New Methods to Synthesise Sulfur-Containing Compounds

Pui Kin Tony Lo



The Queen's College

University of Oxford

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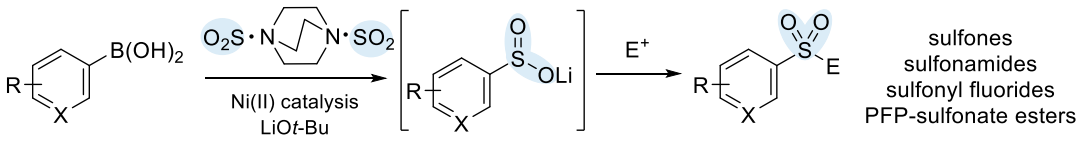
Doctor of Philosophy in Organic Chemistry

Abstract

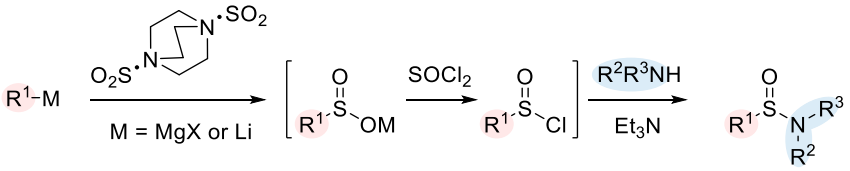
In this thesis, novel methodologies towards the synthesis of a range of sulfur-containing compounds are documented. These compounds include sulfinamides, sulfonimidamides, sulfonimidoyl fluorides and a range of sulfonyl containing functional groups, for example, sulfones and sulfonamides. These developed methods employ easy-to-handle sulfur dioxide surrogates, DABSO, and the sulfinylamine, TrNSO, exploiting nickel catalysis and organometallic reagents.

Chapter 1 provides an overview of the properties, applications and synthesis of sulfonyl-containing compounds and sulfonimidamides. An introduction to the use of sulfur dioxide in organic chemistry is given.

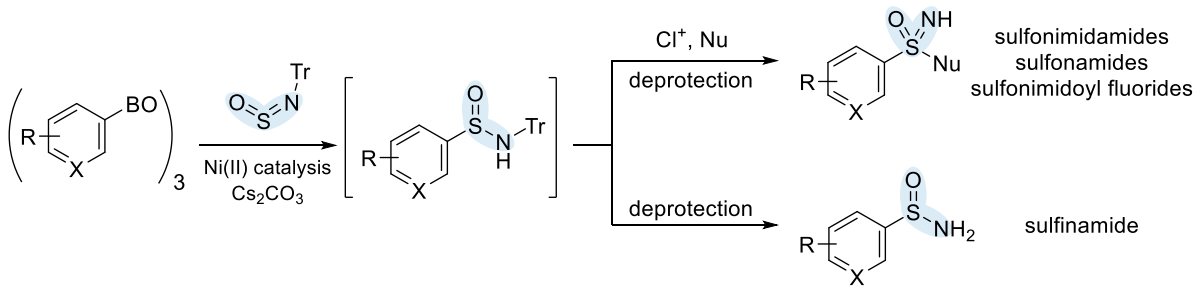
Chapter 2 describes the development of a new nickel-catalysed sulfination of (hetero)aryl boronic acids, using DABSO to synthesise aryl sulfinates *in situ*. The sulfinates are trapped using a range of electrophiles to form a variety of sulfonyl-containing compounds. This protocol tolerates an unprecedented range of electron-deficient and pharmaceutically relevant (hetero)aryl boronic acids, allowing the direct synthesis of active pharmaceutical ingredients (APIs).[1]



Chapter 3 documents the preparation of sulfinamides using organometallic reagents and nitrogen-based nucleophiles in a streamlined one-pot, three-step procedure. Metal sulfinates, first generated from the addition of organometallic reagents to DABSO, are reacted with thionyl chloride to form sulfinyl chlorides as the key intermediates. Subsequently treating the sulfinyl chlorides with a range of nitrogen-nucleophiles delivers sulfinamides.[2]



Chapter 4 presents the discovery of a new method to synthesise sulfinamides from aryl boroxines and sulfinylamine, TrNSO, through a nickel-catalysed protocol. The sulfinamides are further converted into sulfonimidamides, sulfonamides and sulfonimidoyl fluorides in a one-pot multi-step reaction sequence. Deprotection of the trityl-protected sulfinamide is also demonstrated to give the primary sulfinamide.



Chapter 5 summarises the research and presents potential future work.

Chapter 6 documents the experimental procedures and data.

Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated. This thesis has not been previously submitted for a degree, diploma or any other qualification at the University of Oxford or elsewhere.

The results discussed in Chapter 2 in this thesis were carried out in collaboration with Dr Yiding Chen, a former DPhil student in the Willis group, and have been published in *ACS Catalysis* in 2019.[1]

The results discussed in Chapter 3 in this thesis have been published in *The Journal of Organic Chemistry* in 2020.[2]

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Abbreviations and Acronyms

Ac	acetyl
acac	acetylacetone
app.	apparent
aq.	aqueous
Ar	aryl
Boc	*tert*-butoxycarbonyl
bpy	2,2'-bipyridine
br.	broad
Bu	butyl
Bz	benzoyl
℃	degrees Celsius
CAN	ceric ammonium nitrate
cat.	catalyst
cbz	carboxybenzyl
CI	chemical ionisation
COE	cyclooctene
CPME	cyclopentyl methyl ether
CRL	Chemistry Research Laboratory
Cy	cyclohexyl
d	doublet or deuterated
DABCO	1,4-diazabicyclo[2.2.2]octane

DABSO	1,4-diazabicyclo[2.2.2]octane-*bis*(sulfur dioxide) adduct
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DFT	density-functional theory
dioxane	1,4-dioxane
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMB	3,4-dimethoxybenzyl
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DMSO	dimethyl sulfoxide
dNbpy	4,4’-dinonyl-2,2’-dipyridyl
DPhil	Doctor of Philosophy
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
E^+	electrophile
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	enantiomeric excess
EI	electron ionisation
eq.	equation

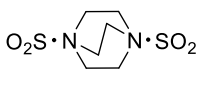
equiv.	equivalent(s)
ESI	electrospray ionisation
Et	ethyl
et al.	et alii (Latin: and others)
FDA	United States Food and Drug Administration
g	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
i	iso
IR	infrared
J	coupling constant
L	ligand or liter
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
M	molar or metal
m	milli (10^{-3}) or multiplet
m	*meta*
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minute(s)

mol	mole(s)
m.p.	melting point
MS	mass spectrometry
Ms	methanesulfonyl
mw	molecular weight
n	normal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Nu	nucleophile
o	*ortho*
p	*para*
Pd/C	palladium on carbon
PFPOH	pentafluorophenol
pin	pinacolate
Ph	phenyl
ppb	parts per billion
ppm	parts per million
R	generic group/substituent
R_f	retention factor

rt	room temperature
s	singlet or solid
sat.	saturated
S_N2	bimolecular nucleophilic substitution
S_N1	unimolecular nucleophilic substitution
t	tertiary
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TCCA	trichloroisocyanuric acid
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
Tf	trifluoromethanesulfonate/triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIMSO	sulfur dioxide 1-methylpyrrolidine adduct
TLC	thin layer chromatography
TMS	trimethylsilyl
TPS	triphenylsilyl
Tr	trityl, triphenylmethyl
Ts	4-toluenesulfonyl
TYL	Tony Lo
UV	ultraviolet
wt	weight

X	X (pseudo)halide (unless stated otherwise)
δ	chemical shift
μ	micro (10^{-6})
ν_{max}	infrared absorption maximum

Ligands and Chemical Structures



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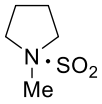
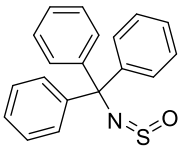
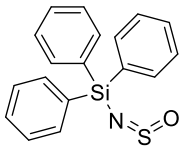


TIMSO



TrNSO



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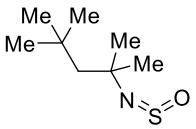
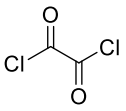


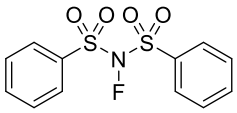
t-OctNSO



$(COCl)_2$



$SOCl_2$



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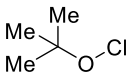

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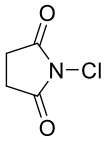

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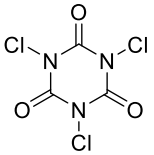

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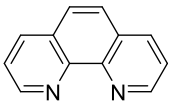

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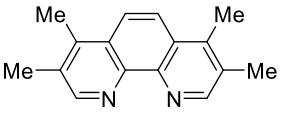

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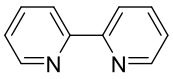
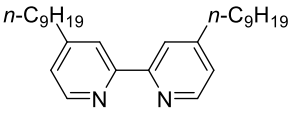
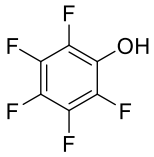


bpy



dNbpy



PFPOH

1. Introduction

1.1 Applications of sulfur-containing compounds

Sulfur-containing compounds have a long history in human civilisation. Elemental sulfur could be found in volcanic regions and is used as an ingredient in gunpowder. In nature, sulfur often presents in the form of sulfide (e.g. FeS, known as pyrite) and sulfate minerals (e.g. $CaSO_4$, known as gypsum).[3] Sulfur-containing compounds play a crucial role in human life. Sodium dodecyl sulfate (SDS) is widely used as an anionic surfactant in cleaning. Sulfur is one of the essential elements for life, usually in organosulfur compounds, including amino acids and vitamins (Figure 1.1).

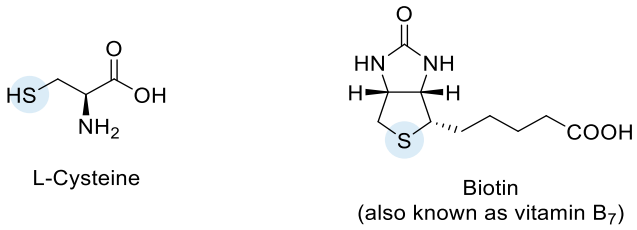


Figure 1.1 Sulfur-containing amino acid and vitamin.

A collection of important sulfur-containing functional groups are listed in Figure 1.2. This ranges from functional groups with S(II), such as thiols and disulfides, to S(IV), for example, sulfoxides and sulfinic acids, to S(VI), exemplified by sulfones and sulfonamides. Some key sulfur-containing reagents in organic chemistry are also listed, including thionyl chloride, sulfur dioxide, sulfinylamine and sulfuryl chloride.

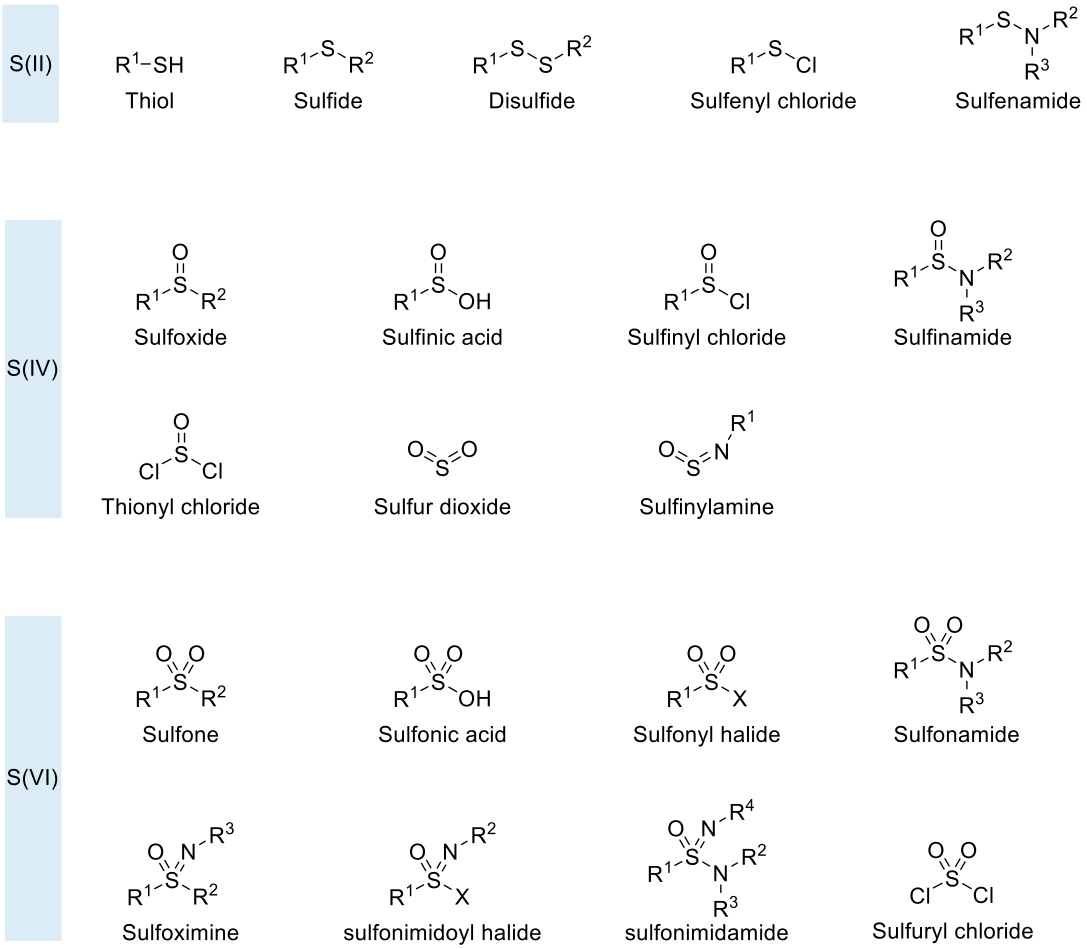


Figure 1.2 Selected examples of sulfur-containing functional groups

Sulfur-containing compounds such as sulfide, sulfoxides, sulfones, sulfonamides, sulfonic acid esters and sulfoximines have broad applications in fields ranging from pharmaceuticals and agrochemicals to materials science (Figure 1.3).[4] Among these, compounds with sulfonyl moieties (–SO_2–), such as sulfones and sulfonamides, are well-known for their antibacterial properties and are widely used as antibiotics.[5] In fact, 25% of the sulfur-containing FDA-approved drugs are sulfonamide medicinal agents, which accordingly are usually represented by the term “sulfa drugs”.[5f]

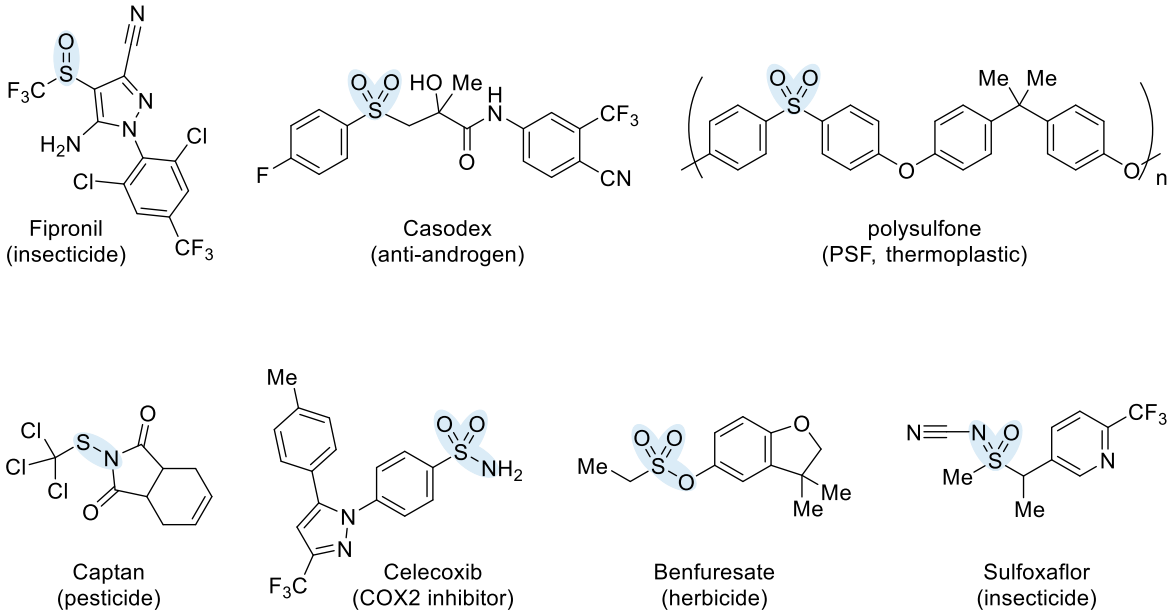
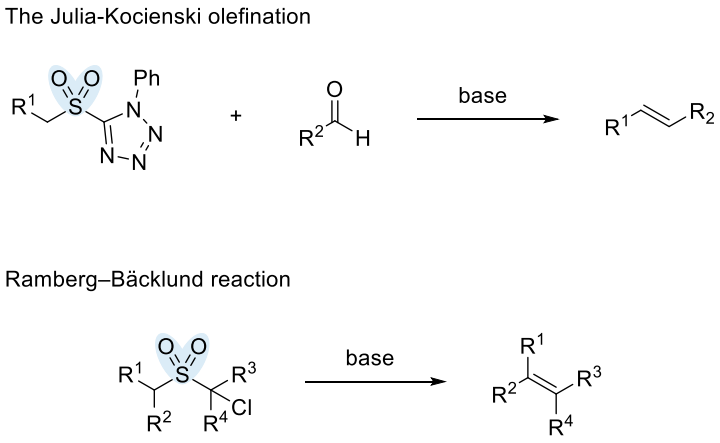


Figure 1.3 Examples of pharmaceuticals, agrochemicals and materials containing sulfur.

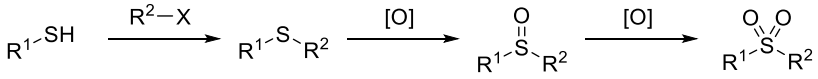
Apart from the biological activities, sulfonyl-containing molecules have found utility in synthetic organic chemistry. Sulfonamides are often used as protecting groups for amines,[6] while sulfones are employed as intermediates to prepare alkenes with the –SO_2– unit as the leaving group (Scheme 1.1).[7]



Scheme 1.1 Examples of sulfones in organic synthesis.

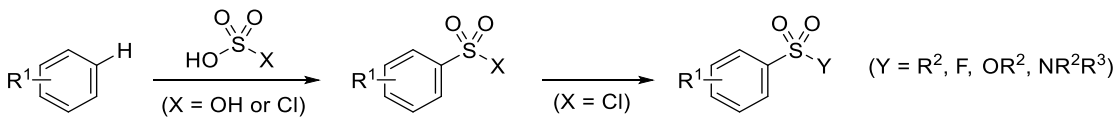
1.2 Synthesis of sulfonyl-containing compounds

Conventional approaches to synthesise sulfonyl groups can generally be divided into three strategies. Firstly, sulfones can be prepared by oxidation of the corresponding sulfides, which are usually synthesised from the alkylation of thiols (Scheme 1.2).[8] Hydrogen peroxide[8c] and *m*-CPBA[8a, 8b] are commonly used as oxidants. It is undesirable to use thiols as the starting materials because they are usually odorous and have limited availability from commerical sources.



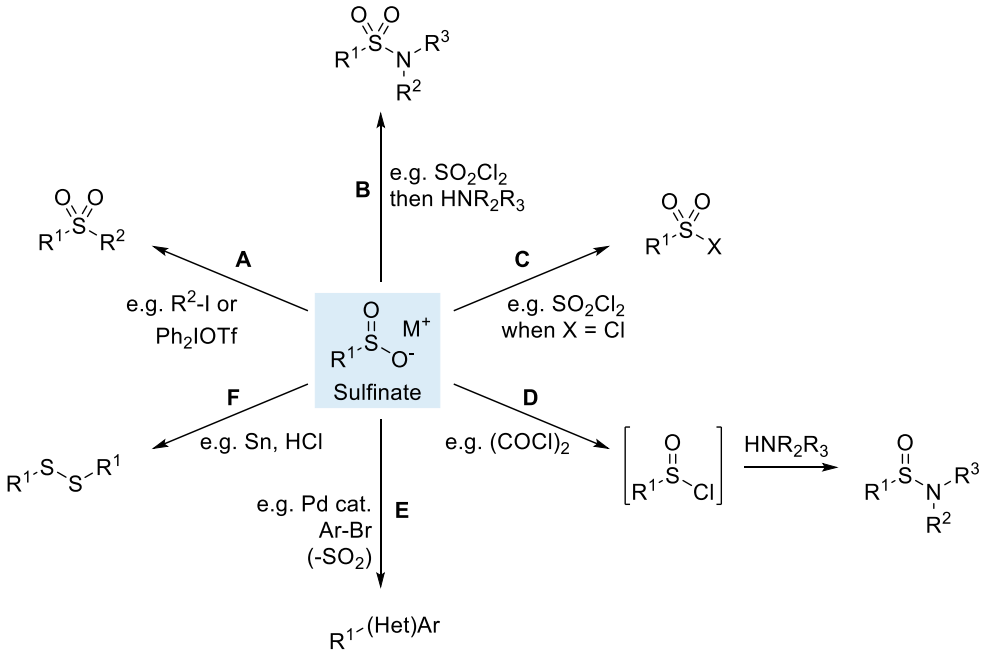
Scheme 1.2 Preparation of sulfones by oxidation of sulfides

Secondly, arylsulfonic acid derivatives can be prepared from the electrophilic aromatic substitution (S_EAr) of arenes using sulfuric acid or chlorosulfuric acid (Scheme 1.3).[9] Using chlorosulfuric acid in these reaction produces arylsulfonyl chlorides, which are important precursors to other useful sulfonyl-containing functional groups, such as sulfones,[10] sulfonamides,[11] sulfonate esters[12] and sulfonyl fluorides.[13] However, harsh acidic conditions are often required for the S_EAr processes, limiting functional group tolerance. Also, the regioselectivity of the reactions often results in mixtures of products, and it can be difficult to obtain certain regioisomers.



Scheme 1.3 Preparation of arylsulfonic acid derivatives by S_EAr of arenes

Finally, sulfinate salts are often used as versatile intermediates in organic synthesis.[14] They are readily derivatised to a range of valuable sulfonyl-containing compounds (Scheme 1.4). For example, they can undergo alkylation[15] and arylation[15d, 16] to form sulfones (eq. A), amination to yield sulfonamides (eq. B),[17] and halogenation to produce sulfonyl halides[17b] (eq. C). They can also be converted into sulfinyl chlorides (eq. D), which can be trapped with amines to form sulfinamides (Chapter 3).[18] In recent years, sulfinate salts have also found uses as reagents in desulfinylative reactions in palladium cross-coupling chemistry[19] and radical chemistry, giving access to useful building blocks such as biaryls and heterocyclic compounds (eq. E).[20] In addition, sulfinates can be reduced to prepare disulfides (eq. F).[21]

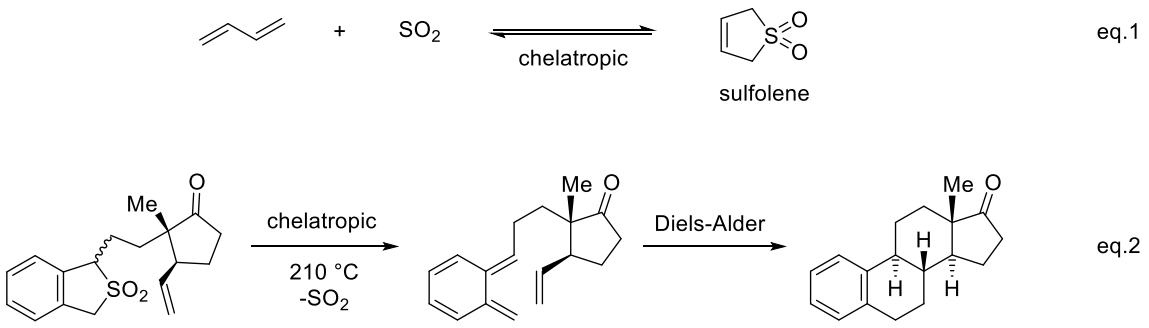


Scheme 1.4 Selected derivatisations of sulfinate salts.

1.3 Sulfur dioxide in organic chemistry

As a colourless, malodorous and toxic gas, sulfur dioxide (SO_2) exists at a very low concentration (~1 ppb level) in the atmosphere. It has been used as a food preservative, and referred to as E220 and its used for preserving wine and dried fruits. Although SO_2 is known as an air pollutant and a cause of acid rain, it is mainly produced and then used as a precursor for manufacturing sulfuric acid in the contact process.

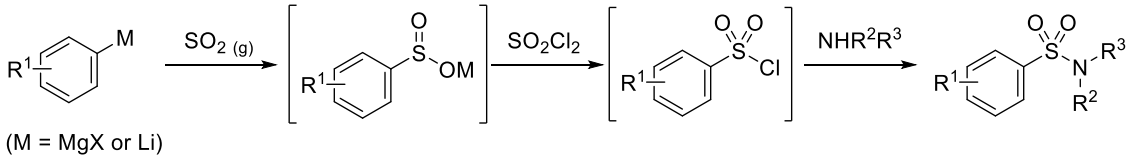
Despite the fact that SO_2 is a toxic gaseous reagent and is required to be handled in a specially equipped and well-ventilated laboratory, it still found some success in organic chemistry. Pericyclic reactions are the most studied organic reactions that use sulfur dioxide. For example, SO_2 undergoes chelatropic reactions with dienes to form sulfolene (Scheme 1.5, eq. 1).[22] The cheletropic extrusion of SO_2 means that sulfolenes can be used as masked dienes because the reaction is reversible, and its application to synthesise a steroid core is presented (eq. 2).[23]



Scheme 1.5 Chelatropic reaction of SO_2 and its application as a masked diene

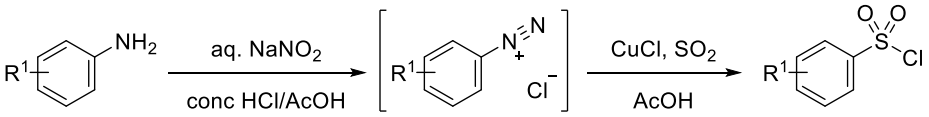
Sulfur dioxide gas can be used directly by adding it to organometallic reagents to form metal sulfinate salts, which can then be treated with sulfuryl chloride to produce sulfonyl

chlorides (Scheme 1.6).[24] Further trapping the sulfonyl chlorides with amines produces the corresponding sulfonamides in a one-pot reaction.[17b]



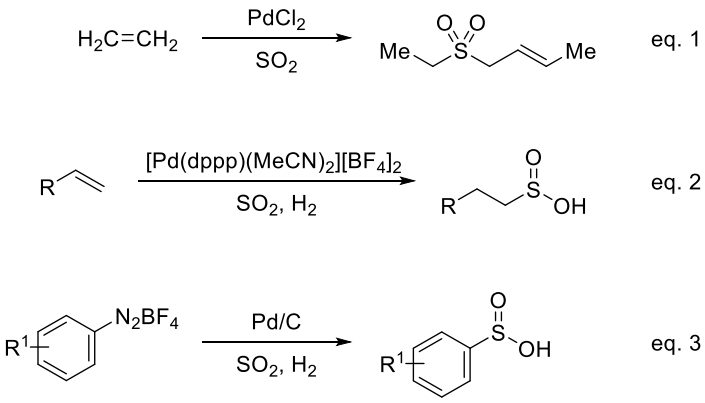
Scheme 1.6 Preparation of sulfonamides from organometallic reagents and sulfur dioxide gas

Sulfur dioxide can also be introduced into organic molecules using metal catalysis. In 1957, Meerwein *et al.* studied the chlorosulfonylation of diazonium salts using SO_2 in the presence of a copper salt, based on the Sandmeyer reaction (Scheme 1.7).[25] This method is important because it uses inexpensive and widely available anilines as the starting materials and solves the regioselectivity issues in the direct chlorosulfonylation of arenes as discussed in Scheme 1.3. But diazonium salts are known to be unstable which hinder their uses in organic chemistry.[26]



Scheme 1.7 Meerwein's chlorosulfonylation of diazonium salts

In 1968, Klein pioneered the palladium catalysed reaction of SO_2 and ethylene (Scheme 1.8, eq. 1).[27] In the 1990s, Keim studied the synthesis of sulfinic acids using alkenes (eq. 2) or aryldiazonium salts (eq. 3).[28] These studies built a solid foundation for the modern development of palladium catalysed sulfination using SO_2.



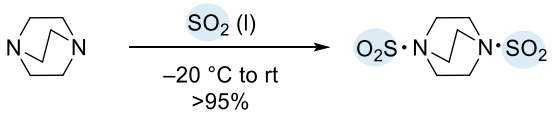
Scheme 1.8 Palladium-catalysed reactions using SO_2 gas

1.4 Sulfur dioxide surrogates

Although several applications of sulfur dioxide have been developed as described above, it is still not widely accepted as a reliable reagent in modern organic synthesis. This may be due to its toxic gaseous nature and the need to use pressurised gas cylinders and glassware with extreme safety precautions. It is also difficult to control the amount of SO_2 used in reactions because of its gaseous nature, and generally, it is used in excess. These would potentially produce undesired side reactions, or even poison the metal catalyst. Accordingly, developing new and safe reagents that are easy to handle and release an accurate amount of SO_2 to the reactions was needed.

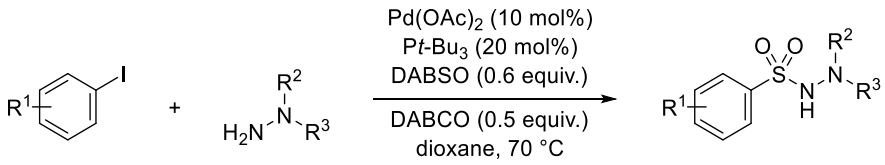
Sulfur dioxide surrogates are complexes or compounds that consist of a "SO_2" unit or that can undergo decomposition under certain conditions to deliver SO_2 in the reactions. Sulfur dioxide forms 1:1 complexes with amines. Although these amine-SO_2 complexes have been known in the literature for a century, research has mainly focused on investigating their structure, rather than developing their applications in organic chemistry.[4a] In 1988,

Santos and Mello reported the complex of DABCO and SO_2, DABCO·$(SO_2)_2$, which was later denominated as "DABSO" and analysed the compound with Raman spectroscopy. DABSO is an air-stable, odourless white solid that is easily prepared by condensing SO_2 onto DABCO at low temperature (Scheme 1.9).



Scheme 1.9 Preparation of DABSO

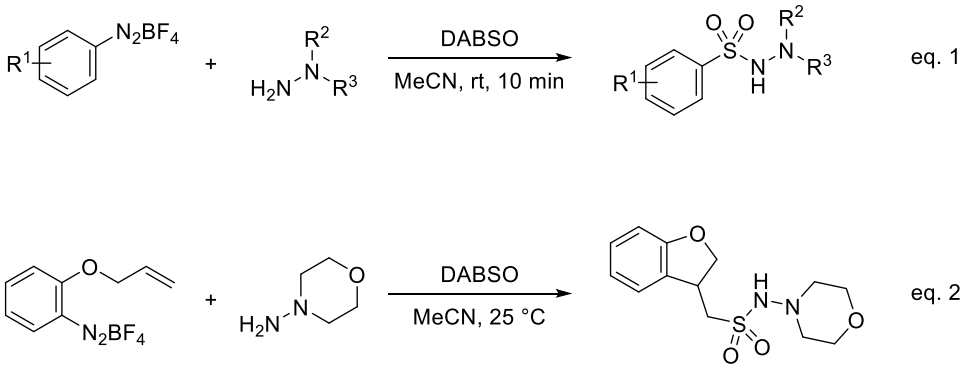
In 2010, the Willis group re-examined this complex and used it as a SO_2 surrogate in an aminosulfonylation of aryl iodides using a palladium catalyst (Scheme 1.10).[29] More importantly, DABSO is an easy-to-handle solid, and hence it is convenient for controlling the quantity of SO_2 that is added to the reaction.



Scheme 1.10 Palladium-catalysed aminosulfonylation of aryl iodides

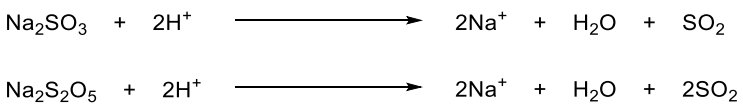
Since then, other groups around the world have joined the field and reported several publications in the area. The Wu group used aryl boronic acids instead of aryl iodides with a palladium catalyst under oxidative conditions.[30] This chemistry could also be performed by using aryl triethoxysilanes and a copper catalyst as described by the Wang group.[31]

The Wu group also developed a similar aminosulfonylation using aryl diazonium salts under metal-free conditions (Scheme 1.11, eq. 1).[32] 2-(Allyloxy)phenyldiazonium salt gave only the cyclised product, suggesting a radical-based mechanism (eq. 2).



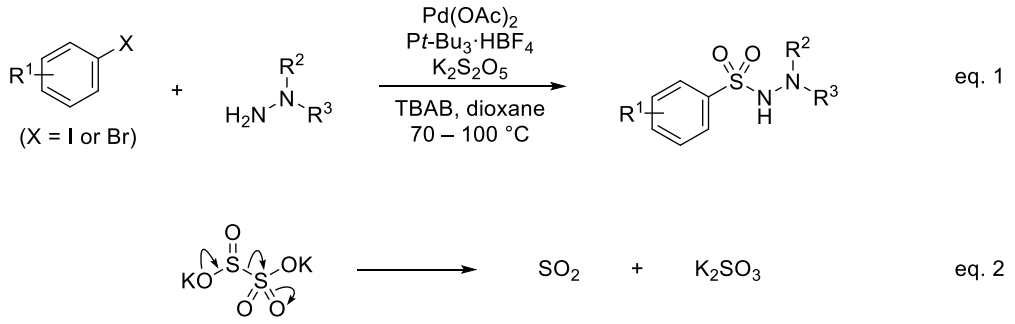
Scheme 1.11 Wu's radical-based aminosulfonylation

Metal sulfites in the form of M_nSO_3 and $M_nS_2O_5$ undergo decomposition to release sulfur dioxide under acidic conditions (Scheme 1.12), and hence they can also be used as an SO_2 surrogate.



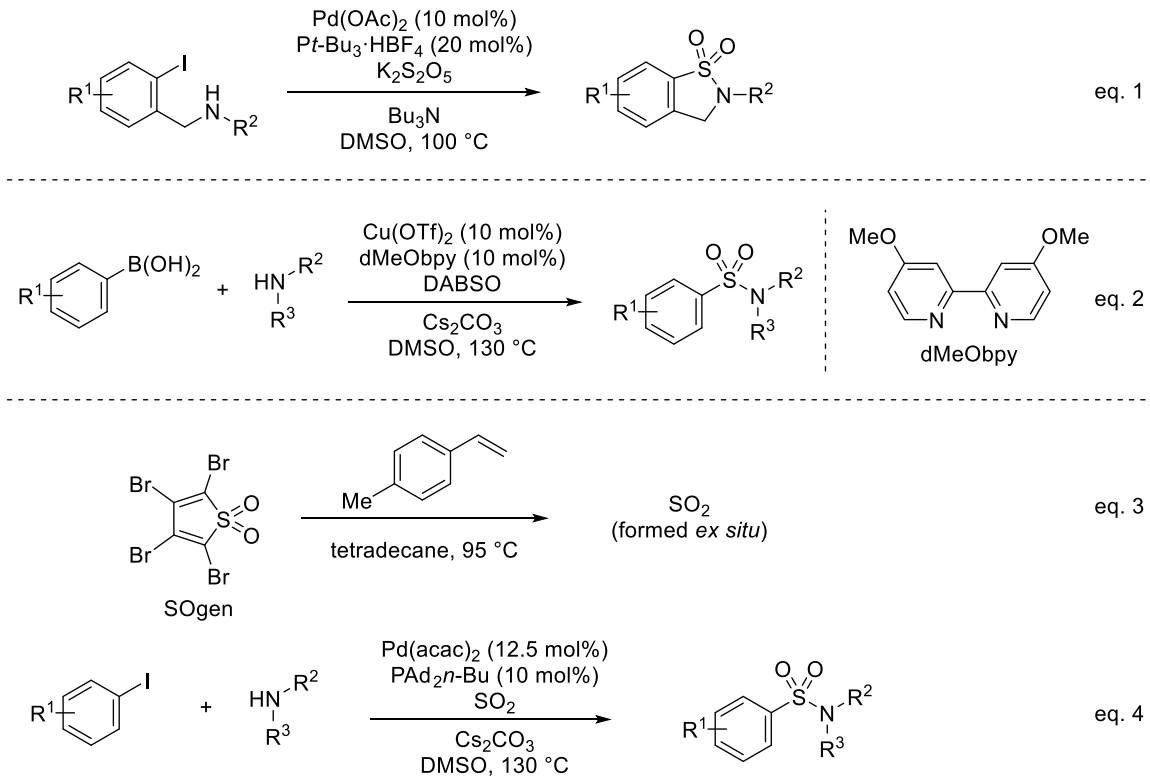
Scheme 1.12 Decomposition of metal sulfites under acidic conditions

The Wu group modified the first aminosulfonylation reported by the Willis group and used $K_2S_2O_5$ as the SO_2 surrogate (Scheme 1.13, eq. 1). Although the authors did not discuss the mechanism for the generation of SO_2 from $K_2S_2O_5$ under basic conditions, SO_2 may be formed from the thermal decomposition of $K_2S_2O_5$ (eq. 2).



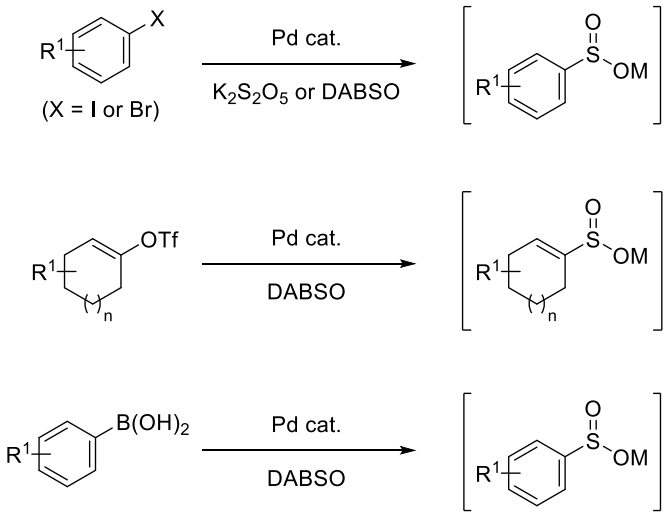
Scheme 1.13 Palladium-catalysed aminosulfonylation using $K_2S_2O_5$ as SO_2 surrogate

In all these early reports of aminosulfonylation, the nucleophiles were limited to hydrazines. Other nucleophiles, including anilines, hydroxylamines and hydrazones, were shown to be unsuccessful in the reaction as described in Section 2.7 in Edward Emmett's DPhil thesis.[33] Recently, this chemistry has been developed further to allow for nucleophiles other than hydrazines. In 2017, Manabe *et al.* reported a palladium-catalysed intramolecular aminosulfonylation to form cyclic sulfonamides with secondary amines as the nucleophiles (Scheme 1.14, eq. 1).[34] One year later, the Willis group studied the aminosulfonylation of aryl boronic acids catalysed by a copper(II) salt using secondary amines and anilines as the nitrogen coupling partners (eq. 2).[35] While preparing this thesis, the Lian group published the palladium catalysed aminosulfonylation of aryl iodides using secondary amines as the nucleophiles (eq. 3 and 4).[36] SOgen, a new SO_2 surrogate, was developed, which underwent a Diels–Alder reaction with styrene, followed by cheletropic reaction to release SO_2 *ex situ*.



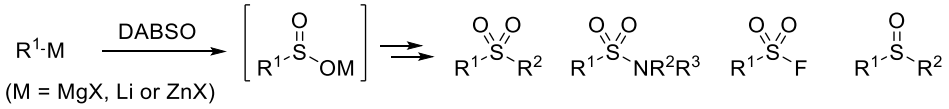
Scheme 1.14 Recent development of aminosulfonylations using secondary amines as nucleophilies

Since 2013, the chemistry has been modified without the addition of nitrogen nucleophiles. A group from Pfizer coupled aryl iodides or bromides and SO_2, using $K_2S_2O_5$ as the SO_2 surrogate, to generate sulfinate salts with a palladium catalyst. The sulfinate salts were then derivatised to other sulfonyl functional groups, such as sulfones and sulfonamides.[37] The Willis group reported a similar palladium-catalysed sulfination of aryl iodides using DABSO as the SO_2 surrogate.[21c] Since these two reports, the sulfination chemistry has been extended to use aryl bromides,[38] alkenyl triflates,[39] and aryl boronic acids as the coupling partners (Scheme 1.15). The metal-catalysed sulfination of aryl boronic acids has been well-developed and is detailed in Section 2.2.



Scheme 1.15 Palladium-catalysed Sulfination using SO_2 surrogates

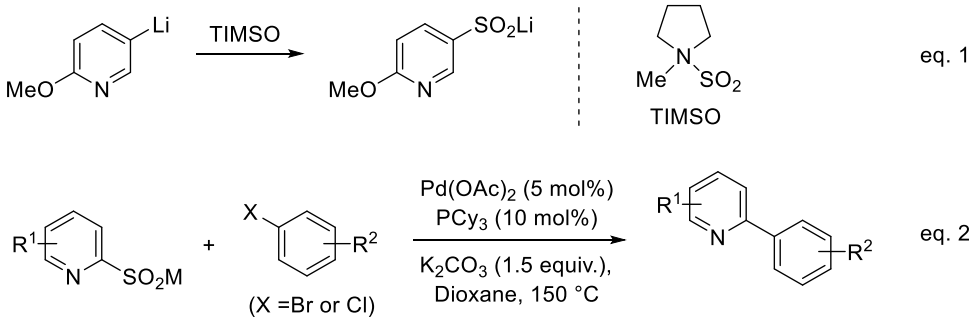
Inspired by the addition of SO_2 gas to organometallic reagents (Scheme 1.6), DABSO can replace the SO_2 gas to form sulfinate salts in a similar manner (Scheme 1.16). The *in situ* formed sulfinate salts can be further derivatised to other sulfonyl- or sulfinyl-containing groups, including sulfones,[15d, 16b, 40] sulfonamides,[41] sulfonyl fluorides[38] and sulfoxides.[42]



Scheme 1.16 Formation of sulfinate salts from organometallic reagents and DABSO

The chemistry was also applied to synthesise a series of pyridine sulfinate salts using *N*-methylpyrrolidine-SO_2 adduct (TIMSO, named by its inventor Dr Tim Markovic) (Scheme 1.17, eq. 1).[19b] The utility of TIMSO instead of DABSO is because the TIMSO and its byproduct, *N*-methylpyrrolidine, have low boiling points and can be easily removed *in vacuo* after workup. The Willis group demonstrated that pyridine sulfinates are effective nucleophilic coupling partners in palladium-catalysed desulfinative cross-coupling

reactions with aryl halides, forming a range or biaryl products in high yields (eq. 2).[19b, 19c] The desulfinatative coupling is an excellent replacement for the traditional Suzuki–Miyaura reaction because pyridinyl boronates generally show poor reactivity and have low success rates.[43] The desulfinatative coupling was extended to use pyridinyl allylsulfones as the nucleophiles due to ease of purification compared to the sulfinate salts.[19d]



Scheme 1.17 Preparation of pyridine sulfinates and its utility in palladium cross-couplings

1.5 Sulfonimidamides

1.5.1 Properties and applications of sulfonimidamides

Sulfonamides have a long history in medicinal chemistry and are viewed as bioisosteres of amides and carboxylic acids (Figure 1.18). Sulfonimidamides, the mono aza-analogue of sulfonamides in which one of the S=O bonds is replaced by an S=N bond, are bioisosteres of sulfonamides and have shown potential in medicinal and agrochemical applications recently.[44]

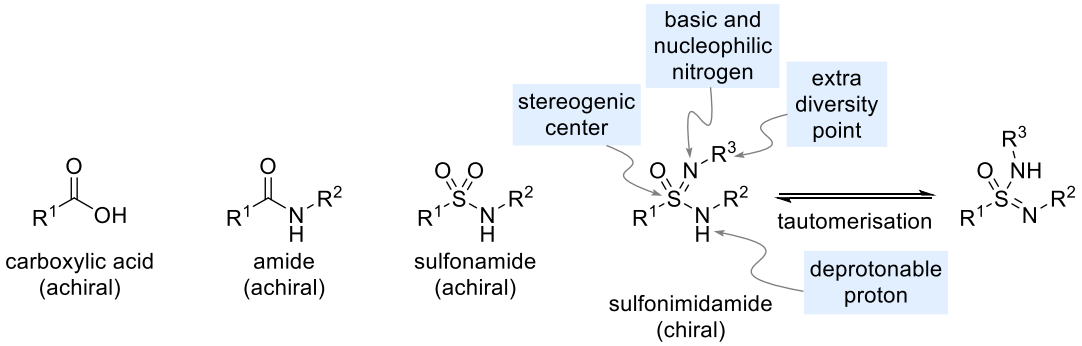


Figure 1.18 Bioisosteres of sulfonimidamide

This modification provides significant changes to the chemistry and properties of sulfonimidamides when compared with sulfonamides. The newly introduced imidic nitrogen offers an extra handle for structural modifications (i.e. substituent R^3) and directed hydrogen bonding, in addition to making the sulfur atom a stereogenic centre. Sulfonimidamides contain a sp^2 hybridised imidic nitrogen and a sp^3 hybridised amidic nitrogen. If the sp^3 amide nitrogen is attached to one or more hydrogen atom(s), the sulfonimidamide can undergo tautomerisation, allowing the proton to exchange between the two nitrogen atoms. The position of the equilibrium of tautomerisation depends on the

substituent attached to the nitrogen atom. For example, tautomer **1A** is more stable when the imino nitrogen is attached to an electron-withdrawing group, or one which could stabilise the partial negative charge on the imino atom by delocalisation, such as an acyl group. The stabilities of the tautomer **1A** and **1B** have been studied by theoretical calculations (Figure 1.19).[45]

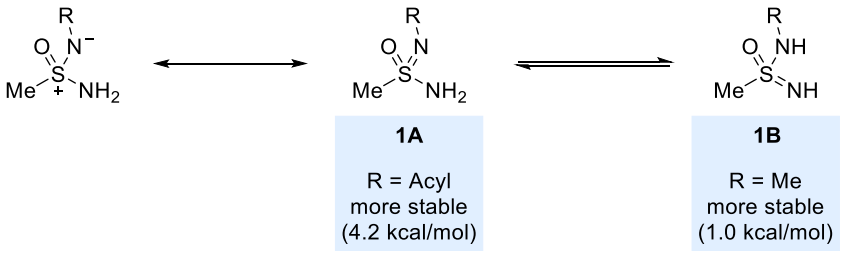
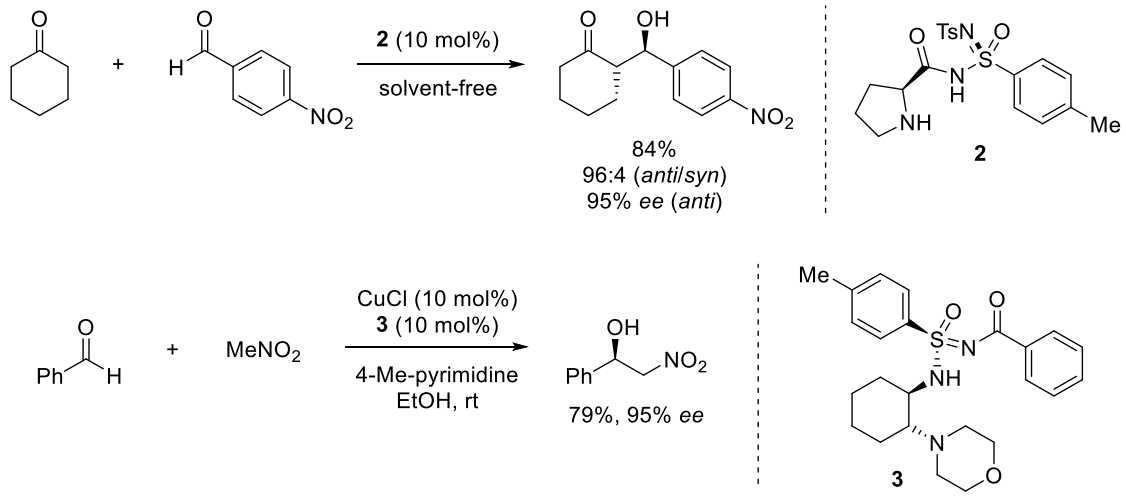


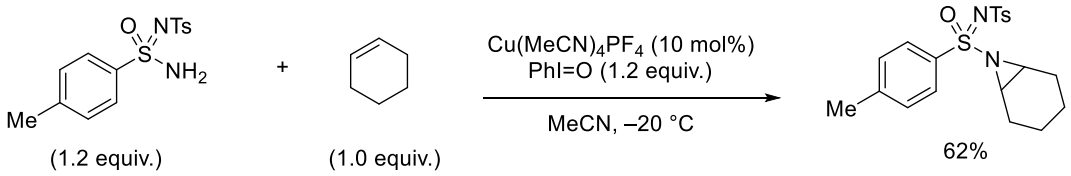
Figure 1.19 Stabilities of the two tautomers of sulfonimidamides

Several applications of sulfonimidamides have been studied. The Bolm group pioneered the use of sulfonimidamides as organocatalysts and ligands in organic chemistry. In 2009, they utilised prolyl-substituted sulfonimidamides as organocatalysts in asymmetric aldol reactions.[46] One year later, they used sulfonimidamides as chiral ligands in copper-catalysed asymmetric Henry reactions (Scheme 1.20).[47]



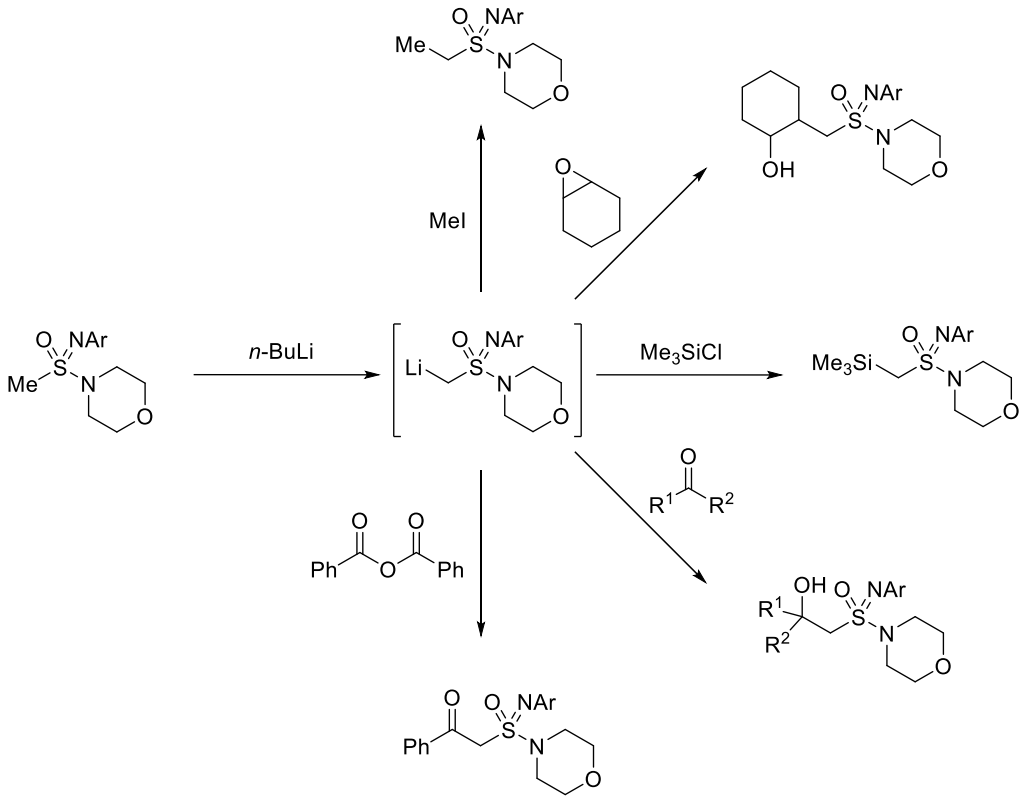
Scheme 1.20 Using sulfonimidamides as organocatalysts and ligands

Sulfonimidamides can also be used as nitrene transfer agents in the presence of hypervalent iodine reagents and metal catalysts.[48] For example, a copper-catalysed aziridination of olefins is shown in Scheme 1.21.[48a]



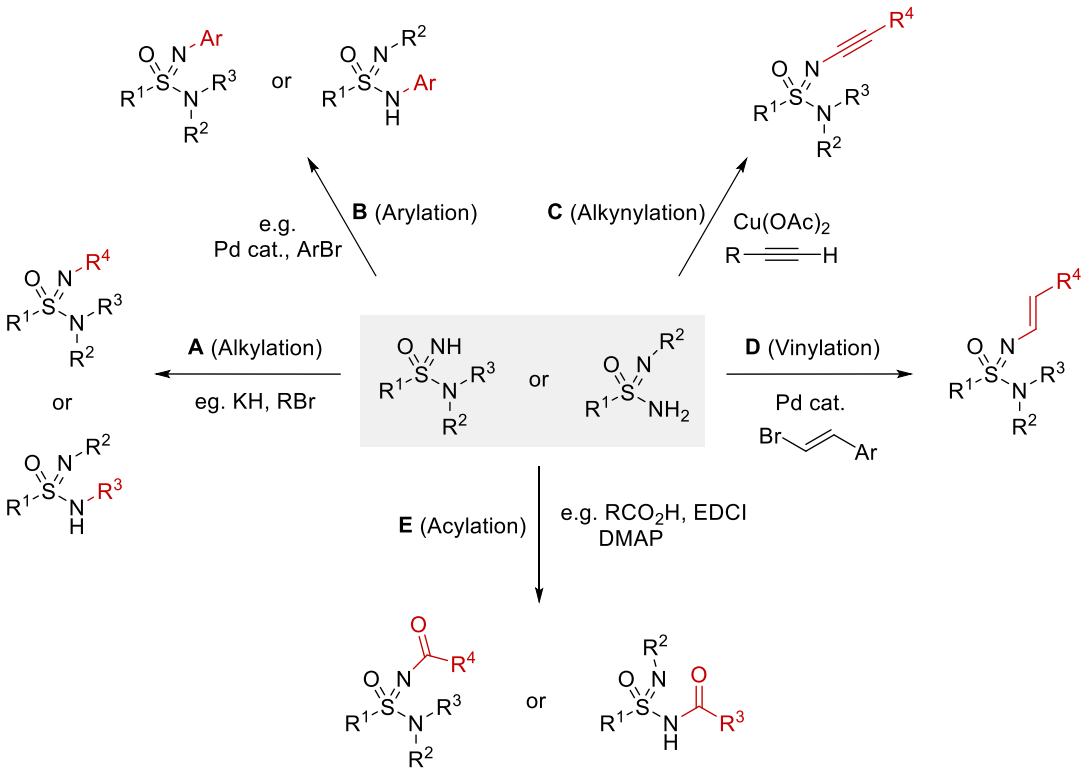
Scheme 1.21 Copper-catalysed aziridination of olefins

Various sulfonimidamide derivatives could be prepared by functionalisation of the α-carbon of sulfonimidamides. Deprotonation of the α-hydrogen with *n*-BuLi gave the corresponding anions, which were trapped with different electrophiles (Scheme 1.22).[49]



Scheme 1.22 α-Carbon functionalisation of sulfonimidamides

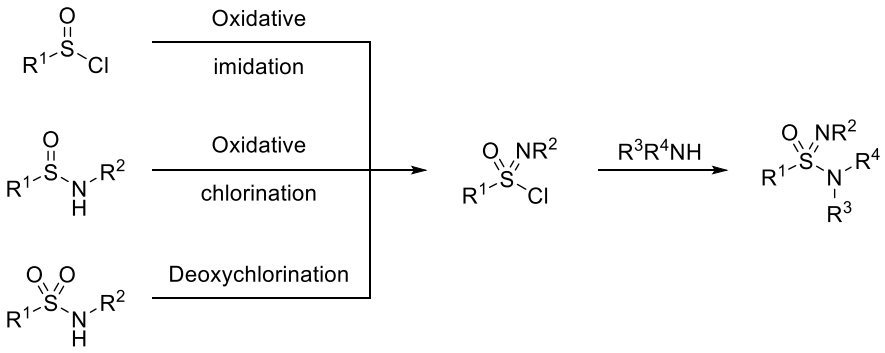
Different nitrogen functionalisations of sulfonimidamides have been reported (Scheme 1.23),[44a] including alkylation (eq. A), arylation (eq. B), alkynylation (eq. C), vinylation (eq. D), and acylation (eq. E).



Scheme 1.23 Nitrogen functionalisations of sulfonimidamides

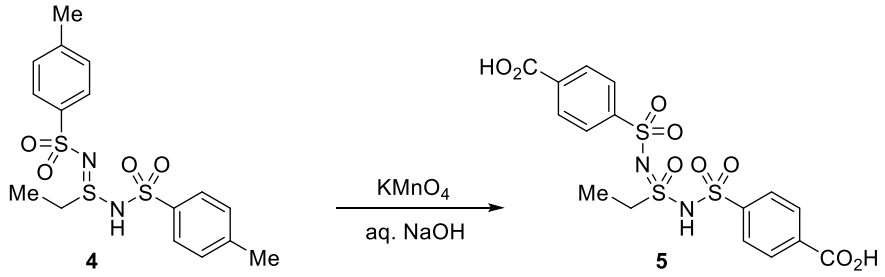
1.5.2 Synthesis of sulfonimidamides

In general, the synthesis of sulfonimidamides has been dominated by the nucleophilic substitution of sulfonimidoyl chlorides with amines. This is still the most universal and commonly used procedure to afford sulfonimidamides (Scheme 1.24).[44a, 50] Sulfonimidoyl chlorides are typically prepared by oxidative imidation, oxidative chlorination (or halogenation to prepare other sulfonimidoyl halides), and deoxychlorination.



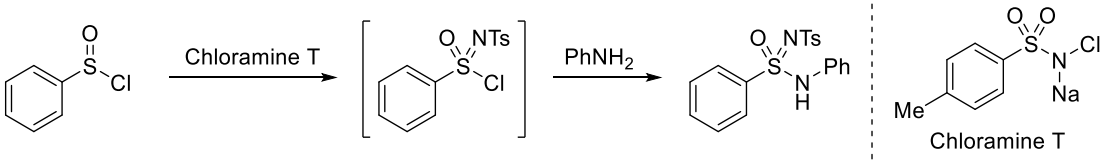
Scheme 1.24 Preparation of sulfonimidoyl chlorides and sulfonimidamides

Although the earliest synthesis of sulfonimidamides is widely cited as Levchenko's studies in the 1960s,[44a, 51] in fact a prior report can be traced back to 1930 by the Kenyon group.[52] Sulfinamidine **4** was oxidised by $KMnO_4$ in aqueous NaOH to produce the sulfonimidamide **5** (Scheme 1.25). The strong oxidising conditions also oxidised the aromatic methyl groups to carboxylic acids.



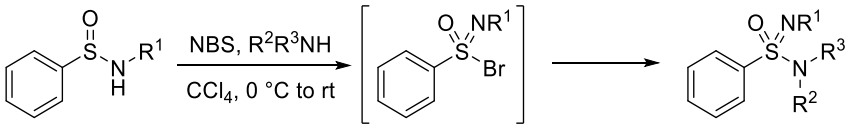
Scheme 1.25 The first preparation of sulfonimidamides

In 1962, Levchenko *et al.* developed a new method to access sulfonimidamides by combining sulfonimidoyl chlorides with amines (Scheme 1.26). The *N*-tosyl sulfonimidoyl chloride was prepared by treating sulfinyl chloride with Chloramine T.[44a, 51] However, this method was not suitable to prepare the corresponding *N*-alkyl and *N*-aryl sulfonimidoyl chlorides because the related sodium *N*-chloroalkyl or aryl salts were difficult to handle in pure forms.[53]



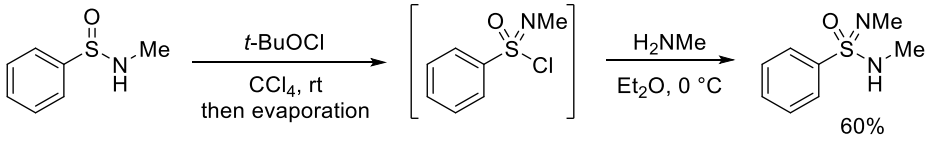
Scheme 1.26 Levchenko's preparation of sulfonimidamides using chloramine T

In 1965, Takei, Watanabe and Mukaiyama reacted sulfonimidoyl bromides with amines to give sulfonimidamides (Scheme 1.27).[53] The sulfonimidoyl bromides could be prepared *in situ* by oxidising the corresponding sulfinamides with bromine or *N*-bromosuccinimide; however, attempts at isolating the sulfonimidoyl bromides were unsuccessful. Additionally, the sulfonimidamide products were formed in lower yields when a longer reaction time was used for the oxidation step, indicating the sulfonimidoyl bromides were unstable.



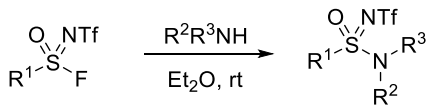
Scheme 1.27 Preparation of sulfonimidamides from sulfonimidoyl bromides

In the 1970s, the Johnson group published a number of methods to prepare sulfonimidoyl chlorides by oxidising sulfinamides with an appropriate oxidant. Chlorine and *N*-chlorobenzotriazole were initially employed, but significant disadvantages were identified.[54] When chlorine was used, the HCl formed in the reaction would decompose the sulfonimidoyl chlorides, and undesired chlorination on arenes was observed. When *N*-chlorobenzotriazole was employed, the benzotriazole byproduct would react with the sulfonimidoyl chlorides. The group found that *tert*-butyl hypochlorite (*t*-BuOCl) was an excellent replacement, as it produced *t*-BuOH as a non-nucleophilic byproduct that could be removed easily by evaporation, and more importantly no over-chlorination was observed.[55] Several sulfonimidoyl chlorides were further reacted with amines to produce sulfonimidamides (Scheme 1.28).



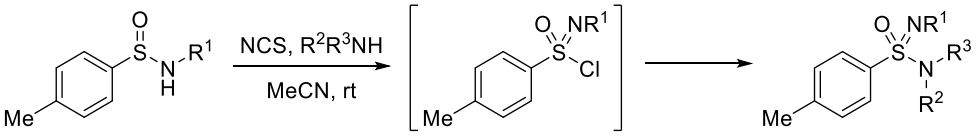
Scheme 1.28 Preparation of sulfonimidamides using *t*-BuOCl as the chlorinating agent

In 1994, the Yagupolskii group published a method to prepare *N*-triflyl sulfonimidamides from sulfonimidoyl fluorides (Scheme 1.29).[56] Initially, sulfonimidoyl chlorides were tested in the amination conditions, but they simply acted as a source of "Cl^+" and were reduced to the corresponding sulfinamides because of the electron-withdrawing property of the triflyl group. The sulfonimidoyl fluorides, however, produce the desired sulfonimidamides.



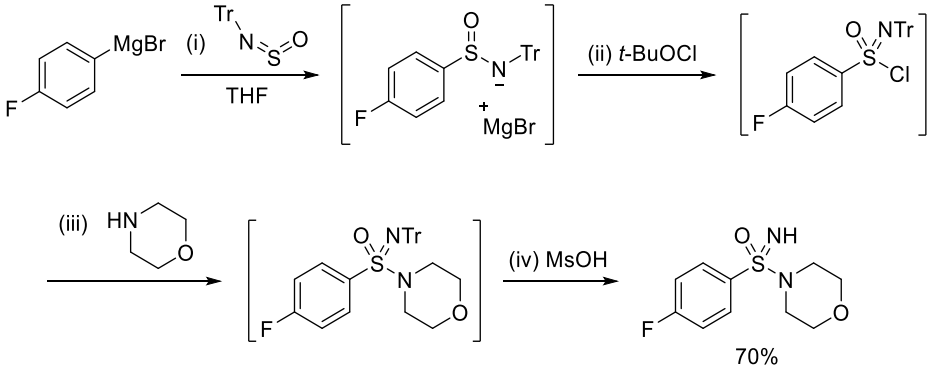
Scheme 1.29 Preparation of sulfonimidamides from sulfonimidoyl fluorides

In 2007, Bolm et al. synthesised sulfonimidoyl chlorides from sulfinamides using *N*-chlorosuccinimide (NCS) as a chlorinating agent (Scheme 1.30).[57] The use of NCS as the oxidant is preferable to *t*-BuOCl, which is potentially explosive and decomposes on exposure to heat or light.



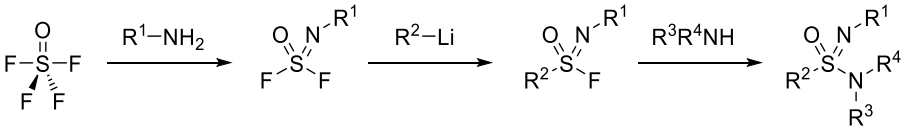
Scheme 1.30 Preparation of sulfonimidamides using NCS as the chlorinating Agent

In 2017, the Willis group prepared sulfonimidamides from organometallic reagents (Scheme 1.31).[58] The addition of an organometallic reagent to *N*-sulfinyltritylamine (TrNSO) produced a sulfinamide that was converted to a sulfonimidoyl chloride by *t*-BuOCl. Further amination and deprotection of the trityl group gave a *N*H sulfonimidamide as the product.



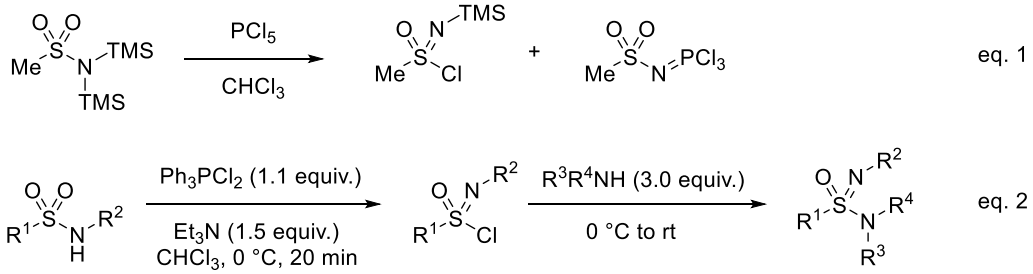
Scheme 1.31 Willis' synthesis of sulfonimidamides from organometallic reagent and TrNSO

Recently, sulfonimidoyl fluorides were also used in amination reactions by Sharpless and co-workers to produce sulfonimidamides by performing sulfur fluoride exchange (SuFEx) chemistry, with amine nucleophiles (Scheme 1.32).[59] Amines were firstly reacted with SOF_4 to give iminosulfur difluorides, which were trapped with organolithium reagents to yield sulfonimidoyl fluorides. These were then reacted with a second amine to form sulfonimidamides.



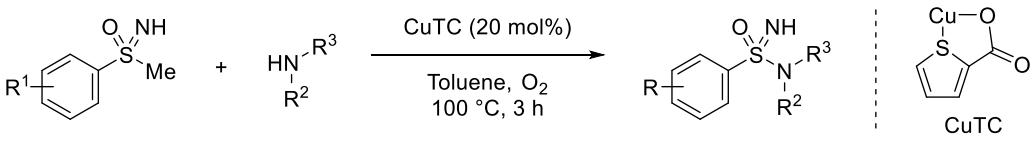
Scheme 1.32 Sharpless' synthesis of sulfonimidamides from organometallic reagents, SOF_4 and amines

Levchenko and co-workers developed a deoxychlorination reaction to convert *N*-substituted sulfonamides to sulfonimidoyl chlorides using PCl_5.[44a] Later, Roy further developed this method and found that *bis*-*N*-silylsulfonamide gave a 1:1 mixture of the desired sulfonimidoyl chloride and phosphoranylidene product when reacted with PCl_5 (Scheme 1.33, eq. 1). When a more sterically demanding phosphorus(V) chloride, PPh_3Cl_2, was used instead, only the desired sulfonimidoyl chloride was observed.[60] In 2015, Chen and Gibson employed this method and further performed an amination to the *in situ* formed sulfonimidoyl chloride to produce sulfonimidamides (eq. 2).[61]



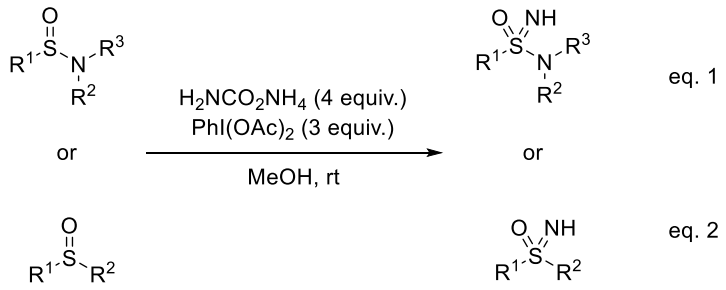
Scheme 1.33 Synthesis of sulfonimidamides from sulfonamides

In the past few years, other methods that do not involve a sulfonimidoyl halide intermediate to prepare sulfonimidamides have been developed. In 2016, the Bolm group reported a copper-catalysed de-alkylation/amination reaction to synthesise sulfonimidamides from sulfoximines (Scheme 1.34).[62]



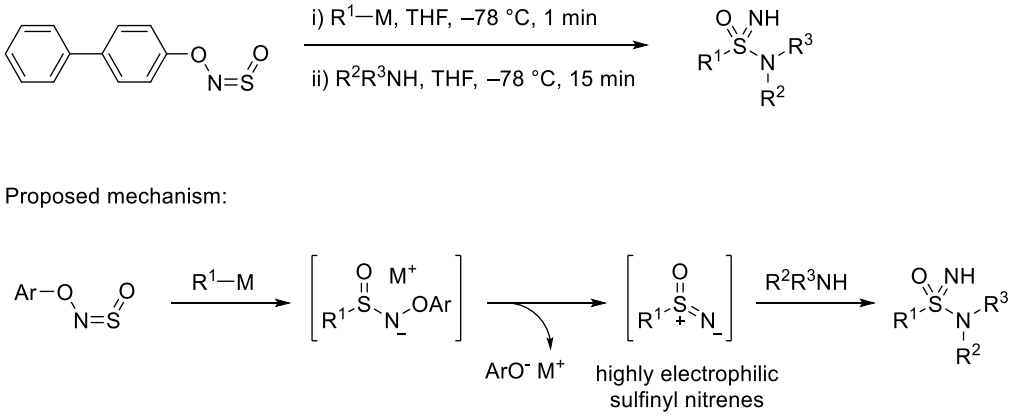
Scheme 1.34 Bolm's synthesis of sulfonimidamides from sulfoximines

In 2017, Lücking and co-workers used a *N*H transfer method to convert sulfinamides to sulfonimidamides using $PhI(OAc)_2$ and $NH_2CO_2NH_4$ (Scheme 1.35, eq. 1).[63] These conditions were originally developed by the Bull group to synthesise sulfoximines from sulfoxides (eq. 2).[64]



Scheme 1.35 Direct synthesis of *N*H sulfonimidamides and sulfoximines from sulfinamides and sulfoxides

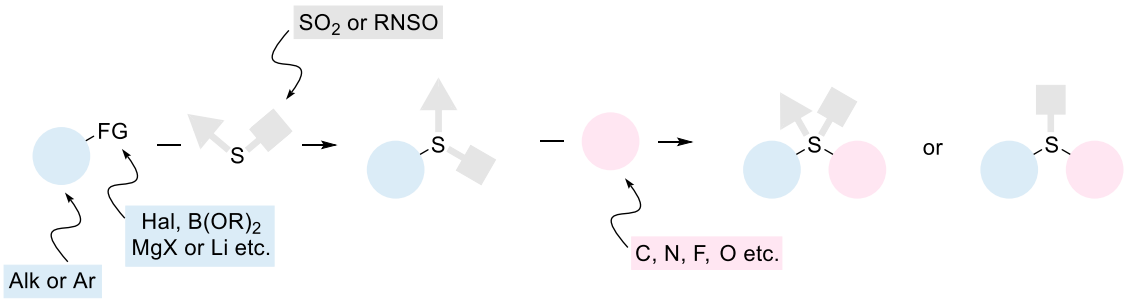
In 2020, the Willis group developed a new sulfinylhydroxylamine reagent, BiPhONSO (Scheme 1.36).[65] Treating the reagent with one equivalent of an organometallic reagent leads to the formation of a sulfinyl nitrene intermediate which was suggested by both experimental and DFT computational studies. Trapping the sulfinyl nitrene with amines or organometallic reagents gave the desired sulfonimidamides or sulfoximines respectively.



Scheme 1.36 Willis' synthesis of sulfonimidamides from organometallic reagents and BiPhONSO

1.6 Research aims

Although many methods have been developed to prepare valuable sulfur-containing functional groups, more general and straightforward protocols that use commercially available and easy to access starting materials, in simple reaction setups, to assemble complex molecules rapidly, are still highly sought after. Hence, the objective of this DPhil program was to develop new methods to incorporate sulfur atoms into organic molecules using convenient sources of SO_2 (e.g. DABSO) and "NSO" (e.g. TrNSO) based on previous developments in the group (Scheme 1.37). After introducing these moieties, the intermediates would further undergo multiple functionalisations, ideally in a one-pot reaction, to produce various important sulfur(IV) and sulfur(VI) compounds. These one-pot multi-step sequences would ideally be easy to set up, and would tolerate a range of heterocyclic and pharmaceutically relevant moieties, allowing molecular complexity to be built up with minimal experimental effort. These rapid and streamlined procedures would find potential uses in medicinal and agrochemical applications.



Scheme 1.37 Research aims of the DPhil Project

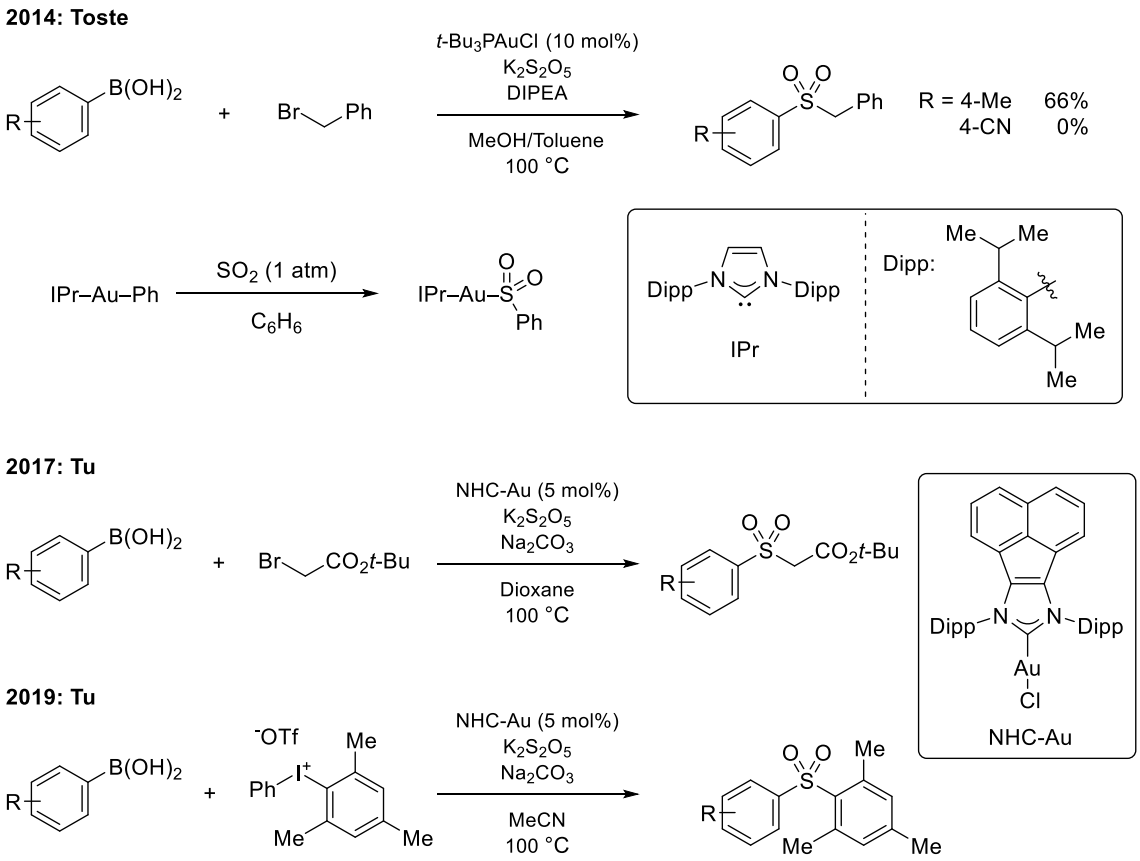
2. Nickel(II)-Catalysed Synthesis of Sulfinates from Aryl and Heteroaryl Boronic Acids and DABSO

2.1 Metal-catalysed preparation of sulfinates salts using aryl boronic acids and their limitations

The Willis group, and others, have developed methods to expand the accessibility of sulfinates using sulfur dioxide surrogates (Chapter 1.4). The direct sulfination of aryl boronic acids using metal-catalysis and sulfur dioxide surrogates represented a signficant advance. These protocols are redox-neutral and employ widely available aryl boronic acids as the starting materials.

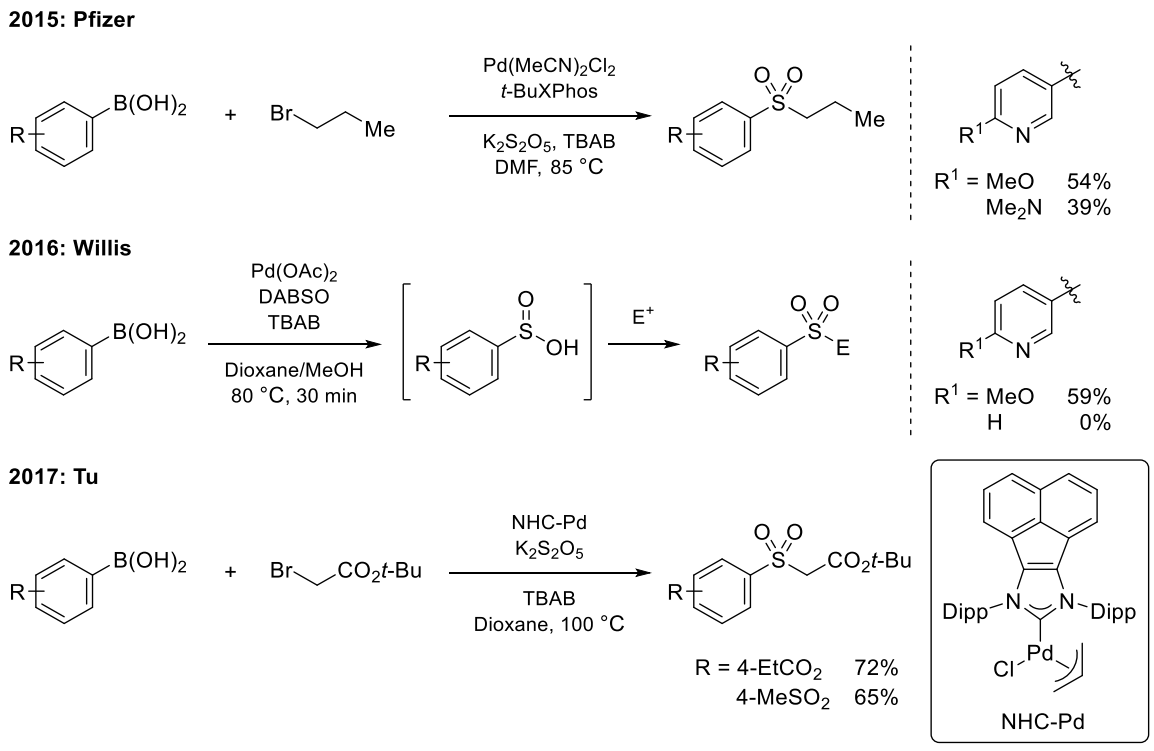
In 2014, the Toste group developed an Au(I)-catalysed sulfination of aryl boronic acids using $K_2S_2O_5$ as the sulfur dioxide surrogate (Scheme 2.1).[66] The sulfinate formed *in situ* reacts with an alkyl halide to form the corresponding sulfone. However, the scope was limited, and only electron-neutral and -rich aryl boronic acids could react smoothly. Electron-poor 4-cyanophenyl boronic acid was completely unreactive under the reaction conditions. They also studied the fundamental organometallic chemistry of the sulfur dioxide insertion into carbon–gold bonds of a NHC–Au–R complex, and characterised the NHC–Au–SO_2R complex crystallographically. In 2017, Tu *et al.* improved this work using a different NHC–Au complex and largely expanded the scope of aryl boronic acids.[67] Electron-withdrawing substituents on the boronic acid starting materials such as ketones, esters and halogens were tolerated. In 2019, they replaced the alkyl halides with

sterically-hindered diaryliodonium salts, allowing the synthesis of difficult-to-access (poly)*ortho*-substituted diaryl sulfones.[68] However, apart from halogen-substituted aryl boronic acids, no other electron-deficient systems were employed. In general, only sulfones can be prepared using this Au-catalysed process while no other sulfonyl functional groups were accessed.



Scheme 2.1 Gold(I)-catalysed sulfination of aryl boronic acids.

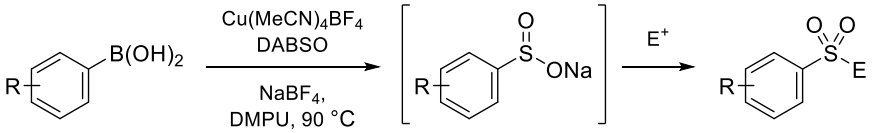
In 2015, a group from Pfizer explored a similar sulfone synthesis using palladium catalysis (Scheme 2.2).[69] However, pyridine boronic acids were challenging, giving poor to moderate yields. Later, Jiang and co-workers extended this method to aryl methyl sulfone synthesis using dimethyl carbonate as a low toxicity and highly biodegradable methylating reagent.[70] In 2016, the Willis group developed the synthesis of aryl sulfinate salts from aryl boronic acids using $Pd(OAc)_2$ as a catalyst.[71] This process had short reaction times and did not require any specialised and often costly phosphine ligands. The sulfinates could be further derivatised to useful sulfonyl-containing compounds including sulfones and sulfonamides, using appropriate electrophiles. The catalyst loading could be reduced to 1 mol% on a multi-gram scale. The scope of aryl boronic acids, however, was limited to electron-neutral and -rich systems.



Scheme 2.2 Palladium(II)-catalysed sulfination of aryl boronic acids.

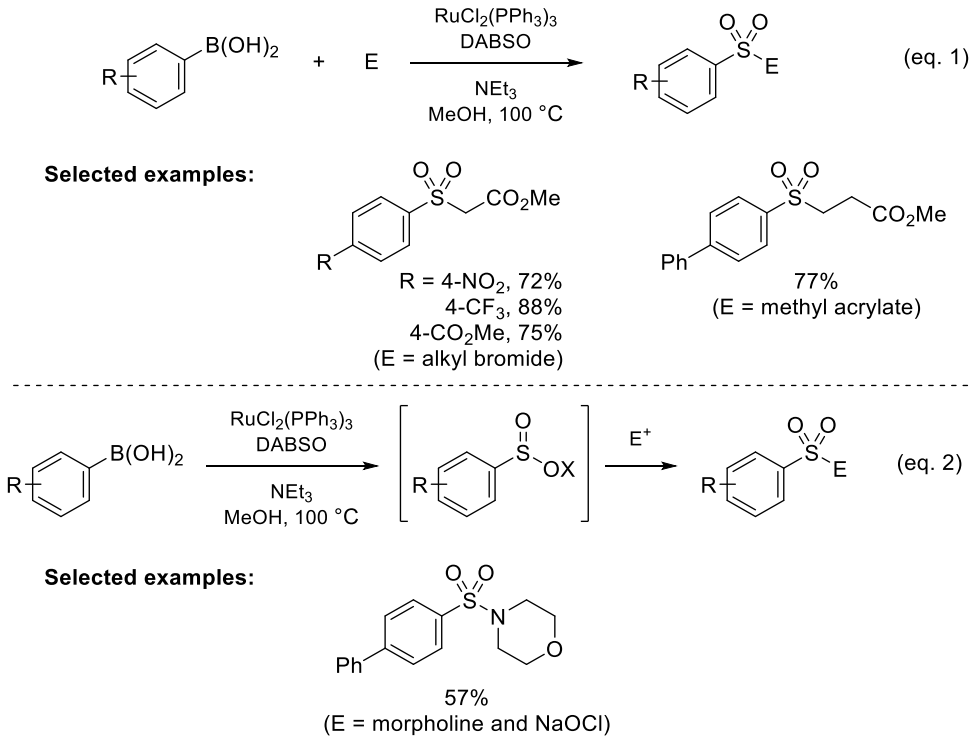
It was noted that 2-substitution to the pyridine nitrogen was required for the formation of the sulfone, while using pyridine-3-boronic acid resulted in no product with only homocoupled product detected.[72] In 2017, the Tu group used NHC–Pd complex as the catalyst for the sulfone synthesis and they found some success with electron-poor aryl boronic acids.[73]

In 2017, Chen and Willis developed a copper(I)-catalysed sulfonylative Suzuki–Miyaura cross-coupling using aryl iodides and aryl boronic acids as the coupling reagents.[74] They found that the aryl boronic acid was converted into aryl sulfinate before reacting with aryl iodide under the action of copper catalysis. Based on this finding, they identified $NaBF_4$ as a reagent for stabilising the sulfinates formed *in situ*, which could then be treated with different electrophiles to form sulfones, sulfonamides and sulfonyl fluorides (Scheme 2.3).



Scheme 2.3 Chen and Willis' copper(I)-catalysed sulfination of aryl boronic acids.

In 2020, Bulbe and Turks reported a Ru(II)-catalysed sulfination of boronic acids, using commercially available $RuCl_2(PPh_3)_3$ as a catalyst, DABSO as the sulfur dioxide surrogate and methanol as solvent (Scheme 2.4).[75] The method tolerated a range of electron-withdrawing substituents, including trifluoromethyl, nitro and ester groups. Sulfones could be synthesised by performing the reaction in a one-pot three-component, or two-step process, with alkyl halides and epoxides as electrophiles or methyl acrylate as a Michael acceptor. Sulfonamides could also be accessed *via* the one-pot two-step manner using NaOCl as an oxidant.



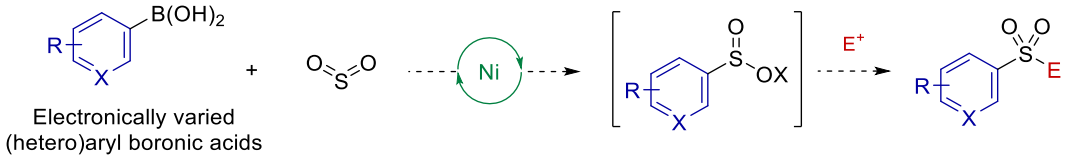
Scheme 2.4 Bulbe and Turks' ruthenium(II)-catalysed sulfination of aryl boronic acids.

Despite this success in the aforementioned sulfinate synthesis using metal catalysts and aryl boronic acids, several problems remain unsolved. For example, a bespoke *N*-heterocyclic carbene ligand is often used, which is not commercially available. The scope of these protocols is generally limited to electron-neutral and -rich aryl boronic acids. Electron-deficient aryl and heteroaryl systems are still challenging and often result in low yields of products, or fail completely.

2.2 Project aims

Because of the limitations of the current methods discussed above, a more universal catalytic protocol that uses commercial reaction components and can tolerate a wide range of electronically varied boronic acids is therefore highly sought.

Recently, the use of abundant base-metal catalysts in synthetic chemistry has become increasingly popular in both industrial and academic communities. Replacing precious metal catalysts with these inexpensive and sustainable base-metals that are less susceptible to the risk of supply, has attracted significant attention.[76] Nickel catalysis features noticeably in this area, not only because of its remarkable lower cost, compared to palladium, but also because it often provides alternative and complementary reactivity.[77] For instance, nickel undergoes rapid oxidative addition with less reactive, but more abundant electrophiles, including aryl chlorides.[77a-c] Moreover, it can be employed, alongside photoredox catalysts, to deliver different modes of reactivity[78] which are challenging to perform with palladium catalysts. Based on these advantages, we envisioned that nickel catalysis could provide new opportunities in sulfination chemistry, and solve the shortcomings of previous developed catalytic systems (Scheme 2.5).

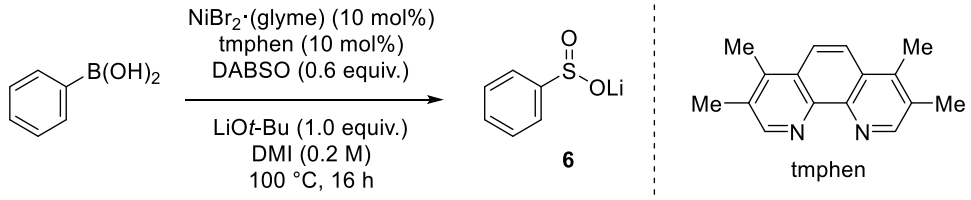


Scheme 2.5 Proposed nickel-catalysed sulfination of (hetero)aryl boronic acids.

2.3 Optimisation of the reaction conditions

Dr Yiding Chen carried out the entire optimisation of the reaction condition for the sulfination of phenylboronic acid and the key findings are summarised in Table 2.1. Full details of the reaction optimisation can be found in the supporting information of our published paper, selected data is shown below.[1] Dr Yiding Chen chose the combination of phenylboronic acid and DABSO as an initial attempt and tested a range of Ni(II) catalysts (Table 2.1). To our delight, he identified that the use of 10 mol% of commercially available and air-stable $NiBr_2$·(glyme), and 10 mol% of 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen) as a ligand, was able to promote the reaction, resulting in the desired sulfinate **6** in excellent 91% yield (entry 1). The reaction operated with 1,3-dimethyl-2-imidazolidinone (DMI) as a solvent at 100 ℃ and used only 0.6 equiv of DABSO and 1.0 equiv of LiO*t*-Bu. A lower reaction temperature (90 ℃), higher loading of ligand or base, or increasing the concentration, all resulted in diminished yields (entries 2−6). He also found that using a strong base was necessary for this reaction, with LiO*t*-Bu being optimal; using KO*t*-Bu or a weaker base provided less efficient reactions (entries 7 and 8). Replacing DABSO for an inorganic source of sulfur dioxide ($K_2S_2O_5$), or substituting phenylboronic acid with potassium phenyltrifluoroborate was shown to be ineffective (entries 9 and 10).

Table 2.1 Variations of the optimised conditions.



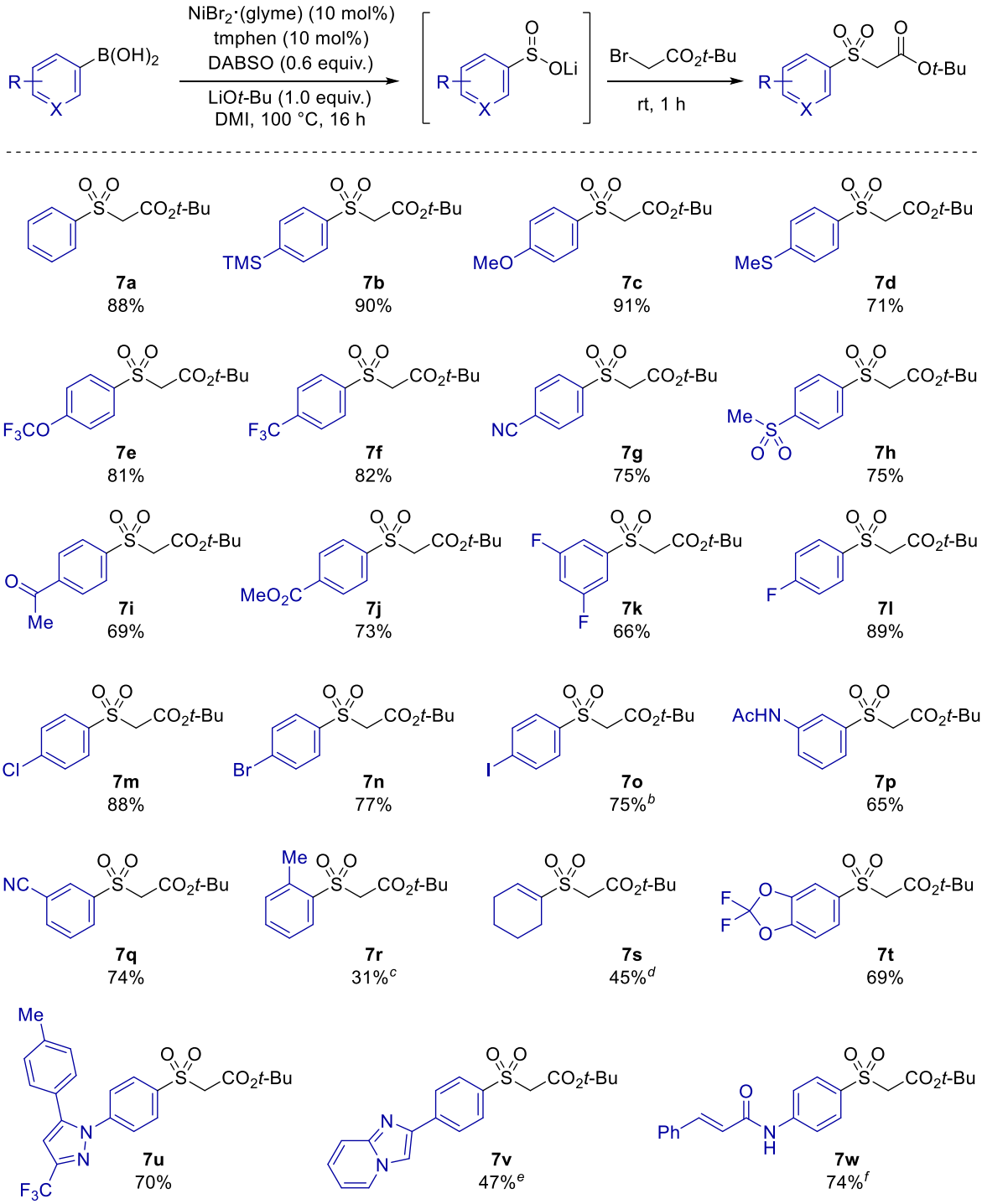
Entry	Variations	Yield of **6** (%)
1	-	91
2	90 ℃	31
3	20 mol% tmphen	28
4	1.0 equiv. DABSO	90
5	2.0 equiv. LiO*t*-Bu	68
6	0.4 M DMI	78
7	0.4 M DMI, Li_2CO_3 instead of LiO*t*-Bu	33
8	0.4 M DMI, KO*t*-Bu instead of LiO*t*-Bu	64
9	1.0 equiv. $K_2S_2O_5$ instead of DABSO	0
10	1.0 equiv. $PhBF_3K$ instead of $PhB(OH)_2$	0

Reaction conditions: Phenylboronic acid (0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (10 mol%), tmphen (10 mol%), DABSO (0.12 mmol, 0.6 equiv.), LiO*t*-Bu (0.20 mmol, 1.0 equiv.), DMI (1.0 mL, 0.2 M), 100 ℃, 16 h. Yields of **6** and boronic acid conversion were calculated from HPLC analysis using acetophenone as an internal standard. All entries were performed by Dr Yiding Chen.

2.3.1 Scope of the boronic acids

Having established the optimal reaction conditions, the scope of the reaction was examined, with respect to aryl boronic acids, by treating the *in situ* formed aryl sulfinates with *tert*-butyl bromoacetate as the electrophile, producing the corresponding sulfones in a one-pot two-step process (Table 2.2).

Table 2.2 Scope of the aryl boronic acid[a]



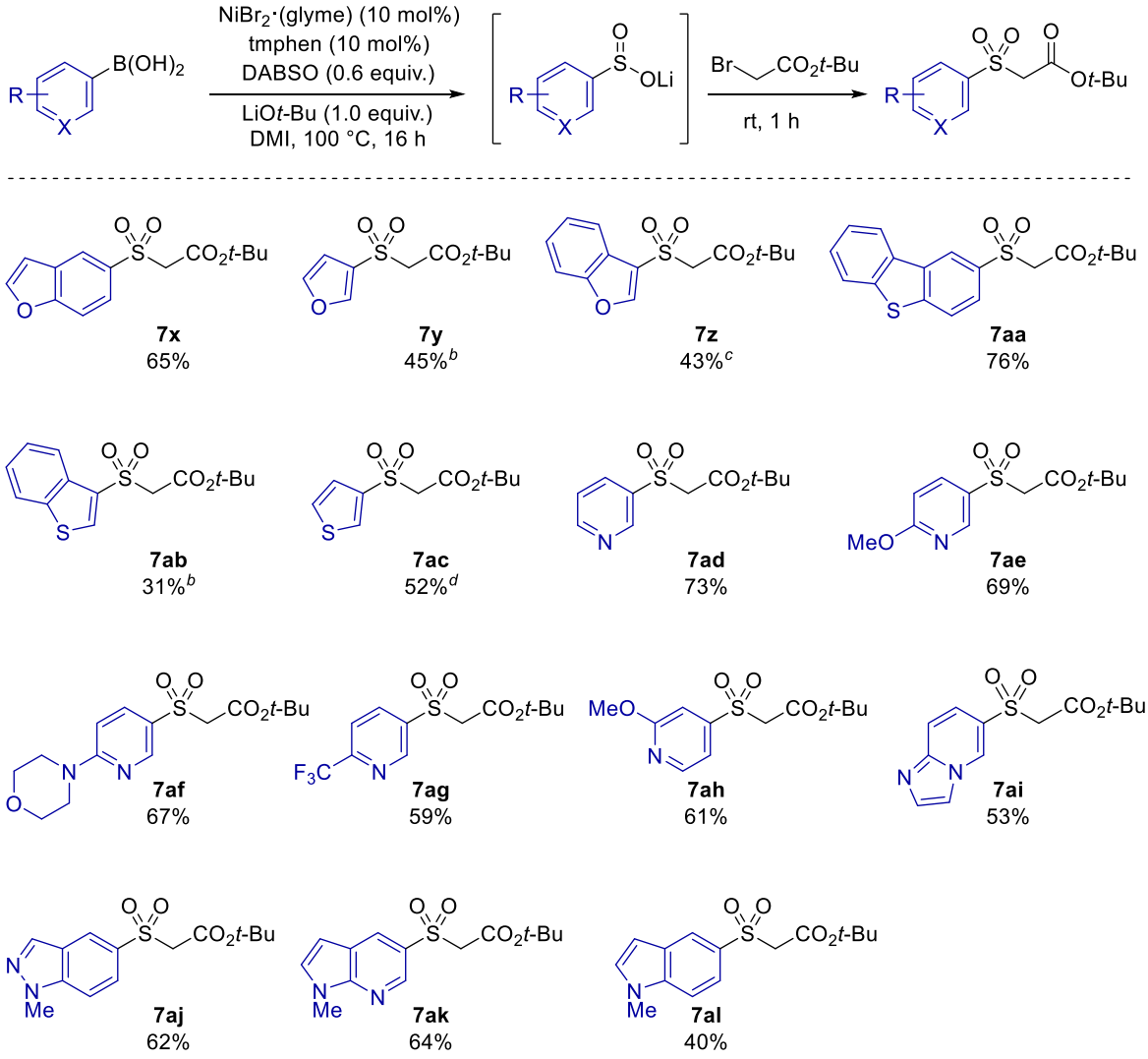
[a]Reaction conditions: (hetero)aryl boronic acid (0.2 mmol, 1.0 equiv), $NiBr_2$·(glyme) (10 mol %), tmphen (10 mol %), DABSO (0.12 mmol, 0.6 equiv), LiO*t*-Bu (0.2 mmol, 1.0 equiv), DMI (1.0 mL, 0.2 M), 100 °C, 16 h, then *tert*-butyl bromoacetate (2.0 equiv), rt, 1 h. [b]NiI_2 used as catalyst. [c]120 °C. [d]110 °C. [e]6 h for second step. [f]2 h for second step.

In general, a broad range of aryl boronic acids could be efficiently transformed into sulfinates and then to sulfones. Different electronic substitutions on the boronic acids were well-tolerated, with electronically neutral phenyl (**7a**) and *p*-trimethylsilyl (**7b**), and electron-rich *p*-methoxy (**7c**) and *p*-thiomethyl (**7d**) substituents resulting in good to excellent isolated yields. Previously challenging arene units bearing electron-withdrawing motifs could also be introduced in the system with sensitive functional groups such as nitrile (**7g**), ketone (**7i**), and ester (**7j**), as well as the first example of a trifluoromethyl-substituted aryl boronic acid being used in metal-catalysed sulfination chemistry (**7f**). Various halogen-substituted boronic acids (**7k**–**7o**) were well-tolerated using this reaction protocol, with the caveat that using NiI_2 as the nickel source was necessary when *p*-iodophenyl boronic acid (**7o**) was the reaction partner. For this substrate, using the original $NiBr_2$·(glyme) catalyst produced an inseparable mixture of bromo/iodo substitution in the sulfinate and sulfone. The catalyst loading could be reduced to 2.5 mol%, isolating 70% yield of sulfone (**7m**) on a 0.2 mmol scale, and a 71% yield when performed on a gram scale (7 mmol) at a slightly elevated temperature (110 ℃). Further lowering the catalyst loading to 1.0 mol% resulted in a much lower yield (43%). Boronic acids bearing methylthio (**7d**) and methanesulfonyl (**7h**) demonstrated the potential utility of this process, showcasing the possibility to prepare sulfur-centers with mixed-oxidation states, as well as disparate sulfonyl functional groups. Systems with *meta*-substitutions were also reacted smoothly, producing identical yields comparing to the *para*-substituted counterpart (**7g** and **7q**). Unfortunately, *ortho*-substituted (**7r**) and alkenyl boronic acid (**7s**) were less efficient, with only poor to modest product yields isolated even at elevated temperature. Further

increasing the indicated reaction temperature or reaction time resulted in less product, probably because the corresponding sulfinate salts were unstable under the reaction conditions. A range of pharmaceutically relevant boronic acids performed well under the conditions, producing the sulfonylarene core of the COX2 inhibitor Celecoxib (**7u**), antiulcer drug Zolimidine (**7v**), and CrtN inhibitor NP16 (**7w**).[4b]

Several heteroaryl boronic acids were also suitable reaction partners (Table 2.3), for example, oxygen- (**7x**–**7z**) and sulfur-heterocycles (**7aa**–**7ac**), and a range of challenging substituted pyridyl groups with electron-donating and withdrawing motifs (**7ad**–**7ah**). Note that the reaction time of step 1 for furan (**7y**), benzofuran (**7z**), benzothiophene (**7ab**) and thiophene (**7ac**) systems was shortened because the sulfinates decomposed, yielding <10% product using the original 16 h reaction conditions. Unsubstituted pyridine-3-boronic acid (**7ad**), a substrate that failed with the palladium-catalysed protocol developed by the Willis group in 2014 (Scheme 2.2), also reacted smoothly, delivering a good 73% yield of sulfone. Imidazopyridine (**7ai**), indazole (**7aj**), azaindole (**7ak**), and indole (**7al**) groups were also introduced, giving the corresponding sulfones in modest to good yields. It is worth mentioning that, in previously reported sulfinations of aryl boronic acids using Au(I),[66-68] Pd(II)[30, 69-73] or Cu(I)[74] catalytic systems, electron-poor aryl (e.g., nitrile, trifluoromethyl) and pyridine-derived boronic acids generally reacted less efficiently or totally failed (Scheme 2.1 and 2.2). Nevertheless, these substrates reacted smoothly under our Ni(II) catalytic protocol, highlighting the utility of the present chemistry.

Table 2.3 Scope of the heteroaryl boronic acid[a]



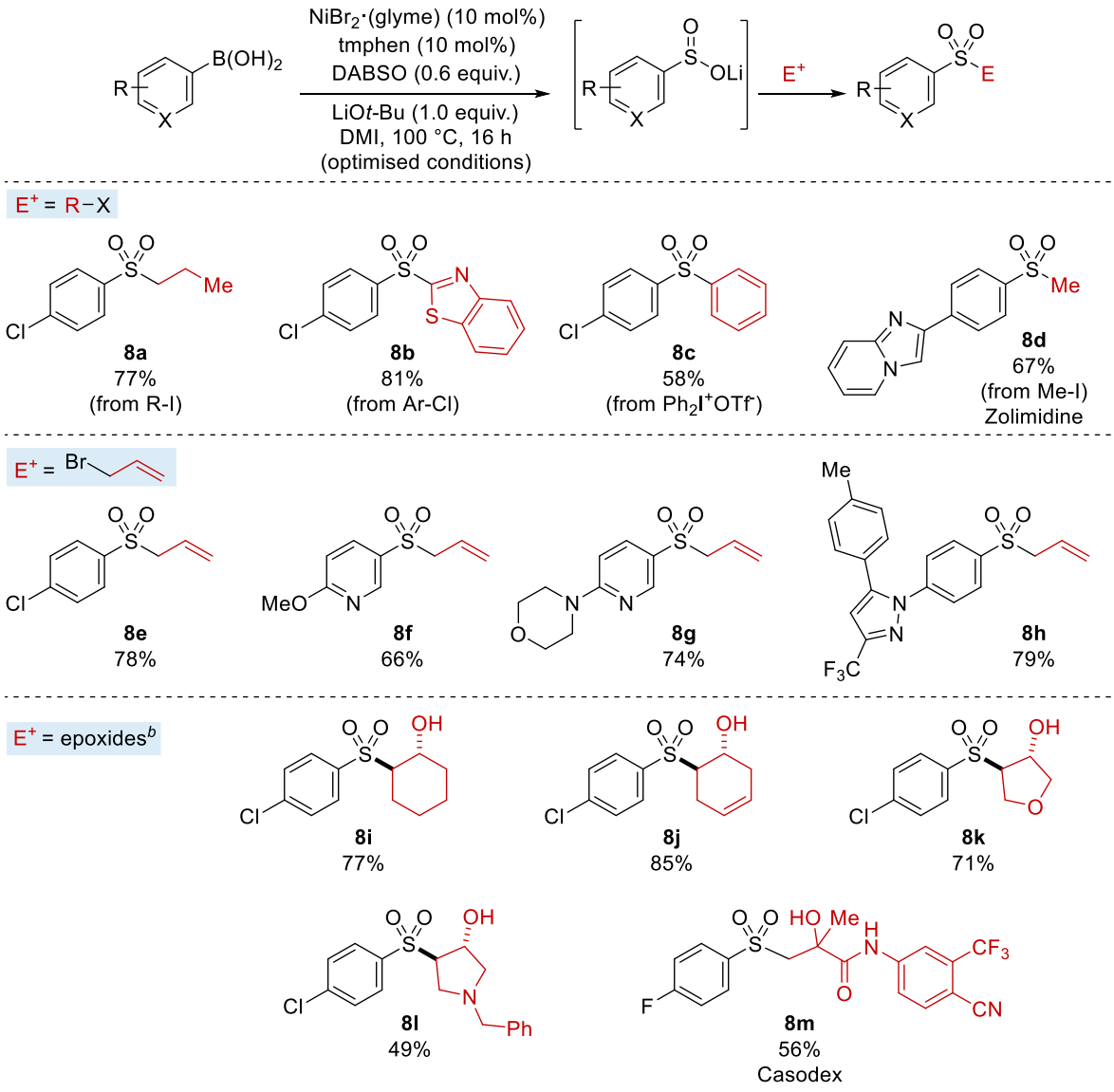
[a]Conditions as Table 2.2. [b]1 h for first step. [c]20 min for first step. [d]2 h for first step.

2.3.2 Derivatisations of sulfinates

We next performed alternative derivatisation reactions for the sulfinate intermediates. *p*-Chlorophenylboronic acid was chosen as the model substrate. The sulfones synthesised by reacting the sulfinates *in situ* with a range of carbon-based electrophiles, such as alkyl halides (**8a**), heteroaryl halides (**8b**), diphenyl iodonium salts (**8c**), and epoxides are listed in Table 2.4. The antiulcer drug Zolimidine (**8d**) was synthesised using methyl iodide as the

alkylating agent. Alkylation of the sulfinate intermediates *in situ* with allyl bromide produced allyl sulfones (**8e**–**8h**), that are a class of sulfone with applications in desulfinative cross-coupling and aromatic sulfonylation processes.[19d, 79] Particularly, pyridine- (**8f**, **8g**) and Celecoxib-derived (**8h**) allyl sulfones were synthesised in good yields.

Table 2.4 Scope of carbon-based electrophiles to form sulfones[a]

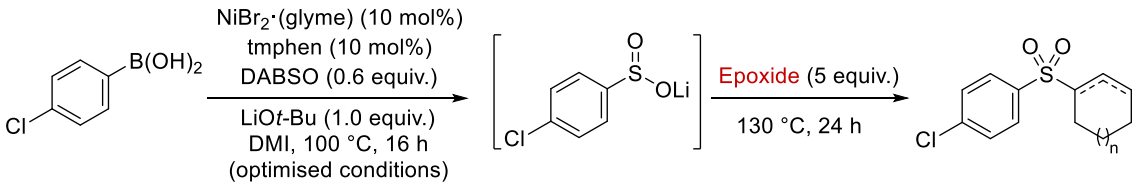


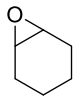
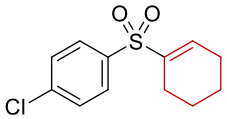
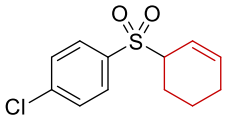
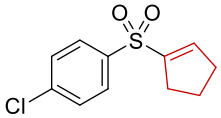
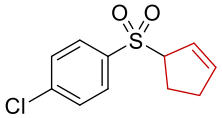
[a]Reaction conditions for sulfinate derivatisation step: E^+ (2 equiv), rt or 100 °C, 1 h. [b]For epoxides: aqueous workup, DIPEA (3 equiv), epoxide (5 equiv), H_2O, 100 °C, 48 h. For individual variations, see the experimental section.

Epoxides were also suitable carbon-based electrophiles. *β*-Hydroxysulfones (**8i**–**8m**) were afforded in modest to good yields by epoxide ring-opening and allowed the direct synthesis of the antiandrogen pharmaceutical Casodex (**8m**).

We found that an acid-base aqueous workup before the epoxide opening reaction was necessary. If cyclohexene oxide was added directly to the crude sulfinate without any workup and the reaction was heated to 100 ℃, a mixture of *β*-hydroxysulfone **8i** along with some elimination products were observed. We briefly explored the formation of these eliminated products. When increasing the temperature of this reaction to 130 ℃ for 24 h, no *β*-hydroxysulfone **8i** was observed, instead, the elimination products vinyl sulfone **9a** and allyl sulfone **10a** were observed in 1.5:1 ratio by NMR analysis (Table 2.5, entry 1). These two sulfones were inseparable using standard column chromatography, but could be isolated in a total 60% yield. It was proposed that without carrying out a workup, the strongly basic conditions (with LiO*t*-Bu) and high temperature (130 ℃) promoted the elimination. When an acid-base aqueous workup was performed, no elimination was observed under the weakly basic environment (with DIPEA). Treating this mixture of vinyl sulfone **9a** and allyl sulfone **10a** with HCl in MeCN or LDA in THF resulted no change in the ratio. Other epoxides were also examined under the optimised elimination conditions (entry 2–4). When cyclopentene oxide was used, the vinyl sulfone **9b** and allyl sulfone **10b** could be separated with the latter as the predominant product (entry 2). The two epoxides showed in entry 3 and 4 gave disappointing results. Overall, conditions could not be identified to give the elimination products in synthetically useful yields.

Table 2.5 Scope of vinyl and allyl sulfones[a]



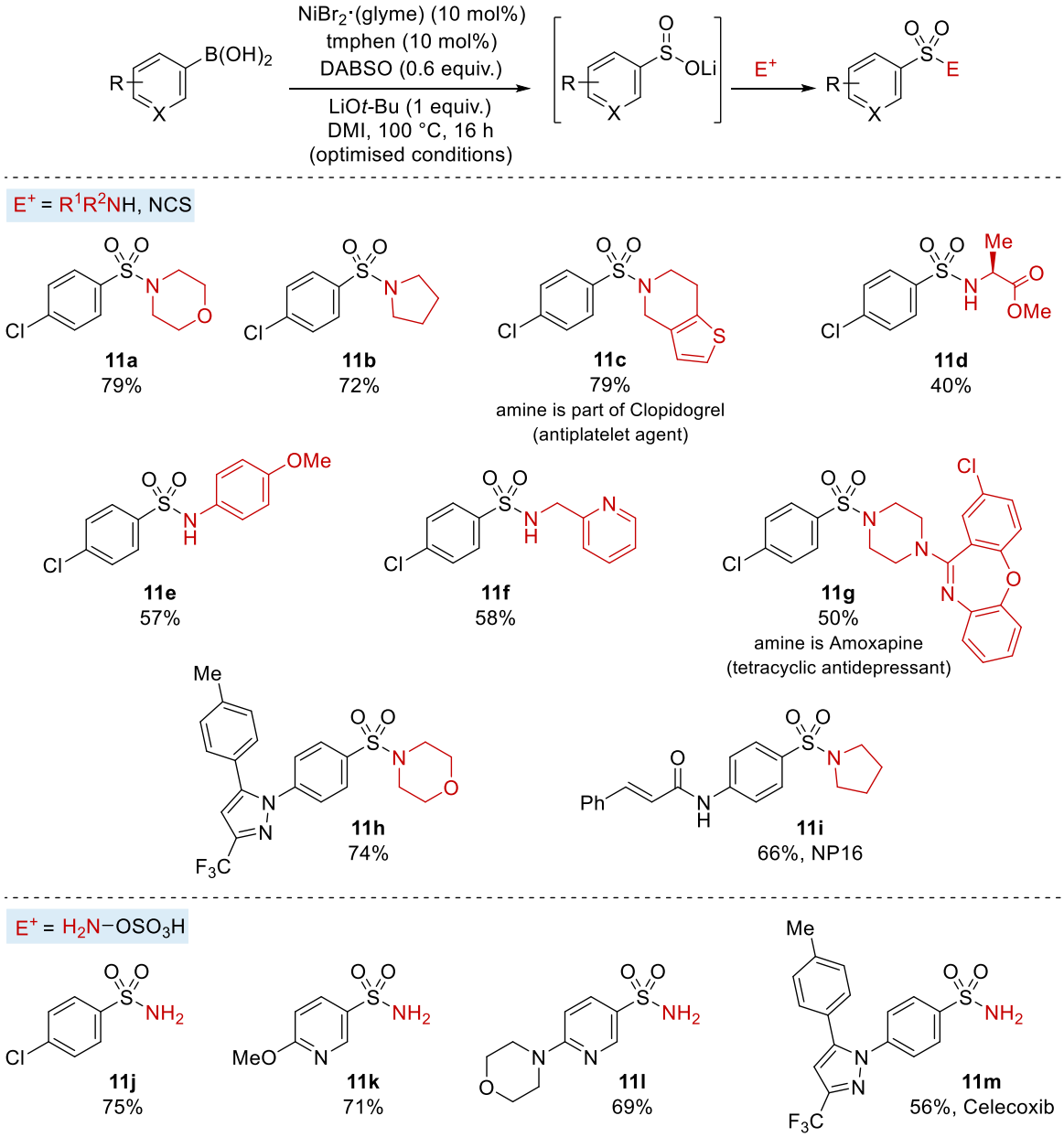
Entry	Epoxide	Results
1		 **9a**  **10a** 60% (inseparable) (1.5 : 1)
2		 **9b** ~8%  **10b** 39% (1 : 8)[b]
3		no elimination product observed[b]
4		complex mixture[c]

[a]Reaction conditions as Table 2.2, then epoxide (5 equiv), 130 °C, 24 h. [b]observed by ^{1}H NMR analysis. [c]observed by HPLC analysis.

Sulfonamides were also prepared when *N*-electrophiles were used (Table 2.6). Secondary and tertiary sulfonamides were accessible using an electrophile generated by combining a suitable amine and *N*-chlorosuccinimide (NCS).[80] Both secondary (**11a**–**11c**) and primary (**11f**) amines, including amino acids (**11d**) and anilines (**11e**), as well as other biologically relevant amines (**11c**, **11g**) were tolerated. Different boronic acid reaction components were

also used, affording an analogue of Celecoxib (**11h**) and the CrtN inhibitor NP16 (**11i**). Primary sulfonamides were prepared by reacting the *in situ* generated sulfinates with hydroxylamine-*O*-sulfonic acid (H_2NOSO_3H).[81] Several pyridyl (**11k**, **11l**) examples and the primary sulfonamide Celecoxib (**11m**) were synthesised in good yields.

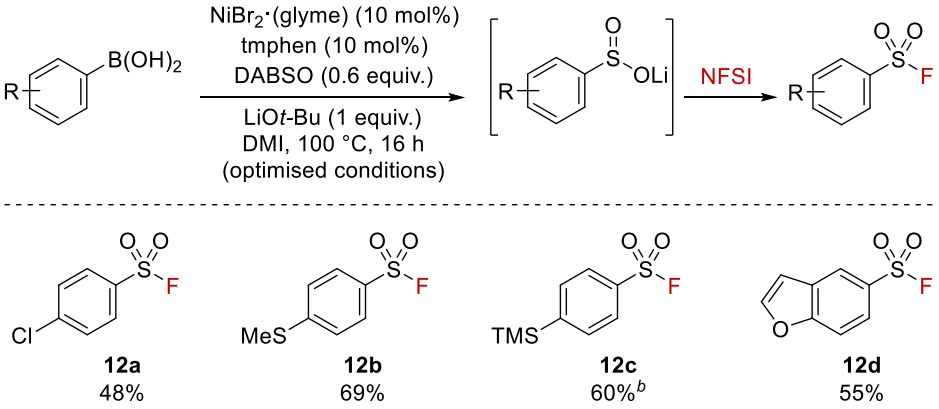
Table 2.6 Scope of nitrogen-based electrophiles to form sulfonamides[a]



[a]Reaction conditions for sulfonamides: R_1R_2NH (1.5 equiv), NCS (1.5 equiv), 0 ℃ to rt, 1 h; H_2N-OSO_3H (2 equiv), rt, H_2O, 24 h. [b]For products 3i–3l, dr >20:1. For individual variations, see the experimental section.

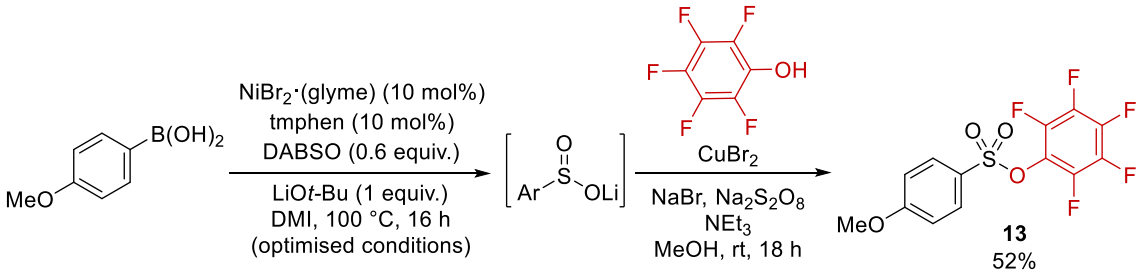
In recent years, sulfonyl fluorides have received increased recognition in the field of chemical biology, because of their unconventional balance between reactivity and stability under physiological conditions.[13] Using *N*-fluorobenzenesulfonimide (NFSI) as the electrophile, several sulfonyl fluorides were prepared in modest to good yields (Table 2.7).

Table 2.7 Preparation of sulfonyl fluorides, using NFSI as the electrophilic reagent[a]



[a]Reaction conditions for fluorination step: aqueous workup, then DIPEA (3.0 equiv), NFSI (1.5 equiv), rt, 1 h. [b]NFSI (1.0 equiv) used.

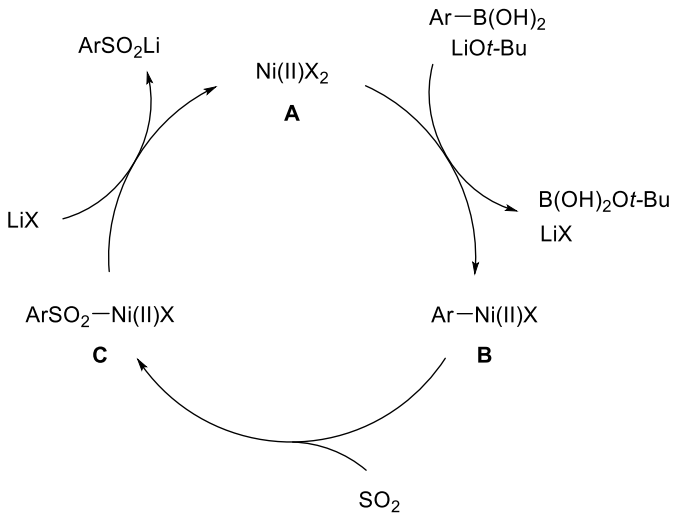
Pentafluorophenyl (PFP) sulfonate esters are usually bench-stable and crystalline alternative to sulfonyl chlorides.[82] The Willis group has recently studied the preparation of PFP sulfonate esters using copper-catalysed oxidative coupling of sulfinates and pentafluorophenol.[82d] We were able to show that the copper-catalysed PFP sulfonate ester synthesis can be combined with nickel-catalysed sulfinate formation. Accordingly, PFP-ester **13** was synthesised in 52% yield from the 4-methoxyphenyl boronic acid (Scheme 2.6).



Scheme 2.6 Synthesis of a PFP sulfonate ester

2.4 Reaction mechanism

We proposed that the reaction mechanism starts with the transmetalation of arylboronic acid to the Ni(II) catalyst **A** to give Ar-Ni(II) complex **B** (Scheme 2.7). This step is facilitated by a strong base, LiO*t*-Bu. Migratory insertion of SO_2 into this complex gives nickel sulfinate complex **C**, which undergoes ligand exchange with a lithium salt to release the desired lithium sulfinate salt and regenerates the Ni(II) complex **A**.



Scheme 2.7 Proposed mechanism of the nickel-catalysed sulfination of arylboronic acids

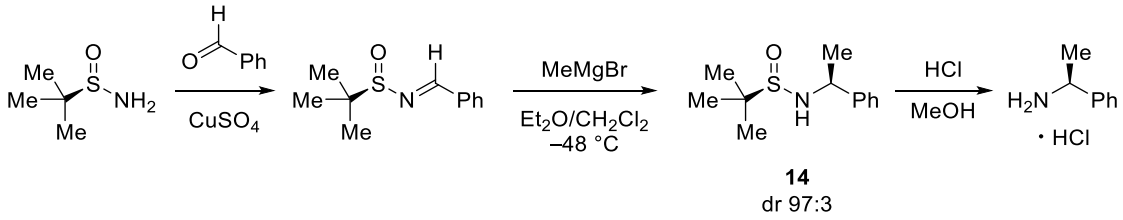
2.5 Summary

In summary, the first example of nickel-catalysed sulfination was developed. This protocol is redox-neutral, combining (hetero)aryl boronic acids and DABSO as the source of sulfur dioxide. The method could tolerate an unprecedentedly broad range of boronic acids with different electronics, including electron-deficient heterocyclic and pyridyl systems. These boronic acids were challenging to react, and only delivered low yields or failed completely with previously reported methods, which were based predominantly on precious-metal catalysts, sometimes requiring bespoke ligands, and often preparing only sulfones. Our nickel-catalysed method can be scaled up to a gram scale using 2.5 mol% catalyst. A range of sulfonyl-containing molecules, including sulfones, sulfonamides, sulfonyl fluorides, and PFP sulfonate esters were efficiently synthesised by elaborating the *in-situ* formed sulfinates. The method was successfully applied to the direct synthesis of three active pharmaceutical ingredients, demonstrating the good functional group compatibility of the protocol.

3. Sulfinamide Synthesis using Organometallic reagents, DABSO and Amines

3.1 Application of sulfinamides

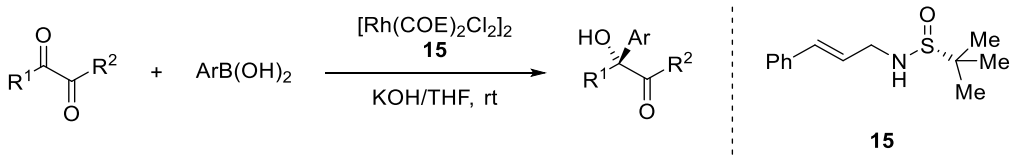
Sulfinamides have found widespread applications in organic synthesis. Chiral sulfinamides have been commonly used as chiral auxiliaries,[83] as ligands in transition metal catalysis,[84] and as organocatalysts (Scheme 3.1–3.3).[85] In 1997, the Ellman group reported the use of *tert*-butanesulfinamide (known as Ellman's auxiliary) as a useful chiral auxiliary. *tert*-Butanesulfinyl imines, prepared from the condensation of *tert*-butanesulfinamide with aldehydes or ketones, underwent nucleophilic addition to provide sulfinamide **14** with high diastereoselectivity. Removal of the sulfinyl group under the treatment of HCl in a protic solvent delivered the desired enantioenriched amine HCl salts (Scheme 3.1).[86]



14
dr 97:3

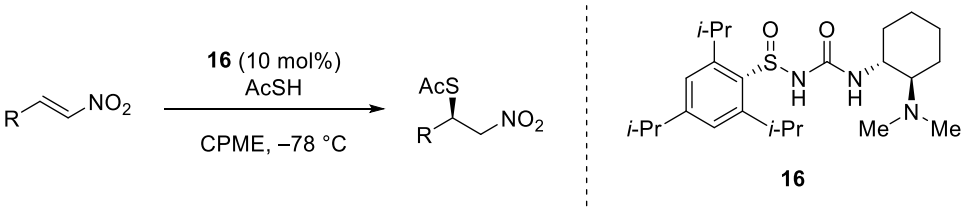
Scheme 3.1 Synthesis of chiral amines using the Ellman's auxiliary.

Chiral sulfinamide **15** was exploited as a ligand in a rhodium-catalysed 1,2-addition of aryl boronic acids to unsymmetrical α-diketones, resulting in α-hydroxyketones in high yield and high ee, as reported by Xu and co-workers (Scheme 3.2).[87]



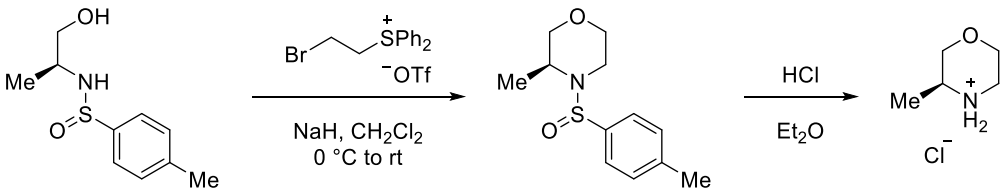
Scheme 3.2 Rhodium-catalysed enantioselective addition of arylboronic acids to unsymmetrical α-diketones

In 2009, Ellman and co-workers studied the enantioselective addition of thioacetic acid to nitroalkenes using *N*-sulfinyl urea **16** as an organocatalyst (Scheme 3.3).[88]



Scheme 3.3 Enantioselective addition of thioacetic acid to nitroalkenes

Sulfinamides can also act as a protecting group for amines. For example, this was exploited by Aggarwal and co-workers in their morpholine synthesis (Scheme 3.4).[89] The *N*-sulfinyl protecting group was removed using mild acidic conditions. Other *N*-protecting groups, such as Boc, Cbz and Ac, were ineffective in the reaction sequence because their use led to undesired products.

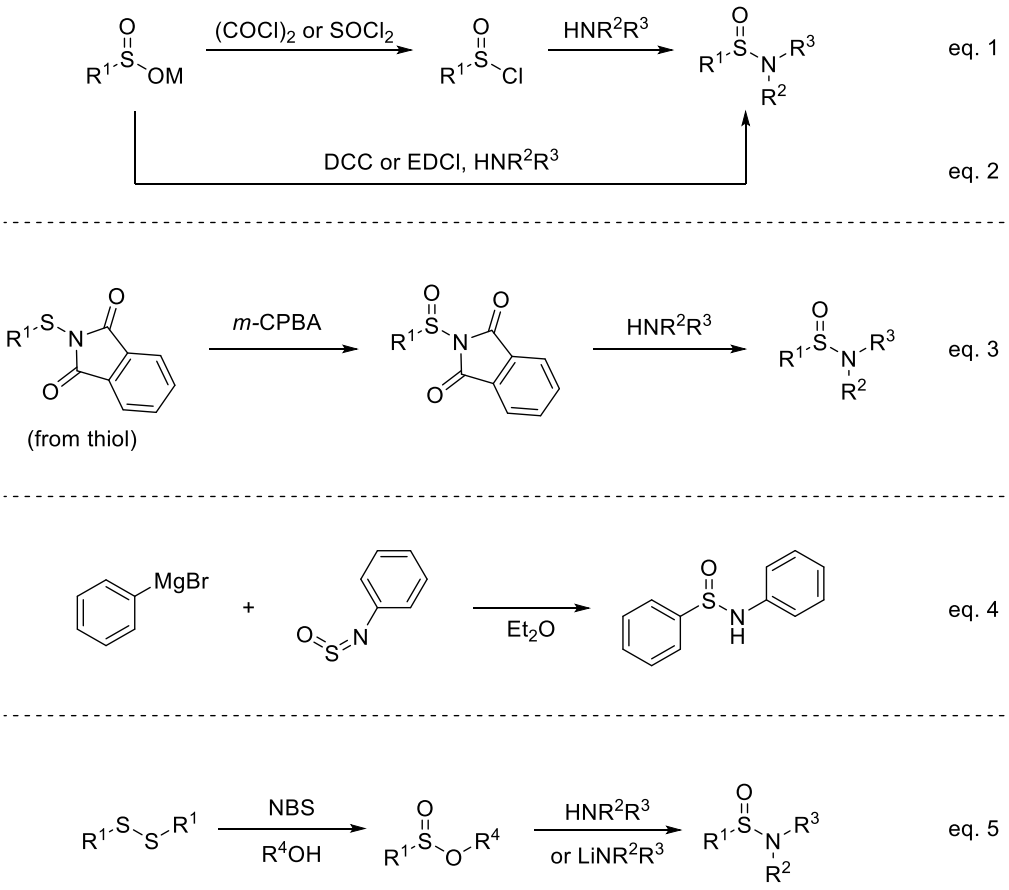


Scheme 3.4 Using sulfinamides as *N*-protecting groups for morpholine synthesis

As shown in Chapter 1.5.2, sulfinamides are frequently employed as intermediates to access sulfonimidamides, the mono aza-analogues of sulfonamides, which have attracted increased attention in medicinal chemistry in recent years.[44a, 44b]

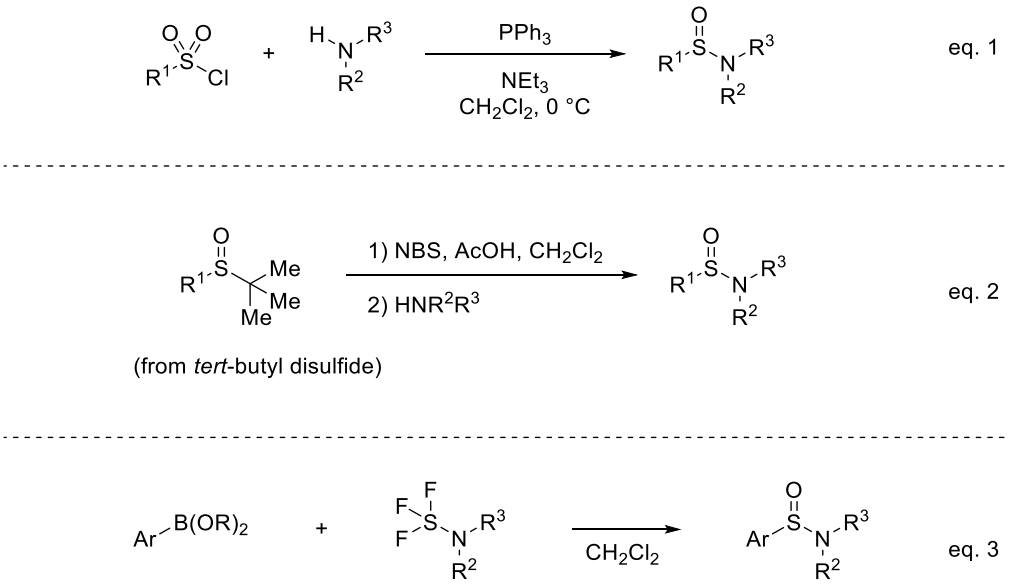
3.2 Preparation of racemic sulfinamides and their limitations

Racemic sulfinamides are often synthesised from sulfinate salts or their acid form, usually by treatment with oxalyl chloride[18, 90] or thionyl chloride,[90d, 91] to form sulfinyl chloride intermediates which subsequently react with amines (Scheme 3.5, eq. 1), or from the direct coupling with amines using DCC[92] or EDCI[93] (eq. 2). Alternative methods include the reaction of sulfinylphthalimides with amines (eq. 3),[94] the reaction of Grignard reagent with sulfinylamines (eq. 4),[95] and the oxidation of disulfides to form sulfinate esters,[96] that further react with amines[97] or lithium amides (eq. 5).[96b]



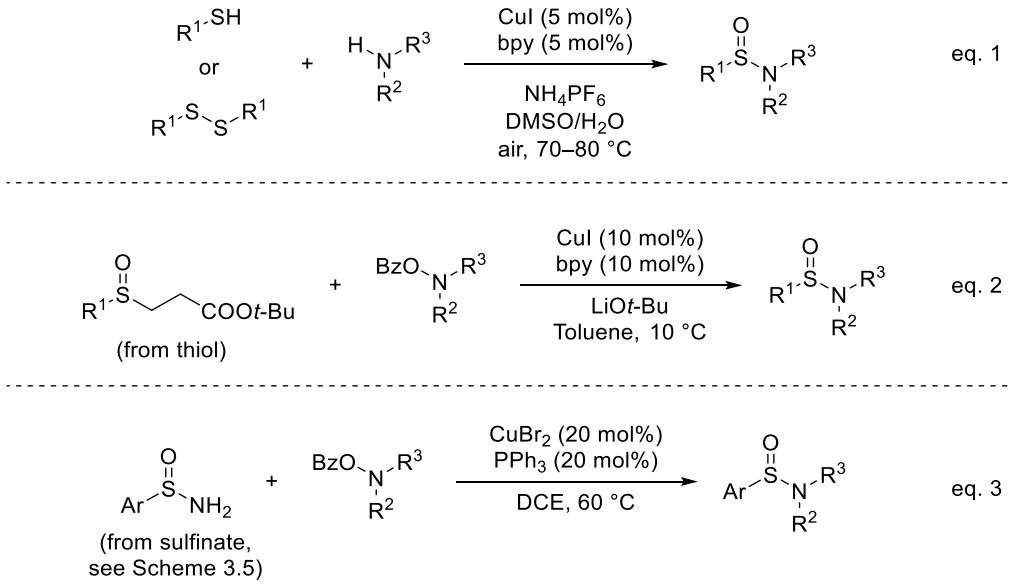
Scheme 3.5 Traditional methods for sulfinamide synthesis

In 2007, Harmata and co-workers described the preparation of aryl sulfinamides from aryl sulfonyl chlorides and amines using triphenylphosphine as a reducing agent (Scheme 3.6, eq. 1).[98] In 2015, Wei and Sun detailed a method to activate *tert*-butyl sulfoxides with NBS and acetic acid, followed by treating the reactions with a range of nucleophiles including amines to access sulfinamides (eq. 2).[99] (Hetero)aryl boronic acid and pinacol esters have also been used in combination with DAST-type reagents at room temperature to synthesise sulfinamides, as described by Shi *et. al* (eq. 3).[100]



Scheme 3.6 Recent methods for sulfinamide synthesis

The synthesis of sulfinamides using transition-metal catalysts have become more popular in recent years. The oxidative copper-catalysed synthesis of sulfinamides (Scheme 3.7), using thiols (eq. 1) or β-sulfinyl ester (eq. 2) as starting materials, has been studied, as well as the copper-catalysed transsulfinamidation (eq. 3).[101]



Scheme 3.7 Copper-catalysed synthesis of sulfinamides

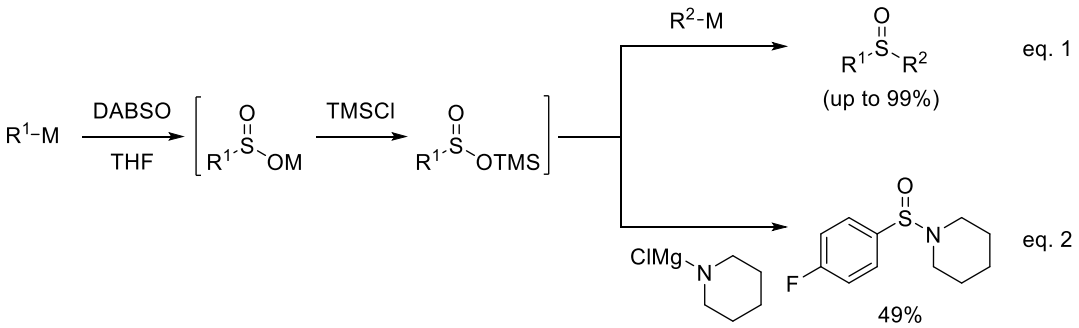
Although a certain amount of success has been achieved as described above, several limitations remain unsolved. For instance, sulfinate salts (or their acid form),[18, 90-93, 101c] odorous thiols,[101a, 101b] disulfides[96a, 99, 101a] and sulfonyl chlorides[98] are commonly reacted directly or used as precursors to the starting materials (Scheme 3.5–3.7), and these pre-installed sulfur functionalities have limited availability from commercial vendors, particularly in complex structure settings. In addition, nitrogen based-nucleophiles are commonly restricted to secondary and primary amines.[99-101] Ammonia could exclusively be employed when sulfinyl chlorides were used as intermediates.[18, 83b, 90b, 90d, 91a] Preformed amination components have sometimes been employed (Scheme 3.6, eq. 3,

Scheme 3.7, eq. 2 and 3), which are not supplied commercially and involve extra steps to prepare. The scope of sulfinamides accessible was commonly restricted to aryl and alkyl systems, while the synthesis of heteroaryl sulfinamides was less common using these protocols, probably because of the limited supply of heteroaryl sulfur-containing precursors. The exceptions to this were the reactions between sulfinyl chlorides and amines (Scheme 3.5 eq. 1), and the direct reaction of heteroaryl boronic acids and DAST-type reagents (Scheme 3.6, eq. 3).

3.3 Project aims

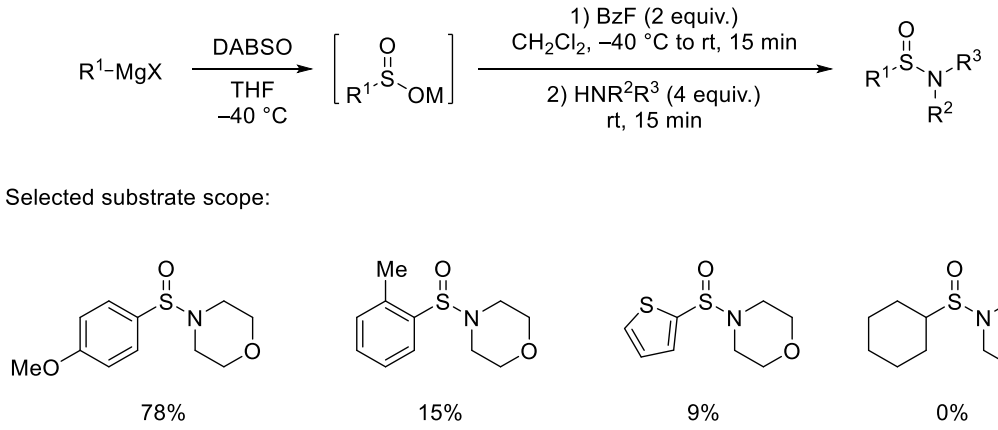
Because of the limitations of the previous methods, a more general and versatile method to synthesise sulfinamides, which facilitates access to a broad scope of sulfinyl core structures, and also tolerate a range of nitrogen-based nucleophiles is highly sought. As described in Chapter 1.4, our group has built strong expertise on the use of DABSO as a sulfur dioxide surrogate. The addition of organometallic reagents to this easy-to-handle solid leads to the formation of sulfinates, which can then been converted to different sulfonyl functional groups. We envisioned that the use of compounds with pre-installed sulfur functional groups could be avoided by generating sulfinate salts *in situ*, followed by their direct transformation to sulfinamides, in a one-pot protocol. This would gain access to a variety of complex sulfinamides, as the proposed strategy would use organometallic reagents that are either commercialy available, easily prepared *via* metal-halogen exchange or direct deprotonation methods.

This strategy was attempted based on the sulfoxide chemistry developed by former colleagues in our group.[42] The sulfinates formed upon addition of organometallic reagents to DABSO were first converted to silyl sulfinate esters, which were then treated with a second organometallic reagent to prepare sulfoxides in excellent yields (Scheme 3.8, eq. 1). However, this method was not successfully transposed to the synthesis of sulfinamides. The addition of magnesium piperidine to the silyl sulfinate esters delivered the desired sulfinamide in only 49% yield, while other metal amide complexes led to poorer yields (eq. 2).[102]



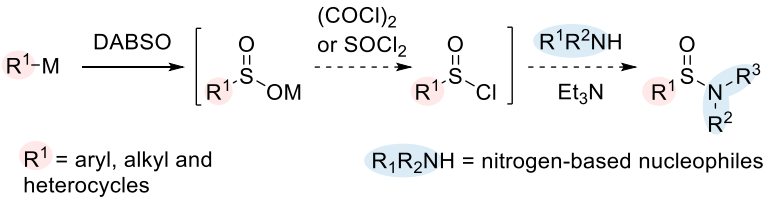
Scheme 3.8 Lenstra and Vedovato's sulfoxides and sulfinamide synthesis

It was also found that treating the sulfinates with benzoyl fluoride, followed by the addition of amines, could afford the desired sulfinamides. Although phenyl-derived sulfinamides were obtained in good yields, thienyl and alkyl systems were unsuccessful (Scheme 3.9).[103]



Scheme 3.9 Oliver's sulfinamide synthesis

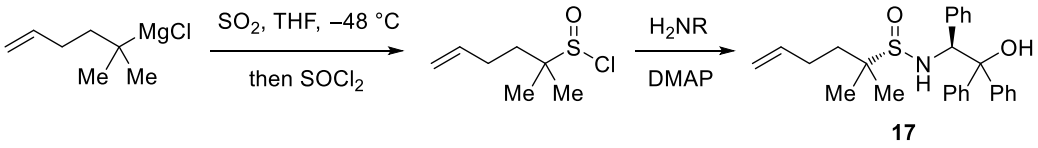
As shown above, previous attempts to synthesise sulfinamides using TMSCl or benzoyl fluoride to activate the sulfinate salts formed *in situ* from organometallic reagents were less successful. Hence, we decided to explore the same strategy using $(COCl)_2$ and $SOCl_2$ to produce the easy-to-access and reactive sulfinyl chloride intermediate toward the sulfinamide synthesis (Scheme 3.10). Also, previous works had demonstrated that a broad scope of sulfinyl chlorides, including heteroaryl sulfinyl chlorides, had shown remarkable reactivity with nitrogen-based nucleophiles.[90d] We also aimed to develop this method in a one-pot room temperature reaction that is easy to set up.



Scheme 3.10 Proposed sulfinamide synthesis through sulfinyl chloride

The preparation of sulfinyl chlorides from organometallic reagents and sulfur dioxide to generate metal sulfinate salts, followed by treatment with thionyl chloride, has been described before. For example, Ellman and co-workers used this procedure to afford

sulfinamide **17** as a single diastereomer (Scheme 3.11).[104] However, liquid sulfur dioxide, afforded by condensing the gaseous reagent at low temperature, was used in this reaction, and as such provides an obstacle to use in certain laboratories. We postulated that employing DABSO as an easy-to-handle sulfur dioxide reagent would provide a streamlined, user-friendly sulfinamide synthesis.



17

Scheme 3.11 Step-wise synthesis of sulfinamide from Grignard reagent using sulfur dioxide

3.4 Reaction conditions

With these goals in mind, we began our investigation, and were delighted to discover that the 4-fluorophenylsulfinate salt, prepared *in situ* from the addition of 4-fluorophenylmagnesium bromide to DABSO, reacted efficiently with 1.1 equivalents of thionyl chloride to produce the corresponding sulfinyl chloride. This was then treated with 1.5 equivalents of morpholine and 1.5 equivalents of triethylamine, to afford the corresponding sulfinamide **18a** in 83% yield on a 0.5 mmol scale, and 79% yield on a gram scale (Table 3.1). Each step of this one-pot three-step reaction was carried out for 30 min at room temperature under a nitrogen atmosphere using THF as a solvent. The reaction temperature, time and stoichiometry of the reaction components were not further optimised because the reaction was simple enough to set up, giving high yields of products with just slightly excess reagents. The reaction time was initially set for 30 min for each step because

we monitored the reaction at ~20 min by HPLC analysis. Toward the end of the project, we realised that the reaction time for each step could be potentially shortened to just 1 min because every step was basically an instant reaction.

Although oxalyl chloride could be used to replace thionyl chloride, the reaction with the sulfinates salts was vigorous with gas formation, and needed to be conducted at 0 ℃. Furthermore, the use of oxalyl chloride led to the formation of 1,2-diamides. These side products sometimes co-eluted with alkyl sulfinamides in standard column chromatography, causing purification difficulties. Consequently, thionyl chloride was selected for further studies.

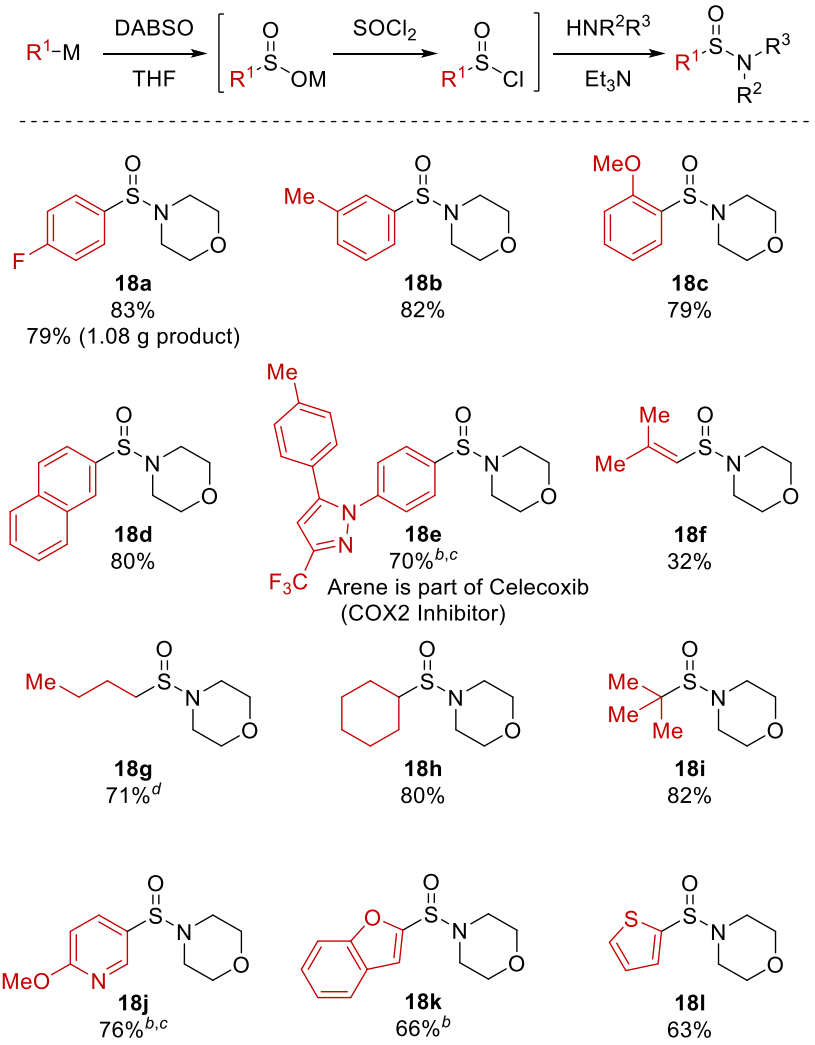
3.5 Reaction scope

3.5.1 Scope of the organometallic reagents

Having identified the optimised conditions, we then investigated the reaction scope of organometallic reagents, using morpholine as the nucleophile (Table 3.1). In general, a broad variety of aryl, alkyl and heteroaryl organometallic reagents could be smoothly transformed into sulfinyl chlorides and onto the desired sulfinamides. Aryl Grignard reagents substituted at different positions were suitable substrates, providing *para* (**18a**, **18e**), *meta* (**18b**) and *ortho* (**18c**) substituted phenyl and naphthyl (**18d**) sulfinamides in 70−83% isolated yields. A pharmaceutically relevant organolithium reagent was tolerated, affording the arene core of the COX2 inhibitor Celecoxib (**18e**). Unfortunately, alkenyl Grignard reagent (**18f**) was less successful, with only 32% of the product isolated.

Primary (**18g**), secondary (**18h**) and tertiary (**18i**) alkyl Grignard reagents performed well under the optimised conditions, with 71−82% yields of the corresponding sulfinamides being isolated. The primary alkyl sulfinamide (**18g**) was obtained in a slightly lower yield compared to the corresponding secondary and tertiary alkyl systems, probably because of the instability of the sulfinyl chloride intermediate and the sulfinamide product. Nitrogen, oxygen and sulfur-containing heteroaromatics were suitable organometallic reagents, affording pyridine (**18j**), benzofuran (**18k**) and thiophene (**18l**) sulfinamides in 63−76% yield.

Table 3.1 Scope of the organometallic reagent[a]



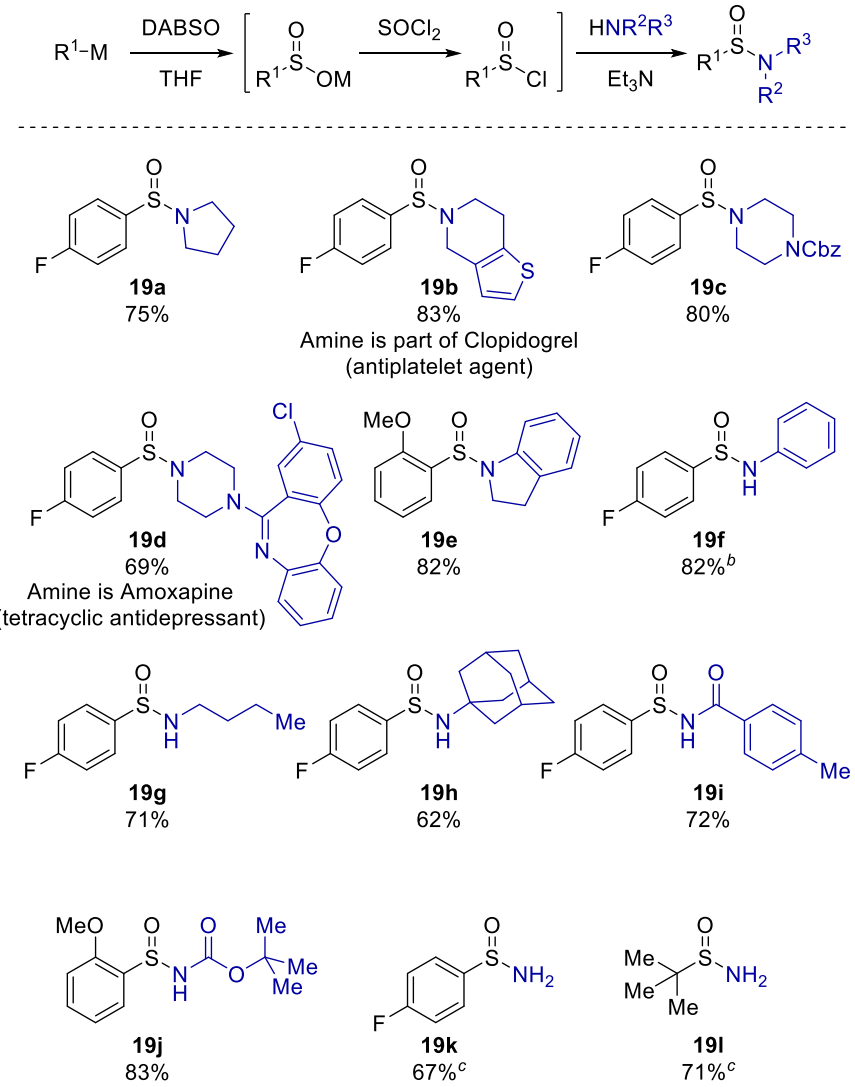
[a]Reaction conditions: RMgX (0.5 mmol, 1.0 equiv.), DABSO (0.25 mmol, 0.5 equiv.), THF, rt, 30 min, then $SOCl_2$ (1.1 equiv.), rt, 30 min followed by Et_3N (1.5 equiv.) and morpholine (1.5 equiv.), rt, 30 min. [b]Organolithium reagent was used. [c]A suspension of DABSO (0.6 equiv.) in THF was added to the organolithium reagent at –78 ℃ then warmed to rt. [d]5 min for step 2.

3.5.2 Scope of nitrogen-based nucleophiles

We next examined the scope of nitrogen-based nucleophiles, employing *p*-fluorophenylmagnesium bromide as the organometallic reagent (Table 3.2). Secondary amines, such as pyrrolidine (**19a**), piperidine (**19b**), piperazine (**19c**, **19d**), and indoline

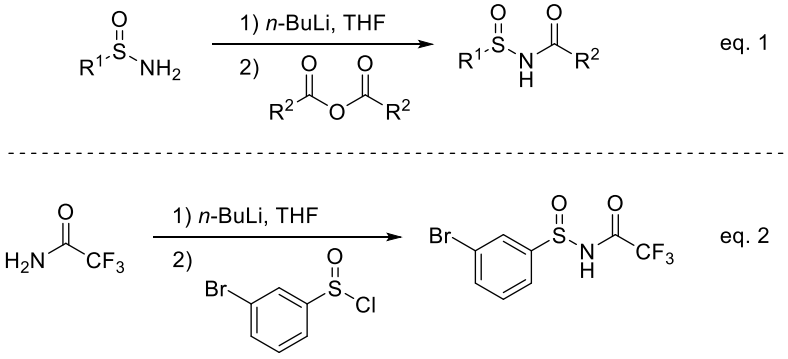
(**19e**), and including biologically relevant amines (**19b**, **19d**), were suitable substrates, affording the desired tertiary sulfinamides in 69−83% isolated yields.

Table 3.2 Scope of nitrogen-based nucleophiles[a]



[a]Reaction conditions: RMgX (0.5 mmol, 1.0 equiv.), DABSO (0.25 mmol, 0.5 equiv.), THF, rt, 30 min, then $SOCl_2$ (1.1 equiv.), rt, 30 min followed by Et_3N (1.5 equiv.) and nucleophile (1.5 equiv.), rt, 30 min. Nucleophile was added as a solution in THF if it was a solid. [b]Sulfinyl chloride was added to a solution of aniline (3.0 equiv.) in THF. [c]Sulfinyl chloride was added to a biphasic mixture of 35% aq. NH_3/Ethyl acetate at 0 ℃.

For aniline (**19f**), a significant quantity of the double *N*-substituted sulfinamide was observed as a side product, showing that the nitrogen of the desired sulfinamide product was still nucleophilic. This could be completely suppressed by reversing the addition sequence of the reagents, and transferring the sulfinyl chloride intermediate to a THF solution of aniline, affording 82% yield of the desired sulfinamide. Primary amines were also tolerated, including *n*-butylamine (**19g**) and bulky adamantylamine (**19h**). Surprisingly, nucleophiles with reduced nucleophilicities, including amide (**19i**) and carbamate (**19j**), also reacted smoothly, affording 72% and 83% yields of the sulfinamides. These amide and carbamate-substituted sulfinamides are commonly prepared from the primary sulfinamides using a strong base (e.g. *n*-BuLi) with anhydrides[18, 45, 105] or dicarbonates (e.g. Boc anhydride) (Scheme 3.12, eq. 1),[45, 106] whereas their direct synthesis from sulfinyl chlorides (or sulfinic anhydrides) was less frequent (eq. 2).[107] Compared to these previous methods, the protocol described in Table 3.2 minimises the number of steps and purifications required.



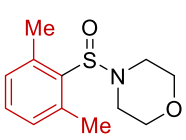
Scheme 3.12 Previous methods to synthesise amide and carbamate-substituted sulfinamides

In contrast to the aniline substituted sulfinamide, significant amounts of double-substituted sulfinamides were not observed when primary amines (**19g**, **19h**), amide (**19i**), and carbamate (**19j**) nucleophiles were used. For substrates **19e** and **19j**, a different aryl Grignard was used as the corresponding *p*-fluorophenyl derived sulfinamides co-eluted with the nitrogen-nucleophiles in standard column chromatography. Finally, a biphasic mixture of ammonium hydroxide solution and ethyl acetate was used for the synthesis of primary sulfinamides **19k** and the racemic form of Ellman's auxiliary **19l**, in 67% and 71% yield, respectively.[90b] Using NH_3 in dioxane or THF instead gave a complex mixture, as observed by HPLC analysis.

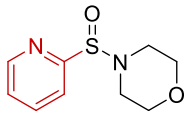
3.5.3 Low yielding and unsuccessful reactions

Although a wide range of organometallic reagents and amines were tolerated under the reaction conditions, there were some limitations (Table 3.3). Sulfinate formation was not observed when 2,6-dimethylphenyl lithium **20a** was used, most likely due to the steric hindrance around the carbon reaction centre. In contrast to 3-pyridyl lithium reagent **18j** (Table 3.1), which produced the corresponding sulfinamide in 76% yield (Table 3.1), 2-pyridyl nucleophiles led to poor yields of sulfinamides **20b** and **20c**, in 20% and 45%, respectively. Alkynyl organometallic reagents **20d** and **20e** were unsuccessful, with no sulfinamide observed. Using 3-amino-2-cyclohexen-1-one (**21a**) as the nitrogen-nucleophile only afforded 30% yield of the desired sulfinamide.[108]

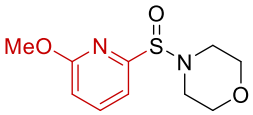
Table 3.3 Limitations of the sulfinamide synthesis



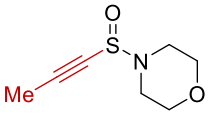
20a
n.d.[a]



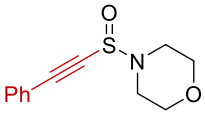
20b
<20%[b]



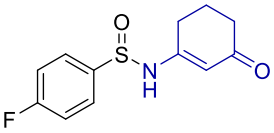
20c
45%[b]



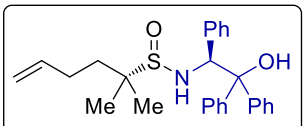
20d
n.d.[b]



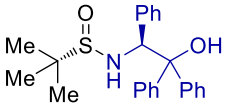
20e
n.d.[b]



21a
30%[b]



17
d.r. 16:1[c]
(From the Ellman group)



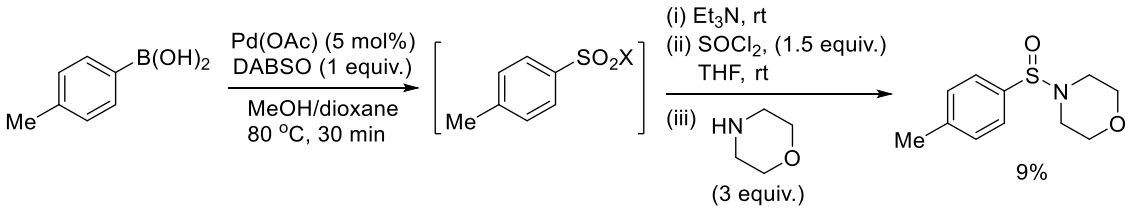
21b
d.r. 5:1[b,d]

[a]No sulfinate was observed. [b]Yields were calculated from NMR analysis. [c]using 16 mol% DMAP as additive. [d]using 1.0 equivalent DMAP as additive.

The Ellman group used (*S*)-2-amino-1,1,2triphenylethanol to synthesise a 16:1 diastereomeric ratio of the sulfinamide **17** with 16 mol% DMAP as sulfinyl transfer catalyst (Scheme 3.11).[104] Combining this amine with the sulfinyl chloride formed from *t*-butyl Grignard and DABSO only afforded a 5:1 diastereomeric ratio of the sulfinamide (**21b**) using 1 equivalent of DMAP, while a lower diastereomeric ratio was observed using 16 mol% DMAP.

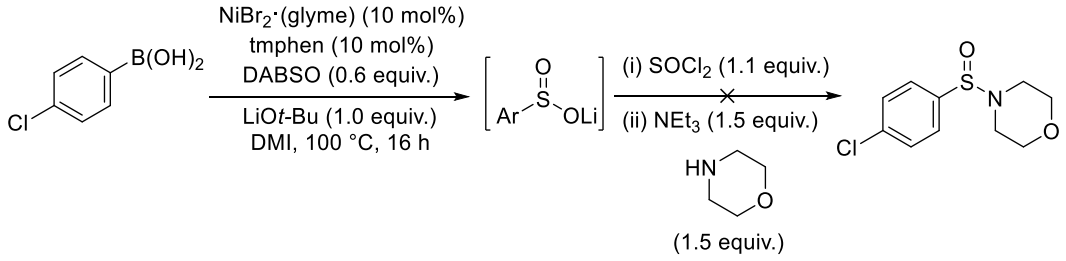
Previous members in the group, Edward Emmett and Alex Deeming, had developed a palladium-catalysed sulfination of aryl iodides and aryl boronic acids, respectively.[21c, 71] They also attempted to combine the *in situ* formed sulfinates with thionyl chloride to access

the sulfinyl oxidation level, but only little success had been achieved. Emmett was not able to prepare sulfinyl chloride *via* the sulfinate produced from aryl iodide.[33] Deeming obtained 9% of the desired sulfinamide using morpholine as nitrogen nucleophile (Scheme 3.13).[72]



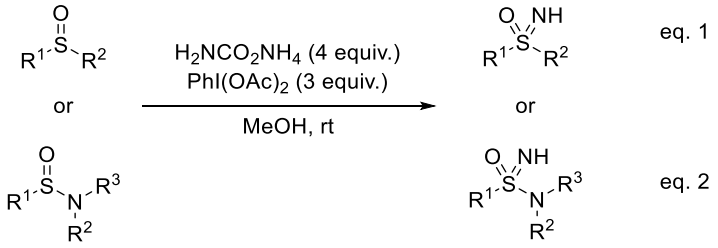
Scheme 3.13 Deeming's attempts on sulfinamide synthesise using palladium-catalysed sulfinylation

Given the success of the nickel-catalysed sulfination of aryl boronic acids presented in Chapter 2, a one-pot procedure was attempted to generate the sulfinyl chloride and sulfinamide directly from the crude reaction mixture (Scheme 3.14). However, no sulfinyl chloride or sulfinamide were detected, with only metal sulfinate salt being observed by HPLC analysis. This indicated the sensitive nature of thionyl chloride and sulfinyl chloride.



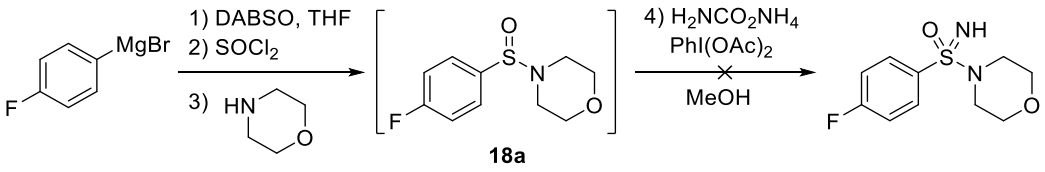
Scheme 3.14 Attempt to sulfinamide synthesis using Ni-catalysed sulfinylation

In 2016, the Bull group developed a direct synthesis of *N*H sulfoximines from sulfoxides using ammonium carbamate and (diacetoxyiodo)benzene in MeOH (Scheme 3.15, eq. 1).[64a] In 2017, Lücking and co-workers extended the method to prepare sulfonimidamides from sulfinamides (eq. 2).[63]



Scheme 3.15 Direct synthesis of *N*H sulfoxides and sulfonimidamides from sulfoxides and sulfinamides

However, using these same conditions with our sulfinamide synthesis in a one-pot reaction resulted in no sulfonimidamide, with only sulfinamide **18a** observed (Scheme 3.16).



Scheme 3.16 Attempt on sulfonimidamide synthesise in a one-pot reaction

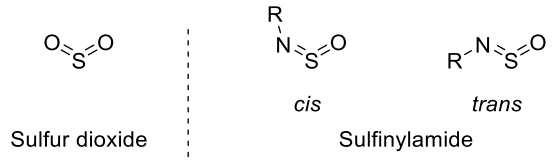
3.6 Summary

In summary, a high yielding one-pot three-component synthesis of sulfinamides employing organometallic reagents and nitrogen based-nucleophiles, using sulfinyl chlorides as the reactive intermediates, has been developed. The established protocol combines Grignard or organolithium reagents with easy-to-handle DABSO as the sulfur dioxide surrogate to synthesise sulfinates salts which are then reacted with thionyl chloride to afford sulfinyl chloride intermediates. A selection of organometallics was tolerated under the conditions, including (hetero)aryl and alkyl systems. Secondary and primary amines, aniline, amide, carbamate, and ammonia are suitable nitrogen-nucleophiles. The reaction was shown to be scalable to a preparative gram scale. Finally, several biologically relevant aryl systems and amines were used, demonstrating the applicability of the described protocol to complex targets.

4. Nickel(II)-Catalysed Synthesis of Sulfinamides from Aryl and Heteroaryl Boroxines and TrNSO

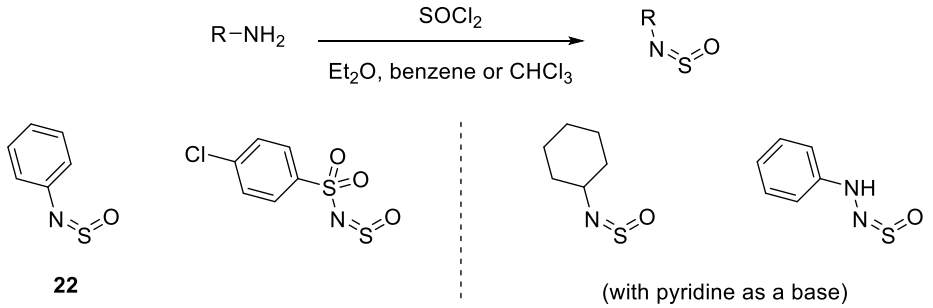
4.1 Preparation and applications of sulfinylamines

In previous chapters, the chemistry centred on the insertion of sulfur dioxide, with the nickel-catalysed synthesis of sulfinate salts from aryl boronic acids to access a range of sulfonyl-containing compounds (Chapter 2) and the synthesis of metal sulfinates from organometallic reagents to prepare a variety of sulfinamides (Chapter 3). In this chapter, we will focus on the chemistry of sulfinylamines, the mono-aza analogue of sulfur dioxide in which one of the oxygens is replaced by a nitrogen substituent (Scheme 4.1). In theory, sulfinylamines can be present in the *cis* or *trans* configuration. However, to date all the compounds in this class have been observed in the *cis* orientation exclusively.[109] This is supported by calculations, showing that the *cis* form is at least 8 kcal/mol more stable than the corresponding *anti* form in *N*-sulfinylaniline, PhNSO **22** (Scheme 4.2).[109-110]



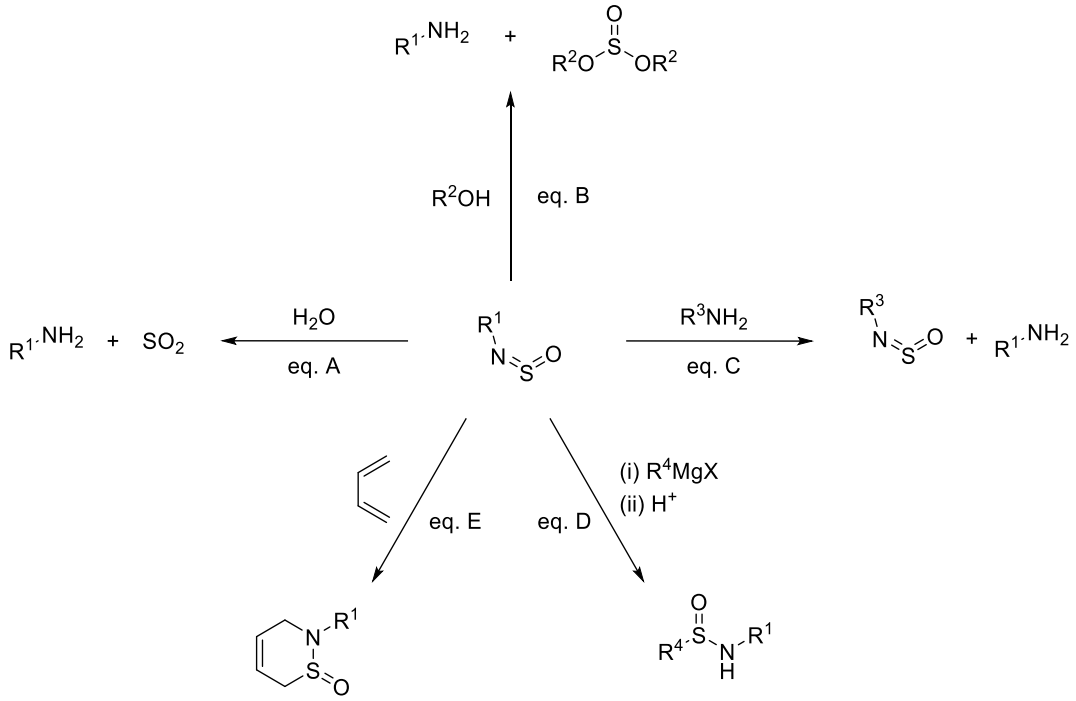
Scheme 4.1 Sulfinylamines, a mono-aza analogue of sulfur dioxide

Sulfinylamines are generally prepared from the reaction of thionyl chloride and primary amines including aniline, alkyl amines, hydrazines and sulfonamides (Scheme 4.2).[111] A tertiary amine or pyridine could be added as a base. But for less basic amines, the HCl could be removed by heating the reaction mixture to reflux.



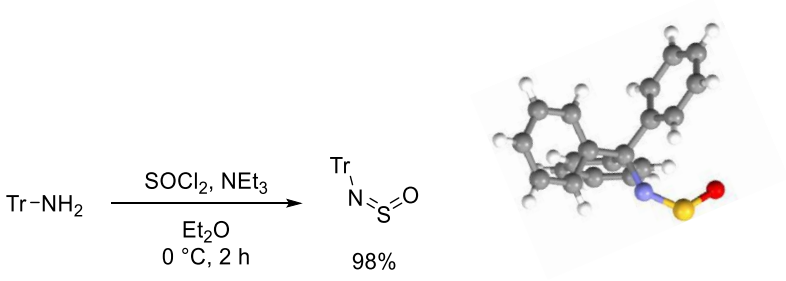
Scheme 4.2 Preparation of sulfinylamines

Sulfinylamines are electrophilic species capable of reacting with a range of nucleophiles (Scheme 4.3).[111a] Many sulfinylamines can be hydrolysed easily in moist air, giving the parent amines and gaseous sulfur dioxide (eq. A).[112] This property is somewhat problematic as it means sulfinylamines are typically difficult to purify and store for a prolonged period. They can also react with alcohols to form the corresponding sulfite and parent amines (eq. B). Trans-sulfinylation with more basic amines produces other sulfinylamines, which is a useful strategy for accessing less stable sulfinylamines *in situ* (eq. C). The addition of Grignard reagents to sulfinylamines provides the corresponding sulfinamides (eq. D). Sulfinylamines can undergo a variety of cycloaddition reactions, including acting as dienophiles in Diels-Alder reactions (eq. E).



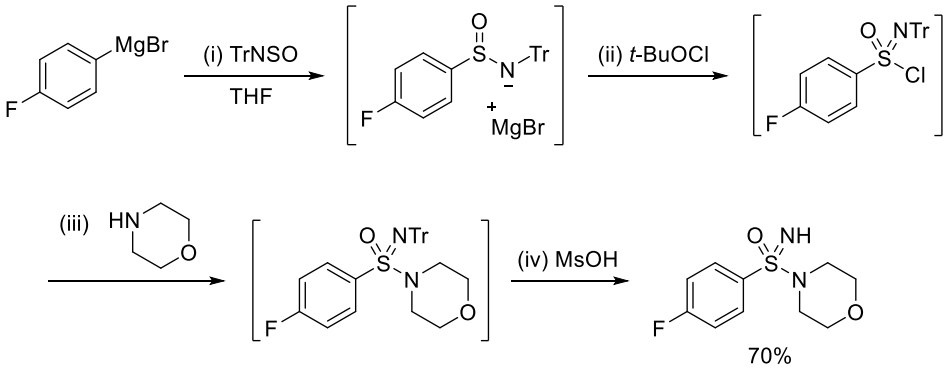
Scheme 4.3 Applications of sulfinylamines

To develop moisture-insensitive sulfinylamines, a former DPhil student in the group, Dr. Thomas Davies, explored the use of sterically hindered sulfinylamines. Treatment of triphenylmethylamine (tritylamine) with thionyl chloride and triethylamine in diethyl ether produced the corresponding *N*-sulfinyltritylamine, TrNSO, in excellent 98% yield (Scheme 4.4).[58, 113] It was cleanly isolated by filtration of the reaction mixture through Celite. TrNSO is a white crystalline solid, which is insensitive to moist air and could be stored at –20 ℃ for several months without observable decomposition. A crystal structure of TrNSO, obtained by X-ray crystallography, showed the expected *cis* configuration.[114]



Scheme 4.4 Preparation and crystal structure of *N*-sulfinyltritylamine, TrNSO

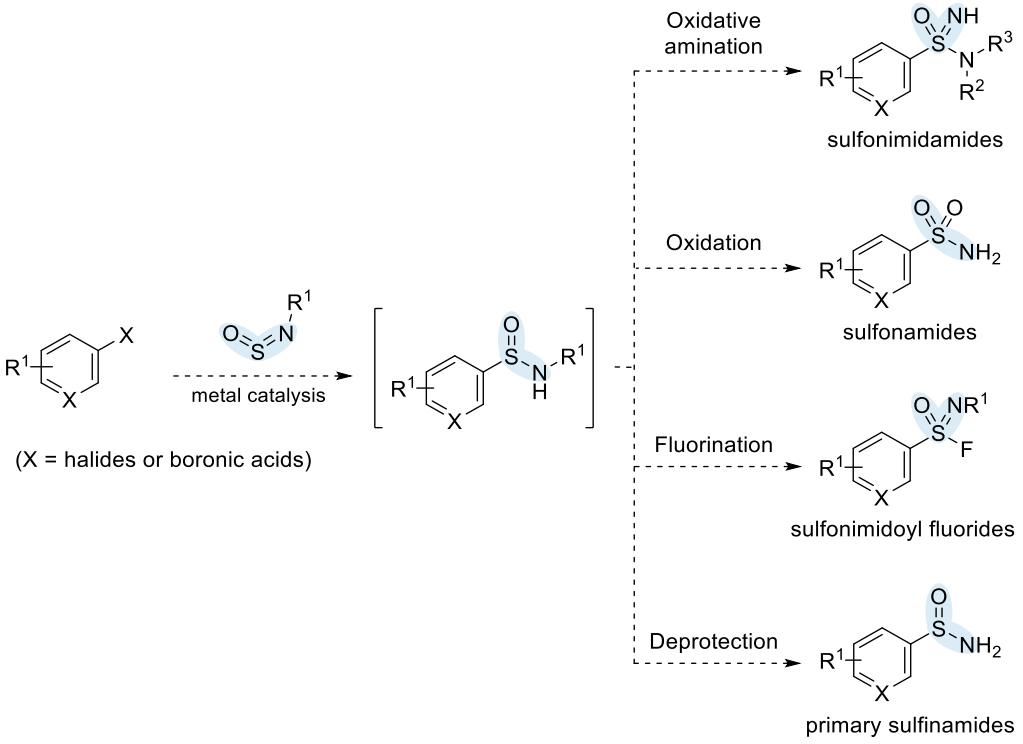
Based on the precedented reaction of Grignard reagents with sulfinylamines (Scheme 4.3, eq. D), TrNSO was used as a lynchpin for the one-pot synthesis of sulfonimidamides (Scheme 4.5).[58] The addition of Grignard reagents to TrNSO in THF resulted in the corresponding sulfinamides, which underwent oxidative chlorination using *tert*-butyl hypochlorite (*t*-BuOCl) to generate sulfonimidoyl chlorides. Subsequent reaction with amines and deprotection using methanesulfonic acid produced the desired *N*H sulfonimidamides. (Hetero)aryl and alkyl Grignard and organolithium reagents were suitable organometallic reagents, while primary and secondary amines and anilines were competent nucleophiles, allowing the synthesis of a range of sulfonimidamides.



Scheme 4.5 Davies' one-pot synthesis of sulfonimidamides

4.2 Project aims

The utility of sulfinamides and the limitations of the current methods of their synthesis has been discussed in Chapter 3.1. Based on these issues, and inspired by Davies' synthesis of sulfinamides from organometallic reagents and sulfinylamines, we were interested in developing a metal-catalysed protocol, using aryl halides or boronic acids with sulfinylamines, to generate sulfinamides. To the best of our knowledge, sulfinylamines have rarely been used in metal-catalysed processes to synthesise sulfinamides.[115] The proposed strategy would avoid the use of air-sensitive organometallic reagents and potentially allow a broader scope and functional group tolerance. Moreover, sulfinamides are versatile organic intermediates, thus we envision they can undergo oxdiative amination to generate sulfonimidamides, oxidation to form sulfonamides, fluorination to afford sulfonimidoyl fluorides and deprotection to produce primary sulfinamides (Scheme 4.6).



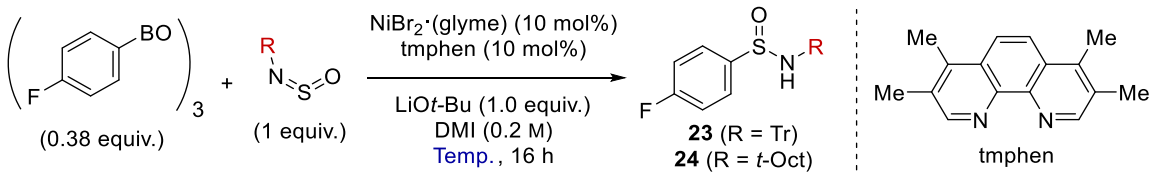
Scheme 4.6 Proposed metal-catalysed synthesis of sulfinamides using sulfinylamines

4.3 Optimisation of the reaction conditions

A batch of 4-fluorophenylboronic acid and TrNSO were initially used for the reaction optimisation. However, when examining the scope of reaction in the later course of the project, we realised that the batch of 4-fluorophenylboronic acid consisted of 10% boronic acid and 90% boroxine. During prolonged storage of boronic acids, an equilibrium is commonly established with the formation of boroxine and H_2O.[116] This amount of H_2O would hydrolyse the TrNSO under the reaction conditions. Accordingly, using boroxines prepared from dehydration of boronic acids is essential for obtaining high yields in the reactions.

Based on the success of nickel-catalysed sulfination of aryl boronic acids (Chapter 2),[1] we initially used the same conditions, replacing aryl boronic acid with 4-fluorophenylboroxine, and DABSO with TrNSO to examine the reactivity (Table 4.1). The desired sulfinamide **23** was observed in 4% yield by HPLC analysis at 100 ℃ using 0.38 equiv. of 4-fluorophenylboroxine (i.e. 1.15 equiv. of the arene core) (entry 1). A brief examination of the reaction temperature showed that there was an increase in yield to 19% at 80 °C (entry 2), while only trace product was observed at 60 °C (entry 3). An alternative sulfinylamine, *N*-sulfinyl-*tert*-octylamine (*t*-OctNSO),[117] was also tested, affording the corresponding sulfinamide in 13% yield at 100 ℃ (entry 4). However, less product was observed at lower temperatures (entry 5 and 6).

Table 4.1 Initial attempts for the nickel-catalysed synthesis of sulfinamide from aryl boroxines



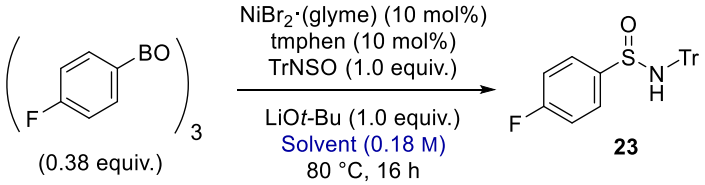
Entry	R-NSO	Temp. (°C)	Yield of 23 or 24 (%)
1	TrNSO	100	4
2	TrNSO	80	19
3	TrNSO	60	<1
4	*t*-OctNSO	100	13
5	*t*-OctNSO	80	9
6	*t*-OctNSO	60	7

Reaction conditions: tris(4-fluorophenyl)boroxine (0.077 mmol, 0.38 equiv.), $NiBr_2$·(glyme) (10 mol%), tmphen (10 mol%), RNSO (0.200 mmol, 1.00 equiv.), LiO*t*-Bu (0.200 mmol, 1.00 equiv.), DMI (1.0 mL, 0.2 M), 100 °C, 16 h, then quenched with MeOH. Yields of **23** and **24** were calculated from HPLC analysis using *α*,*α*,*α*-trifluorotoluene as an internal standard.

Diluting the reaction mixture slightly (0.18 M instead of 0.20 M) resulted in an increased yield to 25% (Table 4.2, entry 1). Encouraged by these initial promising results, we decided to use TrNSO at 80 °C to further pursue the reaction conditions by screening a range of solvents. Polar aprotic solvents, including DMF and DMSO, and ethereal solvents, namely dioxane, THF and CPME, provided similar quantities of the desired sulfinamide (entry 2−6), with dioxane giving the best yield. However, toluene proved ineffective (entry 7). These results contrasted with the developed nickel-catalysed sulfination reaction (Chapter 2), in which only DMI and DMPU gave approximately 25% conversion of phenylboronic acids in the initial attempts, but other solvents, including dioxane, DMF and DMSO, gave negligible conversion (see the supporting information associated with the

publication).[1] Dioxane was then used as the reaction solvent for further optimisation reactions.

Table 4.2 Solvent screening for the nickel-catalysed synthesis of sulfinamide from aryl boroxines



Entry	Solvent	Yield of 23 (%)
1	DMI	25
2	DMF	20
3	DMSO	26
4	Dioxane	29
5	THF	21
6	CPME	16
7	Toluene	1

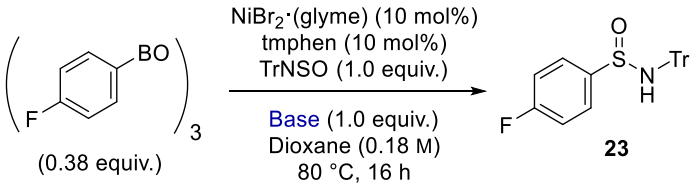
Reaction conditions: tris(4-fluorophenyl)boroxine (0.077 mmol, 0.38 equiv.), $NiBr_2$·(glyme) (10 mol%), tmphen (10 mol%), TrNSO (0.200 mmol, 1.00 equiv.), LiO*t*-Bu (0.200 mmol, 1.00 equiv.), solvent (1.1 mL, 0.18 M), 80 °C, 16 h, then quenched with MeOH. Yields of **23** was calculated from HPLC analysis using *α*,*α*,*α*-trifluorotoluene as an internal standard.

Different bases were then investigated (Table 4.3). A range of *tert*-butoxides, methoxides, phenoxides and hydroxides with different counter ions were examined, providing 4−55% of the sulfinamide (entry 1−10). Of note, a considerable increase in yield was observed by switching LiO*t*-Bu to NaO*t*-Bu (entry 1 and 2). However, no further improvement was achieved using the other alkoxide bases. Carbonate bases were also tested (entry 11−13), with Cs_2CO_3 proving optimal, giving 56% yield of product (entry 13). In general, the solubility of Cs_2CO_3 in organic solvents is up to ten times higher than other alkaline

carbonates, which could be accounted by the "caesium effect", in which the softness of the caesium cation makes its salts more soluble in organic solvents.[118] The special properties of Cs_2CO_3 can account for its better performance in our nickel-catalysed reaction compared to other alkaline carbonates. K_3PO_4, metal fluorides and organic bases were also employed, but less product was obtained in comparison to Cs_2CO_3 (entry 14−18).

Overall, it seemed that the product yield simply increased from 29% to 56% by replacing LiO*t*-Bu with Cs_2CO_3 as the base. However, the HPLC spectra of these two reactions were markedly different. When Cs_2CO_3 was used, only four major peaks were observed on the HPLC spectrum after the reaction; the unreacted starting materials, tris(4-fluorophenyl)boroxine and TrNSO, the desired sulfinamide product **23**, and $TrNH_2$ (from hydrolysis of TrNSO). As well as these four compounds, several unidentified side products were also observed when LiO*t*-Bu was employed. In order to probe this, TrNSO and LiO*t*-Bu were stirred in dioxane at rt. HPLC analysis showed that most of the TrNSO was consumed, forming $TrNH_2$ after stirring for 1 min. Although the mechanism is unclear, the result suggests that LiO*t*-Bu degrades TrNSO directly, causing the consistent low yields observed with LiO*t*-Bu as the base. Although both NaO*t*-Bu and Cs_2CO_3 (entry 2 and 13) provided compared yields, we decided to use Cs_2CO_3 for further investigations because it provided more consistent results and is a weaker, non-nucleophilic base which may allow for better functional group tolerance.

Table 4.3 Base screening for the nickel-catalysed synthesis of sulfinamide from aryl boroxines

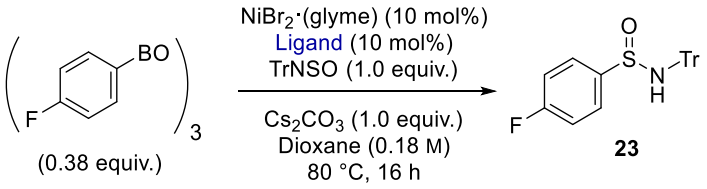


Entry	Base	Yield of 23 (%)
1	LiO*t*-Bu	29
2	NaO*t*-Bu	55
3	KO*t*-Bu	4
4	LiOMe	29
5	NaOMe	9
6	KOMe	33
7	NaOPh	28
8	LiOH	14
9	NaOH	28
10	KOH	11
11	Li_2CO_3	<1
12	K_2CO_3	24
13	Cs_2CO_3	56
14	K_3PO_4	39
15	KF	16
16	CsF	4
17	Et_3N	7
18	DBU	<1

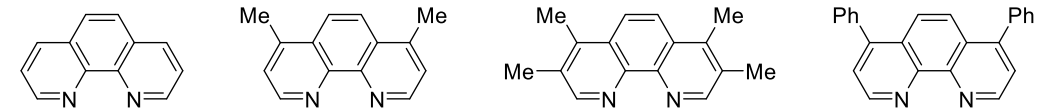
Reaction conditions: tris(4-fluorophenyl)boroxine (0.077 mmol, 0.38 equiv.), $NiBr_2$·(glyme) (10 mol%), tmphen (10 mol%), TrNSO (0.200 mmol, 1.00 equiv.), base (0.200 mmol, 1.00 equiv.), dioxane (1.1 mL, 0.18 M), 80 °C, 16 h, then quenched with MeOH. Yields of **23** were calculated from HPLC analysis using *α*,*α*,*α*-trifluorotoluene as an internal standard.

Different ligands were then examined in the reaction (Table 4.4). In general, up to 60% of sulfinamide was afforded using phenanthroline-type ligands (**L1**–**L8**). We were delighted to find that several bipyridine-type ligands gave more than 60% yields (**L9**, **L11** and **L12**), with **L11** (dNbpy) the best, producing 72% of the desired sulfinamide. Increasing steric bulk adjacent to the coordinating nitrogen provided a less efficient reaction (**L6**, **L7**, **L13** and **L14**). Terpyridine-type ligands proved ineffective in the reaction (**L15** and **L16**). Mono- and diphosphine, and NHC ligand were also tested in the reaction, but only <10% of the product was observed.

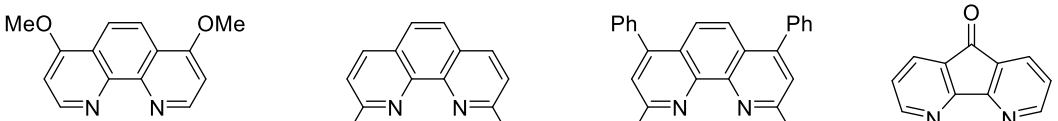
Table 4.4 Selected ligand screening for the nickel-catalysed synthesis of sulfinamide from aryl boroxines



1,10-Phenanthroline-type

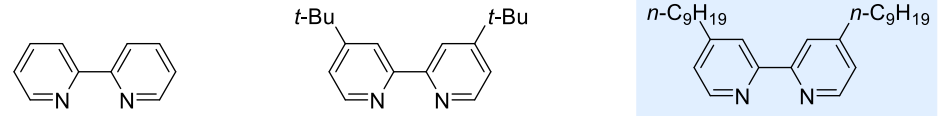


L1 58%; **L2** 60%; **L3**, tmphen 56%; **L4** 59%[a]

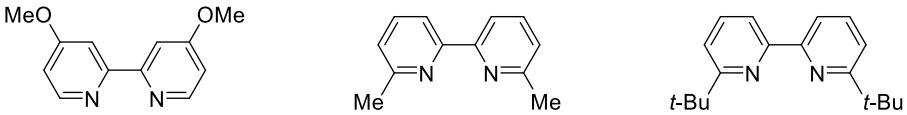


L5 44%; **L6** 41%; **L7** 30%[a]; **L8** 12%[a]

2,2'-bipyridine-type

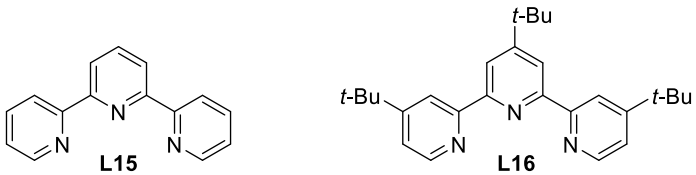


L9 68%; **L10** 54%; **L11**, dNbpy 72%



L12 66%; **L13** 37%; **L14** <1%

Terpyridine-type

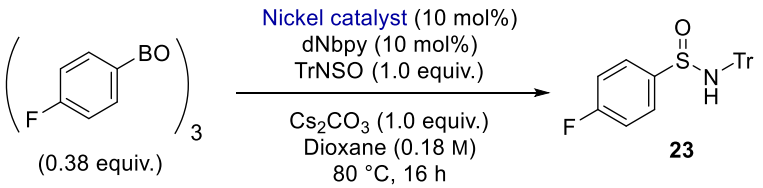


L15 2%; **L16** 6%

Reaction conditions: tris(4-fluorophenyl)boroxine (0.077 mmol, 0.38 equiv.), $NiBr_2$·(glyme) (10 mol%), ligand (10 mol%), TrNSO (0.200 mmol, 1.00 equiv.), Cs_2CO_3 (0.200 mmol, 1.00 equiv.), dioxane (1.1 mL, 0.18 M), 80 °C, 16 h, then quenched with MeOH. Yields of **23** were calculated from HPLC analysis using 1,3,5-triisopropylbenzene as an internal standard. [a]Yields of **23** were calculated from ^{19}F NMR analysis using octafluoronaphthalene as an internal standard.

With the best performing dNbpy ligand in hand, a screening of different nickel catalysts was undertaken (Table 4.5). All nickel(II) halides were effective catalysts. Anhydrous $NiBr_2$ with or without supporting ethereal ligands gave the same performance (entry 1–3). $NiCl_2$·(glyme) raised the reaction yield to 80% (entry 4) while anhydrous and hydrated $NiCl_2$ gave lower yields (entry 5 and 6). Anhydrous NiI_2 was also a suitable catalyst (entry 7). Other nickel catalysts performed less efficiently (entry 8–12). Therefore, $NiCl_2$·(glyme) was selected as the nickel salt of choice for further optimisation.

Table 4.5 Catalyst screening for the nickel-catalysed synthesis of sulfinamide from aryl boroxines

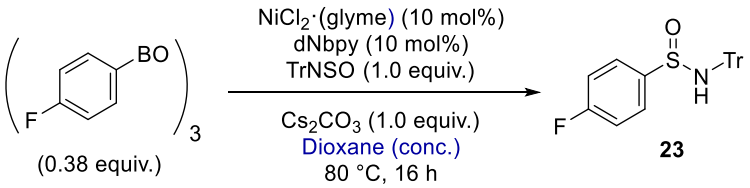


Entry	Nickel catalyst	Yield of 23 (%)
1	$NiBr_2$	72
2	$NiBr_2$·(diglyme)	73
3	$NiBr_2$·(glyme)	73
4	$NiCl_2$·(glyme)	80
5	$NiCl_2$	57
6	$NiCl_2·6H_2O$	45
7	NiI_2	70
8	$NiCO_3$	<1
9	$Ni(OAc)_2$	4
10	$Ni(OAc)_2·4H_2O$	36
11	$Ni(OTf)_2$	44
12	$Ni(acac)_2$	<1

Reaction conditions: tris(4-fluorophenyl)boroxine (0.077 mmol, 0.38 equiv.), nickel catalyst (10 mol%), dNbpy (10 mol%), TrNSO (0.200 mmol, 1.00 equiv.), Cs_2CO_3 (0.200 mmol, 1.00 equiv.), dioxane (1.1 mL, 0.18 M), 80 °C, 16 h, then quenched with MeOH. Yields of **23** were calculated from HPLC analysis using 1,3,5-triisopropylbenzene as an internal standard.

Further investigating the reaction concentration, by examining the volume of dioxane, showed the reaction was best performed with 1.2 mL dioxane (i.e. 0.17 M), producing 85% of the sulfinamide (Table 4.6, entry 5). Less dioxane (i.e. more concentrated reactions) was detrimental (entry 1−4) while more dioxane (i.e. less concentrated reactions) resulted in similar yields (entry 6−7).

Table 4.6 Concentration screening for the nickel-catalysed synthesis of sulfinamide from aryl boroxines



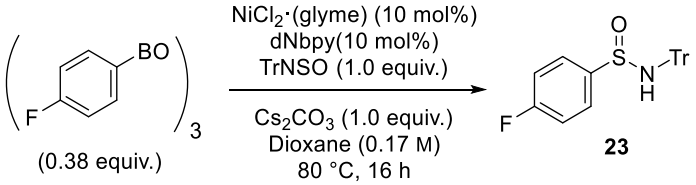
Entry	Volume of dioxane (mL)	Concentration (M)	Yield of 23 (%)
1	0.50	0.40	61
2	0.75	0.27	78
3	1.0	0.20	81
4	1.1	0.18	80
5	1.2	0.17	85
6	1.5	0.13	83
7	2.0	0.10	83

Reaction conditions: tris(4-fluorophenyl)boroxine (0.077 mmol, 0.38 equiv.), $NiCl_2$·(glyme) (10 mol%), dNbpy (10 mol%), TrNSO (0.200 mmol, 1.00 equiv.), Cs_2CO_3 (0.200 mmol, 1.00 equiv.), dioxane, 80 °C, 16 h, then quenched with MeOH. Yields of **23** was calculated from HPLC analysis using 1,3,5-triisopropylbenzene as an internal standard.

We further investigated the reaction conditions based on the optimisations above (Table 4.7, entry 1). Although replacing the dNbpy with inexpensive 2,2'-bipyridine (bpy) ligand was detrimental (entry 2), increasing the stoichiometry of TrNSO to 2 equiv. raised the yield of sulfinamide to 89% with dNbpy as ligand and a comparable 84% yield with bpy (entry 3−4). However, we decided to employ dNbpy as the ligand and 1 equiv of TrNSO as the optimised conditions (entry 1), initially because using an extra equivalent of TrNSO

with a high molecular weight trityl group (mw = 255) would be impractical and inefficient in terms of atom economy. Moreover, later experiments suggested a reaction similar to *trans*-sulfinylation (Scheme 4.3, eq. C) occurred in derivatisation of sulfinamide products, namely the amination of sulfonimidoyl chlorides (Chapter 4.3), in which extra but wasteful equivalents of triethylamine and amine were required to consume the unreacted TrNSO. Accordingly, the equivalents of TrNSO was limited to 1 equiv.

Table 4.7 Variations of optimised reaction conditions.



Entry	Variation	Yield of 23 (%)
1	as above	85
2	bpy as ligand	67
3	2 equiv. TrNSO, 0.18 M dioxane	89
4	2 equiv. TrNSO, 0.18 M dioxane, bpy instead of dNbpy	84
5	15 mol% dNbpy	77
6	70 °C	70
7	1.5 equiv Cs_2CO_3	85
8	No $NiCl_2$·(glyme)	<1
9	No dNbpy	<1
10	No Cs_2CO_3	1
11	4-F-Ph-Bpin instead of $(4\text{-F-Ph-BO})_3$	<1
12	4-F-Ph-BF_3K instead of $(4\text{-F-Ph-BO})_3$	<1
13	DMI instead of dioxane	55
14	K_2CO_3 instead of Cs_2CO_3	9

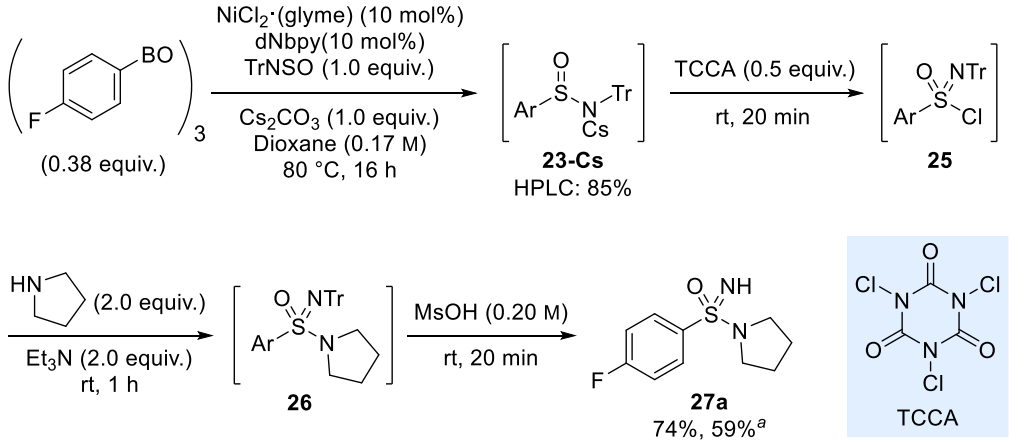
Reaction conditions: tris(4-fluorophenyl)boroxine (0.077 mmol, 0.38 equiv.), $NiCl_2$·(glyme) (10 mol%), dNbpy (10 mol%), TrNSO (0.200 mmol, 1.0 equiv.), Cs_2CO_3 (0.200 mmol, 1.0 equiv.), dioxane (1.2 mL, 0.17 M), 80 °C, 16 h, then quenched with MeOH. Yields of **23** were calculated from HPLC analysis using 1,3,5-triisopropylbenzene as an internal standard.

Higher loading of ligand, and lowering the reaction temperature resulted in less efficient reactions (entry 5 and 6). Adding more Cs_2CO_3 as the base had no impact on the product yield (entry 7). As expected, the nickel salt, ligand and base were essential for the reaction (entry 8−10). Replacing the arylboroxine with alternative boron reagents, boronic acid pinacol ester and potassium trifluoroborate, were unproductive (entry 11−12). Substituting dioxane with DMI, or K_2CO_3 with Cs_2CO_3 resulted in diminished yields (entry 13−14).

4.4 Derivatisations of sulfinamides

4.4.1 Preparation of sulfonimidamides

With the optimised conditions in hand (Table 4.7, entry 1), we next focused on the derivatisations of the *in situ* formed sulfinamides. We first converted sulfinamide **23-Cs** into sulfonimidamide **27** (Scheme 4.7) by a reaction sequence of chlorination, amination and deprotection, as developed by Dr. Thomas Davies in Scheme 4.5.



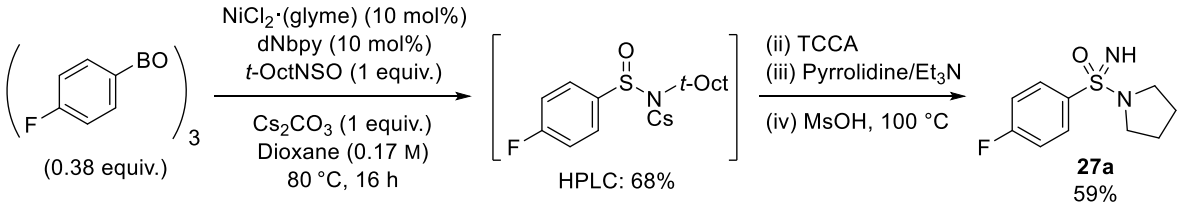
[a]1 mmol scale with 5 mol% $NiCl_2$(glyme) and dNbpy, 100 ℃ for first step.

Scheme 4.7 Sulfonimidamide synthesise using arylboroxine, TrNSO and nickel catalysis

A range of chlorinating reagents were examined for the conversion of sulfinamide **23-Cs** formed *in situ* to sulfonimidoyl chloride **25** at rt. Both *t*-BuOCl and trichloroisocyanuric acid (TCCA) performed identically with >95% conversions within 30 minutes at rt as observed by HPLC analysis. 1,3-Dichloro-5,5-dimethylhydantoin (DCDMH) gave ~30% conversions after few hours. Both *N*-chlorosuccinimide (NCS) and chlorobis(methoxycarbonyl)guanidine (CBMG)[119] were unreactive after 16 h. Compared to the light-sensitive and potentially explosive nature of *t*-BuOCl,[120] TCCA is a safe, stable and inexpensive oxidative chlorinating agent that is widely used as a disinfectant, and bactericide in swimming pools, bathrooms, and laundry bleach.[121] Accordingly, the use of TCCA is preferable over *t*-BuOCl and was selected for further studies.

Further treatment of the reaction mixture with pyrrolidine (2 equiv.) and triethylamine (2 equiv.) at rt converted sulfonimidoyl chloride fully to trityl-sulfonimidamide **26** in 1 h, with ~5% of *N*-trityl sulfonamide generated, indicating hydrolysis of the sulfonimidoyl chloride was a competing reaction. When 2 equivalents of TrNSO were used in step 1, a significant amount of $TrNH_2$ was observed in the amination step. As discussed earlier, this result suggested that pyrrolidine was reacting with TrNSO directly, probably *via* a mechanism similar to *trans*-sulfinylation (Scheme 4.3, eq. C) to liberate $TrNH_2$ as a side product. Treatment of the *N*-trityl sulfonimidamide intermediate **26** with MsOH at rt afforded the deprotected *N*H sulfonimidamide **27a** in a 74% isolated yield. This represents an average of 96% for each of the three steps in the chlorination/amination/deprotection sequence. All four steps were performed in a one-pot reaction, providing a convenient synthesis of *N*H-sulfonimidamides. The reaction can also be scaled up to 1 mmol scale using only 5 mol%

catalyst, producing a 59% isolated yield of the sulfonimidamide **27a**. Further lowering the catalyst loadings resulted in poorer conversion of the boroxine. It is worth noting that EtOAc could not be used as an extraction solvent in the aqueous workup, as a significant amount of trityl-protected sulfonimidamide **26** was regenerated, with only 44% *N*H sulfonimidamide **27a** isolated. Retritylation is sometimes a problem when using acid-deprotection of trityl group.[122] Using CH_2Cl_2 for extraction instead only regenerated the protected sulfonimidamide **26** in trace quantities, thus extraction with CH_2Cl_2 is essential. The reaction also worked effectively with *t*-OctNSO as an alternative sulfinylamine using the optimised conditions, producing 68% HPLC yield of the corresponding sulfinamide and 59% isolated yield of sulfonimidamide **27a** (Scheme 4.8).

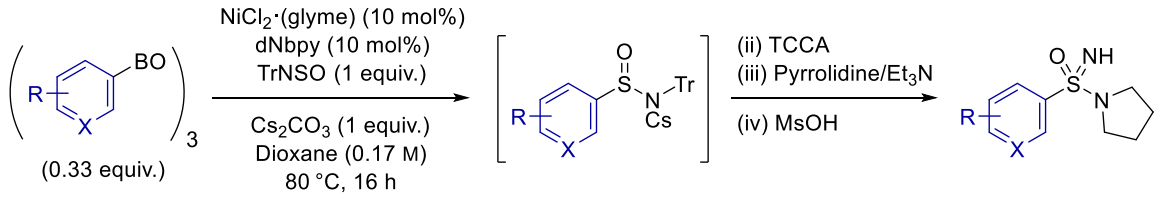


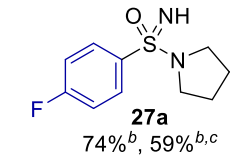
Scheme 4.8 Sulfonimidamide synthesis using aryl boronic acids, *t*-OctNSO and nickel catalysis

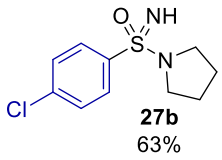
After identifying the optimised conditions, the scope of the reaction for the aryl boroxines, using TrNSO as the sulfinylamine and pyrrolidine as the nucleophile, was examined to prepare the corresponding sulfonimidamides (Table 4.8). *p*-Chlorophenylboroxine (**27b**) and *p*-biphenylboroxine (**27c**) provided the products in good yields. Boroxines bearing different electronic substitutions were well tolerated, with electron-donating *p*-methoxy (**27d**), and electron-withdrawing *p*-trifluoromethyl (**27e**) and *p*-methyl ester (**27f**) substituents delivering modest to good isolated yields. The hydrolysis of the ester

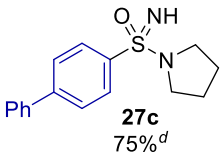
functional group under acidic conditions in the deprotection step may account for the lower yield of the sulfonimidamide **27f**. *Meta*-substituted boroxines (**27g** and **27h**) also reacted well, delivering comparable yields to the *para*-substituted counterpart (**27d** and **27g**). *ortho*-Substituted (**27i**) phenyl core provided a surprisingly useful 57% yield of the product under the optimised conditions. This is in contrast to the nickel-catalysed sulfination reactions in which the same substrate reacted poorly, affording the desired sulfone in only 31% yield at elevated temperature (Chapter 2, Table 2.2). This result gives further evidence that the sulfur centre of TrNSO is non-sterically demanding as suggested by its crystal structure (Scheme 4.4), permitting migratory insertion of a sterically demanding *ortho*-substituted phenyl core. A pharmaceutically relevant boroxine bearing the arene core of the COX2 inhibitor Celecoxib was also well tolerated, delivering a good yield of the sulfonimidamide (**27j**). Alkenyl boroxine (**27k**) was a less successful coupling partner, with reduced yield of the targeted sulfonimidamide isolated. Although low yielding, these compounds are of potential interest as electrophilic partners with reaction of nucleophiles plausible in a Michael-addition manner. A range of nitrogen-, oxygen-, and sulfur-containing heteroaryl boroxines were also suitable substrates, including benzofuran (**27l**), indazole (**27m**), pyridine (**27n**), furan (**27o**) and thiophene (**27p**), providing useful yields of the desired sulfonimidamides.

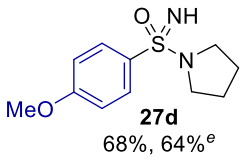
Table 4.8 Scope of the boroxines[a]

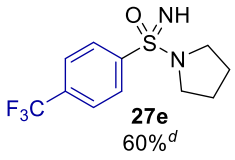


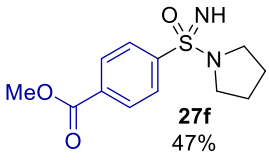

27a
74%[b], 59%[b,c]

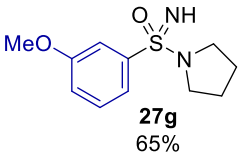

27b
63%

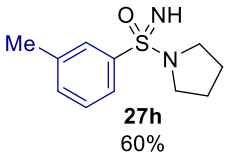

27c
75%[d]

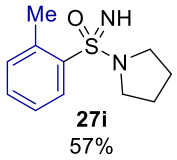

27d
68%, 64%[e]

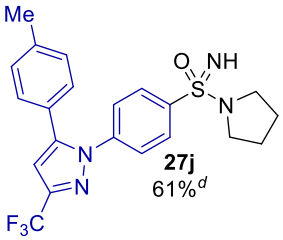

27e
60%[d]

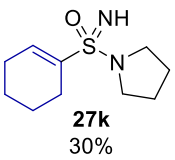

27f
47%

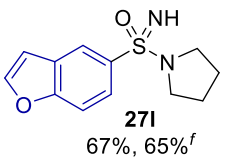

27g
65%

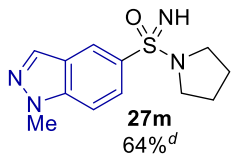

27h
60%

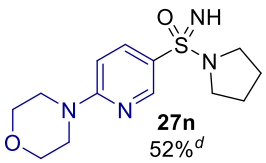

27i
57%

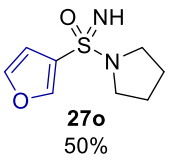

27j
61%[d]

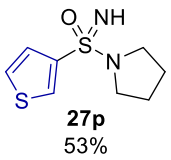

27k
30%


27l
67%, 65%[f]


27m
64%[d]


27n
52%[d]

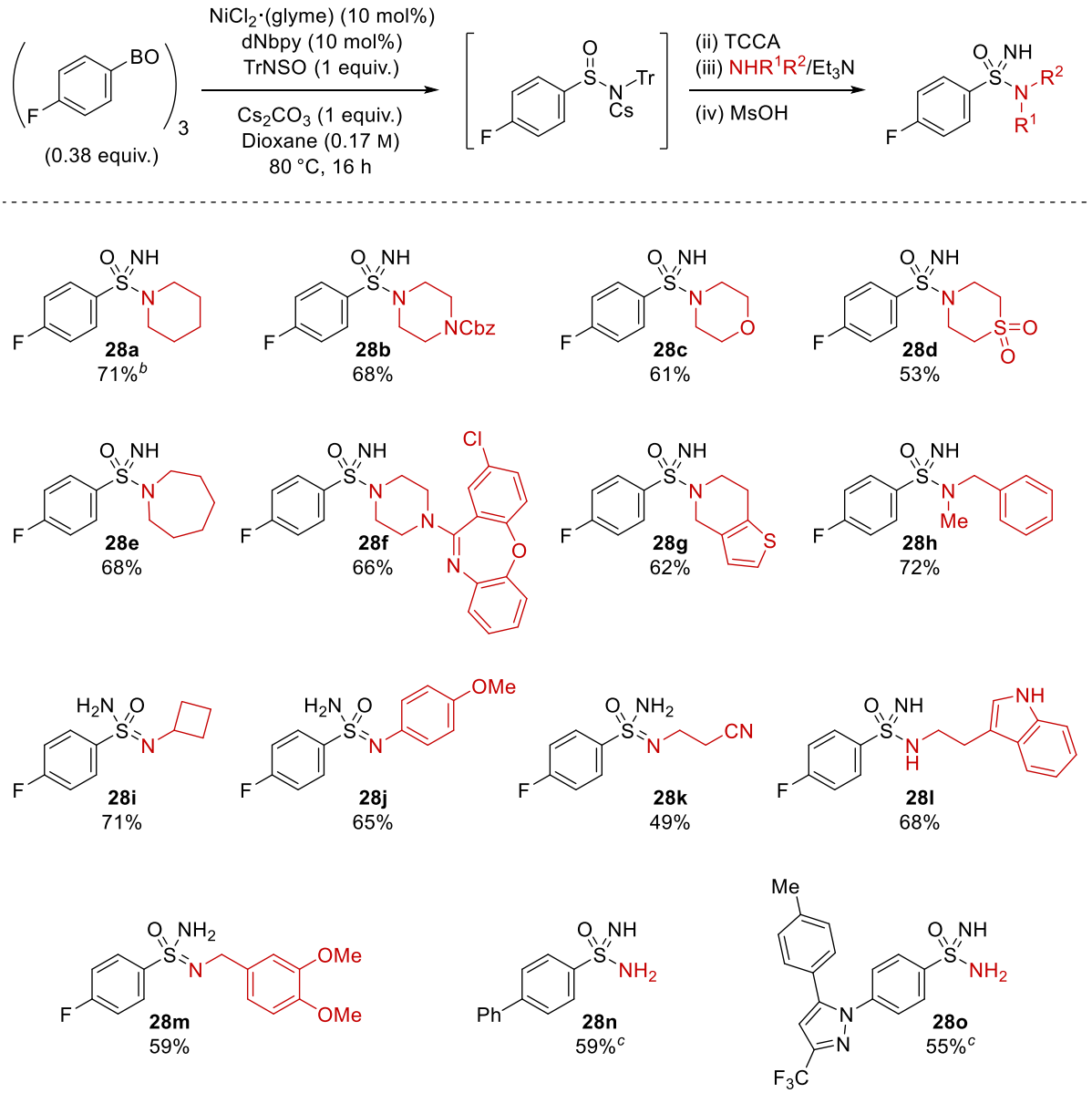

27o
50%


27p
53%

[a]Reaction conditions: (hetero)aryl boroxine (0.067 mmol, 0.33 equiv.), $NiCl_2$·(glyme) (10 mol%), dNbpy (10 mol%), TrNSO (0.200 mmol, 1.0 equiv.), Cs_2CO_3 (0.200 mmol, 1.0 equiv.), dioxane (1.2 mL, 0.17 M), 80 °C, 16 h. (ii) TCCA (0.5 equiv.), rt, 20 min. (iii) Pyrrolidine (2.0 equiv.), Et_3N (2.0 equiv.), rt, 1 h. (iv) MsOH (1.00 M), rt, 20 min. [b]Tris(4-fluorophenyl)boroxine (0.077 mmol, 0.38 equiv.). [c]1 mmol scale with 5 mol% $NiCl_2$·(glyme) and dNbpy, 100 ℃ for first step. [d](hetero)aryl boroxine (0.133 mmol, 0.67 equiv.), 100 ℃ for first step. [e]Boroxine prepared directly from the dehydration of commercial aryl boronic acid (0.20 mol, 1.0 equiv.) in a one-pot reaction. [f]0.4 mmol scale with heteroaryl boroxine (0.50 equiv.), 1 mol% $NiCl_2$·(glyme) and dNbpy, 100 ℃, 48 h.

It is worth noting that sulfonimidamides **27c**, **27e**, **27j**, **27m** and **27n** required a higher temperature (100 °C) and the use of 0.67 equivalents of the corresponding boroxines (i.e. 2 equiv. of the arene cores) to achieve good yields of the corresponding sulfinamides in step 1, as the original conditions only provided poor conversions of boroxines. We also demonstrated that this transformation could be performed with reduced catalyst loadings; the nickel catalyst and ligand loading was lowered to 1 mol% for the benzofuran substrate **27l**, providing 65% yield of product, which was comparable with the original conditions (67%). In order to provide a more convenient and user-friendly method, we also showed that the reaction could be performed directly from the commercial boronic acid. The initial dehydration to the corresponding boroxine could be performed in the same reaction flask/tube as the nickel catalysed reaction. For example, sulfonimidamide **27d** was isolated in a comparable 64% yield using a one-pot reaction from the commercial 4-methoxyphenylboronic acid.

Table 4.9 Scope of the amines[a]

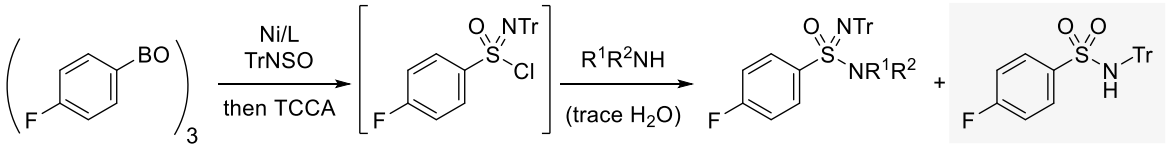


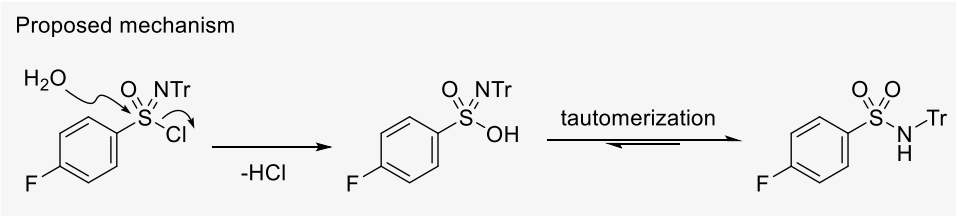
[a]Reaction conditions for step (iii) (amination step): R^1R^2NH (2.0 equiv.), Et_3N (2.0 equiv.), rt, 24 h. [b]5 h for step (iii). [c]A biphasic mixture of 35% aq NH_3/ethyl acetate (1:2) was used as the nitrogen nucleophile and 30 min for step (iii).

We then examined the scope of nitrogen-based nucleophiles that could be used, using tris(4-fluorophenyl)boroxine as the carbon-coupling partner (Table 4.9). A range of secondary amines, including biologically relevant amines (**28f**, **28g**) reacted smoothly to produce the corresponding sulfonimidamides in modest to good isolated yields (**28a**–**28h**). Primary amines (**28i**–**28m**), including aniline (**28j**) were also suitable nucleophiles.

Although in Chapter 1.5.1, we discussed that stabilities of sulfonimidamides relied on the substituents on nitrogen, in practice, we found that the tautomerisation was highly solvent dependent. For example, in $CDCl_3$, sulfonimidamide **28i** (as well as **28j**, **28k** and **28m**) showed the product with the substituent on the imidic S=N as observed by the analysis of ^{1}H NMR spectra. However, in DMSO-d_6, there were two discernible sets of N−H protons observed in ^{1}H NMR spectra for sulfonimidamides **28i** (as well as **28l)**, indicating a N−H on both imidic S=N and amidic S−N.

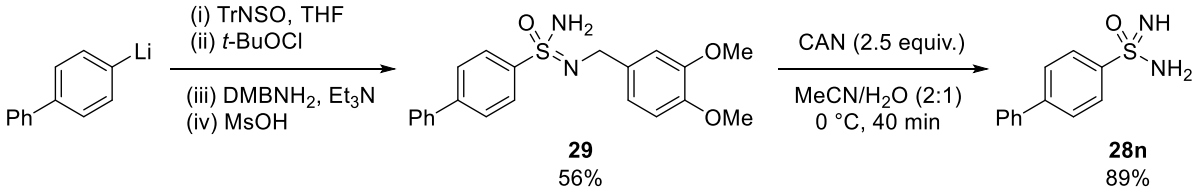
We found that the hydrolysis of the intermediate sulfonimidoyl chloride to give the trityl-protected sulfonamide was the major side product observed during the amination reaction (Scheme 4.9). This side reaction was problematic especially when less nucleophilic amines (e.g. **28d** and **28k**) were used, as the amination step became slower at the sterially hindered sulfur center, allowing competitive reaction of water as a nucleophile. Hence, the desired product yields became lower. Although the hydrolysis of sulfonimidoyl chlorides to give sulfonamides was puzzling when exploring the scope of amines, the result suggested that it was a feasible way to generate sulfonamides in later chapter (Table 4.11).





Scheme 4.9 Side product formation and the proposed mechanism for hydrolysis.

We then investigated the synthesis of the primary sulfonimidamides, which are of interest due to their multiple hydrogen bond donor sites. Davies *et al.* had previously encountered issues with the direct conversion of *N*-trityl sulfonimidoyl chlorides to the primary sulfonimidamides using ammonia in THF as the amine component.[114] They instead utilized 3,4-dimethoxybenzyl-protected sulfonimidamide **29** as a precursor, with oxidative cleavage using cerium ammonium nitrate (CAN) affording the desired sulfonimidamide **30** in excellent yields (Scheme 4.10).

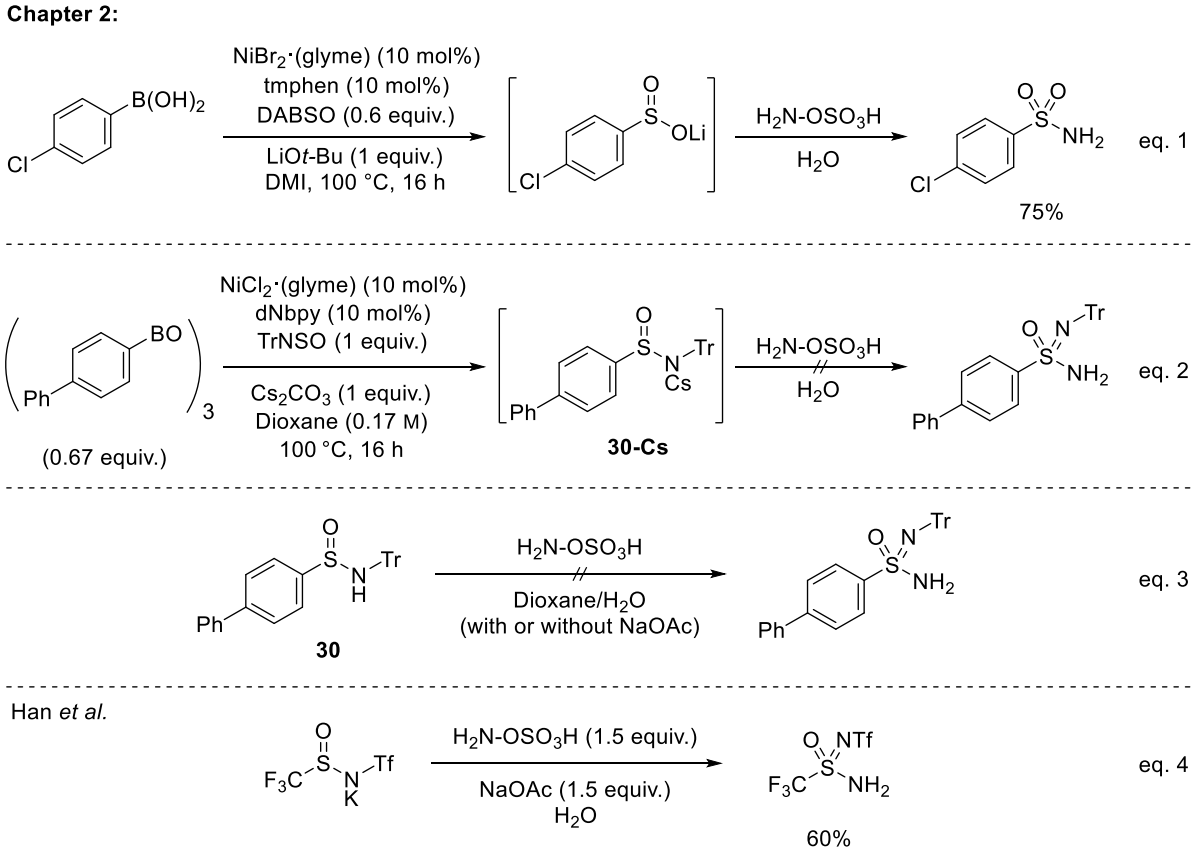


Scheme 4.10 Davies' synthesis of primary sulfonimidamides

Despite these challenges, we were interested in the use of ammonia sources as the amine component under our conditions. Using NH_3 in dioxane only produced a small amount of amination product but also gave a complex reaction with multiple side products, which was consistent with Davies' findings.[114] In Chapter 3, a biphasic mixture of ammonium hydroxide solution and ethyl acetate was used to react with sulfinyl chloride to synthesise primary sulfinamides **19k** and **19l** (Table 3.2). In an analogous manner, we employed this setup for reaction with the intermediate sulfonimidoyl chloride and cleanly produced the primary sulfonimidamide (**28n** and **28o**) in good yield after deprotection. These results suggest that the biphasic mixture of ammonium hydroxide solution and ethyl acetate is a unique ammonia source, able to undergo substitution reactions with S(IV) and S(VI)-chloride electrophiles. Using aq. NH_3 to convert sulfonimidoyl chlorides into

primary sulfonimidamides has been previously reported by the Bolm group.[123]

In Chapter 2, we reacted aryl sulfinates with an electrophilic aminating reagent, H_2N-OSO_3H, to give primary sulfonamides (Scheme 4.11, eq. 1).[1] However, treating the trityl-sulfinamide **30-Cs** with the same conditions gave no reaction, with only the sulfinamide **30-Cs** recovered (eq. 2). A separate reaction treating the pure, isolated trityl-sulfinamide **30** with H_2N-OSO_3H was also unproductive, even with NaOAc as a buffer (eq. 3).[81] Converting sulfinamides directly into sulfonimidamides has been reported previously by Han *et al.* (eq. 4),[124] hence the failure of the eq. 2 and 3 may be accounted for by the bulky trityl group which hindered the process.

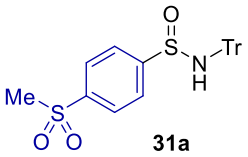


Scheme 4.11 using H_2N-OSO_3H as an electrophilic aminating reagent

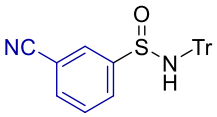
4.4.2 Low yielding and unsuccessful scope

Although a range of arylboroxines and amines were successfully employed to synthesise sulfonimidamides using the above-mentioned conditions, there remained some limitations (Table 4.10). 4-(Methylsulfonyl)phenyl and 3-cyanophenyl systems failed to give the corresponding sulfinamides **31a** and **31b** because they formed an emulsion under the conditions and mainly the unreacted boroxines were recovered after the reactions. We propose that boroxines can form an ate complex with Cs_2CO_3, followed by transmetallation on the nickel centre. The ate complex, as a salt, would have lower solubility in an organic solvent. For boroxines bearing polar functional groups ($MeSO_2$– and –CN), the ate complexes would have even poorer solubilities and hence are insoluble in dioxane, forming an emulsion. Accordingly, the boroxines were unreactive under the conditions. We propose that replacing the Cs_2CO_3 with other bases (e.g. dried NaO*t*-Bu) and/or dioxane with other solvents may solve these issues. Although the dibenzothienyl system reacted smoothly in the sulfinate chemistry documented in Chapter 2 (Table 2.3, sulfone **7aa**), it surprisingly gave a complex mixture to produce sulfinamide **31c** using the nickel/TrNSO conditions.

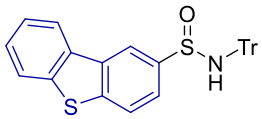
Table 4.10 Limitations of the Sulfinamide and Sulfonimidamides Synthesis



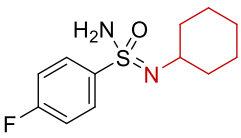
31a
Boroxine sticked together



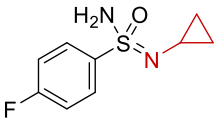
31b
Boroxine sticked together



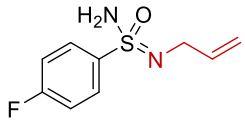
31c
Step 1: complex mixture



32a
46%



32b
45%



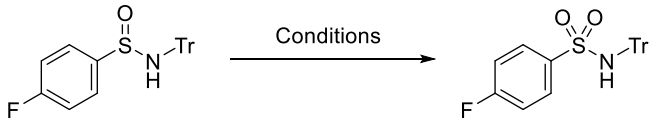
32c
~40-50%
(observed hydrolysis product, $ArSO_2NHTr$)

As discussed in Scheme 4.9, hydrolysis of sulfonimidoyl chlorides to give sulfonamides was the major issue when exploring the scope of amines. This was also true when synthesising sulfonimidamides **32a**, **32b** and **32c**.

4.4.3 Preparation of primary sulfonamides

An extensive screening was conducted to oxidise the pure trityl-protected sulfinamide **23** into sulfonamide (Table 4.10). *m*-CPBA was shown to be the optimal oxidant, producing an excellent yield of the trityl-sulfonamide **33** (entry 1) in dioxane. Surprisingly, when CH_2Cl_2 was used as the solvent, the deprotected sulfonamide was observed by HPLC analysis and further confirmed as the product after isolation (entry 2). It was proposed that after oxidation, the trityl group was cleaved by *m*-chlorobenzoic acid in CH_2Cl_2.

Table 4.10 Oxidation of trityl-sulfinamide[a]



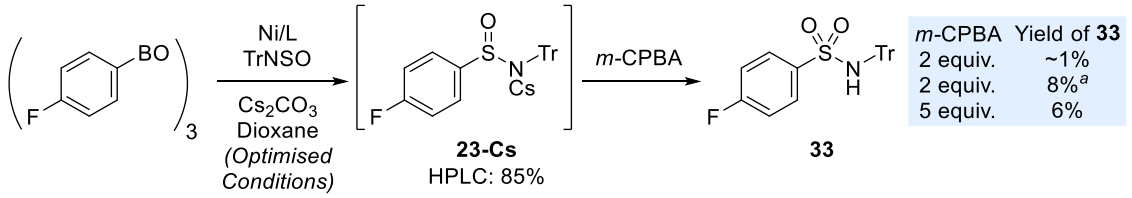
23 **33**

Entry	Condition[a]	Result[b]
1	*m*-CPBA (2), dioxane (0.36 M), rt	97% prod **33**[c]
2	*m*-CPBA (2), CH_2Cl_2 (0.36 M), rt	91% of 4−F−Ph−SO_2NH_2 isolated
3	H_2O_2 (2), dioxane (0.18 M), 80, 60, 40 ℃ or rt	· Mainly SM **23** + hydrolysis, but no prod **33** at a higher temp. (60 or 80 ℃) · Mainly SM **23**, no prod or hydrolysis at a lower temp. (40 ℃, rt)
4	$Na_2WO_4 \cdot H_2O$ (10 mol%), H_2O_2 (1.5), dioxane or EtOH (0.18 M), rt or 80 ℃ (in dioxane)	Mainly SM **23**, no prod **33**
5	$(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ (3 mol%), H_2O_2 (2), dioxane (0.18 M) or DMF (0.83 M), 80, 60, 40 ℃ or rt	· Mainly prod **33** + hydrolysis at 80 and 60 ℃ · Some prod **33** + SM **23** + hydrolysis at 40 ℃ · Mainly SM **23**, no hydrolysis at rt
6	CAN (2.5), MeCN (0.92 M), H_2O (1.71 M), 0 ℃ to rt	Mainly hydrolysis, no prod **33**

[a]Equivalents of reagent was written in the brackets. H_2O_2 was used as 30% solution in H_2O. [b]analysed by HPLC spectroscopy unless specified. Hydrolysis means $TrNH_2$ and 4−F−Ph−SO_3H (sometimes) were observed by HPLC spectroscopy. SM means starting material. Prod means product. [c]Determined by ^{19}F NMR.

Alternative oxidants were also explored. When H_2O_2 was used alone as the oxidant or with sodium tungstate[8c] as a catalyst, mainly starting material **23** was recovered, along with significant quantities of tritylamine $TrNH_2$ formed from the hydrolysis of trityl-sulfinamide **23** (entry 3 and 4). It suggested that the S−N bond was cleaved under the aqueous conditions especially upon heating. When a molybdenum(VI) catalyst was employed,[125] the desired oxidation occurred to give the trityl-sulfonamide **33** upon heating (60 or 80 ℃), but was unavoidably accompanied with the hydrolysis side reaction (entry 5). In general, H_2O_2 was unsuitable in this oxidation. Finally, the oxidation using ceric ammonium nitrate was unsuccessful, with mainly hydrolysis observed (entry 6).

We were interested in performing the oxidation in a one-pot reaction sequence yielding sulfonamides directly from boroxines. Accordingly, we set up the nickel-catalysis to form trityl-sulfinamide **23-Cs** *in situ* and added *m*-CPBA as the oxidant (Scheme 4.12). However, the reaction was unsuccessful with only <10% desired trityl-sulfonamide **33** formed and mainly trityl-sulfinamide **23-Cs** recovered, along with lots of unknown side products produced. Perhaps because the *m*-CPBA oxidised the nickel catalyst instead which caused its decomposition. Overall, its use as an oxidant in the nickel-catalysed reaction failed. Therefore, alternatives methods were investigated.

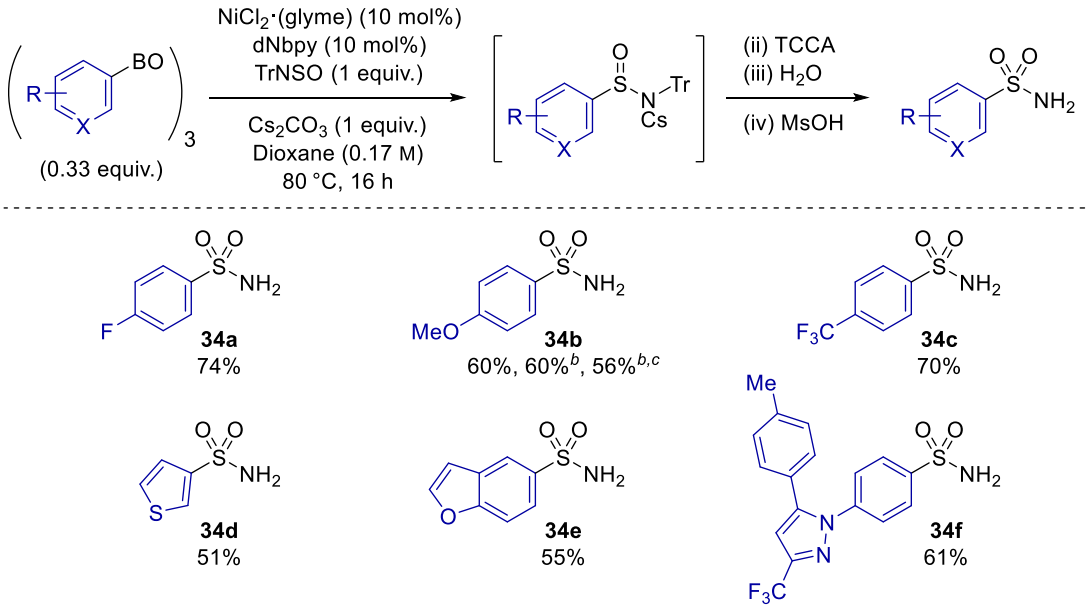


[a]An aqueous workup was performed after step 1.

Scheme 4.12 Using *m*-CPBA as an oxidant

In Scheme 4.9, we found that the hydrolysis of sulfonimidoyl chlorides to produce sulfonamides was the major side reaction during amination. We then further explored the use of H_2O as a nucleophile to generate primary sulfonamides in a one-pot reaction (Table 4.11).[50] Substrates bearing electron-poor (**34a** and **34c**), electron-rich (**34b**), heterocyclic arenes (**34d** and **34e**) and a biologically relevant core (**34f**) smoothly reacted to form the corresponding primary sulfonamides after hydrolysis and deprotection. The reaction could also be performed on a 1 mmol scale using just 1 mol% catalyst to produce the sulfonamide **34b**. Again, the desired product could be obtained in a comparable yield using 1 mol% nickel catalyst from the commercial boronic acid with an extra dehydration step in a one-pot reaction. We believed that the electron-rich *p*-methoxylphenyl core transmetalates to the nickel center faster and hence allowing lower catalyst loading, when compared to the electron-poor *p*-fluorophenyl core (Scheme 4.7).

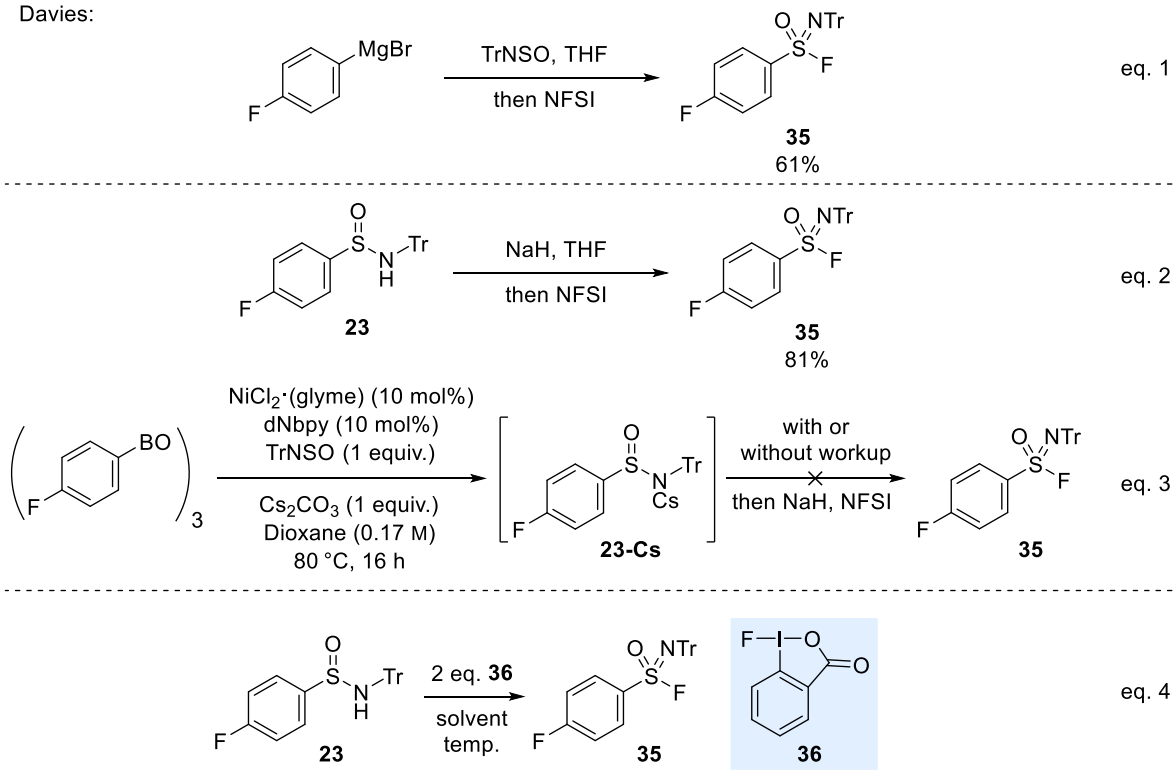
Table 4.11 Scope of sulfonamides[a]



[a]Reaction conditions: (iii) H_2O (0.1 mL, 2.00 M), rt, 24 h. (iv) MsOH (0.20 M), rt, 20 min. [b]1 mmol scale with 1 mol% $NiCl_2$·(glyme) and dNbpy, aryl boroxine (0.40 mmol, 0.40 equiv.), 100 °C and 48 h for first step. [c]Boroxine was prepared from the dehydration of commercial aryl boronic acid (1.1 mol, 1.1 equiv.) in a one-pot reaction.

4.4.4 Preparation of sulfonimidoyl fluorides

Sulfonimidoyl fluorides are chiral isosteres of sulfonyl fluorides, with potential applications in the field of chemical biology.[59, 126] Hence, we turned our attention to make these functional groups. Inspired by Davies' synthesis of sulfonimidoyl fluoride **35** (Scheme 4.13, eq. 1),[114] we were also able to prepare the same compound using pure sulfinamide **23**, NaH as a base and NFSI as the electrophilic fluorinating source (eq. 2). However, subjecting the same conditions to the sulfinamide prepared from our nickel-catalysis reaction was unsuccessful, with only the unreacted sulfinamide **23-Cs** recovered (eq. 3).

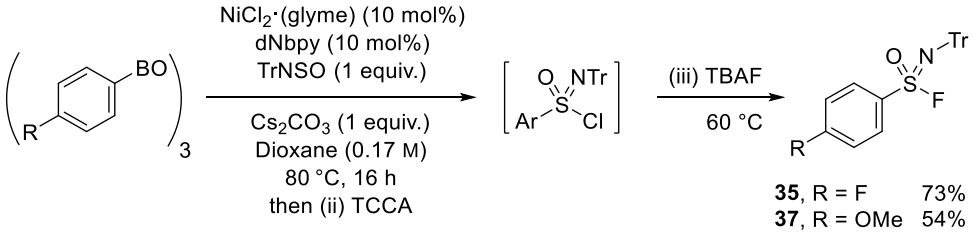


solvent	temp	Results
MeCN	rt or 80 °C	no/trace product **35** at rt
CH_2Cl_2	rt or 40 °C	or
Dioxane	rt or 100 °C	complex mixture at 80 or 100 °C

Scheme 4.13 Fluorination using electrophilic fluorine sources

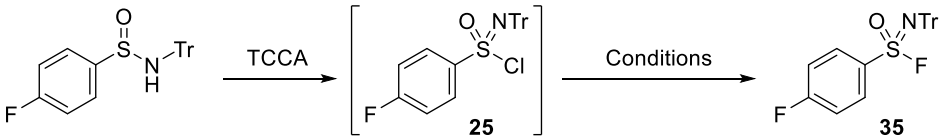
A DPhil member in our group, Charlie Bell, had demonstrated the use of hypervalent iodine reagent **36** as a competent fluorinating agent to make sulfonimidoyl fluorides from sulfinamides. The advantage of this reagent was that no base was required for the reaction. Unfortunately, the reagent failed to produce the desired sulfonimidoyl fluoride **35**, generally with no conversion at room temperature or producing a complex mixture at higher temperature (eq. 4), perhaps due to the steric bulk of the trityl substituent.

Sulfonimidoyl chlorides are known to undergo halogen exchange reactions with a variety of different fluoride sources to form the corresponding sulfonimidoyl fluorides.[127] We then investigated the halogen exchange reaction into our method. The intermediate sulfonimidoyl chloride underwent fluorination smoothly using TBAF as the soluble fluorine source (Scheme 4.14).



Scheme 4.14 Fluorination using TBAF as the fluorine source

Using KHF_2 instead recovered the sulfonimidoyl chloride **25** only (Scheme 4.15). Addition of water to provide extra solvation and hydrogen bonding to enhance the reactivity of fluoride did produce some sulfonimidoyl fluoride **35,**[13, 128] but the major product was the *N*-trityl-sulfonamide **33** and the deprotected sulfonamide **34a**, probably by the hydrolysis of the sulfonimidoyl chloride **25**, while the deprotection should be mediated by the acidic KHF_2.

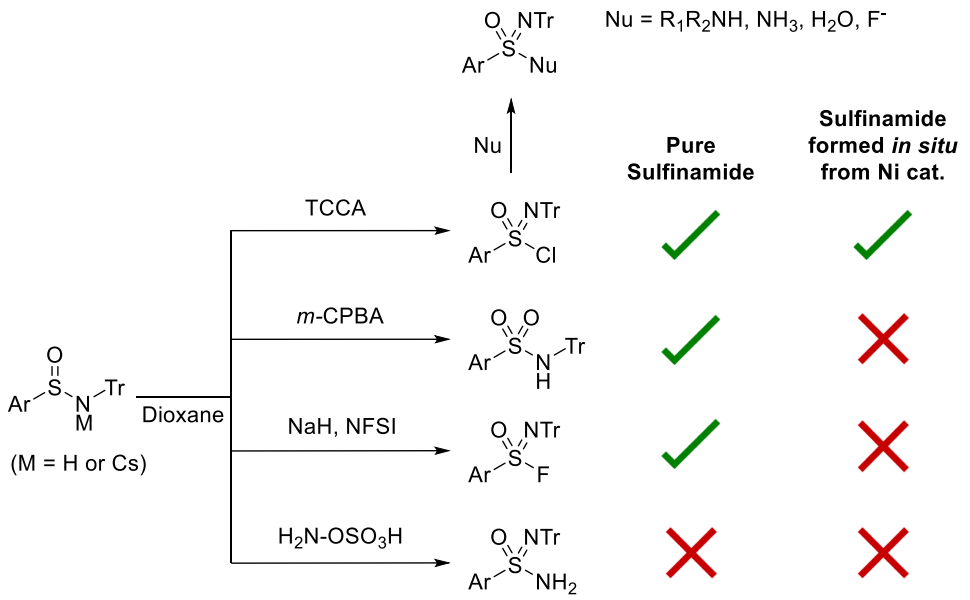


Conditions	Results
KHF_2 (2 equiv.), rt, 4 days, dioxane or MeCN	only **25** recovered with no product **35**
sat. aq. KHF_2 (0.33 M) MeCN (0.33 M), dioxane (0.17 M)	small amount product **35** + mainly $ArSO_2NHTr$ **33** and $ArSO_2NH_2$ **34a**

Scheme 4.15 Using KHF_2 as the fluorine source

4.4.5 Source of electrophilic oxidation agents

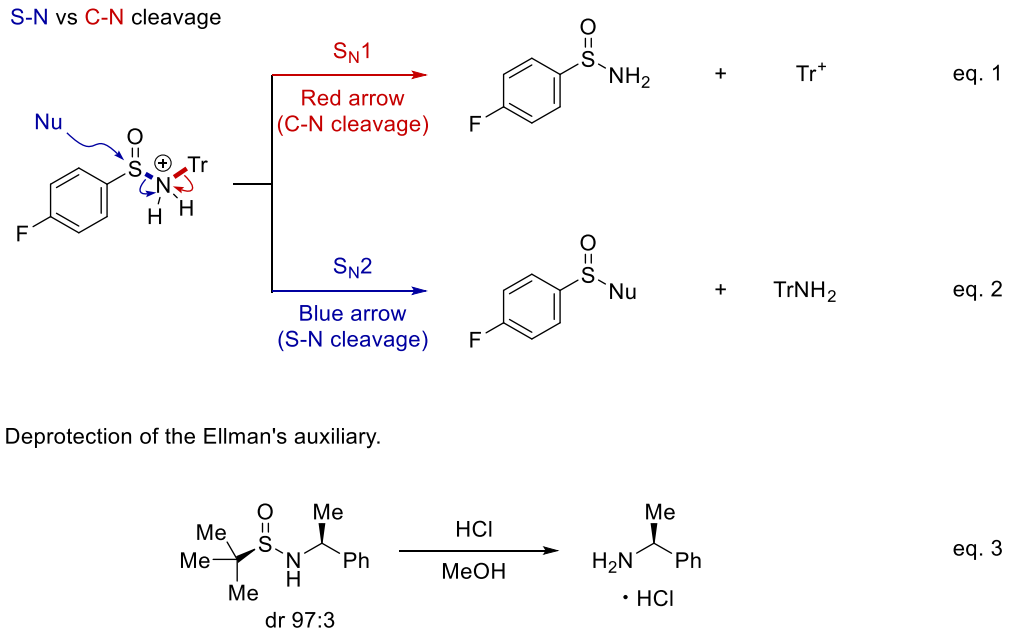
We summarised the trend to oxidise sulfur (IV) centre in trityl-sulfinamide to sulfur (VI) in various compounds from Chapter 4.4.1 to 4.4.4 (Scheme 4.16). Oxidation of sulfinamide to sulfonimidoyl chloride with TCCA was robust and general (Chapter 4.4.1), meaning that the sulfinamide could be used in pure form or when it was prepared *in situ* from the nickel-catalysed reaction of boroxines. However, oxidation with *m*-CPBA (Chapter 4.4.3), and NFSI (Chapter 4.4.4) could only be performed when the sulfinamides were used in their pure form but not when they were generated from nickel catalysis without purification. The reasons behind this phenomenon could be explained by the oxidation of the nickel catalyst instead of the sulfinamides, hence decomposing the oxidants. Amination using $H_2N\text{-}OSO_3H$ was unsuccessful either when the sulfinamides were pure or formed *in situ* using nickel catalysis. Although sulfonamides, sulfonimidoyl fluorides and primary sulfonimidamides could not be made from the direct oxidation of nickel-catalysed generated sulfinamides, they could be synthesised by treating the sulfonimidoyl chloride intermediates with an appropriate nucleophile, allowing convenient one-pot reactions.



Scheme 4.16 Summary of oxidation of sulfur (IV) centre in trityl-sulfinamide to sulfur (VI)

4.4.6 Preparation of primary sulfinamides

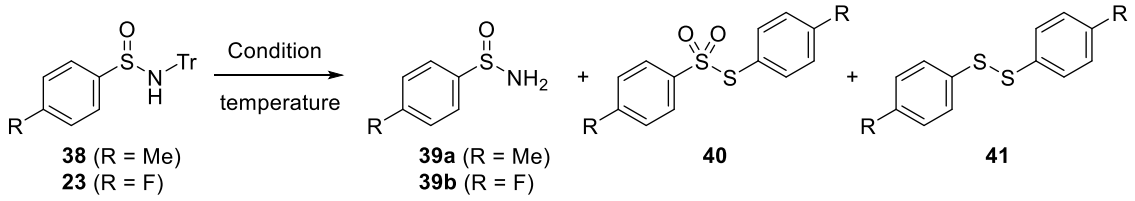
Finally, we attempted to perform a deprotection of the trityl group in order to access the corresponding primary sulfinamide. We realised that under acidic conditions, the protonated sulfinamide could undergo two different pathways (Scheme 4.17). One of which would undergo the desired C−N bond cleavage to give the primary sulfinamide and the trityl cation (Tr^+) by an S_N1 mechanism, which was quenched by water to give TrOH in HPLC spectroscopy (eq. 1, red arrows). Alternatively, a nucleophile could attack the sulfur centre directly, cleaving the S−N bond to release $TrNH_2$ as the leaving group by a S_N2-like mechanism (eq. 2, blue arrows). We believed that the S−N bond cleavage of protonated sulfinamide was a common reaction pathway and difficult to be suppressed, typified by the removal of *tert*-butanesulfinamide (Ellman's auxiliary) under acidic conditions (eq. 3).



Scheme 4.17 S−N and C−N bond cleavage of protonated sulfinamide

Extensive screening for the deprotection was carried out (Table 4.12), however, only $TrNH_2$ (formed by S−N bond cleavage) was observed exclusively when the trityl-sulfinamide was treated with acids (Entry 1−8, 10−14, 18 and 19), hydrogenation (Entry 9) or radical conditions (Entry 15−17) in various organic solvents. Further analysis of two of the reactions (Entry 11 and 13) indicated that thiosulfonate **40** and disulfide **41** were the only identifiable side products along with numerous unknown side products by ^{19}F NMR spectroscopy. Et_3SiH was known as an excellent scavenger for trapping Tr^+,[129] however, adding this reagent in the reactions did not prove beneficial (Entry 5−6, 11, 14, 19).

Table 4.12 Deprotection of trityl-sulfinamide

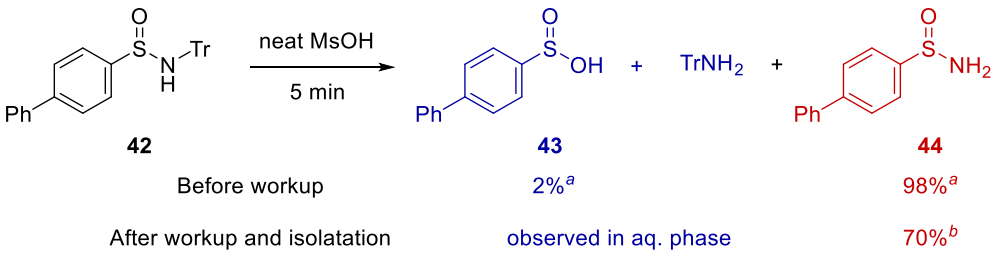


Entry	R	Reagent[a]	Temperature	Result[b]
1	Me	$BF_3 \cdot Et_2O$ (1.5), dioxane (0.13 M)	rt	No reaction
2	Me	1 M BCl_3 in CH_2Cl_2 (2), dioxane (0.13 M)	rt	Mainly $TrNH_2$
3	Me	2 M HCl in Et_2O (2), dioxane (0.13 M)	rt	Mainly $TrNH_2$
4	Me	TsOH (2), dioxane (0.13 M)	rt	Mainly $TrNH_2$
5	Me	TsOH (2), Et_3SiH (2), dioxane (0.13 M)	rt	Mainly $TrNH_2$
6	Me	TsOH (2), Et_3SiH (2), CH_2Cl_2 (0.13 M)	rt or 0 ℃→rt	Mainly $TrNH_2$
7	Me	MsOH (5), THF (0.17 M)	rt	Mainly $TrNH_2$
8	Me	MsOH (5), Et_3SiH (2), THF (0.17 M),	rt	Mainly $TrNH_2$
9	Me	10 mol% Pd/C, H_2 (ballon), EtOH (0.1 M)	45 ℃	Mainly $TrNH_2$
10	F	TFA (0.5 M), CH_2Cl_2 (0.4 M)	rt	Mainly $TrNH_2$
11	F	TFA (0.5 M), Et_3SiH (2), CH_2Cl_2 (0.4 M)	rt	Complex[c]+$TrNH_2$
12	F	TsOH (1), CH_2Cl_2 (0.4 M)	rt	Mainly $TrNH_2$
13	F	TfOH (1.1), CH_2Cl_2 (0.4 M)	rt	Complex[c]+$TrNH_2$
14	F	TfOH (1.1), Et_3SiH (2), CH_2Cl_2 (0.4 M)	rt	Complex+$TrNH_2$
15	F	CAN (2.5), MeCN (0.92 M), H_2O (1.71 M)	0 ℃	Mainly $TrNH_2$
16	F	CAN (2.5), MeCN (0.92 M), H_2O (1.71 M)	80 ℃	Complex+$TrNH_2$
17	F	CAN (20 mol%), AcOH (10), H_2O (15), CH_2Cl_2 (1 M)	rt	Mainly $TrNH_2$
18	F	MsOH (0.63 M), THF (0.18 M)	−78 ℃→rt	Mainly $TrNH_2$
19	F	MsOH (0.63 M), Et_3SiH (3.1), THF (0.18 M),	−78 ℃→rt	Mainly $TrNH_2$
20	F	Neat MsOH (0.04 M)	rt	19% $TrNH_2$ + 81% TrOH[d]
21	F	MsOH (1), *t*-AmylOH (0.1 M)	rt	Mainly $TrNH_2$

[a]Equivalents of reagent was written in the brackets. [b]analysed by HPLC spectroscopy. $TrNH_2$ meant the S−N bond was cleaved (followed by the blue arrow in Scheme 4.17). TrOH meant the desired C−N bond was cleaved (followed by the red arrow in Scheme 4.17). No TrOH was observed for all entries except entry 20. [c]thiosulfonate **40** and disulfide **41** was identified as the side products by ^{19}F NMR analysis [d]The yields of $TrNH_2$ and TrOH were determined by the absorption areas by HPLC analysis.

Although MsOH (melting point: 20 ℃) instantly solidified when it was added into the THF solution of trityl-sulfinamide **23** at −78 ℃ (Entry 18), a distinctive yellow colour of trityl cation Tr^+ was surprisingly observed around the solidified MsOH. This phenomenon suggested that the deprotection may be feasible when neat MsOH was used, even though the yellow colour disappeared and only $TrNH_2$ (formed by S−N bond cleavage) was detected when the reaction was warmed up to rt. Gratefully, the desired C−N bond cleavage and the primary sulfinamide **39b** was observed for the first time when neat MsOH was used (Entry 20), along with some S−N bond cleavage products. The result was surprising as the C−N bond could only be cleaved in neat acid but not in any other organic solvents tested. This may be because MsOH is a protic polar solvent that favours the S_N1 mechanism to cleave the C−N bond, producing the trityl cation Tr^+ over the competing S_N2 mechanism to cleave the S−N bond. Using *t*-AmylOH as the polar protic solvent with 1 equiv. of MsOH was also unsuccessful (entry 21).

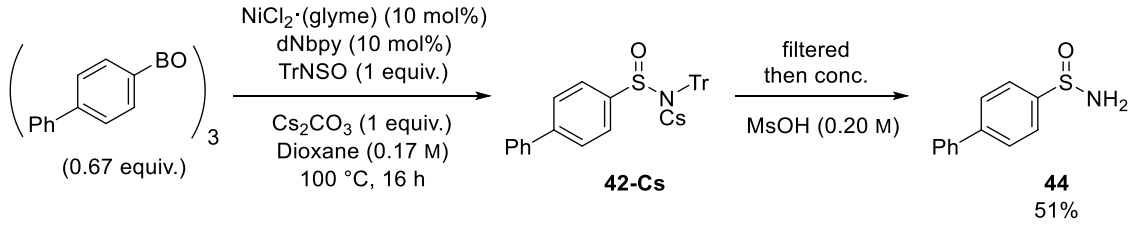
We then changed the core of trityl-sulfinamide from the 4−fluorophenyl core with a biphenyl core because the latter was more UV active and was therefore more easily observable on HPLC spectrometry. The trityl group of sulfinamide **42** was cleanly deprotected in neat MsOH, giving an excellent 98% of C−N bond cleavage product (primary sulfinamide **44**) before aqueous workup (Scheme 4.18). However, after quenching the reaction with sat. aq. $NaHCO_3$, a significant amount of the undesired biphenyl sulfinate **43** was observed in the aqueous phase and only 70% of the desired primary sulfinamide **44** was isolated. This indicated that the protonated primary sulfinamide **44** was still able to undergo S_N2 reaction with H_2O as the nucleophile. Quenching the reaction with non-aqueous bases, NEt_3 or the non-nucleophilic DIPEA, was unsuccessful, as mainly sulfinate **43** was detected after the aqueous workup.



[a]The yields of the sulfinic acid **43** and the sulfinamide **44** were determined by the absortion areas by HPLC analysis. [b]Isolated yield

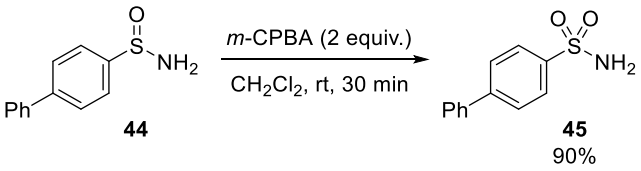
Scheme 4.18 Deprotection of trityl-sulfinamide **42**

Accordingly, we set up the nickel-catalysis to form trityl-sulfinamide **42-Cs** and then filtered any insoluble solid, in particular the base, Cs_2CO_3. The filtrate was then concentrated to dryness and treated with neat MsOH. After quenching with sat. aq. $NaHCO_3$, the desired primary sulfinamide **44** was isolated in a moderate 51% yield.



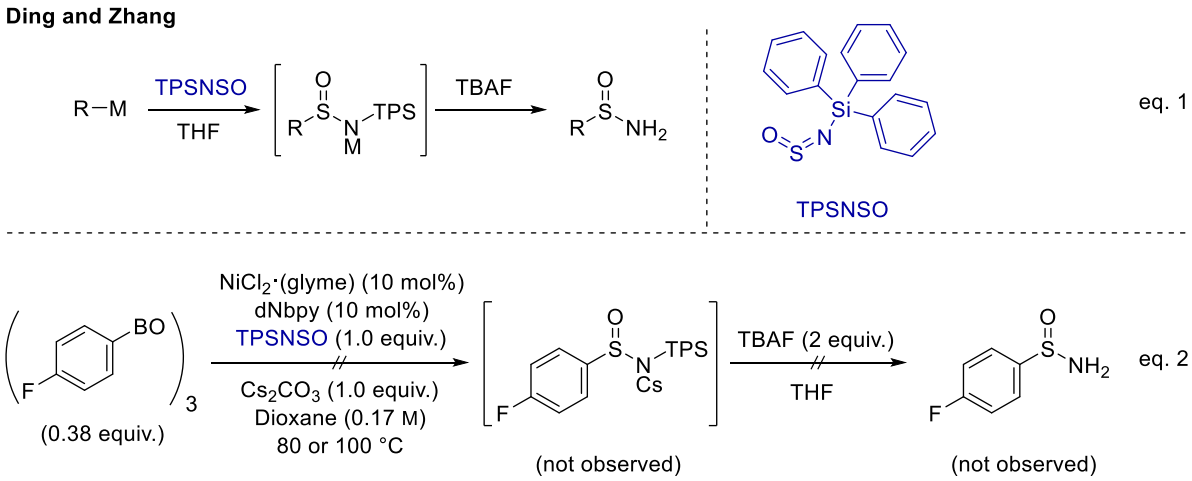
Scheme 4.19 Nickel-catalysed synthesis of trityl-sulfinamide and its deprotection

We also showed that the primary sulfinamide **44** can be smoothly oxidised to the primary sulfonamide **45** with *m*-CPBA in CH_2Cl_2 (Scheme 4.20), providing an alternative pathway to access primary sulfonamide.[97a] However, the hydrolysis of sulfonimidoyl chlorides to synthesise sulfonamides shown in Table 4.11 is more preferable because it is a one-pot reaction and generally gives high yields of products.



Scheme 4.20 Oxidation of primary sulfinamide to primary sulfonamide

An alternative method to access primary sulfinamides was also explored. Two DPhil members in our group, Mingyan Ding and Ze-Xin Zhang, developed a new sulfinylamine reagent, TPSNSO (Scheme 4.21). Treating TPSNSO with organometallic reagents produced the silyl-protected sulfinamides, which could be deprotected by treatment with a fluoride source to give primary sulfinamides (eq. 1). However, using the developed nickel-catalysed conditions and replacing TrNSO with TPSNSO did not produce the corresponding silyl-protected or primary sulfinamide (eq. 2). This may be due to the TPSNSO being thermally unstable and hence decomposed under the heating conditions.

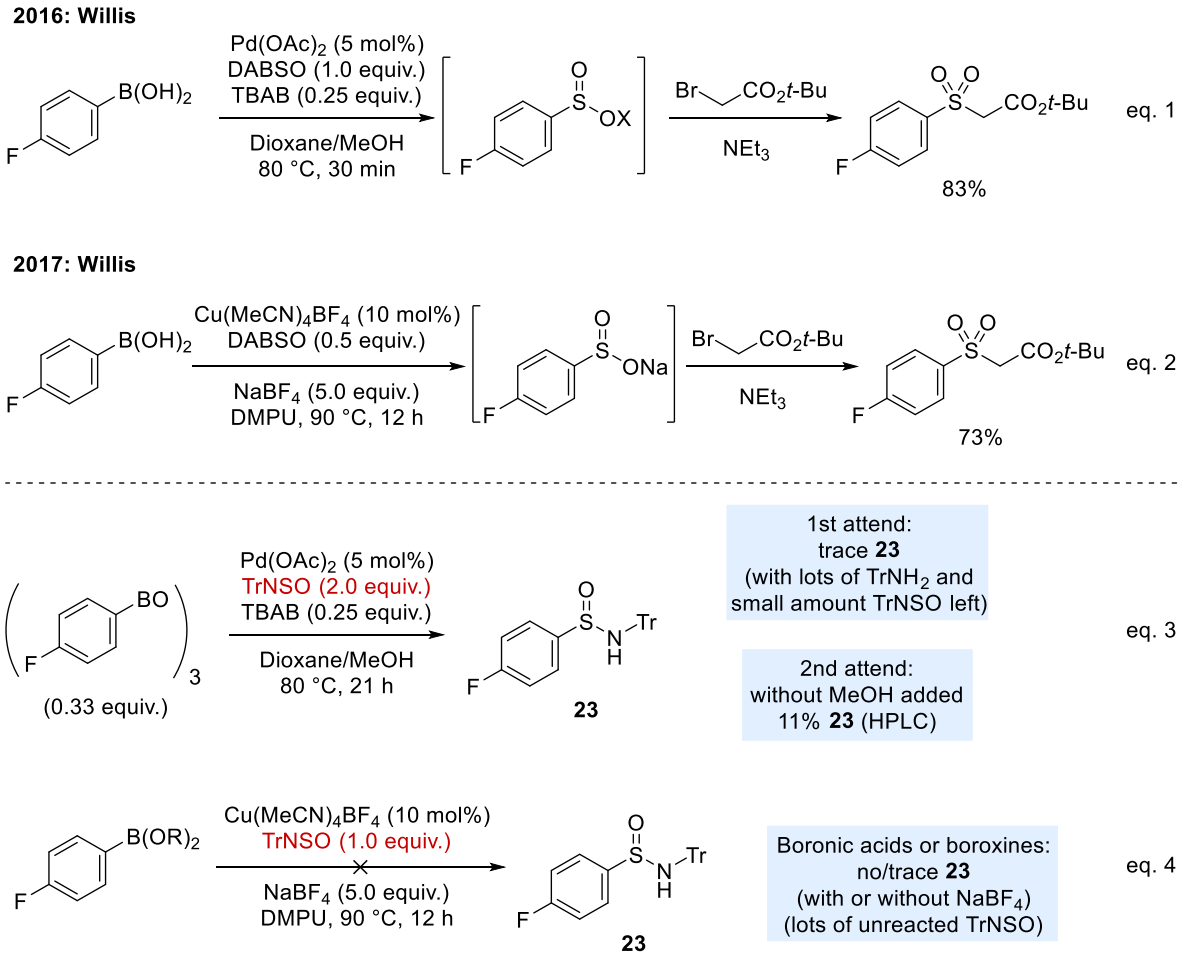


Scheme 4.21 Primary sulfinamide synthesis using TPSNSO as the sulfinylamine

4.4.7 Alternative metal catalysis

Methods using alternative metal catalysis to make sulfinamides with TrNSO as the sulfinylamine were also explored. Our group had previously developed the sulfination of aryl boronic acids using palladium[71] or copper catalysis (Scheme 4.22, eq. 1 and 2).[74] Using the same palladium-catalysed conditions, but replacing DABSO with TrNSO and

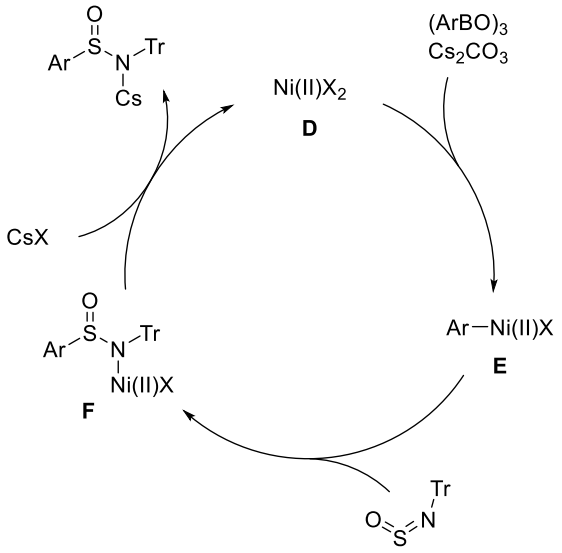
boronic acid with boroxine, gave only a trace amount of the sulfinamide **23**, along with lots of $TrNH_2$ perhaps from the reaction between TrNSO and MeOH (eq. 3). Repeating the reaction without the addition of MeOH produced 11% of the sulfinamide **23** as the preliminary result. However, no sulfinamide **23** was observed in copper-catalysed conditions, neither with a boronic acid or boroxine as the starting materials. TrNSO was recovered, suggesting that it was unreactive under the copper-catalysed process.



Scheme 4.22 Alternative metal catalysis to make sulfinamides with TrNSO

4.5 Reaction mechanism

We proposed that the reaction mechanism (Scheme 4.23) would be similar to the nickel-catalysed sulfination of arylboronic acids (chapter 2.4). First, arylboroxine undergoes transmetalation to the Ni(II) catalyst **D** with the facilitation of the base Cs_2CO_3 to give the Ar–Ni(II) complex **E**. Migratory insertion of TrNSO into this complex gives nickel sulfinamide complex **F**, which undergoes ligand exchange with a caesium salt to release the desired caesium sulfinamide salt and regenerates the Ni(II) complex **D**.



Scheme 4.23 Proposed mechanism of the nickel-catalysed synthesis of sulfinamides

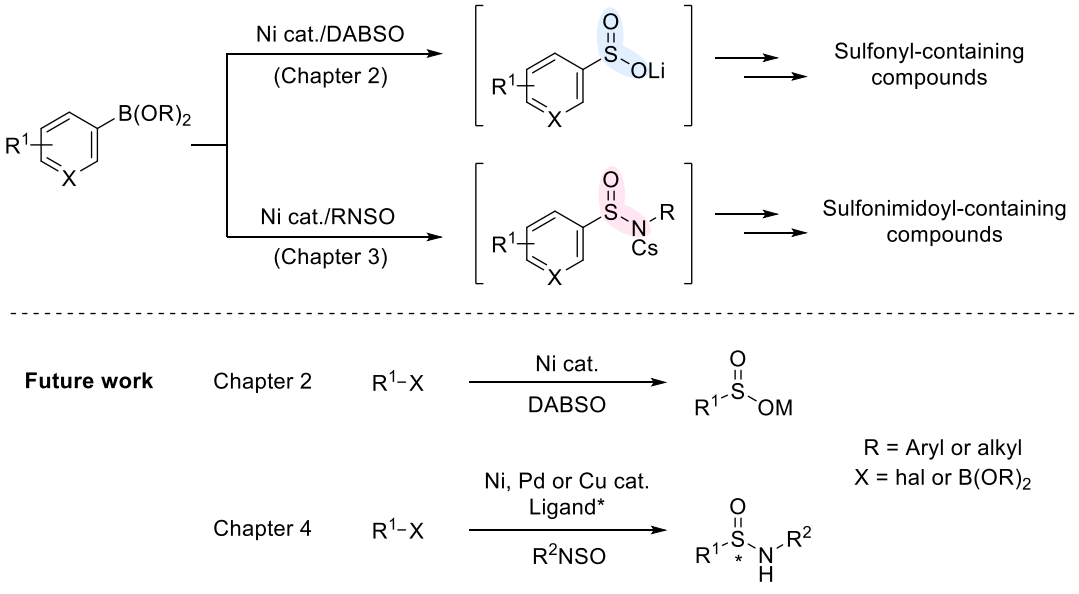
4.6 Summary

In summary, the first example of the nickel-catalysed synthesis of sulfinamides using sulfinylamines has been developed. This method is redox-neutral, using (hetero)arylboroxines and TrNSO as the sulfinylamine. The nickel-catalysed method can be scaled up to a 1 mmol scale using just 1 mol% catalyst. The *in situ* formed trityl-sulfinamides were efficiently chlorinated to sulfonimidoyl chlorides with TCCA as an inexpensive and safe oxidant. A range of sulfonimidoyl-containing compounds, including sulfonimidamides, sulfonamides and sulfonimidoyl fluorides were prepared by elaborating the sulfonimidoyl chlorides in a one-pot reaction. Deprotection of the trityl-sulfinamide was also feasible to produce the primary sulfinamide. A biologically relevant aryl system and several amines were employed, providing a good demonstration of this method in complex compound synthesis. An alternative palladium-catalysed synthesis of sulfinamide, from arylboroxines and TrNSO, also showed a promising preliminary result.

5. Conclusion and Future Work

A range of synthetically useful methods has been developed by our group and others to access sulfonyl or sulfinyl-containing compounds since the pioneering work to use DABSO as a convenient and easy-to-use sulfur dioxide surrogate in a palladium-catalysed aminosulfonylation. These transformations have recently been extended to sulfinylamines, the mono-aza analogue of sulfur dioxide, to deliver nitrogen-containing sulfur functional groups. In this thesis, we further demonstrated the use of DABSO as the SO_2 surrogate and sulfinylamines in combination with metal catalysis or organometallic reagents to synthesise pharmaceutically relevant sulfur-containing compounds.

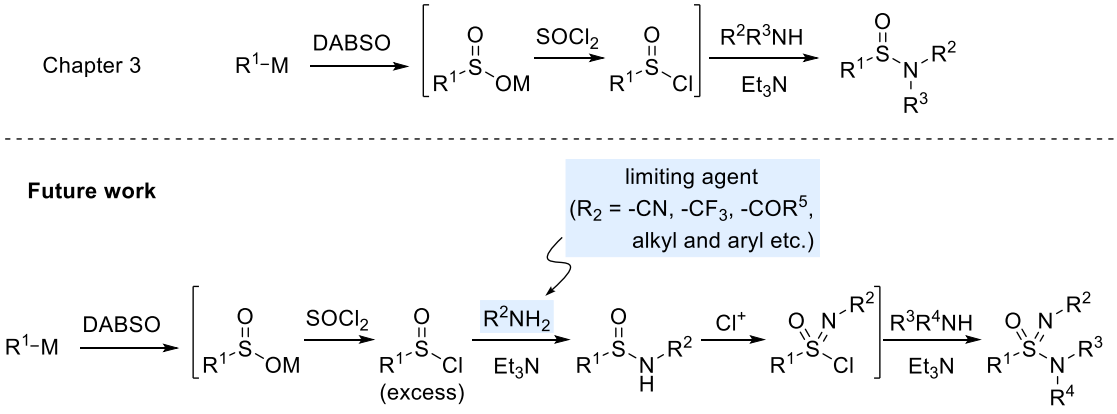
In chapters 2 and 4, aryl boron reagents were combined with DABSO as the SO_2 surrogate, and TrNSO or *t*-OctNSO as sulfinylamines under nickel catalysis to prepare sulfinate salts and sulfinamides as the intermediates, respectively. These two building blocks were further derivatised to yield a range of sulfonyl and sulfonimidoyl-containing functional groups.



Scheme 5.1 Summary of chapters 2 and 4 and their potential future works

Future work would extend the chemistry to aryl halides and alkyl systems, thus allowing the use of a broader spectrum of starting materials (Scheme 5.1). In addition, chiral ligands would be used in the Ni/TrNSO protocol to allow the asymmetric synthesis of sulfinamides, which would be a ground-breaking development in the sulfinylamine chemistry. Methods using other metal catalysts, such as palladium and copper, and other sulfinylamines will also be studied.

In chapter 3, sulfinates were formed by treating DABSO with organometallic reagents and were subsequently treated with thionyl chloride and amines to give sulfinamides (Scheme 5.2). The chemistry would be further studied to react the *in situ* formed sulfinamide with a chlorinating agent and an amine to form sulfonimidamides rapidly in a one-pot five-step reaction (Scheme 5.2). The first amine would be a functionised primary amine and will be used as a limiting agent, which would all be consumed and hence would not react with sulfonimidoyl chloride. Compared to the use of TrNSO, this reaction sequence would not require a deprotection step to remove the trityl group and instead would install the desired functional group R^2 directly in the amination step.



Scheme 5.2 Summary of chapters 2 and 4 and the potential future works

6. Experimental Section

6.1 General information

Reactions were performed under inert nitrogen atmosphere with anhydrous solvent unless otherwise stated. Reagents were purchased from Sigma-Aldrich, Fisher Scientific, Fluorochem, Tokyo Chemical Industry UK or Strem Chemicals and were used as supplied unless otherwise stated. Other solvents, if stated as anhydrous, were collected fresh from an in-house solvent purification system, which involves passing the solvent through anhydrous alumina columns. Glassware was oven-dried, and allowed to cool to room temperature under nitrogen. Cooling to 0 ℃ was achieved using ice-water bath. Reactions were monitored by HPLC analysis and/or thin layer chromatography (TLC) using pre-coated aluminum-backed silica plates (Merck Kieselgel 60 F254). Plates were visualised under ultraviolet light (254 nm) followed by staining with $KMnO_4$. Flash column chromatography was carried out using Geduran® Si 60, 40-63 micron silica gel; the compound to be purified was either loaded as oil or pre-absorbed onto silica. Petrol refers to the fraction of light Petroleum ether boiling in the range 40-60 ℃.

^{1}H NMR spectra were obtained on a Bruker AVIII HD 400 (400 MHz), AVII 500 (500 MHz) or AVIII HD 500 (500 MHz) spectrometer using the residual solvent as an internal standard. ^{13}C NMR spectra were obtained on a Bruker AVIII HD 400 (101 MHz), AVII 500 (126 MHz) or AVIII HD 500 (126 MHz) spectrometer using the ^{1}H decoupling method and the residual solvent as an internal standard. ^{19}F NMR spectra were obtained on a Bruker AVIII

HD 400 (377 MHz) spectrometer using the ^{1}H decoupling method. Acquisitions were carried out at room temperature unless otherwise stated. Chemical shifts (δ) are reported in parts per million (ppm) from the residual solvent peak and coupling constants (*J*) were given in Hertz (Hz) and rounded to the nearest 0.5 Hz. Proton multiplicity is assigned using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), quintet (p), multiplet (m), broad (br), apparent (app.).

Low resolution ESI mass spectra were recorded on a Waters LCT Premier spectrometer. High resolution mass spectra were recorded either on a Bruker MicroTOF spectrometer under electrospray ionization conditions (ESI) or on a Waters LCT Premier spectrometer under the conditions of chemical ionization (CI) by the internal service at Chemistry Research Laboratory, University of Oxford. Samples for mass spectra were prepared as 1 mg/mL solution in MeOH (LRMS, HRMS-ESI) or submitted neat (HRMS-CI). Values quoted are a ratio of mass to charge in Daltons. High resolution values are calculated to four decimal places from the molecular formula, all found within a tolerance of five ppm.

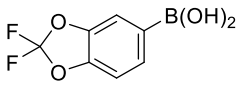
Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Melting points were determined using a Stuart Scientific Melting Point Apparatus SMP1.

Optical rotations were measured on a Schmidt Haensch UniPol L2000 polarimeter at 589 nm, 25 °C. $[\alpha]_D^T$ is expressed in deg cm^3 g^{-1} dm^{-1} and c is expressed in g/100 cm^3. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC in a Dionex P680 chromatograph with a Dionex UVD170U detector (Daicel Chiralpak IC column).

6.2 Data for chapter 2

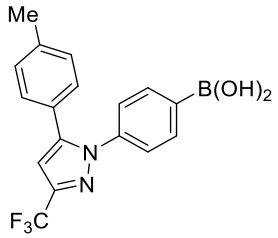
6.2.1 Preparation of aryl boronic acids

Preparation of (2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)boronic acid[130]



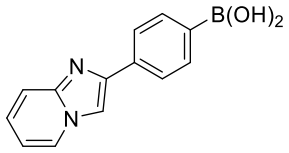
The title boronic acid was prepared using a literature method.[130]

Preparation of (4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)boronic acid[35]



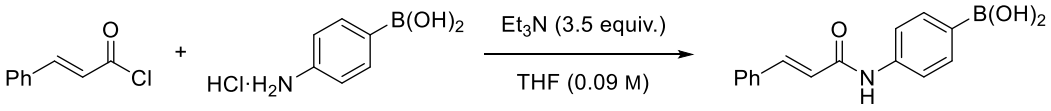
The title boronic acid was prepared using a modified literature method.[35] The trituration was done with pentane instead of EtOAc.

Preparation of (4-(imidazo[1,2-*a*]pyridin-2-yl)phenyl)boronic acid[131]



The title boronic acid was prepared using a literature method.[131]

Synthesis of (4-cinnamamidophenyl)boronic acid



In a 50 mL round bottom flask, 4-aminophenylboronic acid hydrochloride (173 mg, 1.0 mmol, 1.0 equiv.) in THF (10 mL) was added Et_3N (0.49 mL, 3.5 mmol, 3.5 equiv.) (*note 1*). With stirring, cinnamoyl chloride (167 mg, 1.0 mmol, 1.0 equiv.) in THF (1 mL) was added dropwise to the mixture. The mixture was stirred at rt overnight. With stirring and/or sonication, the mixture was acidified to pH 2-3 with conc. HCl (*ca.* 11-12 drops). All volatiles were removed under reduced pressure. To the resultant solid was added CH_2Cl_2 and H_2O (*ca.* 10 mL each). The mixture was sonicated until the solid became free-flowing. The solid was filtered under vacuum, washed with CH_2Cl_2 and a small amount of Et_2O, and further dried under suction to afford the product as an off-white solid (84 mg, 31%) (*note 2*).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H, N*H*), 7.91 (s, 2H, B(O*H*)$_2$), 7.75 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.69 – 7.55 (m, 5H, Ar-*H* and COCH=C*H*), 7.48 – 7.39 (m, 3H, Ar-*H*), 6.85 (d, *J* = 15.5 Hz, 1H, COC*H*=CH); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 163.6, 140.9, 140.3, 134.9, 134.7, 129.8, 129.0, 128.7, 127.7, 122.3, 118.0; **LRMS** (ESI$^+$) *m/z* 535.2 ([2M+H]$^+$); **HRMS** (ESI$^+$) *m/z* $C_{15}H_{15}O_3NB^+$ requires 268.1140 [M+H]$^+$, found 268.1141; **IR** (thin film, ν_{max}/cm^{-1}) 3293, 2360, 1660, 1344; **m.p.** (Et_2O): 173-175 ℃.

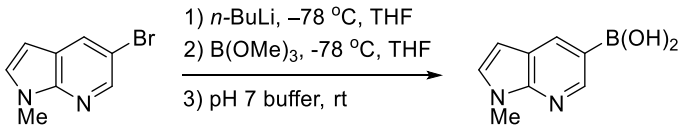
Note:

1. 4-Aminophenylboronic acid hydrochloride was purchased from Carbosynth (CAS No: 80460-73-7; Product Code: FA33740). It was quite insoluble in THF. All solvent used in this reaction was not dried.

2. The desired product is very soluble in THF, modest soluble in acetone, MeOH and EtOAc, slightly soluble in Et_2O, and almost insoluble in CH_2Cl_2.

3. Later reactions showed that using the corresponding boronic acid, by free basing the boronic acid·HCl with sat. aq. $NaHCO_3$ before use, gave cleaner reactions with better product yields.

Synthesis of (1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)boronic acid[35, 82d]



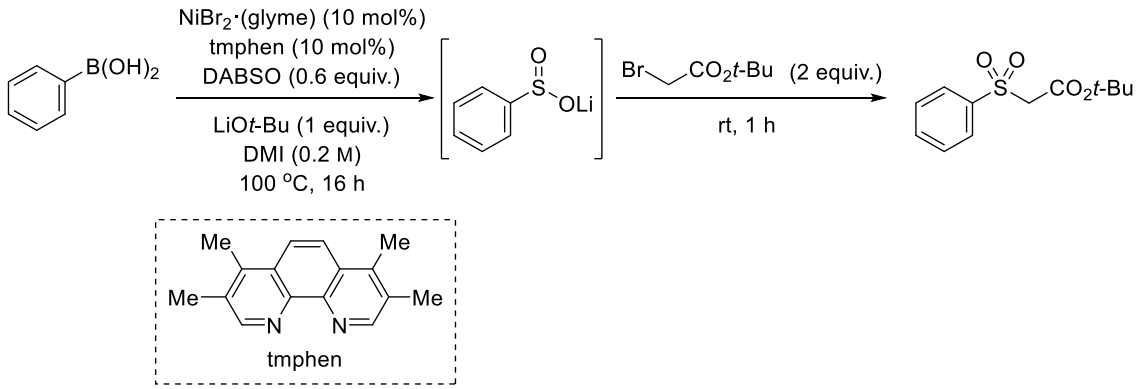
5-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine[132] (307 mg, 1.45 mmol, 1.0 equiv.) was dissolved in anhydrous THF (9 mL) and cooled to –78 °C. *n*-BuLi (0.73 mL of a 2.2 M solution in hexane, 1.61 mmol, 1.1 equiv.) was added dropwise. The resulting solution was stirred at –78 °C for 1.5 h. $B(OMe)_3$ (0.25 mL, 2.24 mmol, 1.5 equiv.) was added dropwise, before the solution was warmed to rt and stirred at this temperature for 1.5 h. pH 7 buffer solution (9 mL) was then added and the mixture was stirred at rt for 2 h. The mixture was partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc (× 2). The combined organic phases were washed with water and brine, dried (Na_2SO_4) and concentrated. The resultant solid was triturated with Et_2O to afford the product as a pale yellow solid (95 mg, 37%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (d, *J* = 1.5 Hz, 1H, Ar-*H*), 8.34 (d, *J* = 1.5 Hz, 1H, Ar-*H*), 8.06 (s, 2H, B(O*H*)$_2$), 7.46 (d, *J* = 3.5 Hz, 1H, Ar-*H*), 6.46 (d, *J* = 3.5 Hz, 1H, Ar-*H*), 3.81 (s, 3H, N*Me*); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 148.5, 134.7, 129.7, 119.4, 119.1, 99.2, 30.81, 1 × Ar*C* not observed; **LRMS** (ESI$^+$) *m/z* 177.1 ([M+H]$^+$); **HRMS** (ESI$^+$) *m/z* $C_8H_{10}O_2N_2B^+$ requires 177.0830 [M+H]$^+$, found 177.0831; **IR** (thin film, ν_{max}/cm^{-1}) 3102, 1598, 1331, 1262, 1186, 721; **m.p.** (Et_2O): 288-289 °C.

6.2.2 Synthesis of sulfones

General Procedure A: Two-step synthesis of sulfones (exemplified by the preparation of sulfone **7a**)

***tert*-Butyl 2-(phenylsulfonyl)acetate (7a)**[71]



Phenylboronic acid (24.4 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) were added to a 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 (× 4) (*note 4*). DMI (1.0 mL) was added and the reaction mixture was heated at 100 ℃ for 16 h. The solution was cooled to rt. *tert*-Butylbromoacetate (60 µL, 0.40 mmol, 2.0 equiv.) was then added and the reaction was stirred at rt for 1 h. The reaction was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (40% Et_2O in Petrol) afforded the product as a colourless oil (44.9 mg, 88%).

R_f (40% Et_2O in Petrol) = 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.67 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.57 (t, *J* = 8.0 Hz, 2H, Ar-*H*), 4.03 (s, 2H, C*H*$_2$), 1.34 (s, 9H, C*Me*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.3, 139.0, 134.2, 129.2, 128.6, 83.7, 62.2, 27.8; **LRMS** (ESI^+) *m/z* 279.0 ($[M+Na]^+$), 535.1 ($[2M+Na]^+$). Data is consistent with the literature.[71]

Note:

1. $NiBr_2$·(glyme) was purchased from Sigma-Aldrich or Strem Chemicals. Tmphen was purchased from Sigma-Aldrich, Tokyo Chemical Industry UK or Alfa Aesar. DABSO was prepared using literature method.[29] LiO*t*-Bu was purchased from Strem Chemicals. DMI was from a Sigma-Aldrich Sure/Seal bottle (≥99.5% (GC), catalog no.: 40725-100ML).

2. $NiBr_2$·(glyme) is slightly deliquescent and discolours from orange to yellow after exposure to air for prolonged time. Although we did not recognise any significant change in reactivity, we suggest the catalyst is flushed and stored under N_2 every time after used.

3. We find that anhydrous DMI gave more consistent results.

4. The reaction was evacuated (< 5 mbar) and filled with N_2 (× 4). The first evacuation was at least 5 min. The remaining three times were at least 1 min.

5. All reaction were easily monitored by HPLC analysis for the conversion of boronic acids to sulfinates in step 1 and the conversion of sulfinates to products in step 2.

6. In step 1, protodeboronation products were generally the major and usually the only side products formed.

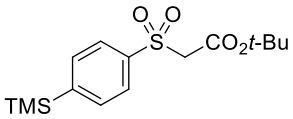
7. In some cases, the reaction mixture would become a gel in the alkylation step (step 2), especially with the less reactive boronic acids. The alkylation reactions were generally fast and all sulfinates should have converted into the desired product (observed by HPLC analysis) before the mixture turned to a gel.

8. In some cases, the aqueous and organic phases did not separate. Usually, adding more water and EtOAc would solve the problem.

9. The crude product was dry-loaded with silica gel on a pre-packed silica gel column.

10. DMI has a high boiling point (225 ℃) and it dissolves in both water and EtOAc, but is only slightly soluble in Et_2O. Generally the crude products contain certain amount of DMI especially when EtOAc was used in the aqueous workup. The DMI in the crude product can be removed using flash column chromatography. More silica gel is suggested to use if > 60% EtOAc in Petrol is used as the eluting solvent because DMI could coelute with the desired product. Occasionally, DMI could be removed by washing the combined organic phases in aqueous workup with H_2O five times.

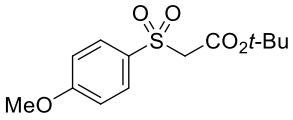
tert-Butyl 2-((4-(trimethylsilyl)phenyl)sulfonyl)acetate (7b)[21c]



Prepared according to general procedure A using 4-(trimethylsilyl)phenylboronic acid (38.8 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (20% Et_2O in Petrol) afforded the title product as a colourless oil (58.9 mg, 90%).

R_f (20% Et_2O in Petrol) = 0.12; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.70 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.02 (s, 2H, CH_2), 1.34 (s, 9H, CMe_3), 0.29 (s, 9H, SiMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.4, 149.0, 139.2, 134.0, 127.4, 83.6, 62.2, 27.7, -1.3; **LRMS** (ESI^+) *m/z* 351.1 ($[M+Na]^+$), 679.2 ($[2M+Na]^+$). Data is consistent with the literature.[21c]

tert-Butyl 2-((4-methoxyphenyl)sulfonyl)acetate (7c)[71]

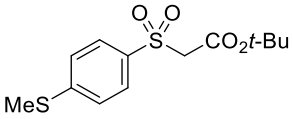


Prepared according to general procedure A using 4-methoxyphenylboronic acid (30.4 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (40% Et_2O in Petrol)

afforded the title product as a colourless oil (52.3 mg, 91%).

R_f (40% Et_2O in Petrol) = 0.22; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.01 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 3.99 (s, 2H, CH_2), 3.87 (s, 3H, O*Me*), 1.37 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.2, 161.6, 130.9, 130.5, 114.4, 83.5, 62.4, 55.8, 27.8; **LRMS** (ESI^+) *m/z* 309.1 ($[M+Na]^+$), 595.1 ($[2M+Na]^+$). Data is consistent with the literature.[71]

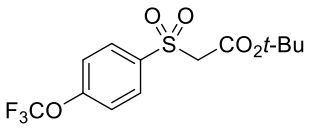
***tert*-Butyl 2-((4-(methylthio)phenyl)sulfonyl)acetate (7d)**[21c]



Prepared according to general procedure A using 4-(methylthio)phenylboronic acid (33.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (25% EtOAc in Petrol) afforded the title product as a yellow oil (42.7 mg, 71%).

R_f (25% EtOAc in Petrol) = 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.33 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.00 (s, 2H, CH_2), 2.51 (s, 3H, S*Me*), 1.38 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.5, 148.0, 134.6, 128.9, 125.3, 83.7, 62.3, 27.8, 14.8; **LRMS** (ESI^+) *m/z* 325.1 ($[M+Na]^+$), 627.1 ($[2M+Na]^+$). Data is consistent with the literature.[21c]

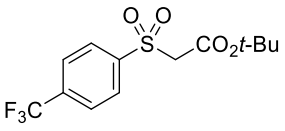
tert-Butyl 2-((4-(trifluoromethoxy)phenyl)sulfonyl)acetate (7e)[73]



Prepared according to general procedure A using 4-(trifluoromethoxy)phenylboronic acid (41.2 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (10-15% EtOAc in Petrol) afforded the title product as a colourless oil (54.8 mg, 81%).

R_f (10% EtOAc in Petrol) = 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 – 7.97 (m, 2H, Ar-*H*), 7.42 – 7.36 (m, 2H, Ar-*H*), 4.05 (s, 2H, CH_2), 1.36 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.1, 153.3 (q, *J* = 1.5 Hz), 137.1, 131.0, 120.8, 120.2 (q, *J* = 260.0 Hz), 83.9, 62.0, 27.7; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -57.7; **LRMS** (ESI^+) *m/z* 363.0 ($[M+Na]^+$). Data is consistent with the literature.[73]

tert-Butyl 2-((4-(trifluoromethyl)phenyl)sulfonyl)acetate (7f)

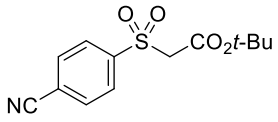


Prepared according to general procedure A using 4-(trifluoromethyl)phenylboronic acid (38.0 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu

(16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (40% Et_2O in Petrol) afforded the title product as a colourless oil which solidified to an off-white solid when left standing (53.5 mg, 82%).

R_f (40% Et_2O in Petrol) = 0.35; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.85 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 4.07 (s, 2H, C*H*$_2$), 1.37 (s, 9H, C*Me*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.1, 142.5, 135.9 (q, J_{CF} = 33.5 Hz), 129.4, 126.4 (q, J_{CF} = 4.0 Hz), 123.2 (q, J_{CF} = 273.0 Hz), 84.2, 61.9, 27.8; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -63.3; **LRMS** (ESI^+) *m/z* 347.1 ($[M+Na]^+$), 671.1 ($[2M+Na]^+$); **HRMS** (ESI^+) *m/z* $C_{13}H_{15}O_4F_3NaS^+$ requires 347.0535 $[M+Na]^+$, found 347.0536; **IR** (thin film, ν_{max}/cm^{-1}) 1733, 1404, 1322, 1165, 1145, 1187, 1063; **m.p.** (CH_2Cl_2): 95-97 °C.

***tert*-Butyl 2-((4-cyanophenyl)sulfonyl)acetate (7g)**[21c]

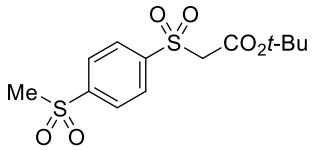


Prepared according to general procedure A using 4-cyanophenylboronic acid (29.4 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (40% Et_2O in Petrol) afforded the title product as a pale yellow solid (42.1 mg, 75%).

R_f (40% Et_2O in Petrol) = 0.19; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.87 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.07 (s, 2H, C*H*$_2$), 1.38 (s, 9H, C*Me*$_3$); **^{13}C NMR**

(101 MHz, $CDCl_3$) δ 161.0, 143.0, 133.0, 129.5, 118.0, 117.1, 84.4, 61.7, 27.8; **LRMS** (ESI^+) *m/z* 304.1 ($[M+Na]^+$), 585.1 ($[2M+Na]^+$). Data is consistent with the literature.[21c]

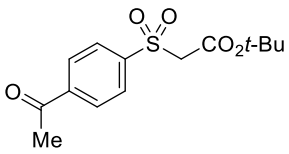
***tert*-Butyl 2-((4-(methylsulfonyl)phenyl)sulfonyl)acetate (7h)**[73]



Prepared according to general procedure A using 4-(methanesulfonyl)phenylboronic acid (40.0 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (50% EtOAc in Petrol) afforded the title product as a white solid (49.9 mg, 75%).

R_f (50% EtOAc in Petrol) = 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (app. s, 4H, Ar-*H*), 4.09 (s, 2H, C*H*$_2$), 3.09 (s, 3H, SO_2*Me*), 1.37 (s, 9H, C*Me*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.9, 145.8, 144.0, 129.9, 128.4, 84.4, 61.8, 44.4, 27.8; **LRMS** (ESI^+) *m/z* 357.1 ($[M+Na]^+$), 691.1 ($[2M+Na]^+$). Data is consistent with the literature.[73]

***tert*-Butyl 2-((4-acetylphenyl)sulfonyl)acetate (7i)**[21c]

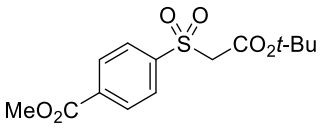


Prepared according to general procedure A using 4-acetylphenylboronic acid (32.8 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg,

0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (60% Et_2O in Petrol) afforded the title product as a white solid (41.4 mg, 69%).

R_f (60% Et_2O in Petrol) = 0.22; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 8.03 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.06 (s, 2H, CH_2), 2.65 (s, 3H, CO*Me*), 1.36 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.7, 161.1, 142.7, 141.2, 129.1, 128.9, 84.1, 61.9, 27.8, 27.0; **LRMS** (ESI^+) *m/z* 321.1 ($[M+Na]^+$), 619.2 ($[2M+Na]^+$). Data is consistent with the literature.[21c]

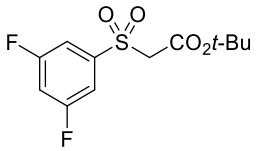
Methyl 4-((2-(*tert*-butoxy)-2-oxoethyl)sulfonyl)benzoate (7j)[21c]



Prepared according to general procedure A using 4-methoxycarbonylphenylboronic acid (36.0 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (40% Et_2O in Petrol) afforded the title product as a white solid (46.0 mg, 73%).

R_f (40% Et_2O in Petrol) = 0.17; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 8.01 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.06 (s, 2H, CH_2), 3.96 (s, 3H, CO_2*Me*), 1.35 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.5, 161.1, 142.8, 135.2, 130.3, 128.8, 84.1, 62.0, 52.9, 27.8; **LRMS** (ESI^+) *m/z* 337.1 ($[M+Na]^+$), 651.1 ($[2M+Na]^+$). Data is consistent with the literature.[21c]

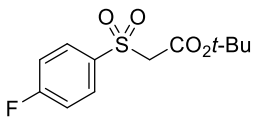
tert-Butyl 2-((3,5-difluorophenyl)sulfonyl)acetate (7k)[73]



Prepared according to general procedure A using 3,5-difluorophenylboronic acid (31.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (10% EtOAc in Petrol) afforded the title product as a colourless oil (38.8 mg, 66%).

R_f (10% EtOAc in Petrol) = 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 2H, Ar-*H*), 7.13 (tt, *J* = 8.4, 2.3 Hz, 1H, Ar-*H*), 4.05 (s, 2H, CH_2), 1.40 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 (dd, *J* = 255.5, 11.5 Hz), 160.9, 142.2 (t, *J* = 8.5 Hz), 112.4 (m), 109.9 (t, *J* = 25.0 Hz), 84.4, 61.9, 27.8; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -105.0; **LRMS** (ESI^+) *m/z* 293.0 ($[M+H]^+$), 315.0 ($[M+Na]^+$). Data is consistent with the literature.[73]

tert-Butyl 2-((4-fluorophenyl)sulfonyl)acetate (7l)[71]

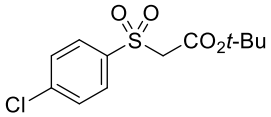


Prepared according to general procedure A using 4-fluorophenylboronic acid (28.0 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (40% Et_2O in Petrol)

afforded the title product as a colourless oil (49.0 mg, 89%).

R_f (40% Et_2O in Petrol) = 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 – 7.94 (m, 2H, Ar-*H*), 7.30 – 7.22 (m, 2H, Ar-*H*), 4.04 (s, 2H, CH_2), 1.39 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.2 (d, J_{CF} = 257.0 Hz), 161.4, 135.1 (d, J_{CF} = 3.0 Hz), 131.7 (d, J_{CF} = 10.0 Hz), 116.6 (d, J_{CF} = 23.0 Hz), 83.9, 62.2, 27.8; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -102.7; **LRMS** (ESI^+) *m/z* 571.1 ($[2M+Na]^+$). Data is consistent with the literature.[71]

***tert*-Butyl 2-((4-chlorophenyl)sulfonyl)acetate (7m)**[21c]



Prepared according to general procedure A using 4-chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (30% Et_2O in Petrol) afforded the title product as a colourless oil (51.1 mg, 88%).

The same procedure was followed but using $NiBr_2$·(glyme) (3.1 mg, 0.01 mmol, 5 mol%) and tmphen (2.4 mg, 0.02 mmol, 5 mol%) instead, affording the title product (46.1 mg, 79%).

The same procedure was followed but using $NiBr_2$·(glyme) (1.5 mg, 0.005 mmol, 2.5 mol%) and tmphen (1.2 mg, 0.005 mmol, 2.5 mol%) at 110 °C instead, affording the title product (40.9 mg, 70%).

The same procedure was followed but in 0.50 mmol scale using 4-chlorophenylboronic acid (76.0 mg, 0.50 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (1.5 mg, 0.005 mmol, 1 mol%), tmphen (1.2 mg, 0.005 mmol, 1 mol%), DABSO (72.1 mg, 0.30 mmol, 0.6 equiv.) and LiO*t*-Bu (40.0 mg, 0.50 mmol, 1.0 equiv.), DMI (2.5 mL) at 110 ℃ and *tert*-butylbromoacetate (150 µL, 1.0 mmol, 2.0 equiv.), affording the title product (62.6 mg, 43%).

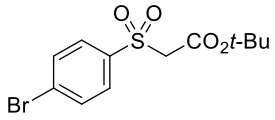
Gram scale reaction: the same procedure was followed but on a 7.0 mmol scale using 4-chlorophenylboronic acid (1095 mg, 7.0 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (54 mg, 0.175 mmol, 2.5 mol%), tmphen (41 mg, 0.175 mmol, 2.5 mol%), DABSO (1009 mg, 4.2 mmol, 0.6 equiv.) and LiO*t*-Bu (560 mg, 7.0 mmol, 1.0 equiv.), DMI (35 mL) at 110 ℃ and *tert*-Butylbromoacetate (2.1 mL, 14 mmol, 2.0 equiv.). In the aqueous workup, the combined organic phases were washed with H_2O five times to remove DMI. Purification by flash column chromatography (30% Et_2O in Petrol) afforded the title product (1.45 g, 71%).



Figure S1. Gram scale reaction.

R_f (30% Et_2O in Petrol) = 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.54 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.03 (s, 2H, CH_2), 1.38 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.3, 141.1, 137.5, 130.2, 129.6, 84.0, 62.1, 27.8; **LRMS** (ESI^+) *m/z* 313.0 ($[M+Na]^+$), 603.0 ($[2M+Na]^+$). Data is consistent with the literature.[21c]

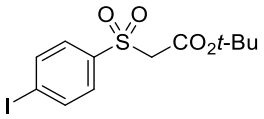
***tert*-Butyl 2-((4-bromophenyl)sulfonyl)acetate (7n)**[21c]



Prepared according to general procedure A using 4-bromophenylboronic acid (40.2 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (40% Et_2O in Petrol) afforded the title product as a colourless oil (51.5 mg, 77%).

R_f (40% Et_2O in Petrol) = 0.32; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.71 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.02 (s, 2H, CH_2), 1.38 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.3, 138.0, 132.6, 130.3, 129.7, 84.0, 62.1, 27.8; **LRMS** (ESI^+) *m/z* 357.0 ($[M+Na]^+$). Data is consistent with the literature.[21c]

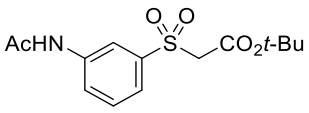
tert-Butyl 2-((4-iodophenyl)sulfonyl)acetate (7o)



Prepared according to general procedure A using 4-iodophenylboronic acid (49.6 mg, 0.20 mmol, 1.0 equiv.), NiI_2 (6.3 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (15% EtOAc in Petrol) afforded the title product as an off-white solid (57.6 mg, 75%).

R_f (15% EtOAc in Petrol) = 0.31; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.64 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.02 (s, 2H, CH_2), 1.38 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) 161.2, 138.6, 138.5, 130.0, 102.4, 84.0, 62.0, 27.8; **LRMS** (ESI^+) *m/z* 405.0 ($[M+Na]^+$), 786.9 ($[2M+Na]^+$). **HRMS** (ESI^-) *m/z* $C_{12}H_{14}O_4IS^-$ requires 380.9663 $[M-H]^-$, found 380.9663; **IR** (thin film, ν_{max}/cm^{-1}) 1730, 1568, 1327, 1293, 1145, 1082, 1006; **m.p.** (CH_2Cl_2): 96-97 °C.

tert-Butyl 2-((3-acetamidophenyl)sulfonyl)acetate (7p)[71]

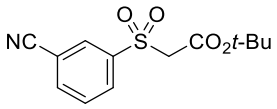


Prepared according to general procedure A using 3-acetamidophenylboronic acid (35.8 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg,

0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (60% EtOAc in Petrol) afforded the title product as a colourless oil (40.8 mg, 65%).

R_f (60% EtOAc in Petrol) = 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (s, 1H, CON*H*), 8.17 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.95 (s, 1H, Ar-*H*), 7.61 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.50 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 4.06 (s, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.33 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 161.2, 139.6, 139.1, 130.1, 125.3, 123.2, 118.9, 84.1, 62.0, 27.8, 24.5; **LRMS** (ESI^+) *m/z* 336.1 ($[M+Na]^+$), 649.2 ($[2M+Na]^+$). Data is consistent with the literature.[71]

***tert*-Butyl 2-((3-cyanophenyl)sulfonyl)acetate (7q)**

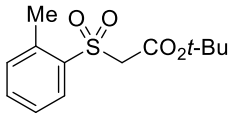


Prepared according to general procedure A using 3-cyanophenylboronic acid (29.4 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (40-60% Et_2O in Petrol) afforded the title product as a colourless oil (41.5 mg, 74%).

R_f (60% Et_2O in Petrol) = 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.25 – 8.22 (m, 1H, Ar-*H*), 8.18 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar-*H*), 7.96 (app. dt, *J* = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.74 (app. td, *J* = 8.0, 0.5 Hz, 1H, Ar-*H*), 4.08 (s, 2H, CH_2), 1.39 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) 161.0, 140.6, 137.3, 132.8, 132.6, 130.3, 117.0, 113.9, 84.4, 61.8, 27.8;

LRMS (ESI^+) *m/z* 304.1 ($[M+Na]^+$), 585.1 ($[2M+Na]^+$); **HRMS** (ESI^+) *m/z* $C_{13}H_{15}O_4NNaS^+$ requires 304.0614 $[M+Na]^+$, found 304.0615; **IR** (thin film, ν_{max}/cm^{-1}) 2980, 2360, 1731, 1473, 1335, 1142, 1087.

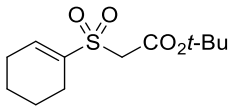
***tert*-Butyl 2-(*o*-tolylsulfonyl)acetate (7r)**[21c]



Prepared according to general procedure A using *o*-tolylboronic acid (27.2 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) at 120 °C. Purification by flash column chromatography (30% Et_2O in Petrol) afforded the title product as a pale yellow oil (17.0 mg, 31%).

R_f (30% Et_2O in Petrol) = 0.25; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.54 (app. td, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.41 – 7.33 (m, 2H, Ar-*H*), 4.08 (s, 2H, CH_2), 2.71 (s, 3H, Ar*Me*), 1.29 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) 161.2, 138.3, 137.2, 134.2, 132.8, 130.9, 126.6, 83.7, 61.7, 27.7, 20.4; **HRMS** (ESI^+) *m/z* $C_{13}H_{18}O_4NaS^+$ requires 293.0818 $[M+Na]^+$, found 293.0816. Data is consistent with the literature.[21c]

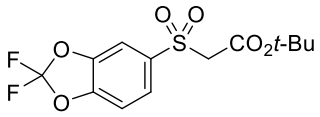
tert-Butyl 2-(cyclohex-1-en-1-ylsulfonyl)acetate (7s)[71]



Prepared according to general procedure A using 1-cyclohexen-1-yl-boronic acid (25.2 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) at 110 °C. Purification by flash column chromatography (20% EtOAc in Petrol) afforded the title product as a white solid (23.2 mg, 45%).

R_f (20% EtOAc in Petrol) = 0.36; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95 (tt, *J* = 4.0, 1.5 Hz, 1H, CH_2CH), 3.84 (s, 2H, SO_2CH_2), 2.43 – 2.33 (m, 2H, CH_2), 2.33 – 2.19 (m, 2H, CH_2), 1.83 – 1.70 (m, 2H, CH_2), 1.71 – 1.57 (m, 2H, CH_2), 1.45 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.8, 141.5, 138.1, 83.5, 58.5, 27.9, 25.7, 23.6, 22.0, 20.8; **LRMS** (ESI^+) *m/z* 283.1 ($[M+Na]^+$), 543.2 ($[2M+Na]^+$). Data is consistent with the literature.[71]

tert-Butyl 2-((2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)sulfonyl)acetate (7t)

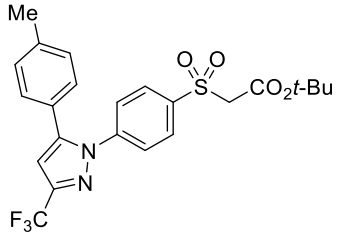


Prepared according to general procedure A using (2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)boronic acid (40.4 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.).

Purification by flash column chromatography (20% EtOAc in Petrol) afforded the title product as a white solid (46.5 mg, 69%).

R_f (20% EtOAc in Petrol) = 0.35; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar-*H*), 7.67 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.26 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 4.05 (s, 2H, C*H*$_2$), 1.41 (s, 9H, C*Me*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.3, 147.8, 143.8, 135.1, 131.9 (t, J_{CF} = 259.5 Hz), 126.2, 110.5, 110.0, 84.2, 62.3, 27.9; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -49.3; **LRMS** (ESI^+) *m/z* 359.0 ($[M+Na]^+$), 695.0 ($[2M+Na]^+$); **HRMS** (ESI^+) *m/z* $C_{13}H_{14}O_6F_2NaS^+$ requires 359.0371 $[M+Na]^+$, found 359.0370; **IR** (thin film, ν_{max}/cm^{-1}) 1729, 1483, 1234, 1155, 1126, 824; **m.p.** (CH_2Cl_2): 139-140 ℃.

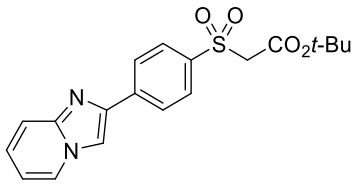
***tert*-butyl 2-((4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)sulfonyl)acetate (7u)**



Prepared according to general procedure A using (4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)boronic acid (69.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (15-30% EtOAc in Petrol) afforded the title product as a yellow oil which solidified on-standing to an off-white solid (67.7 mg, 70%).

R_f (15% EtOAc in Petrol) = 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.53 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.18 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.10 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.74 (s, 1H, Ar-*H*), 4.04 (s, 2H, CH_2), 2.38 (s, 3H, Ar-*Me*), 1.39 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.1, 145.4, 144.3 (q, J_{CF} = 39.0 Hz), 143.8, 140.0, 138.2, 129.9, 129.8, 128.8, 125.8, 125.4, 121.1 (q, J_{CF} = 269.5 Hz), 106.7, 84.0, 62.0, 27.8, 21.4; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.5; **HRMS** (ESI^+) *m/z* $C_{23}H_{24}O_4N_2F_3S^+$ requires 481.1403 $[M+H]^+$, found 481.1400; **IR** (thin film, ν_{max}/cm^{-1}) 1732, 1596, 1332, 1236, 1135, 975, 809; **m.p.** (CH_2Cl_2): 144-145 °C.

tert-Butyl 2-((4-(imidazo[1,2-*a*]pyridin-2-yl)phenyl)sulfonyl)acetate (7v)

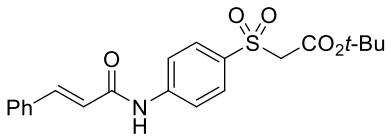


Prepared according to general procedure A using (4-(imidazo[1,2-*a*]pyridin-2-yl)phenyl)boronic acid (47.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). The step 2 alkylation was left for 6 h. Purification by flash column chromatography (60-70% EtOAc in Petrol) afforded the title product as an off-white solid (35.2 mg, 47%).

R_f (60% EtOAc in Petrol) = 0.19; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 – 8.10 (m, 3H, Ar-*H*), 7.99 – 7.93 (m, 3H, Ar-*H*), 7.62 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.24 – 7.17 (m, 1H, Ar-*H*), 6.85 – 6.78 (m, 1H, Ar-*H*), 4.07 (s, 2H, CH_2), 1.35 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$)

δ 161.4, 146.0, 143.5, 139.8, 137.6, 129.1, 126.4, 126.0, 125.7, 117.9, 113.2, 110.0, 83.8, 62.3, 27.8; **HRMS** (ESI^+) *m/z* $C_{19}H_{21}O_4N_2S^+$ requires 373.1217 $[M+H]^+$, found 373.1219; **IR** (thin film, ν_{max}/cm^{-1}) 1730, 1600, 1371, 1320, 1145, 1086, 737; **m.p.** (CH_2Cl_2): 179-181 °C.

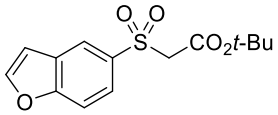
***tert*-Butyl 2-((4-cinnamamidophenyl)sulfonyl)acetate (7w)**



Prepared according to general procedure A using (4-cinnamamidophenyl)boronic acid (53.4 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). The step 2 alkylation was left for 2 h. Purification by flash column chromatography (40% EtOAc in Petrol) afforded the title product as a colourless viscous oil which solidified on-standing to an off-white solid (59.4 mg, 74%).

$\mathbf{R_f}$ (40% EtOAc in Petrol) = 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.51 (s, 1H, CON*H*), 7.92 – 7.83 (m, 4H, Ar-*H*), 7.76 (d, *J* = 15.5 Hz, 1H, C*H*=CH-CO), 7.52 – 7.45 (m, 2H, Ar-*H*), 7.38 – 7.31 (m, 3H, Ar-*H*), 6.67 (d, *J* = 15.5 Hz, 1H, CH=C*H*-CO), 4.04 (s, 2H, CH_2), 1.37 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.8, 161.4, 144.0, 143.8, 134.3, 133.1, 130.5, 129.9, 129.0, 128.2, 120.3, 119.6, 84.0, 62.3, 27.8; **LRMS** (ESI^+) *m/z* 803.2 ($[2M+H]^+$), 825.3 ($[2M+Na]^+$); **HRMS** (ESI^+) *m/z* $C_{21}H_{24}O_5NS^+$ requires 402.1370 $[M+H]^+$, found 402.1371; **IR** (thin film, ν_{max}/cm^{-1}) 3658, 2981, 1731, 1628, 1395, 1142, 726; **m.p.** (CH_2Cl_2): 158-159 °C.

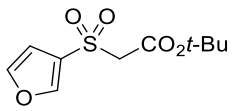
tert-Butyl 2-(benzofuran-5-ylsulfonyl)acetate (7x)[21c]



Prepared according to general procedure A using benzofuran-5-ylboronic acid (32.4 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (20% EtOAc in Petrol) afforded the title product as a pale yellow oil (38.8 mg, 65%).

R_f (20% EtOAc in Petrol) = 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.88 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar-*H*), 7.77 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 7.65 (app. dt, *J* = 8.5, 1.0 Hz, 1H, Ar-*H*), 6.90 (dd, *J* = 2.5, 1.0 Hz, 1H, Ar-*H*), 4.07 (s, 2H, CH_2), 1.34 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.5, 157.6, 147.6, 133.7, 128.0, 124.7, 123.3, 112.3, 107.3, 83.7, 62.6, 27.8; **LRMS** (ESI^+) *m/z* 314.1 ($[M+NH_4]^+$), 615.1 ($[2M+Na]^+$). Data is consistent with the literature.[21c]

tert-butyl 2-(furan-3-ylsulfonyl)acetate (7y)[71]

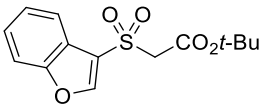


Prepared according to general procedure A using 3-furanylboronic acid (22.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg,

0.20 mmol, 1.0 equiv.). The first step of the reaction was performed in 1 h instead of 16 h, due to the instability of the corresponding sulfinate. Purification by flash column chromatography (25% EtOAc in Petrol) afforded the title product as a colourless oil (22.2 mg, 45%).

R_f (25% EtOAc in Petrol) = 0.25; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 2.0, 1.0 Hz, 1H, Ar-*H*), 7.53 (app. t, *J* = 2.0 Hz, 1H, Ar-*H*), 6.75 (dd, *J* = 2.0, 1.0 Hz, 1H, Ar-*H*), 4.03 (s, 2H, CH_2), 1.44 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.5, 148.0, 144.8, 127.1, 109.4, 84.0, 62.4, 27.9; **LRMS** (ESI^+) *m/z* 269.0 ($[M+Na]^+$). Data is consistent with the literature.[71]

***tert*-Butyl 2-(benzofuran-3-ylsulfonyl)acetate (7z)**

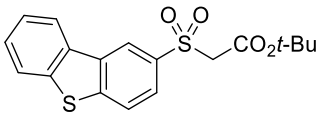


Prepared according to general procedure A using benzofuran-3-ylboronic acid (32.4 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). The first step was carried out for 20 min instead of 16 h, due to the instability of the corresponding sulfinate. Purification by flash column chromatography (15% EtOAc in Petrol) afforded the title product as a colourless oil (25.6 mg, 43%).

R_f (15% EtOAc in Petrol) = 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 (s, 1H, Ar-*H*), 7.90 – 7.86 (m, 1H, Ar-*H*), 7.62 – 7.58 (m, 1H, Ar-*H*), 7.48 – 7.40 (m, 2H, Ar-*H*), 4.14 (s, 2H,

C*H*$_2$), 1.35 (s, 9H, C*Me*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.2, 155.6, 151.3, 126.6, 125.1, 122.6, 122.0, 120.6, 112.5, 84.0, 62.3, 27.8; **LRMS** (ESI$^+$) *m/z* 319.0 ([M+Na]$^+$); **HRMS** (ESI$^+$) *m/z* $C_{14}H_{16}O_5NaS$ requires 319.0611 [M+Na]$^+$, found 319.0611; **IR** (thin film, ν_{max}/cm^{-1}) 1730, 1539, 1450, 1370, 1331, 1292, 1124, 1104, 748, 706.

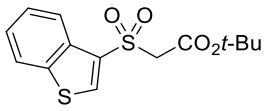
***tert*-Butyl 2-(dibenzo[*b*,*d*]thiophen-2-ylsulfonyl)acetate (7aa)**[73]



Prepared according to general procedure A using dibenzo[*b*,*d*]thiophen-2-ylboronic acid (45.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (20% EtOAc in Petrol) afforded the title product as a pale yellow viscous oil (54.8 mg, 76%).

R$_f$ (20% EtOAc in Petrol) = 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.70 (s, 1H, Ar-*H*), 8.21 (app. d, *J* = 7.5 Hz, 1H, Ar-*H*), 8.01 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.97 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.88 (app. d, *J* = 7.5 Hz, 1H, Ar-*H*), 7.58 – 7.48 (m, 2H, Ar-*H*), 4.14 (s, 2H, C*H*$_2$), 1.34 (s, 9H, C*Me*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.4, 145.7, 140.0, 135.8, 135.2, 134.5, 128.1, 125.6, 125.4, 123.5, 123.1, 122.3, 122.2, 83.8, 62.6, 27.8; **LRMS** (ESI$^+$) *m/z* 385.0 ([M+Na]$^+$). Data is consistent with the literature.[73]

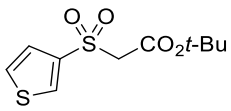
tert-Butyl 2-(benzo[*b*]thiophen-3-ylsulfonyl)acetate (7ab)[21c]



Prepared according to general procedure A using benzo[b]thien-3-ylboronic acid (35.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). The first step was carried out for 1 h due to the instability of the corresponding sulfinate. Purification by flash column chromatography (15% EtOAc in Petrol) afforded the title product as an off-white solid (19.1 mg, 31%).

R_f (15% EtOAc in Petrol) = 0.25; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (s, 1H, Ar-*H*), 8.24 (app. dt, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 7.93 (app. dt, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 7.59 – 7.45 (m, 2H, Ar-*H*), 4.14 (s, 2H, CH_2), 1.31 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.2, 140.5, 138.2, 133.9, 132.9, 126.3, 126.1, 123.2, 123.0, 83.8, 62.0, 27.8; **LRMS** (ESI^+) *m/z* 335.0 ($[M+Na]^+$). Data is consistent with the literature.[21c]

tert-Butyl 2-(thiophen-3-ylsulfonyl)acetate (7ac)[21c]

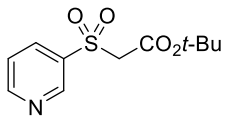


Prepared according to general procedure A using 3-thienylboronic acid (25.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg,

0.20 mmol, 1.0 equiv.). The first step of the reaction was performed in 2 h instead of 16 h, due to the instability of the corresponding sulfinate. Purification by flash column chromatography (20% EtOAc in Petrol) afforded the title product as an off-white solid (27.4 mg, 52%).

R_f (20% EtOAc in Petrol) = 0.32; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 3.0, 1.5 Hz, 1H, Ar-*H*), 7.47 (dd, *J* = 5.0, 3.0 Hz, 1H, Ar-*H*), 7.43 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar-*H*), 4.04 (s, 2H, CH_2), 1.40 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.4, 139.5, 133.8, 128.1, 126.6, 83.8, 62.4, 27.9; **LRMS** (ESI^+) *m/z* 285.0 ($[M+Na]^+$). Data is consistent with the literature.[21c]

tert-Butyl 2-(pyridin-3-ylsulfonyl)acetate (7ad)

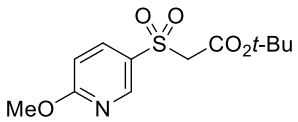


Prepared according to general procedure A using 3-pyridinylboronic acid (24.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (50% EtOAc in Petrol) afforded the title product as a colourless oil (37.7 mg, 73%).

R_f (50% EtOAc in Petrol) = 0.25; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.13 (app. d, *J* = 2.0 Hz, 1H, Ar-*H*), 8.89 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar-*H*), 8.22 (ddd, *J* = 8.0, 2.0, 1.5 Hz, 1H, Ar-*H*), 7.53 (dd, *J* = 8.0, 5.0 Hz, 1H, Ar-*H*), 4.08 (s, 2H, CH_2), 1.36 (s, 9H, CMe_3); **^{13}C NMR** (101

MHz, $CDCl_3$) 161.1, 154.6, 149.7, 136.7, 135.5, 123.8, 84.3, 62.2, 27.8; **LRMS** (ESI^+) *m/z* 258.1 ($[M+H]^+$), 280.1 ($[M+Na]^+$); **HRMS** (ESI^+) *m/z* $C_{11}H_{16}O_4NS^+$ requires 258.0795 $[M+H]^+$, found 258.0794; **IR** (thin film, ν_{max}/cm^{-1}) 2981, 2361, 1732, 1323, 1150, 702.

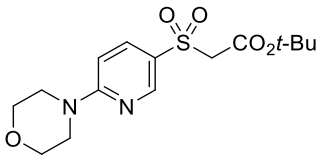
***tert*-Butyl 2-((6-methoxypyridin-3-yl)sulfonyl)acetate (7ae)**[21c]



Prepared according to general procedure A using 6-methoxy-3-pyridinylboronic acid (30.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2 \cdot$(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (30% Et_2O in Petrol) afforded the title product as a pale yellow oil (39.7 mg, 69%).

$\mathbf{R_f}$ (30% Et_2O in Petrol) = 0.16; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 2.5, 0.5 Hz, 1H, Ar-*H*), 8.01 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar-*H*), 6.85 (dd, *J* = 9.0, 0.5 Hz, 1H, Ar-*H*), 4.02 (s, 2H, C*H*$_2$), 4.02 (s, 3H, O*CH*$_3$), 1.41 (s, 9H, C*Me*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.5, 161.5, 149.6, 138.7, 128.3, 111.5, 84.0, 62.6, 54.6, 27.9; **LRMS** (ESI^+) *m/z* 288.1 ($[M+H]^+$), 310.1 ($[M+Na]^+$). Data is consistent with the literature.[21c]

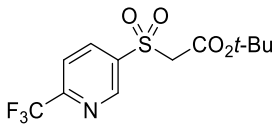
tert-Butyl 2-((6-morpholinopyridin-3-yl)sulfonyl)acetate (7af)



Prepared according to general procedure A using 6-(morpholino)pyridine-3-boronic acid (41.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (30-50% EtOAc in Petrol) afforded the title product as an orange oil which solidified on-standing to a yellow solid (46.0 mg, 67%).

R_f (50% EtOAc in Petrol) = 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 2.5, 0.5 Hz, 1H, Ar-*H*), 7.85 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar-*H*), 6.61 (dd, *J* = 9.0, 0.5 Hz, 1H, Ar-*H*), 3.98 (s, 2H, C*H*$_2$), 3.80 – 3.76 (m, 4H, OC*H*$_2$), 3.70 – 3.66 (m, 4H, NC*H*$_2$), 1.41 (s, 9H, C*Me*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.8, 160.8, 150.2, 137.8, 122.7, 105.0, 83.7, 66.6, 62.7, 44.9, 27.9; **LRMS** (ESI^+) *m/z* 343.1 ($[M+H]^+$); **HRMS** (ESI^+) *m/z* $C_{15}H_{23}O_5N_2S^+$ requires 343.1322 $[M+H]^+$, found 343.1322; **IR** (thin film, ν_{max}/cm^{-1}) 1729, 1589, 1308, 1258, 1141, 944; **m.p.** (CH_2Cl_2): 101-103 °C.

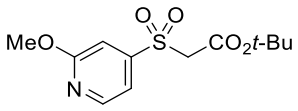
tert-Butyl 2-((6-(trifluoromethyl)pyridin-3-yl)sulfonyl)acetate (7ag)



Prepared according to general procedure A using 6-(trifluoromethyl)-3-pyridinylboronic acid (38.2 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (10-20% EtOAc in Petrol) afforded the title product as a white solid (38.1 mg, 59%).

R_f (20% EtOAc in Petrol) = 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.23 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 8.45 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar-*H*), 7.91 (dd, *J* = 8.5, 1.0 Hz, 1H, Ar-*H*), 4.12 (s, 2H, C*H*$_2$), 1.40 (s, 9H, C*Me*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.9, 152.6 (q, J_{CF} = 35.5 Hz), 150.1, 138.9, 138.2, 120.8 (q, J_{CF} = 275.5 Hz), 120.8 (q, J_{CF} = 3.1 Hz), 84.9, 62.0, 27.8; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -68.3; **LRMS** (ESI^+) m/z 348.1 ($[M+Na]^+$), 673.1 ($[2M+Na]^+$); **HRMS** (ESI^+) *m/z* $C_{12}H_{14}F_3NNaO_4S^+$ requires 348.0488 $[M+Na]^+$, found 348.0489; **IR** (thin film, ν_{max}/cm^{-1}) 2981, 2361, 1733, 1381, 1333, 1151, 1078; **m.p.** (CH_2Cl_2): 107-109 ℃.

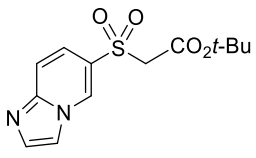
tert-Butyl 2-((2-methoxypyridin-4-yl)sulfonyl)acetate (7ah)



Prepared according to general procedure A using 2-methoxypyridine-4-boronic acid (30.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (20% EtOAc in Petrol) afforded the title product as a pale yellow oil (35.1 mg, 61%).

R_f (20% EtOAc in Petrol) = 0.31; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 5.5, 0.5 Hz, 1H, Ar-*H*), 7.32 (dd, *J* = 5.5, 1.5 Hz, 1H, Ar-*H*), 7.23 (dd, *J* = 1.5, 0.5 Hz, 1H, Ar-*H*), 4.04 (s, 2H, CH_2), 3.99 (s, 3H, O*Me*), 1.38 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.8, 160.8, 149.3, 148.9, 113.9, 110.5, 84.3, 61.5, 54.5, 27.8; **LRMS** (ESI^+) *m/z* 310.0 ($[M+Na]^+$), 597.2 ($[2M+Na]^+$); **HRMS** (ESI^+) *m/z* $C_{12}H_{18}O_5NS^+$ requires 288.0900 $[M+H]^+$, found 288.0901; **IR** (thin film, ν_{max}/cm^{-1}) 2981, 1732, 1383, 1333, 1143.

tert-Butyl 2-(imidazo[1,2-*a*]pyridin-6-ylsulfonyl)acetate (7ai)

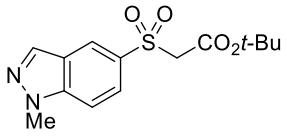


Prepared according to general procedure A using (imidazo[1,2-*a*]pyridin-6-yl)boronic acid (32.4 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu

(16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (100% EtOAc) afforded the title product as a yellow oil which solidified on-standing to a pale yellow solid (31.2 mg, 53%).

R_f (100% EtOAc) = 0.32; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.88 (dd, *J* = 2.0, 1.0 Hz, 1H, Ar-*H*), 7.84 – 7.69 (m, 3H, Ar-*H*), 7.53 (dd, *J* = 9.5, 2.0 Hz, 1H, Ar-*H*), 4.11 (s, 2H, CH_2), 1.36 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.3, 145.2, 136.5, 130.7, 125.6, 121.7, 118.3, 114.5, 84.3, 62.0, 27.8; **LRMS** (ESI^+) *m/z* 297.1 ($[M+H]^+$), 593.2 ($[2M+H]^+$); **HRMS** (ESI^+) *m/z* $C_{13}H_{17}O_4N_2S$ requires 297.0904 $[M+H]^+$, found 297.0900; **IR** (thin film, ν_{max}/cm^{-1}) 1729, 1628, 1306, 1128, 729; **m.p.** (CH_2Cl_2): 122-124 ℃.

tert-Butyl 2-((1-methyl-1*H*-indazol-5-yl)sulfonyl)acetate (7aj)[71]

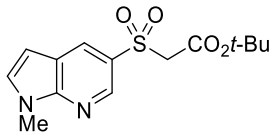


Prepared according to general procedure A using 1-methyl-1*H*-indazol-5-yl-5-boronic acid (35.2 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (40-50% EtOAc in Petrol) afforded the title product as a pale yellow oil (38.7 mg, 62%).

R_f (50% EtOAc in Petrol) = 0.39; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 1.5, 1.0 Hz, 1H, Ar-*H*), 8.14 (d, *J* = 1.0 Hz, 1H, Ar-*H*), 7.87 (dd, *J* = 9.0, 1.5 Hz, 1H, Ar-*H*), 7.53 (d, *J* = 9.0, 1H, Ar-*H*), 4.12 (s, 3H, N*Me*), 4.06 (s, 2H, CH_2), 1.34 (s, 9H, CMe_3); **^{13}C NMR** (101

MHz, $CDCl_3$) 161.6, 141.4, 134.9, 131.1, 125.3, 124.6, 123.3, 109.8, 83.7, 62.6, 36.1, 27.8; **LRMS** (ESI^+) *m/z* 311.1 ($[M+H]^+$), 643.2 ($[2M+Na]^+$). Data is consistent with the literature.[71]

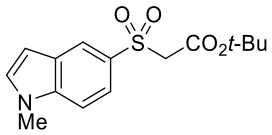
tert-Butyl 2-((1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)sulfonyl)acetate (7ak)



Prepared according to general procedure A using (1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)boronic acid (35.2 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (40% EtOAc in Petrol) afforded the title product as a yellow solid (40.0 mg, 64%).

R_f (40% EtOAc in Petrol) = 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 8.42 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.35 (d, *J* = 3.5 Hz, 1H, Ar-*H*), 6.60 (d, *J* = 3.5 Hz, 1H, Ar-*H*), 4.07 (s, 2H, CH_2), 3.93 (s, 3H, N*Me*), 1.35 (s, 9H, CMe_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.6, 149.4, 143.0, 132.2, 130.2, 126.9, 119.5, 101.5, 83.7, 63.1, 31.8, 27.8; **LRMS** (ESI^+) *m/z* 311.1 ($[M+H]^+$), 621.2 ($[2M+H]^+$); **HRMS** (ESI^+) *m/z* $C_{14}H_{19}O_4N_2S^+$ requires 311.1060 $[M+H]^+$, found 311.1060; **IR** (thin film, ν_{max}/cm^{-1}) 1729, 1326, 1143, 1074, 730; **m.p.** (CH_2Cl_2): 110-112 ℃.

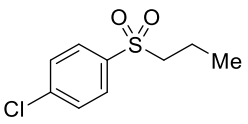
tert-Butyl 2-((1-methyl-1H-indol-5-yl)sulfonyl)acetate (7al)



Prepared according to general procedure A using *N*-methylindole-5-boronic acid (35.0 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (35% EtOAc in Petrol) afforded the title product as an off-white solid (25.0 mg, 40%).

R_f (35% EtOAc in Petrol) = 0.25; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (app. d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.74 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar-*H*), 7.43 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.20 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 6.63 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 4.05 (s, 2H, C*H*$_2$), 3.85 (s, 3H, N*Me*), 1.34 (s, 9H, C*Me*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) 161.8, 139.1, 131.6, 129.5, 128.0, 123.3, 121.1, 109.7, 103.1, 83.3, 63.0, 33.3, 27.8; **HRMS** (ESI^+) *m/z* $C_{15}H_{19}O_4NNaS^+$ requires 332.0927 $[M+Na]^+$, found 332.0928; **IR** (thin film, ν_{max}/cm^{-1}) 2981, 2361, 1730 (CO), 1319 (SO_2), 1138 (SO_2); **m.p.** (CH_2Cl_2): 134-136 °C.

1-Chloro-4-(propylsulfonyl)benzene (8a)[69]

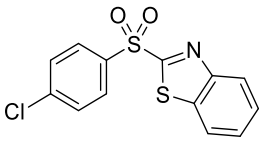


4-Chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12

mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) were added to a 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 (× 4). DMI (1.0 mL) was added and the reaction mixture was heated at 100 ℃ for 16 h. 1-Iodopropane (40 μL, 0.40 mmol, 2.0 equiv.) was then added. The reaction was stirred at 100 ℃ for 30 min before cooling to rt. The reaction was diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (10-40% Et_2O in Petrol) afforded the title product as an off-white solid (33.8 mg, 77%).

R_f (40% Et_2O in Petrol) = 0.36; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.53 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.10 – 3.01 (m, 2H, SO_2CH_2), 1.80 – 1.65 (m, 2H, CH_2CH_3), 0.99 (t, *J* = 7.4 Hz, 3H, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.5, 137.7, 129.7 (overlapping of two carbons), 58.1, 16.6, 13.1; **LRMS** (ESI^+) *m/z* 241.0 ($[M+Na]^+$), 459.0 ($[2M+Na]^+$). Data is consistent with the literature.[69]

2-((4-Chlorophenyl)sulfonyl)benzo[*d*]thiazole (8b)

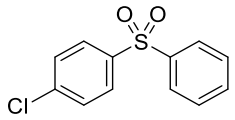


4-Chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) were added to a 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2

(× 4). DMI (1.0 mL) was added and the reaction mixture was heated at 100 ℃ for 16 h. 2-Chlorobenzothiazole (50 μL, 0.40 mmol, 2.0 equiv.) was then added. The reaction was stirred at 100 ℃ for 1.5 h before cooling to rt. The reaction was diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (25% Et_2O in Petrol) afforded the title product as an off-white solid (50.4 mg, 81%).

R_f (25% Et_2O in Petrol) = 0.34; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 – 8.12 (m, 1H, Ar-*H*), 8.09 (dt, *J* = 8.5, 2.0 Hz, 2H, Ar-*H*), 7.99 – 7.92 (m, 1H, Ar-*H*), 7.60 – 7.52 (m, 4H, Ar-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.9, 153.0, 141.6, 137.1, 137.0, 130.5, 130.0, 128.2, 127.8, 125.7, 122.4; **LRMS** (ESI^+) *m/z* 332.0 ($[M+Na]^+$); **HRMS** (ESI^+) *m/z* $C_{13}H_9O_2N^{35}ClS_2^+$ requires 309.9758 $[M+H]^+$, found 309.9760; **IR** (thin film, ν_{max}/cm^{-1}) 1473, 1339, 1161, 1088, 757, 636; **m.p.** (CH_2Cl_2): 173-175 ℃.

1-Chloro-4-(phenylsulfonyl)benzene (8c)[16d]

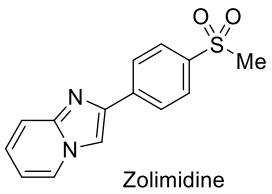


4-Chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) were added to a 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 (× 4). DMI (1.0 mL) was added and the reaction mixture was stirred at 100 ℃ for 16 h. The reaction was cooled to rt before diphenyliodonium triflate (172 mg, 0.40 mmol, 2.0 equiv.)

was added. The reaction was then stirred at 100 ℃ for 3 h before cooling to rt and was diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (20% Et_2O in Petrol) afforded the title product as an off-white solid (29.3 mg, 58%).

R_f (20% Et_2O in Petrol) = 0.25; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 – 7.90 (m, 2H, Ar-*H*), 7.90 – 7.85 (m, 2H, Ar-*H*), 7.60 – 7.55 (m, 1H, Ar-*H*), 7.54 – 7.45 (m, 4H, Ar-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.3, 140.3, 140.0, 133.6, 129.7, 129.5, 129.2, 127.8; **LRMS** (ESI^+) *m/z* 275.0 ($[M+Na]^+$), 527.0 ($[2M+Na]^+$). Data is consistent with the literature.[16d]

Zolimidine (8d)[133]



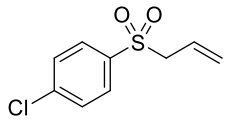
Zolimidine

(4-(imidazo[1,2-*a*]pyridin-2-yl)phenyl)boronic acid (47.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) were added to a 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 (× 4). DMI (1.0 mL) was added and the reaction mixture was heated at 100 ℃ for 16 h. The reaction was cooled to rt. Methyl iodide (40 μL, 0.6 mmol, 3.0 equiv.) was then added and the reaction was stirred at rt for 6 h. The reaction was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases

were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (90% EtOAc in Petrol) afforded the title product as an off-white solid (36.6 mg, 67%).

R_f (90% EtOAc in Petrol) = 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 – 8.09 (m, 3H, Ar-*H*), 8.01 – 7.92 (m, 3H, Ar-*H*), 7.63 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.22 (ddd, *J* = 9.0, 7.0, 1.0 Hz, 1H, Ar-*H*), 6.82 (app. td, *J* = 7.0, 1.0 Hz, 1H, Ar-*H*), 3.08 (s, 3H, *Me*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.1, 143.6, 139.4, 139.3, 128.0, 126.7, 126.0, 125.7, 117.9, 113.2, 109.8, 44.7; **HRMS** (ESI^+) *m/z* $C_{14}H_{13}O_2N_2S^+$ requires 273.0692 $[M+H]^+$, found 273.0691. Data is consistent with the literature.[133]

1-(Allylsulfonyl)-4-chlorobenzene (8e)[134]

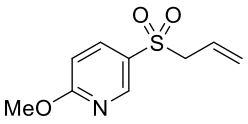


Prepared according to general procedure A using 4-chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) and allyl bromide (35 μL, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (20% EtOAc in Petrol) afforded the title product as a yellow oil (34.0 mg, 78%).

R_f (20% EtOAc in Petrol) = 0.31; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (dt, *J* = 8.5, 2.0 Hz, 2H, Ar-*H*), 7.52 (dt, *J* = 8.5, 2.0 Hz, 2H, Ar-*H*), 5.78 (ddt, *J* = 17.5, 10.0, 7.5 Hz, 1H,

C*H*=CH_2), 5.34 (app. dq, *J* = 10.0, 1.0 Hz, 1H, cis CH=CH_aH_b), 5.15 (app. dq, *J* = 17.0, 1.0 Hz, 1H, trans CH=CH_aH_b), 3.80 (app. dt, *J* = 7.5, 1.0 Hz, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.7, 136.8, 130.1, 129.5, 125.2, 124.6, 61.0; **LRMS** (ESI^+) *m/z* 239.0 ($[M+Na]^+$). Data is consistent with the literature.[134]

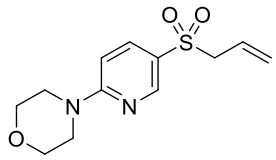
5-(Allylsulfonyl)-2-methoxypyridine (8f)[19d]



Prepared according to general procedure A using 6-methoxy-3-pyridinylboronic acid (30.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) and allyl bromide (35 μL, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (25% EtOAc in Petrol) afforded the title product as a white solid (28.2 mg, 66%).

R_f (25% EtOAc in Petrol) = 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 2.5, 0.5 Hz, 1H, Ar-*H*), 7.93 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar-*H*), 6.83 (dd, *J* = 9.0, 0.5 Hz, 1H, Ar-*H*), 5.81 (ddt, *J* = 17.0, 10.0, 7.5 Hz, 1H, C*H*=CH_2), 5.36 (dd, *J* = 10.0, 1.0 Hz, 1H, cis CH=CH_aH_b), 5.17 (dq, *J* = 17.0, 1.0 Hz, 1H, trans CH=CH_aH_b), 4.01 (s, 3H, O*Me*), 3.80 (dt, *J* = 7.5, 1.0 Hz, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.3, 149.3, 138.6, 127.6, 125.2, 124.8, 111.4, 61.5, 54.5; **LRMS** (ESI^+) *m/z* 236.0 ($[M+Na]^+$), 449.0 ($[2M+Na]^+$); **HRMS** (ESI^+) *m/z* $C_9H_{12}NO_3S^+$ requires 214.0532 $[M+H]^+$, found 214.0532. Data is consistent with the literature.[19d]

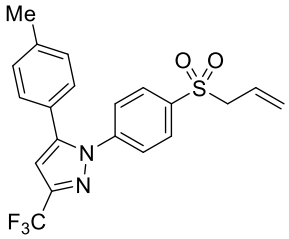
4-(5-(Allylsulfonyl)pyridin-2-yl)morpholine (8g)



Prepared according to general procedure A using 6-(morpholino)pyridine-3-boronic acid (41.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) and allyl bromide (35 μL, 0.40 mmol, 2.0 equiv.). The alkylation step was left for 24 h instead. Purification by flash column chromatography (50-60% EtOAc in Petrol) afforded the title product as a pale yellow solid (39.9 mg, 74%).

R_f (50% EtOAc in Petrol) = 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 2.5, 0.5 Hz, 1H, Ar-*H*), 7.79 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar-*H*), 6.60 (dd, *J* = 9.0, 0.5 Hz, 1H, Ar-*H*), 5.81 (ddt, *J* = 17.5, 10.0, 7.5 Hz, 1H, C*H*=CH_2), 5.35 (app. dq, *J* = 10.0, 1.0 Hz, 1H, cis CH=C$H_a$$H_b$), 5.18 (app. dq, *J* = 17.0, 1.5 Hz, 1H, trans CH=$CH_a$$H_b$), 3.82 – 3.74 (m, 6H, SO_2CH_2 and OCH_2), 3.70 – 3.63 (m, 4H, NCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.8, 150.0, 137.7, 125.2, 124.8, 122.4, 105.1, 66.6, 61.6, 45.0; **LRMS** (ESI^+) *m/z* 269.1 ($[M+H]^+$), 537.2 ($[2M+H]^+$); **HRMS** (ESI^+) *m/z* $C_{12}H_{17}O_3N_2S^+$ requires 269.0954 $[M+H]^+$, found 269.0954; **IR** (thin film, ν_{max}/cm^{-1}) 1587, 1499, 1304, 1136, 1115, 942; **m.p.** (CH_2Cl_2): 148-149 °C.

1-(4-(Allylsulfonyl)phenyl)-5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazole (8h)[19d]

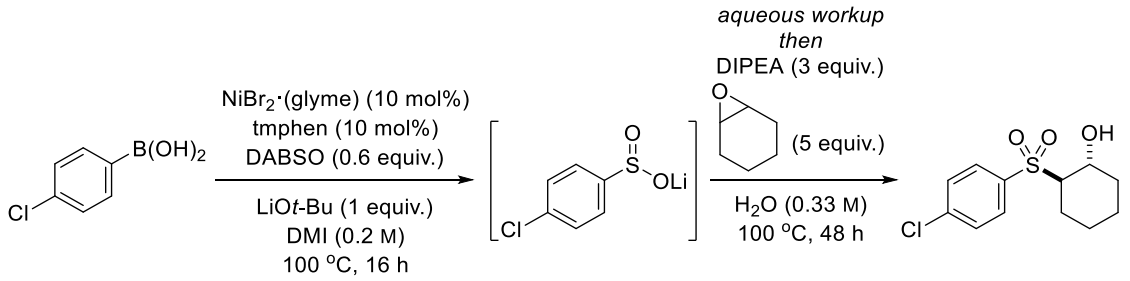


Prepared according to general procedure A using (4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)boronic acid (69.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) and allyl bromide (35 μL, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (15-30% EtOAc in Petrol) afforded the title product as a colourless viscous oil (64.2 mg, 79%).

R_f (15% EtOAc in Petrol) = 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (dt, *J* = 9.0, 2.0 Hz, 2H, Ar-*H*), 7.50 (dt, *J* = 9.0, 2.0 Hz, 2H, Ar-*H*), 7.16 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.08 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.74 (s, 1H, Ar-*H*), 5.77 (ddt, *J* = 17.0, 10.0, 7.5 Hz, 1H, C*H*=CH_2), 5.32 (app. dd, *J* = 10.0, 1.0 Hz, 1H, cis CH=C$H_a$$H_b$), 5.13 (app. dq, *J* = 17.0, 1.0 Hz, 1H, trans CH=$CH_a$$H_b$), 3.81 (d, *J* = 7.5 Hz, 2H, CH_2), 2.37 (s, 3H, *Me*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.5, 144.3 (q, J_{CF} = 39.0 Hz), 143.5, 140.0, 137.5, 129.9, 129.7, 128.8, 125.7, 125.5, 125.2, 124.5, 121.1 (q, J_{CF} = 269.0 Hz), 106.5, 61.0, 21.4; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.4; **LRMS** (ESI^+) *m/z* 407.1 ($[M+H]^+$), 813.2 ($[2M+H]^+$). Data is consistent with the literature.[19d]

General Procedure B: Two-Step synthesis of *β*-hydroxysulfones (exemplified by the preparation of *β*-hydroxysulfones **8i**)

2-((4-Chlorophenyl)sulfonyl)cyclohexan-1-ol (8i)[15d]



4-Chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) were added to a 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 (× 4). DMI (1.0 mL) was added and the reaction mixture was heated at 100 ℃ for 16 h. After cooling the solution to rt, aq. H_3PO_4 (3 mL, 2 M) and brine (1 mL) were added to the mixture. The mixture was then extracted with EtOAc (3 × 2 mL) (*note 1*). The combined organic phases was transferred to a 10 mL round-bottom flask and was added DIPEA (0.11 mL, 0.60 mmol, 3.0 equiv.). The solution became cloudy after adding DIPEA indicating the formation of sulfinate salt from sulfinic acid. The volatiles was removed under reduced pressure (< 20 mbar for at least 1 min). H_2O (0.6 mL) and cyclohexene oxide (100 µL, 1.0 mmol, 5.0 equiv.) were added. The reaction mixture was then stirred at 100 ℃ for 48 h. The reaction was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by

flash column chromatography (30% EtOAc in Petrol) afforded the title product as a white solid (42.2 mg, 77%).

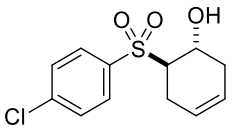
R_f (30% EtOAc in Petrol) = 0.43; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.54 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.07 (s, 1H, O*H*), 3.88 (app. td, *J* = 10.0, 5.0 Hz, 1H, C*H*OH), 2.97 (ddd, *J* = 12.5, 9.5, 4.0 Hz, 1H, SC*H*), 2.17 – 2.05 (m, 1H, CH(OH)CH_aH$_b$), 1.95 – 1.84 (m, 1H, SCHCH_aH$_b$), 1.76 – 1.65 (m, 2H, CH_2), 1.38 – 1.10 (m, 4H, CH(OH)CH$_a$$H_b$, SCHCH$_a$$H_b$ and CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0, 135.6, 130.6, 129.7, 69.2, 68.4, 34.4, 25.8, 24.6, 23.7; **HRMS** (ESI^+) *m/z* $C_{12}H_{16}O_3{}^{35}ClS^+$ requires 275.0503 $[M+H]^+$, found 275.0506. Data is consistent with the literature.[15d]

Note:

1. Ring-opening reaction followed by elimination was observed if the aqueous workup was not performed.

(Also see the notes in general procedure A)

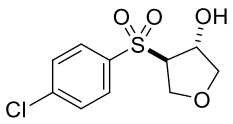
6-((4-Chlorophenyl)sulfonyl)cyclohex-3-en-1-ol (8j)



Prepared according to general procedure B using 4-chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2 \cdot$(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.), 7-oxabicyclo[4.1.0]hept-3-ene[135] (97 mg, 1.0 mmol, 5.0 equiv.). Purification by flash column chromatography (30% EtOAc in Petrol) afforded the title product as an off-white solid (46.2 mg, 85%).

R_f (30% EtOAc in Petrol) = 0.35; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.55 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 5.64 – 5.54 (m, 1H, C*H*=CH), 5.54 – 5.44 (m, 1H, CH=C*H*), 4.17 (td, *J* = 9.5, 6.0 Hz, 1H, C*H*OH), 3.86 (s, 1H, O*H*), 3.31 (td, *J* = 10.5, 6.5 Hz, 1H, SC*H*), 2.62 – 2.51 (m, 1H, CH(OH)CH_aH_b), 2.37 – 2.07 (m, 3H, SCHCH_2 and CH(OH)CH_aH_b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.1, 135.9, 130.5, 129.7, 124.7, 122.7, 66.0, 65.4, 34.2, 26.1; **HRMS** (ESI^+) *m/z* $C_{12}H_{13}O_3{}^{35}ClNaS^+$ requires 295.0166 $[M+Na]^+$, found 295.0167; **IR** (thin film, ν_{max}/cm^{-1}) 3492, 1307, 1275, 1143, 1088, 759; **m.p.** (CH_2Cl_2): 112-114 ℃.

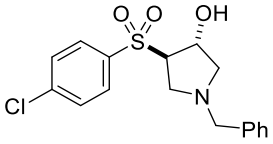
4-((4-Chlorophenyl)sulfonyl)tetrahydrofuran-3-ol (8k)



Prepared according to general procedure B using 4-chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.), 3,4-epoxytetrahydrofuran (72 µL, 1 mmol, 5.0 equiv.). Purification by flash column chromatography (40–50% EtOAc in Petrol) afforded the title product as an off-white solid (37.2 mg, 71%).

R_f (50% EtOAc in Petrol) = 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.58 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.94 – 4.81 (m, 1H, C*H*OH), 4.14 – 3.94 (m, 3H, SCHCH_2 and CH(OH)CH_aH$_b$), 3.77 – 3.67 (m, 2H, SC*H* and CH(OH)CH$_a$$H_b$), 3.11 – 2.96 (m, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.4, 136.5, 130.1, 129.9, 75.1, 72.5, 72.1, 67.2; **HRMS** (ESI^+) *m/z* $C_{10}H_{12}O_4{}^{35}ClS^+$ requires 263.0139 $[M+Na]^+$, found 263.0140; **IR** (thin film, ν_{max}/cm^{-1}) 3388, 1311, 1146, 1084, 908; **m.p.** (CH_2Cl_2): 138-140 °C.

1-Benzyl-4-((4-chlorophenyl)sulfonyl)pyrrolidin-3-ol (8l)

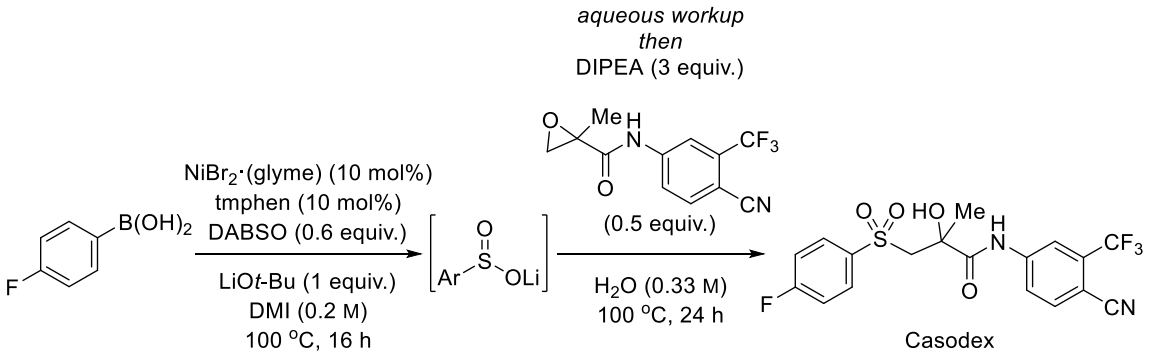


Prepared according to general procedure B using 4-chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg,

0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.), 3-benzyl-6-oxa-3-azabicyclo[3.1.0]hexane[136] (175 mg, 1.0 mmol, 5.0 equiv.). Purification by flash column chromatography (30–35–40% EtOAc in Petrol) afforded the title product as a pale yellow solid (34.7 mg, 49%).

R_f (40% EtOAc in Petrol) = 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.79 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.51 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.35 – 7.22 (m, 3H, Ar-*H*), 7.22 – 7.14 (m, 2H, Ar-*H*), 4.67 (app. dt, *J* = 6.0, 3.5 Hz, 1H, C*H*OH), 3.65 – 3.52 (m, 3H, NCH_2Ph, SC*H*), 3.39 (br. s, 1H, O*H*), 2.97 (dd, *J* = 10.5, 8.5 Hz, 1H, SCHCH_aH$_b$), 2.80 – 2.66 (m, 3H, SCHCH$_a$$H_b$ and CH(OH)CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.9, 137.5, 136.7, 130.1, 129.9, 128.8, 128.5, 127.6, 71.7, 71.5, 61.5, 59.3, 52.8; **LRMS** (ESI^+) *m/z* 352.1 ($[M+H]^+$), 703.2 ($[2M+H]^+$); **HRMS** (ESI^+) *m/z* $C_{17}H_{19}O_3N^{35}ClS^+$ requires 352.0769 $[M+H]^+$, found 352.0764; **IR** (thin film, ν_{max}/cm^{-1}) 3383, 1311, 1148, 1089, 756, 627; **m.p.** (CH_2Cl_2): 102-104 ℃.

Casodex (8m)[137]



4-Fluorophenylboronic acid (56.0 mg, 0.40 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (12.3 mg, 0.04 mmol, 10 mol%), tmphen (9.5 mg, 0.04 mmol, 10 mol%), DABSO (57.7 mg, 0.24

mmol, 0.6 equiv.) and LiO*t*-Bu (32.0 mg, 0.40 mmol, 1.0 equiv.) were added to a 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 (× 4). DMI (2.0 mL) was added and the reaction mixture was heated at 100 ℃ for 16 h. After cooling the solution to rt, aq. H_3PO_4 (6 mL, 2 M), brine (2 mL) and EtOAc (4 mL) were added to the reaction mixture. The two layers were separated and the aqueous phase was further extracted with EtOAc (2 × 4 mL). The combined organic phases was transferred to a 25 mL round-bottom flask and DIPEA (0.22 mL, 1.2 mmol, 3.0 equiv.) was added. The solution became cloudy after adding DIPEA, indicating the formation of sulfinate salt from sulfinic acid. The volatiles were removed under reduced pressure (< 20 mbar for at least 1 min). H_2O (1.2 mL) and *N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-methyloxirane-2-carboxamide (54.0 mg, 0.20 mmol, 0.5 equiv.) were added. The reaction mixture was then stirred at 100 ℃ for 24 h. The reaction was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (50% EtOAc in Petrol) afforded the product as a white solid (48.2 mg, 56%). *(Product yield was calculated based on the epoxide.)*

R_f (50% EtOAc in Petrol) = 0.33; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.38 (s, 1H, N*H*), 8.43 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 8.22 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar-*H*), 8.10 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.98 – 7.88 (m, 2H, Ar-*H*), 7.43 – 7.32 (m, 2H, Ar-*H*), 6.41 (s, 1H, O*H*), 3.95 (d, *J* = 15.0 Hz, 1H, $SO_2CH_aH_b$), 3.72 (d, *J* = 15.0 Hz, 1H, $SO_2CH_aH_b$), 1.41 (s, 3H, *Me*); **^{13}C NMR** (126 MHz, DMSO-d_6) δ 173.7, 164.9 (d, J_{CF} = 252.0 Hz), 143.2, 137.1 (d, J_{CF} = 3.0 Hz), 136.2, 131.41 (q, J_{CF} = 32.0 Hz), 131.38 (d, J_{CF} = 10.0 Hz), 122.9, 122.5 (q, J_{CF} =

273.5 Hz), 117.5 (q, J_{CF} = 5.0 Hz), 116.1 (d, J_{CF} = 23.0 Hz), 115.8, 101.9 (q, J_{CF} = 2.0 Hz), 73.1, 63.5, 27.2; **^{19}F NMR** (376 MHz, DMSO-d_6) δ -61.1, -105.6; **HRMS** (ESI^-) *m/z* $C_{18}H_{13}O_4N_2F_4S^-$ requires 429.0538 $[M-H]^-$, found 429.0538. Data is consistent with the literature.[137]

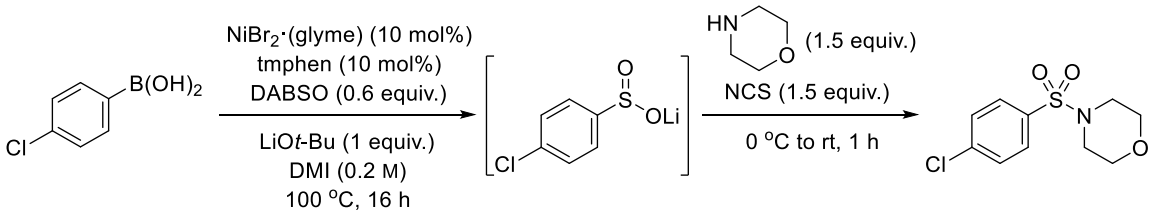
Using the original general procedure B also gave the desired product, but with *ca.* 15% inseparable side product.

(See the notes in general procedure A and B)

6.2.3 Synthesis of sulfonamides

General Procedure C: Two-Step Synthesis of Substituted Sulfonamides (Exemplified by the Preparation of Sulfonamide **11a**)

4-((4-Chlorophenyl)sulfonyl)morpholine (11a)[35]



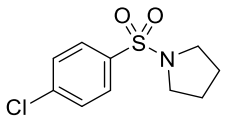
4-Chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) were added to a 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 (× 4). DMI (1.0 mL) was added and the reaction mixture was heated at 100 ℃ for 16 h. After cooling the solution to 0 ℃, morpholine (26 µL, 0.30 mmol, 1.5 equiv.) and NCS (40.1 mg, 0.30 mmol, 1.5 equiv.) were added. The reaction mixture was then stirred at rt for 1 h. The reaction was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (20% EtOAc in Petrol) afforded the title product as a white solid (41.1 mg, 79%).

R_f (20% EtOAc in Petrol) = 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.52 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.77 – 3.69 (m, 4H, OCH_2), 3.02 – 2.95 (m, 4H,

NC*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.8, 133.8, 129.6, 129.3, 66.1, 46.0; **LRMS** (ESI^+) *m/z* 284.0 ($[M+Na]^+$), 545.0 ($[2M+Na]^+$). Data is consistent with the literature.[35]

Note: replacing NCS with SO_2Cl_2 or aq. NaOCl also resulted the desired sulfonamide but with lower yield (50-60%). (Also see the notes in general procedure A)

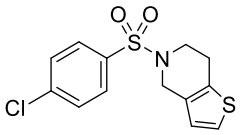
1-((4-Chlorophenyl)sulfonyl)pyrrolidine (11b)[17a]



Prepared according to general procedure C using 4-chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.), pyrrolidine (25 µL, 0.30 mmol, 1.5 equiv.) and NCS (40.1 mg, 0.30 mmol, 1.5 equiv.). Purification by flash column chromatography (20% EtOAc in Petrol) afforded the title product as an off-white solid (35.2 mg, 72%).

R$_f$ (20% EtOAc in Petrol) = 0.31; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.50 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.26 – 3.20 (m, 4H, NC*H*$_2$), 1.80 – 1.74 (m, 4H, NCH_2CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.2, 135.7, 129.4, 129.0, 48.1, 25.4; **LRMS** (ESI^+) *m/z* 246.0 ($[M+H]^+$), 268.0 ($[M+Na]^+$). Data is consistent with the literature.[17a]

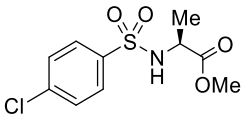
5-((4-Chlorophenyl)sulfonyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (11c)



Prepared according to general procedure C using 4-chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2 \cdot$(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.), 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (41.8 mg, 0.30 mmol, 1.5 equiv.) and NCS (40.1 mg, 0.30 mmol, 1.5 equiv.). Purification by flash column chromatography (10% EtOAc in Petrol) afforded the title product as a white solid (49.4 mg, 79%).

R_f (10% EtOAc in Petrol) = 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.49 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.11 (d, *J* = 5.0 Hz, 1H, Ar-*H*), 6.72 (d, *J* = 5.0 Hz, 1H, Ar-*H*), 4.23 (s, 2H, NCH_2C), 3.45 (t, *J* = 5.5 Hz, 2H, NCH_2CH_2), 2.90 (t, *J* = 5.5 Hz, 2H, NCH_2CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.5, 135.5, 132.6, 130.4, 129.5, 129.0, 124.7, 123.9, 45.9, 44.0, 25.2; **LRMS** (ESI^+) *m/z* 649.0 ($[2M+Na]^+$); **HRMS** (ESI^+) *m/z* $C_{13}H_{13}{}^{35}ClNO_2S_2{}^+$ requires 314.0071 $[M+H]^+$, found 314.0071; **IR** (thin film, ν_{max}/cm^{-1}) 2918, 1346, 1166, 937, 763; **m.p.** (CH_2Cl_2): 180-181 °C.

Methyl ((4-chlorophenyl)sulfonyl)-*L*-alaninate (11d)[138]

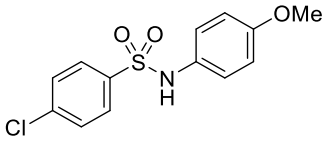


4-Chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) were added to a 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 (× 4). DMI (1.0 mL) was added and the reaction mixture was heated at 100 °C for 16 h. After cooling the solution at 0 °C, L-alanine methyl ester hydrochloride (41.6 mg, 0.30 mmol, 1.5 equiv.), DIPEA (70 µL, 0.40 mmol, 2.0 equiv.) and NCS (40.1 mg, 0.30 mmol, 1.5 equiv.) were added. The reaction mixture was then stirred at rt for 1 h. The reaction was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (30-40% EtOAc in Petrol) afforded the title product as a white solid (22.0 mg, 40%, >99% ee).

R_f (40% EtOAc in Petrol) = 0.50; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.47 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 5.34 (d, *J* = 8.5 Hz, 1H, N*H*), 4.00 (dq, *J* = 8.5, 7.0 Hz, 1H, NHC*H*), 3.57 (s, 3H, O*Me*), 1.39 (d, *J* = 7.0 Hz, 3H, *Me*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.6, 139.5, 138.5, 129.5, 128.8, 52.8, 51.6, 20.0; **HRMS** (ESI^+) *m/z* $C_{10}H_{12}O_4N^{35}ClNaS^+$ requires 300.0068 $[M+Na]^+$, found 300.0068; the **ee** was determined by HPLC using a Chiralpak IA-3 column (*n*-hexane/*i*-PrOH, 96:4); flow rate 1.0 mL/min;

τ_{major} = 41.87 min, τ_{minor} = 45.65 min (>99% ee); $[\alpha]_D^{25}$ +5.6° (*c* = 1.0, $CHCl_3$). Data is consistent with the literature.[138]

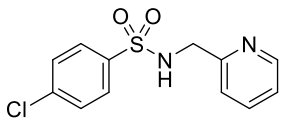
4-Chloro-*N*-(4-methoxyphenyl)benzenesulfonamide (11e)[139]



Prepared according to general procedure C using 4-chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.), 4-methoxyaniline (36.9 mg, 0.30 mmol, 1.5 equiv.) and NCS (40.1 mg, 0.30 mmol, 1.5 equiv.). Purification by flash column chromatography (20% EtOAc in Petrol) afforded the title product as a brown solid (34.2 mg, 57%).

R_f (20% EtOAc in Petrol) = 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.40 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 6.97 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 6.78 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 6.39 (s, 1H, N*H*), 3.77 (s, 3H, O*Me*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.4, 139.5, 137.6, 129.4, 128.9, 128.5, 125.8, 114.7, 55.6; **HRMS** (ESI^+) *m/z* $C_{13}H_{12}O_3N^{35}ClNaS^+$ requires 320.0119 $[M+Na]^+$, found 320.0120. Data is consistent with the literature.[139]

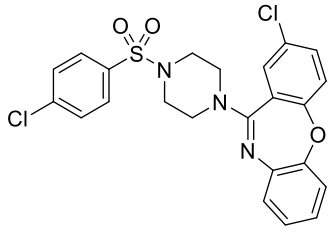
4-Chloro-*N*-(pyridin-2-ylmethyl)benzenesulfonamide (11f)



Prepared according to general procedure C using 4-chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.), 2-pyridinylmethanamine (31 µL, 0.30 mmol, 1.5 equiv.) and NCS (40.1 mg, 0.30 mmol, 1.5 equiv.). Purification by flash column chromatography (60% EtOAc in Petrol) afforded the title product as an off-white solid (32.6 mg, 58%).

R_f (60% EtOAc in Petrol) = 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 5.0, 2.0 Hz, 1H, Ar-*H*), 7.75 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.60 (app. td, *J* = 7.5, 2.0 Hz, 1H, Ar-*H*), 7.38 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.20 – 7.12 (m, 2H, Ar-*H*), 6.42 (t, *J* = 5.0 Hz, 1H, N*H*), 4.26 (d, *J* = 5.0 Hz, 2H, NCH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.7, 149.1, 139.1, 138.4, 137.0, 129.3, 128.7, 122.9, 122.2, 47.5; **HRMS** (ESI^+) *m/z* $C_{12}H_{12}O_2N_2{}^{35}ClS^+$ requires 283.0303 $[M+H]^+$, found 283.0301; **IR** (thin film, ν_{max}/cm^{-1}) 2981, 2360, 1332, 1161, 1094, 753; **m.p.** (CH_2Cl_2): 118-119 °C.

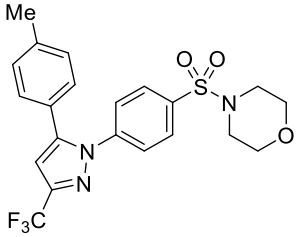
2-Chloro-11-(4-((4-chlorophenyl)sulfonyl)piperazin-1-yl)dibenzo[*b,f*][1,4]oxazepine (11g)



Prepared according to general procedure C using 4-chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.), amoxapine (94.1 mg, 0.30 mmol, 1.5 equiv.) and NCS (40.1 mg, 0.30 mmol, 1.5 equiv.). Purification by flash column chromatography (30% Et_2O in Petrol) afforded the title product as a colourless viscous oil which solidified in a freezer to an off-white solid (49.1 mg, 50%).

R_f (30% Et_2O in Petrol) = 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.53 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.39 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar-*H*), 7.21 – 7.15 (m, 2H, Ar-*H*), 7.12 – 7.05 (m, 3H, Ar-*H*), 7.03 – 6.97 (m, 1H, Ar-*H*), 3.63 (s, 4H, $SO_2NC\mathit{H}_2$), 3.14 (s, 4H, $SO_2NCH_2C\mathit{H}_2N$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 158.3, 151.7, 139.9, 139.7, 134.4, 133.0, 130.6, 129.8, 129.2, 128.8, 127.2, 126.0, 125.2, 124.6, 123.0, 120.3, 46.9, 45.7; **LRMS** (ESI^+) *m/z* 488.1 ($[M+H]^+$), 975.2 ($[2M+H]^+$); **HRMS** (ESI^+) *m/z* $C_{23}H_{20}O_3N_3{}^{35}Cl_2S^+$ requires 488.0597 $[M+H]^+$, found 488.0596; **IR** (thin film, ν_{max}/cm^{-1}) 2981, 1587, 1471, 1353, 1167, 944, 761; **m.p.** (CH_2Cl_2): 209-211 °C.

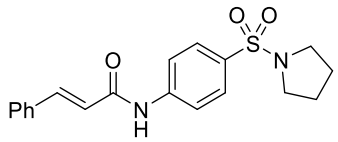
4-((4-(5-(*p*-Tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)sulfonyl)morpholine (11h)[35]



Prepared according to general procedure C using (4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)boronic acid (69.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.), morpholine (26 µL, 0.30 mmol, 1.5 equiv.) and NCS (40.1 mg, 0.30 mmol, 1.5 equiv.). Purification by flash column chromatography (20% EtOAc in Petrol) afforded the title product as a white solid (66.7 mg, 74%).

R_f (20% EtOAc in Petrol) = 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.52 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.18 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.10 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.75 (s, 1H, Ar-*H*), 3.77 – 3.69 (m, 4H, OCH_2), 3.03 – 2.94 (m, 4H, NCH_2), 2.38 (s, 3H, *Me*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.4, 144.3 (q, J_{CF} = 38.5 Hz), 143.0, 140.0, 134.8, 129.9, 128.9, 128.8, 125.69, 125.66, 121.1 (q, J_{CF} = 269.0 Hz), 106.5, 66.1, 46.0, 21.4; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.4; **LRMS** (ESI^+) *m/z* 452.1 ($[M+H]^+$), 903.2 ($[2M+H]^+$); **HRMS** (ESI^+) *m/z* $C_{21}H_{21}F_3N_3O_3S^+$ requires 452.1250 $[M+H]^+$, found 452.1244; **IR** (thin film, ν_{max}/cm^{-1}) 1472, 1353, 1236, 1163, 1113, 944, 765, 731. Data is consistent with the literature.[35]

_N_-(4-(Pyrrolidin-1-ylsulfonyl)phenyl)cinnamamide, NP16 (11i)

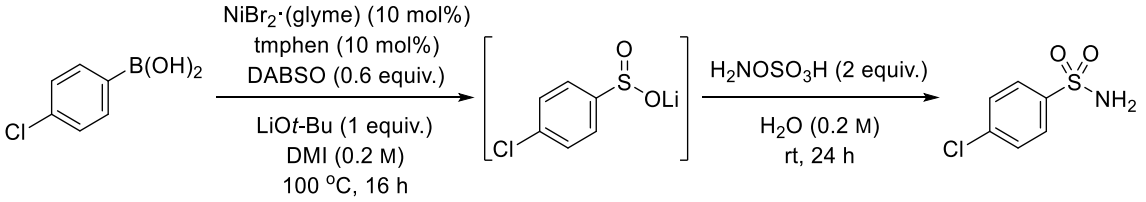


Prepared according to general procedure C using (4-cinnamamidophenyl)boronic acid (53.4 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) pyrrolidine (34 µL, 0.40 mmol, 2.0 equiv.) and NCS (53.4 mg, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (50% EtOAc in Petrol) afforded the title product as a pale yellow viscous oil which solidified on-standing to an off-white solid. (47.2 mg, 66%).

R_f (50% EtOAc in Petrol) = 0.38; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.59 (s, 1H, CON*H*), 7.87 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.80 – 7.73 (m, 3H, Ar-*H* and Ph-C*H*=CH), 7.52 – 7.47 (m, 2H, Ar-*H*), 7.38 – 7.30 (m, 3H, Ar-*H*), 6.72 (d, *J* = 15.5 Hz, 1H, Ph-CH=C*H*), 3.27 – 3.15 (m, 4H, NC*H*$_2$CH$_2$), 1.76 – 1.66 (m, 4H, NCH$_2$C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) 164.8, 143.5, 142.7, 134.5, 131.2, 130.4, 129.0, 128.8, 128.2, 120.5, 119.7, 48.2, 25.3; **LRMS** (ESI$^+$) *m/z* 713.2 ([2M+H]$^+$), 735.2 ([2M+Na]$^+$); **HRMS** (ESI$^+$) *m/z* $C_{19}H_{21}O_3N_2S^+$ requires 357.1267 [M+H]$^+$, found 357.1268; **IR** (thin film, ν_{max}/cm^{-1}) 3340, 1694, 1629, 1591, 1531, 1335, 1150; **m.p.** (CH_2Cl_2): 244-245 °C.

General Procedure D: Two-step synthesis of primary sulfonamides (exemplified by the preparation of sulfonamide **11j**)

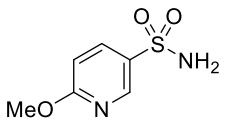
4-Chlorobenzenesulfonamide (11j)[140]



4-Chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) were added to a 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 (× 4). DMI (1.0 mL) was added and the reaction mixture was heated at 100 °C for 16 h. After cooling the solution to rt, hydroxylamine-*O*-sulfonic acid (45.2 mg, 0.40 mmol, 2.0 equiv.) and H_2O (1.0 mL) were added. The reaction mixture was then stirred at rt for 24 h. The reaction was quenched with sat. $NaHCO_3$ (10 mL) (caution: gas formation) and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (35% EtOAc in Pentane) afforded the product as a white solid (28.7 mg, 75%).

R_f (35% EtOAc in Pentane) = 0.29; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.83 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.65 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.45 (s, 2H, N*H*$_2$); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 143.0, 136.5, 129.0, 127.6; **LRMS** (ESI$^+$) *m/z* 209.0 ([M+NH_4]$^+$), 405.0 ([2M+Na]$^+$). Data is consistent with the literature.[140] (Also see the notes in general procedure A)

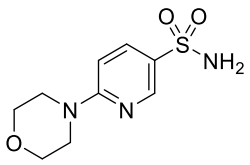
6-Methoxypyridine-3-sulfonamide (11k)[141]



Prepared according to general procedure D using 6-methoxy-3-pyridinylboronic acid (30.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.), hydroxylamine-*O*-sulfonic acid (45.2 mg, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (50% EtOAc in Petrol) afforded the title product as an off-white solid (26.6 mg, 71%).

R_f (50% EtOAc in Petrol) = 0.31; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.57 (dd, *J* = 2.5, 0.5 Hz, 1H, Ar-*H*), 8.06 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar-*H*), 7.44 (s, 2H, NH_2), 7.00 (dd, *J* = 9.0, 0.5 Hz, 1H, Ar-*H*), 3.92 (s, 3H, O*Me*); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.2, 145.2, 137.0, 133.9, 111.0, 54.0; **LRMS** (ESI^+) *m/z* 189.0 ($[M+H]^+$), 399.0 ($[2M+Na]^+$); **HRMS** (ESI^-) *m/z* $C_6H_7N_2O_3S^-$ requires 187.0183 $[M-H]^-$, found 187.0183; **IR** (thin film, ν_{max}/cm^{-1}) 3334, 3233, 2981, 2361, 1589, 1481, 1337, 1306, 1160, 741. Data is consistent with the literature.[141]

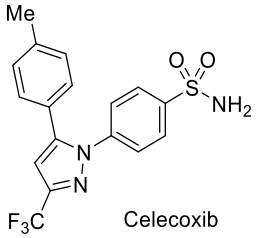
6-Morpholinopyridine-3-sulfonamide (11l)[142]



Prepared according to general procedure D using 6-(morpholino)pyridine-3-boronic acid (41.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.), hydroxylamine-*O*-sulfonic acid (45.2 mg, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (80% EtOAc in Petrol) afforded the title product as a yellow solid (33.7 mg, 69%).

R_f (80% EtOAc in Petrol) = 0.30; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.46 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 7.85 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar-*H*), 7.22 (s, 2H, NH_2), 6.94 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 3.71 – 3.65 (m, 4H, OCH_2), 3.60 – 3.55 (m, 4H, NCH_2); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 159.8, 145.8, 135.3, 128.7, 106.0, 65.8, 44.7; **LRMS** (ESI^+) *m/z* 244.1 ($[M+H]^+$), 487.2 ($[2M+H]^+$); **HRMS** (ESI^-) *m/z* $C_9H_{12}N_3O_3S^-$ requires 242.0605 $[M-H]^-$, found 242.0607; **IR** (thin film, ν_{max}/cm^{-1}) 3252, 2361, 1591, 1309, 1148, 1112, 943, 606. Data is consistent with the literature.[142]

Celecoxib (11m)[143]



Celecoxib

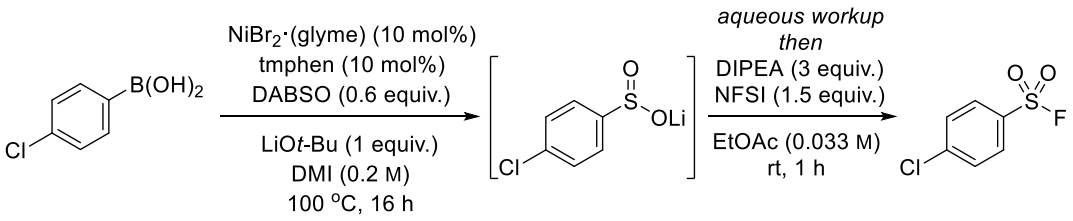
(4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)boronic acid (69.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) were added to a 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 four times. DMI (1.0 mL) was added and the reaction mixture was heated at 100 °C for 16 h. After cooling the solution at rt, hydroxylamine-*O*-sulfonic acid (113 mg, 1.0 mmol, 5.0 equiv) and H_2O (1.0 mL) were added. The reaction mixture was then stirred at 60 °C for 2 h. The reaction was quenched with sat. $NaHCO_3$ (10 mL) (caution: gas formation) and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (25-30% EtOAc in Petrol) afforded the product as an off-white solid (42.9 mg, 56%).

R_f (30% EtOAc in Petrol) = 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.46 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.18 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.10 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.74 (s, 1H, Ar-*H*), 5.11 (s, 2H, N*H*$_2$), 2.37 (s, 3H, *Me*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.4, 144.2 (q, J_{CF} = 38.5 Hz), 142.7, 141.4, 140.0, 129.9, 128.9, 127.6, 125.8, 125.6, 121.2 (q, J_{CF} = 269.5 Hz), 106.5, 21.5; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.4; **LRMS** (ESI^+) *m/z* 382.1 ($[M+H]^+$), 763.2 ($[2M+H]^+$). Data is consistent with the literature.[143]

6.2.4 Synthesis of sulfonyl fluorides

General Procedure E: Two-step synthesis of sulfonyl fluorides (exemplified by the preparation of sulfonyl fluoride **12a**)

4-Chlorobenzenesulfonyl fluoride (12a)[38]

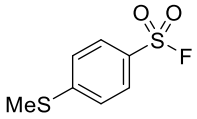


4-Chlorophenylboronic acid (31.3 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.) and LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.) were added to a 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 four times. DMI (1.0 mL) was added and the reaction mixture was heated at 100 ℃ for 16 h. After cooling the solution to rt, aq. H_3PO_4 (3 mL, 2 M) and brine (1 mL) were added to the mixture. The mixture was then extracted with EtOAc (3 × 2 mL). The combined organic phase was transferred to a 25 mL round-bottom flask and was added DIPEA (0.11 mL, 0.60 mmol, 3.0 equiv.). The solution became cloudy after adding DIPEA indicating the formation of sulfinate salt from sulfinic acid. NFSI (95 mg, 0.30 mmol, 1.5 equiv.) was added to the mixture, flushed with N_2 and sealed. The reaction mixture was then stirred at rt for 1 h. Without further workup, the reaction mixture was dry-loaded to silica gel which was then purified by flash column chromatography (10% CH_2Cl_2 in Petrol) to afford the product as a colourless oil (18.6 mg, 48%).

R_f (10% CH_2Cl_2 in Petrol) = 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.92 (m, 2H, Ar-*H*), 7.66 – 7.58 (m, 2H, Ar-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.8, 131.6 (d, J_{CF} = 26.0 Hz), 130.3, 130.0; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 66.5. Data is consistent with the literature.[38]

Note: Fluorination without aqueous workup in step 2 resulted in much lower yields (20-30%), possibly due to the intolerance of sulfonyl fluorides with strong base such as LiO*t*-Bu. Hence, an aqueous workup, previously adopted by Pfizer,[80] is required to achieve good yields of sulfonyl fluorides. (Also see the notes in general procedure A)

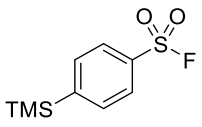
4-(Methylthio)benzenesulfonyl fluoride (12b)[38]



Prepared according to general procedure E using 4-(methylthio)phenylboronic acid (33.6 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.), NFSI (95 mg, 0.30 mmol, 1.5 equiv.). Purification by flash column chromatography (5% EtOAc in Petrol) afforded the title product as a white solid (28.5 mg, 69%).

R_f (5% EtOAc in Petrol) = 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.37 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 2.55 (s, 3H, S*Me*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.4, 128.7, 128.1 (d, J_{CF} = 24.5 Hz), 125.5, 14.8; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 66.9. Data is consistent with the literature.[38]

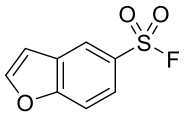
4-(Trimethylsilyl)benzenesulfonyl fluoride (12c)[38]



Prepared according to general procedure E using 4-(trimethylsilyl)phenylboronic acid (38.8 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.), NFSI (63 mg, 0.20 mmol, 1.0 equiv.). Purification by flash column chromatography (10% CH_2Cl_2 in Petrol) afforded the title product as a pale yellow oil (27.7 mg, 60%).

R_f (10% CH_2Cl_2 in Petrol) = 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.77 (app. dd, *J* = 8.5, 1.0 Hz, 2H, Ar-*H*), 0.33 (s, 9H, Si*Me*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.3, 134.5, 133.2 (d, J_{CF} = 24.0 Hz), 127.2, -1.4; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 65.9. Data is consistent with the literature.[38]

Benzofuran-5-sulfonyl fluoride (12d)



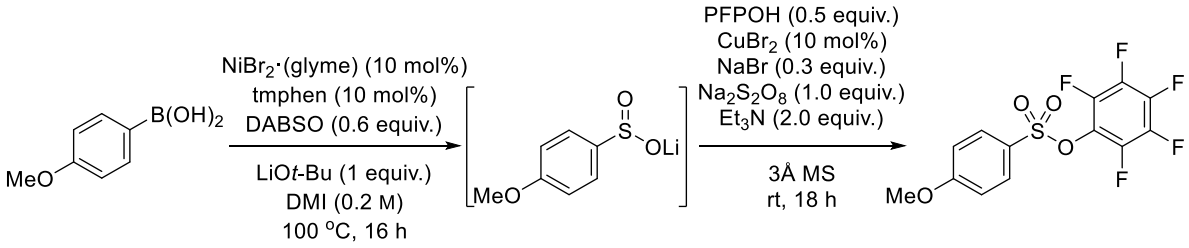
Prepared according to general procedure E using benzofuran-5-ylboronic acid (32.4 mg, 0.20 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (6.1 mg, 0.02 mmol, 10 mol%), tmphen (4.7 mg, 0.02 mmol, 10 mol%), DABSO (28.8 mg, 0.12 mmol, 0.6 equiv.), LiO*t*-Bu (16.0 mg, 0.20 mmol, 1.0 equiv.), NFSI (95 mg, 0.30 mmol, 1.5 equiv.). Purification by flash column

chromatography (5% EtOAc in Petrol) afforded the title product as a colourless oil (21.9 mg, 55%).

R_f (5% EtOAc in Petrol) = 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.96 (dd, *J* = 9.0, 2.0 Hz, 1H, Ar-*H*), 7.83 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 7.72 (app. dq, *J* = 9.0, 1.0 Hz, 1H, Ar-*H*), 6.95 (dd, *J* = 2.5, 1.0 Hz, 1H, Ar-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.2, 148.2, 128.4, 127.6 (d, J_{CF} = 24.5 Hz), 124.5, 123.4, 113.0, 107.3; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 67.9; **HRMS** (APCI$^-$) *m/z* $C_8H_4O_3FS^-$ requires 198.9871 $[M-H]^-$, found 198.9868; **IR** (thin film, ν_{max}/cm^{-1}) 2922, 2360, 1405, 1257, 1212, 1174, 764.

6.2.5 Synthesis of PFP sulfonate ester

Preparation of perfluorophenyl 4-methoxybenzenesulfonate (13)[82d]



Procedure for step 2 was adopted from a publication from our group,[82d] with a slightly different workup procedure.

4-Methoxyphenylboronic acid (76.0 mg, 0.50 mmol, 1.0 equiv.), $NiBr_2$·(glyme) (15.4 mg, 0.05 mmol, 10 mol%), tmphen (11.8 mg, 0.05 mmol, 10 mol%), DABSO (72.1 mg, 0.30 mmol, 0.6 equiv.) and LiO*t*-Bu (40.0 mg, 0.50 mmol, 1.0 equiv.) were added to a 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 (× 4). DMI (2.5 mL) was added and the reaction mixture was heated at 100 ℃ for 16 h. After cooling the solution to rt, pentafluorophenol (46 mg, 0.25 mmol, 0.5 equiv.) (*note 1*), $CuBr_2$ (11.2 mg, 0.05 mmol, 10 mol%), $Na_2S_2O_8$ (119 mg, 0.50 mmol, 1.0 equiv.), NaBr (15.5 mg, 0.15 mmol, 0.30 equiv.), 3 Å molecular sieves (*ca.* 250 mg) (*note 2*) and Et_3N (140 µL, 1 mmol, 2.0 equiv.) were added. The reaction vial was resealed under air and was stirred at rt for 18 h. The reaction was filtered through a plug of silica and washed with Et_2O and water (*ca.* 10 mL each). The two layers were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with aq. Na_2CO_3 (2 × 15 mL, 1M) (*note 3*), dried (Na_2SO_4), filtered and concentrated. Purification

by flash column chromatography (20% Et_2O in Petrol) afforded the title product as a pale yellow oil (36.5 mg, 52%). *(Product yield was calculated based on the pentafluorophenol.)*

R_f (20% Et_2O in Petrol) = 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.05 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 3.93 (s, 3H, O*Me*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.2, 142.4 (app. ddq, *J* = 257.5, 12.0, 3.5 Hz), 140.3 (app. dtt, *J* = 255.5, 13.5, 4.0 Hz), 138.0 (app. dtdd, *J* = 253.5, 14.5, 5.5, 3.0 Hz), 131.1, 125.9, 124.4 (app. tdt, *J* = 14.3, 5.0, 2.0 Hz), 114.9, 56.0; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -150.7, -155.7, -161.2; **LRMS** (ESI^+) *m/z* 377.0 ($[M+Na]^+$), 731.0 ($[2M+Na]^+$). Data is consistent with the literature.[82d]

Note:

1. Pentafluorophenol (mp 34-36 ℃) always melts while weighing to form a mixture of liquid and solid. Hence, it is advised to add pentafluorophenol by the following procedure: using a glass pipette to transfer a small amount of the reaction mixture from step 1 to a small vial containing pentafluorophenol (caution: a white fume formed). The solution containing pentafluorophenol was then transferred back to the mother liquid in the 10 mL reaction vial. These were done for another two times to ensure a quantitative transfer of the pentafluorophenol. (Adding warmed and melted pentafluorophenol using a syringe is not advised as it may solidify in the syringe and cause blockage.)

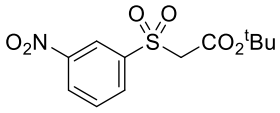
2. The molecular sieves were activated at *ca.* 200 ℃ under vacuum (< 1 mbar) overnight, crushed to powder and stored in 200 ℃ oven.

3. The aq. Na_2CO_3 removes any remaining pentafluorophenol which may coelute with the desired product on flash column chromatography. (pK_{aH} of CO_3^{2-}: 3.7; pK_a of pentafluorophenol: 5.5)

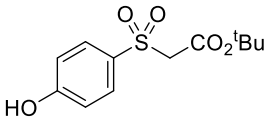
(Also see the notes in general procedure A)

6.2.6 Low yielding/unsuccessful substrate scope

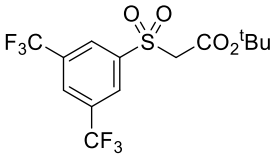
Sulfones (using general procedure A)



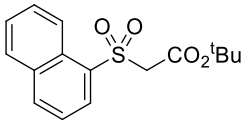
~32% isolated



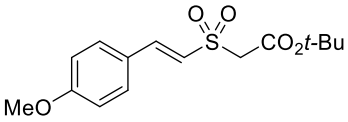
~24% isolated



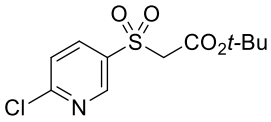
(NMR: 18%)



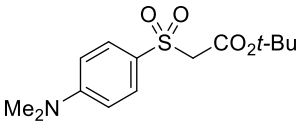
(NMR: 15-18%)



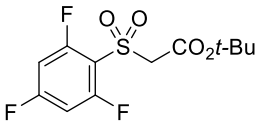
(NMR: 12%)



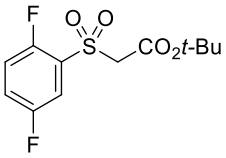
(NMR: 8%)



(NMR: no product)



(NMR no product)



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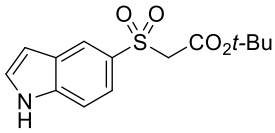
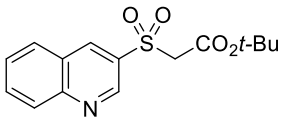
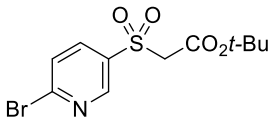


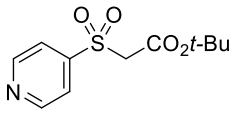
(NMR: no/trace product)



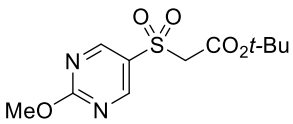
(NMR: no/trace product)



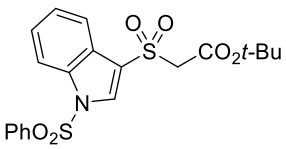
(NMR: no/trace; MS: no prod)



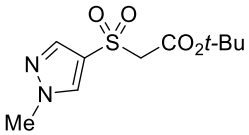
(NMR: no product)



(NMR: no product)

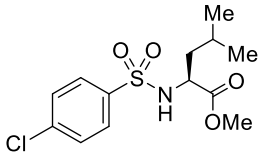


(NMR/MS: no product)

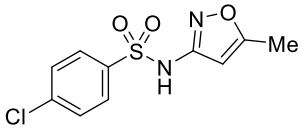


(NMR: no/trace product)

Sulfonamides (using general procedure C)

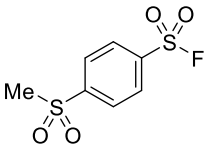


~33% isolated

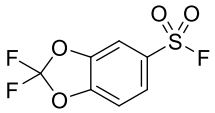


~26% isolated

Sulfonyl fluorides (using general procedure E)



~37%
(v.weak on TLC under UV+KMnO4
difficult column)

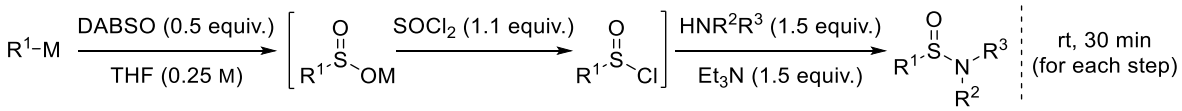


~16%

6.3 Data for chapter 3

6.3.1 Synthesis of sulfinamides

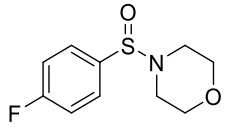
General Procedure F: One-pot Synthesis of sulfinamides.



Pre-dried DABSO (60 mg, 0.25 mmol, 0.5 equiv.) was added to an oven-dried 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 (× 3). Anhydrous THF (2 mL) was added. The organometallic reagent (0.50 mmol, 1.0 equiv.) was added dropwise to the resulting suspension at rt and the reaction mixture was stirred for 30 min. $SOCl_2$ (40 µL, 0.55 mmol, 1.1 equiv.) was then added dropwise and the mixture was stirred at rt for 30 min. After this, Et_3N (110 µL, 0.75 mmol, 1.5 equiv.) was added, followed by the corresponding amine (0.75 mmol, 1.5 equiv.). The mixture was stirred at rt for 30 min, then quenched with brine (10 mL) and extracted with EtOAc (3 × 10 mL). A few drops of water were added to dissolve any solid formed during the workup. The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography afforded the product.

Note: Anhydrous tetrahydrofuran (99.5%, Extra dry over molecular sieves, stabilized, AcroSeal) was purchased and used. DABSO was prepared using a literature method[29] and dried under reduced pressure (< 1 mbar) for at least 2 h before use. If the nucleophile was a solid, it was added as a solution in THF, otherwise, a complex mixture of products were observed.

4-((4-Fluorophenyl)sulfinyl)morpholine (18a)[100]

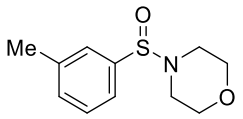


Prepared according to general procedure F using 4-fluorophenylmagnesium bromide (0.55 mL, 0.91 M in THF, 0.50 mmol, 1.0 equiv.) and morpholine (70 µL, 0.75 mmol, 1.5 equiv.). Purification by flash column chromatography (50% EtOAc in Petrol) afforded the title product as a white solid (95 mg, 83%).

Gram scale synthesis of **2a**: the same procedure was followed using 4-fluorophenylmagnesium bromide (6.0 mL, 1.01 M in THF, 6.0 mmol, 1.0 equiv.), DABSO (721 mg, 3.0 mmol, 0.5 equiv.), $SOCl_2$ (0.48 mL, 6.6 mmol, 1.1 equiv.), Et_3N (1.25 mL, 9.0 mmol, 1.5 equiv.), morpholine (0.79 mL, 9.0 mmol, 1.5 equiv.) and THF (24 mL), affording the title product (1.08 g, 79%).

***R*$_f$** (50% EtOAc in Petrol) = 0.32; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 – 7.57 (m, 2H, Ar-*H*), 7.20 – 7.11 (m, 2H, Ar-*H*), 3.71 – 3.61 (m, 4H, 2 × OCH_2), 3.11 (ddd, *J* = 12.0, 6.0, 3.5 Hz, 2H, 2 × NCH_aH$_b$), 2.90 (ddd, *J* = 12.0, 6.0, 3.5 Hz, 2H, 2 × NCH$_a$$H_b$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.5 (d, $^1J_{CF}$ = 251.5 Hz), 138.0 (d, $^4J_{CF}$ = 3.0 Hz), 128.5 (d, $^3J_{CF}$ = 9.0 Hz), 116.2 (d, $^2J_{CF}$ = 22.5 Hz), 66.9, 45.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.0; **LRMS** (ESI^+) *m/z* 481.7 ($[2M+Na]^+$). Data is consistent with the literature.[100]

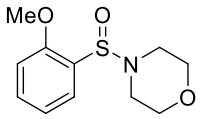
4-(*m*-Tolylsulfinyl)morpholine (18b)[101b]



Prepared according to general procedure F using *m*-tolylmagnesium chloride (0.65 mL, 0.77 M in THF, 0.50 mmol, 1.0 equiv.) and morpholine (70 µL, 0.75 mmol, 1.5 equiv.). Purification by flash column chromatography (50% EtOAc in Petrol) afforded the title product as a colourless oil (92 mg, 82%).

***R*$_f$** (50% EtOAc in Petrol) = 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.48 (s, 1H, Ar-*H*), 7.43 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.38 (app. t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.28 (d, *J* = 7.0 Hz, 1H, Ar-*H*), 3.77 – 3.63 (m, 4H, 2 × OCH_2), 3.19 – 3.10 (m, 2H, 2 × NCH_aH$_b$), 3.01 – 2.91 (m, 2H, 2 × NCH$_a$$H_b$), 2.42 (s, 3H, Ar-*Me*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.1, 139.1, 131.9, 128.8, 126.5, 123.2, 66.9, 45.8, 21.4; **LRMS** (ESI$^+$) *m/z* 226.0 ([M+H]$^+$), 248.0 ([M+Na]$^+$). Data is consistent with the literature.[101b]

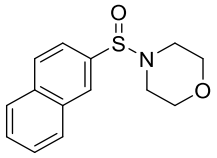
4-((2-Methoxyphenyl)sulfinyl)morpholine (18c)[100]



Prepared according to general procedure F using 2-methoxyphenylmagnesium bromide solution (0.49 mL, 1.02 M in THF, 0.50 mmol, 1.0 equiv.) and morpholine (70 µL, 0.75 mmol, 1.5 equiv.). Purification by flash column chromatography (60% EtOAc in Petrol) afforded the title product as a pale yellow oil which solidified on-standing to an off-white solid (95 mg, 79%).

***R*$_f$** (60% EtOAc in Petrol) = 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 7.45 (app. t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.12 (app. t, *J* = 7.5 Hz, 1H, Ar-*H*), 6.94 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 3.88 (s, 3H, O*Me*), 3.72 – 3.61 (m, 4H, 2 × OCH_2), 3.16 – 3.08 (m, 2H, 2 × NCH_aH_b), 2.94 – 2.86 (m, 2H, 2 × NCH_aH_b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.9, 132.9, 129.6, 127.2, 120.9, 111.4, 67.3, 56.0, 45.4; **LRMS** (ESI^+) *m/z* 264.0 ($[M+Na]^+$). Data is consistent with the literature.[100]

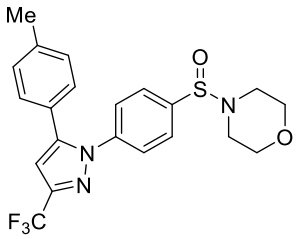
4-(Naphthalen-2-ylsulfinyl)morpholine (18d)[101b]



Prepared according to general procedure F using 2-naphthylmagnesium bromide (0.98 mL, 0.51 M in THF, 0.50 mmol, 1.0 equiv.) and morpholine (70 µL, 0.75 mmol, 1.5 equiv.). Purification by flash column chromatography (50% EtOAc in Petrol) afforded the title product as a pale yellow viscous oil (105 mg, 80%).

***R*$_f$** (50% EtOAc in Petrol) = 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (s, 1H, Ar-*H*), 7.99 – 7.85 (m, 3H, Ar-*H*), 7.63 – 7.52 (m, 3H, Ar-*H*), 3.78 – 3.63 (m, 4H, 2 × OCH_2), 3.20 (ddd, *J* = 12.0, 6.0, 3.5 Hz, 2H, 2 × NCH_aH_b), 2.98 (ddd, *J* = 12.0, 6.0, 3.5 Hz, 2H, 2 × NCH_aH_b); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.5, 134.5, 132.8, 129.1, 128.9, 128.03, 127.96, 127.3, 122.0, 67.0, 46.0, 1 × ArC not observed; **LRMS** (ESI^+) *m/z* 284.0 ($[M+Na]^+$). Data is consistent with the literature.[101b]

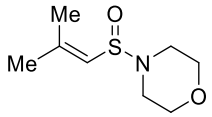
4-((4-(5-(*p*-Tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)sulfinyl)morpholine (18e)



1-(4-Bromophenyl)-5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazole[58] (191 mg, 0.50 mmol, 1.0 equiv.) and anhydrous THF (5 mL) were added to an oven-dried 25 mL RBF under N_2 (balloon) and cooled to –78 °C. *n*-Butyllithium (0.21 mL, 2.37 M in THF, 0.50 mmol, 1.0 equiv.) was added dropwise and the reaction was stirred at –78 °C for 1 h. A sonicated suspension (prepared in an oven-dried vial under N_2) of pre-dried DABSO (72 mg, 0.30 mmol, 0.6 equiv.) in anhydrous THF (5 mL) was added slowly before warming to rt for 30 min. $SOCl_2$ (40 µL, 0.55 mmol, 1.1 equiv.) was then added dropwise and the mixture was stirred at rt for 30 min. Et_3N (110 µL, 0.75 mmol, 1.5 equiv.) and morpholine (70 µL, 0.75 mmol, 1.5 equiv.) were added. The mixture was stirred at rt for 30 min, then quenched with brine (10 mL) and extracted with EtOAc (3 × 10 mL). A few drops of water were added to dissolve any solid formed during the workup. The combined organic phases were dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (50% EtOAc in Petrol) afforded the title product as a pale yellow viscous oil (154 mg, 70%).

***R*$_f$** (50% EtOAc in Petrol) = 0.31; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 2H, Ar-*H*), 7.50 – 7.44 (m, 2H, Ar-*H*), 7.16 – 7.11 (m, 2H, Ar-*H*), 7.11 – 7.06 (m, 2H, Ar-*H*), 6.73 (s, 1H, Ar-*H*), 3.77 – 3.62 (m, 4H, 2 × OC*H*$_2$), 3.20 – 3.11 (m, 2H, 2 × NC*H*$_a$H$_b$), 2.99 – 2.89 (m, 2H, 2 × NCH$_a$*H*$_b$), 2.35 (s, 3H, *Me*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.3, 143.9 (q, $^2J_{CF}$ = 38.5 Hz), 142.4, 141.6, 139.7, 129.7, 128.8, 127.3, 125.9, 125.8, 121.2 (q, $^1J_{CF}$ = 269.5 Hz), 106.0, 66.9, 46.0, 21.4; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.4; **LRMS** (ESI^+) *m/z* 436.0 ($[M+H]^+$); 458.0 ($[M+Na]^+$); **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{21}O_2N_3F_3S$ 436.1301; Found 436.1296; **IR** (thin film, *ν*max/cm^{-1}) 1472, 1373, 1235, 1160, 1133, 1096, 1069, 976, 916, 807, 729.

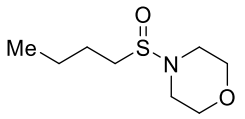
4-((2-Methylprop-1-en-1-yl)sulfinyl)morpholine (18f)



Prepared according to general procedure F using 2-methyl-1-propenylmagnesium bromide (1.01 mL, 0.49 M in THF, 0.50 mmol, 1.0 equiv.), THF (5 mL) and morpholine (70 µL, 0.75 mmol, 1.5 equiv.). Purification by flash column chromatography (0 − 5% MeOH in EtOAc) afforded the title product as a pale yellow oil (30 mg, 32%).

***R*$_f$** (100% EtOAc) = 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.93 (app. h, *J* = 1.5 Hz, 1H, SC*H*), 3.74 (app. t, *J* = 5.0 Hz, 4H, 2 × OC*H*$_2$), 3.11 (app dd, *J* = 5.5, 4.0 Hz, 4H, 2 × NC*H*$_2$), 1.91 (d, *J* = 1.0 Hz, 3H, C*H*$_3$), 1.87 (d, *J* = 1.0 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.9, 129.1, 66.9, 45.4, 25.8, 20.1; **LRMS** (ESI^+) *m/z* 190.0 ($[M+H]^+$); 212.0 ($[M+Na]^+$); **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_8H_{16}O_2NS$ 190.0896; Found 190.0896; **IR** (thin film, *ν*max/cm^{-1}) 2855, 1635, 1442, 1258, 1110, 1064, 1037, 914, 795, 695.

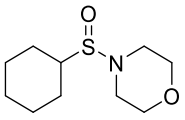
4-(Butylsulfinyl)morpholine (18g)



Prepared according to general procedure F using butylmagnesium chloride (0.23 mL, 2.14 M in THF, 0.50 mmol, 1.0 equiv.) and morpholine (70 µL, 0.75 mmol, 1.5 equiv.). The step 2 was left for 5 min instead. Purification by flash column chromatography (100% EtOAc) afforded the title product as a pale yellow oil (68 mg, 71%).

***R*$_f$** (100% EtOAc) = 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.82 – 3.69 (m, 4H, 2 × OC*H*$_2$), 3.21 – 3.06 (m, 4H, 2 × NC*H*$_2$), 2.83 – 2.67 (m, 2H, 2H, SC*H*$_2$), 1.58 (app. dq, *J* = 15.0, 8.0 Hz, 2H, 2H, SCH_2CH_2), 1.44 (p, *J* = 7.5 Hz, 2H, CH_2CH_3), 0.93 (t, *J* = 7.5 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 67.0, 51.9, 45.9, 25.6, 22.1, 13.8; **LRMS** (ESI^+) *m/z* 192.0 ($[M+H]^+$), 214.0 ($[M+Na]^+$); **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_8H_{18}O_2NS$ 192.1053; Found 192.1054; **IR** (thin film, *ν*max/cm^{-1}) 2980, 1653, 1455, 1382, 1259, 1111, 1068, 1038, 920.

4-(Cyclohexylsulfinyl)morpholine (18h)

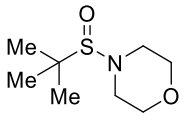


Prepared according to general procedure F using cyclohexylmagnesium chloride (0.26 mL, 1.90 M in Et_2O, 0.50 mmol, 1.0 equiv.) and morpholine (70 µL, 0.75 mmol, 1.5 equiv.). Purification by flash column chromatography (0−5% MeOH in EtOAc) afforded the title

product as a colourless oil (87 mg, 80%).

***R*$_f$** (5% MeOH in EtOAc) = 0.50; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.82 – 3.68 (m, 4H, 2 × OC*H*$_2$), 3.21 – 3.04 (m, 4H, 2 × NC*H*$_2$), 2.75 – 2.63 (m, 1H, SC*H*), 2.15 – 2.05 (m, 1H, Alk-*H*), 1.93 – 1.60 (m, 4H, Alk-*H*), 1.46 – 1.14 (m, 5H, Alk-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 67.0, 58.8, 46.3, 27.2, 26.8, 25.6, 25.3; **LRMS** (ESI^+) *m/z* 218.2 ($[M+H]^+$), 240.0 ($[M+Na]^+$); **HRMS** (ESI) *m/z*: Calcd $[M+H]^+$ for $C_{10}H_{20}O_2NS$ 218.1209; Found 218.1211; **IR** (thin film, ν_{max}/cm^{-1}) 2925, 2853, 1450, 1257, 1111, 1066, 917.

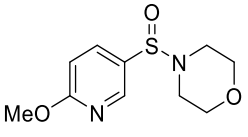
4-(*tert*-Butylsulfinyl)morpholine (18i)[144]



Prepared according to general procedure F using *tert*-butylmagnesium chloride solution (0.53 mL, 0.94 M in THF, 0.50 mmol, 1.0 equiv.) and morpholine (70 µL, 0.75 mmol, 1.5 equiv.). Purification by flash column chromatography (100% EtOAc) afforded the title product as a white solid (79 mg, 82%).

***R*$_f$** (100% EtOAc) = 0.35; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.77 – 3.69 (m, 4H, 2 × OC*H*$_2$), 3.21 – 3.13 (m, 2H, 2 × NC*H*$_a$H$_b$), 3.13 – 3.05 (m, 2H, 2 × NCH$_a$*H*$_b$), 1.19 (s, 9H, C*Me*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 67.3, 58.8, 47.5, 23.2; **LRMS** (ESI^+) *m/z* 192.3 ($[M+H]^+$), 214.3 ($[M+Na]^+$); **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_8H_{18}O_2NS$ 192.1053; Found 192.1055. Data is consistent with enantiomerically pure compound.[144]

4-((6-Methoxypyridin-3-yl)sulfinyl)morpholine (18j)

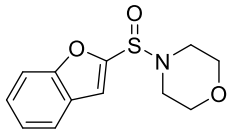


5-Bromo-2-methoxypyridine (65 µL, 0.50 mmol, 1.0 equiv.) and anhydrous THF (5 mL) were added to an oven-dried 25 mL RBF under N_2 (balloon) and cooled to –78 °C. *n*-Butyllithium (0.21 mL, 2.37 M in THF, 0.50 mmol, 1.0 equiv.) was added dropwise and the reaction was stirred at –78 °C for 40 min. A sonicated suspension (prepared in an oven-dried vial under N_2) of pre-dried DABSO (72 mg, 0.30 mmol, 0.6 equiv.) in anhydrous THF (5 mL) was added slowly before warming to rt for 30 min. $SOCl_2$ (40 µL, 0.55 mmol, 1.1 equiv.) was then added dropwise and the mixture was stirred at rt for 30 min. Et_3N (110 µL, 0.75 mmol, 1.5 equiv.) and morpholine (70 µL, 0.75 mmol, 1.5 equiv.) were added. The mixture was stirred at rt for 30 min, then quenched with brine (10 mL) and extracted with EtOAc (3 × 10 mL). A few drops of water were added to dissolve any solid formed during the workup. The combined organic phases were dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (70% EtOAc in Petrol) afforded the title product as a pale yellow viscous oil (92 mg, 76%).

***R*$_f$** (70% EtOAc in Petrol) = 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 2.5, 0.5 Hz, 1H, Ar-*H*), 7.76 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar-*H*), 6.81 (dd, *J* = 8.5, 0.5 Hz, 1H, Ar-*H*), 3.95 (s, 3H, O*Me*), 3.75 – 3.64 (m, 4H, 2 × OCH_2), 3.18 – 3.10 (m, 2H, 2 × NCH_aH$_b$), 3.02 – 2.93 (m, 2H, 2 × NCH$_a$$H_b$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.1, 146.4, 136.6, 130.9, 111.5, 66.9, 54.1, 45.8; **LRMS** (ESI$^+$) *m/z* 243.0 ([M+H]$^+$); 265.0 ([M+Na]$^+$); **HRMS** (ESI) *m/z*:

$[M+H]^+$ Calcd for $C_{10}H_{15}O_3N_2S$ 243.0798; Found 243.0798; **IR** (thin film, ν_{max}/cm^{-1}) 2854, 1587, 1477, 1366, 1281, 1257, 1095, 1069, 1015, 916, 834, 694.

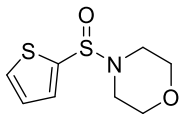
4-(Benzofuran-2-ylsulfinyl)morpholine (18k)[100]



Benzofuran (55 µL, 0.50 mmol, 1.0 equiv.) and anhydrous THF (1.5 mL) were added to an oven-dried 10 mL reaction vial under N_2 (balloon) and cooled to 0 ℃. *n*-Butyllithium (0.21 mL, 2.37 M in THF, 0.50 mmol, 1.0 equiv.) was added dropwise and the reaction was stirred at 0 ℃ for 5 min before reaching to rt for 1 h. The mixture was transferred *via* a syringe and added dropwise to a stirred suspension of pre-dried DABSO (60 mg, 0.25 mmol, 0.5 equiv.) in THF (2.0 mL) in an oven-dried 10 mL reaction vial at rt. The mixture was then stirred at rt for 30 min. $SOCl_2$ (40 µL, 0.55 mmol, 1.1 equiv.) was added dropwise and the mixture was stirred at rt for 30 min. Et_3N (110 µL, 0.75 mmol, 1.5 equiv.) and morpholine (70 µL, 0.75 mmol, 1.5 equiv.) were added. The mixture was stirred at rt for 30 min, then quenched with brine (10 mL) and extracted with EtOAc (3 × 10 mL). A few drops of water were added to dissolve any solid formed during the workup. The combined organic phases were dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (40% EtOAc in Petrol) afforded the title product as a yellow oil (83 mg, 66%).

***R*$_f$** (40% EtOAc in Petrol) = 0.25; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (app. dt, *J* = 7.5, 1.0 Hz, 1H, Ar-*H*), 7.53 (app. dq, *J* = 8.5, 1.0 Hz, 1H, Ar-*H*), 7.38 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H, Ar-*H*), 7.34 (d, *J* = 1.0 Hz, 1H, Ar-*H*), 7.30 (app. td, *J* = 7.5, 1.0 Hz, 1H, Ar-*H*), 3.83 – 3.65 (m, 4H, 2 × OCH_2), 3.31 (ddd, *J* = 12.5, 6.0, 4.0 Hz, 2H, 2 × NCH_aH$_b$), 3.14 (ddd, *J* = 12.5, 6.0, 4.0 Hz, 2H, 2 × NCH$_a$$H_b$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.9, 154.4, 126.9, 126.5, 123.9, 122.3, 112.3, 112.1, 67.0, 46.1; **LRMS** (ESI$^+$) *m/z* 274.0 ([M+Na]$^+$). Data is consistent with the literature.[100]

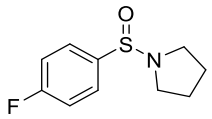
4-(Thiophen-2-ylsulfinyl)morpholine (18l)[101c]



Prepared according to general procedure F using 2-thienylmagnesium bromide solution (0.59 mL, 0.85 M in THF, 0.50 mmol, 1.0 equiv.) and morpholine (70 µL, 0.75 mmol, 1.5 equiv.). Purification by flash column chromatography (50% EtOAc in Petrol) afforded the title product as an orange oil (68 mg, 63%).

***R*$_f$** (50% EtOAc in Petrol) = 0.31; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar-*H*), 7.41 (dd, *J* = 3.5, 1.5 Hz, 1H, Ar-*H*), 7.14 (dd, *J* = 5.0, 3.5 Hz, 1H, Ar-*H*), 3.81 – 3.70 (m, 4H, 2 × OCH_2), 3.25 – 3.17 (m, 2H, 2 × NCH_aH$_b$), 3.16 – 3.08 (m, 2H, 2 × NCH$_a$$H_b$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.3, 131.8, 130.6, 128.1, 67.1, 45.9; **LRMS** (ESI$^+$) *m/z* 240.0 ([M+Na]$^+$). Data is consistent with the literature.[101c]

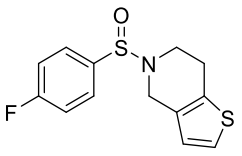
1-((4-Fluorophenyl)sulfinyl)pyrrolidine (19a)



Prepared according to general procedure F using 4-fluorophenylmagnesium bromide (0.51 mL, 0.98 M in THF, 0.50 mmol, 1.0 equiv.) and pyrrolidine (63 µL, 0.75 mmol, 1.5 equiv.). Purification by flash column chromatography (30% EtOAc in Petrol) afforded the title product as a pale yellow oil (80 mg, 75%).

***R*$_f$** (30% EtOAc in Petrol) = 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 2H, Ar-*H*), 7.20 – 7.12 (m, 2H, Ar-*H*), 3.37 – 3.28 (m, 2H, 2 × NC*H*$_a$H$_b$), 3.03 – 2.92 (m, 2H, 2 × NCH$_a$*H*$_b$), 1.90 – 1.78 (m, 4H, 2 × NCH$_2$C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.2 (d, $^1J_{CF}$ = 250.5 Hz), 140.4 (d, $^4J_{CF}$ = 3.0 Hz), 128.2 (d, $^3J_{CF}$ = 9.0 Hz), 116.1 (d, $^2J_{CF}$ = 22.5 Hz), 46.1, 26.1; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -110.2; **LRMS** (ESI^+) *m/z* 236.3 ($[M+Na]^+$); **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{10}H_{13}ONFS$ 214.0696; Found 214.0699; **IR** (thin film, ν_{max}/cm^{-1}) 2967, 2876, 1587, 1488, 1222, 1084, 1062, 969, 836, 814.

5-((4-Fluorophenyl)sulfinyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (19b)

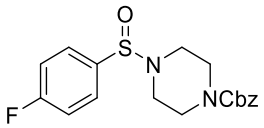


Prepared according to general procedure F using 4-fluorophenylmagnesium bromide (0.51 mL, 0.98 M in THF, 0.50 mmol, 1.0 equiv.) and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (90 µL, 0.75 mmol, 1.5 equiv.). Purification by flash column chromatography (20% EtOAc

in Petrol) afforded the title product as a pale yellow viscous oil (116 mg, 83%).

***R*$_f$** (20% EtOAc in Petrol) = 0.22; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 2H, Ar-*H*), 7.23 – 7.16 (m, 2H, Ar-*H*), 7.10 (d, *J* = 5.0 Hz, 1H, Ar-*H*), 6.68 (d, *J* = 5.0 Hz, 1H, Ar-*H*), 4.26 (d, *J* = 15.0 Hz, 1H, NC*H*$_a$H$_b$C), 3.90 (d, *J* = 15.0 Hz, 1H, NCH$_a$*H*$_b$C), 3.61 – 3.52 (m, 1H, NC*H*$_c$H$_d$CH$_e$H$_f$), 3.48 – 3.39 (m, 1H, NCH$_c$*H*$_d$CH$_e$H$_f$), 3.04 – 2.93 (m, 1H, NCH$_c$H$_d$C*H*$_e$H$_f$), 2.92 – 2.83 (m, 1H, NCH$_c$H$_d$CH$_e$*H*$_f$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.5 (d, $^1J_{CF}$ = 252.0 Hz), 138.7 (d, $^4J_{CF}$ = 2.9 Hz), 133.0, 131.8, 128.7 (d, $^3J_{CF}$ = 9.5 Hz), 125.1, 123.5, 116.3 (d, $^2J_{CF}$ = 22.5 Hz), 45.7, 43.9, 26.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -109.2; **LRMS** (ESI$^+$) *m/z* 282.4 ([M+H]$^+$), 304.4 ([M+Na]$^+$); **HRMS** (ESI) *m/z*: [M+Na]$^+$ Calcd for $C_{13}H_{12}ONFNaS_2$ 304.0237; Found 304.0237; **IR** (thin film, ν_{max}/cm^{-1}) 2848, 1587, 1488, 1223, 1086, 1064, 906, 836, 704.

Benzyl 4-((4-fluorophenyl)sulfinyl)piperazine-1-carboxylate (19c).

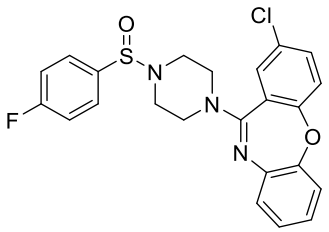


Prepared according to general procedure F using 4-fluorophenylmagnesium bromide (0.51 mL, 0.98 M in THF, 0.50 mmol, 1.0 equiv.) and benzyl piperazine-1-carboxylate (0.15 mL, 0.75 mmol, 1.5 equiv.). Purification by flash column chromatography (40% EtOAc in Petrol) afforded the title product as a pale yellow viscous oil (145 mg, 80%).

***R*$_f$** (40% EtOAc in Petrol) = 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 – 7.61 (m, 2H, Ar-*H*), 7.37 – 7.27 (m, 5H, Ar-*H*), 7.23 – 7.16 (m, 2H, Ar-*H*), 5.12 (s, 2H, C*H*$_2$), 3.65 – 3.45 (m, 4H,

2 × C(O)NCH$_2$), 3.18 – 3.08 (m, 2H, 2 × SNCH_aH$_b$), 3.02 – 2.90 (m, 2H, 2 × SNCH$_a$$H_b$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.6 (d, $^1J_{CF}$ = 252.0 Hz), 155.1, 138.2 (d, $^4J_{CF}$ = 3.0 Hz), 136.5, 128.6, 128.5 (d, $^3J_{CF}$ = 9.0 Hz), 128.3, 128.0, 116.3 (d, $^2J_{CF}$ = 22.5 Hz), 67.5, 45.8, 44.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -108.7; **LRMS** (ESI^+) *m/z* 385.0 ($[M+Na]^+$); **HRMS** (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{19}O_3N_2FNaS$ 385.0993; Found 385.1000; **IR** (thin film, ν_{max}/cm^{-1}) 1698, 1587, 1489, 1427, 1240, 1124, 1086, 1067, 914, 837, 697.

2-Chloro-11-(4-((4-fluorophenyl)sulfinyl)piperazin-1-yl)dibenzo[*b,f*][1,4]oxazepine (19d)

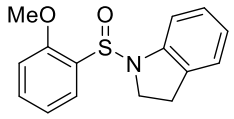


Prepared according to general procedure F using 4-fluorophenylmagnesium bromide (0.51 mL, 0.98 M in THF, 0.50 mmol, 1.0 equiv.) and Amoxapine (235 mg, 0.75 mmol, 1.5 equiv.). Purification by flash column chromatography (20% EtOAc in Petrol) afforded the title product as a pale yellow foam (158 mg, 69%).

R$_f$ (20% EtOAc in Petrol) = 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 2H, Ar-*H*), 7.34 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar-*H*), 7.25 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 7.22 – 7.15 (m, 2H, Ar-*H*), 7.15 – 7.09 (m, 2H, Ar-*H*), 7.09 – 7.03 (m, 2H, Ar-*H*), 7.01 – 6.95 (m, 1H, Ar-*H*), 3.53 (s, 4H, CNCH_2), 3.37 – 3.20 (m, 2H, 2 × SNCH_aH$_b$), 3.20 – 2.99 (m, 2H, 2 × SNCH$_a$$H_b$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.4 (d, $^1J_{CF}$ = 251.5 Hz), 159.3, 158.6, 151.7,

139.8, 138.2 (d, $^4J_{CF}$ = 3.0 Hz), 132.7, 130.4, 128.8, 128.5 (d, $^3J_{CF}$ = 9.0 Hz), 127.1, 125.8, 124.9, 124.7, 122.7, 120.1, 116.2 (d, $^2J_{CF}$ = 22.5 Hz), 47.7, 45.5; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -108.8; **LRMS** (ESI^+) *m/z* 478.1 ($[M+Na]^+$); **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{20}O_2N_3{}^{35}ClFS$ 456.0943; Found 456.0939; **IR** (thin film, *ν*max/cm^{-1}) 1561, 1471, 1399, 1238, 1086, 905, 836, 725; **m.p.** (CH_2Cl_2): 108-109 ℃.

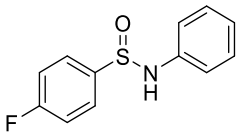
1-((2-Methoxyphenyl)sulfinyl)indoline (19e)



Prepared according to general procedure F using 2-methoxyphenylmagnesium bromide solution (0.49 mL, 1.02 M in THF, 0.50 mmol, 1.0 equiv.) and indoline (85 µL, 0.75 mmol, 1.5 equiv.). Purification by flash column chromatography (15−25% EtOAc in Petrol) afforded the title product as a brown solid (113 mg, 82%).

***R*$_f$** (15% EtOAc in Petrol) = 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.47 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, Ar-*H*), 7.23 – 7.13 (m, 3H, Ar-*H*), 7.11 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 6.95 – 6.85 (m, 2H, Ar-*H*), 4.06 – 3.93 (m, 1H, NH_aH$_b$), 3.76 (s, 3H, O*Me*), 3.13 – 2.88 (m, 3H, NH$_a$*H$_b$* and NH$_2$C*H$_2$*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.6, 146.6, 132.8, 130.7, 130.2, 127.5, 126.5, 125.1, 121.9, 120.8, 111.5, 111.2, 56.0, 42.1, 28.4; **LRMS** (ESI^+) *m/z* 296.0 ($[M+Na]^+$), 569.2 ($[2M+Na]^+$); **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{16}O_2NS$ 274.0896; Found 274.0895; **IR** (thin film, ν_{max}/cm^{-1}) 1590, 1477, 1274, 1240, 1088, 1050, 1016, 931, 749; **m.p.** (CH_2Cl_2): 116-118 ℃.

4-Fluoro-*N*-phenylbenzenesulfinamide (19f)[99]

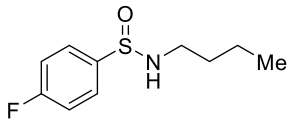


Pre-dried DABSO (60 mg, 0.25 mmol, 0.5 equiv.) was added to an oven-dried 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 (× 3). Anhydrous THF (2 mL) was added. 4-Fluorophenylmagnesium bromide (0.50 mL, 1.01 M in THF, 0.50 mmol, 1.0 equiv.) was added dropwise to the resulting suspension at rt and the reaction mixture was stirred for 30 min. $SOCl_2$ (40 µL, 0.55 mmol, 1.1 equiv.) was then added dropwise and the mixture was stirred at rt for 30 min. The reaction mixture was transferred *via* a syringe and added dropwise to a solution of Et_3N (110 µL, 0.75 mmol, 1.5 equiv.) and aniline (140 µL, 1.5 mmol, 3 equiv.) in THF (2 mL) in a 25 mL oven-dried RBF under N_2 at rt. Anhydrous THF (2 mL × 2) was then added to the reaction vial and transferred to the 25 mL RBF to ensure a quantitative transfer of the sulfinyl chloride. After addition, the mixture was stirred at rt for 30 min, then quenched with brine (10 mL) and extracted with EtOAc (3 × 10 mL). A few drops of water were added to dissolve any solid formed during the workup. The combined organic phases were dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (20−25% EtOAc in Petrol) afforded the title product as a pale yellow solid (97 mg, 82%).

***R*$_f$** (20% EtOAc in Petrol) = 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 – 7.71 (m, 2H, Ar-*H*), 7.31 – 7.24 (m, 2H, Ar-*H*), 7.23 – 7.17 (m, 2H, Ar-*H*), 7.11 – 7.04 (m, 3H, Ar-*H*), 6.30 (s, 1H, N-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.7 (d, $^1J_{CF}$ = 252.0 Hz), 140.4, 140.2 (d, $^4J_{CF}$

= 3.0 Hz), 129.6, 128.1 (d, $^{3}J_{CF}$ = 9.0 Hz), 124.0, 119.4, 116.4 (d, $^{2}J_{CF}$ = 23.0 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -108.4; **LRMS** (ESI^+) *m/z* 258.0 ($[M+Na]^+$); **HRMS** (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{12}H_{10}ONFNaS$ 258.0359; Found 258.0361; **IR** (thin film, ν_{max}/cm^{-1}) 3174, 1586, 1487, 1224, 1154, 1085, 1055, 882, 816, 745, 688; **m.p.** (CH_2Cl_2): 115-117 ℃.

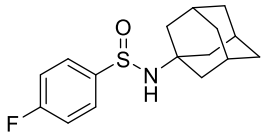
***N*-Butyl-4-fluorobenzenesulfinamide (19g)**[145]



Prepared according to general procedure F using 4-fluorophenylmagnesium bromide (0.51 mL, 0.98 M in THF, 0.50 mmol, 1.0 equiv.) and *n*-butylamine (74 µL, 0.75 mmol, 1.5 equiv.). Purification by flash column chromatography (30% EtOAc in Petrol) afforded the title product as a pale yellow oil (77 mg, 71%).

***R*$_f$** (30% EtOAc in Petrol) = 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 2H, Ar-*H*), 7.17 – 7.10 (m, 2H, Ar-*H*), 4.28 (t, *J* = 6.0 Hz, 1H, N-*H*), 3.11 – 3.01 (m, 1H, $NHCH_aH_b$), 2.80 – 2.69 (m, 1H, $NHCH_aH_b$), 1.49 – 1.40 (m, 2H, $NHCH_2CH_2$), 1.33 – 1.23 (m, 2H, CH_2CH_3), 0.83 (t, *J* = 7.3 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.4 (d, $^{1}J_{CF}$ = 250.5 Hz), 140.1 (d, $^{4}J_{CF}$ = 3.0 Hz), 128.4 (d, $^{3}J_{CF}$ = 9.0 Hz), 116.0 (d, $^{2}J_{CF}$ = 22.5 Hz), 40.8, 32.6, 20.0, 13.7; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -109.8; **LRMS** (ESI^+) *m/z* 216.0 ($[M+H]^+$), 238.1 ($[M+Na]^+$). Data is consistent with the literature.[145]

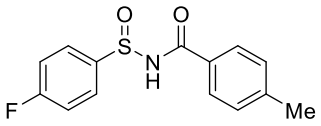
_N_-((3_s_,5_s_,7_s_)-Adamantan-1-yl)-4-fluorobenzenesulfinamide (19h)



Prepared according to general procedure F using 4-fluorophenylmagnesium bromide (0.50 mL, 1.01 M in THF, 0.50 mmol, 1.0 equiv.) and an emulsion of 1-adamantylamine (114 mg, 0.75 mmol, 1.5 equiv.) in THF (3 mL). During aqueous workup, the combined organic phases were dried over $MgSO_4$. Purification by flash column chromatography (25% EtOAc in Petrol) afforded the title product as a white solid (91 mg, 62%).

R_f_ (25% EtOAc in Petrol) = 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 – 7.63 (m, 2H, Ar-*H*), 7.20 – 7.11 (m, 2H, Ar-*H*), 3.83 (s, 1H, N*H*), 2.19 – 2.10 (m, 3H, Alk-*H*), 2.04 – 1.94 (m, 3H, Alk-*H*), 1.94 – 1.86 (m, 3H, Alk-*H*), 1.75 – 1.63 (m, 6H, Alk-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.3 (d, $^1J_{CF}$ = 251.0 Hz), 142.4 (d, $^4J_{CF}$ = 3.0 Hz), 128.2 (d, $^3J_{CF}$ = 9.0 Hz), 115.9 (d, $^2J_{CF}$ = 22.0 Hz), 54.7, 44.8, 36.1, 29.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.2; **LRMS** (ESI^+) *m/z* 294.1 ($[M+H]^+$); **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{21}ONFS$ 294.1322; Found 294.1326; **IR** (thin film, ν_{max}/cm^{-1}) 3090, 2981, 2903, 2849, 1588, 1490, 1452, 1396, 1224, 1159, 1086, 1040, 948, 835, 744; **m.p.** (CH_2Cl_2): 264-266 ℃.

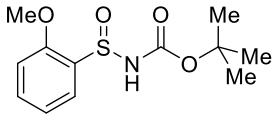
_N_-((4-Fluorophenyl)sulfinyl)-4-methylbenzamide (19i).



Prepared according to general procedure F using 4-fluorophenylmagnesium bromide (0.50 mL, 1.01 M in THF, 0.50 mmol, 1.0 equiv.) and a solution of *p*-toluamide (101 mg, 0.75 mmol, 1.5 equiv.) in THF (4.0 mL). During aqueous workup, the combined organic phases were dried over $MgSO_4$. Purification by flash column chromatography (40% EtOAc in Petrol) afforded the title product as a white solid (100 mg, 72%).

$\boldsymbol{R_f}$ (40% EtOAc in Petrol) = 0.38; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.95 (s, 1H, N-*H*), 7.75 – 7.66 (m, 4H, Ar-*H*), 7.21 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.19 – 7.13 (m, 2H, Ar-*H*), 2.38 (s, 3H, Ar-*Me*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.5, 164.9 (d, *J* = 252.5 Hz), 144.3, 139.5 (d, *J* = 3.0 Hz), 129.6, 128.7, 128.3, 127.5 (d, *J* = 9.0 Hz), 116.8 (d, *J* = 23.0 Hz), 21.7; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -107.1; **LRMS** (ESI^+) *m/z* 300.0 ($[M+Na]^+$); **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{13}O_2NFS$ 278.0646; Found 278.0646; **IR** (thin film, ν_{max}/cm^{-1}) 3181, 1670, 1587, 1491, 1420, 1395, 1231, 1090, 1060, 888, 833, 750; **m.p.** (CH_2Cl_2): 135-136 ℃.

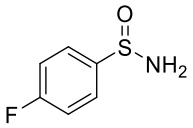
tert-Butyl ((2-methoxyphenyl)sulfinyl)carbamate (19j)



Prepared according to general procedure F using 2-methoxyphenylmagnesium bromide solution (0.49 mL, 1.02 M in THF, 0.50 mmol, 1.0 equiv.) and a solution of *tert*-butyl carbamate (88 mg, 0.75 mmol, 1.5 equiv.) in THF (2.0 mL). Purification by flash column chromatography (30−40% EtOAc in Petrol) afforded the title product as a colourless viscous oil (113 mg, 83%).

***R*$_f$** (30% EtOAc in Petrol) = 0.15; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.48 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, Ar-*H*), 7.11 (app. td, *J* = 7.5, 1.0 Hz, 1H, Ar-*H*), 6.99 (s, 1H, N-*H*), 6.95 (dd, *J* = 8.5, 1.0 Hz, 1H, Ar-*H*), 3.89 (s, 3H, O*Me*), 1.48 (s, 9H, C*Me*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.3, 152.7, 133.6, 131.3, 126.0, 121.2, 111.5, 83.1, 56.1, 28.2.; **LRMS** (ESI^+) *m/z* 294.0 ($[M+Na]^+$); **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{17}O_4NNaS$ 294.0771; Found 294.0770; **IR** (thin film, ν_{max}/cm^{-1}) 3156, 2979, 1707, 1590, 1478, 1369, 1276, 1241, 1154, 1087, 1051, 1019, 904, 820, 755, 727.

4-Fluorobenzenesulfinamide (19k)[105b]



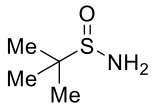
Pre-dried DABSO (60 mg, 0.25 mmol, 0.5 equiv.) was added to an oven-dried 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2

(× 3). Anhydrous THF (2.0 mL) was added. 4-Fluorophenylmagnesium bromide (0.50 mL, 1.01 M in THF, 0.50 mmol, 1.0 equiv.) was added dropwise to the resulting suspension at rt and the reaction mixture was stirred for 30 min. $SOCl_2$ (40 µL, 0.55 mmol, 1.1 equiv.) was then added dropwise and the mixture was stirred at rt for 30 min. The reaction mixture was transferred *via* a syringe and added dropwise to a stirred solution of 35% aq. NH_3 (0.5 mL) and EtOAc (1.0 mL) in a 25 mL RBF at 0 °C. Anhydrous THF (2.0 mL × 2) was added to the reaction vial and transferred to the 25 mL RBF to ensure a quantitative transfer of the sulfinyl chloride. After addition, the mixture was stirred at rt for 30 min, then quenched with brine (10 mL) and extracted with EtOAc (3 × 10 mL). A few drops of water were added to dissolve any solid formed during the workup. The combined organic phases were dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (100% EtOAc) afforded the title product as a white solid (53 mg, 67%).

$\boldsymbol{R_f}$ (100% EtOAc) = 0.50; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.75 – 7.64 (m, 2H, Ar-*H*), 7.41 – 7.30 (m, 2H, Ar-*H*), 6.29 (s, 2H, NH_2); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 163.2 (d, $^1J_{CF}$ = 247.0 Hz), 144.2 (d, $^4J_{CF}$ = 2.5 Hz), 127.9 (d, $^3J_{CF}$ = 9.0 Hz), 115.6 (d, $^2J_{CF}$ = 22.0 Hz); **^{19}F NMR** (377 MHz, DMSO) δ -111.4; **LRMS** (ESI$^+$) *m/z* 341.4 ([2M+Na]$^+$). Data is consistent with the literature.[105b]

Note: Instead of the aq. NH_3/EtOAc mixture, adding NH_3 in THF or dioxane to the solution of sulfinyl chloride led to messy mixtures in HPLC analysis.

2-Methylpropane-2-sulfinamide (19l)[146]



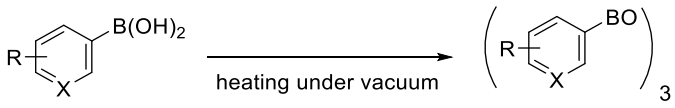
Pre-dried DABSO (60 mg, 0.25 mmol, 0.5 equiv.) was added to an oven-dried 10 mL reaction vial. The vial was then sealed with a rubber septum, evacuated and filled with N_2 (× 3). Anhydrous THF (2.0 mL) was added. *tert*-Butylmagnesium chloride (0.53 mL, 0.94 M in THF, 0.50 mmol, 1.0 equiv.) was added dropwise to the resulting suspension at rt and the reaction mixture was stirred for 30 min. $SOCl_2$ (40 µL, 0.55 mmol, 1.1 equiv.) was then added dropwise and the mixture was stirred at rt for 30 min. The reaction mixture was transferred *via* a syringe and added dropwise to a stirred solution of 35% aq. NH_3 (0.5 mL) and EtOAc (0.5 mL) in a 25 mL RBF at 0 ℃. Anhydrous THF (2.0 mL × 2) was added to the reaction vial and transferred to the 25 mL RBF to ensure a quantitative transfer of the sulfinyl chloride. After addition, the mixture was stirred at rt for 30 min, then quenched with brine (10 mL) and extracted with EtOAc (3 × 10 mL). A few drops of water were added to dissolve any solid formed during the workup. The combined organic phases were dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (0−5% MeOH in EtOAc) afforded the title product as a pale yellow viscous oil (43 mg, 71%).

***R*$_f$** (100% EtOAc) = 0.17; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.72 (s, 2H, N*H*$_2$), 1.22 (s, 9H, C*Me*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 55.5, 22.3; **LRMS** (ESI^+) *m/z* 122.0 ($[M+H]^+$); 144.0 ($[M+Na]^+$). Data is consistent with the literature.[146]

6.4 Data for chapter 4

6.4.1 Preparation of arylboroxines

General Procedure G: Preparation of arylboroxines



A 25 mL RBF charged with aryl boronic acid (~ 100 – 200 mg) was heated to the indicated temperature and time under high vacuum (< 1 mbar). After cooling to rt, the flask was filled with N_2. The arylboroxine was used without further purification.

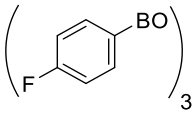
Note:

1. ^{1}H NMR analysis was used to check the ratio of boroxine:boronic acid (BRX:BA) with $CDCl_3$ as the NMR solvent. The ratio of BRX:BA was generally greater than 90:10 after heating under vacuum.

2. Some boroxines (and boronic acids) did not dissolve sufficiently in $CDCl_3$, so instead an ampoule of d_6-DMSO was frequently used as the NMR solvent. As DMSO absorbs water from moist air quickly and boroxines are moisture sensitive, this could lower the ratio observed in ^{1}H NMR spectra for BRX:BA to ~80:20 or lower. Generally, we assumed the samples were all boroxines. Indeed, all boroxines were sufficiently dry to be used in the nickel catalysis reactions (see General Procedure H), i.e. only a small amount of $TrNH_2$ (from the hydrolysis of TrNSO) was observed after the reaction.

3. when using d_6-DMSO as the NMR solvent, two ^{1}H NMR spectrums were recorded, one with an ampoule of d_6-DMSO (i.e. "dry" DMSO) to check the ratio of BRX:BA and another one with a previously opened bottle of d_6-DMSO (i.e. "wet" DMSO) to record the NMR spectrum of the boronic acid and check if there was any decomposition. In general, only the boronic acid was observed in the wet sample of d_6-DMSO. Therefore, no decomposition was observed after heating the sample of boronic acid under the indicated temperature and time.

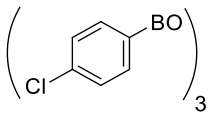
Tris(4-fluorophenyl)boroxine



Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 160 ℃ for 16 h. When a large sample (~ 1 – 2 g) was used, it may needed 2 or 3 days of heating instead. After preparation, the sample could be reused (e.g. to expand the scope of amines) after subjected to the same procedure, but heating for only 2 h.

Boroxine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.86 (m, 6H, Ar-*H*), 7.24 – 7.11 (m, 6H, Ar-*H*); **Boronic acid: ^{1}H NMR (400 MHz, DMSO-d_6)** δ 8.07 (s, 2H, B(O*H*)$_2$), 7.87 – 7.78 (m, 2H, Ar-*H*), 7.18 – 7.08 (m, 2H, Ar-*H*).

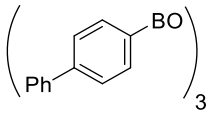
Tris(4-Chlorophenyl)boroxine[147]



Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 120 ℃ for 3 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.10 (m, 6H, Ar-*H*), 7.52 – 7.45 (m, 6H, Ar-*H*). Data is consistent with the literature.[147]

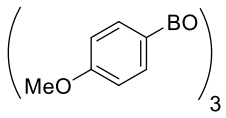
Tris([1,1'-biphenyl]-4-yl)boroxine



Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 160 ℃ for 16 h.

Boroxine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 – 7.97 (m, 6H, Ar-*H*), 7.74 – 7.66 (m, 12H, Ar-*H*), 7.52 – 7.45 (m, 6H, Ar-*H*), 7.41 – 7.36 (m, 3H, Ar-*H*); **Boronic acid: ^{1}H NMR (400 MHz, DMSO-d_6)** δ 8.08 (s, 2H, B(O*H*)$_2$), 7.92 – 7.85 (m, 2H, Ar-*H*), 7.72 – 7.66 (m, 2H, Ar-*H*), 7.66 – 7.60 (m, 2H, Ar-*H*), 7.50 – 7.43 (m, 2H, Ar-*H*), 7.40 – 7.34 (m, 1H, Ar-*H*).

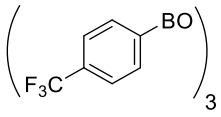
Tris(4-methoxyphenyl)boroxine[148]



Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 120 °C for 3 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.11 (m, 6H, Ar-*H*), 7.06 – 6.95 (m, 6H, Ar-*H*), 3.90 (s, 9H, O*Me*). Data is consistent with the literature.[148]

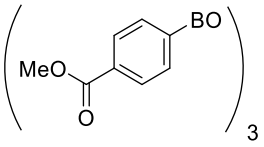
Tris(4-(trifluoromethyl)phenyl)boroxine[148]



Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 120 °C for 1 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.32 (m, 6H, Ar-*H*), 7.82 – 7.75 (m, 6H, Ar-*H*). Data is consistent with the literature.[148]

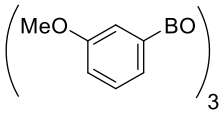
Tris(4-methoxycarbonylphenyl)boroxine[149]



Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 160 ℃ for 2.5 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 – 8.27 (m, 6H, Ar-*H*), 8.19 – 8.14 (m, 6H, Ar-*H*), 3.98 (s, 9H, CO_2*Me*). Data is consistent with the literature.[149]

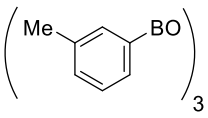
Tris(3-methoxyphenyl)boroxine



Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 160 ℃ for 16 h.

Boroxine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, *J* = 7.0 Hz, 3H, Ar-*H*), 7.37 (app. dd, *J* = 3.0, 1.0 Hz, 3H, Ar-*H*), 7.30 (dd, *J* = 8.0, 7.0 Hz, 3H, Ar-*H*), 6.98 – 6.92 (m, 3H, Ar-*H*), 3.78 (s, 9H, O*Me*); **Boronic acid: ^{1}H NMR (400 MHz, DMSO-d_6)** δ 8.02 (s, 2H, B(O*H*)$_2$), 7.38 – 7.32 (m, 2H, Ar-*H*), 7.28 – 7.21 (m, 1H, Ar-*H*), 6.98 – 6.91 (m, 1H, Ar-*H*), 3.74 (s, 3H, O*Me*).

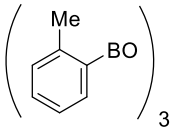
Tris(*m*-tolyl)boroxine



Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 160 ℃ for 16 h.

Boroxine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 – 7.63 (m, 6H, Ar-*H*), 7.26 (app. t, *J* = 7.5 Hz, 3H, Ar-*H*), 7.23 – 7.17 (m, 3H, Ar-*H*), 2.34 (s, 9H, *Me*); **Boronic acid: ^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.97 (s, 2H, $B(OH)_2$), 7.61 – 7.53 (m, 2H, Ar-*H*), 7.24 – 7.17 (m, 2H, Ar-*H*), 2.29 (s, 3H, *Me*).

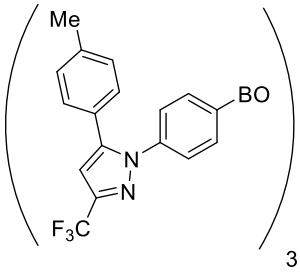
Tris(*o*-tolyl)boroxine



Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 120 ℃ for 1 h.

Boroxine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (dd, *J* = 7.5, 1.5 Hz, 3H, Ar-*H*), 7.25 (app. td, *J* = 7.5, 1.5 Hz, 3H, Ar-*H*), 7.15 (m, 6H, Ar-*H*), 2.65 (s, 9H, *Me*); **Boronic acid: ^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.98 (s, 2H, $B(OH)_2$), 7.41 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.25 – 7.18 (m, 1H, Ar-*H*), 7.10 (m, 2H, Ar-*H*), 2.38 (s, 3H, *Me*)

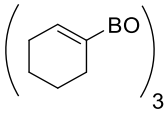
Tris(4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)boroxine



Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 160 ℃ for 16 h.

Boroxine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.90 (m, 6H, Ar-*H*), 7.36 – 7.31 (m, 6H, Ar-*H*), 7.21 – 7.13 (m, 15H, Ar-*H*), 2.29 (s, 9H, *Me*); **Boronic acid: ^{1}H NMR (400 MHz, DMSO-d_6)** δ 8.22 (s, 2H, B(O*H*)$_2$), 7.86 – 7.78 (m, 2H, Ar-*H*), 7.33 – 7.26 (m, 2H, Ar-*H*), 7.21 – 7.11 (m, 5H, Ar-*H*), 2.30 (s, 3H, *Me*).

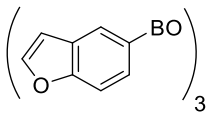
Tris(cyclohex-1-en-1-yl)boroxine



Prepared according to general procedure G using the corresponding boronic acid and heated the sample at 120 ℃ for 1 h.

Boroxine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.33 – 6.27 (m, 3H, C=C*H*), 2.08 – 1.92 (m, 12H, Alk-*H*), 1.58 – 1.39 (m, 12H, Alk-*H*); **Boronic acid: ^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.29 (s, 2H, B(O*H*)$_2$), 6.42 – 6.31 (m, 1H, C=C*H*), 2.08 – 1.90 (m, 4H, Alk-*H*), 1.58 – 1.42 (m, 4H, Alk-*H*).

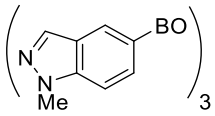
Tris(benzofuran-5-yl)boroxine



Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 120 °C for 1.5 h.

Boroxine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (app. s, 3H, Ar-*H*), 7.97 (d, *J* = 2.0 Hz, 3H, Ar-*H*), 7.91 (dd, *J* = 8.0, 1.0 Hz, 3H, Ar-*H*), 7.59 (d, *J* = 8.0, 1.0 Hz, 3H, Ar-*H*), 7.02 (dd, *J* = 2.0, 1.0 Hz, 3H, Ar-*H*); **Boronic acid: ^{1}H NMR (400 MHz, DMSO-d_6)** δ 8.10 (app. s, 1H, Ar-*H*), 8.01 (s, 2H, B(O*H*)$_2$), 7.95 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.74 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 7.53 (dt, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 6.96 (dd, *J* = 2.0, 1.0 Hz, 1H, Ar-*H*).

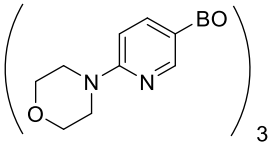
Tris(1-methyl-1*H*-indazol-5-yl)boroxine



Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 120 °C for 1 h.

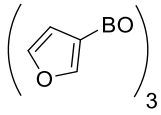
Boroxine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 3H, Ar-*H*), 8.11 (d, *J* = 1.0 Hz, 3H, Ar-*H*), 7.98 (dd, *J* = 8.5, 1.0 Hz, 3H, Ar-*H*), 7.62 (d, *J* = 8.5, 3H, Ar-*H*), 4.06 (s, 9H, *Me*); **Boronic acid: ^{1}H NMR (400 MHz, DMSO-d_6)** δ 8.23 (s, 1H, Ar-*H*), 8.06 (d, *J* = 1.0 Hz, 1H, Ar-*H*), 7.98 (s, 2H, B(O*H*)$_2$), 7.80 (dd, *J* = 8.5, 1.1 Hz, 1H, Ar-*H*), 7.55 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 4.03 (s, 3H, *Me*).

Tris(6-morpholinopyridin-3-yl)boroxine



Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 160 ℃ for 16 h. No satisfying ^{1}H NMR was recorded.

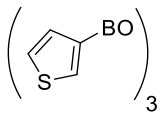
Tris(furan-3-yl)boroxine



Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 100 ℃ for 1 h.

Boroxine: ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.76 (t, *J* = 1.0 Hz, 3H, Ar-*H*), 7.63 (t, *J* = 1.5 Hz, 3H, Ar-*H*), 6.55 (dd, *J* = 1.5, 0.5 Hz, 3H, Ar-*H*); **Boronic acid: ^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.91 (s, 2H, B(O*H*)$_2$), 7.83 (dd, *J* = 1.5, 1.0 Hz, 1H, Ar-*H*), 7.62 (t, *J* = 1.5 Hz, 1H, Ar-*H*), 6.63 (dd, *J* = 1.5, 1.0 Hz, 1H, Ar-*H*).

Tris(thiophen-3-yl)boroxine

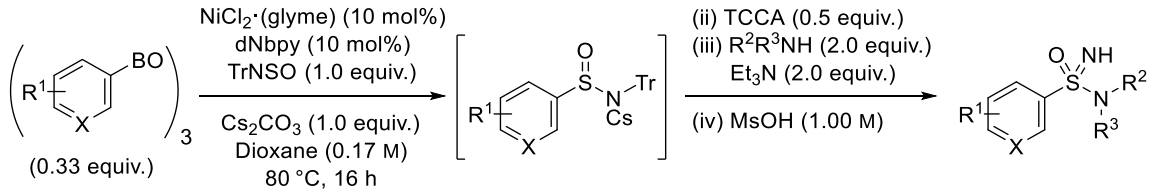


Prepared according to general procedure G using the corresponding arylboronic acid and heated the sample at 120 ℃ for 1 h.

Boroxine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 – 7.85 (m, 3H, Ar-*H*), 7.49 (dd, *J* = 5.0, 2.5 Hz, 3H, Ar-*H*), 7.40 (dd, *J* = 5.0, 1.0 Hz, 3H, Ar-*H*); **Boronic acid: ^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.99 (s, 2H, B(O*H*)$_2$), 7.96 (dd, *J* = 2.5, 1.0 Hz, 1H, Ar-*H*), 7.47 (dd, *J* = 5.0, 2.5 Hz, 1H, Ar-*H*), 7.40 (dd, *J* = 5.0, 1.0 Hz, 1H, Ar-*H*).

6.4.2 Synthesis of sulfonimidamides

General Procedure H: Four-step synthesis of sulfonimidamides



Cs_2CO_3 (65.2 mg, 0.200 mmol, 1.00 equiv.) was added to an oven-dried 10 mL reaction tube. The tube was then sealed with a rubber septum and heated at 160 ℃ under vacuum for at least 2 h or overnight to dry the Cs_2CO_3. After cooling the tube to rt and filling with N_2, pre-weighted arylboroxine (0.067 mmol, 0.33 equiv.), $NiCl_2$·(glyme) (4.4 mg, 0.020 mmol, 10 mol%), dNbpy (8.2 mg, 0.020 mmol, 10 mol%) and TrNSO (61.1 mg, 0.200 mmol, 1.00 equiv.) were quickly added. The tube was re-sealed, evacuated and filled with N_2 (× 4). Dioxane (1.2 mL, 0.17 M) was added and the reaction mixture was heated at 80 ℃ for 16 h. After cooling to rt, trichloroisocyanuric acid (23.2 mg, 0.100 mmol, 0.50 equiv.) was added and the mixture was stirred at rt for 20 min. Et_3N (56 μL, 0.40 mmol, 2.0 equiv.) and amine (2.00 equiv.) were added and the mixture was stirred at rt for 1 h. MsOH (0.2 mL, 1.00 M) was added dropwise (caution: gas formation) and the mixture was stirred at rt for 30 min. The mixture was diluted with CH_2Cl_2 (10 mL) and transferred to a 50 mL separating funnel, before neutralising with sat. aq $NaHCO_3$ (10 mL) (caution: gas formation). After collecting the organic phase, the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated at ≤25 ℃. Purification by flash column chromatography afforded the product.

Note:

1. ***Hydrolysis of TrNSO under the conditions is the major issue in this reaction. Hence, exclusion of H_2O in step 1 is the top priority to the success of the reaction.***

Arylboroxines and especially Cs_2CO_3 were the major sources of H_2O. Arylboroxines were freshly prepared before use by heating the corresponding arylboronic acids under vaccum at the indicated temperature and time.

Cs_2CO_3 tended to absorb H_2O while being weighed out, thus limiting its contact with air as minimum as possible was very important. Cs_2CO_3 (~ 2 – 3 g) was added to a 25 mL RBF and dried by heating to 160 ℃, under vacuum (< 5 mbar), overnight. It was further dried ***__everytime before use__*** as indicated in the General Procedure H. The other solid reagents (boroxine, $NiCl_2$·(glyme), dNbpy, TrNSO) were weighed out first and quickly added into the reaction tube to minimise the contact of Cs_2CO_3 with air.

2. $NiCl_2$·(glyme) was purchased from Sigma-Aldrich. dNbpy was purchased from Sigma-Aldrich or Alfa Aesar. TrNSO was prepared using the literature method, stored under N_2 at −20 ℃ and checked for its purity by ^{13}C NMR analysis.[58] Cs_2CO_3 was purchased from Fluorochem and dried as indicated in note 1. Anhydrous 1,4-dioxane was purchased from a Sigma-Aldrich or Acros Organic. Trichloroisocyanuric acid (TCCA) and MsOH were purchased from Alfa Aesar. Anhydrous Et_3N was purchased from Sigma-Aldrich.

3. The reaction was evacuated (< 5 mbar) and back filled with N_2 (× 4). The first evacuation lasted for at least 5 min. The remaining three times lasted for at least 1 min.

4. Stirring speed in step 1 was setted to be 1400 rpm. This high stirring speed seemed to be important, probably for better stirring of Cs_2CO_3.

5. Each step was easily monitored by HPLC analysis for the conversion of starting materials to intermediates and products.

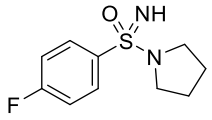
6. Using EtOAc as an extraction solvent in aqueous workup would cause significant retritylation in this NH sulfonimidamide synthesis. Using CH_2Cl_2 instead would only form a negligible amount of the retritylation product. Keeping the rotary evaporator water bath below 25 ℃ would reduce the chance of retritylation.

7. The crude product was dry-loaded with silica gel or loaded as a CH_2Cl_2 solution onto a pre-packed silica gel column.

8. Ninhydrin is an excellent TLC stain for most compounds with NH bonds in this study, including sulfonimidamides, primary sulfonamides and primary sulfinamide.

9. The *N*H sulfonimidamides may sometimes decomposed in $CDCl_3$, maybe due to the trace amount of acidic substrates in this solvent and hence DMSO-d_6 was used in some cases. Basifying $CDCl_3$ with K_2CO_3 may help suppress the decomposition.

1-(4-Fluorophenylsulfonimidoyl)pyrrolidine (27a)[58]



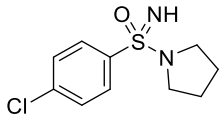
Prepared according to general procedure H using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (50% EtOAc in Petrol) afforded the title product as a pale yellow oil which solidified on-standing to a pale yellow solid (34.0 mg, 74%).

Using *t*-OctNSO as the sulfinylamine: the same procedure was followed as above but *t*-OctNSO (37 μL, density = 0.95 g/mL, 0.20 mmol, 1.0 equiv.) was used instead of TrNSO. In step 4, MsOH (1.0 mL, 0.2 M) was used and the mixture was stirred at 100 ℃ for 1 h. Purification by flash column chromatography afforded the same product (26.8 mg, 59%).

Scale up reaction using TrNSO: the same procedure was followed but on a 1.0 mmol scale using Cs_2CO_3 (325.8 mg, 1.000 mmol, 1.00 equiv.), tris(4-fluorophenyl)boroxine (139.0 mg, 0.380 mmol, 0.38 equiv.), $NiCl_2$·(glyme) (11.0 mg, 0.050 mmol, 5 mol%), dNbpy (20.4 mg, 0.050 mmol, 10 mol%), TrNSO (305.4 mg, 1.000 mmol, 1.00 equiv.) and dioxane (6.00 mL) at 100 ℃ in a 25 mL RBF. The reaction was heated on an aluminium heating block covered with tin foil and cotton. Trichloroisocyanuric acid (116.2 mg, 0.500 mmol, 0.50 equiv.), Et_3N (0.17 mL, 2.0 mmol, 2.0 equiv.), pyrrolidine (0.28 mL, 2.0 mmol, 2.0 equiv.) and MsOH (1.00 mL, 1.00 M) were used in the following steps. Purification by flash column chromatography afforded the same product (135.0 mg, 59%).

***R*$_f$** (50% EtOAc in petrol) = 0.24; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.01 – 7.92 (m, 2H, Ar-*H*), 7.20 – 7.12 (m, 2H, Ar-*H*), 3.25 – 3.09 (m, 4H, 2 × NC*H*$_2$), 3.32 – 2.33 (br. s, 1H, N-*H*), 1.76 – 1.64 (m, 4H, 2 × NCH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 165.1 (d, $^1J_{CF}$ = 254.0 Hz), 133.3 (d, $^4J_{CF}$ = 3.5 Hz), 130.6 (d, $^3J_{CF}$ = 9.0 Hz), 116.0 (d, $^2J_{CF}$ = 22.5 Hz), 48.8, 25.4; **^{19}F NMR (376 MHz, CDCl$_3$)** δ -106.7; **LRMS (ESI)** *m/z* 229.1 ([M+H]$^+$). Data is consistent with the literature.[58]

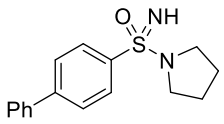
1-(4-Chlorophenylsulfonimidoyl)pyrrolidine (27b)



Prepared according to general procedure H using tris(4-chlorophenyl)boroxine (27.7 mg, 0.067 mmol, 0.33 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (50% EtOAc in Petrol) afforded the title product as a colourless oil (31.0 mg, 63%).

***R*$_f$** (50% EtOAc in petrol) = 0.29; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.92 – 7.87 (m, 2H, Ar-*H*), 7.50 – 7.44 (m, 2H, Ar-*H*), 3.25 – 3.12 (m, 4H, 2 × NC*H*$_2$), 3.03 – 2.32 (br. s, 1H, N-*H*), 1.77 – 1.65 (m, 4H, 2 × NCH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$)** 138.8, 135.9, 129.4, 129.2, 48.8, 25.4; **LRMS (ESI)** *m/z* 245.0 ([M+H]$^+$); **HRMS (ESI)** *m/z*: Calcd [M+H]$^+$ for $C_{10}H_{14}ON_2{}^{35}ClS$ 245.0510; found 245.0511; **IR (thin film, ν_{max}/cm^{-1})** 3275, 1582, 1474, 1255, 1133, 1088, 997, 829, 754.

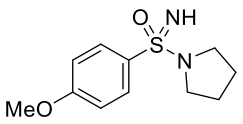
1-([1,1'-Biphenyl]-4-sulfonimidoyl)pyrrolidine (27c)



Prepared according to general procedure H using tris([1,1'-biphenyl]-4-yl)boroxine (72.0 mg, 0.133 mmol, 0.67 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). In step 1, the reaction was heated to 100 °C instead. Purification by flash column chromatography (30 – 50% EtOAc in pentane) afforded the title product as an off-white solid (43.0 mg, 75%).

***R*$_f$** (50% EtOAc in pentane) = 0.24; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.08 – 7.99 (m, 2H, Ar-*H*), 7.76 – 7.68 (m, 2H, Ar-*H*), 7.65 – 7.58 (m, 2H, Ar-*H*), 7.50 – 7.44 (m, 2H, Ar-*H*), 7.43 – 7.37 (m, 1H, Ar-*H*), 3.33 – 3.16 (m, 4H, 2 × NC*H*$_2$), 3.01 – 2.51 (br. s, 1H, N-*H*), 1.81 – 1.66 (m, 4H, 2 × NCH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 145.2, 139.6, 136.0, 129.1, 128.6, 128.4, 127.5, 127.4, 48.8, 25.4; **HRMS (ESI) *m/z*:** Calcd $[M+H]^+$ for $C_{16}H_{19}ON_2S$ 287.1213; found 287.1212; **IR (thin film, ν_{max}/cm^{-1})** 3239, 1593, 1478, 1255, 1135, 986, 841; **m.p.** (CH_2Cl_2): 124 – 125 °C.

1-(4-Methoxyphenylsulfonimidoyl)pyrrolidine (27d)

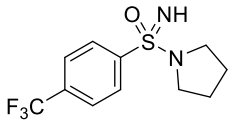


Prepared according to general procedure H using tris(4-methoxyphenyl)boroxine (26.8 mg, 0.067 mmol, 0.33 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (70% EtOAc in Petrol) afforded the title product as a pale yellow oil which solidified on-standing to an off-white solid (32.5 mg, 68%).

Using arylboronic acid as the starting materials in a one-pot reaction: Commercial 4-methoxyphenylboronic acid (30.4 mg, 0.200 mmol, 1.00 equiv.) and Cs_2CO_3 (65.2 mg, 0.200 mmol, 1.00 equiv.) were added to an oven-dried 10 mL reaction tube. The tube was then sealed with a rubber septum and heated at 120 ℃ under vacuum for 3 h. After cooling the tube to rt and filling with N_2, other reagents including $NiCl_2$·(glyme), dNbpy, TrNSO and dioxane were added according to the same procedure. Purification by flash column chromatography afforded the same product (30.8 mg, 64%).

***R*$_f$** (70% EtOAc in petrol) = 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.92 – 7.85 (m, 2H, Ar-*H*), 6.99 – 6.93 (m, 2H, Ar-*H*), 3.85 (s, 3H, O*Me*), 3.24 – 3.11 (m, 4H, 2 × NC*H*$_2$), 2.81 – 2.41 (br. s, 1H, N-*H*), 1.74 – 1.61 (m, 4H, 2 × NCH_2CH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** 162.8, 130.2, 128.9, 114.0, 55.7, 48.8, 25.3; **LRMS (ESI)** *m/z* 241.1 ($[M+H]^+$); **HRMS (ESI)** *m/z*: Calcd $[M+H]^+$ for $C_{11}H_{17}O_2N_2S$ 241.1005; found 241.1005; **IR (thin film, ν_{max}/cm^{-1})** 3275, 1594, 1495, 1308, 1250, 1130, 994, 837; **m.p.** (CH_2Cl_2): 94 – 96 ℃.

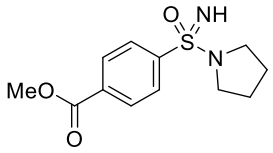
1-(4-(Trifluoromethyl)phenylsulfonimidoyl)pyrrolidine (27e)



Prepared according to general procedure H using tris(4-(trifluoromethyl)phenyl)boroxine (68.8 mg, 0.133 mmol, 0.67 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). In step 1, the reaction was heated to 100 °C instead. Purification by flash column chromatography (30% EtOAc in Petrol) afforded the title product as a white solid (33.4 mg, 60%).

***R*$_f$** (30% EtOAc in petrol) = 0.26; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.13 – 8.07 (m, 2H, Ar-*H*), 7.80 – 7.74 (m, 2H, Ar-*H*), 3.54 – 3.36 (br. s, 1H, N-*H*), 3.29 – 3.15 (m, 4H, 2 × NC*H*$_2$), 1.78 – 1.70 (m, 4H, 2 × NCH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 141.0, 134.1 (q, $^2J_{CF}$ = 33.0 Hz), 128.5, 126.1 (q, $^3J_{CF}$ = 3.5 Hz), 123.5 (d, $^1J_{CF}$ = 273.0 Hz), 48.8, 25.5; **^{19}F NMR (376 MHz, CDCl$_3$)** δ -63.0; **HRMS (ESI)** *m/z*: Calcd $[M+H]^+$ for $C_{11}H_{14}ON_2F_3S$ 279.0773; found 279.0773; **IR (thin film, ν_{max}/cm^{-1})** 3275, 1461, 1321, 1260, 1126, 1061, 1000; **m.p.** (CH_2Cl_2): 114 – 116 °C.

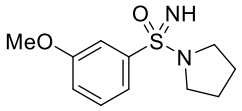
Methyl 4-(pyrrolidine-1-sulfonimidoyl)benzoate (27f)



Prepared according to general procedure H using tris(4-methoxycarbonylphenyl)boroxine (32.4 mg, 0.067 mmol, 0.33 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (55% EtOAc in Petrol) afforded the title product as an off-white solid (25.3 mg, 47%).

***R*$_f$** (55% EtOAc in petrol) = 0.24; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.18 – 8.13 (m, 2H, Ar-*H*), 8.05 – 8.00 (m, 2H, Ar-*H*), 3.94 (s, 3H, O*Me*), 3.27 – 3.14 (m, 4H, 2 × NC*H*$_2$), 3.04 – 2.61 (br. s, 1H, N-*H*), 1.73 – 1.66 (m, 4H, 2 × NCH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$)** 166.0, 141.4, 133.5, 130.1, 127.9, 52.7, 48.8, 25.4; **LRMS (ESI)** *m/z* 269.0 ([M+H]$^+$); **HRMS (ESI)** *m/z*: Calcd [M+H]$^+$ for $C_{12}H_{17}O_3N_2S$ 269.0954; found 269.0954; **IR (thin film, ν_{max}/cm^{-1})** 3291, 2954, 1725, 1436, 1278, 1261, 1107, 999; **m.p.** (CH_2Cl_2): 137 – 139 °C.

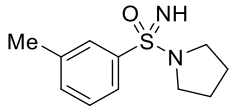
1-(3-Methoxyphenylsulfonimidoyl)pyrrolidine (27g)



Prepared according to general procedure H using tris(3-methoxyphenyl)boroxine (26.8 mg, 0.067 mmol, 0.33 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (60% EtOAc in pentane) afforded the title product as a pale yellow oil (31.1 mg, 65%).

***R*$_f$** (60% EtOAc in pentane) = 0.27; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.49 (app. t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.42 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H, Ar-*H*), 7.33 (dd, *J* = 2.5, 1.5 Hz, 1H, Ar-*H*), 7.19 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, Ar-*H*), 4.41 (s, 1H, N-*H*), 3.82 (s, 3H, OCH_3), 3.14 – 2.98 (m, 4H, 2 × NCH_2), 1.66 – 1.50 (m, 4H, 2 × NCH$_2$CH_2); **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** 159.2, 139.0, 130.0, 119.7, 117.7, 112.7, 55.5, 48.2, 24.8; **LRMS (ESI)** *m/z* 241.0 ([M+H]$^+$); **HRMS (ESI)** *m/z*: Calcd [M+H]$^+$ for $C_{11}H_{17}O_2N_2S$ 241.1005; found 241.1004; **IR (thin film, ν_{max}/cm^{-1})** 3275, 1595, 1475, 1257, 1127, 1001, 985, 684.

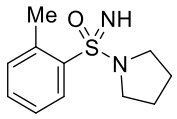
1-(3-Methylphenylsulfonimidoyl)pyrrolidine (27h)



Prepared according to general procedure H using tris(*m*-tolyl)boroxine (23.6 mg, 0.067 mmol, 0.33 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (50% EtOAc in pentane) afforded the title product as a pale yellow oil which solidified on-standing to an off-white solid (27.0 mg, 60%).

***R*$_f$** (50% EtOAc in pentane) = 0.24; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.70 – 7.60 (m, 2H, Ar-*H*), 7.50 – 7.39 (m, 2H, Ar-*H*), 4.33 (s, 1H, N-*H*), 3.14 – 2.95 (m, 4H, 2 × NC*H*$_2$), 2.40 (s, 3H, C*H*$_3$), 1.66 – 1.50 (m, 4H, 2 × NCH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** 138.3, 137.5, 132.6, 128.6, 127.8, 124.8, 48.2, 24.7, 20.9; **HRMS (ESI)** *m/z*: Calcd $[M+H]^+$ for $C_{11}H_{17}ON_2S$ 225.1056; found 225.1057; **IR (thin film, ν_{max}/cm^{-1})** 3275, 1474, 1254, 1125, 989; **m.p.** (EtOAc): 61 – 63 °C.

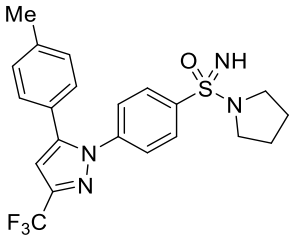
1-(2-Methylphenylsulfonimidoyl)pyrrolidine (27i)



Prepared according to general procedure H using tris(*o*-tolyl)boroxine (23.6 mg, 0.067 mmol, 0.33 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (60% EtOAc in Petrol) afforded the title product as a pale yellow oil (25.5 mg, 57%).

***R*$_f$** (60% EtOAc in Petrol) = 0.30; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.93 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.40 (app. td, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.32 – 7.27 (m, 2H, Ar-*H*), 3.37 – 3.30 (m, 2H, 2 × NC*H*$_a$H$_b$), 3.30 – 3.22 (m, 2H, 2 × NCH$_a$*H*$_b$), 3.00 – 2.60 (br. s, 1H, N-*H*), 2.71 (s, 3H, *Me*), 1.94 – 1.86 (m, 4H, 2 × NCH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 139.3, 138.0, 133.0, 132.1, 128.9, 126.0, 47.7, 25.8, 21.0; **LRMS (ESI)** *m/z* 225.0 ([M+H]$^+$), 247.0 ([M+Na]$^+$); **HRMS (ESI)** *m/z*: Calcd [M+H]$^+$ for $C_{11}H_{17}ON_2S$ 225.1056; found 225.1057; **IR (thin film, ν_{max}/cm^{-1})** 3276, 1458, 1241, 1109, 1066, 995.

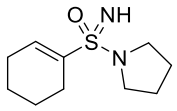
1-(4-(pyrrolidine-1-sulfonimidoyl)phenyl)-5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazole (27j)



Prepared according to general procedure H using tris(4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)boroxine (131.2 mg, 0.133 mmol, 0.67 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). In step 1, the reaction was heated to 100 °C instead. Purification by flash column chromatography (40% EtOAc in pentane) afforded the title product as a pale yellow oil which solidified on-standing to an off-white solid (53.4 mg, 61%).

***R*$_f$** (40% EtOAc in pentane) = 0.19; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.92 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.53 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.23 – 7.12 (m, 5H, Ar-*H*), 4.60 (s, 1H, N*H*), 3.20 – 2.96 (m, 4H, 2 × NC*H*$_2$), 2.30 (s, 3H, C*H*$_3$), 1.66 – 1.49 (m, 4H, 2 × NCH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 145.3, 142.2 (q, $^2J_{CF}$ = 37.5 Hz), 141.4, 139.1, 137.8, 129.3, 128.7, 126.0, 125.3, 121.3 (d, $^1J_{CF}$ = 269.0 Hz), 105.9, 48.3, 24.8, 20.8, 1 × Ar*C* not observed; **^{19}F NMR (376 MHz, DMSO-*d*$_6$)** δ -61.0; **HRMS (ESI)** *m/z*: Calcd $[M+H]^+$ for $C_{21}H_{22}ON_4F_3S$ 435.1461; found 435.1453; **IR (thin film, ν_{max}/cm^{-1})** 3334, 2881, 1596, 1472, 1374, 1235, 1131, 975; **m.p.** (EtOAc): 121 – 123 °C.

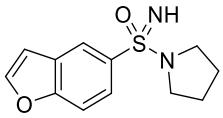
1-(Cyclohex-1-ene-1-sulfonimidoyl)pyrrolidine (27k)



Prepared according to general procedure H using tris(cyclohex-1-en-1-yl)boroxine (21.6 mg, 0.067 mmol, 0.33 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (90% EtOAc in pentane) afforded the title product as a yellow oil (12.9 mg, 30%).

***R*$_f$** (90% EtOAc in pentane) = 0.23; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 6.59 (t, *J* = 3.0 Hz, 1H, C=C*H*), 3.79 (s, 1H, N-*H*), 3.21 – 2.98 (m, 4H, 2 × NC*H*$_2$), 2.42 – 2.28 (m, 1H, Alk-*H*), 2.27 – 2.11 (m, 3H, Alk-*H*), 1.84 – 1.70 (m, 4H, Alk-*H*), 1.68 – 1.47 (m, 4H, 2 × NCH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 137.6, 134.9, 47.8, 25.3, 24.7, 24.6, 22.0, 20.8; **HRMS (ESI)** *m/z*: Calcd $[M+H]^+$ for $C_{10}H_{19}ON_2S$ 215.1213; found 215.1215; **IR (thin film, ν_{max}/cm^{-1})** 3276, 1437, 1245, 1113, 1054, 992.

1-(Benzofuran-5-sulfonimidoyl)pyrrolidine (27l)

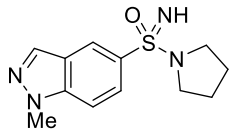


Prepared according to general procedure H using tris(benzofuran-5-yl)boroxine (28.8 mg, 0.067 mmol, 0.33 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (65% EtOAc in Petrol) afforded the title product as a pale yellow viscous oil (33.6 mg, 67%).

Using 1 mol% catalyst: the same procedure was followed but on a 0.4 mmol scale using Cs_2CO_3 (130.3 mg, 0.400 mmol, 1.00 equiv.), tris(benzofuran-5-yl)boroxine (86.4 mg, 0.200 mmol, 0.50 equiv.), $NiCl_2$·(glyme) (0.9 mg, 0.004 mmol, 1 mol%), dNbpy (1.7 mg, 0.004 mmol, 1 mol%), TrNSO (122.2 mg, 0.400 mmol, 1.00 equiv.) and dioxane (2.4 mL) at 100 °C for 48 h. The reaction was heated on an aluminium heating block covered with tin foil and cotton. Trichloroisocyanuric acid (46.5 mg, 0.200 mmol, 0.50 equiv.), Et_3N (112 μL, 0.800 mmol, 2.00 equiv.), pyrrolidine (67 μL, 0.80 mmol, 2.0 equiv.) and MsOH (0.40 mL, 1.0 M) were used in the following steps. Purification by flash column chromatography afforded the same product (64.8 mg, 65%).

***R*$_f$** (65% EtOAc in petrol) = 0.26; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.27 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.93 (dd, *J* = 9.0, 2.0 Hz, 1H, Ar-*H*), 7.72 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.58 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.86 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 3.30 – 3.12 (m, 4H, 2 × NCH_2), 3.00 – 2.50 (br. s, 1H, N-*H*), 1.71 – 1.62 (m, 4H, 2 × NCH_2CH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 156.7, 146.9, 131.9, 127.8, 124.4, 122.2, 111.7, 107.3, 48.8, 25.3; **LRMS (ESI)** *m/z* 251.0 ($[M+H]^+$); **HRMS (ESI)** *m/z*: Calcd $[M+H]^+$ for $C_{12}H_{15}O_2N_2S$ 251.0849; found 251.0849; **IR (thin film, ν_{max}/cm^{-1})** 3275, 1450, 1250, 1104, 1059, 996.

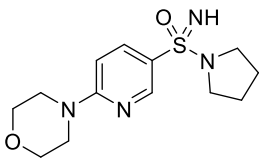
1-Methyl-5-(pyrrolidine-1-sulfonimidoyl)-1*H*-indazole (27m)



Prepared according to general procedure H using tris(1-methyl-1*H*-indazol-5-yl)boroxine (63.2 mg, 0.133 mmol, 0.67 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). In step 1, the reaction was heated to 100 °C instead. Purification by flash column chromatography (90% EtOAc in Petrol) afforded the title product as an off-white solid (33.7 mg, 64%).

***R*$_f$** (90% EtOAc in petrol) = 0.24; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.42 (s, 1H, Ar-*H*), 8.10 (s, 1H, Ar-*H*), 7.98 (dd, *J* = 9.0, 1.5 Hz, 1H, Ar-*H*), 7.47 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 4.11 (s, 3H, N-*Me*), 3.28 – 3.13 (m, 4H, 2 × NC*H*$_2$), 2.77 (s, 1H, N-*H*), 1.71 – 1.63 (m, 4H, 2 × NCH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 141.0, 134.5, 129.6, 125.6, 123.5, 123.0, 109.3, 48.8, 36.0, 25.3; **HRMS (ESI) *m/z*:** Calcd $[M+H]^+$ for $C_{12}H_{17}ON_4S$ 265.1118; found 265.1118; **IR (thin film, ν_{max}/cm^{-1})** 3270, 1611, 1492, 1249, 1058, 987; **m.p.** (CH_2Cl_2): 192 – 194 °C.

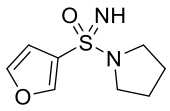
4-(5-(Pyrrolidine-1-sulfonimidoyl)pyridin-2-yl)morpholine (27n)



Prepared according to general procedure H using tris(6-morpholinopyridin-3-yl)boroxine (76.0 mg, 0.133 mmol, 0.67 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). In step 1, the reaction was heated to 100 °C instead. Purification by flash column chromatography (100% EtOAc) afforded the title product as an off-white solid (31.1 mg, 52%).

***R*$_f$** (100% EtOAc) = 0.18; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 8.49 (dd, *J* = 2.5, 0.5 Hz, 1H, Ar-*H*), 7.88 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar-*H*), 6.91 (dd, *J* = 9.0, 0.5 Hz, 1H, Ar-*H*), 4.26 (s, 1H, N-*H*), 3.73 – 3.64 (m, 4H, 2 × OC*H*$_2$), 3.63 – 3.54 (m, 4H, 2 × OCH$_2$C*H*$_2$), 3.08 – 2.96 (m, 4H, 2 × SNC*H*$_2$), 1.66 – 1.56 (m, 4H, 2 × SNCH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** 159.8, 147.9, 137.2, 121.7, 105.6, 65.8, 48.2, 44.5, 24.7; **HRMS (ESI)** *m/z*: Calcd $[M+H]^+$ for $C_{13}H_{21}O_2N_4S$ 297.1380; found 297.1379; **IR (thin film, ν_{max}/cm^{-1})** 3163, 2854, 1585, 1489, 1257, 1121, 1019, 942; **m.p.** (EtOAc): 143 – 145 °C.

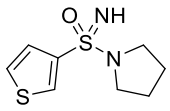
1-(Furan-3-sulfonimidoyl)pyrrolidine (27o)



Prepared according to general procedure H using tris(furan-3-yl)boroxine (18.8 mg, 0.067 mmol, 0.33 equiv.) and pyrrolidine (33 μL, 0.400 mmol, 2.0 equiv.). Purification by flash column chromatography (70% EtOAc in Petrol) afforded the title product as a yellow oil (20.0 mg, 50%).

***R*$_f$** (70% EtOAc in petrol) = 0.24; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.94 (dd, *J* = 2.0, 1.0 Hz, 1H, Ar-*H*), 7.49 (app. t, *J* = 2.0 Hz, 1H, Ar-*H*), 6.68 (dd, *J* = 2.0, 1.0 Hz, 1H, Ar-*H*), 3.32 – 3.16 (m, 4H, 2 × NC*H*$_2$), 2.72 (s, 1H, N-*H*), 1.83 – 1.73 (m, 4H, 2 × NCH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 145.9, 144.5, 124.6, 109.7, 49.1, 25.6; **LRMS (ESI)** *m/z* 201.0 ([M+H]$^+$); **HRMS (ESI)** *m/z*: Calcd [M+H]$^+$ for $C_8H_{13}O_2N_2S$ 201.0692; found 201.0694; **IR (thin film, ν_{max}/cm^{-1})** 3272, 3132, 1494, 1258, 1149, 1007.

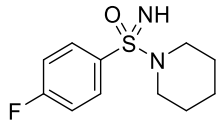
1-(Thiophene-3-sulfonimidoyl)pyrrolidine (27p)



Prepared according to general procedure H using tris(thiophen-3-yl)boroxine (22.0 mg, 0.067 mmol, 0.33 equiv.) and pyrrolidine (33 μL, 0.40 mmol, 2.0 equiv.). Purification by flash column chromatography (60% EtOAc in Petrol) afforded the title product as a pale yellow oil which solidified on-standing to a white solid (22.9 mg, 53%).

R*$_f$** (60% EtOAc in petrol) = 0.23; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.97 (app. t, *J* = 2.0 Hz, 1H, Ar-*H*), 7.39 (app. d, *J* = 2.0 Hz, 2H, Ar-*H*), 3.30 – 3.15 (m, 4H, 2 × NC*H*$_2$), 2.99 – 2.54 (br. s, 1H, N-*H*), 1.78 – 1.64 (m, 4H, 2 × NCH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 137.8, 130.5, 127.3, 126.8, 48.9, 25.5; **LRMS (ESI)** *m/z* 217.0 ([M+H]$^+$); **HRMS (ESI)** ***m/z: Calcd [M+H]$^+$ for $C_8H_{13}ON_2S_2$ 217.0464; found 217.0465; **IR (thin film, ν_{max}/cm^{-1})** 3248, 3058, 1264, 1203, 1123, 1001, 732; **m.p.** (CH_2Cl_2): 72 – 74 °C.

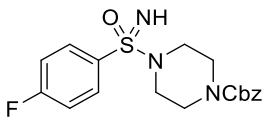
1-(4-Fluorophenylsulfonimidoyl)piperidine (28a)[65]



Prepared according to general procedure H using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.) and piperidine (40 μL, 0.40 mmol, 2.0 equiv.). The step 3 was stirred for 5 h instead. Purification by flash column chromatography (30% EtOAc in Petrol) afforded the title product as a colourless oil (34.5 mg, 71%).

***R*$_f$** (30% EtOAc in petrol) = 0.23; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.90 – 7.83 (m, 2H, Ar-*H*), 7.20 – 7.12 (m, 2H, Ar-*H*), 3.05 – 2.85 (m, 4H, 2 × NC*H*$_2$), 2.73 – 2.19 (br. s, 1H, N-*H*), 1.66 – 1.55 (m, 4H, 2 × NCH$_2$C*H*$_2$), 1.42 – 1.32 (m, 2H, NCH$_2$CH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 165.1 (d, $^1J_{CF}$ = 253.5 Hz), 132.5 (d, $^4J_{CF}$ = 3.0 Hz), 130.7 (d, $^3J_{CF}$ = 9.0 Hz), 116.0 (d, $^2J_{CF}$ = 22.5 Hz), 48.0, 25.7, 23.7; **^{19}F NMR (376 MHz, CDCl$_3$)** δ -106.7; **LRMS (ESI)** *m/z* 243.0 ([M+H]$^+$), 265.0 ([M+Na]$^+$). Data is consistent with the literature.[65]

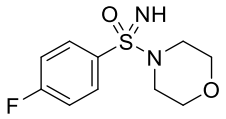
Benzyl 4-(4-fluorophenylsulfonimidoyl)piperazine-1-carboxylate (28b)[58]



Prepared according to general procedure H using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.) and 1-(benzyloxycarbonyl)piperazine (77 μL, 0.40 mmol, 2.0 equiv.). The step 2 was stirred for 24 h instead. Purification by flash column chromatography (50 – 70% EtOAc in Petrol) afforded the title product as a pale yellow oil which solidified on-standing to an off-white solid (51.3 mg, 68%).

***R*$_f$** (50% EtOAc in petrol) = 0.23; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.91 – 7.83 (m, 2H, Ar-*H*), 7.37 – 7.27 (m, 5H, Ar-*H*), 7.23 – 7.14 (m, 2H, Ar-*H*), 5.07 (s, 2H, OC*H*$_2$), 3.56 (app. br. s, 4H, 2 × C(O)NC*H*$_2$), 2.97 (app. br. s, 4H, 2 × SNC*H*$_2$), 2.74 – 2.43 (br. s, 1H, N-*H*); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 165.3 (d, $^1J_{CF}$ = 255.0 Hz), 154.9, 136.3, 131.5 (d, $^4J_{CF}$ = 3.0 Hz), 130.8 (d, $^3J_{CF}$ = 9.0 Hz), 128.6, 128.3, 128.2, 116.3 (d, $^2J_{CF}$ = 22.5 Hz), 67.6, 46.9, 43.7; **^{19}F NMR (376 MHz, CDCl$_3$)** δ -105.6; **LRMS (ESI$^+$)** *m/z* 378.1 ([M+H]$^+$), 400.1 ([M+Na]$^+$). Data is consistent with the literature.[58]

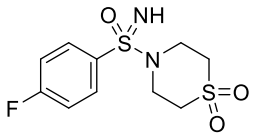
4-(4-Fluorophenylsulfonimidoyl)morpholine (28c)[58]



Prepared according to general procedure H using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.) and morpholine (35 μL, 0.40 mmol, 2.0 equiv.). The step 3 was stirred for 24 h instead. Purification by flash column chromatography (60% EtOAc in Petrol) afforded the title product as a white solid (30.0 mg, 61%).

***R*$_f$** (60% EtOAc in petrol) = 0.28; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.93 – 7.83 (m, 2H, Ar-*H*), 7.24 – 7.14 (m, 2H, Ar-*H*), 3.76 – 3.64 (m, 4H, 2 × OC*H*$_2$), 3.05 – 2.88 (m, 4H, 2 × NC*H*$_2$), 2.57 (s, 1H, N-*H*); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 165.3 (d, $^1J_{CF}$ = 254.5 Hz), 131.2 (d, $^4J_{CF}$ = 3.0 Hz), 130.9 (d, $^3J_{CF}$ = 9.0 Hz), 116.2 (d, $^2J_{CF}$ = 22.5 Hz), 66.5, 47.2; **^{19}F NMR (376 MHz, CDCl$_3$)** δ -105.8; **LRMS (ESI$^+$)** *m/z* 245.0 ([M+H]$^+$). Data is consistent with the literature.[58]

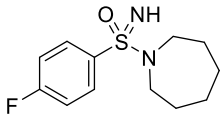
4-(4-Fluorophenylsulfonimidoyl)thiomorpholine 1,1-dioxide (28d)



Prepared according to general procedure H using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.) and thiomorpholine 1,1-dioxide (54 mg, 0.40 mmol, 2.0 equiv.). The step 3 was stirred for 24 h instead. Purification by flash column chromatography (70 – 80% EtOAc in pentane) afforded the title product as an off-white solid (30.9 mg, 53%).

***R*$_f$** (70% EtOAc in pentane) = 0.24; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.95 – 7.85 (m, 2H, Ar-*H*), 7.50 – 7.39 (m, 2H, Ar-*H*), 4.86 (s, 1H, N-*H*), 3.43 (app. br. s, 4H, 2 × SC*H*$_2$), 3.26 – 3.11 (m, 4H, 2 × NC*H*$_2$); **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 164.3 (d, $^1J_{CF}$ = 251.0 Hz), 134.5 (d, $^4J_{CF}$ = 3.0 Hz), 130.2 (d, $^3J_{CF}$ = 9.5 Hz), 116.3 (d, $^2J_{CF}$ = 22.5 Hz), 50.7, 45.4; **^{19}F NMR (376 MHz, DMSO-*d*$_6$)** δ -107.2; **LRMS (ESI)** *m/z* 293.0 ($[M+H]^+$), 315.0 ($[M+Na]^+$); **HRMS (ESI) *m/z*:** Calcd $[M+H]^+$ for $C_{10}H_{14}O_3N_2FS_2$ 293.0424; found 293.0426; **IR (thin film, ν_{max}/cm^{-1})** 3282, 1589, 1491, 1307, 1260, 1223, 1123, 1021, 893, 841, 695; **m.p.** (EtOAc): 159 – 160 °C.

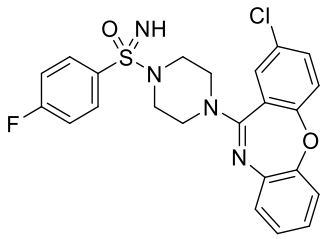
1-(4-Fluorophenylsulfonimidoyl)azepane (28e)[65]



Prepared according to general procedure H using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.) and azepane (45 μL, 0.40 mmol, 2.0 equiv.). The step 3 was stirred for 24 h instead. Purification by flash column chromatography (20 – 30% EtOAc in pentane) afforded the title product as a light yellow oil (35.0 mg, 68%).

***R*$_f$** (30% EtOAc in pentane) = 0.29; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.97 – 7.88 (m, 2H, Ar-*H*), 7.19 – 7.10 (m, 2H, Ar-*H*), 3.27 (t, *J* = 6.0 Hz, 4H, 2 × NC*H*$_2$), 2.93 – 2.27 (br. s, 1H, N*H*), 1.80 – 1.61 (m, 4H, Alk-C*H*), 1.61 – 1.50 (m, 4H, Alk-C*H*); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 164.9 (d, $^1J_{CF}$ = 253.0 Hz), 136.0 (d, $^4J_{CF}$ = 3.5 Hz), 129.9 (d, $^3J_{CF}$ = 9.0 Hz), 116.0 (d, $^2J_{CF}$ = 22.5 Hz), 49.3, 29.5, 26.9; **^{19}F NMR (376 MHz, CDCl$_3$)** δ -107.3; **LRMS (ESI)** *m/z* 257.0 ([M+H]$^+$), 279.0 ([M+Na]$^+$). Data is consistent with the literature.[65]

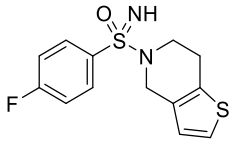
2-chloro-11-(4-(4-fluorophenylsulfonimidoyl)piperazin-1-yl)dibenzo[*b,f*][1,4]oxazepine (28f)[65]



Prepared according to general procedure H using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.) and Amoxapine (125.5 mg, 0.400 mmol, 2.00 equiv.). The step 3 was stirred for 24 h instead. Purification by flash column chromatography (40 – 60% EtOAc in Petrol) afforded the title product as a light yellow viscous oil (62.3 mg, 66%).

***R*$_f$** (40% EtOAc in Petrol) = 0.29; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.96 – 7.86 (m, 2H, Ar-*H*), 7.38 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar-*H*), 7.25 – 7.14 (m, 4H, Ar-*H*), 7.14 – 7.04 (m, 3H, Ar-*H*), 7.03 – 6.95 (m, 1H, Ar-*H*), 3.59 (app. s, 4H, SNCH$_2$C*H*$_2$), 3.13 (app. br. s, 4H, SNC*H*$_2$), 2.96 – 2.47 (br. s, 1H, N*H*); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 165.3 (d, $^1J_{CF}$ = 254.5 Hz), 159.4, 158.4, 151.8, 139.6, 133.0, 131.8 (d, $^4J_{CF}$ = 3.0 Hz), 130.8 (d, $^3J_{CF}$ = 9.0 Hz), 130.5, 128.8, 127.1, 126.0, 125.2, 124.6, 123.0, 120.2, 116.4 (d, $^2J_{CF}$, *J* = 22.5 Hz), 47.3, 46.8; **^{19}F NMR (376 MHz, CDCl$_3$)** δ -105.6; **LRMS (ESI)** *m/z* 471.1 ([M+H]$^+$). Data is consistent with the literature.[65]

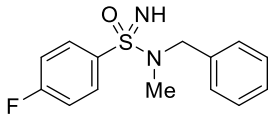
5-(4-Fluorophenylsulfonimidoyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (28g)[65]



Prepared according to general procedure H using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.) and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (47 μL, 0.40 mmol, 2.0 equiv.). The step 3 was stirred for 24 h instead. Purification by flash column chromatography (25% EtOAc in pentane) afforded the title product as a colourless visous oil (37.0 mg, 62%).

***R*$_f$** (25% EtOAc in pentane) = 0.18; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.00 – 7.92 (m, 2H, Ar-*H*), 7.19 – 7.13 (m, 2H, Ar-*H*), 7.09 (d, *J* = 5.0 Hz, 1H, Ar-*H*), 6.71 (d, *J* = 5.0 Hz, 1H, Ar-*H*), 4.25 – 4.15 (m, 2H, Ar-C*H*$_2$-N), 3.50 – 3.37 (m, 2H, N*CH*$_2$CH$_2$), 2.93 – 2.84 (m, 2H, NCH$_2$C*H*$_2$), 2.83 – 2.48 (br. s, 1H, N*H*); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 165.2 (d, $^1J_{CF}$ = 254.5 Hz), 132.84 (d, $^4J_{CF}$ = 3.0 Hz), 132.77, 131.3, 130.6 (d, $^3J_{CF}$ = 9.0 Hz), 124.8, 123.8, 116.1 (d, $^2J_{CF}$ = 22.5 Hz), 47.1, 45.0, 25.6; **^{19}F NMR (376 MHz, CDCl$_3$)** δ -106.1; **LRMS (ESI)** *m/z* 297.0 ([M+H]$^+$). Data is consistent with the literature.[65]

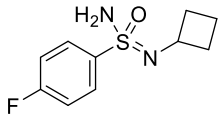
_N_-benzyl-4-fluoro-_N_-methylbenzenesulfonimidamide (28h)[58]



Prepared according to general procedure H using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.) and *N*-benzylmethylamine (52 μL, 0.40 mmol, 2.0 equiv.). The step 3 was stirred for 24 h instead. Purification by flash column chromatography (15 – 25% EtOAc in pentane) afforded the title product as a pale yellow oil (40.2 mg, 72%).

***R*$_f$** (25% EtOAc in pentane) = 0.24; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.98 – 7.89 (m, 2H, Ar-*H*), 7.48 – 7.40 (m, 2H, Ar-*H*), 7.36 – 7.26 (m, 5H, Ar-*H*), 4.64 (s, 1H, N*H*), 4.15 (d, *J* = 14.0 Hz, 1H, NC*H*$_a$H$_b$), 3.97 (d, *J* = 14.0 Hz, 1H, NCH$_a$*H*$_b$), 2.46 (s, 3H, NC*H*$_3$); **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 164.1 (d, $^1J_{CF}$ = 250.0 Hz), 137.0, 134.5 (d, $^4J_{CF}$ = 3.0 Hz), 130.3 (d, $^3J_{CF}$ = 9.0 Hz), 128.4, 128.2, 127.4, 116.0 (d, $^2J_{CF}$ = 22.5 Hz), 54.2, 35.1; **^{19}F NMR (376 MHz, DMSO-*d*$_6$)** δ -108.1; **LRMS (ESI)** *m/z* 279.0 ([M+H]$^+$); **HRMS (ESI) *m/z*:** Calcd [M+H]$^+$ for $C_{14}H_{16}ON_2FS$ 279.0962; found 279.0963; **IR (thin film, ν_{max}/cm^{-1})** 3280, 1588, 1491, 1256, 1224, 1136, 976, 928, 900, 839, 719, 694.

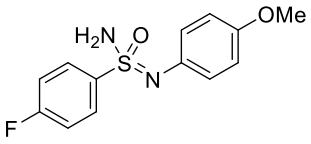
N'-cyclobutyl-4-fluorobenzenesulfonimidamide (28i)[58]



Prepared according to general procedure H using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.) and cyclobutylamine (35 μL, 0.40 mmol, 2.0 equiv.). The step 3 was stirred for 24 h instead. Purification by flash column chromatography (50% EtOAc in Petrol) afforded the title product as a light yellow oil (32.3 mg, 71%).

***R*$_f$** (50% EtOAc in Petrol) = 0.21; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.03 – 7.93 (m, 2H, Ar-*H*), 7.18 – 7.08 (m, 2H, Ar-*H*), 4.61 – 4.03 (br. s, 2H, N*H*$_2$), 3.76 (app. p, *J* = 8.5 Hz, 1H, NC*H*), 2.15 – 1.91 (m, 2H, Alk-C*H*), 1.83 – 1.43 (m, 4H, Alk-C*H*); **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.94 – 7.84 (m, 2H, Ar-*H*), 7.38 – 7.30 (m, 2H, Ar-*H*), 7.25 (br. s, 1H, N*H*), 4.17 (br. s, 1H, N*H*), 3.71 – 3.52 (m, 1H, NC*H*), 1.94 – 1.75 (m, 2H, Alk-C*H*), 1.75 – 1.58 (m, 2H, Alk-C*H*), 1.52 – 1.35 (m, 2H, Alk-C*H*); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 165.0 (d, $^1J_{CF}$ = 254.0 Hz), 138.3 (d, $^4J_{CF}$ = 3.0 Hz), 130.0 (d, $^3J_{CF}$ = 9.0 Hz), 116.1 (d, $^2J_{CF}$ = 22.5 Hz), 48.6, 31.9, 31.8, 15.1; **^{19}F NMR (376 MHz, CDCl$_3$)** δ -106.5; **LRMS (ESI)** *m/z* 229.0 ($[M+H]^+$). Data is consistent with the literature.[58]

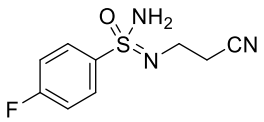
4-fluoro-*N'*-(4-methoxyphenyl)benzenesulfonimidamide (28j)[58]



Prepared according to general procedure H using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.) and *p*-anisidine (49.3 mg, 0.400 mmol, 2.00 equiv.). The step 3 was stirred for 24 h instead. Purification by flash column chromatography (30 – 50% EtOAc in Petrol) afforded the title product as a brown solid (36.6 mg, 65%).

***R*$_f$** (30% EtOAc in Petrol) = 0.08; **^{1}H NMR (400 MHz, Acetone-*d*$_6$)** δ 8.08 – 7.98 (m, 2H, Ar-*H*), 7.32 – 7.22 (m, 2H, Ar-*H*), 7.06 – 6.98 (m, 2H, Ar-*H*), 6.77 – 6.71 (m, 2H, Ar-*H*), 6.66 – 5.92 (br. s, 2H, N*H*$_2$), 3.70 (s, 3H, O*CH*$_3$); **^{13}C NMR (101 MHz, Acetone-*d*$_6$)** δ 165.3 (d, $^1J_{CF}$ = 250.5 Hz), 156.3, 140.8, 131.1 (d, $^4J_{CF}$ = 3.0 Hz), 130.8 (d, $^3J_{CF}$ = 9.0 Hz), 125.4, 116.4 (d, $^2J_{CF}$ = 22.5 Hz), 114.8, 55.6; **^{19}F NMR (376 MHz, Acetone-*d*$_6$)** δ -109.9; **LRMS (ESI)** *m/z* 279.1 ([M-H]$^-$). Data is consistent with the literature.[58]

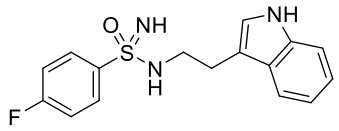
_N'_-(2-cyanoethyl)-4-fluorobenzenesulfonimidamide (28k)[58]



Prepared according to general procedure H using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.) and 3-aminopropionitrile (29 μL, 0.40 mmol, 2.0 equiv.). The step 3 was stirred for 24 h instead. Purification by flash column chromatography (60% EtOAc in pentane) afforded the title product as a light yellow oil (22.3 mg, 49%).

***R*$_f$** (60% EtOAc in pentane) = 0.20; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.05 – 7.95 (m, 2H, Ar-*H*), 7.23 – 7.14 (m, 2H, Ar-*H*), 4.87 – 3.84 (br. s, 2H, N*H*$_2$), 3.32 – 3.13 (m, 2H, SNC*H*$_2$), 2.65 – 2.46 (m, 2H, NCC*H*$_2$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.2 (d, $^1J_{CF}$ = 255.0 Hz), 137.3 (d, $^4J_{CF}$ = 3.5 Hz), 130.0 (d, $^3J_{CF}$ = 9.5 Hz), 118.1, 116.5 (d, $^2J_{CF}$ = 22.5 Hz), 39.4, 19.9; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -105.4; **LRMS (ESI)** *m/z* 228.1 ([M+H]$^+$). Data is consistent with the literature.[58]

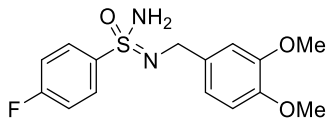
_N'_-(2-(1_H_-indol-3-yl)ethyl)-4-fluorobenzenesulfonimidamide (28l)



Prepared according to general procedure H using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.) and tryptamine (64.1 mg, 0.400 mmol, 2.00 equiv.). The step 3 was stirred for 24 h instead. Purification by flash column chromatography (65 – 75% EtOAc in Petrol) afforded the title product as an off-white solid (43.2 mg, 68%).

R_f_ (75% EtOAc in Petrol) = 0.29; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.78 (s, 1H, indole N*H*), 8.06 – 7.83 (m, 2H, Ar-*H*), 7.49 – 7.20 (m, 4H, Ar-*H*), 7.20 – 6.76 (m, 4H, Ar-*H* and SN*H*), 4.52 – 4.00 (br. s, 1H, SN*H*), 3.06 – 2.89 (m, 2H, CH_2), 2.85 – 2.67 (m, 2H, CH_2); **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 163.6 (d, $^{1}J_{CF}$ = 249.0 Hz), 139.2 (d, $^{4}J_{CF}$ = 2.5 Hz), 136.2, 129.6 (d, $^{3}J_{CF}$ = 9.0 Hz), 127.0, 122.8, 120.9, 118.2, 118.0, 115.6 (d, $^{2}J_{CF}$ = 22.5 Hz), 111.4, 44.2, 25.7, 1 × Ar*C* not observed; **^{19}F NMR (376 MHz, DMSO-*d*$_6$)** δ -109.1; **LRMS (ESI)** *m/z* 318.1 ([M+H]$^+$); **HRMS (ESI) *m/z*:** Calcd [M+H]$^+$ for $C_{16}H_{17}ON_3FS$ 318.1071; found 318.1070; **IR (thin film, ν_{max}/cm^{-1})** 3413, 3291, 2359, 2341, 1590, 1492, 1230, 1008, 838, 743; **m.p.** (EtOAc): 172 – 173 °C.

_N'_-(3,4-Dimethoxybenzyl)-4-fluorobenzenesulfonimidamide (28m)[58]

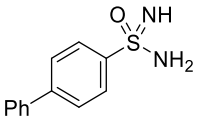


Prepared according to general procedure H using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.) and 3,4-dimethoxybenzylamine (60 μL, 0.40 mmol, 2.0 equiv.). The step 3 was stirred for 24 h instead. Purification by flash column chromatography (70 – 90% EtOAc in Petrol) afforded the title product as a light yellow oil (38.5 mg, 59%).

R_f (70% EtOAc in Petrol) = 0.22; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.04 – 7.93 (m, 2H, Ar-*H*), 7.21 – 7.10 (m, 2H, Ar-*H*), 6.77 – 6.63 (m, 3H, Ar-*H*), 4.09 (d, *J* = 13.5 Hz, 1H, NCH_aH$_b$), 3.99 (d, *J* = 13.5 Hz, 1H, NCH$_a$$H_b$), 3.84 (s, 3H, ArO$CH_3$), 3.81 (s, 3H, ArO$CH_3$), 3.58 – 2.68 (br. s, 2H, NH_2); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.1 (d, $^{1}J_{CF}$ = 254.5 Hz), 149.3, 148.9, 137.2 (d, $^{4}J_{CF}$ = 4.0 Hz), 130.2 (d, $^{3}J_{CF}$ = 9.0 Hz), 129.2, 120.3, 116.2 (d, $^{2}J_{CF}$ = 22.5 Hz), 111.2, 111.1, 56.1, 56.0, 48.0; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -106.3; **LRMS (ESI)** *m/z* 323.1 ([M-H]$^-$). Data is consistent with the literature.[58]

General Procedure I: Four-step synthesis of primary sulfonimidamides

[1,1'-Biphenyl]-4-sulfonimidamide (28n)[58]

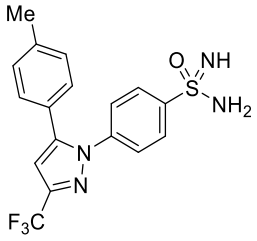


Cs_2CO_3 (65.2 mg, 0.200 mmol, 1.00 equiv.) was added to an oven-dried 10 mL reaction tube. The tube was then sealed with a rubber septum and heated at 160 ℃ under vacuum for at least 2 h to dry the Cs_2CO_3. After cooling the tube to rt and filling with N_2, the tube was quickly added with pre-weighted tris([1,1'-biphenyl]-4-yl)boroxine (72.0 mg, 0.133 mmol, 0.67 equiv.), $NiCl_2$·(glyme) (4.4 mg, 0.020 mmol, 10 mol%), dNbpy (8.2 mg, 0.020 mmol, 10 mol%) and TrNSO (61.1 mg, 0.200 mmol, 1.00 equiv.) were quickly added. The tube was re-sealed, evacuated and filled with N_2 (× 4). Dioxane (1.2 mL, 0.17 M) was added and the reaction mixture was heated at 100 ℃ for 16 h. After cooling to rt, trichloroisocyanuric acid (23.2 mg, 0.100 mmol, 0.50 equiv.) was added and the mixture was stirred at rt for 20 min. A stirred solution of 35% aq NH_3 (0.2 mL) and EtOAc (0.4 mL) was added and the reaction was stirred at rt for 1 h. MsOH (2.0 mL, 0.10 M) was added dropwise (caution: gas formation) and the mixture was stirred at rt for 30 min. The mixture was transferred to a separating funnel with CH_2Cl_2 (40 mL), before neutralising with sat. aq $NaHCO_3$ (50 mL) (caution: gas formation). After collecting the organic phase, the aqueous phase was extracted with CH_2Cl_2 (4 × 40 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated at ≤ 25 °C. Purification by flash column chromatography (80 – 100% EtOAc in pentane) afforded the title product as an off-white solid (27.5 mg, 59%).

(The procedure for step 1 and 2 was the same as General Procedure H, used to synthesise the corresponding sulfonimidoyl chlorides. See the notes for setting up step 1 in general procedure H.)

***R*$_f$** (80% EtOAc in pentane) = 0.11; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 8.04 – 7.91 (m, 2H, Ar-*H*), 7.86 – 7.77 (m, 2H, Ar-*H*), 7.77 – 7.67 (m, 2H, Ar-*H*), 7.54 – 7.47 (m, 2H, Ar-*H*), 7.46 – 7.39 (m, 1H, Ar-*H*), 7.30 – 6.05 (br. s, 3H, N*H* and N*H*$_2$); **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 145.6, 142.5, 139.0, 129.1, 128.1, 127.0, 126.7, 126.6; **LRMS (ESI$^+$)** *m/z* 233.0 ([M+H]$^+$). Data is consistent with the literature.[58]

4-(5-(*p*-Tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonimidamide (28o)[58]

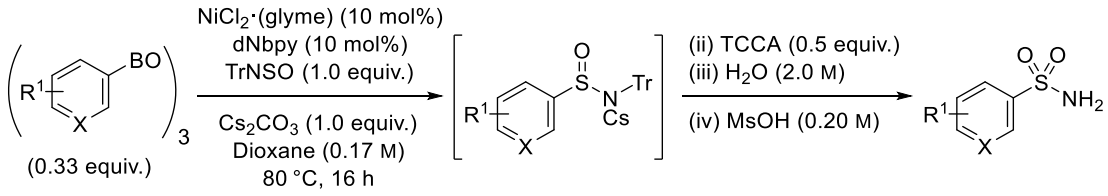


Prepared according to general procedure I using tris(4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)boroxine (131.2 mg, 0.133 mmol, 0.67 equiv.). In the aqueous workup, CH_2Cl_2 (3 × 20 mL) and sat. aq $NaHCO_3$ (20 mL) were used instead. Purification by flash column chromatography (100% EtOAc) afforded a light yellow oil which solidified on-standing to an off-white solid (41.6 mg, 55%).

***R*$_f$** (70% EtOAc in pentane) = 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06 – 7.87 (m, 2H, Ar-*H*), 7.46 – 7.37 (m, 2H, Ar-*H*), 7.16 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.10 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.73 (s, 1H, Ar-*H*), 4.89 – 4.15 (br. s, 3H, N*H*$_2$ and N*H*), 2.36 (s, 3H, C*H*$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.3, 144.1 (q, $^2J_{CF}$ = 38.5 Hz), 143.7, 142.3, 139.9, 129.9, 128.9, 127.7, 125.9, 125.5, 121.2 (q, $^1J_{CF}$ = 269.0 Hz), 106.4, 21.4; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -62.4; **LRMS (ESI)** *m/z* 381.0 ($[M+H]^+$). Data is consistent with the literature.[58]

6.4.3 Synthesis of primary sulfonamides

General Procedure J: Four-step synthesis of primary sulfonamides



Cs_2CO_3 (65.2 mg, 0.200 mmol, 1.00 equiv.) was added to an oven-dried 10 mL reaction tube. The tube was then sealed with a rubber septum and heated at 160 ℃ under vacuum for at least 2 h, or overnight to dry the Cs_2CO_3. After cooling the tube to rt and filling with N_2, pre-weighted arylboroxine (0.067 mmol, 0.33 equiv.), $NiCl_2$·(glyme) (4.4 mg, 0.020 mmol, 10 mol%), dNbpy (8.2 mg, 0.020 mmol, 10 mol%) and TrNSO (61.1 mg, 0.200 mmol, 1.00 equiv.) were quickly added. The tube was re-sealed, evacuated and filled with N_2 (× 4). Dioxane (1.2 mL, 0.17 M) was added and the reaction mixture was heated at 80 ℃ for 16 h. After cooling to rt, trichloroisocyanuric acid (23.2 mg, 0.100 mmol, 0.50 equiv.) was added and the mixture was stirred at rt for 20 min. H_2O (0.10 mL, 2.0 M) was added and the mixture was stirred at rt for 24 h. MsOH (1.0 mL, 0.20 M) was added dropwise (caution: gas formation), and the mixture was stirred at rt for 30 min. The mixture was then diluted with EtOAc (10 mL) and transferred to a 50 mL separating funnel, before neutralising with sat. aq $NaHCO_3$ (30 mL) (caution: gas formation). After collecting the organic phase, the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated at ≤ 30 ℃. Purification by flash column chromatography afforded the product.

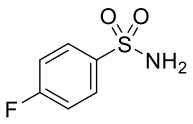
Note:

1. The procedure for step 1 and 2 was the same as General Procedure H, used to synthesise the corresponding sulfonimidoyl chlorides. See the notes for setting up step 1 in general procedure H.

2. In the hydrolysis step (step 3), drops of a white emulsion (probably the emulsion of water and Cs_2CO_3) were formed. However it would not affect the reaction, as full conversion of the sulfonimidoyl chlorides was still observed after stirring the reaction for 24 h.

3. CH_2Cl_2 was not used as an extraction solvent because it poorly dissolved primary sulfonamides, thus EtOAc was used instead. Unlike the NH sulfonimidamide synthesis, using EtOAc as the extraction solvent would not cause retritylation.

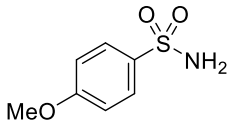
4-Fluorobenzenesulfonamide (34a)[150]



Prepared according to general procedure J using tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.). Purification by flash column chromatography (35% EtOAc in Petrol) afforded the title product as a white solid (26.1 mg, 74%).

***R*$_f$** (35% EtOAc in Petrol) = 0.22; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.92 – 7.84 (m, 2H, Ar-*H*), 7.48 – 7.35 (m, 4H, Ar-*H* and N*H*$_2$); **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 163.7 (d, $^1J_{CF}$ = 249.5 Hz), 140.6 (d, $^4J_{CF}$ = 3.0 Hz), 128.5 (d, $^3J_{CF}$ = 9.5 Hz), 116.0 (d, $^2J_{CF}$ = 22.5 Hz); **^{19}F NMR (376 MHz, DMSO-*d*$_6$)** δ -108.1; **LRMS (ESI)** *m/z* 174.0 ([M-H]$^-$). Data is consistent with the literature.[150]

4-Methoxybenzenesulfonamide (34b)[151]



Prepared according to general procedure J using tris(4-methoxyphenyl)boroxine (26.8 mg, 0.067 mmol, 0.33 equiv.). Purification by flash column chromatography (40% EtOAc in pentane) afforded the title product as an off-white solid (22.5 mg, 60%).

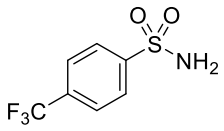
Scale up reaction: the same procedure was followed but on a 1.0 mmol scale using Cs_2CO_3 (325.8 mg, 1.000 mmol, 1.00 equiv.), 4-methoxyphenylboroxine (146.3 mg, 0.400 mmol, 0.40 equiv.), $NiCl_2$·(glyme) (2.2 mg, 0.010 mmol, 1 mol%), dNbpy (4.1 mg, 0.010 mmol, 1 mol%), TrNSO (305.4 mg, 1.000 mmol, 1.00 equiv.) and dioxane (6.00 mL) at 100 ℃ for 48 h in a 25 mL RBF. The reaction was heated on an aluminium heating block covered with tin foil and cotton. Trichloroisocyanuric acid (116.2 mg, 0.500 mmol, 0.50 equiv.), H_2O (0.50 mL, 2.0 M) and MsOH (5.0 mL, 0.2 M) were used in the following steps. Purification by flash column chromatography afforded the same product (112.8 mg, 60%).

Scale-up reaction using arylboronic acid as the starting materials in a one-pot reaction: Commercial 4-methoxyphenylboronic acid (167.4 mg, 1.100 mmol, 1.10 equiv.) and Cs_2CO_3 (325.8 mg, 1.000 mmol, 1.00 equiv.) were added to an oven-dried 25 mL RBF. The RBF was then sealed with a rubber septum and heated at 120 ℃ under vacuum for 3 h. After cooling the RBF to rt and filling with N_2, other reagents including

$NiCl_2$·(glyme), dNbpy, TrNSO and dioxane were added according to the same scale-up procedure. Purification by flash column chromatography afforded the same product (103.9 mg, 56%).

R_f (40% EtOAc in pentane) = 0.20; **^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.79 – 7.71 (m, 2H, Ar-*H*), 7.20 (s, 2H, N*H*$_2$), 7.12 – 7.04 (m, 2H, Ar-*H*), 3.82 (s, 3H, OC*H*$_3$); **^{13}C NMR (101 MHz, DMSO-d_6)** δ 161.6, 136.2, 127.7, 114.0, 55.6; **HRMS (ESI)** *m/z*: Calcd $[M+H]^+$ for $C_7H_9O_3NNaS$ 210.0195; found 210.0198. Data is consistent with the literature.[151]

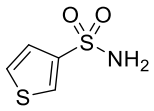
4-(Trifluoromethyl)benzenesulfonamide (34c)[152]



Prepared according to general procedure J using tris(4-(trifluoromethyl)phenyl)boroxine (68.8 mg, 0.133 mmol, 0.67 equiv.) The step 1 was heated at 100 °C instead. Purification by flash column chromatography (30% EtOAc in pentane) afforded the title product as an white solid (31.6 mg, 70%).

***R*$_f$** (30% EtOAc in pentane) = 0.25; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 8.04 (app. d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.97 (d, app. *J* = 8.5 Hz, 2H, Ar-*H*), 7.62 (s, 2H, N*H*$_2$); **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 147.9, 131.7 (q, $^2J_{CF}$ = 32.5 Hz), 126.6, 126.3 (q, $^3J_{CF}$ = 4.0 Hz), 123.6 (q, $^1J_{CF}$ = 272.5 Hz); **^{19}F NMR (377 MHz, DMSO-*d*$_6$)** δ -61.5; **LRMS (ESI$^-$)** *m/z* 224.0 ([M-H]$^-$). Data is consistent with the literature.[152]

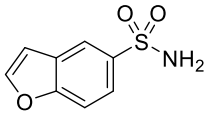
Thiophene-3-sulfonamide (34d)



Prepared according to general procedure J using tris(thiophen-3-yl)boroxine (22.0 mg, 0.067 mmol, 0.33 equiv.). Purification by flash column chromatography (30% EtOAc in pentane) afforded the title product as an off-white solid (16.8 mg, 51%).

***R*$_f$** (30% EtOAc in pentane) = 0.16; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 8.06 (dd, *J* = 3.0, 1.5 Hz, 1H, Ar-*H*), 7.71 (dd, *J* = 5.0, 3.0 Hz, 1H, Ar-*H*), 7.42 – 7.30 (m, 3H, Ar-*H* and N*H*$_2$); **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 144.4, 128.6, 128.3, 125.1; **HRMS (ESI) *m/z*:** Calcd $[M-H]^-$ for $C_4H_4O_2NS_2$ 161.9689; found 161.9677; **IR (thin film, ν_{max}/cm^{-1})** 3351, 3263, 1541, 1288, 1158, 929, 807; **m.p.** (EtOAc): 144 – 145 ℃.

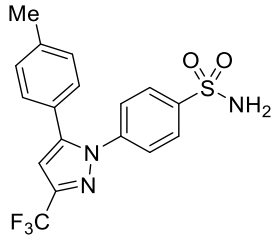
Benzofuran-5-sulfonamide (34e)



Prepared according to general procedure J using tris(benzofuran-5-yl)boroxine (28.8 mg, 0.067 mmol, 0.33 equiv.). Purification by flash column chromatography (30 – 40% EtOAc in pentane) afforded the title product as an off-white solid (21.5 mg, 55%).

***R*$_f$** (30% EtOAc in pentane) = 0.14; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 8.26 – 8.06 (m, 2H, Ar-*H*), 7.80 (app. d, *J* = 1.5 Hz, 2H, Ar-*H*), 7.33 (s, 2H, N*H*$_2$), 7.14 (d, *J* = 2.5 Hz, 1H, Ar-*H*); **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 155.4, 148.1, 139.3, 127.2, 122.2, 119.6, 111.7, 107.3; **HRMS (ESI) *m/z*:** Calcd $[M-H]^-$ for $C_8H_6O_3NS$ 196.0074; found 196.0065; **IR (thin film, ν_{max}/cm^{-1})** 3342, 3251, 1536, 1454, 1345, 1259, 1149, 868, 769, 712; **m.p.** (EtOAc): 153 – 154 ℃.

Celecoxib (34f)[143]



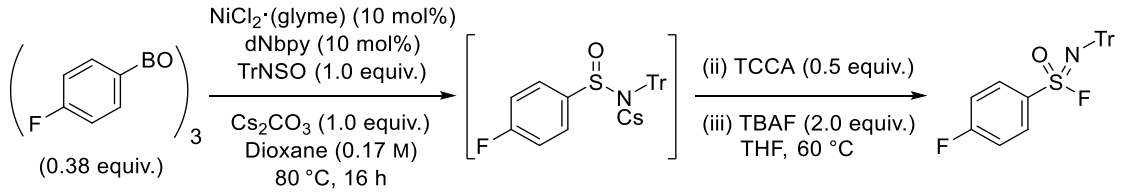
Prepared according to general procedure J using tris(4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)boroxine (131.2 mg, 0.133 mmol, 0.67 equiv.). The step 1 was heated at 100 ℃ instead. Purification by flash column chromatography (30% EtOAc in pentane) afforded the title product as a light yellow oil which solidified on-standing to an off-white solid (46.4 mg, 61%).

***R*$_f$** (30% EtOAc in pentane) = 0.25; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.96 – 7.81 (m, 2H, Ar-*H*), 7.50 – 7.42 (m, 2H, Ar-*H*), 7.20 – 7.14 (m, 2H, Ar-*H*), 7.14 – 7.07 (m, 2H, Ar-*H*), 6.74 (s, 1H, Ar-*H*), 5.30 – 4.91 (br. s, 2H, N*H*$_2$), 2.37 (s, 3H, C*H*$_3$); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 145.4, 144.2 (q, $^2J_{CF}$ = 38.5 Hz), 142.7, 141.5, 140.0, 129.9, 128.9, 127.6, 125.8, 125.6, 121.2 (q, $^1J_{CF}$ = 269.5 Hz), 106.5, 21.5; **^{19}F NMR (377 MHz, CDCl$_3$)** δ -62.4; **LRMS (ESI)** *m/z* 382.0 ([M+H]$^+$). Data is consistent with the literature.[143]

6.4.4 Synthesis of sulfonimidoyl fluorides

General Procedure K: Four-step synthesis of sulfonimidoyl fluorides

4-Fluoro-*N*-tritylbenzenesulfonimidoyl fluoride (35)[114]

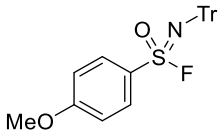


Cs_2CO_3 (65.2 mg, 0.200 mmol, 1.00 equiv.) was added to an oven-dried 10 mL reaction tube. The tube was then sealed with a rubber septum and heated at 160 ℃ under vacuum for 2 h to dry the Cs_2CO_3. After cooling the tube to rt and filling with N_2, pre-weighted tris(4-fluorophenyl)boroxine (28.0 mg, 0.077 mmol, 0.38 equiv.), $NiCl_2$·(glyme) (4.4 mg, 0.020 mmol, 10 mol%), dNbpy (8.2 mg, 0.020 mmol, 10 mol%) and TrNSO (61.1 mg, 0.200 mmol, 1.00 equiv.) were quickly added. The tube was re-sealed, evacuated and filled with N_2 (× 4). Dioxane (1.2 mL, 0.17 M) was next added, and the reaction mixture was heated at 80 ℃ for 16 h. After cooling to rt, trichloroisocyanuric acid (23.2 mg, 0.100 mmol, 0.50 equiv.) was added and the mixture was stirred at rt for 20 min. TBAF (0.40 mL, 1.0 M in THF, 0.40 mmol, 2.0 equiv.) was added and the mixture was heated at 60 ℃ for 30 min. The mixture was cooled to rt, diluted with CH_2Cl_2 (10 mL) and transferred to a 50 mL separating funnel, then quenched with sat. aq $NaHCO_3$ (10 mL). After collecting the organic phase, the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (2 – 5% Et_2O in pentane) afforded the title product as an off-white solid (61.6 mg, 73%).

(The procedure for step 1 and 2 was the same as General Procedure H, used to synthesise sulfonimidoyl chlorides. See the notes for setting up step 1 in general procedure H.)

***R*$_f$** (5% Et_2O in pentane) = 0.29; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.20 – 8.03 (m, 2H, Ar-*H*), 7.46 – 7.36 (m, 6H, Ar-*H*), 7.31 – 7.18 (m, 11H, Ar-*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.9 (d, $^1J_{CF}$ = 256.5 Hz), 146.3 (d, $^4J_{CF}$ = 4.0 Hz), 134.3 (dd, $^2J_{CF}$/$^4J_{CF}$ = 30.5, 3.0 Hz), 130.4 (d, $^3J_{CF}$ = 9.5 Hz), 128.9, 128.0, 127.3, 116.6 (d, $^2J_{CF}$ = 23.0 Hz), 74.4 (d, $^3J_{CF}$ = 4.5 Hz); **^{19}F NMR (377 MHz, $CDCl_3$) δ** 92.2, -103.3; **HRMS (ESI) *m/z*:** Calcd $[M+Na]^+$ for $C_{25}H_{19}ONF_2NaS$ 442.1048; found 442.1048; **IR (thin film, ν_{max}/cm^{-1})** 3059, 1591, 1491, 1366, 1215, 1154, 698; **m.p.** (Et_2O): 160 – 161 ℃. Data is consistent with Thomas' data.[114]

4-Methoxy-*N*-tritylbenzenesulfonimidoyl fluoride (37)[115]

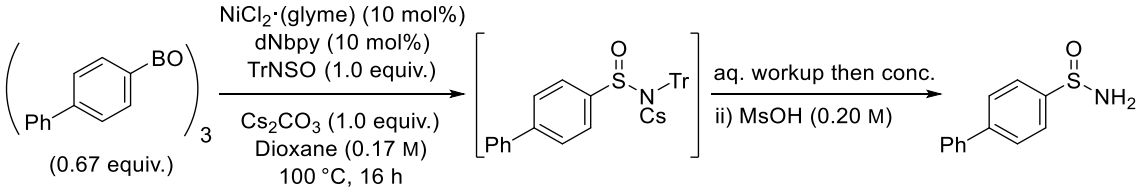


Prepared according to general procedure K using tris(4-methoxyphenyl)boroxine (26.8 mg, 0.067 mmol, 0.33 equiv.). Purification by flash column chromatography (15% Et_2O in pentane) afforded the title product as an off-white solid (46.8 mg, 54%).

***R*$_f$** (15% Et_2O in pentane) = 0.20; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.10 – 8.03 (m, 2H, Ar-*H*), 7.50 – 7.40 (m, 6H, Ar-*H*), 7.34 – 7.23 (m, 9H, Ar-*H*), 7.06 – 7.00 (m, 2H, Ar-*H*), 3.90 (s, 3H, O*CH*$_3$).; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 163.9, 146.5 (d, $^3J_{CF}$ = 4.5 Hz), 129. 9 (d, $^2J_{CF}$ = 29.0 Hz), 129.8, 128.9, 127.9, 127.1, 114.5, 74.0 (d, $^3J_{CF}$ = 4.0 Hz), 55.9; **^{19}F NMR (377 MHz, $CDCl_3$)** δ 91.8; **HRMS (ESI, APCI or EI)** not found; **IR (thin film, ν_{max}/cm^{-1})** 3058, 1594, 1496, 1358, 1264, 1213, 1171, 1103, 1026, 833; **m.p.** (Et_2O): 119 – 120 °C. Data is consistent with with the literature.[115]

6.4.5 Synthesis of primary sulfinamide

[1,1'-Biphenyl]-4-sulfinamide (44)



Cs_2CO_3 (65.2 mg, 0.200 mmol, 1.00 equiv.) was added to an oven-dried 10 mL reaction tube. The tube was then sealed with a rubber septum and heated at 160 ℃ under vacuum for 2 h to dry the Cs_2CO_3. After cooling the tube to rt and filling with N_2, pre-weighted tris([1,1'-biphenyl]-4-yl)boroxine (72.0 mg, 0.133 mmol, 0.67 equiv.), $NiCl_2$·(glyme) (4.4 mg, 0.020 mmol, 10 mol%), dNbpy (8.2 mg, 0.020 mmol, 10 mol%) and TrNSO (61.1 mg, 0.200 mmol, 1.00 equiv.) were quickly added. The tube was re-sealed, evacuated and filled with N_2 (× 4). Dioxane (1.2 mL, 0.17 M) was added and the reaction mixture was heated at 100 ℃ for 16 h. After cooling to rt, the mixture was diluted with CH_2Cl_2 (~ 7 mL) and filtered through a short plug of celite into a 25 mL RBF. The celite plug was further washed with CH_2Cl_2 (10 mL). The clear yellow solution was concentrated under reduced pressure. All volatiles were further removed under < 20 mbar at 50 ℃ on a rotary evaporator for 15 min. After cooling to rt, MsOH (1.0 mL, 0.20 M) was added and a bright yellow colour (probably due to the formation of Tr^+) was observed. The mixture was stirred at rt for 5 min. The mixture was quickly diluted with EtOAc (~ 2 – 3 mL) and quickly transferred to a stirring solution of sat. aq $NaHCO_3$ (10 mL) (caution: gas formation) in a 50 mL breaker. The addition of EtOAc and transfer to aq. $NaHCO_3$ solution was quickly repeated 8 times,

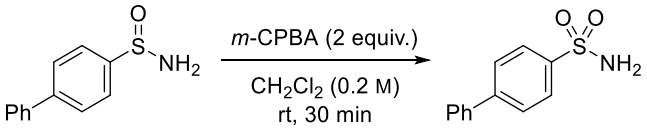
until no yellow colour was observed in the reaction tube. After collecting the organic phase, the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated at ≤ 25 °C. Purification by flash column chromatography (80% EtOAc in pentane) afforded the product as an off-white solid (22.0 mg, 51%).

(The procedure for step 1 was the same as General Procedure H, used to synthesise the trityl-sulfinamide. See the notes for setting up step 1 in general procedure H.)

R_f (80% EtOAc in pentane) = 0.28; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.87 – 7.78 (m, 2H, Ar-*H*), 7.77 – 7.65 (m, 4H, Ar-*H*), 7.54 – 7.45 (m, 2H, Ar-*H*), 7.45 – 7.37 (m, 1H, Ar-*H*), 6.31 (s, 2H, N*H*$_2$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 147.1, 142.1, 139.2, 129.1, 128.0, 127.0, 126.9, 126.1; **HRMS (ESI) *m/z*:** Calcd $[M+H]^+$ for $C_{12}H_{12}ONS$ 218.0634; found 218.0635; **IR (thin film, ν_{max}/cm^{-1})** 3283, 3168, 3077, 1478, 1023, 1003, 835, 756; **m.p.** (EtOAc): 183 – 184 °C.

6.4.6 Synthesis of primary sulfonamide from primary sulfinamide

[1,1'-Biphenyl]-4-sulfonamide (45)[153]



The title sulfonamide was prepared using a modified literature method. [97a]

m-CPBA (58.0 mg, ~60 wt%, 0.200 mmol, 2.0 equiv.) was added to a solution of [1,1'-biphenyl]-4-sulfinamide (21.7 mg, 0.100 mmol, 1.00 equiv.) in CH_2Cl_2 (0.5 mL). After stirring at rt for 30 min, the mixture was diluted with EtOAc, sat aq. $Na_2S_2O_3$ and sat. aq $NaHCO_3$ (10 mL each). After collecting the organic phase, the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (30% EtOAc in pentane) afforded the product as an off-white solid (20.9 mg, 90%).

***R*$_f$** (30% EtOAc in pentane) = 0.17; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.91 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.86 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.76 – 7.70 (m, 2H, Ar-*H*), 7.54 – 7.48 (m, 2H, Ar-*H*), 7.46 – 7.42 (m, 1H, Ar-*H*), 7.41 (s, 2H, N*H*$_2$); **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ 143.4, 142.9, 138.7, 129.1, 128.4, 127.2, 127.0, 126.3; **LRMS (ESI)** *m/z* 256.0 ($[M+Na]^+$). Data is consistent with the literature.[153]

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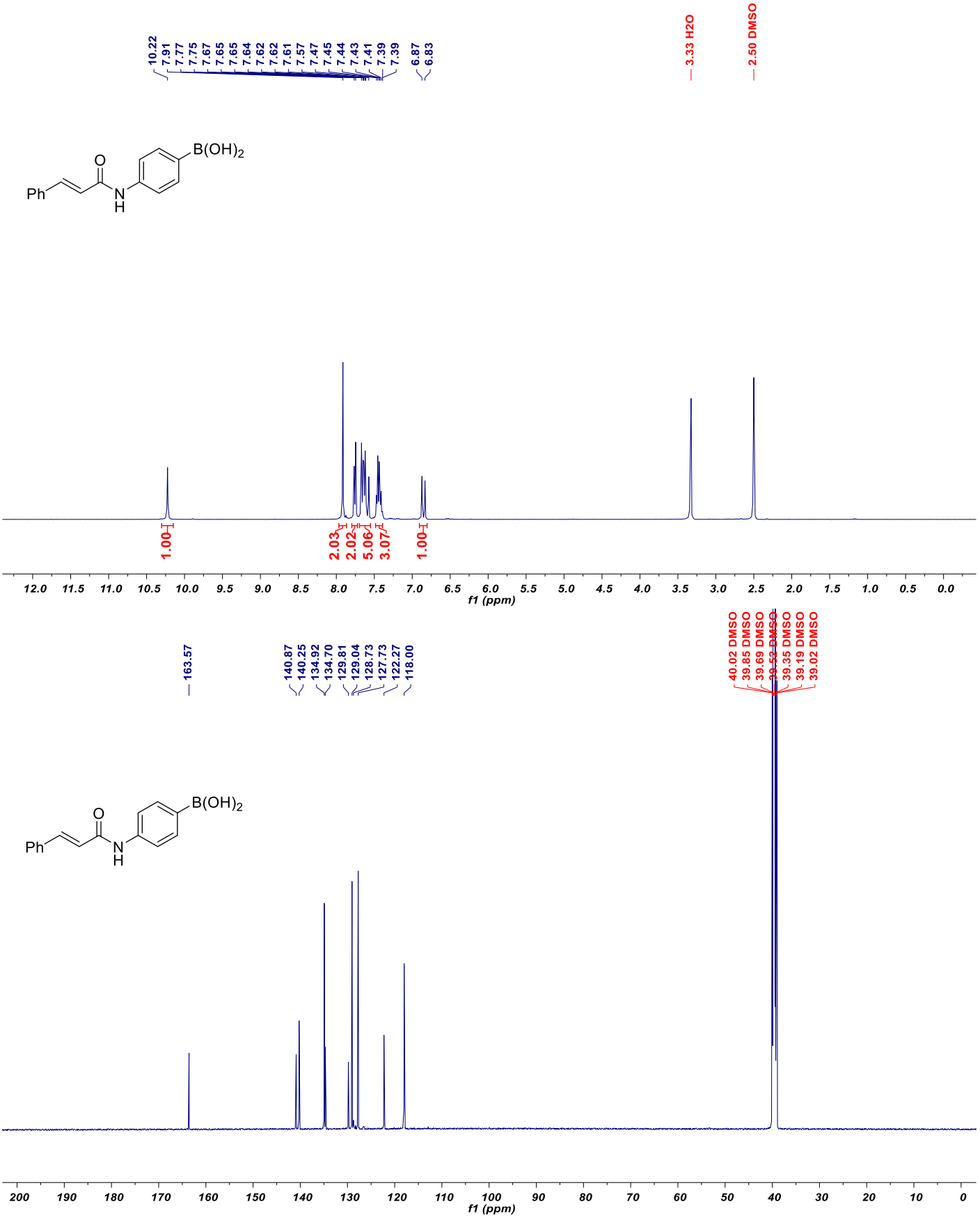
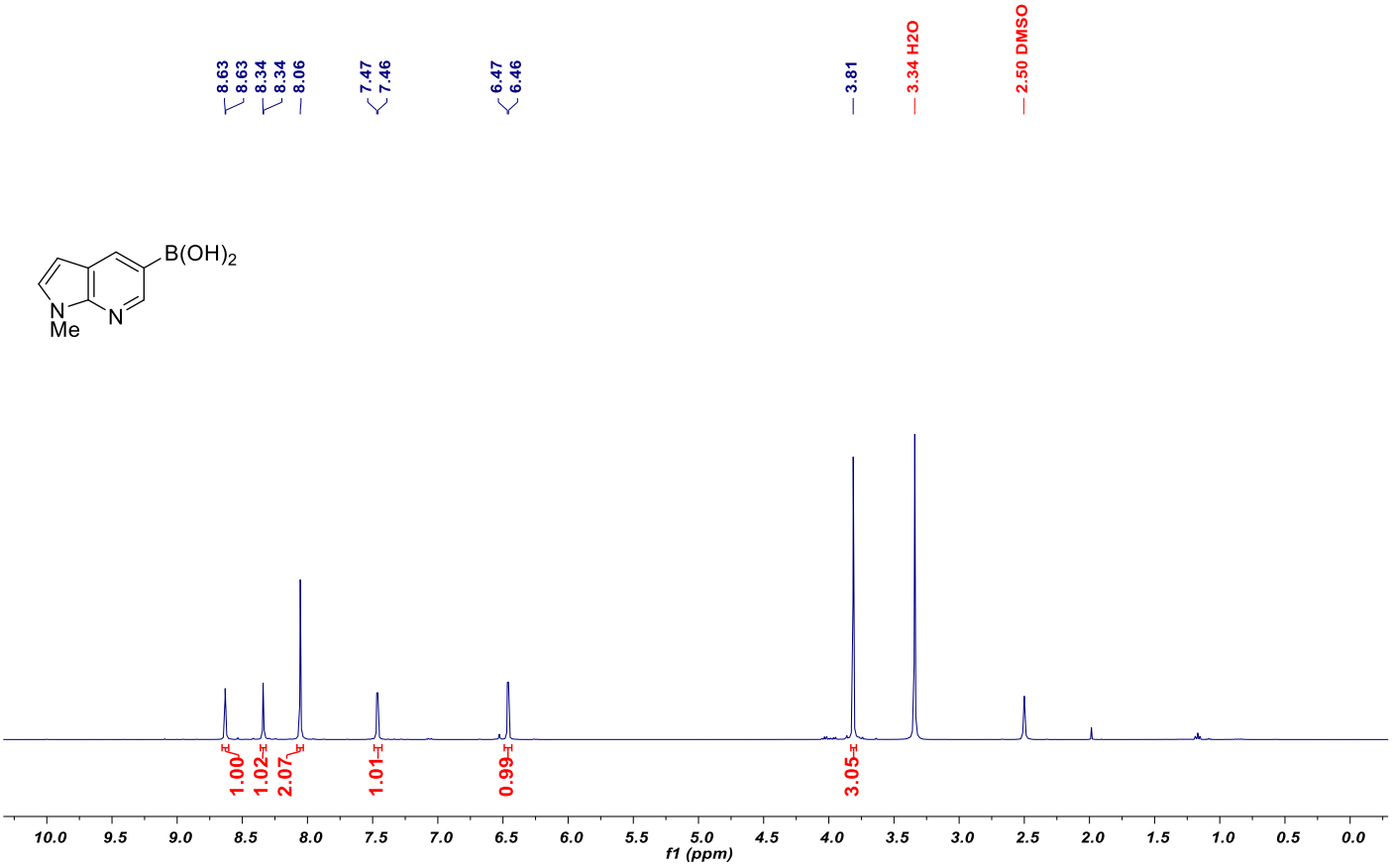
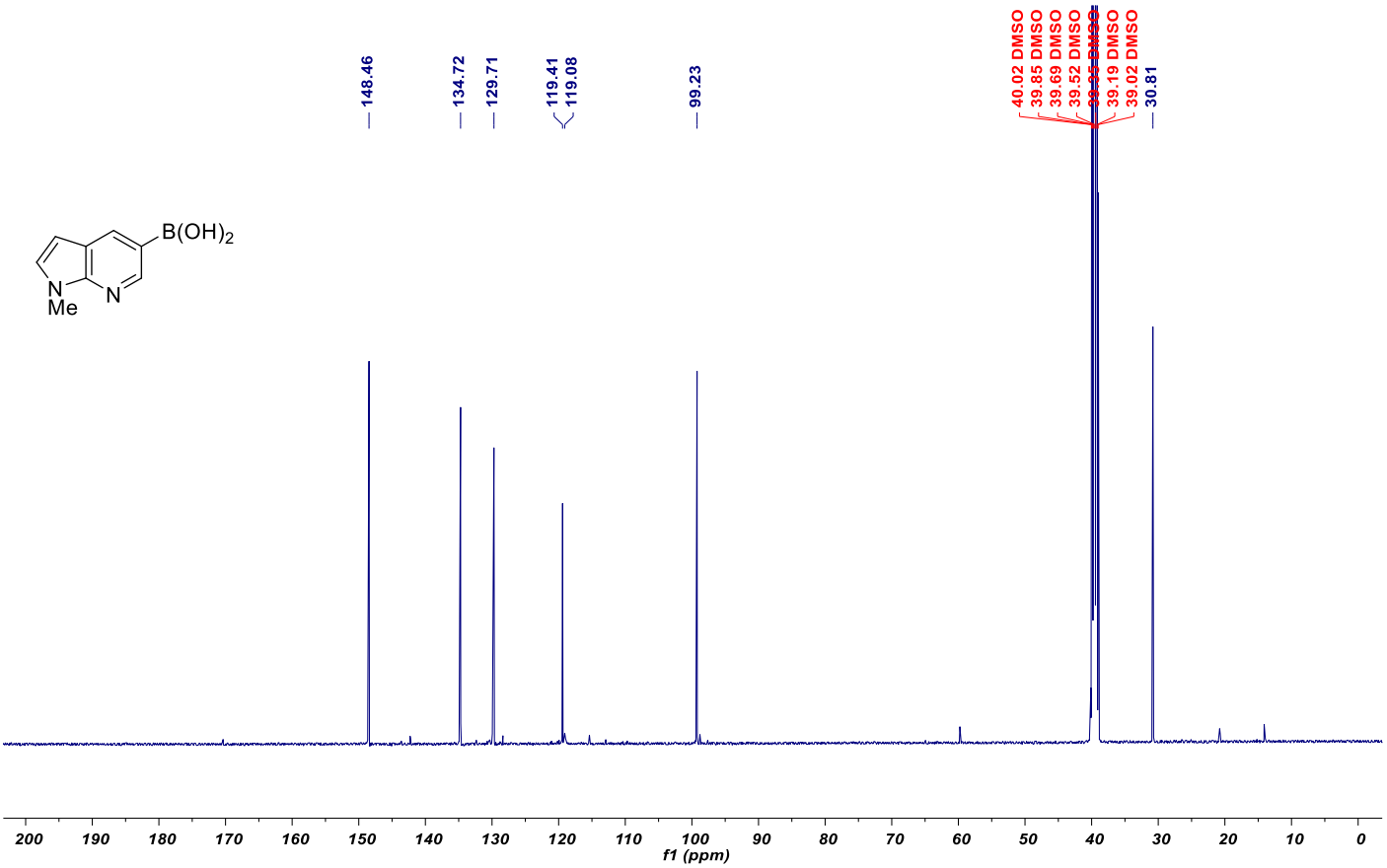
NMR Spectra

NMR spectrum of (4-cinnamamidophenyl)boronic acid

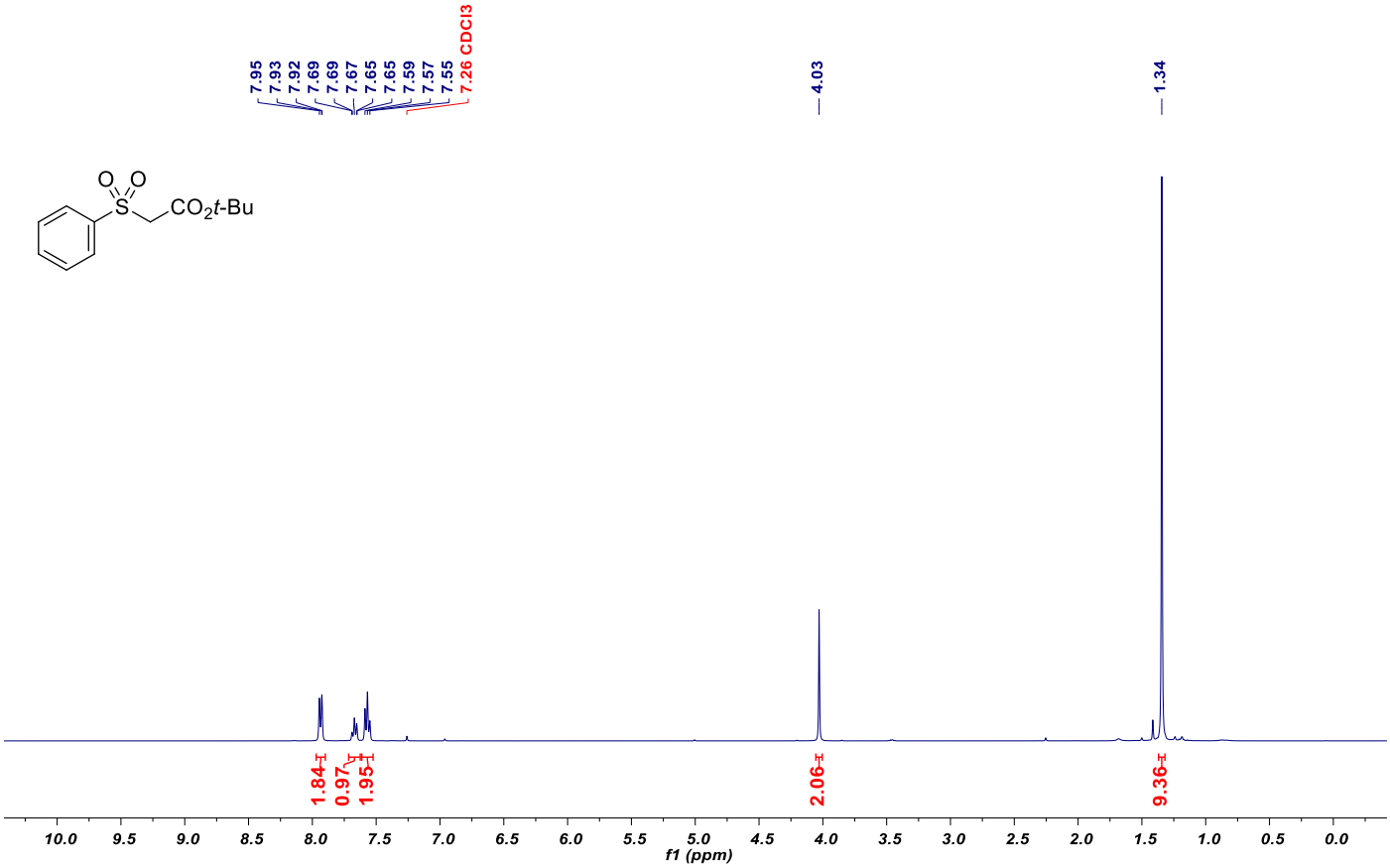


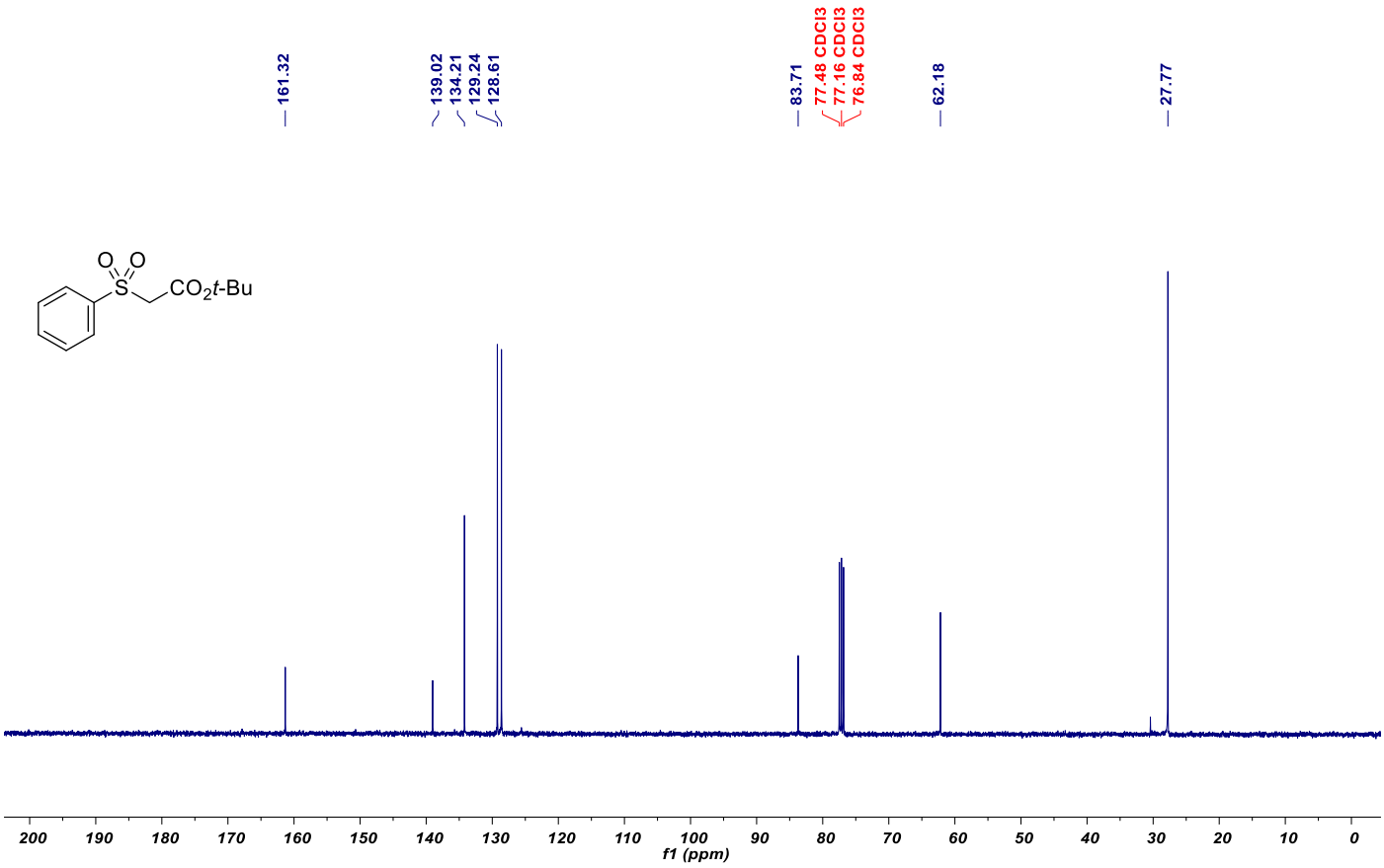
NMR spectrum of (1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)boronic acid



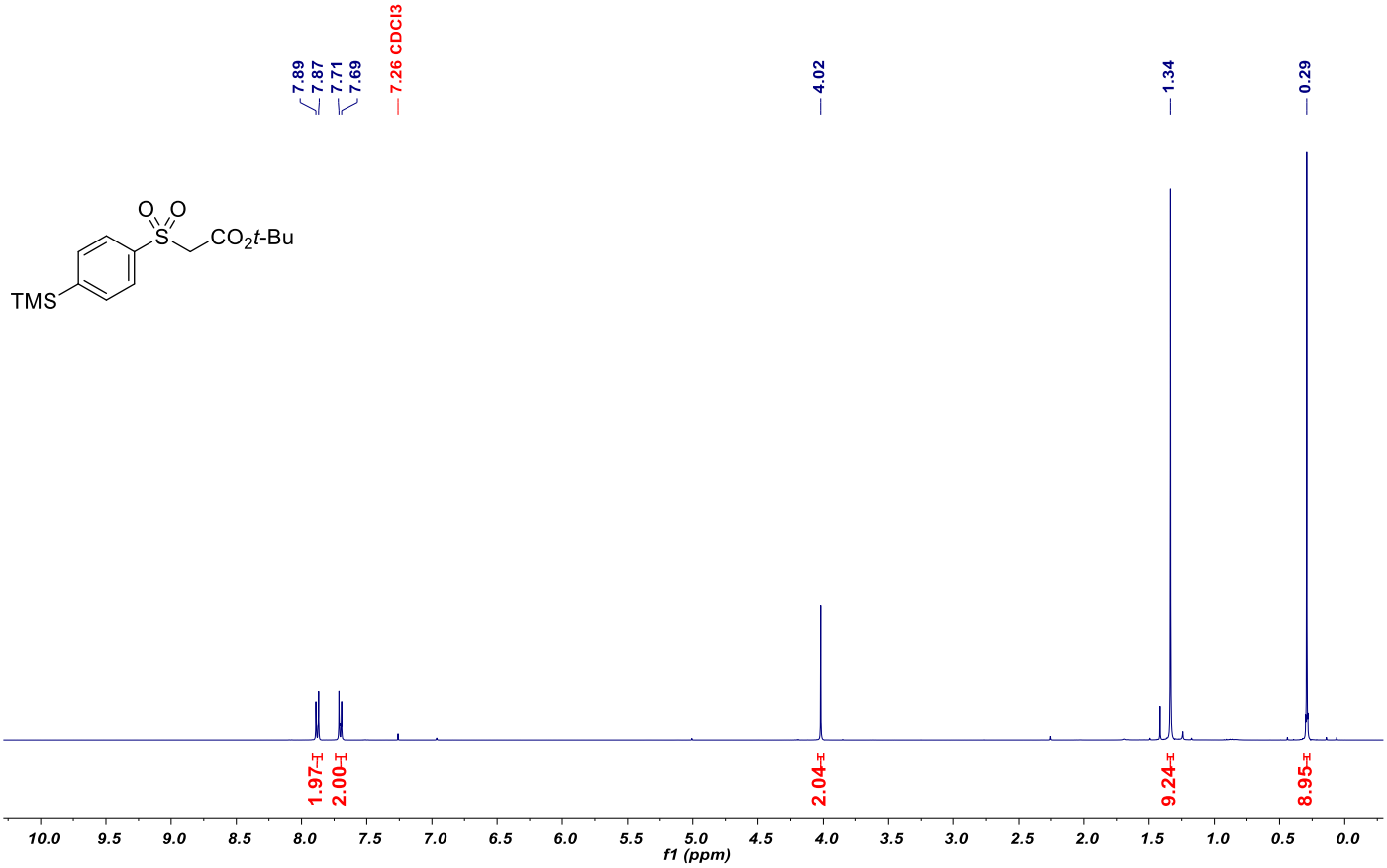


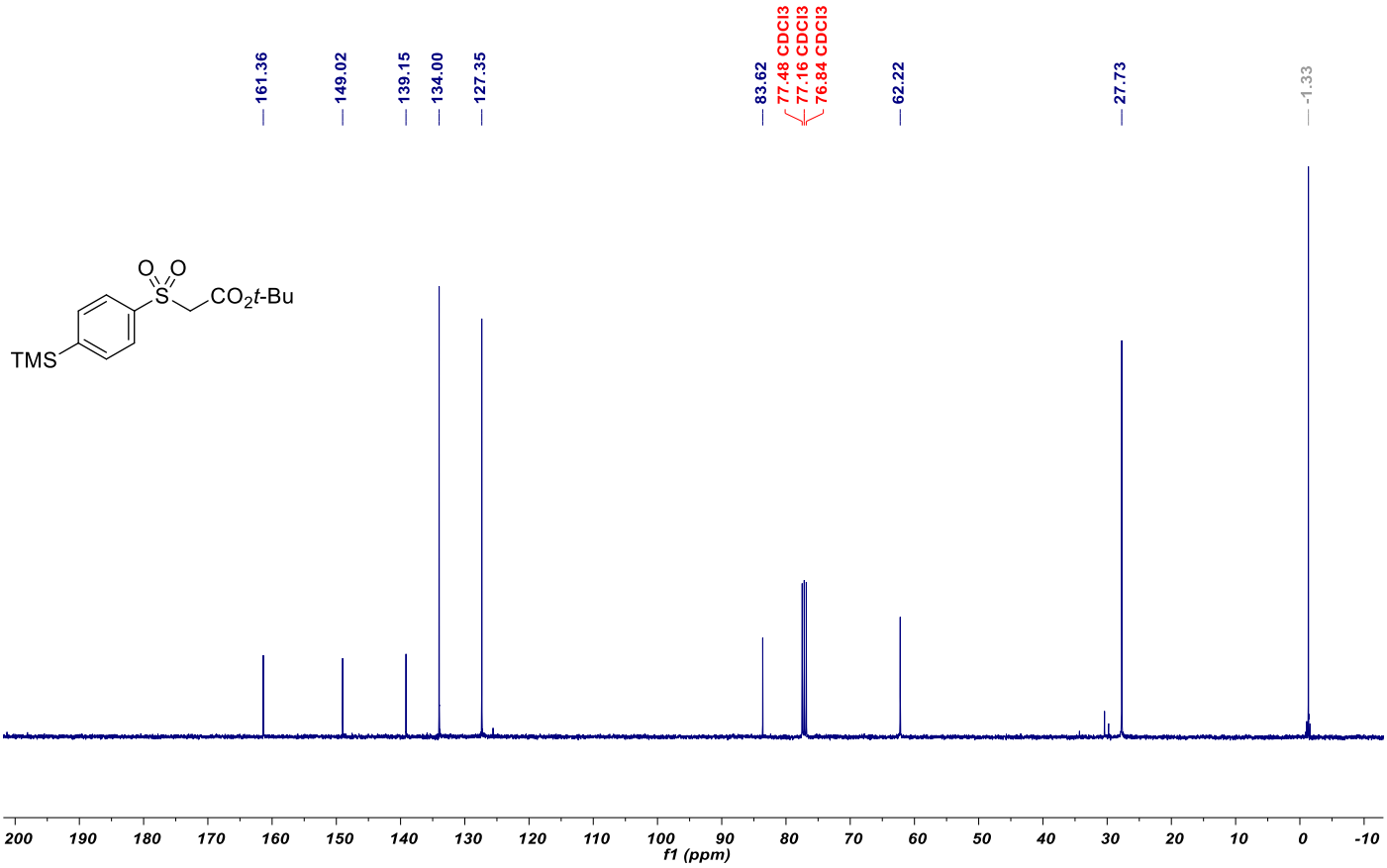
NMR spectrum of sulfone **7a**



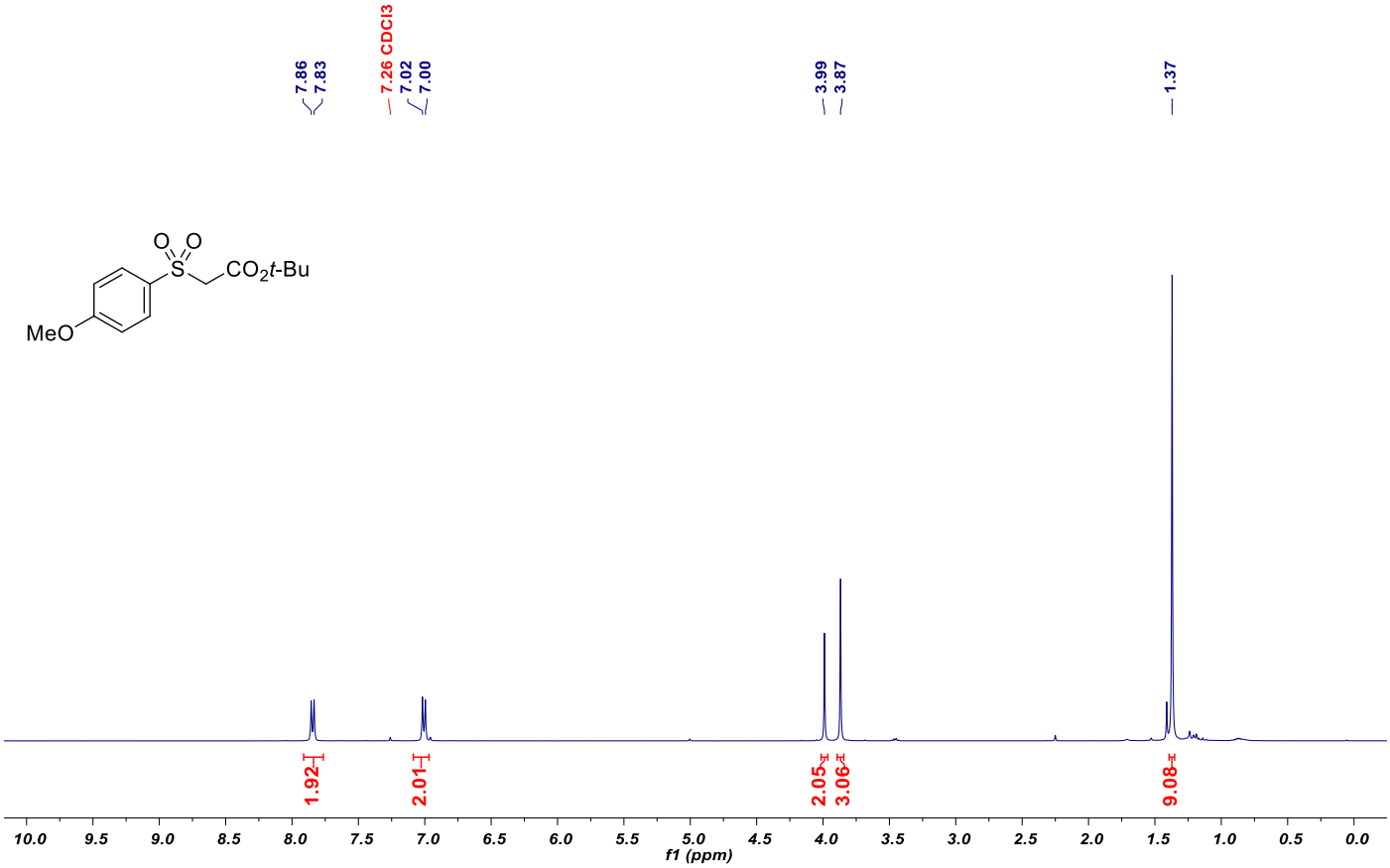


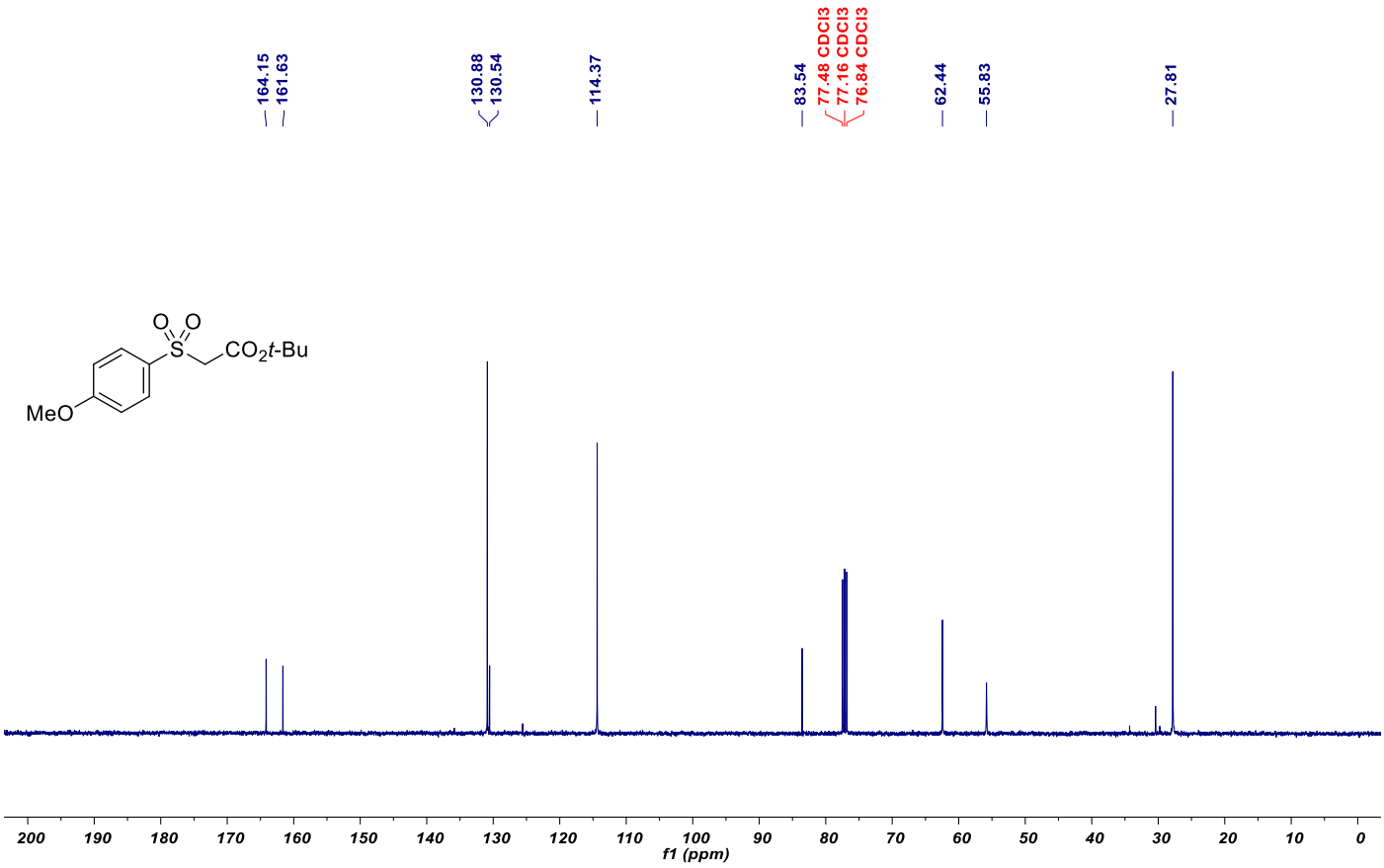
NMR spectrum of sulfone **7b**



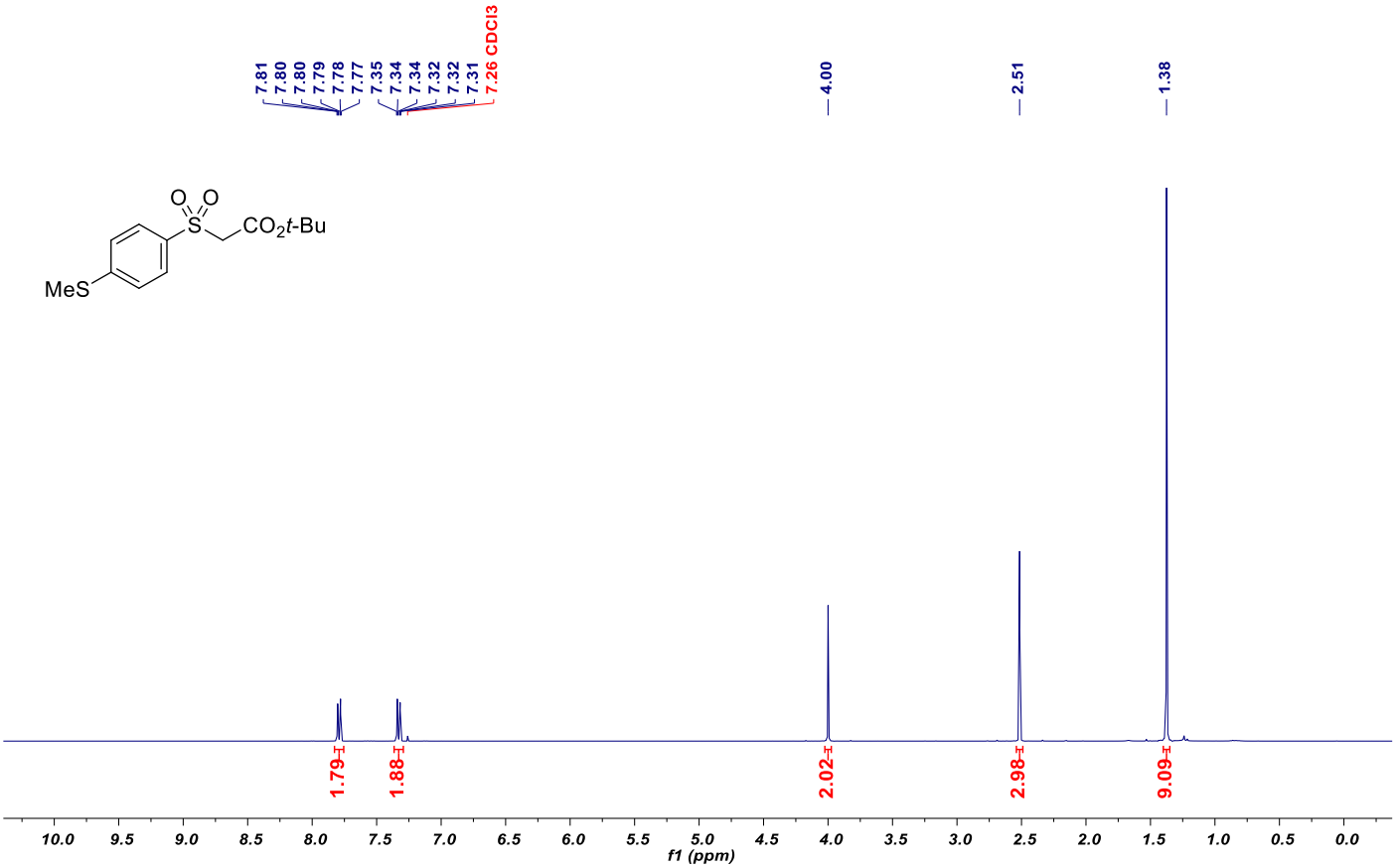


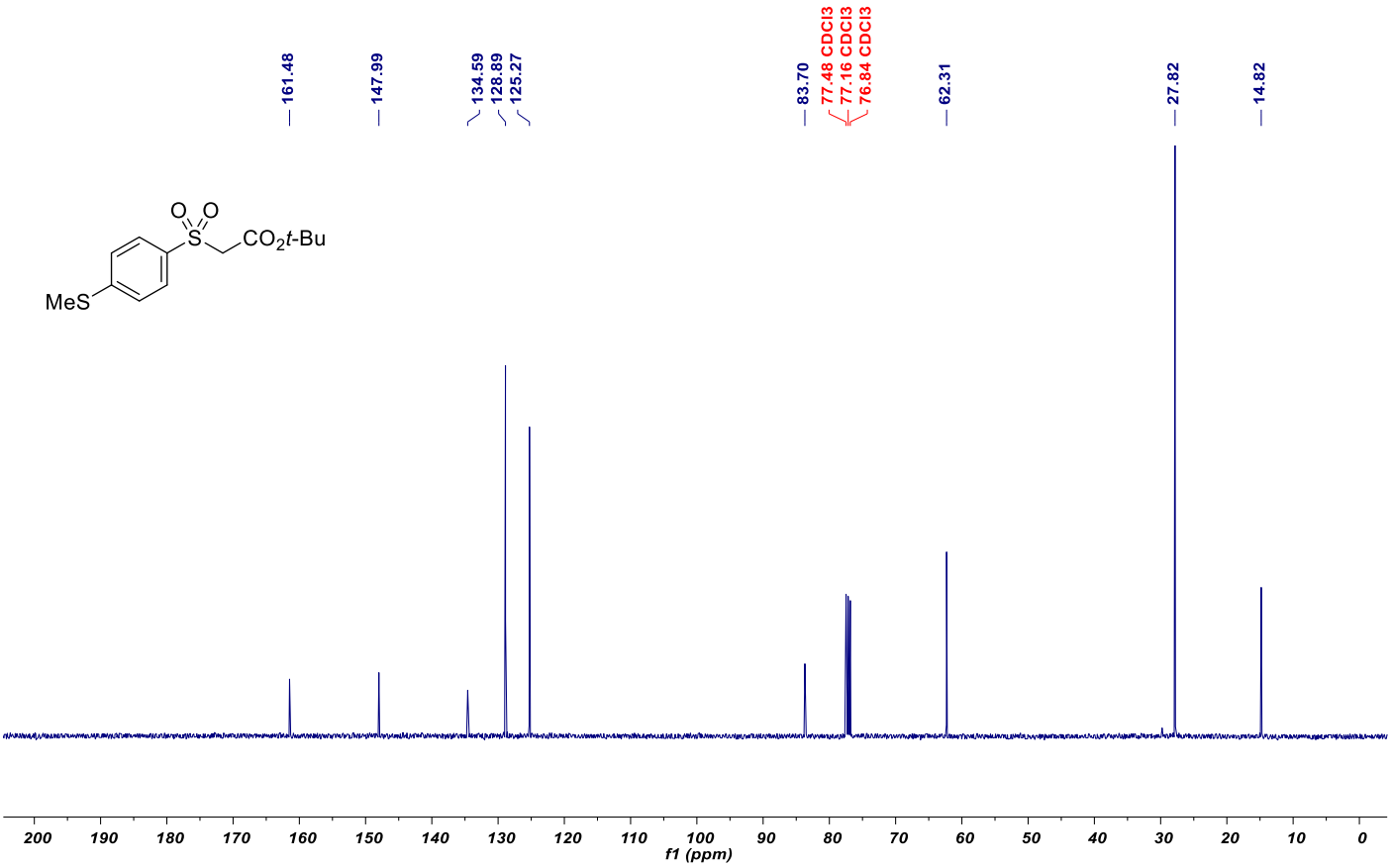
NMR spectrum of sulfone **7c**



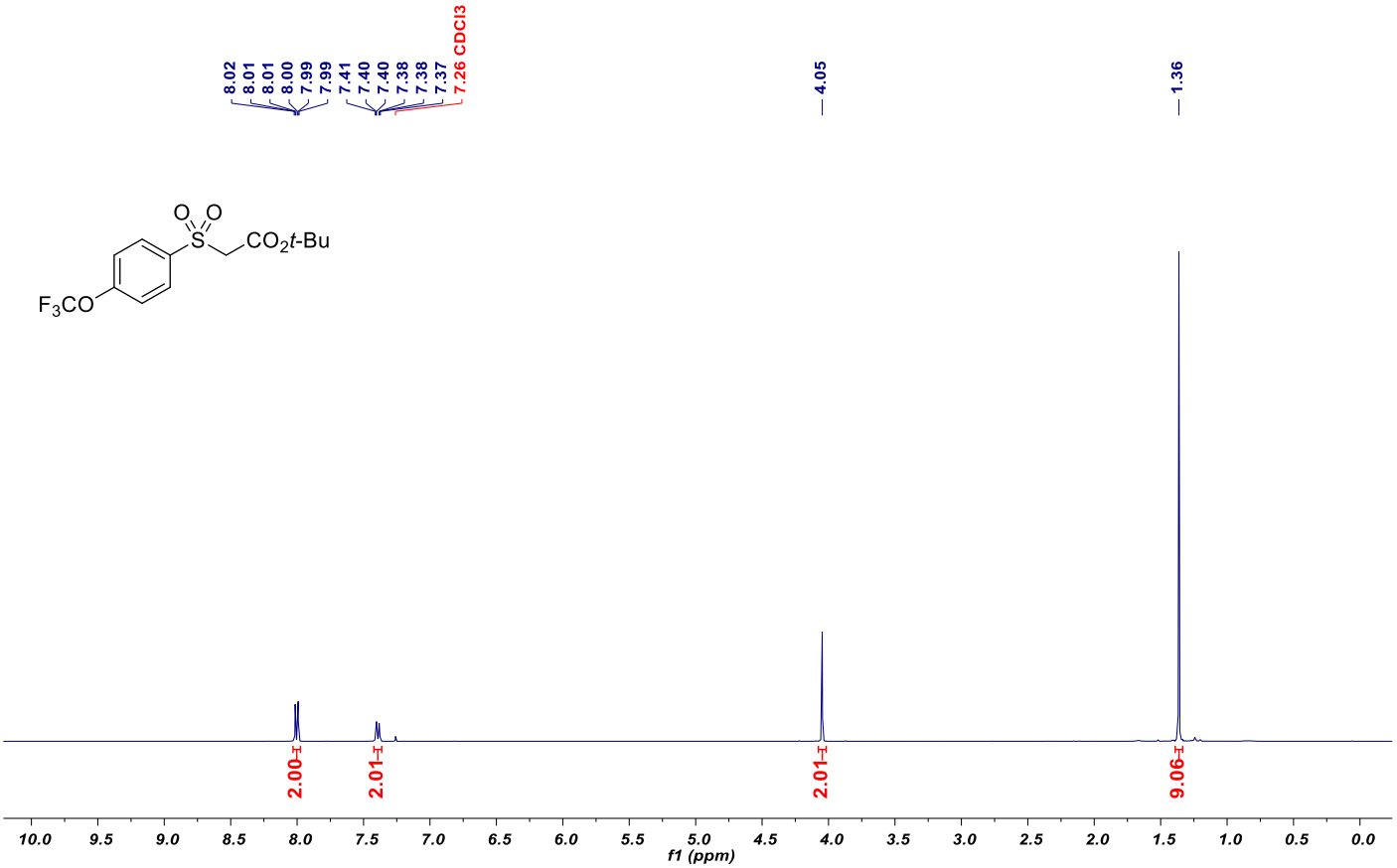


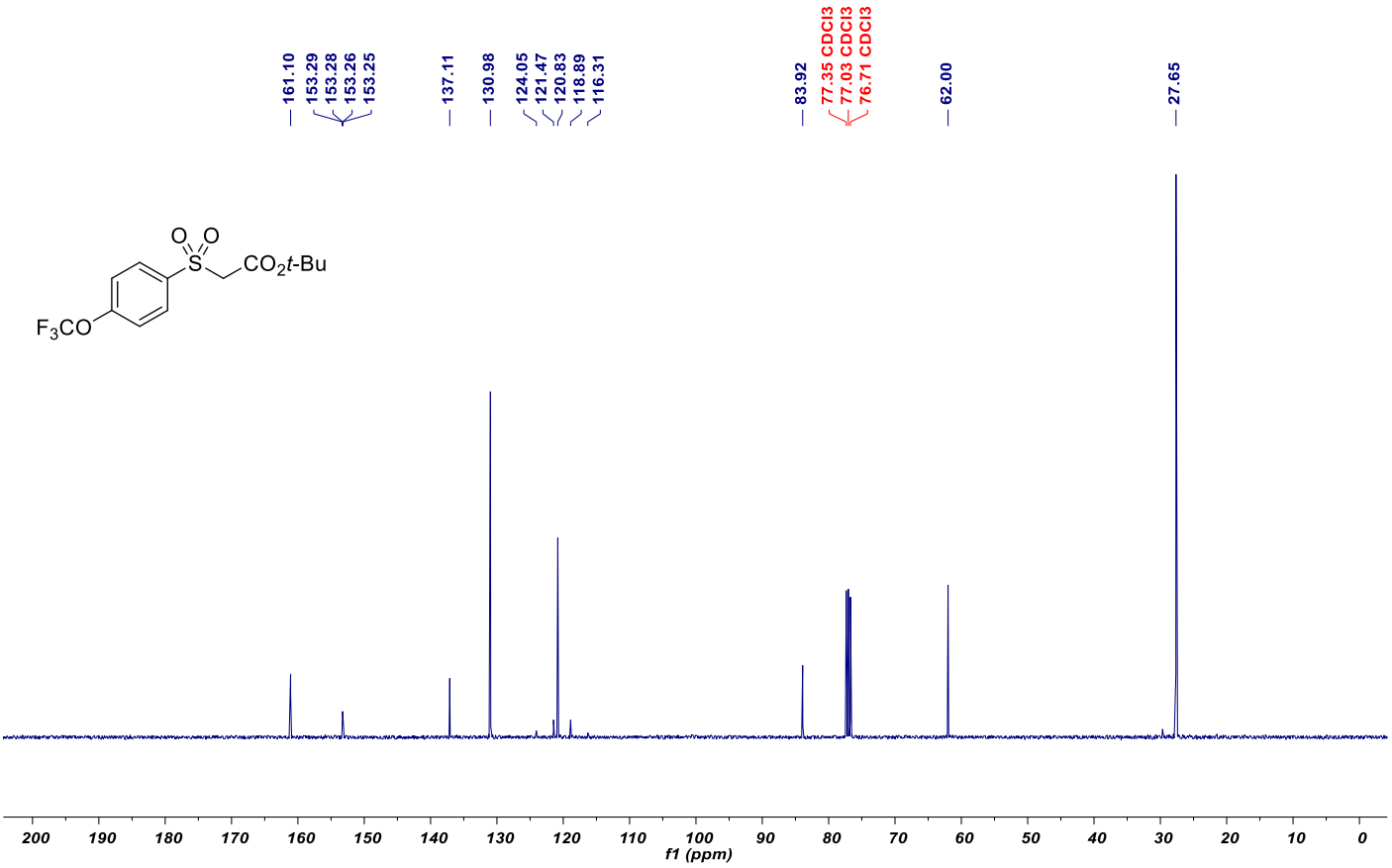
NMR spectrum of sulfone **7d**

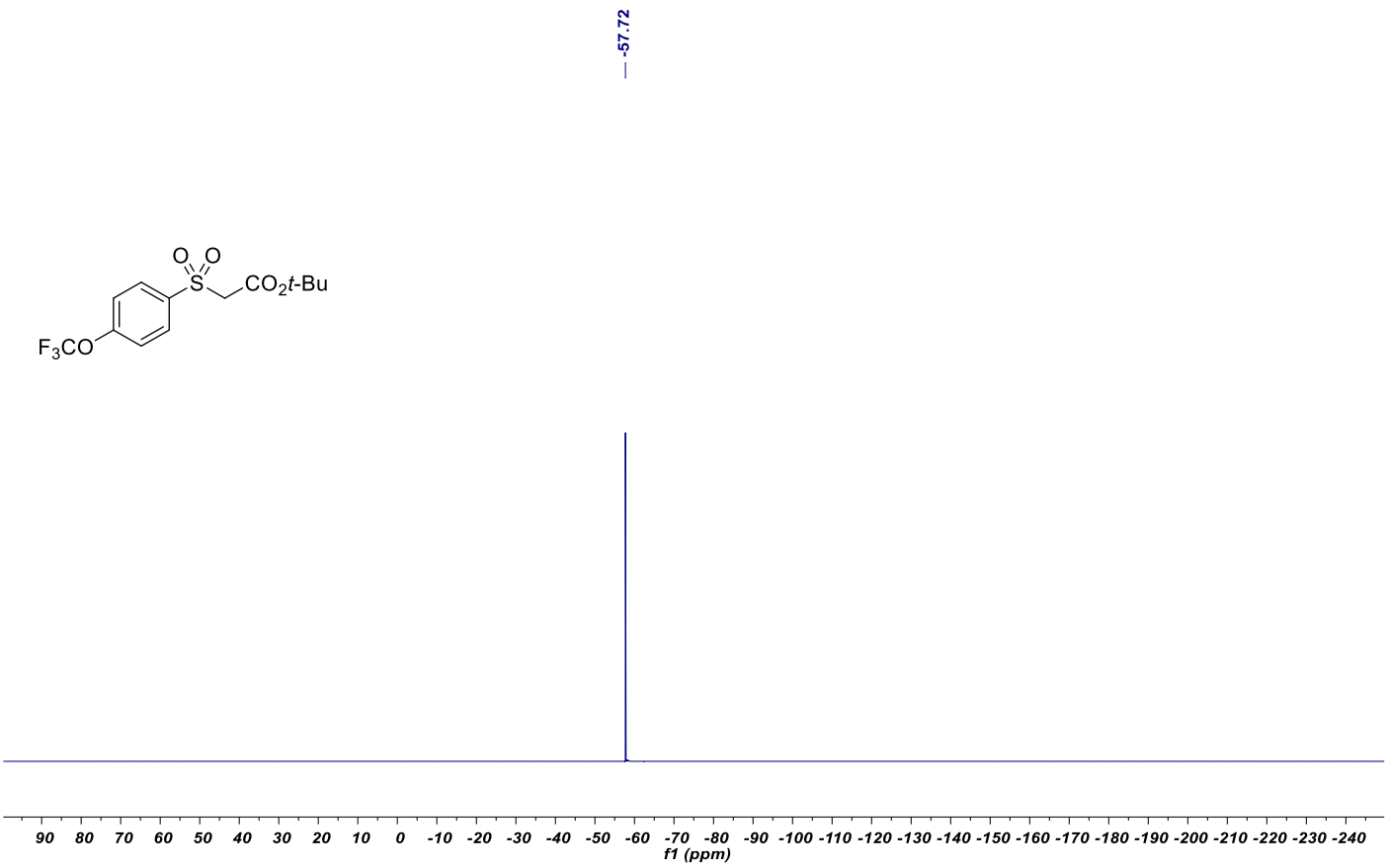




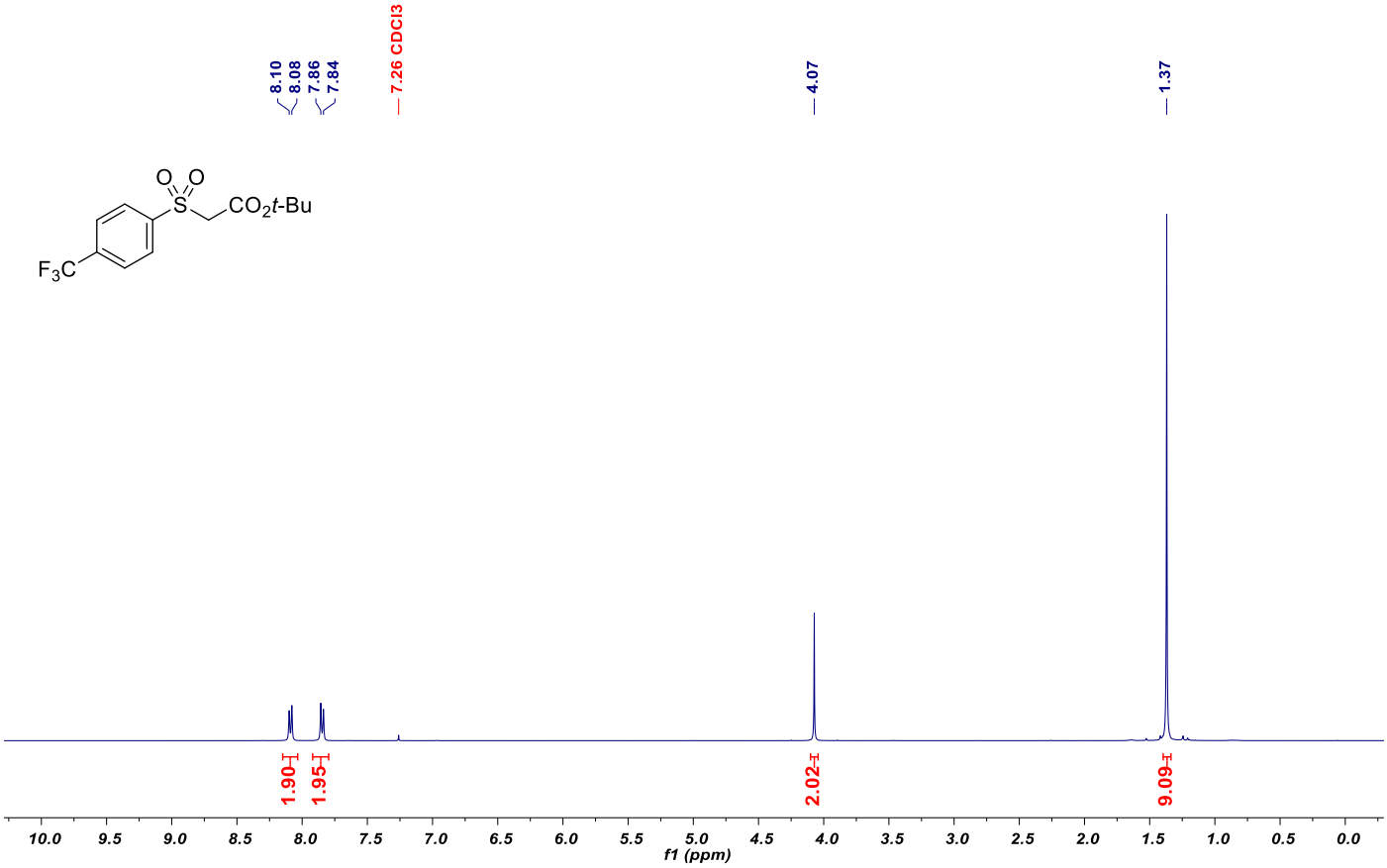
NMR spectrum of sulfone **7e**

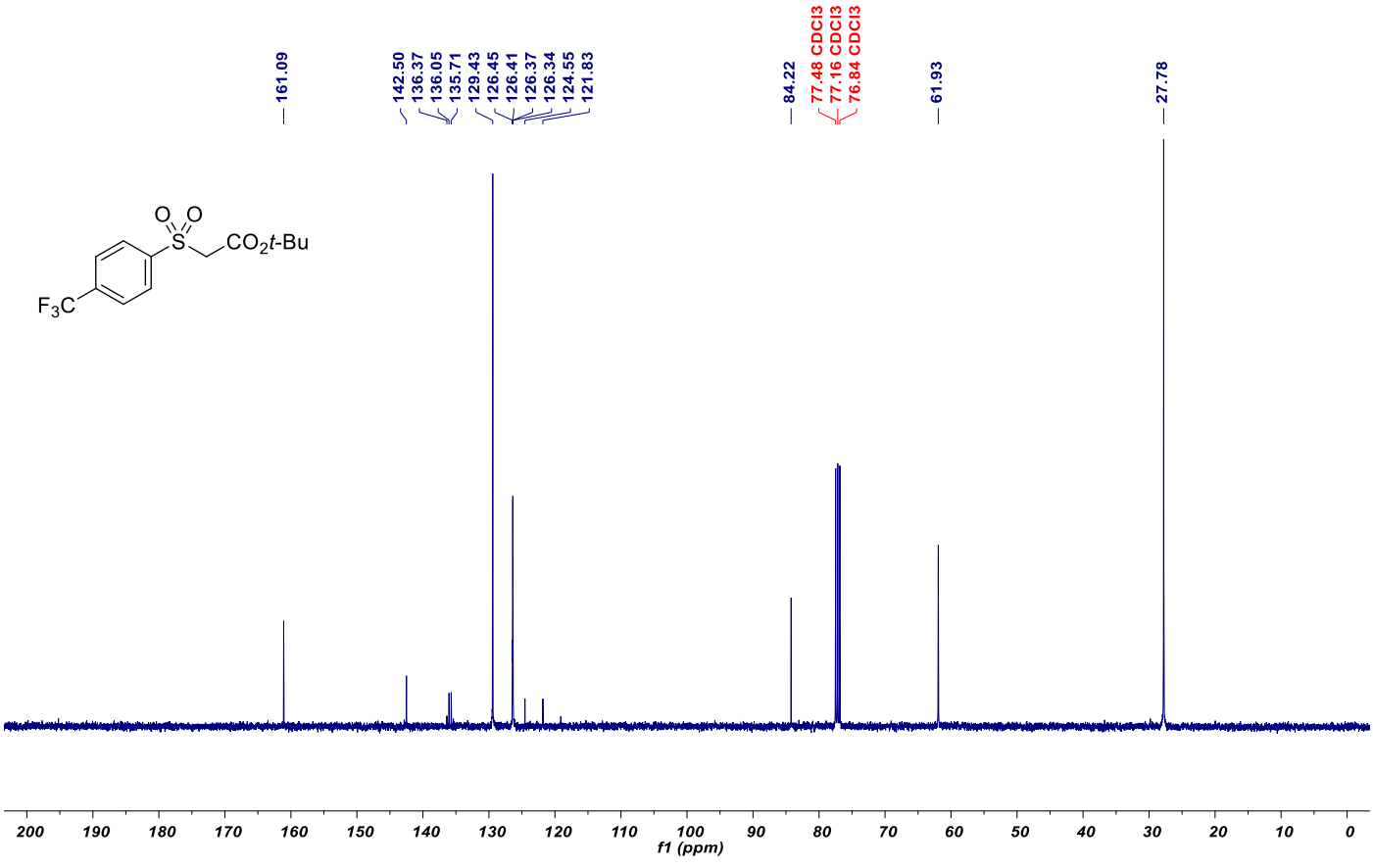


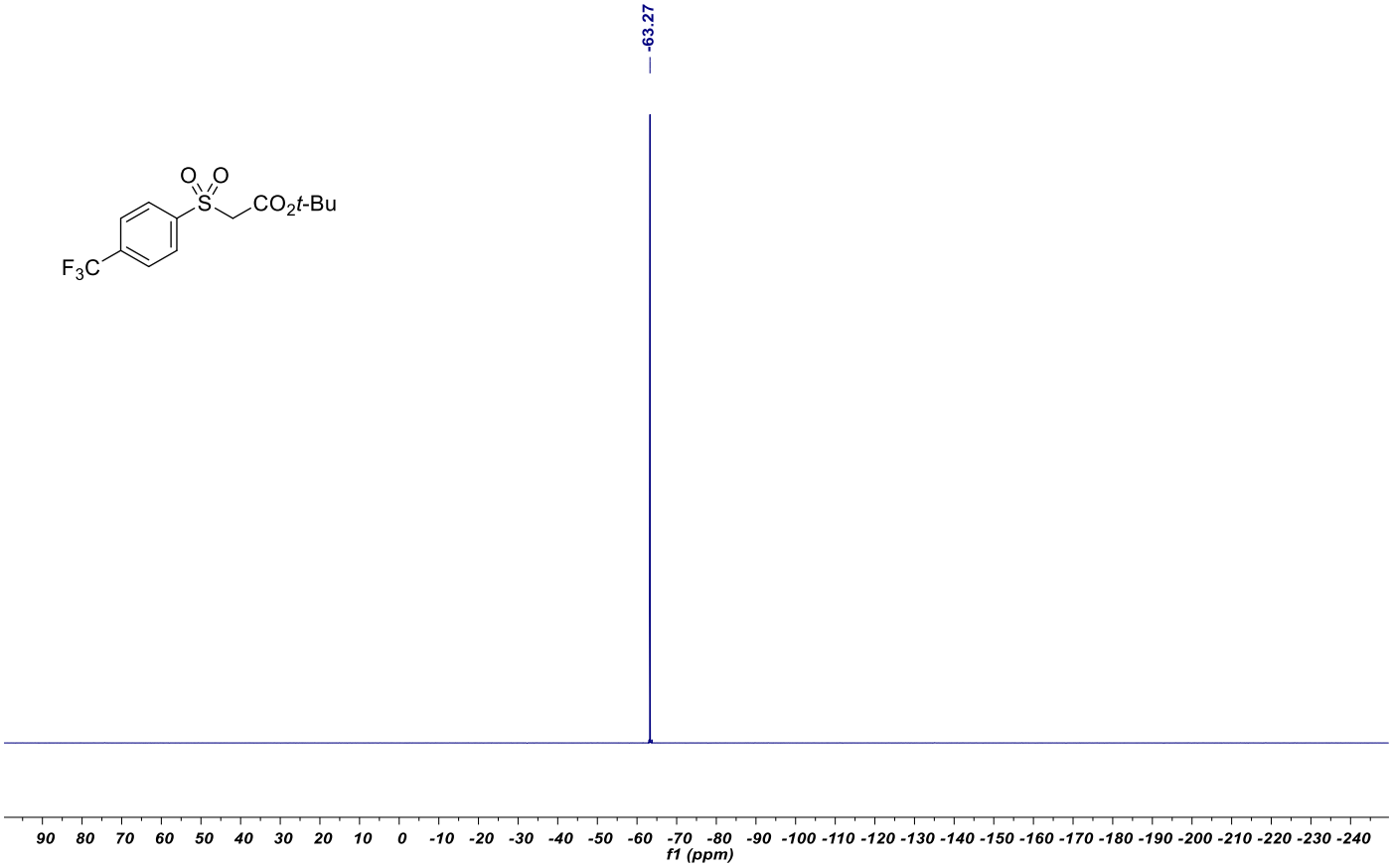



-57.72
O
O
S
CO2t-Bu
F3CO
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

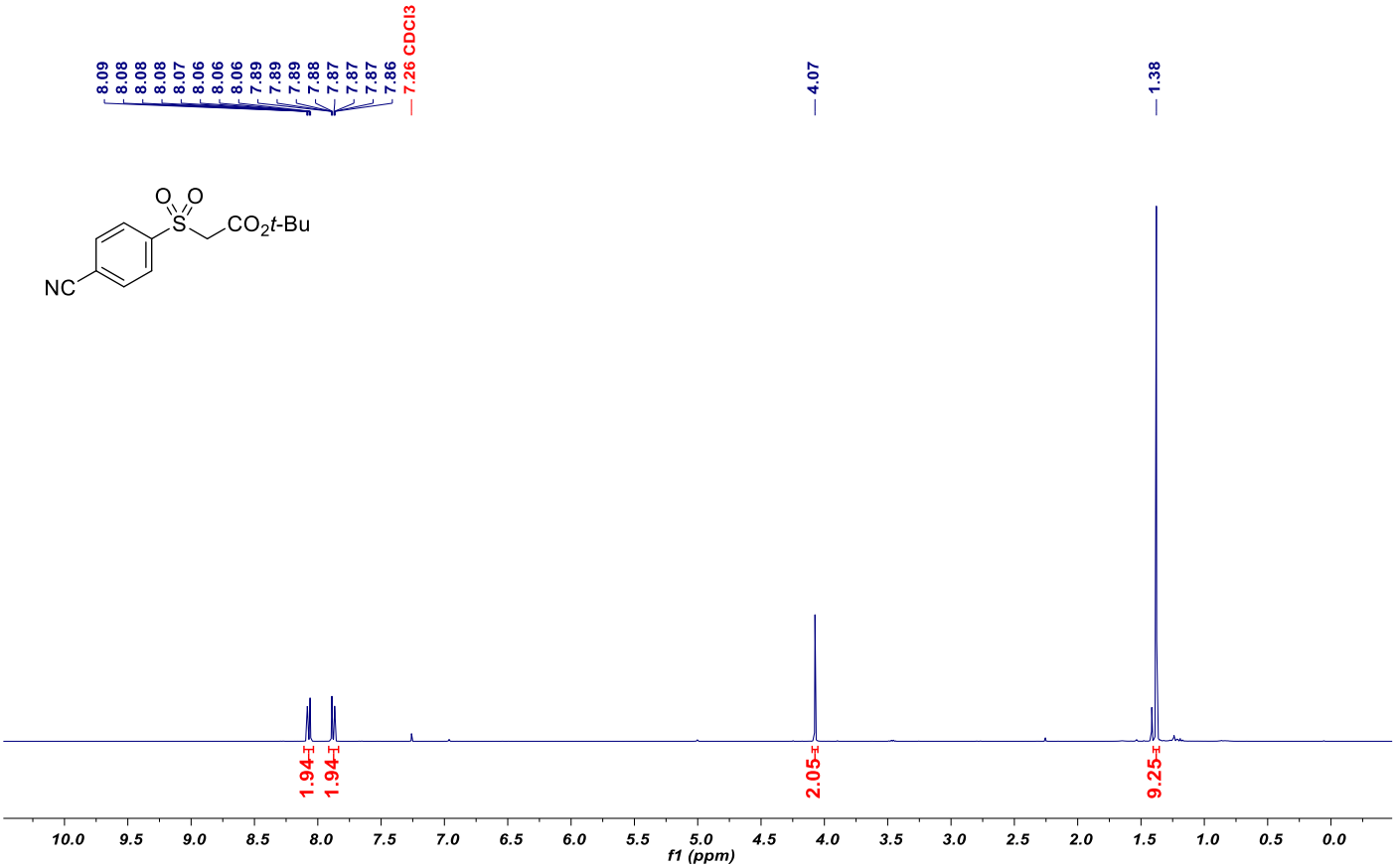
NMR spectrum of sulfone **7f**

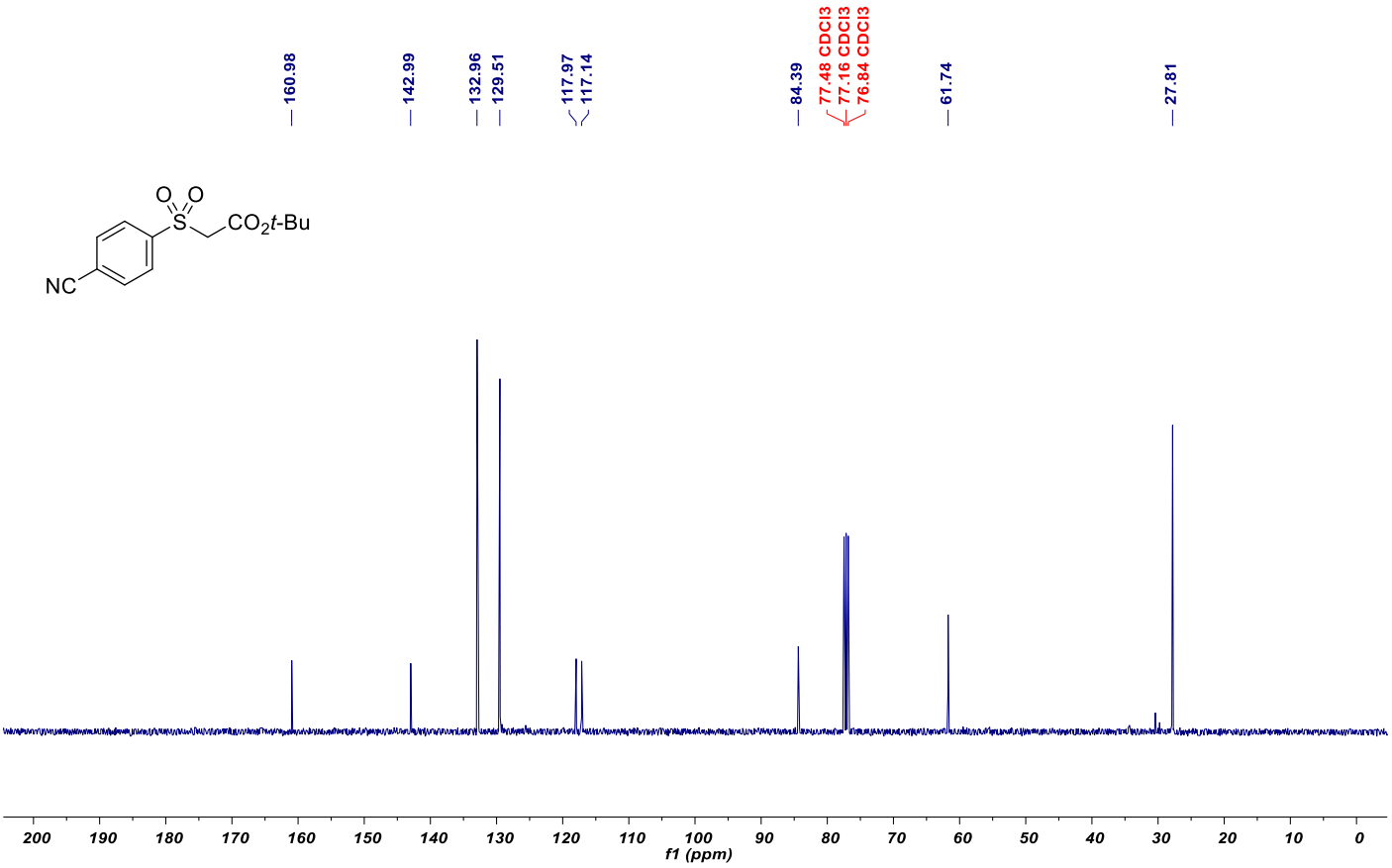




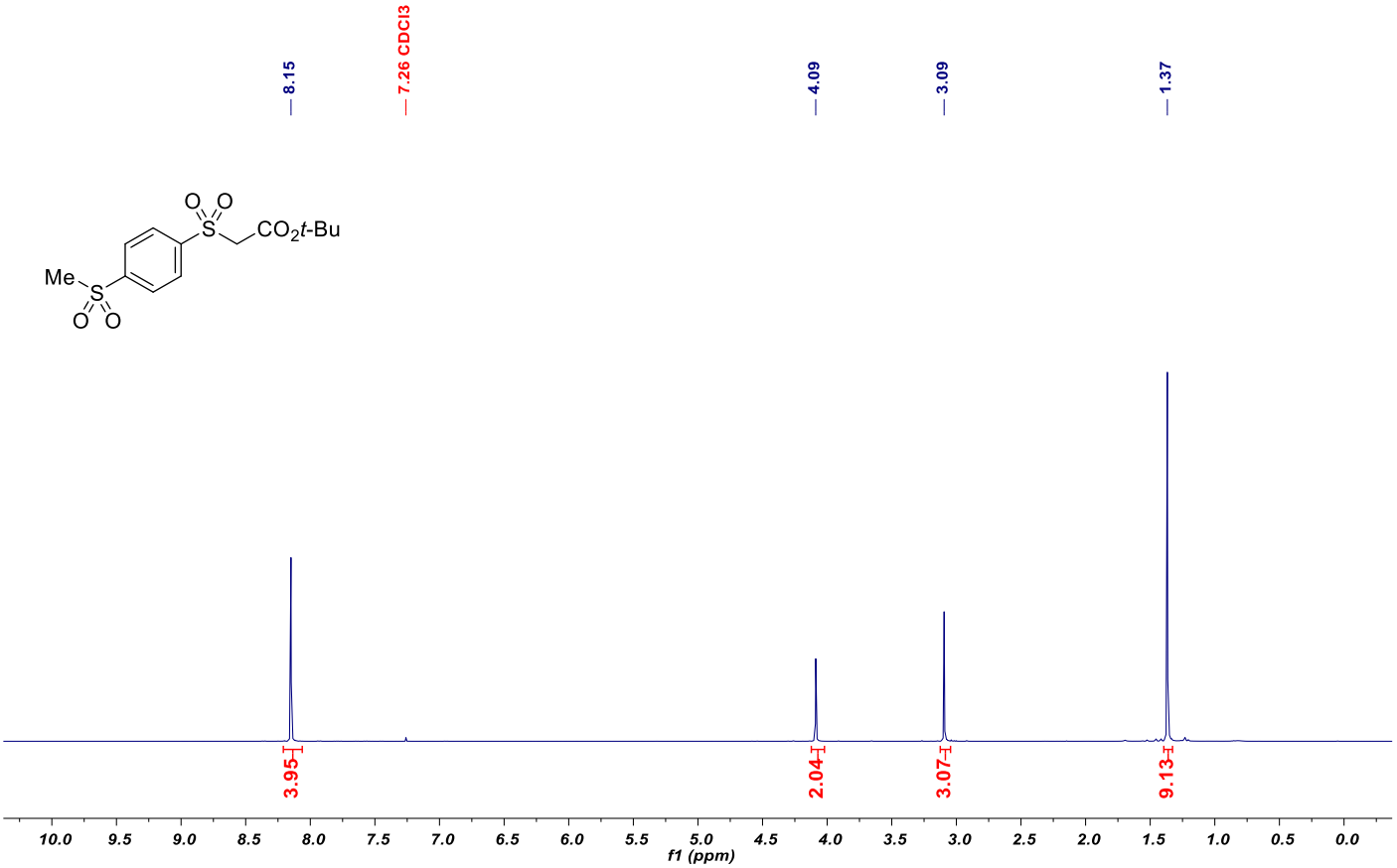

-63.27
O
O
S
CO2t-Bu
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

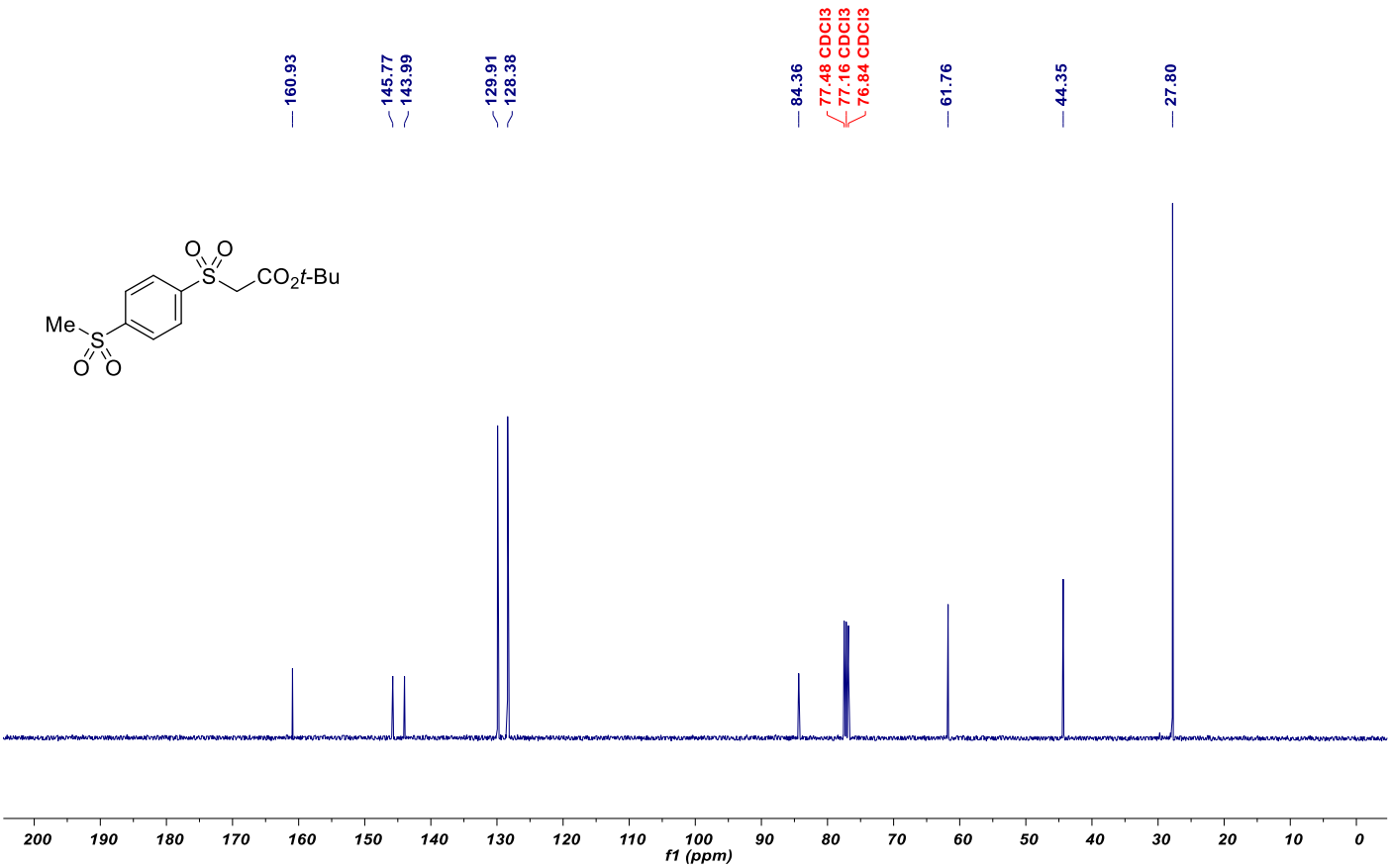
NMR spectrum of sulfone **7g**



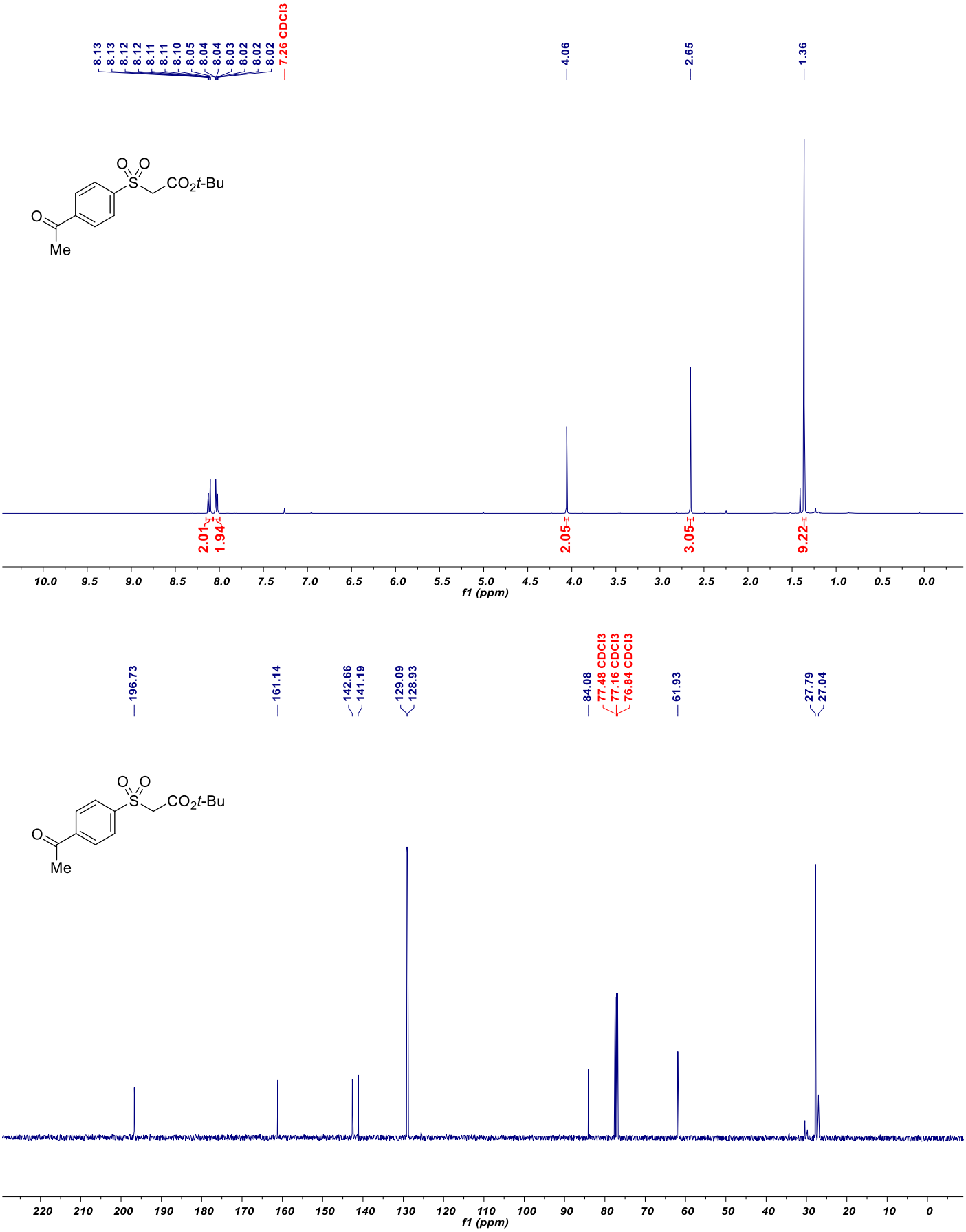


NMR spectrum of sulfone **7h**

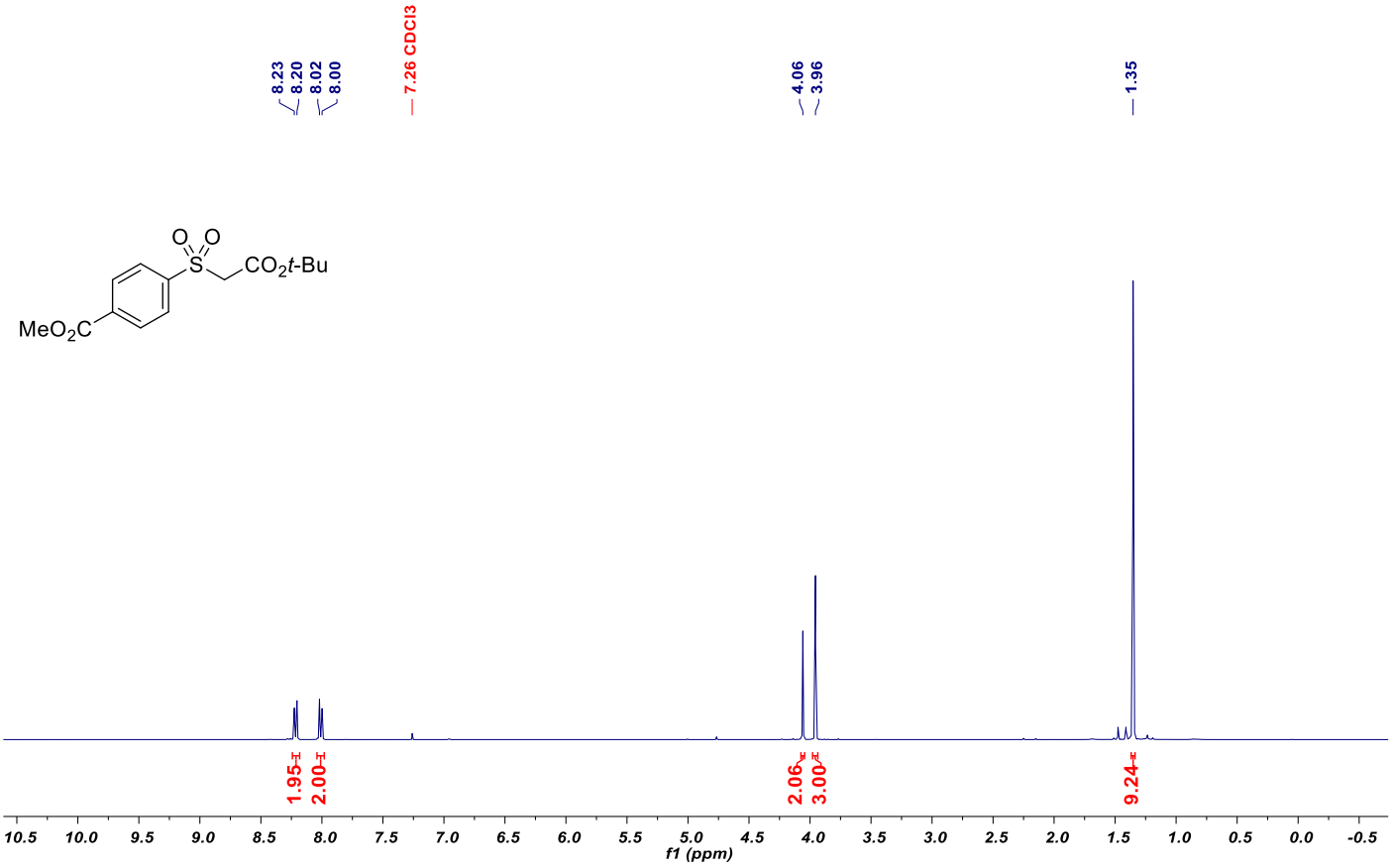


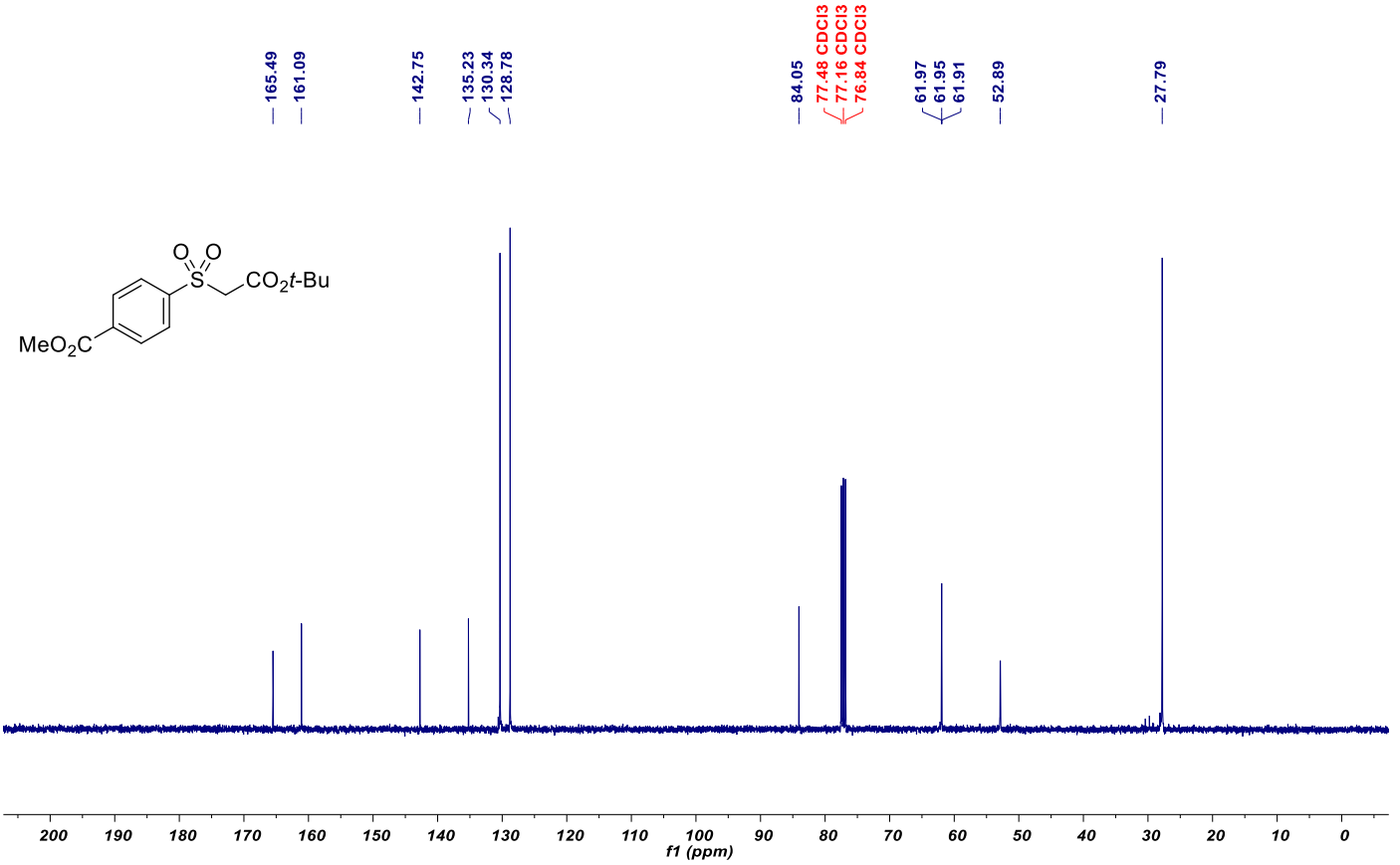


NMR spectrum of sulfone **7i**

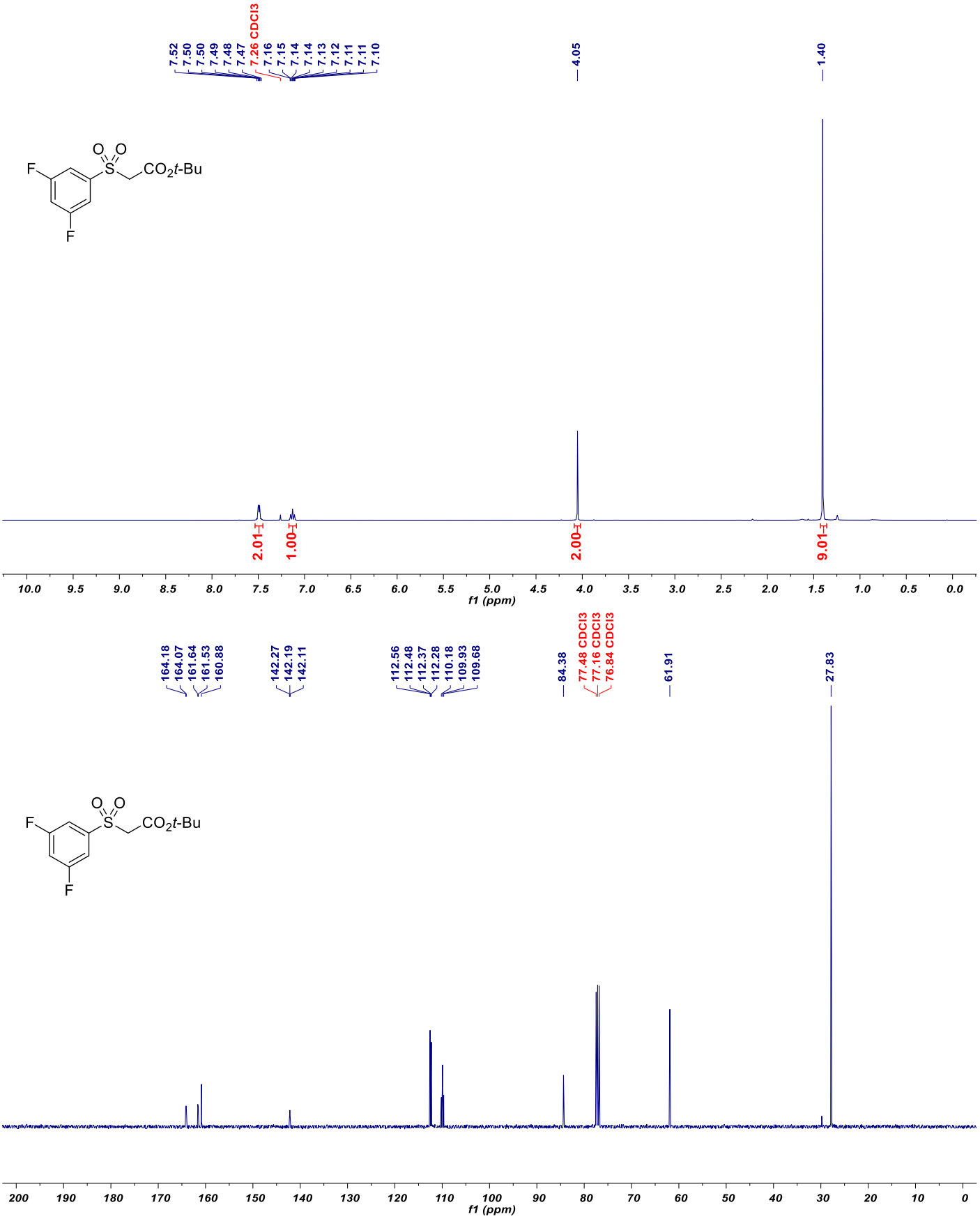


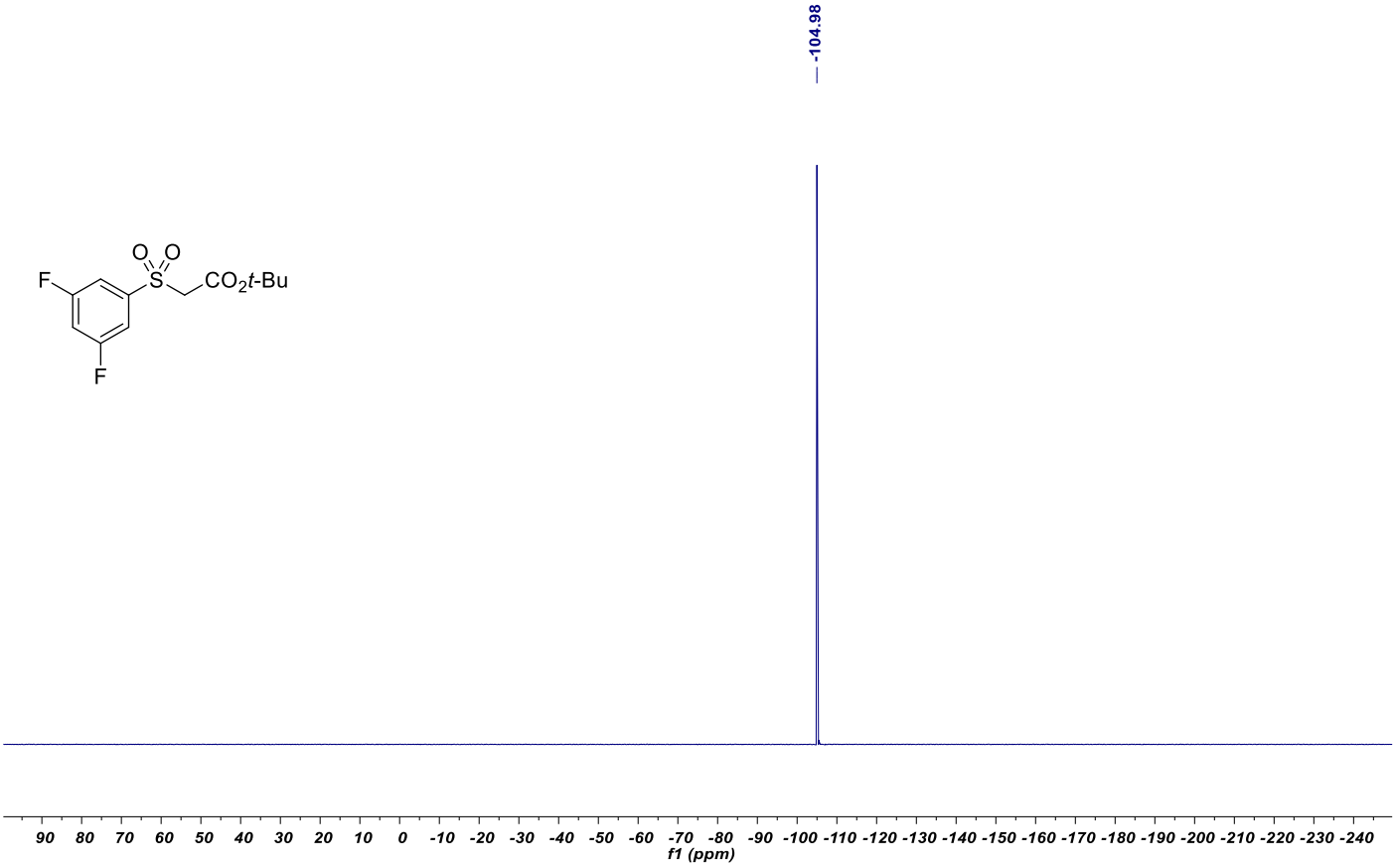
NMR spectrum of sulfone **7j**



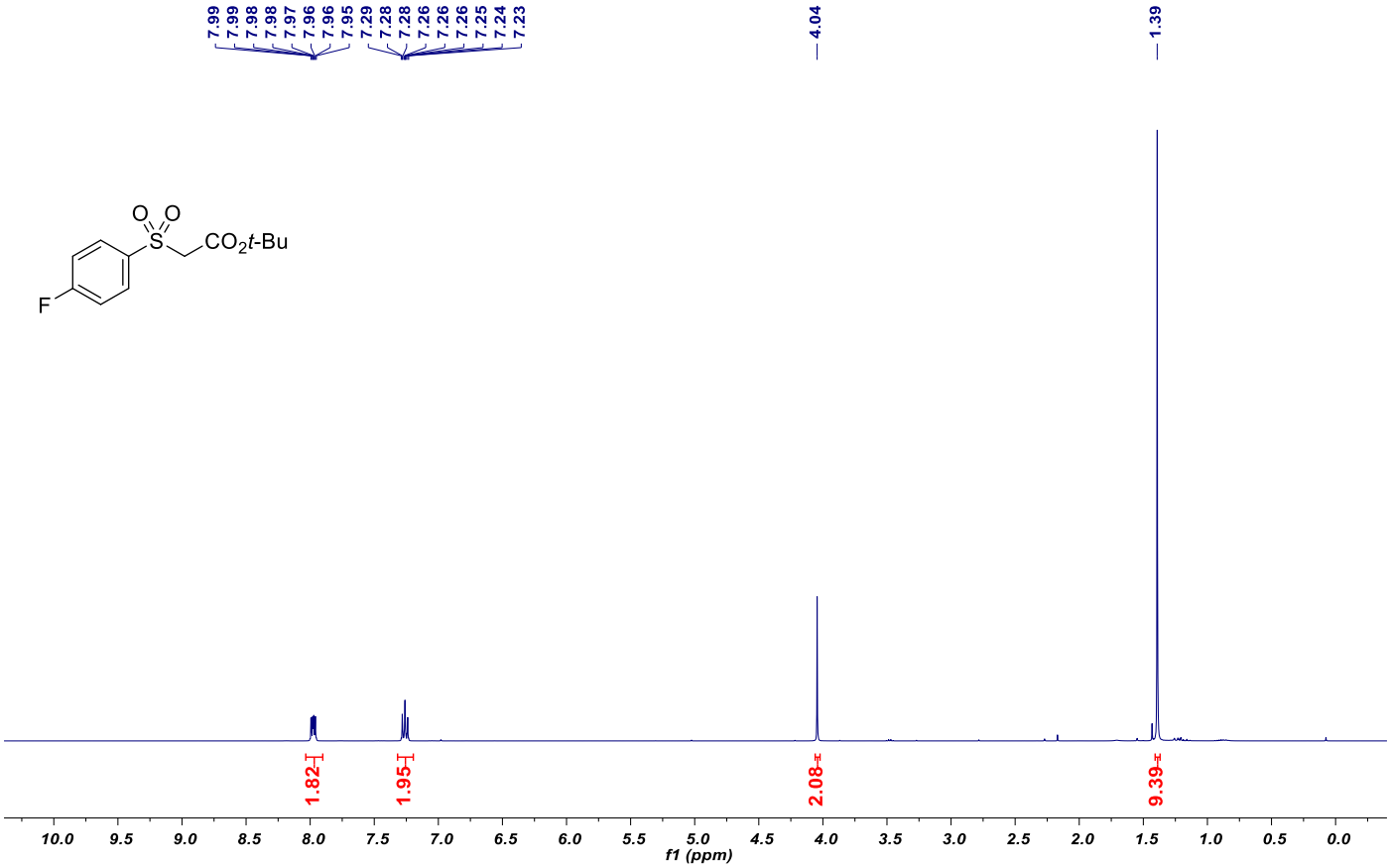


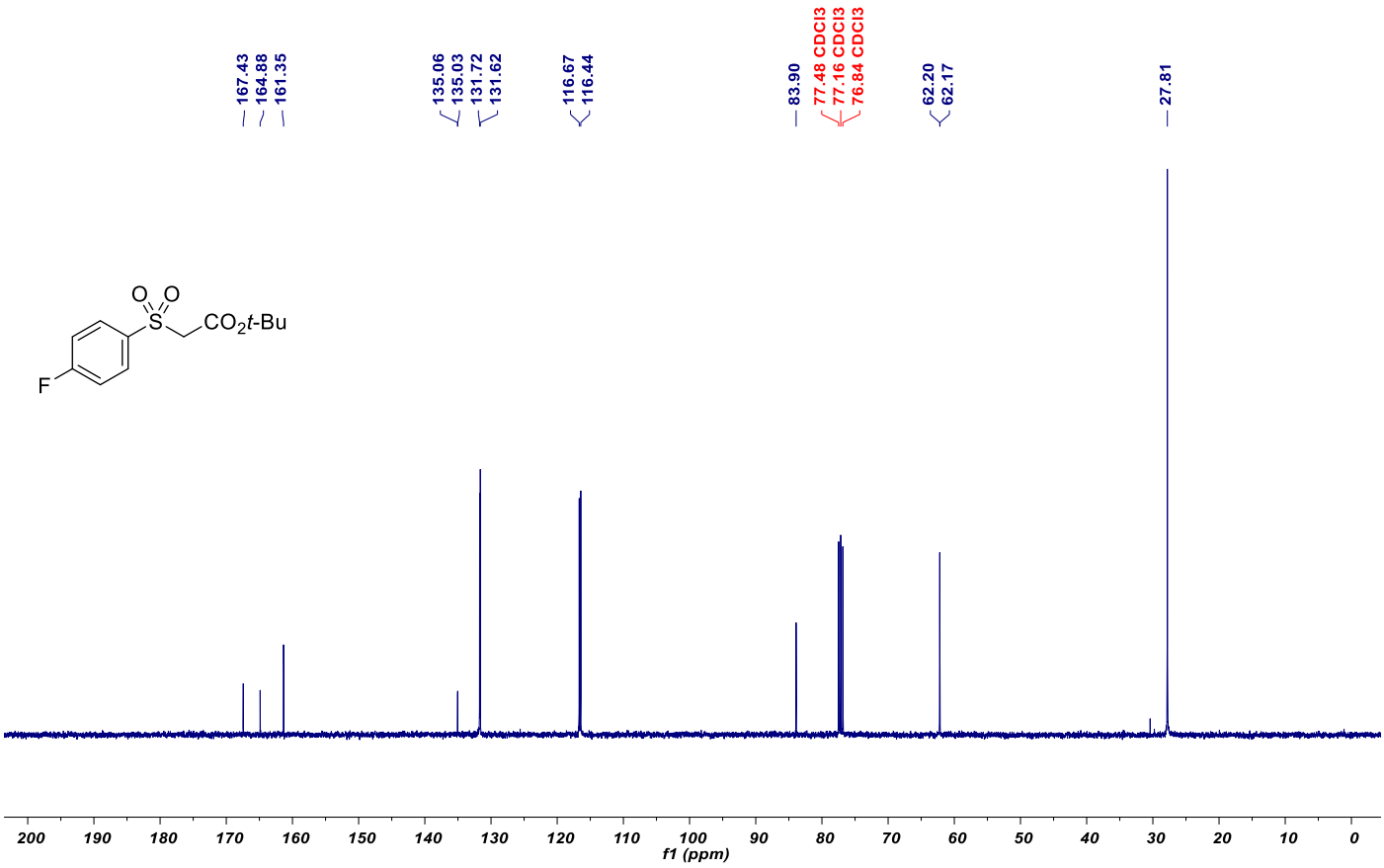
NMR spectrum of sulfone **7k**

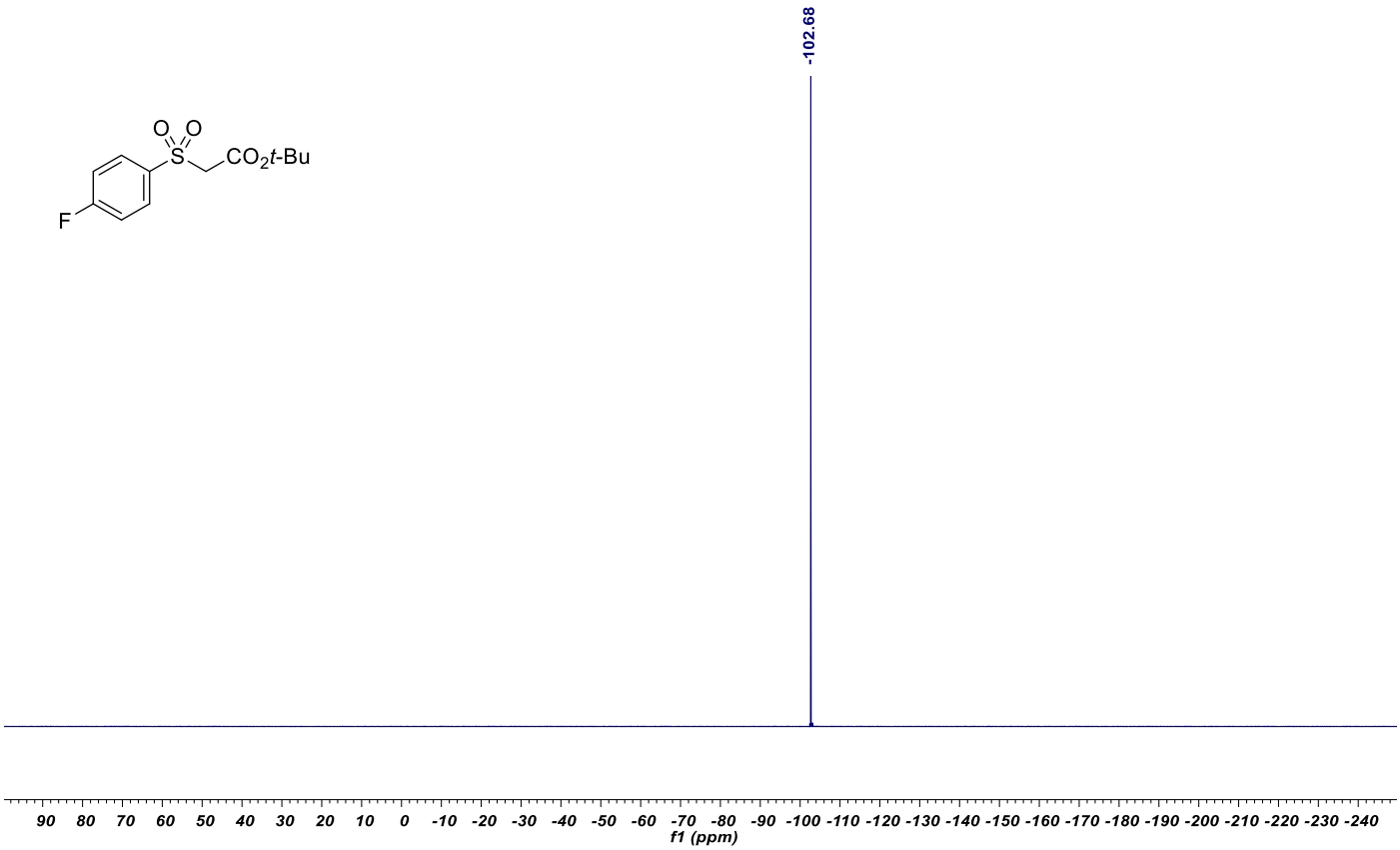



-104.98
F
O
O
S
CO2t-Bu
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

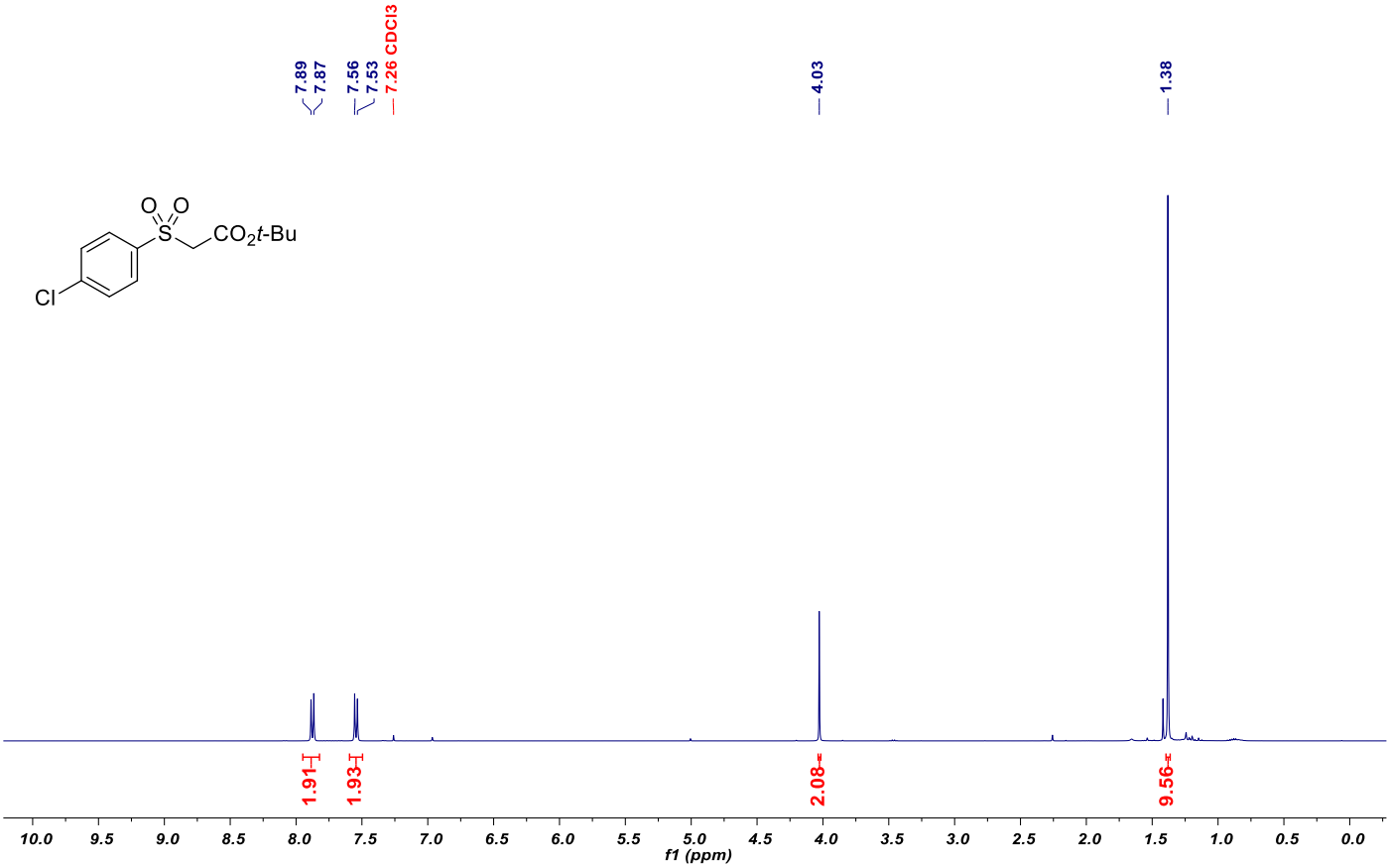
NMR spectrum of sulfone **7l**

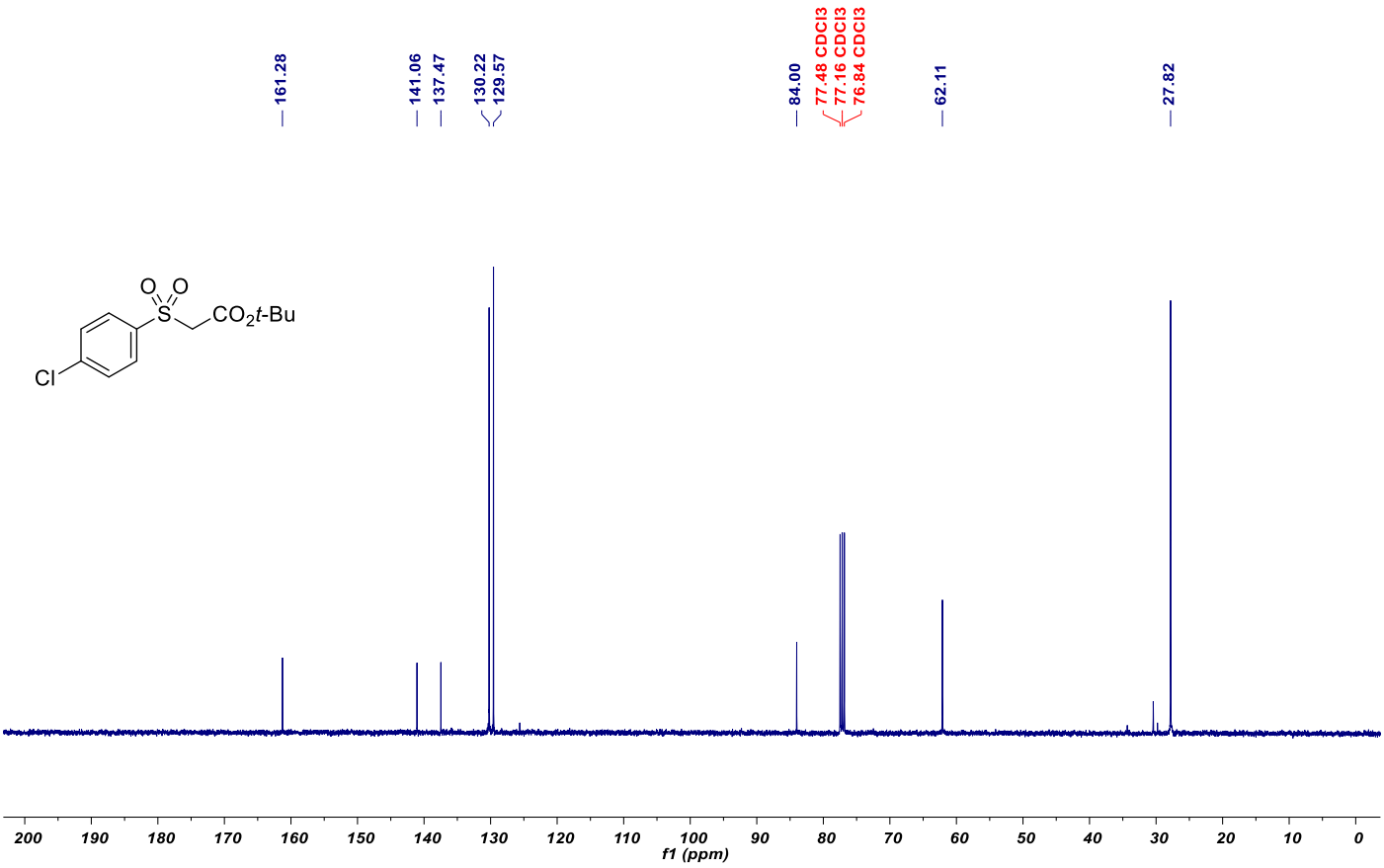




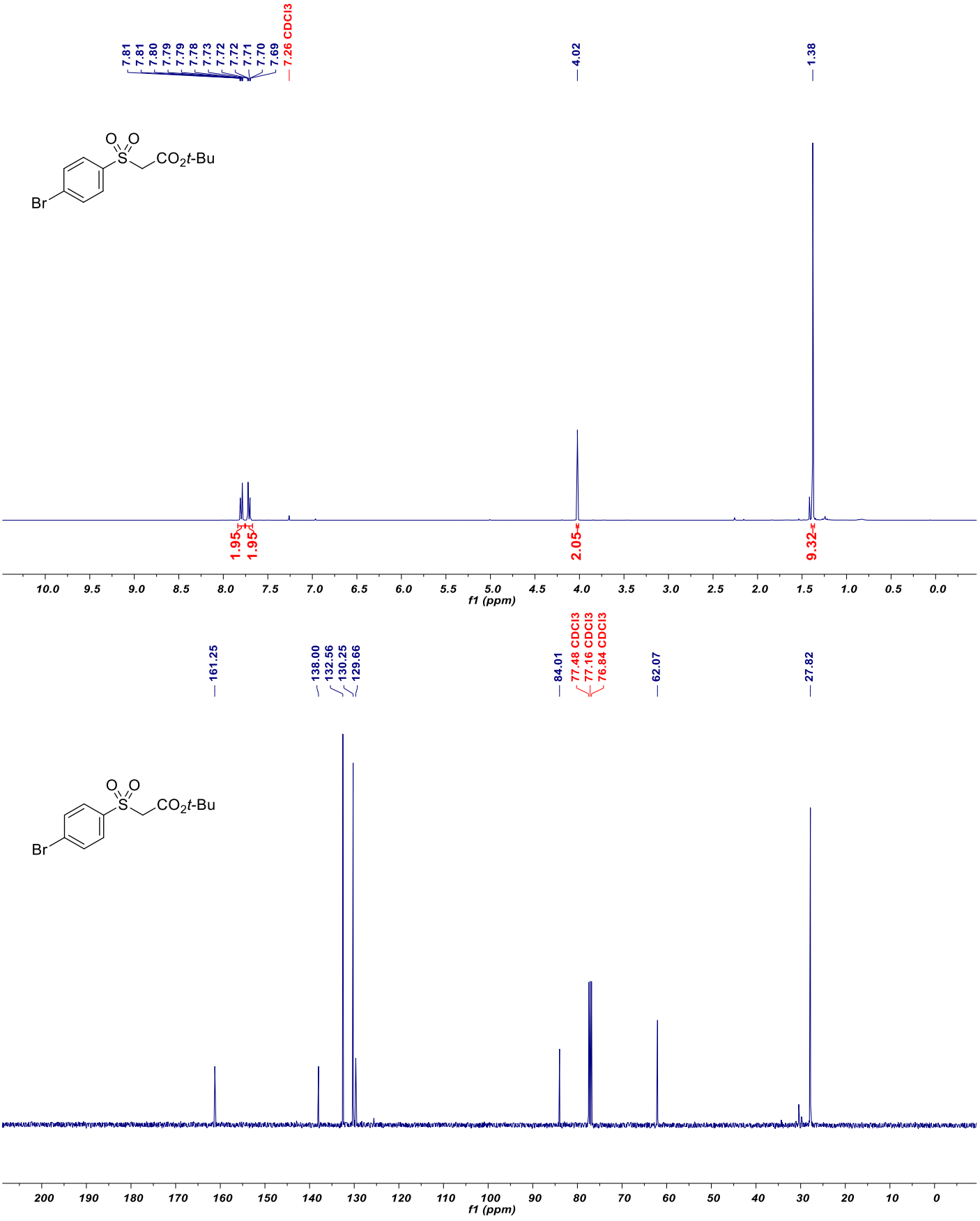

-102.68
O
O
S
CO2t-Bu
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

NMR spectrum of sulfone **7m**

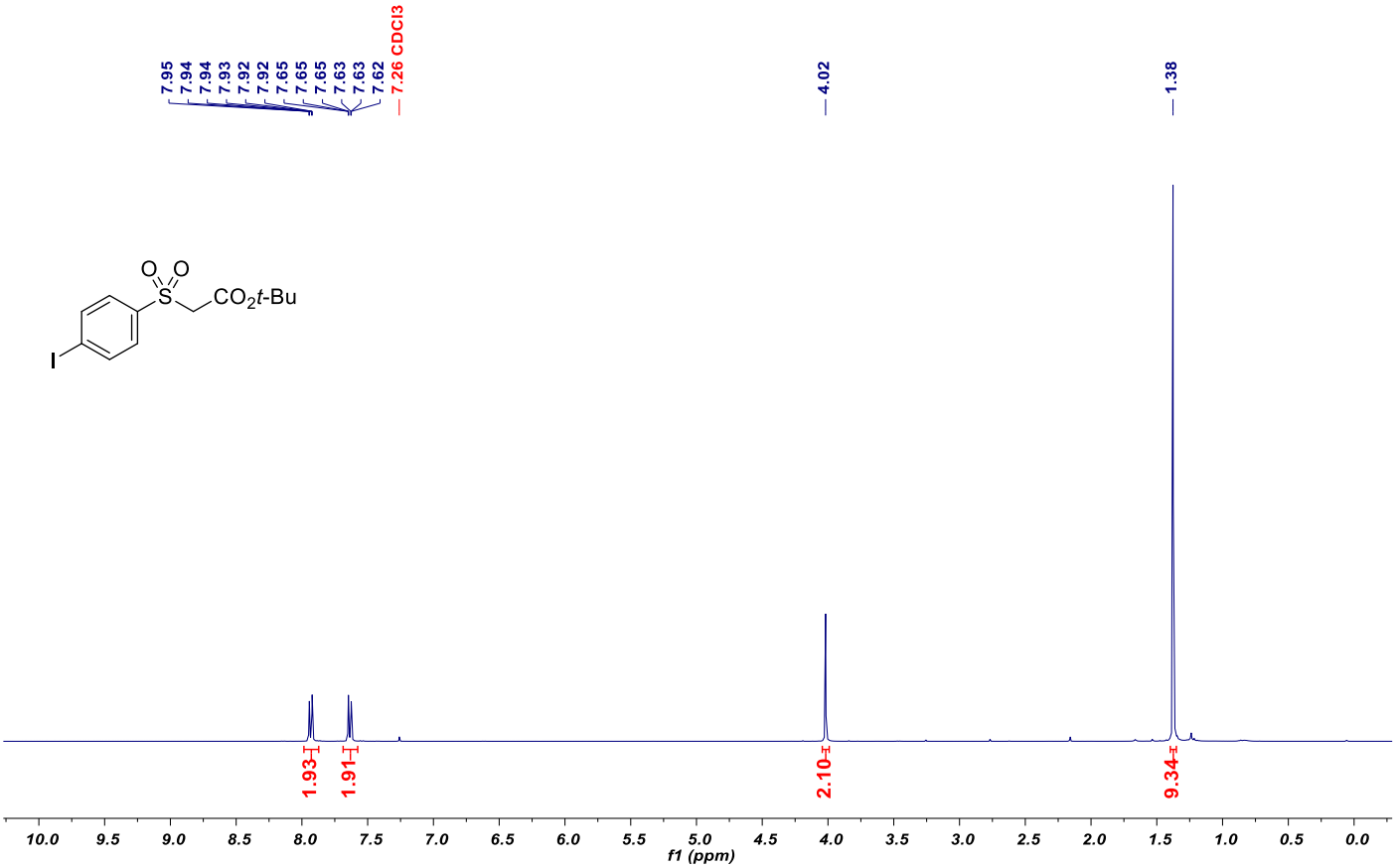


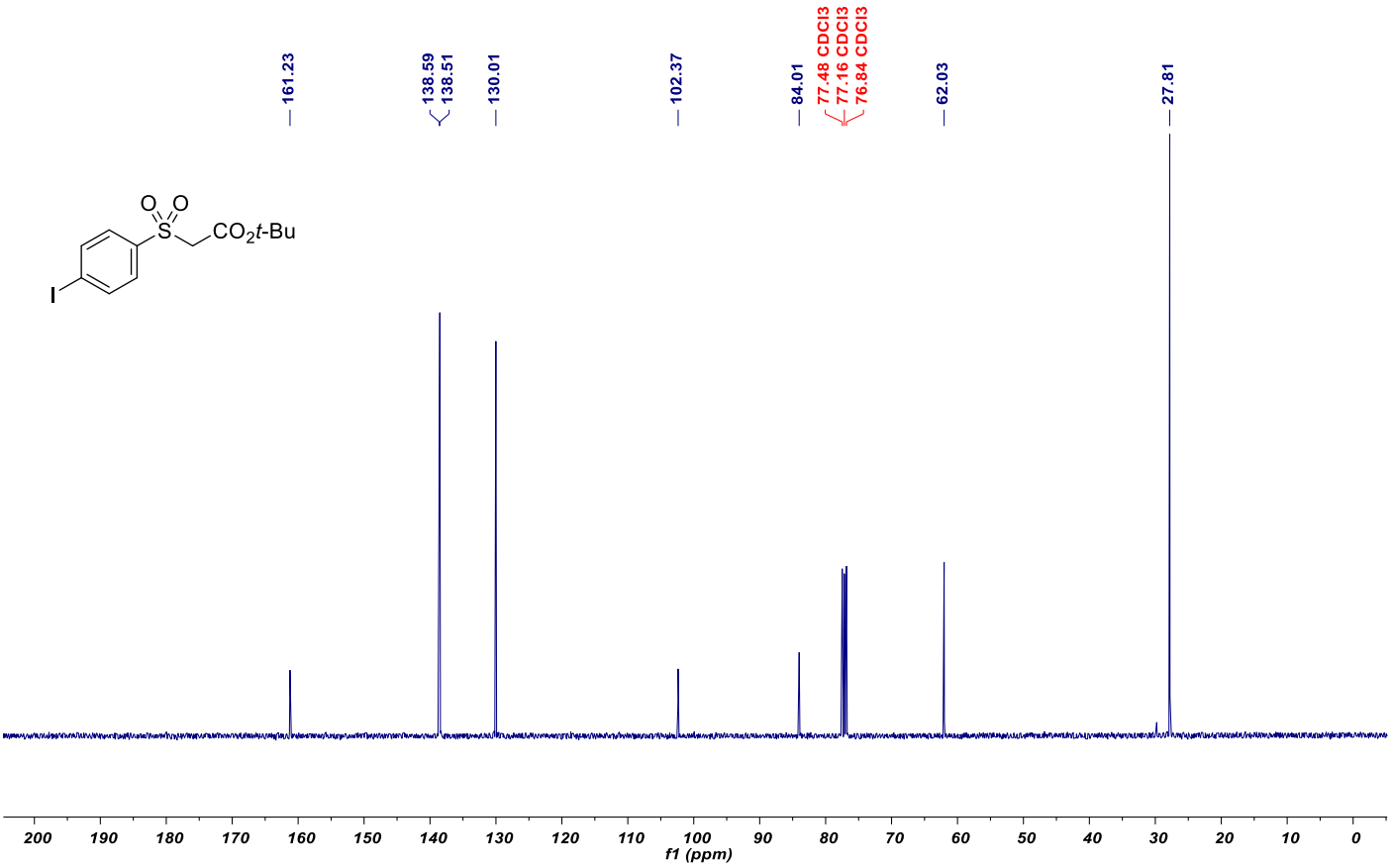


NMR spectrum of sulfone **7n**

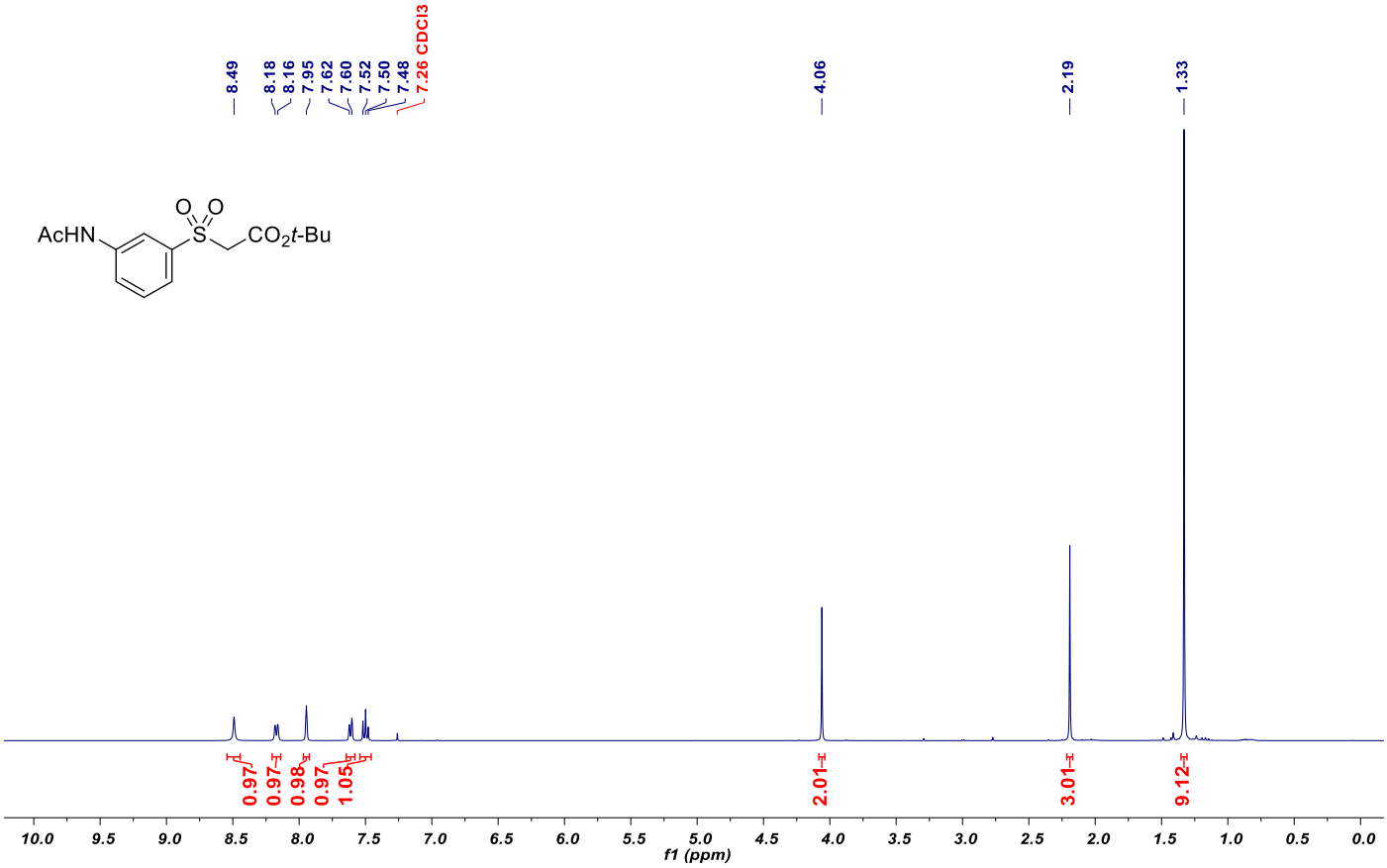


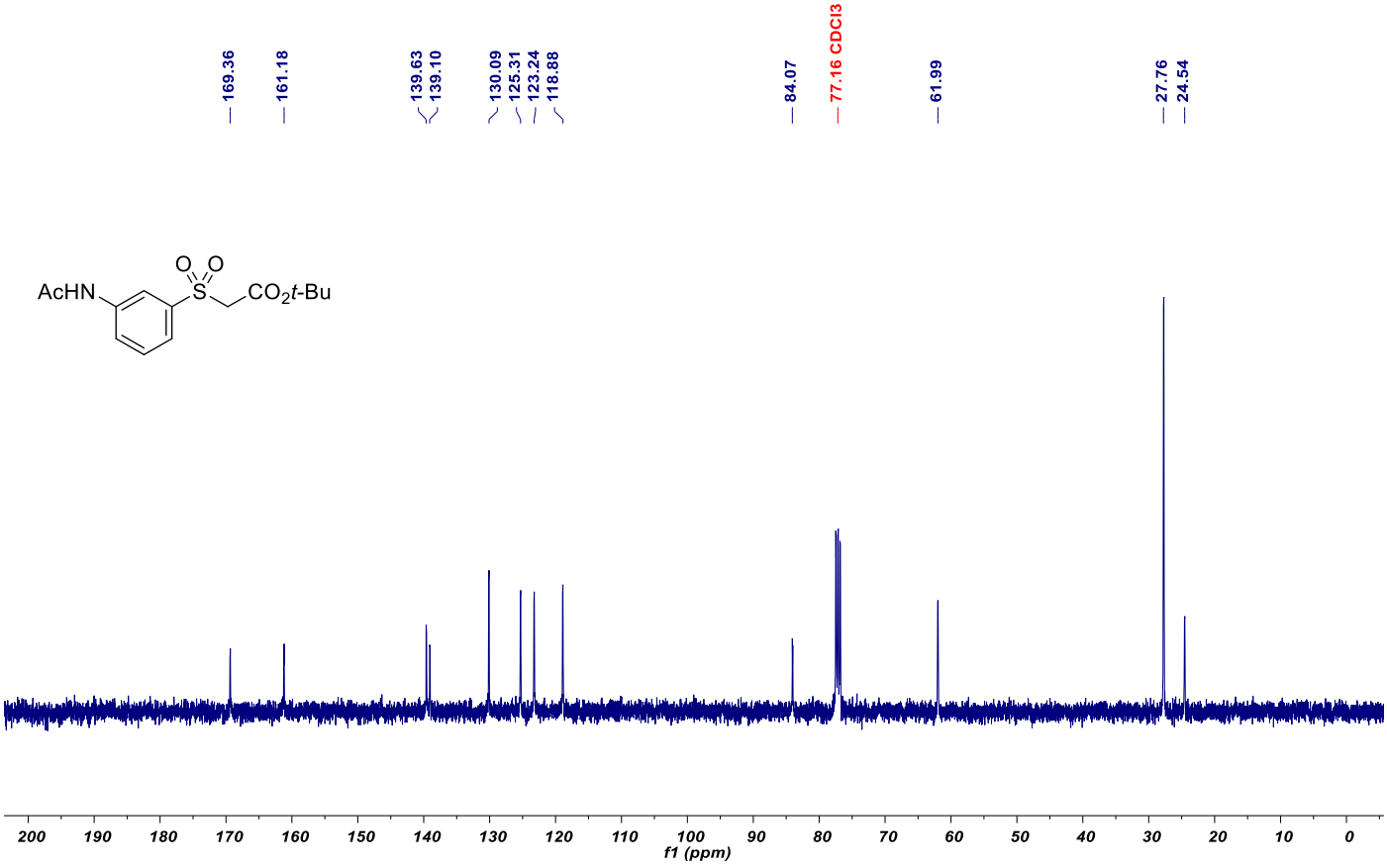
NMR spectrum of sulfone **7o**



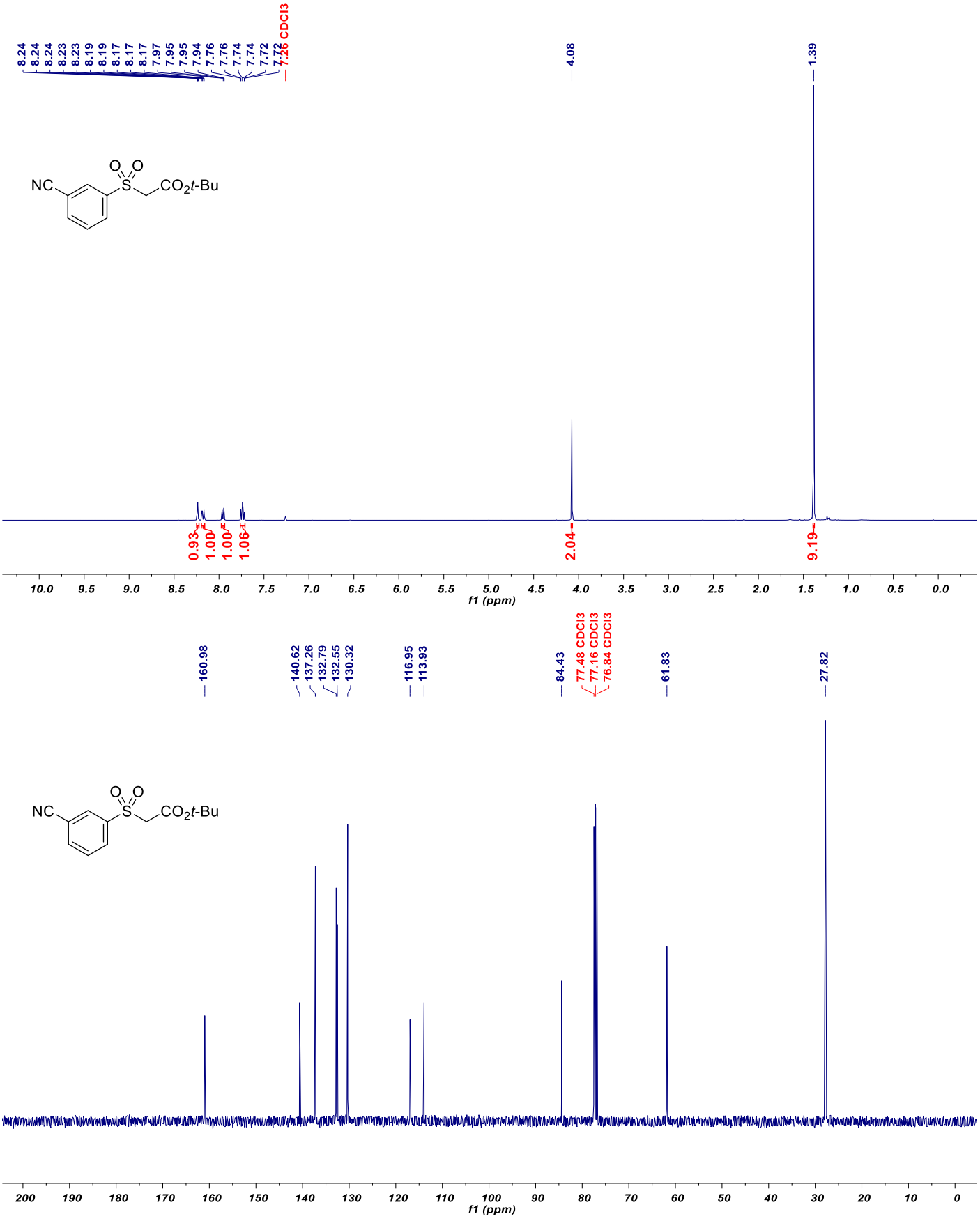


NMR spectrum of sulfone **7p**

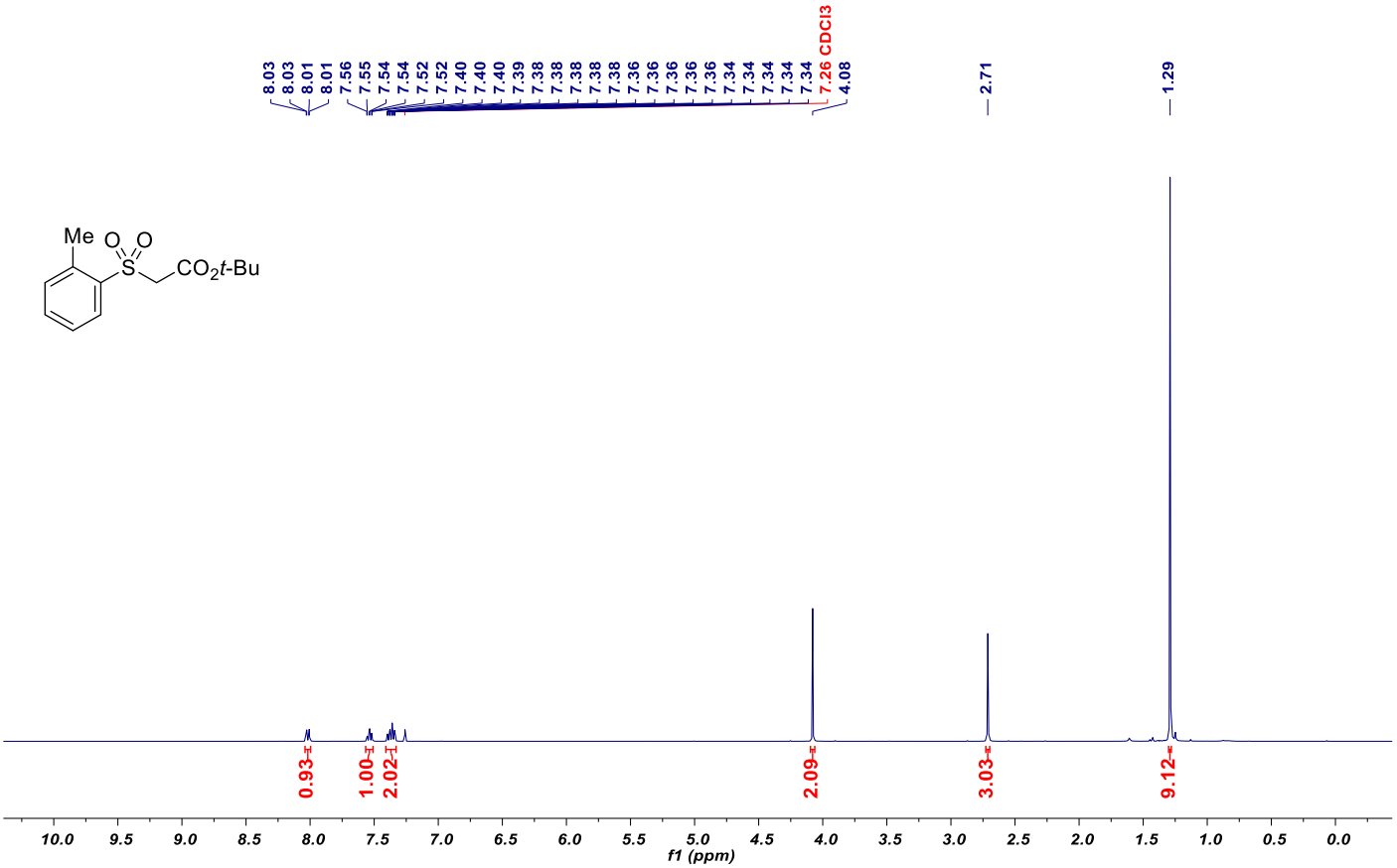


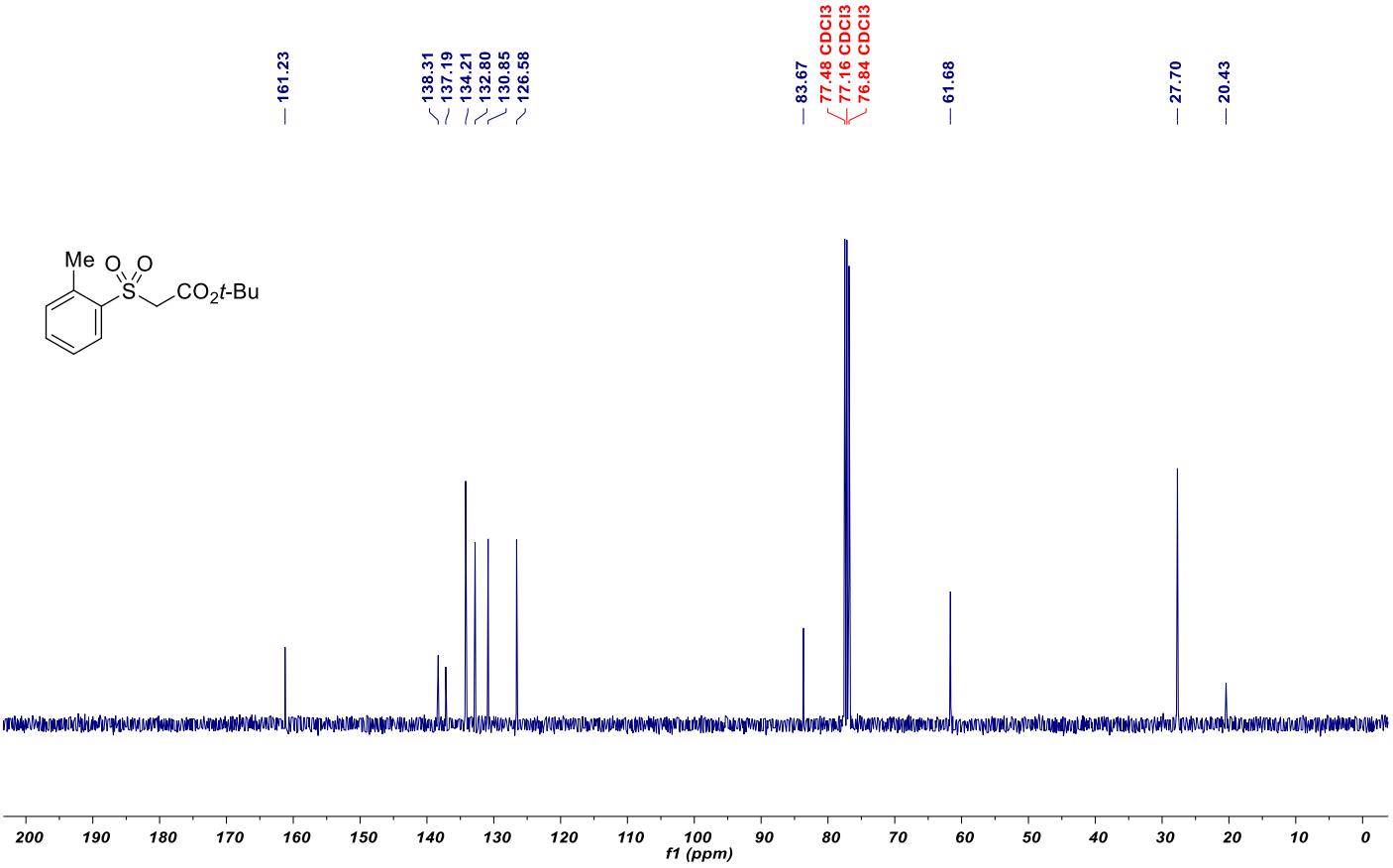


NMR spectrum of sulfone **7q**

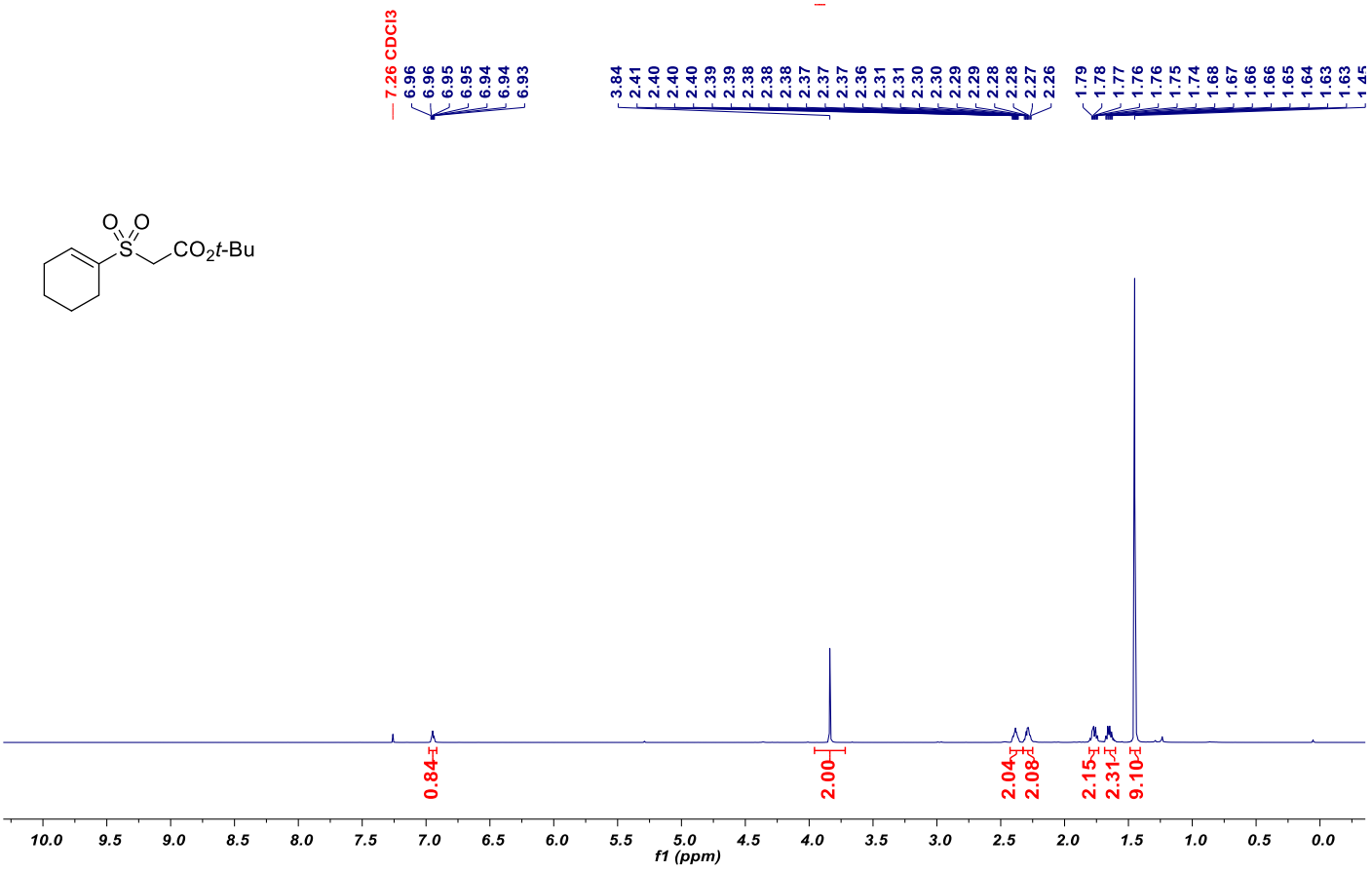


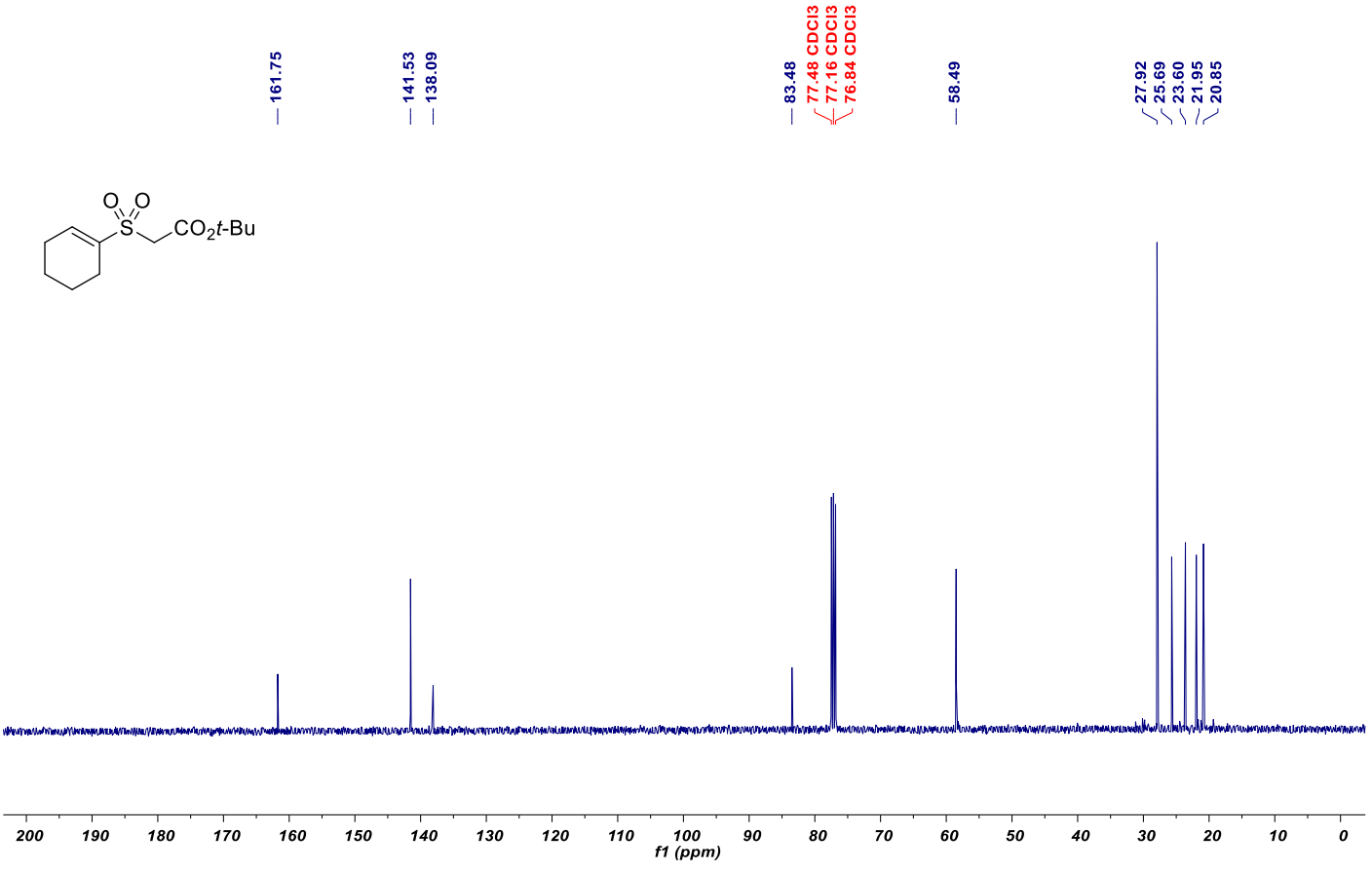
NMR spectrum of sulfone **7r**



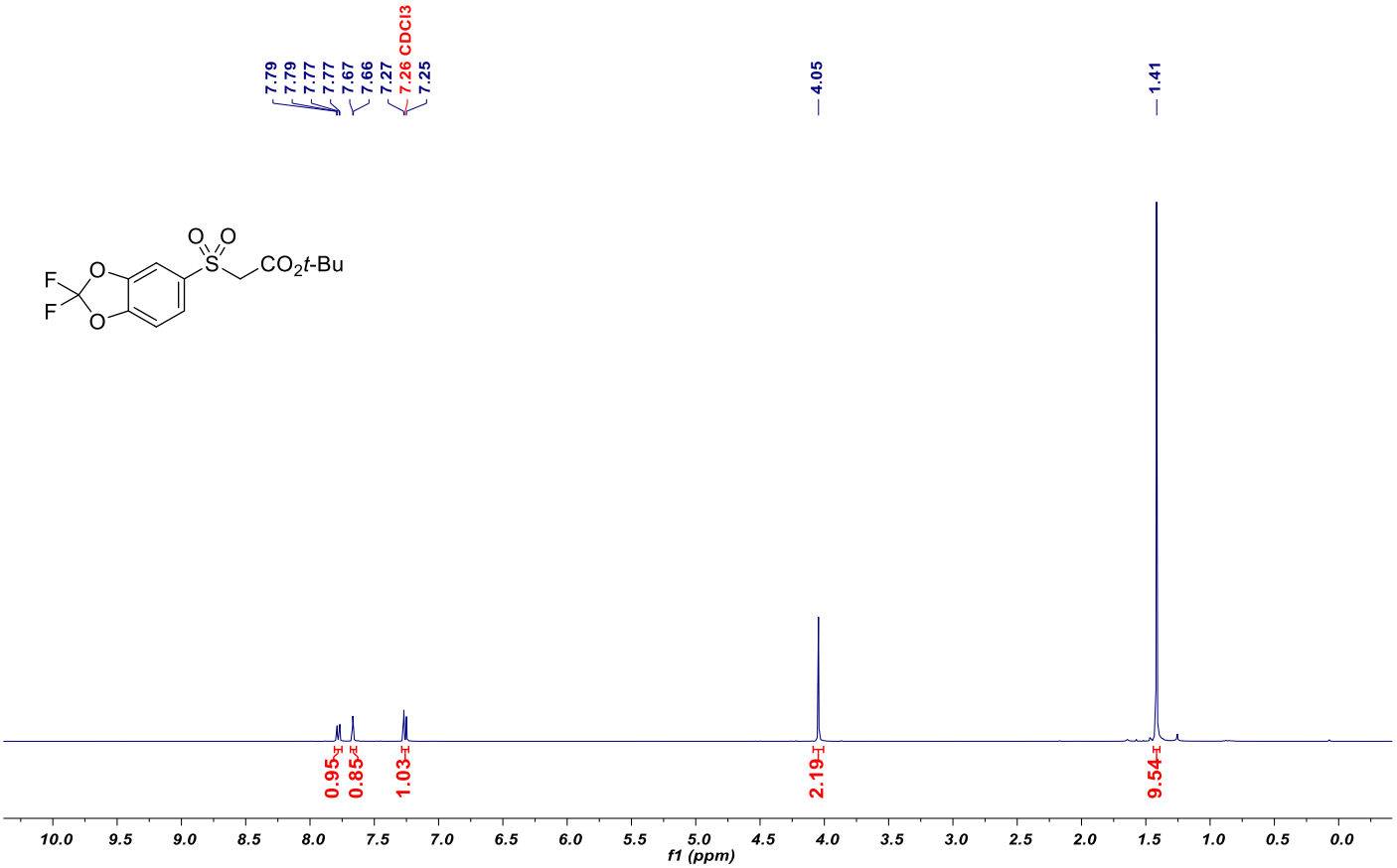


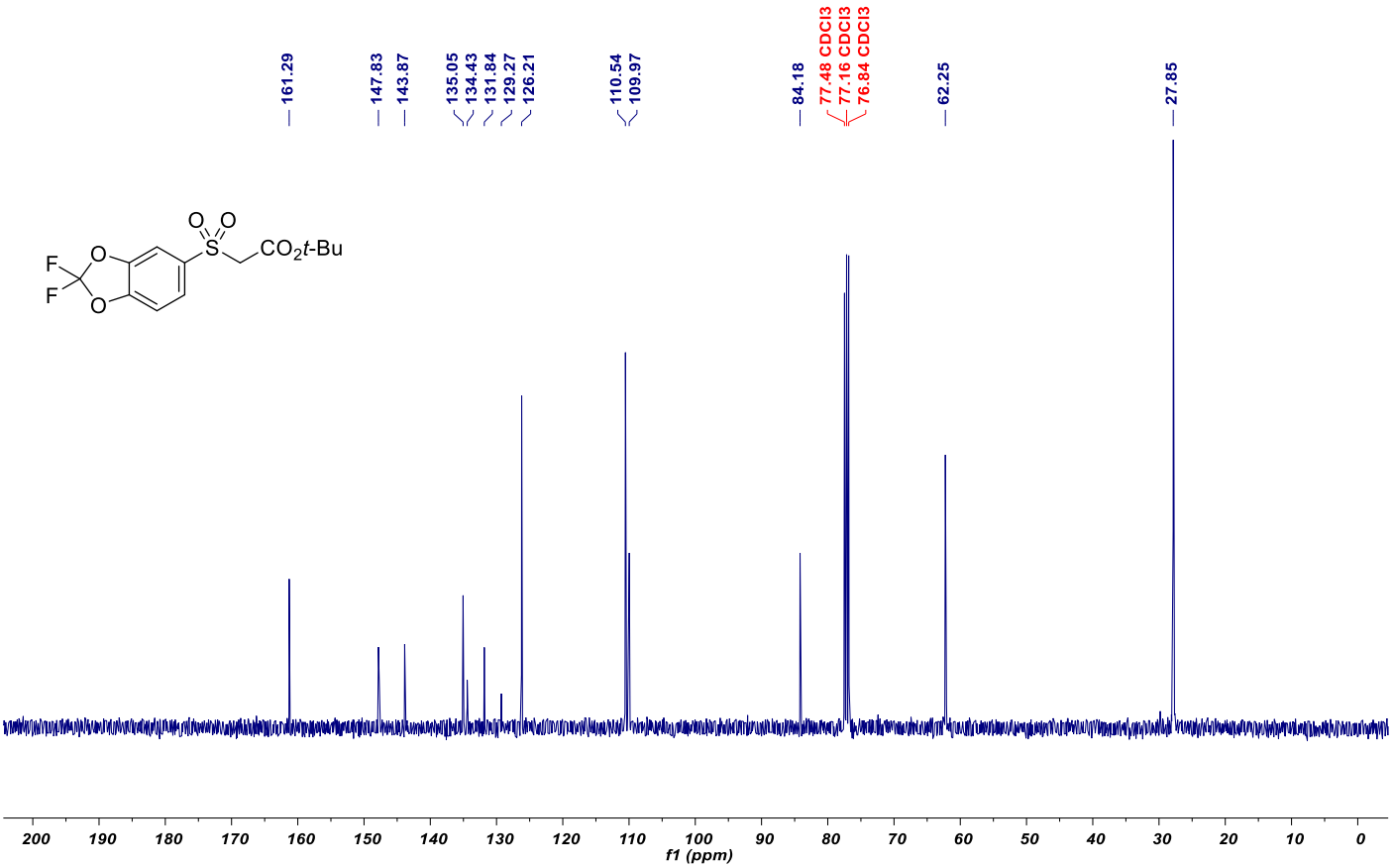
NMR spectrum of sulfone **7s**

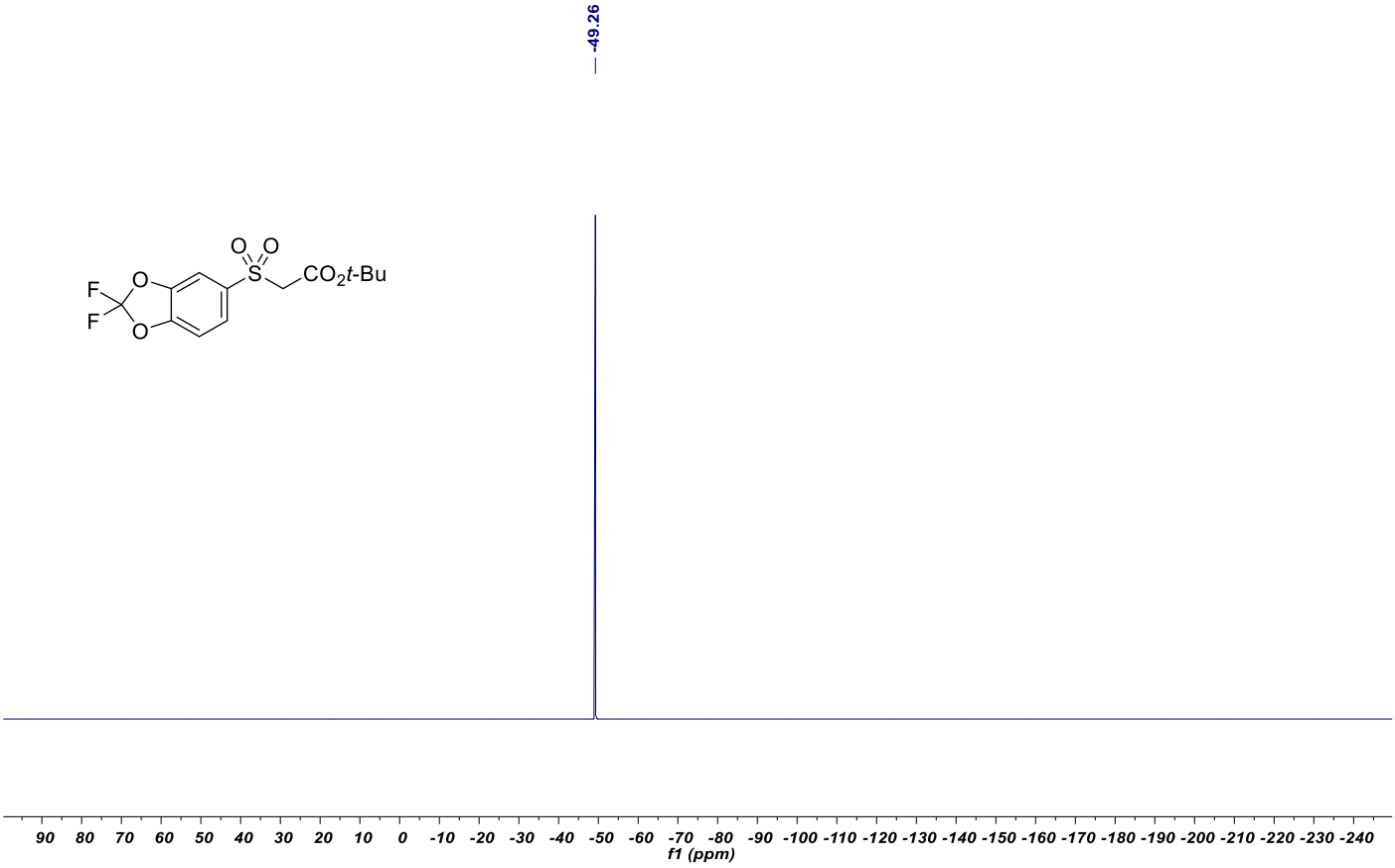




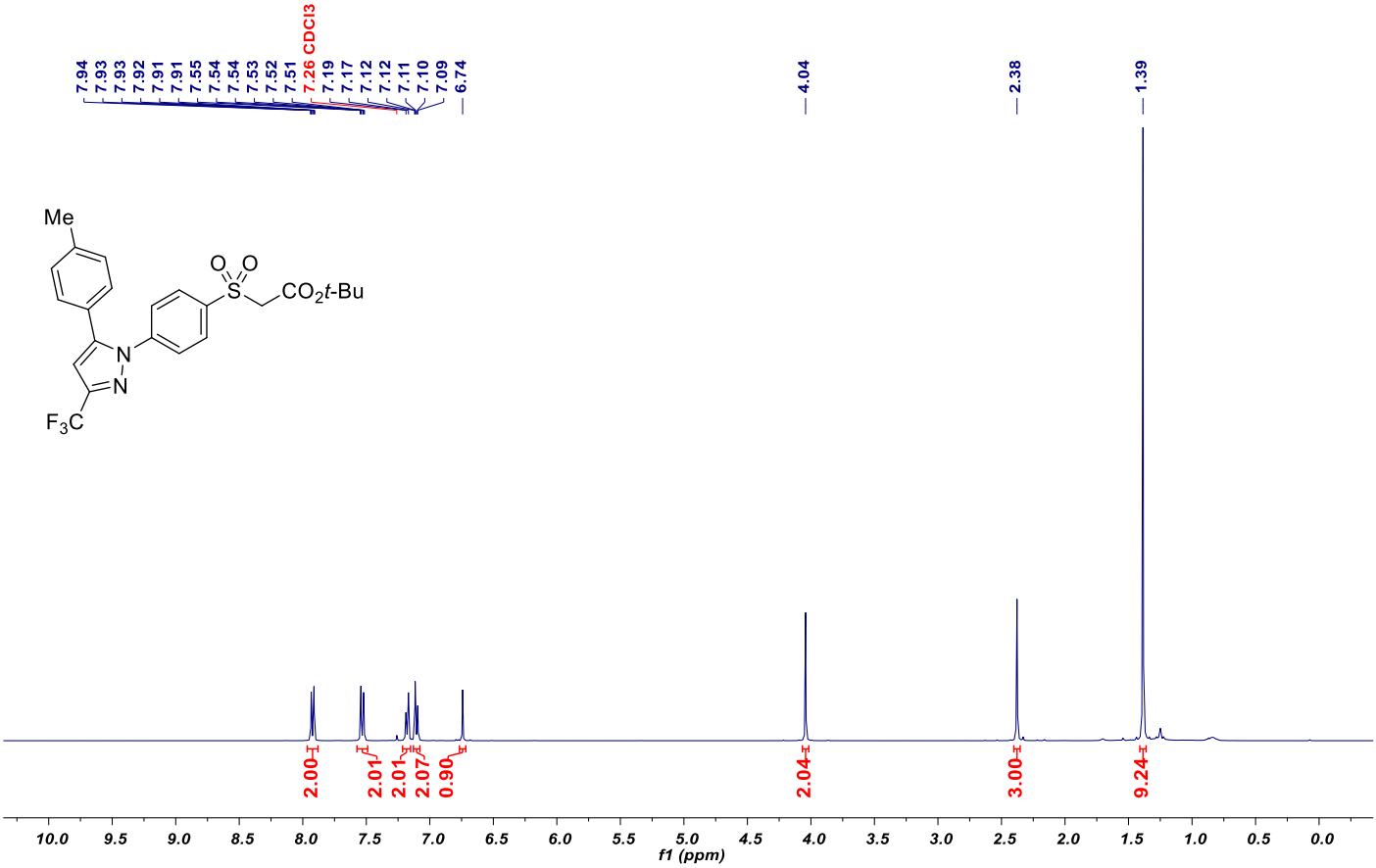
NMR spectrum of sulfone **7t**

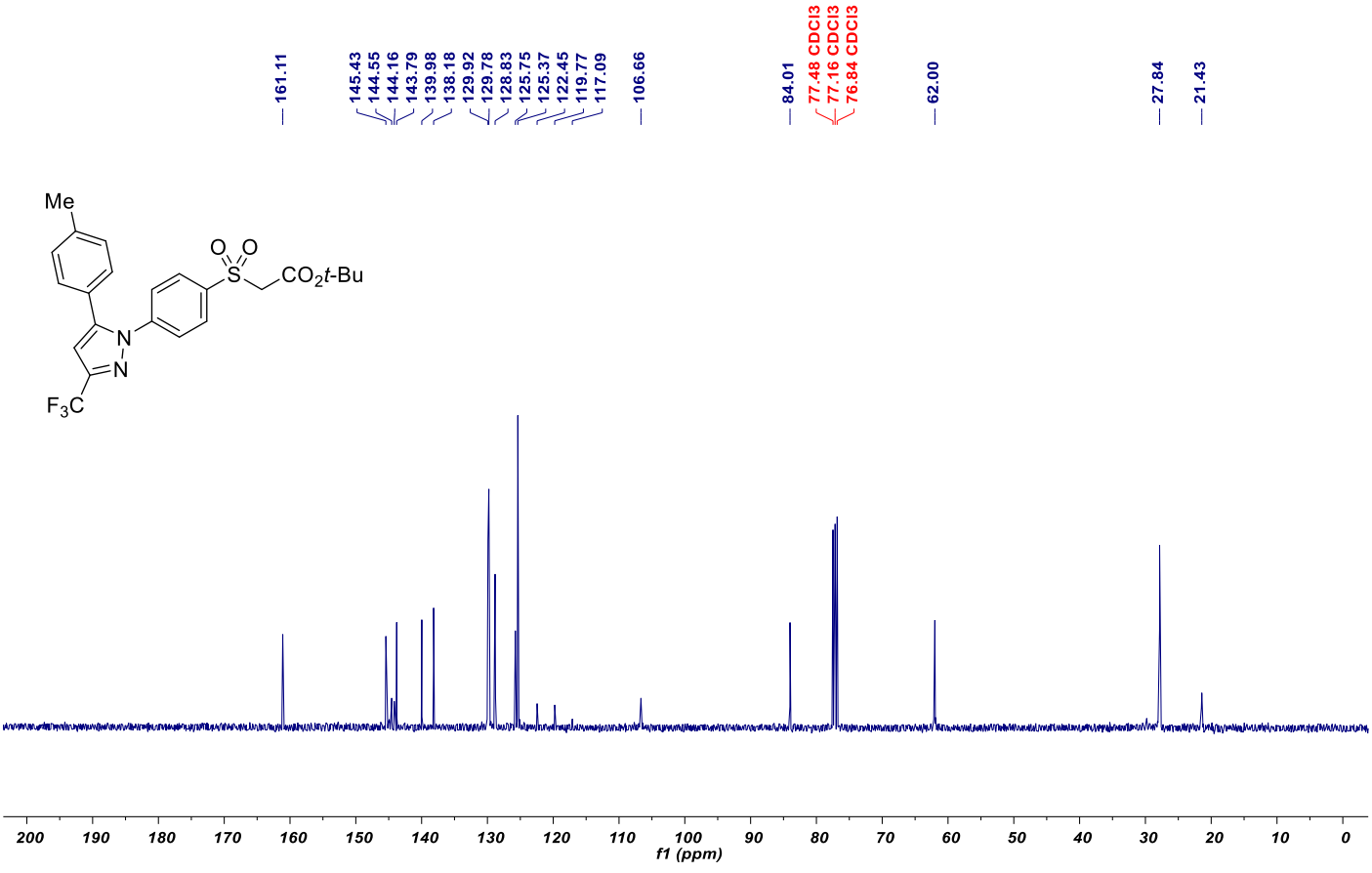


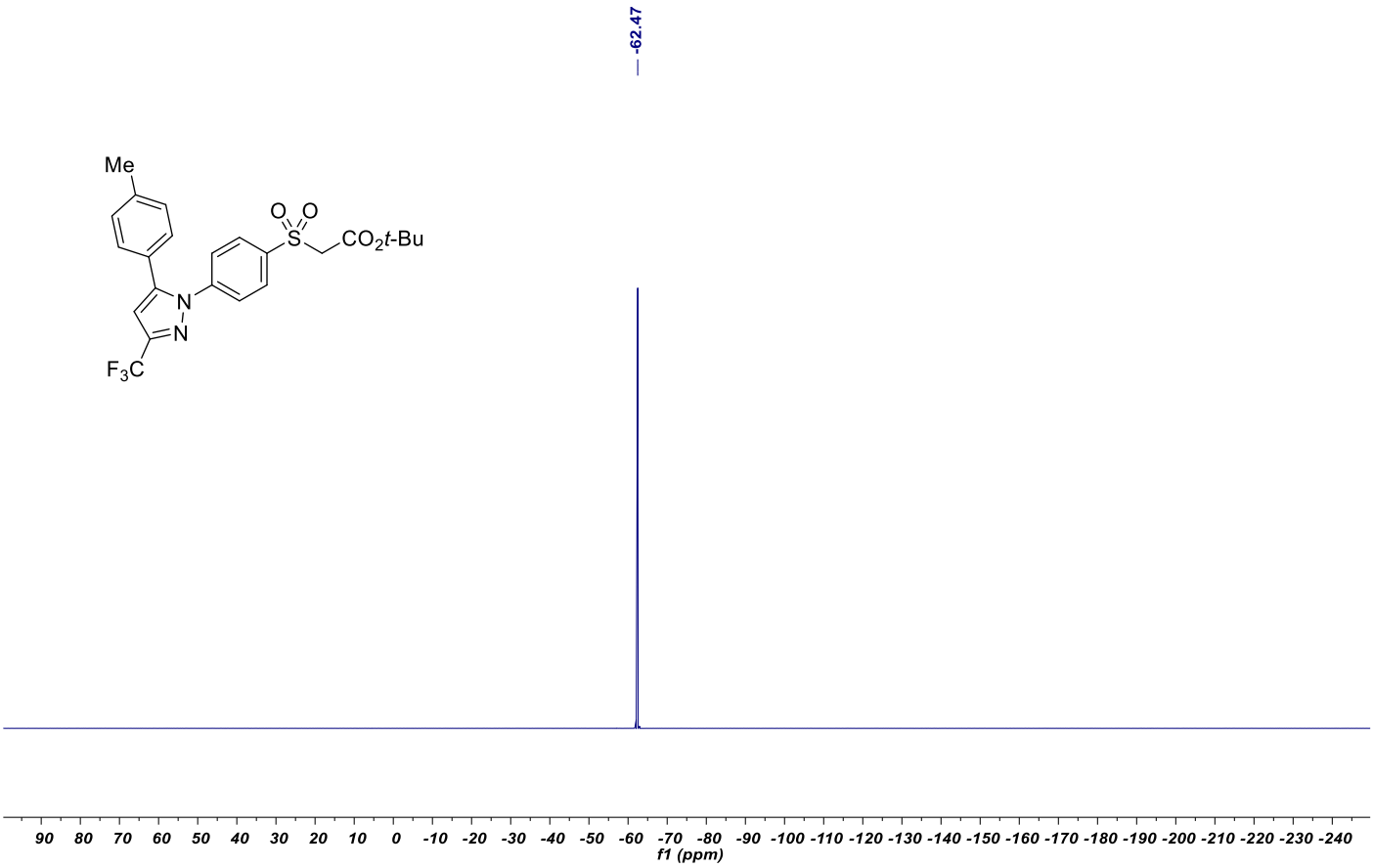



-49.26
O
O
S
CO2t-Bu
F
F
O
O
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

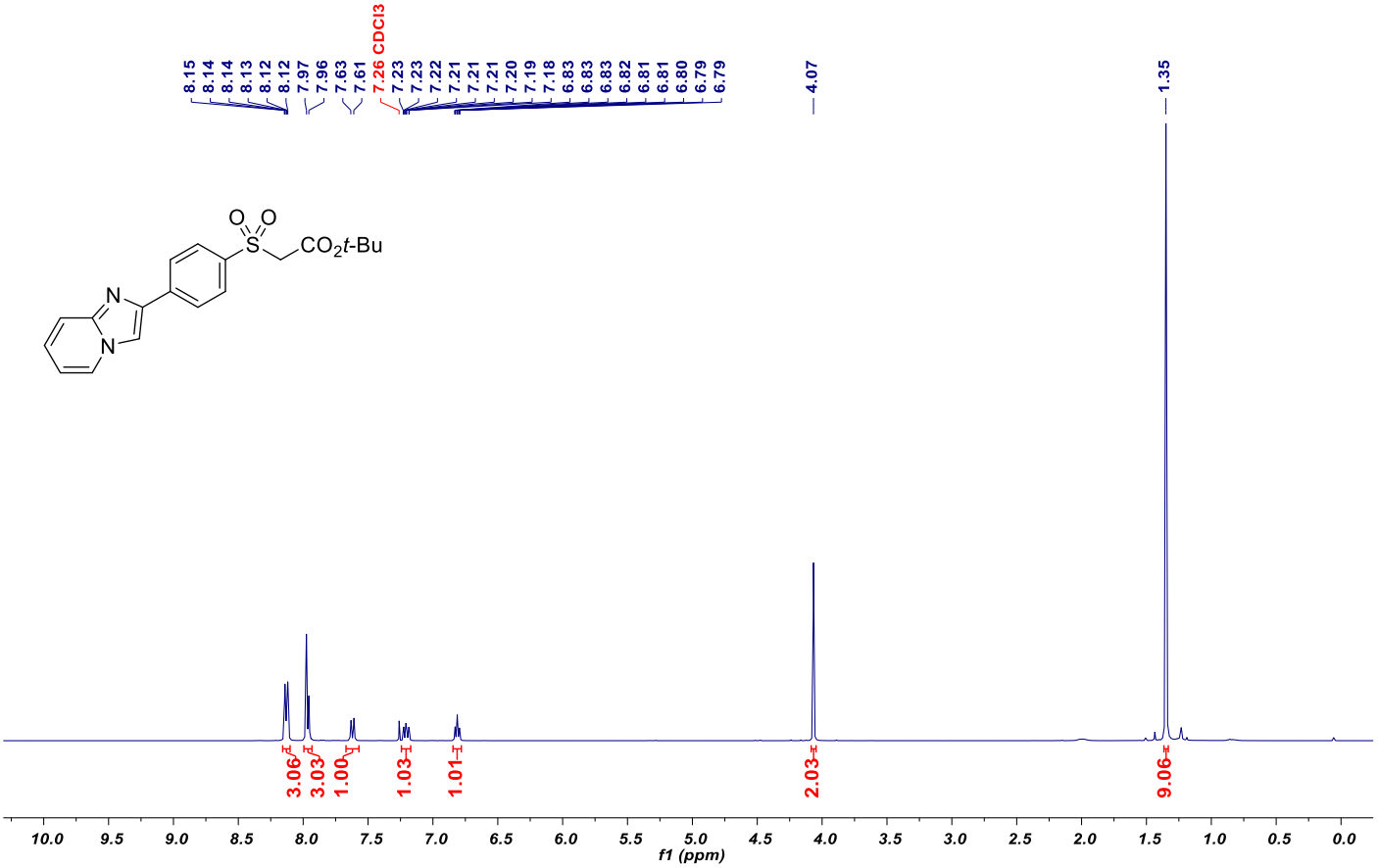
NMR spectrum of sulfone **7u**

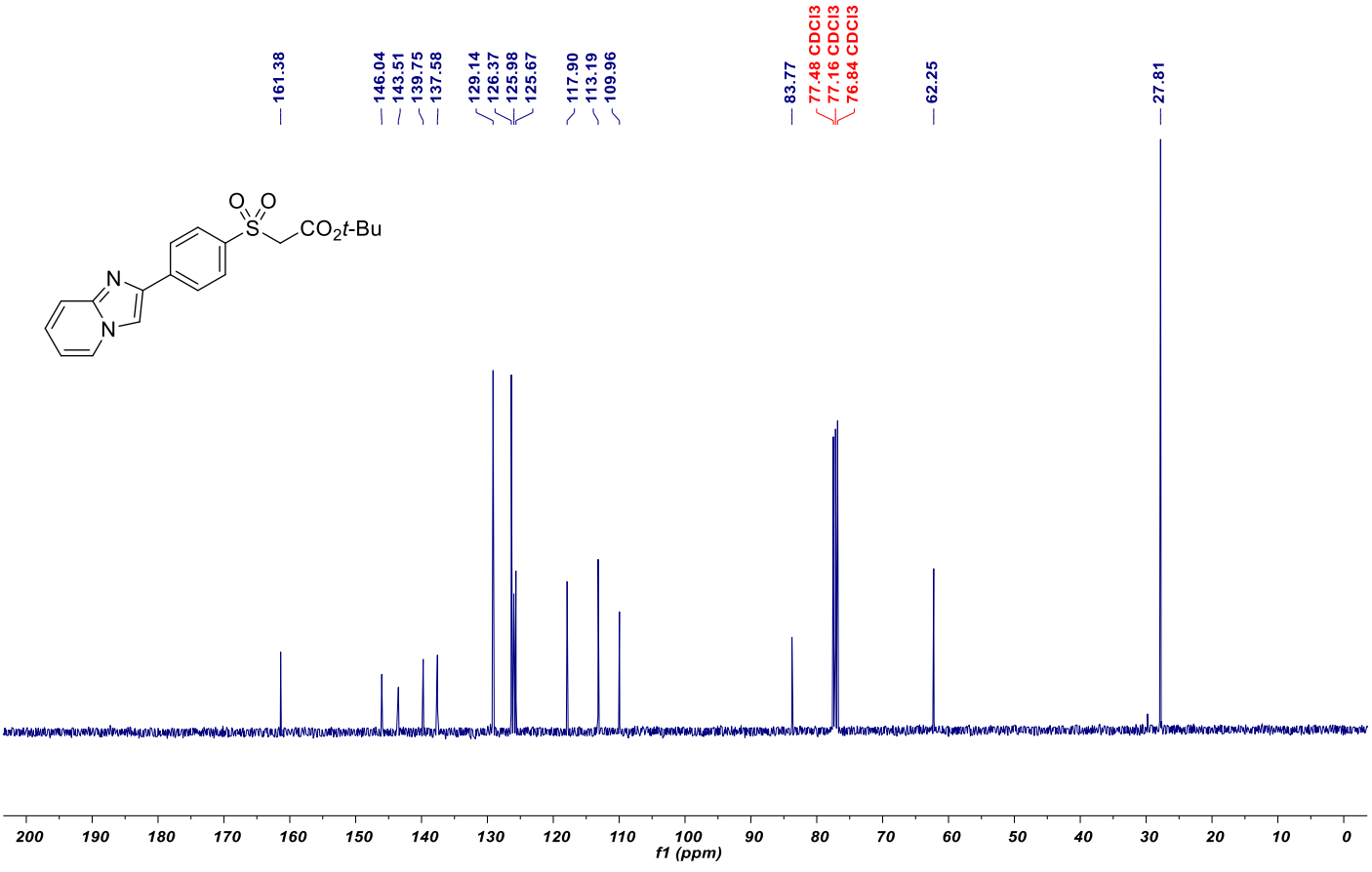




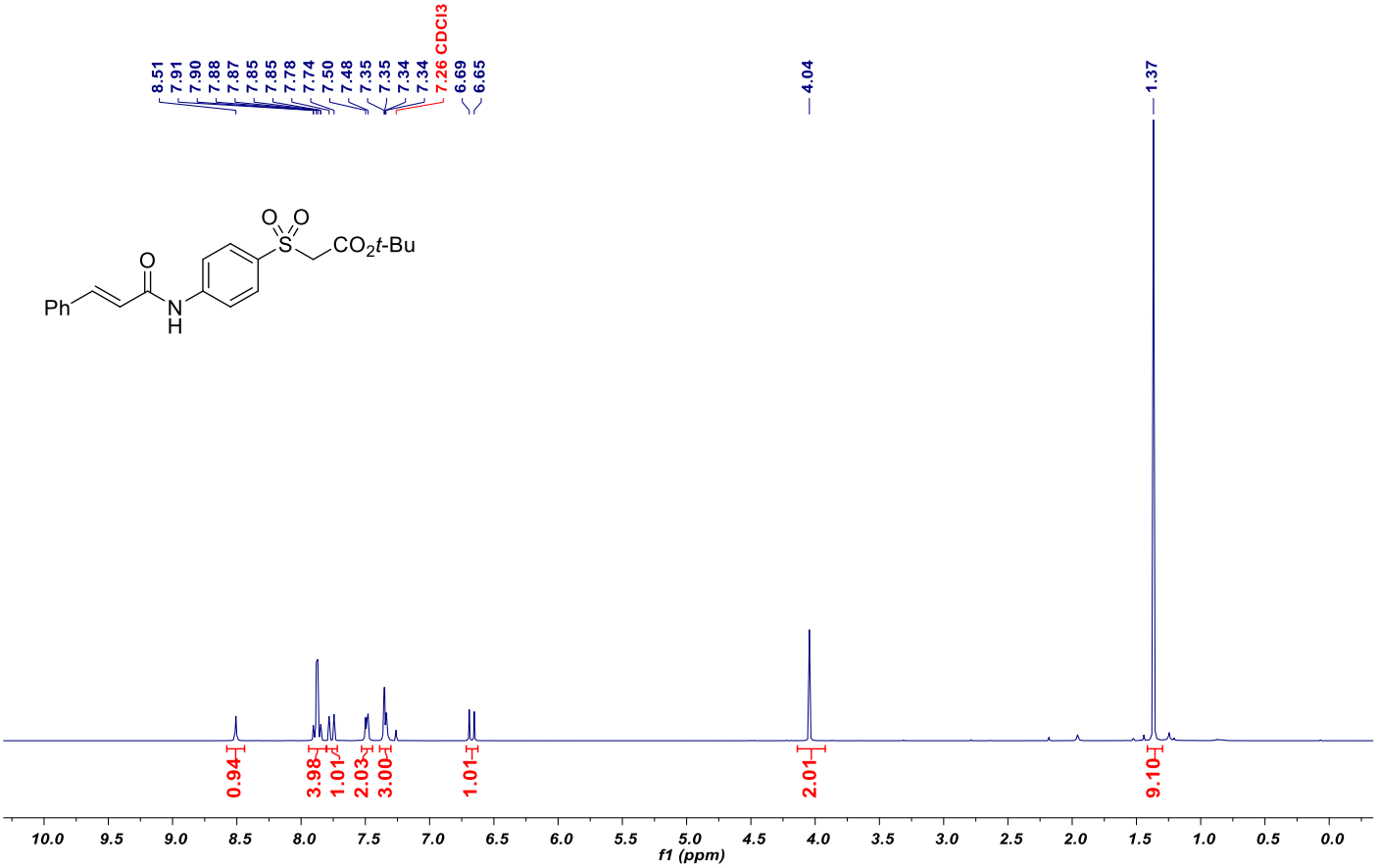

-62.47
Me
O
O
S
CO2t-Bu
N
N
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

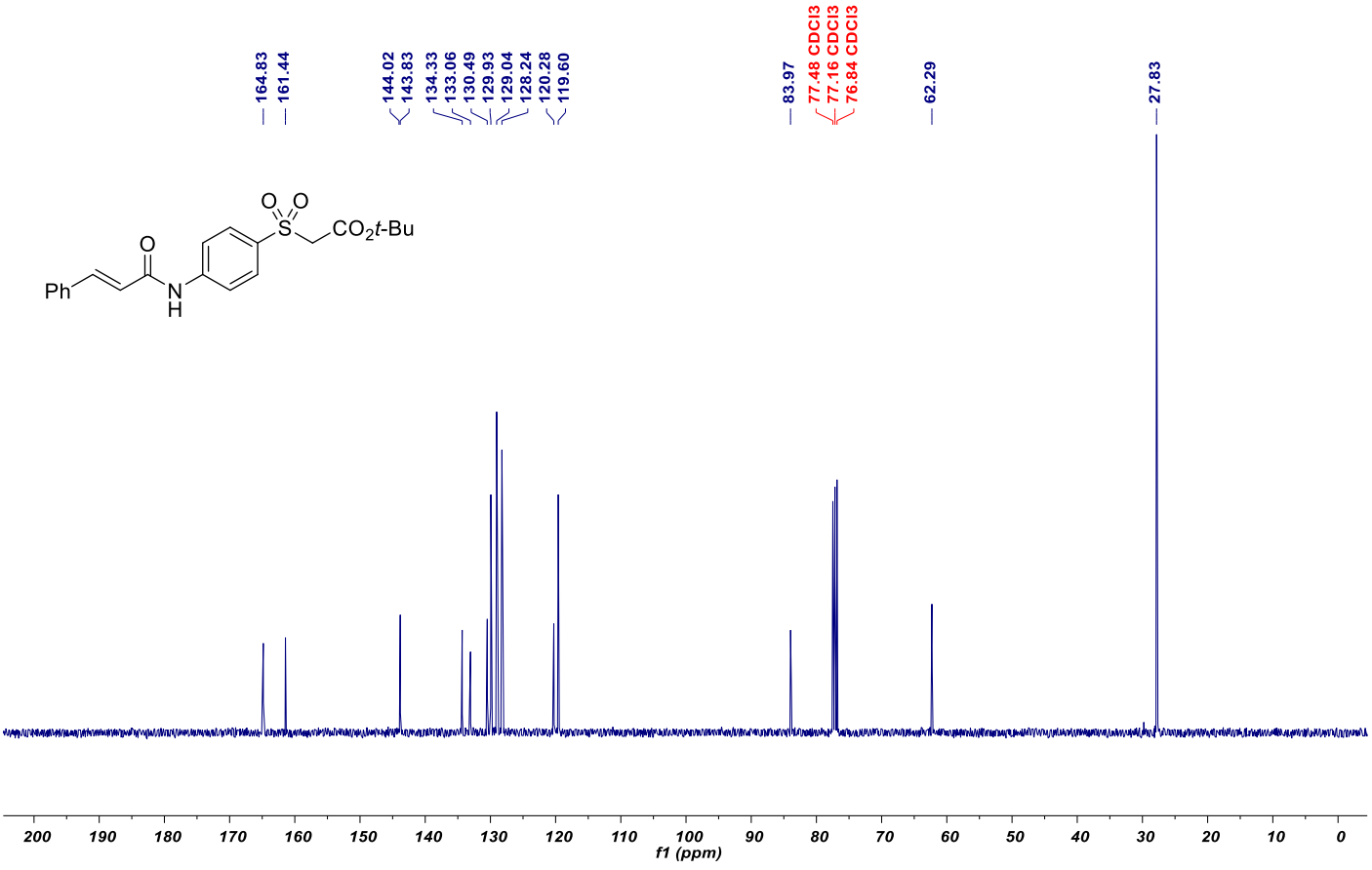
NMR spectrum of sulfone **7v**



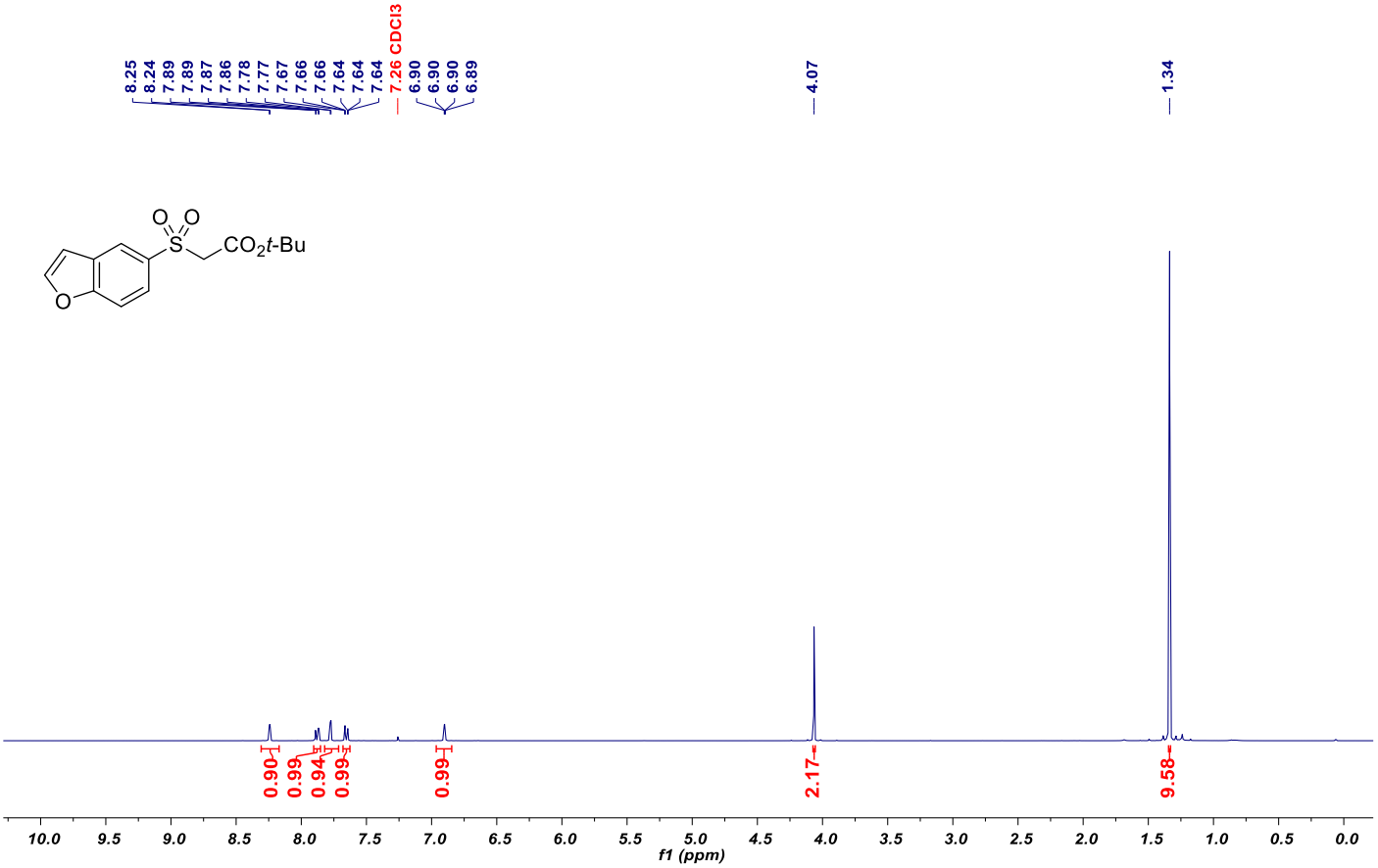


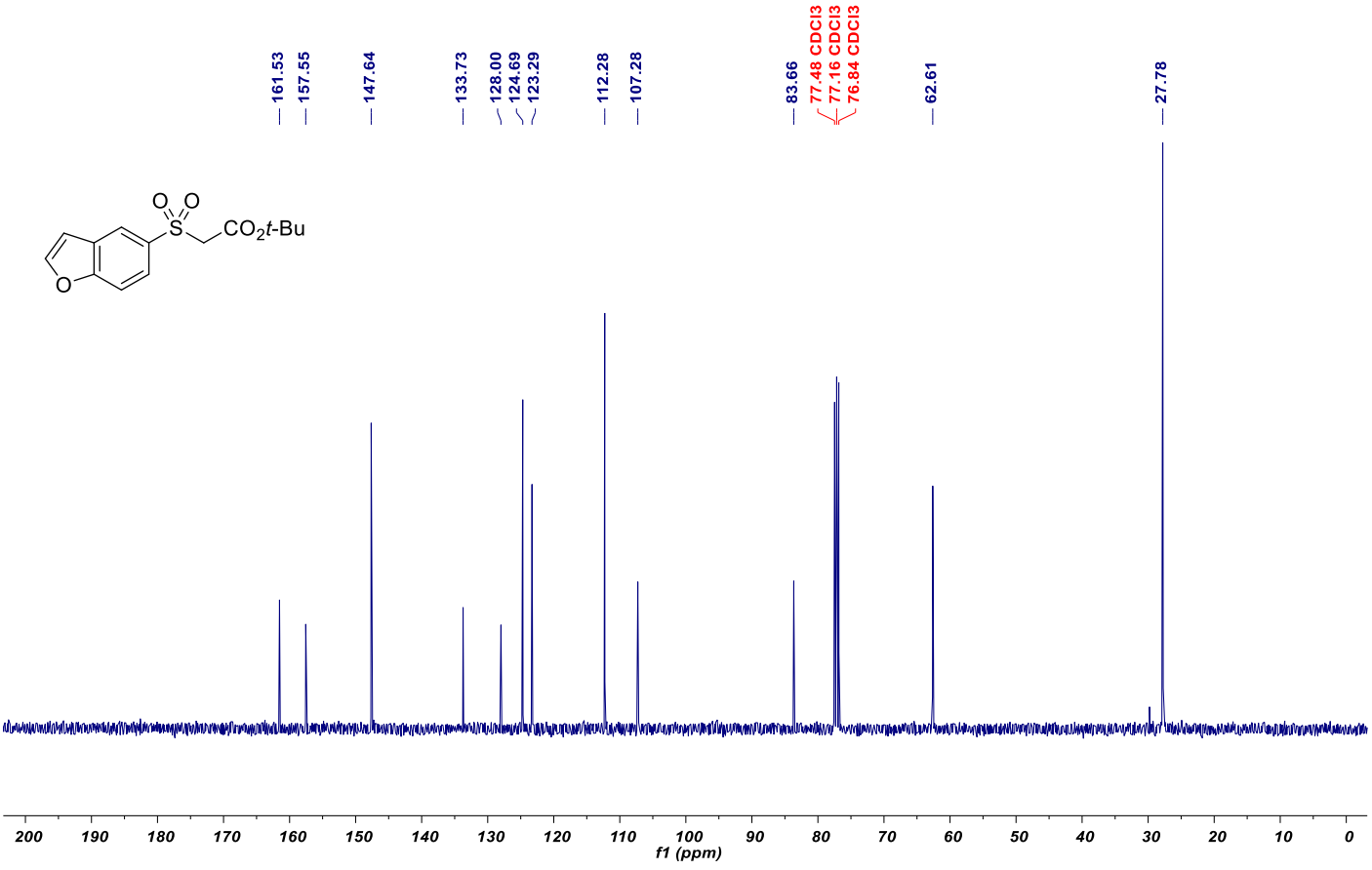
NMR spectrum of sulfone **7w**



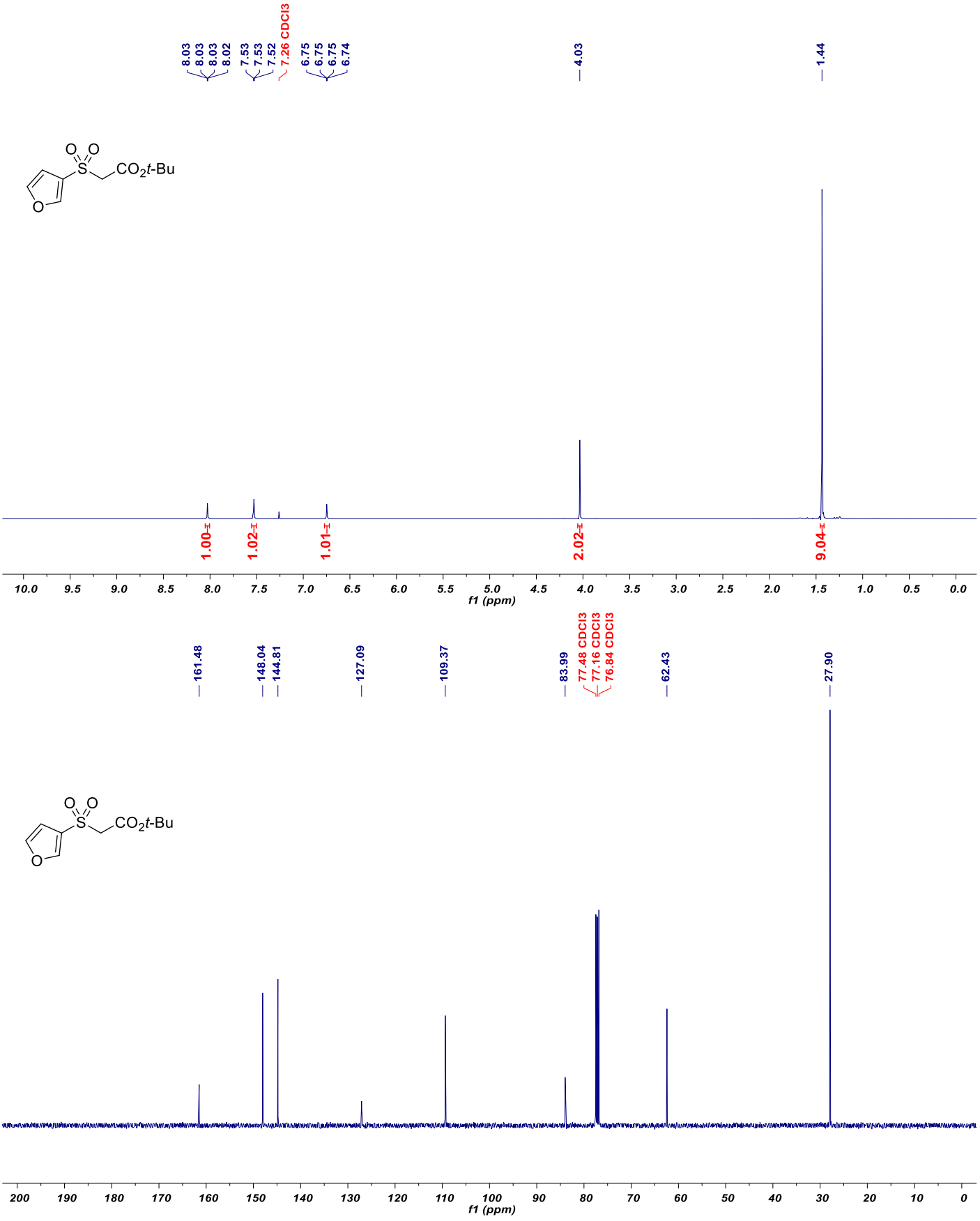


NMR spectrum of sulfone **7x**

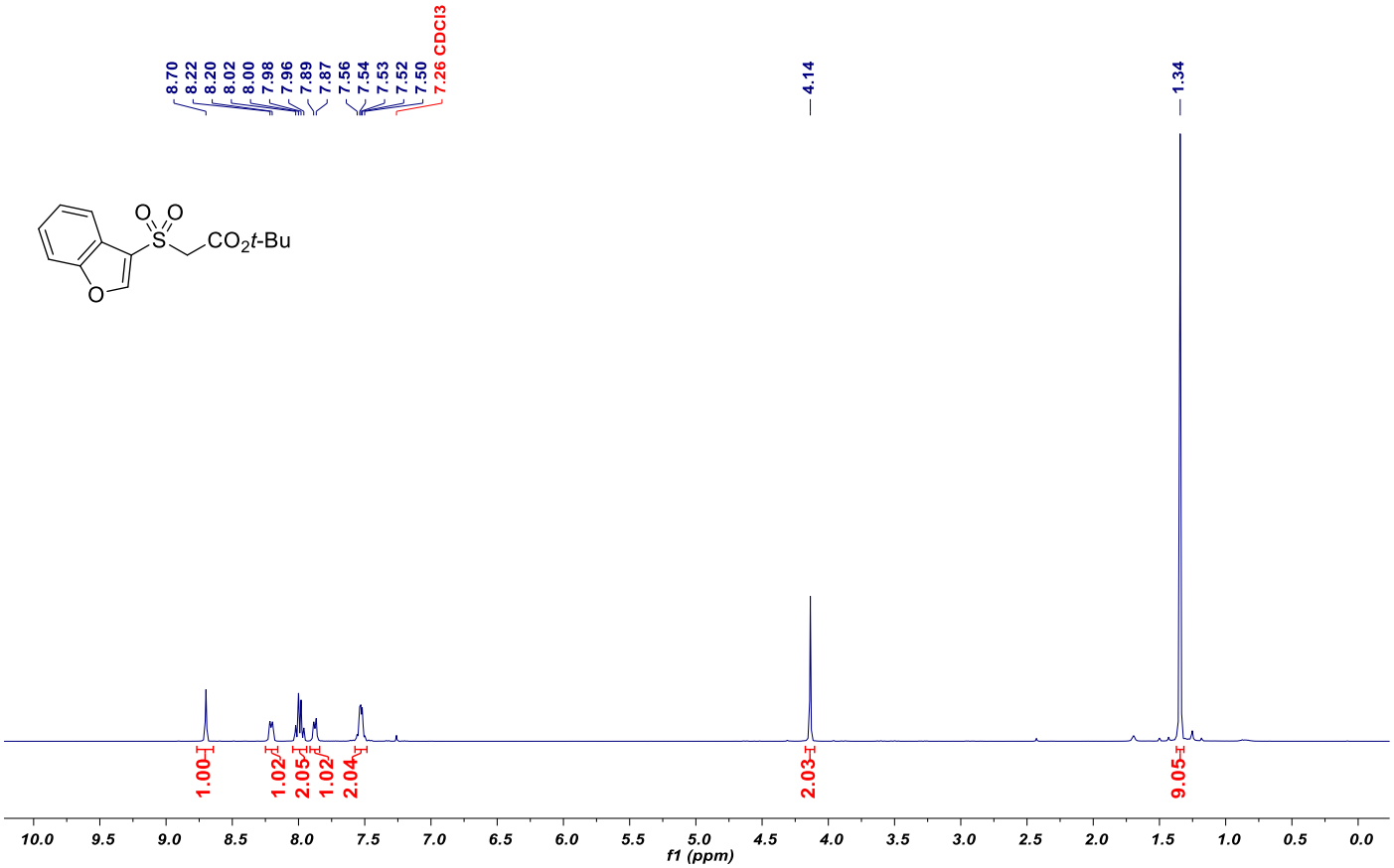


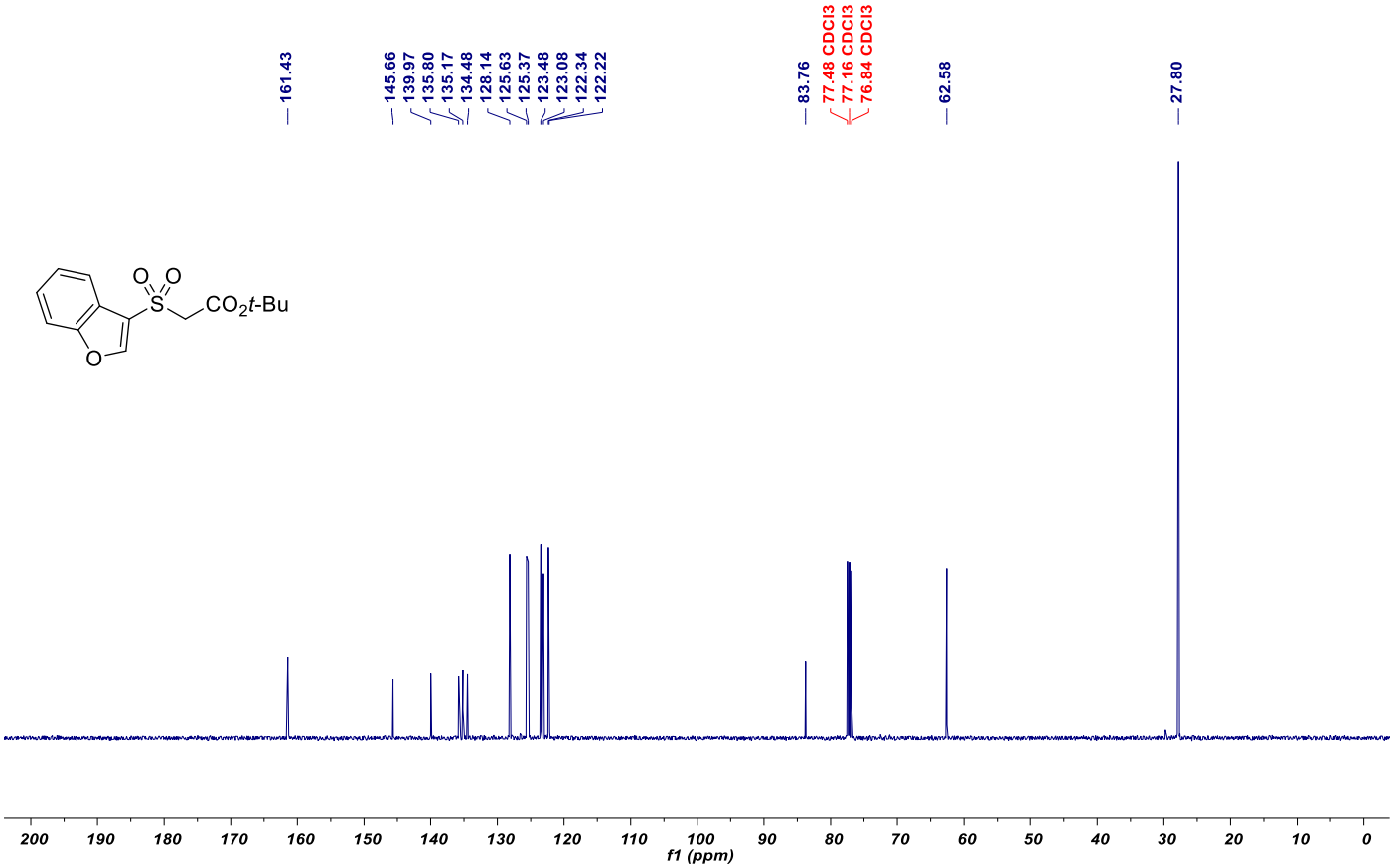


NMR spectrum of sulfone **7y**

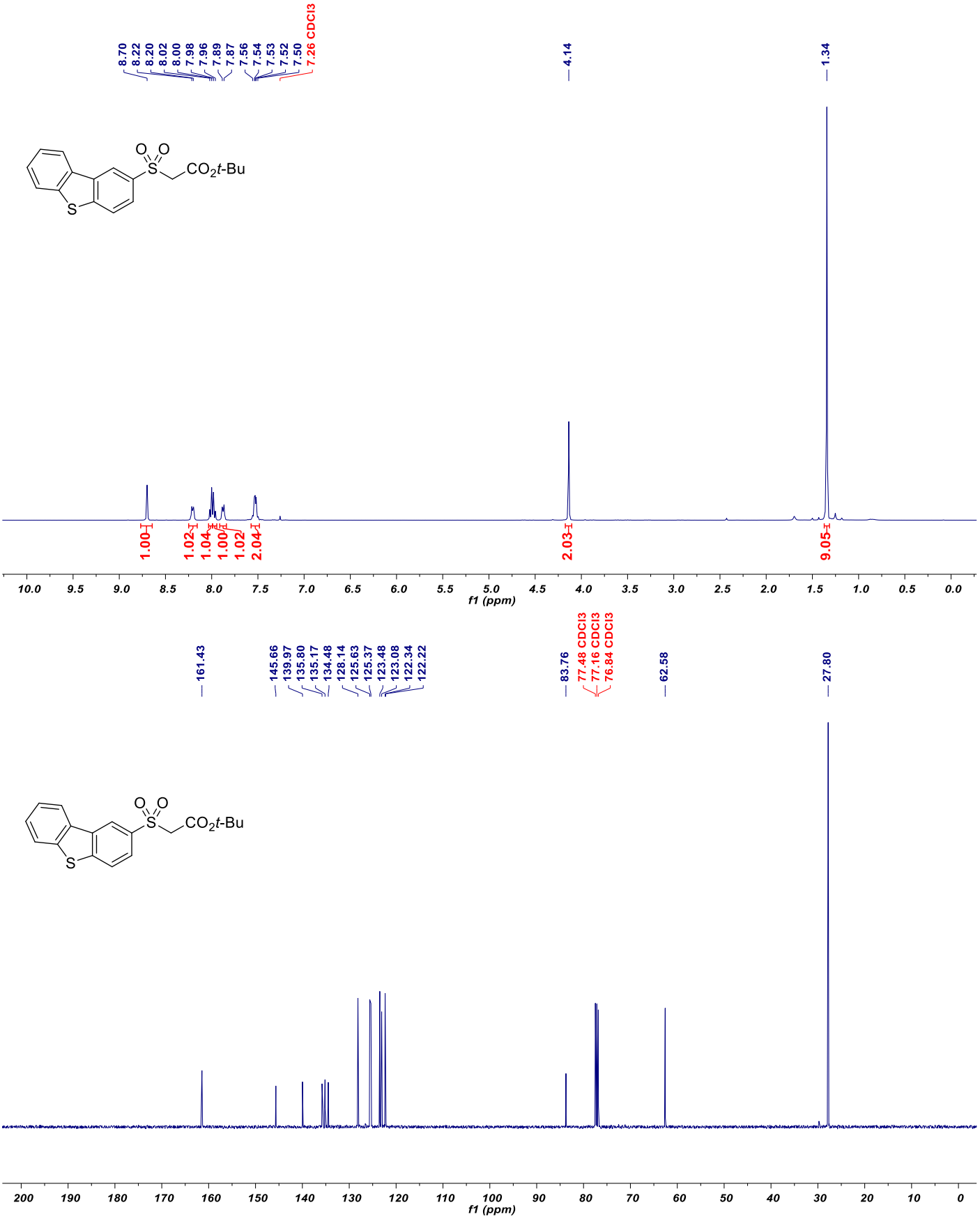


NMR spectrum of sulfone **7z**

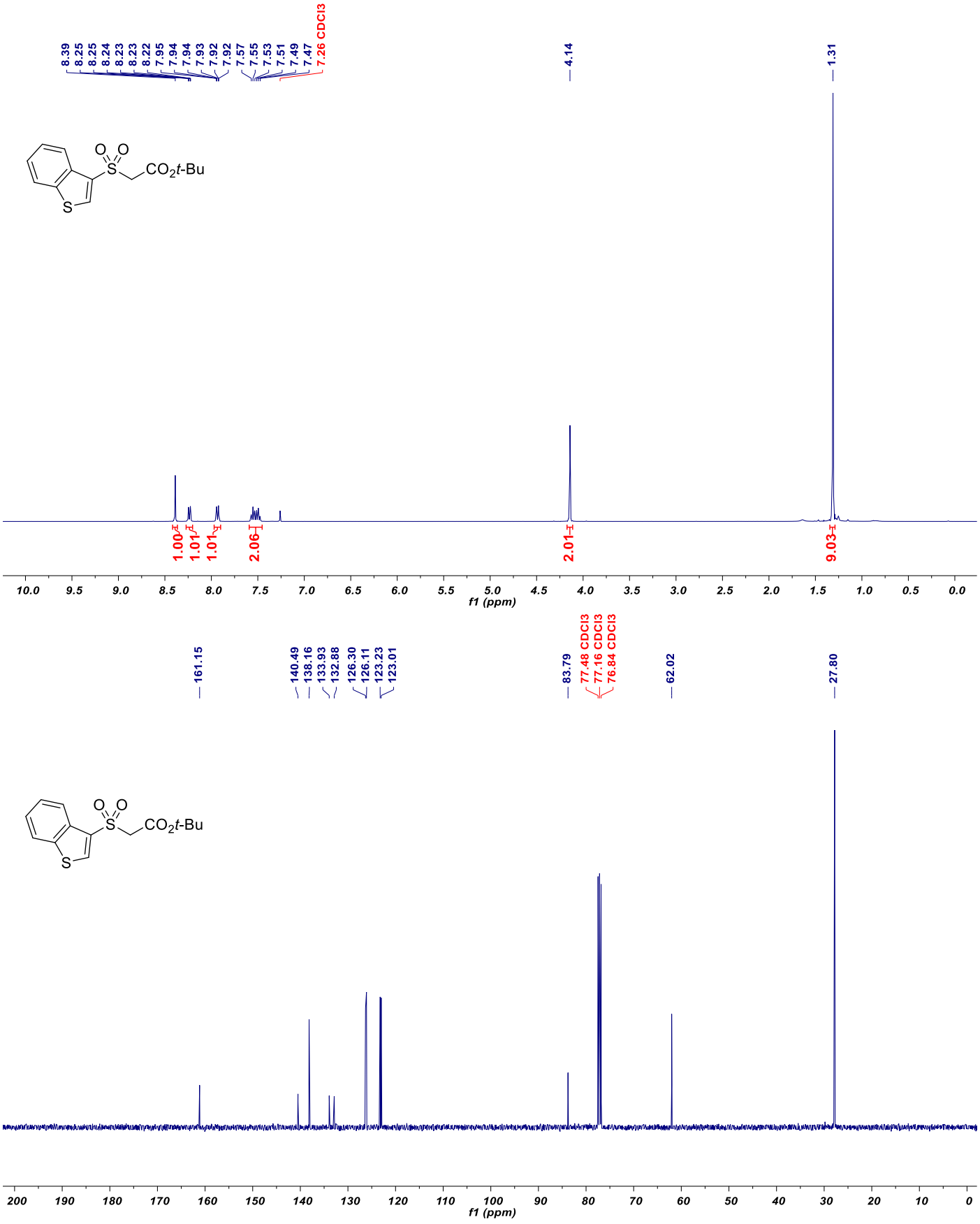




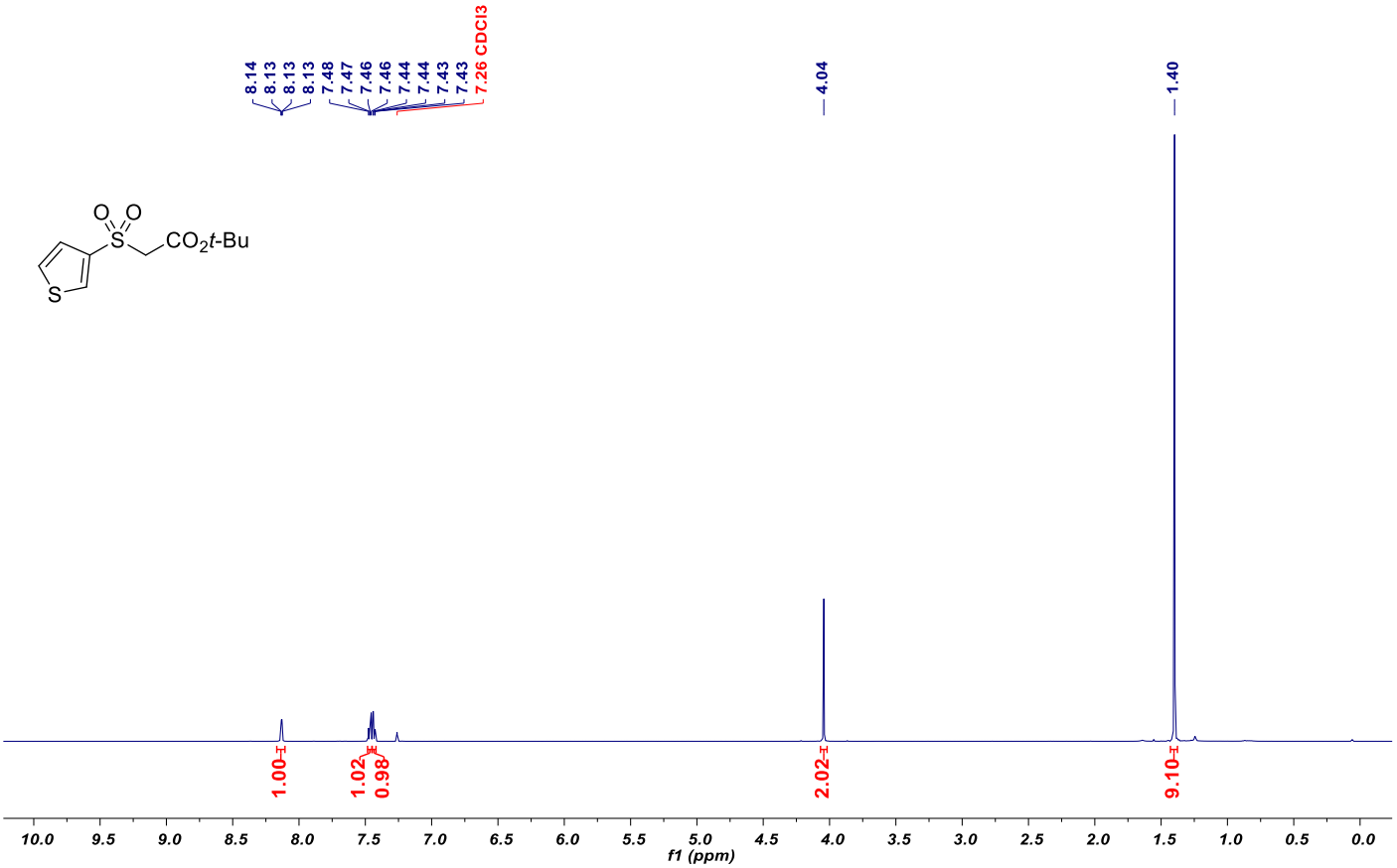
NMR spectrum of sulfone **7aa**

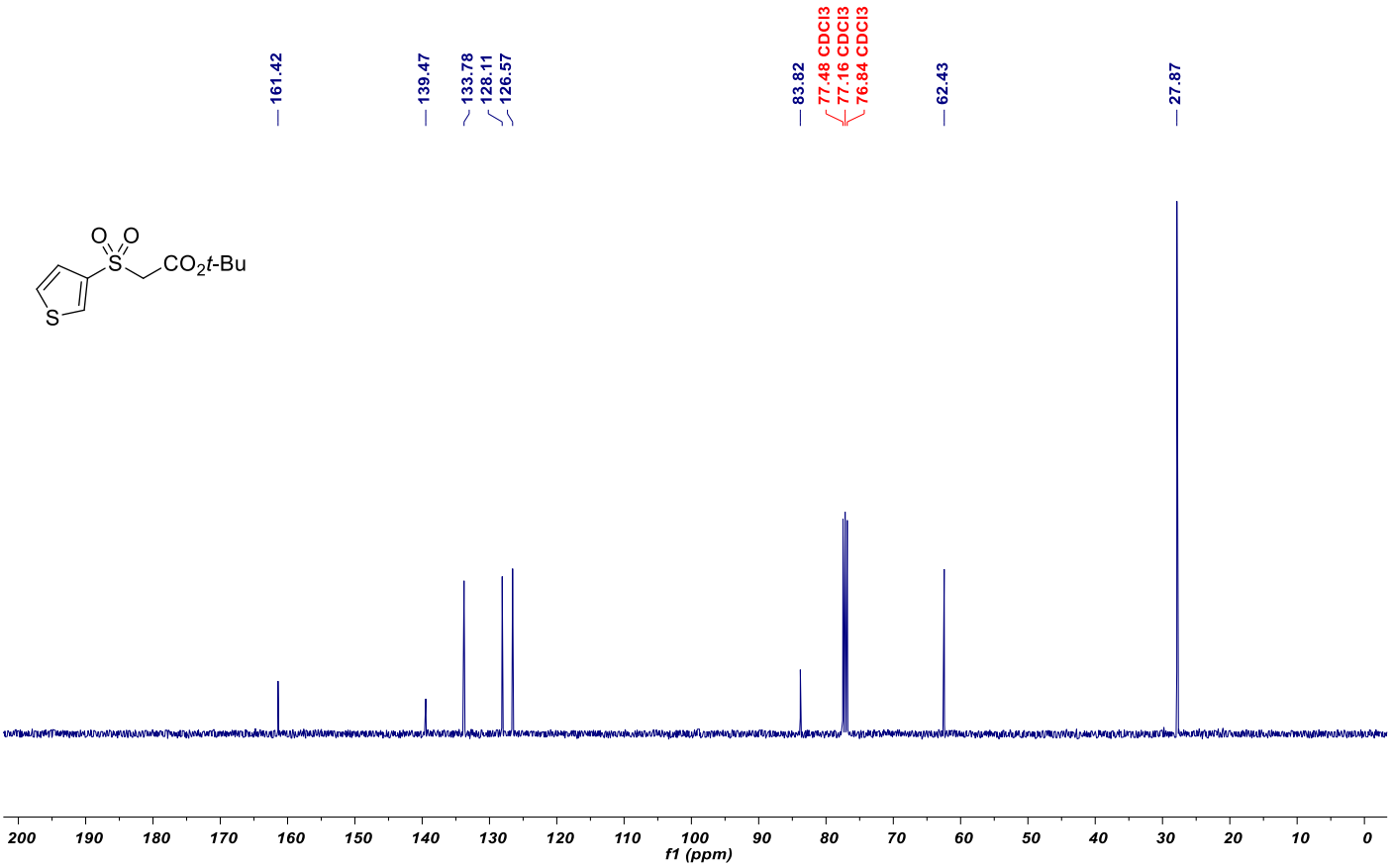


NMR spectrum of sulfone **7ab**

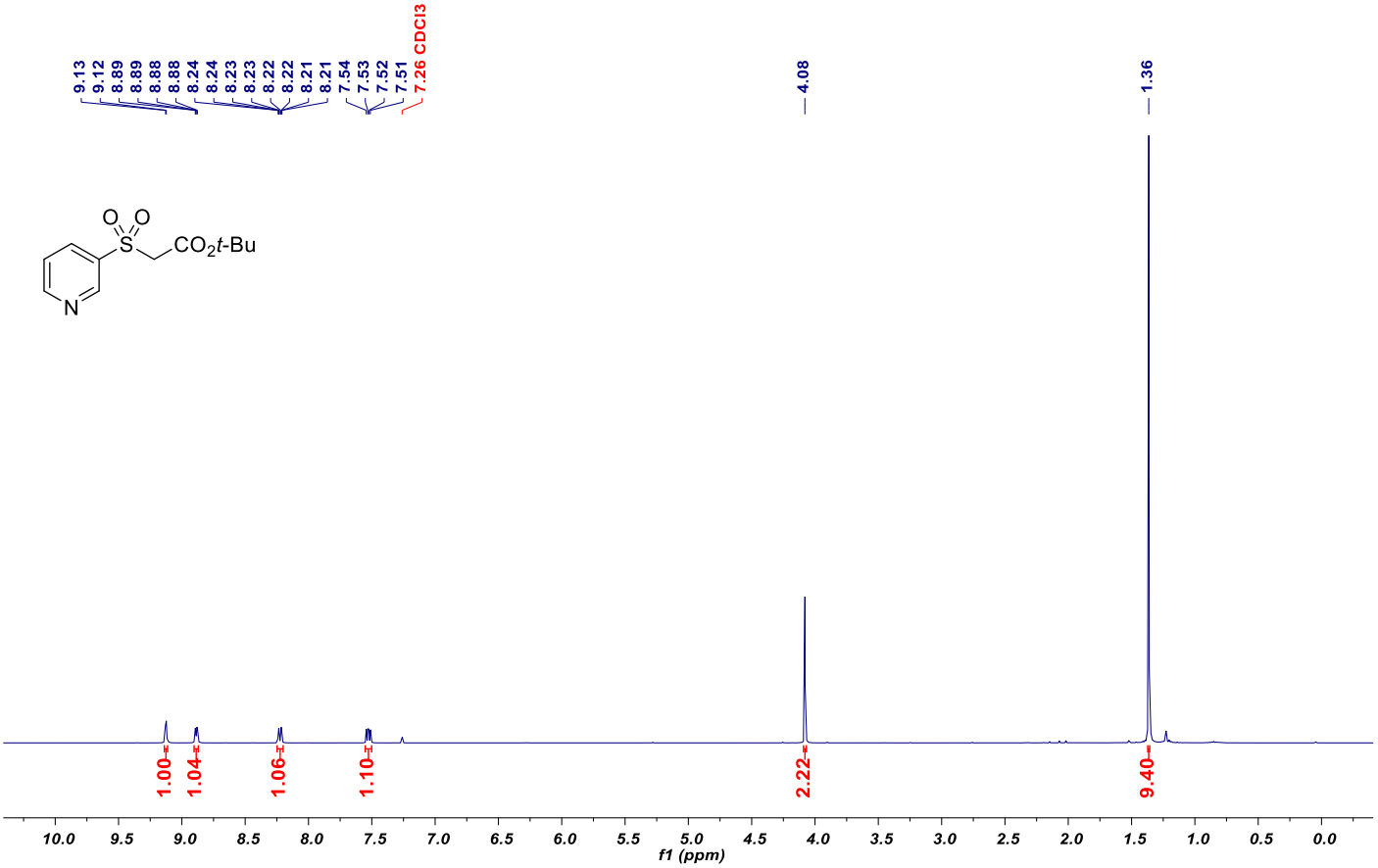


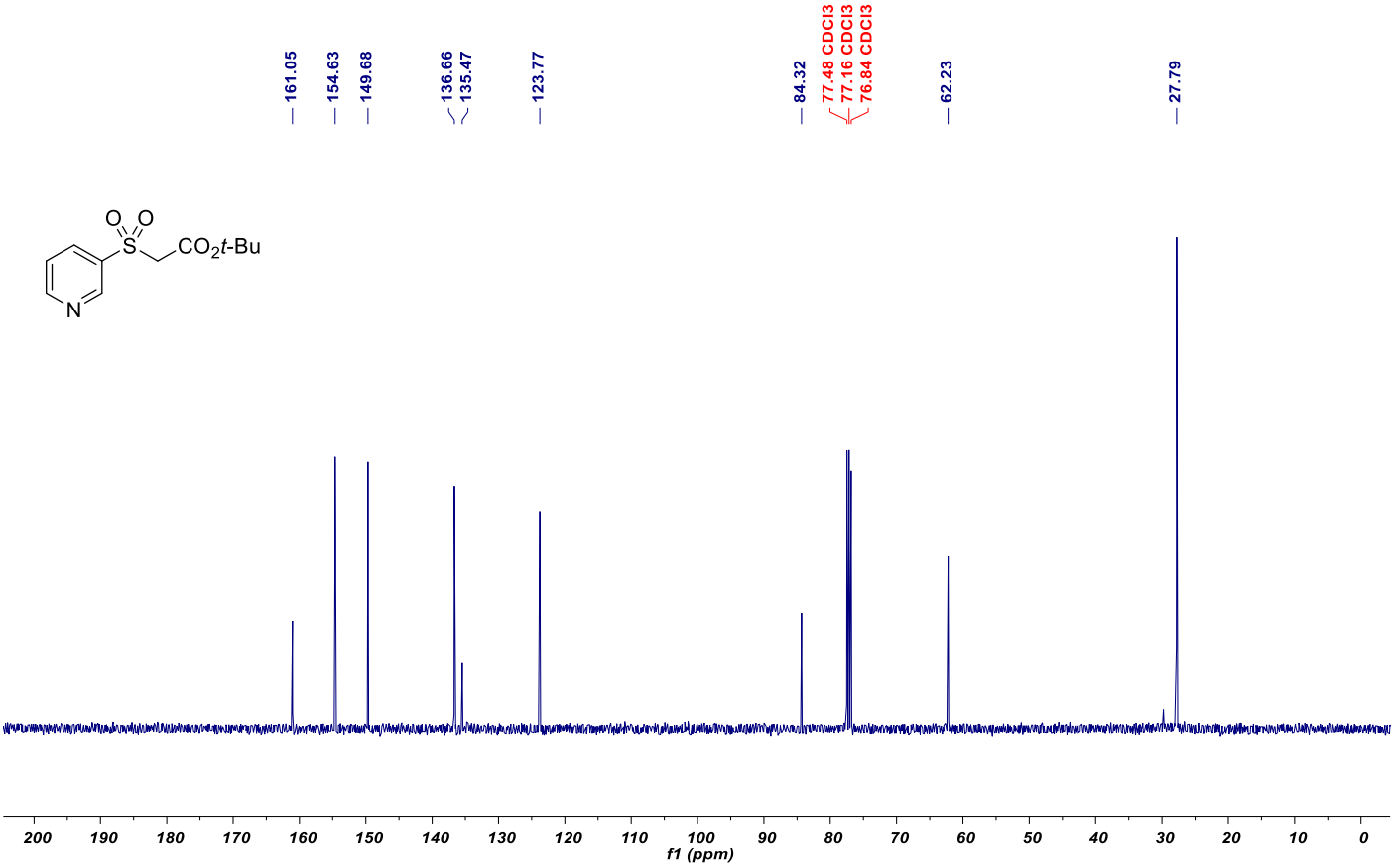
NMR spectrum of sulfone **7ac**



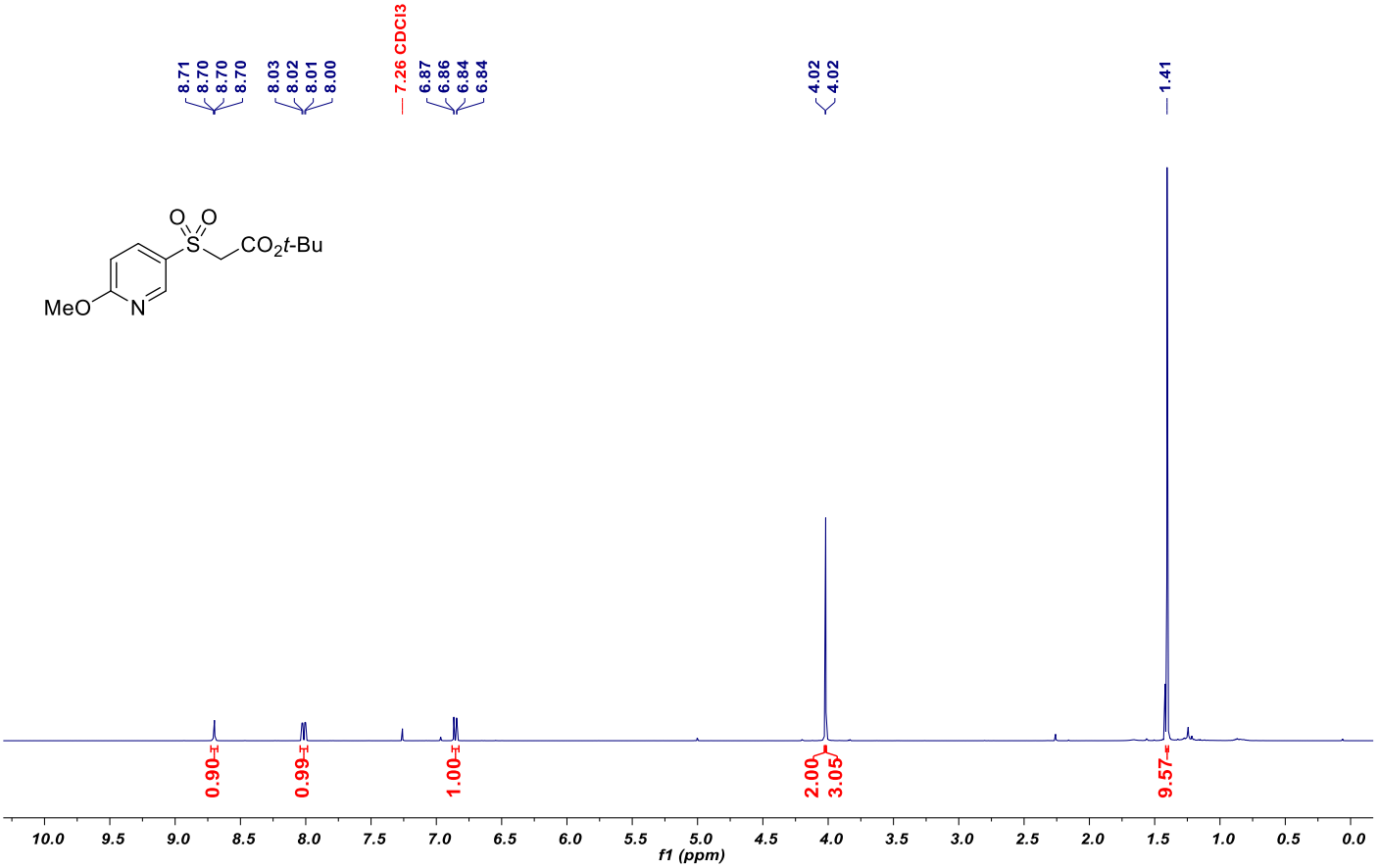


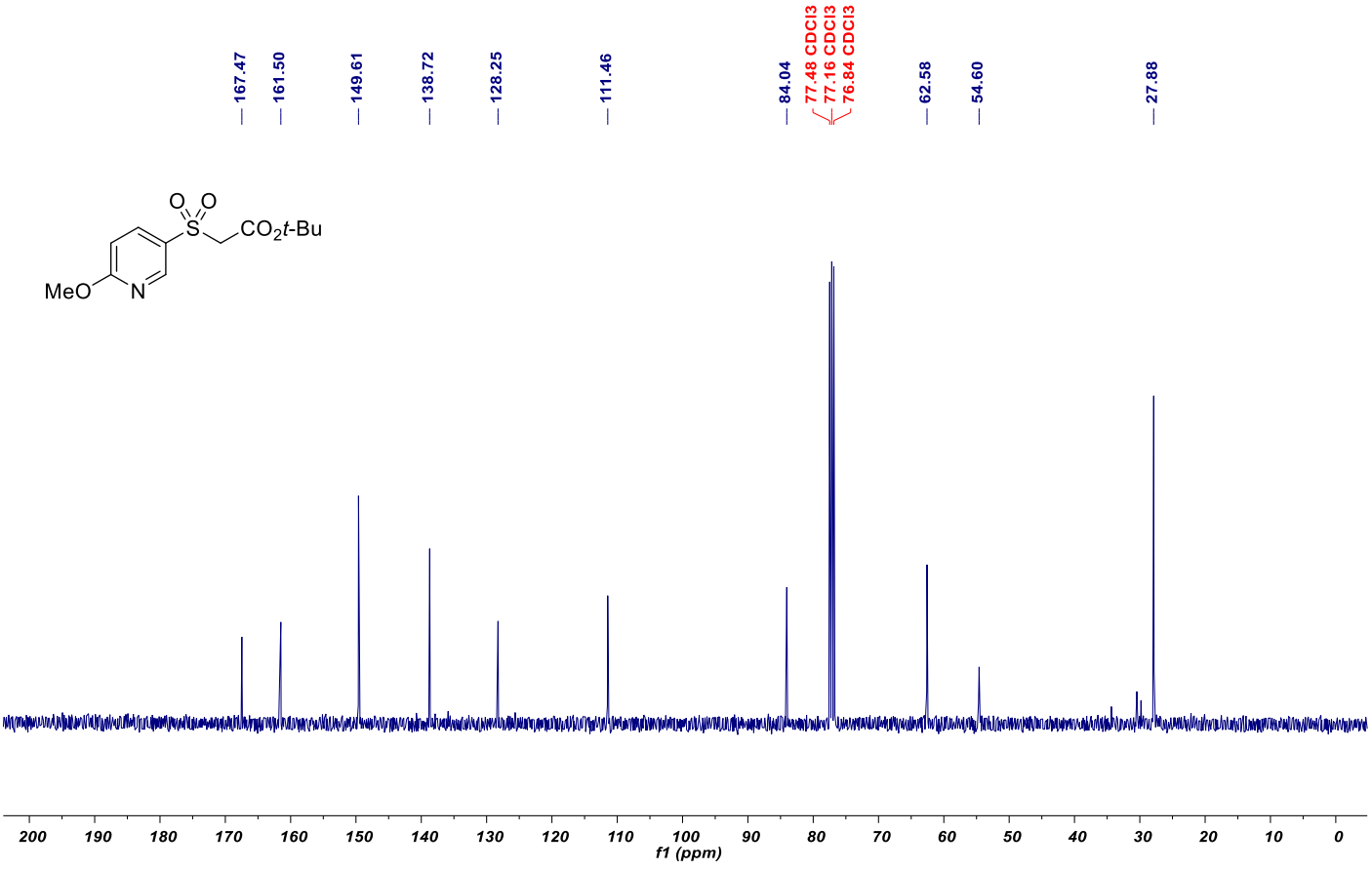
NMR spectrum of sulfone **7ad**



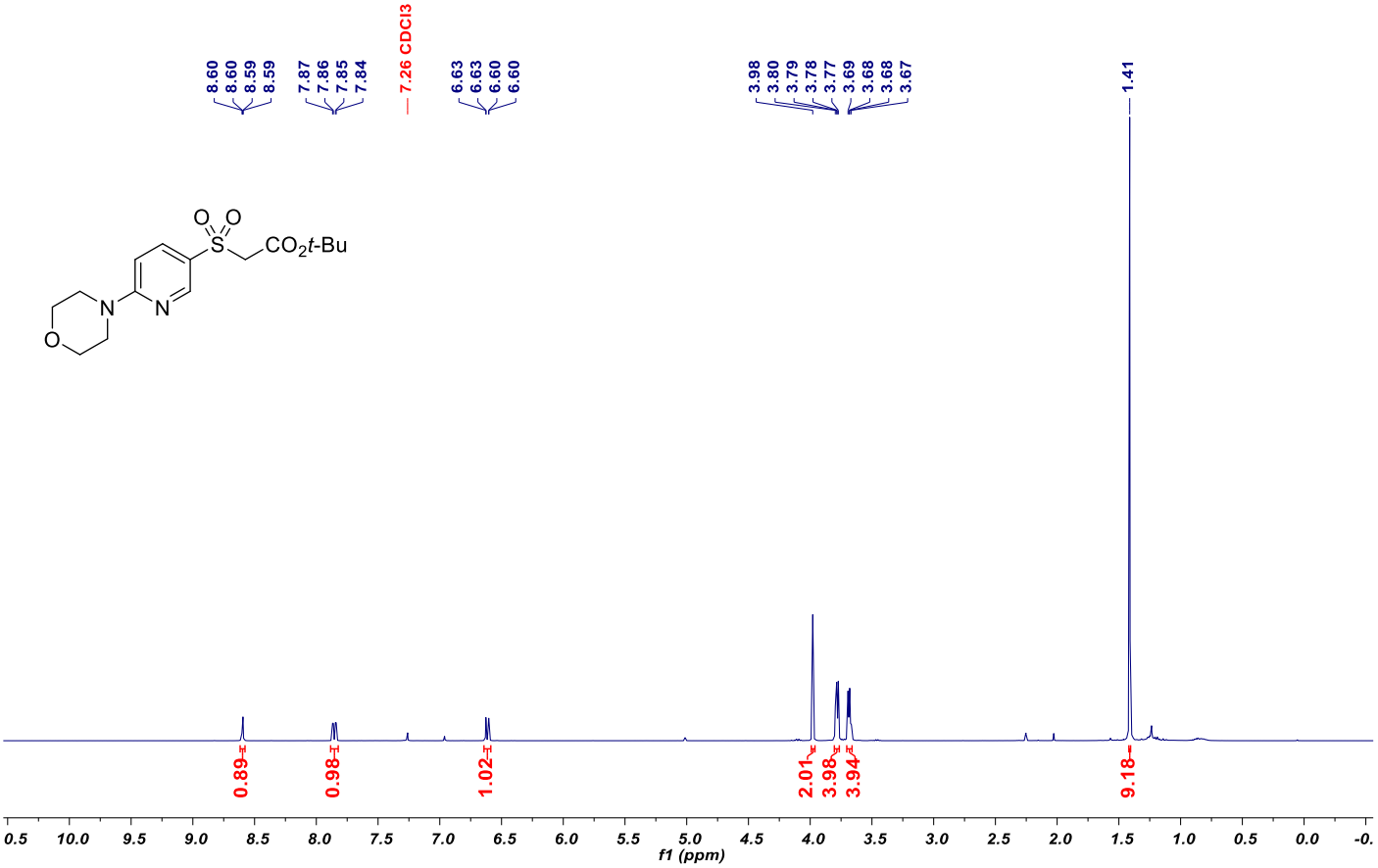


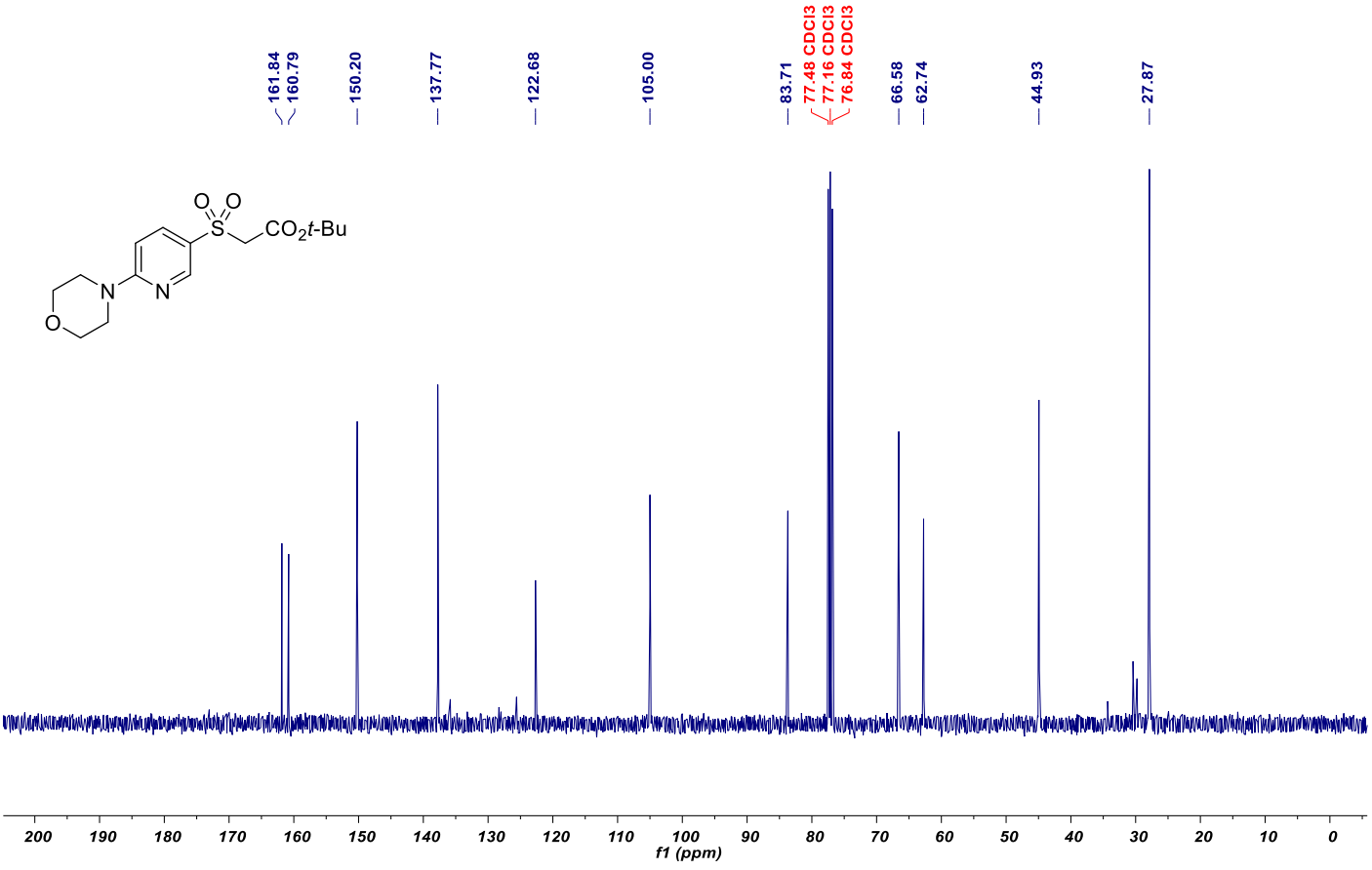
NMR spectrum of sulfone **7ae**



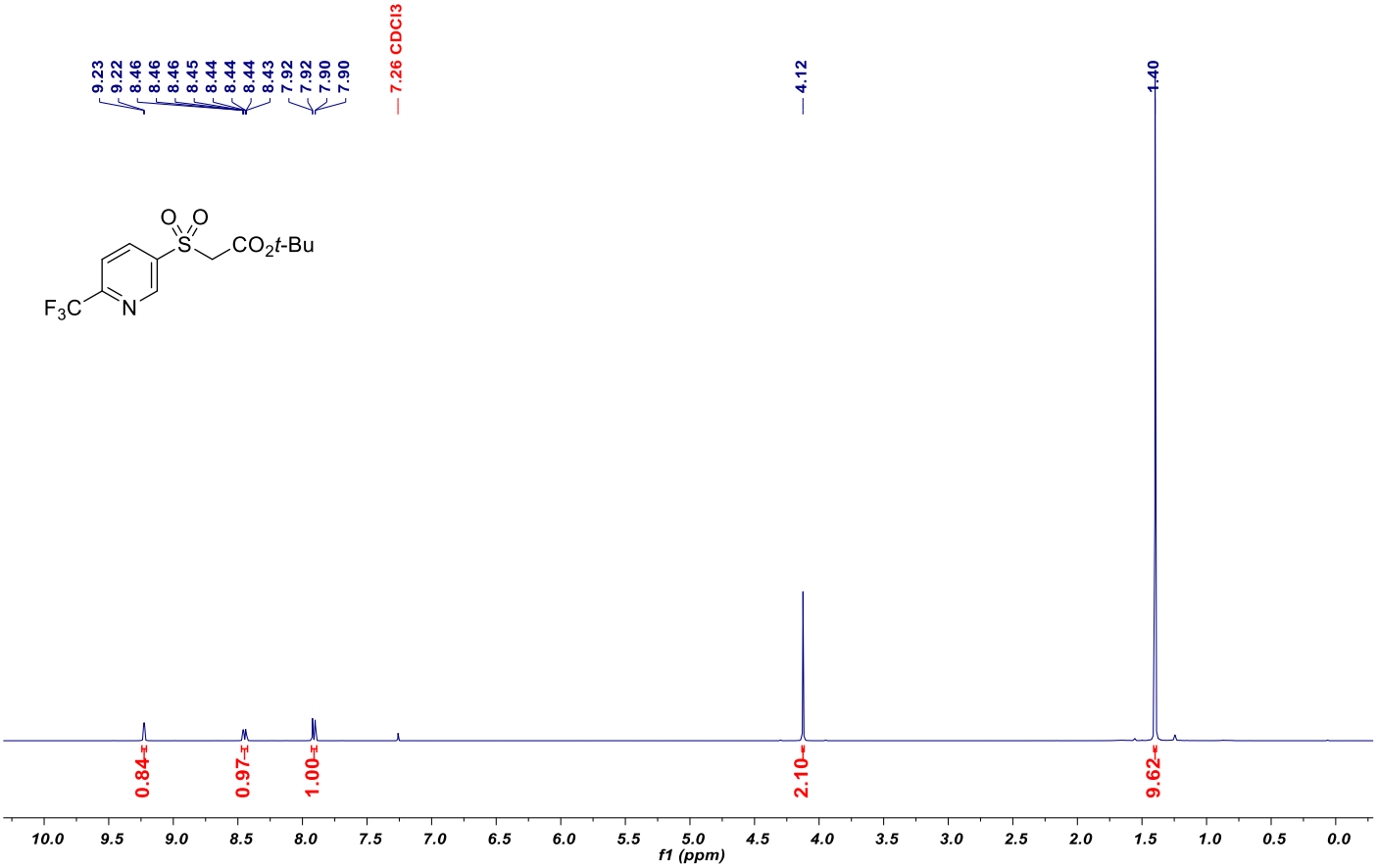


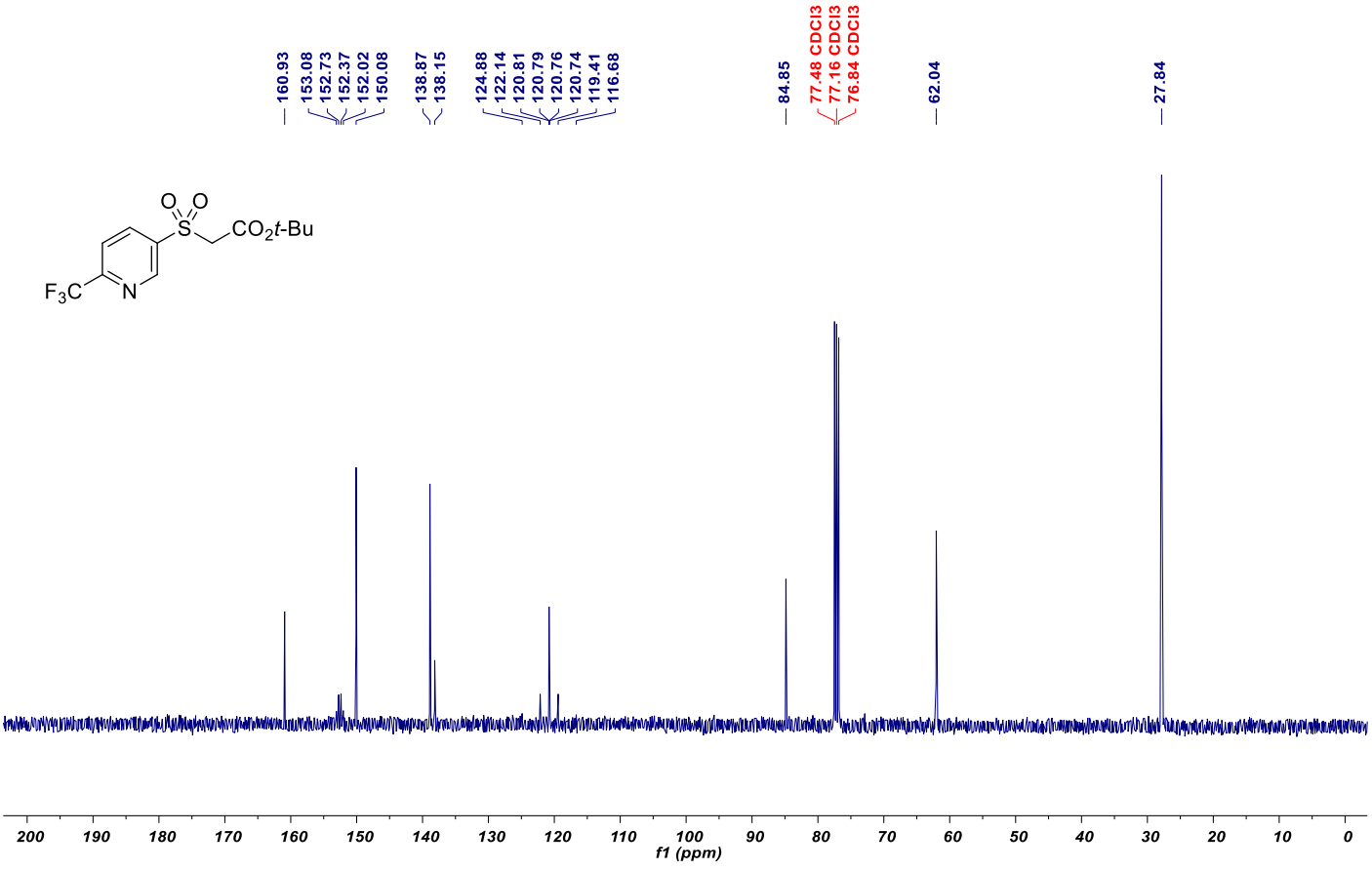
NMR spectrum of sulfone **7af**

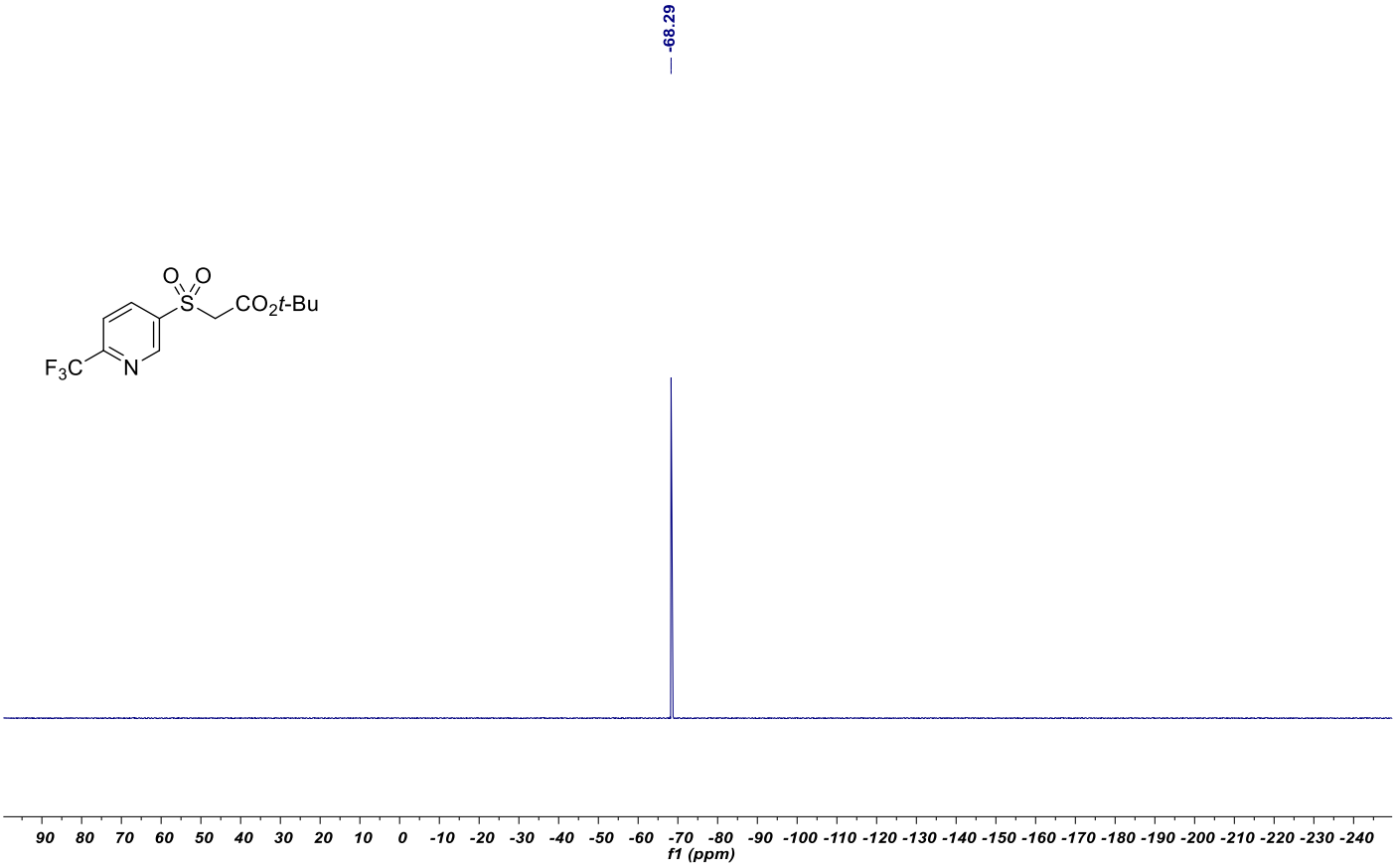




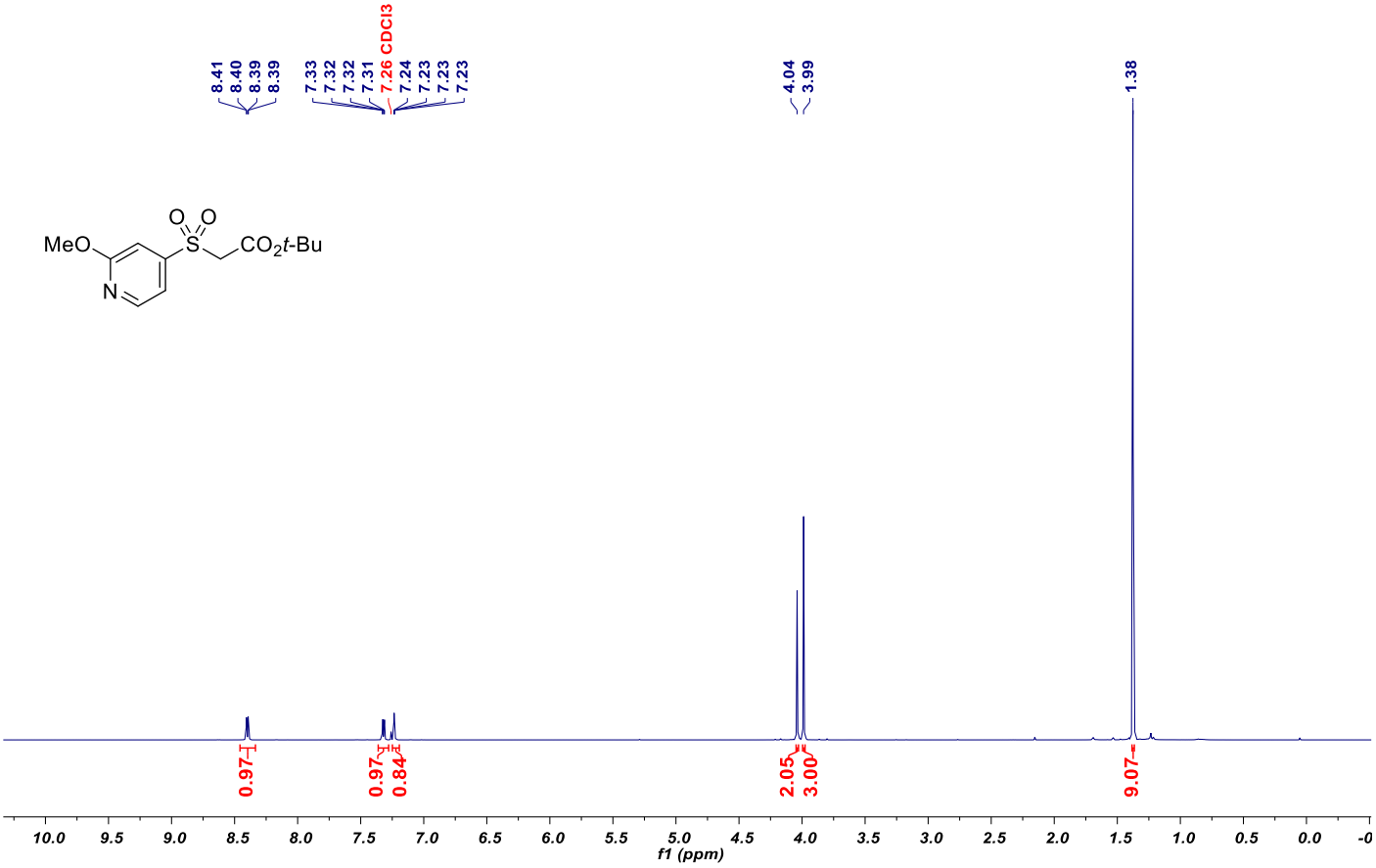
NMR spectrum of sulfone **7ag**

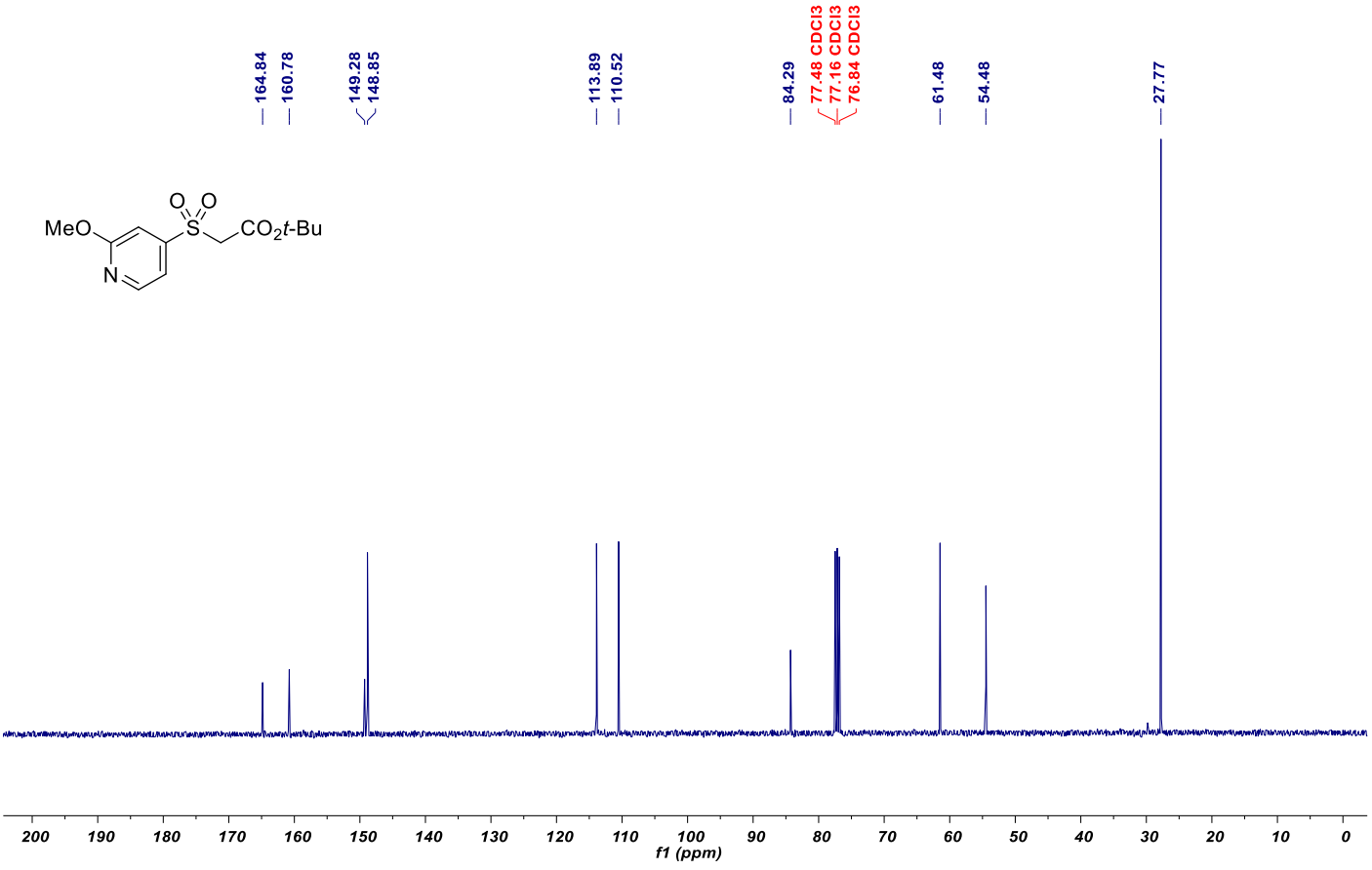




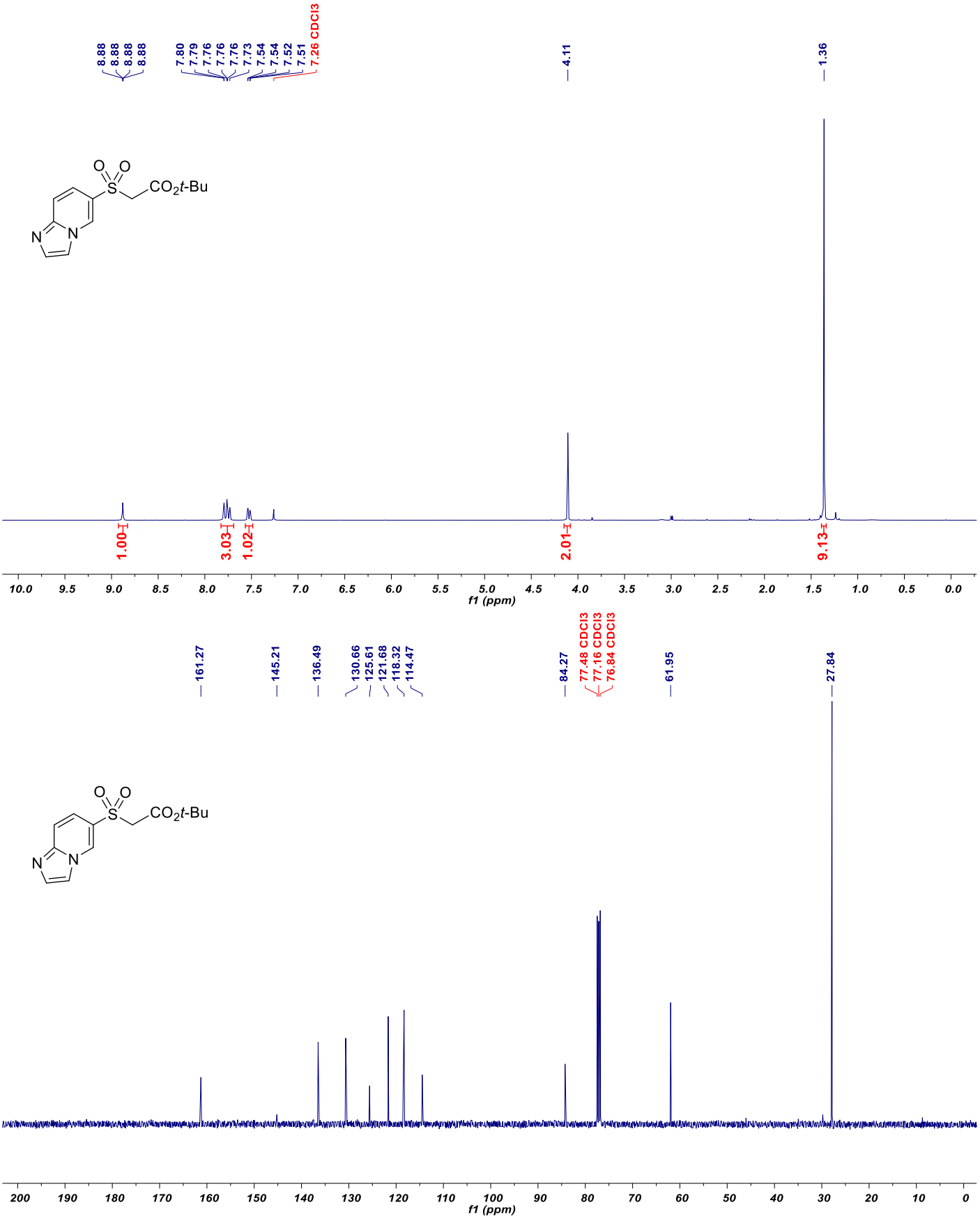

-68.29
O
O
S
CO2t-Bu
F3C
N
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

NMR spectrum of sulfone **7ah**

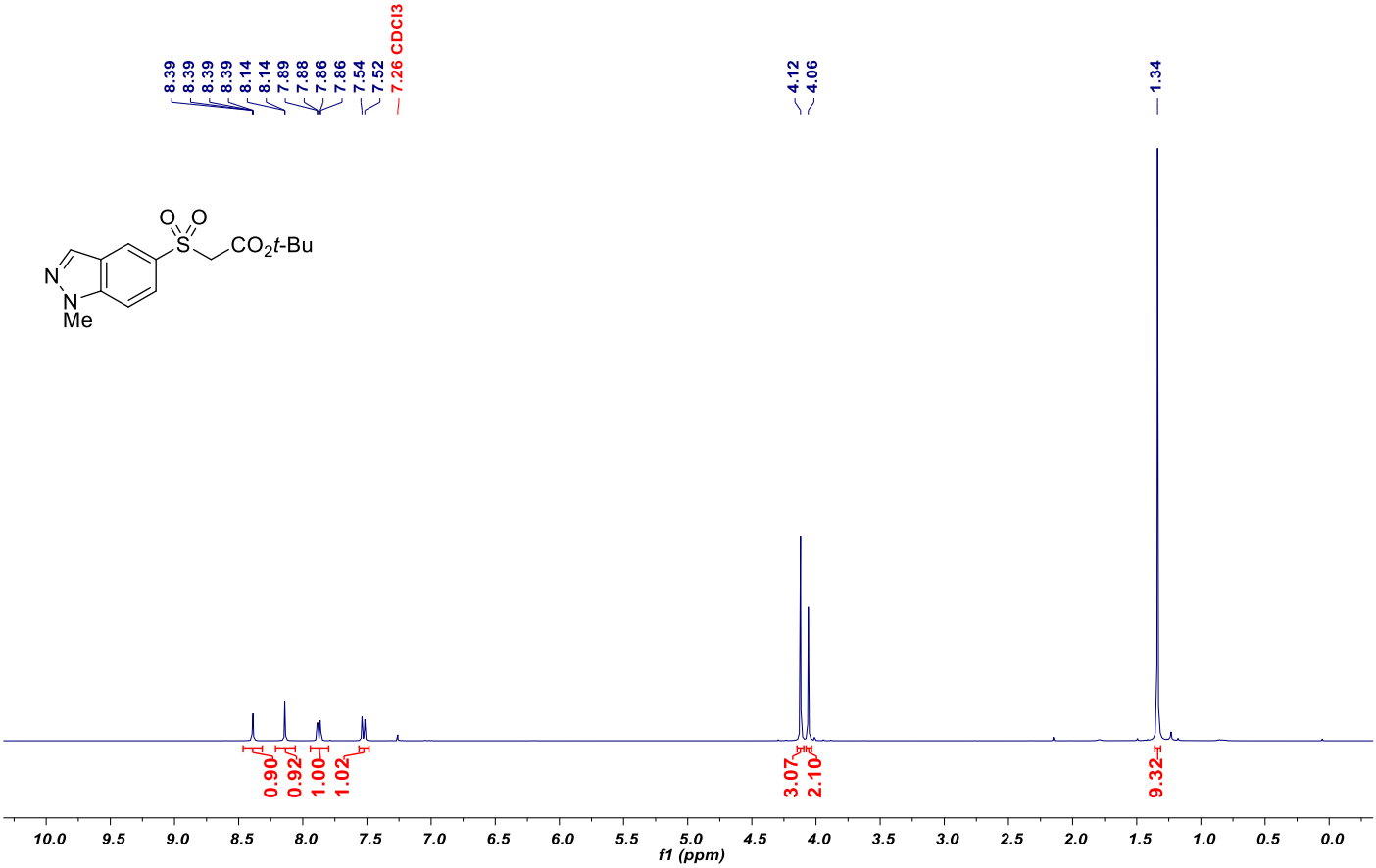


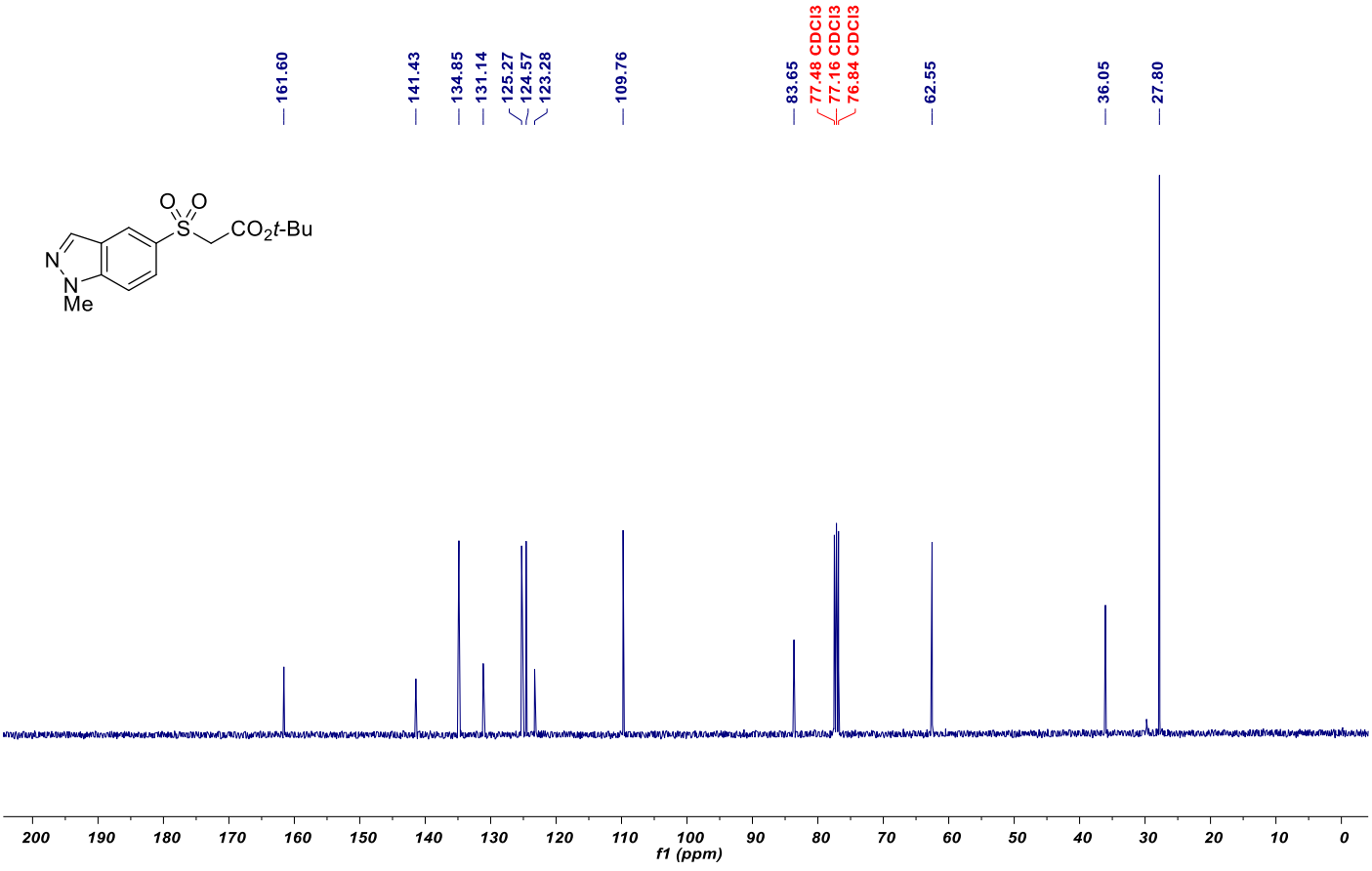


NMR spectrum of sulfone **7ai**

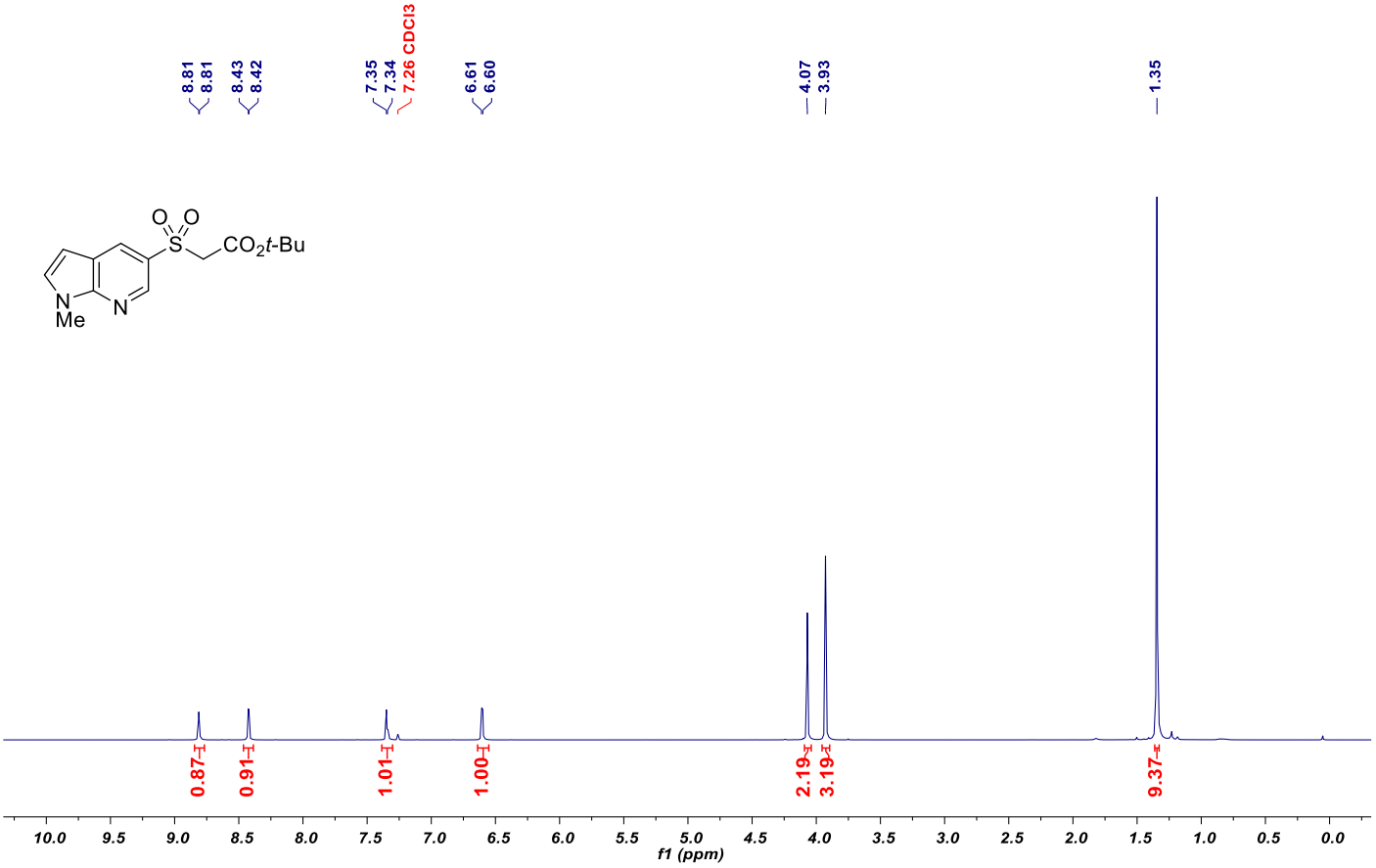


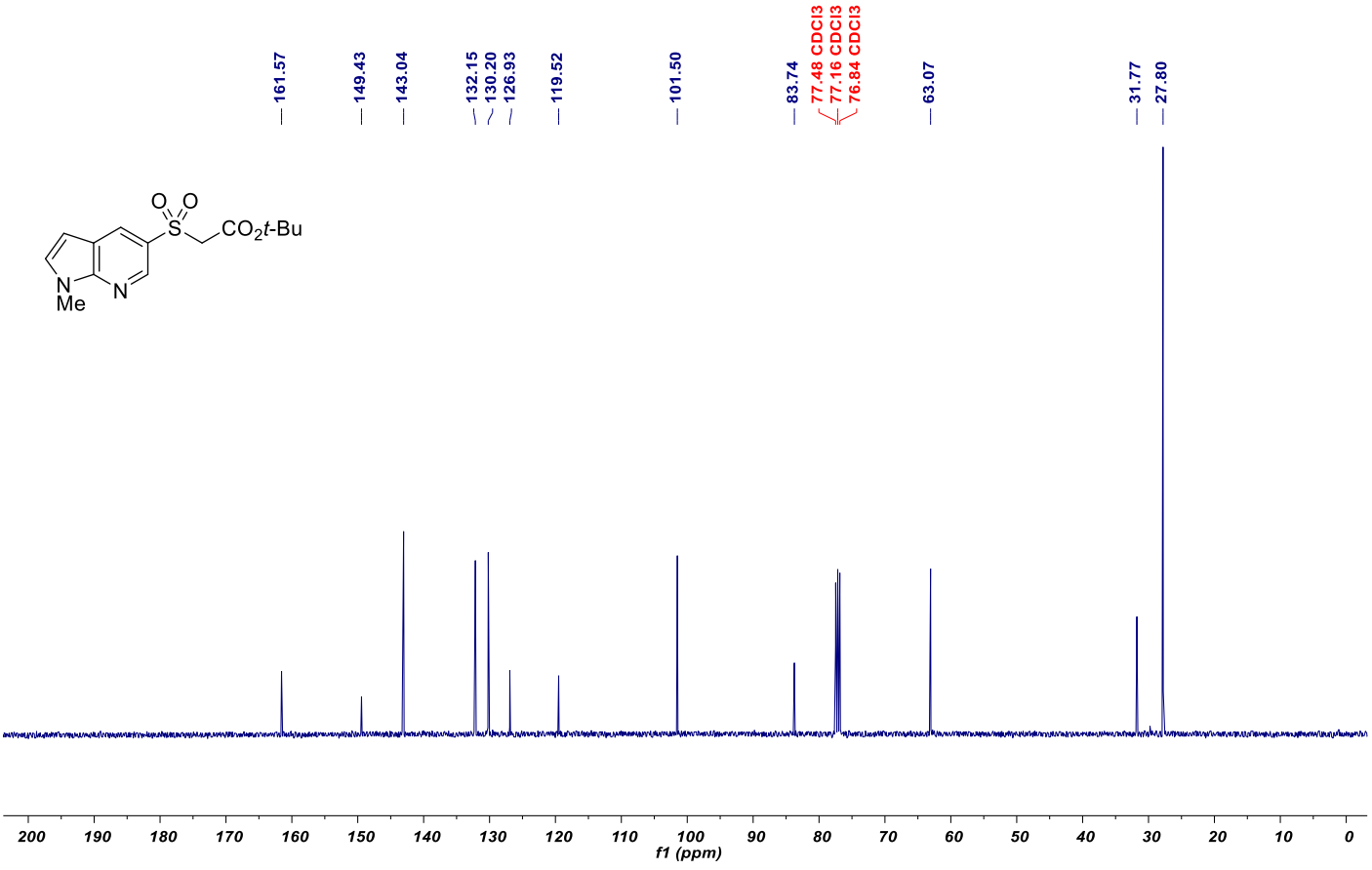
NMR spectrum of sulfone **7aj**



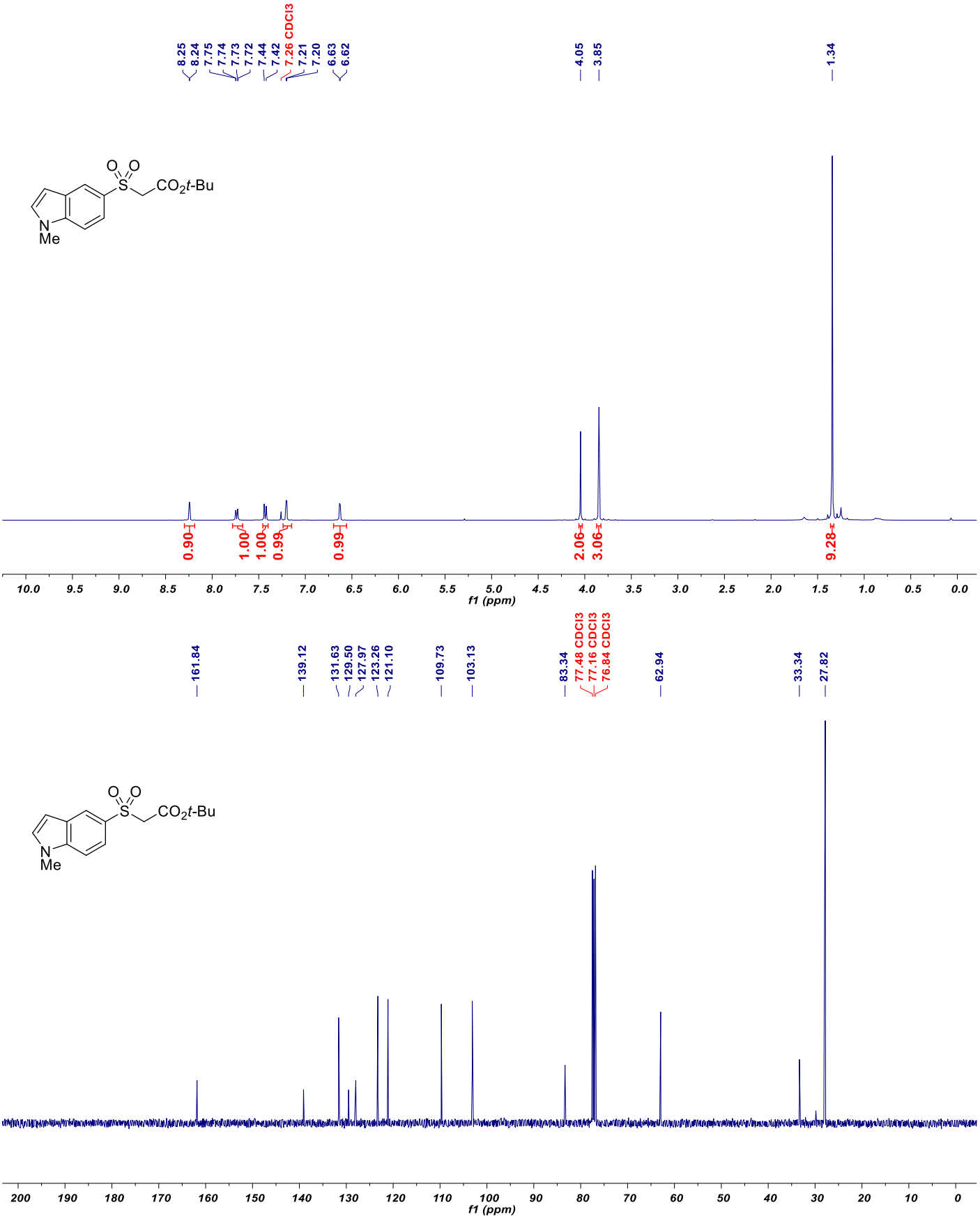


NMR spectrum of sulfone **7ak**

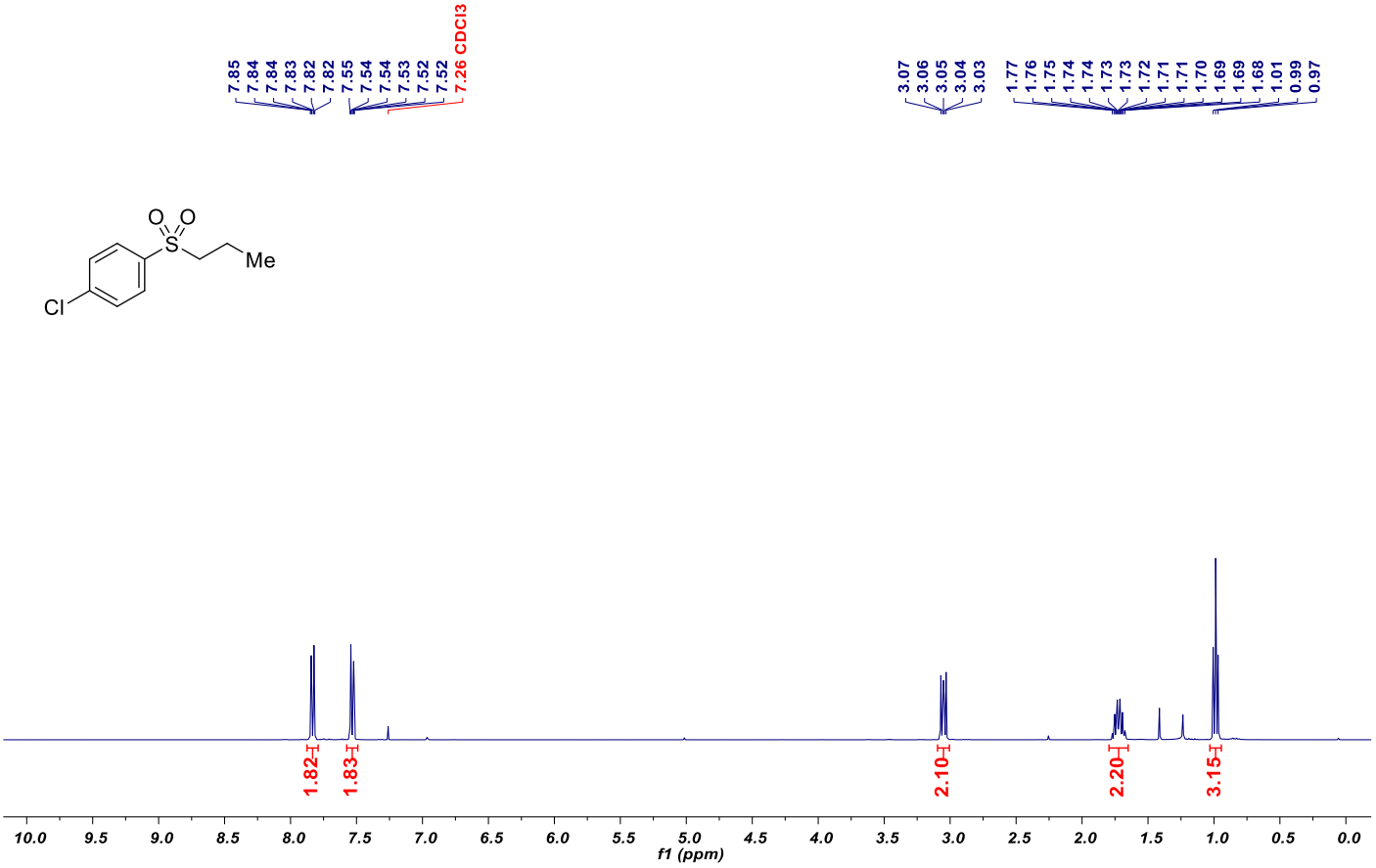


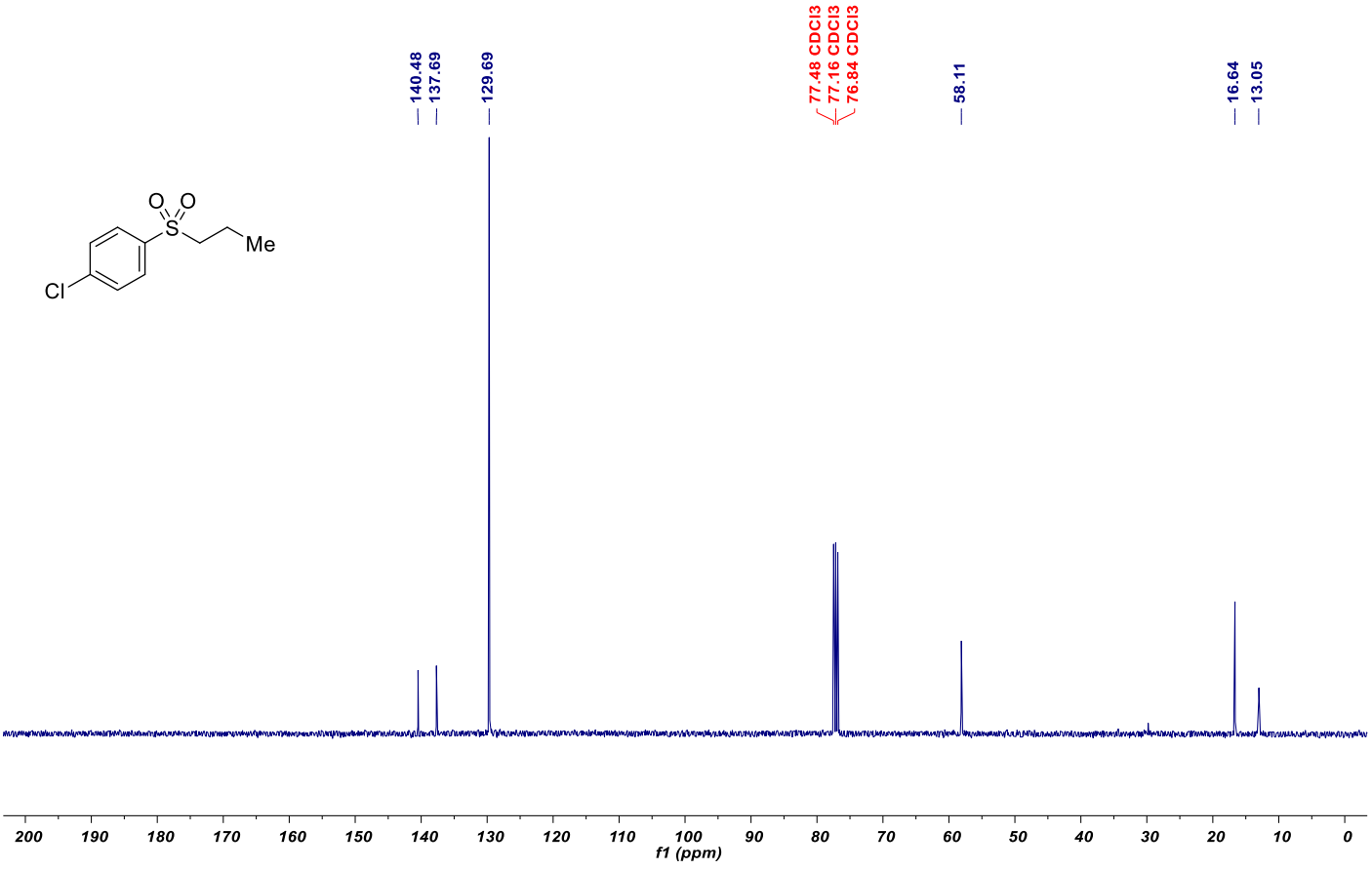


NMR spectrum of sulfone **7al**



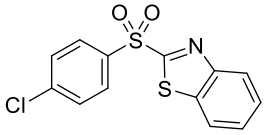
NMR spectrum of sulfone **8a**

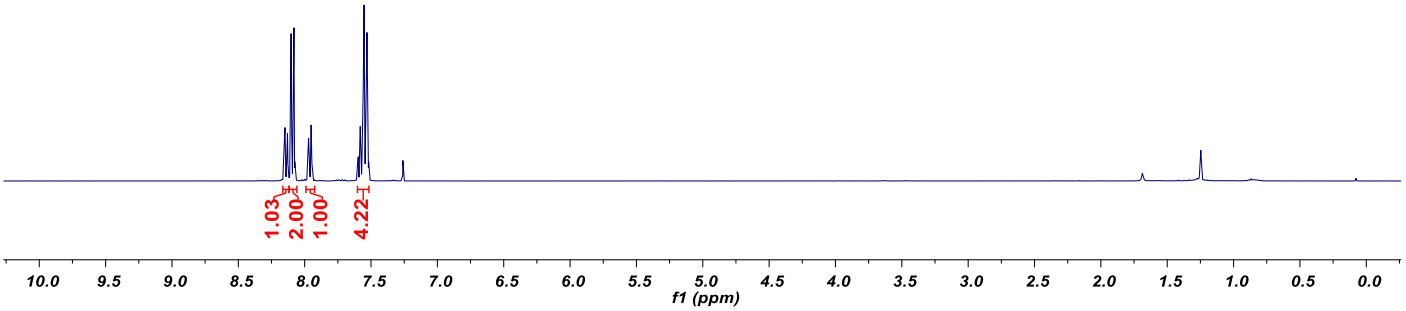


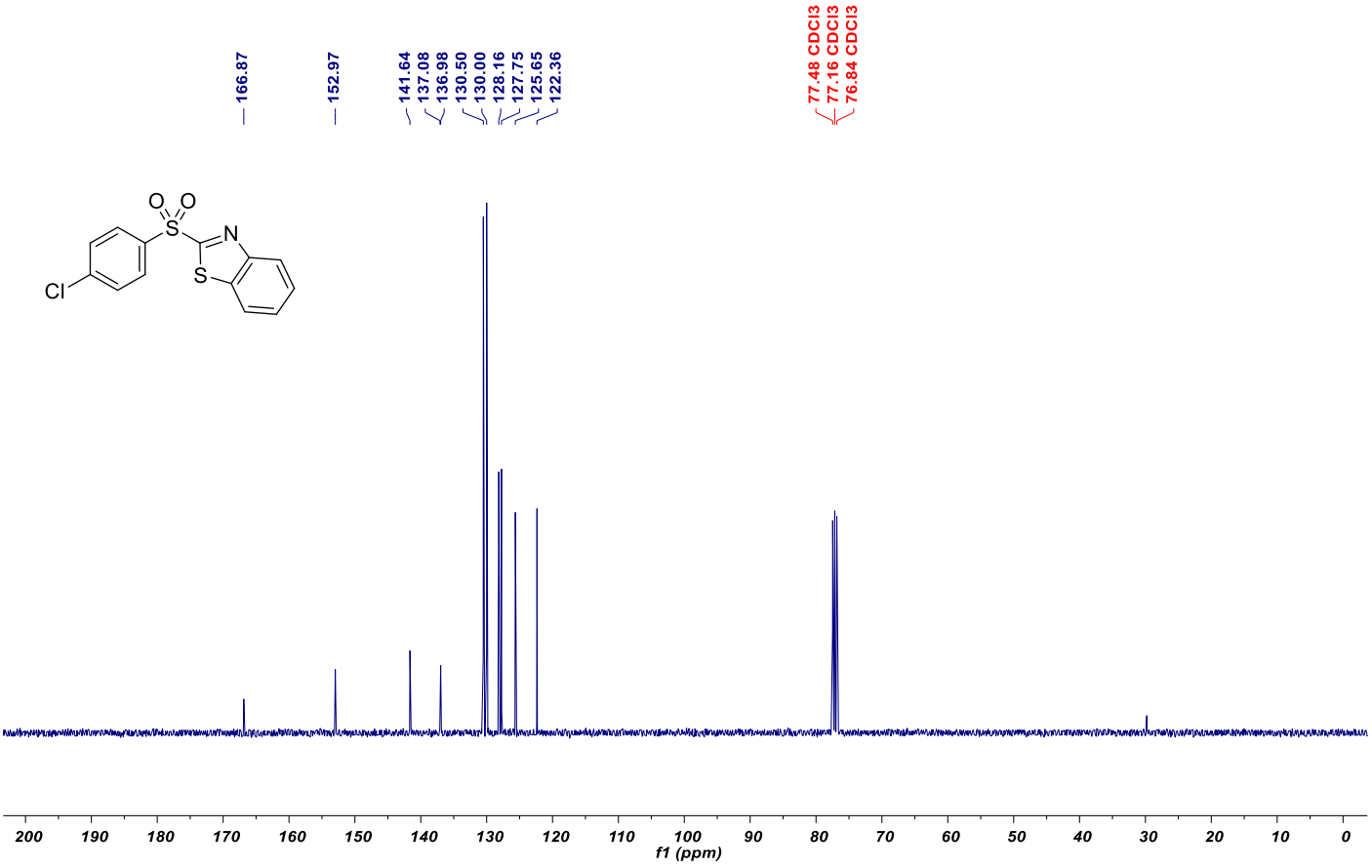


NMR spectrum of sulfone **8b**

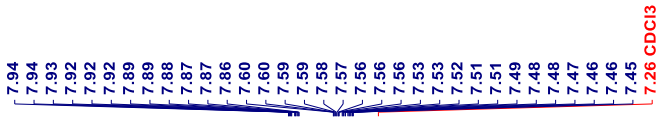


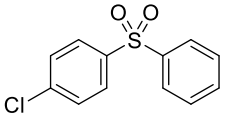


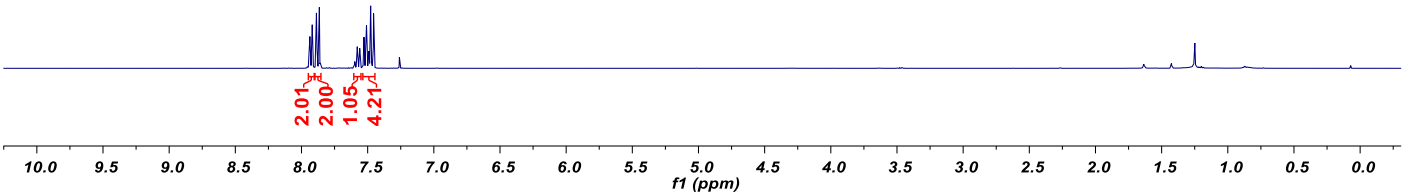




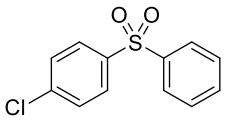
NMR spectrum of sulfone **8c**

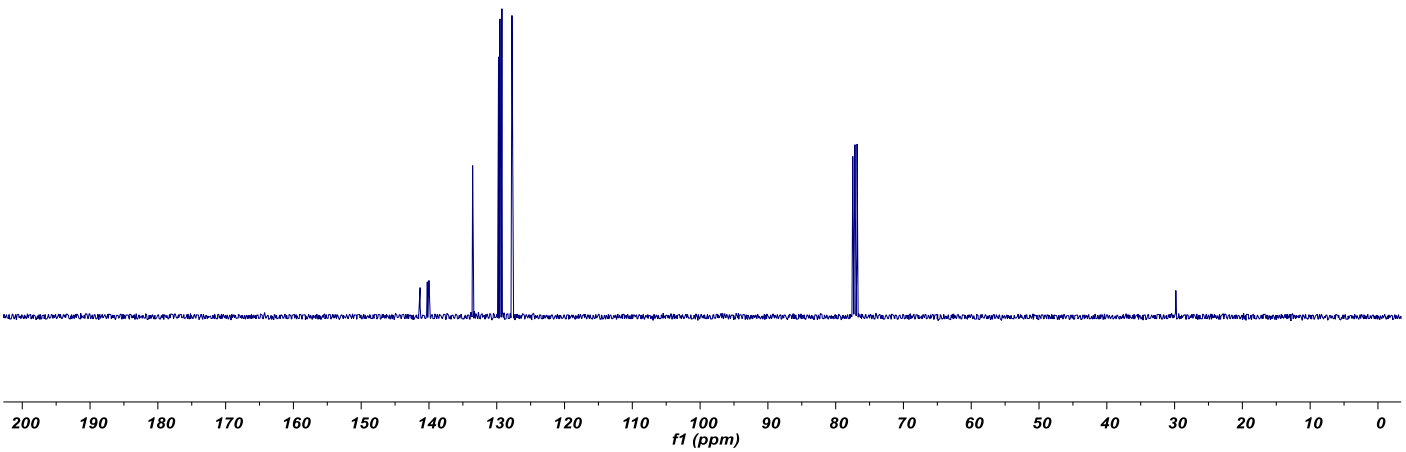




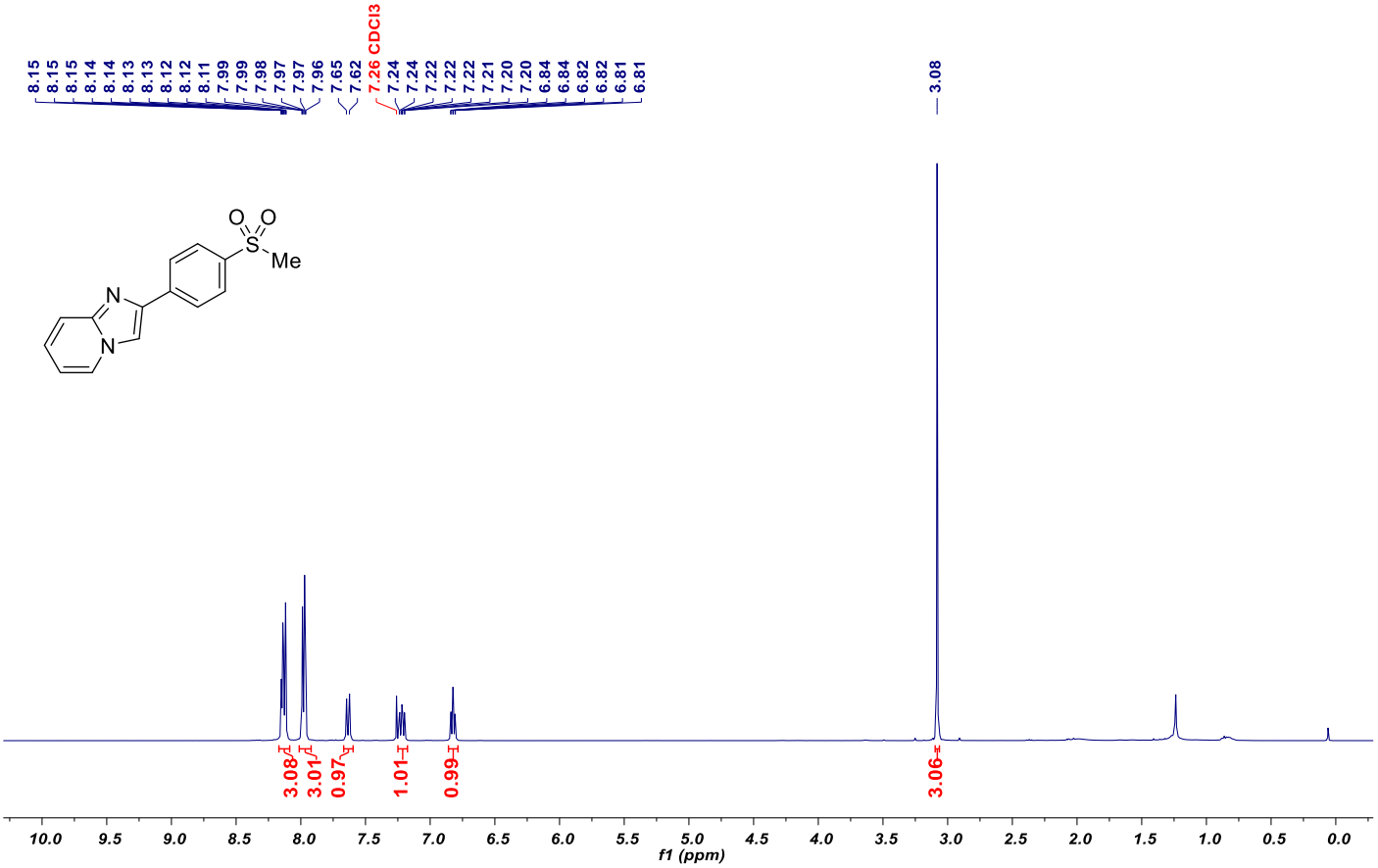


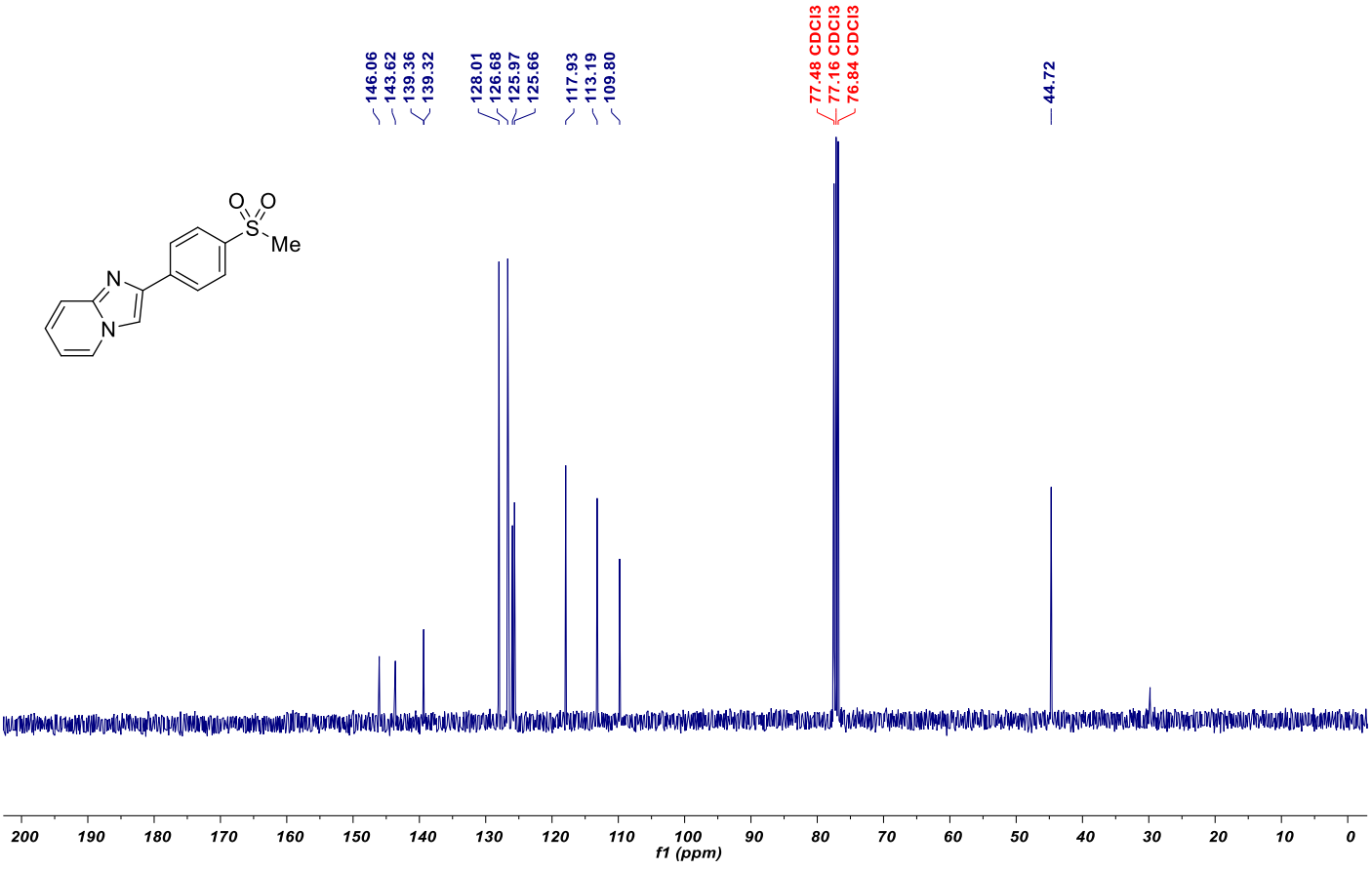




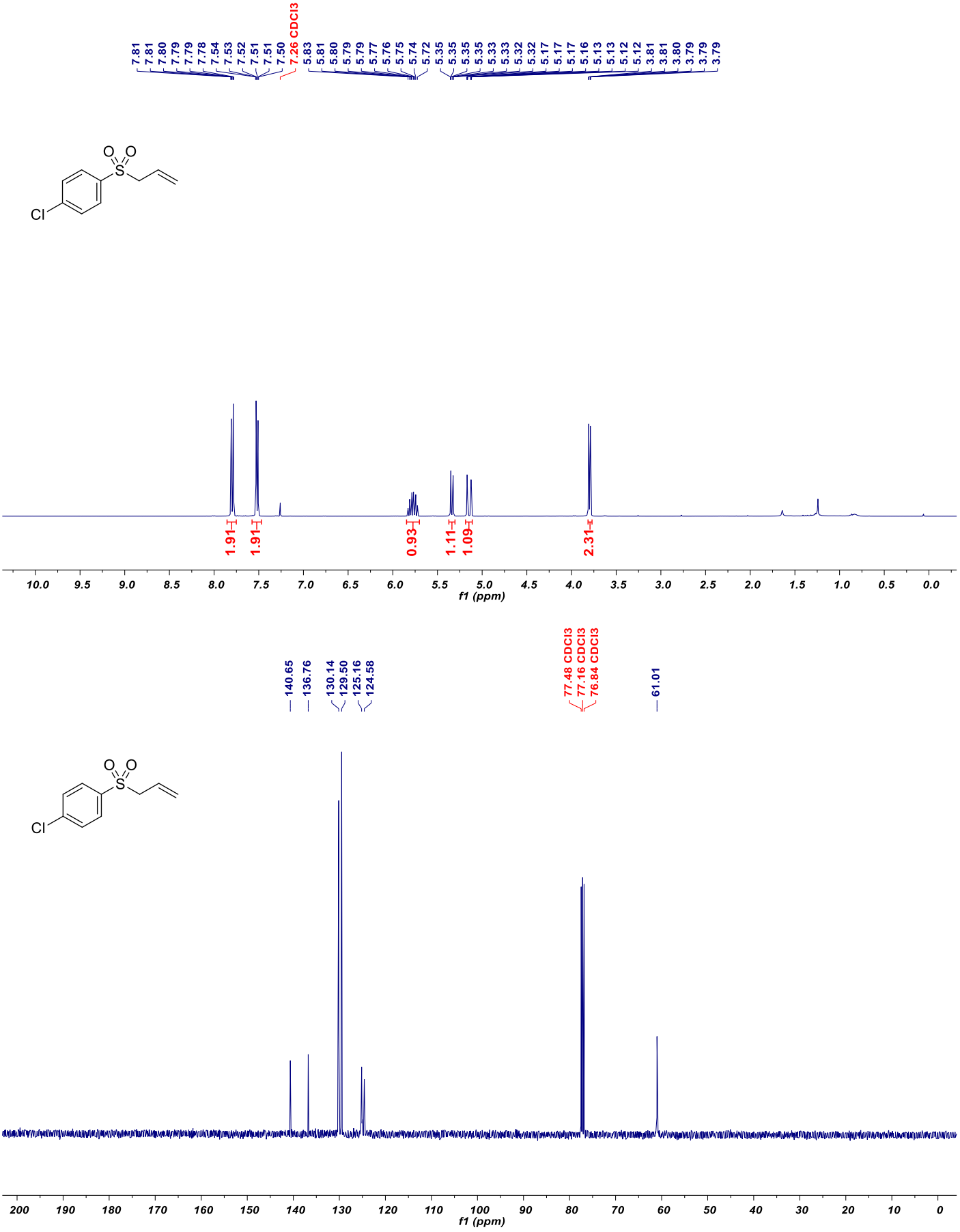


NMR spectrum of sulfone **8d**

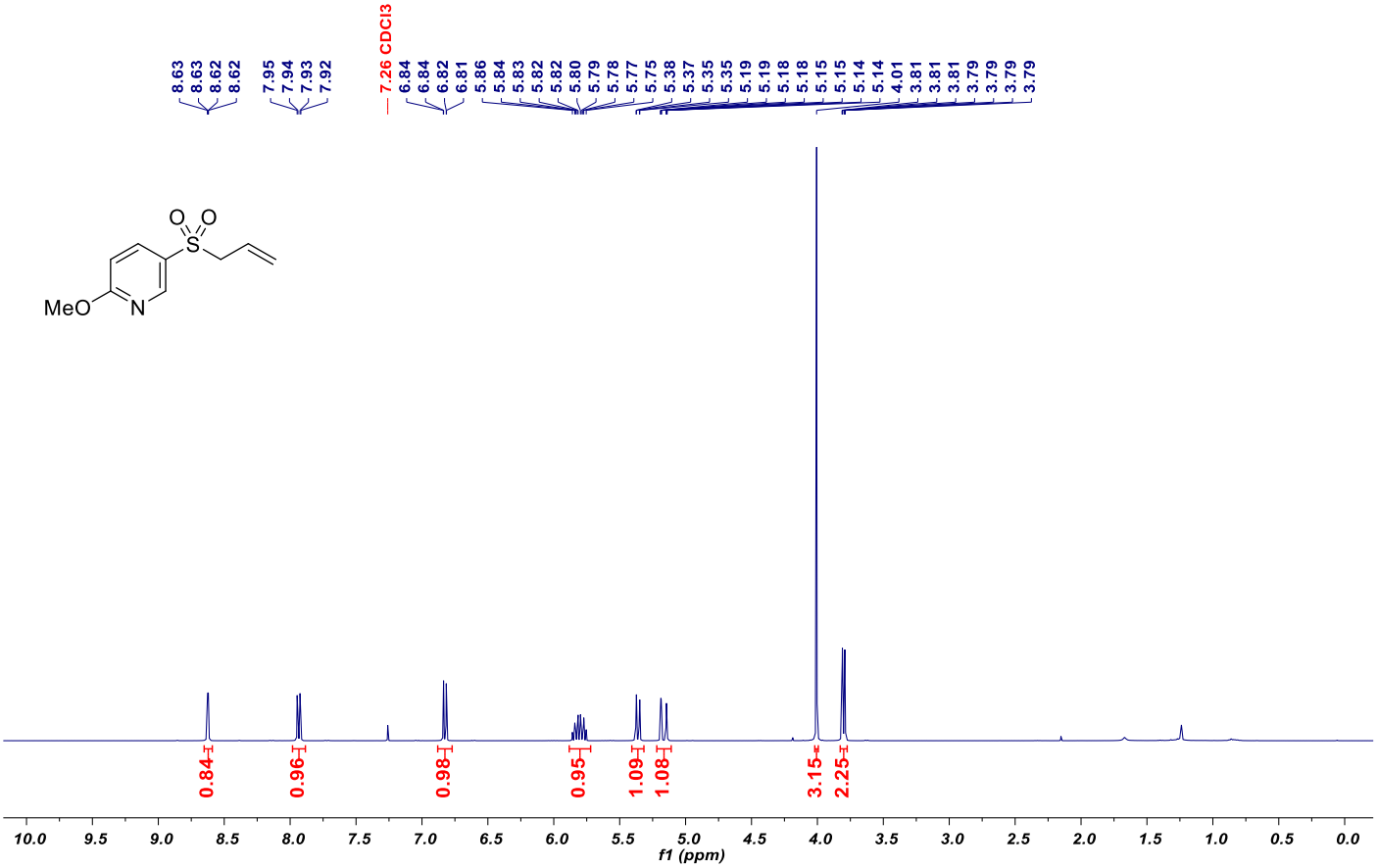


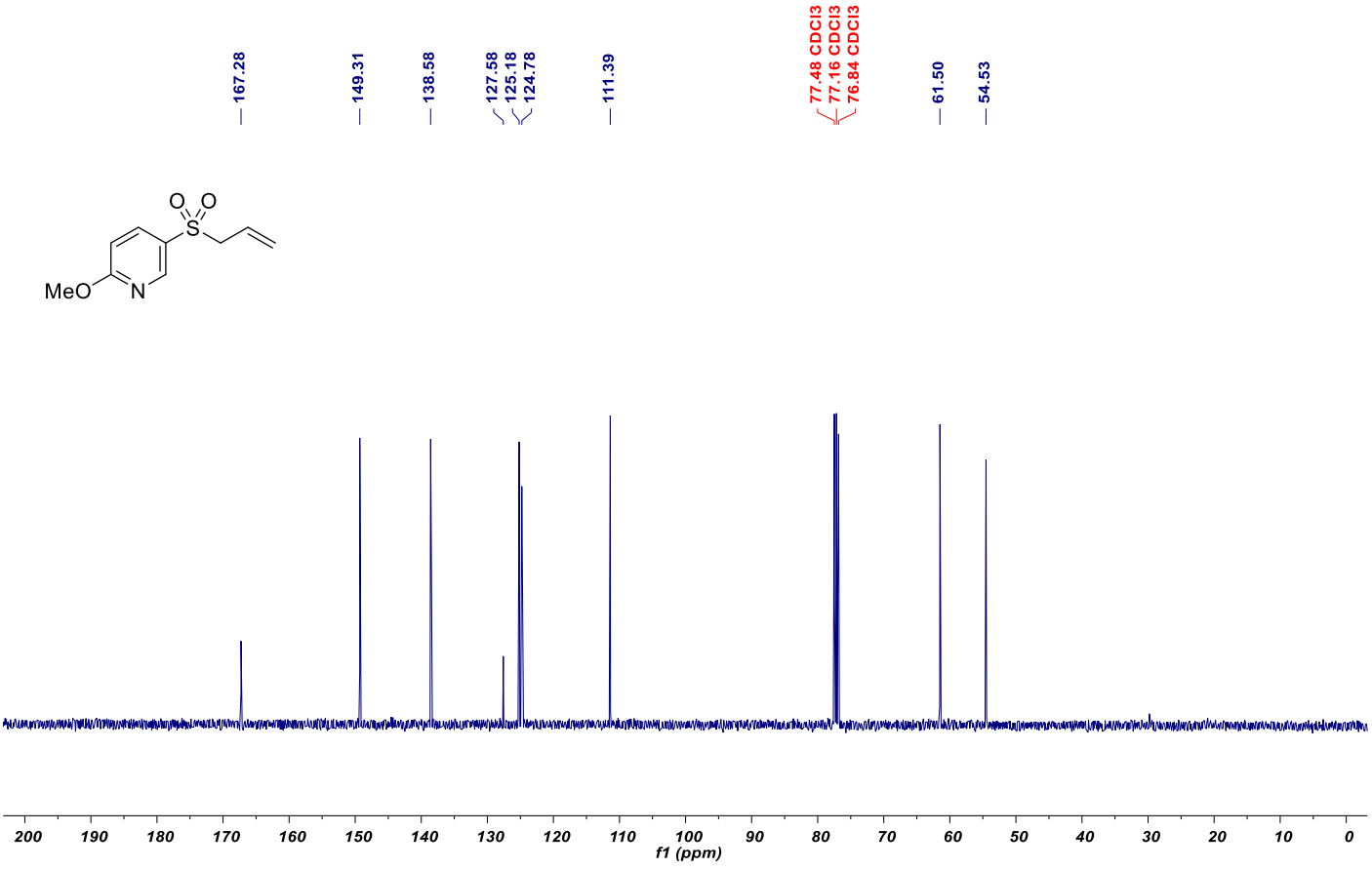


NMR spectrum of sulfone **8e**

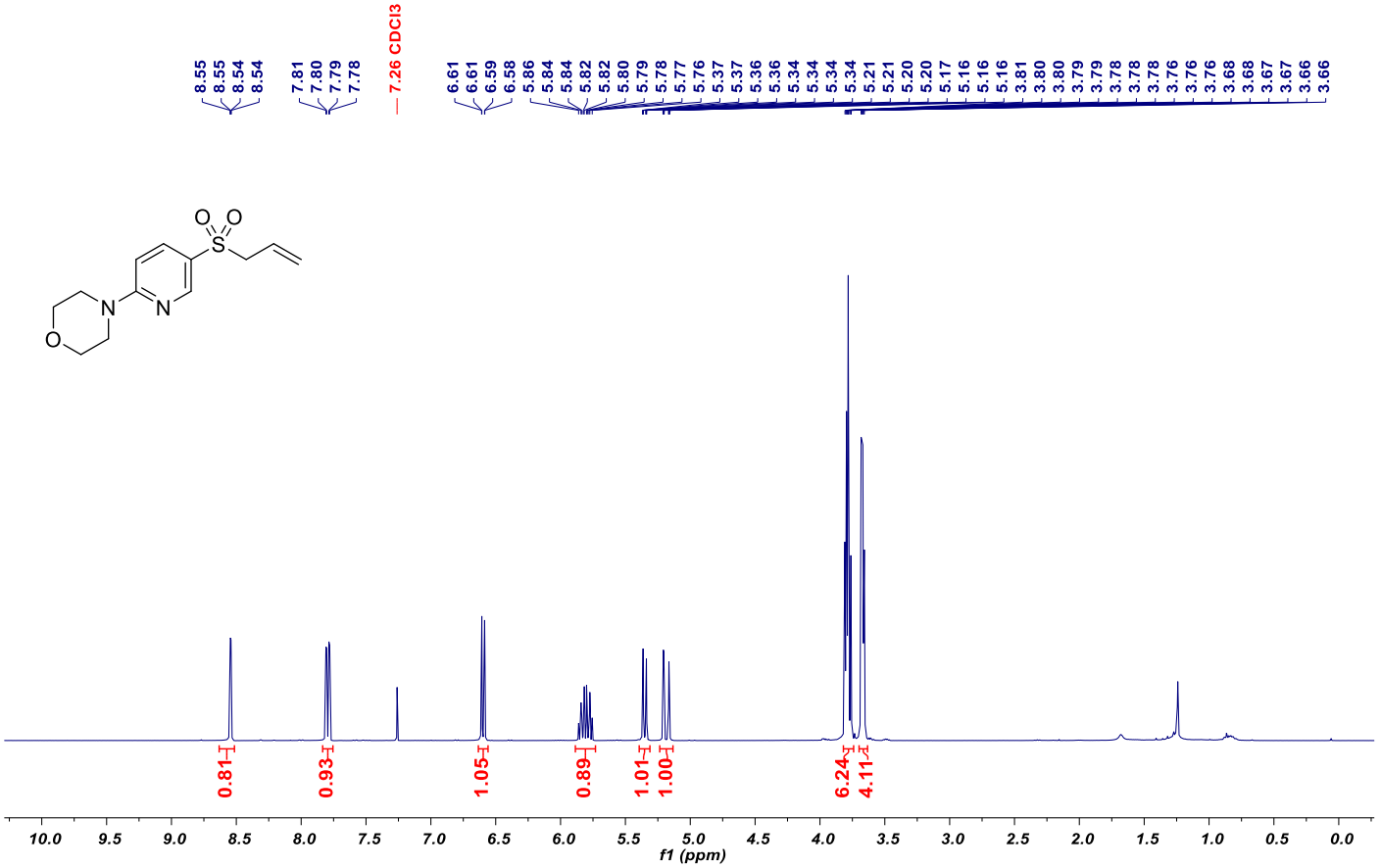


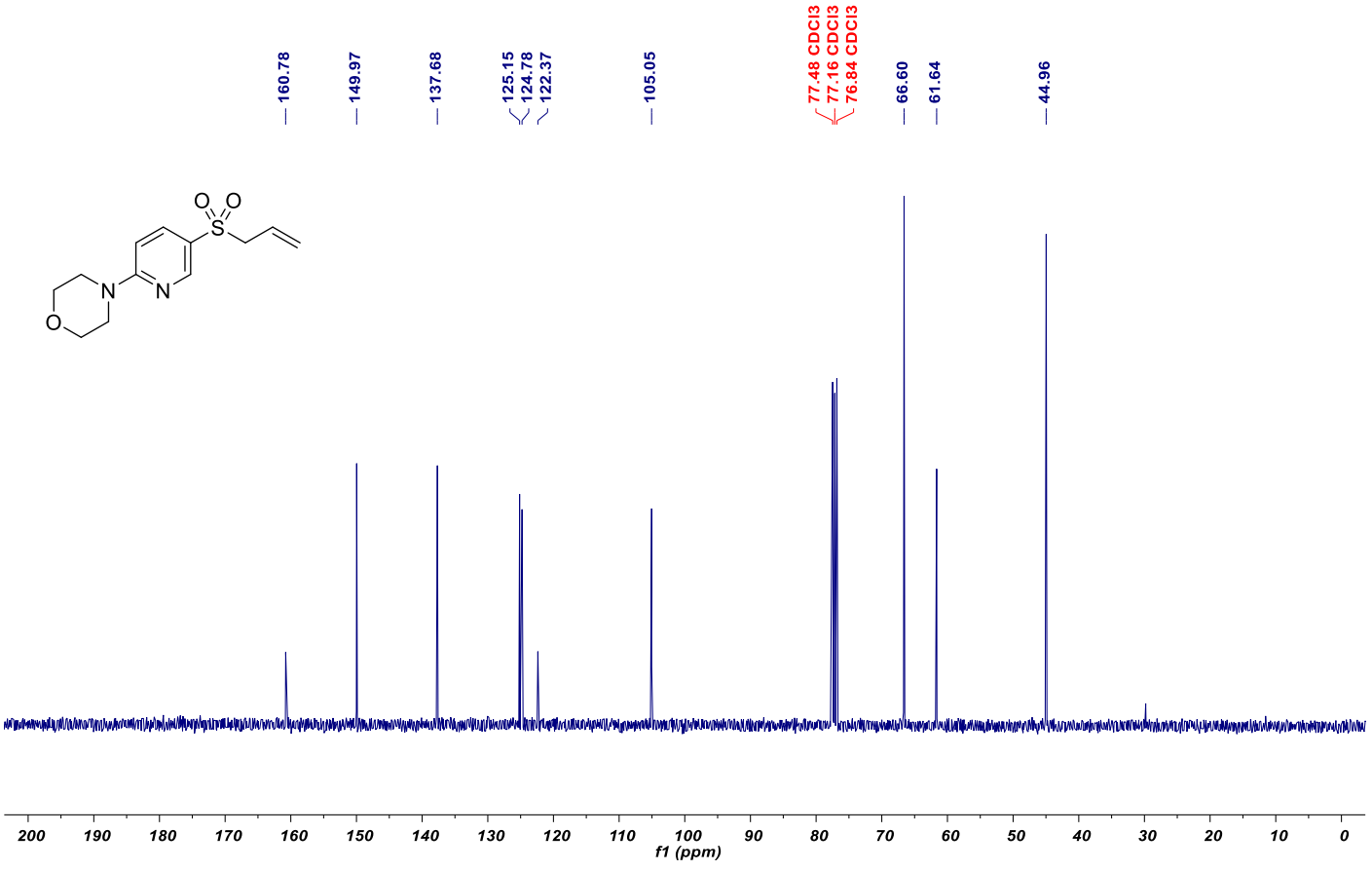
NMR spectrum of sulfone **8f**



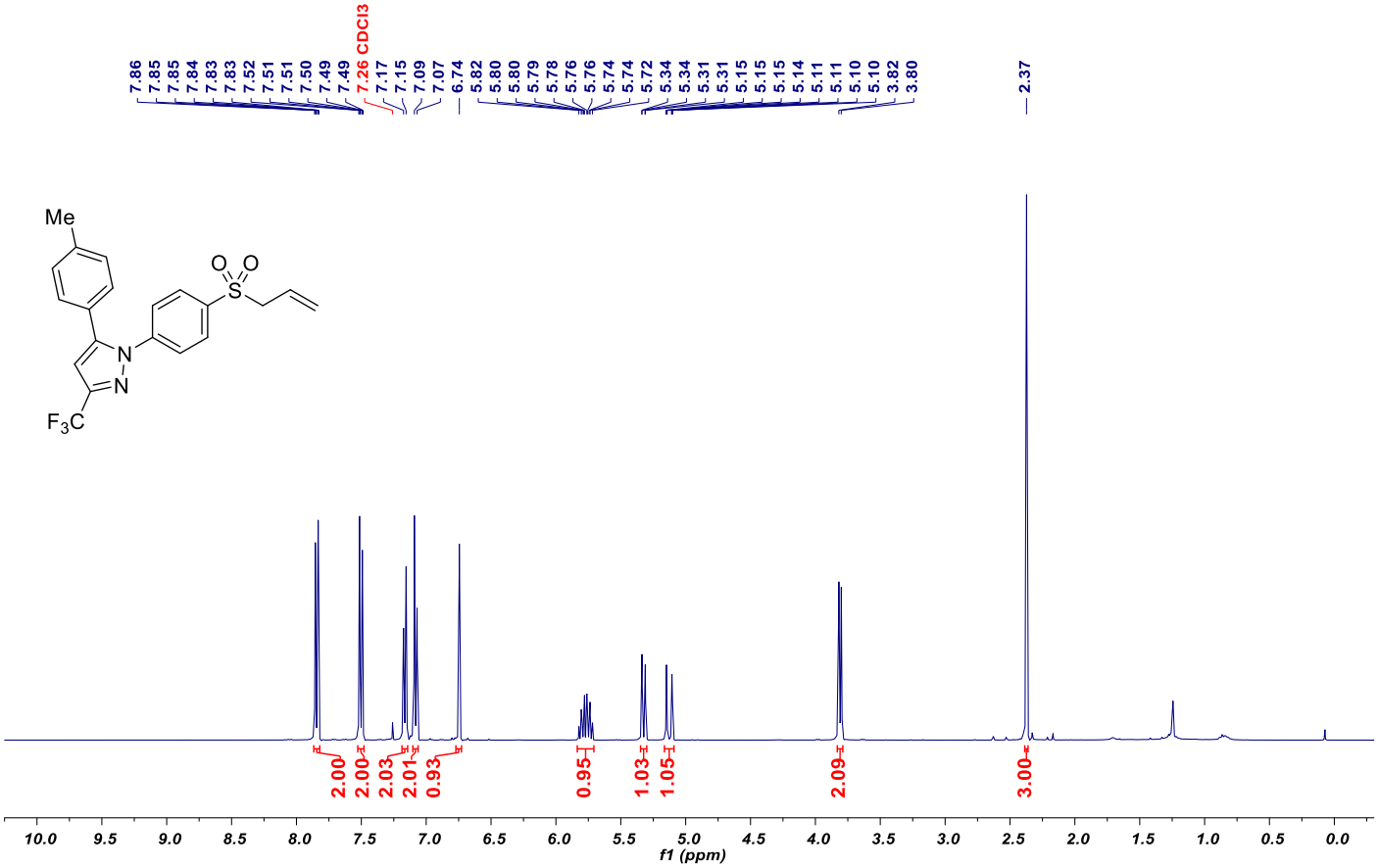


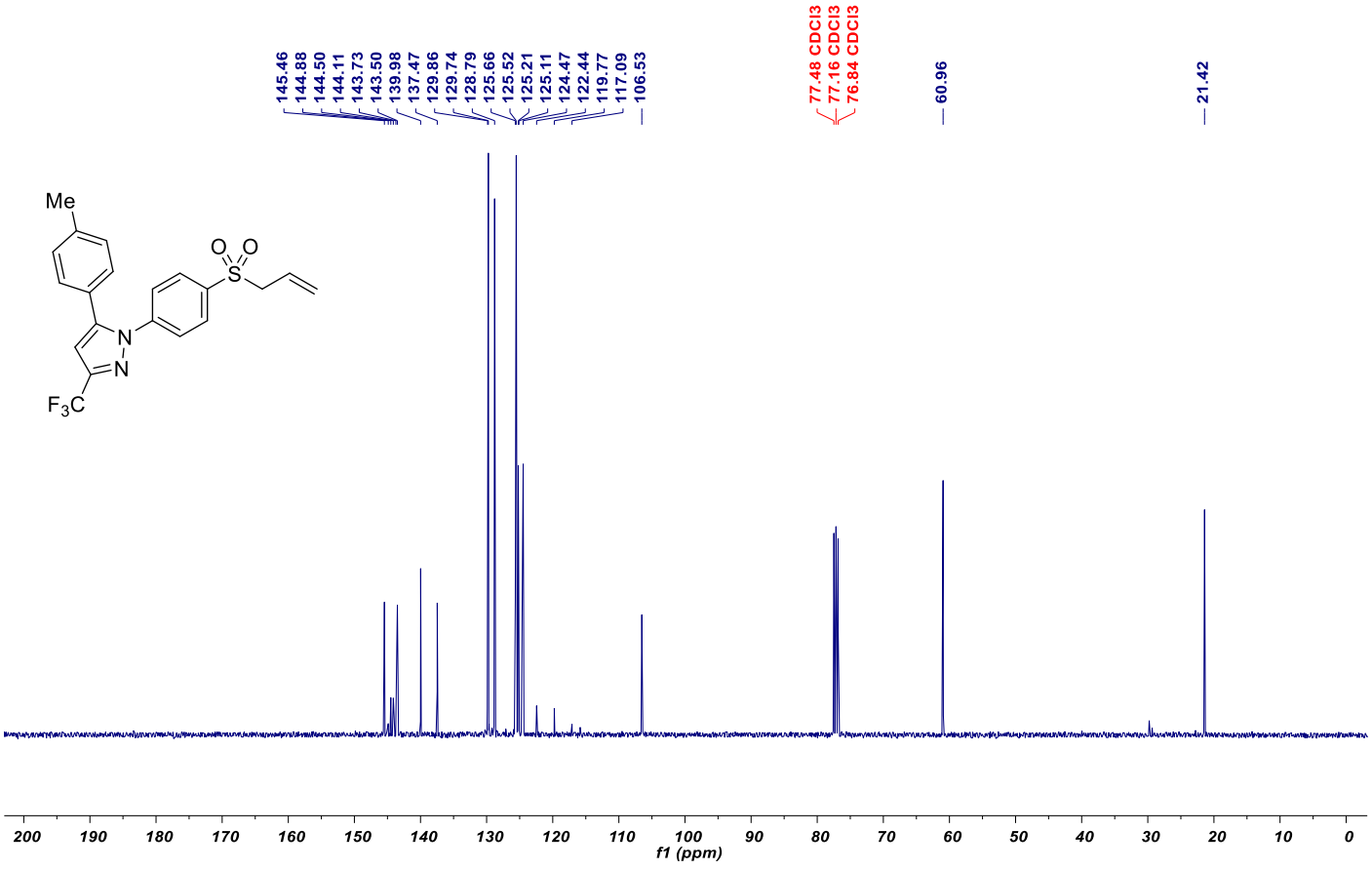
NMR spectrum of sulfone **8g**

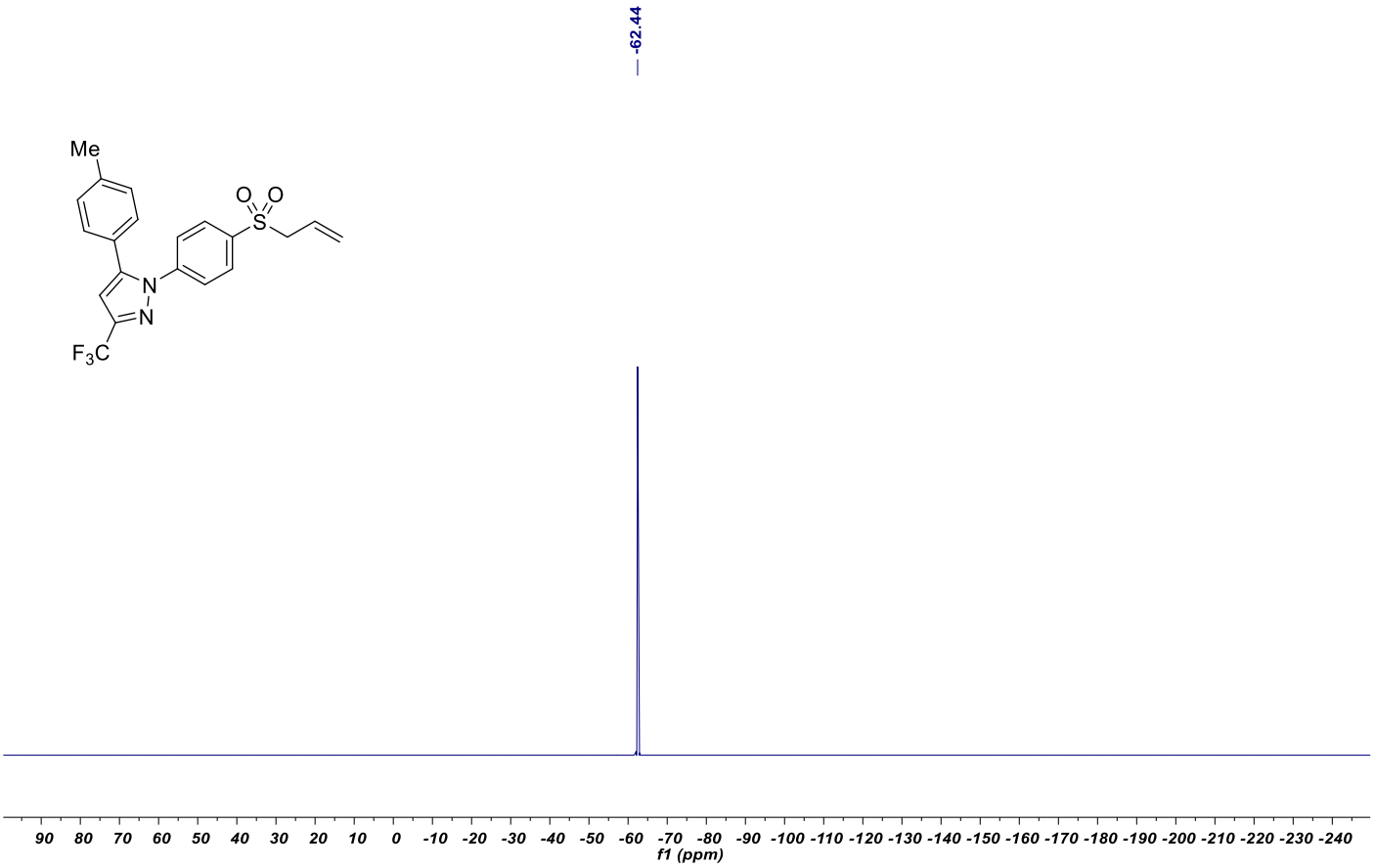




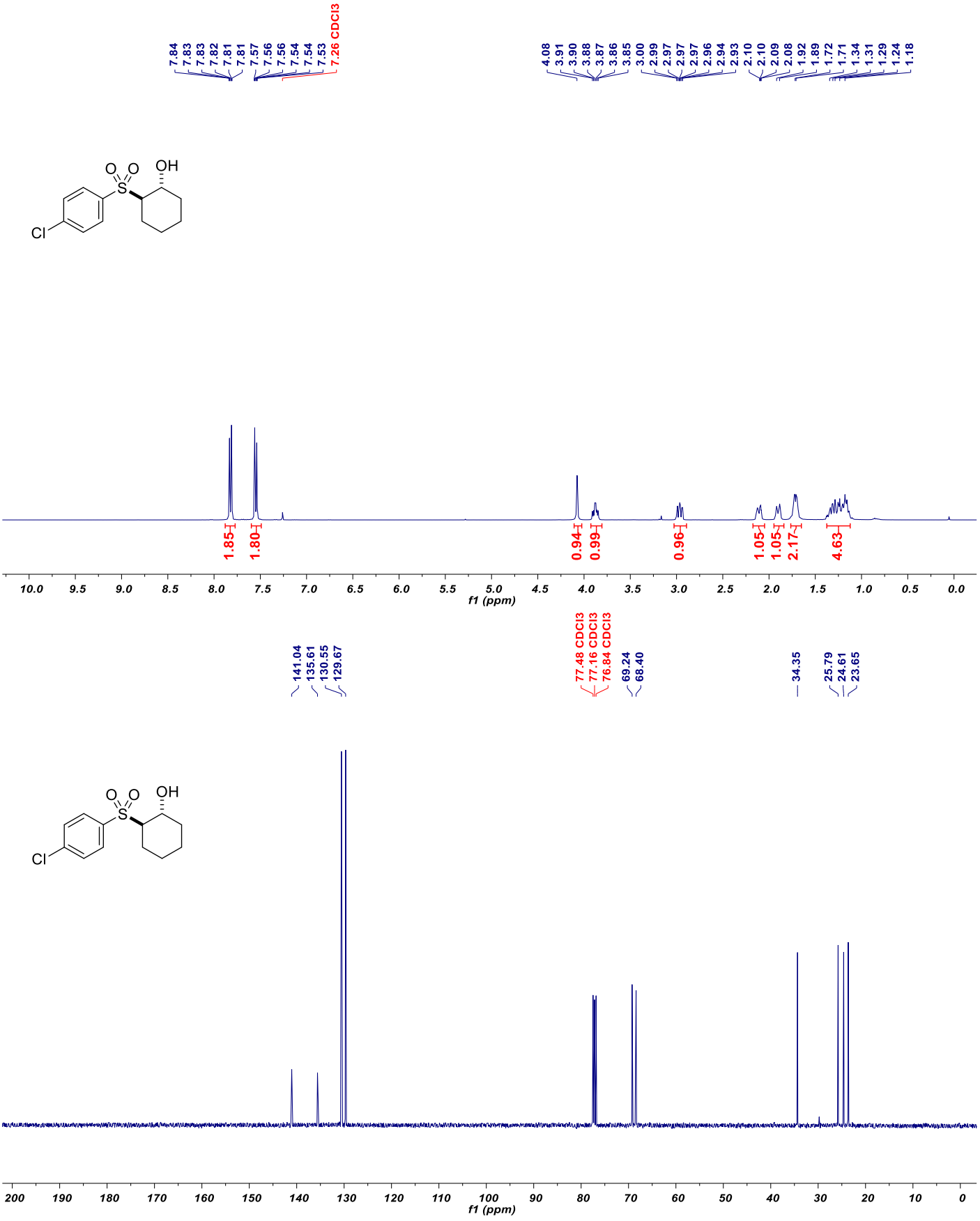
NMR spectrum of sulfone **8h**



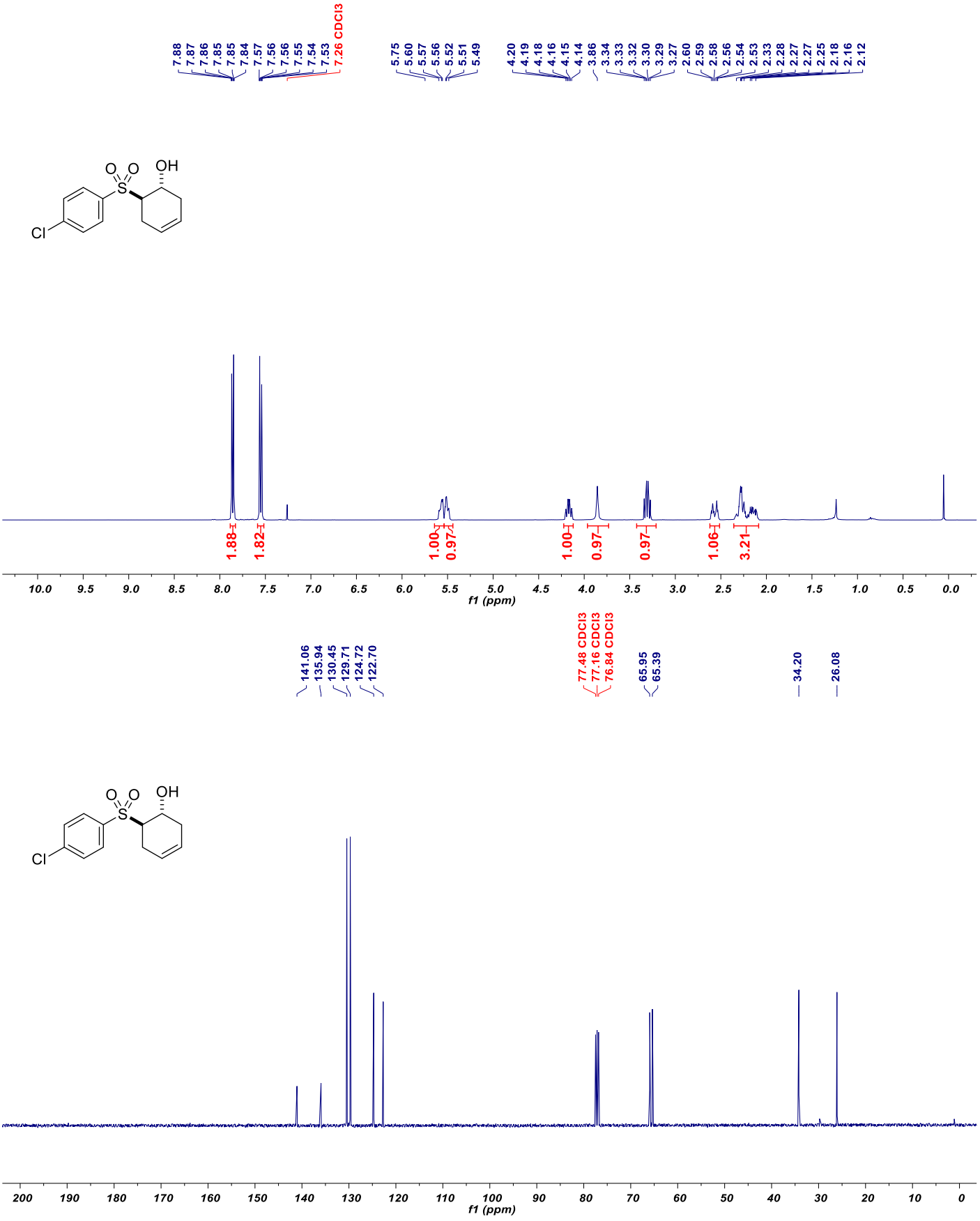



-62.44
Me
O
O
S
N
N
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

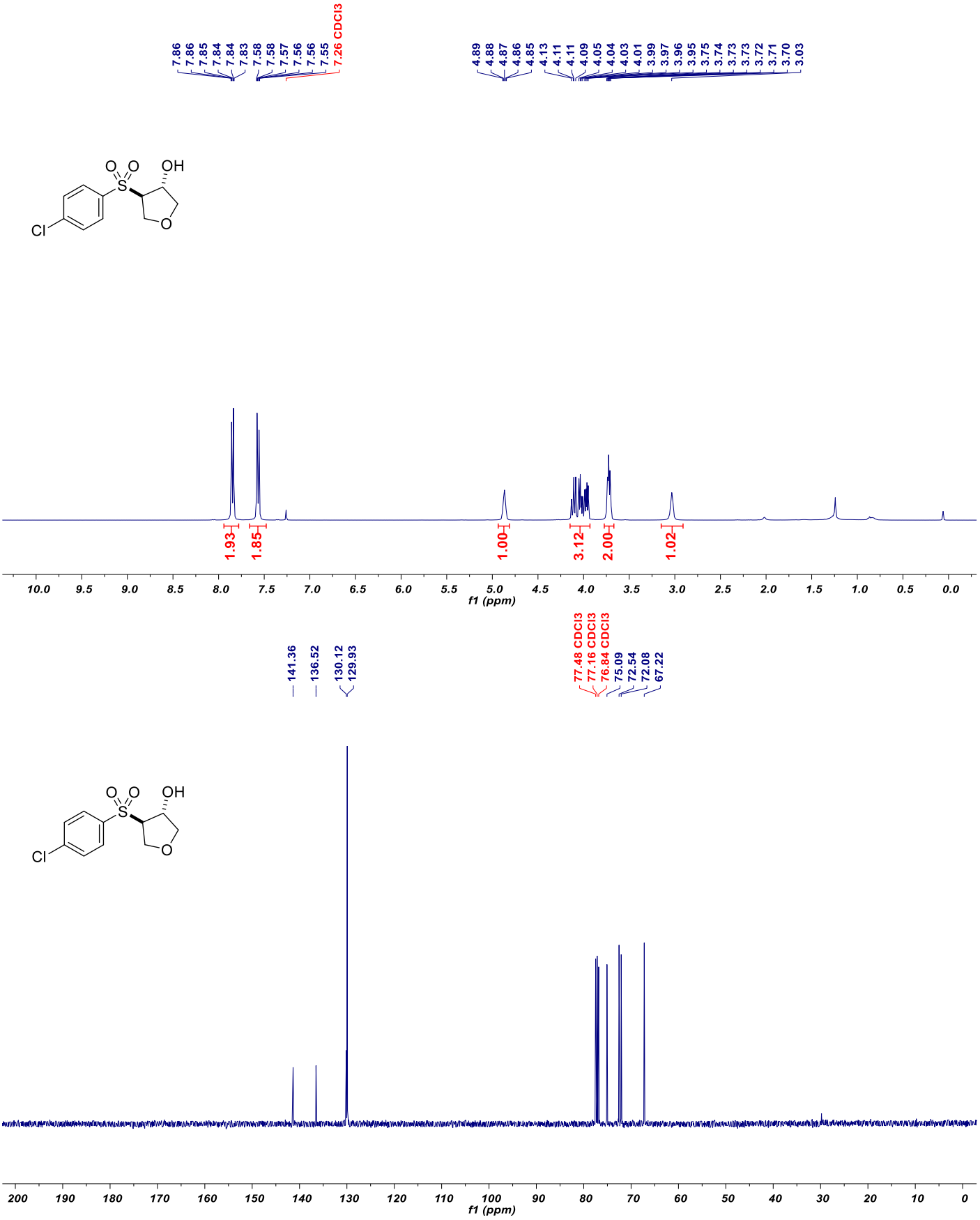
NMR spectrum of β-hydroxysulfone **8i**



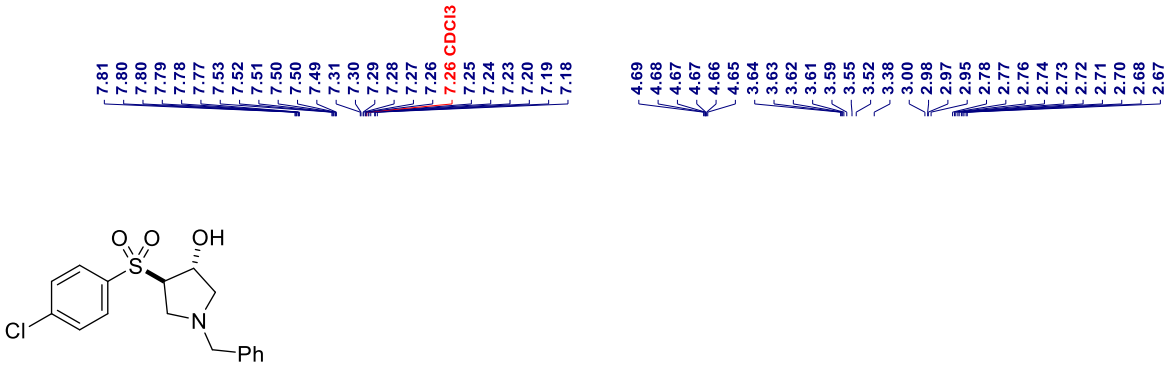
NMR spectrum of β-hydroxysulfone **8j**

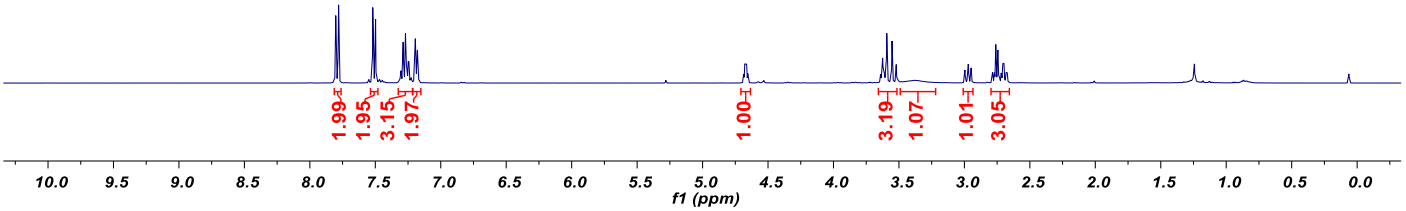


NMR spectrum of β-hydroxysulfone **8k**

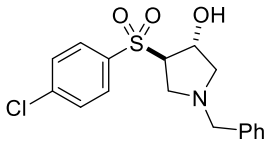


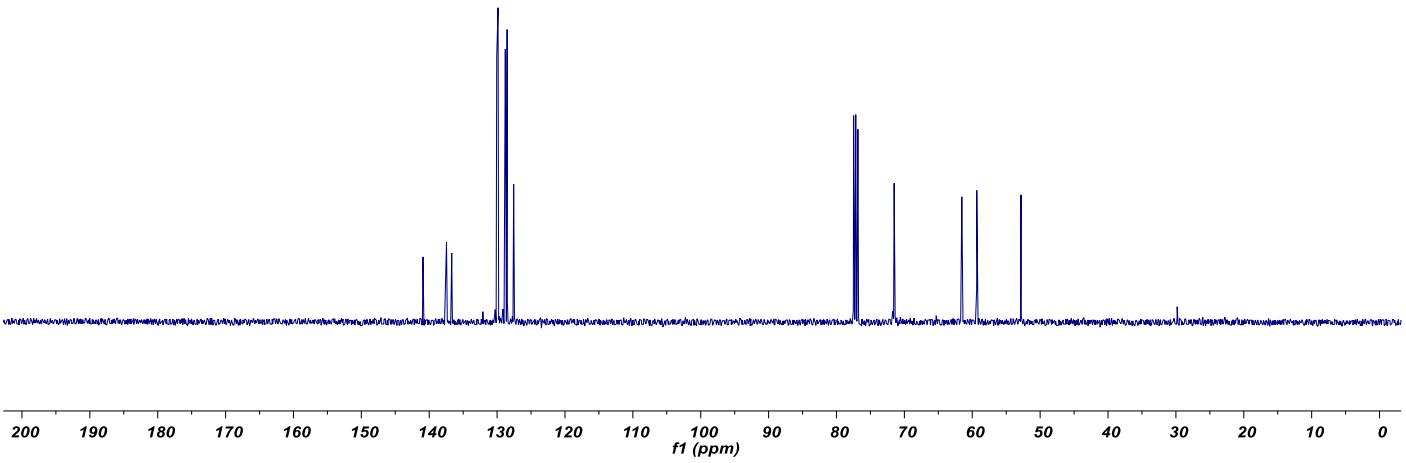
NMR spectrum of β-hydroxysulfone **8l**



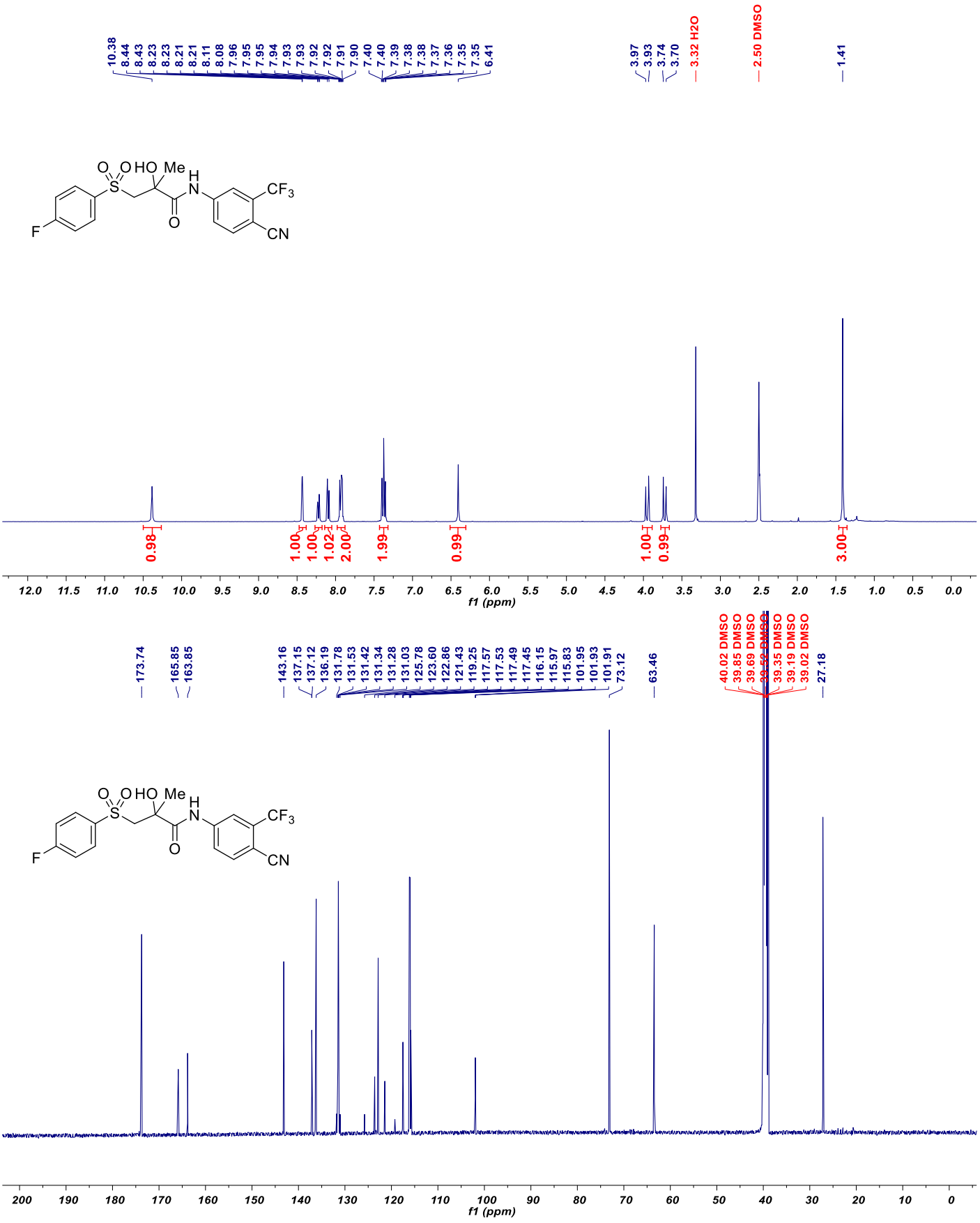


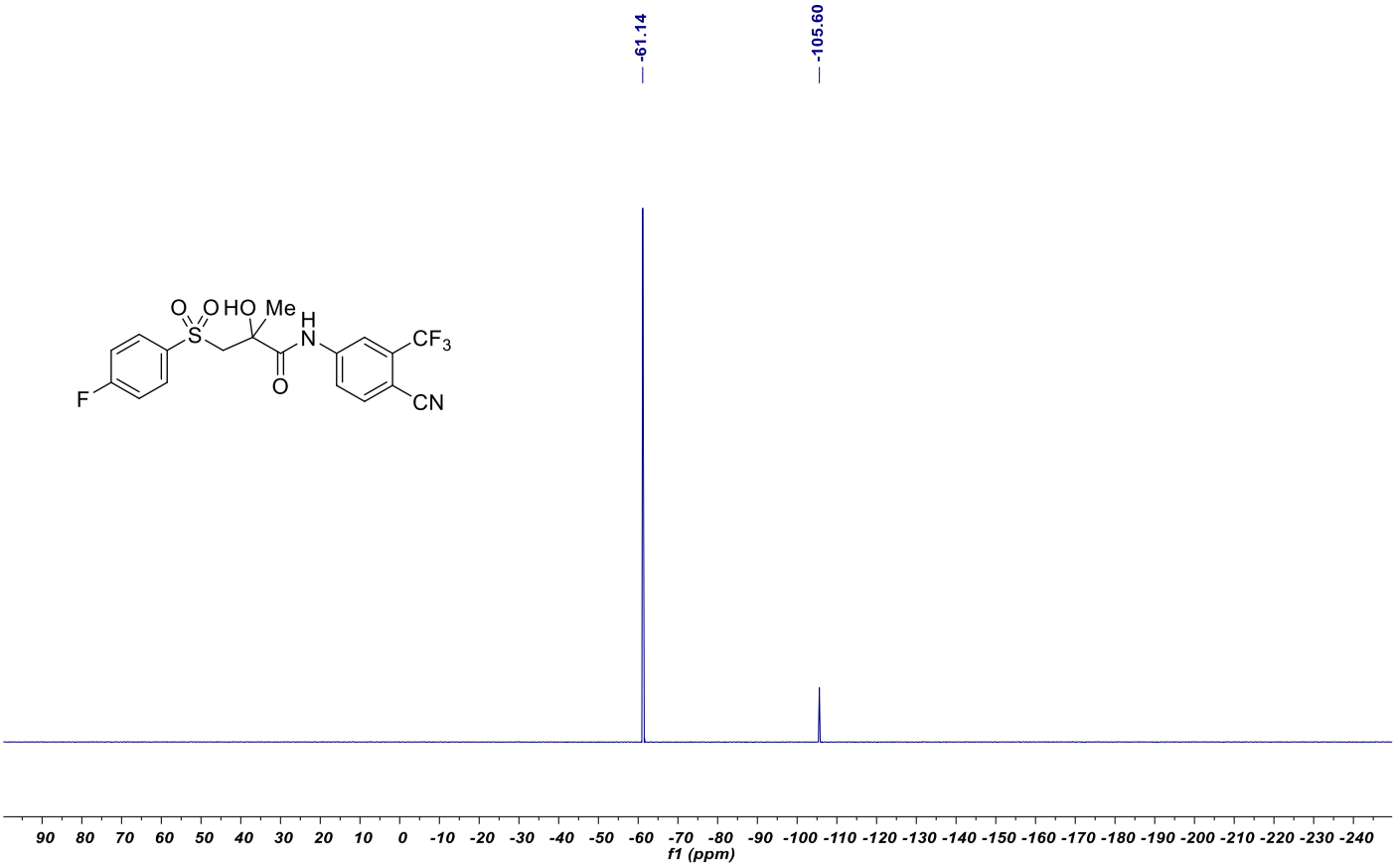




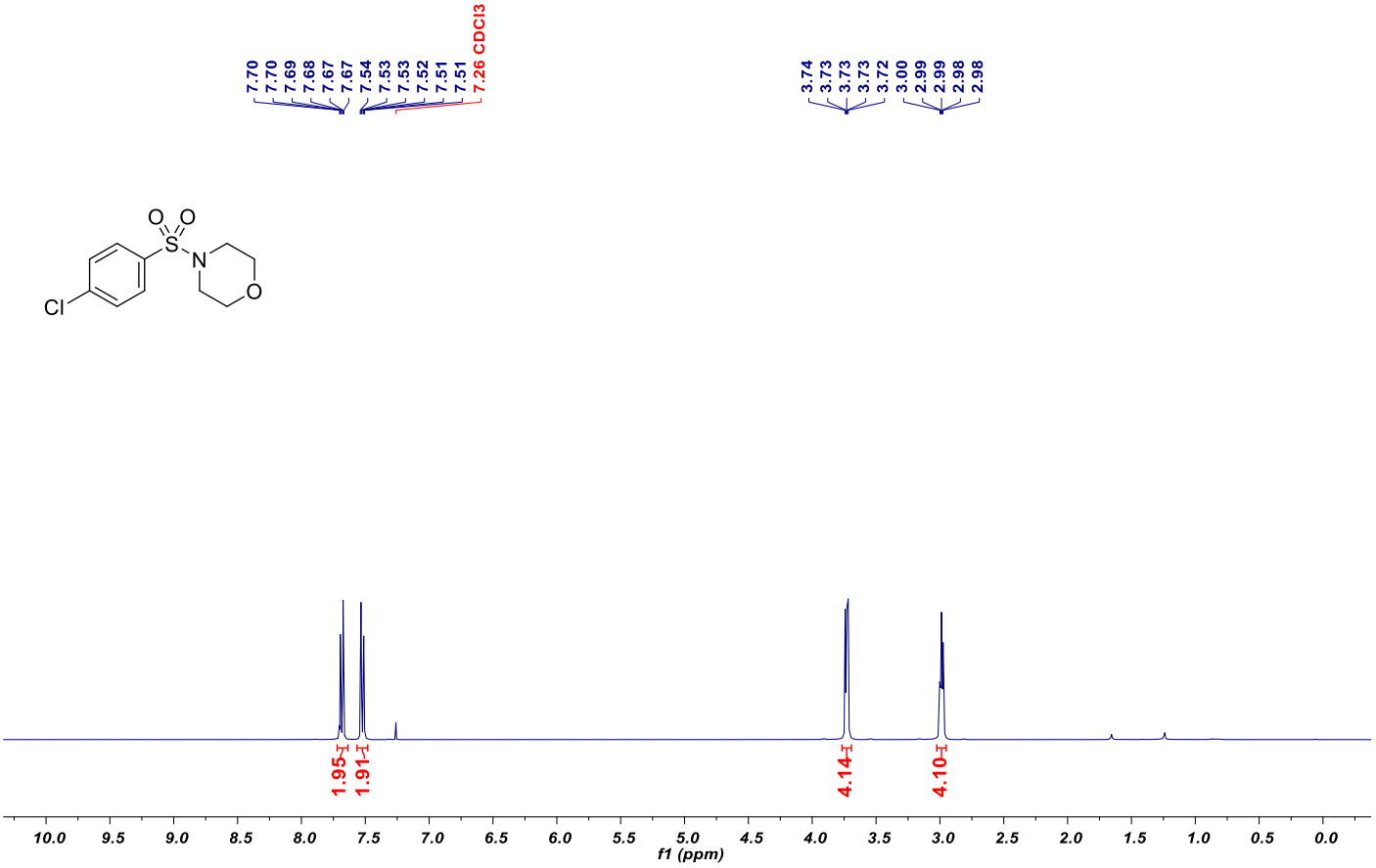


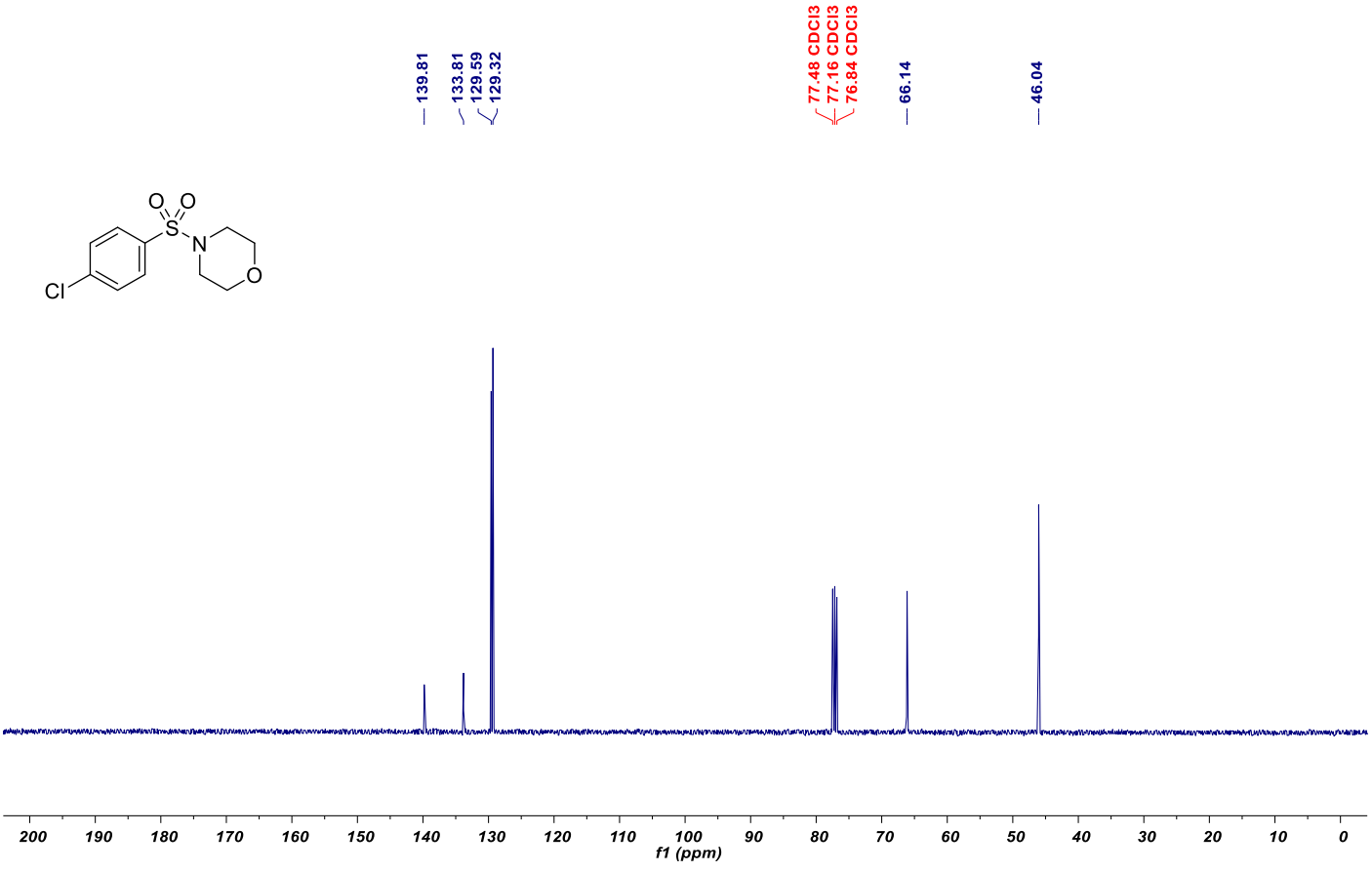
NMR spectrum of β-hydroxysulfone **8m**



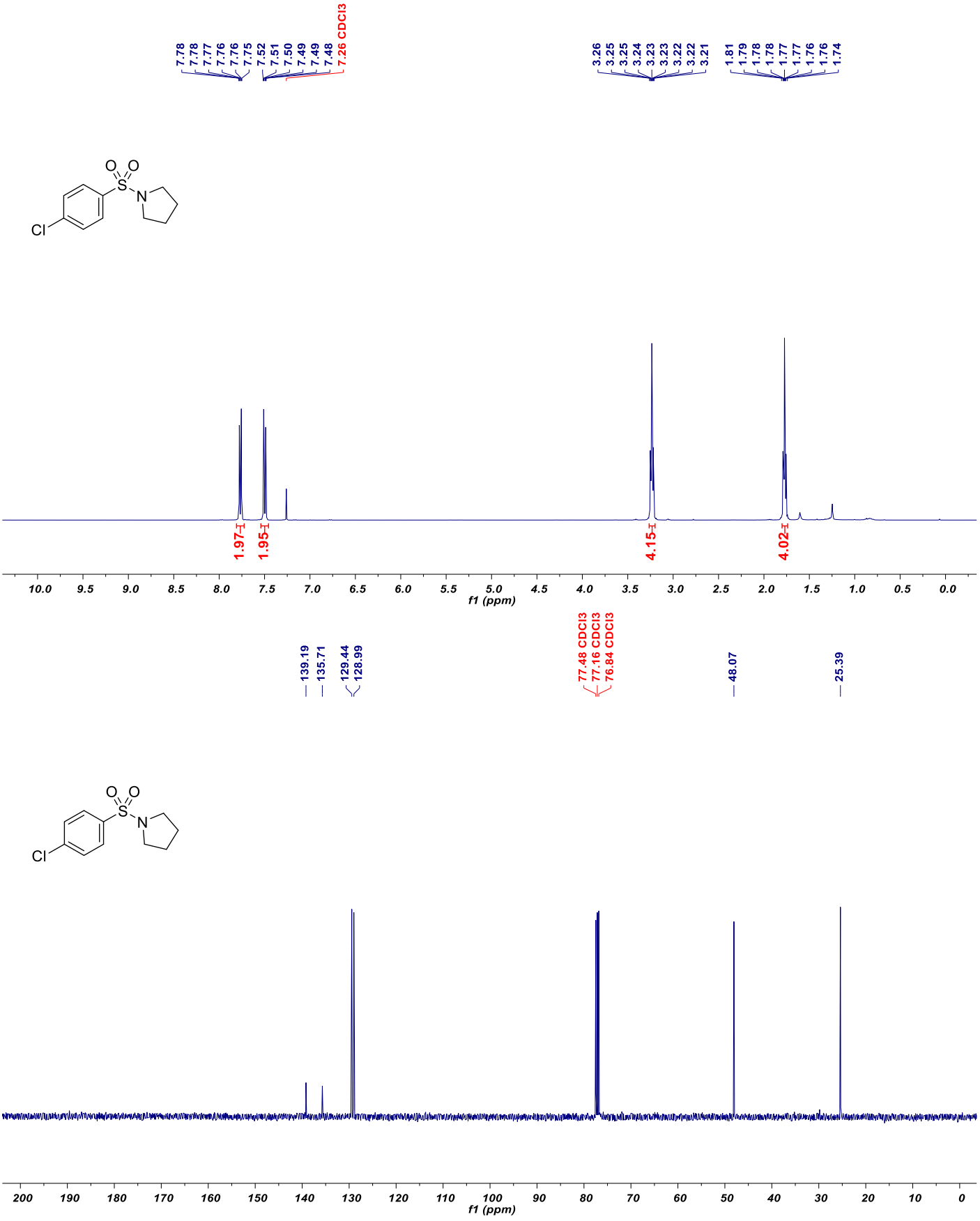

-61.14
-105.60
O
O
HO
Me
S
H
N
CF3
F
O
CN
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

NMR spectrum of sulfonamide **11a**

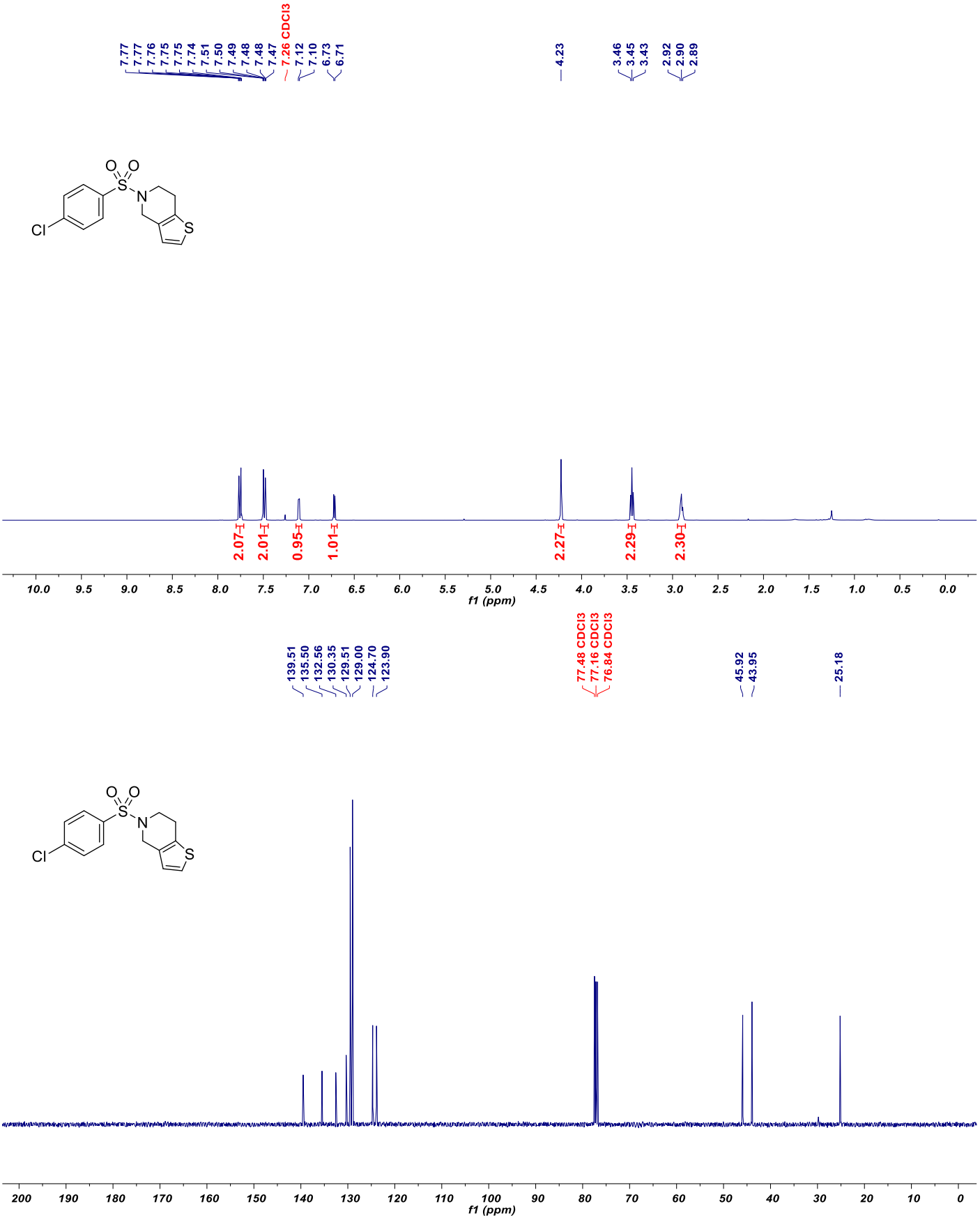




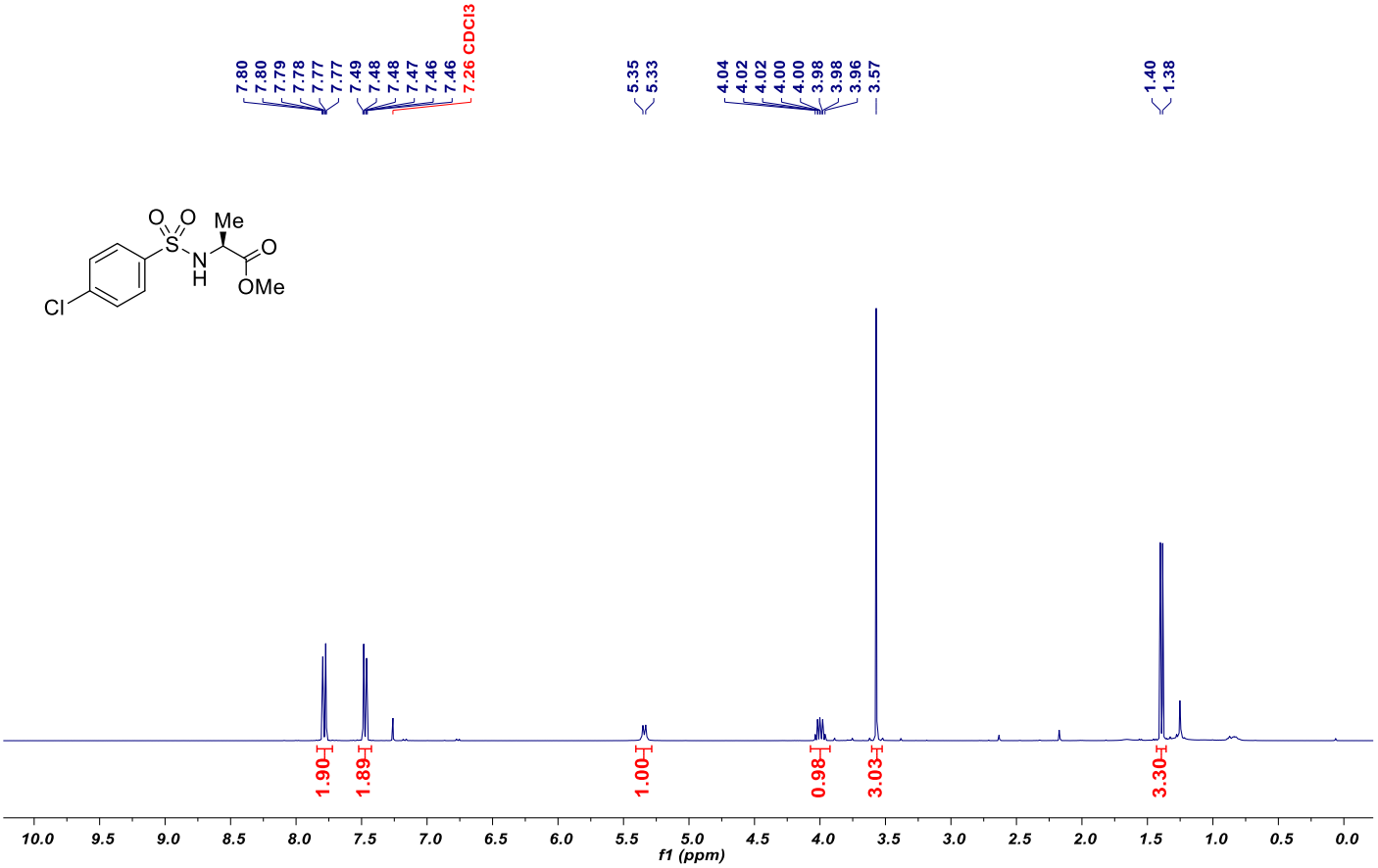
NMR spectrum of sulfonamide **11b**

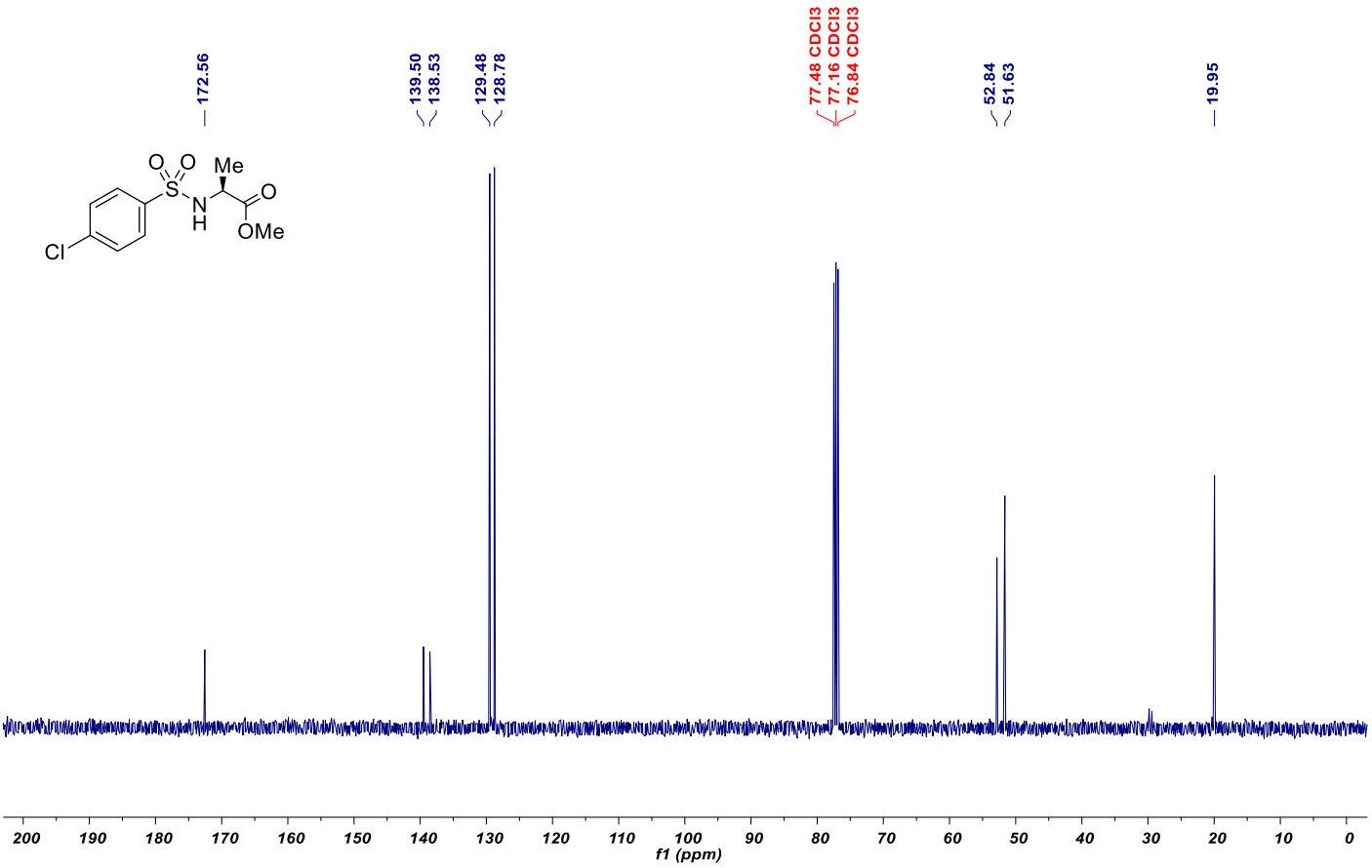


NMR spectrum of sulfonamide **11c**

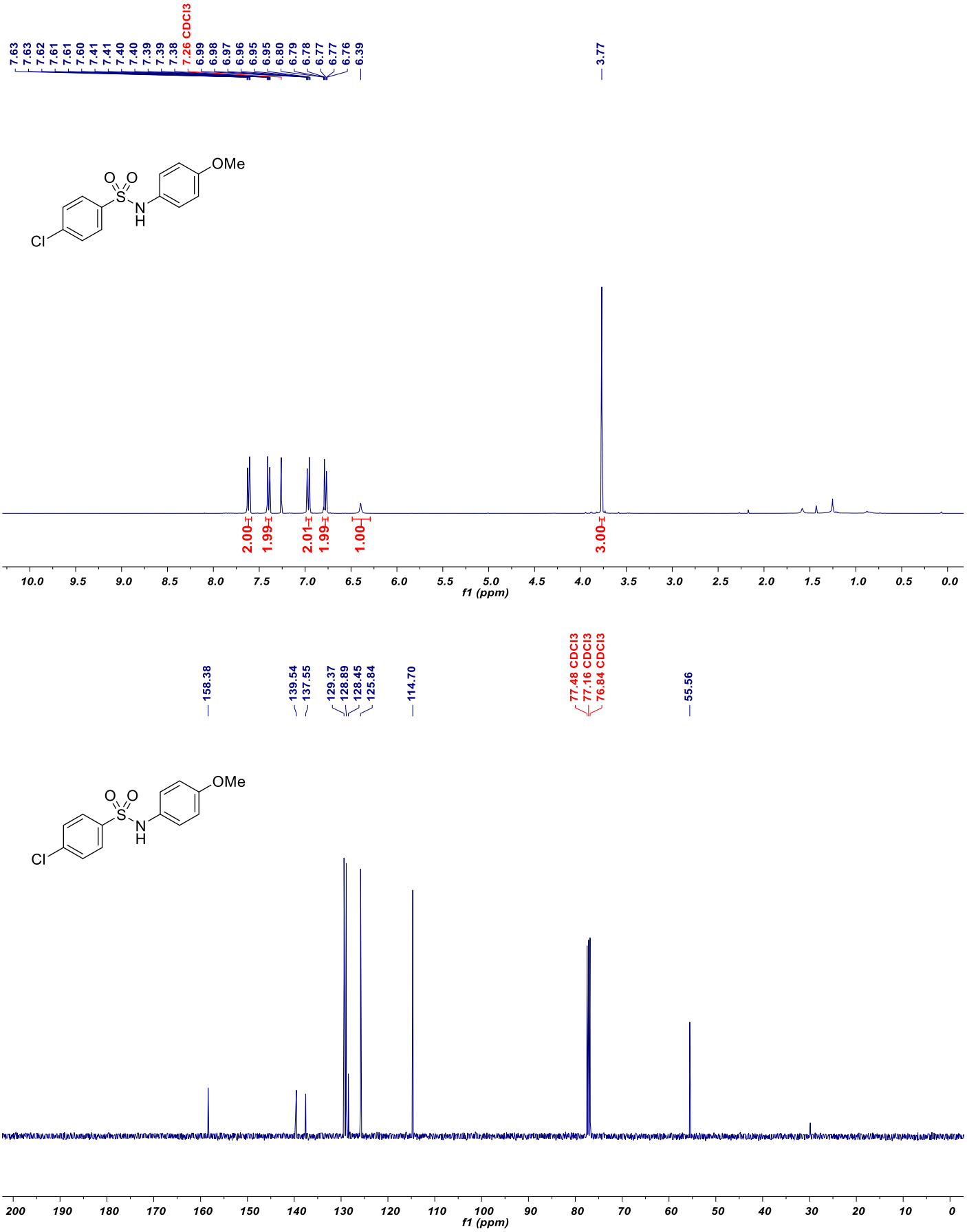


NMR spectrum of sulfonamide **11d**

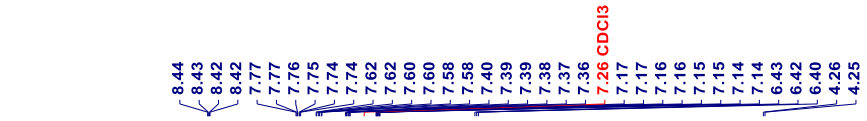


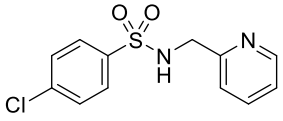


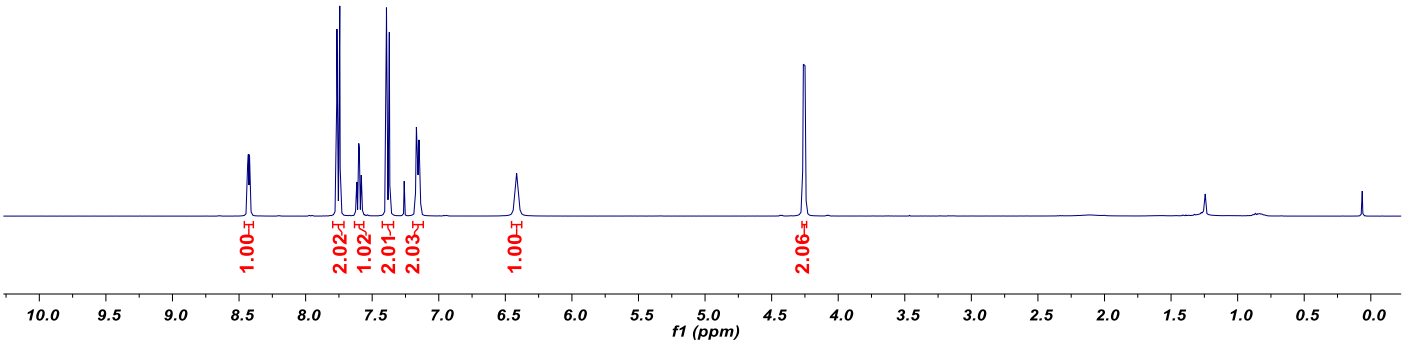
NMR spectrum of sulfonamide **11e**



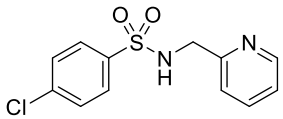
NMR spectrum of sulfonamide **11f**

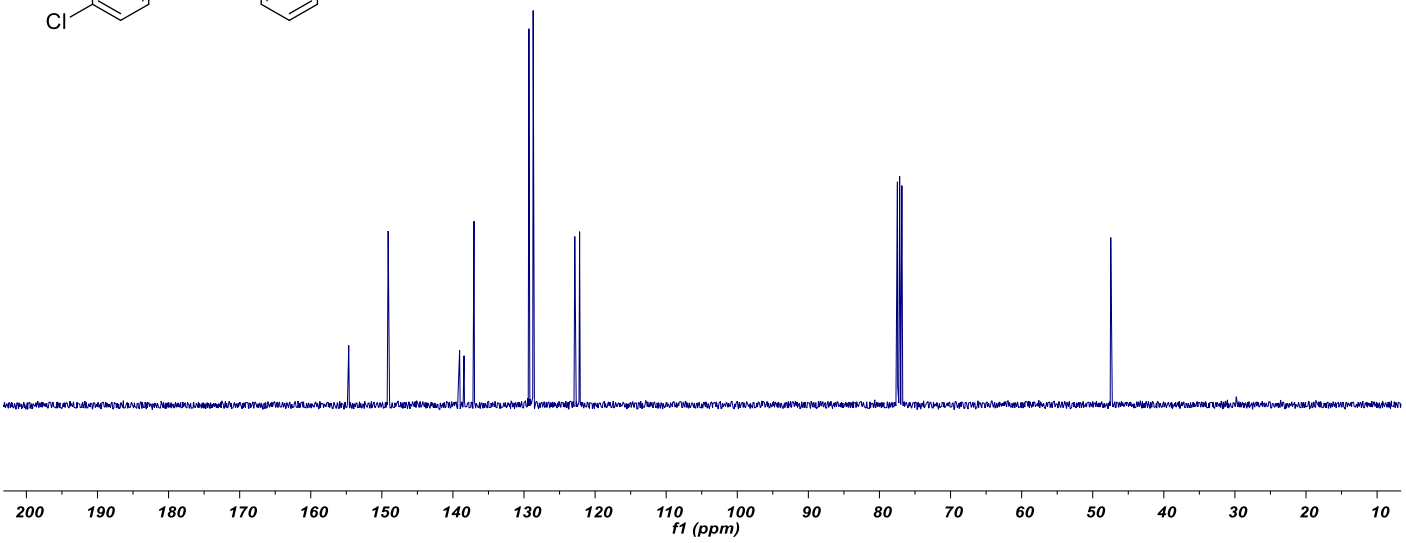




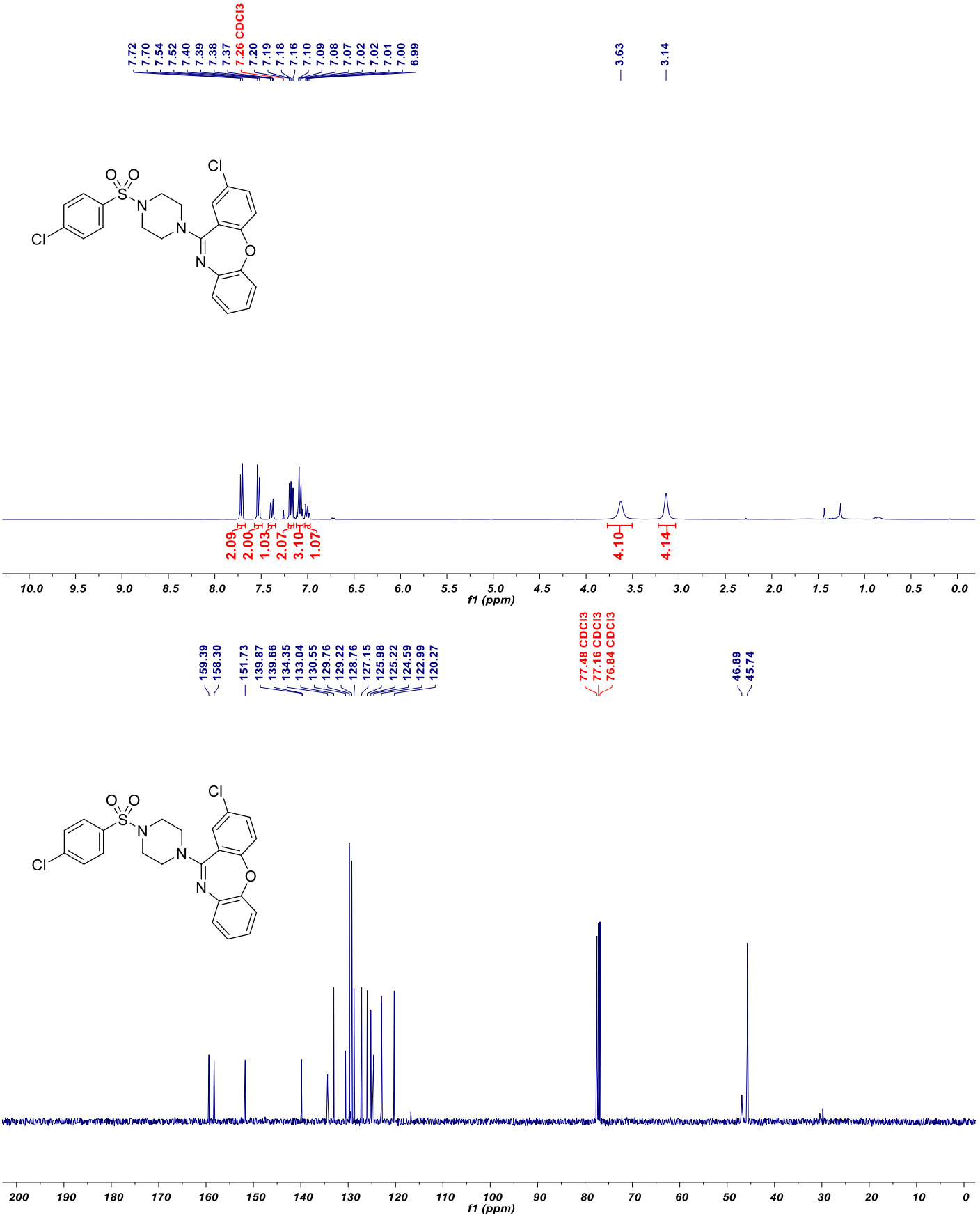




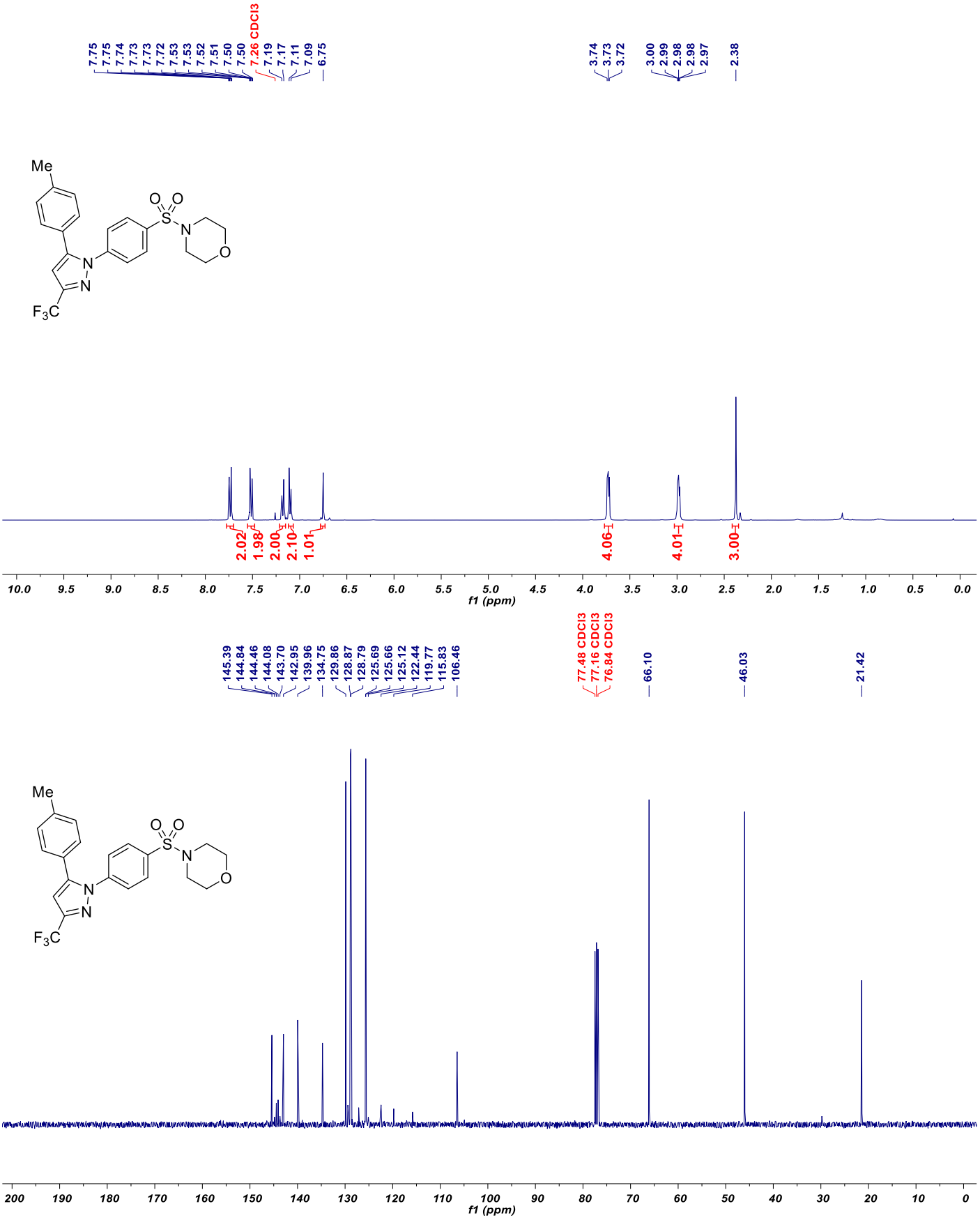


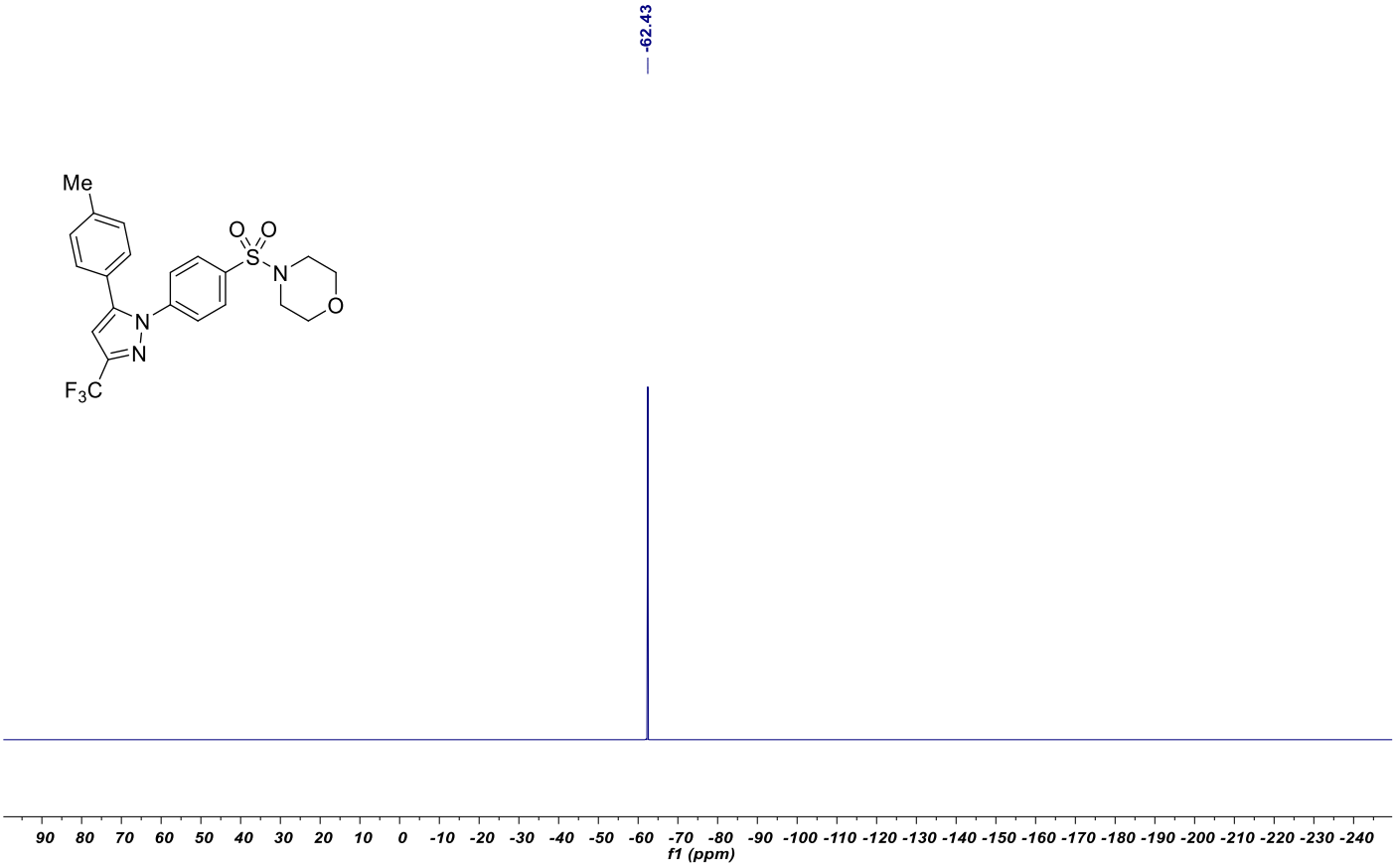


NMR spectrum of sulfonamide **11g**

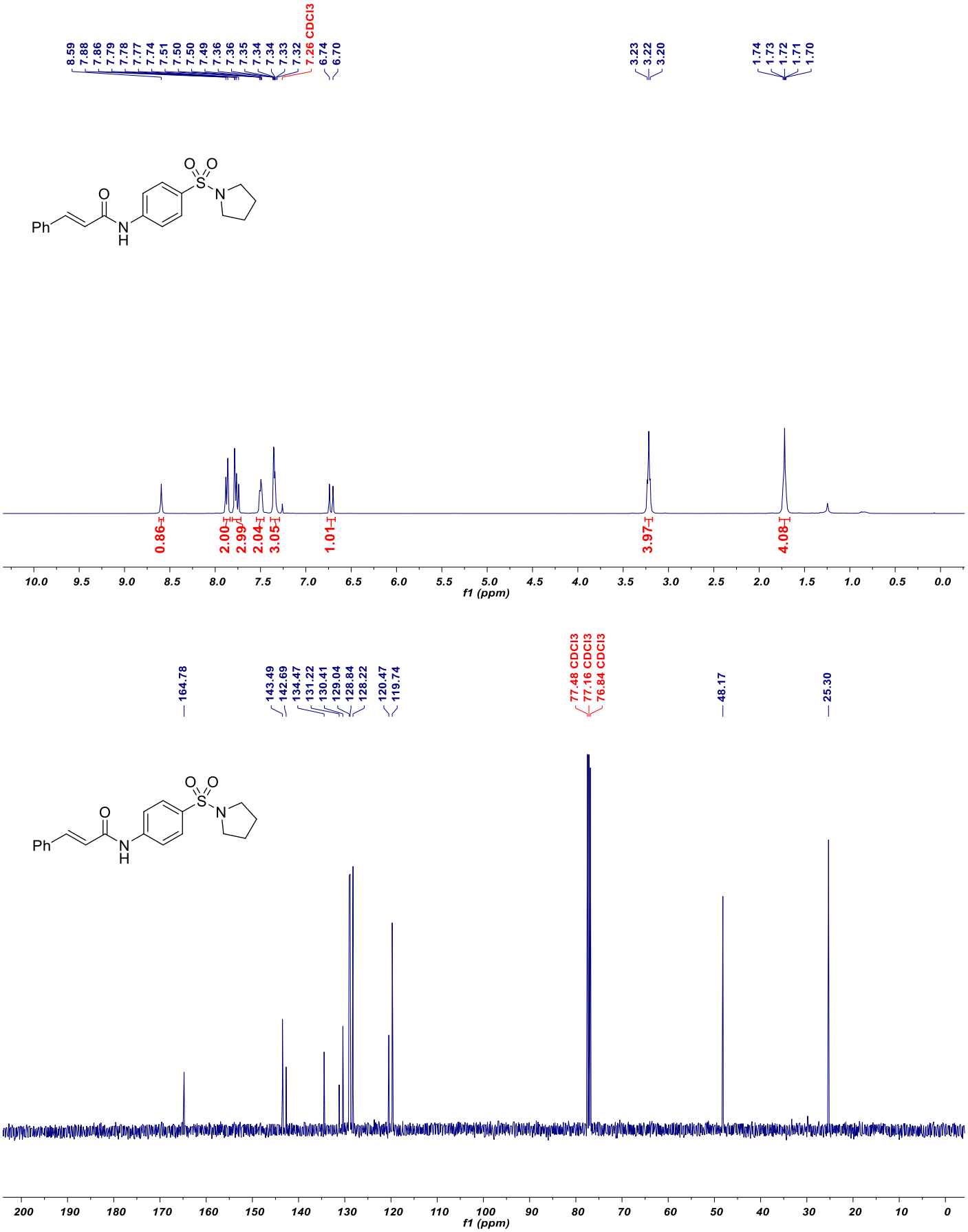


NMR spectrum of sulfonamide **11h**

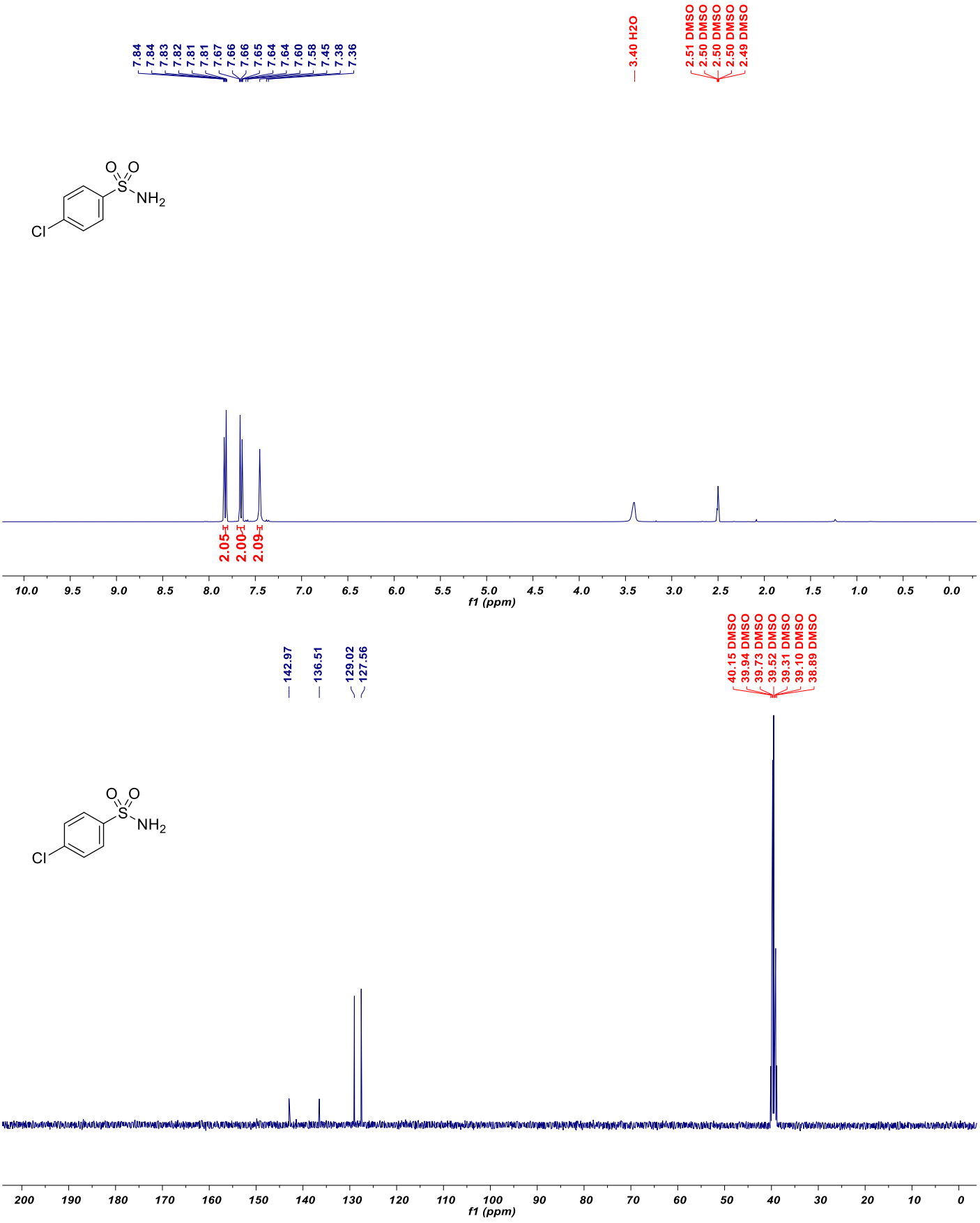



-62.43
Me
O
O
S
N
O
N
N
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

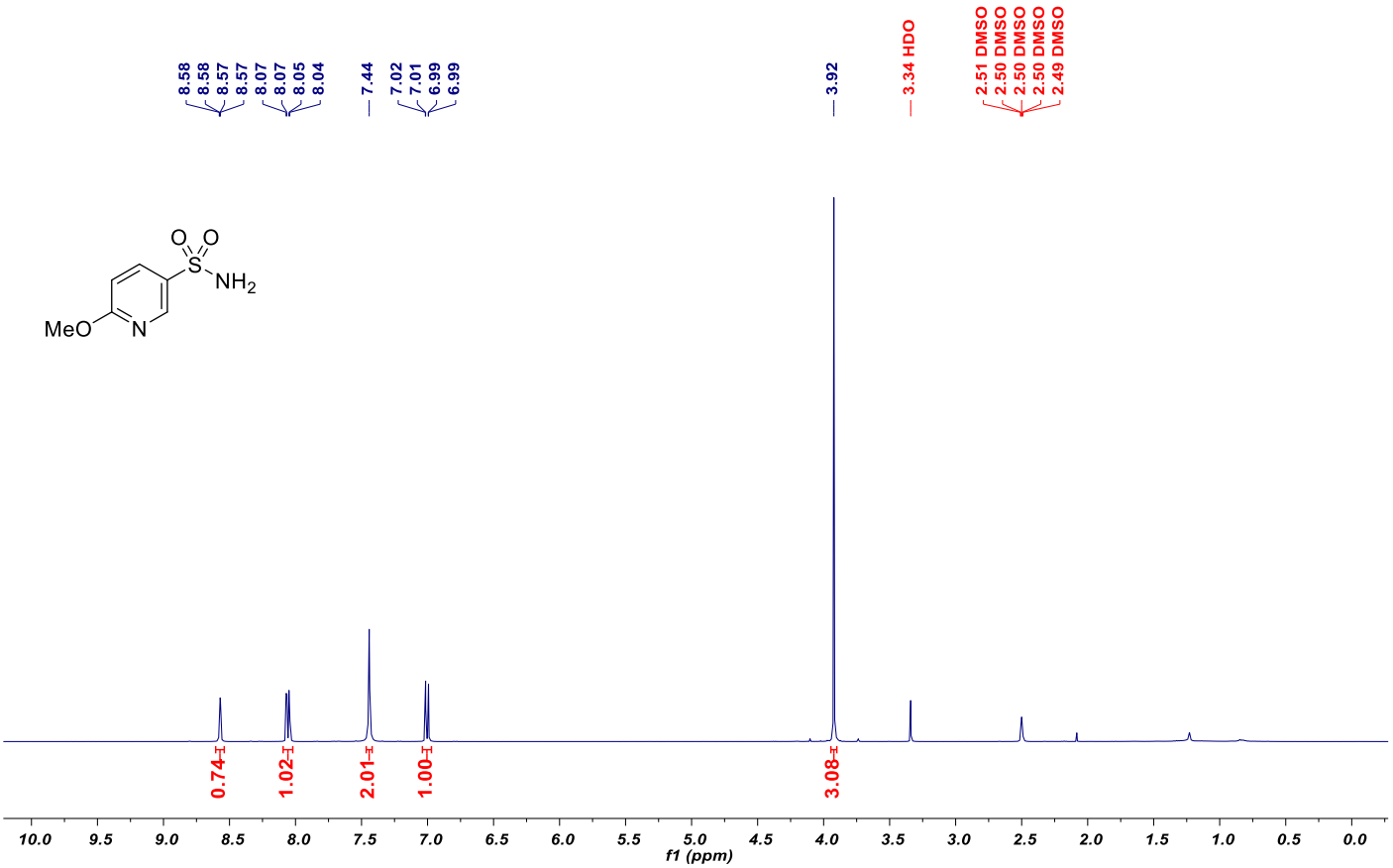
NMR spectrum of sulfonamide **11i**

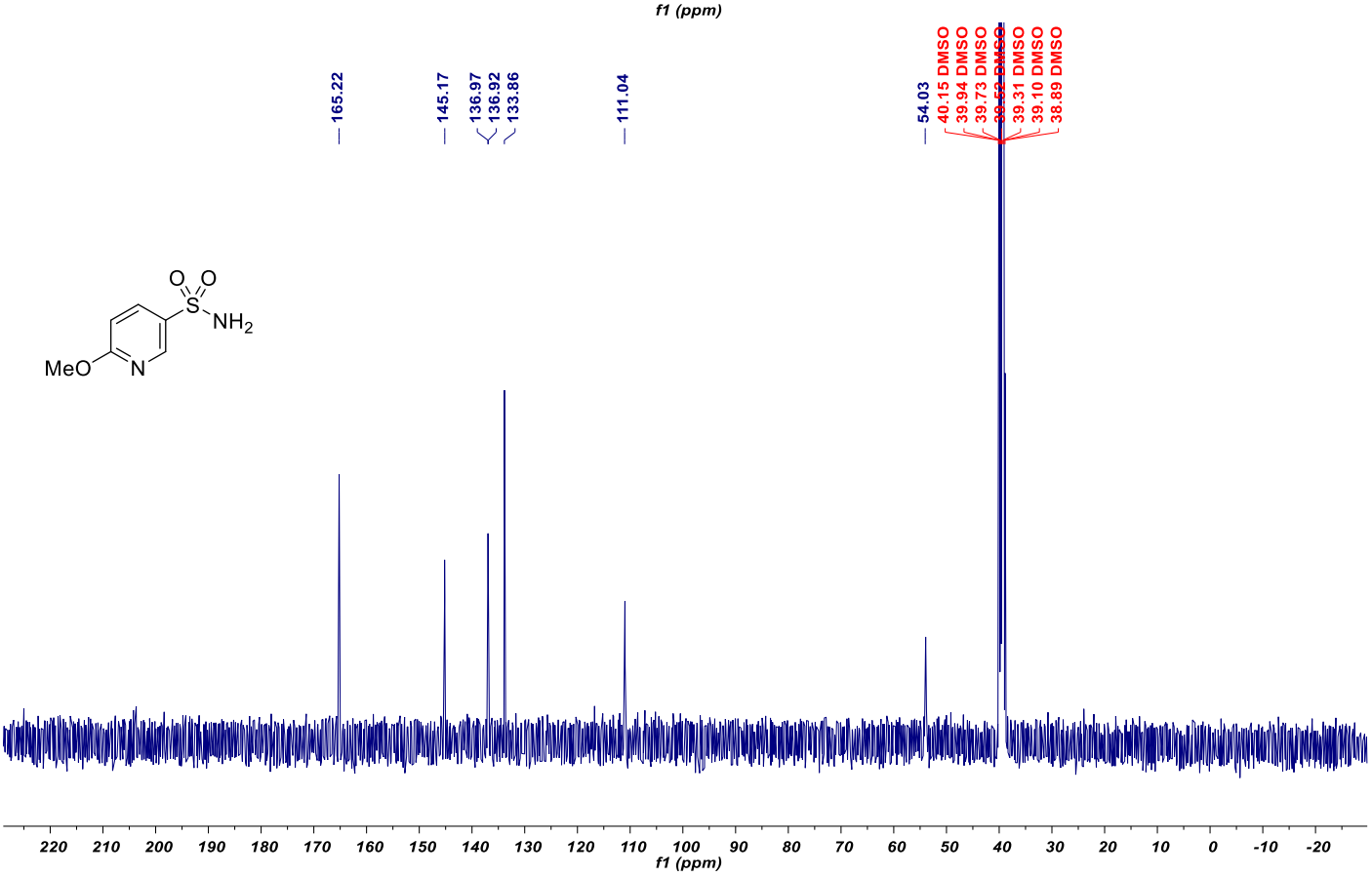


NMR spectrum of sulfonamide **11j**

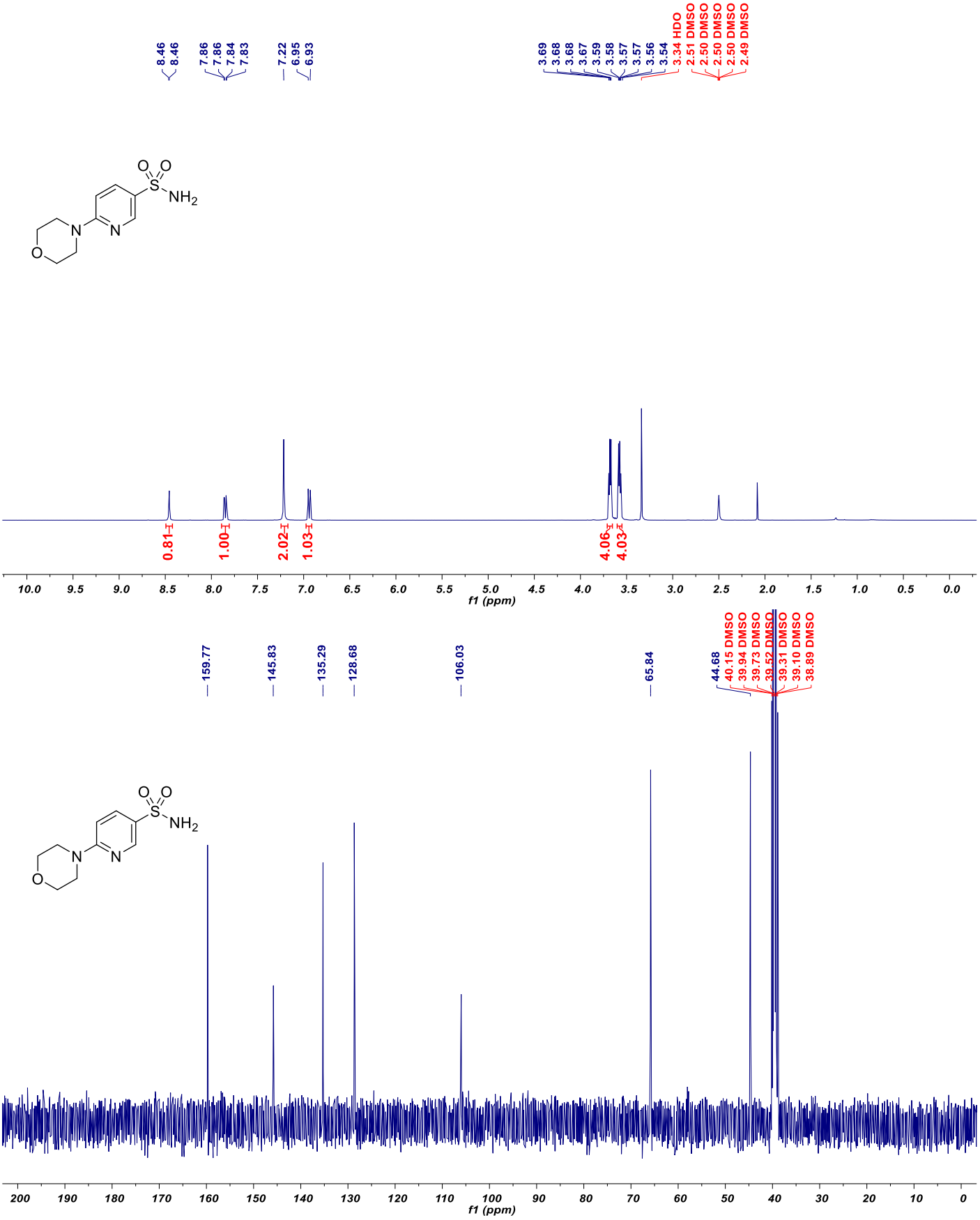


NMR spectrum of sulfonamide **11k**

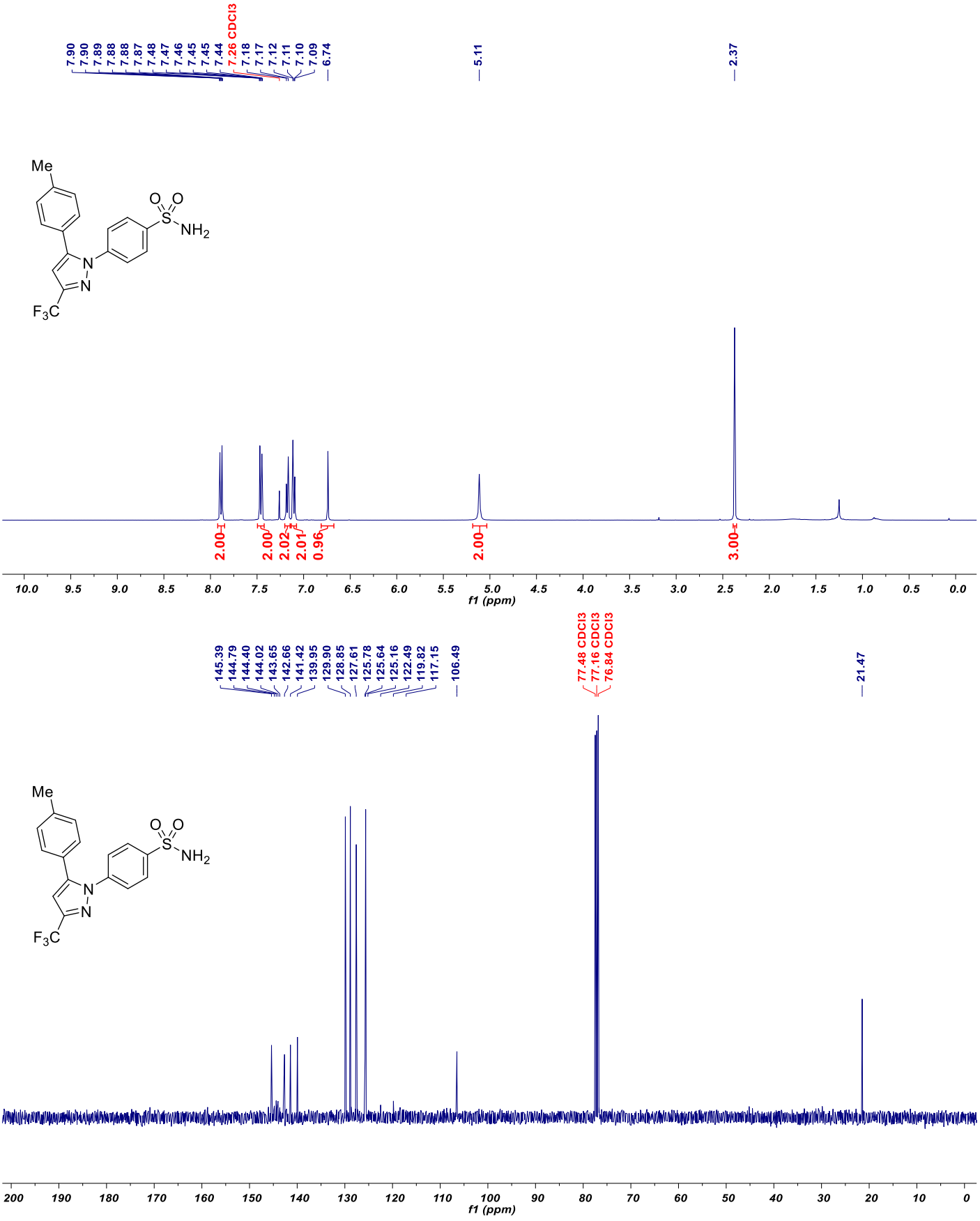


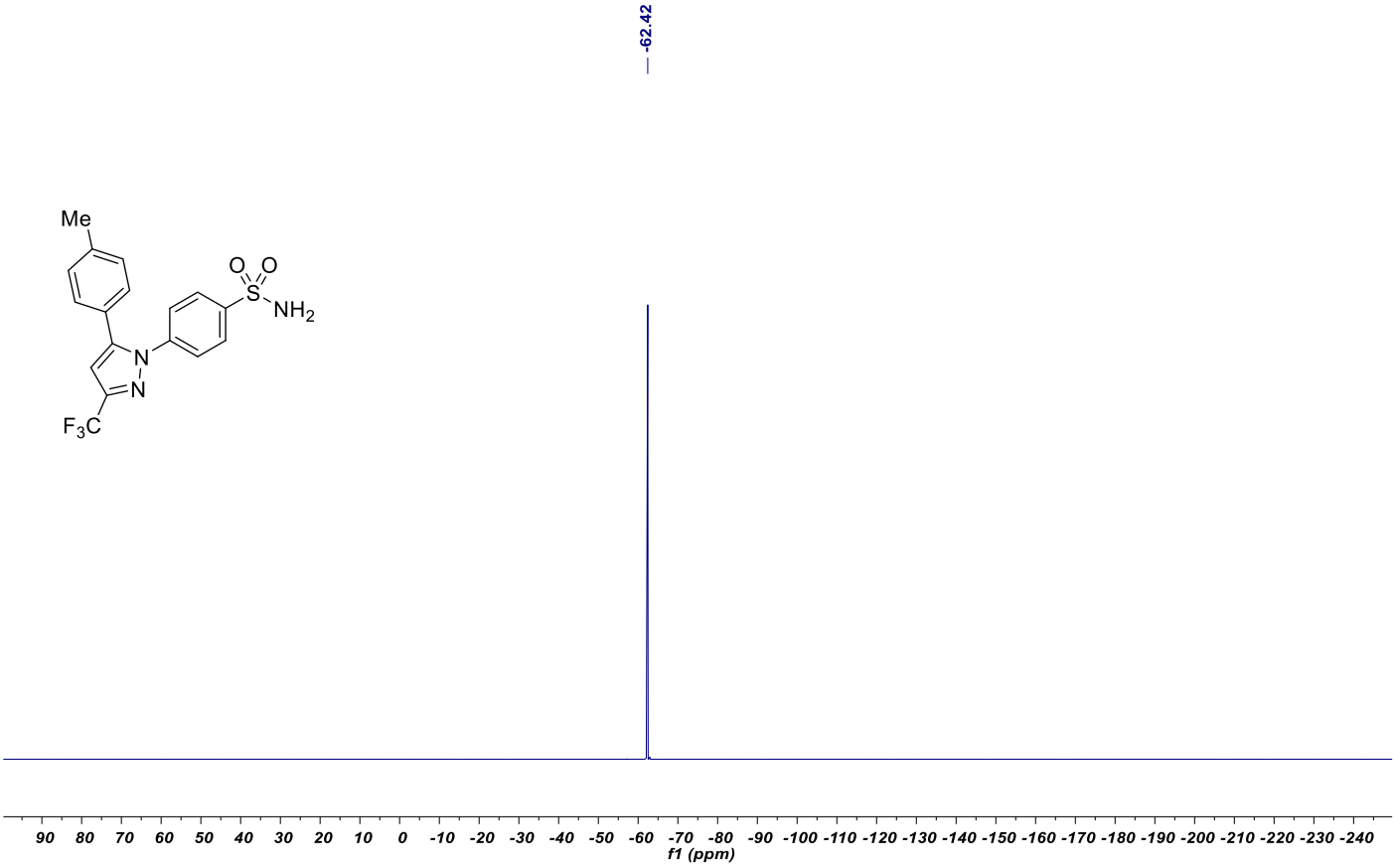


NMR spectrum of sulfonamide **11l**

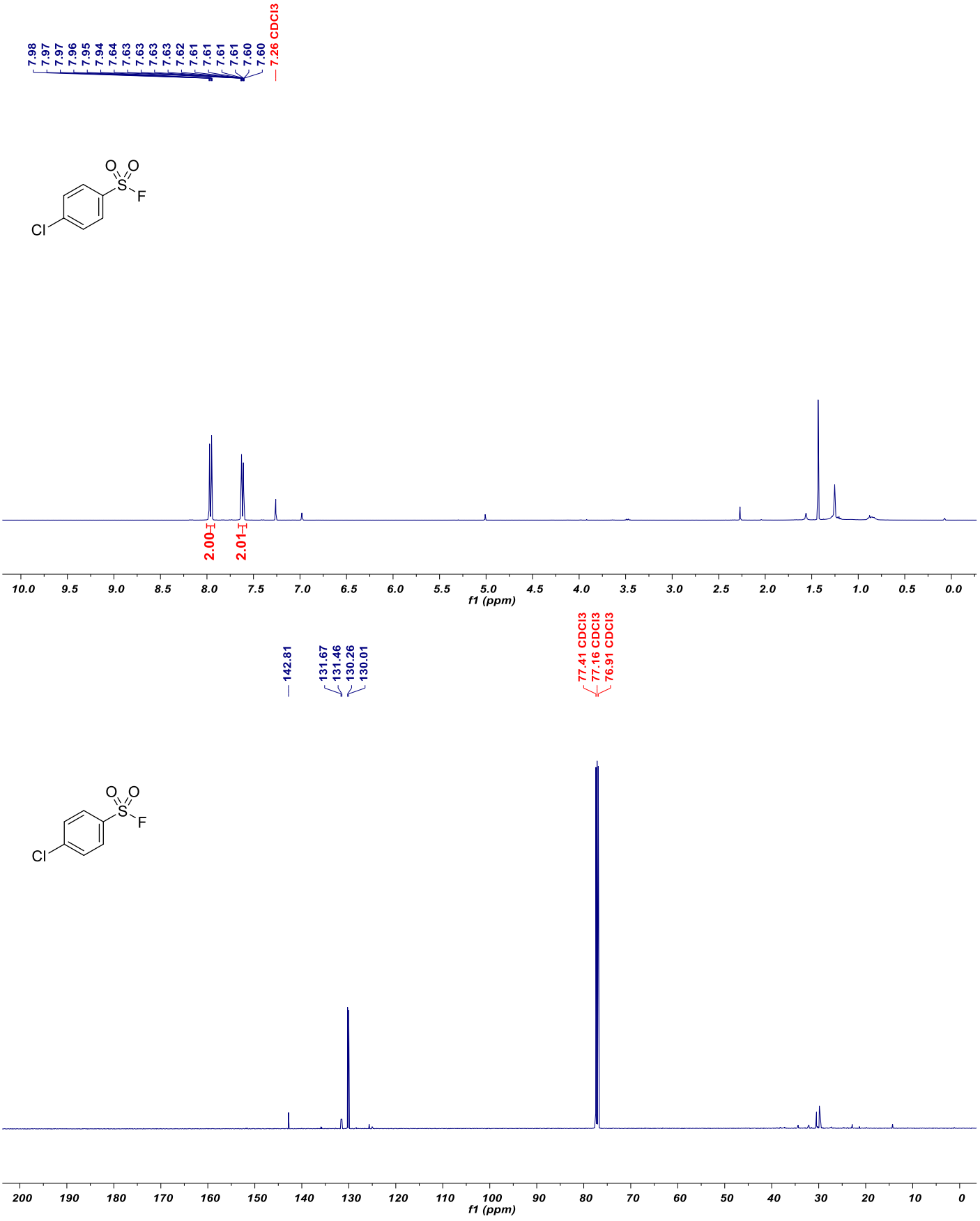


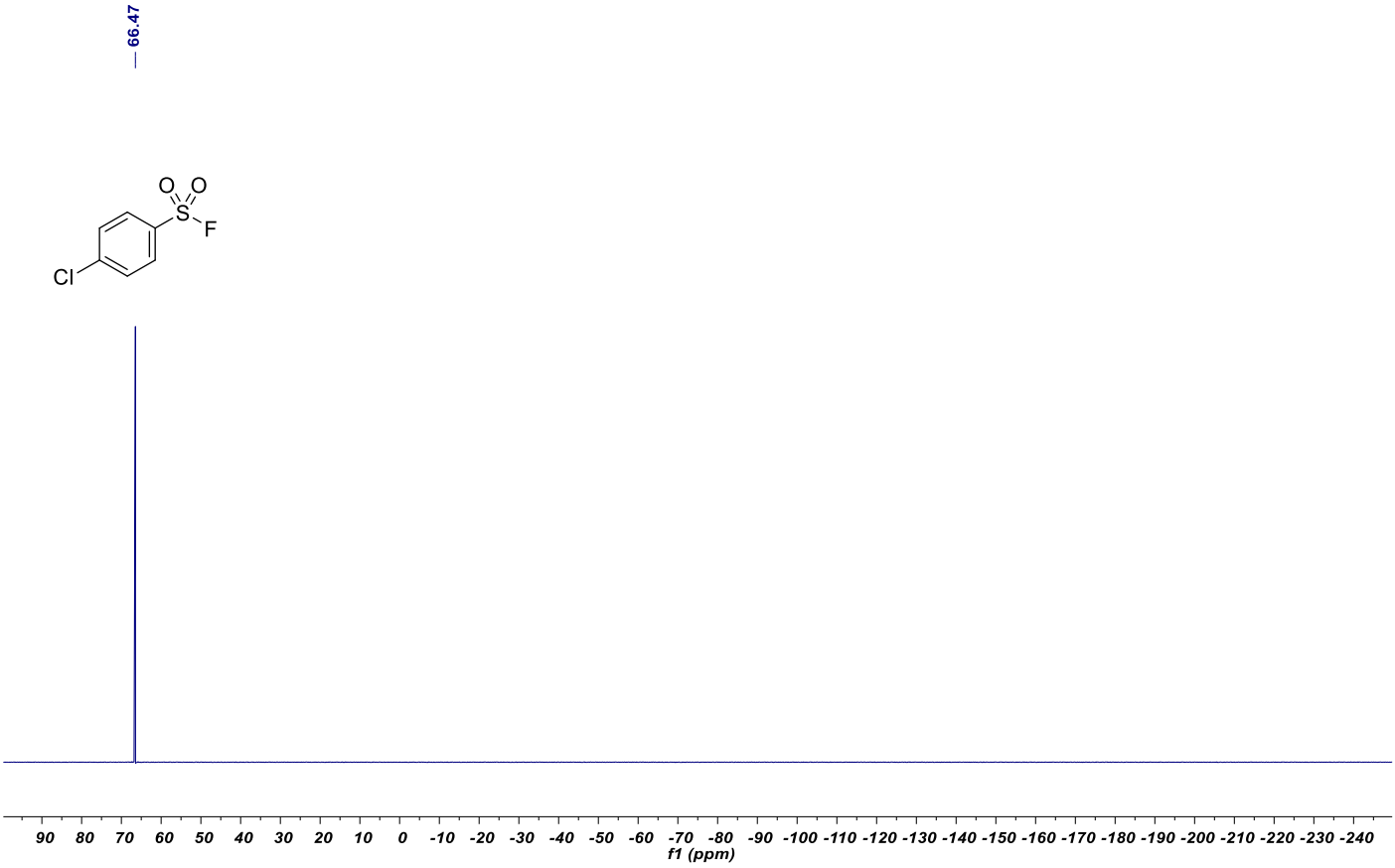
NMR spectrum of sulfonamide **11m**



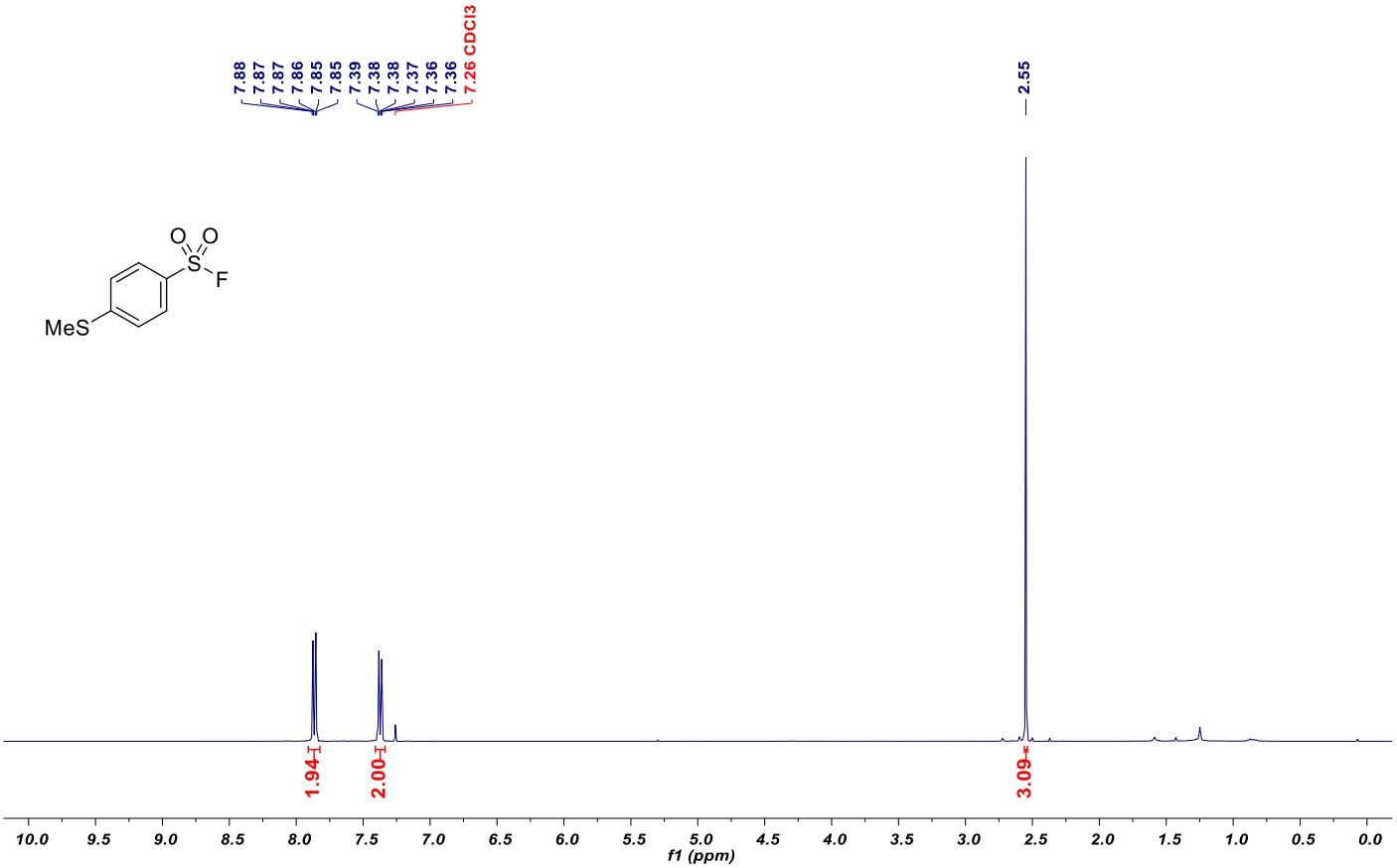

-62.42
Me
O
O
S
NH2
N
N
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

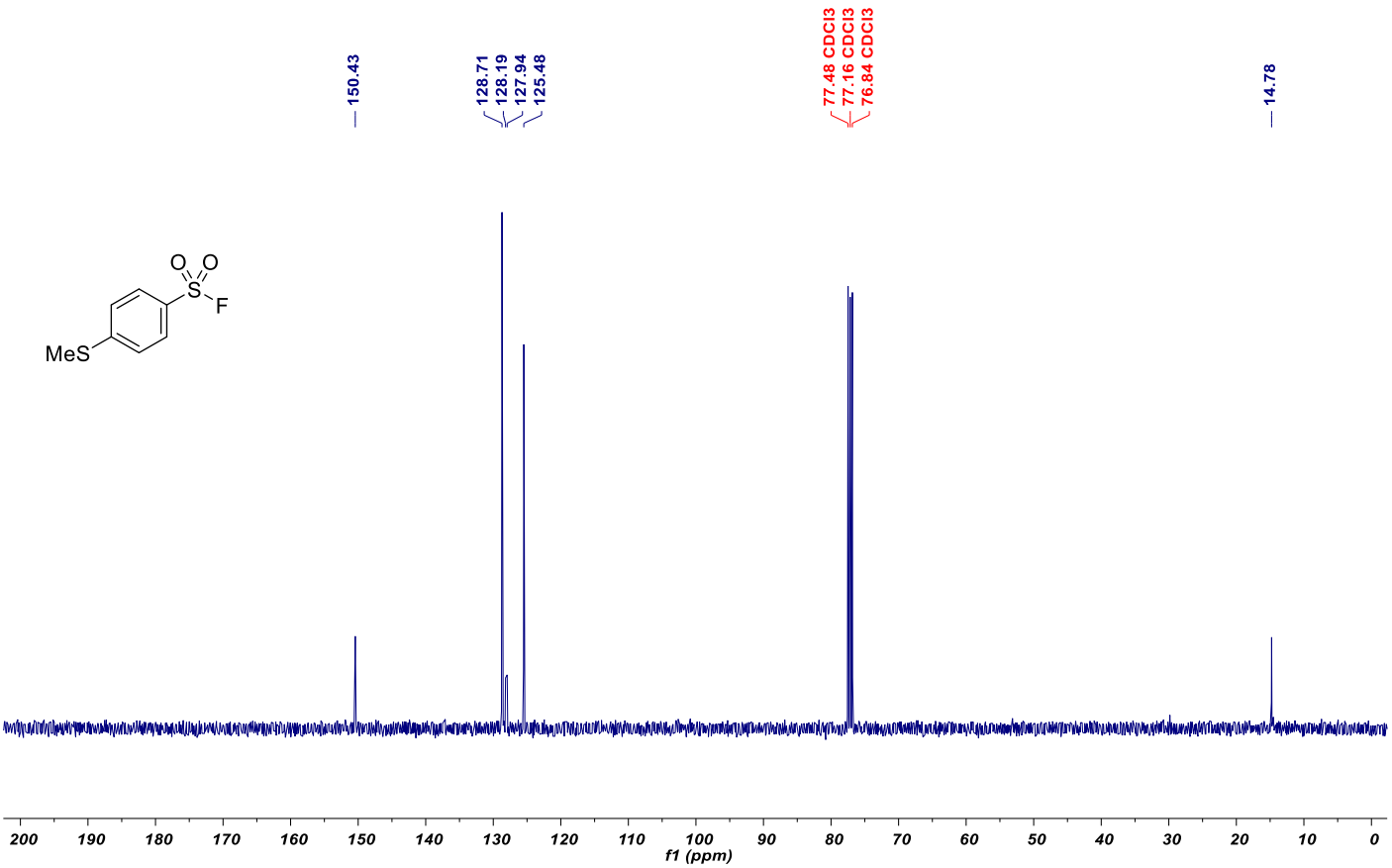
NMR spectrum of sulfonyl fluoride **12a**

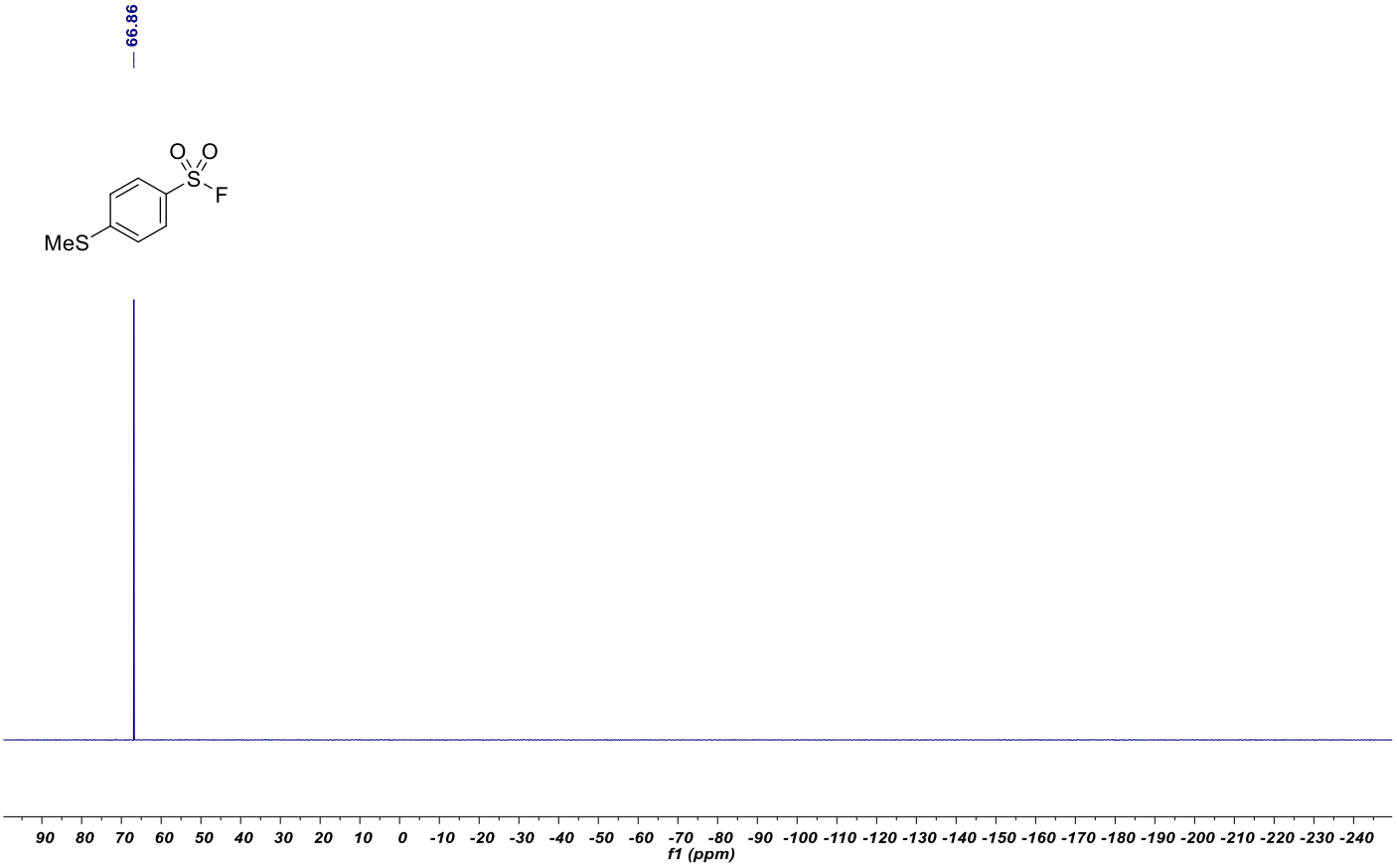



66.47
O
O
S
F
Cl
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

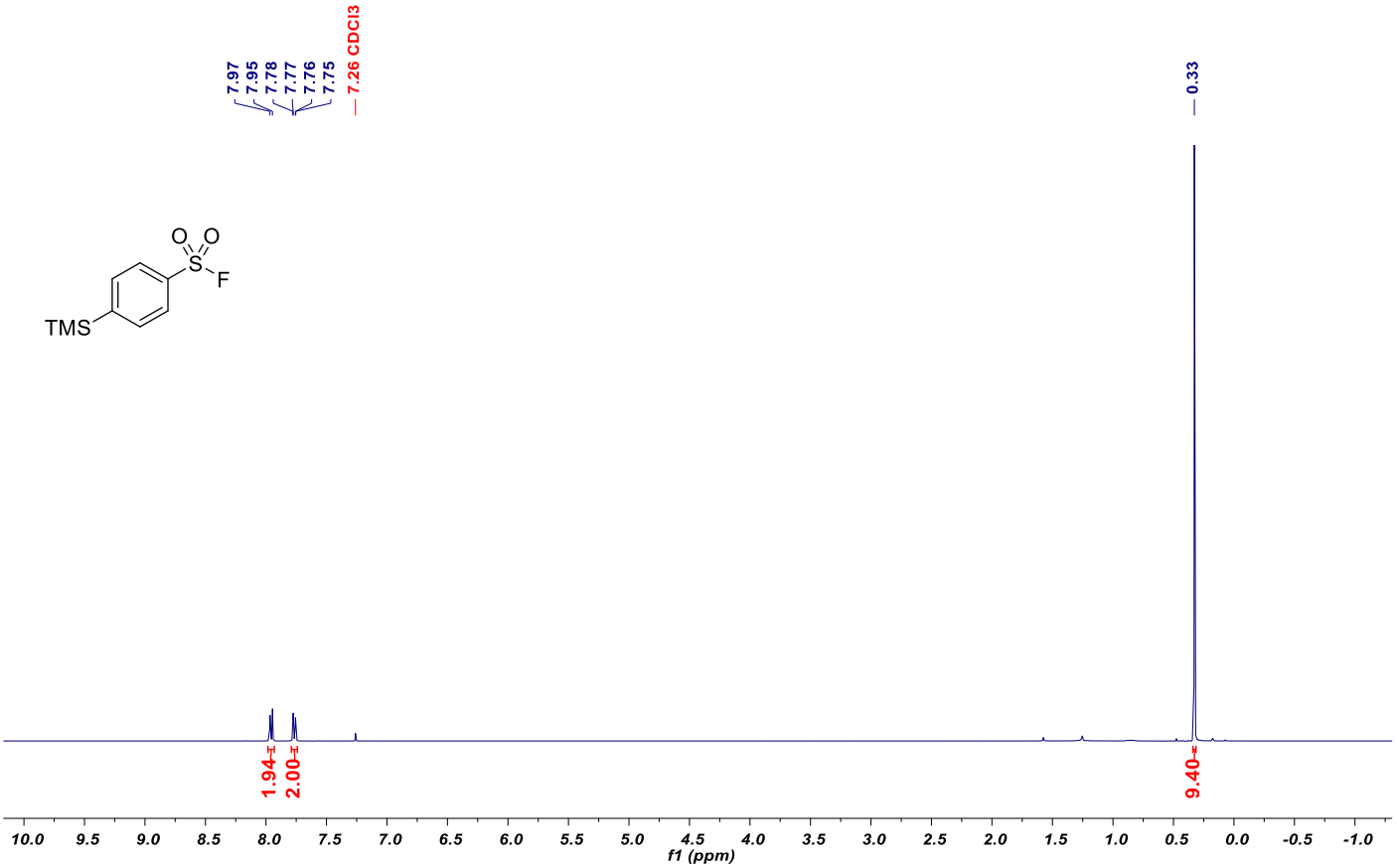
NMR spectrum of sulfonyl fluoride **12b**

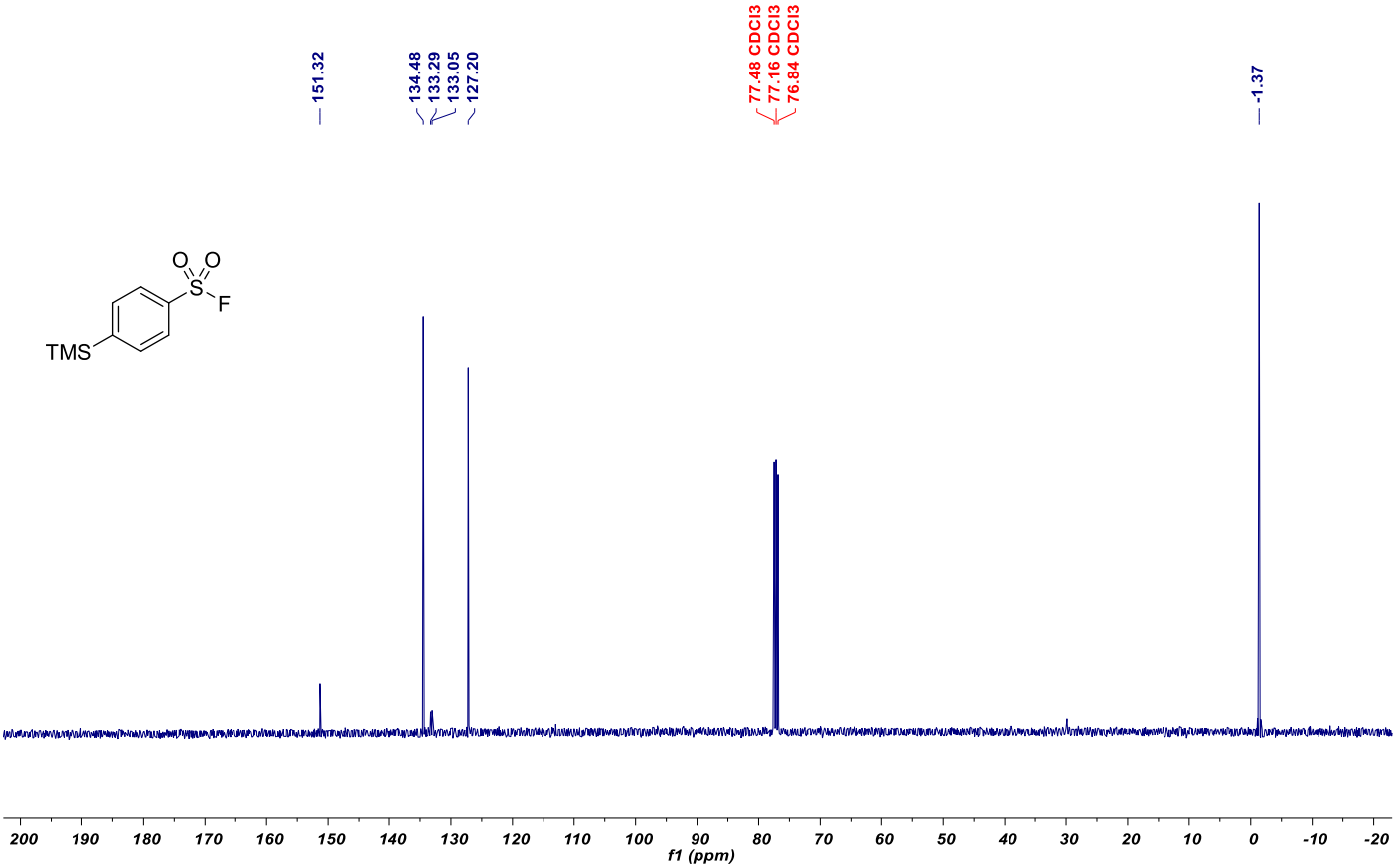


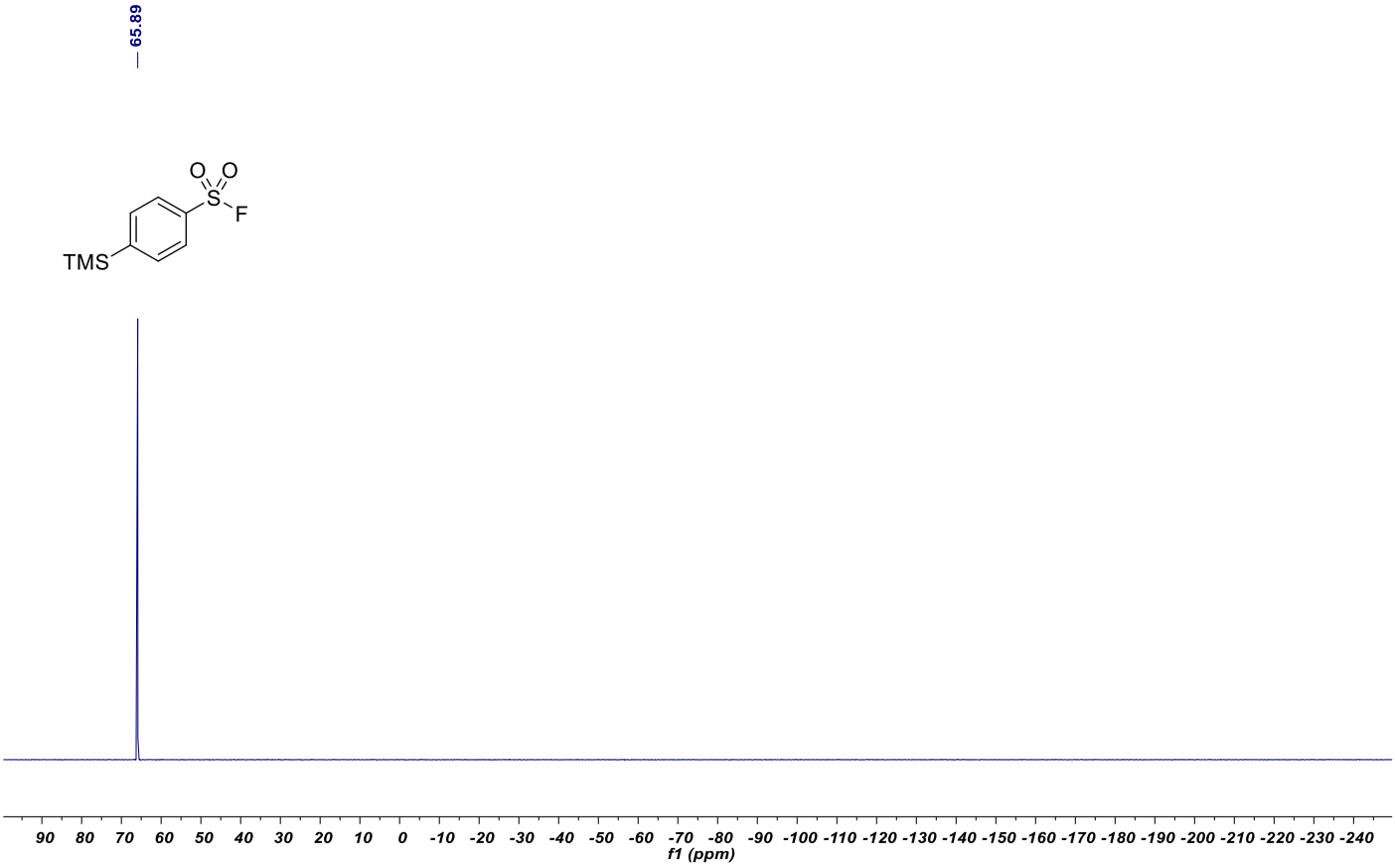



66.86
O
O
S
F
MeS
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

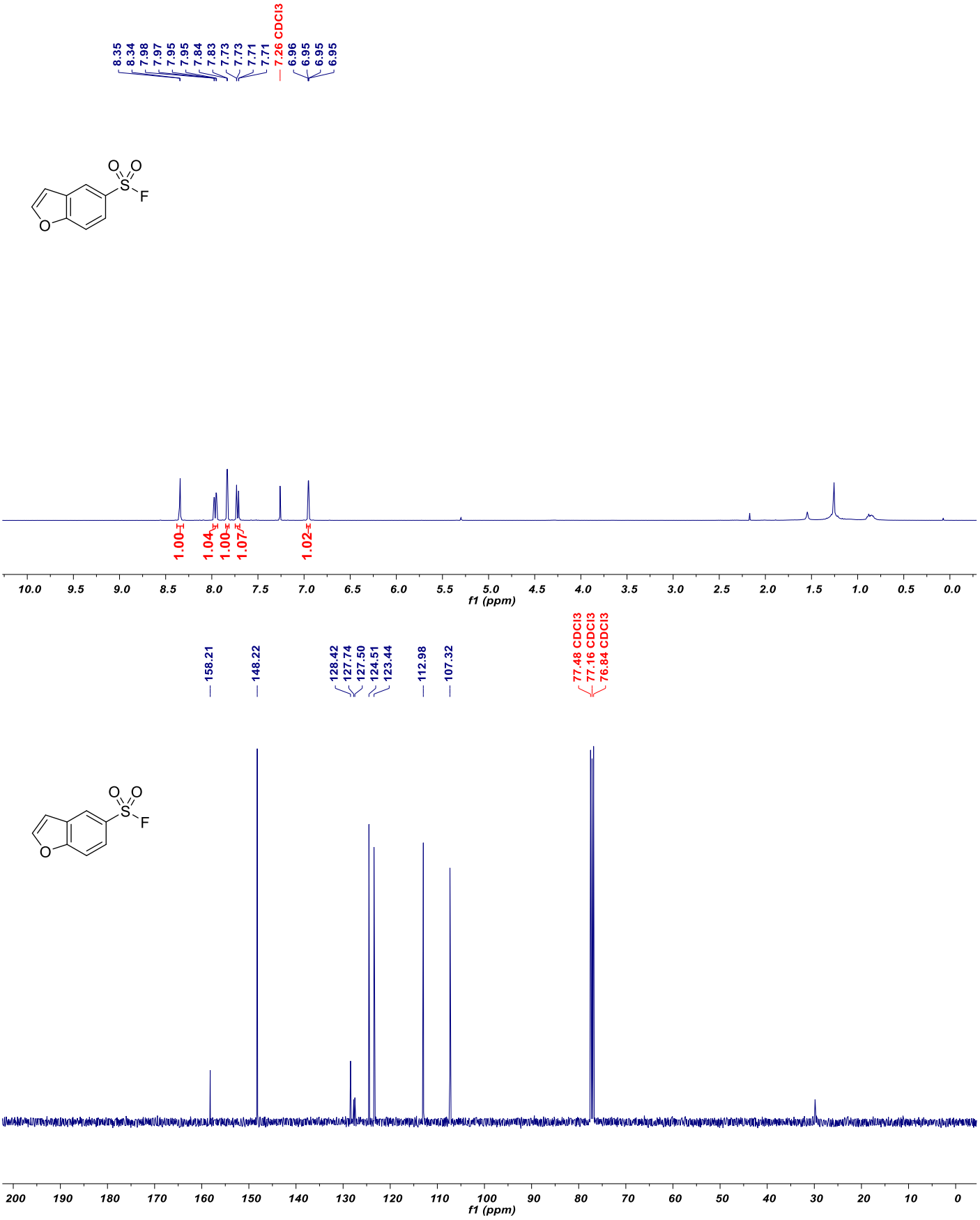
NMR spectrum of sulfonyl fluoride **12c**

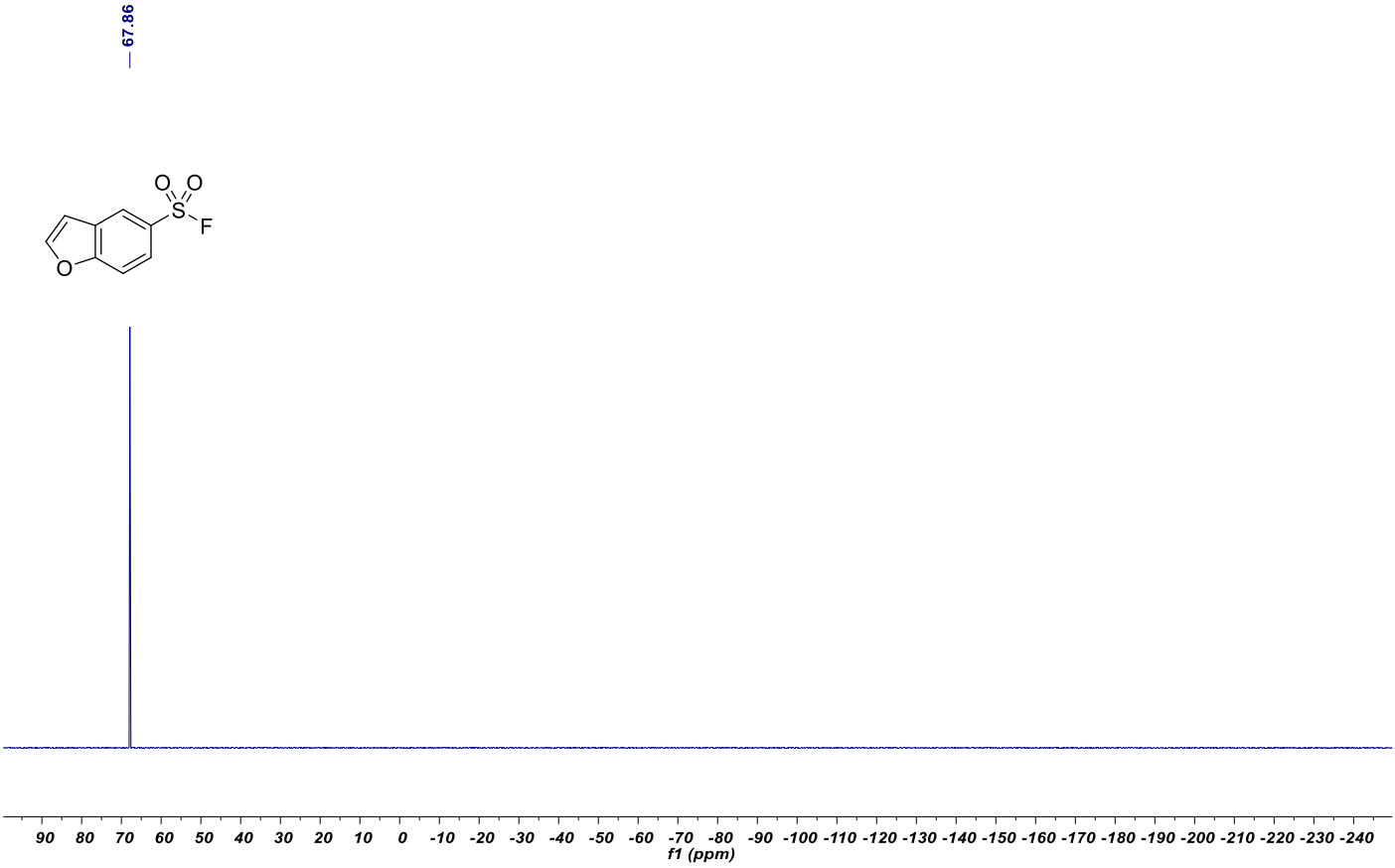




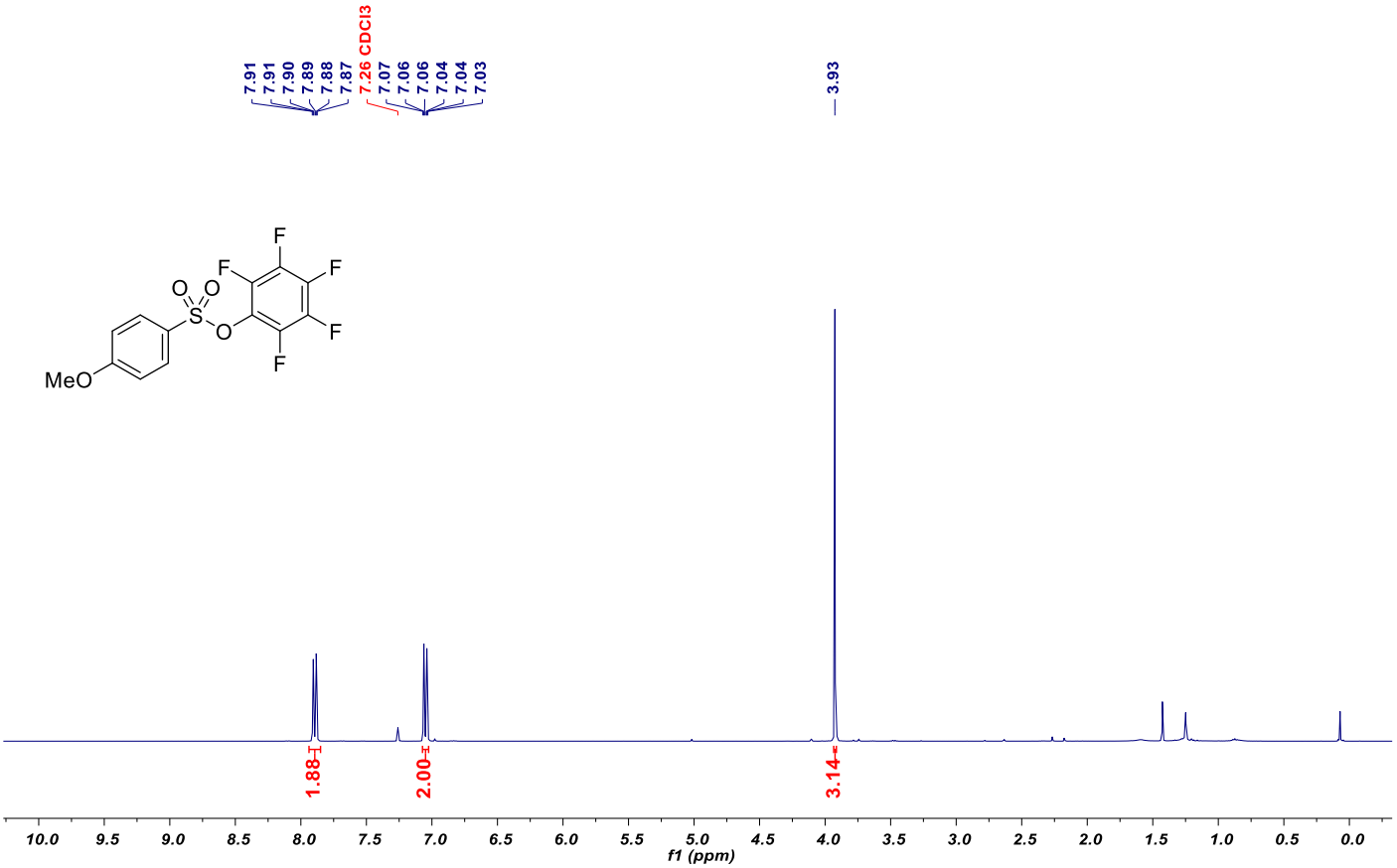

65.89
O
O
S
F
TMS
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

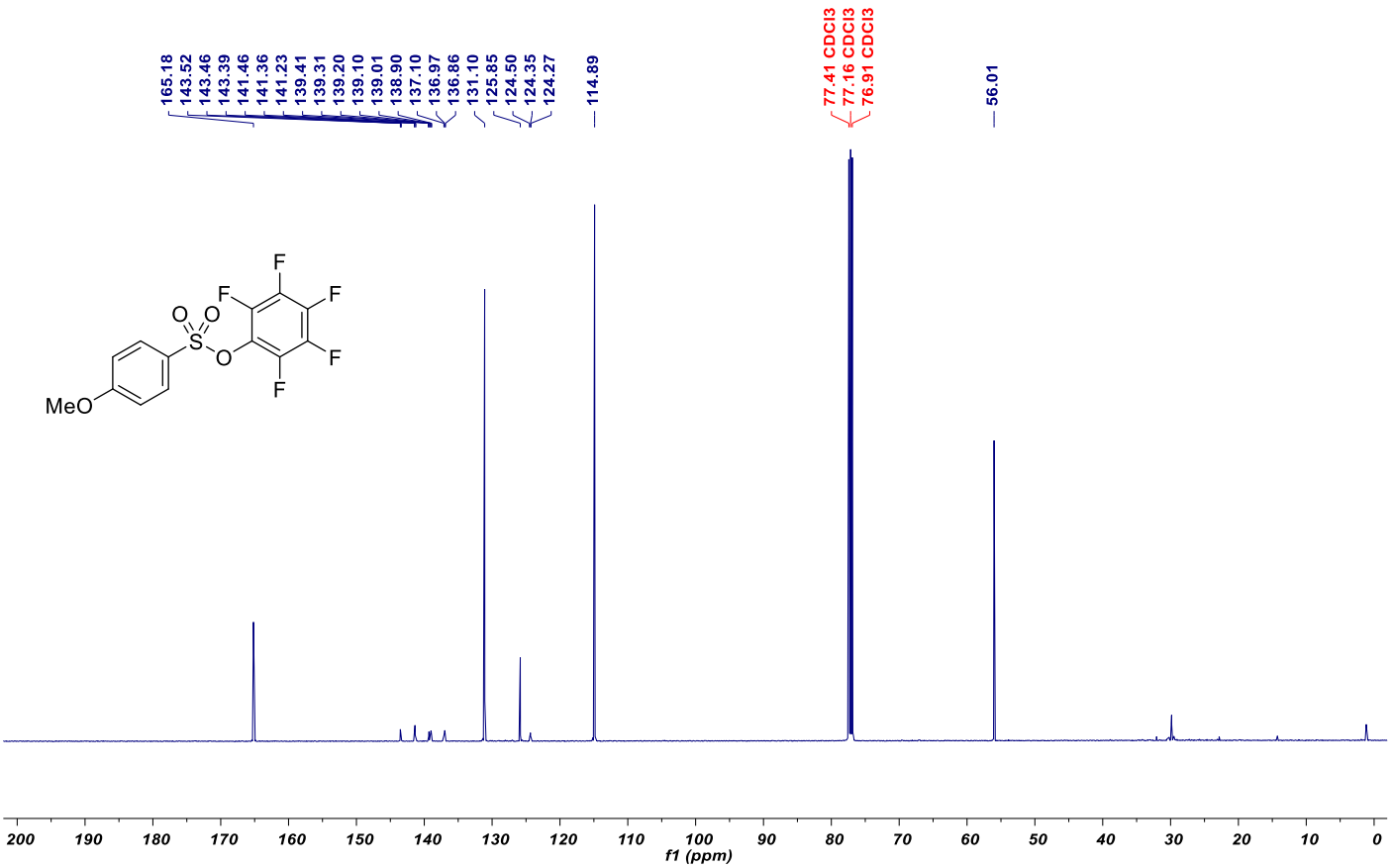
NMR spectrum of sulfonyl fluoride **12d**



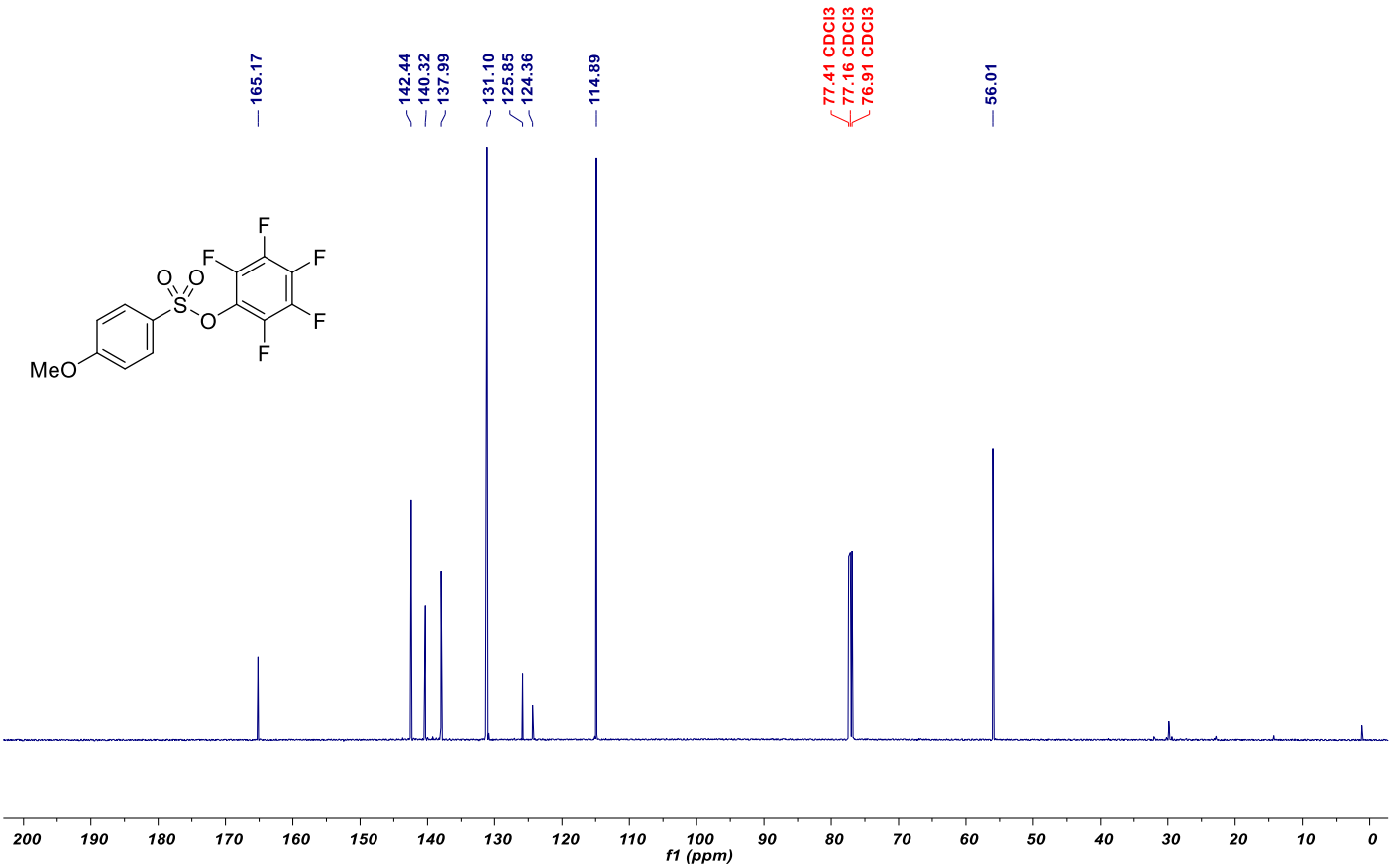

67.86
O
O
S
F
O
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

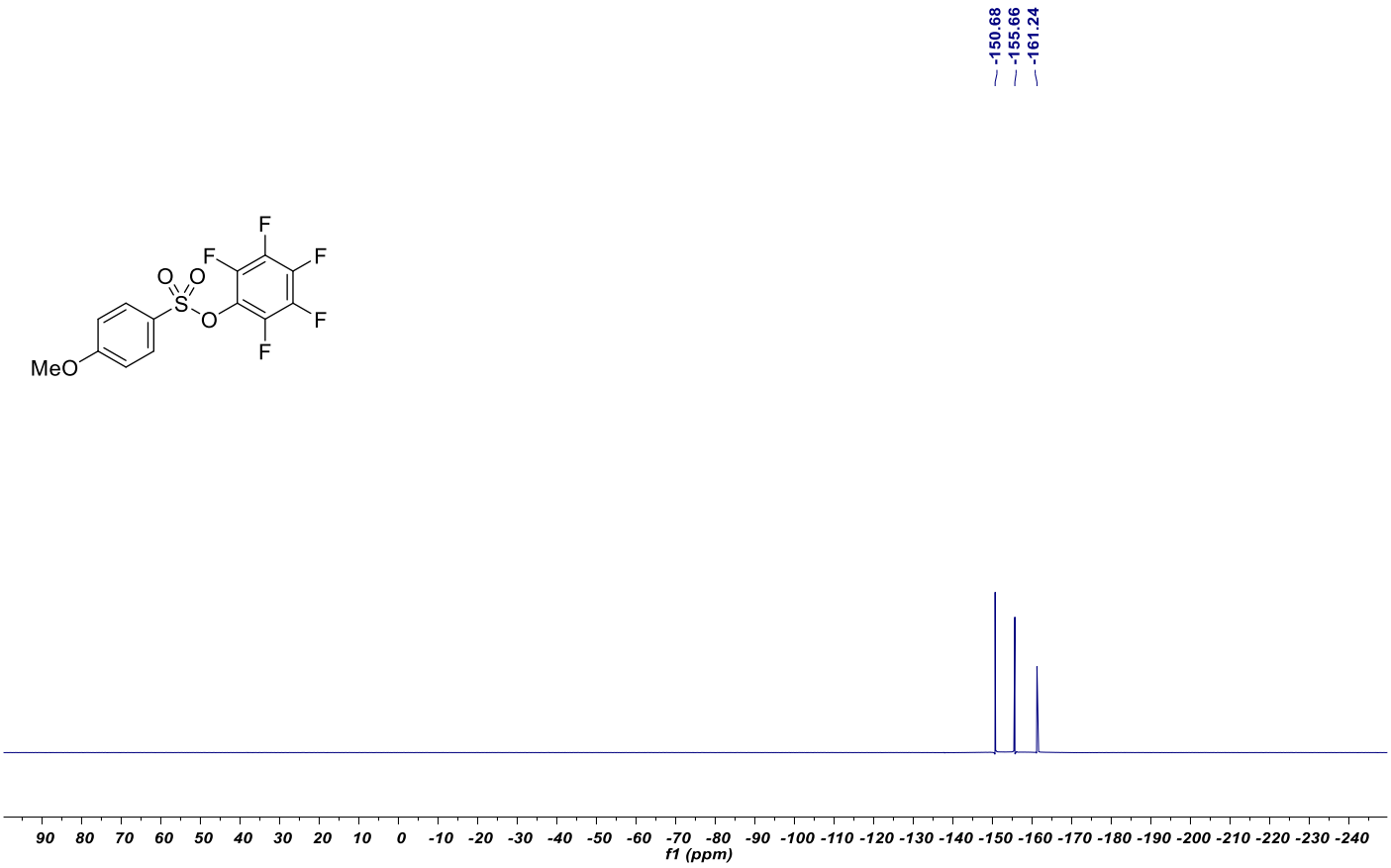
NMR spectrum of sulfonate ester **13**



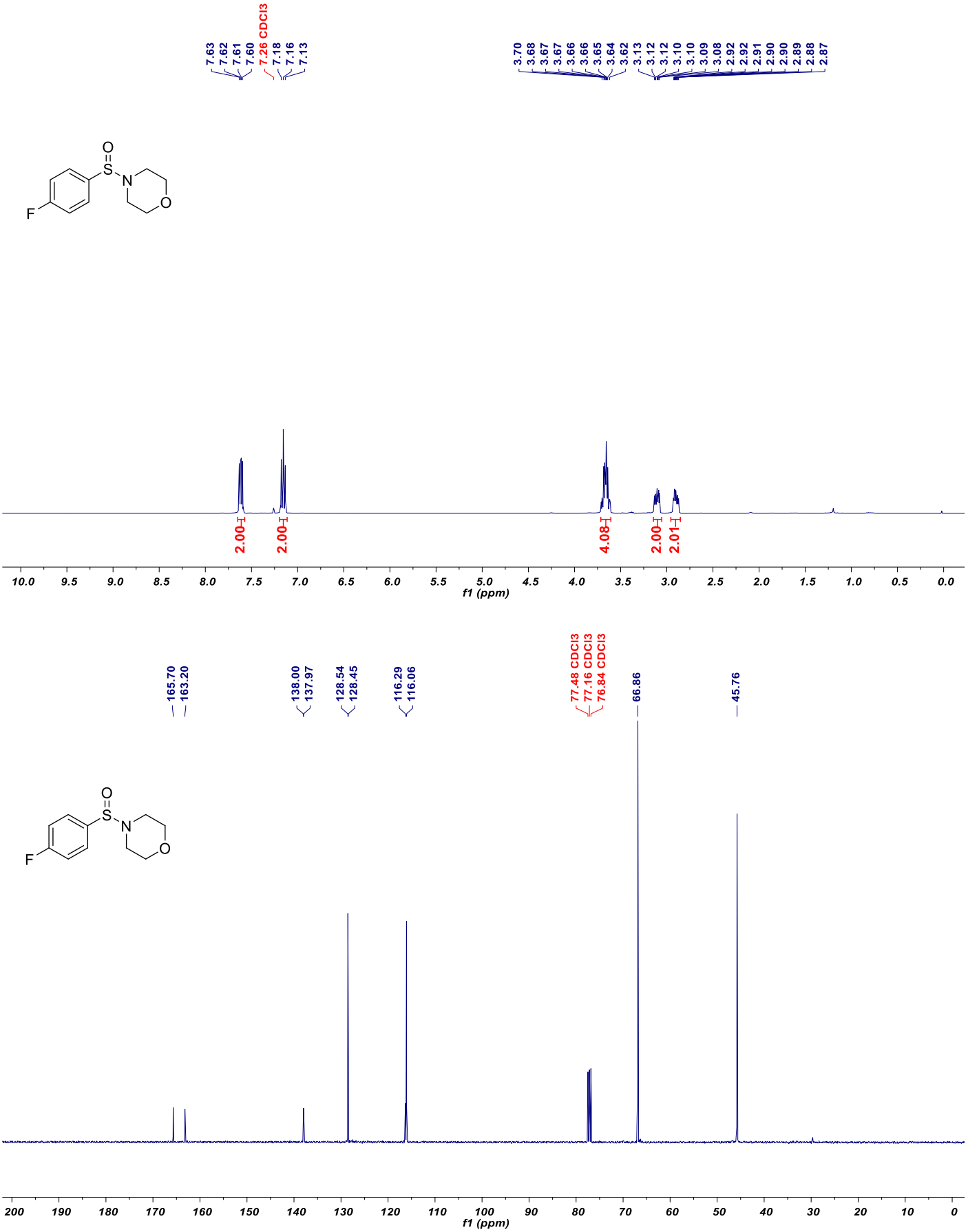


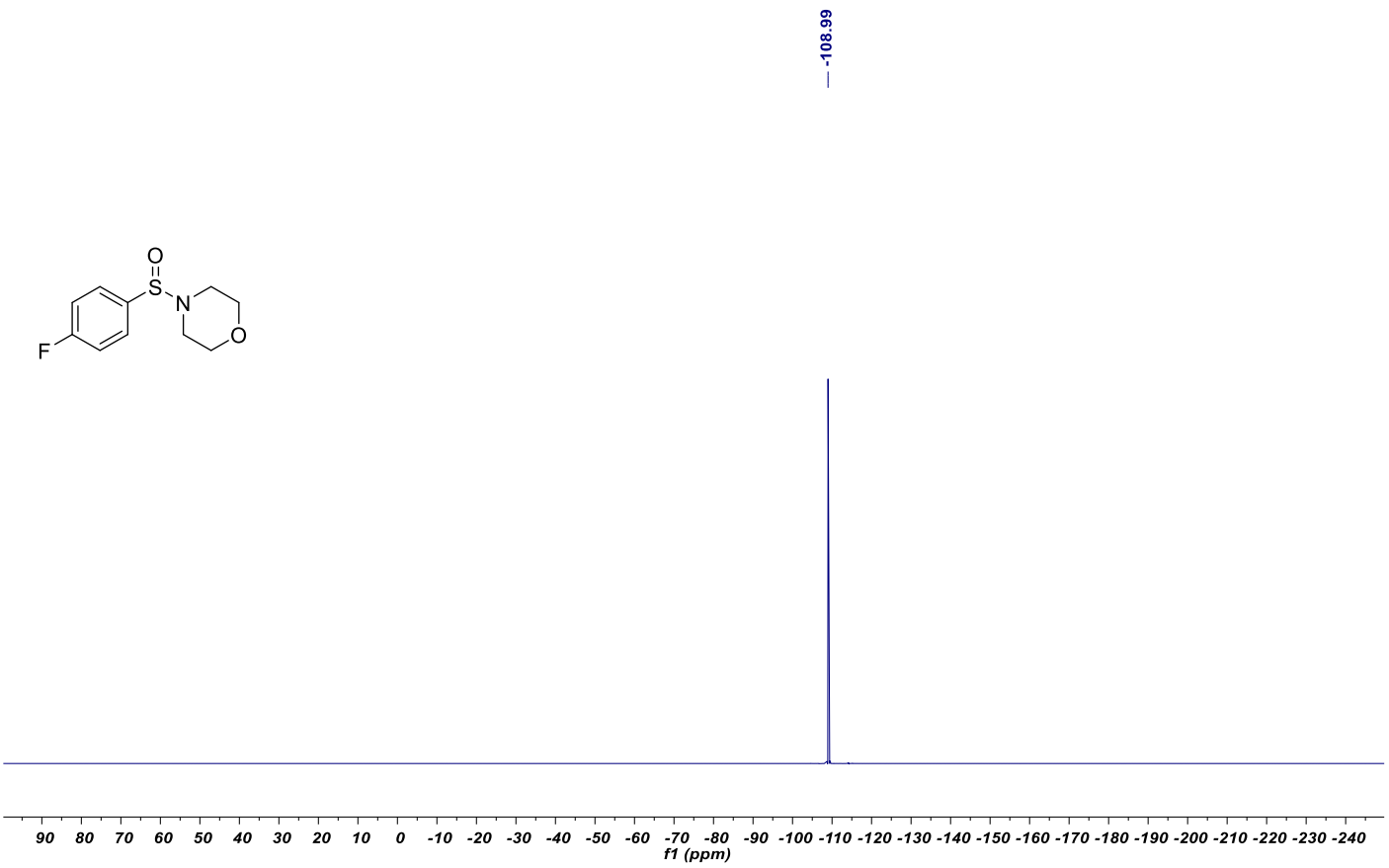
^{13}C NMR spectra of sulfonate ester **13** using the ^{1}H and ^{19}F decoupling method.



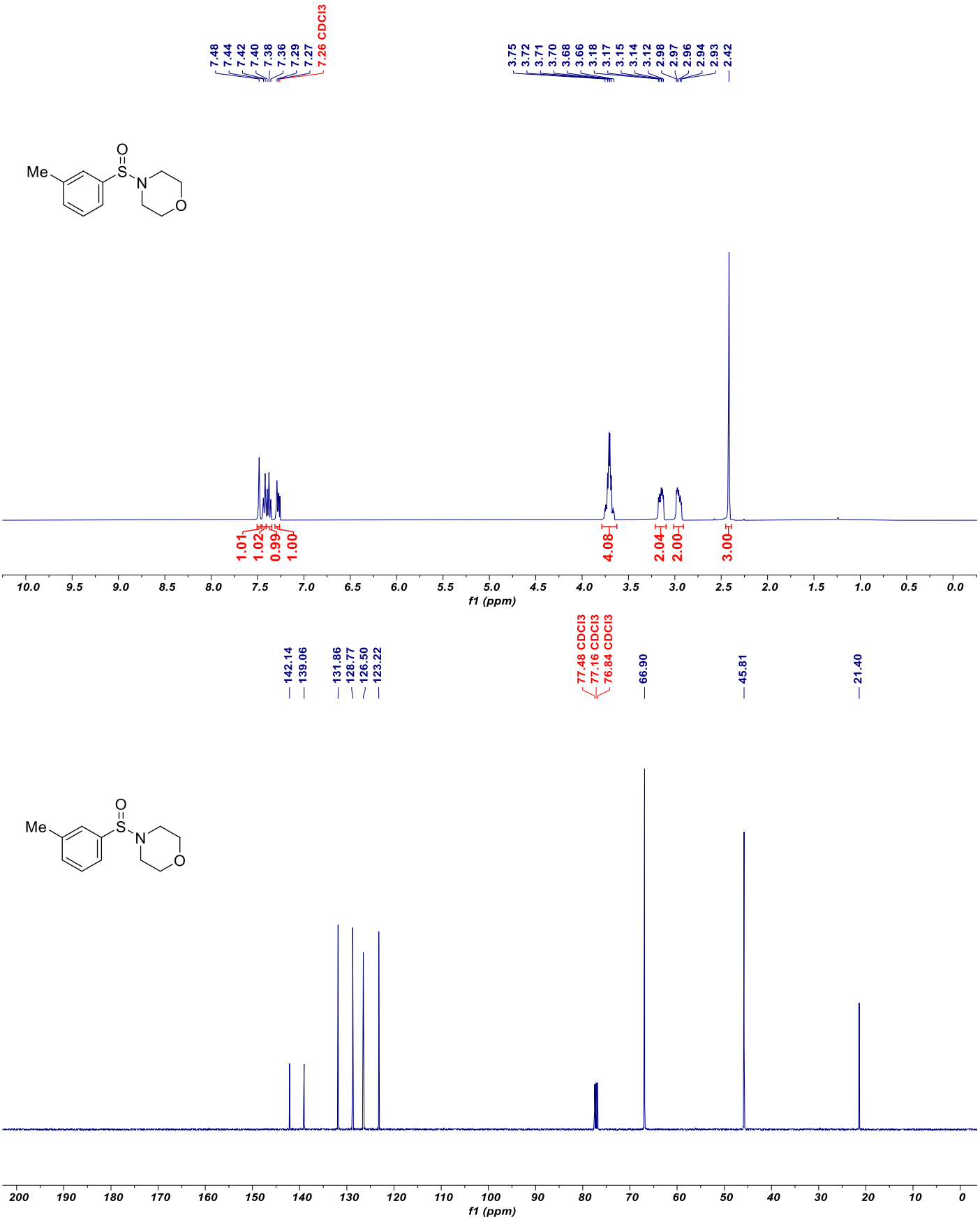


NMR spectrum of sulfinamide **18a**

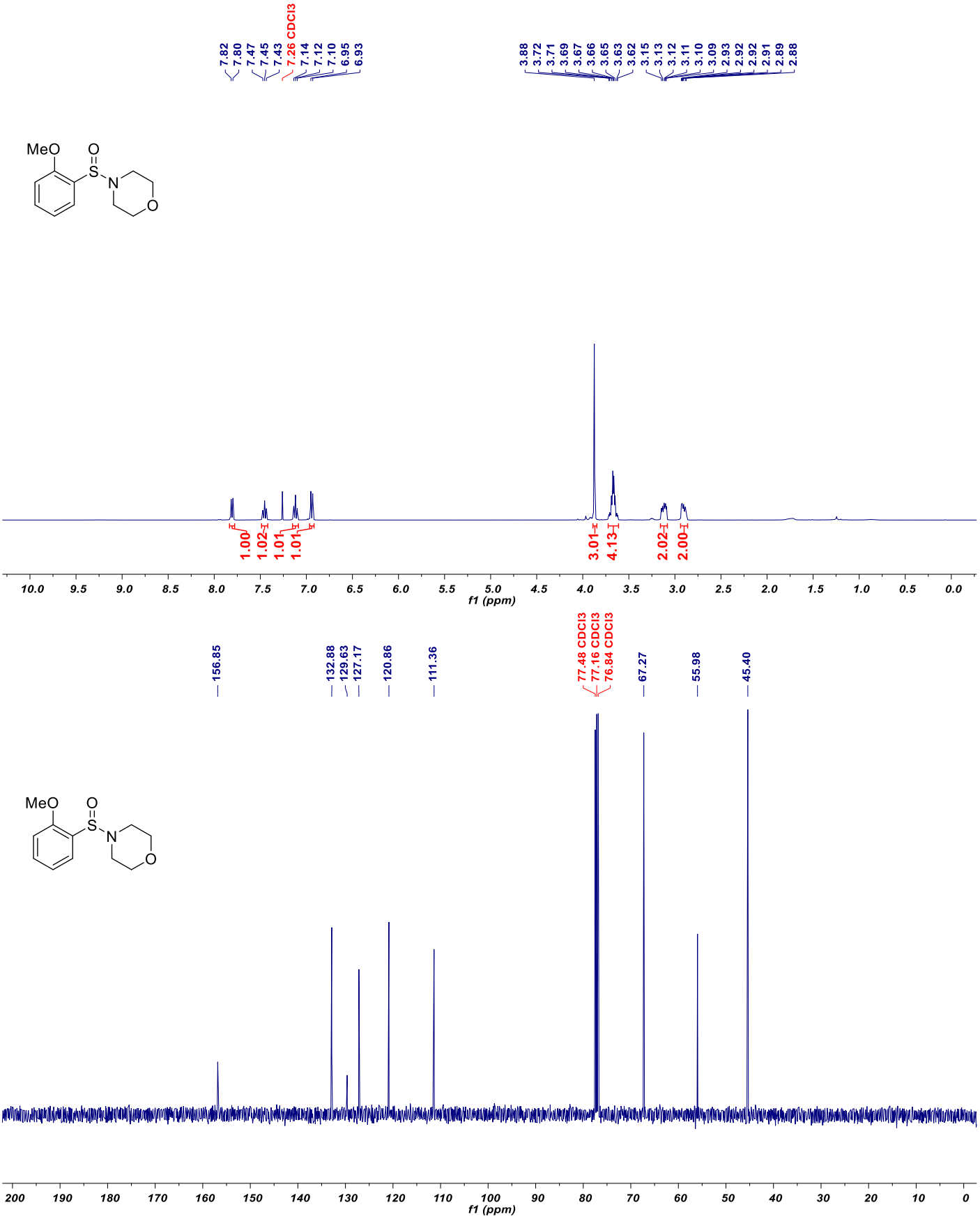



-108.99
O
S
N
O
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

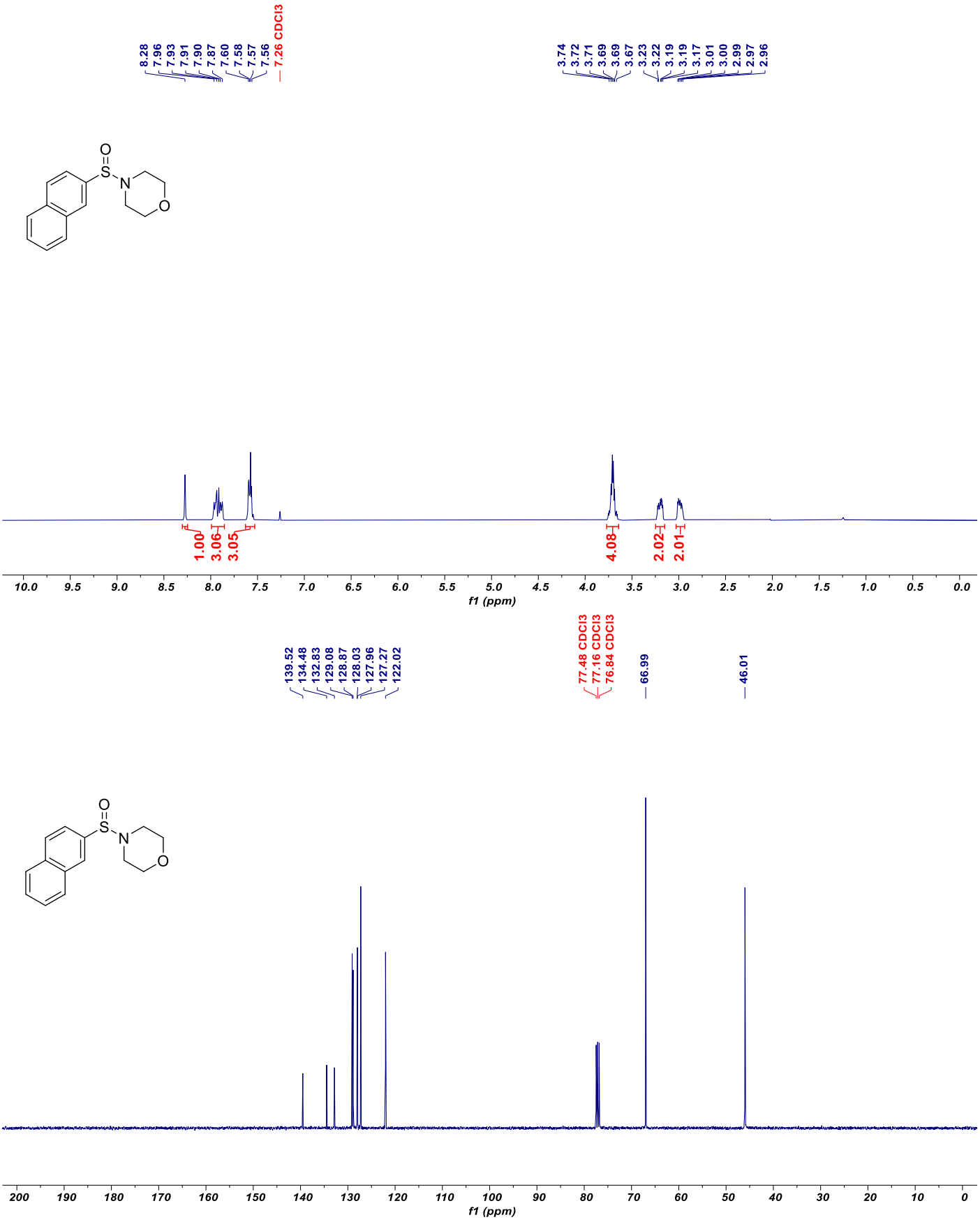
NMR spectrum of sulfinamide **18b**



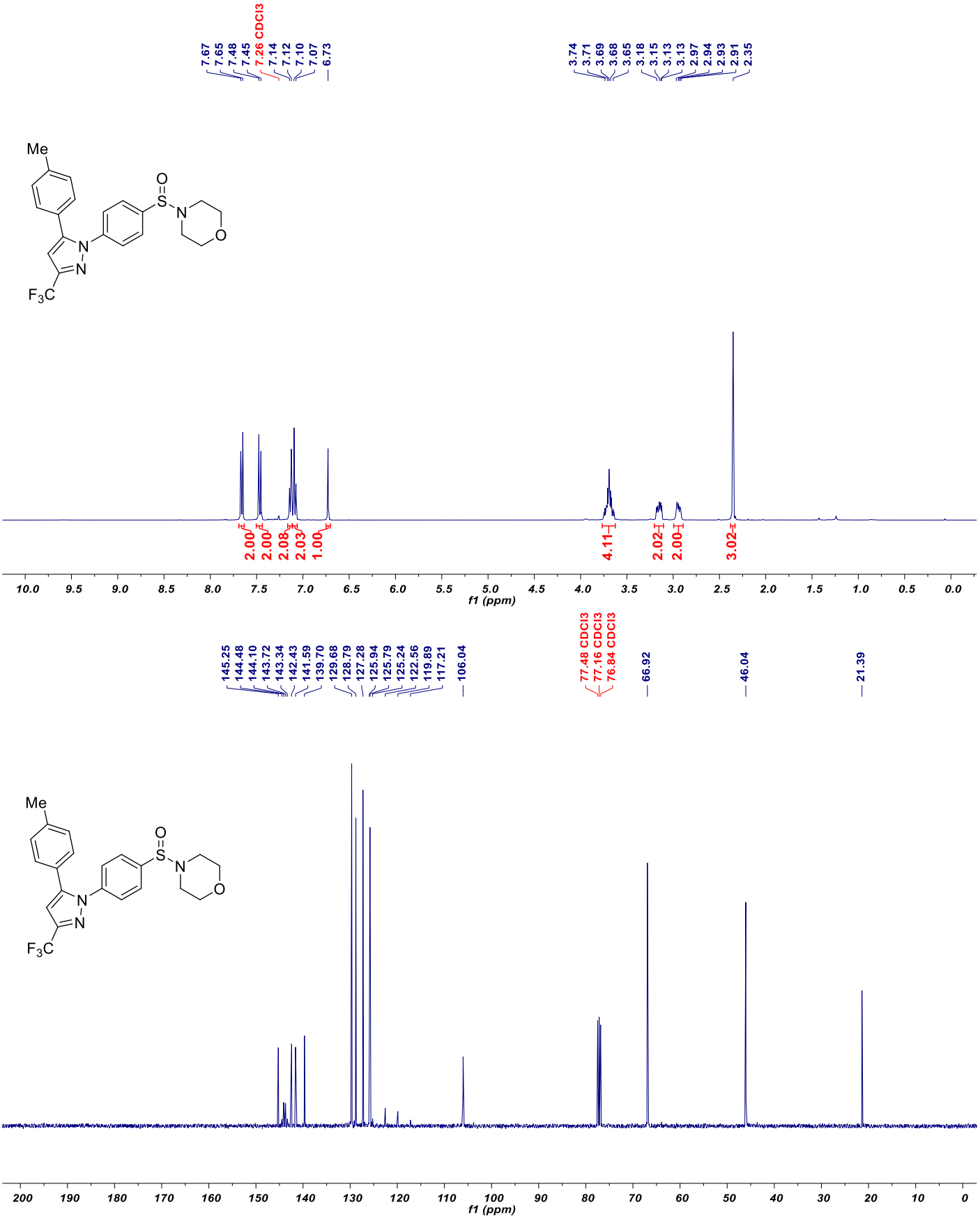
NMR spectrum of sulfinamide **18c**



NMR spectrum of sulfinamide **18d**

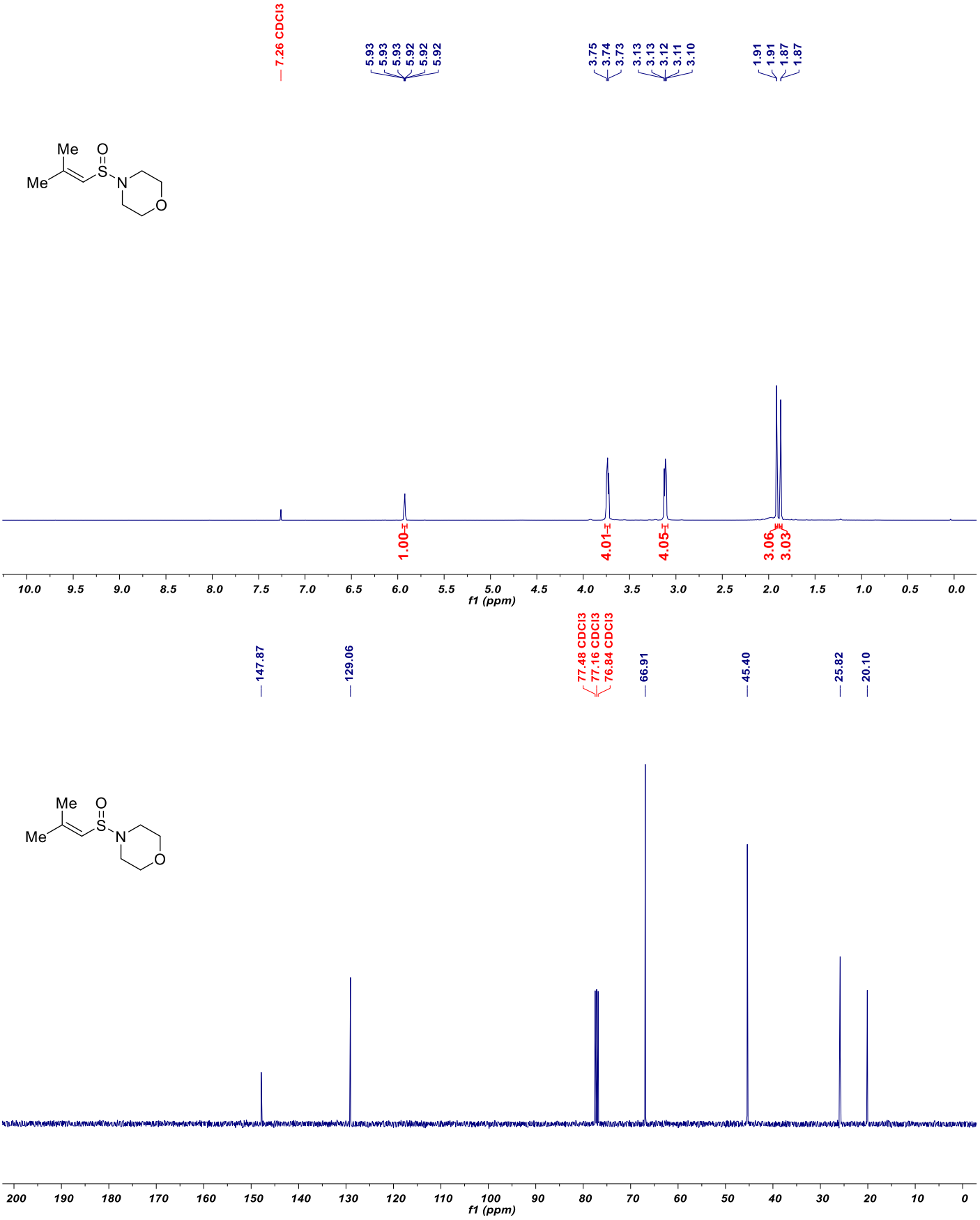


NMR spectrum of sulfinamide **18e**

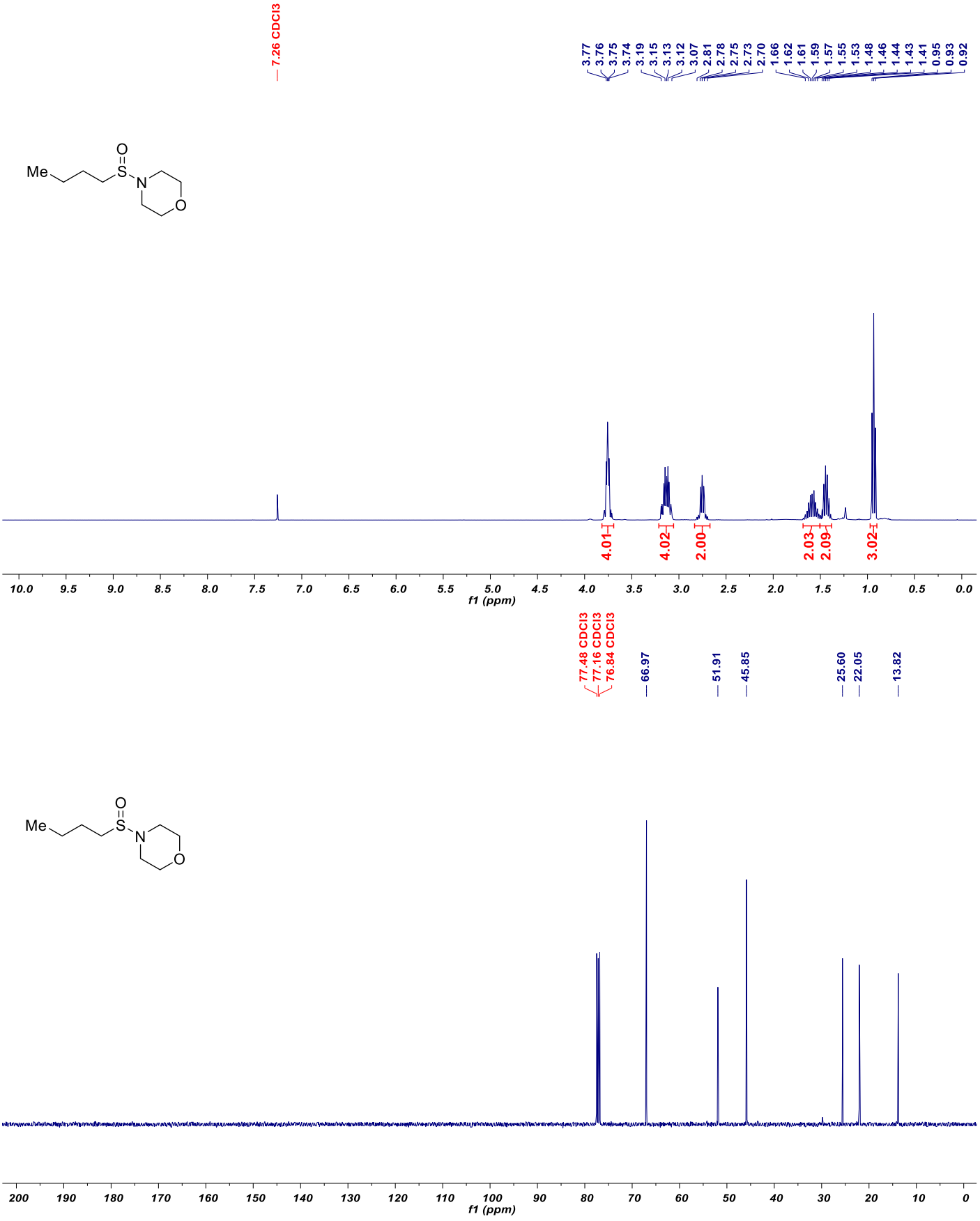



-62.37
Me
O
S
N
O
N
N
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

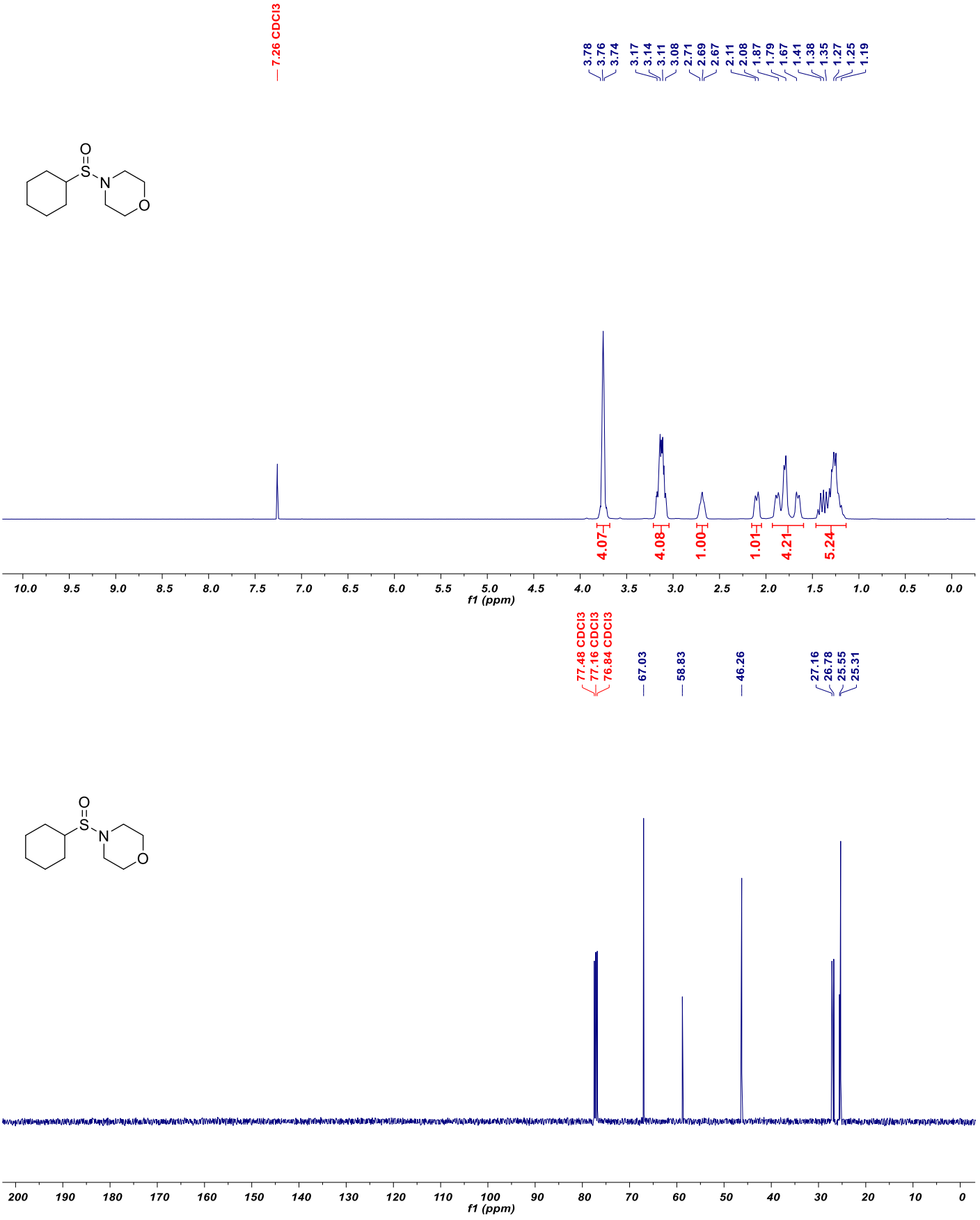
NMR spectrum of sulfinamide **18f**



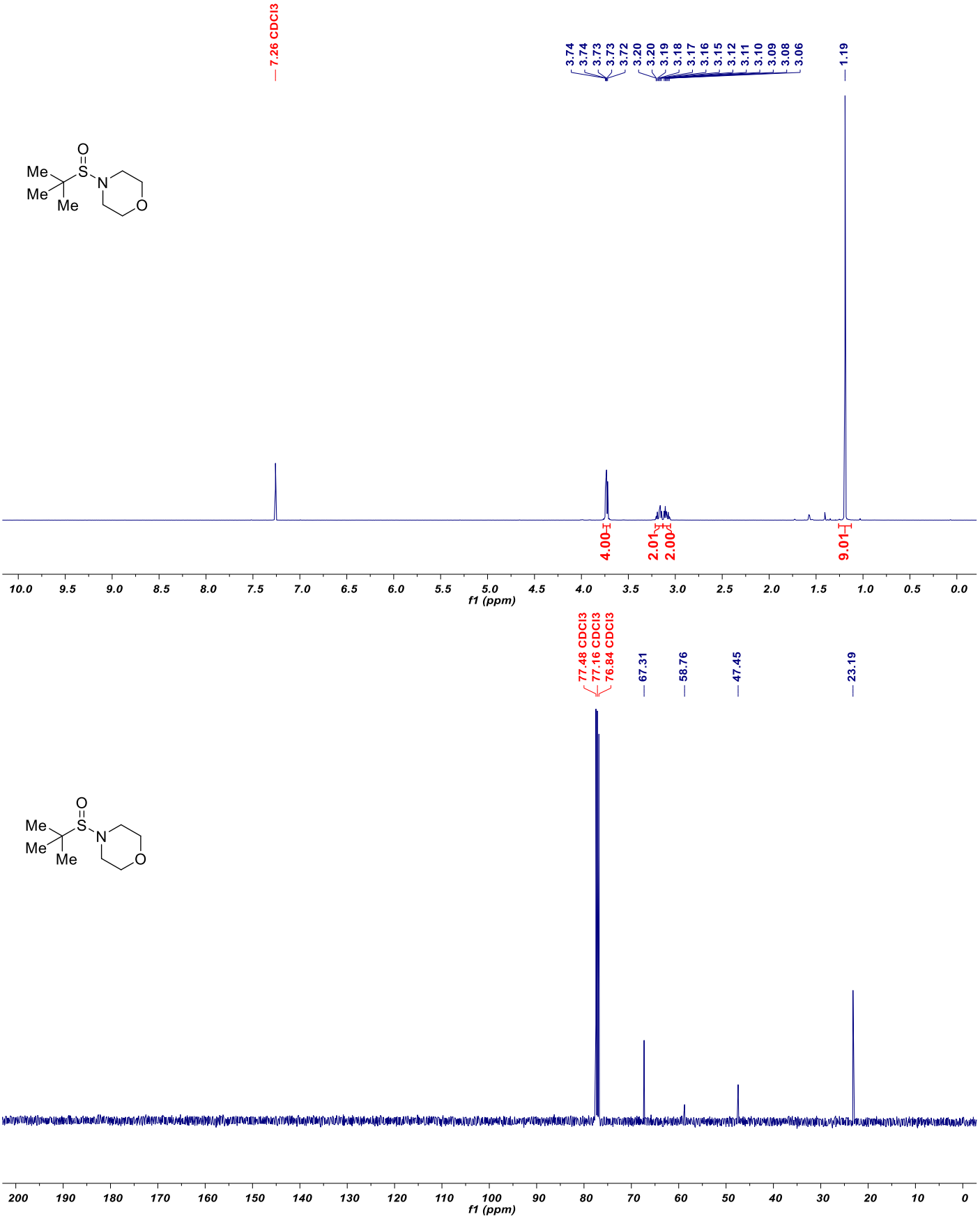
NMR spectrum of sulfinamide **18g**



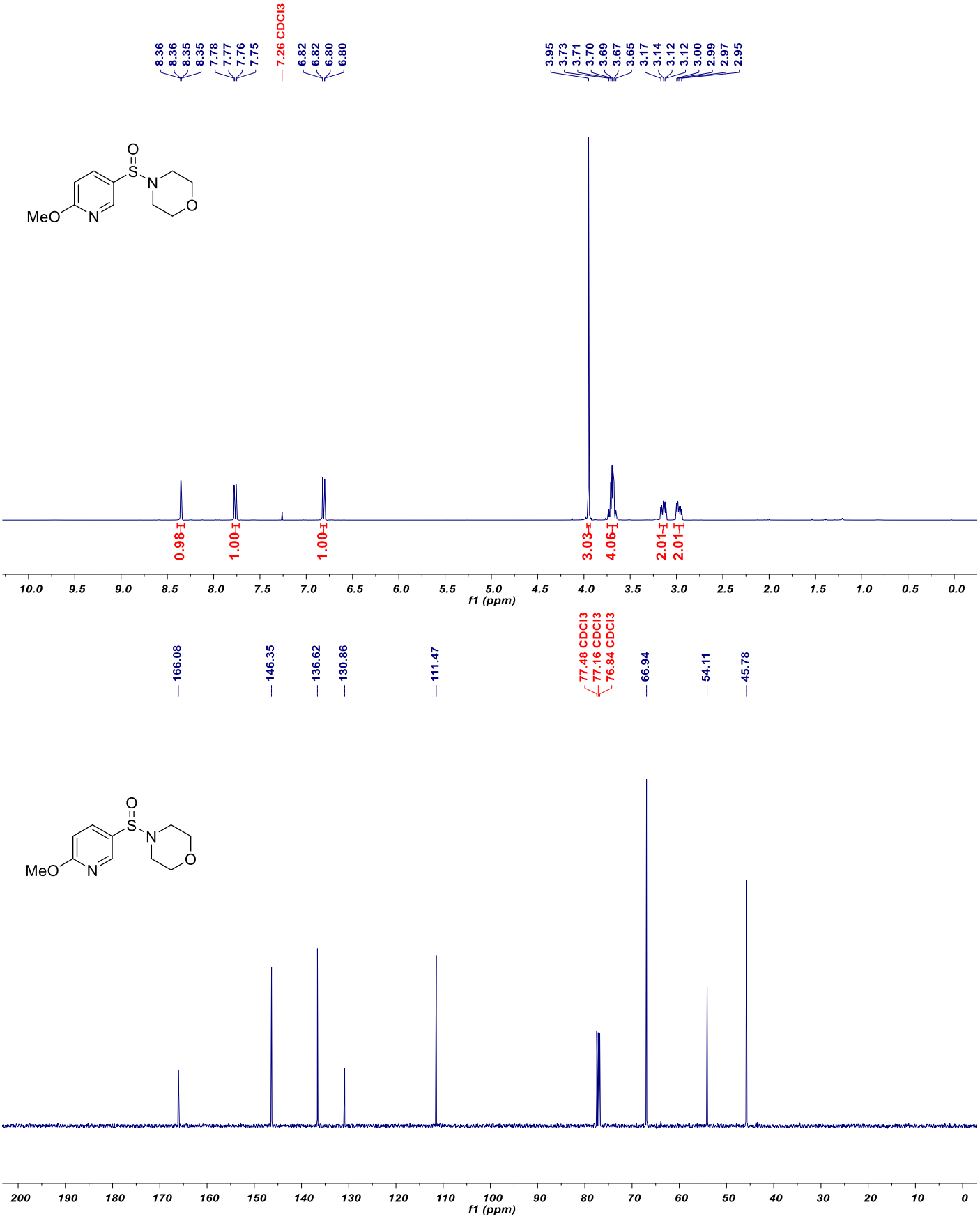
NMR spectrum of sulfinamide **18h**



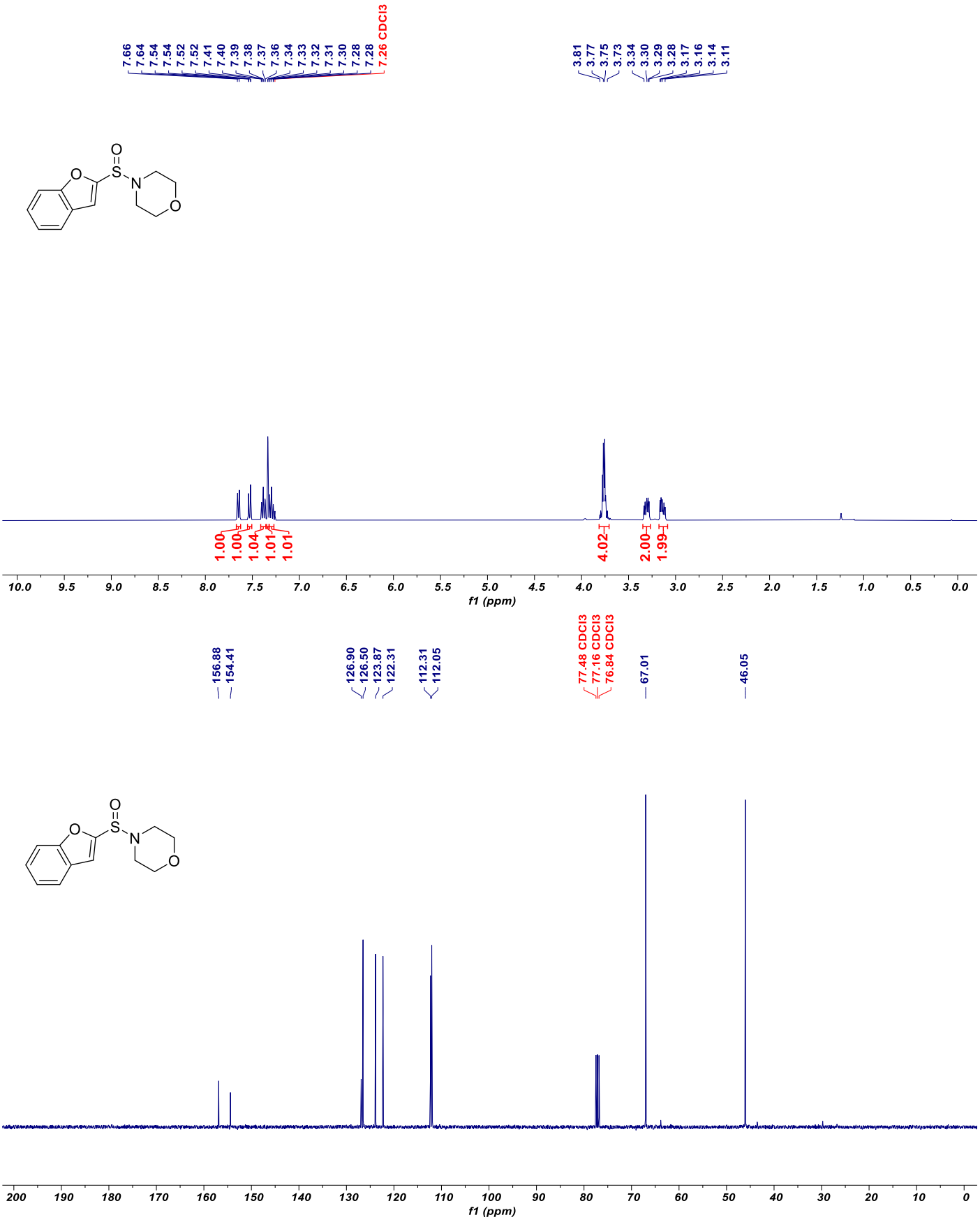
NMR spectrum of sulfinamide **18i**



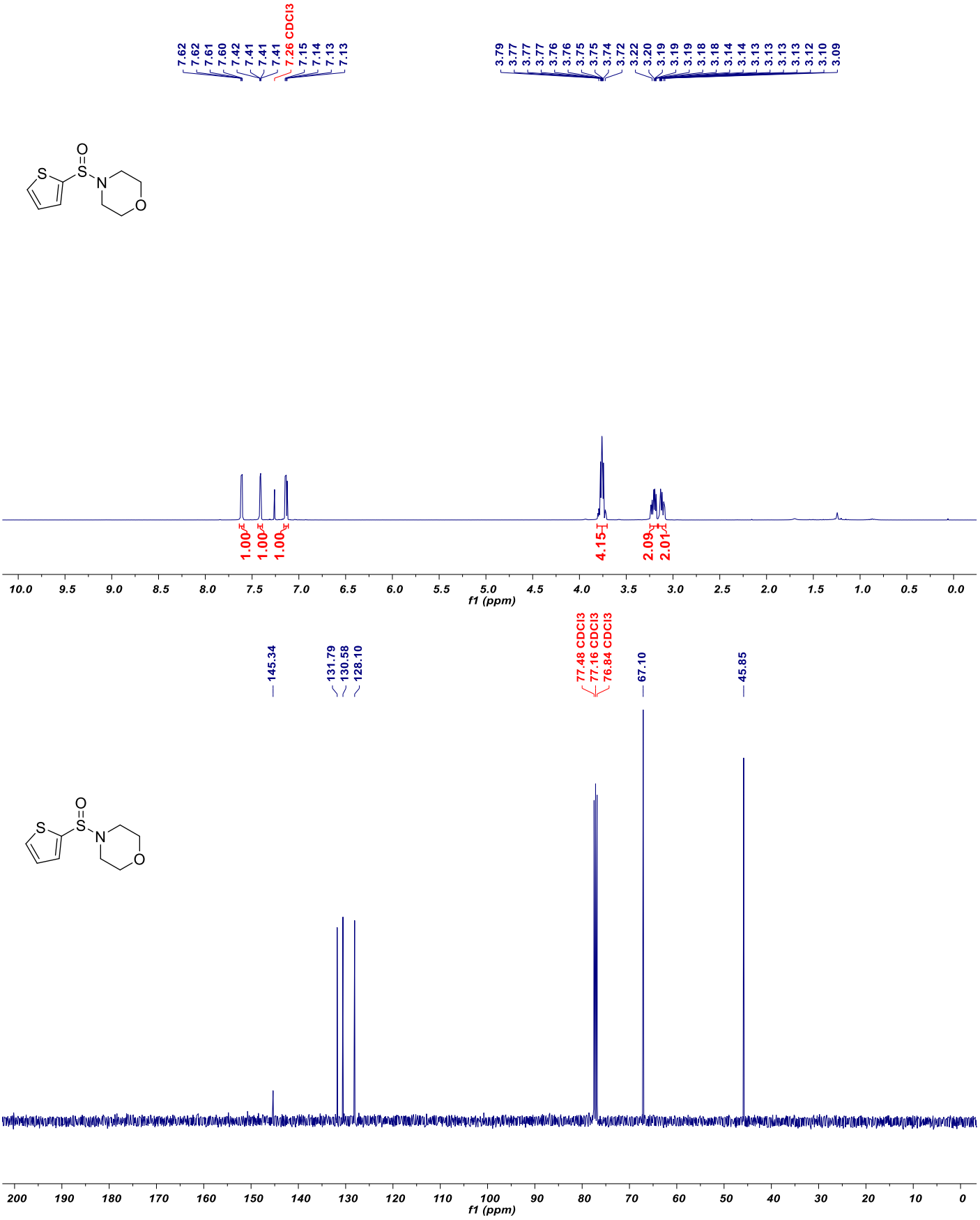
NMR spectrum of sulfinamide **18j**



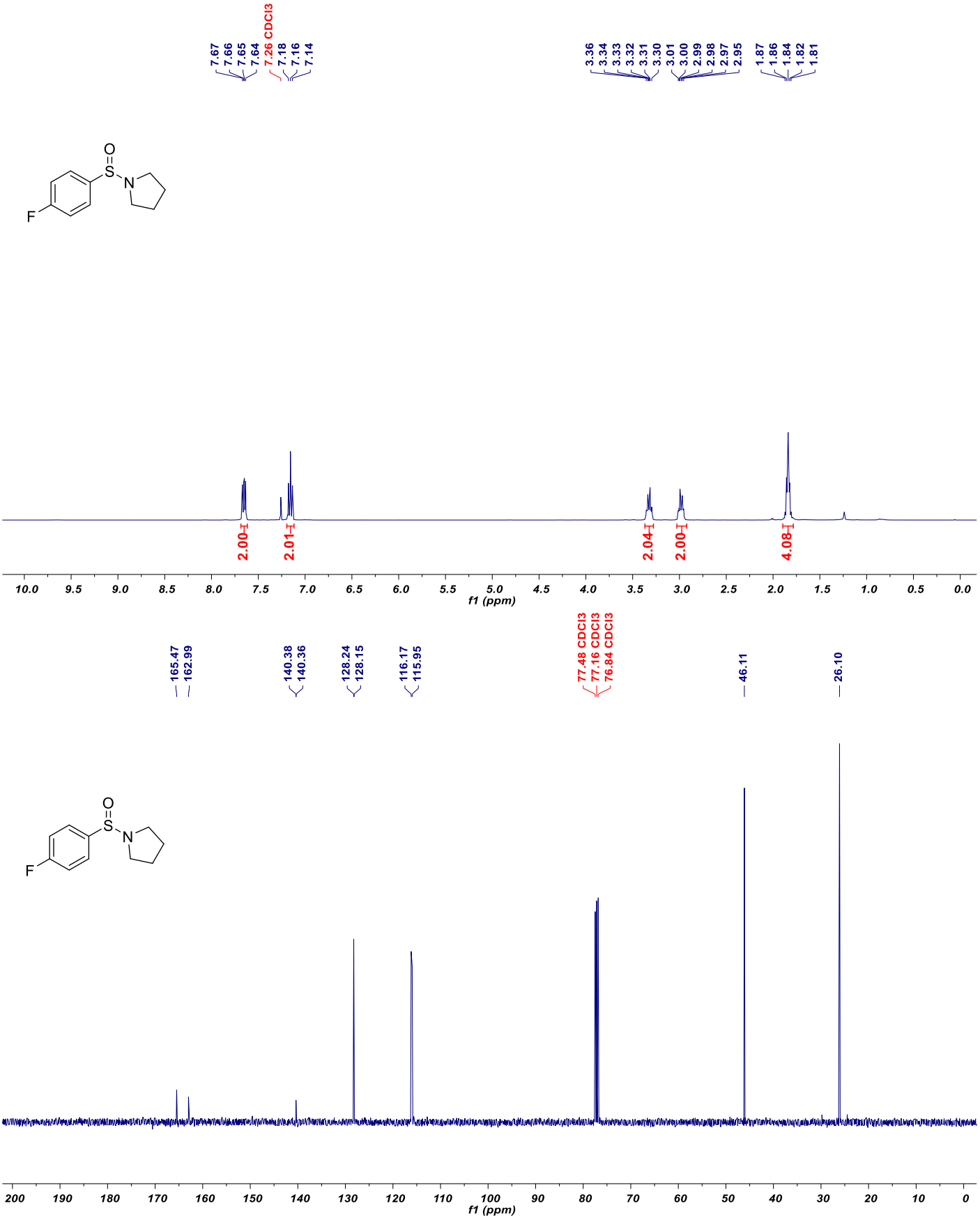
NMR spectrum of sulfinamide **18k**

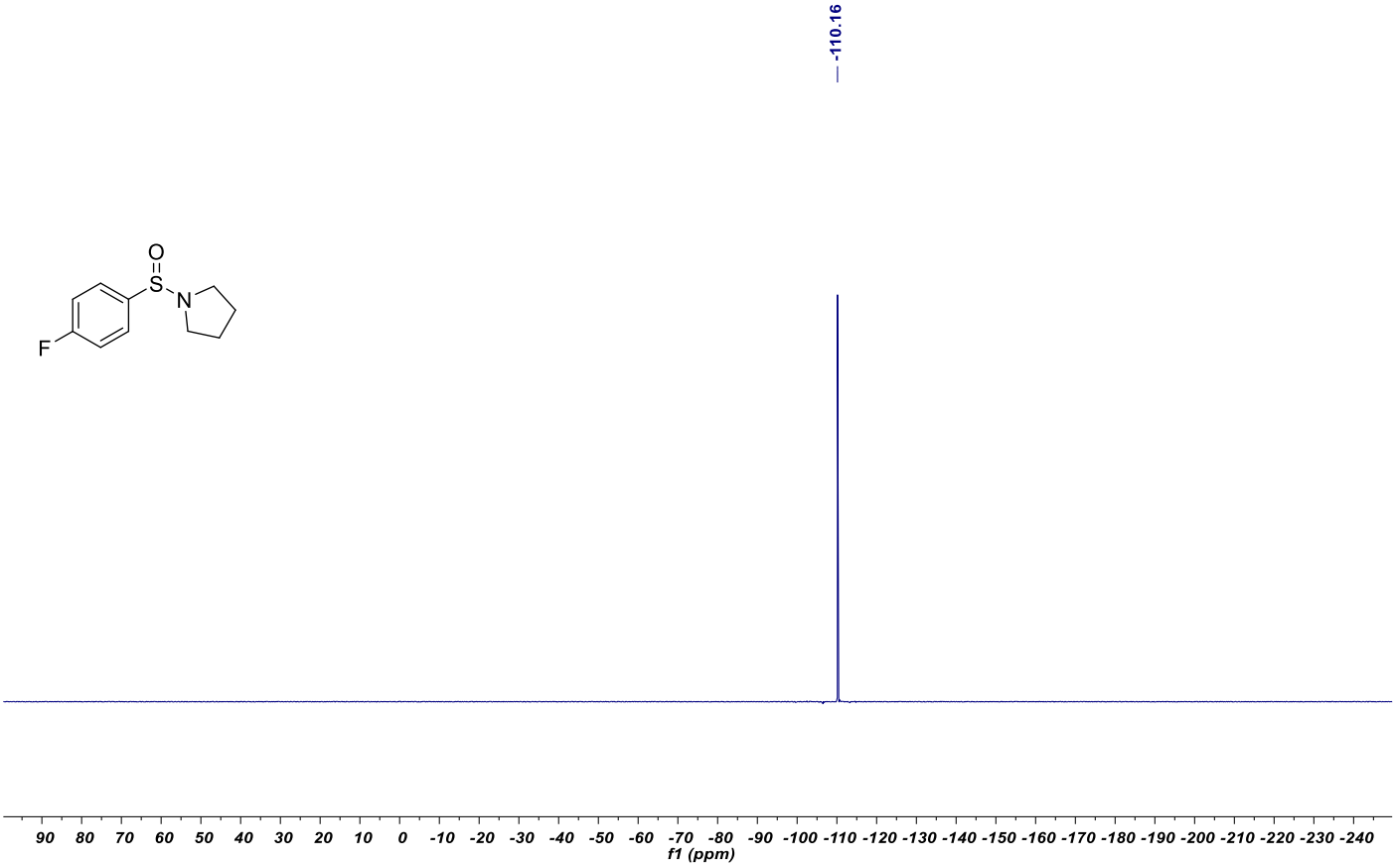


NMR spectrum of sulfinamide **18l**

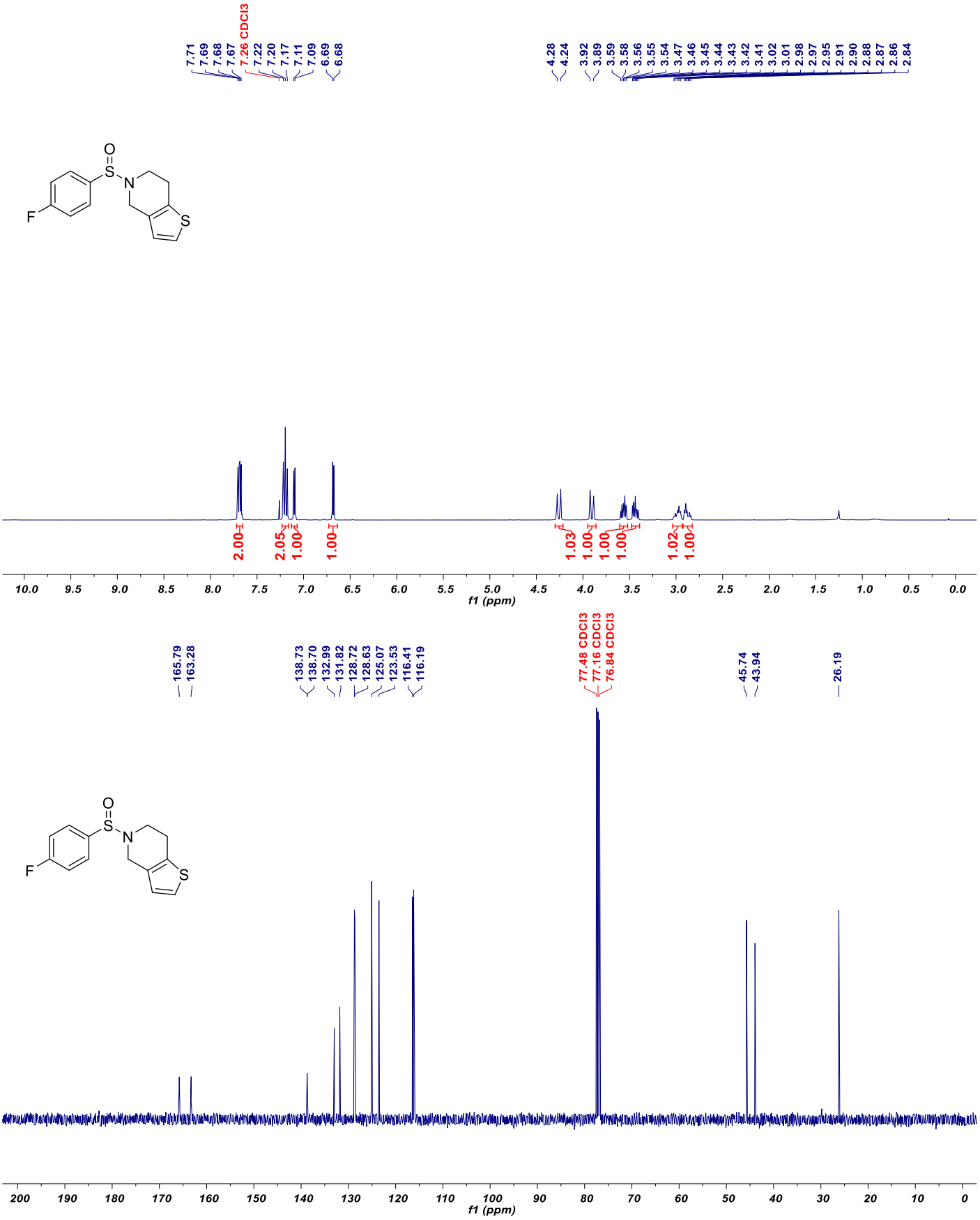


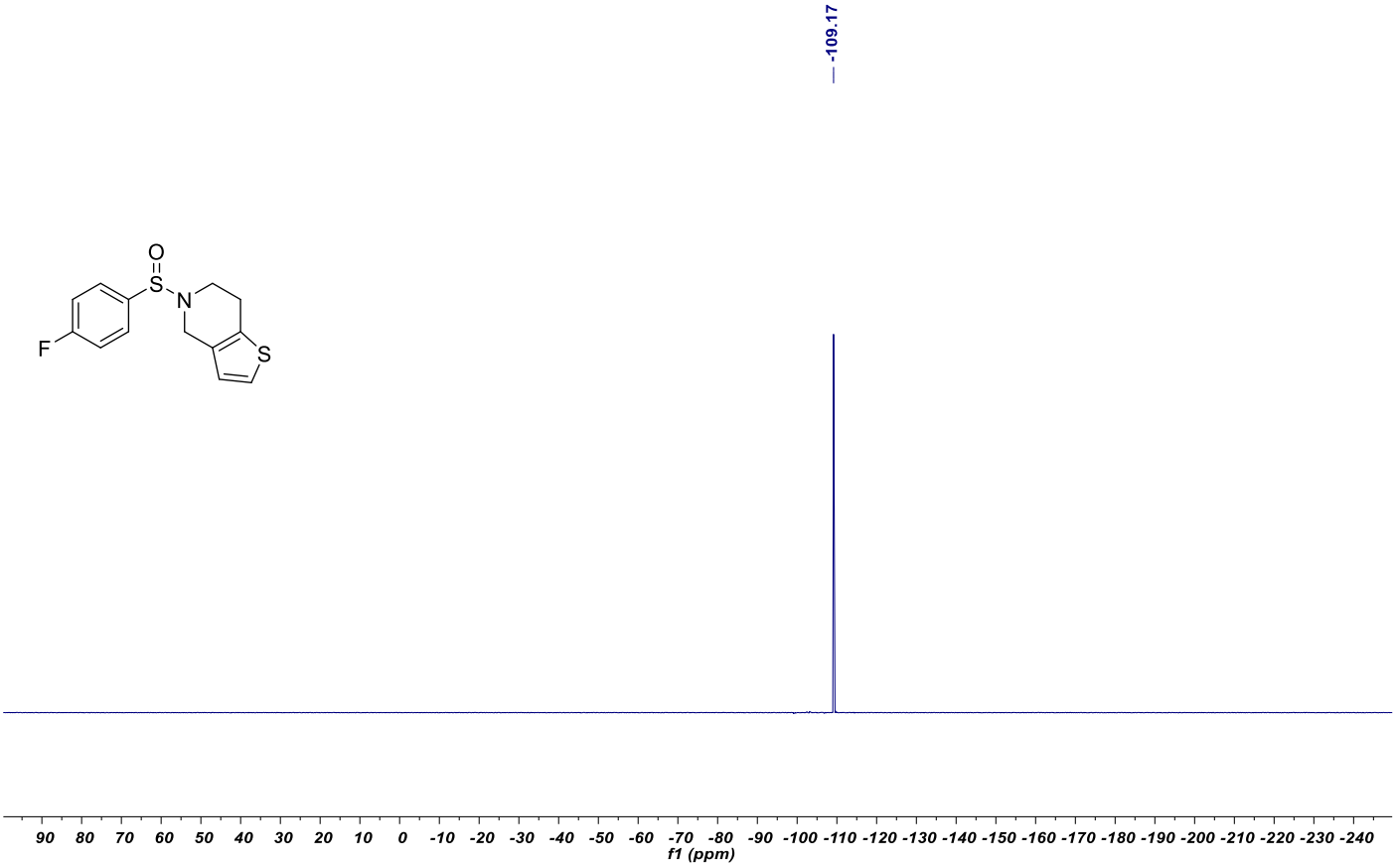
NMR spectrum of sulfinamide **19a**



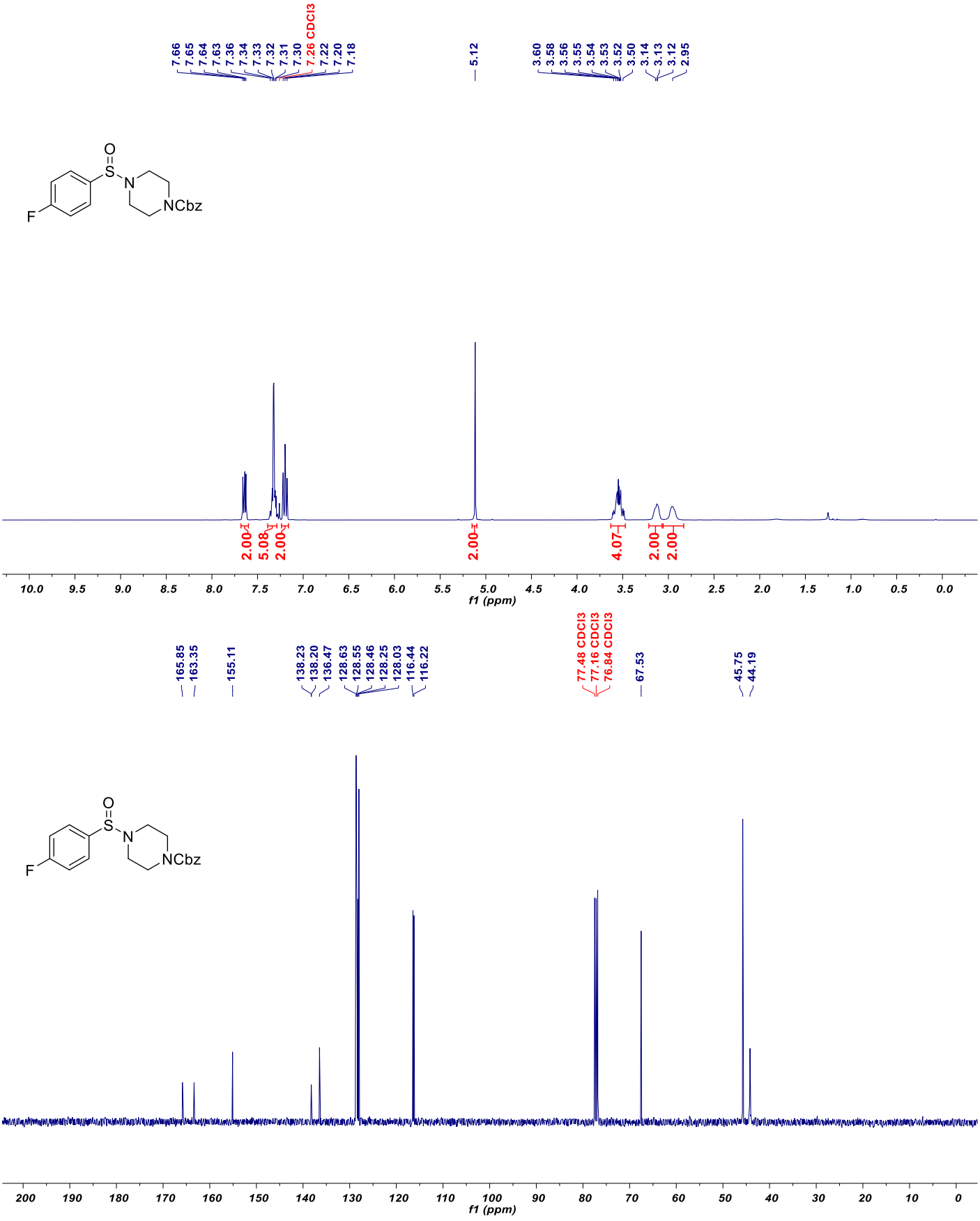

-110.16
O
S
N
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

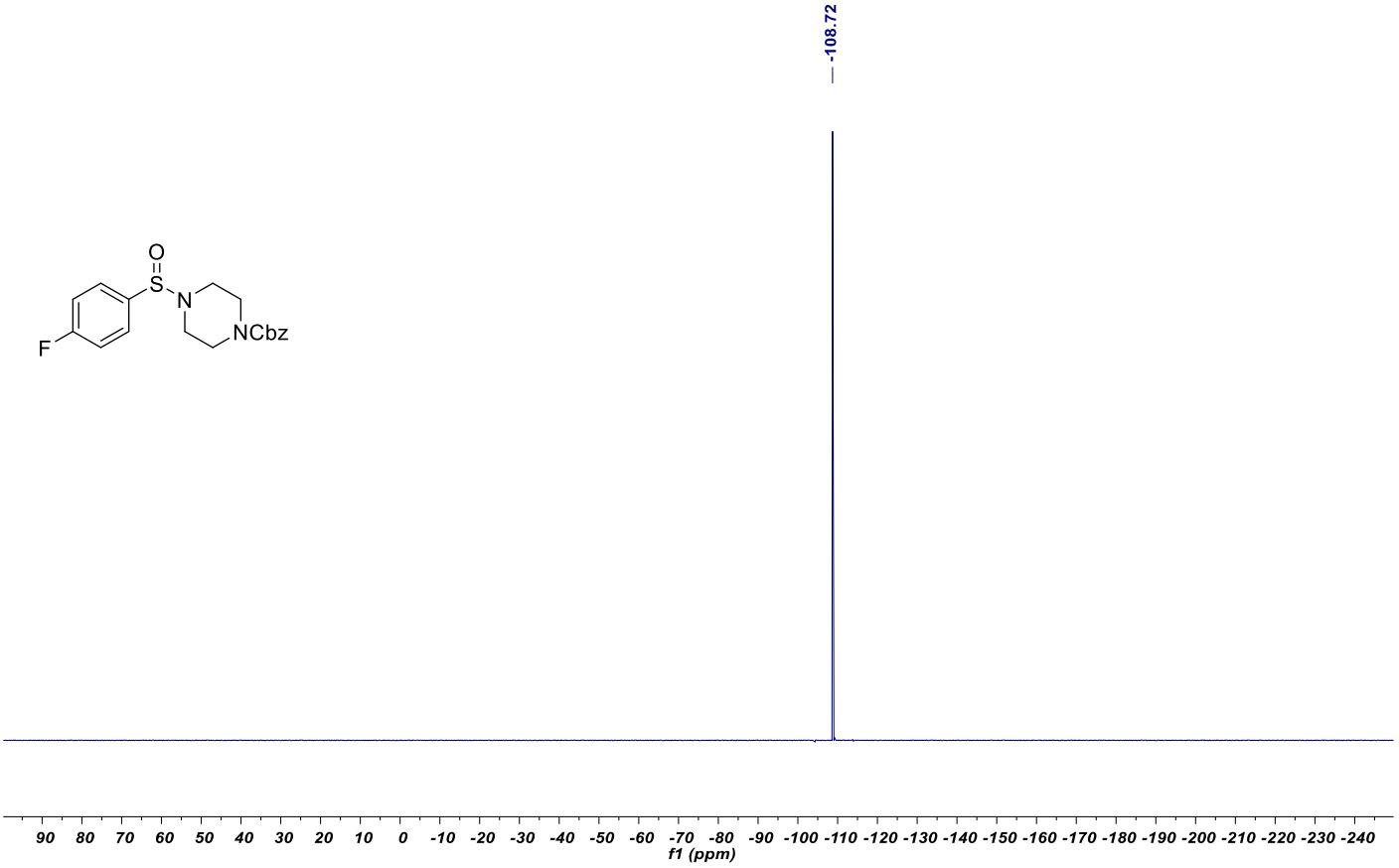
NMR spectrum of sulfinamide **19b**



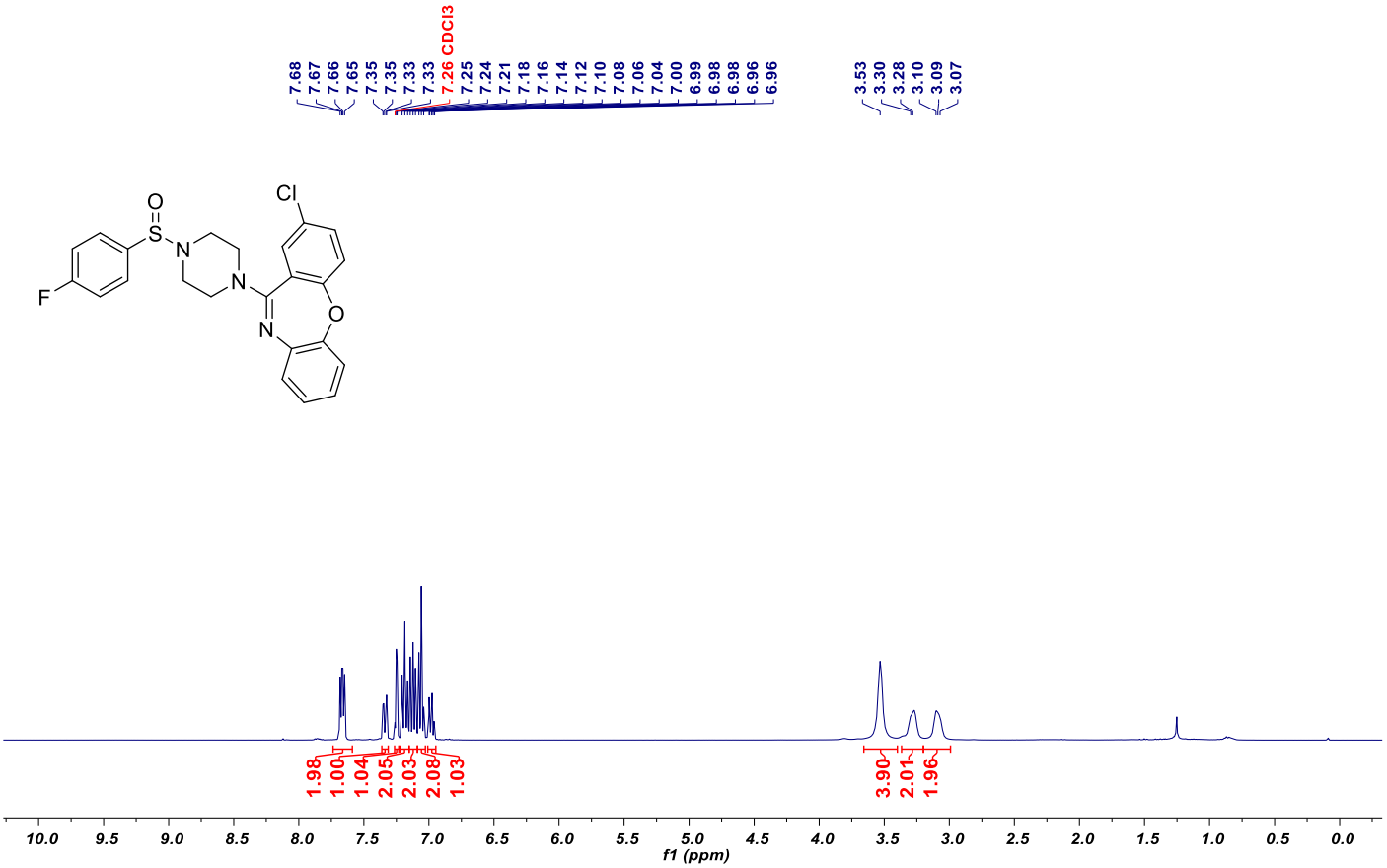

-109.17
O
S
N
F
S
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

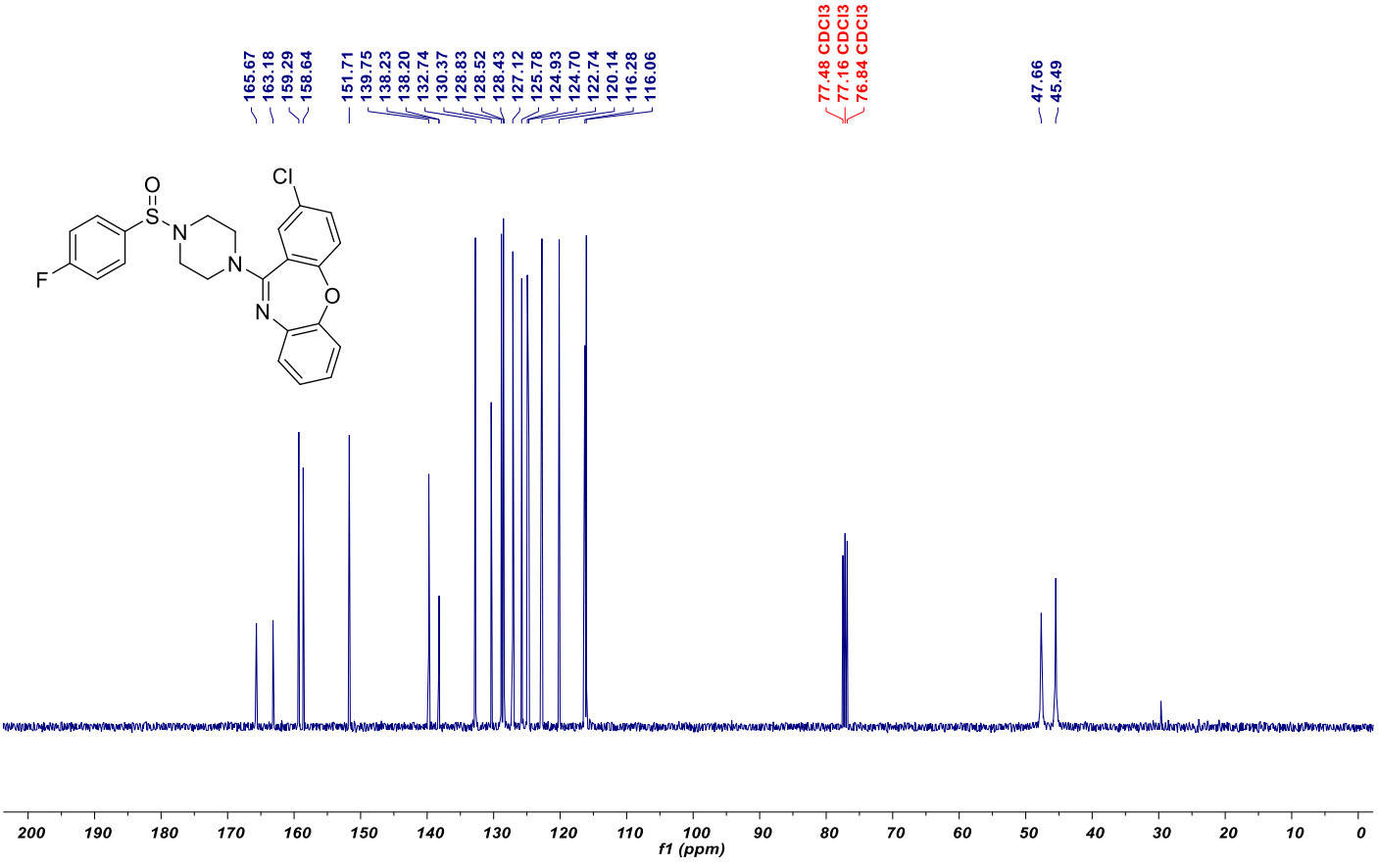
NMR spectrum of sulfinamide **19c**

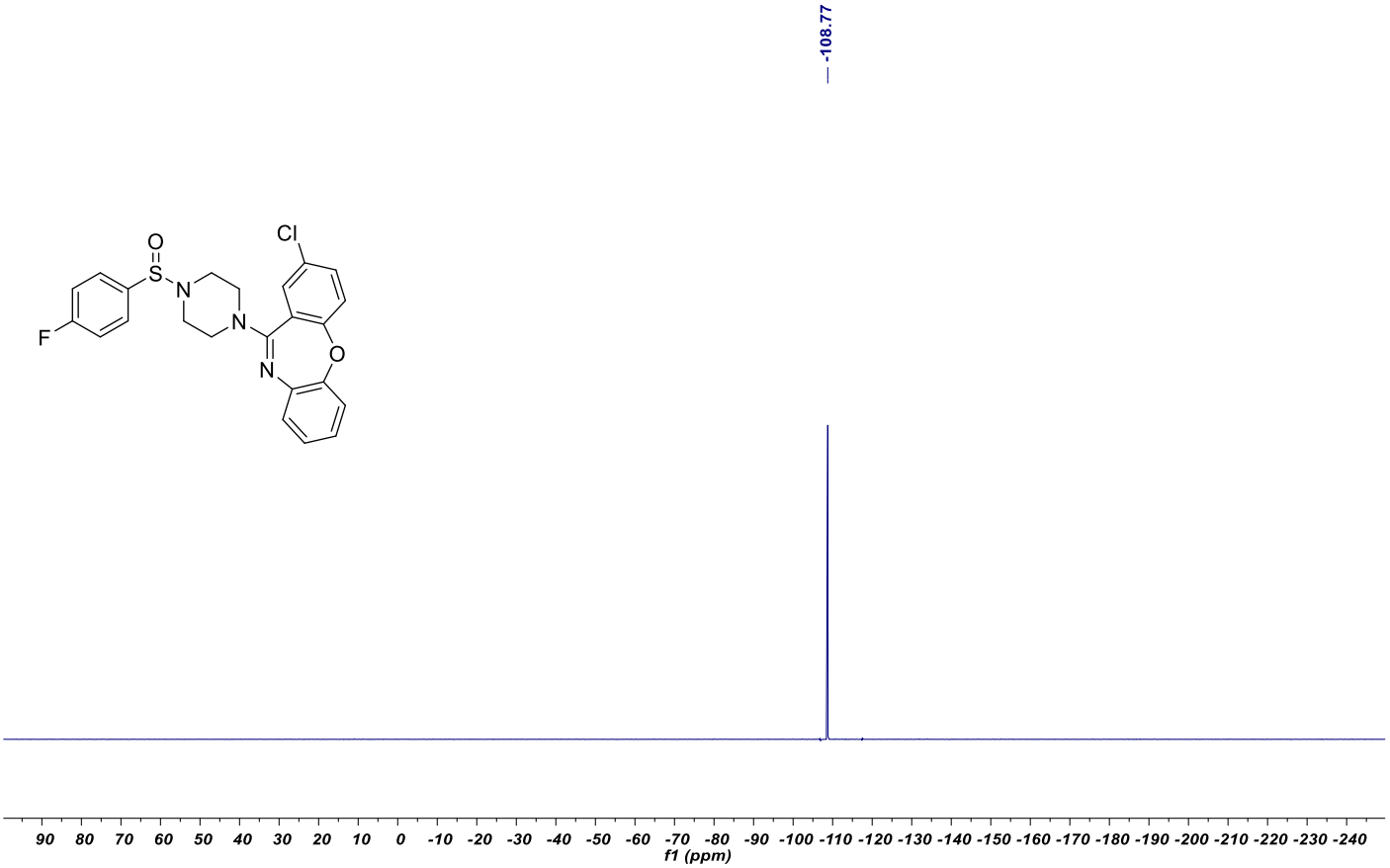



-108.72
O
S
N
NCbz
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

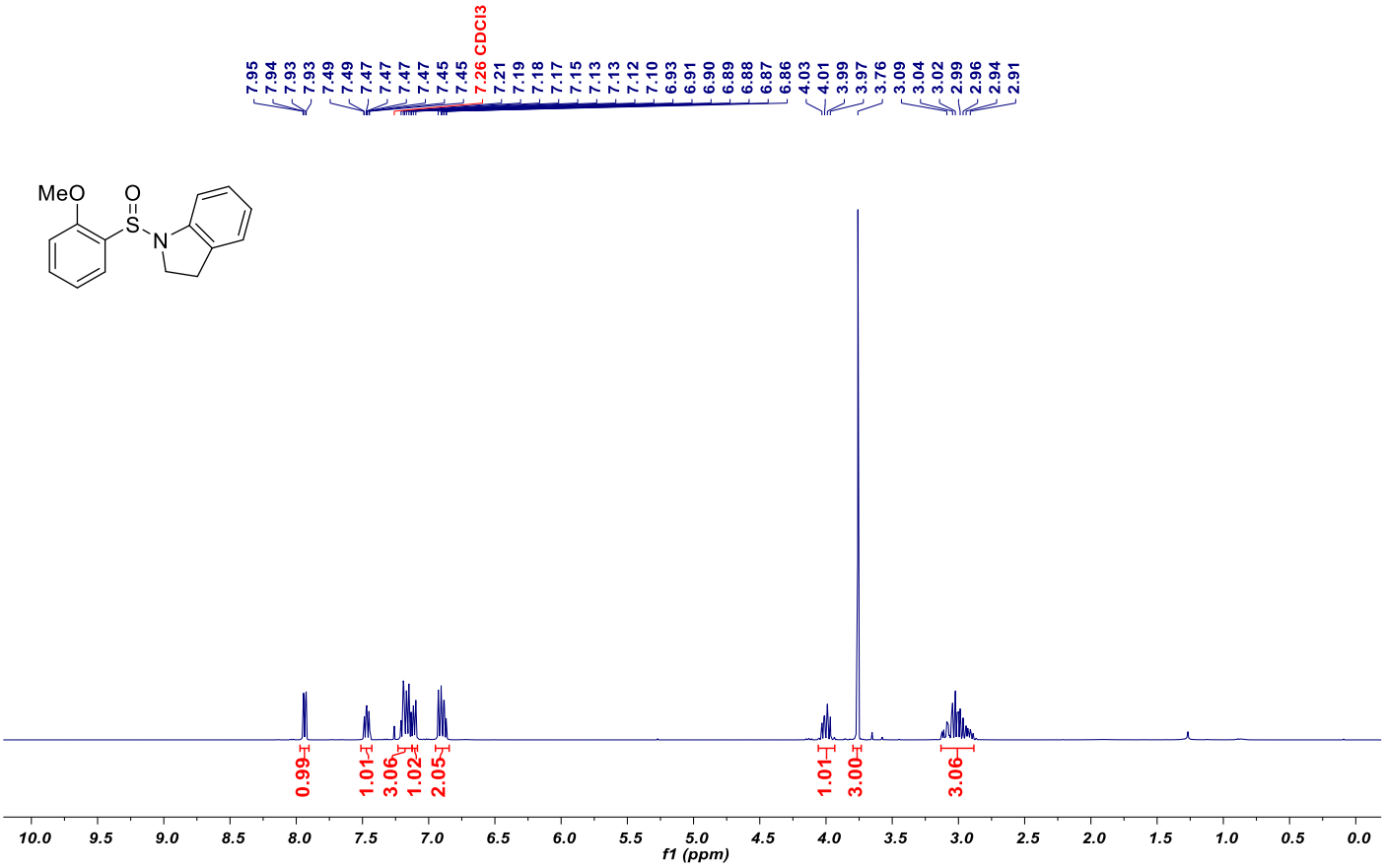
NMR spectrum of sulfinamide **19d**

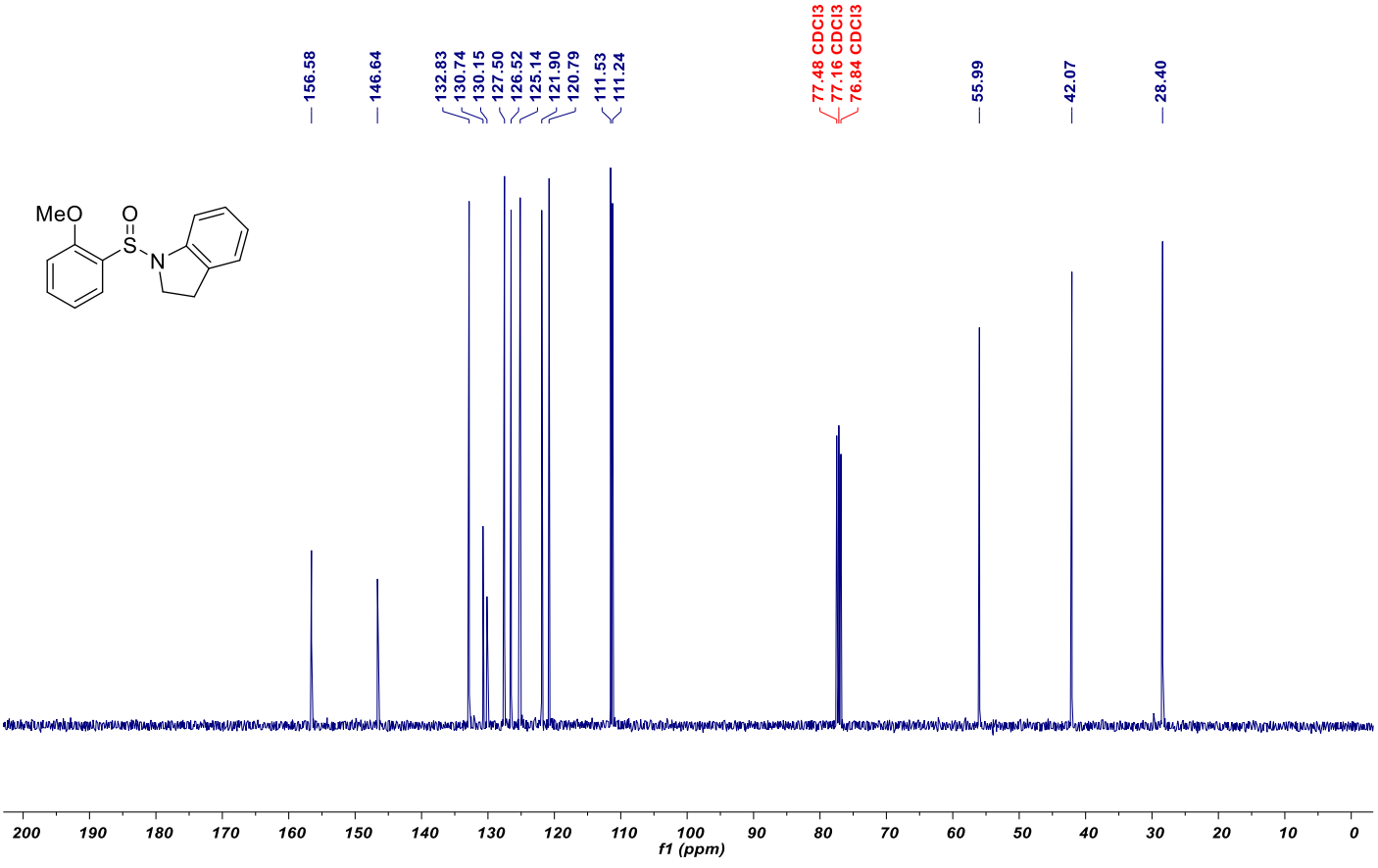




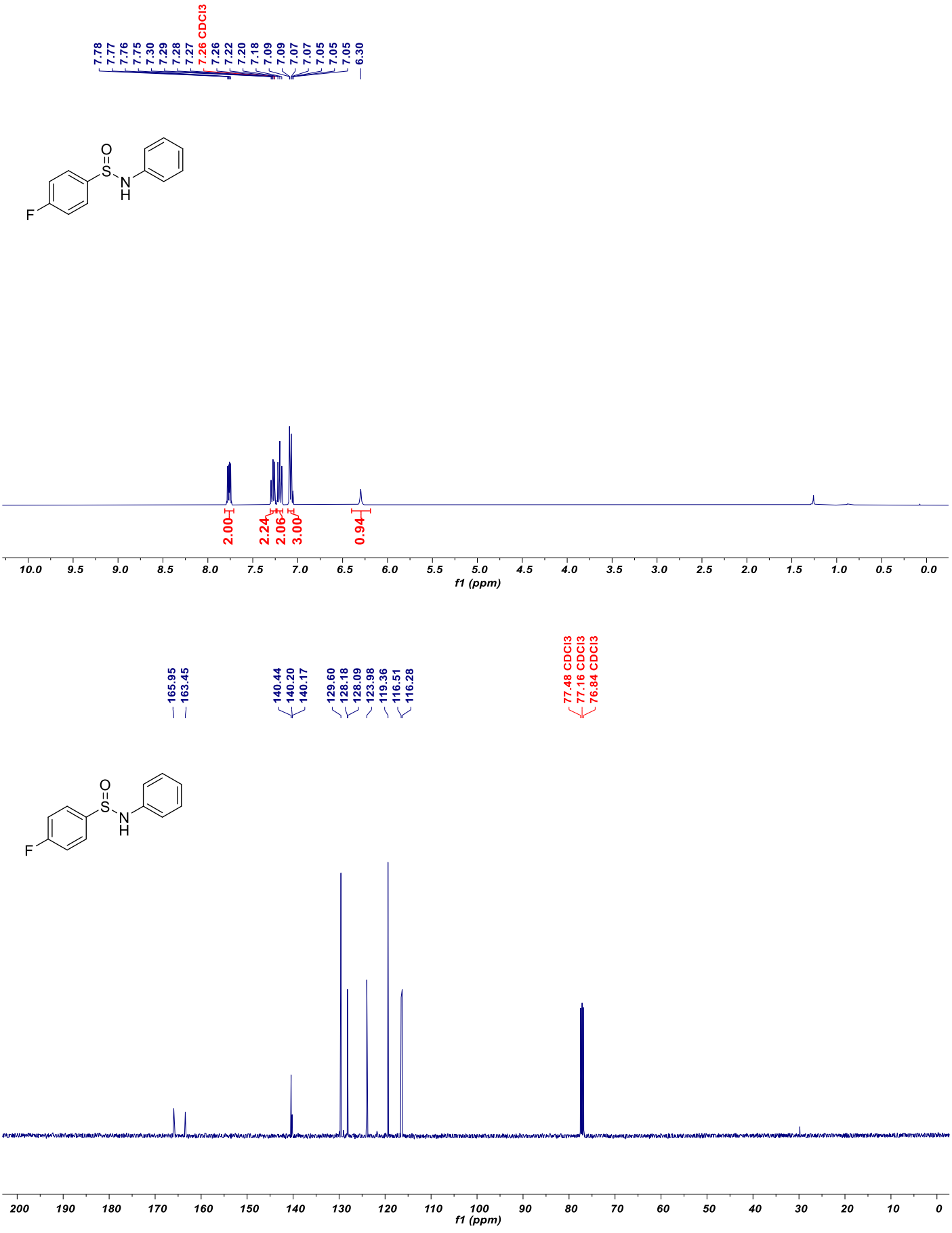

-108.77
O
S
N
N
N
O
Cl
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

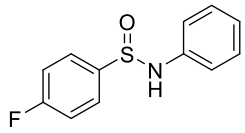
NMR spectrum of sulfinamide **19e**





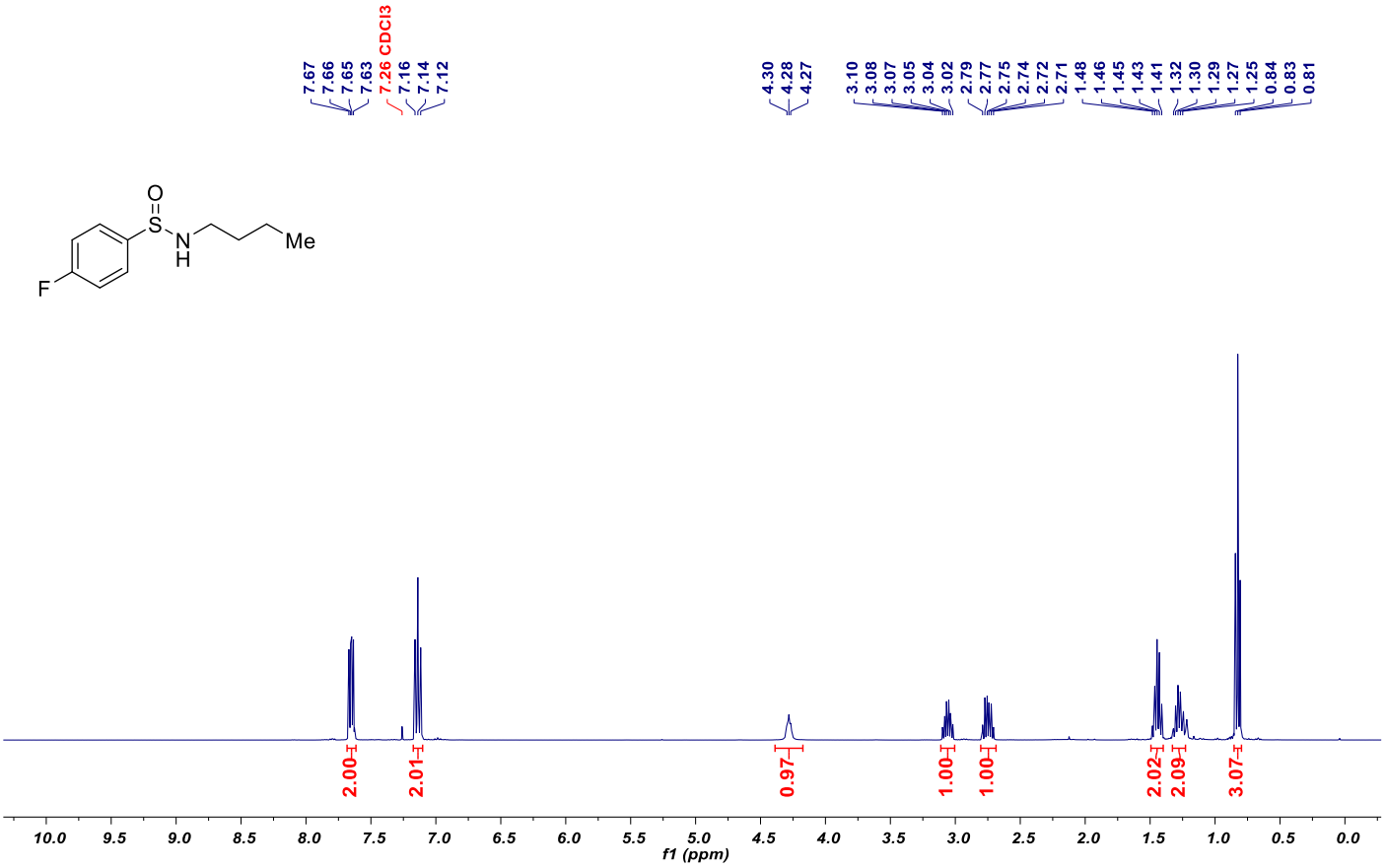
NMR spectrum of sulfinamide **19f**

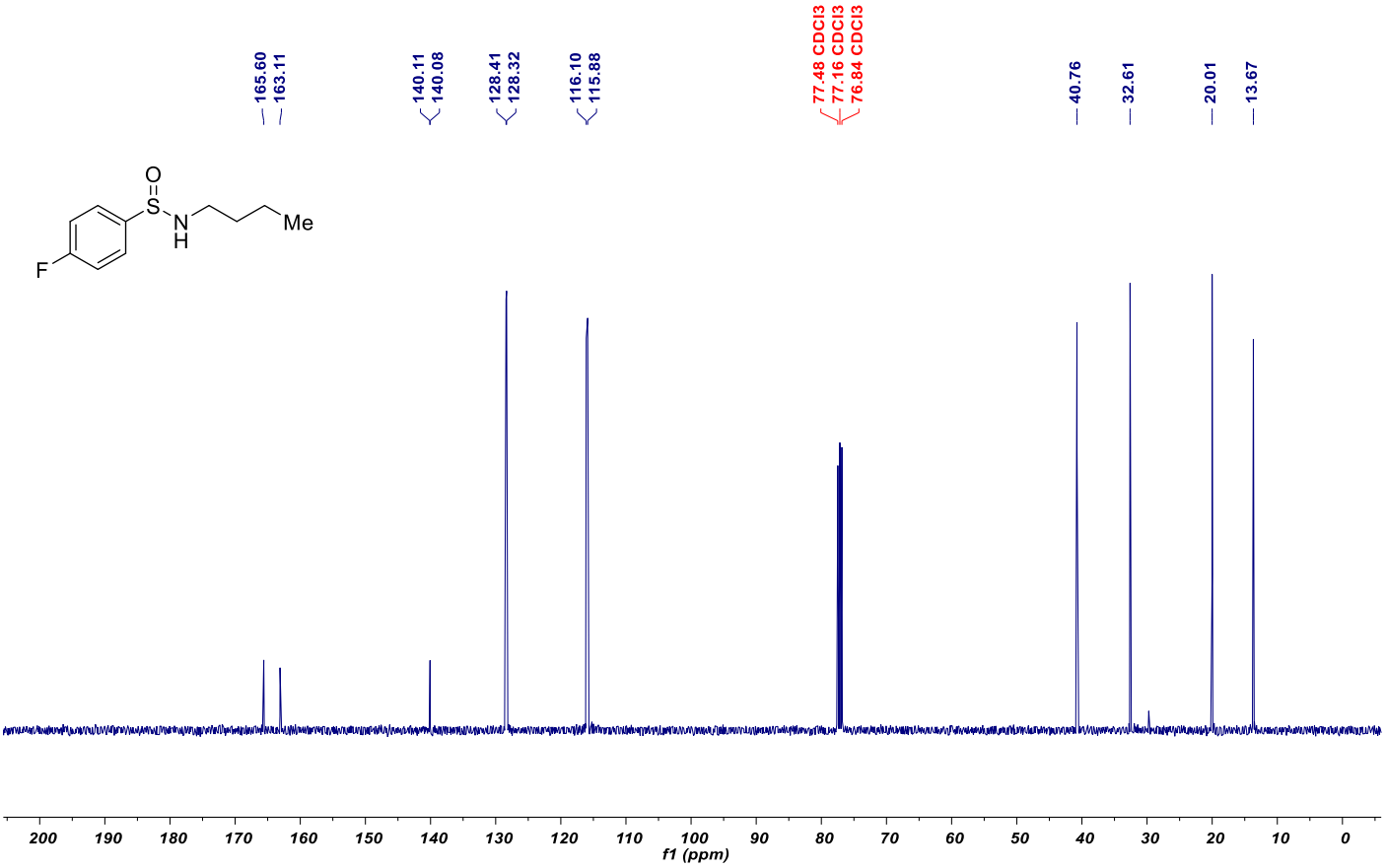


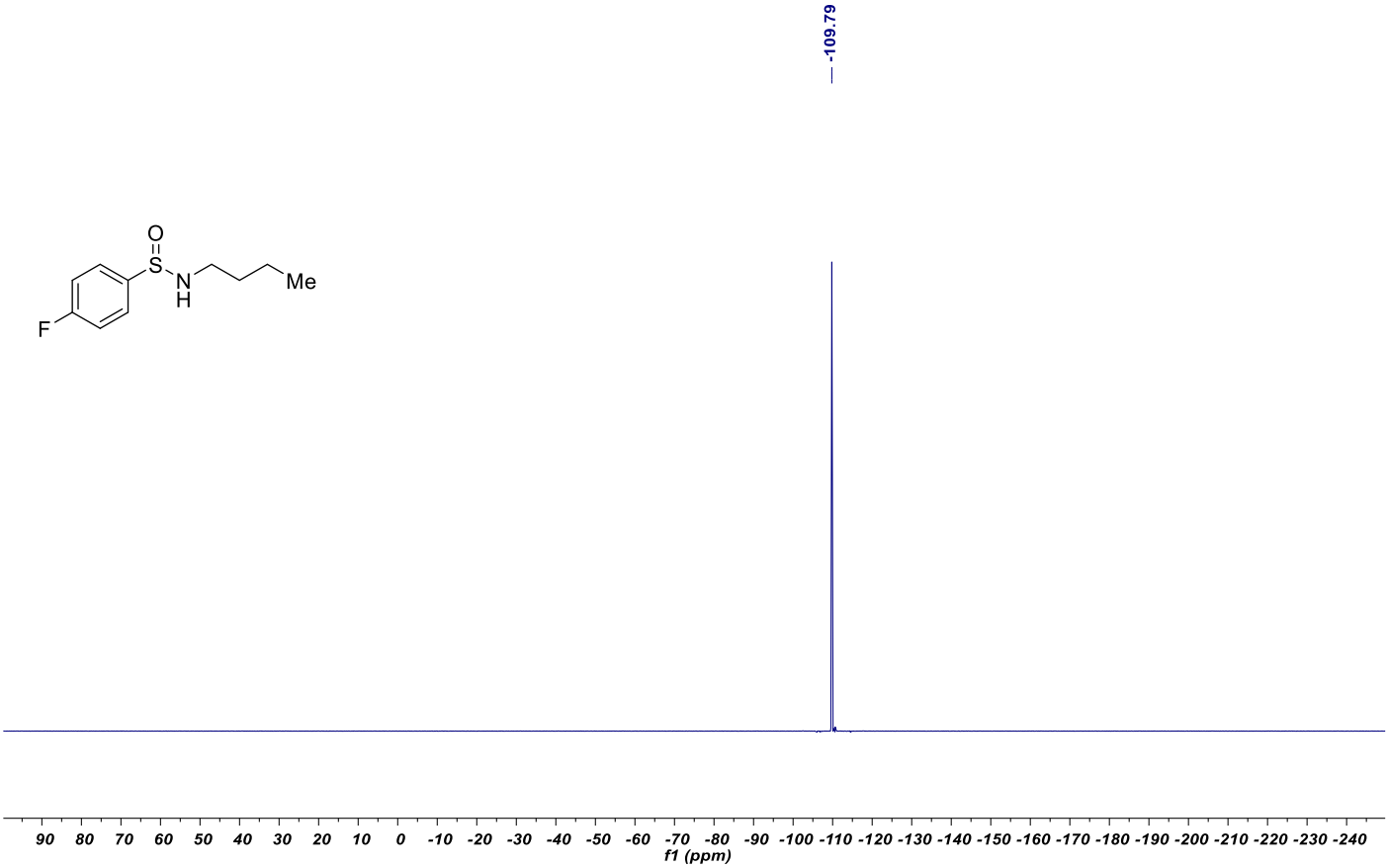

O
S
N
H
F

-108.35
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

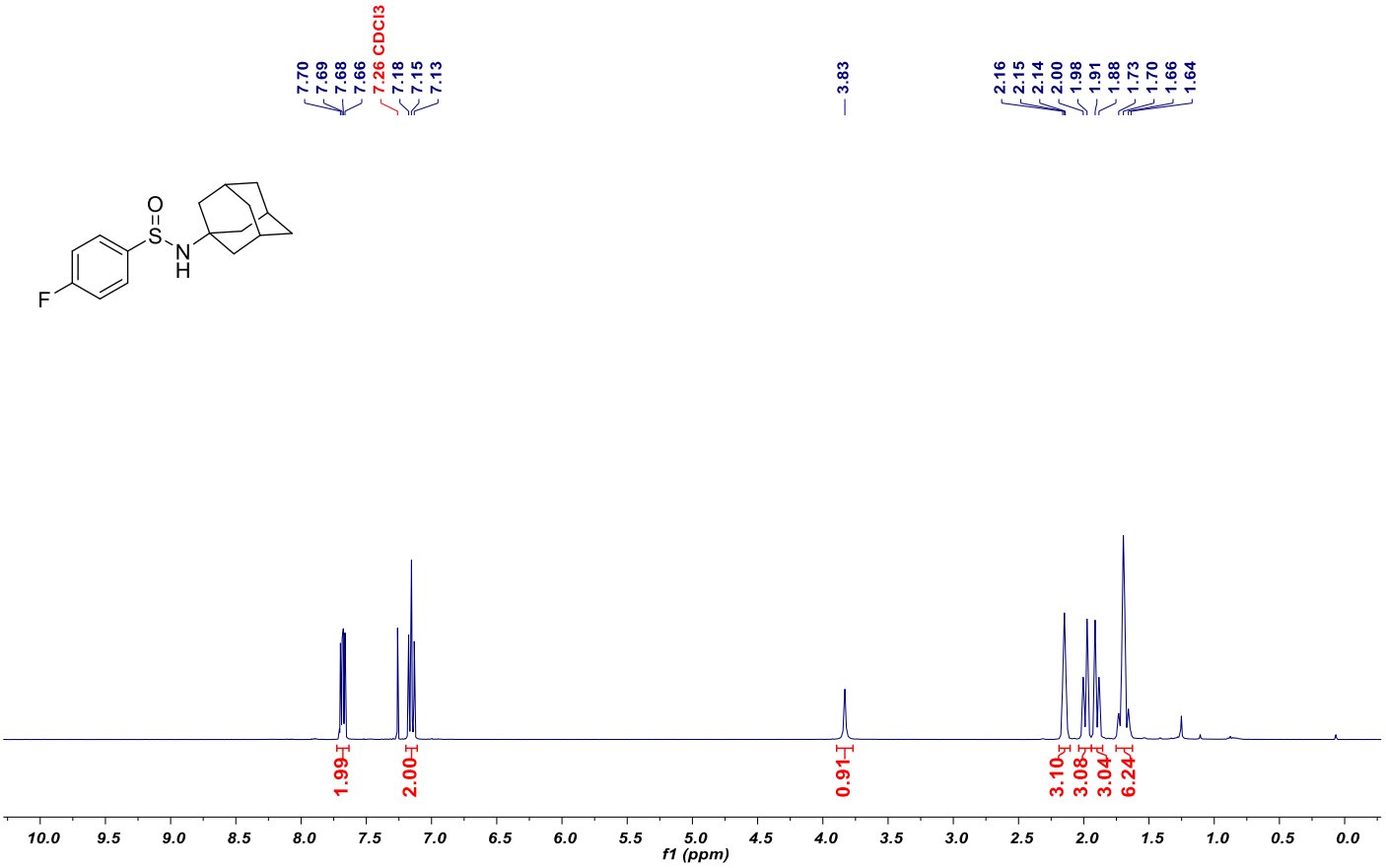
NMR spectrum of sulfinamide **19g**

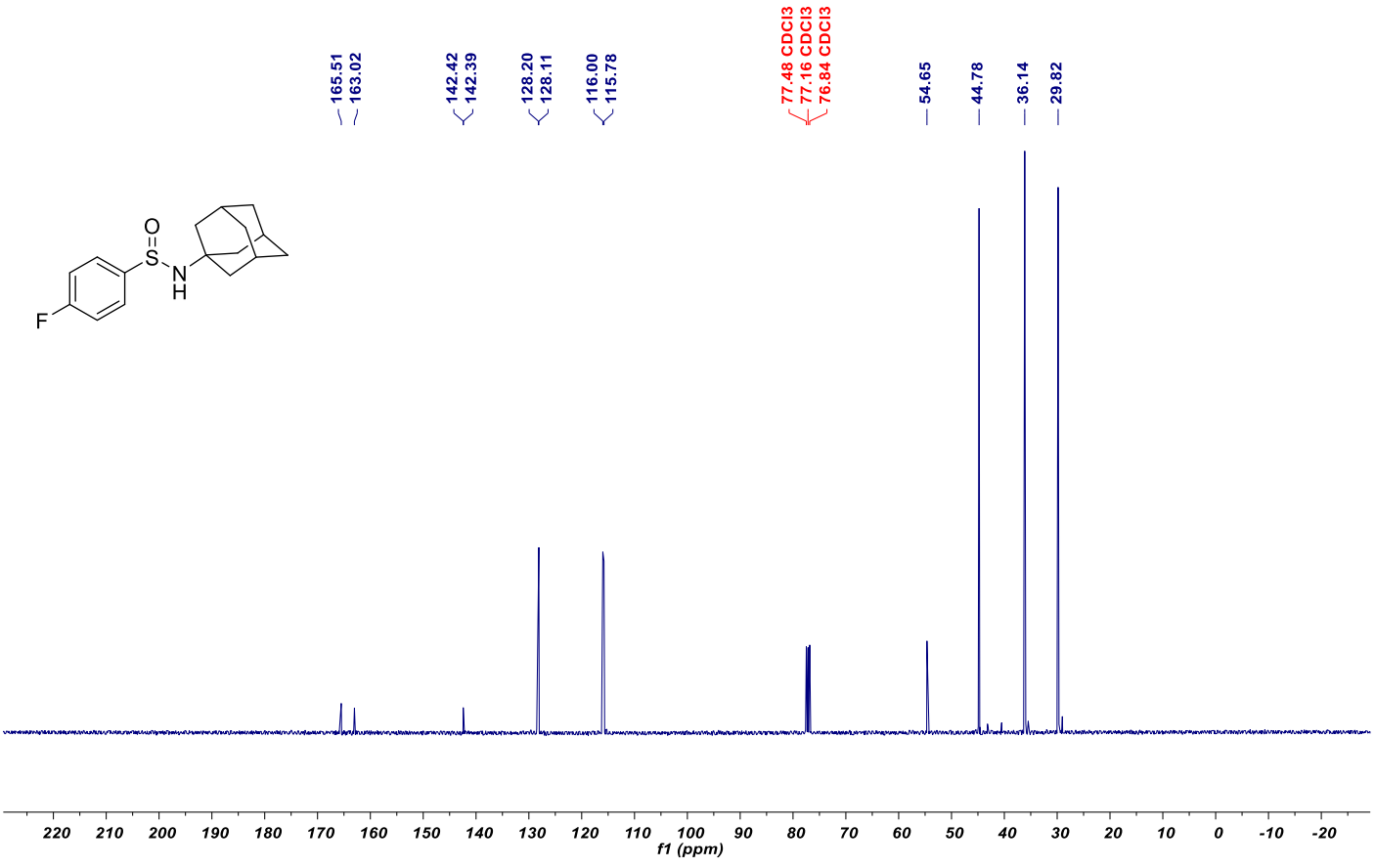


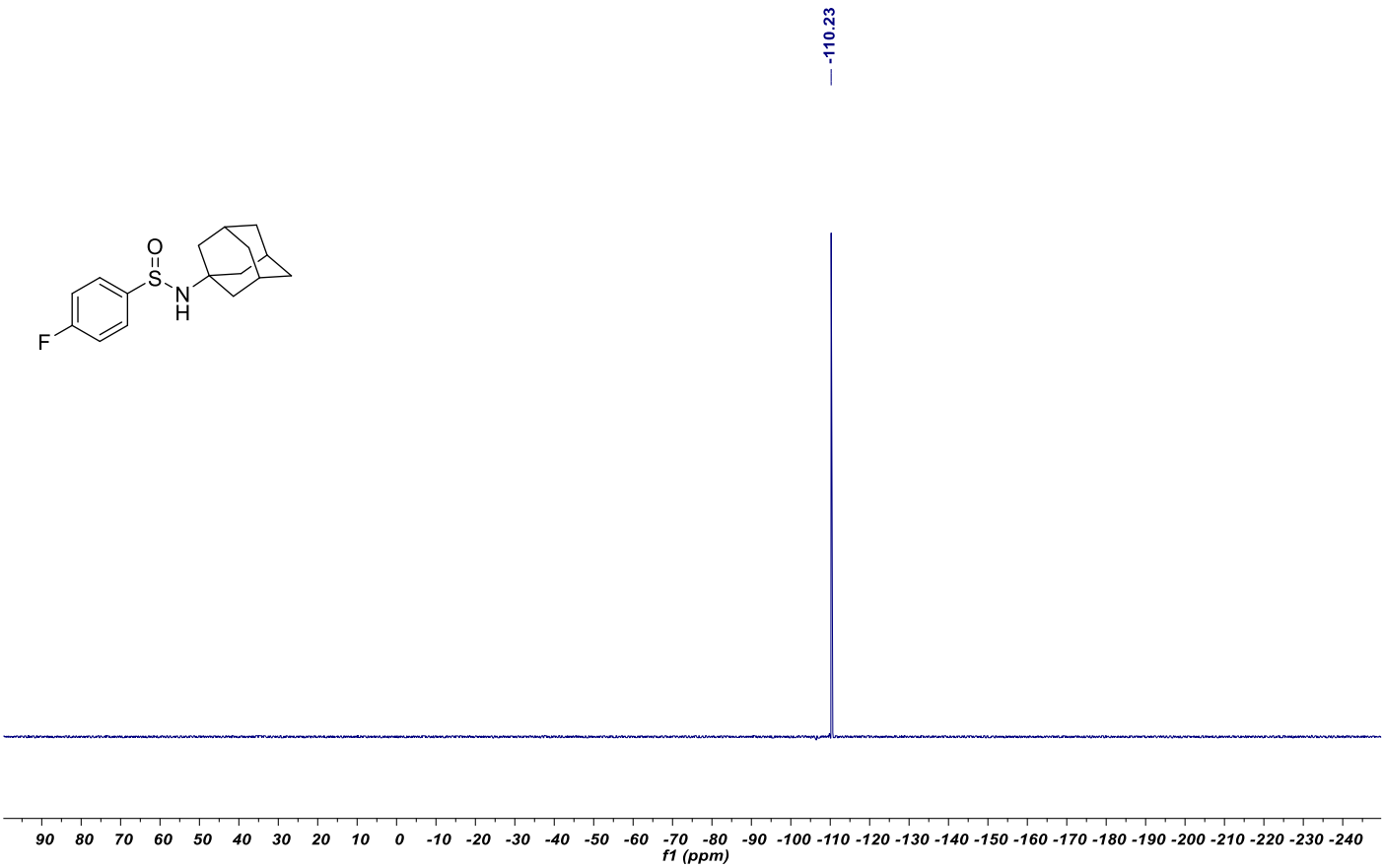



-109.79
O
S
N
H
Me
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

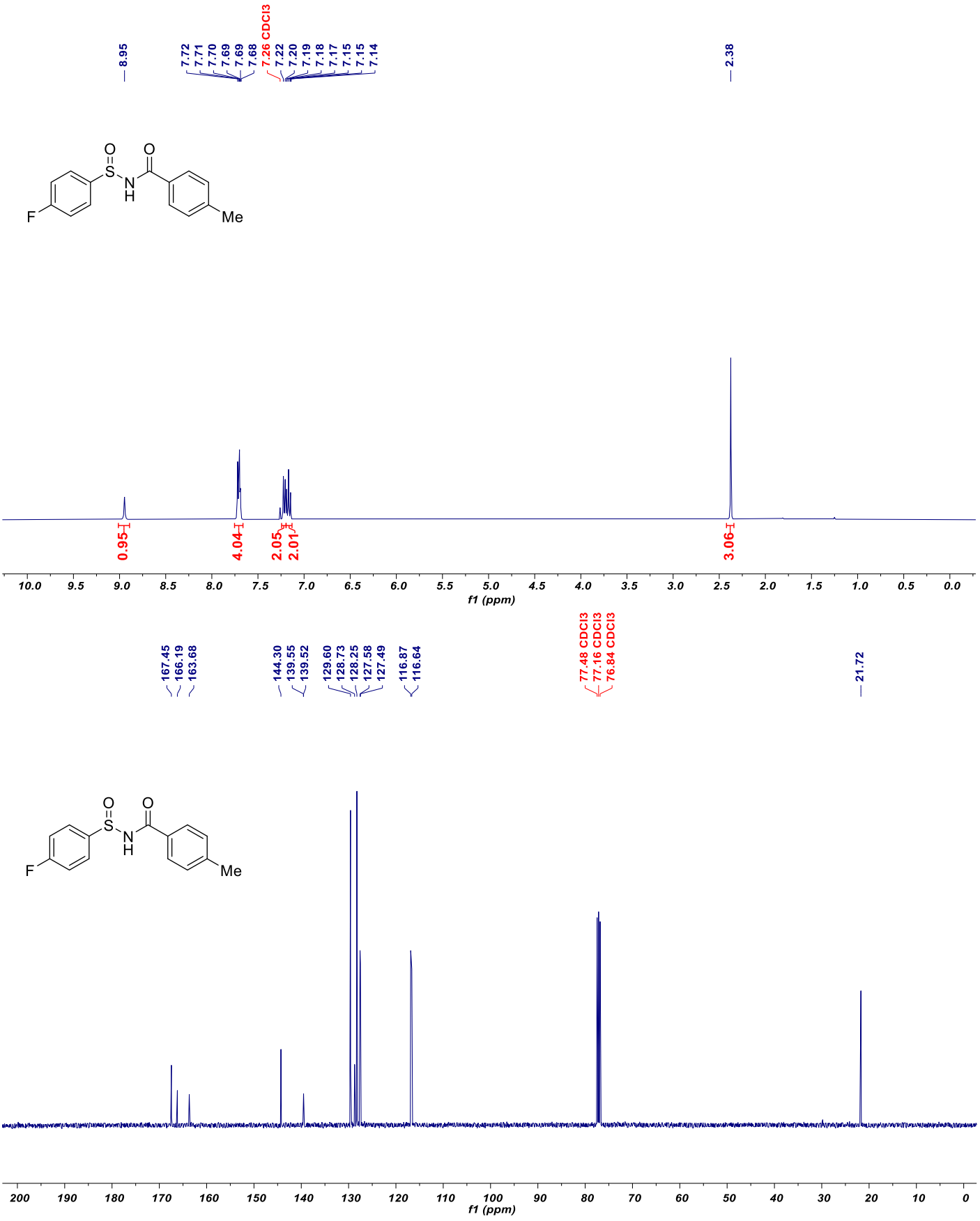
NMR spectrum of sulfinamide **19h**

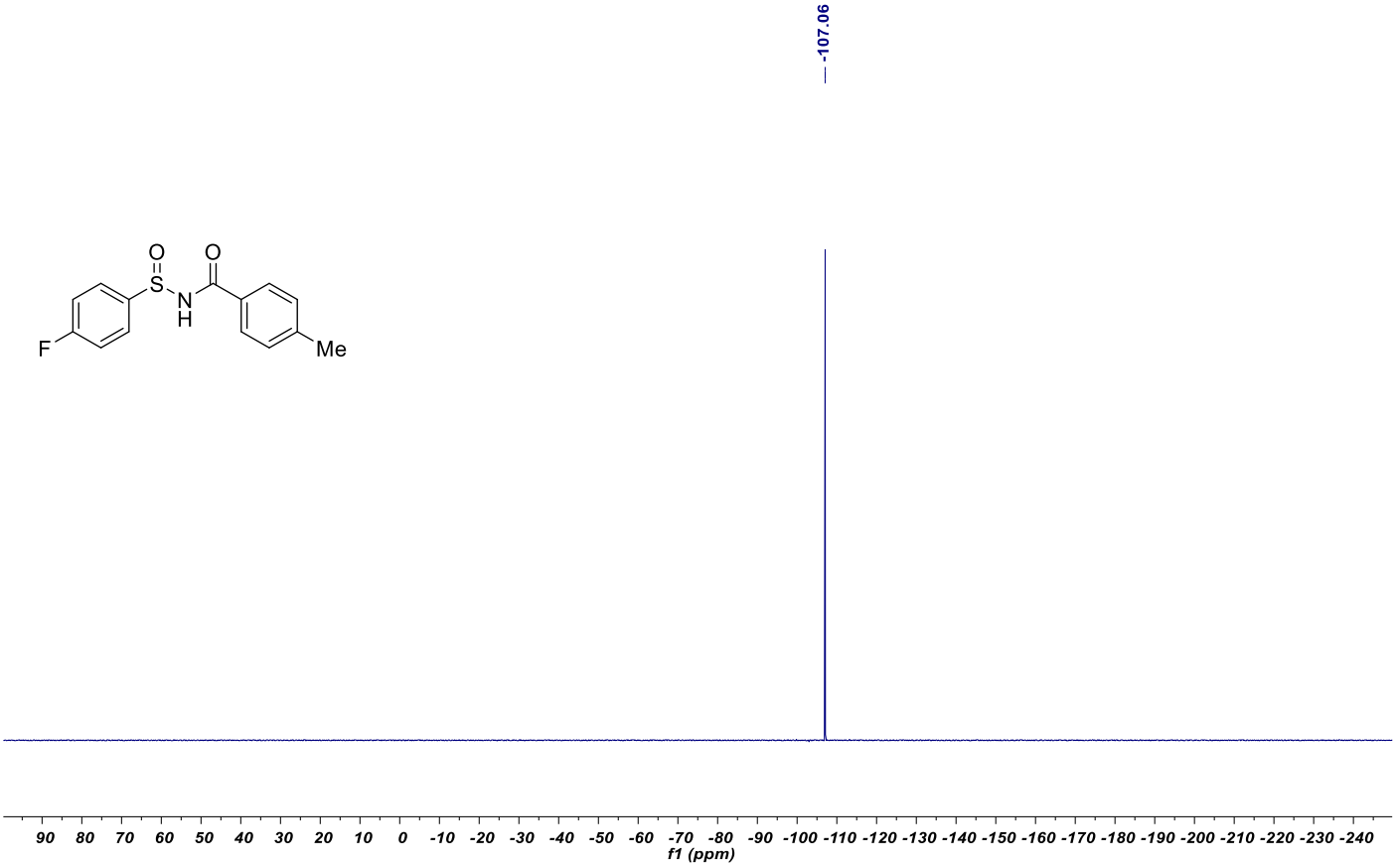




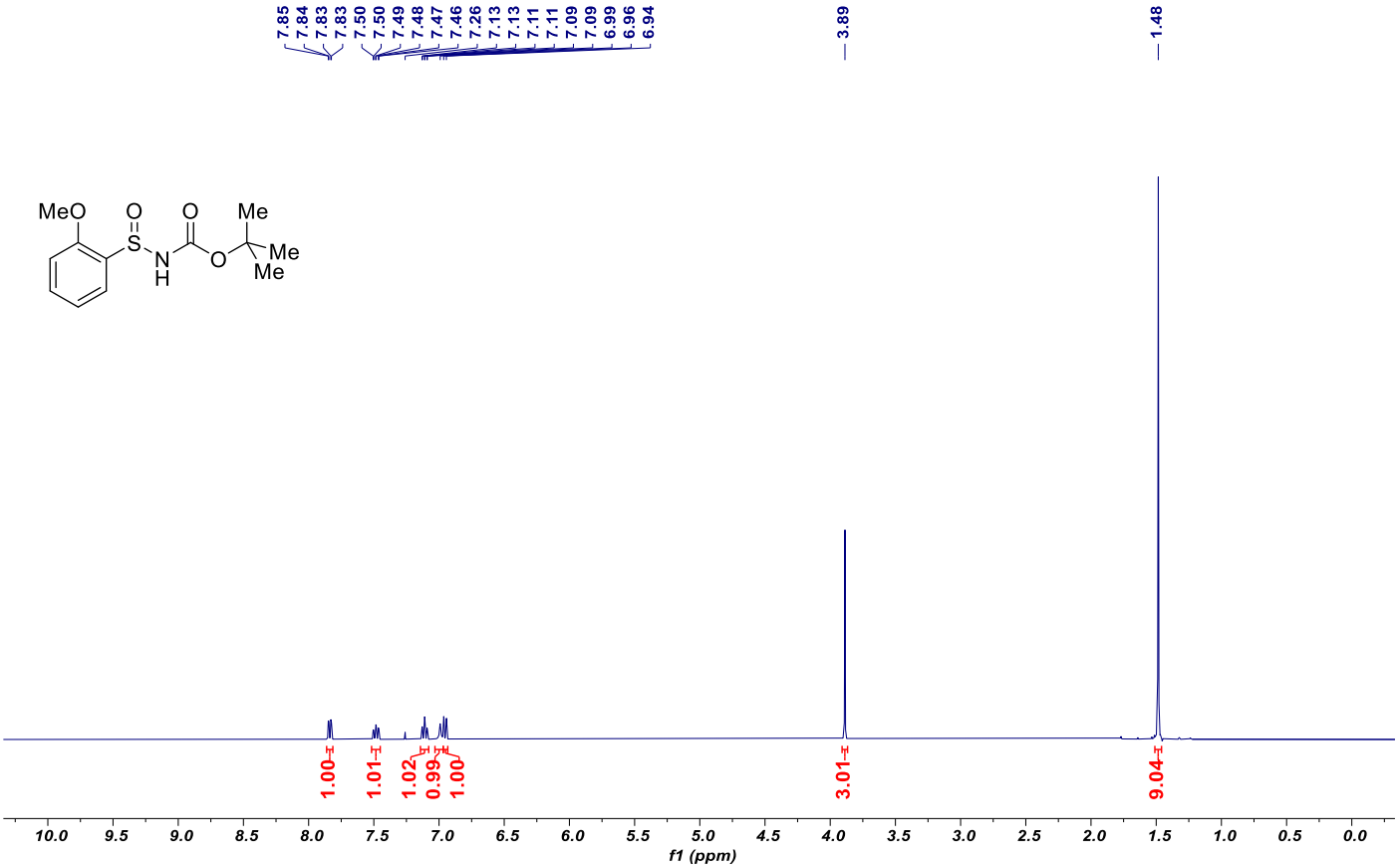

-110.23
O
S
N
H
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

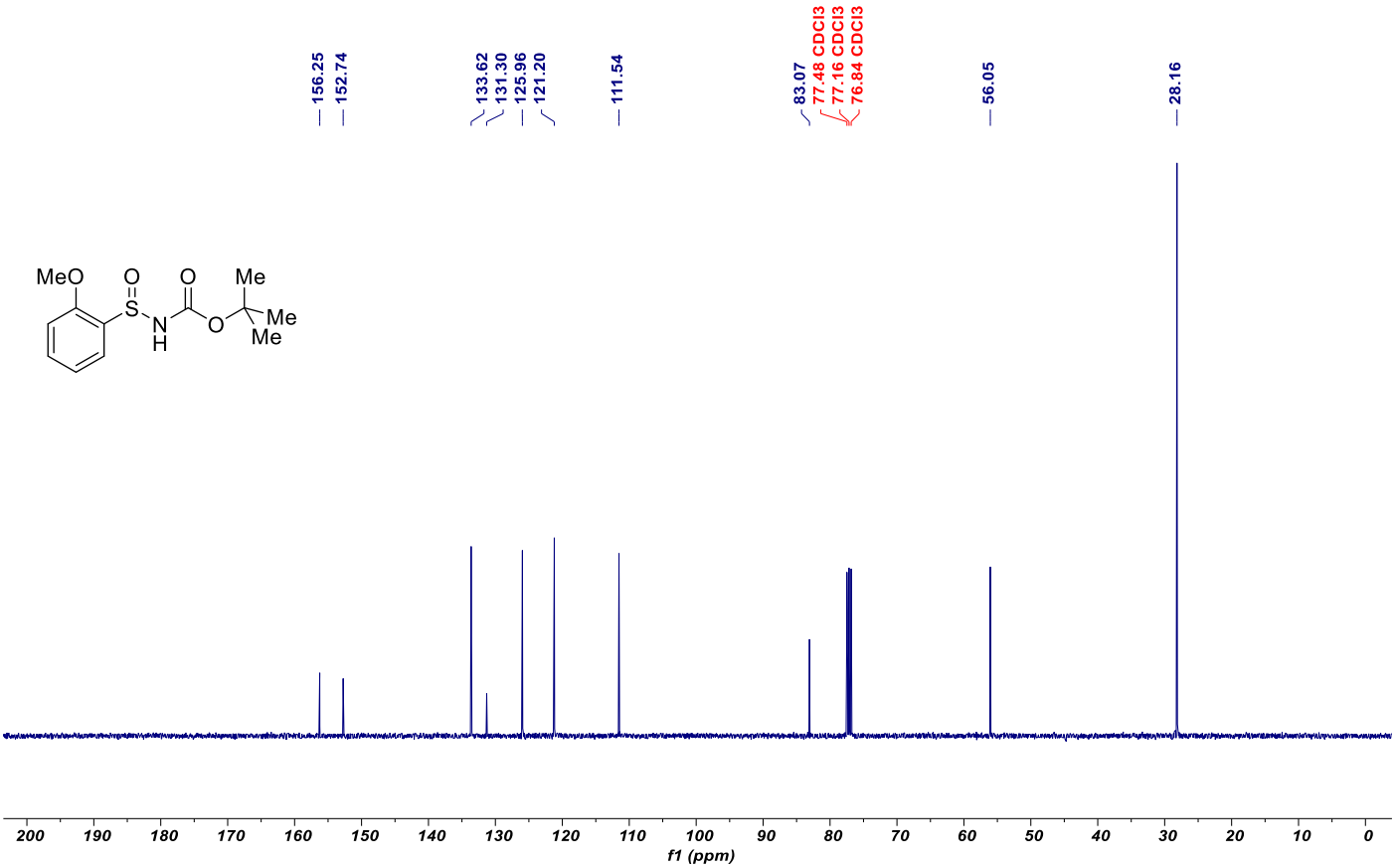
NMR spectrum of sulfinamide **19i**



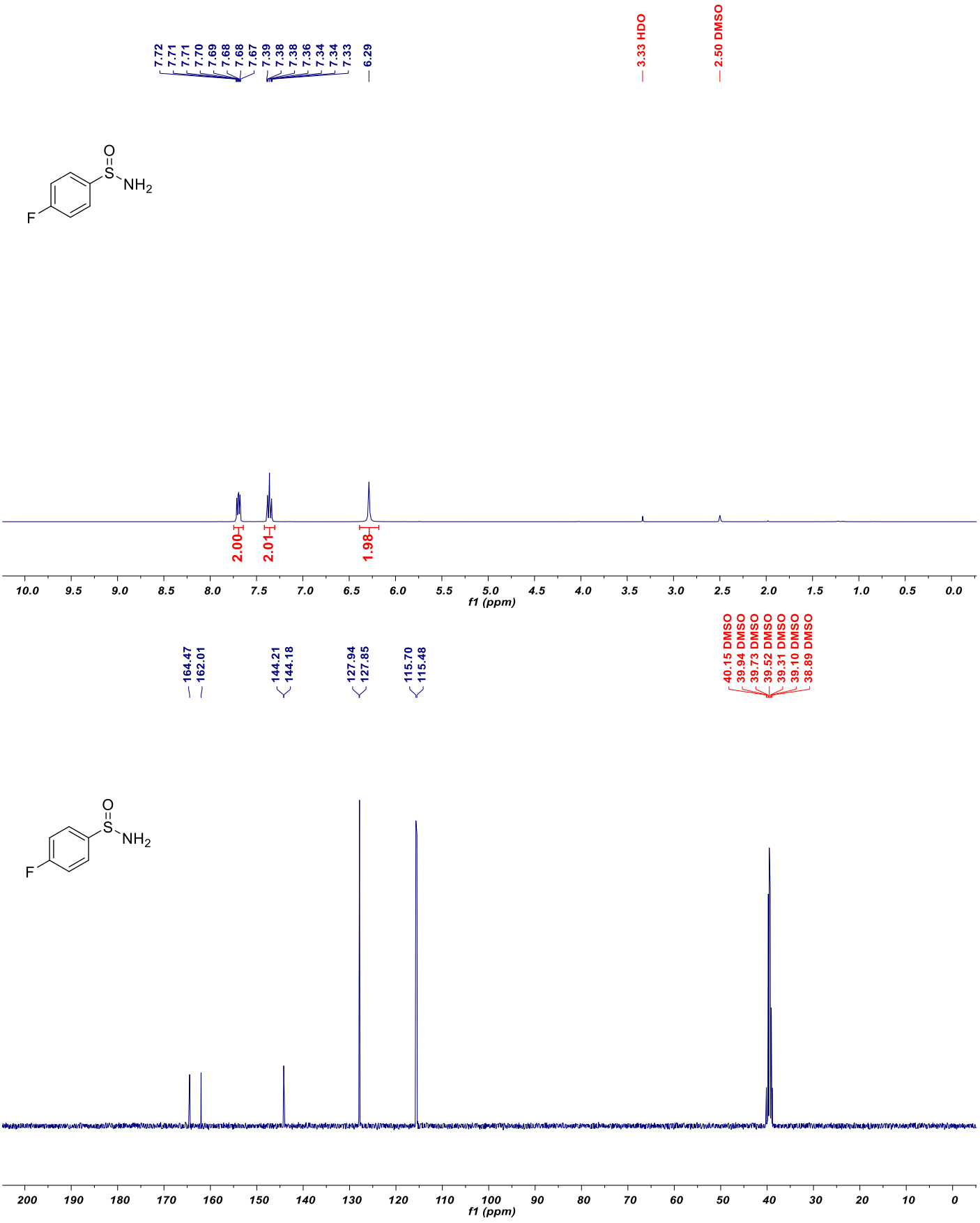

-107.06
O
O
S
N
H
F
Me
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

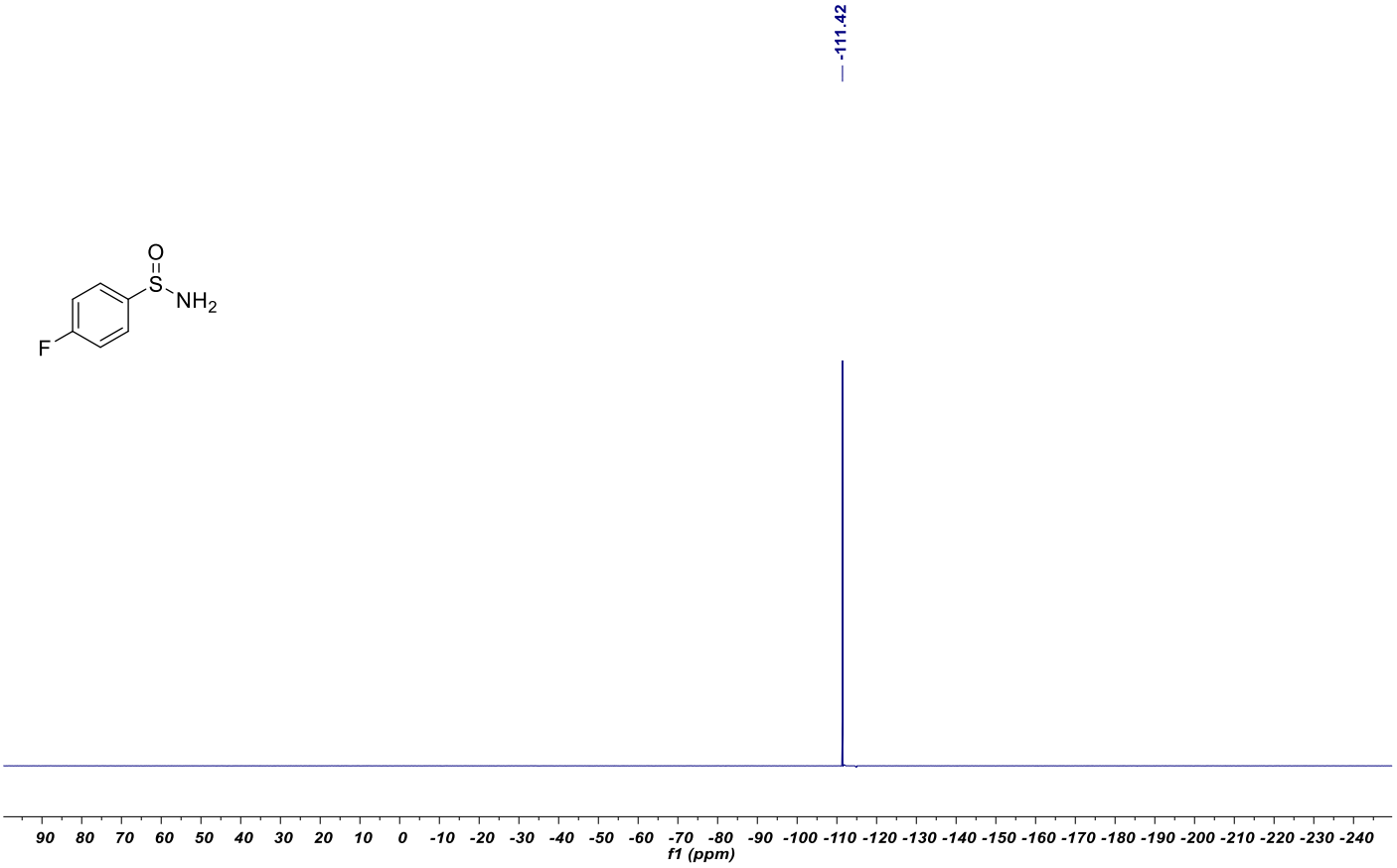
NMR spectrum of sulfinamide **19j**



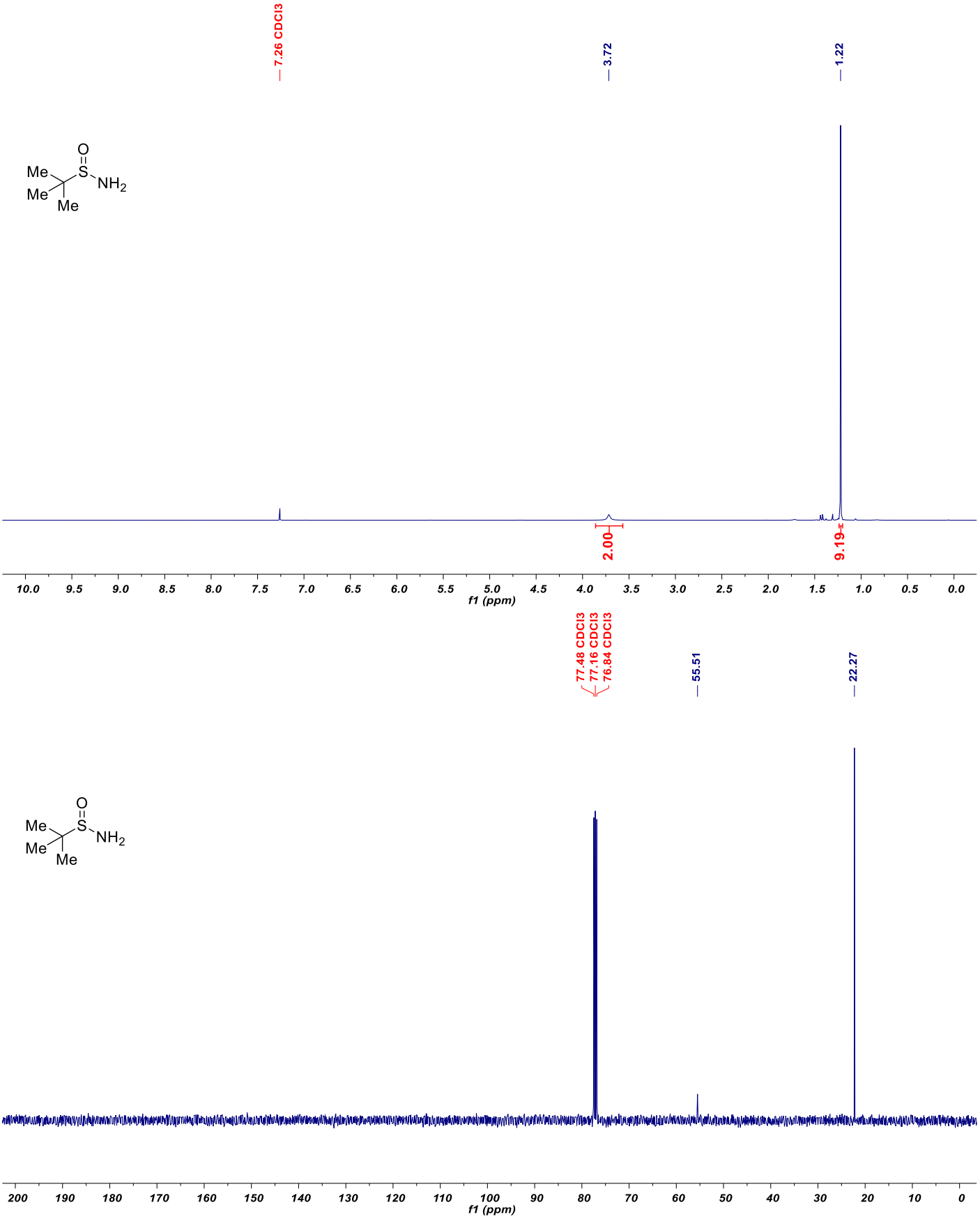


NMR spectrum of sulfinamide **19k**

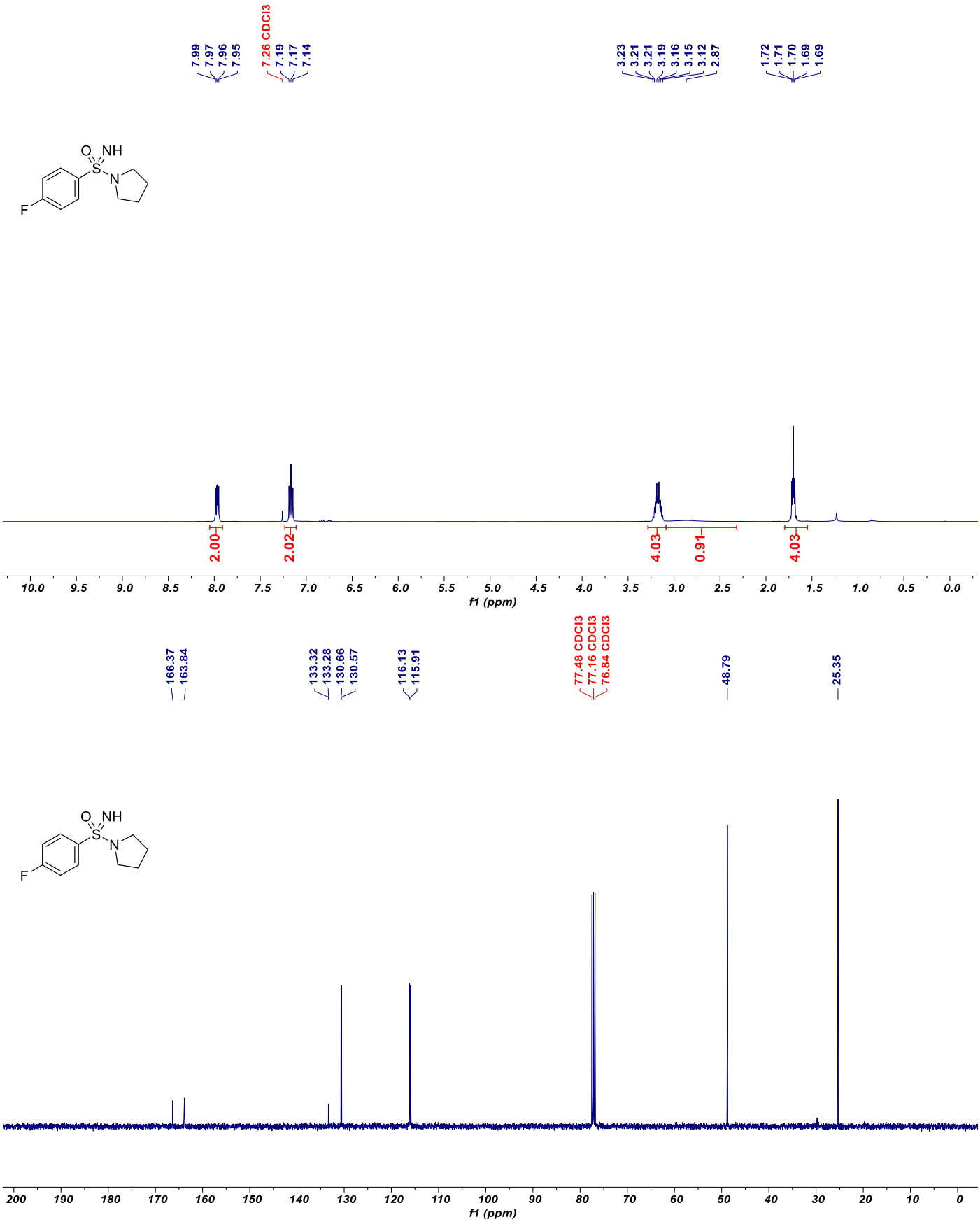


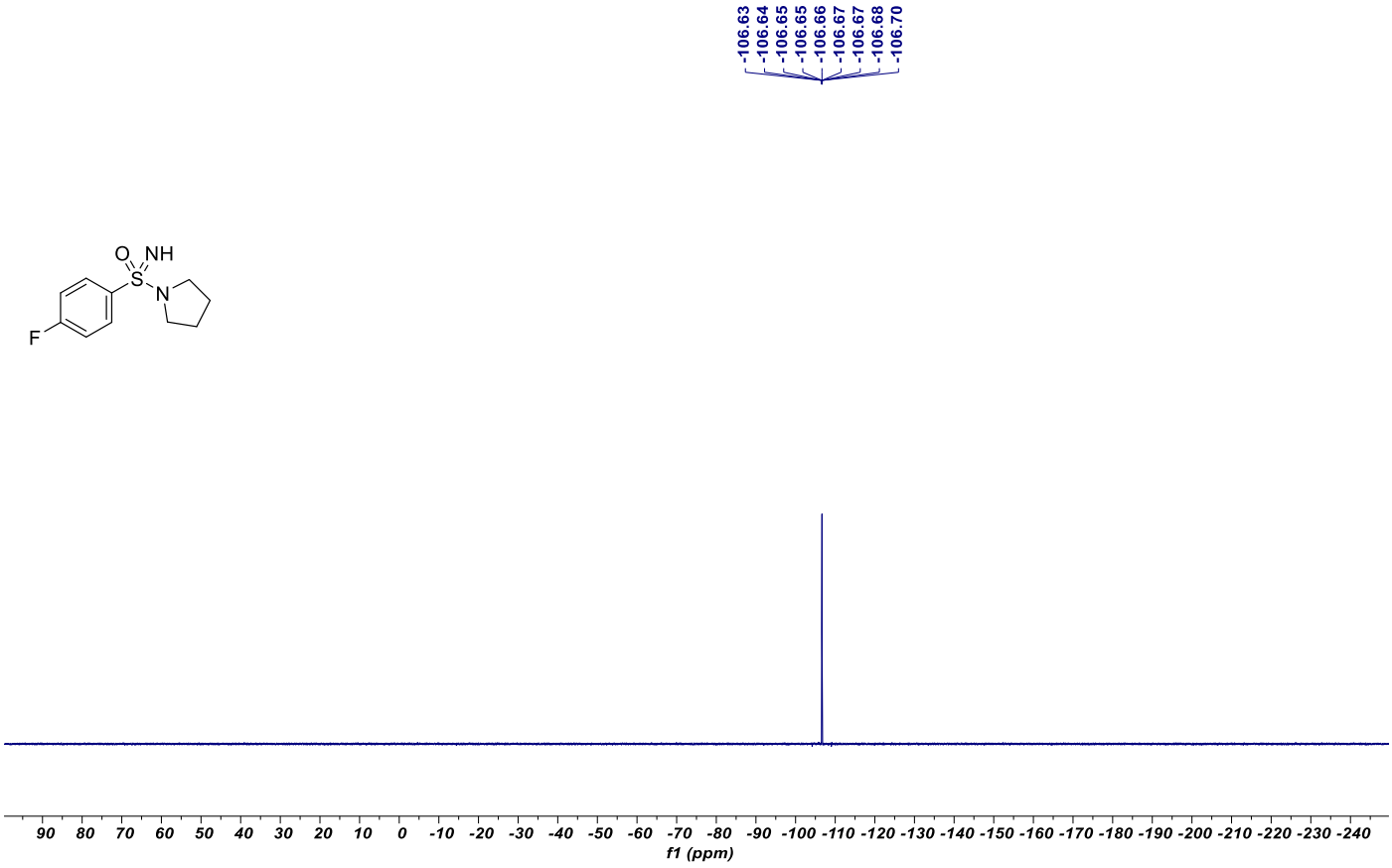

-111.42
O
S
NH2
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

NMR spectrum of sulfinamide **19l**

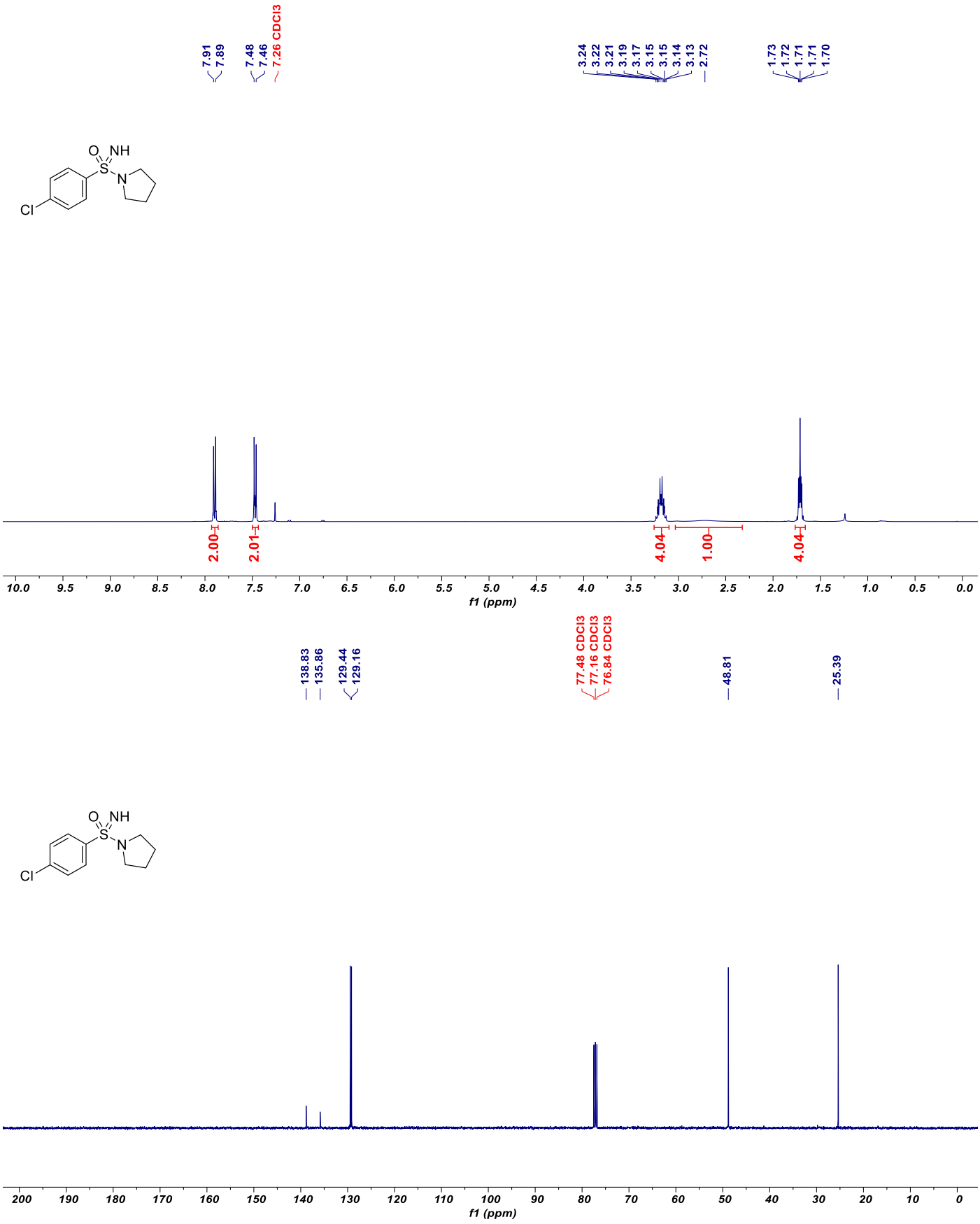


NMR spectrum of sulfonimidamide **27a**

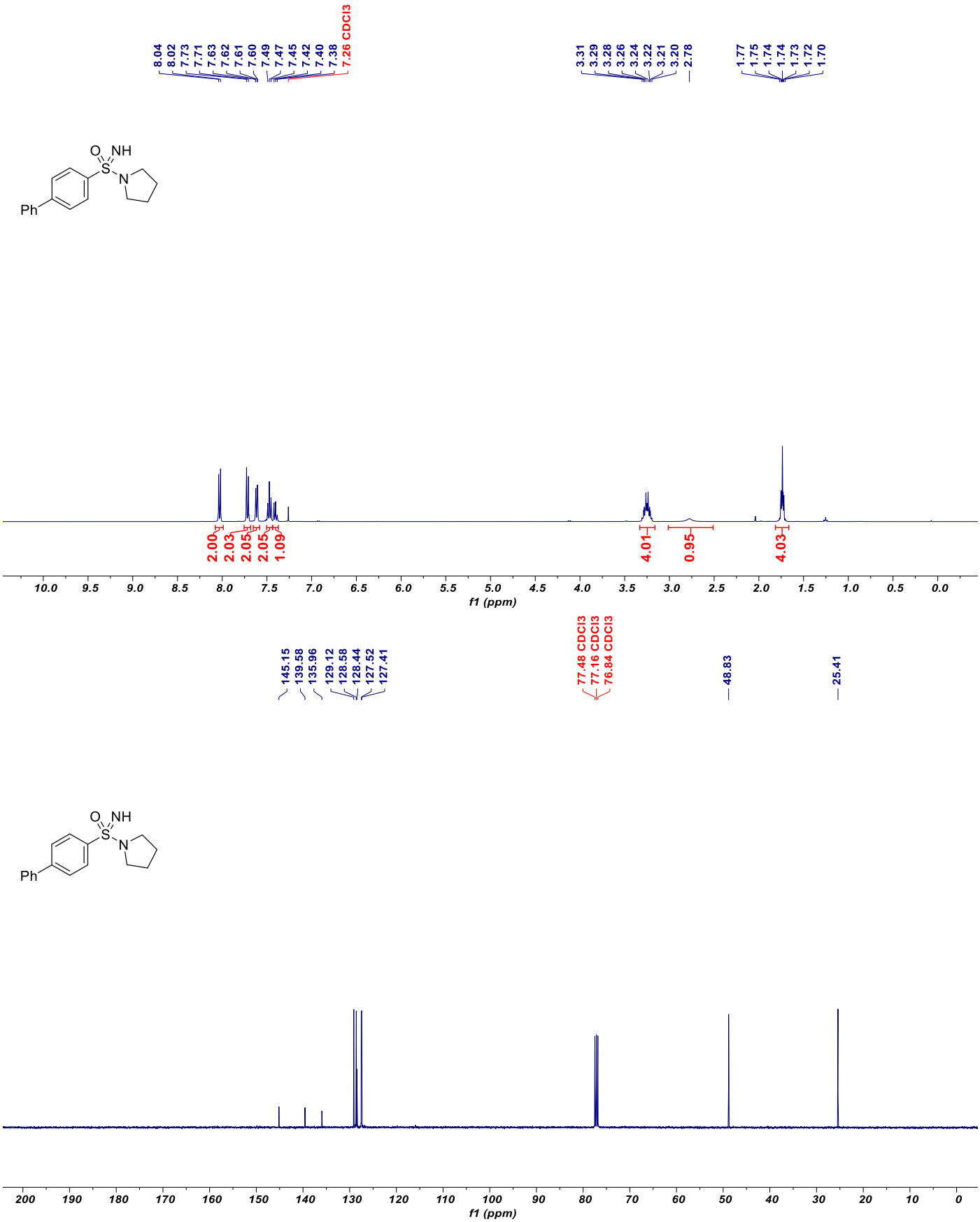



-106.63
-106.64
-106.65
-106.65
-106.66
-106.67
-106.67
-106.68
-106.70
O
NH
S
N
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

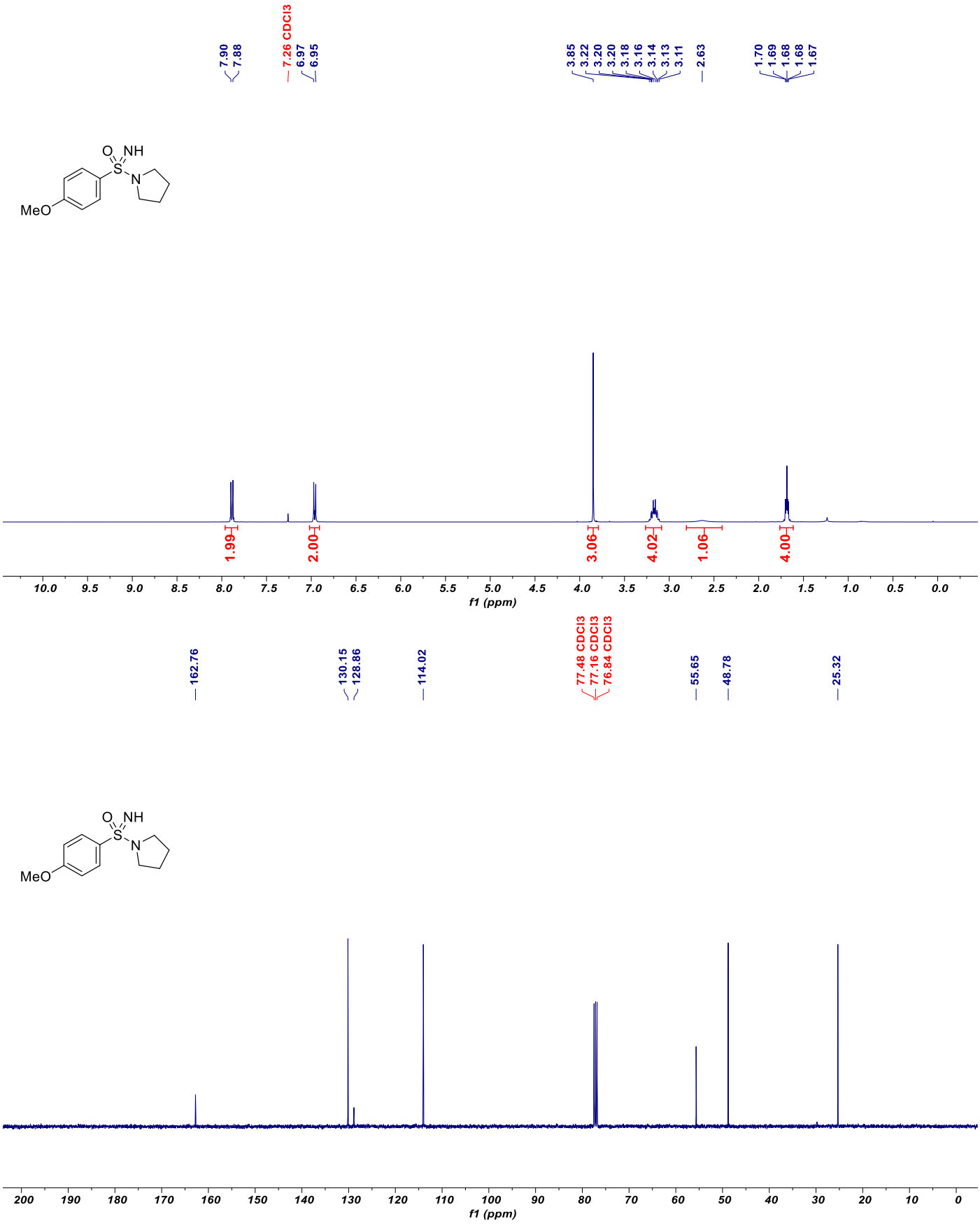
NMR spectrum of sulfonimidamide **27b**



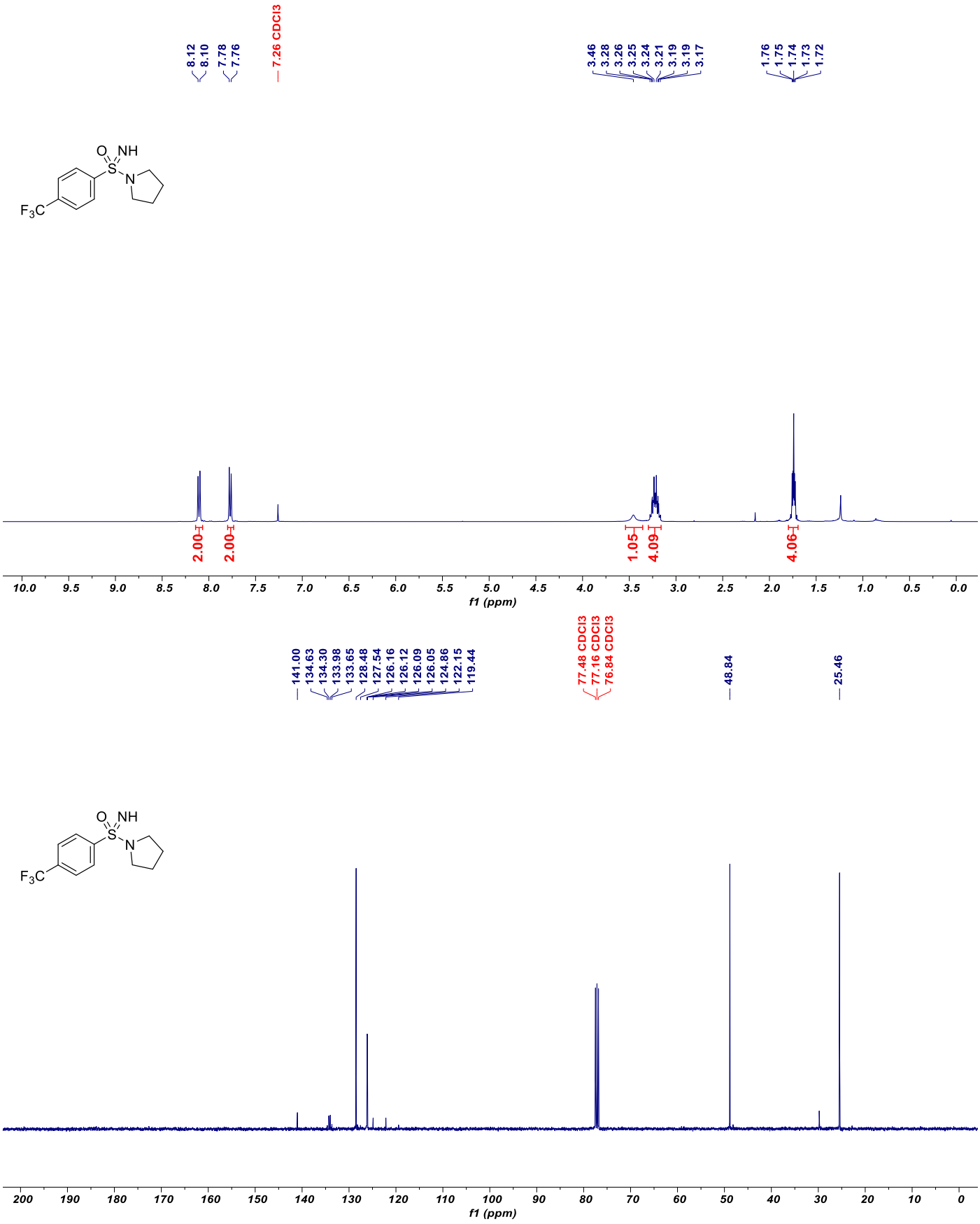
NMR spectrum of sulfonimidamide **27c**

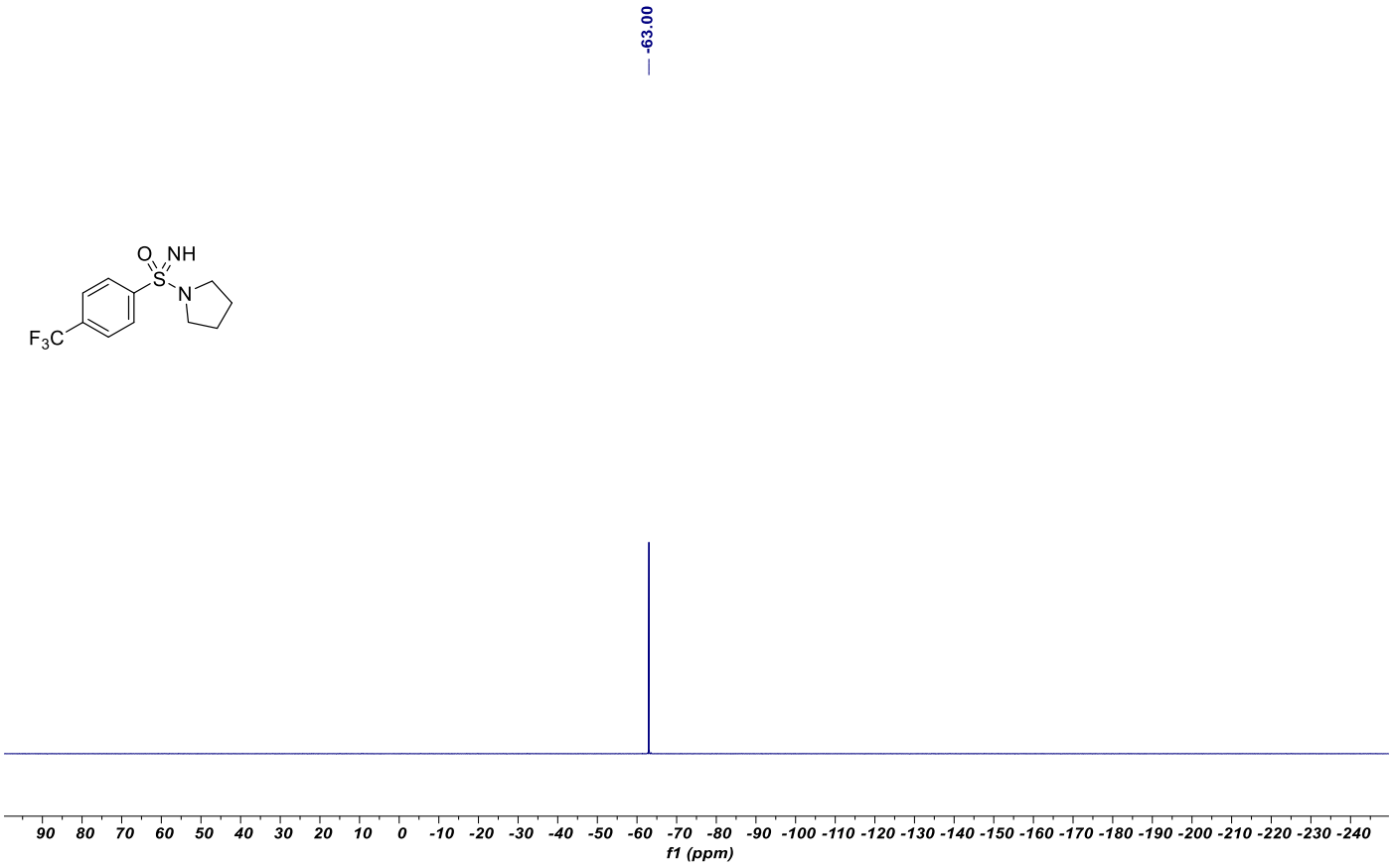


NMR spectrum of sulfonimidamide **27d**

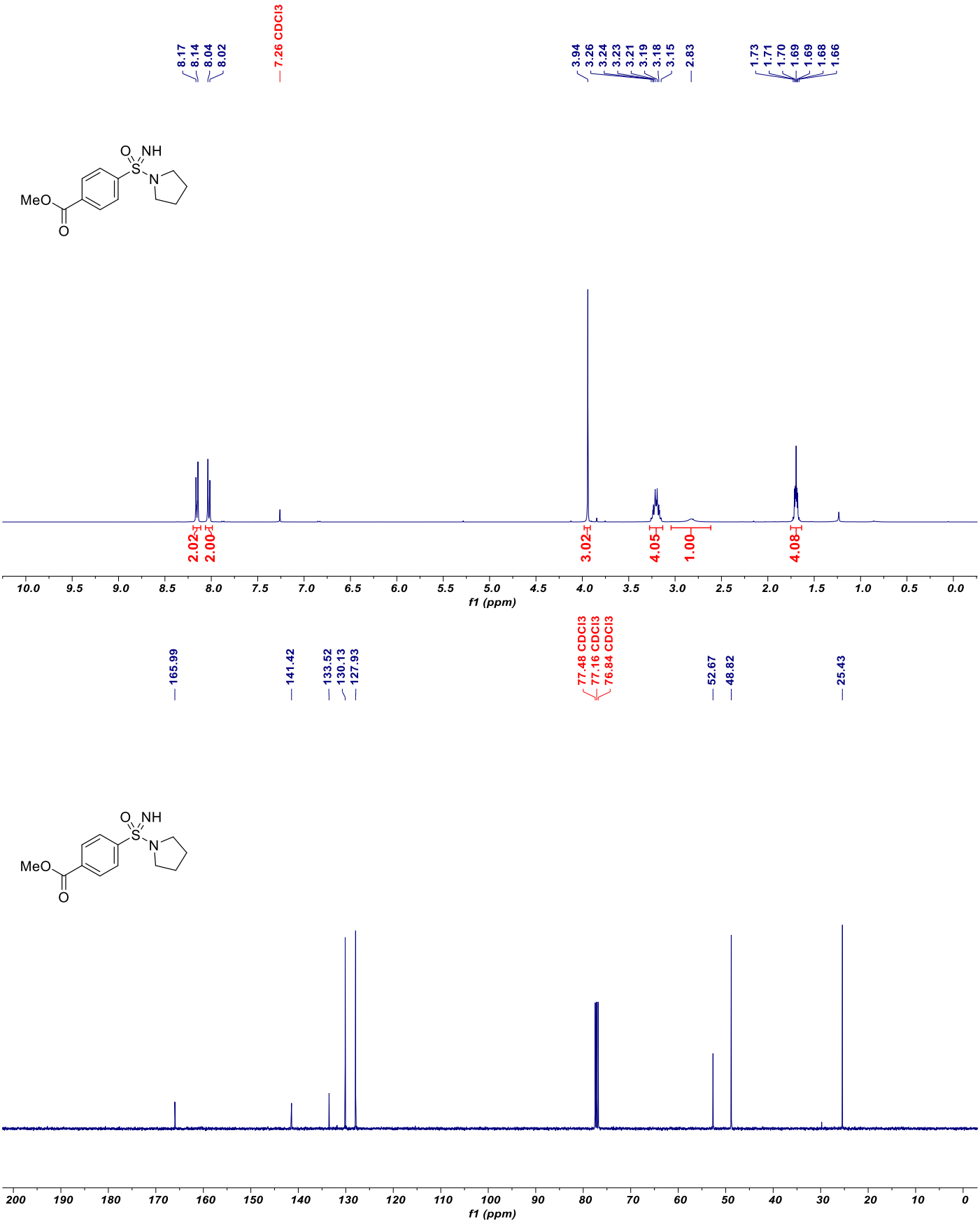


NMR spectrum of sulfonimidamide **27e**

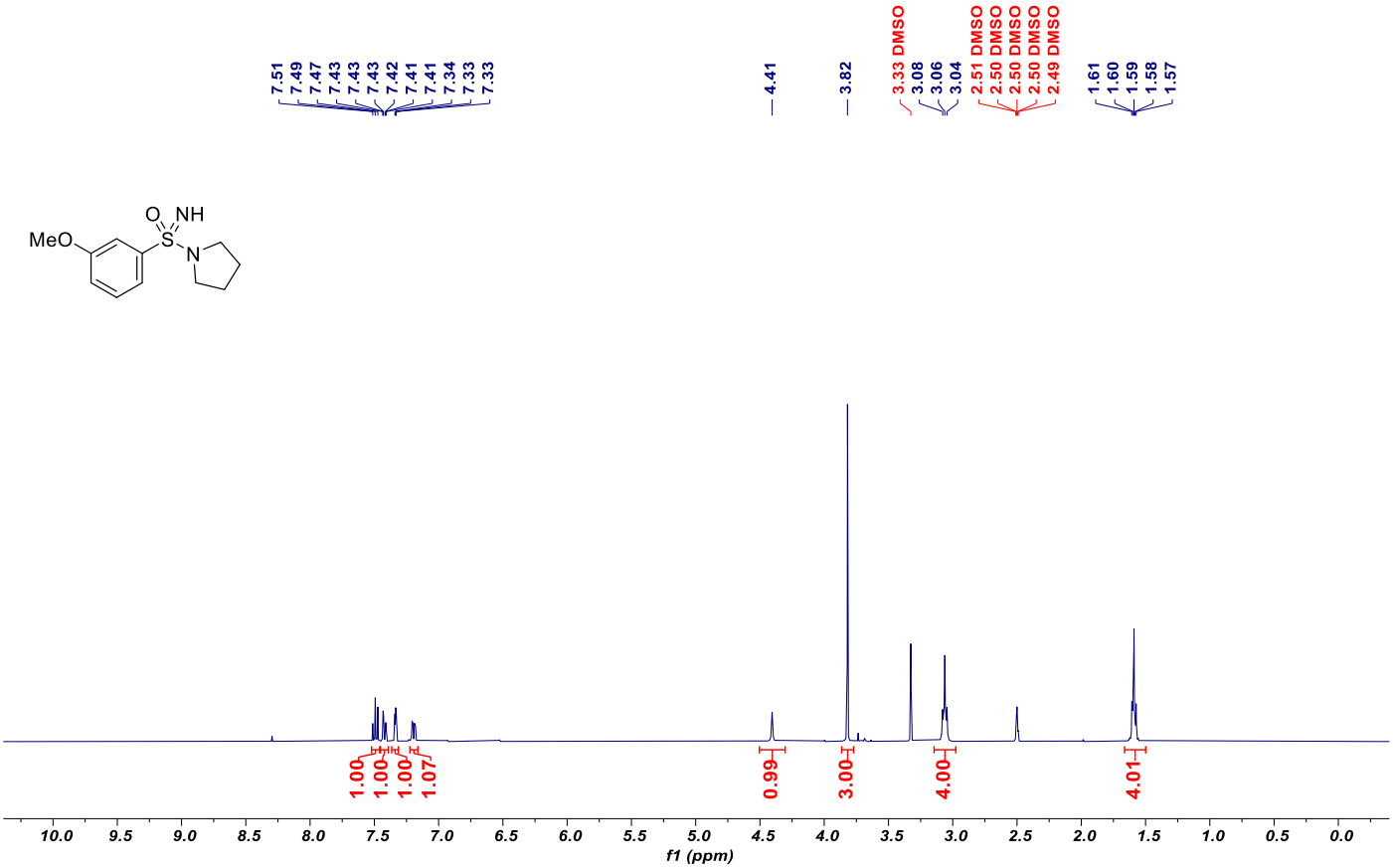


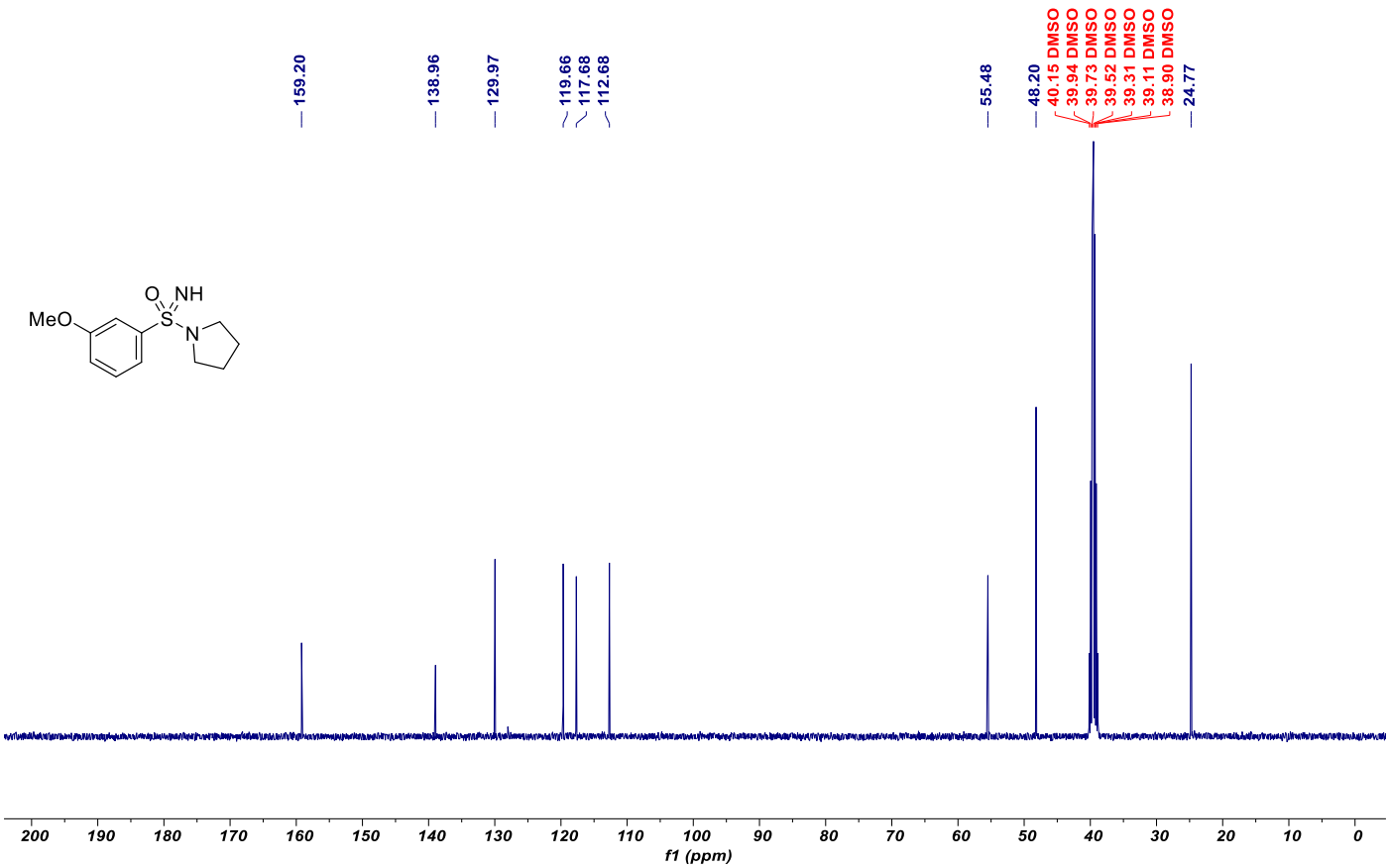

-63.00
O
NH
S
N
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

NMR spectrum of sulfonimidamide **27f**

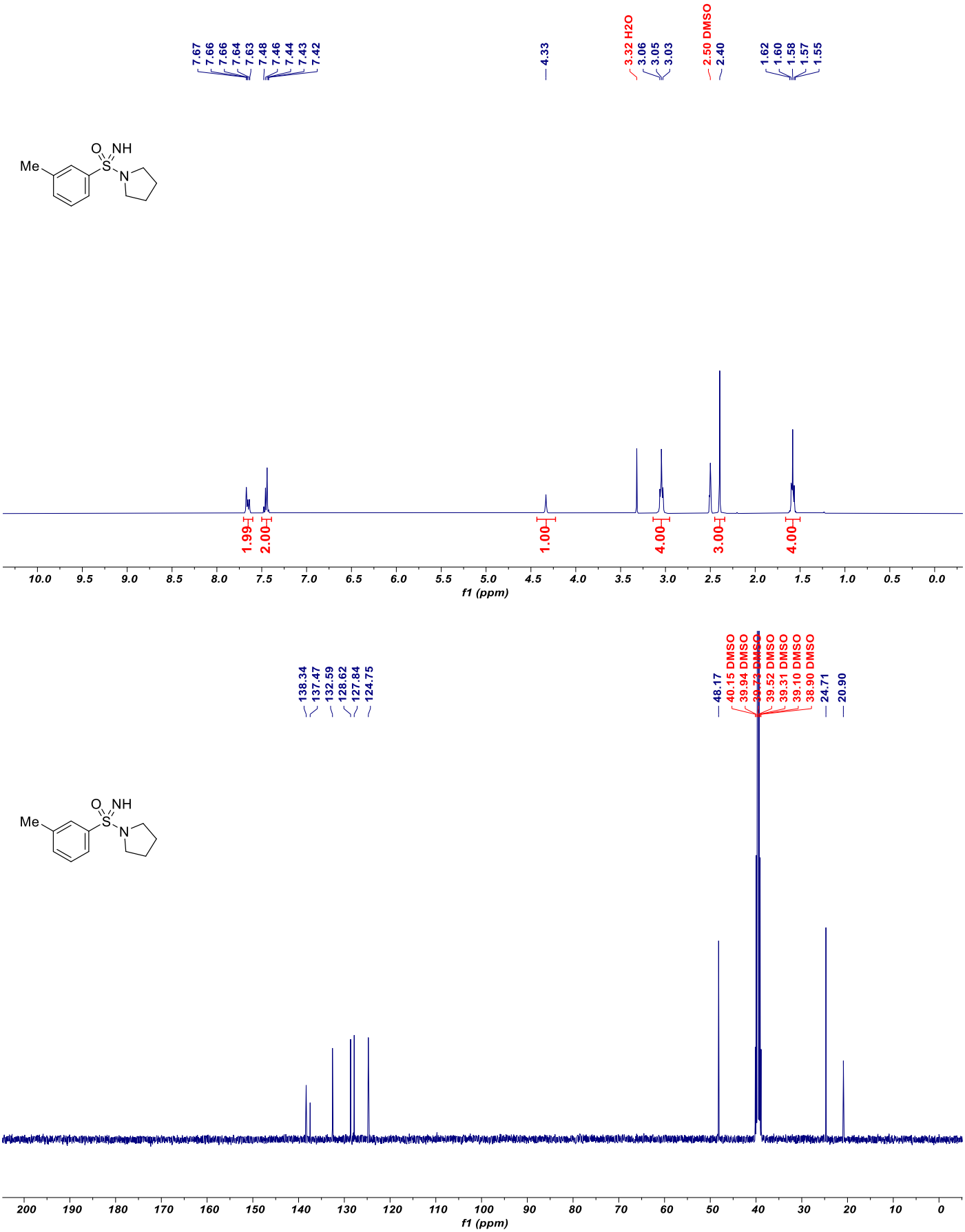


NMR spectrum of sulfonimidamide **27g**

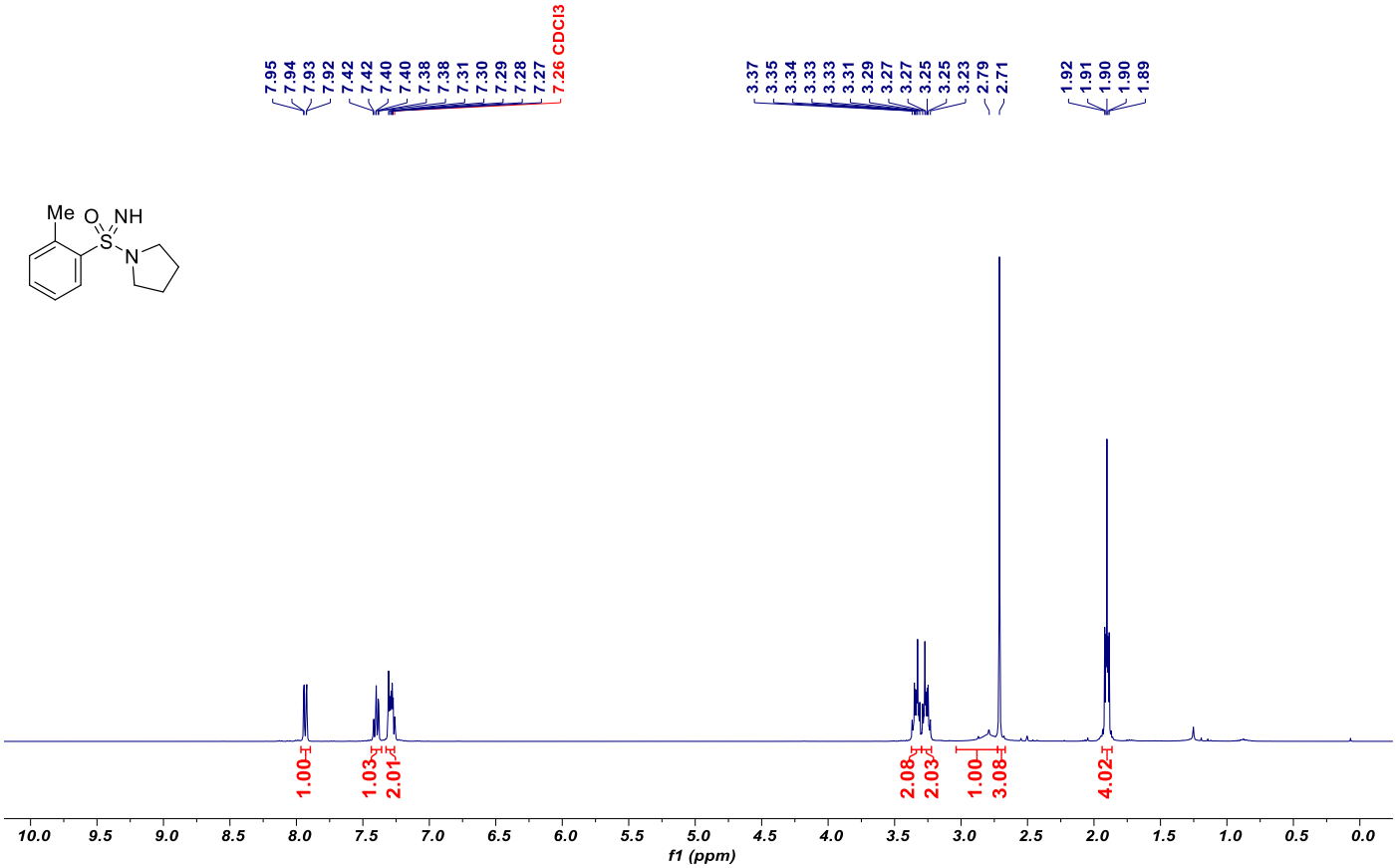


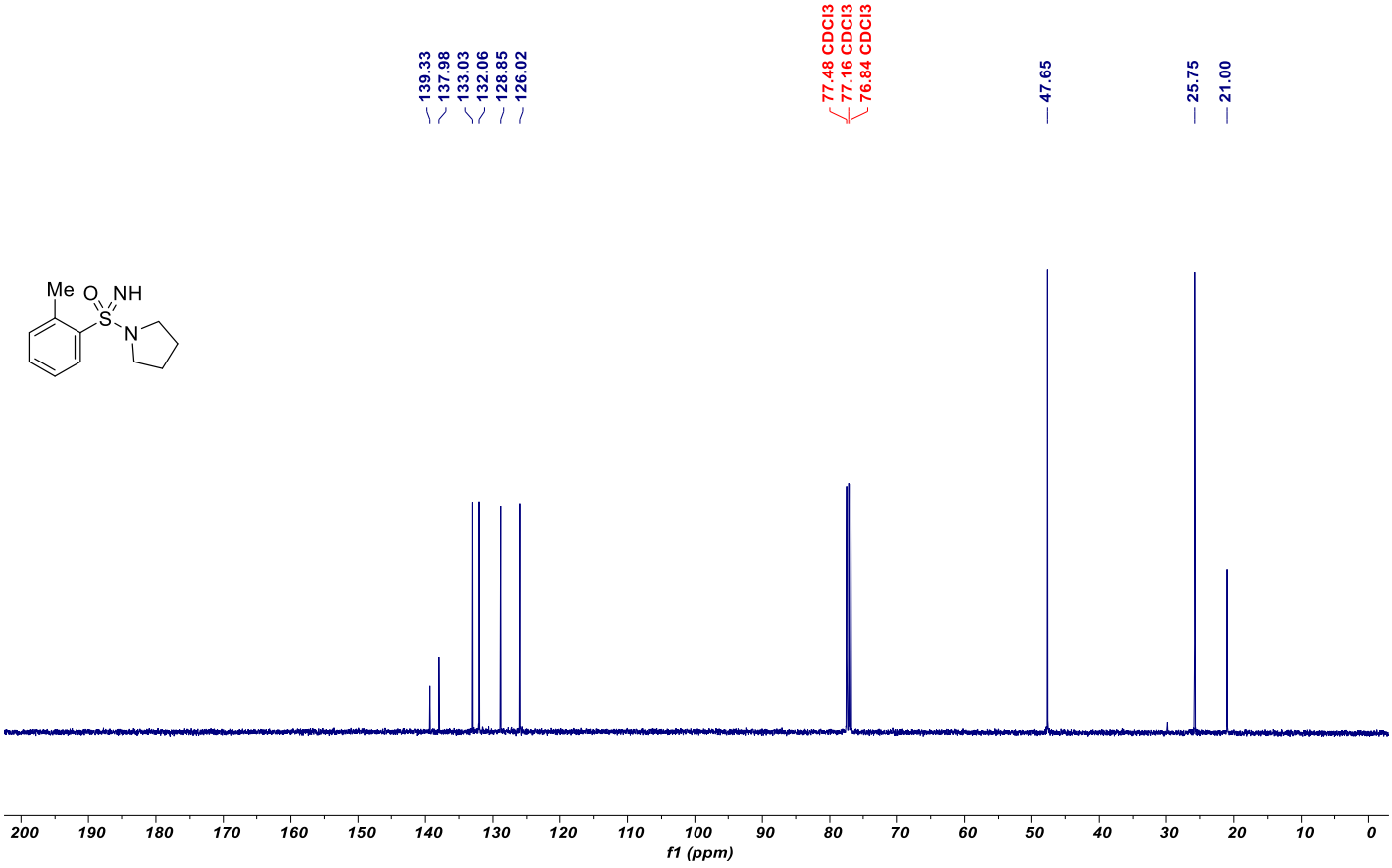


NMR spectrum of sulfonimidamide **27h**

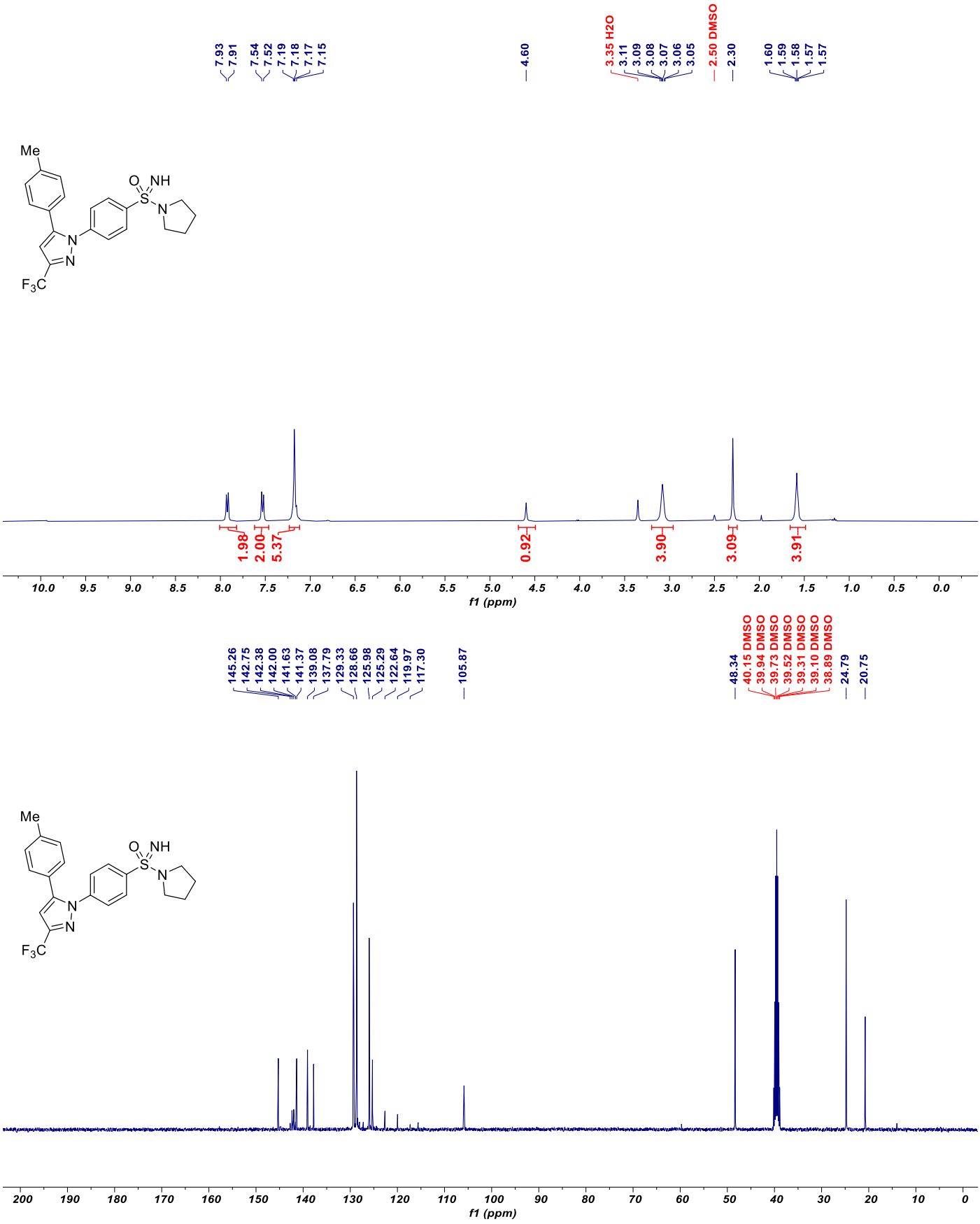


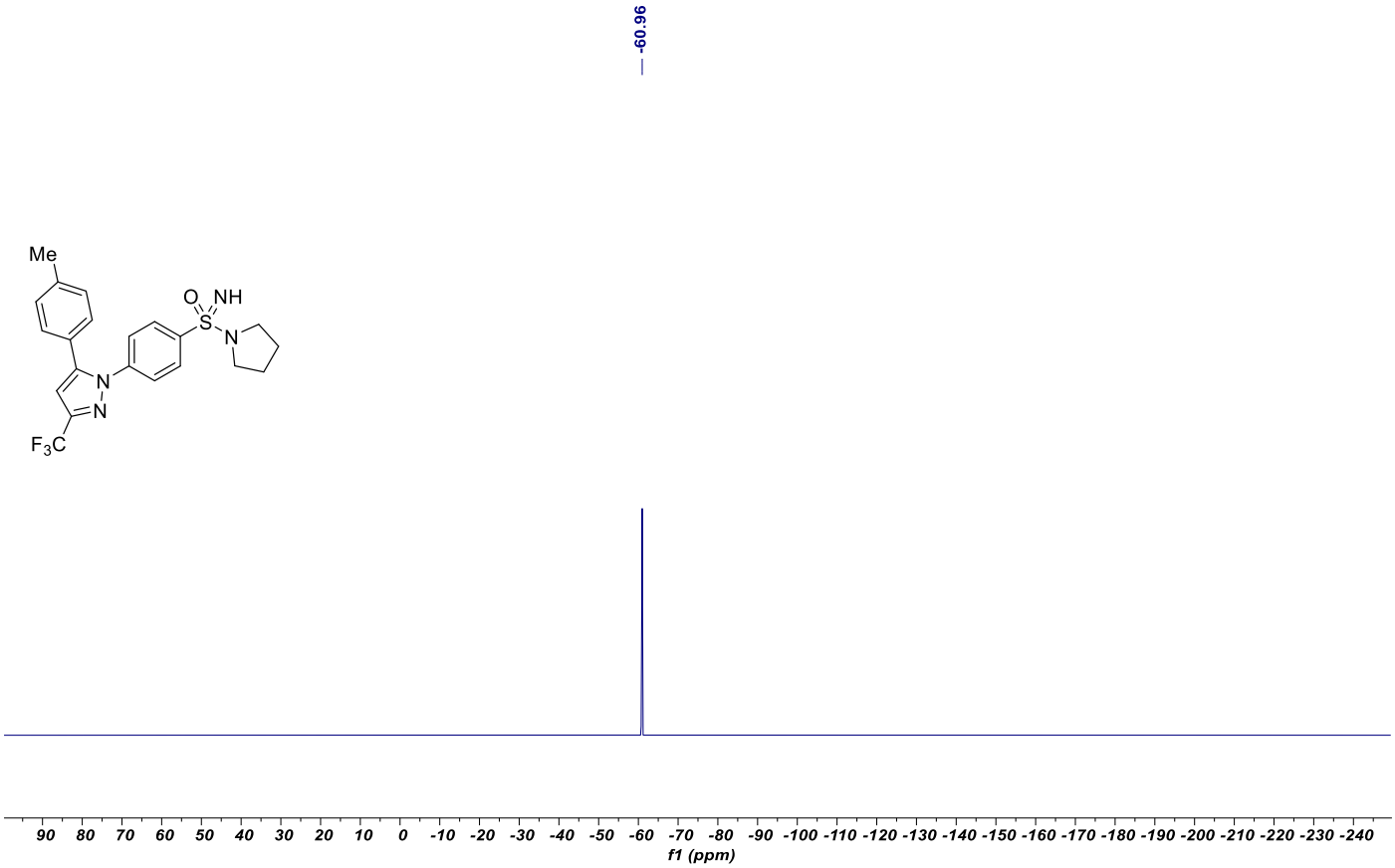
NMR spectrum of sulfonimidamide **27i**



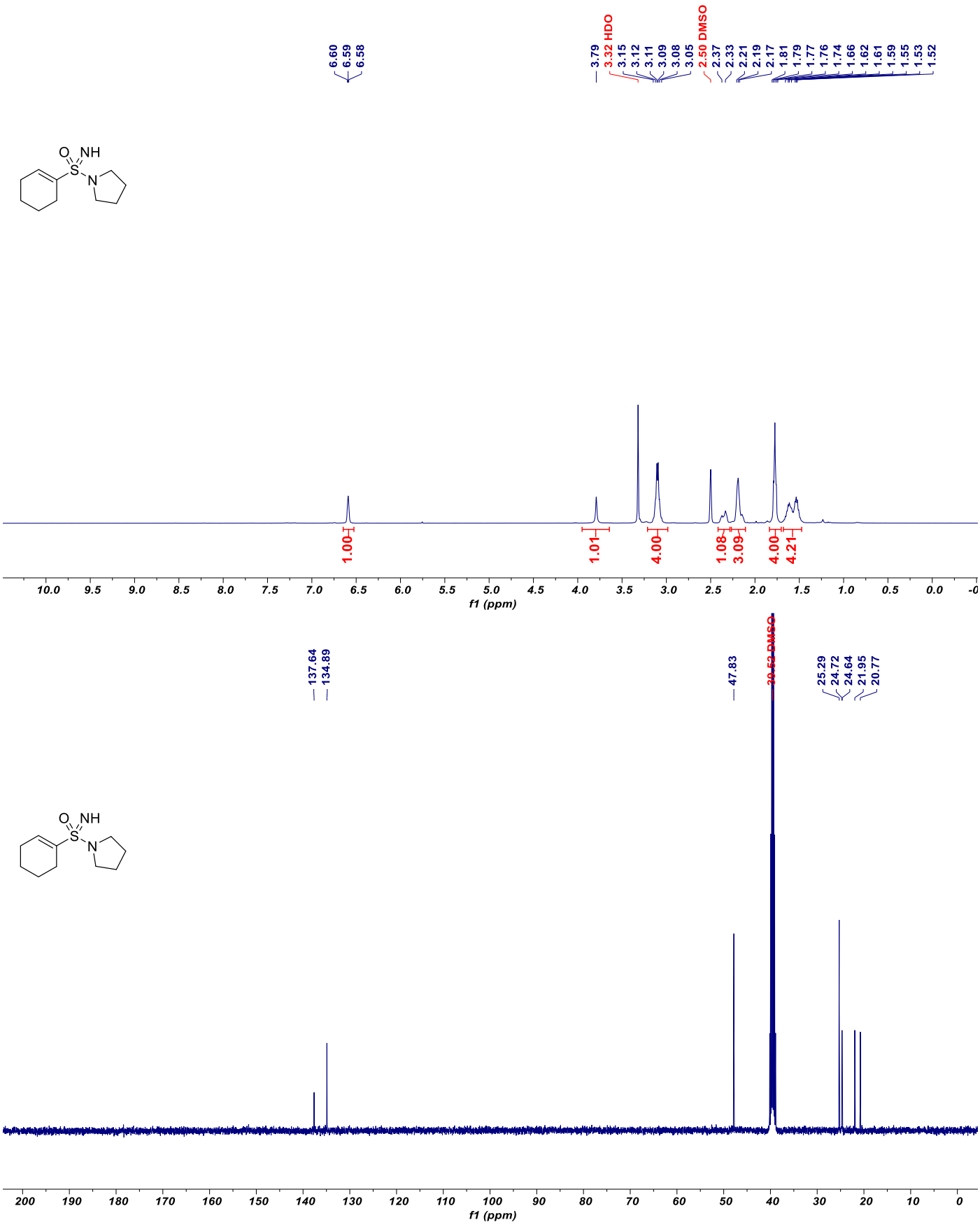


NMR spectrum of sulfonimidamide **27j**

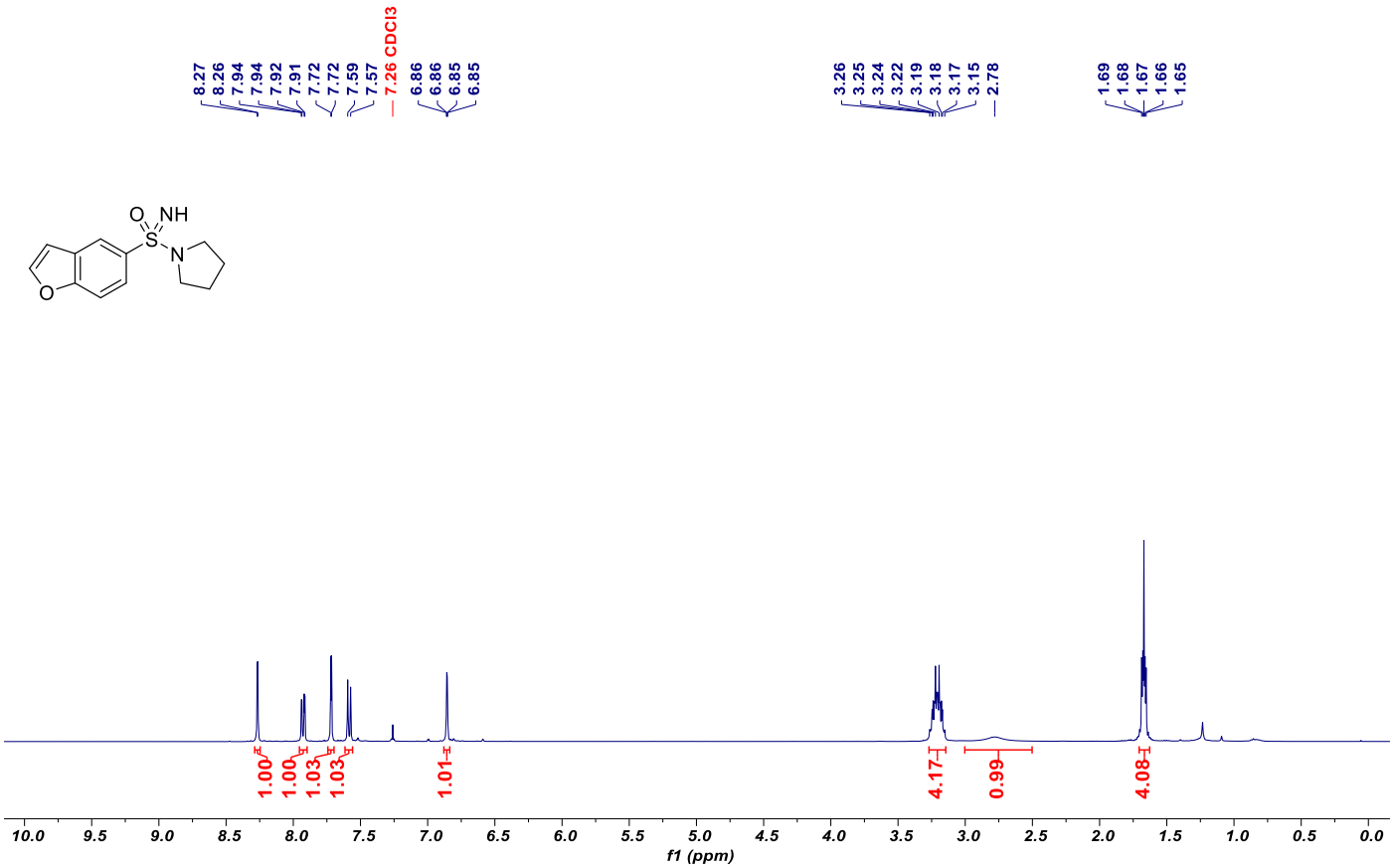


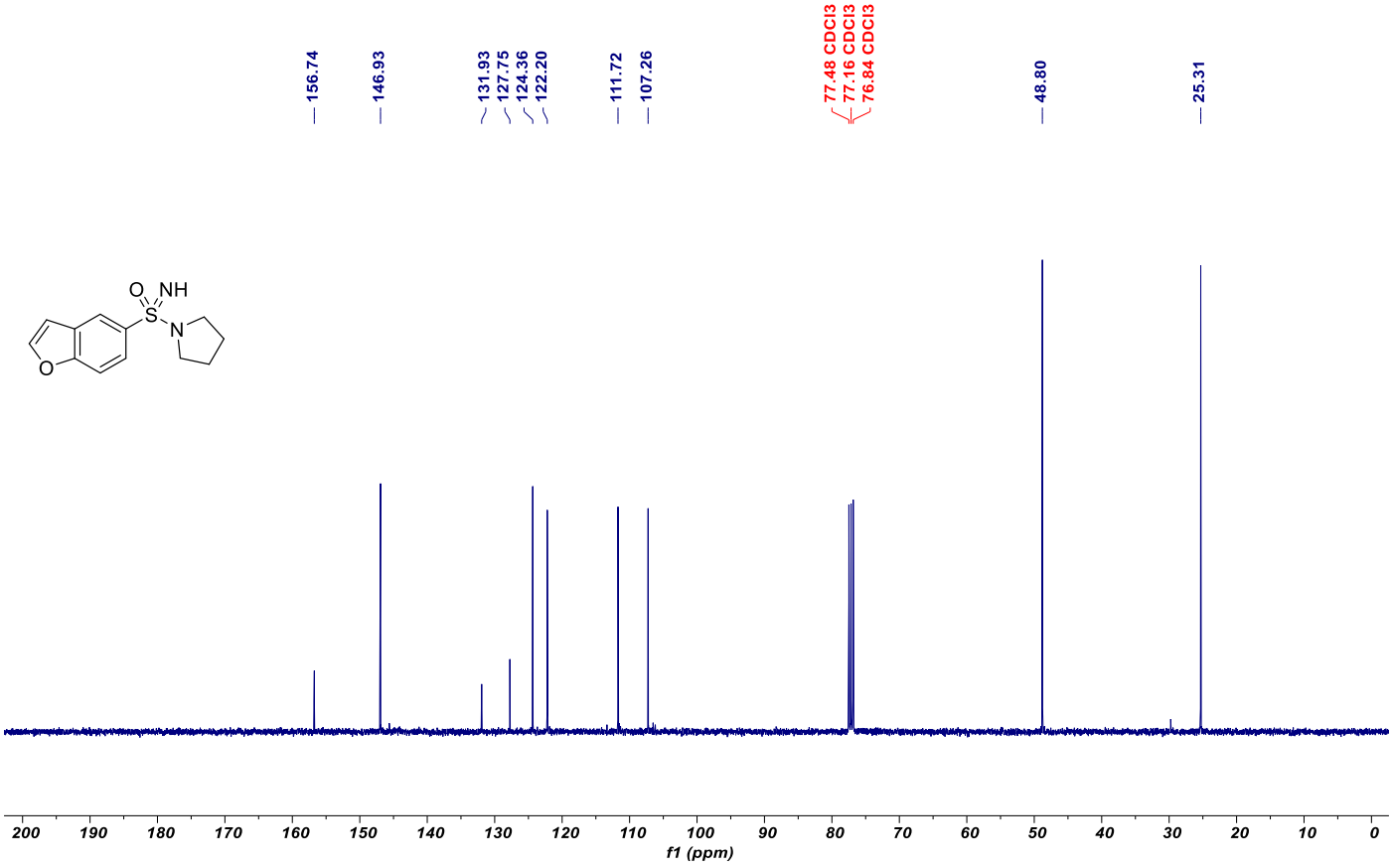

-60.96
Me
O
NH
S
N
N
N
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

NMR spectrum of sulfonimidamide **27k**

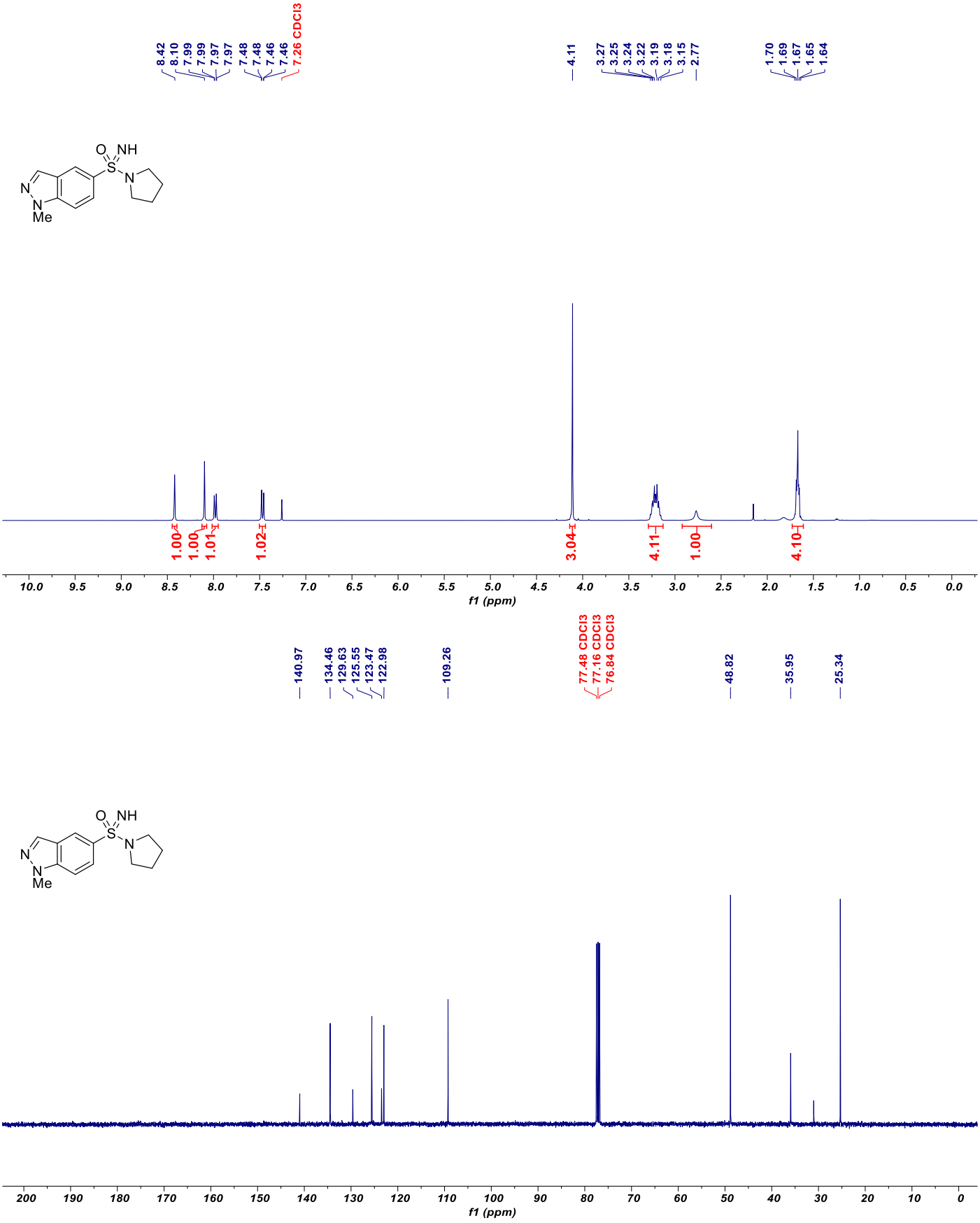


NMR spectrum of sulfonimidamide **27l**

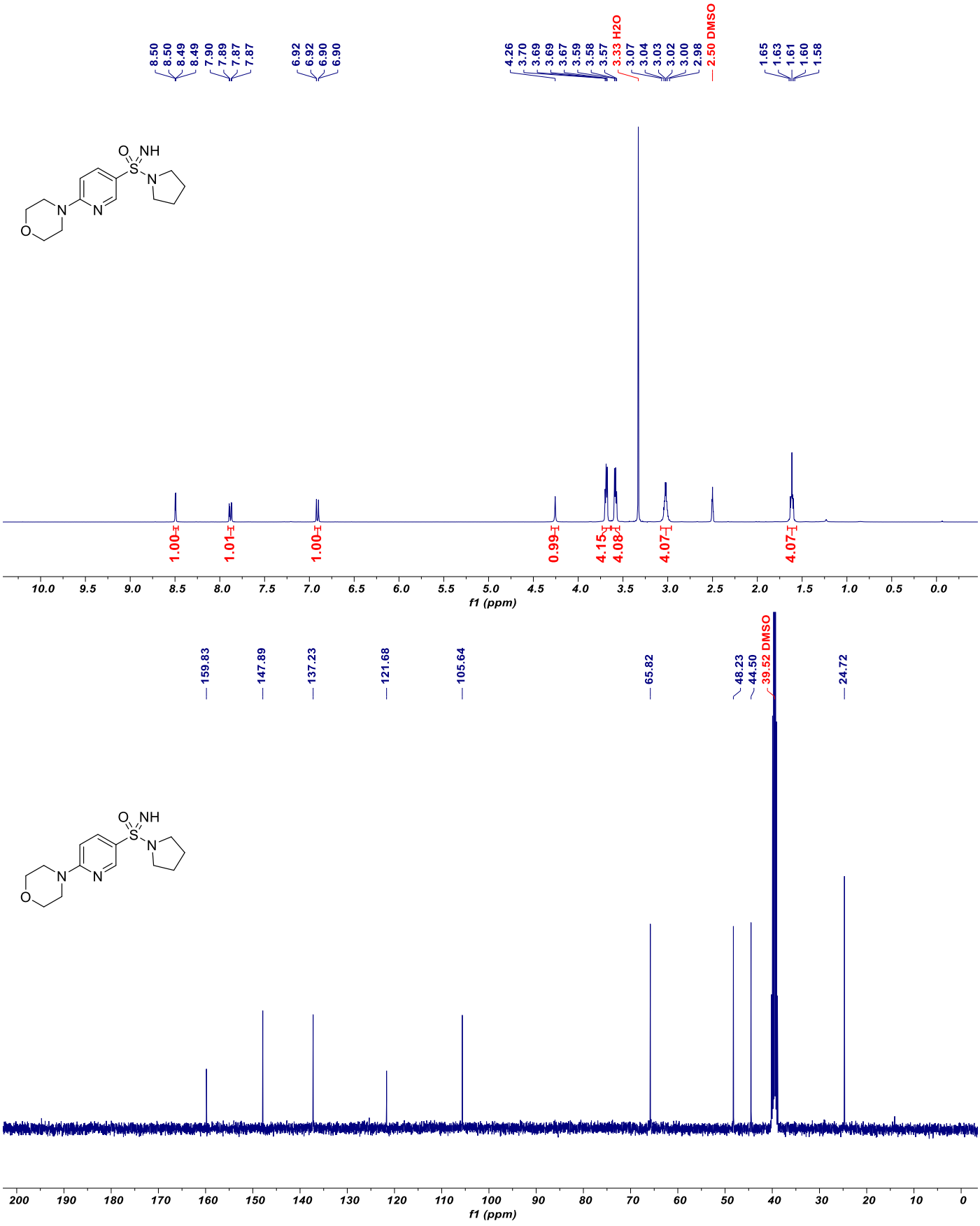




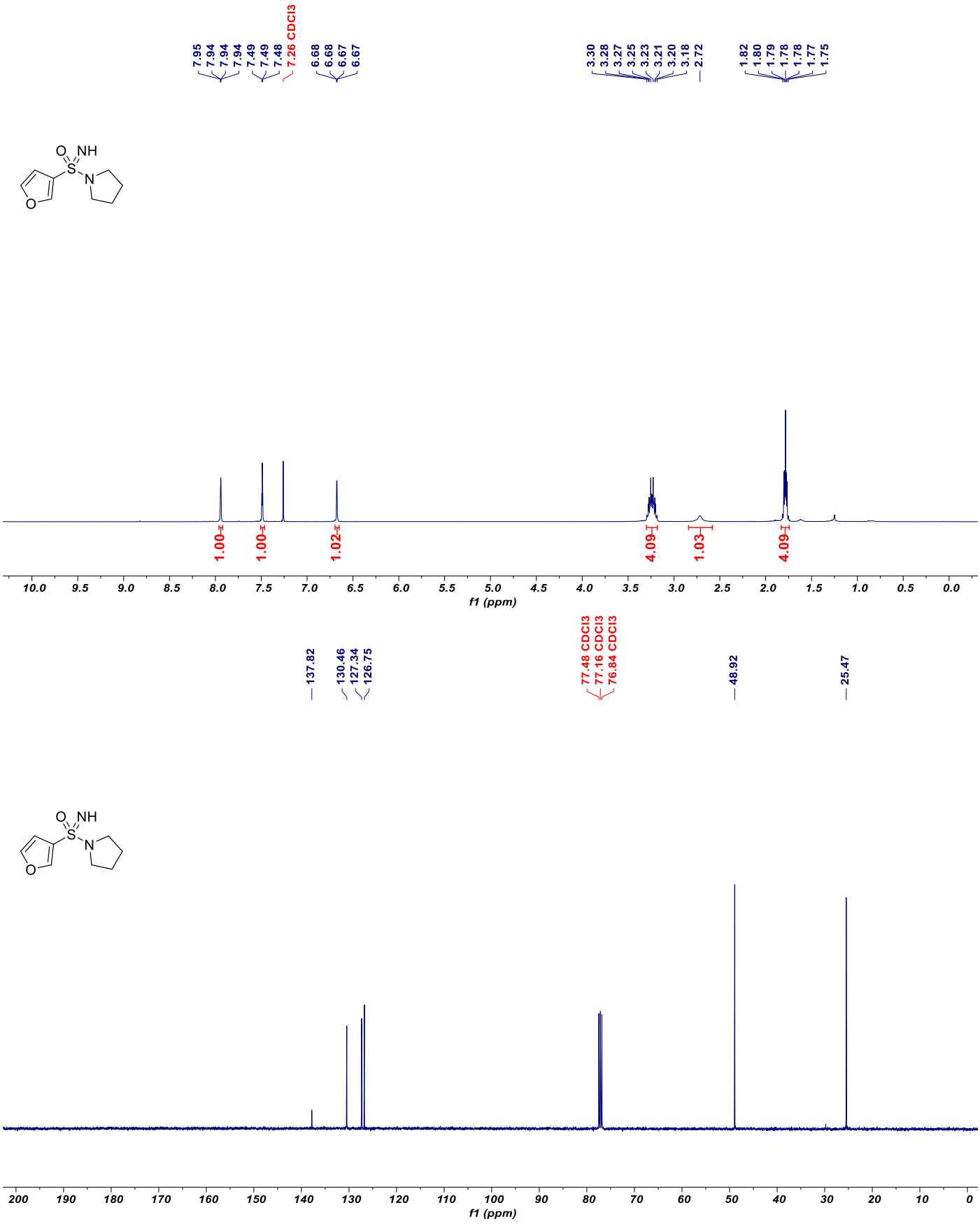
NMR spectrum of sulfonimidamide **27m**



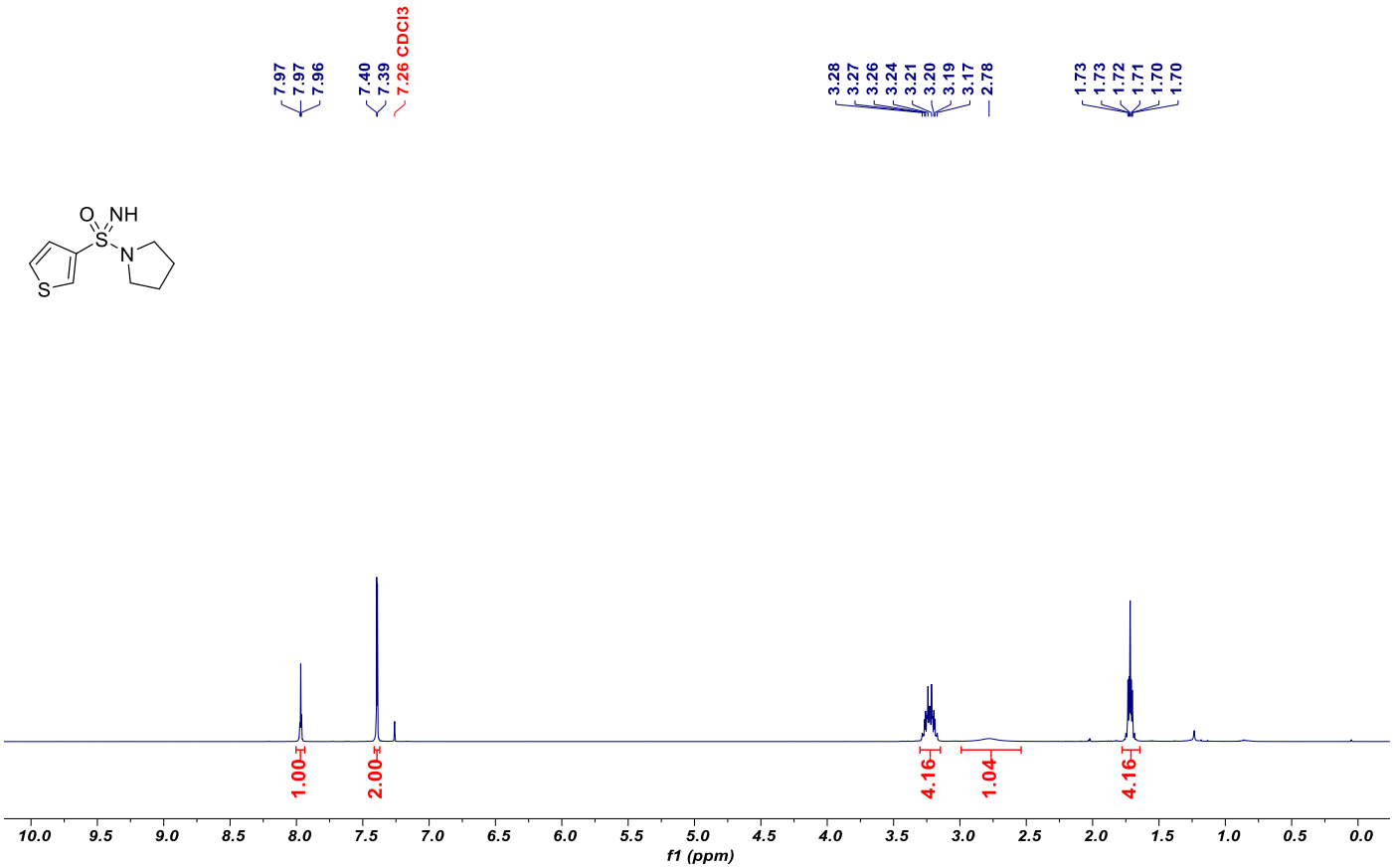
NMR spectrum of sulfonimidamide **27n**

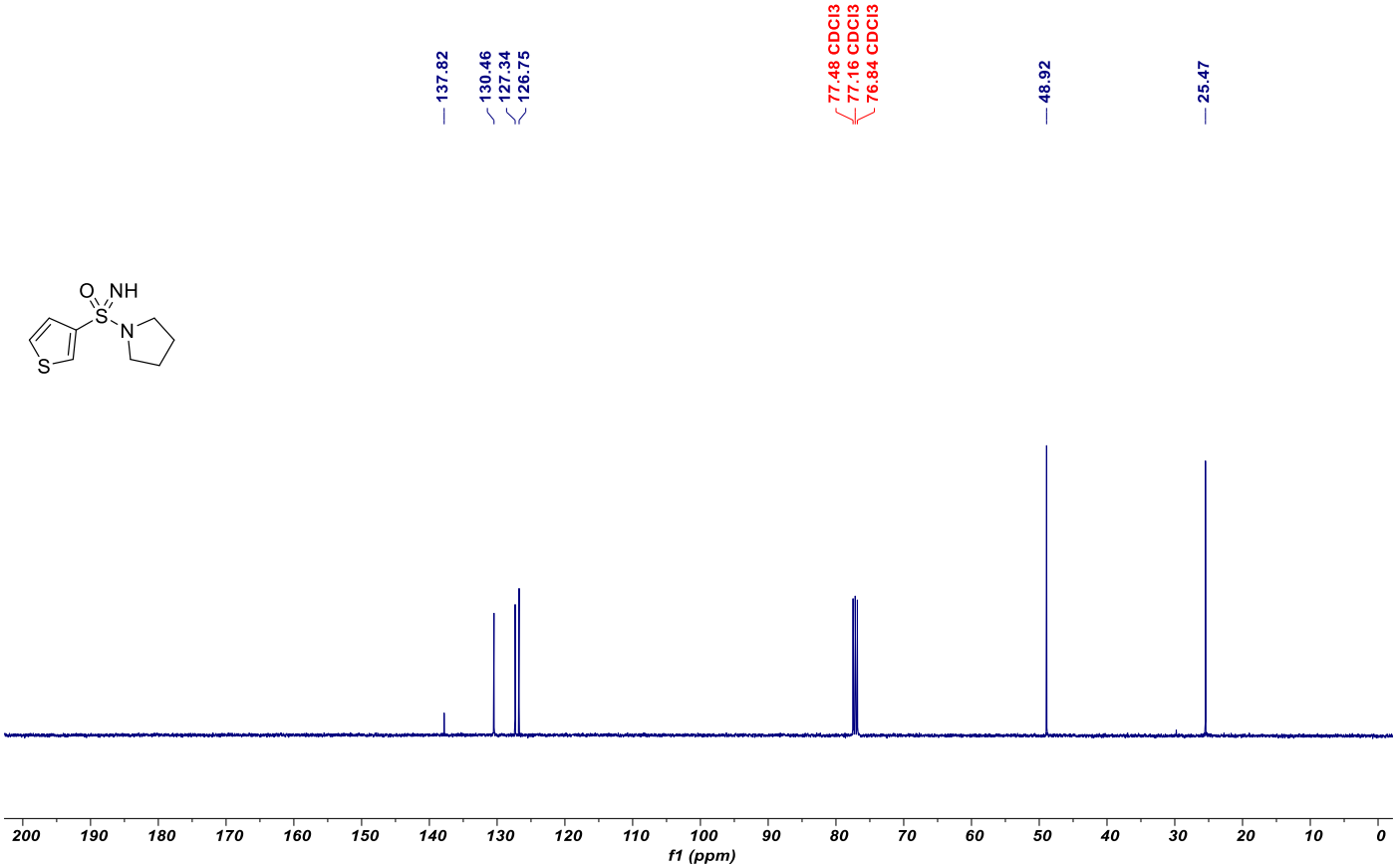


NMR spectrum of sulfonimidamide **27o**

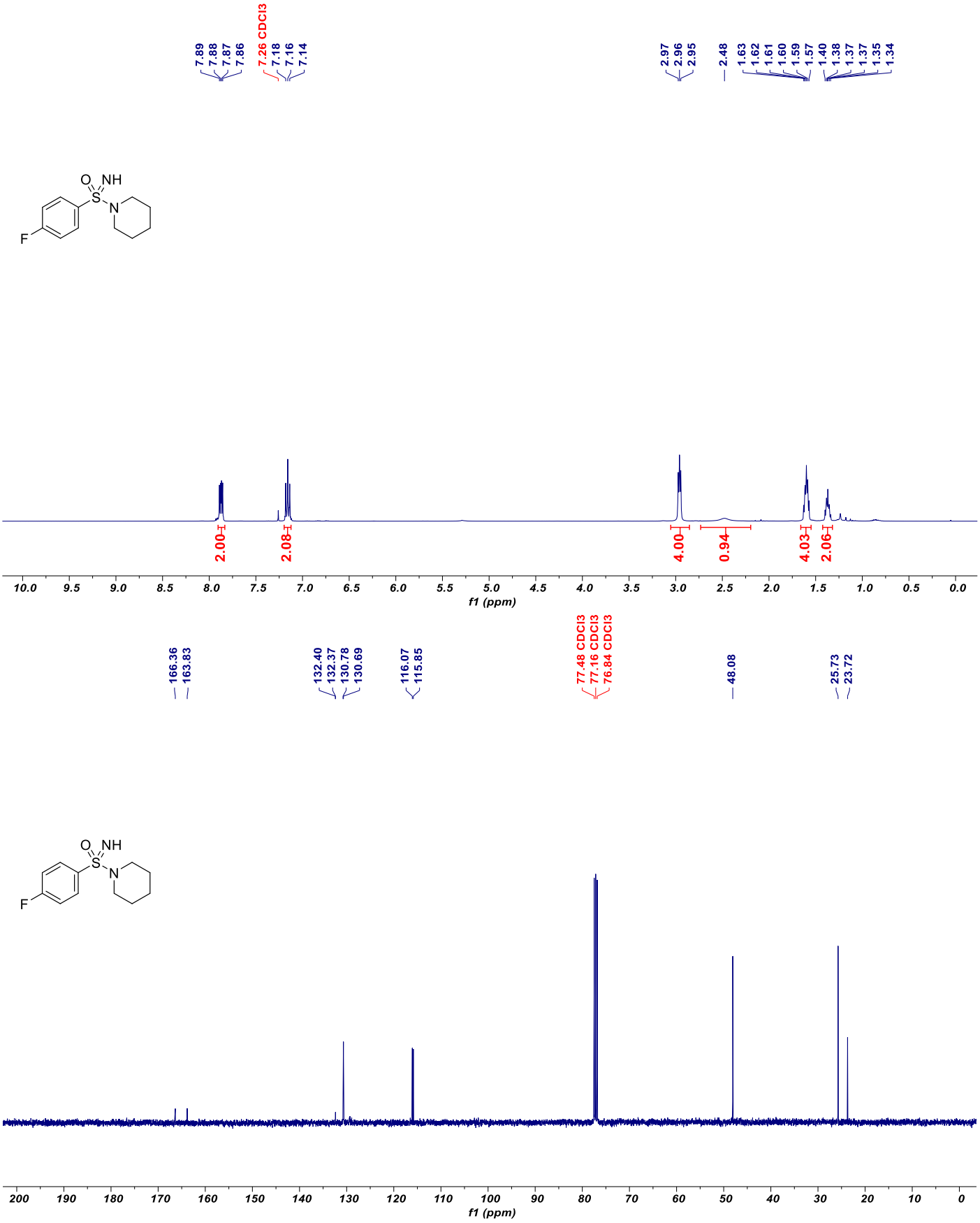


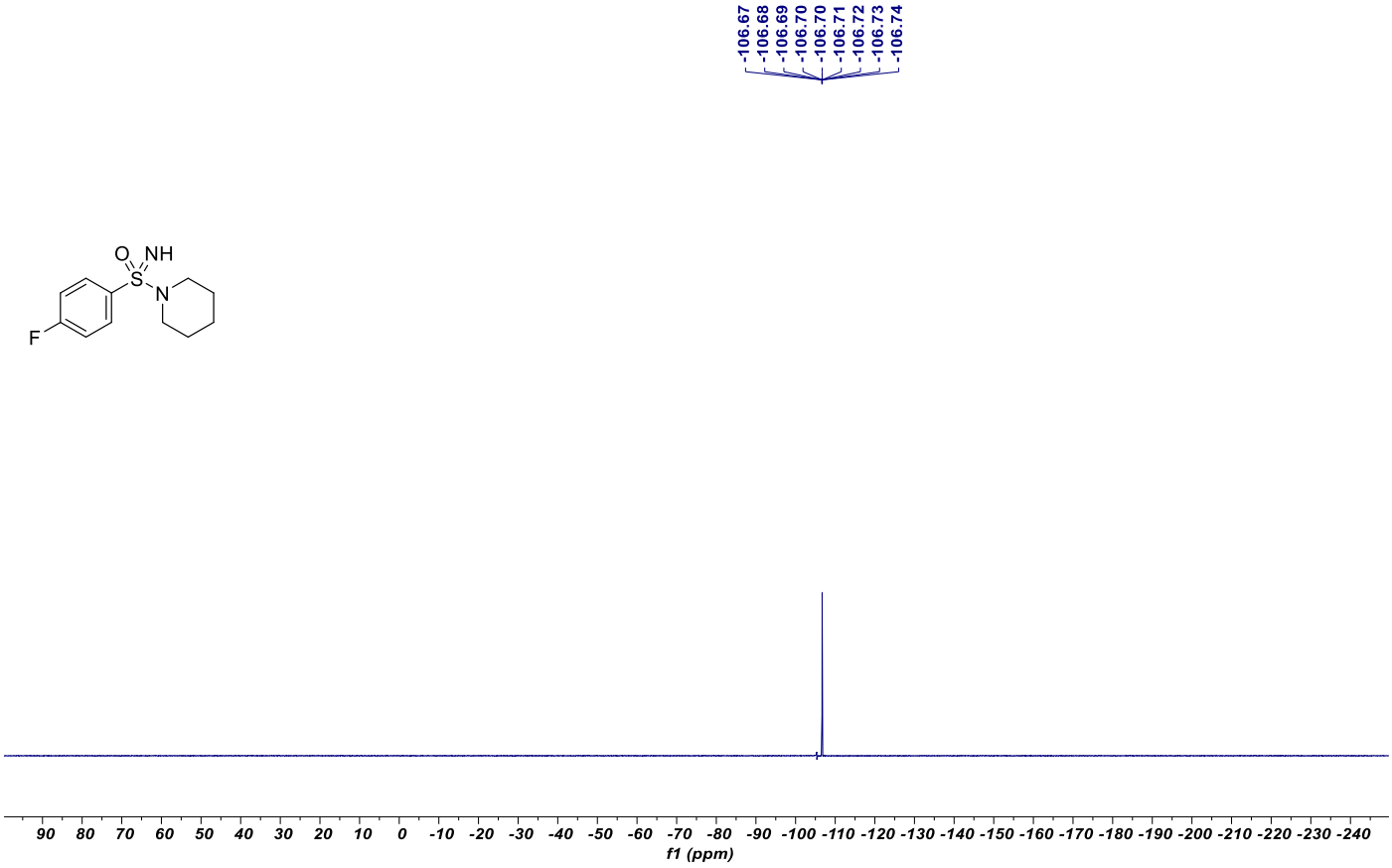
NMR spectrum of sulfonimidamide **27p**



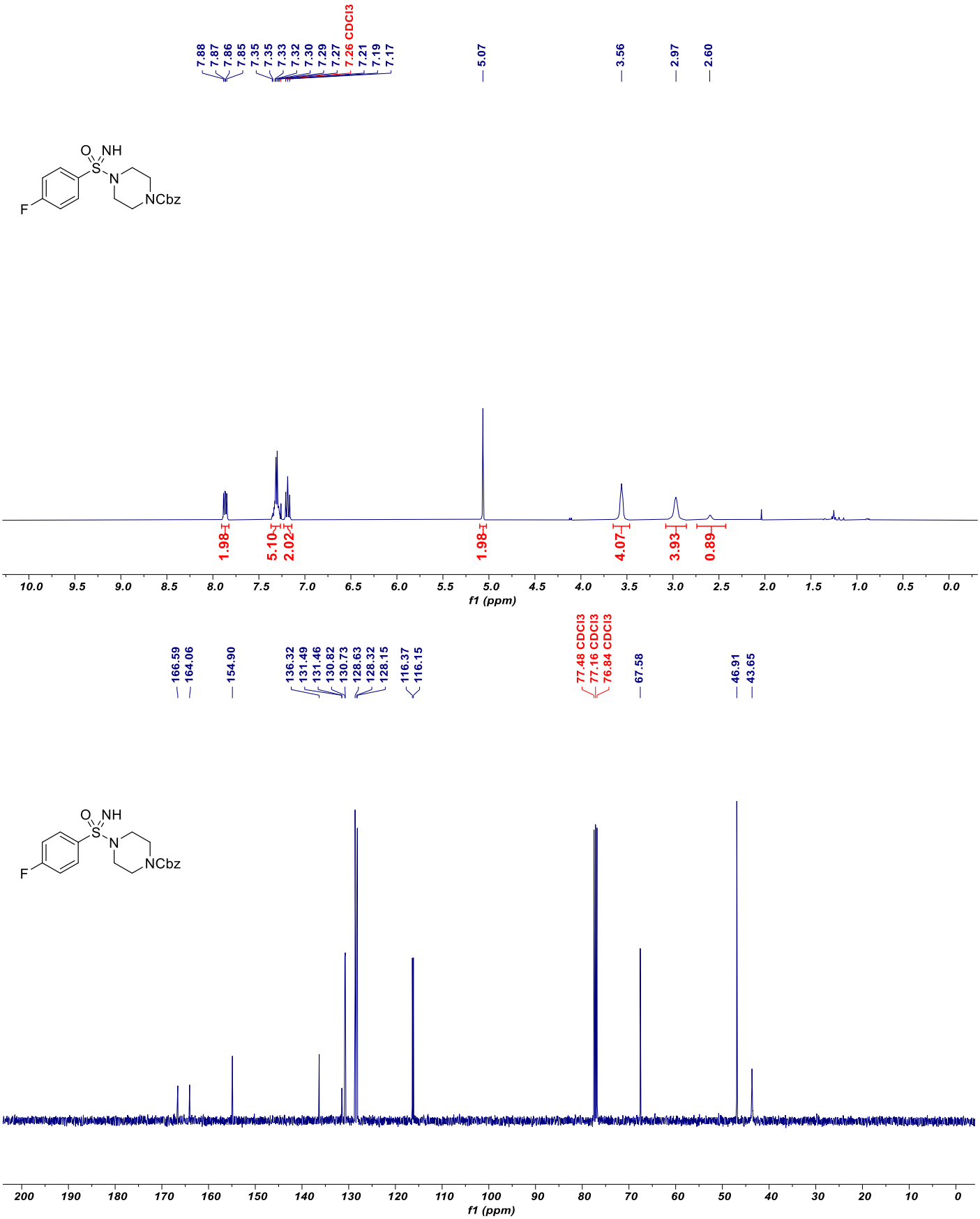


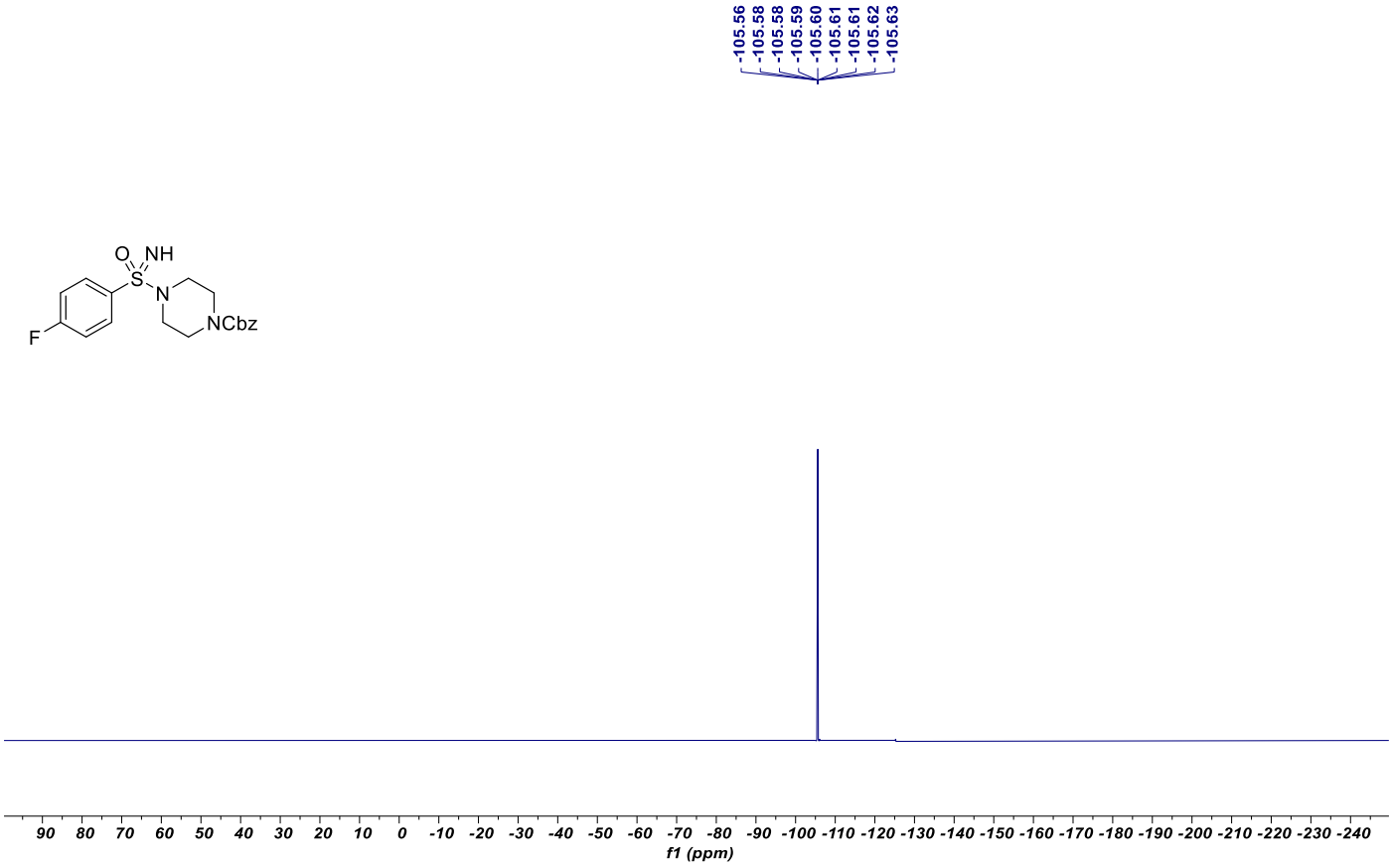
NMR spectrum of sulfonimidamide **28a**



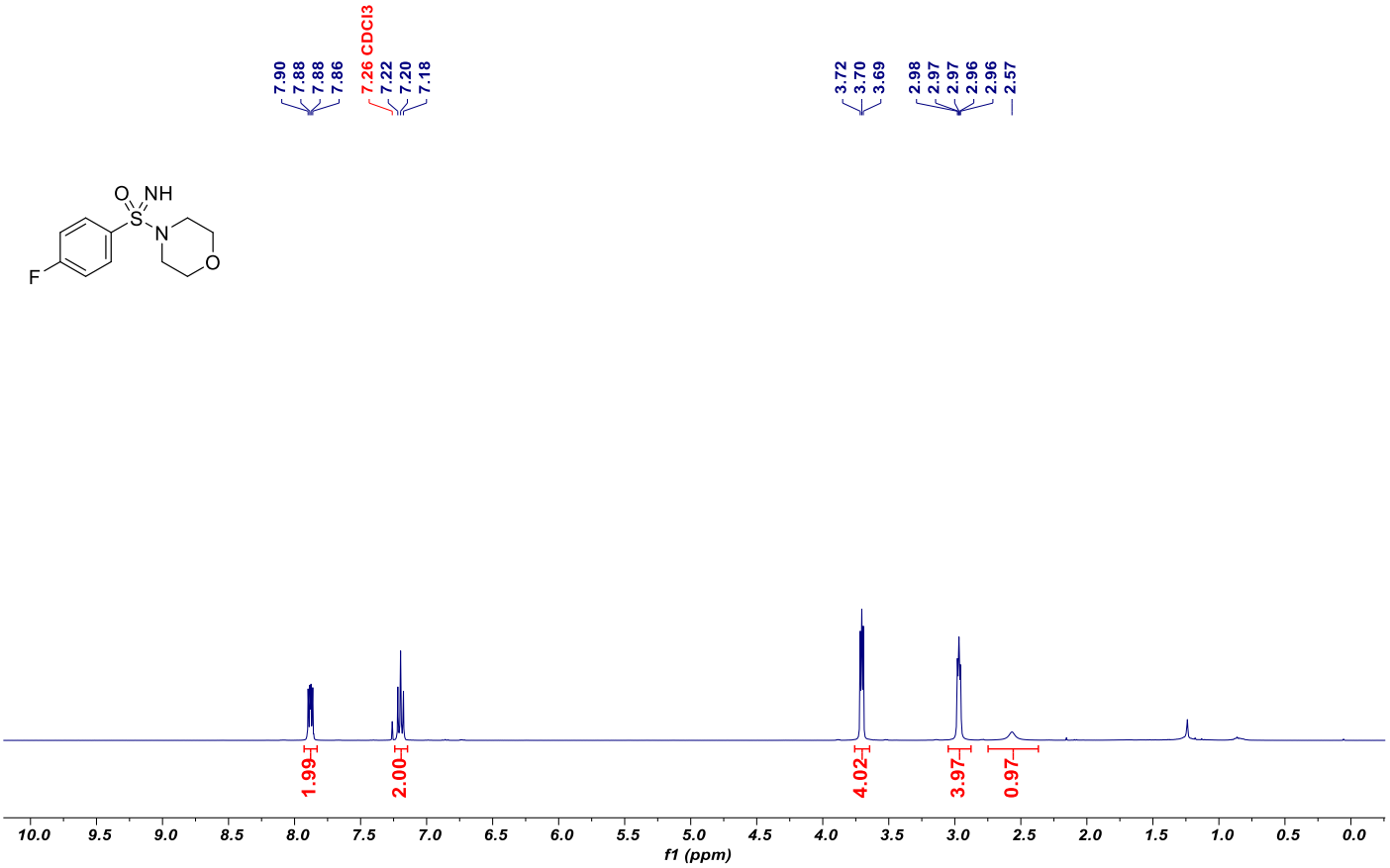

-106.67
-106.68
-106.69
-106.70
-106.70
-106.71
-106.72
-106.73
-106.74
O
NH
S
N
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

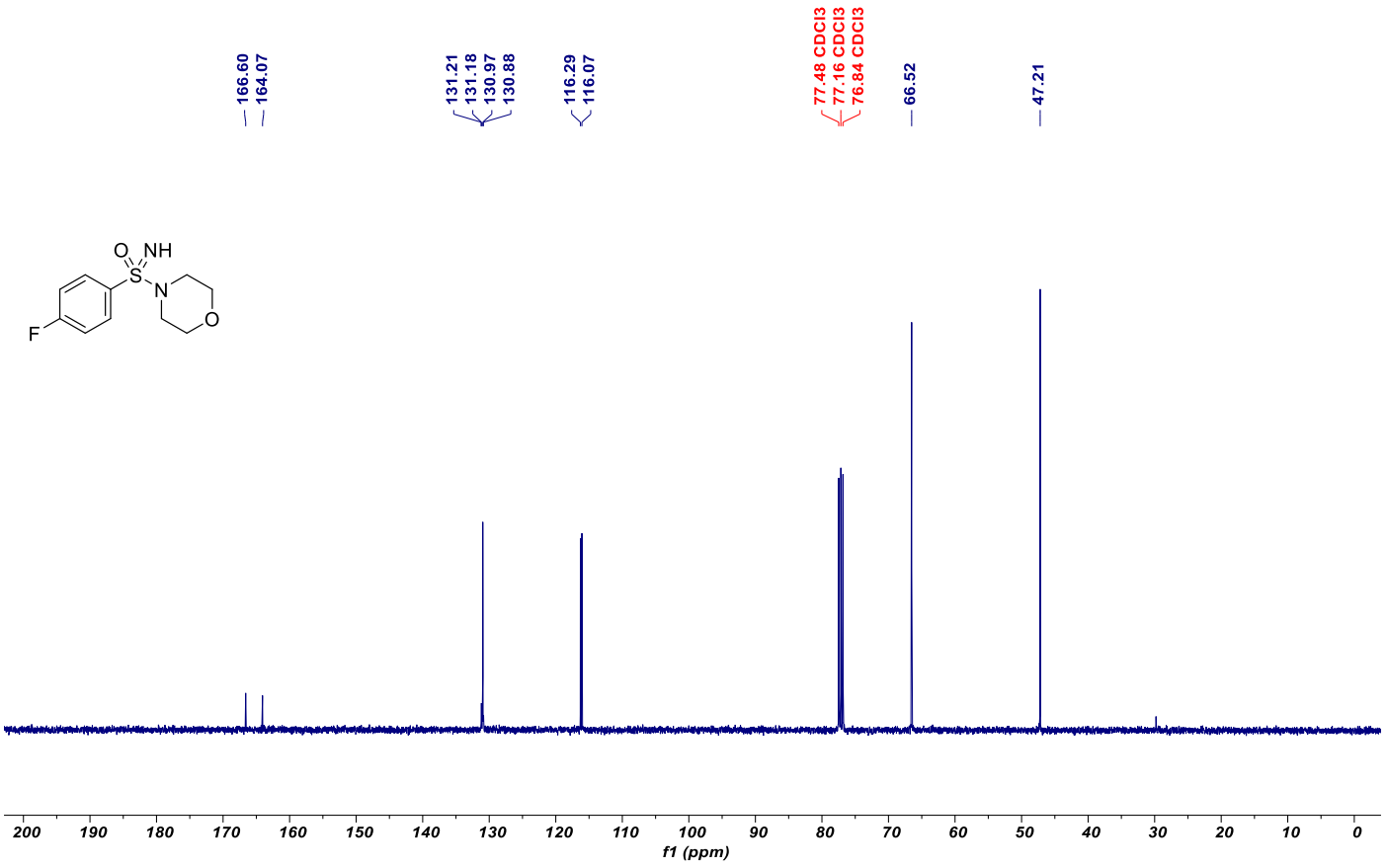
NMR spectrum of sulfonimidamide **28b**

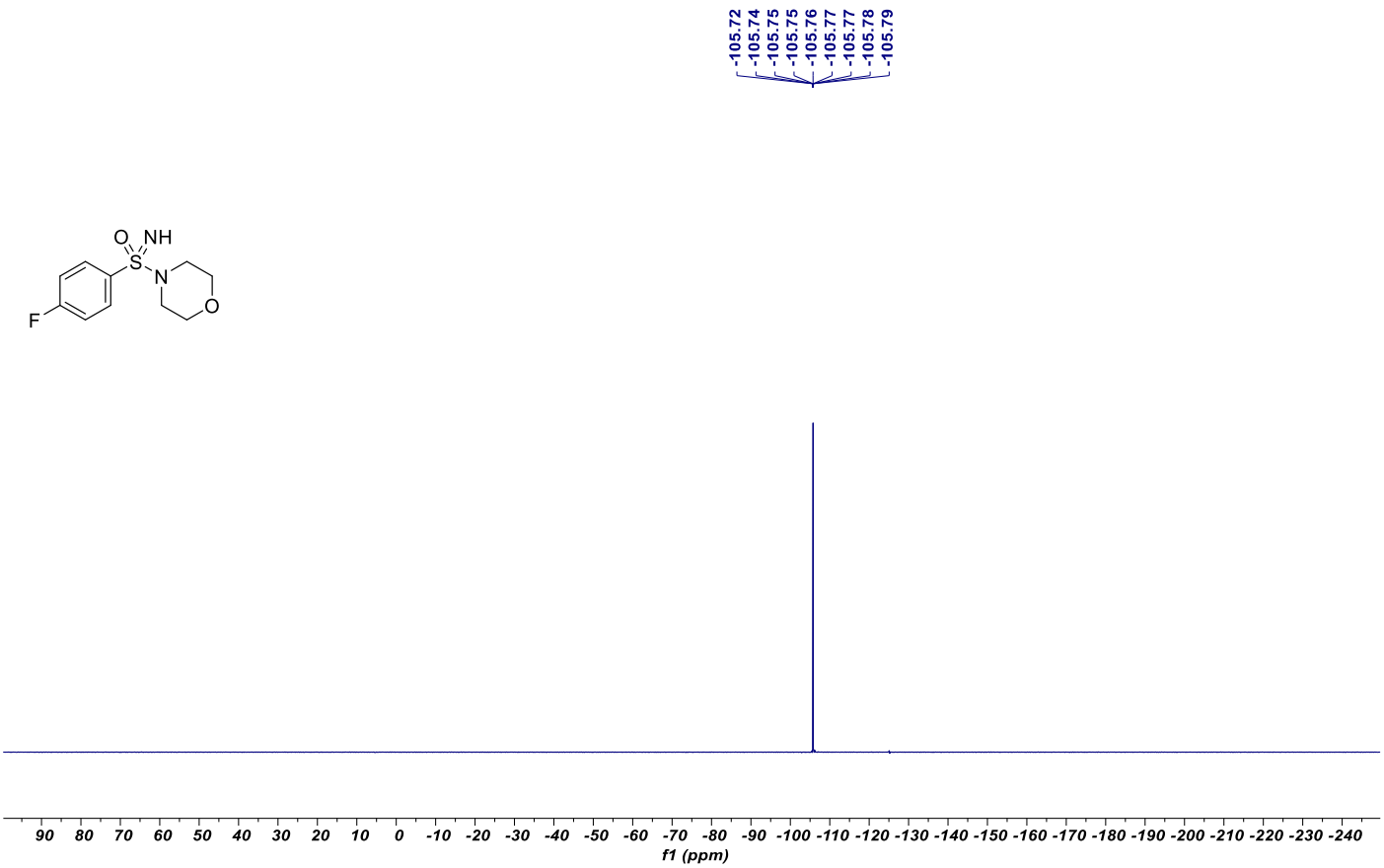



-105.56
-105.58
-105.58
-105.59
-105.60
-105.61
-105.61
-105.62
-105.63
O
NH
S
N
NCbz
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

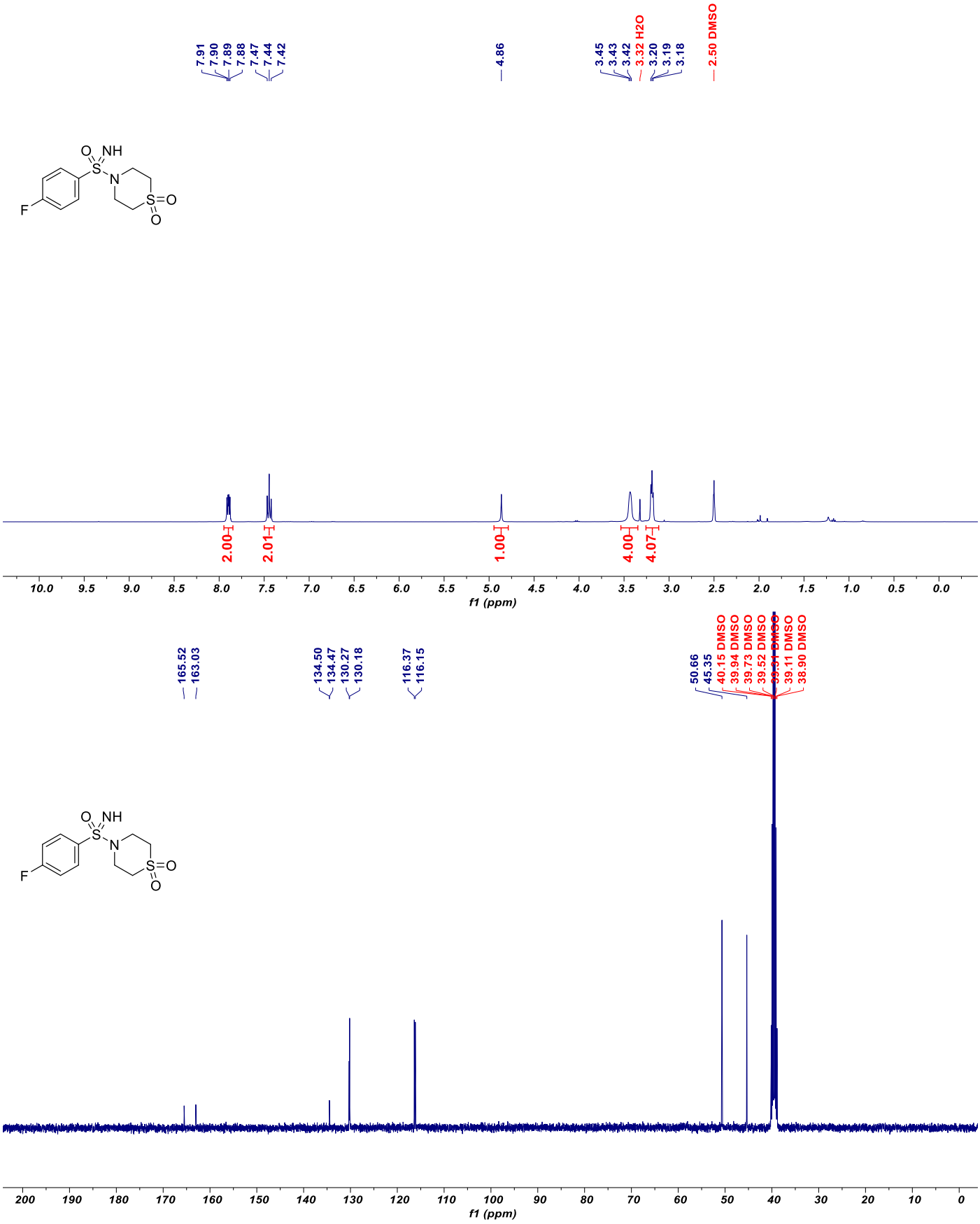
NMR spectrum of sulfonimidamide **28c**

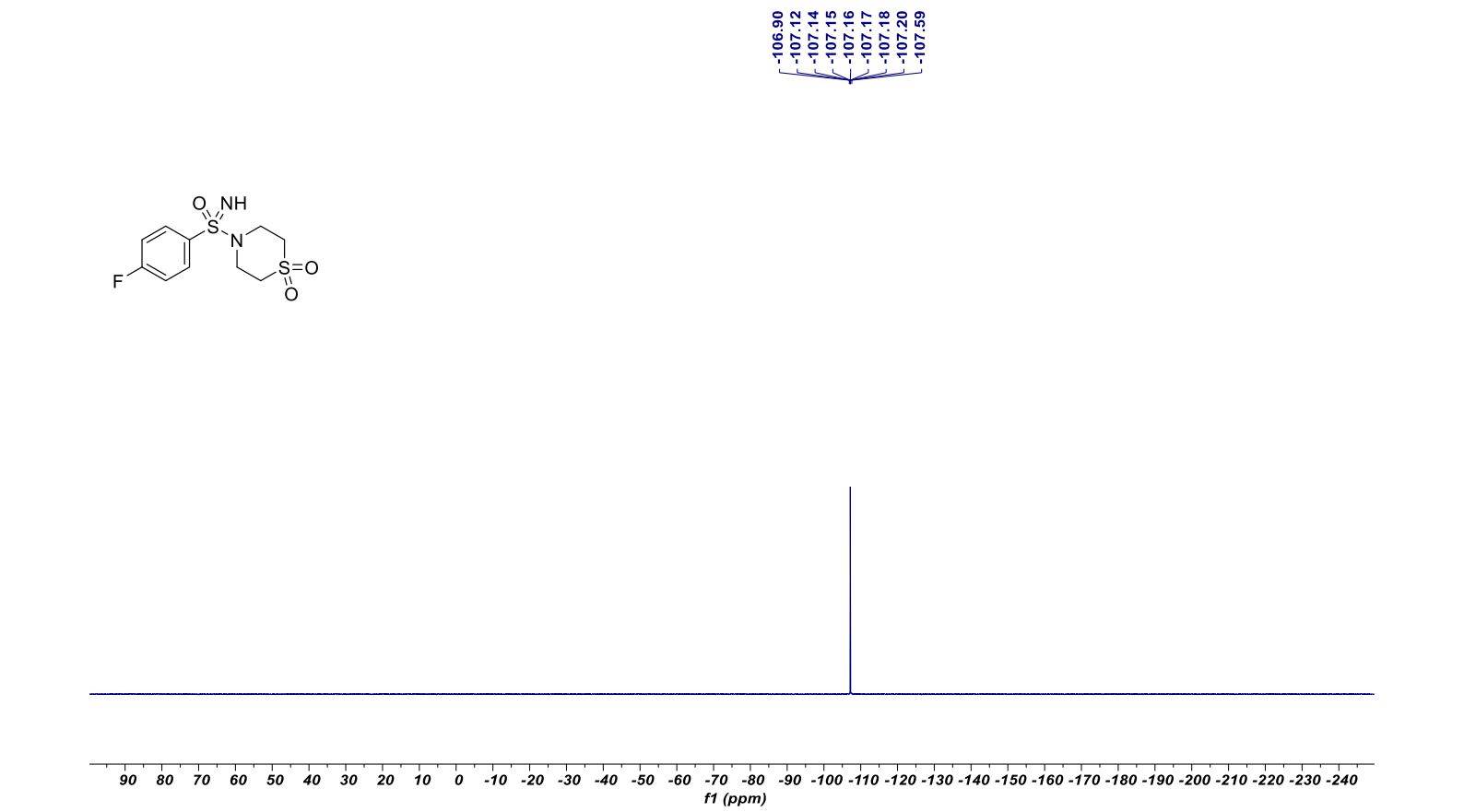




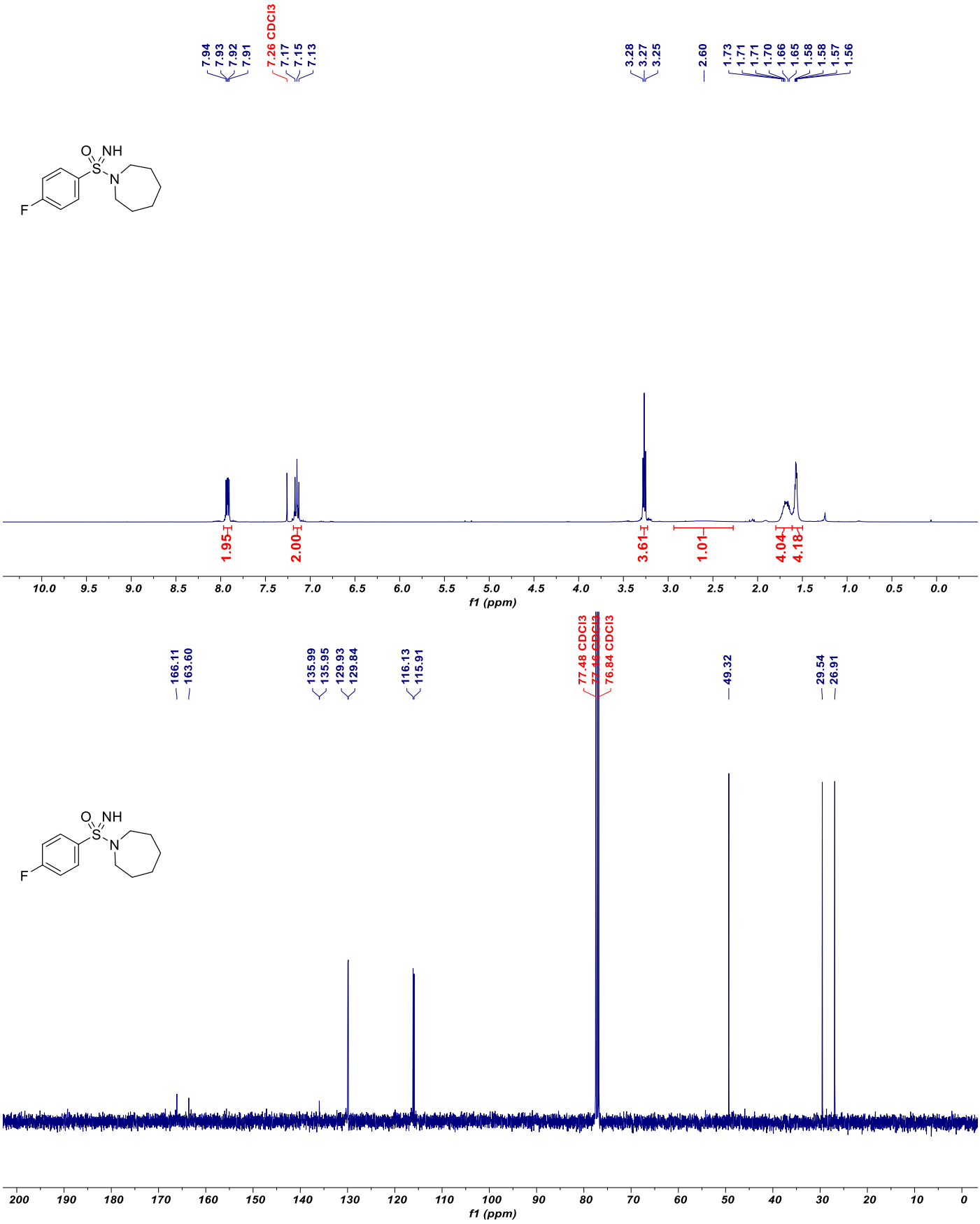

-105.72
-105.74
-105.75
-105.75
-105.76
-105.77
-105.77
-105.78
-105.79
O
NH
S
N
O
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

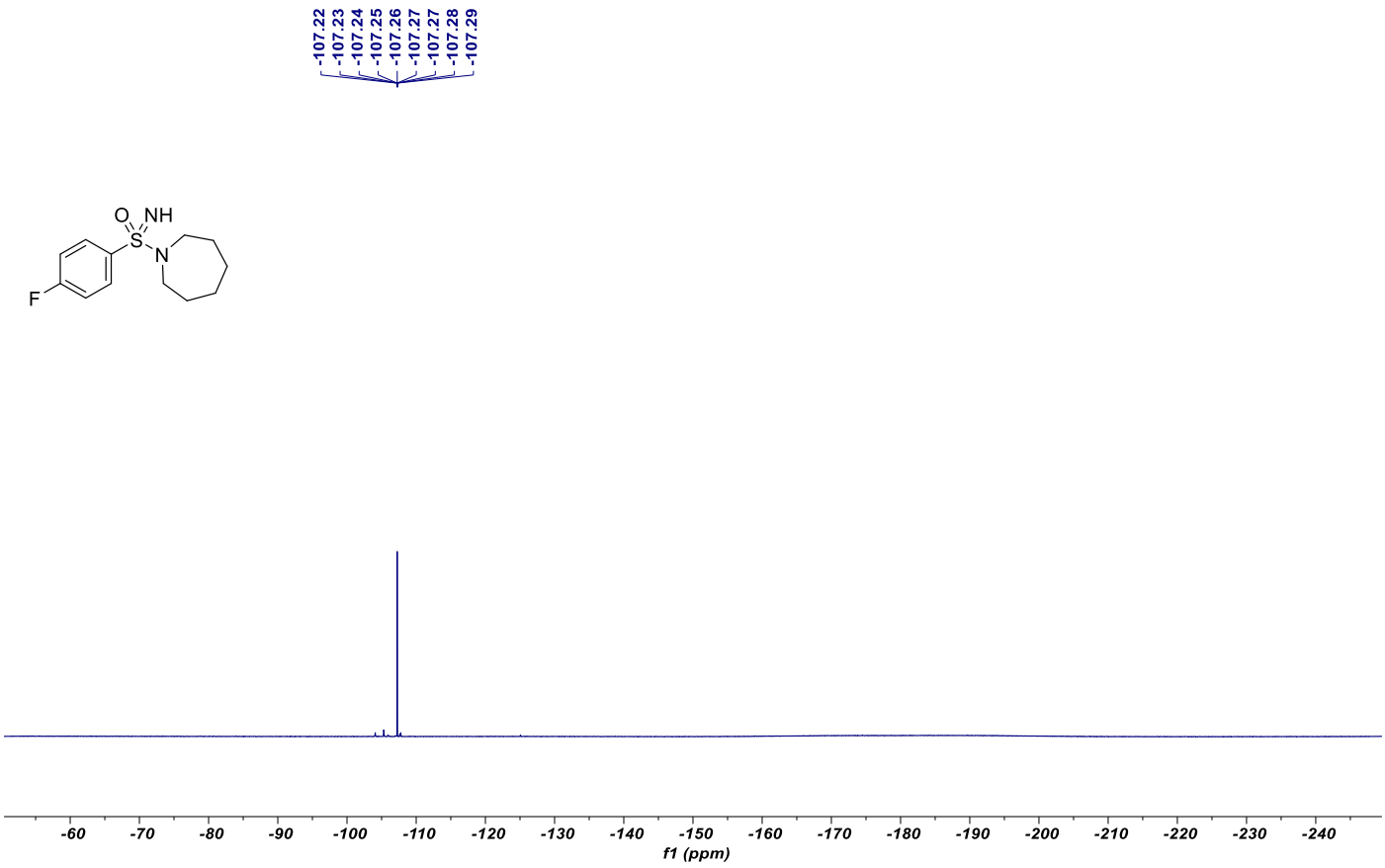
NMR spectrum of sulfonimidamide **28d**



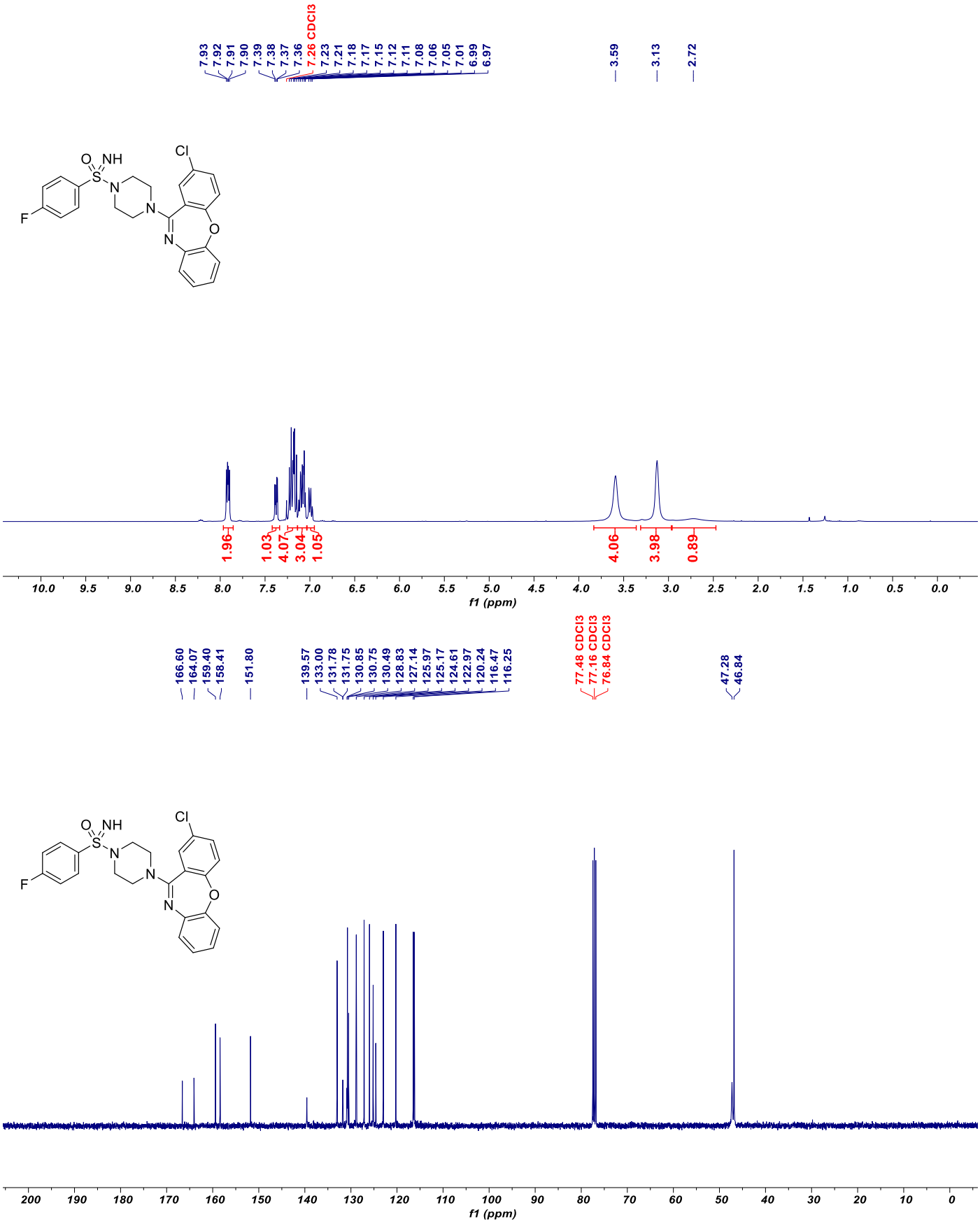

-106.90
-107.12
-107.14
-107.15
-107.16
-107.17
-107.18
-107.20
-107.59
O
NH
S
N
S=O
O
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

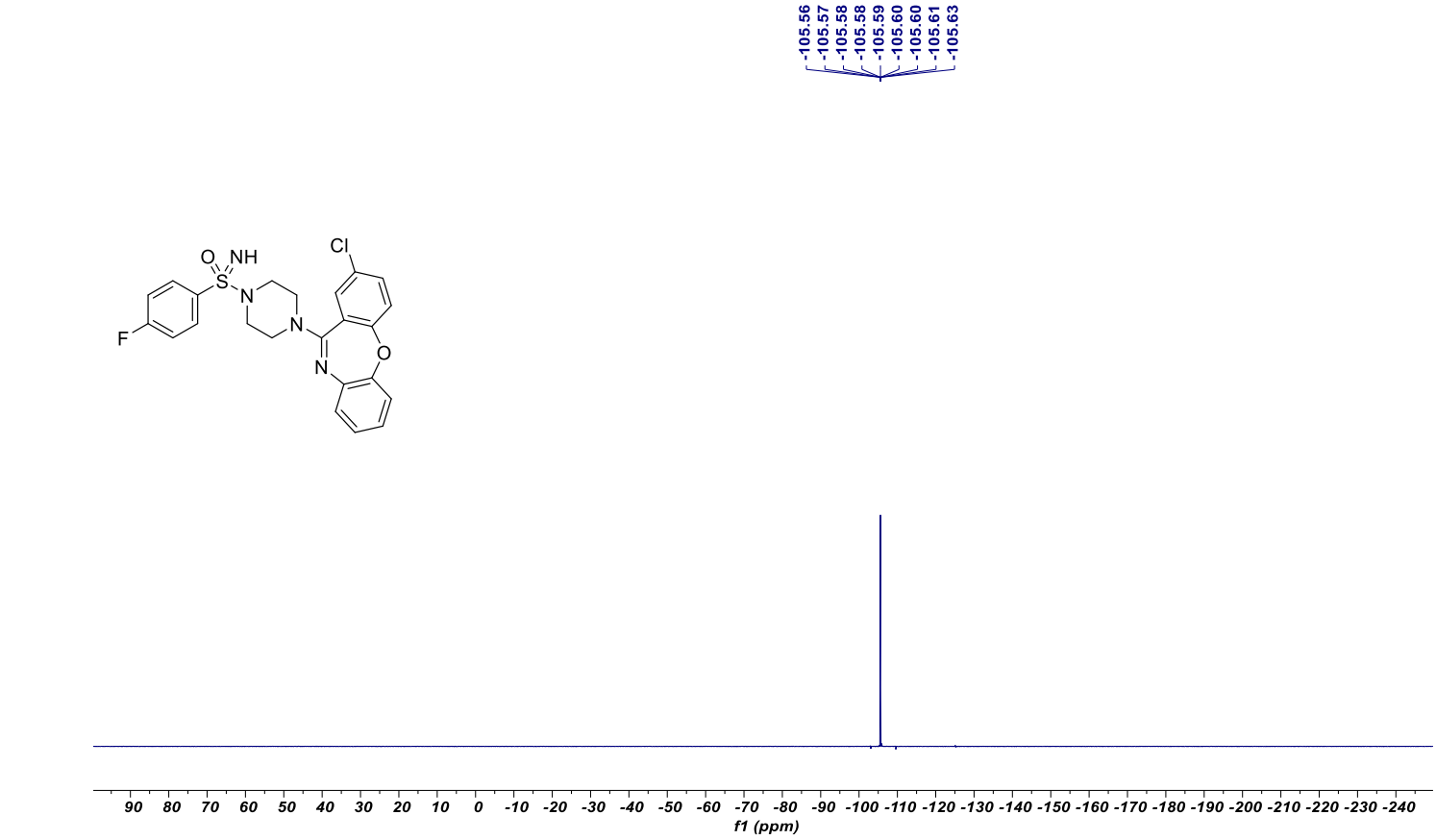
NMR spectrum of sulfonimidamide **28e**



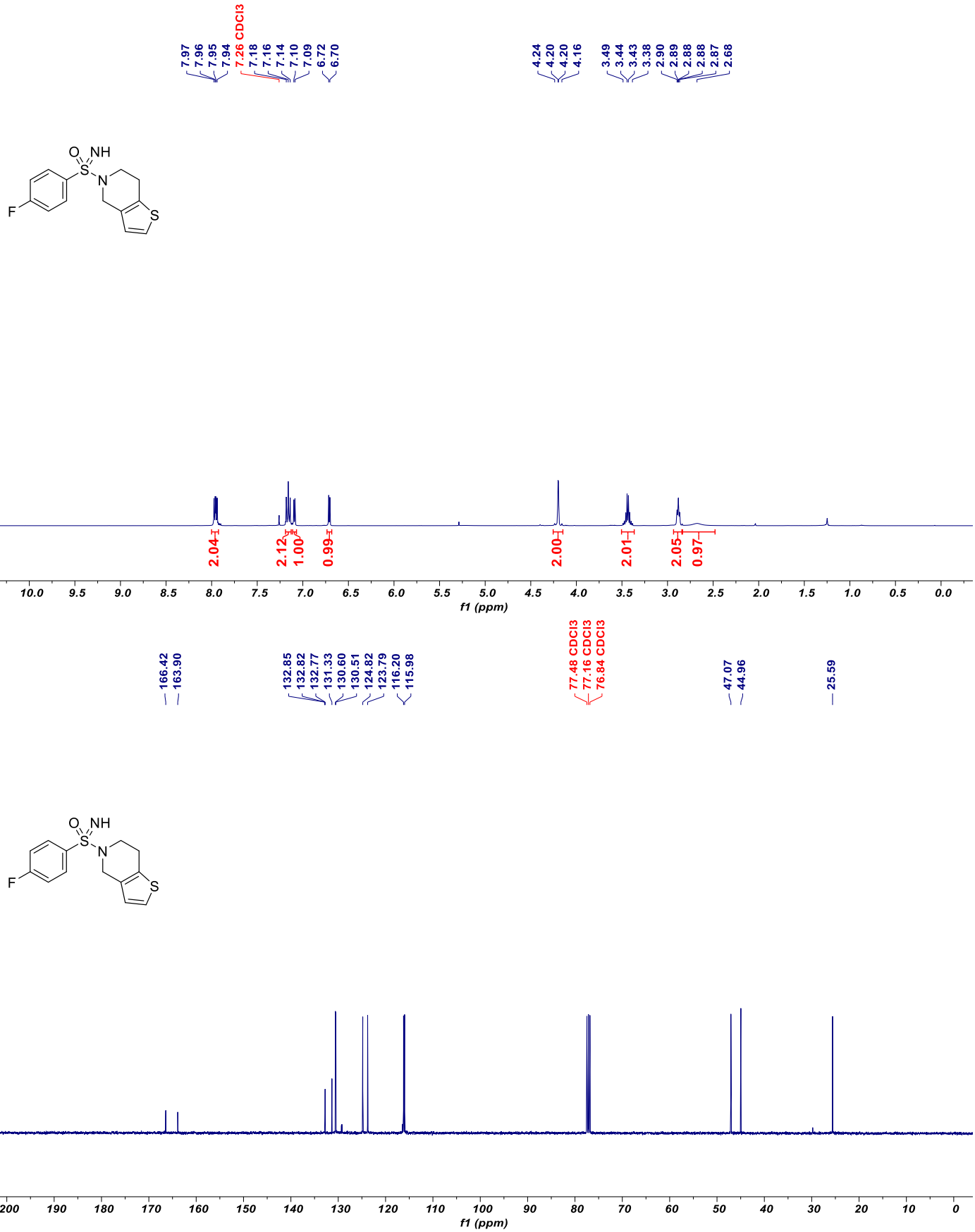

-107.22
-107.23
-107.24
-107.25
-107.26
-107.27
-107.27
-107.28
-107.29
O
NH
S
N
F
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
f1 (ppm)

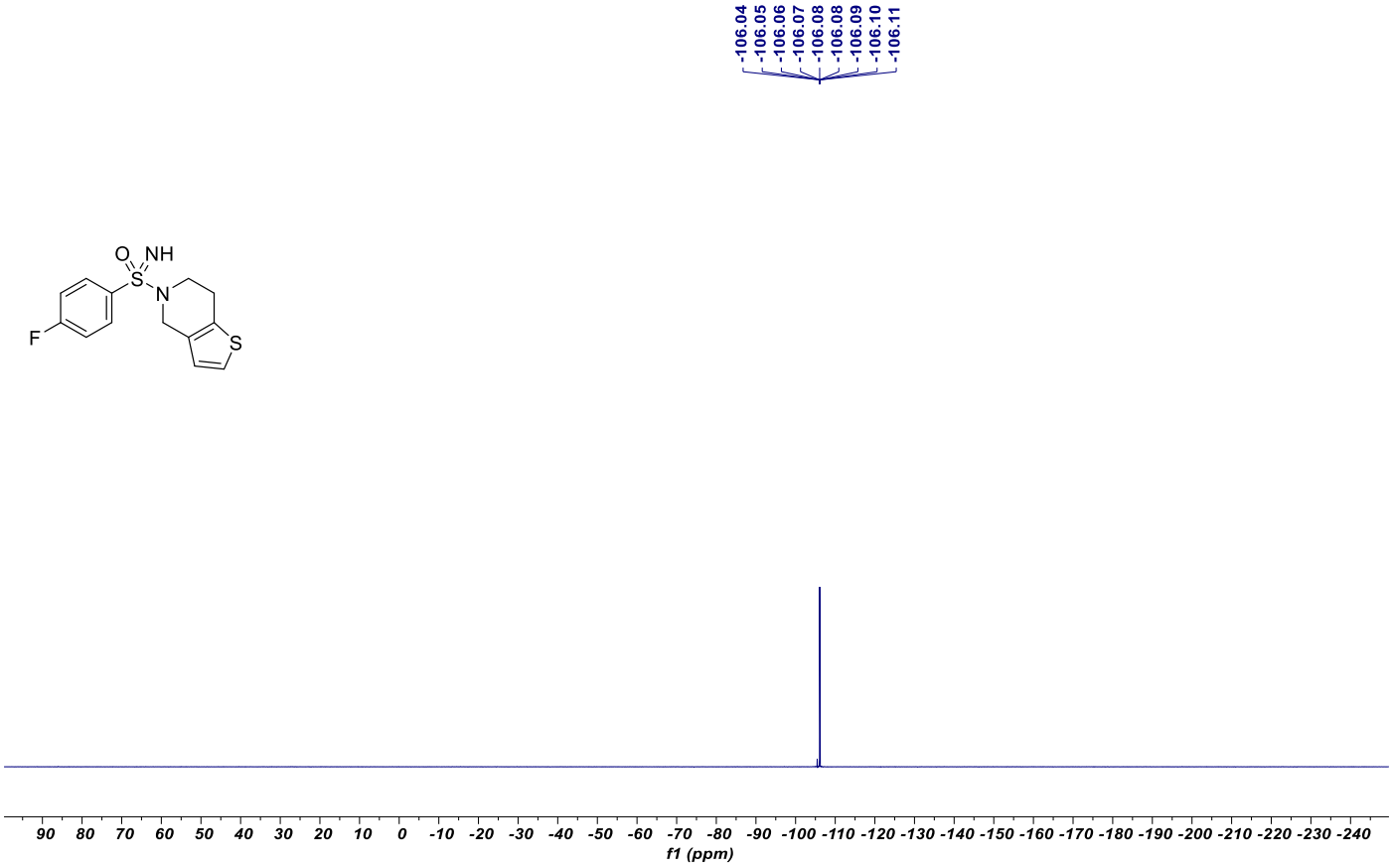
NMR spectrum of sulfonimidamide **28f**



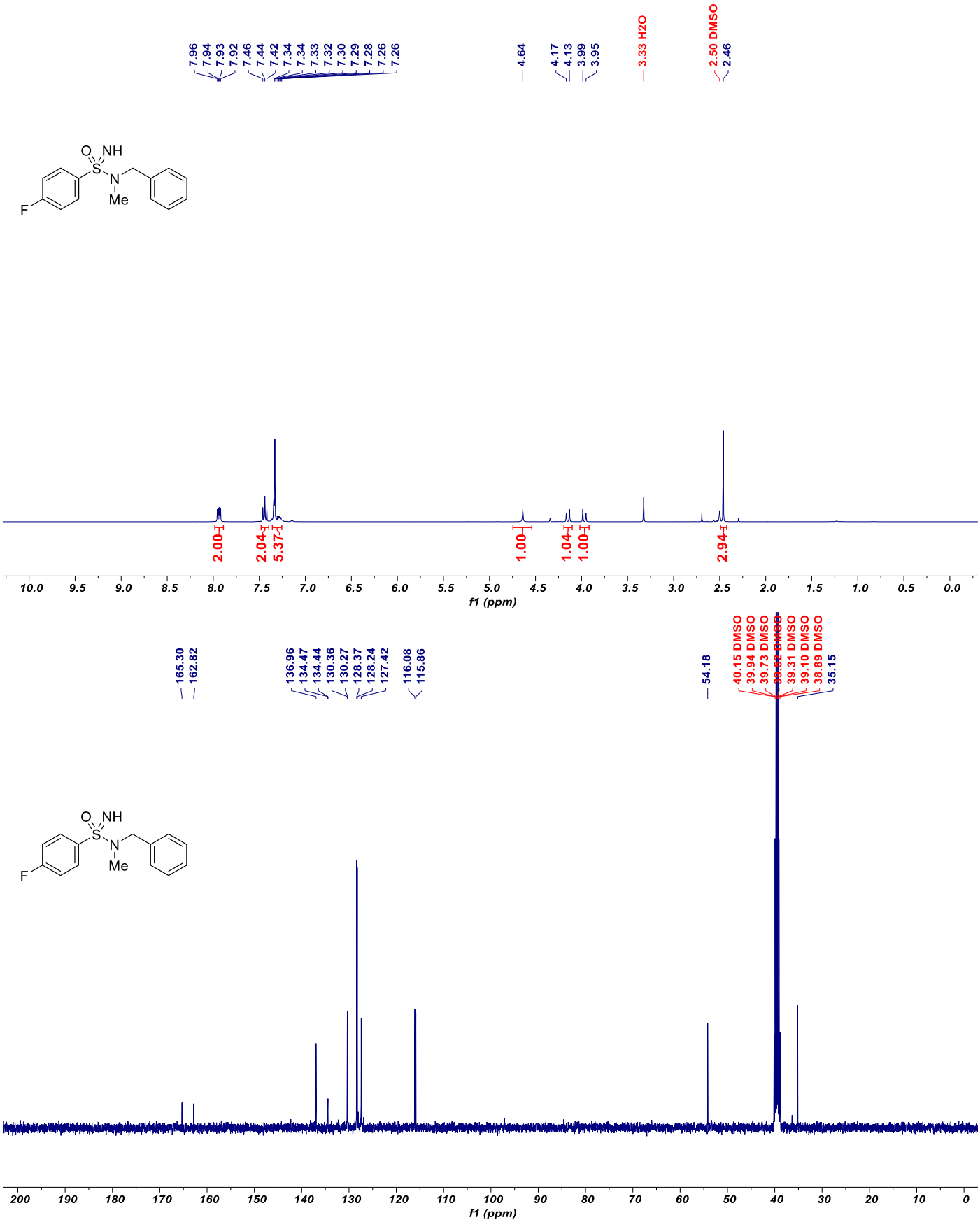

-105.56
-105.57
-105.58
-105.58
-105.59
-105.60
-105.60
-105.61
-105.63
O
NH
S
N
N
F
Cl
N
O
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

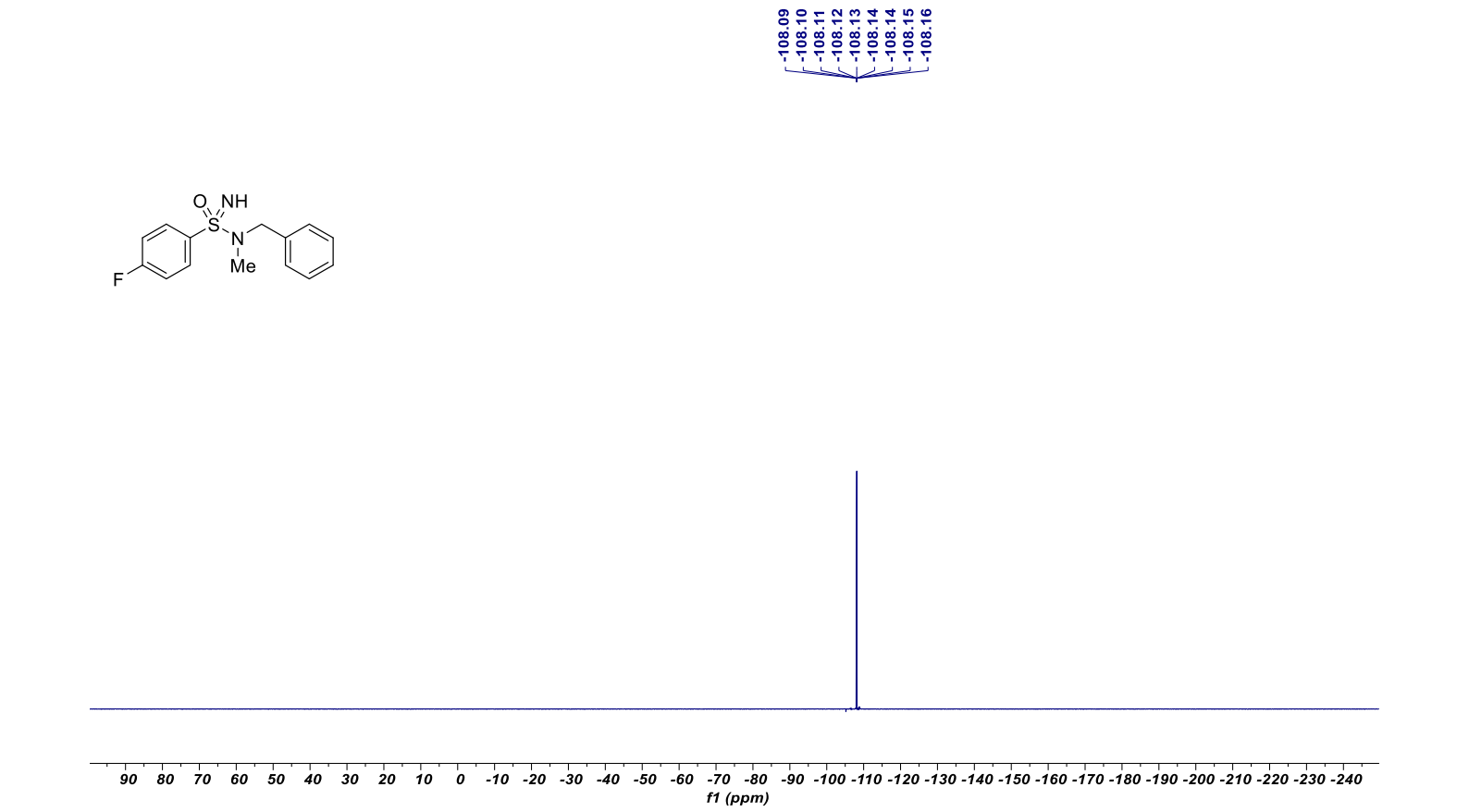
NMR spectrum of sulfonimidamide **28g**



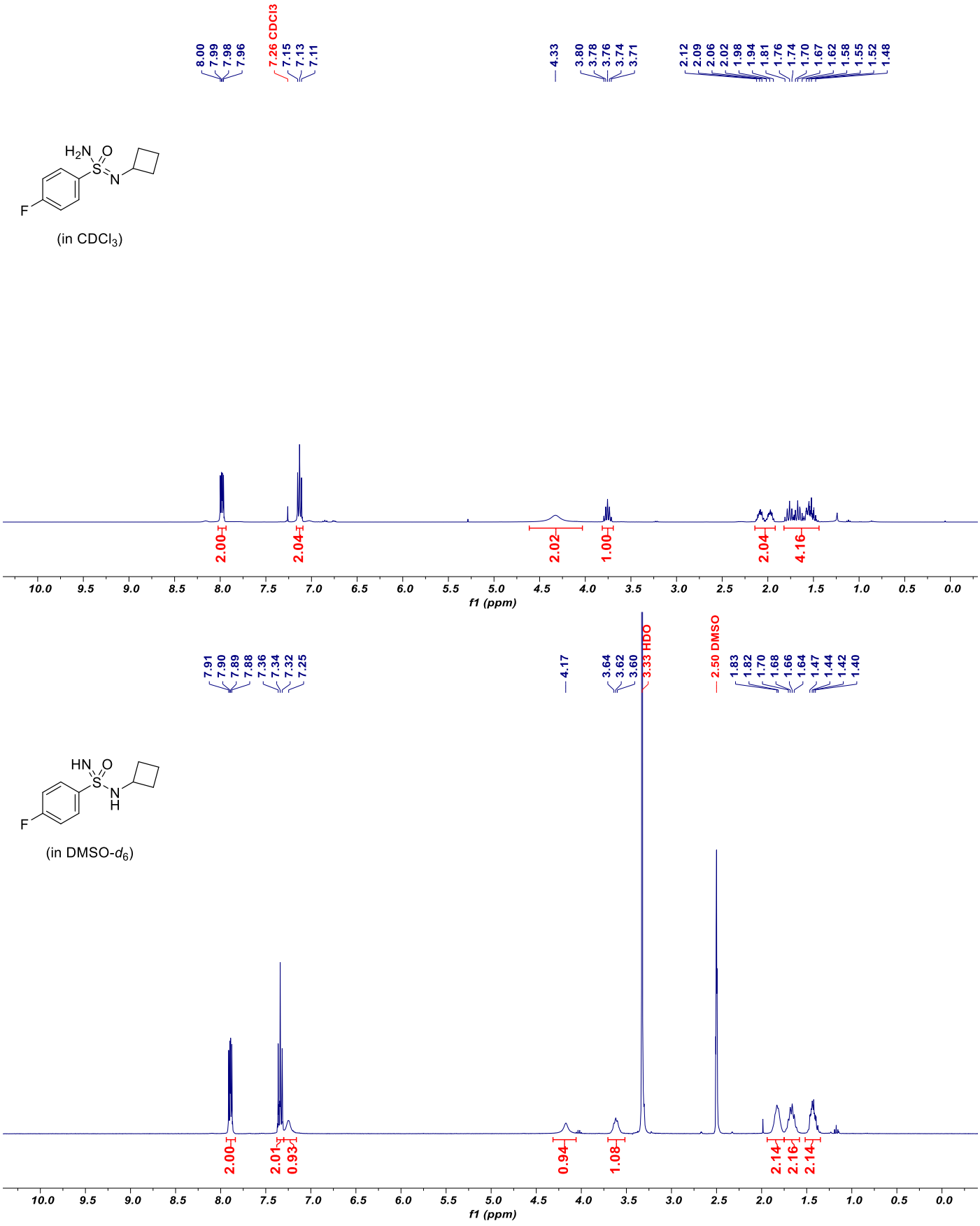

-106.04
-106.05
-106.06
-106.07
-106.08
-106.08
-106.09
-106.10
-106.11
O
NH
S
N
F
S
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

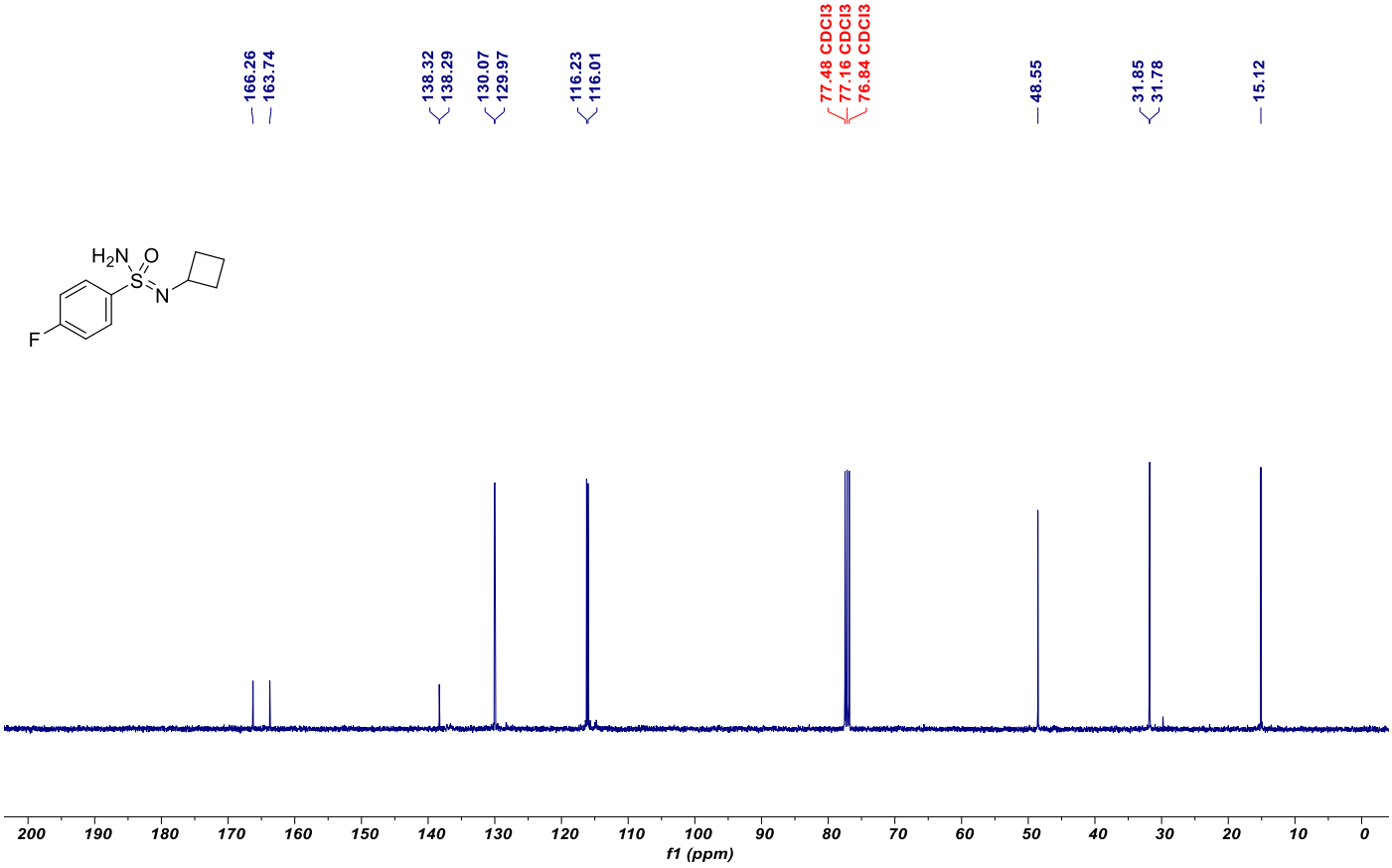
NMR spectrum of sulfonimidamide **28h**

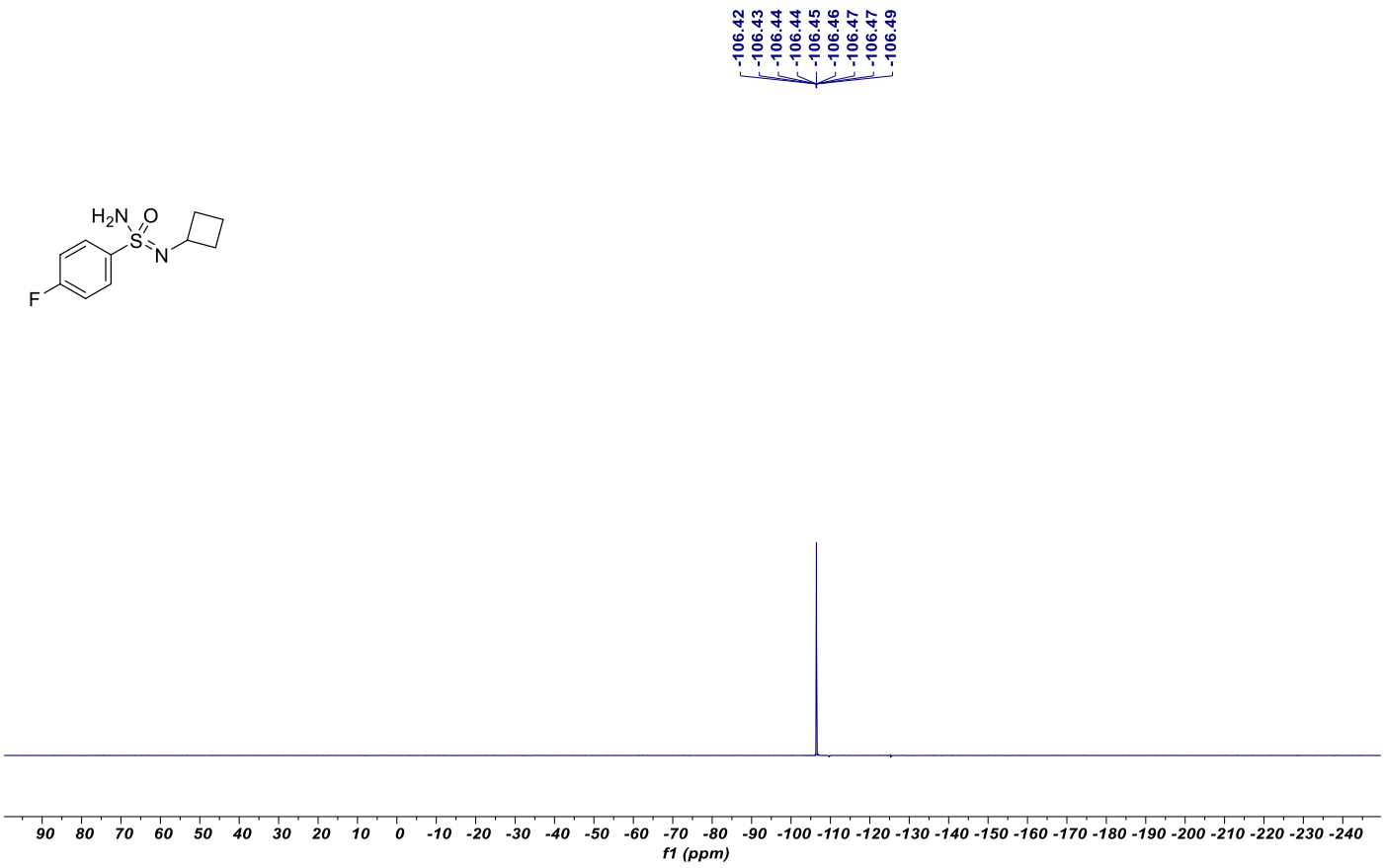



-108.09
-108.10
-108.11
-108.12
-108.13
-108.14
-108.14
-108.15
-108.16
O
NH
S
N
Me
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

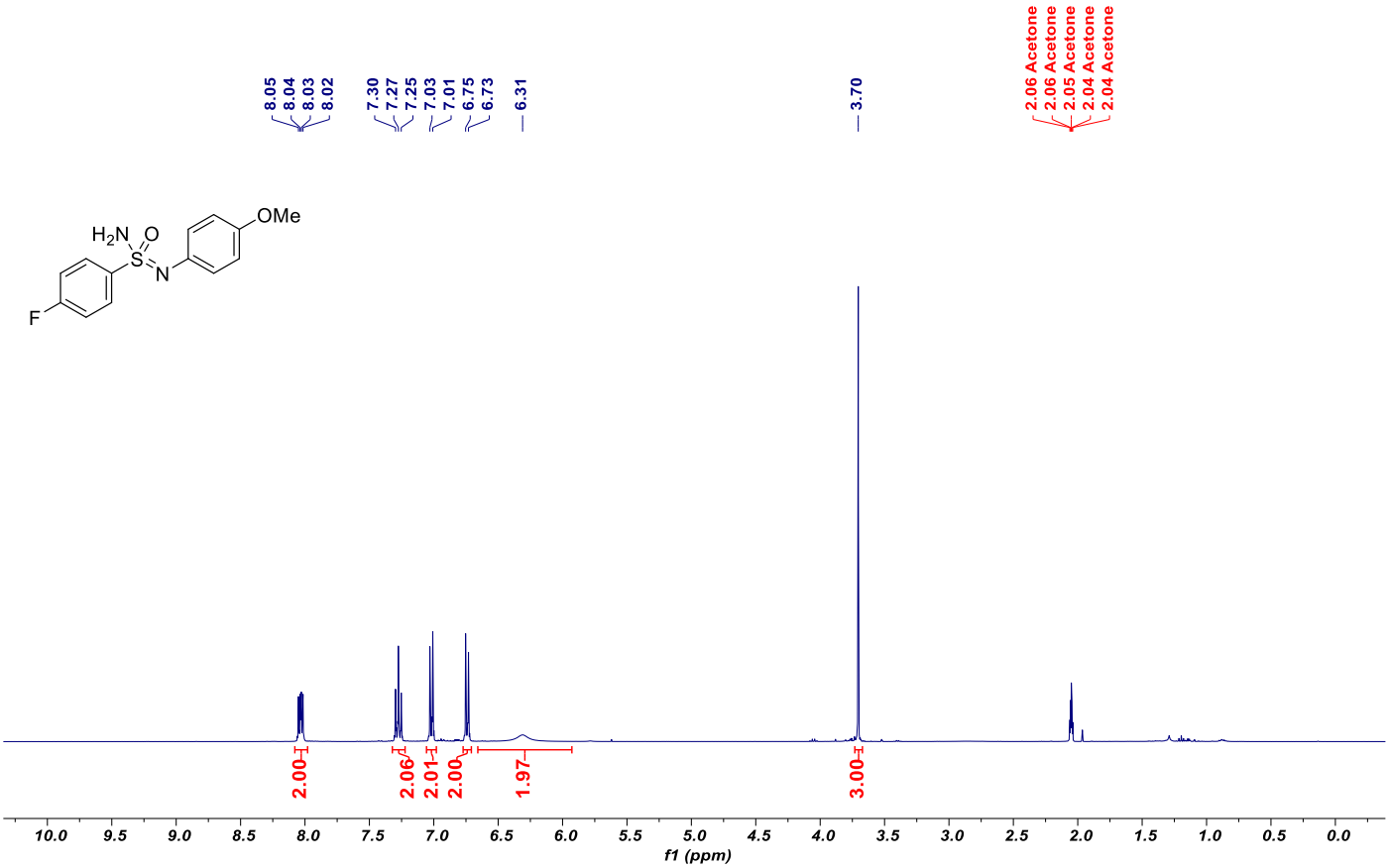
NMR spectrum of sulfonimidamide **28i**

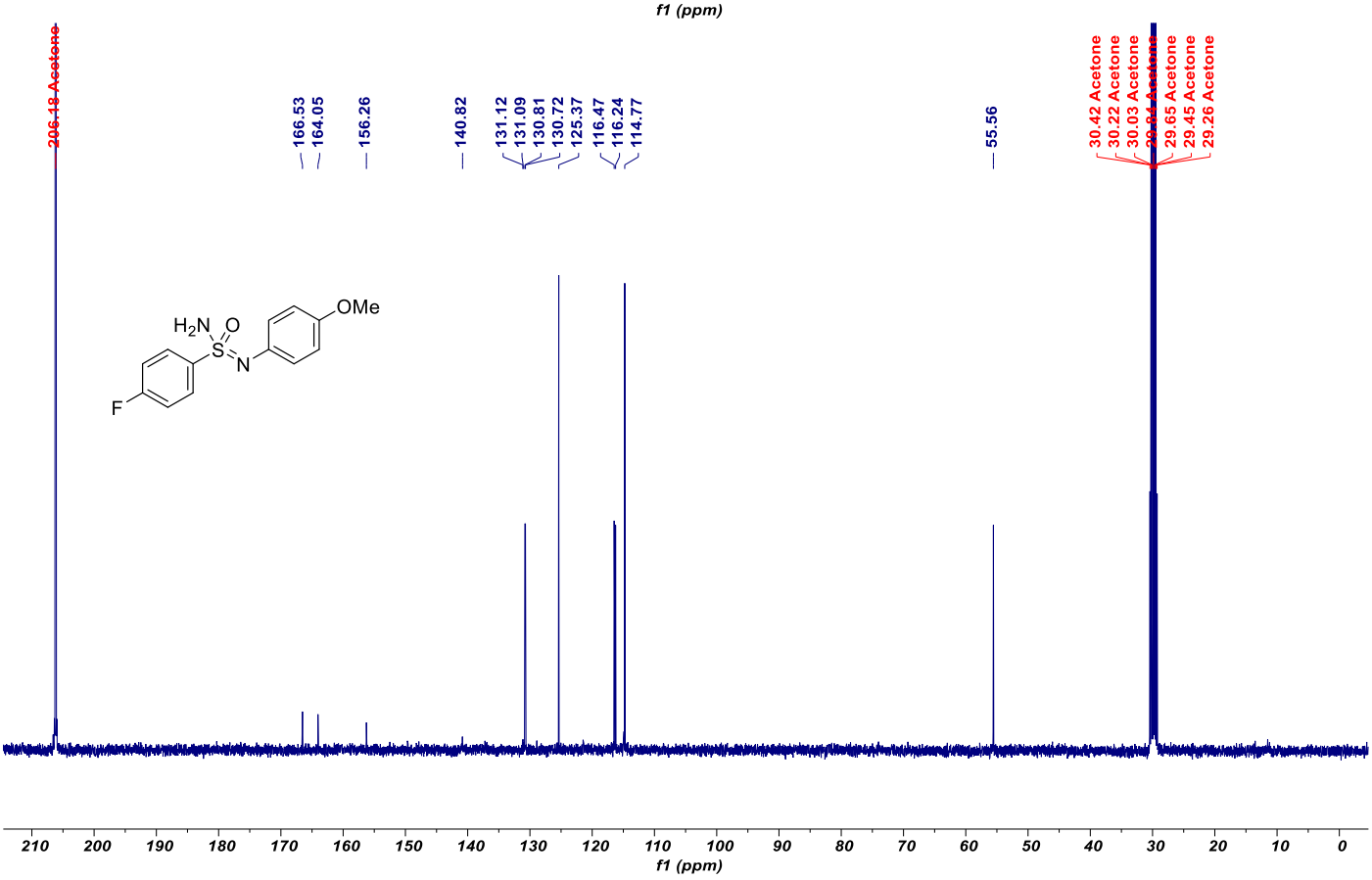


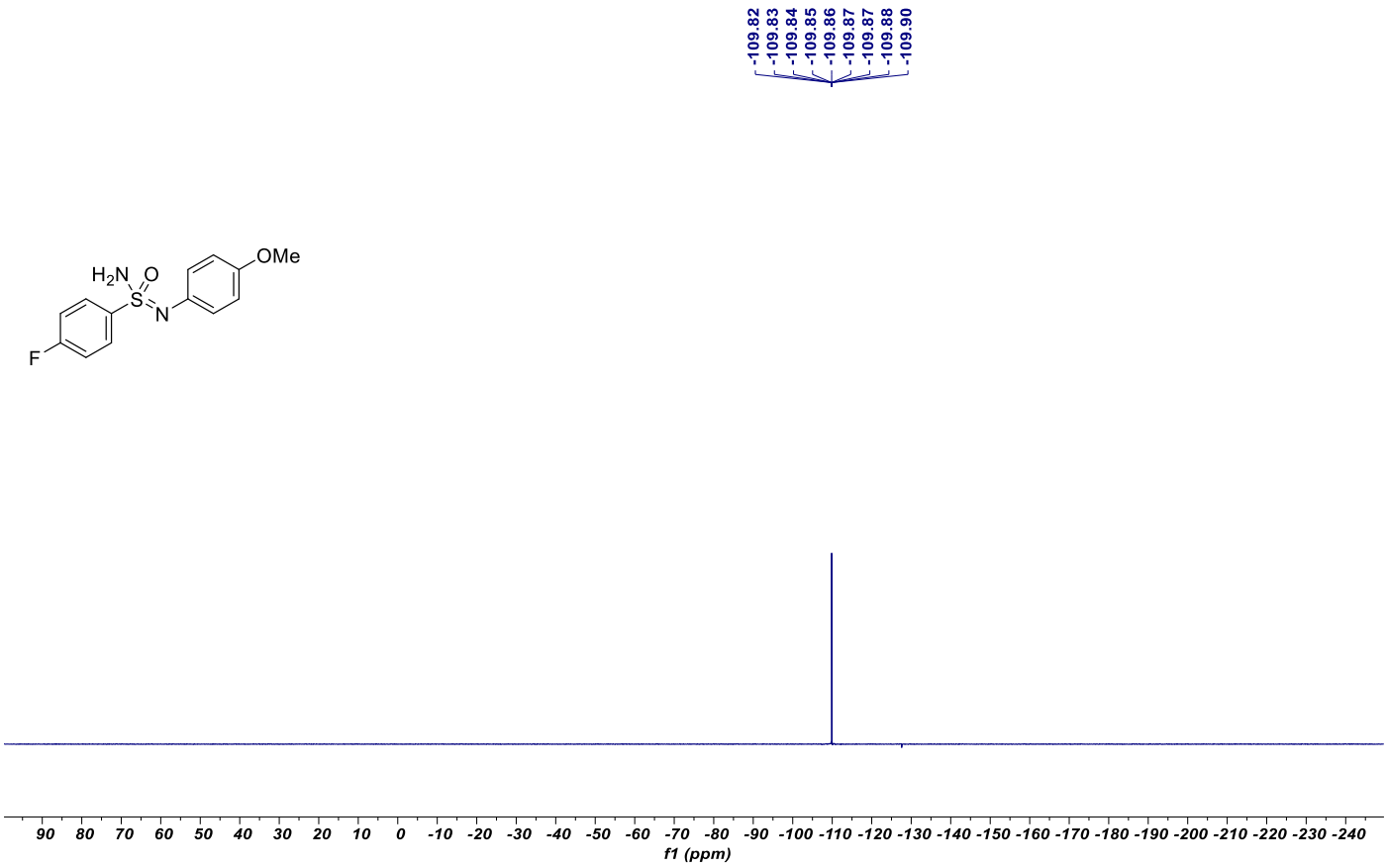

166.26
163.74
138.32
138.29
130.07
129.97
116.23
116.01
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
48.55
31.85
31.78
15.12
H2N
O
S
N
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-106.42
-106.43
-106.44
-106.44
-106.45
-106.46
-106.47
-106.47
-106.49
H2N
O
S
N
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

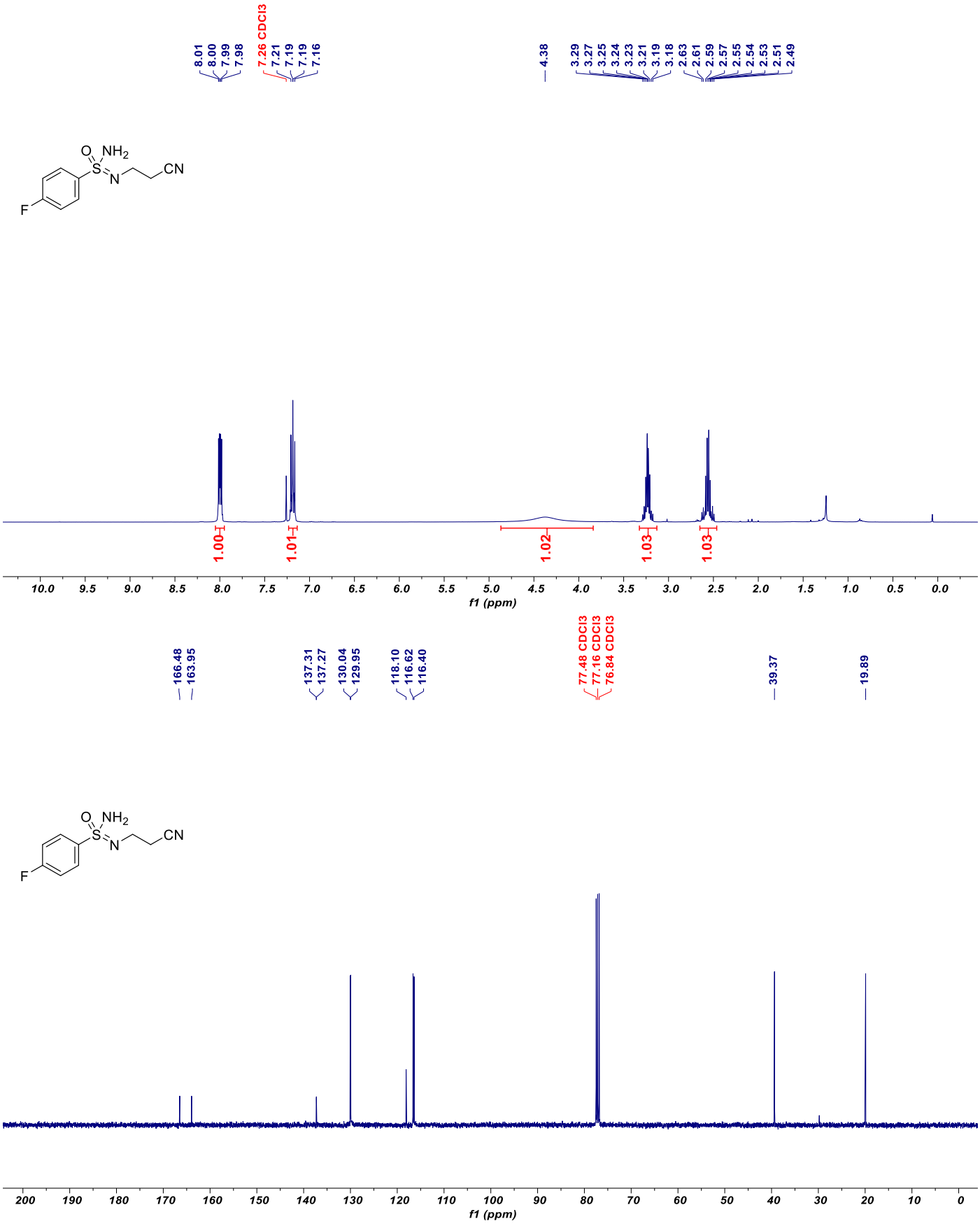
NMR spectrum of sulfonimidamide **28j**

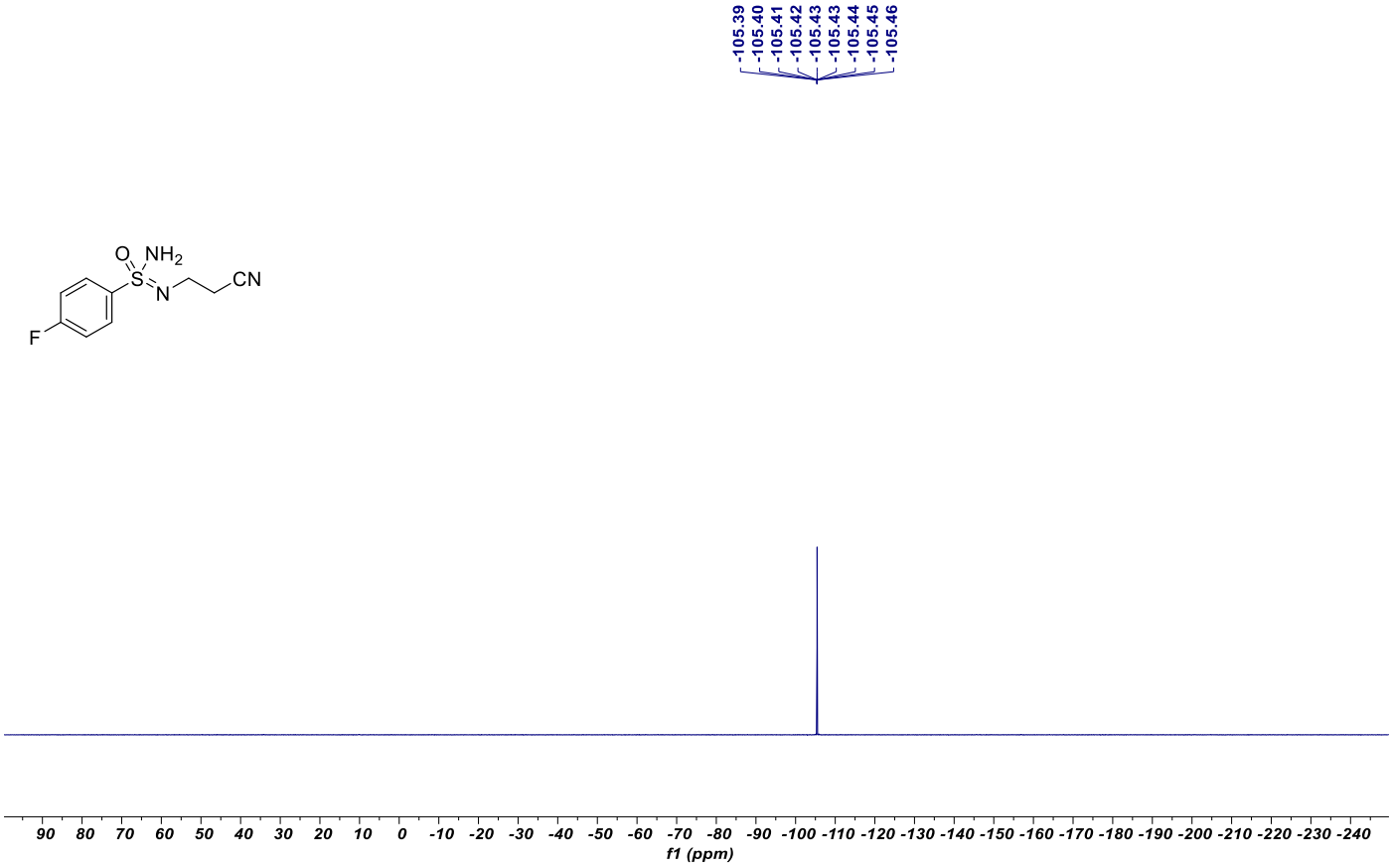




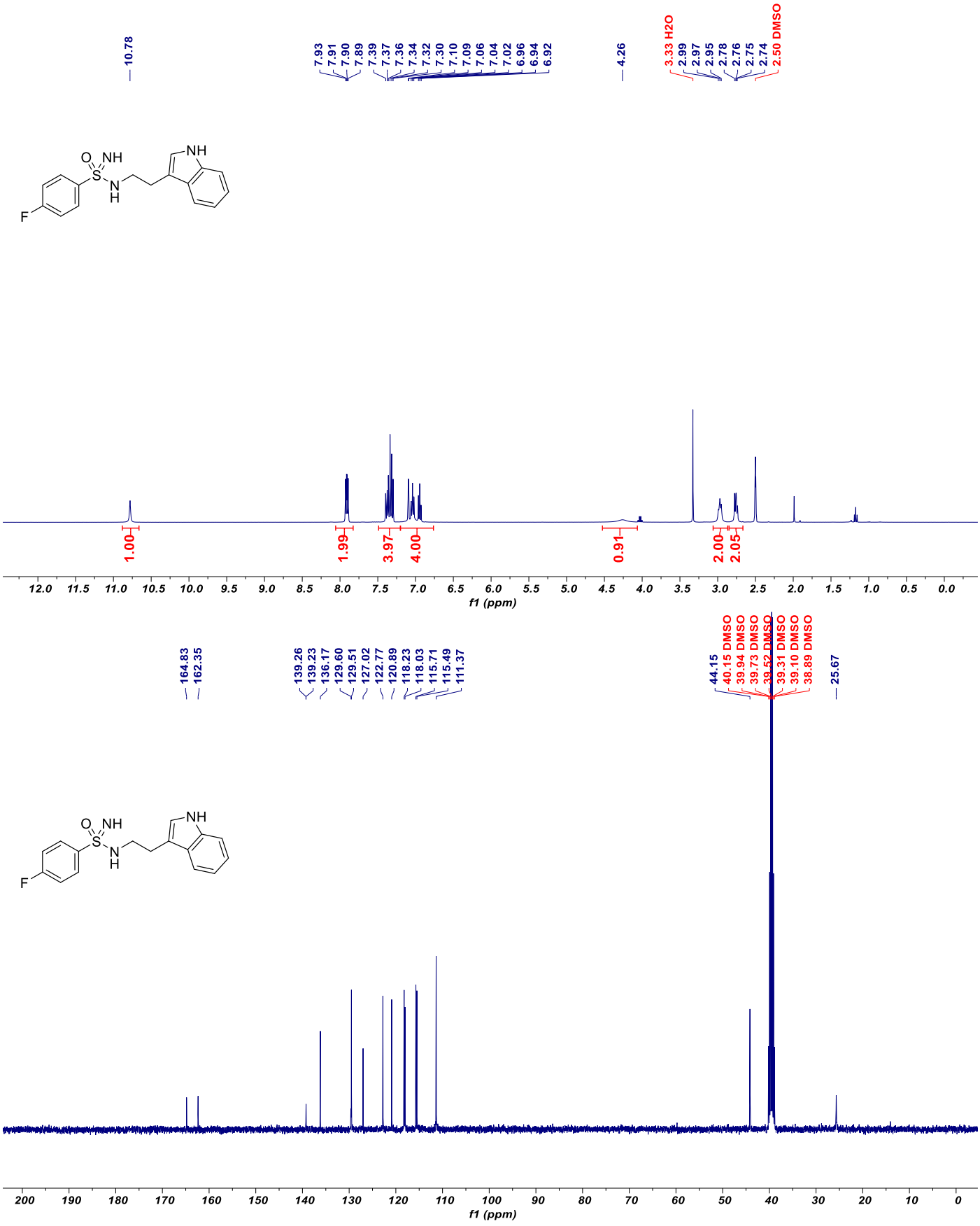

-109.82
-109.83
-109.84
-109.85
-109.86
-109.87
-109.87
-109.88
-109.90
H2N
O
S
N
OMe
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

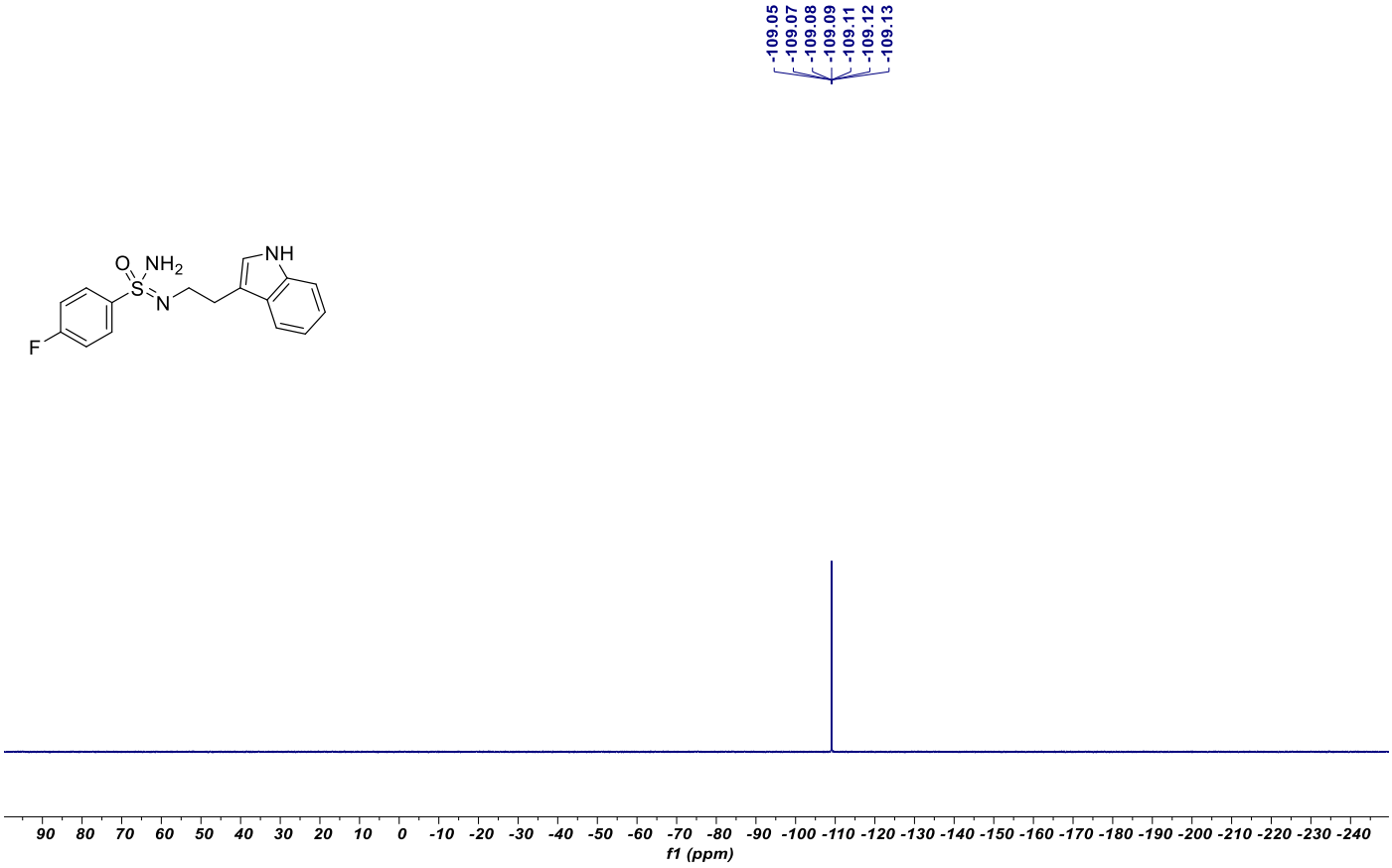
NMR spectrum of sulfonimidamide **28k**



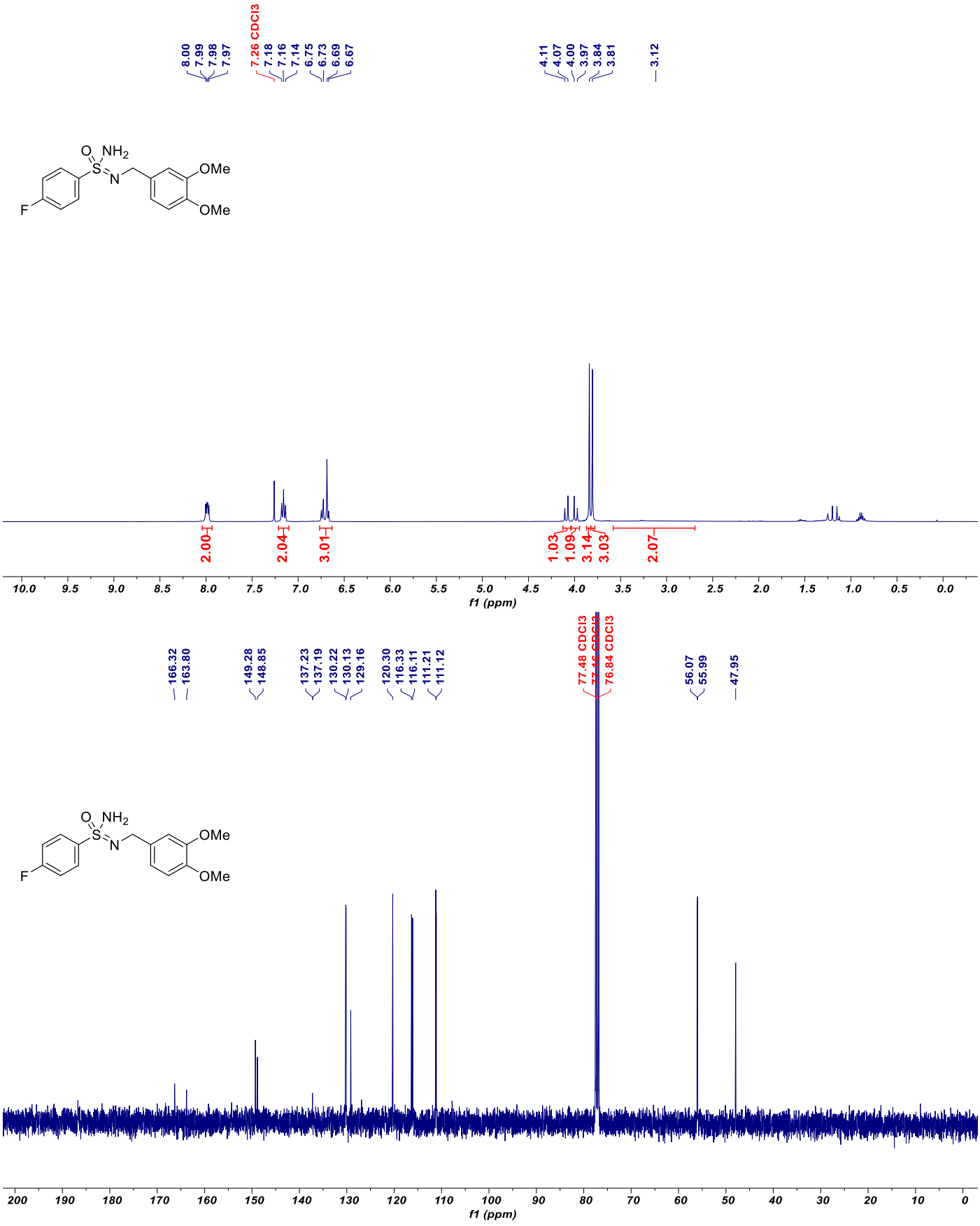

-105.39
-105.40
-105.41
-105.42
-105.43
-105.43
-105.44
-105.45
-105.46
O
NH2
S
N
CN
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

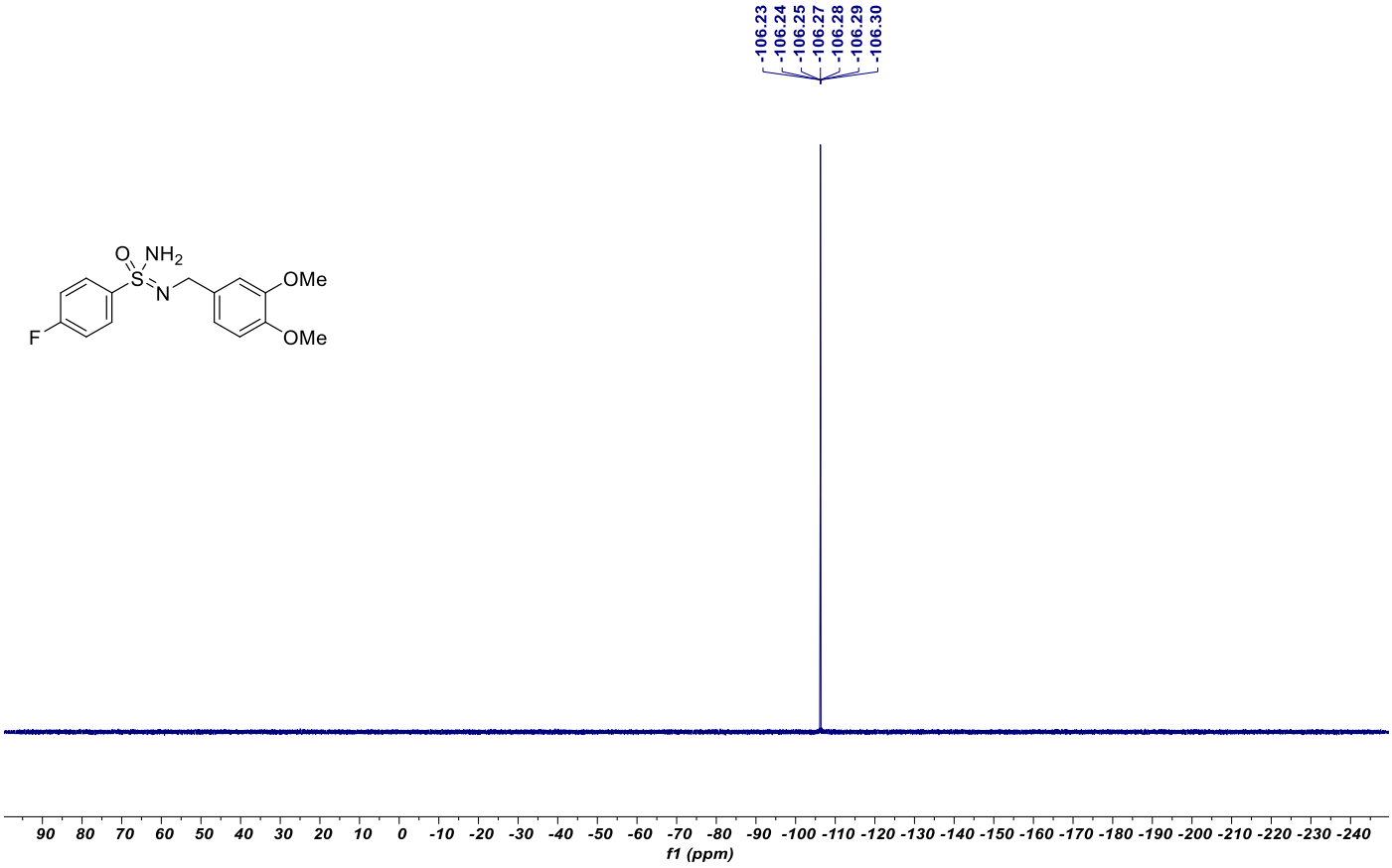
NMR spectrum of sulfonimidamide **28l**



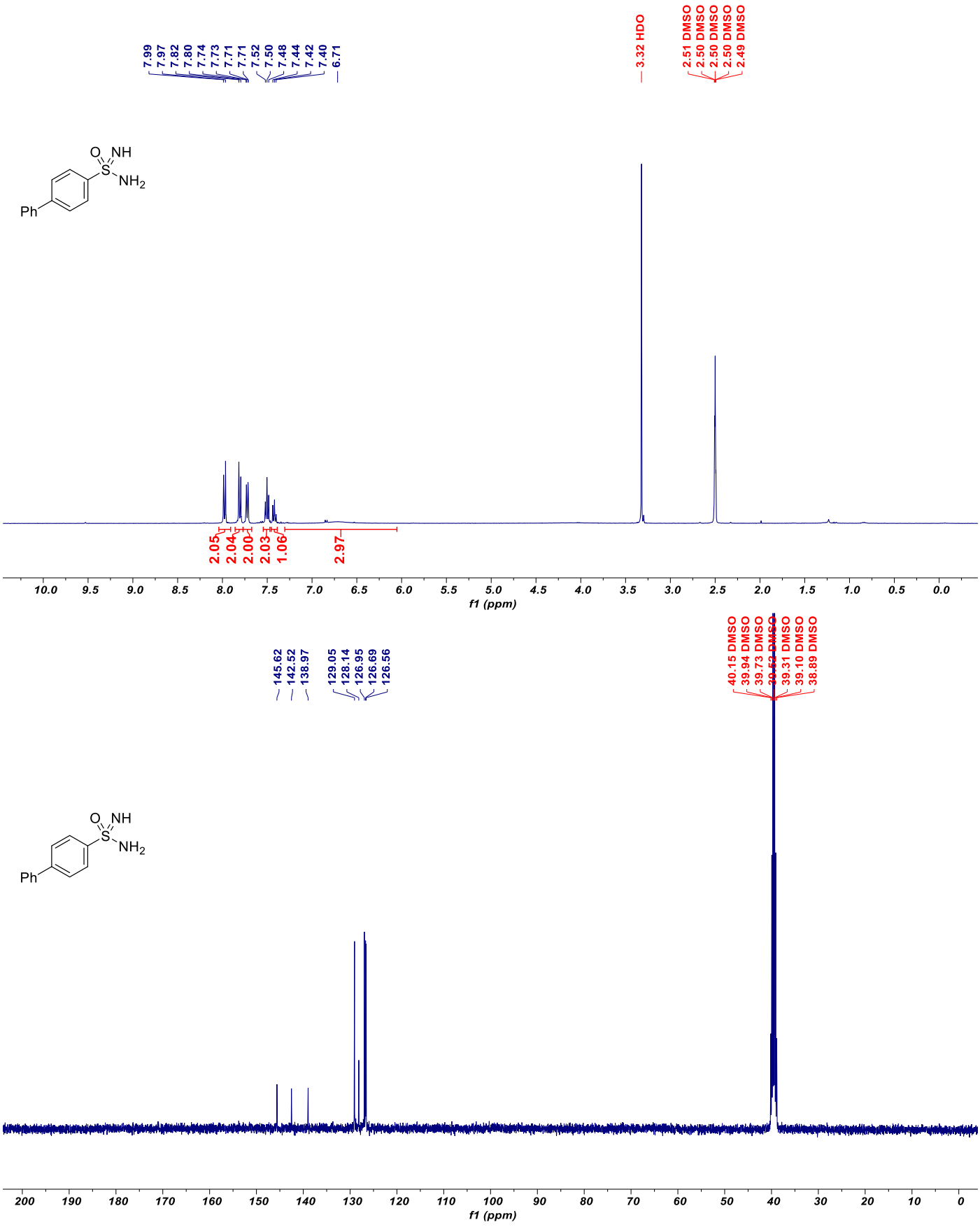

-109.05
-109.07
-109.08
-109.09
-109.11
-109.12
-109.13
O
NH2
S
N
NH
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

NMR spectrum of sulfonimidamide **28m**

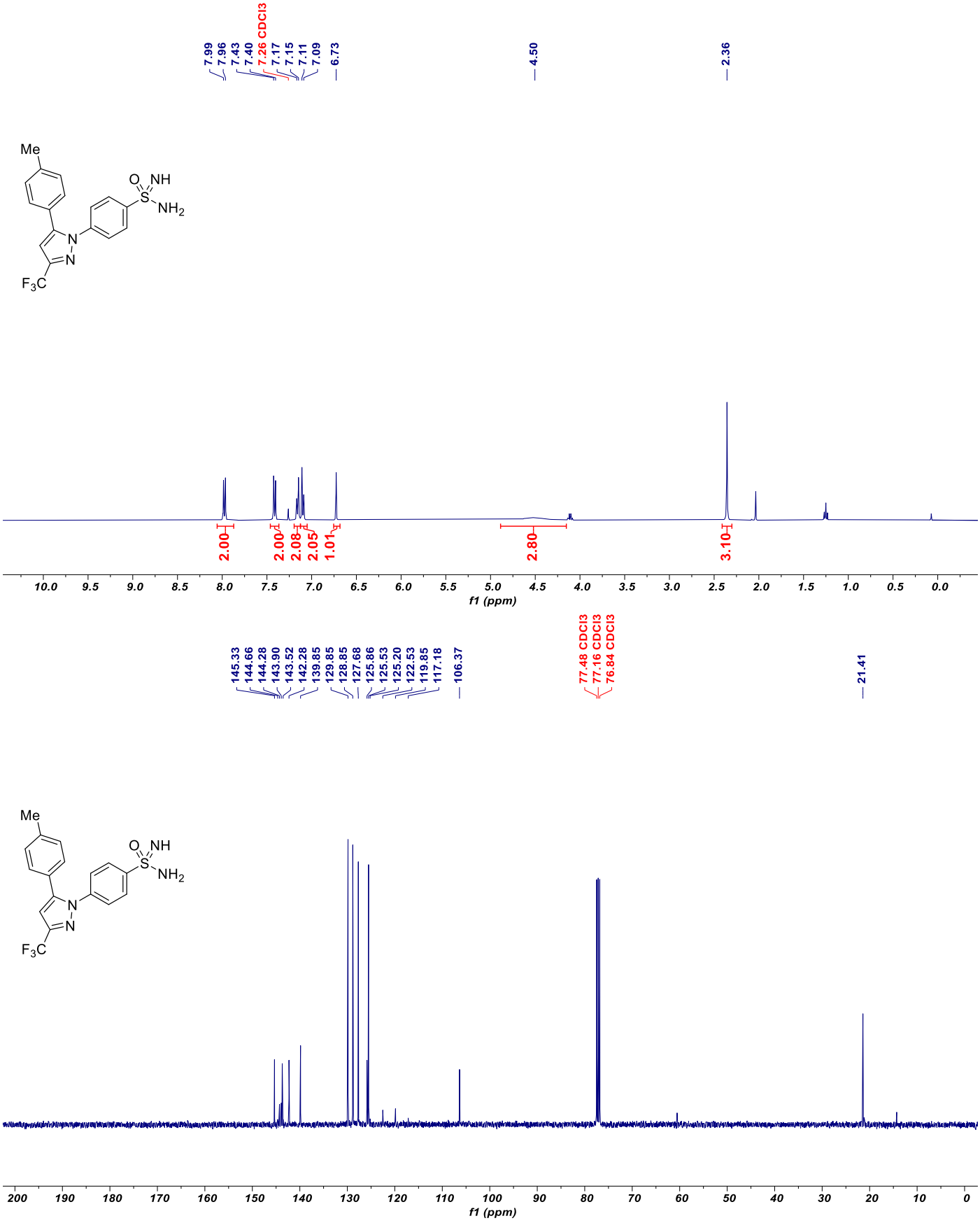


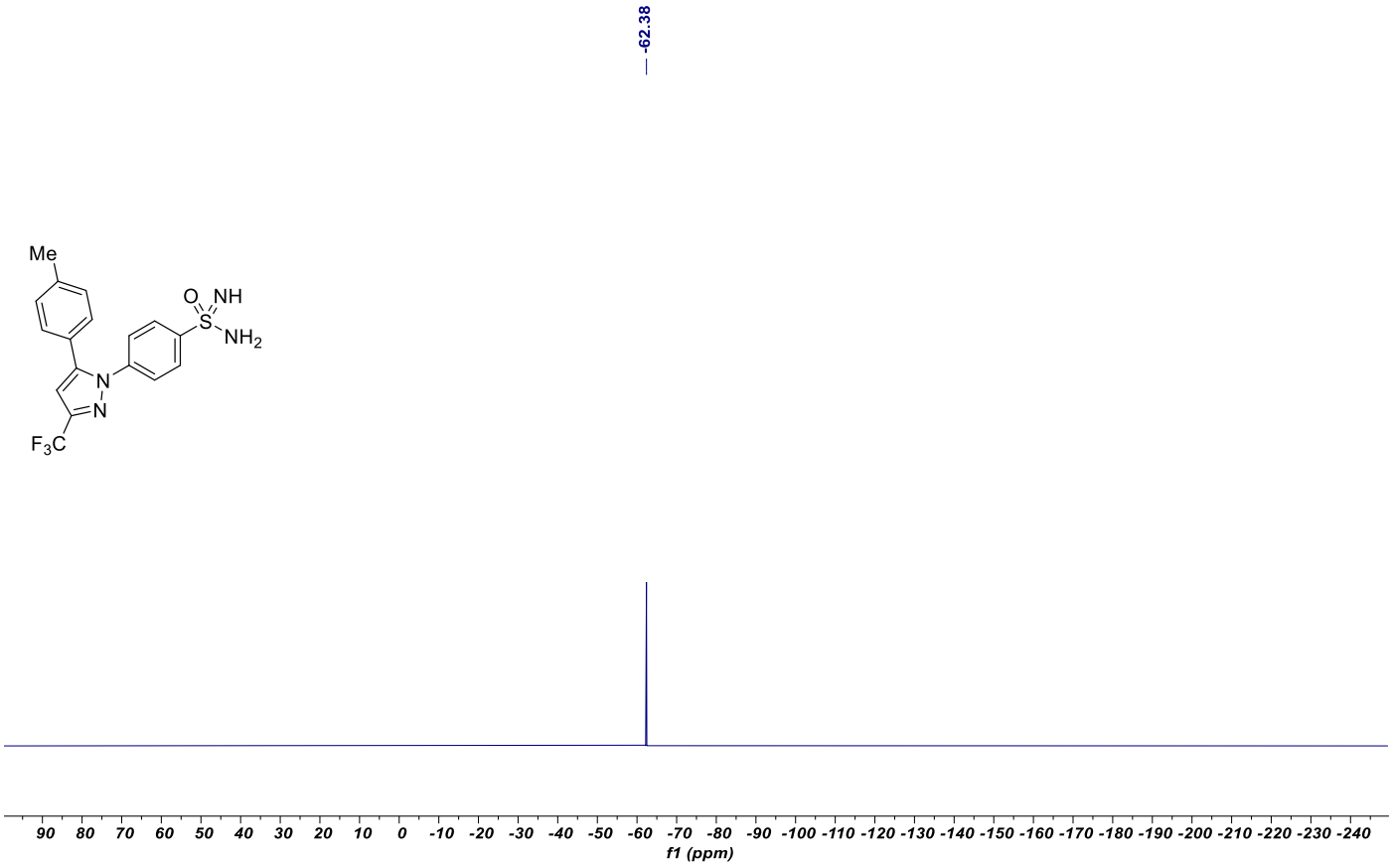

-106.23
-106.24
-106.25
-106.27
-106.28
-106.29
-106.30
O
NH2
S
N
OMe
OMe
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

NMR spectrum of sulfonimidamide **28n**

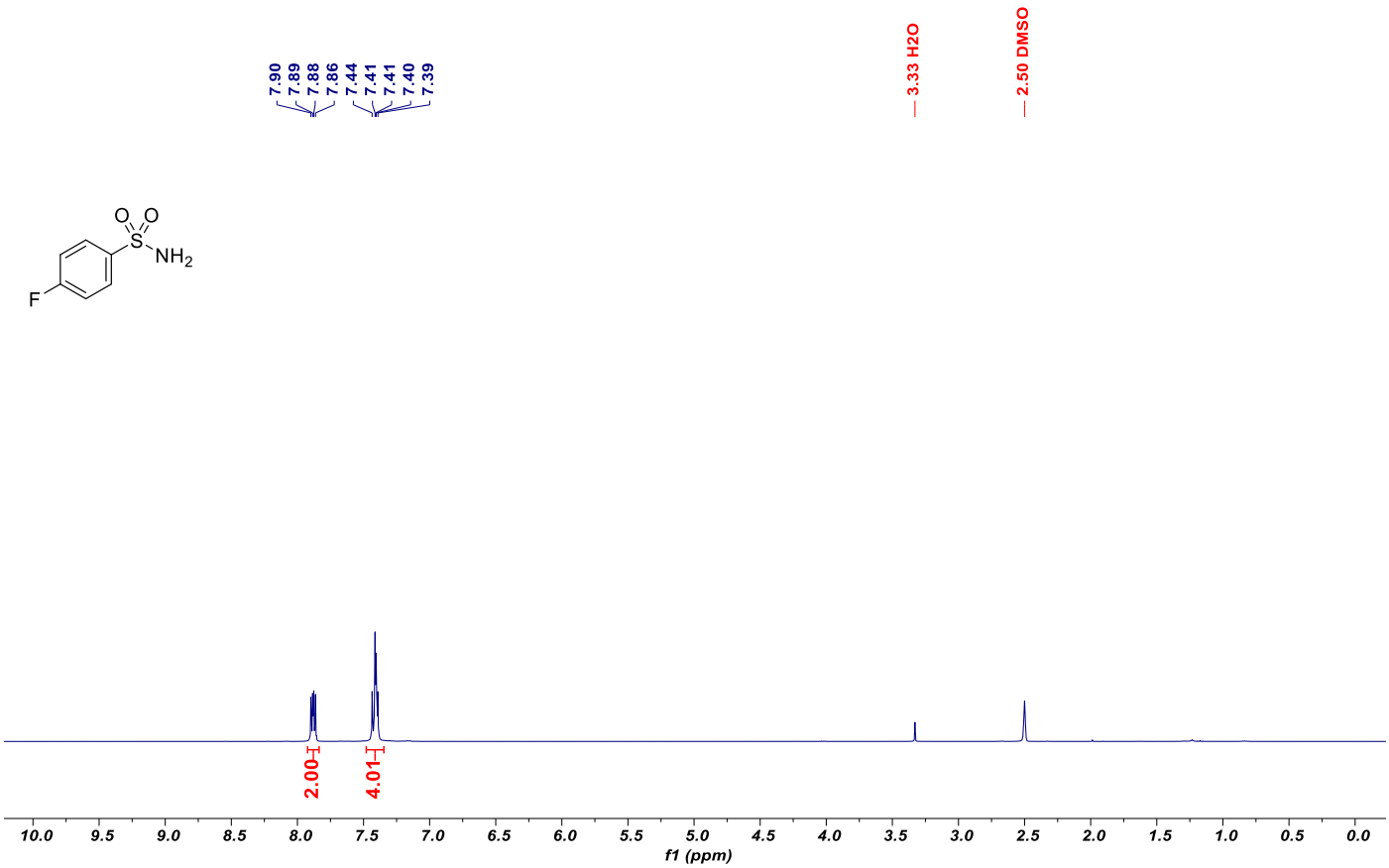


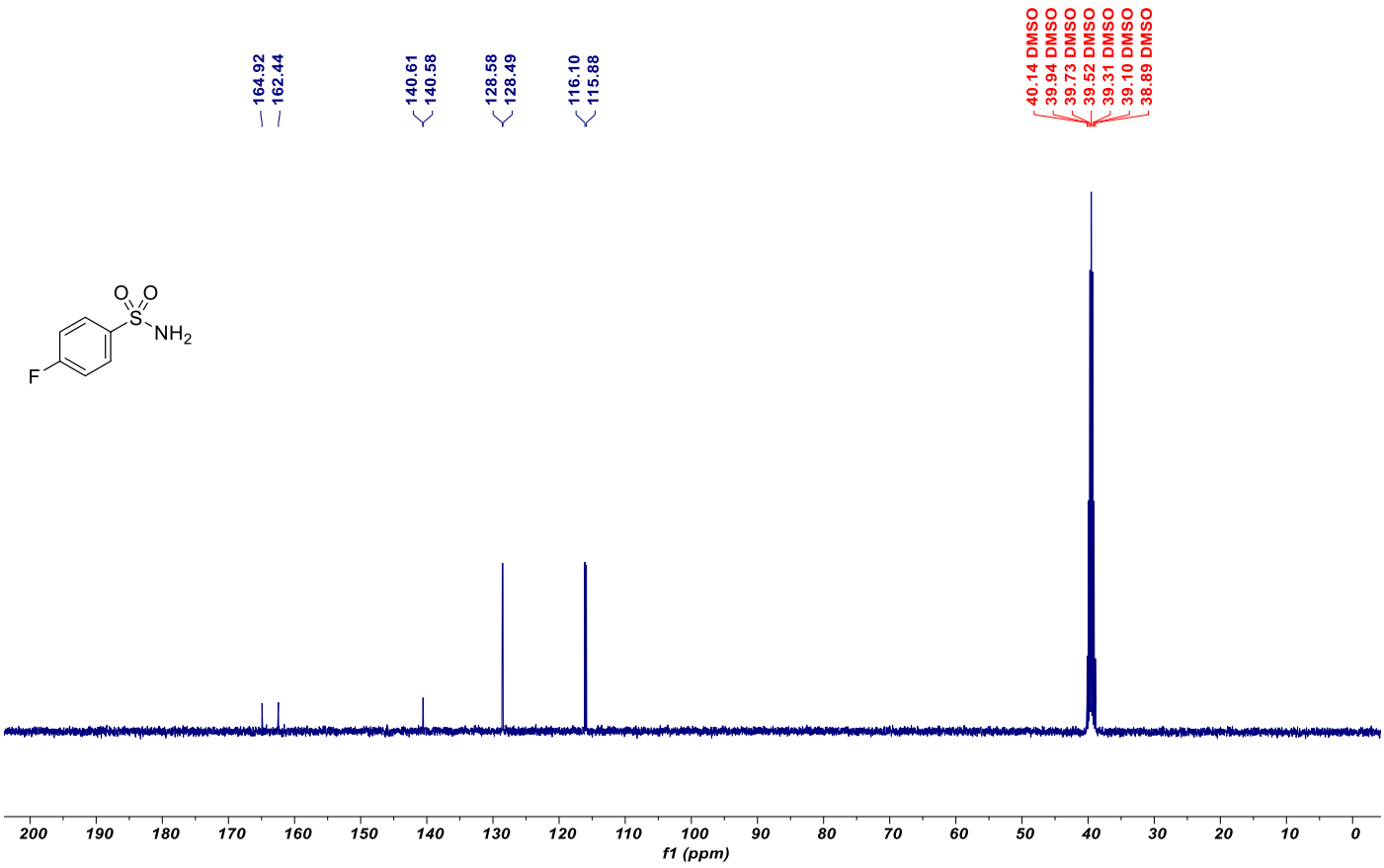
NMR spectrum of sulfonimidamide **28o**

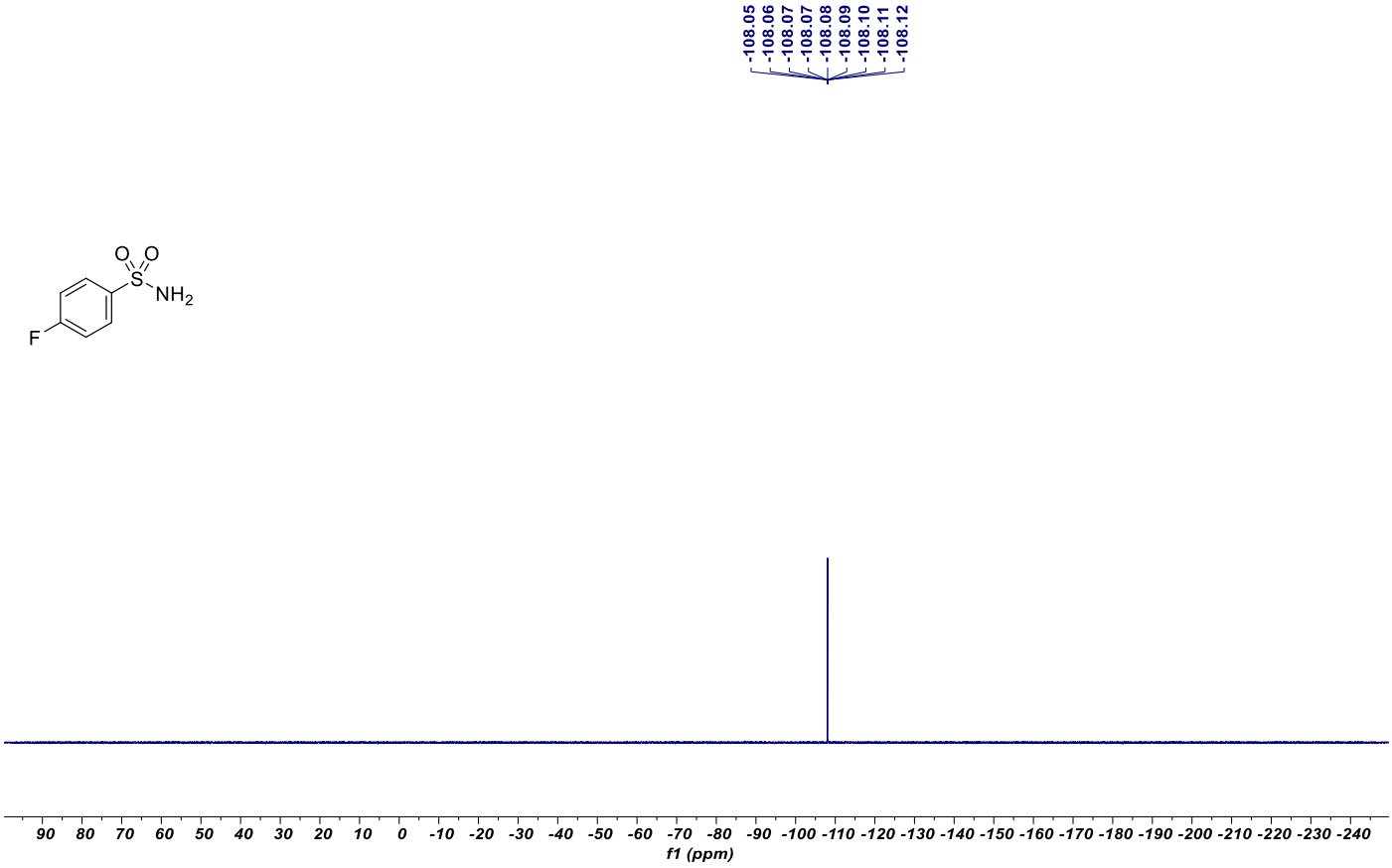



-62.38
Me
O
NH
S
NH2
N
N
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

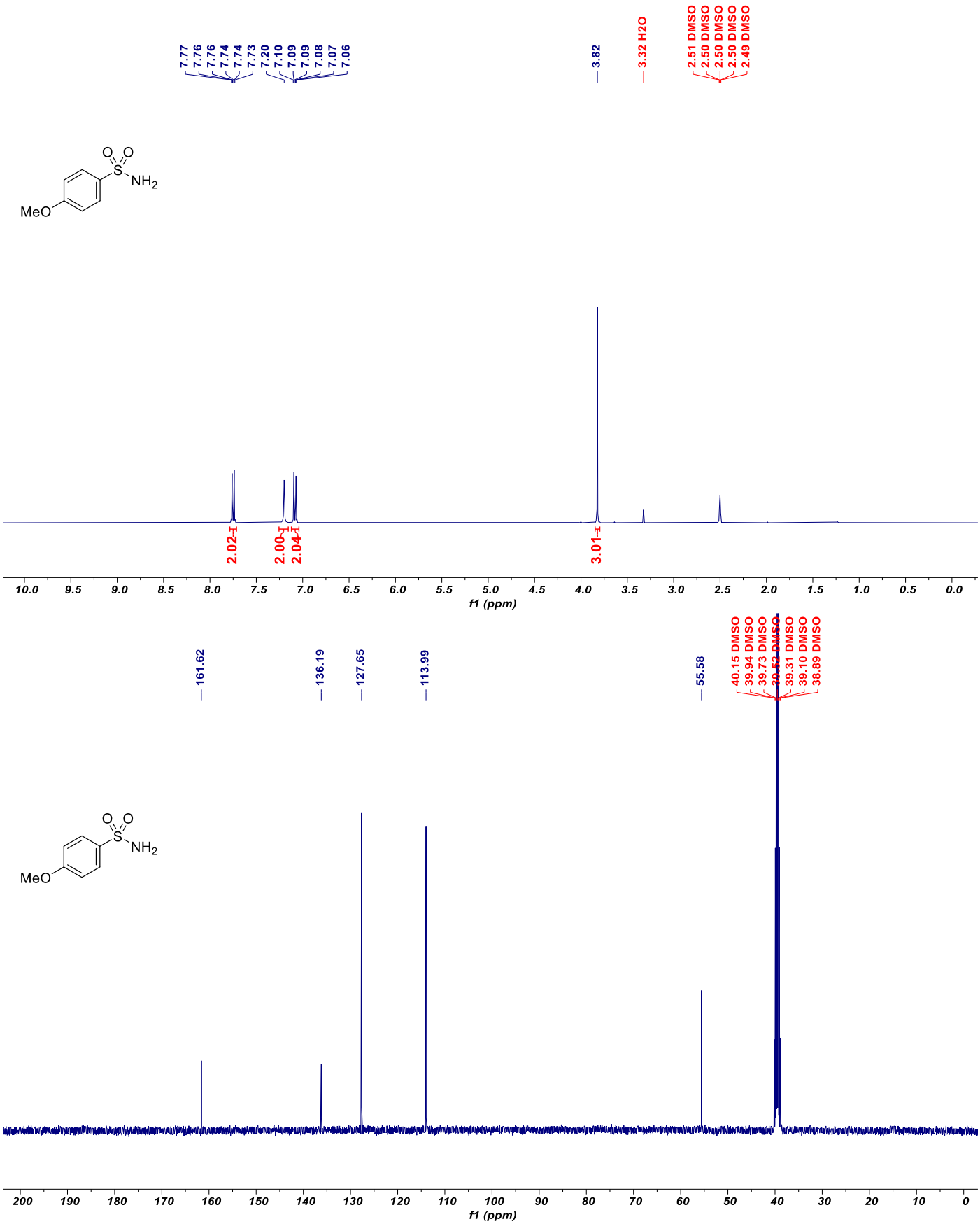
NMR spectrum of sulfonimidamide **34a**



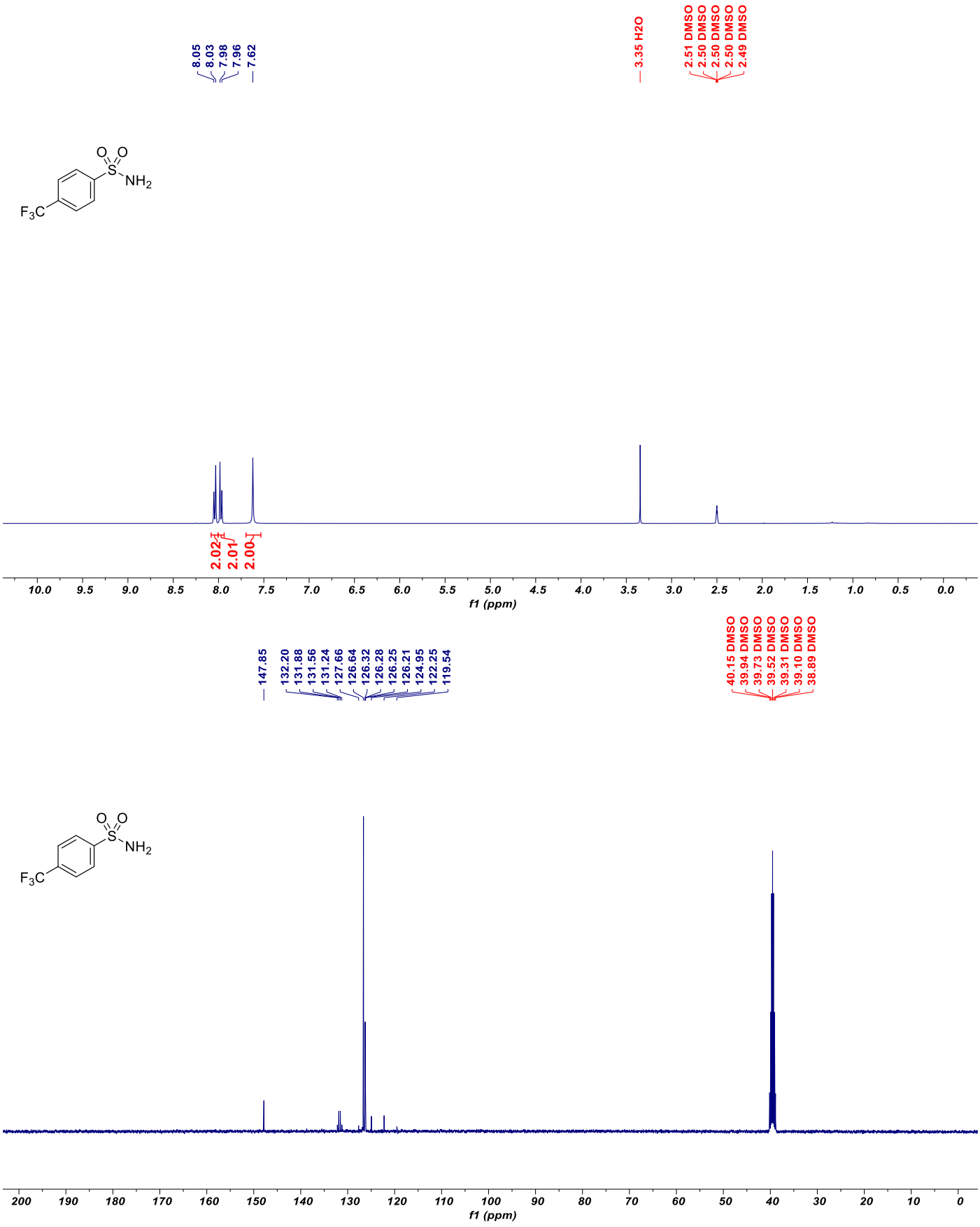


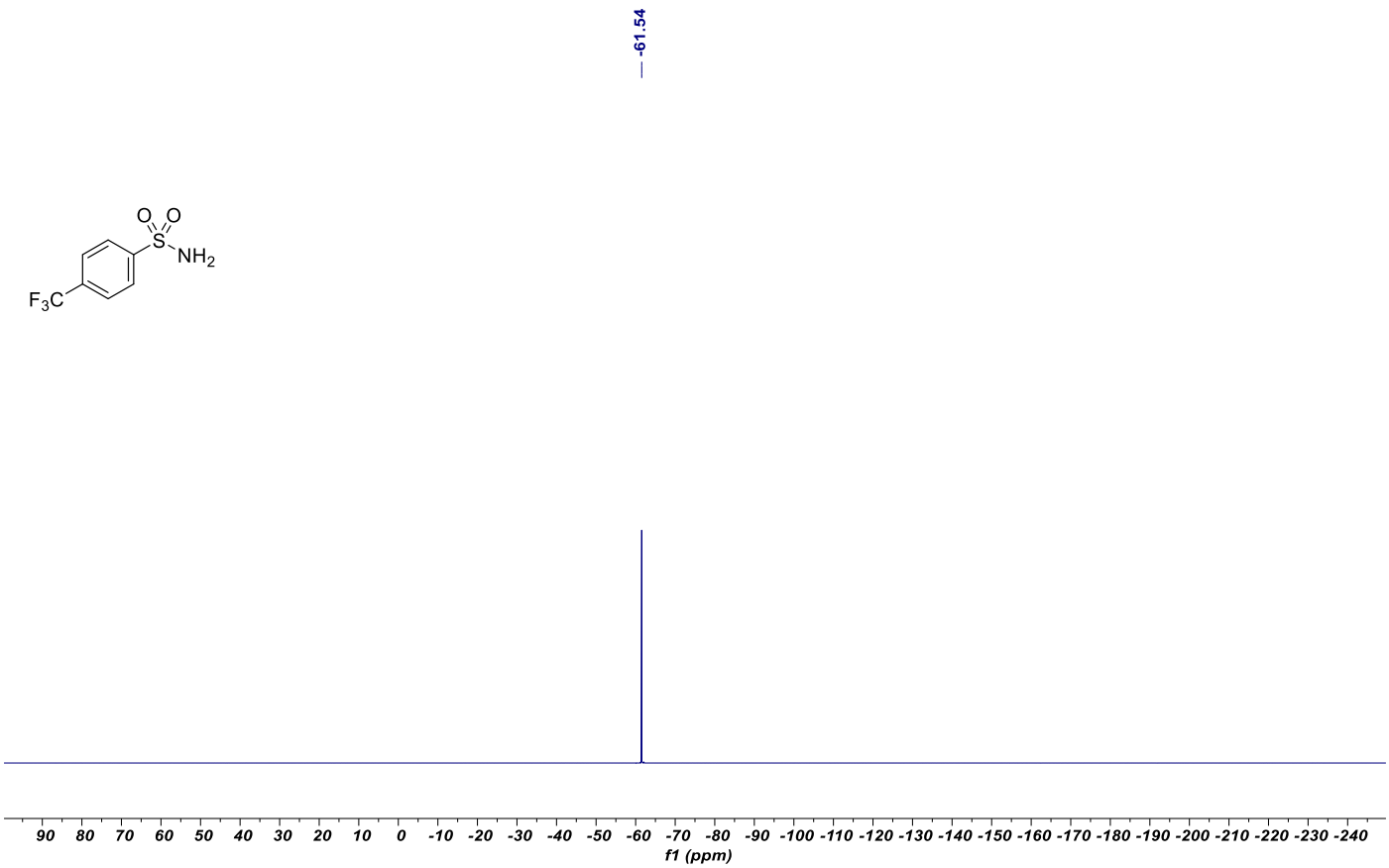

-108.05
-108.06
-108.07
-108.07
-108.08
-108.09
-108.10
-108.11
-108.12
O
O
S
NH2
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

NMR spectrum of sulfonamide **34b**

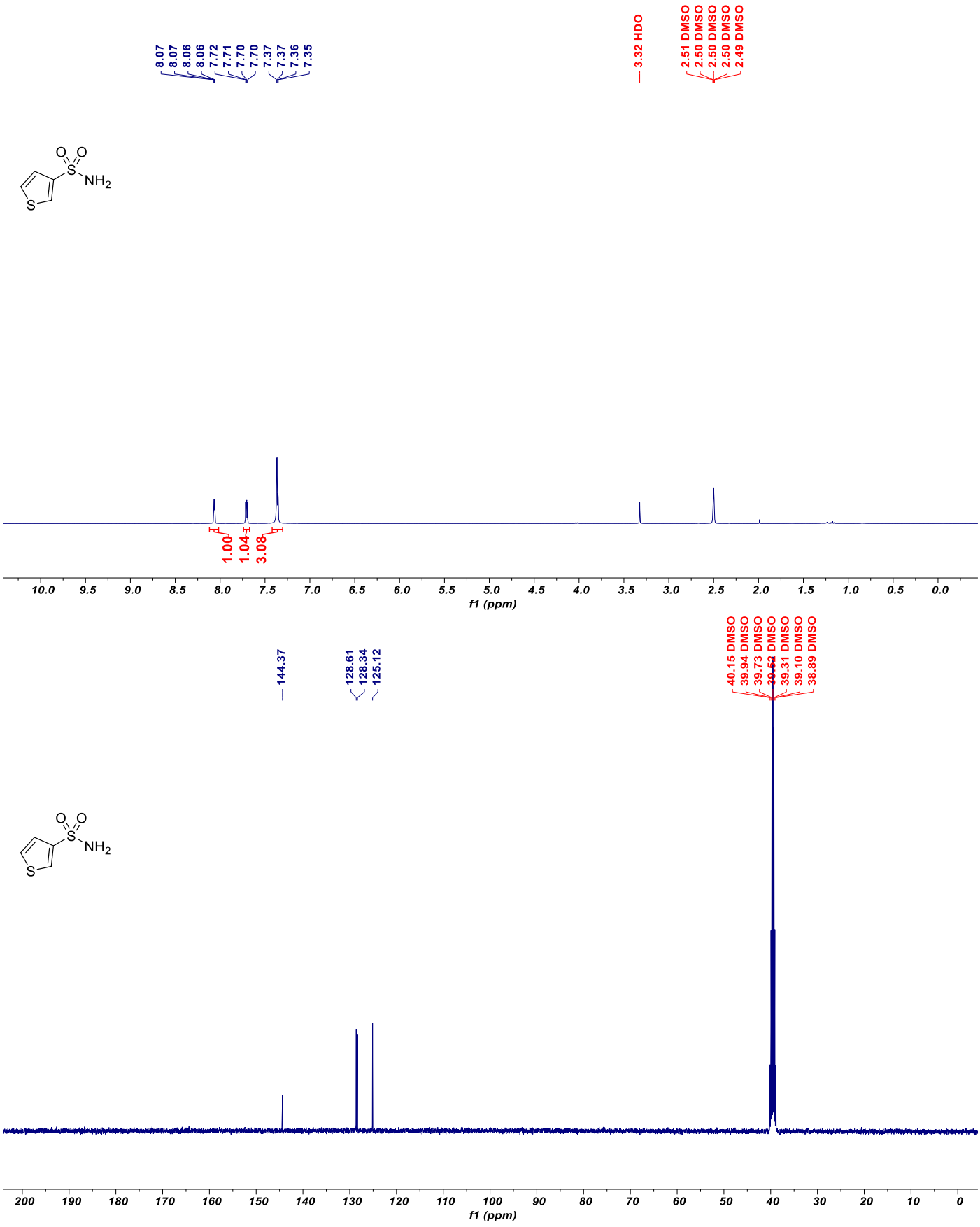


NMR spectrum of sulfonamide **34c**

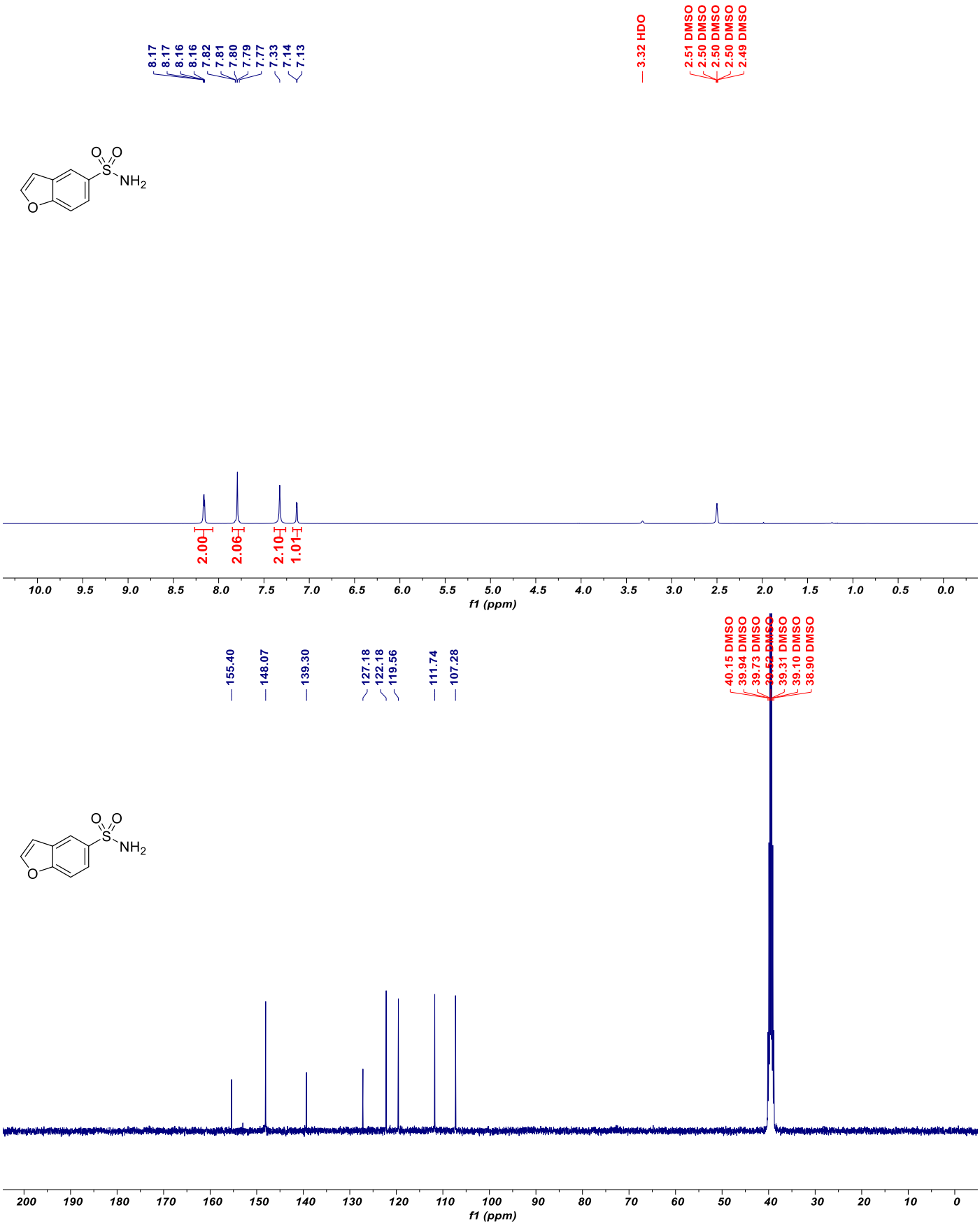



-61.54
O
O
S
NH2
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

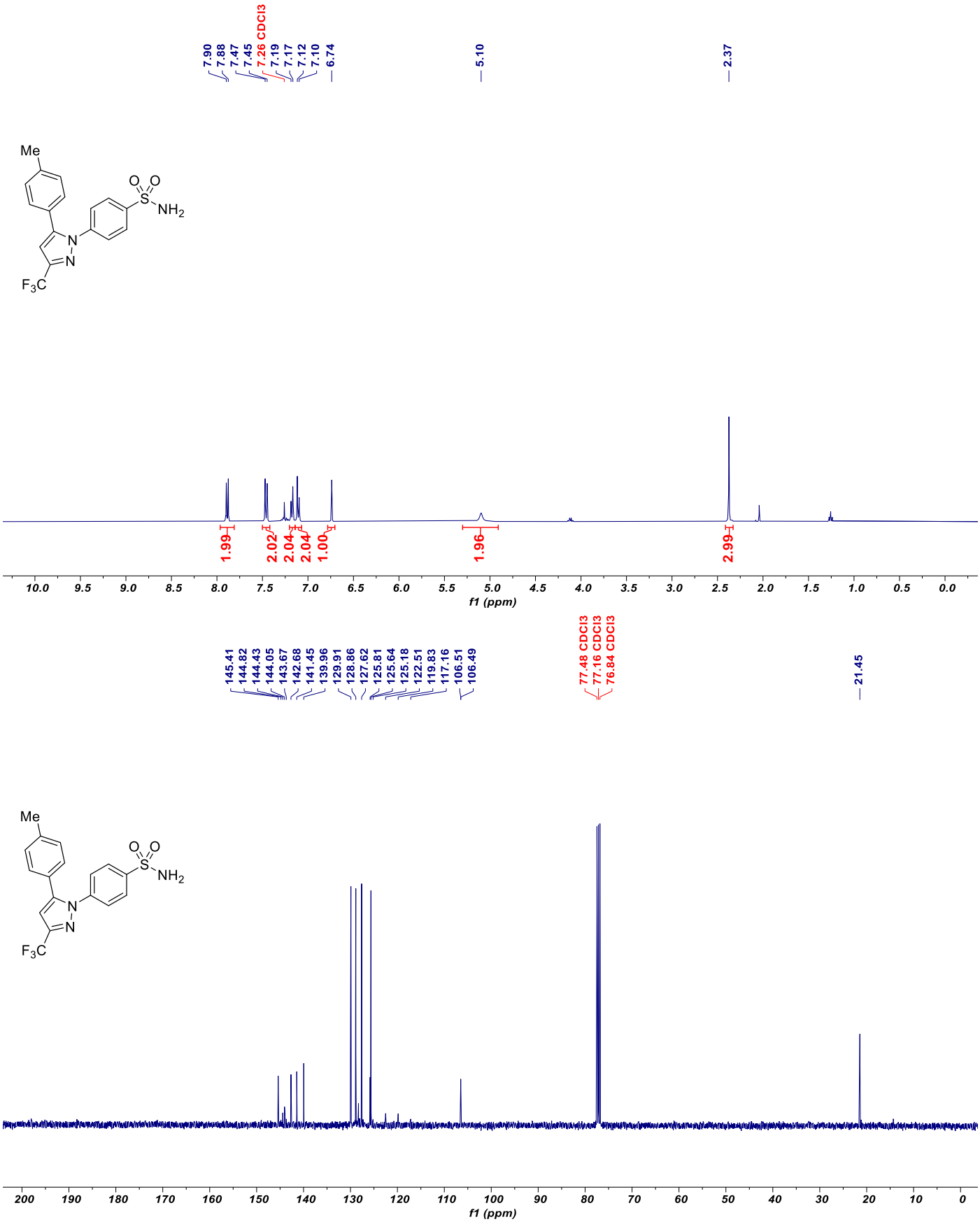
NMR spectrum of sulfonamide **34d**

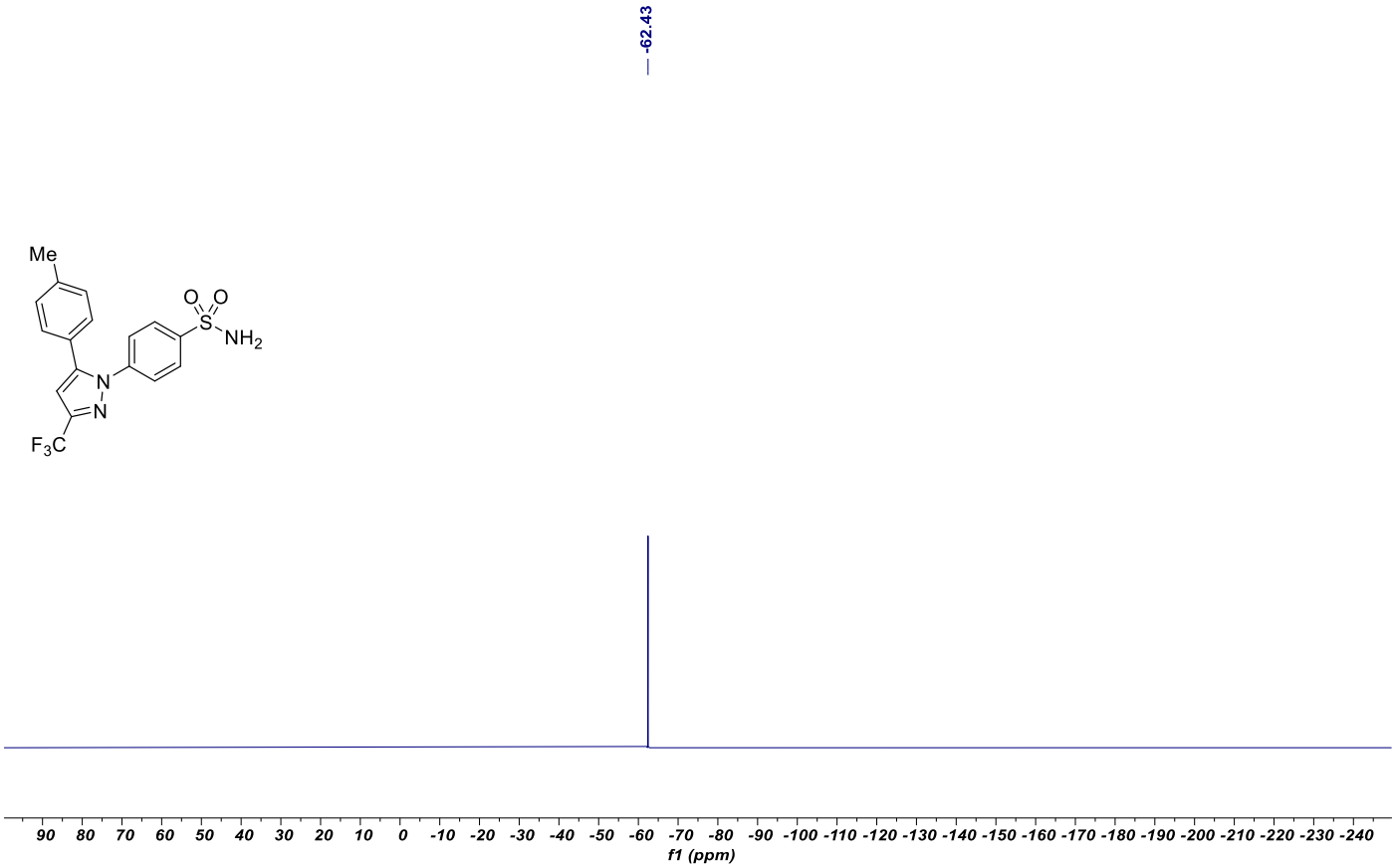


NMR spectrum of sulfonamide **34e**

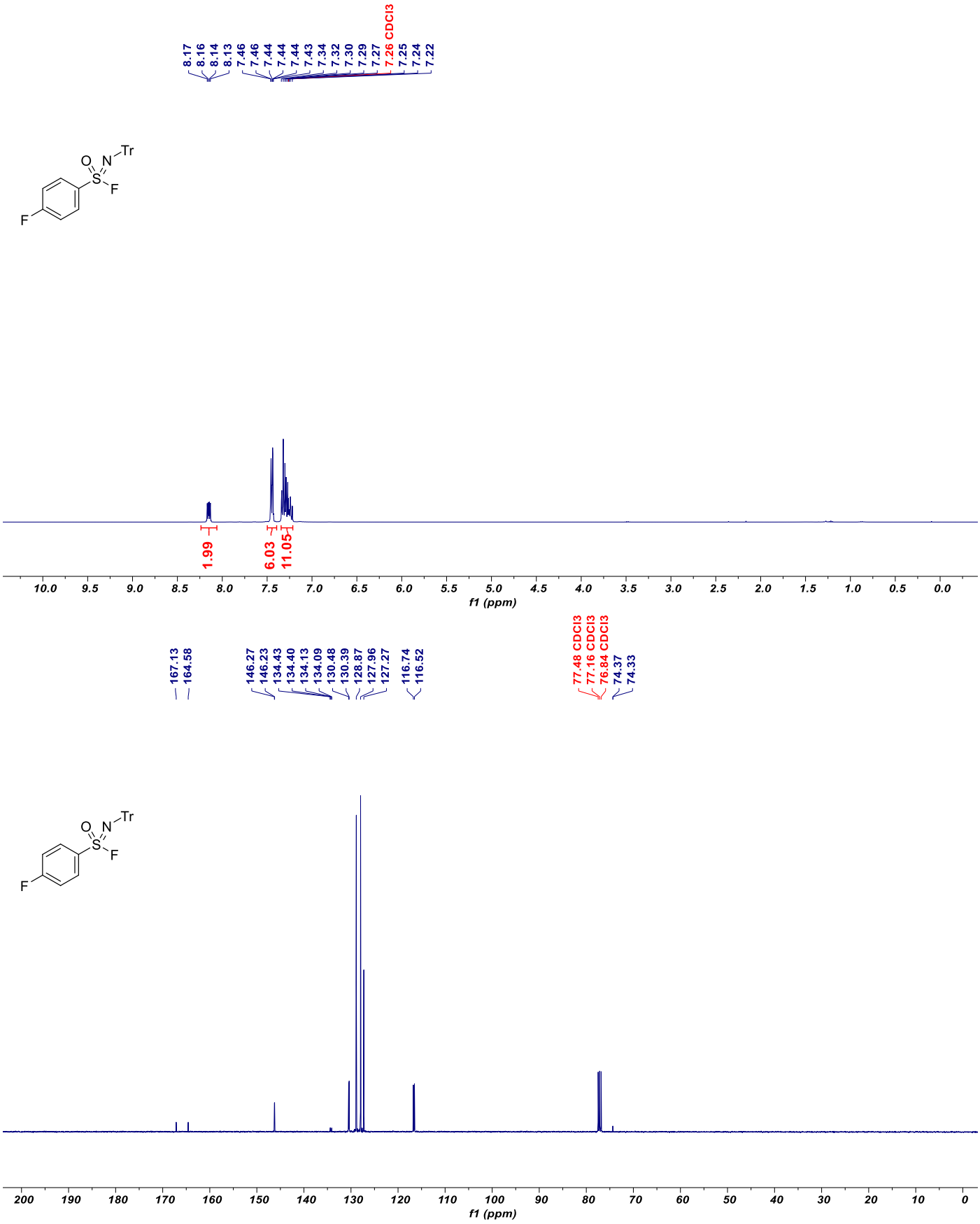


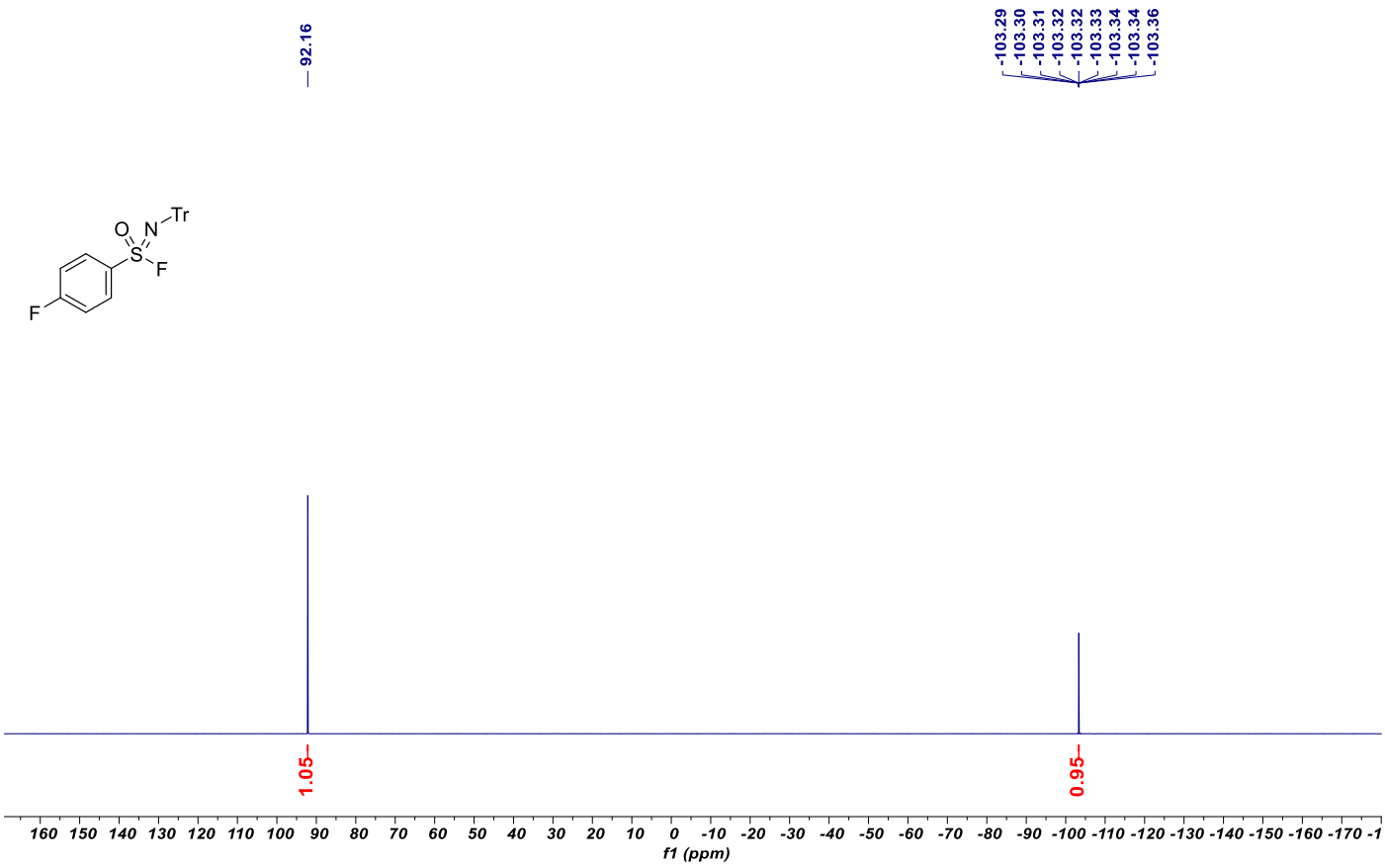
NMR spectrum of sulfonamide **34f**



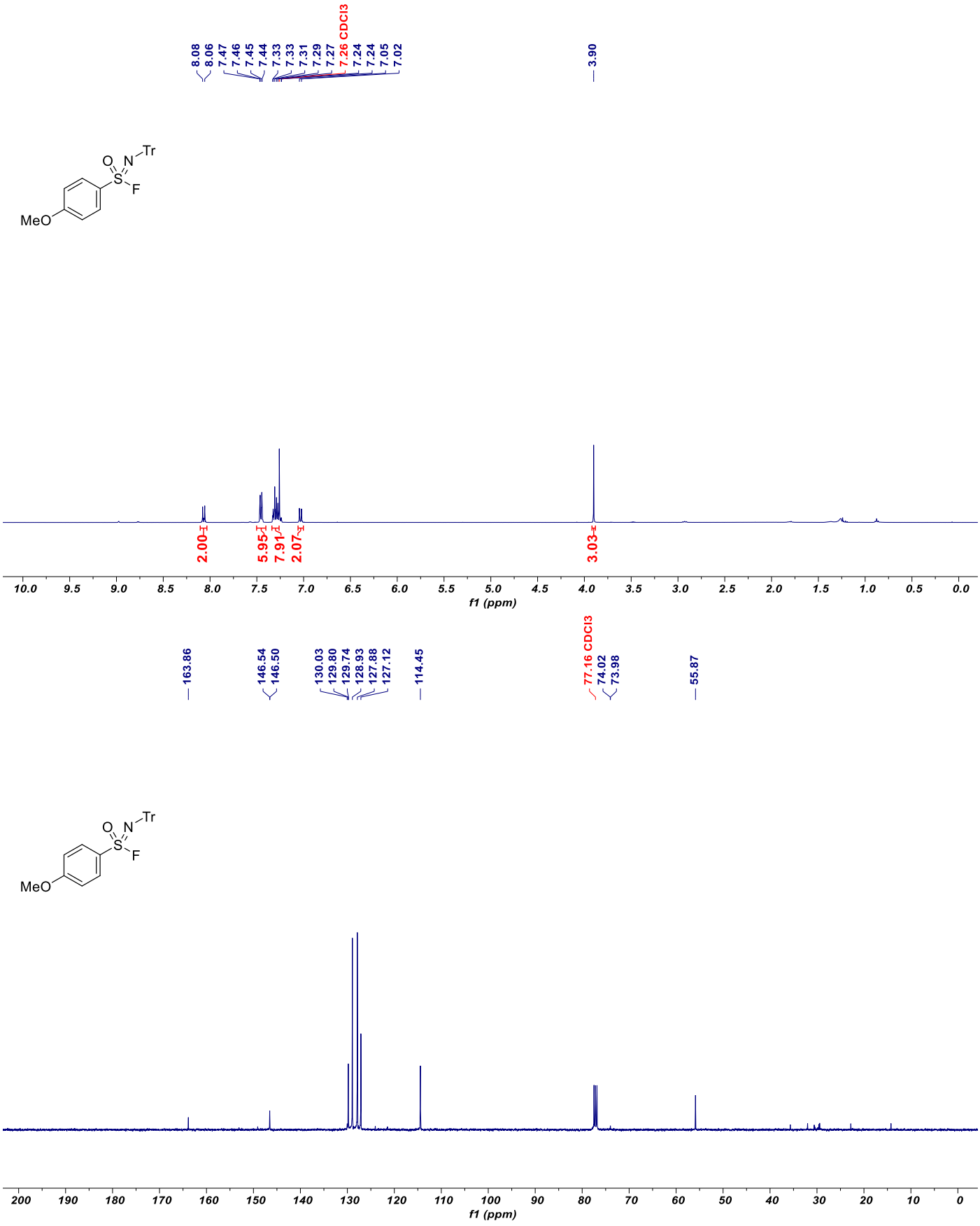

-62.43
Me
O
O
S
NH2
N
N
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

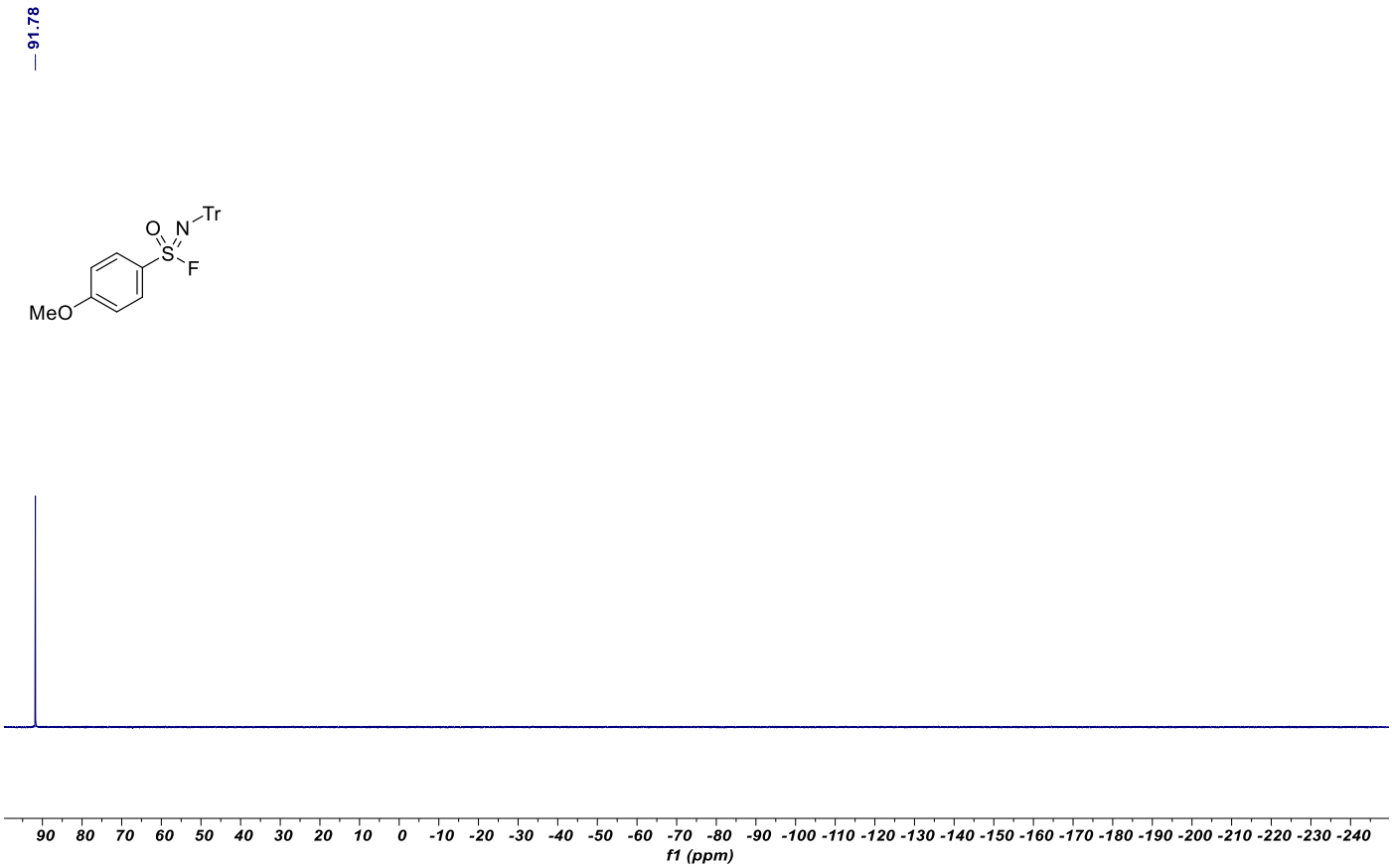
NMR spectrum of sulfonimidoyl fluoride **35**



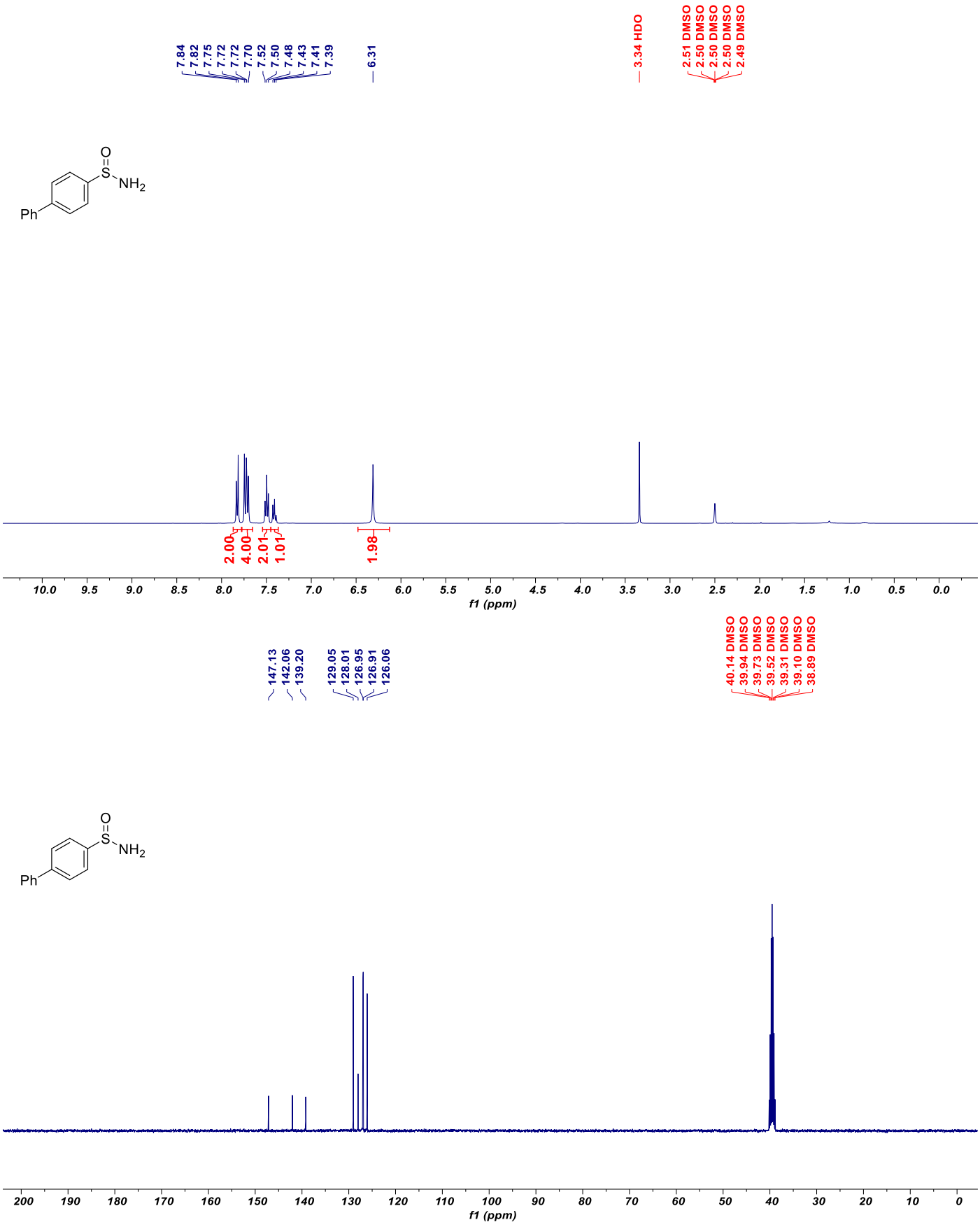

92.16
-103.29
-103.30
-103.31
-103.32
-103.32
-103.33
-103.34
-103.34
-103.36
O
N
Tr
S
F
F
1.05
0.95
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -1
f1 (ppm)

NMR spectrum of sulfonimidoyl fluoride **37**

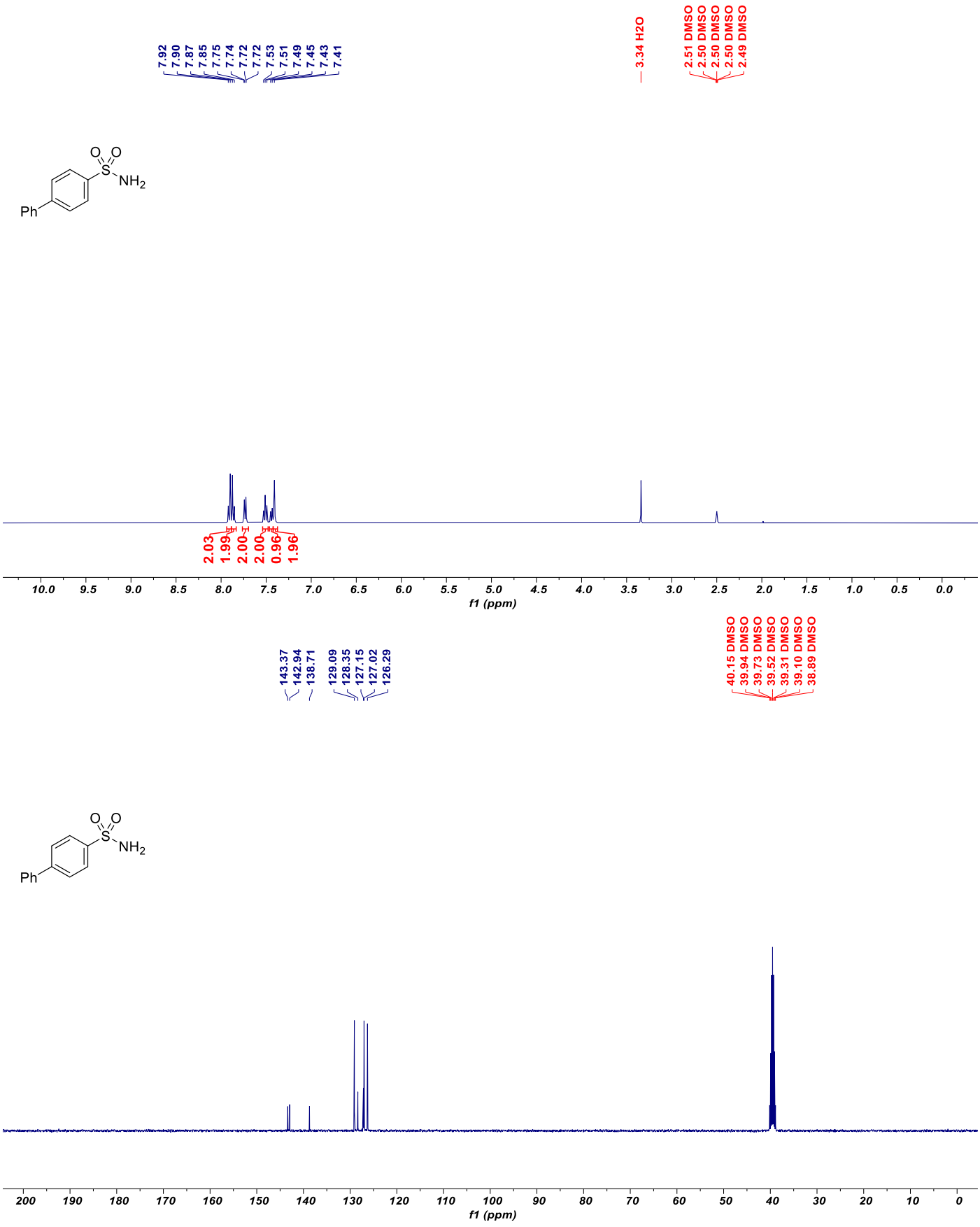



91.78
O
N
Tr
S
F
MeO
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

NMR spectrum of primary sulfinamide **44**

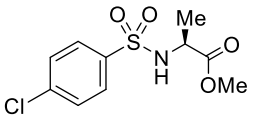


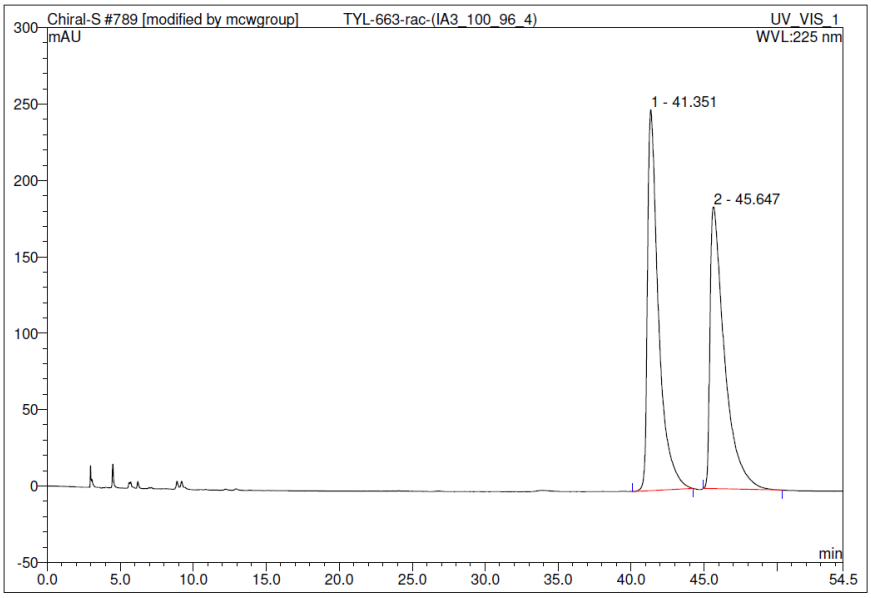
NMR spectrum of primary sulfonamide **45**



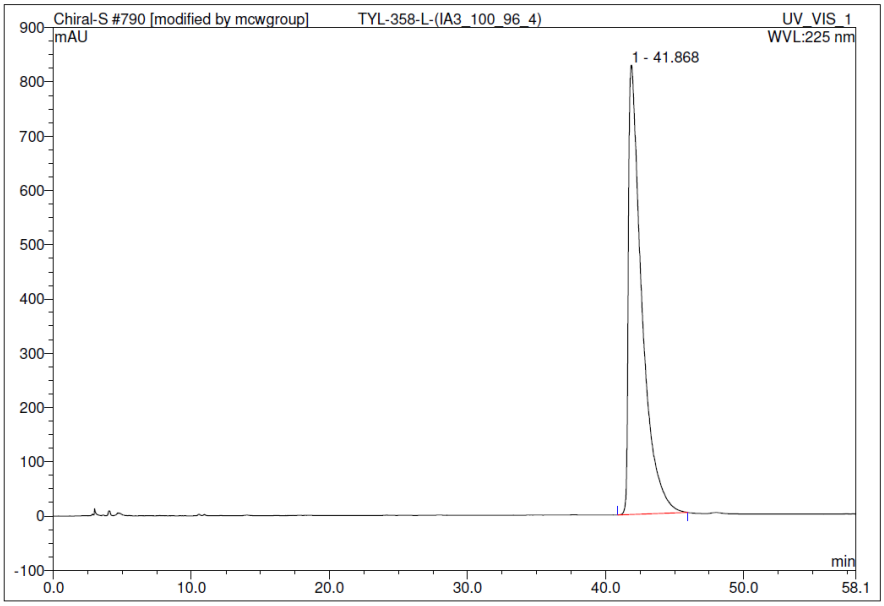
Chiral HPLC Traces

Methyl ((4-chlorophenyl)sulfonyl)-*L*-alaninate (Xd)





No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	41.35	n.a.	249.325	218.568	50.71	n.a.	BMB*
2	45.65	n.a.	184.458	212.416	49.29	n.a.	BMB*
Total:			433.783	430.984	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	41.87	n.a.	827.696	932.640	100.00	n.a.	BMB*
Total:			827.696	932.640	100.00	0.000	