Synthesis of Pentafluorosulfanyl Analogs of Mefloquine

by

Tingting Mo

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This thesis was presented

by

Tingting Mo

It was defended on

May 13, 2010

and approved by

Dennis P. Curran, Distinguished Service Professor, Department of Chemistry

Paul Floreancig, Associate Professor, Department of Chemistry

Thesis Director: Peter Wipf, Distinguished University Professor, Department of Chemistry

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Tingting Mo, M.S.

University of Pittsburgh, 2010

The pentafluorosulfanyl (SF_5) group is of increasing interest as a functional group in pharmaceutical and agrochemical research, and was recently labeled as the "substituent of the future". It imparts unique properties to organic compounds and enhances their biological activities because of its high electronegativity, substantial steric effect, significant hydrophobicity and high chemical resistance. To improve the activity and alleviate the neurotoxicity of the antimalarial drug mefloquine, we introduced the SF_5 group into the quinoline methanolamine scaffold in place of the trifluoromethyl (CF_3) group. Three novel mefloquine analogs were synthesized in high yields from simple phenyl SF_5 building blocks through short synthetic routes. Two analogs were found to have improved activity and selectivity against malarial parasites, and one analog demonstrated lower membrane permeability, which is potentially advantageous for the reduction of the neurotoxic side effects. As part of this work, we also report the first SF_5-containing quinoline heterocycles and the first *ortho* SF_5 aniline.

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1.0 INTRODUCTION TO MEFLOQUINE

Malaria is an acute or chronic tropical mosquito-borne disease of man caused by the genus *Plasmodium*. The coccidian genus contains 172 species and four of them infect humans: *Plasmodium falciparum, P. malariae, P. ovale* and *P. vivax.* Only *P. falciparum* pose a substantial risk of death and are responsible for as many as 2.7 million casualties per year.[1] The geographic extension of *P. falciparum* and its developing resistance to conventional antimalarial drugs have necessitated the development of new drugs that are active against resistant parasite strains and have good compliance.[2]

Mefloquine is an orally-administered antimalarial drug used as a prophylaxis and treatment for malaria, especially against chloroquine-resistant parasite strains.[3] However, its potential is limited due to its adverse central nervous system (CNS) effects, which include anxiety, depression, hallucinations and seizures.[4] Despite the relatively high incidence of side effects, mefloquine continues to be used due to its long half-life, relative safety in pregnancy, activity against resistant strains, and the absence of effective alternatives. In order to ameliorate the neurotoxity profile of mefloquine, we set out to develop analogs that are less readily absorbed through the blood-brain barrier while still retaining the antimalarial activity.

The chemistry of compounds that have a pentafluorosulfanyl (SF_5) substituent is currently experiencing a renaissance, after their initial synthesis and characterization more than half a century ago.[5,6] This novel functional group imparts unique properties to organic

compounds and enhances their biological activities because of its high electronegativity, substantial steric effect, significant hydrophobicity, and high chemical resistance.

This document summarizes studies on the synthesis of three mefloquine analogs containing pentafluorosulfanyl (SF_5) group as a replacement for the trifluoromethyl (CF_3) group. Biological assays determined that the new analogs have equivalent or improved activities against *P. falciparum* parasites. Additionally, the 8-SF_5 analog exhibits lower membrane permeability in an MDCK cell line screen, thus potentially reducing the adverse CNS effects of the parent antimalarial agent.

1.1 TRANSMISSION OF MALARIA

Malaria remains one of the world's most important parasitic diseases with approximately 300 million clinical cases and as many as 2.7 million of deaths per year. The female anopheles mosquito causes the transmission of malaria in man. And the human body is a host for mosquitoes, where sexual recombination can occur.

1.1.1 Life cycle of causative plasmodia

The essential features of the life cycle of the causative plasmodia are illustrated in Figure 1.[7] This cycle is divided into the sexual and asexual phases, with the sexual phase taking place in the female mosquito and the asexual phase taking place in man. When a human is infected through the salivary gland of the anopheles mosquito, sporozoites (fertilized zygotes) move rapidly away from the site of injection and enter liver cells in 30-60 min. They remain within the

hepatocytes for 9-16 days and undergo an asexual replication known as exo-erythrocytic schizogony. Each sporozoite gives rise to tens of thousands of merozoites inside the hepatocytes, which are released to the circulatory system following a rupture of the host hepatocytes.

The merozoite recognizes specific proteins on the surface of the erythrocyte (a red blood cell, RBC) and actively invades the cell. The parasite starts a trophic period followed by an asexual replication. Trophozoite enlargement is accompanied by a highly active metabolism, which includes the ingestion of host cell cytoplasm and the proteolysis of haemoglobin into amino acids. The heme byproduct cannot be digested and polymerizes into the hemozoin (malaria pigment). After multiple rounds of nuclear division without cytokinesis, schizonts are formed and each mature schizont gives rise to about 12-16 merozoites. These merozoites are released through the ruptured schizont to invade further uninfected RBCs. This release coincides with a sharp increase in body temperature and is responsible for the characteristic clinical manifestations observed in a malaria attack.

In the erythrocytic stage, a small portion of the merozoites in the RBCs is differentiated to produce male and female gametocytes. When an infected individual is bitten by a subsequent female anopheles mosquito, these gametocytes are taken up by the mosquito and undergo gametogenesis to form male and female gametes. These gametes fuse, undergo fertilization and form a zygote. The zygote develops to form an ookinete, which penetrates the wall of a cell in the midgut and forms an oocyst. The oocyst matures, undergoes several nuclear divisions, and finally ruptures to release hundreds of sporozoites. These sporozoites migrate to the salivary glands and thereafter the mosquito remains infective. The life cycle of plasmodium is completed.

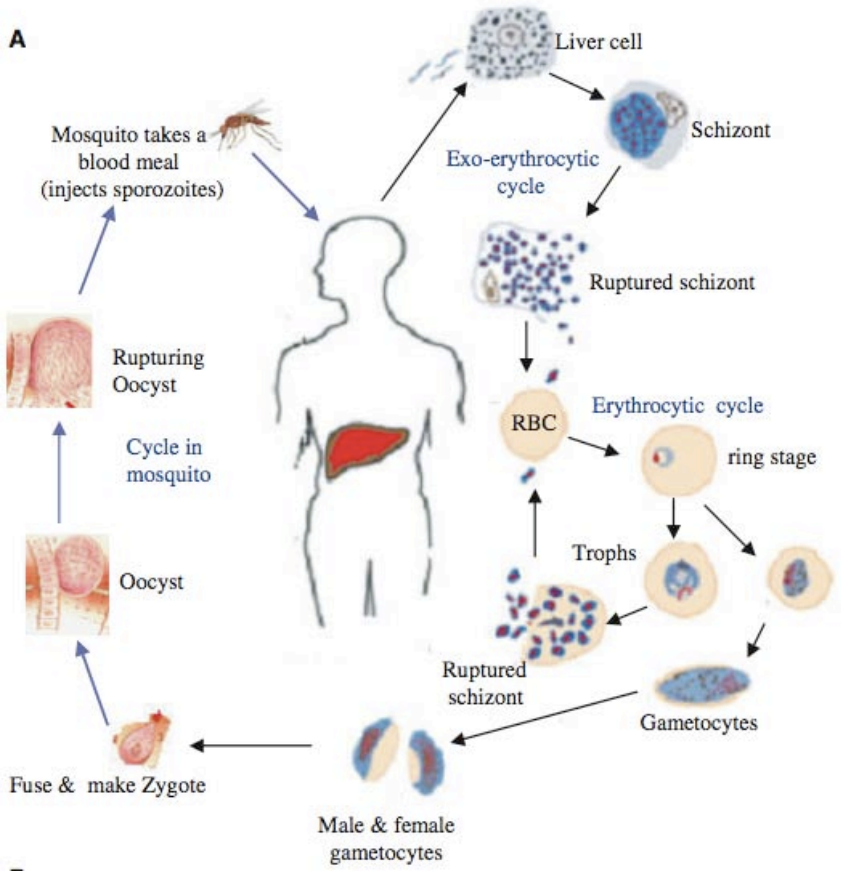


Figure 1 Life cycle of the plasmodium causing malaria (reproduced from Ref. 7)

1.1.2 Clinical manifestation

The clinical manifestation of a malaria attack is caused by the asexual erythrocytic schizogony in the blood. The rupture of RBCs by merozoites reduces the number of circulatory RBC, which results in low blood haemoglobin levels and causes the acute fever associated with malarial illness.[8] Lowered haemoglobin levels contribute to anorexia in severe cases. In endemic areas, malaria often presents with other manifestations, such as pain in the joints, watery diarrhea, vomiting and convulsions.[9] In some cases, secondary infections such as pneumonia or urinary tract infection can add to the difficulty of diagnosis.

1.1.3 Prevention and control of malaria

Currently, no effective malaria vaccines are available. In endemic areas, prevention involves keeping mosquitoes away from humans and using prophylactic drugs to impede the malaria occurrence. The vector control measures include the use of insecticides to kill the mosquitoes and their eggs and larvae. Other preventive actions involve use of nets, closing of door and windows and use of mosquito repellents. Chemoprophylaxis is the use of medicine to prevent the infection in the human body. Man plays the major role in malaria control, and taking medicines is essential for people in areas where malaria is endemic.

1.2 ANTIMALARIAL DRUGS

An antimalarial drug is a drug used either to prevent or to cure malaria. The oldest and most famous drug is quinine, but there are many others on the market, such as chloroquine, sulfadoxine-pyrimethamine, mefloquine, proguanil, and artemesinin and its derivatives (Figure 2).

1.2.1 Quinine

The history of quinine dates back to the 17th century in Peru when Jesuit priests learned from the Incas that powder from the cinchona tree bark relieved the shivering induced by the cold and the chills from malaria.[10] Currently, it serves as a malaria treatment, but not for prophylaxis. It acts as a blood schizonticidal and weak gametocide during the asexual stage of

the parasite life cycle and it also inhibits the hemozoin biocrystallization to facilitate an aggregation of cytotoxic heme.[11] Oral quinine is used to treat uncomplicated malaria in areas where there is known to be a high level of resistance to chloroquine, mefloquine and sulfa drug combinations with pyrimethamine.

The use of quinine causes a syndrome known as cinchonism, which has adverse effects including primarily tinnitus, nausea and vertigo. Cardiovascular toxic effects are experienced in some cases because the drug is capable of prolonging the QT interval and the drug also has neurotoxic properties.[12] A synthetic route toward quinine was described by Woodward and Doering in 1944,[13] but this route is too complicated for commercial production. The perceived side effects along with the synthetic difficulty provided the impetus for scientists to develop synthetic alternatives.

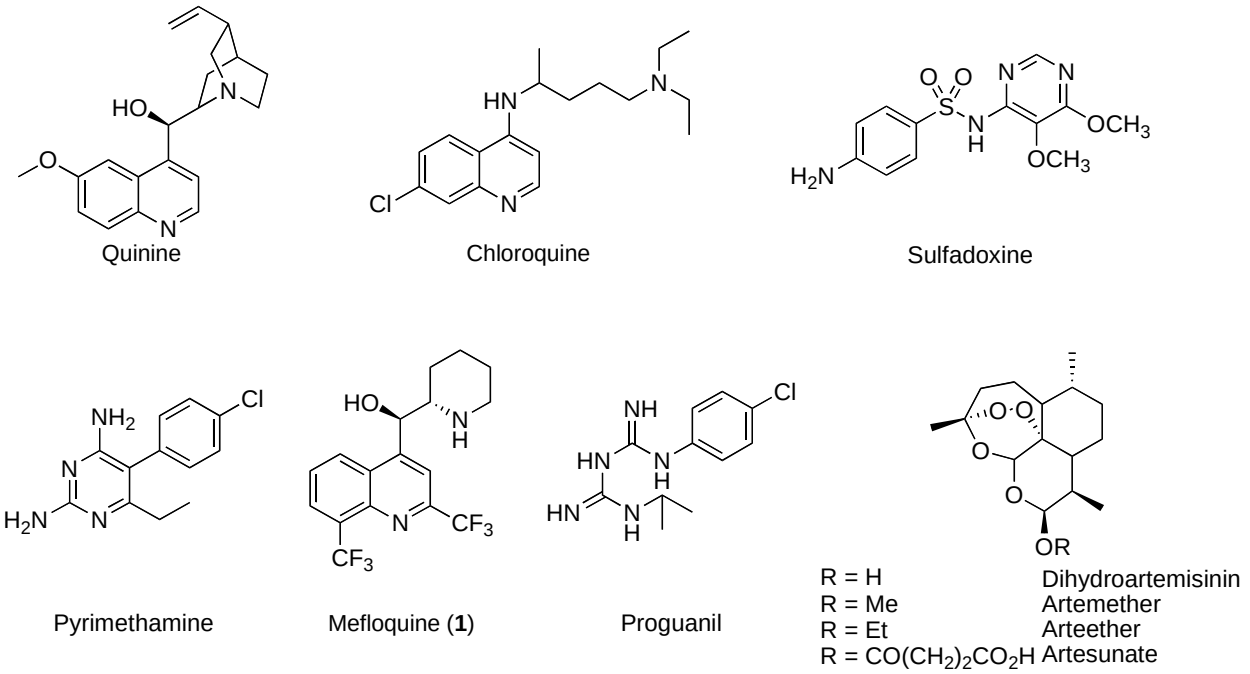


Figure 2 The Structures of the main antimalarial drugs

1.2.2 Chloroquine

Chloroquine was developed by scientists at the Bayer laboratories in Germany[14] and patented as an antimalarial drug in 1946. It has been used for the treatment of malaria since the 1960s. Its popularity over two decades has been due to its high efficacy, easy administration and good tolerability when used in the prescribed doses. Chloroquine is believed to reach high concentrations in the vacuoles of the parasite and raise the internal pH. It inhibits the biocystallization of hemozoin, causing the toxic heme to accumulate in the parasite and consequently poisons it through excess levels of toxicity.[15]

Chloroquine resistance in *P. falciparum* occurred in the late 1950s in Thailand and Columbia. Shortly afterwards, chloroquine resistance reached all regions of the world except Central America and some regions of Southwest Asia. It is now often used in combination with other antimalarial drugs to extend its effective usage.

1.2.3 Sulfadoxine-Pyrimethamine

The sulfadoxine-pyrimethamine combination is mainly used for treating *P. falciparum* infections and is less active against other *Plasmodium* strains. It is the standard second-line therapy against chloroquine-resistant *falciparum* malaria.[16] This combination acts on the schizonts during the hepatic and erythrocytic phases and synergistically against folate synthesis, inhibiting dihydropteroate synthase and dihydrofolate reductase in the parasite.[17] Since severe idiosyncratic skin allergies have been observed, this combination is not recommended for chemoprophylaxis yet; it is used frequently for clinical episodes of the disease. Resistance was

first recognized at the Thai-Cambodian border in the 1960s and has spread in sub-Saharan Africa and eastern Africa.[18]

1.2.4 Mefloquine

Due to problems in Vietnam with chloroquine-resistant malaria, the Walter Reed Army Institute for Research started a large-scale screening of potential antimalarial drugs, and mefloquine was synthesized and demonstrated to have potent activity against both *P. falciparum* and *P. Vivax*.[19] Roche Pharmaceuticals is the major commercial manufacturer and markets the drug under the trade name "Lariam". Mefloquine is effective for prophylaxis and for acute therapy and it is currently strictly used for resistant strains. Until recently, it was the drug of choice for U.S. military deployments in regions where malaria is endemic, primarily because of its long half-life, which allows weekly administration. However, associations of mefloquine with adverse neuropsychiatric effects, namely anxiety disorders, hallucinations, sleep disturbances and delirium, have curtailed its use.[4] Mefloquine can only be taken for up to 6 months due to those side effects and subsequently, alternative drugs need to be taken.

1.2.5 Proguanil

Proguanil is a synthetic derivative of pyrimidine and was developed in the 1940s by a British antimalarial research group (Figure 2).[20] It inhibits the malarial dihydrofolate reductase enzyme on the primary tissue stages of *P. falciparum*, *P. vivax* and *P. ovale*.[21] When combined with atovaquone or chloroquine (in areas where there is no chloroguine resistance), it is useful in prophylaxis due to fewer side effects, which include slight hair loss and mouth ulcers.[22] Thus,

proguanil is considered safe during pregnancy and breastfeeding, but insufficient drug is excreted in the milk to protect a breastfed infant.[23]

1.2.6 Artemisinin and its derivatives

Artemesinin is a Chinese herb (Qinghongsu) that has been used in the treatment of fevers for over 1,000 years. In 1985, the Journal of Traditional Chinese Medicine described its satisfactory efficacy in 100 patients, and artemisinin derivatives were soon thereafter recognized as having powerful antimalarial activity.[24] Although the target within the parasite remains controversial, the derivatives have been shown to have potent activity against early trophozoite forms and to reduce rapidly heavy parasite infections.[25] Now, it is strictly controlled under WHO guidelines because it has proven effective against all forms of multi-drug resistant *P. falciparum*, thus great care is taken to prevent resistance from developing. It is only given in combination with other antimalarials, such as mefloquine, in terms of parasite clearance.[26] The most commonly reported adverse effects are mild abdominal pain, anorexia, nausea, diarrhea and CNS involvement,[27] thus this antimalarial agent shows a favorable safety profile for the treatment of acute, uncomplicated *P. falciparum* malaria.

1.2.7 Trends in antimalarial treatments

The major problem in the use of conventional antimalarial drugs is parasite resistance, especially against chloroquine.[28] Development of new drugs, combination of two or more drugs and development of vaccines are the three main trends in the control of malaria. The new drugs, like dihydroartemisinine, artesunate and artemether (Figure 2), have a different mechanism of

action towards the parasite, which explains their rapid effects as well as their efficacy against drug-resistant malarial strains.[29] The combination drugs, including artesunate/mefloquine, have been shown to be highly active against multidrug resistant *P. falciparum* infections. This combination may have played a role in both slowing down the development of resistance to mefloquine as well as reducing malaria transmission.[30] Since vaccines based on a single antigen have a limited role in malaria due to the fact that not all people respond to the same antigen, development of multi-stage, multi-epitope, multi-component vaccines is undergoing.[31] The use of antimalarial vaccine is currently in clinical trials and holds a great promise for antimalarial therapy.

1.3 MEFLOQUINE

There has been a growing public unease toward mefloquine, due to its severe neuropsychiatric effects, which were first publicized by a BBC Watchdog television program that appeared in the early 1990s. However, mefoquine is still the only weekly-administered drug that is efficacious against chloroquine-resistant *P. falciparum* malaria; therefore, mefloquine has a very important place in malaria treatment.

1.3.1 Mechanism of action

Like the structurally related chloroquine, mefloquine acts primarily on the erythrocytic asexual stages of the parasite (Figure 2). An early study of the ultrastructural changes induced by mefloquine in mice infected with *P. falciparum*, showed that the parasites' food vacuoles

swelled with gradual loss of pigment granules when treated with mefloquine, indicating that the parasites' food vacuoles are the drug target.[32] However, mefloquine was shown to have relatively weak interactions with heme[33] and too low of a basicity to change the pH in the food vacuole, making it unlikely that mefloquine would reach the intravacuolar concentration required to inhibit heme polymerization. Furthermore, a late study showed that mefloquine had no effect on hemozoin production of *P. berghei* infected mice.[11] When a photoaffinity-labeling technique was used to identify mefloquine-binding proteins, two proteins with apparent molecular masses of 22 and 36 kDa were found in three different strains of *P. falciparum.* They may be involved in the uptake of mefloquine or may represent macromolecular targets of mefloquine action in the parasites.[34] The identities of these two polypeptides have not yet been established, and the detailed mechanism of action of mefloquine is still unclear.

1.3.2 Adverse effects

Mefloquine's neuropsychiatric adverse effects range from anxiety and paranoia to depression, hallucinations and suicide.[35] The incidence of adverse neuropsychiatric effects in malarial treatment users is 1:215 and 1:13,000 for chemoprophylactic users.[36] One explanation for these undesirable events is the ability of mefloquine to interact and modulate the function of human P-glycoprotein.[37] P-glycoprotein is thought to have a physiological role in regulating the entry of certain molecules into the central nervous system, especially as a detoxifier at the blood-brain barrier.[38] One recent study in 89 healthy white travelers showed that neuropsychiatric adverse effects of mefloquine are associated with polymorphisms in the MDR1/ABCB1 gene that encodes the efflux pump P-glycoprotein in women.[39] The inhibitory effect of mefloquine on human P-glycoprotein could allow the drug to cross the blood-brain barrier and accumulate in

the central nervous system to exert the neurotoxic effect. Despite the relatively high frequency of adverse effects compared with other antimalarial drugs, mefloquine continues to be used due to the absence of effective alternatives. In order to ameliorate the neurotoxicity profile of the drug, we set out to develop analogs that are less readily absorbed through the blood-brain barrier but retain the antimalarial efficacy of the 4-quinolinecarbinolamine scaffold.

1.3.3 Miscellaneous

To aid in the efficient design of the 4-quinolinecarbinolamine antimalarial drugs, a detailed computational study on a series of compounds in this class was performed using the semiempirical Austin model 1 (AM1) to correlate the electronic features with the antimalarial activity.[40] This investigation shows that the large, broad, laterally extended negative potential region adjacent to the quinoline ring would be expected to increase the lipophilicity of the molecule because of high electron density and consequent hydrophobicity in the region. In order to modulate the electron density, electron-withdrawing groups such as CF_3, F or Cl should be placed at both the 2- and 8- positions of the quinoline ring. Our first strategy for generating new analogs was the replacment of the CF_3 group with another highly electron withdrawing group.

Aside from electronic properties, the stereochemistry of mefloquine plays an important role in its biological activities. The enantiomer (+)-(11*R*,2'*S*)-mefloquine showed a significantly lower incident of side effects in comparison to the (-)-enantiomer in a study of the behavioral effects in mice dosed daily with the two enantiomers.[41] This study also demonstrated that the (-)-enantiomer is a selective ligand for the adenosine A_{2A} receptor subtype *in vitro*, whereas the binding of the (+)-enantiomer is over two orders of magnitude weaker. These data lead to the conclusion that treating or preventing malaria with the (+)-enantiomer of mefloquine may be

effective in reducing the side effects. This result prompted us to separate the two enantiomers and test the efficacy of (+)-enantiomers separately.

2.0 INTRODUCTION OF THE PENTAFLUOROSULFANYL GROUP

The pentafluorosulfanyl (SF_5) group is an organic derivative of the hypervalent molecule sulfur hexafluoride (SF_6). Due to its kinetic stability, SF_6 is not a useful reagent in chemical reactions; nucleophilic attack on SF_6 has a high activation energy due to steric hindrance. Therefore, the SF_5 group is an important derivative for investigating the special features of these hypervalent moieties. The total number of well-characterized R-SF_5 compounds is already quite large, but there are only limited and difficult routes for the preparation of this special functional group.

2.1 PHYSICAL CHEMISTRY OF ORGANIC SF_5 COMPOUNDS

The SF_5 group has special properties due to its octahedral geometry and five electron-withdrawing fluorine atoms. Its properties can be compared with the CF_3 group, which is a common functional group in biologically active compounds.

2.1.1 X-ray structure

The structure of the SF_5 group is characteristic of the octahedral environment around sulfur, as shown in the X-ray structure of 3-(pentafluorosulfanyl)benzoic acid (Figure 3).[42] The

sixth coordination site for the center sulfur atom is occupied by the phenyl carbon with the equatorial fluorine atoms staggered to the flat benzene moiety to be energetically favorable. The bond length of the S-F_{ax} bond (1.587(3) Å) is slightly longer than that of the S-F_{eq} bond (1.561(4) Å), and the C-S bond distance is 1.804(2) Å. Both bond angles of F_{ax}-S-F_{eq} (87.6(3)˚, average) and F_{eq}-S-F_{eq} (90.9(3)˚, average) are comparable to those of other SF_5 analogs, and all of them are close to 90˚.[43]

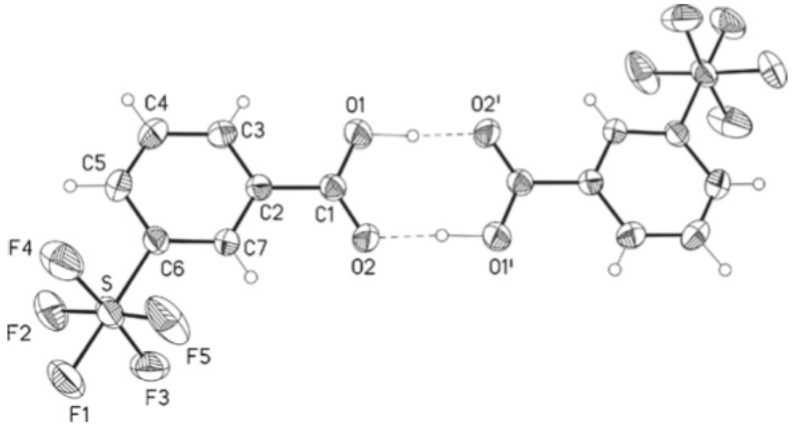


Figure 3 X-ray structure of 3-(pentafluorosulfanyl)benzoic acid

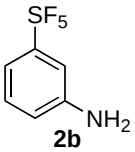
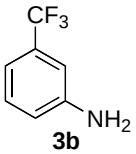
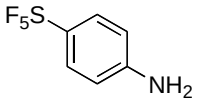
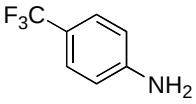
2.1.2 Steric hindrance

The rigidity of the bonds within the SF_5 group is characteristic of a bulky group. The S-C-S bond angle in F_5S-CH_2-SF_5 is 126.1(8)˚ while the central C-C-C angle in di-*t*-butylmethane is 128˚.[44] For comparison, F_3C-CFI-CF_3 has a C-C-C angle of 113.2˚, which is smaller than the two angles above, but the influence of the large iodine atom should be considered.[45] The relative steric demand of the SF_5 group is similar to that of a *tert*-butyl group and therefore significantly greater than that of a CF_3 group.

2.1.3 Electronic properties

The electronegativity of the SF_5 group has been proposed to be as high as 3.65, vs 3.36 for the CF_3 group, according to the effects of the substituent on the carbon 1s ionization energies and the acidities of trifluoropropyne ($CF_3C{\equiv}CH$) and ethynylsulfur pentafluoride ($SF_5C{\equiv}CH$).[46] These data show that the electronegativity of SF_5 and CF_3 groups lies between fluorine and chlorine. In another study, the electronic effects of SF_5 and CF_3 groups on aniline are calculated by *ab inito* molecular orbital methods.[43] The electrostatic potential (ESP) surfaces in Table 1 demonstrate that the SF_5 group is more electron-withdrawing than the CF_3 group. The electrostatic potential on nitrogen is diminished considerably in SF_5-anilines **2a** and **2b,** and the molecular dipole increases upon exchange of a CF_3 group for an SF_5 group.

Table 1 Calculated (HF/6-31G(d)) properties of SF_5-anilines and the corresponding CF_3-anilines

structure	 **2b**	 **3b**	 **2a**	 **3a**
ESP_{min} $(NH_2)^a$	-11.1	-33.8	-8.23	-12.5
Dipole (D)	5.22	3.70	6.27	4.87

[a] Minimum value (in kcal) of the electrostatic potential surface centered on the nitrogen atom of the amino group

2.1.4 Chemical stability

Due to the strength ($D_0°(F_4S\text{-}F) = 53.1 \pm 6.0$ kcal/mol)[47] and rigidity of the S-F bond, the SF_5 group is considered stable under a variety of chemical conditions. In the first paper reporting the synthesis of aryl sulfur pentafluoride, the stability of phenylsulfur pentafluoride ($Ph\text{-}SF_5$) was investigated.[48] When the compound was subjected to a 1.0 N NaOH solution at 94 °C for 4 h, no

fluoride ion was detected. In sulfuric acid (98 - 100%), the compound started to decompose to form benzenesulfonyl fluoride only after the temperature went up to 100 °C. In a control hydrolysis of benzotrifluoride (Ph-CF_3) under the same acidic conditions, it was found that the benzotrifluoride was hydrolyzed at 90 °C in less than 5 min.

Another recent study of hydrolysis of SF_5-anilines also demonstrated that the SF_5 group exhibits higher chemical resistance than the CF_3 group. The study indicated that in a 2.0 N NaOH solution at room temerature, 4-CF_3-aniline **3a** readily hydrolyzed whereas 4-SF_5-aniline **2a** was recovered in high yield (91%).[43]

2.2 PREPARATION OF PENTAFLUOROSULFANYL COMPOUNDS

Despite their origins dating back half a century, only a limited number of pentafluorosulfanyl compounds have been prepared, mainly due to the difficulty of preparation and the small amount of commercially available SF_5 building blocks.

2.2.1 First organic SF_5 derivative

The first organic SF_5 compound was an unexpected product in the attempted preparation of trifluoromethyl mercaptan (CF_3SF_5) (eq 1). Under the harsh conditions with cobalt trifluoride at more than 200 °C, the novel trifluoromethylsulfur pentafluoride (CF_3SF_5) was detected in 20% yield (eq 1).[5] The attractive properties of this novel substituent, such as its chemical inertness and its electron demand, sparked an interest for further study.

$$CH_3SH \xrightarrow[250 - 275\ °C]{CoF_3,\ Cu} \underset{20\%}{CF_3SF_5} + CF_4 + CHF_3 + SF_6 \qquad (1)$$

2.2.2 Preparation of aliphatic SF_5 compounds

The oldest and most common way to add the SF_5 group to an aliphatic chain is vigorous fluorination of a sulfur-containing precursor. When pentafluorosulfanyl chloride (SF_5Cl) became more readily available, it turned into the main reagent for incorporation of the SF_5 group and has been used since the 1960s. Recently, a growing number of chemical companies have started to sell SF_5 building blocks, and using commercially available materials has become more feasible.

2.2.2.1 Vigorous fluorination

Vigorous fluorination was the first reported method to generate the SF_5 group. It requires the harsh conditions, resulting in many side products and low yields. The common conditions are the use of hydrogen fluoride with a Simons Cell (eq 2) and elemental fluorine in nitrogen (eq 3). In these environments, the sulfur atom on the substrate undergoes the maximum fluorination and forms the stable SF_5 group.[49, 50]

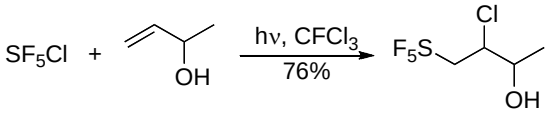
$$[(CH_3CH_2)NCH_2CH_2S]_2 \xrightarrow[13\%]{HF,\ Simons\ Cell} (CF_3CF_2)NCF_2CF_2SF_5 \qquad (2)$$

$$SF_3CN \xrightarrow[-120\ °C,\ 10\%]{F_2/N_2\ (1:10)} SF_5CN \qquad (3)$$

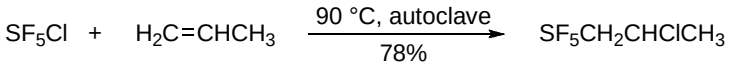
2.2.2.2 Radical reactions of SF_5Cl and SF_5Br

Radical reactions of SF_5Cl and SF_5Br allow for the selective introduction of the SF_5 group at unsaturated carbons and generally result in much higher yields than vigorous

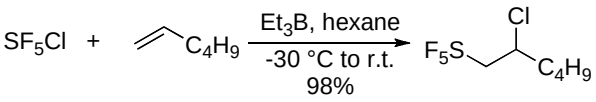
fluorination methods. Photochemical[51] (eq 4), thermal[52] (eq 5) and radical initiated[53] (eq 6) additions are applied and specialized conditions are required for different substrates.



(4)



(5)



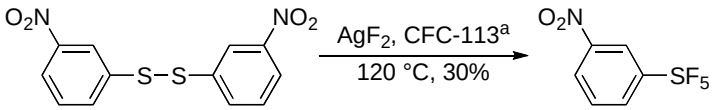
(6)

2.2.3 Preparation of aromatic SF_5 compounds

To date, only a limited amount of aromatic pentafluorosulfanes have been prepared, although the first aromatic SF_5 compound was synthesized more than half a century ago.[48] Oxidative fluorination of bis-nitrophenyl disulfide under harsh conditions is still the generally preferred procedure. All improved routes involve expensive silver difluoride or dangerous elemental fluorine, and there is still a considerable need for practical synthetic routes.

2.2.3.1 First aromatic SF_5 compounds

The first aromatic SF_5 compounds were reported by Sheppard in 1962 (eq 7 and 8) and their electrical effects were studied shortly after.[48,54] The synthesis was accomplished by the reaction of bis-nitrophenyl disulfide with silver difluoride at 120 °C. The *meta*- and *para*-nitrophenylsulfur pentafluorides were successfully prepared in low yields (eq 7 and 8). In contrast, the corresponding *ortho*-nitro product was not formed from the *ortho*-nitrophenyl disulfide, presumably due to the steric hindrance from the *ortho*-nitro group preventing further fluorination of the triflurosulfanyl (SF_3) intermediate to give the SF_5 moiety.



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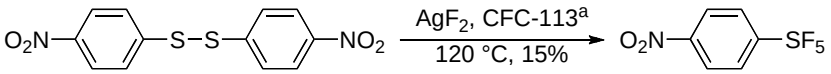
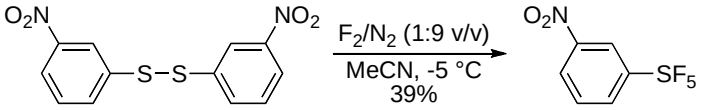


(8)

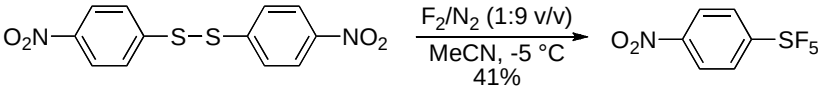
[a] CFC-113: 1,1,2-trichloro-1,2,2-trifluoroethane

2.2.3.2 Direct fluorination

Recently, direct fluorination of bis-nitrophenyl disulfide by a mixture of F_2 and N_2 gas (1:9 v/v) in anhydrous acetonitrile was developed as a new method with higher yields and cheaper reagents (eq 9 and 10).[43] This procedure has been successfully applied to the preparation of multi-kilogram quantities of *m*- and *p*-SF_5-benzenes (eq 9 and 10), but it could not be applied to the *ortho*-substituted starting materials, which gave only the intermediate trifluorosulfanyl compounds as major products.



(9)



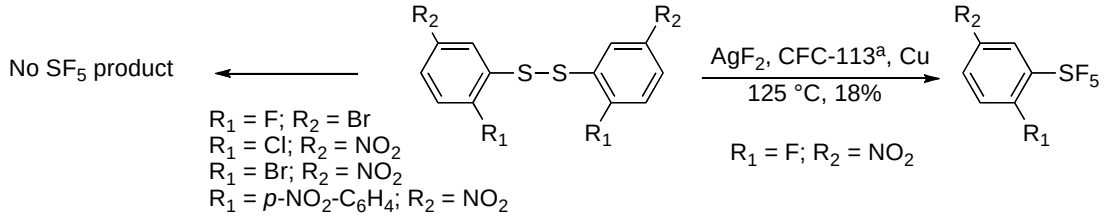
(10)

2.2.3.3 Improved AgF_2 fluorination to prepare the first *ortho*-SF_5 arenes

The only diphenyl disulfur substrate containing an *ortho*-substituent suitable for direct fluorination is the bis-*ortho*-fluorodiphenyl disulfide.[55] This substrate was converted to the *ortho*-fluoro-SF_5-benzene by AgF_2 with copper at high temperature. Although the yield is low (18%), this route is the only reported example of fluorination of a disulfide bond to yield an SF_5 arene with an *ortho*-substituent (Scheme 1). The success on this substrate is due to the small size of the *ortho*-fluoride atom to avoid steric hindrance and the electron-withdrawing nitro group. Combinations of other functional groups gave no SF_5-containing products. The fluoride

substituent can subsequently be converted to other functional groups, such as the amino group and the ethoxy group (Scheme 3).

Scheme 1 First synthesis of the *ortho*-substituted SF_5-benzenes

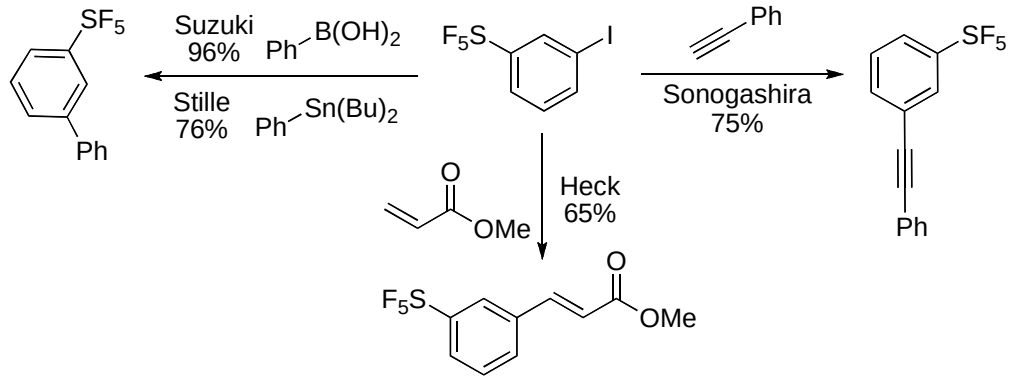


[a] CFC-113: 1,1,2-trichloro-1,2,2-trifluoroethane

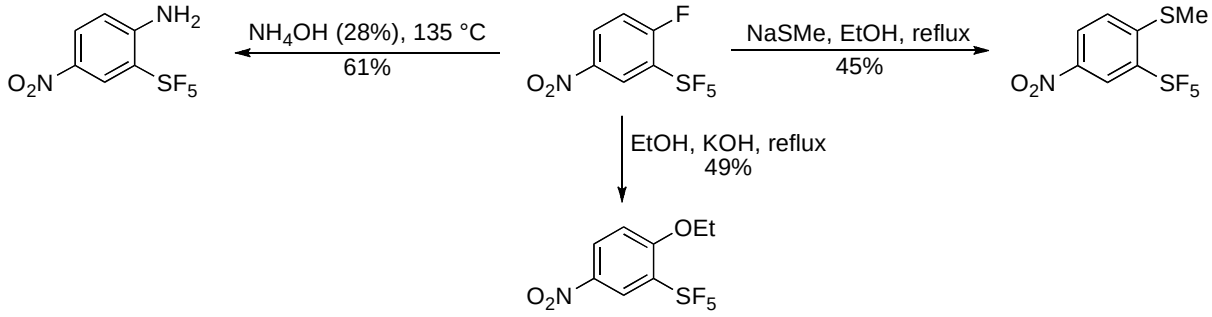
2.2.3.4 Transformations of SF_5 arene building blocks

There are a few commercially available *m*- and *p*-substituted SF_5 aromatic building blocks, and their chemical inertness allows a variety of transformations, such as organometallic coupling[43] (Scheme 2) and nucleophilic aromatic substitution reactions[55] (Scheme 3).

Scheme 2 Organometallic coupling of the SF_5 aryl iodide



Scheme 3 Nucleophilic aromatic substitution of the *ortho*-SF_5 fluorobenzene



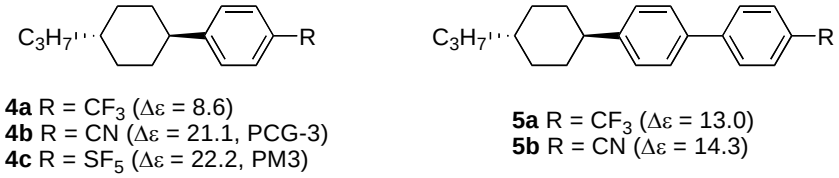
2.3 APPLICATIONS OF SF_5 COMPOUNDS

Because of the similar structure and electronic properties of the SF_5 and CF_3 groups, the novel SF_5 substituent is often used as a CF_3 replacement. Compounds containing an SF_5 group have shown useful properties ranging from liquid crystals to pesticides to pharmaceutical agents.

2.3.1 Liquid crystals

Since the 1980s, the SF_5 group has been the subject of preliminary investigations in some liquid crystal research groups due to its high polarity and stability. It's the most polar terminal group that is compatible with active matrix technology and induces a high dielectric anisotropy ($\Delta\varepsilon$). Regarding the liquid crystals in Figure 4, the current limit for compatible materials is achieved with the trifluoromethyl group (**4a**, $\Delta\varepsilon$ = 8.6). Unfortunately, the much more polar materials based on a terminal cyano group (**4b**, $\Delta\varepsilon$ = 21.1, PCG-3) cannot be used since the cyano group tends to solvate ionic impurities, resulting in a low voltage holding ratio.[56] To further increase the $\Delta\varepsilon$ of these materials, the quite polar SF_5 group was introduced to replace the

CF_3 group and a PM3 calculation on **4c** gave aΔ ε value of 22.2.[56] This result predicted a considerable potential of the SF_5 group as a structural component. In a later study, the SF_5-containing compound **5b** showed a higher Δε (14.3) than its CF_3 congener **5a** (Δε = 13.0).[57]



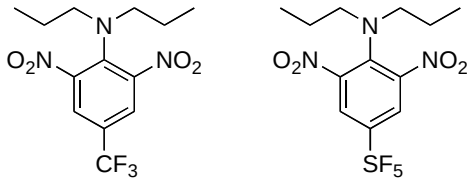
4a R = CF_3 (Δε = 8.6)
4b R = CN (Δε = 21.1, PCG-3)
4c R = SF_5 (Δε = 22.2, PM3)

5a R = CF_3 (Δε = 13.0)
5b R = CN (Δε = 14.3)

Figure 4 Dielectric anisotropies of liquid crystals with fluorinated and cyanated groups

2.3.2 Pesticides

Many pesticides contain CF_3 groups, and the emergence of the SF_5 group inspired the site-to-site replacement studies on these biologically active compounds. Trifluralin (2, 6-dinitro-*N*,*N*-dipropyl-4-trifluoromethylaniline, **6a**, Figure 5) is one of the top five herbicides produced in the US, and it was chosen as the parent compound to study the biological effects of the replacement of the CF_3 group with the SF_5 group. The SF_5 analog **6b** was synthesized from commercially available *p*-nitro-SF_5-benzene, and it was found to be approximately twice as potent as trifluralin with the same general spectrum of activity. Furthermore, in pre-emergence tests, the herbicidal activity of **6b**, in terms of crop injury and weed control, is nearly five fold greater than the parent agent **6a**.[58]

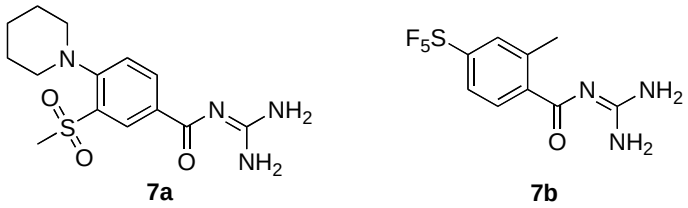


Trifluralin **6a** **6b**

Figure 5 Trifluralin and its SF_5 analog

2.3.3 Pharmaceutical agents

The application of the SF_5 group in pharmaceutical agents is slowly emerging, and there are a significant number of patents covering this topic. The investigation of inhibitors for sodium-proton exchanger (NHE) involves the synthesis of SF_5-containing compounds. The first class of inhibitors include benzoylguanidine compound HOE 694 (**7a**), in which the guanidinium component mimics the sodium ion to block membrane transport (Figure 6). Further studies demonstrated that the activity might be enhanced by a lipophilic, bulky group at the 4-position of the benzene ring. Thus, the SF_5 was installed in that position to arrive at analog **7b**. The latter agent demonstrated improved bioavailability and half-life *in vivo* in comparison to other NHE inhibitors.[59]



7a **7b**

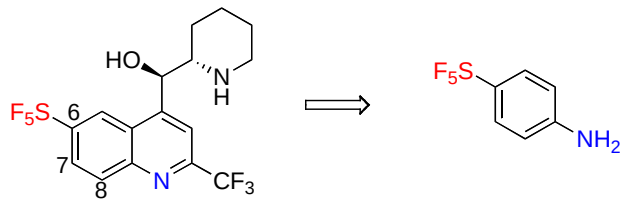
Figure 6 Benzoylguanidine NHE inhibitors

3.0 RESULTS AND DISCUSSION

In this study, we seek to modify the quinoline methanol scaffold with the SF_5 functional group to yield derivatives that exhibit fewer adverse neurological effects while retaining their antimalarial efficacy.

3.1 SYNTHESIS OF THE 6-SF_5-QUINOLYL MEFLOQUINE ANALOG

Because installation of the SF_5 group demands harsh conditions and is low yielding, we began our study using commercially available SF_5 building blocks. Presumably, one of the accessible aromatic building blocks, 4-SF_5-aniline (**2a**), would be a suitable staring material for the 6-SF_5-quinolyl mefloquine analog **8a** (Figure 7).



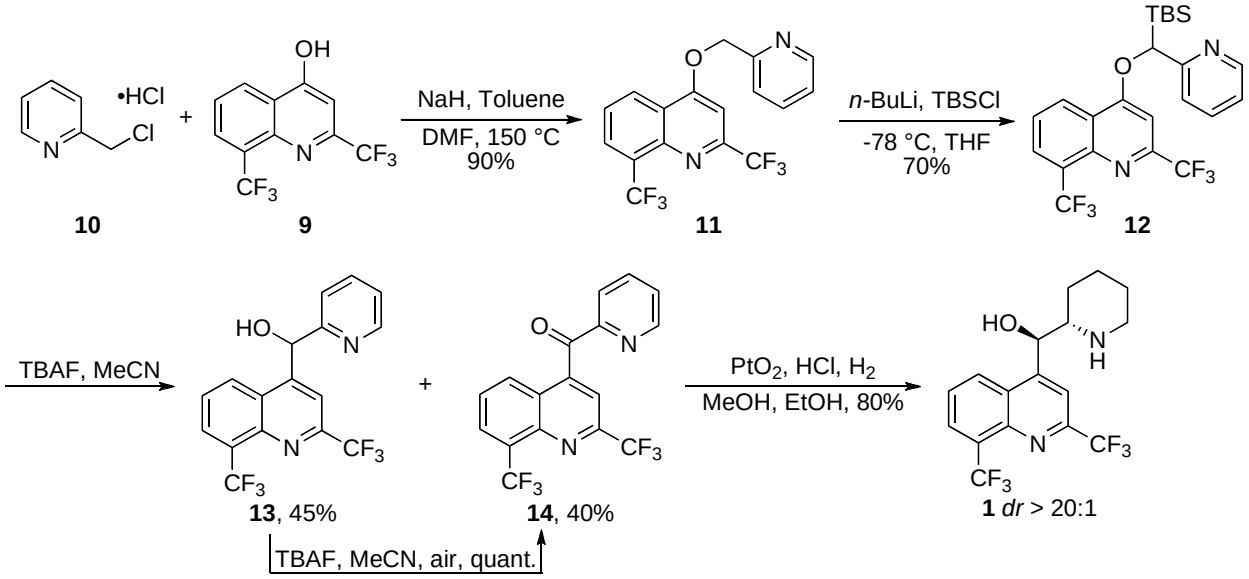
6-SF_5-quinolyl analog (**8a**) 4-SF_5-aniline (**2a**)

Figure 7 The starting material chosen for the synthesis of the 6-SF_5 analog of mefloquine

3.1.1 Fluoride ion-catalyzed Wittig rearrangement route

The first synthesis of mefloquine was published in 1971,[60] and several other routes have been developed since then.[61] At first, an expedient and high yielding synthesis of mefloquine via a fluoride ion-catalyzed Wittig-[1,2]-rearrangement was selected as the route to access compound **8a**.[62] This is the first example of a fluoride ion catalyzed Wittig rearrangement. This synthesis is summarized in Scheme 4.

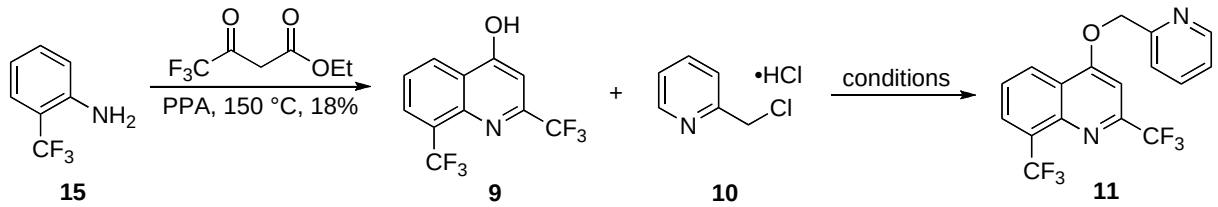
Scheme 4 Reported synthesis of mefloquine through fluoride ion catalyzed Wittig rearrangement



Prior to the use of the SF_5 substrate, we first attempted to reproduce these results. The hydroxyquinoline **9** was synthesized from 2-trifluoromethyl aniline (Table 2) through a Conrad-Limpach reaction with ethyl 4,4,4-trifluoroacetoacetate in the presence of polyphosphoric acid. Although the yield was low (18%), the reaction afforded enough material to attempt the next step formation of aryl ether **11**. The ratio of the two solvents toluene and DMF was not mentioned in the previous example so we explored the suitable conditions. Starting with a 1:1 ratio of DMF/toluene and changing it to 1:10 and neat toluene, all conditions gave no comparable yields

as in the paper. However, milder reaction conditions using KI as a catalyst with Na_2CO_3 in DMF were found to give aryl ether **11** in good yield (88%).

Table 2 Conditions for the synthesis of aryl ether **11**



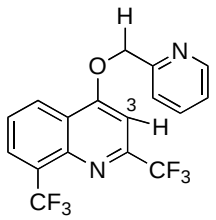
entry	solvent	Temp. (°C)	base (equiv)	catalyst	time (h)	results
1	1:1 (DMF/toluene)	110	NaH (2.2)	none	18	**9** + **11**[a]
2	1:10 (DMF/toluene)	110	NaH (2.7)	none	15	**11** (31%)[b]
3	toluene	110	NaH (3.2)	none	8	**11** (4%)[b]
4	DMF	80	Na_2CO_3 (3.8)	KI (0.15 equiv)	3	**11** (88%)[b]

[a] TLC showed both **9** and **11** after 18 h.
[b] These are isolated yields.

The next step was the key fluoride ion-catalyzed rearrangement. The important features of the Wittig-[1,2]-rearrangement are: a) the substituent at the ether oxygen has to be able to stabilize the carbanion, b) yields are usually moderate due to the harsh reaction conditions and c) a [1,4]-pathway can compete.[63] Based on the literature example, aryl ether **11** should be a suitable substrate for the conversion to arylcarbinol **13**. However, the author mentioned that treatment with strong bases, such as phenyl lithium, *n*-butyl lithium or sodium amide at varying temperatures gave only decomposition and tar products.[62] This result prompted the author to prepare a substrate that would lead to a more stabilized carbanion intermediate. The trialkylsilyl moiety acts as a protected carbanion[64] that may be easily unmasked with catalytic amounts of fluoride ion, and introduction of a trialkyl silyl substituent onto **11** ought to facilitate the rearrangement. The substrate **11** was deprotonated with *n*-butyl lithium and then trapped by TBSCl to form compound **12**. The TBS group was removed using TBAF in MeCN and the

resulting carbanion underwent the rearrangement smoothly to give the desired product **13** (45%) and its oxidized form **14** (40%).

When we applied the reported conditions to form organosilicon compound **12**, no desired product was detected. To investigate the feasibility of the deprotonation, the carbanion was trapped with deuterated methanol. According to the integrations of ^{1}H NMR, when 1.1 equiv of *s*-BuLi was used, 20% of both protons on the methylene and 3-position methine (Figure 8) were exchanged with deuterium. 30% of the protons were exchanged while 2.0 equiv of base was used. Due to these results, the acidities of these two protons are similar. Thus, two equivalents of base are required for complete deprotonation on the methylene and subsequent formation of organosilicon compound **12**.

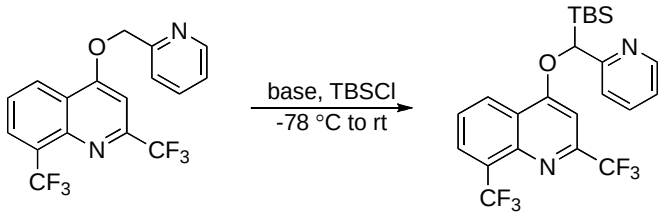


11

Figure 8 Deprotonation substrate **11**

We screened several bases in THF and toluene at -78 °C (Table 3). Most of these conditions led to decomposition or recovered starting material. Only *n*-butyl lithium (3.0 equiv) in toluene (entry 8) provided a mixture of product and starting material. However, attempts to push the reaction to completion through increasing the equivalents of base resulted in decomposition and gave complex mixtures.

Table 3 Conditions screened for preparation of Wittig rearrangement precursor

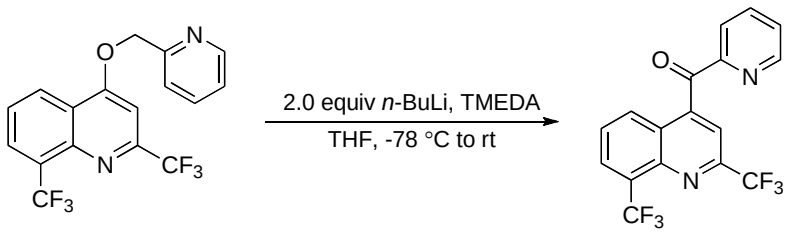


11 **12**

entry	base (equiv)	solvent	results[a]
1	n-BuLi (2.0)	THF	dec.
2	*s*-BuLi (2.0)	THF	**11** (64%)
3	LDA (2.0)	THF	**11** (13%)
4	*t*-BuOK/*n*-BuLi (2.0)	THF	dec.
5	$LiNEt_2$ (2.0)	THF	dec.
6	LiHMDS (2.0)	THF	dec.
7	*n*-BuLi (2.0)	toluene	**11** (30%)
8	*n*-BuLi (3.0)	toluene	**12** (21%) and **11** (25%)
9	*n*-BuLi (4.0)	toluene	dec.

[a] The starting material and product are isolated after reaction.

Direct Wittig-[1,2]-rearrangement to give product **14** was observed when TMEDA was used to increase the reactivity of *n*-butyl lithium (eq 11).[65] This observation was made on a reaction scale of 15 mg, and the product was identified as the ketone **14** from the oxidation of the alcohol precursor **13**.

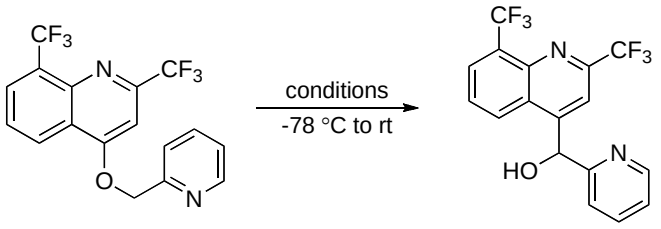


(11)

11 **14**

Inspired by this observation, we carried out an optimization of the base, additive, and solvent, and selected conditions are listed in Table 4. The best results were obtained using LiTMP (1.0 equiv) and *n*-butyl lithium (1.0 equiv) in THF to provide product **13** in 43% yield.[66]

Table 4 Conditions screened for direct Wittig rearrangement



11 **13**

entry	base (equiv)	additive	solvent	results
1	*n*-BuLi (1.2)	TMEDA	Et_2O	**11**[a]
2	*n*-BuLi (2.0)	TMEDA	Et_2O	**13** (30%)[b]
3	n-BuLi (1.2)	DMPU	THF	dec.
4	*n*-BuLi (2.0)	DMPU	THF	dec.
5	LiTMP/*n*-BuLi (1.0)	none	THF	**13** (43%)[b]
6	LiTMP/n-BuLi (2.0)	none	THF	dec.

[a] TLC showed starting material **11** as the main spot.
[b] These are isolated yields.

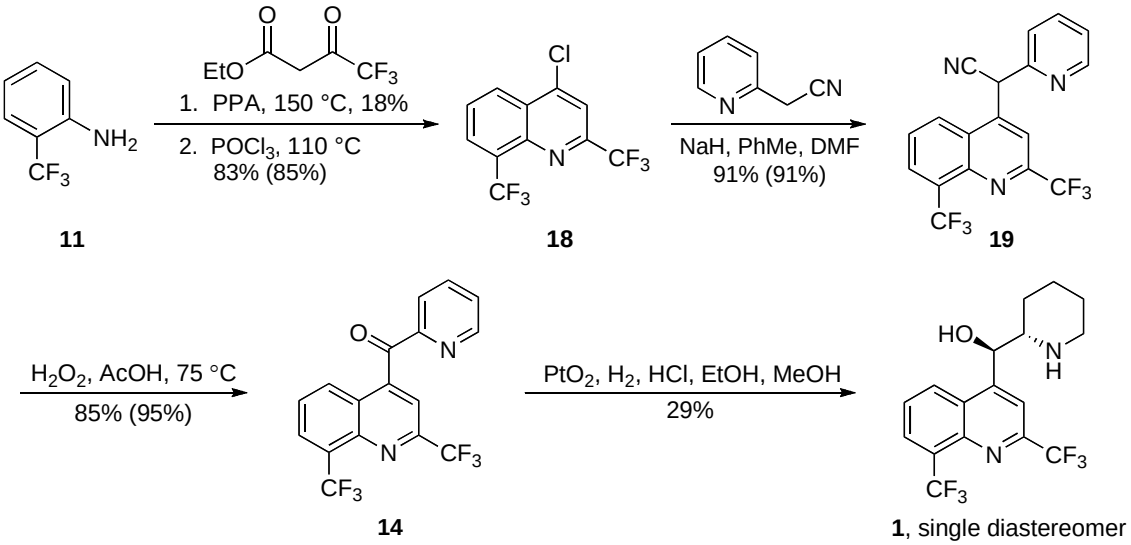
The Wittig-[1,2]-rearrangement step was not scalable (only up to a 60 mg reaction scale), and therefore limited the utility of this route. At this point, we decided to explore other routes for mefloquine synthesis.

3.1.2 Oxidative decyanation route

A few years after the Wittig rearrangement approach to mefloquine, a straightforward and high yielding synthesis based on the oxidative decyanation of a secondary aryl nitrile was reported.[67] We selected this route to access the 6-SF_5 analog **8a**. To examine the feasibility of this chemistry, the sequence was followed to synthesize mefloquine, and most reactions afforded comparable results as reported in the literature (Scheme 5).[67] After cyclization to form the hydroxyquinoline **9** under acidic conditions, the hydroxyl group was converted to the chloride using phosphorus oxychloride at 110 °C. Subsequent nucleophilic aromatic substitution by the 2-

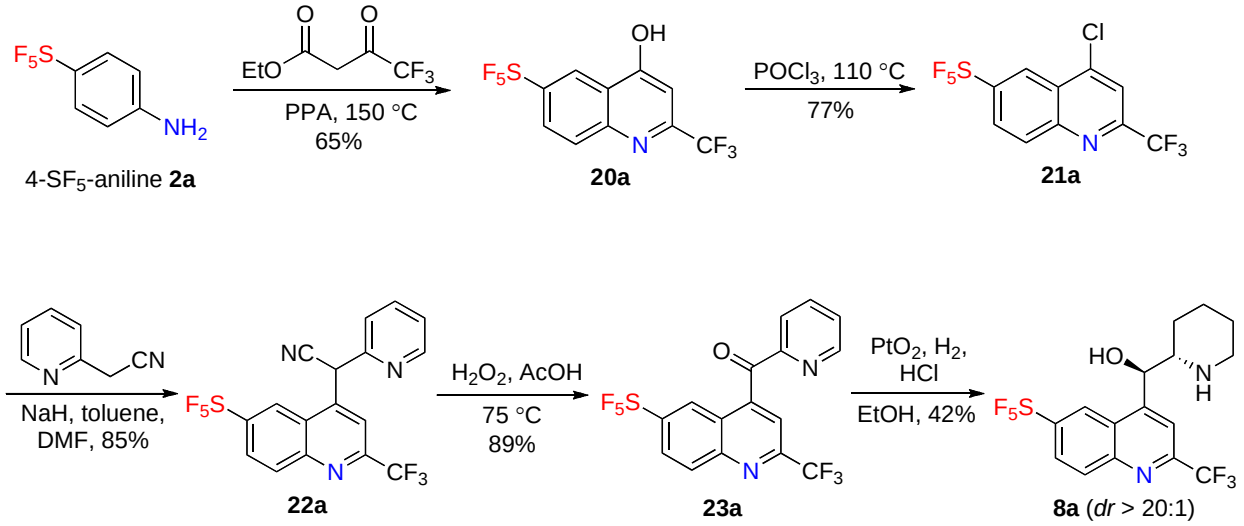
pyridylacetonitrile carbanion to the quinolyl chloride provided **19** in 91% yield. The desired aryl ketone **14** was obtained in 85% yield by oxidation with hydrogen peroxide under acidic conditions, and subsequent hydrogenation afforded mefloquine as a single *anti*-diastereomer.

Scheme 5 A straightforward and high yielding synthesis of mefloquine. Literature yields are in the parentheses.



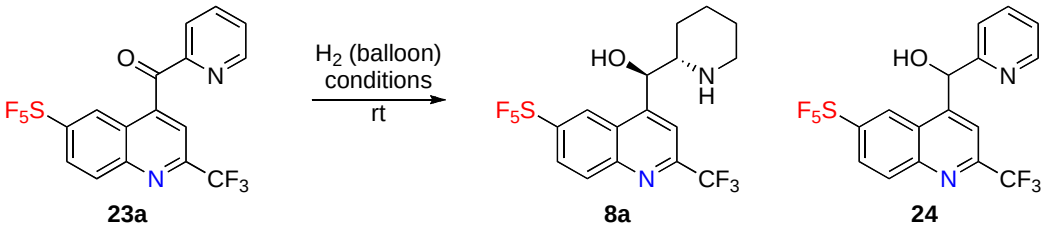
Because the reactions in this route were reproducible and scalable using the CF_3 substrate, we decided to apply an analogous sequence for the SF_5 building block to access the 6-SF_5 analog (Scheme 6). Condensation of the commercially available **2a** and ethyl 4,4,4-trifluoroacetoacetate in the presence of polyphosphoric acid led to 4-hydroxyquinoline **20a**, which represents the first reported SF_5-substituted quinoline compound. Chlorination with phosphorus oxychloride provided the corresponding 4-chloroquinoline **21a** in good yields. Subsequent nucleophilic aromatic substitution by the 2-pyridylacetonitrile carbanion afforded the secondary nitrile **22a**. Exposure to a mixture of hydrogen peroxide and acetic acid at 75 °C then provided the decyanated 4-quinolylketone **23a**.

Scheme 6 Synthesis of 6-SF_5 mefloquine analog **8a**



The concomitant reduction of the carbonyl and pyridyl groups in the presence of the quinoline ring was achieved using catalytic hydrogenation under acidic conditions (Table 5). This step of the synthesis proved to be problematic. The main side reaction is over-reduction of the quinoline moiety. In entry 1, the major compound isolated after the reaction showed M + 2 ion peak in MS analysis. When the less active catalyst palladium on carbon was used, only the ketone was reduced and the alcohol **24** was isolated with 50% yield. This intermediate showed up on TLC immediately in the reaction catalyzed by platinum oxide and disappeared while the desired product **8a** was formed. After screening different solvents, acids, and catalysts, optimal conditions for substrate **23a** were found to be 0.4 equivalent of platinum oxide in ethanol containing hydrochloric acid, followed by recrystallization of crude **8a** in MeOH (Table 5). After recystallization, **8a** was obtained as one predominating diastereomer (*dr* > 20:1).

Table 5 Conditions screened for selective reduction of **23a**

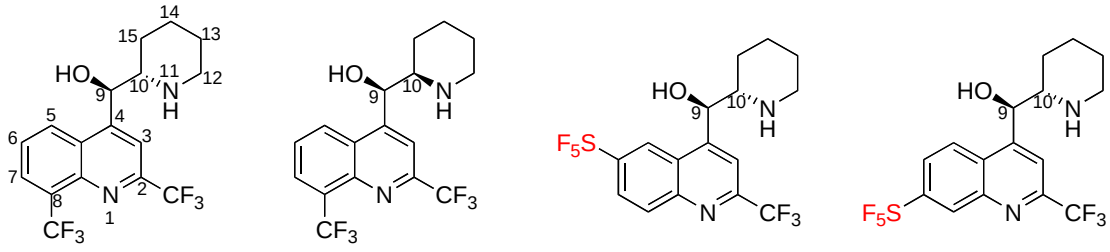


23a **8a** **24**

entry	catalyst (%)	acid (equiv)	solvent	time (h)	results
1	PtO_2 (20)	HCl (1.2)	EtOH/MeOH (1:1)	1.5	over-reduced[a]
2	Pd/C (3)	HCl (6.0)	EtOH	14	**24** (50%)[b]
3	PtO_2 (40)	AcOH (40)	EtOH	5.0	**8a** (25%)[b]
4	PtO_2 (40)	HCl (5.0)	EtOH	2.0	**8a** (42%)[b]

[a] The main compound after reaction was isolated and its MS was M(**8a**) + 2, detected by LC/MS .
[b] These are isolated yields.

This diastereomer was assigned to be *anti* according to the analysis of coupling constants in the ^{1}H NMR spectra. The *J* value of the 9-proton and 10-proton in mefloquine **1** is 6.0 Hz while it is 3.0 Hz in the *syn*-diastereomer **1a**.[68] For compound **8a**, the coupling constant is 4.8 Hz, which is closer to mefloquine than **1a**. Thus, compound **8a** was assigned as *anti* structure. Later X-ray crystallography study of 7-SF_5 analog **8b** (*J* = 4.8 Hz for 9-proton and 10-proton) confirmed the *anti* relative stereochemistry of these two chiral centers.

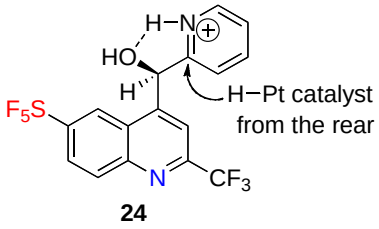


1 **1a** **8a** **8b**

Figure 9 Diastereomer of mefloquine and relative stereochemistry of **8a** and **8b**

The diastereoselectivity of this reduction reaction was thought to be caused by steric hindrance of the quinolyl group. Because alcohol **24** was observed on TLC as the intermediate between the ketone starting material **23a** and product **8a**, we assumed that in acidic conditions

the oxygen atom in **24** formed an hydrogen bond with the proton on the pyridinium nitrogen, and this locked conformation has the rear of the pyridine much more accessible than the front (Figure 10). Thus, the hydrogen absorbed on platinum catalyst approached the pyridine from the less hindered rear face to form the desired diastereomer.

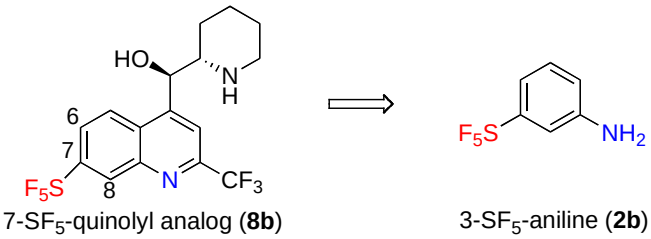


24

Figure 10 Possible mechanism of the diatereoselectivity of the reduction reaction

3.2 SYNTHESIS OF THE 7-SF_5 MEFLOQUINE ANALOG

Because the route for preparation of the 6-SF_5 analog was successful, we decided to follow the same synthetic sequence to prepare the 7-SF_5 analog **8b** from commercially available 3-SF_5-aniline (**2b**) (Figure 11).



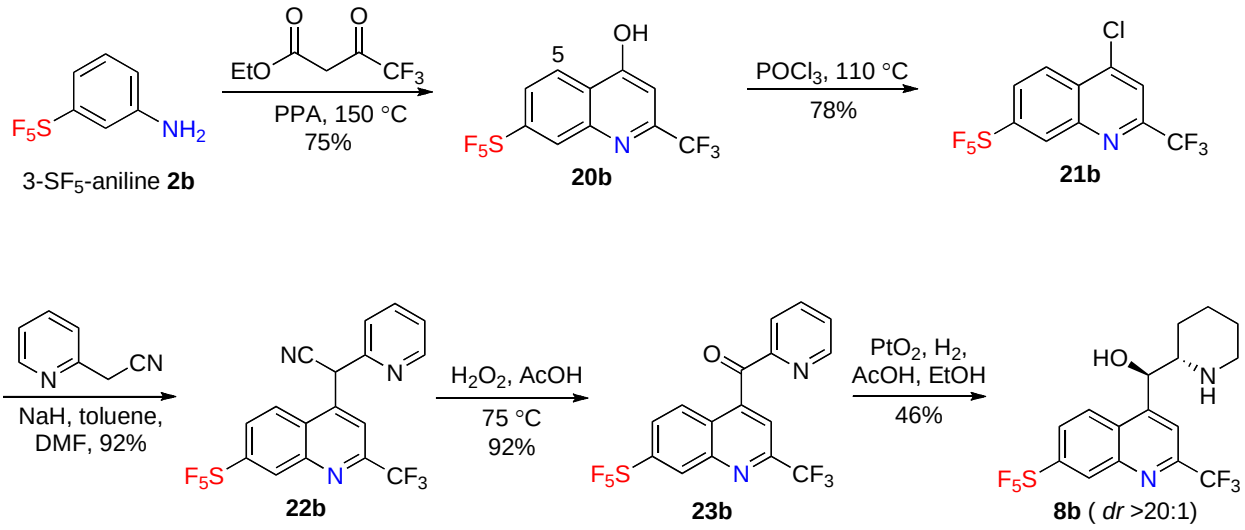
7-SF_5-quinolyl analog (**8b**) 3-SF_5-aniline (**2b**)

Figure 11 The starting material chosen for the synthesis of the 7-SF_5 analog

The Conrad-Limpach reaction of **2b** and ethyl 4,4,4-trifluoroacetoacetate provided exclusively the desired 4-hydroxy-7-SF_5-quinoline **20b** in 75% yield. The absence of the 5-SF_5-quinoline isomer is probably due to the large steric demand of the SF_5 group and/or electrostatic

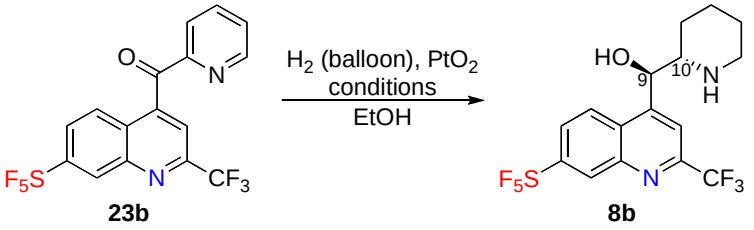
repulsion of the 4-hydroxy substituent. Subsequent chlorination, substitution and oxidation went smoothly, affording the desired products in good yields.

Scheme 7 Synthesis of the 7-SF_5 mefloquine analog **8b**



The selective reduction of **23b** demanded different conditions than its 6-SF_5 congener **23a**. 7-SF_5 analog **8b** was best obtained in the presence of milder acid (AcOH) as opposed to the use of hydrochloric acid (Table 6). The low yield in HCl conditions may be due to the over-reduction of the quinoline ring because HCl is strong enough to form the quinolinium ion and accelerate the reduction of the quinoline.

Table 6 Conditions screened for the selective reduction of **23b**



entry	PtO_2 (equiv)	acid (equiv)	time (h)	yield
1[a]	0.2	HCl (2.5)	0.5	22%
2	0.4	AcOH (60)	3.0	46%

[a] The starting material was subjected to PtO_2 (0.1 equiv), HCl (1.2 equiv) and EtOH/MeOH (1:1) conditions first. There was no desired product after 2 h and the reaction mixture was filtered and concentrated. The residue was then subjected to the conditions in the table.

Gratifyingly, the reduction was highly selective and afforded the desired *anti*-diastereomer. Furthermore, slow evaporation of a methanolic solution of **8b** provided needle-like crystals suitable for X-ray diffraction analysis (Figure 12). The sulfur atom of the SF_5 group is situated in an octahedral environment, and the disposition of the two stereocenters is *anti* as in mefloquine. The dihedral angle of H-C(9)-C(10)-H is 72°, which matches its *J* value (4.8 Hz) in the Karplus equation. Since the 6-SF_5 analog **8a** has the same coupling constant of these two protons, it is also assigned as the *anti*-diastereomer. The crystal system is monoclinic and its unit cell contains both enantiomers and two MeOH molecules.

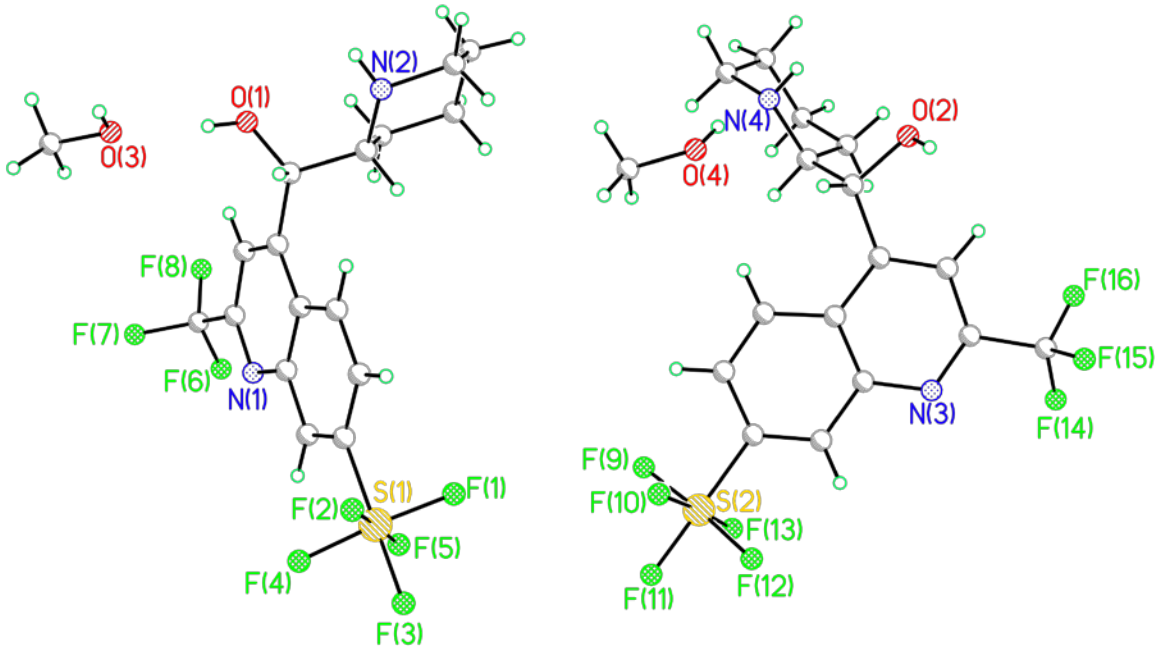


Figure 12 The unit cell of X-ray structure of **8b**

3.3 BIOLOGICAL EVALUATION OF ANALOGS 8a AND 8b

Biological data were collected by the Division of Experimental Therapeutics, Walter Reed Army Institute of Research. The antimalarial activities and selectivities of **8a** and **8b** were compared to those of mefloquine and mefloquine analogs in which the quinoline ring was substituted at the 6- and 7-positions with a trifluoromethyl group (**25** and **26**, Figure 13).

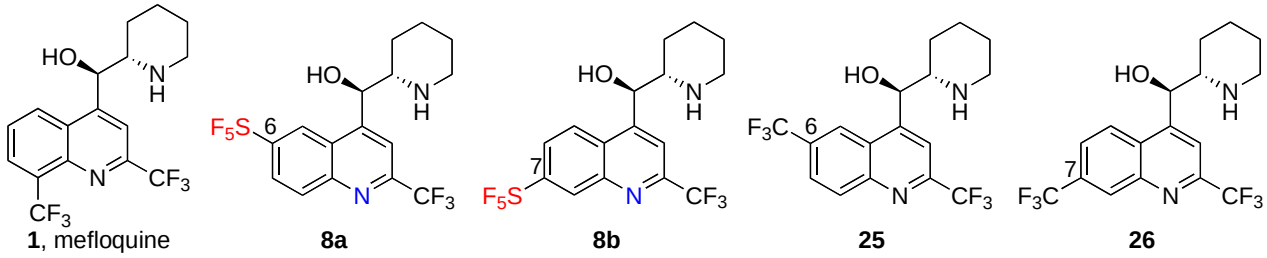


Figure 13 Structures of mefloquine and its analogs

The 50% and 90% inhibitory concentrations (IC_{50}s and IC_{90}s) against the chloroquine-resistant *P. falciparum* strain PfW2 and three mefloquine-resistant strains, PfD6, PfC235 and PfC2A, and the lethal concentration (LC_{50}s) against a mammalian cell line were determined as previously described (Table 7).[69]

Table 7 Antimalarial activity and toxicity of selected quinoline methanols. The units are ng/mL for IC_{50}, IC_{90} and LC_{50} data. The selectivity index (SI) is the ratio of the LC_{50} against RAW macrophages relative to the PfW2 IC_{50}.

analogs	Pf W2		Pf D6		Pf C235		Pf C2A		RAW	SI
	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}	LC_{50}	
1	2.5	9.8	8.0	20	18	63	22	87	5064	2026
8a	3.3	11	9.2	33	9.8	39	14	52	13740	4164
8b	3.3	13	12	45	12	47	16	80	ND	ND
25	5.0	16	17	67	53	140	21	130	ND	ND
26	3.0	17	12	37	30	86	13	60	ND	ND

The 6-SF_5 analog **8a** exhibited generally equivalent or lower IC_{50} and IC_{90} values, with greater selectivities than its CF_3-congener **25** and mefloquine. The IC_{50} and IC_{90} values of the 7-

SF_5 analog **8b** were generally equivalent to those of the CF_3-congener **26** and mefloquine. These data demonstrate the effective biological mimicry as well as the considerable pharmaceutical potential of substituting the CF_3 group with the SF_5 group in quinoline containing antimalarials.

3.4 SYNTHESIS OF THE 8-SF_5 MEFLOQUINE ANALOG

In the previous biological evaluation of mefloquine analogs, both 6- and 7-SF_5 analogs (**8a** and **8b**) exhibited better activity than their 6- and 7-CF_3-congeners (**25** and **26**). This encouraging finding demonstrated the effective biological mimicry of the CF_3-SF_5 switch in quinoline containing antimalarial drugs and prompted us to prepare the synthetically considerably more challenging 8-SF_5-congener **27** of mefloquine. According to the previous synthetic route, the target can be accessed from *ortho*-SF_5-aniline **28** (Figure 14).

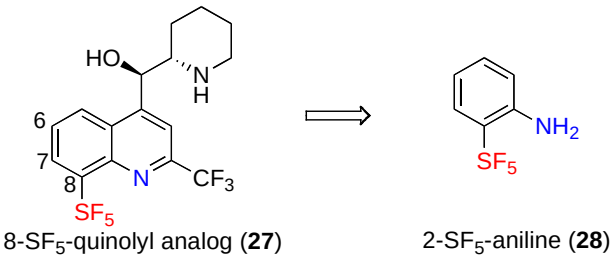
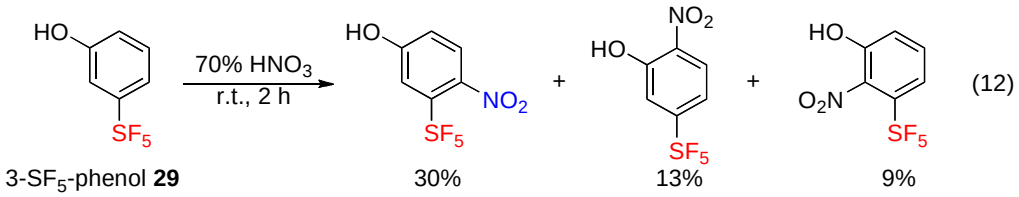


Figure 14 The starting material chosen for the synthesis of the 8-SF_5 analog

Given the absence of a practical, high-yielding method for installing the SF_5 group, there are still only a very limited number of SF_5-containing building blocks accessible. In the case of SF_5-arenes, oxidative fluorination of bis-nitrophenyl disulfide is still the generally preferred procedure. All improved routes involved expensive silver difluoride or highly dangerous fluorine gas, and the yields are generally low (<40%). Furthermore, the disulfide method is only applicable to a few substituted benzenes. In contrast to *meta*/*para*-nitro-SF_5-benzene, the

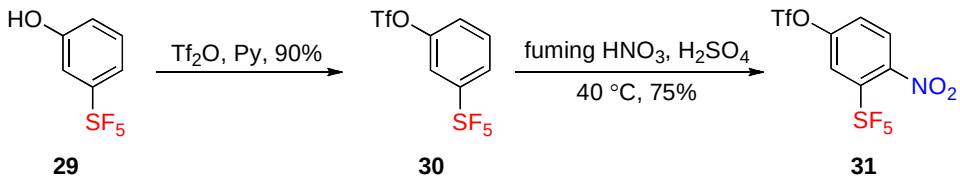
corresponding *ortho*-nitro product is not formed. To date, the only substrate containing an *ortho*-substituent suitable for direct fluorination is the bis-*ortho*-fluorodiphenyl disulfide. The desired starting material *ortho*-SF_5-aniline **28** has not been made before.

Because the disulfide fluorination conditions are dangerous, harsh, and low yielding, as well as unsuccessful for the preparation of the *ortho*-substituted SF_5 arene, we envisioned installing the *ortho*-amino group by regioselective nitration of a suitable pentafluorosulfanyl arene, followed by reduction.[70] Accordingly, we chose the commercially available 3-SF_5-phenol **29** as the nitration substrate because the strong electron-donating effect of the hydroxyl group should direct the nitro group to the *ortho*-position of the SF_5 moiety. However, the regioselectivity of the nitration of the phenol was poor, presumably because the hydroxyl group activates the benzene ring, resulting in the formation of all possible *ortho*/*para*-nitrated products (eq 12).

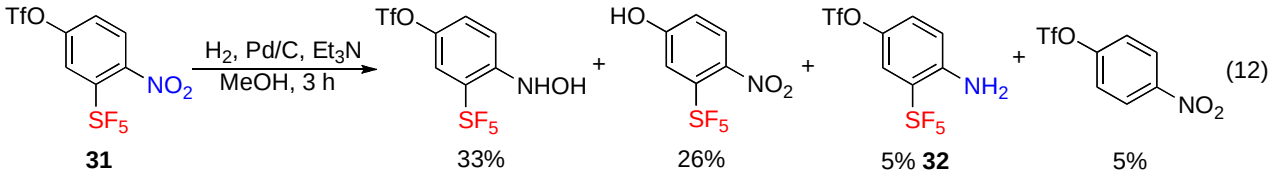


To diminish the strong *ortho*-directing effect, phenol **29** was converted to the less electron-donating trifluoromethane sulfonate **30** in 90% yield, and nitration now proceeded in 75% yield to give exclusively the desired *para*-nitrated product **31**, where the nitro group is placed *ortho* to the SF_5 group (Scheme 8).

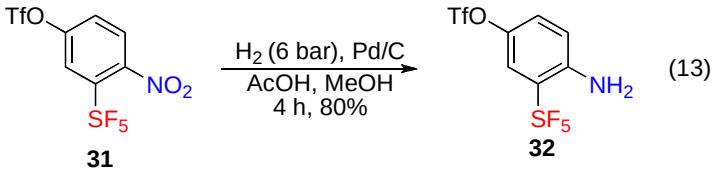
Scheme 8 Successful regioselective nitration to generate the *ortho*-nitro SF_5 benzene



We envisioned that the removal of the triflate group and the reduction of the nitro group could be achieved via a single step of hydrogenation catalyzed by palladium on carbon under basic conditions.[71] However, these hydrogenation conditions provided only mixtures with no desired product (eq 13). The only useful isolated compound was the 2-SF_5-(4-triflate)aniline **32**, which was obtained in 5% yield, but it decomposed soon after recovery from flash column chromatography.

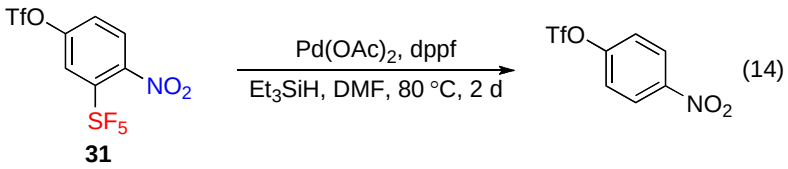


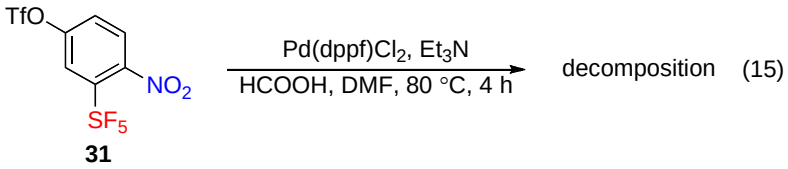
We changed the strategy to a stepwise conversion of triflate and nitro groups to produce the important intermediate **28**. Reduction of the nitro group seemed feasible by hydrogenation (eq 12). This transformation was conducted by applying the harsher conditions based on our previous results and provided aniline **32** in 80% yield (eq 13).[72] This intermediate turned from colorless to black directly after concentration of the chromatography fractions. ^{1}H NMR analysis of the black sample indicated partial decomposition.



With this aniline in hand, we examined reduction and hydrogen transfer conditions to remove the triflate group. The first reaction we tried was a newly reported reduction method using magnesium and palladium on carbon and it gave no conversion.[73] Traditional hydrogenations conducted with palladium on carbon and a Raney-Ni reduction also failed. Starting material **32** was recovered in all these conditions. Standard hydrogen transfer with a palladium(II) catalyst also gave no reaction, even after heating at 80 °C in DMF for 4 days.[74]

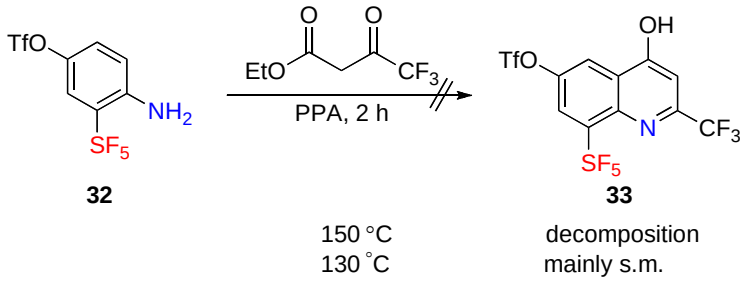
Due to the difficulty of removing the triflate after reduction of the nitro group, we thought it might be feasible to remove it prior to nitro group reduction, because the electron-withdrawing nature of the nitro group might facilitate the oxidative addition of the palladium catalyst. Two conditions with different hydrogen sources were examined in DMF. The first condition using triethylsilane gave the product with the SF_5 group cleaved (eq 14), and the second, formic acid condition, gave only decomposition (eq 15).





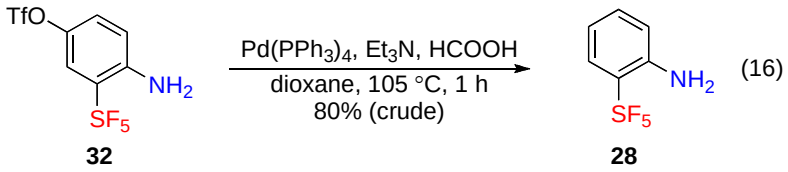
We assumed that the desired intermediate **28** was unstable and the removal of the triflate after the Conrad-Limpach reaction might be more feasible. Typical cyclization conditions using polyphosphoric acid at 150 °C with ethyl 4,4,4-trifluoroacetoacetate and **32** led to decomposition. Once the temperature was reduced to 130 °C, most of starting material was recovered (Scheme 9).

Scheme 9 Attempted Conrad-Limpach cyclization of aniline **32**



Since all of these attempts failed, we revisited the triflate removal of the aniline **32**. The failure of the hydrogen transfer process might be due to an unsuccessful oxidative addition of the

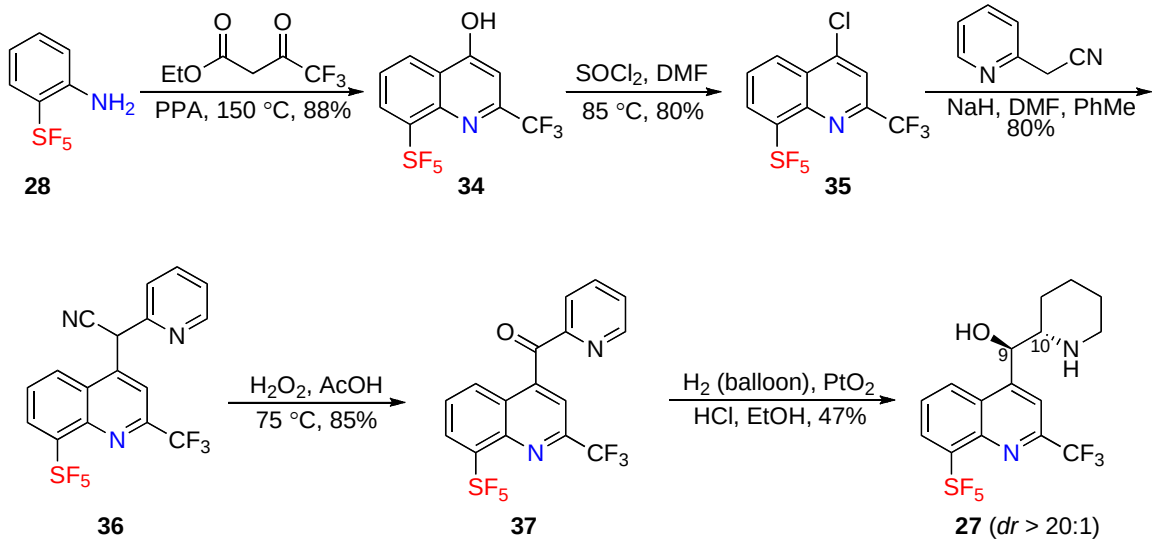
palladium catalyst to the oxygen-carbon bond; therefore, the more reactive tetrakis(triphenylphosphine) palladium(0) was employed instead of the palladium(II) precatalyst. In the presence of palladium(0), formic acid and triethylamine in dry dioxane, compound **32** was converted to the expected *ortho*-SF_5-aniline **28** in 80% yield (crude) (eq 16). This novel compound is a colorless liquid at room temperature and solidifies upon cooling.



32 **28** (16)

With this key intermediate in hand, we next focused our attention on the synthesis of the 8-SF_5 mefloquine analog according to the previous route (Scheme 10). The Conrad-Limpach reaction of **28** with ethyl 4,4,4-trifluoroacetoacetate in polyphosphoric acid led to the 8-SF_5 quinolyl intermediate **34** in 88% yield. The previously used chlorination conditions with phosphorous oxychloride at 110 °C proved to be too harsh for quinoline **34** and gave the product in low yield (18%). Milder conditions (thionyl chloride in DMF at 85 °C) afforded quinolyl chloride **35** in good yields. After nucleophilic aromatic substitution with 2-pyridyl-acetonitrile, oxidation of the carbon-nitrile bond, and Pt-catalyzed reduction of the ketone and pyridine moieties in **37**, the target molecule **27** was obtained in moderate yields. This synthesis was used to prepare **27** on 100 mg scale.

Scheme 10 Synthesis of 8-SF_5 analog **27**



The *J* value of the 9- and 10-position protons is 3.6 Hz and the major diastereomer is assigned to be *anti*. This assignment was confirmed by X-ray crystallography of **27** (Figure 15). The dihedral angle of H-C(9)-C(10)-H is 64°, which matches its *J* value.

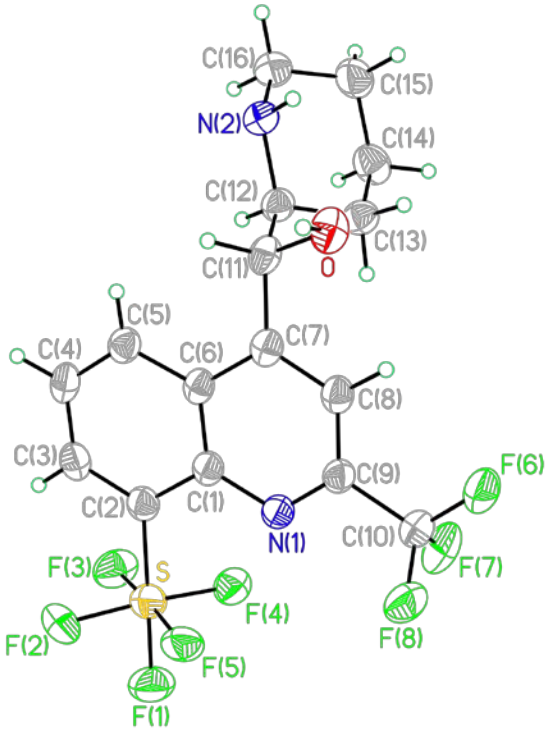


Figure 15 X-ray structure of **27**

3.5 BIOLOGICAL EVALUATION OF 27

The *in vitro* antimalarial activity,[69] cytotoxicity,[69] permeability,[75] plasma protein,[76] and brain tissue binding properties[76] of 8-SF_5 mefloquine analog **27** were compared to those of mefloquine (**1**) and the 6- and 7-SF_5 analogs **8a** and **8b**, respectively (Table 8). These biological data were collected by the Division of Experimental Therapeutics, Walter Reed Army Institute of Research and Biological Chemistry and the College of Life Sciences, University of Dundee.

Table 8 Antimalarial activity, toxicity, permeability, plasma protein and brain tissue binding of mefloquine and its SF_5 analogs

analog	Pf W2	Pf D6	Pf C235	Pf C2A	RAW LC_{90}[a]	SI[b]	Papp[c] A-B MDCK	Fu[d] mouse brain	Fu[d] mouse plasma	Fu[d] human plasma
	IC_{90}[a]									
1	16	92	182	183	8934	559	9.4	0.002	0.0163	0.0305
8a	19	55	91	110	53604	2795	13.8	NT	NT	NT
8b	27	92	146	165	6254	230	9.7	NT	NT	NT
27	9.6	74	91	165	8934	932	5.0	0.0008	0.004	0.0072

[a]The units are nM of IC_{90} and LC_{90} data. [b]The selectivity index (SI) is the ratio of the LC_{90} against RAW macrophages relative to the Pf W2 IC_{90}. [c]The MDCK permeability is the apparent permeability in the A-B direction in MDR1-transfected MDCK cells in the presence of a PgP inhibitor (10 μM cyclosporine A). The units for apparent permeability are 10^{-6} cm/s. [d]Fu in brain tissue and plasma protein binding studies represents the fraction of unbound drug.

Analogs **27** and **8a** were generally more potent than mefloquine against all the tested parasite strains and they were up to two-fold more potent and exhibited greater selectivity than analog **8b**. Analog **27** has lower MDCK permeability than analog **8a** and mefloquine, which indicates lower blood-brain barrier permeability. Accordingly, agent **27** outperformed other SF_5-analogs and would be predicted to be more efficacious *in vivo* than mefloquine. Furthermore, **27** has moderately better selectivity than mefloquine. In the study of the unbound drugs in mouse brain, mouse plasma and human plasma, analog **27** has significantly fewer unbound fractions than mefloquine. This may also be advantageous if the affinity for the hERG receptor is similar,

and *in vivo* efficacy is not driven by the free plasma concentration. Overall, we anticipate that analog **27** will exhibit a superior safety profile at its minimum efficacious dose than mefloquine *in vivo*.

3.6 SYNTHESIS OF SF_5-DIAMINE ANALOGS

In the early lead evaluation of the mefloquine analogs in the Division of Experimental Therapeutics, Walter Reed Army Institute of Research, it was found that the diamine analogs of mefloquine **38** and **39** (Figure 16) have high efficacy in curing mice with malaria.

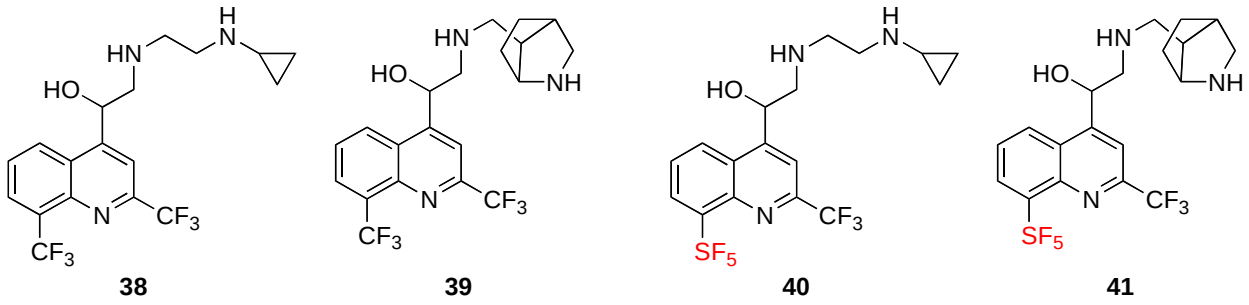


Figure 16 Diamine mefloquine analogs and their SF_5-congeners

Based on the biological data of the 8-SF_5-mefloquine analogs, the 8-SF_5-congeners of **38** and **39** should be more efficacious. Compound **40** and **41** were designed for lead synthesis. Both of them could be obtained from epoxide opening of **42** by the corresponding amine. The epoxide could be synthesized through a Corey-Chaykovsky reaction of the aldehyde **43**, which originates from the previously synthesized alcohol **34** (Fig. 17).

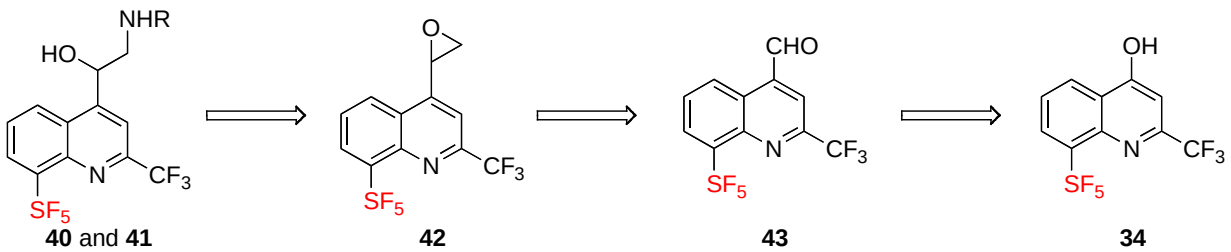
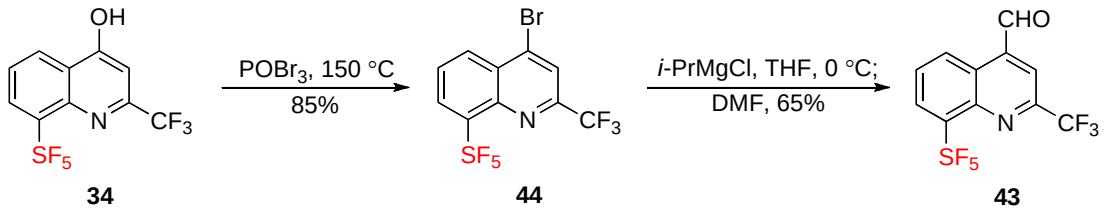


Figure 17 Retrosynthetic plan for compounds **40** and **41**

Bromination of the quinolyl hydroxy **34** with phosphorous oxybromide gave the quinolyl bromide **44** in 85% yield. Treatment of **44** with Grignard reagent at 0 °C formed the quinolyl anion, which was trapped with dry DMF to provide the aldehyde **43** after work-up (Scheme 11).

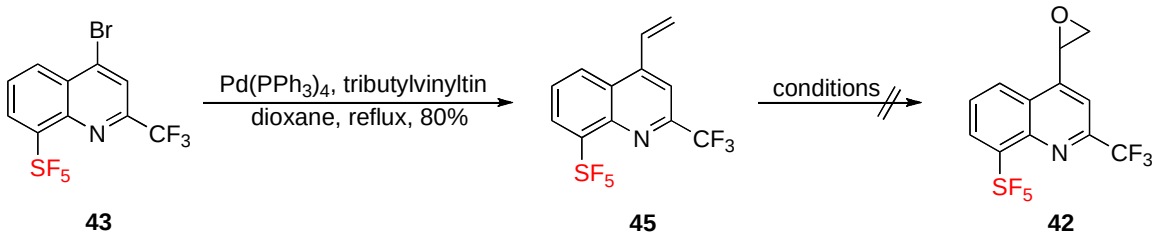
Scheme 11 Synthesis of the Corey-Chaykovsky precursor **43**



The traditional and the modified Corey-Chaykovsky conditions using trimethylsulfonium iodide, trimethyloxosulfonium iodide and dimethylsulfide, only gave complex mixtures after work-up, and no desired product was detected.

We changed to an epoxidation strategy of the carbon-carbon double bond to prepare **42**. To our delight, Stille coupling between quinolyl bromide **44** and tributylvinyltin catalyzed by tetrakis(triphenylphosphine)palladium(0) in dioxane afforded product **45** in 80% yield. We next examined the feasibility of the expoxidation. After several trials of standard conditions of epoxidation of the electrophilic double bond using *m*CPBA and UHP, this reaction proved to be problematic, and no product was detected (Scheme 12).

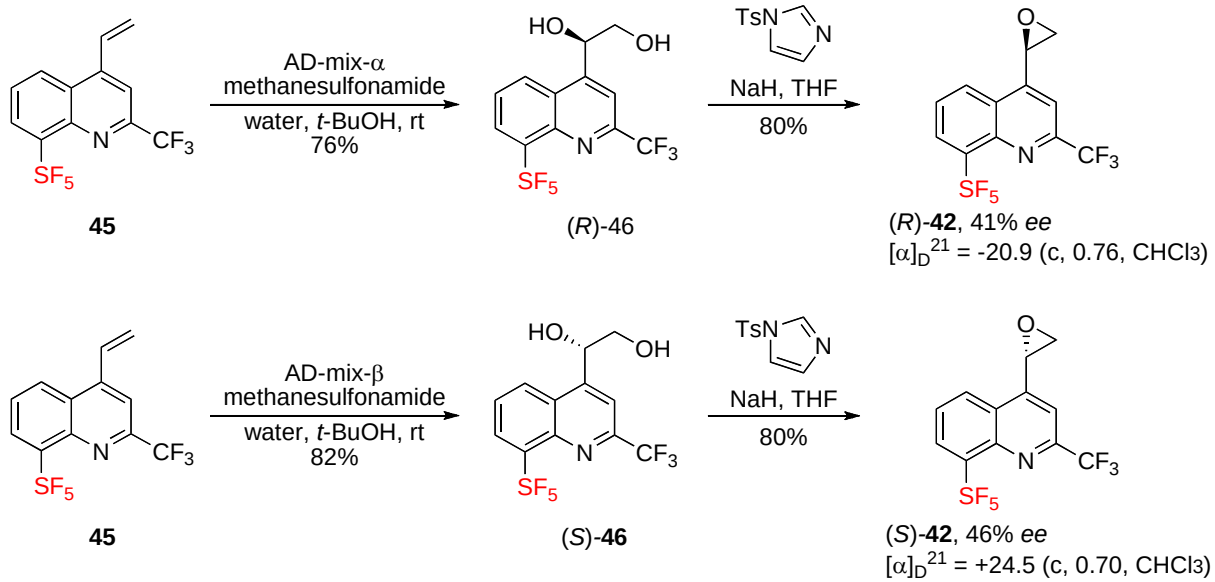
Scheme 12 Successful Stille coupling of substrate **43** and failed epoxidation of **45**



43 **45** **42**

With **45** in hand, we tried a two-step protocol to obtain the epoxide. Sharpless asymmetric dihydroxylation of the exocyclic double bond with AD-mix-α and AD-mix-β provided two batches of enantiomerically enriched diols **46** in 76% and 82% yields, respectively. Subsequent tosylation of the primary alcohol followed by substitution afforded quinolyl epoxides **42** in 80% and 69% yields. The enantiomeric excess of **42** from the synthesis using AD-mix-α was 41%, and another batch formed with AD-mix-β had an ee of 46% (Scheme 13, based on chiral SFC analysis). These two enantiomers can be separated by preparative SFC.

Scheme 13 Asymmetric synthesis of quinolyl epoxide **42**



45 (*R*)-46 (*R*)-**42**, 41% *ee*
$[\alpha]_D^{21}$ = -20.9 (c, 0.76, $CHCl_3$)

45 (*S*)-**46** (*S*)-**42**, 46% *ee*
$[\alpha]_D^{21}$ = +24.5 (c, 0.70, $CHCl_3$)

The absolute stereochemistry was determined by X-ray crystallography of the pure enantiomer obtained from an SFC separation (Figure 18). This enantiomer was the main

component synthesized from the AD-mix-β and the stereocenter was assigned as (*S*) according to the X-ray.

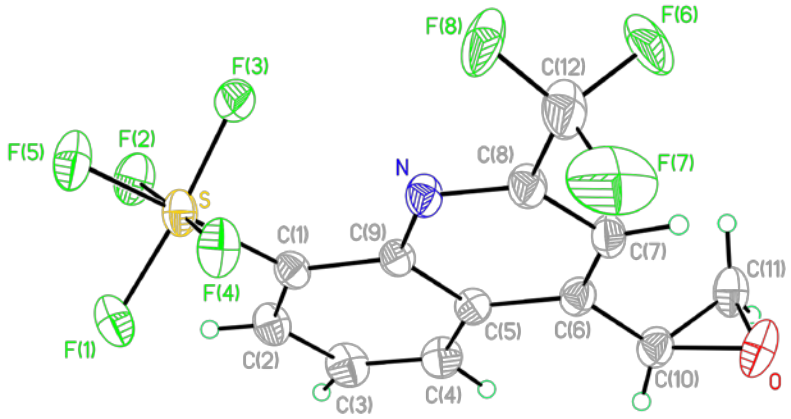
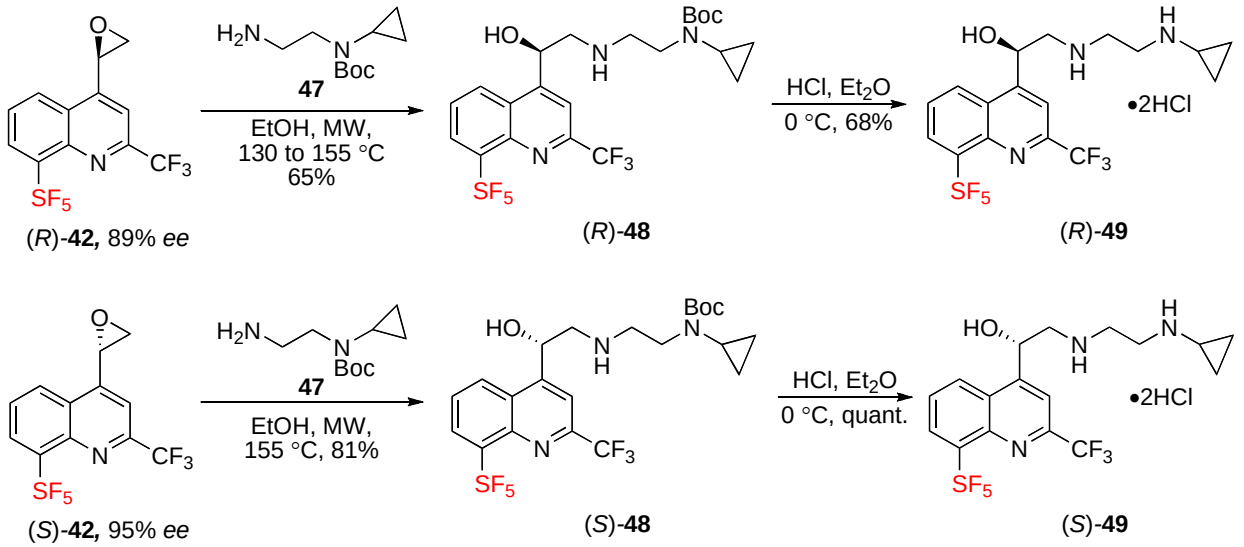


Figure 18 X-ray structure of the (*S*)-**42** obtained from AD-mix-β

The SFC separation of 40 mg **42** (20 mg synthesized from AD-mix-α and 20 mg from AD-mix-β) provided (*R*)-**42** 15 mg (89% *ee*) and (*S*)-**42** in 12 mg (95% *ee*) quantity. With these enantiomers in hand, the epoxides were opened by the diamine **47** in good yields (Scheme 14). The *t*-Boc protection of the secondary amine proved to be necessary for good regioselectivity. The final deprotection of the *t*-Boc group went well under the HCl conditions and provided the pure target molecules **49** in good yields.

Scheme 14 Synthesis of target molecules (*R*)-**49** and (*S*)-**49**



The biological evaluation of both enantiomers of **49** is pursued under the aspiration of in the Division of Experimental Therapeutics, Walter Reed Army Institute of Research.

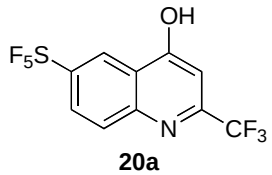
4.0 CONCLUSION

We have synthesized the 6-SF_5 and 7-SF_5 mefoquine analogs in 5 steps and 10-23% overall yields. These analogs were found to have equivalent or improved activities and selectivities against *P. falciparum* parasites in *in vitro* studies as opposed to the parent drug and the corresponding C-6 and C-7 trifluoromethyl isomers. Inspired by this result, the 8-SF_5-substituted mefloquine analog was synthezised in 9 steps from commercial starting materials and in 5 steps from a novel *ortho*-SF_5-substituted aniline intermediate. Preclinical assays determined that this compound has improved activity against *P. falciparum* parasites and exhibits lower membrane permeability in an MDCK cell line screen, thus potentially reducing the adverse CNS effects of the parent antimalarial agent. These biological data demonstrate not only the effective biological mimcry but also the added potential therapeutic value that may be feasible with the CF_3-SF_5 switch strategy. Further *in vivo* studies of this 8-SF_5 analog are underway. Other novel SF_5-analogs synthesis are also in progress.

During this work, the first SF_5-substituted quinolines were reported, and a novel preparation of the versatile *ortho*-SF_5-aniline was achieved.

4.1 EXPERIMENTAL SECTION

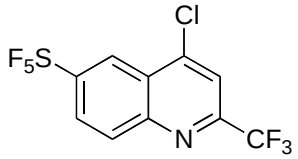
General Information. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (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 $(NH_4)_6Mo_7O_{24}\cdot 4\ H_2O$ 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 a 0.1% NaOH solution). Flash chromatography on SiO_2 was used to purify the crude reaction mixtures. ^1H spectra were obtained at 300 or 600 MHz in $CDCl_3$ unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard. ^1H NMR spectra were obtained and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu=quintet, m = multiplet, app = apparent), number of protons, and coupling constant(s). ^{13}C NMR spectra were obtained at 75 or 150 MHz using a proton-decoupled pulse sequence and are tabulated by observed peak. ^{19}F NMR spectra were obtained at 282 MHz using a proton-decoupled pulse sequence in the presence of fluorobenzene as an internal standard.



20a

4-Hydroxy-6-pentafluorosulfanyl-2-(trifluoromethyl)quinoline (20a). A solution of 4-aminophenylsulfur pentafluoride (110 mg, 0.502 mmol) in polyphosphoric acid (7.0 mL) at 110 °C was treated with ethyl 4,4,4-trifluoroacetoacetate (1.5 mL, 10.0 mmol) and heated up to

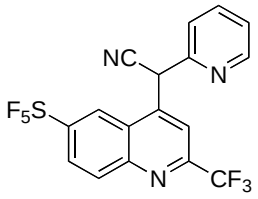
reflux at 150 °C for 3 h. The reaction mixture was quenched with 5% NaOH solution (30 mL), extracted with EtOAc (2x), washed with brine, dried ($MgSO_4$) and concentrated. The brown residue was purified by chromatography on SiO_2 (25% EtOAc/Hexanes) to yield **20a** (76.4 mg, 44%) as a beige solid: Mp 252.0 °C (dec.); IR (neat) 3200-3000 (br), 2337, 1580, 1208, 1142, 822, 777 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.68 (d, 1 H, J = 2.4 Hz), 8.23 (dd, 1 H, J =2.7, 9.3 Hz), 8.09 (d, 1 H, J = 9.3 Hz), 7.03 (s, 1 H); ^{13}C NMR (acetone-d_6) δ 170.7, 151.4 (qu, $^2J_{C\text{-}SF4}$ = 18.0 Hz), 146.7, 135.1, 129.5 (appt, $^2J_{C\text{-}SF4}$ = 4.5 Hz), 127.0, 123.5 (appt, $^2J_{C\text{-}SF4}$ = 5.3 Hz), 122.0 (q, $^1J_{C\text{-}F}$ = 272.3 Hz), 117.3, 105.5; ^{19}F NMR δ 85.2 (qu, J = 145.5 Hz), 64.6 (d, J = 145.5 Hz), -67.0; HRMS (TOF-ESI) *m/z* calcd for $C_{10}H_6F_8NOS$ (M + 1) 340.0042, found 340.0032.



21a

4-Chloro-6-pentafluorosulfanyl-2-(trifluoromethyl)quinoline (21a). After addition of preheated (60 °C) phosphorus oxychloride (108 mg, 0.701 mmol) to **20a** (23.8 mg, 0.0702 mmol), the reaction mixture was warmed to 110 °C and stirred at this temperature for 1.5 h. The conversion was monitored by TLC (10% EtOAc/Hexanes) and the solution was cooled down to room temperature upon the disappearance of the starting material, quenched with ice water (3.0 mL), extracted with Et_2O, washed with sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated. The yellow residue was purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to provide **21a** (19.3 mg, 77%) as a beige solid: Mp 107.9-109.0 °C; IR (neat) 2922, 1343, 1202, 1135, 1100, 833, 818, 768 cm^{-1}; ^1H NMR δ 8.75 (d, 1 H, J = 2.4 Hz), 8.37 (d, 1 H, J = 9.3 Hz), 8.22 (dd, 1 H, J = 2.4, 9.3 Hz), 7.96 (s, 1 H); ^{13}C NMR δ 154.1 (qu, $^2J_{C\text{-}SF4}$ = 18.0 Hz), 150.6 (q,

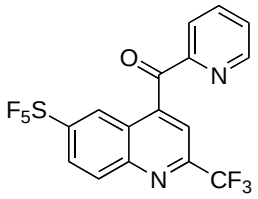
$^{2}J_{C\text{-}CF_3}$ = 36.0 Hz), 148.3, 146.5, 132.0, 128.5 (appt, $^{2}J_{C\text{-}SF_4}$ = 4.5 Hz), 126.5, 123.4 (qu, $^{2}J_{C\text{-}SF_4}$ = 5.3 Hz), 120.8 (q, $^{1}J_{C\text{-}F}$ = 273.8 Hz), 118.9 (appd, $^{2}J_{C\text{-}SF_4}$ = 2.3 Hz); ^{19}F NMR δ82̃ (qu, *J* = 149.3 Hz), 63.3 (d, *J* = 149.7 Hz), -67.9; EI-MS *m/z* 357 (M^+, 100), 249 (55), 180 (70), 84 (75); HRMS (EI) *m/z* calcd for $C_{10}H_4NF_8SCl$ 356.9625, found 356.9622.



22a

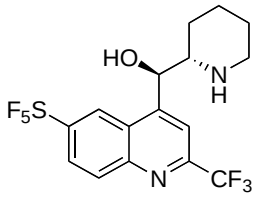
α-(2-Pyridyl)-6-pentafluorosulfanyl-(2-trifluoromethyl)-4-quinolylacetonitrile (22a). A cooled (0 - 5 °C) suspension of sodium hydride (11.9 mg, 0.494 mmol) in toluene (1.2 mL) and DMF (0.60 mL) was treated under Ar with a solution of 2-pyridylacetonitrile (27 μL, 0.247 mmol) in toluene (0.60 mL) and DMF (0.15 mL) over 5 min. The resulting yellow-brown colored suspension was stirred for 1 h at the same temperature. A solution of **8a** (58.9 mg, 0.165 mmol) in toluene (1.2 mL) and DMF (0.50 mL) was added drop by drop to the suspension over 5 min. After 0.5 h, the reaction mixture was quenched with ice water (10 mL), extracted with EtOAc, washed with water (3x) and brine, dried ($MgSO_4$) and concentrated. The orange residue was purified by chromatography on SiO_2 (25% EtOAc/Hexanes) to provide **22a** (62.0 mg, 86%) as a light orange solid: Mp 113.5-115.5 °C; IR (neat) 2251, 1187, 1141, 1109, 820 cm^{-1}; ^{1}H NMR δ 8.87 (d, 1 H, *J* = 2.1 Hz), 8.60 (appd, 1 H, *J* = 4.8 Hz), 8.37 (d, 1 H, *J* = 9.3 Hz), 8.18 (s, 1 H), 8.16 (dd, 1 H, *J* = 2.1, 9.3 Hz), 7.78 (ddd, 1 H, *J* = 1.5, 7.5, 7.8 Hz), 7.53 (d, 1 H, *J* = 7.8 Hz), 7.32 (appdd, 1 H, *J* = 4.8, 7.5 Hz), 6.09 (s, 1 H); ^{13}C NMR δ 153.6 (qu, $^{2}J_{C\text{-}SF_4}$ = 18.8 Hz), 152.8, 150.8 (q, $^{2}J_{C\text{-}CF_3}$ = 35.3 Hz), 150.5, 148.1, 144.6, 138.4, 132.3, 127.9 (appt, $^{2}J_{C\text{-}SF_4}$ = 3.8 Hz), 125.4, 124.3, 123.4 (appt, $^{2}J_{C\text{-}SF_4}$ = 5.3 Hz), 122.6, 121.0 (q, $^{1}J_{C\text{-}F}$ = 273.8 Hz), 117.7 (d, $^{2}J_{C\text{-}$

$_{SF4}$ = 2.3 Hz), 117.2, 43.3; ^{19}F NMR δ82̃2 (qu, *J* = 149.2 Hz), 63.2 (d, *J* = 148.3 Hz), -67.8; EI-MS *m/z* 439 (M^+, 100), 311 (40), 78 (22); HRMS (EI) *m/z* calcd for $C_{17}H_9N_3F_8S$ 439.0389, found 439.0385.



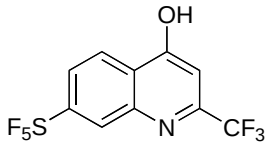
23a

2-Pyridyl-6-pentafluorosulfanyl-(2-trifluoromethyl)-4-quinolylketone (23a). A suspension of **22a** (60.0 mg, 0.137 mmol) in acetic acid (0.24 mL) was treated dropwise with H_2O_2 (53 μL, 0.683 mmol) at room temperature. The reaction mixture was placed in a preheated (75 °C) oil bath until the color turned to light yellow. The mixture was quenched with ice water (3.0 mL), extracted with Et_2O, washed with sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated. The yellow residue was purified by chromatography on SiO_2 (16% EtOAc/Hexanes) to provide **23a** (49.6 mg, 85%) as a white solid: Mp 122.0-124.0 °C; IR (neat) 1683, 1182, 1133, 1105, 835, 820, 768, 764 cm^{-1}; ^{1}H NMR δ 8.65 (ddd, 1 H, *J* = 0.9, 1.5, 4.8 Hz), 8.46-8.41 (m, 2 H), 8.39 (s, 1 H), 8.18 (dd, 1 H, *J* = 2.4, 9.6 Hz), 8.06 (ddd, 1 H, *J* = 1.8, 7.8, 7.8 Hz), 8.01 (s, 1 H), 7.62 (ddd, 1 H, *J* = 0.9, 4.5, 7.5 Hz); ^{13}C NMR δ 193.5, 153.8 (qu, $^2J_{C-SF4}$ = 18.0 Hz), 152.8, 149.9 (q, $^2J_{C-CF3}$ = 36.0 Hz), 149.7, 148.0, 147.1, 137.9, 131.7, 128.5, 127.7 (appt, $^2J_{C-SF4}$ = 4.5 Hz), 125.3, 124.8 (appt, $^2J_{C-SF4}$ = 5.3 Hz), 124.7, 121.2 (q, $^1J_{C-F}$ = 273.8 Hz), 118.9 (d, $^2J_{C-SF4}$ = 1.5 Hz); ^{19}F NMR δ82.4 (qu, *J* = 151.9 Hz), 62.6 (d, *J* = 151.1 Hz), -67.8; EI-MS *m/z* 428 (M^+, 30), 399 (40), 273 (100), 78 (80); HRMS (EI) *m/z* calcd for $C_{16}H_8N_2OF_8S$ 428.0230, found 428.0210.



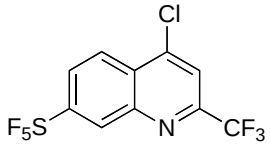
8a

α-(2-Piperidyl)-6-pentafluorosulfanyl-(2-trifluoromethyl)-4-quinolinemethanol (8a). A solution of **23a** (20.0 mg, 0.0467 mmol) in conc. hydrochloric acid (58.0 μL, 0.233 mmol) and abs EtOH (0.56 mL) was treated with platinum oxide (4.2 mg, 0.0187 mmol). The reaction mixture was purged with hydrogen twice and hydrogenated under balloon pressure. After 2 h, there was no alcohol intermediate left by TLC analysis (10% MeOH/DCM). The mixture was filtered through florisil, concentrated, and extracted with Et_2O. The combined organic layers were washed with sat $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated. The black residue was purified by chromatography on SiO_2 (5% NEt_3 in EtOAc then 5% NEt_3 and 5% MeOH in EtOAc). The crude product was recrystallized to get pure **8a** (8.5 mg, 42%) as a white solid and a dr 20:1: Mp 198 °C (dec.); IR (neat) 3000-2900 (br), 1368, 1258, 1139, 1105, 835, 822, 798 cm^{-1}; ^1H NMR (acetone-d_6, 600 MHz) δ 9.01 (d, 1 H, J = 2.4 Hz), 8.38 (d, 1 H, J = 9.0 Hz), 8.31 (dd, 1 H, J = 2.4, 9.0 Hz), 8.16 (s, 1 H), 5.54 (d, 1 H, J = 4.8 Hz), 3.04 (ddd, 1 H, J = 2.4, 5.4, 7.8 Hz), 2.97 (bd, 1 H, J = 8.4 Hz), 2.54 (dt, 1 H, J = 2.4, 12.0 Hz), 1.76-1.71 (m, 1 H), 1.58-1.53 (m, 1 H), 1.51-1.46 (m, 1 H), 1.35-1.20 (m, 4 H); ^{13}C NMR (acetone-d_6, 600 MHz) δ 155.5, 153.0 (qu, $^2J_{C\text{-}SF_4}$ = 18.0 Hz), 150.6 (q, $^2J_{C\text{-}CF_3}$ = 34.5 Hz), 148.7, 132.7, 127.6 (appt, $^2J_{C\text{-}SF_4}$ = 4.5 Hz), 127.2, 124.9 (appt, $^2J_{C\text{-}SF_4}$ = 4.5 Hz), 122.6 (q, $^1J_{C\text{-}F}$ = 273.0 Hz), 117.5 (d, $^2J_{C\text{-}SF_4}$ = 1.5 Hz), 74.2, 62.6, 47.7, 28.0, 27.0, 25.2; ^{19}F NMR δ84.7 (qu, J = 152.2 Hz), 64.5 (d, J = 149.5 Hz), -66.8; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}N_2OF_8S$ (M + 1) 437.0928, found 437.0893.



20b

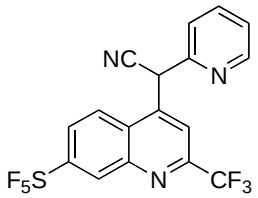
4-Hydroxy-7-pentafluorosulfanyl-2-(triflurомethyl)quinoline (20b). A solution of 3-aminophenylsulfur pentafluoride (110 mg, 0.502 mmol) in polyphosphoric acid (2.0 mL) at 110 °C was treated with ethyl 4,4,4-trifluoroacetoacetate (1.5 mL, 10.0 mmol) and the mixture was heated up to 150 °C to reflux for 4 h. The reaction mixture was quenched with 5% NaOH solution (30 mL), extracted with EtOAc (2x), washed with brine, dried ($MgSO_4$) and concentrated. The crude brown residue was purified by chromatography on SiO_2 (25% EtOAc/Hexanes) to yield **20b** (128 mg, 75%) as a beige solid: Mp 261.2-262.2 °C; IR (neat) 3200-3000 (br), 1580, 1277, 1198, 1157, 839, 820 cm $^{-1}$; ^{1}H NMR (acetone-d_6) δ 8.48 (d, 1 H, *J* = 2.4 Hz), 8.47 (d, 1 H, *J* = 9.0 Hz), 8.05 (dd, 1 H, *J* = 2.4, 9.0 Hz), 7.27 (s, 1 H); ^{13}C NMR (acetone-d_6) δ 165.8, 156.0 (qu, $^{2}J_{C\text{-}SF4}$ = 18.0 Hz), 149.9 (q, $^{2}J_{C\text{-}CF3}$ = 35.3 Hz), 147.5, 127.2, 125.5, 124.6, 124.0 (appt, $^{2}J_{C\text{-}SF4}$ = 4.5 Hz), 122.5 (q, $^{1}J_{C\text{-}F}$ = 272.3 Hz), 104.1; ^{19}F NMR δ 84.3 (qu, *J* = 151.4 Hz), 64.0 (d, *J* = 151.4 Hz), -67.0; EI-MS *m/z* 339 (M^+, 40), 231 (15), 137 (30), 95 (30), 81 (100); HRMS (EI) *m/z* calcd for $C_{10}H_5NOF_8S$ 338.9964, found 338.9953.



21b

4-Chloro-7-pentafluorosulfanyl-2-(triflurомethyl)quinoline (21b). After addition of preheated (60 °C) phosphorus oxychloride (306 mg, 1.99 mmol) to **20b** (135 mg, 0.399 mmol), the reaction mixture was warmed to 110 °C and stirred at this temperature for 0.5 h. The

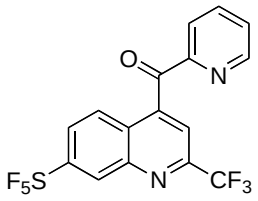
conversion was monitored by TLC (10% EtOAc/Hexanes) and the solution was cooled down to room temperature after the disappearance of the starting material, quenched with ice water (3.0 mL), and extracted with Et_2O. The combined organic layers were washed with sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated. The yellow residue was purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to provide **21b** (112 mg, 78%) as a beige solid: Mp 94.8-96.8 °C; IR (neat) 1558, 1433, 1336, 1206, 1150, 1105, 1079, 835, 816 cm^{-1}; ^1H NMR δ 8.74 (d, 1 H, J = 2.1 Hz), 8.42 (d, 1 H, J = 9.3 Hz), 8.12 (dd, 1 H, J = 2.1, 9.3 Hz), 7.97 (s, 1 H); ^{13}C NMR δ 155.7 (qu, $^2J_{C\text{-}SF_4}$ = 18.8 Hz), 149.9 (q, $^2J_{C\text{-}CF_3}$ = 36.0 Hz), 147.1, 145.1, 129.5 (appt, $^2J_{C\text{-}SF_4}$ = 5.3 Hz), 128.4, 126.4 (qu, $^2J_{C\text{-}SF_4}$ = 4.5 Hz), 125.5, 120.8 (q, $^1J_{C\text{-}F}$ = 274.5 Hz), 119.6 (appd, $^2J_{C\text{-}SF_4}$ = 2.3 Hz); ^{19}F NMR δ81.8 (qu, J = 149.5 Hz), 63.1 (d, J = 149.5 Hz), -67.8; EI-MS *m/z* 357 (M^+, 50), 249 (25), 180 (25), 117 (30), 84 (100); HRMS (EI) *m/z* calcd for $C_{10}H_4NF_8SCl$ 356.9625, found 356.9630.



22b

α-(2-Pyridyl)-7-pentafluorosulfanyl-(2-trifluoromethyl)-4-quinolylacetonitrile (22b). A cooled (0 – 5 °C) suspension of sodium hydride (19.9 mg, 0.830 mmol) in toluene (2.0 mL) and DMF (1.0 mL) was treated under Ar with a solution of 2-pyridylacetonitrile (46 μL, 0.415 mmol) in toluene (1.0 mL) and DMF (0.25 mL) over 5 min. The resulting yellow-brown colored suspension was stirred for 1 h at the same temperature. A solution of **21b** (98.9 mg, 0.277 mmol) in toluene (2.0 mL) and DMF (1.0 mL) was added drop by drop to the suspension over 5 min. After 0.5 h, the reaction mixture was quenched with ice water (10 mL), extracted with EtOAc,

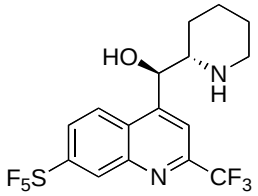
washed with water (3x) and brine, dried ($MgSO_4$) and concentrated. The orange residue was purified by chromatography on SiO_2 (25% EtOAc/Hexanes) to provide **22b** (111 mg, 92%) as an orange foam: IR (neat) 2249, 1588, 1435, 1366, 1258, 1187, 1142, 1111, 1085, 839, 811 cm^{-1}; ^1H NMR δ 8.73 (d, 1 H, *J* = 2.1 Hz), 8.60 (ddd, 1 H, *J* = 0.9, 1.5, 4.8 Hz), 8.35 (d, 1 H, *J* = 9.3 Hz), 8.14 (s, 1 H), 8.03 (dd, 1 H, *J* = 2.4, 9.6 Hz), 7.79 (ddd, 1 H, *J* = 1.8, 7.8, 7.8 Hz), 7.49 (d, 1 H, *J* = 7.8 Hz), 7.33 (ddd, 1 H, *J* = 0.9, 4.8, 7.8 Hz), 6.08 (s, 1 H); ^{13}C NMR δ 155.0 (qu, $^2J_{C\text{-}SF_4}$ = 18.8 Hz), 152.7, 150.6, 150.1 (q, $^2J_{C\text{-}CF_3}$ = 36.0 Hz), 147.0, 143.1, 138.4, 129.9 (appt, $^2J_{C\text{-}SF_4}$ = 4.5 Hz), 127.5, 126.2 (appt, $^2J_{C\text{-}SF_4}$ = 4.5 Hz), 125.0, 124.3, 126.6, 121.0 (q, $^1J_{C\text{-}F}$ = 274.5 Hz), 118.9 (d, $^2J_{C\text{-}SF_4}$ = 2.3 Hz), 117.3, 43.0; ^{19}F NMR δ81.8 (qu, *J* = 152.3 Hz), 63.0 (d, *J* = 152.3 Hz), -67.6; EI-MS *m/z* 439 (M^+, 35), 412 (10), 119 (30), 91 (100), 84 (60); HRMS (EI) *m/z* calcd for $C_{17}H_9N_3F_8S$ 439.0389, found 439.0380.



23b

2-Pyridyl-7-pentafluorosulfanyl-(2-trifluoromethyl)-4-quinolylketone (23b). To a suspension of **22b** (109 mg, 0.248 mmol) in acetic acid (0.43 mL) was added H_2O_2 (98 μL, 1.24 mmol) dropwise at room temperature. The reaction mixture was placed in a preheated (75 °C) oil bath until the color turned to light yellow. The mixture was quenched with ice water (10 ml), extracted with Et_2O, washed with sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated. The yellow residue was purified by chromatography on SiO_2 (16% EtOAc/Hexanes) to provide **23b** (98.0 mg, 92%) as a white solid: Mp 99.5-101.1 °C; IR (neat)

1687, 1437, 1189, 1135, 1105, 826, 813, 801 cm^{-1}; ^{1}H NMR δ 8.78 (d, 1 H, *J* = 2.1 Hz), 8.64 (ddd, 1 H, *J* = 0.9, 1.5, 4.8 Hz), 8.38 (appd, 1 H, *J* = 7.2 Hz), 8.07 (d, 1 H, *J* = 9.6 Hz), 8.01 (dd, 1 H, *J* = 1.8, 7.8 Hz), 8.00 (s, 1 H), 7.99 (ddd, 1 H, *J* = 2.4, 9.3, 9.3 Hz), 7.61 (ddd, 1 H, *J* = 1.2, 4.8, 7.8 Hz); ^{13}C NMR δ 193.8, 154.9 (qu, $^{2}J_{C\text{-}SF4}$ = 18.8 Hz), 152.9, 149.8, 149.2 (q, $^{2}J_{C\text{-}CF3}$ = 36.0 Hz), 146.9, 146.2, 137.8, 129.4 (appt, $^{2}J_{C\text{-}SF4}$ = 4.5 Hz), 128.5, 127.3, 126.7, 126.0 (appt, $^{2}J_{C\text{-}SF4}$ = 4.5 Hz), 124.5, 121.2 (q, $^{1}J_{C\text{-}F}$ = 273.4 Hz), 119.3 (d, $^{2}J_{C\text{-}SF4}$ = 2.3 Hz); ^{19}F NMR δ82.2 (qu, *J* = 152.3 Hz), 63.1 (d, *J* = 152.3 Hz), -67.6; EI-MS *m/z* 428 (M^{+}, 100), 399 (95), 331 (35), 301 (40), 119 (50), 99 (50); HRMS (EI) *m/z* calcd for $C_{16}H_8N_2OF_8S$ 428.0230, found 428.0231.

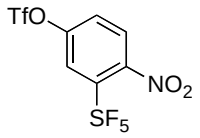


8b

α-(2-Piperidyl)-7-pentafluorosulfanyl-(2-trifluoromethyl)-4-quinolinemethanol (8b)

A solution of **23b** (70.5 mg, 0.165 mmol) in acetic acid (0.57 mL, 9.88 mmol) and abs EtOH (1.1 mL) was treated with platinum oxide (15.0 mg, 0.0658 mmol). The reaction mixture was purged with hydrogen twice and hydrogenated under balloon pressure. After 4 h, there was no alcohol intermediate detected by TLC (10% MeOH/DCM). The solution was filtered through florisil, concentrated, and extracted with Et_2O. The combined organic layers were washed with sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated. The black residue was purified by chromatography on SiO_2 (5% NEt_3 in EtOAc then 5% NEt_3 and 5% MeOH in EtOAc). The crude product was recrystallized from MeOH to get 33.1 mg (46%) of product as a white solid with a dr 20:1: Mp 179.2-180.2 °C; IR (neat) 3000-2900 (br), 1442, 1366, 1256, 1182, 1139, 1109, 1083, 932, 848, 816 cm^{-1}; ^{1}H NMR (acetone-d_6, 600MHz) δ 8.66 (d, 1 H, *J* =

2.4 Hz), 8.64 (d, 1 H, *J* = 9.6 Hz), 8.20 (s, 1 H), 8.17 (dd, 1 H, *J* = 2.4, 9.6 Hz), 5.54 (d, 1 H, *J* = 4.8 Hz), 3.04 (ddd, 1 H, *J* = 3.0, 4.8, 10.8 Hz), 2.97 (dm, 1 H, *J* = 12.0 Hz), 2.55 (dt, 1 H, *J* = 2.4, 12.0 Hz), 1.74-1.69 (m, 1 H), 1.50-1.42 (m, 2 H), 1.36-1.27 (m, 2 H), 1.22 (tq, 1 H, *J* = 3.6, 12.6 Hz); ^{13}C NMR (acetone-d_6, 600 MHz) δ 154.9 (qu, $^{2}J_{C\text{-}SF4}$ = 18.0 Hz), 154.2, 150.0 (q, $^{2}J_{C\text{-}CF3}$ = 34.5 Hz), 147.1, 129.7 (appt, $^{2}J_{C\text{-}SF4}$ = 4.5 Hz), 129.3, 127.3, 125.3 (appt, $^{2}J_{C\text{-}SF4}$ = 4.5 Hz), 122.6 (q, $^{1}J_{C\text{-}F}$ = 273.0 Hz), 118.1 (d, $^{2}J_{C\text{-}SF4}$ = 1.5 Hz), 73.4, 62.2, 47.6, 27.4, 27.0, 25.1; ^{19}F NMR δ84.2 (qu, *J* = 149.5 Hz), 64.1 (d, *J* = 149.5 Hz), -66.7; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}N_2OF_8S$ (M + 1) 437.0928, found 437.0948.

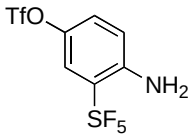


31

4-Nitro-3-(pentafluorosulfanyl)phenyl trifluoromethanesulfonate (31). A solution of 3-(pentafluorothio)phenol (0.998 g, 4.40 mmol) in distilled pyridine (5.0 mL) was treated with triflic anhydride (0.91 mL, 5.28 mmol) dropwise at 0 ^{o}C and stirred for 10 min at this temperature. The reaction mixture was then allowed to stir at room temperature for 1.5 h, diluted with diethyl ether (40 mL), and extracted with a 1 M solution of copper sulfate (3x). The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (10% diethyl ether/pentane) to yield 3-(pentafluorosulfanyl)phenyl trifluoromethanesulfonate (**30**) (1.40 g, 91%) as a colorless oil that was used immediately for the next reaction.

A solution of 3-(pentafluorosulfanyl)phenyl trifluoromethanesulfonate (**30**) (1.40 g, 4.00 mmol) in conc. sulfuric acid (13 mL) was slowly treated with fuming nitric acid (11 mL) at 0 °C.

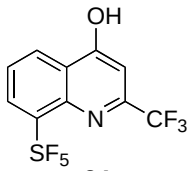
The reaction mixture was stirred for 7.5 h at 40 °C, quenched with ice (40 g), extracted with diethyl ether (40 mL), washed with sat. $NaHCO_3$ (2x 30 mL) and brine, dried ($MaSO_4$) and concentrated. The yellow residue was purified by chromatography on SiO_2 (10 %AcOEt/Hexanes) to provide compound **31** (1.25 g, 79%) as a white solid: Mp 70.2~71.8 °C; IR (neat) 3105, 1549, 1431, 1366, 1250, 1211, 1131, 822, 781, 749 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.48 (d, 1 H, *J* = 2.4 Hz), 8.26 (d, 1 H, *J* = 9.0 Hz), 8.20 (dd, 1 H, *J* = 2.1, 9.0 Hz); ^{13}C NMR (acetone-d_6) δ 150.5, 146.7, 144.8 (qu, $^2J_{C\text{-}SF4}$ = 22.5 Hz), 129.3, 128.6, 124.4 (qu, $^2J_{C\text{-}SF4}$ = 5.3 Hz), 119.7 (q, $^1J_{C\text{-}F}$ = 318.0 Hz); ^{19}F NMR (acetone-d_6) δ 76.4 (qu, *J* = 155.1 Hz), 68.7 (d, *J* = 152.3 Hz), -72.2; EIMS *m/z* 397 (M^+, 4), 84 (75), 69 (99), 57 (100); HRMS (EI) *m/z* calcd for $C_7H_3NO_5F_8S_2$ 396.9325, found 396.9311.



32

4-Amino-3-(pentafluorosulfanyl)phenyl trifluoromethanesulfonate (32). A solution of **31** (126 mg, 0.317 mmol) in acetic acid (1.0 mL) and methanol (1.0 mL) was treated with Pd on carbon (10%) (33.8 mg, 0.0317 mmol). The reaction mixture was hydrogenated under 6 bar H_2 pressure in a Parr apparatus for 4 h and filtered through Celite. The filtrate was concentrated, extracted with diethyl ether, washed with sat. $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (10% diethyl ether/pentane) to provide **32** (96.7 mg, 83%) as a white solid: Mp 66.4~66.7 °C; IR (neat) 3547, 3431, 1634, 1502, 1407, 1247, 1215, 1133, 850, 801 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51 (d, 1 H, *J* = 2.7 Hz), 7.20 (dd, 1 H, *J* = 2.7, 9.0 Hz), 6.79 (d, 1 H, *J* = 9.0 Hz), 4.64 (bs, 2 H); ^{13}C NMR ($CDCl_3$) δ 141.9, 138.9, 138.3 (qu, $^2J_{C\text{-}SF4}$ = 17.2 Hz), 126.0, 122.0 (qu, $^2J_{C\text{-}SF4}$ = 5.3 Hz), 120.2, 118.9 (q, $^1J_{C\text{-}F}$ =

318.8 Hz); ^{19}F NMR ($CDCl_3$) δ 85.6 (qu, *J* = 152.3 Hz), 64.4 (d, *J* = 149.5 Hz), -72.6; EIMS *m/z* 367 (M^+, 10), 234 (55), 106 (60), 84 (100), 69 (40); HRMS (EI) *m/z* calcd for $C_7H_5NO_3F_8S_2$ 366.9583, found 366.9571.

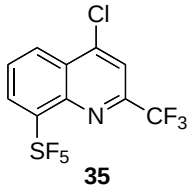


34

4-Hydroxy-8-pentafluorosulfanyl-2-(trifluoromethyl)quinoline (34). To a solution of **32** (1.46 g, 3.98 mmol) in anhydrous degassed dioxane (65 mL) at room temperature was added tetrakis(triphenylphosphine) palladium(0) (0.209 g, 0.199 mmol), triethylamine (2.0 mL, 14.3 mmol) and formic acid (0.54 mL, 14.3 mmol). The mixture was heated at reflux for 1 h under a nitrogen atmosphere, cooled to room temperature, and filtered through Celite. The filtrate was concentrated and extracted with DCM, washed with water (3x) and brine, dried ($MgSO_4$), and concentrated. The brown residue was purified by chromatography on SiO_2 (1% triethylamine and 10% diethyl ether in pentane) to provide crude 2-aminophenylsulfur pentafluoride (**28**) (0.700 g, 3.19 mmol) as a colorless liquid.

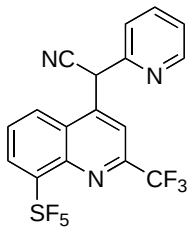
A solution of crude 2-aminophenylsulfur pentafluoride (**28**) (0.700 g, 3.19 mmol) in polyphosporic acid (10 mL) at 110 °C was treated with ethyl 4,4,4-trifluoroacetoacetate (4.3 mL, 29.4 mmol) and heated at reflux at 150 °C for 1 h. The reaction mixture was cooled to room temperature, quenched by addition of 40 g ice, neutralized to pH=5 by adding 5% NaOH solution and NaOH pellets, extracted with EtOAc (2x), washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude brown residue was purified by chromatography on SiO_2 (25% EtOAc/Hexanes) to yield **34** (0.980 g, 90% purity, 70% over two steps) as a beige solid: ^{1}H

NMR ($CDCl_3$) δ 8.89 (bs, 1 H), 8.65 (d, 1 H, *J* = 7.8 Hz), 8.21 (dd, 1 H, *J* = 1.5, 8.1 Hz), 7.54 (app t, 1 H, *J* = 8.1 Hz), 6.71 (d, 1 H, *J* = 1.5 Hz); ^{19}F NMR ($CDCl_3$) δ 84.9 (qu, *J* = 155.1 Hz), 68.6 (d, *J* = 146.6 Hz), -68.7; EIMS *m/z* 339 (M^+, 100), 211 (50), 183 (25); HRMS *m/z* calcd for $C_{10}H_5F_8NOS$ 338.9964, found 338.9954.



35

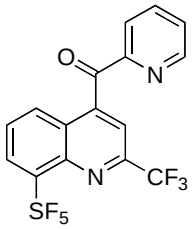
4-Chloro-8-pentafluorosulfanyl-2-(trifluoromethyl)quinoline. A solution of **34** (0.373 g, 0.990 mmol) in thionyl chloride (4.0 mL) was treated with a catalytic amount of DMF (6 drops). The reaction mixture was heated to 80 °C and kept at reflux for 1 h. The mixture was cooled to 0 °C and quenched with 20 g of ice. The suspension was extracted with diethyl ether (20 mL). The organic layer was washed with sat. $NaHCO_3$ (2x) and brine, dried ($MgSO_4$) and concentrated. The yellow residue was purified by chromatography on SiO_2 (15% EtOAc/Hexanes) to provide 4-chloro-8-pentafluorosulfanyl-2-(trifluoromethyl)quinoline (**35**) (0.304 g, 86%) as a beige solid: Mp 108.7~109.6 °C; IR (neat) 1336, 1263, 1185, 1141, 1114, 1021, 1075, 844, 818, 757, 721, 667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.59 (dd, 1 H, *J* = 1.2, 8.4 Hz), 8.46 (dd, 1 H, *J* = 1.2, 7.8 Hz), 7.94 (s, 1 H), 7.87 (dd, 1 H, *J* = 8.1, 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 151.8 (qu, $^2J_{C\text{-}SF4}$ = 15.0 Hz), 148.4 (q, $^2J_{C\text{-}CF3}$ = 36.0 Hz), 145.4, 142.0, 133.1 (app t, $^2J_{C\text{-}SF4}$ = 4.5 Hz), 129.4, 128.2, 128.2, 120.7 (q, $^1J_{C\text{-}F}$ = 274.5 Hz), 118.3 (app d, $^2J_{C\text{-}SF4}$ = 1.5 Hz); ^{19}F NMR ($CDCl_3$) δ 83.6 (qu, *J* = 157.9 Hz), 71.7 (d, *J* = 177.7 Hz), -68.1; EIMS *m/z* 357 (M^+, 100), 249 (25), 149 (55), 180 (60), 89 (20); HRMS (EI) *m/z* calcd for $C_{10}H_4NF_8SCl$ 356.9625, found 356.9633.



36

α-(2-Pyridyl)-8-pentafluorosulfanyl-(2-trifluoromethyl)-4-quinolylacetonitrile (36). A cooled (0 ~ 5°C) suspension of sodium hydride (38.8 mg, 1.54 mmol) in toluene (6.0 mL) and DMF (3.0 mL) was treated under argon gas with a solution of 2-pyridylacetonitrile (0.18 mL, 1.66 mmol) in toluene (5.0 mL) and DMF (1.5 mL) for 10 min. The resulting yellow-brown colored suspension was stirred for 1 h at the same temperature. A solution of 4-chloro-8-pentafluorosulfanyl-2-(trifluoromethyl)quinoline (0.458 g, 1.28 mmol) in toluene (8.0 mL) and DMF (3.0 mL) was added dropwise to the suspension over 5 min. After 0.5 h, the reaction mixture was quenched with ice water (50 mL), extracted with EtOAc, washed with water (3x) and brine, dried ($MgSO_4$) and concentrated. The orange residue was purified by chromatography on SiO_2 (25% EtOAc/Hexanes) to provide **36** (0.450 g, 80%) as a light orange solid: Mp 146.2 °C (dec.); IR (neat) 2876, 1368, 1275, 1179, 1144, 1122, 846, 833, 793, 654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.61 (ddd, 1 H, *J* = 0.9, 1.8, 5.1 Hz), 8.47 (d, 1 H, *J* = 8.7 Hz), 8.41 (dd, 1 H, *J* = 0.9, 8.1 Hz), 8.10 (s, 1 H), 7.79 (dd, 1 H, *J* = 8.1, 8.4 Hz), 7.78 (ddd, 1 H, *J* = 2.1, 7.8, 7.8 Hz), 7.46 (d, 1 H, *J* = 8.1 Hz), 7.33 (ddd, 1 H, *J* = 0.9, 5.1, 7.5 Hz), 6.07 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 153.0, 152.4 (qu, $^2J_{C\text{-}SF4}$ = 15.8 Hz), 150.6, 148.7 (q, $^2J_{C\text{-}CF3}$ = 36.0 Hz), 143.2, 141.9, 138.4, 132.6 (app t, $^2J_{C\text{-}SF4}$ = 5.3 Hz), 128.6, 128.2, 127.3, 124.3, 122.6, 120.9 (q, $^1J_{C\text{-}F}$ = 273.8 Hz), 117.5, 117.4, 43.4; ^{19}F NMR ($CDCl_3$) δ 83.7 (qu, *J* = 157.9 Hz), 71.6 (d, *J* = 169.2 Hz), -68.1;

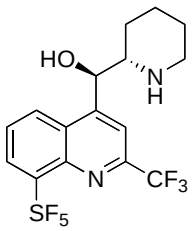
EIMS *m/z* 439 (M^+, 60), 428 (25), 273 (25), 89 (30), 78 (100); HRMS (EI) *m/z* calcd for $C_{17}H_9N_3F_8S$ 439.0389, found 439.0388.



37

2-Pyridyl-8-pentafluorosulfanyl-(2-trifluoromethyl)-4-quinolylketone (37). A suspension of **36** (197 mg, 0.448 mmol) in acetic acid (2.6 mL) was treated with H_2O_2 (0.35 mL, 4.48 mmol) dropwise at room temperature. The reaction mixture was placed in a preheated (75 °C) oil bath until it turned to light yellow. The mixture was quenched with ice water (10 mL), extracted with diethyl ether (10 mL), washed with sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated. The yellow residue was purified by chromatography on SiO_2 (16% EtOAc/Hexanes) to provide 2-pyridyl-8-pentafluorosulfanyl-(2-trifluoromethyl)-4-quinolylketone (**37**) (171 mg, 89%) as a white solid: Mp 98.9~99.7 °C; IR (neat)1687, 1271, 1245, 1211, 1182, 1137, 1114, 844, 829, 759, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.62 (ddd, 1 H, *J* = 0.9, 1.8, 4.5 Hz), 8.42 (dd, 1 H, *J* = 1.2, 7.8 Hz), 8.38 (ddd, 1 H, *J* = 0.9, 0.9, 8.1 Hz), 8.12 (dd, 1 H, *J* = 1.2, 8.4 Hz), 8.04 (ddd, 1 H, *J* = 1.8, 7.8, 7.8 Hz), 7.90 (s, 1 H), 7.72 (app t, 1 H, *J* = 8.1 Hz), 7.60 (ddd, 1 H, *J* = 1.2, 4.5, 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 194.4, 152.9, 151.8 (appt, $^2J_{C\text{-}SF4}$ = 15.0 Hz), 149.8, 147.8 (q, $^2J_{C\text{-}CF3}$ = 35.3 Hz), 147.2, 141.6, 137.8, 132.4 (appt, $^2J_{C\text{-}SF4}$ = 5.3 Hz), 130.6, 128.5, 127.8, 127.1, 124.4, 121.1 (q, $^1J_{C\text{-}F}$ = 273.8 Hz), 117.2 (d, $^2J_{C\text{-}SF4}$ = 2.3 Hz); ^{19}F NMR ($CDCl_3$) δ 84.1 (qu, *J* = 157.9 Hz), 71.7 (d, *J* = 149.5 Hz), -68.0; EIMS *m/z* 428 (M^+,

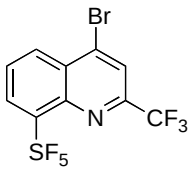
65), 399 (100), 273 (95), 272 (30); HRMS (EI) *m/z* calcd for $C_{16}H_8N_2OF_8S$ 428.0230, found 439.0215.



27

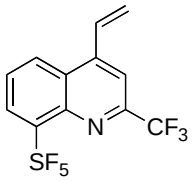
α-(2-Piperidyl)-8-pentafluorosulfanyl-(2-trifluoromethyl)-4-quinolinemethanol (27). A solution of 2-pyridyl-8-pentafluorosulfanyl-(2-trifluoromethyl)-4-quinolylketone (**37**) (83.2 mg, 0.194 mmol) in conc. hydrochloric acid (79 μL, 0.971 mmol) and abs EtOH (2.0 mL) was treated with platinum oxide (4.4 mg, 0.0194 mmol). The flask was purged with hydrogen twice and hydrogenated under balloon pressure of H_2. After 2 h, no alcohol intermediate appeared on TLC (50% EtOAc/Hexanes to check for the alcohol intermediate by UV, followed by 75% dichloromethane/EtOH to check for the final product by UV and ninhydrin staining) anymore. The mixture was filtered through florisil, concentrated, extracted with diethyl ether (20 mL), washed with sat. $NaHCO_3$ and NaOH aqueous solution (pKa = 13) and brine, dried ($MgSO_4$) and concentrated. The yellow residue was purified by chromatography on SiO_2 (5% triethylamine in EtOAc then 5% triethylamine and 5% MeOH in EtOAc). The crude product (65.0 mg) was crystallized from MeOH to obtain **6** (40.0 mg, 47%) as a white solid in a dr: 20>1: Mp 182.0 °C (dec.); IR (neat) 3088, 2937, 2600 (br), 1422, 1366, 1267, 1224, 1183, 1113, 846, 826, 785, 721, 652 cm^{-1}; ^1H NMR (acetone-d_6, 600 MHz) δ 8.75 (d, 1 H, *J* = 8.4 Hz), 8.58 (d, 1 H, *J* = 7.8 Hz), 8.19 (s, 1 H), 7.97 (dd, 1 H, *J* = 7.8, 8.4 Hz), 5.58 (d, 1 H, *J* = 3.6 Hz), 3.03 (ddd, 1 H, *J* = 3.0, 4.8, 10.8 Hz), 2.98 (app d, 1 H, *J* = 12.0 Hz), 2.56 (dt, 1 H, *J* = 3.0, 12.0 Hz), 1.72 (app d, 1 H, *J*

= 12.6 Hz), 1.47 (app d, 1 H, *J* = 12.6 Hz), 1.42 (app d, 1 H, *J* = 12.6 Hz), 1.39-1.22 (m, 2 H), 1.57 (tq, 1 H, *J* = 3.6, 13.2 Hz); ^{13}C NMR (acetone-d_6, 600 MHz) δ 154.5, 152.1 (qu, $^{2}J_{C\text{-}SF_4}$ = 13.5 Hz), 148.4 (q, $^{2}J_{C\text{-}CF_3}$ = 34.5 Hz), 141.7, 133.1 (appt, $^{2}J_{C\text{-}SF_4}$ = 4.5 Hz), 131.0, 129.1, 127.9, 122.5 (q, $^{1}J_{C\text{-}F}$ = 273.0 Hz), 116.5 (d, $^{2}J_{C\text{-}SF_4}$ = 1.5 Hz), 73.5, 62.3, 47.6, 27.3, 27.0, 25.1; ^{19}F NMR (acetone-d_6) δ 86.6 (qu, *J* = 150.2 Hz), 72.8 (d, *J* = 144.7 Hz), -67.1; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}N_2OF_8S$ (M+1) 437.0934, found 437.0923.



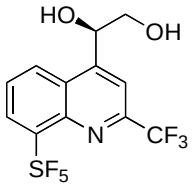
43

4-Bromo-8-pentafluorosulfanyl-2-(trifluoromethyl)quinoline (43). After addition of phosphorus oxybromide (160 mg, 0.557 mmol) to **34** (19.0 mg, 0.0557 mmol), the reaction mixture was warmed to 110 °C and stirred at this temperature for 0.5 h. The mixture was cooled to 0 °C and quenched with 20 g of ice. The suspension was extracted with diethyl ether (20 mL). The organic layer was washed with sat. $NaHCO_3$ (2x) and brine, dried ($MgSO_4$) and concentrated. The yellow residue was purified by chromatography on SiO_2 (5% EtOAc/Hexanes) to provide 4-bromo-8-pentafluorosulfanyl-2-(trifluoromethyl)quinoline (**43**) (19.1 mg, 85%) as a beige solid: ^{1}H NMR ($CDCl_3$) δ 8.57 (dd, 1 H, *J* = 0.9, 8.4 Hz), 8.46 (dd, 1 H, *J* = 1.2, 7.8 Hz), 8.14 (s, 1 H), 7.86 (dd, 1 H, *J* = 7.8, 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 151.7 (qu, $^{2}J_{C\text{-}SF_4}$ = 15.0 Hz), 148.3 (q, $^{2}J_{C\text{-}CF_3}$ = 36.0 Hz), 141.8, 136.5, 133.1 (app t, $^{2}J_{C\text{-}SF_4}$ = 5.3 Hz), 132.1, 129.5, 128.3, 122.1 (app d, $^{2}J_{C\text{-}SF_4}$ = 1.5 Hz), 120.5 (q, $^{1}J_{C\text{-}F}$ = 274.5 Hz); ^{19}F NMR ($CDCl_3$) δ 83.2 (qu, *J* = 149.5 Hz), 71.7 (d, *J* = 152.3 Hz), -68.1.



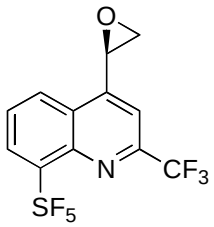
45

4-ethenyl-8-pentafluorosulfanyl-2-(trifluoromethyl)quinoline (45). A solution of **43** (30.0 mg, 0.0747 mmol) in dry degassed dioxane (1.5 mL) was treated with tetrakis(triphenylphosphine)palladium(0) (15.7 mg, 0.0149 mmol) and tri-*n*-butyl(vinyl)tin (27 μL, 0.0895 mmol). The reaction mixture was heated to 105 °C and kept at reflux for 1 h. The mixture was cooled to rt and quenched with KF (34.0 mg in 1.0 mL water). The suspension was extracted with diethyl ether (20 mL). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. The yellow residue was purified by chromatography on SiO_2 (15% EtOAc/Hexanes) to provide **45** (20.9 mg, 80%) as a white solid: Mp 108.7~109.6 °C; IR (neat) 1193, 1139, 1120, 833, 824, 759, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.41 (s, 1H), 8.38 (d, 1 H, *J* = 1.8 Hz), 7.87 (s, 1 H), 7.76 (dd, 1 H, *J* = 8.1, 8.1 Hz), 7.44 (dd, 1 H, *J* = 11.1, 17.1 Hz), 6.09 (d, 1 H, *J* = 17.1 Hz), 5.85 (d, 1 H, *J* = 11.1 Hz); ^{13}C NMR (CDCl3, 600 MHz) δ 152.0 (qu, $^2J_{C\text{-}SF4}$ = 13.5 Hz), 148.6 (q, $^2J_{C\text{-}CF3}$ = 36.0 Hz), 146.9, 141.6, 132.1 (qu, $^2J_{C\text{-}SF4}$ = 4.5 Hz), 131.5, 128.8, 128.0, 126.9, 123.8, 121.3 (q, $^1J_{C\text{-}F}$ = 274.5 Hz), 114.4; ^{19}F NMR ($CDCl_3$) δ 84.5 (qu, *J* = 155.1 Hz), 71.5 (d, *J* = 153.3 Hz), -68.2; EIMS *m/z* 349 (M^+, 5), 222 (50), 202 (100), 152 (90), 127 (70), 89 (90), 69 (85).



46

4-(1,2-dihydroxyethyl)-8-pentafluorosulfanyl-2-(trifluoromethyl)quinoline (46). A round-bottom flask was charged with a stir bar, AD-mix-α (0.401 g) and methanesulfonamide (0.0887 g, 0.904 mmol). Water (1.7 mL) and *t*-BuOH (1.7 mL) were added, and the mixture was cooled to 0 °C. Olefin **45** (0.0987 g, 0.283 mmol) in *t*-BuOH (1.0 mL) was added to the mixture and the reaction was sirred for 2 h at rt. Sodium sulfite (0.500 g) was added and the reaction was stirred for 1 h. The reaction was pored into water (40 mL), extracted with DCM (3x) and the organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on SiO_2 (50% EtOAc/Hexanes) to provide **46** (0.107 g, 99%) as a white solid: Mp 176.9~178.2 °C; IR (neat) 3258, 1137, 1182, 1120, 1087, 1029, 854, 833, 824 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.73 (d, 1 H, *J* = 8.5 Hz), 8.58 (d, 1 H, *J* = 8.0 Hz), 8.25 (s, 1 H), 7.98 (dd, 1 H, *J* = 8.0, 8.5 Hz), 5.77 (t, 1 H, *J* = 5.5), 5.23 (s, 1 H), 4.20 (s, 1 H), 3.97 (dd, 1 H, *J* = 4.5, 11.5), 3.85 (dd, 1 H, *J* = 6.0, 11.0); ^{13}C NMR (acetone-d_6) δ 154.4, 152.1 (qu, $^2J_{C\text{-}SF4}$ = 12.8 Hz), 148.6 (q, $^2J_{C\text{-}CF3}$ = 34.5 Hz), 141.6, 133.1 (qu, $^2J_{C\text{-}SF4}$ = 5.3 Hz), 130.8, 129.1, 128.0, 122.5 (q, $^1J_{C\text{-}F}$ = 273.0 Hz), 116.2 (app d, $^2J_{C\text{-}SF4}$ = 2.3 Hz), 71.7, 68.0; ^{19}F NMR (acetone-d_6) δ 84.9 (qu, *J* = 146.6 Hz), 71.1 (d, *J* = 146.6 Hz), -68.8; EIMS *m/z* 383 (M^+, 90), 353 (100), 225 (30), 197 (25), 128 (25), 69 (25), 57 (35).

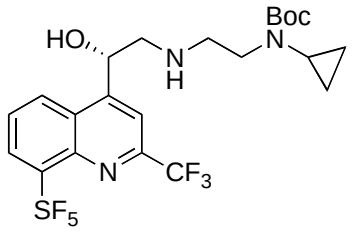


42

4-[(2S)-oxiran-2-yl]-8-(pentafluorosulfanyl)-2-(trifluoromethyl)quinoline (42). A solution of **46** (0.0780 g, 0.204 mmol) in dry THF (1.5 mL) was treated with NaH (0.0103 g,

0.407 mmol) and N-(*p*-toluenesulfonyl)imidazole (0.114 g, 0.509 mmol). The reaction was stirred for 1 h and it was quenched with water, extracted with diethyl ether (3*) and the organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on SiO_2 (20% EtOAc/Hexanes) to provide **42** (0.0596 g, 80%) as a white solid: Mp 106.9~108.1 °C; $[\alpha]_D^{21}$ -20.9 (c 0.76, $CHCl_3$); 41% *ee*; IR (neat) 1191, 1131, 1114, 841, 826, 807, 766, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.42 (d, 2 H, *J* = 8.1 Hz), 7.82 (dd, 2 H, *J* = 7.5, 8.4 Hz), 4.54 (dd, 1 H, *J* = 2.7, 3.6 Hz), 3.44 (dd, 1 H, *J* = 4.2, 5.4 Hz), 2.83 (dd, 1 H, *J* = 2.4, 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 152.1 (qu, $^2J_{C\text{-}SF4}$ = 14.3 Hz), 149.0 (q, $^2J_{C\text{-}CF3}$ = 36.0 Hz), 147.1, 140.9, 132.2 (qu, $^2J_{C\text{-}SF4}$ = 4.5 Hz), 128.2, 127.9, 127.5, 121.1 (q, $^1J_{C\text{-}F}$ = 273.8 Hz), 113.4 (app d, $^2J_{C\text{-}SF4}$ = 2.3 Hz), 51.0, 49.6; ^{19}F NMR ($CDCl_3$) δ 84.1 (qu, *J* = 149.5 Hz), 71.5 (d, *J* = 152.3 Hz), -68.3; EIMS *m/z* 365 (M^+, 5), 238 (25), 210 (35), 127 (40), 89 (100), 69 (100).

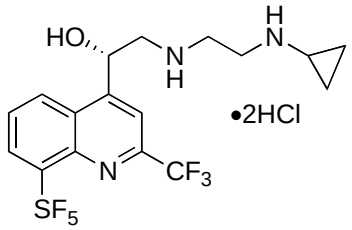
4-[(2S)-oxiran-2-yl]-8-(pentafluorosulfanyl)-2-(trifluoromethyl)quinoline(42). $[\alpha]_D^{21}$ +24.5 (c 0.70, $CHCl_3$); 46% *ee*.



S-**48**

***tert*-butyl N-cyclopropyl-N-(2-{[(2s)-2-hydroxyl-2-[8-pentafluorosulfanyl)-2-(trifluoromethyl)quinolin-4-yl]ethyl]amino}ethyl)carbamate (48)**. A solution of *S*-**42** (0.0090 g, 0.0246 mmol) in EtOH (0.8 mL) was treated with *t*-butyl N-(2-aminoethyl)-N-cyclopropyl carbamate (0.0054 g, 0.0296 mmol). The mixture was irradiated at 155 °C by microwave for 1 h and was concentrated to afford light yellow oil. The residue was purified by chromatography on

SiO_2 (2% MeOH and 0.5% NH_4OH in DCM) to provide **48** (0.0113 g, 81%) as a white solid: ^1H NMR ($CDCl_3$) δ 8.38 (dd, 1 H, *J* = 1.2, 8.1 Hz), 8.29 (d, 1 H, *J* = 8.1 Hz), 8.16 (s, 1 H), 7.75 (dd, 1 H, *J* = 8.1, 8.1 Hz), 5.51 (dd, 1 H, *J* = 3.6, 8.7 Hz), 3.38 (m, 2 H), 3.25 (dd, 1 H, *J* = 3.6, 12.6 Hz), 2.92 (m, 2 H), 2.78 (dd, 1 H, *J* = 8.4, 12.3 Hz), 2.52 (ddd, 1 H, *J* = 3.9, 7.2, 10.8 Hz), 1.47 (s, 9 H), 0.77 (m, 2 H), 0.61 (m, 2 H).



S-**49**

(1S)-2-{[2-(cyclopropylamino)ethyl]amino}-1-[8-pentafluorosulfanyl)-2-(trifluoro-methyl)quinolin-4-yl]ethanol (48). A solution of *S*-**48** (0.0110 g, 0.0200 mmol) in Et_2O (0.1 mL) was treated with 2 N HCl in Et_2O (0.30 mL, 0.600 mmol) at 0 °C and the mixture was stirred for 4 h and was concentrated by Argon flow to afford **49** (0.0093 g, 99%) as a white solid: ^1H NMR (MeOD) δ 8.80 (d, 1 H, *J* = 6.0 Hz), 8.58 (d, 1 H, *J* = 6.0 Hz), 8.27 (s, 1 H), 7.99 (dd, 1 H, *J* = 6.0, 6.0 Hz), 6.07 (d, 1 H, *J* = 6.9 Hz), 3.70 ~ 3.40 (m, 6 H), 2.89 (m, 1 H), 1.04 (m, 2 H), 0.97 (d, 1 H, *J* = 5.1 Hz).

Procedure for analyses of enantiomeric excess of epoxide 42 via chiral SFC.

SFC was performed on a Metter Toledo-MiniGram instrument with a CHIRALPAK IB column (250 x 4.6 mm) at room temperature using a Berger KNR-2501 Detector (220 nm). Samples were prepared by dissolving 1.0 – 2.0 mg of the pure compounds in 1.0 – 2.0 mL of MeOH (HPLC grade). Ten microliter (10 μL) of the solution was injected for analyses. HPLC grade 2-

propanyol (5%) was used for the elution. The flow rate was 1.5 mL/min and the outlet pressure was 100 bar. The retention time of *R*-isomer is 12.09 min and the retention time of *S*-isomer is 12.89 min.

APPENDIX A X-ray data of 8B

Table 9 Crystal data and structure refinement for **8b**

Identification code	ting127s	
Empirical formula	C17 H20 F8 N2 O2 S	
Formula weight	468.41	
Temperature	203(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 21.098(3) Å	a= 90°.
	b = 23.909(3) Å	b= 109.994(3)°.
	c = 17.404(2) Å	g = 90°.
Volume	8250.2(18) $Å^3$	
Z	16	
Density (calculated)	1.508 Mg/m^3	
Absorption coefficient	0.244 mm^{-1}	
F(000)	3840	
Crystal size	0.24 x 0.14 x 0.14 mm^3	
Theta range for data collection	1.57 to 27.50°.	
Index ranges	-27<=h<=27, -31<=k<=31, -22<=l<=22	
Reflections collected	39637	
Independent reflections	9475 [R(int) = 0.0637]	
Completeness to theta = 27.50°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9667 and 0.9438	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9475 / 0 / 567	
Goodness-of-fit on F^2	1.006	

Final R indices [I>2sigma(I)]	R1 = 0.0551, wR2 = 0.1342
R indices (all data)	R1 = 0.0900, wR2 = 0.1508
Largest diff. peak and hole	0.405 and -0.269 e.Å^{-3}

Table 10 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **8b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	3595(1)	1264(1)	6519(1)	51(1)
O(1)	5508(1)	-1763(1)	6530(1)	43(1)
N(1)	5644(1)	324(1)	6168(1)	39(1)
F(1)	2928(1)	1003(1)	5918(1)	78(1)
C(1)	5047(1)	230(1)	6296(1)	34(1)
N(2)	4088(1)	-2061(1)	5785(1)	38(1)
C(2)	4676(1)	709(1)	6358(1)	37(1)
F(2)	3421(1)	1033(1)	7268(1)	78(1)
S(2)	1378(1)	1295(1)	2761(1)	53(1)
O(2)	-346(1)	-1787(1)	1136(1)	43(1)
F(3)	3177(1)	1806(1)	6555(1)	77(1)
C(3)	4075(1)	646(1)	6477(1)	38(1)
N(3)	-573(1)	288(1)	613(1)	39(1)
O(3)	6369(1)	-1672(1)	8062(1)	55(1)
F(4)	4235(1)	1567(1)	7125(1)	75(1)
C(4)	3822(1)	115(1)	6559(2)	41(1)
N(4)	1086(1)	-2044(1)	1756(1)	39(1)
O(4)	1346(1)	-1651(1)	3263(1)	55(1)
F(5)	3741(1)	1539(1)	5776(1)	76(1)
C(5)	4181(1)	-352(1)	6514(1)	40(1)
C(6)	4802(1)	-311(1)	6368(1)	34(1)
F(6)	6633(1)	444(1)	5542(1)	86(1)
C(7)	5200(1)	-779(1)	6299(1)	35(1)
F(7)	7127(1)	102(1)	6713(1)	87(1)
C(8)	5796(1)	-676(1)	6173(1)	39(1)
F(8)	6874(1)	-420(1)	5675(1)	82(1)
C(9)	5988(1)	-121(1)	6110(1)	38(1)
F(9)	2074(1)	1027(1)	2806(1)	65(1)
C(10)	4975(1)	-1372(1)	6372(1)	37(1)
F(10)	1496(1)	1075(1)	3651(1)	77(1)

C(11)	4414(1)	-1561(1)	5588(1)	38(1)
F(11)	1779(1)	1839(1)	3159(1)	80(1)
C(12)	3541(1)	-2273(1)	5064(2)	52(1)
F(12)	719(1)	1598(1)	2754(1)	91(1)
C(13)	3759(2)	-2378(1)	4333(2)	57(1)
F(13)	1308(1)	1548(1)	1901(1)	80(1)
C(14)	4084(2)	-1862(1)	4127(2)	62(1)
F(14)	-1594(1)	380(1)	-814(1)	82(1)
C(15)	4658(2)	-1658(1)	4877(2)	54(1)
F(15)	-2048(1)	-60(1)	-89(1)	96(1)
C(16)	6652(1)	2(1)	6003(2)	49(1)
F(16)	-1711(1)	-489(1)	-933(1)	89(1)
C(17)	14(1)	221(1)	1263(1)	36(1)
C(18)	355(1)	711(1)	1636(2)	41(1)
C(19)	926(1)	667(1)	2303(1)	39(1)
C(20)	1177(1)	146(1)	2638(1)	39(1)
C(21)	855(1)	-332(1)	2284(1)	39(1)
C(22)	270(1)	-313(1)	1576(1)	34(1)
C(23)	-86(1)	-794(1)	1166(1)	34(1)
C(24)	-666(1)	-716(1)	519(1)	39(1)
C(25)	-886(1)	-168(1)	279(1)	37(1)
C(26)	161(1)	-1378(1)	1462(1)	35(1)
C(27)	781(1)	-1553(1)	1247(1)	37(1)
C(28)	1691(1)	-2244(1)	1592(2)	53(1)
C(29)	1561(1)	-2369(1)	705(2)	58(1)
C(30)	1260(2)	-1866(1)	179(2)	60(1)
C(31)	629(1)	-1658(1)	340(2)	48(1)
C(32)	-1561(1)	-78(1)	-388(2)	47(1)
C(33)	7056(2)	-1556(2)	8373(2)	90(1)
C(34)	2008(2)	-1476(2)	3621(2)	85(1)

Table 11 Bond lengths [Å] and angles [°] for **8b**.

S(1)-F(1)	1.5666(18)
S(1)-F(2)	1.5708(18)
S(1)-F(5)	1.5718(18)
S(1)-F(4)	1.5767(18)
S(1)-F(3)	1.5792(16)
S(1)-C(3)	1.807(2)
O(1)-C(10)	1.416(3)
O(1)-H(1O)	0.78(3)
N(1)-C(9)	1.311(3)
N(1)-C(1)	1.370(3)
C(1)-C(2)	1.411(3)
C(1)-C(6)	1.416(3)
N(2)-C(12)	1.474(3)
N(2)-C(11)	1.476(3)
N(2)-H(2N)	0.84(2)
C(2)-C(3)	1.361(3)
C(2)-H(2A)	0.9400
S(2)-F(12)	1.5640(19)
S(2)-F(10)	1.5732(18)
S(2)-F(13)	1.5739(19)
S(2)-F(11)	1.5766(16)
S(2)-F(9)	1.5781(17)
S(2)-C(19)	1.811(2)
O(2)-C(26)	1.416(3)
O(2)-H(2O)	0.79(3)
C(3)-C(4)	1.404(3)
N(3)-C(25)	1.303(3)
N(3)-C(17)	1.371(3)
O(3)-C(33)	1.391(3)
O(3)-H(3O)	0.79(3)
C(4)-C(5)	1.368(3)
C(4)-H(4A)	0.9400
N(4)-C(27)	1.478(3)

N(4)-C(28)	1.481(3)
N(4)-H(4N)	0.81(2)
O(4)-C(34)	1.387(3)
O(4)-H(4O)	0.88(3)
C(5)-C(6)	1.419(3)
C(5)-H(5A)	0.9400
C(6)-C(7)	1.429(3)
F(6)-C(16)	1.320(3)
C(7)-C(8)	1.370(3)
C(7)-C(10)	1.513(3)
F(7)-C(16)	1.321(3)
C(8)-C(9)	1.403(3)
C(8)-H(8A)	0.9400
F(8)-C(16)	1.321(3)
C(9)-C(16)	1.502(3)
C(10)-C(11)	1.538(3)
C(10)-H(10A)	0.9900
C(11)-C(15)	1.512(4)
C(11)-H(11A)	0.9900
C(12)-C(13)	1.515(4)
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(13)-C(14)	1.515(4)
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(14)-C(15)	1.525(4)
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
F(14)-C(32)	1.311(3)
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
F(15)-C(32)	1.302(3)
F(16)-C(32)	1.325(3)
C(17)-C(18)	1.411(3)
C(17)-C(22)	1.420(3)
C(18)-C(19)	1.362(3)

C(18)-H(18A)	0.9400
C(19)-C(20)	1.399(3)
C(20)-C(21)	1.363(3)
C(20)-H(20A)	0.9400
C(21)-C(22)	1.417(3)
C(21)-H(21A)	0.9400
C(22)-C(23)	1.423(3)
C(23)-C(24)	1.364(3)
C(23)-C(26)	1.517(3)
C(24)-C(25)	1.405(3)
C(24)-H(24A)	0.9400
C(25)-C(32)	1.514(3)
C(26)-C(27)	1.538(3)
C(26)-H(26A)	0.9900
C(27)-C(31)	1.521(3)
C(27)-H(27A)	0.9900
C(28)-C(29)	1.502(4)
C(28)-H(28A)	0.9800
C(28)-H(28B)	0.9800
C(29)-C(30)	1.512(4)
C(29)-H(29A)	0.9800
C(29)-H(29B)	0.9800
C(30)-C(31)	1.534(4)
C(30)-H(30A)	0.9800
C(30)-H(30B)	0.9800
C(31)-H(31A)	0.9800
C(31)-H(31B)	0.9800
C(33)-H(33A)	0.9700
C(33)-H(33B)	0.9700
C(33)-H(33C)	0.9700
C(34)-H(34A)	0.9700
C(34)-H(34B)	0.9700
C(34)-H(34C)	0.9700

F(1)-S(1)-F(2)	90.17(12)
F(1)-S(1)-F(5)	90.11(11)

F(2)-S(1)-F(5)	175.57(9)
F(1)-S(1)-F(4)	175.81(9)
F(2)-S(1)-F(4)	89.69(11)
F(5)-S(1)-F(4)	89.71(11)
F(1)-S(1)-F(3)	88.12(9)
F(2)-S(1)-F(3)	87.89(10)
F(5)-S(1)-F(3)	87.70(9)
F(4)-S(1)-F(3)	87.69(9)
F(1)-S(1)-C(3)	92.00(10)
F(2)-S(1)-C(3)	92.24(10)
F(5)-S(1)-C(3)	92.17(10)
F(4)-S(1)-C(3)	92.19(10)
F(3)-S(1)-C(3)	179.83(12)
C(10)-O(1)-H(1O)	110(2)
C(9)-N(1)-C(1)	116.44(19)
N(1)-C(1)-C(2)	116.47(19)
N(1)-C(1)-C(6)	123.22(19)
C(2)-C(1)-C(6)	120.31(19)
C(12)-N(2)-C(11)	111.81(19)
C(12)-N(2)-H(2N)	105.0(16)
C(11)-N(2)-H(2N)	109.8(16)
C(3)-C(2)-C(1)	119.6(2)
C(3)-C(2)-H(2A)	120.2
C(1)-C(2)-H(2A)	120.2
F(12)-S(2)-F(10)	90.16(12)
F(12)-S(2)-F(13)	91.13(12)
F(10)-S(2)-F(13)	175.52(10)
F(12)-S(2)-F(11)	87.85(10)
F(10)-S(2)-F(11)	87.85(10)
F(13)-S(2)-F(11)	87.91(10)
F(12)-S(2)-F(9)	175.69(9)
F(10)-S(2)-F(9)	89.15(10)
F(13)-S(2)-F(9)	89.24(11)
F(11)-S(2)-F(9)	87.87(10)
F(12)-S(2)-C(19)	92.75(10)
F(10)-S(2)-C(19)	92.19(10)

F(13)-S(2)-C(19)	92.03(10)
F(11)-S(2)-C(19)	179.39(12)
F(9)-S(2)-C(19)	91.52(10)
C(26)-O(2)-H(2O)	106(2)
C(2)-C(3)-C(4)	121.4(2)
C(2)-C(3)-S(1)	118.75(17)
C(4)-C(3)-S(1)	119.87(17)
C(25)-N(3)-C(17)	116.51(18)
C(33)-O(3)-H(3O)	110(2)
C(5)-C(4)-C(3)	119.7(2)
C(5)-C(4)-H(4A)	120.2
C(3)-C(4)-H(4A)	120.2
C(27)-N(4)-C(28)	111.67(19)
C(27)-N(4)-H(4N)	107.8(16)
C(28)-N(4)-H(4N)	105.7(16)
C(34)-O(4)-H(4O)	112.3(18)
C(4)-C(5)-C(6)	121.1(2)
C(4)-C(5)-H(5A)	119.4
C(6)-C(5)-H(5A)	119.4
C(1)-C(6)-C(5)	117.85(19)
C(1)-C(6)-C(7)	117.69(19)
C(5)-C(6)-C(7)	124.5(2)
C(8)-C(7)-C(6)	118.11(19)
C(8)-C(7)-C(10)	120.8(2)
C(6)-C(7)-C(10)	121.05(19)
C(7)-C(8)-C(9)	119.3(2)
C(7)-C(8)-H(8A)	120.4
C(9)-C(8)-H(8A)	120.4
N(1)-C(9)-C(8)	125.3(2)
N(1)-C(9)-C(16)	114.6(2)
C(8)-C(9)-C(16)	120.1(2)
O(1)-C(10)-C(7)	112.59(18)
O(1)-C(10)-C(11)	107.34(17)
C(7)-C(10)-C(11)	111.69(18)
O(1)-C(10)-H(10A)	108.4
C(7)-C(10)-H(10A)	108.4

C(11)-C(10)-H(10A)	108.4
N(2)-C(11)-C(15)	112.48(18)
N(2)-C(11)-C(10)	108.08(17)
C(15)-C(11)-C(10)	113.3(2)
N(2)-C(11)-H(11A)	107.6
C(15)-C(11)-H(11A)	107.6
C(10)-C(11)-H(11A)	107.6
N(2)-C(12)-C(13)	113.5(2)
N(2)-C(12)-H(12A)	108.9
C(13)-C(12)-H(12A)	108.9
N(2)-C(12)-H(12B)	108.9
C(13)-C(12)-H(12B)	108.9
H(12A)-C(12)-H(12B)	107.7
C(14)-C(13)-C(12)	110.8(2)
C(14)-C(13)-H(13A)	109.5
C(12)-C(13)-H(13A)	109.5
C(14)-C(13)-H(13B)	109.5
C(12)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	108.1
C(13)-C(14)-C(15)	110.5(2)
C(13)-C(14)-H(14A)	109.6
C(15)-C(14)-H(14A)	109.6
C(13)-C(14)-H(14B)	109.6
C(15)-C(14)-H(14B)	109.6
H(14A)-C(14)-H(14B)	108.1
C(11)-C(15)-C(14)	110.9(2)
C(11)-C(15)-H(15A)	109.5
C(14)-C(15)-H(15A)	109.5
C(11)-C(15)-H(15B)	109.5
C(14)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	108.1
F(6)-C(16)-F(7)	106.2(2)
F(6)-C(16)-F(8)	106.8(2)
F(7)-C(16)-F(8)	105.9(2)
F(6)-C(16)-C(9)	113.3(2)
F(7)-C(16)-C(9)	111.2(2)

F(8)-C(16)-C(9)	112.9(2)
N(3)-C(17)-C(18)	117.23(19)
N(3)-C(17)-C(22)	122.6(2)
C(18)-C(17)-C(22)	120.1(2)
C(19)-C(18)-C(17)	119.5(2)
C(19)-C(18)-H(18A)	120.2
C(17)-C(18)-H(18A)	120.2
C(18)-C(19)-C(20)	121.4(2)
C(18)-C(19)-S(2)	119.41(18)
C(20)-C(19)-S(2)	119.15(18)
C(21)-C(20)-C(19)	119.9(2)
C(21)-C(20)-H(20A)	120.0
C(19)-C(20)-H(20A)	120.0
C(20)-C(21)-C(22)	121.2(2)
C(20)-C(21)-H(21A)	119.4
C(22)-C(21)-H(21A)	119.4
C(21)-C(22)-C(17)	117.8(2)
C(21)-C(22)-C(23)	124.3(2)
C(17)-C(22)-C(23)	117.9(2)
C(24)-C(23)-C(22)	118.3(2)
C(24)-C(23)-C(26)	120.82(19)
C(22)-C(23)-C(26)	120.85(19)
C(23)-C(24)-C(25)	119.0(2)
C(23)-C(24)-H(24A)	120.5
C(25)-C(24)-H(24A)	120.5
N(3)-C(25)-C(24)	125.6(2)
N(3)-C(25)-C(32)	115.0(2)
C(24)-C(25)-C(32)	119.2(2)
O(2)-C(26)-C(23)	112.05(18)
O(2)-C(26)-C(27)	107.61(17)
C(23)-C(26)-C(27)	112.89(18)
O(2)-C(26)-H(26A)	108.0
C(23)-C(26)-H(26A)	108.0
C(27)-C(26)-H(26A)	108.0
N(4)-C(27)-C(31)	112.62(18)
N(4)-C(27)-C(26)	107.64(17)

C(31)-C(27)-C(26)	113.76(19)
N(4)-C(27)-H(27A)	107.5
C(31)-C(27)-H(27A)	107.5
C(26)-C(27)-H(27A)	107.5
N(4)-C(28)-C(29)	113.3(2)
N(4)-C(28)-H(28A)	108.9
C(29)-C(28)-H(28A)	108.9
N(4)-C(28)-H(28B)	108.9
C(29)-C(28)-H(28B)	108.9
H(28A)-C(28)-H(28B)	107.7
C(28)-C(29)-C(30)	110.8(2)
C(28)-C(29)-H(29A)	109.5
C(30)-C(29)-H(29A)	109.5
C(28)-C(29)-H(29B)	109.5
C(30)-C(29)-H(29B)	109.5
H(29A)-C(29)-H(29B)	108.1
C(29)-C(30)-C(31)	111.0(2)
C(29)-C(30)-H(30A)	109.4
C(31)-C(30)-H(30A)	109.4
C(29)-C(30)-H(30B)	109.4
C(31)-C(30)-H(30B)	109.4
H(30A)-C(30)-H(30B)	108.0
C(27)-C(31)-C(30)	110.8(2)
C(27)-C(31)-H(31A)	109.5
C(30)-C(31)-H(31A)	109.5
C(27)-C(31)-H(31B)	109.5
C(30)-C(31)-H(31B)	109.5
H(31A)-C(31)-H(31B)	108.1
F(15)-C(32)-F(14)	107.6(2)
F(15)-C(32)-F(16)	106.3(2)
F(14)-C(32)-F(16)	105.1(2)
F(15)-C(32)-C(25)	111.2(2)
F(14)-C(32)-C(25)	114.0(2)
F(16)-C(32)-C(25)	112.1(2)
O(3)-C(33)-H(33A)	109.5
O(3)-C(33)-H(33B)	109.5

H(33A)-C(33)-H(33B)	109.5
O(3)-C(33)-H(33C)	109.5
H(33A)-C(33)-H(33C)	109.5
H(33B)-C(33)-H(33C)	109.5
O(4)-C(34)-H(34A)	109.5
O(4)-C(34)-H(34B)	109.5
H(34A)-C(34)-H(34B)	109.5
O(4)-C(34)-H(34C)	109.5
H(34A)-C(34)-H(34C)	109.5
H(34B)-C(34)-H(34C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 12 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **8b**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	45(1)	42(1)	71(1)	-2(1)	27(1)	10(1)
O(1)	45(1)	32(1)	47(1)	3(1)	10(1)	8(1)
N(1)	35(1)	35(1)	51(1)	1(1)	19(1)	0(1)
F(1)	40(1)	69(1)	113(2)	-11(1)	10(1)	14(1)
C(1)	33(1)	34(1)	37(1)	-1(1)	13(1)	0(1)
N(2)	34(1)	31(1)	45(1)	3(1)	7(1)	3(1)
C(2)	37(1)	32(1)	45(1)	1(1)	16(1)	2(1)
F(2)	96(1)	70(1)	96(1)	3(1)	67(1)	22(1)
S(2)	53(1)	40(1)	65(1)	-9(1)	19(1)	-14(1)
O(2)	38(1)	30(1)	65(1)	-4(1)	22(1)	-6(1)
F(3)	64(1)	52(1)	127(2)	-4(1)	48(1)	21(1)
C(3)	37(1)	35(1)	43(1)	-3(1)	15(1)	8(1)
N(3)	38(1)	33(1)	45(1)	4(1)	14(1)	5(1)
O(3)	38(1)	75(1)	52(1)	7(1)	16(1)	-2(1)
F(4)	60(1)	54(1)	106(1)	-31(1)	24(1)	4(1)
C(4)	33(1)	42(1)	52(1)	0(1)	19(1)	1(1)
N(4)	32(1)	32(1)	56(1)	4(1)	17(1)	0(1)
O(4)	38(1)	71(1)	56(1)	-6(1)	14(1)	-4(1)
F(5)	89(1)	57(1)	96(1)	29(1)	51(1)	32(1)
C(5)	38(1)	37(1)	47(1)	0(1)	17(1)	-3(1)
C(6)	34(1)	32(1)	35(1)	0(1)	11(1)	0(1)
F(6)	60(1)	79(1)	138(2)	50(1)	58(1)	15(1)
C(7)	35(1)	32(1)	36(1)	0(1)	11(1)	1(1)
F(7)	38(1)	126(2)	93(1)	-14(1)	18(1)	-9(1)
C(8)	37(1)	34(1)	48(1)	0(1)	16(1)	6(1)
F(8)	72(1)	68(1)	134(2)	-16(1)	72(1)	0(1)
C(9)	35(1)	36(1)	44(1)	0(1)	16(1)	2(1)
F(9)	45(1)	62(1)	87(1)	-5(1)	21(1)	-16(1)
C(10)	40(1)	31(1)	39(1)	3(1)	13(1)	4(1)
F(10)	104(1)	73(1)	57(1)	-21(1)	32(1)	-37(1)

C(11)	44(1)	28(1)	39(1)	4(1)	10(1)	4(1)
F(11)	80(1)	51(1)	98(1)	-19(1)	17(1)	-29(1)
C(12)	42(1)	47(1)	56(2)	-2(1)	1(1)	0(1)
F(12)	67(1)	51(1)	152(2)	-44(1)	35(1)	-5(1)
C(13)	58(2)	51(2)	49(2)	-12(1)	0(1)	1(1)
F(13)	95(1)	53(1)	76(1)	16(1)	12(1)	-28(1)
C(14)	85(2)	60(2)	38(2)	-2(1)	16(1)	3(2)
F(14)	61(1)	80(1)	82(1)	36(1)	-7(1)	-2(1)
C(15)	74(2)	49(2)	40(1)	0(1)	23(1)	-8(1)
F(15)	38(1)	175(2)	77(1)	26(1)	23(1)	22(1)
C(16)	37(1)	45(1)	70(2)	4(1)	24(1)	4(1)
F(16)	70(1)	81(1)	80(1)	-23(1)	-20(1)	17(1)
C(17)	36(1)	34(1)	42(1)	1(1)	18(1)	3(1)
C(18)	44(1)	30(1)	52(1)	2(1)	21(1)	2(1)
C(19)	39(1)	35(1)	45(1)	-5(1)	18(1)	-7(1)
C(20)	34(1)	41(1)	41(1)	0(1)	12(1)	-4(1)
C(21)	37(1)	35(1)	44(1)	4(1)	15(1)	1(1)
C(22)	31(1)	31(1)	43(1)	0(1)	16(1)	2(1)
C(23)	33(1)	33(1)	41(1)	0(1)	17(1)	-1(1)
C(24)	36(1)	34(1)	45(1)	-4(1)	13(1)	-3(1)
C(25)	33(1)	38(1)	42(1)	2(1)	14(1)	4(1)
C(26)	31(1)	30(1)	45(1)	1(1)	13(1)	-2(1)
C(27)	37(1)	28(1)	49(1)	1(1)	18(1)	-1(1)
C(28)	39(1)	48(1)	78(2)	5(1)	29(1)	8(1)
C(29)	52(2)	54(2)	80(2)	-6(1)	38(2)	2(1)
C(30)	68(2)	60(2)	67(2)	-5(1)	43(2)	-6(1)
C(31)	54(2)	46(1)	48(2)	3(1)	22(1)	4(1)
C(32)	36(1)	47(1)	54(2)	3(1)	11(1)	3(1)
C(33)	43(2)	142(4)	87(3)	4(2)	22(2)	-15(2)
C(34)	39(2)	118(3)	84(2)	-5(2)	2(2)	0(2)

Table 13 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **8b.**

	x	y	z	U(eq)
H(1O)	5759(15)	-1726(12)	6972(19)	63(10)
H(2N)	4367(12)	-2323(10)	5927(14)	35(6)
H(2A)	4842	1068	6317	45
H(2O)	-643(15)	-1713(11)	1300(17)	53(9)
H(3O)	6257(16)	-1839(13)	8390(20)	74(11)
H(4A)	3407	81	6645	49
H(4N)	815(12)	-2299(10)	1622(14)	34(6)
H(4O)	1279(13)	-1827(12)	2801(18)	57(9)
H(5A)	4015	-707	6581	48
H(8A)	6072	-974	6129	47
H(10A)	4798	-1386	6830	44
H(11A)	4071	-1259	5428	45
H(12A)	3170	-2001	4911	63
H(12B)	3369	-2622	5211	63
H(13A)	4080	-2690	4453	69
H(13B)	3365	-2483	3861	69
H(14A)	3746	-1565	3934	75
H(14B)	4260	-1949	3688	75
H(15A)	5021	-1936	5031	64
H(15B)	4841	-1308	4746	64
H(18A)	188	1064	1427	49
H(20A)	1566	126	3107	47
H(21A)	1026	-680	2514	46
H(24A)	-916	-1024	238	47
H(26A)	288	-1383	2065	42
H(27A)	1112	-1244	1411	45
H(28A)	1858	-2584	1912	63
H(28B)	2046	-1960	1776	63
H(29A)	1251	-2686	534	69
H(29B)	1986	-2472	629	69

H(30A)	1140	-1967	-399	71
H(30B)	1595	-1565	297	71
H(31A)	470	-1311	35	58
H(31B)	270	-1938	146	58
H(33A)	7176	-1313	7998	136
H(33B)	7309	-1902	8440	136
H(33C)	7163	-1372	8899	136
H(34A)	2125	-1227	3250	128
H(34B)	2305	-1798	3738	128
H(34C)	2058	-1279	4126	128

APPENDIX B X-ray data of 27

Table 14 Crystal data and structure refinement for **27**

Identification code	tt18157s	
Empirical formula	C16 H16 F8 N2 O S	
Formula weight	436.37	
Temperature	203(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	P4(2)/n	
Unit cell dimensions	a = 20.557(4) Å	a= 90°.
	b = 20.557(4) Å	b= 90°.
	c = 8.708(2) Å	g= 90°.
Volume	3679.9(14) $Å^3$	
Z	8	
Density (calculated)	1.575 Mg/m^3	
Absorption coefficient	0.263 mm^{-1}	
F(000)	1776	
Crystal size	0.25 x 0.16 x 0.09 mm^3	
Theta range for data collection	1.98 to 25.00°.	
Index ranges	-24<=h<=24, -24<=k<=24, -10<=l<=10	
Reflections collected	28259	
Independent reflections	3245 [R(int) = 0.0878]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	None	
Max. and min. transmission	0.9767 and 0.9372	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3245 / 1 / 316	
Goodness-of-fit on F^2	0.946	

Final R indices [I>2sigma(I)]	R1 = 0.0464, wR2 = 0.1153
R indices (all data)	R1 = 0.0801, wR2 = 0.1300
Largest diff. peak and hole	0.273 and -0.159 e.Å^{-3}

Table 15 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **27**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	1273(1)	6909(1)	343(1)	62(1)
O	1478(1)	3462(1)	-3137(3)	58(1)
N(1)	764(1)	5686(1)	-1410(2)	48(1)
C(1)	1399(1)	5641(1)	-981(3)	43(1)
F(1)	908(1)	7566(1)	785(2)	90(1)
N(2)	2736(1)	3635(1)	-4426(3)	60(1)
F(2)	1562(1)	6907(1)	2021(2)	89(1)
C(2)	1699(1)	6166(1)	-157(3)	48(1)
F(3)	1864(1)	7345(1)	-205(2)	80(1)
C(3)	2338(1)	6122(2)	274(3)	53(1)
F(4)	963(1)	6974(1)	-1305(2)	66(1)
C(4)	2710(1)	5571(2)	-72(3)	53(1)
F(5)	657(1)	6533(1)	943(2)	71(1)
C(5)	2445(1)	5073(2)	-869(3)	48(1)
C(6)	1785(1)	5088(1)	-1347(3)	41(1)
F(6)	-430(1)	4782(1)	-3371(3)	94(1)
F(7)	-270(1)	5802(1)	-3495(2)	87(1)
C(7)	1490(1)	4574(1)	-2190(3)	43(1)
F(8)	-572(1)	5372(1)	-1398(2)	82(1)
C(8)	845(1)	4627(1)	-2560(3)	46(1)
C(9)	512(1)	5190(1)	-2151(3)	46(1)
C(10)	-190(1)	5283(2)	-2602(4)	59(1)
C(11)	1878(1)	3995(1)	-2732(3)	47(1)
C(12)	2291(1)	4174(1)	-4137(3)	46(1)
C(13)	1884(2)	4347(2)	-5544(3)	52(1)
C(14)	2300(2)	4452(2)	-6962(4)	64(1)
C(15)	2763(2)	3885(2)	-7211(4)	76(1)
C(16)	3152(2)	3757(2)	-5779(4)	80(1)

Table 16 Bond lengths [Å] and angles [°] for **27.**

S-F(5)	1.5730(18)
S-F(4)	1.5760(19)
S-F(2)	1.577(2)
S-F(3)	1.5827(19)
S-F(1)	1.5929(19)
S-C(2)	1.812(3)
O-C(11)	1.416(3)
O-H(1O)	0.89(4)
N(1)-C(9)	1.313(3)
N(1)-C(1)	1.363(3)
C(1)-C(6)	1.422(4)
C(1)-C(2)	1.435(4)
N(2)-C(12)	1.458(3)
N(2)-C(16)	1.477(4)
N(2)-H(2N)	0.860(10)
C(2)-C(3)	1.368(4)
C(3)-C(4)	1.401(4)
C(3)-H(3)	0.89(3)
C(4)-C(5)	1.351(4)
C(4)-H(4)	0.95(3)
C(5)-C(6)	1.420(4)
C(5)-H(5)	0.92(2)
C(6)-C(7)	1.422(4)
F(6)-C(10)	1.323(3)
F(7)-C(10)	1.332(4)
C(7)-C(8)	1.369(4)
C(7)-C(11)	1.509(4)
F(8)-C(10)	1.322(3)
C(8)-C(9)	1.391(4)
C(8)-H(8)	0.96(3)
C(9)-C(10)	1.507(4)
C(11)-C(12)	1.533(4)
C(11)-H(11)	0.99(2)

C(12)-C(13)	1.525(4)
C(12)-H(12)	0.92(2)
C(13)-C(14)	1.517(4)
C(13)-H(13A)	0.95(3)
C(13)-H(13B)	0.98(3)
C(14)-C(15)	1.520(5)
C(14)-H(14A)	0.92(3)
C(14)-H(14B)	1.04(4)
C(15)-C(16)	1.504(5)
C(15)-H(15A)	1.04(3)
C(15)-H(15B)	0.94(4)
C(16)-H(16A)	0.99(4)
C(16)-H(16B)	1.02(3)

F(5)-S-F(4)	91.07(10)
F(5)-S-F(2)	89.66(11)
F(4)-S-F(2)	174.85(11)
F(5)-S-F(3)	174.78(10)
F(4)-S-F(3)	89.27(11)
F(2)-S-F(3)	89.55(12)
F(5)-S-F(1)	87.45(10)
F(4)-S-F(1)	87.52(11)
F(2)-S-F(1)	87.43(12)
F(3)-S-F(1)	87.37(10)
F(5)-S-C(2)	93.21(11)
F(4)-S-C(2)	92.82(11)
F(2)-S-C(2)	92.22(11)
F(3)-S-C(2)	91.97(11)
F(1)-S-C(2)	179.25(12)
C(11)-O-H(1O)	105(2)
C(9)-N(1)-C(1)	117.4(2)
N(1)-C(1)-C(6)	121.9(2)
N(1)-C(1)-C(2)	119.9(2)
C(6)-C(1)-C(2)	118.3(2)
C(12)-N(2)-C(16)	111.8(3)
C(12)-N(2)-H(2N)	110(2)

C(16)-N(2)-H(2N)	109(2)
C(3)-C(2)-C(1)	120.0(3)
C(3)-C(2)-S	116.9(2)
C(1)-C(2)-S	123.07(19)
C(2)-C(3)-C(4)	121.2(3)
C(2)-C(3)-H(3)	117.1(18)
C(4)-C(3)-H(3)	121.7(18)
C(5)-C(4)-C(3)	120.3(3)
C(5)-C(4)-H(4)	121.4(16)
C(3)-C(4)-H(4)	118.3(16)
C(4)-C(5)-C(6)	121.2(3)
C(4)-C(5)-H(5)	118.5(15)
C(6)-C(5)-H(5)	120.3(15)
C(7)-C(6)-C(5)	122.8(2)
C(7)-C(6)-C(1)	118.2(2)
C(5)-C(6)-C(1)	119.0(2)
C(8)-C(7)-C(6)	118.3(2)
C(8)-C(7)-C(11)	120.1(2)
C(6)-C(7)-C(11)	121.5(2)
C(7)-C(8)-C(9)	118.9(3)
C(7)-C(8)-H(8)	119.5(15)
C(9)-C(8)-H(8)	121.6(14)
N(1)-C(9)-C(8)	125.2(2)
N(1)-C(9)-C(10)	114.1(2)
C(8)-C(9)-C(10)	120.7(2)
F(8)-C(10)-F(6)	106.8(3)
F(8)-C(10)-F(7)	106.1(2)
F(6)-C(10)-F(7)	106.4(3)
F(8)-C(10)-C(9)	112.3(2)
F(6)-C(10)-C(9)	112.9(3)
F(7)-C(10)-C(9)	111.8(2)
O-C(11)-C(7)	112.5(2)
O-C(11)-C(12)	108.0(2)
C(7)-C(11)-C(12)	110.7(2)
O-C(11)-H(11)	109.5(14)
C(7)-C(11)-H(11)	108.1(14)

C(12)-C(11)-H(11)	108.1(14)
N(2)-C(12)-C(13)	112.5(2)
N(2)-C(12)-C(11)	107.6(2)
C(13)-C(12)-C(11)	113.2(2)
N(2)-C(12)-H(12)	105.5(15)
C(13)-C(12)-H(12)	105.6(14)
C(11)-C(12)-H(12)	112.2(14)
C(14)-C(13)-C(12)	112.2(3)
C(14)-C(13)-H(13A)	106.3(15)
C(12)-C(13)-H(13A)	110.4(15)
C(14)-C(13)-H(13B)	112.1(15)
C(12)-C(13)-H(13B)	109.2(15)
H(13A)-C(13)-H(13B)	106(2)
C(13)-C(14)-C(15)	111.1(3)
C(13)-C(14)-H(14A)	109(2)
C(15)-C(14)-H(14A)	108(2)
C(13)-C(14)-H(14B)	108.0(18)
C(15)-C(14)-H(14B)	111.3(19)
H(14A)-C(14)-H(14B)	110(3)
C(16)-C(15)-C(14)	110.5(3)
C(16)-C(15)-H(15A)	109.0(17)
C(14)-C(15)-H(15A)	109.1(17)
C(16)-C(15)-H(15B)	109(2)
C(14)-C(15)-H(15B)	108(2)
H(15A)-C(15)-H(15B)	112(3)
N(2)-C(16)-C(15)	112.5(3)
N(2)-C(16)-H(16A)	105(2)
C(15)-C(16)-H(16A)	111(2)
N(2)-C(16)-H(16B)	108.6(17)
C(15)-C(16)-H(16B)	108.3(18)
H(16A)-C(16)-H(16B)	111(3)

Symmetry transformations used to generate equivalent atoms:

Table 17 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **27**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	52(1)	69(1)	65(1)	-16(1)	2(1)	-1(1)
O	57(1)	47(1)	70(1)	11(1)	-9(1)	-12(1)
N(1)	41(1)	64(2)	38(1)	1(1)	2(1)	2(1)
C(1)	40(1)	59(2)	31(1)	6(1)	3(1)	-2(1)
F(1)	69(1)	81(1)	120(2)	-38(1)	7(1)	8(1)
N(2)	49(2)	60(2)	72(2)	-16(1)	-9(1)	11(1)
F(2)	86(1)	115(2)	65(1)	-39(1)	-7(1)	6(1)
C(2)	46(2)	59(2)	38(1)	1(1)	2(1)	-4(1)
F(3)	58(1)	64(1)	119(2)	-12(1)	6(1)	-6(1)
C(3)	55(2)	62(2)	41(2)	-2(1)	-5(1)	-7(2)
F(4)	61(1)	69(1)	68(1)	2(1)	-4(1)	10(1)
C(4)	44(2)	69(2)	47(2)	7(1)	-11(1)	-5(2)
F(5)	56(1)	90(1)	67(1)	-17(1)	18(1)	-3(1)
C(5)	46(2)	56(2)	41(1)	6(1)	-3(1)	3(1)
C(6)	40(1)	53(2)	32(1)	11(1)	-1(1)	-2(1)
F(6)	51(1)	99(2)	130(2)	-43(1)	-28(1)	6(1)
F(7)	59(1)	107(2)	95(1)	24(1)	-24(1)	8(1)
C(7)	41(1)	51(2)	36(1)	12(1)	1(1)	-5(1)
F(8)	45(1)	125(2)	76(1)	-8(1)	8(1)	8(1)
C(8)	41(2)	56(2)	41(1)	2(1)	-2(1)	-6(1)
C(9)	37(1)	62(2)	39(1)	-1(1)	2(1)	0(1)
C(10)	42(2)	71(2)	64(2)	-9(2)	-3(1)	1(1)
C(11)	43(2)	45(2)	52(2)	9(1)	-9(1)	-2(1)
C(12)	40(2)	43(2)	56(2)	-3(1)	-2(1)	-1(1)
C(13)	51(2)	52(2)	51(2)	4(1)	2(1)	4(2)
C(14)	67(2)	69(2)	55(2)	-5(2)	6(2)	-13(2)
C(15)	57(2)	104(3)	68(2)	-27(2)	6(2)	-5(2)
C(16)	51(2)	108(3)	82(2)	-37(2)	-2(2)	18(2)

Table 18 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **27.**

	x	y	z	U(eq)
H(1O)	1480(17)	3201(17)	-2310(50)	88(12)
H(2N)	2522(14)	3280(9)	-4560(40)	72
H(3)	2507(13)	6462(13)	780(30)	50(8)
H(4)	3151(13)	5562(12)	250(30)	46(7)
H(5)	2700(12)	4718(12)	-1080(30)	40(7)
H(8)	636(12)	4281(12)	-3100(30)	43(7)
H(11)	2177(12)	3864(11)	-1890(30)	44(7)
H(12)	2551(11)	4528(11)	-3960(20)	36(6)
H(13A)	1593(12)	4002(13)	-5790(30)	48(7)
H(13B)	1614(13)	4727(13)	-5310(30)	52(7)
H(14A)	2546(16)	4821(16)	-6820(30)	76(10)
H(14B)	1991(17)	4512(16)	-7890(40)	90(11)
H(15A)	2494(15)	3470(15)	-7480(30)	70(9)
H(15B)	3053(17)	3998(16)	-8010(40)	85(11)
H(16A)	3421(17)	3361(17)	-5890(40)	86(11)
H(16B)	3433(15)	4152(16)	-5560(30)	73(10)

APPENDIX C X-ray data of *S*-42

Table 19 Crystal data and structure refinement for ***S*-42.**

Identification code	ting2s	
Empirical formula	C12 H7 F8 N O S	
Formula weight	365.25	
Temperature	203(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2_1	
Unit cell dimensions	a = 9.574(2) Å	a = 90°.
	b = 7.9132(18) Å	b = 116.638(4)°.
	c = 9.783(2) Å	g = 90°.
Volume	662.5(3) $Å^3$	
Z	2	
Density (calculated)	1.831 Mg/m^3	
Absorption coefficient	0.344 mm^{-1}	
F(000)	364	
Crystal size	0.25 x 0.10 x 0.08 mm^3	
Theta range for data collection	2.33 to 27.49°.	
Index ranges	-12<=h<=12, -10<=k<=10, -12<=l<=12	
Reflections collected	6412	
Independent reflections	3017 [R(int) = 0.0466]	
Completeness to theta = 27.49°	99.9 %	
Absorption correction	Multi-scan (Sadabs)	
Max. and min. transmission	0.9730 and 0.9190	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3017 / 25 / 266	
Goodness-of-fit on F^2	0.987	

Final R indices [I>2sigma(I)]	R1 = 0.0431, wR2 = 0.1048
R indices (all data)	R1 = 0.0540, wR2 = 0.1111
Absolute structure parameter	0.00(10)
Largest diff. peak and hole	0.293 and -0.198 e.Å^{-3}

Table 20 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for ***S*-42**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	3279(1)	1548(1)	-181(1)	37(1)
O	-1125(3)	1862(4)	4800(3)	59(1)
N	2896(3)	1185(3)	2799(2)	37(1)
F(1)	2754(3)	3146(3)	-1280(2)	54(1)
C(1)	1507(3)	1621(5)	55(3)	33(1)
F(2)	2466(2)	361(3)	-1650(2)	51(1)
C(2)	125(3)	1864(4)	-1237(3)	41(1)
F(3)	3908(2)	-63(2)	851(2)	47(1)
C(3)	-1297(3)	1938(5)	-1142(3)	49(1)
F(4)	4189(2)	2741(3)	1212(2)	49(1)
C(4)	-1329(3)	1811(4)	226(3)	44(1)
F(5)	4803(2)	1490(4)	-435(2)	57(1)
C(5)	63(3)	1593(4)	1589(3)	33(1)
F(6)	4185(14)	-425(18)	6368(12)	74(4)
C(6)	91(3)	1475(4)	3050(3)	35(1)
F(7)	4700(19)	2152(19)	6359(19)	109(5)
C(7)	1472(3)	1181(4)	4298(3)	40(1)
F(8)	5520(20)	300(40)	5240(20)	91(5)
C(8)	2823(3)	1045(4)	4083(3)	41(1)
C(9)	1518(3)	1468(4)	1514(3)	31(1)
C(10)	-1354(3)	1682(5)	3251(3)	42(1)
C(11)	-1889(5)	378(5)	3947(4)	52(1)
C(12)	4350(4)	731(6)	5497(4)	60(1)
F(6')	4630(11)	1710(30)	6605(11)	125(6)
F(7')	5543(13)	920(40)	5217(15)	115(7)
F(8')	4430(20)	-860(20)	6000(30)	165(7)

Table 21 Bond lengths [Å] and angles [°] for ***S*-42**.

S-F(4)	1.5624(19)
S-F(3)	1.569(2)
S-F(5)	1.5864(17)
S-F(1)	1.589(2)
S-F(2)	1.598(2)
S-C(1)	1.812(3)
O-C(11)	1.437(5)
O-C(10)	1.439(3)
N-C(8)	1.295(3)
N-C(9)	1.372(3)
C(1)-C(2)	1.373(3)
C(1)-C(9)	1.428(3)
C(2)-C(3)	1.406(4)
C(2)-H(2)	0.85(3)
C(3)-C(4)	1.357(4)
C(3)-H(3)	0.99(4)
C(4)-C(5)	1.410(4)
C(4)-H(4)	0.95(3)
C(5)-C(6)	1.421(3)
C(5)-C(9)	1.431(3)
F(6)-F(8')	0.62(3)
F(6)-C(12)	1.307(11)
F(6)-F(6')	1.74(2)
C(6)-C(7)	1.358(4)
C(6)-C(10)	1.490(3)
F(7)-C(12)	1.355(12)
C(7)-C(8)	1.404(4)
C(7)-H(7)	0.89(3)
F(8)-F(7')	0.49(5)
F(8)-C(12)	1.298(13)
F(8)-F(8')	1.77(3)
C(8)-C(12)	1.516(4)
C(10)-C(11)	1.451(5)

C(10)-H(10)	0.84(4)
C(11)-H(11A)	0.95(4)
C(11)-H(11B)	0.91(4)
C(12)-F(6')	1.262(10)
C(12)-F(7')	1.297(13)
C(12)-F(8')	1.336(13)

F(4)-S-F(3)	91.55(11)
F(4)-S-F(5)	87.82(11)
F(3)-S-F(5)	87.86(12)
F(4)-S-F(1)	89.60(13)
F(3)-S-F(1)	174.89(12)
F(5)-S-F(1)	87.21(12)
F(4)-S-F(2)	174.98(11)
F(3)-S-F(2)	89.58(12)
F(5)-S-F(2)	87.34(11)
F(1)-S-F(2)	88.86(11)
F(4)-S-C(1)	93.30(12)
F(3)-S-C(1)	93.16(13)
F(5)-S-C(1)	178.46(11)
F(1)-S-C(1)	91.74(14)
F(2)-S-C(1)	91.52(12)
C(11)-O-C(10)	60.6(2)
C(8)-N-C(9)	117.0(2)
C(2)-C(1)-C(9)	120.3(2)
C(2)-C(1)-S	117.3(2)
C(9)-C(1)-S	122.46(17)
C(1)-C(2)-C(3)	120.5(3)
C(1)-C(2)-H(2)	116(2)
C(3)-C(2)-H(2)	124(2)
C(4)-C(3)-C(2)	120.8(3)
C(4)-C(3)-H(3)	126(2)
C(2)-C(3)-H(3)	113(2)
C(3)-C(4)-C(5)	120.8(3)
C(3)-C(4)-H(4)	119.1(19)
C(5)-C(4)-H(4)	120.0(19)

C(4)-C(5)-C(6)	122.9(2)
C(4)-C(5)-C(9)	119.3(2)
C(6)-C(5)-C(9)	117.8(2)
F(8')-F(6)-C(12)	79.2(18)
F(8')-F(6)-F(6')	119(2)
C(12)-F(6)-F(6')	46.4(5)
C(7)-C(6)-C(5)	119.1(2)
C(7)-C(6)-C(10)	119.2(2)
C(5)-C(6)-C(10)	121.7(2)
C(6)-C(7)-C(8)	118.0(2)
C(6)-C(7)-H(7)	122.7(19)
C(8)-C(7)-H(7)	119.3(19)
F(7')-F(8)-C(12)	79(2)
F(7')-F(8)-F(8')	125(3)
C(12)-F(8)-F(8')	48.6(9)
N-C(8)-C(7)	126.4(2)
N-C(8)-C(12)	116.7(3)
C(7)-C(8)-C(12)	116.9(2)
N-C(9)-C(1)	120.2(2)
N-C(9)-C(5)	121.5(2)
C(1)-C(9)-C(5)	118.3(2)
O-C(10)-C(11)	59.6(2)
O-C(10)-C(6)	116.0(2)
C(11)-C(10)-C(6)	121.8(3)
O-C(10)-H(10)	110(3)
C(11)-C(10)-H(10)	115(3)
C(6)-C(10)-H(10)	119(2)
O-C(11)-C(10)	59.8(2)
O-C(11)-H(11A)	115(2)
C(10)-C(11)-H(11A)	114(2)
O-C(11)-H(11B)	116(2)
C(10)-C(11)-H(11B)	118(2)
H(11A)-C(11)-H(11B)	119(3)
F(6')-C(12)-F(8)	117.3(12)
F(6')-C(12)-F(7')	104.0(10)
F(8)-C(12)-F(7')	22(2)

F(6')-C(12)-F(6)	85.0(9)
F(8)-C(12)-F(6)	107.9(12)
F(7')-C(12)-F(6)	126.4(11)
F(6')-C(12)-F(8')	108.1(11)
F(8)-C(12)-F(8')	84.7(14)
F(7')-C(12)-F(8')	105.8(10)
F(6)-C(12)-F(8')	27.0(14)
F(6')-C(12)-F(7)	19.1(11)
F(8)-C(12)-F(7)	110.2(14)
F(7')-C(12)-F(7)	92.3(12)
F(6)-C(12)-F(7)	104.1(10)
F(8')-C(12)-F(7)	126.5(10)
F(6')-C(12)-C(8)	115.4(6)
F(8)-C(12)-C(8)	115.5(9)
F(7')-C(12)-C(8)	111.7(7)
F(6)-C(12)-C(8)	111.1(6)
F(8')-C(12)-C(8)	111.2(7)
F(7)-C(12)-C(8)	107.5(7)
C(12)-F(6')-F(6)	48.6(6)
F(8)-F(7')-C(12)	79(3)
F(6)-F(8')-C(12)	74(2)
F(6)-F(8')-F(8)	114(3)
C(12)-F(8')-F(8)	46.7(8)

Symmetry transformations used to generate equivalent atoms:

Table 22 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for ***S*-42**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

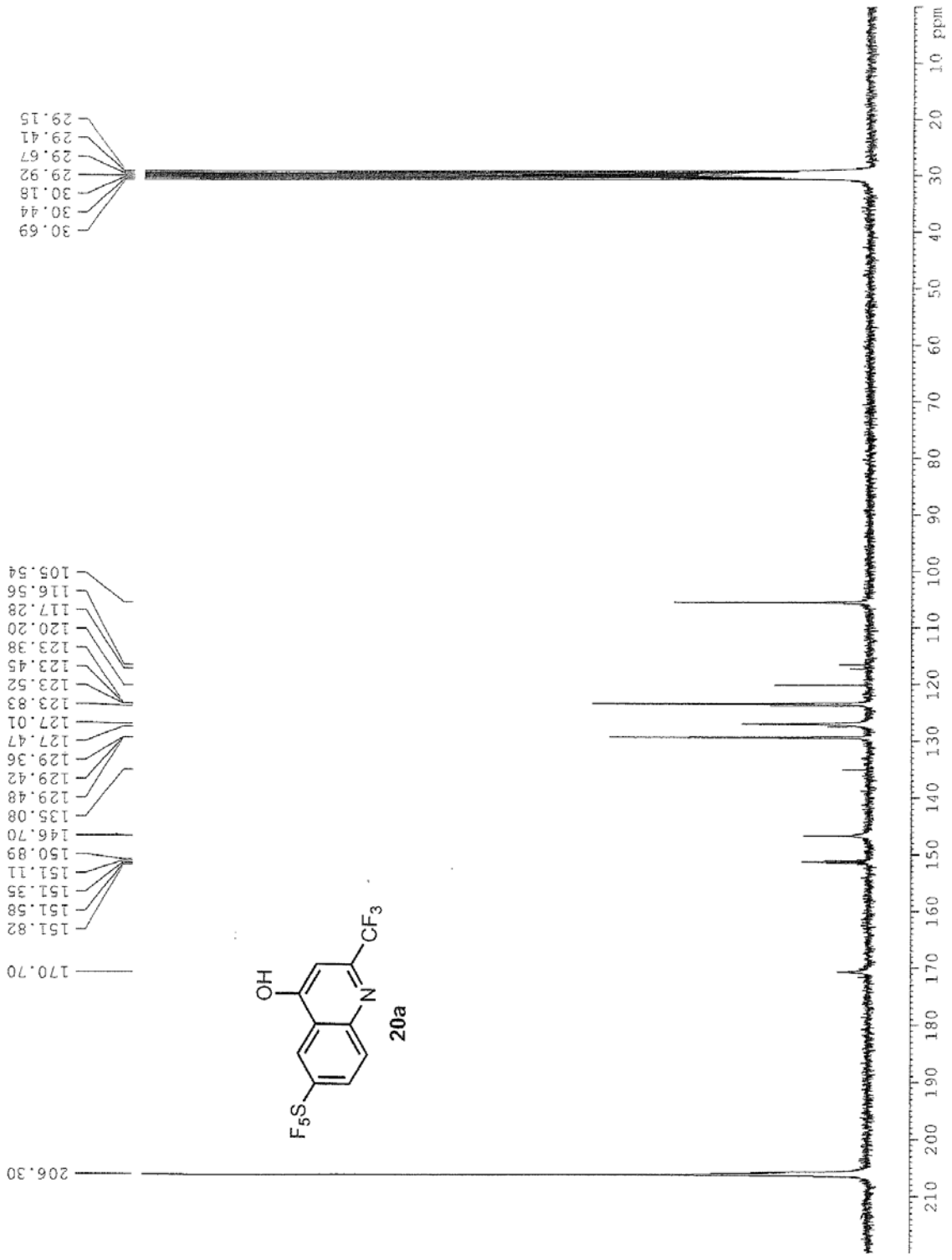
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	38(1)	49(1)	27(1)	-3(1)	15(1)	-6(1)
O	54(1)	84(2)	51(1)	-21(1)	35(1)	-7(1)
N	32(1)	52(2)	25(1)	2(1)	10(1)	4(1)
F(1)	62(1)	60(1)	45(1)	13(1)	28(1)	-4(1)
C(1)	35(1)	35(1)	27(1)	2(1)	11(1)	-1(1)
F(2)	56(1)	65(1)	35(1)	-16(1)	21(1)	-8(1)
C(2)	40(1)	51(2)	24(1)	2(1)	8(1)	-2(1)
F(3)	43(1)	56(1)	45(1)	9(1)	24(1)	11(1)
C(3)	32(1)	64(2)	35(1)	5(1)	2(1)	1(1)
F(4)	45(1)	64(1)	38(1)	-14(1)	20(1)	-19(1)
C(4)	28(1)	55(2)	44(2)	2(2)	12(1)	3(1)
F(5)	45(1)	87(1)	47(1)	-1(1)	29(1)	-5(1)
C(5)	29(1)	35(1)	34(1)	0(1)	13(1)	-1(1)
F(6)	52(4)	124(8)	45(4)	54(4)	19(3)	30(4)
C(6)	36(1)	36(1)	39(1)	-2(1)	21(1)	-2(1)
F(7)	77(7)	92(8)	79(8)	-20(5)	-37(5)	7(4)
C(7)	42(2)	50(2)	30(1)	4(1)	19(1)	5(1)
F(8)	52(6)	190(13)	39(4)	29(5)	27(4)	67(7)
C(8)	36(1)	55(2)	27(1)	5(1)	12(1)	7(1)
C(9)	31(1)	34(1)	26(1)	0(1)	10(1)	0(1)
C(10)	39(1)	51(2)	42(1)	2(2)	22(1)	5(2)
C(11)	53(2)	67(2)	50(2)	-1(2)	33(2)	-7(2)
C(12)	39(2)	104(3)	31(2)	10(2)	11(1)	15(2)
F(6')	43(3)	296(19)	25(3)	-41(6)	4(2)	27(7)
F(7')	33(3)	270(20)	30(3)	9(7)	2(3)	24(6)
F(8')	106(8)	160(10)	152(11)	85(9)	-11(7)	38(7)

Table 23 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for ***S*-42**.

	x	y	z	U(eq)
H(2)	200(40)	1970(50)	-2070(40)	51(10)
H(3)	-2220(40)	2010(50)	-2160(40)	60(11)
H(4)	-2300(40)	1940(40)	270(40)	43(9)
H(7)	1550(30)	1070(40)	5240(40)	33(8)
H(10)	-2060(40)	2360(50)	2680(40)	49(10)
H(11A)	-1270(50)	-610(50)	4210(50)	60(12)
H(11B)	-2930(50)	300(50)	3650(40)	50(10)

APPENDIX D ^{1}H and ^{13}C NMR spectra of selected compounds

2.066
2.058
2.051
2.043
2.036
7.031
8.688
8.680
8.248
8.239
8.217
8.208
8.108
8.077
OH
N
CF3
F5S
20a
1.02
1.03
1.07
1.00
ppm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146.70
135.08
129.48
129.42
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127.47
127.01
123.83
123.52
123.45
123.38
120.20
117.28
116.56
105.54
30.69
30.44
30.18
29.92
29.67
29.41
29.15
OH
N
CF3
F5S
20a
10 ppm

8.757
8.749
8.382
8.351
8.242
8.235
8.211
8.203
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Cl
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CF3
F5S
21a
ppm
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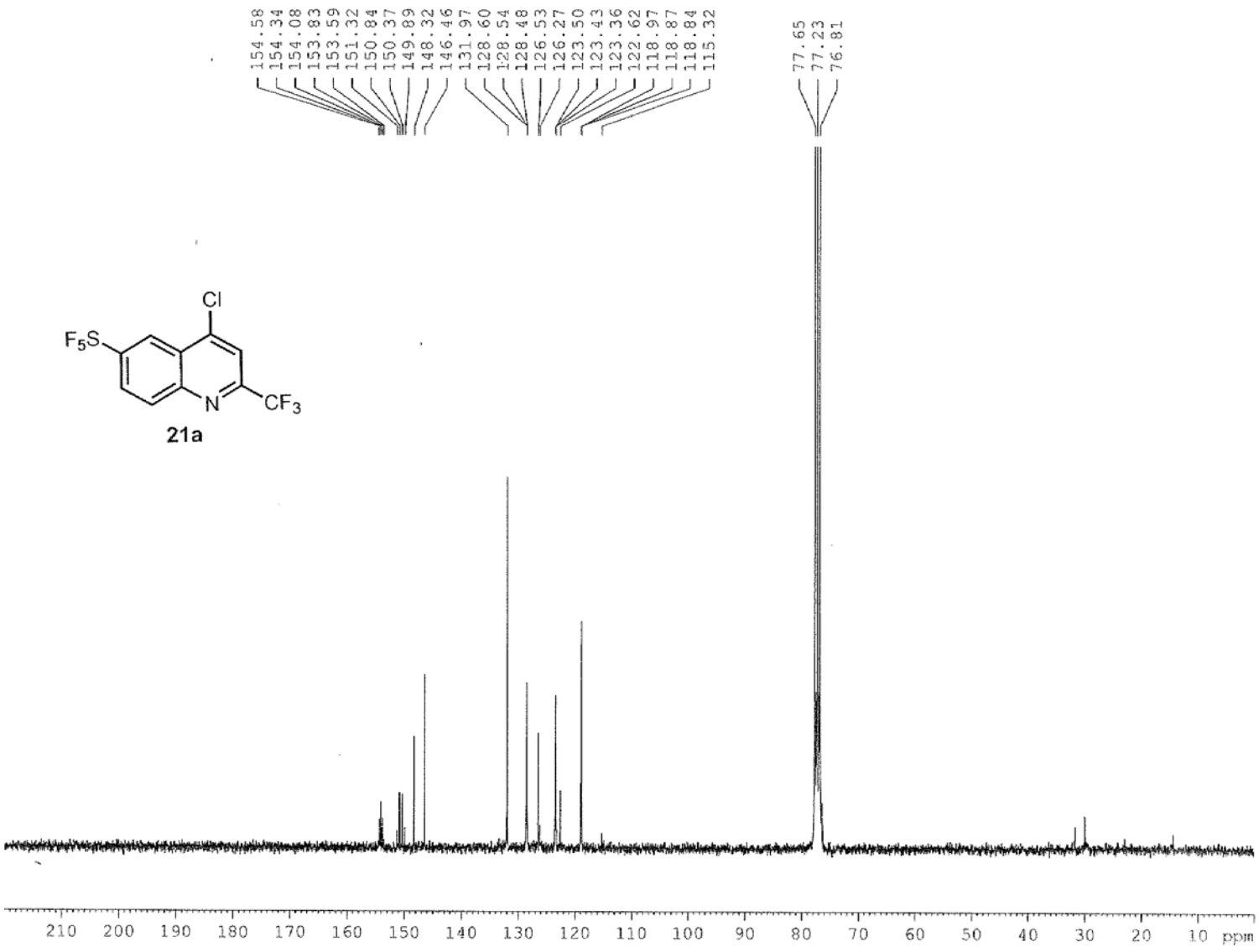
1.06
1.15
0.93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153.59
151.32
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150.37
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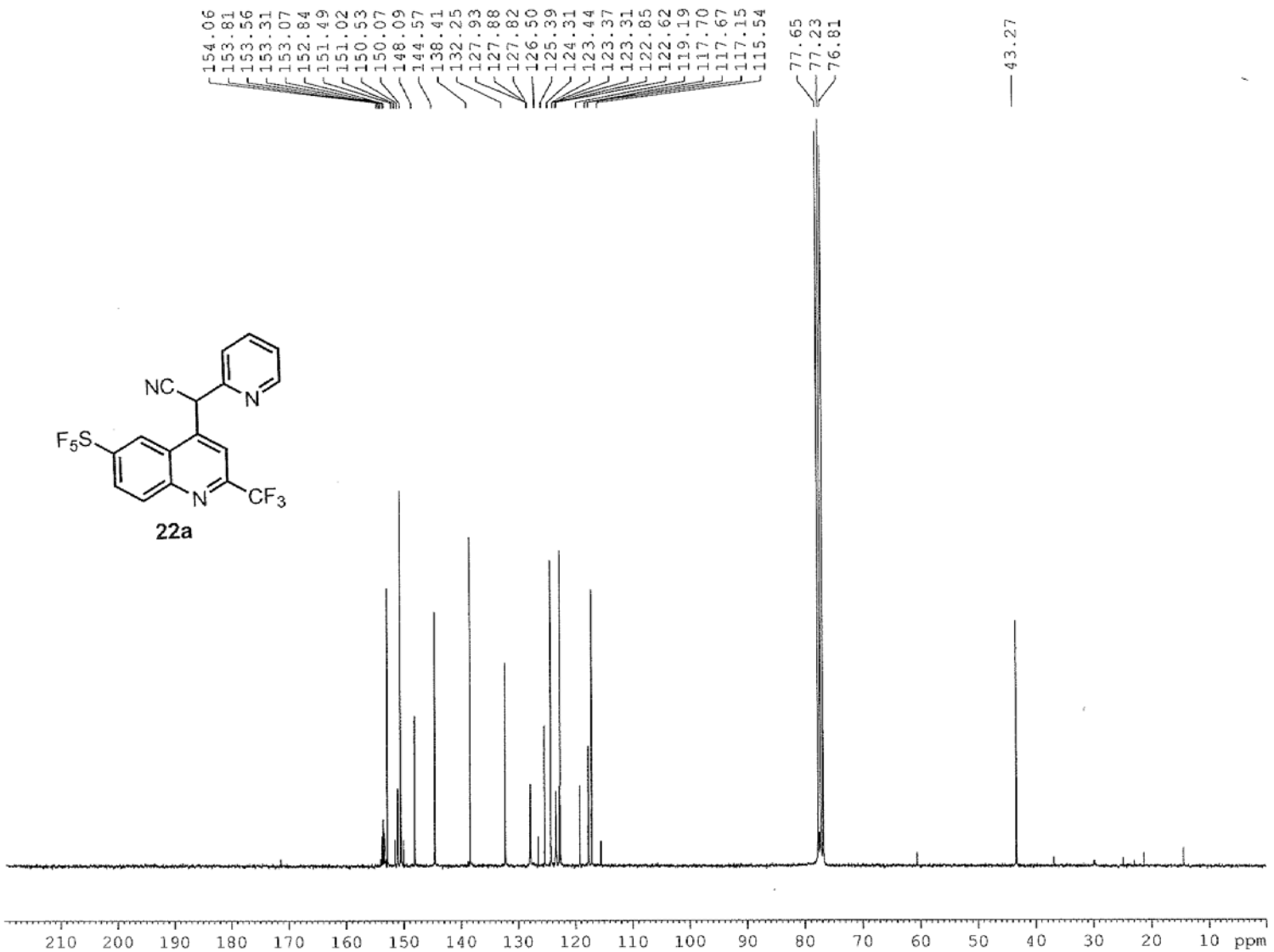
148.32
146.46
131.97
128.60
128.54
128.48
126.53
126.27
123.50
123.43
123.36
122.62
118.97
118.87
118.84
115.32
77.65
77.23
76.81
Cl
F5S
N
CF3
21a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

8.873
8.866
8.605
8.589
8.383
8.352
8.179
8.168
8.144
8.137
7.813
7.808
7.787
7.782
7.762
7.756
7.547
7.521
7.340
7.324
7.322
7.315
7.299
7.271
6.087
1.573
NC
N
N
CF3
F5S
22a
ppm
0
1
2
3
4
5
6
7
8
9
10
11
1.00
0.86
0.92
1.90
0.97
0.96
0.94
1.04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151.02
150.53
150.07
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138.41
132.25
127.93
127.88
127.82
126.50
125.39
124.31
123.44
123.37
123.31
122.85
122.62
119.19
117.70
117.67
117.15
115.54
77.65
77.23
76.81
43.27
NC
N
F5S
N
CF3
22a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

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8.661
8.659
8.657
8.648
8.646
8.643
8.641
8.442
8.435
8.421
8.418
8.392
8.201
8.193
8.169
8.161
8.087
8.081
8.061
8.056
8.035
8.030
8.010
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7.638
7.626
7.622
7.616
7.612
7.600
7.596
7.270
1.00
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1.13
1.14
1.11
0.91
1.10
ppm
23a

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76.81
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118.85
118.87
119.36
123.01
124.71
124.76
124.83
125.29
126.66
127.61
127.67
127.73
128.49
131.73
137.90
147.11
148.04
149.17
149.67
150.11
150.59
152.80
153.27
153.52
153.77
154.01
154.25
193.52
N
O
N
CF3
F5S
23a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

ppm
0 1 2 3 4 5 6 7 8 9 10 11
1.11
1.09
1.17
4.01
1.08
1.07
0.30
0.04
0.83
1.00
0.07
0.05
0.99
0.04
0.96
0.05
0.58
0.03
0.37
0.93
0.06
1.228 1.243 1.248 1.254 1.262 1.268 1.276 1.280 1.287 1.292 1.295 1.298 1.301 1.307 1.321 1.472 1.475 1.493 1.496 1.543 1.547 1.750 1.753 2.043 2.047 2.050 2.054 2.058 2.519 2.523 2.539 2.543 2.559 2.959 2.961 2.964 2.978 2.981 3.028 3.032 3.037 3.041 3.045 3.050 5.538 5.546 8.159 8.303 8.307 8.318 8.322 8.371 8.386 9.011 9.015
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N
H
N
CF3
F5S
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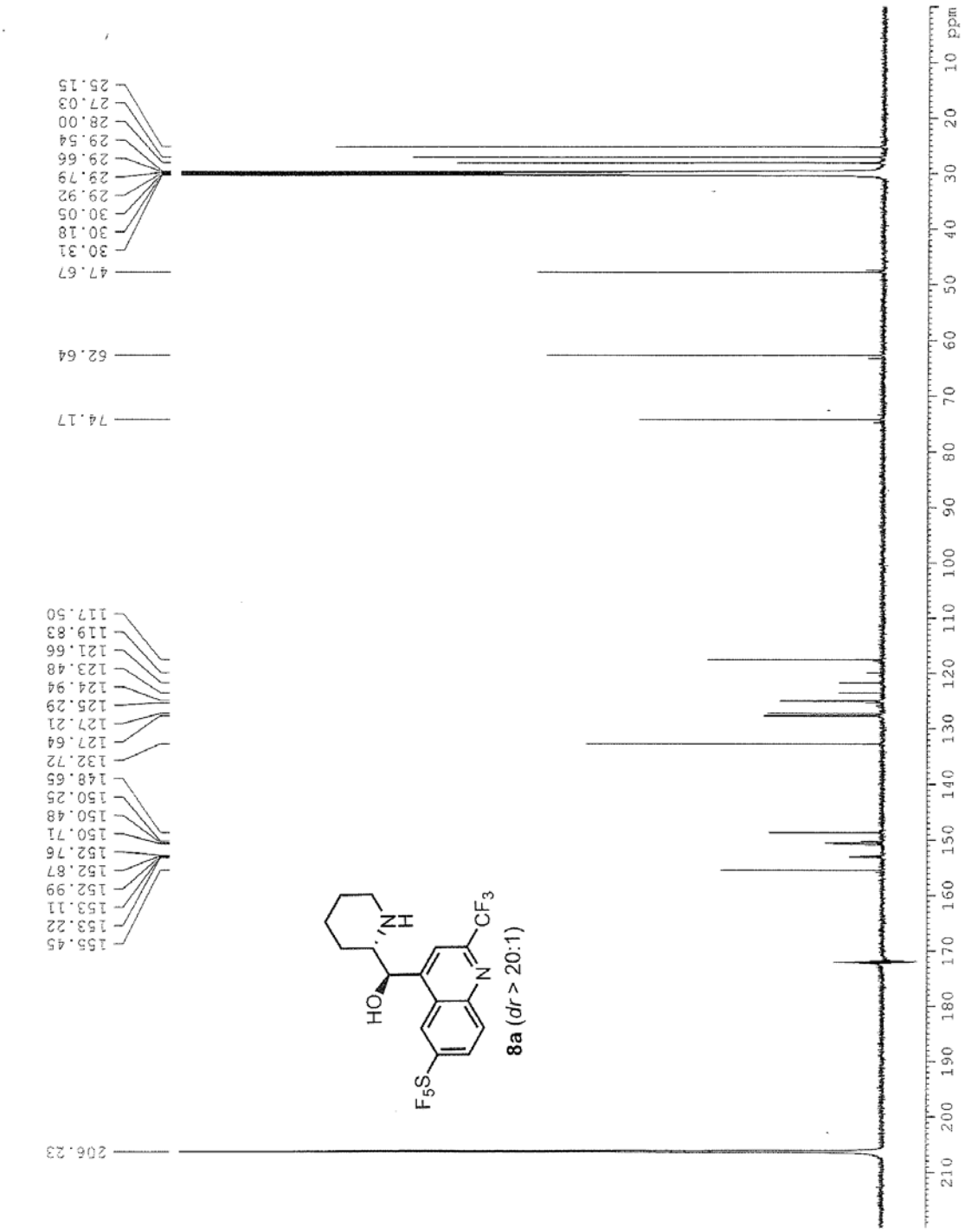
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127.21
125.29
124.94
123.48
121.66
119.83
117.50
74.17
62.64
47.67
30.31
30.18
30.05
29.92
29.79
29.66
29.54
28.00
27.03
25.15
HO
N
H
N
CF3
F5S
8a (dr > 20:1)
ppm

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8.474
8.453
8.069
8.062
8.038
8.031
7.267
2.064
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20b
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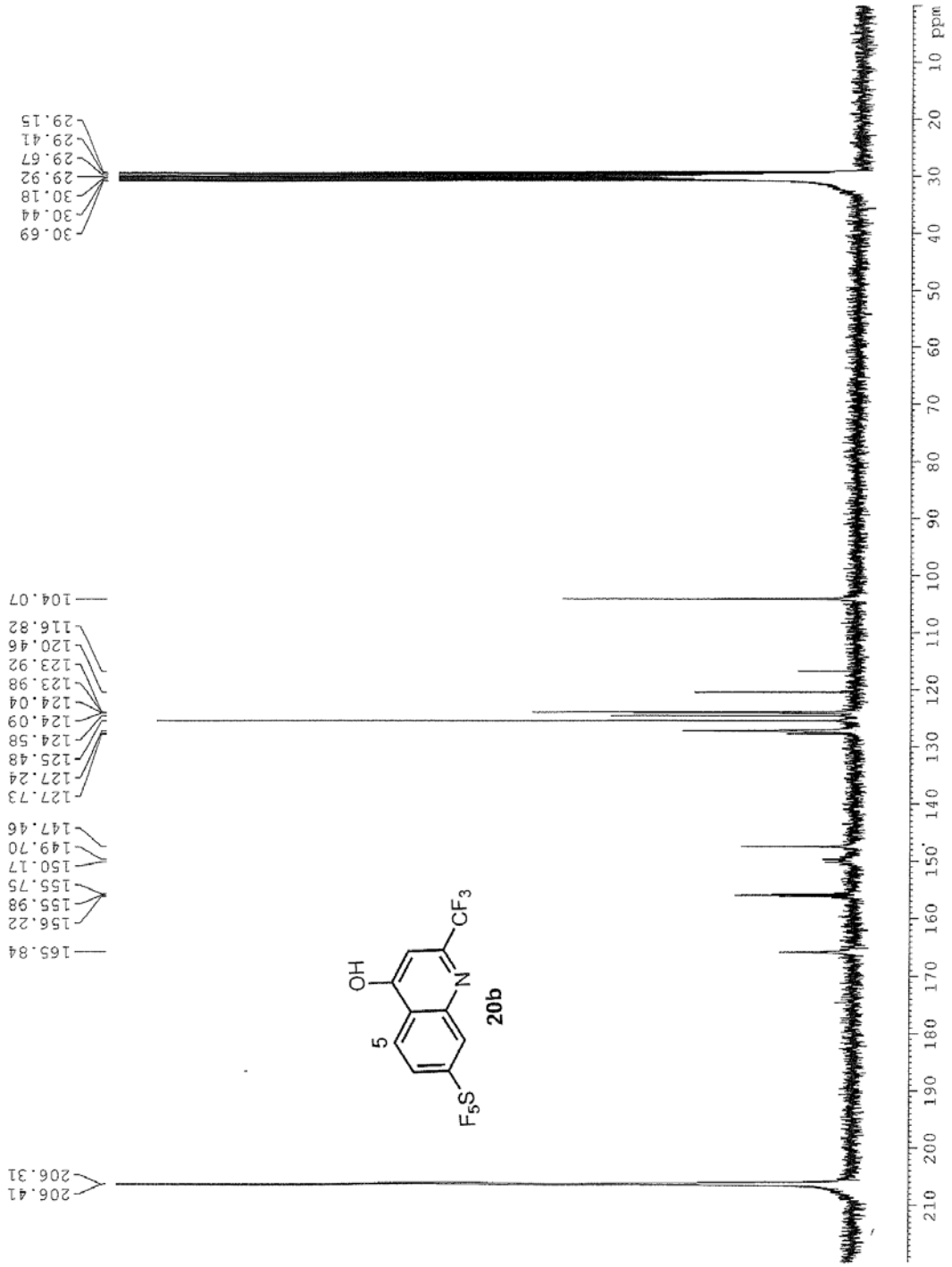
ppm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155.75
150.17
149.70
147.46
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127.24
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124.58
124.09
124.04
123.98
123.92
120.46
116.82
104.07
30.69
30.44
30.18
29.92
29.67
29.41
29.15
OH
N
CF3
F5S
5
20b
ppm

8.741
8.734
8.439
8.408
8.140
8.133
8.109
8.102
7.971
7.270
1.567
1.00
1.04
1.13
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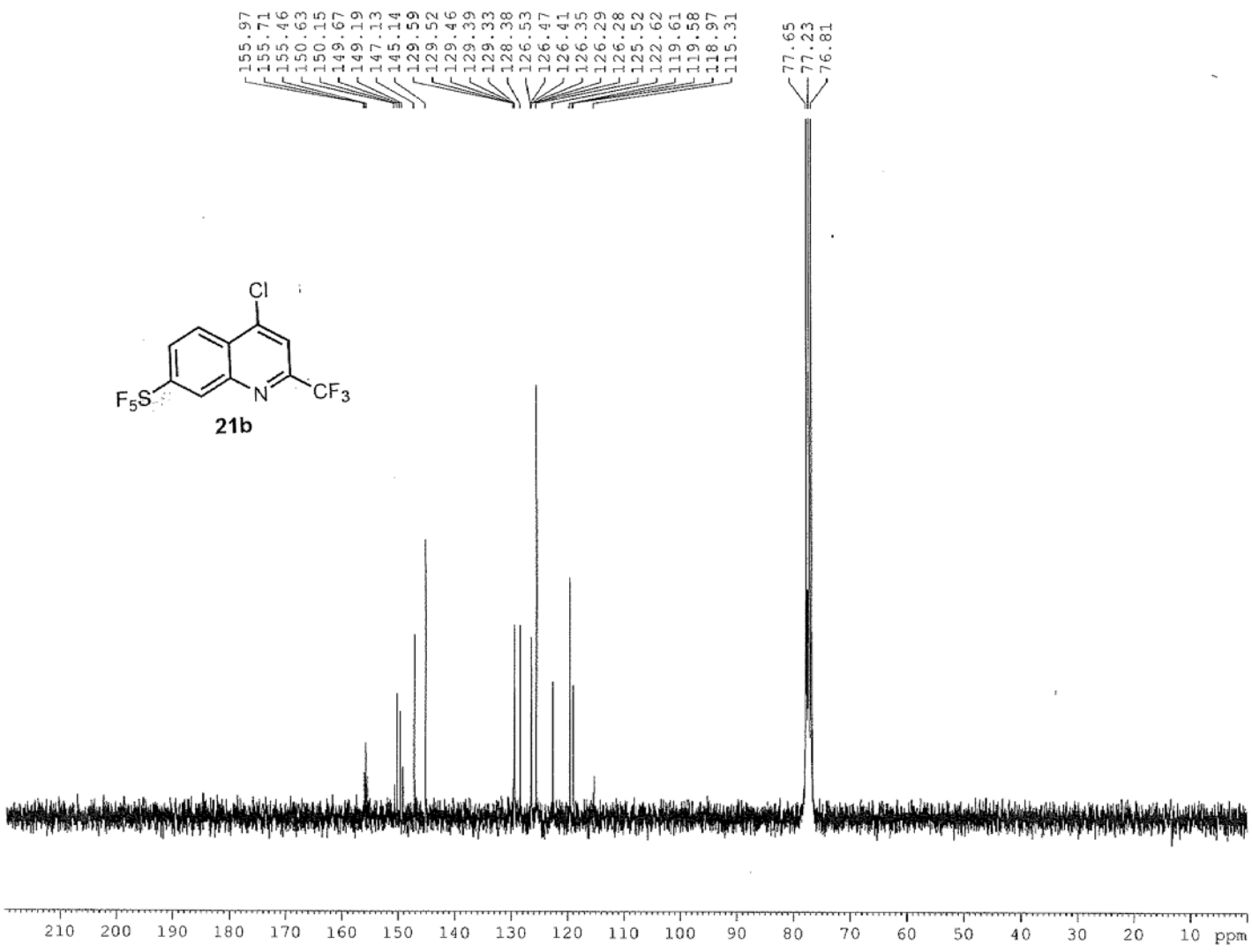
2
3
4
5
6
7
8
9
10
11
Cl
N
CF3
F5S
21b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129.33
128.38
126.53
126.47
126.41
126.35
126.29
126.28
125.52
122.62
119.61
119.58
118.97
115.31
77.65
77.23
76.81
Cl
F5S
N
CF3
21b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

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8.726
8.611
8.609
8.606
8.598
8.595
8.593
8.590
8.369
8.338
8.139
8.047
8.039
8.015
8.008
7.815
7.809
7.789
7.783
7.763
7.757
7.506
7.480
7.354
7.351
7.338
7.335
7.329
7.326
7.313
7.309
7.270
6.077
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1.00
0.94
1.16
1.02
1.11
1.06
1.03
1.00
1.12
ppm
22b

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8.772
8.649
8.647
8.644
8.636
8.633
8.631
8.628
8.398
8.371
8.082
8.072
8.066
8.046
8.040
8.020
8.014
8.001
7.993
7.985
7.962
7.954
7.629
7.625
7.613
7.610
7.604
7.600
7.588
7.584
7.270
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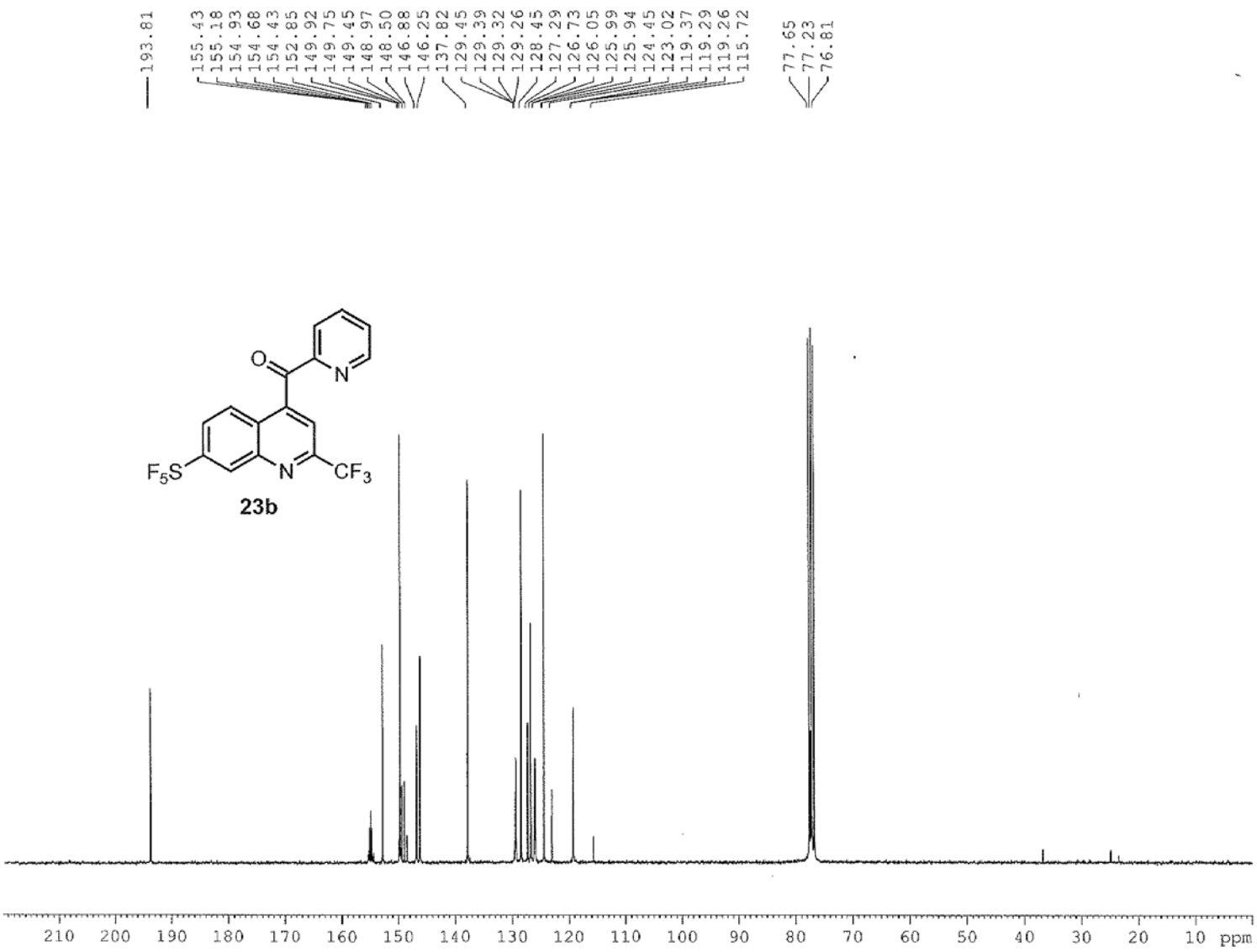
0.32
0.82
0.81
0.37
1.08
ppm
23b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149.45
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146.25
137.82
129.45
129.39
129.32
129.26
128.45
127.29
126.73
126.05
125.99
125.94
124.45
123.02
119.37
119.29
119.26
115.72
77.65
77.23
76.81
O
N
F5S
N
CF3
23b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

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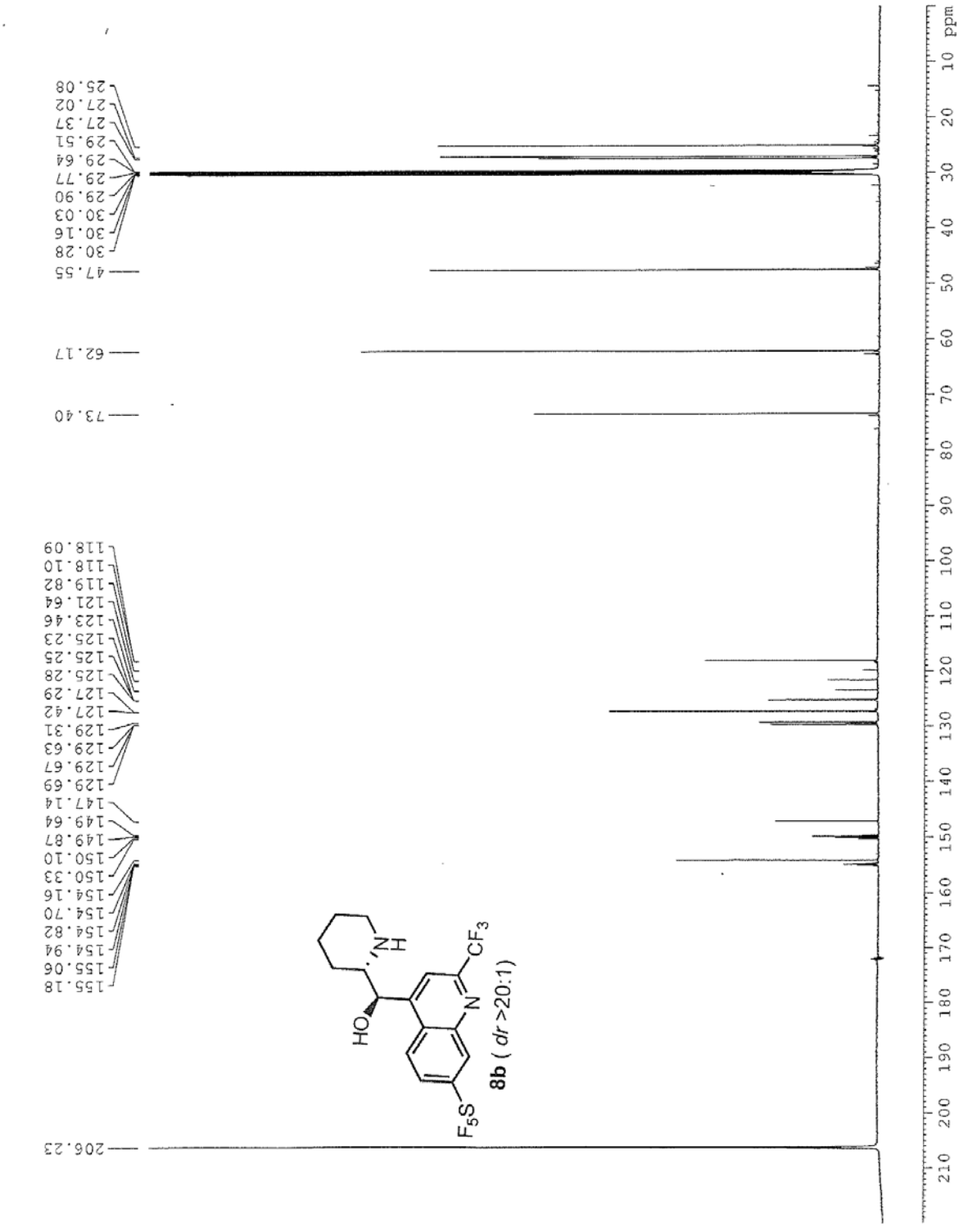
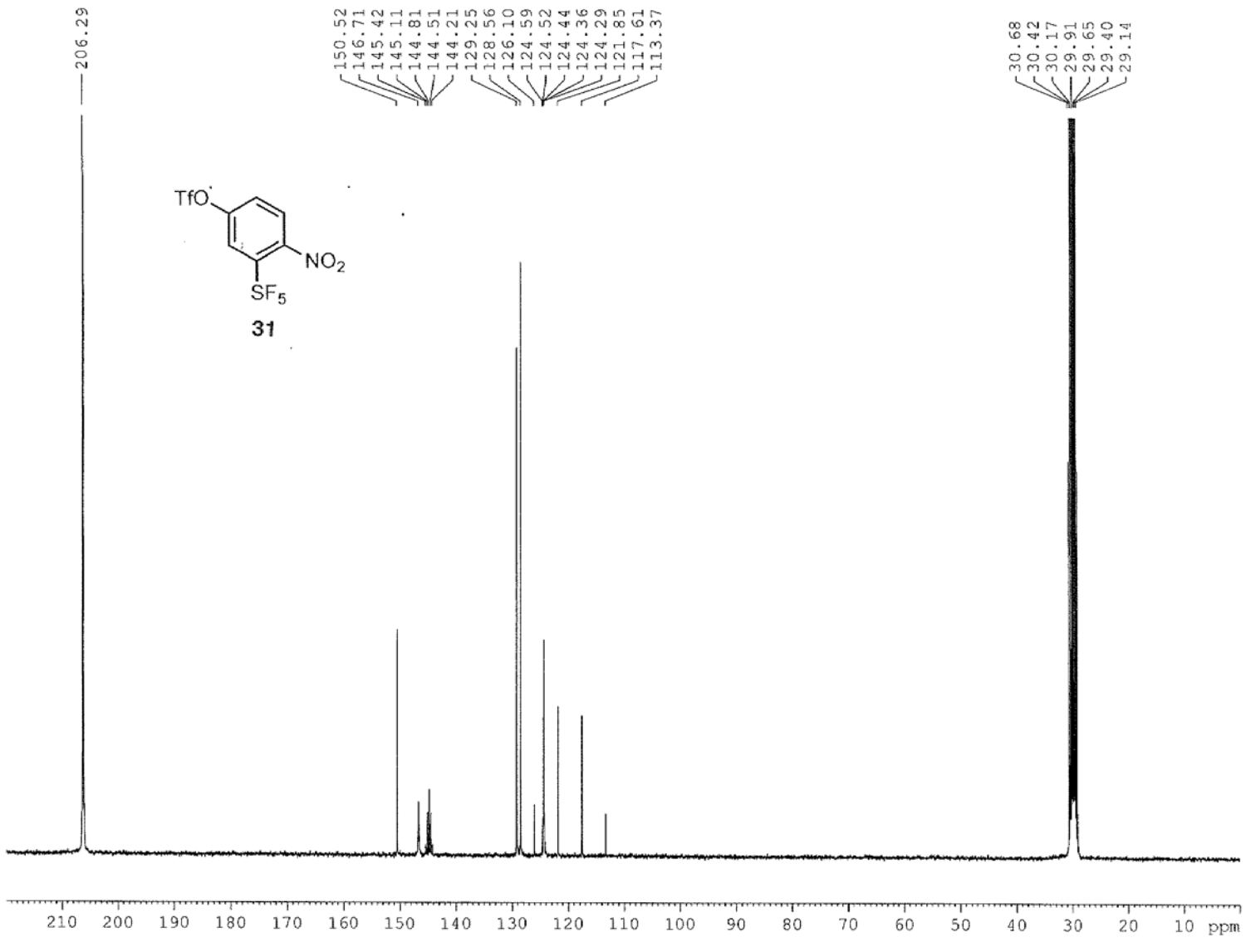
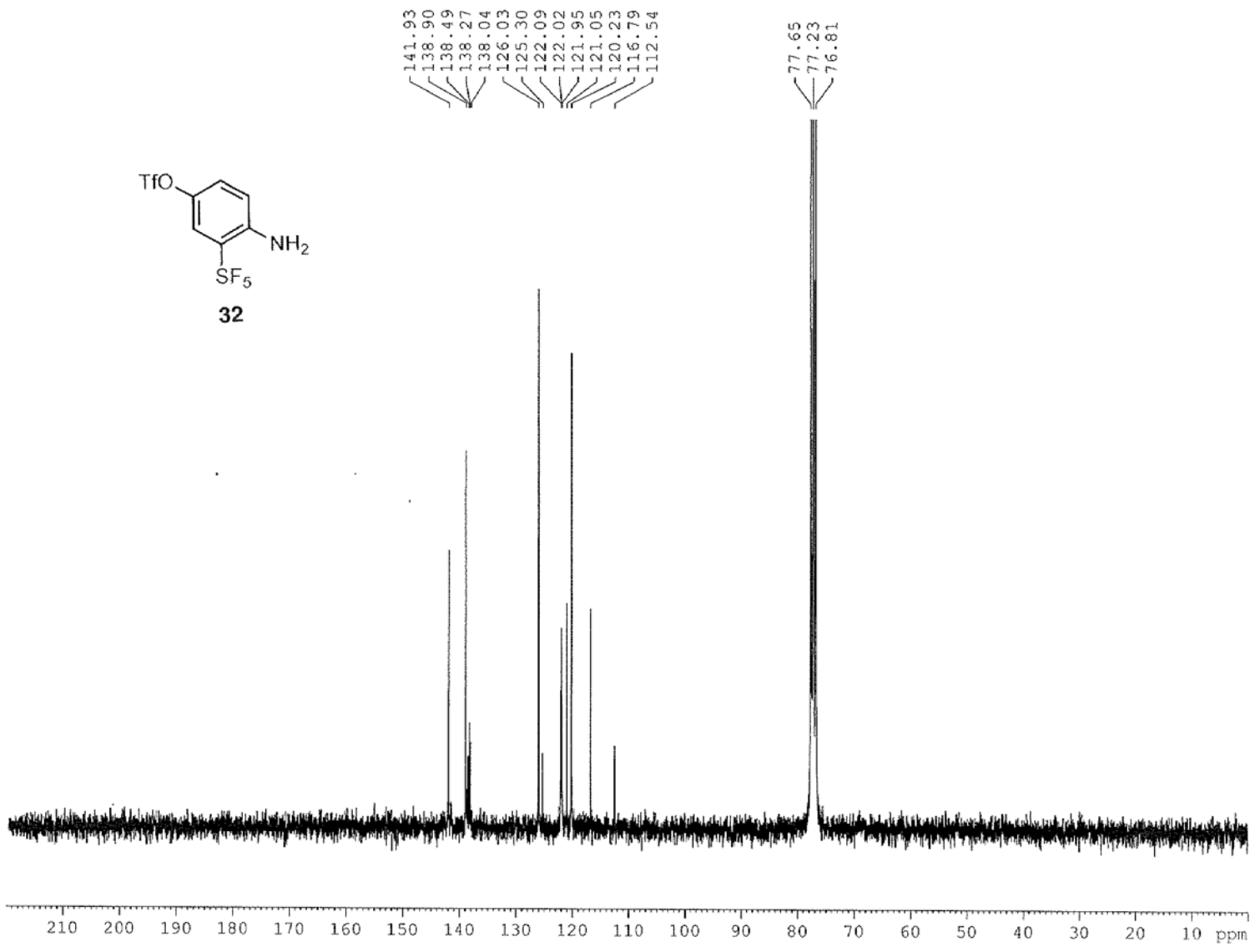
8.656
8.648
8.632
8.195
8.175
8.171
8.159
8.155
5.548
5.540
3.057
3.052
3.049
3.045
3.039
3.034
3.031
3.026
2.986
2.983
2.980
2.966
2.963
2.960
2.576
2.572
2.556
2.552
2.536
2.532
2.058
2.054
2.050
2.047
2.043
1.734
1.731
1.710
1.485
1.462
1.439
1.435
1.333
1.329
1.326
1.320
1.314
1.308
1.306
1.299
1.293
1.227
1.221
1.200
ppm
0 1 2 3 4 5 6 7 8 9 10 11
1.09
2.26
2.10
1.08
1.02
1.02
1.01
0.03
1.00
1.02
0.96
1.03
0.95
HO
N
H
N
CF3
F5S
8b (dr >20:1)

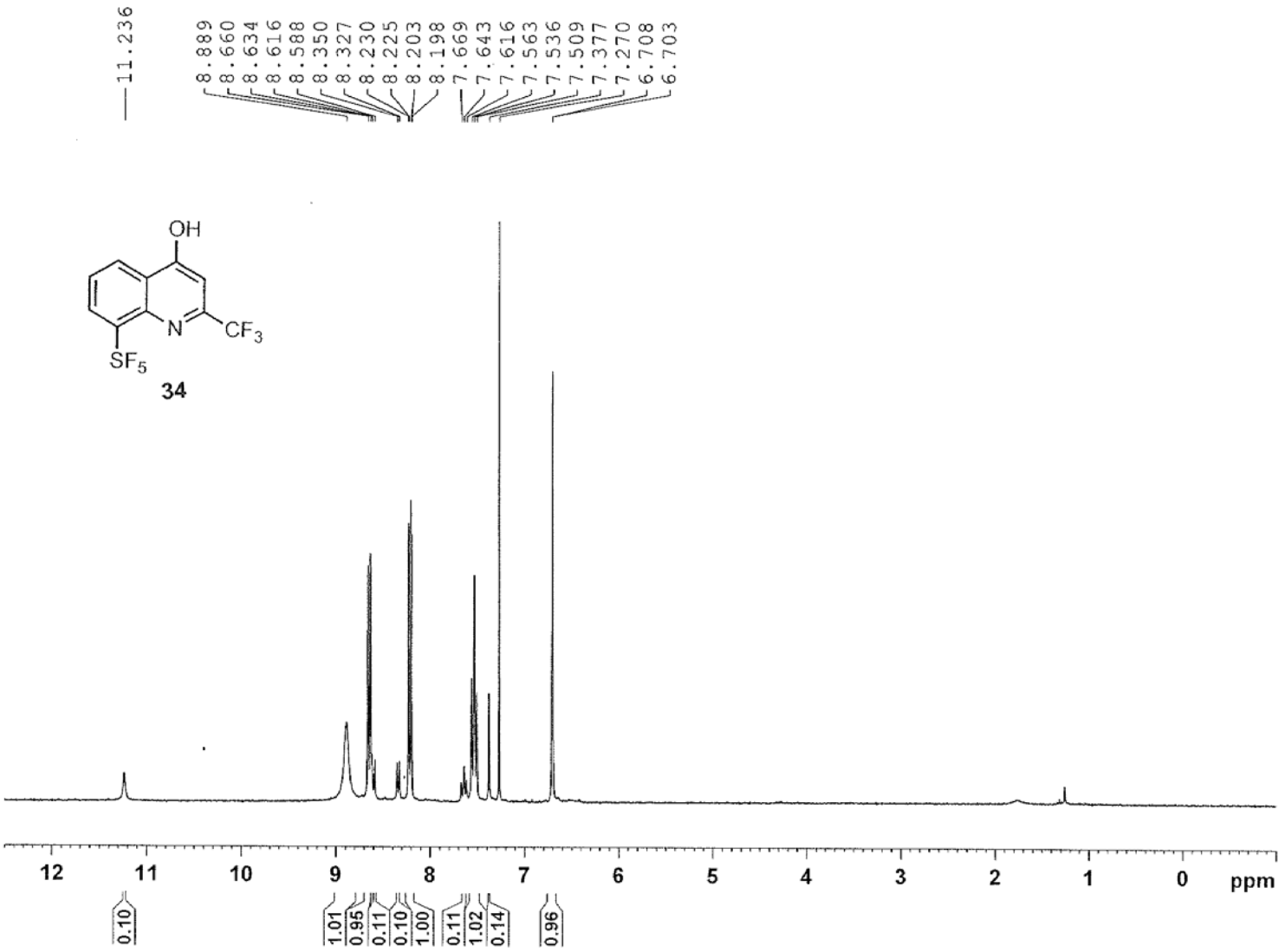

25.08
27.02
27.37
29.51
29.64
29.77
29.90
30.03
30.16
30.28
47.55
62.17
73.40
118.09
118.10
119.82
121.64
123.46
125.23
125.25
125.28
127.29
127.42
129.31
129.63
129.67
129.69
147.14
149.64
149.87
150.10
150.33
154.16
154.70
154.82
154.94
155.06
155.18
206.23
HO
N
H
N
CF3
F5S
8b (dr >20:1)
10 ppm

8.483
8.475
8.272
8.242
8.214
8.207
8.184
8.177
2.086
2.064
2.057
2.050
2.043
2.035
TfO
SF5
NO2
31
1.00
1.01
1.08
ppm


206.29
150.52
146.71
145.42
145.11
144.81
144.51
144.21
129.25
128.56
126.10
124.59
124.52
124.44
124.36
124.29
121.85
117.61
113.37
30.68
30.42
30.17
29.91
29.65
29.40
29.14
TfO
NO2
SF5
31
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

7.515
7.506
7.270
7.218
7.209
7.188
7.179
6.807
6.777
4.636
1.266
1.00
0.99
1.00
1.97
ppm
NH2
SF5
TfO
32


141.93
138.90
138.49
138.27
138.04
126.03
125.30
122.09
122.02
121.95
121.05
120.23
116.79
112.54
77.65
77.23
76.81
TfO
NH2
SF5
32
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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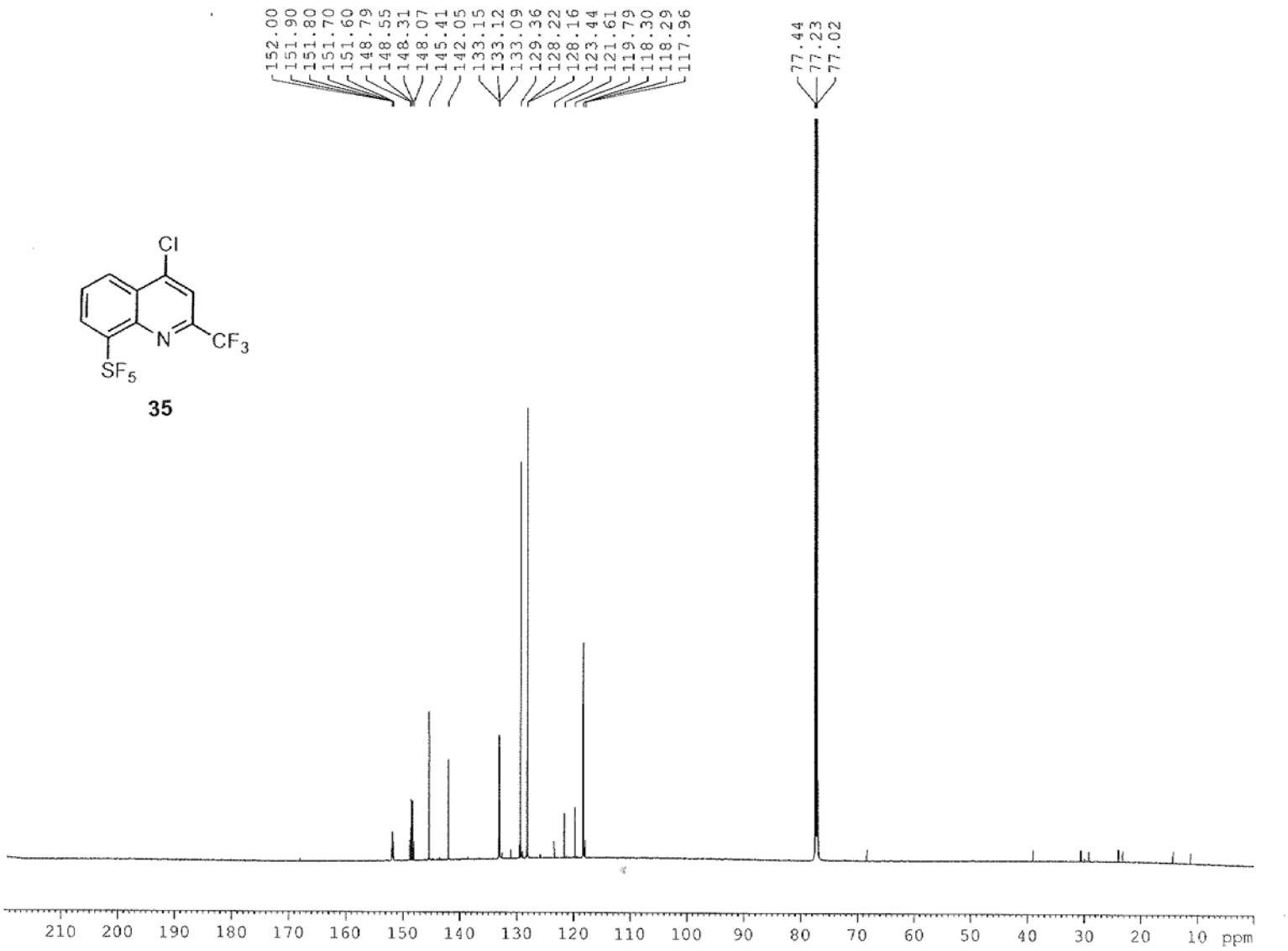
8.889
8.660
8.634
8.616
8.588
8.350
8.327
8.230
8.225
8.203
8.198
7.669
7.643
7.616
7.563
7.536
7.509
7.377
7.270
6.708
6.703
OH
N
CF3
SF5
34
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.10
1.01
0.95
0.11
0.10
1.00
0.11
1.02
0.14
0.96

1.559
8.610
8.606
8.581
8.578
8.479
8.475
8.453
8.449
7.944
7.893
7.865
7.838
7.270
1.00
0.99
1.02
ppm
0
1
2
3
4
5
6
7
8
9
10
11
12
Cl
N
CF3
SF5

35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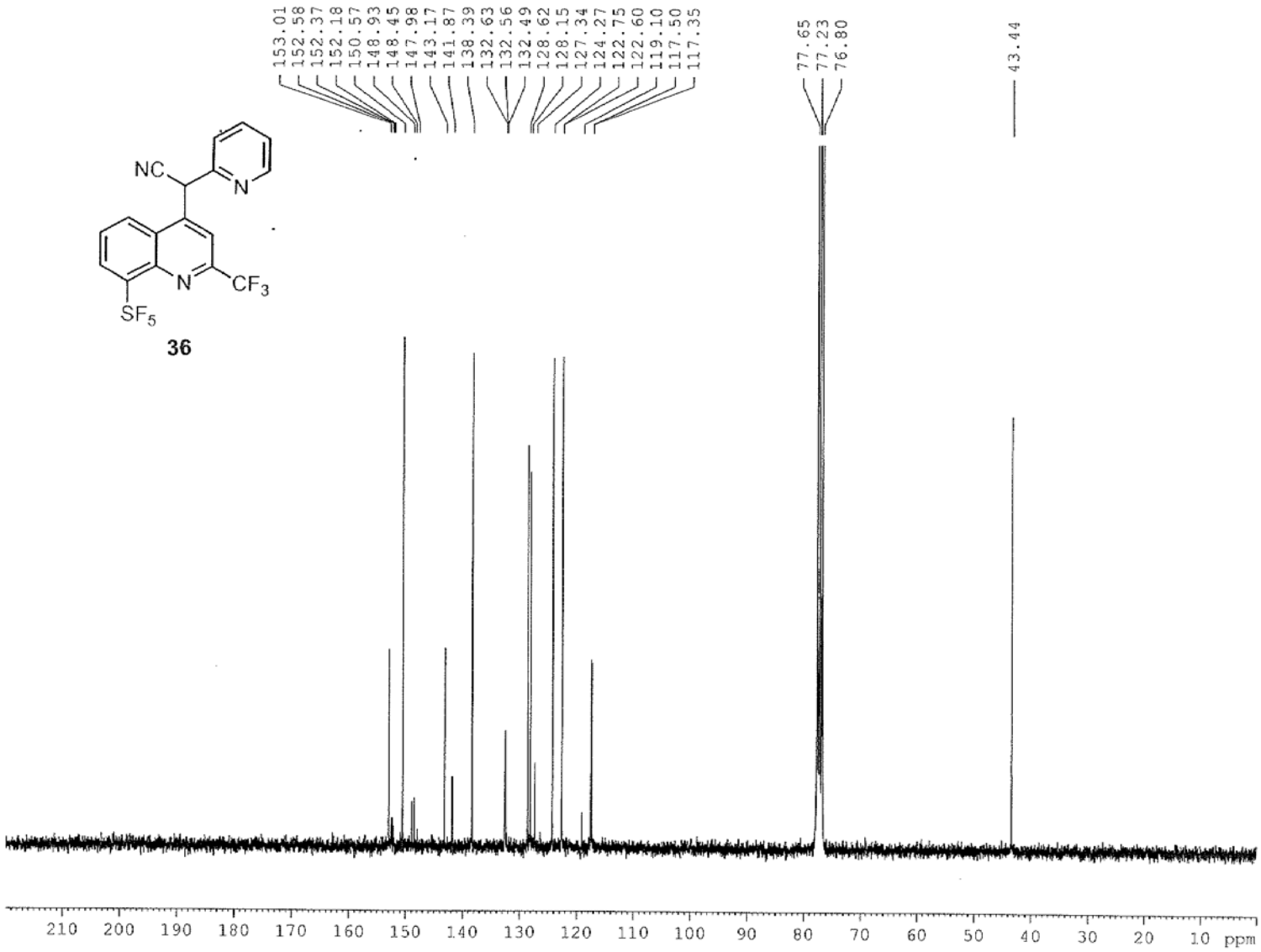
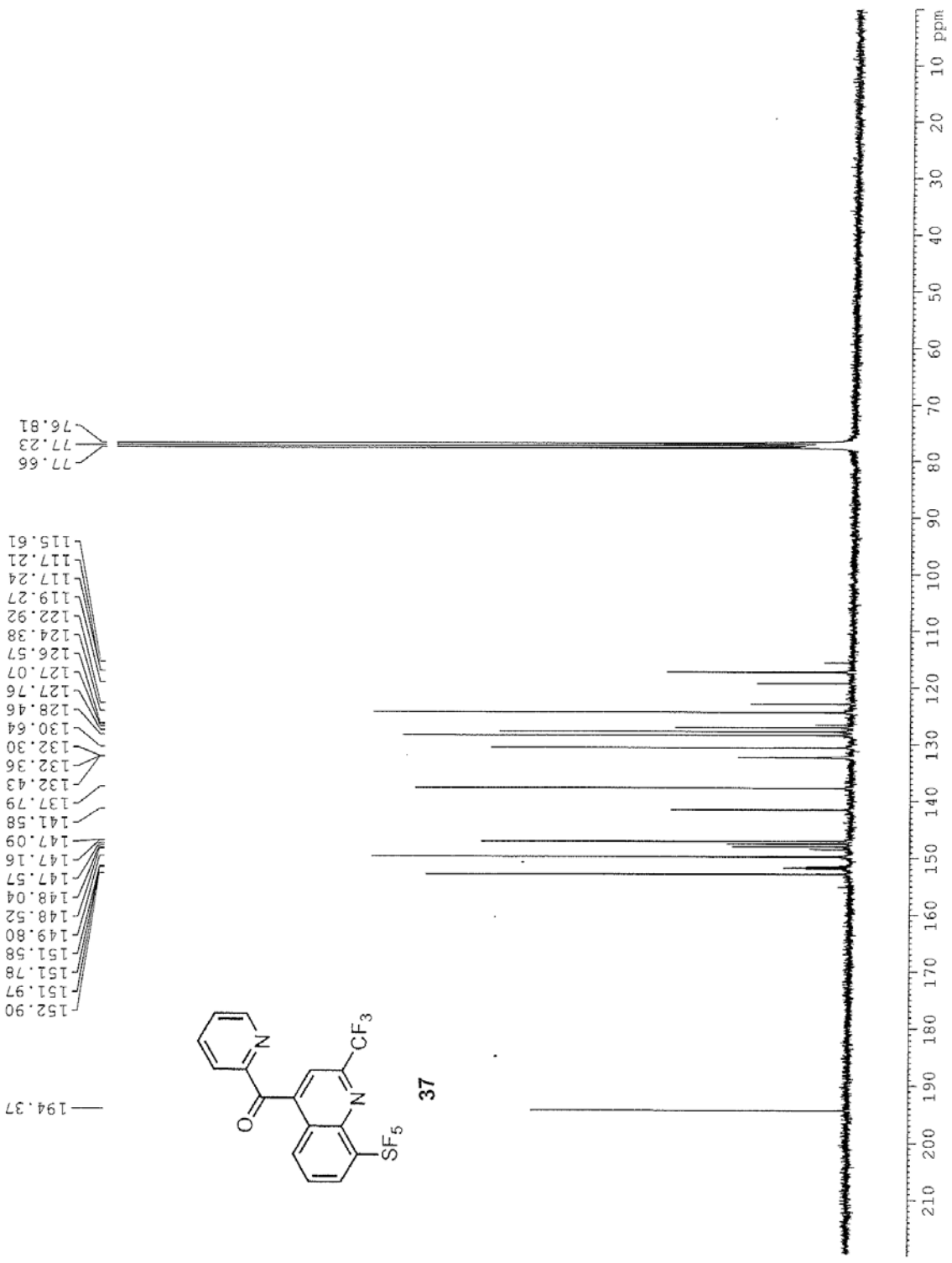
151.90
151.80
151.70
151.60
148.79
148.55
148.31
148.07
145.41
142.05
133.15
133.12
133.09
129.36
128.22
128.16
123.44
121.61
119.79
118.30
118.29
117.96
77.44
77.23
77.02
Cl
N
CF3
SF5
35
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

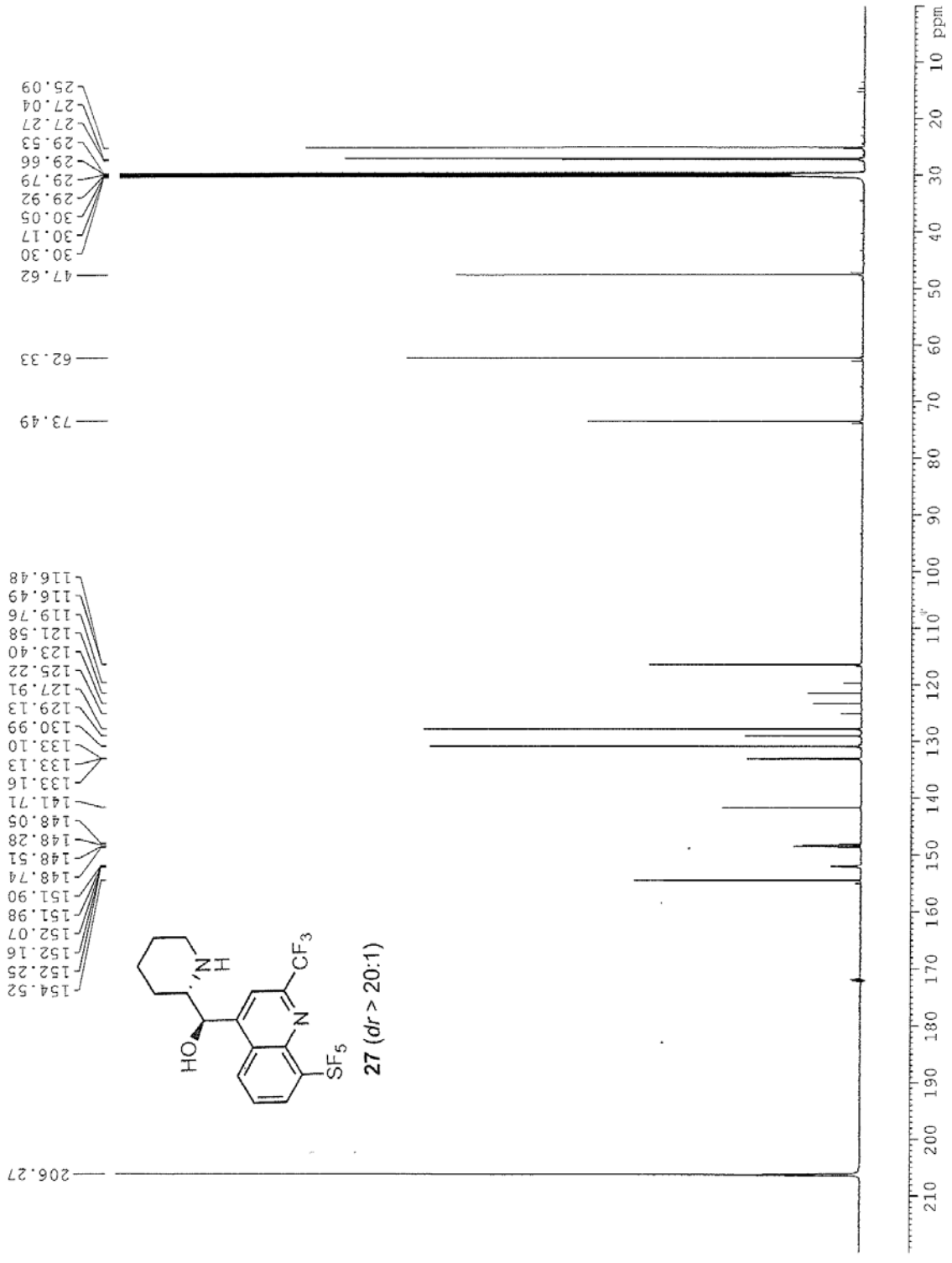
1.591
6.072
7.271
7.308
7.310
7.324
7.327
7.333
7.335
7.349
7.352
7.444
7.471
7.749
7.755
7.761
7.775
7.781
7.788
7.800
7.807
7.816
8.102
8.397
8.400
8.424
8.427
8.454
8.483
8.597
8.599
8.602
8.605
8.613
8.616
8.618
8.621
N
NC
N
CF3
SF5
36
ppm
0
1
2
3
4
5
6
7
8
9
10
11
12
1.01
0.98
1.13
1.12
1.00
2.21
1.04
1.02


153.01
152.58
152.37
152.18
150.57
148.93
148.45
147.98
143.17
141.87
138.39
132.63
132.56
132.49
128.62
128.15
127.34
124.27
122.75
122.60
119.10
117.50
117.35
77.65
77.23
76.80
43.44
NC
N
N
CF3
SF5
36
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

8.628
8.621
8.618
8.615
8.613
8.432
8.428
8.406
8.402
8.397
8.393
8.373
8.370
8.367
8.139
8.136
8.111
8.107
8.066
8.060
8.040
8.034
8.014
8.008
7.898
7.742
7.715
7.688
7.619
7.615
7.604
7.600
7.594
7.590
7.578
7.574
7.270
N
O
N
CF3
SF5
37
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0
1.00
2.19
1.02
1.16
0.97
1.13
1.12


194.37
152.90
151.97
151.78
149.80
148.52
148.04
147.57
147.16
147.09
141.58
137.79
132.43
132.36
132.30
130.64
128.46
127.76
127.07
126.57
124.38
122.92
119.27
117.24
117.21
115.61
77.66
77.23
76.81
O
N
N
CF3
SF5
37
ppm

8.740
8.584
8.571
8.194
7.978
7.965
7.951
5.583
5.577
3.041
3.036
3.033
3.028
3.023
3.018
3.015
3.010
2.990
2.986
2.984
2.969
2.966
2.964
2.579
2.574
2.559
2.554
2.538
2.534
2.057
2.054
2.050
2.047
2.043
1.731
1.710
1.482
1.461
1.435
1.414
1.353
1.348
1.332
1.326
1.319
1.311
1.305
1.298
1.234
1.218
1.212
1.206
1.191
HO
N
H
N
CF3
SF5
27 (dr > 20:1)
ppm
1.00
1.01
0.95
0.03
1.00
1.02
0.04
1.06
1.08
1.06
1.05
1.06
1.03
2.16
1.12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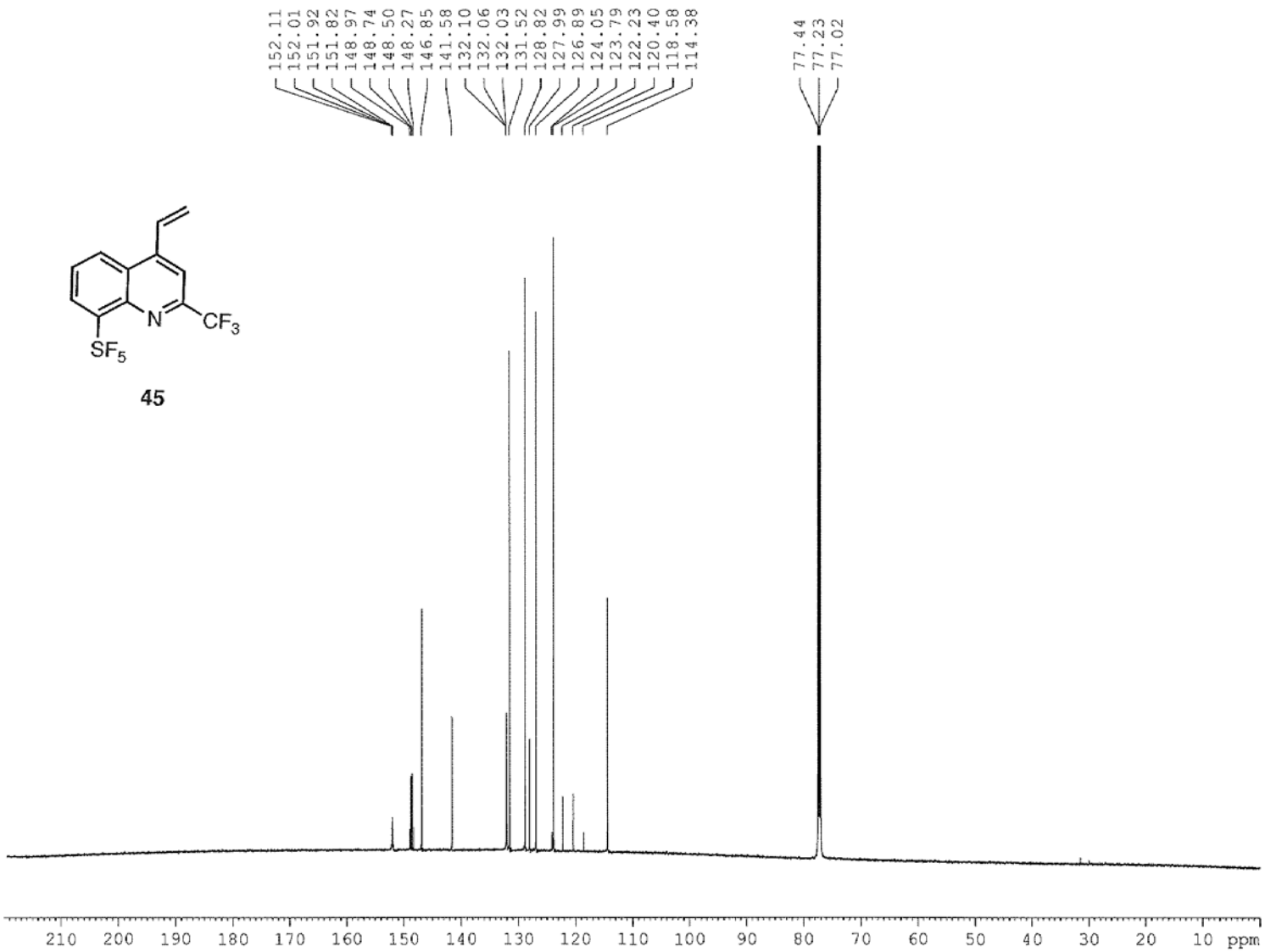
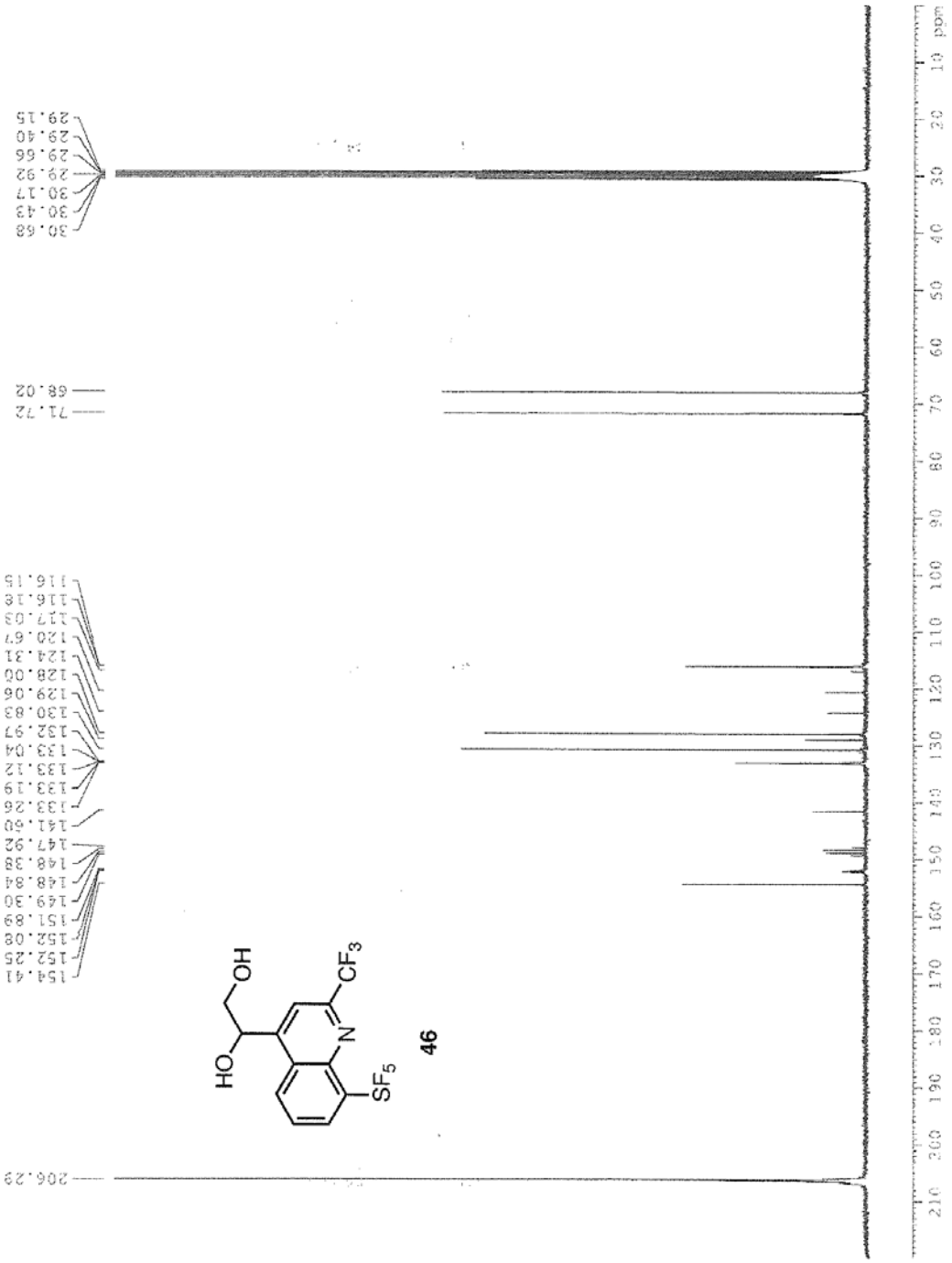
154.52
152.25
152.16
152.07
151.98
151.90
148.74
148.51
148.28
148.05
141.71
133.16
133.13
133.10
130.99
129.13
127.91
125.22
123.40
121.58
119.76
116.49
116.48
73.49
62.33
47.62
30.30
30.17
30.05
29.92
29.79
29.66
29.53
27.27
27.04
25.09
HO
H
N
N
CF3
SF5
27 (dr > 20:1)
ppm

1.556
8.406
8.380
8.374
7.865
7.783
7.756
7.729
7.489
7.453
7.432
7.395
7.269
6.114
6.057
5.869
5.832
0.98
1.03
1.00
1.13
1.17
1.04
1.02
ppm
45


152.11
152.01
151.92
151.82
148.97
148.74
148.50
148.27
146.85
141.58
132.10
132.06
132.03
131.52
128.82
127.99
126.89
124.05
123.79
122.23
120.40
118.58
114.38
77.44
77.23
77.02
N
CF3
SF5
45
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

8.738
8.721
8.589
8.573
8.248
7.994
7.978
7.961
5.780
5.769
5.759
5.234
4.203
3.981
3.972
3.958
3.950
3.867
3.855
3.845
3.832
2.059
2.055
2.050
2.046
2.042
1.00
0.92
0.85
0.91
1.03
0.85
0.84
1.04
1.05
ppm
HO
OH
N
CF3
SF5
46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152.25
152.08
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148.38
147.92
141.60
133.26
133.19
133.12
133.04
132.97
130.83
129.06
128.00
124.31
120.67
117.03
116.16
116.15
71.72
68.02
30.68
30.43
30.17
29.92
29.66
29.40
29.15
HO
OH
N
CF3
SF5
46
10 ppm

8.429
8.402
7.848
7.823
7.795
7.270
4.555
4.543
4.534
3.453
3.435
3.421
2.842
2.834
2.824
2.816
ppm
2.00
2.00
1.00
1.00
1.00
O
N
CF3
SF5
42

49.60
50.96
76.81
77.23
77.66
113.41
113.44
115.67
119.32
122.97
126.63
127.50
127.92
128.21
132.02
132.09
132.16
132.22
140.86
147.14
148.25
148.72
149.20
149.67
151.72
151.93
152.12
152.31
152.51
F3C
N
O
SF5
42

0.584
0.600
0.608
0.612
0.621
0.636
0.743
0.750
0.761
0.784
0.791
1.262
1.473
2.488
2.501
2.511
2.524
2.536
2.547
2.748
2.777
2.790
2.818
2.839
2.860
2.880
2.900
2.917
2.938
2.959
3.221
3.232
3.262
3.274
3.363
3.383
3.401
3.421
5.310
5.492
5.503
5.520
5.532
7.271
7.372
7.719
7.747
7.774
8.146
8.276
8.303
8.368
8.371
8.394
ppm
0
1
2
3
4
5
6
7
8
9
10
11
1.00
1.01
0.92
1.03
1.00
2.09
1.04
2.24
1.23
1.16
9.14
2.02
1.97
Boc
N
N
H
HO
CF3
N
SF5
48

8.812
8.792
8.586
8.566
8.267
8.012
7.993
7.973
6.080
6.057
4.879
3.641
3.610
3.562
3.314
3.310
3.307
2.906
2.889
2.879
2.871
2.627
2.179
1.458
1.248
1.045
1.037
1.025
0.976
0.959
1.00
1.06
1.06
1.07
0.98
5.74
1.05
2.07
2.04
ppm
0
1
2
3
4
5
6
7
8
9
10
11
HO
H
N
N
H
•2HCl
CF3
N
SF5
49

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