Development of New Chemotherapeutics for Head & Neck Squamous Cell Carcinoma (HNSCC)

by

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Zhuzhu Wang, M.S.

University of Pittsburgh, 2013

The signal transducers and activators of transcription STAT3 and STAT1 share common structure and targets, but they play opposing roles in tumorigenesis. While STAT3 is considered an oncogene that promotes cell survival, proliferation, motility, and immune tolerance, STAT1 enhances inflammation, favors cell cycle arrest, and apoptosis in most tumor cells. STAT3 has been found to be constitutively active in head and neck squamous cell carcinomas (HNSCC) where it promotes the cell cycle and prevents apoptosis, resulting in the proliferation and survival of HNSCC cells. We hypothesize that a small molecule inhibitor of STAT3 that is selective over STAT1 in HNSCC would serve as a powerful cancer therapeutic. The lead compound **669** that was identified through high content screening (HCS) displayed a pSTAT3 inhibition with 10-fold greater selectivity over pSTAT1 in HNSCC cells (pSTAT3 IC_{50} 5.50 ± 1.50 μM (n = 7) vs. pSTAT1 > 50 μM). The mechanism of **669**'s effect on the STAT3 pathway remains unknown, however, it does not proceed by a kinase inhibition pathway. This thesis describes the development of a structure activity relationship (SAR) for pSTAT3 inhibitors related to **669**. The key reaction to synthesize these analogs is performed in a microwave reactor, which saves time, and is convenient for parallel synthesis.

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1.0 INTRODUCTION AND BACKGROUND

Head and neck squamous cell carcinoma (HNSCC) is the 6th most common malignancy in the world with more than 500,000 new yearly cases and a 50% mortality rate.[1-3] Risk factors for HNSCC include smoking, alcohol use, age, and HPV 16.[4,5] HNSCC occurs in the areodigective tract, most commonly in the oral cavity, oropharynx, supraglottis, hypopharynx and glottis.[6,7] Typical symptoms are otalgia, dysphagia, dysphonia, and sore throat.[6,7] Typical treatment regimens often combine radiotherapies with head and neck surgery which can significantly alter physical appearance.[8] Current chemotherapeutics include cis-platin, methotrexate (MTX), 5-Flurouracil, paclitaxel, and the monoclonal antibody (MAb) cetuximab (Erbitux®).[2,9,10] These current treatments are not devoid of side effects and have very limited effects on overall survival rates.[1,2,9] Thus, a new chemotherapeutic which would selectively target HNSCC cells would be very beneficial.

Inhibition of the oncogenic signal transducer and activator of transcription (STAT3) is a potential strategy in treating this difficult cancer.[11,12] On a molecular level, STAT3 serves as a transcription factor that affects cell differentiation, proliferation, apoptosis, angiogenesis, metastasis, and immune response.[13-16] Elevated levels of constitutively activated STAT3 together with its increased transcription-regulated gene expression were found in most human cancers[13,16-18] which results in poor prognosis.[14,15,17,19] In HNSCC cells, the level of inherently activated STAT3 is greater than that of normal epithelial cells.[20,21] In HNSCC, the activated STAT3 promotes tumor cell proliferation while preventing apoptosis.[13] Treatment with dominant-

negative STAT3 mutant transfection constructs or antisense STAT3 oligonucleotides results in tumor growth inhibition, apoptosis, and decreased STAT3 target gene expression.[20,22,23]

In contrast to STAT3, STAT1 is anti-oncogenic. The STAT protein family has similar structural domains and common targets includes interferons (IFNs)[24-26] / cytokines belonging to the gp130 family (such as interleukin (IL)-6[27]), growth factors such as platelet-derived growth factor receptor (PDGFR), and epidermal growth factor receptor (EGFR).[28] In many tumor cell types, STAT1 serves to induce anti-proliferative and pro-apoptotic genes that directly arrest the cell cycle.[29-35] In addition, STAT1 plays a key role in the inhibition of angiogenesis through acting on both endothelial and tumor cells.[36-38]

1.1 STAT3 PROTEIN STRUCTURE

STAT3 is one of the 7 members of the STAT family of proteins (the other six being STAT1, STAT2, STAT4, STAT5a, STAT5b and STAT6, which all serve in different cell signal pathways).[11,39] STAT3 and STAT1 are the most studied of these proteins due to their opposite roles in tumorigenesis despite their structural similarities.[12,40] STAT3 contains a *N*-terminal coiled-coil domain that is responsible for STAT dimer-dimer interactions, a DNA binding domain, a linker domain, a Src homology (SH2) domain, which is essential for the recruitment of STAT3 to the phosphorylated receptors followed by dimerization of activated STAT3 via phosphor-tyrosine (pTyr)-SH2 domain interaction, and a *C*-terminal transactivation domain.[11,41]

1.2 STAT3 SIGNALING PATHWAY

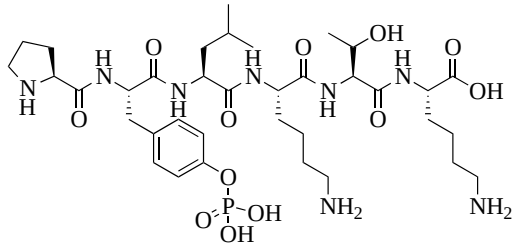
In HNSCC, STAT3 is activated by both receptor and non-receptor tyrosine kinases via the tyrosine phosphorylation cascade. For the receptor tyrosine kinase, the transforming growth factor ((TGF)-α/EGFR) signaling activates STAT3 via the direct recruitment of the STAT3 SH2 domains by the EGFR itself on its tyrosine residues, Y1068 and Y1086.[20,42] The non-receptor tyrosine kinase constitutively associates with Janus kinase (Jak) proteins.[43,44] Following the interleukin (IL)-6/gp130 interaction[45] and aggregation of the receptor subunits, two associated Jak proteins promote tyrosine transphosphorylation, effecting reciprocal activation.[46,47] These activated Jaks transmit cytokine signaling via recruitment and activation of STAT3 through the SH2 domain.[43,46,48-50] Once recruited, STAT3 is activated by phosphorylation at Tyr705 by JAK or SRC. The activated STAT3 proteins undergo dimerization via the interaction between the pTyr705 and SH2 domain, respectively. STAT3 dimers then disassociate from the receptor and undergo nucleus translocation, where they bind to specific DNA sequences such as the cis-element IFN-stimulated response element (ISRE) and regulate the transcription of target genes involved in cell cycle progression such as Fos, $p21^{WAF1/CIP2}$, cyclins D1,[22,51-53] D2, D3, CDC25A, APE1/Ref-1, c-Myc,[54-56] and Pim1, or gene involved in angiogenesis such as VEGF,[57-59] and anti-apoptosis genes including surviving,[60,61] and Bcl-2, and Bcl-xL.[21,62]

STAT3 inhibitors can be divided into two categories: peptides/peptidomimetics and small molecule non-peptidic inhibitors.[11,62] These inhibitors can either indirectly block the targets (ex., interferons, cytokines) that are upstream of STAT3, tyrosine kinases such as JAK, SRC and EGFR that are crucial for STAT3 activation, or directly interact with STAT3 protein by targeting the SH2 domain, DNA binding domain, *N*-terminal domain which result in the either the

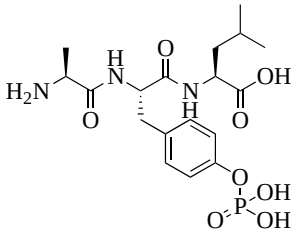
suppression of STAT3 phosphorylation, pSTAT3 dimerization, nuclear translocation, STAT3–DNA binding, and expression of STAT3 target genes.[11,62]

The first phosphopeptide inhibitor PY*LKTK (Y* represents pTyr) was designed based on the sequence of amino acids in the STAT3 SH2-binding region surrounding Tyr705 (**1.1**, Figure 1**)**.[11,63,64] The PY*LKTK peptide competitively binds to STAT3 which, effectively disrupts the pSTAT3-pSTAT3 dimerization and DNA binding activity, albeit at a DB_{50} of 235 μM in Src-transformed NIH 3T3/v-Src fibroblasts (DB_{50} represents the concentration of peptide at which DNA binding activity is reduced by 50%).[63,64] Additionally, the PY*LKTK exhibited a high selectivity for STAT3 over STAT5, but was only two-fold selective over STAT1.[64] Further investigations have suggested that the tripeptide XY*L (Figure 1) contain the crucial sequence for the disruption of pSTAT3 dimerization and DNA binding. For example, the AY*L (**1.2**, Figure 1), and PY*L (**1.3**, Figure 1), disrupted STAT3 DNA binding, with nearly identical DB_{50} values (DB_{50} = 217 μM and DB_{50} = 182 μM, respectively) as PY*LKTK but they do not inhibit STAT3-STAT1 or STA1-STAT1 dimers as effectively.[11,63] The second phosphopeptide Ac-Y*LPQTV-NH_2 (**1.4**, Figure 1) was derived from the 904-909 amino acid residues of the STAT3 receptor docking site on the gp130 subunit of the IL-6 receptor. Hexapeptide **1.4** was able to inhibit dimer formation and STAT3-DNA binding activity *in vitro* at sub-micromolar concentrations (IC_{50} = 0.15 μM), which represents a 133-fold improvement in inhibitory activity over the STAT3-derived peptide Ac-Y*LKTKF-NH_2 (**1.6**, IC_{50} = 20 μM**,** Figure 1**)**.[11,64-66] However, the biggest challenges of peptide inhibitors are their poor membrane permeabilities. Therefore, a hydrophobic membrane translocation sequence (mts) AAVLLPVLLAAP was attached to the *C*-terminus of the peptide to overcome this shortcoming. Cellular studies showed that the PY*LKTK-mts induced only 28% inhibition of STAT3 dimerization and DNA binding

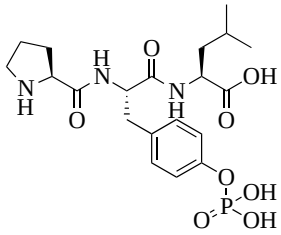
activity, even at 1mM concentration.[11,63,64,66] Whereas the Y*LPQTV-NH_2-mts conjugate (**1.5**, Figure 1) was inactive.[11]



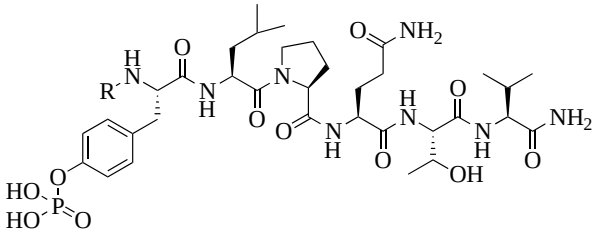
1.1: PY*LKTK



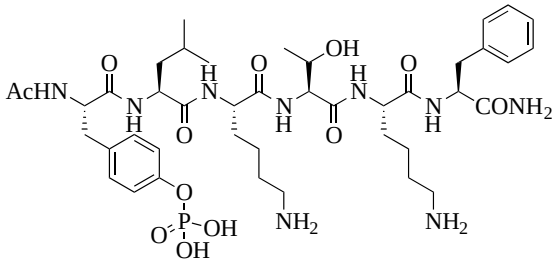
1.2: AY*L



1.3: PY*L



1.4: R = Acetyl: Ac-Y*LPQTV-NH_2
1.5: R = H: Y*LPQTV-NH_2



1.6: Ac-Y*LKTKF-NH_2

Figure 1. Direct inhibition of STAT3: peptides

Further peptidomimetics efforts based on tripeptides **1.2** and **1.3** have led to *N*-terminal structural modifications such as the replacement of pTyr-1 proline (or alanine) with 4-cyanobenzoyl (ISS610 (**1.7**), Figure 2) that improved the inhibition of STAT3 dimerization and DNA binding activity (IC_{50} = 42 μM vs 182 μM (for PY*L) and 217 μM (for AY*L). Moreover, there was a significant increase in selectivity with IC_{50}'s of STAT1-STAT1 and STAT5-STAT5 dimers of 310 μM and 285 μM, respectively (as determined by electrophoretic mobility shift assay (EMSA) analysis).[64,66,67] Docking studies suggested that the improved potency may be attributed to the 4-CN benzoyl moiety which occupies a hydrophobic pocket giving rise to additional interactions of the protein surface.[11,66] The STAT3-DNA binding suppression of ISS610 has been demonstrated using mouse fibroblast cells (NIH3T3/v-Src), as well as human

breast tumor cells such as MDA-MB-231, MDA-MB-435 and MDA-MB-468, and lung carcinoma cells (A549).[11,66] An additional peptidomimetic library derived from the ISS610 through functionalization of the *C*-terminus has been developed.[11,66,68] Unfortunately, all of these peptides were poor inhibitors of STAT3, but it is interesting to note that the m-methoxyaniline amide derivative ISS840 (**1.8**, Figure 2) exhibited a 20-fold preference toward STAT1 homodimer inhibition (IC_{50} = 31 μM) compared with the STAT3 homodimer (IC_{50} = 560 μM), possibly due to additional hydrophobic contacts with Y603 and I616.[11,66]

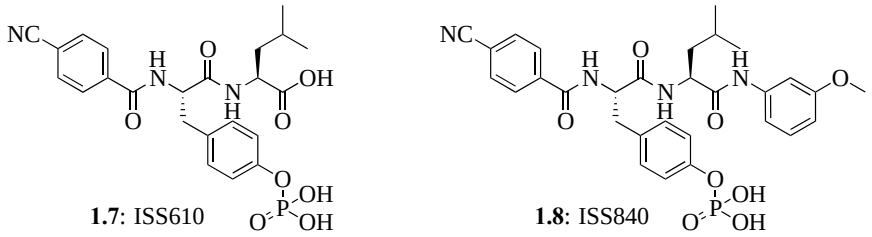


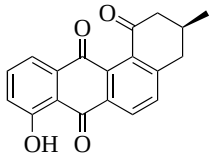
Figure 2: Direct inhibitors: peptidomimetics

Small molecules constitute the largest class of nonpeptide STAT3 inhibitors with numerous methods to identify possible molecular candidates including high-throughput screening (HTS) of large chemical libraries, virtual screening, rational design based on peptides and peptidomimetic inhibitors, fragment-based drug design, and drug repositioning using multiple ligand simultaneous docking (MLSD).[62]

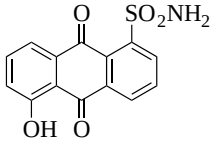
STA-21 (**1.9**, Figure 3) was discovered to inhibit STAT3-dependent luciferase activity in breast and ovarian cancer cell lines through virtual screening.[69] It was 5-fold more potent than the untreated controls (at 20 μM) in inhibiting luciferase activity of the MDA-MB-435s cells that were stably transfected with a STAT3-dependent luciferase reporter pLucTKS3.[62,69] STA-21 also inhibited STAT3 dimerization, nuclear translocation, and STAT3-DNA binding activity in MDA-MB-435s cells at 20 or 30 μM.[62,69] In addition, STA-21 inhibited the STAT3-regulated

downstream regulator Bcl-X_L and cyclin D1 in MDA-MB-468 cells, but did not affect the phosphorylation of STAT3 upstream regulators JAC2 (P-JACK2), Src (P-Src), and the EGFR receptor (P-EGFR). This observation suggests that STA-21 is a direct inhibitor at the STAT3 protein level.[69]

Several more potent STA-21 analogs like LLL-12 (**1.10**, Figure 3) have recently been reported[11,62] and represent an emerging class of selective small molecule STAT3 inhibitors with improved drug like properties.[62,70] Using breast cancer MDA-MB-231-cloned cells that stably integrate the STAT3-dependent luciferase reporter pLucTKS3, LLL-12 inhibited luciferase activity by 10-fold (at 5 μM) compared to untreated controls.[70] Furthermore, LLL-12 not only inhibited STAT3 activation at 5-10 μM in six cancer cell lines (MDA-MB-231 and SK-BR-3 (breast), HPAC and PANC-1 (pancreatic), U87 and U373 (glioblastoma)) that express elevated levels of STAT3 phosphorylation but also inhibited STAT3 phosphorylation induced by IL-6 in MDA-MB-453 cells in a dose dependent manner.[70] The inhibition of STAT3 DNA binding and transcription of STAT3-regulated gene was observed with LLL-12 at 10 μM. In addition, LLL-12 suppressed tumor growth in mouse xenograft models of breast cancer and glioblastoma with daily intraperitoneal dosage of 2.5 to 5 mg/kg.[70]



1.9: STA-21

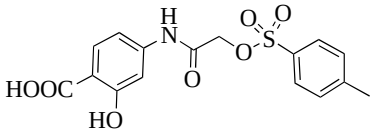


1.10: LLL-12

Figure 3: STA-21 and its analog

S31-201 (**1.11**, Figure 4) was also discovered through structure-based virtual screening[71] where the salicylic acid moiety was incorporated as the phosphate mimetic.[66,72] In the nuclear

extract of EGF-stimulated mouse fibroblasts NIH 3T3/hEGFR, S31-201 preferentially inhibited the DNA binding ability of STAT3-STAT3 dimer (IC_{50} = 86 μM) compared to STAT1-STAT3 dimers (IC_{50} = 160 μM) and STAT1-STAT1 dimers (IC_{50} > 300 μM).[62,71] In the normal mouse fibroblasts (NIH 3T3) that were transiently cotransfected with the STAT3-dependent luciferase reporter pLucTKS3, S31-201 significantly inhibited the luciferase signal in a dose-dependent manner.[71] S31-201 also induced apoptosis of malignant cells harboring constitutively active STAT3 (ex: MDA-MB-435), where they repressed the expression of the STAT3-regulated genes encoding cyclin D1, Bcl-xL, and survivin.[71] S31-201 also suppressed tumor growth in mouse xenograft models of hepatocellular carcinoma and breast cancer.[62,71,73]

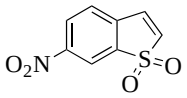


1.11: S31-201

Figure 4: S31-201

Stattic (**1.12**, Figure 5) was identified as a STAT3 SH2 domain inhibitor via high-throughput screening of a diverse chemical library using a fluorescence polarization-based binding assay.[74] This compound inhibited the binding of STAT3 SH2 domain and the phosphotyrosine-containing peptide on the gp130 receptor with a IC_{50} of 5.1 μM at the physiologically relevant temperature of 37 ℃.[62,74] It also inhibited STAT3 DNA binding at 10 μM in the EMSA performed at 37 ℃ while the binding of STAT1 DNA was not significantly effected at concentrations up to 200 μM in the nuclear extracts from EGF-stimulated cells.[62,74] Stattic selectively inhibited IL-6 induced phosphorylation of STAT3 at Tyr705 in HepG2 liver carcinoma cells (20 μM), without interfering with the IFN- γ induced activation of STAT1 at Tyr701.[74] However, it showed equipotent activities against phosphorylation of STAT3 and

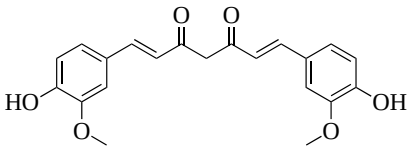
STAT1 induced by IL-6 or leukemia inhibitory factor (LIF) in human ovarian cancer OVZAR-8 cells at 5 or 10 μM.[62]



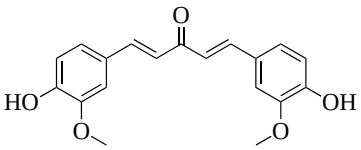
1.12: Stattic

Figure 5: Stattic

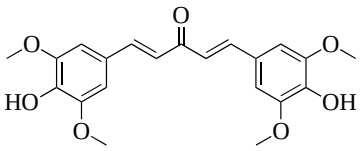
Curcumin (**1.13**, Figure 6) also has been shown to inhibit IL-6-induced STAT3 phosphorylation and nuclear translocation.[62,75] The related analogs FLLL11 (**1.14**, Figure 6) and FLLL12 (**1.15**, Figure 6) are more effective than curcumin at inhibiting STAT3 phosphorylation and inducing apoptosis in pancreatic cancer cell lines in a dose-dependent manner.[62,75] FLLL12 was the most potent (10 μM) of these three compounds in pSTAT3 inhibition, STAT3-DNA binding, and transcriptional activity in breast and prostate cancer cells.[62,76] Another analog, FLLL32 (**1.16**, Figure 6) down-regulated STAT3 phosphorylation, DNA binding, and the expression of STAT3 target genes at 10 μM in MDA-MB-231 and PANC1 cells[77] and inhibited JAK2 kinase activity (IC_{50} = 5 μM). A series of *in vivo* studies showed that the administration of FLLL32 significantly inhibited tumor growth and vascularity in chicken embryo xenografts and reduced tumor volumes in mouse xenografts.[77]



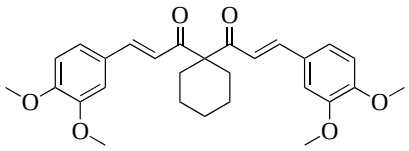
1.13: Curcumin



1.14: FLLL11



1.15: FLLL12



1.16: FLLL32

Figure 6: Curcumin and its analogs

1.3 STAT3 INHIBITORS IN CLINICAL TRIALS

At present, there are no approved STAT3 inhibitors, but there are several promising compounds currently under investigation in clinical trials for treatment of advanced tumors and cancers.[62] The double-stranded oligodeoxynucleotide (dsODN) is the only drug candidate that has completed a phase 0 pharmacodynamic clinical study to evaluate the safety and biological effects of intratumoral injection in HNSCC patients.[17,78] dsODN decreased the tumoral expression of STAT3 target genes following a single intralesional injection, but its rapid degradation in serum prevents systemic administration. Chemical modification of the decoy may be able to improve metabolic stability, which would allow for alternative means of delivery. However, these modified dsODNs would introduce additional significant pharmacokinetic challenges.[17]

2.0 THE STAT3 INHIBITOR 669

Previous studies in our center have identified **669** (Figure 7) as a lead compound that selectively targets STAT3 over STAT1 in CAL33 cells with an IC_{50} = 5.50 ± 1.50 μM (n = 7) for pSTAT3 versus an IC_{50} > 50 μM for pSTAT1 (Table 1). The IC_{50} values were assessed by measuring the concentration of **669** at which the translocation of pSTAT3-pSTAT3 dimers into the nucleus is reduced by 50% in CAL33 cells upon the initial pSTAT3 induction using interleukin-6 (IL-6). The net effect of the compound treatment would be a reduction of active STAT3-STAT3 dimers available to bind DNA. These values were measured from the high content screening (HCS) of 97,000 compounds from the MLSCN (molecular library screening center network), which was performed by Dr. Paul Johnston and based upon an assay by Dr. Jennifer Grandis. Additional HNSCC cellular growth inhibition studies of **669** from Dr. Johnston's lab indicated IC_{50} values of less than 10 μM (e.g., CAL-33, 686 LN, FADU, OSC) (Table 1). Kinase-profiling studies (Millipore UK) indicated that **669** only weakly inhibited six of the 83 tested kinases (20-40% at 9 μM), suggesting that **669** is neither a potent nor promiscuous kinase inhibitor, but rather a direct inhibitor of the STAT3 pathway.

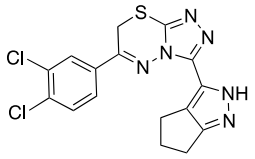


Figure 7: Structure of lead compound 669

Table 1. Properties of lead compounds 669

	SID-864669
HCS STAT3 IC_{50} (μM)	5.50 ± 1.5 (n = 7)
HCS STAT1 IC_{50} (μM)	> 50 (n = 7)
Luciferase (% decrease, 8h)	30
GI CAL-33 IC_{50} (μM)	9
GI 686 LN IC_{50} (μM)	8.7
GI FADU IC_{50} (μM)	4.6
GI OSC IC_{50} (μM)	5.2
FP binding assay @50 μM (% inhibition)	< 10
Western blot: Cyclin D1	+
Western blot: Bcl-XL	+
MW	391.3
cLogP	3.17
Ligand efficiency (LE)	0.31
Ligand-lipophilicity efficiency (LLE)	2.57

3.0 SYNTHESIS OF 669 ANALOGS

3.1 SPECIFIC AIM 1

Our first specific aim was to attain an inhibitor with a high selectivity and potency for targeting pSTAT3 over pSTAT1 in order to develop a HNSCC drug with a good safety and efficacy profile. To fulfill this goal, a series of **669** analogs was prepared. We maintained the triazolothiadiazine substituted pyrazole scaffold and focused on substitutions and ring sizes at the R_1 and R_2 positions (Figure 8).

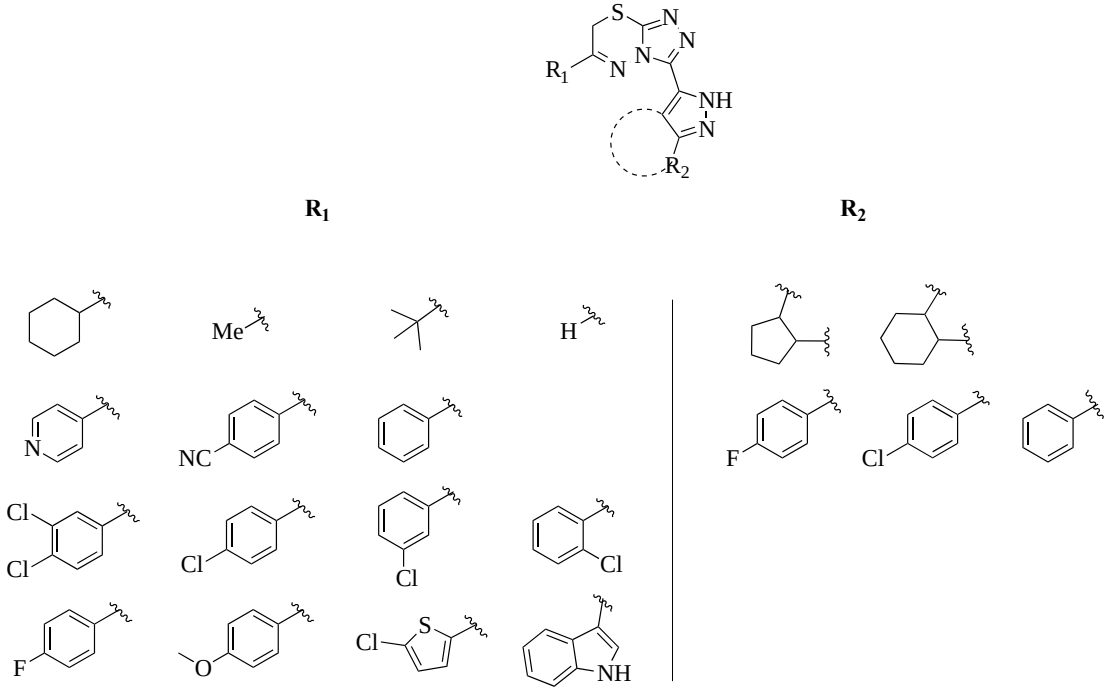
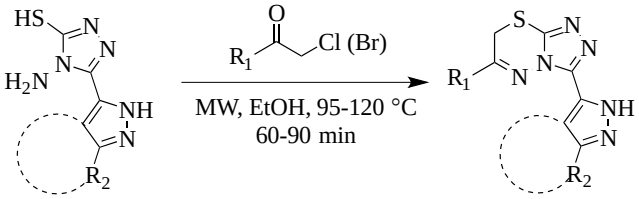


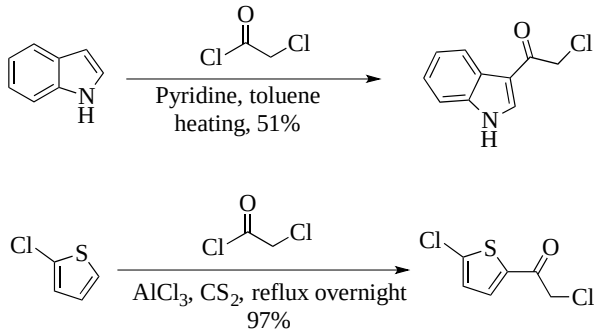
Figure 8. 669 Matrix library

The procedure to synthesize the key triazolothiadiazine moiety involved a microwave-assisted cyclodehydration similar to a Hantzsch thiazole synthesis (Scheme 1).[79]



Scheme 1. Synthesis strategy of 669 analogs

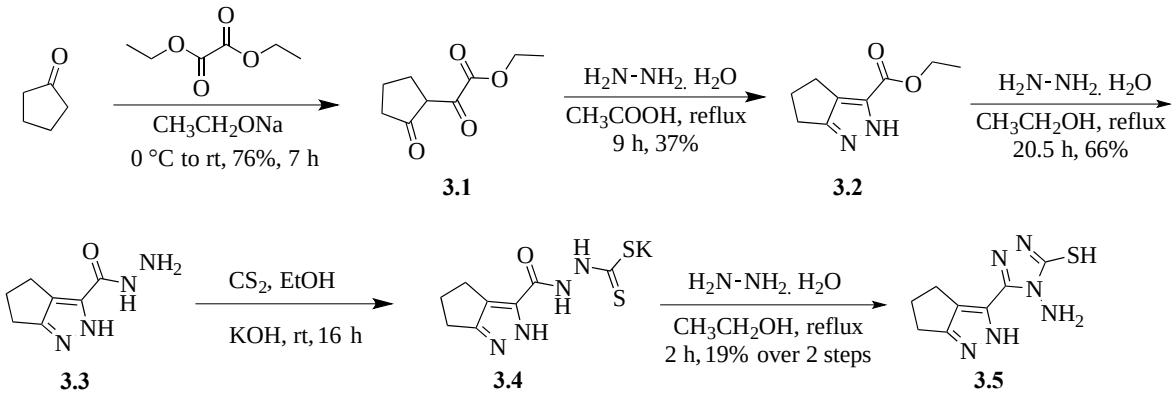
The α-chloro (bromo) ketone reagents were either commercially available, or synthesized in very good yields via a one-step addition of 2-chloroacetyl chloride. (Scheme 2).[80,81]



Scheme 2. Synthesis of 2-chloro-1-(1H-indole-3-yl)ethan-1-one and 2-chloro-1-(5-chlororhiophen-2-yl)ethan-1-one

The pivotal triazole intermediates were not commercially available, but were synthesized following literature protocols (Scheme 3).[82,83] Cyclopentanone was treated with diethyloxalate for 7 h in the presence of freshly made sodium ethoxide solution to afford ethyl 2-oxo-2-(2-oxocyclopentyl)acetate (**3.1**) in 76% yield (Scheme 3). The subsequent cyclodehydration of the 1,3-diketone with hydrazine hydrate in acetic acid afforded the cyclopentapyrazole (**3.2**) in 37% yield, which was then converted to the primary amine (**3.3**) after treatment with hydrazine hydrate in absolute ethanol. The amine (**3.3**) was converted to the potassium salt (**3.4**) in

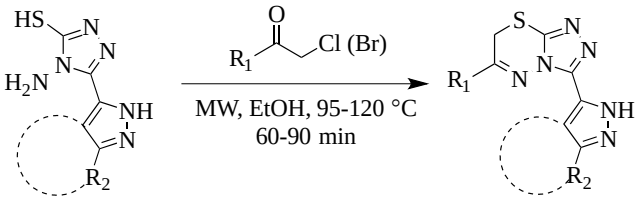
quantitative yield after 16 h treatment with CS_2. The product was immediately subjected to ring closure to form the 4-amino-5-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-4*H*-1,2,4-triazole-3-thiol (**3.5**) after 2 h reflux in absolute ethanol in the presence of hydrazine hydrate.



Scheme 3. Synthesis of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4H-(1,2,4)-triazole-3-thiol

According to the cyclization condition depicted in Scheme 1, a total of fifty-six **669** analogs were synthesized and their structures are listed in Table 2.

Table 2. pSTAT3 inhibitors of 669 analogs

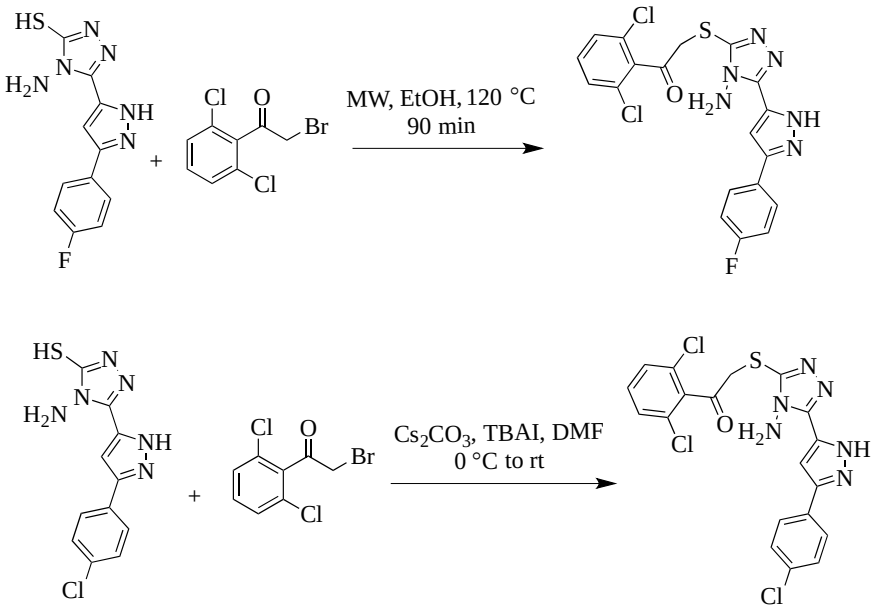


Compd	R_1	R_2	Yield (%)	Compd	R_1	R_2	Yield (%)
3.6	3,4-Cl-Ph	$-C_3H_6-$	88	**3.34**	3,4-Cl-Ph	Ph	65
3.7	4-OMe-Ph	$-C_3H_6-$	78	**3.35**	3-Cl-Ph	Ph	74
3.8	2-Cl-Thiophen-5-yl	$-C_3H_6-$	54	**3.36**	4-Cl-Ph	Ph	82
3.9	3-Cl-Ph	$-C_3H_6-$	40	**3.37**	4-F-Ph	Ph	46

3.10	4-Cl-Ph	-C_3H_6-	43	**3.38**	Ph	Ph	74
3.11	4-CN-Ph	-C_3H_6-	56	**3.39**	Indol-3-yl	Ph	69
3.12	Pyridine-4-yl	-C_3H_6-	63	**3.40**	4-CN-Ph	Ph	67
3.13	*t*-Bu	-C_3H_6-	61	**3.41**	2-Cl-Thiophen-5-yl	Ph	77
3.14	H	-C_3H_6-	24	**3.42**	Pyridin-4-yl	Ph	72
3.15	4-F-Ph	-C_3H_6-	50	**3.43**	H	Ph	68
3.16	Ph	-C_3H_6-	70	**3.44**	Me	Ph	90
3.17	Indol-3-yl	-C_3H_6-	67	**3.45**	2-Cl-Ph	Ph	74
3.18	Me	-C_3H_6-	61	**3.46**	*t*-Bu	Ph	90
3.19	Hexanyl	-C_3H_6-	83	**3.47**	4-OMe-Ph	Ph	67
3.20	3,4-Cl-Ph	-C_4H_8-	92	**3.48**	Hexanyl	Ph	79
3.21	4-OMe-Ph	-C_4H_8-	97	**3.49**	3,4-Cl-Ph	4-F-Ph	72
3.22	2-Cl-Thiophen-5-yl	-C_4H_8-	80	**3.50**	4-Cl-Ph	4-F-Ph	55
3.23	3-Cl-Ph	-C_4H_8-	49	**3.51**	4-F-Ph	4-F-Ph	57
3.24	4-Cl-Ph	-C_4H_8-	70	**3.52**	4-OMe-Ph	4-F-Ph	60
3.25	4-F-Ph	-C_4H_8-	72	**3.53**	4-CN-Ph	4-F-Ph	39
3.26	Indol-3-yl	-C_4H_8-	60	**3.54**	t-Bu	4-F-Ph	83
3.27	4-CN-Ph	-C_4H_8-	73	**3.55**	Me	4-F-Ph	32
3.28	Pyridin-4-yl	-C_4H_8-	50	**3.56**	Ph	4-F-Ph	69
3.29	*t*-Bu	-C_4H_8-	52	**3.57**	2-Cl-Thiophen-5-yl	4-F-Ph	59
3.30	H	-C_4H_8-	43	**3.58**	3,4-Cl-Ph	4-Cl-Ph	69
3.31	Me	-C_4H_8-	89	**3.59**	4-CN-Ph	4-Cl-Ph	63

3.32	Ph	-C_4H_8-	90	**3.60**	Ph	4-Cl-Ph	84
3.33	2-Cl-Ph	-C_4H_8-	89	**3.61**	2-Cl-Ph	4-Cl-Ph	64

However, attempts to prepare the 2,6-Cl-Ph at the R_1 position were not successful (Scheme 4). The cyclodehydration of the ketone on the 2-bromo-1-(2,6-dichlorophenyl)ethanone was inefficient. Treatment with Cs_2CO_3 and tetrabutylammonium iodide (TBAI) also did not facilitate the cyclodehydration, as both reactions afforded the acyclic intermediates in very low isolated yield. Ultimately, these analogs had no inhibitory pSTAT3 activities.



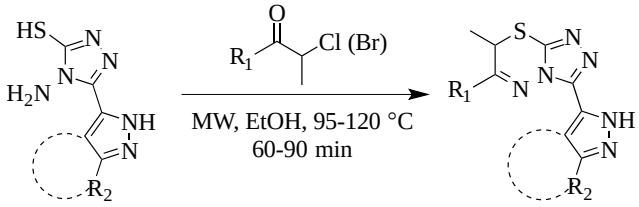
Scheme 4. Attempts at substituting a 2,6-Cl-Ph analog at the R1 position

3.2 SPECIFIC AIM 2

The ADMET properties of **669** including the *in vitro* clearance have been evaluated at the NCI using human and mouse microsomes. Unfortunately, the half-lives of the compound **669** in

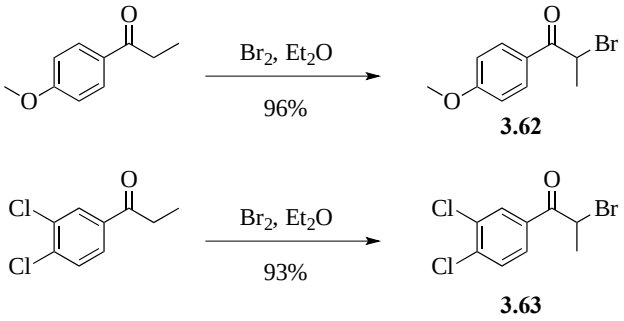
human microsomes are 14 and 4.4 min, respectively. The metabolites of **669** in mouse microsomes have been analyzed and a major oxidation product (M+16) was observed, presumably occurring via a phase I metabolic process, which could be the result of *S*-dealkylation, *S*-oxidation, or oxidation of the arene.

Initial attempts to improve metabolism were realized through the preparation of a second library of **669** analogs where the α-position to the sulfur was substituted with a methyl group. The synthetic strategy is demonstrated in Scheme 5, and the original α-chloro (bromo) ketone was replaced by the α-methyl, α-chloro (bromo) ketone for incorporation of the desired methyl substituent.



Scheme 5. Synthetic strategy of SOM blocked 669 analogs

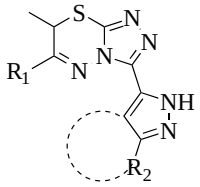
The α-methyl, α-chloro (bromo) ketones were either commercially available or synthesized via one-step α-bromination of the corresponding ketone precursors. For example, the 2-bromo-1-(4-methyoxyphenyl)propan-1-one (**3.62**) was obtained by treatment of 4-methoxypropiophenone with Br_2 in dry diethyl ether and the 2-bromo-1-(3,4-dichlorophenyl)propan-1-one (**3.63**) obtained in high yield using analogous conditions (Scheme 6).[84]



Scheme 6. Synthesis of 2-bromo-1-(4-methoxyphenyl)propan-1-one and 2-bromo-1-(3,4-dichlorophenyl)propan-1-one

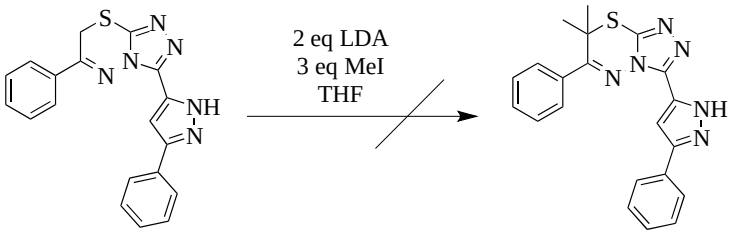
The second generation library of **669** analogs (11 compounds) that contain the α-methyl group at a potential site of metabolism is tabulated in Table 3.

Table 3. SOM blocked pSTAT3 inhibitors of 669 analogs



Compd	R_1	R_2	Yield (%)	Compd	R_1	R_2	Yield (%)
3.64	4-OMe-Ph	$-C_3H_6-$	93	**3.70**	Ph	4-F-Ph	95
3.65	3,4-Cl-Ph	$-C_3H_6-$	71	**3.71**	4-OMe-Ph	4-F-Ph	84
3.66	Ph	$-C_3H_6-$	77	**3.72**	4-OMe-Ph	4-Cl-Ph	72
3.67	4-Cl-Ph	$-C_3H_6-$	28	**3.73**	Ph	4-Cl-Ph	84
3.68	4-F-Ph	$-C_3H_6-$	60	**3.74**	Ph	Ph	93
3.69	Ph	$-C_4H_8-$	91				

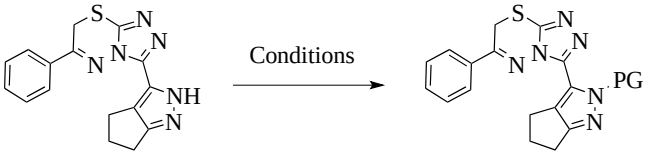
However, attempts to prepare the gem-dimethyl substitution at the α-position directly from the unsubstituted precursor were unsuccessful (Scheme 7). The use LDA (2 eq.) and MeI (3 eq.) resulted in an unidentified compound.



Scheme 7. Attempt at preparing a gem-dimethyl substitution

As an alternative, we wanted to protect the pyrazole before attempting additional deprotonation and alkylations. However, the protection of pyrazole amine was unsuccessful under a variety of conditions (Table 4). The reaction did not proceed upon treatment with TBSCl and imidazole in THF even when warmed to 60 ℃ (Table 4, entry 1-2). Microwave assisted heating at 100 ℃ also did not facilitate this reaction (Table 4, entry 3). The use of strong base only resulted in unidentifiable products (Table 4, entry 4-6).

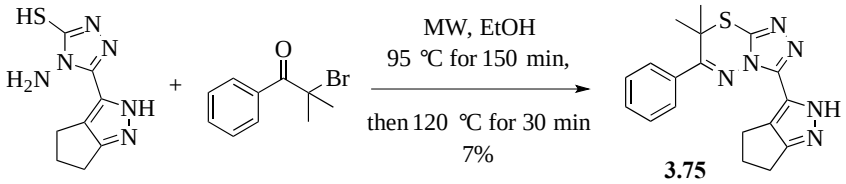
Table 4. Attempts to protect the pyrazole



Entry	Conditions	Results
1	TBSCl, imidazole, 0 ℃ to rt, THF	No reaction
2	TBSCl, imidazole, 60 ℃, THF	No reaction
3	TBSCl, imidazole, MW, 100 ℃, THF	No reaction

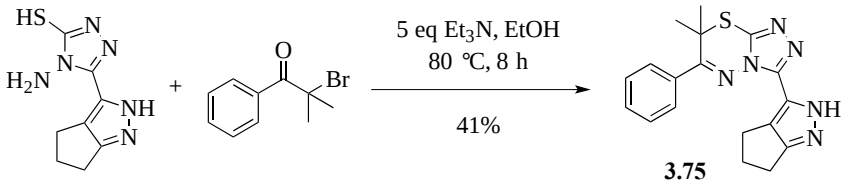
4	n-BuLi, TIPSCl, THF/DMF, -78 ℃	Unidentified material
5	HMDS, $(NH_4)_2SO_4$, 80 ℃	Unidentified material
6	NaH, TIPSCl, DMF, 0 ℃ to rt	Incorrect mass by LCMS

We then decided to use the cyclodehydration conditions for the corresponding α-halo intermediate (Scheme 8). Upon treatment of the 4-amino-5-(1,4,5,6-tetrahydrocyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol with 2-bromoisobutyrophenone at 95 ℃ in a microwave for 150 min, followed by 120 ℃ for 30 min, the desired product (**3.75**) was obtained in 7% yield.



Scheme 8. MW-assisted 669 analog synthesis

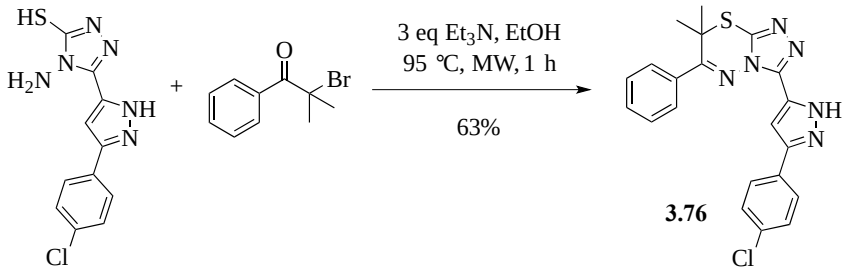
The use of Et_3N as an additive provided the desired gem-dimethyl analog (**3.75**) in 41% yield after 8 h at 80 ℃ in EtOH (Scheme 9).[85]



Scheme 9. Synthesis of geminal methyl substituted 669 analog

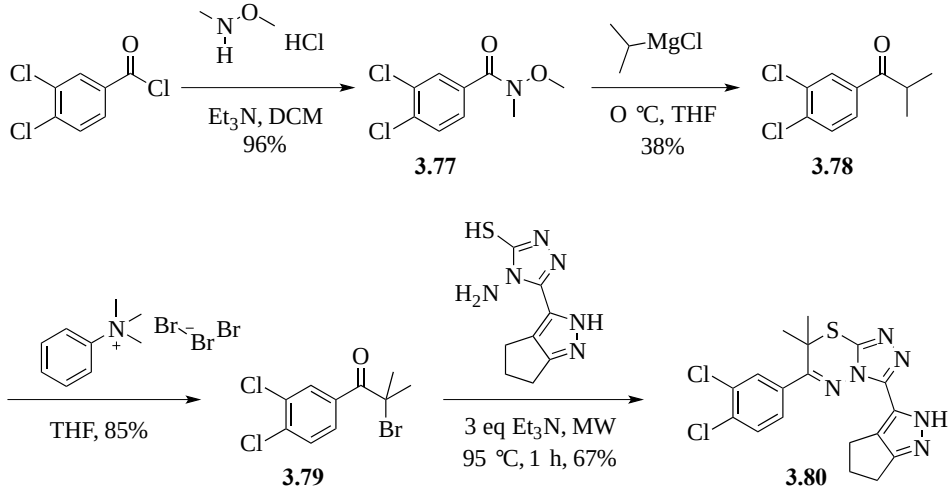
Subsequent reactions using microwave conditions in the presence of Et_3N afforded the desired product in higher yield (Scheme 10). The addition of 3 eq of Et_3N, 4-Amino-5-(5-(4-chloro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol and 2-bromoisobutyrophenone

afforded the desired product (**3.76**) in 63% yield after 1 h heating in the microwave at 95 ℃ in EtOH.



Scheme 10. Microwave assisted 669 analog synthesis in the presence of Et_3N

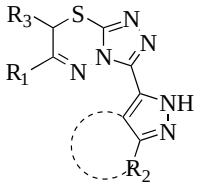
The gem-dimethyl substituted **669** analog has also been prepared (Scheme 11). Commercially available 3,4-dichlorobenzoyl chloride was converted to the Weinreb amide (**3.77**) in 96% yield,[86] which was then converted to the corresponding ketone (**3.78**) upon treatment with 1 eq of isopropylmagnesium chloride.[87] Bromination at the α position of the ketone was achieved by the treatment of phenyltrimethylammonium tribromide in THF at room temperature, and afforded the desired precursor (**3.79**) in 85% yield. Finally, cyclodehydration in the presence of 3 eq of Et_3N afforded the desired analog (**3.80**) in 67% yield.



Scheme 11. Synthesis of compound 3.80

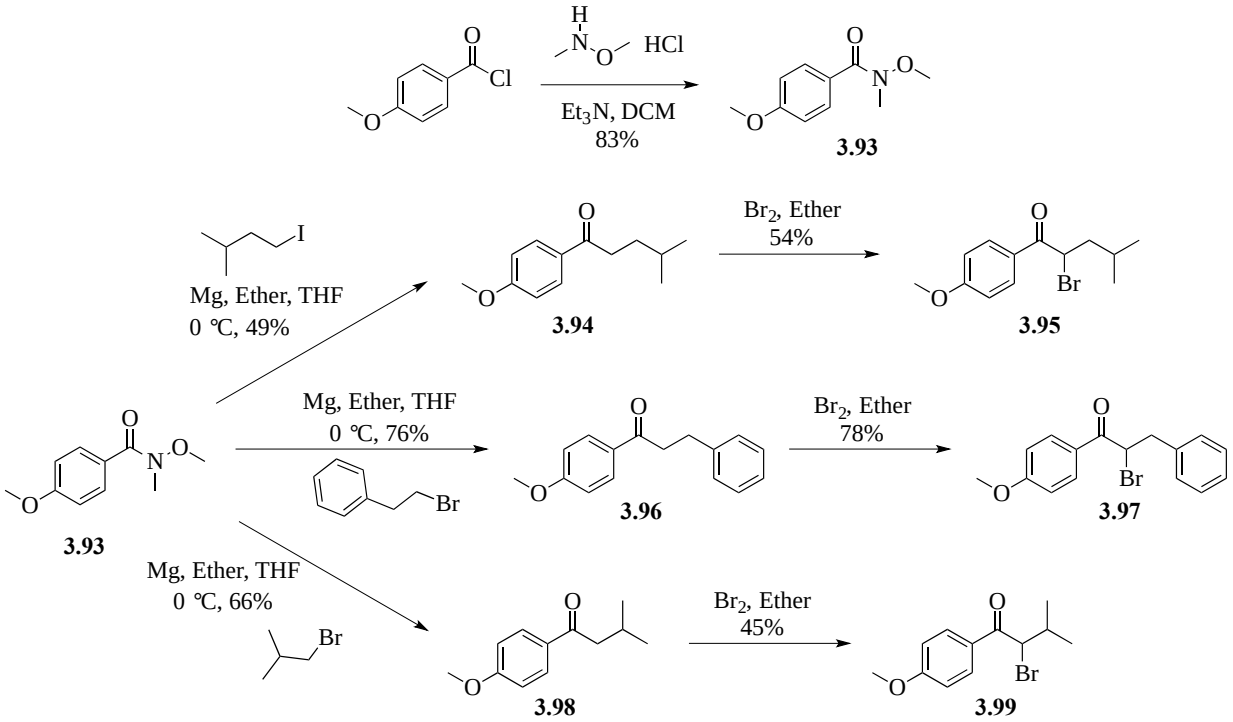
Other analogs have also been synthesized with larger groups such as Ph, *iso*-Pr, Bn, and *iso*-butyl blocking the position alpha to the sulfur (Table 5).

Table 5. SOM blocked pSTAT3 inhibitors of 669 analogs



Compd	R_1	R_2	R_3	Yield (%)
3.81	Ph	-C_3H_6-	Ph	42
3.82	3,4-Cl-Ph	-C_3H_6-	*i*-Pr	62
3.83	4-OMe-Ph	-C_3H_6-	*i*-Pr	61
3.84	4-OMe-Ph	Ph	*i*-Pr	59
3.85	3,4-Cl-Ph	-C_3H_6-	Bn	64
3.86	4-OMe-Ph	-C_3H_6-	Bn	82
3.87	3,4-Cl-Ph	Ph	Bn	88
3.88	4-OMe-Ph	Ph	Bn	94
3.89	3,4-Cl-Ph	Ph	*i*-Bu	81
3.90	4-OMe-Ph	Ph	*i*-Bu	87
3.91	3,4-Cl-Ph	-C_3H_6-	*i*-Bu	66
3.92	4-OMe-Ph	-C_3H_6-	*i*-Bu	65

The requisite ketones for this series were not commercially available, but were readily prepared from the Weinreb amide and the corresponding Grignard reagent followed by bromination. (Scheme 12).

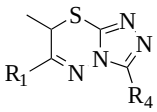


Scheme 12. Synthesis of brominated precursor ketones

3.3 SPECIFIC AIM 3

In order to investigate the importance of the pyrazole present in the **669** series, the *n*-propyl, Bn, *iso*-propyl, and Ph containing analogs were prepared using the standard microwave mediated cyclization conditions (Table 6).

Table 6. 669 Analogs lacking the 1,2-pyrazole

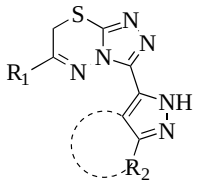


Compd	R_1	R_4	Yield (%)
3.100	4-OMe-Ph	*n*-propyl	78
3.101	4-OMe-Ph	Bn	67
3.102	4-OMe-Ph	*iso*-propyl	85
3.103	4-OMe-Ph	Ph	81
3.104	3,4-Cl-Ph	Bn	91

4.0 BIOLOGICAL RESULTS AND DISCUSSION

All the synthesized **669** analogs were evaluated for their inhibitory activity against pSTAT3 and pSTAT1 in CAL33 cells with the HCS assay performed in Dr. Paul Johnston's lab and these results are summarized in Table 7.

Table 7. SAR of pSTAT3 inhibitors



Compd	R_1	R_2	cLogP	pSTAT3 IC_{50} (μM)	pSTAT1 IC_{50} (μM)
3.6	3,4-Cl-Ph	$-C_3H_6-$	3.41	5.50 ± 1.50 (n = 7)	> 50
3.7	4-OMe-Ph	$-C_3H_6-$	2.03	4.70 ± 3.70 (n = 2)	> 50
3.8	2-Cl-Thiophen-5-yl	$-C_3H_6-$	2.97	6.30 ± 1.80 (n = 2)	> 50
3.9	3-Cl-Ph	$-C_3H_6-$	2.82	1.80 ± 3.60 (n = 2)	> 50
3.10	4-Cl-Ph	$-C_3H_6-$	2.82	25.7 (n = 1)	> 50
3.11	4-CN-Ph	$-C_3H_6-$	1.54	> 50	> 50
3.12	Pyridine-4-yl	$-C_3H_6-$	0.611	> 50	> 50
3.13	*t*-Bu	$-C_3H_6-$	1.91	> 50	> 50
3.14	H	$-C_3H_6-$	-0.203	> 50	> 50

3.15	4-F-Ph	-C_3H_6-	2.25	> 50	> 50
3.16	Ph	-C_3H_6-	2.11	> 30	> 50
3.17	Indol-3-yl	-C_3H_6-	2.10	> 50	> 50
3.18	Me	-C_3H_6-	0.673	> 50	> 50
3.19	Hexanyl	-C_3H_6-	2.61	> 50	> 50
3.20	3,4-Cl-Ph	-C_4H_8-	3.97	13.57 ± 3.91 (n = 4)	> 50
3.21	4-OMe-Ph	-C_4H_8-	2.59	19.2 ± 2.10 (n = 2)	> 50
3.22	2-Cl-Thiophen-5-yl	-C_4H_8-	3.53	33.2 ± 1.60 (n = 2)	> 50
3.23	3-Cl-Ph	-C_4H_8-	3.38	40.5 ± 1.60 (n = 2)	> 50
3.24	4-Cl-Ph	-C_4H_8-	3.38	13.5 ± 0.70 (n = 2)	> 50
3.25	4-F-Ph	-C_4H_8-	2.81	> 50	> 50
3.26	Indol-3-yl	-C_4H_8-	2.66	27.6 ± 3.70 (n = 2)	> 50
3.27	4-CN-Ph	-C_4H_8-	2.10	> 50	> 50
3.28	Pyridin-4-yl	-C_4H_8-	1.17	> 50	> 50
3.29	*t*-Bu	-C_4H_8-	2.47	> 50	> 50
3.30	H	-C_4H_8-	0.36	> 50	> 50
3.31	Me	-C_4H_8-	1.23	> 50	> 50
3.32	Ph	-C_4H_8-	2.67	> 50	> 50
3.33	2-Cl-Ph	-C_4H_8-	3.38	> 50	> 50
3.34	3,4-Cl-Ph	Ph	4.96	25.3 ± 0.01 (n = 2)	> 50
3.35	3-Cl-Ph	Ph	4.37	9.80 (n = 1)	> 50
3.36	4-Cl-Ph	Ph	4.37	5.60 ± 1.60 (n = 4)	> 50
3.37	4-F-Ph	Ph	3.80	14.1 ± 4.20 (n = 2)	> 50

3.38	Ph	Ph	3.65	25.7 (n = 1)	> 50
3.39	Indol-3-yl	Ph	3.64	4.30 ± 2.30 (n = 2)	> 50
3.40	4-CN-Ph	Ph	3.09	18.3 ± 0.05 (n = 2)	> 50
3.41	2-Cl-Thiophen-5-yl	Ph	4.05	> 50	> 50
3.42	Pyridin-4-yl	Ph	2.16	> 50	> 50
3.43	H	Ph	1.34	> 50	> 50
3.44	Me	Ph	2.22	> 50	> 50
3.45	2-Cl-Ph	Ph	4.37	13.9 ± 4.81 (n = 4)	> 50
3.46	*t*-Bu	Ph	3.45	> 50	> 50
3.47	4-OMe-Ph	Ph	3.57	3.64 ± 2.13 (n = 4)	> 50
3.48	Hexanyl	Ph	4.16	> 30	> 50
3.49	3,4-Cl-Ph	4-F-Ph	5.10	14.6 ± 5.70 (n = 2)	> 50
3.50	4-Cl-Ph	4-F-Ph	4.51	16.2 ± 3.00 (n = 2)	> 50
3.51	4-F-Ph	4-F-Ph	3.94	25.6 ± 1.30 (n = 2)	> 50
3.52	4-OMe-Ph	4-F-Ph	3.72	> 50	> 50
3.53	4-CN-Ph	4-F-Ph	3.23	> 50	> 50
3.54	*t*-Bu	4-F-Ph	3.60	> 50	> 50
3.55	Me	4-F-Ph	2.37	> 50	> 50
3.56	Ph	4-F-Ph	3.80	> 30	> 30
3.57	2-Cl-Thiophen-5-yl	4-F-Ph	4.20	19.2 ± 6.53 (n = 4)	> 50
3.58	3,4-Cl-Ph	4-Cl-Ph	5.68	14.5 ± 3.80 (n = 2)	> 50
3.59	4-CN-Ph	4-Cl-Ph	3.80	> 50	> 50
3.60	Ph	4-Cl-Ph	4.37	> 50	> 50

3.61	2-Cl-Ph	4-Cl-Ph	5.08	25.1 ± 3.65 (n = 2)	> 30

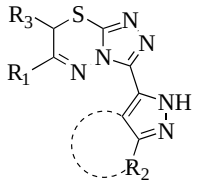
As indicated in Table 7, all compounds had a pSTAT1 IC_{50} > 50 μM. In general, larger electron donating groups (EDG) such as the *t*-Bu group (**3.13**, **3.29**, **3.46**, **3.54**) or small alkyl groups (**3.18**, **3.31**, **3.44**, **3.55**) at the R_1 position exhibited no pSTAT3 activity, and these analogs exhibited potential membrane-permeability issues, as most of their cLogP are less than 2.5. In addition, the unsubstituted imines (**3.14**, **3.30**, **3.43**) were also inactive, and their cLogP are less than 1. Electron withdrawing groups (EWG) at the R_1 position such as the pyridinyl (**3.12**, **3.28**, **3.42**) and cyanophenyl group (**3.11**, **3.27**, **3.40**, **3.59**) showed no pSTAT3 inhibition and they also demonstrated lower cLogP values. Preferred electronic effects at R_1 were observed as the unsubstituted phenyl analog had a fair potency and monosubstituted electro-donating groups at the *meta*- or *para*- positions were beneficial to potency. The *p*-Cl phenyl analogs were more potent than the analogous *p*-F compounds and the former demonstrated higher cLogP values (**3.24** vs. **3.25**, **3.36** vs. **3.37**, **3.50** vs. **3.51**).

The substitution at the R_2 position of the pyrazole also affected pSTAT3 potency, with the fused cyclopentyl-pyrazole proving to be adequate. Other replacement did not increase their activities, albeit their increased cLogP values. For example, replacement of the cyclopentyl-pyrazole (**3.6**) with indazole (**3.20**), phenyl (**3.34**), 4-F-Phenyl (**3.49**) or 4-Cl-Phenyl (**3.58**) groups led to a 2- to 5-fold decrease of the inhibition of pSTAT3. Similarly, the cyclopentyl-pyrazole (**3.7**) was 4-fold more active than the 4-F-phenyl-substituted pyrazole (**3.52**). The 2-Cl-cyclopentyl-pyrazole analogs were also similar in terms of potency (**3.8** vs. **3.22**, **3.41**, **3.57**). Encouragingly, with the cyclopentapyrazole at the R_2 position, compound **3.9** (3-Cl-Ph) showed

a 3-fold improvement in inhibitory activity of pSTAT3 over the lead compound **669**, and it was 20-fold more potent than its analog **3.23** (-C_4H_8-).

The bioassay profiles for the α-methyl containing analogs are summarized in Table 8 (**3.64**-**3.74**). Consistent with the earlier SAR results, the analogs with para-electron-donating groups at the R1 position maintained potencies and selectivities for pSTAT3 over pSTAT1 (**3.64**, **3.71**, and **3.72**). In addition, the α-substitution provided increased metabolic stabilities, with **3.74** showing a $t_{1/2}$ = 26.6 min and 10.2 min in human and mouse microsomes. A 5-fold increase in pSTAT3 potency was also obtained for compound 3.74. Additional analogs displayed similar enhanced potencies and selectivities (**3.52** vs. **3.71**, **3.56** vs. **3.70**), and they all had an increased cLogP values than their original analogs where the α-position of sulfur was not substituted. These preliminary results inspired us to further investigate this position with a larger substitution such as iso-propyl, benzyl, or iso-butyl groups (Table 8, **3.82**-**3.92**). While these larger substituents had increased their cLogP values to around 5, the combination of the 4-OMe-Ph substitution at the R1 position with these substitutions maintained the pSTAT3 potencies and selectivities against pSTAT1 (Table 8, **3.83**, **3.84**, **3.86**, **3.88** and **3.92**). The gem-dimethyl substituted compounds were significantly less active (**Table 9**). Although the investigation of the non-pyrazole containing analogs are still in progress, it appears that the pyrazole is an important feature contributing to the activities of these inhibitors since several early MLSCN library compounds with phenyl- or pyridinyl- groups showed poor activity.

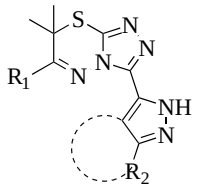
Table 8. SAR of SOM blocked pSTAT3 inhibitors of 669 analogs



Compd	R_1	R_2	R_3	cLogP	pSTAT3 IC_{50} (μM)	pSTAT1 IC_{50} (μM)
3.64	4-OMe-Ph	$-C_3H_6-$	Me	2.55	8.78 ± 0.27 (n = 2)	> 50
3.65	3,4-Cl-Ph	$-C_3H_6-$	Me	3.93	7.90 ± 1.27 (n = 2)	> 50
3.66	Ph	$-C_3H_6-$	Me	2.63	20.4 ± 4.85 (n = 3)	> 50
3.67	4-Cl-Ph	$-C_3H_6-$	Me	3.34	I.P.	I.P.
3.68	4-F-Ph	$-C_3H_6-$	Me	2.77	I.P	I.P.
3.69	Ph	$-C_4H_8-$	Me	3.19	> 20	> 50
3.70	Ph	4-F-Ph	Me	4.32	3.81 ± 0.70 (n = 4)	> 30
3.71	4-OMe-Ph	4-F-Ph	Me	4.24	4.16 ± 0.325 (n = 2)	31.1 ± 4.25 (n = 2)
3.72	4-OMe-Ph	4-Cl-Ph	Me	4.81	3.84 ± 0.48 (n = 2)	29.5 ± 8.40 (n = 2)
3.73	Ph	4-Cl-Ph	Me	4.89	5.69 ± 1.28 (n = 3)	> 50
3.74	Ph	Ph	Me	4.17	4.82 ± 0.70 (n = 2)	> 50
3.81	Ph	$-C_3H_6-$	Ph	3.87	I.P.	I.P.
3.82	3,4-Cl-Ph	$-C_3H_6-$	*i*-Pr	4.86	I.P.	I.P.
3.83	4-OMe-Ph	$-C_3H_6-$	*i*-Pr	3.47	2.23 (n = 1)	> 50
3.84	4-OMe-Ph	Ph	*i*-Pr	5.02	2.37 (n = 1)	> 50
3.85	3,4-Cl-Ph	$-C_3H_6-$	Bn	5.35	7.5 (n = 1)	> 50
3.86	4-OMe-Ph	$-C_3H_6-$	Bn	3.96	3.15 (n = 1)	> 50
3.87	3,4-Cl-Ph	Ph	Bn	6.90	22.65 (n = 1)	> 50

3.88	4-OMe-Ph	Ph	Bn	5.51	5.78 (n = 1)	> 50
3.89	3,4-Cl-Ph	Ph	*i*-Bu	6.93	> 50	> 50
3.90	4-OMe-Ph	Ph	*i*-Bu	5.55	13.57 (n = 1)	> 50
3.91	3,4-Cl-Ph	-C_3H_6-	*i*-Bu	5.39	4.14 (n =1)	> 50
3.92	4-OMe-Ph	-C_3H_6-	*i*-Bu	4.00	5.14 (n =1)	> 50

Table 9. SAR of geminal methyl substituted 669 analogs



Compd	R_1	R_2	cLogP	pSTAT3 IC_{50} (μM)	pSTAT1 IC_{50} (μM)
3.75	Ph	-C_3H_6-	3.15	> 50	> 50
3.80	3,4-Cl-Ph	-C_3H_6-	4.45	I.P.	I.P.
3.76	Ph	4-Cl-Ph	5.40	22.3 ± 11.5 (n = 2)	> 50

5.0 CONCLUSION AND PERSPECTIVES

A first generation **669** library produced a total of 56 analogs in > 95% purity based on LC/MS which were submitted for inhibition of pSTAT3 and pSTAT1. The analogs with electron-donating *para*-substituents (4-OMe-Ph, 3,4-di-Cl-Ph) at the R_1 position proved to be most potent and selective in targeting pSTAT3 over pSTAT1. Subsequent attempts to address metabolic liabilities led to the synthesis of another 32 compounds. The novel α-methyl-containing compounds showed increased half-lives in both human and mouse microsomes and enhanced pSTAT3 inhibition. The activity and selectivity were not affected when this methyl group was replaced by larger *iso*-propyl or *iso*-butyl groups. However, geminal dimethyl substitution was not tolerated.

Future work on this scaffold is ongoing and should consist of further SAR development with a focus on triazolothiadiazine modification and an emphasis on improving water solubility and cellular growth inhibition.

6.0 EXPERIMENTAL SECTION OF COMPOUND 3.6-3.104

6.1 INDEX OF COMPOUNDS

6-(3,4-Dichlorophenyl)-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.6**) 42

6-(4-Methoxyphenyl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.7**) 43

6-(5-Chlorothiophen-2-yl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.8**)..... 44

6-(3-Chlorophenyl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.9**) 45

6-(4-Chlorophenyl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.10**) 46

4-(3-(2,4,5,6-Tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)benzonitrile (**3.11**) 46

6-(Pyridin-4-yl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.12**) 47

6-(*tert*-Butyl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.13**) 48

3-(2,4,5,6-Tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.14**) 49

6-(4-Fluorophenyl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.15**) 49

6-Phenyl-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.16**) 50

6-(1*H*-indol-3-yl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.17**) 51

Compound 13. 6-Methyl-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.18**) 51

6-Cyclohexyl-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.19**) 52

6-(3,4-Dichlorophenyl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.20**) 53

6-(4-Methoxyphenyl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.21**) 54

6-(5-Chlorothiophen-2-yl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.22**) 55

6-(3-Chlorophenyl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.23**) 55

6-(4-Chlorophenyl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.24**) 56

6-(4-Fluorophenyl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.25**) 57
6-(1*H*-indol-3-yl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.26**) 58
4-(3-(4,5,6,7-Tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)benzonitrile (**3.27**) 58
6-(Pyridin-4-yl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.28**) 59
6-(*tert*-Butyl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.29**) 60
3-(4,5,6,7-Tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.30**) 61
6-Methyl-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.31**) 62
6-Phenyl-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.32**) 62
6-(2-Chlorophenyl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.33**) 63
6-(3,4-Dichlorophenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.34**) 64
6-(3-Chlorophenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.35**) 65
6-(4-Chlorophenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.36**) 65

6-(4-Fluorophenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.37**) 66

6-Phenyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.38**) 67

6-(1*H*-indol-3-yl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.39**) 67

4-(3-(3-Phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)benzonitrile (**3.40**) 68

6-(5-Chlorothiophen-2-yl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.41**) 69

3-(3-Phenyl-1*H*-pyrazol-5-yl)-6-(pyridin-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.42**) 69

3-(3-Phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.43**) 70

6-Methyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.44**) 71

6-(2-Chlorophenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.45**) 71

6-(*Tert*-butyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.46**) 72

6-(4-Methoxyphenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.47**) 73

6-Cyclohexyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.48**) 74

6-(3,4-Dichlorophenyl)-3-(3-(4-fluorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.49**) 74

6-(4-Chlorophenyl)-3-(3-(4-fluorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.50**) 75

6-(4-Fluorophenyl)-3-(3-(4-fluorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.51**) 76
3-(3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl)-6-(4-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.52**) 77
4-(3-(3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)benzonitrile (**3.53**) 77
6-(Tert-butyl)-3-(3-(4-fluorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.54**) 78
3-(3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl)-6-methyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.55**) 79
3-(3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.56**) 80
6-(5-Chlorothiophen-2-yl)-3-(3-(4-fluorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.57**) 80
3-(3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl)-6-(3,4-dichlorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.58**) 81
4-(3-(3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)benzonitrile (**3.59**) 82
3-(3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.60**) 83
6-(2-Chlorophenyl)-3-(3-(4-chlorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.61**) 83

6-(4-Methoxyphenyl)-7-methyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.64**) 84
6-(3,4-Dichlorophenyl)-7-methyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.65**) 85
7-Methyl-6-phenyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.66**) 86
6-(4-Chlorophenyl)-7-methyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.67**) 87
6-(4-Fluorophenyl)-7-methyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.68**) 87
7-Methyl-6-phenyl-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.69**) 88
3-(3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl)-7-methyl-6-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.70**) 89
3-(3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl)-6-(4-methoxyphenyl)-7-methyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.71**) 90
3-(3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl)-6-(4-methoxyphenyl)-7-methyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.72**) 91
3-(3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl)-7-methyl-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.73**) 92
7-Methyl-6-phenyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.74**) 93

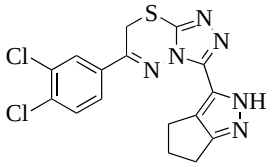
6,7-Diphenyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.81**) 94
6-(3,4-Dichlorophenyl)-7-isopropyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.82**) 95
7-Isopropyl-6-(4-methoxyphenyl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.83**) 96
7-Isopropyl-6-(4-methoxyphenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.84**) 97
7-Benzyl-6-(3,4-dichlorophenyl)-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.85**) 98
7-Benzyl-6-(4-methoxyphenyl)-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.86**) 99
7-Benzyl-6-(3,4-dichlorophenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.87**) 100
7-Benzyl-6-(4-methoxyphenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.88**) 101
6-(3,4-Dichlorophenyl)-7-*iso*-butyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.89**) 102
7-*iso*-Butyl-6-(4-methoxyphenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.90**) 103
6-(3,4-Dichlorophenyl)-7-*iso*-butyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.91**) 104

7-*iso*-Butyl-6-(4-methoxyphenyl)-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.92**)..... 104
7,7-Dimethyl-6-phenyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.75**) 105
6-(3,4-Dichlorophenyl)-7,7-dimethyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.80**)..... 106
3-(3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl)-7,7-dimethyl-6-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**3.76**) 107
6-(4-Methoxyphenyl)-7-methyl-3-propyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.100**). 107
3-Benzyl-6-(4-methoxyphenyl)-7-methyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.101**) 108
3-Isopropyl-6-(4-methoxyphenyl)-7-methyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.102**) 109
6-(4-Methoxyphenyl)-7-methyl-3-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.103**) 110
3-Benzyl-6-(3,4-dichlorophenyl)-7-methyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3.104**) 110

6.2 EXPERIMENTAL PROCEDURES

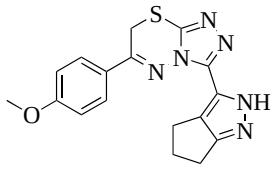
General: All reactions were performed under an argon atmosphere and all glassware were dried in an oven at 130 ℃ for 2 h prior to use. EtOH was distilled over Br_2/Mg turnings. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F254 plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95%EtOH), p-anisaldehyde solution (2.5

mL of p-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}$•4 H_2O and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a0.1% NaOH solution). Purifications by chromatography were performed using SiO_2 (SiliaFlash ® F60, Silicycle) or using an ISCO-Companion flash chromatography system. Decantation was performed in distilled hexane. IR spectra were determined on a Smith Detection IdentifyIR FT-IR spectrometer (ATR). ^1H spectra were obtained at 400 MHz at 100 ℃ in DMSO-d_6 unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard. ^1H NMR spectra are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint =quintet, m = multiplet, br = broad), number of protons, and coupling constant(s). ^{13}C NMR spectra were run at 100 MHz at 100 ℃ using a proton-decoupled pulse sequence with a d1 of 3 sec, and are tabulated by observed peaks. Mass spectra were obtained on a Micromass Autospec double focusing instrument. Microwave reactions were performed using a Biotage Initiator in glass microwave vials (cap sealed) with continuous magnetic stirring and an external surface temperature sensor. LCMS analyses were completed on a Waters MicroMass ZQ with 2525 Binary Gradient Module, 2420 ELSD, 2996 PDA using MeCN/H2O with 0.1% TFA. Melting points (uncorrected) were determined using a Mel-Temp instrument.



6-(3,4-Dichlorophenyl)-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.6)

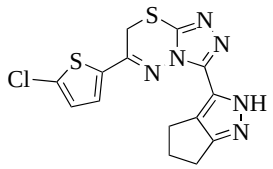
A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0250 g, 0.112 mmol) and 2,3',4'-trichloroacetophenone (0.0251 g, 0.112 mmol) in EtOH (1 mL) was heated at 95 ℃ in a microwave for 30 min, and LC-MS analysis showed that the conversion was complete. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/ CH_2Cl_2) and provided 38.7 mg (88%) of 3.6 as a colorless powder: Mp 209 ℃; IR (ATR) 3154, 2902, 1506, 1458, 818 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 8.27 (d, 1 H, *J* = 2.4 Hz), 7.99 (dd, *J* = 8.4 Hz, 2 Hz, 1 H), 7.87 (d, 1 H, *J* = 8.4 Hz), 4.45 (s, 2 H), 2.73-2.68 (m, 4 H), 2.43-2.40 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 153.7, 141.6, 134.0, 132.0, 131.2, 129.4, 127.6, 30.0, 24.0, 23.6, 22.9, 4 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{16}H_{12}Cl_2N_6S$ ($[M+H]^+$) 391.0299, found 391.0308.



6-(4-Methoxyphenyl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.7)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.225 mmol) and 4-methoxyphenacyl chloride (0.0415 g, 0.225 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min, and LC-MS analysis showed that

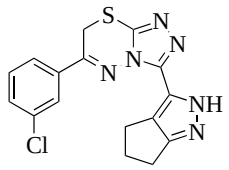
the conversion was complete. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/ CH_2Cl_2) and provided 62 mg (78%) of **3.7** as a colorless powder: Mp 251.8 ℃; IR (ATR) 3415, 2941, 1605, 1517, 1450, 1277, 1178, 956 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 ℃) 7.99-7.96 (m, 2 H), 7.13-7.09 (m, 2 H), 4.34 (s, 2 H), 3.88 (s, 3 H), 2.78-2.69 (m, 4 H), 2.47-2.42 (br m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 162.0, 154.5, 140.8, 128.9, 125.4, 125.2, 114.1, 55.1, 29.5, 23.2, 22.7, 3 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{17}H_{16}N_6SO$ ($[M+H]^+$) 353.1185, found 353.1176.



6-(5-Chlorothiophen-2-yl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.8)

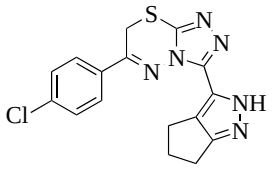
A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.225 mmol) and 2-chloro-1-(5-chlorothiophen-2-yl)ethan-1-one(0.0439 g, 0.225 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residues in dry hexane provided 44.4 mg (54%) of **3.8** as a colorless powder: Mp 249 ℃; IR (ATR) 3156, 2907, 1564, 1433, 1291, 956 cm^{-1}; ^1H NMR (100 MHz, DMSO-d_6, 100 ℃) 7.80 (d, J = 4 Hz, 1 H), 7.28 (d, J = 4.4 Hz, 1

H), 4.38 (s, 2 H), 2.82 (br s, 2 H), δ 2.74-2.71 (m, 2 H), 2 aliphatic H overlapped with DMSO peak; ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 149.7, 140.8, 135.7, 134.5, 132.1, 127.8, 125.2, 29.5, 23.7, 23.1, 22.3, 3 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{14}H_{11}ClN_6S_2$ ($[M+H]^+$) 363.0253, found 363.0246.



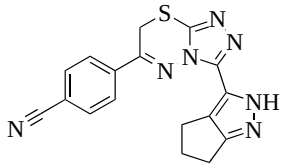
6-(3-Chlorophenyl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.9)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.225 mmol) and 2-bromo-3'-chloroacetophenone (0.0525 g, 0.225 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min, and LC-MS analysis showed that the conversion was complete. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/ CH_2Cl_2) and provided 31.9 mg (40%) of **3.9** as a colorless powder: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.65 (br s, 1 H), 8.05 (s, 1 H), 7.95 (d, *J* = 8 Hz, 1 H), 7.65 (dd, *J* = 1.6 Hz, 6.8 Hz, 1 H), 7.59 (t, *J* = 7.8 Hz, 1 H), 4.40 (s, 2 H), 2.75 (t, *J* = 7.2 Hz, 2 H), 2.72 (t, *J* = 7.2 Hz, 2 H), 2.45 (br s, 2 H); HRMS (ES) *m/z* calcd for $C_{16}H_{14}N_6SCl$ ($[M+H]^+$) 357.0684, found 357.0675.



6-(4-Chlorophenyl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.10)

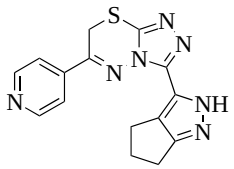
A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.225 mmol) and 2,4'-dichloroacetophenone (0.0425 g, 0.225 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 34.5 mg (43%) of **3.10** as a colorless powder: Mp 243 ℃; IR (ATR) 3163, 2906, 1591, 1452, 1297, 952 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.62 (s br, 1 H), 8.02 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 8.8 Hz, 2 H), 4.38 (s, 2 H), 2.76-2.69 (m, 4 H), 2.44 (br s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 154.0, 140.7, 136.3, 132.1, 128.8, 128.5, 125.3, 29.5, 23.5, 23.1, 22.8, 3 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{16}H_{13}ClN_6S$ ($[M+H]^+$) 357.0689, found 357.0688;



4-(3-(2,4,5,6-Tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)benzonitrile (3.11)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.225 mmol) and 4-cyanophenacyl bromine (0.0504 g, 0.225 mmol) in EtOH

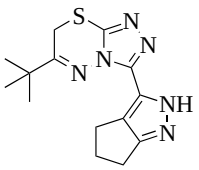
(2 mL) was heated at 95 ℃ in a microwave for a total of 150 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in distilled hexane provided 43.9 mg (56%) of **3.11** as a colorless powder: Mp 254 ℃; IR (ATR) 3167, 2912, 2226, 1452, 1294, 954, 820 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 8.16 (d, *J* = 8.4 Hz, 2 H), 7.99 (d, *J* = 8.8 Hz, 2 H), 4.43 (s, 2 H), 2.74 (t, *J* = 7.3 Hz, 2 H), 2.72 (t, *J* = 8.4 Hz, 2 H), 2.47-2.40 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 153.6, 140.7, 137.4, 132.2, 127.8, 125.4, 117.5, 113.6, 29.5, 23.5, 23.1, 22.8, 3 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{17}H_{13}N_7S$ ($[M+H]^+$) 348.1031, found 348.1050.



6-(Pyridin-4-yl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.12)

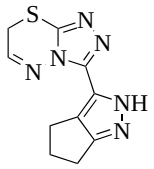
A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.225 mmol) and 4-(bromoacetyl)pyridine hydrobromide (0.0632 g, 0.225 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 45.8 mg (63%) of **3.12** as a colorless powder: Mp 273 ℃; IR (ATR) 3107, 2891, 1599, 1456, 1402, 1295, 951 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.65 (s, NH 1 H), 8.80 (d, *J* = 2 Hz, 1 H), 8.79 (d, *J* = 1.6 Hz, 1 H), 7.90 (d, 1 H, *J* = 1.6 Hz, 1 H), 7.89 (d, *J* = 1.6 Hz, 1 H), 4.42 (s, 2 H), 2.75

(t, *J* = 6.8 Hz, 2 H), 2.72 (t, *J* = 6.8 Hz, 2 H), 2.45 (br s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 150.0, 140.7, 140.4, 120.6, 23.5, 23.1, 22.5, 1 aliphatic C and 5 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{15}H_{14}N_7S$ ($[M+H]^+$) 324.1026, found 324.1017.



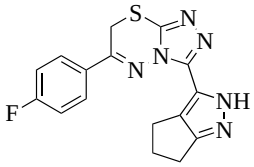
6-(*tert*-Butyl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.13)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.225 mmol) and 1-bromopinacolone (0.0403 g, 0.225 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for a total of 150 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 41.5 mg (61%) of **3.13** as a colorless powder: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.43 (s, NH 1 H), 3.91 (s, 2 H), 2.75 (t, *J* = 6.8 Hz, 2 H), 2.70 (t, *J* = 7.2 Hz, 2 H), 2.46-2.43 (m, 2 H), 1.30 (s, 9 H); HRMS (ES) *m/z* calcd for $C_{14}H_{19}N_6S$ ($[M+H]^+$) 303.1386, found 303.1380.



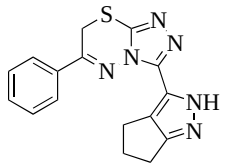
3-(2,4,5,6-Tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.14)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0700 g, 0.315 mmol) and 2-chloro-1,1-diethoxyethane (0.0872 g, 0.630 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 150 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/ CH_2Cl_2) and provided 18.3 mg (23.6%) of **3.14** as a colorless powder: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.5 (br s, 1 H), 7.86 (t, *J* = 4 Hz, 1 H), 3.86 (d, *J* = 3.86 Hz, 2 H), 2.76 (t, *J* = 7 Hz, 2 H), 2.70 (t, *J* = 7.2 Hz, 2 H), 2.46-2.45 (m, 2 H). HRMS (ES) *m/z* calcd for $C_{10}H_{11}N_6S$ ($[M+H]^+$) 247.0760, found 247.0752.



6-(4-Fluorophenyl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.15)

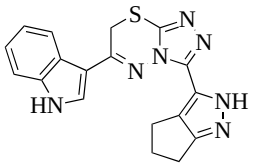
A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.225 mmol) and 2-chloro-4'-fluoroacetophenone (0.0388 g, 0.225 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 38.5 mg (50%) of **3.15** as a colorless powder: Mp 243 ℃; IR (ATR) 3184, 2070, 1599, 1448, 1223, 954.3, 810.8 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 8.09-8.05 (m, 2 H); 7.40-7.34 (m, 2 H), 4.39 (s, 2 H), 2.77-2.69 (m, 4 H), 2.46-2.42 (br t, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 165.2, 162.7, 154.3, 141.0, 129.8, 129.7, 125.6, 115.7, 115.5, 30.0, 29.6, 23.6, 23.3, 23.1, 1 quaternary C was missing; HRMS (ES) *m/z* calcd for $C_{16}H_{13}FN_6S$ ($[M+H]^+$) 341.0985, found 341.0982.



6-Phenyl-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.16)

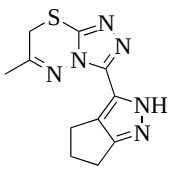
A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.225 mmol) and 2-chloroacetophenone (0.0348 g, 0.225 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 50.7 mg (70%) of **3.16** as a colorless powder: ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.64 (br s, 1 H), 8.01-7.99 (m, 2

H); 7.63-7.54 (m, 3 H), 4.39 (s, 2 H), 2.77-2.69 (m, 4 H), 2.43 (br s, 2 H); HRMS (ES) *m/z* calcd for $C_{16}H_{15}N_6S$ ($[M+H]^+$) 323.1073, found 323.1065.



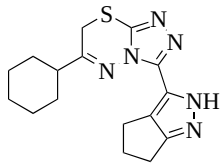
6-(1*H*-indol-3-yl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.17)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.225 mmol) and 2-chloro-1-(1*H*-indol-3-yl)ethan-1-one (0.0436 g, 0.225 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 54.1 mg (67%) of **3.17** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.61-12.56 (br s, NH 1 H), 11.8 (s, NH 1H), 8.23 (s, 1 H), 7.51 (d, *J* = 8.4 Hz, 1 H), 7.25 (t, *J* = 7.6 Hz, 1 H), 7.16 (t, *J* = 7.6 Hz, 1 H), 4.33 (s, 2 H), 2.70-2.74 (br m, 4 H), 2.42 (br s, 2 H); HRMS (ES) *m/z* calcd for $C_{18}H_{15}N_7S$ ($[M+H]^+$) 362.1182, found 362.1171.



6-Methyl-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.18)

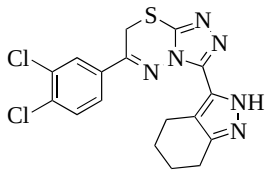
A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.225 mmol) and chloroacetone (0.0208 g, 0.225 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 35.7 mg (61%) of **3.18** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.55 (br s, 1 H), 3.85 (s, 2 H), 2.79 (t, *J* = 6.8 Hz, 2 H), 2.70 (t, *J* = 7.4 Hz, 2 H), 2.46-2.42 (br t, 2 H), 2.34 (s, 3 H); HRMS (ES) *m/z* calcd for $C_{11}H_{12}N_6S$ ($[M+H]^+$) 261.0917, found 261.0909.



6-Cyclohexyl-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.19)

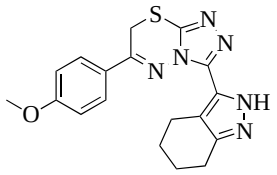
A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.225 mmol) and 2-bromo-1-cyclohexylethanone (0.0461 g, 0.225 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/ CH_2Cl_2) and provided 61.5 mg (83%) of **3.19** as a solid: Mp 189 ℃; IR (ATR) 3178, 3074, 2911, 2854, 1610, 1504 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 3.86 (s, 2 H), 2.76 (t, *J* = 8 Hz, 2 H), 2.70 (t, *J* = 8 Hz, 2 H), 2.67-2.60 (m, 1 H), 2.48-2.41 (m, 2 H), 1.96-1.92 (m, 2 H), 1.84-1.79 (m, 2 H), 1.73-1.67 (m, 1 H), 1.53-1.44 (m, 2 H), 1.42-1.31 (m, 2 H), 1.30-1.12 (m, 1 H); ^{13}C NMR (100 MHz,

DMSO-d_6, 100 °C) δ 164.1, 145.7, 141.0, 125.1, 44.8, 29.5, 28.7, 24.9, 24.7, 23.6, 23.2, 23.1, 2 quaternary C were missing; HRMS (ES) *m/z* calcd for C16H21N6S ($[M+H]^+$) 329.1548, found 329.1546.



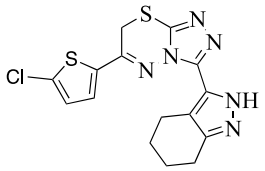
6-(3,4-Dichlorophenyl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.20)

A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0250 g, 0.106 mmol) and 2,3',4'-trichloroacetophenone (0.0236 g, 0.106 mmol) in EtOH (1 mL) was heated at 95 ℃ in a microwave for 30 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 39.6 mg (92%) of **3.20** as a solid: Mp 220 ℃; IR (ATR) 3081, 2930, 2854, 1541, 1445 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 8.21 (d, *J* = 2 Hz, 1 H), 7.95 (dd, *J* = 2 Hz, 8.4 Hz, 1 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 4.38 (s, 2 H), 2.68 (t, *J* = 6 Hz, 2 H), 2.66 (t, *J* = 6 Hz, 2 H), 1.84-1.78 (m, 2 H), 1.77-1.70 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 161.4, 152.5, 147.4, 141.0, 140.6, 133.8, 131.6, 130.6, 128.8, 127.0, 115.4, 22.4, 22.3, 21.9, 20.7, 20.5; HRMS (ES) *m/z* calcd for $C_{17}H_{14}Cl_2N_6S$ ($[M+H]^+$) 405.0456, found 405.0462.



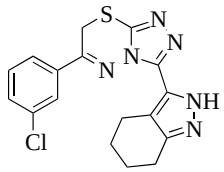
6-(4-Methoxyphenyl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.21)

A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.212 mmol) and 4-methoxyphenacyl chloride (0.0391 g, 0.212 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 75.1 mg (97%) of **3.21** as a solid: Mp 148 ℃; IR (ATR) 3067, 2999, 2843, 1603, 1448, 1255, 1176 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 7.98-7.94 (m, 2 H), 7.10-7.07 (m, 2 H), 4.32 (s, 2 H), 3.87 (s, 3 H), 2.68 (t, *J* = 6 Hz, 2 H), 2.65 (t, *J* = 6 Hz, 2 H), 1.84-1.75 (m, 4 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 161.9, 154.0, 147.2, 140.7, 128.8, 125.5, 115.3, 114.0, 55.1, 22.5, 22.4, 21.9, 20.8, 20.5, 2 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{18}H_{18}N_6SO$ ($[M+H]^+$) 367.1341, found 367.1332.



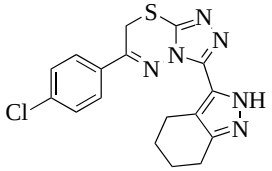
6-(5-Chlorothiophen-2-yl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.22)

A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.212 mmol) and 2-chloro-1-(5-chlorothiophen-2-yl)ethan-1-one (0.0413 g, 0.212 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 63.8 mg (80%) of **3.22** as a solid: Mp 265.3 ℃; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 7.77 (d, *J* = 4 Hz, 1 H), 7.25 (d, *J* = 4.4 Hz, 1 H), 4.37 (s, 2 H), 2.69-2.63 (m, 4 H), 1.84-1.80 (m, 2 H), 1.79-1.74 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 149.1, 140.4, 136.0, 134.3, 131.6, 127.6, 115.2, 22.3, 22.1, 21.9, 20.4, 1 aliphatic C and 2 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{15}H_{13}N_6S_2Cl$ ($[M+H]^+$) 377.0410, found 377.0407.



6-(3-Chlorophenyl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.23)

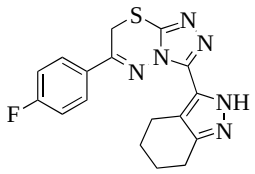
A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.212 mmol) and 2-bromo-3'-chloroacetophenone (0.0494 g, 0.212 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 38.2 mg (49%) of **3.23** as a solid: Mp 160 ℃; IR (ATR) 3144, 2932, 1560, 1445, 781 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 8.03 (s, 1 H), 7.94 (d, *J* = 8 Hz, 1 H), 7.65-7.62 (m, 1 H), 7.57 (t, *J* = 7.8 Hz, 1 H), 4.32 (s, 2 H), 2.68 (t, *J* = 5.6 Hz, 2 H), 2.66 (t, *J* = 5.6 Hz, 2 H), 1.84-1.78 (m, 1 H), 1.77-1.71 (m, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 153.2, 140.7, 135.4, 133.4, 130.8, 126.6, 125.7, 22.6, 22.4, 21.9, 20.5, 1 aliphatic and 4 quaternary carbon were missing; HRMS (ES) *m/z* calcd for $C_{17}H_{16}N_6SCl$ ($[M+H]^+$) 371.0846, found 371.0854.



6-(4-Chlorophenyl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.24)

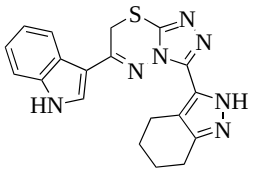
A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.212 mmol) and 2,4'-dichloroacetophenone (0.0400 g, 0.212 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for a total of 120 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 54.6 mg (70%) of **3.24** as a solid: Mp 255 ℃; IR (ATR) 3197, 2928, 1558, 1441, 850 cm^{-1}; ^1H NMR (400 MHz,

DMSO-d_6, 100 °C) δ 8.02-7.99 (m, 2 H), 7.61-7.58 (m, 2 H), 4.37 (s, 2 H), 2.69-2.63 (m, 4 H), 1.84-1.75 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 153.5, 147.4, 141.0, 140.7, 136.2, 132.2, 132.1, 128.7, 128.4, 115.4, 22.5, 22.3, 21.9, 20.7, 20.5; HRMS (ES) *m/z* calcd for $C_{17}H_{16}ClN_6S$ ($[M+H]^+$) 371.0846, found 371.0854.



6-(4-Fluorophenyl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.25)

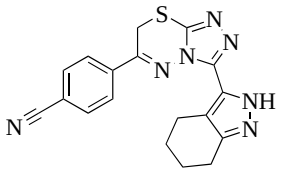
A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.212 mmol) and 2-chloro-4'-fluoroacetophenone (0.0370 g, 0.212 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 50.1 mg (72%) of **3.25** as a solid: Mp 253 ℃; IR (ATR) 3161, 2932, 1597, 1450, 1225, 848 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100°C) δ 8.08-8.04 (m, 2 H), 7.38-7.34 (m, 2 H), 4.37 (s, 2 H), 2.67 (t, *J* = 6.4 Hz, 2 H), 2.65 (t, *J* = 6.4 Hz, 2 H), 1.84-1.74 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 165.0, 162.5, 153.6, 147.4, 141.1, 140.7, 132.3, 129.8, 129.8, 129.6, 129.5, 22.6, 22.3, 21.9, 20.7, 20.5; HRMS (ES) *m/z* calcd for $C_{17}H_{16}FN_6S$ ($[M+H]^+$) 355.1141, found 355.1146.



6-(1*H*-indol-3-yl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine

(3.26)

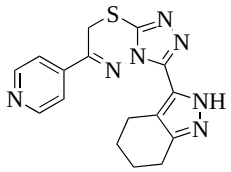
A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.212 mmol) and 2-chloro-1-(1*H*-indol-3-yl)ethan-1-one (0.0410 g, 0.212 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for a total of 120 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 47.8 mg (60%) of **3.26** as a solid: Mp 307 ℃; IR (ATR) 2917, 1556, 1445, 1240, 744 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 8.38 (d, *J* = 8 Hz, 1 H), 8.19 (s, 1 H), 7.47 (d, *J* = 8 Hz, 1 H), 7.20 (t, *J* = 7.2 Hz, 1 H), 7.11 (t, *J* = 7.6 Hz, 1 H), 4.30 (s, 2 H), 2.72 (t, *J* = 6.4 Hz, 2 H), 2.67 (t, *J* = 6 Hz, 2 H), 1.85-1.79 (m, 2 H), 1.79-1.71 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 151.7, 140.4, 137.0, 131.2, 124.0, 122.5, 120.7, 115.1, 111.4, 110.3, 22.9, 22.3, 21.9, 20.4, 1 aliphatic C and 4 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{19}H_{17}N_7S$ ($[M+H]^+$) 376.1344, found 376.1337.



4-(3-(4,5,6,7-Tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)benzonitrile

(3.27)

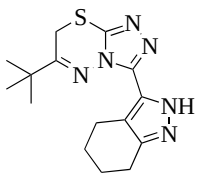
A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.212 mmol) and 4-cyanophenacyl bromine (0.0474 g, 0.212 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 56.1 mg (73%) of **3.27** as a solid: Mp 250 ℃; IR (ATR) 2927, 2228, 1450, 1286, 818 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 8.15 (d, *J* = 8.4 Hz, 2 H), 7.97 (d, *J* = 8.4 Hz, 2 H), 4.41 (s, 2 H), 2.67 (t, *J* = 6.4 Hz, 2 H), 2.66 (t, *J* = 6 Hz, 2 H), 1.84-1.74 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 ℃) δ 153.1, 147.6, 140.6, 137.5, 132.2, 127.7, 117.5, 115.4, 113.5, 22.5, 22.3, 21.9, 20.7, 20.5, 2 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{18}H_{15}N_7S$ ($[M+H]^+$) 362.1188, found 362.1227.



6-(Pyridin-4-yl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.28)

A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.212 mmol) and 4-(bromoacetyl)pyridine hydrobromide (0.069 g, 0.212 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and

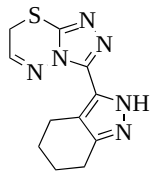
the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 36 mg (50%) of **3.28** as a solid: Mp 232 ℃; IR (ATR) 3145, 2925, 1592, 1452, 1288, 807 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.64 (br s, NH 1 H), 8.78-8.77 (m. 2 H), 7.88 (d, *J* = 6 Hz, 2 H), 4.40 (s, 2 H), 2.68 (t, *J* = 6.4 Hz, 2 H), 2.66 (t, *J* = 6 Hz, 2 H), 1.84-1.80 (m, 2 H), 1.79-1.75 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 152.8, 150.0, 140.7, 140.5, 120.6, 115.4, 22.3, 21.9, 20.5, 1 aliphatic C and 2 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{16}H_{15}N_7S$ ($[M+H]^+$) 338.1188, found 338.1185.



6-(*tert*-Butyl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.29)

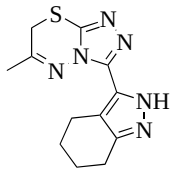
A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.212 mmol) and 1-bromopinacolone (0.0379 g, 0.212 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for a total of 150 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 34.9 mg (52%) of **3.29** as a solid: Mp 209 ℃; IR (ATR) 3411, 2930, 1452, 960, 818 cm^{-1}; ^1H NMR (100 MHz,

DMSO-d_6, 100 °C) δ 12.54 (br s, 1 H), 3.90 (s, 2H), 2.67-2.61 (m, 4 H), 1.83-1.69 (m, 4 H), 1.28 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 166.1, 141.2, 115.2, 38.4, 26.3, 22.4, 22.0, 21.4, 20.4, 3 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{15}H_{20}N_6S$ ($[M+H]^+$) 317.1548, found 317.1550.



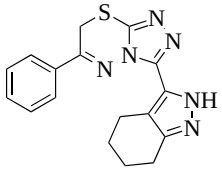
3-(4,5,6,7-Tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.30)

A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.100 g, 0.423 mmol) and 2-chloro-1,1-diethoxyethane (127 uL, 0.846 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 47.1 mg (43%) of **3.30** as a solid: Mp 264 ℃; IR (ATR) 3184, 2934, 1558, 1456, 954 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.5 (s, NH 1 H), 7.83 (t, *J* = 4 Hz, 1 H), 3.83 (d, *J* = 4 Hz, 2 H), 2.67-2.60 (m, 4 H), 1.83-1.75 (m, 4 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 148.1, 140.4, 115.3, 22.3, 21.9, 21.6, 20.4, 1 aliphatic C and 3 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{11}H_{12}N_6S$ ($[M+H]^+$) 261.0917, found 261.0910.



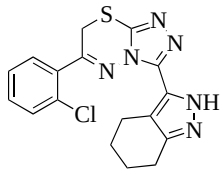
6-Methyl-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.31)

A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.212 mmol) and chloroacetone (16.8 uL, 0.212 mmol) in EtOH (2 mL) was heated at 95 ℃ in microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 51.9 mg (89%) of **3.31** as a solid: Mp 246 ℃; IR (ATR) 3081, 2930, 1556, 1454, 1284, 954 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 3.80 (s, 2 H), 2.66-2.59 (m, 4 H), 2.31 (s, 3 H), 1.82-1.74 (m, 4 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 157.8, 140.2, 115.5, 25.0, 22.5, 22.5, 22.0, 20.6, 1 aliphatic C and 3 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{12}H_{14}N_6S$ ($[M+H]^+$) 275.1079, found 275.1082.



6-Phenyl-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.32)

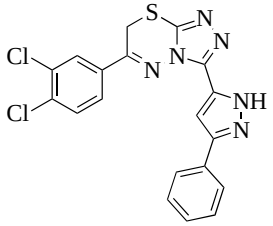
A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.212 mmol) and 2-chloroacetophenone (24.7 uL, 0.212 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 64 mg (90%) of **3.32** as a solid: Mp 190 ℃; IR (ATR) 3139, 2923, 1452, 1290, 950.6 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 ℃) δ 12.61 (s, NH 1H), 7.99 (d, *J* = 7.2 Hz, 2 H), 7.61-7.53 (m, 3 H), 4.37 (s, 2 H), 2.69-2.66 (m, 4 H), 1.84-1.74 (m, 4 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 154.5, 140.8, 133.3, 131.0, 128.3, 127.0, 115.3, 22.7, 22.4, 21.9, 20.5, 1 aliphatic C and 3 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{17}H_{16}N_6S$ ($[M+H]^+$) 337.1235, found 337.1194.



6-(2-Chlorophenyl)-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.33)

A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.212 mmol) and 2-bromo-2'-chloroacetophenone (0.0494 g, 0.212 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic

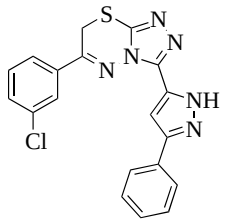
phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 69.9 mg (89%) of **3.33** as a solid: Mp 268 ℃; IR (ATR) 3413, 2930, 1446, 1128, 761 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.54 (br s, 1 H), 7.63-7.47 (m, 4 H), 4.25 (s, 2 H), 2.64 (t, *J* = 6.3 Hz, 2 H), 2.64 (t, *J* = 6.2 Hz, 2 H), 1.81-1.71 (m, 4 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 155.2, 147.8, 140.9, 134.3, 131.5, 130.9, 130.4, 129.5, 127.0, 115.4, 25.7, 22.3, 21.8, 20.6, 20.4, 2 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{17}H_{16}N_6SCl$ ($[M+H]^+$) 371.0846, found 371.0840.



6-(3,4-Dichlorophenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.34)

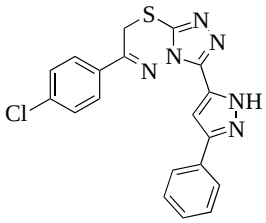
A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and 2,3',4'-trichloroacetophenone (0.0433 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for a total of 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 54 mg (65%) of **3.34** as a solid: Mp 270 ℃;IR (ATR) 3145, 3065, 1450, 1299, 807.2 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.63 (br s, NH 1 H), 8.28 (d, *J* = 2 Hz, 1 H), 8.03 (dd, *J* = 8.4 Hz, 2 Hz, 1 H), 7.84 (d, *J* = 7.2 Hz, 2 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.38 (t, *J* = 7.4 Hz, 1 H), 7.23 (s, 1 H), 4.44 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 141.0, 134.2, 133.8, 131.7, 130.7,

129.0, 128.3, 127.6, 127.1, 124.9, 102.7, 22.6, 5 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{19}H_{13}N_6SCl_2$ ($[M+H]^+$) 427.0299, found 427.0305.



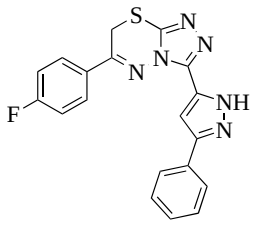
6-(3-Chlorophenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.35)

A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and 2-bromo-3'-chloroacetophenone (0.0452 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 120 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 55.9 mg (73.5%) of **3.35** as a solid: Mp 237 ℃; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.6 (s, 1 H), 8.10 (s, 1 H), 8.01 (d, 1 H, J = 7.6 Hz), 7.84 (d, J = 7.6 Hz, 2 H), 7.68-7.60 (m, 2 H), 7.48 (t, J = 7.6 Hz, 2 H), 7.38 (t, J = 7.2 Hz, 1 H), 7.23 (s, 1 H), 4.44 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 141.1, 135.3, 133.5, 130.9, 130.3, 128.3, 127.6, 126.8, 125.7, 124.9, 102.7, 22.7, 5 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{19}H_{14}N_6SCl$ ($[M+H]^+$) 393.0689, found 393.0673.



6-(4-Chlorophenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.36)

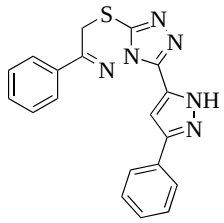
A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and 2,4'-dichloroacetophenone (0.0366 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 minutes. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 62.6 mg (82%) of **3.36** as a solid: Mp 259 ℃; IR (ATR) 3133, 2913, 1588, 1450, 1092, 960 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.58 (s, NH 1 H), 8.07 (d, *J* = 8.4 Hz, 2 H), 7.84 (d, *J* = 6.8, 2 H), 7.65 (d, *J* = 8.8 Hz, 2 H), 7.48 (t, *J* = 7.2 Hz, 2 H), 7.38 (t, *J* = 7.2 Hz, 1 H), 7.21 (s, 1 H), 4.42 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 141.0, 136.4, 132.0, 128.8, 128.3, 127.6, 125.0, 102.6, 22.6, 5 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{19}H_{13}N_6SCl$ ($[M+H]^+$) 393.0684, found 393.0675.



6-(4-Fluorophenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.37)

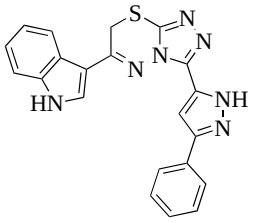
A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and 2-chloro-4'-fluoroacetophenone (0.0334 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 33.7 mg (46%) of **3.37** as a solid: ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.58 (br s, 1 H), 8.14 (d, *J* = 5.6 Hz, 1 H), 8.12 (d, *J*

= 5.6 Hz, 1 H), 7.84 (d, *J* = 7.2 Hz, 2 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.42-7.36 (m, 3 H), 7.22 (s, 1 H), 4.42 (s, 2 H); HRMS (ES) *m/z* calcd for $C_{19}H_{13}N_6SF$ ($[M+H]^+$) 377.0979, found 377. 0971.



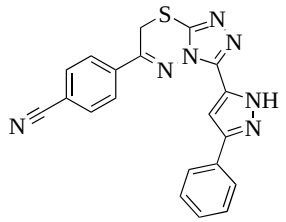
6-Phenyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.38)

A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and 2-chloroacetophenone (0.0299 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 51.1 mg (73.7%) of **3.38** as a solid: Mp 237 ℃; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.59 (s, 1 H), 8.06 (d, *J* = 6.4 Hz, 2 H), 7.84 (d, *J* = 7.6 Hz, 2 H), 7.64-7.57 (m, 3 H), 7.47 (t, *J* = 7.6 H, 2 H), 7.37 (t, *J* = 7.0 Hz, 1 H), 7.23 (s, 1 H), 4.43 (s, 2 H); HRMS (ES) *m/z* calcd for $C_{19}H_{15}N_6S$ ($[M+H]^+$) 359.1073, found 359.1057.



6-(1*H*-indol-3-yl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.39)

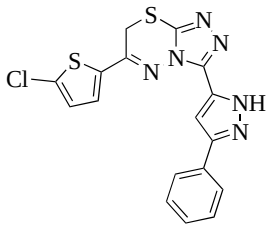
A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and 2-chloro-1-(1*H*-indol-3-yl)ethan-1-one (0.0375 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 52.9 mg (69%) of **3.39** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 11.81 (br s, 1 H), 8.52 (d, *J* = 8 Hz, 1 H), 8.28 (d, *J* = 3.2 Hz, 1 H), 7.86 (d, *J* = 7.2 Hz, 2 H), 7.54 (d, *J* = 8 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.40 (s, 1 H), 7.38 (t, *J* = 7.2 Hz, 1 H), 7.28 (t, *J* = 7.6 Hz, 1 H), 7.16 (t, *J* = 7.6 Hz, 1 H), 4.37 (s, 2 H); HRMS (ES) *m/z* calcd for $C_{21}H_{15}N_7S$ ($[M+H]^+$) 398.1182, found 398.1171.



4-(3-(3-Phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)benzonitrile (3.40)

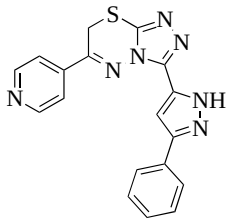
A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and 4-cyanophenacyl bromine (0.0434 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for a total of 90 minutes. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 49.8 mg (67%) of **3.40** as a solid: Mp 274 ℃; IR (ATR) 3145, 2964, 2230, 1450, 962, 818 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100 ℃) δ 8.21 (d, *J* = 8.8 Hz, 2 H), 8.01 (d, *J* = 8.4 Hz, 2 H), 7.83 (d, *J* = 7.2 Hz, 2 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.37 (t, *J* = 7.4 Hz, 1 H), 7.21 (s, 1 H), 4.46 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 153.7, 141.0, 137.4, 132.2, 128.3, 127.8, 127.6, 125.0, 117.4, 113.6, 102.7,

22.6, 4 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{20}H_{13}N_7S$ ($[M+H]^+$) 384.1031, found 384.1025.



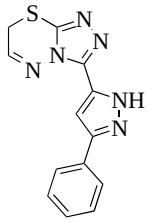
6-(5-Chlorothiophen-2-yl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.41)

A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and 2-chloro-1-(5-chlorothiophen-2-yl)ethan-1-one(0.0378 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for a total of 90 minutes. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 59.4 mg (77%) of **3.41** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.64 (br s, 1 H), 7.83 (m, 3 H), 7.49-7.42 (m, 2 H), 7.38 (s, 1 H), 7.29-7.28 (m, 1 H), 7.19 (s, 1 H), 4.42 (s, 2 H); HRMS (ES) *m/z* calcd for $C_{17}H_{11}N_6S_2Cl$ ($[M+H]^+$) 399.0248, found 399.0241.



3-(3-Phenyl-1*H*-pyrazol-5-yl)-6-(pyridin-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.42)

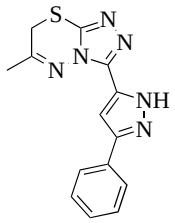
A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and 4-(bromoacetyl)pyridine hydrobromide (0.0544 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for a total of 90 minutes. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 50.1 mg (72%) of **3.42** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.6 (br s, 1 H), 8.82 (d, *J* = 5.6 Hz, 2 H), 7.95 (d, *J* = 4.8 Hz, 2 H), 7.85 (d, *J* = 7.2 Hz, 2 H), 7.48 (t, *J* = 7.2 Hz, 2 H), 7.38 (t, *J* = 6.8 Hz, 1 H), 7.23 (s, 1 H), 4.45 (s, 2 H); HRMS (ES) *m/z* calcd for $C_{18}H_{13}N_7S$ ($[M+H]^+$) 360.1026, found 360.1015.



3-(3-Phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.43)

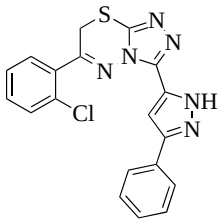
A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0700 g, 0.271 mmol) and 2-chloro-1,1-diethoxyethane (0.0751 g, 0.542 mmol) in EtOH (3 mL) was heated at 95 ℃ in a microwave for 150 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 51.9 mg (67.8%) of **3.43** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.5 (br s, 1 H), 7.93 (br s, 1 H), 7.82

(d, *J* = 7.2 Hz, 2 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 7.37 (t, *J* = 7.0 Hz, 1 H), 7.16 (s, 1 H), 3.90 (d, *J* = 4 Hz, 2 H); HRMS (ES) *m/z* calcd for $C_{13}H_{11}N_6S$ ($[M+H]^+$) 283.0760, found 283.0750.



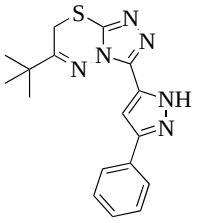
6-Methyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.44)

A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and chloroacetone (0.0179 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 51.4 mg (90%) of **3.44** as a solid: ^{1}H NMR (100 MHz, DMSO-d_6, 100 °C) δ 13.48 (s, NH 1 H), 7.84 (d, *J* = 7.2 Hz, 2 H), 7.46 (t, *J* = 7.4 Hz, 2 H), 7.37 (t, *J* = 7.2 Hz, 1 H), 7.19 (s, 1 H), 3.88 (s, 2 H), 2.39 (s, 3 H); HRMS (ES) *m/z* calcd for $C_{14}H_{12}N_6S$ ($[M+H]^+$) 297.0917, found 297.0909.



6-(2-Chlorophenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.45)

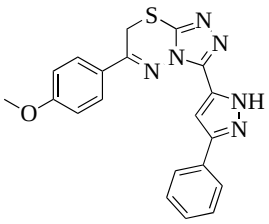
A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and 2-bromo-2'-chloroacetophenone (0.0452 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 120 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 56.6 mg (74.4%) of **3.45** as a solid: Mp 223 ℃; IR (ATR) 3059, 1454, 1303, 1199, 755 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 7.78 (d, *J* = 7.6 Hz, 2 H), 7.73 (d, *J* = 7.6 Hz, 1 H), 7.65 (d, *J* = 7.6 Hz, 1 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.53 (t, *J* = 7.6 Hz, 1 H), 7.45 (t, *J* = 7.2 Hz, 2 H), 7.35 (t, *J* = 7.2 Hz, 1 H), 7.16 (s, 1 H), 4.30 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 155.8, 141.2, 134.1, 131.6, 130.9, 130.5, 129.7, 128.3, 127.5, 124.9, 102.6, 25.7, 4 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{19}H_{14}N_6SCl$ ($[M+H]^+$) 393.0689, found 393.0707.



6-(*Tert*-butyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.46)

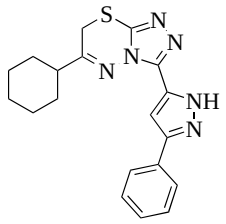
A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and 1-bromopinacolone (0.0375 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with

brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 59.1 mg (90%) of **3.46** as a solid: ^{1}H NMR (100 MHz, DMSO-d_6, 100 °C) δ 13.56 (br s, NH 1 H), 7.80 (d, *J* = 7.6 Hz, 2 H), 7.47 (t, *J* = 7.4 Hz, 2 H), 7.36 (t, *J* = 7.2 Hz, 1 H), 7.20 (s, 1 H), 3.97 (s, 3 H), 1.35 (s, 9 H); HRMS (ES) *m/z* calcd for $C_{17}H_{18}N_6S$ ($[M+H]^+$) 339.1386, found 339.1377.



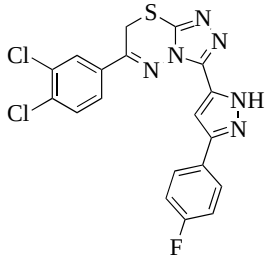
6-(4-Methoxyphenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.47)

A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and 4-methoxyphenacyl chloride (0.0357 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for a total of 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 50 mg (67%) of **3.47** as a solid: Mp 258 ℃; IR (ATR) 3061, 2911, 1605, 1450, 1256, 960 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 8.04 (d, *J* = 9.2 Hz, 2 H), 7.84 (d, *J* = 7.2 Hz, 2 H), 7.47 (t, *J* = 7.2 Hz, 2 H), 7.37 (t, *J* = 7.4 Hz, 1 H), 7.21 (s, 2 H), 7.13 (d, *J* = 9.2 Hz, 2 H), 4.38 (s, 2 H), 3.89 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 162.0, 154.7, 141.1, 128.9, 128.3, 127.5, 125.4, 124.9, 114.2, 102.5, 55.1, 22.6, 4 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{20}H_{16}N_6SO$ ($[M+H]^+$) 389.1179, found 389.1169.



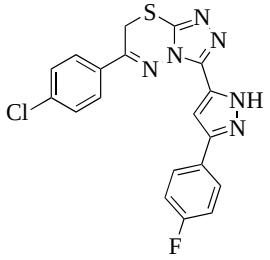
6-Cyclohexyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.48)

A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and 2-bromo-1-cyclohexylethanone (0.0397 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 55.9 mg (79.2%) of **3.48** as a solid powder: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 7.81 (d, *J* = 7.2 Hz, 2 H), 7.47 (t, *J* = 7.2 Hz, 2 H), 7.18 (s, 1 H), 3.37 (t, *J* = 7.2 Hz, 1 H), 3.90 (s, 2 H), 2.71-2.65 (m, 1 H), 2.04-2.00 (m, 2 H), 1.84 (m, 2 H), 1.73-1.68 (m, 2 H), 1.59-1.50 (m, 2 H), 1.46-1.28 (m, 3 H); HRMS (ES) *m/z* calcd for $C_{19}H_{21}N_6S$ ($[M+H]^+$) 365.1543, found 365.1529.



6-(3,4-Dichlorophenyl)-3-(3-(4-fluorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.49)

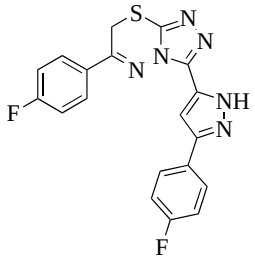
A solution of 4-amino-5-(5-(4-fluoro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0250 g, 0.0905 mmol) and 2,3',4'-trichloroacetophenone (0.0202 g, 0.0905 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for a total of 60 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 50.1 mg (72%) of **3.49** as a solid: Mp 261 ℃; IR (ATR) 3353, 2913, 1607, 1443, 1226, 840.6 cm^{-1}; ^1H NMR (100 MHz, DMSO-d_6, 100 °C) δ 13.62 (s, NH 1H), 8.27 (d, *J* = 2 Hz, 1 H), 8.03 (dd, *J* = 8.4 Hz, 2 Hz, 1 H), 7.88 (td, *J* = 5.2 Hz, 2 Hz, 3.6 Hz, 2 H), 7.83 (d, *J* = 8.8 Hz, 1 H), 7.27 (t, *J* = 9 Hz, 2 H), 7.21 (s, 1 H), 4.44 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 162.9, 160.4, 153.2, 141.0, 134.2, 133.7, 131.7, 130.7, 129.0, 127.1, 127.0, 115.3, 115.1, 102.7, 22.6, 2 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{19}H_{11}N_6SCl_2F$ ($[M+H]^+$) 445.0205, found 445.0214.



6-(4-Chlorophenyl)-3-(3-(4-fluorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.50)

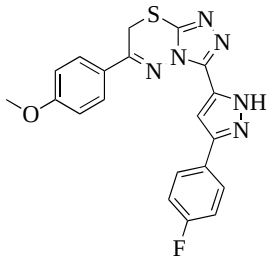
A solution of 4-amino-5-(5-(4-fluoro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.181 mmol) and 2,4'-dichloroacetophenone (0.0342 g, 0.181 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 41.1 mg (55.3%) of **3.50** as a solid:

^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.6 (br s, 1 H), 8.08 (d, *J* = 8.4 Hz, 2 H), 7.89 (dd, *J* = 5.6 Hz, 8.4 Hz, 2 H), 7.64 (d, *J* = 8.8 Hz, 2 H), 7.28 (d, *J* = 8.8 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 7.20 (s, 1 H), 4.24 (s, 2 H). HRMS (ES) *m/z* calcd for $C_{19}H_{13}N_6SClF$ ($[M+H]^+$) 411.0589, found 411.0573.



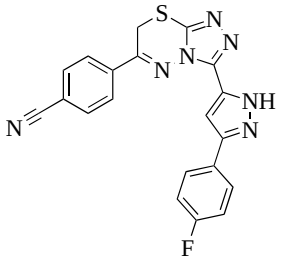
6-(4-Fluorophenyl)-3-(3-(4-fluorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.51)

A solution of 4-amino-5-(5-(4-fluoro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.181 mmol) and 2-chloro-4'-fluoroacetophenone (0.0312 g, 0.181 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 40.3 mg (56.5%) of **3.51** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.61 (br s, 1 H), 8.14 (d, *J* = 7.2 Hz, 1 H), 8.12 (d, *J* = 5.6 Hz, 1 H), 7.89 (d, *J* = 7.6 Hz, 1 H), 7.87 (d, *J* = 5.2 Hz, 1 H), 7.41 (d, *J* = 8.8 Hz, 1 H), 7.39 (d, *J* = 8.4 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 7.20 (s, 1 H), 4.24 (s, 2 H); HRMS (ES) *m/z* calcd for $C_{19}H_{13}N_6SF_2$ ($[M+H]^+$) 395.0885, found 395.0872.



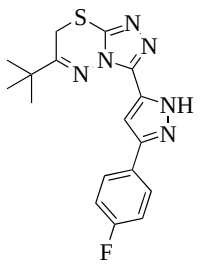
3-(3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl)-6-(4-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.52)

A solution of 4-amino-5-(5-(4-fluoro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.181 mmol) and 4-methoxyphenacyl chloride (0.0334 g, 0.181 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 44.2 mg (60.1%) of **3.52** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.59 (br s, 1 H), 8.04 (d, *J* = 8.4 Hz, 2 H), 7.88 (t, *J* = 4 Hz, 2 H), 7.27 (t, *J* = 8 Hz, 2 H), 7.21 (br s, 1 H), 7.13 (d, *J* = 8.8 Hz, 2 H), 4.38 (s, 2 H), 3.89 (s, 3 H). HRMS (ES) *m/z* calcd for $C_{20}H_{16}N_6SOF$ ($[M+H]^+$) 407.1085, found 407.1067.



4-(3-(3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)benzonitrile (3.53)

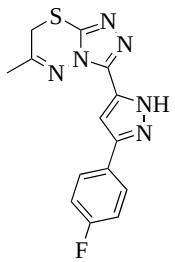
A solution of 4-amino-5-(5-(4-fluoro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.181 mmol) and 4-cyanophenacyl bromine (0.0405 g, 0.181 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for a total of 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 28.2 mg (39%) of **3.53** as a solid: Mp 279 ℃; IR (ATR) 3141, 2914, 2230, 1458, 815 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.65 (s, NH 1H), 8.22 (d, *J* = 8 Hz, 2 H), 8.02 (d, *J* = 8.4 Hz, 2 H), 7.88 (br t, 2 H), 7.27 (br t, 2 H), 7.21 (s, 1 H), 4.47 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 132.3, 127.9, 127.1, 117.5, 115.2, 115.1, 113.7, 102.7, 22.7, 5 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{20}H_{12}N_7SF$ ($[M+H]^+$) 402.0937, found 402.0992.



6-(Tert-butyl)-3-(3-(4-fluorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.54)

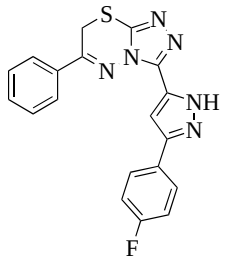
A solution of 4-amino-5-(5-(4-fluoro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.181 mmol) and 1-bromopinacolone (0.0324 g, 0.181 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by

chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 53.2 mg (82.5%) of **3.54** as a solid: Mp 264 ℃; IR (ATR) 3152, 2919, 1609, 1441, 1212, 835 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.57 (s, 1 H), 7.85 (d, *J* = 5.6 Hz, 1 H), 7.83 (d, *J* = 5.6 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.26 (d, *J* = 8.8 Hz, 1 H), 7.17 (s, 1 H), 3.97 (s, 2 H), 1.35 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 162.8, 160.4, 126.9, 115.3, 115.1, 102.4, 38.7, 26.3, 21.5, 5 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{17}H_{18}N_6SF$ ($[M+H]^+$) 357.1298, found 357.1315.



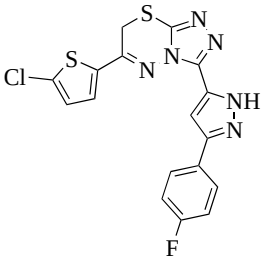
3-(3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl)-6-methyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.55)

A solution of 4-amino-5-(5-(4-fluoro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.181 mmol) and chloroacetone (0.0167 g, 0.181 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 18.3 mg (32.2%) of **3.55** as a solid: ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 7.89 (d, *J* = 5.2 Hz, 1 H), 7.87 (d, *J* = 5.6 Hz, 1 H), 7.27 (d, *J* = 8.8 Hz, 1 H), 7.25 (d, *J* = 8.8 Hz, 1 H), 7.18 (s, 1 H), 3.88 (s, 2 H), 2.39 (s, 3 H); HRMS (ES) *m/z* calcd for $C_{14}H_{12}N_6SF$ ($[M+H]^+$) 315.0823, found 315.0816.



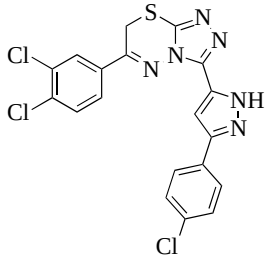
3-(3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.56)

A solution of 4-amino-5-(5-(4-fluoro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.181 mmol) and 2-chloroacetophenone (0.0280 g, 0.181 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 46.9 mg (68.9%) of **3.56** as a solid: Mp 260 ℃; IR (ATR) 3144, 2913, 1605, 1443, 1215, 962 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 8.06 (d, *J* = 6.8 Hz, 2 H), 7.88 (t, *J* = 6 Hz, 2 H), 7.57-7.63 (m, 3 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.26 (d, *J* = 8 Hz, 1 H), 7.21 (s, 1 H), 4.43 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 162.8, 160.4, 133.2, 131.2, 128.5, 127.1, 127.0, 115.3, 115.1, 102.6, 22.8, 4 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{19}H_{14}N_6SF$ ($[M+H]^+$) 377.0985, found 393.0967.



6-(5-Chlorothiophen-2-yl)-3-(3-(4-fluorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.57)

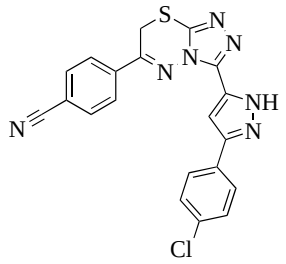
A solution of 4-amino-5-(5-(4-fluoro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.181 mmol) and 2-chloro-1-(5-chlorothiophen-2-yl)ethan-1-one (0.0353 g, 0.181 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 44.5 mg (59.0%) of **3.57** as a solid: Mp 280 ℃; IR (ATR) 3070, 2857, 1607, 1428, 1219, 961.8 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.63 (br s, 1 H), 7.89 (d, *J* = 5.6 Hz, 1 H), 7.87 (d, *J* = 5.6 Hz, 1 H), 7.82 (d, *J* = 3.6 Hz, 1 H), 7.31-7.27 (m, 3 H), 7.17 (s, 1 H), 4.42 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 162.9, 160.4, 149.8, 135.9, 134.8, 127.9, 126.9, 115.3, 102.4, 22.2 cm^{-1}, 5 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{17}H_{11}N_6S_2FCl$ ($[M+H]^+$) 417.0159, found 417.0155.



3-(3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl)-6-(3,4-dichlorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.58)

A solution of 4-amino-5-(5-(4-chloro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0250 g, 0.0854 mmol) and 2,3',4'-trichloroacetophenone (0.0191 g, 0.0854 mmol) in EtOH (1 mL) was heated at 95 ℃ in a microwave for 30 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined

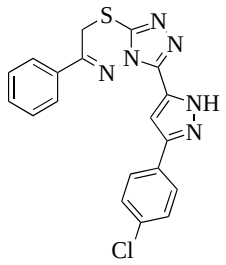
organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 27.3 mg (69%) of **3.58** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 13.83 (s, NH 1 H), 8.29 (br d, 1 H), 8.05 (br s, 1 H), 7.87 (br s, 3 H), 7.40 (br d, 2 H), 7.28 (d, 1 H), 4.47 (s, 2 H); HRMS (ES) *m/z* calcd for $C_{19}H_{11}N_6SCl_3$ ($[M+H]^+$) 460.9910, found 460.9915.



4-(3-(3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)benzonitrile (3.59)

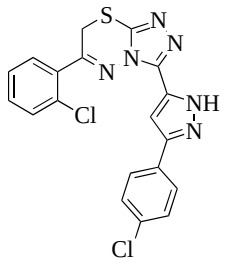
A solution of 4-amino-5-(5-(4-chloro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.171 mmol) and 4-cyanophenacyl bromine (0.0383 g, 0.171 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 44.9 mg (63%) of **3.59** as a powder: Mp 272 ℃; IR (ATR) 3143, 2919, 2230, 1603, 1290 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.72 (s, NH 1 H), 8.22 (d, *J* = 8.4 Hz, 2 H), 8.02 (d, *J* = 8.8 Hz, 2 H), 7.86 (d, *J* = 8 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 7.25 (s, 1 H), 4.47 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 141.1, 137.4, 132.3, 128.4, 127.9, 126.7, 117.5, 113.7, 103.0, 22.7, 6

quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{20}H_{12}N_7SCl$ ($[M+H]^+$) 418.0642, found 418.0691.



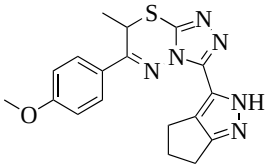
3-(3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.60)

A solution of 4-amino-5-(5-(4-chloro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.171 mmol) and 2-chloroacetophenone (0.0264 g, 0.171 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 56.5 mg (84.2%) of **3.60** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.70 (br s, 1 H), 8.06 (br s, 2 H), 7.86 (br s, 2 H), 7.61 (br s, 3 H), 7.51 (br s, 2 H), 7.27 (s, 1 H), 4.44 (s, 2 H). HRMS (ES) *m/z* calcd for $C_{19}H_{14}N_6SCl$ ($[M+H]^+$) 393.0684, found 393.0678.



6-(2-Chlorophenyl)-3-(3-(4-chlorophenyl)-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.61)

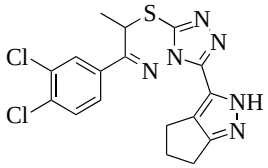
A solution of 4-amino-5-(5-(4-chloro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.171 mmol) and 2-bromo-2'-chloroacetophenone (0.0399 g, 0.171 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 46.7 mg (64.0%) of **3.61** as a solid powder: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.66 (br s, 1 H), 7.80 (d, *J* = 8 Hz, 2 H), 7.74 (m, 1 H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1 H), 7.55-7.48 (m, 3 H), 7.19 (s, 1 H), 4.31 (s, 2 H); HRMS (ES) *m/z* calcd for $C_{19}H_{13}N_6SCl_2$ ($[M+H]^+$) 427.0294, found 427.0287.



6-(4-Methoxyphenyl)-7-methyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.64)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.100 g, 0.450 mmol) and 2-bromo-1-(4-methoxyphenyl)propan-1-one (0.109 g, 0.450 mmol) in EtOH (4 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The

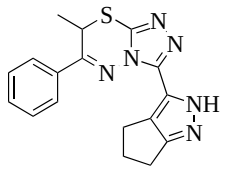
combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 153 mg (93.1%) of **3.64** as a solid: Mp 241 ℃; IR (ATR) 3202, 2956, 1560, 1437, 1260 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.63 (br s, 1 H), 8.00 (ddd, *J* = 2 Hz, 3.2 Hz, 8.8 Hz, 2 H), 7.11 (ddd, *J* = 2 Hz, 3.2 Hz, 8.8 Hz, 2 H), 4.93 (q, *J* = 7.2 Hz, 1 H), 3.88 (s, 3 H), 2.84-2.65 (m, 4 H), 2.48-2.43 (m, 2 H), 1.46 (d, *J* = 8 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 162.1, 157.7, 139.2, 128.8, 124.4, 114.3, 31.4, 29.5, 24.6, 23.4, 23.2, 18.7, 4 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{18}H_{19}N_6SO$ ($[M+H]^+$) 367.1341, found 367.1348.



6-(3,4-Dichlorophenyl)-7-methyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.65)

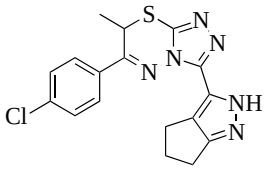
A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.100 g, 0.450 mmol) and 2-bromo-1-(3,4-dichlorophenyl)propan-1-one (0.127 g, 0.450 mmol) in EtOH (4 mL) was heated at 95 ℃ in a microwave for 60 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 130 mg (71.4%) of **3.65** as a solid: Mp 158 ℃; 3279, 2921, 1508, 1454, 1303, 958 cm^-

[1]; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.70 (br s, 1 H), 8.24 (s, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 4.97 (q, *J* = 7.2 Hz, 1 H), 2.72-2.66 (m, 4 H), 2.43-2.32 (m, 2 H), 1.48 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 155.9, 139.2, 134.3, 132.8, 131.8, 130.7, 128.8, 127.0, 31.3, 29.5, 23.4, 23.1, 18.5, 4 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{17}H_{15}N_6SCl_2$ ($[M+H]^+$) 405.0456, found 405.0465.



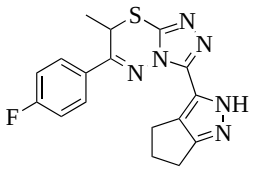
7-Methyl-6-phenyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.66)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.225 mmol) and 2-bromopropiophenone (0.0479 g, 0.225 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 58 mg (76.6%) of **3.66** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.65 (br s, 1 H), 8.01 (d, *J* = 7.2 Hz, 2 H), 7.62-7.56 (m, 3 H), 4.96 (q, *J* = 7.2 H, 1 H), 2.78-2.67 (m, 4 H), 2.46 (br s, 2 H), 1.49 (d, *J* = 7.2 Hz, 3 H); HRMS (ES) *m/z* calcd for $C_{17}H_{17}N_6S$ ($[M+H]^+$) 337.1230, found 337.1227.



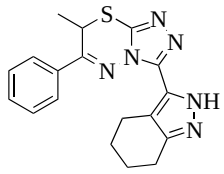
6-(4-Chlorophenyl)-7-methyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.67)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.100 g, 0.450 mmol) and 2-bromo-1-(4-chlorophenyl)propan-1-one (0.111 g, 0.450 mmol) in EtOH (4 mL) was heated at 95 ℃ in a microwave for 60 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 47.1 mg (28.2%) of **3.67** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.67 (br s, 1 H), 8.03 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 8.4 Hz, 2 H), 4.94 (q, *J* = 6.8 Hz, 1 H), 2.71 (br s, 4 H), 2.43 (br s, 2 H), 1.48 (d, *J* = 6.8 Hz, 3 H); HRMS (ES) *m/z* calcd for $C_{17}H_{16}N_6SCl$ ($[M+H]^+$) 371.0840, found 371.0837.



6-(4-Fluorophenyl)-7-methyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.68)

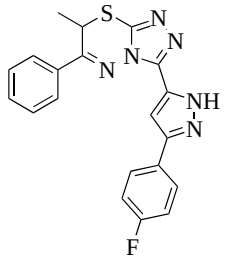
A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.100 g, 0.450 mmol) and 2-bromo-1-(4-fluorophenyl)propan-1-one (0.104 g, 0.450 mmol) in EtOH (4 mL) was heated at 95 ℃ in a microwave for 60 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 95.6 mg (60%) of **3.68** as a solid: Mp 233 ℃; IR (ATR) 3191, 2917, 1500, 1215, 859.2 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.66 (br s, 1 H), 8.10 (d, J = 6 Hz, 1 H), 8.08 (d, *J* = 6.8 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 1 H), 7.37 (d, J = 8.8 Hz, 1 H), 4.95 (q, *J* = 7.2 Hz, 1 H), 2.71 (br s, 1 H), 2.44 (br s, 2 H), 1.48 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 165.2, 162.7, 157.1, 139.1, 129.6, 129.5, 128.8, 128.8, 125.4, 115.7, 115.5, 31.5, 29.5, 23.3, 23.1, 18.5; HRMS (ES) *m/z* calcd for $C_{17}H_{16}N_6SF$ ($[M+H]^+$) 355.1141, found 355.1142.



7-Methyl-6-phenyl-3-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.69)

A solution of 4-amino-5-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0500 g, 0.212 mmol) and 2-bromopropiophenone (0.0451 g, 0.212 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were

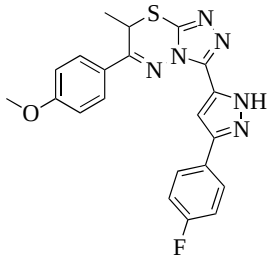
separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 67.2 mg (90.6%) of **3.69** as a solid: Mp 160 ℃; IR (ATR) 3137, 2924, 1566, 1445, 973 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.61 (br s, 1 H), 8.00 (d, J = 7.2 Hz, 2 H), 7.62-7.54 (m, 3 H), 4.96 (q, *J* = 7.2 Hz, 1 H), 2.70-2.60 (m, 4 H), 1.85-1.72 (m, 4 H), 1.47 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 157.5, 139.1, 132.4, 131.2, 128.5, 126.9, 115.3, 31.3, 22.4, 21.9, 20.4, 18.5 cm^{-1}, 1 aliphatic C and 3 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{18}H_{19}N_6S$ ($[M+H]^+$) 351.1392, found 351.1382.



3-(3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl)-7-methyl-6-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.70)

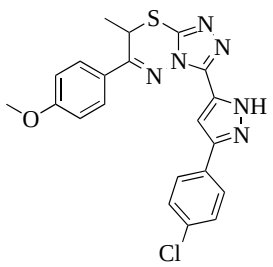
A solution of 4-amino-5-(5-(4-fluoro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.181 mmol) and 2-bromopropiophenone (0.0386 g, 0.181 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 66.8 mg (94.5%) of

3.70 as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 8.08 (d, *J* = 6.4 Hz, 2 H), 7.90 (d, *J* = 5.6 Hz, 1 H), 7.88 (d, *J* = 5.6 Hz, 1 H), 7.66-7.58 (m, 3 H), 7.29-7.25 (m, 3 H), 5.02 (q, *J* = 7.2 Hz, 1 H), 1.50 (d, *J* = 7.2 Hz, 3 H); HRMS (ES) *m/z* calcd for $C_{20}H_{16}N_6SF$ ($[M+H]^+$) 391.1136, found 391.1123.



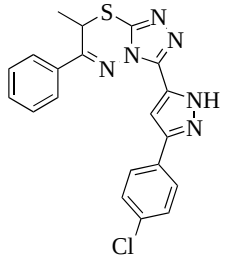
3-(3-(4-Fluorophenyl)-1*H*-pyrazol-5-yl)-6-(4-methoxyphenyl)-7-methyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.71)

A solution of 4-amino-5-(5-(4-fluoro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.181 mmol) and 2-bromo-1-(4-methoxyphenyl)propan-1-one (0.0440 g, 0.181 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 64 mg (84.1%) of **3.71** as a powder: Mp 245 ℃; IR (ATR) 3075, 2932, 1603, 1443, 1254 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.61 (br s, 1 H), 8.05-7.89 (m, 4 H), 7.27-7.13 (m, 5 H), 4.99 (m, 1 H), 3.89 (s, 3 H), 1.48 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 162.8, 162.1, 160.4, 157.8, 139.4, 130.6, 128.9, 127.1, 124.3, 115.2, 115.0, 114.3, 102.6, 55.1, 31.2, 18.9; HRMS (ES) *m/z* calcd for $C_{21}H_{18}N_6SFO$ ($[M+H]^+$) 421.1247, found 421.1237.



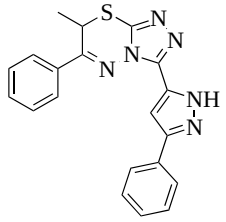
3-(3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl)-6-(4-methoxyphenyl)-7-methyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.72)

A solution of 4-amino-5-(5-(4-chloro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.171 mmol) and 2-bromo-1-(4-methoxyphenyl)propan-1-one (0.0415 g, 0.171 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 53.9 mg (72.2%) of **3.72** as a powder: Mp 258 ℃; IR (ATR) 3070, 2924, 1603, 1439, 1254, 1027 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.68 (br s, 1 H), 8.05 (d, *J* = 7.2 Hz, 2 H), 7.87 (br s, 2 H), 7.51 (br s, 2 H), 7.29 (br s, 1 H), 7.14 (d, *J* = 8 Hz, 2 H), 5.01-5.00 (m, 1 H), 3.89 (s, 3 H), 1.48 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 162.2, 128.9, 128.3, 126.7, 124.3, 114.4, 102.9, 31.2, 29.9, 18.9, 7 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{21}H_{18}N_6SClO$ ($[M+H]^+$) 437.0951, found 437.0954.



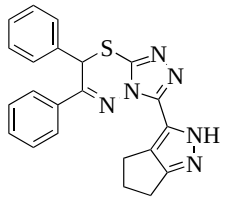
3-(3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl)-7-methyl-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.73)

A solution of 4-amino-5-(5-(4-chloro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.171 mmol) and 2-bromopropiophenone (0.0364 g, 0.171 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 58.2 mg (83.8%) of **3.73** as a solid: Mp 246 ℃; IR (ATR) 3144, 2924, 1443, 1307, 1087, 954 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.7 (br s, 1 H), 8.08 (d, *J* = 6.4 Hz, 2 H), 7.87 (br s, 2 H), 7.64-7.60 (m, 3 H), 7.51 (br s, 3 H), 7.29 (br s 1 H), 5.02 (q, *J* = 8 Hz, 1 H), 1.51 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 132.3, 131.4, 128.6, 128.3, 127.0, 126.7, 103.0, 31.44, 18.77, 7 ^{13}C peaks were missing; HRMS (ES) *m/z* calcd for $C_{20}H_{17}N_6SCl$ ($[M+H]^+$) 407.0846, found 407.0837.



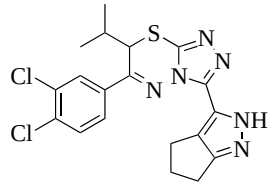
7-Methyl-6-phenyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.74)

A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0500 g, 0.194 mmol) and 2-bromopropiophenone (0.0412 g, 0.194 mmol) in EtOH (2 mL) was heated at 95 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 67 mg (92.9%) of **3.74** as a solid: Mp 206 ℃; IR (ATR) 3139, 3057, 1607, 1452, 1308, 956 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 8.08 (d, *J* = 6.4 Hz, 2 H); 7.85 (d, *J* = 7.2 Hz, 2 H), 7.64-7.59 (m, 3 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.38 (t, *J* = 6.8 Hz, 1 H), 7.26 (s, 1 H), 5.02 (q, *J* = 7.2 Hz, 1 H), 1.51 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 158.3, 132.3, 131.4, 128.5, 128.4, 127.6, 127.2, 127.0, 125.0, 102.7, 31.5, 18.8, 3 quaternary ^{13}C peaks were missing; HRMS (ES) *m/z* calcd for $C_{20}H_{18}N_6S$ ($[M+H]^+$) 373.1235, found 373.1252.



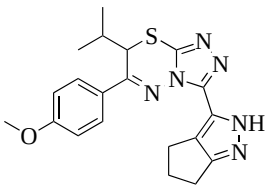
6,7-Diphenyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.81)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.100 g, 0.450 mmol), desyl chloride (0.104 g, 0.450 mmol) and Et_3N (0.130 mL, 0.900 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 60 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/ CH_2Cl_2) and provided 75 mg of **3.81** (42.0%) as a solid: Mp 257 ℃; IR (ATR) 3247, 2926, 1622, 1445, 951 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 7.98 (d, *J* = 7.2 Hz, 2 H), 7.62-7.53 (m, 3 H), 7.35-7.27 (m, 5 H), 6.29 (s, 1 H), 2.88-2.73 (m, 4 H), 2.48 (br s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 155.8, 146.0, 139.0, 135.5, 133.0, 131.4, 128.7, 128.6, 128.2, 127.0, 126.3, 125.4, 29.5, 23.5, 23.1, 1 aliphatic C and 2 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{22}H_{19}N_6S$ ($[M+H]^+$) 399.1392, found 399.1399.



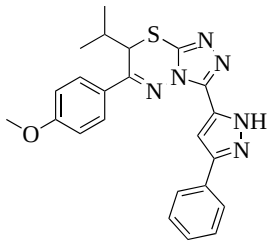
6-(3,4-Dichlorophenyl)-7-isopropyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.82)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.150 g, 0.674 mmol), 2-bromo-1-(3,4-dichlorophenyl)-3-methylbutan-1-one (0.209 g, 0.674 mmol) and Et_3N (0.136 g, 1.35 mmol) in EtOH (5 mL) was stirred at 120 ℃ in a microwave for 60 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 182 mg (62%) of **3.82** as a solid: Mp 150 ℃; IR (ATR) 3161, 2958, 1446, 1368, 952 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.75 (s, 1 H), 8.30 (s, 1 H), 8.04 (d, *J* = 8.4 Hz, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 4.80 (d, *J* = 7.6 Hz, 1 H), 2.74 (br s, 4 H), 2.46 (br s, 2 H), 1.97 (m, 1 H), 0.93 (d, *J* = 6.8 Hz, 6 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 155.2, 139.8, 134.2, 131.8, 130.7, 128.9, 127.2, 125.4, 42.4, 30.5, 29.6, 23.3, 23.1, 19.2, 18.0, 4 quaternary ^{13}C peaks were missing; HRMS (ES) *m/z* calcd for $C_{19}H_{19}N_6SCl_2$ ($[M+H]^+$) 433.0763, found 433.0752.



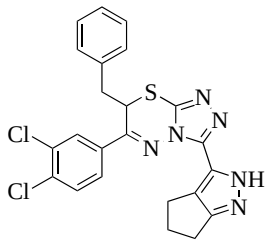
7-Isopropyl-6-(4-methoxyphenyl)-3-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.83)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0600 g, 0.270 mmol),2-bromo-1-(4-methoxyphenyl)-3-methylbutan-1-one (0.0732 g, 0.270 mmol) and Et_3N (0.0546 g, 0.540 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 2 h. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 65.2 mg (61%) **3.83** as a solid: Mp 117 ℃; IR (ATR) 3168.6, 2959.8, 1602.9, 1446.4, 1258.1 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.66 (br s, 1 H), 8.04 (d, *J* = 8.8 Hz, 2 H), 7.11 (d, *J* = 9.2 Hz, 2 H), 4.73-4.70 (m, 1 H), 3.88 (s, 3 H), 2.77-2.62 (m, 4 H), 2.46 (br m, 2 H), 1.97-1.89 (m, 1 H), 0.95-0.92 (m, 6 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 161.9, 156.8, 139.8, 129.0, 125.7, 125.2, 114.2, 55.1, 42.6, 30.5, 29.5, 23.3, 23.1, 19.3, 18.1, 3 quaternary ^{13}C peaks were missing; HRMS (ES) *m/z* calcd for $C_{20}H_{23}N_6SO$ ($[M+H]^+$) 395.1649, found 395.1638.



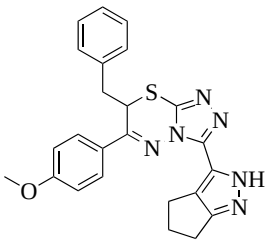
7-Isopropyl-6-(4-methoxyphenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.84)

A solution of 4-amino-5-(5-phenyl-2H-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0600 g, 0.232 mmol), 2-bromo-1-(4-methoxyphenyl)-3-methylbutan-1-one (0.0630 g, 0.232 mmol) and Et_3N (0.0470 g, 0.465 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 2 h. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 59.4 mg (59%) of **3.84** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.66 (br s, 1 H), 8.09 (d, *J* = 8.8 Hz, 2 H), 7.86 (d, *J* = 7.2 Hz, 2 H), 7.49 (t, *J* = 7.2 Hz, 2 H), 7.38 (t, *J* = 7.2 Hz, 1 H), 7.25 (s, 1 H), 7.14 (d, *J* = 8.8 Hz), 4.78 (d, 7.6 Hz, 1 H), 3.89 (s, 3 H), 2.00-1.92 (m, 1 H), 0.93 (dd, *J* = 2.8, 6.8 Hz, 6 H); HRMS (ES) *m/z* calcd for $C_{23}H_{23}N_6SO$ ($[M+H]^+$) 431.1649, found 431.1638.



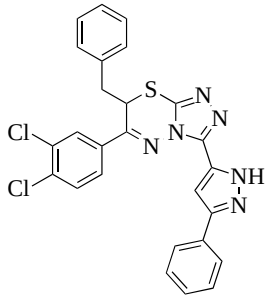
7-Benzyl-6-(3,4-dichlorophenyl)-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.85)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.100 g, 0.450 mmol), 2-bromo-1-(3,4-dichlorophenyl)-3-phenylpropan-1-one (0.161 g, 0.450 mmol), and Et_3N (0.0911 g, 0.900 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 1 h. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 140 mg (64%) of **3.85** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.71 (br s, 1 H), 8.01 (s, 1 H), 7.85 (d, *J* = 6.8 Hz, 1 H), 7.70 (d, *J* = 8.4, 1 H), 7.23-7.16 (m, 5 H), 5.18 (t, *J* = 7.2 Hz, 1 H), 3.08-3.01 (m, 3 H), 2.75 (br s, 4 H), 2.47 (br s, 2 H); HRMS (ES) *m/z* calcd for $C_{23}H_{19}N_6SCl_2$ ($[M+H]^+$) 481.0763, found 481.0754.



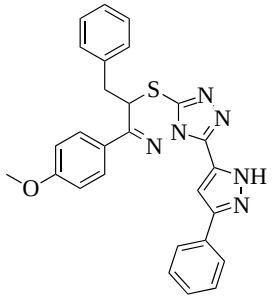
7-Benzyl-6-(4-methoxyphenyl)-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.86)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.0600 g, 0.270 mmol), 2-bromo-1-(4-methoxyphenyl)-3-phenylpropan-1-one (0.0862 g, 0.270 mmol), and Et_3N (0.0546 g, 0.540 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 1 h. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/ CH_2Cl_2) and provided 98.1 mg (82%) **3.86** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.62 (br s, 1 H), 7.90 (d, *J* = 8.8 Hz, 2 H), 7.24-7.17 (m, 5 H), 7.04 (d, *J* = 8.8 Hz, 2 H), 5.10 (t, *J* = 6.8 Hz, 3 H), 3.08 (dd, *J* = 6 Hz, 14 Hz, 2 H), 2.87-2.72 (m, 4 H), 2.47 (br s, 2 H); HRMS (ES) *m/z* calcd for $C_{24}H_{23}N_6SO$ ($[M+H]^+$) 433.1649, found 433.1637.



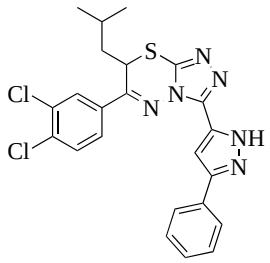
7-Benzyl-6-(3,4-dichlorophenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.87)

A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.100 g, 0.387 mmol), 2-bromo-1-(3,4-dichlorophenyl)-3-phenylpropan-1-one (0.139 g, 0.387 mmol), and Et_3N (0.0784 g, 0.774 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 1 h. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 176 mg (88%) of **3.87** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.68 (br s, 1 H), 8.08 (br s, 1 H), 7.88 (br s, 3 H), 7.75 (br s, 1 H), 7.50 (t, *J* = 6.4 Hz, 2 H), 7.41-7.38 (m, 1 H), 7.22-7.13 (m, 6 H), 5.25 (t, *J* = 7.2 Hz, 1 H), 3.12-3.01 (m, 2 H); HRMS (ES) *m/z* calcd for $C_{26}H_{19}N_6SCl_2$ ($[M+H]^+$) 517.0763, found 517.0747.



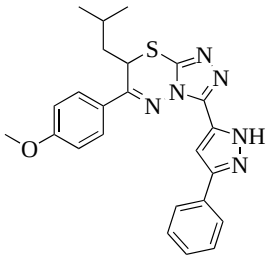
7-Benzyl-6-(4-methoxyphenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.88)

A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0600 g, 0.232 mmol), 2-bromo-1-(4-methoxyphenyl)-3-phenylpropan-1-one (0.0741 g, 0.232 mmol), and Et_3N (0.0470 g, 0.465 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 1 h. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 104 mg (94%) of **3.88** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 13.58 (br s, 1 H), 7.97 (d, *J* = 8.4 Hz, 2 H), 7.86 (d, *J* = 7.6 Hz, 2 H), 7.49 (t, *J* = 7.2 Hz, 2 H), 7.39 (t, *J* = 7.2 Hz, 1 H), 7.23-7.14 (m, 6 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 5.17 (t, *J* = 7.2 Hz, 1 H), 3.10-3.05 (m, 2 H); HRMS (ES) *m/z* calcd for $C_{27}H_{23}N_6SO$ ($[M+H]^+$) 479.1649, found 479.1633.



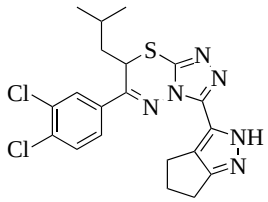
6-(3,4-Dichlorophenyl)-7-*iso*-butyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.89)

A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.0800 g, 0.310 mmol),2-bromo-1-(3,4-dichlorophenyl)-4-methylpentan-1-one(0.100 g, 0.310 mmol), and Et_3N (0.0627 g, 0.619 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 1 h. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 121 mg (81%) of **3.89** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 ℃) δ 13.67 (br s, 1 H), 8.29 (s, 1 H), 8.03 (d, *J* = 8.4 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 3 H), 7.48-7.26 (m, 4 H), 4.95 (q, *J* = 6 Hz, 1 H), 1.91-1.81 (m, 1 H), 1.61-1.49 (m, 2 H); HRMS (ES) *m/z* calcd for $C_{23}H_{21}N_6SCl_2$ ($[M+H]^+$) 483.0920, found 483.0908.



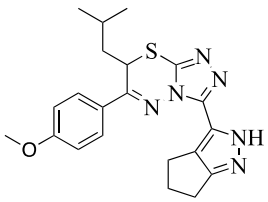
7-*iso*-Butyl-6-(4-methoxyphenyl)-3-(3-phenyl-1*H*-pyrazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.90)

A solution of 4-amino-5-(5-phenyl-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.100 g, 0.387 mmol), 2-bromo-1-(4-methoxyphenyl)-4-methylpentan-1-one (0.110 g, 0.387 mmol), and Et_3N (0.0784 g, 0.774 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 1 hour. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 150 mg (87%) of **3.90** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ13.63 (br s, 1 H), 8.06 (d, *J* = 8.4 Hz, 2 H), 7.86-7.83 (m, 2 H), 7.51-7.49 (m, 2 H), 7.40 (d, *J* = 6.4 Hz, 1 H), 7.26 (br s, 1 H), 7.17 (d, *J* = 8.4 Hz, 1 H), 7.06 (d, *J* = 8.4 Hz, 2 H), 4.91 (q, *J* = 5.2 Hz, 1 H), 3.90 (s, 3 H), 1.92-1.84 (m, 1 H), 1.61-1.49 (m, 2 H); HRMS (ES) *m/z* calcd for $C_{24}H_{25}N_6SO$ ($[M+H]^+$) 445.1805, found 445.1793.



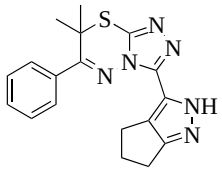
6-(3,4-Dichlorophenyl)-7-*iso*-butyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.91)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.100 g, 0.450 mmol), 2-bromo-1-(3,4-dichlorophenyl)-4-methylpentan-1-one (0.146 g, 0.450 mmol), and Et_3N (0.0911 g, 0.900 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 1 h. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 133 mg (66%) of **3.91** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.71 (br s, 1 H), 8.24 (s, 1 H), 7.98 (dd, *J* = 2 Hz, 8.4 Hz, 1 H), 7.83 (d, *J* = 8.8 Hz, 1 H), 4.90 (t, *J* = 7.6 Hz, 1 H), 2.73 (br s, 4 H), 2.47 (br s, 2 H), 1.89-1.79 (m, 1 H), 1.55-1.52 (m, 2 H); HRMS (ES) *m/z* calcd for $C_{20}H_{21}N_6SCl_2$ ($[M+H]^+$) 447.0920, found 447.0911.



7-*iso*-Butyl-6-(4-methoxyphenyl)-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.92)

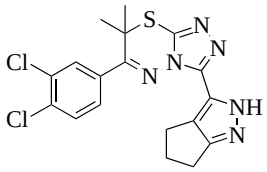
A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.100 g, 0.450 mmol), 2-bromo-1-(4-methoxyphenyl)-4-methylpentan-1-one (0.128 g, 0.450 mmol), and Et_3N (0.0911 g, 0.900 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 1 hour. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combine organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 120 mg (65%) of **3.92** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.65 (br s, 1 H), 8.03-7.97 (m, 2 H), 7.14-7.03 (m, 2 H), 4.85 (t, *J* = 6.4 Hz, 1 H), 3.88 (s, 3 H), 2.72 (br s, 4 H), 2.44 (br s, 2 H), 1.89-1.80 (m, 1 H), 1.53-1.51 (m, 2 H), 0.96-0.93 (m, 6 H); HRMS (ES) *m/z* calcd for $C_{21}H_{25}N_6SO$ ($[M+H]^+$) 409.1805, found 409.1796.



7,7-Dimethyl-6-phenyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.75)

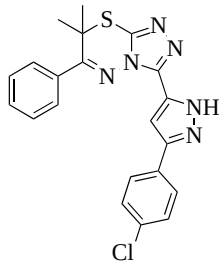
A solution of 2-bromoisobutyrophenone (0.100 g, 0.440 mmol), 4-Amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.300 g, 1.32 mmol) and Et3N (0.223 g, 2.20 mmol) in EtOH (5 mL) was stirred at 80 ℃ for 8 h and then concentrated under reduced pressure. The residue was diluted with sat. $NaHCO_3$ solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, the resulting

residue was purified by column chromatography on SiO_2 with EtOAc/MeOH (20:1) to give 63 mg (41%) of **3.75** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.62 (br s, 1 H), 7.58-7.51 (m, 5 H), 2.66-2.58 (m, 4 H), 2.34-2.33 (m, 2 H), 1.61 (s, 6 H); HRMS (ES) m/z calcd for $C_{18}H_{19}N_6S$ ($[M+H]^+$) 351.1386, found 351.1379.



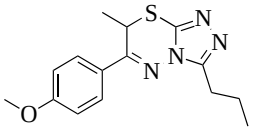
6-(3,4-Dichlorophenyl)-7,7-dimethyl-3-(2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.80)

A solution of 4-amino-5-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-4*H*-(1,2,4)-triazole-3-thiol (0.139 g, 0.623 mmol), 2-bromo-1-(3,4-dichlorophenyl)propan-1-one (0.221 g, 0.748 mmol), and Et_3N (0.189 g, 1.87 mmol) in EtOH (4 mL) was heated at 95 ℃ in a microwave for a total of 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 174 mg (66.7%) of **3.80** as a solid: Mp 232 ℃; IR (ATR) 3098, 2900, 1681, 1452, 1031, 816 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.63 (br s, 1 H), 7.86 (s, 1 H), 7.75 (d, *J* = 8.4 Hz, 1 H), 7.60 (d, *J* = 7.6 Hz, 1 H), 2.64-2.61 (m, 4 H), 2.37 (br s, 2 H), 1.63 (s, 6 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 161.2, 141.0, 133.7, 132.9, 131.1, 130.1, 130.0, 128.2, 42.6, 25.9, 23.6, 1 aliphatic C and 5 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{18}H_{17}N_6SCl_2$ ($[M+H]^+$) 419.0612, found 419.0630.



3-(3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl)-7,7-dimethyl-6-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (3.76)

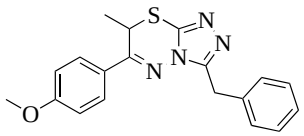
A solution of 2-bromoisobutyrophenone (0.233 g, 1.02 mmol), 4-amino-5-(5-(4-chloro-phenyl)-2*H*-pyrazol-3-yl)-4*H*-(1,2,4)triazole-3-thiol (0.100 g, 0.342 mmol) and Et_3N (0.143 mL, 1.02 mmol) in EtOH (4 mL) was stirred at 95 ℃ in a microwave for a total of 90 min. After cooling to rt, the reaction mixture was treated with sat. Na_2CO_3 and the resulting precipitate was filtered, washed with H_2O, and dried (Na_2SO_4). Decantation of the residue in dry hexane provided 90 mg (62.9%) of **3.76** as a solid: Mp 275 ℃; IR (ATR) 3150, 3027, 1582, 1452, 1195, 805 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 100 °C) δ 12.64 (br s, 1 H); 7.77 (d, J = 6.8 Hz, 2 H), 7.62-7.48 (m, 7 H), 7.13 (s, 1 H), 1.64 (s, 6 H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 163.9, 141.6, 133.4, 132.3, 129.6, 128.3, 127.9, 126.6, 102.9, 42.7, 26.2, 6 quaternary C were missing; HRMS (ES) *m/z* calcd for $C_{21}H_{18}N_6SCl$ ($[M+H]^+$) 421.1002, found 421.1016.



6-(4-Methoxyphenyl)-7-methyl-3-propyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.100)

A solution of 4-amino-5-propyl-4*H*-[1,2,4]triazole-3-thiol (0.0600 g, 0.379 mmol), 2-bromo-1-(4-methoxyphenyl)propan-1-one (0.0922 g, 0.379 mmol), and Et_3N (0.0767 g, 0.758

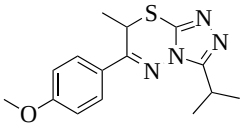
mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 1 h. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 89.4 mg (78%) of **3.100** as a solid: Mp 135 ℃; IR (ATR) 3059, 2956, 1605, 1458, 1184, 988 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, *J* = 8.8 Hz, 2 H), 7.13 (d, *J* = 8.8 Hz, 2 H), 5.00 (q, *J* = 7.2 Hz, 1 H), 3.85 (s, 3 H), 2.91-2.86 (m, 2 H), 1.80-1.70 (m, 2 H), 1.34 (d, *J* = 7.2 Hz, 3 H), 0.94 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) 162.3, 157.1, 153.0, 138.4, 129.1, 124.6, 114.7, 55.6, 31.4, 25.8, 20.0, 19.4, 13.5; HRMS (ES) *m/z* calcd for $C_{15}H_{19}N_4SO$ ($[M+H]^+$) 303.1280, found 303.1268.



3-Benzyl-6-(4-methoxyphenyl)-7-methyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.101)

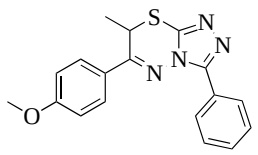
A solution of 4-amino-5-benzyl-4*H*-1,2,4-triazole-3-thiol (0.0600 g, 0.291 mmol), 2-bromo-1-(4-methoxyphenyl)propan-1-one (0.0707 g, 0.291 mmol), and Et_3N (0.0589 g, 0.582 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 2 h. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and

provided 67.8 mg (67%) of **3.101** as a solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, *J* = 8.8 Hz, 2 H), 7.33-7.20 (m, 5 H), 7.11 (d, *J* = 8.8 Hz, 2 H), 4.99 (q, *J* = 7.2 Hz, 1 H), 4.32 (s, 2 H), 3.85 (s, 3 H), 1.26 (d, *J* = 7.2 Hz, 3 H); HRMS (ES) *m/z* calcd for $C_{19}H_{19}N_4SO$ ($[M+H]^+$) 351.1274, found 351.1263.



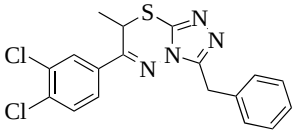
3-Isopropyl-6-(4-methoxyphenyl)-7-methyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.102)

A solution of 4-amino-5-(propan-2-yl)-4*H*-1,2,4-triazole-3-thiol (0.0600 g, 0.379 mmol), 2-bromo-1-(4-methoxyphenyl)propan-1-one (0.0922 g, 0.379 mmol), and Et_3N (0.0767g, 0.758 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 2 h. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 97.1 mg (85%) of **3.102** as a solid: Mp 141 ℃; IR (ATR) 3061, 2965, 1607, 1456, 1185, 988 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.00 (ddd, *J* = 2.4 Hz, 4.4 Hz, 8 Hz, 2 H), 7.14 (ddd, *J* = 2.4 Hz, 4 Hz, 8 Hz, 2 H), 5.00 (q, *J* = 6 Hz, 1 H), 3.86 (s, 3 H), 3.38-3.34 (m, 1 H), 1.39 (d, *J* = 5.6 Hz, 3 H), 1.35 (d, *J* = 5.6 Hz, 3 H), 1.31 (d, *J* = 5.6 Hz, 3 H); HRMS (ES) *m/z* calcd for $C_{15}H_{19}N_4SO$ ($[M+H]^+$) 303.1280, found 303.1285.



6-(4-Methoxyphenyl)-7-methyl-3-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.103)

A solution of 4-amino-5-phenyl-4*H*-1,2,4-triazole-2-thiol (0.100 g, 0.520 mmol), 2-bromo-1-(4-methoxyphenyl)propan-1-one (0.126 g, 0.520 mmol), and Et_3N (0.105 g, 1.04 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 90 min. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat. Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 141 mg (81%) of **3.103** as a solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20-7.97 (m, 4 H), 7.61-7.56 (m, 3 H), 7.13 (d, *J* = 8.7 Hz, 2 H), 5.04 (q, *J* = 7.2 Hz, 1 H), 3.85 (s, 3 H), 1.44 (d, *J* = 7.2 Hz, 3 H); HRMS (ES) *m/z* calcd for $C_{18}H_{17}N_4SO$ ($[M+H]^+$) 337.1118, found 337.1110.



3-Benzyl-6-(3,4-dichlorophenyl)-7-methyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (3.104)

A solution of 4-amino-5-benzyl-4*H*-1,2,4-triazole-3-thiol (0.0800 g, 0.388 mmol), 2-bromo-1-(3,4-dichlorophenyl)propan-1-one (0.109 g, 0.388 mmol), and Et_3N (0.0785 g, 0.776 mmol) in EtOH (4 mL) was stirred at 120 ℃ in a microwave for 2 h. The solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2, followed by treatment with sat.

Na_2CO_3. The layers were separated and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by chromatography on SiO_2 (10% MeOH/CH_2Cl_2) and provided 137 mg (91%) of **3.104** as a solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.95 (s, 1 H), 7.94 (d, *J* = 2 Hz, 1 H), 7.85 (d, *J* = 8.5 Hz, 1 H), 7.33-7.21 (m, 5 H), 5.00 (q, *J* = 7 Hz, 1 H), 4.35 (d, *J* = 2.5 Hz, 2 H), 1.28 (d, *J* = 7 Hz, 3 H); HRMS (ES) *m/z* calcd for $C_{18}H_{15}N_4SCl_2$ ($[M+H]^+$) 389.0389, found 389.0377.

APPENDIX A

SELECTED ^{1}H AND ^{13}C NMR DATA

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Cl
S
N
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1.02
2.00
4.11
2.13
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1.012
1.020
8.274
8.268
8.005
8.000
7.984
7.978
7.882
7.861
4.445
2.726
2.709
2.692
2.675
2.509
2.505
2.500
2.496
2.491
2.428
2.411
2.395
ppm

1
153.65
141.56
134.59
133.98
131.95
131.24
129.44
127.57
30.03
24.01
23.58
22.92
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

2
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2.01
1.99
2.00
3.08
4.36
1.92
7.993
7.988
7.975
7.971
7.963
7.126
7.119
7.114
7.102
7.097
7.089
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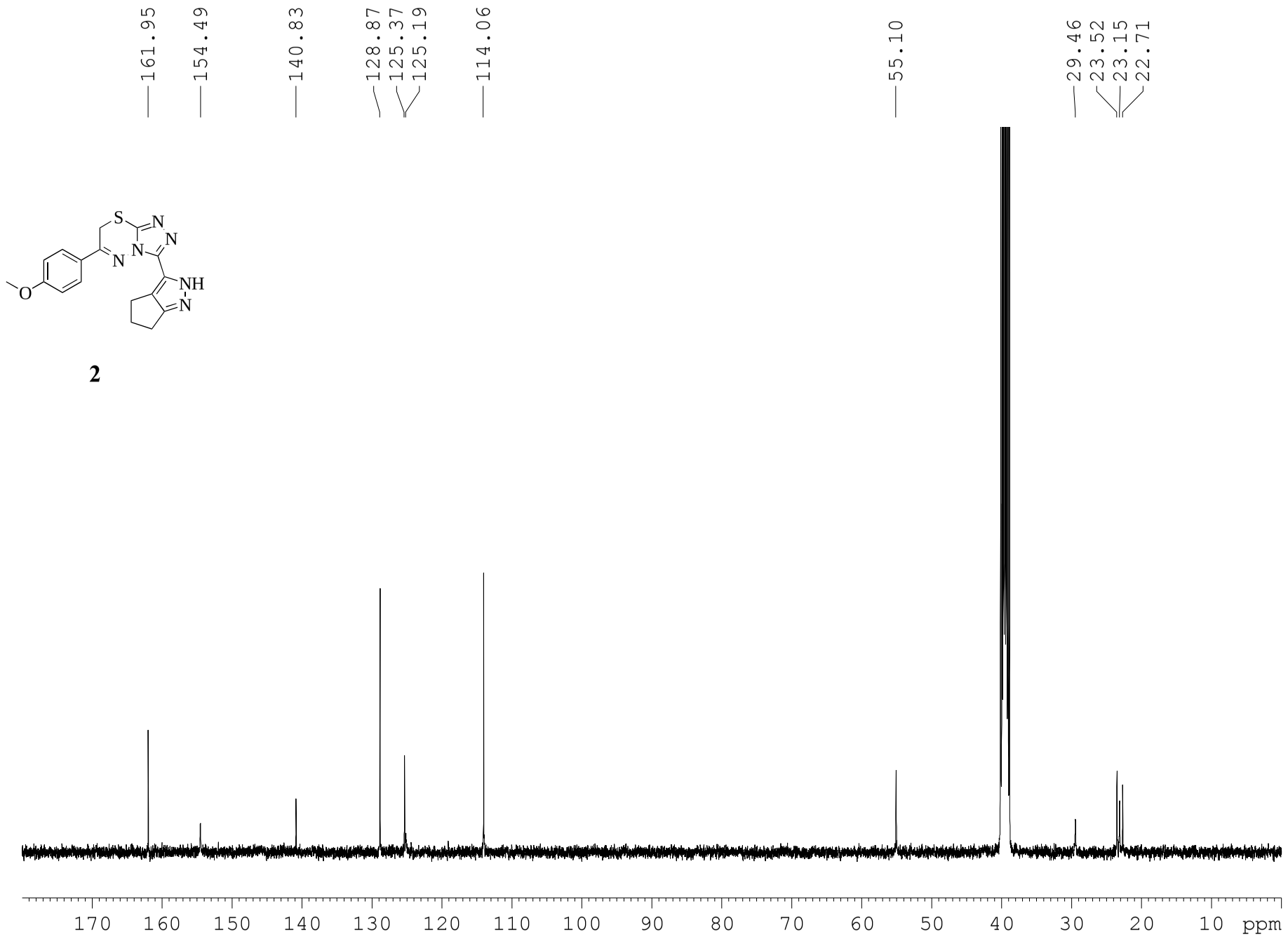
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125.19
114.06
55.10
29.46
23.52
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22.71
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N
N
N
N
NH
N
O
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150
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130
120
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80
70
60
50
40
30
20
10
ppm

2

3
Cl
S
N
S
N
N
N
NH
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0.94
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2.33
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4.384
2.824
2.743
2.725
2.708
ppm

3
Cl
S
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N
N
S
N
N
NH
N
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135.68
134.50
132.12
127.77
125.16
29.53
23.66
23.14
22.32
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

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7.943
7.661
7.657
7.644
7.640
7.610
7.591
7.571
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2.718
2.700
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0.98
2.00
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1.77
ppm

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0.92
2.00
4.21
1.82
12.516
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7.859
7.850
3.864
3.854
2.773
2.756
2.738
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2.700
2.682
2.463
2.447
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

19

Cl
S
N
NH
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7.613
7.607
7.602
7.590
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7.579
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2.689
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2.665
2.657
2.650
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1.837
1.829
1.822
1.814
1.810
1.799
1.794
1.783
1.778
1.758
1.754
2.00
1.96
2.49
4.04
2.03
2.11
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13
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11
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9
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7
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5
4
3
2
1
ppm

19
Cl
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N
NH
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132.24
132.10
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128.44
115.38
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21.89
20.73
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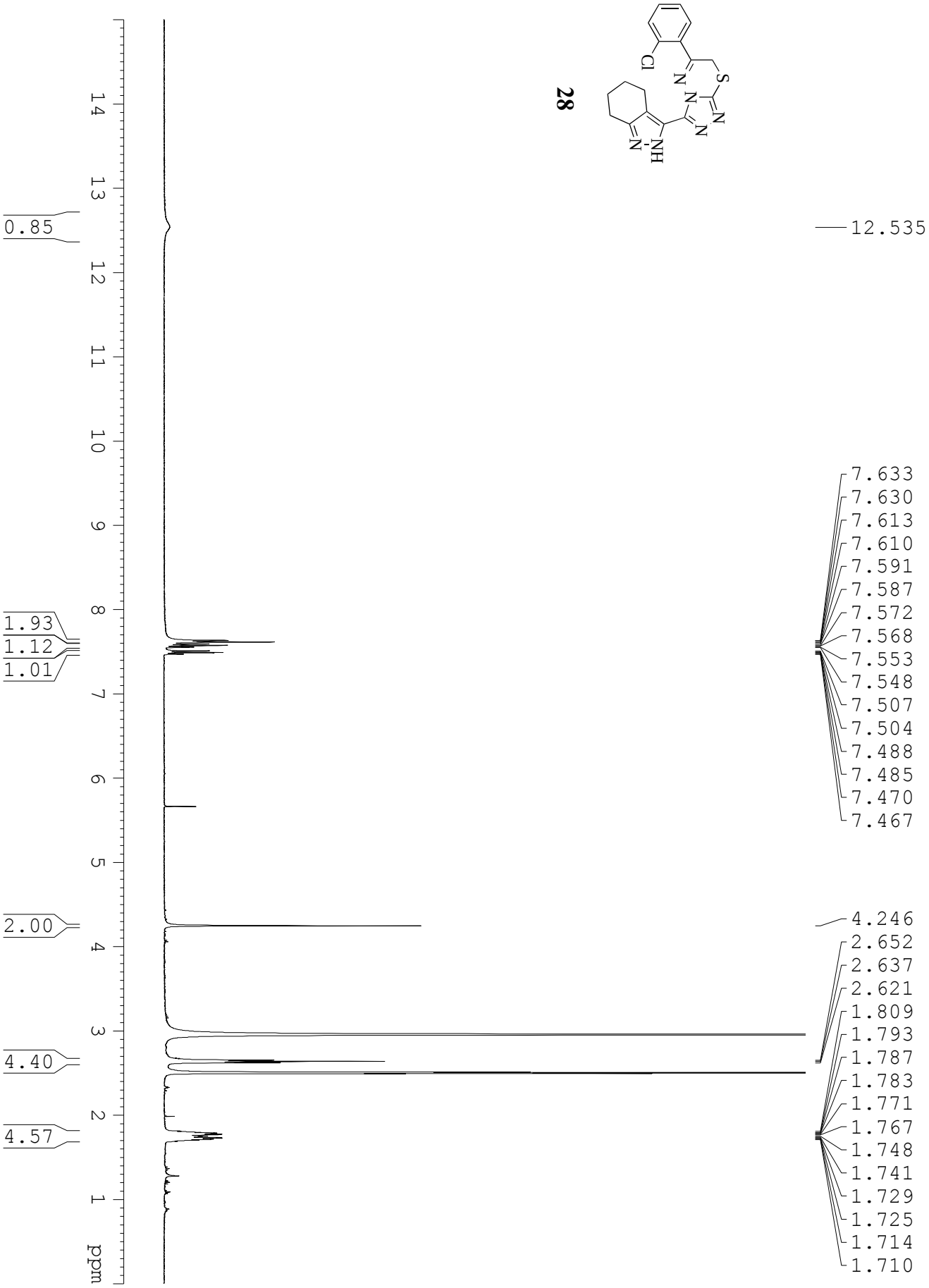
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N
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7.572
7.568
7.553
7.548
7.507
7.504
7.488
7.485
7.470
7.467
4.246
2.652
2.637
2.621
1.809
1.793
1.787
1.783
1.771
1.767
1.748
1.741
1.729
1.725
1.714
1.710
0.85
1.93
1.12
1.01
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7
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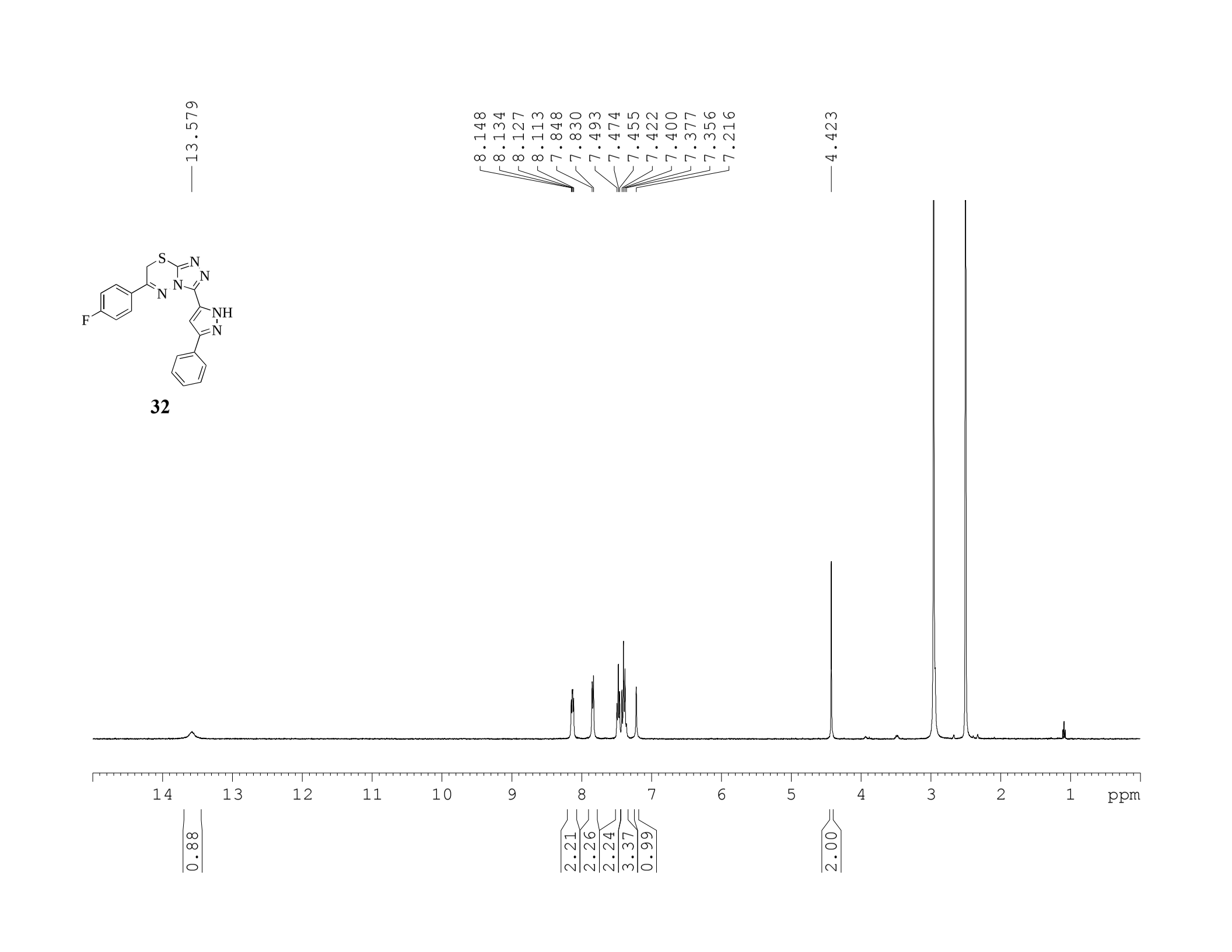
ppm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7.356
7.216
4.423
S
N
N
N
N
NH
N
F
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13
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10
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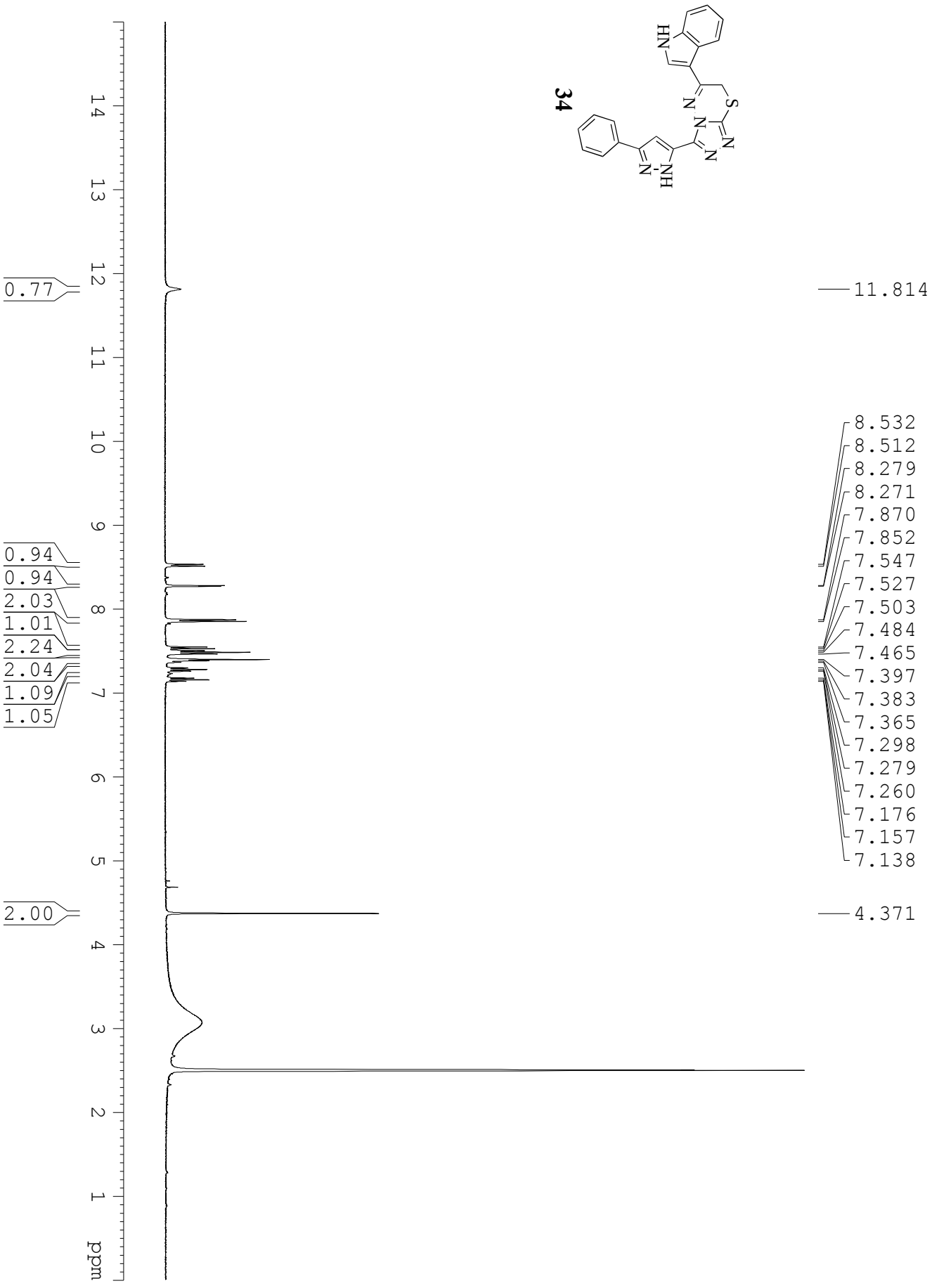
32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N
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N
N
N
N
NH
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7.465
7.397
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7.298
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7.138
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0.94
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2.24
2.04
1.09
1.05
2.00
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13
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11
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9
8
7
6
5
4
3
2
1
ppm

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S
N
N
NH
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2.33
1.19
1.04
0.95
2.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

37
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13.594
8.824
8.810
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7.837
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7.364
7.229
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2.08
2.08
2.19
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2
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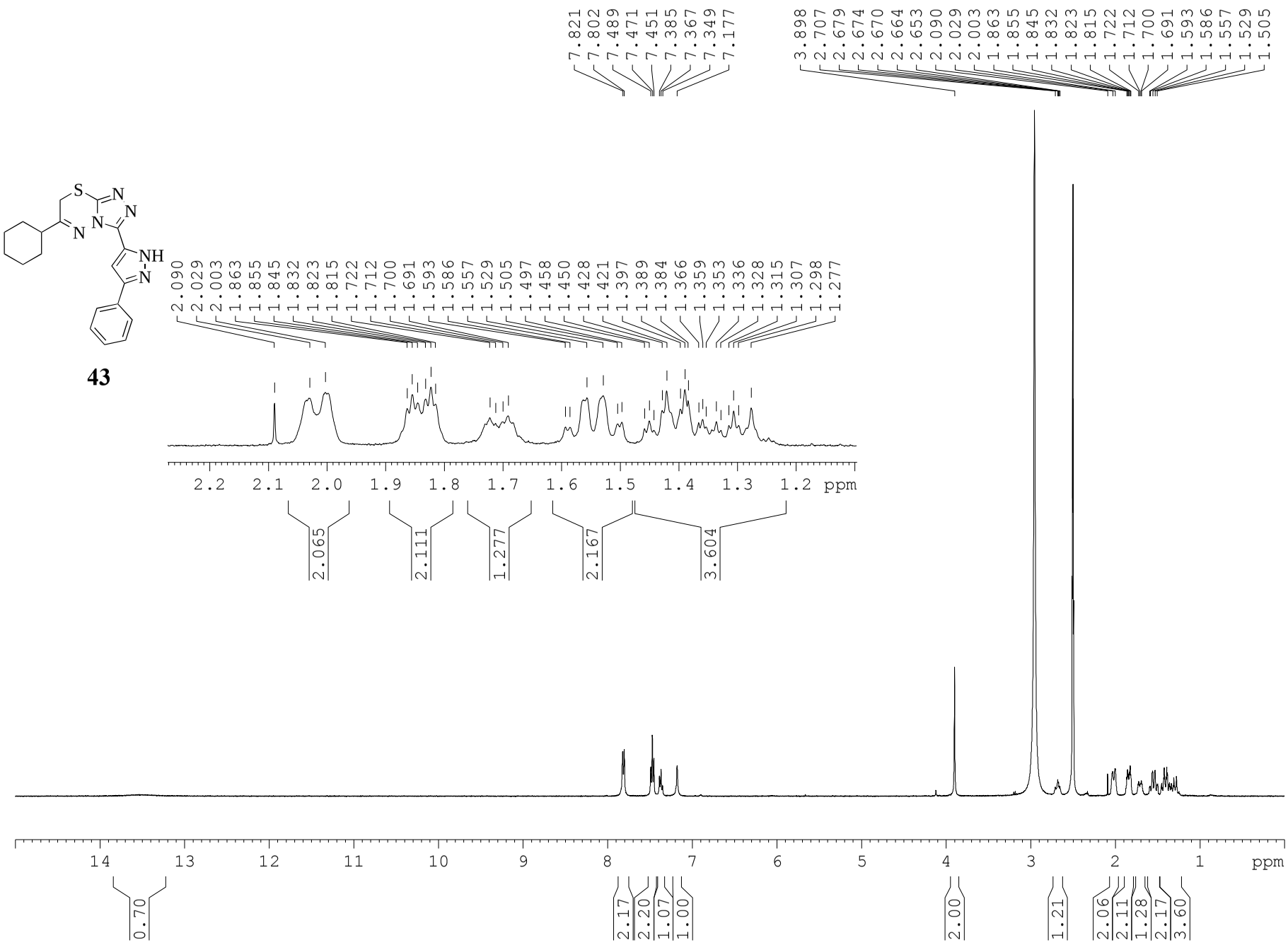
ppm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2.674
2.670
2.664
2.653
2.090
2.029
2.003
1.863
1.855
1.845
1.832
1.823
1.815
1.722
1.712
1.700
1.691
1.593
1.586
1.557
1.529
1.505
2.090
2.029
2.003
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1.855
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1.328
1.315
1.307
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1.277
2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 ppm
2.065
2.111
1.277
2.167
3.604
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
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2.11
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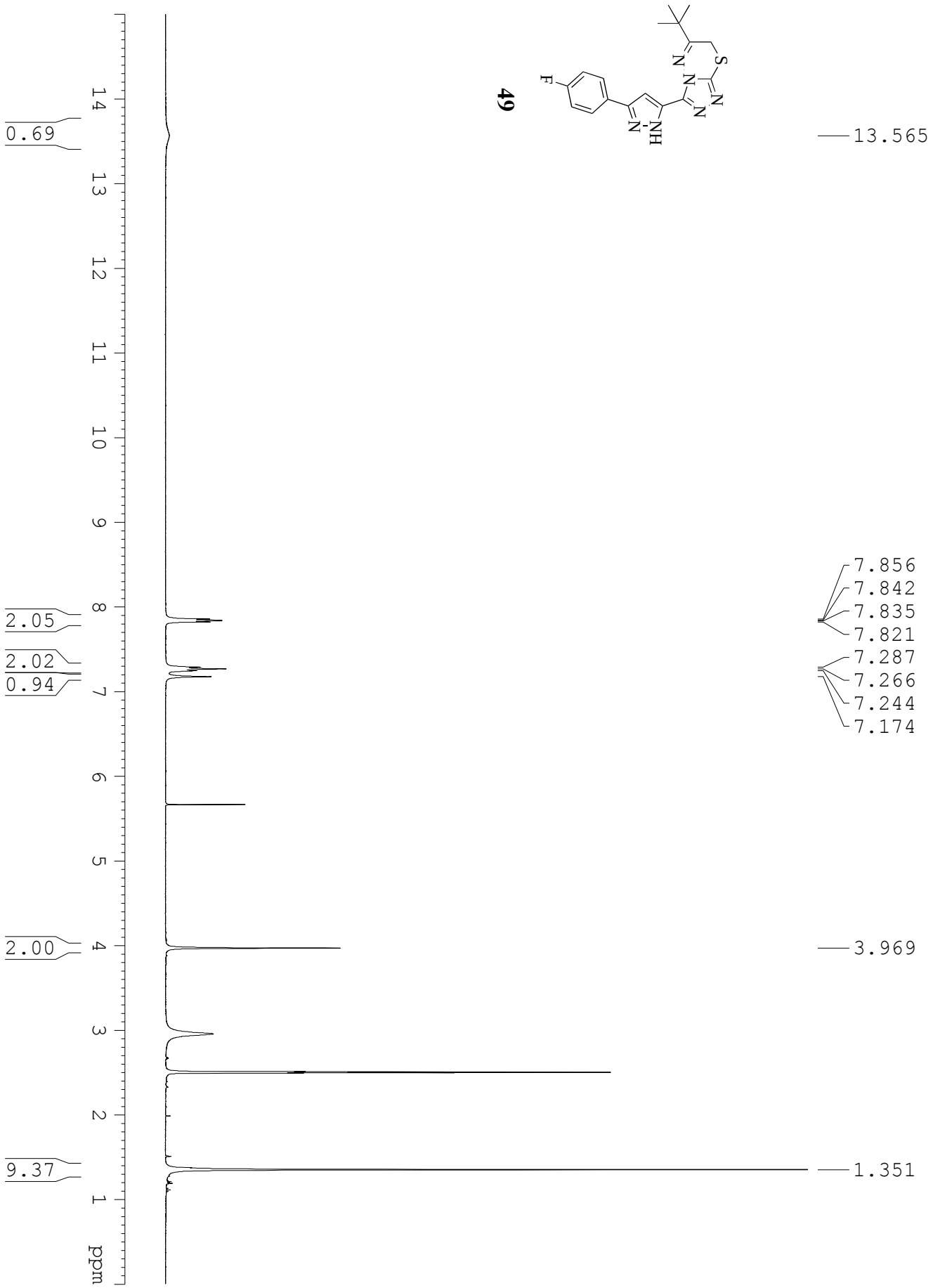
2.17
3.60

43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ppm

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F
S
N
NH
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2.10
0.92
2.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
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8.054
8.049
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7.889
7.880
7.872
7.864
7.859
7.652
7.648
7.644
7.641
7.637
7.627
7.625
7.619
7.614
7.610
7.606
7.602
7.594
7.590
7.587
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7.572
7.565
7.290
7.268
7.246
7.212
8.065
7.902
7.851

51
F
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S
N
N
N
N
NH
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133.20
131.24
128.46
127.06
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115.27
115.05
102.59
22.77
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

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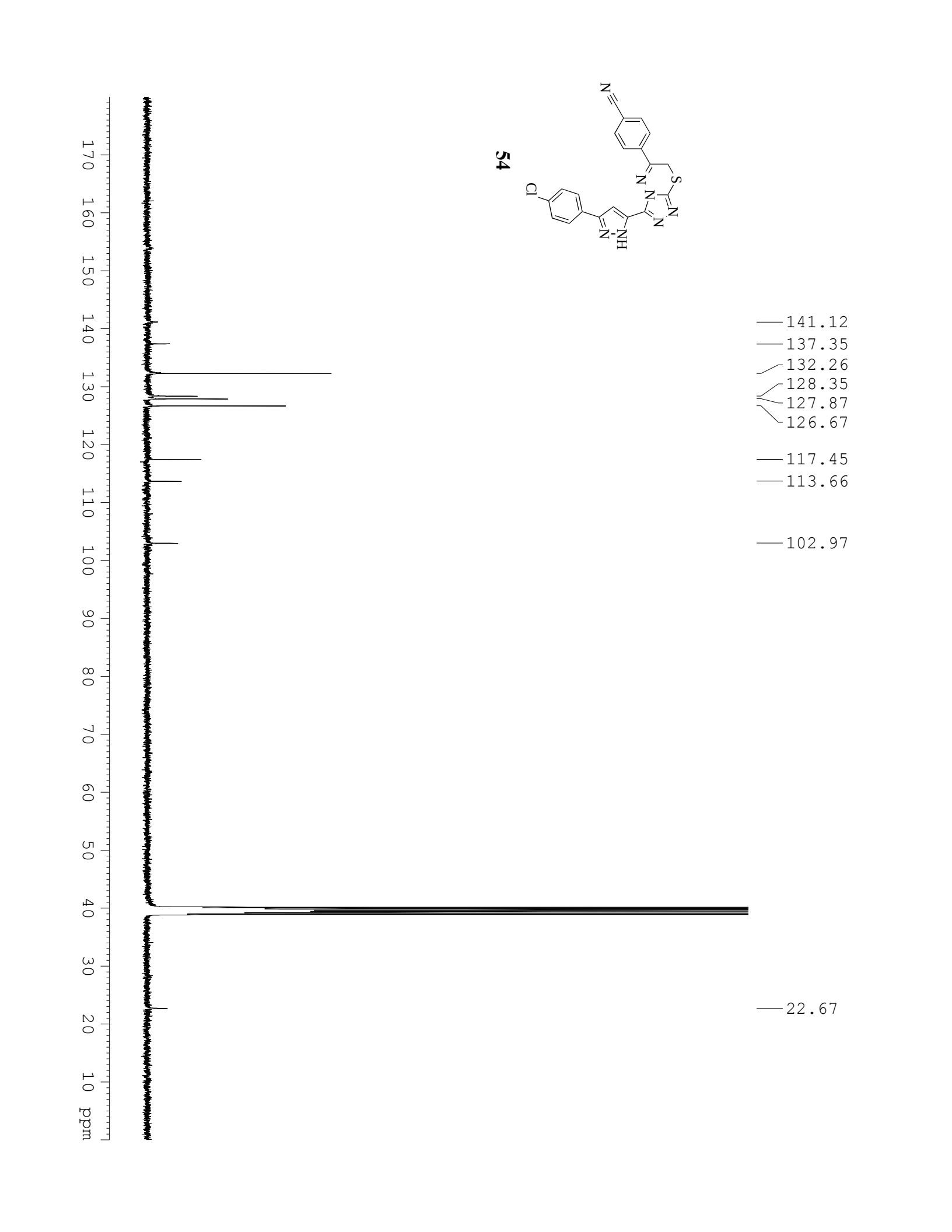
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130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

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7.103
7.095
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4.905
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2.824
2.804
2.786
2.768
2.739
2.731
2.721
2.702
2.687
2.669
2.664
2.649
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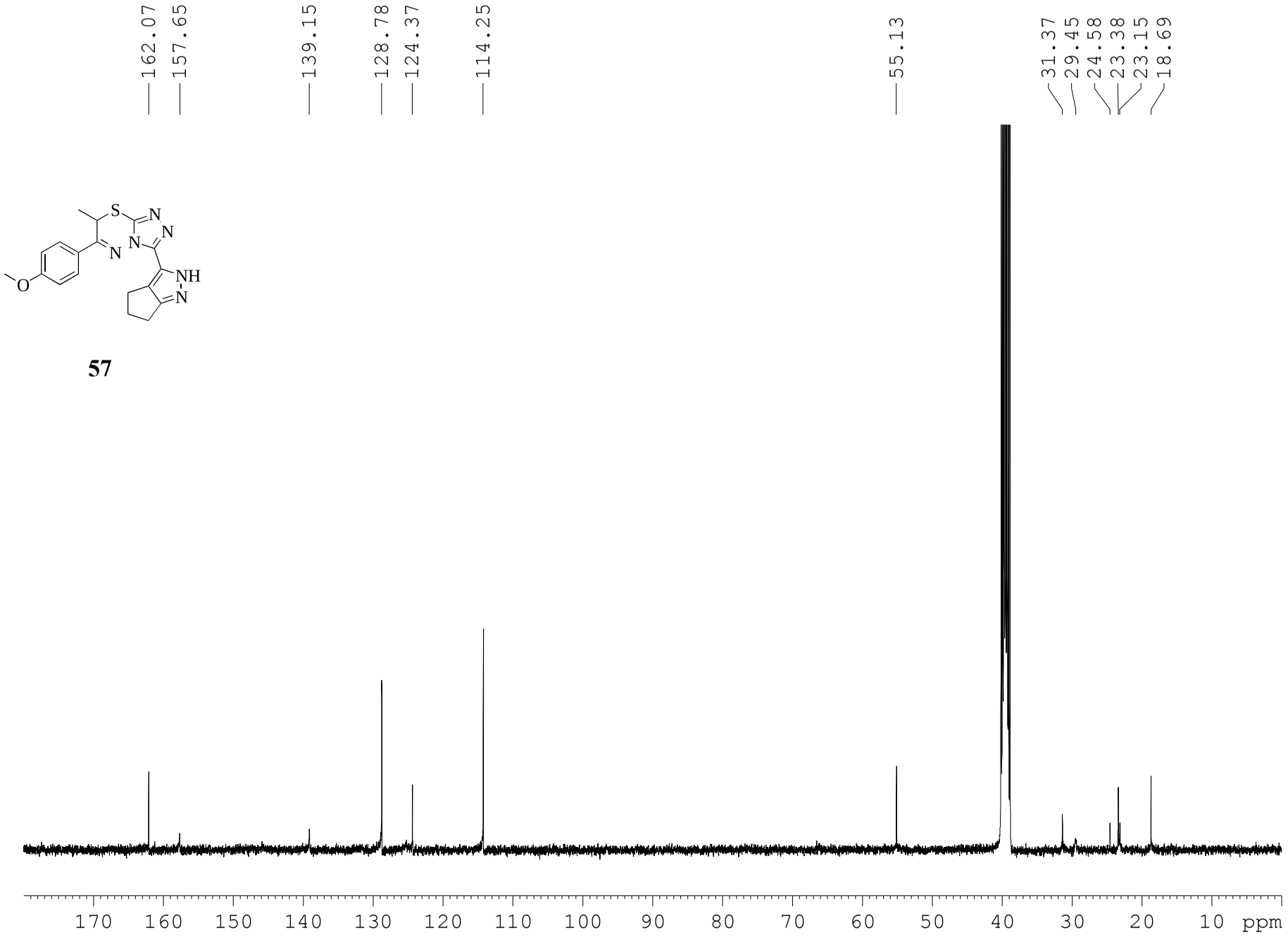
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55.13
31.37
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23.15
18.69
S
N
N
N
N
NH
N
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

57

58

Cl
Cl
S
N
N
N
N
N
NH
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7.995
7.974
7.829
7.808
5.001
4.983
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2.669
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2.426
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1.467
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0.89
0.87
0.99
0.96
1.00
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1.78
2.95
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

6l
F
S
N
NH
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0.92
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1.97
1.00
4.27
1.50
3.07
ppm

6l
F
S
N
N
N
N
NH
165.15
162.65
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139.14
129.63
129.54
128.79
128.75
125.37
115.71
115.49
31.54
29.51
23.34
23.13
18.53
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

63
F
S
N
NH
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7.885
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7.657
7.654
7.638
7.622
7.618
7.599
7.583
7.578
7.292
7.271
7.247
5.046
5.028
5.010
4.992
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1.495
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2.09
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3.07
ppm

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1.466
0.94
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5.18
0.99
3.00
3.03
ppm

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8.070
8.066
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7.656
7.637
7.618
7.600
7.585
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7.476
7.457
7.393
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7.257
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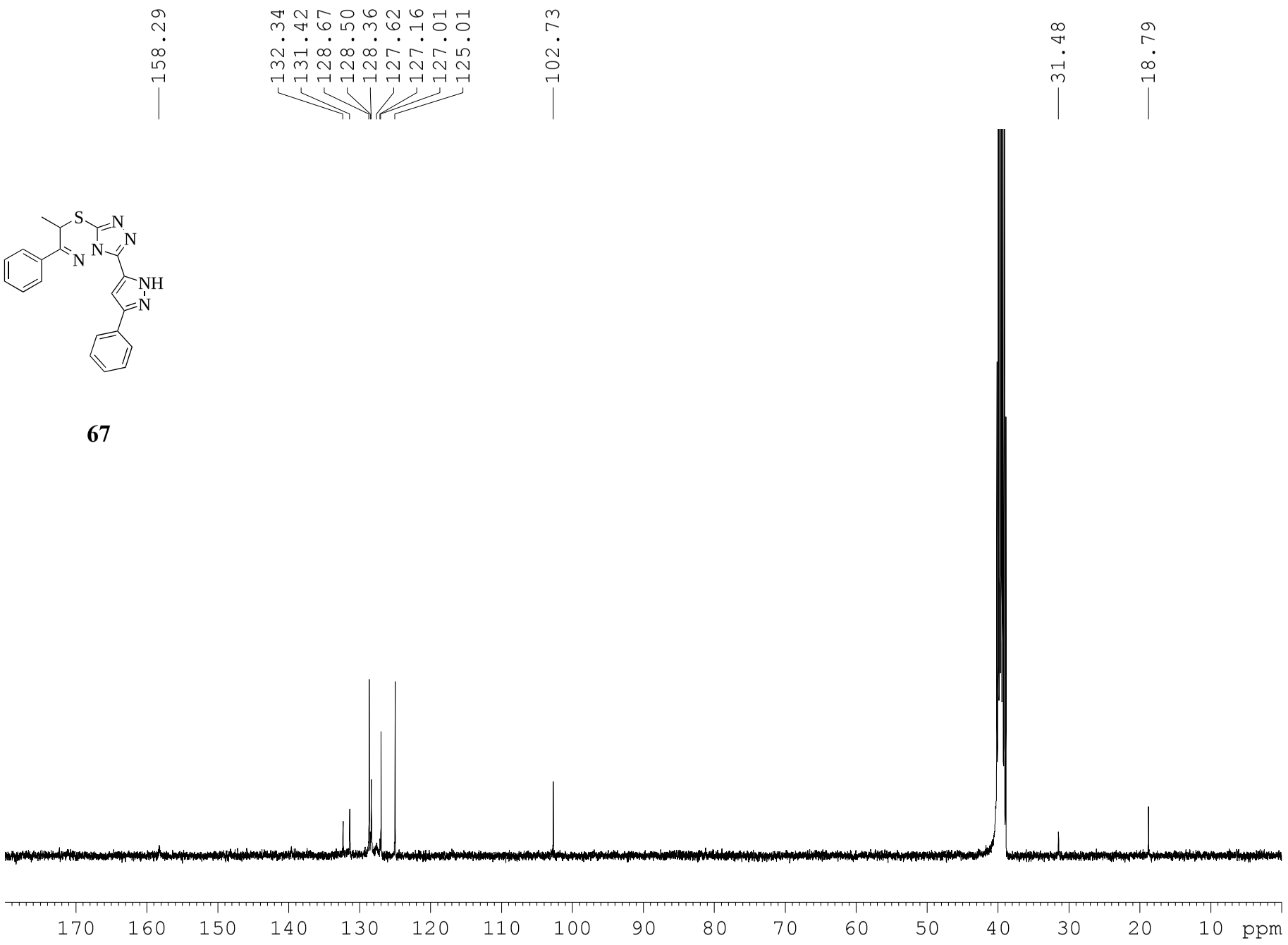
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S
N
N
N
N
NH
N
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

67

69
Cl
Cl
N
S
N
N
N
NH
N
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0.98
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1.00
1.00
4.33
1.55
1.12
6.45
12.747
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8.031
7.824
7.803
4.807
4.788
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2.003
1.984
1.970
1.953
1.936
1.919
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0.919
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

69
Cl
Cl
N
S
N
N
N
N
NH
155.16
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131.75
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127.18
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30.53
29.60
23.32
23.11
19.15
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90
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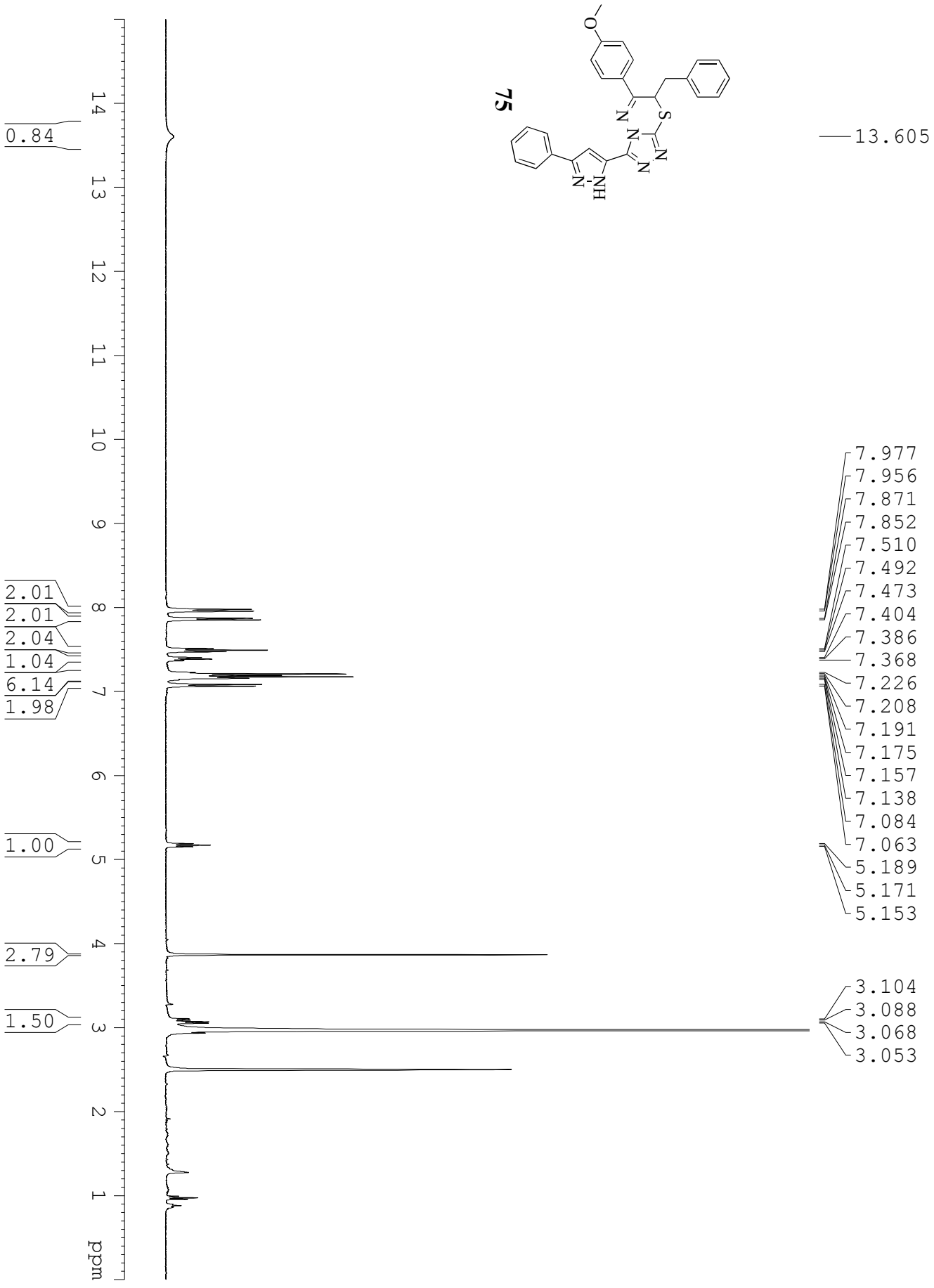
70
60
50
40
30
20
10
ppm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7.157
7.138
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1.890
1.873
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2.16
2.19
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1.00
3.30
1.26
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3.32
3.00
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Cl
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N
N
N
N
NH
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7.614
7.595
2.639
2.622
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0.92
0.94
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Cl
S
N
N
N
N
NH
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42.64
25.93
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20
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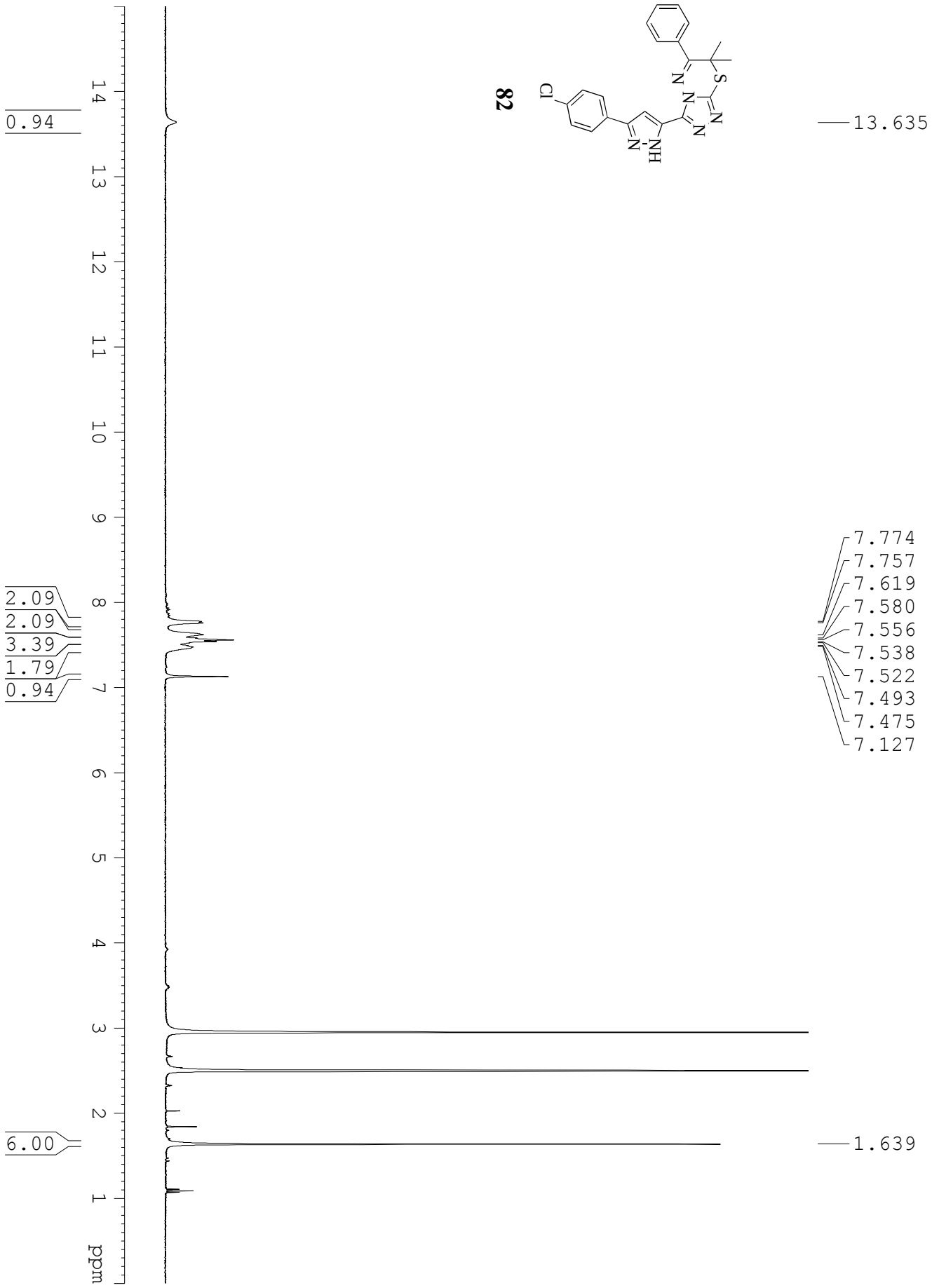
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2.09
2.09
3.39
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11
10
9
8
7
6
5
4
3
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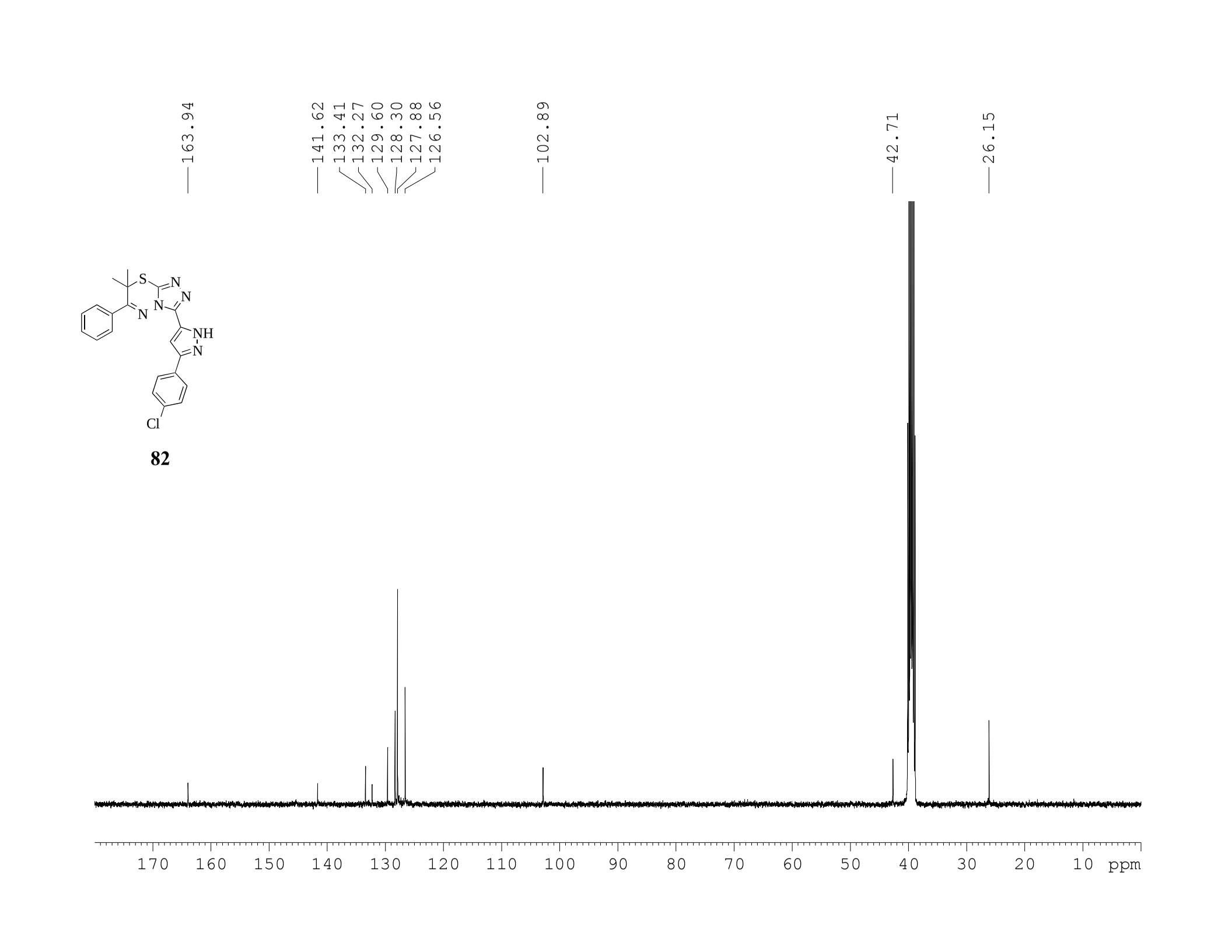
1
ppm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N
N
NH
N
Cl
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160
150
140
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120
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100
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80
70
60
50
40
30
20
10
ppm

82

83
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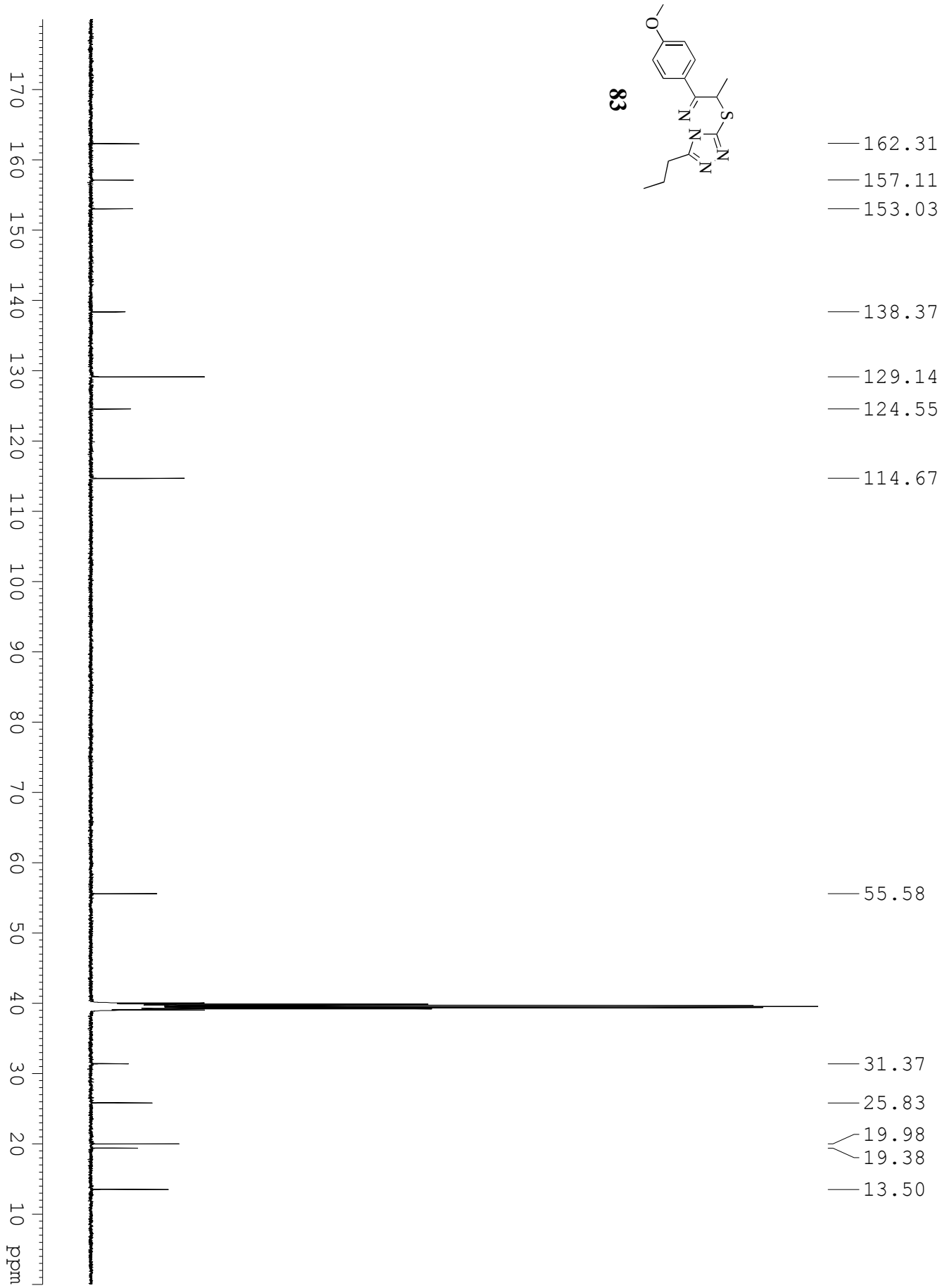
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13.50
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

85
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7.994
7.987
7.151
7.145
7.141
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7.127
7.121
5.018
5.003
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4.974
3.862
3.383
3.372
3.369
3.355
3.350
3.345
3.341
1.400
1.386
1.356
1.342
1.312
1.298
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1.86
1.00
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3.48
ppm

87
Cl
Cl
N
S
N
N
N
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14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

APPENDIX B

KINASE INHIBITION BY 669

	% of DMSO Control Kinase Activity		% of DMSO Control Kinase Activity		% of DMSO Control Kinase Activity
Kinase	**669** @ 9 μM	Kinase	**669** @ 9 μM	Kinase	**669** @ 9 μM
Ab1(h)	106	FGFR1(h)	97	PKCη(h)	101
Ab1(T315I)(h)	107	FGFR2(h)	92	PKCθ(h)	83
Arg(h)	103	FGFR3(h)	91	PKCι(h)	105
Aurora-A(h)	97	FGFR4(h)	86	PKCμ(h)	93
Ax1(h)	108	Lck(h)	104	PKD2(h)	104
Bmx(h)	91	Lyn(h)	87	PRAK(h)	89
BTK(h)	95	MAPK1(h)	103	PRK2(h)	117
CaMKIIβ(h)	80	MAPK2(h)	113	Pyk2(h)	108
CaMKIV(h)	89	MEK1(h)	101	F1t1(h)	92
CDK1/cyclinB(h)	113	Met(h)	100	F1t3(h)	81

CDK2/cyclinA(h)	118	MST2(h)	98	F1t4(h)	96
CDK2/cyclinE(h)	89	NEK2(h)	113	Fms(h)	92
CDK3/cyclinE(h)	88	p70S6K(h)	82	Fyn(h)	108
CDK5/p35(h)	99	PAK2(h)	107	GSK3β(h)	65
CDK6/cyclinD3(h)	108	PAR-1Bα(h)	104	1GF-1R(h)	107
CDK7/cyclinH/MAT1(h)	104	PDGFRα(h)	112	JAK2(h)	123
CHK1(h)	96	PDGFRβ(h)	90	JAK3(h)	82
CHK2(h)	93	PDK1(h)	90	Ret(h)	106
CK1(y)	93	PKA(h)	90	Ros(h)	105
CK1δ(h)	84	PKBα(h)	92	Rsk1(h)	88
CK2(h)	107	PKBβ(h)	86	Rsk1®	70
cKit(h)	102	PKBγ(h)	77	Rsk2(h)	88
c-RAF(h)	96	PKCα(h)	104	Rsk3(h)	79
CSK(h)	100	PKCβII(h)	103	SGK(h)	70
cSRC(h)	110	PKCγ(h)	97	Syk(h)	84
EGFR(h)	95	PKCδ(h)	109	Tie2(h)	75
EphB2(h)	136	PKCε(h)	111	Yes(h)	81
EphB4(h)	102	PKCζ(h)	97		

APPENDIX C

ADME STUDY OF LEAD COMPOUND 669

Compd	Test conc (mM)	Test species	NADPH-dependent CL_{int}[a] (ml $min^{-1}mg^{-1}$	NADPH-dependent $T_{1/2}$[b] (min)	NADPH-free CL_{int}[a] (mlmin-$^{1}mg^{-1}$	NADPH-free $T_{1/2}$[b] (min)	Comment
Verapamil	1.0	Human	274	8.4	6.2	374	High-metabolized control
	1.0	Mouse	336	6.9	0	> 200	
Warfarin	1.0	Human	0.4	> 180	0	> 180	High-metabolized control
	1.0	Mouse	5	> 180	0	> 180	
669	1.0	Human	166	14.0	2.5	928	
	1.0	Mouse	521	4.4	31.1	74	

[a]Microsomal Intrinsic Clearance
[b]Half-life

APPENDIX D

METABOLITE IDENTIFICATION OF 669 IN MOUSE MICROSOMES

Compd	Mass	Retention time (min)	MW difference	Possible metabolic pathway	Product Ion mass	Comment
669	390	3.4	-	-	133,161	Parent
	319	2.9, 3.1	- 71			
	347	3.2	- 43			
	361	3.2	- 29			
	385	2.8	- 5			
	406	2.9	+ 16	hydroxylation		

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