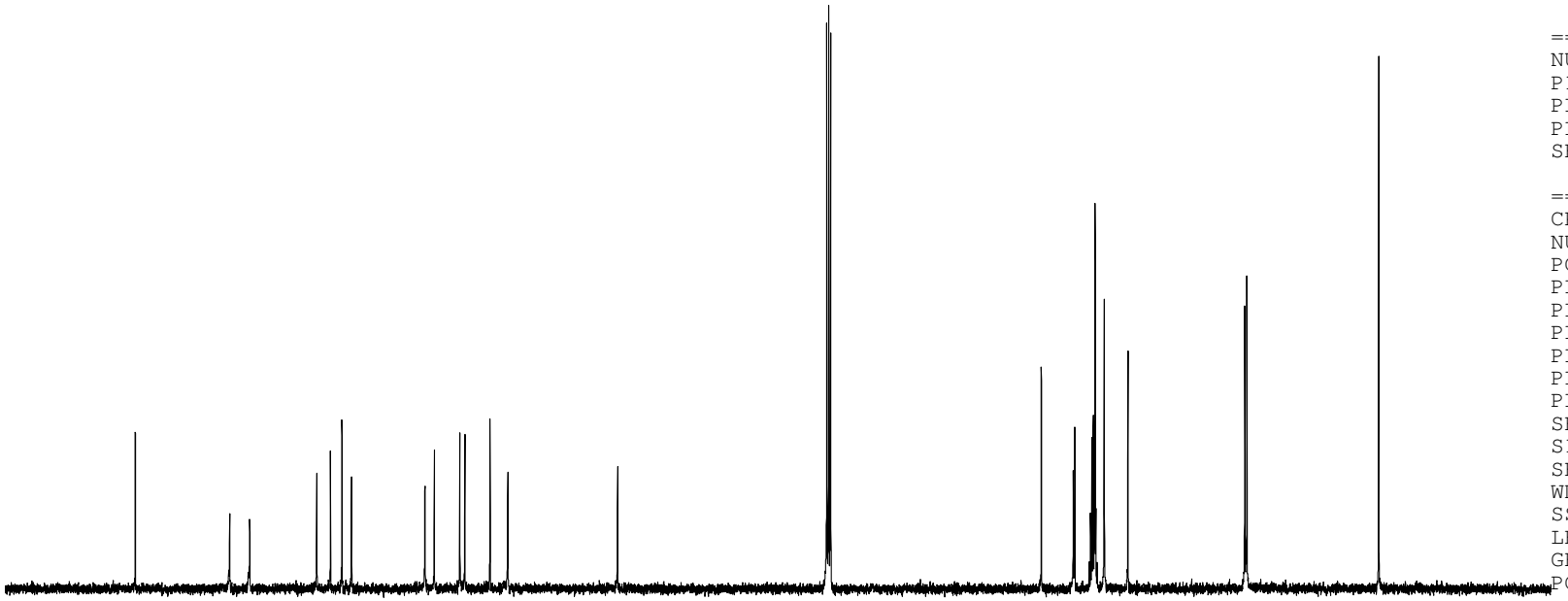
NAME	CNA-637-32
EXPNO	5
PROCNO	1
Date_	20150312
Time	1.42
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	12335.526 Hz
FIDRES	0.188225 Hz
AQ	2.6564426 sec
RG	40.3
DW	40.533 usec
DE	6.50 usec
TE	298.2 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.86 usec
PL1	-2.00 dB
PL1W	19.70630455 W
SFO1	600.7137096 MHz
SI	32768
SF	600.7100138 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-637-32, 13C, CDCl3/MeOD, 600 MHz

151.70
141.55
139.40
132.23
130.77
129.53
128.49
120.61
119.59
116.84
116.31
113.60
111.68
99.87
77.37
77.16
76.95
54.29
50.86
50.69
49.14
49.00
48.86
48.71
48.57
48.50
48.43
48.29
47.52
44.98
32.40
32.18
17.99



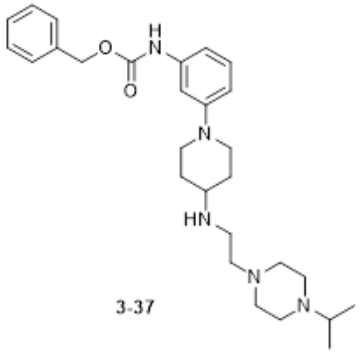
3-34



NAME	CNA-637-32
EXPNO	3
PROCNO	1
Date_	20150312
Time	0.42
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	256
DS	4
SWH	36057.691 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	203
DW	13.867 usec
DE	6.50 usec
TE	298.3 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	11.50 usec
PL1	0.00 dB
PL1W	97.46119690 W
SFO1	151.0637542 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	70.00 usec
PL2	-2.00 dB
PL12	14.19 dB
PL13	120.00 dB
PL2W	19.70630455 W
PL12W	0.47381112 W
PL13W	0.00000000 W
SFO2	600.7124028 MHz
SI	32768
SF	151.0492641 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-617-17, CDCl3, 1H, 500 MHz

7.379 7.363 7.347 7.332 7.324 7.320 7.317 7.307 7.260 7.129 7.113 7.097 7.008 6.683 6.668 6.620 6.616 6.604 6.600 5.163 3.643 3.618 2.746 2.733 2.721 2.709 2.635 2.622 2.609 2.596 2.569 2.548 2.527 2.521 2.492 2.480 2.468 1.935 1.912 1.458 1.443 1.245 1.039 1.026



3-37

Current Data Parameters
NAME CNA-617-17
EXPNO 2
PROCNO 1

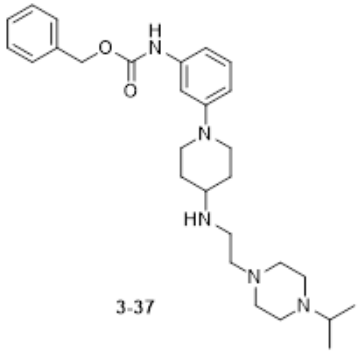
F2 - Acquisition Parameters
Date_ 20141112
Time 15.12
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 22.6
DW 50.000 usec
DE 6.50 usec
TE 298.4 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 500.1630887 MHz
NUC1 1H
P1 11.45 usec
PLW1 18.00000000 W

F2 - Processing parameters
SI 32768
SF 500.1600117 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

CNA-617-17, CDCl3, 13C, 500 MHz

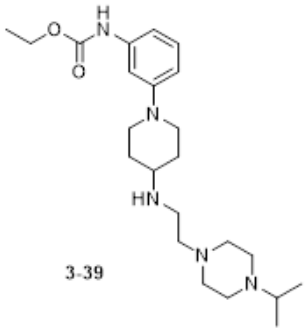
153.40
152.23
138.74
136.17
129.41
128.59
128.29
128.28
122.23
111.49
109.50
106.67
77.36
77.11
76.85
66.84
58.04
55.07
54.44
53.55
48.75
48.38
43.39
32.51
29.70
28.50
18.70



3-37


```
Current Data Parameters
NAME          CNA-617-17
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141112
Time               15.30
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   256
DS                     2
SWH            29761.904 Hz
FIDRES          0.454131 Hz
AQ             1.1010048 sec
RG                   203
DW                16.800 usec
DE                 6.50 usec
TE                298.7 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.7779080 MHz
NUC1                 13C
P1                10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.36873001 W
PLW13    0 W

F2 - Processing parameters
SI                 32768
SF           125.7653320 MHz
WDW                  EM
SSB      0
LB                1.00 Hz
GB       0
PC                1.40
```

CNA-617-20, CDCl3, 1H, 500 MHz



7.260 7.142 7.119 7.103 7.087 6.847 6.670 6.654 6.608 6.592 4.198 4.183 4.169 4.155 3.653 3.629 2.765 2.733 2.720 2.641 2.629 2.616 2.603 2.589 2.573 2.552 2.522 2.488 2.476 2.464 1.943 1.919 1.492 1.486 1.468 1.445 1.423 1.285 1.271

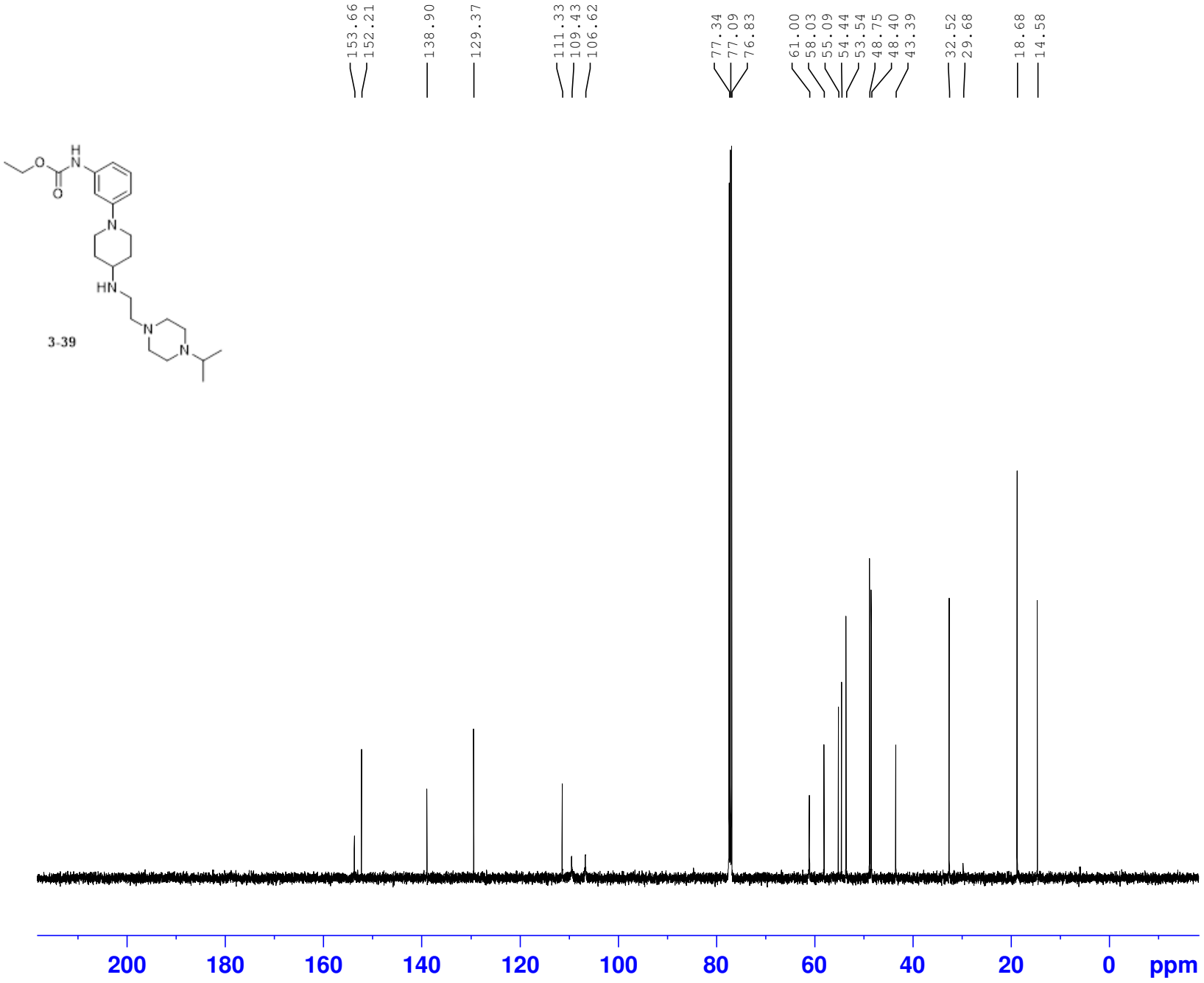
Current Data Parameters
NAME CNA-617-20
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20141112
Time 15.45
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 25.4
DW 50.000 usec
DE 6.50 usec
TE 298.4 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 500.1630887 MHz
NUC1 1H
P1 11.45 usec
PLW1 18.00000000 W

F2 - Processing parameters
SI 32768
SF 500.1600123 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

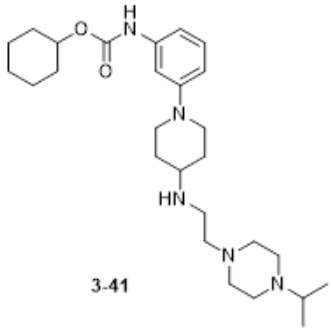
CNA-617-20, CDCl3, 13C, 500 MHz




```
Current Data Parameters
NAME          CNA-617-20
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141112
Time               16.01
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   256
DS                     2
SWH            29761.904 Hz
FIDRES          0.454131 Hz
AQ             1.1010048 sec
RG                   203
DW                16.800 usec
DE                 6.50 usec
TE                298.7 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.7779080 MHz
NUC1                 13C
P1                10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                 1H
CPDPRG[2          waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.36873001 W
PLW13    0 W

F2 - Processing parameters
SI                   32768
SF           125.7653320 MHz
WDW                    EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```

CNA-617-26, CDCl3, 1H, 500 MHz

7.260 7.139 7.123 7.107 6.656 6.653 6.640 6.637 6.624 6.620 6.607 6.603 6.578 3.681 3.656 2.765 2.752 2.740 2.636 2.623 2.572 2.563 2.550 2.542 2.510 2.498 2.485 2.162 1.962 1.939 1.915 1.908 1.742 1.732 1.725 1.488 1.482 1.466 1.460 1.444 1.426 1.407 1.387 1.381 1.361 1.247 1.052 1.039



3-41

Current Data Parameters
NAME CNA-617-26
EXPNO 1
PROCNO 1

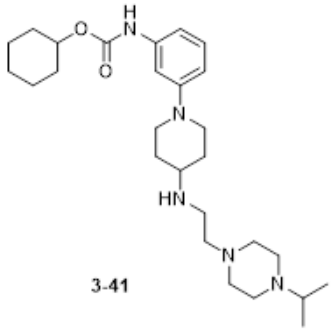
F2 - Acquisition Parameters
Date_ 20141122
Time 20.36
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 64
DW 50.000 usec
DE 6.50 usec
TE 298.4 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 500.1630887 MHz
NUC1 1H
P1 11.45 usec
PLW1 18.00000000 W

F2 - Processing parameters
SI 32768
SF 500.1600129 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

CNA-617-26, CDCl3, 13C, 500 MHz

153.19
152.24
139.00
129.38
111.23
109.28
106.49
77.29
77.03
76.78
73.54
58.06
55.98
55.12
54.48
53.54
48.76
48.41
43.43
32.55
31.97
30.92
29.70
25.39
23.83
18.69

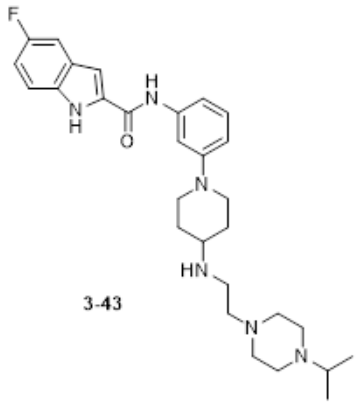


3-41


```
Current Data Parameters
NAME          CNA-617-26
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141123
Time                1.16
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 5120
DS                    2
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ            1.1010048 sec
RG                  203
DW               16.800 usec
DE                6.50 usec
TE                298.4 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        125.7779080 MHz
NUC1                13C
P1                10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2        500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.36873001 W
PLW13     0 W

F2 - Processing parameters
SI                 32768
SF          125.7653320 MHz
WDW                EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

CNA-617-38, 1H, CDCl3, 500 MHz

8.018 7.368 7.345 7.336 7.327 7.318 7.269 7.265 7.260 7.251 7.246 7.241 7.225 7.208 7.041 7.027 7.014 7.010 6.996 6.991 6.962 6.753 6.750 6.737 6.734 3.691 3.666 2.799 2.775 2.755 2.743 2.731 2.640 2.627 2.614 2.601 2.591 2.570 2.561 2.529 2.501 2.489 2.477 1.946 1.922 1.499 1.478 1.459 1.044 1.031



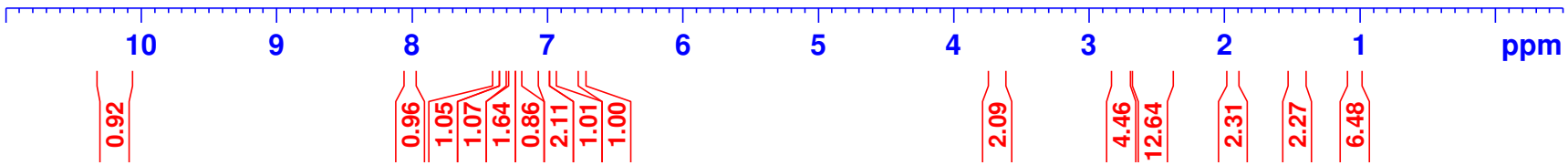
3-43

Current Data Parameters
NAME CNA-617-38
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20141125
Time 18.25
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 36
DW 50.000 usec
DE 6.50 usec
TE 298.3 K
D1 1.00000000 sec
TD0 1

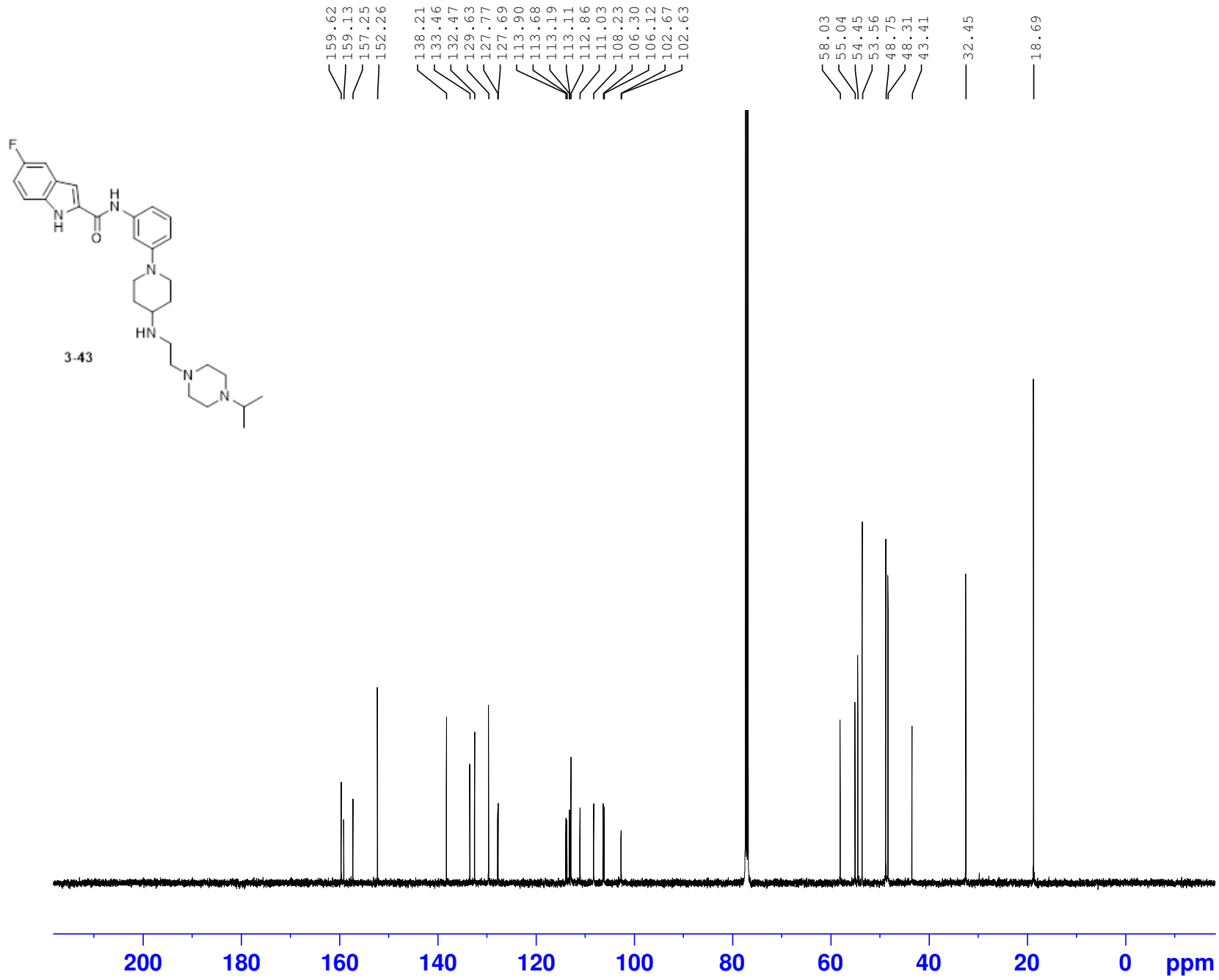
======== CHANNEL f1 ========
SFO1 500.1630887 MHz
NUC1 1H
P1 11.45 usec
PLW1 18.00000000 W

F2 - Processing parameters
SI 32768
SF 500.1600125 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



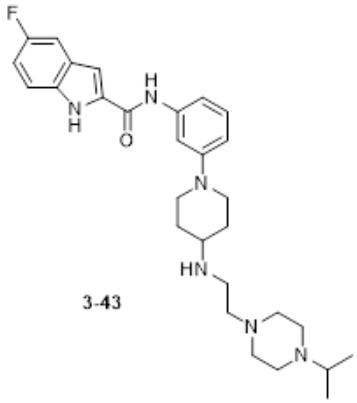
0.92 0.96 1.05 1.07 1.64 0.86 2.11 1.01 1.00 2.09 4.46 12.64 2.31 2.27 6.48

CNA-617-38, 13C, CDCl3, 500 MHz




```
Current Data Parameters
NAME          CNA-617-38
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141125
Time               18.43
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  2300
DS                     2
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ            1.1010048 sec
RG                   203
DW                16.800 usec
DE                 6.50 usec
TE                298.6 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1        125.7779080 MHz
NUC1                  13C
P1                 10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2        500.1620006 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              80.00 usec
PLW2        18.00000000 W
PLW12        0.36873001 W
PLW13    0 W

F2 - Processing parameters
SI                 32768
SF          125.7653320 MHz
WDW                   EM
SSB      0
LB                 1.00 Hz
GB       0
PC                 1.40
```

CNA-617-38, 19F, CDCl3, 500 MHz

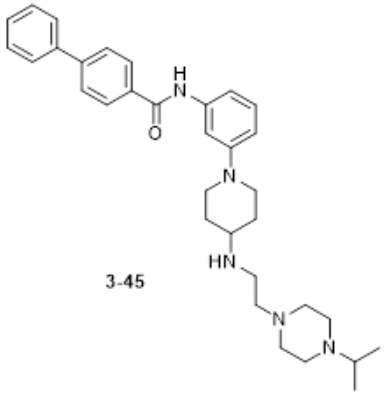


3-43


```
Current Data Parameters
NAME          CNA-617-38
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141125
Time               18.28
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgflqn
TD              131072
SOLVENT           CDCl3
NS                   16
DS                    4
SWH           93750.000 Hz
FIDRES         0.715256 Hz
AQ            0.6990507 sec
RG                  203
DW                5.333 usec
DE                6.50 usec
TE                298.3 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        470.5621062 MHz
NUC1               19F
P1                5.00 usec
PLW1        10.00000000 W

F2 - Processing parameters
SI                65536
SF          470.6206054 MHz
WDW                EM
SSB      0
LB                0.30 Hz
GB       0
PC                1.00
```

CNA-617-34, 1H, CDCl3, 500 MHz

7.953 7.930 7.913 7.676 7.660 7.615 7.613 7.598 7.488 7.473 7.459 7.443 7.400 7.385 7.260 7.219 7.203 7.187 6.961 6.959 6.943 6.730 6.726 6.713 6.709 3.714 3.689 2.790 2.786 2.763 2.751 2.738 2.644 2.631 2.618 2.577 2.569 2.563 2.555 2.536 2.510 2.497 2.485 1.970 1.947 1.493 1.050 1.037



3-45

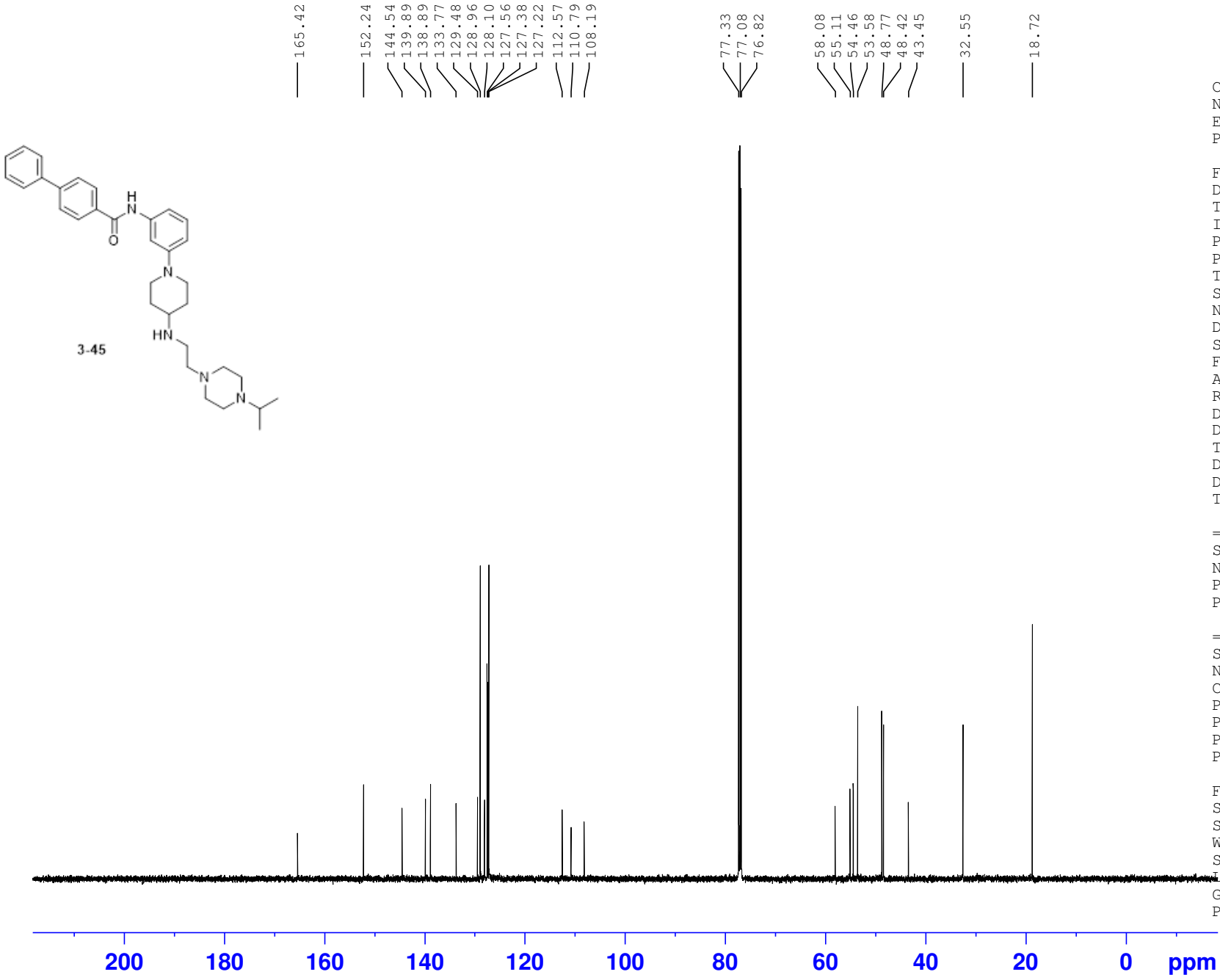
Current Data Parameters
NAME CNA-617-34
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20141123
Time 17.22
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 32
DW 50.000 usec
DE 6.50 usec
TE 296.7 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 500.1630887 MHz
NUC1 1H
P1 11.45 usec
PLW1 18.00000000 W

F2 - Processing parameters
SI 32768
SF 500.1600133 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

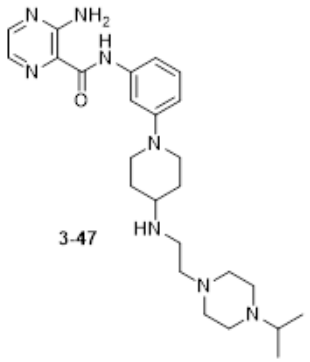
CNA-617-34, 13C, CDCl3, 500 MHz




```
Current Data Parameters
NAME          CNA-617-34
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141123
Time               17.51
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  512
DS                    2
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ             1.1010048 sec
RG                  203
DW                16.800 usec
DE                 6.50 usec
TE                297.1 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        125.7779080 MHz
NUC1                13C
P1                10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2        500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2        18.00000000 W
PLW12        0.36873001 W
PLW13    0 W

F2 - Processing parameters
SI                 32768
SF          125.7653320 MHz
WDW                EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

CNA-617-35, CDCl3, 1H, 500 MHz

9.731 8.173 8.168 7.829 7.824 7.387 7.383 7.379 7.260 7.226 7.209 7.193 7.061 7.058 7.045 7.042 6.724 6.720 6.707 6.703 3.714 3.689 2.818 2.798 2.794 2.774 2.766 2.753 2.740 2.636 2.623 2.611 2.597 2.583 2.576 2.562 2.554 2.529 2.508 2.496 2.483 1.984 1.962 1.509 1.503 1.486 1.481 1.041 1.028



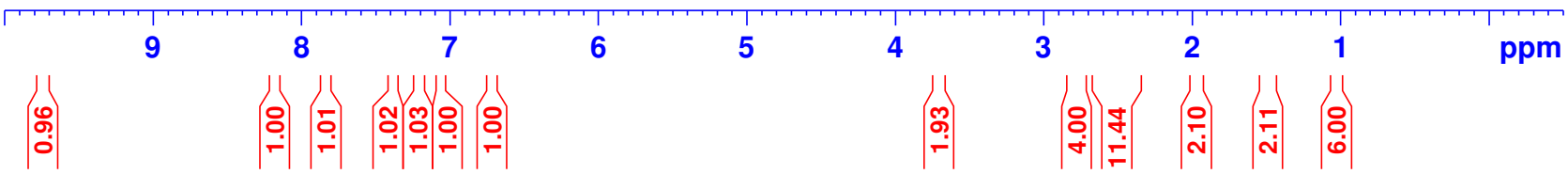
3-47

Current Data Parameters
NAME CNA-617-35
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20141123
Time 16.35
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 36
DW 50.000 usec
DE 6.50 usec
TE 296.6 K
D1 1.00000000 sec
TD0 1

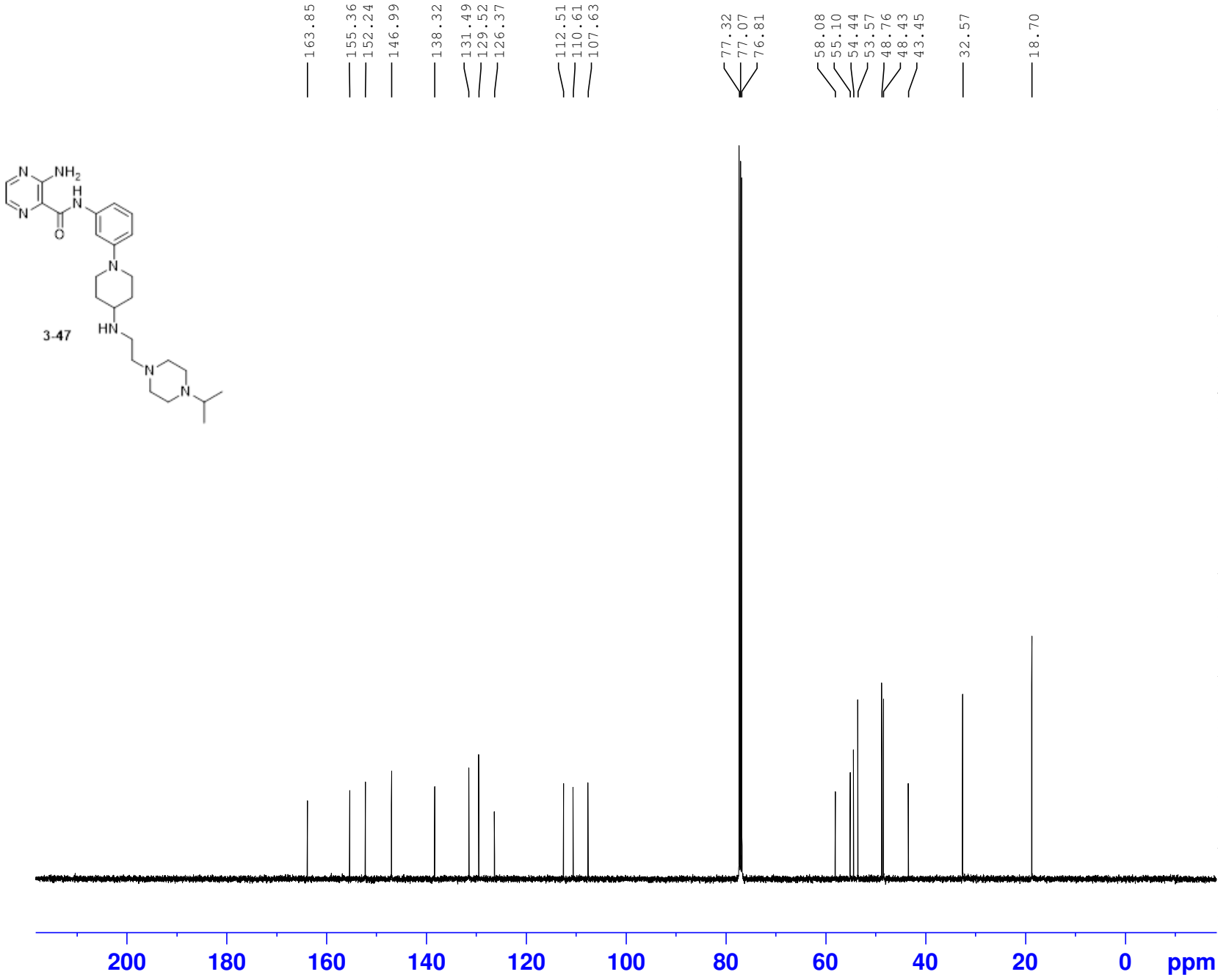
======== CHANNEL f1 ========
SFO1 500.1630887 MHz
NUC1 1H
P1 11.45 usec
PLW1 18.00000000 W

F2 - Processing parameters
SI 32768
SF 500.1600133 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



0.96 1.00 1.01 1.02 1.03 1.00 1.00 1.93 4.00 11.44 2.10 2.11 6.00

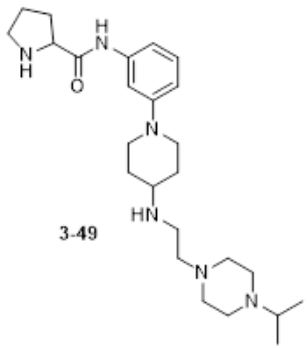
CNA-617-35, CDCl3, 13C, 500 MHz




```
Current Data Parameters
NAME          CNA-617-35
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141123
Time               17.05
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   512
DS                     2
SWH            29761.904 Hz
FIDRES          0.454131 Hz
AQ              1.1010048 sec
RG                   203
DW                16.800 usec
DE                 6.50 usec
TE                297.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.7779080 MHz
NUC1                 13C
P1                 10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2              80.00 usec
PLW2         18.00000000 W
PLW12         0.36873001 W
PLW13    0 W

F2 - Processing parameters
SI                   32768
SF           125.7653320 MHz
WDW                    EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

CNA-617-36, 1H, CDCl3, 500 MHz

9.628 7.418 7.414 7.409 7.260 7.178 7.162 7.146 6.914 6.911 6.898 6.896 6.673 6.669 6.657 6.653 3.849 3.838 3.830 3.820 3.705 3.679 3.065 2.981 2.803 2.798 2.776 2.764 2.751 2.591 2.583 2.562 2.554 2.524 2.512 2.499 1.977 1.953 1.773 1.759 1.754 1.745 1.740 1.502 1.496 1.479 1.473 1.064 1.051



3-49

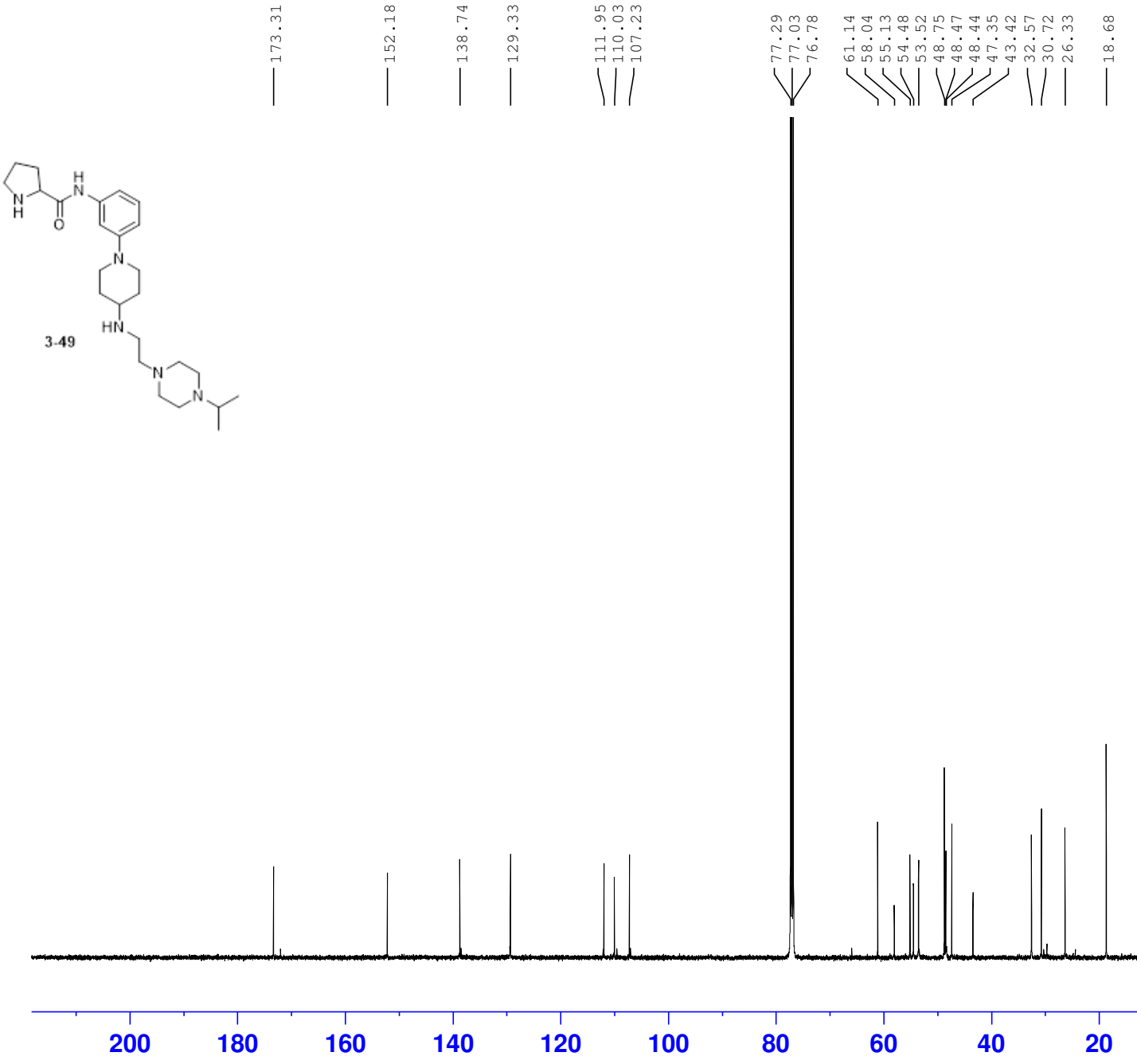
Current Data Parameters
NAME CNA-617-36
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20141125
Time 14.03
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 161
DW 50.000 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 500.1630887 MHz
NUC1 1H
P1 11.45 usec
PLW1 18.00000000 W

F2 - Processing parameters
SI 32768
SF 500.1600123 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

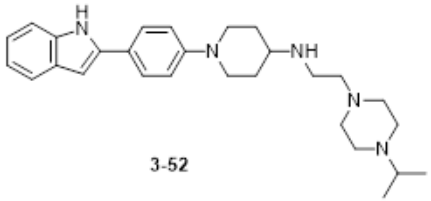
CNA-617-36, 13C, CDCl3, 500 MHz



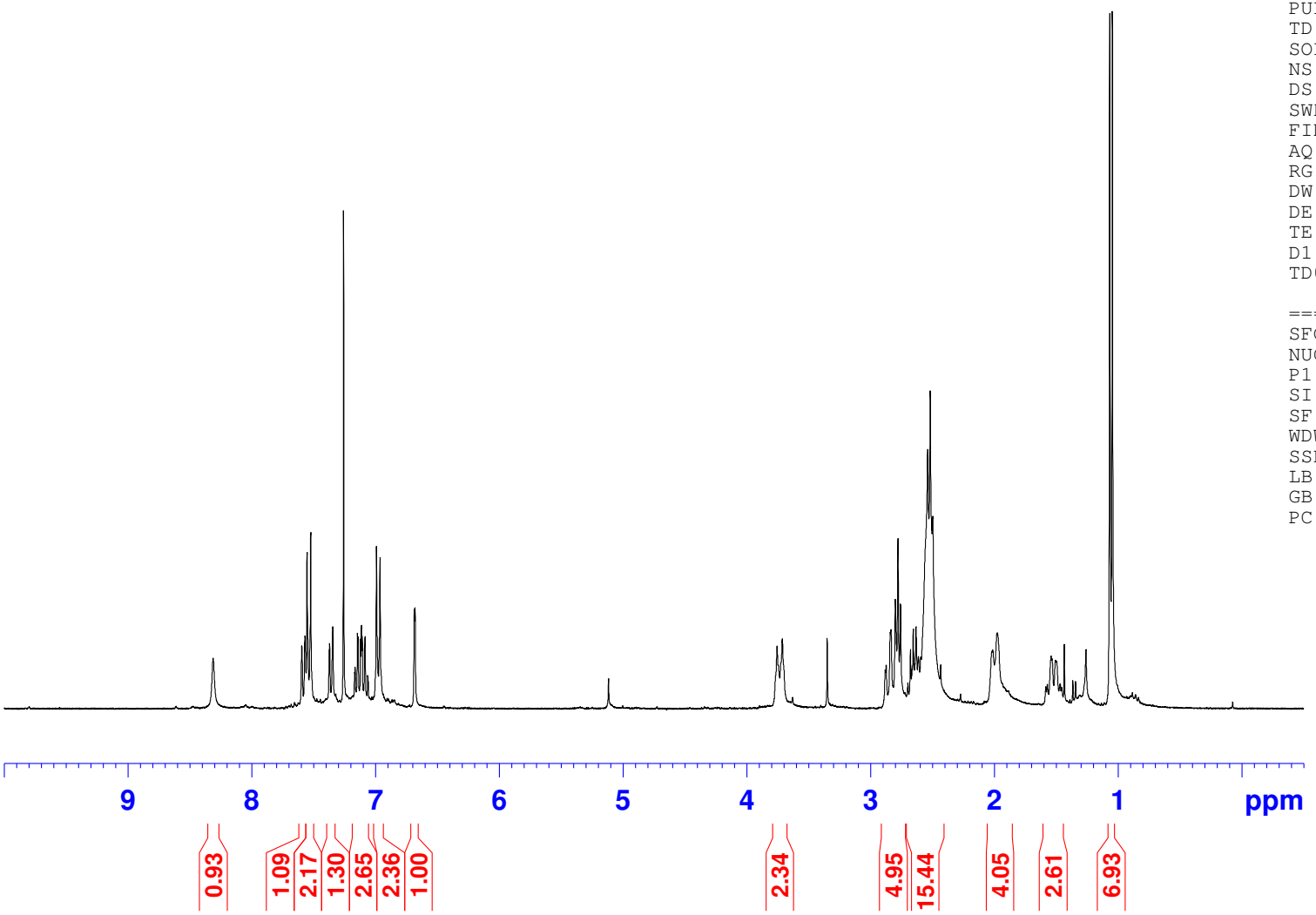

```
Current Data Parameters
NAME          CNA-617-36
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141125
Time                8.37
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  8250
DS                     2
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ            1.1010048 sec
RG                   203
DW                16.800 usec
DE                 6.50 usec
TE                298.8 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1        125.7779080 MHz
NUC1                13C
P1                10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2        500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.36873001 W
PLW13    0 W

F2 - Processing parameters
SI                 32768
SF          125.7653320 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

CNA-617-45, 1H, CDCl3, 300 MHz

8.315 7.598 7.573 7.556 7.526 7.373 7.347 7.260 7.148 7.144 7.123 7.115 7.110 7.089 7.086 6.995 6.965 6.688 6.684 3.757 3.714 2.841 2.836 2.801 2.780 2.759 2.678 2.656 2.634 2.614 2.596 2.539 2.519 2.498 2.434 2.014 1.977 1.542 1.534 1.507 1.499 1.435 1.068 1.047

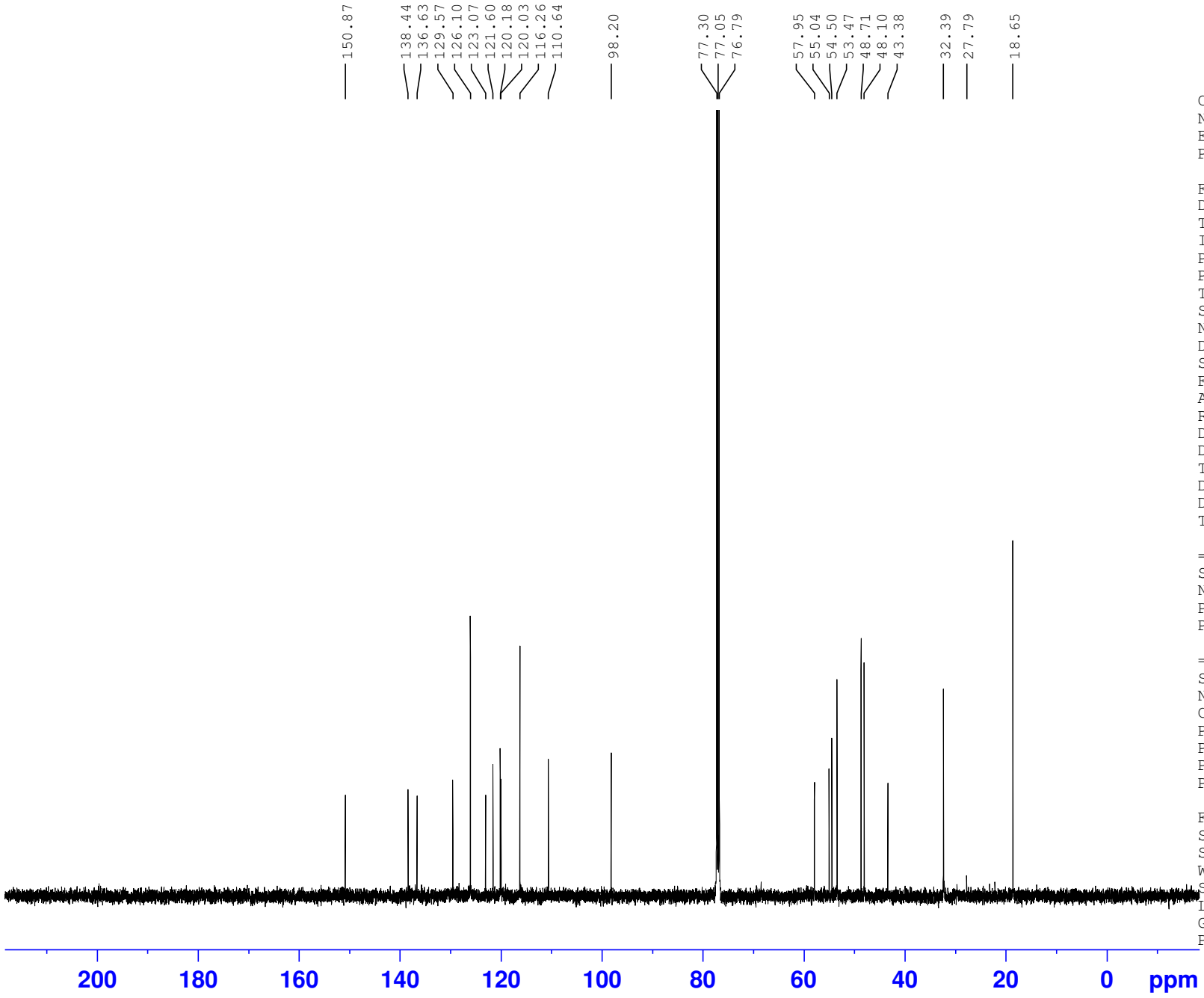


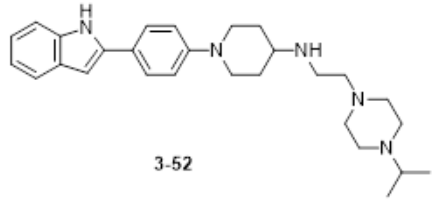
3-52



NAME	CNA-617-45	
EXPNO	1	
PROCNO	1	
Date_	20141211	
Time	11.29	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg30	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	2	
SWH	6188.119	Hz
FIDRES	0.188846	Hz
AQ	2.6477044	sec
RG	128	
DW	80.800	usec
DE	6.50	usec
TE	-926.3	K
D1	1.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
SFO1	300.2318540	MHz
NUC1	1H	
P1	12.71	usec
SI	32768	
SF	300.2300085	MHz
WDW	EM	
SSB	0	
LB	0.10	Hz
GB	0	
PC	1.00	

CNA-617-45, 13C, CDCl3, 500 MHz



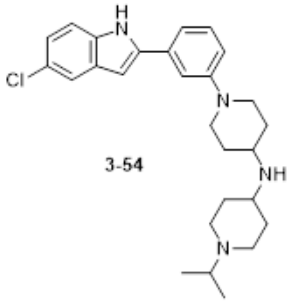


3-52

```
Current Data Parameters
NAME          CNA-617-45
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141210
Time               19.14
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1100
DS                    2
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ            1.1010048 sec
RG                  203
DW                16.800 usec
DE                 6.50 usec
TE                298.6 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        125.7779080 MHz
NUC1                13C
P1                10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2        500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.36873001 W
PLW13     0 W

F2 - Processing parameters
SI                 32768
SF          125.7653320 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

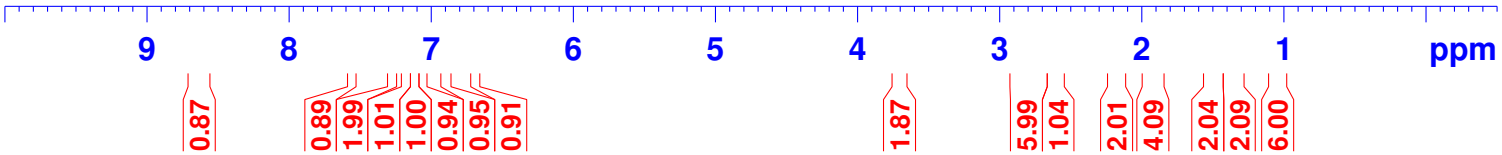
CNA-617-81, 1H, CDCl3, 400 MHz

7.560 7.556 7.299 7.278 7.275 7.260 7.253 7.175 7.171 7.122 7.117 7.100 7.095 7.065 7.046 6.907 6.902 6.886 6.881 6.692 3.723 3.692 2.876 2.845 2.814 2.789 2.719 2.703 2.203 2.177 2.174 1.949 1.918 1.884 1.508 1.502 1.481 1.474 1.362 1.357 1.335 1.329 1.047 1.031



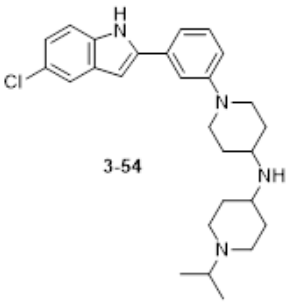
3-54

NAME	CNA-617-81
EXPNO	1
PROCNO	1
Date_	20150128
Time	18.41
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	40.3
DW	60.800 usec
DE	6.50 usec
TE	298.0 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300122 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



0.87 0.89 1.99 1.01 1.00 0.94 0.95 0.91 1.87 5.99 1.04 2.01 4.09 2.04 2.09 6.00

CNA-617-81, 13C, CDCl3, 400 MHz

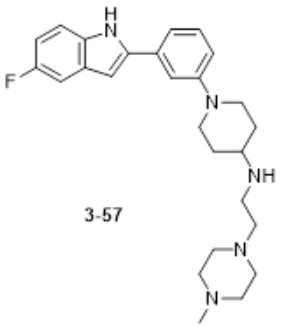


152.02
140.17
135.06
132.78
130.34
129.72
125.65
122.29
119.85
116.35
116.18
113.47
111.86
99.37
77.42
77.30
77.10
76.78
54.44
51.63
51.10
48.53
47.83
33.81
33.03
18.48

NAME	CNA-617-81
EXPNO	2
PROCNO	1
Date_	20150128
Time	18.51
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	425
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	57
DW	20.800 usec
DE	6.50 usec
TE	298.0 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-695-61, 1H, acetone-d6, 300 MHz

7.442 7.398 7.383 7.369 7.354 7.283 7.260 7.226 7.217 6.937 6.930 6.914 6.909 6.901 6.878 6.868 6.858 6.848 3.777 3.766 3.746 3.735 3.562 2.904 2.896 2.858 2.825 2.817 2.762 2.741 2.721 2.659 2.461 2.441 2.421 2.347 2.169 2.050 1.996 1.987 1.946 1.912 1.495 1.458

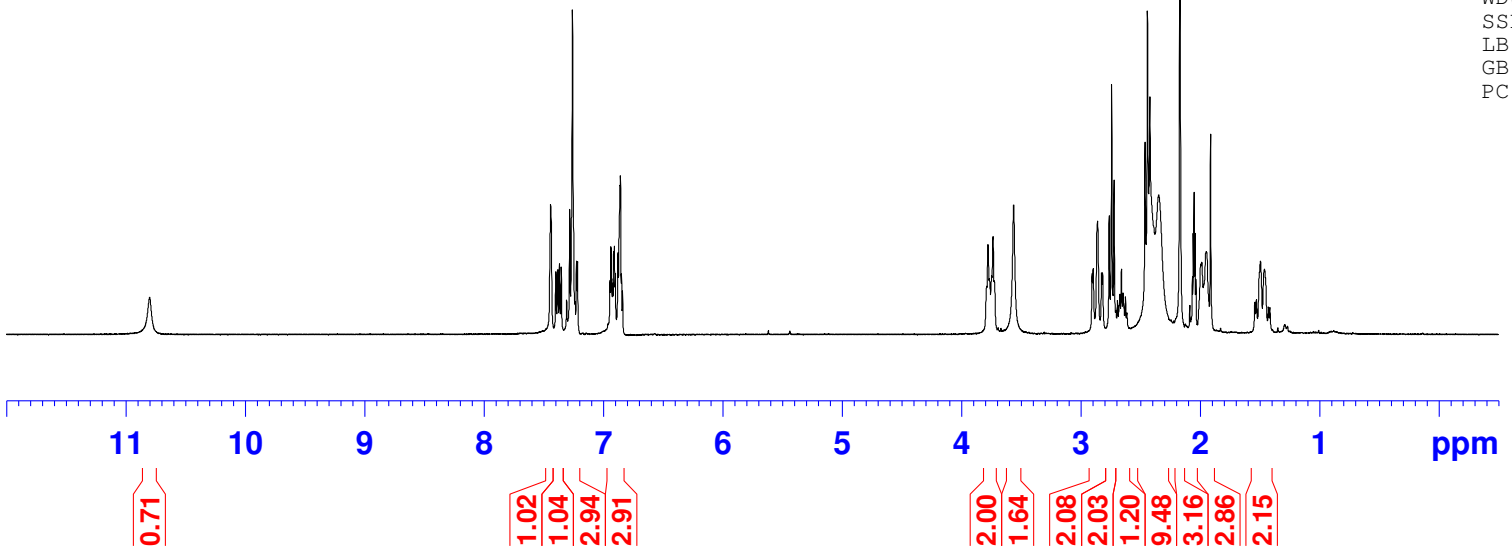


3-57

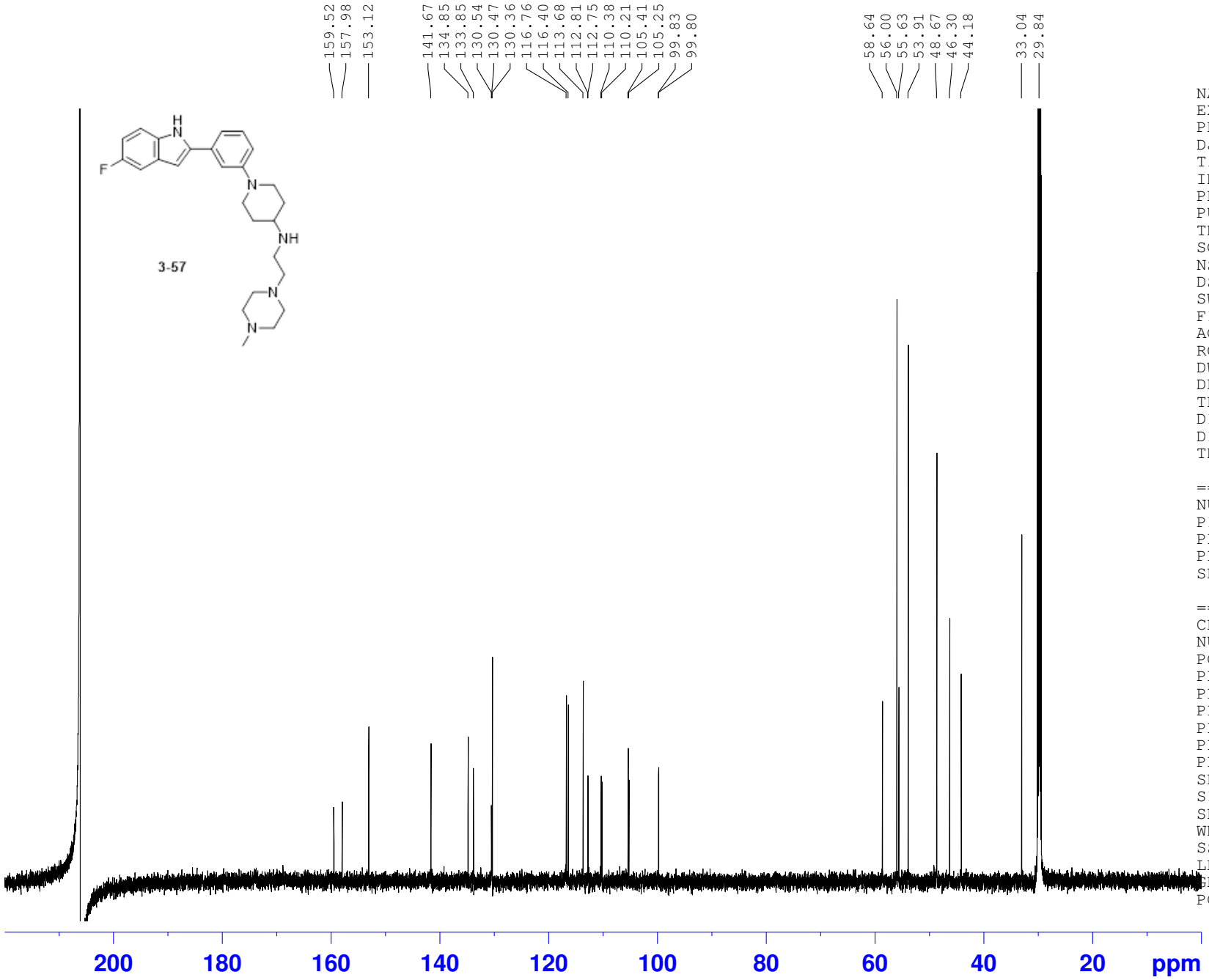
NAME	CNA-695-61
EXPNO	1
PROCNO	1
Date_	20160216
Time	21.41
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	32768
SOLVENT	Acetone
NS	16
DS	2
SWH	6188.119 Hz
FIDRES	0.188846 Hz
AQ	2.6477044 sec
RG	101
DW	80.800 usec
DE	6.50 usec
TE	-928.2 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

SFO1	300.2318540 MHz
NUC1	1H
P1	12.71 usec
SI	32768
SF	300.2300064 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

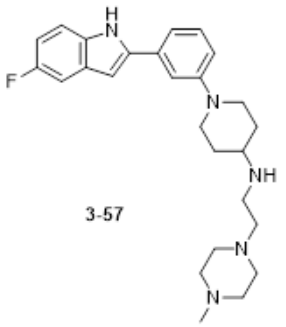


CNA-695-61, 13C, acetone-d6, 600 MHz



NAME	CNA-695-61
EXPNO	2
PROCNO	1
Date_	20160217
Time	15.19
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	Acetone
NS	350
DS	4
SWH	36057.691 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	203
DW	13.867 usec
DE	6.50 usec
TE	297.5 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	11.50 usec
PL1	0.00 dB
PL1W	97.46119690 W
SFO1	151.0637542 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	70.00 usec
PL2	-2.00 dB
PL12	14.19 dB
PL13	120.00 dB
PL2W	19.70630455 W
PL12W	0.47381112 W
PL13W	0.00000000 W
SFO2	600.7124028 MHz
SI	32768
SF	151.0485175 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

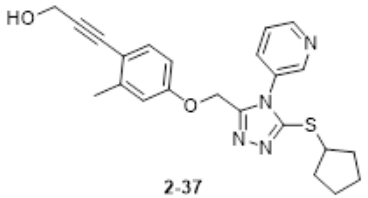
CNA-695-651, 19F, acetone-d6, 600 MHz



3-57

NAME	CNA-695-61
EXPNO	3
PROCNO	1
Date_	20160217
Time	17.33
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgfhigqn
TD	131072
SOLVENT	Acetone
NS	16
DS	4
SWH	85227.273 Hz
FIDRES	0.650232 Hz
AQ	0.7690057 sec
RG	203
DW	5.867 usec
DE	6.50 usec
TE	297.4 K
D1	3.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	19F
P1	11.00 usec
PL1	-4.00 dB
PL1W	44.04082108 W
SFO1	565.1484826 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	70.00 usec
PL2	-2.00 dB
PL12	14.19 dB
PL2W	19.70630455 W
PL12W	0.47381112 W
SFO2	600.7124028 MHz
SI	65536
SF	565.2321340 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

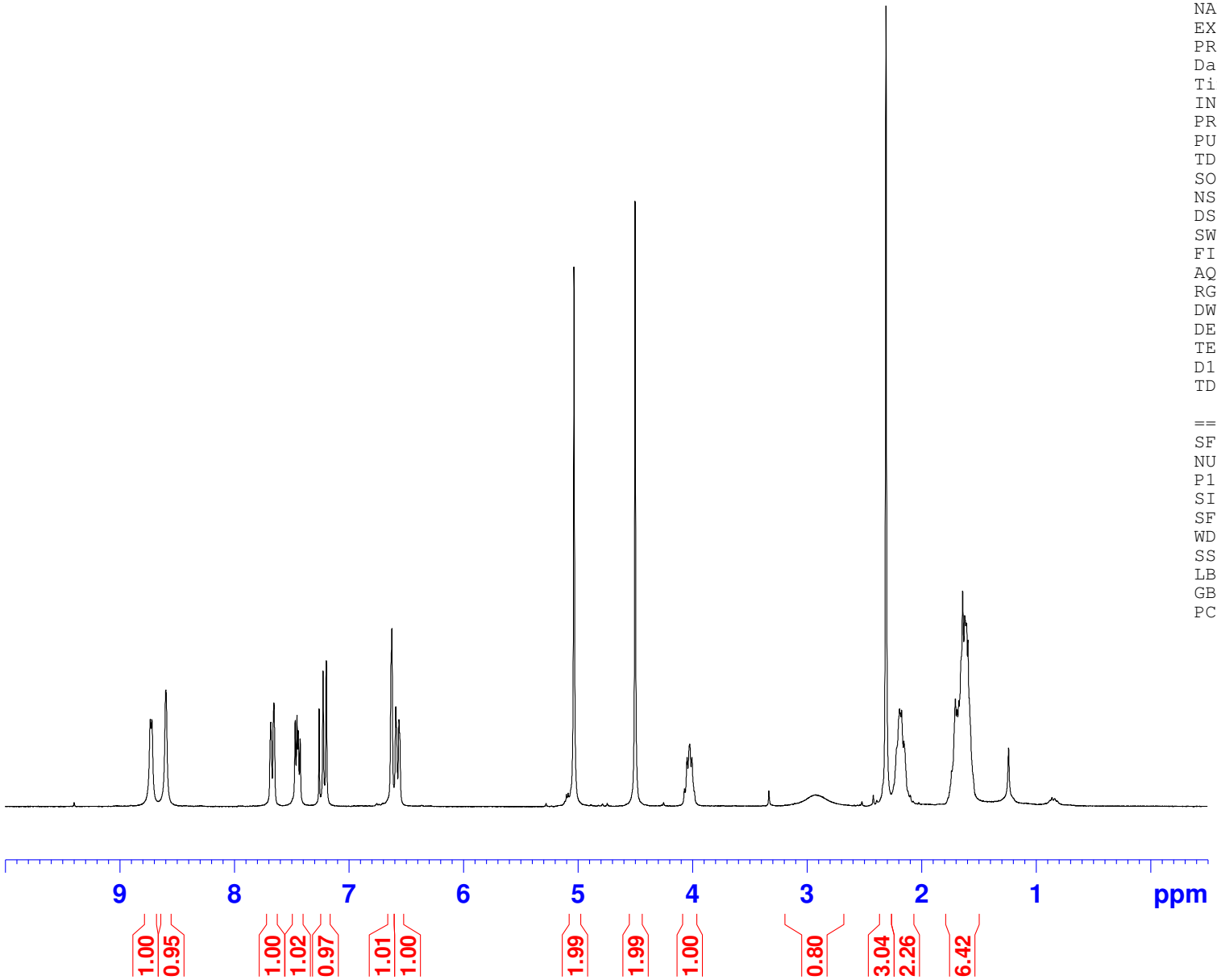
CNA-695-21, 1H, CDCl3, 300 MHz



2-37

8.735 8.722 8.599 7.683 7.656 7.469 7.453 7.442 7.426 7.260 7.226 7.198 6.625 6.591 6.563

5.035 4.500 4.070 4.047 4.024 4.005 2.935 2.309 2.191 2.185 2.174 2.154 1.736 1.704 1.689 1.674 1.640 1.622 1.610 1.593

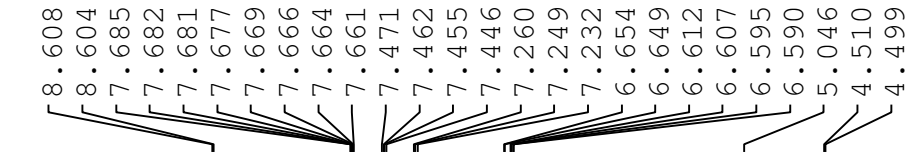


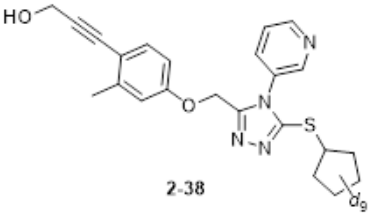
NAME	CNA-695-21
EXPNO	1
PROCNO	1
Date_	20160223
Time	20.51
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6188.119 Hz
FIDRES	0.188846 Hz
AQ	2.6477044 sec
RG	71.8
DW	80.800 usec
DE	6.50 usec
TE	-929.1 K
D1	1.00000000 sec
TD0	1

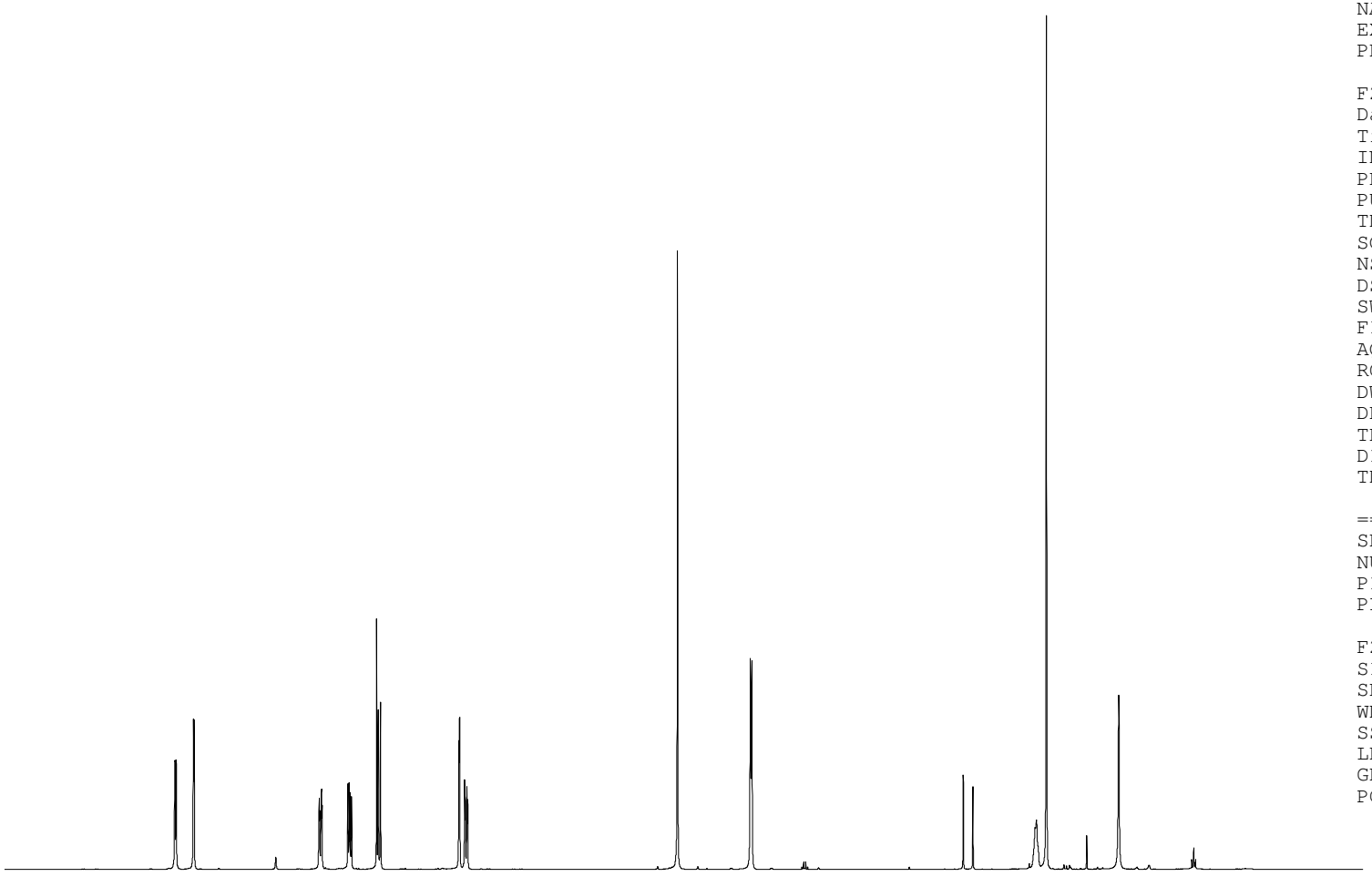
======== CHANNEL f1 ========

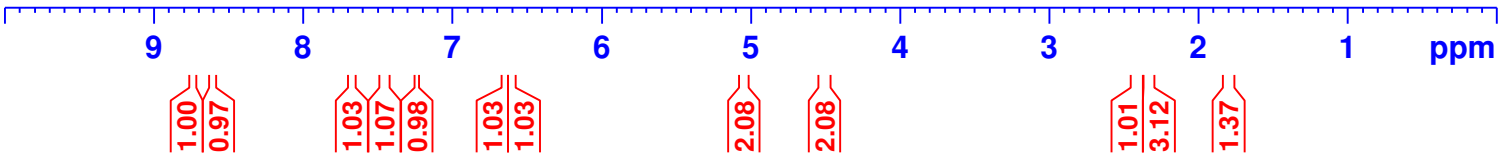
SFO1	300.2318540 MHz
NUC1	1H
P1	12.71 usec
SI	32768
SF	300.2300091 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

CNA-710-87, 1H, CDCl3, 500 MHz



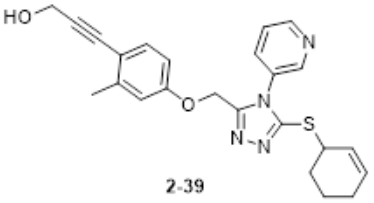






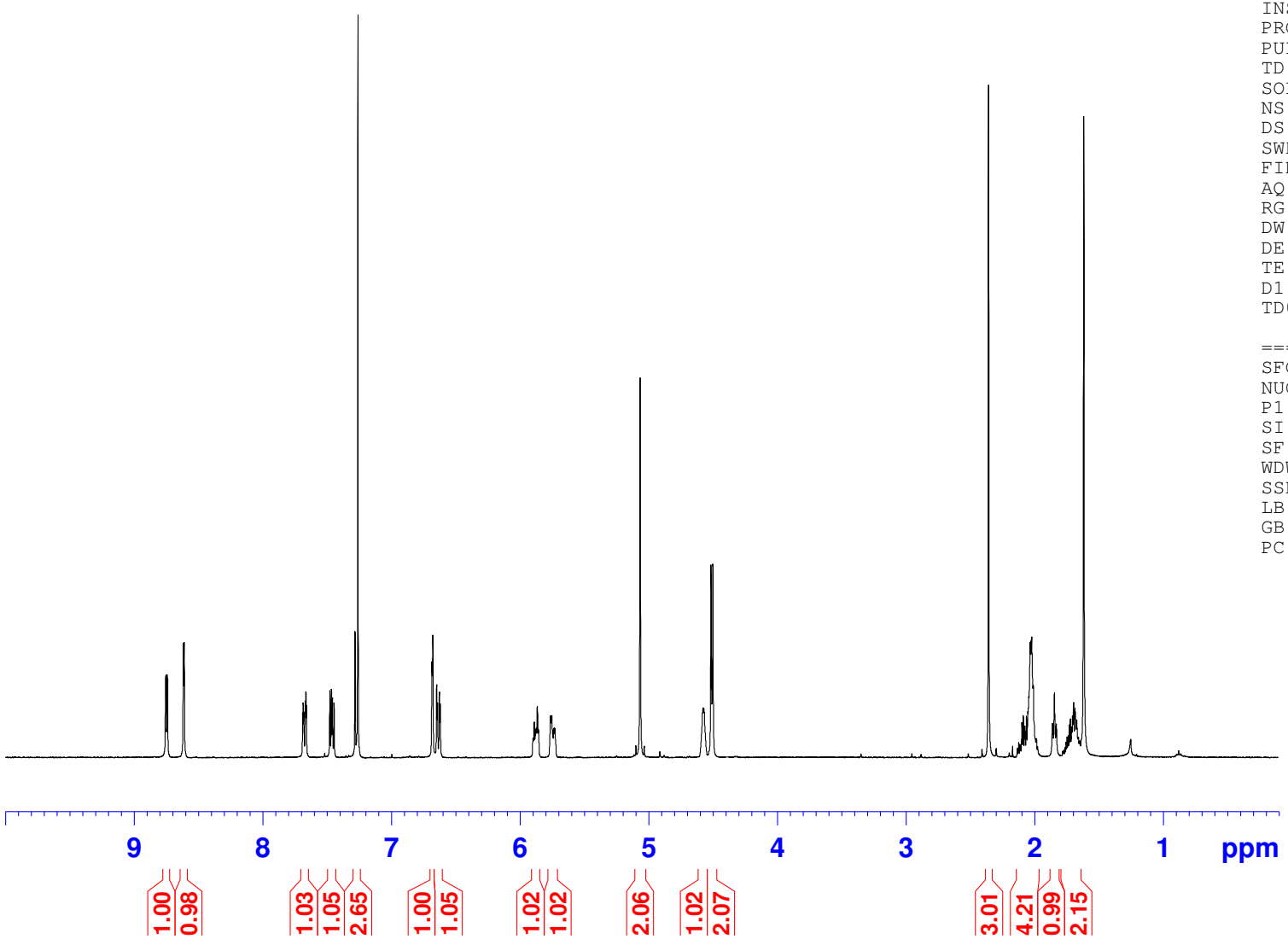

```
Current Data Parameters
NAME          CNA-710-87
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20161013
Time               16.19
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES             0.152588 Hz
AQ             3.2767999 sec
RG                   101
DW                50.000 usec
DE                 6.50 usec
TE                295.9 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1630887 MHz
NUC1                   1H
P1                 11.50 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1600130 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-710-47, 1H, CDCl3, 400 MHz



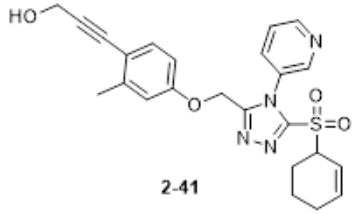
8.756 8.752 8.744 8.740 8.617 8.611 7.686 7.684 7.680 7.670 7.666 7.664 7.660 7.478 7.466 7.458 7.446 7.282 7.260 6.684 6.678 6.648 6.641 6.626 6.620 5.866 5.864 5.066 4.577 4.571 4.515 4.500 2.356 2.051 2.043 2.034 2.030 2.025 2.020 2.008 1.844 1.694 1.685 1.616

NAME	CNA-710-47
EXPNO	2
PROCNO	1
Date_	20160515
Time	19.12
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8012.820 Hz
FIDRES	0.122266 Hz
AQ	4.0894966 sec
RG	144
DW	62.400 usec
DE	6.50 usec
TE	97.3 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	400.1324710 MHz
NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300105 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



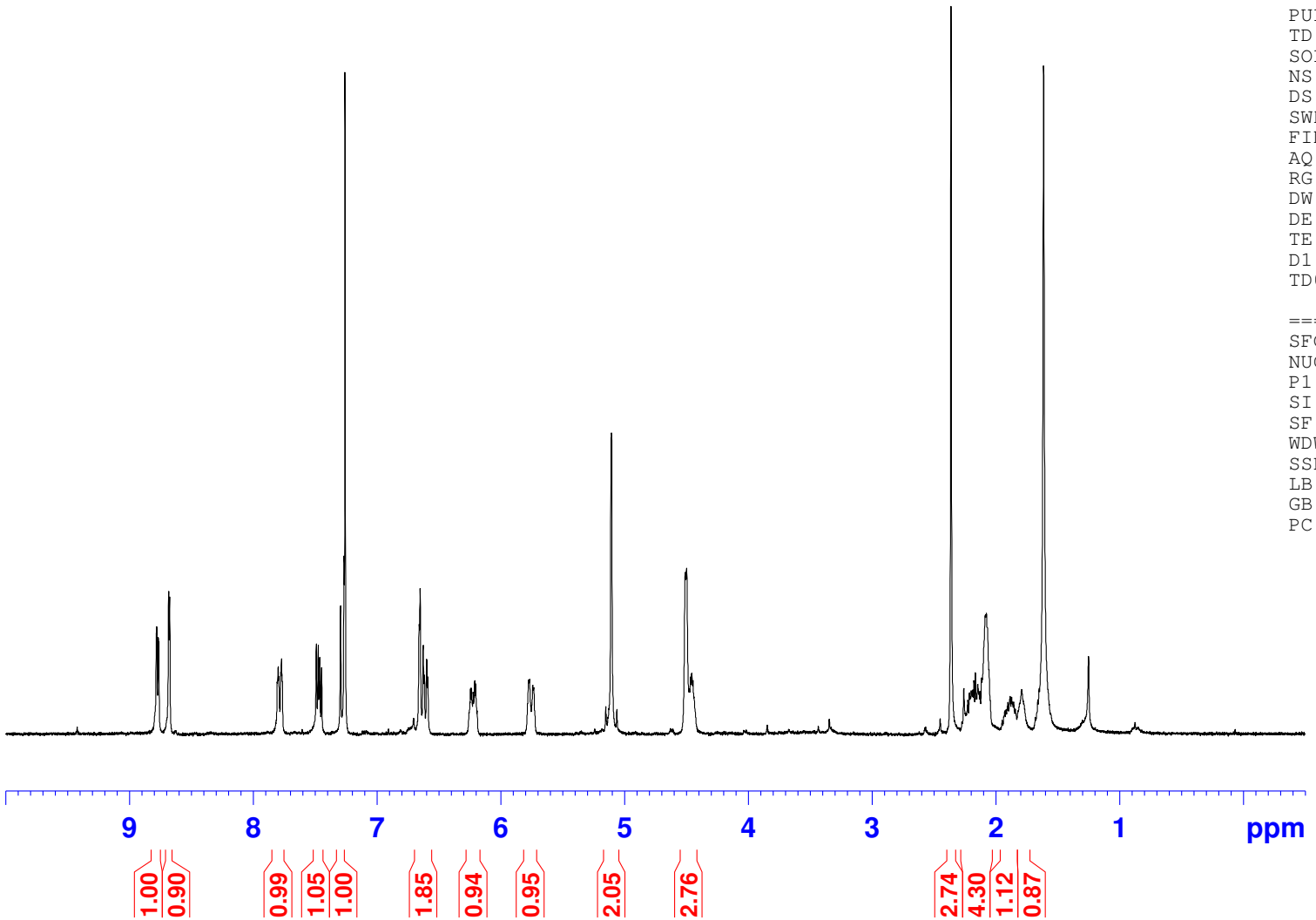
CNA-710-78, 1H, CDCl3, 300 MHz

8.781 8.769 8.765 8.685 8.677 7.800 7.795 7.779 7.772 7.767 7.492 7.476 7.465 7.449 7.297 7.268 7.260 6.661 6.653 6.628 6.619 6.600 6.591 6.239 6.212 6.205 5.777 5.768 5.743 5.734 5.110 5.105 4.510 4.499 4.467 4.458 4.448 2.362 2.178 2.165 2.146 2.115 2.086 2.075

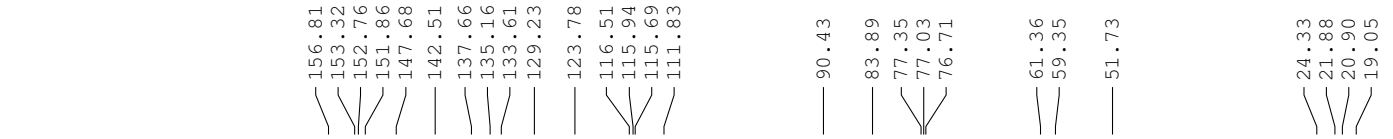


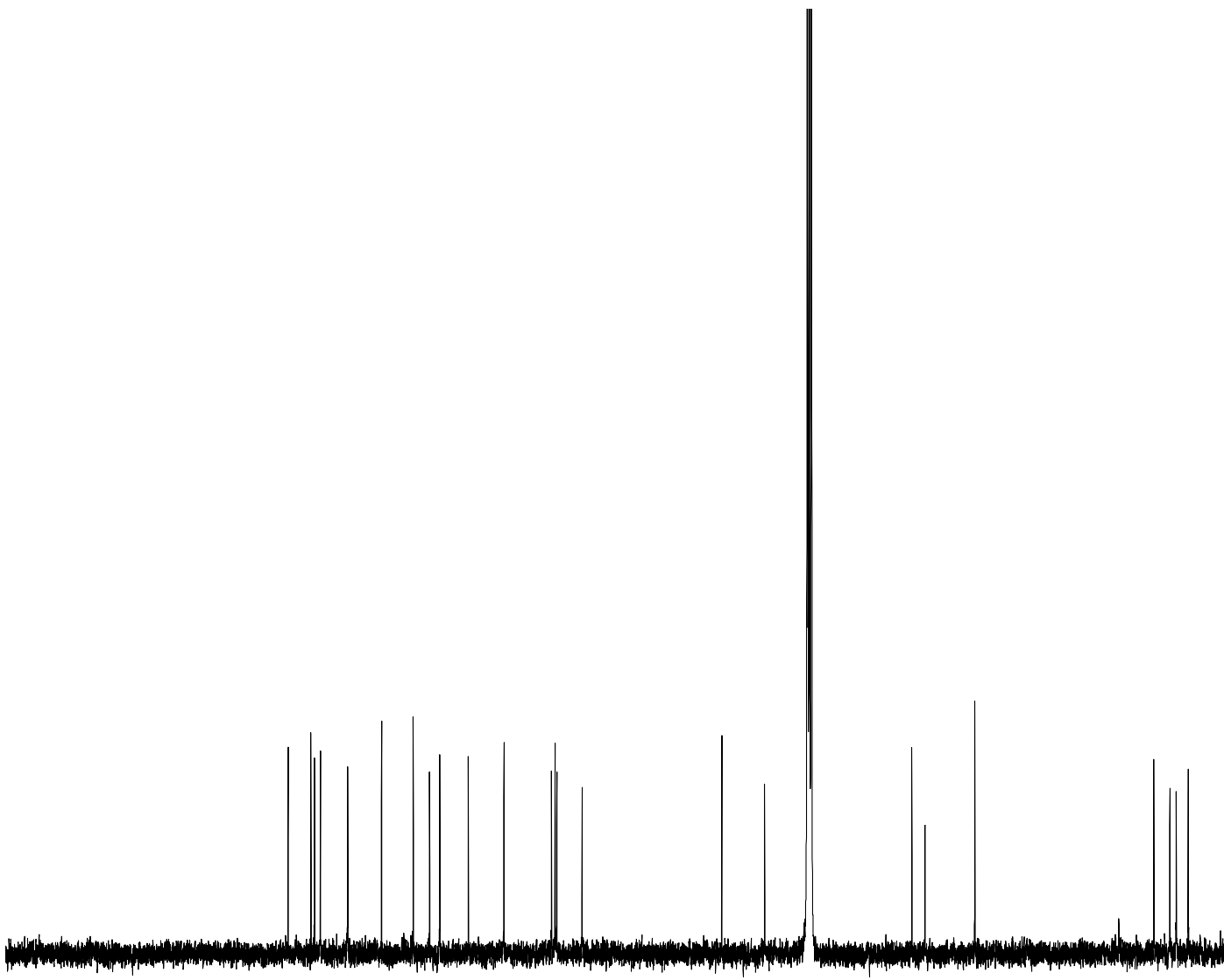
2-41

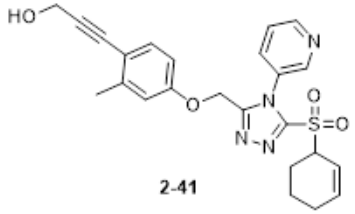
NAME	CNA-710-78
EXPNO	2
PROCNO	1
Date_	20161012
Time	18.18
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6188.119 Hz
FIDRES	0.188846 Hz
AQ	2.6477044 sec
RG	322
DW	80.800 usec
DE	6.50 usec
TE	-925.0 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	300.2318540 MHz
NUC1	1H
P1	12.71 usec
SI	32768
SF	300.2300093 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00



CNA-710-78, 13C, CDCl3, 400 MHz



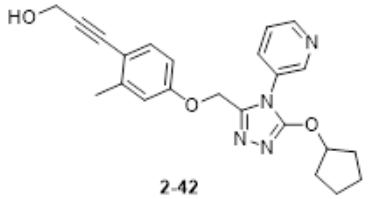




2-41

NAME	CNA-710-78
EXPNO	3
PROCNO	1
Date_	20161010
Time	23.52
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	9216
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	298.2 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	9
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-710-83/95, 1H, CDCl3, 600 MHz



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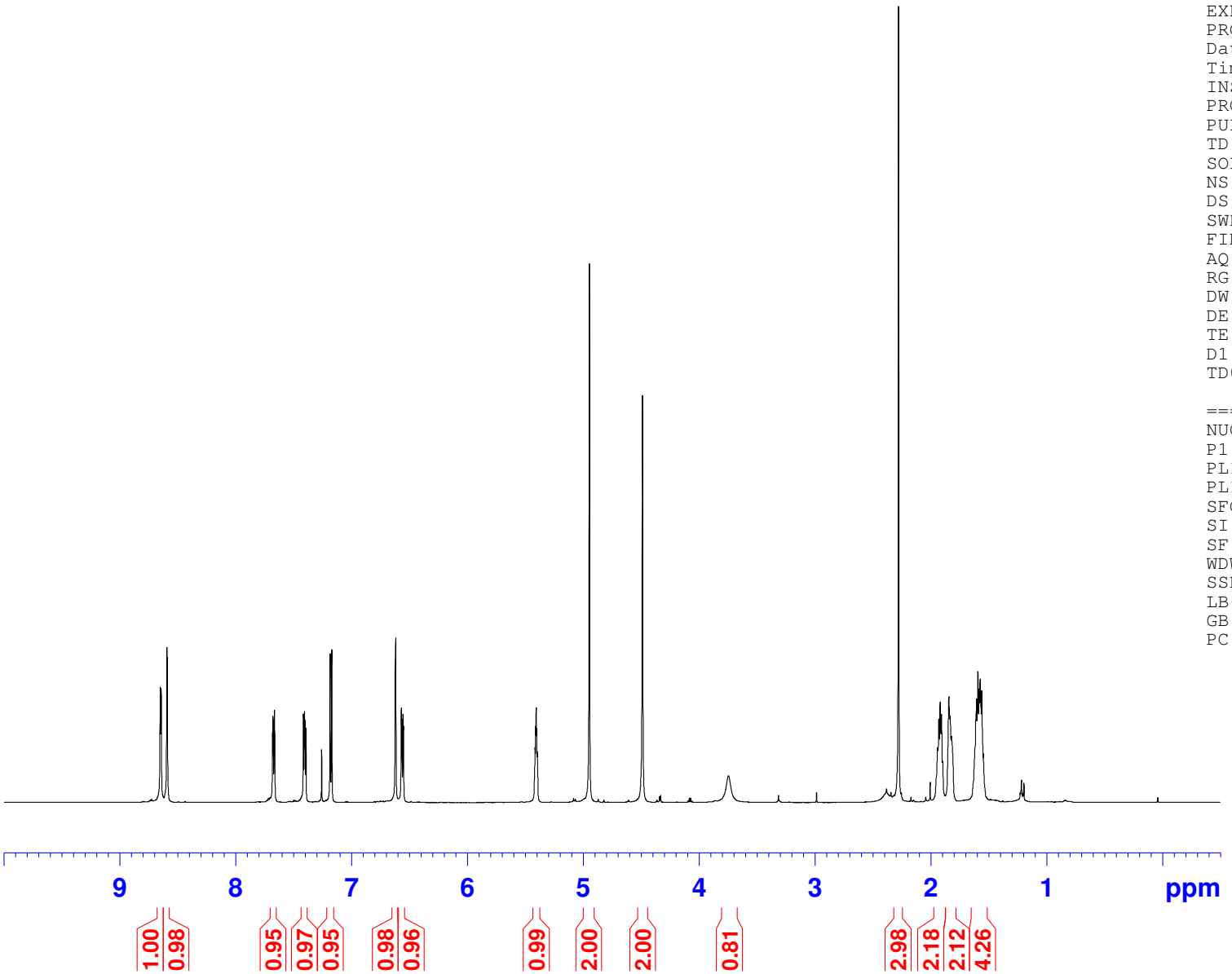
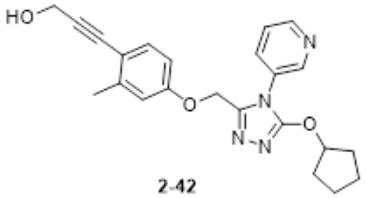
8.653 8.646 8.596 8.592 7.681 7.668 7.417 7.409 7.404 7.396 7.260 7.187 7.173 6.623 6.620 6.572 6.568 6.558 6.554 5.417 5.412 5.408 5.403 5.399 4.949 4.491 2.280 1.943 1.939 1.931 1.920 1.909 1.845 1.834 1.822 1.619 1.607 1.599 1.595 1.584 1.582 1.574 1.562 1.548



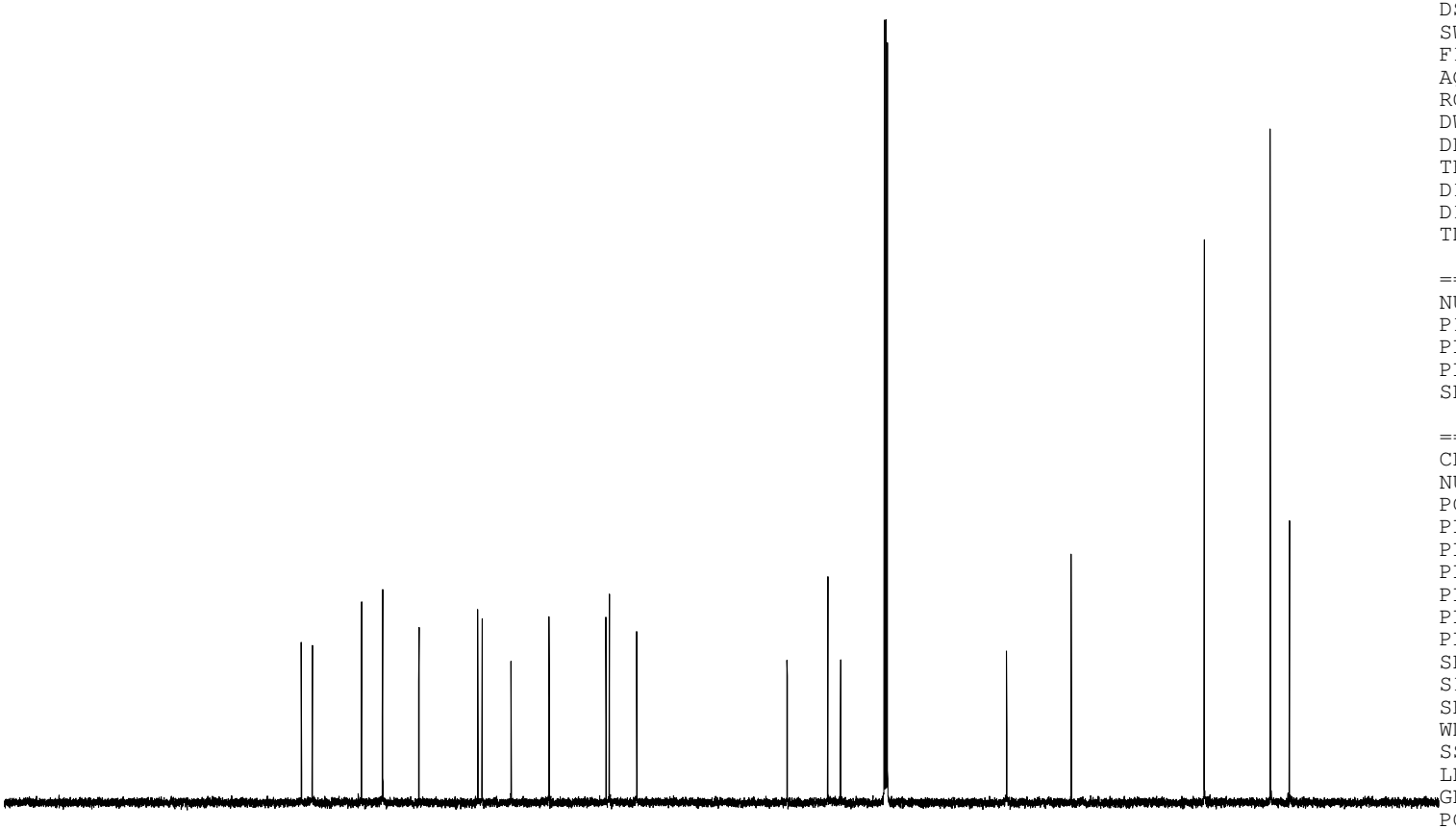
NAME	CNA-710-83-95
EXPNO	1
PROCNO	1
Date_	20161012
Time	18.21
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	12335.526 Hz
FIDRES	0.188225 Hz
AQ	2.6564426 sec
RG	32
DW	40.533 usec
DE	6.50 usec
TE	294.4 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.86 usec
PL1	-2.00 dB
PL1W	19.70630455 W
SFO1	600.7137096 MHz
SI	32768
SF	600.7100139 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-710-83/95, 13C, CDCl3, 600 MHz



2-42

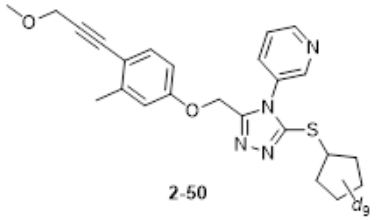
158.61
157.08
150.22
147.30
147.25
142.22
134.01
133.40
129.37
124.07
116.13
115.66
111.85
90.88
85.20
83.43
77.33
77.12
76.91
60.28
51.28
32.72
23.52
20.85



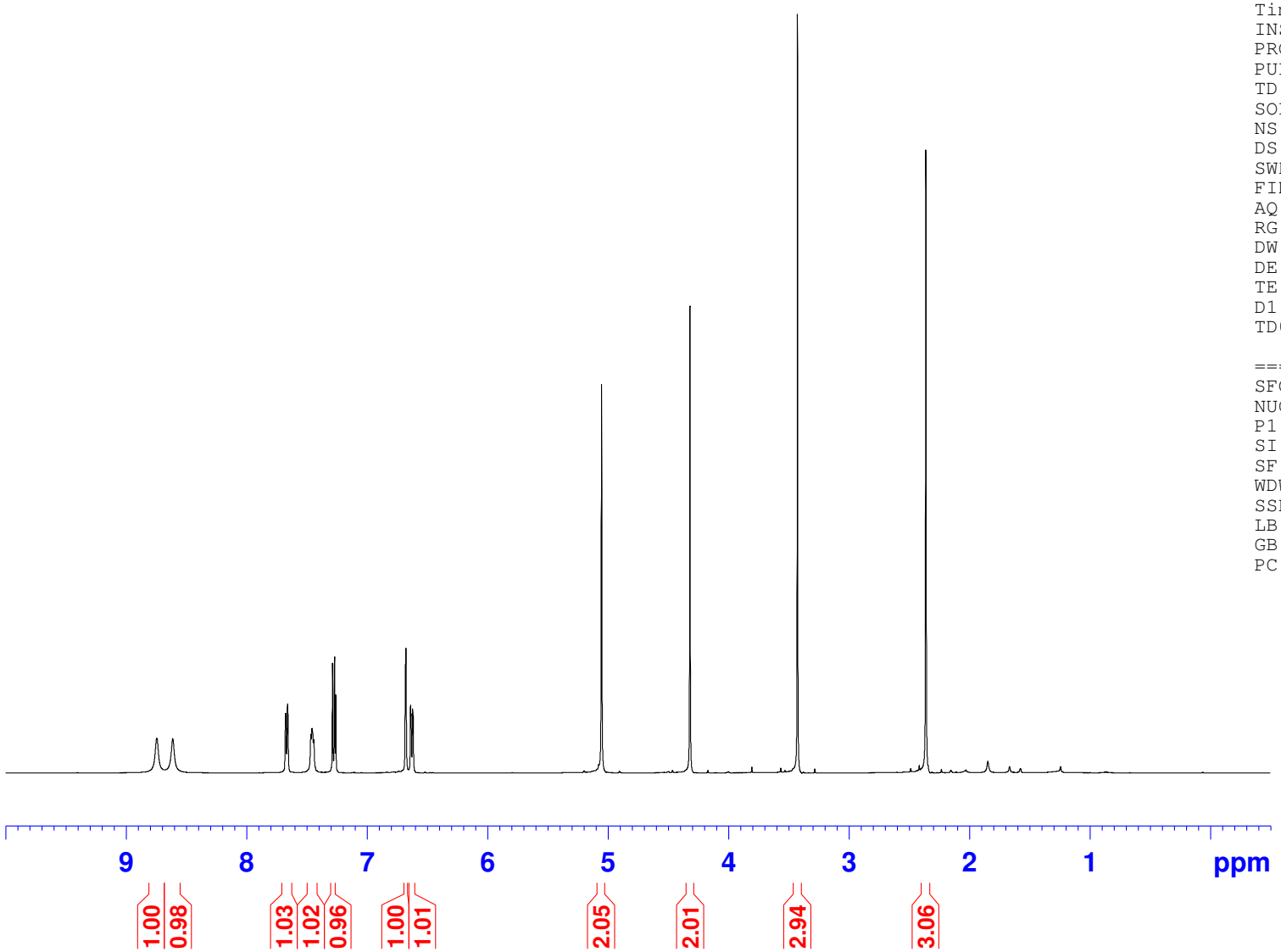
180 160 140 120 100 80 60 40 20 ppm

NAME	CNA-710-83-95	
EXPNO	2	
PROCNO	1	
Date_	20161012	
Time	18.38	
INSTRUM	spect	
PROBHD	5 mm PABBO BB-	
PULPROG	zgpg30	
TD	65536	
SOLVENT	CDCl3	
NS	253	
DS	4	
SWH	36057.691	Hz
FIDRES	0.550197	Hz
AQ	0.9088159	sec
RG	203	
DW	13.867	usec
DE	6.50	usec
TE	294.8	K
D1	2.00000000	sec
D11	0.03000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	13C	
P1	11.50	usec
PL1	0.00	dB
PL1W	97.46119690	W
SFO1	151.0637542	MHz
======== CHANNEL f2 ========		
CPDPRG2	waltz16	
NUC2	1H	
PCPD2	70.00	usec
PL2	-2.00	dB
PL12	14.19	dB
PL13	120.00	dB
PL2W	19.70630455	W
PL12W	0.47381112	W
PL13W	0.00000000	W
SFO2	600.7124028	MHz
SI	32768	
SF	151.0486500	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

CNA-695-31, 1H, CDCl3, 500 MHz

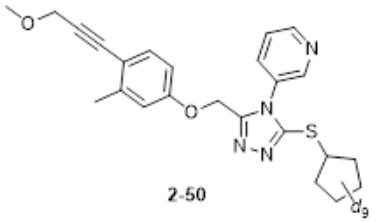


8.747
8.614
7.676
7.660
7.468
7.458
7.453
7.443
7.287
7.270
7.260
6.678
6.639
6.635
6.622
6.618
5.054
4.320
3.427
2.361



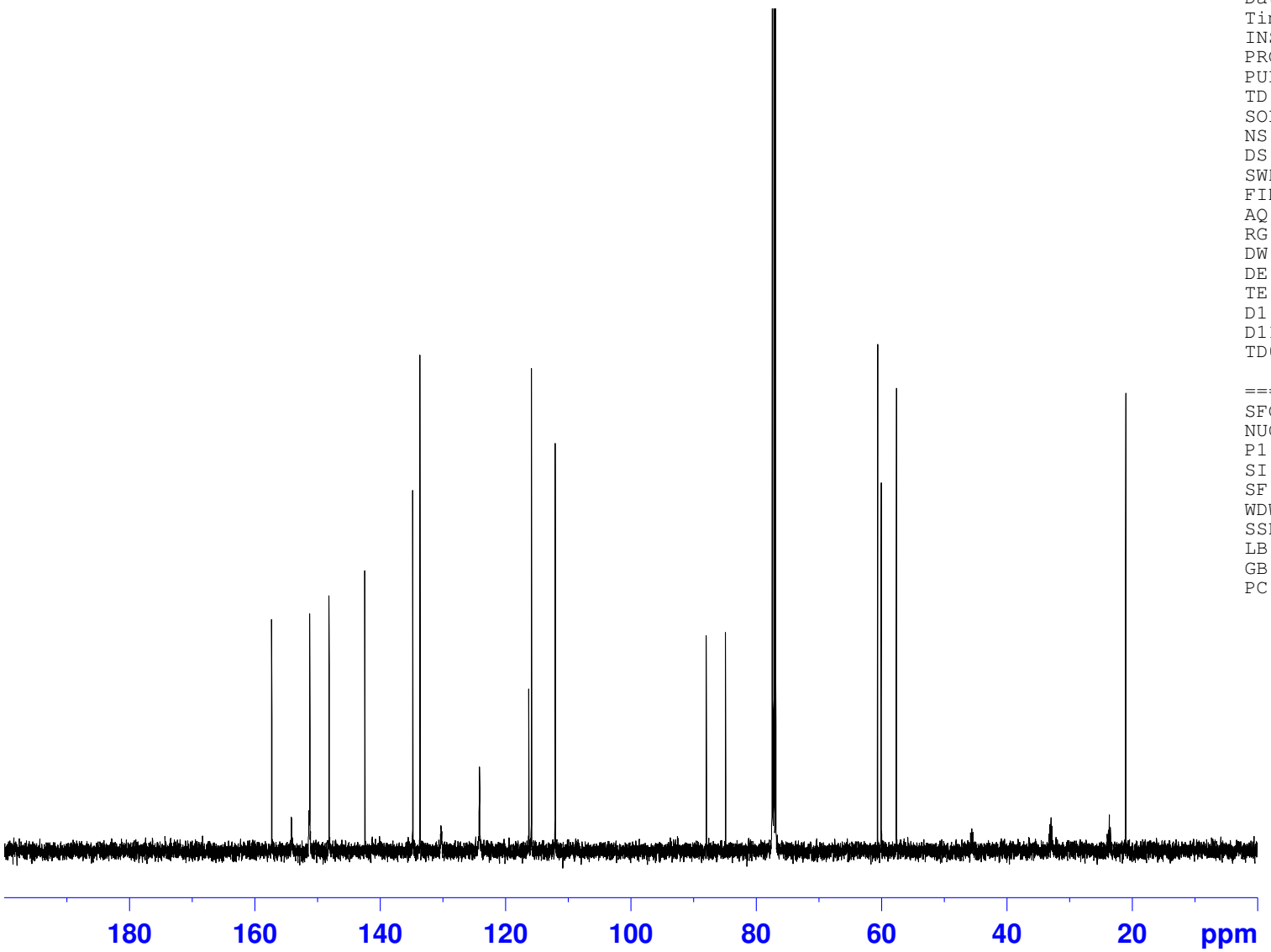
NAME	CNA-695-31
EXPNO	1
PROCNO	1
Date_	20160121
Time	11.12
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	10000.000 Hz
FIDRES	0.152588 Hz
AQ	3.2768500 sec
RG	71.8
DW	50.000 usec
DE	6.50 usec
TE	299.6 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	500.1630887 MHz
NUC1	1H
P1	11.45 usec
SI	65536
SF	500.1600130 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-695-31, 1H, CDCl3, 500 MHz



157.316
154.174
151.357
151.244
148.167
142.461
134.818
133.662
130.297
124.159
116.306
115.876
112.088

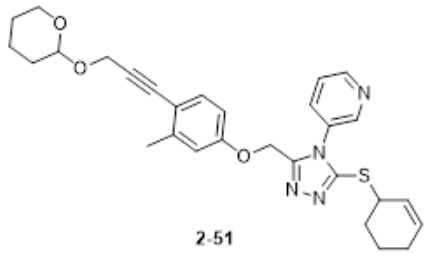
87.964
84.886
77.412
77.158
76.904
60.617
60.053
57.618
45.790
45.595
45.408
33.118
32.957
32.800
23.806
23.635
23.485
21.018

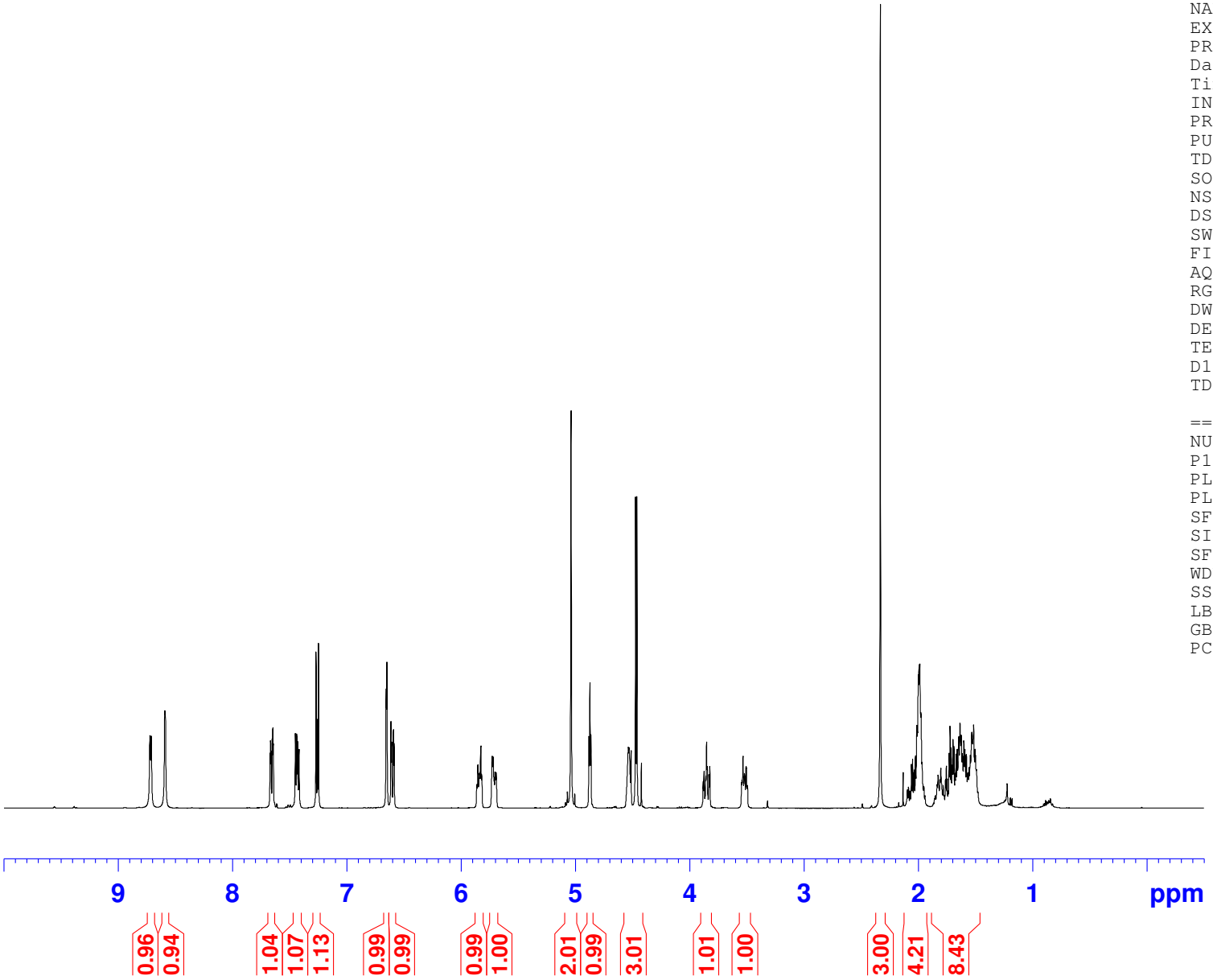


NAME	CNA-695-31
EXPNO	2
PROCNO	1
Date_	20160121
Time	11.43
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	565
DS	2
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 usec
DE	6.50 usec
TE	300.6 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	125.7779086 MHz
NUC1	13C
P1	10.50 usec
SI	32768
SF	125.7653166 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-695-20, 1H, CDCl3, 400 MHz

8.721 8.711 8.591 8.587 7.671 7.654 7.651 7.648 7.453 7.441 7.271 7.260 7.250 6.658 6.652 6.617 6.595 5.040 4.884 4.875 4.867 4.476 4.464 3.854 2.334 2.014 2.009 2.000 1.996 1.991 1.987 1.978 1.723 1.697 1.649 1.646 1.636 1.626 1.624 1.603 1.533 1.529 1.522 1.517



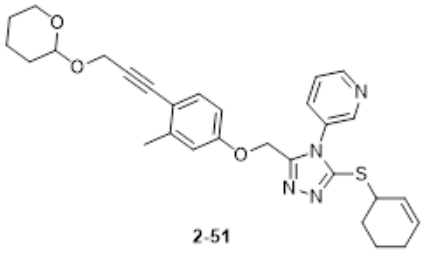


NAME	CNA-695-20
EXPNO	1
PROCNO	1
Date_	20160107
Time	22.44
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	36
DW	60.800 usec
DE	6.50 usec
TE	295.5 K
D1	2.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300095 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-695-20, 13C, CDCl3, 400 MHz



157.14
153.47
151.42
151.19
148.07
142.48
134.80
133.64
132.42
132.07
130.04
125.43
124.09
116.24
115.71
111.91
96.71
88.04
84.22
77.48
77.36
77.16
76.84
62.13
59.88
54.85
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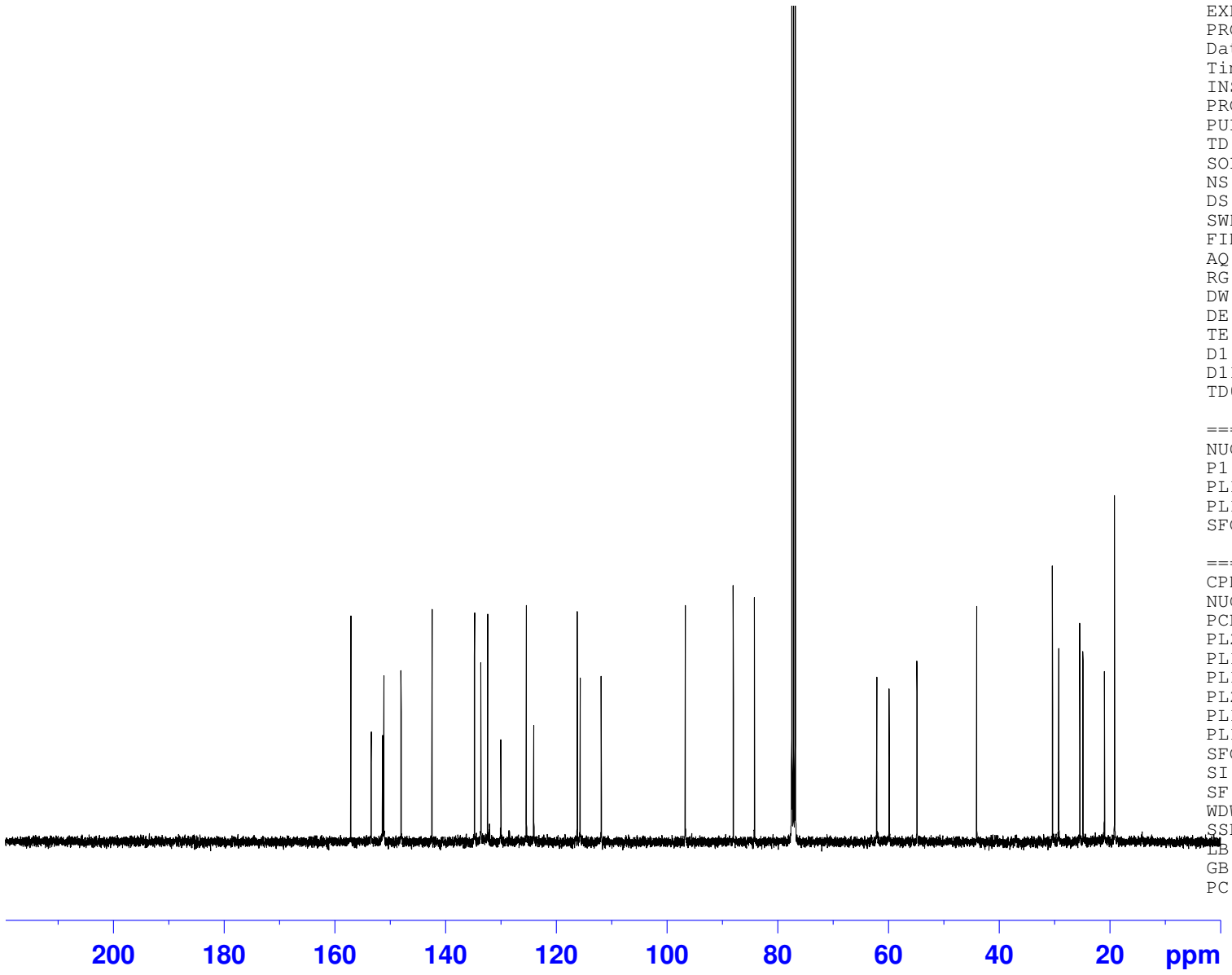
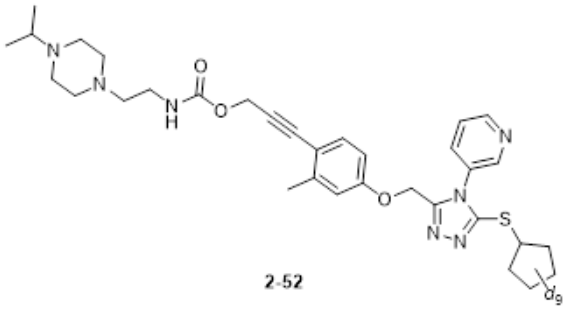
30.37
29.23
25.43
24.87
20.98
19.17



NAME	CNA-695-20
EXPNO	2
PROCNO	1
Date_	20160107
Time	23.24
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	295.7 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379094 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-695-29, 1H, CDCl3, 400 MHz

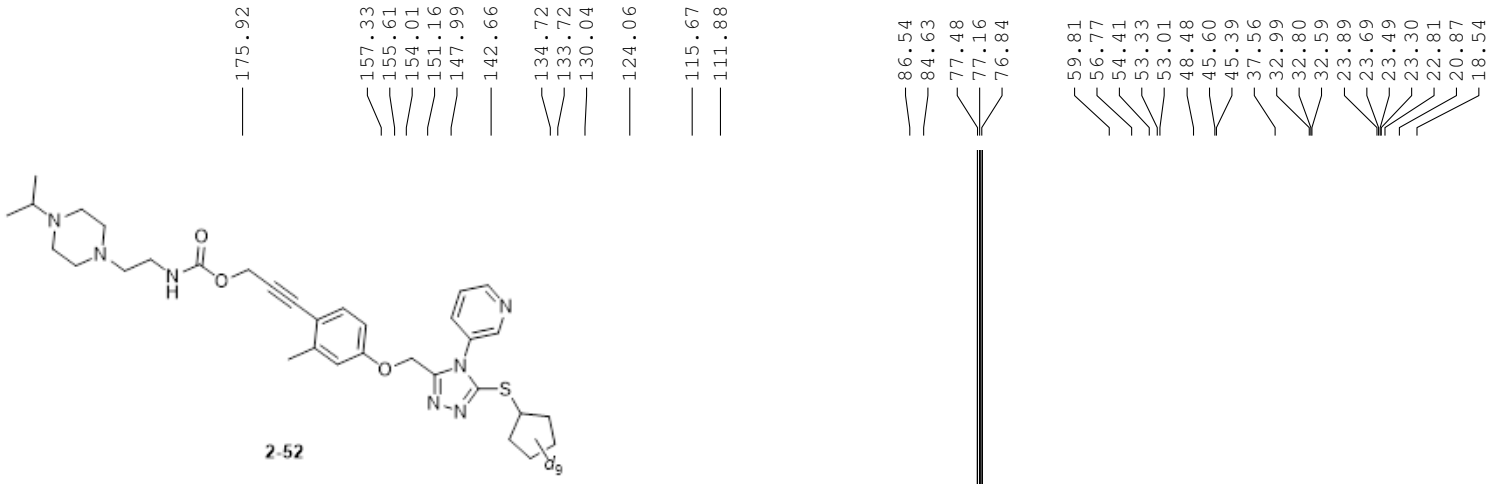
8.567 8.561 7.653 7.649 7.644 7.633 7.628 7.624 7.432 7.420 7.412 7.399 7.260 7.247 7.225 6.633 6.627 6.594 6.587 6.572 6.566 5.455 5.012 4.864 3.269 3.255 3.241 3.227 2.640 2.624 2.608 2.591 2.575 2.484 2.462 2.446 2.431 2.416 2.305 1.000 0.984



NAME	CNA-695-29
EXPNO	1
PROCNO	1
Date_	20160120
Time	19.12
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	36
DW	60.800 usec
DE	6.50 usec
TE	295.6 K
D1	2.00000000 sec
TD0	1

======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300095 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-695-29, 13C, CDCl3, 400 MHz

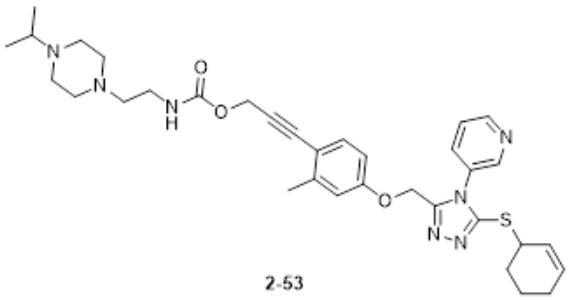


175.92
157.33
155.61
154.01
151.16
147.99
142.66
134.72
133.72
130.04
124.06
115.67
111.88
86.54
84.63
77.48
77.16
76.84
59.81
56.77
54.41
53.33
53.01
48.48
45.60
45.39
37.56
32.99
32.80
32.59
23.89
23.69
23.49
23.30
22.81
20.87
18.54

NAME	CNA-695-29
EXPNO	2
PROCNO	1
Date_	20160120
Time	19.24
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	256
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	295.8 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379126 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

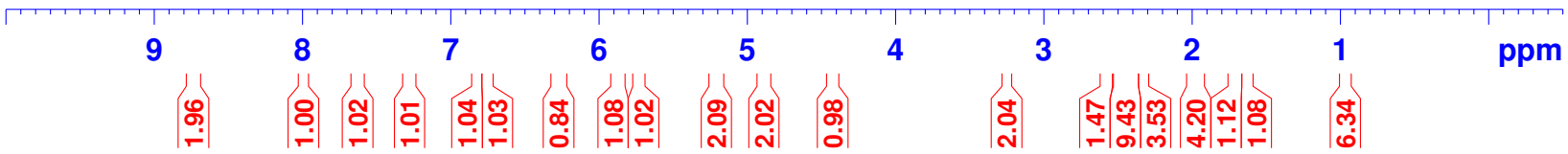
CNA-695-60, 1H, acetone-d6, 600 MHz

8.746 8.744 8.738 8.736 8.716 8.712 7.986 7.985 7.975 7.972 7.630 7.622 7.617 7.609 7.276 7.262 6.817 6.813 6.755 6.751 6.741 6.737 5.195 4.877 4.410 4.407 3.263 3.252 3.242 3.232 2.590 2.579 2.568 2.453 2.434 2.423 2.413 2.322 2.016 2.011 2.008 2.006 2.003 1.999 1.994 1.991 0.966 0.956

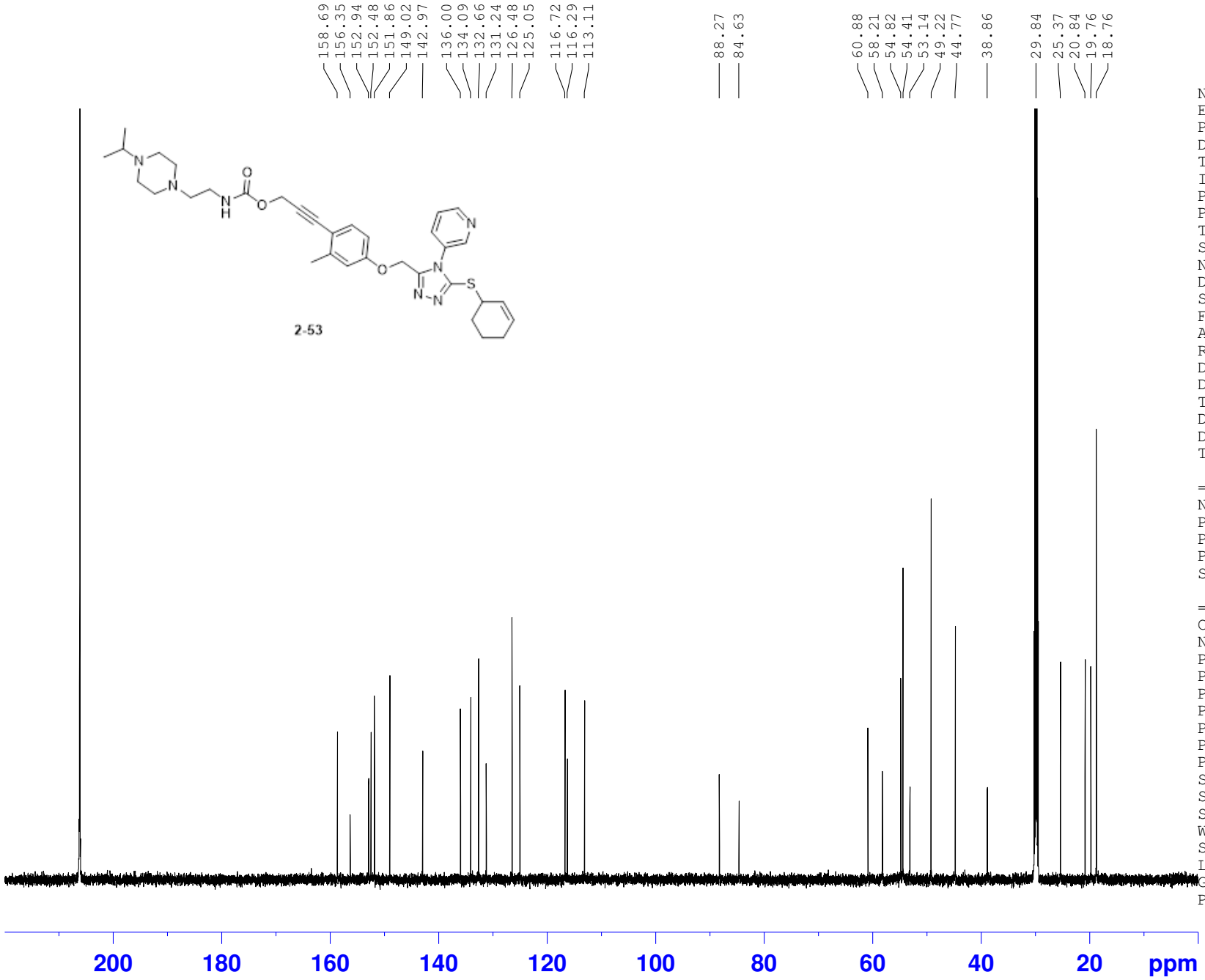


2-53

NAME	CNA-695-60
EXPNO	1
PROCNO	1
Date_	20160217
Time	14.42
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	16
DS	2
SWH	12335.526 Hz
FIDRES	0.188225 Hz
AQ	2.6564426 sec
RG	25.4
DW	40.533 usec
DE	6.50 usec
TE	297.0 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.86 usec
PL1	-2.00 dB
PL1W	19.70630455 W
SFO1	600.7137096 MHz
SI	32768
SF	600.7100094 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

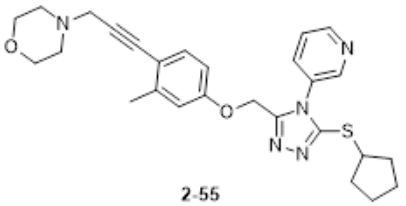


CNA-695-60, 13C, acetone-d6, 600 MHz

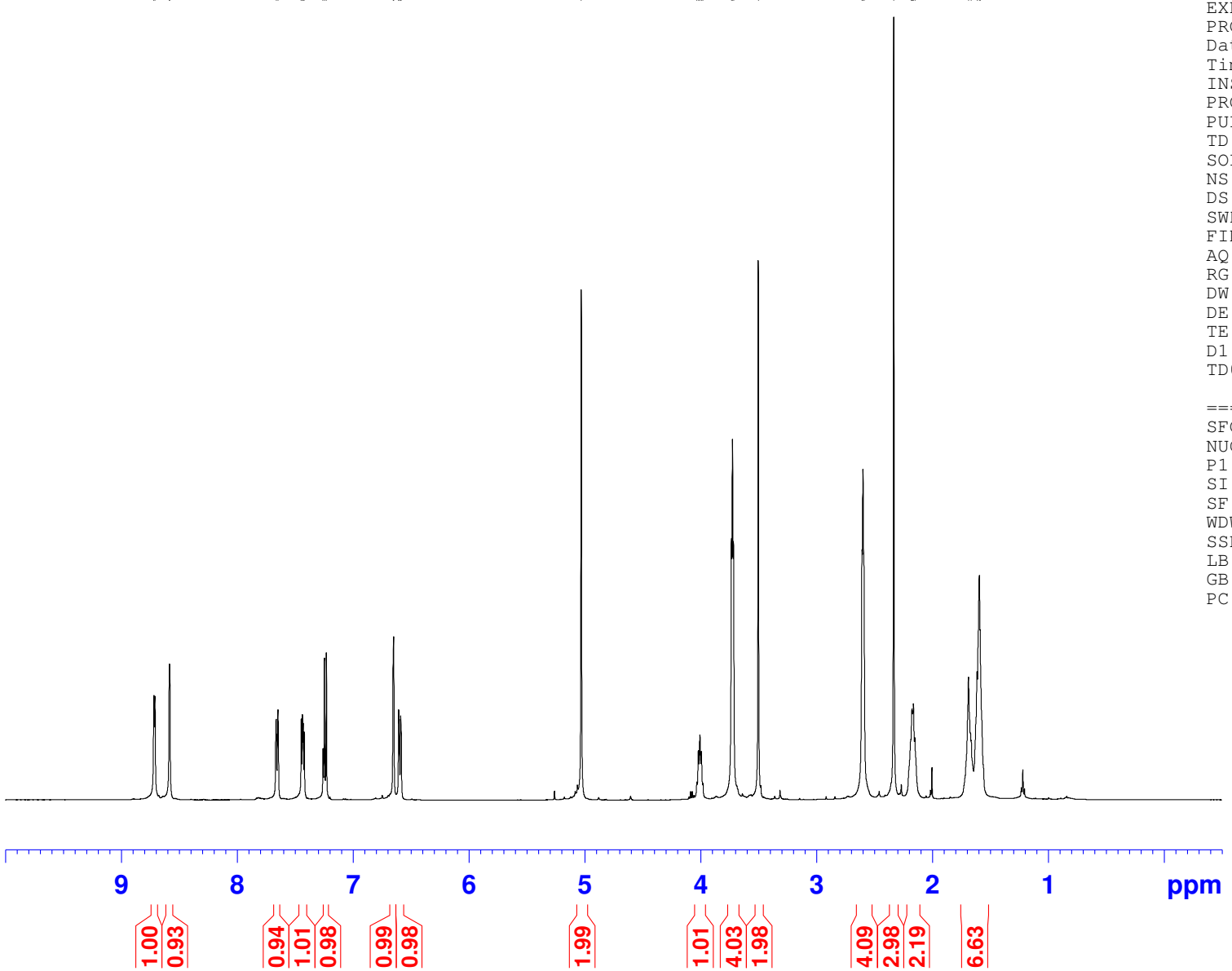


NAME	CNA-695-60
EXPNO	2
PROCNO	1
Date_	20160217
Time	14.49
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	Acetone
NS	200
DS	4
SWH	36057.691 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	203
DW	13.867 usec
DE	6.50 usec
TE	297.4 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	11.50 usec
PL1	0.00 dB
PL1W	97.46119690 W
SFO1	151.0637542 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	70.00 usec
PL2	-2.00 dB
PL12	14.19 dB
PL13	120.00 dB
PL2W	19.70630455 W
PL12W	0.47381112 W
PL13W	0.00000000 W
SFO2	600.7124028 MHz
SI	32768
SF	151.0485252 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-675-56, 1H, CDCl3, 500 MHz



8.720 8.711 8.586 8.583 7.665 7.648 7.447 7.438 7.431 7.421 7.260 7.248 7.231 6.654 6.650 6.606 6.602 6.590 6.585 5.031 4.033 4.019 4.006 3.993 3.980 3.734 3.725 3.716 3.502 2.607 2.598 2.590 2.333 2.185 2.174 2.169 2.163 2.151 1.687 1.664 1.613 1.593 1.587

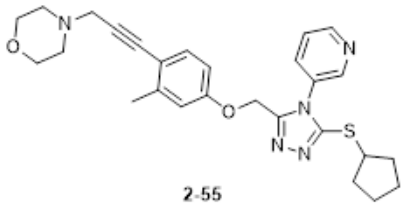


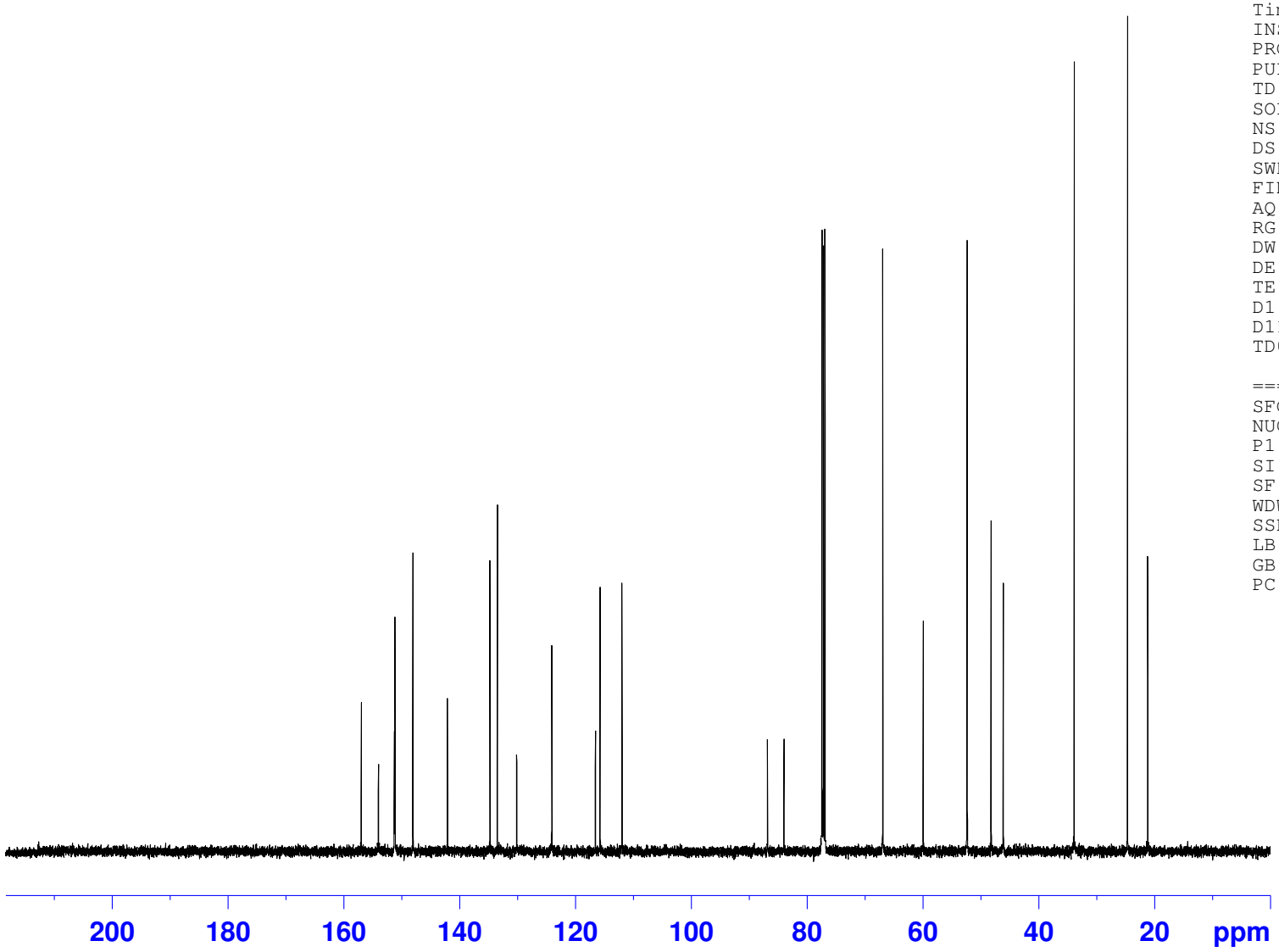
NAME	CNA-675-56
EXPNO	1
PROCNO	1
Date_	20151104
Time	15.32
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	10000.000 Hz
FIDRES	0.152588 Hz
AQ	3.2768500 sec
RG	32
DW	50.000 usec
DE	6.50 usec
TE	297.2 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	500.1630887 MHz
NUC1	1H
P1	11.45 usec
SI	65536
SF	500.1600135 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-675-56, 1H, CDCl3, 500 MHz

157.000
154.040
151.294
151.184
148.075
142.122
134.780
133.494
130.148
124.084
116.560
115.754
111.968

86.849
83.999
77.415
77.160
76.906
66.922
59.938
52.351
48.210
46.118
33.860
24.647
21.158





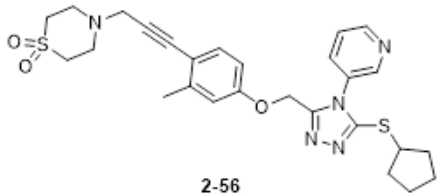
NAME	CNA-675-56
EXPNO	2
PROCNO	1
Date_	20151104
Time	15.47
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	256
DS	2
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 usec
DE	6.50 usec
TE	298.2 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1

======== CHANNEL f1 ========

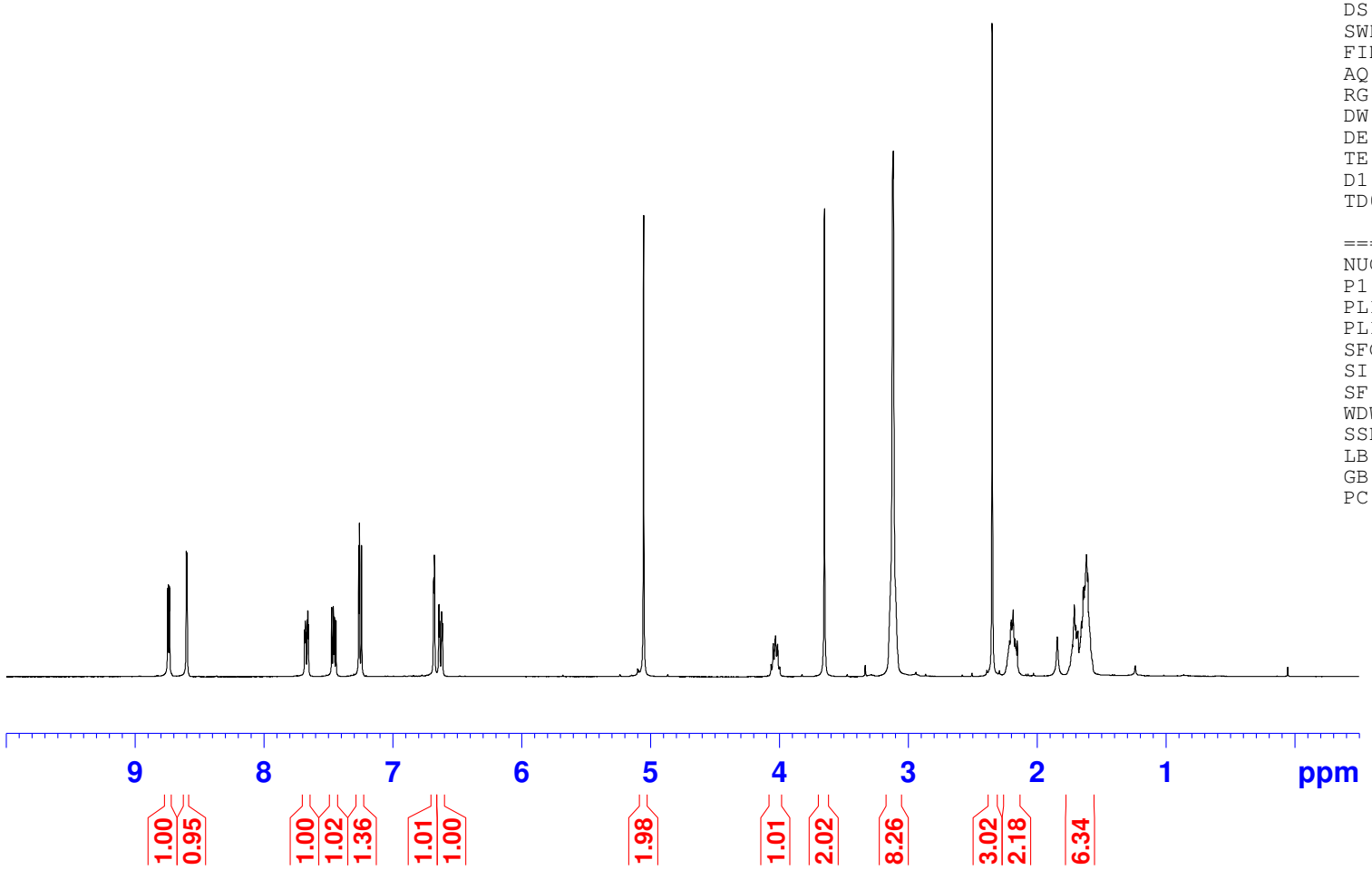
SFO1	125.7779086 MHz
NUC1	13C
P1	10.50 usec
SI	32768
SF	125.7653253 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-695-7, 1H, CDCl3, 400 MHz

8.749 8.746 8.737 8.734 8.605 8.599 7.683 7.681 7.666 7.662 7.660 7.656 7.476 7.464 7.456 7.444 7.266 7.260 7.244 6.684 6.678 6.644 6.638 6.623 6.617 5.055 3.652 3.122 3.117 2.349 2.204 2.200 2.192 2.186 1.712 1.657 1.648 1.643 1.638 1.631 1.619 1.617 1.607 1.601

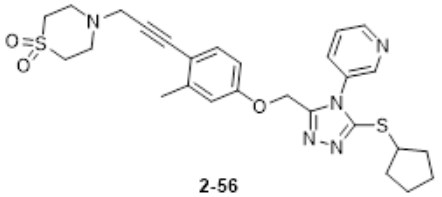


2-56

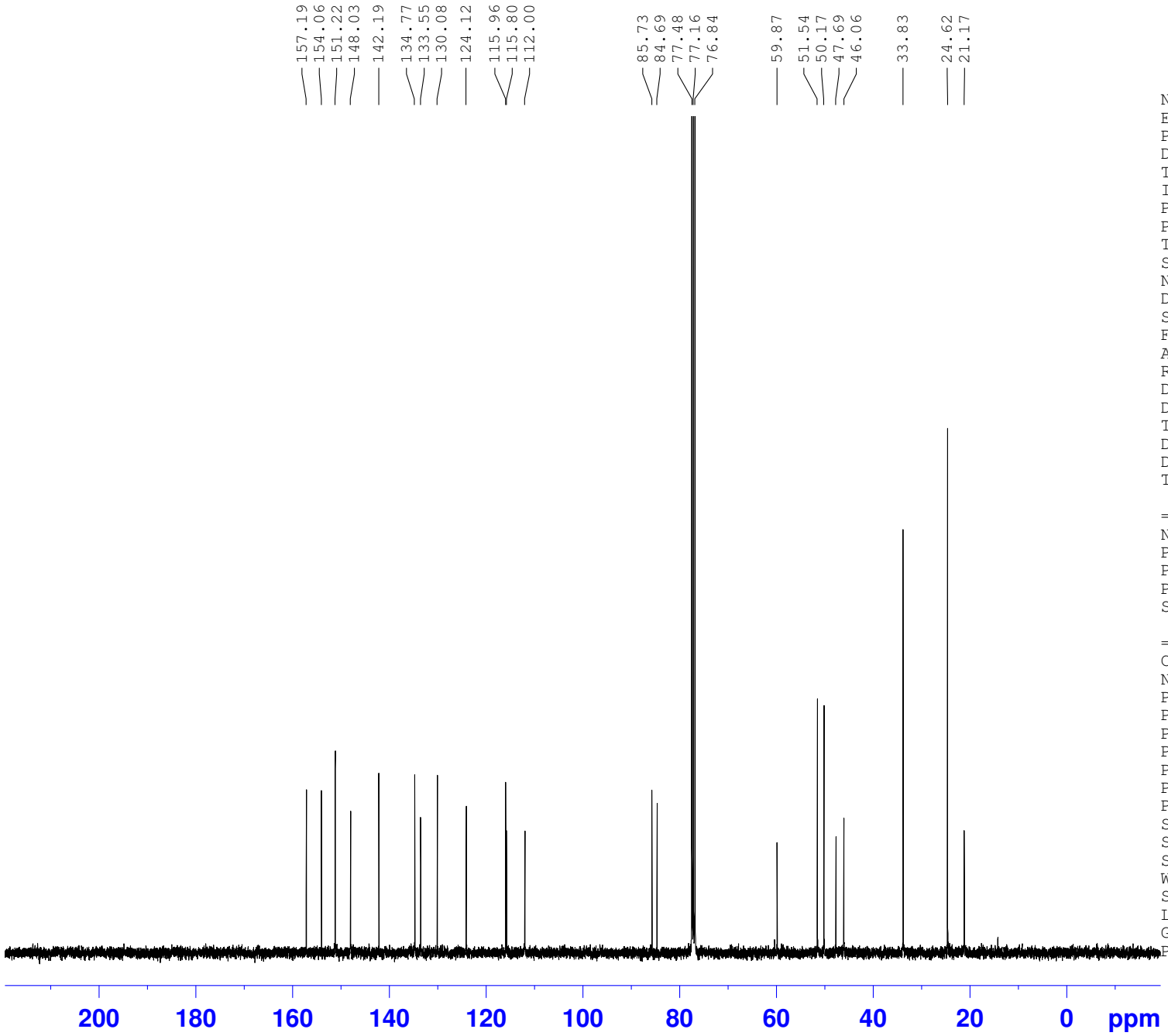


NAME	CNA-695-7
EXPNO	4
PROCNO	1
Date_	20151217
Time	1.24
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	71.8
DW	60.800 usec
DE	6.50 usec
TE	296.0 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300096 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-695-7, 13C, CDCl3, 400 MHz



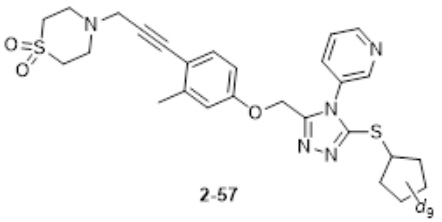
2-56



NAME	CNA-695-7
EXPNO	2
PROCNO	1
Date_	20151216
Time	22.48
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	256
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	64
DW	20.800 usec
DE	6.50 usec
TE	296.2 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379108 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

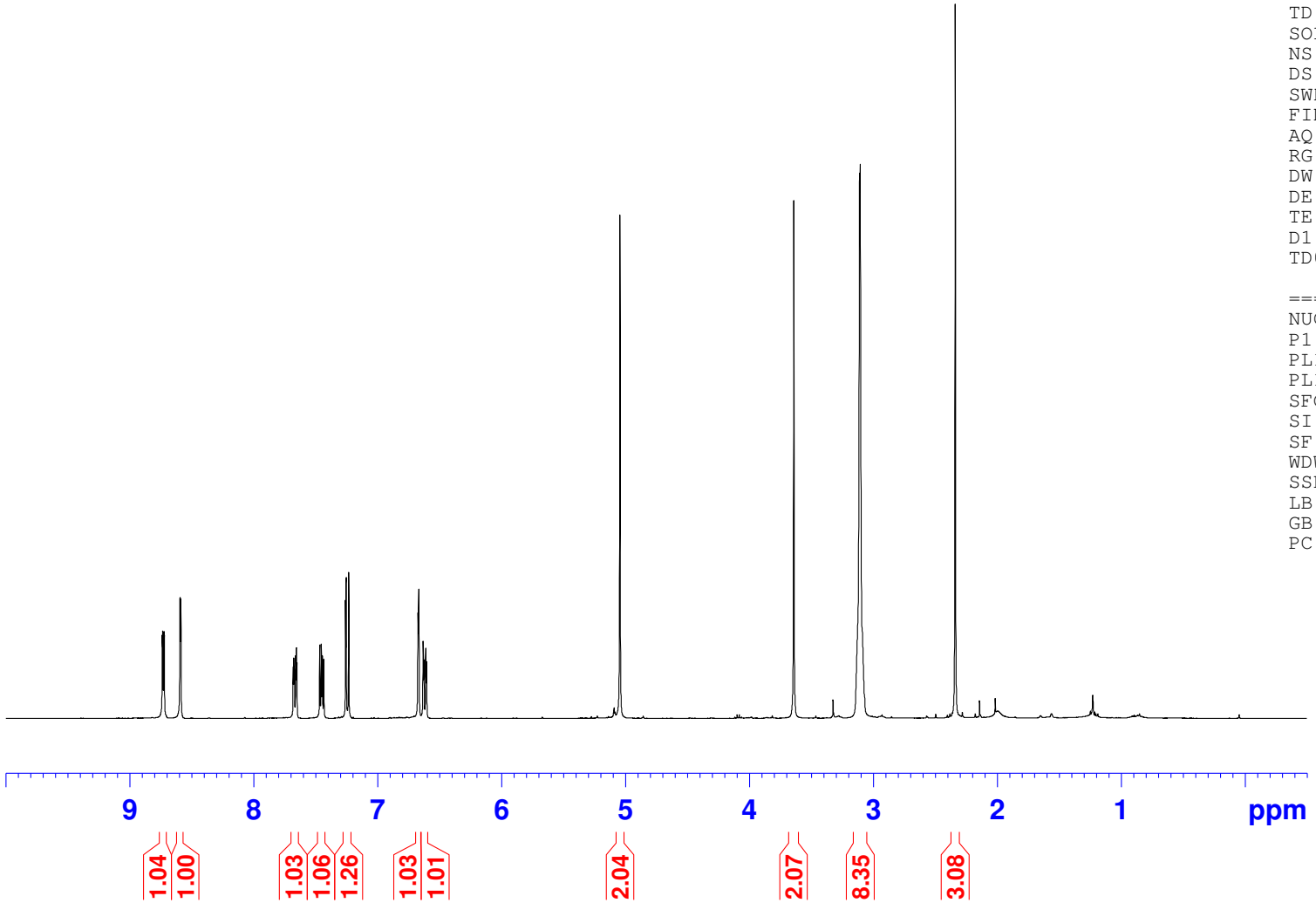
CNA-695-2, 1H, CDCl3, 400 MHz

8.590
7.683
7.679
7.677
7.673
7.663
7.659
7.657
7.653
7.468
7.456
7.448
7.436
7.436
7.260
7.255
7.234
6.675
6.669
6.634
6.628
6.613
6.607
5.045
3.642
3.111
3.106
2.339

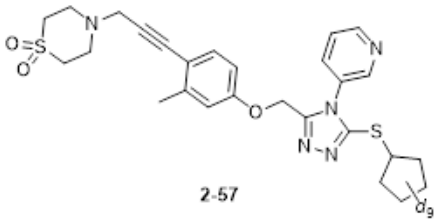


NAME	CNA-695-2
EXPNO	1
PROCNO	1
Date_	20151216
Time	21.59
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	71.8
DW	60.800 usec
DE	6.50 usec
TE	296.0 K
D1	2.00000000 sec
TD0	1

======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300096 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



CNA-695-2, 13C, CDCl3, 400 MHz



157.22
154.13
151.24
148.07
142.23
134.80
133.59
130.12
124.15
115.99
115.83
112.04
85.74
84.73
77.48
77.16
76.84
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51.57
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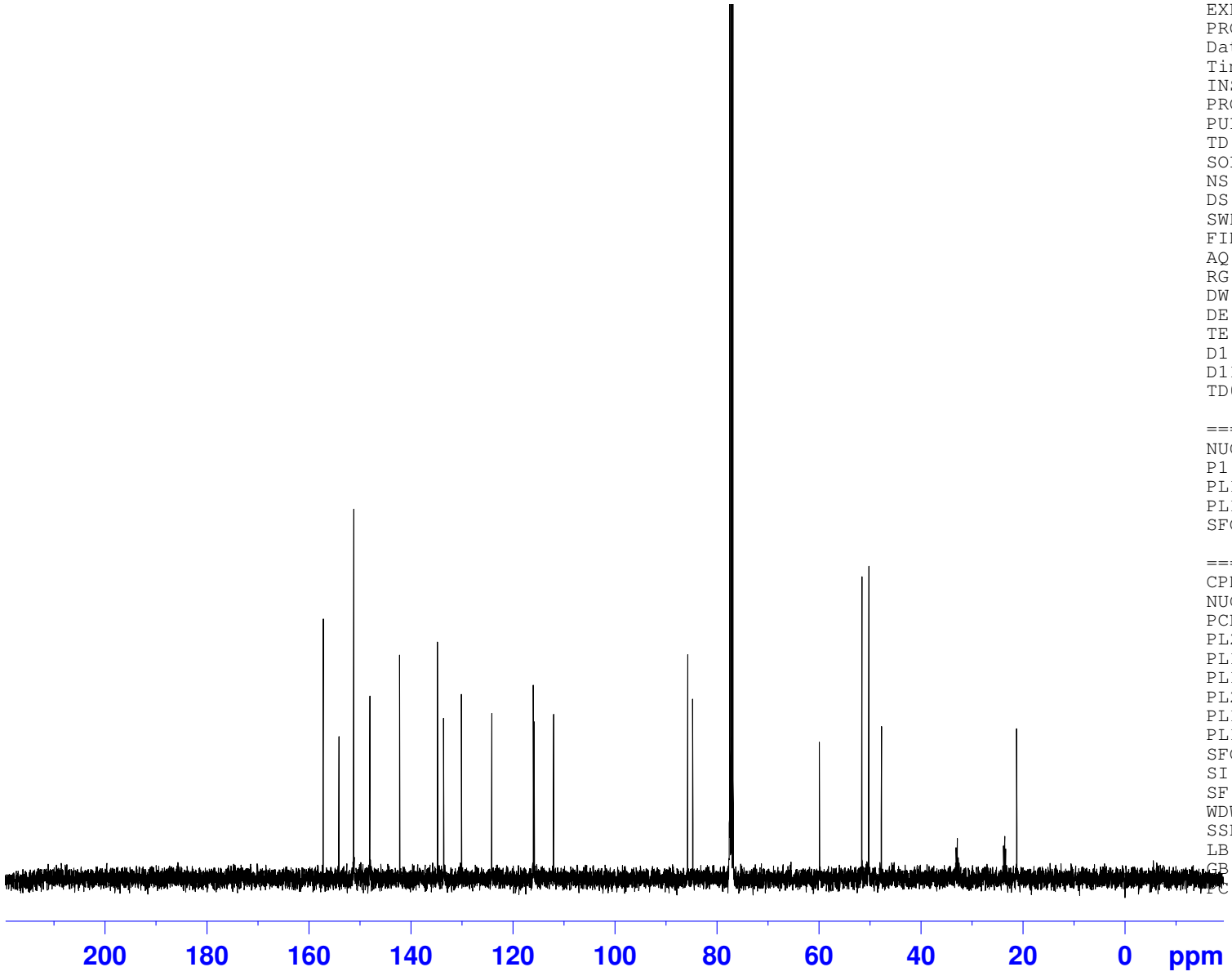
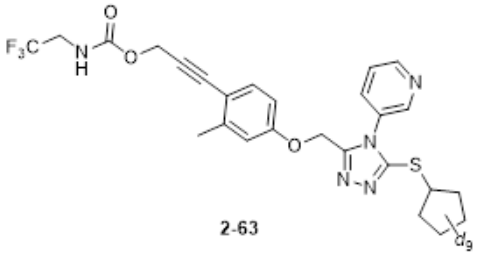
33.07
32.87
32.69
23.77
23.57
23.37
21.20

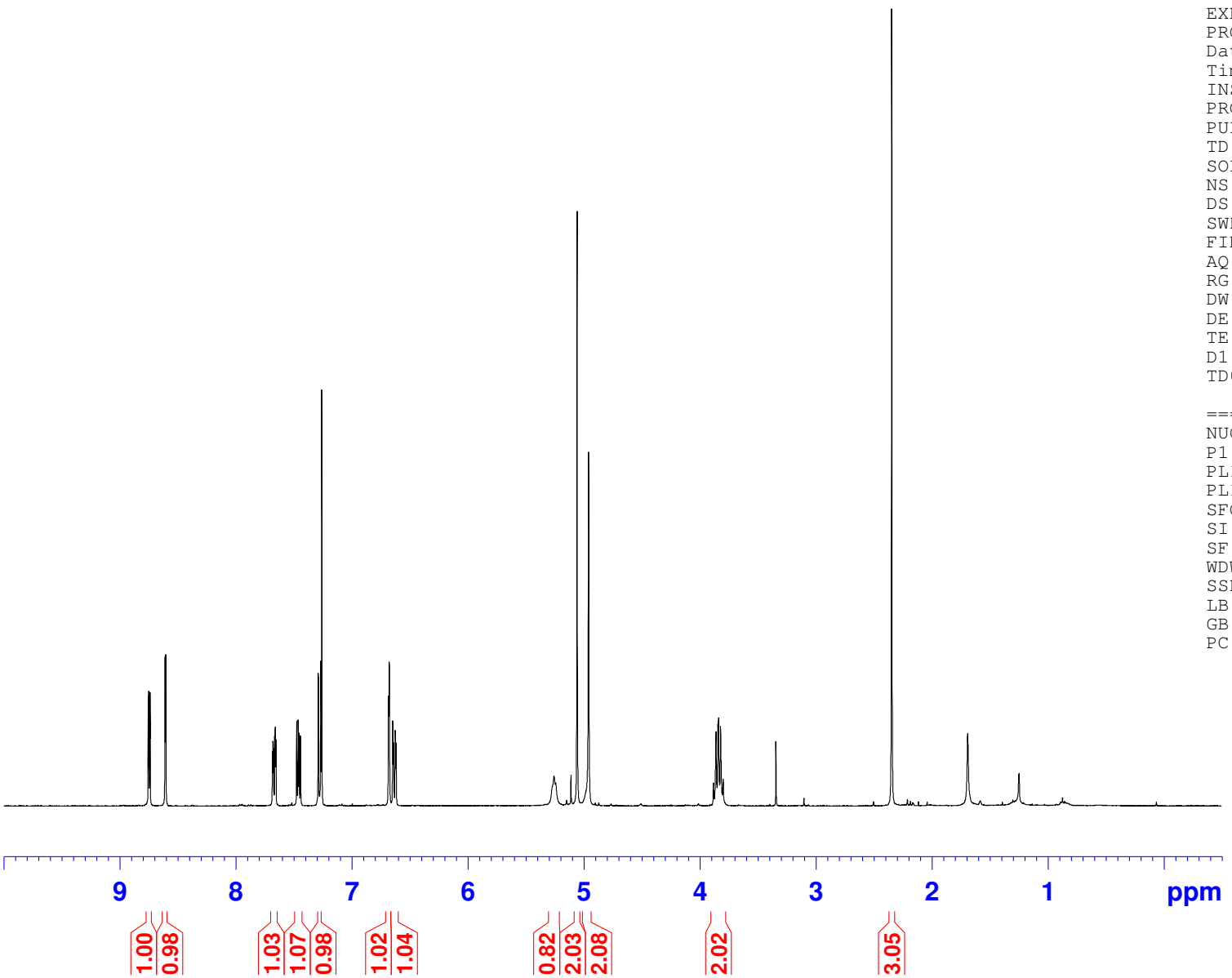


NAME	CNA-695-2
EXPNO	2
PROCNO	1
Date_	20151216
Time	22.20
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	256
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	296.2 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379079 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-695-26, 1H, CDCl3, 400 MHz



7.686
7.682
7.680
7.676
7.665
7.661
7.659
7.655
7.476
7.464
7.456
7.444
7.290
7.268
7.260
6.684
6.678
6.648
6.641
6.627
6.620
5.258
5.242
5.059
4.959
3.883
3.861
3.844
3.839
3.821
3.800
2.346

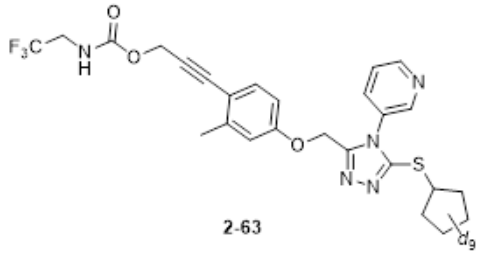


NAME	CNA-695-26
EXPNO	1
PROCNO	1
Date_	20160120
Time	14.57
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	144
DW	60.800 usec
DE	6.50 usec
TE	295.6 K
D1	2.00000000 sec
TD0	1

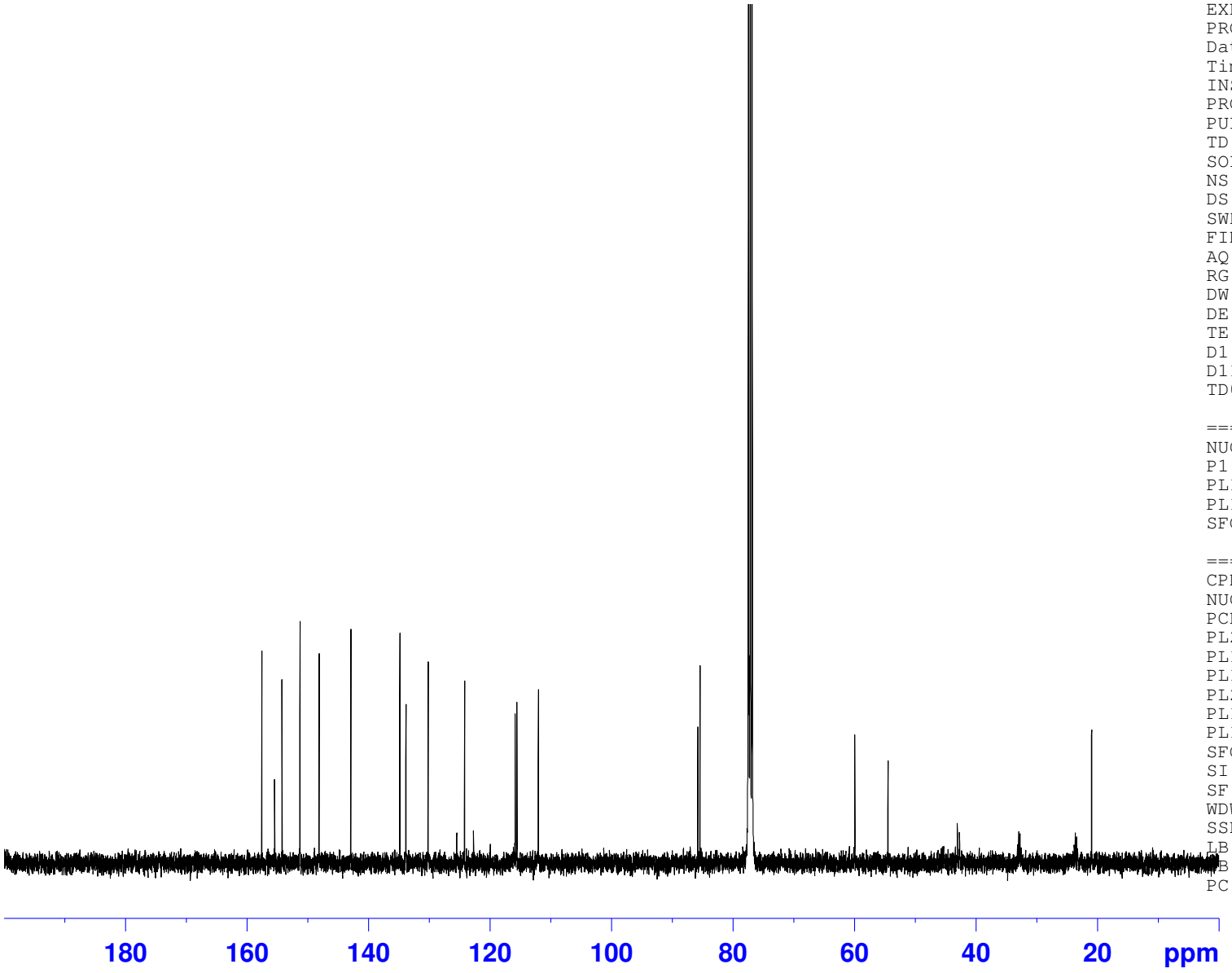
======== CHANNEL f1 ========

NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300096 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-695-26, 13C, CDCl3, 400 MHz

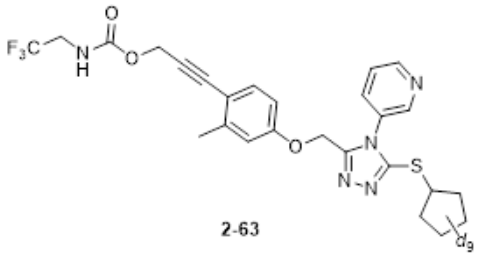


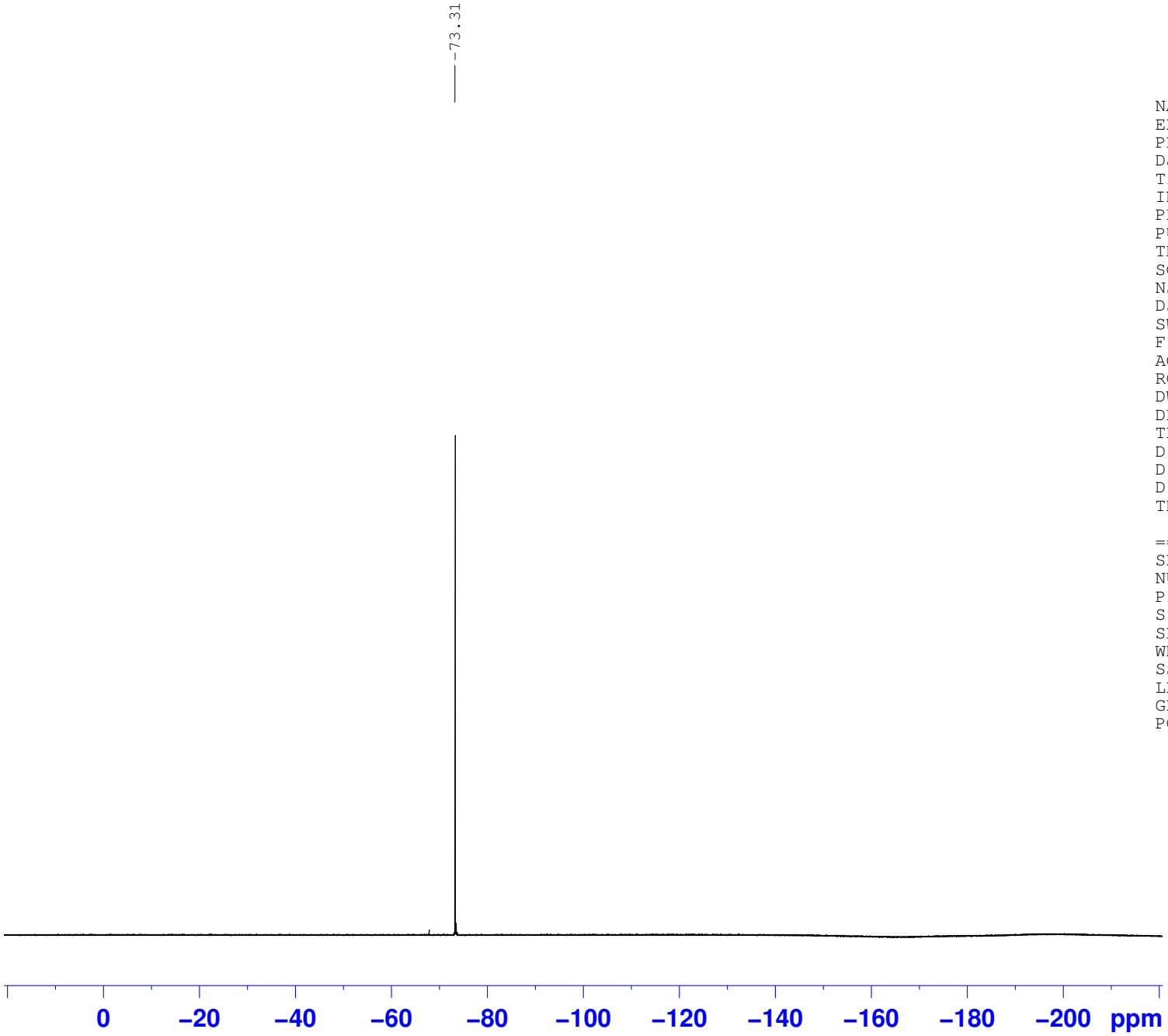
157.57
155.48
154.26
151.31
151.27
148.14
142.91
134.86
133.86
130.19
125.49
124.20
122.72
115.86
115.58
112.05
85.78
85.42
77.47
77.36
77.16
76.84
59.94
54.47
43.05
42.70
32.94
32.75
23.64
23.44
20.95



NAME	CNA-695-26	
EXPNO	2	
PROCNO	1	
Date_	20160120	
Time	18.05	
INSTRUM	spect	
PROBHD	5 mm PADUL 13C	
PULPROG	zgpg30	
TD	65536	
SOLVENT	CDCl3	
NS	2500	
DS	4	
SWH	24038.461	Hz
FIDRES	0.366798	Hz
AQ	1.3631988	sec
RG	203	
DW	20.800	usec
DE	6.50	usec
TE	295.8	K
D1	3.00000000	sec
D11	0.03000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	13C	
P1	10.00	usec
PL1	-0.44	dB
PL1W	39.19395828	W
SFO1	100.6479773	MHz
======== CHANNEL f2 ========		
CPDPRG2	waltz16	
NUC2	1H	
PCPD2	90.00	usec
PL2	-3.90	dB
PL12	15.81	dB
PL13	120.00	dB
PL2W	21.64248466	W
PL12W	0.23137002	W
PL13W	0.00000000	W
SFO2	400.2316009	MHz
SI	32768	
SF	100.6379016	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

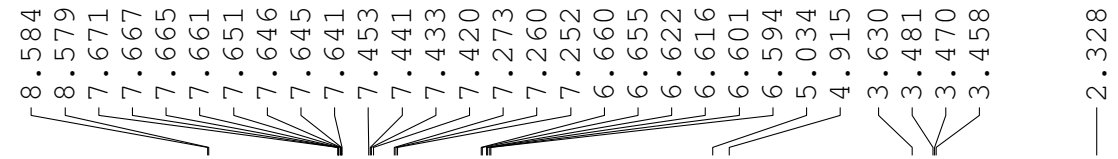
CNA-695-26, 19F, CDCl3, 500 MHz

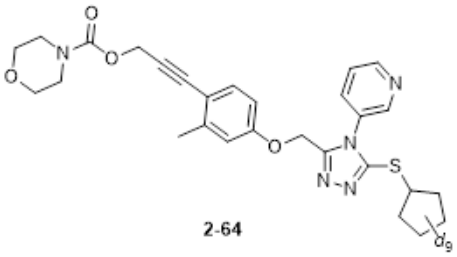




NAME	CNA-695-26
EXPNO	1
PROCNO	1
Date_	20160120
Time	18.30
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	113636.367 Hz
FIDRES	0.866977 Hz
AQ	0.5767668 sec
RG	203
DW	4.400 usec
DE	6.50 usec
TE	299.2 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	470.5735434 MHz
NUC1	19F
P1	5.00 usec
SI	65536
SF	470.6206054 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

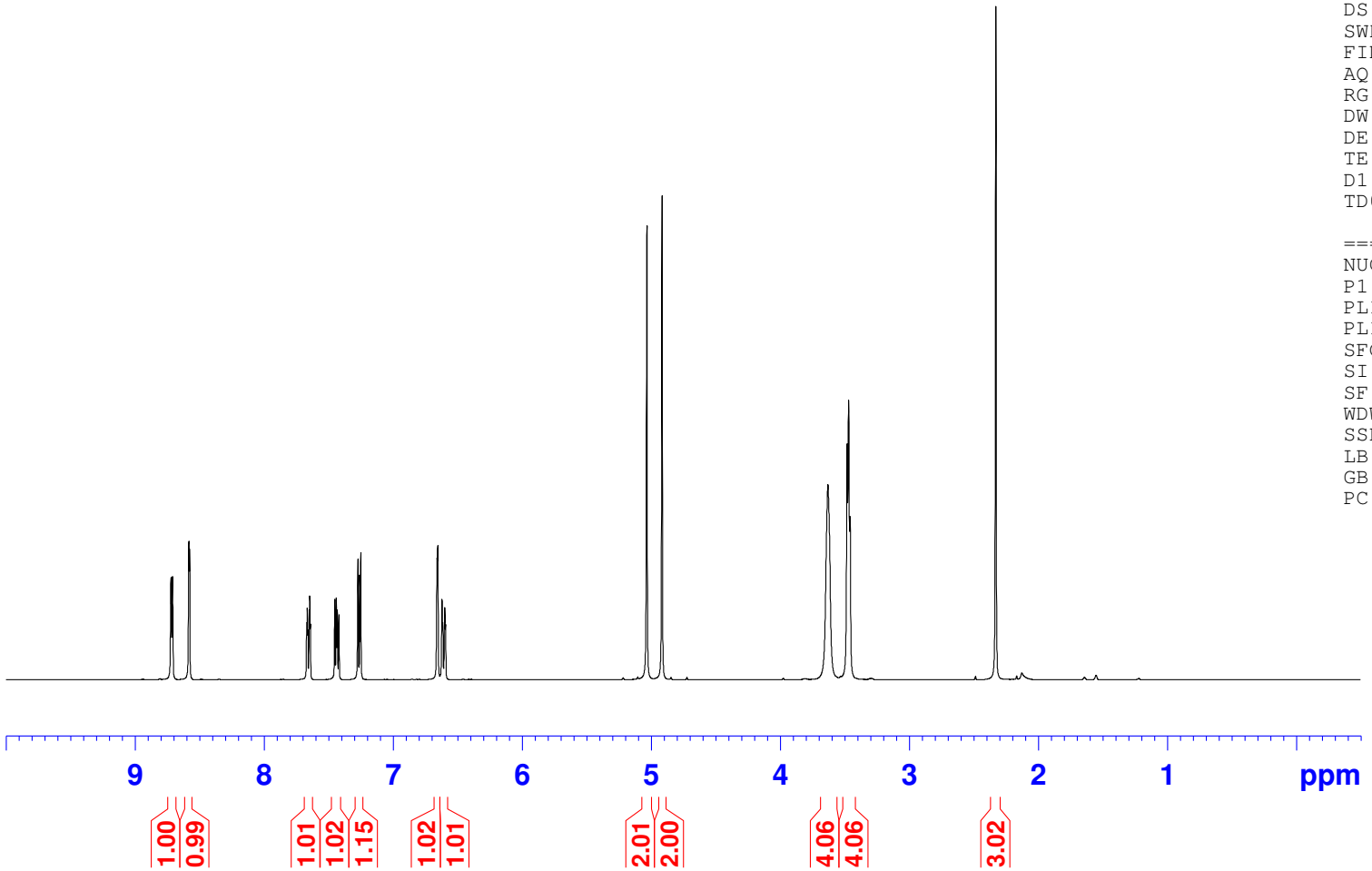
CNA-695-27, 1H, CDCl3, 400 MHz



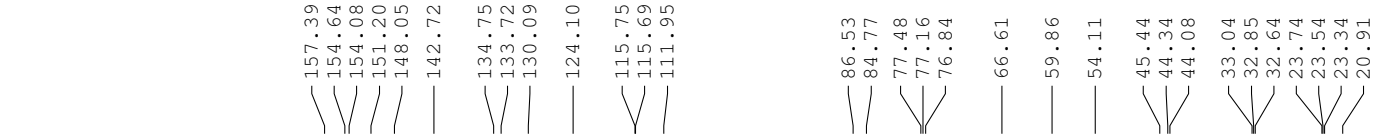


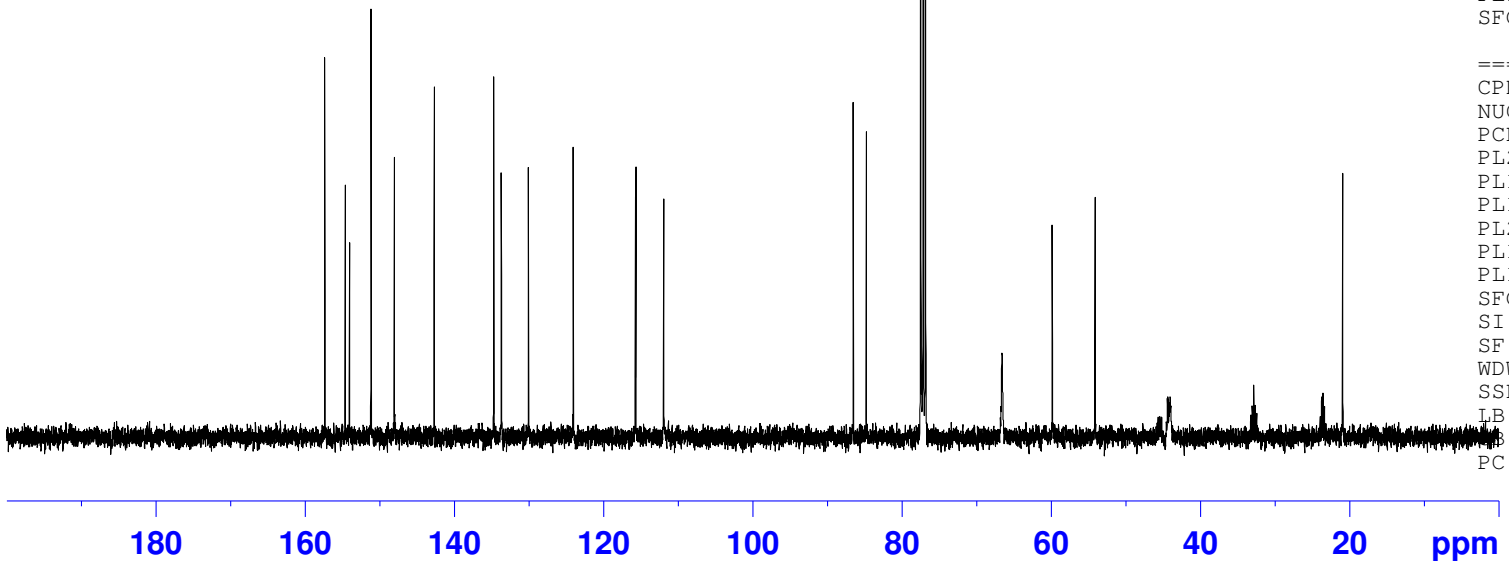
NAME	CNA-695-27
EXPNO	1
PROCNO	1
Date_	20160120
Time	19.40
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	57
DW	60.800 usec
DE	6.50 usec
TE	295.7 K
D1	2.00000000 sec
TD0	1

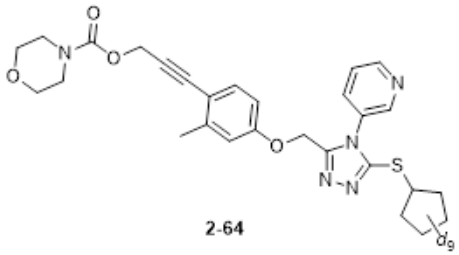
======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300095 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



CNA-695-27, 13C, CDCl3, 400 MHz



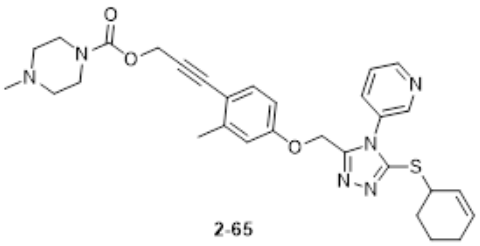




NAME	CNA-695-27	
EXPNO	2	
PROCNO	1	
Date_	20160120	
Time	19.52	
INSTRUM	spect	
PROBHD	5 mm PADUL 13C	
PULPROG	zgpg30	
TD	65536	
SOLVENT	CDCl3	
NS	256	
DS	4	
SWH	24038.461	Hz
FIDRES	0.366798	Hz
AQ	1.3631988	sec
RG	203	
DW	20.800	usec
DE	6.50	usec
TE	295.8	K
D1	3.00000000	sec
D11	0.03000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	13C	
P1	10.00	usec
PL1	-0.44	dB
PL1W	39.19395828	W
SFO1	100.6479773	MHz
======== CHANNEL f2 ========		
CPDPRG2	waltz16	
NUC2	1H	
PCPD2	90.00	usec
PL2	-3.90	dB
PL12	15.81	dB
PL13	120.00	dB
PL2W	21.64248466	W
PL12W	0.23137002	W
PL13W	0.00000000	W
SFO2	400.2316009	MHz
SI	32768	
SF	100.6379097	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

CNA-710-10, 1H, CDCl3, 300 MHz

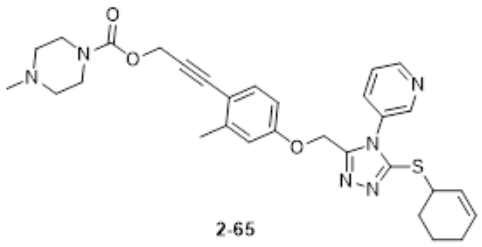
8.758 8.754 8.742 8.738 8.613 8.606 7.688 7.682 7.674 7.660 7.655 7.652 7.647 7.479 7.463 7.452 7.436 7.312 7.284 7.260 6.688 6.681 6.652 6.643 6.624 6.615 5.861 5.770 5.764 5.756 5.070 4.934 4.577 3.548 3.531 3.514 2.393 2.363 2.300 1.735 1.722 1.702 1.688 1.668



2-65

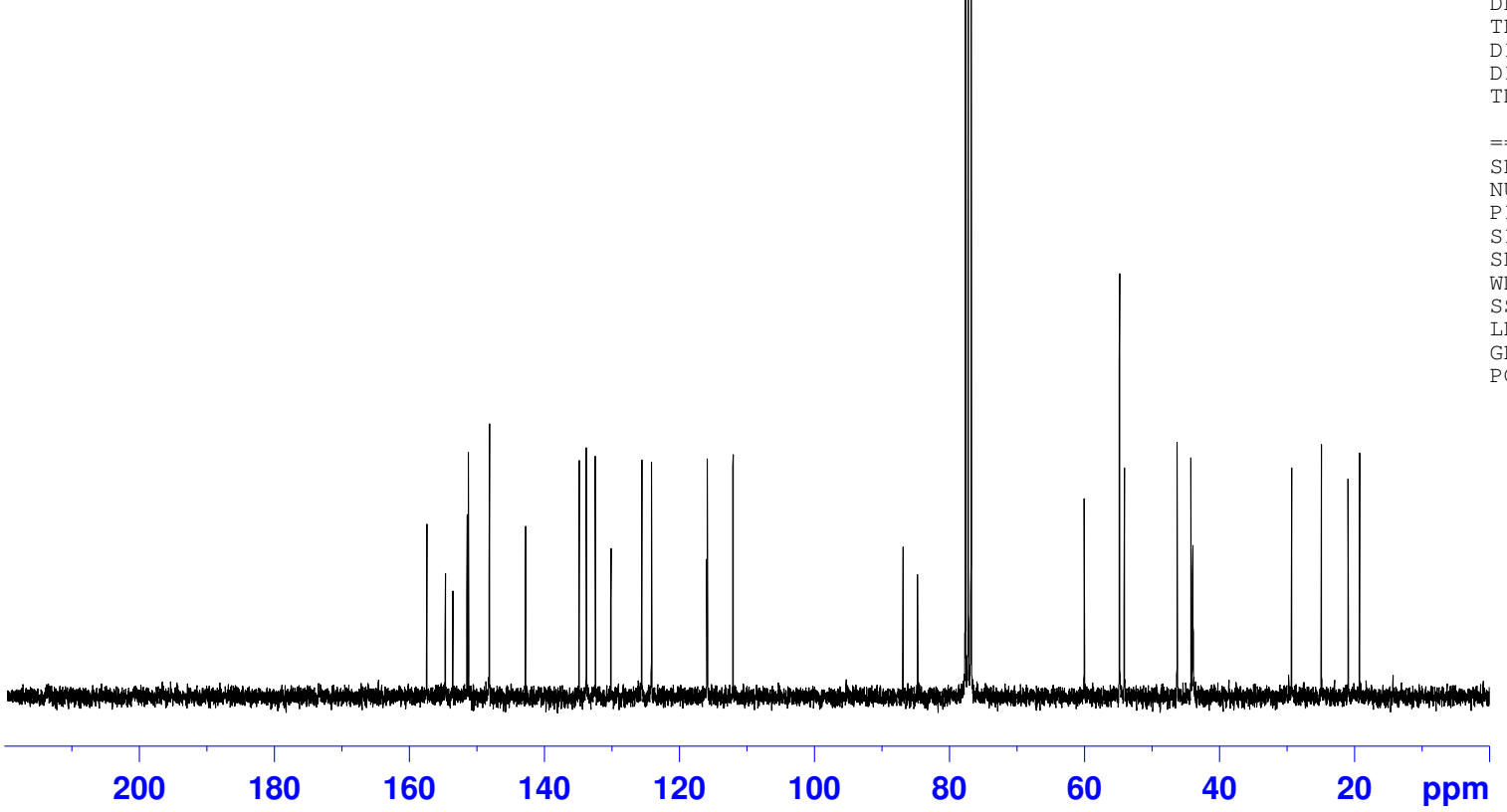
NAME	CNA-710-10
EXPNO	4
PROCNO	1
Date_	20160401
Time	10.25
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	48
DS	2
SWH	6188.119 Hz
FIDRES	0.188846 Hz
AQ	2.6477044 sec
RG	322
DW	80.800 usec
DE	6.50 usec
TE	-927.9 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	300.2318540 MHz
NUC1	1H
P1	12.71 usec
SI	32768
SF	300.2300087 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

CNA-710-10, 1H, CDCl3, 300 MHz



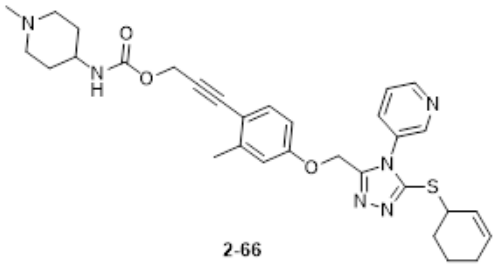
157.41
154.66
153.53
151.44
151.23
148.13
142.77
134.83
133.76
132.42
130.12
125.54
124.10
115.93
115.83
112.03
86.82
84.69
77.58
77.36
77.16
76.74
59.98
54.75
54.03
46.22
44.17
43.88
29.33
24.91
20.94
19.25

NAME	CNA-710-10
EXPNO	2
PROCNO	1
Date_	20160331
Time	23.02
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	18028.846 Hz
FIDRES	0.275098 Hz
AQ	1.8175818 sec
RG	256
DW	27.733 usec
DE	6.50 usec
TE	-928.0 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	75.5004428 MHz
NUC1	13C
P1	12.00 usec
SI	32768
SF	75.4928866 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



CNA-710-9, 1H, CDCl3, 300 MHz

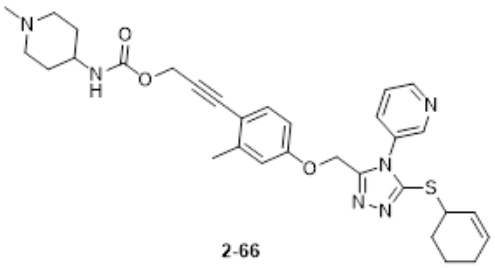
8.727 8.714 8.591 8.584 7.667 7.665 7.645 7.640 7.638 7.456 7.440 7.429 7.413 7.270 7.260 7.242 6.652 6.623 6.595 5.832 5.740 5.735 5.044 4.877 4.544 4.537 2.749 2.711 2.328 2.104 2.060 2.044 2.026 2.011 1.993 1.979 1.945 1.909 1.673 1.658 1.639 1.487 1.477 1.446



2-66

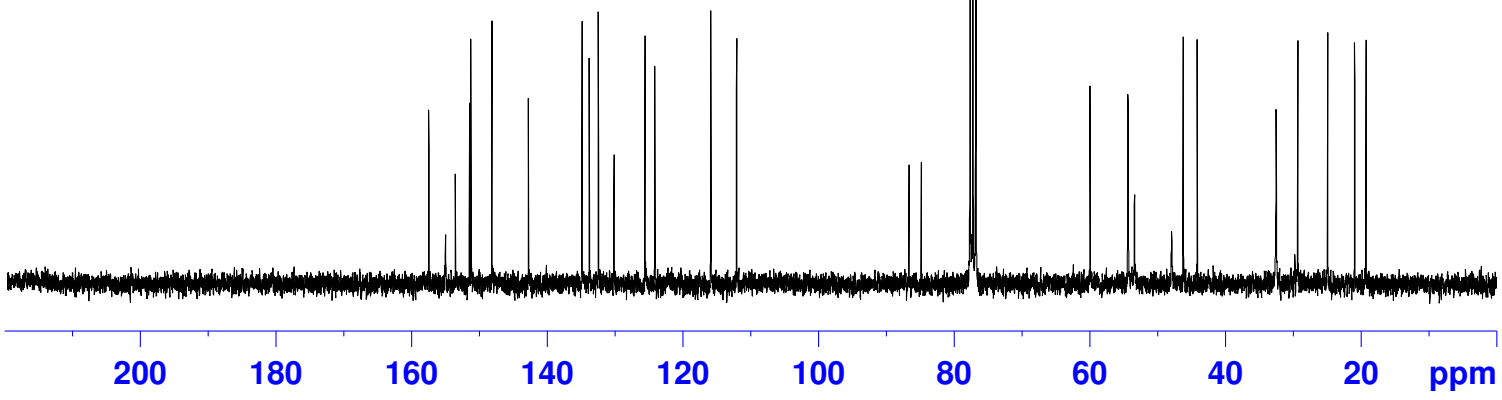
NAME	CNA-710-9
EXPNO	1
PROCNO	1
Date_	20160331
Time	22.23
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6188.119 Hz
FIDRES	0.188846 Hz
AQ	2.6477044 sec
RG	64
DW	80.800 usec
DE	6.50 usec
TE	-927.0 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	300.2318540 MHz
NUC1	1H
P1	12.71 usec
SI	32768
SF	300.2300084 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

CNA-710-9, 1H, CDCl3, 300 MHz



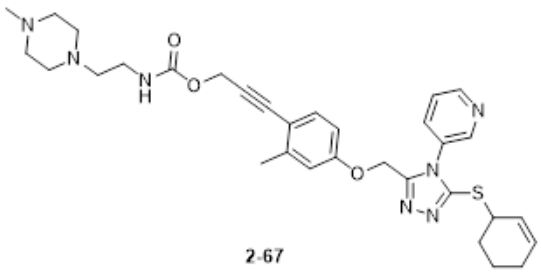
157.43
154.96
153.53
151.43
151.22
148.12
142.75
134.83
133.76
132.42
130.11
125.54
124.10
115.82
112.02
86.59
84.78
77.58
77.16
76.74
59.97
54.36
53.41
47.93
46.22
44.17
32.52
29.32
24.91
20.92
19.25

NAME	CNA-710-9
EXPNO	2
PROCNO	1
Date_	20160331
Time	23.40
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	18028.846 Hz
FIDRES	0.275098 Hz
AQ	1.8175818 sec
RG	256
DW	27.733 usec
DE	6.50 usec
TE	-928.0 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	75.5004428 MHz
NUC1	13C
P1	12.00 usec
SI	32768
SF	75.4928868 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



CNA-695-66, 1H, CDCl3, 400 MHz

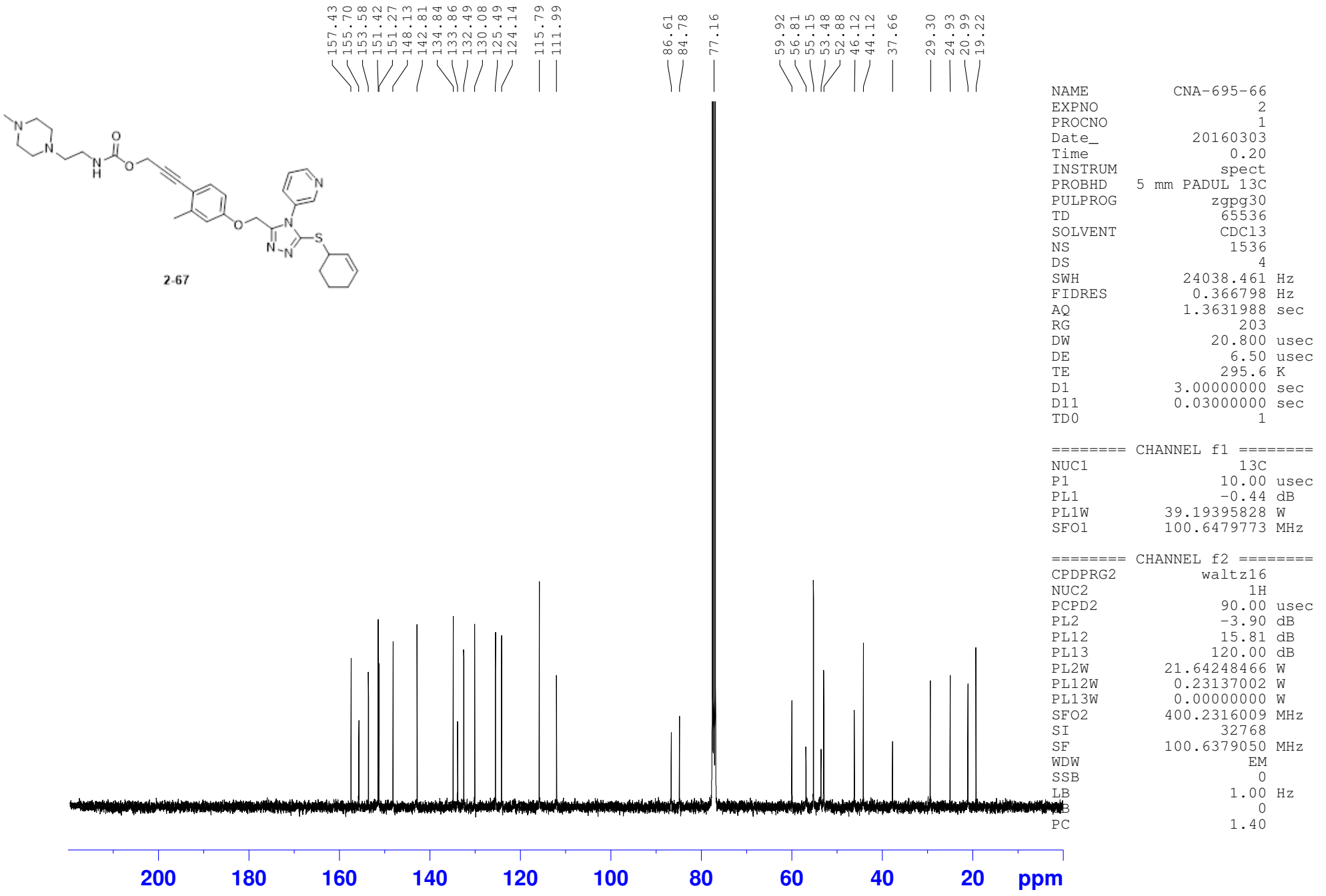
8.739 8.736 8.727 8.724 8.600 8.595 7.671 7.669 7.655 7.651 7.649 7.461 7.449 7.441 7.429 7.292 7.271 7.260 6.671 6.665 6.633 6.626 6.611 6.605 5.846 5.052 4.905 4.559 4.553 3.289 3.275 2.481 2.466 2.451 2.427 2.347 2.262 2.030 2.017 2.012 2.007 2.003 1.995 1.678



2-67

NAME	CNA-695-66
EXPNO	1
PROCNO	1
Date_	20160302
Time	22.24
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	71.8
DW	60.800 usec
DE	6.50 usec
TE	295.4 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300123 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

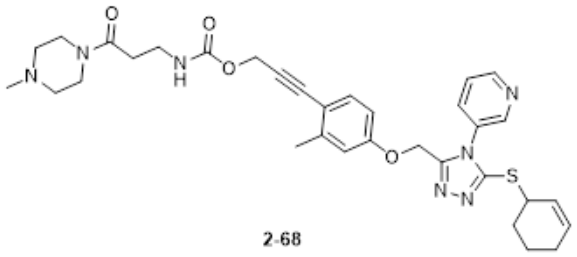
CNA-695-66, 13C, CDCl3, 400 MHz



NAME	CNA-695-66	
EXPNO	2	
PROCNO	1	
Date_	20160303	
Time	0.20	
INSTRUM	spect	
PROBHD	5 mm PADUL 13C	
PULPROG	zgpg30	
TD	65536	
SOLVENT	CDCl3	
NS	1536	
DS	4	
SWH	24038.461	Hz
FIDRES	0.366798	Hz
AQ	1.3631988	sec
RG	203	
DW	20.800	usec
DE	6.50	usec
TE	295.6	K
D1	3.00000000	sec
D11	0.03000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	13C	
P1	10.00	usec
PL1	-0.44	dB
PL1W	39.19395828	W
SFO1	100.6479773	MHz
======== CHANNEL f2 ========		
CPDPRG2	waltz16	
NUC2	1H	
PCPD2	90.00	usec
PL2	-3.90	dB
PL12	15.81	dB
PL13	120.00	dB
PL2W	21.64248466	W
PL12W	0.23137002	W
PL13W	0.00000000	W
SFO2	400.2316009	MHz
SI	32768	
SF	100.6379050	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

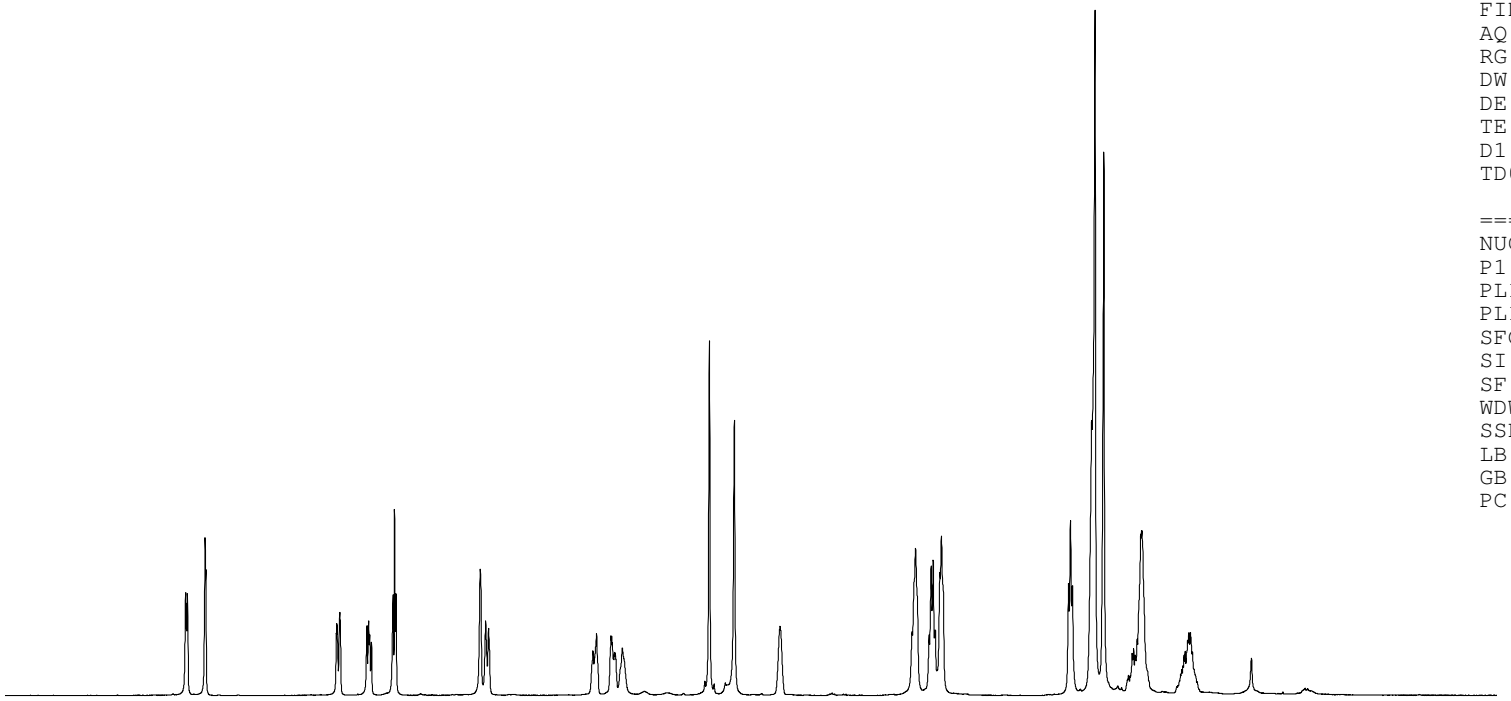
CNA-695-68, 1H, CDCl3, 400 MHz

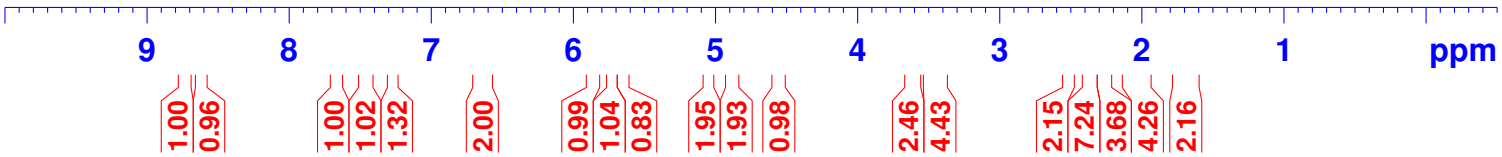
8.730 8.726 8.718 8.715 8.593 8.588 7.668 7.665 7.648 7.645 7.643 7.454 7.442 7.270 7.260 7.249 6.657 6.619 6.598 5.839 5.043 4.868 4.546 3.617 3.593 3.497 3.482 3.468 3.457 3.453 3.421 3.410 2.515 2.502 2.488 2.353 2.329 2.267 2.007 2.003 1.998 1.994 1.668 1.657



2-68

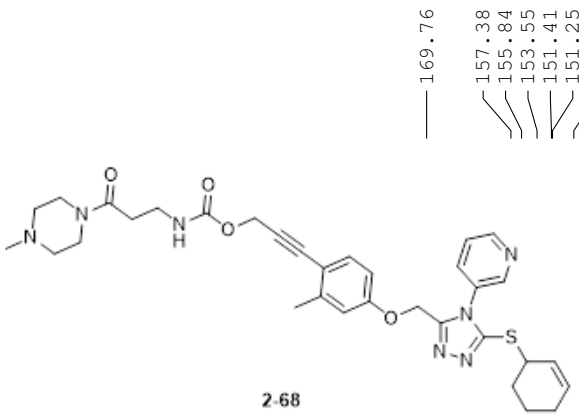
NAME	CNA-695-68
EXPNO	5
PROCNO	1
Date_	20160302
Time	14.29
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	64
DW	60.800 usec
DE	6.50 usec
TE	295.5 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300122 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00





1.00 0.96 1.00 1.02 1.32 2.00 0.99 1.04 0.83 1.95 1.93 0.98 2.46 4.43 2.15 7.24 3.68 4.26 2.16

CNA-695-68, 13C, CDCl3, 400 MHz

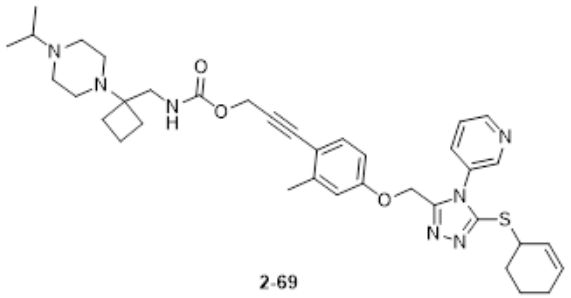


169.76
157.38
155.84
153.55
151.41
151.25
148.11
142.75
134.82
133.76
132.47
130.06
125.47
124.12
115.81
115.76
111.96
86.64
84.65
77.16
59.91
55.01
54.68
53.40
46.09
45.20
44.10
41.51
36.88
33.18
29.27
24.90
20.96
19.20

NAME	CNA-695-68
EXPNO	6
PROCNO	1
Date_	20160302
Time	15.59
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1200
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	295.7 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379064 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

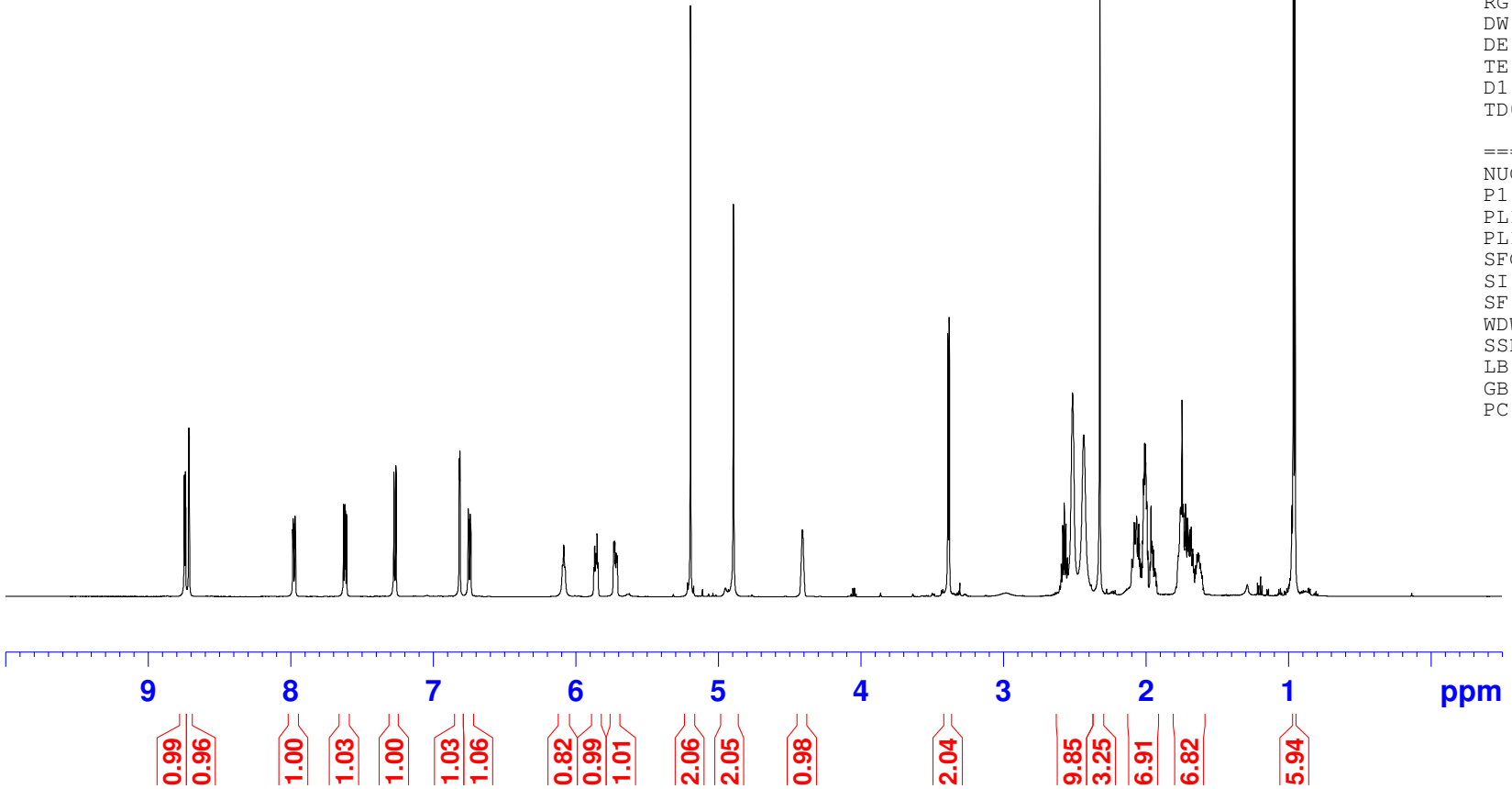
CNA-695-67, 1H, acetone-d6, 600 MHz

8.748 8.745 8.739 8.737 8.715 8.711 7.983 7.982 7.970 7.968 7.629 7.621 7.616 7.608 7.275 7.261 6.816 6.813 6.755 6.750 6.740 5.194 4.893 3.389 3.379 2.572 2.514 2.436 2.323 2.065 2.017 2.013 2.011 2.009 2.004 2.001 1.999 1.993 1.964 1.761 1.757 1.746 1.739 1.735 1.722 1.710 0.964 0.953

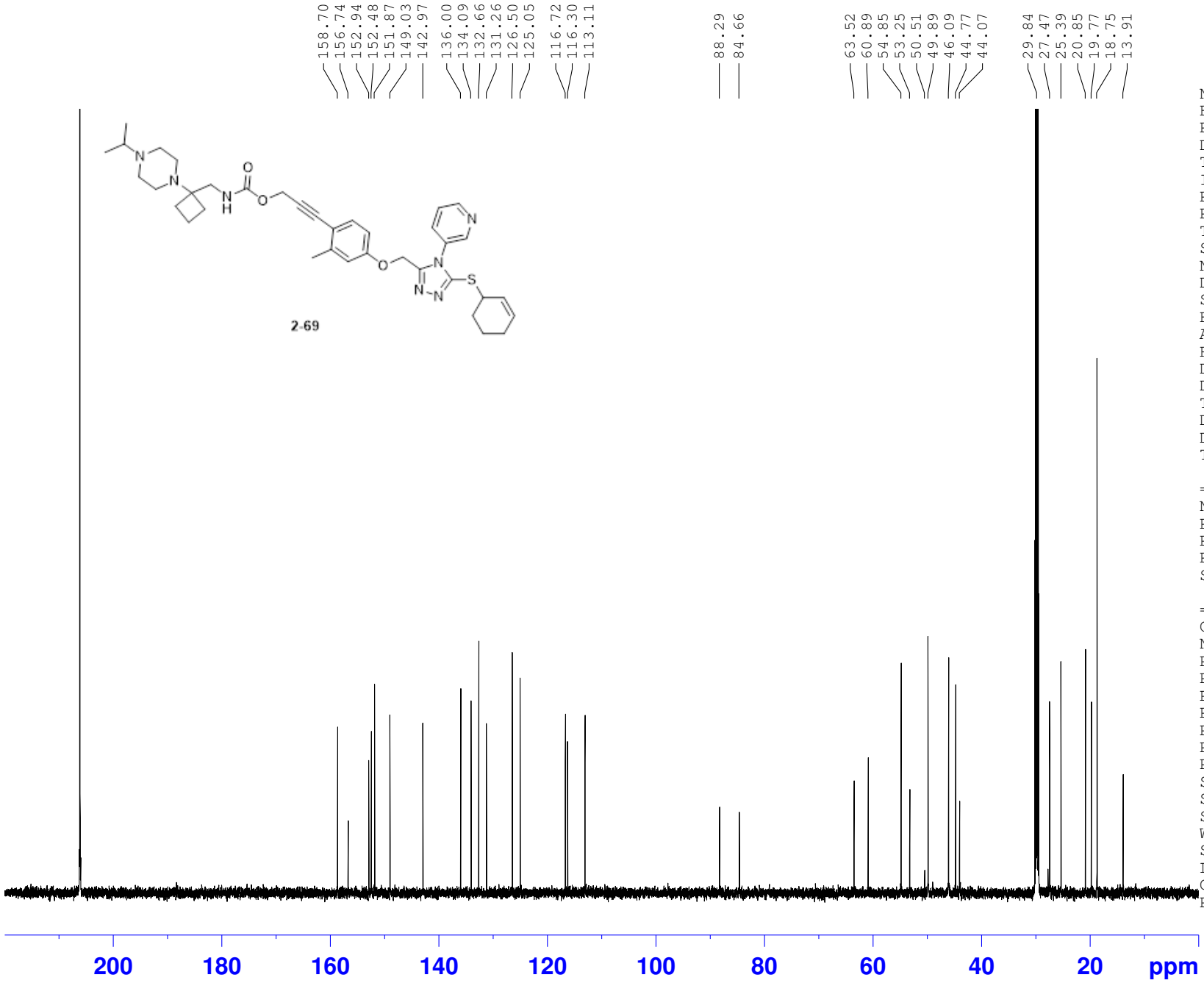


2-69

NAME	CNA-695-67
EXPNO	1
PROCNO	1
Date_	20160217
Time	15.52
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	16
DS	2
SWH	12335.526 Hz
FIDRES	0.188225 Hz
AQ	2.6564426 sec
RG	22.6
DW	40.533 usec
DE	6.50 usec
TE	297.2 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.86 usec
PL1	-2.00 dB
PL1W	19.70630455 W
SFO1	600.7137096 MHz
SI	32768
SF	600.7100093 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

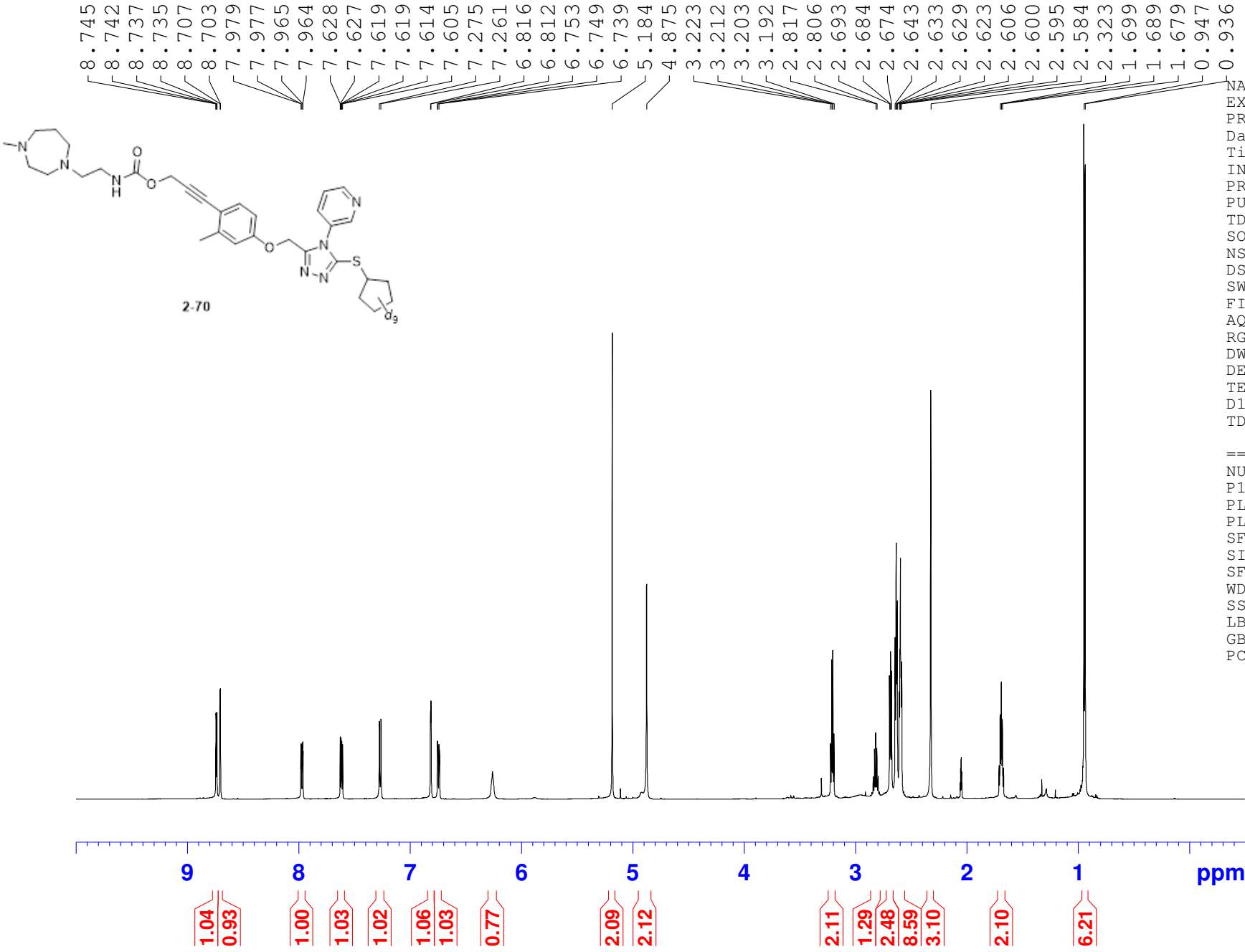


CNA-695-67, 13C, acetone-d6, 600 MHz



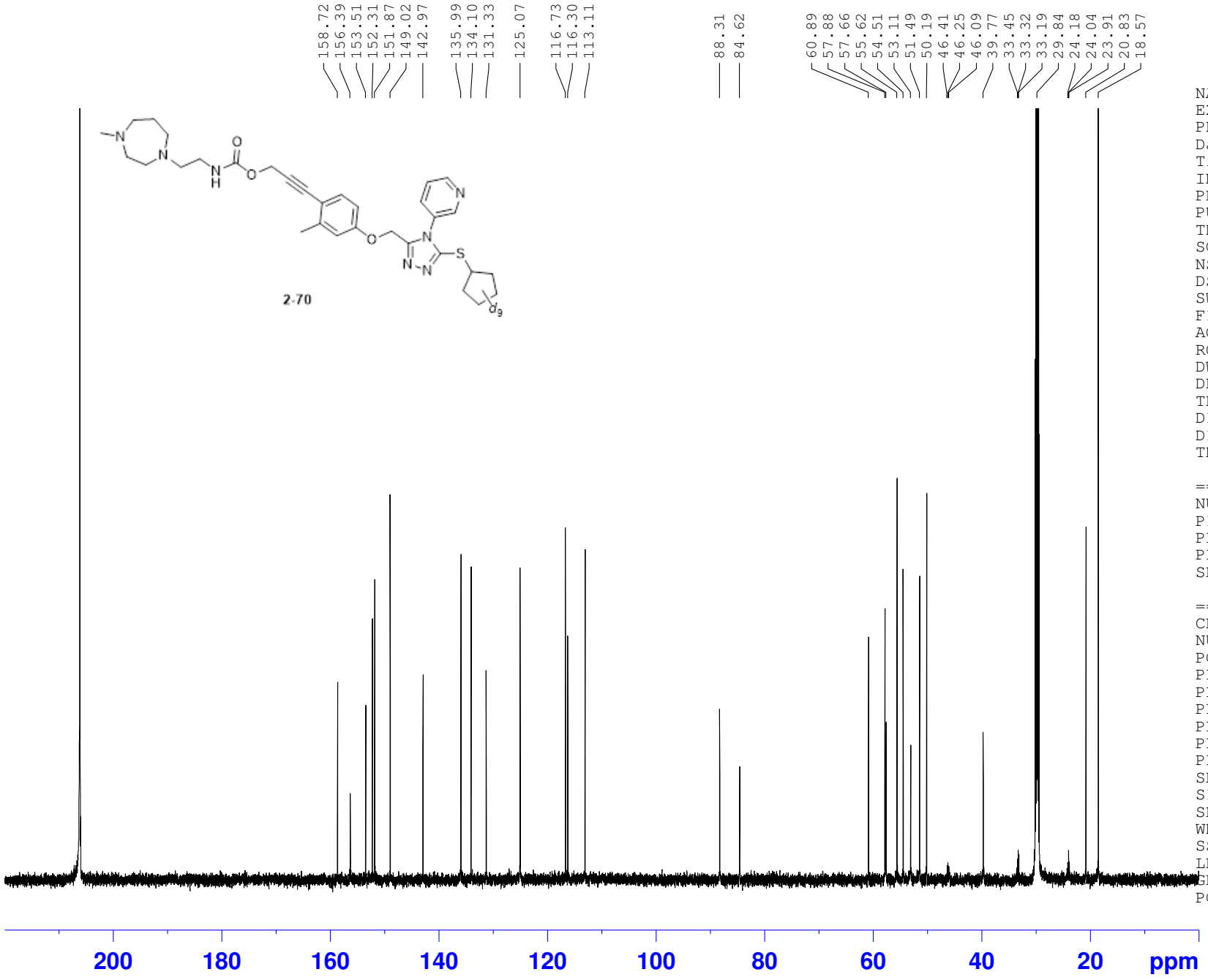
NAME	CNA-695-67
EXPNO	2
PROCNO	1
Date_	20160217
Time	16.04
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	Acetone
NS	170
DS	4
SWH	36057.691 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	203
DW	13.867 usec
DE	6.50 usec
TE	297.6 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	11.50 usec
PL1	0.00 dB
PL1W	97.46119690 W
SFO1	151.0637542 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	70.00 usec
PL2	-2.00 dB
PL12	14.19 dB
PL13	120.00 dB
PL2W	19.70630455 W
PL12W	0.47381112 W
PL13W	0.00000000 W
SFO2	600.7124028 MHz
SI	32768
SF	151.0485241 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-695-70, 1H, acetone-d6, 600 MHz



NAME	CNA-695-70
EXPNO	1
PROCNO	1
Date_	20160217
Time	16.40
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	16
DS	2
SWH	12335.526 Hz
FIDRES	0.188225 Hz
AQ	2.6564426 sec
RG	32
DW	40.533 usec
DE	6.50 usec
TE	297.2 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.86 usec
PL1	-2.00 dB
PL1W	19.70630455 W
SFO1	600.7137096 MHz
SI	32768
SF	600.7100094 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

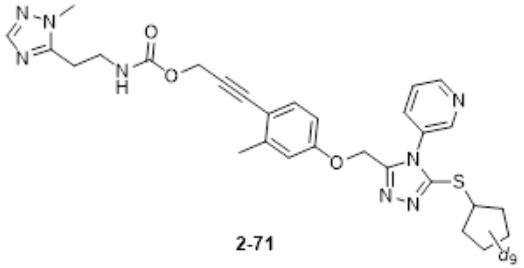
CNA-695-70, 13C, acetone-d6, 600 MHz



NAME	CNA-695-70
EXPNO	3
PROCNO	1
Date_	20160217
Time	17.16
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	Acetone
NS	512
DS	4
SWH	36057.691 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	203
DW	13.867 usec
DE	6.50 usec
TE	297.7 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	11.50 usec
PL1	0.00 dB
PL1W	97.46119690 W
SFO1	151.0637542 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	70.00 usec
PL2	-2.00 dB
PL12	14.19 dB
PL13	120.00 dB
PL2W	19.70630455 W
PL12W	0.47381112 W
PL13W	0.00000000 W
SFO2	600.7124028 MHz
SI	32768
SF	151.0485223 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

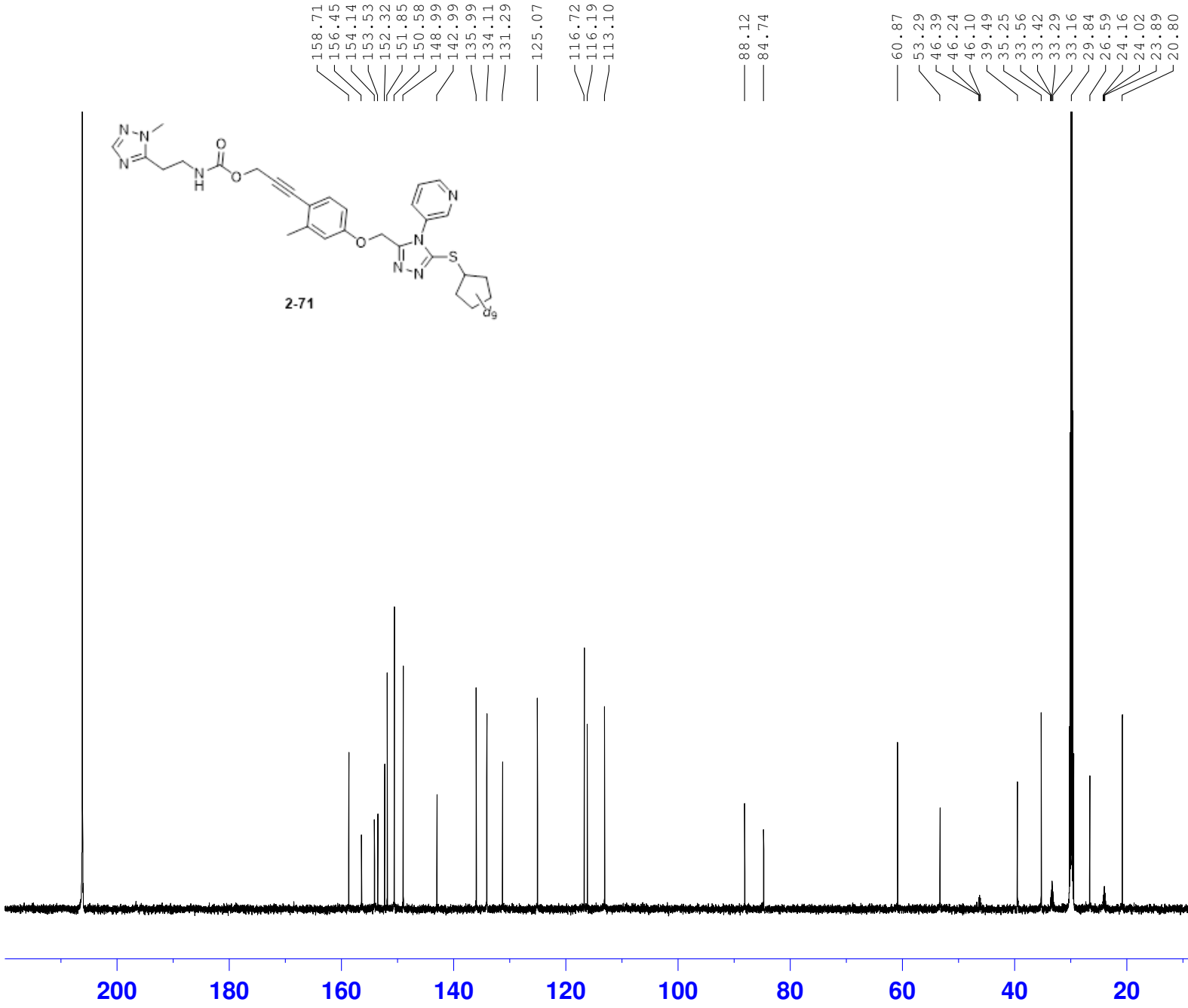
CNA-695-69, 1H, acetone-d6, 600 MHz

8.712 7.990 7.988 7.986 7.984 7.979 7.977 7.975 7.973 7.971 7.685 7.628 7.620 7.615 7.607 7.275 7.260 6.814 6.810 6.754 6.750 6.740 6.736 5.194 4.894 3.813 3.565 3.555 3.544 3.533 3.005 2.994 2.983 2.313 2.050



NAME	CNA-695-69
EXPNO	1
PROCNO	1
Date_	20160217
Time	16.18
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	16
DS	2
SWH	12335.526 Hz
FIDRES	0.188225 Hz
AQ	2.6564426 sec
RG	32
DW	40.533 usec
DE	6.50 usec
TE	297.2 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.86 usec
PL1	-2.00 dB
PL1W	19.70630455 W
SFO1	600.7137096 MHz
SI	32768
SF	600.7100094 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-695-69, 13C, acetone-d6, 600 MHz

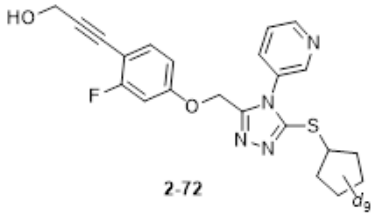


NAME	CNA-695-69
EXPNO	2
PROCNO	1
Date_	20160217
Time	16.32
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	Acetone
NS	256
DS	4
SWH	36057.691 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	203
DW	13.867 usec
DE	6.50 usec
TE	297.6 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	11.50 usec
PL1	0.00 dB
PL1W	97.46119690 W
SFO1	151.0637542 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	70.00 usec
PL2	-2.00 dB
PL12	14.19 dB
PL13	120.00 dB
PL2W	19.70630455 W
PL12W	0.47381112 W
PL13W	0.00000000 W
SFO2	600.7124028 MHz
SI	32768
SF	151.0485268 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-752-6, 1H, CDCl3, 400 MHz

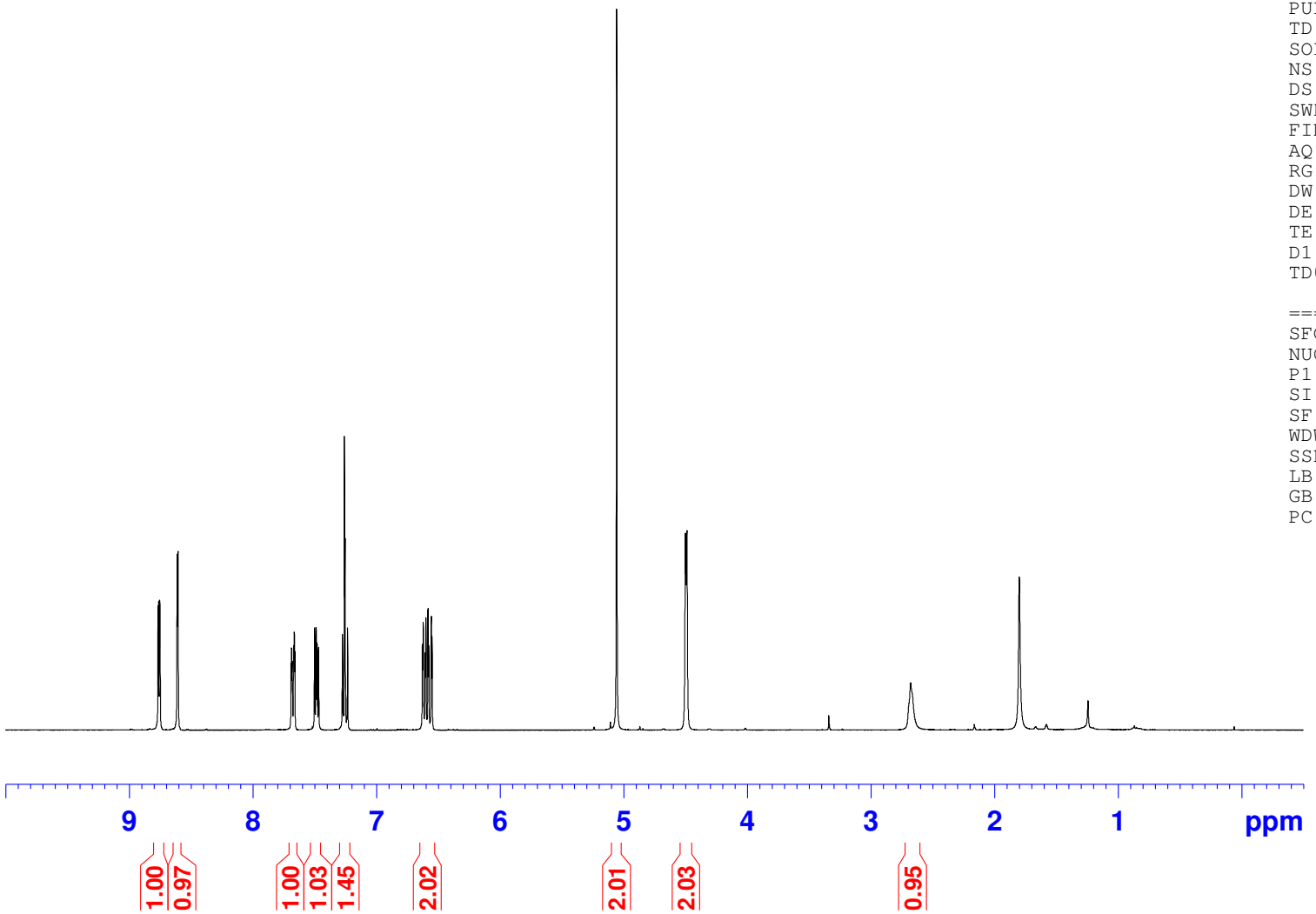
7.692
7.688
7.685
7.681
7.671
7.667
7.665
7.661
7.502
7.490
7.481
7.469
7.276
7.260
7.255
7.234
6.628
6.622
6.607
6.601
6.584
6.578
6.557
6.551
5.057
4.501
4.488

2.678

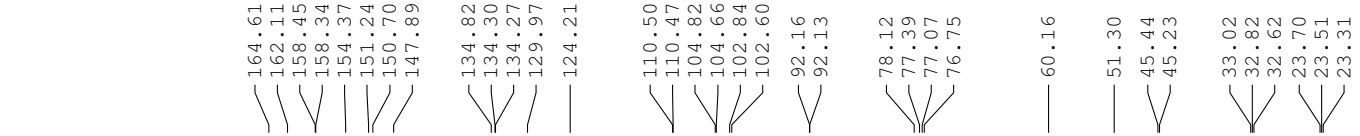


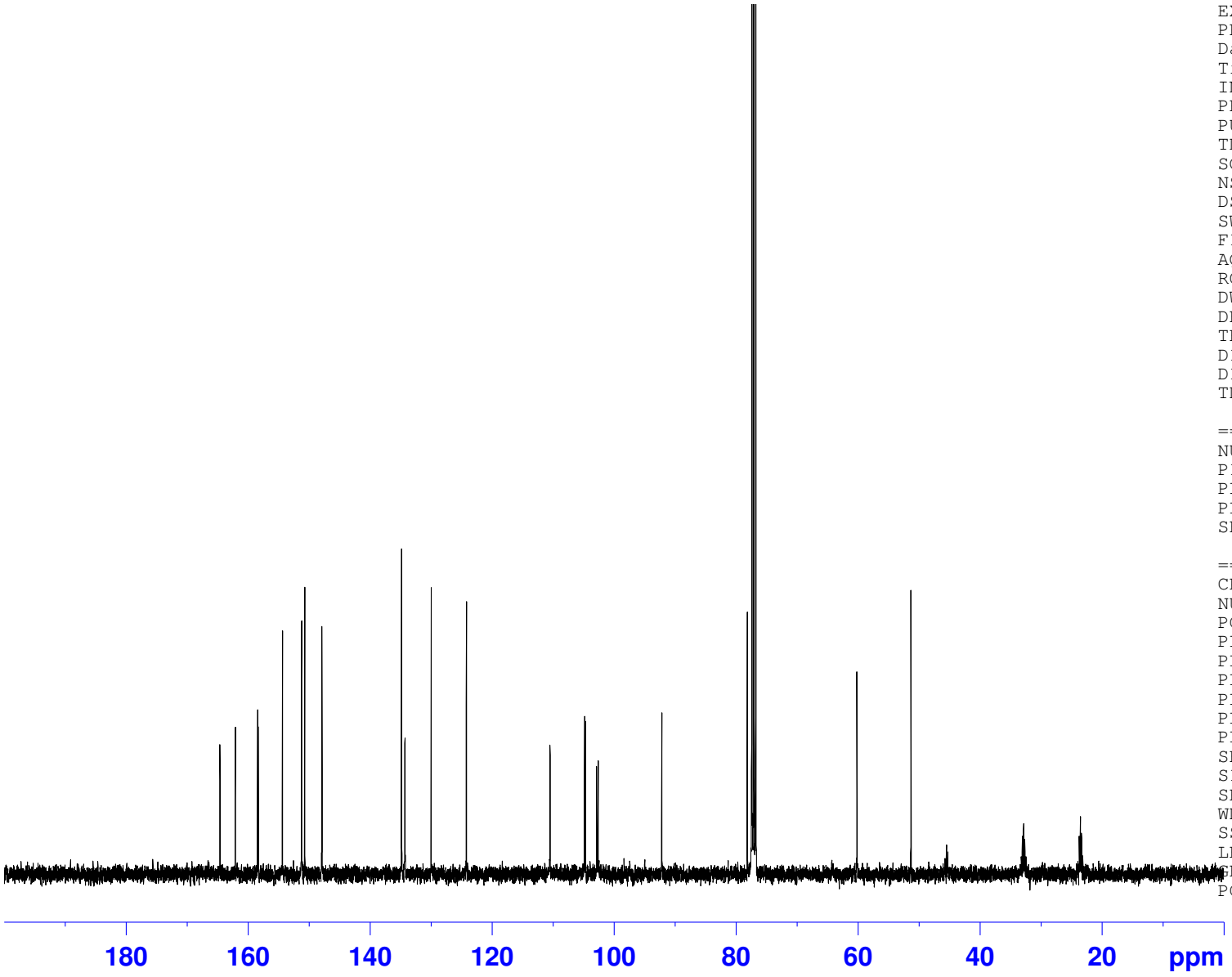
NAME	CNA-752-6
EXPNO	1
PROCNO	1
Date_	20161027
Time	11.38
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8012.820 Hz
FIDRES	0.122266 Hz
AQ	4.0894966 sec
RG	114
DW	62.400 usec
DE	6.50 usec
TE	90.0 K
D1	1.00000000 sec
TD0	1

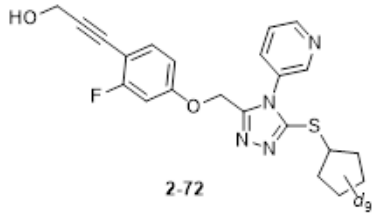
======== CHANNEL f1 ========	
SFO1	400.1324710 MHz
NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300104 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



CNA-752-6, 13C, CDCl3, 400 MHz

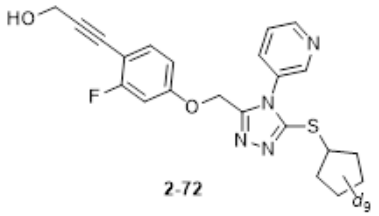






NAME	CNA-752-6
EXPNO	2
PROCNO	1
Date_	20161026
Time	18.23
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	301.2 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-752-6, 19F, CDCl3, 400 MHz



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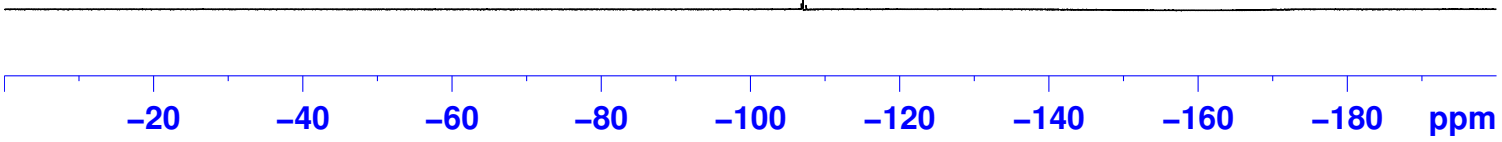
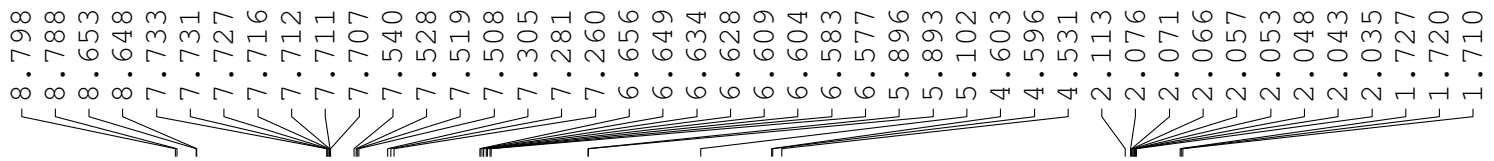


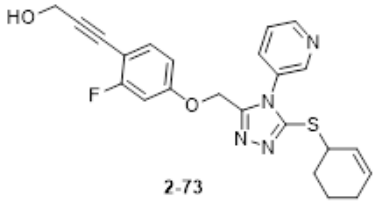
NAME	CNA-752-6
EXPNO	2
PROCNO	1
Date_	20161027
Time	11.40
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	89285.711 Hz
FIDRES	0.681196 Hz
AQ	0.7340532 sec
RG	203
DW	5.600 usec
DE	6.50 usec
TE	89.9 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1

======== CHANNEL f1 ========

SFO1	376.4607164 MHz
NUC1	19F
P1	14.20 usec
SI	65536
SF	376.4983662 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

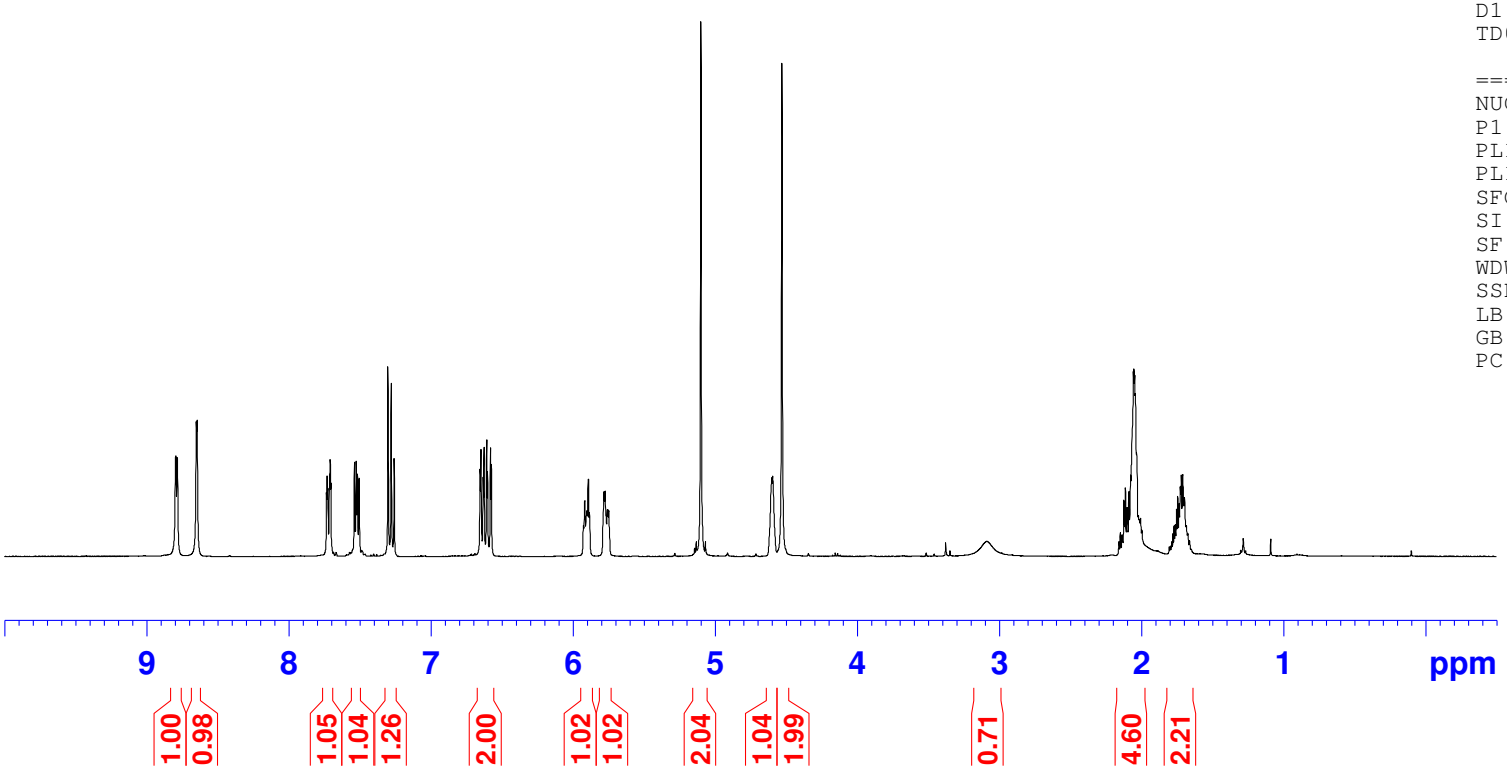
CNA-710-27, 1H, CDCl3, 400 MHz



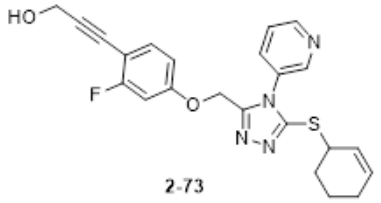


NAME	CNA-710-27
EXPNO	1
PROCNO	1
Date_	20161006
Time	20.54
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	80.6
DW	60.800 usec
DE	6.50 usec
TE	298.2 K
D1	2.00000000 sec
TD0	1

======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2299944 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

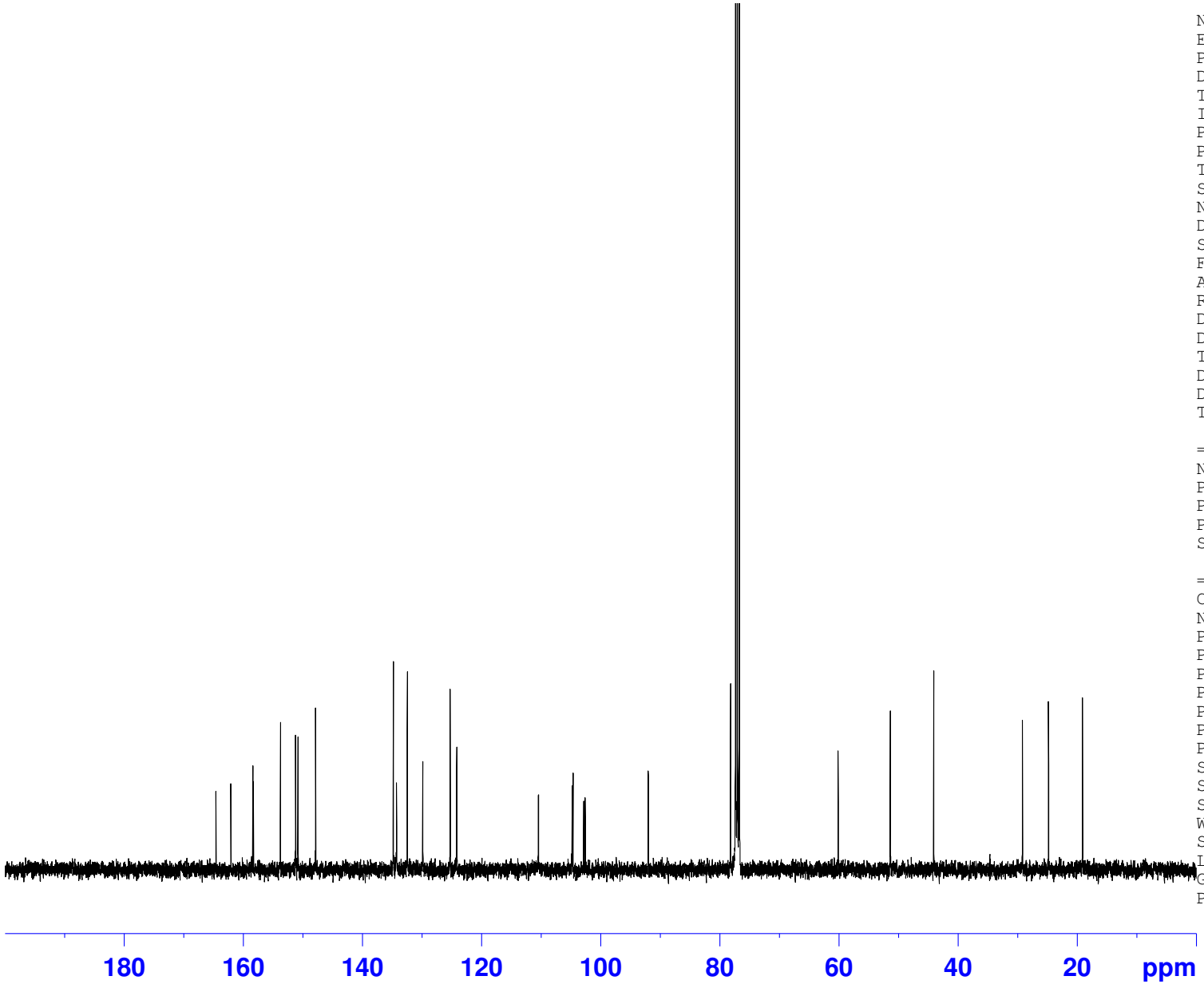


CNA-710-27, 13C, CDCl3, 400 MHz



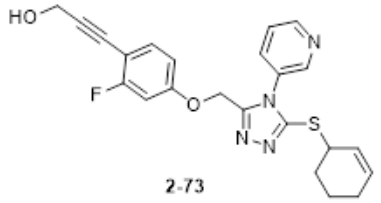
2-73

164.64
162.13
158.45
158.34
153.80
151.26
150.84
147.90
134.84
134.33
134.30
132.50
129.89
125.30
124.21
110.51
110.48
104.82
104.66
102.86
102.62
92.05
92.02
78.22
77.38
77.06
76.75
60.15
51.38
44.10
29.20
24.82
19.12



NAME	CNA-710-27
EXPNO	2
PROCNO	1
Date_	20161006
Time	21.31
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	500
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	298.2 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-710-27, 1H, CDCl3, 400 MHz



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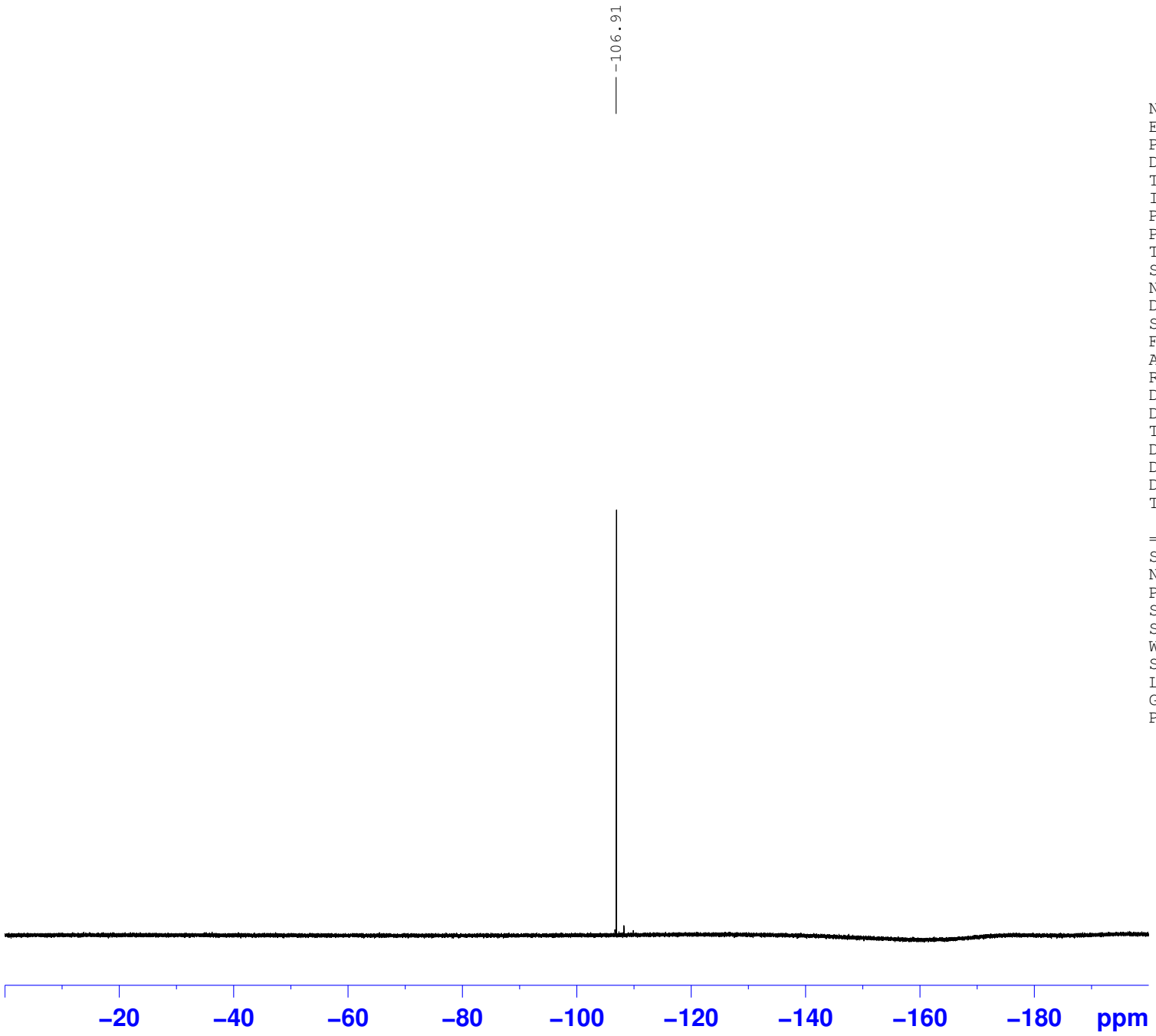
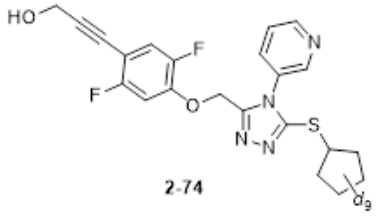


NAME	CNA-710-27
EXPNO	1
PROCNO	1
Date_	20161007
Time	15.58
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	89285.711 Hz
FIDRES	0.681196 Hz
AQ	0.7340532 sec
RG	203
DW	5.600 usec
DE	6.50 usec
TE	88.7 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	376.4607164 MHz
NUC1	19F
P1	14.20 usec
SI	65536
SF	376.4983662 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-752-65, 1H, CDCl3/MeOD, 400 MHz

8.616 8.610 7.875 7.872 7.870 7.866 7.855 7.851 7.849 7.846 7.595 7.583 7.574 7.562 7.502 7.067 7.051 7.040 7.023 6.911 6.893 6.886 6.868 5.132 4.530 4.382

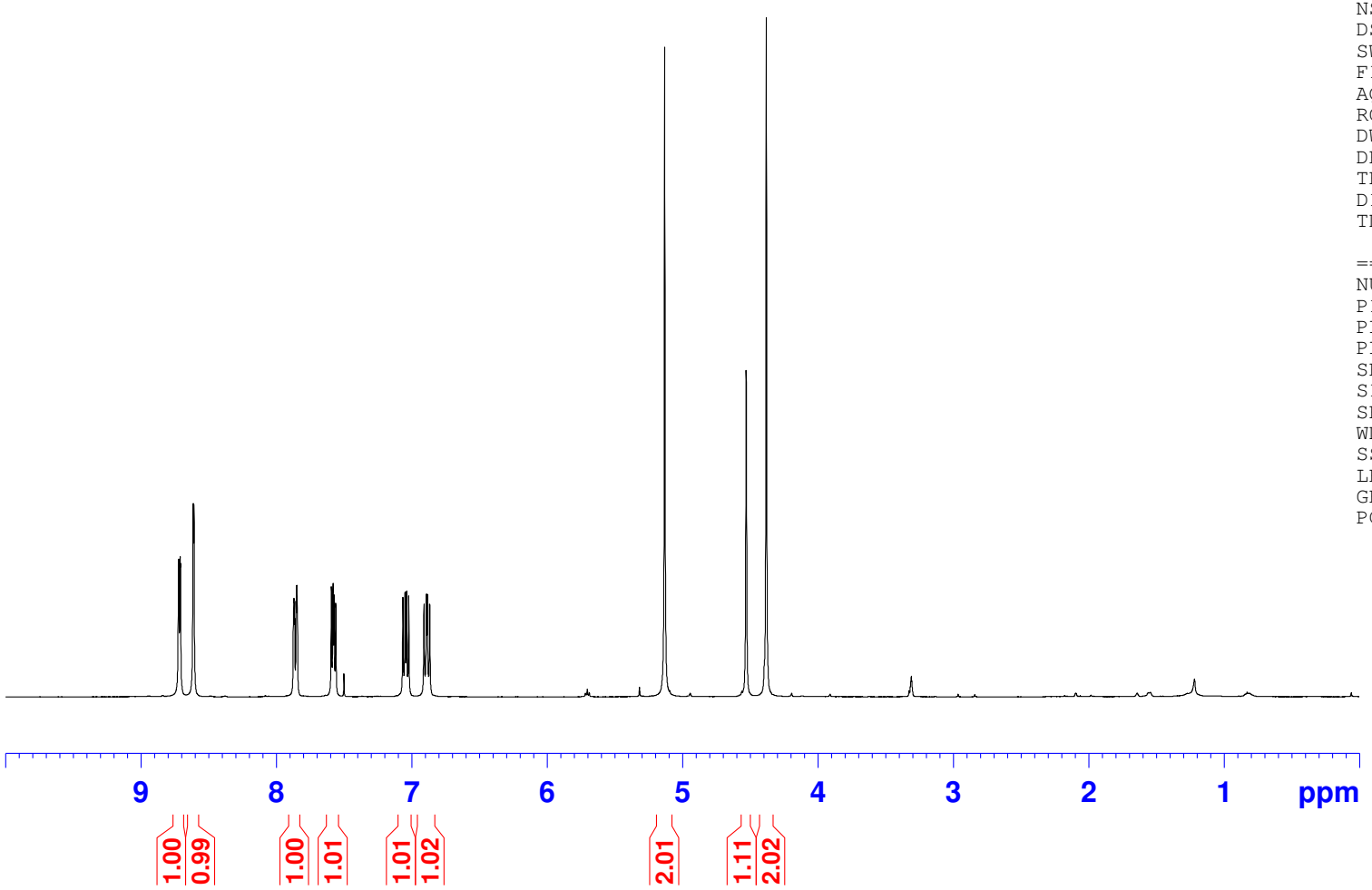
3.314 3.310 3.306



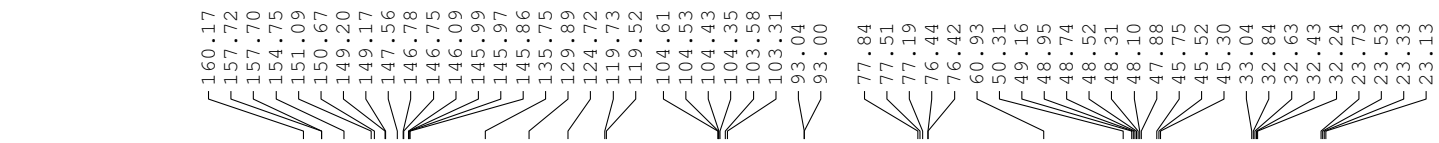
NAME	CNA-752-65
EXPNO	1
PROCNO	1
Date_	20170116
Time	17.28
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	MeOD
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	57
DW	60.800 usec
DE	6.50 usec
TE	294.7 K
D1	2.00000000 sec
TD0	1

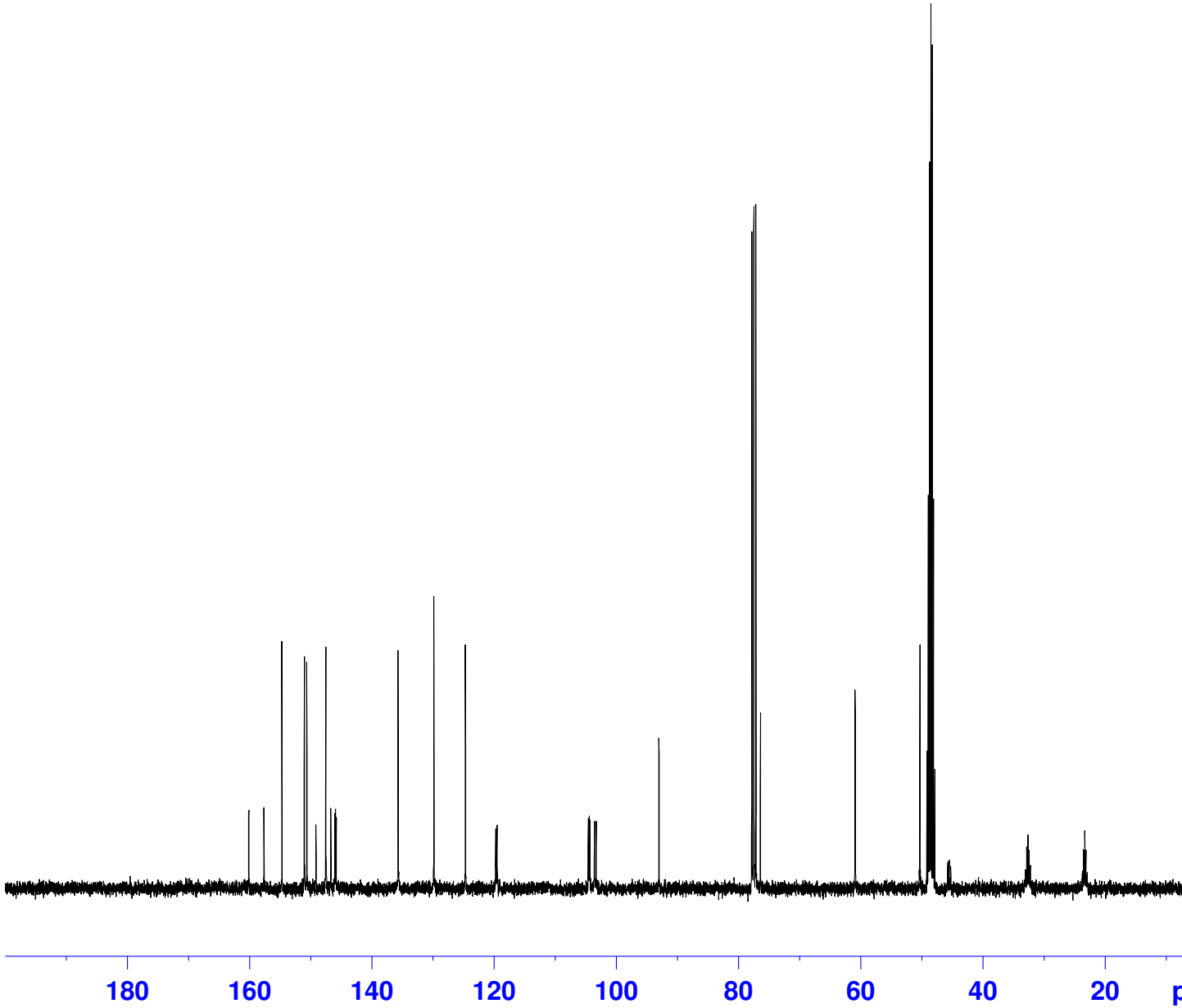
======== CHANNEL f1 ========

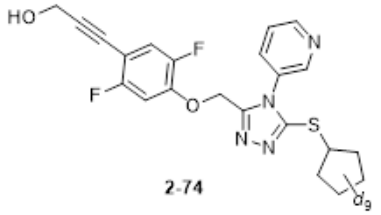
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300104 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



CNA-752-65, 13C, CDCl3/MeOD, 400 MHz

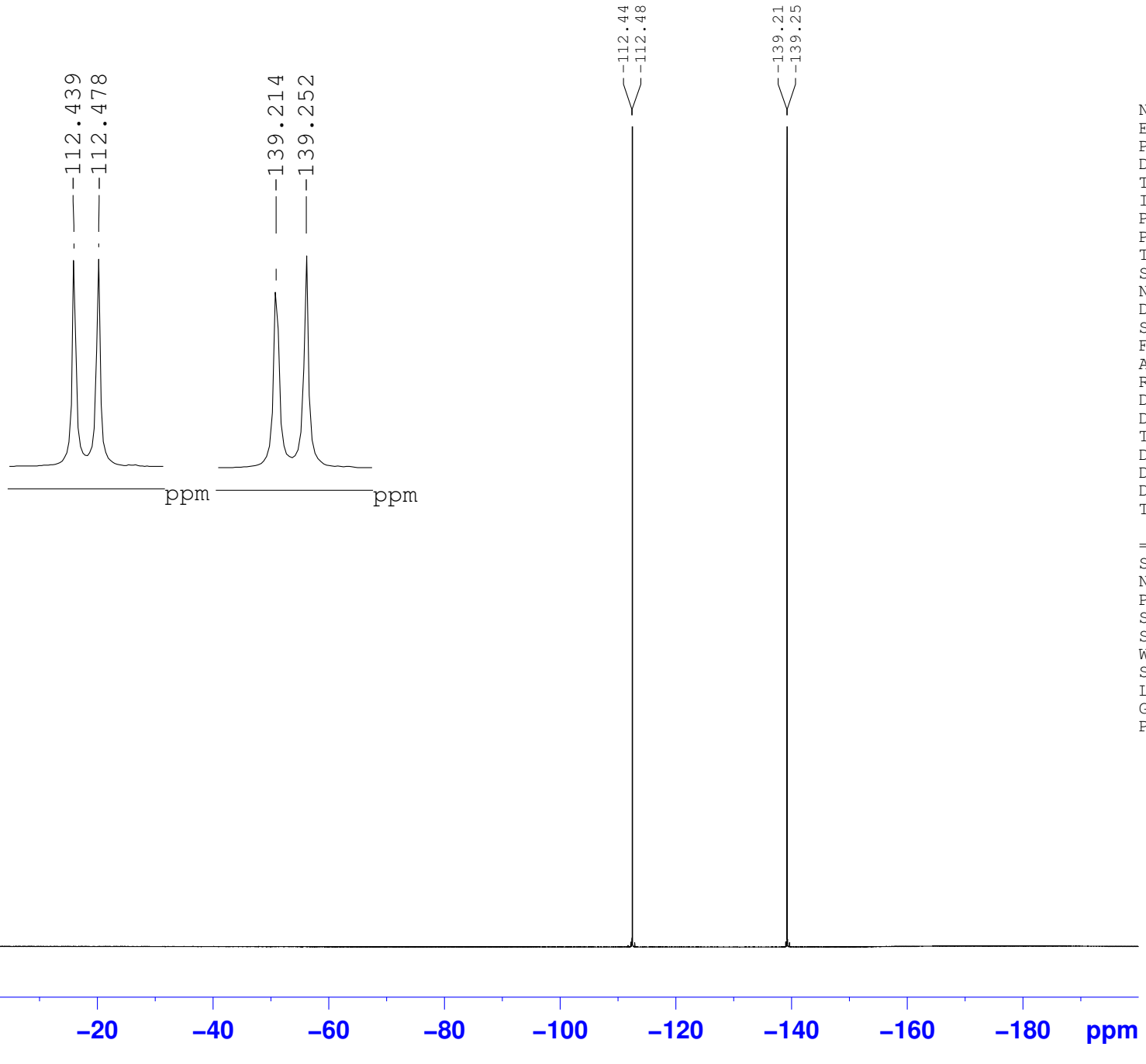


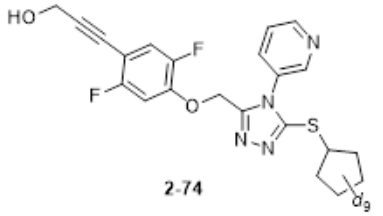




NAME	CNA-752-65
EXPNO	2
PROCNO	1
Date_	20170116
Time	17.45
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	MeOD
NS	200
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	294.9 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

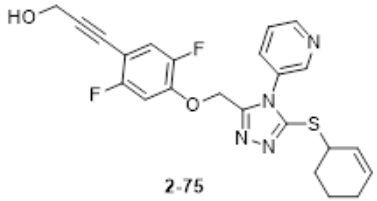
CNA-752-65, 19F, CDCl3/MeOD, 400 MHz



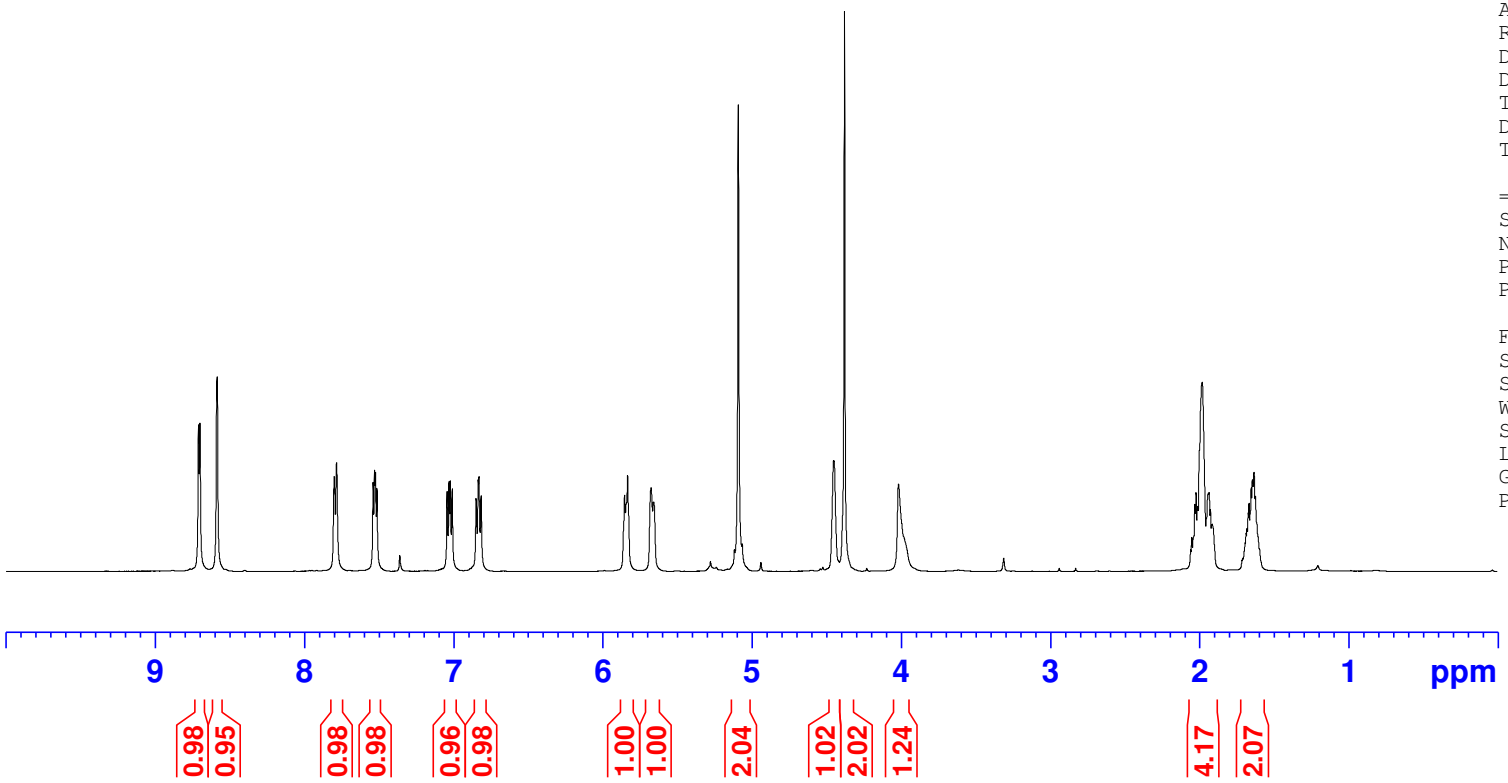


NAME	CNA-752-65
EXPNO	3
PROCNO	1
Date_	20170116
Time	17.55
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	MeOD
NS	16
DS	4
SWH	89285.711 Hz
FIDRES	0.681196 Hz
AQ	0.7340532 sec
RG	203
DW	5.600 usec
DE	6.50 usec
TE	90.3 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	376.4607164 MHz
NUC1	19F
P1	14.20 usec
SI	65536
SF	376.4983662 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-752-55, 1H, CDCl3/MeOD, 500 MHz



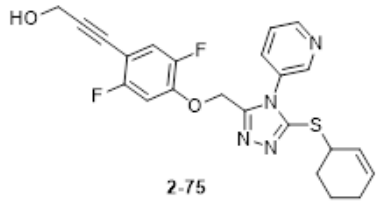
8.708 8.699 8.586 8.583 7.798 7.783 7.538 7.528 7.522 7.512 7.042 7.029 7.020 7.007 6.847 6.833 6.828 6.814 5.851 5.840 5.832 5.675 5.673 5.659 5.657 5.090 4.451 4.447 4.378 4.015 2.029 2.021 2.009 1.982 1.979 1.938 1.933 1.925 1.665 1.657 1.651 1.643 1.632 1.623




```
Current Data Parameters
NAME          CNA-752-55
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170102
Time               14.56
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT              MeOD
NS                     16
DS                      2
SWH           10000.000 Hz
FIDRES         0.152588 Hz
AQ            3.2767999 sec
RG                     32
DW               50.000 usec
DE                6.50 usec
TE               297.4 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1630887 MHz
NUC1                   1H
P1                 11.50 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1600094 MHz
WDW                   EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

CNA-752-55, 19F, CDCl3/MeOD, 500 MHz

159.92
157.92
154.14
151.14
150.65
148.98
148.96
147.62
147.04
147.02
145.99
145.91
145.89
145.81
135.58
132.68
129.79
124.96
124.56
119.83
119.81
119.66
119.64
104.70
104.63
104.55
104.49
103.63
103.41
93.11
93.09
76.54
61.00
50.50
44.22
29.06
24.69
18.95



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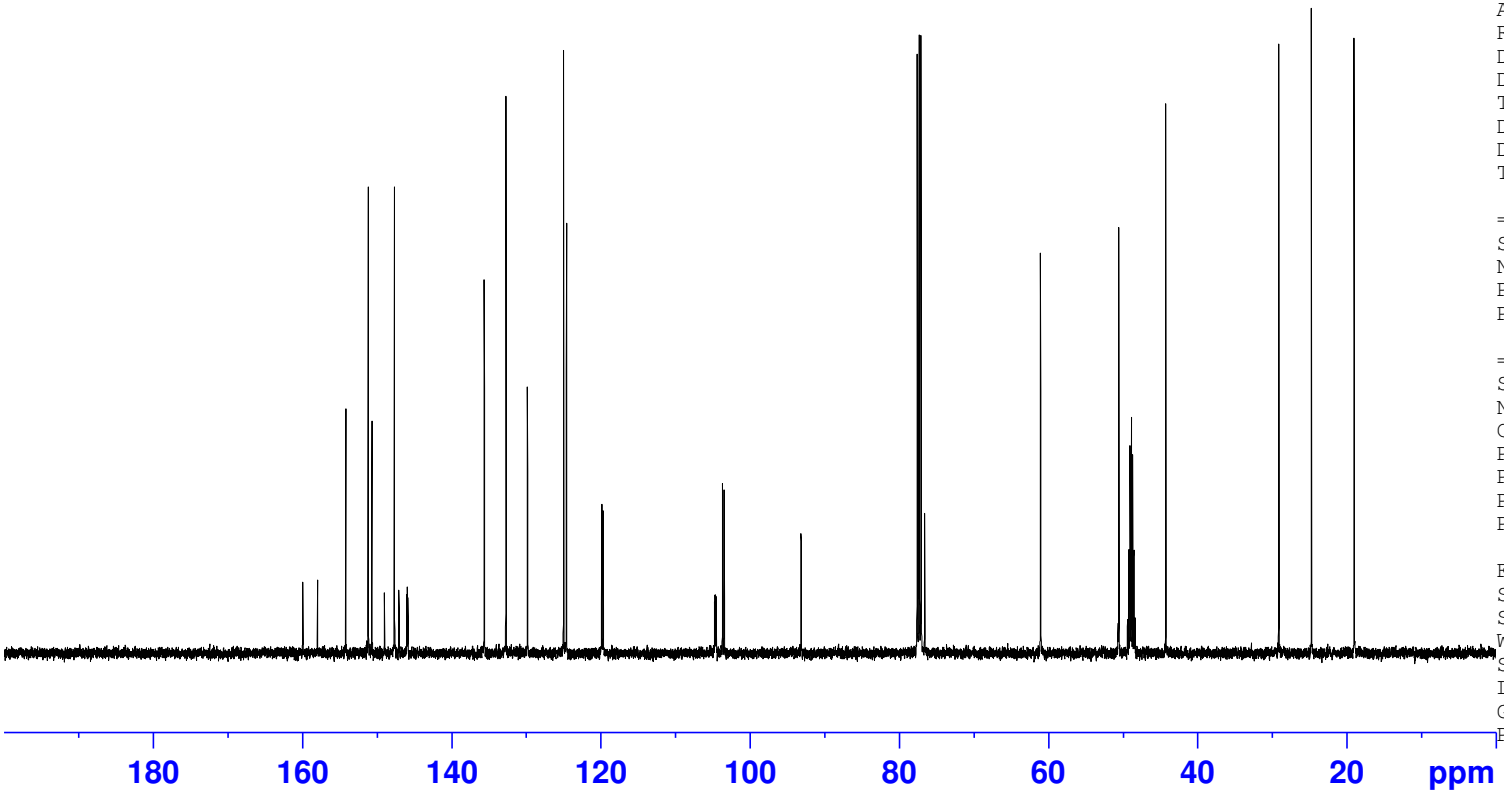
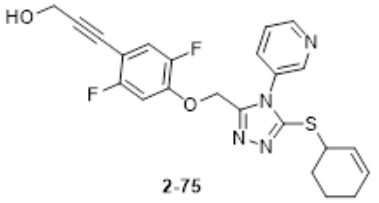



```
Current Data Parameters
NAME          CNA-752-55
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170102
Time               15.18
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT             MeOD
NS                   330
DS                     2
SWH            29761.904 Hz
FIDRES          0.454131 Hz
AQ             1.1010048 sec
RG                   203
DW                16.800 usec
DE                 6.50 usec
TE                298.3 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.7779086 MHz
NUC1                  13C
P1                 10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2              80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W
PLW13         0.23805000 W

F2 - Processing parameters
SI                 32768
SF           125.7653320 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

CNA-752-55, 19F, CDCl3/MeOD, 500 MHz



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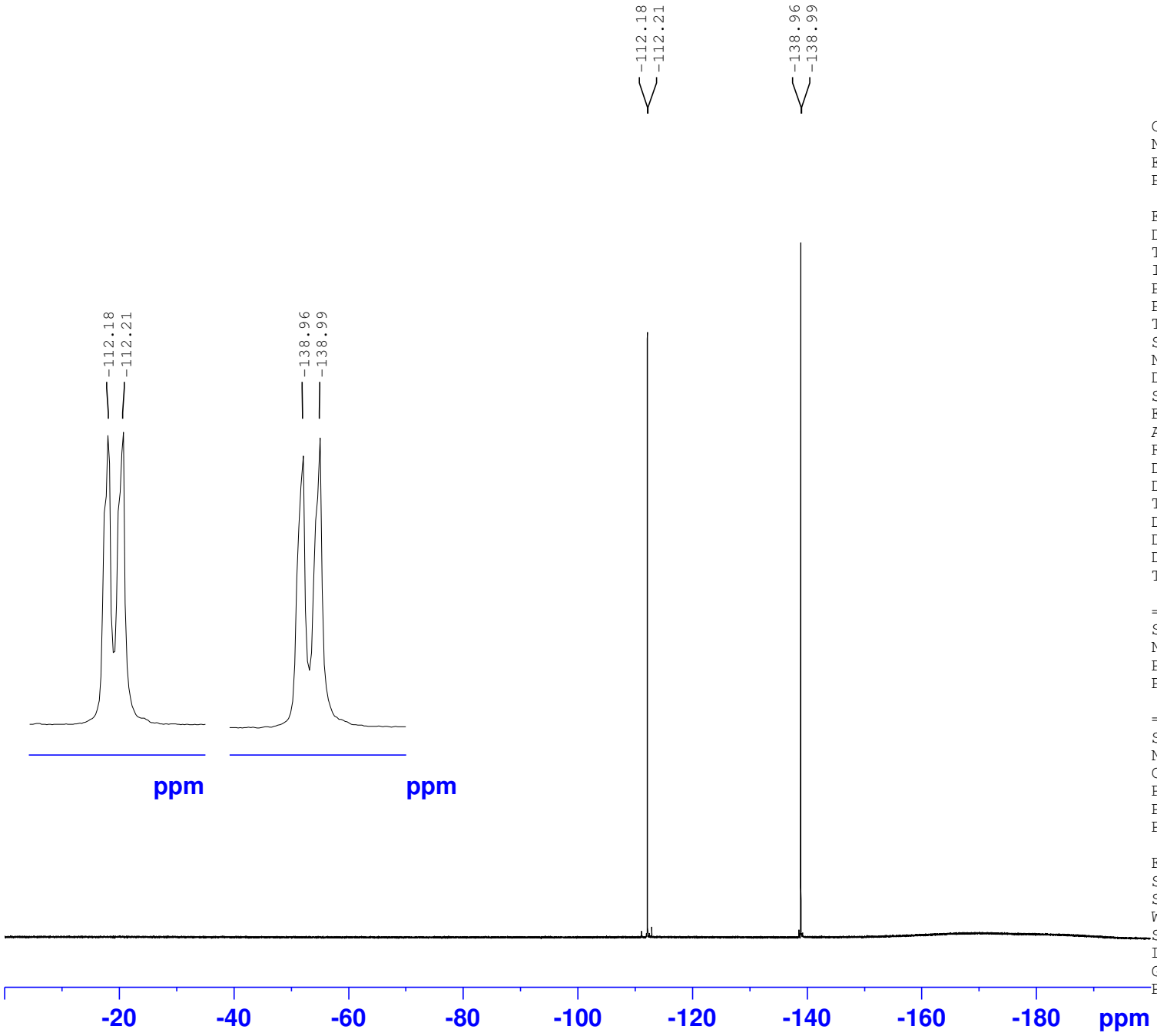
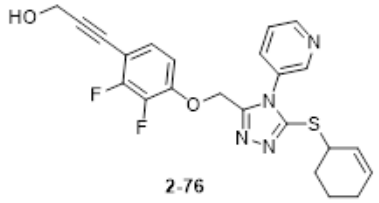



```
Current Data Parameters
NAME          CNA-752-55
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170102
Time               14.59
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG      zgfhigqn.2
TD                131072
SOLVENT              MeOD
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                297.4 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                  19F
P1                 5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-752-54, 1H, CDCl3/MeOD, 300 MHz

8.694 8.684 8.551 7.743 7.716 7.501 7.484 7.475 7.458 7.260 7.048 7.041 7.018 6.995 6.790 6.784 6.760 6.736 5.837 5.804 5.673 5.668 5.641 5.081 4.455 4.374 3.312 3.307 3.202 2.054 2.021 2.006 1.961 1.895 1.678 1.632 1.616

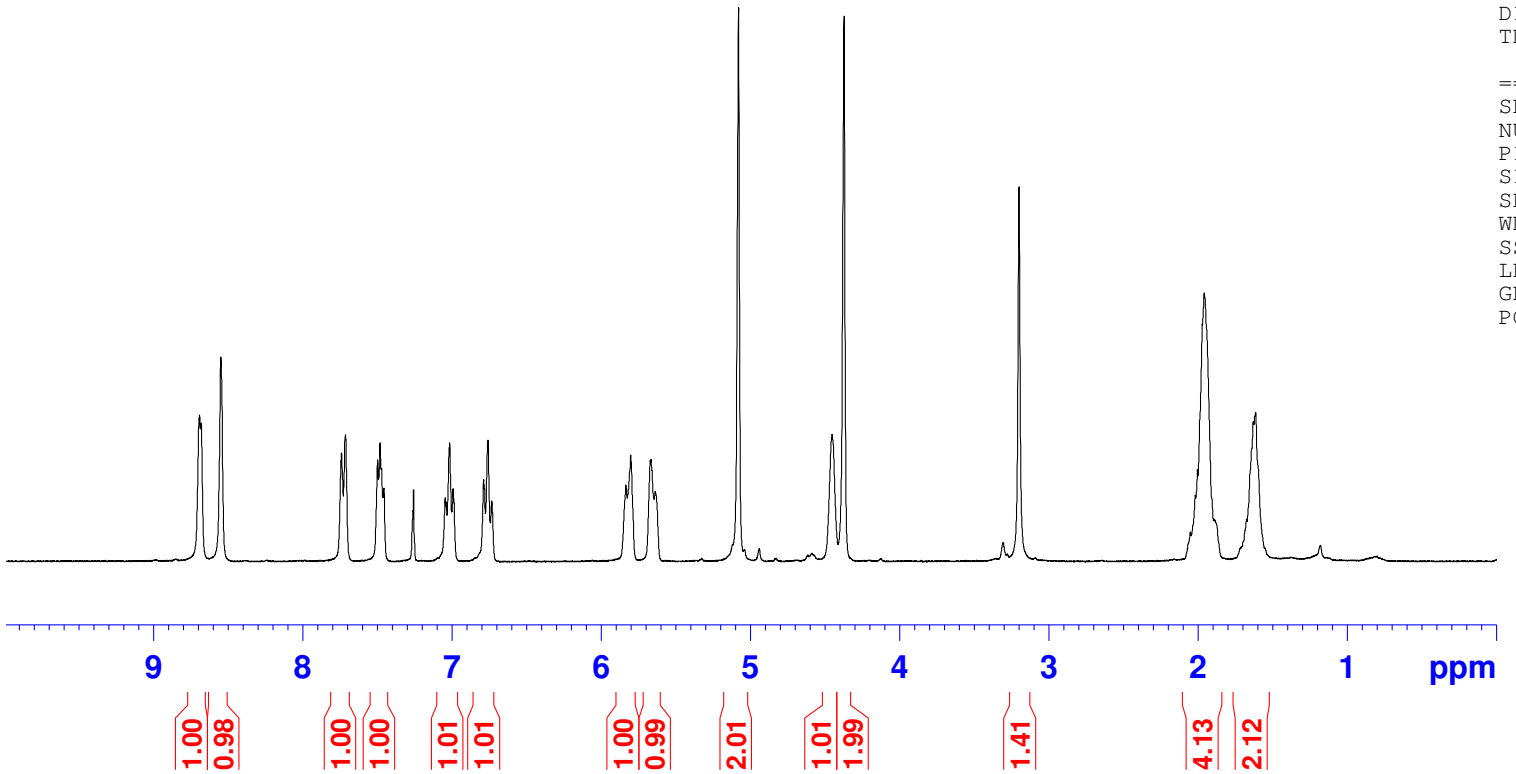


2-76

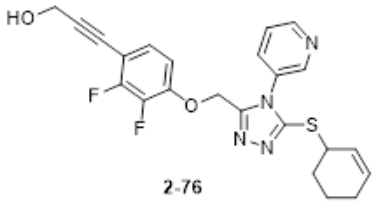
NAME	CNA-752-54
EXPNO	2
PROCNO	1
Date_	20170102
Time	21.08
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6188.119 Hz
FIDRES	0.188846 Hz
AQ	2.6477044 sec
RG	101
DW	80.800 usec
DE	6.50 usec
TE	-927.0 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

SFO1	300.2318540 MHz
NUC1	1H
P1	12.71 usec
SI	32768
SF	300.2300082 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

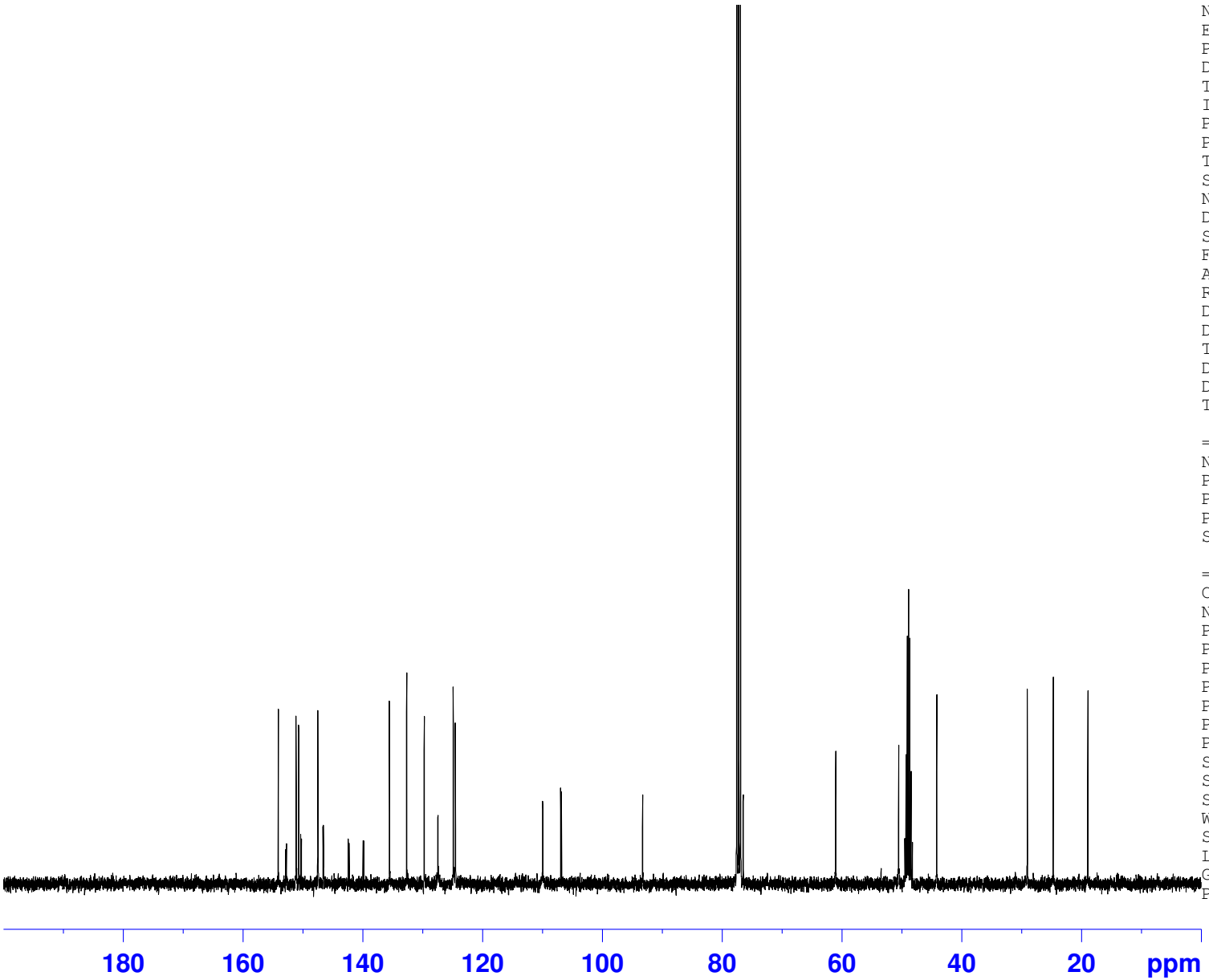


CNA-752-54, 13C, CDCl3/MeOD, 400 MHz



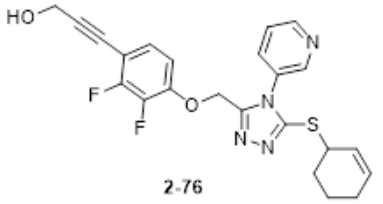
2-76

154.15
152.91
152.80
151.17
150.74
150.40
150.29
147.56
146.71
146.68
146.60
142.47
142.33
140.00
139.86
135.59
132.72
129.78
127.49
124.93
124.58
110.01
109.98
106.98
106.85
93.31
93.28
76.51
76.47
61.06
50.54
44.18
29.05
24.71
18.95

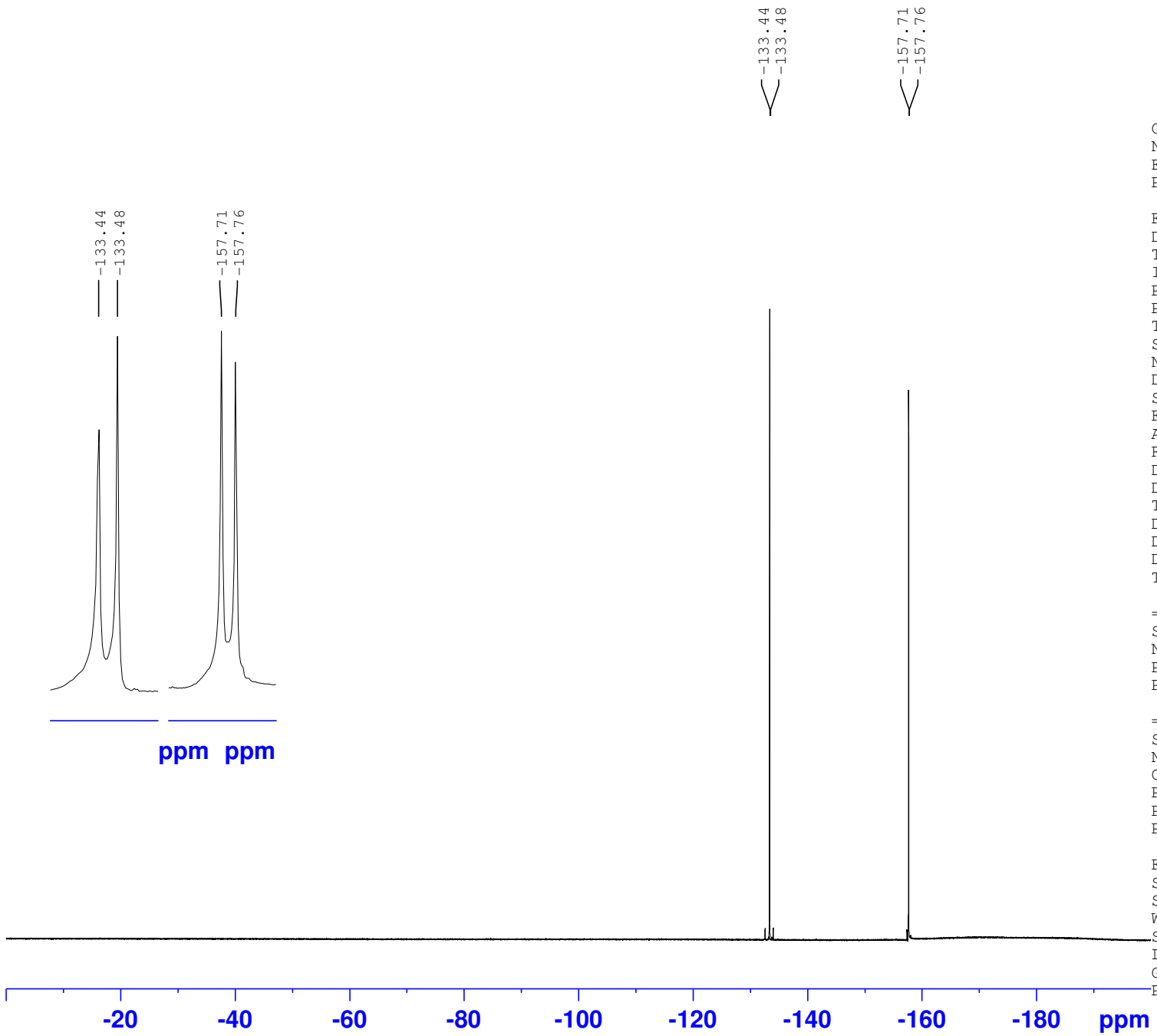


NAME	CNA-752-54	
EXPNO	2	
PROCNO	1	
Date_	20170102	
Time	15.16	
INSTRUM	spect	
PROBHD	5 mm PADUL 13C	
PULPROG	zgpg30	
TD	65536	
SOLVENT	MeOD	
NS	256	
DS	4	
SWH	24038.461	Hz
FIDRES	0.366798	Hz
AQ	1.3631988	sec
RG	203	
DW	20.800	usec
DE	6.50	usec
TE	295.1	K
D1	3.00000000	sec
D11	0.03000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	13C	
P1	10.00	usec
PL1	-0.44	dB
PL1W	39.19395828	W
SFO1	100.6479773	MHz
======== CHANNEL f2 ========		
CPDPRG2	waltz16	
NUC2	1H	
PCPD2	90.00	usec
PL2	-3.90	dB
PL12	15.81	dB
PL13	120.00	dB
PL2W	21.64248466	W
PL12W	0.23137002	W
PL13W	0.00000000	W
SFO2	400.2316009	MHz
SI	32768	
SF	100.6379140	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

CNA-752-54, 19F, CDCl3/MeOD, 500 MHz



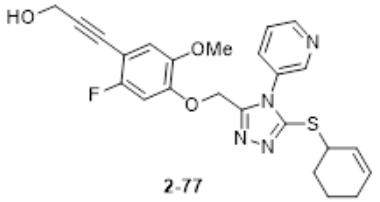
2-76



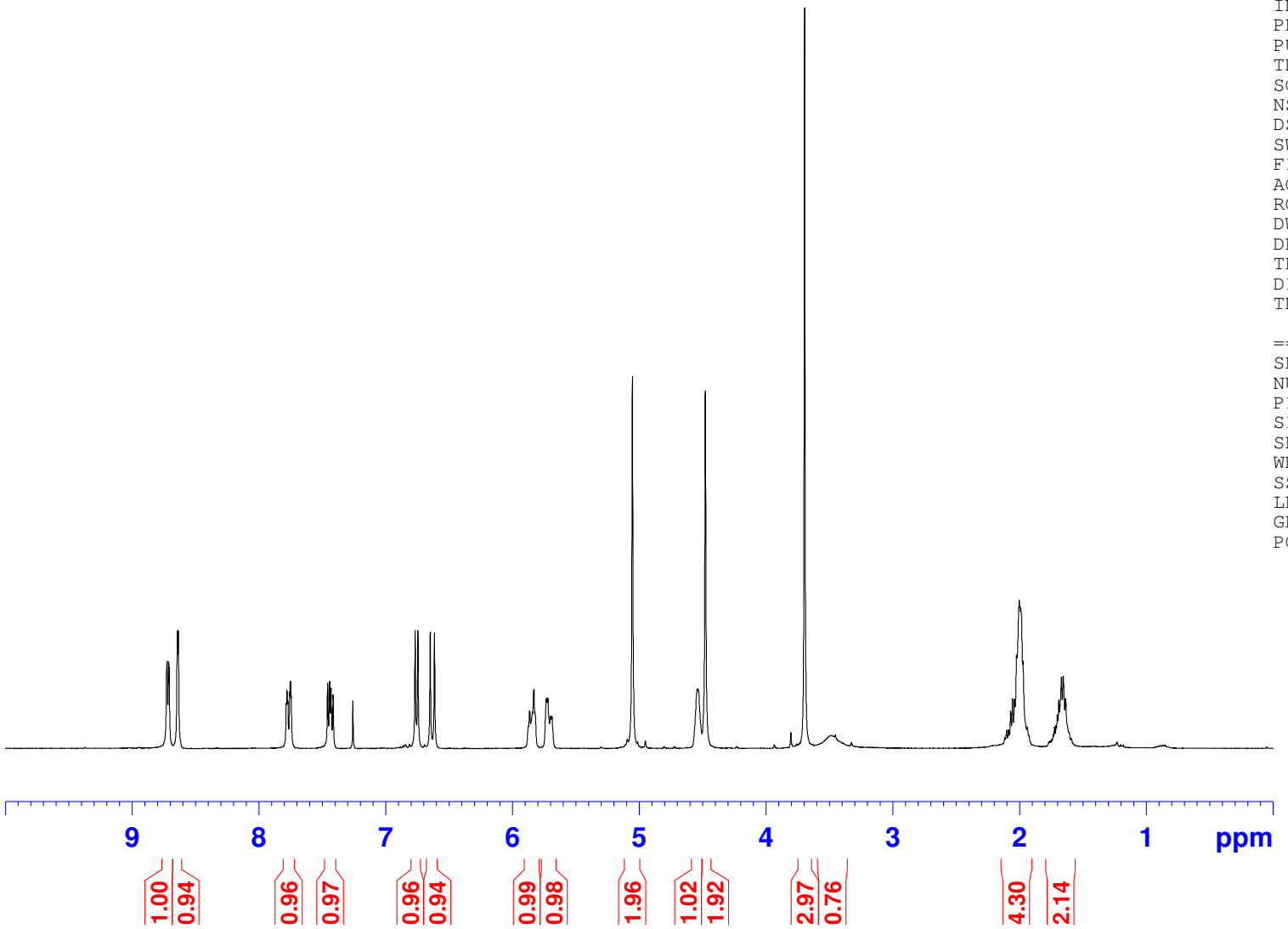

```
Current Data Parameters
NAME          CNA-752-54
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170102
Time               15.52
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG      zgfhigqn.2
TD                131072
SOLVENT              MeOD
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                297.7 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                  19F
P1                 5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-752-58, 1H, CDCl3, 300 MHz

8.730 8.726 8.714 8.710 8.646 8.638 7.786 7.781 7.779 7.774 7.759 7.754 7.752 7.747 7.460 7.444 7.433 7.417 7.260 6.769 6.747 6.650 6.616 5.831 5.735 5.729 5.722 5.055 4.544 4.536 4.479 3.696 2.071 2.056 2.040 2.023 2.002 1.996 1.990 1.972 1.689 1.670 1.655 1.636



2-77

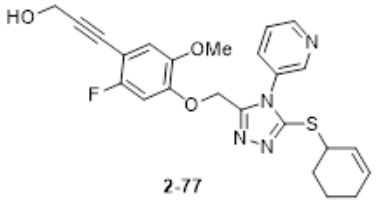


NAME	CNA-752-58
EXPNO	1
PROCNO	1
Date_	20170102
Time	20.54
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6188.119 Hz
FIDRES	0.188846 Hz
AQ	2.6477044 sec
RG	71.8
DW	80.800 usec
DE	6.50 usec
TE	-927.1 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

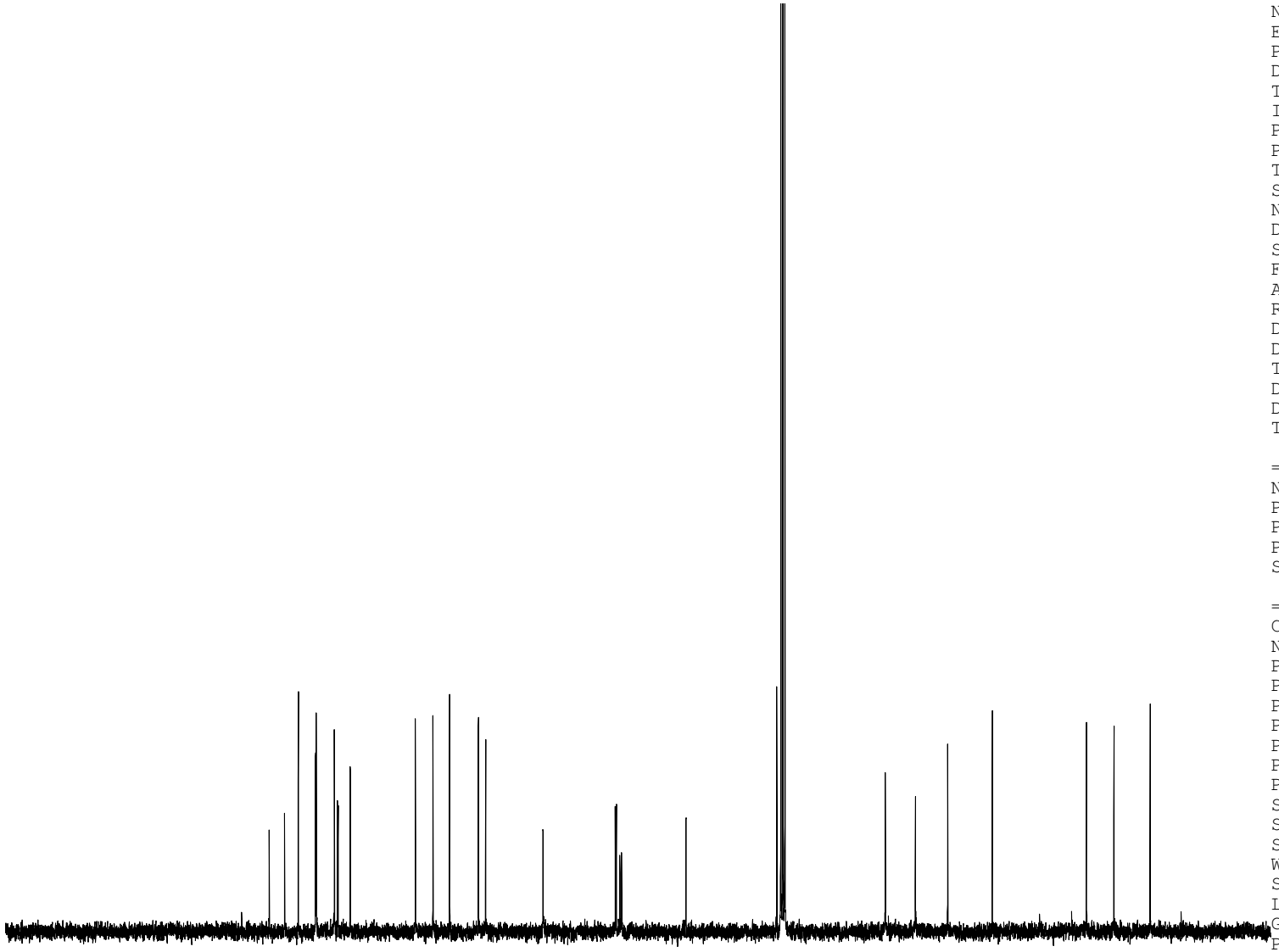
SFO1	300.2318540 MHz
NUC1	1H
P1	12.71 usec
SI	32768
SF	300.2300087 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

CNA-752-58, 13C, CDCl3, 400 MHz



2-77

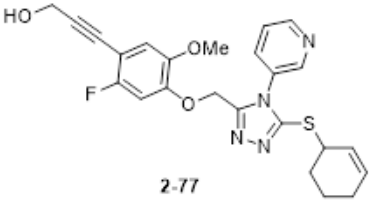
158.35
155.91
153.74
151.02
150.90
148.04
147.54
147.45
145.53
145.50
135.23
132.46
129.82
125.28
124.11
115.07
103.64
103.47
102.90
102.64
92.48
92.45
78.09
60.95
56.18
51.09
44.02
29.14
24.80
19.07



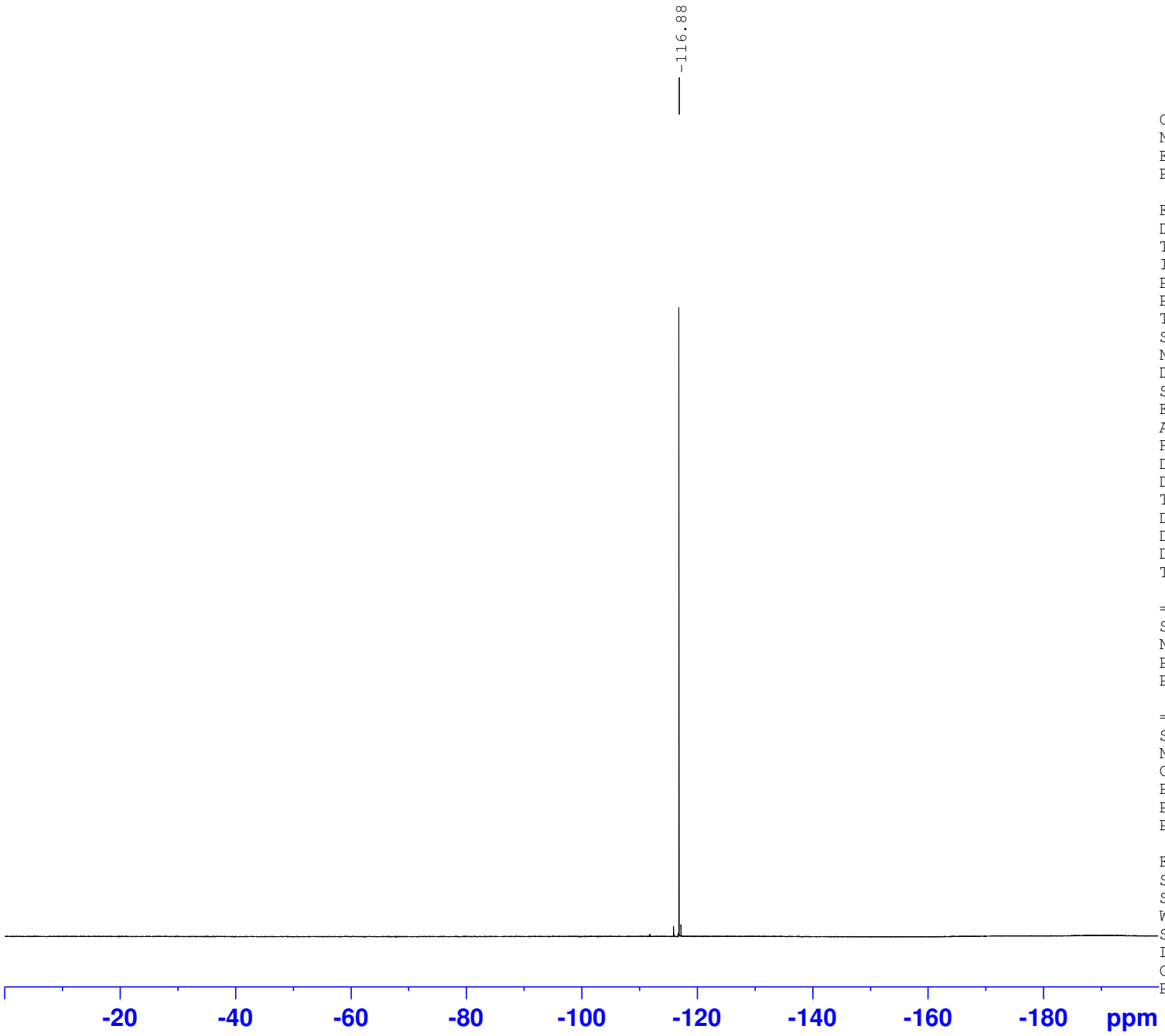
180 160 140 120 100 80 60 40 20 ppm

NAME	CNA-752-58
EXPNO	2
PROCNO	1
Date_	20170102
Time	15.40
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	200
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	295.2 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-752-58, 19F, CDCl3, 500 MHz



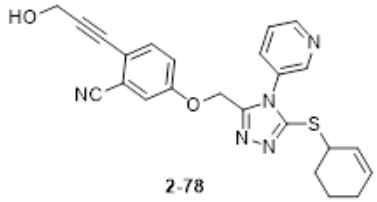
2-77



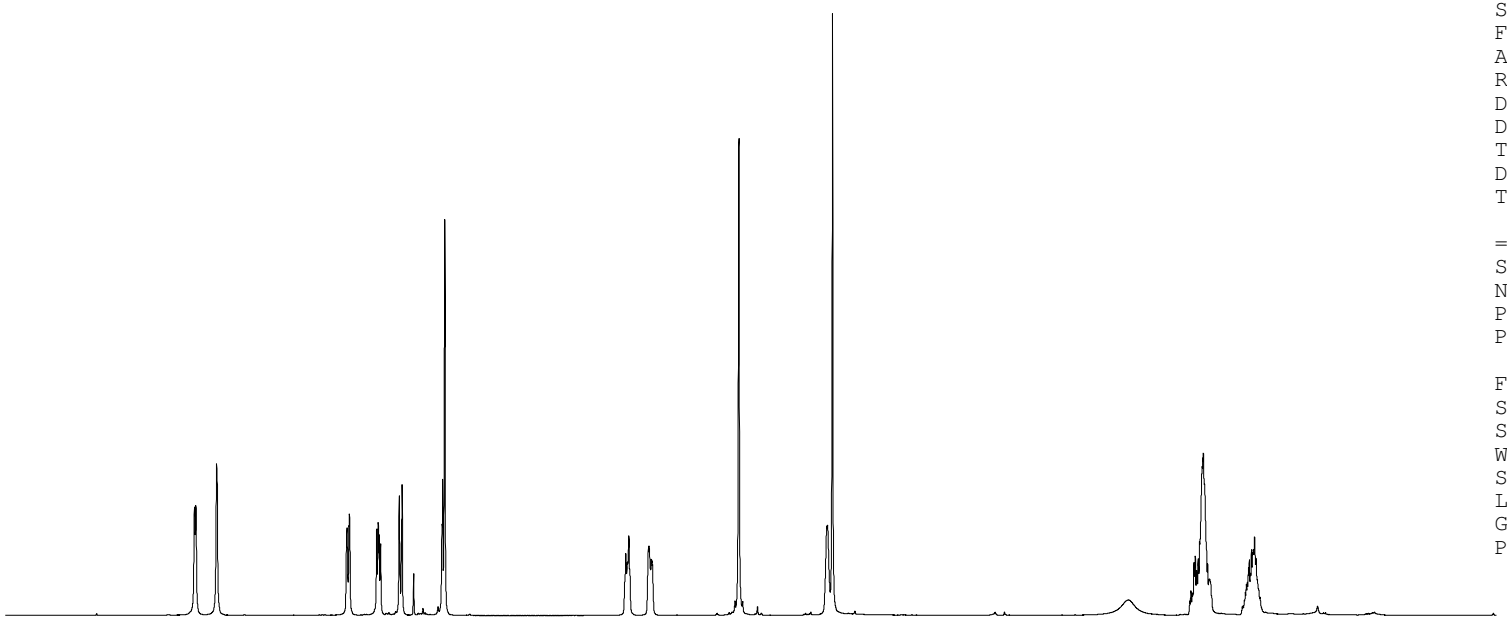

```
Current Data Parameters
NAME          CNA-752-58
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170102
Time               16.00
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG       zgfhigqn.2
TD                131072
SOLVENT             CDCl3
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                297.6 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                  19F
P1                 5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

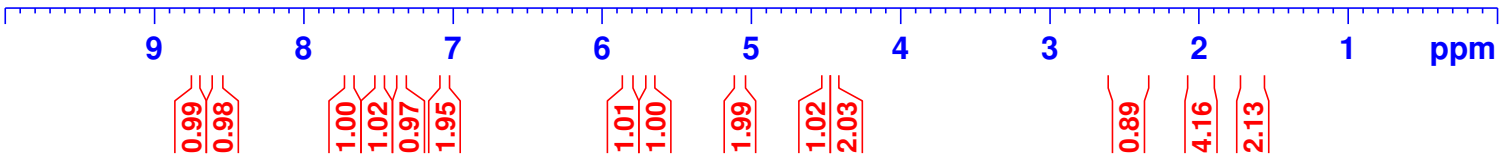
CNA-752-57, 1H, CDCl3/MeOD, 500 MHz

8.730 8.721 8.582 8.579 7.711 7.708 7.703 7.694 7.691 7.687 7.508 7.498 7.492 7.482 7.357 7.338 7.071 7.066 7.051 5.839 5.819 5.687 5.683 5.679 5.667 5.663 5.080 4.490 4.485 4.453 2.021 2.001 1.992 1.977 1.974 1.970 1.966 1.958 1.658 1.644 1.636 1.631 1.623 1.614



2-78

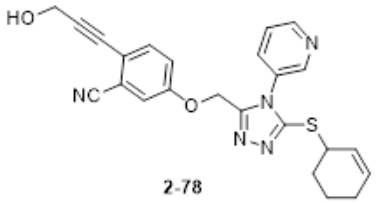




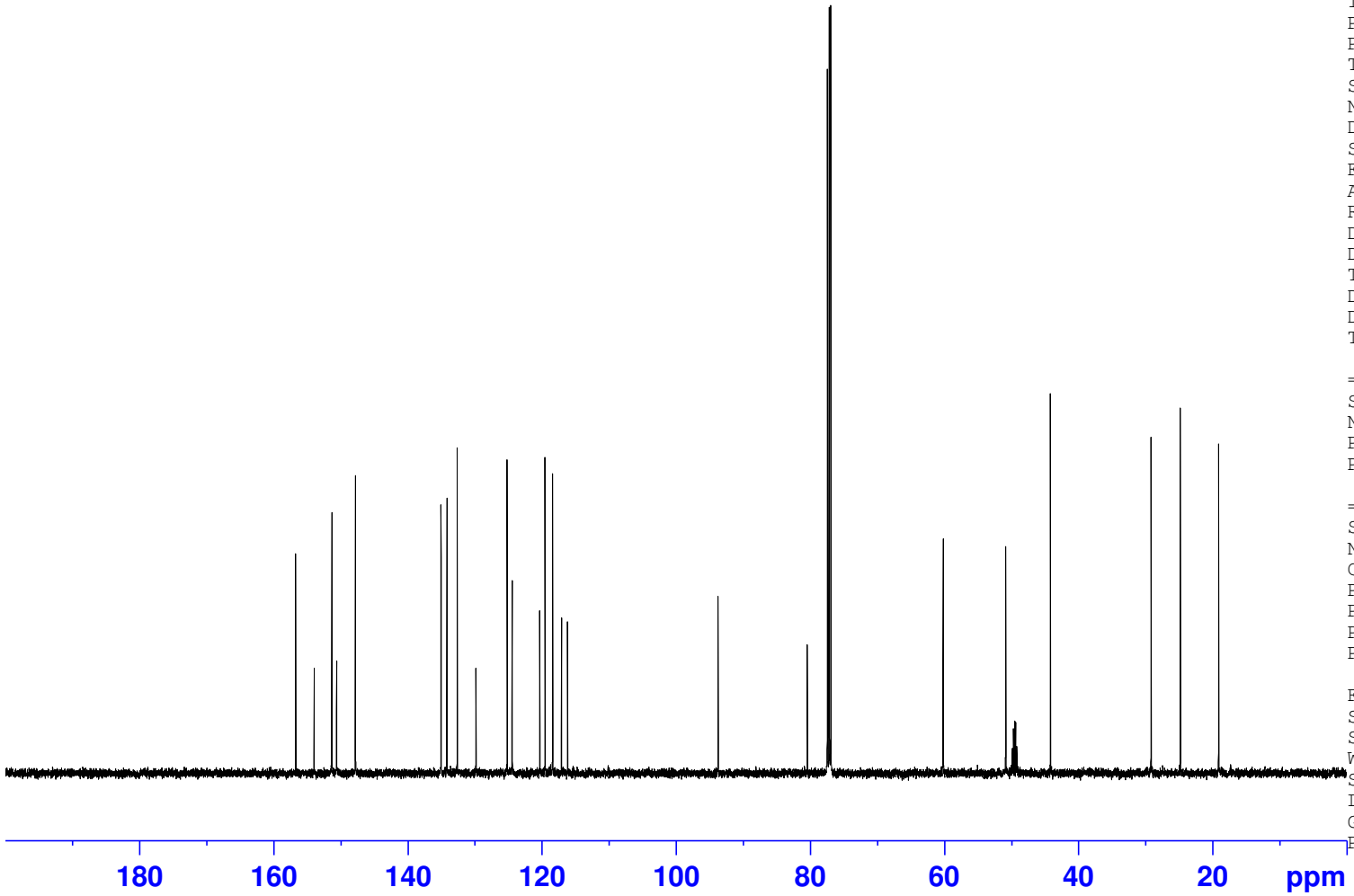

```
Current Data Parameters
NAME          CNA-752-57
EXPNO                  5
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170102
Time               18.56
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                    32
DW                50.000 usec
DE                 6.50 usec
TE                297.3 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1630887 MHz
NUC1                   1H
P1                 11.50 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1600122 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-752-57, 13C, CDCl3/MeOD, 500 MHz

156.69
153.93
151.29
150.58
147.78
135.01
134.13
132.58
129.81
125.15
124.40
120.28
119.51
118.36
117.04
116.15
93.68
80.38
60.13
50.80
44.15
29.13
24.76
19.06



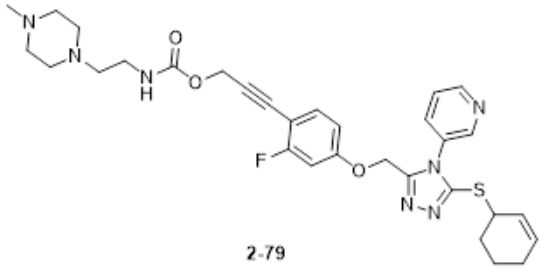
2-78




```
Current Data Parameters
NAME          CNA-752-57
EXPNO                  7
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170102
Time               19.21
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  300
DS                    2
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ            1.1010048 sec
RG                  203
DW               16.800 usec
DE                6.50 usec
TE               298.2 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         125.7779086 MHz
NUC1                13C
P1                10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W
PLW13         0.23805000 W

F2 - Processing parameters
SI                 32768
SF           125.7653320 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

CNA-710-28_752-2, 1H, CDCl3, 400 MHz

8.757 8.753 8.745 8.741 8.595 8.589 7.666 7.664 7.649 7.645 7.643 7.639 7.480 7.468 7.460 7.449 7.324 7.304 7.282 7.260 6.647 6.641 6.620 6.617 6.590 6.584 5.854 5.851 5.063 4.896 3.289 3.275 3.261 2.486 2.471 2.457 2.275 2.030 2.022 2.017 2.013 2.008 1.996 1.683



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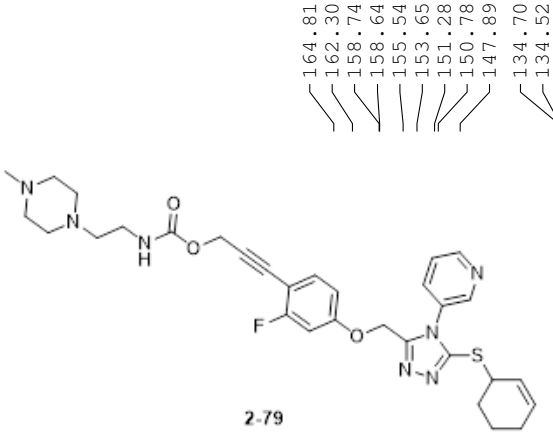
NAME	CNA-710-28_752-2
EXPNO	200
PROCNO	1
Date_	20161006
Time	20.54
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	80.6
DW	60.800 usec
DE	6.50 usec
TE	298.2 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300122 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

9 8 7 6 5 4 3 2 1 ppm

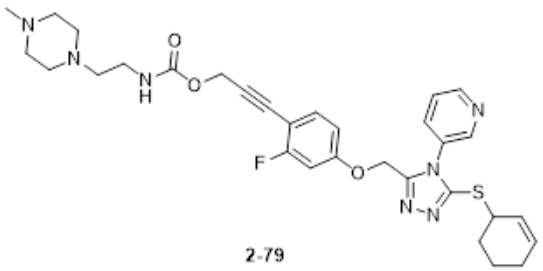
1.00 0.98 1.03 1.02 1.04 2.03 1.05 1.04 0.82 2.06 2.08 1.03 2.11 10.20 3.37 4.50 2.22

CNA-710-28, 13C, CDCl3, 400 MHz



NAME	CNA-710-28
EXPNO	2
PROCNO	1
Date_	20161006
Time	21.59
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	257
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	298.2 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

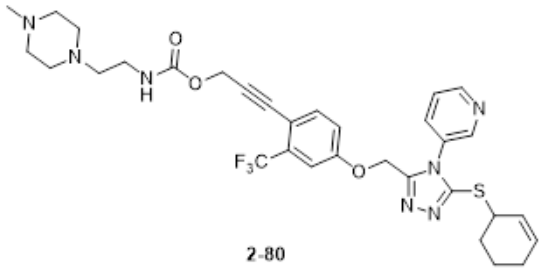
CNA-710-28, 19F, CDCl3, 500 MHz




```
Current Data Parameters
NAME       CNA-710-28_2
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20161007
Time              16.25
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG      zgfhigqn.2
TD               131072
SOLVENT            CDCl3
NS                    16
DS                     4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                   203
DW                4.400 usec
DE                6.50 usec
TE               295.6 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                19F
P1                 5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-710-33, 1H, CDCl3, 400 MHz

8.777 8.774 8.765 8.762 8.623 8.617 7.685 7.679 7.669 7.665 7.659 7.503 7.491 7.482 7.471 7.260 7.082 7.057 7.051 5.869 5.118 4.903 4.593 4.587 3.304 3.290 3.277 2.500 2.485 2.470 2.283 2.258 2.247 2.092 2.068 2.049 2.036 2.031 2.027 2.017 2.007 1.703 1.696 1.687



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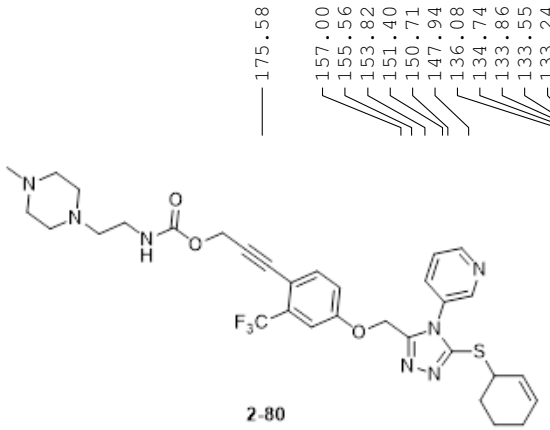
NAME	CNA-710-33
EXPNO	4
PROCNO	1
Date_	20160428
Time	12.50
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8012.820 Hz
FIDRES	0.122266 Hz
AQ	4.0894966 sec
RG	114
DW	62.400 usec
DE	6.50 usec
TE	95.3 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	400.1324710 MHz
NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300107 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-710-33, 13C, CDCl3, 400 MHz

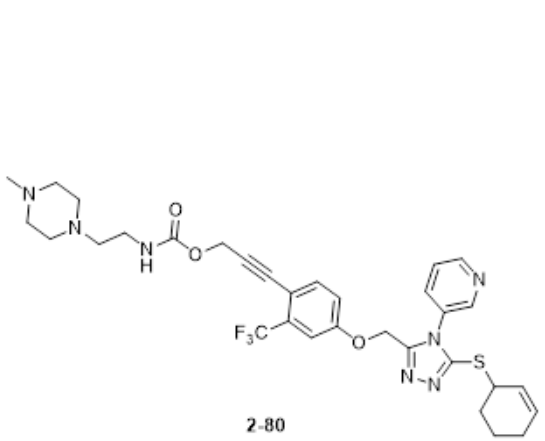


175.58
157.00
155.56
153.82
151.40
150.71
147.94
136.08
134.74
133.86
133.55
133.24
132.93
132.54
129.87
126.95
125.34
124.22
121.50
118.78
117.12
113.80
113.29
113.24
113.19
113.13
88.27
81.50
77.48
77.16
76.84
60.22
56.75
54.90
53.08
52.65
45.86
44.10
37.63
29.23
24.85
19.16

NAME	CNA-710-33
EXPNO	1
PROCNO	1
Date_	20160428
Time	12.19
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	685
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	64
DW	20.800 usec
DE	6.50 usec
TE	296.2 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379090 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

180 160 140 120 100 80 60 40 20 ppm

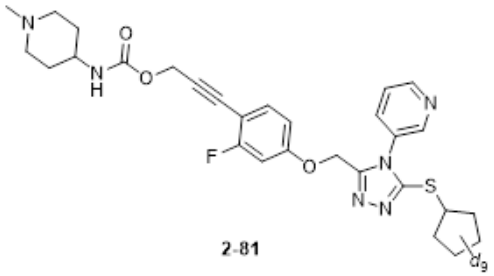
CNA-710-33, 19F, CDCl3, 400 MHz



NAME	CNA-710-33
EXPNO	3
PROCNO	1
Date_	20160428
Time	12.15
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	89285.711 Hz
FIDRES	0.681196 Hz
AQ	0.7340532 sec
RG	203
DW	5.600 usec
DE	6.50 usec
TE	95.4 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	376.4607164 MHz
NUC1	19F
P1	14.20 usec
SI	65536
SF	376.4983662 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

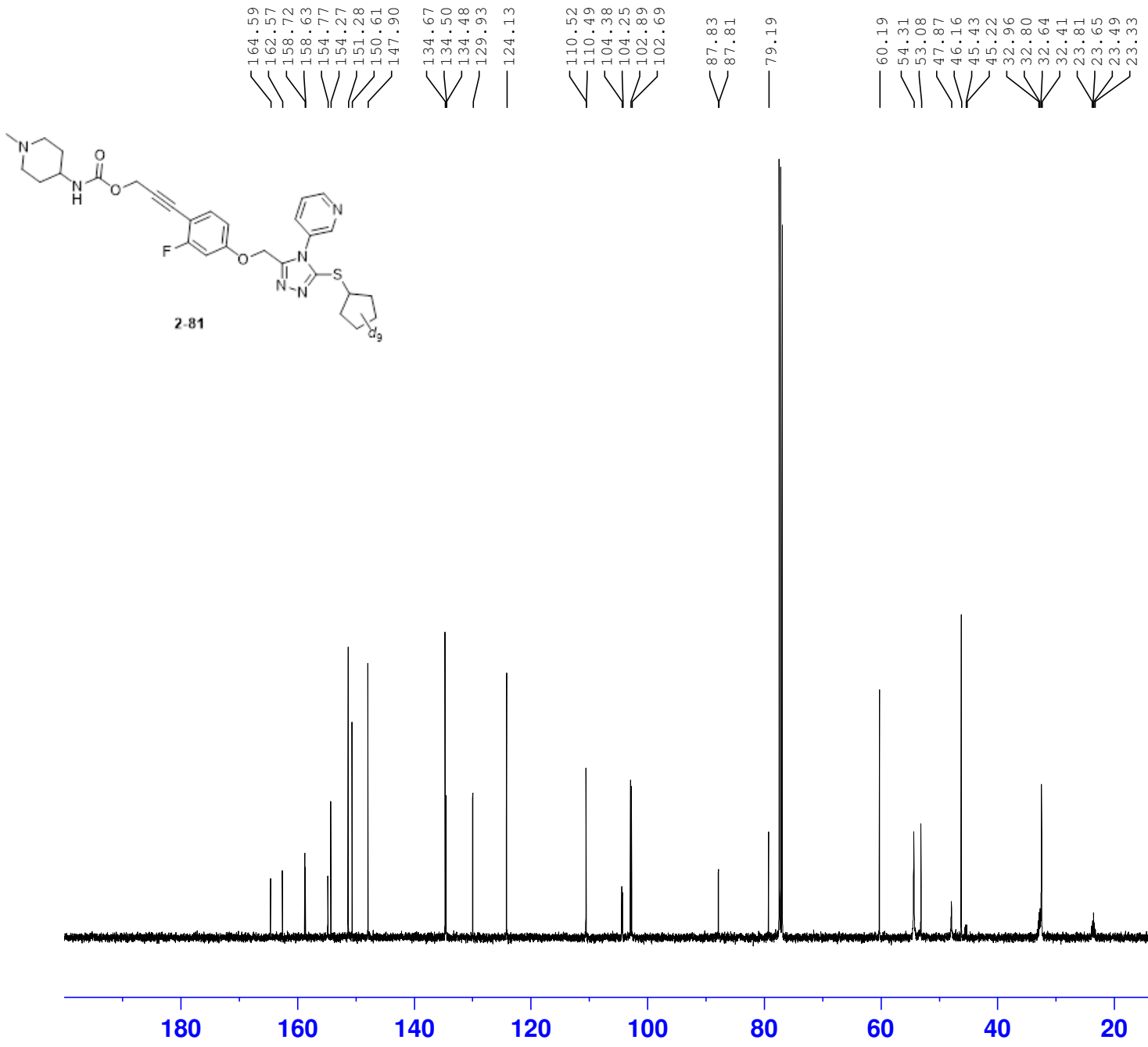
CNA-752-78, 1H, CDCl3, 500 MHz

8.739 8.593 8.589 7.676 7.673 7.659 7.657 7.482 7.473 7.466 7.456 7.289 7.286 7.273 7.257 6.632 6.628 6.615 6.610 6.602 6.581 6.577 5.055 5.034 4.866 3.502 3.495 3.488 2.740 2.720 2.236 2.075 2.053 2.031 1.934 1.913 1.504 1.497 1.475 1.456 1.435 1.428



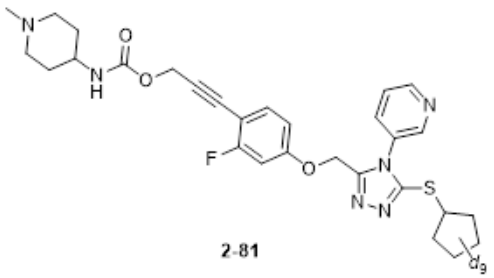

```
Current Data Parameters
NAME        CNA-752-78_g
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170202
Time               11.41
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES             0.152588 Hz
AQ             3.2767999 sec
RG                    32
DW                50.000 usec
DE                 6.50 usec
TE                297.1 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          500.1630887 MHz
NUC1                  1H
P1                 11.50 usec
PLW1          18.00000000 W

F2 - Processing parameters
SI                 65536
SF            500.1600000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-752-78, 13C, CDCl3, 500 MHz




```
Current Data Parameters
NAME       CNA-752-78_g
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20170202
Time              11.56
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG         zgpg30
TD                65536
SOLVENT           CDCl3
NS                  256
DS                    2
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ            1.1010048 sec
RG                  203
DW               16.800 usec
DE                6.50 usec
TE               298.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        125.7779086 MHz
NUC1                13C
P1                10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2        500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W
PLW13         0.23805000 W

F2 - Processing parameters
SI                32768
SF          125.7653320 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

CNA-752-78, 19F, CDCl3, 500 MHz

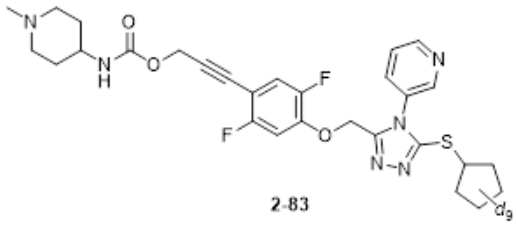



```
Current Data Parameters
NAME       CNA-752-78_g
EXPNO                 4
PROCNO                1

F2 - Acquisition Parameters
Date_          20170202
Time              11.58
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG      zgfhigqn.2
TD               131072
SOLVENT            CDCl3
NS                    16
DS                     4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                   203
DW                4.400 usec
DE                6.50 usec
TE                297.5 K
D1           1.00000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                19F
P1                 5.00 usec
PLW1        10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2        18.00000000 W
PLW12        0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

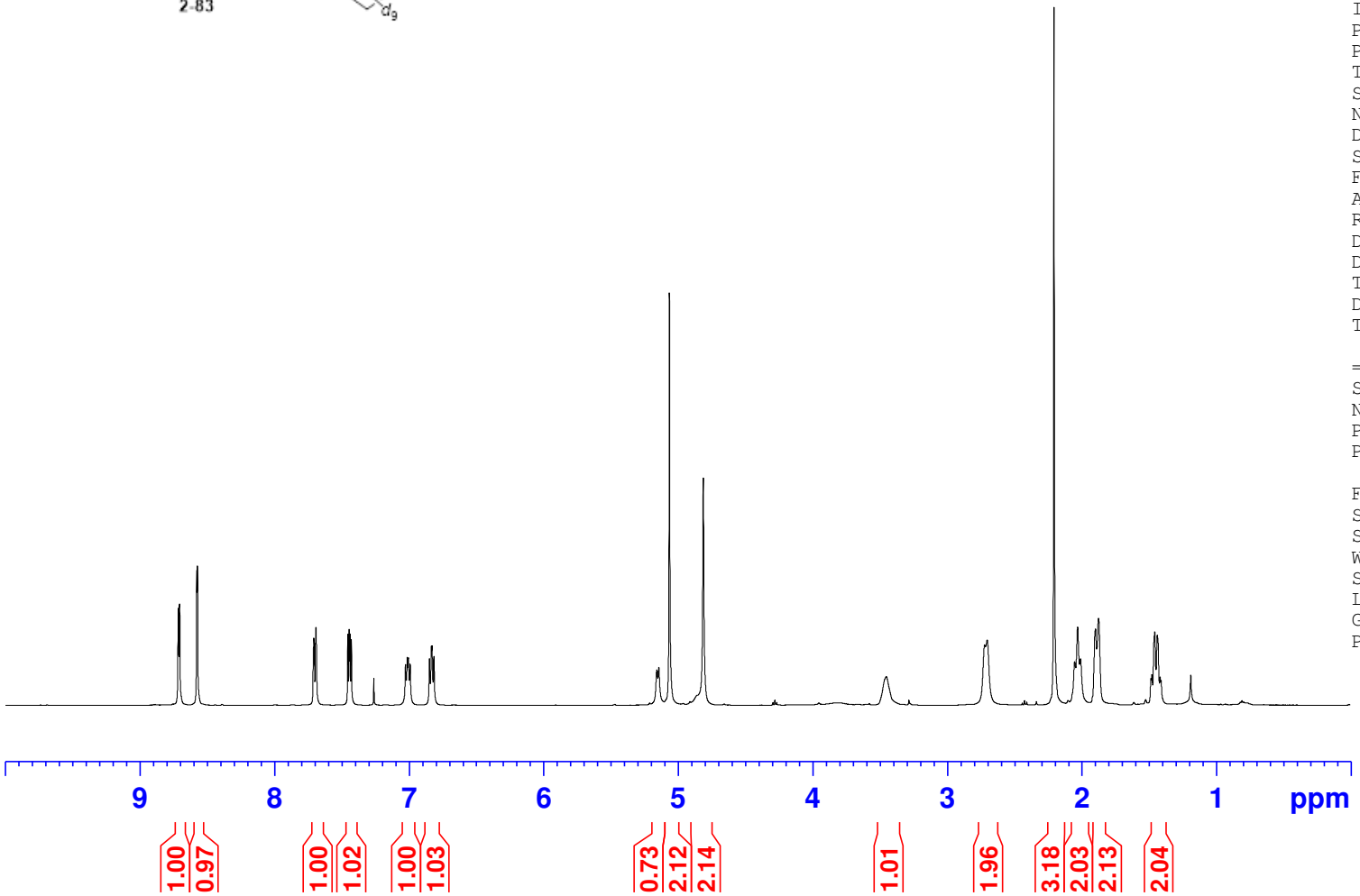
CNA-752-66, 1H, CDCl3, 500 MHz

8.713 8.705 8.576 8.572 7.707 7.690 7.453 7.444 7.437 7.428 7.260 7.024 7.011 7.003 6.990 6.847 6.832 6.828 6.813 5.157 5.142 5.063 4.811

3.450 2.720 2.701 2.204 2.050 2.029 2.007 1.896 1.874 1.484 1.477 1.456 1.436 1.415 1.408



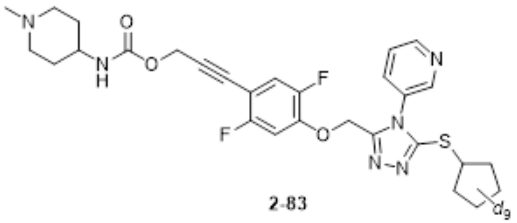
2-83




```
Current Data Parameters
NAME          CNA-752-66
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170118
Time               17.08
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES             0.152588 Hz
AQ             3.2767999 sec
RG                    32
DW                50.000 usec
DE                 6.50 usec
TE                297.0 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1630887 MHz
NUC1                   1H
P1                 11.50 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1600129 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-752-66, 13C, CDCl3, 500 MHz

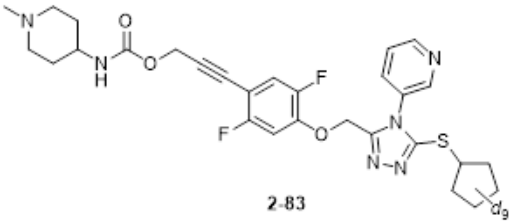
160.13
158.15
154.71
154.53
151.34
150.17
148.94
147.85
146.97
146.50
146.42
146.40
146.32
134.96
129.76
124.18
119.96
119.77
103.93
103.87
103.79
103.72
103.65
103.43
88.80
88.77
78.12
77.40
77.14
76.89
61.14
54.26
52.84
47.84
46.07
45.56
45.39
45.21
33.10
32.94
32.78
32.62
32.28
23.80
23.63
23.48
23.32
23.16

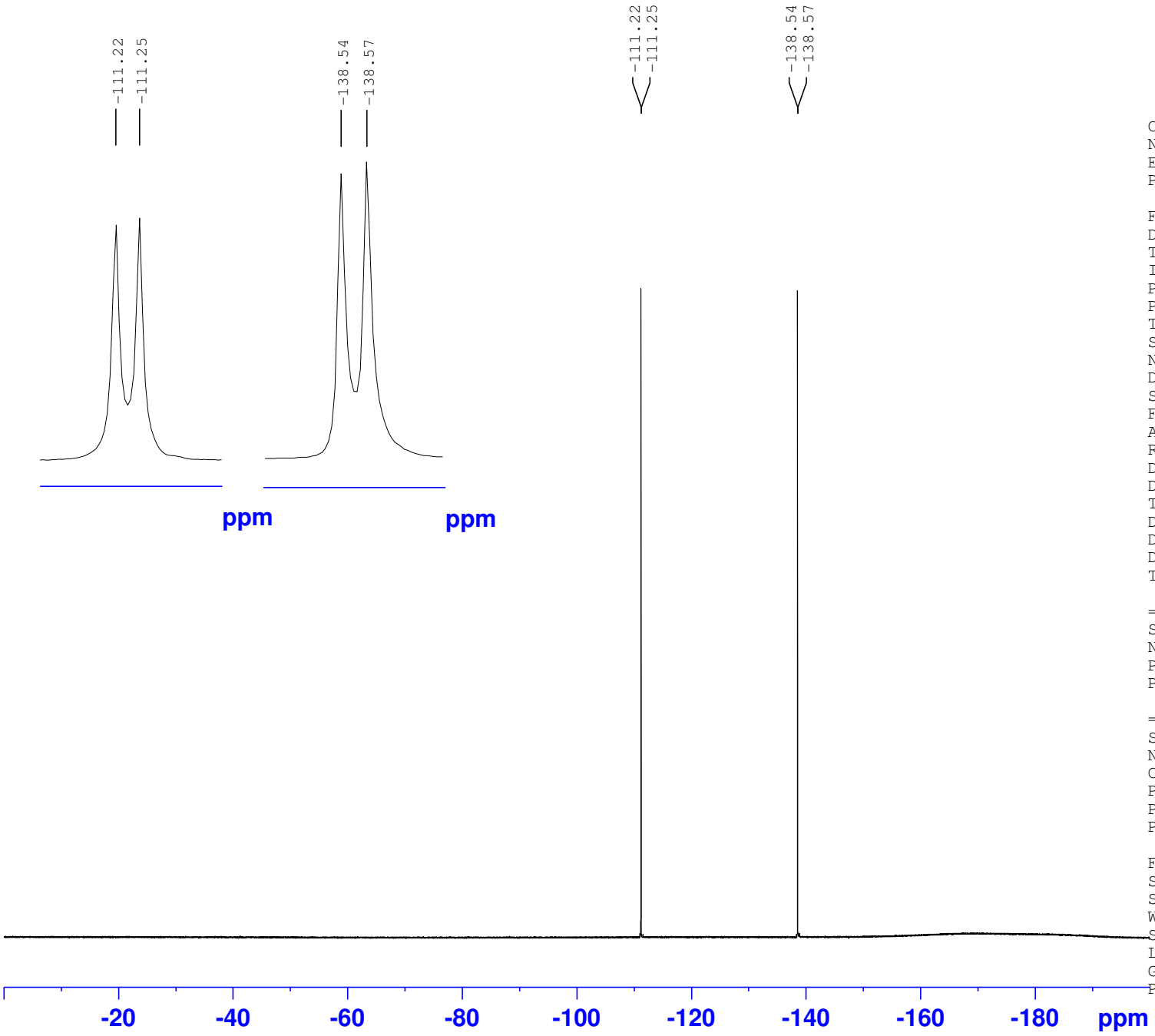


2-83


```
Current Data Parameters
NAME          CNA-752-66
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170118
Time               17.41
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  256
DS                    2
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ            1.1010048 sec
RG                  203
DW               16.800 usec
DE                6.50 usec
TE               298.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        125.7779086 MHz
NUC1                13C
P1                10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2        500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W
PLW13         0.23805000 W

F2 - Processing parameters
SI                 32768
SF          125.7653320 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

CNA-752-66, 19F, CDCl3, 500 MHz

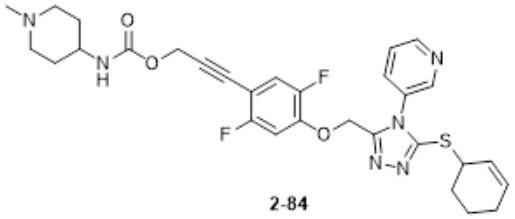





```
Current Data Parameters
NAME          CNA-752-66
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170118
Time               17.25
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG       zgfhigqn.2
TD                131072
SOLVENT             CDCl3
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                297.3 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                  19F
P1                 5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-752-60, 1H, CDCl3, 400 MHz

8.728 8.725 8.716 8.713 8.589 8.583 7.719 7.717 7.703 7.699 7.697 7.693 7.467 7.455 7.447 7.435 6.843 6.836 5.818 5.815 5.079 4.826 4.521 2.715 2.222 2.053 2.045 2.034 2.023 2.021 2.009 1.996 1.991 1.982 1.978 1.973 1.969 1.960 1.922 1.887 1.644 1.634 1.476 1.453



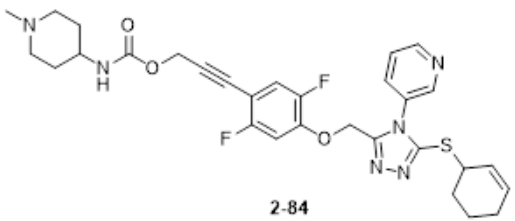
2-84

NAME	CNA-752-60
EXPNO	2
PROCNO	1
Date_	20170117
Time	16.27
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	40.3
DW	60.800 usec
DE	6.50 usec
TE	296.2 K
D1	2.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300125 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-752-60, 13C, CDCl3, 400 MHz

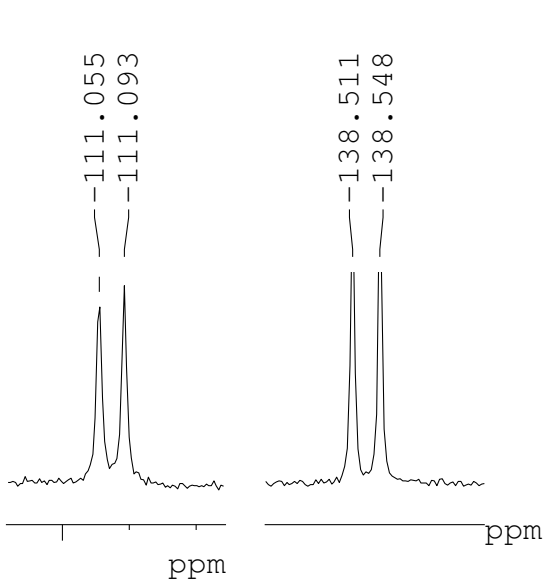


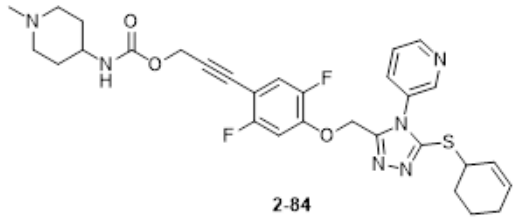
160.41
157.92
154.72
154.00
151.37
150.33
149.19
149.15
147.87
146.76
146.73
146.50
146.40
146.37
146.28
135.01
132.48
129.67
125.28
124.20
120.02
119.81
103.98
103.90
103.80
103.72
103.66
103.39
88.80
88.77
78.15
78.13
77.45
77.34
77.13
76.81
61.12
54.26
52.88
47.81
46.06
44.04
32.26
29.17
24.79
19.09

180 160 140 120 100 80 60 40 20 ppm

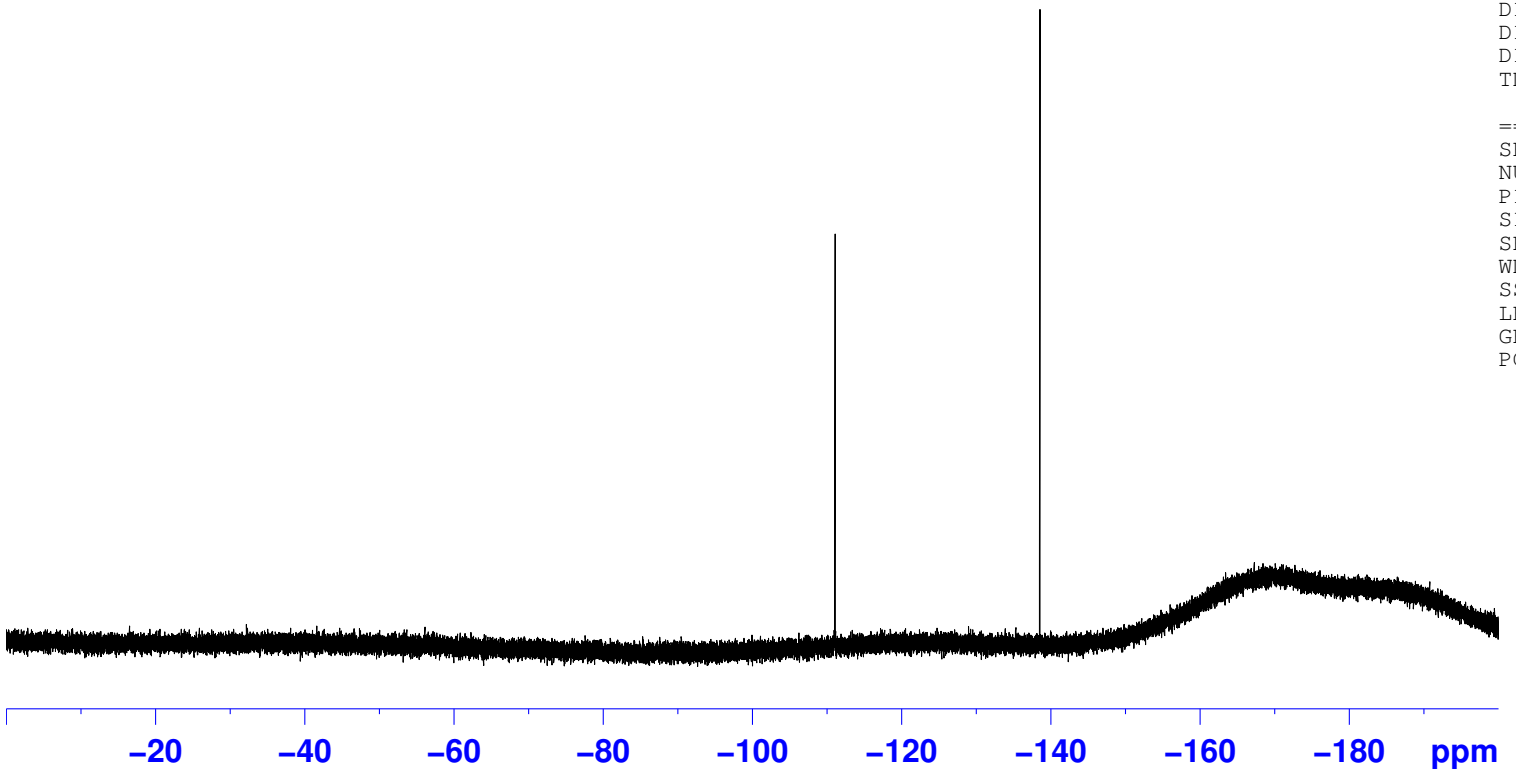
NAME	CNA-752-60
EXPNO	3
PROCNO	1
Date_	20170117
Time	17.06
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	295.7 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-752-60, 19F, CDCl3, 400 MHz



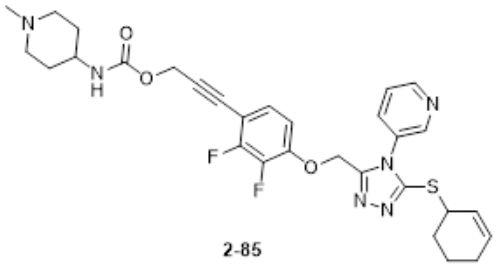


NAME	CNA-752-60
EXPNO	4
PROCNO	1
Date_	20170118
Time	17.05
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	89285.711 Hz
FIDRES	0.681196 Hz
AQ	0.7340532 sec
RG	203
DW	5.600 usec
DE	6.50 usec
TE	88.3 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	376.4607164 MHz
NUC1	19F
P1	14.20 usec
SI	65536
SF	376.4983662 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



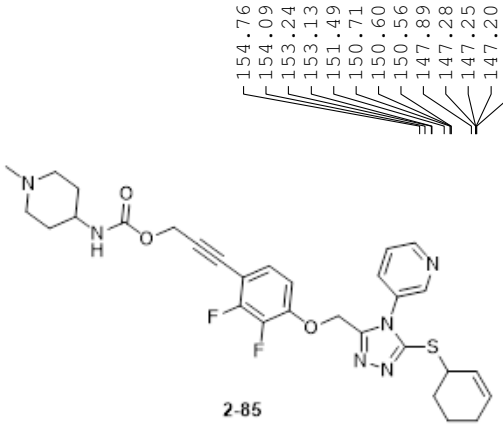
CNA-752-59, 1H, CDCl3, 300 MHz

8.775 8.771 8.759 8.755 8.617 8.609 7.742 7.722 7.717 7.715 7.511 7.495 7.484 7.260 7.093 6.849 5.857 5.853 5.141 4.884 4.571 4.564 2.779 2.740 2.265 2.128 2.094 2.080 2.063 2.047 2.028 2.023 2.011 1.998 1.985 1.974 1.964 1.929 1.692 1.678 1.519 1.508 1.477



NAME	CNA-752-59	
EXPNO	4	
PROCNO	1	
Date_	20170117	
Time	21.19	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg30	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	2	
SWH	6188.119	Hz
FIDRES	0.188846	Hz
AQ	2.6477044	sec
RG	114	
DW	80.800	usec
DE	6.50	usec
TE	-928.6	K
D1	1.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
SFO1	300.2318540	MHz
NUC1	1H	
P1	12.71	usec
SI	32768	
SF	300.2300090	MHz
WDW	EM	
SSB	0	
LB	0.10	Hz
GB	0	
PC	1.00	

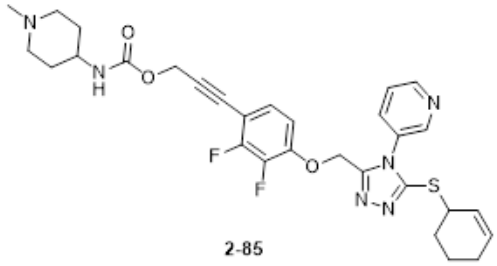
CNA-752-59, 13C, CDCl3, 400 MHz

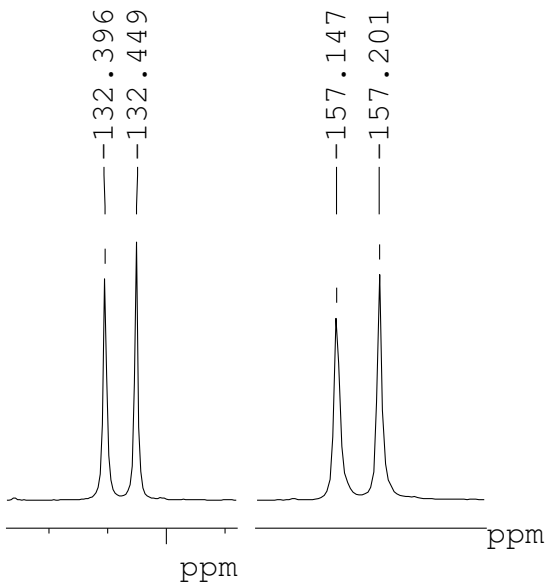


2-85

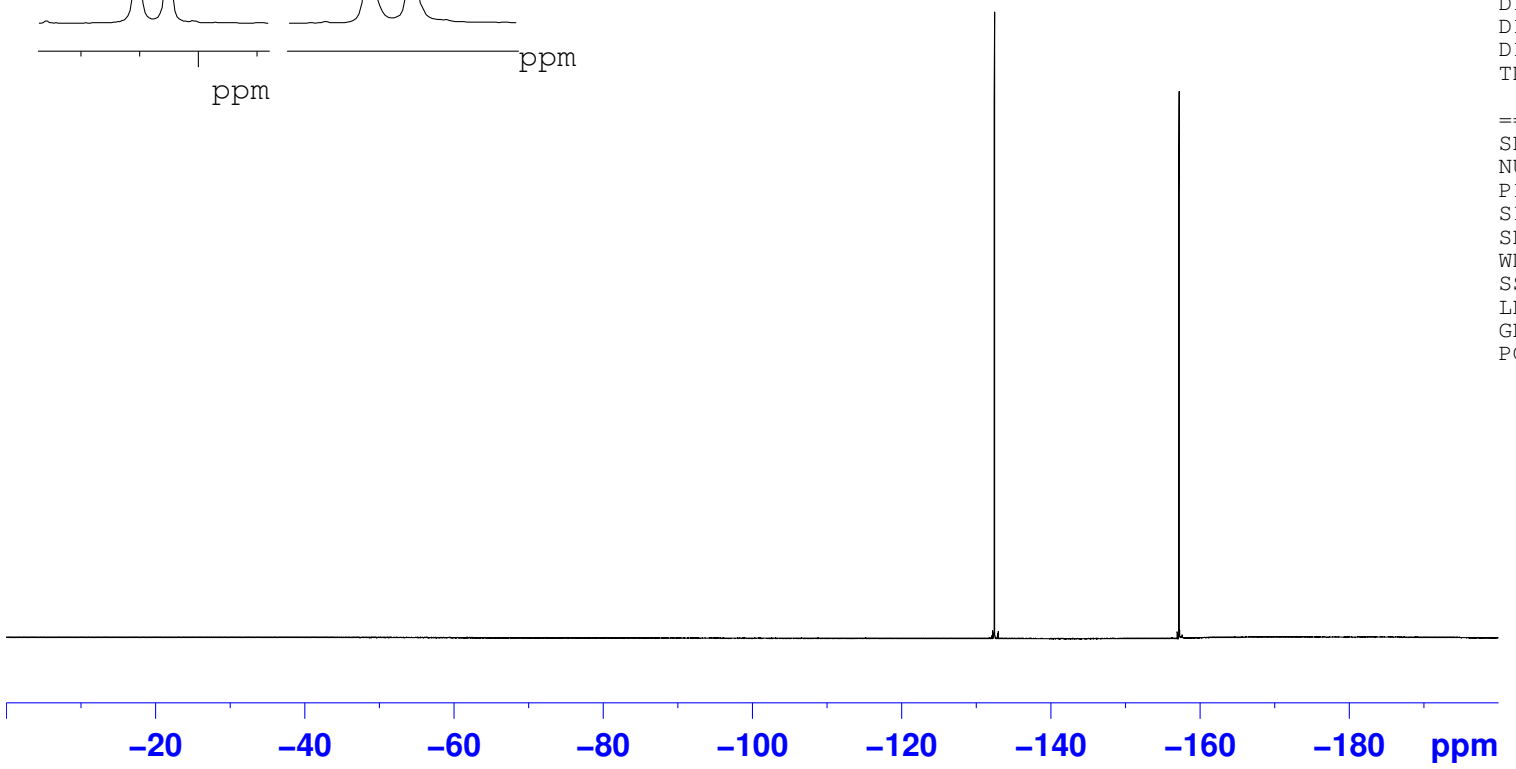
NAME	CNA-752-59
EXPNO	2
PROCNO	1
Date_	20170116
Time	16.38
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	294.9 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379076 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-752-59, 19F, CDCl3, 400 MHz



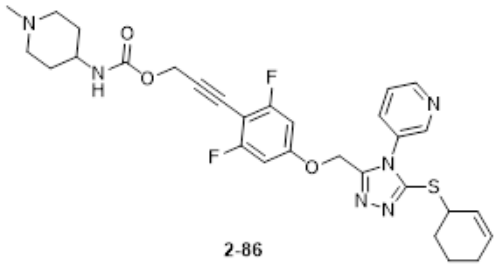


NAME	CNA-752-59
EXPNO	3
PROCNO	1
Date_	20170116
Time	16.57
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	89285.711 Hz
FIDRES	0.681196 Hz
AQ	0.7340532 sec
RG	203
DW	5.600 usec
DE	6.50 usec
TE	90.1 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	376.4607164 MHz
NUC1	19F
P1	14.20 usec
SI	65536
SF	376.4983662 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



CNA-752-61, 1H, CDCl3, 400 MHz

8.761 8.758 8.749 8.746 8.585 8.579 7.668 7.666 7.652 7.648 7.646 7.642 7.497 7.495 7.484 7.483 7.476 7.475 7.464 7.463 7.260 6.473 6.452 5.039 4.884 2.241 2.073 2.063 2.052 2.038 2.027 2.022 2.019 2.010 2.005 2.000 1.996 1.988 1.944 1.909 1.903 1.674 1.659 1.483

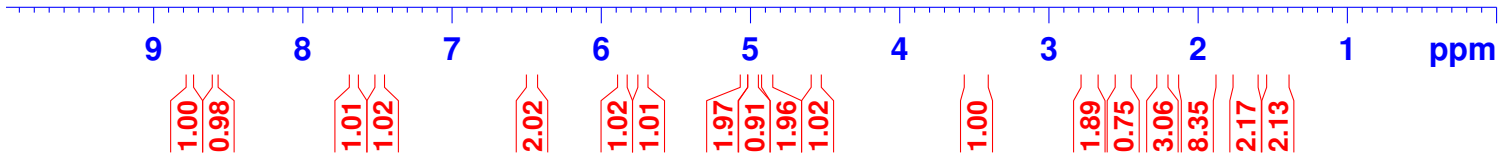


2-86

NAME	CNA-752-61
EXPNO	1
PROCNO	1
Date_	20170117
Time	18.00
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	57
DW	60.800 usec
DE	6.50 usec
TE	295.2 K
D1	2.00000000 sec
TD0	1

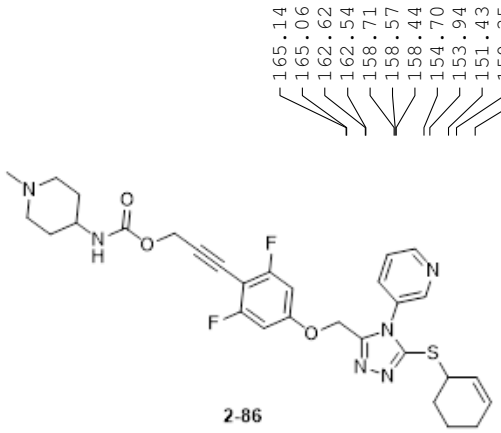
======== CHANNEL f1 ========

NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300124 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



1.00 0.98 1.01 1.02 2.02 1.02 1.01 1.97 0.91 1.96 1.02 1.00 1.89 0.75 3.06 8.35 2.17 2.13

CNA-752-61, 13C, CDCl3, 400 MHz

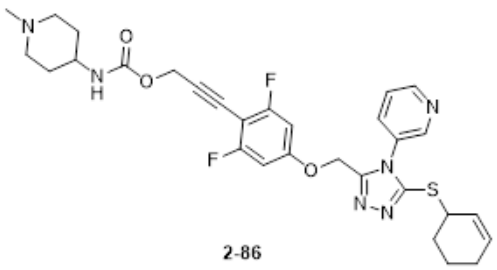


165.14
165.06
162.62
162.54
158.71
158.57
158.44
154.70
153.94
151.43
150.35
147.88
134.68
132.54
129.74
125.26
124.22
99.01
98.73
95.27
95.07
94.87
92.45
77.41
77.09
76.77
72.92
60.37
54.28
53.08
47.81
46.12
44.06
32.33
29.19
24.81
19.11

180 160 140 120 100 80 60 40 20 ppm

NAME	CNA-752-61
EXPNO	2
PROCNO	1
Date_	20170117
Time	19.18
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1024
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	295.2 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

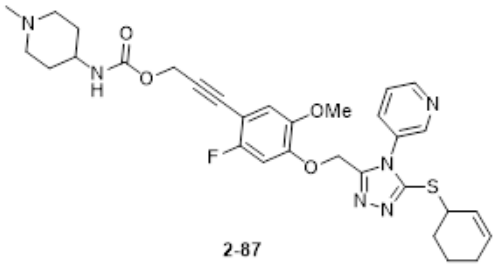
CNA-752-61, 1H, CDCl3, 400 MHz



NAME	CNA-752-61
EXPNO	3
PROCNO	1
Date_	20170117
Time	19.35
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	89285.711 Hz
FIDRES	0.681196 Hz
AQ	0.7340532 sec
RG	203
DW	5.600 usec
DE	6.50 usec
TE	90.0 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	376.4607164 MHz
NUC1	19F
P1	14.20 usec
SI	65536
SF	376.4983662 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-752-63, 1H, CDCl3, 400 MHz

8.718 8.714 8.706 8.702 8.617 8.611 7.740 7.738 7.724 7.720 7.718 7.428 7.416 7.408 7.396 7.260 6.800 6.784 6.707 6.682 5.824 5.057 4.867 3.695 2.739 2.709 2.237 2.069 2.057 2.047 2.044 2.002 1.997 1.993 1.988 1.984 1.970 1.943 1.934 1.909 1.903 1.495 1.487 1.464



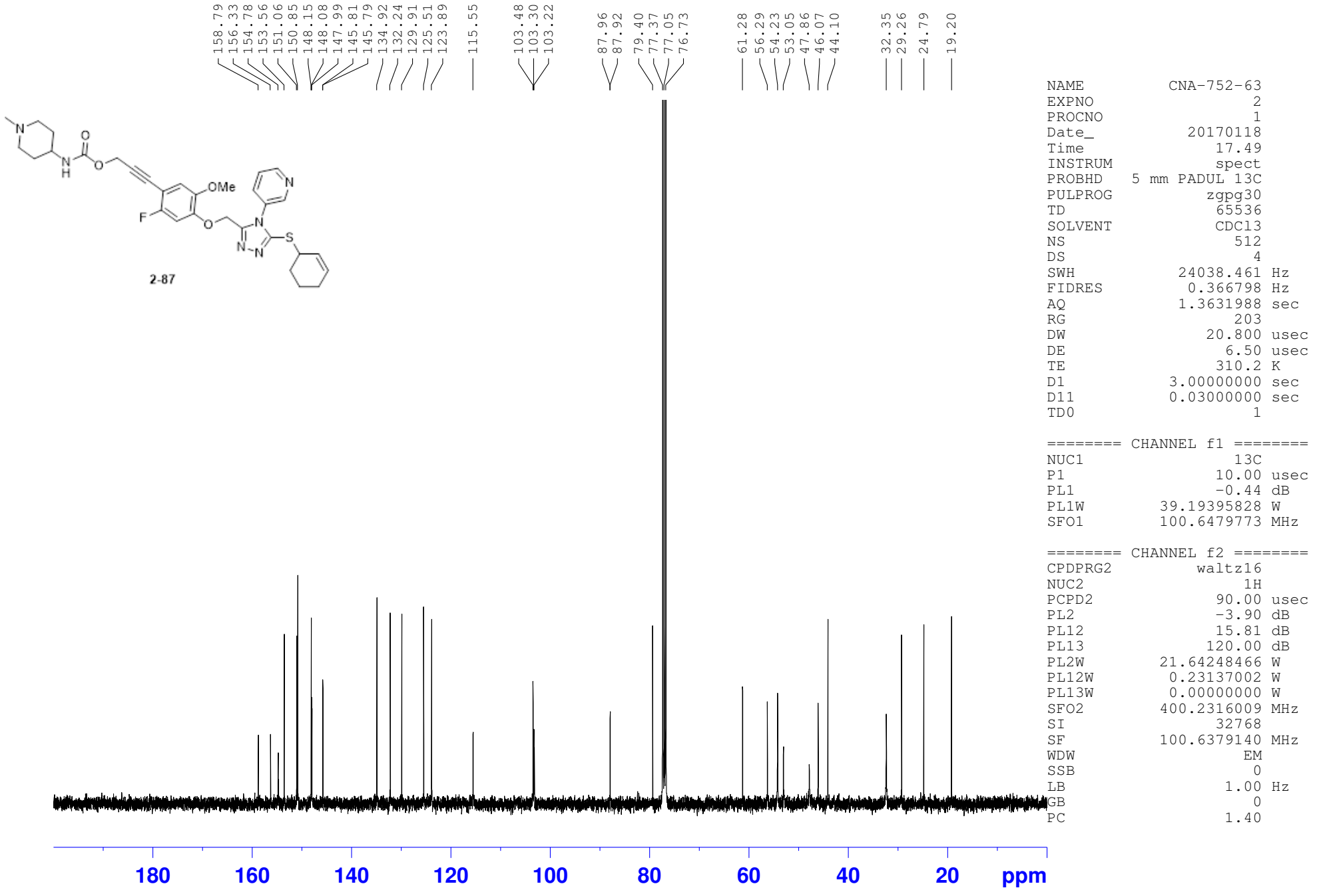
2-87

NAME	CNA-752-63
EXPNO	1
PROCNO	1
Date_	20170118
Time	17.09
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	57
DW	60.800 usec
DE	6.50 usec
TE	310.1 K
D1	2.00000000 sec
TD0	1

======== CHANNEL f1 ========

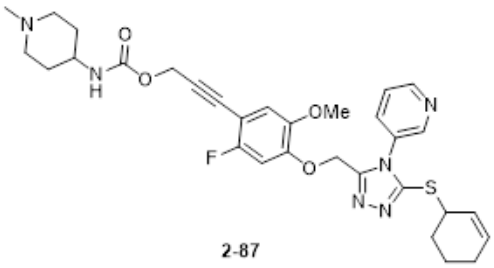
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300119 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-752-63, 13C, CDCl3, 400 MHz



NAME	CNA-752-63
EXPNO	2
PROCNO	1
Date_	20170118
Time	17.49
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	310.2 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-752-63, 19F, CDCl3, 400 MHz

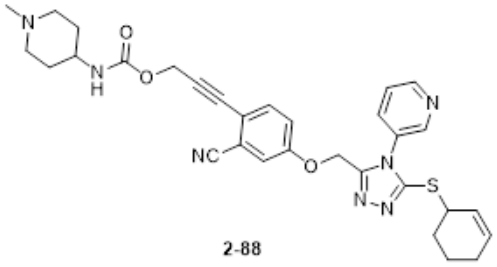


2-87

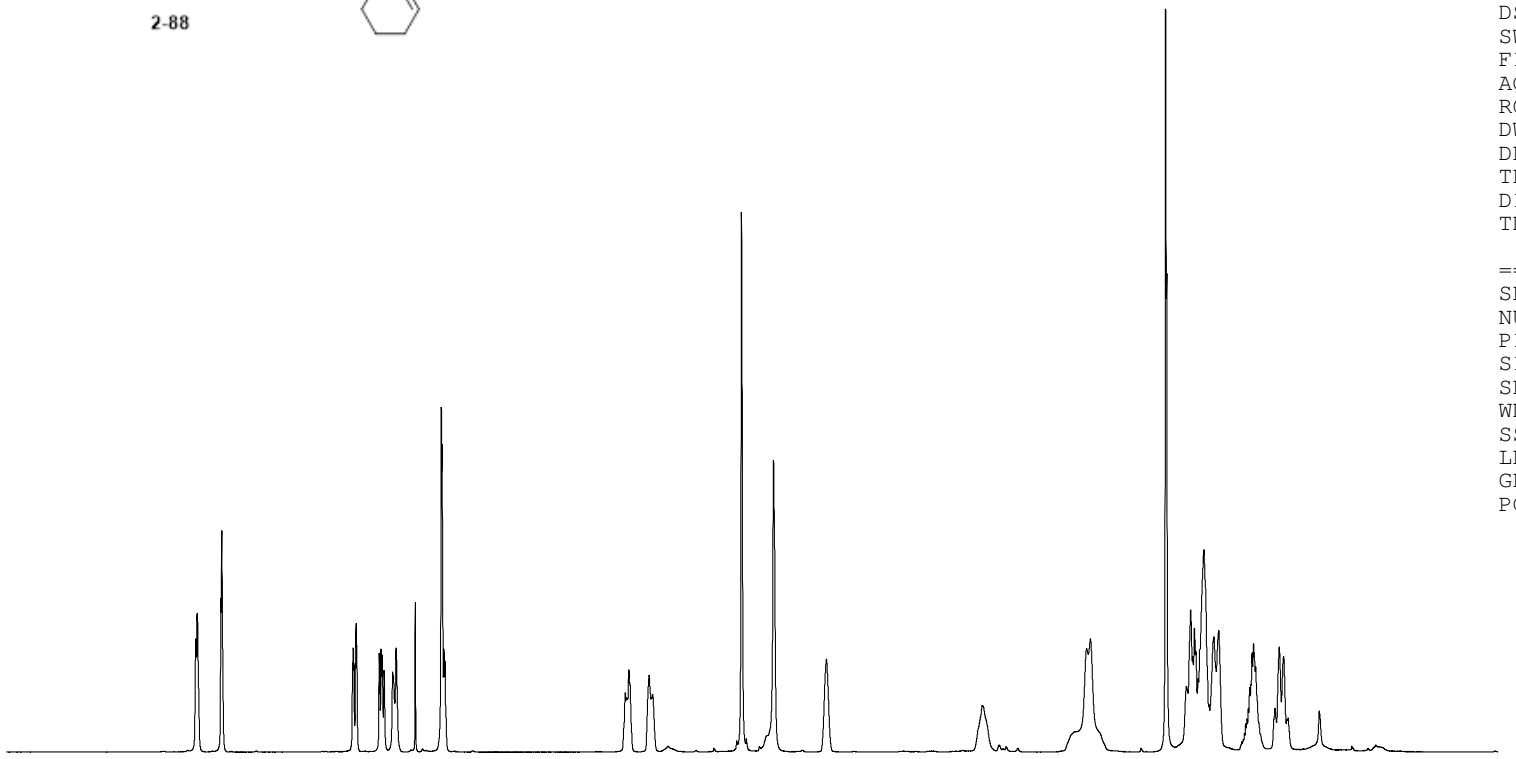
NAME	CNA-752-63
EXPNO	3
PROCNO	1
Date_	20170118
Time	18.00
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	89285.711 Hz
FIDRES	0.681196 Hz
AQ	0.7340532 sec
RG	203
DW	5.600 usec
DE	6.50 usec
TE	88.2 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	376.4607164 MHz
NUC1	19F
P1	14.20 usec
SI	65536
SF	376.4983662 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

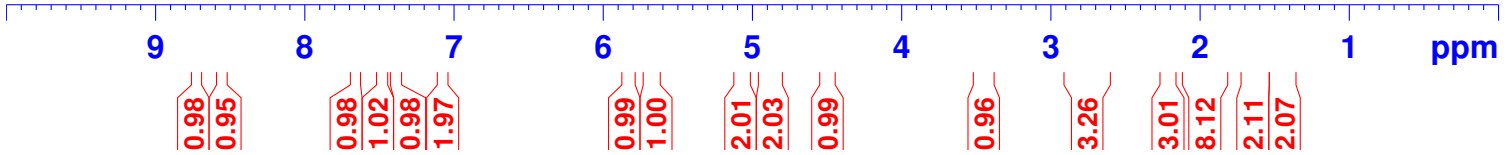
CNA-752-62, 1H, CDCl3/MeOD, 400 MHz

8.732 8.723 8.721 8.563 8.557 7.678 7.676 7.673 7.662 7.658 7.656 7.653 7.502 7.490 7.483 7.470 7.413 7.389 7.260 7.086 7.081 7.069 7.062 5.828 5.074 4.859 4.504 2.760 2.734 2.231 2.224 2.063 2.049 2.037 2.028 2.001 1.974 1.907 1.875 1.651 1.642 1.627 1.468 1.439



2-88

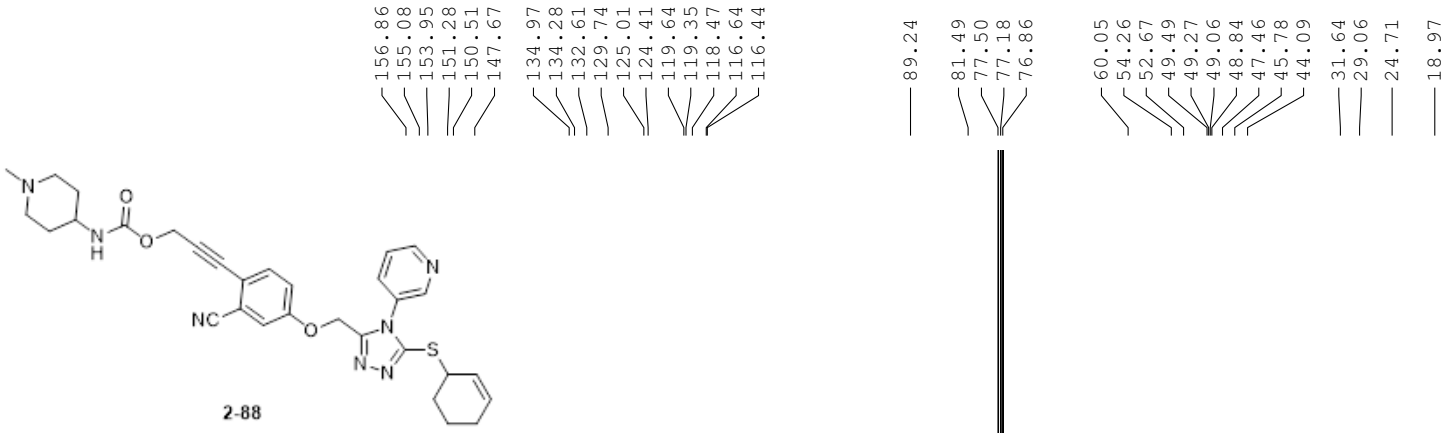




0.98 0.95 0.98 1.02 0.98 1.97 0.99 1.00 2.01 2.03 0.99 0.96 3.26 3.01 8.12 2.11 2.07

NAME	CNA-752-62
EXPNO	3
PROCNO	1
Date_	20170117
Time	19.24
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8012.820 Hz
FIDRES	0.122266 Hz
AQ	4.0894966 sec
RG	57
DW	62.400 usec
DE	6.50 usec
TE	90.4 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	400.1324710 MHz
NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300092 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

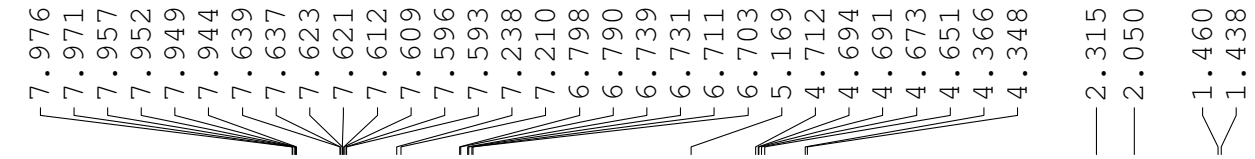
CNA-752-62, 13C, CDCl3/MeOD, 400 MHz

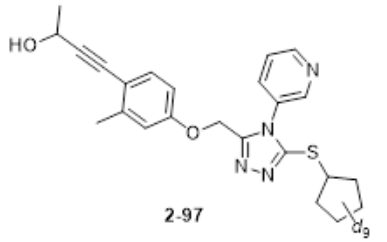


156.86
155.08
153.95
151.28
150.51
147.67
134.97
134.28
132.61
129.74
125.01
124.41
119.64
119.35
118.47
116.64
116.44
89.24
81.49
77.50
77.18
76.86
60.05
54.26
52.67
49.49
49.27
49.06
48.84
47.46
45.78
44.09
31.64
29.06
24.71
18.97

NAME	CNA-752-62
EXPNO	2
PROCNO	1
Date_	20170117
Time	17.51
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	401
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	295.4 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-695-38, 1H, acetone-d6, 300 MHz

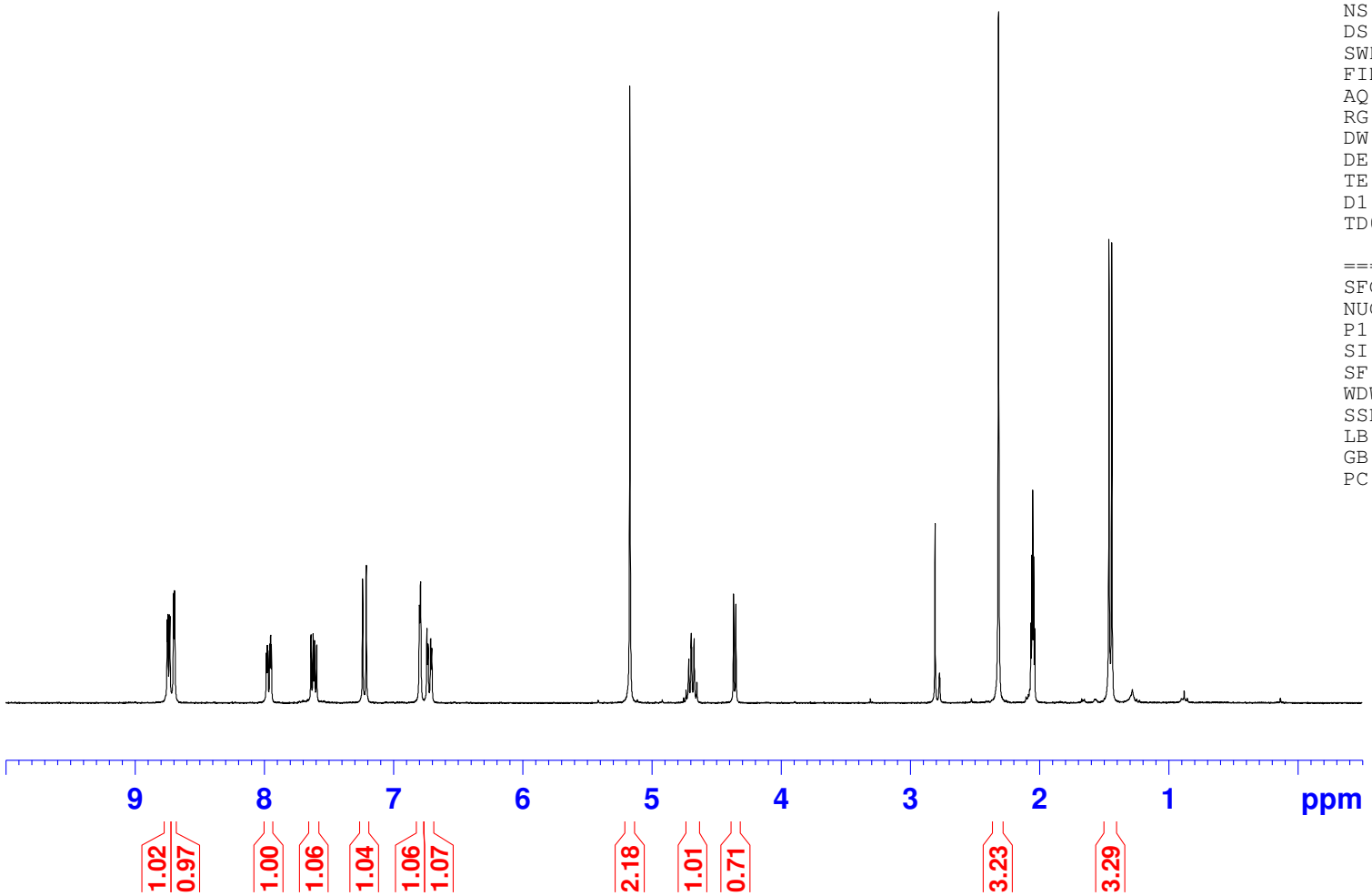




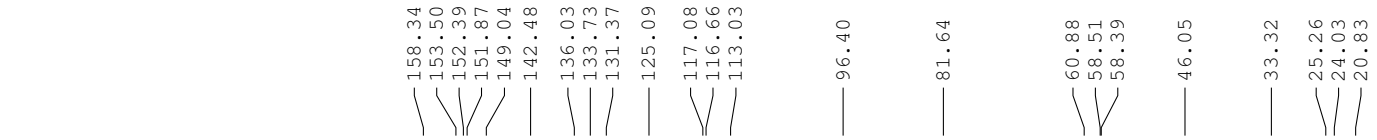
NAME	CNA-695-38
EXPNO	1
PROCNO	1
Date_	20160204
Time	10.39
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	32768
SOLVENT	Acetone
NS	16
DS	2
SWH	6188.119 Hz
FIDRES	0.188846 Hz
AQ	2.6477044 sec
RG	322
DW	80.800 usec
DE	6.50 usec
TE	-927.9 K
D1	1.00000000 sec
TD0	1

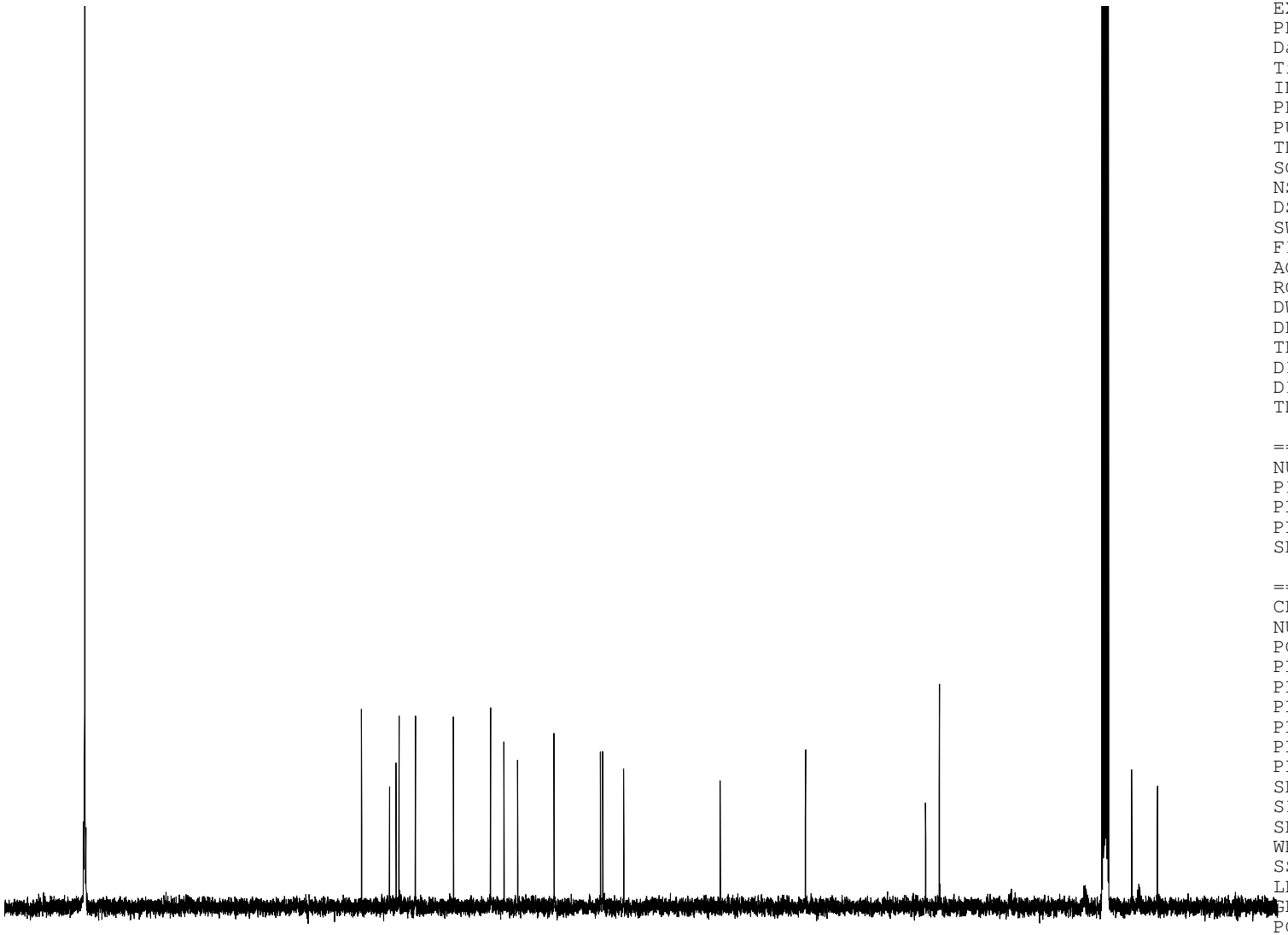
======== CHANNEL f1 ========

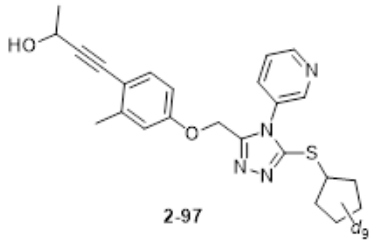
SFO1	300.2318540 MHz
NUC1	1H
P1	12.71 usec
SI	32768
SF	300.2300065 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00



CNA-695-38, 13C, acetone-d6, 400 MHz

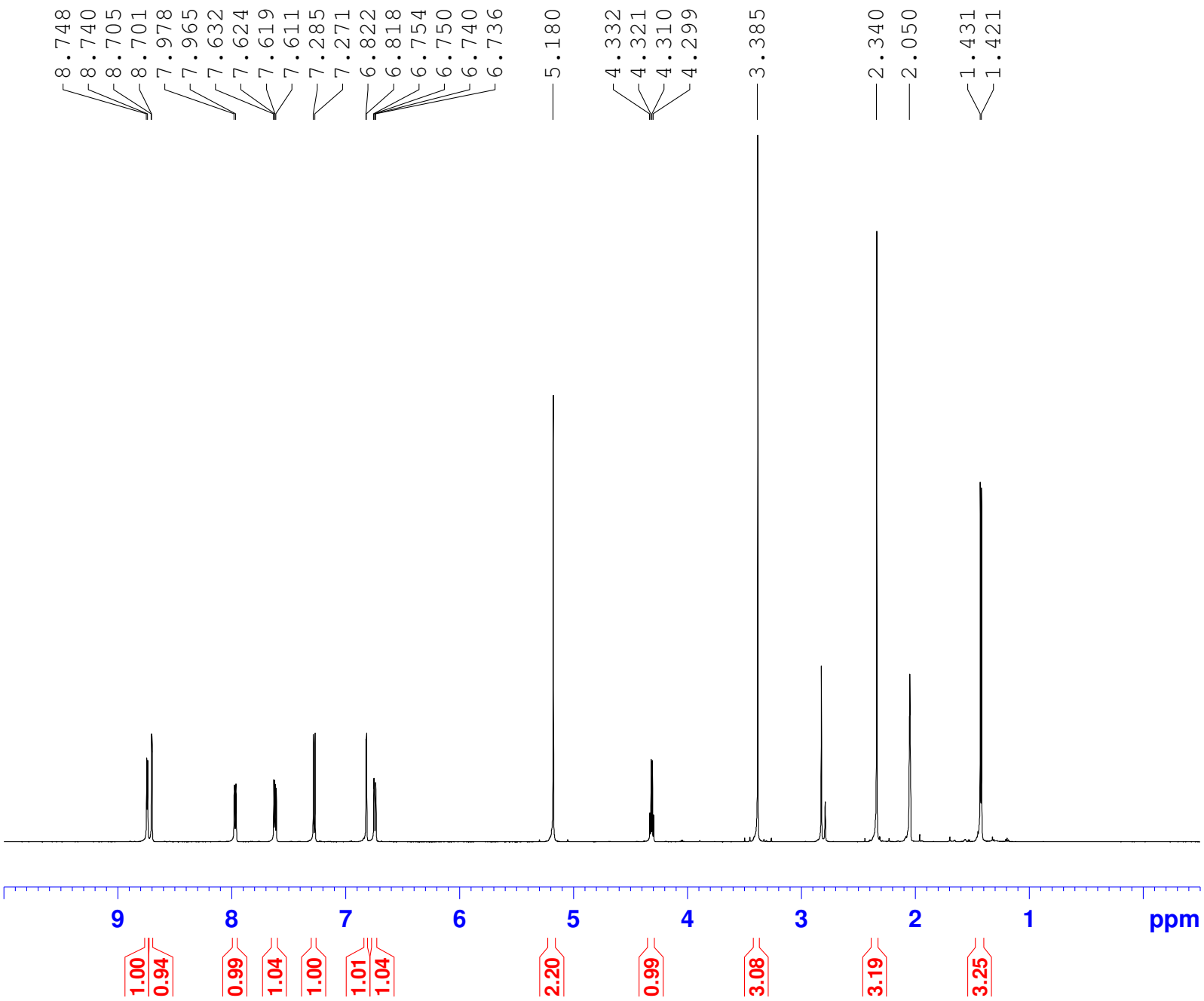


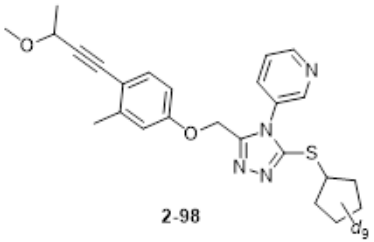




NAME	CNA-695-38
EXPNO	2
PROCNO	1
Date_	20160203
Time	23.30
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	Acetone
NS	350
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	50.8
DW	20.800 usec
DE	6.50 usec
TE	295.9 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6378272 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-695-42, 1H, acetone-d6, 600 MHz

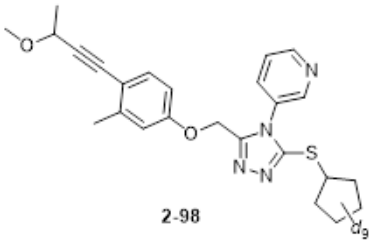


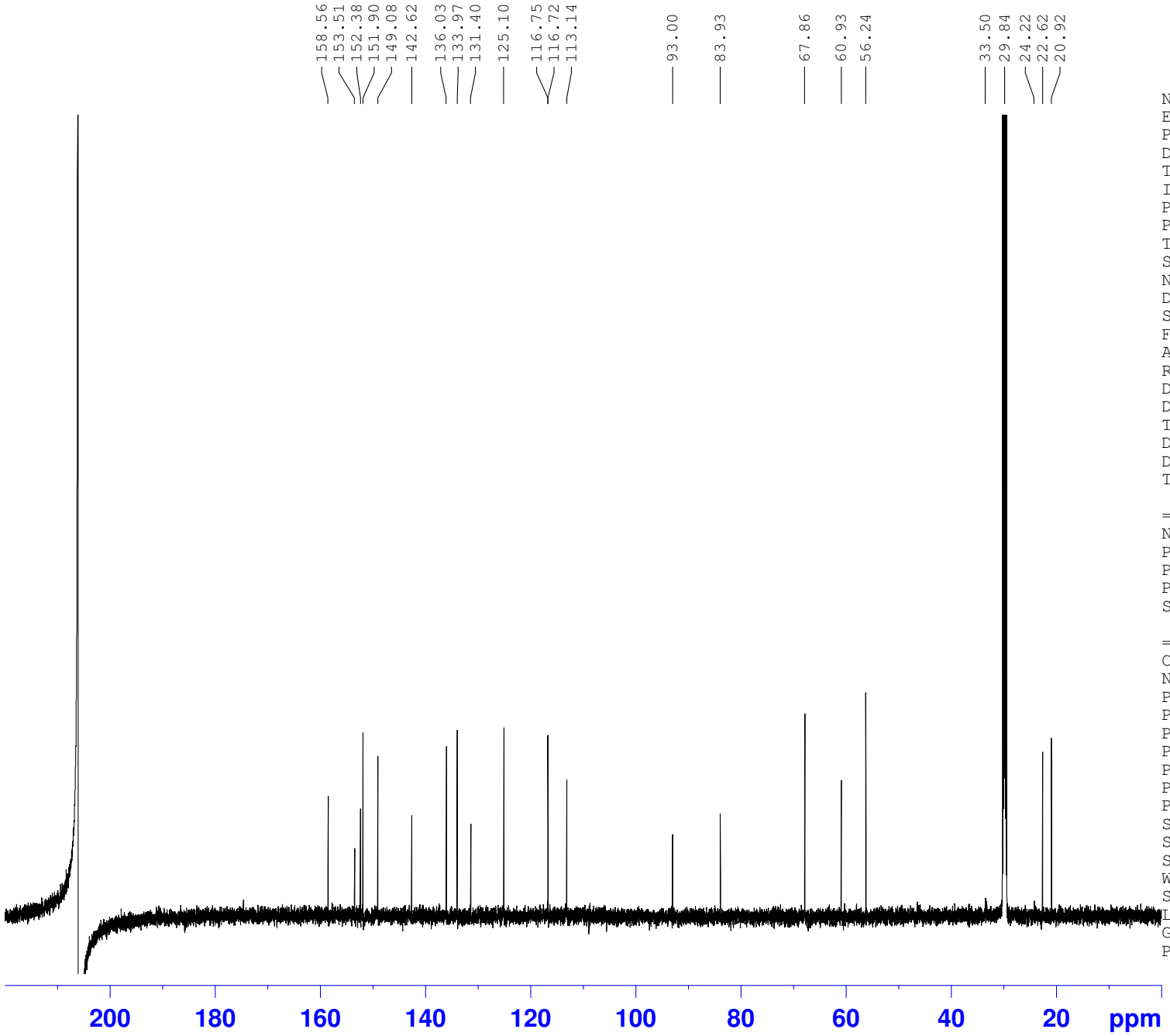


NAME	CNA-695-42
EXPNO	1
PROCNO	1
Date_	20160204
Time	10.30
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	16
DS	2
SWH	12335.526 Hz
FIDRES	0.188225 Hz
AQ	2.6564426 sec
RG	144
DW	40.533 usec
DE	6.50 usec
TE	296.0 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========	
NUC1	1H
P1	10.86 usec
PL1	-2.00 dB
PL1W	19.70630455 W
SFO1	600.7137096 MHz
SI	32768
SF	600.7100094 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

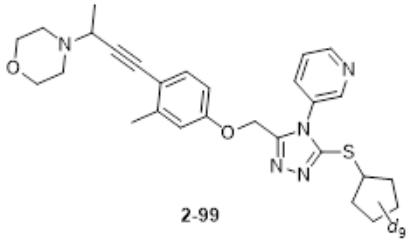
CNA-695-42, 13C, acetone-d6, 600 MHz



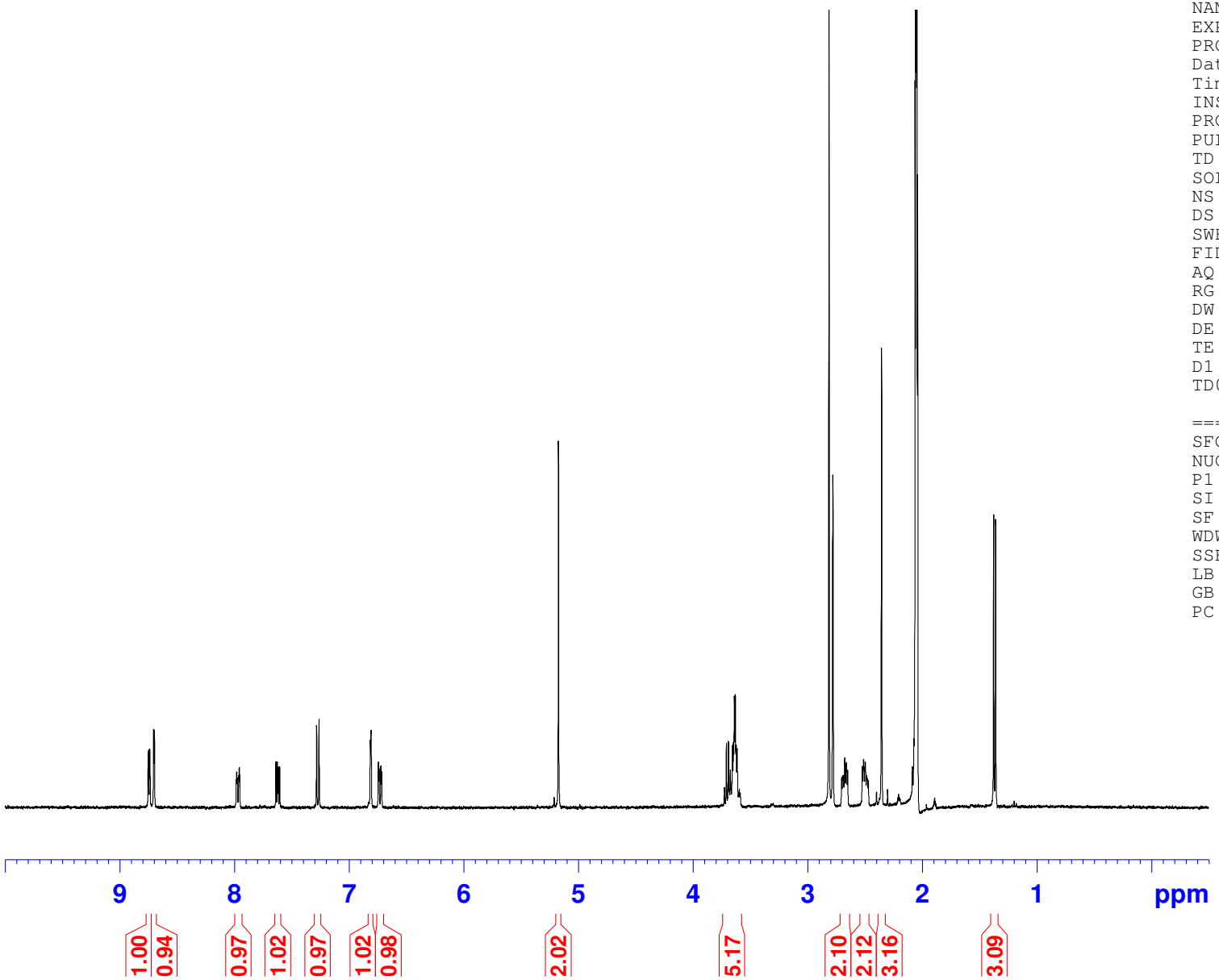


NAME	CNA-695-42
EXPNO	2
PROCNO	1
Date_	20160204
Time	10.46
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	Acetone
NS	1024
DS	4
SWH	36057.691 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	203
DW	13.867 usec
DE	6.50 usec
TE	296.3 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	11.50 usec
PL1	0.00 dB
PL1W	97.46119690 W
SFO1	151.0637542 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	70.00 usec
PL2	-2.00 dB
PL12	14.19 dB
PL13	120.00 dB
PL2W	19.70630455 W
PL12W	0.47381112 W
PL13W	0.00000000 W
SFO2	600.7124028 MHz
SI	32768
SF	151.0485148 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-695-43, 1H, acetone-d6, 400 MHz

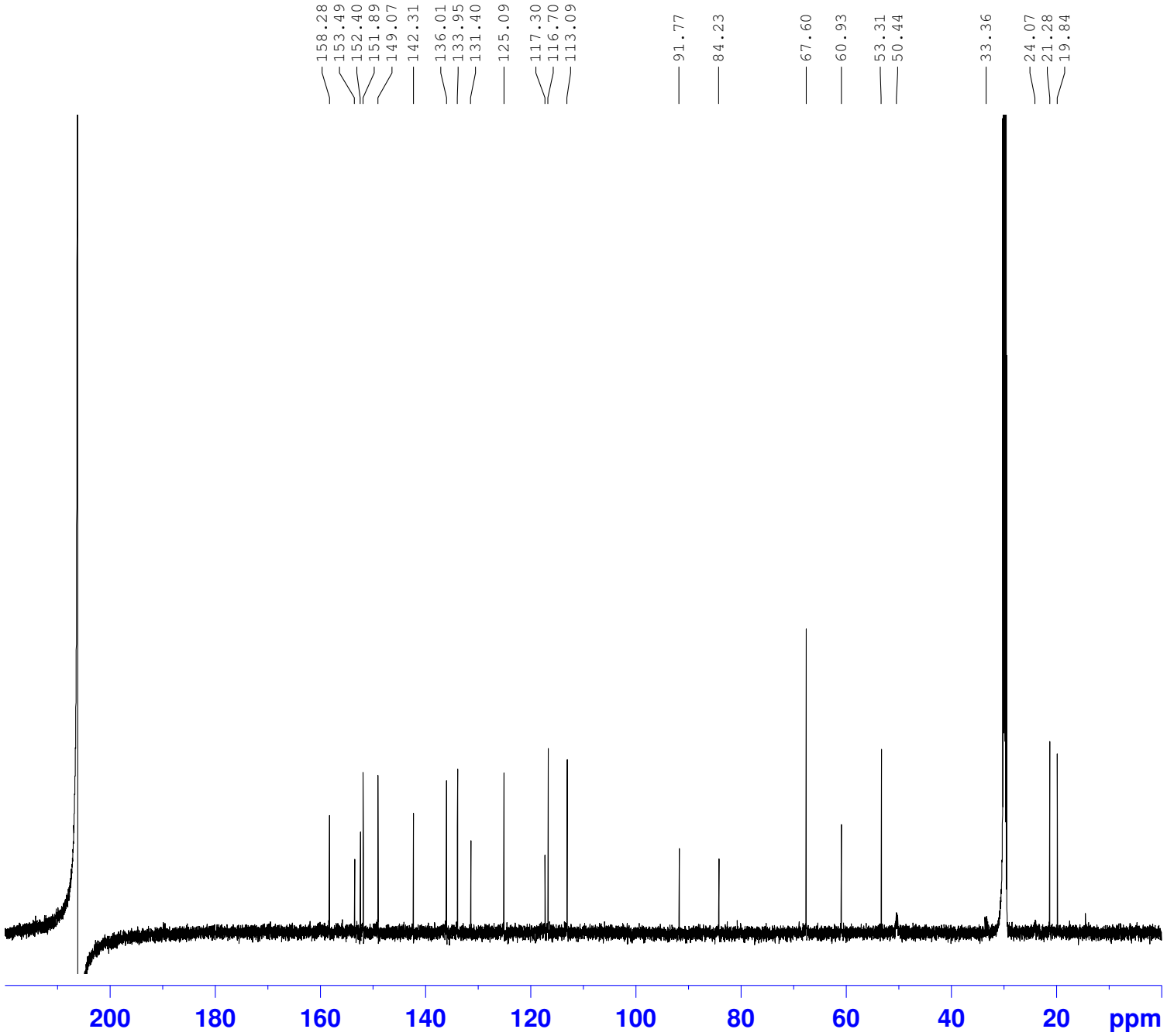


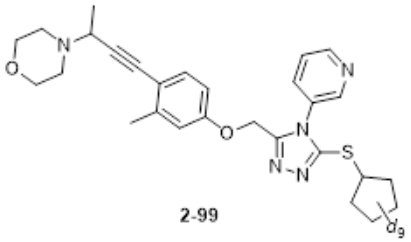
8.752 8.749 8.740 8.737 8.705 8.699 7.980 7.958 7.954 7.638 7.625 7.617 7.605 7.283 7.262 6.814 6.808 6.744 6.737 6.723 6.716 5.173 3.707 3.690 3.673 3.654 3.646 3.638 3.630 3.622 3.614 2.693 2.686 2.675 2.660 2.650 2.521 2.511 2.496 2.483 2.354 2.050 1.376 1.358



NAME	CNA-695-43
EXPNO	5
PROCNO	1
Date_	20160204
Time	13.56
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	32
DS	2
SWH	8012.820 Hz
FIDRES	0.122266 Hz
AQ	4.0894966 sec
RG	181
DW	62.400 usec
DE	6.50 usec
TE	297.1 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	400.1324710 MHz
NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300070 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-695-43, 13C, acetone-d6, 600 MHz

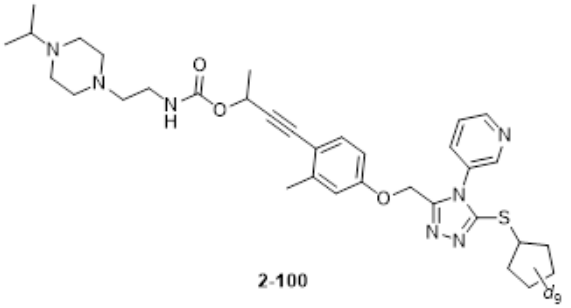




NAME	CNA-695-43	
EXPNO	3	
PROCNO	1	
Date_	20160204	
Time	12.26	
INSTRUM	spect	
PROBHD	5 mm PABBO BB-	
PULPROG	zgpg30	
TD	65536	
SOLVENT	Acetone	
NS	750	
DS	4	
SWH	36057.691	Hz
FIDRES	0.550197	Hz
AQ	0.9088159	sec
RG	203	
DW	13.867	usec
DE	6.50	usec
TE	296.4	K
D1	2.00000000	sec
D11	0.03000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	13C	
P1	11.50	usec
PL1	0.00	dB
PL1W	97.46119690	W
SFO1	151.0637542	MHz
======== CHANNEL f2 ========		
CPDPRG2	waltz16	
NUC2	1H	
PCPD2	70.00	usec
PL2	-2.00	dB
PL12	14.19	dB
PL13	120.00	dB
PL2W	19.70630455	W
PL12W	0.47381112	W
PL13W	0.00000000	W
SFO2	600.7124028	MHz
SI	32768	
SF	151.0485164	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

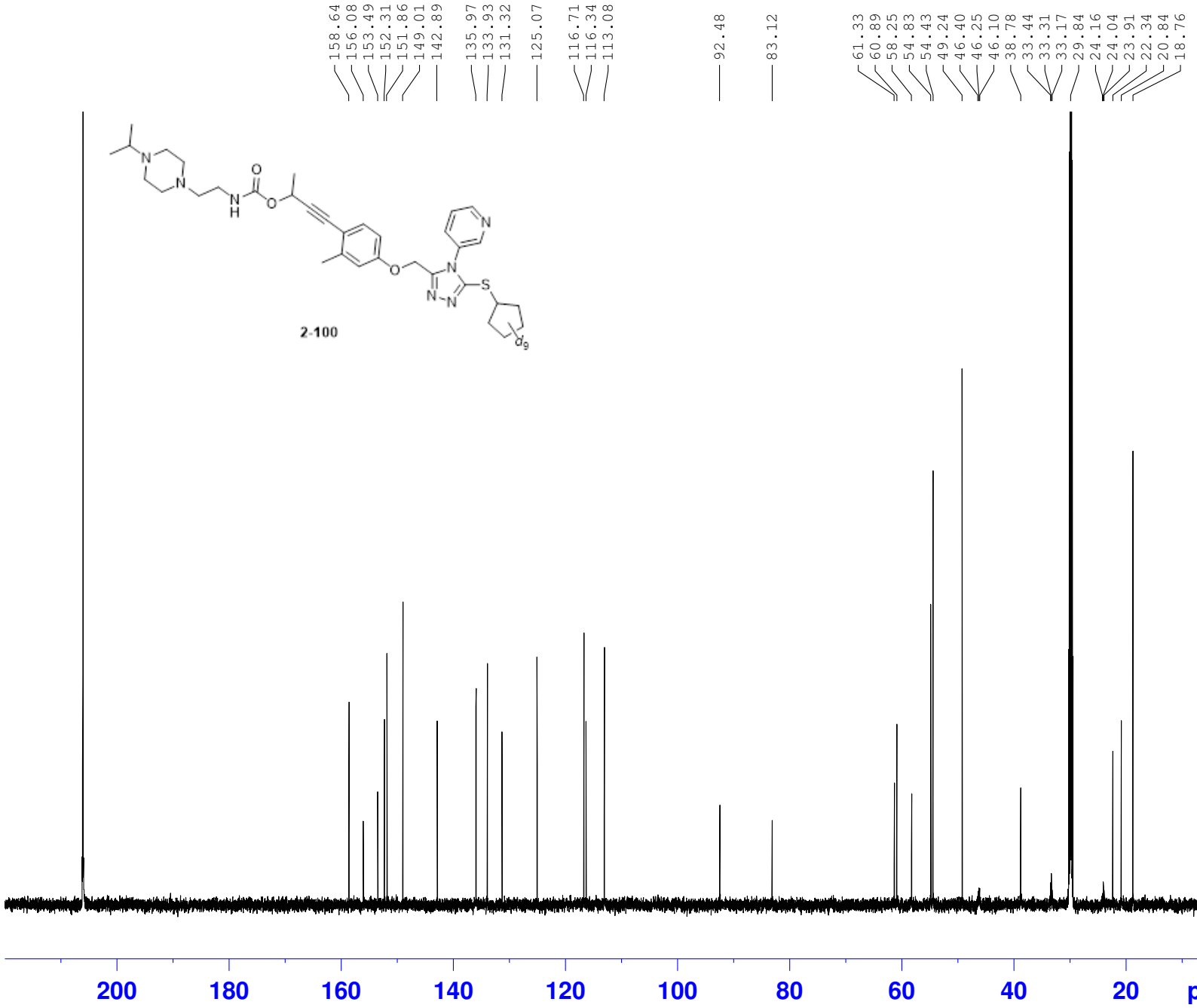
CNA-695-65, 1H, acetone-d6, 600 MHz

8.745 8.743 8.737 8.735 8.707 8.703 7.980 7.977 7.974 7.967 7.964 7.961 7.627 7.619 7.614 7.606 7.258 7.243 6.812 6.808 6.746 6.742 6.732 6.728 6.187 5.597 5.586 5.575 5.182 3.257 3.246 3.236 3.226 2.602 2.591 2.580 2.569 2.558 2.454 2.433 2.422 2.411 2.318 2.050 1.510 1.498 0.967 0.957



NAME	CNA-695-65
EXPNO	1
PROCNO	1
Date_	20160217
Time	15.34
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	16
DS	2
SWH	12335.526 Hz
FIDRES	0.188225 Hz
AQ	2.6564426 sec
RG	32
DW	40.533 usec
DE	6.50 usec
TE	297.2 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.86 usec
PL1	-2.00 dB
PL1W	19.70630455 W
SFO1	600.7137096 MHz
SI	32768
SF	600.7100094 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

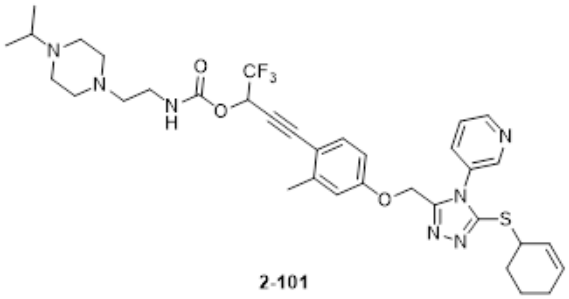
CNA-695-65, 13C, acetone-d6, 600 MHz



NAME	CNA-695-65
EXPNO	2
PROCNO	1
Date_	20160217
Time	15.41
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	Acetone
NS	200
DS	4
SWH	36057.691 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	203
DW	13.867 usec
DE	6.50 usec
TE	297.5 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	11.50 usec
PL1	0.00 dB
PL1W	97.46119690 W
SFO1	151.0637542 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	70.00 usec
PL2	-2.00 dB
PL12	14.19 dB
PL13	120.00 dB
PL2W	19.70630455 W
PL12W	0.47381112 W
PL13W	0.00000000 W
SFO2	600.7124028 MHz
SI	32768
SF	151.0485235 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

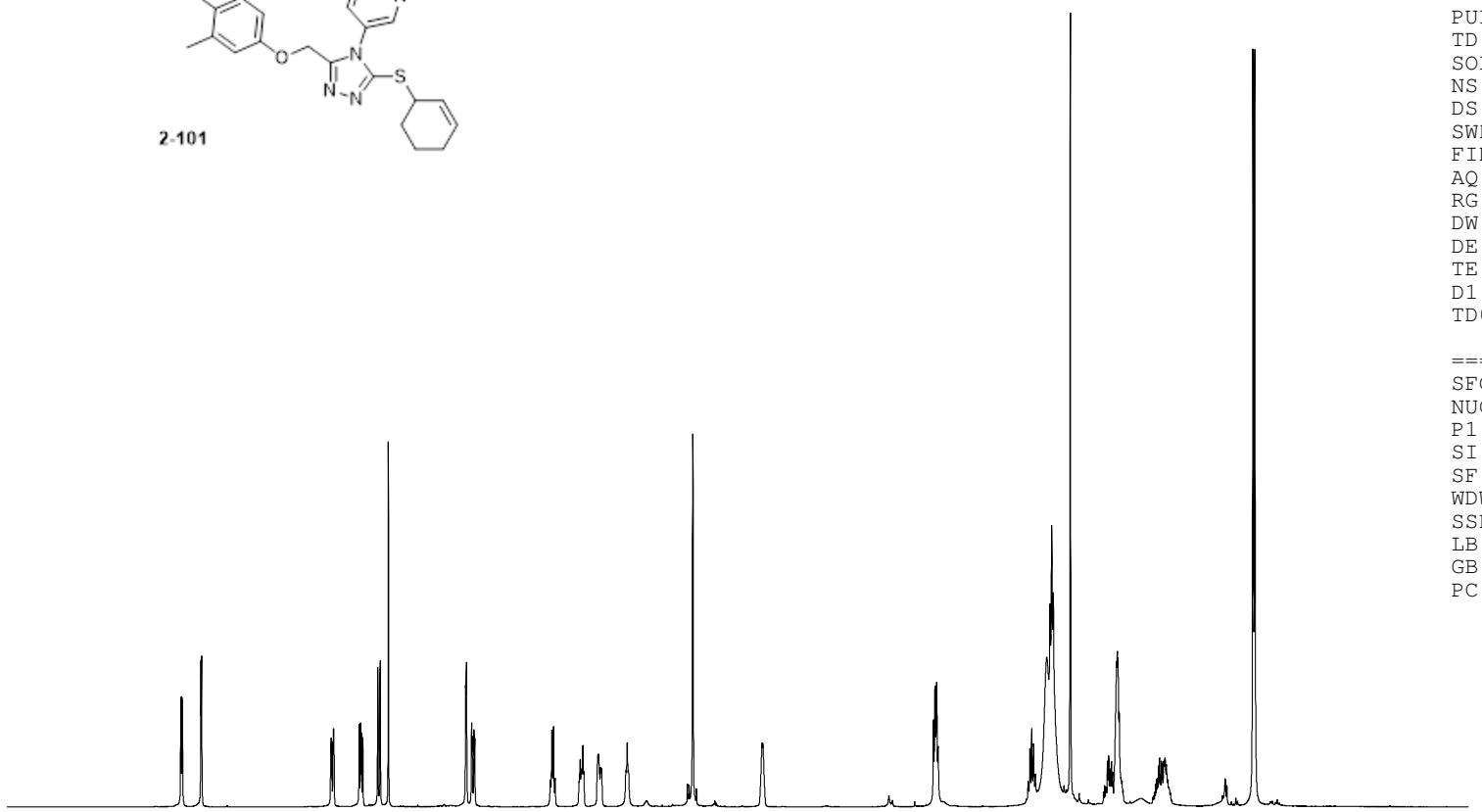
CNA-695-84, 1H, CDCl3, 500 MHz

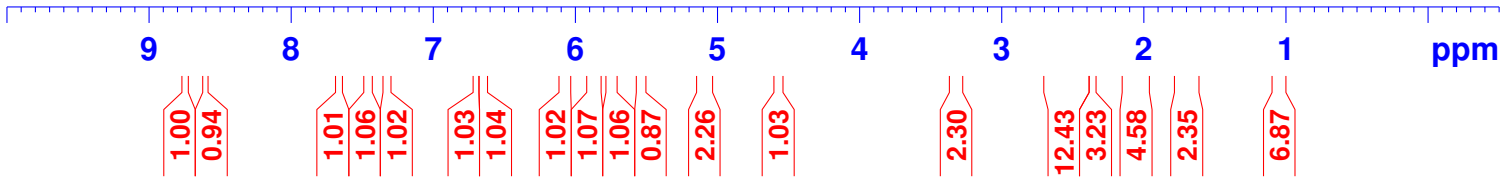
8.752 8.750 8.743 8.740 8.607 8.602 7.672 7.670 7.659 7.655 7.654 7.470 7.461 7.454 7.445 7.336 7.319 7.260 6.704 6.699 6.662 6.657 6.645 6.640 6.085 6.073 5.073 5.072 3.344 3.332 3.320 2.637 2.529 2.506 2.494 2.482 2.360 2.029 2.026 2.022 2.018 2.008 1.048 1.035



2-101

NAME	CNA-695-84
EXPNO	3
PROCNO	1
Date_	20160303
Time	0.27
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	10000.000 Hz
FIDRES	0.152588 Hz
AQ	3.2768500 sec
RG	80.6
DW	50.000 usec
DE	6.50 usec
TE	297.8 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	500.1630887 MHz
NUC1	1H
P1	11.45 usec
SI	65536
SF	500.1600124 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00





1.00 0.94 1.01 1.06 1.02 1.03 1.04 1.02 1.07 1.06 0.87 2.26 1.03 2.30 12.43 3.23 4.58 2.35 6.87

CNA-695-84, 13C, CDCl3, 500 MHz

158.098
153.746
153.688
151.343
148.191
143.563
134.839
134.160
132.513
130.142
125.577
124.161
123.388
121.154
115.967
114.486
112.187
86.734
81.528
77.160
63.377
63.074
62.781
62.484
60.020
56.653
54.555
53.372
53.217
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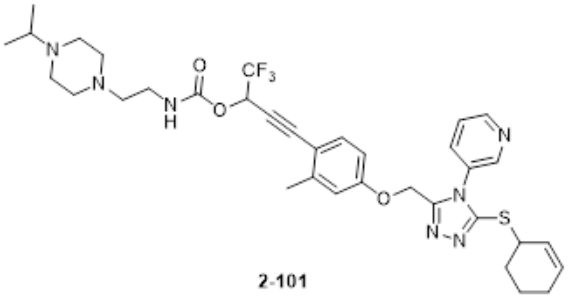
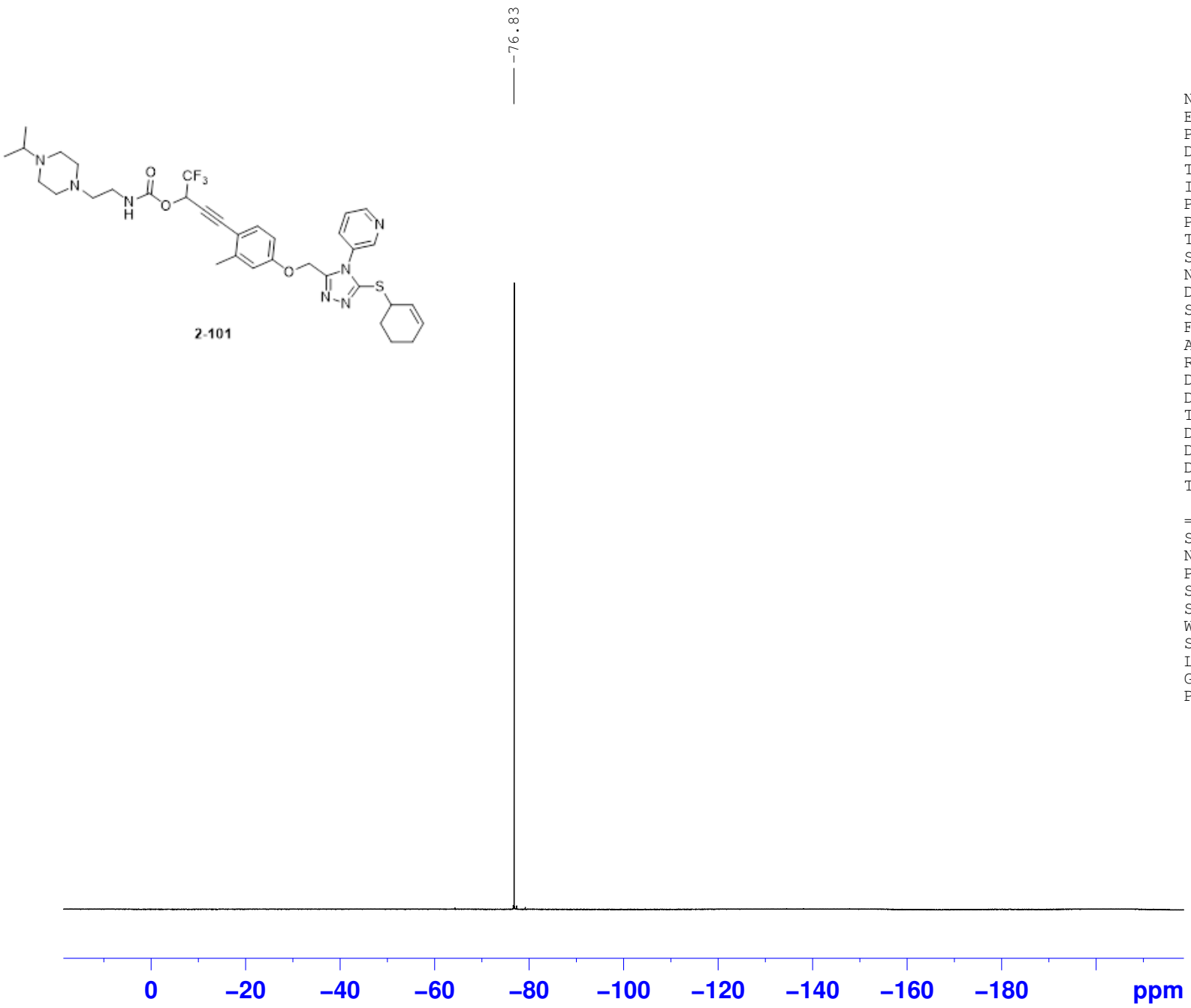
44.217
37.998
29.384
24.970
20.819



2-101

NAME	CNA-695-84
EXPNO	2
PROCNO	1
Date_	20160303
Time	6.01
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	6144
DS	2
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 usec
DE	6.50 usec
TE	298.7 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	125.7779086 MHz
NUC1	13C
P1	10.50 usec
SI	32768
SF	125.7653144 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

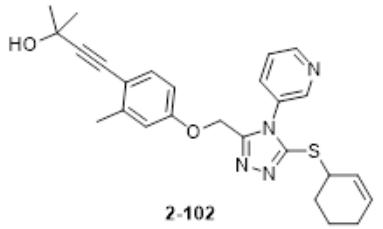
CNA-695-84, 19F, CDCl3, 400 MHz



NAME	CNA-695-84
EXPNO	4
PROCNO	1
Date_	20160303
Time	12.22
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	89285.711 Hz
FIDRES	0.681196 Hz
AQ	0.7340532 sec
RG	203
DW	5.600 usec
DE	6.50 usec
TE	298.6 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	376.4607164 MHz
NUC1	19F
P1	14.20 usec
SI	65536
SF	376.4983662 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-695-50, 1H, acetone-d6, 400 MHz

8.751 8.748 8.739 8.736 8.709 8.703 7.987 7.983 7.981 7.977 7.967 7.963 7.960 7.957 7.638 7.626 7.618 7.606 7.220 7.199 6.798 6.791 6.734 6.727 6.712 6.706 5.857 5.853 5.740 5.736 5.731 5.177 2.314 2.050 2.028 2.023 2.019 2.009 1.996 1.991 1.982 1.973 1.958 1.527

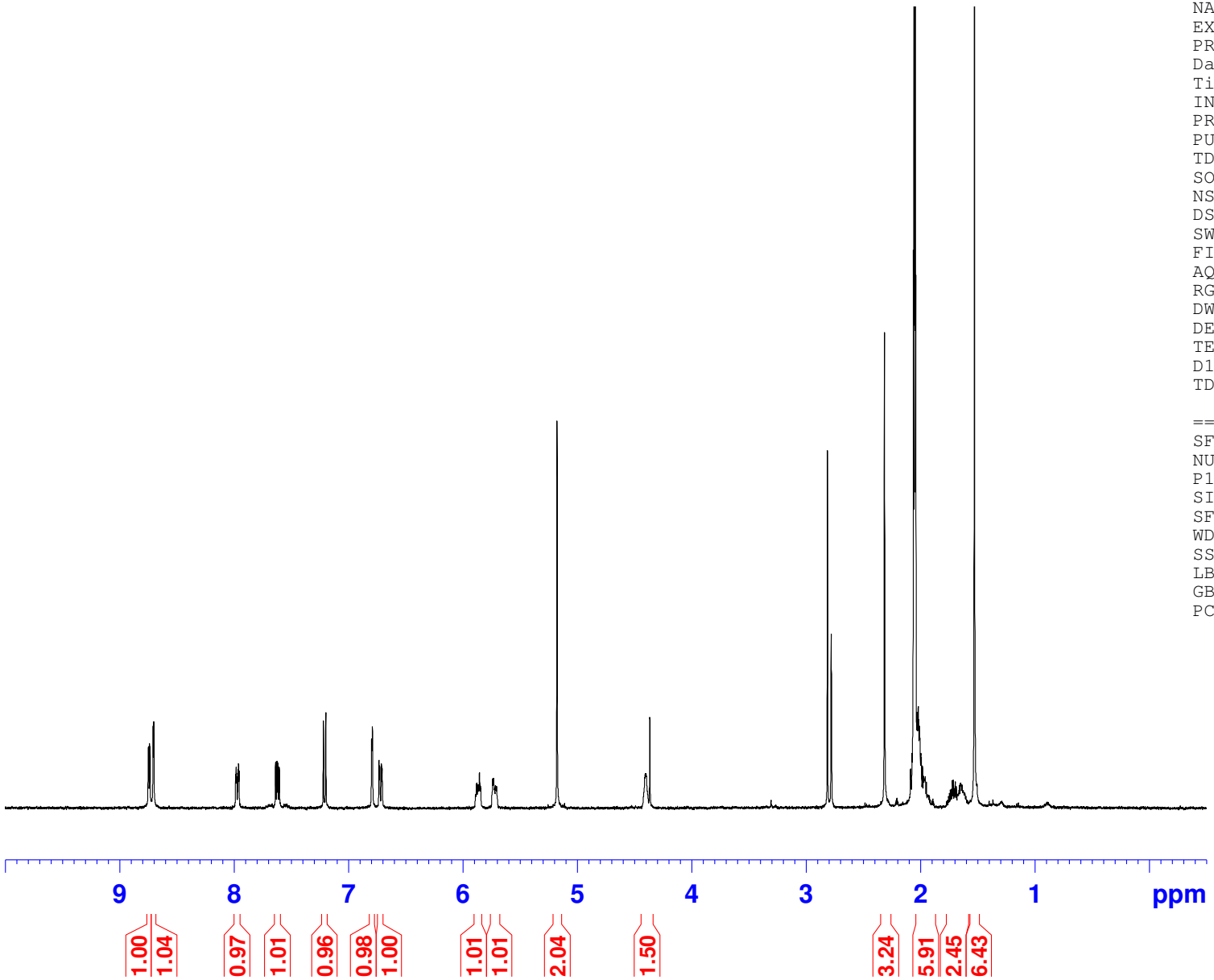


2-102

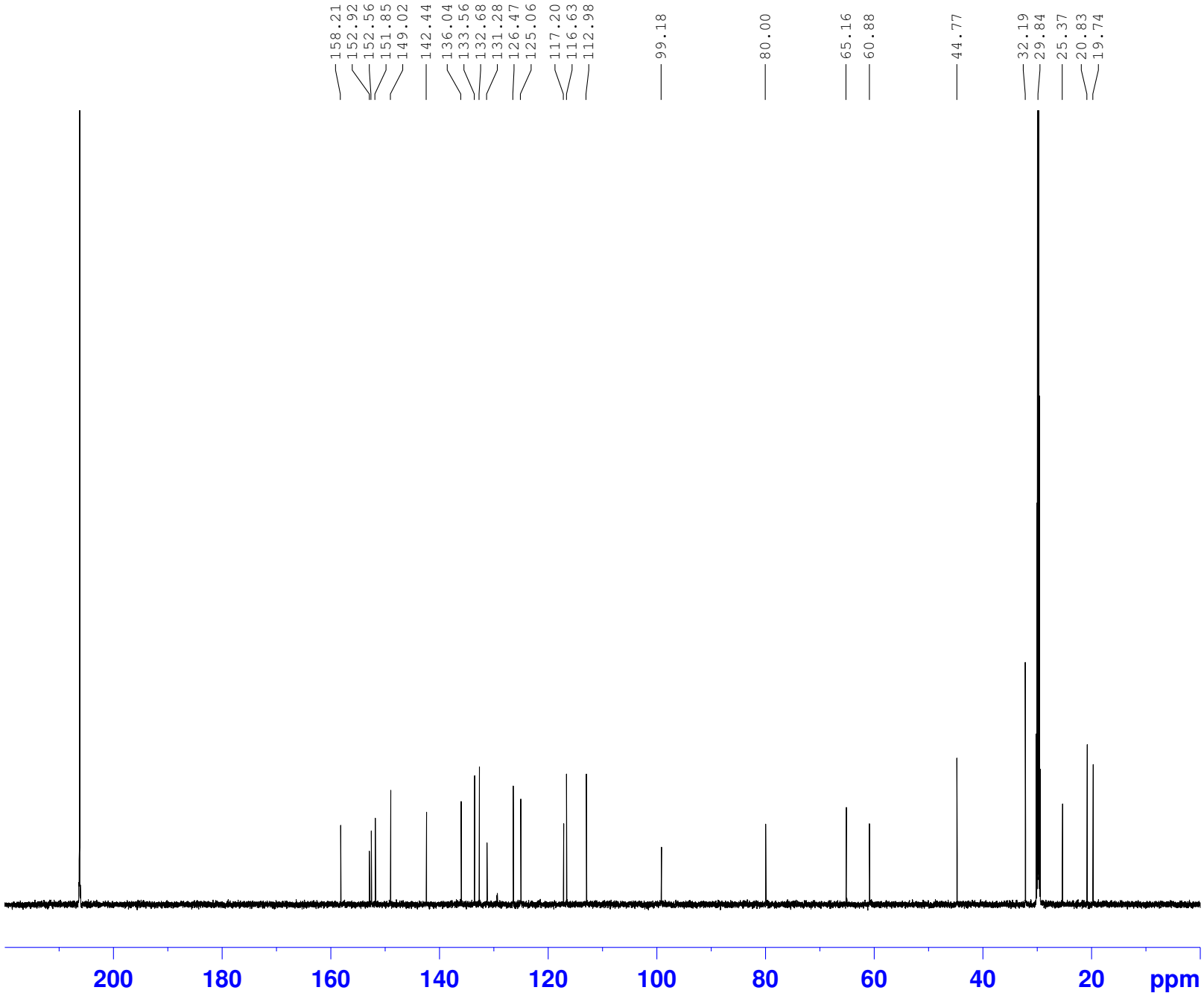
NAME	CNA-695-50
EXPNO	3
PROCNO	1
Date_	20160204
Time	12.03
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	16
DS	2
SWH	8012.820 Hz
FIDRES	0.122266 Hz
AQ	4.0894966 sec
RG	161
DW	62.400 usec
DE	6.50 usec
TE	297.1 K
D1	1.00000000 sec
TD0	1

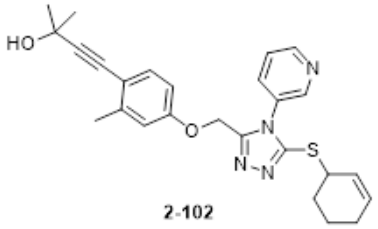
======== CHANNEL f1 ========

SFO1	400.1324710 MHz
NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300069 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



CNA-695-50, 13C, acetone-d6, 600 MHz





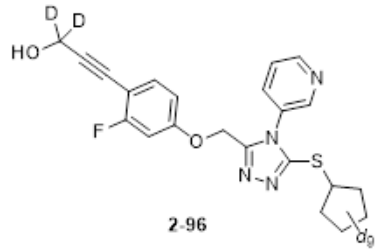
2-102

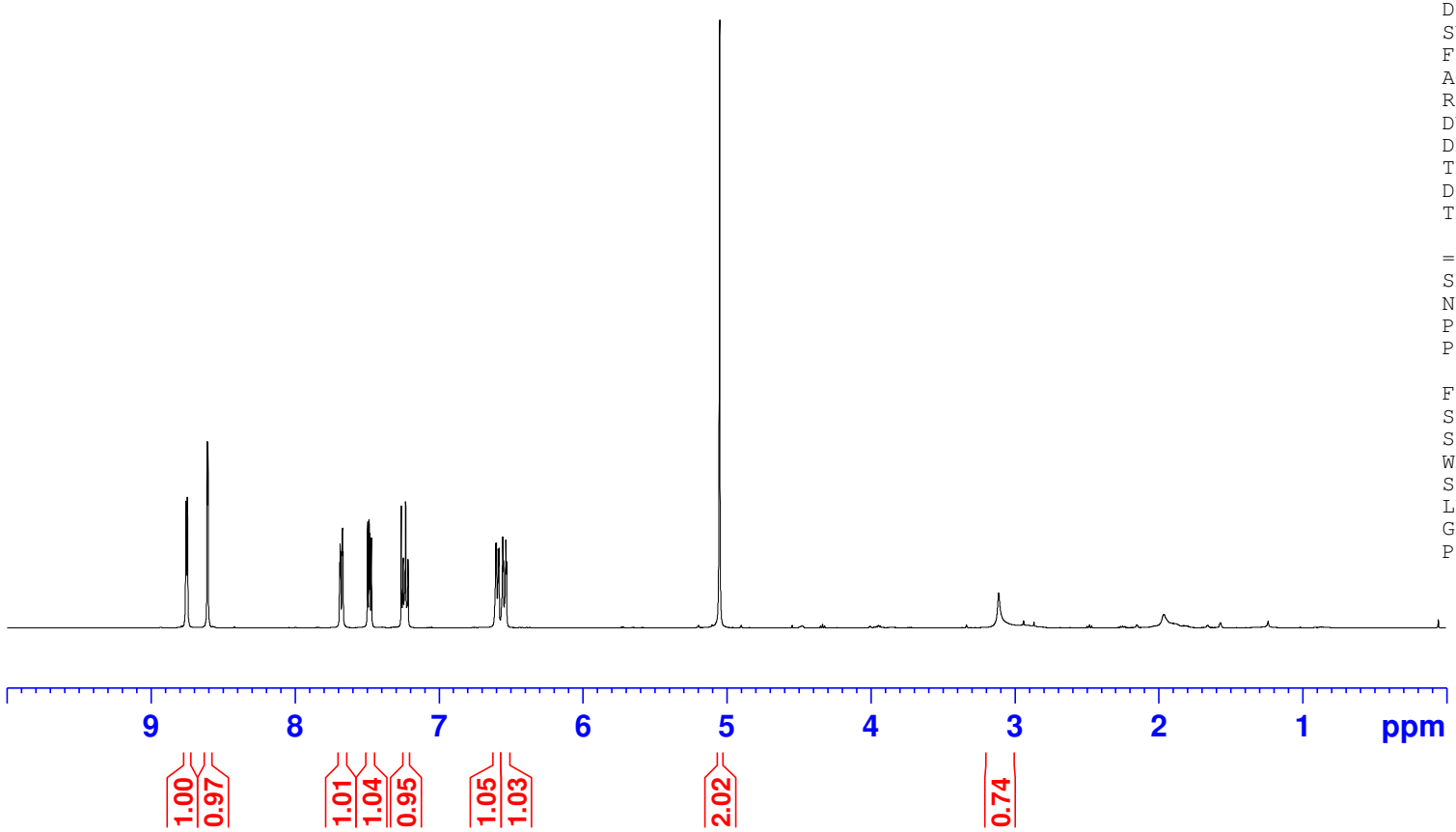
NAME	CNA-695-50
EXPNO	3
PROCNO	1
Date_	20160203
Time	22.38
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	Acetone
NS	128
DS	4
SWH	36057.691 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	203
DW	13.867 usec
DE	6.50 usec
TE	295.9 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	11.50 usec
PL1	0.00 dB
PL1W	97.46119690 W
SFO1	151.0637542 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	70.00 usec
PL2	-2.00 dB
PL12	14.19 dB
PL13	120.00 dB
PL2W	19.70630455 W
PL12W	0.47381112 W
PL13W	0.00000000 W
SFO2	600.7124028 MHz
SI	32768
SF	151.0485241 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-752-26, 1H, CDCl3, 500 MHz

8.608 8.603 7.689 7.684 7.681 7.672 7.668 7.665 7.493 7.484 7.477 7.467 7.260 7.246 7.230 7.213 6.603 6.598 6.586 6.581 6.555 6.550 6.534 6.529 5.048

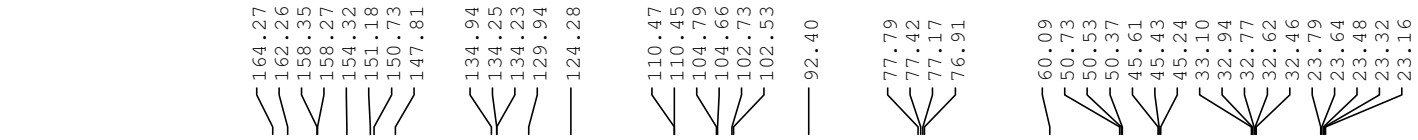
3.109

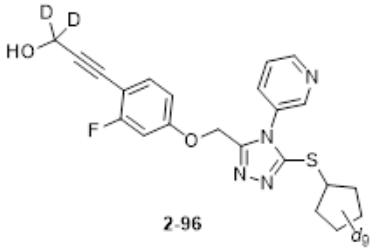


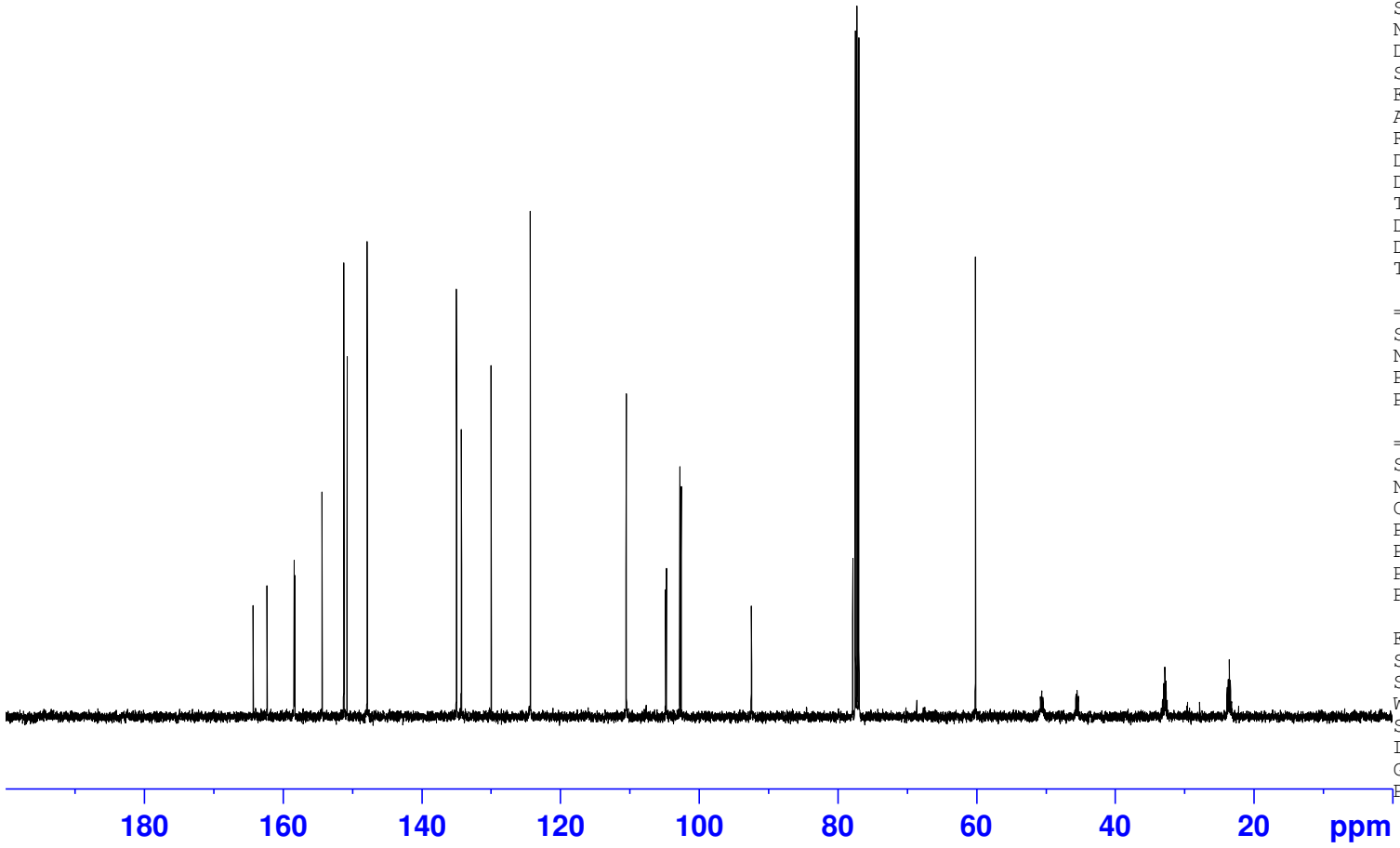



```
Current Data Parameters
NAME          CNA-752-26
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parameters
Date_           20161122
Time               18.41
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES             0.152588 Hz
AQ             3.2767999 sec
RG                  90.5
DW                50.000 usec
DE                 6.50 usec
TE                297.1 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1630887 MHz
NUC1                   1H
P1                 11.50 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1600130 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-752-26, 13C, CDCl3, 500 MHz

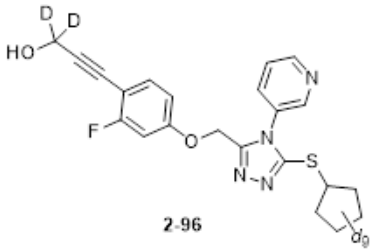


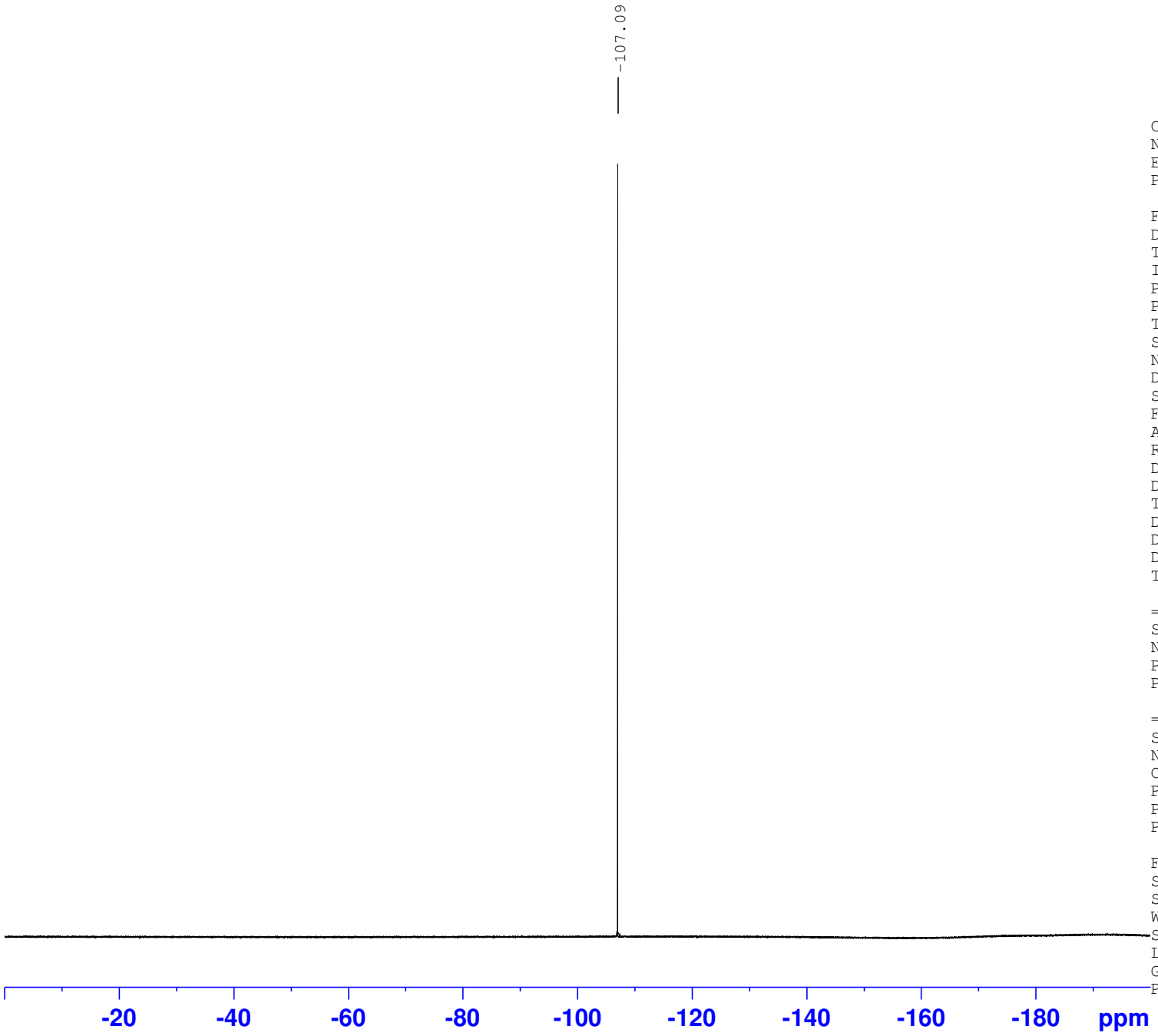





```
Current Data Parameters
NAME          CNA-752-26
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20161122
Time               18.10
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  256
DS                    2
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ            1.1010048 sec
RG                  203
DW               16.800 usec
DE                6.50 usec
TE               298.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         125.7779086 MHz
NUC1                 13C
P1                10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W
PLW13         0.23805000 W

F2 - Processing parameters
SI                32768
SF           125.7653320 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

CNA-752-26, 19F, CDCl3, 500 MHz

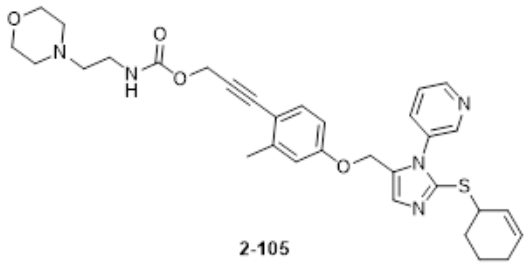




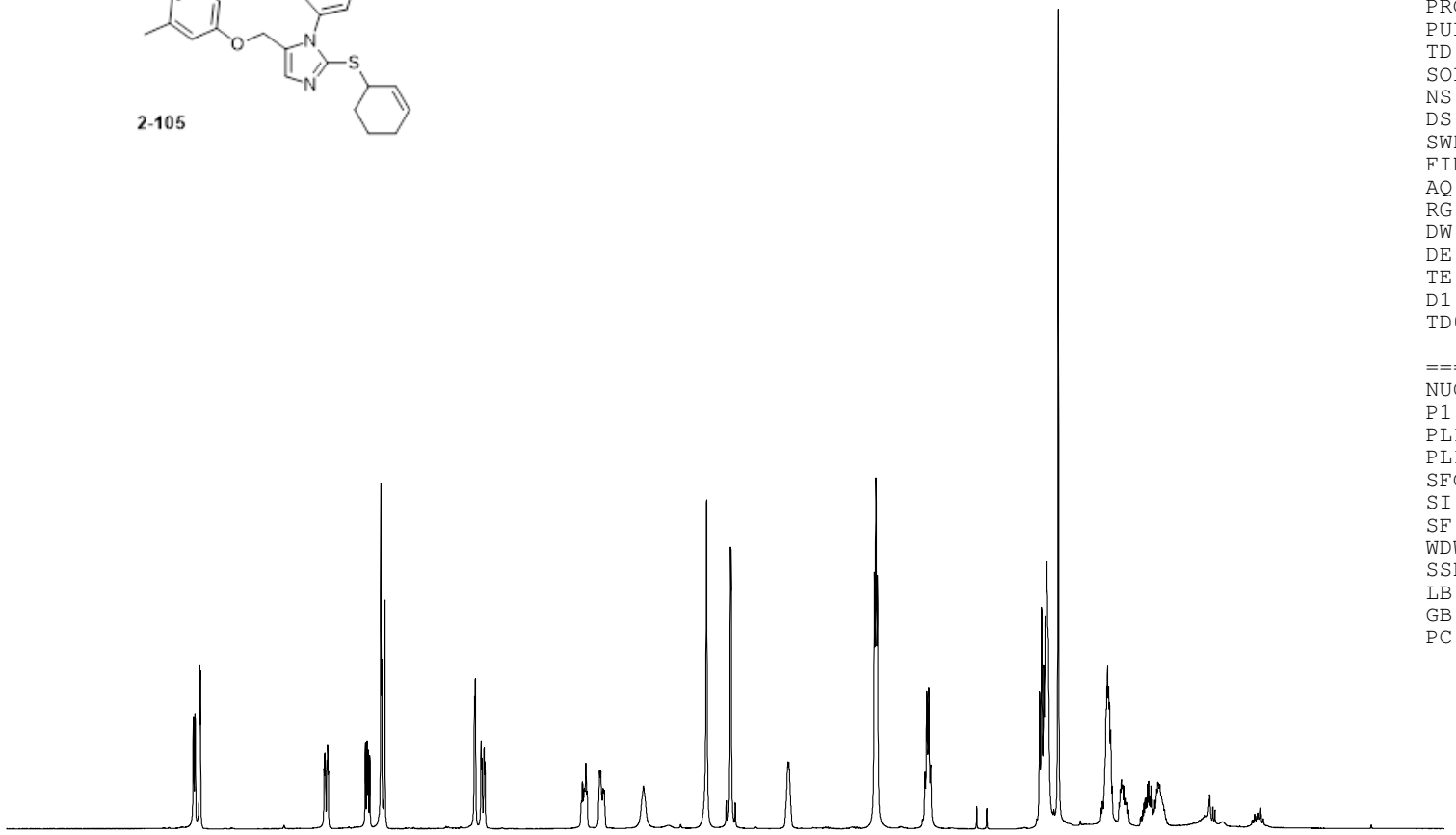

```
Current Data Parameters
NAME          CNA-752-26
EXPNO                  5
PROCNO                 1

F2 - Acquisition Parameters
Date_           20161122
Time               18.43
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG       zgfhigqn.2
TD                131072
SOLVENT             CDCl3
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                297.2 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                  19F
P1                 5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2              80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

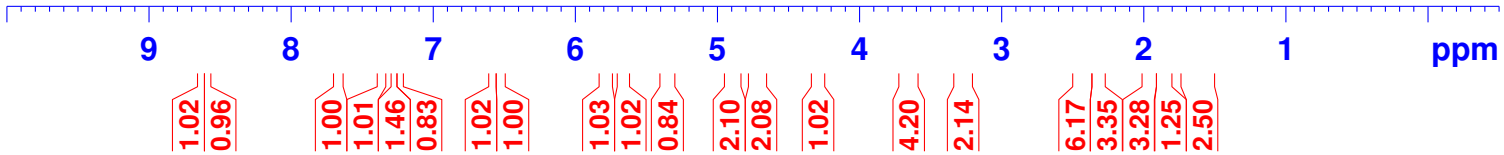
CNA-710-57, 1H, CDCl3, 400 MHz

8.636 8.633 8.624 8.621 8.590 8.584 7.676 7.660 7.656 7.379 7.367 7.359 7.346 7.266 7.260 7.237 6.582 6.576 6.533 6.527 6.512 6.506 4.887 4.713 4.708 4.286 3.660 3.649 3.638 3.278 3.263 2.455 2.440 2.425 2.412 2.402 2.318 1.966 1.962 1.958 1.953 1.949 1.944 1.936



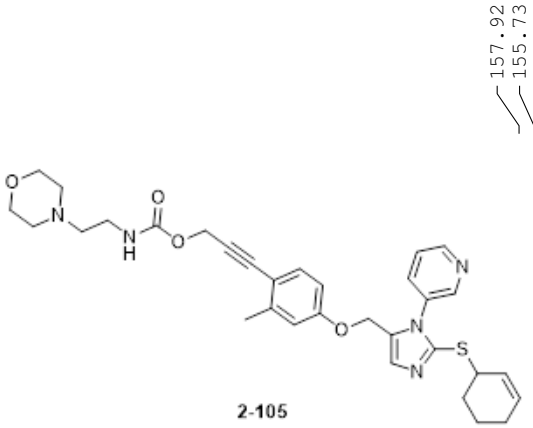
NAME	CNA-710-57
EXPNO	2
PROCNO	1
Date_	20160525
Time	21.37
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	64
DW	60.800 usec
DE	6.50 usec
TE	295.8 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300218 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00





1.02 0.96 1.00 1.01 1.46 0.83 1.02 1.00 1.03 1.02 0.84 2.10 2.08 1.02 4.20 2.14 6.17 3.35 3.28 1.25 2.50

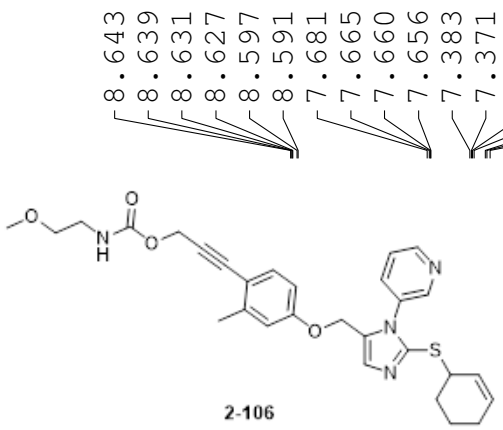
CNA-710-57, 13C, CDCl3, 400 MHz



157.92
155.73
150.37
148.91
145.69
142.65
135.57
133.77
132.24
131.69
131.47
129.47
126.03
123.82
115.84
115.22
111.96
86.36
84.97
77.16
66.99
59.44
57.38
53.56
53.40
44.46
37.34
29.27
24.93
19.23

NAME	CNA-710-57
EXPNO	3
PROCNO	1
Date_	20160525
Time	21.46
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	771
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	296.0 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379056 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-710-50, 1H, CDCl3, 400 MHz



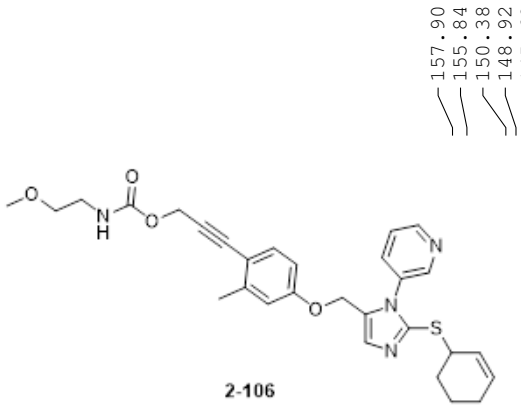
8.643 8.639 8.631 8.627 8.597 8.591 7.681 7.665 7.660 7.656 7.383 7.371 7.362 7.350 7.273 7.260 7.240 6.585 6.580 6.537 6.530 6.515 6.509 5.774 4.886 4.717 4.712 4.298 4.293 3.438 3.426 3.413 3.373 3.358 3.346 3.315 2.320 1.973 1.968 1.964 1.955 1.950 1.942 1.881

NAME	CNA-710-50
EXPNO	1
PROCNO	1
Date_	20160512
Time	19.54
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	71.8
DW	60.800 usec
DE	6.50 usec
TE	296.0 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300199 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

9 8 7 6 5 4 3 2 1 ppm

1.00 0.94 1.00 1.01 2.20 0.98 0.96 0.99 0.98 0.80 2.10 1.97 0.97 2.04 5.07 2.96 3.08 1.95 2.17

CNA-710-50, 13C, CDCl3, 400 MHz

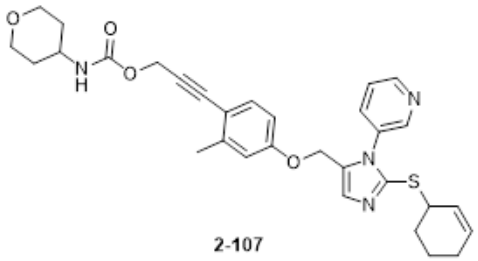


157.90
155.84
150.38
148.92
145.68
142.65
135.57
133.73
132.25
131.68
131.48
129.50
126.05
123.82
115.84
115.30
111.96
86.38
84.92
77.48
77.16
76.84
71.41
59.45
58.89
53.59
44.47
40.98
29.28
24.94
20.96
19.24

NAME	CNA-710-50	
EXPNO	2	
PROCNO	1	
Date_	20160512	
Time	20.40	
INSTRUM	spect	
PROBHD	5 mm PADUL 13C	
PULPROG	zgpg30	
TD	65536	
SOLVENT	CDCl3	
NS	600	
DS	4	
SWH	24038.461	Hz
FIDRES	0.366798	Hz
AQ	1.3631988	sec
RG	203	
DW	20.800	usec
DE	6.50	usec
TE	296.1	K
D1	3.00000000	sec
D11	0.03000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	13C	
P1	10.00	usec
PL1	-0.44	dB
PL1W	39.19395828	W
SFO1	100.6479773	MHz
======== CHANNEL f2 ========		
CPDPRG2	waltz16	
NUC2	1H	
PCPD2	90.00	usec
PL2	-3.90	dB
PL12	15.81	dB
PL13	120.00	dB
PL2W	21.64248466	W
PL12W	0.23137002	W
PL13W	0.00000000	W
SFO2	400.2316009	MHz
SI	32768	
SF	100.6379050	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

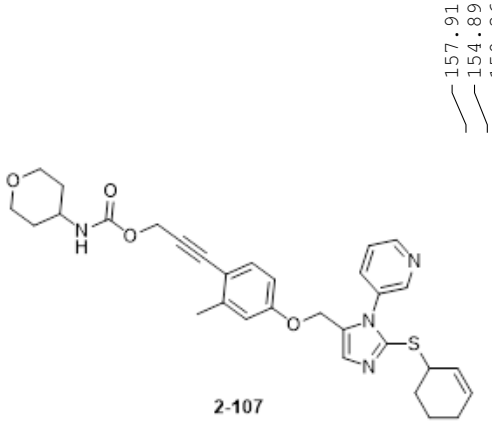
CNA-710-49, 1H, CDCl3, 400 MHz

8.630 8.626 8.618 8.614 8.583 8.577 7.649 7.647 7.371 7.359 7.351 7.260 7.243 7.231 7.222 6.574 6.568 6.524 6.503 4.866 4.703 4.698 3.911 3.890 3.882 3.437 3.413 3.408 2.304 1.962 1.959 1.954 1.950 1.945 1.941 1.936 1.928 1.896 1.890 1.865 1.858 1.450 1.438 1.418



NAME	CNA-710-49
EXPNO	2
PROCNO	1
Date_	20160512
Time	20.48
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	64
DW	60.800 usec
DE	6.50 usec
TE	296.0 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300237 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-710-49, 13C, CDCl3, 400 MHz

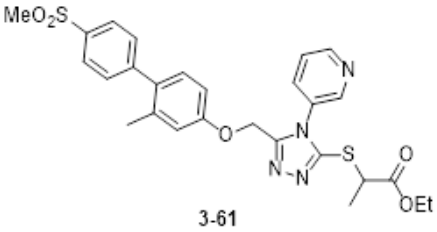


157.91
154.89
150.36
148.90
145.67
142.63
135.57
133.70
132.24
131.68
131.48
129.46
126.02
123.81
115.85
115.22
111.97

86.28
85.00
77.48
77.16
76.84
66.73
59.44
53.52
47.52
44.46
33.40
29.26
24.93
20.95
19.22

NAME	CNA-710-49
EXPNO	3
PROCNO	1
Date_	20160512
Time	21.43
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	700
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	296.1 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379061 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-653-17, 1H, CDCl3, 400 MHz



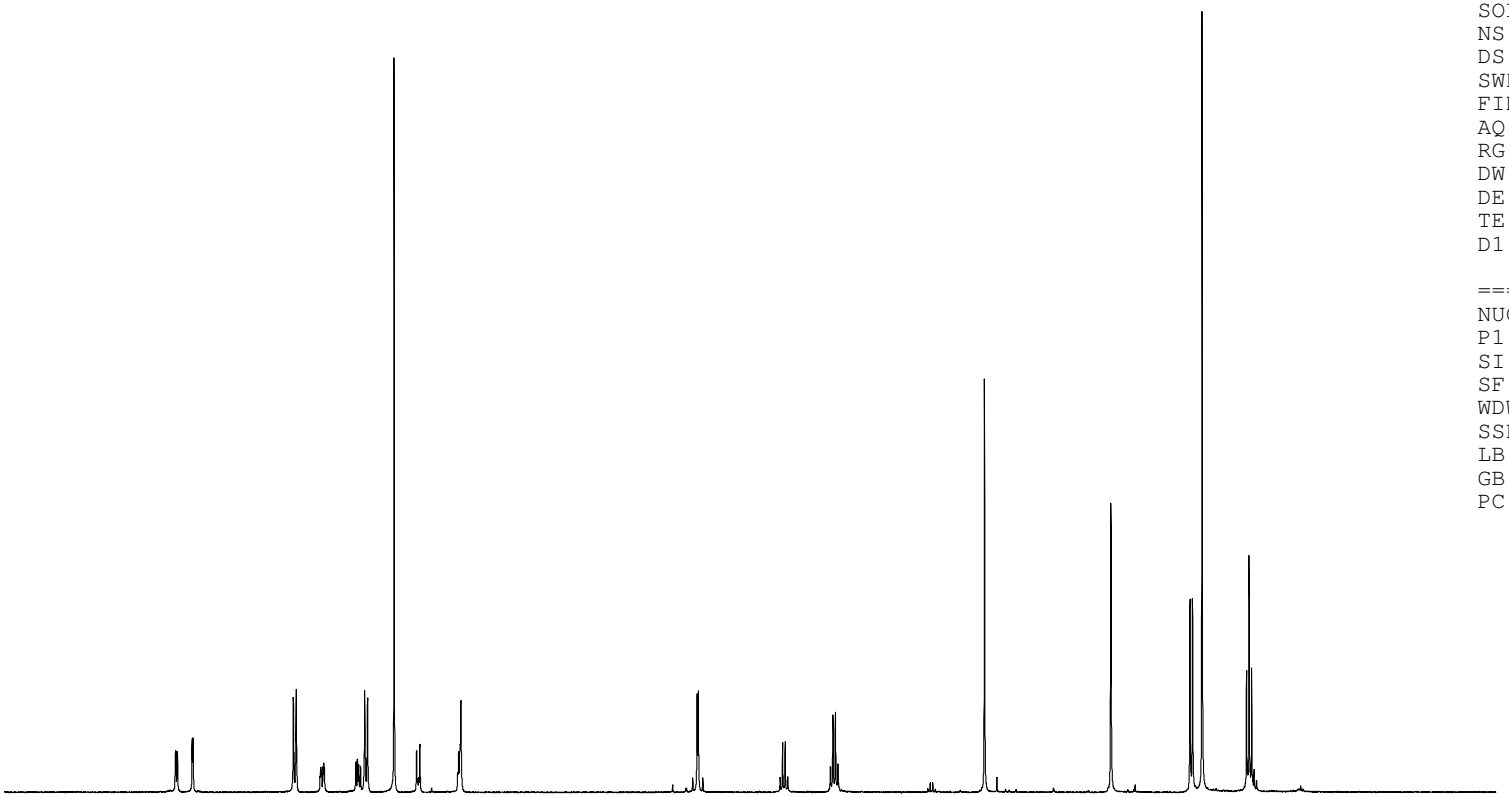
3-61

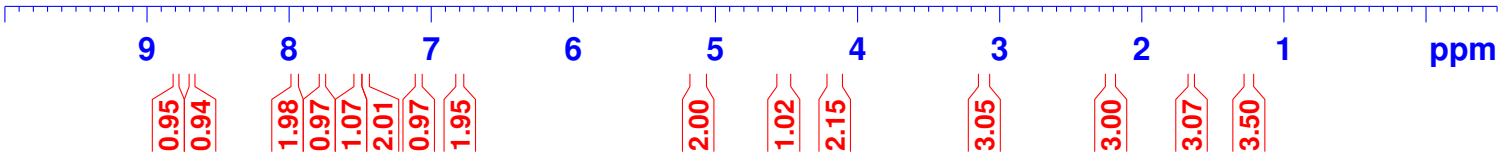
8.800 8.797 8.788 8.785 8.681 8.675 7.970 7.949 7.777 7.774 7.760 7.757 7.754 7.750 7.529 7.519 7.510 7.509 7.498 7.497 7.468 7.447 7.260 7.102 7.079 6.806 6.796 6.790 5.127 5.119 4.525 4.507 4.189 4.171 4.153 4.136 3.105 2.215 1.658 1.640 1.573 1.260 1.242 1.224

NAME	CNA-653-17
EXPNO	1
PROCNO	1
Date_	20150526
Time	12.49
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	161
DW	60.800 usec
DE	6.50 usec
TE	93.2 K
D1	1.00000000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300106 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

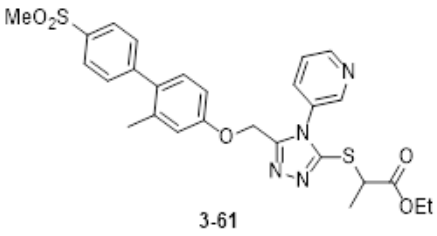




0.95 0.94 1.98 0.97 1.07 2.01 0.97 1.95 2.00 1.02 2.15 3.05 3.00 3.07 3.50

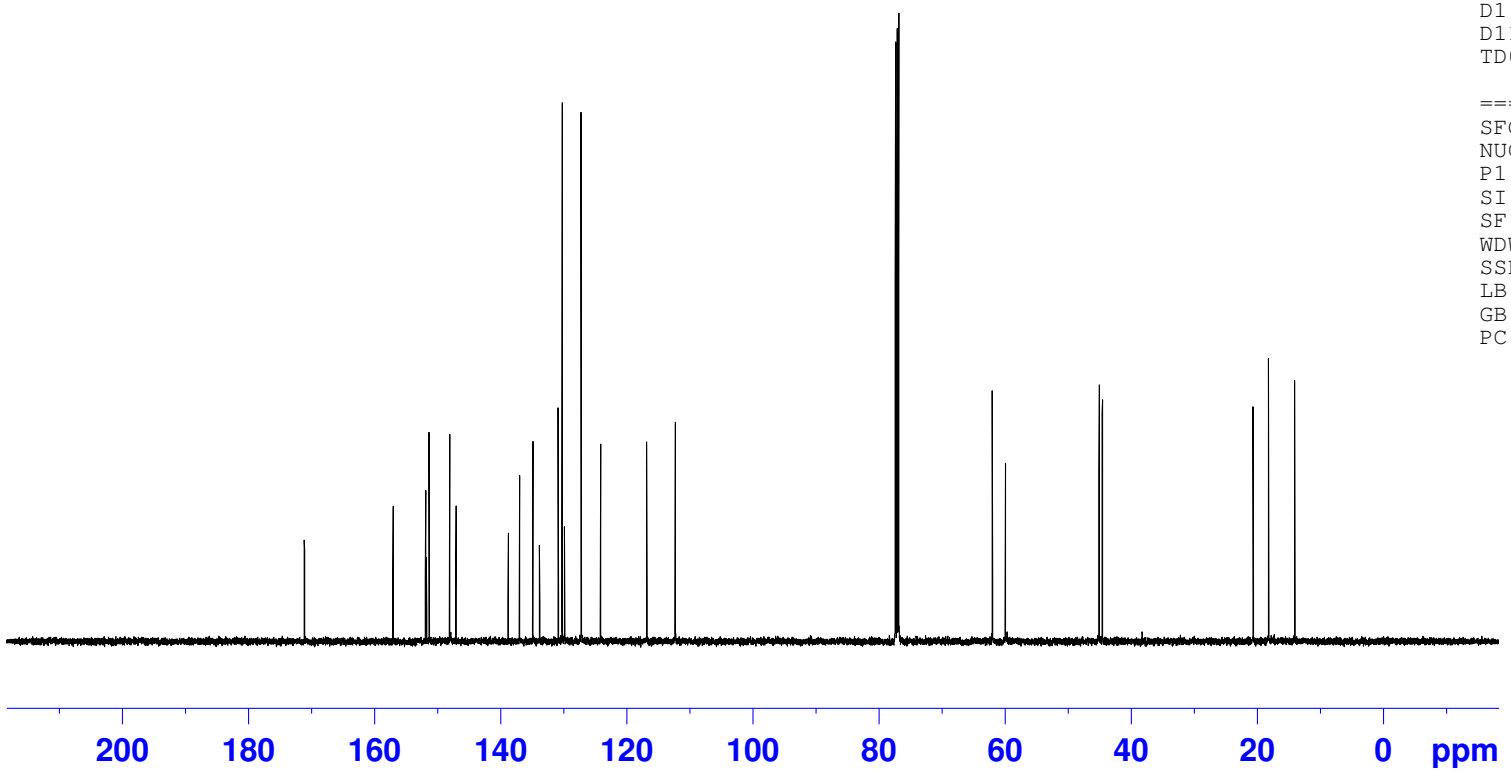
CNA-653-17, 1H, CDCl3, 500 MHz

171.115
157.063
151.900
151.744
151.344
148.053
147.083
138.792
136.994
134.862
133.805
130.849
130.235
129.866
127.223
124.126
116.813
112.273
77.361
77.106
76.851
61.980
59.908
45.046
44.543
20.605
18.172
14.015

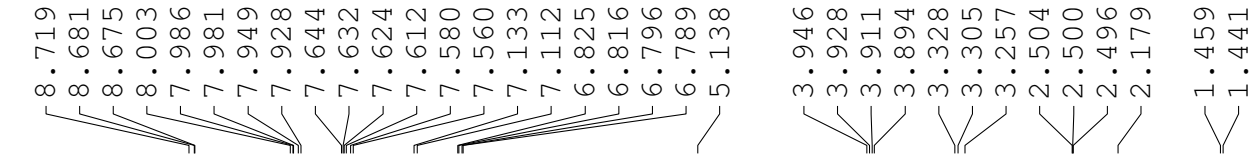


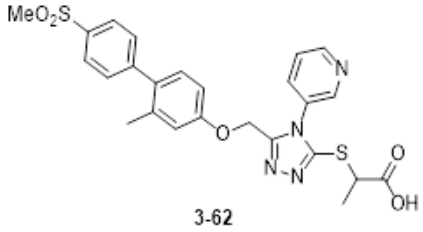
3-61

NAME	CNA-653-17
EXPNO	4
PROCNO	1
Date_	20150526
Time	15.49
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	300
DS	2
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 usec
DE	6.50 usec
TE	298.2 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	125.7779086 MHz
NUC1	13C
P1	10.50 usec
SI	32768
SF	125.7653320 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



CNA-653-18, 1H, DMSO, 400 MHz

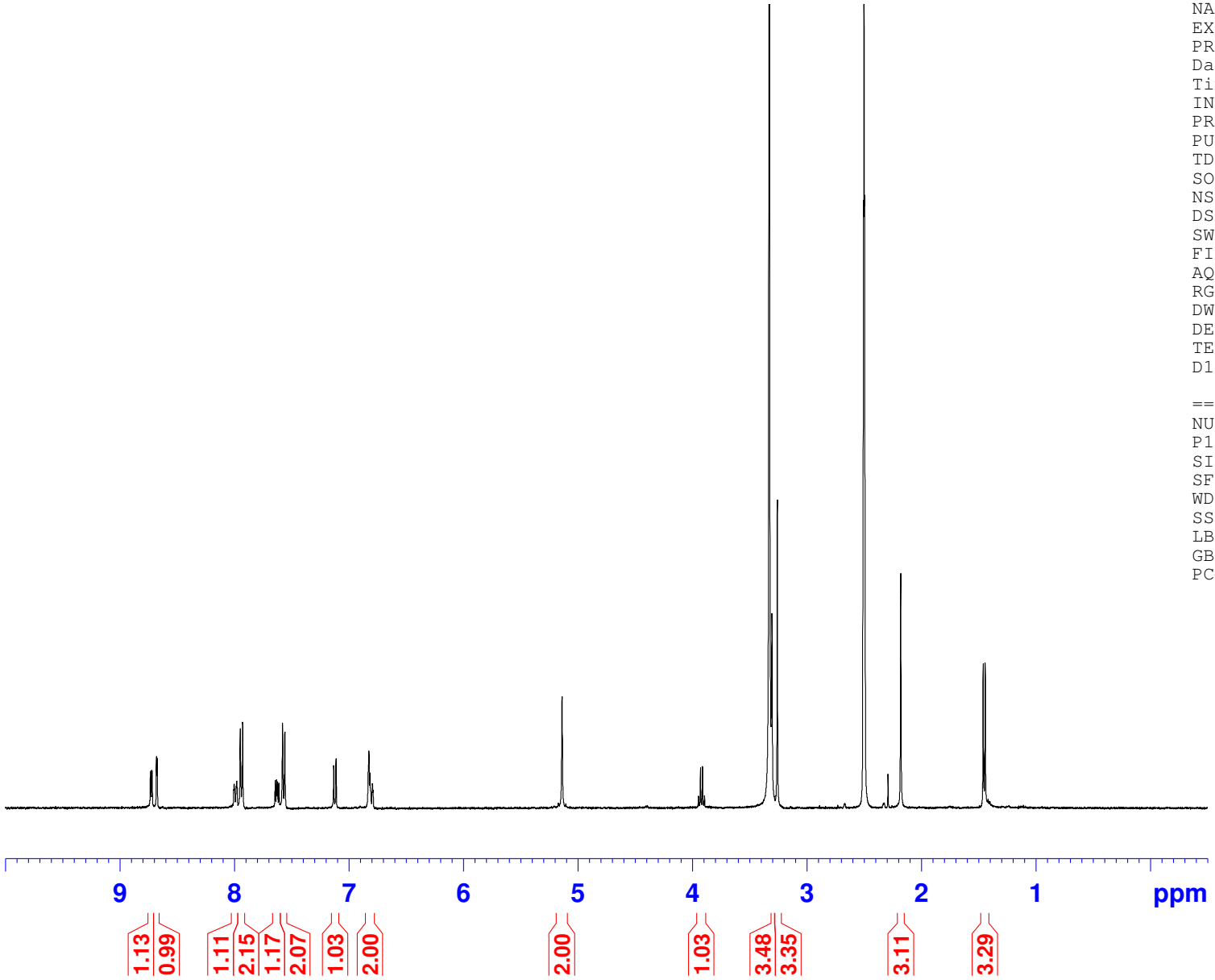




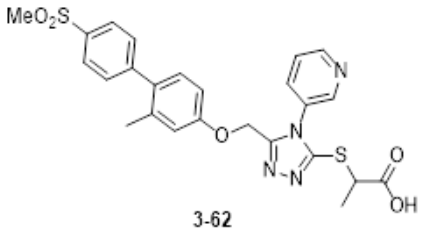
3-62

NAME	CNA-653-18
EXPNO	3
PROCNO	1
Date_	20150604
Time	14.11
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	181
DW	60.800 usec
DE	6.50 usec
TE	-158.0 K
D1	1.00000000 sec

======== CHANNEL f1 ========	
NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300047 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

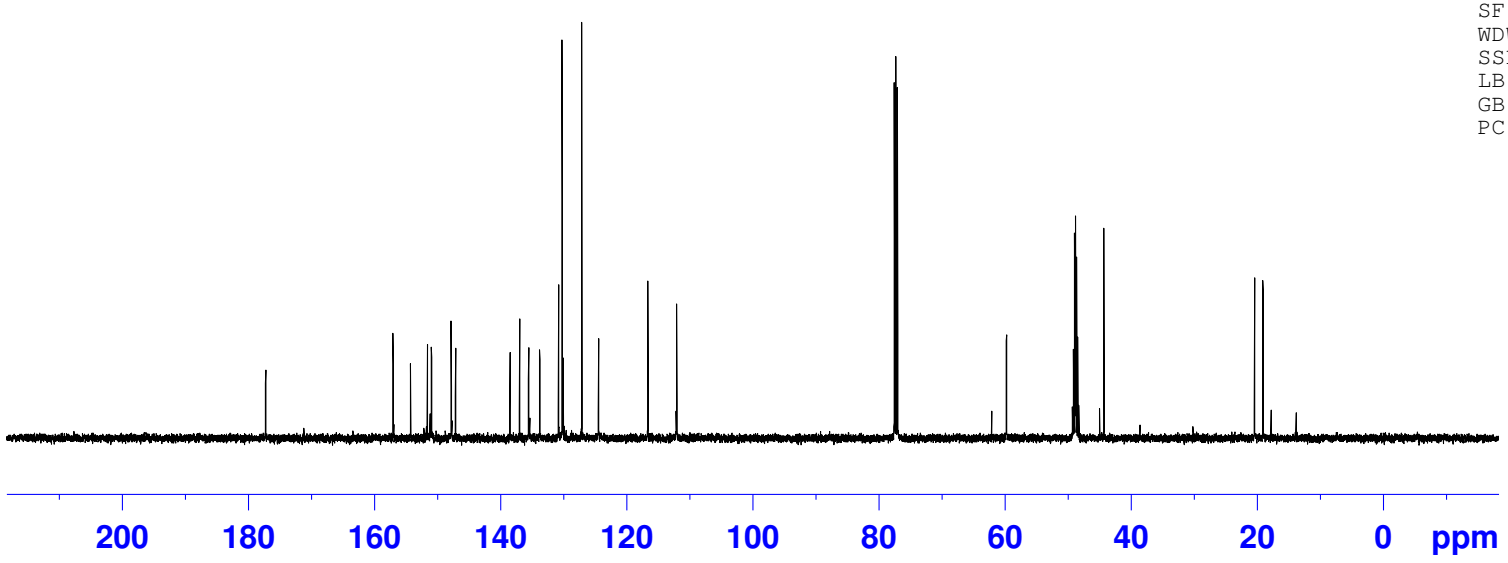


CNA-653-18, 13C, CDCl3/MeOD, 500 MHz



3-62

177.286
157.070
154.306
151.623
150.982
147.855
147.762
147.161
138.526
136.981
135.569
133.800
130.800
130.249
130.104
127.143
124.463
116.685
116.642
112.077
77.561
77.305
77.049
62.101
59.765
49.300
49.129
48.959
48.932
48.788
48.618
48.447
48.276
45.010
44.309
20.392
19.073
17.776
13.805

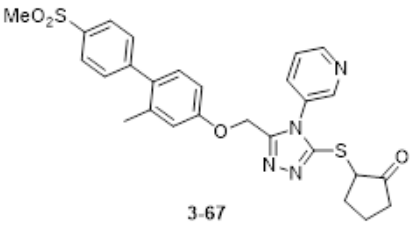


NAME	CNA-653-18
EXPNO	4
PROCNO	1
Date_	20150604
Time	3.35
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgpg30
TD	65536
SOLVENT	MeOD
NS	256
DS	2
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 usec
DE	6.50 usec
TE	298.7 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1

======== CHANNEL f1 ========

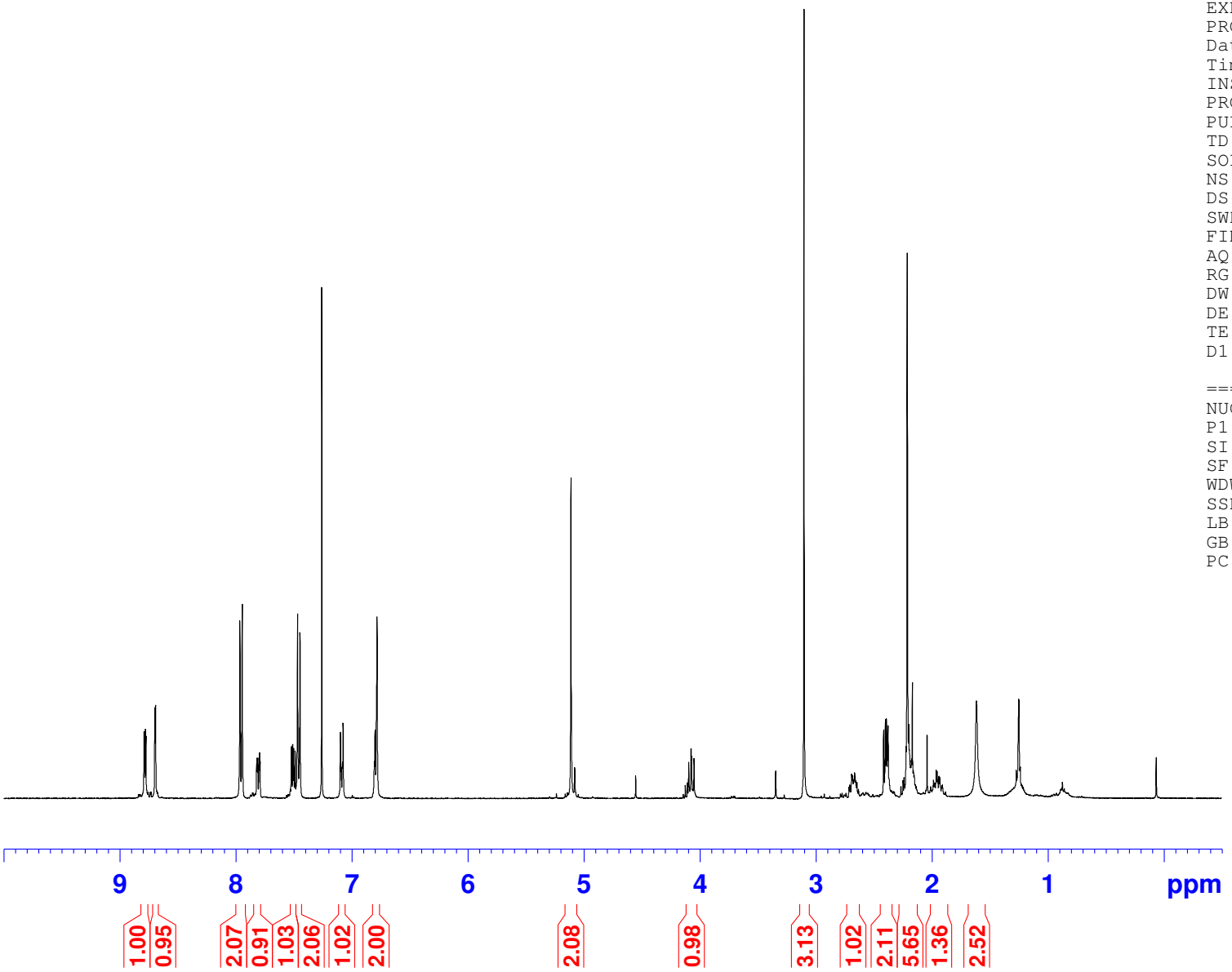
SFO1	125.7779086 MHz
NUC1	13C
P1	10.50 usec
SI	32768
SF	125.7653320 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-653-44, 1H, CDCl3, 400 MHz



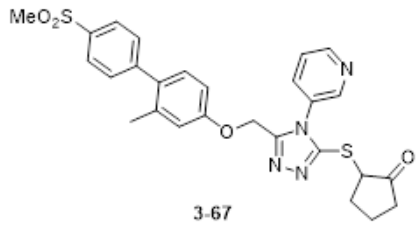
3-67

8.792 8.789 8.780 8.777 8.699 8.693 7.966 7.946 7.818 7.816 7.802 7.798 7.795 7.792 7.522 7.511 7.502 7.491 7.469 7.452 7.448 7.260 7.099 7.076 6.807 6.801 6.784 5.112 4.076 4.072 4.051 3.103 2.416 2.401 2.392 2.378 2.223 2.212 2.199 2.193 2.178 2.174 2.168 1.616



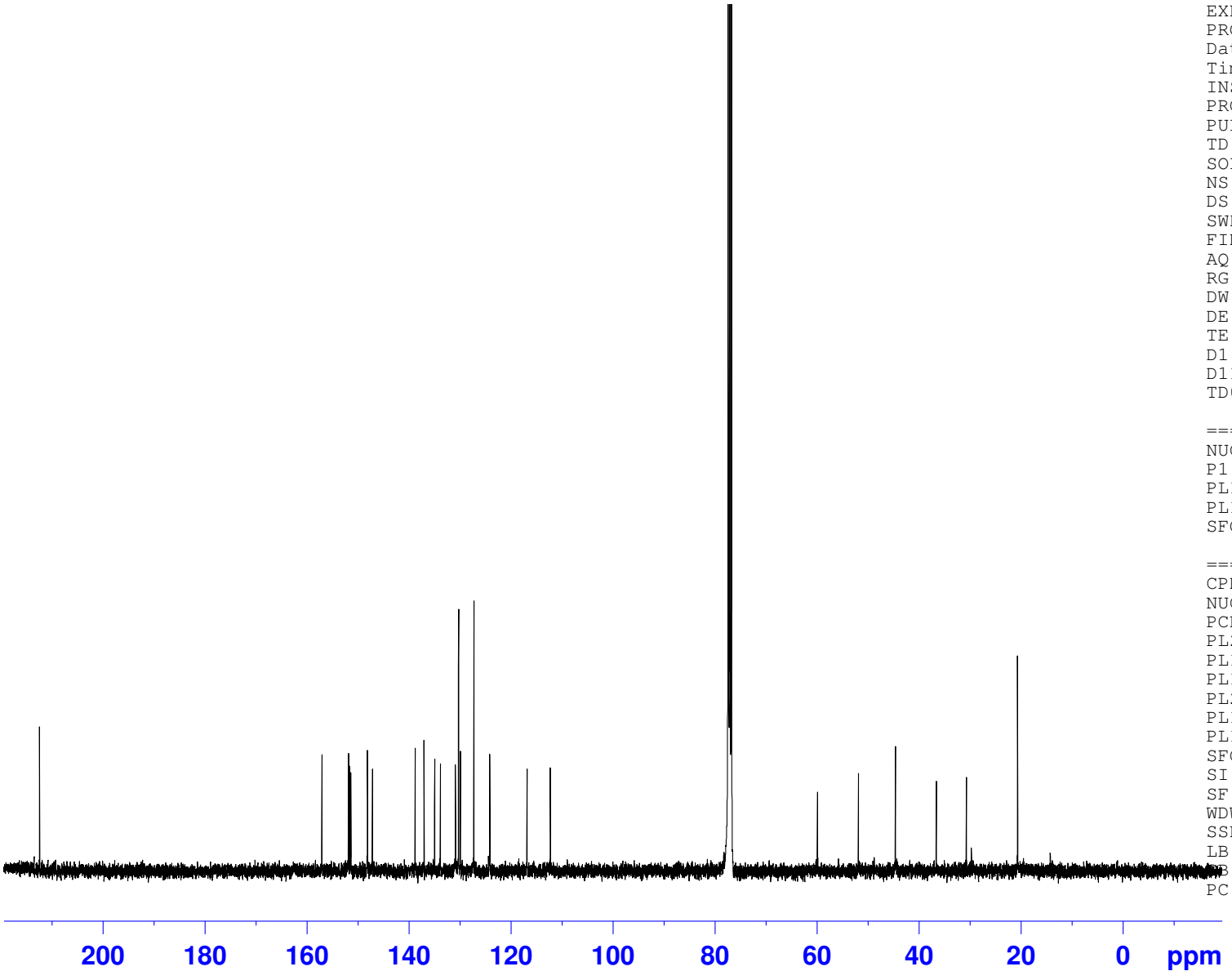
NAME	CNA-653-44
EXPNO	1
PROCNO	1
Date_	20150618
Time	12.21
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	144
DW	60.800 usec
DE	6.50 usec
TE	96.1 K
D1	1.00000000 sec
======== CHANNEL f1 ========	
NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300097 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-653-44, 13C, CDCl3, 400 MHz



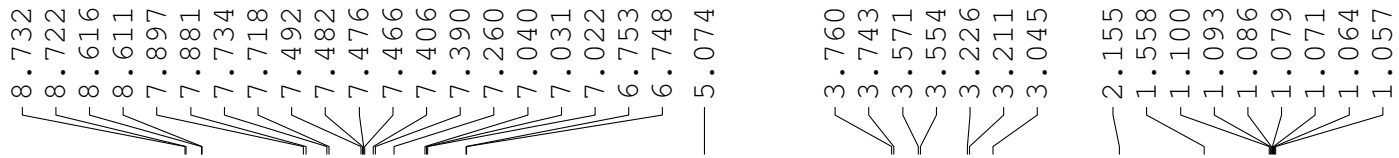
3-67

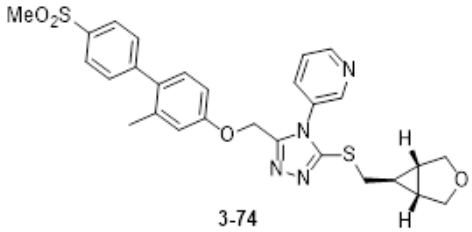
212.45
157.06
151.84
151.63
151.39
148.12
147.13
138.77
137.03
134.96
133.83
130.88
130.27
129.89
127.25
124.13
116.83
112.26
77.36
77.04
76.72
59.86
51.84
44.58
36.57
30.65
20.63



NAME	CNA-653-44
EXPNO	3
PROCNO	1
Date_	20150618
Time	1.54
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	5120
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	298.0 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	5
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-675-32, 1H, CDCl3, 500 MHz

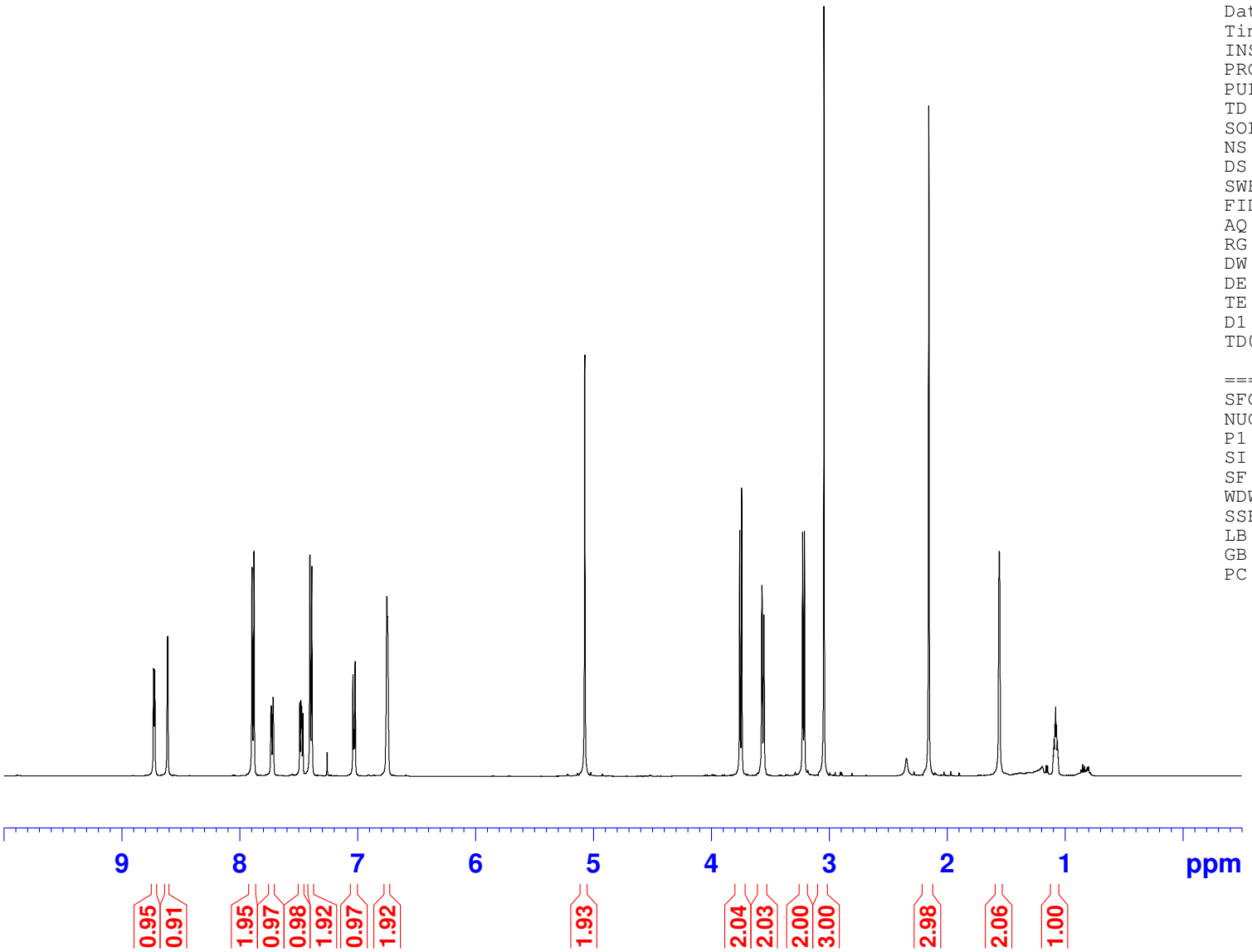




NAME	CNA-675-32
EXPNO	3
PROCNO	1
Date_	20150924
Time	11.33
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	10000.000 Hz
FIDRES	0.152588 Hz
AQ	3.2768500 sec
RG	25.4
DW	50.000 usec
DE	6.50 usec
TE	297.3 K
D1	1.00000000 sec
TD0	1

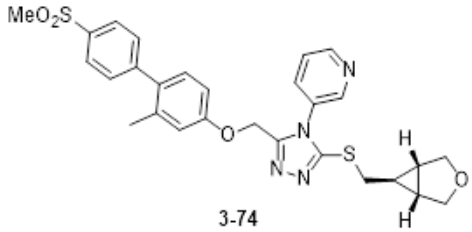
======== CHANNEL f1 ========

SFO1	500.1630887 MHz
NUC1	1H
P1	11.45 usec
SI	65536
SF	500.1600126 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



CNA-675-32, 1H, CDCl3, 500 MHz

157.071
153.571
151.662
151.271
147.955
147.048
138.747
136.958
134.759
133.715
130.840
130.223
129.952
127.194
124.212
116.789
112.265
77.478
77.222
76.967
69.380
59.850
44.512
35.208
20.608
19.443

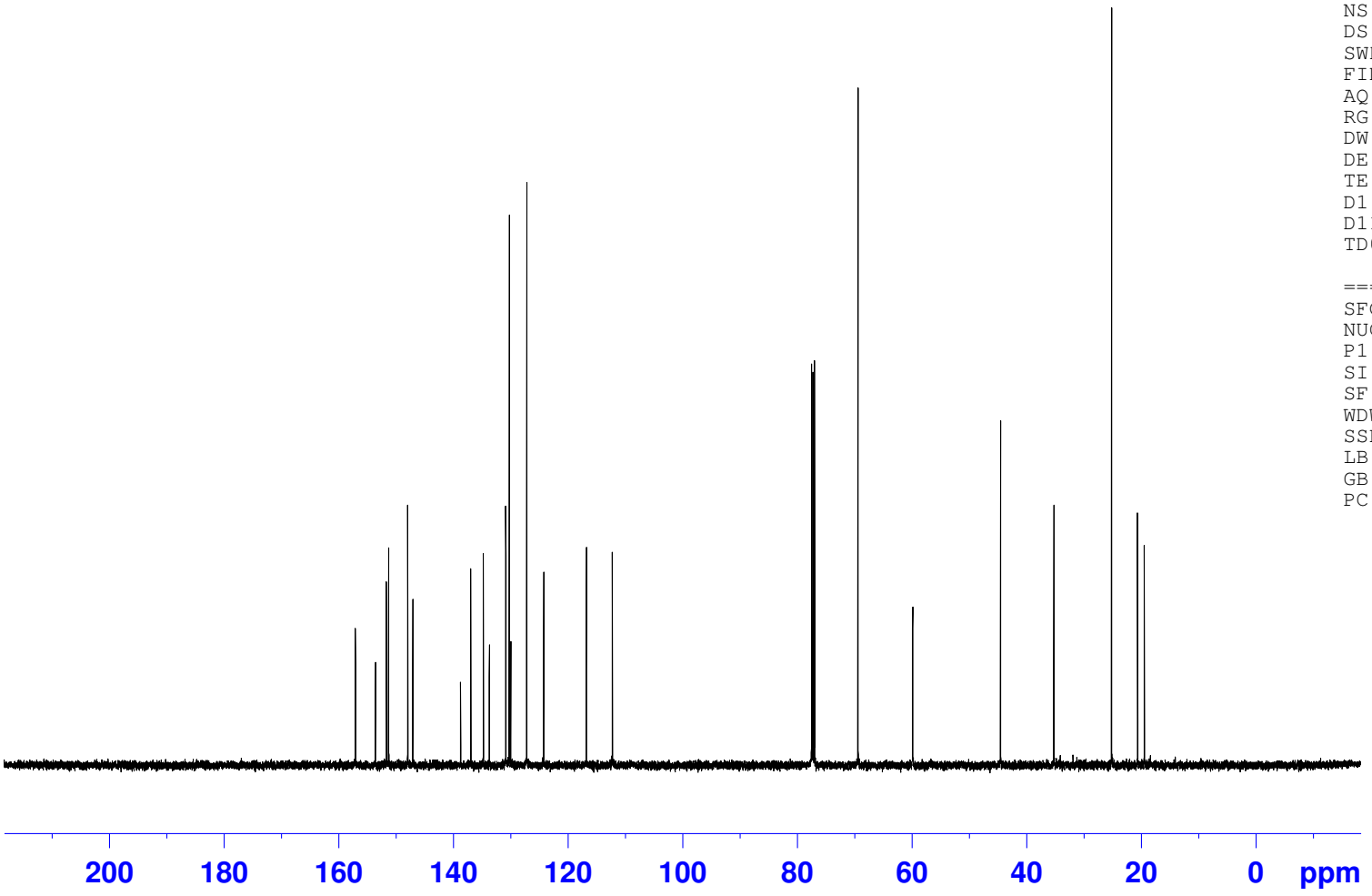


3-74

NAME	CNA-675-32
EXPNO	4
PROCNO	1
Date_	20150924
Time	11.40
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	101
DS	2
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 usec
DE	6.50 usec
TE	297.9 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1

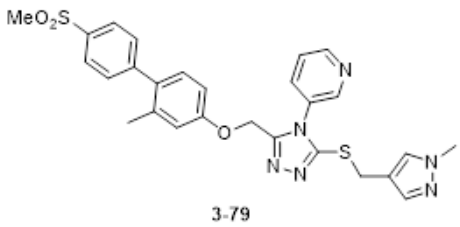
======== CHANNEL f1 ========

SFO1	125.7779086 MHz
NUC1	13C
P1	10.50 usec
SI	32768
SF	125.7653320 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



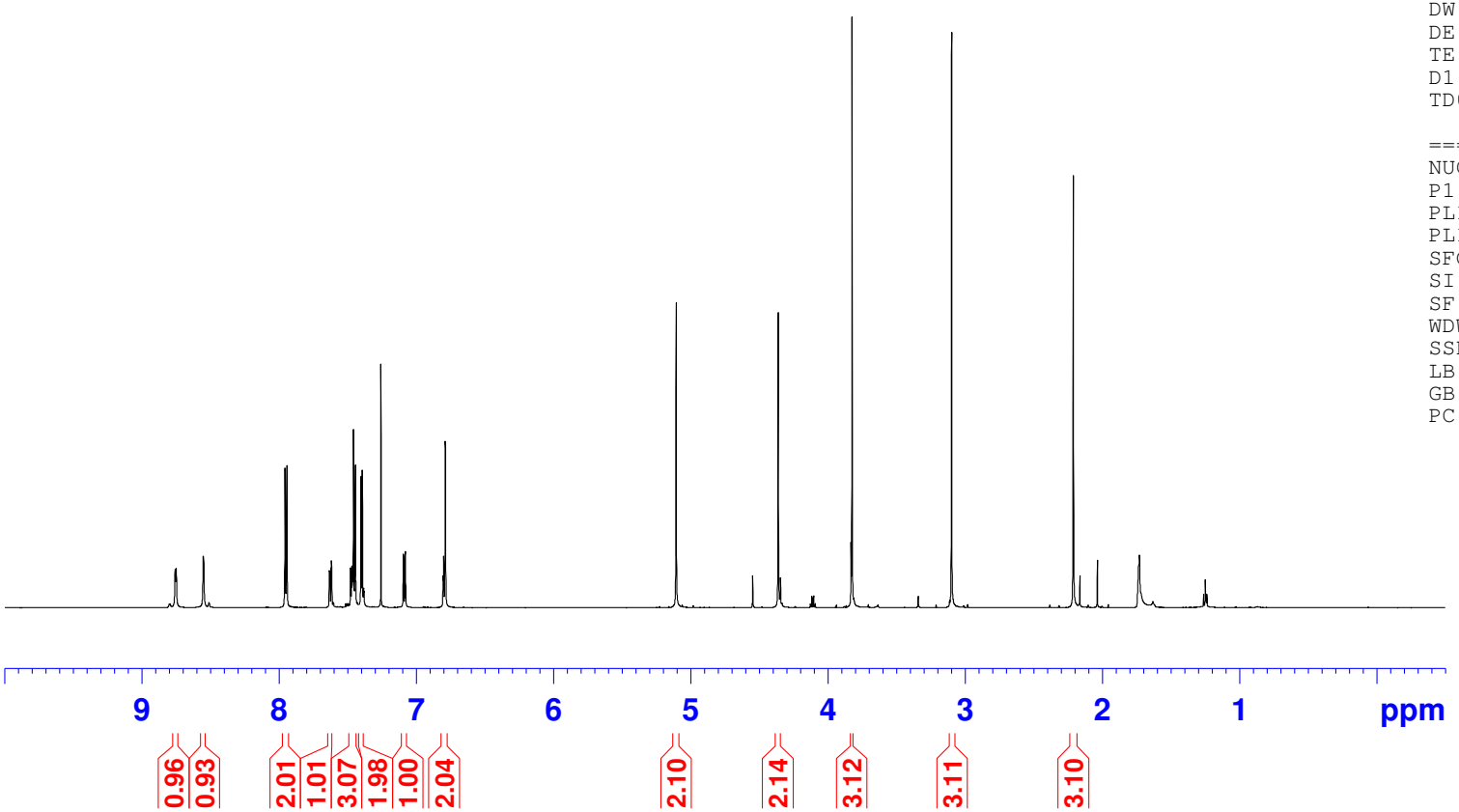
CNA-653-74, 1H, CDCl3, 600 MHz

7.946 7.638 7.635 7.634 7.631 7.624 7.622 7.620 7.618 7.481 7.473 7.467 7.460 7.449 7.446 7.405 7.395 7.260 7.096 7.083 7.082 6.807 6.803 6.790 5.108 4.363 3.825 — 3.100 — 2.212

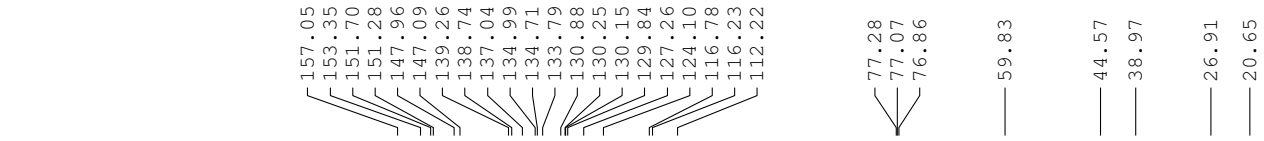


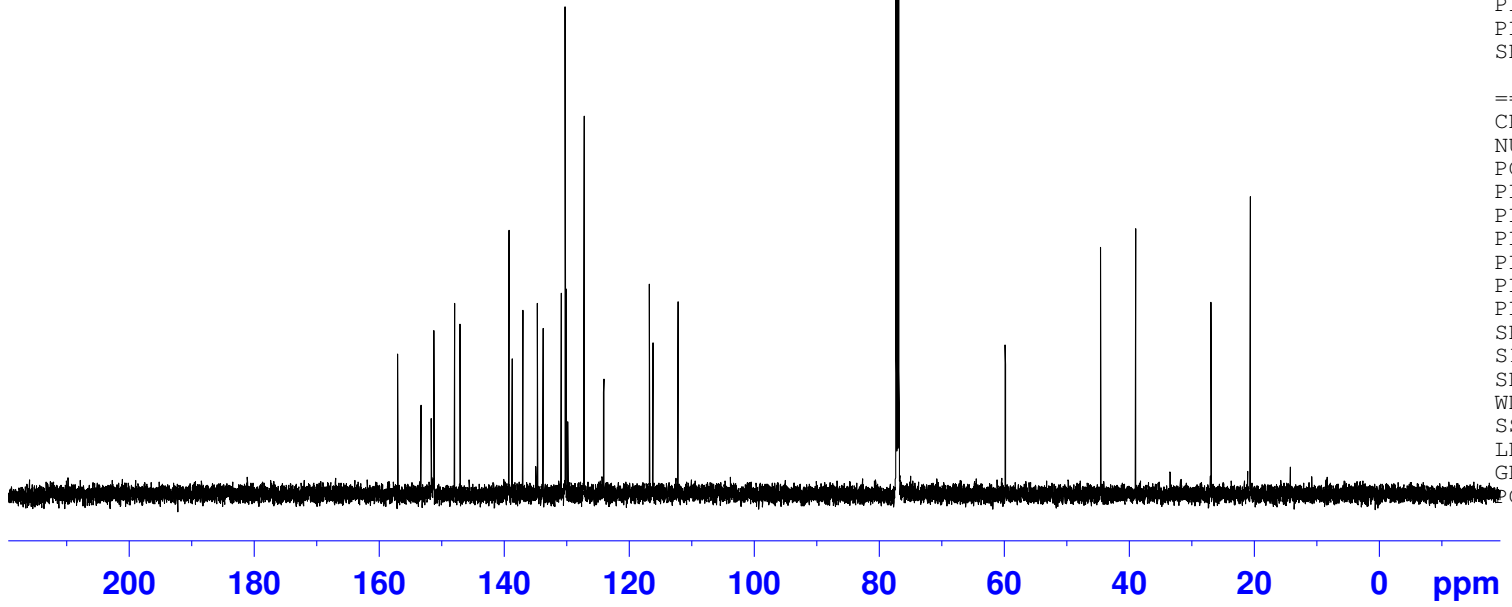
3-79

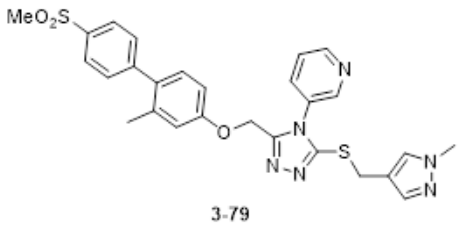
NAME	CNA-653-74	
EXPNO	3	
PROCNO	1	
Date_	20150715	
Time	21.08	
INSTRUM	spect	
PROBHD	5 mm PABBO BB-	
PULPROG	zg30	
TD	65536	
SOLVENT	CDCl3	
NS	16	
DS	2	
SWH	12335.526	Hz
FIDRES	0.188225	Hz
AQ	2.6564426	sec
RG	128	
DW	40.533	usec
DE	6.50	usec
TE	295.1	K
D1	1.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	10.86	usec
PL1	-2.00	dB
PL1W	19.70630455	W
SFO1	600.7137096	MHz
SI	32768	
SF	600.7100142	MHz
WDW	EM	
SSB	0	
LB	0.30	Hz
GB	0	
PC	1.00	



CNA-653-74, 13C, CDCl3, 600 MHz





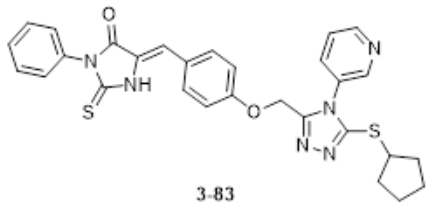


3-79

NAME	CNA-653-74	
EXPNO	2	
PROCNO	1	
Date_	20150715	
Time	20.16	
INSTRUM	spect	
PROBHD	5 mm PABBO BB-	
PULPROG	zgpg30	
TD	65536	
SOLVENT	CDCl3	
NS	512	
DS	4	
SWH	36057.691	Hz
FIDRES	0.550197	Hz
AQ	0.9088159	sec
RG	203	
DW	13.867	usec
DE	6.50	usec
TE	295.3	K
D1	2.00000000	sec
D11	0.03000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	13C	
P1	11.50	usec
PL1	0.00	dB
PL1W	97.46119690	W
SFO1	151.0637542	MHz
======== CHANNEL f2 ========		
CPDPRG2	waltz16	
NUC2	1H	
PCPD2	70.00	usec
PL2	-2.00	dB
PL12	14.19	dB
PL13	120.00	dB
PL2W	19.70630455	W
PL12W	0.47381112	W
PL13W	0.00000000	W
SFO2	600.7124028	MHz
SI	32768	
SF	151.0486500	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

CNA-675-6, 1H, CDCl3, 300 MHz

8.794 8.790 8.778 8.774 8.540 8.533 7.718 7.713 7.705 7.691 7.686 7.678 7.538 7.516 7.507 7.490 7.476 7.456 7.428 7.381 7.376 7.353 7.260 6.968 6.939 6.749 5.145 4.050 4.028 2.215 2.209 2.200 2.191 2.167 1.722 1.708 1.693 1.673 1.658 1.642 1.635 1.623 1.613 1.602

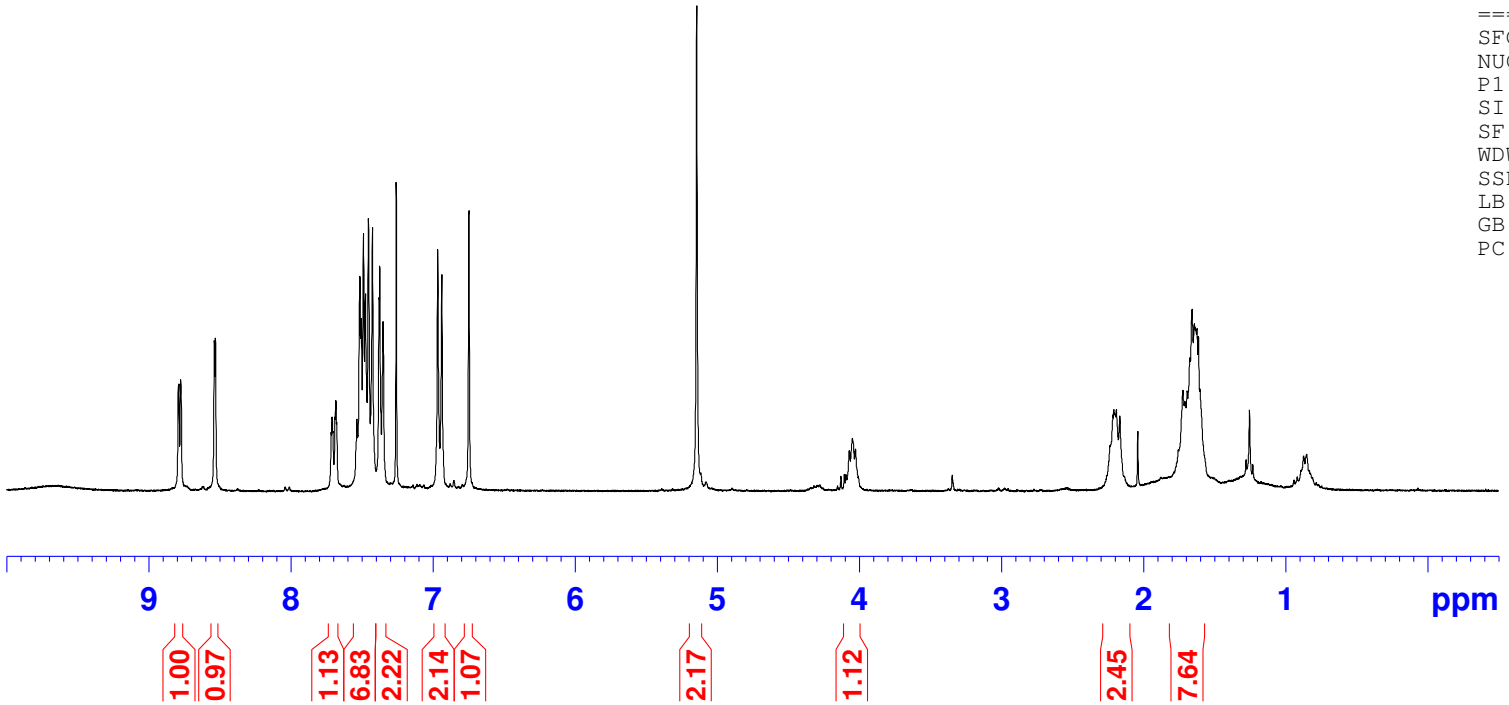


3-83

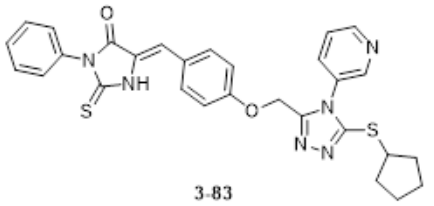
NAME	CNA-675-6
EXPNO	1
PROCNO	1
Date_	20150826
Time	22.37
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6188.119 Hz
FIDRES	0.188846 Hz
AQ	2.6477044 sec
RG	161
DW	80.800 usec
DE	6.50 usec
TE	-922.4 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

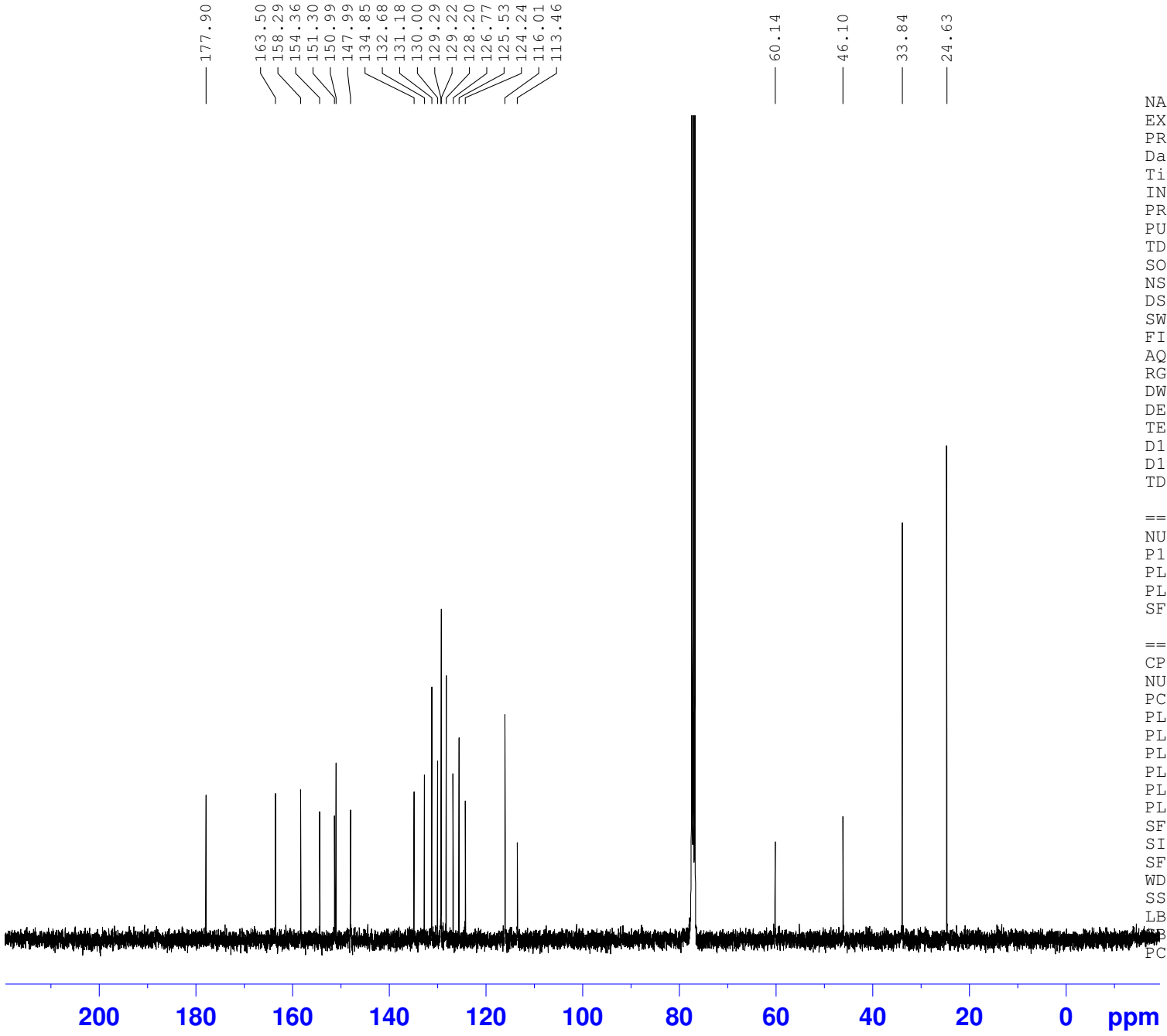
SFO1	300.2318540 MHz
NUC1	1H
P1	12.71 usec
SI	32768
SF	300.2300087 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00



CNA-675-6, 1H, CDCl3, 400 MHz

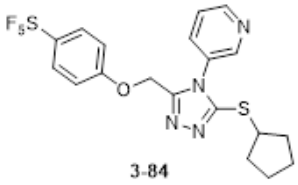


3-83

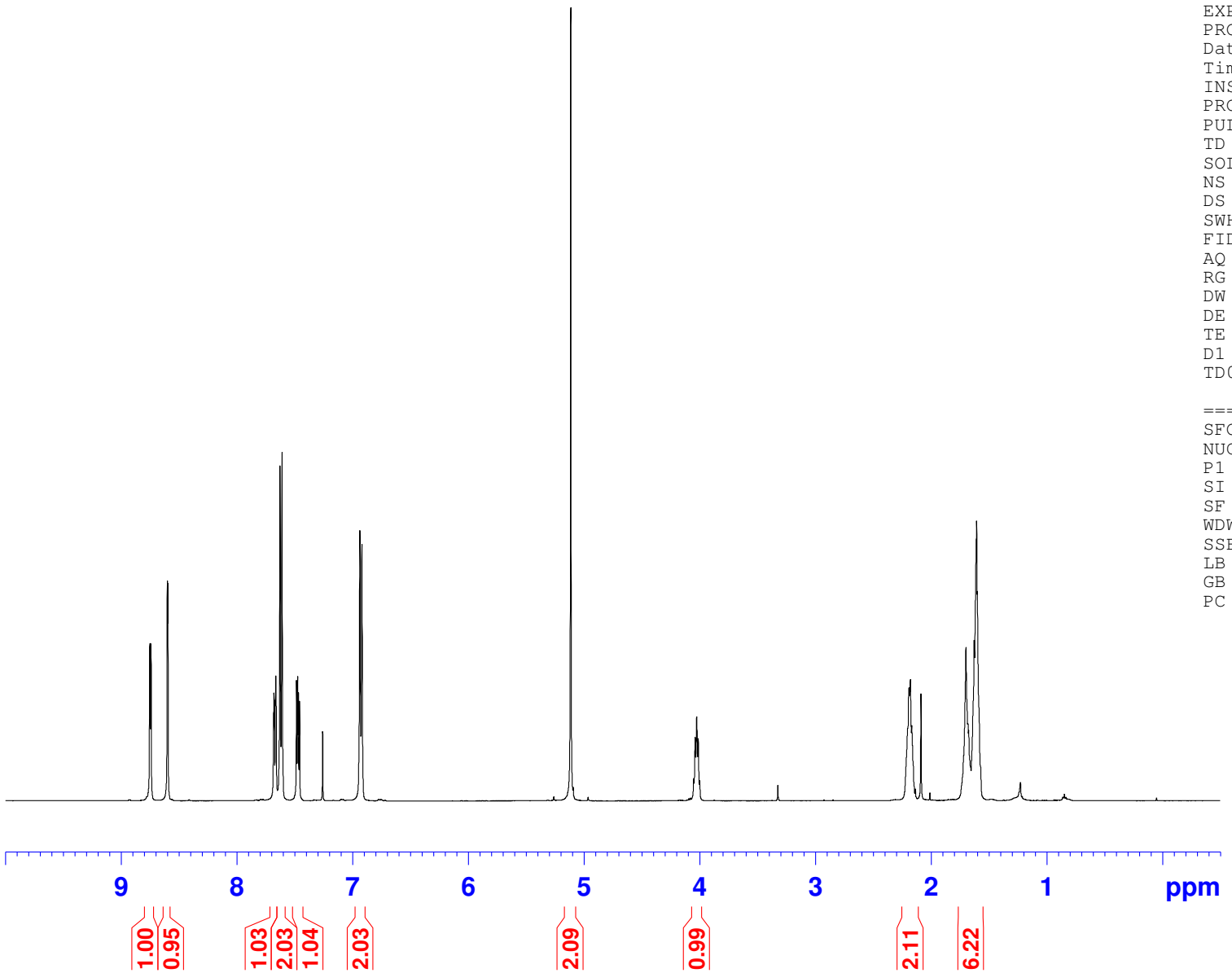


NAME	CNA-675-6
EXPNO	1
PROCNO	1
Date_	20150826
Time	23.03
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	2100
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	296.1 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	30
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-653-93, 1H, CDCl3, 500 MHz



8.755 8.753 8.745 8.744 8.603 8.598 7.681 7.665 7.629 7.611 7.486 7.476 7.470 7.460 7.260 6.939 6.921 5.116 4.053 4.040 4.027 4.014 4.000 2.201 2.193 2.190 2.185 2.179 2.167 1.699 1.691 1.682 1.675 1.628 1.627 1.607 1.600



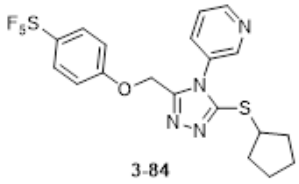
NAME	CNA-653-93
EXPNO	1
PROCNO	1
Date_	20150813
Time	11.19
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	10000.000 Hz
FIDRES	0.152588 Hz
AQ	3.2768500 sec
RG	32
DW	50.000 usec
DE	6.50 usec
TE	297.1 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

SFO1	500.1630887 MHz
NUC1	1H
P1	11.45 usec
SI	65536
SF	500.1600128 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-653-93, 13C, CDCl3, 500 MHz

158.902
154.386
151.344
150.604
147.966
147.735
147.594
147.451
134.645
129.943
127.872
127.837
127.801
124.146
114.406
77.327
77.073
76.819
60.070
46.079
33.813
24.587

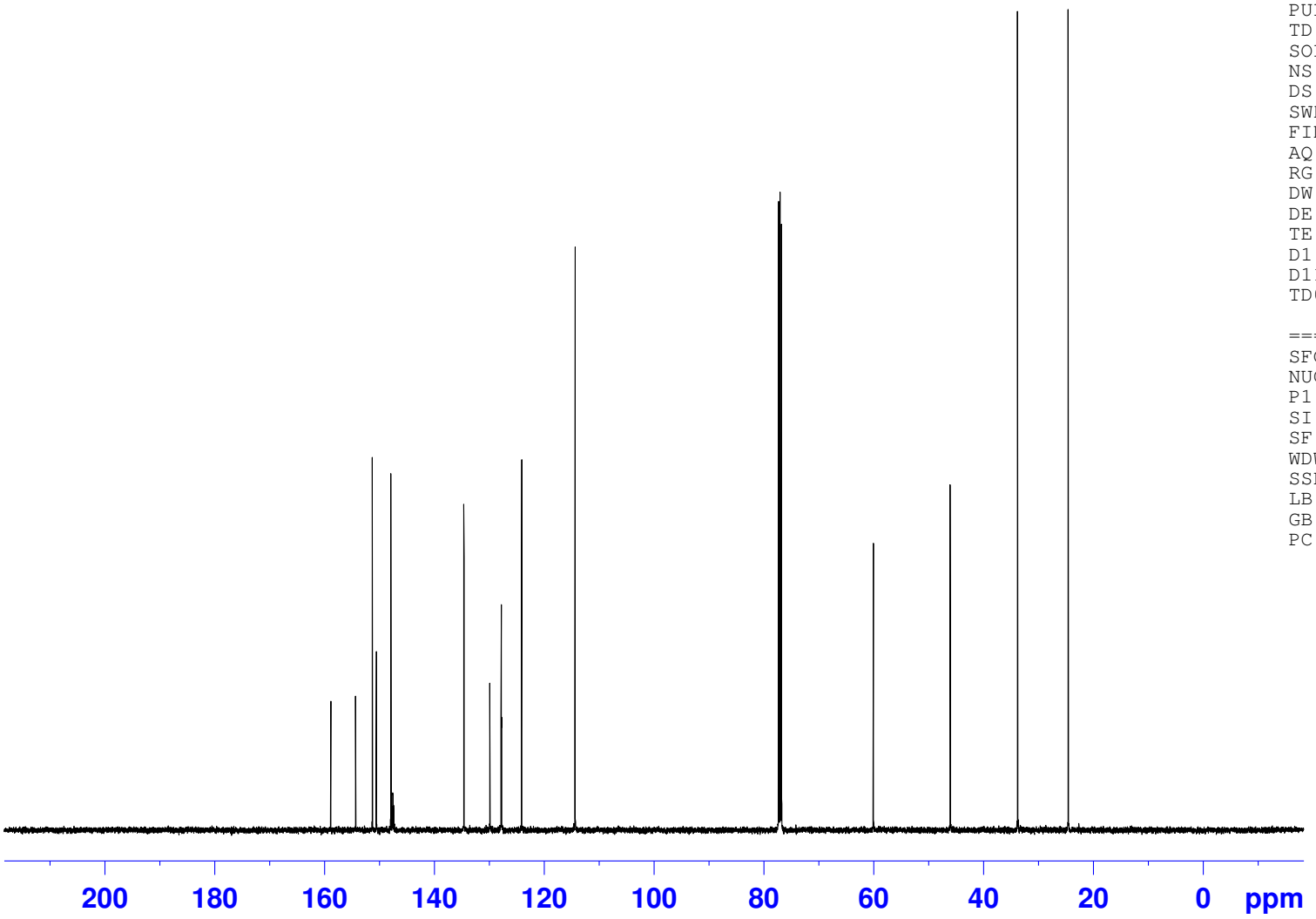


3-84

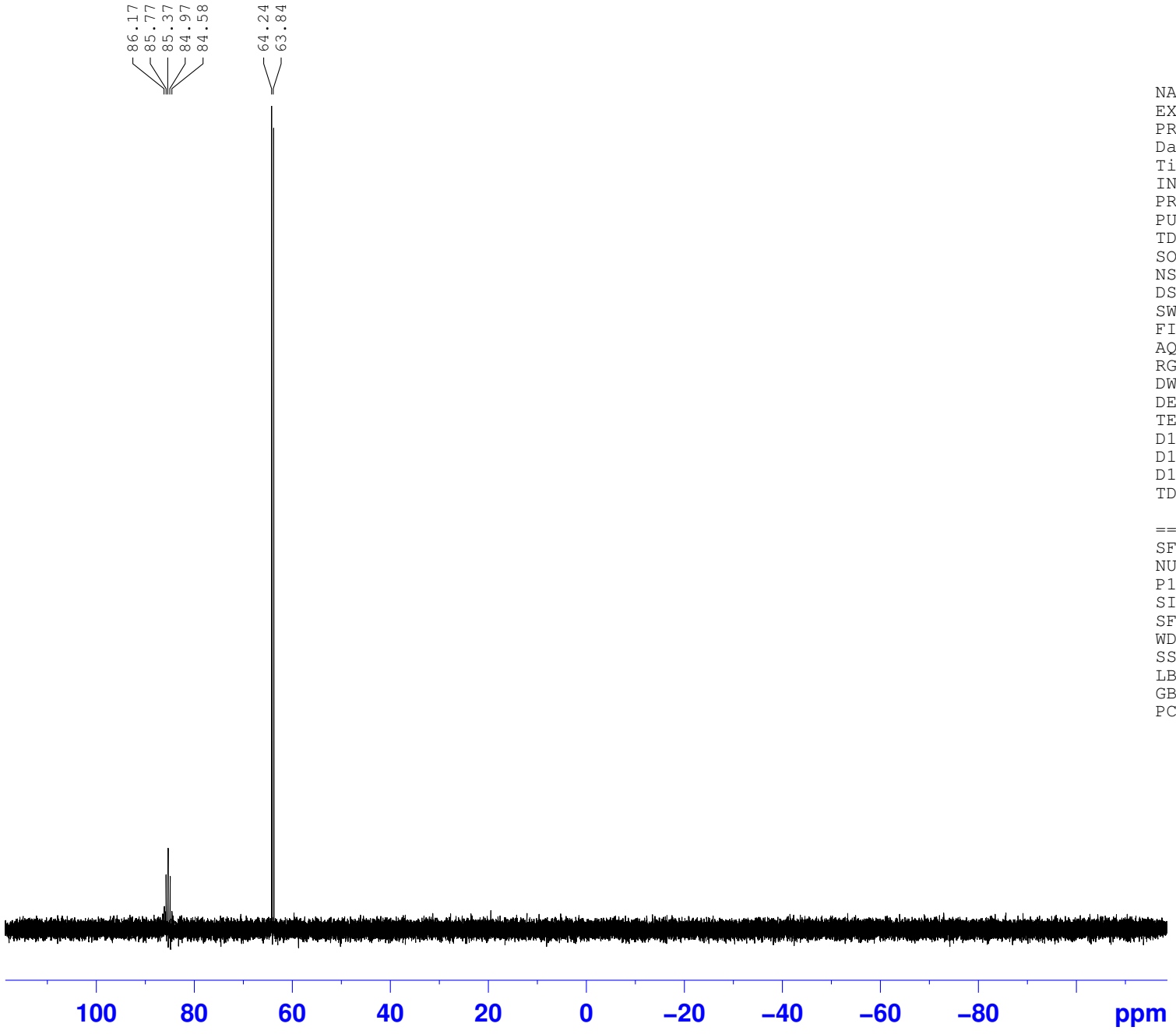
NAME	CNA-653-93
EXPNO	2
PROCNO	1
Date_	20150813
Time	11.47
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	2
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 usec
DE	6.50 usec
TE	297.8 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1

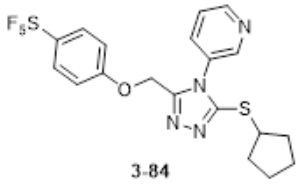
======== CHANNEL f1 ========

SFO1	125.7779086 MHz
NUC1	13C
P1	10.50 usec
SI	32768
SF	125.7653320 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



CNA-653-93, 19F, CDCl3, 400 MHz



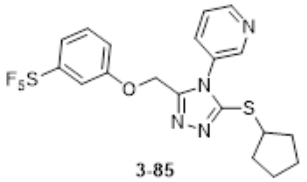


3-84

NAME	CNA-653-93	
EXPNO	4	
PROCNO	1	
Date_	20151019	
Time	17.17	
INSTRUM	spect	
PROBHD	5 mm PABBO BB-	
PULPROG	zgfhigqn.2	
TD	131072	
SOLVENT	CDCl3	
NS	16	
DS	4	
SWH	89285.711	Hz
FIDRES	0.681196	Hz
AQ	0.7340532	sec
RG	203	
DW	5.600	usec
DE	6.50	usec
TE	96.5	K
D1	1.00000000	sec
D11	0.03000000	sec
D12	0.00002000	sec
TD0	1	
======== CHANNEL f1 ========		
SFO1	376.4983662	MHz
NUC1	19F	
P1	14.20	usec
SI	65536	
SF	376.4983662	MHz
WDW	EM	
SSB	0	
LB	0.30	Hz
GB	0	
PC	1.00	

CNA-653-94, 1H, CDCl3, 300 MHz

8.744 8.729 8.611 8.604 7.697 7.670 7.488 7.472 7.461 7.445 7.327 7.312 7.260 7.160 7.098 7.087 5.102 4.056 4.034 4.012 3.991 2.215 2.205 2.176 2.158 2.139 1.690 1.676 1.660 1.626 1.611 1.601 1.592 1.583



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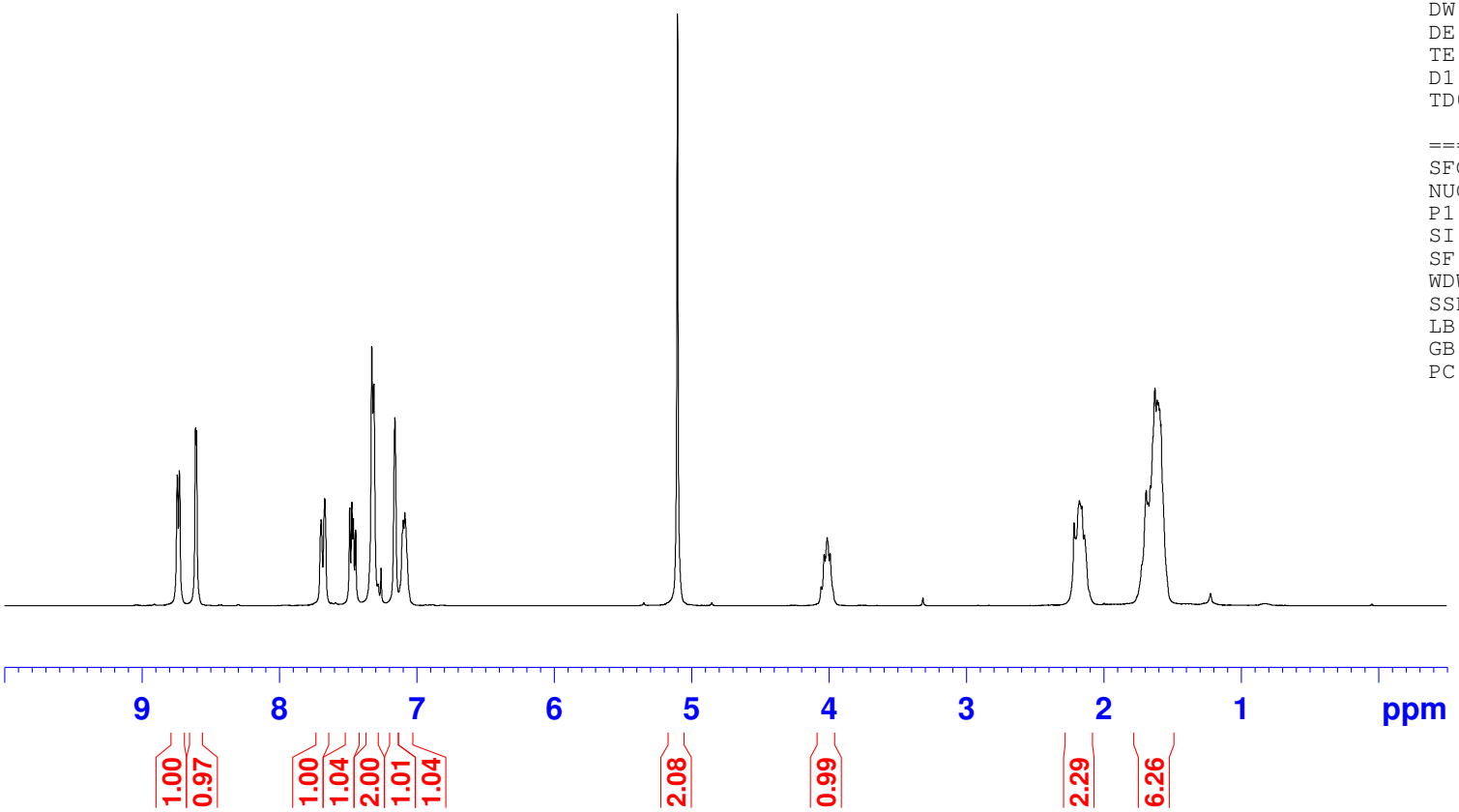
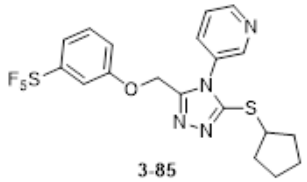
NAME	CNA-653-94
EXPNO	1
PROCNO	1
Date_	20150813
Time	2.03
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	6188.119 Hz
FIDRES	0.188846 Hz
AQ	2.6477044 sec
RG	57
DW	80.800 usec
DE	6.50 usec
TE	-922.2 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

SFO1	300.2318540 MHz
NUC1	1H
P1	12.71 usec
SI	32768
SF	300.2300087 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00



CNA-653-94, 13C, CDCl3, 300 MHz



3-85

157.03
154.86
154.63
154.39
154.23
151.31
150.67
147.89
134.68
129.99
129.74
124.13
119.47
119.40
119.34
117.58
113.61
113.54
113.48

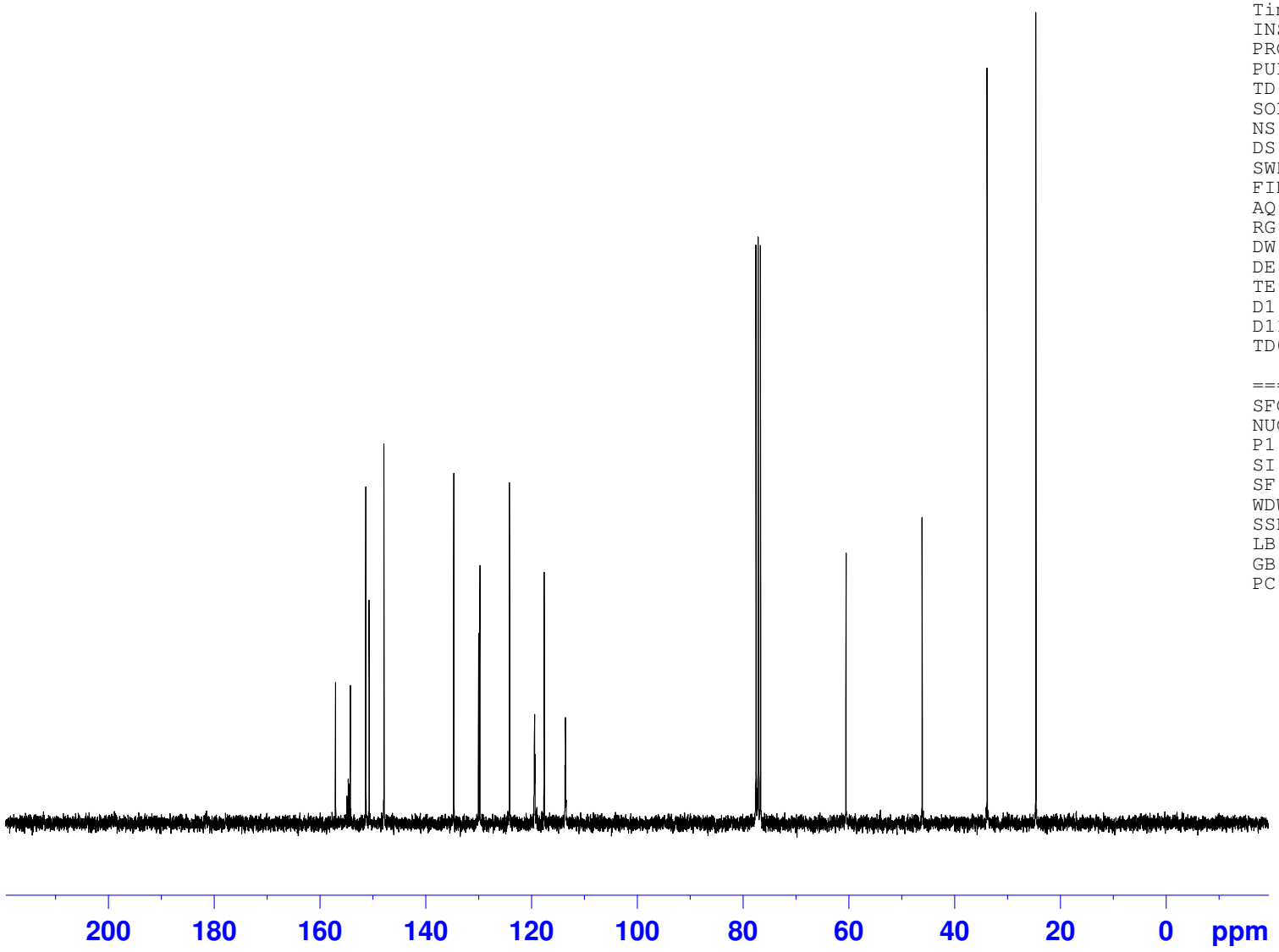
77.51
77.29
77.09
76.67

60.49

46.10

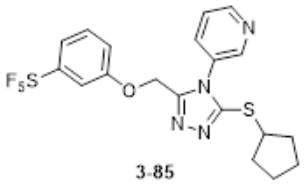
33.79

24.57

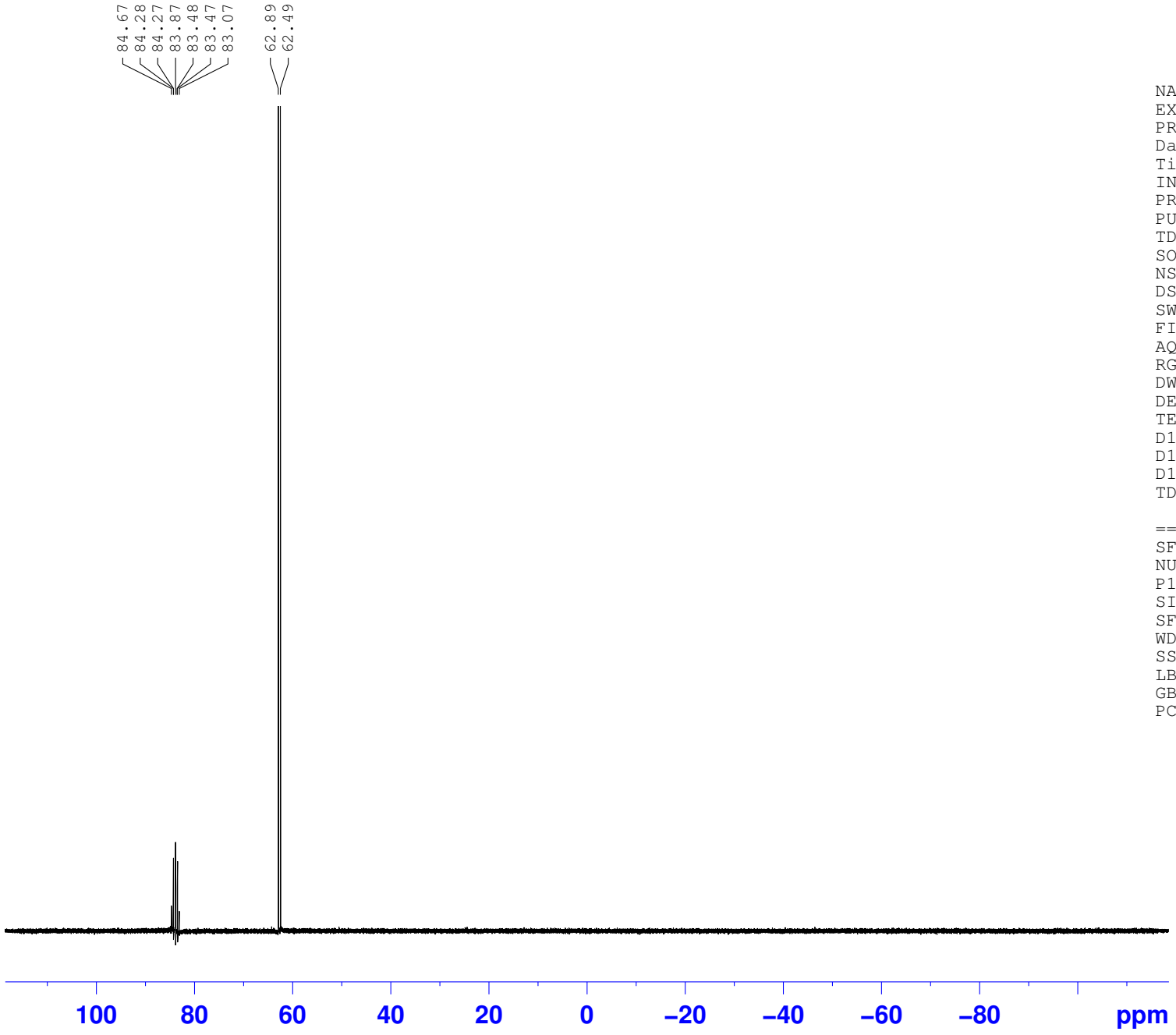


NAME	CNA-653-94
EXPNO	2
PROCNO	1
Date_	20150813
Time	2.28
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	256
DS	4
SWH	18028.846 Hz
FIDRES	0.275098 Hz
AQ	1.8175818 sec
RG	256
DW	27.733 usec
DE	6.50 usec
TE	-922.4 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	75.5004428 MHz
NUC1	13C
P1	12.00 usec
SI	32768
SF	75.4928940 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-653-94, 19F, CDCl3, 400 MHz

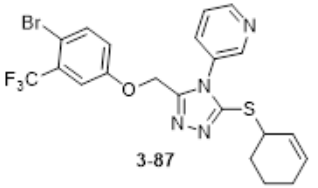


3-85



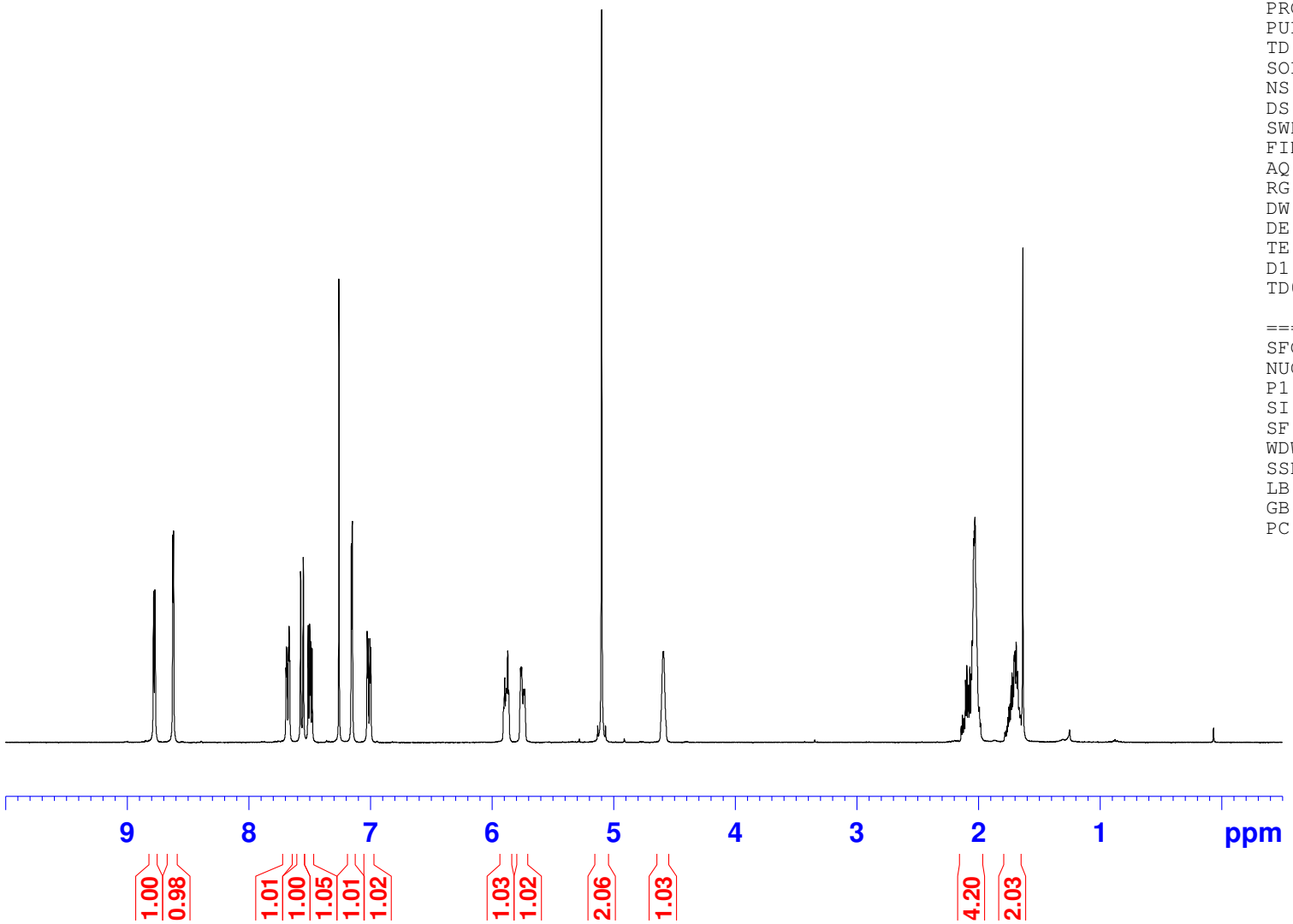
NAME	CNA-653-94
EXPNO	4
PROCNO	1
Date_	20151019
Time	17.23
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	89285.711 Hz
FIDRES	0.681196 Hz
AQ	0.7340532 sec
RG	203
DW	5.600 usec
DE	6.50 usec
TE	96.3 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	376.4983662 MHz
NUC1	19F
P1	14.20 usec
SI	65536
SF	376.4983662 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-710-22, 1H, CDCl3, 400 MHz

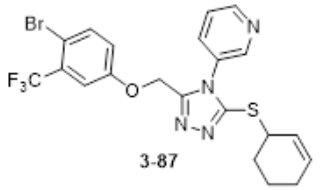


8.786 8.783 8.774 8.771 8.627 8.621 7.692 7.690 7.686 7.676 7.672 7.670 7.665 7.576 7.554 7.513 7.502 7.493 7.481 7.260 7.158 7.150 7.028 7.021 7.006 6.999 5.873 5.871 5.761 5.757 5.100 4.595 4.589 2.095 2.071 2.052 2.039 2.035 2.030 2.027 2.021 1.706 1.699 1.690

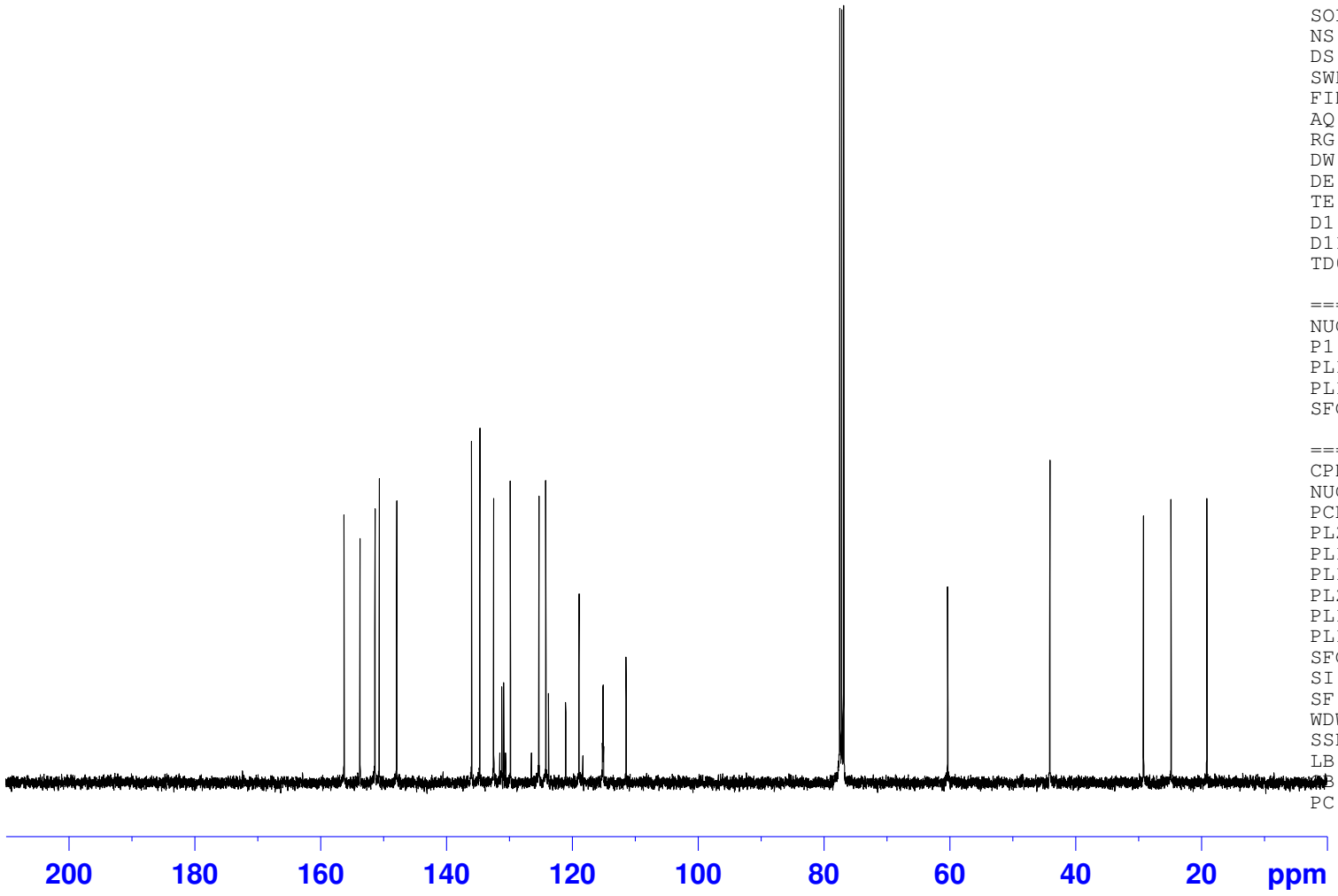
NAME	CNA-710-22
EXPNO	1
PROCNO	1
Date_	20160414
Time	11.32
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8012.820 Hz
FIDRES	0.122266 Hz
AQ	4.0894966 sec
RG	128
DW	62.400 usec
DE	6.50 usec
TE	96.4 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	400.1324710 MHz
NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300109 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



CNA-710-22, 13C, CDCl3, 400 MHz

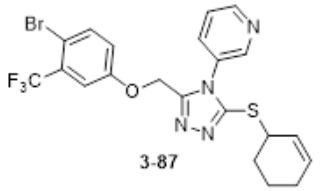


156.27
153.72
151.36
150.67
147.90
135.99
134.69
132.48
131.52
131.21
130.89
130.58
129.83
126.47
125.27
124.19
123.75
121.03
118.91
118.31
115.13
115.07
115.02
111.42
77.47
77.15
76.83
60.31
44.06
29.17
24.79
19.10



NAME	CNA-710-22
EXPNO	1
PROCNO	1
Date_	20160414
Time	11.48
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	256
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	57
DW	20.800 usec
DE	6.50 usec
TE	296.2 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-710-22, 19F, CDCl3, 400 MHz



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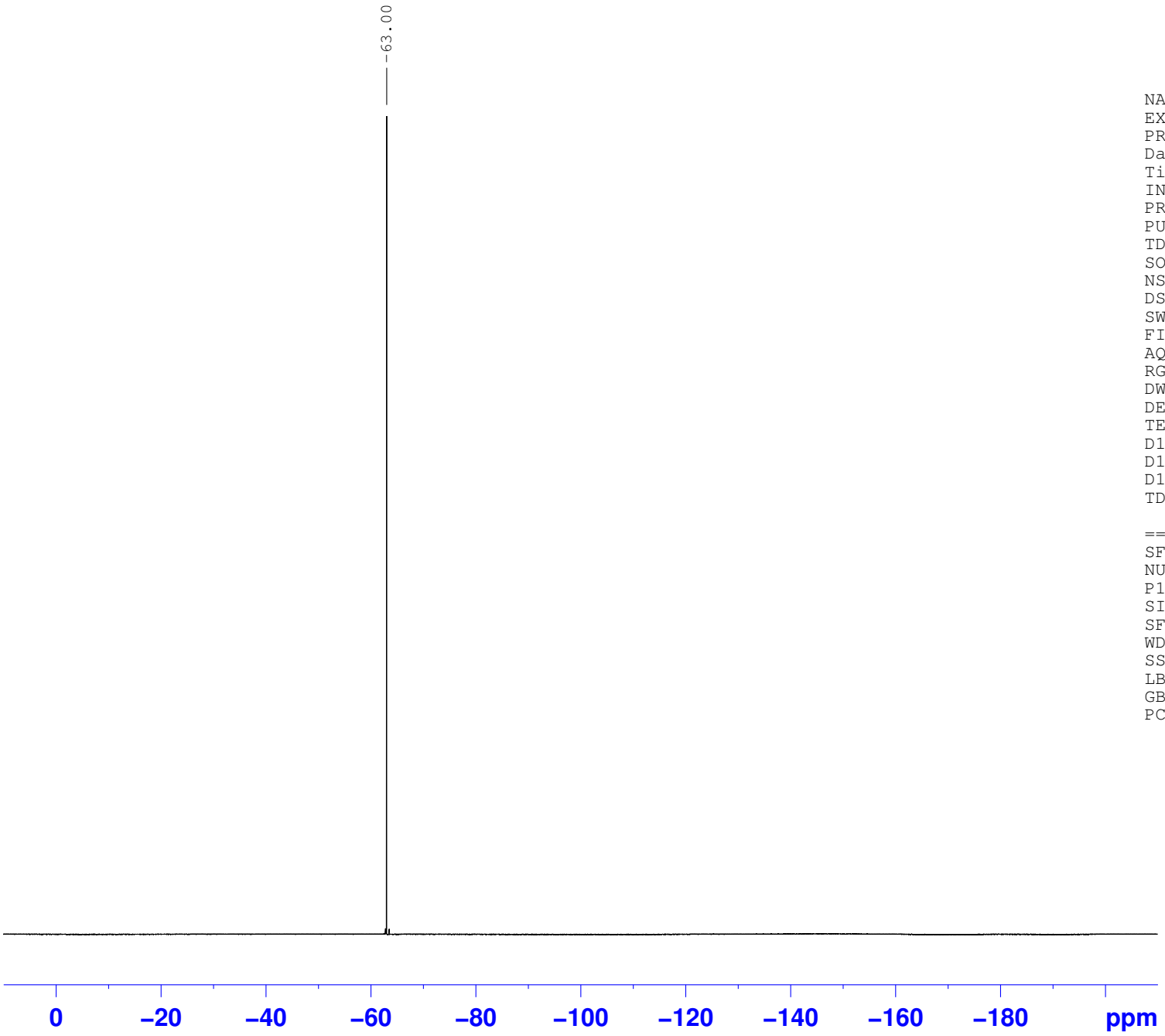
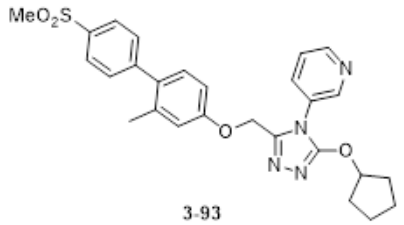


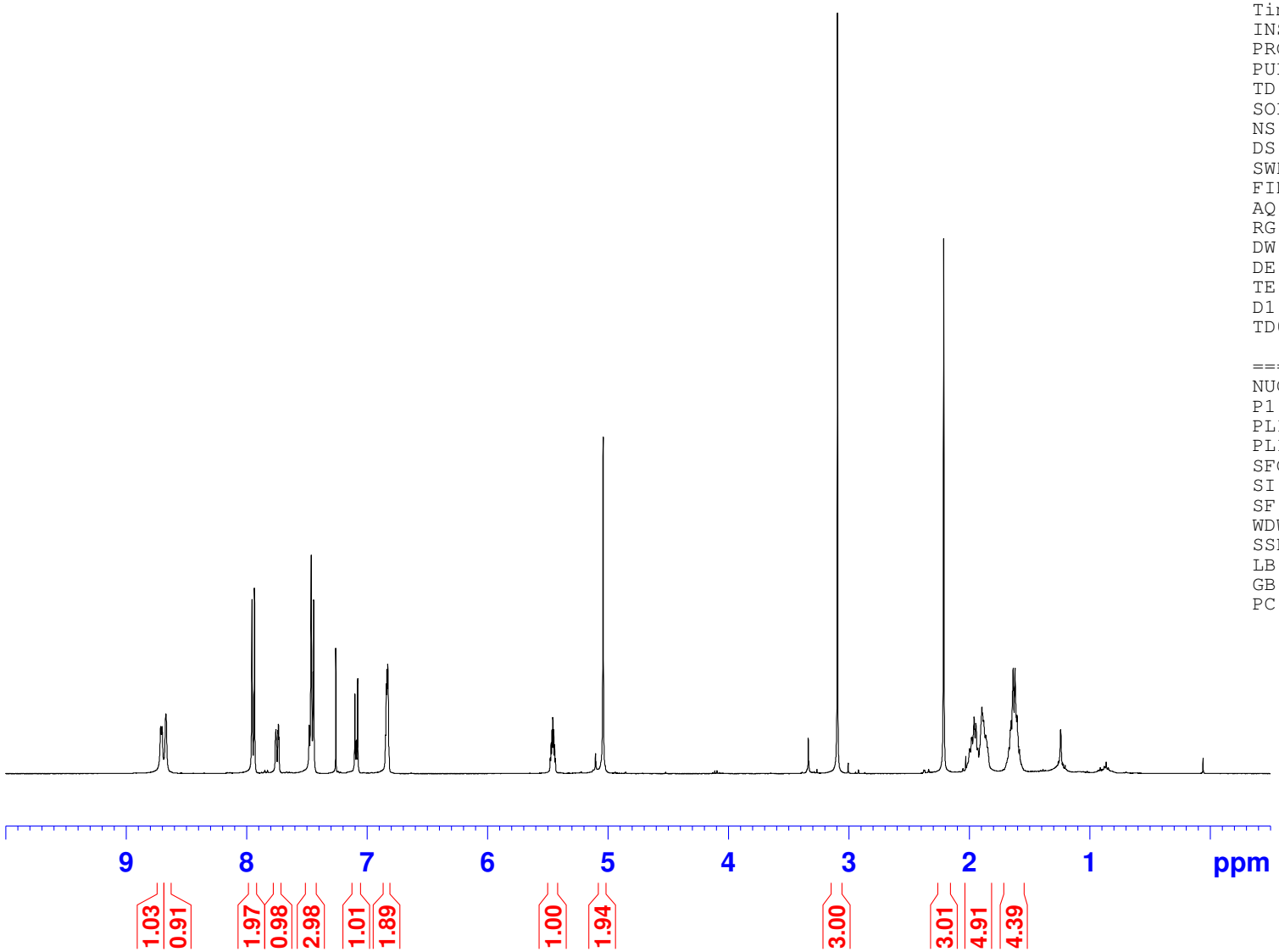
NAME	CNA-710-22
EXPNO	2
PROCNO	1
Date_	20160414
Time	11.34
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	89285.711 Hz
FIDRES	0.681196 Hz
AQ	0.7340532 sec
RG	203
DW	5.600 usec
DE	6.50 usec
TE	96.4 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	376.4607164 MHz
NUC1	19F
P1	14.20 usec
SI	65536
SF	376.4983662 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-675-66, 1H, CDCl3, 400 MHz



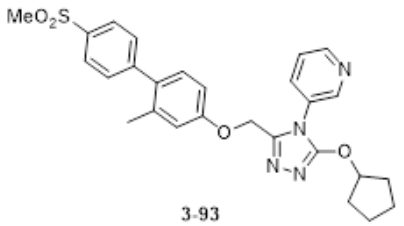
3-93

8.711 8.700 8.669 7.957 7.936 7.763 7.759 7.753 7.742 7.738 7.737 7.733 7.482 7.465 7.449 7.444 7.260 7.102 7.091 7.079 6.847 6.841 6.836 6.829 5.465 5.458 5.452 5.041 3.095 2.212 1.981 1.976 1.960 1.955 1.945 1.895 1.890 1.881 1.864 1.660 1.651 1.636 1.619 1.603



NAME	CNA-675-66
EXPNO	1
PROCNO	1
Date_	20151118
Time	19.36
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	80.6
DW	60.800 usec
DE	6.50 usec
TE	295.8 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300123 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-675-66, 13C, CDCl3, 400 MHz



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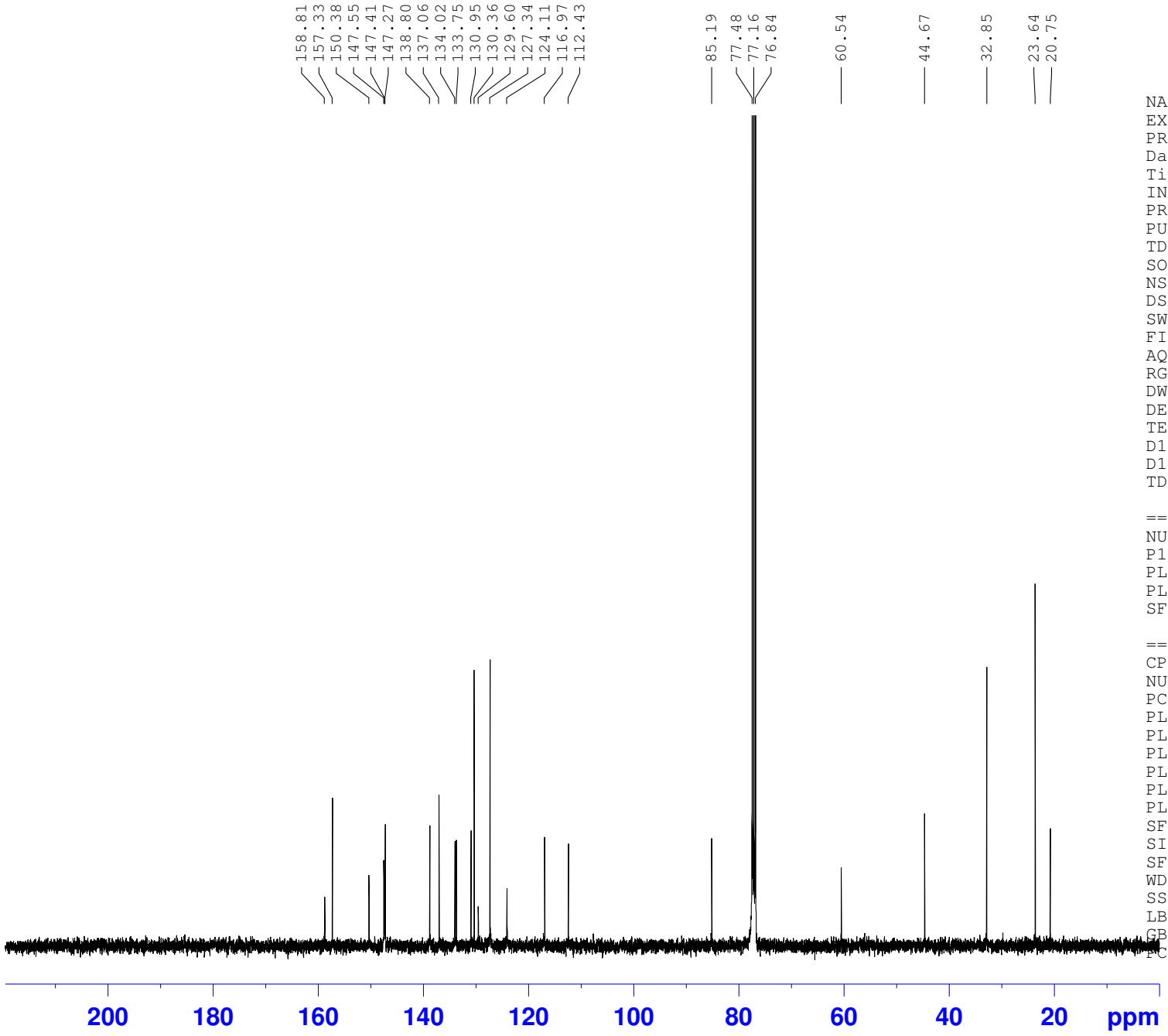
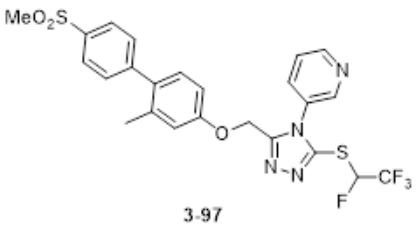


NAME	CNA-675-66
EXPNO	2
PROCNO	1
Date_	20151118
Time	19.50
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	649
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	296.0 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	4
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379051 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-653-79A, 1H, CDCl3, 500 MHz



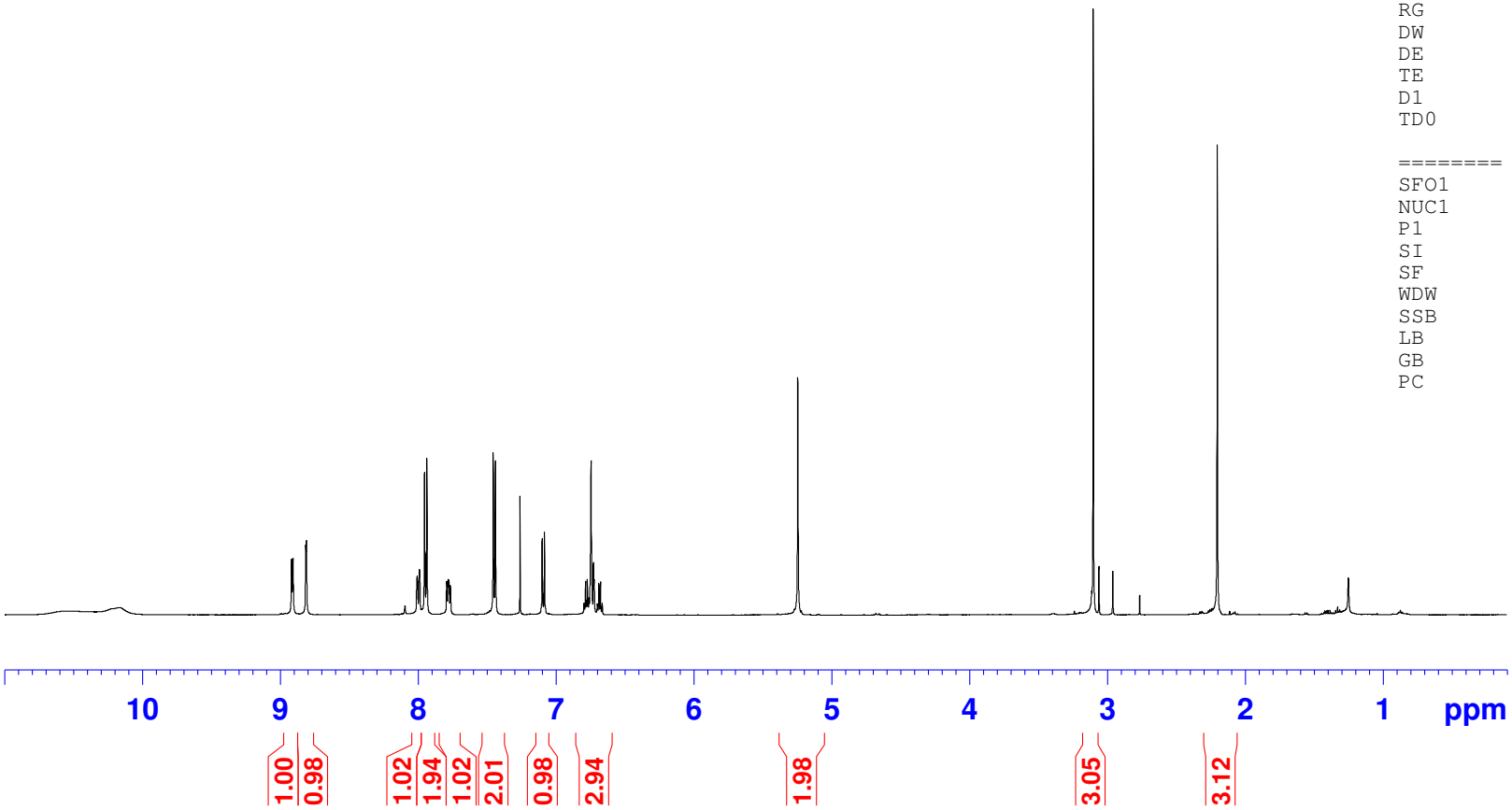
3-97

8.916
8.906
8.813
8.809
8.006
7.989
7.952
7.936
7.792
7.782
7.776
7.765
7.454
7.437
7.260
7.099
7.082
6.784
6.771
6.744
6.726
6.721
6.687
6.675
5.245

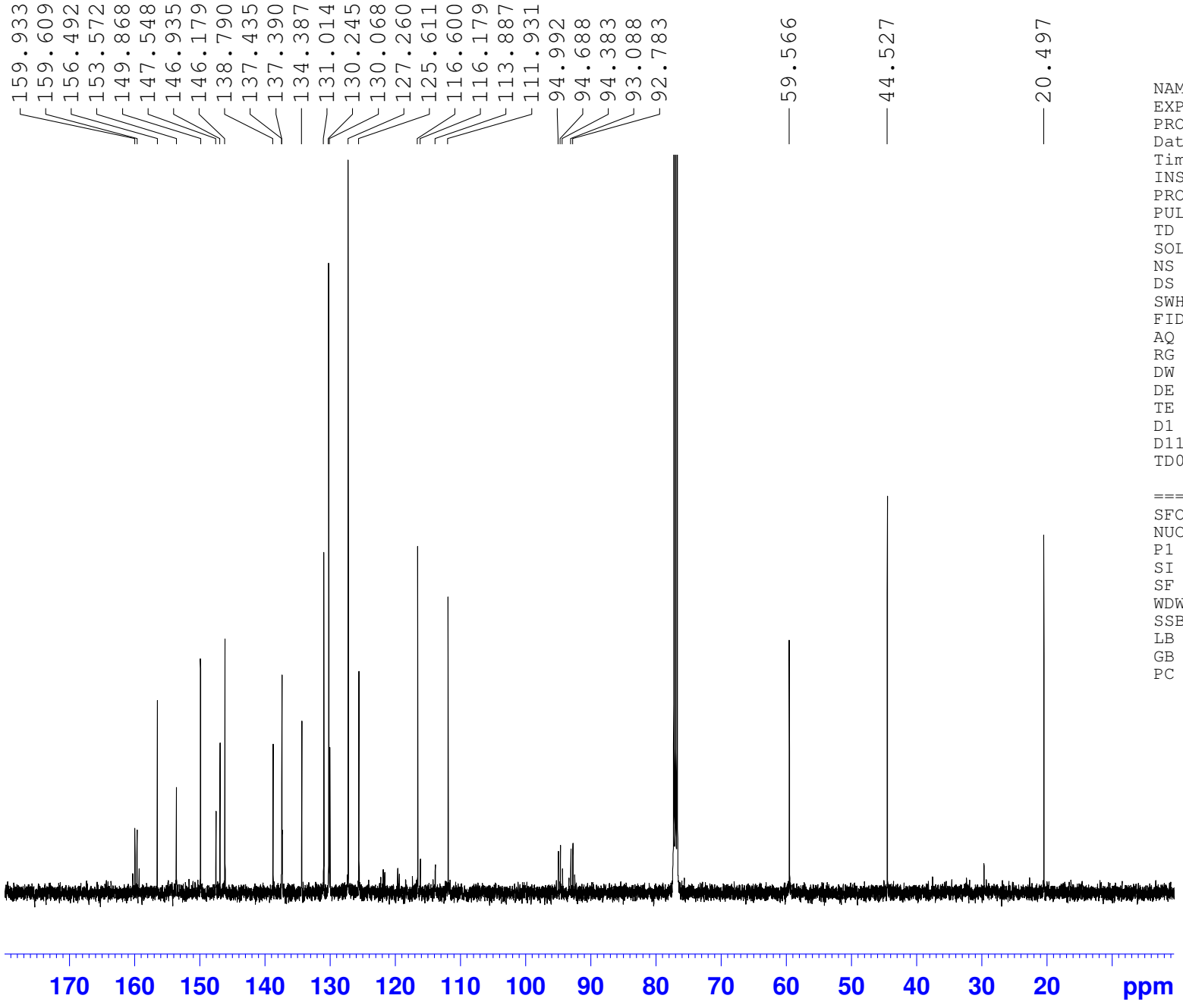
3.102

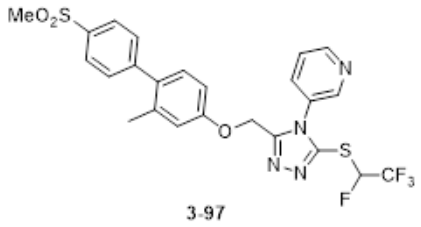
2.202

NAME	CNA-653-79A-H
EXPNO	1
PROCNO	1
Date_	20150724
Time	21.16
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	10000.000 Hz
FIDRES	0.152588 Hz
AQ	3.2768500 sec
RG	90.5
DW	50.000 use
DE	6.50 use
TE	297.2 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 =======	
SFO1	500.1630887 MH:
NUC1	1H
P1	11.45 use
SI	65536
SF	500.1600129 MH:
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



CNA-653-79A, 13C, CDCl3, 500 MHz

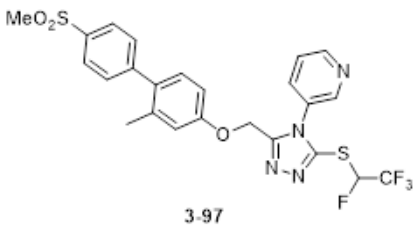




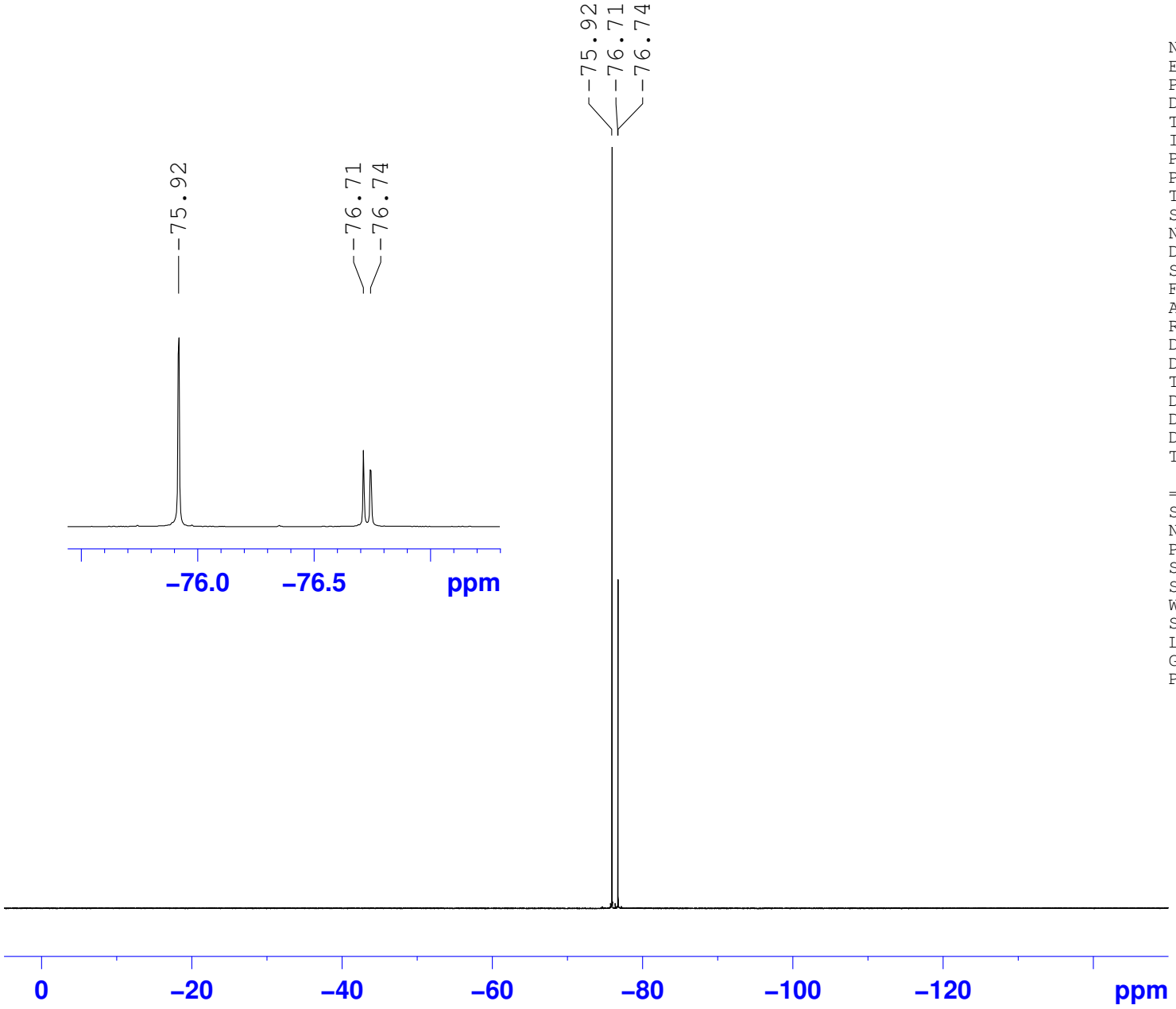
3-97

NAME	CNA-653-79A
EXPNO	2
PROCNO	1
Date_	20150724
Time	22.25
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1280
DS	2
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 use
DE	6.50 use
TE	299.2 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 =======	
SFO1	125.7779086 MHz
NUC1	13C
P1	10.50 use
SI	32768
SF	125.7653320 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-653-79A, 19F, CDCl3, 500 MHz

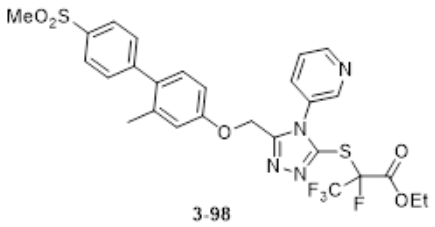


3-97



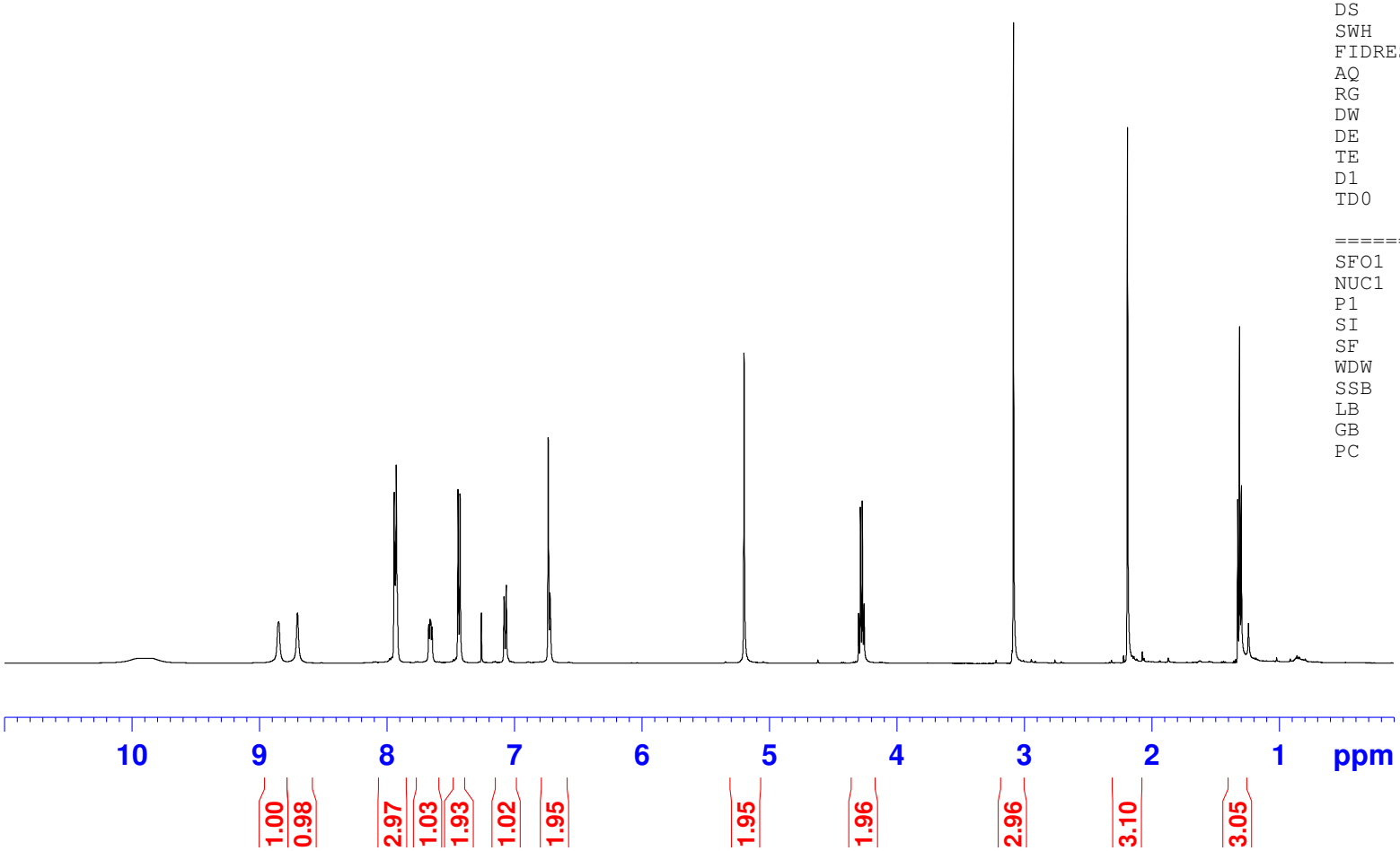
NAME	CNA-653-79A
EXPNO	3
PROCNO	1
Date_	20150724
Time	22.27
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	113636.367 Hz
FIDRES	0.866977 Hz
AQ	0.5767668 sec
RG	203
DW	4.400 usec
DE	6.50 usec
TE	298.9 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	470.5735434 MHz
NUC1	19F
P1	5.00 usec
SI	65536
SF	470.6206054 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-653-79B, 1H, CDCl3, 500 MHz



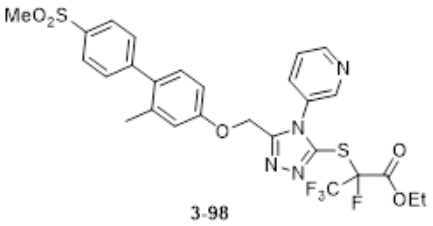
3-98

8.850 8.703 7.945 7.928 7.673 7.663 7.657 7.647 7.443 7.427 7.260 7.082 7.065 6.736 6.721 5.199 4.301 4.286 4.272 4.258 3.086 2.191 1.327 1.312 1.298



NAME	CNA-653-79B
EXPNO	1
PROCNO	1
Date_	20150724
Time	22.36
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	10000.000 Hz
FIDRES	0.152588 Hz
AQ	3.2768500 sec
RG	50.8
DW	50.000 use
DE	6.50 use
TE	298.7 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 =======	
SFO1	500.1630887 MHz
NUC1	1H
P1	11.45 use
SI	65536
SF	500.1600126 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-653-79B, 13C, CDCl3, 500 MHz



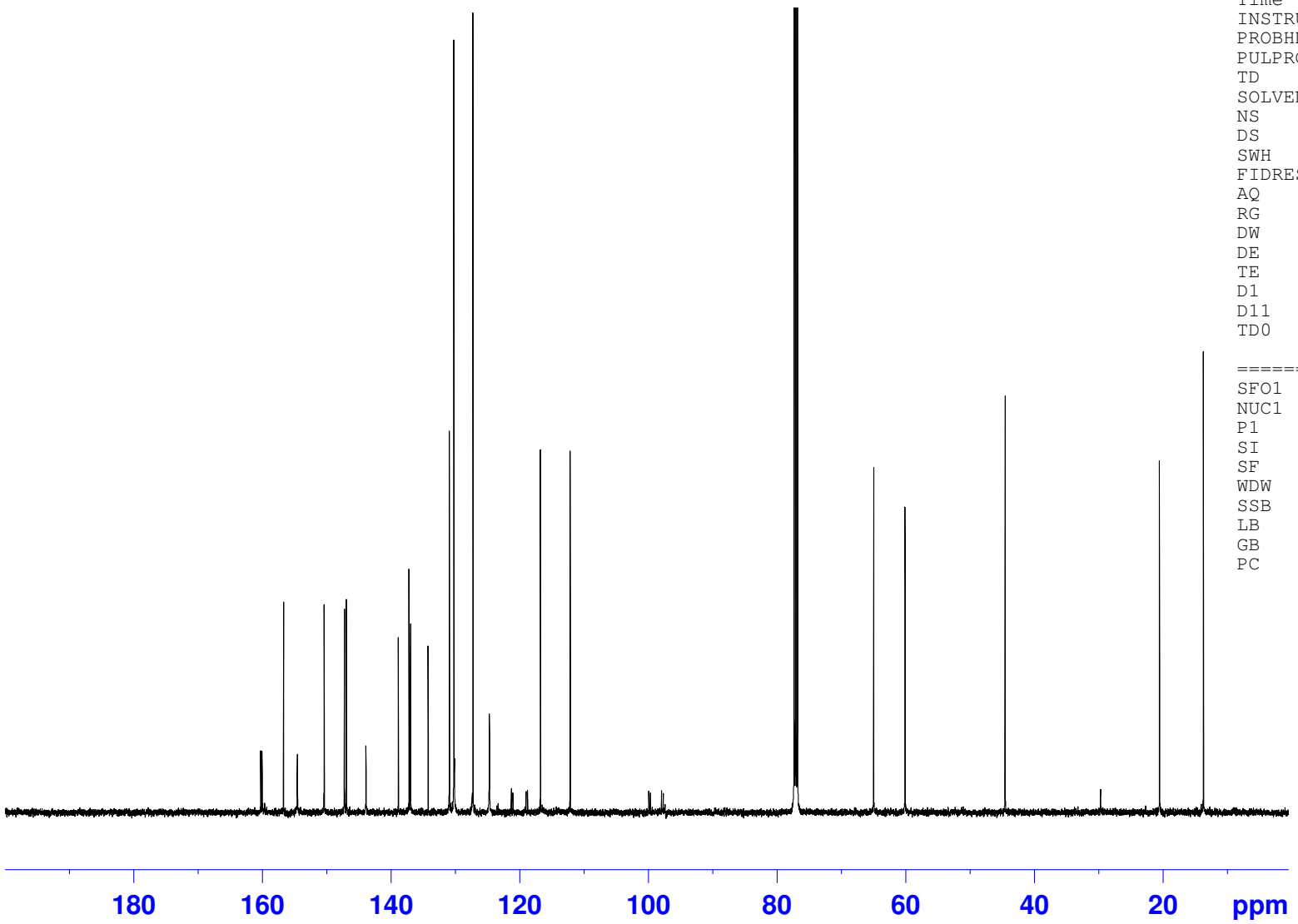
3-98

160.251
160.034
159.636
156.694
154.555
150.397
147.233
146.952
143.891
138.858
137.210
136.965
134.219
130.921
130.225
130.141
127.375
127.251
124.696
121.285
121.045
119.008
118.766
116.767
112.137
99.947
99.674
97.945
97.672
64.952
60.073
44.523
20.524
13.702

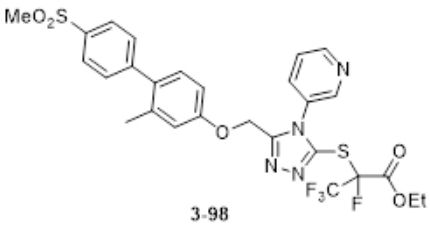
NAME	CNA-653-79B
EXPNO	2
PROCNO	1
Date_	20150725
Time	0.12
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1792
DS	2
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	203
DW	16.800 use
DE	6.50 use
TE	298.2 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1

======== CHANNEL f1 ========

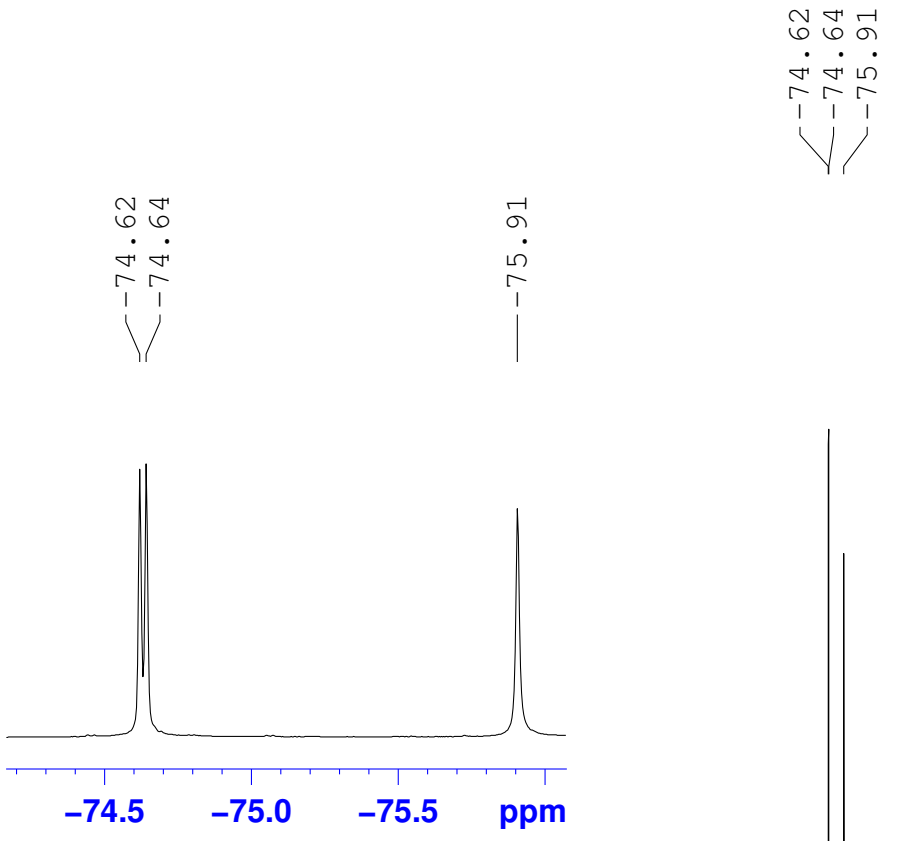
SFO1	125.7779086 MHz
NUC1	13C
P1	10.50 use
SI	32768
SF	125.7653320 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



CNA-653-79B, 19F, CDCl3, 500 MHz



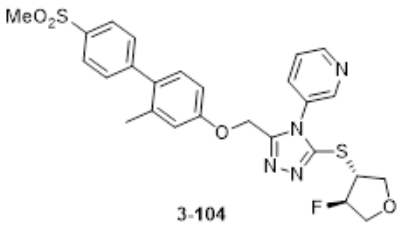
3-98



NAME	CNA-653-79B
EXPNO	3
PROCNO	1
Date_	20150725
Time	0.15
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	113636.367 Hz
FIDRES	0.866977 Hz
AQ	0.5767668 sec
RG	203
DW	4.400 usec
DE	6.50 usec
TE	297.9 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	470.5735434 MHz
NUC1	19F
P1	5.00 usec
SI	65536
SF	470.6206054 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-653-65, 1H, CDCl3, 400 MHz

8.800 8.797 8.788 8.785 8.656 8.650 7.948 7.927 7.759 7.757 7.753 7.742 7.738 7.737 7.733 7.538 7.526 7.518 7.505 7.451 7.430 7.260 7.093 7.070 6.805 6.798 6.782 5.417 5.409 5.281 5.277 5.125 4.375 4.360 4.348 4.093 4.084 4.067 4.005 3.998 3.813 3.796 3.087 2.202

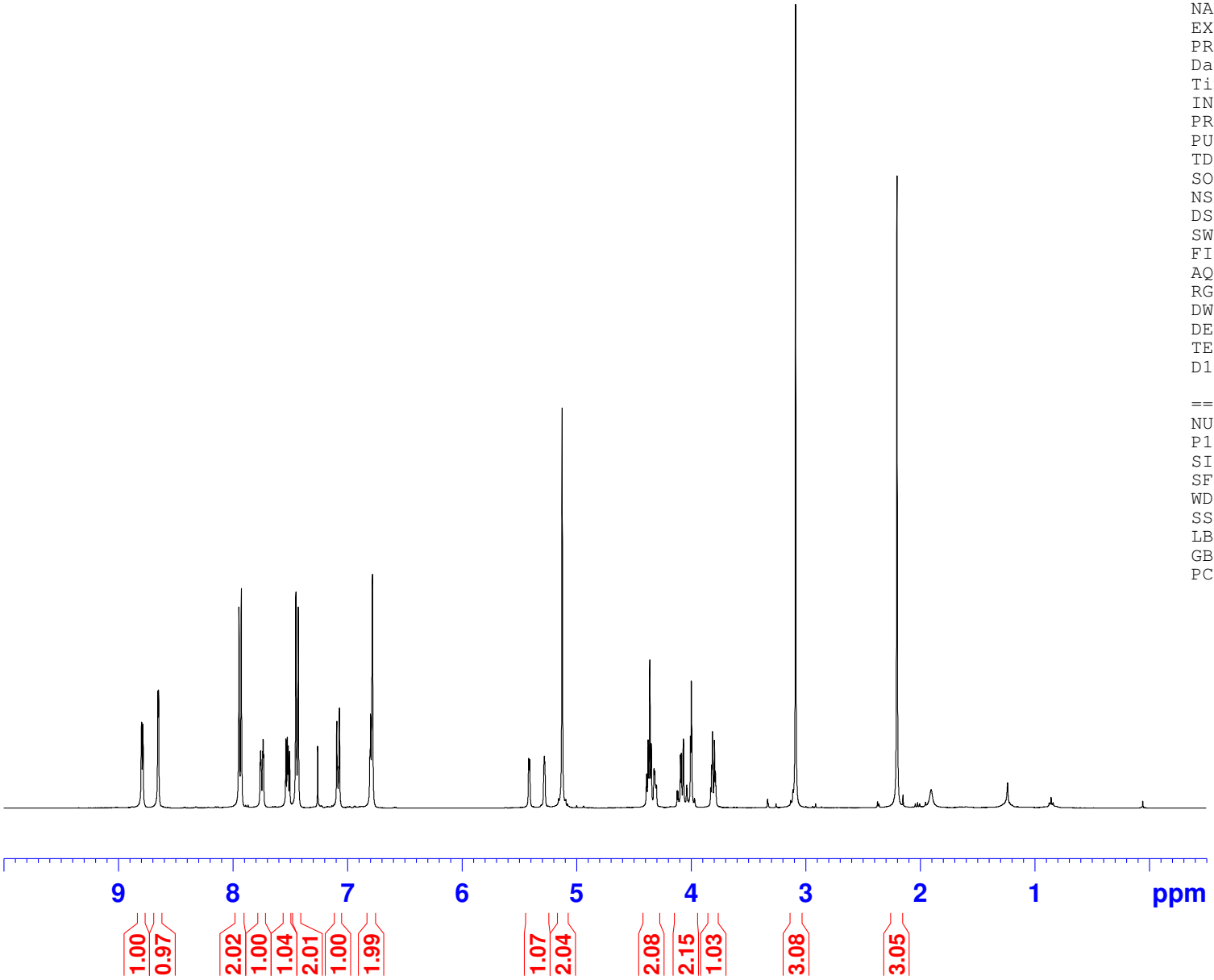


3-104

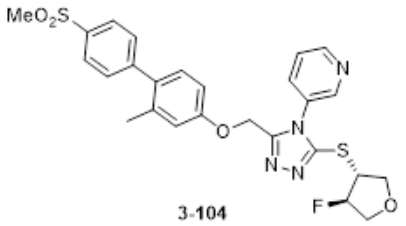
NAME	CNA-653-62
EXPNO	3
PROCNO	1
Date_	20150702
Time	1.50
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	57
DW	60.800 usec
DE	6.50 usec
TE	96.3 K
D1	1.00000000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	13.75 usec
SI	65536
SF	400.1300107 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

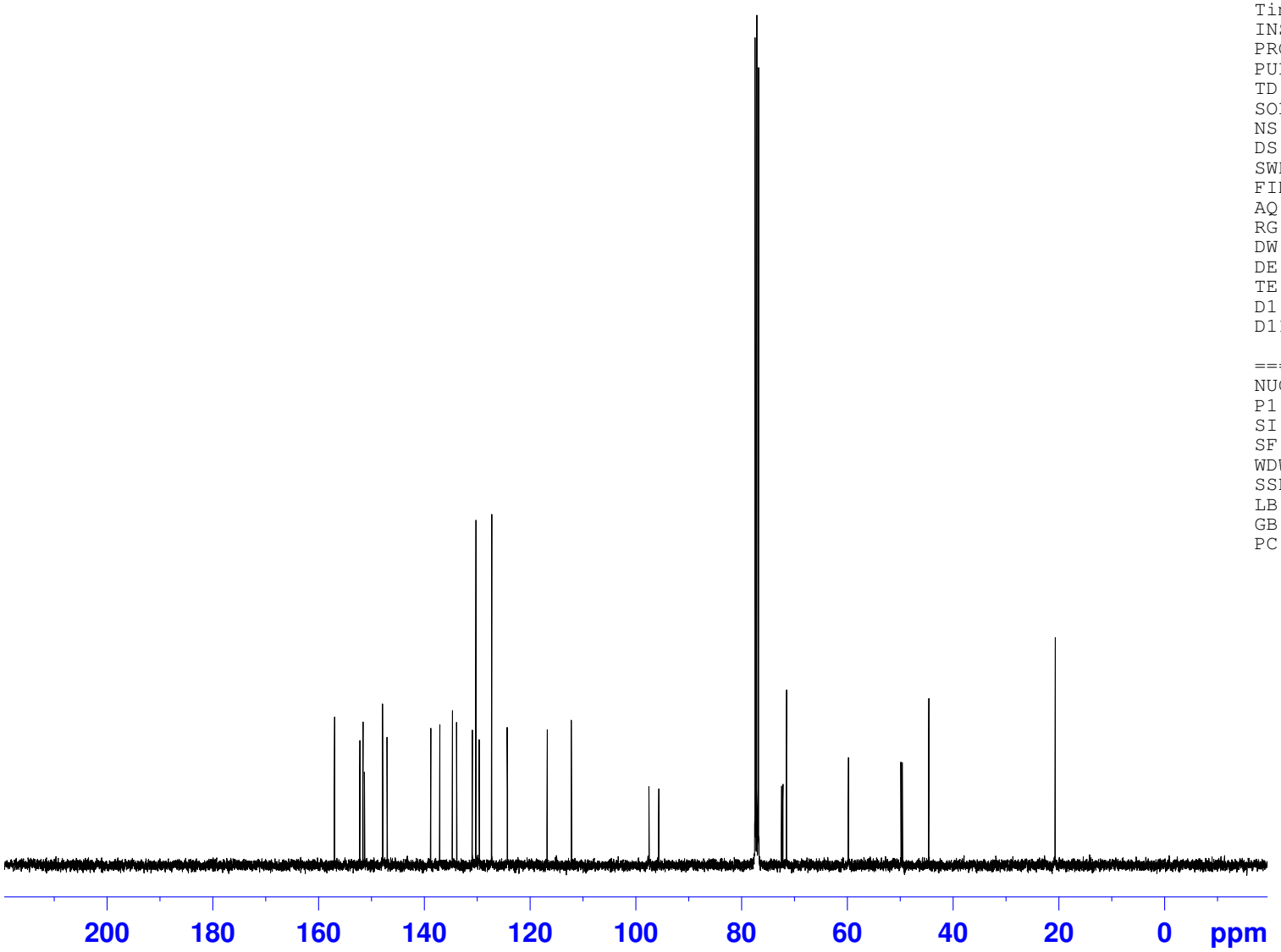


CNA-653-65, 13C, CDCl3, 400 MHz



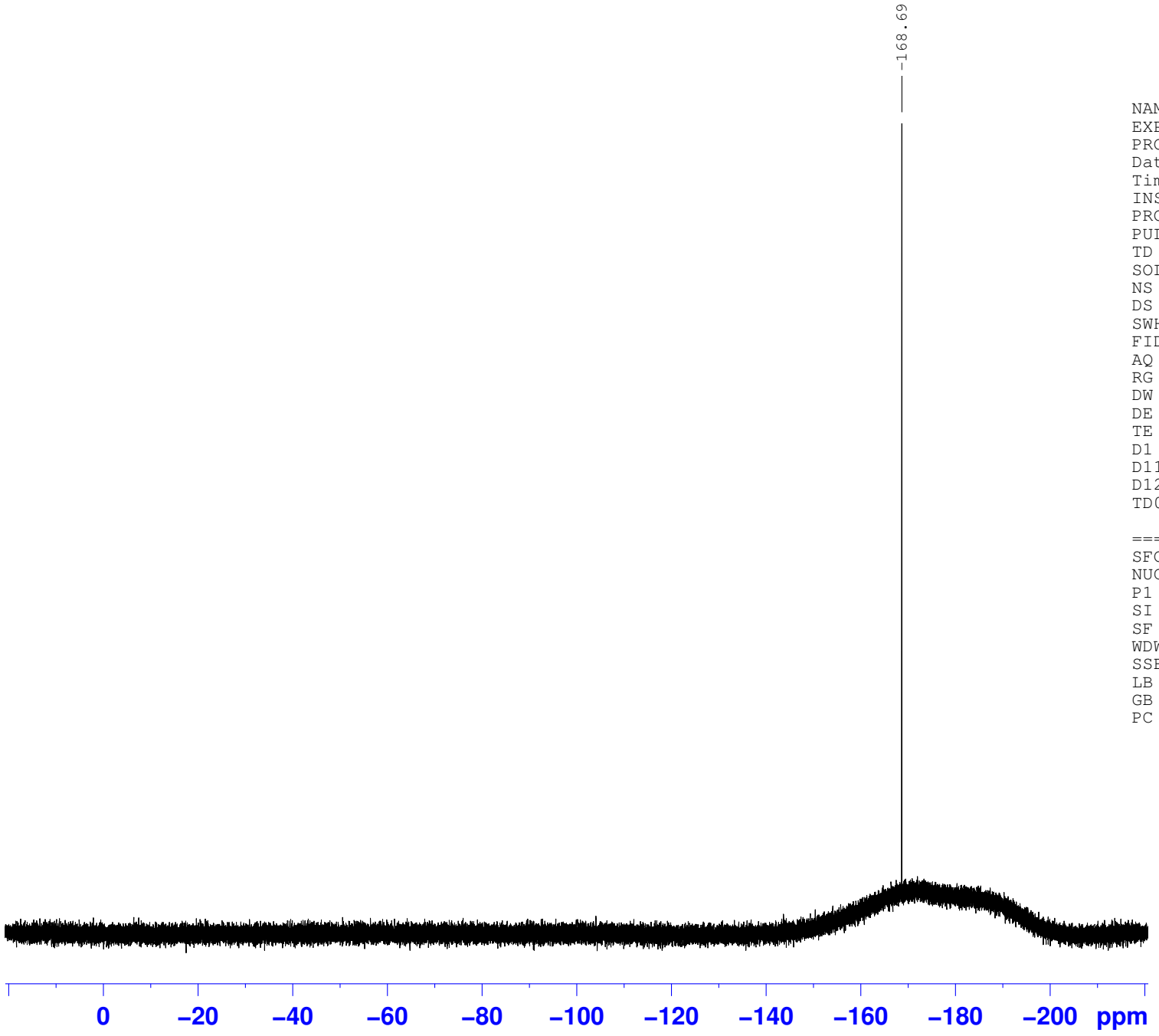
3-104

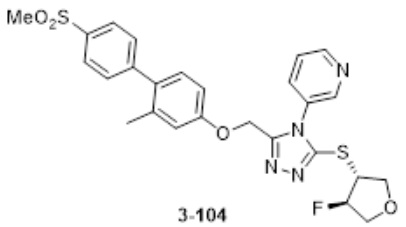
157.00
152.18
151.62
151.34
147.88
147.03
138.78
137.07
134.67
133.88
130.90
130.25
129.62
127.26
124.30
116.76
112.20
97.51
95.64
77.41
77.09
76.78
72.41
72.18
71.49
59.77
49.82
49.57
44.56
20.65



NAME	CNA-653-62
EXPNO	4
PROCNO	1
Date_	20150702
Time	2.22
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	529
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	96.9 K
D1	2.00000000 sec
D11	0.03000000 sec
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
SI	32768
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-653-62, 19F, CDCl3, 500 MHz



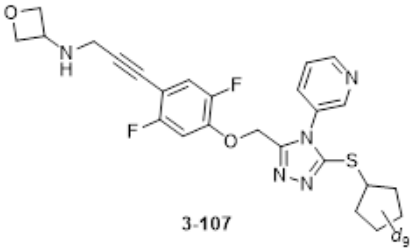


3-104

NAME	CNA-653-62
EXPNO	1
PROCNO	1
Date_	20150824
Time	16.36
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	113636.367 Hz
FIDRES	0.866977 Hz
AQ	0.5767668 sec
RG	203
DW	4.400 usec
DE	6.50 usec
TE	296.8 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	470.5735434 MHz
NUC1	19F
P1	5.00 usec
SI	65536
SF	470.6206054 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-781-33, 1H, CDCl3, 400 MHz

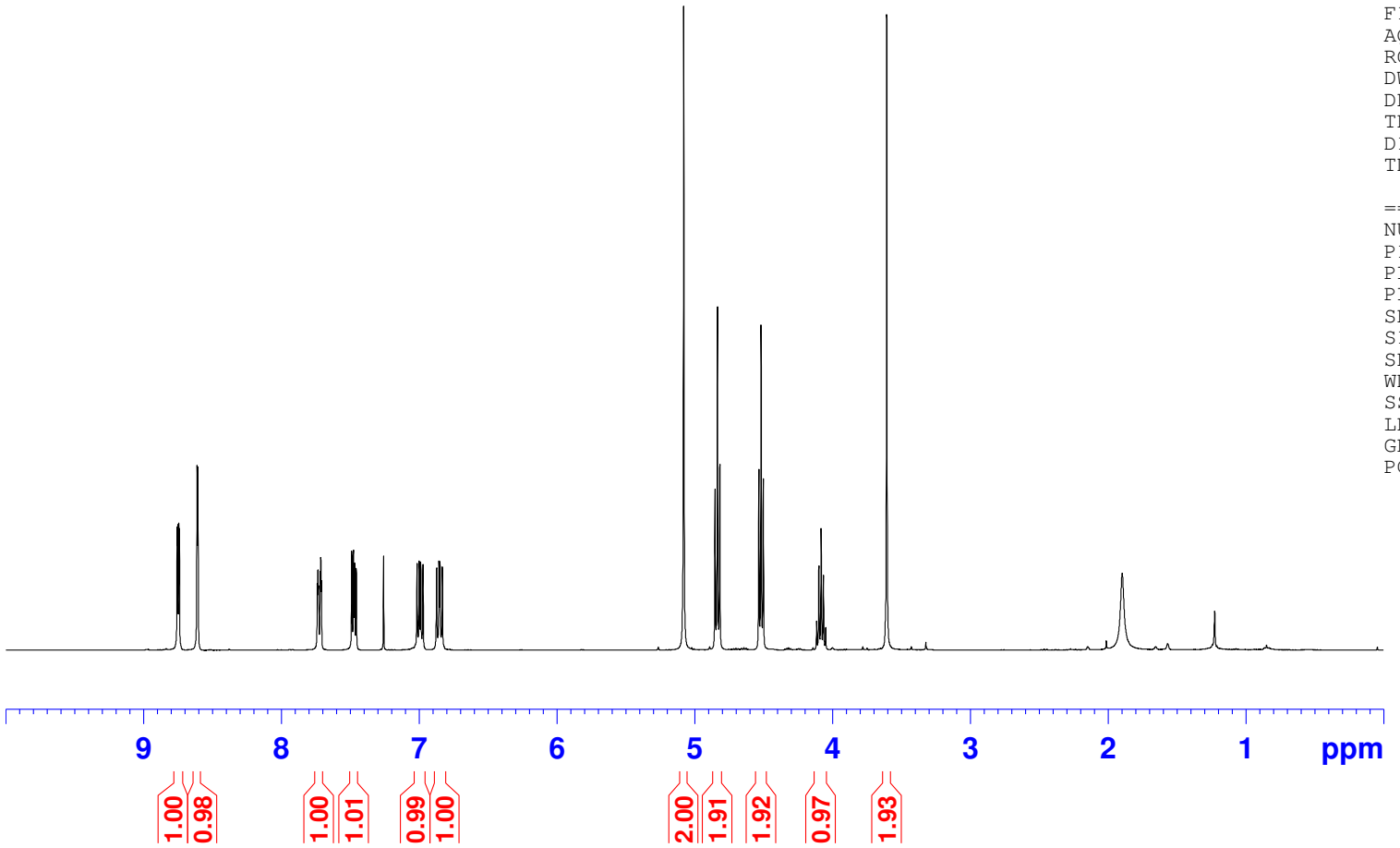
8.608
7.741
7.737
7.731
7.721
7.717
7.715
7.711
7.491
7.479
7.471
7.459
7.260
7.017
7.001
6.990
6.974
6.876
6.858
6.851
6.833
5.082
4.854
4.837
4.819
4.536
4.520
4.504
4.117
4.100
4.084
4.067
4.051
3.607



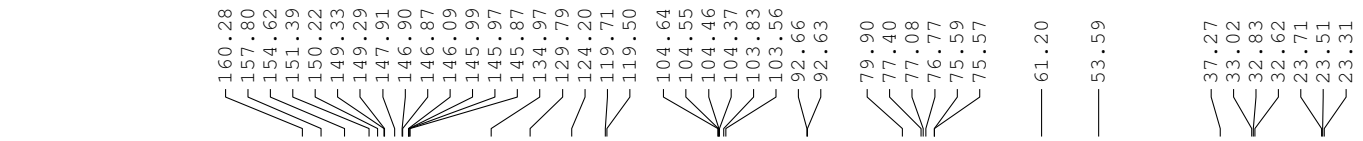
NAME	CNA-781-33
EXPNO	1
PROCNO	1
Date_	20170525
Time	11.30
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	90.5
DW	60.800 usec
DE	6.50 usec
TE	298.0 K
D1	2.00000000 sec
TD0	1

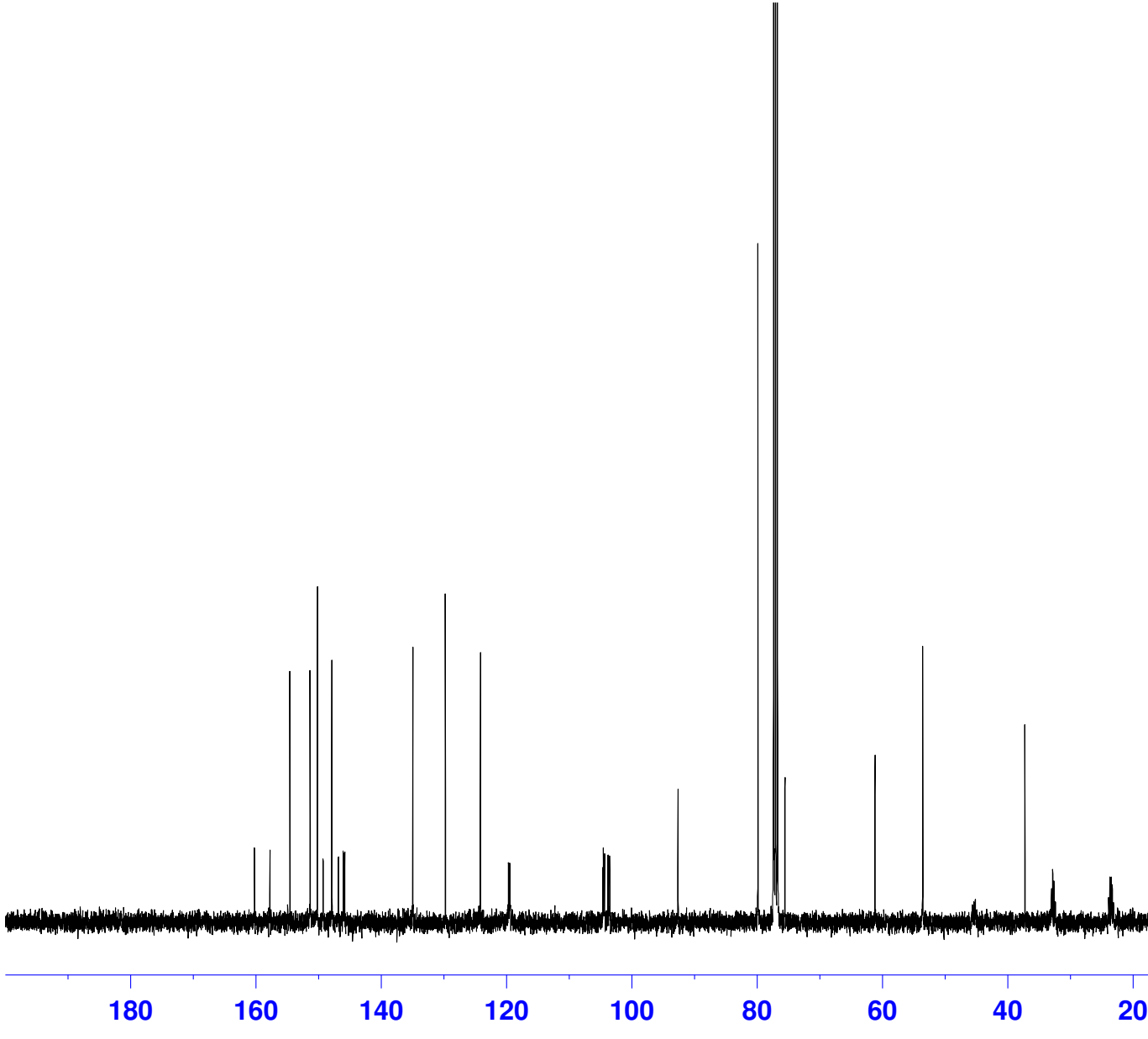
======== CHANNEL f1 ========

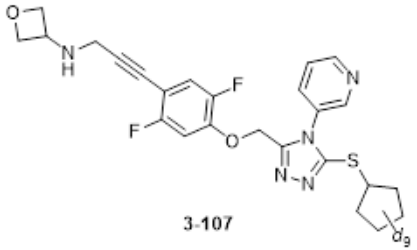
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300124 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



CNA-781-33, 13C, CDCl3, 400 MHz

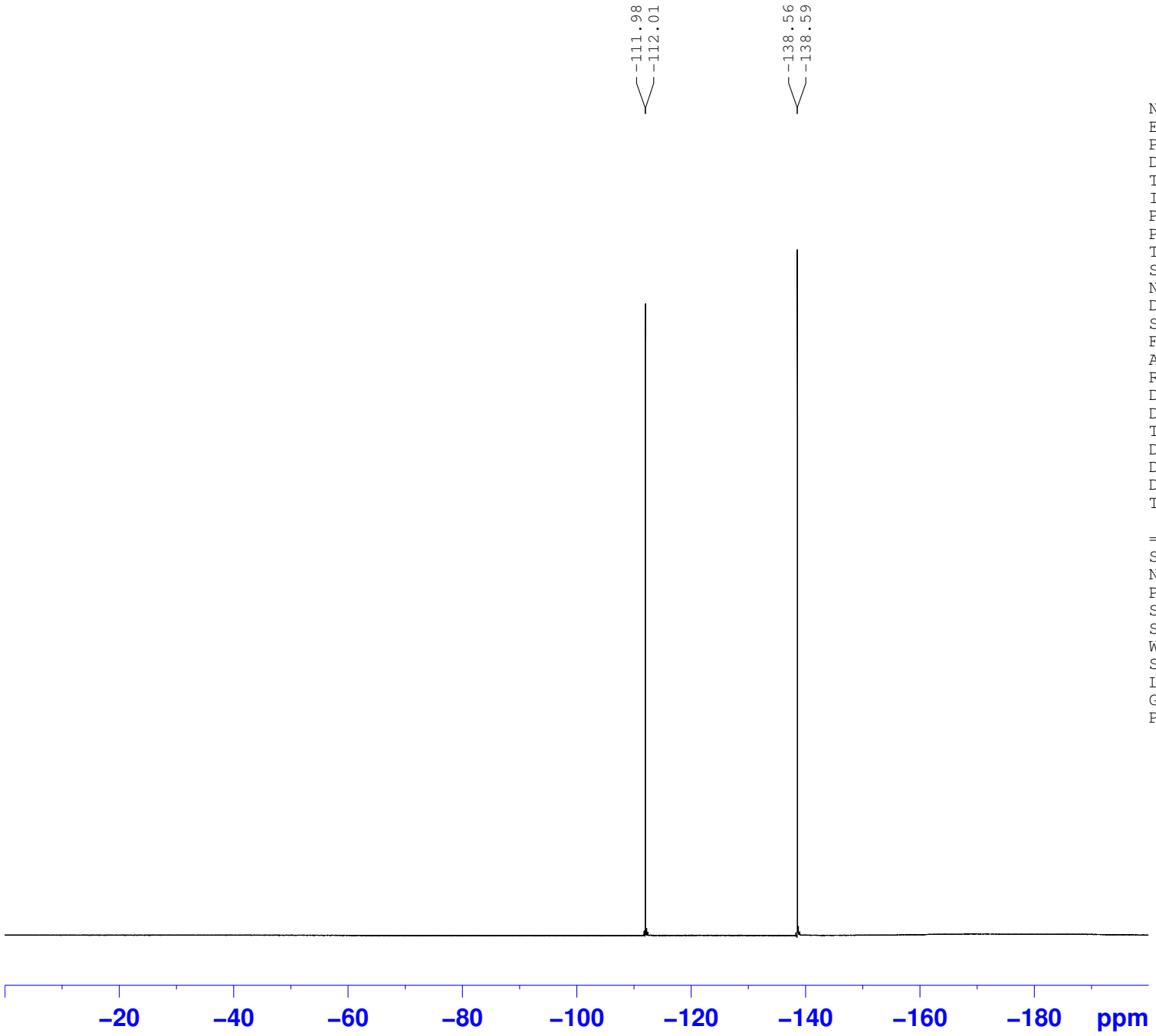


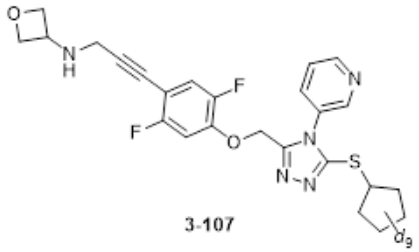




NAME	CNA-781-33
EXPNO	2
PROCNO	1
Date_	20170525
Time	12.02
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	500
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	298.1 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-781-33, 19F, CDCl3, 400 MHz





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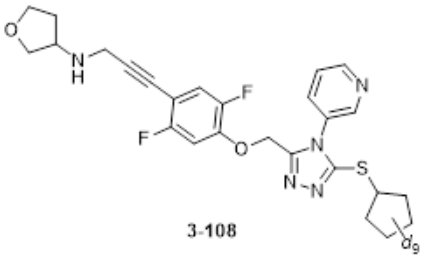
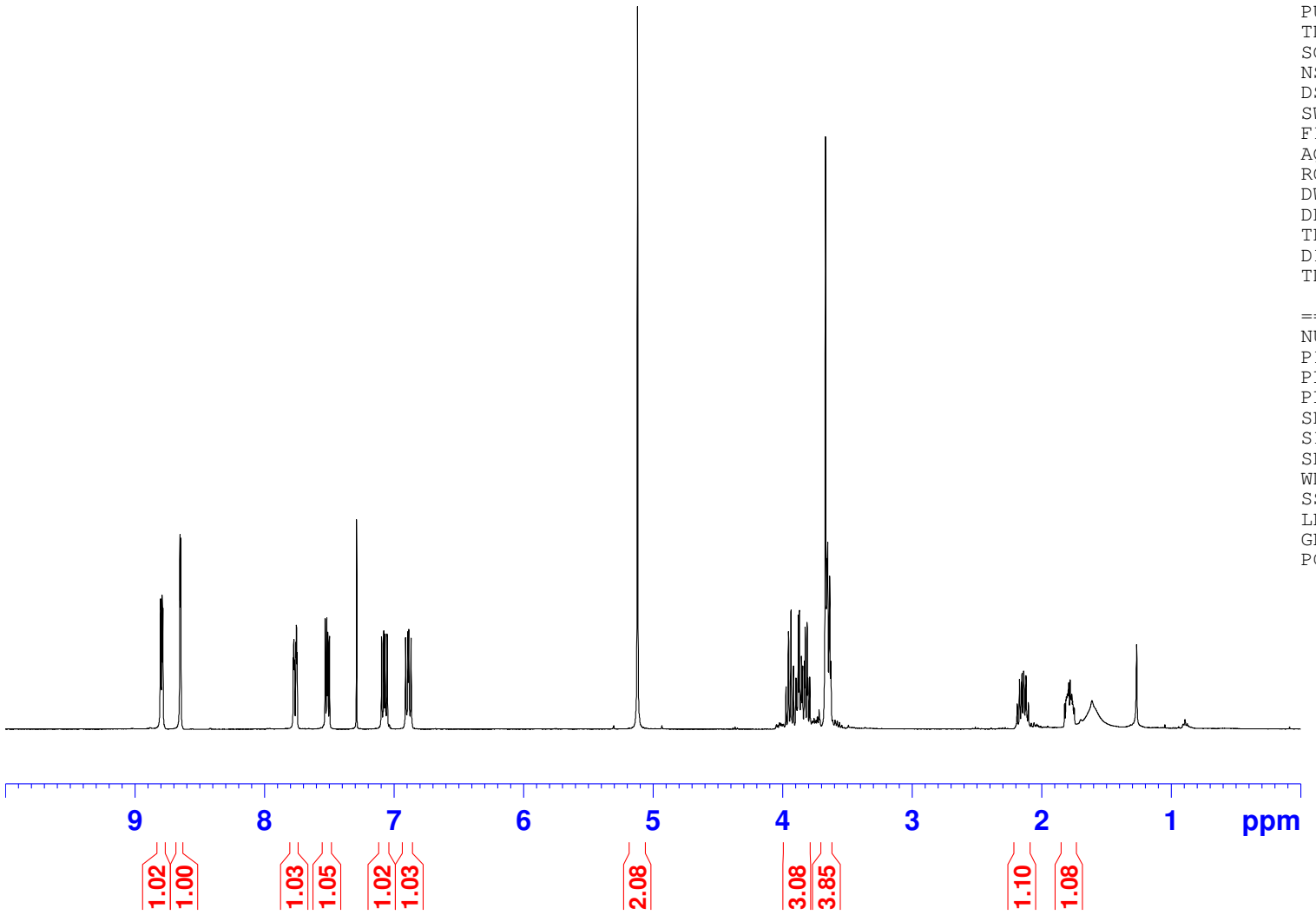
NAME	CNA-781-33	
EXPNO	3	
PROCNO	1	
Date_	20170525	
Time	12.31	
INSTRUM	spect	
PROBHD	5 mm PABBO BB-	
PULPROG	zgfhigqn.2	
TD	131072	
SOLVENT	CDCl3	
NS	16	
DS	4	
SWH	89285.711	Hz
FIDRES	0.681196	Hz
AQ	0.7340532	sec
RG	203	
DW	5.600	usec
DE	6.50	usec
TE	89.0	K
D1	1.00000000	sec
D11	0.03000000	sec
D12	0.00002000	sec
TD0	1	
======== CHANNEL f1 ========		
SFO1	376.4607164	MHz
NUC1	19F	
P1	14.20	usec
SI	65536	
SF	376.4983662	MHz
WDW	EM	
SSB	0	
LB	0.30	Hz
GB	0	
PC	1.00	

CNA-781-26, 1H, CDCl3, 400 MHz

8.802 8.799 8.790 8.787 8.655 8.649 7.780 7.776 7.770 7.760 7.755 7.750 7.533 7.521 7.513 7.501 7.291 7.098 7.081 7.071 7.054 6.912 6.895 6.888 6.870 5.121 3.956 3.936 3.918 3.880 3.872 3.855 3.846 3.832 3.826 3.812 3.670 3.657 3.653 3.637 3.628 2.152 2.140 2.120

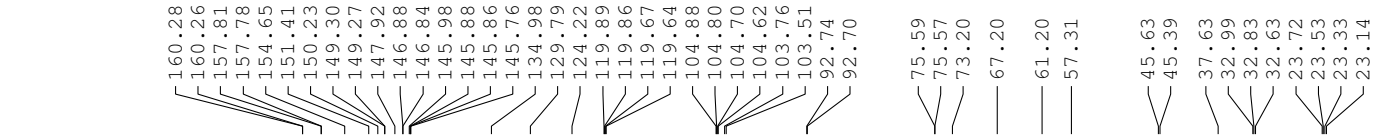


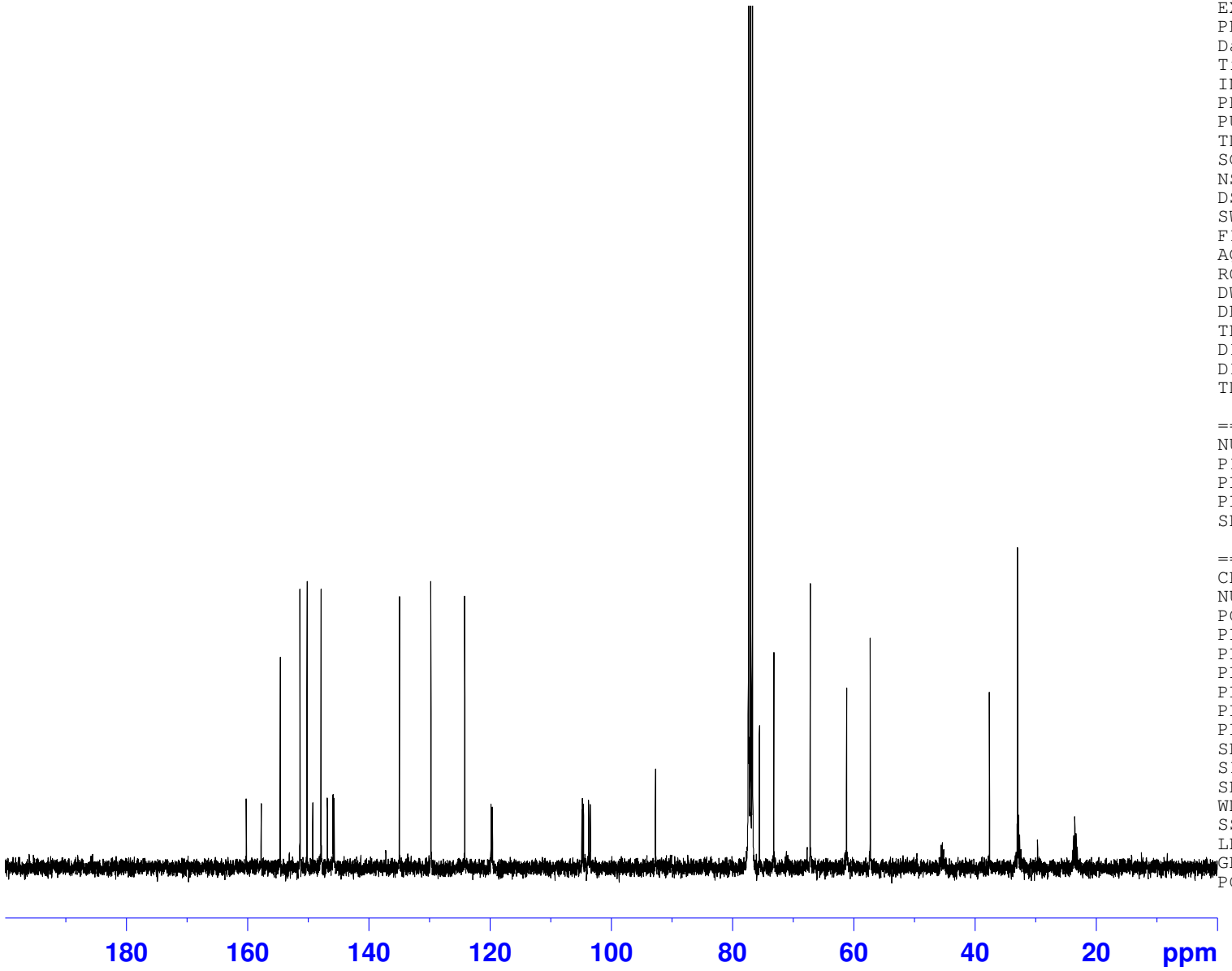


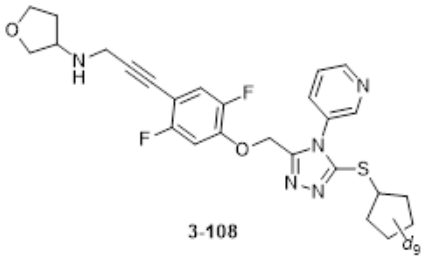
NAME	CNA-781-26
EXPNO	5
PROCNO	1
Date_	20170514
Time	16.19
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	114
DW	60.800 usec
DE	6.50 usec
TE	295.2 K
D1	2.00000000 sec
TD0	1

======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-781-26, 13C, CDCl3, 400 MHz







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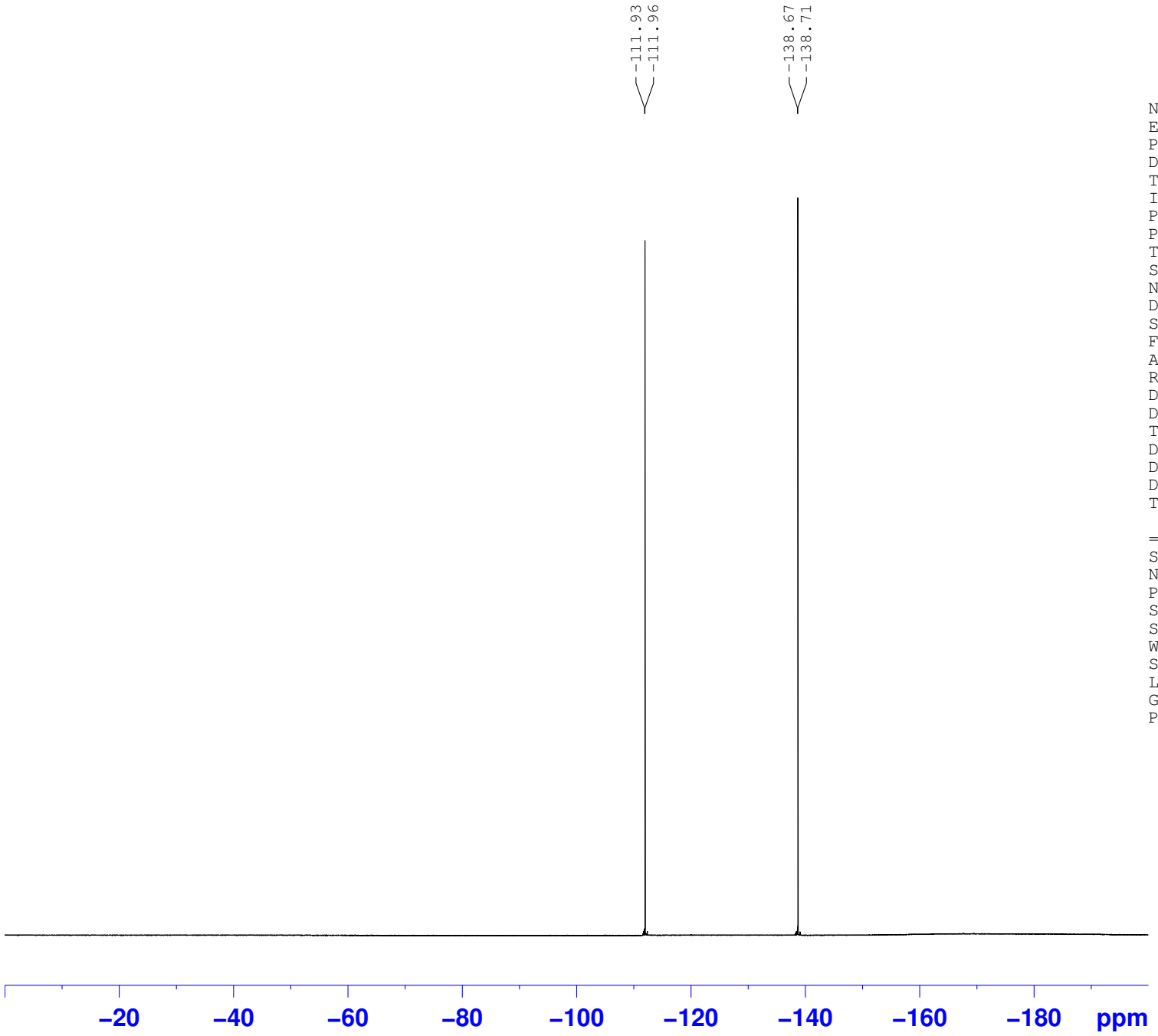
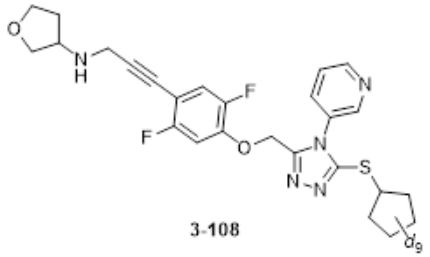
NAME	CNA-781-26
EXPNO	7
PROCNO	1
Date_	20170514
Time	21.14
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	2048
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	295.2 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-781-26, 19F, CDCl3, 400 MHz

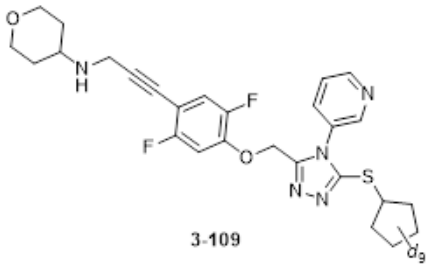




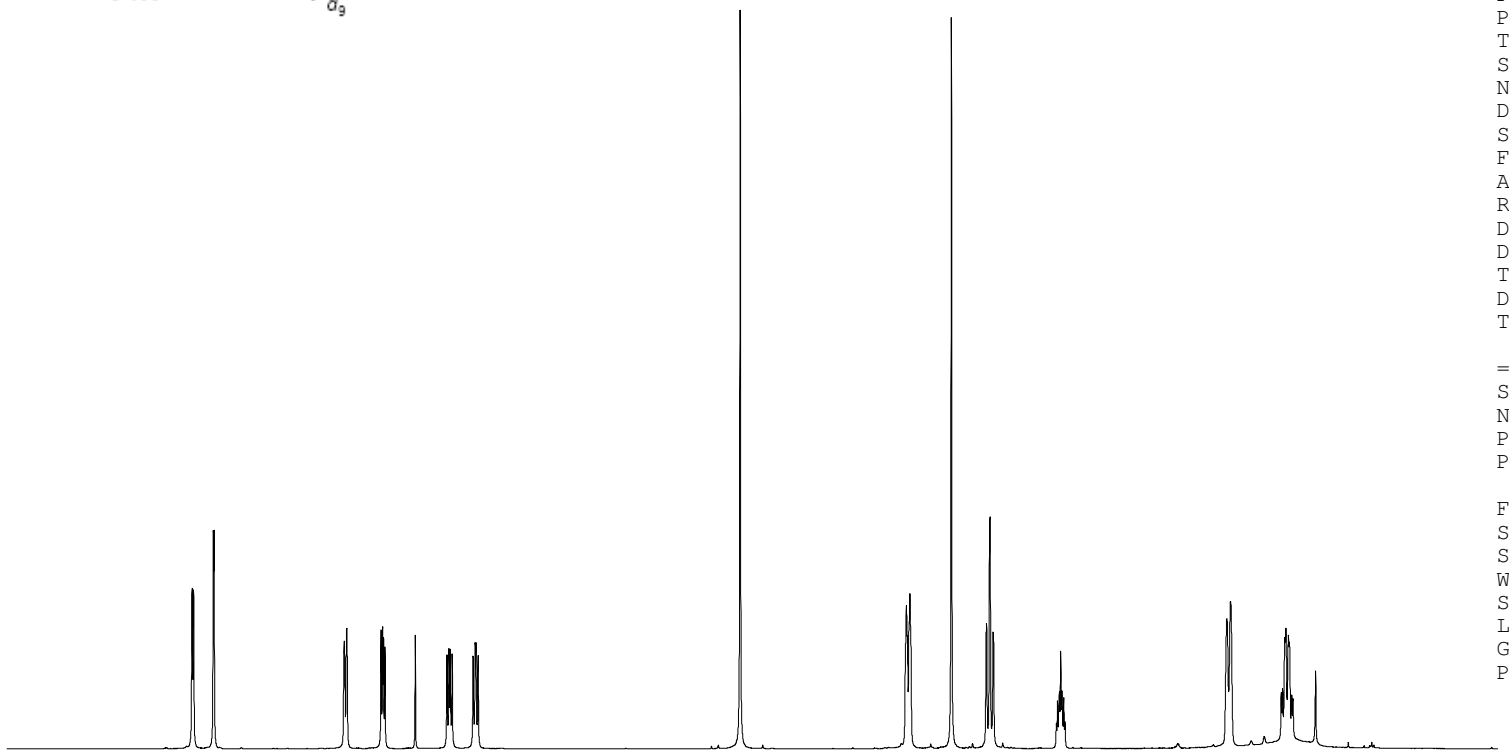
NAME	CNA-781-26	
EXPNO	3	
PROCNO	1	
Date_	20170511	
Time	14.05	
INSTRUM	spect	
PROBHD	5 mm PABBO BB-	
PULPROG	zgfhigqn.2	
TD	131072	
SOLVENT	CDCl3	
NS	16	
DS	4	
SWH	89285.711	Hz
FIDRES	0.681196	Hz
AQ	0.7340532	sec
RG	203	
DW	5.600	usec
DE	6.50	usec
TE	88.4	K
D1	1.00000000	sec
D11	0.03000000	sec
D12	0.00002000	sec
TD0	1	
======== CHANNEL f1 ========		
SFO1	376.4607164	MHz
NUC1	19F	
P1	14.20	usec
SI	65536	
SF	376.4983662	MHz
WDW	EM	
SSB	0	
LB	0.30	Hz
GB	0	
PC	1.00	

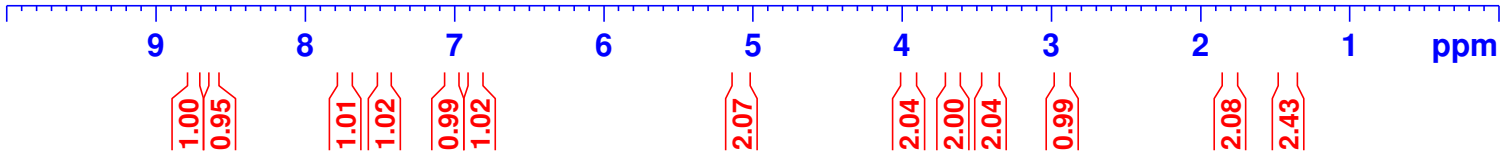
CNA-781-7, 1H, CDCl3, 500 MHz

8.755 8.746 8.613 8.609 7.735 7.719 7.489 7.479 7.473 7.463 7.260 7.047 7.034 7.025 7.012 6.872 6.858 6.853 6.838 5.082 3.967 3.961 3.944 3.666 3.432 3.429 3.409 3.406 3.386 3.383 2.941 2.933 2.925 2.912 1.817 1.795 1.792 1.454 1.445 1.431 1.423 1.407 1.401 1.384



3-109





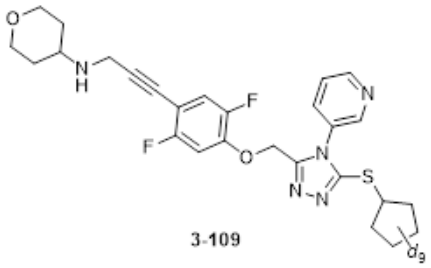

```
Current Data Parameters
NAME          CNA-781-7
EXPNO                11
PROCNO                1

F2 - Acquisition Parameters
Date_          20170330
Time              14.19
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH           10000.000 Hz
FIDRES         0.152588 Hz
AQ            3.2767999 sec
RG                  64
DW               50.000 usec
DE                6.50 usec
TE               296.0 K
D1           1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1        500.1630887 MHz
NUC1                1H
P1                11.50 usec
PLW1        18.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1600130 MHz
WDW                  EM
SSB      0
LB                0.30 Hz
GB       0
PC                1.00
```

CNA-781-7, 13C, CDCl3, 500 MHz



160.02
160.00
158.04
158.03
154.60
151.38
150.24
149.07
149.04
147.91
147.13
147.11
145.89
145.81
145.79
145.71
134.96
129.80
124.19
119.82
119.80
119.65
119.63
104.98
104.91
104.84
104.77
103.79
103.57
92.96
92.93
77.33
77.08
76.83
75.42
66.58
61.21
52.35
45.59
45.42
45.23
35.69
33.19
33.04
32.82
32.66
23.67
23.51
23.35

Current Data Parameters
NAME CNA-781-7
EXPNO 13
PROCNO 1

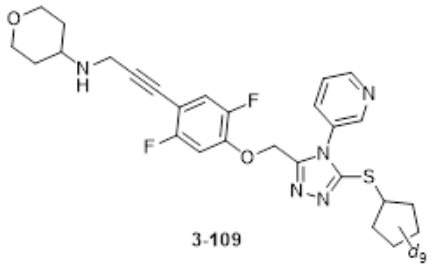
F2 - Acquisition Parameters
Date_ 20170330
Time 14.37
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 2
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 297.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 125.7779086 MHz
NUC1 13C
P1 10.50 usec
PLW1 110.00000000 W

======== CHANNEL f2 ========
SFO2 500.1620006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 18.00000000 W
PLW12 0.37195000 W
PLW13 0.23805000 W

F2 - Processing parameters
SI 32768
SF 125.7653320 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

CNA-781-7, 19F, CDCl3, 500 MHz




```
Current Data Parameters
NAME          CNA-781-7
EXPNO                12
PROCNO                1

F2 - Acquisition Parameters
Date_          20170330
Time              14.21
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG      zgfhigqn.2
TD               131072
SOLVENT            CDCl3
NS                    16
DS                     4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                   203
DW                4.400 usec
DE                6.50 usec
TE                296.1 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                19F
P1                 5.00 usec
PLW1        10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2        18.00000000 W
PLW12        0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

CNA-781-35, 1H, CDCl3, 500 MHz

9.615
8.753
8.746
8.615
7.752
7.736
7.501
7.492
7.485
7.475
7.260
6.988
6.974
6.966
6.953
6.865
6.851
6.846
6.831
5.087
4.292
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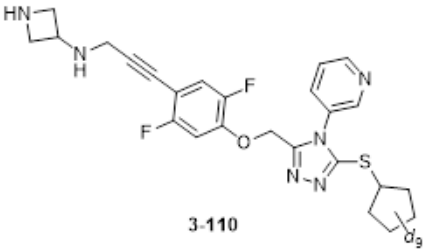
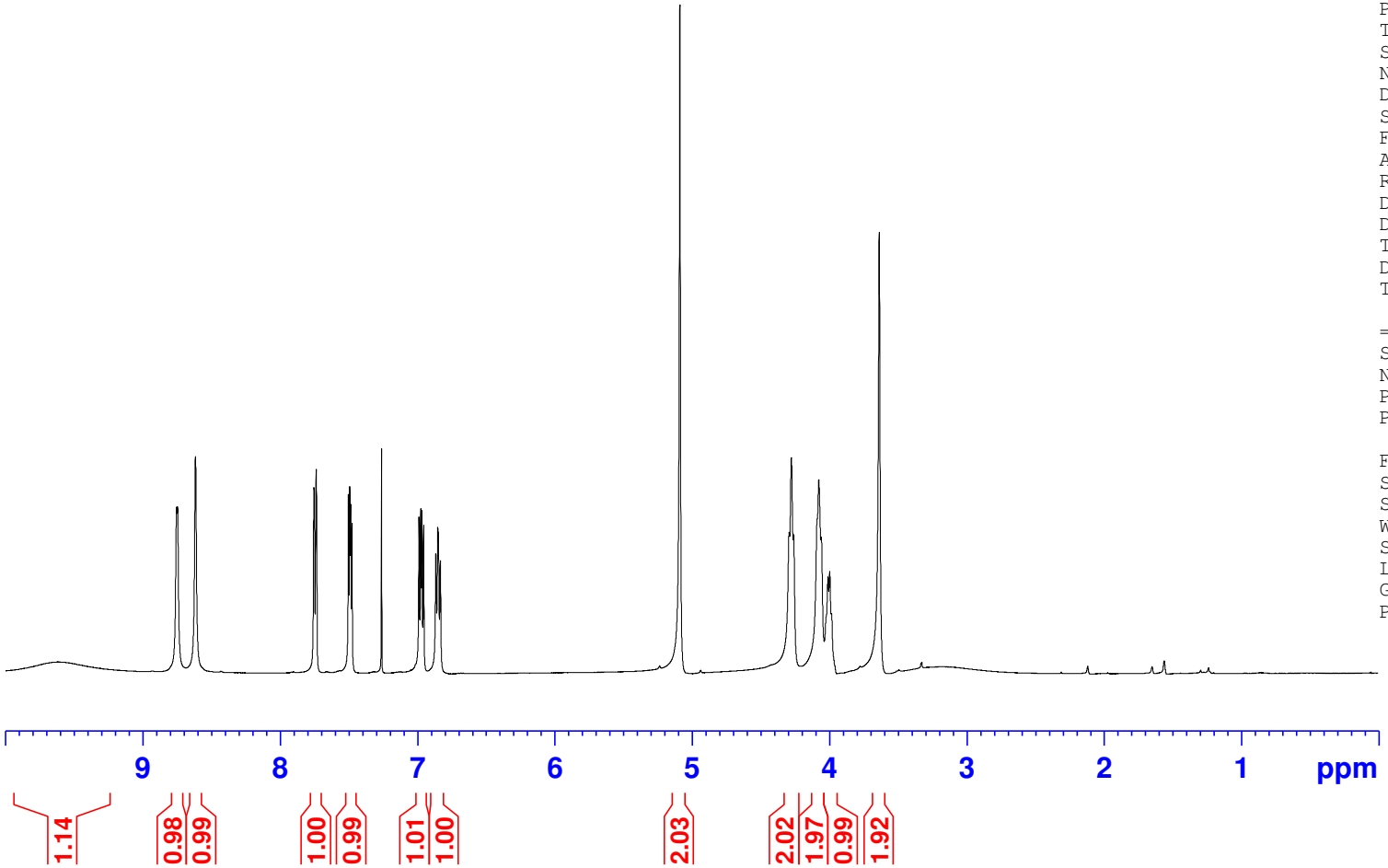
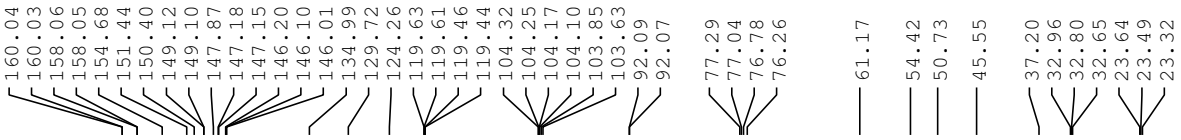
4.057
4.009
3.996
3.983
3.635

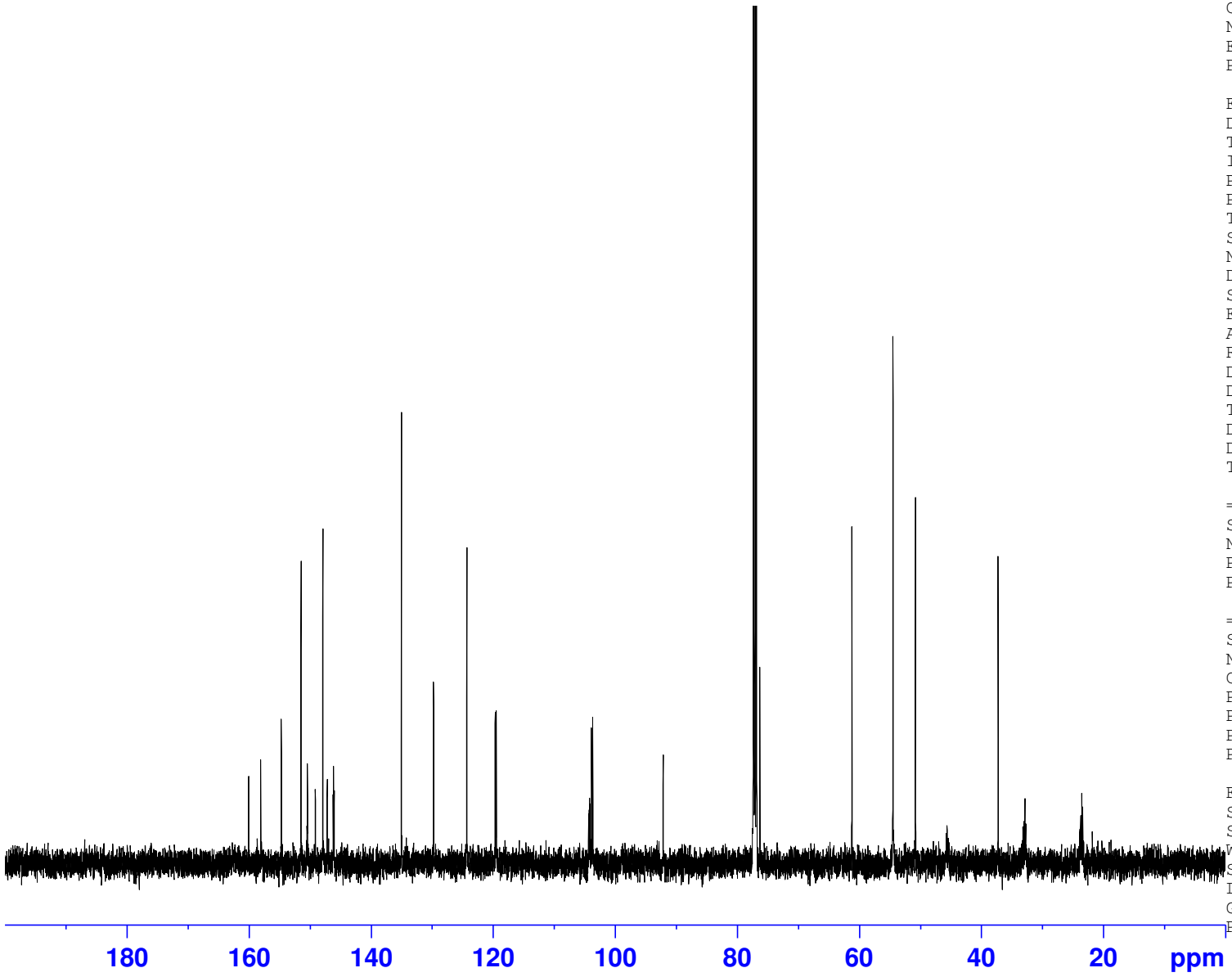


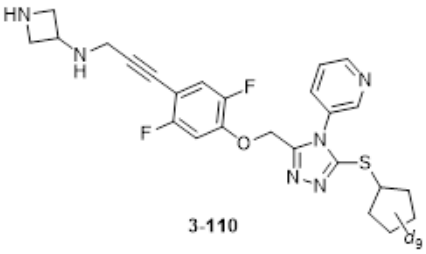



```
Current Data Parameters
NAME          CNA-781-35
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170525
Time               11.57
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                  71.8
DW                50.000 usec
DE                 6.50 usec
TE                298.6 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1630887 MHz
NUC1                   1H
P1                 11.50 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1600123 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-35, 13C, CDCl3, 500 MHz

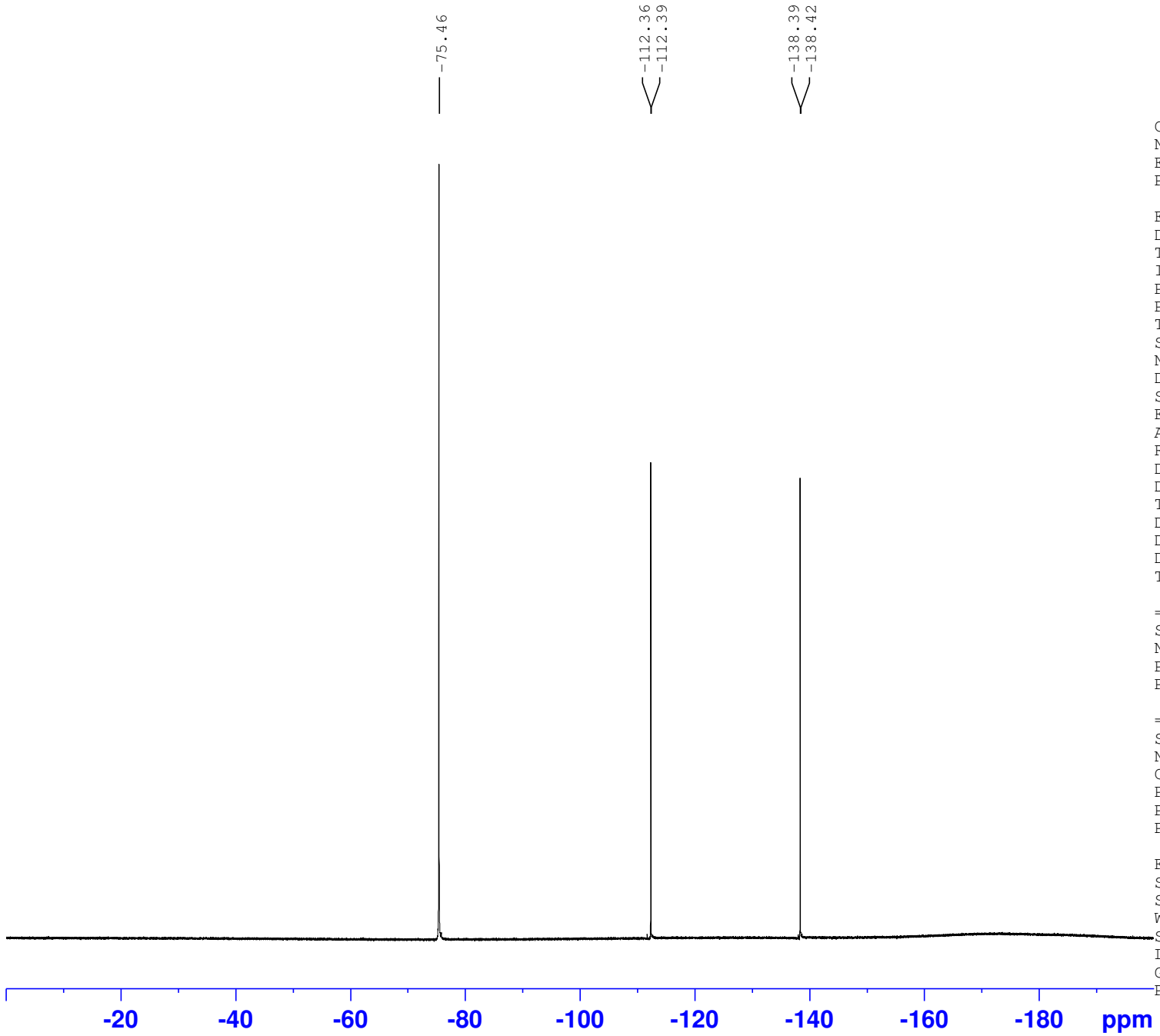


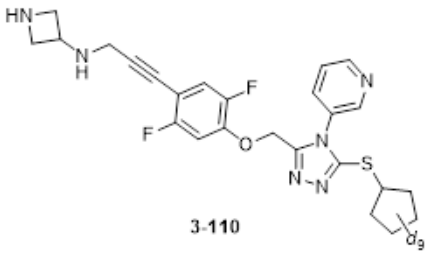





```
Current Data Parameters
NAME          CNA-781-35
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170525
Time               12.28
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  512
DS                    2
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ            1.1010048 sec
RG                  203
DW               16.800 usec
DE                6.50 usec
TE               300.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         125.7779086 MHz
NUC1                 13C
P1                10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W
PLW13         0.23805000 W

F2 - Processing parameters
SI                32768
SF           125.7653320 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

CNA-781-35, 19F, CDCl3, 500 MHz

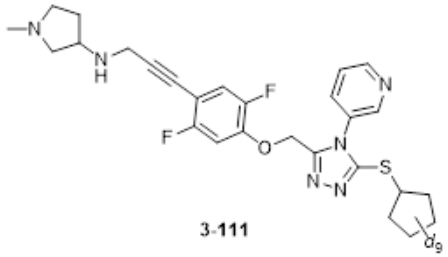


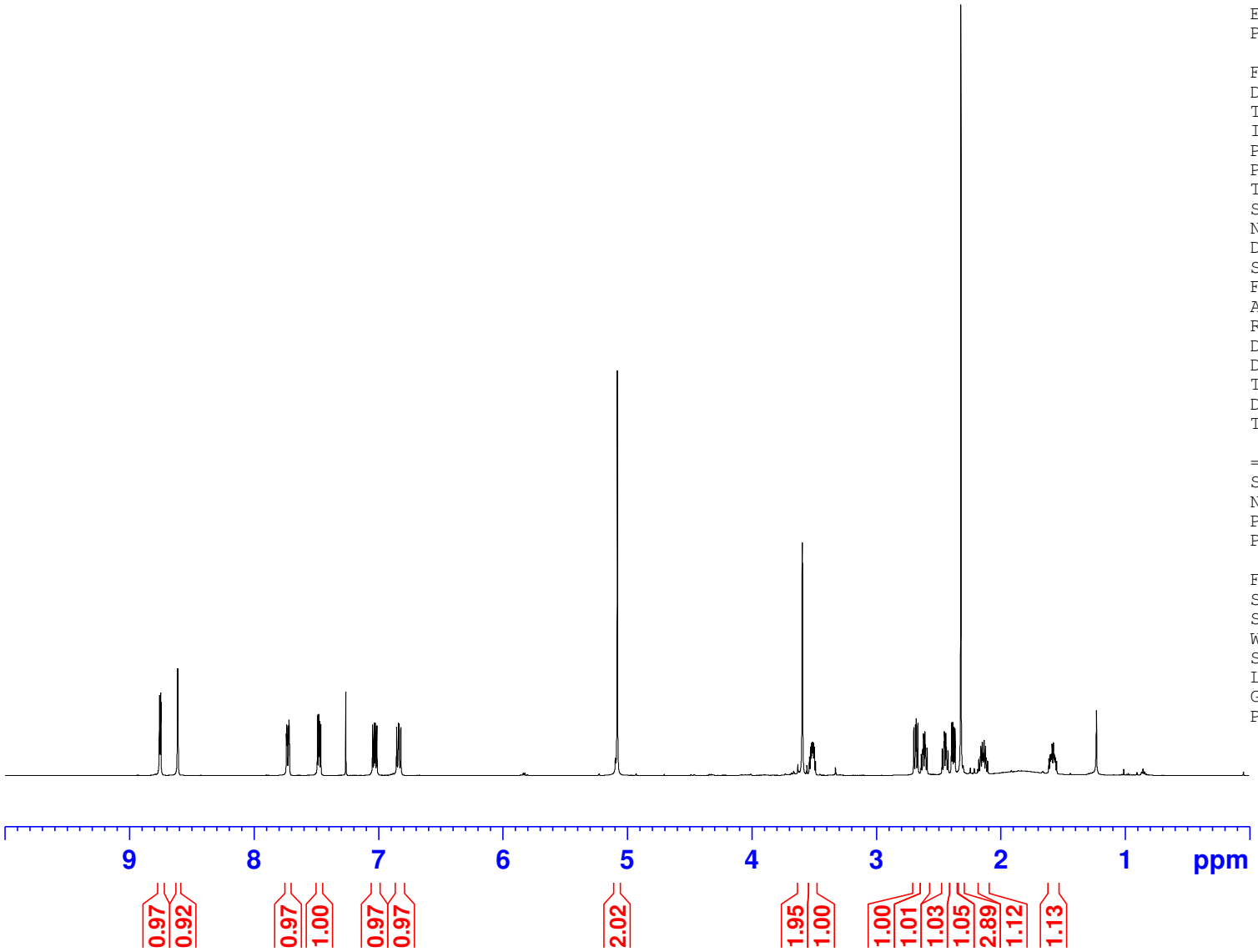



```
Current Data Parameters
NAME          CNA-781-35
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170525
Time               11.59
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG       zgfhigqn.2
TD                131072
SOLVENT             CDCl3
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                298.6 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                  19F
P1                 5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-27, 1H, CDCl3, 500 MHz

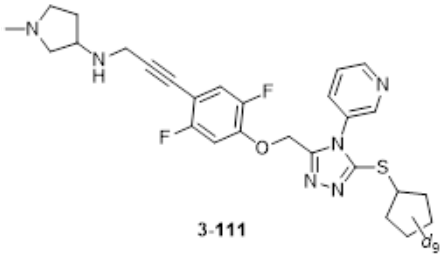
8.758 8.755 8.748 8.745 8.613 8.608 7.737 7.734 7.732 7.729 7.721 7.718 7.716 7.713 7.487 7.478 7.477 7.471 7.462 7.260 7.044 7.031 7.023 7.010 6.851 6.837 6.832 6.818 5.078 3.592 3.590 2.695 2.682 2.676 2.663 2.618 2.606 2.451 2.438 2.393 2.384 2.374 2.365 2.317



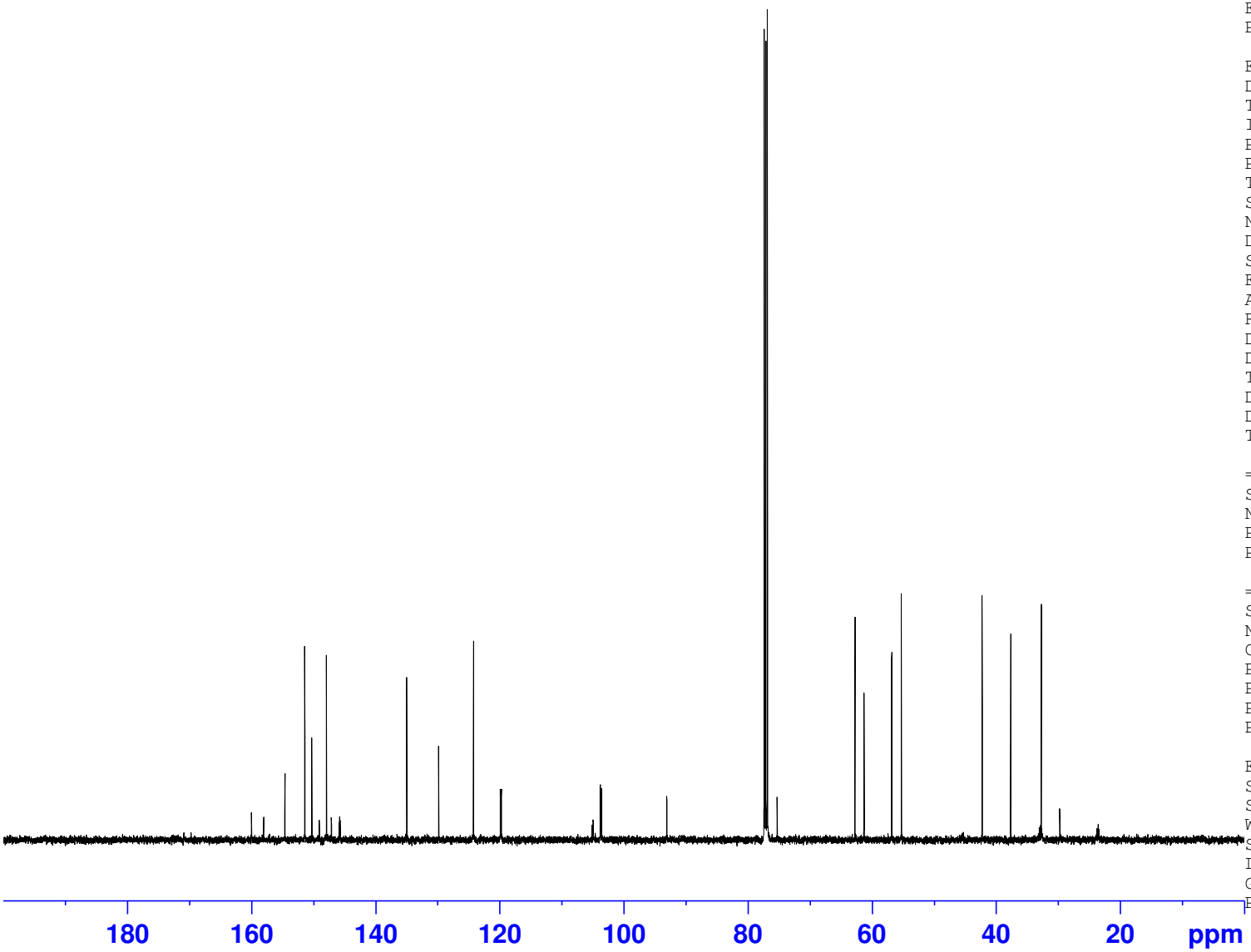



```
Current Data Parameters
NAME          CNA-781-27
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170511
Time               12.22
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                  71.8
DW                50.000 usec
DE                 6.50 usec
TE                297.4 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1630887 MHz
NUC1                   1H
P1                 11.50 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1600127 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-27, 1H, CDCl3, 500 MHz



159.99
159.98
158.01
157.99
154.59
151.38
150.26
149.05
149.03
147.91
147.12
147.09
145.85
145.77
145.75
145.67
134.97
129.81
124.18
119.89
119.86
119.71
119.69
105.07
105.00
104.92
104.86
103.75
103.54
93.05
93.02
77.32
77.06
76.81
75.26
75.24
62.69
61.24
56.78
55.24
42.19
37.58
32.98
32.83
32.64
23.68
23.51
23.36



Current Data Parameters
NAME CNA-781-27
EXPNO 3
PROCNO 1

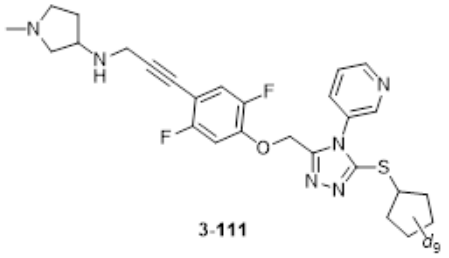
F2 - Acquisition Parameters
Date_ 20170511
Time 12.51
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 2
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 298.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 125.7779086 MHz
NUC1 13C
P1 10.50 usec
PLW1 110.00000000 W

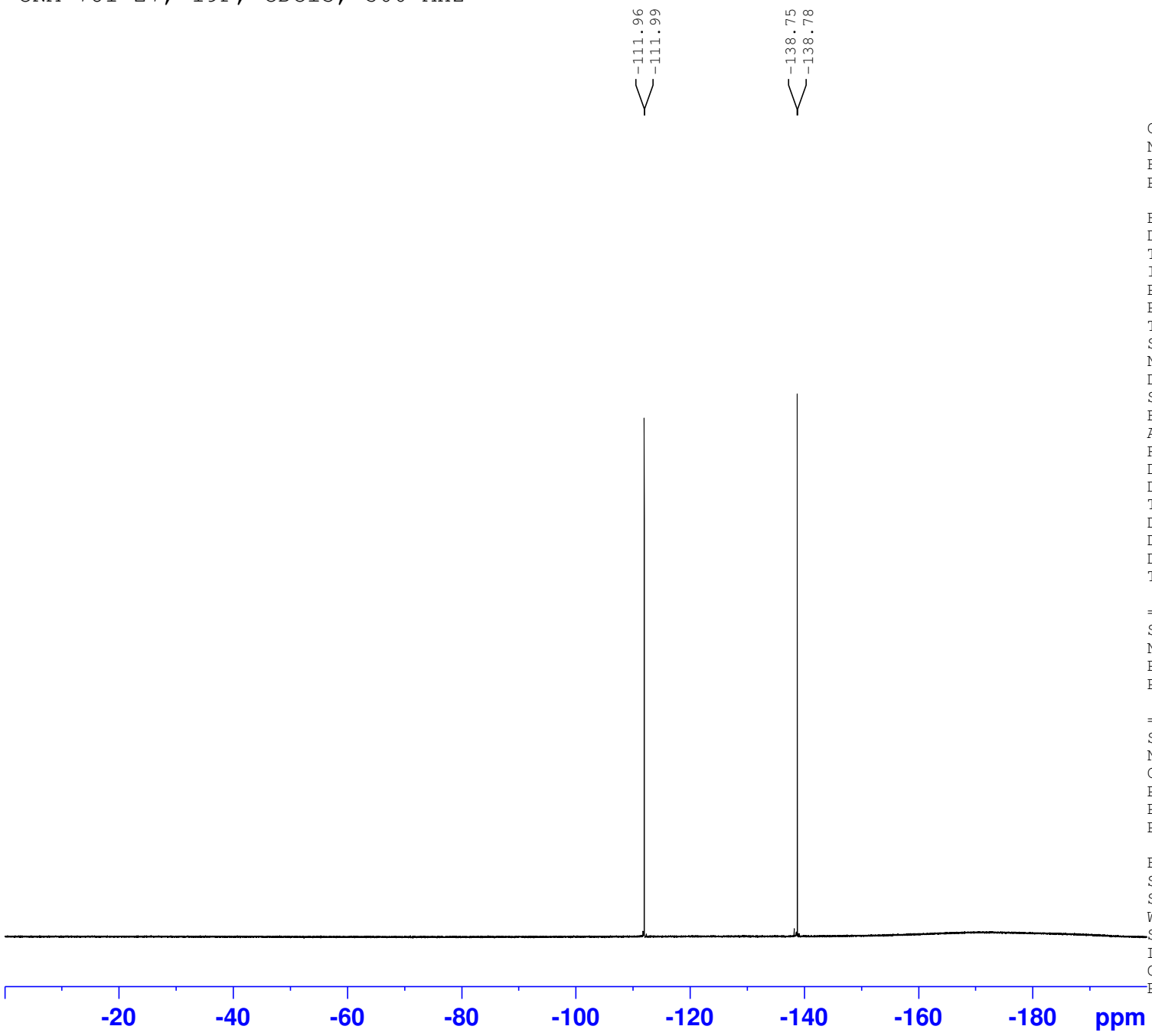
======== CHANNEL f2 ========
SFO2 500.1620006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 18.00000000 W
PLW12 0.37195000 W
PLW13 0.23805000 W

F2 - Processing parameters
SI 32768
SF 125.7653320 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

CNA-781-27, 19F, CDCl3, 500 MHz



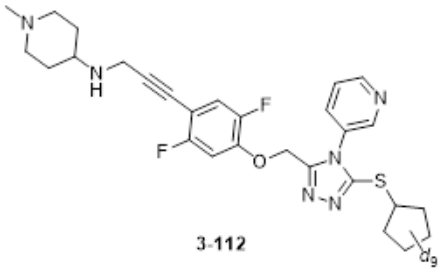
3-111




```
Current Data Parameters
NAME          CNA-781-27
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170511
Time               12.12
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG       zgfhigqn.2
TD                131072
SOLVENT             CDCl3
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                297.5 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                  19F
P1                   5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2               80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-6, 1H, CDCl3, 500 MHz

8.762 8.759 8.756 8.753 8.750 8.616 8.612 7.738 7.735 7.733 7.730 7.722 7.719 7.717 7.714 7.491 7.489 7.481 7.480 7.474 7.473 7.465 7.463 7.260 7.051 7.038 7.030 7.017 6.866 6.852 6.847 6.832 5.082 3.656 2.811 2.788 2.253 2.032 2.010 1.988 1.863 1.839 1.438 1.417



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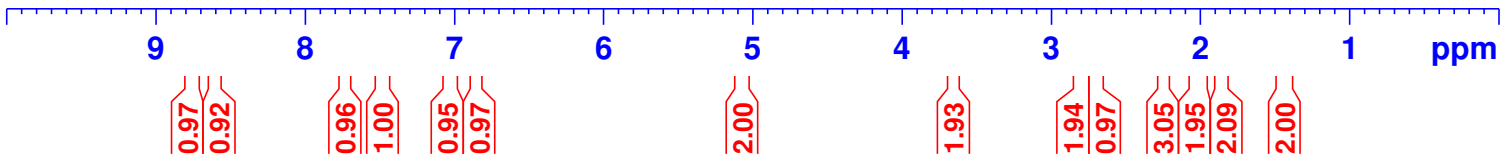
Current Data Parameters
NAME CNA-781-6
EXPNO 6
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170316
Time 19.17
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 71.8
DW 50.000 usec
DE 6.50 usec
TE 297.1 K
D1 1.00000000 sec
TD0 1

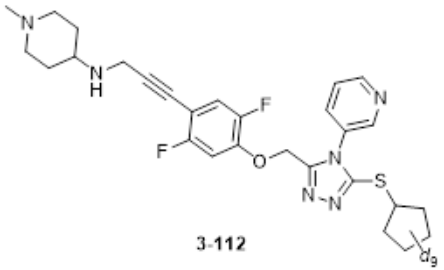
======== CHANNEL f1 ========
SFO1 500.1630887 MHz
NUC1 1H
P1 11.50 usec
PLW1 18.00000000 W

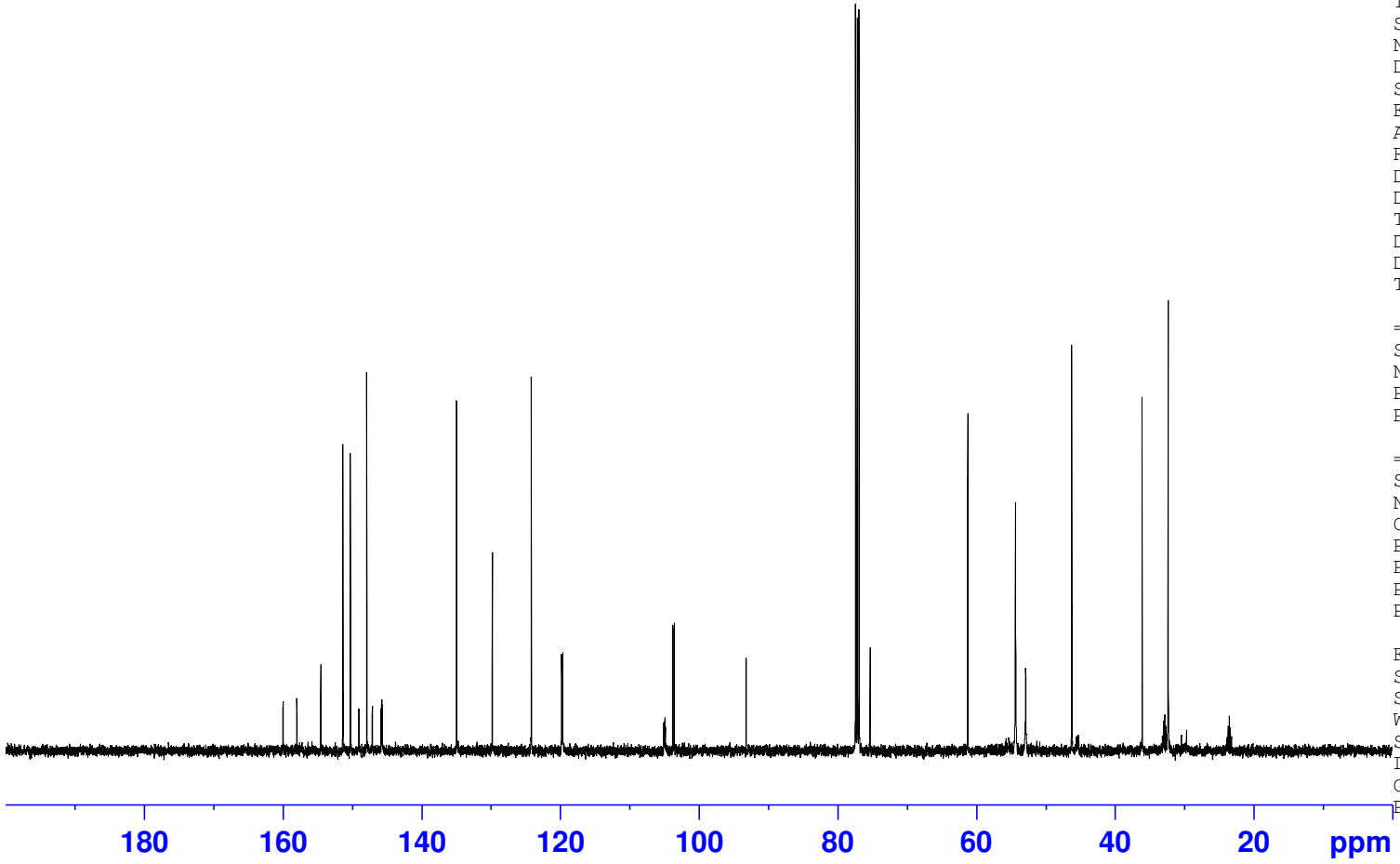
F2 - Processing parameters
SI 65536
SF 500.1600125 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



CNA-781-6, 1H, CDCl3, 500 MHz

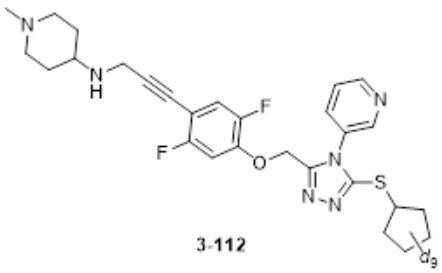
159.95
157.97
154.51
151.34
150.24
149.00
147.88
147.06
145.81
145.74
145.71
145.63
134.93
129.78
124.16
119.79
119.62
105.04
104.97
104.89
104.83
103.76
103.54
93.19
93.16
77.38
77.13
76.87
75.27
61.21
54.31
52.85
46.20
45.57
45.39
45.22
36.06
32.96
32.78
32.63
32.29
23.80
23.64
23.48
23.33
23.16






```
Current Data Parameters
NAME          CNA-781-6
EXPNO                 5
PROCNO                1

F2 - Acquisition Parameters
Date_          20170316
Time              11.55
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG         zgpg30
TD                65536
SOLVENT           CDCl3
NS                  300
DS                    2
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ            1.1010048 sec
RG                  203
DW               16.800 usec
DE                6.50 usec
TE               298.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        125.7779086 MHz
NUC1                13C
P1                10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2        500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2        18.00000000 W
PLW12        0.37195000 W
PLW13        0.23805000 W

F2 - Processing parameters
SI                32768
SF          125.7653320 MHz
WDW                 EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

CNA-781-6, 19F, CDCl3, 500 MHz



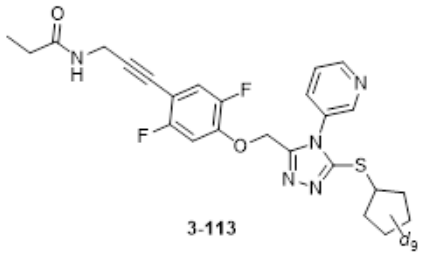

```
Current Data Parameters
NAME          CNA-781-6
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20170315
Time              19.49
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG      zgfhigqn.2
TD               131072
SOLVENT            CDCl3
NS                    16
DS                     4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ              0.5767168 sec
RG                   203
DW                4.400 usec
DE                6.50 usec
TE                297.2 K
D1           1.00000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                19F
P1                 5.00 usec
PLW1        10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2        18.00000000 W
PLW12        0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

CNA-781-3, 1H, CDCl3, 400 MHz

7.749 7.746 7.742 7.732 7.728 7.726 7.722 7.511 7.510 7.499 7.498 7.491 7.490 7.479 7.478 7.260 7.074 7.057 7.047 7.030 6.886 6.869 6.862 6.844 5.810 5.095 4.286 4.273

2.280 2.261 2.242 2.223

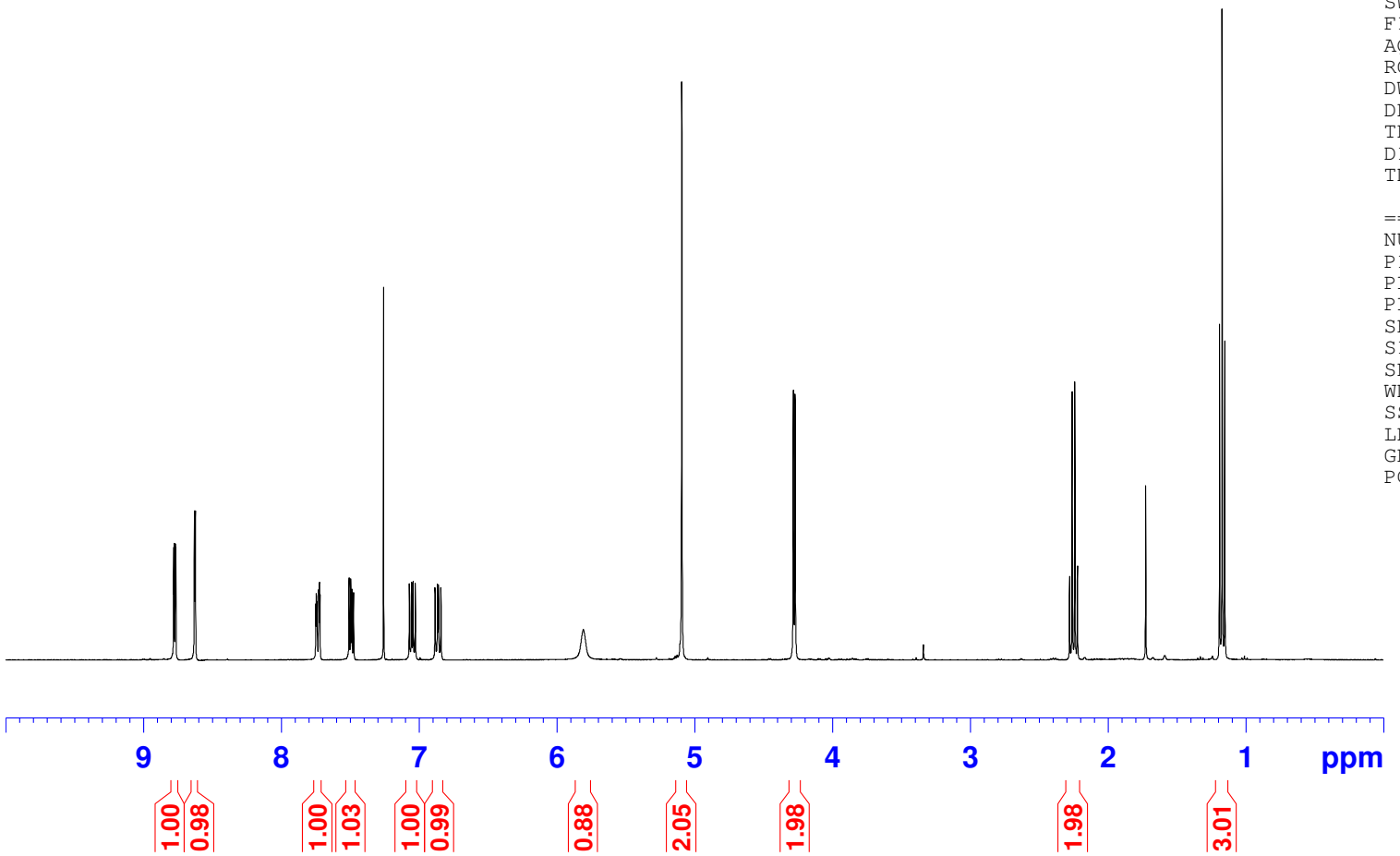
1.192 1.173 1.154



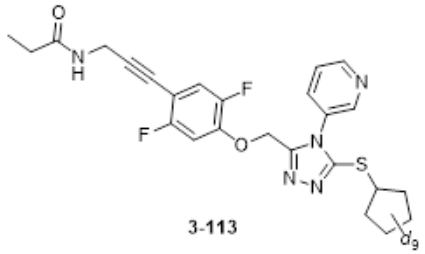
NAME	CNA-781-3
EXPNO	3
PROCNO	1
Date_	20170316
Time	23.02
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	128
DW	60.800 usec
DE	6.50 usec
TE	294.4 K
D1	2.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300122 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



CNA-781-3, 13C, CDCl3, 400 MHz



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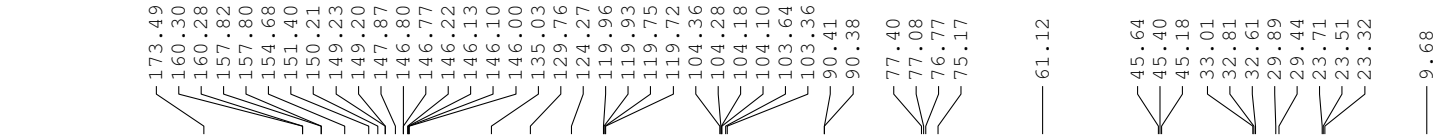
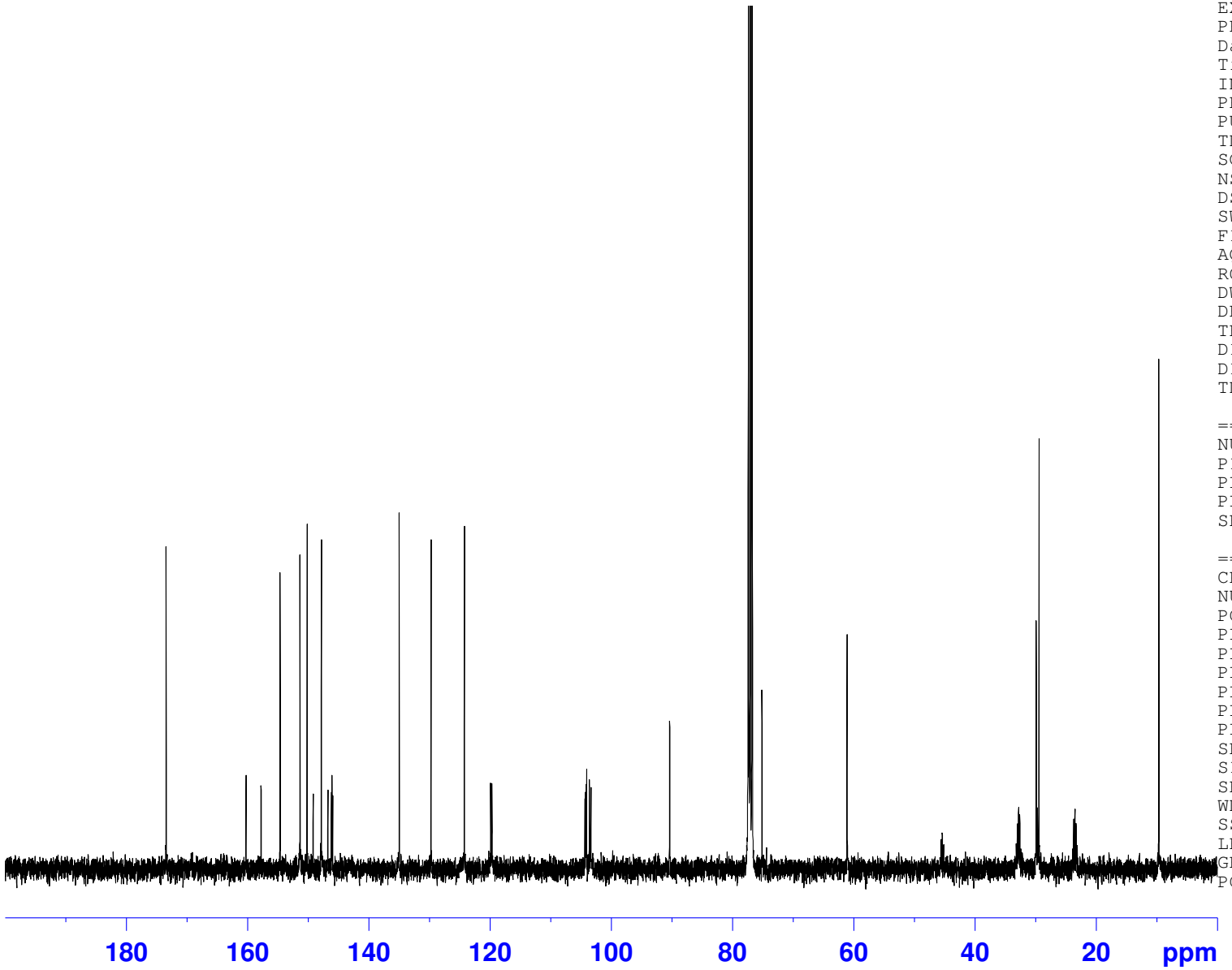
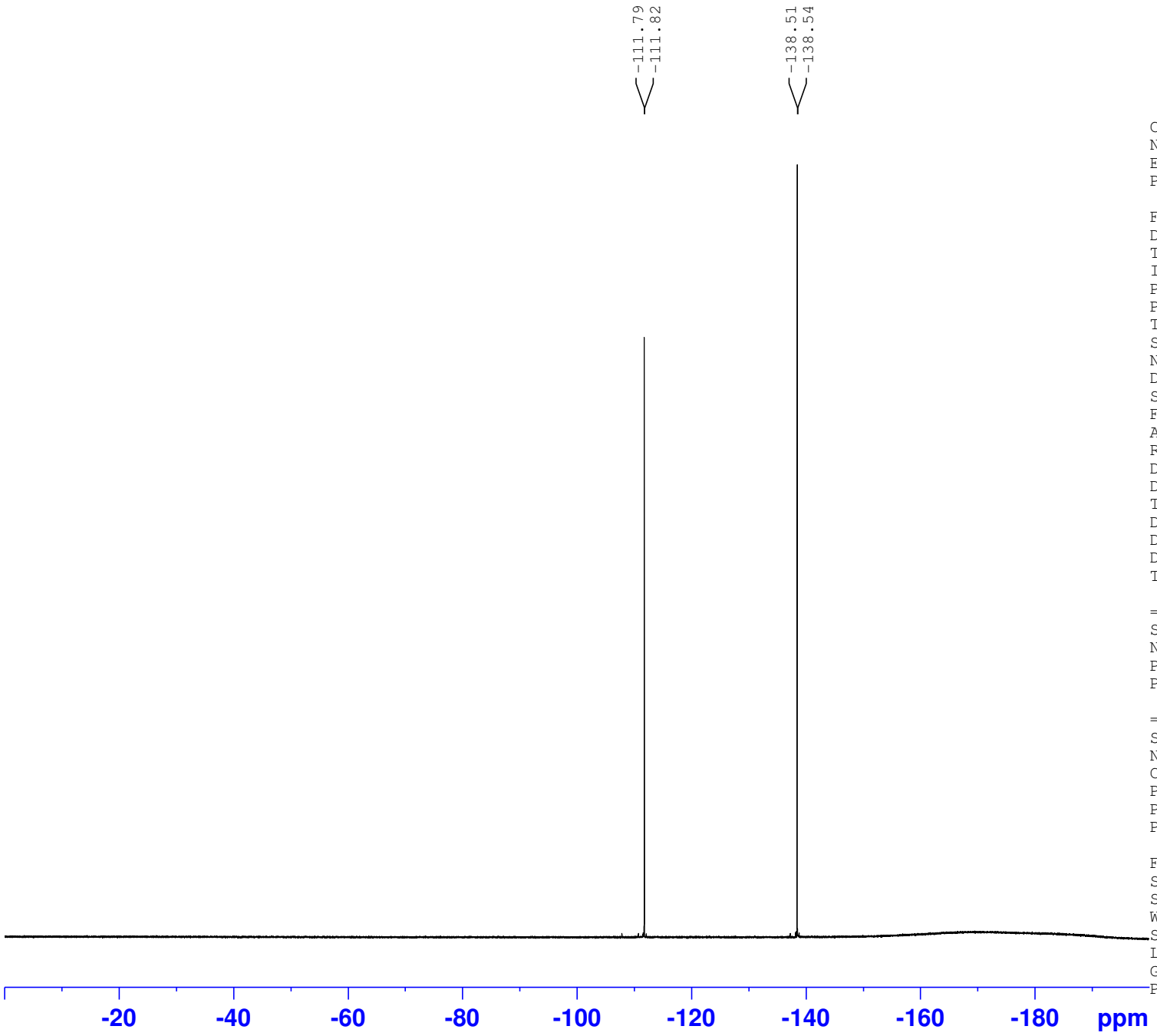
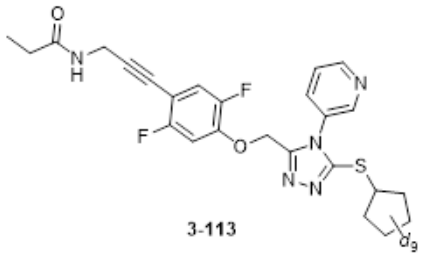




NAME	CNA-781-3
EXPNO	2
PROCNO	1
Date_	20170315
Time	20.32
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	820
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	294.7 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-781-3, 19F, CDCl3, 500 MHz





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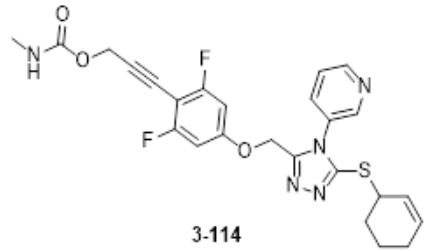
```
Current Data Parameters
NAME          CNA-781-3
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_          20170315
Time              21.02
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG      zgfhigqn.2
TD               131072
SOLVENT            CDCl3
NS                    16
DS                     4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ              0.5767168 sec
RG                   203
DW                4.400 usec
DE                6.50 usec
TE                297.5 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                19F
P1                 5.00 usec
PLW1        10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2        18.00000000 W
PLW12        0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-37, 1H, CDCl3, 500 MHz

8.716 8.713 8.706 8.704 8.555 8.550 7.669 7.666 7.664 7.661 7.653 7.650 7.648 7.645 7.471 7.461 7.455 7.445 6.427 6.410 5.815 5.813 5.795 5.793 5.681 5.677 5.673 5.024 4.845 4.488 4.484 2.747 2.737 2.007 1.968 1.958 1.955 1.951 1.947 1.943 1.938 1.930 1.646 1.607



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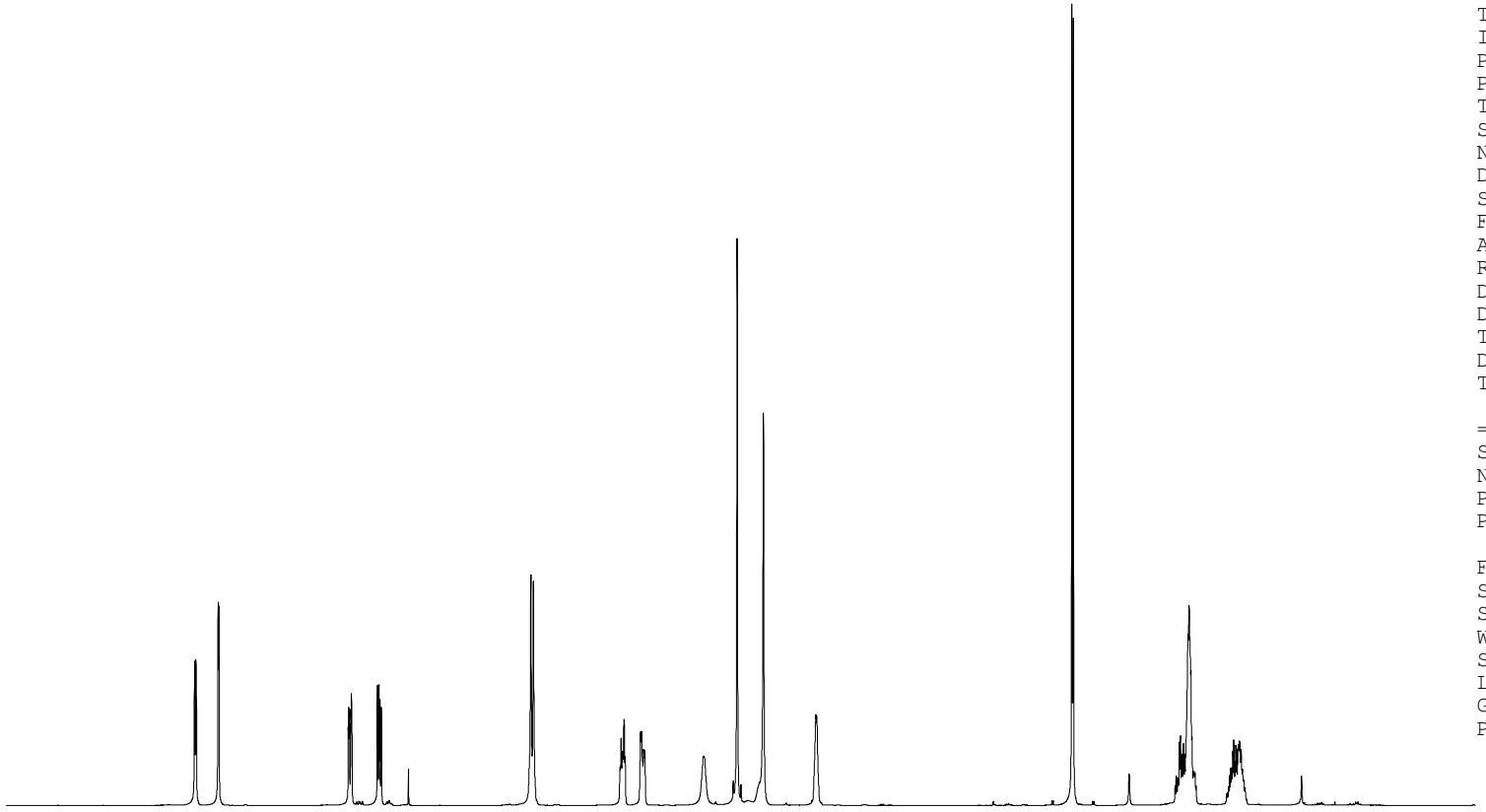
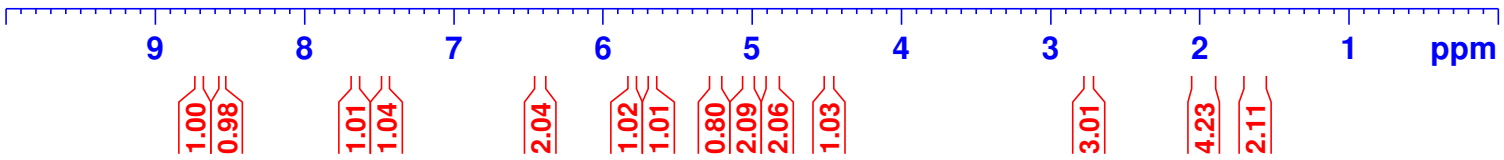
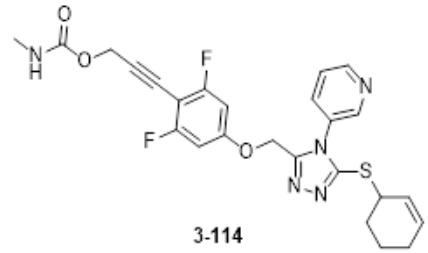


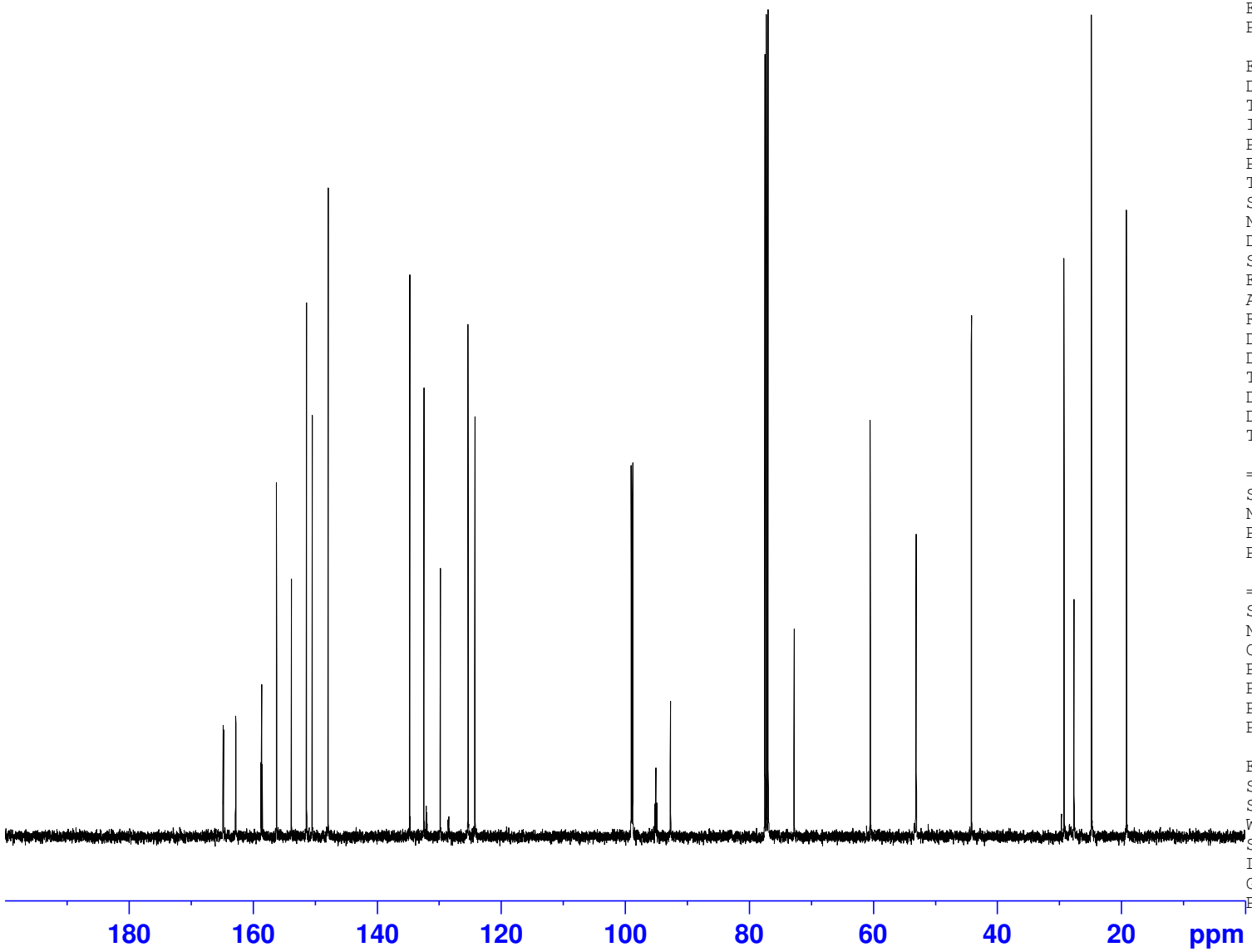



```
Current Data Parameters
NAME          CNA-781-37
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170607
Time               20.11
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                    32
DW                50.000 usec
DE                 6.50 usec
TE                298.8 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1630887 MHz
NUC1                   1H
P1                 11.50 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1600128 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-37, 13C, CDCl3, 500 MHz

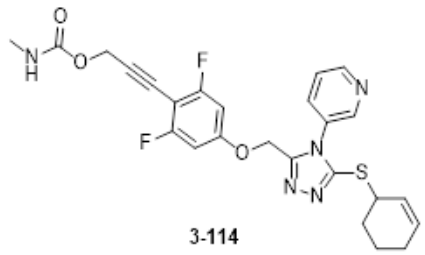


164.81
164.74
162.79
162.73
158.70
158.59
158.49
156.17
153.77
151.35
150.43
147.86
134.69
132.40
129.77
125.30
124.19
98.97
98.93
98.79
98.75
95.17
95.01
94.85
92.65
77.42
77.16
76.91
72.71
60.44
53.03
44.12
29.18
27.57
24.76
19.12




```
Current Data Parameters
NAME          CNA-781-37
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170607
Time               20.29
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  256
DS                    2
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ            1.1010048 sec
RG                  203
DW               16.800 usec
DE                6.50 usec
TE               299.8 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         125.7779086 MHz
NUC1                 13C
P1                10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W
PLW13         0.23805000 W

F2 - Processing parameters
SI                32768
SF           125.7653320 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

CNA-781-37, 19F, CDCl3, 500 MHz



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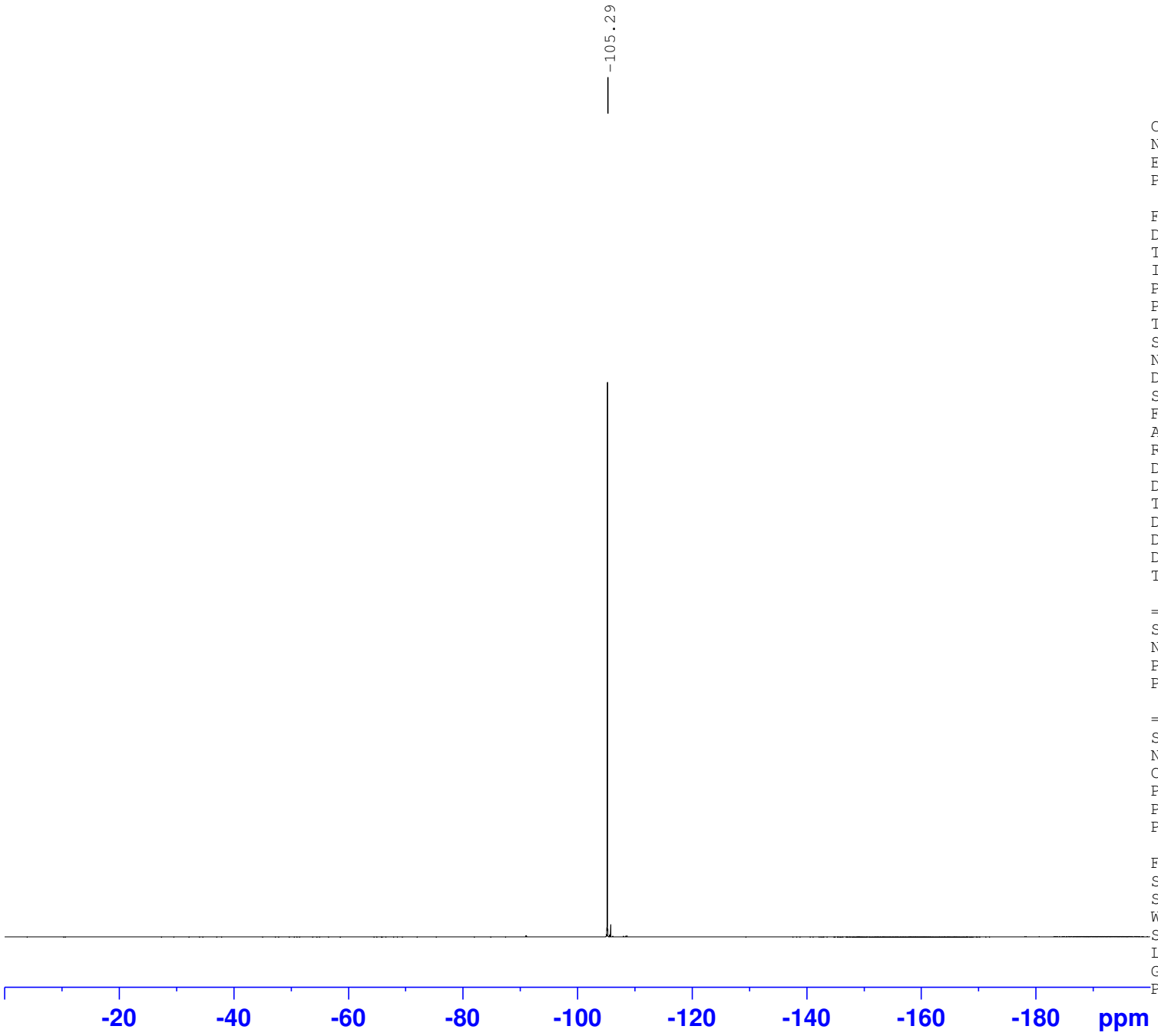
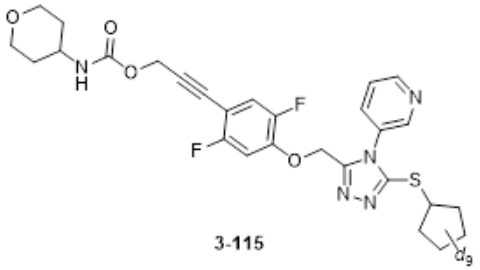
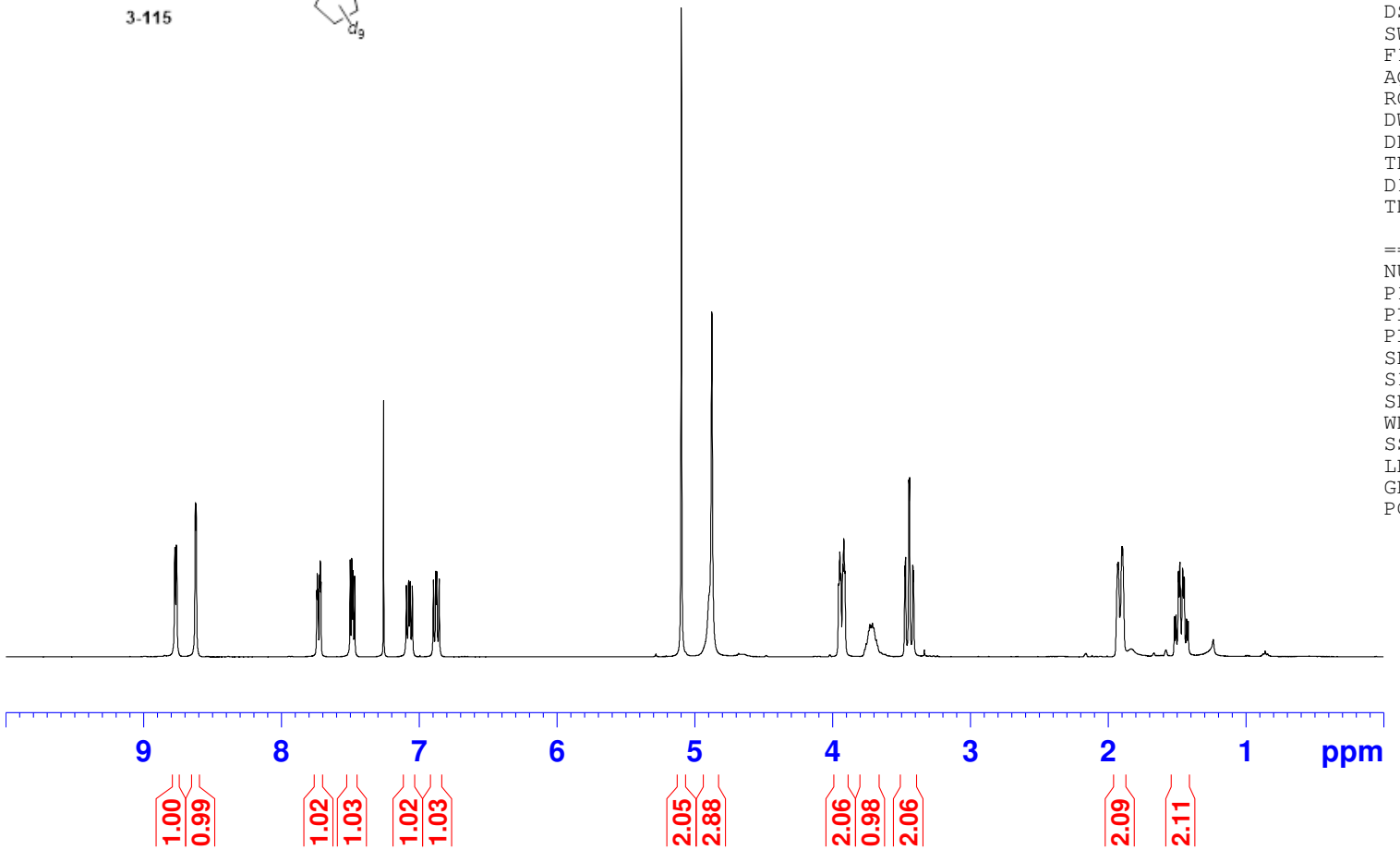



```
Current Data Parameters
NAME          CNA-781-37
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170607
Time               20.13
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG       zgfhigqn.2
TD                131072
SOLVENT             CDCl3
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                298.7 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                  19F
P1                 5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-752-85, 1H, CDCl3, 400 MHz

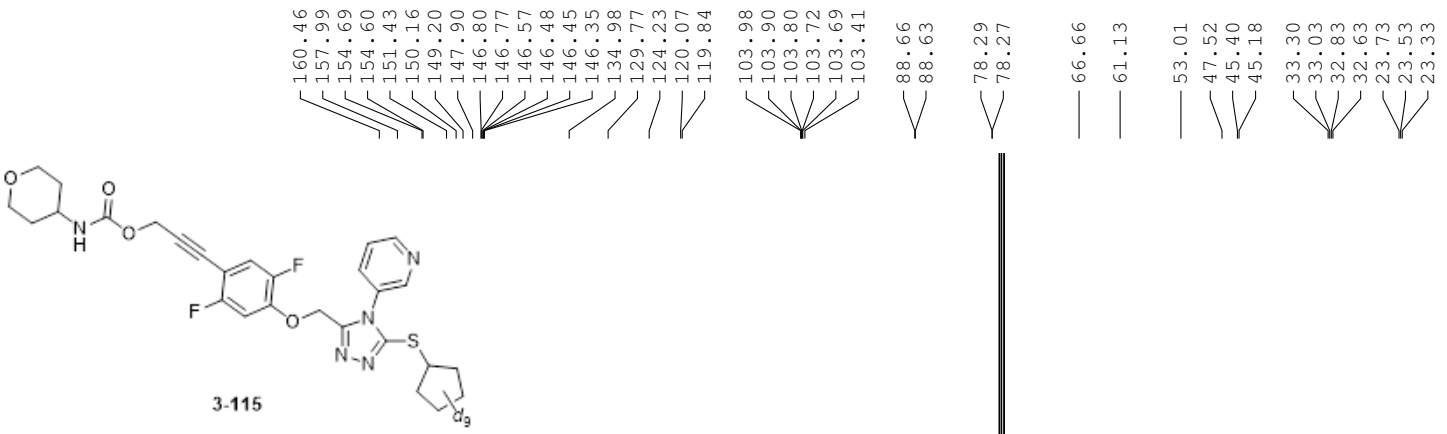
8.773 8.770 8.761 8.759 8.623 8.618 7.742 7.740 7.725 7.721 7.720 7.503 7.491 7.483 7.471 7.260 7.079 7.068 6.899 6.881 6.874 6.857 5.099 4.877 3.948 3.941 3.927 3.920 3.911 3.476 3.471 3.447 3.442 3.418 3.413 1.932 1.927 1.901 1.895 1.491 1.480 1.459 1.451 1.448





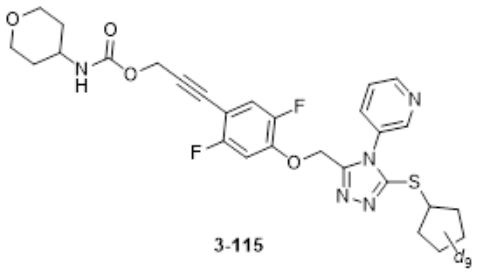
NAME	CNA-752-85
EXPNO	1
PROCNO	1
Date_	20170216
Time	11.41
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	114
DW	60.800 usec
DE	6.50 usec
TE	294.4 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300123 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-752-85, 13C, CDCl3, 400 MHz



NAME	CNA-752-85
EXPNO	2
PROCNO	1
Date_	20170216
Time	12.58
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1536
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 use
DE	6.50 use
TE	294.7 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 use
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 use
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-752-85, 19F, CDCl3, 500 MHz



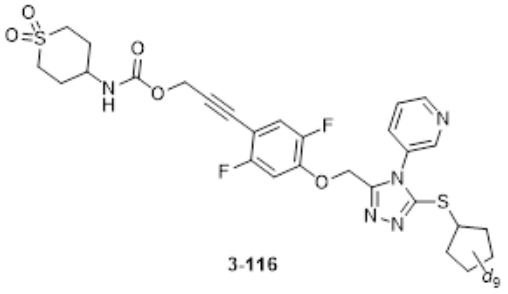
-111.12
-111.15
-138.50
-138.53

-20 -40 -60 -80 -100 -120 -140 -160 -180 ppm

```
Current Data Parameters
NAME          CNA-752-85
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170216
Time               13.54
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG       zgfhigqn.2
TD                131072
SOLVENT             CDCl3
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                297.1 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                19F
P1                 5.00 usec
PLW1        10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2        18.00000000 W
PLW12        0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-752-90, 1H, CDCl3, 500 MHz

8.787 8.784 8.778 8.775 8.633 8.629 7.747 7.744 7.742 7.739 7.731 7.728 7.726 7.723 7.512 7.511 7.502 7.501 7.496 7.495 7.486 7.485 7.260 7.098 7.085 7.077 7.064 6.919 6.905 6.899 6.885 5.112 4.903 3.097 3.083 3.073 2.363 2.356 2.353 2.336 2.334 2.329 2.161 1.576



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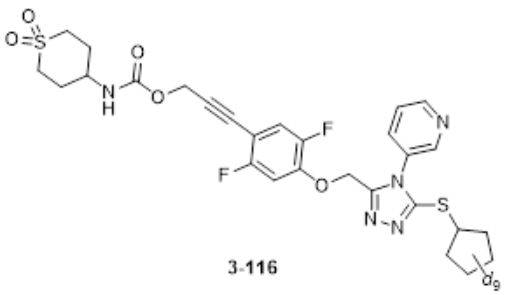
```
Current Data Parameters
NAME          CNA-752-90
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170302
Time               14.22
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10000.000 Hz
FIDRES         0.152588 Hz
AQ            3.2767999 sec
RG                   203
DW                50.000 usec
DE                 6.50 usec
TE                296.5 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1630887 MHz
NUC1                   1H
P1                 11.50 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1600124 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

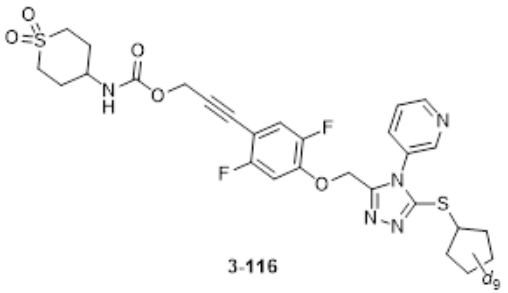
CNA-752-90, 13C, CDCl3, 500 MHz

160.14
158.14
154.88
154.69
151.39
150.20
148.97
147.84
147.01
146.63
146.55
146.45
135.00
129.74
124.26
119.86
119.70
103.72
103.65
103.59
103.51
103.44
88.45
78.44
77.39
77.13
76.88
61.10
60.41
53.24
49.13
46.74
45.60
45.43
45.26
32.96
32.80
32.64
29.70
23.66
23.50
23.35

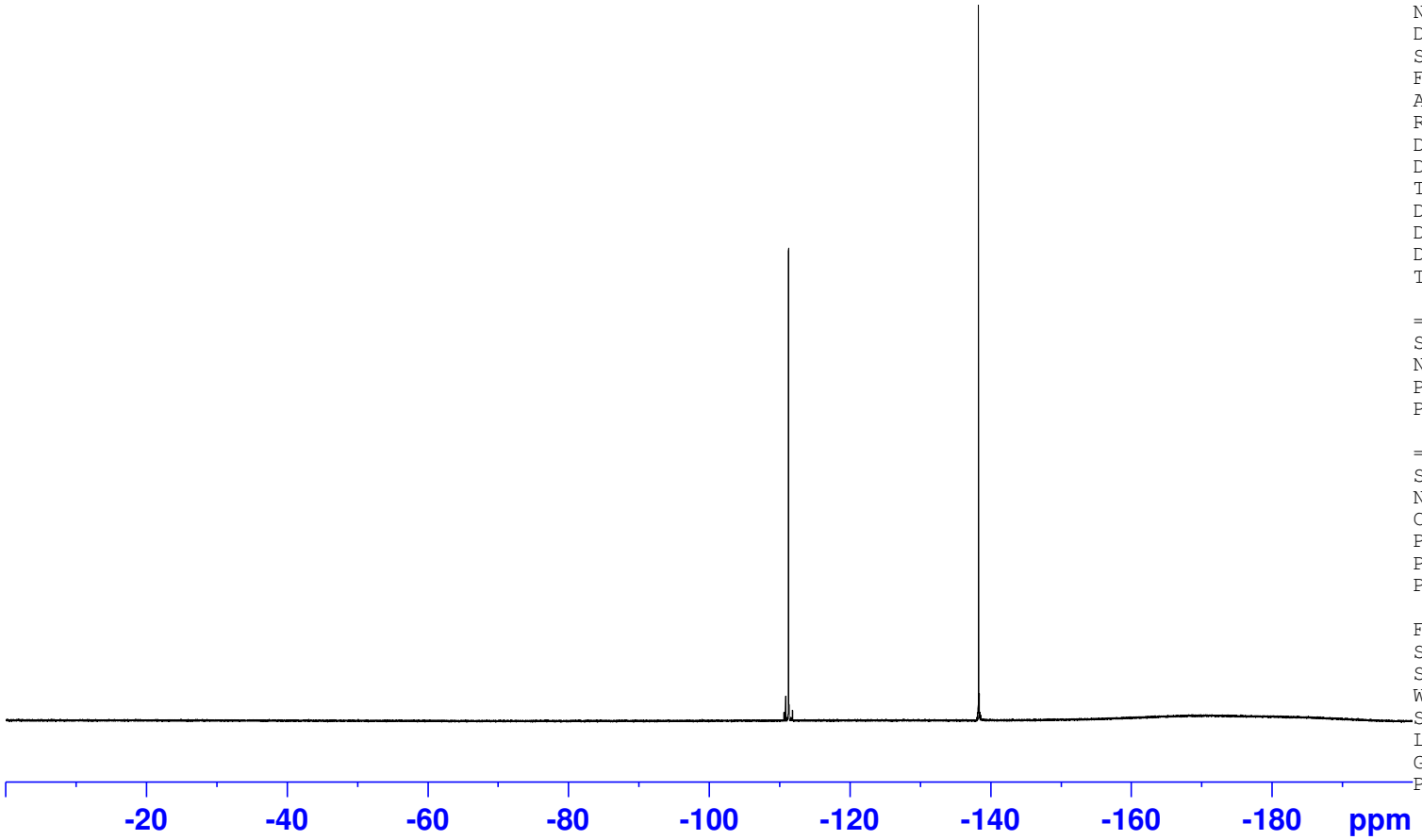



```
Current Data Parameters
NAME          CNA-752-90
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170302
Time               10.59
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  256
DS                    2
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ            1.1010048 sec
RG                  203
DW               16.800 usec
DE                6.50 usec
TE               297.5 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         125.7779086 MHz
NUC1                13C
P1                10.50 usec
PLW1       110.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W
PLW13         0.23805000 W

F2 - Processing parameters
SI                 32768
SF           125.7653320 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

CNA-752-90, 19F CDCl3, 500 MHz



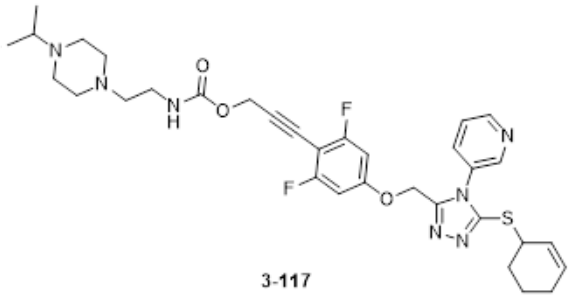
-111.33
-111.36
-138.31
-138.34




```
Current Data Parameters
NAME          CNA-752-90
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170302
Time               11.01
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG       zgfhigqn.2
TD                131072
SOLVENT             CDCl3
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                297.0 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                  19F
P1                 5.00 usec
PLW1        10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              80.00 usec
PLW2        18.00000000 W
PLW12        0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-36, 1H, CDCl3, 500 MHz

8.774 8.772 8.765 8.762 8.597 8.592 7.670 7.665 7.662 7.653 7.649 7.645 7.500 7.490 7.484 7.474 7.260 6.488 6.471 5.863 5.749 5.048 4.922 4.583 4.578 3.288 3.277 3.266 2.635 2.622 2.609 2.511 2.472 2.460 2.448 2.086 2.027 2.023 2.020 2.016 1.699 1.678 1.036 1.023



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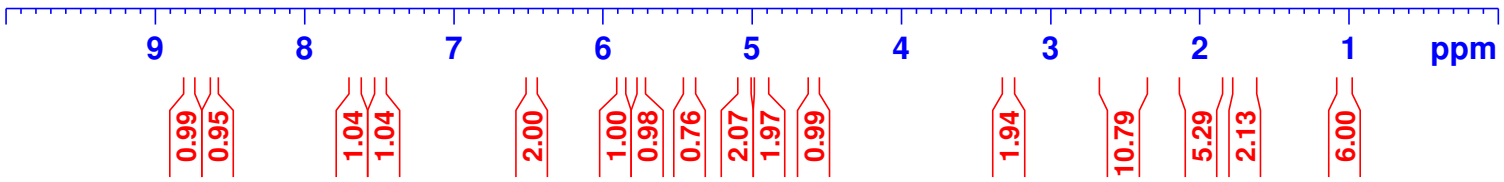
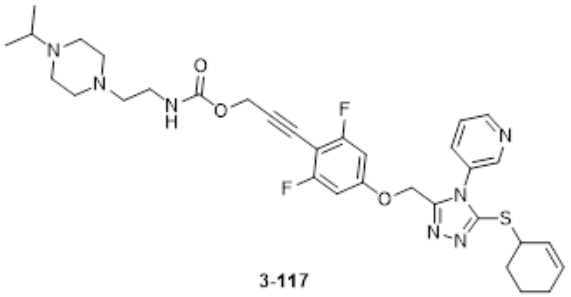



```
Current Data Parameters
NAME          CNA-781-36
EXPNO                  5
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170608
Time               12.40
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10000.000 Hz
FIDRES         0.152588 Hz
AQ            3.2767999 sec
RG                  71.8
DW                50.000 usec
DE                 6.50 usec
TE                298.7 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1630887 MHz
NUC1                   1H
P1                 11.50 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1600134 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-36, 13C, CDCl3, 500 MHz

164.84
164.77
162.82
162.76
158.70
158.59
158.48
155.42
153.76
151.34
150.36
147.86
134.64
132.37
129.76
125.32
124.14
98.97
98.93
98.79
98.75
95.06
94.90
92.59
77.41
77.15
76.90
72.78
60.44
56.80
54.33
53.17
53.02
48.55
44.09
37.65
29.19
24.76
19.12
18.58



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Current Data Parameters
NAME CNA-781-36
EXPNO 4
PROCNO 1

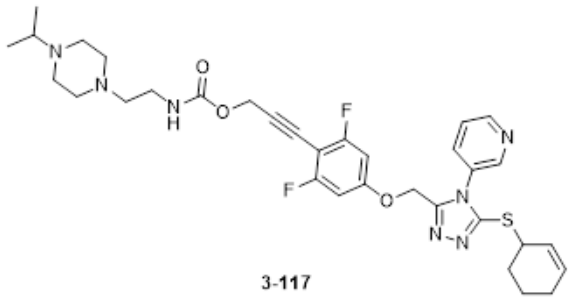
F2 - Acquisition Parameters
Date_ 20170607
Time 20.48
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 2
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 299.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 125.7779086 MHz
NUC1 13C
P1 10.50 usec
PLW1 110.00000000 W

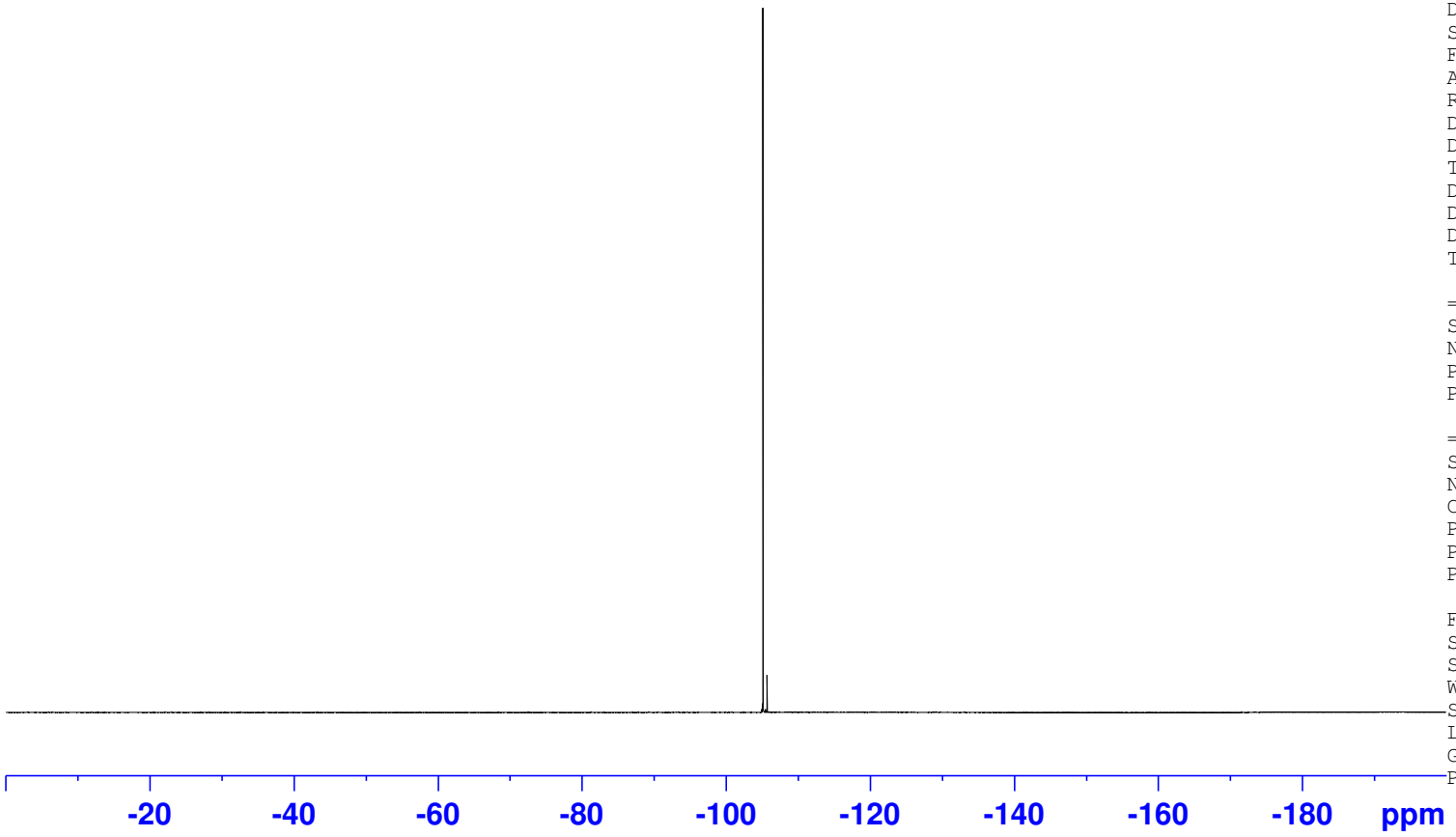
======== CHANNEL f2 ========
SFO2 500.1620006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 18.00000000 W
PLW12 0.37195000 W
PLW13 0.23805000 W

F2 - Processing parameters
SI 32768
SF 125.7653320 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

CNA-781-36, 19F, CDCl3, 500 MHz



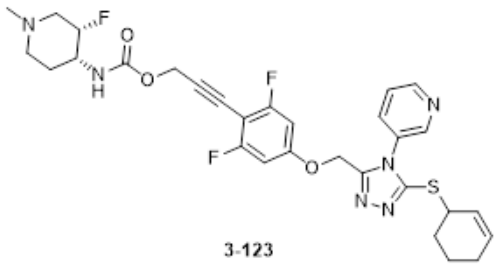
-105.15




```
Current Data Parameters
NAME          CNA-781-36
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170607
Time               19.57
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG       zgfhigqn.2
TD                131072
SOLVENT             CDCl3
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                298.5 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                  19F
P1                 5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-49, 1H, CDCl3, 400 MHz

8.770 8.767 8.758 8.755 8.593 8.587 7.669 7.667 7.663 7.652 7.649 7.646 7.642 7.498 7.486 7.478 7.466 7.260 6.484 6.463 5.852 5.849 5.045 4.912 4.568 4.562 2.273 2.109 2.084 2.072 2.060 2.048 2.037 2.031 2.018 2.014 2.009 2.005 1.996 1.816 1.807 1.684 1.677 1.668



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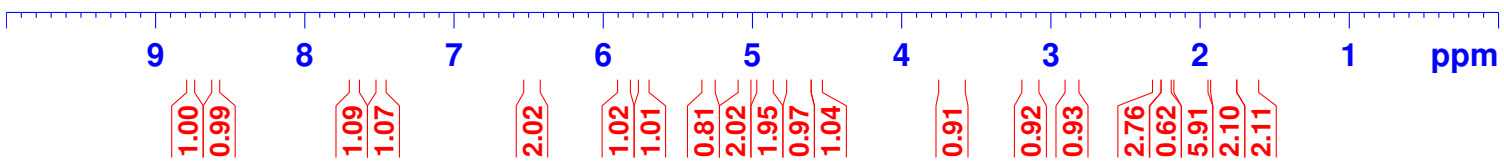
NAME	CNA-781-49
EXPNO	1
PROCNO	1
Date_	20170720
Time	12.21
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	71.8
DW	60.800 usec
DE	6.50 usec
TE	298.2 K
D1	2.00000000 sec
TD0	1

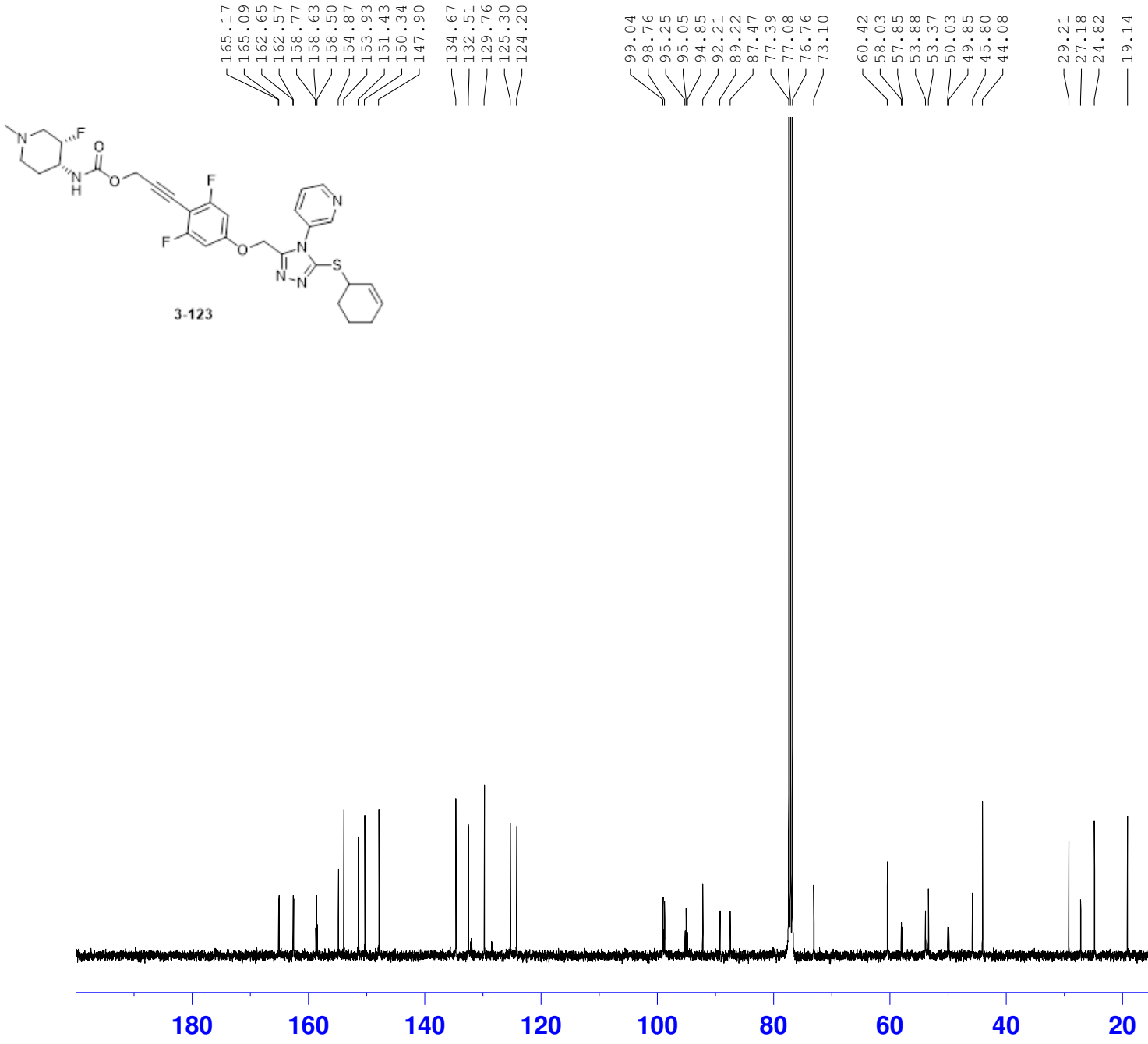
======== CHANNEL f1 ========

NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300125 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



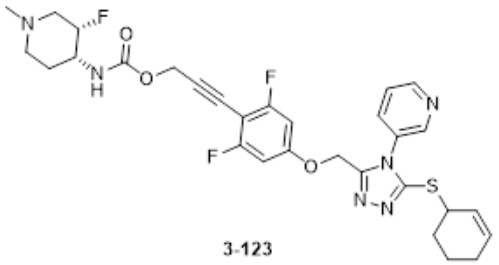
1.00 0.99 1.09 1.07 2.02 1.02 1.01 0.81 2.02 1.95 0.97 1.04 0.91 0.92 0.93 2.76 0.62 5.91 2.10 2.11

CNA-781-49, 13C, CDCl3, 400 MHz



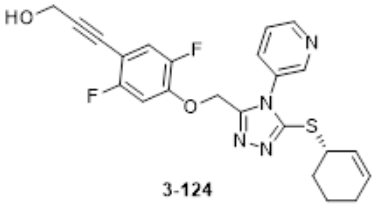
NAME	CNA-781-49
EXPNO	2
PROCNO	1
Date_	20170720
Time	14.28
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1024
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	71.8
DW	20.800 usec
DE	6.50 usec
TE	298.2 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-781-49, 19F, CDCl3, 500 MHz

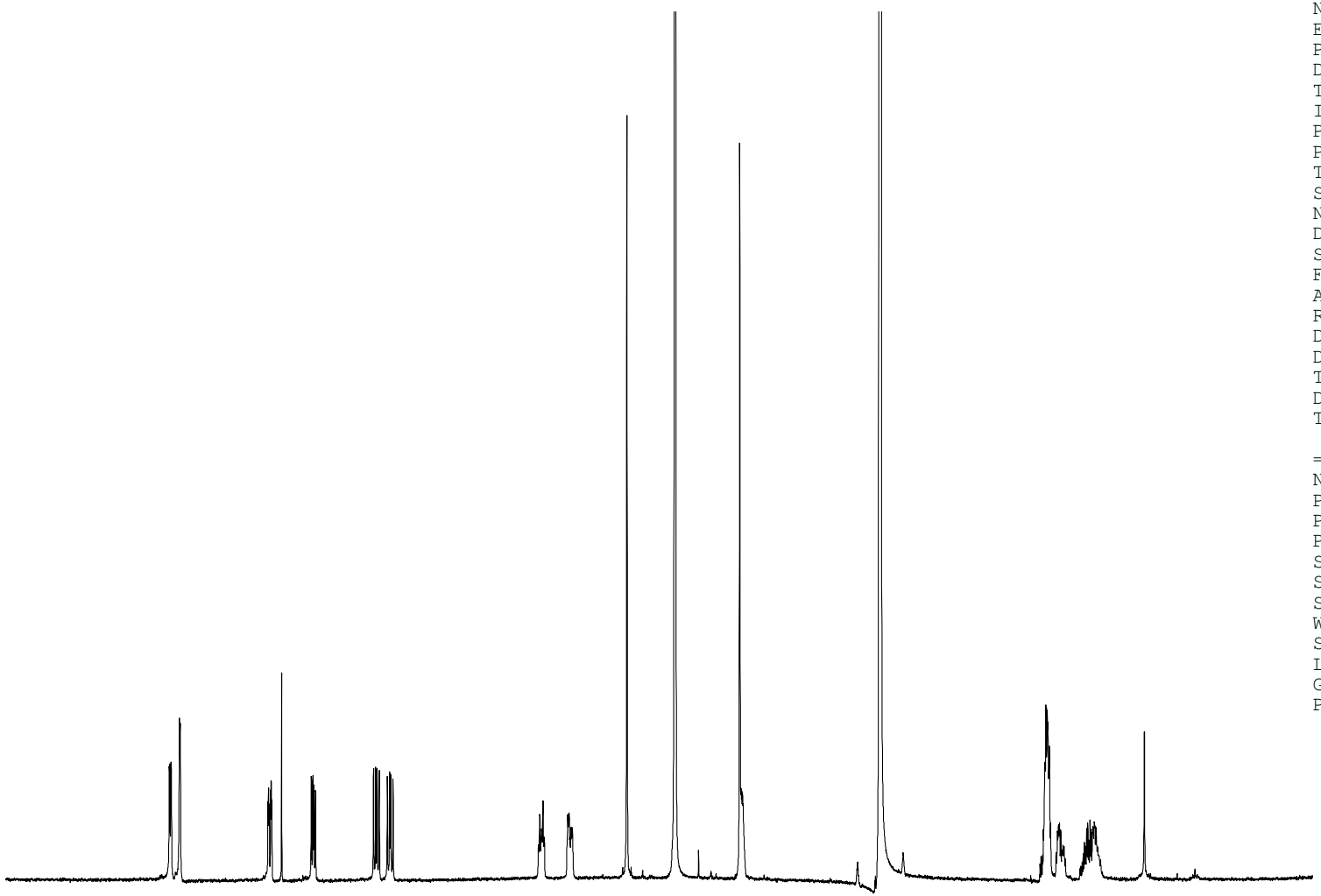


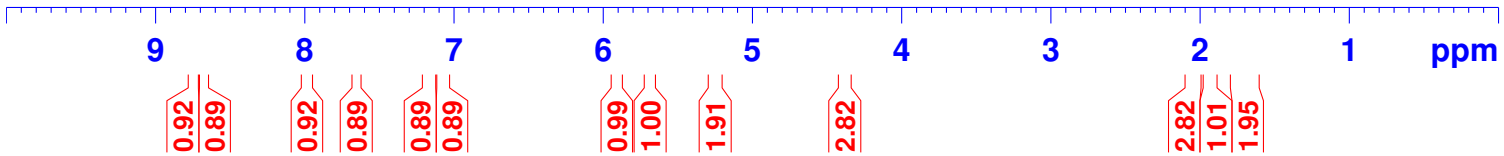

```
Current Data Parameters
NAME          CNA-781-49
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170720
Time               15.18
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG       zgfhigqn.2
TD                131072
SOLVENT             CDCl3
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                297.9 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5656054 MHz
NUC1                  19F
P1                 5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-11, 1H, MeOD/CDCl3, 400 MHz



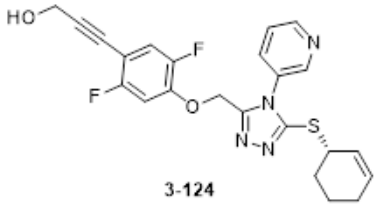
8.748 8.745 8.736 8.733 8.671 8.665 7.994 7.990 7.988 7.984 7.974 7.970 7.968 7.964 7.889 7.662 7.650 7.642 7.630 7.186 7.170 7.159 7.142 7.080 7.063 7.055 7.037 5.891 5.888 5.247 4.384 4.373 4.368 4.362 3.314 3.310 3.306 2.051 2.047 2.042 2.038 2.032 2.027 2.014



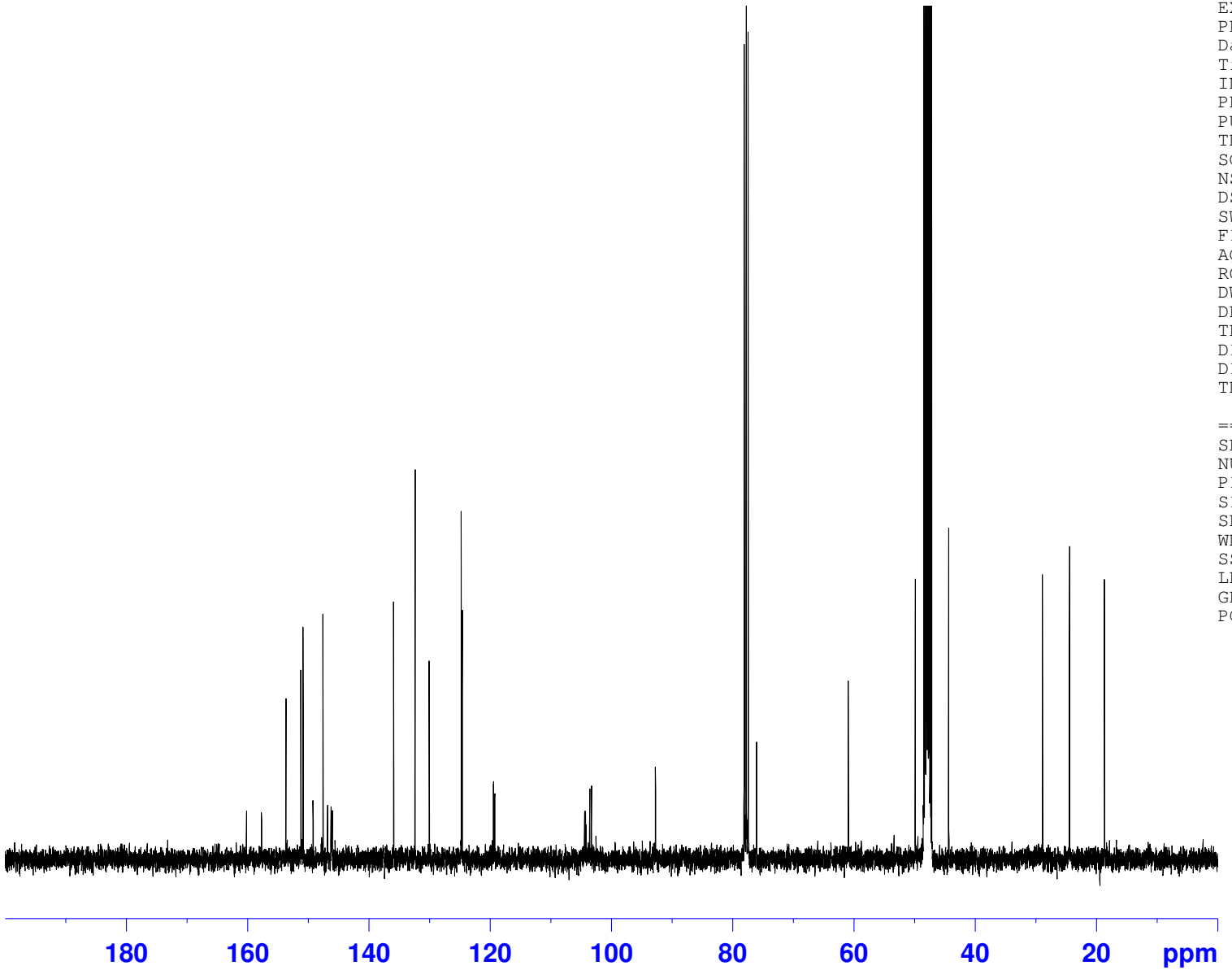


NAME	CNA-781-11
EXPNO	5
PROCNO	1
Date_	20170329
Time	19.05
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zg30
TD	65536
SOLVENT	MeOD
NS	80
DS	2
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	161
DW	60.800 usec
DE	6.50 usec
TE	294.8 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.31 usec
PL1	-3.90 dB
PL1W	21.64248466 W
SFO1	400.2324716 MHz
SI	32768
SF	400.2300102 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-781-11, 13C, MeOD/CDCl3, 400 MHz

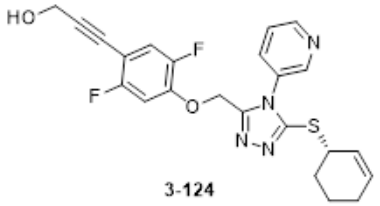


160.23 160.21 157.76 157.73 153.70 151.26 150.88 149.26 149.24 147.61 146.85 146.82 146.29 146.19 146.16 146.06 135.96 132.40 130.08 124.81 124.63 119.50 119.47 119.28 119.25 104.45 104.37 104.27 104.19 103.60 103.58 103.33 103.31 92.77 92.74 78.11 77.78 77.46 76.10 76.08 60.95 49.88 48.48 48.27 48.06 47.84 47.63 47.41 47.20 44.38 28.90 24.45 18.68



NAME	CNA-781-11
EXPNO	3
PROCNO	1
Date_	20170325
Time	5.51
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	Methanol-D4
NS	3072
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	87.6 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	100.6228293 MHz
NUC1	13C
P1	10.00 usec
SI	32768
SF	100.6127685 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-781-11, 19F, MeOD/CDCl3, 400 MHz



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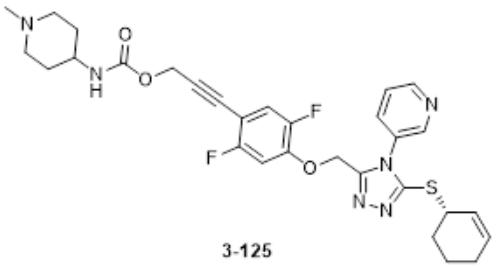
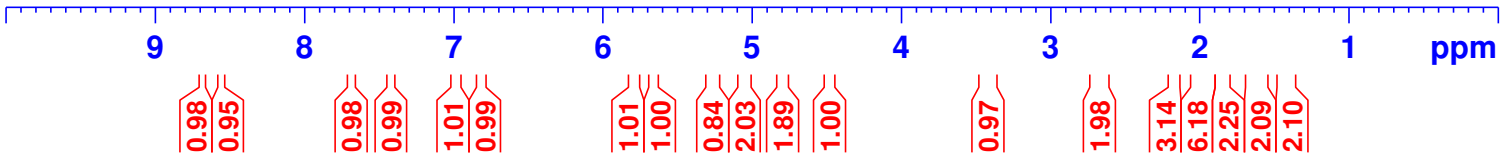
NAME	CNA-781-11
EXPNO	4
PROCNO	1
Date_	20170325
Time	5.53
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	Methanol-D4
NS	16
DS	4
SWH	89285.711 Hz
FIDRES	0.681196 Hz
AQ	0.7340532 sec
RG	203
DW	5.600 usec
DE	6.50 usec
TE	87.7 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	376.4607164 MHz
NUC1	19F
P1	14.20 usec
SI	65536
SF	376.4983662 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-781-12, 1H, CDCl3, 500 MHz

8.691 8.688 8.681 8.678 8.560 8.555 7.696 7.695 7.683 7.680 7.679 7.675 7.436 7.426 7.419 7.410 6.816 5.780 5.778 5.054 4.789 4.483 4.479 2.668 2.171 2.008 2.001 1.992 1.985 1.981 1.972 1.964 1.958 1.954 1.942 1.940 1.936 1.932 1.922 1.874 1.869 1.848 1.425 1.406





0.98 0.95 0.98 0.99 1.01 0.99 1.01 1.00 0.84 2.03 1.89 1.00 0.97 1.98 3.14 6.18 2.25 2.09 2.10

```
Current Data Parameters
NAME          CNA-781-12
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170413
Time               18.41
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                  22.6
DW                50.000 usec
DE                 6.50 usec
TE                296.2 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1630887 MHz
NUC1                   1H
P1                 11.50 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1600125 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-12, 13C, CDCl3, 500 MHz

160.10
158.12
154.72
153.89
151.31
150.33
148.91
148.88
147.84
146.96
146.94
146.46
146.38
146.36
146.28
134.98
132.40
129.67
125.28
124.17
119.93
119.74
103.90
103.84
103.76
103.69
103.62
103.41
88.84
88.81
78.08
78.07
77.44
77.19
76.94
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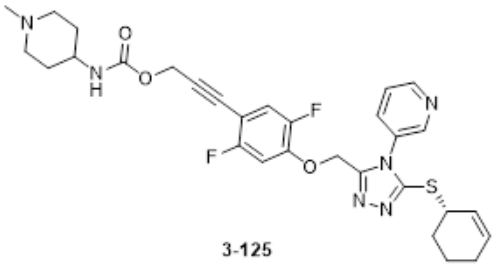
54.31
52.80
47.91
46.13
44.02
32.34
29.14
24.77
19.08



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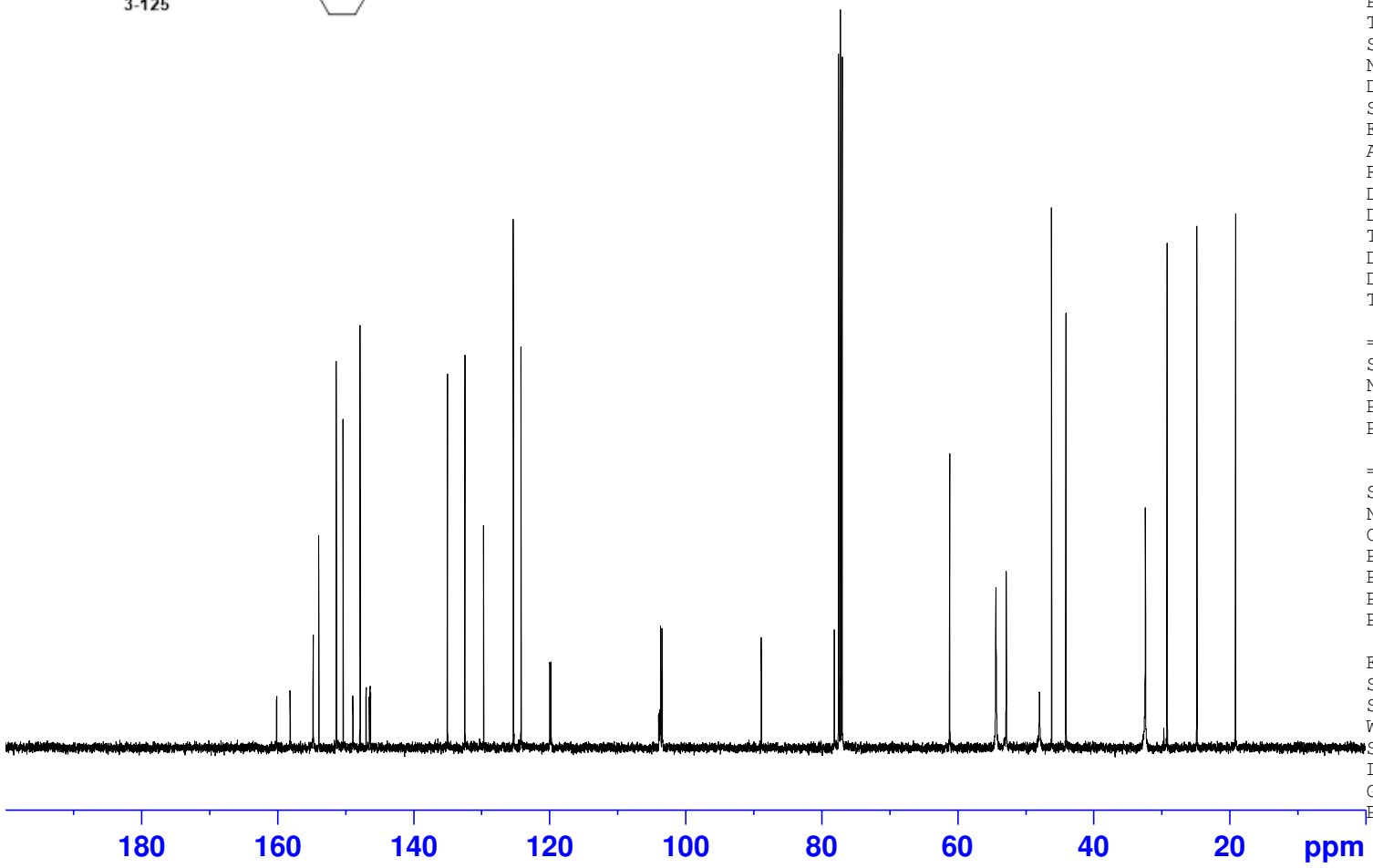


Current Data Parameters
NAME CNA-781-12
EXPNO 3
PROCNO 1

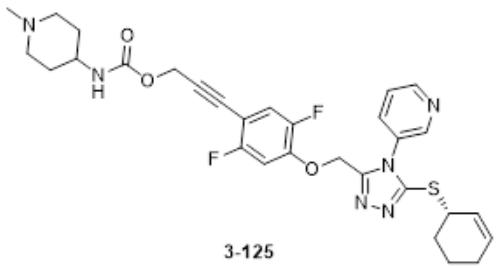
F2 - Acquisition Parameters
Date_ 20170413
Time 18.56
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 200
DS 2
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 296.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 125.7779086 MHz
NUC1 13C
P1 10.50 usec
PLW1 110.00000000 W

======== CHANNEL f2 ========
SFO2 500.1620006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 18.00000000 W
PLW12 0.37195000 W
PLW13 0.23805000 W

F2 - Processing parameters
SI 32768
SF 125.7653320 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

CNA-781-12, 19F, CDCl3, 500 MHz



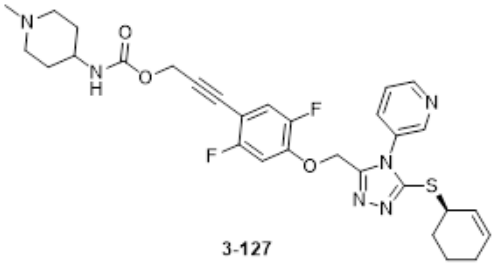
-111.25
-111.28
-138.54
-138.57

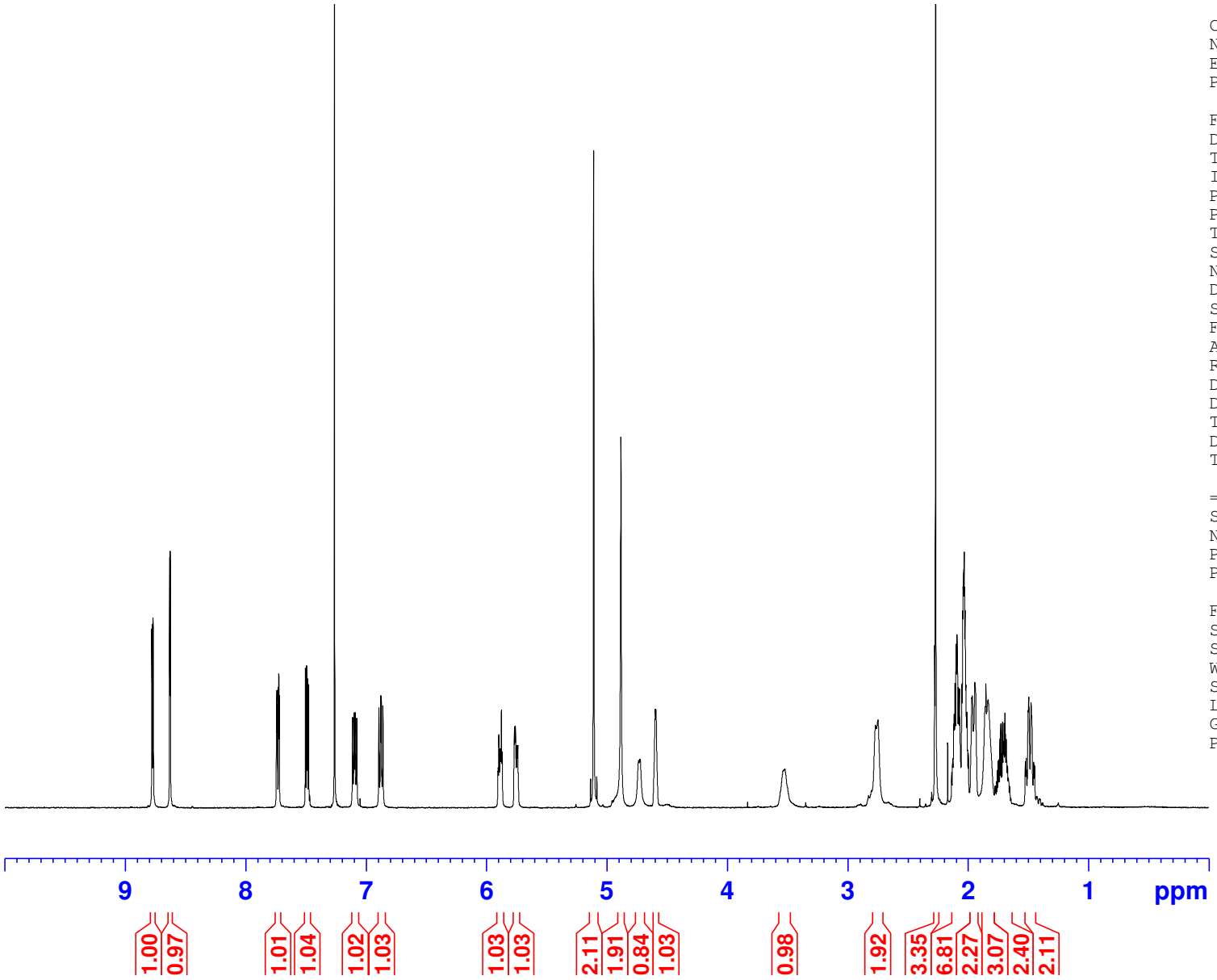
-20 -40 -60 -80 -100 -120 -140 -160 -180 ppm

```
Current Data Parameters
NAME          CNA-781-12
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170413
Time               18.43
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG       zgfhigqn.2
TD                131072
SOLVENT             CDCl3
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                296.2 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                  19F
P1                 5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-52, 1H, CDCl3, 500 MHz

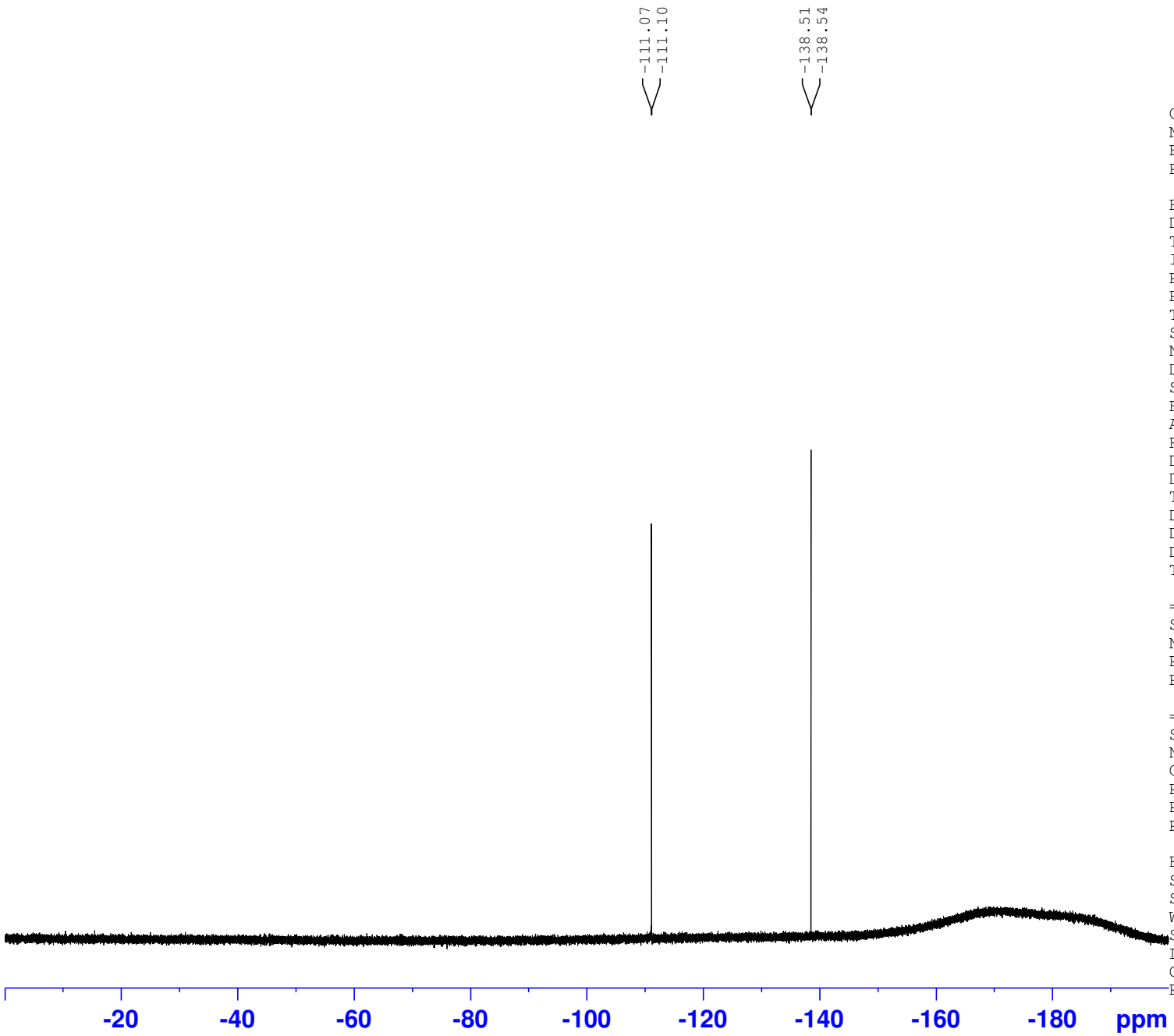
8.778 8.775 8.768 8.765 8.629 8.625 7.740 7.738 7.727 7.724 7.722 7.719 7.502 7.492 7.486 7.476 7.260 6.878 6.872 5.108 4.881 2.267 2.106 2.096 2.089 2.086 2.077 2.068 2.048 2.041 2.037 2.034 2.030 2.027 2.022 2.016 1.967 1.964 1.940 1.935 1.849 1.831 1.492 1.474

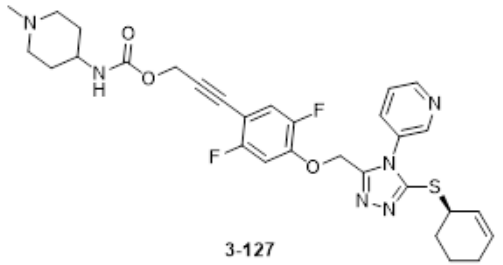





```
Current Data Parameters
NAME          CNA-781-52
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170807
Time               13.14
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                   128
DW                50.000 usec
DE                 6.50 usec
TE                296.9 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1630887 MHz
NUC1                   1H
P1                 11.50 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1600127 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-52, 19F, CDCl3, 500 MHz





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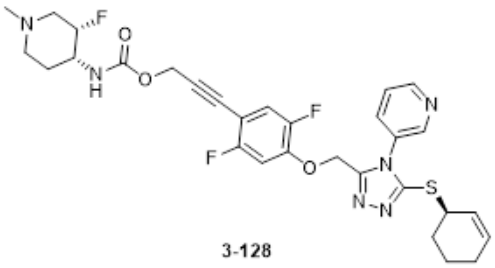
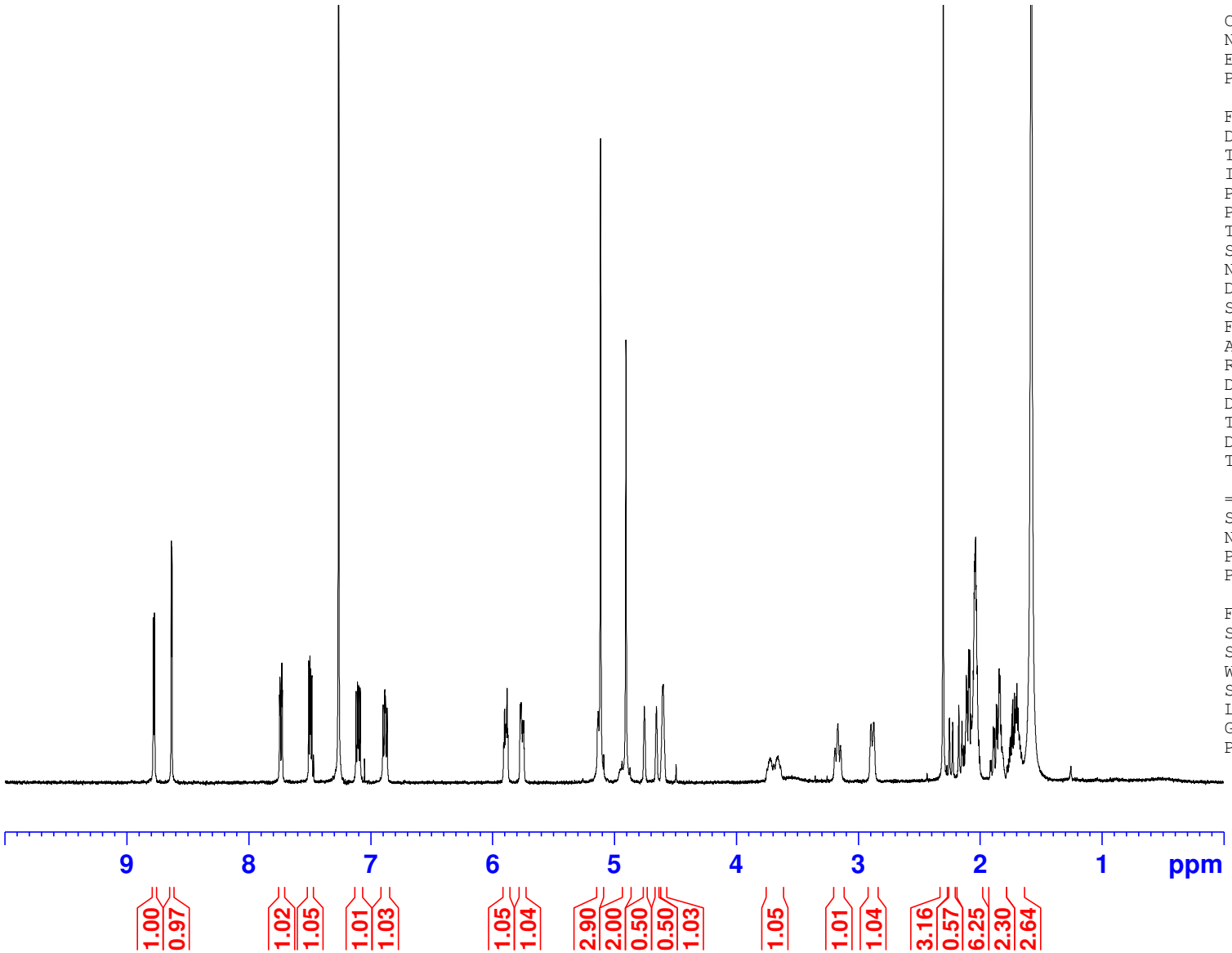
```
Current Data Parameters
NAME          CNA-781-52
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170807
Time               13.16
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG       zgfhigqn.2
TD                131072
SOLVENT             CDCl3
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                296.8 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                19F
P1                 5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2              80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-53, 1H, CDCl3, 500 MHz

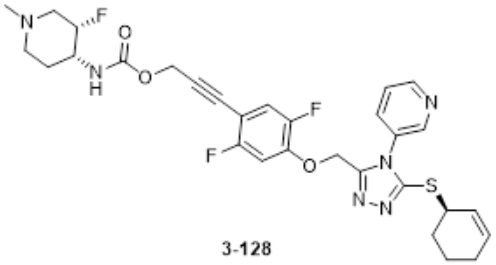
8.782 8.779 8.772 8.769 8.633 8.628 7.742 7.741 7.729 7.726 7.725 7.721 7.505 7.496 7.489 7.479 7.260 7.105 7.096 7.083 6.882 5.880 5.878 5.111 4.903 4.601 4.597 2.300 2.110 2.090 2.082 2.052 2.045 2.041 2.038 2.034 2.030 2.026 2.020 1.841 1.834 1.715 1.694 1.576



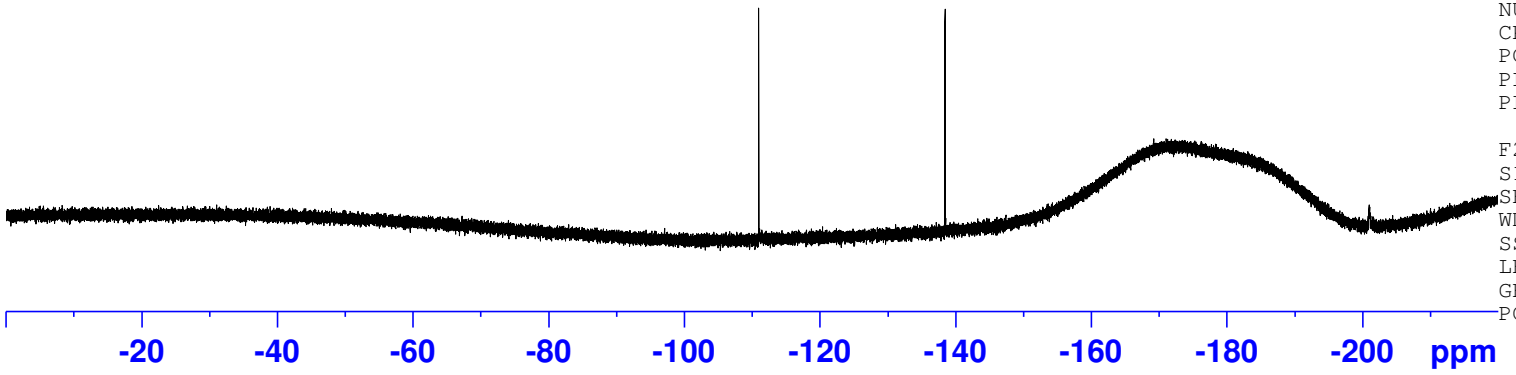



```
Current Data Parameters
NAME          CNA-781-53
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170807
Time               13.25
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10000.000 Hz
FIDRES         0.152588 Hz
AQ             3.2767999 sec
RG                   203
DW                50.000 usec
DE                 6.50 usec
TE                296.6 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1630887 MHz
NUC1                   1H
P1                 11.50 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1600130 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-53, 19F, CDCl3, 500 MHz



-111.01
-111.04
-138.50
-138.53
-201.09



Current Data Parameters
NAME CNA-781-53
EXPNO 3
PROCNO 1

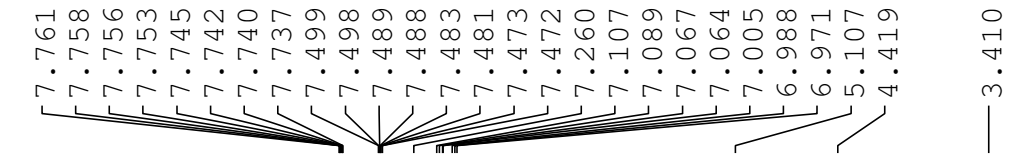
F2 - Acquisition Parameters
Date_ 20170807
Time 13.37
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgfhigqn.2
TD 131072
SOLVENT CDCl3
NS 64
DS 4
SWH 113636.367 Hz
FIDRES 0.866977 Hz
AQ 0.5767168 sec
RG 203
DW 4.400 usec
DE 6.50 usec
TE 296.7 K
D1 1.00000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
TD0 1

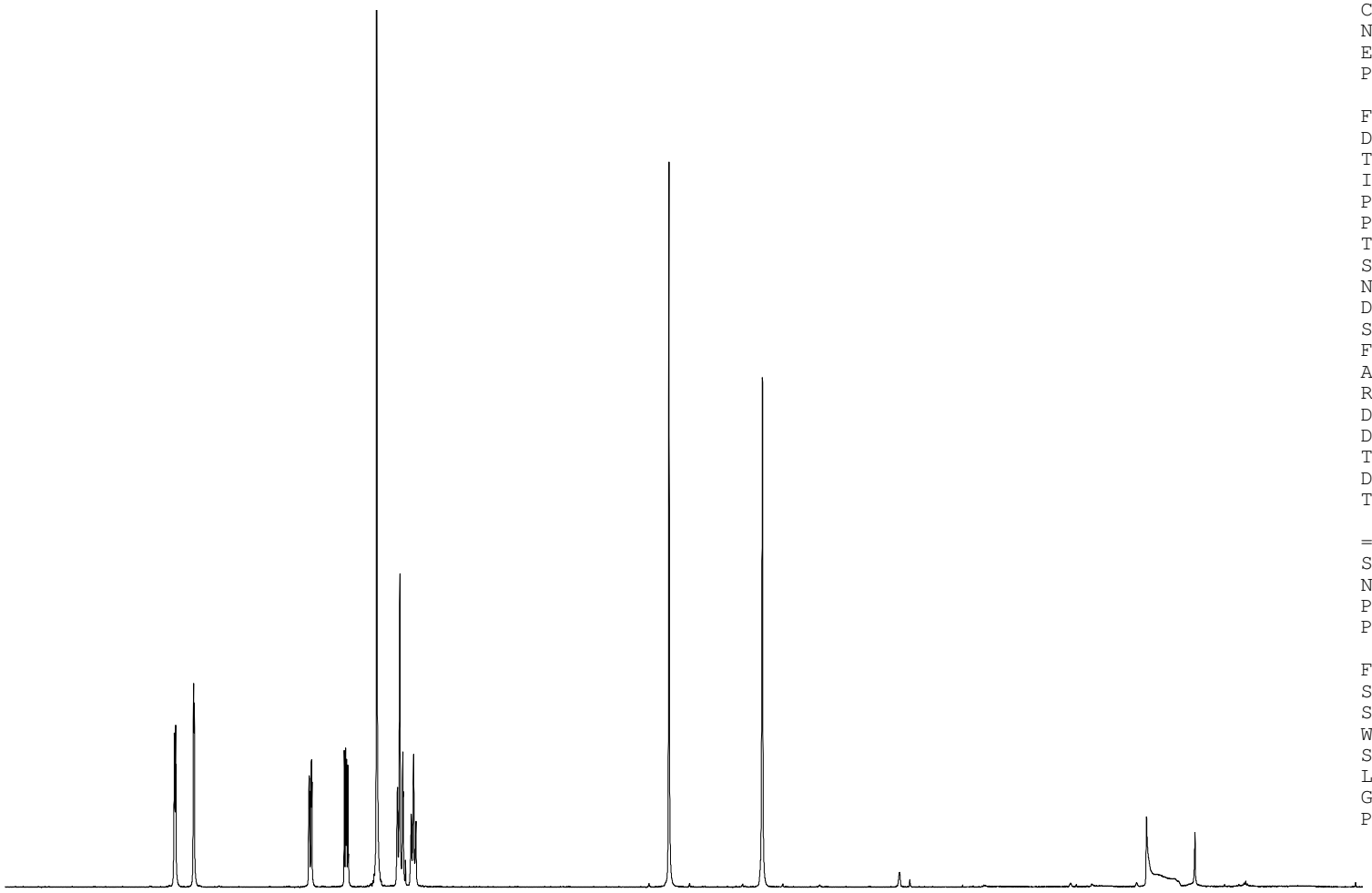
======== CHANNEL f1 ========
SFO1 470.5735434 MHz
NUC1 19F
P1 5.00 usec
PLW1 10.00000000 W

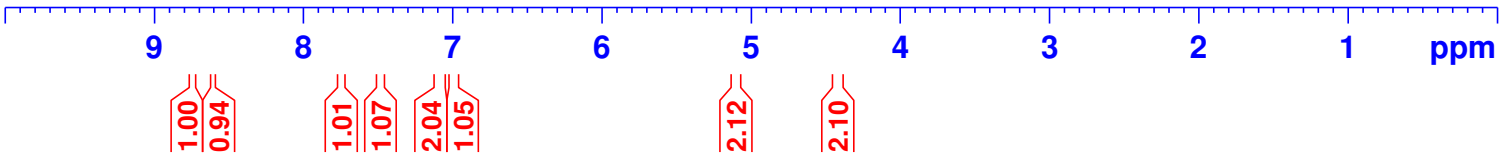
======== CHANNEL f2 ========
SFO2 500.1620006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 18.00000000 W
PLW12 0.37195000 W

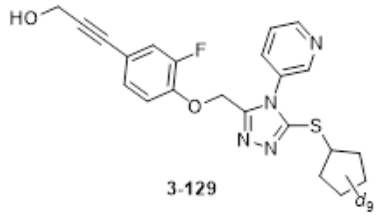
F2 - Processing parameters
SI 65536
SF 470.6206054 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

CNA-752-93, 1H, CDCl3/MeOD, 500 MHz



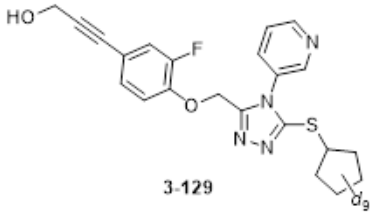


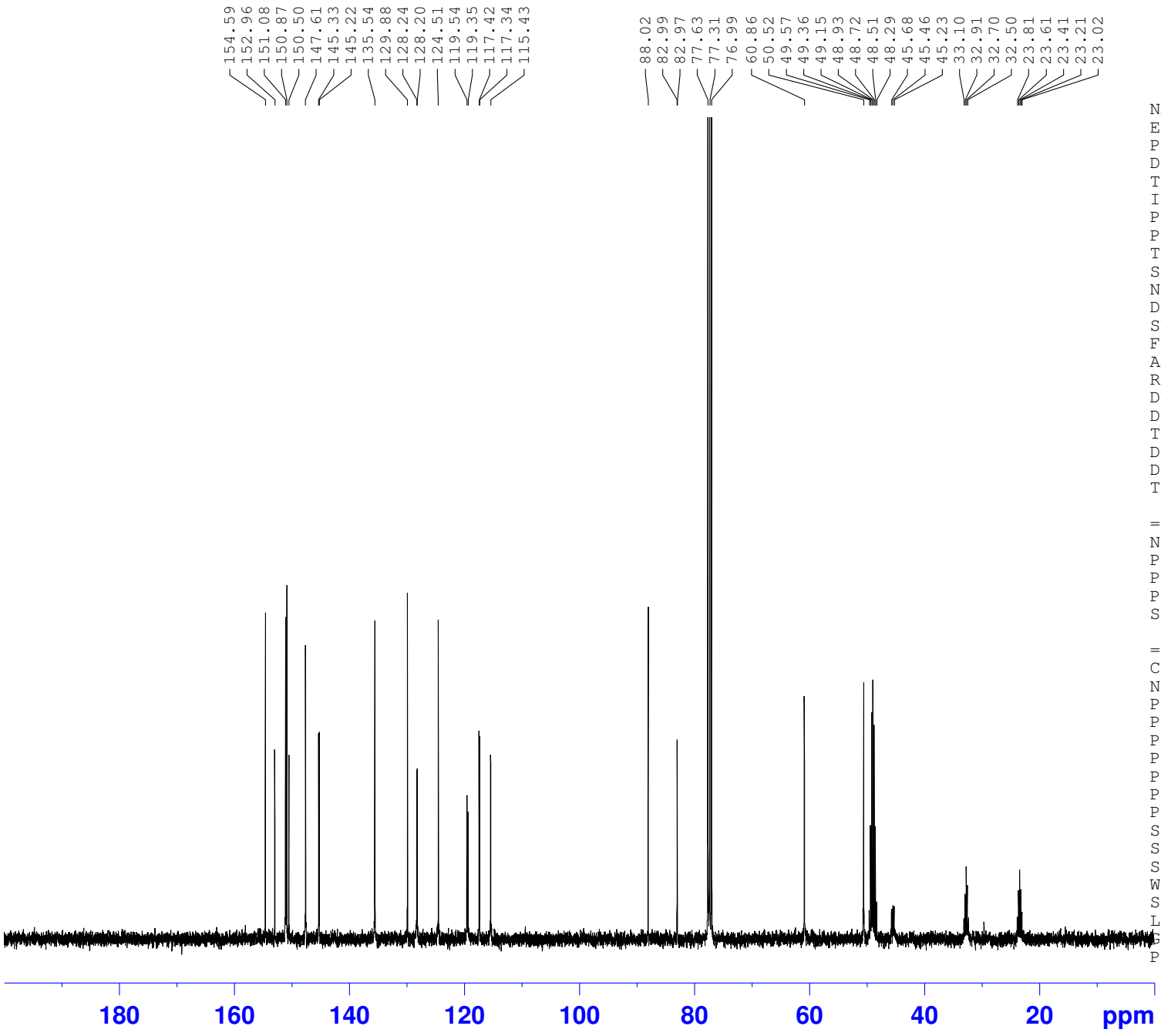





```
Current Data Parameters
NAME        CNA-752-93_2
EXPNO                 12
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170302
Time               14.13
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            10000.000 Hz
FIDRES             0.152588 Hz
AQ             3.2767999 sec
RG                   203
DW                50.000 usec
DE                 6.50 usec
TE                296.5 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          500.1630887 MHz
NUC1                  1H
P1                 11.50 usec
PLW1          18.00000000 W

F2 - Processing parameters
SI                 65536
SF            500.1600133 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

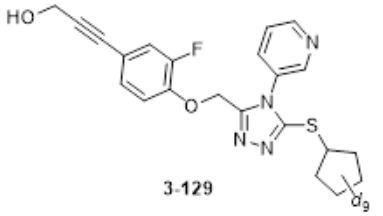
CNA-752-93, 13C, CDCl3/MeOD, 400 MHz

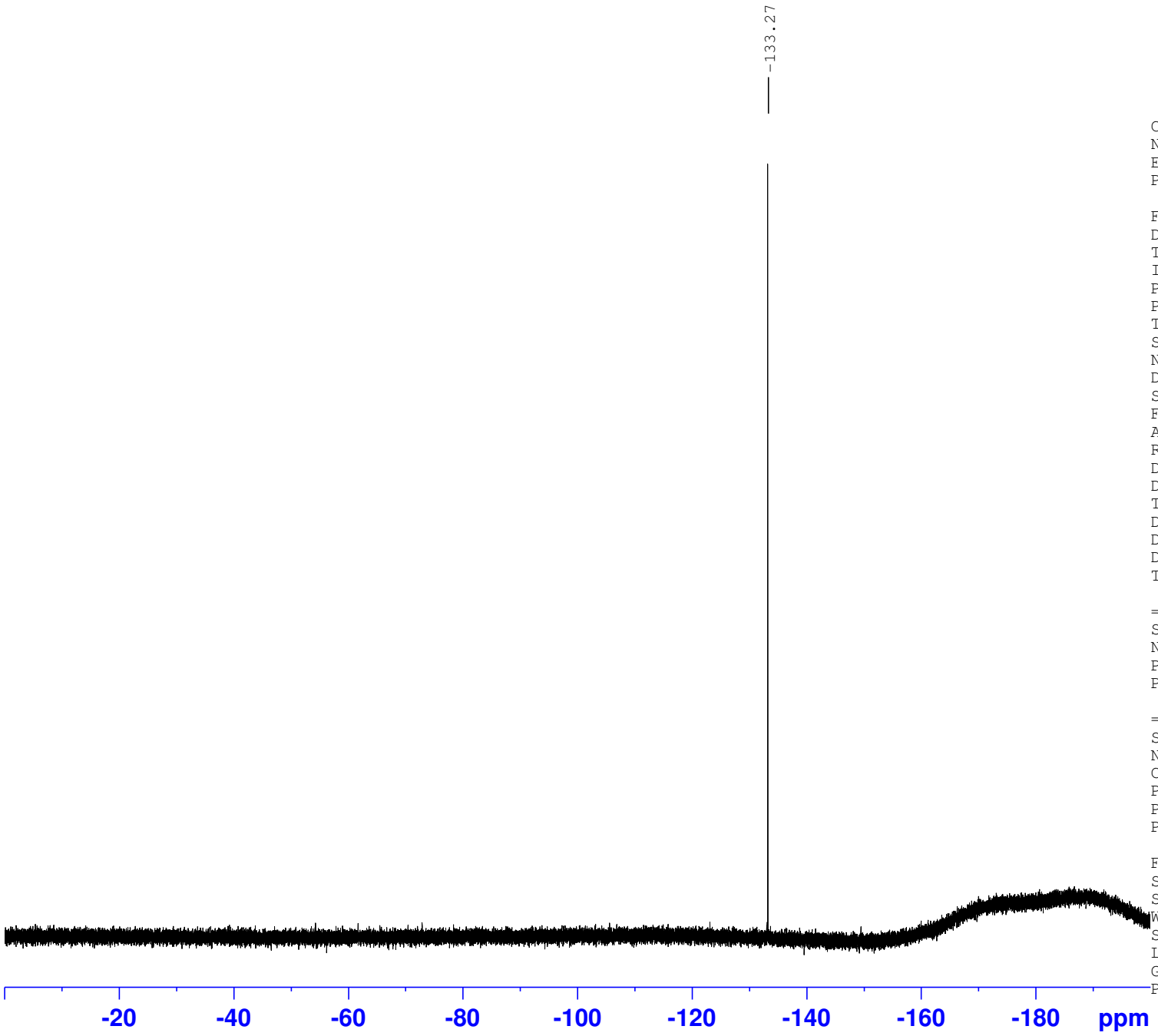




NAME	CNA-752-93
EXPNO	2
PROCNO	1
Date_	20170301
Time	22.01
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	MeOD
NS	256
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	295.0 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-752-93, 19F, CDCl3/MeOD, 500 MHz



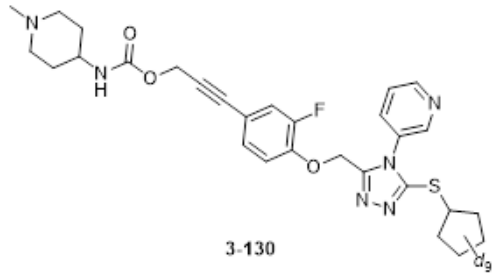


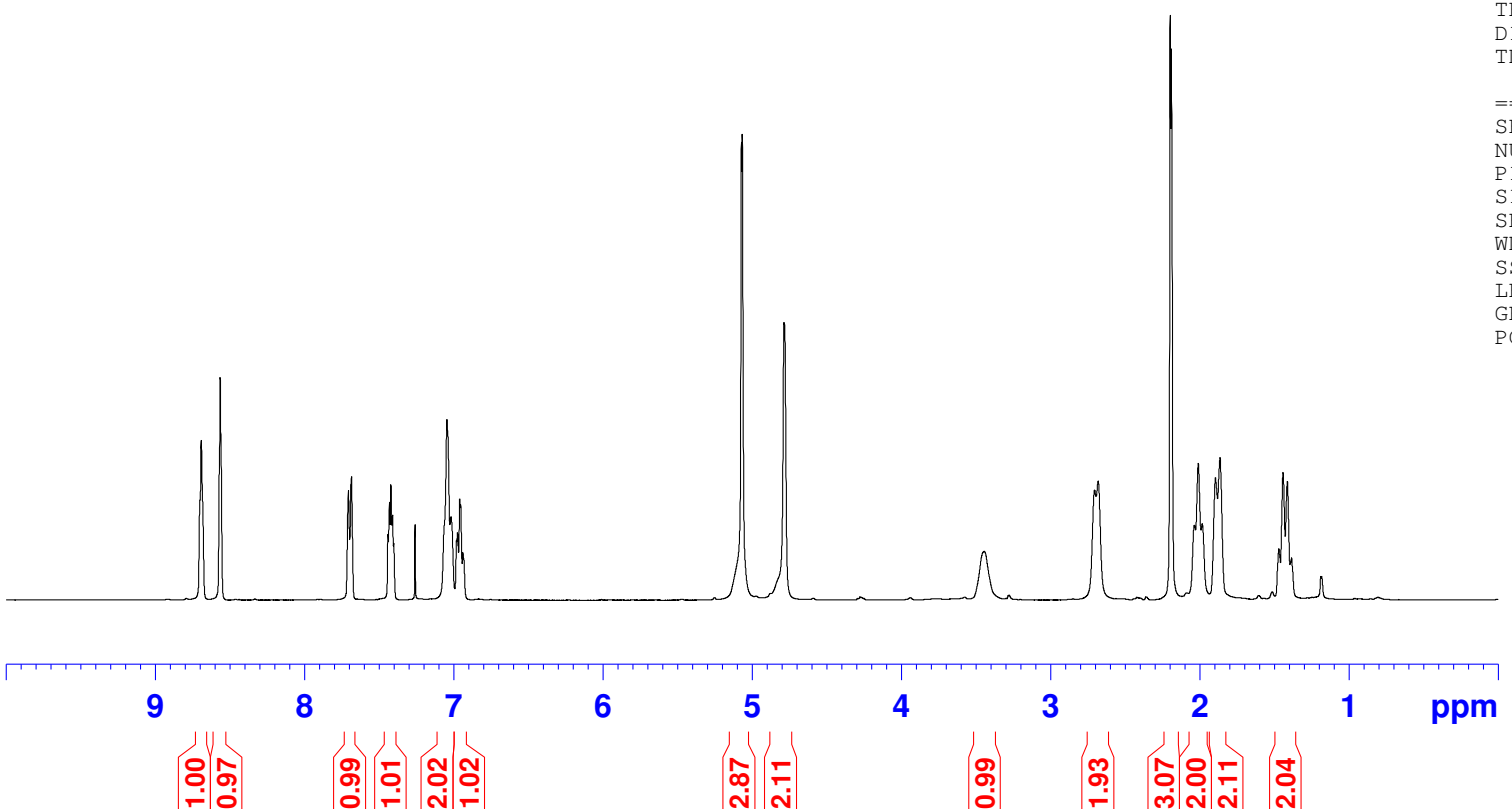

```
Current Data Parameters
NAME          CNA-752-93
EXPNO                 13
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170302
Time               14.15
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG       zgfhigqn.2
TD                131072
SOLVENT             CDCl3
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                296.6 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                19F
P1                5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

CNA-752-95, 1H, CDCl3, 400 MHz

8.694 8.567 7.710 7.706 7.696 7.689 7.686 7.442 7.431 7.423 7.416 7.411 7.404 7.260 7.047 7.020 6.983 6.976 6.961 6.955 6.941 6.934 5.073 5.067 4.787

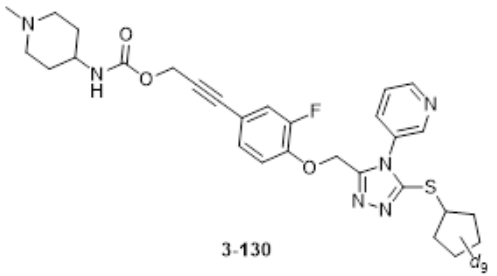
3.446 2.705 2.681 2.198 2.191 2.037 2.010 1.983 1.895 1.864 1.470 1.442 1.413 1.385



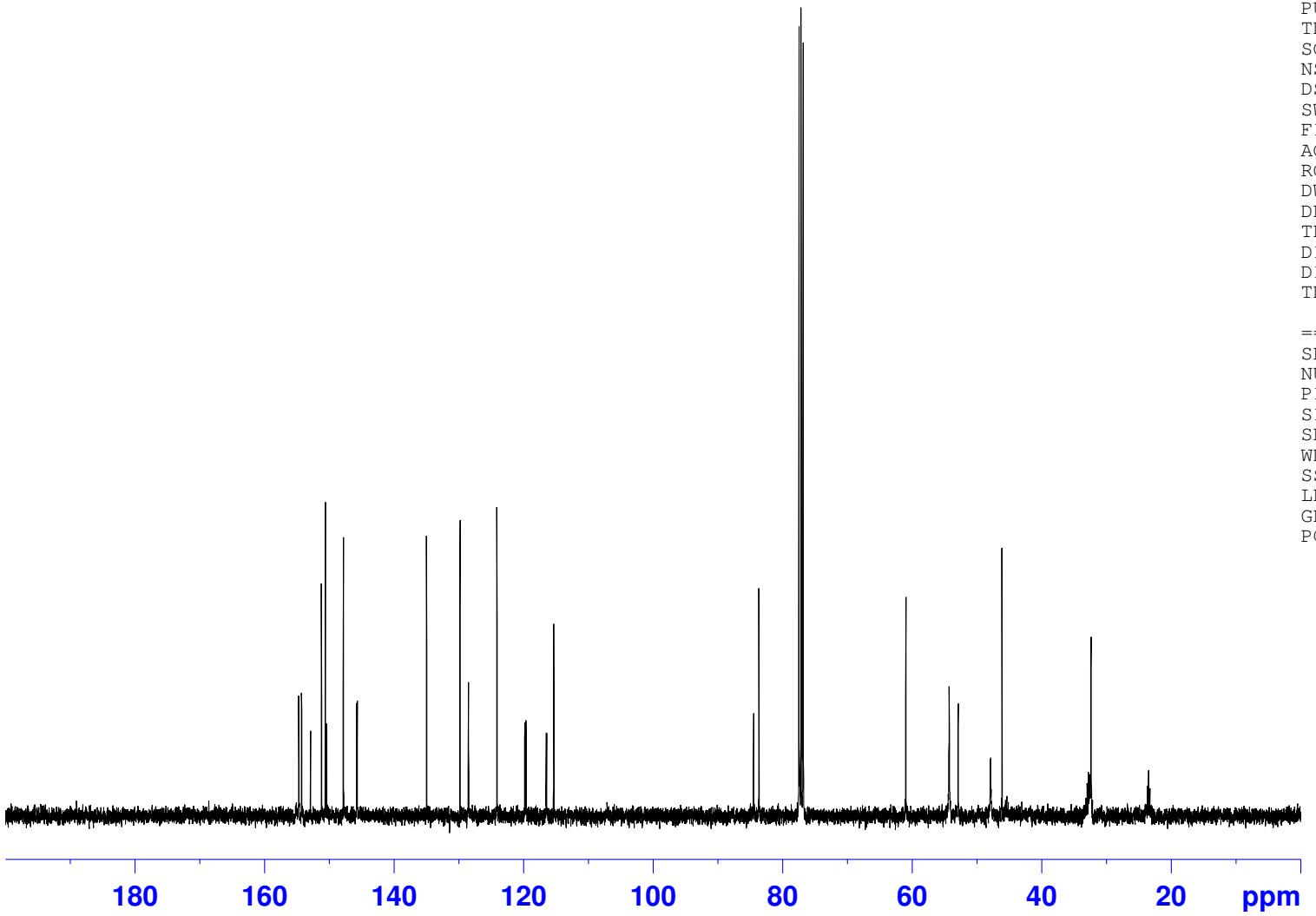


NAME	CNA-752-95	
EXPNO	4	
PROCNO	1	
Date_	20170316	
Time	19.12	
INSTRUM	spect	
PROBHD	5 mm PABBO BB-	
PULPROG	zg30	
TD	65536	
SOLVENT	CDCl3	
NS	16	
DS	2	
SWH	8012.820	Hz
FIDRES	0.122266	Hz
AQ	4.0894966	sec
RG	32	
DW	62.400	usec
DE	6.50	usec
TE	88.9	K
D1	1.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
SFO1	400.1324710	MHz
NUC1	1H	
P1	13.75	usec
SI	65536	
SF	400.1300102	MHz
WDW	EM	
SSB	0	
LB	0.30	Hz
GB	0	
PC	1.00	

CNA-752-95, 13C, CDCl3, 400 MHz

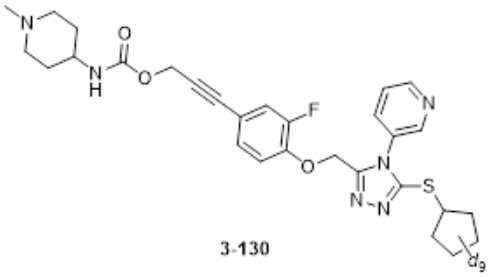


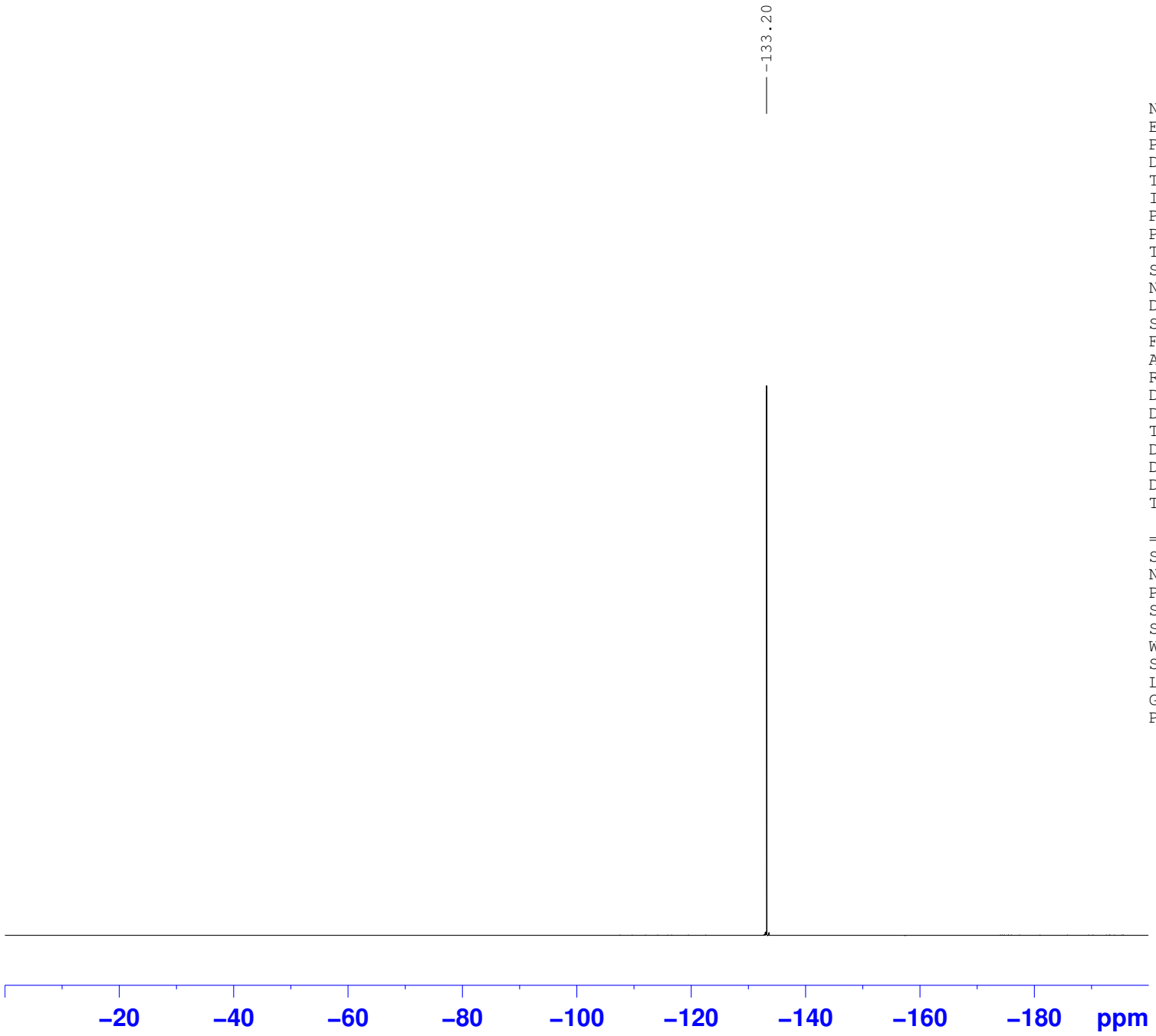
154.76
154.32
152.93
151.24
150.65
150.46
147.86
145.82
145.71
135.01
129.85
128.55
128.52
124.13
119.84
119.64
116.53
116.45
115.37
84.48
83.69
77.48
77.16
76.85
60.98
54.30
52.90
47.89
46.15
45.62
45.38
45.16
32.97
32.77
32.56
32.38
23.68
23.48
23.28



NAME	CNA-752-95
EXPNO	5
PROCNO	1
Date_	20170316
Time	19.28
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	256
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	161
DW	20.800 usec
DE	6.50 usec
TE	88.9 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	100.6228293 MHz
NUC1	13C
P1	10.00 usec
SI	32768
SF	100.6127685 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-752-95, 19F, CDCl3, 400 MHz

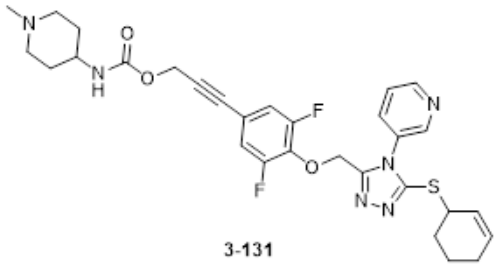




NAME	CNA-752-95
EXPNO	3
PROCNO	1
Date_	20170315
Time	19.54
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgfhigqn.2
TD	131072
SOLVENT	CDCl3
NS	16
DS	4
SWH	89285.711 Hz
FIDRES	0.681196 Hz
AQ	0.7340532 sec
RG	203
DW	5.600 usec
DE	6.50 usec
TE	88.6 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	376.4607164 MHz
NUC1	19F
P1	14.20 usec
SI	65536
SF	376.4983662 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

CNA-781-20, 1H, CDCl3, 500 MHz

8.778 8.776 8.769 8.766 8.681 8.677 7.825 7.824 7.808 7.807 7.511 7.501 7.494 7.485 7.260 6.926 6.910 5.846 5.096 4.822 4.532 4.527 2.723 2.243 2.087 2.080 2.059 2.052 2.050 2.042 2.038 2.031 2.028 2.022 2.011 2.005 2.000 1.996 1.957 1.943 1.929 1.920 1.474 1.456



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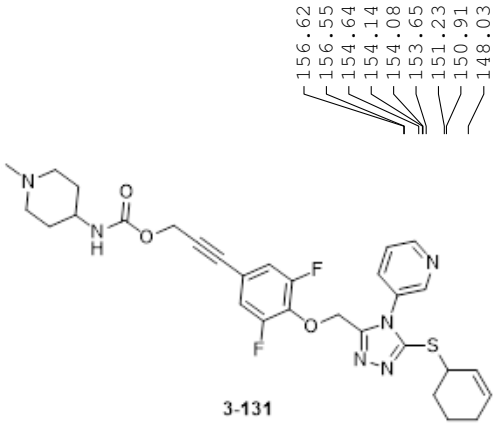
```
Current Data Parameters
NAME          CNA-781-20
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170427
Time               12.45
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ             3.2767999 sec
RG                    57
DW                50.000 usec
DE                 6.50 usec
TE                298.2 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1630887 MHz
NUC1                  1H
P1                 11.50 usec
PLW1         18.00000000 W

F2 - Processing parameters
SI                 65536
SF           500.1600127 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

CNA-781-20, 13C, CDCl3, 400 MHz

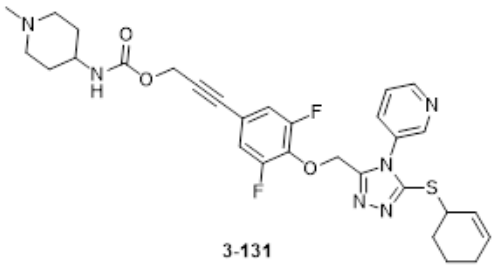


3-131

156.62
156.55
154.64
154.14
154.08
153.65
151.23
150.91
148.03
135.06
134.56
134.42
134.27
132.39
129.89
125.38
124.18
118.75
118.64
118.52
116.14
116.07
115.96
115.90
85.39
83.41
77.43
77.11
76.79
64.60
54.30
52.70
47.92
46.14
44.16
32.38
29.15
24.82
19.10

NAME	CNA-781-20
EXPNO	2
PROCNO	1
Date_	20170426
Time	20.12
INSTRUM	spect
PROBHD	5 mm PADUL 13C
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	500
DS	4
SWH	24038.461 Hz
FIDRES	0.366798 Hz
AQ	1.3631988 sec
RG	203
DW	20.800 usec
DE	6.50 usec
TE	295.0 K
D1	3.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-0.44 dB
PL1W	39.19395828 W
SFO1	100.6479773 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	90.00 usec
PL2	-3.90 dB
PL12	15.81 dB
PL13	120.00 dB
PL2W	21.64248466 W
PL12W	0.23137002 W
PL13W	0.00000000 W
SFO2	400.2316009 MHz
SI	32768
SF	100.6379140 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

CNA-781-20, 19F, CDCl3, 500 MHz



3-131


```
Current Data Parameters
NAME          CNA-781-20
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20170427
Time               12.48
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG       zgfhigqn.2
TD                131072
SOLVENT             CDCl3
NS                     16
DS                      4
SWH           113636.367 Hz
FIDRES          0.866977 Hz
AQ             0.5767168 sec
RG                    203
DW                4.400 usec
DE                6.50 usec
TE                298.3 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         470.5735434 MHz
NUC1                  19F
P1                 5.00 usec
PLW1         10.00000000 W

======== CHANNEL f2 ========
SFO2         500.1620006 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.00000000 W
PLW12         0.37195000 W

F2 - Processing parameters
SI                 65536
SF           470.6206054 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```