Exploiting sulfinate coupling partners for the preparation of diversely functionalised heterocycles



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I dedicate this thesis to my late father, Geoffrey McKnight, who was my biggest supporter when I started the DPhil; I wish he could have been here to see me reach the end.

I am forever grateful for his humour, bravery, and encouragement for me to achieve academic success.

Abstract

In the following thesis, sulfinates have been exploited for the formation of di(hetero)arylmethanes and bi(hetero)aryls, either by being formed *in situ* or through a straightforward synthetic sequence.

Chapter 1 discusses previously developed desulfinative cross-coupling methodologies, an overview of the application of sulfinate salts in synthetic chemistry, and cross-coupling reactions to construct $C(sp^2)$-$C(sp^3)$ bonds.

Chapter 2 details the route development for the synthesis of benzyl sulfinate starting materials.

Chapter 3 presents a palladium catalysed $C(sp^2)$- $C(sp^3)$ desulfinative cross-coupling to form di(hetero)arylmethanes from benzyl sulfinates and heteroaryl halides.

Chapter 4 demonstrates further developments to the palladium catalysed $C(sp^2)$-$C(sp^3)$ desulfinative cross-coupling to form di(hetero)arylmethanes, through a one-pot protocol. The benzyl sulfinate is formed *in situ* before entering the cross-coupling step. This methodology avoids problematic preparation and storage of unstable benzyl sulfinates, allowing a wider variety of di(hetero)arylmethanes to be accessed.

Chapter 5 describes practical and safety improvements made to the palladium catalysed C(sp^2)-C(sp^2) desulfinative cross-coupling process, to form bi(hetero)aryls on large scale.

Chapter 6 concludes the work and evaluates potential avenues for future research.

Chapter 7 details the experimental procedures and data.

Declaration

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

Janette McKnight

May 2022

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I never would have gotten to this stage without support from you all. Thank you everyone.

Abbreviations

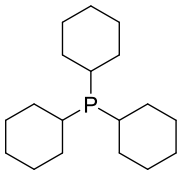
Ac	Acetyl
ACS	American chemical society
Alk	Alkyl
app.	apparent
aq.	Aqueous
Ar	Aryl
atm.	Atmosphere
Å	Angstrom
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Br.	Broad
cat	Catalyst
cm^{-1}	Wavenumber(s)
conc.	Concentrated
Cy	Cyclohexyl
d	Doublet
DABSO	1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
dcpe	1,2-Bis(dicyclohexylphosphino)ethane
dcpp	1,3-Bis(dicyclohexylphosphino)propane
decomp.	Decomposition
DIBAL-H	Diisobutylaluminium hydride
diglyme	Bis(2-methoxyethyl) ether
DIPEA	Diisopropylamine
DMA	Dimethylacetamide

DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMPU	*N,N'*-Dimethylpropylene urea
DMSO	Dimethylsulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
e.g.	*Exempli gratia*
EDG	Electron-donating group
EDTA	Ethylenediaminetetraacetic acid
equiv.	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl
et al.	Et al*ii*
EWG	Electron-withdrawing group
g	Gram(s)/gas
glyme	Dimethoxyethane
h	Hour(s)
Het	Heteroaryl
HPLC	High performance liquid chromatography
HRMS	High-resolution mass spectrometry
Hz	Hertz
I.S.	Internal standard
^{i}Pr	*iso*-Propyl
IR	Infra-red spectroscopy
J	Coupling constant
LRMS	Low-resolution mass spectrometry
m	Multiplet/milli
M	Molar concentration/generic metal

m/z	Mass to charge ratio
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
min	Minute(s)
mol	Mole(s)
MP	Melting point
Ms	Methanesulfonyl
MTBE	*tert*-Butyl methyl ether
NBS	*N*-Bromosuccinimide
nBu	*n*-Butyl
NMR	Nuclear magnetic resonance
o	Ortho
p	Para
petrol	Petroleum ether
Ph	Phenyl
ppm	Parts per million
q	Quartet
quant.	Quantitative
R	Any element or chemical group, unless described
rbf	Round-bottom flask
R_f	Retention factor
rpm	Rotations per minute
rt	Room temperature
s	Singlet/second/solid/sharp
sat.	Saturated
SMOPS	Sodium 3-methoxy-3-oxopropane-1-sulfinate
t	Time/triplet
TBAB	Tetrabutylammonium bromide

TBS	*tert*-Butyldimethylsilyl
^{t}Bu	*tert*-Butyl
Tf	Trifluoromethylsulfonyl/triflyl
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMEDA	Tetramethylethylenediamine
Ts	4-Toluenesulfonyl/tosyl
µ	Micro
vs.	*Versus*
β-nitrile sulfinate	Sodium 2-cyanoethane-1-sulfinate
°C	Degrees Celsius

Ligand Structures



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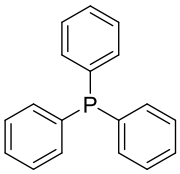

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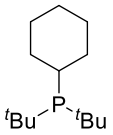

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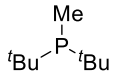

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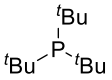

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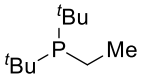

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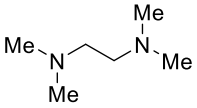

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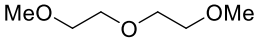

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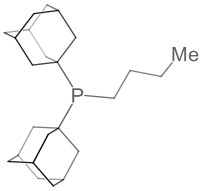

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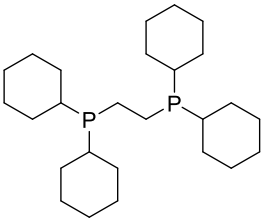

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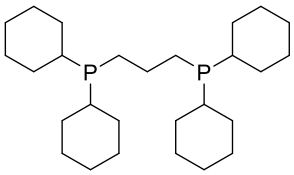

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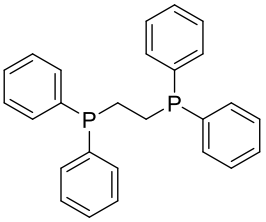

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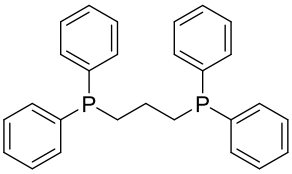

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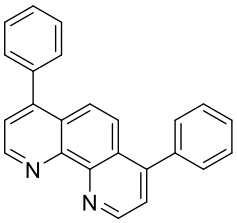

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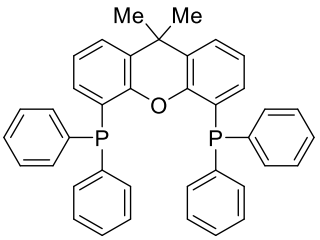

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Chapter 1. Introduction

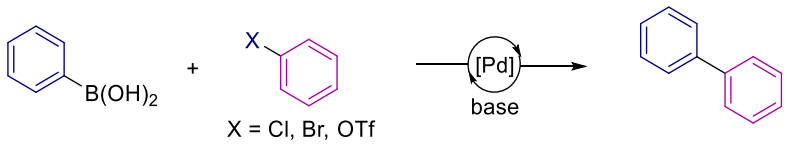
In this introduction chapter we will first briefly discuss the classical Suzuki-Miyaura reaction and the issues associated with specific substrates. Discussion of these issues, and how this led our research group to utilise sulfinate salts as alternative coupling partners, will follow. Next, an overview of sulfinates and their general uses in organic chemistry will feature. Then, the focus of the introduction will turn to C(sp^2)-C(sp^3) cross-coupling reactions and the application of desulfinative methods in this area.

1.1 Cross-coupling reactions to form biaryls

Aryl-aryl cross-coupling reactions have become a crucial component of an organic chemist's synthetic toolbox. Preliminary works were carried out in the 1970s,[1] and since these early developments, the area of cross-coupling chemistry has continued to grow exponentially.[2] Such is the impact of these reactions that the Nobel Prize in Chemistry was awarded to Richard Heck, Ei-ichi Negishi, and Akira Suzuki in 2010.[3]

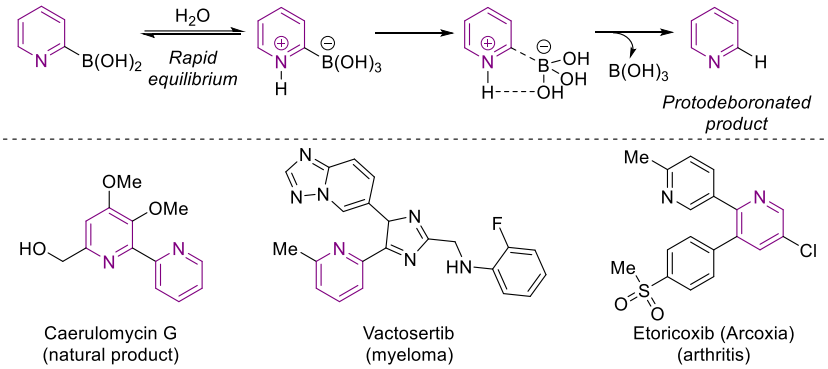
1.1.1 The Suzuki-Miyaura cross-coupling

The Suzuki-Miyaura cross-coupling reaction[4] is widely used among both academic and medicinal chemists[5] to form C-C bonds from boronic acids (or boron-derivatives) and aryl halides (or pseudohalides) under palladium catalysis (Scheme 1). The process tolerates a broad variety of functional groups,[6] and has allowed for the synthesis of pharmaceutically important compounds.[7] Milder reaction conditions have also been developed since the reaction was first reported in 1979.[8]



Scheme 1. General Suzuki-Miyaura cross-coupling reaction.

Unfortunately, 2-pyridyl boronic acids and other 2-heteroaryl boronic acids are unable to tolerate the reaction conditions, which Fagnou and co-workers described as the '2-pyridyl problem'.[9] Lloyd-Jones and co-workers later found that 2-pyridyl boronic acids undergo rapid protodeboronation (with a half-life of just 26 seconds between a pH range of 4 – 10).[10] 5-Thiazolyl and 5-pyrazolyl boronic acids were also found to be unstable to an even wider pH range. This is a considerable problem as the 2-pyridyl motif is ubiquitous in medicinally-relevant compounds as well as ligands (Scheme 2).[11]



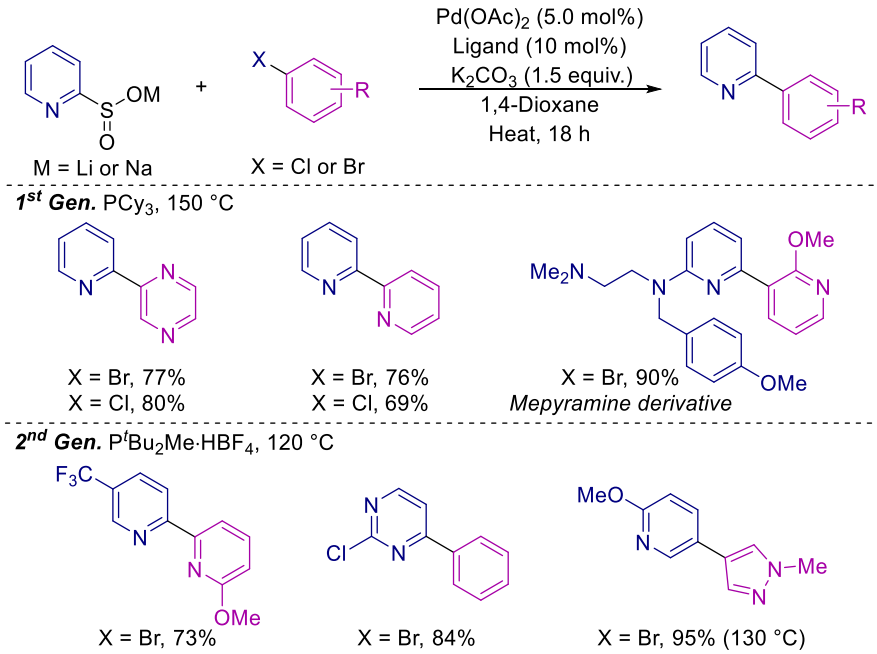
Scheme 2. Protodeboronation process of 2-pyridyl boronic acid and pharmaceutically-relevant compounds containing the 2-pyridyl motif.

This issue can often be circumvented by using the aryl halide rather than the boronic acid for the 2-pyridyl fragment, however, this removes the possibility of synthesising 2,2'-bipyridines (useful structures in ligands[12]). Over the years, there have been many advances to address the 2-pyridyl boronic acid issue, such as improving the stability of boron-derivatives (e.g. MIDA-boronates,[13] (dan)-boronates,[14] (aam)-boronates[15]), and using alternative starting materials.[16]

1.1.2 Sulfinates as alternatives to boronic acids

As well as many others,[16-17] Willis and co-workers sought to provide a solution to the '2-pyridyl problem'. To this end, heteroaryl sulfinates were explored as an alternative to unstable boronic acids in Suzuki-Miyaura cross-couplings (Scheme 3).[18] Desulfinative

cross-couplings of aryl sulfinates had been previously reported,[19] but heteroaryl examples were limited until our group commenced work in this area. Willis and co-workers found that sodium or lithium pyridine-2-sulfinate salts were efficiently coupled to heteroaryl chlorides and bromides, including 2-pyridines, pyrimidines and pyrazines (over 80 examples with up to 99% yield). A drawback of this work was the high 150 °C temperature required to achieve excellent yields. The group later found that changing the ligand from PCy_3 to $P^tBu_2Me{\cdot}HBF_4$ allowed the reaction to proceed at a lower temperature (120 °C) whilst maintaining excellent yields.[20] Thus, a broader range of motifs could be accessed that were not previously compatible with the reaction conditions (e.g. alcohol, carboxylic acid, sulfonamide groups).

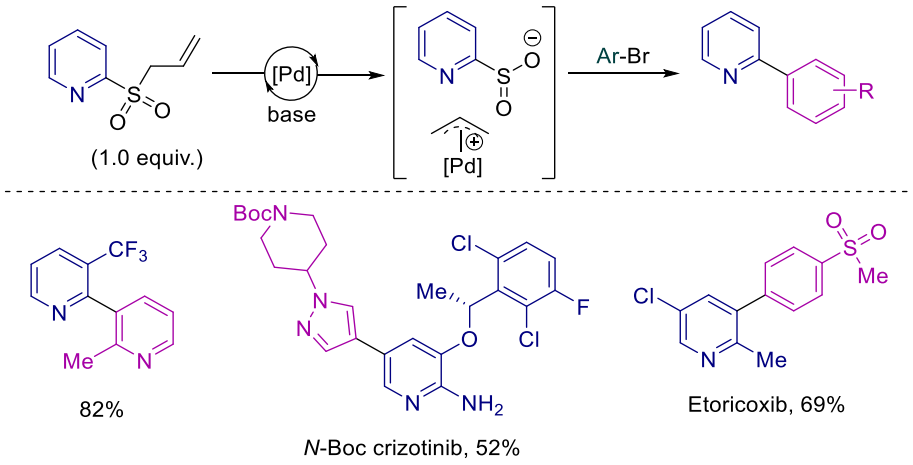


Scheme 3. Heteroaryl sulfinates as coupling partners for the synthesis of bi(hetero)aryls.

It was speculated that the potential emission of toxic SO_2 gas in the reaction would be disadvantageous for its use. However, studies into the mechanism suggested that the potassium carbonate, used as a basic additive in these reactions, had two roles.[21] The first was to perform a counter-ion swap with sodium to the more active potassium sulfinate

salt, and it was suggested that the second was for the carbonate anion to trap the SO_2 gas and release CO_2 gas instead.

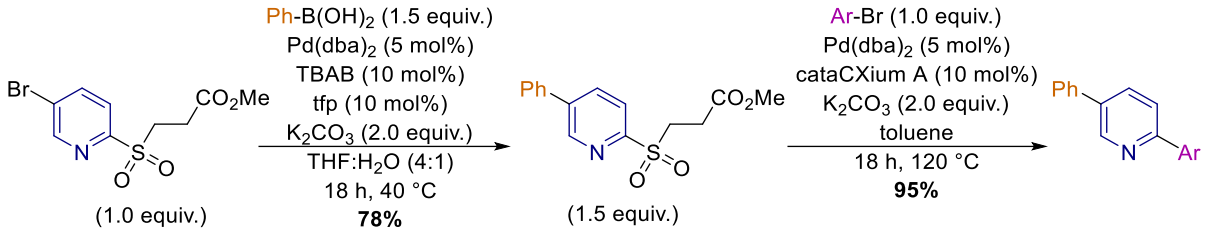
Although sulfinate salts were demonstrated to be excellent coupling partners, key issues were that, due to being salts, they are not amenable to multi-step elaboration, and sulfinates with complex scaffolds are both difficult to prepare and have limited solubility in organic media. Sulfinates have been prepared by base-promoted elimination from *N*-aminosulfonamides by Willis and co-workers,[22] and from thiosulfonates by Jang and co-workers.[23] In a similar manner, the Willis group employed heteroaryl allylsulfones as latent sulfinate reagents, which deallylate *in situ* by the same palladium catalyst used for the subsequent desulfinative cross-coupling to form bi(hetero)aryls (Scheme 4).[24] A broad-range of heterocycles were compatible for either coupling partner, and complex drug-fragments could be prepared such as the *N*-Boc-derivative of the Pfizer lung cancer drug crizotinib (52%) and the COX-2 inhibitor etoricoxib (69%).



Scheme 4. Pyridylallyl sulfone as a latent sulfinate reagent.

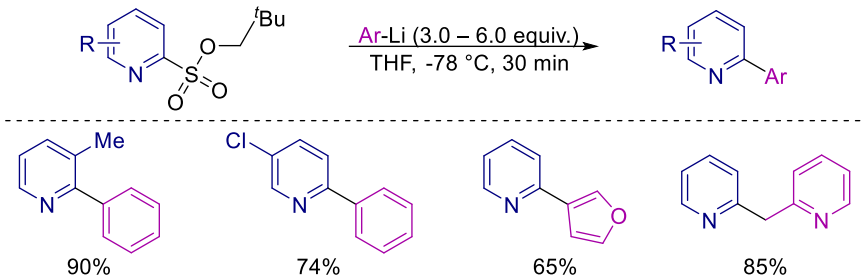
Whilst the method had an excellent scope, substrate-specific conditions needed to be developed for many allyl sulfones to give optimum yields. As a result, other latent sulfinate reagents were explored to determine whether a more general method could be developed.

In 2021, heteroaryl β-nitrile and β-ester sulfones were shown to readily liberate the desired aryl sulfinate *in situ* through base-activated elimination of acrylonitrile or methyl acrylate, respectively (Scheme 5). The sulfinate was then available to undergo desulfinative cross-coupling with (hetero)aryl halides.[25] The method allowed access to a diverse range of 2-arylpyridines and pharmaceutically relevant scaffolds, and the latent groups were shown to be stable to several orthogonal metal-catalysed processes and alkene functionalisation reactions, which would not have been possible for the allyl sulfones (Scheme 5).



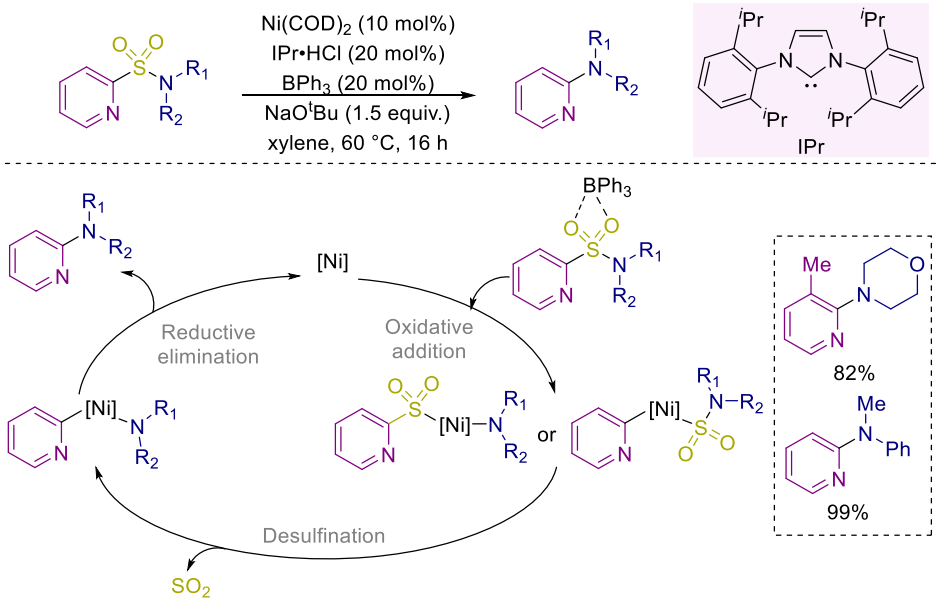
Scheme 5. Orthogonal reactivity of the β-ester latent sulfinate through a Suzuki-Miyaura cross-coupling and the optimised desulfinative reaction conditions.

A recent strategy has emerged to react pyridine sulfonates with an organolithium reagent ((hetero)aryl and benzyl examples) at low temperature, under a desulfonative S_NAr-type protocol, to afford substituted pyridines at the 2-position (Scheme 6).[26] This method avoids the use of any transition metals, however, due to the use of pre-formed organometallic reagents, there were no examples featuring electrophilic or protic functional groups.



Scheme 6. (Hetero)aryl-Li addition reactions to neopentyl 2-pyridyl sulfonates.

Desulfinative reactions have also been shown to be compatible with nickel-catalysis. For example, in 2020 Lian and co-workers presented the intramolecular desulfinative reaction of pyridyl-2-sulfonamides to give pyridine-2-amines (Scheme 7).[27] Interestingly, this process occurs at 60 °C, which is a substantially lower temperature than that needed for C-C desulfinative cross-coupling reactions of 2-pyridyl sulfinates. Unfortunately, only trace products were observed when the C-N bond formation was attempted using sulfonamides in the 3- or 4-position, so it is assumed that pyridine-nitrogen coordination assists the oxidative addition process.



Scheme 7. Intramolecular desulfinative C-N bond formation.

1.2 General overview of sulfinate salts

Sulfinates have been known for over 100 years,[28] however, it has primarily been over the past two decades where their synthetic utility has been reinvestigated.[29] This spike in interest is partially due to their ability to act as either an electrophile or nucleophile, allowing for their use in a broad variety of chemical reactions. Furthermore, they are generally bench stable, easy to handle free-flowing solids, and have increasing commercial availability, all contributing to the appeal for both academic and industrial chemists.

Although sodium, zinc and lithium sulfinate cations are most common, other counterions have also been reported (for example, ammonium,[30] gold,[31] and silyl[32]).

The recent development of sulfur dioxide surrogates has enabled the synthesis of sulfinates without employing toxic sulfur dioxide gas, further increasing their appeal.[33] Common sulfur dioxide surrogates include DABSO,[34] a solid Lewis adduct between DABCO and two molecules of SO_2, and inorganic sulfites such as potassium or sodium metabisulfite[35] and sodium sulfite.[36]

1.2.1 Sulfinates as starting materials

Sulfinate salts are often employed as starting materials to form sulfones through *S*-alkylation methods, but they can also be used to synthesise sulfonamides (which are of high medicinal interest),[37] sulfonates,[38] thiosulfonates[39] and sulfides (Figure 1).[40] *O*-alkylation is also possible to provide sulfinate esters,[39, 41] however examples are more scarce. Owing to the ability of sulfinates to act as either a nucleophile or an electrophile, in Suzuki-Miyaura cross-couplings, sulfinates can replace the aryl halide or the boronic acid coupling partner.[42] Moreover, their use can be extended to C-H functionalisation reactions.[43]

Sulfinates have also been employed in oxidative cross-couplings and radical cyclisations by silver catalysis, to form benzofurans,[44] phenanthridines[45] and dihydronaphthalenes[46] with sulfone functionality. Visible-light photo-redox/nickel dual-catalysis has emerged as an efficient alternative to classical oxidation of sulfides or metal-catalysed cross-couplings for the synthesis of aryl sulfones.[47] Moreover, aryl sulfones can now be accessed through electrochemical approaches.[48]

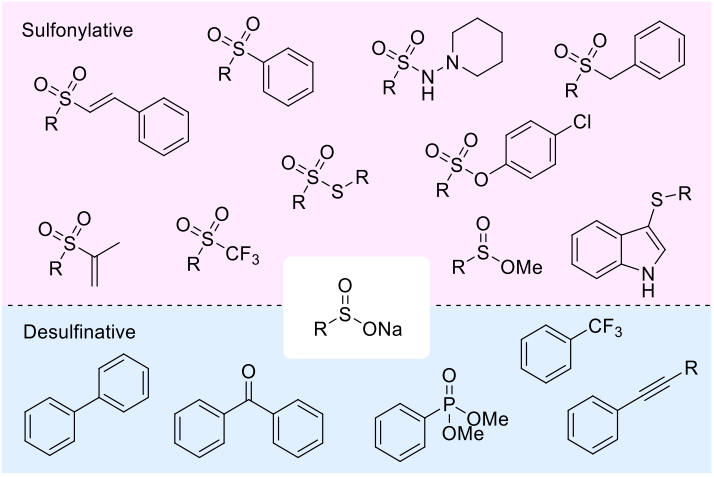


Figure 1. Examples of products possible to synthesise from sulfinate starting materials.

Reactions with aryl sulfinates are by far the most commonly seen in publications, with alkyl sulfinates featuring less often. Benzyl sulfinates were reported in the 1960s,[49] however have not been utilised with wide application.

1.2.2 Sulfinates as reagents

Sulfinates have proven to be useful reagents over the last 50 years. For example, in the late 1970s, BNA-SO_2Na was developed as a reducing agent for carbonyl compounds (Figure 2).[50] Moreover, the Langlois reagent (sodium triflinate) is an affordable and commercially available sulfinate that was first reported in the 1980s for the radical installation of trifluoromethyl groups onto aryl rings.[51] This reagent has since been utilised by many research groups, leading to the recent publication of review articles surrounding the application of this sulfinate reagent in alkyl, aryl, alkenyl and heteroatom trifluoromethylation as well as C-H functionalisation reactions.[52]

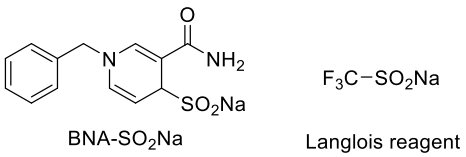


Figure 2. Historic sulfinate reagents.

In 2012, Baran and co-workers developed a new difluoromethylation reagent, zinc difluoromethanesulfinate (DFMS, Figure 3a), which was used in the C-H functionalisation of heterocycles (pyridines, pyrazine, pyrroles, xanthines, purines and others).[53] The radical reaction was conducted at room temperature, under air. Products were formed in moderate to excellent yields (30 – 90%), with a wide variety of functional groups tolerated (free amines, amides, halides, and carbonyl groups). For some pyridine coupling partners, poor regioselectivity was observed, giving lower yields. Convenient methods for the installation of the CF_2H unit are of high interest to medicinal chemists, as this group can be employed as a bioisostere for OH or SH.[54]

Next, Baran developed a sulfinate late-stage functionalisation toolkit, which was marketed as the Diversinates™ by Sigma-Aldrich (Figure 3a). Remarkably, enhanced reactivity was found with zinc sulfinates, in comparison to the corresponding sodium salts, in radical additions to heterocycles.[55] Some of these reagents included zinc trifluoromethanesulfinate (TFMS), zinc trifluoroethanesulfinate (TFES), zinc monofluoromethanesulfinate (MFMS), zinc isopropylsulfinate (IPS), and zinc triethyleneglycolsulfinate (TEGS). They were proposed to exist as dihydrates in the solid state.[56] Sodium 1,1-difluoroethanesulfinate (DFES) was later developed to install the difluoroethane group as a bioisostere for a methoxy group. This reagent was also commercialised by Sigma-Aldrich (Figure 3a).[57] After considerable work towards the development of a versatile sulfinate radical methylating agent, zinc bis(phenylsulfonylmethanesulfinate) (PSMS) was identified; however, harsh conditions were necessary to perform desulfonylation to reveal the methyl group (e.g. SmI_2 and Raney nickel).[58] Later, Baran and co-workers demonstrated the synthesis of alkyl sulfinates from carboxylic acids (Figure 3b).[59] An example from this work is sodium

1-(trifluoromethyl)cyclopropanesulfinate (TFCS), used to install trifluoromethyl cyclopropyl groups onto heterocycles. The utility of the Diversinates™ was realised during late-stage functionalisation to prepare papaverine derivatives.[60]

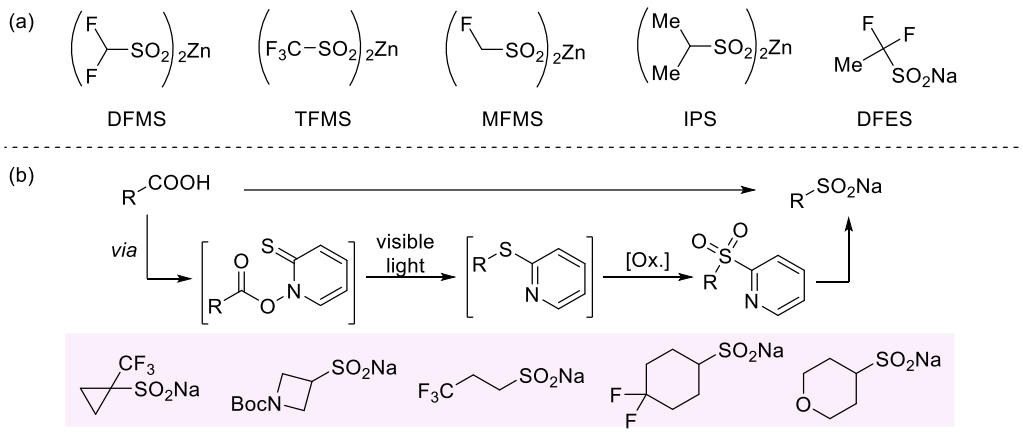
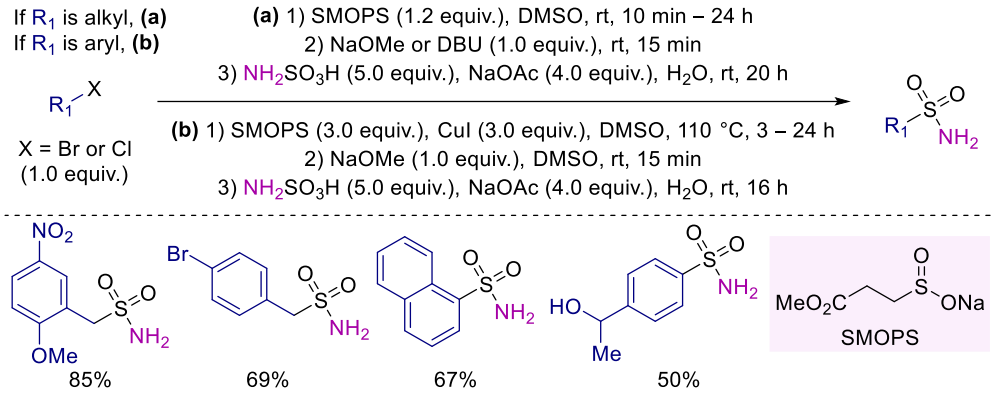


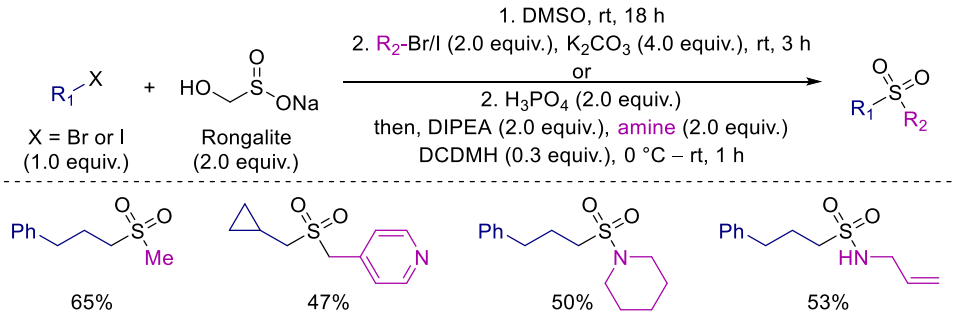
Figure 3. (a)Select examples of Diversinates™. (b) Sulfinate synthesis from carboxylic acids.

In 2002, Baskin et al presented sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS) as a reagent for the synthesis of sulfinates, avoiding the necessity of harsh oxidising conditions or organometallic reagents (Scheme 8).[61] Benzyl sulfinates were prepared by an S_N2-type *S*-alkylation using SMOPS, followed by a β-elimination using sodium methoxide. SMOPS could also be used to prepare aryl sulfinates via a S_NAr-type mechanism using stoichiometric copper, followed by base-assisted cleavage. One-pot and telescoped procedures to sulfonamides from the sulfinate products were also demonstrated.



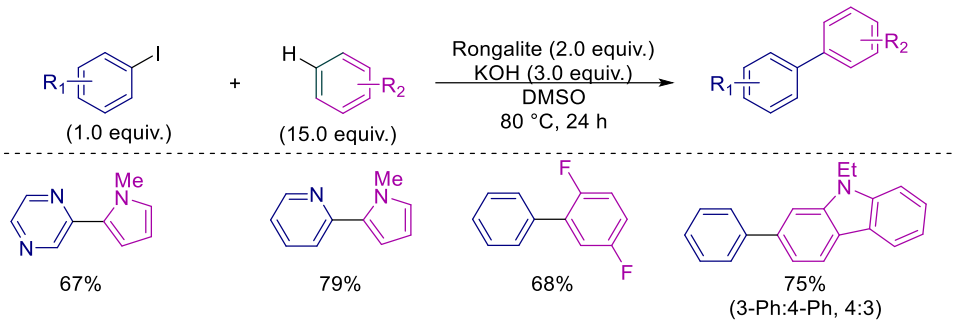
Scheme 8. SMOPS facilitated synthesis of alkyl and aryl sulfonamides.

Rongalite (sodium hydroxymethanesulfinate) is an inexpensive and easily accessible reagent that has found enormous application in synthetic chemistry and material science. As such, there have been review articles published specifically on the use of this important reagent.[62] In 2016, Shavnya et al envisioned that they could intercept the reaction of Rongalite with alkyl halides after *S*-alkylation, prior to *O*-alkylation, to afford an alkyl sulfinate to then synthesise sulfone-derivatives (Scheme 9).[63] Rongalite is insoluble in most organic media, and is only sparingly soluble in DMSO, meaning reactions had to be run with high dilution, thus limiting its industrial utility. While alkyl halides were compatible with the reaction, pseudohalides generally gave poor product yields. A maximum yield of 65% was achieved for unsymmetrical sulfone products. Despite these disadvantages, the mild conditions and use of Rongalite as an inexpensive reagent are attractive.



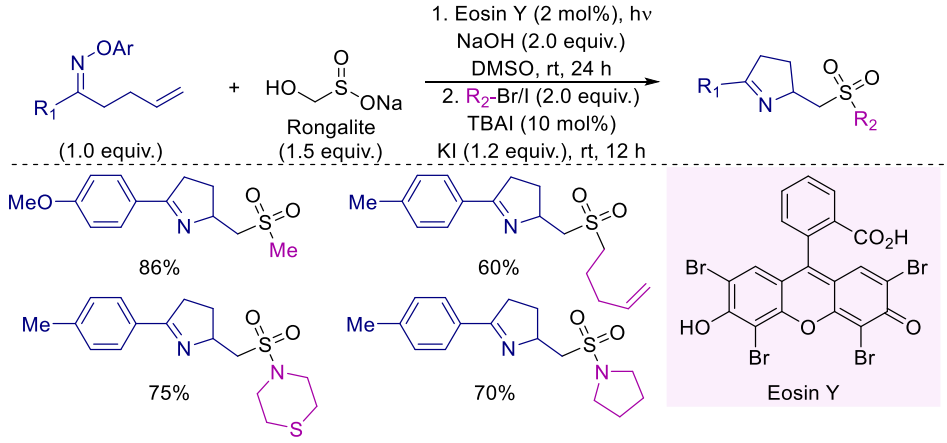
Scheme 9. Sulfones and sulfonamides synthesised through a telescoped approach from Rongalite.

More recently, Rongalite has been utilised as a cheap SO_2 source in a cascade reaction to synthesise 1-thiaflavanone sulfone-derivatives using copper-catalysis.[64] Wang and co-workers found that Rongalite could function as a new type of super electron donor, due to its ability to form the highly reductive SO_2^{-}/HSO_2^{-} species and therefore generate aryl radicals from aryl halides.[65] Radical trapping with aryls allowed the formation of biaryls (up to 90% yield), although only limited functionality was tolerated (methoxy, fluoro and methyl groups) and a lack of regiocontrol was demonstrated in some cases (Scheme 10).



Scheme 10. Rongalite-promoted C-H arylation to for bi(hetero)aryls.

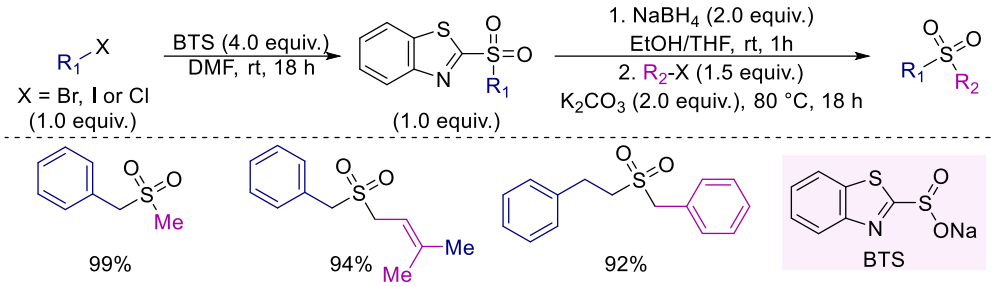
The use of Rongalite for the generation of sulfur dioxide radicals was utilised by He et al in a photoinduced sulfonylation reaction, with an iminyl radical-mediated cyclisation under mild conditions.[66] This method afforded pyrrole-substituted aliphatic sulfones and sulfonamides (Scheme 11). In 2022, Rongalite was shown to have three functions in the sulfonylmethylation of sulfoxonium ylides: a sulfone source, a radical initiator, and a potential reducing reagent.[67] Hence, developments of methods utilising Rongalite will likely continue to frequent the literature.



Scheme 11. Photoredox-catalysed reaction of oximes, Rongalite and electrophiles.

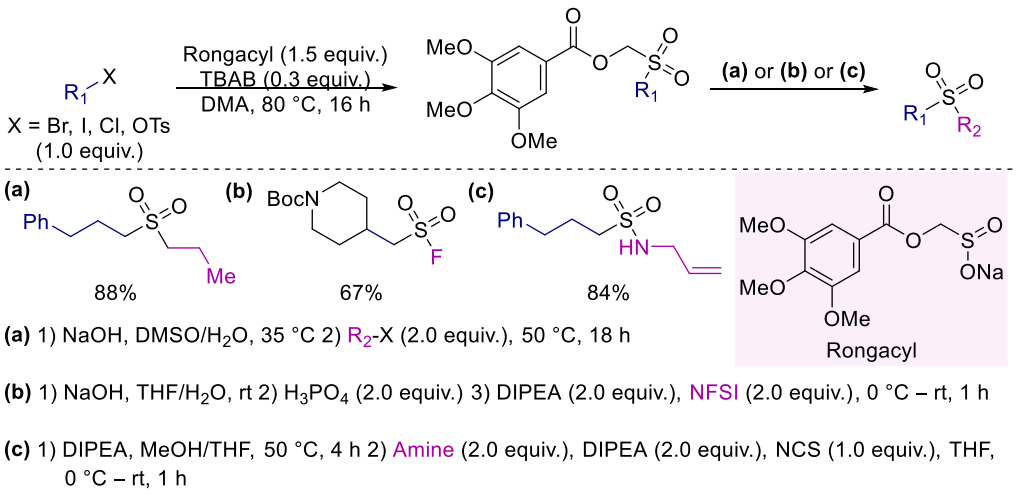
The sulfinate sodium benzo[d]thiazole-2-sulfinate (BTS), was found to slowly decompose under acidic conditions to release sulfur dioxide.[68] This led Xian and co-workers to realise its potential to act as a sulfinate transfer agent.[69] Sulfinate synthesis was achieved by sulfone formation from BTS and alkyl bromides, followed by release of benzothiazole using sodium borohydride (Scheme 12). This method has several disadvantages, including the

requirement to have four equivalents of BTS to achieve quantitative yield of sulfone, as well as employing harsh conditions for the release of benzothiazole, and the requirement for BTS to be stored in a freezer.



Scheme 12. Examples of sulfones synthesised from the BTS reagent.

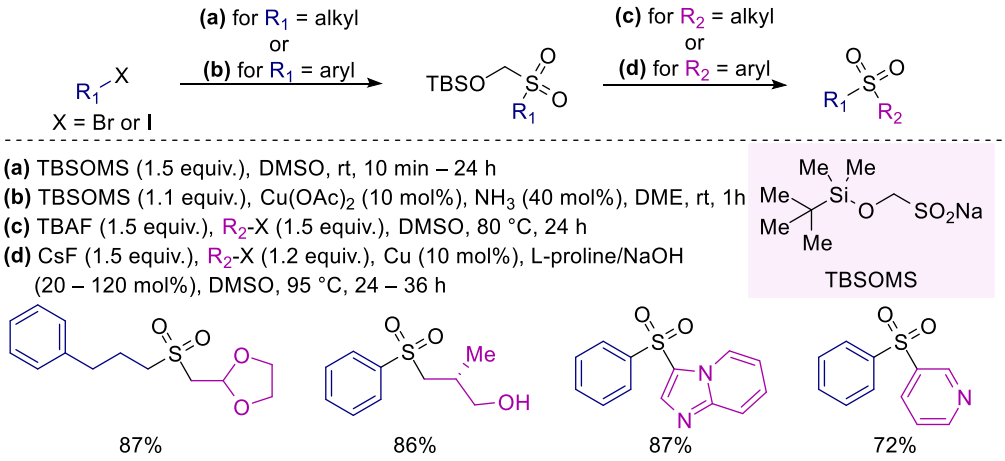
In an effort to overcome some of the issues surrounding use of Rongalite and BTS, and to provide a wider scope than that demonstrated using SMOPS, Shavnya et al presented Rongacyl, prepared from Rongalite, as a versatile sulfonylating reagent (Scheme 13).[70] Isolated sulfinate salts were synthesised, and telescoped procedures were demonstrated to give sulfonamides, sulfonyl fluorides and unsymmetrical sulfones. Notably, the mild sulfone cleavage conditions allowed a base and acid-sensitive glycoside motif to remain intact during sulfonyl fluoride synthesis.



Scheme 13. Rongacyl assisted preparation of sulfones, sulfonyl fluorides and sulfonamides.

Another sulfinate transfer reagent, sodium *tert*-butyldimethylsilyloxymethane sulfinate (TBSOMS), was developed by Lee and co-workers to access a diverse range of sulfone

products including alkyl, alkenyl, alkynyl, and aryl derivatives.[71] TBSOMS was shown to be more versatile that the other previously discussed sulfonylating reagents. *S*-Alkylation of TBSOMS was achieved at room temperature with no additives. Arylation of TBSOMS could be achieved using copper catalysis, however, the catalyst could be employed in a quantity of 10 mol% (compared to 3.0 equiv. [Cu] with SMOPS) and the reactions were conducted at either room temperature or 35 °C (compared to 110 °C with SMOPS). Furthermore, instead of strong bases, the sulfinate could be released by treatment with fluoride sources such as TBAF or CsF.



Scheme 14. Sulfone examples synthesised with the TBSOMS reagent.

1.3 Cross-coupling reactions to form C(sp^2)-C(sp^3) bonds

While there has been significant advances in the synthesis of biaryls *via* metal-catalysed cross-coupling reactions,[72] there has been concern within the medicinal chemistry community that there is an unmet need for more developments in the construction of alkyl C-C bonds.[73] This is because the presence of a higher proportion of sp^3-hybridised carbon atoms often leads to improved physicochemical properties.[74] For example, decreasing the degree of aromaticity and planarity by incorporating more 3D structure into a molecule has been shown to improve some aqueous solubility and crystallinity; important parameters for the success of a drug molecule.[75] Hence, many protocols have been

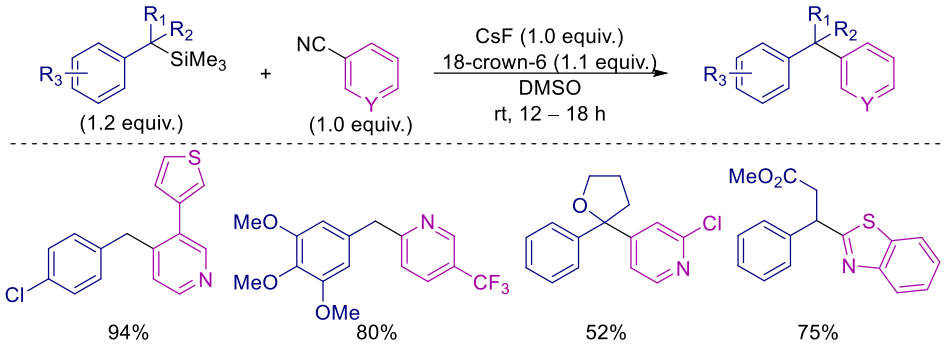
developed to incorporate more 3D functionality.[76] There are several useful methods for the incorporation of alkyl motifs, such as conjugate additions,[77] but we will focus on cross-coupling methods in this section.

1.3.1 Recent developments in $C(sp^2)$-$C(sp^3)$ cross-couplings

Traditional palladium-catalysed cross-coupling approaches with alkyl coupling partners can often suffer from β-hydride elimination, however, this is not an issue for benzyl substrates. Suzuki–Miyaura type stereospecific cross-couplings have been achieved with benzylic ammonium triflates,[78] and boronates,[79] although these reagents can suffer from instability. Decarboxylative cross-couplings under palladium,[80] and dual photoredox/nickel catalysis[81] have been reported to couple benzyl moieties.

Classical methods such as three-component vicarious nucleophilic substitution (VNS),[82] transition-metal-catalysed cross-coupling of benzyl organometallic reagents[83] and Friedel–Crafts alkylations allow the installation of benzyl groups onto aryl rings.[84] These methods often suffer from limited reaction scopes (for example, due to the use of organometallic reagents), poor regioselectivity, or the need for tailored starting materials. However, many of these methods are still used, and research into solving some of these issues are being developed.[85]

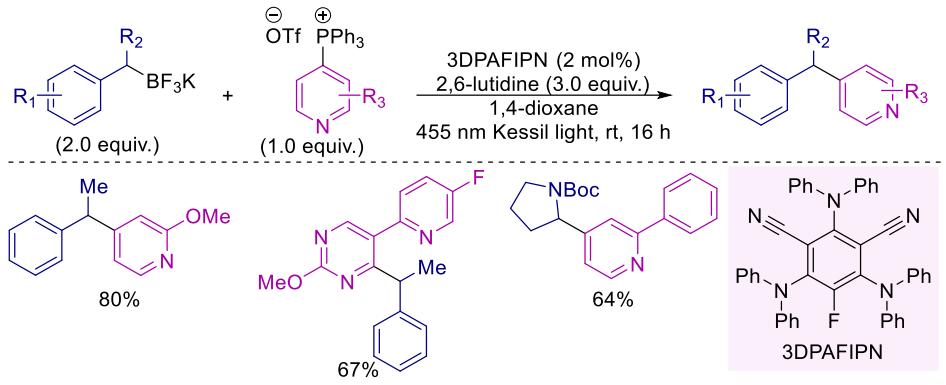
Benzylation can also be achieved using alternative methods. Recently, a report by Reidl and Bandar demonstrated the coupling of benzyltrimethylsilanes to aryl and heteroaryl nitriles, using a Lewis base-promoted method rather than transition-metal catalysis (Scheme 15).[86] Over-arylation is a common issue for this approach; the authors prevented this by using CsF as the limiting reagent. Borane catalysis has also been presented as an alternative to transition-metal catalysts for the synthesis of diarylmethanes.[87]



Scheme 15. Diarylmethane synthesis from benzyl silanes and cyanoarenes.

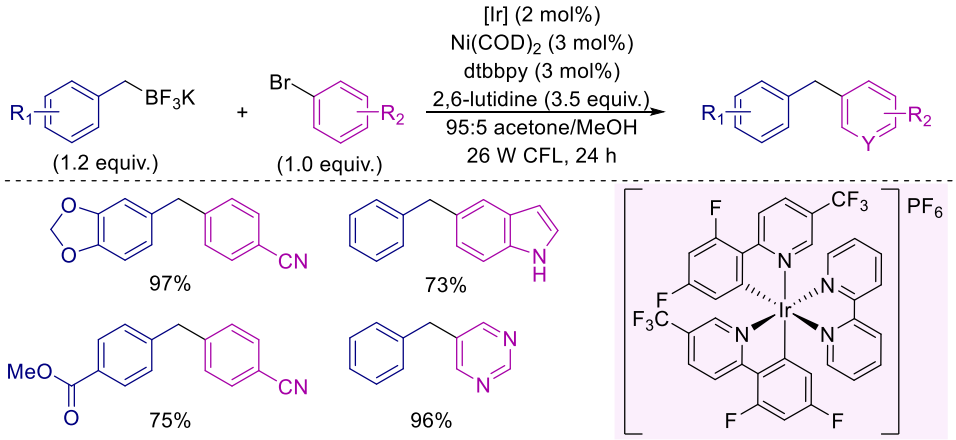
The growth in research utilising radical chemistry in recent years has resulted in the development of several methods for installing alkyl groups onto complex heterocycles and natural products.[88] Baran and co-workers capitalised on the innate reactivity of pyridines under radical Minisci-type protocols to prepare alkylated pyridines.[55, 89] However, the preparation of C4-alkylated pyridines is not possible due to the preferential radical addition to the C2 position. A disadvantage of this methodology is that mixtures of products are often formed. One tactic to overcome this issue utilises C2-blocking groups bound to the pyridine nitrogen. For example, Baran and co-workers used a fumarate-based blocking group to regioselectively prepare C4-alkylated pyridines from primary, secondary and tertiary carboxylic acids, under an acid-free Minisci method.[90]

Benzyl BF_3K salts have also proven to be useful coupling partners for the synthesis of diarylmethanes. McNally and co-workers were also able to achieve pyridine C4-alkylation through a radical-radical coupling procedure using phosphonium salts and benzyl BF_3K salts (Scheme 16).[91]



Scheme 16. Pyridylphosphonium salts in radical– radical coupling reactions with benzyl BF_3K salts.

In 2014, Molander and co-workers pioneered the use of photoredox cross-coupling of secondary alkyl nucleophiles as an alternative to conventional cross-couplings (Scheme 17).[92] In this work, diarylmethanes were synthesised from benzyl BF_3K salts and aryl bromides under nickel and iridium dual-photoredox catalysis.



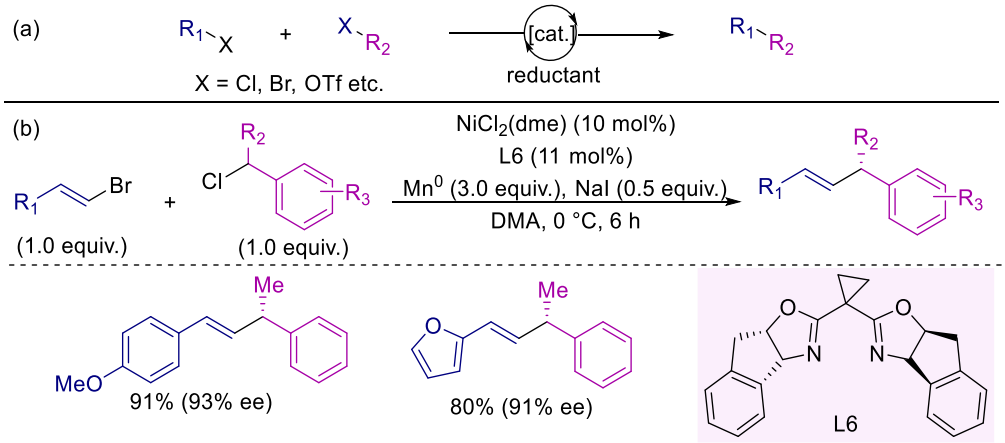
Scheme 17. Photoredox cross-coupling of benzylic trifluoroborates and aryl bromides.

Cross-electrophile reductive couplings

Transition metal-catalysed reductive cross-electrophile couplings have become a subject of significant research (Scheme 18a). Due to the breadth of this research topic and the many excellent reviews in this area,[93] this section will focus on an overview with a few notable examples of $C(sp^2)$-$C(sp^3)$ bond formation from recent years.

An advantage of this chemistry is that alkyl and aryl electrophiles are widely commercially available or easily accessible, whereas access to some nucleophiles can prove difficult.[94]

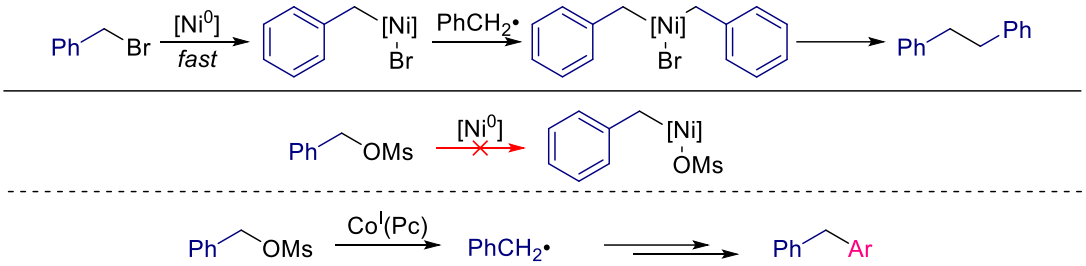
Reductive couplings of alkyl electrophiles has allowed the formation of C(sp^2)-C(sp^3) bonds; commonly nickel catalysts are used[95] but examples with cobalt have also been reported.[96] Often, zinc or manganese are employed as stoichiometric metal reductants, but there are some examples of the use of boron reagents.[97] Additionally, many cross-electrophile couplings utilise halide coupling partners,[93c] however, strategies of cross-electrophile couplings with carbonyl compounds[98] and other electrophiles[99] have emerged. Reisman and co-workers reported an asymmetric reductive cross-coupling to form C-C(sp^3) bonds, using a $NiCl_2$(dme) catalyst under mild conditions (Scheme 18b).[100] Moreover, C(sp^3)-C(sp^3) bond formation has also been possible through cross-electrophile coupling methods.[99b]



Scheme 18. (a) General cross-electrophile cross-coupling reaction. (b) Enantioselective reductive cross-coupling between vinyl bromides and benzyl chlorides.

Ulmann-type homocouplings are often observed as competitive pathways to the desired cross-electrophile coupling. This is due to the two electrophile substrates often being similar in reactivity.[101] As there are subtle differences between alkyl and aryl electrophiles, selectivity can be achieved with these coupling partners[93c] and often dual-catalytic systems are used.[102]

Weix and co-workers have made several impactful developments in the area of cross-electrophile couplings,[103] but found benzyl halides to be incompatible with the methodology (Scheme 19).[104] Benzyl halides were found to be too reactive when coupling to aryl halides, and homocoupling of the benzyl electrophile dominated rather than the desired cross-coupled diarylmethane product. To avoid this, a cobalt co-catalyst (Co(PC)) was used to generate the benzyl radical from benzyl mesylate. Selectivity was achieved because this radical generation was slow with nickel, but nickel could form the aryl radical efficiently. A telescoped procedure, using benzyl alcohol and aryl bromide or iodide coupling partners, allowed the formation of diarylmethane products in moderate to very good yields (53 – 88%, 17 examples). Broad functionality was tolerated (carbonyls, halides, boronates), however, heterocyclic examples were limited. The dual nickel/cobalt catalytic system inspired other groups to extend this work to other alkyl sulfonates.[105]

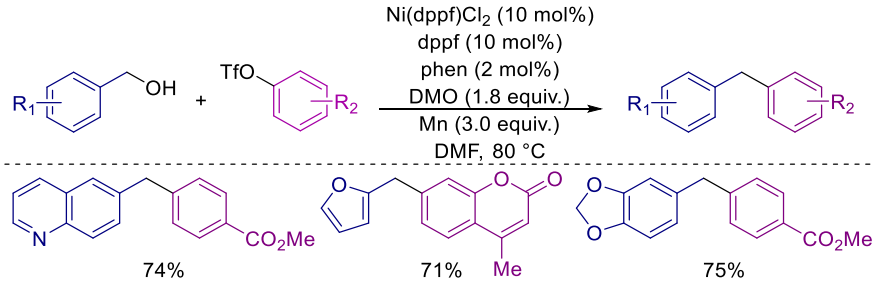


Scheme 19. Achieved benzyl radical coupling from a mesylate.

In 2018, Ukaji was able to perform a cross-electrophile coupling between benzyl alcohols and aryl halides.[106] Instead of cobalt, the benzyl radical was generated by titanium-mediated homolytic C–O bond cleavage, and subsequent nickel-catalysis led to diarylmethane product formation. The reaction tolerated various functional groups (trifluoromethyl, halides, esters, nitrile groups), however a thiophene containing alcohol was the only heterocyclic alcohol in the reaction scope. Overall, this method employed

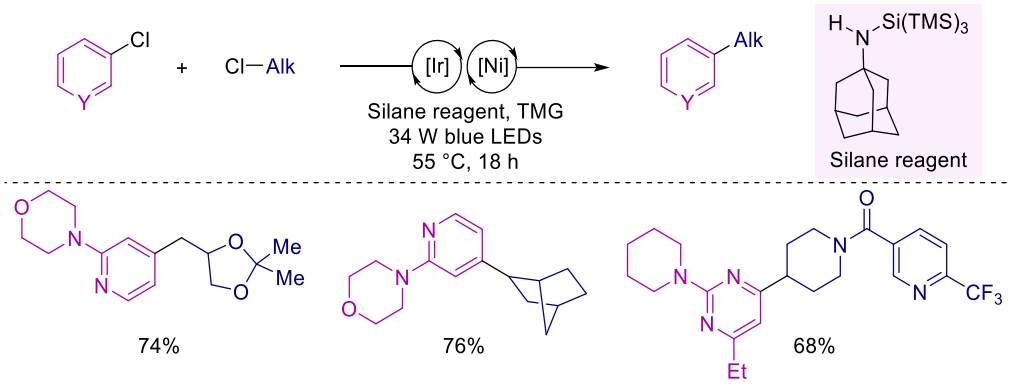
widely available alcohols without having to undergo *in situ* transformation to a more reactive electrophile.

Recently, Shu and co-workers reported a cross-electrophile coupling between a broad scope of benzyl alcohols and aryl halides (bromides, chlorides and iodides were all tolerated) (Scheme 20).[107] This was proposed to proceed *via* nickel-catalysed transesterification of dimethyl oxalate (DMO) with the benzyl alcohol to give the more reactive benzyl oxalate, which had previously been shown to be an efficient coupling partner.[99b] The same nickel-catalyst was used to facilitate the cross-coupling. Notably, a range of benzyl alcohols with heterocyclic motifs were shown to react efficiently (e.g. furan, thiophene, pyridine). However, for most heterocyclic examples, $AlCl_3$ was used as an additive to afford improved yields. The protocol was also successfully applied in the synthesis of biologically active molecules.



Scheme 20. Coupling benzyl alcohols to aryl triflate via an oxalate intermediate.

In 2020, MacMillan and co-workers presented a cross-electrophile cross-coupling of unactivated alkyl chlorides and heteroaryl chlorides, under silane-mediated, iridium and nickel photoredox catalysis (Scheme 21).[108] The generality of the method was demonstrated by an impressive scope containing drug-like fragments.



Scheme 21. Silane-mediated cross-electrophile coupling under iridium and nickel catalysis.

Reliable methods to form C(sp^2)-C(sp^3) bonds are becoming increasingly important to medicinal chemists. As such, in 2020, a team from AbbVie Inc. evaluated seven methods that have received considerable attention to install alkyl groups on heteroaromatic cores:[109] Negishi coupling,[110] nickel/photoredox coupling of BF_3K salts,[111] Suzuki-Miyaura coupling of BF_3K salts,[112] Suzuki-Miyaura coupling of MIDA boronates,[13a] nickel/photoredox decarboxylative coupling,[113] nickel and iridium photoredox cross-electrophile coupling,[114] and nickel-catalysed reductive cross-electrophile coupling[93c, 115] (Table 1, for all examples and detailed reaction conditions please refer to the paper). Availability of building blocks is a crucial factor for whether a method will be adopted by medicinal chemists due to the fast-paced nature of early drug discovery. Unfortunately, MIDA boronate reagent availability is limited, and Negishi zinc reagents can lack diversity compared to other coupling partner options such as alkyl carboxylic acids and halides. Of those tested, there was no one method that worked efficiently for all the classes of alkyl building blocks (cyclic ethers, protected cyclic amines, primary, secondary, tertiary and benzylic), with *tert*-butyl and secondary benzylic groups proving to be challenging under all the methods. The researchers found that both cross-electrophile coupling methods were efficient for nearly all alkyl substrates but were unsuccessful for benzyl partners.

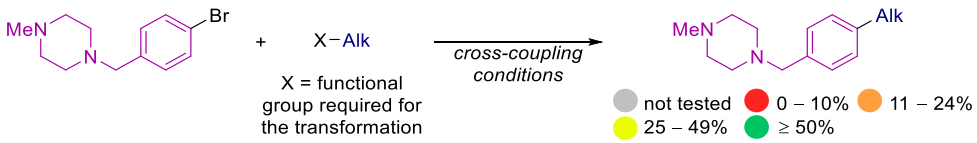


Table 1. Evaluation of seven methods cross-couple medicinally relevant alkyl motifs.

Coupling method	Me		CO_2Me	^tBu	Ph	Me, Ph
Negishi (X = ZnBr)						
Nickel/photoredox (X = BF_3K)						
Suzuki-Miyaura (X = BF_3K)						
Suzuki-Miyaura (X = B(MIDA))						
Nickel/photoredox decarboxylative (X = COOH)						
Nickel/photoredox cross-electrophile (X = Br)						
Nickel reductive cross-electrophile (X = Br)						

1.3.2 Desulfinative $C(sp^2)$-$C(sp^3)$ cross-couplings

Desulfinative processes were investigated as early as 1905,[116] but in recent years, this has been applied to C-C bond formation reactions. As previously shown in this chapter, these have been developed to give biaryls, but also alkyl aryls, stilbenes, and diaryl ketones (through carbonylative coupling) can be accessed.[117]

Unlike aryl sulfinates,[19] there have been fewer reports of desulfinative cross-couplings with alkyl sulfinates. Desulfinative conjugate 1,4-addition reactions using palladium-catalysis have allowed installation of alkyl groups onto aryl rings, albeit with the sulfinate partner as the aryl coupling partner (Figure 4).[118] Heck-type side-products, formed through β-hydride elimination, were frequently observed. As previously discussed,

arylsulfonyl hydrazides can undergo desulfinative cross-coupling reactions. Cheng and co-workers demonstrated a denitrogenative and desulfinative addition of arylsulfonyl hydrazides with either an aryl and alkyl nitrile coupling partner to form arylketones.[119] Although this method is used for coupling an sp^3 fragment, the sulfinate-derivative again features as the aryl component.

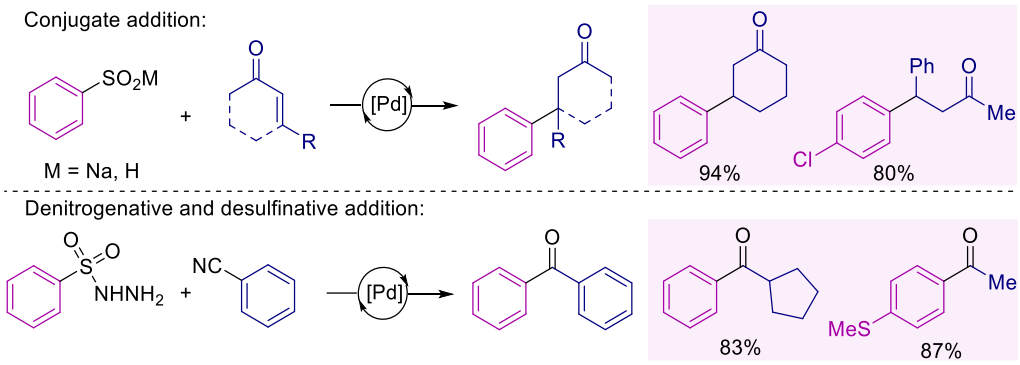


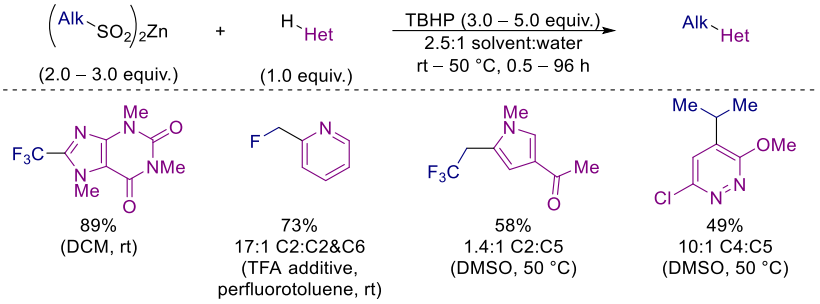
Figure 4. Formation of alkyl and aryl ketones through desulfinative processes.

Sulfonyl chlorides have also been used in desulfinative reactions. For example, to achieve C-H functionalisation of electron-rich aryl rings, albeit with poor regiocontrol. Kamigata and co-workers used readily available perfluoroalkylsulfonyl chlorides in a direct desulfinative cross-coupling reaction using ruthenium catalysis.[120] This was later extended to heteroaryls.[121] This section will now focus on desulfinative cross-couplings with alkyl sulfinates.

Radical methods

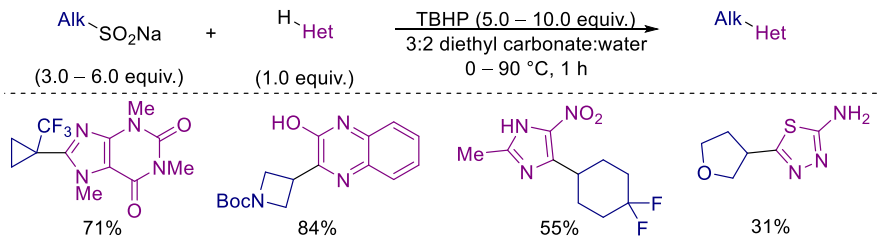
The Langlois reagent was originally demonstrated to allow desulfinative addition of the trifluoromethyl group onto aryls in the 1990s,[51b] before being more recently exploited by Baran and co-workers in the desulfinative C-H functionalisation of heterocycles through a Minisci-type radical protocol.[43] Notably, Baran's team later demonstrated that zinc alkyl sulfinate salts could form alkyl radicals under milder conditions than for the corresponding carboxylic acids, and a toolkit of these reagents was developed (Scheme 22).[55] Xanthines,

pyridines, quinoxalines, pyrimidines, pyridazines and pyrroles were successfully alkylated. Nitriles, carbonyls, halides, and even boronate groups on the aryl rings were left intact. A limitation was that the reaction conditions needed to be tailored depending on the sulfinate employed. These methods have been employed for the synthesis of natural products.[122]



Scheme 22. C-H functionalisation of (hetero)aryls with zinc alkyl sulfinate salts.

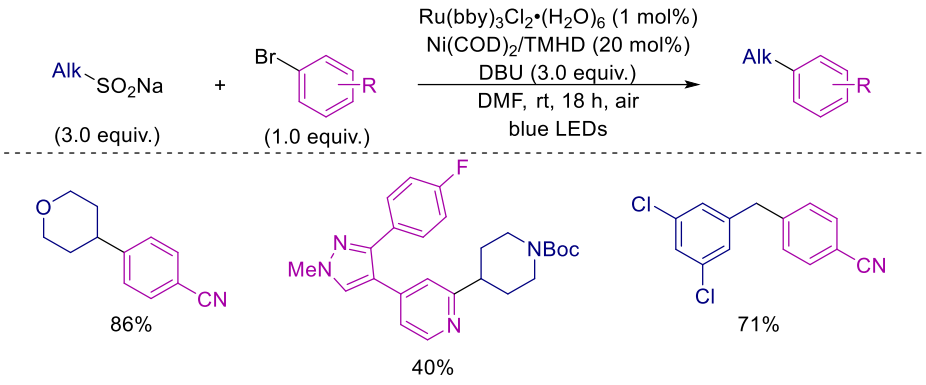
Indirect methylation was possible using PSMS.[58] First, (phenylsulfonyl)methylation of C-H bonds on heterocycles took place under mild reaction conditions. Then, a desulfonylation reaction afforded the methylated products, albeit under harsh conditions (e.g. use of SmI_2 or Raney nickel). Moreover, the development of a route to synthesise alkyl sulfinate reagents from carboxylic acids broadened the scope of alkyl groups installed through Baran's Minisci-type protocol (tetrahydro-2H-pyran, tetrahydrofuran, pyrrolidine, alkyl chains, cyclopropyl, 1,1-difluorocyclohexane, Scheme 23).[59]



Scheme 23. C-H functionalisation of (hetero)aryls with sodium alkyl sulfinate salts.

Inspired by the work of the MacMillan and Doyle groups in Ir/Ni dual catalytic decarboxylative metallaphotoredox reactions, the Baran group in desulfinative Minisci-type reactions, and Molander's photoredox coupling of alkyl BF_3K salts, Knauber and co-

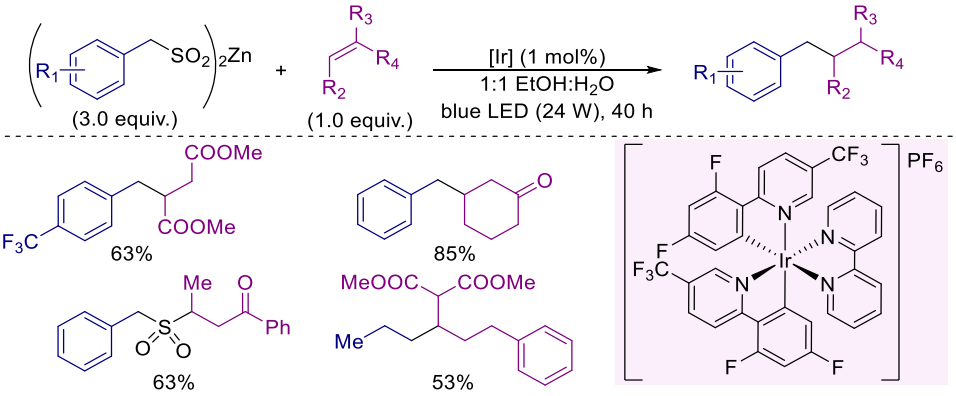
workers at Pfizer presented the first Ru/Ni dual catalytic desulfinative photoredox C(sp^2)-C(sp^3) cross-coupling of alkyl sulfinate salts and (hetero)aryl halides (Scheme 24).[123] A range of alkyl sulfinates, including medicinally relevant motifs, were successfully coupled to 4-bromobenzonitrile in low to very good yields (30 – 86%), including tetrahydropyran, tetrahydrofuran, azetidine and protected piperidine groups. A benzyl sulfinate coupled efficiently to 4-bromobenzonitrile (71%), however, poor yields were obtained when using a 2-bromopyridine fragment (2%). Scaling the reaction up from 0.25 mmol scale to 1.0 mmol scale led to a dramatic reduction in yield (86% → 1%). Scale-up of photochemical reactions is often difficult as ensuring the light can permeate through the reaction mixture is critical. Although flow chemistry protocols have been used for applying photochemical reactions on a large scale,[124] this is not practical in all cases.



Scheme 24. Desulfinative metallaphotoredox reaction to form C(sp^2)-C(sp^3) bonds.

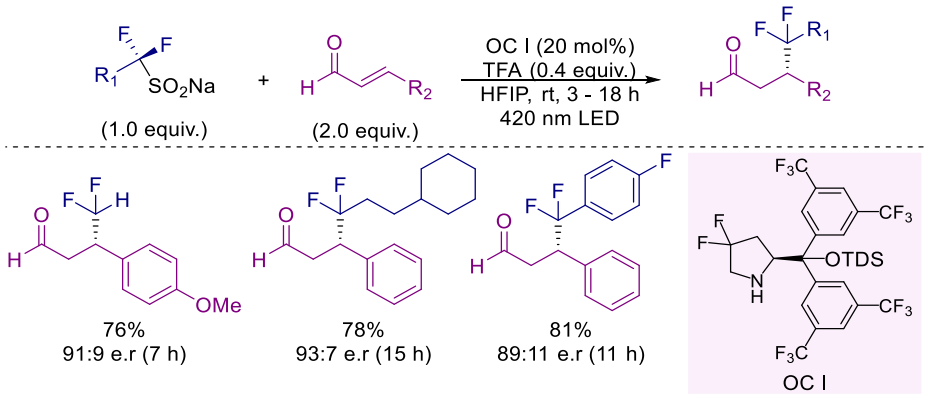
Benzyl radicals have proven difficult to trap using Michael acceptors due to their large resonance stabilisation and ready formation of homocoupled dibenzyl products.[125] Similar to the work of Wu and co-workers, which was reported around the same time,[126] Gualandi et al were able to accomplish the difficult radical benzylation of electrophilic alkenes, using zinc benzyl sulfinate salts with a photocatalyst and visible light irradiation (Scheme 25).[127] A small scope of just five benzyl sulfinates was shown, but a broader range of alkenes were explored (15 examples). Interestingly, some of the reactions did not give the desulfinative

products but instead sulfone formation occurred. The authors showed that with strongly electrophilic Michael acceptors, zinc benzyl sulfinates behaved as nucleophiles to give the corresponding sulfone,[128] without any radical formation.



Scheme 25. Benzylation of alkenes by photocatalysis.

In 2022, Alemán and co-workers described a visible-light-driven enantioselective C(sp^3)-C(sp^3) bond formation process from sulfinates (perfluoroalkyl, alkyl and benzyl) and α,β-unsaturated aldehydes (Scheme 26).[129] Comparable yields were observed for both sodium and zinc sulfinate salts (81% *vs* 82%). The authors showed that the reaction was efficient when run under sunlight (during summer, in Madrid), and also worked in a flow reactor.



Scheme 26. Enantioselective C(sp^3)-C(sp^3) bond formation.

Cross-coupling methods employing benzyl sulfinates through non-radical methods are scarce in the literature. In 2015, Doucet and co-workers stated that no example of direct desulfinative alkylations under palladium catalysis had been reported.[130] In 2012, Luo and co-workers reported a desulfinative homocoupling with oxygen as the terminal oxidant, in

boiling water.[131] The catalytic system, composed of $PdCl_2$ and Cu_2O, was able to be reused up to five times without observing reduction in yields. The report primarily focuses on aryl sulfinates, with one example employing sodium benzyl sulfinate, which gave the homocoupled dibenzyl product in moderate yield (35%) after 40 hours. Generally, reaction times were much shorter (20 – 30 hours) and yields far higher (up to 90%) for aryl sulfinates.

1.4 Project aims

As discussed within this first chapter, sulfinate salts have proven to be highly useful reagents and starting materials for the synthesis of a host of medicinally important scaffolds. However, there is still more chemical space to explore, particularly in the area of desulfinative cross-coupling reactions. Widening the scope of desulfinative cross-coupling reactions beyond aryl sulfinates, to medicinally relevant 3D scaffolds, is critical.

While there have been significant developments to afford $C(sp^2)$-$C(sp^3)$ products through reductive cross-electrophile and desulfinative photoredox reactions, often these reactions suffer from poor regioselectivity, require multi-catalytic systems, employ stoichiometric metal reductants and need special reaction set-ups (UV lamps/photoreactors) that may not be available in all laboratories. The development of simple protocols, that are efficient for a broad range of medicinally relevant motifs, is still in demand.

Hence, the focus of this thesis surrounds refining the synthesis and isolation of sulfinates, and the development of straight-forward synthetic methods to exploit sulfinates for the formation of C-C bonds between sp^2 and sp^3 fragments. We also explore the industrial application of desulfinative cross-couplings through development of safe and robust, larger-scale procedures.

Chapter 2. Development of an effective and reliable synthesis of benzyl sulfinate salts

2.1. Origin and outline of project

2.1.1 Background

Aryl and alkyl sulfinate salts are routinely used as nucleophiles in the synthesis of sulfones, sulfonamides and other sulfonyl-derivatives,[29b, 29d, 29g, 132] and are generally attractive reagents for organic synthesis.[29a, 53, 55-56, 58-59, 133] In contrast to other sulfur(VI) precursors such as highly reactive sulfonyl chlorides[134] and unstable sulfinic acids,[135] which are often generated *in situ* to avoid instability issues,[136] sulfinate salts are typically odourless, bench stable and insensitive to air or moisture.[29d] Albeit there have been some recent advances using both sulfonyl chlorides[137] and sulfinic acids[138] directly to afford sulfones and sulfonamides.

Historically, the use of sulfinate salts was limited due to the challenge of their preparation and purification. However, in recent years sulfinates have enjoyed greater commercial availability, in part due to the many procedures developed to synthesise (hetero)aryl and alkyl sulfinates. Such methods include quenching an organometallic reagent with a sulfur dioxide adduct (e.g. DABSO,[34, 41a, 139] TIMSO[18, 20]), generation of SO_2 from Na_2SO_3,[36] oxidation of thiols,[140] sulfonylation and cleavage[141] (SMOPS,[61] Rongalite,[63] BTS,[69] and Rongacyl[70]) (Figure 5). The latter method allows easy counter-ion and structural diversification, albeit with poor atom economy and requiring several synthetic steps.

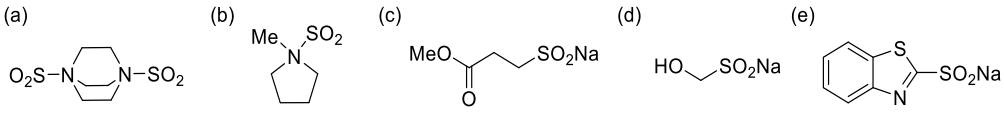


Figure 5. Molecular structures of (a) DABSO, (b) TIMSO, (c) SMOPS, (d) Rongalite® and (e) BTS.

2.1.2 Project aims

We wanted to devise a straightforward synthesis of alkyl and benzyl sulfinates. The method needed to be efficient, reliable, functional group tolerant and scalable, because these sulfinates would next be employed as starting materials in desulfinative cross-coupling processes (Figure 6). The current chapter seeks to explore the formation of benzyl sulfinate salts for use as starting materials in later chapters.

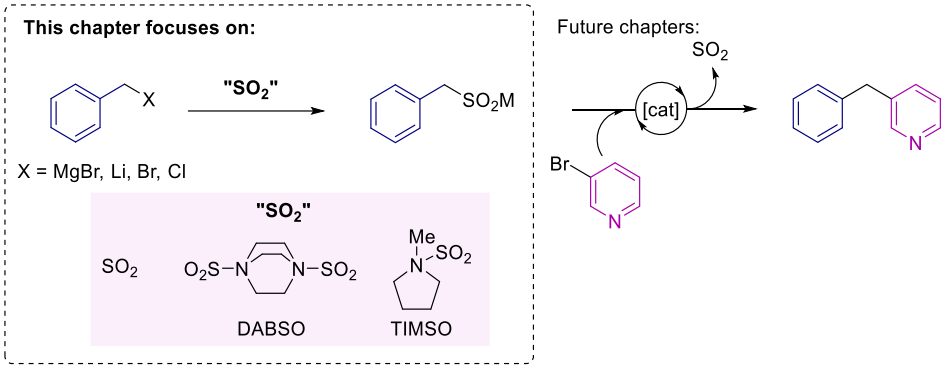


Figure 6. Project strategy for synthesising sulfinates.

2.2. Route investigations

2.2.1 Organometallic reagent use

Our starting point focussed on reacting an organometallic reagent, such as a Grignard or organolithium reagent, with a sulfur dioxide adduct to form alkyl and benzyl sulfinates. This straight-forward method proved highly efficient in our group's previous work using DABSO[34, 41a, 139] as well as by many others.[139a, 142] Although the direct reaction of an organometallic reagent with SO_2 gas has been previously used to form sulfinate salts,[136c] its high toxicity and the practical challenges of working with SO_2 gas on a small scale meant that adducts were preferable to use in its place.[143] Similarly, forming sulfinates through oxidation was undesirable due to the necessity to use often pungent and toxic thiol starting materials, as well as highly reactive oxidants.[144] While there are a selection of sulfur dioxide adducts available, for this work, we chose the *N*-methylpyrrolidine SO_2 adduct (TIMSO). In contrast to many other solid SO_2 adducts, including DABSO, TIMSO is liquid at room temperature, and so can be easily added neat into air sensitive reaction mixtures.

We initially attempted to synthesise some alkyl and benzylic sulfinates through lithium-halogen exchange followed by quenching with TIMSO (Table 2). To our surprise, we were either unable to isolate the desired sulfinate salts, due to resulting complex reaction mixtures, or low yields were obtained. In some cases lithium ethoxide was observed instead of the desired products, which could have arisen during the recrystallisation from ethanol, although this has not been documented in literature procedures. Due to the poor results, we decided to explore other routes, rather than pursuing this method further.

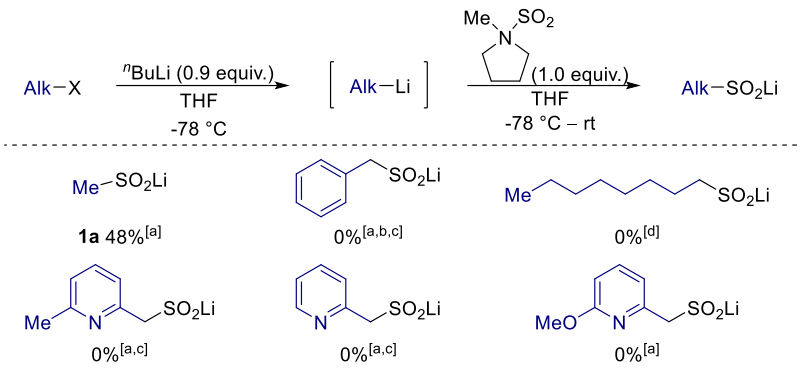
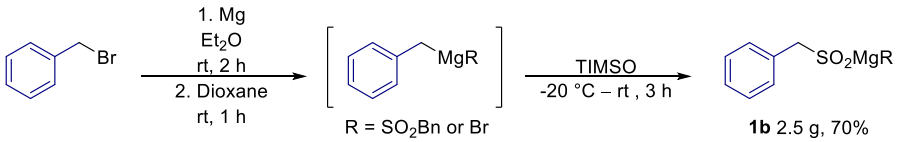


Table 2. Attempts to form sulfinates through lithium-halogen exchange.

[a] 15 mmol scale. [b] Recrystallised from ethanol. [c] ^{1}H NMR spectroscopy showed the presence of LiOEt instead of the desired product. [d] 7.5 mmol scale.

As the lithium-halogen exchange method proved ineffective, we next explored whether a similar route using Grignard reagents could be more beneficial to access these structures (Scheme 27). To form the magnesium benzyl sulfinate salt (**1b**), we prepared the corresponding Grignard reagent *in situ* and quenched with TIMSO. Pleasingly, this method yielded the desired salt in good yield; a great improvement on the lithiation method.

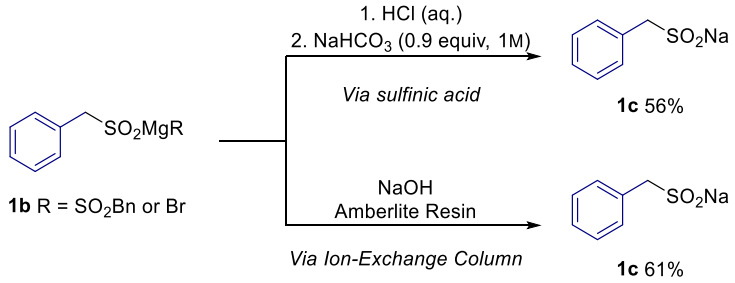


Scheme 27. Generation of the magnesium benzyl sulfinate salt.

As magnesium is a divalent cation, there was some uncertainty over whether the salt product formed was the monosulfinate salt $BnSO_2MgBr$, the disulfinate salt $(BnSO_2)_2Mg$ or a mixture of both.[145] To try to solve this problem, we attempted two methods to perform a cation swap from magnesium to sodium (Scheme 28). In the initial method, we converted the magnesium salt to the corresponding sulfinic acid by protonation with aqueous hydrochloric acid. To reduce the likelihood of sulfinic acid decomposition,[146] this was then quickly extracted with ethyl acetate. Addition of 1 M aqueous solution of sodium bicarbonate (0.94 equiv.), followed by solvent removal, afforded the desired sodium sulfinate salt (**1c**). The moderate yield achieved was likely due to decomposition of the

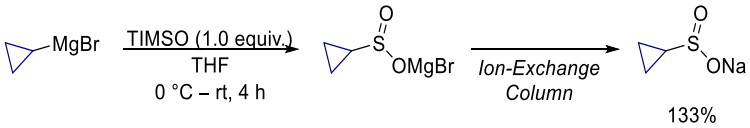
sulfinic acid, and use of ethyl acetate as an extraction solvent led to the presence of sodium acetate as an impurity in the final product.

Next, we decided to isolate the sodium sulfinate salt (**1c**) by subjecting the magnesium salt (**1b**) to an ion-exchange column. This method did give the product in a higher yield than the sulfinic acid route; however, it was rather time consuming to prepare the resin as well as run the column, it generated a lot of solvent waste and the yield was not excellent.



Scheme 28. Magnesium cation swap to sodium.

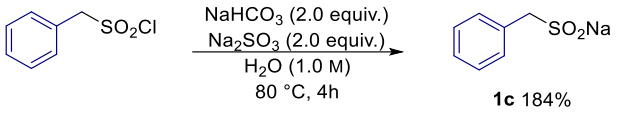
To form the cyclopropyl sulfinate, we followed the same method as for the benzyl sulfinate followed by an ion-exchange column to form the sodium salt (Scheme 29). Pleasingly, the magnesium sulfinate salt was produced in seemingly high purity as determined by ^{1}H NMR spectroscopy; however, the ion exchange column resulted in product with a mass far too high to be pure. Due to our difficulty in obtaining pure material, we purchased this particular sulfinate for use in the desulfinative cross-couplings.



Scheme 29. Unsuccessful attempts to form pure sodium cyclopropanesulfinate.

2.2.2 Sulfinate formation from sulfonyl chlorides

Instead of further pursuing the sulfinate synthesis using organolithium or Grignard reagents, we decided to look into alternative methods. Another established method to generate sulfinates, which requires no organometallic reagents, was to use sodium bicarbonate and sodium sulfite to reduce a sulfonyl chloride to the corresponding sulfinate salt.[127, 147] We attempted this procedure, and although the product (**1c**) appeared to be pure by ^{1}H NMR spectroscopy, the obtained mass was far too high for this to be the case (Scheme 30). This can be attributed to the presence of inorganic salt impurities, which were not visible by NMR spectroscopy. Attempts to separate the benzyl sulfinate salt from the inorganic salts were unsuccessful.

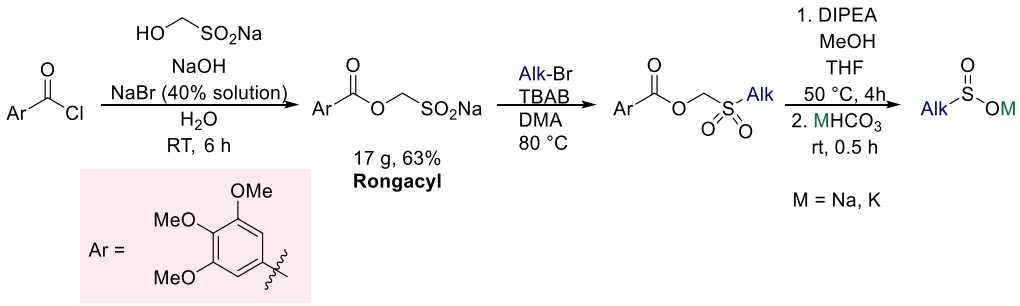


Scheme 30. Reduction of a benzyl sulfonyl chloride to a benzyl sulfinate.

Interestingly, this method is commonly used in the literature to synthesise sulfinates as starting materials for sulfone formation reactions, where often yields are not given[147-148] or quantitative yields are reported. The gaps or high yields are potentially reported not due to efficient reaction, but because they are very likely contaminated with salt impurities causing the belief that they were formed quantitatively. Or, this could be a consideration and a reason as to why often sulfinates are employed in excess.[149] Clearly, this method would not be feasible for our future aim of using the sulfinates in transition metal catalysed cross-couplings; it is important to use high quality starting materials, rather than those containing unquantifiable amounts of impurities. Moreover, the scientific community needs a method where the yield accuracy can be relied upon.

2.2.3 Rongacyl

Around the time that we were looking for an alternative method to synthesise benzyl sulfinates in high purity, our collaborators at Pfizer published a method to prepare sulfinate salts using their newly developed Rongacyl reagent (Scheme 31).[70] One key benefit of this method was that the sulfone intermediate, which was synthesised in high yield, could be purified by column chromatography. The sulfinate could then be generated in the final step, where easy diversification of the counter-ion could be achieved. This meant that there was a lower risk of inorganic contamination in the final sulfinate salt, unlike the methods previously described. Furthermore, this route would likely pose far greater functional group tolerance, due to avoidance of highly reactive organometallic reagents. With this in mind, we were able to synthesise the key Rongacyl sulfinate reagent on a large scale and in one step from the cheap and commercial sulfinate Rongalite® and an acyl chloride (either easily prepared in one-step or purchased).



Scheme 31. Synthesis of Rongacyl and subsequent conversion into alkyl sulfinate salts.

The literature conditions from Shavnya et al[70] were then applied to form compounds **2a** – **2h** (Table 3). Compounds bearing a variety of electron-withdrawing and electron-donating groups were tolerated (**2a** – **2d**), but low yields were observed for a pyridine substrate and some cyclic alkyl groups (**2e** – **2h**). It is possible that this reduced yield could have been due to the low stability of the pyridine halide starting material; hydrolysis is reported to readily occur in air and at elevated temperatures.[150] Attempts at

using freshly synthesised halide or the hydrobromide or hydrochloride salt led to low yields in all cases.

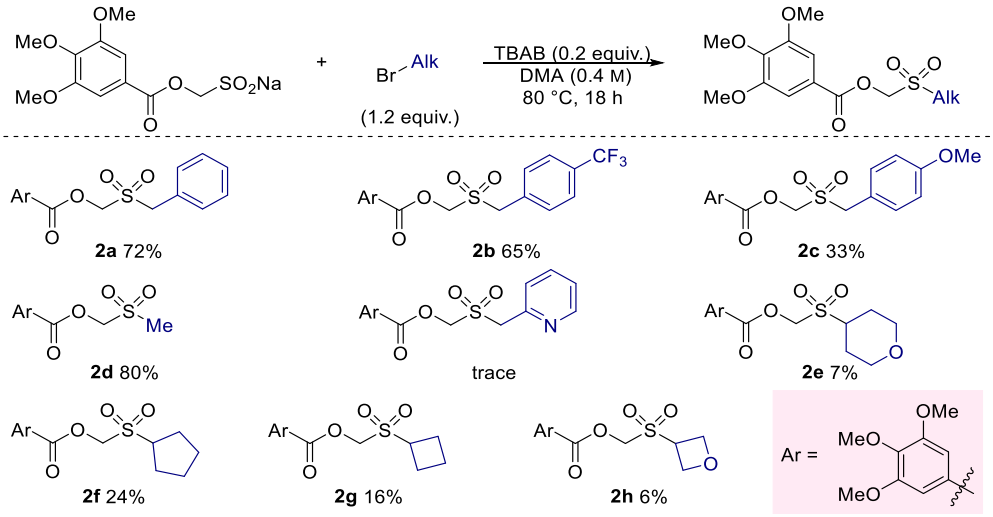


Table 3. Scope of sulfones produced from the Rongacyl sulfinate reagent.

Next, we followed the literature procedure to form the sulfinates (Table 4). As formation of the potassium sulfinate salt proceeded in low yield (**1c'**), we instead focused on forming the sodium salt (**1c**). Although benzylic sodium sulfinate salts (**1c** – **1e**) and cycloalkyl sodium sulfinate salts (**1g** and **1h**) were obtained in good yields, sodium methanesulfinate (**1f**) was obtained in a lower 31% yield. Disappointingly, cyclic ether sulfinate salts were not isolated under the reaction conditions.

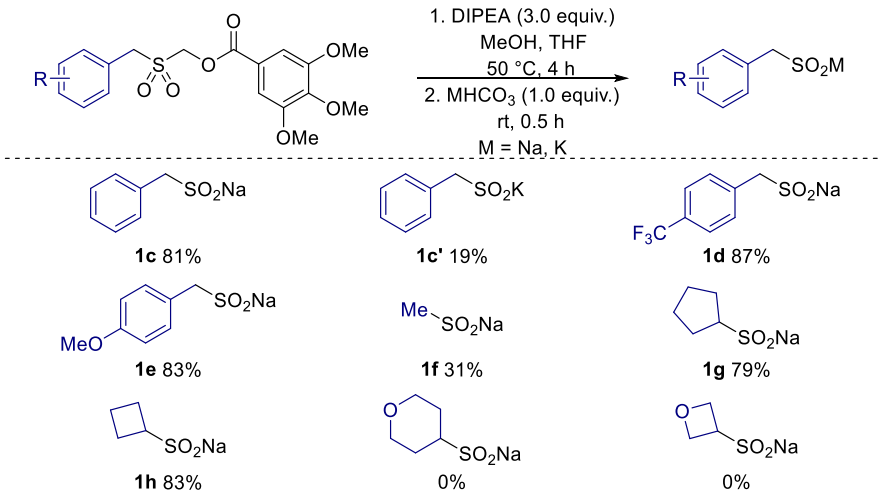


Table 4. Scope of sulfinates produced from the Rongacyl-sulfones.

While the Rongacyl method does yield the final sulfinate product with minimal inorganic impurities, there were several issues associated with this route. Firstly, generation of the key Rongacyl substrate proved to have challenges with reproducibility (Table 5). In the literature, Rongacyl was produced in 63% on a 17 g scale.[70] After an initial low yield due to use of poor quality acyl chloride (entry 1), and inexperience with the unusual reaction methodology (entry 2), we were able to replicate Pfizer's result (entry 3) and even raise it slightly (entry 4). For seemingly no apparent reason, the yields then began to decrease on subsequent syntheses (entries 5 – 6), whether performed on the same or smaller scale.

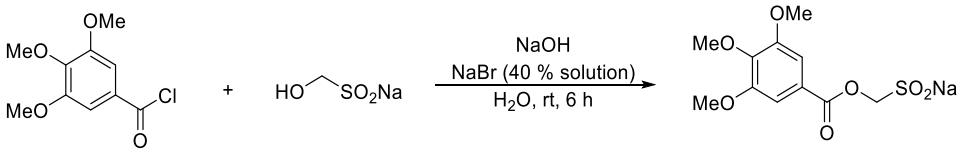


Table 5. Attempts at the preparation of the Rongacyl sulfinate reagent.

Entry[a]	Date	Isolated yield /%	Scale /mmol
1	27.02.2018	8[b]	21.7
2	05.03.2018	53	21.7
3	08.03.2018	63	86.7
4	18.07.2018	67	43.4
5	05.09.2018	30	86.7
6	09.10.2018	18	13.0

[a] New, unopened bottles of acyl chloride were used for each synthesis of Rongacyl. [b] Old bottle of acyl chloride used. After purification of the reaction, ^{1}H NMR confirmed the acyl chloride used was impure.

Secondly, synthesis of the sulfone precursor was also not always reproducible (Table 6). Again, the sulfone would sometimes be formed in good yield and sometimes in poor yield, with no clear explanation. Seemingly, the scale of the reaction did not make a significant difference (e.g. entry 2 *vs* entry 3). One possible explanation could be due to the presence of impurities in the Rongacyl reagent. Given that its synthesis involves the introduction of inorganic salts, it is feasible that there could have been varying amounts of these impurities in the different batches used to form the sulfones.

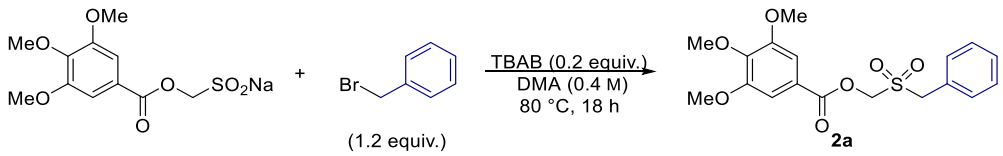


*Table 6. Representative varied yields observed for the synthesis of Rongacyl-benzyl sulfone **2a**.*

Entry	Date	Isolated yield /%	Scale /mmol
1	06.03.2018	72	4.0
2	11.04.2018	63	6.0
3	26.04.2018	68	16.6
4	05.06.2018	72	14.8
5	23.07.2018	29	3.7
6	31.08.2018	26	6.4
7	11.09.2018	36	14.8
8	15.10.2018	69	2.3

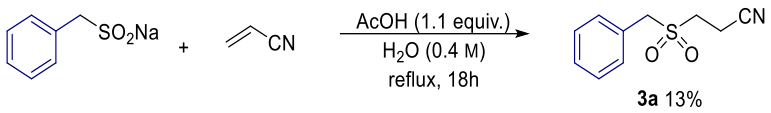
Thirdly, the overall synthetic sequence to generate the final sulfinate salt is lengthy (Scheme 31). Due to its high molecular weight, the use of Rongacyl leads to poor atom economy which is accentuated when the reactions prove to be low yielding. Given that no excellent yields were observed for sulfone or sulfinate formation, we looked again to identify an improved route to synthesise sulfinates.

2.3. Novel method and optimisation

Concurrently with this work, another member of the Willis group (Xinlan Cook) was investigating 2-pyridyl sulfones as latent sulfinate reagents, whereby the sulfinate would be released *in situ* for desulfinative cross-coupling to then occur. Akin to the Rongacyl work and inspired by the synthesis of the SMOPS reagent,[61] we wondered if we could apply this methodology to form benzyl sulfones, which we could then cleave to form the corresponding benzyl sulfinates. Here, the atom economy would see a large improvement over the Rongacyl route due to the lower molecular weight masking group.

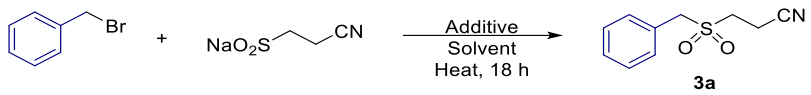
In Xinlan Cook's work, nucleophilic addition of the pyridyl or aryl sulfinate to acrylonitrile was one viable method to produce β-cyanoethyl (β-nitrile) protected pyridine sulfinates.[25]

Unfortunately, applying these conditions to form the benzylic sulfone **3a** proved to be low yielding (Scheme 32). Additionally, this would not be a viable approach to produce benzyl sulfinates due to needing to start with a sulfinate salt.



Scheme 32. Synthesis of 3-(benzylsulfonyl)propanenitrile from the corresponding sulfinate.

Still encouraged by the idea of forming the sulfinate *via* these sulfone structures, we next considered previous literature approaches using efficient S_N2 reactions with sulfinate reagents such as SMOPS.[61] The sodium 2-cyanoethane-1-sulfinate (β-nitrile sulfinate) reagent was selected for optimisation (Table 7), as we had a large quantity of the 3,3'-sulfonyldipropionitrile precursor already available within the Willis group (prepared by Dr Philip R. Murray). We knew from previous work that base can achieve the deprotection of the sulfinate group,[24] so it was unsurprising that when potassium carbonate was present as an additive the yield of the desired sulfone was fairly low (entry 1). Based upon the Rongacyl route conditions, use of tetrabutylammonium chloride (TBACl) as an additive and heating the reaction led to a considerable jump in yield (entry 2). However, we found that the reaction gave excellent yields when simply conducted at room temperature with no additives present in the reaction mixture (entries 3 – 4). A marginal benefit was observed when using dimethyl sulfoxide over dimethyl acetamide. During these experiments the reaction time was left as 18 hours for consistency; however, we later found that some sulfones could be formed in excellent yield within 2 hours if the temperature was raised to 45 °C. Interestingly, 3-(benzylsulfonyl)propanenitrile (**3a**) displays biological activity and has been shown to be an effective compound for treating inflammatory skin diseases, such as dermatitis, psoriasis, acne, or rosacea.[151]



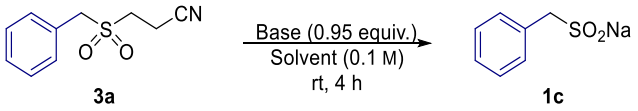
3a

Table 7. Optimisation for the synthesis of 3-(benzylsulfonyl)propanenitrile.

Entry	Additive	Solvent (0.34 M)	Temperature /°C	Isolated yield /%
1	K_2CO_3[a]	DMSO	40	20
2	TBACl[b]	DMA	75	87
3	-	DMSO	21	91
4	-	DMA	21	89

[a] 1.0 equiv. used. [b] 0.3 equiv. used.

With the β-nitrile benzyl sulfone (**3a**) in hand, several bases were tested to identify the most suitable for the β-elimination step to afford the desired benzyl sulfinate product (**1c**, Table 8). Although by HPLC and TLC the reactions appeared complete after 3 hours, ^{1}H NMR spectroscopy showed starting material remaining for entries 1 and 4. To aid the solubility of $NaHCO_3$ and Na_2CO_3 in the reaction mixture, water was used in a 1:1 ratio with methanol. However, this led to decomposition of the starting material rather than full conversion to the desired elimination sulfinate product (entries 2 and 3). In entry 5, it is likely that fresh NaOMe was made *in situ*. To ensure complete conversion of starting material, the reactions shown in entries 5 and 6 were run for 14 hours. The optimal base, both in terms of ease of use and product yield, was identified to be sodium hydroxide.



3a 1c

Table 8. Optimisation for the synthesis of sodium benzyl sulfinate.

Entry	Base	Solvent	Isolated yield /%[a]
1	NaOMe	MeOH	43
2	$NaHCO_3$	1:1 H_2O/MeOH	27
3	Na_2CO_3	1:1 H_2O/MeOH	65
4	NaOH	MeOH	75
5[b]	NaH	MeOH	91
6[b]	NaOH	MeOH	98

[a] Yields given in relation to the base as the limiting reagent. [b] Reactions were run for 14 hours.

2.4. Sulfone synthesis and scope

Other benzyl bromides were subjected to the alkylation reaction to expand the scope of β-nitrile protected benzyl sulfinates (Table 9). Pleasingly, the reaction was tolerant to benzyl halides bearing electron-donating groups (**3b**), electron-withdrawing groups (**3c**, **3d** and **3g**), and halides (**3e** and **3f**). Heteroaromatic rings were successfully incorporated (**3h** – **3m**), including a benzimidazole with a free NH (**3i**). A Boc protected benzimidazole was subjected to the S_N2 reaction conditions, however, no desired sulfone product was formed. Instead, the process led to Boc group cleavage to give the unprotected 2-(chloromethyl)-1*H*-benzo[d]imidazole. This issue was avoided by protection with a tosyl group instead, and sulfone **3j** was formed in excellent yield (92%). Secondary benzylic bromides were also tolerated, giving sulfones **3n** and **3o** in moderate to good yield.

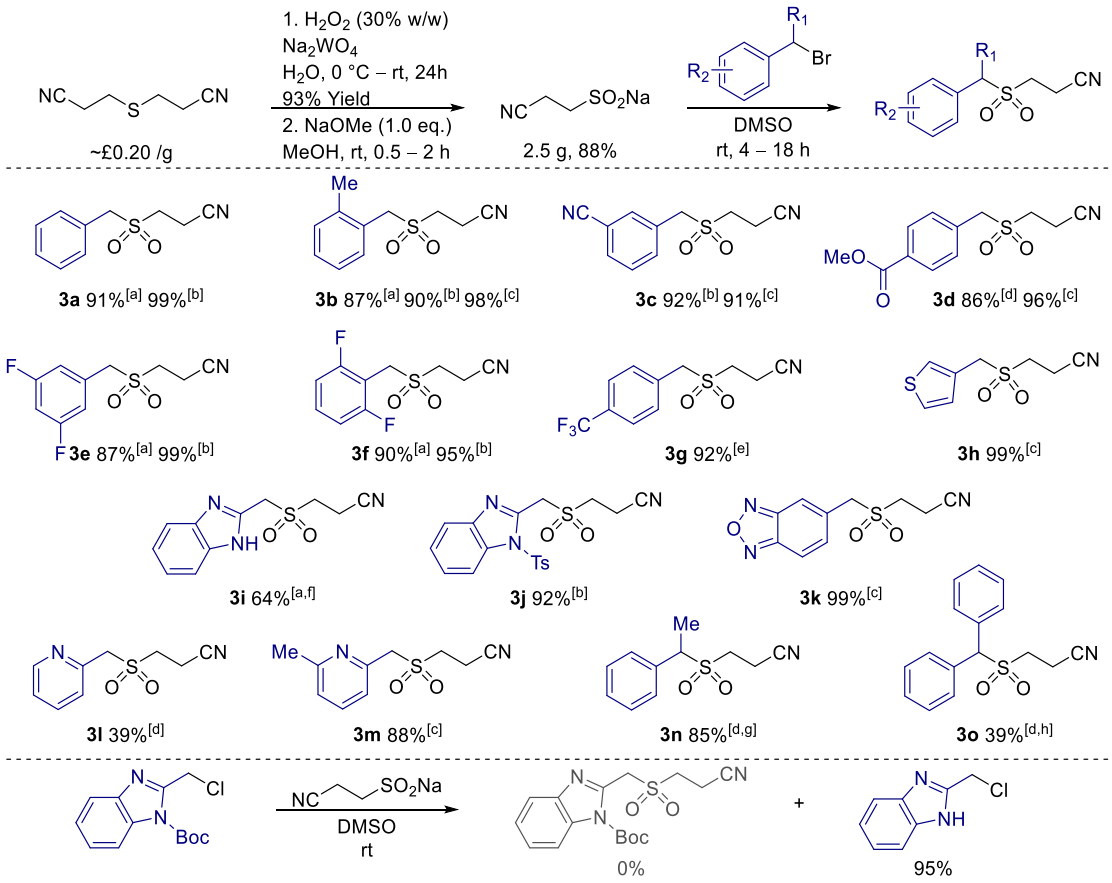


Table 9. Scope of β-nitrile benzylsulfones.

[a] 0.5 mmol scale. [b] 1.5 mmol scale. [c] 3.0 mmol scale. [d] 1.0 mmol scale. [e] 2.0 mmol scale. [f] The isolated yield does not reflect poor conversion to product as some was lost during purification due to its highly polar nature. [g] Racemic starting material used. [h] When MeOH was used instead of DMSO, the product was obtained in 3% yield.

2.5. Sulfinate synthesis and scope

Pleasingly, we were able to access benzyl sulfinates in generally good yields through applying our optimised conditions (Table 10). Both electron-deficient (**1d**, **1i**, **1j**, **1k** and **1m**) and electron-rich (**1c**, **1e** and **1l**) benzyl sulfinates were synthesised in good yields. The reaction was more efficient on a larger scale, as illustrated by the increase in yield from 29% to 74% for **1j**. Example **1k** includes an ester, which would not have been tolerated in combination with organolithium or Grignard reagents. We wondered if the method would be successful for some heterocyclic variants, which we had not been previously able to access. Pleasingly, synthesis of thiophene **1n** was successful and gave the desired product in 74% yield. Unfortunately, no sulfinates containing benzimidazole or pyridine rings were isolated. When **3j** was subjected to the reaction conditions, instead of isolation of the desired sulfinate, 2-methyl-1-tosyl-benzimidazole was isolated in 45% yield, along with unreacted starting material. If the sulfinate had been formed at all, its existence was likely short-lived as it could have undergone subsequent protodesulfination to give the methyl product (**4a**). Furthermore, it was also not possible to form the sulfinate when substituents were placed on the secondary benzylic position. For example, deprotonation of the pink coloured proton on sodium diphenylmethanesulfinate would have led to a stabilised charge, rendering the desired sulfone deprotection unlikely.

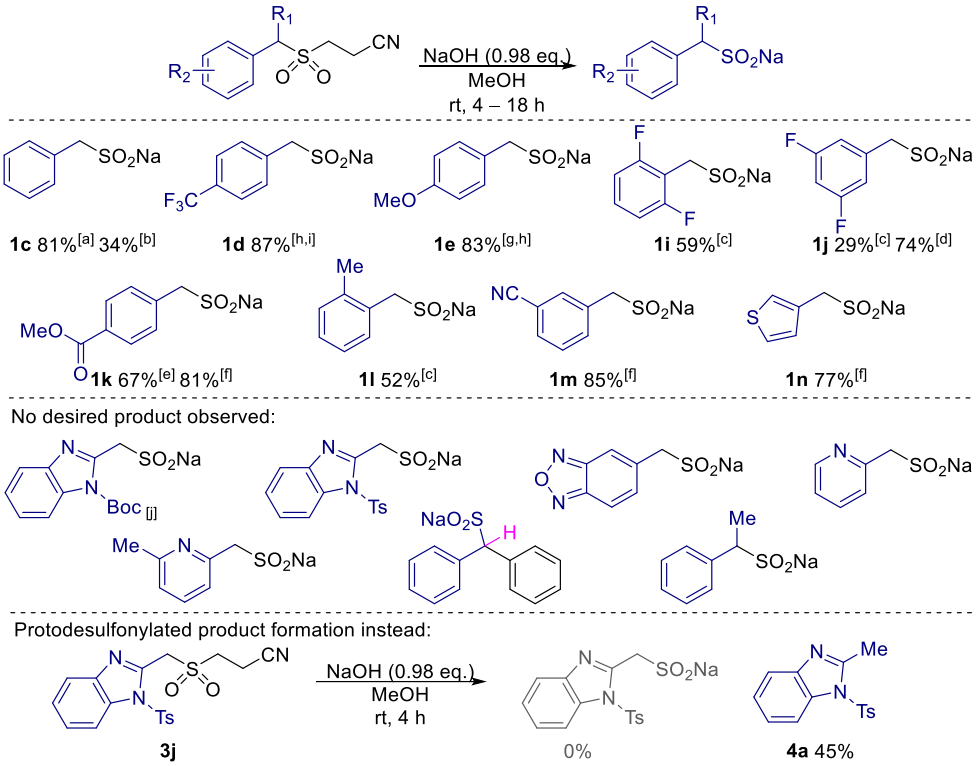


Table 10. Scope of benzyl sulfinates.

[a] 0.8 mmol scale. [b] 1.5 mmol scale, KOH used to form the potassium sulfinate salt. [c] 0.2 mmol scale. [d] 1.0 mmol scale. [e] 0.75 mmol scale. [f] 2.6 mmol scale. [g] 1.2 mmol scale. [h] From the Rongacyl method. [i] 1.6 mmol scale. [j] The sulfone starting material was synthesised by boc protection of **3i**.

2.6. Problems with sulfinate stability

In the literature, both (hetero)aryl and alkyl sulfinates are reported as highly bench stable solids.[55] We were therefore somewhat surprised when we were unable to isolate some sulfinates, initially thinking there must be a problem during purification. Thanks to discussions with our industrial collaborators at Pfizer, we realised that pyridinemethyl sulfinate is unstable, and decomposes by loss of SO_2. Furthermore, benzyl sulfinates bearing electron-withdrawing groups, or containing heteroaryl rings, were far more unstable to storage than those with electron-donating substituents. They were found to decompose readily under air at room temperature in a short period of time ranging from a matter of hours to a few days. In our hands, we also observed that other seemingly bench

stable benzyl sulfinates, such as sodium benzyl sulfinate, began to decompose within a few weeks to a month of storage under air at room temperature. These findings were not consistent with previous literature reports about the stability of sulfinate salts.[57, 152]

A way to reduce this issue was to store the sulfone precursors, and then generate the needed sulfinate salt as required. Both the sulfone precursors made through the Rongacyl and β-nitrile methods were stored on the laboratory bench without any signs of degradation (used after 1 year with no issue). When a desulfinative cross-coupling reaction was performed with (4-trifluoromethyl)benzyl sulfinate salt (**1d**) made on the previous day, high yields were achieved (95%); when this was stored for a few days under air at room temperature, the product yield was significantly reduced (20%). Storing the isolated sulfinates under nitrogen, sealed with parafilm and placed in a vacuum desiccator slowed down degradation from a few days to a couple of weeks. It is important to note that when the sulfinate had decomposed fully or began to decompose, there was no marked change in appearance; they remained as white solids with no liquid or discolouration present.

2.7. Project summary

The project began by investigating the use of organometallic reagents to synthesise sulfinate salts. However, we realised this was an ineffective way of producing sulfinates in high yields, and would lead to poor functional group tolerance in any eventual scope had we pursued this further. Other commonly used methods led to significant contamination with other inorganic salt impurities.

Next, we found that Rongacyl could be used to form sulfones and subsequently the corresponding sulfinates in another step. This method proved effective at limiting the introduction of potential inorganic impurities until the final step, and avoided highly reactive pyrophoric reagents. Unfortunately, production of the key Rongacyl sulfinate reagent and synthesis of the sulfones and sulfinates were found to be unreliable.

Use of the key β-nitrile sulfinate reagent afforded fifteen sulfones in generally very good yields (39 – 99%), with excellent tolerance of a range of different functional groups. Base was applied to eliminate the acrylonitrile group and form benzyl sulfinate salts in good to very good yields (52 – 87%). Unfortunately, many sulfinates containing heteroaryl rings were unable to be formed even through this milder route. Additionally, some sulfinates were shown to be unstable under ambient conditions. To reduce their decomposition, we were able to store these as the sulfone precursor and then convert them to the sulfinate as required.

Chapter 3. Palladium-catalysed desulfinative cross-couplings with benzyl sulfinates

3.1 Origin and outline of project

3.1.1 Background

Sulfinate salts are useful and attractive reagents in a chemist's toolbox. Desulfinative cross-couplings have been explored over the last few decades, primarily focusing on aryl sulfinates.[29c, 153] Electron-poor heterocyclic sulfinate nucleophiles were underexplored in desulfinative cross-couplings until the Willis group reported pyridine-2-sulfinates as efficient alternatives to 2-pyridyl boronic derivatives in Suzuki-Miyaura-type cross-couplings.[18] Due to the wide substrate scope in the coupling reaction as well as the straight-forward synthesis and high stability of pyridine sulfinates (as opposed to pyridine boronic acids[10, 154]), this chemistry has proven valuable for chemists seeking to generate key biaryls featuring the challenging to couple 2-pyridyl motif.[16]

We envisaged that the chemistry of heteroaryl sulfinates could be extended to tackle other challenges associated with heterocycle functionalisation. Increasing importance is being placed on incorporating more 3D character into drug molecules, because this can lead to improved binding interactions between a drug candidate and target. These interactions may not be possible with a flat aromatic ring, and so this structural change could in turn improve potency and selectivity.[73]

In this regard, diarylmethanes can be considered. These building blocks are prevalent motifs in pharmaceutically relevant molecules (Figure 7), host-guest chemistry and polymer science, plus are useful starting materials for the synthesis of triarylmethanes.[155]

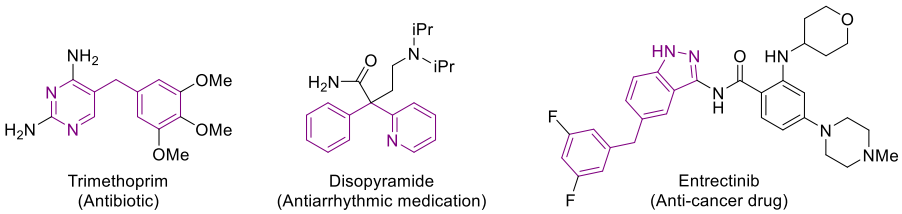


Figure 7. Examples of pharmaceutically relevant compounds containing the diarylmethane moiety.

Understandably, due to their prevalence, the synthesis of diarylmethanes has become a popular research area over the past two decades.[156] However, as mentioned in the introduction (Chapter 1), traditional approaches (e.g. Friedel-Crafts arylation[84-85, 87]) may suffer from over-arylation and are often not amenable to complex functionality, due to employing organometallic reagents. Contemporary methods include acid[13b] or base-promoted benzylation,[86] radical-radical cross-coupling reactions,[81, 91] and C-H activation approaches,[157] but often feature poor site-selectivity. Suzuki-Miyaura type cross-couplings are commonly employed, but often these methods feature narrow scopes due to use of unstable boronate reagents.[78]

3.1.2 Project aims

Given the success of our group's C(sp^2)-C(sp^2) desulfinative cross-coupling work, we sought to extend this methodology to C(sp^2)-C(sp^3) couplings, utilising palladium or nickel catalysis to solve another key synthetic issue. We aimed our investigations towards incorporating benzyl groups before approaching trickier alkyl substrates; alkyl sulfinates had proven to be more difficult to synthesise and isolate (Chapter 2). Although a method to cross-couple diverse alkyl sulfinates would be useful, a reliable method specifically using benzyl sulfinate salts as coupling partners to form di(hetero)arylmethanes would remain valuable. Hence, the current chapter seeks to explore the formation of di(hetero)arylmethanes through desulfinative C(sp^2)-C(sp^3) cross-coupling methodology (Figure 8).

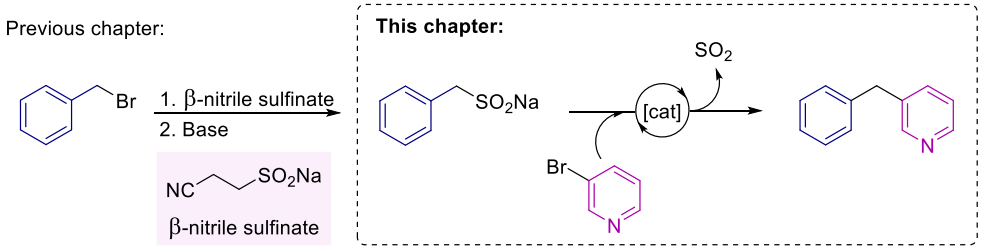
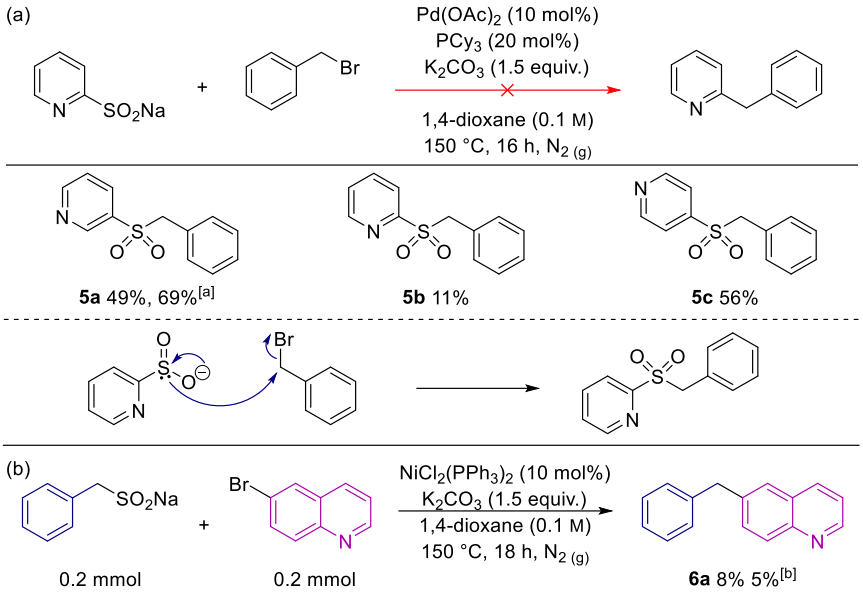


Figure 8. Project strategy for C(sp^2)-C(sp^3) desulfinative cross-couplings.

3.2 Initial investigations

A sensible starting point, directly following on from the previous Willis group work, was to subject pyridine sulfinates and benzyl halides to the desulfinative cross-coupling conditions, to afford di(hetero)arylmethanes (Scheme 33a). Unlike the desulfinative work of Deng and co-workers,[158] unfortunately we produced solely sulfone products (**5a**, **5b** and **5c**). Here, the reactions clearly proceed through an S_N2 mechanism to form the sulfones, rather than the desired desulfinative cross-coupling. The difference between the success of Deng and co-workers and our results, was likely due to the relatively slow release of SO_2 for pyridyl sulfinates compared to aryl sulfinates;[159] when there is a S_N2 background reaction, the desulfinative process is out competed. That being said, benzyl halides are known to react at room temperature with aryl sulfinates to form sulfones.[160] When no catalyst was employed, the yield increased, signalling that no palladium was necessary for sulfone formation.

Since a strategy employing (hetero)aryl sulfinates with benzyl electrophiles to undergo desulfinative cross-coupling was unsuccessful, we next looked at employing benzyl sulfinates as coupling partners (Scheme 33b). As nickel catalysts are often cheaper[161] than palladium catalysts, we decided to start by exploring whether a nickel precatalyst could be viable. $NiCl_2(PPh_3)_2$ afforded the desired product (**6a**) in low yield, and we found that the product could still be formed under air. This provided an initial hit to build upon.



Scheme 33. Formation of sulfones rather than the desired desulfinative product and an initial hit with Ni-catalysis.

[a] No $Pd(OAc)_2$ or PCy_3 used. [b] Conducted under air.

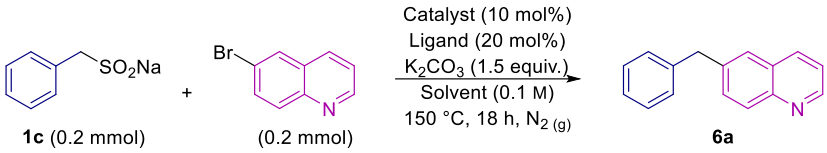
3.3 Reaction optimisation

3.3.1 Catalyst evaluation

With a reliable synthesis of benzyl sulfinates in hand (Chapter 2), we performed an initial catalyst evaluation with 6-bromoquinoline and sodium benzyl sulfinate (**1c**) as the coupling partners (Table 11). When the precatalyst was swapped from our initial hit (Scheme 33), to contain the more electron-rich tricyclohexylphosphine,[162] over triphenylphosphine, only trace product was observed (entry 1). No benefit was observed with a bidentate ligand replacement (entry 2). Pleasingly, $NiBr_2$·diglyme and the somewhat less commonly used bathophenanthroline ligand[163] provided 6-benzylquinoline in 32% yield (entry 3). The ligand was then switched to triphenylphosphine, however, only trace product was observed (entry 4). Switching to a pre-catalyst, [(TMEDA)Ni(*o*-tolyl)Cl],[164] did not offer any improvement (entry 5).

The nickel-catalysed reactions all led to complex reaction mixtures, and so we decided to investigate palladium-based systems. We were inspired by the work of Luo and co-workers,[131] who successfully formed biaryls through a ligand-free, palladium catalysed desulfinative homocoupling, conducted in water and with a copper additive. We wondered if their system could be successful for our diarylmethane synthesis; unfortunately, no product was observed (entry 6). We alternatively generated the homocoupled product of two benzyl sulfinate molecules, 1,2-diphenylethane, in 19% yield, and the 3-bromoquinoline starting material was recovered in 56% yield. Use of a 1:1 ratio of water to 1,4-dioxane did lead to some product formation, albeit in low yield (entry 7), with homocoupling observed again. We were excited about this result, given that the reaction was conducted at 100 °C. The copper additive proved essential; removal led to trace product formation, observed by LRMS (entry 8). As we had seen some success employing bathophenanthroline with a nickel catalyst, we wondered if this would work with palladium(II) chloride, but only trace amounts of product were observed by LRMS (entry 9). The same was seen when we switched to palladium(II) acetate (entry 10).

While we could have further investigated nickel options, at this point, we decided to return to the catalytic systems our group had previous success with for $C(sp^2)$-$C(sp^2)$ desulfinative cross-couplings.[18, 20] Pleasingly, this gave promising product yield; essentially no difference in yield was observed when PCy_3 was swapped to $P(^tBu)_2Me{\cdot}HBF_4$ (entries 11 – 12). As palladium(II) chloride gave a slightly lower yield (entry 13), palladium(II) acetate was selected and this became our starting point for further optimisation.



1c (0.2 mmol) (0.2 mmol) **6a**

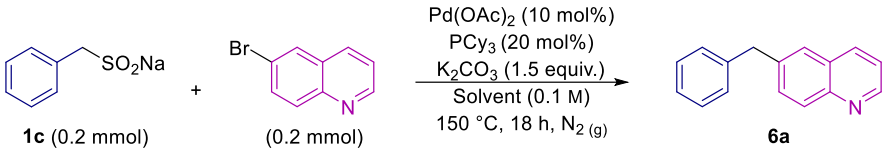
Table 11. Preliminary catalytic system evaluation.

Entry	Catalyst	Ligand	Solvent	Isolated yield /%
1	$NiCl_2(PCy_3)_2$	-	1,4-Dioxane	Trace
2	$NiCl_2$(1,3-dppp)	-	1,4-Dioxane	Trace
3[a]	$NiBr_2$·diglyme	BPhen	DMSO	32
4	$NiBr_2$·diglyme	PPh_3	DMSO	Trace
5	(TMEDA)Ni(*o*-tolyl)Cl	PCy_3	1,4-Dioxane	0
6[b][c]	$PdCl_2$	-	H_2O	0
7[b][c]	$PdCl_2$	-	1:1 H_2O/1,4-Dioxane	24
8[b][d]	$PdCl_2$	-	1:1 H_2O/1,4-Dioxane	Trace
9[a]	$PdCl_2$	BPhen	1,4-Dioxane	Trace
10[a]	$Pd(OAc)_2$	BPhen	1,4-Dioxane	Trace
11	$Pd(OAc)_2$	PCy_3	1,4-Dioxane	69
12	$Pd(OAc)_2$	$P(^tBu)_2Me{\cdot}HBF_4$	1,4-Dioxane	70
13	$PdCl_2$	PCy_3	1,4-Dioxane	62

[a] Ligand (10 mol%). [b] An oxygen atmosphere and 100 °C. [c] Cu_2O additive instead of K_2CO_3. [d] No additive or base used.

3.3.2 Solvent selection

With palladium(II) acetate identified as the optimal catalyst, and two ligands showing promise, it was at this point that we wanted to examine whether altering the solvent could improve the yield; we focused on a range of high boiling point options. There appeared to be very little difference in yield for the polar aprotic solvents (entries 1 – 4), with them all performing well. In contrast, the non-polar solvents tested yielded no product (entries 5 – 6). Although the reaction mixtures were heterogeneous for all at room temperature, bar the reaction with dimethyl sulfoxide, it is likely that there would be some beneficial solubility assistance from the polar solvents compared to the non-polar at the elevated reaction temperatures. Although the amide type solvents gave good yields (entries 3 – 4), more complex HPLC profiles were observed. From these results, 1,4-dioxane and dimethyl sulfoxide were found to be optimal.



1c (0.2 mmol) (0.2 mmol) **6a**

Table 12. Solvent screen.

Entry	Solvent	HPLC yield /%[a]
1	1,4-Dioxane	71 (69)
2	DMSO	73 (69)
3	DMAc	69
4	DMF	75
5	Toluene	0
6	Anisole	0

[a] Isolated yields given in brackets.

3.3.3 Ligand screen

Because we had identified several good solvent options, we selected 1,4-dioxane due its relative ease of removal post-reaction for our ligand optimisation. As seen before, PCy_3 performed well (entry 1) but not as efficiently as $P(^tBu)_2Me{\cdot}HBF_4$ (entry 2). These findings and that PPh_3 performed poorly (entry 3), demonstrated that more electron-rich ligands afforded more product. Although an even greater electron-donor, it was likely that $P(^tBu)_3{\cdot}HBF_4$ was too sterically hindered,[165] resulting in a detrimental impact on yield (entry 4). It was interesting that XantPhos produced the desired product, albeit in very low quantity (entry 5), as this ligand has been shown to promote sulfone products rather than undergo desulfinative coupling.[139d] The more electron rich *p*-OMe-Dppe ligand gave a marginal increase compared to Dppe (entry 6 *vs* 7), however, none of the bidentate ligands tested came close to the yield from $P(^tBu)_2Me{\cdot}HBF_4$. When the temperature was lowered from 150 °C to 120 °C for the top two performing ligands (entries 1 – 2), we found that $P(^tBu)_2Me{\cdot}HBF_4$ tolerated the change (entry 9), whereas the reaction with PCy_3 saw a large reduction in yield (entry 8).

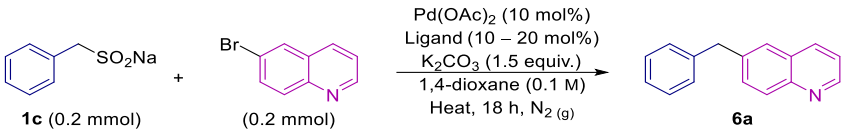


Table 13. Comparison of phosphine ligands for the synthesis of 6-benzylquinoline.

Entry	Ligand	Temperature /°C	HPLC yield /%
1	PCy_3	150	71
2	$P(^tBu)_2Me{\cdot}HBF_4$	150	82
3	PPh_3	150	21
4	$P(^tBu)_3{\cdot}HBF_4$	150	7
5	XantPhos	150	12
6	Dppe	150	33
7	*p*-OMe-Dppe	150	35
8	PCy_3	120	49
9	$P(^tBu)_2Me{\cdot}HBF_4$	120	76

3.3.4 Optimisation of a more challenging substrate

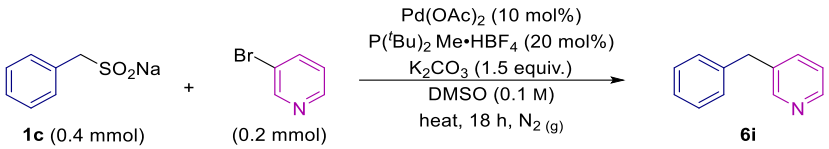
Before commencing a full scope, we wanted to first determine if there were any difficulties coupling a more challenging substrate than 6-bromoquinoline. Hence, we turned our attention to optimise for 3-bromopyridine, where the nitrogen atom on the heteroaryl halide was more likely to interfere with productive palladium coordination (Table 14). Unfortunately, HPLC yields were unobtainable for this substrate system.

For this substrate, it quickly became obvious that 1,4-dioxane would not be sufficient (entry 1). Altering the solvent to DMSO immediately doubled the yield, despite a temperature reduction of 30 °C (entry 2). Next, increasing the equivalents of sulfinate to 2.0 raised the yield (entry 3) and to 3.0 gave excellent yield of product (entry 4). Because 3.0 equivalents of a non-commercial starting material would lower the utility of the process, we tried other ways to increase the yield. Interestingly, increasing the equivalents of base had a devastating impact on yield (entry 5).

Next, we tried some ligands that we had not attempted when screening against the 6-bromoquinoline coupling partner. Our group had seen some recent success when using CataCXium A for desulfinative cross-coupling to form biaryls,[25] however, low yields were achieved for the benzylic system (entry 6). Tweaking our optimal $P(^tBu)_2Me{\cdot}HBF_4$ ligand, by increasing the alkyl chain to ethyl (entry 7) or methyl replacement with a cyclohexyl group (entry 8) led to poor yields in both cases; likely the steric bulk was limited to a methyl. A palladium precatalyst featuring the bidentate dcpe ligand, with a similar cone angle to PCy_3, provided product in moderate yield (entry 9). A structurally similar ligand, dcpp, with a slight increase in the bridging alkyl chain, improved the yield (entry 10), however, still lower yields were observed than with $P(^tBu)_2Me{\cdot}HBF_4$. The only ligand to provide a similar yield was PCy_2Et (entry 11), however, due to it being a pyrophoric liquid, it was easier to continue use of the crystalline solid, and less hazardous, $P(^tBu)_2Me{\cdot}HBF_4$.

As we found no suitable alternative ligand, we relooked at optimising the reaction conditions of entry 3. The simple change of running the reaction at higher concentration meant better reactivity, as well as easier work-up procedures, and gave the product in excellent yield (entry 12). Sulfolane has emerged as an attractive alternative to other more common dipolar aprotic solvents.[166] Conducting the reaction in sulfolane provided good product yield (entry 13), although complete solvent removal proved to be non-trivial. Returning to DMSO, we found that raising the reaction temperature to 150 °C gave no further improvement in yield (entry 14). Conversely, when the temperature was lowered to 110 °C (entry 15), we still achieved excellent yield (entry 12). Lowering further to 100 °C saw a dramatic reduction in yield (entry 16). Furthermore, altering the base to caesium carbonate surprisingly saw a large reduction in yield (entry 17), given that we have seen previous success with this base.[24] Alternatives to carbonate bases were not explored, as

these were found to be crucial for desulfinative cross-coupling.[159] Interestingly, when degassed water was added, there was very little reduction in yield (entry 18), however, unsurprisingly for a palladium catalysed process, the presence of air considerably reduced the yield (entry 19).



1c (0.4 mmol) (0.2 mmol) **6i**

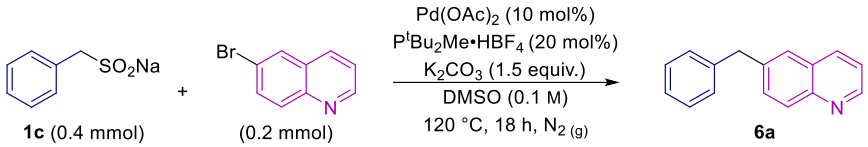
Table 14. Optimisation for the synthesis of 3-benzyl pyridine.

Entry	Deviation from scheme	Temperature /°C	Isolated yield /%
1	Sodium benzyl sulfinate (1.0 equiv.), 1,4-dioxane (0.1 M)	150	28
2	Sodium benzyl sulfinate (1.0 equiv.)	120	63
3	none	120	70
4	Sodium benzyl sulfinate (3.0 equiv.)	120	89
5	K_2CO_3 (2.0 equiv.)	120	20
6	CataCXium A (20 mol%)	120	26
7	$P(^tBu)_2Et$ (20 mol%)	120	6
8	$P(^tBu)_2Cy$ (20 mol%)	120	4
9	(dcpe)Pd(II)Cl (10 mol%), no $Pd(OAc)_2$	120	32
10	dcpp.HBF_4 (10 mol%)	120	45
11	PCy_2Et (20 mol%)	120	89
12	DMSO (0.2 M)	120	99
13	Sulfolane (0.2 M)	120	75
14	DMSO (0.2 M)	150	91
15	DMSO (0.2 M)	110	99
16	DMSO (0.2 M)	100	20
17	Cs_2CO_3 used instead of K_2CO_3	120	31
18	H_2O added (1.0 equiv., degassed)	120	93
19	Reaction performed under air	120	54

3.3.5 Control Reactions

With optimal conditions in hand, we wanted to justify that all components were necessary for efficient reaction (Table 15). We applied our optimal conditions from coupling 3-bromopyridine to the reaction of benzyl sulfinate (**1c**) with 6-bromoquinoline which produced 6-benzyl quinoline (**6a**) in quantitative yield (entry 1). While there was a small

amount of product produced when no base was used, there was clearly a detrimental impact (entry 2). Similarly, when we performed the coupling with 3-bromopyridine in the absence of base, no desired product (**6a**) was formed. Instead, we produced the benzyl sulfinate homocoupled product, 1,2-diphenylethane (**S8**) in low yield (15%). The palladium and ligand catalytic system was essential for any product conversion (entries 3 – 4). For these control reactions, it is worth noting that the sodium benzyl sulfinate was prepared the day before use and the base was freshly dried. During optimisation, whenever there was a lower yield than expected for any given result, a sample of the benzyl sulfinate used was analysed by NMR to determine if it had begun to decompose. Often this was the case, and numerous experiments were repeated with fresh batches of sulfinate. Alike to the sulfinate, we would see some reduction in yield if the base had not been recently dried. Although this was less rapid than benzyl sulfinate decomposition.



1c (0.4 mmol) + (0.2 mmol) **6a**

Table 15. Control experiments.

Entry	$Pd(OAc)_2$	$P^tBu_2Me.HBF_4$	K_2CO_3	HPLC yield /%
1	Yes	Yes	Yes	99
2	Yes	Yes	-	6
3	-	-	Yes	0
4	-	-	-	0

3.3.6 Alternative counter-ions for the benzyl sulfinate salt

While the sodium salt provided efficient couplings, it is worth mentioning that alternative cations were investigated for the reaction with 3-bromoquinoline (Table 16). When the benzyl sulfinate was synthesised through the Pfizer Rongacyl method,[70] instead of performing the counter-ion swap step, the sequence was halted at the generation of the

benzyl sulfinate DIPEA salt intermediate and isolated. We saw reduced yield for this substrate (entry 2) as compared to the sodium sulfinate salt (69% yield under the same reaction conditions). Sulfinate synthesis through quenching a Grignard reagent with a sulfur dioxide adduct eluded to the magnesium bromide benzyl sulfinate salt (entry 3). Again, reduced yield was observed in comparison to the synthesis of 3-benzylquinoline from the sodium salt, under the same reaction conditions (entry 1). This could have been in part due to not knowing whether the amount of sulfinate employed was indeed 2.0 equivalents, since magnesium is divalent. The sulfinate species could have existed as $BnSO_2MgBr$, $(BnSO_2)_2Mg$ or as a mixture of both in an unknown ratio. Lithium benzyl sulfinate prepared through a similar method to the magnesium salt, but from a benzyl lithium reagent, gave a comparable yield to that of sodium (entry 4). Although we expect ion-exchange occurs during the cross-coupling reaction between sodium and the potassium of the base,[159] we observed faster decomposition of the isolated potassium sulfinate compared to the isolated sodium sulfinate (1 week *vs* approximately 2 weeks when stored in a vacuum desiccator). Perhaps under the reaction conditions, with elevated temperature, the potassium salt deteriorates more rapidly to give a lower yield (entry 5).



Table 16. Alternative cations to sodium.

Entry	M	Ligand	Solvent	Temperature /°C	Isolated yield /%
1	Na	$P(^tBu)_2Me{\cdot}HBF_4$	DMSO	120	87
2	H·DIPEA	PCy_3	1,4-dioxane	150	33
3	MgBr	$P(^tBu)_2Me{\cdot}HBF_4$	DMSO	120	44
4	Li	$P(^tBu)_2Me{\cdot}HBF_4$	DMSO	120	80
5	K	$P(^tBu)_2Me{\cdot}HBF_4$	DMSO	120	77

3.4 Substrate scope

3.4.1 Successful examples

With conditions in hand for efficient cross-coupling to afford di(hetero)arylmethanes, we next explored the scope of the reaction (Table 17). No difference in yield was observed between benzyl sulfinates bearing electron-donating or electron-withdrawing groups on the aromatic ring when coupled with quinolines (**6c**, **6d**, **6e**, **6f**, **6h**). When investigating bromo *vs* chloro selectivity, we found, unsurprisingly, preferential reactivity for the bromo to give **6g** in low yield. The protodechlorinated side-product (with benzylation at the bromo-site) was also observed (6%), and the bis-benzylated quinoline was given as the major product (**S7**, 57%). We did not observe benzylation at the chloro-site with the bromo intact.

When coupling to 3-bromopyridine, unfortunately, we saw reduction in yield for electron-withdrawing groups (**6j**) compared to electron-donating groups (**6k**), unlike for the quinolines. Acidic protons (**6l**), variation in electronics (**6m**, **6n**) and *ortho*-substituents (**6o**) were tolerated for the reaction with 3-bromopyridines. In the reaction to form **6p**, the heteroaryl halide starting material was reclaimed in 7% yield and the protodesulfinated starting material, methyl 4-methylbenzoate, was obtained in 34% yield. This low product yield, and the isolation of side-products, demonstrates the instability of the methyl ester sulfinate salt under the reaction conditions. This was reiterated by the excellent yield of **6q**, where a more stable benzyl sulfinate salt was applied. Benzylation of 2-bromo and 4-bromo pyridines has proven more difficult (**6r**, **6u**) than the 3-pyridines. Interestingly, 2-bromopyridine coupled in low yield (18%), but moderate improvement was observed with 2-chloropyridine (32%) to generate **6r**. When the ring was made more electron-rich,

excellent yield was observed (**6s**). When the pyridine halide coupling partner had one heteroaryl chloride and one benzylic chloride available to react, we observed desulfinative cross-coupling at the sp^2 site and sulfone formation at the sp^3 site to give **6t** in moderate yield. This finding demonstrated that C(sp^3)-C(sp^3) desulfinative cross-coupling was not possible under these reaction conditions. Initially we thought the reaction was not tolerated by pyrimidines (**6v**), however, removal of a methoxy group, that may have posed steric hindrance, gave a cross-coupled pyrimidine in excellent yield (**6w**). The scope was expanded to other important heteroaromatic classes, including a quinoxaline (**6x**), azaindole (**6y**), imidazo[1,2-α]pyridine (**6z**), and thiazole (**6aa**) with moderate to excellent yields achieved. Lower yields were observed for 2-benzylquinoxaline (**6x**) when 2-chlorobenzylquinoxaline (40%) was used over the corresponding bromide (51%). The coupling with 4-bromo-3,5-dimethylisoxazole appeared to have gone to completion by TLC, however the product was isolated in very poor yield (**6ab**, 11%).

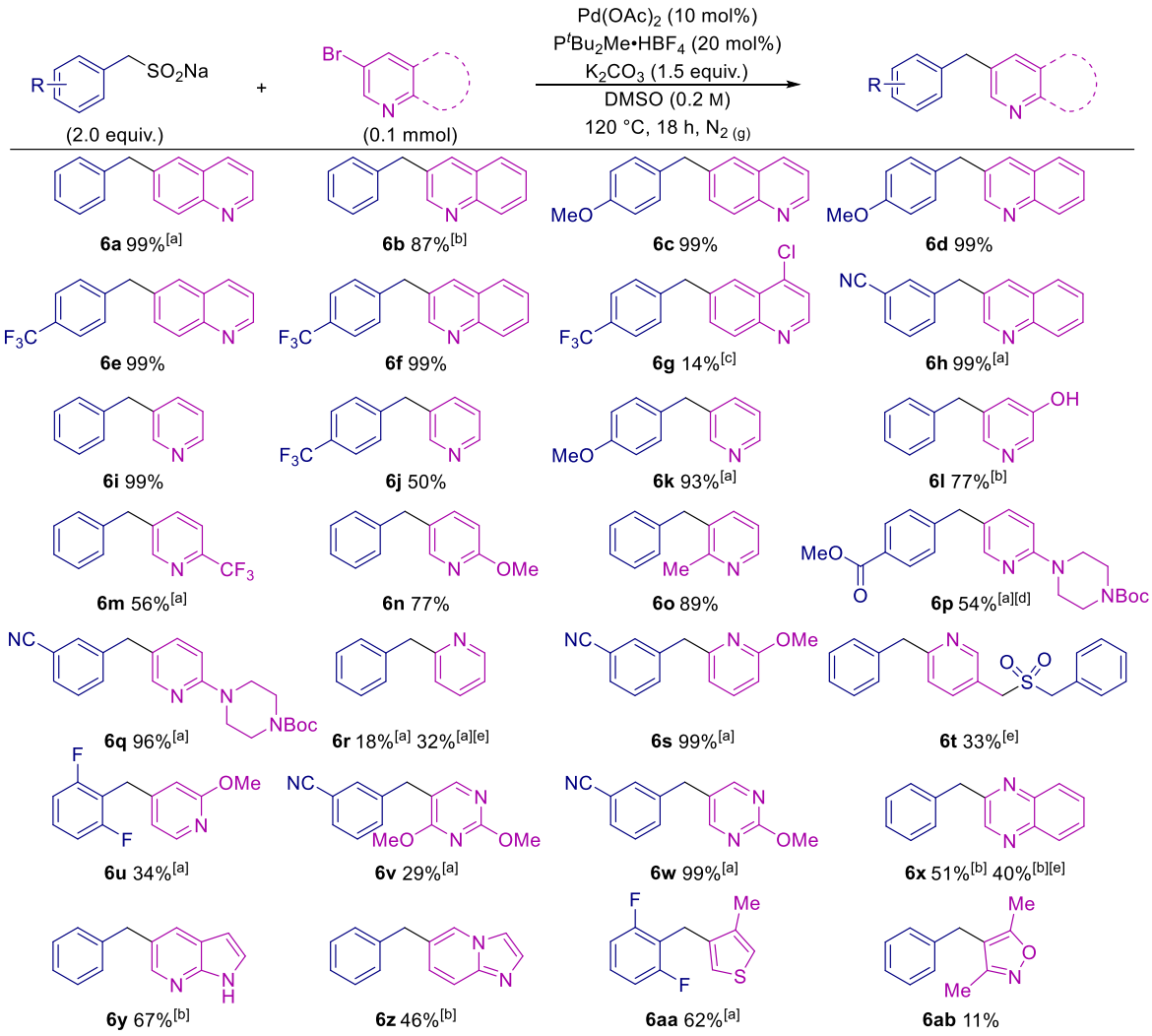
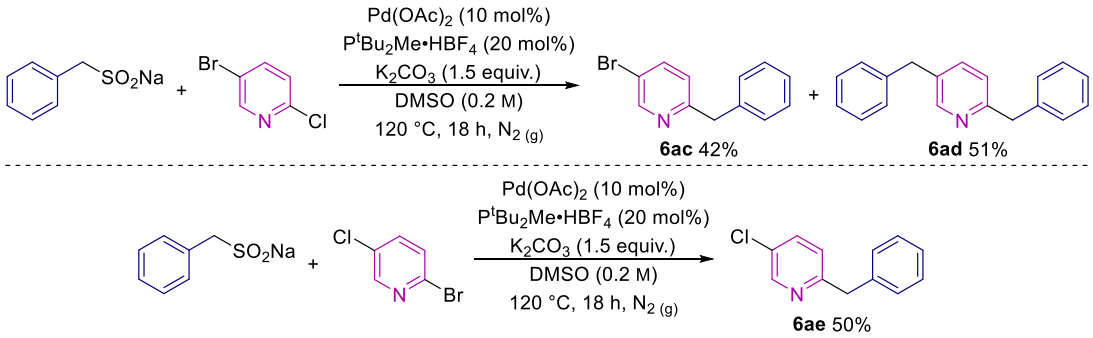


Table 17. Scope for the desulfinative cross-coupling.

[a] 0.2 mmol scale. [b] 0.15 mmol scale. [c] The bis-benzylated product was given in 57% yield. [d] Methyl 4-methylbenzoate was obtained in 34% yield as a by-product and 7% (hetero)aryl halide starting material remained. [e] X = Cl.

3.4.2 Preferential reactivity

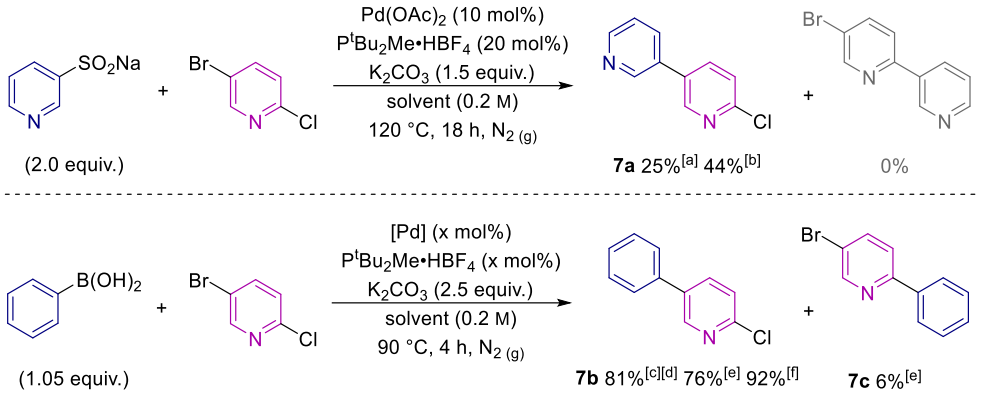
We observed some reaction selectivity when halogens were present on both the 2 and 5 positions of the pyridine coupling partner (Scheme 34). Interestingly, we observed preferential coupling of the 2-position over the 5-position to give **6ac**. The disubstituted product (**6ad**) was also isolated in good yield, demonstrating that **6ac** would have been formed first with subsequent addition of the benzyl group at the 5-position. This was interesting, because during the scope, generally 3-bromopyridines coupled in far superior yields than 2-halopyridines (e.g. **6i** vs **6r**). We found that this selectivity was due to the position rather than the halide choice, as benzylation occurred at the more activated 2-position (**6ae**) when 2-bromo-5-chloropyridine was used instead of 2-chloro-5-bromopyridine.



Scheme 34. Selective cross-coupling at the pyridine 2-position.

Next, we wanted to investigate whether the same selectivity was observed for cross-coupling reactions with (hetero)aryl sulfinates. Interestingly, we found that there was a difference. When the same pyridine halide reagents were treated with sodium pyridine-3-sulfinate, alternatively, cross-coupling occurred selectively at the 5-position (**7a**, Scheme 35). The selectivity did not change when 1,4-dioxane or DMSO were used, illustrating that the selectivity was not simply due to solvent effects but rather the innate reactivity of the different sulfinate reagents. Traditional Suzuki-Miyaura cross-coupling

conditions[167] were applied to the 2-chloro-5-bromo pyridine and phenyl boronic acid giving the same selectivity as before (**7b**). The conditions were varied to see if the selectivity would switch; in all but one case, 0% of **7c** was isolated.



Scheme 35. Selective C(sp^2)-C(sp^2) cross couplings at the pyridine 5-position.

[a] DMSO used. [b] 1,4-Dioxane used. [c] $Pd(PPh_3)_4$ (3 mol%) and toluene were used. [d] $Pd(OAc)_2$ (10 mol%), $P^tBu_2Me{\cdot}HBF_4$ (20 mol%) and toluene were used. [e] $Pd(PPh_3)_4$ (3 mol%), $P^tBu_2Me{\cdot}HBF_4$ (6 mol%) and toluene were used. [f] $Pd(OAc)_2$ (10 mol%), $P^tBu_2Me.HBF_4$ (20 mol%), K_2CO_3 (1.5 equiv.) and DMSO were used.

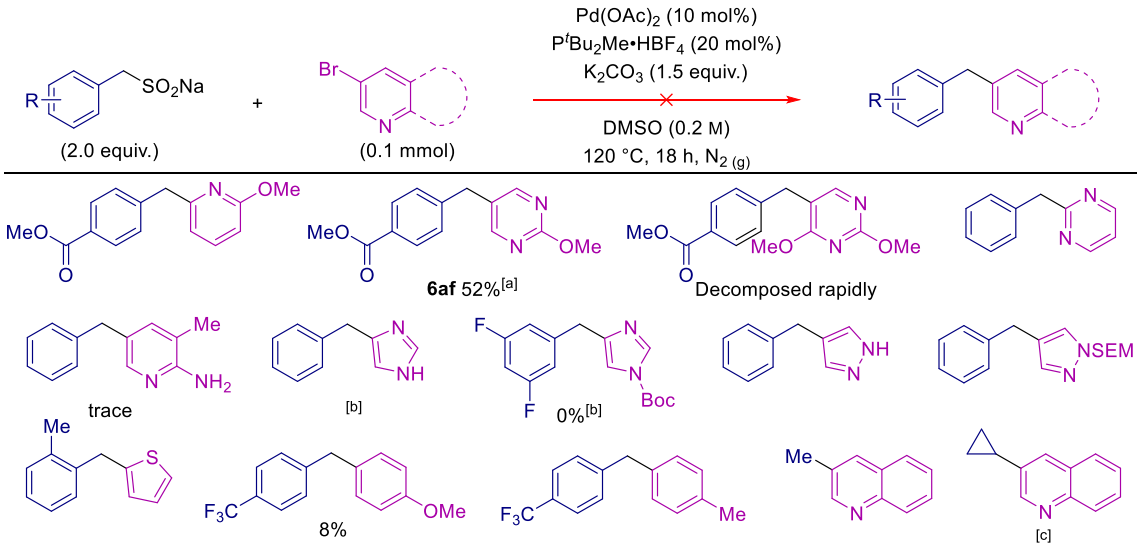
In summary, whether the sulfinate coupling partner was aromatic or benzylic effected site-selectivity. The selectivity being caused by the other reaction components was ruled out, so there must be a different desulfinative reaction mechanism at play for each case. A radical trap experiment showed that the benzylic desulfinative cross-coupling does not proceed through a radical mechanism.[168] We know this also does not occur for the pyridine sulfinate desulfinative cross-couplings.[159]

3.4.3 Unsuccessful cross-couplings

Unfortunately, there were many substrates that did not yield cross-coupled di(hetero)arylmethane products (Scheme 36). For unsuccessful reactions, we commonly observed unreacted heteroaryl halide starting material, protodehalogenated products, or trace desired products were seen by mass spectrometry analysis however were not in isolable quantities. Reactions utilising sodium *p*-methylbenzoate sulfinate, gave generally low yields owing to the sulfinate instability. When this sulfinate was reacted with

pyrimidine coupling partners, desulfinative cross-coupling was successful, however, the products proved to be too unstable to fully characterise after isolation (decomposition within 1 hour after purification by column chromatography was observed). An unsubstituted pyrimidine also was unsuccessful. This was surprising given our group was previously able to perform desulfinative arylation at this site.[20]

When 4-iodo-1*H*-imidazole was subjected to the reaction conditions, we observed some sulfone formation; we did not see this in any other cases. Protection of the free NH did not help promote product formation. Likewise, pyrazole with a free NH or protected with a SEM group, only led to trace amounts of product observed by LRMS. Again, our group did not previously have issue cross-coupling these substrates.[20] Surprisingly, we could not achieve benzylation in the 2-position of a thiophene. The low yields shown when employing 4-trifluoromethyl benzyl sulfinate can be attributed to sulfinate starting material instability and difficult separation of the product from non-polar side-products during purification. Additionally, we were unable to couple alkyl sulfinates.



Scheme 36. Unsuccessful scope examples.

[a] Decomposed within 12 hours after isolation. [b] Heteroaryl iodide used. [c] Sodium cyclopropyl sulfinate was purchased rather than made in house.

3.5 Project summary and future work

In summary, we have reported the desulfinative benzylation of heteroaryl halides to form diarylmethanes in moderate to excellent yields (29 – 99%). Our aim of producing high-yielding desulfinative cross couplings to form structurally flexible compounds was achieved through a straight-forward reaction set-up, from easy-to-prepare and diverse sulfinate coupling partners. While there was less of an impact for coupling to 6-bromoquinoline, we found that dimethyl sulfoxide was crucial to achieve excellent yields when employing 3-bromopyridine as the coupling partner. As some reduced yields were observed when using unstable benzyl sulfinate salts, future work could involve employing an alternative strategy. Either finding a way to stabilise the sulfinates by additives or *in situ* generation of the sulfinate salts during the cross-coupling could circumvent some of the issues we observed.

Chapter 4. One-pot palladium-catalysed desulfinative cross-coupling to synthesise diarylmethanes

4.1 Origin and outline of project

4.1.1. Background

Although our desulfinative cross-coupling of benzyl sulfinates was generally a high yielding process (Chapter 3), these coupling partners pose several problems; unlike (hetero)aryl sulfinates and alkyl sulfinates, which are frequently described as bench stable solids,[18, 55] we found that many benzylic sulfinate salts decompose readily in reaction media at elevated temperatures (≥ 50 °C) or within a couple of weeks when stored at room temperature, under either air or in a vacuum desiccator. This finding was most notable for those bearing electron-withdrawing groups. Furthermore, unless formed in excellent yield, sulfinate salts will often be contaminated with inorganic salts that are difficult to remove as well as quantify. This can additionally lead to reduced yields in the cross-coupling process. Moreover, in terms of wider synthetic use and late-stage functionalisation, the sulfinate functionality is not suitable for multistep elaboration.

Our group, and others, have previously combated similar issues by using latent nucleophiles, where the sulfinate is unmasked *in situ* for the coupling reaction to follow.[24-25, 169] We were additionally inspired by the work of both Baskin et al[61] and Shavnya et al,[70] to create a system where the benzyl sulfinate could be formed *in situ*, as well as the sulfinate's immediate precursor. A desulfinative one-pot protocol would complement existing reductive cross-coupling methodologies for the synthesis of di(hetero)arylmethanes.

4.1.2. Project aims

As outlined in previous chapters, there was a considerable issue with the stability of sulfinates, leading to either poor yields of desulfinative cross-coupled products or none at all. Avoiding the laborious preparation and purification of sulfinates, which then may decompose before being used as coupling partners, was highly desirable.

Hence, this chapter focuses on exploration of a one-pot desulfinative cross-coupling protocol to synthesise di(hetero)arylmethanes, with *in situ* generation of the benzyl sulfinate salt to circumvent stability and isolation issues (Figure 9). The vast commercial availability of both benzyl halides and heteroaryl halides compared to sulfinate starting materials, would be another advantage of this strategy, in addition to metal reductants not being needed.

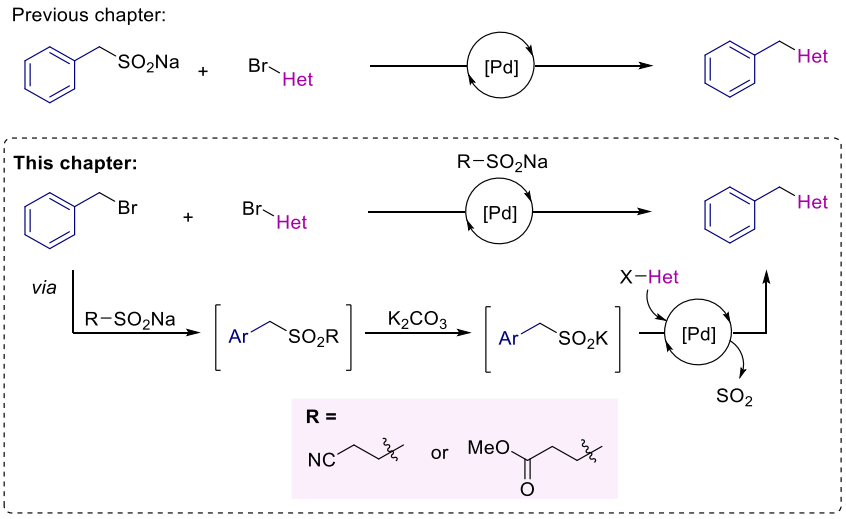
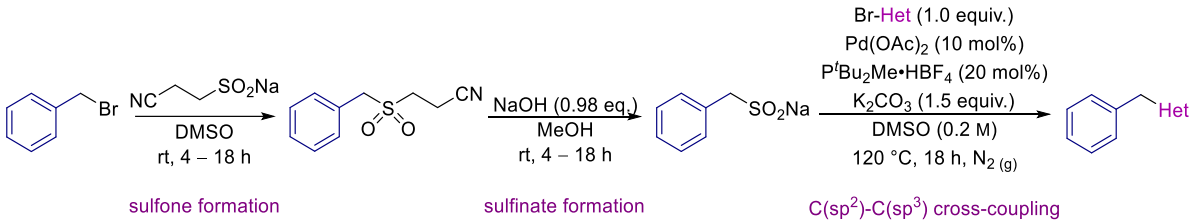


Figure 9. Project strategy for one-pot C(sp^2)-C(sp^3) desulfinative cross-couplings.

4.2 Initial Investigations

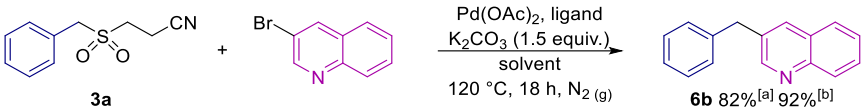
4.2.1 β-nitrile sulfones as latent sulfinate reagents

When considering our complete reaction sequence to form di(heteroaryl)methanes as the final products in Chapter 3, there are several common factors we noticed (Scheme 37). Firstly, all the reactions are under basic conditions (or should be able to tolerate it) and, secondly, polar solvents are used throughout. We envisaged that combining the reaction steps, and removing the purification of intermediates, could prove successful, eliminating potential decomposition issues of unstable sulfinates. While methanol was used for the sulfinate formation step, due to its easy removal to give the isolated salt, we did not foresee issue with using DMSO for all steps.



Scheme 37. Pre-existing route to di(hetero)arylmethanes from sulfinates.

We commenced our investigations into whether the benzyl sulfone, the β-nitrile masked precursor to the benzyl sulfinate, would couple under our previously developed desulfinative cross-coupling conditions. Initially we chose to subject benzyl sulfone (**3a**) to the conditions found optimal in Chapter 3, as well as those developed by Xinlan Cook et al for cross-coupling heteroaryl β-nitrile sulfones (Scheme 38).[25] Under both sets of conditions, the desired product was synthesised in high yield. This was interesting because when optimising the cross-coupling of sodium benzyl sulfinate (**1c**), we found both CataCXium A and toluene to be far less efficient than our optimal ligand and solvent (Table 12 and Table 14, Chapter 3). These findings established that we could avoid the isolation of benzyl sulfinates.



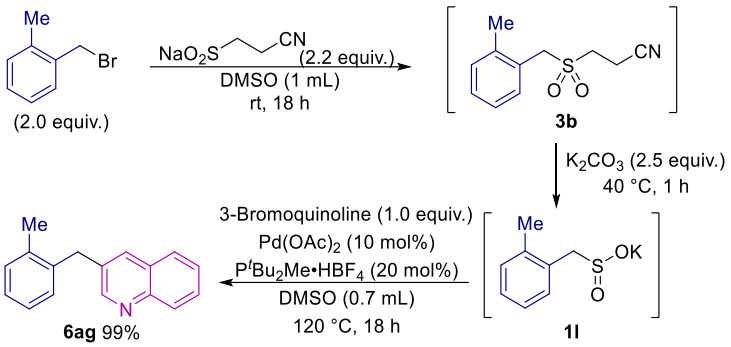
Scheme 38. Preliminary investigations for benzyl sulfone cross-coupling.

[a] $Pd(OAc)_2$ (10 mol%), $P^tBu_2Me{\cdot}HBF_4$ (20 mol%), DMSO (0.2 M). [b] $Pd(OAc)_2$ (5 mol%), CataCXium A (10 mol%), toluene (0.1 M).

4.2.2 Desulfinative cross-coupling from benzyl bromide tests

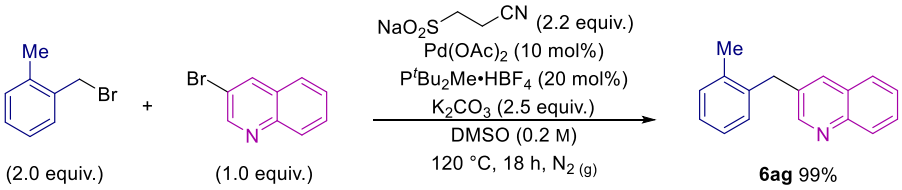
Since we had found success with cross-coupling the sulfone directly, thus removing the need to isolate and store benzyl sulfinates, we next wanted to explore whether we could form the benzyl sulfone *in situ,* in addition to the sulfinate. To investigate this, we monitored the telescoped formation of the masked benzyl sulfinate, release to the sulfinate salt and subsequent cross-coupling, without any purification of these intermediates (Scheme 39). The reaction conditions chosen resulted from combination of the optimised conditions for the individual synthetic steps to the sulfone, sulfinate and di(hetero)arylmethane.

Firstly, the S_N2 reaction between the benzyl bromide and β-nitrile sulfinate reagent to form the sulfone (**3b**) was attempted. Once complete consumption was observed by TLC, this reaction mixture was carefully added to potassium carbonate to generate the sulfinate (**1l**). A greater excess of potassium carbonate was used in order to ensure complete conversion to the potassium sulfinate salt before introduction of the Pd-catalyst. Finally, the remaining cross-coupling reagents were added as a pre-combined solution and the reaction mixture heated to 120 °C. Pleasingly, the telescoped reaction was very successful, producing the desired product in 99% isolated yield.



Scheme 39. Telescoped reaction sequence on 0.2 mmol scale.

The next step was to test whether it was necessary to perform the cross-coupling in a telescoped manner. Hence, we subjected the same coupling partners to one-pot reaction conditions (Scheme 40). Remarkably, this first attempt of a one-pot single-step protocol also resulted in 99% isolated yield of the di(hetero)arylmethane product (**6ag**).



Scheme 40. Initial one-pot reaction test on 0.2 mmol scale.

4.2.3 Control Reactions

Before commencement of a full optimisation, we wanted to ensure that addition of the β-nitrile sulfinate was necessary and the expected benzyl bromide → benzyl sulfone → benzyl sulfinate sequence was indeed occurring. It was important to check that we were not instead performing a direct cross-electrophile coupling process which would not involve a sulfinate intermediate. Our control reactions demonstrated that all reaction components were necessary to achieve good yields of di(hetero)arylmethane product through our one-pot protocol (Table 18). When the reaction was run in the absence of benzyl bromide, we observed homocoupled 3,3'-biquinoline (**9a**) in low yield, likely formed through a reductive pathway (entry 5).

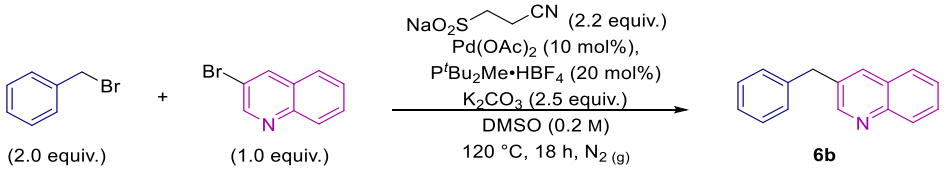


Table 18. One-pot desulfinative cross-coupling control reactions.

Entry	NaO_2S–CN	$Pd(OAc)_2$ and $P^tBu_2Me{\cdot}HBF_4$	K_2CO_3	Yield /%
1	Yes	Yes	Yes	78
2	No	Yes	Yes	0
3	Yes	No	Yes	Trace[a]
4	Yes	Yes	No	0
5[b]	Yes	Yes	Yes	0

[a] Observed by LRMS. [b] No benzyl bromide employed. 3,3'-Biquinoline obtained in 22% yield.

4.2.4 The one-pot route advantage for sulfinates with stability issues

Alike to the work in Chapter 3, we wanted to next evaluate how well the reaction performed with pyridyl halides, as generally the quinolines had proven to be more efficient coupling partners. Before commencing optimisation, it was important to compare the efficiency when the starting material was altered from a sulfinate to a sulfone, or to the bromide and β-nitrile sulfinate reagent one-pot constituents (Table 19). As expected, due

to the conditions being optimised for the sulfinate, the coupling was very successful with the sulfinate coupling partner (**1c**, entry 1). Interestingly, the yield was halved when the sulfone (**3a**) was used instead, although this may be explained by only 1.5 equivalents of base being present (entry 2). However, when the benzyl bromide was utilised in combination with the β-nitrile sulfinate, the product was obtained in high yield (entry 3). The yield difference between entries 1 and 3, although appearing to be large, can be considered a minor issue when the multiple, time consuming, steps to generate the sulfinate are considered. The one-pot conditions eliminate the need to isolate and purify intermediates, leading to considerable cost and time savings.

Although the one-pot route has clear advantages for the rapid generation of di(hetero)arylmethanes, we wondered if it could also pose a solution for cross-coupling sulfinates with instability issues (Table 19). Previously, we saw that sodium (4-(trifluoromethyl)phenyl)methane sulfinate (**1d**) gave lower yields than electron-rich sulfinates, when coupling to 3-bromopyridines (**6j** *vs* **6k** Table 17, Chapter 3). The reduced yield was likely due to the poor stability of this isolated sulfinate salt (entry 4). When we performed the cross-coupling with the corresponding β-nitrile sulfone (**3g**), an excellent yield was observed (entry 5). Clearly, generating the sulfinate *in situ* where it could be consumed quickly, under the inert conditions, avoided low yields. Furthermore, while the unoptimised one-pot conditions led to a slightly lower yield (entry 6), these excellent yields do indeed demonstrate that the use of precursors could be a good alternative to sulfinate reagents known to be less stable.

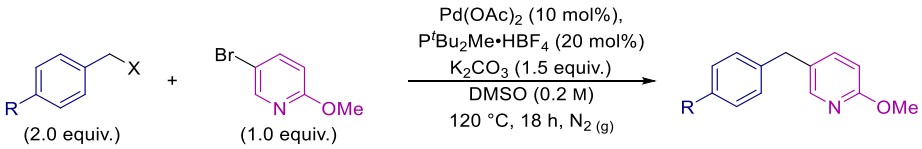


Table 19. Comparison of benzyl starting materials in the desulfinative cross-coupling.

Entry	R	X	Deviation from the scheme	Yield /%
1	H	SO_2Na	-	99
2	H	$SO_2CH_2CH_2CN$	-	50
3	H	Br	β-nitrile sulfinate (2.2 equiv.), K_2CO_3 (2.5 equiv.), DMSO (0.13 M)	78
4	CF_3	SO_2Na	-	50
5	CF_3	$SO_2CH_2CH_2CN$	-	99
6	CF_3	Br	β-nitrile sulfinate (2.2 equiv.), K_2CO_3 (2.5 equiv.), DMSO (0.13 M)	90

4.3 Reaction optimisation

With the knowledge that the process was likely proceeding through the sequence we designed, we next focused on optimising the coupling of benzyl bromide and 5-bromo-2-methoxypyridine (**6n**, Table 20). Using the optimal conditions for the benzyl sulfinate desulfinative cross-coupling (Chapter 3) led to a very promising first result of 78% yield (entry 1). Halving the equivalents of the benzyl bromide and β-nitrile sulfinate reagents to form the sulfinate species led to slight reduction in yield (entry 2). Interestingly, increasing the equivalents of these reagents to the in-between value afforded the product in excellent yield (entry 3). When the reaction was performed at lower concentration, we saw dramatic increase in yield (entry 1 *vs* 4). Applying the altered stoichiometry of benzyl bromide and β-nitrile sulfinate coupled with a more dilute reaction mixture gave excellent yield (entry 5). Further attempts to lower the equivalents of both reagents led to reduction in yield (entries 6 – 9). The equivalents shown in the scheme were found to be optimal (entry 10). Unfortunately, reducing the amount of catalyst used decreased the yield significantly (entries 11 – 12). Although the product was obtained in lower yield, the

reaction set-up was compatible to be run at atmospheric pressure in a round-bottom flask, rather than in a sealed microwave vial (entry 13). Unfortunately, reducing the temperature by just 10 °C reduced the product yield by nearly 30% (entry 14). Commonly unreacted heteroaryl halide and homocoupled heteroaryl halide were observed for lower yielding reactions.

We deemed it important to investigate whether a small selection of solvents listed in green solvent guides[170] could be efficient alternatives to DMSO (entries 15 – 19). Of these, only anisole showed promise. Our group had previously seen success using anisole as the solvent,[25] so in an effort to increase the yield, higher reaction temperatures were tested. Strangely, we saw odd fluctuations in yield (entries 19 – 22). During the first attempt at 150 °C (entry 19), a solid black clump formed almost instantly. The reaction was removed from the hot-plate, sonicated for 5 minutes to break up the clumps and then replaced in the hot-plate for 18 hours. During the second attempt at 150 °C (entry 20), no clump formation occurred. Lowering the temperature avoided formation of clumps. However, the yields were poor (entries 21 – 22). From this, we elucidated that DMSO would remain our selected solvent. Similarly, to the control reactions previously performed (Table 18), when the β-nitrile sulfinate was absent for the coupling of 5-bromo-2-methoxypyridine, no desired product was observed (entry 23). Instead, aside from unreacted starting material, the homocoupled product 6,6'-dimethoxy-3,3'-bipyridine (**9b**) was isolated in 10% yield.

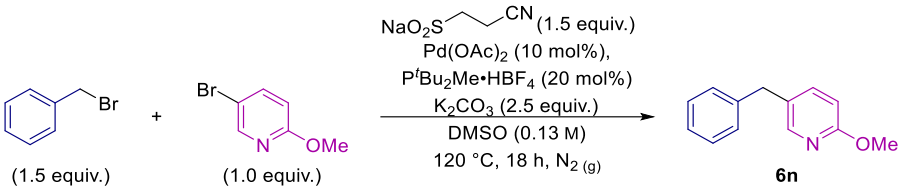


Table 20. Optimisation for the one-pot desulfinative cross-coupling reaction.

Entry	Deviation from the scheme	HPLC yield[a] /%
1	BnBr (2.0 equiv.), β-nitrile sulfinate (2.2 equiv.), DMSO (0.2 M)	78
2	BnBr (1.0 equiv.), β-nitrile sulfinate (1.1 equiv.), DMSO (0.2 M)	70
3	BnBr (1.5 equiv.), β-nitrile sulfinate (1.65 equiv.), DMSO (0.2 M)	90
4	BnBr (2.0 equiv.), β-nitrile sulfinate (2.2 equiv.)	96
5	BnBr (1.5 equiv.), β-nitrile sulfinate (1.65 equiv.)	94
6	BnBr (1.1 equiv.), β-nitrile sulfinate (1.1 equiv.)	77
7	BnBr (1.2 equiv.), β-nitrile sulfinate (1.2 equiv.)	86
8	BnBr (1.3 equiv.), β-nitrile sulfinate (1.3 equiv.)	89
9	BnBr (1.4 equiv.), β-nitrile sulfinate (1.4 equiv.)	95
10	none	99
11	$Pd(OAc)_2$ (5 mol%)	82
12	$Pd(OAc)_2$ (7.5 mol%)	84
13[b]	none	76
14	110 °C	72
15	Anisole as solvent	55
16	Sulfolane as solvent	43
17	Diethyl carbonate as solvent	30
18	1-Octanol as solvent	0
19	Anisole, 150 °C, with sonication	15
20	Anisole, 150 °C	30
21	Anisole, 140 °C	8
22	Anisole, 130 °C	17
23	No β-nitrile sulfinate	0

[a] HPLC yields were calculated with *p*-tolyl ether used as the internal standard. [b] Performed in a round-bottom flask fitted with a condenser, rather than in a sealed microwave vial.

4.3.1 Sulfinate reagent selection

We started our research with the β-nitrile sulfinate as we had an abundance of the precursor within our laboratory. However, there are other sulfinate transfer reagents known. Primarily, we wondered if a commercial sulfinate reagent could provide similarly high yields to what we were already achieving, as this would further boost the utility and uptake of the method. To this end, we tested the commercially available sodium 1-methyl 3-sulfinopropanoate (SMOPS) reagent, and found comparable yields were achieved to that of the β-nitrile sulfinate (Table 21, entry 1 *vs* 2).

As Rongacyl had proven to be an effective reagent to form sulfinates (Chapter 2), we wondered if it would afford high product yields under the one-pot desulfinative cross-coupling conditions. When Rongacyl was employed, the product was given in 40% yield (entry 3). Unfortunately, this was a far lower result than the coupling with both the β-nitrile and SMOPS sulfinate reagents. In the literature where Rongacyl was first introduced,[70] there are two conditions to cleave the sulfinate reagent. As long as there was enough base present, cleavage could occur with or without methanol present. To try and improve this yield, we repeated the reaction with the addition of methanol and a larger quantity of base. Unfortunately, this gave no improvement and instead led to a reduction in yield (entry 4).

Recently Lee and co-workers presented that silyloxymethanesulfinate (TBSOMS) could be used as a masked sulfinate species for the synthesis of unsymmetrical sulfones.[71] In this work, the sulfinate was unmasked *in situ* in the presence of tetra-*n*-butylammonium fluoride or caesium fluoride. We wondered if this sulfinate reagent could be amenable to our desulfinative cross-coupling conditions (entry 5); its straight-forward preparation from Rongalite™, a very cheap precursor, makes this reagent an attractive option. Less base was

adopted (1.5 vs 2.5 equiv.) as, unlike for the other sulfinate reagents, potassium carbonate would solely be needed for the palladium catalysis and not necessary for the unmasking step. Instead, caesium fluoride was included for the sulfinate cleavage. The desired product was produced in low yield (14%), so further optimisation would have been necessary. Interestingly, we also saw addition of the sulfinate onto the heteroaryl bromide to give 2-methoxy-5-((methoxymethyl)sulfonyl) pyridine in 18% yield. Unsurprisingly, Rongalite™ was unsuccessful (entry 6).

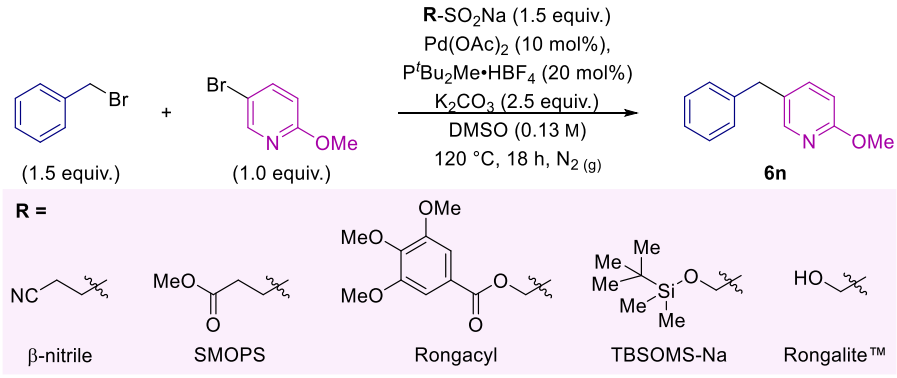


Table 21. Evaluation of alternative sulfinate reagents.

Entry	Sulfinate reagent	HPLC yield[a] /%
1	β-nitrile	99
2	SMOPS	99
3	Rongacyl	40
4[b]	Rongacyl	11
5[c]	TBSOMS-Na	14
6	Rongalite™	0

[a] HPLC yields were calculated with *p*-tolyl ether used as the internal standard. [b] MeOH (3.0 equiv.) and K_2CO_3 (3.0 equiv.) employed. [c] CsF (1.5 equiv.) and K_2CO_3 (1.5 equiv.).

4.3.2 Reaction profile analysis

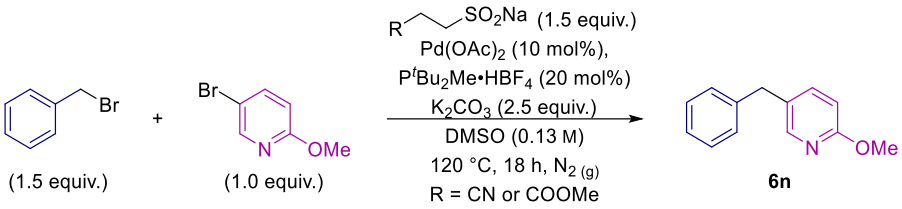
In order to gain further understanding of the individual steps within the one-pot protocol, we followed the reaction profile by HPLC analysis over the course of 18 hours (Scheme 41, up to 2 hours is shown). We were interested in how quickly each intermediate was generated and consumed. To achieve this, calibration curves were generated for each intermediate (the β-nitrile sulfone, SMOPS sulfone and potassium sulfinate salt), which

were used to quantify the species at regular intervals. We noted that decomposition appeared to be quicker for the potassium salt than the sodium sulfinate, which meant that the calibration curve had to be repeated as a high purity sulfinate was initially difficult to obtain. Furthermore, we wanted to determine if there was any benefit to using SMOPS over the β-nitrile sulfinate, aside from the commercial availability.

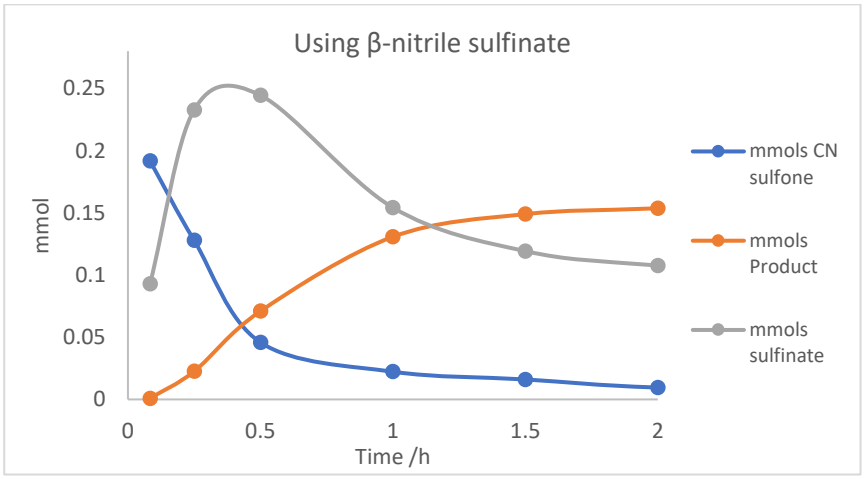
The formation and consumption of both sulfone intermediates were fast; the sulfone concentration peaked within the first 5 minutes of the reaction. After 30 minutes, the sulfones were largely consumed and the sulfinate reached its peak concentration, indicating that unlike 2-pyridyl sulfones,[25] a slow release mechanism of the sulfinate salt cannot be at play. Interestingly, the sulfinate consumption seemed to be faster for the reaction using SMOPS than for the β-nitrile reaction. Perhaps the expelled acrylonitrile was more coordinating to the Pd centre than the expelled methyl acrylate from SMOPS,[171] thus slowing down the ability of palladium to undergo rapid desulfinative cross-coupling with the sulfinate species. Alternatively, the driving force could be associated with the volatility of methyl acrylate *vs* acrylonitrile and the comparative leaving group ability. For the SMOPS reaction, after only 1.5 hours, the product had already reached an 88% yield and quantitative yield was observed at the three-hour timepoint. Contrastingly, in the β-nitrile reaction, the product had reached an 80% yield after only 2 hours, 85% after 3 hours and quantitative yield observed after 24 hours.

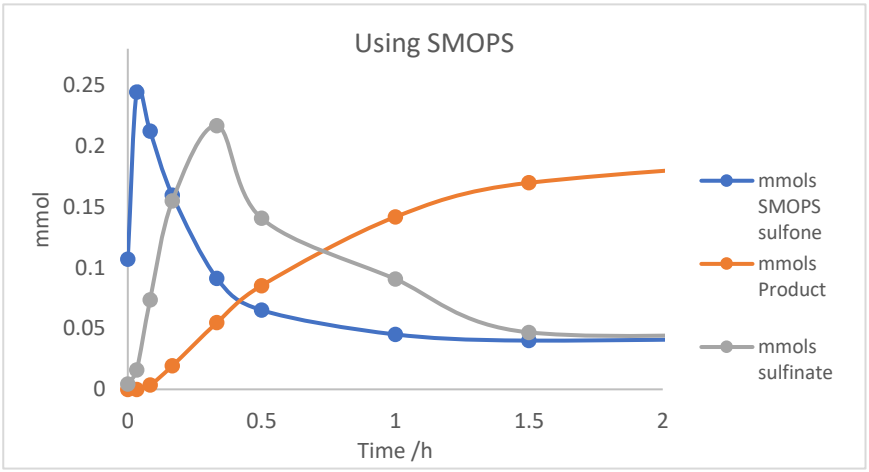
This study showed that SMOPS posed additional benefits over the β-nitrile sulfinate reagent for faster reaction completion, at least for this particular substrate, and the reaction time could be significantly reduced from 18 hours to still achieve quantitative yield of product. We also had a strong indication that the pathway does indeed proceed through the proposed steps to form each intermediate (benzyl bromide to sulfone to sulfinate to

final product), rather than *via* a direct electrophile-electrophile cross-coupling between the two bromide starting materials.



Scheme 41. Monitoring the reaction profile on 0.2 mmol scale.





4.4 Substrate scope

4.4.1 Successful examples

With our optimal reagents and conditions in hand, we first explored the scope of the benzyl bromide coupling partner when coupling to 3-bromoquinoline (Table 22). Although our time-course study showed **6n** could be formed in quantitative yield after 3 hours, this was not the case for all substrates, hence, we selected 18 hours for our general procedure. We found that benzyl bromides bearing electron-donating (**6ah**, **6ai**), electron-withdrawing (**6aj**), sterically demanding (**6ag**) and acidic (**6ak**) groups all resulted in high yields. In regards to **6ak**, firstly we tried coupling the free carboxylic acid directly, however, this proved to be challenging to isolate given its high polarity and we suffered significant product loss during aqueous work-up. To combat this issue, *in situ* methylation was attempted, through the same method used by Tim Markovic,[20] but unfortunately proved to be low yielding (28%). Our group had found the methylating agent, $TMSCH_2N_2$, to be unreliable in other reactions so this may reflect the lower yield. However, the cross-coupling itself may have been poor. To test this, we adapted the ethylation conditions presented by Lee and co-workers;[172] methylation was not further explored in order to avoid use of highly toxic methyl iodide. We found no work-up of the desulfinative cross-coupling reaction mixture to be necessary (Table 22), with ethyl iodide, caesium carbonate and additional DMSO added directly afterwards, giving the ethylated product in good yield (73%). Benzyl bromides bearing additional halides were well tolerated, particularly fluorides and chlorides (**6al**, **6an**, **6ao**, **6ap**). We saw a reduced yield when an additional bromide was situated close to the benzylic site (**6am**). Likely, undesirable palladium activation of this bromide rather than the quinoline bromide resulted in the poor

yield. We found benzylic heterocycles generally trickier to incorporate, particularly pyridyl substrates due to potential chelation of the nitrogen to Pd.[159] However, pleasingly, some medicinally relevant benzylic heterocycles did successfully couple in moderate to very good yields (46 – 89%). These included thiophene (**6aq**), isoxazole (**6ar**), functionalized quinoline (**6as**) and benzothiophene (**6at**) scaffolds. Although the yield for thiophene appears to be somewhat low (46%), this is a notable example. Previously, the isolated benzylic thiophene sulfinate coupled unsuccessfully and could not be stored; whereas with the one-pot route access to this product was possible. We were able to couple cinnamyl bromide efficiently (**6au**), but unfortunately, were unable to retain the position of the double bond, with a mixture of isomers isolated (1:1). Other functionalities that are highly prevalent in pharmaceutical molecules were also well tolerated under the reaction conditions, such as sulfone (**6av**), pentafluorosulfanyl (**6aw**) and trifluoromethyl (**6ax**) groups.

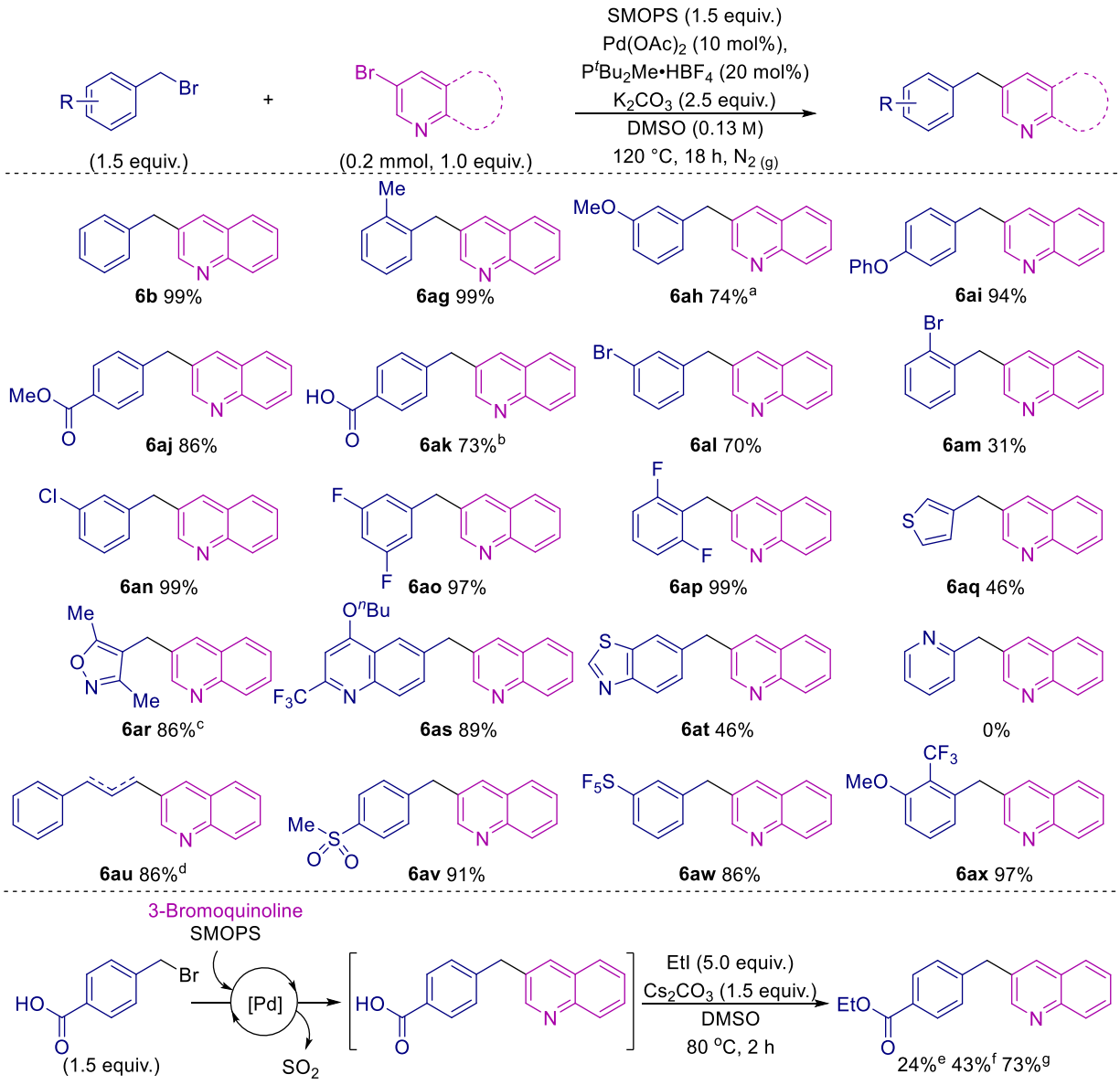


Table 22. One-pot desulfinative cross-coupling of 3-bromoquinoline to various benzyl bromides.

[a] Benzyl tosylate used. [b] Isolated as the ethyl ester. [c] β-nitrile sulfinate used in place of SMOPS. [d] Alkene isomers 1:1 ratio, combined yield of 86%. [e] EtI added directly into the desulfinative cross-coupling reaction after 18 hours. No Cs_2CO_3 or further DMSO employed. [f] Desulfinative reaction was filtered through celite, before the esterification reagents (step 2) were added. [g] EtI, Cs_2CO_3 and DMSO were added directly into the desulfinative cross-coupling after 18 hours without any work up procedure.

Next, we explored the scope of the (hetero)aryl coupling partner, where we found that generally, the reaction was tolerant to a broad range of heterocycles. Again, we found that benzyl bromides bearing electron-donating or electron-withdrawing groups were not an issue for coupling to pyridines (**6k**, **6j**). Pyridines bearing electron-donating (**6n**, **6u**, **6q**, **6ba**), electron-withdrawing (**6m**, **6bb**), and sterically demanding (**6ay**, **6az**) groups could all

be employed with the cross-coupling site at different positions on the pyridine core successful. A free hydroxyl group was tolerated (**6l**) albeit giving the desired product in moderate yield. Alternatively, common heterocycles found in medicinal chemistry achieved high yields, such as pyrazine (**6bc**), functionalised pyrimidines (**6w**, **6bd**, **6be**), thiophene (**6bf**), isoxazole (**6bg**), and a protected pyrazole (**6bh**). Initially we achieved only a 73% yield for **6bh** but repurification of the starting material meant we were able to achieve the higher yield (88%). Imidazolepyrazine (**6bi**) and imidazolepyridine (**6z**, **6bj**) examples also coupled efficiently. Several indazole examples were prepared (**6bk**), including N-H derivatives (**6bl**, **6bm**), albeit in lower yields. We were particularly pleased to form indazole **6bl**; this is notable because it maps directly onto the anticancer compound Entrectinib.[173] Aryl halides were also coupled in high yields (**6bn**, **6bo**). Lower yield was observed for α-bromostyrene (**6bp**). We initially achieved only 34% yield for this coupling, however, we able to increase to 48% when using freshly distilled α-bromostyrene. Moreover, an estrone steroid motif (**6bq**) and a celecoxib fragment (**6br**) were both cross-coupled in excellent yield.

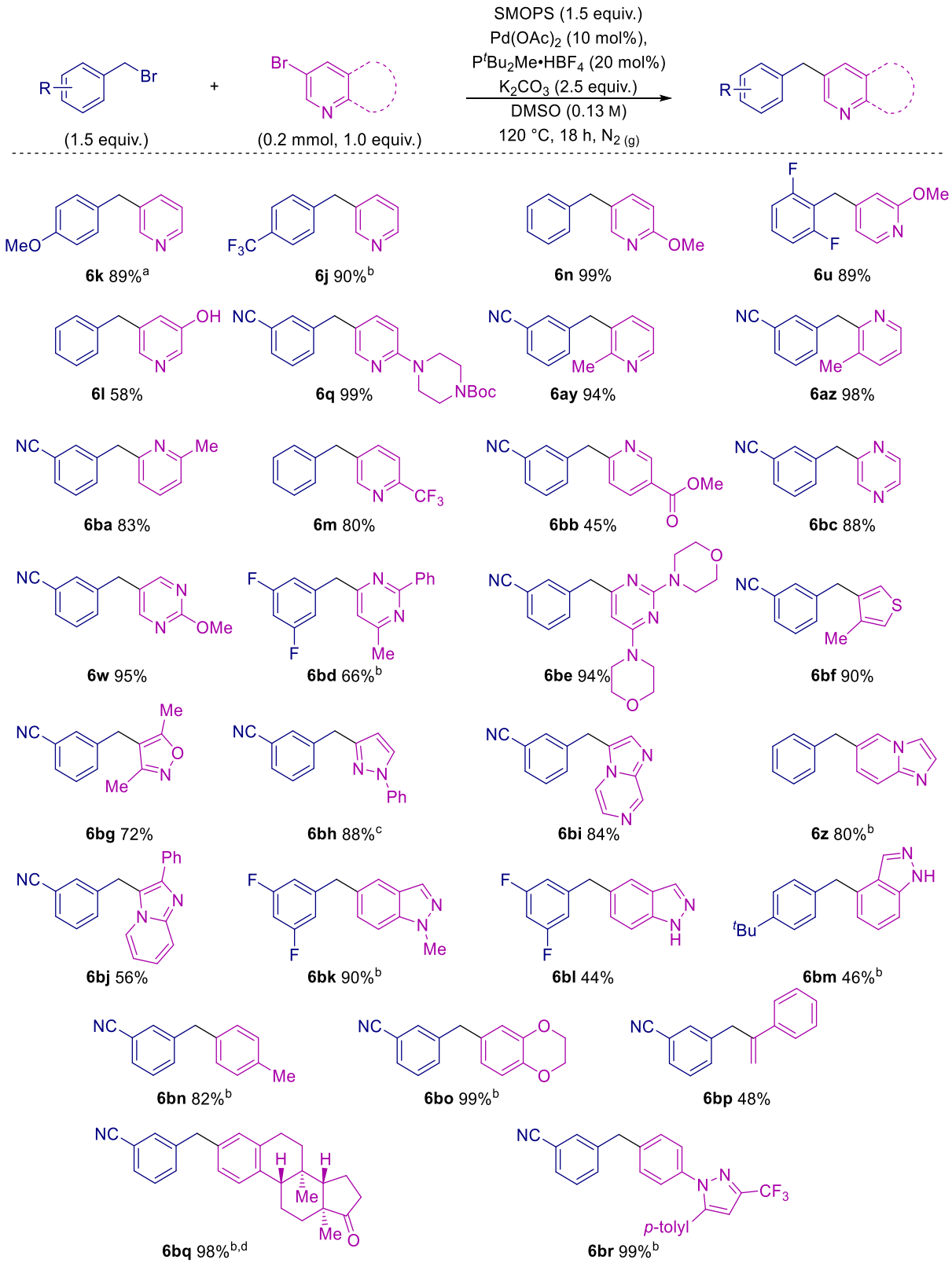


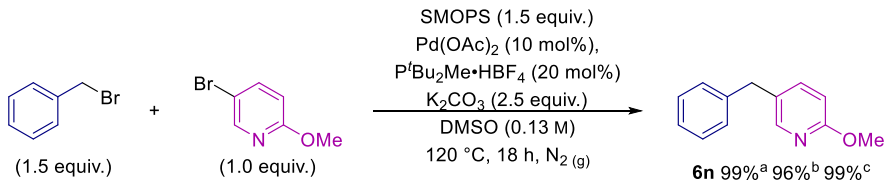
*Table 23. **O**ne-pot desulfinative cross-coupling of benzyl halides to (hetero)aryl halides scope.*

[a] 4-Methoxybenzyl chloride used. [b] β-nitrile sulfinate used in place of SMOPS. [c] Heteroaryl iodide employed. [d] Aryl triflate employed.

4.4.2 Scale up

Since our one-pot desulfinative cross-coupling protocol had proven to be efficient for a range of coupling partners, to ensure our process would have increased utility we deemed it important to test whether the reaction could be conducted on larger than 0.2 mmol scale (Scheme 42). We found that applying our optimal conditions with an increase in scale to 1.0 mmol was without issue, achieving the product (**6n**) in excellent yield (96%). Unsurprisingly, lowering the catalyst loading to 5 mol% achieved a 79% yield (closely matching our initial optimisation result in Table 20). On this same scale, we also tried to alter the solvent to sulfolane, which we had previously had success with in the sulfinate cross-coupling work (Chapter 3). Unfortunately, this was not amenable to the one-pot conditions and the product was given in just 10% yield.

Next, we increased the scale further to 5 mmol. Due to the larger volume of solvent required, we could no longer perform this in a sealed microwave vial. Instead, this was performed in a 250 mL round-bottom flask, fitted to a condenser with a N_2 balloon. We wanted to ensure there was plenty of headspace available in the flask to account for SO_2 release and that the solvent had good contact with the heating block for effective heat transfer during the reaction. Pleasingly, this very straightforward and conventional reaction set-up afforded **6n** in excellent yield (99%, 986 mg).

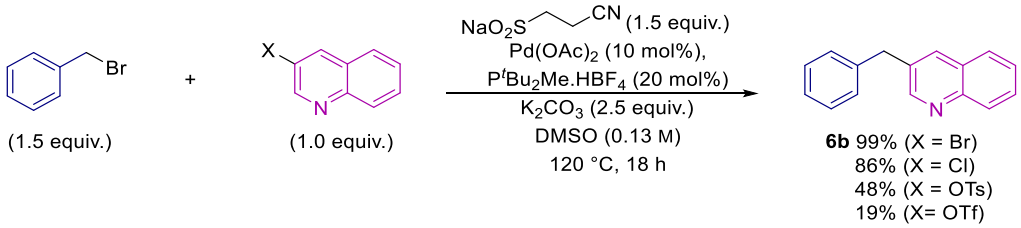


Scheme 42. Scale up of one-pot desulfinative cross-coupling reaction.

[a] 0.2 mmol scale. [b] 1.0 mmol scale. [c] 5.0 mmol scale (986 mg).

4.4.3 Alternatives to (hetero)aryl bromides

To further investigate the broadness and applicability of the methodology, we investigated alternative (pseudo)halides of the (hetero)aryl coupling partner (Scheme 43). As previously shown, when X was a bromide we achieved the product in excellent yield, likewise chloride provided efficient reaction. We saw reduced yields when using the corresponding tosylate and triflate (48% and 19% respectively). The triflate result was surprising, however we believed this could be related to instability of the quinoline-derived triflate relative to the aryl triflate used to form **6bq** in high yield (Table 23). It is worth noting that during our scope we identified that a (hetero)aryl iodide coupled efficiently under our reaction conditions (**6bh**, 88%), although we do not have the comparable data of a quinoline iodide for Scheme 7.

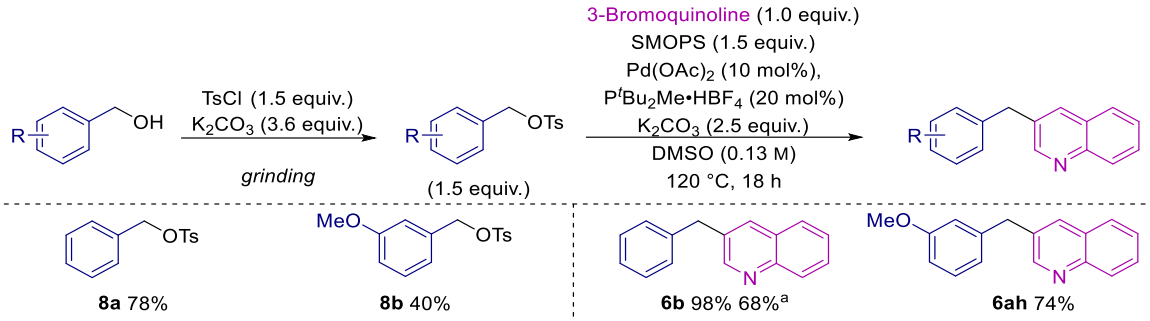


Scheme 43. Alternatives to (hetero)aryl bromides.

4.4.4 Alternatives to benzyl bromides

In a similar manner, we also wanted to explore if we could alter the halide of the benzyl coupling partner to ensure a broad range of substrates could be accessed. Firstly, we considered benzyl tosylates. We found that conventional tosylation synthetic methods were unsuccessful for benzyl substrates. Procedures using 4-toluenesulfonyl chloride[174] or *p*-toluenesulfonic anhydride[175] both yielded no product. It had become apparent that the benzyl tosylate had decomposed in solution. We then identified a solvent free and general method by Kazemi et al,[176] where grinding in a pestle and mortar allowed benzyl tosylate product formation within 5 minutes. We used this method to form two benzyl

tosylates (**8a** and **8b**). The benzyl tosylates had to be stored in the freezer under an inert atmosphere to prevent decomposition; it was clear when this had occurred as the white crystalline solid would become a pink/red sludge within a few hours when left at room temperature. When subjected to the one-pot desulfinative cross-coupling conditions, the benzyl tosylates coupled smoothly. Given their tendency to readily decompose as isolated compounds, variation in yields could be expected. For example, **6b** was formed in 68% yield when the tosylate (**8a**) was used a month after synthesis (despite storage at -18 °C).

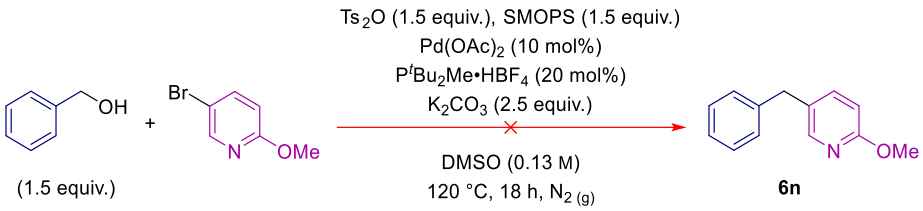


Scheme 44. Application of benzyl tosylates in the one-pot desulfinative cross-coupling.

[a] Benzyl tosylate used 1 month after synthesis.

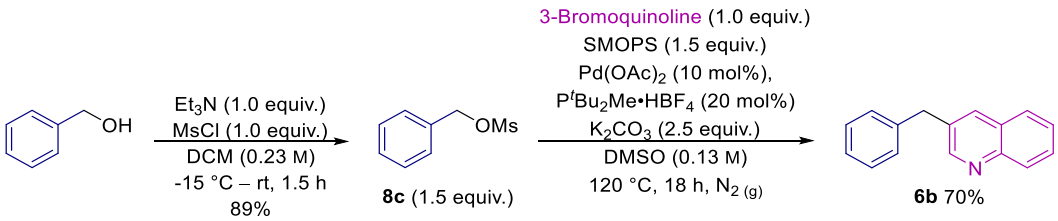
Akin to the premise of our desulfinative one-pot cross-coupling strategy, we next wondered if we could form the benzyl tosylate *in situ* from safe, cheap and widely available benzyl alcohol starting materials in place of halides. As it can be difficult to ensure the desired tosylate product is achieved rather than chlorination when using 4-toluenesulfonyl chloride,[177] we performed some test reactions with *p*-toluenesulfonic anhydride. This reagent also has the benefit of being less toxic and volatile, owing it to be more suitable for our cross-coupling conditions. Firstly, we tried all the reagents added into the reaction vessel, followed by stirring at room temperature for 30 minutes to allow formation of the benzyl tosylate species before initiating the coupling process (Scheme 45). This was then heated to 60 °C for 1 hour, before heating to 120 °C for 18 hours. No product was observed by HPLC. Secondly, we stirred benzyl alcohol, *p*-toluenesulfonic anhydride and potassium

carbonate in DMSO at 0 °C for 1 hour before addition of the remaining reagents and heating to 120 °C for 18 hours. Again, no product was observed by HPLC. Finally, we separated out the steps and ran the reaction in a telescoped fashion, which was to no avail.



Scheme 45. In situ tosylate formation proved unsuccessful.

Instead of pursuing the *in situ* tosylation any further, we turned our attention to mesylates in the hope that they could prove to be more stable coupling partners. Before attempting an *in situ* mesylate formation, it was important to determine how the benzyl mesylate would perform in the coupling compared to other benzyl reagents. We were able to synthesise benzyl mesylate (**8c**) in high yield according to a literature procedure (Scheme 46).[178] When the benzyl mesylate was subjected to our reaction conditions with 3-bromoquinoline as the coupling partner, **6b** was obtained in high yield. However, in comparison to benzyl bromide and benzyl tosylate, the mesylate appeared to be a far less efficient coupling partner.



Scheme 46. Application of benzyl mesylate in the one-pot desulfinative cross-coupling.

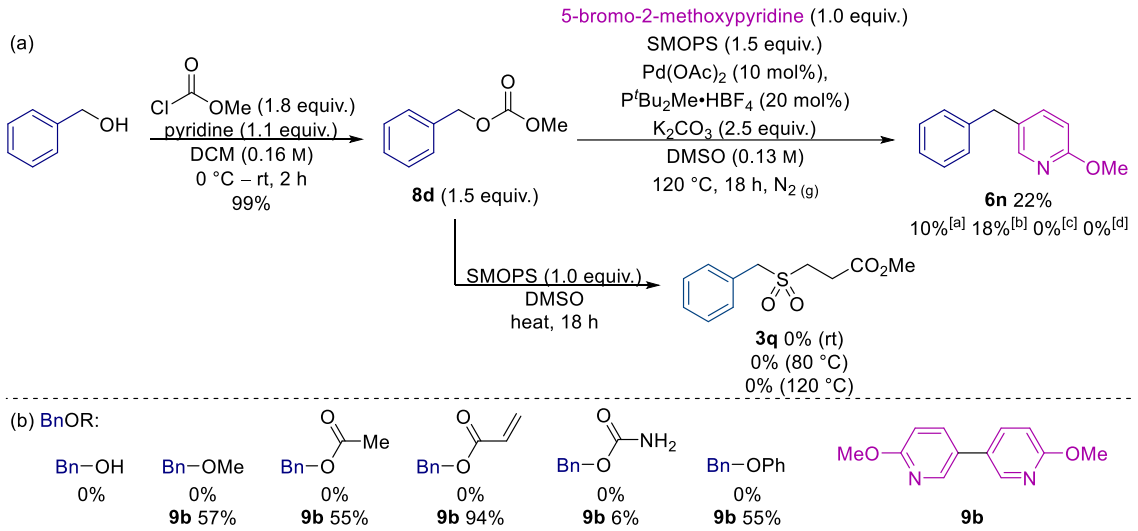
Despite the lower efficiency for the mesylate, we envisaged that being able to perform our process from benzyl alcohols would broaden the applicability of the methodology. As methanesulfonic anhydride is capable of activating DMSO, potentially promoting oxidation of benzyl alcohol with production of dimethyl sulfide,[179] 1,4-dioxane was selected as the

reaction solvent instead for our attempts at *in situ* generation. A lower reaction concentration was applied to account for the decrease in reagent solubility in dioxane over DMSO. The same test reactions as for *in situ* tosylate formation were performed with the mesylate, but again there was no success.

At this point we decided to take a step away from tosylates and mesylates and look into other, more stable alternatives. In this regard, carbonates have emerged as a green alternative[180] to halide leaving groups, and there are examples demonstrating *in situ* formation from alcohols.[181] In a similar manner to the tosylate and mesylate work, benzyl methyl carbonate (**8d**) was synthesised prior to attempting *in situ* formation in the one-pot desulfinative coupling to assess its viability. We were aware that the literature conditions[182] would not be desirable to try and transfer into the one-pot desulfinative cross-coupling, as methyl chloroformate is fatal if inhaled. However, they did prove useful for reliably synthesising sufficient quantity of benzyl methyl carbonate to test in the coupling process (Scheme 47a). Under our one-pot desulfinative cross-coupling conditions, we achieved product **6n** in low yield (22%) with benzyl carbonate (**8d**) as the coupling partner. Increasing the base led to reduction in yield (10%), with 6,6'-dimethoxy-3,3'-bipyridine (**9b**) isolated in 24% yield from homocoupling of the (hetero)aryl bromide. Disappointingly, raising the temperature to 150 °C gave no improvement in yield. In all cases, we reclaimed unreacted heteroaryl bromide starting material and the homocoupled byproduct (**9b**).

As benzyl methyl carbonate provided a poor amount of product under the one-pot conditions, it was important to check how smoothly the S_N2 reaction with SMOPS proceeded to form the intermediate sulfone (**3q**). For benzyl bromides, we could achieve

complete conversion to the sulfone after overnight stirring at room temperature. Unsurprisingly, the benzyl carbonate was less reactive and no product was formed under these conditions. Unfortunately, raising the temperature also led to no desired product formation. Instead, benzyl methyl carbonate was largely reclaimed (85%) after aqueous work-up. From these results we can speculate that the catalytic system required for the cross-coupling process, may also facilitate the reaction of benzyl carbonate with SMOPS. To determine if the benzyl methyl carbonate was coupling directly under the one-pot conditions, without going through the sulfone and sulfinate intermediates, a control reaction was run with no SMOPS present; pleasingly, this led to 0% yield. Next, we employed acetic acid as an additive[25] in order to activate the carbonate leaving group. No desired product was observed, likely due to sulfinic acid formation reducing the nucleophilicity of SMOPS. Neither through a telescoped process nor by addition at the same time as the other one-pot reagents, as per the usual one-pot conditions, afforded any desired product. Instead, unreacted (hetero)aryl bromide, homocoupled bipyridine and protodehalogenated products were identified in the resulting reaction mixtures. Other benzyl alcohol-derived substrates were also tested under the one-pot desulfinative cross-coupling conditions but yielded no desired product (Scheme 47b).



Scheme 47. Synthesis of benzyl carbonate and its use in the cross-coupling.

[a] K_2CO_3 (3.5 equiv.). [b] 150 °C. [c] No SMOPS present. [d] AcOH (1.5 equiv.) and K_2CO_3 (3.0 equiv.).

4.4.5 Unsuccessful substrates

As mentioned in Chapter 2, pyridyl sulfinates were shown to be too unstable to isolate; this was also a common finding for other heteroaryl sulfinates. As shown earlier on in this chapter, the one-pot method proved advantageous for benzyl sulfinates with electron-withdrawing groups that gave lower product yields when cross-coupled directly. We wondered whether the one-pot protocol could prove successful for cross-coupling substrates where the sulfinate was found to be completely inaccessible. Firstly, we attempted the cross-coupling from the β-nitrile sulfone intermediates (Table 24). Unfortunately, the method proved unsuccessful and we were unable to incorporate pyridyl, protected benzimidazole and phenethyl motifs. For the reaction with the unsubstituted 2-pyridyl motif, the Heck or Ramberg-Backland type product was isolated in low yield (**10a**). We saw this previously from reaction with unsubstituted benzyl sulfone, where the corresponding alkane was isolated in 11% yield. The 3-bromoquinoline starting material remained unconsumed. When the highly electron-rich pyridyl sulfone was

subjected to the reaction conditions, the only isolable product was the protodesulfonylated product (**11a**), formed in high yield.

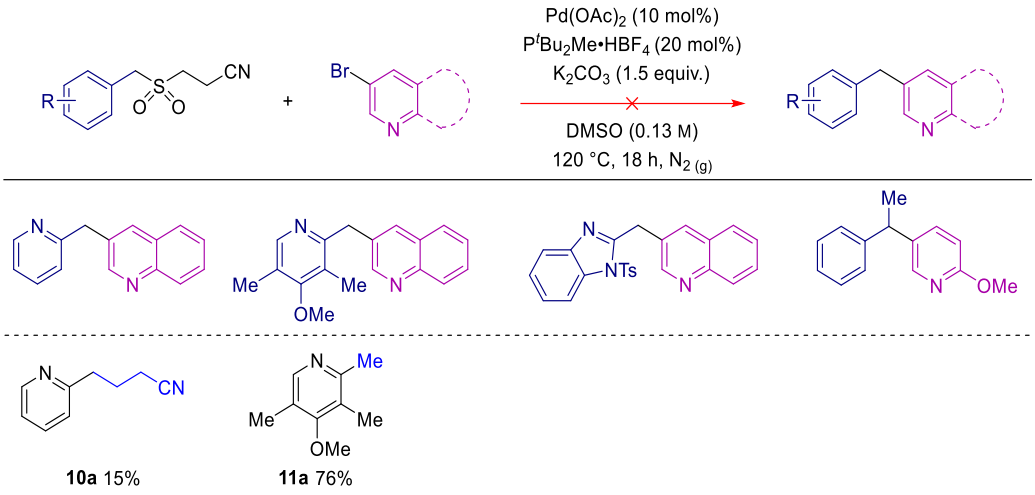
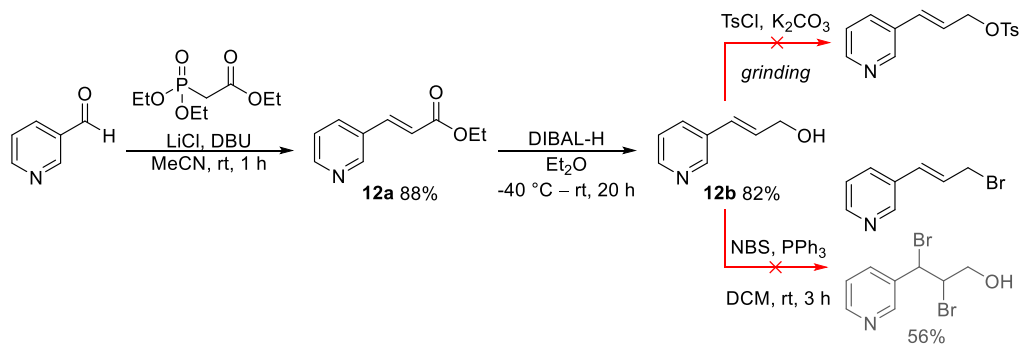


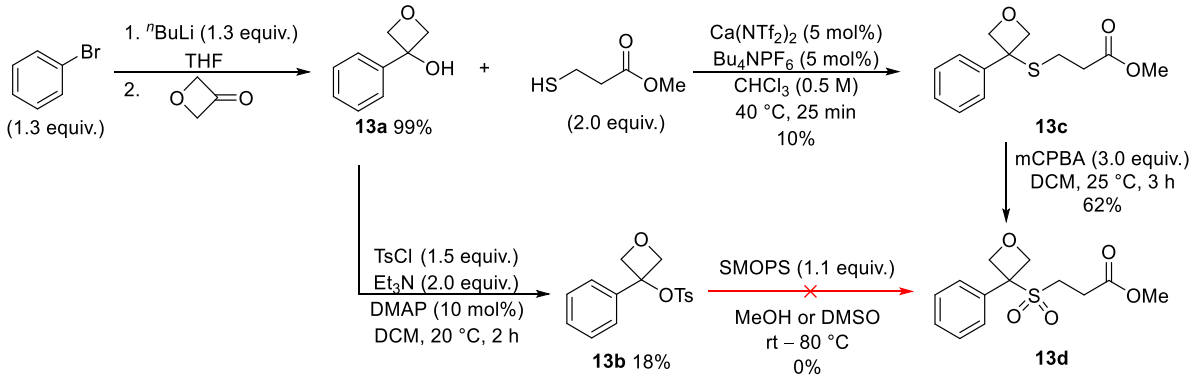
Table 24. Unsuccessful desulfinative cross-coupling examples from β-nitrile sulfones.

In an effort to try and incorporate the pyridyl motif into our scope, starting material was prepared where the pyridine ring would be situated further away from the site of cross-coupling. As (*E*)-(3-bromoprop-1-en-1-yl)benzene was a successful coupling partner in the one-pot route, we reasoned that perhaps the corresponding pyridine would be similarly accessible. Unfortunately, alike to issues observed with benzyl tosylates, the route shown in Scheme 48 was unsuccessful due to instability of the desired tosylate. When bromination of **12b** was attempted,[183] we saw addition across the alkene rather than the desired bromination of the alcohol. After this we decided to halt synthesis of pyridine containing starting materials.



Scheme 48. Attempted sequence to synthesise (E)-3-(pyridin-3-yl)allyl 4-methylbenzenesulfonate.

Next, we were interested to try and incorporate substituents at the benzylic position. Although the methyl group had been unsuccessful (Table 24), we looked into synthesising another coupling partner containing a medicinally relevant group, an oxetane.[184] Unfortunately, the intermediates (**13b**, **13c**) were difficult to synthesise in high yields and the isolated sulfinate salt was inaccessible. Since this work was conducted, Bull and co-workers demonstrated that some oxetane sulfinate salts were unstable in solution so were generated *in situ* for the synthesis of sulfonyl fluorides.[185] The sulfone (**13d**) was subjected to the desulfinative cross-coupling conditions with 3-bromoquinoline, but no desired product was obtained. Unreacted 3-bromoquinoline was reclaimed in 18% yield, the homocoupled heteroaryl halide (**9a**) was isolated in 42% yield and there were trace amounts of the Heck-type product, methyl 3-(quinolin-3-yl)propanoate (**14**). No sulfone starting material was recovered, and there was no evidence that the oxetane ring had remained intact.



Scheme 49. Synthetic sequence to methyl 3-((3-phenyloxetan-3-yl)sulfonyl)propanoate.

A range of other coupling partners were also unsuccessful under the one-pot cross-coupling conditions (Table 25). In a similar manner to the sulfones in Table 24, unfortunately, the one-pot protocol did not allow incorporation of the pyridine motif nor secondary benzyl bromide coupling partners. Alike to the direct benzyl sulfinate cross-coupling work in Chapter 3, a cyclopropyl ring could not be incorporated nor a

fluorene. Extending the benzyl bromide chain by 1 or 2 carbons unfortunately yielded no desired product. We can reason that instead of elimination of methyl acrylate, there could be formation of styrene and regeneration of SMOPS, however, no styrene was isolated after the reaction; unsurprising given its volatility. We also found that pentafluoro, aldehyde, nitro groups and an example with a carboxylic acid on an ether chain were not tolerated. As previously mentioned, we have often had issues with heterocyclic motifs within the benzyl bromide coupling partner, such as furan; benzoxadiazole was coupled but in very low yield. Anthraquinone and 2-quinolone motifs could also not be included. There were also some (hetero)aryl halides which did not afford the desired cross-coupled products, such as benzo[d]oxazole. Initially it appeared as though 4-(*tert*-butyl)cyclohex-1-en-1-yl trifluoromethanesulfonate had coupled to give the desired product in 19% yield, but unfortunately the spectroscopic data did not match. The reaction with 6-bromonicotinonitrile led to a very complex reaction mixture, and it seemed as though some products resulting from polymerisation were present. Across the failed or low yielding reactions, commonly the homocoupled bipyridine (**9a**) was observed (in up to 82% yield) plus the protodehalogenated benzyl bromide starting material could be isolated, when not highly volatile (**11b** – **11e** are shown as illustrative examples).

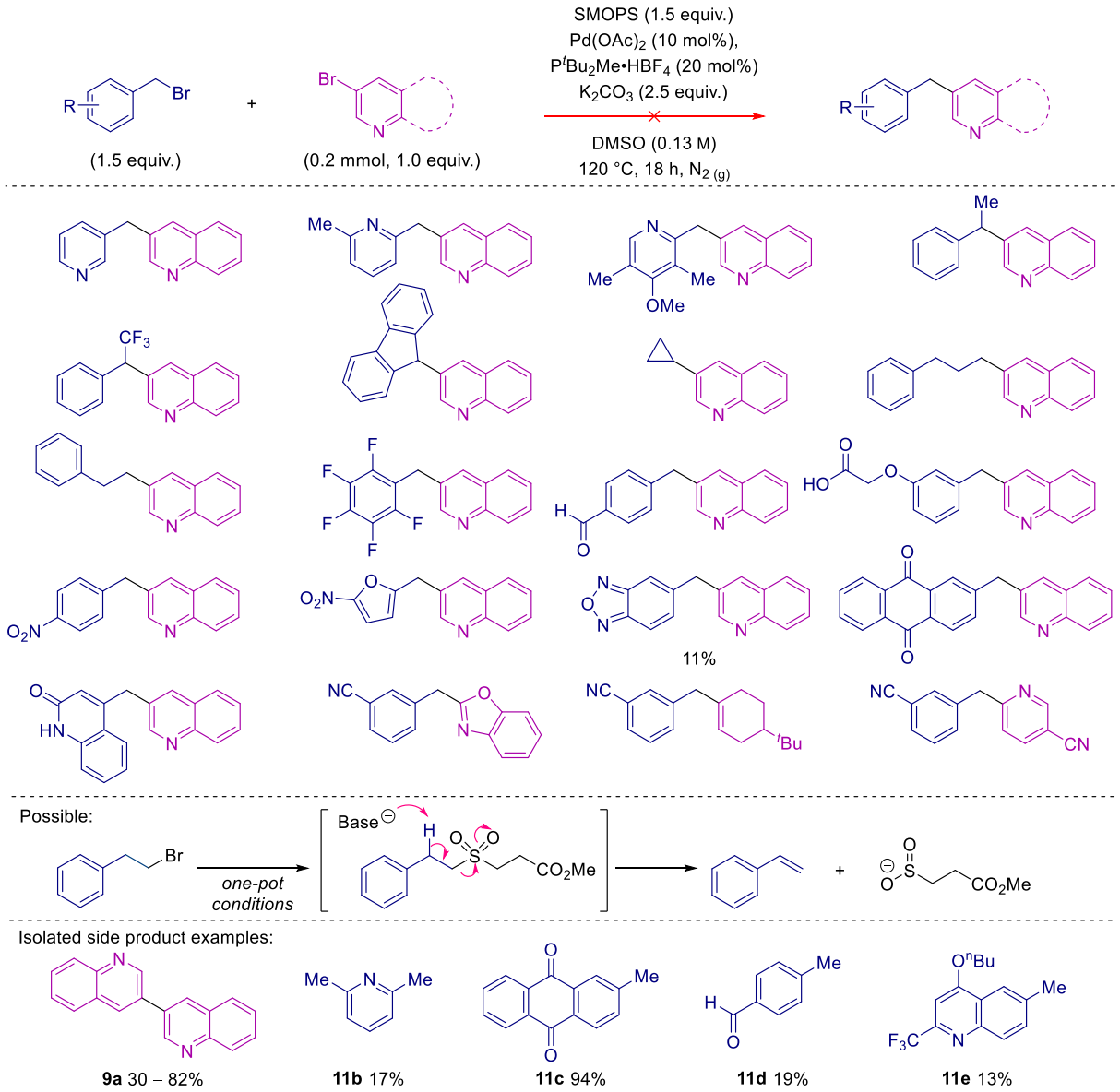
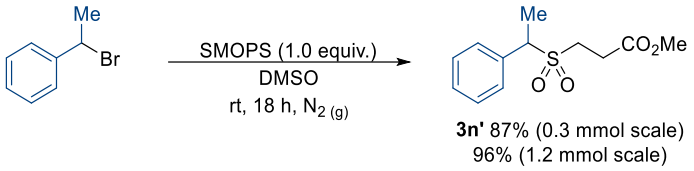


Table 25. Unsuccessful one-pot desulfinative cross-couplings.

4.4.6 Exploring the poor success of secondary sulfinate salts

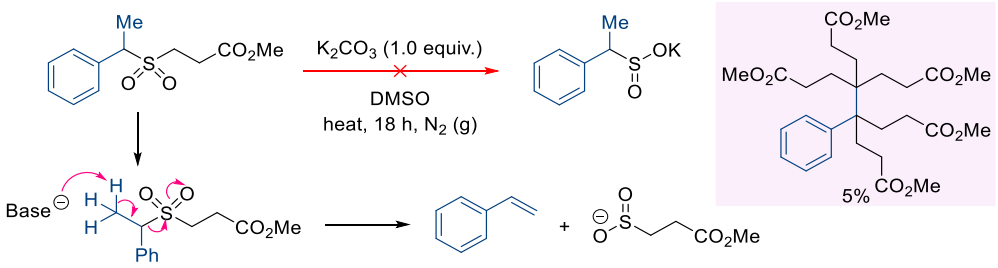
It was important to investigate why secondary benzyl bromides were unachievable coupling partners in our desulfinative cross-coupling reactions. We knew that the S_N2 reaction between (1-bromoethyl)benzene and SMOPS does proceed smoothly to form the sulfone (**3n'**), so this first step in the one-pot should not be the issue (Scheme 50).



Scheme 50. High yielding generation of methyl 3-((1-phenylethyl)sulfonyl)propanoate.

Next, we needed to determine if sulfinate formation occurs. We reacted methyl 3-((1-phenylethyl)sulfonyl)propanoate (**3n'**) with base, firstly at room temperature. Unlike our usual benzyl sulfinate formation reactions, which remain colourless, within 2 minutes the reaction had changed from colourless to orange, and within 5 minutes the reaction mixture had become a bright red solution. Trace amounts of the sulfinate product were seen after 1 minute (by LRMS), which were then not detectable in later samples (at 5 minutes, 10 minutes and onwards). From the room temperature reaction, we reclaimed the sulfone starting material in 70% yield. Methyl acrylate was formed (shown on the TLC plate), however it was not isolated due to its volatility.

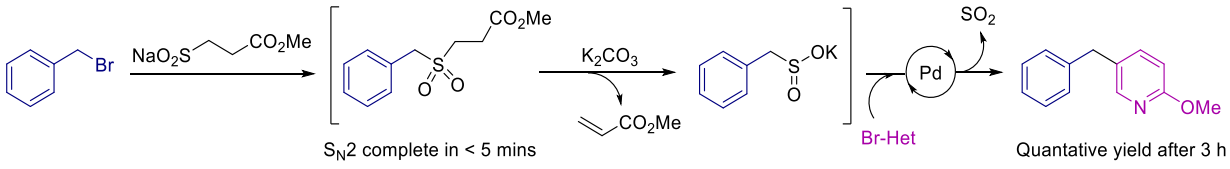
The same rapid colour change was observed on repeating the reaction at 120 °C (our optimal desulfinative cross-coupling conditions). No sulfone starting material remained after 30 minutes. Styrene could potentially be formed during the reaction through the pathway shown in Scheme 51. However, this was not observed in the crude reaction mixture. Ethyl benzene was also not observed. Methyl acrylate was present, although not quantified. We were able to isolate SMOPS in 12% yield and a small quantity of another product, which appeared to have undergone multiple additions of methyl acrylate.



Scheme 51. Unsuccessful formation of potassium 1-phenylethane-1-sulfinate.

4.5 Project summary and future work

A highly efficient palladium-catalysed one-pot desulfinative cross-coupling to access medicinally relevant di(hetero)aryl methanes has been developed (Scheme 52). The method involves two electrophile starting materials; during the reaction, the benzyl halide is converted to a sulfone by S_N2 reaction with a key sulfinate reagent (SMOPS), and then to a benzyl sulfinate. This then undergoes desulfinative cross-coupling with a (hetero)aryl halide. Key advantages of this methodology are that all reaction components are commercially available from multiple sources. Broad functionality is tolerated on either coupling partner. Varying the bromide to other halides or pseudohalides led to high yields, whether present on either the benzyl or (hetero)aryl coupling partner. No deterioration in yield was observed when the coupling was performed on gram scale. Not only is this one-pot method operationally simple, but isolated benzyl sulfinate salts that previously displayed stability problems, and thus poor yields when cross-coupled, were found to couple efficiently when formed *in situ* through this method. For these reasons, we envisage this published methodology to be highly useful for medicinal chemists who require straight-forward methods to quickly synthesise a library of molecules.[186]



- Three-step one-pot route
- Avoids problematic preparation, purification and storage of benzyl sulfinates
- Lower atom economy, greener and faster route to diarylmethanes
- All reaction components are commercially available
- Functional group tolerant
- 50 examples, up to 99% yield

Scheme 52. Summary of the developed one-pot desulfinative cross-coupling method.

Chapter 5. Safety and practicality improvements for scale-up of the desulfinative cross-coupling reaction

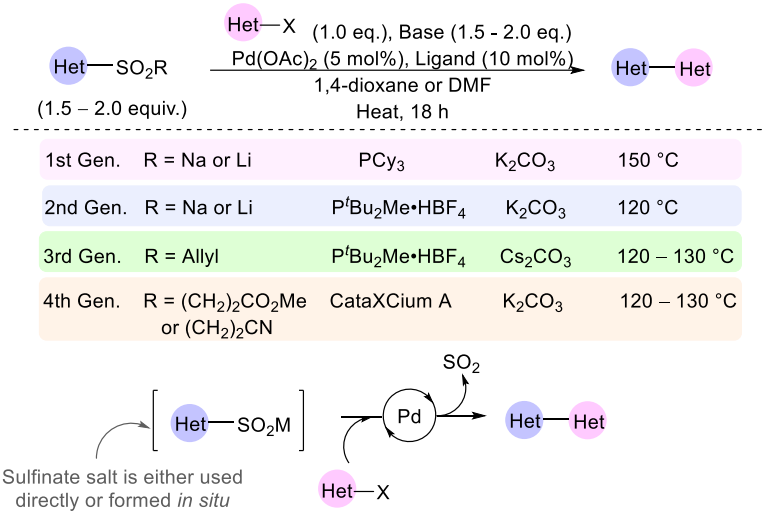
5.1 Origin and outline of project

5.1.1 Background

Biaryls are common motifs in pharmaceutical compounds, where pyridine rings feature prominently.[187] Although the Suzuki-Miyaura cross-coupling is often a convenient method to synthesise biaryls, there are sometimes problems associated with certain boronic acid starting materials.[188] Notably, 2-pyridyl boronic acids undergo rapid protodeboronation.[9-10, 154] As the 2-pyridyl moiety is prevalent in biologically active molecules, many alternative synthetic strategies have been developed.[16, 189] Although these methods prove to be viable options on laboratory scale, a lot of these may not be amenable to industrial scale syntheses. Some examples of these issues include the use of non-commercial and difficult to prepare starting materials,[15] lengthy reagent addition sequences,[190] high reaction temperatures,[191] and use of tailored catalysts.[17]

As a solution for the 2-pyridyl problem, the Willis group previously found that heteroaryl sulfinates were effective nucleophilic coupling partners in desulfinative cross-coupling reactions to form medicinally relevant scaffolds (Scheme 53).[18, 20] The original work focused on utilising sulfinate starting materials, however, these salts are not amenable to multistep sequences. This issue can circumvented by using latent sulfinate reagents, where the sulfinate is exposed *in situ*.[24-25] While we have seen increasing adoption of this Willis group desulfinative methodology in the wider chemistry community, most notably by

pharmaceutical companies,[192] significant draw-backs remain. The high temperature and requirement of closed reaction vessels limit the feasibility for larger scales.



Scheme 53. Previous C(sp^2)-C(sp^2) desulfinative cross-coupling work by the Willis group.

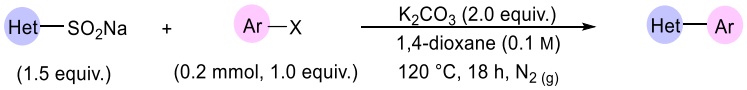
5.1.2 Project aims

Given that we can utilise the Willis group desulfinative methodology to afford highly useful heterobiaryls that are difficult to generate by other methods, we envisaged that improving the process to become safe, robust, and efficient when conducted on large scale would be highly useful to both academic and industrial chemists.[193] For the work within this thesis, large scale can be defined as any reaction using above 1 g of starting material. The main focus of this chapter will be on improvements to the desulfinative cross-coupling, with a brief discussion on synthesis of the sulfinate starting material.

The key issues associated with the current set of reaction conditions are outlined in Figure 10.[194] Firstly, the high reaction temperature of 120 °C is undesirable for several reasons. The lengthy time it would take to heat and subsequently cool the large volume of solvent would incur higher costs than a lower temperature reaction on large scale. Also, higher temperature reactions are understandably more of a safety concern due to the greater difficulty in controlling exotherms.[195] Secondly, the catalyst (palladium source and

phosphine ligand) is the most expensive component of the reaction mixture. Reducing the amount of catalyst and ligand used, whilst also ensuring the reaction remains high yielding, would lead to considerable cost savings. In the same way, lowering the loadings of other reagents such as the base, starting materials and solvent used in the reaction would also reduce costs but to a lesser extent. The currently used solvent, 1,4-dioxane, has associated health and safety concerns; its hazard phrases (H225, H319, H335, and H351) make it an undesirable reaction solvent on an industrial scale,[196] and specific risk assessments would be required for its use. Additionally, the boiling point of 1,4-dioxane is 101 °C, and the reaction is currently performed at 120 °C in a sealed tube. On a large scale, as a batch process, this would be considered hazardous, thus unlikely to be attempted by industrial chemists.[197] The method of purification on scale should also be a point of improvement. The time taken to perform column chromatography and the amount of solvents used during this process can increase costs considerably. Column chromatography is also considered a poor choice for environmental reasons due to the high volume of solvent and silica waste produced.[198]





Current issues:

- X Sealed, pressurised vessel (1,4-dioxane boiling point is 101 °C)
- X High reaction temperature
- X Undesirable solvent choice (toxic, not 'green')
- X Reagents in excess
- X Column chromatography

Goals:

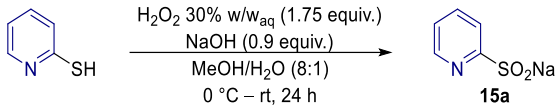
- ✓ Green, non-toxic solvent
- ✓ Work in an unpressurised round-bottom flask
- ✓ Robust, reproducible reaction on scale (5 g)
- ✓ Retain high yields
- ✓ Lower catalyst loading & stoichiometry

Figure 10. Summarised key issues with the current methodology.

5.2 Sulfinate starting material synthesis

5.2.1 Previous work

Firstly, optimisation of the starting material synthesis was investigated before evaluating the desulfinative cross-coupling. A wide variety of sulfinate salts are now available from commercial suppliers, however, reliable and efficient routes to generate them are still essential. A previous post-doctoral researcher in the group (Dr Philip R. Murray) performed the majority of the starting material optimisation, and found that oxidation of the heteroaryl thiol with hydrogen peroxide was the best route to form the corresponding sulfinate salt (Scheme 54). The additional contribution and improvements to this reaction will be discussed herein. Sodium 2-pyridyl sulfinate (**15a**) was selected as the model substrate due to the presence of the 2-pyridyl group in many pharmaceutical molecules, as well as the difficulty in incorporating this moiety by conventional cross-coupling methods.[16]



Scheme 54. Previous sulfinate synthesis reaction conditions developed within the group.

5.2.2 Inclusion of a quench step

As an excess of hydrogen peroxide was used in the reaction, it was important to ensure that this was fully quenched before initiating the work-up procedure. In the previous work, this reagent was assumed to have been consumed by leaving the reaction overnight, however, on large scale, the risk of unreacted remaining peroxide cannot be taken and we needed to ensure that none remained. Hydrogen peroxide test strips (0.5 – 25 mg/L H_2O_2, MQuant®, Supelco) were used to test the reaction mixture after it had stirred at room

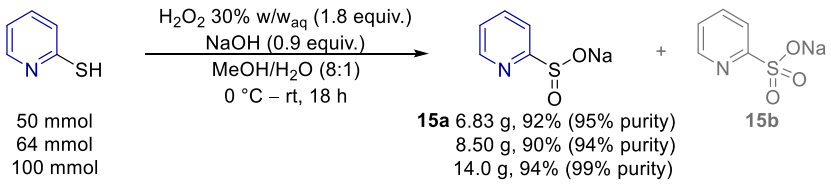
temperature for 18 hours. If the test strip deemed that no peroxide remained, then the quench step could be avoided. If some peroxide still remained, a quench step was required.

Commonly, sodium thiosulfate ($Na_2S_2O_3$) is used to quench hydrogen peroxide.[199] However, in our system it would be incompatible as the sulfinate salt product would likely have been contaminated with inorganic sodium sulfate or sulfite impurities. Manganese(IV) oxide (MnO_2) provided an excellent alternative, as it catalyses the decomposition of hydrogen peroxide to oxygen and water.[200] Manganese(IV) oxide is relatively low cost (£0.24 per 1 g, ≥ 90% purity)[201] and can be easily removed from the reaction mixture by filtration, due to its insolubility in water and organic solvents, thus avoiding inorganic impurity contamination of the sulfinate product. Due to its dark appearance, it was obvious if the reaction mixture needed to be refiltered to ensure full removal of the catalyst.

5.2.3 Optimisation

Slow addition of the hydrogen peroxide was critical in avoiding over-oxidation of the thiol to the sulfonate salt (**15b**) rather than the sulfinate salt (**15a**). Initially, the peroxide was added manually by syringe over 30 minutes. For practical ease and to ensure a consistent rate of addition, the manual syringe was replaced with a dropping funnel. More consistent results were achieved through this change, with low formation of sulfonate salt (0 – 2%) observed, despite a slight increase of hydrogen peroxide used (from 1.75 equiv. Scheme 54, to 1.8 equiv. Scheme 55). We also found that there was no yield improvement when the reaction was run for 24 hours compared to 18 hours, so the shorter time was chosen. Better yields were observed when a new, unopened bottle of 2-mercaptopyridine was used, as this readily oxidises in air to 2,2'-dipyridyl disulfide.[202] Although this process can

occur with hydrogen peroxide under mild conditions,[203] we did not observe this under the reaction conditions. Pleasingly, the sulfinate could be generated on large scale, in excellent yield, and with high purity.



Scheme 55. Modified sulfinate synthesis conditions.

5.3 Desulfinative cross-coupling reaction optimisation

5.3.1 Solvent screen

In the previous Willis group desulfinative cross-coupling work, the solvents used do not share many similarities; the boiling points, polarity and chemical structures of these solvents are vastly different (Figure 11). Compared to toluene and 1,4-dioxane, dimethyl sulfoxide has a considerably better toxicity profile and other green credentials.[170a, 170b] However, dimethyl sulfoxide can solubilise toxic reagents and easily carry them through skin,[204] and can undergo exothermic thermal decomposition at elevated temperatures.[205] Therefore, often it is undesirable to use for high temperature reactions in industry.[206]

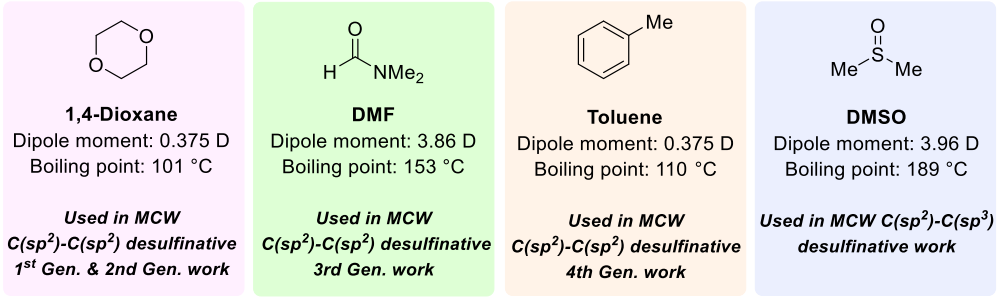


Figure 11. Comparison of different solvents used in previous desulfinative work.

A green solvent guide was used to provide a useful starting point for solvent selection.[170] As the reaction needed to be conducted at atmospheric pressure, it was important to

identify solvents that had high boiling points (≥ 120 °C). Low toxicity and reasonable cost were also important factors to consider. The ACS solvent selection tool proved to be extremely useful at identifying potentially viable solvents, setting high boiling points as a critical parameter as well as filtering by safety, health and environment rankings.[207] This allowed a variety of structurally different, but high boiling point, solvents to be selected for testing.

Firstly, we performed the desulfinative cross-coupling in sealed microwave vials on the same scale as per the previous work (Figure 12, blue bars).[18, 20, 25] Sodium pyridine-2-sulfinate (**15a**) and 4-bromotoluene were chosen as the model substrates, and the yields were calculated from HPLC data analysis against an internal standard (*p*-tolyl ether). Anisole was the clear front-runner, with isoamyl acetate, *p*-xylene, cyclopentanone, dimethyl sulfoxide, and sulfolane also showing promising yields. It is worth noting that unlike the other solvents, the sulfur containing solvents afforded homogeneous reaction mixtures.

Next, additional solvents were identified as potential candidates again through the ACS solvent selection tool. Phenetole (ethoxybenzene) was located in the same quadrant as anisole, which was the top performing solvent in the first screen; it is also considerably safer than anisole and has a higher boiling point (154 °C *vs* 168 °C). Ethoxybenzene has been shown to be an excellent green solvent in a variety of applications.[208]

Reactions with the top performing solvents were run outside a pressurised system, in a round-bottom flask (Figure 12**,** orange bars). There was a drop in yield for every solvent tested; notably for anisole, we saw a dramatic 60% reduction. Ethoxybenzene, sulfolane and tetrahydrothiophene-1-oxide proved most successful here. Interestingly, although 1:1

mixtures of sulfolane with either ethoxybenzene or anisole afforded a homogeneous reaction mixture, low product yields (5 – 15%) were observed in both cases.

Increasing the temperature to 150 °C for reactions with ethoxybenzene and sulfolane as the solvents (Figure 12**,** grey bars), was essential to reach excellent product yields (82% and 99% respectively). Even reducing the temperature by 10 °C (to 140 °C) led to substantially lower yields (50% and 21% respectively). Running the reaction in the absence of solvent at 140 °C, with the aryl bromide in excess (20 equiv.), produced the desired product in low yield (20%), which increased marginally to 23% at 150 °C.

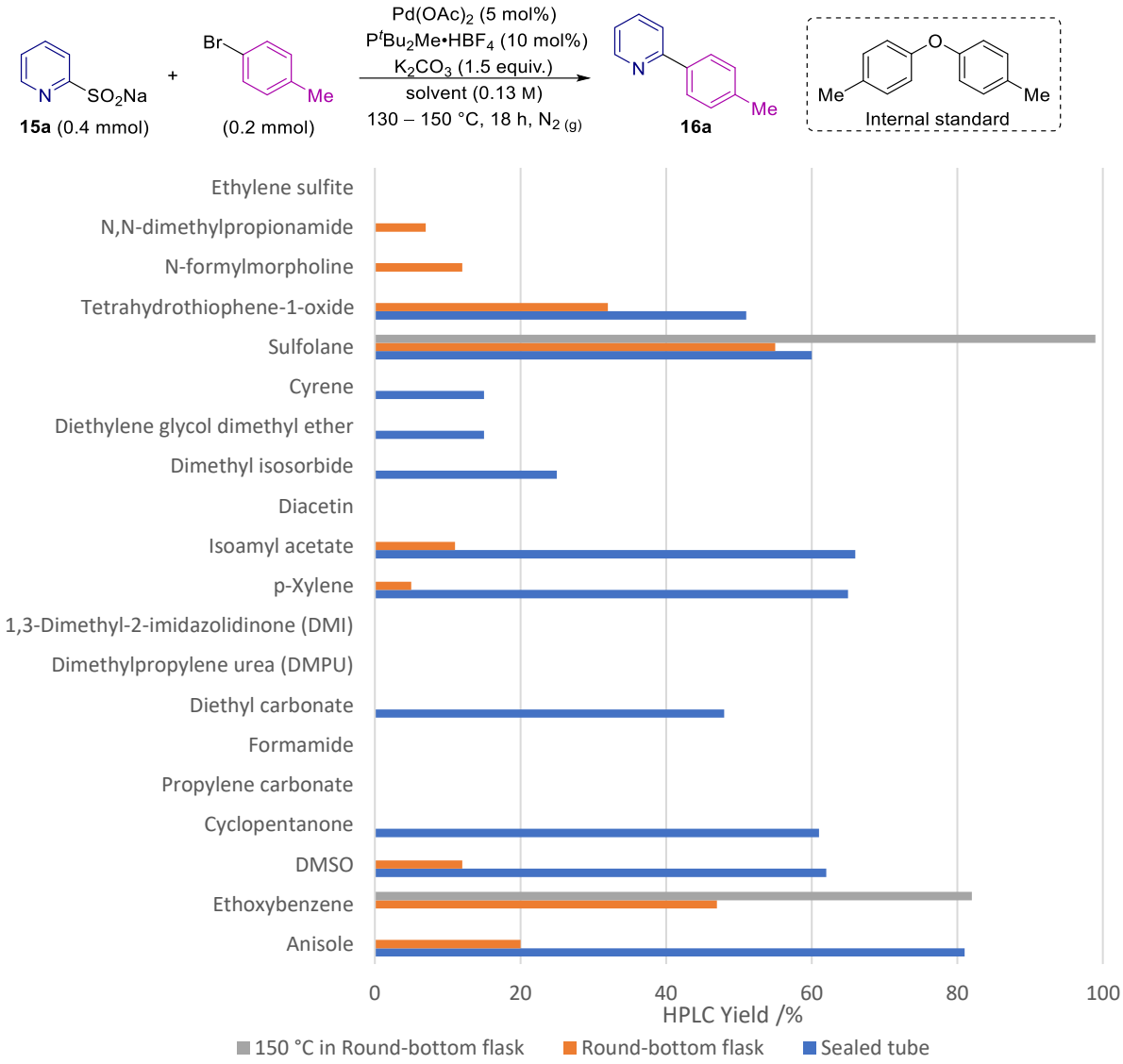


Figure 12. Solvent evaluation, with HPLC yields shown.

5.3.2 Altering the ligand

Previous desulfinative cross-coupling work in the Willis group demonstrated that electron-rich and bulky phosphine ligands were optimal.[18, 20, 24, 159] We investigated whether a cheaper alternative to P^{t}Bu$_2$Me·HBF$_4$ would be efficient (Table 26). Tricyclohexylphosphine is significantly cheaper (£19.10 per gram from Sigma Aldrich)[209] than di-*tert*-butyl(methyl)phosphonium tetrafluoroborate (£44.50 per gram from Sigma Aldrich).[210] CataCXium A was also tested, due to previous success in related desulfinative cross-couplings,[25] however, it did not give any benefit and its higher cost made this an undesirable option (£91.40 per gram from Sigma Aldrich).[211]

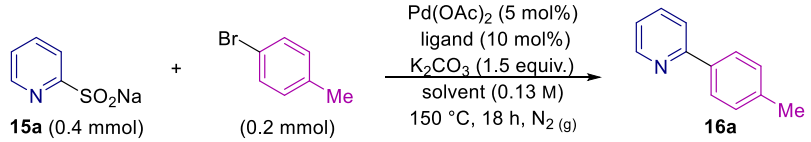


Table 26. Ligand effects on yield for the desulfinative cross-coupling.

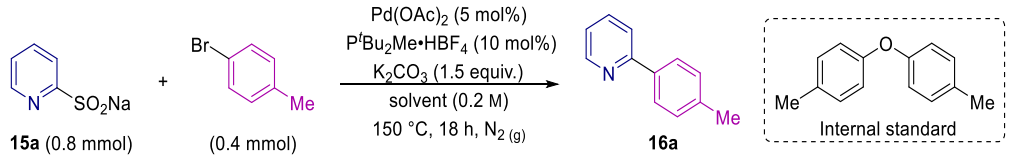
Entry [a]	Solvent	Yield (PCy_3) /%	Yield (P^{t}Bu$_2$Me·HBF$_4$) /%	Yield (CataCXium A) /%
1	Ethoxybenzene	20	82	31
2	Sulfolane	12	99	-

[a]Yields are given as HPLC yields, using *p*-tolyl ether as the internal standard.

5.3.3 Initial scale increase

With two good solvent options in hand, simultaneously the reaction concentration was increased and the scale was doubled (Scheme 56). Very surprisingly this resulted in a dramatic drop in yield for the reaction in sulfolane (16% yield, down 83%), whereas the reaction utilising ethoxybenzene saw an increase in yield (89%, up 7%) compared to the previous conditions (Table 26). Furthermore, a noteworthy drawback of using sulfolane was that its melting point (27.5 °C) made transfer of the solvent into the reaction vessel difficult at room temperature; a heat gun was required to melt the solvent to reduce

needle blockages during accurate addition. The reduced yields observed when using sulfolane, coupled with this practical problem, meant that ethoxybenzene was the solvent taken forward for further work.



15a (0.8 mmol) (0.4 mmol) **16a**

Scheme 56. Scale and reaction concentration increase.

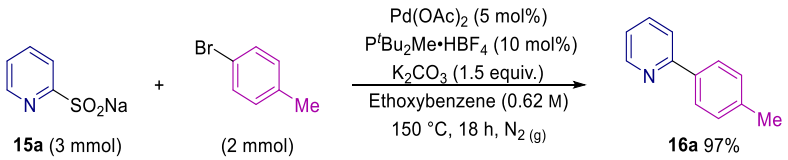
As inefficient stirring can be a limitation in large scale reactions,[193, 212] we next monitored the effect of stirrer-bar size. The reaction scale was increased to 1 mmol and the reactions were conducted in 25 mL round-bottom flasks (Table 27). These results show that the larger stirrer-bar is critical to achieve excellent product yield (entry 2). Pleasingly, increasing the scale to 2.0 mmol and doubling the reaction concentration to 0.4 M led to 95% yield of the desired biaryl. Increasing the reaction concentration is desirable as it reduces the amount of solvent required, incurring lower costs and producing less waste.

Table 27. The effect on yield of the magnetic stirrer-bar size. The stirrer speed set to 400 rpm.

Entry	Stir-bar size	Relative stir-bar size to vessel	HPLC Yield /%
1	15 mm × 6 mm		79
2	20 mm × 10 mm		96

5.3.4 Decreasing reagent amounts

Our next step was to determine if the number of equivalents of sulfinate and base could be reduced, whilst retaining high yield, prior to further scaling up the reaction. No reduction in yield was observed when the equivalents of sulfinate were lowered (from 2.0 to 1.5, 95%), so the lower option was taken forward. No benefit was observed when switching the stoichiometry of sulfinate (**15a**) and aryl bromide (18%). Further attempts to lower the amount of sulfinate led to reduction in yield (1.2 equiv., 59%), and lowering the amount of potassium carbonate led to the same outcome (Table 28, entries 1 – 2). Disappointingly, we found that the catalyst loading could not be lowered without a significant detrimental impact on yield (entries 3 – 5). Prior to addition into the reaction mixtures, the ethoxybenzene solvent was degassed by sparging with N_2 gas and dried over 4Å molecular sieves. It was important to determine if this process was necessary, as being able to use wet solvents purchased directly from the supplier would be advantageous. Our test illustrated that the presence of water and air within the solvent does not cause a devastating impact on yield (entries 6 – 7). Unfortunately, further efforts to lower the reaction temperature, on this slightly larger (2.0 mmol) scale reaction, led to drastic reductions in amount of **16a** (entries 8 – 9). We observed very little difference in yield when the reaction was run more dilute (entry 10), so opted for a more concentrated reaction mixture (0.62 M). Entries 11 – 13 display reactions with even more concentrated reaction mixtures, performed on a 4 mmol scale. From these results we can see that raising the concentration higher than 0.62 M results in a decrease in yield, likely due to poorer solubility of the reagents resulting in an uneven distribution in the mixture.



15a (3 mmol) (2 mmol) **16a** 97%

Table 28. Reducing amounts of reaction components and attempts to lower the temperature.

Entry	Variation from the above	HPLC Yield[a] /%
1	K_2CO_3 (1.3 equiv.)	74
2	K_2CO_3 (1.4 equiv.)	79
3[b]	2.5 mol% [Pd]	41
4[b]	1.25 mol% [Pd]	8
5[b]	0.62 mol% [Pd]	5
6	Not degassed and wet	80
7	Degassed and wet	79
8	140 °C	83
9	130 °C	48
10[c]	0.4 M (14.6 solvent volumes)	95
11[c]	0.67 M (8.8 solvent volumes)	90
12[c]	0.8 M (7.3 solvent volumes)	72
13[c]	1.0 M (5.8 solvent volumes)	71

[a]HPLC yields using *p*-tolyl ether as an internal standard. [b]The amount of ligand used was twice the mol% of the [Pd]. [c]Reactions performed on 4 mmol scale.

5.3.5 Large scale optimisation

After excellent success with reactions on 4 mmol scale, we next wanted to scale up the reaction further and reinvestigate if the catalyst loading could be reduced due to the importance of lowering the most expensive materials in the reaction. Pleasingly, on a larger 10 mmol scale, the reaction tolerated a reduction in palladium loading to 3 mol% (Table 29, entries 1 – 3). Lowering any further resulted in dramatically reduced product yield (entry 4). With the lower, 3 mol% [Pd] loading selected, we doubled the scale again (entry 5) which pleasingly did not lead to any reduction in yield.

When increasing the scale to 35 mmol we began to encounter problems (entry 6). The reduced yield was likely caused by a lower internal reaction temperature than the external hot-plate temperature, as a result of poorer heat transfer when using a greater solvent

volume on larger scale. To test this, the reaction was repeated with an internal temperature probe inserted through the reaction vessel suba-seal® (Figure 13A). To ensure that an inert atmosphere would be maintained, the joint was wrapped in Parafilm®. The heating probe demonstrated that the internal reaction temperature was actually 15 °C lower than the temperature displayed on the stirrer-hot plate (Figure 13B). Raising the external hot plate temperature above 150 °C, and thus the internal temperature to the optimised temperature of 150 °C (Figure 13C & D), highlighted the critical nature of the elevated 150 °C temperature to achieve excellent yields (entries 7 – 8). Even an internal temperature of just 5 °C lower than the optimal, led to nearly a 25% decrease in yield (entry 7 *vs* 8). Here, the temperature effect was far greater than what was previously observed with a 2 mmol scale reaction run at 140 °C (Table 28, entry 8).

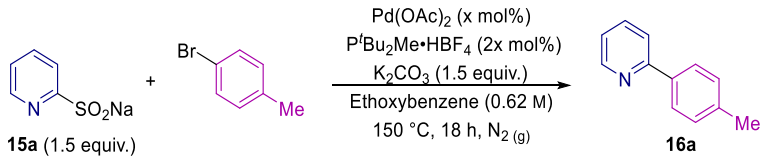


Table 29. Reducing [Pd] loading when scaling up the reaction.

Entry	Scale /mmol	[Pd] /mol%	HPLC Yield /%	Isolated Yield /%
1	10	5	97	98
2	10	4	92	96
3	10	3	93	92
4	10	2	81	82
5	20	3	91	92
6[a]	35	3	58	-
7[b]	35	3	65	63
8[c]	35	3	88	87
9[cd]	35	3	85	89
10[c]	35	3	91	92

[a]150 °C external reaction temperature, likely 135 °C internal temperature (no probe used). [b]145 °C internal reaction temperature. [c]150 °C internal reaction temperature. [d]Reaction vessel with reagents in was purged with N_2 before addition of solvent, rather than vacuum cycling as in the other entries.

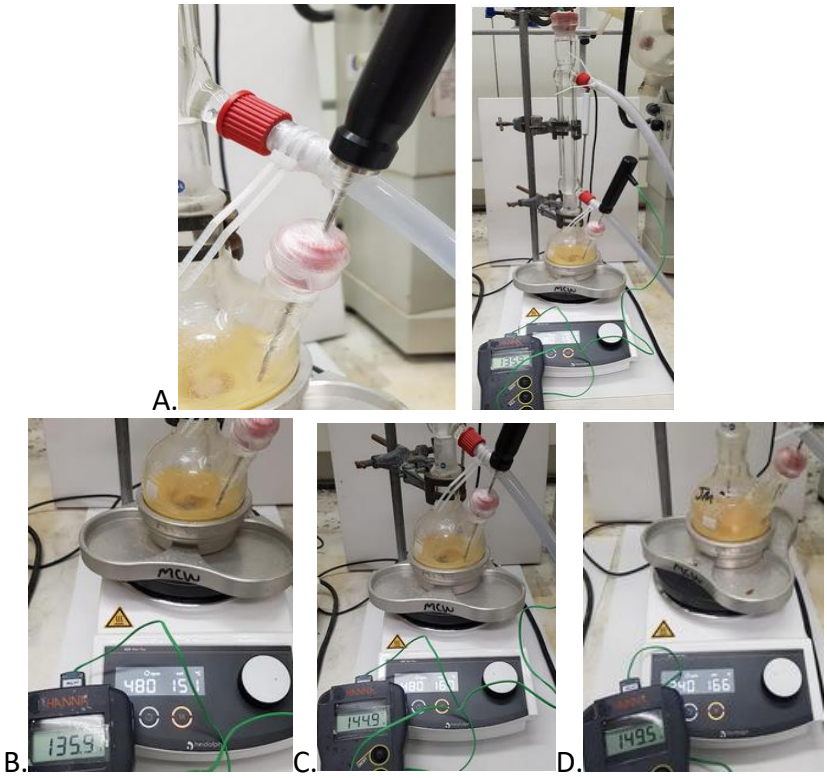


Figure 13. The heating probe showed that the internal reaction temperature was approximately 15 °C lower than the external hot-plate temperature probe reading, for the 35 mmol scale reaction.

5.3.6 Monitoring the reaction profile

Next, we wanted to determine if the reaction could be stopped sooner, as again this would have a financial benefit to industrial chemists. Aliquots of the reaction mixture were taken over a 24-hour period, run on the HPLC and the product (**16a**) yield calculated. The results are displayed in Figure 14. Unfortunately, a prolonged reaction time was shown to be necessary, as after 7 hours only a 59% HPLC yield was observed.

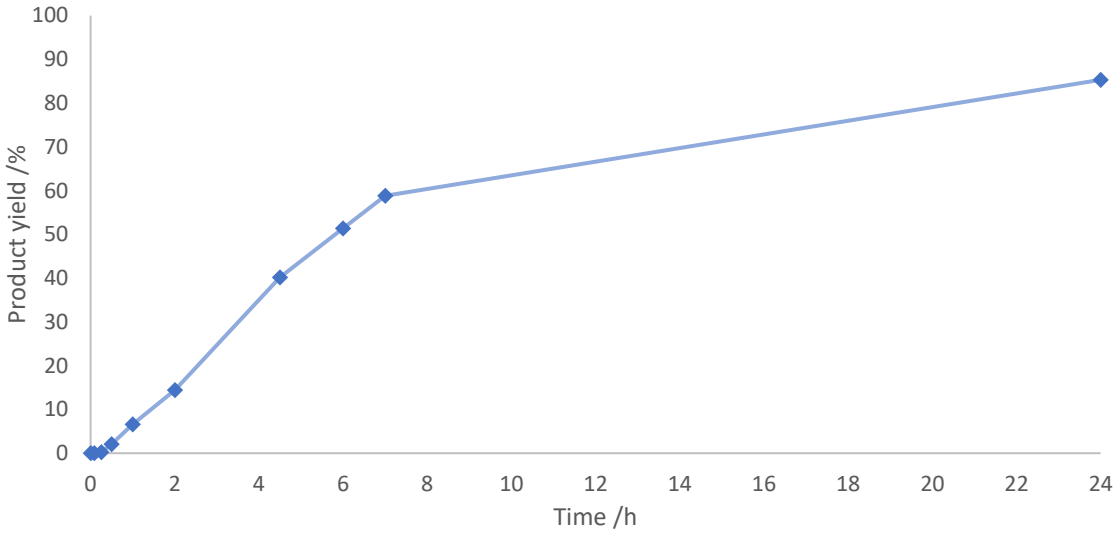


Figure 14. Reaction profile of the large scale (35 mmol) desulfinative cross-coupling monitored over 24 hours using HPLC. HPLC yields calculated using p-tolyl ether as an internal standard.

5.4 Work-up and purification optimisation

5.4.1 Celite filtration and brine washes

Cooling the reaction mixture to room temperature, allowed it to become heterogeneous. Since the product was readily soluble in the ethoxybenzene solvent, we found that the solids could easily be removed by filtration through celite. These solids were unreacted sodium 2-pyridyl sulfinate (**15a**), potassium carbonate and likely palladium black, due to the dark/black appearance of the reaction mixture. The celite cake was washed with organic solvent, and the solvents were then removed by a rotary evaporator.

The concentrated reaction mixture was then transferred to a separating funnel. Isopropyl acetate was chosen as the work-up solvent, over the more commonly used ethyl acetate, as this has a low water solubility (8.7% solubility in water vs 0.7% for isopropyl acetate),[213] reducing the amount of product present in the aqueous layer. To ensure the removal of any residual inorganic impurities and water, the organic layer was washed with brine twice. As a general note, we also wanted to ensure that wash volumes were kept to <10 volumes

(1 solvent volume = 1 mL solvent per 1 g of starting material) to limit the amount of solvent waste generated during work-up.

5.4.2 HCl wash

As ethoxybenzene is a high boiling point solvent, it could not be separated from the desired product easily using a rotary evaporator. This problem could be circumvented by washing the organic layer with an aqueous acidic solution (1M HCl), leading to protonation of the pyridine nitrogen atom. The resulting pyridinium hydrochloride salt (**16c**) was then more soluble in the aqueous phase, whilst the solvent and any remaining aryl bromide starting material remained in the organic phase, which could then be discarded. The aqueous phase could then be neutralised by slow addition of 3.0 M aqueous sodium hydroxide solution to form a cloudy solution. The solution was checked with pH paper to ensure it was now basic. Subsequent extraction with isopropylacetate allowed the product (**16a**) to be separated into the organic layer, with residual inorganic impurities remaining in the aqueous layer.

5.4.3 Removal of by-product through [Cu] washes

The main byproduct of the desulfinative cross-coupling was 2,2'-bipyridine (**16b**), resulting from the homocoupling of two sodium pyridine-2-sulfinate (**15a**) compounds. Sulfinate homocoupling is a known method to generate Pd(0) to enter the desulfinative cross-coupling catalytic cycle.[159] Therefore, it is unsurprising that this byproduct was observed by LRMS in addition to the product. For low yielding reactions, the peak corresponding to 2,2'-bipyridine became more obvious, however, it was still noticeable when reactions were high yielding. When the HCl wash (see section 5.4.2) was performed, the bipyridine side-product was protonated as well as the desired product. Therefore, it

was not removed through this process along with the solvent and any remaining aryl bromide starting material.

Column chromatography is an excellent way of separating organic compounds, however, on a large scale it is undesirable due to the sheer volume of waste solvent generated and the long time they can take to run. We wanted to determine if we could successfully separate the two compounds with minimal time and solvent spent. In an effort to speed up the process, a silica packed column was flushed first with 100% petrol (250 mL), then 20% ethyl acetate in petrol (250 mL) and finally 30% ethyl acetate in petrol (500 mL), with each portion of eluent collected into a separate conical flask. Unfortunately, the similar TLC R_f values of the byproduct and the desired product meant this fast-method of separation proved futile, as they coeluted in the 20% fraction.

As a quick flush through a silica column did not seem to be an appropriate way to ensure complete separation of the byproduct from the product, we needed a different strategy. We envisaged that selective coordination to copper could be efficient to achieve this separation. This idea stemmed from the knowledge that pyridine can be removed from a reaction mixture by complexation to copper,[214] achieved by washing the organic solution during work-up with saturated aqueous copper sulfate solution. The hope was that the product (**16a**) would not complex with copper as efficiently as the 2,2'-bipyridine (**16b**), allowing for selective removal of the side-product in the aqueous layer.

To test whether this approach could be successful, equal amounts of pure 2-tolylpyridine (**16a**, 100 mg) and 2,2'-bipyridine (**16b**, 100 mg) were dissolved in isopropyl acetate (10 mL). This solution was transferred to a separating funnel (50 mL), before addition of saturated $CuSO_4 \cdot 5H_2O$ solution (10 mL). Unfortunately, a precipitate formed that remained

after addition of both isopropyl acetate (10 mL) and water (10 mL). As it was likely the saturated copper solution caused the precipitate to form, the test was performed again but using an aqueous solution with a lower concentration of copper (1% $CuSO_4 \cdot 5H_2O$). Prior to washing, a HPLC sample of 2-tolylpyridine (**16a**) and 2,2'-bipyridine (**16b**) showed a clear 1:1 ratio, as expected. After the first wash, the HPLC sample showed a 1:4.7 ratio of 2,2'-bipyridine to product. The second wash showed that only trace amounts of 2,2'-bipyridine remained in the organic layer. To ensure complete removal of copper residue, the organic layer was washed with aqueous Na_2EDTA solution (1×10^{-4} M, 3 × 10 mL) (Figure 15).[215]

After the organic layer was dried and solvents were removed, 2-tolylpyridine (**16b**) was isolated in 86% yield (99% purity by qNMR). We were delighted that 2,2'-bipyridine could be completely removed from a sample of 2-tolylpyridine by complexation to copper in this small scale test. The reduced yield of 2-tolylpyridine can be attributed to some complexation with copper, so it would be important to limit the number of washes. In the desulfinative cross-coupling reaction, the 2,2'-bipyridine side-product was not formed in a 1:1 ratio with the product, so we envisaged that this method would be efficient for removal of small amounts of 2,2'-bipyridine with minimal effect on product yield.

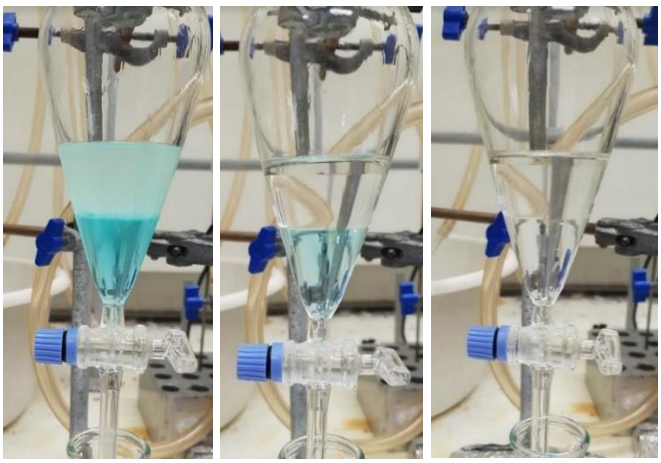


Figure 15. Loss of colour during washes to remove [Cu].

When this process was conducted for the desulfinative cross-coupling on 35 mmol scale, pleasingly, no loss of product was observed and the 2,2'-bipyridine was completely removed from the reaction mixture.

5.4.4 Purification by column chromatography

Unfortunately, after aqueous work-up followed by solvent removal, the resulting oil was very dark in colour. The 2-tolylpyridine product (**16a**) should be a pale yellow oil, not a brown oil, so further purification was required. An effective way of removing this colour was to pass the product through a silica plug (4 x 5 cm), by flushing it through with 100% ethyl acetate to afford the product as an orange oil (Figure 16).

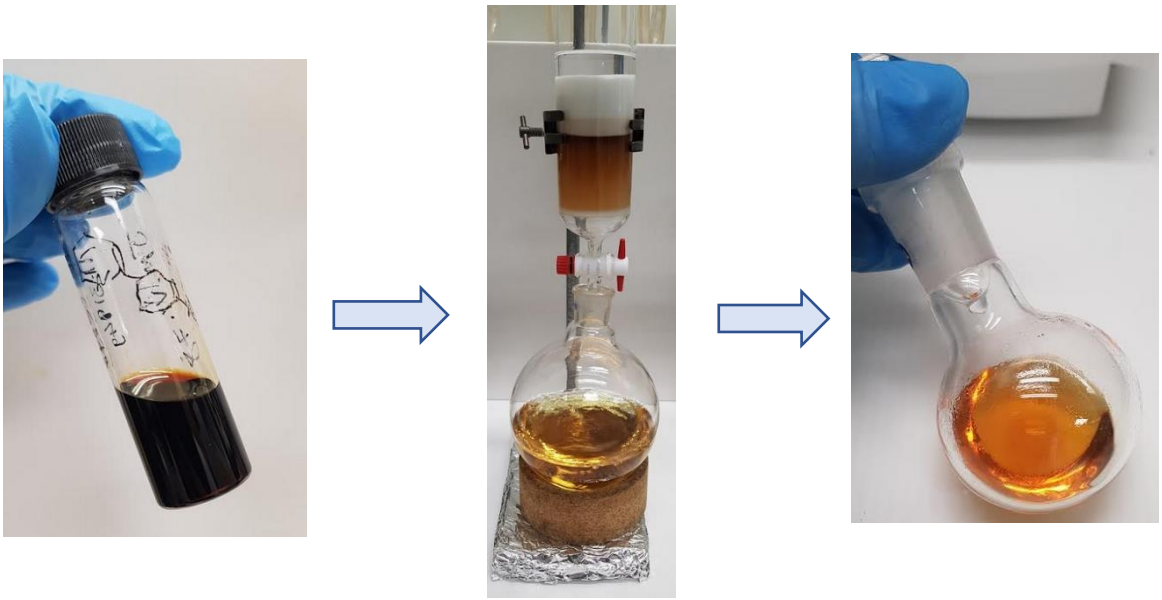


Figure 16. A flush through silica leads to significant removal of colour.

Instead of flushing the product off the silica with 100% ethyl acetate, we found that applying a gradient and collecting the eluent in small vials afforded the product as a yellow oil. A slower, and more conventional column chromatography approach meant further removal of coloured impurities was achieved (Figure 17). A significant drawback of this method of purification is the considerable solvent waste generated in comparison to washings during aqueous work-ups and crystallisations. Here, the column was first flushed

with petrol (400 mL) to remove any grease residues. Then 15% ethyl acetate in petrol (960 mL) followed. This led to a total of 1.36 L solvent used during the column alone, not taking into consideration solvent used in rinsing out the eluent from the vials.

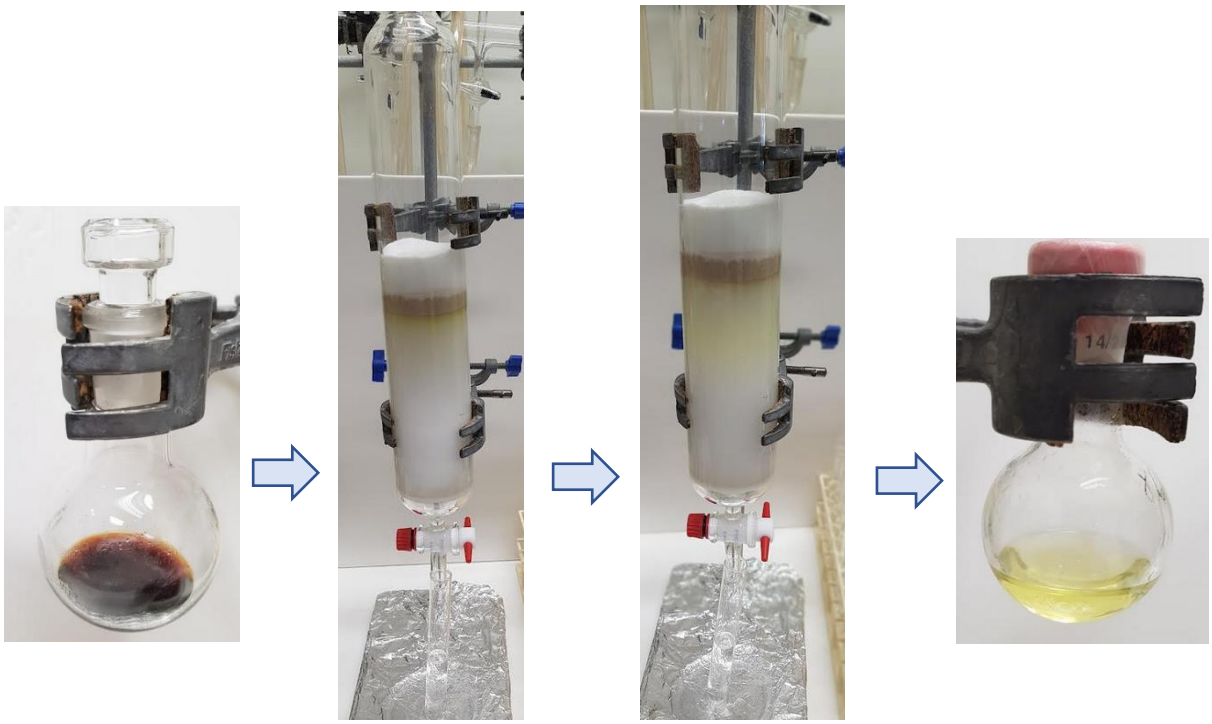


Figure 17. Column chromatography afforded the product as a pale yellow oil.

5.4.5 Purification by salt formation and recrystallisation

An alternative, and greener, purification method to column chromatography was to form the product as a HCl salt (**16c**). After purification by recrystallisation, the material could be converted back to the desired product by treatment with base.

Initially, we wanted to test if this concept would work on smaller scale (1 g). A sample of the product was mixed with diethyl ether (10 solvent volumes) and placed in an ice-water bath, in case any exotherm arose. Further tests showed that this was not necessary. Slow additions of hydrogen chloride solution (2.0 M in diethyl ether, 1.2 equiv.) resulted in precipitation of a white solid. Vacuum filtration afforded 2-tolylpyridine as a hydrochloride

salt. The salt was returned to 2-tolylpyridine by addition of aqueous sodium hydroxide solution (3.0 M, 1.26 equiv.) and extraction with isopropyl acetate. The product was obtained as a yellow oil in 97% yield, with some, but not all, removal of colour clearly taking place through this method (Figure 18).

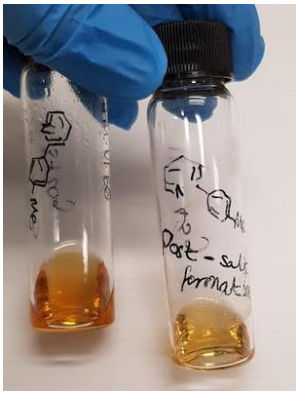


Figure 18. Before (L) and after (R) samples of 2-tolylpyridine display some colour removal.

It was important to determine if further decolourisation of 2-tolylpyridine (**16a**) could be achieved by recrystallisation of the salt (**16c**), prior to free-basing. Small scale tests were performed with multiple polar solvents to determine if they could provide suitable recrystallisation conditions (Table 30). From these investigations it was clear that isopropanol, acetonitrile and acetone were all viable options. Next, larger scale tests were performed with these solvents. In each case, approximately 175 mg of the salt was added to a 25 mL round-bottom flask and placed on a stirrer-hot plate set to 5 °C higher than the solvent boiling point. Hot solvent was then added to the round-bottom flask, in measured increments. Once all the crystals were dissolved, leading to a yellow-tinged solution, the flask was removed from heat, to allow crystals to form, and the solvent volumes were totalled. For isopropanol and acetonitrile (entries 3 – 4), crystals began to appear within 15 minutes but these were left overnight before filtration to ensure full crystallisation could occur (Figure 19). For acetone (entry 5), likely due to the large volume of solvent initially required to solubilise the salt, crystals were exceedingly slow to appear. After 24 hours,

very few were present, so this solvent was deemed not feasible and the contents of the round-bottom flask were discarded. Although the yields were not remarkable for isopropanol and acetonitrile, we thought there may be an improvement when the scale was increased due to potential human error leading to a loss of the fine crystals on the filter funnel frit. As a higher yield was achieved with isopropanol, this was chosen over acetonitrile.

Table 30. Recrystallisation tests.

Entry	Solvent	Initial test comments[a]	Larger scale test
1	Ethanol	Soluble at rt	-
2	Ethyl acetate	Insoluble at rt and insoluble with heat	-
3	Isopropanol	Partially soluble at rt, soluble with heat	3 mL required, 80% yield
4	Acetonitrile	Insoluble at rt, soluble with heat	4 mL required, 71% yield
5	Acetone	Insoluble at rt, soluble with heat	45 mL required

[a]The salt was added to a 2 mL vial before addition of a small volume of solvent. Heat was applied by a heat gun.

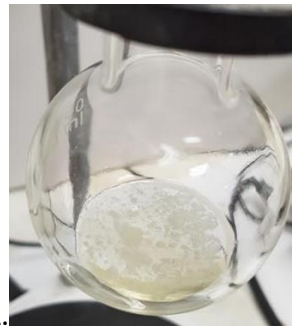
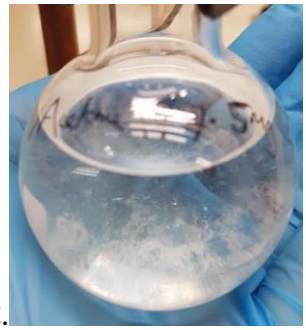
A.  B.  C. 

Figure 19. Crystallisation in 2-propanol (A) and acetonitrile (B), after 15 minutes, and acetone (C) after 24 hours.

Next, it was important to determine whether this recrystallisation could be a successful purification method for the large-scale reaction. After the aqueous work-up procedure described earlier (sections 5.4.1 – 5.4.3), 2-tolylpyridine was obtained as a dark-brown oil with 93% purity (by qNMR). The dark brown oil was diluted in methyl *tert*-butyl ether (MTBE), before slow addition of hydrogen chloride solution (2.0 M in MTBE, 1.2 equiv.) by syringe. Conveniently, hydrogen chloride solutions are commercially available in a variety of organic solvents, however, the majority of these are not amenable to industrial process chemistry laboratories. MTBE was chosen as it is a safer alternative to diethyl ether, due to

it being less likely to form explosive peroxides, and is a commonly used replacement in industry.[216] The mixture was stirred for 15 minutes whereupon a white precipitate could clearly be seen (Figure 20B). Vacuum filtration afforded the salt (**16c**) as a light brown amorphous solid (Figure 20C & D) in quantitative yield.

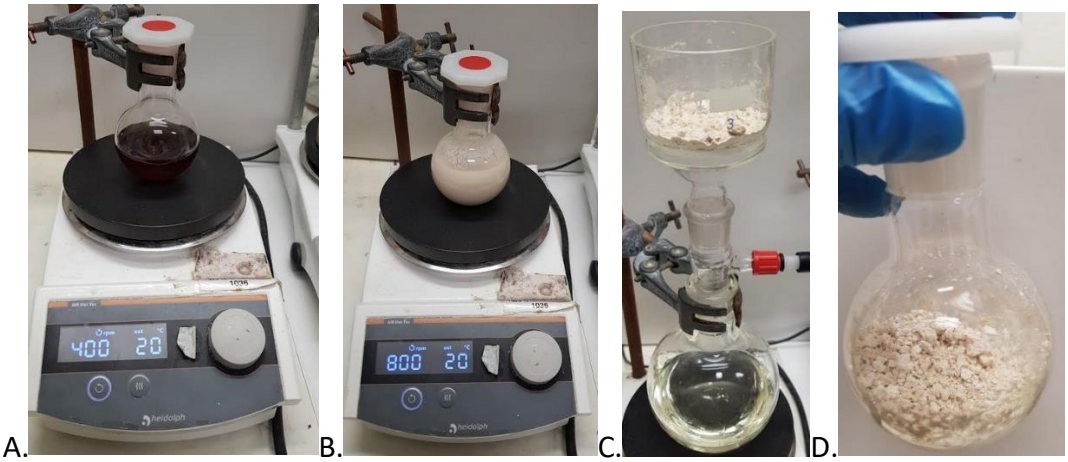


Figure 20. Formation of the 2-(p-tolyl)pyridine-1-ium chloride salt.

Next, the salt (**16c**) was recrystallised with isopropanol (Figure 21). When dissolved in the hot solvent, the solution returned to a dark brown colour alike to before salt formation (Figure 13A). Within 30 minutes of being left at room temperature, white crystals had appeared. The filtrate was retained, the solvents removed and the recrystallisation reattempted. The crystals obtained from the second recrystallisation were darker in colour (Figure 13D), however, qNMR analysis showed that the crystals from both the first and second attempts were of 99% purity, and a combined yield of 95% was achieved.

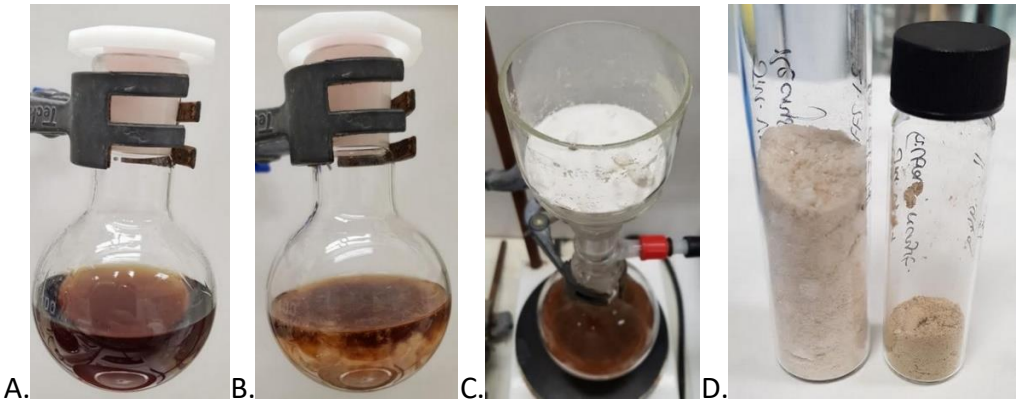


Figure 21. Stages of hydrochloride salt recrystallisation to give the product as off-white crystals.

To regenerate the free pyridine (**16a**), water was added to the crystals (**16c**) and this solution was transferred to a separating funnel. Aqueous sodium hydroxide solution (3.0 M, 1.5 equiv.) was added and the resulting mixture was extracted with isopropyl acetate. Removal of the solvents and drying led to isolation of 2-tolylpyridine (**16a**) as a brown oil. This process achieved the product in quantitative yield with purity of 99% by qNMR analysis, however removal of the brown colour was unsuccessful.

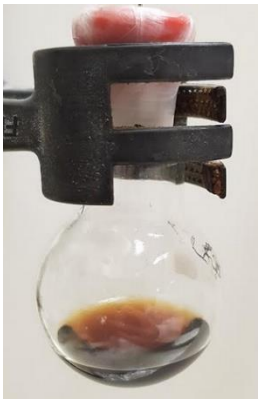


Figure 22. Regeneration of 2-tolylpyridine after salt formation and subsequent recrystallisation.

5.4.6 Activated charcoal filtration

Activated charcoal is known to be an effective decolourising agent, due to its large surface area where non-polar molecules can be adsorbed.[217] The desulfinative cross-coupling reaction was performed on 10 mmol scale, to test if activated charcoal could be a beneficial step to add during purification. Firstly, the filtration through celite was performed and then activated charcoal (one medium spatula) was added to the solution. This was stirred for just five minutes, before filtration through the same celite plug. Pleasingly, decolourisation was noticeable (Figure 23). The other work-up steps were performed as previously described, giving the final isolated 2-tolylpyridine (**16a**) product as a yellow oil (rather than a brown oil). This demonstrated that the activated charcoal was effective at removing most of the dark pigment.

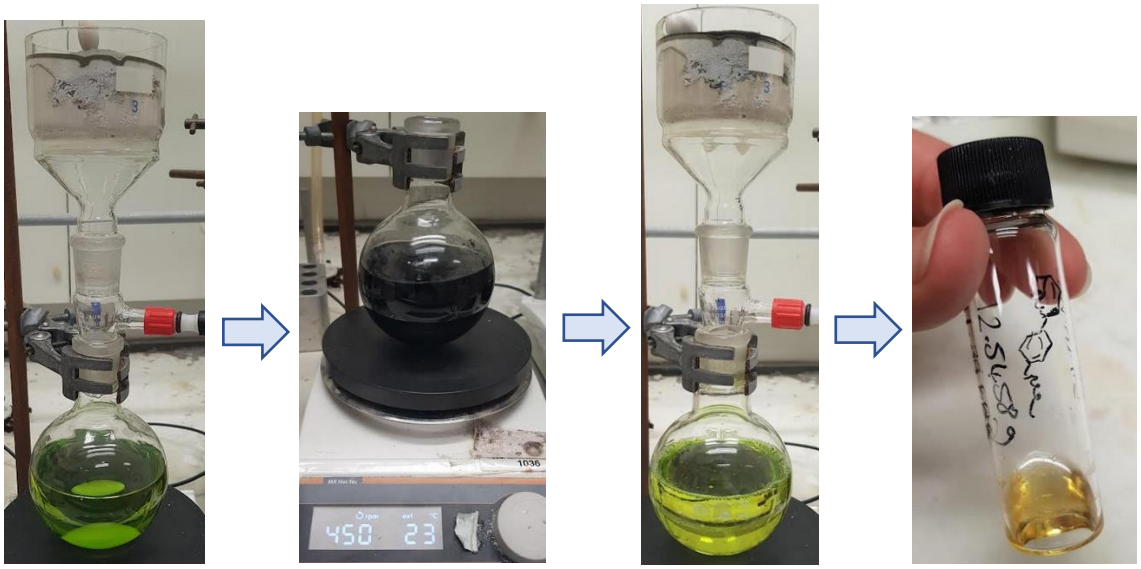
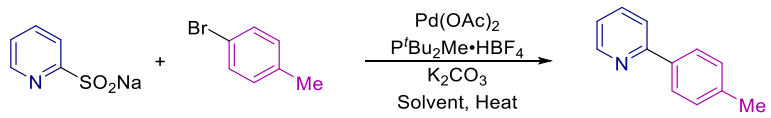


Figure 23. Work up including activated charcoal step to decolourise.

However, it is important to note that once the reaction had cooled to room temperature, and prior to any work-up, a HPLC sample was taken to calculate the yield. The HPLC yield was calculated to be 92% whilst the isolated yield was given as a much lower 68%. Unfortunately, 2-tolylpyridine (**16a**) must be sufficiently non-polar to also be adsorbed onto the activated charcoal. Due to the considerable product loss, and some colouration remaining in the final product, this approach was abandoned.

5.5 Project summary

Our new and improved conditions have reduced the catalyst loading to nearly half the original amount, lowered the equivalents of base, switched to a solvent with a safer toxicity profile and higher boiling point, and lowered volume of solvent needed (Table 31). These changes have lowered the cost of running the reaction on scale significantly, aided the solubility of the reaction mixture and eliminated the need for the reaction to be conducted under pressure in a sealed tube. The only negative to our new set of conditions was that an elevated reaction temperature of 150 °C proved essential. Perhaps with other coupling partners, where the rate-limiting desulfinative step occurs more readily, the reaction temperature could be reduced. A great deal of attention was paid to the work-up and purification procedures. The volume of solvent used contributes to a notable proportion of the cost of these processes on large scale. We found that filtration through celite, followed by an aqueous work-up was efficient at removing the majority of impurities. Both forming the product as a HCl salt with purification by recrystallisation, or purification by column chromatography proved to be efficient methods to give the desired product in excellent purity.



15a (1.5 equiv.) **16a**

Table 31. Comparison of the conditions before this project commenced and on completion.

Before	Now
$Pd(OAc)_2$ (5 mol%)	$Pd(OAc)_2$ (3 mol%)
$P^tBu_2Me{\cdot}HBF_4$ (10 mol%)	$P^tBu_2Me{\cdot}HBF_4$ (6 mol%)
K_2CO_3 (2.0 equiv.)	K_2CO_3 (1.5 equiv.)
1,4-Dioxane (0.1 M)	Ethoxybenzene (0.62 M)
120 °C	150 °C
Celite filtration	Celite filtration
Column chromatography	HCl salt formation and recrystallisation or column chromatography
0.2 mmol scale, 85% yield (28.7 mg)	35 mmol scale, 92% yield, 99% purity (5.43 g)

To further compare the improvements made to the reaction, we also investigated the cost savings for each reagent (Table 32). The total cost for the reagents required to synthesise 2-tolylpyridine (**16a**) in two-steps from 2-mercaptopyridine amounts to £104.58 (on 35 mmol scale). The synthesis of sodium pyridine-2-sulfinate (**15a**) comes to just £16.52, and the palladium catalysed desulfinative cross-coupling step costs £88.06.

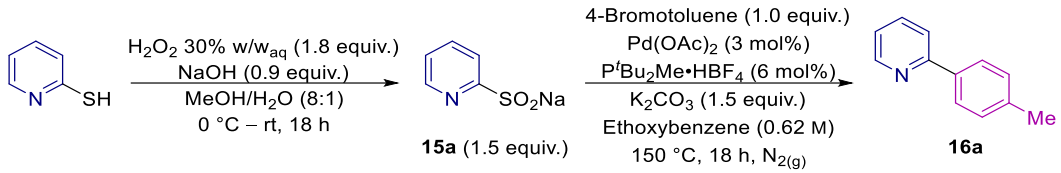


Table 32. Cost breakdown for the synthesis of 2-tolylpyridine from 2-mercaptopyridine.

Chemical	Supplier	Cost per gram or mL /£	Amount needed	Cost per reaction /£
$Pd(OAc)_2$	STREM	109.00	0.236 g	25.69
$P^tBu_2Me{\cdot}HBF_4$	Santa Cruz Biotechnology	54.00	0.521 g	28.13
K_2CO_3	Sigma Aldrich	0.42	7.26 g	3.05
4-Bromotoluene	Sigma Aldrich	3.70	5.99 g	22.16
Ethoxybenzene	Sigma Aldrich	0.16	56.5 mL	9.04
2-Mercaptopyridine	Fluorochem	0.96	7.10 g	6.82
30% H_2O_2	Sigma Aldrich	0.04	11.75 mL	0.47
Methanol	Sigma Aldrich	0.03	288 mL	8.64
NaOH	Sigma Aldrich	0.21	2.30 g	0.48
Manganese(IV) oxide	Sigma Aldrich	0.44	0.25 g	0.11

Excluding the cost of synthesising the sulfinate starting material, if the desulfinative cross-coupling had been conducted on 35 mmol scale with the same conditions as for the 0.2 mmol scale reaction, the total cost for the components would be £148.56. With the improved reaction conditions, the total cost would be £88.06. Therefore, there is a saving of £60.50 compared to the original conditions (Table 33). This means that, as well as the vastly improved safety and practicality aspects of the reaction, we have also achieved a significant cost decrease of 41%. Of course, if the work-up procedure was also to be taken

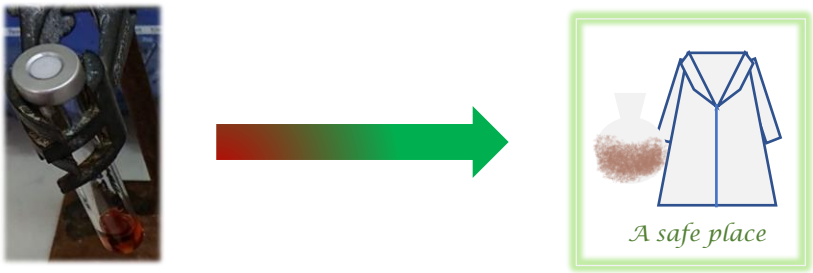
into account, considerable cost savings would be made there too with the vastly reduced solvent waste generated.

Table 33. Cost change summary for each component of the cross-coupling reaction.

Chemical[a]	Cost per gram or mL /£	Cost per reaction (before) /£	Cost per reaction (after) /£	Change /£
$Pd(OAc)_2$	109.00	43.83	25.69	18.14
$P^tBu_2Me.HBF_4$	54.00	46.88	28.13	18.75
K_2CO_3	0.42	4.06	3.05	1.01
4-Bromotoluene	3.70	22.15	22.15	0
Solvent	0.16	31.64	9.04	22.60

[a]$Pd(OAc)_2$ purchased from STREM, $P^tBu_2Me{\cdot}HBF_4$ purchased from Santa Cruz Biotechnology, K_2CO_3 purchased from Sigma Aldrich, 4-bromotoluene purchased from Sigma Aldrich, 1,4-dioxane (anhydrous) purchased from Sigma Aldrich and ethoxybenzene purchased from Sigma Aldrich.

Overall, the $C(sp^2)$-$C(sp^2)$ desulfinative cross-coupling reaction was thoroughly improved in many aspects (Figure 24). We hope that now this methodology will be used more commonly by industrial chemists wishing to synthesise heterobiaryls on scale.



- X Sealed, pressurised vessel (1,4-dioxane boiling point is 101 °C)
- X High reaction temperature
- X Undesirable solvent choice (toxic, not 'green')
- X Reagents in excess
- X Column chromatography

- ✓ Green, non-toxic solvent
- ✓ Works in a rbf, not under pressure
- ✓ **92% yield, 5.4357 g**
- ✓ Lower catalyst loading & stoichiometry
- X High reaction temperature

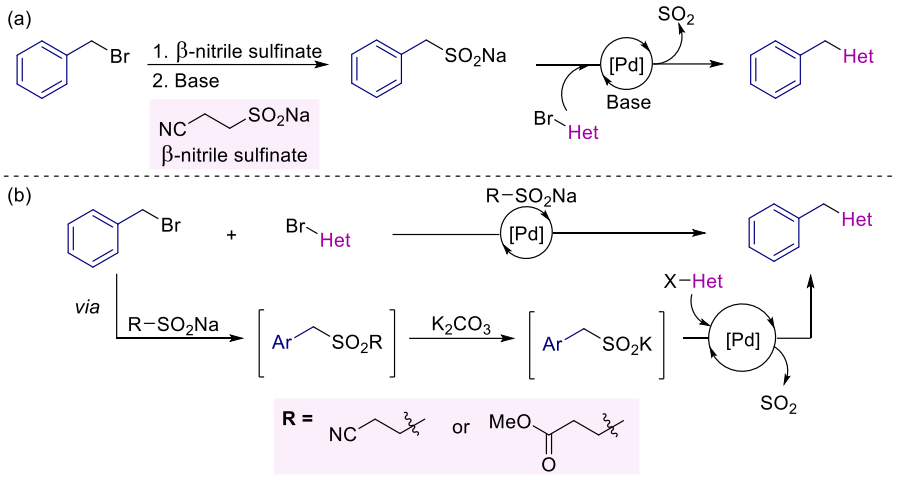
Figure 24. Overview of the reaction improvements.

Chapter 6. Conclusion and future directions

After investigations into several synthetic methods, a route whereby benzyl sulfinates could be formed in high yield, as well as be isolated free from inorganic impurities, was developed (Scheme 57a). The process involved sulfonylation of benzyl bromide, followed by base-assisted elimination of acrylonitrile to afford the sulfinate salt under mild reaction conditions. Di(hetero)arylmethanes could be accessed through a palladium-catalysed desulfinative cross-coupling employing pure benzyl sulfinate salt coupling partners (Scheme 57a). Despite our efforts to develop a reliable synthesis of benzyl sulfinates, some issues remained. The instability of some benzyl sulfinates meant they were difficult to isolate and store for prolonger periods of time without decomposition. Those that could be isolated resulted in either poor or inconsistent yields in the cross-coupling. In order to circumvent these problems, we developed a one-pot desulfinative cross-coupling protocol to synthesise di(hetero)arylmethanes (Scheme 57b).[186] This avoided the problematic preparation, purification and storage of benzyl sulfinates. We saw a significant cross-coupling yield improvement for motifs that performed poorly when employed as isolated benzyl sulfinate salts. Other key advantages were that di(hetero)arylmethanes could be afforded from solely commercial reagents, which allowed their rapid synthesis.

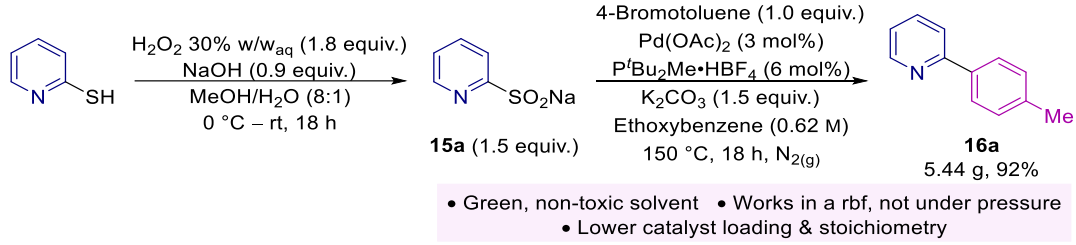
Unfortunately, the one-pot procedure was limited to benzyl coupling partners, and of those, secondary benzyl groups were not tolerated. The neccessity of a high reaction temperature (120 °C) also may reduce the utility of the method. Flow chemistry could potentially combat this issue for industrial application;[218] flow methodology has already been applied for the synthesis of sulfinates.[133] While we found palladium catalysts to be optimal, nickel catalysts did also demonstrate some success.

Extending the methodology to tolerate a diverse range of alkyl partners, seeking ways to lower the reaction temperature while ensuring excellent yields, and exploring the use of cheaper nickel catalysts, are all potential avenues for future work.



Scheme 57. (a) Benzyl sulfinate synthesis and their use in desulfinative cross-coupling to form di(hetero)arylmethanes. (b) One-pot reductant free cross-electrophile coupling to form di(hetero)arylmethanes, via in situ benzyl sulfinate formation.

Finally our group's pre-existing work on desulfinative cross-couplings for the construction of C(sp^2)-C(sp^2) bonds was improved, to become more amenable to scale-up reactions for industrial chemists (Scheme 58). The improvements meant that there was a 41% cost decrease for the desulfinative step, and the reaction could be performed in a safer manner.



Scheme 58. Improved reaction conditions for the desulfinative cross-coupling to form bi(hetero)aryls.

We hope the methodology developed within this thesis will prove useful to both academic and industrial chemists wishing to efficiently and reliably synthesise di(hetero)arylmethanes and biheteroaryls, on scale.

Chapter 7. Experimental data and procedures

7.1. General considerations

Reactions were performed with continuous magnetic stirring under an atmosphere of nitrogen with anhydrous solvents unless otherwise stated using standard Schlenk techniques. All glassware was oven dried at >100 °C, and was allowed to cool to room temperature under a positive nitrogen pressure. Cooling of reaction mixtures to 0 °C was achieved using an ice water bath.

Reagents, ligands and catalysts were purchased from Acros Organics, Alfa Aesar Ltd, Fluorochem Ltd, Insight Biotechnology Ltd, Sigma-Aldrich, Strem Chemicals Inc., and were used as supplied unless stated otherwise. Palladium acetate was purchased from Strem Chemicals Inc. and di-*tert*-butyl(methyl)phosphonium tetrafluoroborate was purchased from Insight Biotechnology Ltd. The reagents 2-bromopyridine, 2-chloropyridine, 3-bromopyridine and 3-chloropyridine were distilled prior to use via short path distillation with a Kugelrohr. Anhydrous DMSO was purchased as anhydrous from Sigma-Aldrich. Potassium carbonate was dried under vacuum (<1 mbar) at 130 °C, with stirring, overnight, and stored in a vacuum dessicator, prior to use in coupling reactions. Organometallic reagents in solution were purchased from a commercial source and titrated prior to use. The volume required was adjusted to ensure the correct equivalents were used. 3,4,5-Trimethoxybenzoyl chloride was prepared according to Pierce et al[219] or used as purchased from Sigma Aldrich. SMOPS was prepared according to Baskin et al[61] or used as purchased from Sigma Aldrich. Lithium methanesulfinate was prepared according to Markovic et al.[18, 220] Tosylate products were stored at -18 °C, in the dark, after synthesis.

Reactions were followed by thin layer chromatography (TLC) when practical. TLC was performed on Merck aluminium silica gel 60 F254 precoated plates. Plates were visualised under an ultraviolet lamp (λ_{max} = 254 nm or 365 nm) and/or by staining with potassium permanganate solution. Flash column chromatography (FCC) was carried out on Merck silica gel 60 (230 – 400 mesh) and the solvent system used reported in parenthesis. The compound to be purified was loaded as an oil or pre-absorbed onto celite. Petrol refers to the fraction of light petroleum ether boiling in the range of 40 – 60 °C. HPLC samples were analyzed using an Ascentis® Express C18 10 cm × 4.6 mm, 2.7 µm column (cat# 53827-U), with an eluent system combining acetonitrile and water. Collection wavelengths were 210 nm, 230, 254 nm, and 280 nm. Data was processed using Chem Station for LC systems Rev.B.04.01.SP1.

^{1}H NMR spectra were recorded on a Bruker AVIII400 (400 MHz) spectrometer using the residual solvent as an internal reference, ^{13}C NMR spectra were recorded on a Bruker AVIII400 (101 MHz) using the residual solvent as an internal reference and 19F NMR spectra were obtained on a Bruker AVIII400 (377 MHz) spectrometer using $CFCl_3$ as an external reference. Both ^{13}C and ^{19}F NMR spectra were recorded proton decoupled. Acquisitions were carried out at room temperature unless otherwise stated. Chemical shifts (δ_H, δ_C and δ_F) are quoted in parts per million (ppm) with the multiplicities of the spectra reported as the following: *s*, singlet; *d*, doublet; *t*, triplet; *q*, quartet; *p*, quintet; *m*, multiplet; *app.*, apparent; *br*, broad; *dd*, doublet of doublets *et cetera*. Coupling constants (*J*) are given in Hertz (Hz) and rounded to the nearest 0.5 Hz. Quantitative NMR (qNMR) yields were calculated using 1,3,5-trimethoxybenzene as the internal standard, with a 1:1 ratio of internal standard to compound (0.1 mmol of each) applied.

High resolution mass spectra (HRMS) were recorded by the mass spectrometry service at the Chemistry Research Laboratory, University of Oxford, using a Bruker Daltonic µTOF spectrometer (ESI). Samples for HRMS were prepared as a <1 mg/mL solution in MeOH (HRMS-ESI). m/z values are reported in Daltons (Da) and high resolution values are calculated to four decimal places from the molecular formula, with all found values in a tolerance of 5 ppm.

Infrared spectra were recorded using a Bruker Tensor 27 Fourier Transform spectrometer using a diamond ATR module. Absorption maximum, ν_{max}, are given in wavenumbers (cm^{-1}) and are assigned as broad (*br*) or strong (*s*) when appropriate.

Melting points were recorded in degrees Celsius (°C) using a Stuart Scientific Melting Point Apparatus SMP1 and are reported uncorrected.

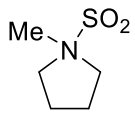
Optical rotations were measured on a Schmidt Haensch UniPol L2000 polarimeter at 589 nm, 25 °C. $[\alpha]_D^{25}$ is expressed in deg cm^3 g^{-1} dm^{-1} and c is expressed in g 100 cm^{-3}.

Systematic names were generated in accordance with the guidelines specified by the International Union of Pure and Applied Chemistry (IUPAC), using the computer program ChemDraw 20.1.

7.2. Chapter 2: Experimental procedures and data

7.2.1. Reagent synthesis

_N_-Methylpyrrolidine SO_2 adduct (TIMSO) (S1)

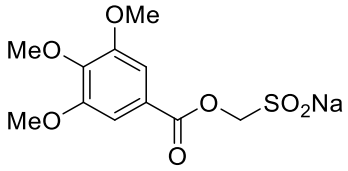


Prepared according to a modified procedure by Markovic et al.[18] A 250 mL round-bottom flask was equipped with a stirrer bar, placed into a Dewar flask and fitted to a condenser. The condenser was attached to a Dreschel bottle oil bubbler system and a flow of nitrogen was applied to the system. *N*-methylpyrrolidine (25.0 mL, 35.8 mmol, 1.0 equiv., freshly distilled) was added to the flask and the system was flushed with nitrogen for 10 minutes. The nitrogen flow was turned off, and a gentle flow of sulfur dioxide was introduced to the system for 5 minutes. Dry-ice and acetone were added to the Dewar flask to cool the reaction flask to -30 °C. Dry-ice and acetone were also slowly added to the condenser to cool to -78 °C, while watching the bubbler to check that no 'suck-back' occurred with a drop in SO_2 pressure. Sulfur dioxide was condensed dropwise onto *N*-methylpyrrolidine, while stirring, until approximately 120 mL SO_2 had filled the flask. The flow of SO_2 gas was then switched off. The reaction mixture was allowed to warm to -10 °C and stirred at reflux for 2 hours. The reaction was allowed to warm to room temperature, and excess SO_2 was left to evaporate over the weekend. The system was flushed with nitrogen to afford TIMSO as a light-yellow oil (32.0 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 – 2.77 (m, 4H, 2 × C*H*$_2$), 2.33 (s, 3H, C*H*$_3$), 1.94 – 1.78 (m, 4H, 2 × C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 53.0, 39.4, 24.0; **LRMS** (ESI, m/z) calculated for $C_5H_{12}NO_2S$, $[M+H]^+$ is 150.1, found 150.1.

Data is in accordance with the literature.[18] Due to the odorous and hygroscopic nature of TIMSO, the vial was wrapped in parafilm and stored in the freezer.

Sodium ((3,4,5-trimethoxybenzoyl)oxy)methanesulfinate (Rongacyl) (S2)

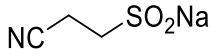


Prepared according to a modified procedure by Shavnya et al.[70] Sodium hydroxymethylsulfinate dihydrate (Rongalite®) (9.25 g, 60.0 mmol, 1.4 equiv.) was dissolved in aqueous NaOH (52.0 mL, 1.0 M, 1.2 equiv.) and the clear solution was kept without stirring at room temperature for 90 min. Aqueous NaBr (25.0 mL, 3.9 M) was added and the resulting solution was cooled to 0 °C under stirring, before addition of 3,4,5-trimethoxybenzoyl chloride (10.0 g, 43.4 mmol, 1.0 equiv.) was added in one portion. The thick slurry was warmed under stirring to room temperature over 1 hour and was stirred for 3 further hours at this temperature (resulting in a thin slurry). NaBr (32.5 g) was added and the mixture was stirred for 1 hour. The solid was filtered, washed with aqueous NaBr (2 × 40 mL, 3.9 M) and EtOAc (2 × 40 mL), dried on the filter and then under vacuum (< 1 mbar) for 18 hours to obtain the title compound as a white solid (9.10 g, 67%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 (s, 2H, 2 × Ar-*H*), 4.12 (s, 2H, OC$H_2$$SO_2$Na), 3.83 (s, 6H, 2 × ArOCH_3), 3.73 (s, 3H, ArOCH_3); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 164.8, 152.8, 141.7, 124.9, 106.6, 85.5, 60.2, 56.1; **HRMS** (ESI, m/z) calculated for $C_{11}H_{13}O_7S$, $[M\text{-}Na]^-$ is 289.0387, found 289.0387.

Data is in accordance with the literature.[70]

Sodium 2-cyanoethane-1-sulfinate (β-nitrile sulfinate) (S3)



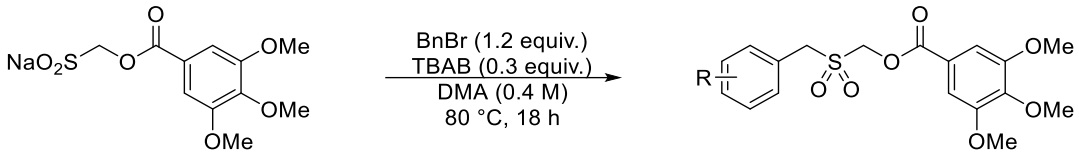
CAUTION: Exothermic and Evolution of $H_{2\,(g)}$.

Prepared according to a modified procedure by Wang et al.[61] To a 250 mL round-bottom flask, fitted with a $CaCl_2$ drying tube and stirrer bar, anhydrous methanol (80 mL) was added. The vessel was placed in an ice-water bath before hexane washed sodium (0.92 g, 40.0 mmol, 1.0 equiv.) was added, in four equal sized pieces, in one portion. The reaction was stirred until all the sodium had dissolved to give a clear, colourless solution. The 3,3'-sulfonyldipropionitrile (6.89 g, 40.0 mmol, 1.0 equiv.) was added with quick removal and replacement of the drying tube from the round-bottom flask. The ice-water bath was removed, and the mixture left to stir for 2 hours. The excess methanol was removed under reduced pressure and the residue was dried by forming an azeotrope with toluene. The crude residue was triturated with EtOAc (100 mL) and stirred for 2 hours before filtration. The solid was washed with EtOAc (200 mL) and Et_2O (200 mL). The title product was afforded as a white crystalline powder (5.32 g, 94% yield).

^{1}H NMR (400 MHz, CD_3OD) δ 2.69 (td, *J* = 7.5, 0.5 Hz, 2H, C*H*$_2$), 2.48 – 2.40 (m, 2H, C*H*$_2$); **^{13}C NMR** (101 MHz, CD_3OD) δ 120.7, 56.0, 10.1; **MP** (EtOAc) 175 – 176 °C; **IR** (neat)/ν_{max} 3391, 2160, 2030, 1658, 1417, 1026, 1009, 749; **HRMS** (ESI, m/z) calculated for $C_3H_4O_2NSNa$, $[M-Na]^-$ is 117.9968, found 117.9967.

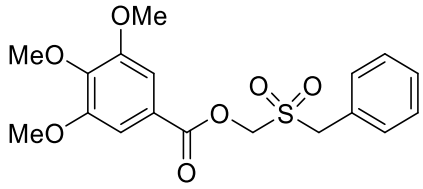
7.2.2. Sulfone synthesis from Rongacyl

General Procedure A



Prepared from a modified procedure by Shavnya et al.[70] A mixture of Rongacyl (1.69 g, 5.40 mmol, 1.0 equiv.), alkyl halide (6.50 mmol, 1.2 equiv.), TBAB (0.52 g, 1.62 mmol, 0.3 equiv.), and DMA (13.5 mL, 0.4 M) was stirred at 80 °C for 18 hours. The reaction was cooled to room temperature, quenched with half-saturated $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure and the crude residue was purified by column chromatography to yield the sulfone product.

((Benzyl)sulfonyl)methyl 3,4,5-trimethoxybenzoate (2a)

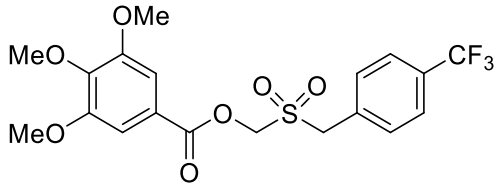


General Procedure A was followed using Rongacyl (4.88 g, 14.8 mmol, 1.0 equiv.), benzyl bromide (2.2 mL, 17.8 mmol, 1.2 equiv.), TBAB (0.96 g, 3.0 mmol, 0.2 equiv.) and DMA (37 mL). Purification of the crude material by flash column chromatography (25 – 70% EtOAc in Petrol) afforded the product as a white solid (4.07 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 2H, Ar-*H*), 7.42 – 7.37 (m, 3H, Ar-*H*), 7.33 (s, 2H, Ar-*H*), 5.18 (s, 2H, $ArCO_2CH_2$), 4.36 (s, 2H, SO_2CH_2Ar), 3.94 (s, 3H, $ArOCH_3$), 3.93 (s, 6H, $Ar(OCH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.3, 153.3, 143.7, 131.0, 129.5, 129.3, 127.0, 122.6, 107.7, 73.2, 61.2, 59.0, 56.5; **HRMS** (ESI, *m/z*) calculated for $C_{18}H_{21}O_7S$, $[M+H]^+$ is 381.1002, found 381.1000.

Data is in accordance with the literature.[70]

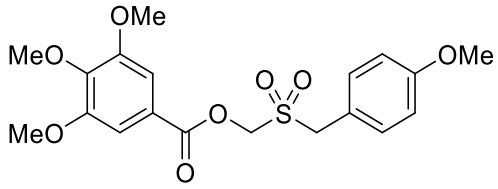
((4-(Trifluoromethyl)benzyl)sulfonyl)methyl 3,4,5-trimethoxybenzoate (2b)



General Procedure A was followed using Rongacyl (0.88 g, 2.82 mmol, 1.0 equiv.), 4-(trifluoromethyl)benzyl bromide (0.81 g, 3.38 mmol, 1.2 equiv.), TBAB (0.18 g, 0.56 mmol, 0.2 equiv.) and DMA (7 mL). Purification of the crude material by flash column chromatography (15 – 70% EtOAc in Petrol) afforded the product as a white solid (0.83 g, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.59 (m, 4H, Ar-*H*), 7.33 (s, 2H, Ar-*H*), 5.23 (s, 2H, $ArCO_2CH_2$), 4.42 (s, 2H, SO_2CH_2Ar), 3.95 (s, 3H, $ArOCH_3$), 3.93 (s, 6H, $Ar(OCH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.5, 153.3, 143.8, 131.6 (q, *J* = 32.5 Hz), 131.5, 130.8, 126.1 (q, *J* = 3.5 Hz), 123.9 (q, *J* = 272.5 Hz), 122.3, 107.7, 73.9, 61.2, 58.7, 56.5; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.86; **MP** (Toluene) 100 – 101 °C; **IR** (neat)/ν_{max} 3012, 2943, 2790, 1733, 1590, 1504, 1464, 1418, 1343, 1324 (s), 1126 (s); **HRMS** (ESI, *m/z*) calculated for $C_{19}H_{20}O_7F_3S$, $[M+H]^+$ is 449.0876, found 449.0875.

((4-Methoxybenzyl)sulfonyl)methyl 3,4,5-trimethoxybenzoate (2c)

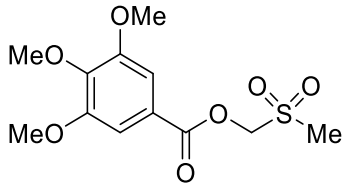


PMB-Br was prepared according to a procedure by K. Ravindar et al.[30] PMB-OH (2.0 g, 14.4 mmol, 2.0 equiv.) was dissolved in Et_2O (40 mL) and cooled to 0 °C. PBr_3 (0.68 mL, 7.23 mmol, 1.0 equiv.) was added under an argon atmosphere, and the reaction was allowed to stir for 2 h. The reaction was poured into a mixture of ice and sat. $NaHCO_3$. The organic layer was separated and washed twice with sat. $NaHCO_3$. The organic layer was dried over $MgSO_4$, then filtered and solvents removed under reduced pressure to give PMP-Br as a light-yellow oil (2.38 g, 82%). This was used directly in the next step without further purification.

General Procedure A was followed, using 4-methoxybenzyl bromide (0.94 mL, 6.50 mmol, 1.2 equiv.). The crude residue was purified by column chromatography (15 – 70% EtOAc in Petrol) to give the title product as a white solid (727 mg, 33% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.36 (m, 2H, 2 × Ar-*H*), 7.33 (s, 2H, Ar-*H*), 6.92 – 6.89 (m, 2H, Ar-*H*), 5.17 (s, 2H, $ArCO_2CH_2$), 4.30 (s, 2H, SO_2CH_2Ar), 3.94 (s, 3H, $ArOCH_3$), 3.93 (s, 6H, $Ar(OCH_3)_2$), 3.79 (s, 3H, $ArOCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.4, 160.5, 153.3, 143.6, 132.2, 122.6, 118.7, 114.7, 107.7, 73.1, 61.2, 58.4, 56.5, 55.4; **MP** (EtOH) 100 – 101 °C; **IR** (neat)/ν_{max} 2981, 2839, 1732, 1588, 1341, 1126; **HRMS** (ESI, *m/z*) calculated for $C_{19}H_{22}O_8SNa$, $[M+Na]^+$ is 433.0928, found 433.0925.

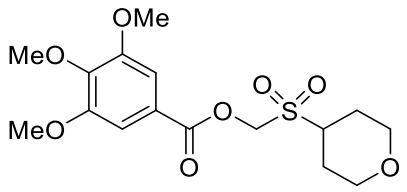
Methylsulfonyl)methyl 3,4,5-trimethoxybenzoate (2d)



General Procedure A was followed using Rongacyl (1.25 g, 5.40 mmol, 1.0 equiv.), methyl iodide (0.3 mL, 4.80 mmol, 1.2 equiv.), TBAB (96.0 mg, 1.20 mmol, 0.3 equiv.) and DMA (11 mL). Purification of the crude material by flash column chromatography (25 – 100% EtOAc in Petrol) afforded the product as a white solid (970 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 2H, Ar-*H*), 5.30 (s, 2H, $ArCO_2CH_2$), 3.93 (s, 3H, $ArOCH_3$), 3.91 (s, 6H, $Ar(OCH_3)_2$), 3.00 (s, 3H, SO_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.4, 153.3, 143.7, 122.4, 107.7, 75.9, 61.2, 56.6, 40.3; **MP** (EtOAc) 142 – 143 °C; **IR** (neat)/ν_{max} 3012, 2947, 1729, 1590, 1503, 1337, 1321, 1211, 1124; **HRMS** (ESI, *m/z*) calculated for $C_{12}H_{17}O_7S$, $[M+H]^+$ is 305.0689, found 305.0689.

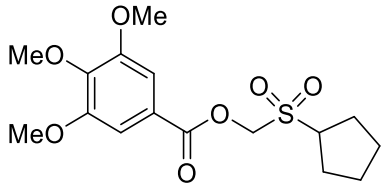
((Tetrahydro-2*H*-pyran-4-yl)sulfonyl)methyl 3,4,5-trimethoxybenzoate (2e)



General Procedure A was followed using Rongacyl (1.25 g, 5.40 mmol, 1.0 equiv.), 4-bromo tetrahydropyran (0.54 mL, 4.80 mmol, 1.2 equiv.), TBAB (387 mg, 1.20 mmol, 0.3 equiv.) and DMA (11 mL). Purification of the crude material by flash column chromatography (25 – 100% EtOAc in petrol) afforded the product as a white solid (100.2 mg, 7%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 2H, 2 × Ar*H*), 5.02 (s, 2H, COOCH_2), 3.73 – 3.70 (m, 1H, C*H*), 3.53 (s, 6H, 2 × OCH_3), 3.52 (s, 3H, OCH_3), 3.04 (qd, *J* = 12.0, 2.5 Hz, 4H, 4 × C*H*), 1.48 (ddd, *J* = 12.5, 4.5, 2.5 Hz, 4H, 4 × C*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.3, 152.4, 142.6, 121.9, 106.7, 71.7, 65.6, 60.1, 56.9, 55.6, 24.1; **MP** (DCM) 108 – 110 °C; **IR** (neat)/ν_{max} 2957, 1736, 1339, 1209, 1105, 891; **LRMS (ESI)** calculated for $C_{16}H_{22}O_8SNa$, $[M+Na]^+$ is 397.1 found 397.0; **HRMS (ESI)** calculated for $C_{16}H_{22}O_8SNa$, $[M+Na]^+$ is 397.0928 (100%), 398.0960 (18%), found 397.0927 (100%), 398.0960 (20%).

(Cyclopentylsulfonyl)methyl 3,4,5-trimethoxybenzoate (2f)

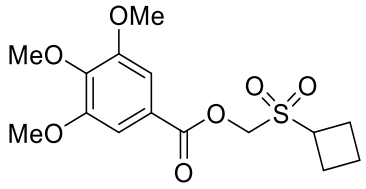


General Procedure A was followed using Rongacyl (1.25 g, 5.40 mmol, 1.0 equiv.), bromocyclopentane (0.51 mL, 4.80 mmol, 1.2 equiv.), TBAB (387 mg, 1.20 mmol, 0.3 equiv.) and DMA (11 mL). Purification of the crude material by flash column chromatography (25 – 100% EtOAc in petrol) afforded the product as a white solid (342 mg, 24%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 2H, 2 × Ar*H*), 5.33 (s, 2H, COOCH_2), 3.94 (s, 3H, OCH_3), 3.93 (s, 6H, 2 × OCH_3), 3.54 (tt, *J* = 9.0, 7.0 Hz, 1H, C*H*), 2.21 – 2.08 (m, 4H, 2 × CH_2), 1.90 – 1.77 (m, 2H, CH_2), 1.69 (dqt, *J* = 10.5, 6.5, 3.5 Hz, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.2, 153.1, 143.3, 122.60, 107.5, 73.9, 61.0, 60.5, 56.3, 26.6, 26.0; **LRMS (ESI)** calculated for $C_{16}H_{22}O_7SNa$, $[M+Na]^+$ is 381.1 found 381.0.

Data is in accordance with the literature.[70]

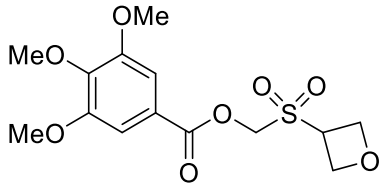
(Cyclobutylsulfonyl)methyl 3,4,5-trimethoxybenzoate (2g)



General Procedure A was followed using Rongacyl (1.25 g, 5.40 mmol, 1.0 equiv.), bromo cyclobutane (0.45 mL, 4.80 mmol, 1.2 equiv.), TBAB (387 mg, 1.20 mmol, 0.3 equiv.) and DMA (11 mL). Purification of the crude material by flash column chromatography (25 – 100% EtOAc in petrol) afforded the product as a white solid (225 mg, 16%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 2H, 2 × Ar*H*), 5.20 (s, 2H, COOCH_2), 3.88 (s, 3H, OCH_3), 3.87 (s, 6H, 2 × OCH_3), 3.86 – 3.78 (m, 1H, C*H*), 2.59 (ddt, *J* = 13.0, 11.0, 8.5 Hz, 2H, 2 × C*H*), 2.28 (dtd, *J* = 13.0, 11.0, 9.5, 6.5 Hz, 2H, 2 × C*H*), 2.10 – 1.95 (m, 2H, 2 × C*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.2, 153.1, 143.4, 122.5, 107.4, 73.3, 61.0, 57.5, 56.3, 22.2, 17.5; **MP** (DCM) 71 – 72 °C; **IR** (neat)/ν_{max} 2972, 1732, 1339, 1209, 1129, 1108; **LRMS (ESI)** calculated for $C_{15}H_{20}O_7SNa$, $[M+Na]^+$ is 367.1 found 367.0; **HRMS (ESI)** calculated for $C_{15}H_{20}O_7SNa$, $[M+Na]^+$ is 367.0822 (100%), 368.0856 (15%), found 367.0822 (100%), 368.0856 (18%).

(Oxetan-3-ylsulfonyl)methyl 3,4,5-trimethoxybenzoate (2h)



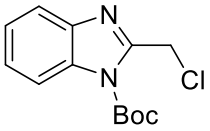
General Procedure A was followed using Rongacyl (1.25 g, 5.40 mmol, 1.0 equiv.), 3-bromo oxetane (0.40 mL, 4.80 mmol, 1.2 equiv.), TBAB (387 mg, 1.20 mmol, 0.3 equiv.) and DMA (11 mL). Purification of the crude material by flash column chromatography (25 – 100% EtOAc in petrol) afforded the product as a white solid (88.6 mg, 6%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 2H, 2 × Ar*H*), 5.38 – 5.35 (m, 2H, COOCH_2), 4.90 (dtdd, *J* = 8.5, 7.0, 4.5, 2.0 Hz, 4H, 4 × C*H*), 4.70 (ddd, *J* = 8.5, 4.5, 2.5 Hz, 1H, C*H*), 3.87 (s, 6H, 2 × OCH_3), 3.86 (s, 3H, OCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.5, 152.5, 142.8, 121.6, 106.7, 73.6, 69.0, 60.1, 55.6, 53.8; **LRMS (ESI)** calculated for $C_{14}H_{18}O_8SNa$, $[M+Na]^+$ is 369.1 found 369.1.

Data is in accordance with the literature.[70]

7.2.3. Other starting materials

tert-Butyl 2-(chloromethyl)-_1H_-benzo[_d_]imidazole-1-carboxylate (S4)

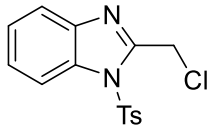


2-(Chloromethyl)benzimidazole (333 mg, 2.00 mmol, 1.0 equiv.) was suspended in dichloromethane (4.0 mL) and 4-dimethylaminopyridine (24.4 mg, 0.20 mmol, 10 mol%) was added. A solution of di-*tert*-butyl carbonate (655 mg, 3.00 mmol, 1.5 equiv.) in dichloromethane (4.0 mL) was added dropwise over 10 minutes. After full addition, a burnt orange solution was observed. The reaction was stirred for 30 minutes at room temperature, before being washed with a 0.1 M aqueous solution of HCl (10 mL). The aqueous phase was extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude residue was purified by column chromatography (0 – 50% EtOAc in petrol) to give the product as a yellow oil (474 mg, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.96 (m, 1H, Het-*H*), 7.78 – 7.73 (m, 1H, Het-*H*), 7.43 – 7.33 (m, 2H, 2 × Het-*H*), 5.07 (s, 2H, HetC*H*$_2$), 1.74 (s, 9H, 3 × C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.4, 148.2, 141.9, 133.5, 125.9, 124.8, 120.6, 115.3, 86.6, 39.8, 28.1; **LRMS** (ESI, *m/*z) calculated for $C_9H_6ClN_2O$, $[M\text{-}OtBu]^+$ is 193.0, found 193.0.

Data is in accordance with the literature.[221]

2-(Chloromethyl)-1-tosyl-*1H*-benzo[*d*]imidazole (S5)



To a solution of 2-(chloromethyl)benzimidazole (666 mg, 4.00 mmol, 1.0 equiv.) in acetone (40 mL, 0.1 M), were added potassium carbonate (553 mg, 4.00 mmol, 1.0 equiv.) and *p*-toluenesulfonyl chloride (1.14 g, 6.00 mmol, 1.5 equiv.). The reaction was stirred at room temperature for 12 hours, and the solvents were then removed under reduced pressure. The crude material was transferred to a separating funnel. Water (50 mL) was added. The mixture was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined, dried over $MgSO_4$ and the solvents removed under vacuum. The residue was purified by column chromatography (10 – 50% EtOAc in petrol) to give the product as a yellow solid (946 mg, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.92 (m, 3H, 3 × Ar-*H*), 7.76 – 7.71 (m, 1H, Ar-*H*), 7.44 – 7.34 (m, 2H, 2 × Ar-*H*), 7.34 – 7.28 (m, 2H, 2 × Ar-*H*), 5.17 (s, 2H, C*H*$_2$), 2.40 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.2, 146.5, 141.8, 134.9, 133.1, 130.3, 127.7, 126.2, 125.3, 121.1, 113.8, 38.0, 21.8; **HRMS** (ESI, *m/*z) calculated for $C_{15}H_{13}ClN_2O_2S$, $[M+H]^+$ is 321.0459, found 321.0459.

Data is in accordance with the literature.[222]

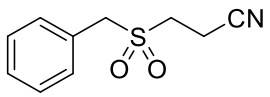
7.2.4. Sulfone synthesis from β-nitrile sulfinate

General Procedure B



A mixture of the benzyl bromide (1.0 equiv.), sodium 2-cyanoethane-1-sulfinate (1.2 equiv.) and DMSO (0.34 M) was stirred at room temperature for 18 hours. The reaction mixture was transferred to a 100 mL separating funnel in EtOAc (20 mL). The organic layer was washed with aqueous LiCl solution (5 mol%, 3 × 10 mL). The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The crude residue was then purified by column chromatography to yield the sulfone product.

3-(Benzylsulfonyl)propanenitrile **(3a)**



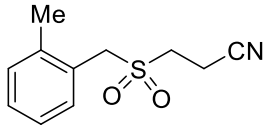
Prepared according to a modified procedure by Cook et al.[25] To a solution of sodium benzyl sulfinate (71.3 mg, 0.40 mmol, 1.0 equiv.) in de-ionised water (1 mL, 0.4 M), was added acetic acid (25 µL, 0.44 mmol, 1.1 equiv.) and acrylonitrile (26 µL, 0.40 mmol, 1.0 equiv.). The reaction mixture was heated to reflux (115 °C) for 3 hours. The reaction mixture was cooled to room temperature. Solid $NaHCO_3$ was added until the reaction mixture reached pH 8. Water (5 mL) was added and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (15 – 70% EtOAc in petrol) to give the desired product as a white crystalline solid (11.2 mg, 13% yield).

General Procedure B was followed using benzyl bromide (357 µL, 3.00 mmol, 1.0 equiv.), β-nitrile sulfinate (508 mg, 3.60 mmol, 1.2 equiv.) and DMSO (8.8 mL, 0.34 M). The crude residue was purified by column chromatography (30 – 60% EtOAc in petrol) to give the product as a white crystalline solid (602 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 5H, 5 × Ar-*H*), 4.35 (s, 2H, ArCH_2), 3.13 (t, *J* = 7.5 Hz, 2H, CH_2CH_2CN), 2.78 (t, *J* = 7.5 Hz, 2H, CH_2CH_2CN); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.8, 129.7, 129.5, 127.1, 116.7, 60.6, 46.2, 11.3; **MP** (CH_2Cl_2) 110 – 111 °C; **HRMS** (ESI, *m/*z) calculated for $C_{10}H_{11}O_2NS$, $[M+Na]^+$ is 232.0403, found 232.0404.

The data is in accordance with the literature.[223]

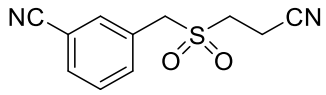
3-((2-Methylbenzyl)sulfonyl)propanenitrile (3b)



General Procedure B was followed using 1-bromomethyl benzene (409 µL, 3.00 mmol, 1.0 equiv.), β-nitrile sulfinate (508 mg, 3.60 mmol, 1.2 equiv.) and DMSO (8.8 mL, 0.34 M). The crude residue was purified by column chromatography (30 – 60% EtOAc in petrol) to give the product as a white crystalline solid (658 mg, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (td, *J* = 7.5, 1.5 Hz, 2H, 2 × Ar-*H*), 7.30 – 7.22 (m, 2H, 2 × Ar-*H*), 4.42 (s, 2H, ArCH_2), 3.23 (t, *J* = 7.5 Hz, 2H, CH_2CH_2CN), 2.82 (t, *J* = 7.5 Hz, 2H, CH_2CH_2CN), 2.46 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.7, 131.7, 131.6, 129.9, 126.9, 125.3, 116.7, 58.2, 46.9, 20.1, 11.2; **MP** (DCM) 90 °C; **IR** (neat)/ν_{max} 2993, 2361, 2244, 1495, 1423, 1317, 1297, 1276, 1131, 1023, 789, 757, 732; **HRMS** (ESI, *m/*z) calculated for $C_{11}H_{13}O_2NS$, $[M+Na]^+$ is 246.0559, found 246.0559.

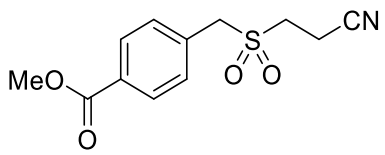
3-(((2-Cyanoethyl)sulfonyl)methyl)benzonitrile (3c)



General Procedure B was followed using 3-(bromomethyl)benzonitrile (294 mg, 1.50 mmol, 1.00 equiv.), β-nitrile sulfinate (254 mg, 1.80 mmol, 1.2 equiv.) and DMSO (4.4 mL, 0.34 M) to give the product as a white solid (325 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.70 (m, 3H, 3 × Ar-*H*), 7.58 (td, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 4.40 (s, 2H, ArCH_2), 3.20 (t, *J* = 7.0 Hz, 2H, C$H_2$$CH_2$CN), 2.93 (t, *J* = 7.0 Hz, 2H, CH_2CH_2CN); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.3, 134.3, 133.3, 130.3, 128.5, 117.9, 116.6, 113.9, 59.5, 47.1, 11.7; **MP** (DCM) 118 – 119 °C; **IR** (neat)/ν_{max} 3065, 2922, 2361, 2233, 1420, 1318, 1124, 1029, 750, 691; **HRMS** (ESI, *m/z*) calculated for $C_{11}H_{10}O_2N_2S$, $[M+Na]^+$ is 257.0355, found 257.0357.

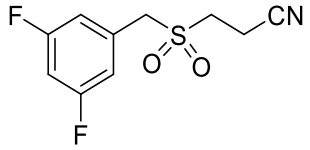
Methyl 4-(((2-cyanoethyl)sulfonyl)methyl)benzoate (3d)



General Procedure B was followed using methyl 4-(bromomethyl)benzoate (687 mg, 3.00 mmol, 1.0 equiv.), β-nitrile sulfinate (508 mg, 3.60 mmol, 1.2 equiv.) and DMSO (8.8 mL, 0.34 M). The crude residue was purified by column chromatography (20 – 100% EtOAc in petrol) to give the product as a white crystalline solid (770 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.07 (m, 2H, 2 × Ar-*H*), 7.58 – 7.50 (m, 2H, 2 × Ar-*H*), 4.42 (s, 2H, ArCH_2), 3.94 (s, 3H, OCH_3), 3.15 (t, *J* = 7.5 Hz, 2H, CH_2CH_2CN), 2.85 (t, *J* = 7.5 Hz, 2H, CH_2CH_2CN); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.4, 131.8, 131.6, 130.9, 130.7, 116.5, 60.3, 52.6, 46.6, 11.5; **MP** (DCM) 146 – 147 °C; **HRMS** (ESI, m/z) calculated for $C_{12}H_{13}O_4NSNa$, $[M+Na]^+$ is 290.0457, found 290.0456; **IR** (neat)/ν_{max} 3031, 2940, 2361, 2255, 1717, 1437, 1419, 1308, 1277, 1134, 1121, 1023, 980, 776, 708; **HRMS** (ESI, *m/*z) calculated for $C_{12}H_{13}O_4NS$, $[M+Na]^+$ is 290.0458, found 290.0458.

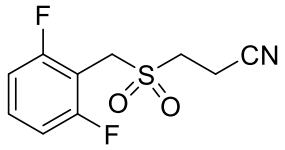
3-((3,5-Difluorobenzyl)sulfonyl)propanenitrile (3e)



General Procedure B was followed using 1-(bromomethyl)-3,5-difluorobenzene (194 µL, 1.50 mmol, 1.0 equiv.), β-nitrile sulfinate (252 mg, 1.80 mmol, 1.2 equiv.) and DMSO (4.4 mL, 0.34 M). The crude residue was purified by column chromatography (20 – 50% EtOAc in petrol) to give the product as a white crystalline solid (364 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (dt, *J* = 6.0, 2.0 Hz, 2H, 2 × Ar-*H*), 6.91 (tt, *J* = 9.0, 2.0 Hz, 1H, Ar-*H*), 4.34 (s, 2H, ArCH_2), 3.20 (t, *J* = 7.0 Hz, 2H, CH_2CH_2CN), 2.90 (t, *J* = 7.0 Hz, 2H, CH_2CH_2CN); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.4 (dd, *J* = 251.5, 12.5 Hz), 130.3 (t, *J* = 10.0 Hz), 116.5, 114.1 (dd, *J* = 18.5, 8.0 Hz), 105.5 (t, *J* = 25.0 Hz), 59.6 (t, *J* = 2.5 Hz), 46.8, 11.5; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -107.31; **MP** (DCM) 110 – 111 °C; **IR** (neat)/ν_{max} 3101, 2936, 2363, 1601, 1453, 1281, 1238, 1124, 994, 861, 709; **HRMS** (ESI, *m/*z) calculated for $C_{10}H_9O_2NF_2S$, $[M+Na]^+$ is 268.0215, found 268.0225.

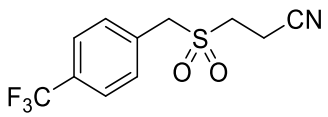
3-((2,6-Difluorobenzyl)sulfonyl)propanenitrile (3f)



General Procedure B was followed using 2-(bromomethyl)-1,3-difluorobenzene (310 mg, 1.50 mmol, 1.0 equiv.), β-nitrile sulfinate (252 mg, 1.80 mmol, 1.2 equiv.) and DMSO (4.4 mL, 0.34 M). The crude residue was purified by column chromatography (20 – 50% EtOAc in petrol) to give the product as a white crystalline solid (335 mg, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (tt, *J* = 8.5, 6.5 Hz, 1H, Ar-*H*), 7.08 – 7.00 (m, 2H, 2 × Ar-*H*), 4.47 (d, *J* = 1.0 Hz, 2H, 2 × Ar-*H*), 3.30 (app t, *J* = 8.0 Hz, 2H, C*H*$_2$$CH_2CN$), 2.90 (app t, *J* = 8.0 Hz, 2H, CH_2C*H*$_2$CN); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.6 (dd, *J* = 252.0, 6.5 Hz), 132.1 (t, *J* = 10.5 Hz), 116.3, 112.24 (dd, *J* = 22.5, 2.5 Hz), 104.9, 48.4 (t, *J* = 2.5 Hz), 47.4 (t, *J* = 2.5 Hz), 11.1; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -111.98; **MP** (DCM) 111 – 112 °C; **IR** (neat)/ν_{max} 3010, 2945, 2361, 2255, 1627, 1595, 1473, 1414, 1301, 1278, 1127, 1003, 789, 749; **HRMS** (ESI, *m/*z) calculated for $C_{10}H_9O_2NF_2S$, $[M+Na]^+$ is 268.0214, found 268.0214.

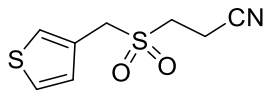
3-((4-(Trifluoromethyl)benzyl)sulfonyl)propanenitrile (3g)



General Procedure B was followed using 4-(trifluoromethyl)benzyl bromide (478 mg, 2.00 mmol, 1.0 equiv.), β-nitrile sulfinate (336 mg, 2.40 mmol, 1.2 equiv.) and DMSO (6 mL, 0.34 M). The crude residue was purified by column chromatography (30 – 60% EtOAc in petrol) to give the product as a white solid (511 mg, 92% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 8.0 Hz, 2H, 2 × Ar-*H*), 7.64 (d, J = 8.0 Hz, 2H, 2 × Ar-*H*), 4.74 (s, 2H, ArCH_2), 3.51 (t, J = 7.0 Hz, 2H, CH_2CH$_2$CN), 3.03 (t, J = 7.0 Hz, 2H, CH$_2$CH_2CN); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 132.7, 132.0, 129.1 (q, J = 32.0 Hz), 125.5 (q, J = 4.0 Hz), 124.1 (q, J = 273.5 Hz), 118.2, 57.2, 46.6, 10.6; **^{19}F NMR** (377 MHz, DMSO-d_6) δ -61.20; **MP** ($CDCl_3$) 104 – 105 °C; **IR** (neat)/ν_{max} 3052, 2938, 1420, 1338, 1135, 1124, 736; **HRMS** (ESI, *m/*z) calculated for $C_{11}H_9O_2NF_3S$ $[M-H]^-$ is 276.0312 (100%), 277.0344 (10%) found 276.0306 (100%), 277.0338 (10%).

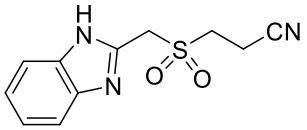
3-((Thiophen-3-ylmethyl)sulfonyl)propanenitrile (3h)



General Procedure B was followed using 3-(bromomethyl)thiophene (531 mg, 3.00 mmol, 1.0 equiv.), β-nitrile sulfinate (508 mg, 3.60 mmol, 1.2 equiv.) and DMSO (9 mL, 0.34 M). The crude residue was purified by column chromatography (30 – 75% EtOAc in petrol) to give the product as a white crystalline solid (639 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (ddt, *J* = 2.0, 1.5, 1.0 Hz, 1H, Het-*H*), 7.43 (dd, *J* = 5.0, 3.0 Hz, 1H, Het-*H*), 7.21 (dd, *J* = 5.0, 1.5 Hz, 1H, Het-*H*), 4.42 (s, 2H, HetCH_2), 3.12 (t, *J* = 7.5 Hz, 2H, CH_2CH_2CN), 2.80 (t, *J* = 7.5 Hz, 2H, CH_2CH_2CN); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 128.8, 127.7 127.4, 127.0, 116.7, 55.3, 46.0, 11.6; **MP** ($CDCl_3$) 104 – 105 °C; **IR** (neat)/ν_{max} 3112, 2938, 1412, 1307, 1209, 1123, 1110; **HRMS** (ESI, *m/*z) calculated for $C_8H_9O_2NS$ $[M+Na]^+$ is 237.9967 (100%) found 237.9970 (100%).

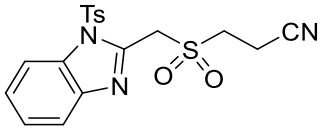
3-(((1*H*-Benzo[*d*]imidazol-2-yl)methyl)sulfonyl)propanenitrile (3i)



General Procedure B was followed using 2-(chloromethyl)-1*H*-benzo[*d*]imidazole (83.3 mg, 0.50 mmol, 1.0 equiv.), β-nitrile sulfinate (84.1 mg, 0.60 mmol, 1.2 equiv.) and DMSO (1.5 mL, 0.34 M). The crude residue was purified by column chromatography (0 – 10% MeOH in EtOAc) to give the product as a white crystalline solid (79.7 mg, 64% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.68 (s, 1H, N*H*), 7.72 – 7.47 (m, 2H, 2 × Het-*H*), 7.22 (*app* t, *J* = 8.0 Hz, 2H, 2 × Het-*H*), 4.92 (s, 2H, HetCH_2), 3.74 (t, *J* = 7.0 Hz, 2H, CH_2CH$_2$CN), 3.10 (t, *J* = 7.0 Hz, 2H, CH$_2$CH_2CN); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 143.1, 142.9, 134.4, 122.8, 121.8, 118.9, 118.2, 111.7, 52.7, 46.8, 10.7; **MP** (DCM) 178 – 180 °C; **IR** (neat)/ν_{max} 3054, 2933, 2361, 1439, 1315, 1295, 1132, 1037, 742; **HRMS** (ESI, *m/*z) calculated for $C_{11}H_{12}O_2N_3S$ $[M+H]^+$ is 250.0645 (100%), 251.0678 (12%), found 250.0646 (100%), 251.0680 (15%).

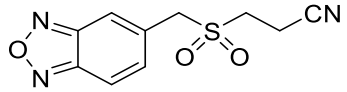
3-(((1-Tosyl-1H-benzo[d]imidazol-2-yl)methyl)sulfonyl)propanenitrile (3j)



General Procedure B was followed using 2-(chloromethyl)-1-tosyl-1H-benzo[d]imidazole (481 mg, 1.50 mmol, 1.0 equiv.), β-nitrile sulfinate (254 mg, 1.80 mmol, 1.2 equiv.) and DMSO (4.4 mL, 0.34 M). The crude residue was purified by column chromatography (20 – 75% EtOAc in petrol) to give the product as a white crystalline solid (559 mg, 92% yield).

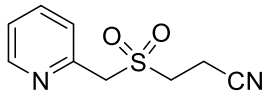
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.94 (m, 2H, 2 × Ar-*H*), 7.91 – 7.86 (m, 1H, Het-*H*), 7.76 – 7.71 (m, 1H, Het-*H*), 7.45 – 7.36 (m, 2H, 2 × Het-*H*), 7.36 – 7.31 (m, 2H, 2 × Ar-*H*), 5.22 (s, 2H, HetCH_2), 3.82 (t, *J* = 8.0 Hz, 2H, CH_2CH_2CN), 2.99 (t, *J* = 8.0 Hz, 2H, CH_2CH_2CN), 2.40 (s, 3H, ArCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.9, 142.1, 141.7, 134.4, 132.6, 130.5, 127.9, 126.4, 125.6, 120.9, 116.4, 114.0, 53.0, 48.2, 21.9, 11.6; **MP** ($CDCl_3$) 122 – 124 °C; **IR** (neat)/ν_{max} 2917, 2251, 1322, 1179, 744, 672; **LRMS** (ESI, *m/*z) calculated for $C_{18}H_{18}O_4N_3S_2$ $[M+H]^+$ is 404.1, found 404.0; **HRMS** (ESI, *m/*z) calculated for $C_{18}H_{18}O_4N_3S_2$ $[M+H]^+$ is 404.0733 (100%), 405.0764 (22%), found 404.0730 (100%), 405.0764 (22%).

3-((Benzo[c][1,2,5]oxadiazol-5-ylmethyl)sulfonyl)propanenitrile (3k)



General Procedure B was followed using 2-(chloromethyl)-1-tosyl-1H-benzo[d]imidazole (639 mg, 3.00 mmol, 1.0 equiv.), β-nitrile sulfinate (508 mg, 3.60 mmol, 1.2 equiv.) and DMSO (9 mL, 0.34 M). The crude residue was purified by column chromatography (50 – 100% EtOAc in petrol) to give the product as a white crystalline solid (753 mg, 99% yield). **^{1}H NMR** (400 MHz, CD_3OD) δ 8.04 (t, *J* = 1.0 Hz, 1H, Het-*H*), 7.96 (dd, *J* = 9.5, 1.0 Hz, 1H, Het-*H*), 7.61 (dd, *J* = 9.5, 1.5 Hz, 1H, Het-*H*), 4.71 (d, *J* = 1.0 Hz, 2H, HetC*H*$_2$), 3.55 (t, *J* = 7.0 Hz, 2H, C*H*$_2$$CH_2CN$), 3.03 (t, *J* = 7.0 Hz, 2H, CH_2C*H*$_2$CN); **^{13}C NMR** (101 MHz, CD_3OD) δ 151.6, 150.4, 135.8, 133.9, 120.2, 118.5, 117.6, 59.7, 48.7, 11.6; **IR** (neat)/ν_{max} 3054, 2936, 2256, 1538, 1412, 1314, 1300, 815; **MP** (CD_3OD) 132 – 133 °C; **HRMS** (ESI, *m/*z) calculated for $C_{10}H_8O_3N_3S$ $[M-H]^-$ is 250.02929 (100%) found 250.0288 (100%).

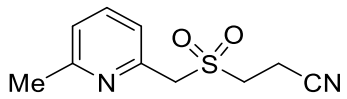
3-((Pyridin-2-ylmethyl)sulfonyl)propanenitrile (3l)



General Procedure B was followed using 2-bromomethyl pyridine (170 mg, 1.00 mmol, 1.0 equiv.), β-nitrile sulfinate (168 mg, 1.20 mmol, 1.2 equiv.) and DMSO (3 mL, 0.34 M). The crude residue was purified by column chromatography (50 – 75% EtOAc in petrol) to give the product as a white solid (81.2 mg, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 – 8.65 (m, 1H, Het-*H*), 7.84 – 7.80 (m, 1H, Het-*H*), 7.69 – 7.66 (m, 1H, Het-*H*), 7.42 – 7.39 (m, 1H, Het-*H*), 5.86 (s, 2H, HetCH_2), 3.78 – 3.75 (m, 2H, CH_2CH_2CN), 2.95 – 2.90 (m, 2H, CH_2CH_2CN); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.7, 150.1, 138.0, 125.6, 125.4, 116.3, 63.3, 45.7, 11.6; **MP** ($CDCl_3$) 92 – 93 °C; **IR** (neat)/ν_{max} 2923, 1590, 1437, 1312, 1028; **HRMS** (ESI, *m/*z) calculated for $C_9H_{11}O_2N_2S$ $[M+H]^+$ is 211.0536 (100%), 212.0569 (10%), 213.0494 (5%) found 211.0539 (100%), 212.0572 (10%), 213.0497 (5%).

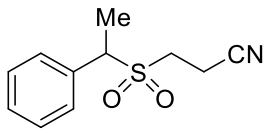
3-(((6-Methylpyridin-2-yl)methyl)sulfonyl)propanenitrile (3m)



General Procedure B was followed using 2-bromomethyl-6-methylpyridine (558 mg, 3.00 mmol, 1.0 equiv.), β-nitrile sulfinate (508 mg, 3.60 mmol, 1.2 equiv.) and DMSO (9 mL, 0.34 M). The crude residue was purified by column chromatography (25 – 75% EtOAc in petrol) to give the product as a white solid (594 mg, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (t, *J* = 8.0 Hz, 1H, Het-*H*), 7.26 (d, *J* = 8.0 Hz, 1H, Het-*H*), 7.20 (d, *J* = 8.0 Hz, 1H, Het-*H*), 4.40 (s, 2H, HetC*H*$_2$), 3.45 – 3.37 (m, 2H, C*H*$_2$CH$_2$CN), 2.96 – 2.87 (m, 2H, CH$_2$C*H*$_2$CN), 2.57 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 148.0, 137.9, 123.8, 123.1, 116.4, 61.8, 47.2, 24.6, 11.6; **MP** ($CDCl_3$) 84 – 85 °C; **IR** (neat)/ν_{max} 3064, 2923, 1595, 1457, 1314, 1213, 1116, 1027; **HRMS** (ESI, *m/*z) calculated for $C_{10}H_{13}O_2N_2S$ $[M+H]^+$ is 225.0692 (100%), 226.0726 (10%) found 225.0695 (100%), 226.0727 (10%).

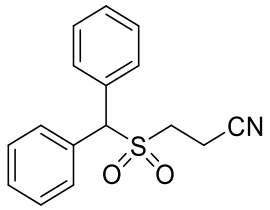
3-((1-Phenylethyl)sulfonyl)propanenitrile (3n)



General Procedure B was followed using 1-bromoethyl benzene (136 µL, 1.00 mmol, 1.0 equiv.), β-nitrile sulfinate (168 mg, 1.20 mmol, 1.2 equiv.) and DMSO (3 mL, 0.34 M). The crude residue was purified by column chromatography (10 – 60% EtOAc in petrol) to give the product as a clear oil (191 mg, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.36 (m, 5H, 5 × Ar-*H*), 4.29 (q, *J* = 7.0 Hz, 1H, ArC*H*(Me)R), 3.11 – 2.92 (m, 2H, C*H*$_2$CH$_2$CN), 2.81 – 2.54 (m, 2H, CH$_2$C*H*$_2$CN), 1.83 (d, *J* = 7.0 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.5, 129.9, 129.6, 129.1, 116.7, 64.8, 45.4, 13.6, 11.1; **IR** (neat)/ν_{max} 3065, 2940, 2361, 2252, 1495, 1455, 1300, 1129, 1028, 775, 701; **HRMS** (ESI, *m/*z) calculated for $C_{11}H_{13}O_2NS$, $[M+Na]^+$ is 246.0559, found 246.0560.

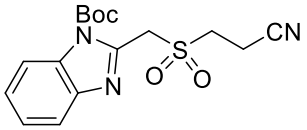
3-(Benzhydrylsulfonyl)propanenitrile (3o)



General Procedure B was followed using bromodiphenyl methane (247 mg, 1.00 mmol, 1.0 equiv.), β-nitrile sulfinate (168 mg, 1.20 mmol, 1.2 equiv.) and DMSO (3 mL, 0.34 M). The crude residue was purified by column chromatography (15 – 65% EtOAc in petrol) to give the product as an off-white crystalline solid (111 mg, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.56 (m, 4H, 4 × Ar-*H*), 7.55 – 7.32 (m, 6H, 6 × Ar-*H*), 5.42 (s, 1H, C*H*), 3.14 (dd, *J* = 8.0, 7.0 Hz, 2H, C$H_2$$CH_2$CN), 2.80 (dd, *J* = 8.0, 7.0 Hz, 2H, CH_2CH_2CN); **^{13}C NMR** (400 MHz, $CDCl_3$) δ 131.6, 130.0, 129.6, 129.5, 116.6, 74.6, 47.0, 11.5; **MP** (DCM) 115 – 116 °C; **IR** (neat)/ν_{max} 3063, 2935, 2252, 1495, 1453, 1313, 1129, 1032, 752, 704; **HRMS** (ESI, *m/*z) calculated for $C_{16}H_{15}O_2NS$, $[M+Na]^+$ is 308.0716, found 308.0715.

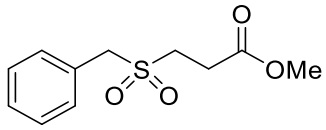
Tert-butyl 2-(((2-cyanoethyl)sulfonyl)methyl)-1H-benzo[d]imidazole-1-carboxyl (3p)



Prepared according to a modified procedure by Merkul et al.[224] 3-(((1H-Benzo[d]imidazol-2-yl)methyl)sulfonyl)propanenitrile (54.8 mg, 0.22 mmol, 1.0 equiv.) was suspended in dichloromethane (0.44 mL) and 4-dimethylaminopyridine (2.7 mg, 0.022 mmol, 10 mol%) was added. A solution of di-tert-butyl carbonate (76 µL, 0.33 mmol, 1.5 equiv.) in dichloromethane (0.44 mL) was added dropwise over 10 minutes. A clear, yellow solution resulted after 2 minutes. The reaction was stirred for 30 minutes at room temperature, before being washed with a 0.1 M aqueous solution of HCl (5 mL). The aqueous phase was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under vacuum. The crude residue was purified by column chromatography (0 – 50% EtOAc in petrol) to give the product as a white crystalline solid (59.1 mg, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.95 (m, 1H, Het-*H*), 7.78 – 7.73 (m, 1H, Het-*H*), 7.46 – 7.36 (m, 2H, 2 × Het-*H*), 5.19 (s, 2H, HetCH_2), 3.61 – 3.53 (m, 2H, CH_2CH_2CN), 2.96 – 2.89 (m, 2H, CH_2CH_2CN), 1.74 (s, 9H, 3 × CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.4, 143.2, 141.8, 133.3, 126.2, 125.1, 120.5, 116.3, 115.5, 87.6, 54.5, 47.8, 28.1, 11.4; **MP** ($CDCl_3$) 120 – 121 °C; **IR** (neat)/ν_{max} 2922, 1752, 1451, 1319, 1216, 1112, 1027; **HRMS** (ESI, *m/*z) calculated for $C_{16}H_{19}O_4N_3S$ $[M+Na]^+$ is 372.0988 (100%), 373.1020 (18%), found 372.0991 (100%), 373.1024 (18%).

Methyl 3-(benzylsulfonyl)propanoate (3q)

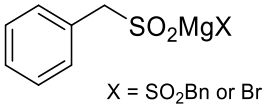


To a 25 mL round bottom flask equipped with a stirrer bar, was added benzyl bromide (214 µL, 1.80 mmol, 1.0 equiv.), SMOPS (376 mg, 2.16 mmol, 1.2 equiv.) and DMSO (5.3 mL, 0.34 M). The reaction was stirred at room temperature for 18 hours. The reaction mixture was transferred to a 100 mL separating funnel in EtOAc (20 mL). The organic layer was washed with aqueous LiCl solution (5 mol%, 3 × 10 mL). The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The crude was then purified by column chromatography (30 – 60% EtOAc in Petrol) to give the product as a white crystalline solid (421 mg, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 5H, 5 × Ar-*H*), 4.28 (s, 2H, ArCH_2), 3.72 (s, 3H, OCH_3), 3.19 (t, *J* = 7.5 Hz, 2H, CH_2CH_2COOMe), 2.80 (t, *J* = 7.5 Hz, 2H, CH_2CH_2COOMe); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0, 130.8, 129.4, 129.3, 127.8, 60.4, 52.6, 46.7, 26.7; **MP** (DCM) 86 – 88 °C; **IR** (neat)/ν_{max} 2942, 1730, 1308, 1282, 1117, 700; **HRMS (ESI)** calculated for $C_{11}H_{15}O_4S$, $[M+H]^+$ is 243.0686 (100%), 244.0719 (12%), found 243.0687 (100%), 244.0721 (12%).

7.2.5. Sulfinate synthesis

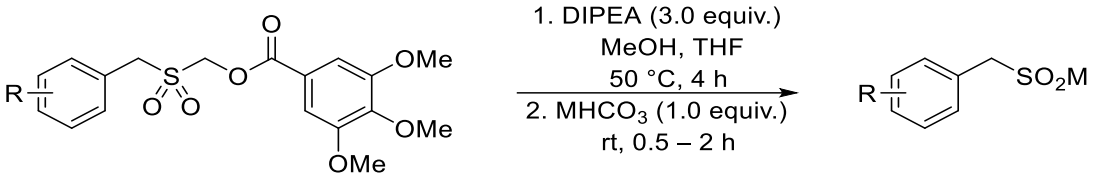
Magnesium benzylsulfinate (1b)



Magnesium benzylsulfinate was prepared according to an adapted procedure by H. Pinnick et al.[31] Magnesium turnings (0.49 g, 20.2 mmol, 1.2 equiv.) and Et_2O (20 mL) were stirred together in a three-neck flask fitted with a condenser and under a nitrogen atmosphere. Benzyl bromide (2 mL, 16.8 mmol, 1.0 equiv.) in Et_2O (10 mL) was added slowly. The reaction was gently warmed by placing hands around the flask until the reaction began to effervesce. Once initiated, the reaction was then left to stir at room temperature for 1.5 h. Anhydrous 1,4-dioxane was added (10 mL), to drive the Shlenk equilibrium to the right ($MgR_2 + MgX_2$),[32] and the precipitate was allowed to settle. A separate round bottom flask, equipped with a magnetic stirrer and under a nitrogen atmosphere, was charged with TIMSO (4.33 mL, 33.7 mmol, 2.0 equiv.) and cooled to -30 °C. The Grignard solution was added dropwise to the cooled TIMSO and further Et_2O (20 mL) was added. The reaction mixture was stirred and allowed to warm to room temperature over 1 h, before being filtered, then washed thoroughly with Et_2O (200 mL) and acetone (200 mL). The crude material was dried under vacuum to remove excess TIMSO before trituration with acetone to afford the product as a fine white powder (2.52 g, 70%).

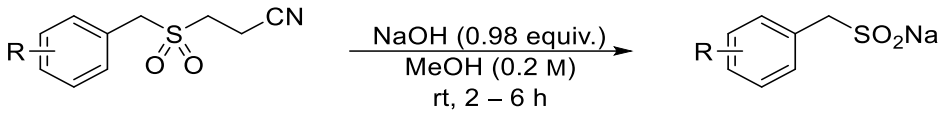
^{1}H NMR (400 MHz, CD_3OD) δ 7.33 – 7.19 (m, 5H, Ar-*H*), 3.57 (s, 2H, ArCH_2); **^{13}C NMR** (101 MHz, CD_3OD) δ 134.3, 131.1, 129.3, 127.9, 70.3; **MP** (Acetone) 185 – 186 °C (decomp.); **IR** (neat)/ν_{max} 3260 (br), 1454, 932 (br); **HRMS** (ESI, *m/z*) calculated for $C_7H_7O_2S$, $[M-(\frac{1}{2}MgX)]^-$ is 155.0172, found 155.0170.

General Procedure C



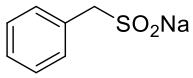
Prepared according to a modified procedure by Shavnya et al.[70] The sulfone made from General Procedure A (1.0 equiv.), methanol (0.2 M) and diisopropylethylamine (3.0 equiv.) were added to a round-bottom flask equipped with a stirrer bar. The reaction was stirred at 50 °C for 0.5 – 2 hours until complete consumption of the sulfone, through monitoring by TLC. The reaction mixture was cooled to room temperature, 1 M aqueous solution of $MHCO_3$ (1.0 equiv.) was added and this was stirred for a further 30 minutes. The solvents were removed under vacuum, and an azeotrope was formed with toluene to achieve dryness. The crude residue was slurried with MTBE (3 × 5 mL), with the solvent removed carefully by pipette each time (without picking up solids), to remove the methyl 3,4,5-trimethoxybenzoate byproduct. The final residue was dried under high vacuum (<1 mbar) until constant weight, to afford the sulfinate salt.

General Procedure D



The sulfone made from General Procedure B (1.0 equiv.), NaOH (0.98 equiv.) and methanol (0.2 M) were added to a round-bottom flask equipped with a stirrer bar. The reaction was stirred at room temperature until complete consumption of the sulfone (2 – 6 hours), through monitoring by TLC. The solvents were removed under reduced pressure, and the residue was dried by forming an azeotrope with toluene to yield the benzyl sulfinate as a sodium salt.

Sodium benzylsulfinate (1c)



Method I: Magnesium benzylsulfinate (0.52 g, 1.55 mmol, 1.0 equiv.) was dissolved in water (100 mL) and washed with EtOAc (100 mL). The organic layer was discarded. HCl (6 M) was added dropwise to acidify the aqueous layer (pH 1), which was then extracted with EtOAc (3 × 100 mL). The organic layer was dried with sodium sulfate and filtered into a 500 mL round bottom flask. Aq. $NaHCO_3$ (1 M, 2.3 mL, 0.94 equiv.) and methanol (25 mL) were added. The mixture was stirred at room temperature for 1 h, then concentrated under vacuum. The residue was dried by forming an azeotrope with toluene to give the product as a white solid (0.15 g, 54%).

Method II: Amberlite® IR120 hydrogen form resin was packed in a column and washed with MeOH until the solvent ran clear. The column was then flushed with water, followed by aq. NaOH (3.75 M). The column was flushed with water, to remove the excess NaOH, and then MeOH, to remove the water. The resin was tipped out of the column into a 1 L round bottom flask, equipped with a stirrer bar. Magnesium benzyl sulfinate (2.0 g, 9.4 mmol) and further MeOH (100 mL) was added. The mixture was stirred at room temperature for 12 h, before being filtered and washed with copious amounts of MeOH (3 × 100 mL). Removal of solvent under vacuum gave the product as a white powder (1.02 g, 61%).

Method III: Benzylsulfonyl chloride (3.81 g, 20.0 mmol, 1.0 equiv), sodium bicarbonate (3.36 g, 40 mmol, 2.0 equiv.) and sodium sulfite (5.04 g, 40.0 mmol, 2.0 equiv.) and distilled water (20 mL, 1.0 M) were added to a round-bottom flask equipped with a stirrer bar. The reaction mixture was heated to 80 °C for 4 hours. The solvents were then removed under

vacuum and by forming an azeotrope with acetonitrile. Cold ethanol (10 mL) was added and solids were collected by vacuum filtration. The solids were washed with further cold ethanol (2 × 10 mL) to afford the product as a white solid (7.06 g, 198% yield). As the mass was very high, the solids were recrystallised with ethanol. The product was given as a white solid (6.56 g, 184% yield). The solids were dissolved in H_2O (20 mL) and acidified with 1 M HCl (20 mL). The mixture was extracted with EtOAc (3 × 50 mL). The organics were then washed with 1 M NaOH (3 × 50 mL). The aqueous layers were combined and the water was removed under vacuum by forming an azeotrope with acetonitrile. The resulting product was given in far too high yield to be pure (11.2 g, 313% yield), so this method was not continued.

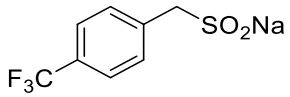
General Procedure C was followed using ((benzyl)sulfonyl)methyl 3,4,5-trimethoxybenzoate (3.0 g, 7.89 mmol, 1.0 equiv.), DIPEA (4.1 mL, 23.7 mmol, 3.0 equiv.), methanol (51.0 mL), THF (16.7 mL) and aq. $NaHCO_3$ (1 M, 7.89 mL, 7.89 mmol, 1.0 equiv.), to give the product as a fine white powder (1.14 g, 81%).

General Procedure D was followed using 3-(benzylsulfonyl)propanenitrile (167 mg, 0.80 mmol, 1.0 equiv.), NaOH (30.4 mg, 0.76 mmol, 0.95 equiv.) and methanol (4.0 mL, 0.2 M) to give the product as a fine white powder (71.2 mg, 81% yield).

^{1}H NMR (400 MHz, CD_3OD) δ 7.29 – 7.25 (m, 4H, 4 × Ar-*H*), 7.24 – 7.17 (m, 1H, Ar-*H*), 3.51 (s, 2H, ArCH_2); **^{13}C NMR** (101 MHz, CD_3OD) δ 134.7, 131.0, 129.2, 127.7, 70.9; **MP** (MTBE) 250 – 251 °C (decomp.); **IR** (neat)/ν_{max} 3030, 1715, 1601, 1454, 1337, 1187, 1131, 1027, 986, 696; **HRMS** (ESI, m/z) calculated for $C_7H_7O_2S$, $[M\text{-}Na]^-$ is 155.0172, found 155.0171.

The data is in accordance with the literature.[225]

Sodium (4-(trifluoromethyl)phenyl)methanesulfinate (1d)

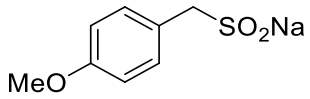


General procedure C was followed using ((4-trifluoromethylbenzyl)sulfonyl)methyl 3,4,5-trimethoxybenzoate (700 mg, 1.56 mmol, 1.0 equiv.), DIPEA (0.82 mL, 4.68 mmol, 3.0 equiv.), methanol (10 mL), THF (2.5 mL) and aq. $NaHCO_3$ (1 M, 1.56 mL) to give the product as a fine white powder (334 mg, 87%).

General Procedure D was followed using 3-((4-(trifluoromethyl)benzyl)sulfonyl)propanenitrile (368 mg, 1.33 mmol, 1.0 equiv.), NaOH (52.0 mg, 0.98 mmol, 0.98 equiv.) and methanol (6.7 mL, 0.2 M) to give the product as a fine white powder (265 mg, 81% yield).

^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (dd, *J* = 55.5, 8.0 Hz, 4H, 4 × Ar-*H*), 3.59 (s, 2H, ArCH_2); **^{13}C NMR** (101 MHz, CD_3OD) δ 139.3, 131.5, 129.7 (q, *J* = 33.5 Hz), 126.0 (q, *J* = 3.5 Hz), 124.6 (q, *J* = 124.5 Hz), 70.2; **^{19}F NMR** (377 MHz, CD_3OD) δ -63.89; **MP** (MTBE) 210 – 215 °C (decomp.); **IR** (neat)/ν_{max} 2161, 2024, 1327, 1118, 1068, 966; **HRMS** (ESI, *m/z*) calculated for $C_8H_6O_2F_3S$, $[M\text{-}Na]^-$ is 223.0046, found 223.0044.

Sodium (4-methoxyphenyl)methanesulfinate (1e)

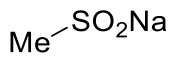


General procedure C was followed using ((4-methoxybenzyl)sulfonyl)methyl 3,4,5-trimethoxybenzoate (488 mg, 1.18 mmol, 1.0 equiv.), DIPEA (0.64 mL, 3.54 mmol, 3.0 equiv.), methanol (7.6 mL), THF (2.5 mL) and aq. $NaHCO_3$ (1 M, 1.18 mL) to give the product as a fine white powder (203 mg, 83%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.22 – 7.16 (m, 2H, Ar-*H*), 6.87 – 6.82 (m, 2H, Ar-*H*), 3.76 (s, 3H, ArOC*H*$_3$), 3.45 (s, 2H, ArC*H*$_2$); **^{13}C NMR** (101 MHz, CD_3OD) δ 160.2, 132.0, 126.8, 114.7, 69.9, 55.6; **MP** (MTBE) 265 – 266 °C (decomp.); **IR** (neat)/ν_{max} 2981, 1611, 1511 (s), 1249 (s), 1013, 973 (s); **HRMS** (ESI) calculated for $C_8H_9O_3S$, $[M\text{-}Na]^-$ is 185.0278, found 185.0275.

The data is in accordance with the literature.[226]

Sodium methanesulfinate (1f)

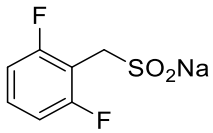


General Procedure C was followed using (methylsulfonyl)methyl 3,4,5-trimethoxybenzoate (200 mg, 0.66 mmol, 1.0 equiv.), DIPEA (0.34 mL, 1.97 mmol, 3.0 equiv.), MeOH (5 mL), THF (1.5 mL) and 1 M aqueous solution of $NaHCO_3$ (0.66 mL, 0.66 mmol, 1.0 equiv.) to give the product as an impure white solid (20.7 mg, 31%).

^{1}H NMR (400 MHz, CD_3OD) δ 2.21 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, CD_3OD) δ 38.03; **LRMS** (ESI, m/z) calculated for CH_3O_2S, $[M\text{-}Na]^-$ is 79.0, found 79.1.

The data is in accordance with the literature.[220]

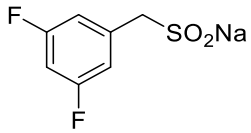
Sodium (2,6-difluorophenyl)methanesulfinate (1i)



General Procedure D was followed using 3-((2,6-difluorobenzyl)sulfonyl)propanenitrile (294 mg, 1.20 mmol, 1.0 equiv.), NaOH (47.2 mg, 1.18 mmol, 0.98 equiv.) and methanol (6 mL) to give the product as a fine white powder (255 mg, 99%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.24 (tt, *J* = 8.5, 6.5 Hz, 1H, Ar-*H*), 6.97 – 6.89 (m, 2H, 2 × Ar-*H*), 3.60 (s, 2H, ArCH_2); **^{13}C NMR** (101 MHz, CD_3OD) δ 163.1 (dd, J = 247.5, 8.5 Hz), 129.5 (t, *J* = 10.0 Hz), 112.0 (dd, *J* = 19.5, 6.5 Hz), 111.7 (t, *J* = 20.5 Hz), 57.3; **^{19}F NMR** (377 MHz, CD_3OD) δ -115.10; **MP** (MTBE) 250 °C (Decomp); **IR** (neat)/ν_{max} 1629, 1595, 1472, 1271, 1225, 1078, 1043, 990, 781; **HRMS** (ESI, *m/*z) calculated for $C_7H_5F_2SO_2$, $[M\text{-}Na]^-$ is 190.9973 (100%), 192.0006 (10%), found 190.9975 (100%), 192.0006 (10%).

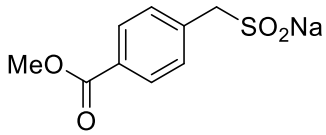
Sodium (3,5-difluorophenyl)methanesulfinate (1j)



General Procedure D was followed using 3-((3,5-difluorobenzyl)sulfonyl)propanenitrile (245 mg, 1.00 mmol, 1.0 equiv.), NaOH (39.2 mg, 0.98 mmol, 0.98 equiv.) and methanol (5 mL) to give the product as a fine white powder (159 mg, 74%).

^{1}H NMR (400 MHz, CD_3OD) δ 6.87 (dtd, *J* = 8.5, 6.0, 2.0 Hz, 2H, 2 × Ar-*H*), 6.77 (tt, *J* = 9.5, 2.5 Hz, 1H, Ar-*H*), 3.49 (s, 2H, ArCH_2); **^{13}C NMR** (101 MHz, CD_3OD) δ 164.2 (dd, *J* = 246.0, 13.0 Hz), 139.0 (t, *J* = 10.0 Hz), 113.8 – 113.5 (dd, *J* = 18.5, 6.5 Hz), 102.6 (t, *J* = 26.0 Hz), 70.0; **^{19}F NMR** (377 MHz, CD_3OD) δ -113.13; **MP** (MTBE) 280 – 281 °C (Decomp); **IR** (neat)/ν_{max} 1628, 1597, 1462, 1327, 1118, 1020, 990, 970; **HRMS** (ESI, *m/*z) calculated for $C_7H_5F_2SO_2$, $[M\text{-}Na]^-$ is 190.9973 (100%), 192.0006 (10%), found 190.9976 (100%), 192.0008 (10%).

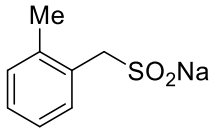
Sodium (4-(methoxycarbonyl)phenyl)methanesulfinate (1k)



General Procedure D was followed using methyl 4-(((2-cyanoethyl)sulfonyl)methyl)benzoate (695 mg, 2.60 mmol, 1.0 equiv.), NaOH (102 mg, 2.55 mmol, 0.98 equiv.) and methanol (13 mL) to give the product as a fine white powder (486 mg, 81%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (d, *J* = 8.3 Hz, 2H, 2 × Ar-*H*), 7.37 (d, *J* = 8.3 Hz, 2H, 2 × Ar-*H*), 3.89 (s, 3H, C*H*$_3$), 3.58 (s, 2H, ArC*H*$_2$); **^{13}C NMR** (101 MHz, CD_3OD) δ 168.7, 140.5, 131.1, 130.4, 129.5, 70.8, 52.5; **MP** (MTBE) 275 – 276 °C (Decomp); **IR** (neat)/ν_{max} 1717, 1437, 1280, 1118, 1055, 977; **HRMS** (ESI, *m/*z) calculated for $C_9H_{10}SO_4Na$, $[M+H]^+$ is 237.0192 (100%), 238.0225 (10%), found 237.0194 (100%), 238.0226 (10%).

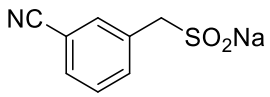
Sodium o-tolylmethanesulfinate (1l)



General Procedure D was followed using 3-((2-methylbenzyl)sulfonyl)propanenitrile (268 mg, 1.20 mmol, 1.0 equiv.), NaOH (47.2 mg, 1.18 mmol, 0.98 equiv.) and methanol (6 mL) to give the product as a fine white powder (131 mg, 57%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.24 – 7.18 (m, 1H, Ar-*H*), 7.16 – 7.07 (m, 3H, 3 × Ar-*H*), 3.60 (s, 2H, ArC*H*$_2$), 2.39 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, CD_3OD) δ 138.03, 133.45, 132.06, 130.82, 127.84, 126.87, 68.95, 20.33; **MP** (MTBE) 175 – 176 °C (Decomp); **IR** (neat)/ν_{max} 1604, 1495, 1189, 1013, 961, 773; **HRMS** (ESI, *m/*z) calculated for $C_8H_{10}SO_2Na$, $[M+H]^+$ is 193.0294 (100%), 194.0327 (10%), found 193.0297 (100%), 194.0330 (10%).

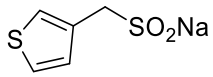
Sodium (3-cyanophenyl)methanesulfinate (1m)



General Procedure D was followed using 3-(((2-cyanoethyl)sulfonyl)methyl)benzonitrile (281 mg, 1.20 mmol, 1.0 equiv.), NaOH (47.2 mg, 1.18 mmol, 0.98 equiv.) and methanol (6 mL) to give the product as a fine white powder (201 mg, 84%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.64 – 7.60 (m, 1H, Ar-*H*), 7.59 – 7.54 (m, 2H, 2 × Ar-*H*), 7.47 (t, *J* = 7.7 Hz, 1H, Ar-*H*), 3.55 (s, 2H, ArC*H*$_2$); **^{13}C NMR** (101 MHz, CD_3OD) δ 136.5, 135.8, 134.5, 131.2, 130.2, 119.9, 113.1, 69.4; **MP** (CD_3OD) 212 – 214 °C; **IR** (neat)/ν_{max} 2244, 1482, 1052, 1033, 987; **HRMS** (ESI, *m/*z) calculated for $C_8H_6O_2NS$, $[M\text{-}Na]^-$ is 180.0125 (100%), 181.0158 (10%), found 180.0123 (100%), 181.0154 (10%).

Sodium thiophen-3-ylmethanesulfinate (1n)



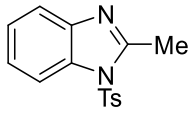
General Procedure D was followed using 3-((thiophen-3-ylmethyl)sulfonyl)propanenitrile (560 mg, 2.60 mmol, 1.0 equiv.), NaOH (102 mg, 40.0 mmol, 0.98 equiv.) and methanol (17 mL, 0.15 M) to give the product as a fine white powder (360 mg, 77% yield).

^{1}H NMR (400 MHz, CD_3OD) δ 7.31 (dd, *J* = 5.0, 3.0 Hz, 1H, Het-*H*), 7.20 (dq, *J* = 3.0, 1.0 Hz, 1H, Het-*H*), 7.07 (dd, *J* = 5.0, 1.0 Hz, 1H, Het-*H*), 4.88 (s, 2H, HetC*H*$_2$); **^{13}C NMR** (101 MHz, CD_3OD) δ 134.9, 130.2, 126.0, 124.0, 64.9; **LRMS** (ESI, *m/z*) calculated for $C_5H_5O_2S_2$, $[M\text{-}Na]^-$ is 161.0, found 161.0.

The data is in accordance with the literature.[226]

7.2.6. Side-products

2-Methyl-1-tosyl-1*H*-benzo[*d*]imidazole (4a)



General Procedure D was followed using 3-(((1-tosyl-1H-benzo[d]imidazol-2-yl)methyl)sulfonyl)propanenitrile (363 mg, 0.90 mmol, 1.0 equiv.), NaOH (35.3 mg, 0.88 mmol, 0.98 equiv.) and methanol (4.5 mL, 0.2 M) to give the product as a white solid (114 mg, 45% yield).

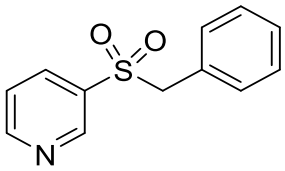
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.01 (m, 1H, Het-*H*), 7.84 – 7.79 (m, 2H, 2 × Ar-*H*), 7.66 – 7.62 (m, 1H, Het-*H*), 7.34 (ddd, *J* = 7.5, 5.2, 1.6 Hz, 2H, 2 × Het-*H*), 7.32 – 7.26 (m, 2H, 2 × Ar-*H*), 2.82 (s, 3H, Ar-CH_3), 2.39 (s, 3H, Het-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.5, 146.1, 142.0, 135.6, 133.3, 130.4, 126.9, 124.8, 124.7, 119.8, 113.6, 21.7, 17.0; **LRMS** (ESI, *m/*z) calculated for $C_{15}H_{15}N_2O_2S$, $[M+H]^+$ is 287.1, found 287.0.

The data is in accordance with the literature.[227]

7.3. Chapter 3: Experimental procedures and data

1.1.3 Synthesis of pyridine sulfones

3-(Benzylsulfonyl)pyridine (5a)

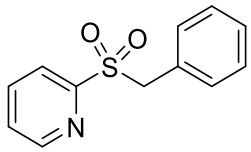


To a 10 mL microwave vial equipped with a stir bar was added, sodium pyridine-3-sulfinate (66.1 mg, 0.40 mmol, 2.0 equiv.), potassium carbonate (41.5 mg, 0.30 mmol, 1.5 equiv.), $Pd(OAc)_2$ (4.5 mg, 10 mol%) and PCy_3 (11.2 mg, 20 mol%). The vial was sealed with a microwave vial cap, evacuated under vacuum (<1 mbar) and back-filled with nitrogen gas. This cycle was repeated a further two times. Addition of benzyl bromide (24 µL, 0.20 mmol, 1.0 equiv.), and 1,4-dioxane (2.0 mL, 0.1 M) followed. The reaction was heated to 150 °C for 18 h before being cooled to room temperature. The reaction mixture was filtered through a pad of celite, rinsed thoroughly with EtOAc (50 mL) and the solvents were removed under reduced pressure. The resulting crude material was purified by silica gel chromatography (25 – 70% EtOAc in petrol) to give the title product as an off-white solid (22.7 mg, 49%). The same reaction repeated with no $Pd(OAc)_2$ and PCy_3 used, yielded 32.4 mg, 69%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 2H, 2 × Het-*H*), 7.85 – 7.81 (m, 1H, Het-*H*), 7.40 – 7.32 (m, 2H, Het-*H*, Ar-*H*), 7.32 – 7.26 (m, 2H, 2 × Ar-*H*), 7.12 – 7.07 (m, 2H, 2 × Ar-*H*), 4.37 (s, 2H, $HetSO_2CH_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.2, 149.5, 136.7, 134.5, 131.0, 129.3, 129.0, 127.6, 123.6, 63.4; **LRMS** (ESI, *m/z*) calculated for $C_{12}H_{12}NO_2S$, $[M+H]^+$ is 234.1, found 234.0.

Data is in accordance with the literature.[228]

2-(Benzylsulfonyl)pyridine (5b)

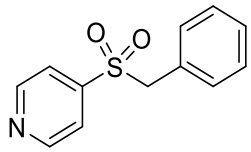


To a 10 mL microwave vial equipped with a stir bar was added, sodium pyridine-2-sulfinate (66.1 mg, 0.40 mmol, 2.0 equiv.), potassium carbonate (41.5 mg, 0.30 mmol, 1.5 equiv.), $Pd(OAc)_2$ (4.5 mg, 10 mol%) and PCy_3 (11.2 mg, 20 mol%). The vial was sealed with a microwave vial cap, evacuated under vacuum (<1 mbar) and back-filled with nitrogen gas. This cycle was repeated a further two times. Addition of benzyl bromide (24 µL, 0.20 mmol, 1.0 equiv.), and 1,4-dioxane (2.0 mL, 0.1 M) followed. The reaction was heated to 150 °C for 18 h before being cooled to room temperature. The reaction mixture was filtered through a pad of celite, rinsed thoroughly with EtOAc (50 mL) and the solvents were removed under reduced pressure. The resulting crude material was purified by silica gel chromatography (25 – 70% EtOAc in petrol) to give the title product as a yellow oil (9.3 mg, 20%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dt, *J* = 5.0, 1.5 Hz, 1H, Het-*H*), 7.85 – 7.78 (m, 2H, 2 × Het-*H*), 7.52 (ddd, *J* = 6.5, 5.0, 2.0 Hz, 1H, Het-*H*), 7.28 – 7.26 (m, 1H, Ar-*H*), 7.26 – 7.22 (m, 2H, 2 × Ar-*H*), 7.19 – 7.16 (m, 2H, 2 × Ar-*H*), 4.64 (s, 2H, $HetSO_2CH_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.5, 150.3, 138.0, 131.1, 128.9, 128.8, 127.6, 127.5, 123.3, 58.5; **LRMS** (ESI, *m/z*) calculated for $C_{12}H_{12}NO_2S$, $[M+H]^+$ is 234.1, found 234.0.

Data is in accordance with the literature.[229]

4-(Benzylsulfonyl)pyridine (5c)



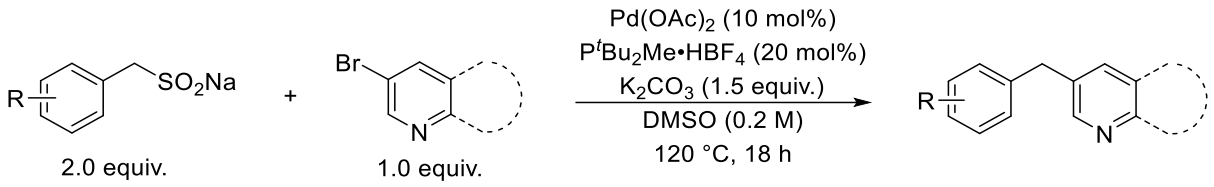
To a 10 mL microwave vial equipped with a stir bar was added, sodium pyridine-4-sulfinate (66.1 mg, 0.40 mmol, 2.0 equiv.), potassium carbonate (41.5 mg, 0.30 mmol, 1.5 equiv.), $Pd(OAc)_2$ (4.5 mg, 10 mol%) and PCy_3 (11.2 mg, 20 mol%). The vial was sealed with a microwave vial cap, evacuated under vacuum (<1 mbar) and back-filled with nitrogen gas. This cycle was repeated a further two times. Addition of benzyl bromide (24 µL, 0.20 mmol, 1.0 equiv.), and 1,4-dioxane (2.0 mL, 0.1 M) followed. The reaction was heated to 150 °C for 18 h before being cooled to room temperature. The reaction mixture was filtered through a pad of celite, rinsed thoroughly with EtOAc (50 mL) and the solvents were removed under reduced pressure. The resulting crude material was purified by silica gel chromatography (25 – 70% EtOAc in petrol) to give the title product as an off-white solid (26.4 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 5.5 Hz, 2H, 2 × Het-*H*), 7.40 (dd, *J* = 4.5, 1.5 Hz, 2H, 2 × Het-*H*), 7.29 – 7.25 (m, 1H, Ar-*H*), 7.24 – 7.19 (m, 2H, 2 × Ar-*H*), 7.03 (dd, *J* = 7.5, 1.5 Hz, 2H, 2 × Ar-*H*), 4.28 (s, 2H, $HetSO_2CH_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.0, 146.0, 130.9, 129.4, 129.0, 127.2, 121.9, 62.7; **LRMS** (ESI, *m/z*) calculated for $C_{12}H_{12}NO_2S$, $[M+H]^+$ is 234.1, found 234.0.

Data is in accordance with the literature.[230]

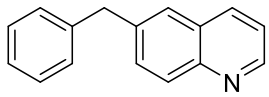
1.1.4 Desulfinative cross-couplings

General Procedure E



To a 10 mL microwave vial equipped with a stirrer bar was added, the sodium benzyl sulfinate (0.40 mmol, 2.0 equiv.), *if solid*, the (hetero)aryl bromide (0.20 mmol, 1.0 equiv.), potassium carbonate (41.5 mg, 0.30 mmol, 1.5 equiv.), $Pd(OAc)_2$ (4.5 mg, 10 mol%) and $P^tBu_2Me{\cdot}HBF_4$ (9.9 mg, 20 mol%). The vial was sealed with a microwave vial cap, evacuated under vacuum (<1 mbar) and back-filled with nitrogen gas. This cycle was repeated a further two times. Addition of, *if liquid*, the heteroaryl bromide (0.20 mmol, 1.0 equiv.), and DMSO (1.0 mL, 0.2 M) followed. The reaction was heated to 120 °C for 18 h before being cooled to room temperature. The reaction mixture was filtered through a pad of celite, rinsed thoroughly with EtOAc (50 mL) and the solvents were removed under reduced pressure. If the product was highly polar, 15 mL EtOAc was added to the crude residue and this was then washed with 5% aqueous LiCl solution (3 × 8 mL) to draw the DMSO into the aqueous layer. The aqueous washings were discarded. The organic layer was dried over $MgSO_4$, before removal of the solvents under reduced pressure. The resulting crude material was purified by silica gel chromatography to give the desired cross-coupled product.

6-Benzylquinoline (6a)

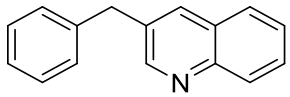


General Procedure E was followed using sodium benzylsulfinate (71.2 mg, 0.40 mmol, 2.0 equiv.), 6-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.). Purification of the crude material by flash column chromatography (10 – 50% EtOAc in petrol) afforded the product as a pale yellow solid (40.4 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (dd, *J* = 4.0, 2.0 Hz, 1H, Het-*H*), 8.08 (dd, *J* = 8.5, 2.0 Hz, 1H, Het-*H*), 8.03 (d, *J* = 8.5 Hz, 1H, Het-*H*), 7.61 – 7.54 (m, 2H, 2 × Het-*H*), 7.37 (dd, *J* = 8.5, 4.0 Hz, 1H, Het-*H*), 7.34 – 7.28 (m, 2H, 2 × Ar-*H*), 7.26 – 7.20 (m, 3H, 3 × Ar-*H*), 4.17 (s, 2H, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.0, 147.3, 140.6, 139.7, 135.8, 131.4, 129.7, 129.2, 128.8, 128.5, 126.9, 126.5, 121.3, 42.0; **HRMS** (ESI, *m/z*) calculated for $C_{16}H_{14}N$, $[M+H]^+$ is 220.1121, found 220.1118.

Data is in accordance with the literature.[231]

3-Benzylquinoline (6b)

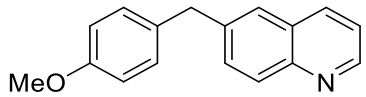


General Procedure E was followed using sodium benzyl sulfinate (71.3 mg, 0.40 mmol, 2.0 equiv.) and 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.). The crude material was purified by column chromatography (10 – 30% EtOAc in petrol) to give the product as an off-white solid (38.1 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.09 (dd, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.88 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.74 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 7.66 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.51 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Het-*H*), 7.37 – 7.28 (m, 2H, 2 × Ar-*H*), 7.25 (td, *J* = 7.0, 1.5 Hz, 3H, 3 × Ar-*H*), 4.17 (s, 2H, Ar-CH_2-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.2, 147.0, 139.8, 134.9, 134.0, 129.3, 129.1, 129.0, 128.9, 128.2, 127.6, 126.8, 126.7, 39.4; **MP** (CH_2Cl_2) 48 °C; **HRMS (ESI)** calculated for $C_{16}H_{14}N$, $[M+H]^+$ is 220.1121, found 220.1121.

The data is consistent with the literature.[232]

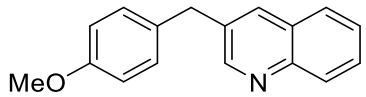
6-(4-Methoxybenzyl)quinoline (6c)



General Procedure E was followed using sodium (4-methoxyphenyl)methanesulfinate (41.6 mg, 0.20 mmol, 2.0 equiv.), 6-bromoquinoline (14 µL, 0.10 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ (5.0 mg, 0.02 mmol, 20 mol%), potassium carbonate (20.8 mg, 0.15 mmol, 1.5 equiv.) and DMSO (0.5 mL). Purification of the crude material by flash column chromatography (5 – 30% EtOAc in petrol) afforded the product as a clear oil (23.9 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (dd, *J* = 4.5, 1.5 Hz, 1H, Het-*H*), 8.08 (ddd, *J* = 8.5, 1.5, 1.0 Hz, 1H, Het-*H*), 8.05 – 8.00 (m, 1H, Het-*H*), 7.57 (s, 1H, Het-*H*), 7.55 (dd, *J* = 6.5, 1.5 Hz, 1H, Het-*H*), 7.36 (dd, *J* = 8.5, 4.5 Hz, 1H, Het-*H*), 7.17 – 7.12 (m, 2H, Ar-*H*), 6.88 – 6.83 (m, 2H, Ar-*H*), 4.11 (s, 2H, C*H*$_2$), 3.79 (s, 3H, Ar-OC*H*$_3$).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.3, 149.9, 147.2, 140.2, 135.9, 132.6, 131.4, 130.1, 129.5, 128.5, 126.7, 121.3, 114.2, 55.4, 41.1; **IR** (neat)/ν_{max} 3030, 2917, 2835, 1511 (s), 1247 (s), 1034; **HRMS** (ESI, *m/z*) calculated for $C_{17}H_{16}NO$, $[M+H]^+$ is 250.1226, found 250.1226.

3-(4-Methoxybenzyl)quinoline (6d)

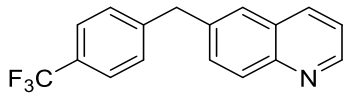


General Procedure E was followed using sodium (4-methoxyphenyl)methanesulfinate (41.6 mg, 0.20 mmol, 2.0 equiv.), 3-bromoquinoline (14 µL, 0.10 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $P(^tBu)_2Me.HBF_4$ (5.0 mg, 0.02 mmol, 20 mol%), potassium carbonate (20.8 mg, 0.15 mmol, 1.5 equiv.) and DMSO (0.5 mL). Purification of the crude material by flash column chromatography (5 – 30% EtOAc in petrol) afforded the product as a yellow oil (24.6 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.08 (d, *J* = 8.5 Hz, 1H, Het-*H*), 7.86 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.73 (dd, *J* = 8.0, 1.5 Hz, 1H, Het-*H*), 7.66 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.51 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Het-*H*), 7.18 – 7.11 (m, 2H, Ar-*H*), 6.89 – 6.82 (m, 2H, Ar-*H*), 4.11 (s, 2H, C*H*$_2$), 3.79 (s, 3H, Ar-OC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.5, 152.2, 146.9, 134.9, 134.5, 131.9, 130.1, 129.2, 128.9, 128.3, 127.6, 126.8, 114.3, 55.4, 38.5; **HRMS** (ESI, *m/z*) calculated for $C_{17}H_{16}NO$, $[M+H]^+$ is 250.1226, found 250.1223.

Data is in accordance with the literature.[233]

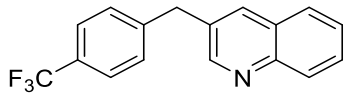
6-(4-(Trifluoromethyl)benzyl)quinoline (6e)



General Procedure E was followed using sodium (4-(trifluoromethyl)phenyl)methanesulfinate (49.3 mg, 0.20 mmol, 2.0 equiv.), 6-bromoquinoline (14 µL, 0.10 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ (5.0 mg, 0.02 mmol, 20 mol%), potassium carbonate (20.8 mg, 0.15 mmol, 1.5 equiv.) and DMSO (0.5 mL). Purification of the crude material by flash column chromatography (10 – 50% EtOAc in petrol) afforded the product as a yellow oil (28.3 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (dd, *J* = 4.5, 2.0 Hz, 1H, Het-*H*), 8.09 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 8.05 (d, *J* = 8.5 Hz, 1H, Het-*H*), 7.60 – 7.50 (m, 4H, 2 × Het-*H,* 2 × Ar-*H*), 7.39 (dd, *J* = 8.5, 4.5 Hz, 1H, Het-*H*), 7.34 (*app.* d, *J* = 8.0 Hz, 2H*,* 2 × Ar-*H*), 4.22 (s, 2H, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.3, 147.4, 144.6, 138.5, 135.9, 131.2, 129.9, 129.5, 129.0 (q, *J* = 32.5 Hz), 128.5, 127.1, 125.7 (q, *J* = 4.0 Hz), 124.4 (q, *J* = 269.5 Hz), 121.5, 41.8; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.36; **IR** (neat)/ν_{max} 3041, 2918, 1324 (s), 1162, 1119, 1066; **HRMS** (ESI, *m/z*) calculated for $C_{17}H_{13}F_3N$, $[M+H]^+$ is 288.0995, found 288.0995.

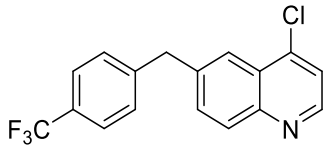
3-(4-(Trifluoromethyl)benzyl)quinoline (6f)



General Procedure E was followed using sodium (4-(trifluoromethyl)phenyl)methanesulfinate (49.3 mg, 0.20 mmol, 2.0 equiv.), 3-bromoquinoline (14 µL, 0.10 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ (5.0 mg, 0.02 mmol, 20 mol%), potassium carbonate (20.8 mg, 0.15 mmol, 1.5 equiv.) and DMSO (0.5 mL). Purification of the crude material by flash column chromatography (10 – 50% EtOAc in Petrol) afforded the product as a pale yellow solid (28.4 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.10 (dd, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.88 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.75 (dd, *J* = 8.0, 1.5 Hz, 1H, Het-*H*), 7.69 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.58 (d, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 7.54 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, Het-*H*), 7.34 (d, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 4.22 (s, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.9, 147.2, 143.9, 135.2, 132.9, 129.4, 129.4, 129.3, 129.2 (q, *J* = 32.5 Hz), 128.2, 127.6, 127.1, 125.9 (q, *J* = 4.0 Hz), 124.3 (q, *J* = 273.5 Hz), 39.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.41; **MP** (Petrol/EtOAc) 55 – 57 °C; **IR** (neat)/ν_{max} 3056, 2918, 1325 (s), 1121, 1067; **HRMS** (ESI, *m/z*) calculated for $C_{17}H_{13}NF_3$, $[M+H]^+$ is 288.0995, found 288.0994.

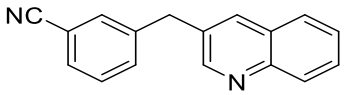
4-Chloro-6-(4-(trifluoromethyl)benzyl)quinoline (6g)



General Procedure E was followed using sodium (4-(trifluoromethyl)phenyl)methanesulfinate (49.3 mg, 0.20 mmol, 2.0 equiv.), 6-bromo-4-chloroquinoline (24.3 mg, 0.10 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ (5.0 mg, 0.02 mmol, 20 mol%), potassium carbonate (20.8 mg, 0.15 mmol, 1.5 equiv.) and DMSO (0.5 mL). Purification of the crude material by flash column chromatography (5 – 50% EtOAc in Petrol) afforded the product as a clear oil (4.4 mg, 14%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 4.5 Hz, 1H, Het-*H*), 8.08 – 8.03 (m, 2H, 2 × Het-*H),* 7.57 (dd, *J* = 8.5, 1.5 Hz, 3H, Het-*H,* 2 × Ar-*H*), 7.50 (d, *J* = 4.5 Hz, 1H, Het-*H*), 7.35 (d, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 4.27 (s, 2H, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.7, 148.3, 144.3, 142.4, 139.8, 135.0, 132.0, 130.4, 129.4, 128.9, 126.7, 125.8 (q, *J* = 4.0 Hz), 123.6, 121.7, 42.0 carbon spectrum too weak to see all the δ_{CF}; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.40; **IR** (neat)/ν_{max} 2917, 2849, 1325 (s), 1163, 1123, 1067; **HRMS** (ESI, *m/z*) calculated for $C_{17}H_{11}ClNF_3$, $[M+H]^+$ is 322.0605, found 322.0604.

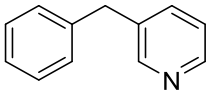
3-(Quinolin-3-ylmethyl)benzonitrile (6h)



General Procedure E was followed using sodium (3-cyanophenyl)methanesulfinate (81.3 mg, 0.40 mmol, 2.0 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.). Purification of the crude material by flash column chromatography (15 – 40% EtOAc in Petrol) afforded the product as a yellow oil (48.8 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H, Het-*H*), 8.15 (d, *J* = 8.5 Hz, 1H, Het-*H*), 7.94 (s, 1H, Het-*H*), 7.79 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 7.73 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.61 – 7.52 (m, 3H*,* Het-*H*, 2 × Ar-*H*), 7.49 – 7.41 (m, 2H*,* 2 × Ar-*H*), 4.22 (s, 2H, CH_2).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.4, 146.8, 141.2, 135.7, 133.5, 132.5, 132.4, 130.6, 129.8, 129.7, 129.1, 128.2, 127.6, 127.4, 118.7, 113.1, 38.9; **IR** (neat)/ν_{max} 2924, 2229, 1496, 1483, 787, 754; **LRMS** 245.0 $[M+H]^+$; **HRMS** (ESI, *m/z*) calculated for $C_{17}H_{13}N_2$, $[M+H]^+$ is 245.1073 (100%), 246.1107 (17%), found 245.1073 (100%), 246.1108 (17%).

3-Benzylpyridine (6i)



General Procedure E was followed using sodium benzylsulfinate (35.6 mg, 0.20 mmol, 2.0 equiv.), 3-bromopyridine (10 µL, 0.10 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ (5.0 mg, 0.02 mmol, 20 mol%), potassium carbonate (20.8 mg, 0.15 mmol, 1.5 equiv.) and DMSO (0.5 mL). Purification of the crude material by flash column chromatography (5 – 50% EtOAc in petrol) afforded the product as a yellow oil (13.0 mg, 77%).

Increasing the temperature to 150 °C and running the reaction on 0.2 mmol scale gave slight improvement in yield (27.7 mg, 82%).

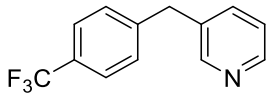
At 120 °C, on 0.2 mmol scale, and increasing the equivalents of sodium benzylsulfinate (106.8 mg, 0.6 mmol, 3.0 equiv.), saw improved yield (30.2 mg, 89%).

When freshly prepared benzyl sulfinate (35.6 mg, 0.20 mmol, 2.0 equiv.), a new bottle of anhydrous DMSO and freshly dried K_2CO_3 were used, 3-benzylpyridine was given in excellent yield (17.0 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 2.0 Hz, 1H, Het-*H*), 8.46 (dd, *J* = 5.0, 2.0 Hz, 1H, Het-*H*), 7.46 (dt, *J* = 8.0, 2.0 Hz, 1H, Het-*H*), 7.34 – 7.27 (m, 2H, 2 × Ar-*H*), 7.25 – 7.15 (m, 4H, Het-*H*, 3 × Ar-*H*), 3.98 (s, 2H, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.3, 147.8, 139.9, 136.6, 136.5, 129.0, 128.8, 126.6, 123.6, 39.1; **HRMS** (ESI, *m/z*) calculated for $C_{12}H_{12}N$, $[M+H]^+$ is 170.0964, found 170.0964.

Data is in accordance with the literature.[234]

3-(4-(Trifluoromethyl)benzyl)pyridine (6j)

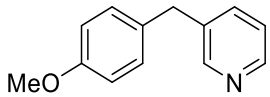


General Procedure E was followed using sodium 4-(trifluoromethyl)benzyl sulfinate (98.5 mg, 0.40 mmol, 2.0 equiv.) and 3-bromopyridine (20 µL 0.20 mmol, 1.0 equiv.). The crude material was purified by column chromatography (10 – 40% EtOAc in petrol) to give the product as a yellow oil (23.7 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 – 8.45 (m, 2H, 2 × Het-*H*), 7.56 (d, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 7.45 (dt, *J* = 8.0, 2.0 Hz, 1H, Het-*H*), 7.29 (d, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 7.22 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H, Het-*H*), 4.03 (s, 2H, Ar-CH_2-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.3, 148.2, 144.0, 136.4, 135.6, 129.3, 129.1 (q, *J* = 32.5 Hz), 125.8 (q, *J* = 4.0 Hz), 124.1 (q, *J* = 272.0 Hz), 123.7, 38.9; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.46; **IR** (neat)/ν_{max} 3030, 2922, 2851, 1619, 1576, 1418, 1325, 1164, 1122, 1067, 1019; **HRMS (ESI)** calculated for $C_{13}H_{11}F_3N$, $[M+H]^+$ is 238.0838 (100%), 239.0872 (15%), found 238.0838 (100%), 239.0871 (15%).

The data is consistent with the literature.[235]

3-(4-Methoxybenzyl)pyridine (6k)

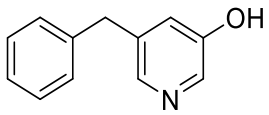


General Procedure E was followed using sodium 4-methoxybenzyl sulfinate (83.3 mg, 0.40 mmol, 2.0 equiv.) and 3-bromopyridine (20 µL 0.20 mmol, 1.0 equiv.). The crude material was purified by column chromatography (10 – 50% EtOAc in petrol) to give the product as a yellow oil (37.1 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H, Het-*H*), 8.45 (d, *J* = 4.5 Hz, 1H, Het-*H*), 7.45 (d, *J* = 8.0 Hz, 1H, Het-*H*), 7.20 (dd, *J* = 8.0, 4.5 Hz, 1H, Het-*H*), 7.12 – 7.05 (m, 2H, 2 × Ar-*H*), 6.86 – 6.82 (m, 2H, 2 × Ar-*H*), 3.92 (s, 2H, Ar-CH_2-Het), 3.78 (s, 3H, Ar-OCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.4, 150.0, 147.5, 137.1, 136.5, 131.9, 129.9, 123.6, 114.2, 55.4, 38.3; **HRMS (ESI)** calculated for $C_{13}H_{14}ON$, $[M+H]^+$ is 200.1070 (100%), 201.1104 (15%), found 200.1073 (100%), 201.1108 (15%)

The data is consistent with the literature.[236]

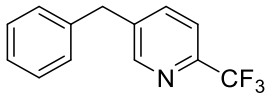
5-Benzylpyridin-3-ol (6l)



General Procedure E was followed using 5-bromopyridin-3-ol (26.1 mg, 0.15 mmol, 1.0 equiv.) and sodium benzyl sulfinate (53.6 mg, 0.3 mmol, 2.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 10 mol%), $P(^tBu)_2Me.HBF_4$ (7.4 mg, 0.03 mmol, 20 mol%), potassium carbonate (31.1 mg, 0.23 mmol, 1.5 equiv.) and DMSO (0.75 mL). Purification of the crude material by flash column chromatography (50 – 100% EtOAc in Petrol) afforded the product as a white solid (21.5 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H, Het-O*H*), 8.08 (d, *J* = 2.5 Hz, 1H, Het-*H*), 7.92 (d, *J* = 2.0 Hz, 1H, Het-*H*), 7.31 – 7.26 (m, 2H, 2 × Ar-*H*), 7.24 – 7.19 (m, 1H, Ar-*H*), 7.18 – 7.14 (m, 2H, 2 × Ar-*H*), 7.11 (t, *J* = 2.5 Hz, 1H, Het-*H*), 3.93 (s, 2H, Ar-C*H*$_2$-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.4, 139.4, 139.2, 139.1, 134.1, 129.0, 128.9, 126.8, 125.8, 39.0; **MP** (CH_2Cl_2) 104 – 106 °C; **IR** (neat)/ν_{max} 3028, 2922, 2840, 2642, 1585, 1495, 1441, 1303, 1178, 1137, 733, 698; **HRMS (ESI)** calculated for $C_{12}H_{12}ON$, $[M+H]^+$ is 186.0913 (100%), 187.0947 (12%), found 186.0914 (100%), 187.0948 (15%).

5-Benzyl-2-(trifluoromethyl)pyridine (6m)

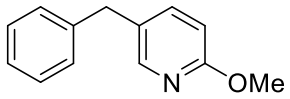


General Procedure E was followed using 5-bromo-2-(trifluoromethyl)pyridine (45.2 mg, 0.20 mmol, 1.0 equiv.) and sodium benzyl sulfinate (71.2 mg, 0.40 mmol, 2.0 equiv.), and DMSO (1.0 mL). Purification of the crude material by flash column chromatography (5 – 40% Et_2O in Petrol) afforded the product as a yellow oil (26.5 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 2.0 Hz, 1H, Het-*H*), 7.63 (dd, *J* = 8.0, 2.0 Hz, 1H, Het-*H*), 7.59 (dd, *J* = 8.0, 1.0 Hz, 1H, Het-*H*), 7.36 – 7.30 (m, 2H, 2 × Ar-*H*), 7.28 – 7.24 (m, 1H, Ar-*H*), 7.20 – 7.16 (m, 2H, 2 × Ar-*H*), 4.06 (s, 2H, Ar-*CH$_2$*-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) 150.5, 146.9 (d, *J* = 34.5 Hz), 140.1, 138.8, 137.6, 129.1, 129.0, 127.0, 121.8 (q, *J* = 273.0 Hz), 120.4 (q, *J* = 2.5 Hz), 39.0; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -67.73; **IR** (neat)/ν_{max} 3029, 2924, 1496, 1336, 1176, 1130, 1085, 1028, 857, 737, 700; **HRMS (ESI)** calculated for $C_{13}H_{11}F_3N$, $[M+H]^+$ is 238.0838 (100%), 239.0872 (15%), found 238.0838 (100%), 239.0872 (17%).

The data is consistent with the literature.[237]

5-Benzyl-2-methoxypyridine (6n)

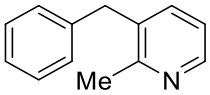


General Procedure E was followed using sodium benzylsulfinate (81.3 mg, 0.40 mmol, 2.0 equiv.), 2-methoxy-5-bromopyridine (26 µL, 0.20 mmol, 1.0 equiv.). Purification of the crude material by flash column chromatography (5 – 30% EtOAc in petrol) afforded the product as a yellow oil (39.4 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.37 (dd, *J* = 8.5, 2.5 Hz, 1H, Het-*H*), 7.32 – 7.26 (m, 2H, 2 × Ar-*H*), 7.23 – 7.18 (m, 1H, Ar-*H*), 7.18 – 7.15 (m, 2H, 2 × Ar-*H*), 6.67 (dd, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 3.92 (s, 3H, Het-OCH_3), 3.90 (s, 2H, Ar-CH_2-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.0, 146.4, 140.7, 139.6, 129.3, 128.9, 128.7, 126.4, 110.9, 53.5, 38.3; **HRMS (ESI)** calculated for $C_{13}H_{14}ON$, $[M+H]^+$ is 200.1070 (100%), 201.1104 (15%), found 200.1071 (100%), 201.1106 (15%).

The data is consistent with the literature.[238]

3-Benzyl-2-methylpyridine (6o)

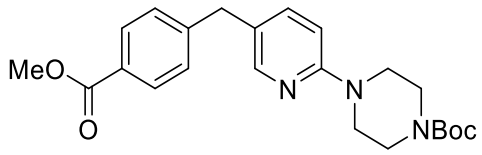


General Procedure E was followed using sodium benzyl sulfinate (35.6 mg, 0.2 mmol, 2.0 equiv.), 3-bromo-2-methylpyridine (12 µL, 0.10 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $P(^tBu)_2Me.HBF_4$ (5.0 mg, 0.02 mmol, 20 mol%), potassium carbonate (20.8 mg, 0.15 mmol, 1.5 equiv.) and DMSO (0.5 mL). Purification of the crude material by flash column chromatography (5 – 40% EtOAc in Petrol) afforded the product as a yellow oil (16.3 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 5.0, 1.5 Hz, 1H, Het-*H*), 7.35 (dd, *J* = 7.5, 1.5 Hz, 1H, Het-*H*), 7.33 – 7.27 (m, 2H, Ar-*H*), 7.25 – 7.19 (m, 1H, Het-*H*), 7.13 – 7.06 (m, 3H, Ar-*H*), 3.98 (s, 2H, C*H*$_2$), 2.50 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.3, 147.1, 139.1, 137.4, 134.3, 128.9, 128.7, 126.5, 121.5, 38.9, 22.7; **HRMS** (ESI, *m/z*) calculated for $C_{13}H_{14}N$, $[M+H]^+$ is 184.1121, found 184.1121.

Data is in accordance with the literature.[239]

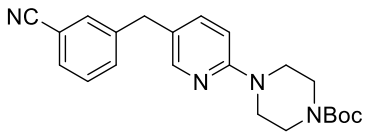
Tert-butyl 4-(5-(4-(methoxycarbonyl)benzyl)pyridin-2-yl)piperazine-1-carboxylate (6p)



General Procedure E was followed using sodium (4-(methoxycarbonyl)phenyl)methanesulfinate (94.5 mg, 0.40 mmol, 2.0 equiv.), 4-boc-1-(5-bromo-2-pyridyl)piperazine (68.4 mg, 0.20 mmol, 1.0 equiv.). Purification of the crude material by flash column chromatography (5 – 30% EtOAc in petrol) afforded the product as an off-white solid (44.4 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 2.5 Hz, 1H, Het-*H*), 7.94 (d, *J* = 8.5 Hz, 2H, 2 × Ar-*H)*, 7.27 (dd, *J* = 9.0, 2.5 Hz, 1H, Het-*H*), 7.22 (d, *J* = 8.5 Hz, 2H, 2 × Ar-*H*), 6.59 (d, *J* = 9.0 Hz, 1H, Het-*H*), 3.89 (app. s, 5H, Ar-CH_2-Het, OC*H*$_3$), 3.56 – 3.45 (m, 8H, 8 × Alk-*H*), 1.48 (s, 9H, 3 × C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.1, 158.4, 155.0, 148.0, 146.5, 138.4, 130.0, 128.8, 128.3, 125.2, 107.4, 80.1, 52.1, 45.4 (*br* s), 38.3, 28.6; **MP** ($CDCl_3$) 94 – 96 °C; **IR** (neat)/ν_{max} 2977, 2919, 2853, 1723, 1688, 1604, 1492, 1313, 1276, 1163; **HRMS** (ESI, *m/z*) calculated for $C_{23}H_{30}N_3O_4$, $[M+H]^+$ is 412.2231, found 412.2230.

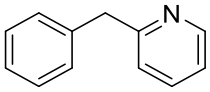
Tert-butyl 4-(5-(3-cyanobenzyl)pyridin-2-yl)piperazine-1-carboxylate (6q)



General Procedure E was followed using sodium (3-cyanophenyl)methanesulfinate (81.3 mg, 0.40 mmol, 2.0 equiv.), tert-butyl 4-(5-bromopyridin-2-yl)piperazine-1-carboxylate (68.4 mg, 0.20 mmol, 1.0 equiv.). Purification of the crude material by flash column chromatography (15 – 40% EtOAc in petrol) afforded the product as an off-white solid (72.5 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 1.6 Hz, 1H, Het-*H*), 7.49 (dt, *J* = 7.0, 2.0 Hz, 1H, Ar-*H*), 7.44 – 7.35 (m, 3H, 2 × Ar-*H*, Het-*H*), 7.28 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 6.62 (d, *J* = 8.5 Hz, 1H, Het-*H*), 3.88 (s, 2H, Ar-CH_2-Ar), 3.56 – 3.50 (m, 8H, 8 × Alk-*H*), 1.48 (s, 9H, 3 × CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.5, 154.9, 148.9, 142.5, 138.2, 133.3, 132.3, 130.22, 130.21, 129.5, 124.4, 118.9, 112.8, 107.7, 80.1, 45.43, 45.42, 37.7, 28.6; **MP** ($CDCl_3$) 118 – 119 °C; **IR** (neat)/ν_{max} 2977, 2919, 2229, 1692, 1607, 1494, 1405, 1241, 1167, 798; **HRMS (ESI)** calculated for $C_{22}H_{27}O_2N_4$, $[M+H]^+$ is 379.2129 (100%), 380.2161 (25%), found 379.2125 (100%), 380.2160 (25%).

2-Benzylpyridine (6r)

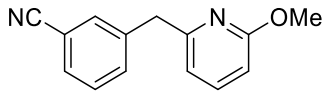


General Procedure E was followed using sodium benzyl sulfinate (71.3 mg, 0.40 mmol, 2.0 equiv.), 2-chloropyridine (19 µL, 0.20 mmol, 1.0 equiv.). Purification of the crude material by flash column chromatography (5 – 25% EtOAc in petrol) afforded the product as a clear oil (10.1 mg, 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dt, *J* = 5.0, 1.5 Hz, 1H, Het-*H*), 7.59 (td, *J* = 7.5, 2.0 Hz, 1H, Het-*H*), 7.34 – 7.27 (m, 4H, Ar-*H*), 7.25 – 7.21 (m, 1H, Het-*H*), 7.14 – 7.10 (m, 2H, Het-*H*, Ar-*H*), 4.17 (s, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.1, 149.4, 138.4, 136.9, 129.3, 128.8, 126.6, 123.3, 121.5, 44.7; **HRMS** (ESI, *m/z*) calculated for $C_{12}H_{12}N$, $[M+H]^+$ is 170.0964, found 170.0964.

Data is in accordance with the literature.[240]

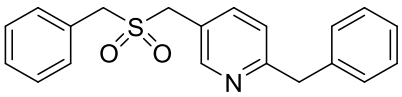
3-((6-Methoxypyridin-2-yl)methyl)benzonitrile (6s)



General Procedure E was followed using sodium (3-cyanophenyl)methanesulfinate (81.3 mg, 0.40 mmol, 2.0 equiv.), 2-bromo-6-methoxypyridine (25 µL, 0.20 mmol, 1.0 equiv.). Purification of the crude material by flash column chromatography (10 – 50% EtOAc in petrol) afforded the product as a yellow crystalline solid (44.8 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (td, *J* = 1.5, 1.0 Hz, 1H, Ar-*H*), 7.55 (dtd, *J* = 7.5, 1.5, 1.0 Hz, 1H, Ar-*H*), 7.52 – 7.44 (m, 2H, 2 × Ar-*H*), 7.38 (t, *J* = 8.0 Hz, 1H, Het-*H*), 6.69 (d, *J* = 8.0 Hz, 1H, Het-*H*), 6.58 (d, *J* = 8.0 Hz, 1H, Het-*H*), 4.03 (s, 2H, C*H*$_2$), 3.89 (s, 3H, OC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.0, 157.0, 141.3, 139.2, 133.8, 132.8, 130.1, 129.2, 119.1, 115.5, 112.4, 108.6, 53.4, 43.7; **MP** ($CDCl_3$) 39 – 40 °C; **IR** (neat)/ν_{max} 2951, 2228, 1577, 1463, 1262, 1034, 794; **HRMS** (ESI, *m/z*) calculated for $C_{14}H_{13}N_2O$, $[M+H]^+$ is 225.1022 (100%), 226.1056 (15%), found 225.1023 (100%), 226.1057 (17%).

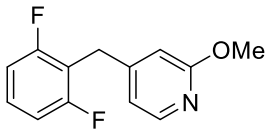
2-Benzyl-5-((benzylsulfonyl)methyl)pyridine (6t)



General Procedure E was followed using sodium benzyl sulfinate (35.6 mg, 0.20 mmol, 2.0 equiv.), 2-chloro-5-(chloromethyl)pyridine (16.2 mg, 0.10 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $P(^tBu)_2Me.HBF_4$ (5.0 mg, 0.02 mmol, 20 mol%), potassium carbonate (20.8 mg, 0.15 mmol, 1.5 equiv.) and DMSO (0.5 mL). Purification of the crude material by flash column chromatography (5 – 40% EtOAc in petrol) afforded the product as a white solid (11.0 mg, 33%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.5 Hz, 1H, Het-*H*), 7.68 (dd, *J* = 8.0, 2.5 Hz, 1H, Het-*H*), 7.43 – 7.38 (m, 5H, 5 × Ar-*H*), 7.35 – 7.29 (m, 2H, 2 × Ar-*H*), 7.29 – 7.21 (m, 3H, 3 × Ar-*H*), 7.15 (dd, *J* = 8.0, 1.0 Hz, 1H, Het-*H*), 4.18 (s, 4H, Ar-C*H*$_2$SO$_2$C*H*$_2$-Het), 4.05 (s, 2H, Het-C*H*$_2$-Ar); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.1, 150.9, 139.0, 138.9, 130.9, 129.4, 129.34, 129.31, 128.8, 127.5, 126.8, 123.4, 121.3, 58.7, 54.7, 44.6; **MP** (EtOAc) 163 – 164 °C; **IR** (neat)/ν_{max} 3031, 2918, 2849, 1489, 1301 (s), 1124 (s); **HRMS** (ESI, *m/z*) calculated for $C_{20}H_{20}O_2NS$, $[M+H]^+$ is 338.1209, found 338.1206.

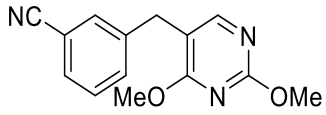
4-(2,6-Difluorobenzyl)-2-methoxypyridine (6u)



General Procedure E was followed using sodium 2,6-difluorobenzyl sulfinate (85.7 mg, 0.40 mmol, 2.0 equiv.) and 4-bromo-2-methoxypyridine (25 µL, 0.20 mmol, 1.0 equiv.). The crude material was purified by column chromatography (10% EtOAc in petrol) to give the product as a colourless oil (16.2 mg, 34%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 5.5, 0.5 Hz, 1H, Het-*H*), 7.20 (tt, *J* = 8.5, 6.5 Hz, 1H, Ar-*H*), 6.89 (dd, *J* = 8.5, 7.5 Hz, 2H, 2 × Ar-*H*), 6.77 (dt, *J* = 5.5, 0.5 Hz, 1H, Het-*H*), 6.58 (dt, *J* = 1.5, 0.5 Hz, 1H, Het-*H*), 3.95 (s, 2H, Ar-*CH_2*-Het), 3.90 (s, 3H, Het-*OCH_3*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.7, 161.5 (dd, *J* = 247.5, 8.5 Hz), 150.9, 146.9, 128.7 (t, *J* = 10.0 Hz), 117.3, 115.0 (t, *J* = 20.0 Hz), 111.5 (dd, *J* = 19.0, 6.5 Hz), 110.4, 53.5, 27.6 (t, *J* = 3.0 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -114.69; **IR** (neat)/ν_{max} 2980, 2949, 1743, 1625, 1611, 1593, 1562, 1482, 1470, 1451, 1398, 1323, 1237, 1152, 1046, 1012, 790, 769; **HRMS (ESI)** calculated for $C_{13}H_{12}F_2ON$, $[M+H]^+$ is 236.0881 (100%), 237.0915 (15%), found 236.0881 (100%), 237.0916 (15%).

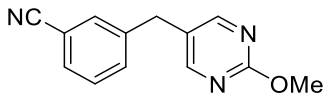
3-((2,4-Dimethoxypyrimidin-5-yl)methyl)benzonitrile (6v)



General Procedure E was followed using sodium (3-cyanophenyl)methanesulfinate (81.3 mg, 0.40 mmol, 2.0 equiv.), 5-bromo-2,4-dimethoxypyrimidine (43.8 mg, 0.20 mmol, 1.0 equiv.). Purification of the crude material by flash column chromatography (10 – 50% EtOAc in petrol) afforded the product as an off-white solid (15.1 mg, 29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H, Het-*H*), 7.50 (dt, *J* = 7.0, 1.5 Hz, 1H, Ar-*H*), 7.47 (tt, *J* = 1.5, 1.0 Hz, 1H, Ar-*H*), 7.43 – 7.36 (m, 2H, 2 × Ar-*H*), 3.98 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.82 (s, 2H, Ar-CH_2-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 164.8, 157.7, 141.0, 133.2, 132.3, 130.3, 129.4, 118.9, 113.3, 112.7, 54.9, 54.2, 32.4; **MP** ($CDCl_3$) 77 – 79 °C; **IR** (neat)/ν_{max}; 2947, 2226, 1603, 1574, 1462, 1294, 1207, 1074, 791; **HRMS** (ESI, *m/z*) calculated for $C_{14}H_{14}O_2N_3$, $[M+H]^+$ is 256.1081 (100%), 257.1114 (15%) found 256.1082 (100%), 257.1113 (15%).

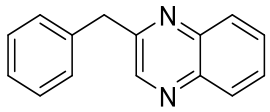
3-((2-Methoxypyrimidin-5-yl)methyl)benzonitrile (6w)



General Procedure E was followed using sodium (3-cyanophenyl)methanesulfinate (81.3 mg, 0.40 mmol, 2.0 equiv.) and 5-bromo-2-methoxypyrimidine (37.8 mg, 0.20 mmol, 1.0 equiv.). The crude material was purified by column chromatography (30 – 70% EtOAc in petrol) to give the product as an off-white solid (44.6 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 2H, 2 × Het-*H*), 7.54 (dt, *J* = 7.0, 1.5 Hz, 1H, Ar-*H*), 7.46 (ddt, *J* = 2.5, 1.5, 1.0 Hz, 1H, Ar-*H*), 7.44 – 7.38 (m, 2H, 2 × Ar-*H*), 4.00 (s, 3H, Het-O*CH$_3$*), 3.94 (s, 2H, Ar-*CH$_2$*-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.9, 159.4, 140.8, 133.2, 132.2, 130.7, 129.8, 126.0, 118.6, 113.2, 55.1, 35.2; **MP** ($CDCl_3$) 96 – 98 °C; **IR** (neat)/ν_{max} 2926, 2855, 2228, 2160, 2030, 1596, 1477, 1452, 1406, 1322, 1291, 1048, 798, 690; **HRMS (ESI)** calculated for $C_{13}H_{12}N_3O$, $[M+H]^+$ is 226.0975 (100%), 227.1009 (15%), found 226.0975 (100%), 227.1010 (15%).

2-Benzylquinoxaline (6x)

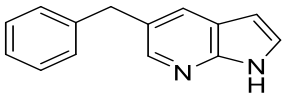


General Procedure E was followed using sodium benzyl sulfinate (53.4 mg, 0.30 mmol, 2.0 equiv.), 2-bromoquinoxaline (31.4 mg, 0.15 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ (7.4 mg, 0.03 mmol, 20 mol%), potassium carbonate (31.1 mg, 0.225 mmol, 1.5 equiv.) and DMSO (0.75 mL, 0.2 M). Purification of the crude material by flash column chromatography (5 – 50% EtOAc in Petrol) afforded the product as a reddish oil (17.1 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H, Het-*H*), 8.11 – 8.04 (m, 2H, 2 × Het-*H*), 7.79 – 7.70 (m, 2H, 2 × Het-*H*), 7.35 – 7.29 (m, 4H, 4 × Ar-*H*), 7.26 – 7.23 (m, 1H, Ar-*H*), 4.38 (s, 2H, Ar-C*H*$_2$-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.0, 146.1, 142.2, 141.3, 138.0, 130.2, 129.4, 129.3, 129.3, 129.2, 129.0, 127.1, 43.2; **HRMS** (ESI, *m/z*) calculated for $C_{15}H_{13}N_2$, $[M+H]^+$ is 221.1073, found 221.1073.

Data is in accordance with the literature.[241]

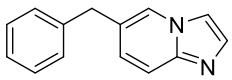
5-Benzyl-1*H*-pyrrolo[2,3-b]pyridine (6y)



General Procedure E was followed using 5-bromo-7-azaindole (29.6 mg, 0.15 mmol, 1.0 equiv.) and sodium benzyl sulfinate (53.6 mg, 0.30 mmol, 2.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ (7.4 mg, 0.03 mmol, 20 mol%), potassium carbonate (31.1 mg, 0.23 mmol, 1.5 equiv.) and DMSO (0.75 mL). Purification of the crude material by flash column chromatography (5 – 70% EtOAc in Petrol) afforded the product as a white solid (20.8 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H, N*H*), 8.23 (s, 1H, Het-*H*), 7.76 (d, *J* = 2.0 Hz, 1H, Het-*H*), 7.34 – 7.27 (m, 3H, Het-*H*, 2 × Ar-*H*), 7.25 – 7.18 (m, 3H, 3 × Ar-*H*), 6.43 (d, *J* = 3.5 Hz, 1H, Het-*H*), 4.10 (s, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.7, 143.6, 141.5, 129.3, 129.0, 128.7, 127.7, 126.3, 125.6, 120.5, 100.6, 39.4; **MP** (EtOAc) 115 – 116 °C; **IR** (neat)/ν_{max} 3132 (br), 3024, 2922 (br), 2360, 1493, 1405, 730 (s); **HRMS** (ESI, *m/z*) calculated for $C_{14}H_{13}N_2$, $[M+H]^+$ is 209.1073, found 209.1074.

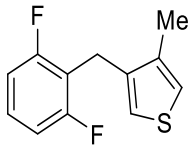
6-Benzylimidazo[1,2-a]pyridine (6z)



General Procedure E was followed using 6-bromoimidazo[1,2-α]pyridine (29.6 mg, 0.15 mmol, 1.0 equiv.) and sodium benzyl sulfinate (53.6 mg, 0.3 mmol, 2.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ (7.4 mg, 0.03 mmol, 20 mol%), potassium carbonate (31.1 mg, 0.23 mmol, 1.5 equiv.) and DMSO (0.75 mL). Purification of the crude material by flash column chromatography (5 – 100% EtOAc in Petrol) afforded the product as a red oil (14.3 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dq, *J* = 2.0, 1.0 Hz, 1H, Het-*H*), 7.59 (d, *J* = 1.0 Hz, 1H, Het-*H*), 7.54 (d, *J* = 9.0 Hz, 1H, Het-*H*), 7.49 (t, *J* = 1.0 Hz, 1H, Het-*H*), 7.33 (tt, *J* = 6.8, 1.0 Hz, 2H, 2 × Ar-*H*), 7.26 – 7.23 (m, 1H, Ar-*H*), 7.23 – 7.18 (m, 2H, 2 × Ar-*H*), 7.02 (dd, *J* = 9.0, 2.0 Hz, 1H, Het-*H*), 3.94 (s, 2H, Ar-*CH_2*-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.7, 139.4, 133.5, 129.0, 128.9, 127.0, 126.8, 125.8, 124.1, 117.6, 112.5, 38.7; **IR** (neat)/ν_{max} 3001, 2980, 2918, 1733, 1532, 1518, 1494, 1479, 1454, 1436, 1312, 1148, 1132, 792, 734, 700; **HRMS (ESI)** calculated for $C_{14}H_{12}N_2$, $[M+H]^+$ is 209.1073, found 209.1074.

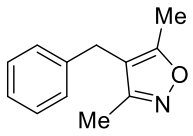
3-(2,6-Difluorobenzyl)-4-methylthiophene (6aa)



General Procedure E was followed using sodium 2,6-difluorobenzyl sulfinate (85.7 mg, 0.40 mmol, 2.0 equiv.), 3-bromo-4-methyl thiophene (22 µL, 0.20 mmol, 1.0 equiv.). Purification of the crude material by flash column chromatography (0 – 30% EtOAc in petrol) afforded the product as an orange oil (27.8 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (tt, *J* = 8.5, 6.5 Hz, 1H, Ar-*H*), 6.94 – 6.85 (m, 3H, 2 × Ar-*H*, Het-*H*), 6.76 (dq, *J* = 3.0, 1.0 Hz, 1H, Het-*H*), 3.88 (d, *J* = 1.5 Hz, 2H, CH_2), 2.27 (d, *J* = 1.0 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.7 (dd, *J* = 247.5, 8.5 Hz), 138.4, 136.8, 128.1 (t, *J* = 10.5 Hz), 122.0, 121.3, 116.2 (t, *J* = 20.0 Hz), 111.4 (dd, *J* = 19.0, 7.0 Hz), 22.1 (t, *J* = 3.5 Hz), 14.6; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -114.73; **IR** (neat)/ν_{max} 2922, 2851, 1625, 1592, 1469, 1009; **HRMS** (APCI, *m/z*) calculated for $C_{12}H_{11}F_2S$, $[M+H]^+$ is 225.0544, found 225.0546.

4-Benzyl-3,5-dimethylisoxazole (6ab)

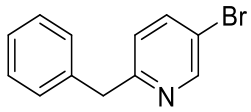


General Procedure E was followed using sodium benzyl sulfinate (53.4 mg, 0.30 mmol, 2.0 equiv.), 4-bromo-3,5-dimethylisoxazole (18 µL, 0.15 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ (7.4 mg, 0.03 mmol, 20 mol%), potassium carbonate (31.1 mg, 0.225 mmol, 1.5 equiv.) and DMSO (0.75 mL, 0.2 M). Purification of the crude material by flash column chromatography (5 – 30% EtOAc in petrol) afforded the product as a yellow oil (3.0 mg, 11%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H, 2 × Ar-*H*), 7.23 – 7.18 (m, 1H, Ar-*H*), 7.10 (m, 2H, 2 × Ar-*H*), 3.67 (s, 2H, Ar-C*H*$_2$-Het), 2.30 (s, 3H, C*H*$_3$), 2.08 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.6, 160.1, 138.9, 128.8, 128.2, 126.6, 113.0, 28.3, 11.2, 10.5; **LRMS** (ESI, *m/z*) calculated for $C_{12}H_{14}NO$, $[M+H]^+$ is 118.1, found 118.0.

Data is in accordance with the literature.[242]

2-Benzyl-5-bromopyridine (6ac)

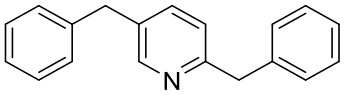


General Procedure E was followed using sodium benzyl sulfinate (35.6 mg, 0.20 mmol, 2.0 equiv.), 5-bromo-2-chloropyridine (19.2 mg, 0.10 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ (5.0 mg, 0.02 mmol, 20 mol%), potassium carbonate (20.8 mg, 0.15 mmol, 1.5 equiv.) and DMSO (0.5 mL). Purification of the crude material by flash column chromatography (5 – 60% EtOAc in petrol) afforded the product as a clear oil (10.5 mg, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.43 (ddt, *J* = 8.0, 2.5, 0.5 Hz, Het-*H*), 7.33 – 7.29 (m, 2H, 2 × Ar-*H*), 7.23 (m, 2H, 2 × Ar-*H*), 7.16 (m, 2H, Ar-*H*, Het-*H*), 3.96 (s, 2H, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.5, 149.9, 139.4, 135.6, 129.0, 128.9, 126.9, 124.6, 124.2, 38.4; **HRMS** (ESI, *m/z*) calculated for $C_{12}H_{11}{}^{79}BrN$, $[M+H]^+$ is 248.0069 and for $C_{12}H_{11}{}^{81}BrN$, $[M+H]^+$ is 250.0049, found 248.0070 and 250.0049.

Data is in accordance with the literature.[243]

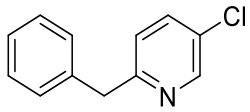
2,5-Dibenzylpyridine (6ad)



General Procedure E was followed using sodium benzyl sulfinate (35.6 mg, 0.20 mmol, 2.0 equiv.), 5-bromo-2-chloropyridine (19.2 mg, 0.10 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ (5.0 mg, 0.02 mmol, 20 mol%), potassium carbonate (20.8 mg, 0.15 mmol, 1.5 equiv.) and DMSO (0.5 mL). Purification of the crude material by flash column chromatography (5 – 60% EtOAc in petrol) afforded the product as a yellow oil (13.3 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.5 Hz, 1H, Het-*H*), 7.36 (dd, *J* = 8.0, 2.5 Hz, 1H, Het-*H*), 7.33 – 7.26 (m, 5H, 5 × Ar-*H*), 7.25 – 7.14 (m, 5H, 5 × Ar-*H*), 7.02 (d, *J* = 8.0 Hz, 1H, Het-*H*), 4.13 (s, 2H, C*H*$_2$), 3.93 (s, 2H, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.9, 149.6, 140.1, 139.7, 137.2, 134.1, 129.2, 129.0, 128.8, 128.7, 126.6, 126.5, 123.0, 44.3, 38.8; **IR** (neat)/ν_{max} 3061, 2918 (br), 1599, 1494, 1454, 1029; **HRMS** (ESI, *m/z*) calculated for $C_{19}H_{18}N$, $[M+H]^+$ is 260.1434, found 260.1431.

2-Benzyl-5-chloropyridine (6ae)

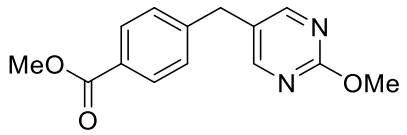


General Procedure E was followed using sodium benzyl sulfinate (53.4 mg, 0.30 mmol, 2.0 equiv.), 2-bromo-5-chloropyridine (28.9 mg, 0.15 mmol, 1.0 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ (7.4 mg, 0.03 mmol, 20 mol%), potassium carbonate (31.1 mg, 0.23 mmol, 1.5 equiv.) and DMSO (0.75 mL). Purification of the crude material by flash column chromatography (5 – 20% EtOAc in petrol) afforded the product as a yellow oil (15.3 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 2.5, 0.5 Hz, 1H, Het-*H*), 7.55 (dd, *J* = 8.5, 2.5 Hz, 1H, Het-*H*), 7.34 – 7.27 (m, 2H, 2 × Ar-*H*), 7.25 – 7.19 (m, 3H, 3 × Ar-*H*), 7.06 (dd, *J* = 8.5, 0.5 Hz, 1H, Het-*H*), 4.13 (s, 2H, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 148.3, 139.1, 136.4, 129.8, 129.2, 128.8, 126.7, 124.0, 44.1; **HRMS** (ESI, *m/z*) calculated for $C_{12}H_{11}ClN$, $[M+H]^+$ is 204.0575, found 204.0575.

Data is in accordance with the literature.[244]

Methyl 4-((2-methoxypyrimidin-5-yl)methyl)benzoate (6af)

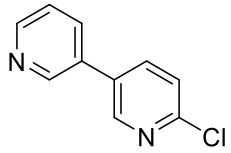


General Procedure E was followed using sodium (4-(methoxycarbonyl)phenyl)methanesulfinate (94.5 mg, 0.40 mmol, 2.0 equiv.), 5-bromo-2-methoxypyrimidine (37.8 mg, 0.20 mmol, 1.0 equiv.). Purification of the crude material by flash column chromatography (10 – 60% EtOAc in petrol) afforded the product as an orange solid (27.1 mg, 52%). The compound decomposed within 12 hours under room temperature storage, after purification. No further compound data was obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 2H, 2 × Het-*H*), 8.00 – 7.96 (m, 2H, 2 × Ar-*H*), 7.25 – 7.21 (m, 2H, 2 × Ar-*H*), 3.98 (s, 3H, OC*H*$_3$), 3.94 (s, 2H, C*H*$_2$), 3.90 (s, 3H, OC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.9, 164.8, 159.4, 144.5, 130.3, 128.8, 126.6, 114.1, 55.0, 52.2, 35.6.

1.1.5 Other cross-coupling products

6-Chloro-3,3'-bipyridine (7a)



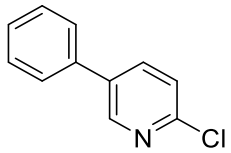
General Procedure E was followed using sodium pyridine-3-sulfinate (66.1 mg, 0.40 mmol, 2.0 equiv.), 5-bromo-2-chloropyridine (38.5 mg, 0.20 mmol, 1.0 equiv.). The crude material was purified by silica gel chromatography (25 – 70% EtOAc in petrol) to give the title product as an off-white solid (16.7 mg, 44%).

The same reaction conditions with DMSO (1 mL, 0.2 M) used in place of 1,4-dioxane produced the title product as an off-white solid in 25% yield (9.5 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 1.5 Hz, 1H, Het-*H*), 8.67 (dd, *J* = 5.0, 1.5 Hz, 1H, Het-*H*), 8.60 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.90 – 7.82 (m, 2H, 2 × Het-*H*), 7.45 (dd, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.43 – 7.40 (m, 1H, Het-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.5, 149.8, 148.2, 148.1, 137.3, 134.5, 132.6, 132.4, 124.7, 124.0; **LRMS** (ESI) m/z calculated for $C_{10}H_8N_2Cl$, $[M+H]^+$ is 191.0, found 191.1.

Data is in accordance with the literature.[245]

2-Chloro-5-phenylpyridine (7b)



Prepared from a modified procedure by Takamasa et al.[167] To a 10 mL microwave vial equipped with a stirrer bar was added, phenylboronic acid (25.6 mg, 0.21 mmol, 1.05 equiv.), 5-bromo-2-chloropyridine (38.5 mg, 0.20 mmol, 1.0 equiv.), potassium carbonate (69.1 mg, 0.50 mmol, 2.5 equiv.) and $Pd(PPh_3)_4$ (6.9 mg, 3 mol%). The vial was sealed with a microwave vial cap, evacuated under vacuum (<1 mbar) and back-filled with nitrogen gas. This cycle was repeated a further two times. Addition of toluene (0.5 mL, anhydrous) followed. The reaction was stirred at room temperature for 15 minutes, before heating to 90 °C for 4 hours. The reaction was then cooled to room temperature, water (1 mL) was added and the layers were separated. The organic layer was recovered, concentrated under vacuum, and the resulting residue was purified by silica gel column chromatography (10 – 60% EtOAc in petrol) to give the title product as an off-white solid (30.6 mg, 81%).

The same reaction repeated with the addition of $P^tBu_2Me{\cdot}HBF_4$ (11.2 mg, 20 mol%) afforded the title product in 76% yield (28.8 mg).

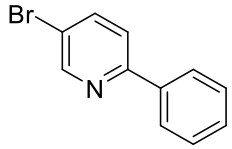
The same reaction repeated with $Pd(OAc)_2$ (4.5 mg, 10 mol%) and $P^tBu_2Me{\cdot}HBF_4$ (11.2 mg, 20 mol%), used in place of $Pd(PPh_3)_4$, afforded the title product in 81% yield (30.7 mg).

The same reaction repeated with $Pd(OAc)_2$ (4.5 mg, 10 mol%) and $P^tBu_2Me{\cdot}HBF_4$ (11.2 mg, 20 mol%), used in place of $Pd(PPh_3)_4$, DMSO (1.0 mL), in place of 1,4-dioxane, and a smaller amount of potassium carbonate (41.4 mg, 0.30 mmol, 1.5 equiv.) afforded the title product in 92% yield (34.8 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.84 (dd, *J* = 8.5, 2.5 Hz, 1H, Het-*H*), 7.57 – 7.52 (m, 2H, 2 × Ar-*H*), 7.51 – 7.45 (m, 2H, 2 × Ar-*H*), 7.45 – 7.41 (m, 1H, Het-*H*), 7.39 (dd, *J* = 8.5, 1.0 Hz, 1H, Ar-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.4, 148.1, 137.3, 136.6, 135.8, 129.3, 128.6, 127.2, 124.3; **LRMS** (ESI, *m/z*) calculated for $C_{11}H_9N$, $[M+H]^+$ is 190.0, found 190.0.

Data is in accordance with the literature.[246]

5-Bromo-2-phenylpyridine (7c)



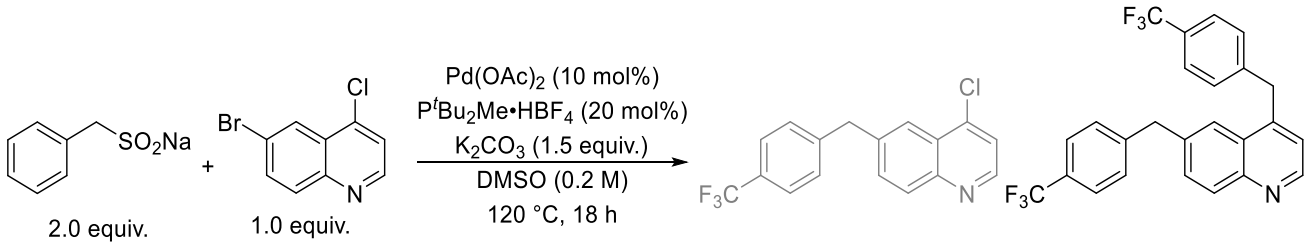
Prepared from a modified procedure by Takamasa et al.[167] To a 10 mL microwave vial equipped with a stirrer bar was added, phenylboronic acid (25.6 mg, 0.21 mmol, 1.05 equiv.), 5-bromo-2-chloropyridine (38.5 mg, 0.20 mmol, 1.0 equiv.), potassium carbonate (69.1 mg, 0.50 mmol, 2.5 equiv.), $Pd(PPh_3)_4$ (6.9 mg, 3 mol%) and $P^tBu_2Me{\cdot}HBF_4$ (11.2 mg, 20 mol%). The vial was sealed with a microwave vial cap, evacuated under vacuum (<1 mbar) and back-filled with nitrogen gas. This cycle was repeated a further two times. Addition of toluene (0.5 mL, anhydrous) followed. The reaction was stirred at room temperature for 15 minutes, before heating to 90 °C for 4 hours. The reaction was then cooled to room temperature, water (1 mL) was added and the layers were separated. The organic layer was recovered, concentrated under vacuum, and the resulting residue was purified by silica gel column chromatography (10 – 60% EtOAc in petrol) to give the title product as an off-white solid (2.8 mg, 6% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.98 – 7.93 (m, 2H, 2 × Ar-*H*), 7.88 (dd, *J* = 8.5, 2.5 Hz, 1H, Het-*H*), 7.63 (dd, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.51 – 7.40 (m, 3H, 3 × Ar-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.2, 150.9, 139.5, 138.4, 129.5, 129.0, 126.9, 121.8, 119.5; HRMS (ESI) calculated for $C_{11}H_9NBr$, $[M+H]^+$ is 233.9913 (100%), 235.9892 (97%), 236.9926 (12%), found 233.9915 (100%), 235.9894 (95%), 236.9926 (15%).

Data is in accordance with the literature.[247]

1.1.6 Side products

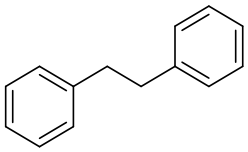
4,6-Bis(4-(trifluoromethyl)benzyl)quinoline (S7)



General Procedure E was followed using sodium (4-(trifluoromethyl)phenyl)methanesulfinate (49.3 mg, 0.20 mmol, 2.0 equiv.), 6-bromo-4-chloroquinoline (24.3 mg, 0.10 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ (5.6 mg, 20 mol%), potassium carbonate (20.8 mg, 0.15 mmol, 1.5 equiv.) and DMSO (0.5 mL). Purification of the crude material by flash column chromatography (5 – 50% EtOAc in Petrol) afforded the product as a yellow oil (25.4 mg, 57%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, *J* = 4.5 Hz, 1H, Het-*H*), 8.39 (d, *J* = 1.5 Hz, 1H, Het-*H*), 8.19 (d, *J* = 8.5 Hz, 1H, Het-*H*), 7.80 (d, *J* = 4.5 Hz, 1H, Het-*H*), 7.66 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 7.60 (d, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 7.47 (d, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 7.36 (d, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 7.08 (d, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 4.46 (s, 2H, C*H*$_2$), 4.25 (s, 2H, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.4, 148.4, 142.2, 141.9, 141.4, 141.1, 132.2, 131.2 (q, *J* = 30.5 Hz), 131.5 – 130.9 (m), 130.9 (q, *J* = 267.5 Hz), 129.6, 129.5, 126.1 – 125.6 (m), 124.6 (q, *J* = 272.5 Hz), 123.3 – 122.8 (m), 62.3, 42.1 (the complex NMR spectrum led to signals hidden among the multiplets); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.41, -62.86; **IR** (neat)/ν_{max} 2917, 2849, 2361, 1324 (s), 1163, 1122, 1067; **HRMS** (ESI, *m/z*) calculated for $C_{25}H_{17}NF_6$, $[M+H]^+$ is 446.1338, found 446.1340.

1,2-Diphenylethane (S8)



To a microwave vial was added sodium benzylsulfinate (66.8 mg, 0.38 mmol, 1.0 equiv.), Cu_2O (10.7 mg, 20 mol%), $PdCl_2$ (1.7 mg, 2.5 mol%) and H_2O (1.0 mL). The vial was sealed and fitted with a balloon of oxygen. An outlet needle was attached to allow the oxygen to bubble through at room temperature for 5 minutes. The balloon and outlet needle were removed. The reaction was heated to 100 °C for 40 hours. After cooling to room temperature, water (15 mL) was added and the mixture was extracted with ether (3 × 15 mL). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the title product as a white solid (78.8 mg, 58%).

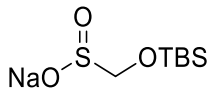
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.34 (m, 10H, 10 × Ar-*H*), 4.13 (s, 4H, 2 × C*H*$_2$); **LRMS (ESI)** calculated for $C_{14}H_{13}$, $[M-H]^-$ is 181.0, found 181.1.

Data is in accordance with the literature.[248]

7.4. Chapter 4: Experimental procedures and data

7.4.1. Reagent and starting material synthesis

Sodium ((tert-butyldimethylsilyl)oxy)methanesulfinate (TBSOMS-Na) (S9)

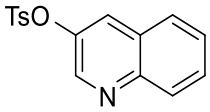


Prepared according to a modified procedure by Kim et al.[71] To an argon-purged and flame-dried flask were added TBSCl (9.04 g, 60.00 mmol, 3.0 equiv.) and Rongalite™ (3.08 g, 20 mmol, 1.0 equiv.). The solid mixture was cooled to 0 °C with an ice-water bath while being gently stirred. Pyridine (20 mL, 1 M) was slowly added to the flask over 5 minutes. The resulting mixture was stirred overnight at room temperature. The solvents were removed under reduced pressure at 50 °C. The resulting residue was filtered through Celite® and washed with pentane (100 mL). The filtrate was concentrated under reduced pressure. The flask was evacuated under vacuum (<1 mbar) and back-filled with nitrogen gas. This cycle was repeated a further two times. DCM (60 mL) was added. The solution was cooled in an ice-water bath and dropwise addition of sodium methoxide (5 M in MeOH, 3.52 mL, 19.00 mmol, 0.95 equiv.) over 10 minutes followed, while the reaction was vigorously stirred. The reaction mixture was stirred for 1 h at room temperature, affording a heterogeneous blue/green solution. The solvents were removed under reduced pressure. The waxy precipitate was collected through washing and trituration with pentane, and dried under vacuum (< 1 mbar). The title product was given as a blue-tinged solid (1.56 g, 34%).

^{1}H NMR (400 MHz, DMSO) δ 3.43 (s, 2H, C*H*$_2$), 0.86 (s, 9H, 3 × C*H*$_3$), 0.05 (s, 6H, 2 × Si-C*H*$_3$); **^{13}C NMR** (101 MHz, DMSO) δ 87.9, 25.9, 18.2, -4.8; **LRMS** (ESI) calculated for $C_7H_{17}O_3SSi$, $[M\text{-}Na]^-$ is 209.1, found 209.1.

The data is consistent with the literature.[71]

Quinolin-3-yl 4-methylbenzenesulfonate (S10)

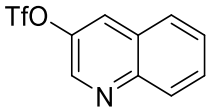


Prepared according to a modified procedure by Cavallito et al.[249] To a 100 mL round-bottom flask was added 3-hydroxyquinoline (435 mg, 3.00 mmol, 1.0 equiv.), pyridine (20 mL, 0.1 M) and then 4-toluenesulfonyl chloride (858 mg, 4.50 mmol, 1.5 equiv.). The reaction mixture was heated to 100 °C for 1 hour. After cooling, water (30 mL) was added and the precipitate was collected by vacuum filtration. The crude was recrystallised in a mixture of 4:1 ethanol to water, to afford the product as a white crystalline solid (300.1 mg, 34%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.08 (dd, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.94 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.80 (dd, *J* = 8.0, 1.5 Hz, 1H, Het-*H*), 7.77 – 7.70 (m, 3H, 2 × Ar-*H*, Het-*H*), 7.59 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, Het-*H*), 7.35 – 7.30 (m, 2H, 2 × Ar-*H*), 2.45 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.7, 146.2, 145.6, 143.2, 132.0, 130.2, 130.0, 129.6, 128.7, 128.1, 127.9, 127.8, 21.9; **LRMS** (ESI) calculated for $C_{16}H_{14}NO_3S$, $[M+H]^+$ is 300.1, found 300.0.

The data is consistent with the literature.[250]

Quinolin-3-yl trifluoromethanesulfonate (S11)

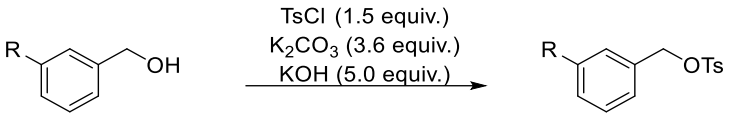


Prepared according to a modified procedure by Huang et al.[251] An argon filled 50 mL two-necked round-bottom flask was charged with 3-hydroxyquinoline (435 mg, 3.00 mmol, 1.0 equiv.), anhydrous DCM (10 mL, 0.3 M) and pyridine (0.29 mL, 3.60 mmol, 1.2 equiv.). The flask was lowered into an ice-water bath, and dropwise addition of triflic anhydride (0.76 mL, 4.50 mmol, 1.5 equiv.) followed. The resulting mixture was slowly warmed up to room temperature, and allowed to stir for an additional 2 hours. The reaction mixture was diluted with Et_2O (10 mL) and then quenched with aq. HCl (1.0 M, 10 mL). The resulting mixture was washed with sat. $NaHCO_3$ (10 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ before removal of the solvents under reduced pressure. The resulting crude material was purified by silica gel chromatography (10 – 50% EtOAc in petrol) to give the title product as an off-white solid (666 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 3.0 Hz, 1H, Het-*H*), 8.19 (dq, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 8.10 (dd, *J* = 3.0, 1.0 Hz, 1H, Het-*H*), 7.89 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 7.82 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.68 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H, Het-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.3, 143.9, 143.4, 130.9, 129.8, 128.6, 128.2, 127.8, 127.1, 118.9 (q, *J* = 319.5 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -72.44. **LRMS** (ESI) calculated for $C_{10}H_7NF_3O_3S$, $[M+H]^+$ is 278.0, found 278.0.

The data is consistent with the literature.[252]

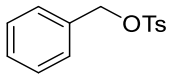
General Procedure F



Prepared according to a procedure by Kazemi et al.[176] A mortar was charged with K_2CO_3 (4.97 g, 36.00 mmol, 3.6 equiv.), the benzyl alcohol (10.00 mmol, 1.0 equiv.) and tosyl chloride (2.86 g, 15.00 mmol, 1.5 equiv.). The reagents were ground together vigorously with a pestle for 5 minutes. KOH (2.81 g, 50.00 mmol, 5.0 equiv.) was added with vigorous grinding for a further 3 minutes. Et_2O (100 mL) was added and the mixture was stirred before vacuum filtration. The solid residue was transferred to a vial before drying under vacuum (< 1 mbar). The resulting white solid tosylate was used directly in the cross-coupling reactions without any further purification.

Note: The tosylates were stored under nitrogen and in the freezer at -18 °C to prevent decomposition. *(At ambient temperature, the white solid darkens within an hour and becomes amorphous overnight).*

Benzyl 4-methylbenzenesulfonate (8a)

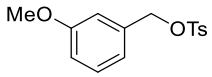


General Procedure F was followed using benzyl alcohol (1.03 mL, 10.00 mmol, 1.0 equiv.) to give the title product as a white crystalline solid (2.06 g, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.71 (m, 2H, 2 × Ar-*H*), 7.29 – 7.22 (m, 5H, 5 × Ar-*H*), 7.21 – 7.17 (m, 2H, 2 × Ar-*H*), 4.99 (s, 2H, ArCH_2), 2.38 (s, 3H, Ar-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.9, 133.4, 133.4, 129.9, 129.1, 128.8, 128.6, 128.1, 72.0, 21.7; **MP** (Et_2O) 48 – 50 °C.

The data is consistent with the literature.[176]

3-Methoxybenzyl 4-methylbenzenesulfonate (8b)

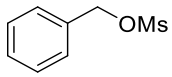


General Procedure F was followed using 3-methoxybenzyl alcohol (1.24 mL, 10.00 mmol, 1.0 equiv.) to give the title product as a white crystalline solid (1.17 g, 40% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 2H, 2 × Ar-*H*), 7.39 – 7.32 (m, 2H, 2 × Ar-*H*), 7.28 – 7.22 (m, 1H, Ar-*H*), 6.91 – 6.82 (m, 2H, 2 × Ar-*H*), 6.79 (dd, *J* = 2.5, 1.5 Hz, 1H, Ar-*H*), 5.05 (s, 2H, ArCH_2), 3.79 (s, 3H, OCH_3), 2.47 (s, 3H, Ar-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.9, 144.9, 134.9, 133.4, 130.0, 129.8, 128.1, 120.8, 114.9, 113.8, 71.9, 55.4, 21.8; **MP** (Et_2O) 68 - 70 °C; **IR** (neat)/ν_{max} 2957, 1440, 1316, 1265, 1169, 1094, 929, 846, 779.

The data is consistent with the literature.[176]

Benzyl methanesulfonate (8c)

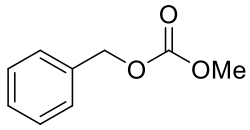


Prepared according to a procedure by Olivito et al.[178] To a round bottom flask were added benzyl alcohol (0.48 mL, 4.60 mmol, 1.0 equiv.) and DCM (20 mL). The flask was cooled to -15 °C, and triethylamine (0.64 mL, 4.60 mmol, 1.0 equiv.) was added under stirring. Methane sulfonyl chloride (0.36 mL, 4.60 mmol, 1 equiv.) was then added dropwise. The reaction was stirred at -15 °C and allowed to warm to 5 °C over 1.5 hours. The reaction mixture was quenched with aq. 1 M HCl (2 mL) and the solution was washed with sat. aq. $NaHCO_3$ (20 mL). The organic phase was washed with water (3 × 20 mL) before being dried over $MgSO_4$. The solvents were removed under reduced pressure to afford the title product as a colourless oil (765.3 mg, 89%), which was used without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 5H, 5 × Ar-*H*), 5.25 (s, 2H, C*H*$_2$), 2.91 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.5, 129.6, 129.1, 129.0, 71.7, 38.5.

The data is consistent with the literature.[253]

Benzyl methyl carbonate (8d)

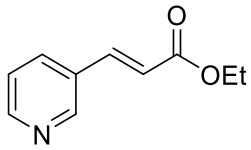


Prepared according to a modified procedure by Ohkoshi et al.[182] To a cooled solution (0 °C) of benzyl alcohol (110 µL, 1.06 mmol, 1.0 equiv.) and pyridine (89 µL, 1.10 mmol, 1.04 equiv.) in DCM (6 mL), methyl chloroformate (139 µL, 1.80 mmol, 1.7 equiv.) was added dropwise. After stirring at room temperature for 2 h, 1 M aq. HCl (3 mL) was added to the solution. Then the resulting mixture was extracted with DCM (3 × 3 mL) and the combined organic layer was washed with 1 M aq. HCl (5 mL). After drying over $MgSO_4$, the solvents were removed under reduced pressure. The resulting crude material was purified by silica gel chromatography (20 – 60% EtOAc in petrol) to give the title product as a colourless oil (176.1 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 5H, 5 × Ar-*H*), 5.17 (s, 2H, C*H*$_2$), 3.80 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.9, 135.4, 128.74, 128.68, 128.4, 69.8, 55.0; **LRMS** (ESI) calculated for $C_9H_9O_3$, $[M-H]^-$ is 165.1, found 165.0.

The data is consistent with the literature.[182]

Ethyl (E)-3-(pyridin-3-yl)acrylate (12a)

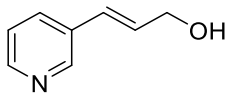


Prepared according to a modified procedure by Blanchette et al.[254] To a stirred suspension of LiCl (509 mg, 12.00 mmol, 1.2 equiv.) in dry acetonitrile (120 ml) under nitrogen at room temperature, was added triethyl phosphonoacetate (2.38 mL, 12.00 mmol, 1.2 equiv.), DBU (1.5 mL, 10.00 mmol, 1.0 equiv.) and finally 3-pyridine carboxaldehyde (0.94 mL, 10.00 mmol, 1.0 equiv.). Almost all of the salt soon dissolved and the reaction was complete within 1 h, monitored by TLC. The reaction was quenched with sat. aq. NH_4Cl solution (100 mL), and diluted with water (50 mL). The mixture was extracted with EtOAc (3 × 125 mL). The organic layers were combined, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude residue was purified by silica gel chromatography (20 – 60% EtOAc in petrol) to give the title product as a colourless oil (1.57 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 – 8.71 (m, 1H, Het-*H*), 8.58 (dd, *J* = 5.0, 1.5 Hz, 1H, Het-*H*), 7.81 (ddd, *J* = 8.0, 3.0, 1.0 Hz, 1H, Het-*H*), 7.65 (d, *J* = 16.0 Hz, 1H, C*H*CH), 7.31 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H, Het-*H*), 6.49 (d, *J* = 16.0 Hz, 1H, C*H*COOEt), 4.26 (q, *J* = 7.0 Hz, 2H, CH_2CH$_3$), 1.32 (t, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.4, 151.1, 149.8, 140.9, 134.3, 130.3, 123.8, 120.6, 60.9, 14.4; **LRMS** (ESI) calculated for $C_{10}H_{12}NO_2$, $[M+H]^+$ is 178.1, found 178.2.

The data is consistent with the literature.[255]

(E)-3-(Pyridin-3-yl)prop-2-en-1-ol (12b)

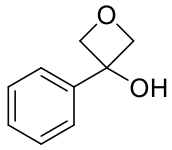


Prepared according to a modified procedure by Li et al.[256] A solution of DIBAL-H in toluene (1.0 M, 12 mL, 12.00 mmol, 2.0 equiv.) was slowly added to a stirring solution of ethyl (E)-3-(pyridin-3-yl)acrylate (**12a**) (1.06 g, 6.00 mmol, 1.0 equiv.) in Et_2O (16 mL) at -40 °C. The reaction mixture was stirred at -40 °C for 1 h before allowing the reaction mixture to warm to room temperature. Stirring was continued for 20 hours to allow completion, monitored by TLC. The solution was cooled to 0 °C before the dropwise addition of water (0.8 mL), 1 M aq. NaOH (0.8 mL) and further water (0.8 mL). The mixture was stirred for a further 2 hours, with a white precipitate formed during this time. The precipitate was removed by vacuum filtration, and washed with Et_2O (50 mL). The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (50 – 100% EtOAc in petrol) to give the title product as a yellow oil (661.5 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 2.0 Hz, 1H, Het-*H*), 8.45 (dd, *J* = 5.0, 1.5 Hz, 1H, Het-*H*), 7.69 (dt, *J* = 8.0, 2.0 Hz, 1H, Het-*H*), 7.24 (ddd, *J* = 8.0, 5.0, 1.5 Hz, 1H, Het-*H*), 6.61 (dt, *J* = 16.0, 2.0 Hz, 1H, C*H*CHOH), 6.43 (dt, *J* = 16.0, 5.5 Hz, 1H, CHC*H*OH), 4.35 (dd, *J* = 5.5, 2.0 Hz, 2H, C*H*$_2$), 2.53 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.6, 148.3, 133.2, 132.7, 131.5, 127.0, 123.7, 63.3; **LRMS** (ESI) calculated for $C_8H_{10}NO$, $[M+H]^+$ is 136.1, found 136.0.

The data is consistent with the literature.[257]

3-Phenyloxetan-3-ol (13a)

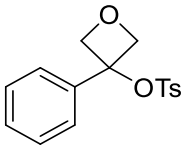


Prepared according to a modified procedure by Croft et al.[258] To a solution of bromobenzene (1.14 mL, 10.82 mmol, 1.3 equiv.) stirring in THF (anhydrous, 32 mL) at -78 °C, a solution of ^{n}BuLi (2.5 M in hexane, 4.33 mL, 10.82 mmol, 1.3 equiv.) was added dropwise. The reaction was stirred at -78 °C for 10 minutes. A solution of 3-oxetanone (534 µL, 8.58 mmol, 1.0 equiv.) in THF (anhydrous, 8 mL) was added dropwise to the reaction mixture. The reaction was stirred at -78 °C for a further 10 minutes, before being allowed to warm to room temperature. After 1.5 hours, water (5 mL) was added to quench the reaction. The aqueous and organic layers were separated. The aqueous layer was washed with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, before drying over $MgSO_4$. The solvents were removed under reduced pressure. The crude residue was purified by column chromatography (20 – 40% EtOAc in petrol) to give the title product as a colourless oil (1.29 g, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 2H, 2 × Ar-*H*), 7.43 (t, *J* = 7.5 Hz, 2H, 2 × Ar-*H*), 7.34 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 4.92 (dd, *J* = 4.1, 2.3 Hz, 4H, 2 × C*H*$_2$), 2.85 (s, 1H, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.4, 128.9, 128.1, 124.6, 85.8, 76.0; **LRMS** (ESI) calculated for $C_9H_9O_2$, $[M-H]^-$ is 149.1, found 149.0.

The data is consistent with the literature.[259]

3-Phenyloxetan-3-yl 4-methylbenzenesulfonate (13b)

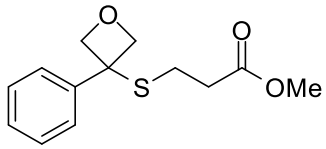


Prepared according to a procedure by Friedrich et al.[260] To a round-bottom flask equipped with a stir-bar, was added DCM (30 mL) and 3-phenyloxetan-3-ol (**13a**) (1.0 g, 6.66 mmol, 1.0 equiv.). *p*-Toluenesulfonyl chloride (1.9 g, 9.99 mmol, 1.5 equiv.), triethylamine (1.85 mL, 13.32 mmol, 2.0 equiv.) and 4-(dimethylamino)pyridine (80.6 mg, 0.66 mmol, 0.1 equiv.) were added. The reaction mixture was stirred at room temperature for 2 hours. The solvents were then removed under reduced pressure. The crude residue was purified by silica gel column chromatography (10 – 35% EtOAc in petrol) to give the title product as a colourless oil (368.4 mg, 18%). Unfortunately, the product readily undergoes decomposition at room temperature; this is reflected in the proton NMR spectrum. The carbon NMR spectrum was unobtainable.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 2H, 2 × Ar-*H*), 7.46 – 7.41 (m, 2H, 2 × Ar-*H*), 7.39 – 7.29 (m, 5H, 5 × Ar-*H*), 4.97 – 4.89 (m, 4H, 2 × C*H*$_2$), 3.70 (s, 3H, C*H*$_3$); **LRMS** (ESI) calculated for $C_{16}H_{17}O_4S$, $[M+H]^+$ is 305.1, found 305.4.

The data is consistent with the literature.[260]

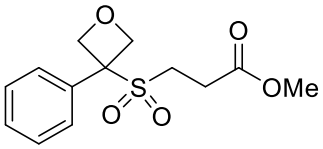
Methyl 3-((3-phenyloxetan-3-yl)thio)propanoate (13c)



Prepared according to a procedure by Croft et al.[261] To a 100 mL round-bottom flask equipped with a stirrer bar, was added 3-phenyloxetan-3-ol (**13a**) (1.2 mL, 10.00 mmol, 1.0 equiv.), methyl 3-mercaptopropionate (2.2 mL, 20.00 mmol, 2.0 equiv.), tetrabutylammonium hexafluorophosphate (194 mg, 0.50 mmol, 0.05 equiv.), and calcium(II) bis(trifluoromethanesulfonimide) (300 mg, 0.50 mmol, 0.05 equiv.). The flask was evacuated under vacuum (<1 mbar) and back-filled with argon. This cycle was repeated a further two times. Chloroform (20 mL) was added and the reaction was heated to 40 °C for 2 hours. The reaction was allowed to cool to room temperature before being transferred to a separating funnel, and was washed with brine (3 × 50 mL). The organics were combined, dried over $MgSO_4$ and the solvents were removed under vacuum. The title product was given as a colourless oil (255.5 mg, 10%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H, 2 × Ar-*H*), 7.37 (t, *J* = 7.5 Hz, 2H, 2 × Ar-*H*), 7.29 (tt, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 3.77 (d, *J* = 11.5 Hz, 1H, OCH*H*), 3.72 (d, *J* = 11.5 Hz, 1H, OC*H*H), 3.68 (s, 3H, OC*H*$_3$), 3.23 (d, *J* = 14.0 Hz, 1H, OCH'*H'*), 3.12 (d, *J* = 14.0 Hz, 1H, OC*H'*H'), 2.60 (t, *J* = 6.5 Hz, 2H, SCH*H*) 2.51 (t, *J* = 6.5 Hz, 2H, SCH_2CH*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 182.7, 128.9, 128.8, 128.1, 124.6, 85.8, 76.1, 51.9, 31.3, 14.4; **IR** (neat)/ν_{max} 3027, 2952, 1734, 1438, 1248, 1198, 702; **HRMS (ESI)** calculated for $C_{13}H_{17}O_3S$, $[M+H]^+$ is 253.0893 (100%), 254.0926 (15%), found 253.0893 (80%), 254.0927 (12%).

Methyl 3-((3-phenyloxetan-3-yl)sulfonyl)propanoate (13d)

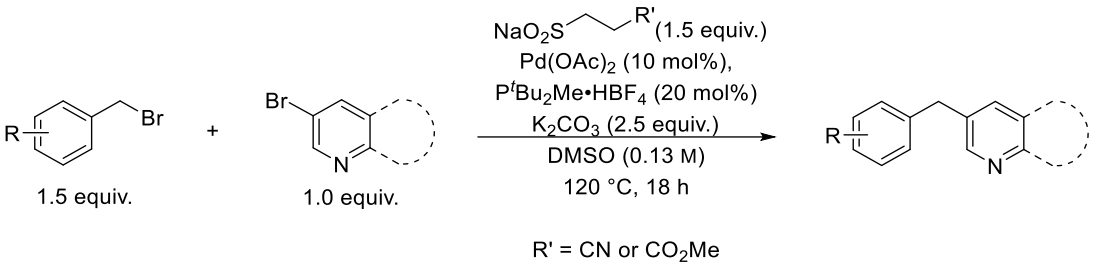


Prepared according to a modified procedure by Pike et al.[262] To a 10 mL round-bottom flask was added methyl 3-((3-phenyloxetan-3-yl)thio)propanoate (**13c**) (200 mg, 0.79 mmol, 1.0 equiv.) and DCM (3.6 mL). Next, 3-chloroperbenzoic acid (410 mg, 2.40 mmol, 3.0 equiv.) was added and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture underwent vacuum filtration, and the residue was washed with further DCM (10 mL). The filtrate was transferred to a separating funnel and was washed with 10% aq. Na_2SO_4 to ensure removal of benzoic acid. The organics were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude residue was purified by silica gel column chromatography (40 – 100% EtOAc in petrol) to afford the title product as a white solid (139.6 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 2H, 2 × Ar-*H*), 7.43 (tt, *J* = 8.0, 1.5 Hz, 2H, 2 × Ar-*H*), 7.35 (tt, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 3.84 – 3.64 (m, 4H, 2 × C*H*$_2$), 3.69 (s, 3H, C*H*$_3$), 3.02 – 2.84 (m, 2H, C*H*$_2$), 2.73 – 2.67 (m, 2H, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.66, 141.1, 129.1, 128.6, 125.2, 69.9, 59.9, 52.6, 50.8, 26.7; **MP** (EtOAc) 80 – 82 °C; **IR** (neat)/ν_{max} 3358, 2951, 1734, 1309, 1222, 1072, 961; **HRMS (ESI)** calculated for $C_{13}H_{17}O_5S$, $[M+H]^+$ is 285.0791 (100%), 286.0824 (15%), found 285.0794 (100%), 286.0828 (17%).

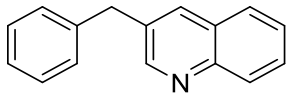
7.4.2. Desulfinative cross-couplings

General Procedure G



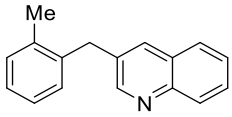
To a 10 mL microwave vial equipped with a stirrer bar was added, *if solid*, the benzyl bromide (0.30 mmol, 1.5 equiv.), *if solid*, the (hetero)aryl bromide (0.20 mmol, 1.0 equiv.), SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.) or β-nitrile sulfinate (42.3 mg, 0.30 mmol, 1.5 equiv.), potassium carbonate (69.1 mg, 0.50 mmol, 2.5 equiv.), $Pd(OAc)_2$ (4.5 mg, 10 mol%) and $P^tBu_2Me{\cdot}HBF_4$ (9.9 mg, 20 mol%). The vial was sealed with a microwave vial cap, evacuated under vacuum (<1 mbar) and back-filled with nitrogen gas. This cycle was repeated a further two times. Addition of, *if liquid*, the heteroaryl bromide (0.20 mmol, 1.0 equiv.), *if liquid*, the benzyl bromide (0.30 mmol, 1.5 equiv.) and DMSO (1.5 mL, 0.13 M) followed. The reaction was heated to 120 °C for 18 h before being cooled to room temperature. The reaction mixture was filtered through a pad of celite, rinsed thoroughly with EtOAc (50 mL) and the solvents were removed under reduced pressure. If the product was highly polar, 15 mL EtOAc was added to the crude residue and this was then washed with 5% aqueous LiCl solution (3 × 8 mL) to draw the DMSO into the aqueous layer. The aqueous washings were discarded. The organic layer was dried over $MgSO_4$, before removal of the solvents under reduced pressure. The resulting crude material was purified by silica gel chromatography to give the desired cross-coupled product.

3-Benzylquinoline (6b)



General Procedure G was followed using benzyl bromide (36 µL, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (10 – 30% EtOAc in petrol) to give the product as an off-white solid (39.5 mg, 90%). Data reported in section 7.2.2.

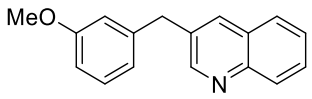
3-(2-Methylbenzyl)quinoline (6ag)



General Procedure G was followed using 2-methyl benzyl bromide (40 µL 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (10 – 50% EtOAc in petrol) to give the product as a yellow oil (46.1 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) 8.82 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.08 (d, *J* = 8.5 Hz, 1H, Het-*H*), 7.77 – 7.73 (m, 1H, Het-*H*), 7.70 (dd, *J* = 8.0, 1.5 Hz, 1H, Het-*H*), 7.66 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.50 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, Het-*H*), 7.23 – 7.13 (m, 4H, 4 × Ar-*H*), 4.17 (s, 2H, Ar-CH_2-Het), 2.28 (s, 3H, Ar-CH_3).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.2, 147.0, 137.7, 136.7, 134.7, 133.3, 130.7, 130.1, 129.3, 128.9, 128.3, 127.6, 127.1, 126.8, 126.4, 37.0, 19.8; **IR** (neat)/ν_{max} 3063, 3022, 2923, 1661, 1494, 734; **HRMS (ESI)** calculated for $C_{17}H_{16}N$, $[M+H]^+$ is 234.1277, found 234.1278.

3-(3-Methoxybenzyl)quinoline (6ah)

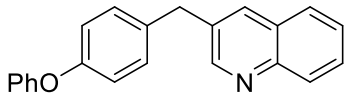


General Procedure G was followed, using 3-methoxybenzyl tosylate (87.7 mg, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (10 – 40% EtOAc in petrol) gave the title product as a colourless oil (39.2 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.0 Hz, 1H, Het-*H*), 8.00 (d, *J* = 8.5 Hz, 1H, Het-*H*), 7.80 (d, *J* = 2.0 Hz, 1H, Het-*H*), 7.64 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 7.57 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H, Het-*H*), 7.42 (t, *J* = 7.5 Hz, 1H, Het-*H*), 7.15 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 6.75 – 6.67 (m, 3H, 3 × Ar-*H*), 4.04 (s, 2H, Ar-CH_2-Het), 3.68 (s, 3H, Ar-OCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.0, 152.1, 147.0, 141.3, 135.0, 133.8, 129.9, 129.2, 129.0, 128.2, 127.6, 126.8, 121.5, 115.0, 111.9, 55.3, 39.4; **HRMS (ESI)** calculated for $C_{17}H_{16}ON$, $[M+H]^+$ is 250.1226 (100%), 251.1260 (18%), found 250.1227 (100%), 251.1261 (18%).

The data is consistent with the literature.[263]

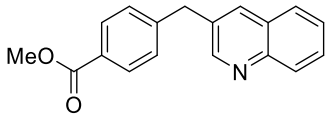
3-(4-Phenoxybenzyl)quinoline (6ai)



General Procedure G was followed, using 4-phenoxybenzyl bromide (78.9 mg, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (20 – 30% EtOAc in petrol) to give the title product as a white solid (58.5 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 2.0 Hz, 1H, Het-*H*), 8.11 (dq, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.91 (dd, *J* = 2.0, 1.0 Hz, 1H, Het-*H*), 7.76 (dd, *J* = 8.0, 1.5 Hz, 1H, Het-*H*), 7.68 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.53 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Het-*H*), 7.35 – 7.30 (m, 2H, 2 × Ar-*H*), 7.21 – 7.17 (m, 2H, 2 × Ar-*H*), 7.12 – 7.07 (m, 1H, Ar-*H*), 7.02 – 6.99 (m, 2H, 2 × Ar-*H*), 6.99 – 6.95 (m, 2H, 2 × Ar-*H*), 4.15 (s, 2H, Ar-CH_2-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.4, 156.0, 152.0, 146.9, 135.1, 134.6, 134.1, 130.3, 129.9, 129.2, 129.1, 128.3, 127.6, 126.9, 123.3, 119.4, 118.9, 38.7; **MP** (CH_2Cl_2) 63 – 65 °C; **IR (neat)/ν_{max}** 3036, 2360, 1735, 1589, 1505, 1488, 1239, 871, 754; **HRMS (ESI)** calculated for $C_{22}H_{18}ON$, $[M+H]^+$ is 312.1383, found 312.1383.

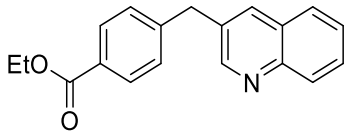
Methyl 4-(quinolin-3-ylmethyl)benzoate (6aj)



General Procedure G was followed, using methyl 4-(bromomethyl)benzoate (68.7 mg, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (15 – 30% EtOAc in petrol) to give the title product as a white crystalline solid (47.5 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* =. 2.5 Hz, 1H, Het-*H*), 8.10 (dq, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 8.01 – 7.97 (m, 2H, 2 × Ar-*H*), 7.88 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.74 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 7.68 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.53 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.32 – 7.28 (m, 2H, 2 × Ar-*H*), 4.22 (s, 2H, Ar-C*H*$_2$-Het), 3.90 (s, 3H, OC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.0, 151.9, 147.0, 145.0, 135.3, 133.0, 130.2, 129.3, 129.2, 129.1, 128.8, 128.2, 127.6, 127.0, 52.2, 39.3; **MP** (CH_2Cl_2) 84 – 86 °C; **IR** (neat)/ν_{max} 3000, 2950, 1718, 1610, 1435, 1280, 1109, 753, 728; **HRMS (ESI)** calculated for $C_{18}H_{16}O_2N$, $[M+H]^+$ is 278.1176, found 278.1176.

Ethyl 4-(quinolin-3-ylmethyl)benzoate (6ak)

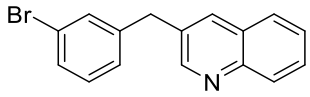


To a microwave vial equipped with a magnetic stirrer bar was added 4-(bromomethyl)benzoic acid (64.5 mg, 0.30 mmol, 1.5 equiv.), SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.), $Pd(OAc)_2$ (4.5 mg, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ ligand (9.9 mg, 20 mol%) and K_2CO_3 (69.1 mg, 0.50 mmol, 2.5 equiv.). The vessel was sealed with a microwave vial cap, evacuated under vacuum (<1 mbar) and back filled with nitrogen gas 3 times. Addition of 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.) and DMSO (1.5 mL) followed. The reaction was heated to 120 °C for 18 hours before being cooled to room temperature. A mixture of ethyl iodide (80 µL, 1.00 mmol, 5.0 equiv.) and Cs_2CO_3 (97.7 mg, 0.30 mmol, 1.5 equiv.) in DMSO (1 mL) was added dropwise to the crude cross-coupling reaction. The resulting mixture was heated to 80 °C, and stirred for a further 2 hours before cooling to room temperature. The reaction mixture was transferred to a separating funnel and EtOAc (20 mL) was added. The organic layer was washed with 20% $NaHCO_3$ aqueous solution (3 × 20 mL), then 5% LiCl aqueous solution (3 × 10 mL), before drying over $MgSO_4$. The solvents were removed under vacuum. The crude material was purified by column chromatography (5 – 40% EtOAc in pentane) to give the title product as a pale yellow oil (42.3 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) 8.80 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.10 (dq, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 8.02 – 7.98 (m, 2H, 2 × Ar-*H*), 7.87 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.74 (dd, *J* = 8.0, 1.5 Hz, 1H, Het-*H*), 7.68 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.53 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Het-*H*), 7.32 – 7.28 (m, 2H, 2 × Ar-*H*), 4.36 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 4.22 (s, 2H, Ar-CH_2-Het), 1.38 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.5, 151.8, 146.9,

144.9, 135.3, 133.1, 130.2, 129.3, 129.2, 129.1, 129.1, 128.2, 127.6, 127.0, 61.1, 39.3, 14.5; **IR** (neat)/ν_{max} 3064, 2982, 2936, 1714, 1610, 1496, 1416, 1367, 1276, 1178, 1106, 1021, 753, 728; **HRMS (ESI)** calculated for $C_{19}H_{18}O_2N$, $[M+H]^+$ is 292.1332 (100%), 293.1366 (22%), found 292.1331 (100%), 293.1365 (22%).

3-(3-Bromobenzyl)quinoline (6al)

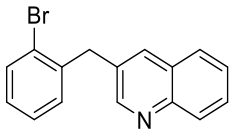


General Procedure G was followed, using 3-bromobenzyl bromide (74.9 mg, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (10 – 40% EtOAc in petrol) to give the title product as a colourless oil (41.8 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.10 (dd, *J* = 8.5, 1.0 Hz, 1H, 1H, Het-*H*), 7.88 (dd, *J* = 2.5, 1.0 Hz, 1H, 1H, Het-*H*), 7.77 – 7.74 (m, 1H, 1H, Het-*H*), 7.71 – 7.65 (m, 1H, 1H, Het-*H*), 7.56 – 7.51 (m, 1H, 1H, Het-*H*), 7.40 – 7.35 (m, 2H, Ar-*H*), 7.21 – 7.13 (m, 2H, Ar-*H*), 4.13 (s, 2H, Ar-CH_2-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.9, 147.0, 142.1, 135.2, 133.1, 132.1, 130.4, 129.9, 129.28, 129.26, 128.2, 127.7, 127.6, 127.0, 123.0, 39.0; **HRMS (ESI)** calculated for $C_{16}H_{13}NBr^{79}$ $[M+H]^+$ is 298.0226 (100%), 299.0260 (17%) and for $C_{16}H_{13}NBr^{81}$ $[M+H]^+$ is 300.0205 (97%), 301.0239 (17%), found 298.0227 (100%), 299.0261 (15%), 300.0205 (95%), 301.0239 (15%).

The data is consistent with the literature.[263]

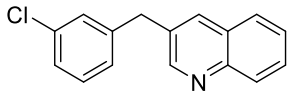
3-(2-Bromobenzyl)quinoline (6am)



General Procedure G was followed, using 2-bromobenzyl bromide (74.9 mg, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (2 – 20% EtOAc in petrol) to give the title product as a yellow oil (18.3 mg, 31%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 2.0 Hz, 1H, Het-*H*), 8.08 (dq, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.85 (dd, *J* = 2.0, 1.0 Hz, 1H, Het-*H*), 7.73 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 7.67 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.61 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.51 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, Het-*H*), 7.30 – 7.26 (m, 1H, Ar-*H*), 7.22 (dd, *J* = 7.5, 2.0 Hz, 1H, Ar-*H*), 7.14 (td, *J* = 7.5, 2.0 Hz, 1H, Ar-*H*), 4.30 (s, 2H, Ar-CH_2-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.2, 147.1, 139.2, 135.1, 133.3, 132.5, 131.3, 129.4, 129.1, 128.6, 128.2, 127.9, 127.6, 126.8, 125.0, 39.4; **IR (neat)/ν_{max}** 3057, 2949, 2921, 2850, 1735, 1605, 1496, 1471, 1439, 1025, 751, 741; **HRMS (ESI)** calculated for $C_{26}H_{28}ON$, $[M+H]^+$ is 298.0226 (100%), 299.0260 (17%), 300.0205 (95%), 301.0239 (17%), found 298.0224 (100%), 299.0261 (18%), 300.0205 (100%), 301.0236 (18%).

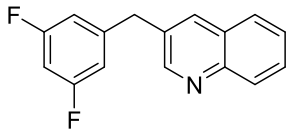
3-(3-Chlorobenzyl)quinoline (6an)



General Procedure G was followed, using 3-chlorobenzyl bromide (39 µL, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (40 – 70% EtOAc in petrol) to give the title product as a colourless oil (50.2 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.10 (dq, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.88 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.75 (dd, *J* = 8.0, 1.5 Hz, 1H, Het-*H*), 7.67 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.52 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, Het-*H*), 7.26 – 7.23 (m, 1H, Ar-*H*), 7.22 – 7.20 (m, 2H, 2 × Ar-*H*), 7.10 (dt, *J* = 7.0, 2.0 Hz, 1H, Ar-*H*), 4.13 (s, 2H, Ar-CH_2-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.9, 147.1, 141.8, 135.2, 134.7, 133.1, 130.1, 129.3, 129.24, 129.18, 129.1, 127.6, 127.6, 126.99, 126.97 39.0; **IR** (neat)/ν_{max} 3063, 3027, 2981, 2923, 1595, 1572, 1495, 1475, 1430, 1378, 857, 786, 753, 735; **HRMS (ESI)** calculated for $C_{16}H_{13}NCl^{35}$ $[M+H]^+$ is 254.0731 (100%), 255.0765 (17%) and for $C_{16}H_{13}NCl^{37}$ $[M+H]^+$ is 256.0702 (32%), 257.0735 (6%), found 254.0732 (100%), 255.0765 (17%), 256.0703 (35%), 257.0735 (7%).

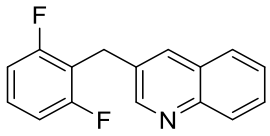
3-(3,5-Difluorobenzyl)quinoline (6ao)



General Procedure G was followed, using 3,5-difluorobenzyl bromide (39 µL, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (5 – 30% EtOAc in petrol) to give the title product as a white solid (49.7 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 2.0 Hz, 1H, Het-*H*), 8.11 (dt, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.91 (dd, *J* = 2.0, 1.0 Hz, 1H, Het-*H*), 7.77 (dd, *J* = 8.0, 1.5 Hz, 1H, Het-*H*), 7.70 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.55 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, Het-*H*), 6.74 (dt, *J* = 7.0, 2.0 Hz, 2H, 2 × Ar-*H*), 6.69 (tt, *J* = 8.5, 2.0 Hz, 1H, Ar-*H*), 4.14 (s, 2H, Ar-CH_2-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.4 (dd, *J* = 249.0, 13.0 Hz), 151.6, 147.0, 143.6 (t, *J* = 9.0 Hz), 135.4, 132.4, 129.5, 129.3, 128.2, 127.6, 127.2, 111.9 (dd, *J* = 18.0, 6.5 Hz), 102.4 (t, *J* = 25.5 Hz), 39.0 (t, *J* = 2.0 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -109.53; **MP** (CH_2Cl_2) 68 – 70 °C; **IR** (neat)/ν_{max} 3061, 2922, 2364, 1735, 1625, 1595, 1460, 1322, 1117, 996, 850, 788, 755; **HRMS (ESI)** calculated for $C_{16}H_{12}F_2N$, $[M+H]^+$ is 256.0932 (100%), 257.0966 (17%), 258.0999 (1%), found 256.0933 (100%), 257.0966 (20%), 258.1000 (1%).

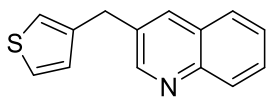
3-(2,6-Difluorobenzyl)quinoline (6ap)



General Procedure G was followed, using 2,6-difluorobenzyl bromide (62.1 mg, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (5 – 20% EtOAc in petrol) to give the title product as a white crystalline solid (50.4 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.08 (dd, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.95 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.74 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 7.66 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.51 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H, Het-*H*), 7.20 (tt, *J* = 8.5, 6.5 Hz, 1H, Ar-*H*), 6.91 (t, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 4.20 (s, 2H, Ar-C*H*$_2$-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.4 (dd, J = 247.5, 8.5 Hz), 151.6, 146.9, 134.8, 132.1, 129.2, 128.7 (t, *J* = 10.0 Hz), 128.2, 127.61, 127.56, 126.9, 115.8 (t, *J* = 20.0 Hz), 111.6 (dd, *J* = 18.5, 6.5 Hz), 25.9 (t, *J* = 3.0 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -114.85; **MP** (CH_2Cl_2) 88 – 90 °C; **IR** (neat)/ν_{max} 3063, 3036, 2941, 1623, 1591, 1498, 1468, 1261, 1007, 789, 769, 754; **HRMS (ESI)** calculated for $C_{16}H_{12}NF_2$, $[M+H]^+$ is 256.0932, found 256.0933.

3-(Thiophen-3-ylmethyl)quinoline (6aq)

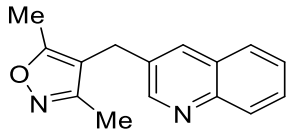


General Procedure G was followed, using 3-(bromomethyl)thiophene (33 µL, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude residue was purified by column chromatography (10 – 30% EtOAc in toluene) to give the product as a yellow oil (20.7 mg, 46%, 90% NMR purity).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.15 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.99 (dd, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.91 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 7.73 – 7.68 (m, 1H, Het-*H*), 7.60 – 7.56 (m, 1H, Het-*H*), 7.49 (dd, *J* = 5.0, 3.0 Hz, 1H, Het-*H*), 7.29 – 7.27 (m, 1H, Het-*H*), 7.04 (dd, *J* = 5.0, 1.5 Hz, 1H), 4.17 (s, 2H, Het-CH_2-Het); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 151.9, 146.3, 140.5, 134.2, 133.9, 128.8, 128.6, 128.4, 127.69, 127.66, 126.7, 126.6, 121.9, 32.9; **IR** (neat)/ν_{max} 3101, 3053, 2918, 2850, 1496, 1265, 752, 732; **HRMS (ESI)** calculated for $C_{14}H_{12}SN$, $[M+H]^+$ is 226.0685 (100%), 227.0718 (15%), found 226.0686 (100%), 227.0720 (15%).

The data is consistent with the literature.[264]

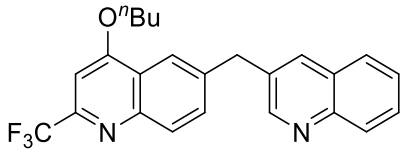
3,5-Dimethyl-4-(quinolin-3-ylmethyl)isoxazole (6ar)



General Procedure G was followed, using 4-chloromethyl-3,5-dimethylisoxazole (37 µL, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and β-nitrile sulfinate (42.3 mg, 0.30 mmol, 1.5 equiv.). The crude residue was purified by column chromatography (10 – 50 % EtOAc in petrol) to give the product as a yellow solid (39.9 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H, Het-*H*), 8.10 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 7.74 (dd, *J* = 8.0, 1.5 Hz, 2H, 2 × Het-*H*), 7.69 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.54 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, Het-*H*), 3.87 (s, 2H, Het-CH_2-Het), 2.36 (s, 3H, Het-CH_3), 2.12 (s, 3H, Het-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.1, 159.9, 151.2, 146.7, 134.2, 131.5, 129.5, 129.2, 128.1, 127.6, 127.3, 111.2, 25.8, 11.3, 10.5; **MP** (CH_2Cl_2) 98 – 100 °C; **IR (neat)/ν_{max}** 3064, 3027, 2981, 2970, 2924, 2850, 2365, 1640, 1606, 1571, 1496, 1452, 1423, 1381, 1333, 1260, 1195, 1126, 983, 791, 766, 753; **HRMS (ESI)** calculated for $C_{15}H_{15}N_2O$, $[M+H]^+$ is 239.1179 (100%), 240.1213 (17%), found 239.1179 (100%), 240.1212 (17%).

4-Butoxy-6-(quinolin-3-ylmethyl)-2-(trifluoromethyl)quinoline (6as)

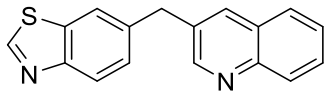


Desulfinative cross-couplings

General Procedure G was followed, using 6-(bromomethyl)-4-butoxy-2-(trifluoromethyl)quinoline (95 mg, 0.26 mmol, 1.3 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude residue was purified by column chromatography (20 – 30 % EtOAc in petrol) to give the product as an off-white solid (73.1 mg, 89%).

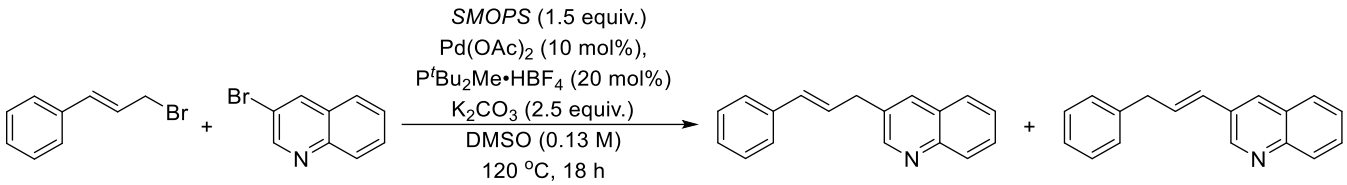
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 2.0 Hz, 1H, Het-*H*), 8.14 (d, *J* = 8.5 Hz, 1H, Het-*H*), 8.11 (d, *J* = 2.0 Hz, 1H, Het-*H*), 8.09 (d, *J* = 8.5 Hz, 1H, Het-*H*), 7.94 (*app* s, 1H, Het-*H*), 7.75 (dd, *J* = 8.0, 1.5 Hz, 1H, Het-*H*), 7.70 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.63 (dd, *J* = 8.5, 2.0 Hz, 1H, Het-*H*), 7.55 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, Het-*H*), 7.04 (s, 1H, Het-*H*), 4.40 (s, 2H, Het-C*H*$_2$-Het), 4.26 (t, *J* = 6.5 Hz, 2H, -O-C*H*$_2$-CH$_2$-), 1.97 – 1.90 (m, 2H, -O-CH$_2$-C*H*$_2$-), 1.56 (h, *J* = 7.5 Hz, 2H, -CH$_2$-*CH*$_2$-CH$_3$), 1.00 (t, *J* = 7.5 Hz, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1, 151.9, 148.9 (q, *J* = 34.0 Hz), 147.3, 147.0, 139.2, 135.3, 133.2, 132.4, 130.3, 129.3, 129.2, 128.2, 127.6, 127.0, 122.0, 121.8 (q, *J* = 275.5 Hz), 121.5, 97.1 (q, *J* = 2.0 Hz), 69.1, 39.5, 30.9, 19.4, 13.9; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -67.71; **MP** (CH_2Cl_2) 81 – 84 °C; **IR** (neat)/ν_{max} 3062, 2959, 2954, 2360, 1591, 1575, 1413, 1375, 1280, 1255, 1181, 1135, 1094, 841, 789, 756, 721; **HRMS (ESI)** calculated for $C_{24}H_{22}ON_2F_3$, $[M+H]^+$ is 411.1679, found 411.1679.

6-(Quinolin-3-ylmethyl)benzo[d]thiazole (6at)



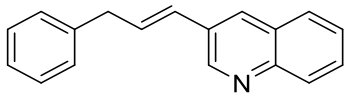
General Procedure G was followed, using 6-(bromomethyl)benzo[d]thiazole (68.4 mg, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (10 – 40% EtOAc in petrol) to give the title product as a white solid (25.2 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H, Het-*H*), 8.85 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.13 – 8.07 (m, 2H, 2 × Het-*H*), 7.92 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.78 (dd, *J* = 1.5, 1.0 Hz, 1H, Het-*H*), 7.75 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 7.68 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.53 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.41 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 4.33 (s, 2H, Het-CH_2-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.9, 152.3, 151.9, 146.9, 137.6, 135.3, 134.5, 133.5, 129.3, 129.2, 128.2, 127.7, 127.6, 127.1, 123.9, 121.9, 39.3; **MP** (CH_2Cl_2) 68 – 70 °C; **IR** (neat)/ν_{max} 3056, 2920, 2849, 1496, 1472, 1441, 1409, 1293, 1269, 1125, 900, 836, 788, 756, 723; **HRMS (ESI)** calculated for $C_{17}H_{13}N_2S$, $[M+H]^+$ is 277.0794, found 277.0796.



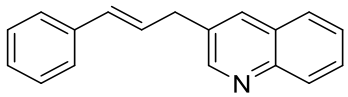
General Procedure G was followed, using 3-bromo-1-phenyl-1-propene (44 µL, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude residue was purified by column chromatography (0 – 20% EtOAc in petrol) to give a mixture of two positional isomers as a yellow oil (42.4 mg, 86%). For analysis, the isomers were separated by preparative thin-layer chromatography (15% EtOAc in petrol) to give (*E*)-3-(3-phenylprop-1-en-1-yl)quinoline (17.2 mg, 35%) and 3-cinnamylquinoline (14.2 mg, 29%), both as yellow oils.

(*E*)-3-(3-Phenylprop-1-en-1-yl)quinoline (6au')



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.08 (d, *J* = 8.5 Hz, 1H, Het-*H*), 8.02 (d, *J* = 2.5 Hz, 1H, Het-*H*), 7.77 (dd, *J* = 8.0, 1.5 Hz, 1H, Het-*H*), 7.66 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.52 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, Het-*H*), 7.39 – 7.32 (m, 2H, 2 × Ar-*H*), 7.31 – 7.23 (m, 3H, 3 × Ar-*H*), 6.67 – 6.54 (m, 2H, 2 × C*H*), 3.64 (d, *J* = 5.0 Hz, 2H, Ar-CH_2-R); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.3, 147.2, 139.6, 132.3, 132.2, 130.5, 129.2, 128.9, 128.80, 128.78, 128.2, 127.90, 127.85, 127.1, 126.6, 39.7; **IR** (neat)/ν_{max} 3061, 3027, 2919, 2850, 2361, 2342, 1602, 1570, 1494, 1453, 966, 789, 751, 699; **HRMS (ESI)** calculated for $C_{18}H_{16}N$, $[M+H]^+$ is 246.1277 (100%), 247.1311 (20%), found 246.1278 (100%), 247.1312 (22%).

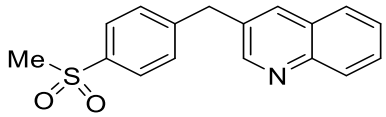
3-Cinnamylquinoline (6au")



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H, Het-*H*), 7.92 (s, 1H, Het-*H*), 7.71 (d, *J* = 8.0 Hz, 1H, Het-*H*), 7.61 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.46 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.32 – 7.28 (m, 2H, 2 × Ar-*H*), 7.27 – 7.21 (m, 2H, 2 × Ar-*H*), 7.19 – 7.13 (m, 1H, Ar-*H*), 6.45 (dt, *J* = 16.0, 1.5 Hz, 1H, C*H*), 6.33 (dt, *J* = 16.0, 6.5 Hz, 1H, C*H*), 3.67 (d, *J* = 6.5 Hz, 2H, Ar-CH_2-R); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.0, 146.9, 137.2, 135.0, 133.0, 132.4, 129.2, 129.1, 128.7, 128.3, 127.7, 127.60, 127.56, 126.9, 126.4, 36.7; **IR (neat)/ν_{max}** 3059, 3026, 2923, 2851, 2361, 2341, 1733, 1599, 1571, 1496, 1449, 966, 787, 752, 693; **HRMS (ESI)** calculated for $C_{18}H_{16}N$, $[M+H]^+$ is 246.1277 (100%), 247.1311 (20%), found 246.1278 (100%), 247.1312 (22%).

The data is consistent with the literature.[265]

3-(4-(Methylsulfonyl)benzyl)quinoline (6av)

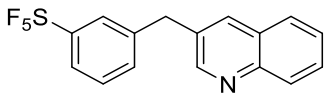


General Procedure G was followed, using 4-(methylsulfonyl)benzyl bromide (79.5 mg, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (20 – 45% EtOAc in petrol) to give the title product as a white solid (54.3 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.09 (dq, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.91 – 7.86 (m, 3H, Het-*H*, 2 × Ar-*H*), 7.76 (dd, *J* = 8.0, 1.5 Hz, 1H, Het-*H*), 7.69 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.54 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H, Het-*H*), 7.45 – 7.40 (m, 2H, 2 × Ar-*H*), 4.25 (s, 2H, Ar-C*H*$_2$-Het), 3.03 (s, 3H, Ar-SO_2-C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.7, 147.1, 146.3, 139.1, 135.4, 132.3, 130.0, 129.5, 129.3, 128.1, 128.0, 127.6, 127.2, 44.7, 39.2; **HRMS (ESI)** calculated for $C_{17}H_{16}O_2NS$, $[M+H]^+$ is 298.0896, found 298.0896.

The data is consistent with the literature.[233]

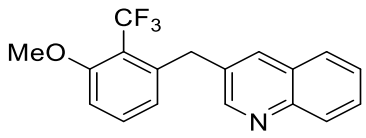
3-(3-(Pentafluorothio)benzyl)quinoline (6aw)



General Procedure G was followed, using 3-(pentafluorothio)benzyl bromide (89.1 mg, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (10 – 30% EtOAc in petrol) to give the title product as a colourless oil (59.7 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.11 (dq, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.89 (dd, *J* = 2.5, 1.0 Hz, 1H, Het-*H*), 7.76 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 7.70 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.67 – 7.62 (m, 2H, 2 × Ar-*H*), 7.54 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Het-*H*), 7.41 (app. t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.35 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 4.23 (s, 2H, Ar-CH_2-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.4 (quint, *J* = 16.5 Hz), 151.7, 147.2, 141.0, 135.3, 132.5, 132.2, 129.4, 129.3, 129.3, 128.2, 127.6, 127.1, 126.5 (quint, *J* = 4.5 Hz), 124.2 (quint, *J* = 4.5 Hz), 39.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 85.37 – 83.38 (m, 1F), 62.82 (d, *J* = 150.5 Hz, 4F); **IR** (neat)/ν_{max} 2981, 2361, 1736, 1496, 837, 808; **HRMS (ESI)** calculated for $C_{16}H_{13}SF_5N$, $[M+H]^+$ is 346.0683, found 346.0682.

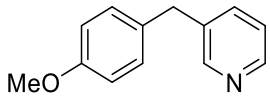
3-(3-Methoxy-2-(trifluoromethyl)benzyl)quinoline (6ax)



General Procedure G was followed, using 3-methoxy-2-(trifluoromethyl)benzyl bromide (80.7 mg, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (15 – 30% EtOAc in petrol) to give the title product as a white solid (61.5 mg, 97%).

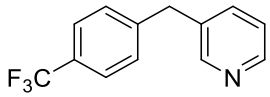
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 2.5 Hz, 1H, Het-*H*), 8.09 (dq, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.75 – 7.68 (m, 2H, 2 × Het-*H*), 7.66 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H, Het-*H*), 7.50 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H, Het-*H*), 7.43 (t, *J* = 8.0 Hz, 1H, Het-*H*), 6.97 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.84 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 4.37 (s, 2H, Ar-C*H*$_2$-Het), 3.90 (s, 3H, Ar-OC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3 (q, *J* = 2.5 Hz), 151.7, 146.8, 139.3 (q, *J* = 1.5 Hz), 134.7, 133.4, 132.8, 129.2, 129.1, 128.2, 127.6, 126.9, 124.9 (q, *J* = 276.5 Hz), 124.8, 117.9 (q, *J* = 29.5 Hz), 111.4, 56.5, 37.6 (q, *J* = 4.5 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -54.54; **MP** (CH_2Cl_2) 74 – 78 °C; **IR** (neat)/ν_{max} 3032, 2843, 2360, 1587, 1476, 1294, 1271, 1120, 1068, 1037, 752; **HRMS (ESI)** calculated for $C_{18}H_{15}ONF_3$, $[M+H]^+$ is 318.1100, found 318.1101.

3-(4-Methoxybenzyl)pyridine (6k)



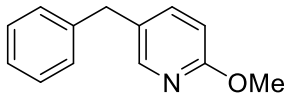
General Procedure G was followed, using 4-methoxybenzyl chloride (41 µL, 0.30 mmol, 1.5 equiv.), 3-bromopyridine (20 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). Purification by column chromatography (10 – 50% EtOAc in petrol) gave the title product as a yellow oil (35.4 mg, 89%). Data reported in section 7.2.2.

3-(4-(Trifluoromethyl)benzyl)pyridine (6j)



General Procedure G was followed, using 4-(trifluoromethyl)benzyl bromide (71.7 mg, 0.30 mmol, 2.0 equiv.), 3-bromopyridine (14 µL, 0.15 mmol, 1.0 equiv.) and β-nitrile sulfinate (46.2 mg, 0.30 mmol, 2.2 equiv.). The crude material was purified by column chromatography (10 – 40% EtOAc in petrol) to give the product as a yellow oil (32.1 mg, 90%). Data reported in section 7.3.2.

5-Benzyl-2-methoxypyridine (6n)

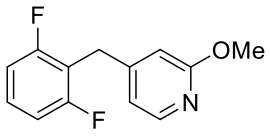


General Procedure G was followed using benzyl bromide (36 µL, 0.30 mmol, 1.5 equiv.), 2-methoxy-5-bromopyridine (26 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (10 – 40% Et_2O in petrol) to give the product as a colourless oil (39.4 mg, 99%).

5 mmol scale up

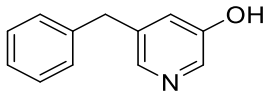
To a 250 mL two-necked round bottom flask equipped with a magnetic stirrer bar was added SMOPS (1.31 g, 7.5 mmol, 1.5 equiv.), $Pd(OAc)_2$ (112 mg, 10 mol%), $P(^tBu)_2Me{\cdot}HBF_4$ ligand (248 mg, 20 mol%) and K_2CO_3 (1.73 g, 12.5 mmol, 2.5 equiv.). One neck of the round bottom flask was fitted with a condenser and the other was fitted with a suba seal. The reaction vessel was evacuated under vacuum (<1 mbar) and back filled with nitrogen gas. This cycle was repeated two further times. Addition of 5-Bromo-2-methoxypyridine (0.65 mL, 5.0 mmol, 1.0 equiv.), benzyl bromide (0.89 mL, 7.5 mmol, 1.5 equiv.) and anhydrous DMSO (38 mL) followed. The reaction mixture was heated to 120 °C for 18 h before cooling to room temperature. The reaction mixture was filtered through celite, and washed with EtOAc. The EtOAc washings were then transferred to a 500 mL separating funnel, and the organics were washed with 5% aqueous LiCl solution until the DMSO was fully extracted from the organic layer. The organic layer was dried over $MgSO_4$, and the solvents removed under vacuum. The crude residue was purified by column chromatography (2 – 10% EtOAc in petrol) to give the title product as a clear oil (986.3 mg, 99%). Data reported in section 7.2.2.

4-(2,6-Difluorobenzyl)-2-methoxypyridine (6u)



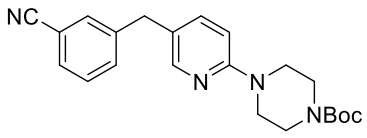
General Procedure G was followed, using 2,6-difluorobenzyl bromide (62.1 mg, 0.30 mmol, 1.5 equiv.), 4-bromo-2-methoxypyridine (25 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (10% EtOAc in petrol) to give the title product as a colourless oil (41.8 mg, 89%). Data reported in section 7.2.2.

5-Benzylpyridin-3-ol (6l)



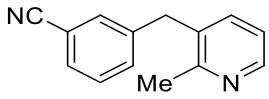
General Procedure G was followed, using benzyl bromide (36 µL, 0.30 mmol, 1.5 equiv.), 3-bromo-5-hydroxypyridine (34.8 mg, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). After filtration through celite, the filtrate was washed with 5% aqueous LiCl solution until the DMSO was fully removed from the organic phase. The crude material was purified by column chromatography (50 – 80% EtOAc in petrol) to give the title product as a yellow solid (21.4 mg, 58%). Data reported in section 7.2.2.

***tert*-Butyl 4-(5-(3-cyanobenzyl)pyridin-2-yl)piperazine-1-carboxylate (6q)**



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), *tert*-butyl 4-(5-bromopyridin-2-yl)piperazine-1-carboxylate (68.4 mg, 0.20 mmol, 1.0 equiv.) and SMOPS (52.0 mg, 0.30 mmol, 1.5 equiv.). The crude residue was purified by column chromatography (20 – 60% EtOAc in petrol) to give the title product as a white solid (75.3 mg, 99%). Data reported in section 7.2.2.

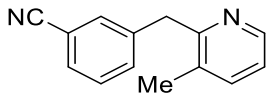
3-((2-Methylpyridin-3-yl)methyl)benzonitrile (6ay)



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), 2-bromo-3-methylpyridine (22 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (30 – 70% EtOAc in petrol) to give the title product as an off-white solid (39.2 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.53 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.43 – 7.33 (m, 4H), 7.14 (dd, *J* = 7.5, 5.0 Hz, 1H), 4.02 (s, 2H), 2.47 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.2, 147.6, 140.7, 137.7, 133.3, 132.8, 132.2, 130.4, 129.6, 121.8, 118.8, 112.9, 38.4, 22.6; **MP** (CH_2Cl_2) 82 – 84 °C; **IR** (neat)/ν_{max} 3055, 2993, 2921, 2852, 2229, 1734, 1583, 1483, 1440, 812, 792, 752, 733, 689; **HRMS (ESI)** calculated for $C_{14}H_{13}N_2$, $[M+H]^+$ is 209.1073 (100%), 210.1107 (15%), found 209.1074 (100%), 210.1108 (15%).

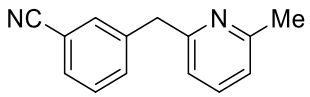
3-((3-Methylpyridin-2-yl)methyl)benzonitrile (6az)



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), 2-bromo-3-methylpyridine (22 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (25 – 65% EtOAc in petrol) to give the title product as a colourless oil (40.7 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 5.0, 1.5 Hz, 1H, Het-*H*), 7.49 – 7.43 (m, 4H, 3 × Ar-*H*, Het-*H*), 7.36 (dd, *J* = 8.5, 7.5 Hz, 1H, Ar-*H*), 7.13 (dd, *J* = 7.5, 5.0 Hz, 1H, Het-*H*), 4.20 (s, 2H, Ar-CH_2-Het), 2.25 (s, 3H, Het-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.3, 147.1, 140.6, 138.6, 133.4, 132.3, 131.8, 130.1, 129.3, 122.3, 119.0, 112.6, 41.4, 19.0; **IR** (neat)/ν_{max} 3053, 2981, 2953, 2930, 2229, 1736, 1574, 1483, 1466, 1450, 1436, 1106, 791, 779, 689; **HRMS (ESI)** calculated for $C_{14}H_{12}N_2$, $[M+H]^+$ is 209.1073 (100%), 210.1107 (15%), found 209.1074 (100%), 210.1108 (15%).

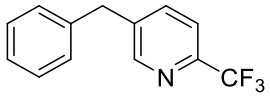
3-((6-Methylpyridin-2-yl)methyl)benzonitrile (6ba)



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), 2-bromo-6-methylpyridine (23 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (20 – 45% Et_2O in pentane) to give the title product as a yellow solid (34.7 mg, 83%).

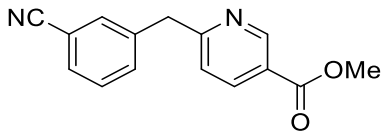
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, 4H, 4 × Ar-*H*), 7.38 (t, *J* = 7.5 Hz, 1H, Het-*H*), 7.02 (d, *J* = 7.5 Hz, 1H, Het-*H*), 6.88 (d, *J* = 7.5 Hz, 1H, Het-*H*), 4.13 (s, 2H, Ar-*CH_2*-Het), 2.54 (s, 3H, Het-*CH_3*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.7, 158.5, 141.3, 137.1, 133.7, 132.6, 130.2, 129.3, 121.4, 120.2, 119.0, 112.6, 44.1, 24.7; **MP** (CH_2Cl_2) 59 - 60 °C; **IR** (neat)/ν_{max} 3064, 2980, 2924, 2229, 1592, 1576, 1483, 1456, 1435, 993, 788, 757, 689; **HRMS (ESI)** calculated for $C_{14}H_{13}N_2$, $[M+H]^+$ is 209.1073 (100%), 210.1107 (15%), found 209.1074 (100%), 210.1109 (15%).

5-Benzyl-2-(trifluoromethyl)pyridine (6m)



General Procedure G was followed, using benzyl bromide (36 µL, 0.30 mmol, 1.5 equiv.), 5-bromo-2-(trifluoromethyl)pyridine (45.2 mg, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (2 – 10% EtOAc in petrol) to give the title product as a colourless oil (38.0 mg, 80%). Data reported in section 7.2.2.

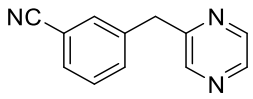
Methyl 6-(3-cyanobenzyl)nicotinate (6bb)



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), 6-chloropyridine-3-carboxylate (34.3 mg, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (10 – 40% EtOAc in petrol) to give the title product as a colourless oil (22.9 mg, 45%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, *J* = 2.0 Hz, 1H, Het-*H*), 8.24 (dd, *J* = 8.0, 2.0 Hz, 1H, Het-*H*), 7.59 – 7.50 (m, 3H, Het-*H*, 2 × Ar-*H*), 7.42 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.22 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 4.24 (s, 2H, Ar-*CH_2*-Het), 3.94 (s, 3H, Het-COO*CH_3*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.6, 163.6, 150.8, 140.1, 138.4, 133.8, 132.7, 130.7, 129.7, 124.6, 123.1, 118.8, 113.0, 52.6, 44.0; **IR** (neat)/ν_{max} 2953, 2850, 2229, 1722, 1596, 1434, 1292, 1195, 1117, 1026, 792, 742, 693; **HRMS (ESI)** calculated for $C_{15}H_{13}O_2N_2$, $[M+H]^+$ is 253.0972 (100%), 254.1005 (17%), found 253.0973 (100%), 254.1006 (17%).

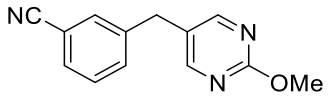
3-(Pyrazin-2-ylmethyl)benzonitrile (6bc)



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), 2-chloropyrazine (18 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (25 – 65% EtOAc in petrol) to give the title product as a yellow oil (34.2 mg, 88%).

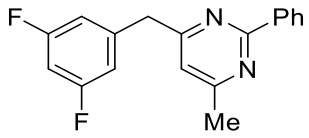
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 – 8.44 (m, 3H, 3 × Het-*H*), 7.61 – 7.56 (m, 1H, Ar-*H*), 7.56 – 7.50 (m, 2H, 2 × Ar-*H*), 7.42 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 4.19 (s, 2H, Ar-CH_2-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.1, 144.7, 144.5, 143.1, 139.7, 133.7, 132.7, 130.7, 129.7, 118.8, 113.0, 41.3; **IR** (neat)/ν_{max} 3058, 2922, 2229, 1734, 1485, 1474, 1434, 1403, 1057, 1018, 797, 768, 692; **HRMS (ESI)** calculated for $C_{12}H_9N_3$, $[M+H]^+$ is 196.0877 (100%), 197.0903 (12%), found 196.0871 (100%), 197.0905 (15%).

3-((2-Methoxypyrimidin-5-yl)methyl)benzonitrile (6w)



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), 5-bromo-2-methoxypyrimidine (37.8 mg, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (30 – 70% EtOAc in petrol) to give the title product as an off-white solid (42.9 mg, 95%). Data reported in section 7.2.2.

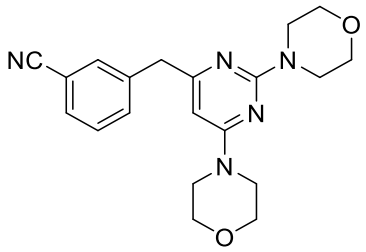
4-(3,5-Difluorobenzyl)-6-methyl-2-phenylpyrimidine (6bd)



General Procedure G was followed, using 3,5-difluorobenzyl bromide (39 µL, 0.30 mmol, 1.5 equiv.), 4-chloro-6-methyl-2-phenyl-pyrimidine (40.9 mg, 0.20 mmol, 1.0 equiv.) and β-nitrile sulfinate (42.3 mg, 0.30 mmol, 1.5 equiv.). The crude residue was purified by column chromatography (5 – 50% EtOAc in petrol) to give the product as a white crystalline solid (39.4 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 – 8.44 (m, 2H, 2 × Ar-*H*), 7.48 (dd, *J* = 5.0, 2.0 Hz, 3H, 3 × Ar-*H*), 6.87 (dt, *J* = 6.5, 2.0 Hz, 2H, 2 × Ar-*H*), 6.84 (s, 1H, Het-*H*), 6.71 (tt, *J* = 9.0, 2.0 Hz, 1H, Ar-*H*), 4.08 (s, 2H, Ar-*CH_2*-Het), 2.54 (s, 3H, Het-*CH_3*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.9, 167.6, 164.4, 163.2 (dd, *J* = 248.5, 13.0 Hz), 141.8 (t, *J* = 9.0 Hz), 137.8, 130.7, 128.6, 128.5, 117.6, 112.3 (dd, *J* = 19.0, 6.5 Hz), 102.5 (t, *J* = 25.5 Hz), 43.9 (t, *J* = 2.0 Hz), 24.5; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -109.80; **MP** (CH_2Cl_2) 78 – 80 °C; **IR** (neat)/ν_{max} 3065, 1626, 1592, 1573, 1543, 1460, 1371, 1322, 1118, 996, 849, 726, 694; **HRMS (ESI)** calculated for $C_{18}H_{15}F_2N_2$, $[M+H]^+$ is 297.1198 (100%), 298.1231 (20%), found 297.1197 (100%), 298.1230 (20%).

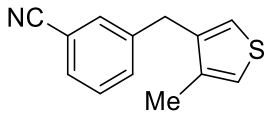
3-((2,6-Dimorpholinopyrimidin-4-yl)methyl)benzonitrile (6be)



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), 4,4'-(6-chloropyrimidine-2,4-diyl)dimorpholine (56.9 mg, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (20 – 60% EtOAc in petrol) to give the title product as an off-white solid (68.6 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H, Ar-*H*), 7.53 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.49 (dt, *J* = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.37 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 5.67 (s, 1H, Het-*H*), 3.79 (s, 2H, Ar-CH_2-Het), 3.76 – 3.72 (m, 12H, 12 × Alk-*H*), 3.51 (t, *J* = 5.0 Hz, 4H, 4 × Alk-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.2, 163.6, 161.7, 140.6, 133.8, 132.8, 130.2, 129.1, 119.1, 112.4, 91.7, 67.0, 66.6, 44.4, 44.3, 44.0; **MP** (CH_2Cl_2) 96 – 100 °C; **IR** (neat)/ν_{max} 2690, 2916, 2894, 2851, 2229, 1734, 1573, 1551, 1468, 1440, 1413, 1365, 1264, 1244, 1192, 1116, 1008, 881, 792, 742; **HRMS (ESI)** calculated for $C_{20}H_{24}O_2N_5$, $[M+H]^+$ is 366.1925 (100%), 367.1957 (22%), found 366.1919 (100%), 367.1950 (25%).

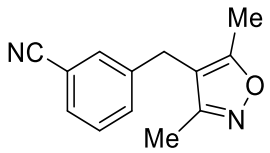
3-((4-Methylthiophen-3-yl)methyl)benzonitrile (6bf)



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), 3-bromo-4-methylthiophene (22 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (5 – 35% EtOAc in petrol) to give the title product as a pale yellow oil (38.4 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dt, *J* = 6.5, 2.0 Hz, 1H, Ar-*H*), 7.45 – 7.39 (m, 3H, 3 × Ar-*H*), 6.96 (dd, *J* = 3.0, 1.0 Hz, 1H, Het-*H*), 6.85 (d, *J* = 3.0 Hz, 1H, Het-*H*), 3.92 (s, 2H, Ar-C*H*$_2$-Het), 2.09 (d, *J* = 1.0 Hz, 3H, Het-C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.7, 138.9, 136.8, 133.3, 132.3, 130.1, 129.3, 122.9, 122.2, 119.0, 112.6, 35.0, 14.6; **IR** (neat)/ν_{max} 3097, 2920, 2229, 1483, 1444, 1431, 861, 789, 737, 690; **HRMS (ESI)** calculated for $C_{13}H_{12}NS$, $[M+H]^+$ is 214.0685 (100%), 215.0718 (15%), found 214.0688 (100%), 215.0719 (10%).

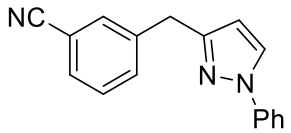
3-((3,5-Dimethylisoxazol-4-yl)methyl)benzonitrile (6bg)



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), 4-bromo-3,5-dimethylisoxazole (24 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (20 – 45% EtOAc in petrol) to give the title product as a colourless oil (30.6 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.50 (m, 1H, Ar-*H*), 7.43 – 7.38 (m, 2H, 2 × Ar-*H*), 7.35 – 7.31 (m, 1H, Ar-*H*), 3.71 (s, 2H, Ar-*CH_2*-Het), 2.32 (s, 3H, Het-*CH_3*), 2.07 (s, 3H, Het-*CH_3*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.1, 159.7, 140.5, 132.6, 131.6, 130.5, 129.7, 118.7, 113.0, 111.2, 29.8, 27.9, 11.2, 10.4; **IR** (neat)/ν_{max} 2956, 2917, 2849, 2231, 1734, 1640, 1483, 1424, 1381, 1261, 1232, 1195, 1095, 800, 757, 736, 687; **HRMS (ESI)** calculated for $C_{13}H_{13}ON_2$, $[M+H]^+$ is 213.1022 (100%), 214.1056 (15%), found 213.1024 (30%), 214.0897 (100%).

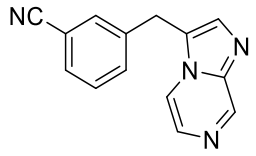
3-((1-Phenyl-1H-pyrazol-3-yl)methyl)benzonitrile (6bh)



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), 3-iodo-1-phenyl-1H-pyrazole (31 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (15 – 30% EtOAc in petrol) to give the title product as a white solid (45.8 mg, 88%).

^{1}H NMR (400 MHz, DMSO) δ 8.41 (d, J = 2.5 Hz, 1H, Het-*H*), 7.83 – 7.74 (m, 3H, 3 × Ar-*H*), 7.71 – 7.61 (m, 2H, 2 × Ar-*H*), 7.53 (dd, J = 7.5, 0.5 Hz, 1H, Ar-*H*), 7.51 – 7.44 (m, 2H, 2 × Ar-*H*), 7.31 – 7.23 (m, 1H, Ar-*H*), 6.38 (d, J = 2.5 Hz, 1H, Het-*H*), 4.07 (s, 2H, Ar-C*H*$_2$-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.2, 141.3, 140.1, 133.5, 132.5, 130.2, 129.6, 129.4, 128.1, 126.6, 119.3, 119.1, 112.6, 107.2, 34.4; **MP** (CH_2Cl_2) 64 – 66 °C; **IR** (neat)/ν_{max} 2980, 2953, 2921, 2229, 1737, 1599, 1528, 1502, 1483, 1389, 1047, 903, 756, 687; **HRMS (ESI)** calculated for $C_{17}H_{13}N_3$, $[M+H]^+$ is 260.1182 (100%), 261.1216 (20%), found 260.1183 (100%), 261.1217 (20%).

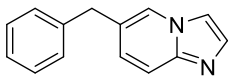
3-(Imidazo[1,2-a]pyrazin-3-ylmethyl)benzonitrile (6bi)



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), 3-bromoimidazo[1,2-a]pyrazine (39.6 mg, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (80 – 100% EtOAc in petrol) to give the title product as an orange solid (38.1 mg, 81%).

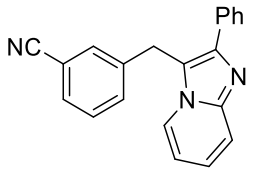
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, *J* = 1.5 Hz, 1H, Het-*H*), 7.86 (d, *J* = 5.0 Hz, 1H, Het-*H*), 7.69 (dd, *J* = 5.0, 1.5 Hz, 1H, Het-*H*), 7.64 (s, 1H, Het-*H*), 7.58 (dt, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.50 – 7.48 (m, 1H, Ar-*H*), 7.45 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.40 (dt, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 4.32 (s, 2H, Ar-C*H*$_2$-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.4, 141.5, 137.4, 135.2, 132.8, 131.9, 131.3, 130.1, 129.8, 122.9, 118.4, 116.1, 113.4, 29.6; **MP** (CH_2Cl_2) 148 – 150 °C; **IR** (neat)/ν_{max} 2981, 2954, 2924, 2229, 1734, 1558, 1522, 1486, 1379, 1341, 1146, 899, 793, 723, 668; **HRMS (ESI)** calculated for $C_{14}H_{10}N_4$, $[M+H]^+$ is 235.0978 (100%), 236.1012 (15%), found 235.0978 (100%), 236.1012 (15%).

6-Benzylimidazo[1,2-a]pyridine (6z)



General Procedure G was followed, using benzyl bromide (36 µL, 0.30 mmol, 1.5 equiv.), 6-bromoimidazo[1,2-α]pyridine (39.4 mg, 0.20 mmol, 1.0 equiv.) and β-nitrile sulfinate (46.6 mg, 0.33 mmol, 1.65 equiv.). Due to the polar nature of the product, the crude material was dissolved into EtOAc (50 mL) and washed with 5% aqueous LiCl solution (3 × 10 mL) until full removal of DMSO from the organic layer was achieved. The organic layer was dried over $MgSO_4$ and the solvents removed under vacuum. The residue was purified by column chromatography (10 – 60% EtOAc in petrol) to give the product as an orange oil (33.3 mg, 80%). Data reported in section 7.2.2.

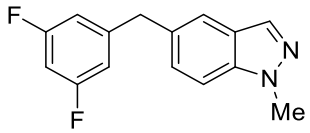
3-((2-Phenylimidazo[1,2-a]pyridin-3-yl)methyl)benzonitrile (6bj)



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), 3-bromo-2-phenylimidazo[1,2-a]pyridine (54.6 mg, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude material was purified by column chromatography (40 – 100% EtOAc in petrol) to give the title product as an orange oil (34.4 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.70 (m, 3H, Het-*H*, 2 × Ar-*H*), 7.64 (dt, *J* = 7.0, 1.5 Hz, 1H, Het-*H*), 7.55 (dt, *J* = 7.5, 1.5 Hz, 1H, Het-*H*), 7.46 – 7.31 (m, 6H, 6 × Ar-*H*), 7.25 – 7.21 (m, 1H, Ar-*H*), 6.79 (td, *J* = 7.0, 1.5 Hz, 1H, Het-*H*), 4.54 (s, 2H, Ar-CH_2-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.2, 144.7, 138.7, 134.1, 132.2, 131.4, 131.0, 130.1, 128.9, 128.3, 128.2, 124.8, 123.0, 118.6, 118.0, 116.16, 113.4, 112.9, 29.6; **IR** (neat)/ν_{max} 2953, 2927, 2230, 1735, 1503, 1483, 1446, 1391, 1359, 878, 752, 730, 701, 686; **HRMS (ESI)** calculated for $C_{21}H_{15}N_3$, $[M+H]^+$ is 310.1339 (100%), 311.1372 (25%), found 310.1337 (100%), 311.1370 (25%).

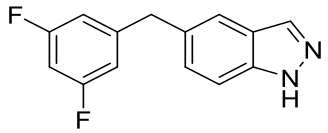
5-(3,5-Difluorobenzyl)-1-methyl-1H-indazole (6bk)



General Procedure G was followed, using 1-(bromomethyl)-3,5-difluorobenzene (52 µL, 0.40 mmol, 2.0 equiv.), 5-bromo-1-methyl-1H-indazole (42.2 mg, 0.20 mmol, 1.0 equiv.), β-nitrile sulfinate (62.1 mg, 0.44 mmol, 2.2 equiv.) and DMSO (1.0 mL, 0.2 M). The crude residue was purified by column chromatography (10 – 40% EtOAc in petrol) to give the product as an off-white solid (46.4 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 1.0 Hz, 1H, Het-*H*), 7.51 (dq, *J* = 1.5, 1.0 Hz, 1H, Het-*H*), 7.34 (dt, *J* = 8.5, 1.0 Hz, 1H, Het-*H*), 7.19 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 6.73 – 6.67 (m, 2H, 2 × Ar-*H*), 6.64 (tt, *J* = 9.0, 2.5 Hz, 1H, Ar-*H*), 4.06 (s, 3H, -N-*CH_3*), 4.05 (s, 2H, Ar-*CH_2*-Het); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.2 (dd, *J* = 248.0, 13.0 Hz), 145.7 (t, *J* = 9.0 Hz), 139.1, 132.6, 131.7, 127.9, 124.5, 120.8, 111.7 (dd, *J* = 18.0, 6.5 Hz), 109.4, 101.7 (t, *J* = 25.5 Hz), 41.5 (t, *J* = 2.0 Hz), 35.7; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -110.31; **MP** (CH_2Cl_2) 74 °C; **IR** (neat)/ν_{max} 3090, 3047, 2929, 2852, 1623, 1594, 1509, 1458, 1321, 1225, 1116, 993, 843, 803, 716; **HRMS (ESI)** calculated for $C_{15}H_{13}F_2N_2$, $[M+H]^+$ is 259.1041 (100%), 260.1075 (15%), found 259.1041 (100%), 260.1075 (15%).

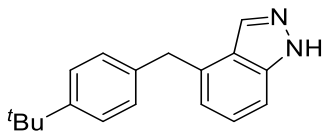
5-(3,5-Difluorobenzyl)-1H-indazole (6bl)



General Procedure G was followed, using 1-(bromomethyl)-3,5-difluorobenzene (39 µL, 0.30 mmol, 1.5 equiv.), 5-bromo-1H-indazole (39.4 mg, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude residue was first purified by column chromatography (10 – 50 % EtOAc in petrol) to give the product as an impure off-white solid. This resulting solid was further purified by preparative TLC (40% EtOAc in toluene) to give the product as a white solid (21.7 mg, 44%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H, N*H*), 8.06 (s, 1H, Het-*H*), 7.56 (d, *J* = 1.0 Hz, 1H, Het-*H*), 7.46 (d, *J* = 9.0 Hz, 1H, Het-*H*), 7.21 (dd, *J* = 8.5, 1.5 Hz, 1H, Het-*H*), 6.71 (dt, *J* = 7.0, 2.0 Hz, 2H, 2 × Ar-*H*), 6.65 (tt, *J* = 9.0, 2.0 Hz, 1H, Ar-*H*), 4.06 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.2 (dd, *J* = 248.5, 13.0 Hz), 145.5 (t, *J* = 9.0 Hz), 139.3, 134.6, 132.5, 128.7, 123.7, 120.6, 111.8 (dd, *J* = 18.5, 6.5 Hz), 110.3, 101.8 (t, *J* = 25.5 Hz), 41.6 (t, *J* = 2.0 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -110.25; **MP** (CH_2Cl_2) 45 – 47 °C; **IR** (neat)/ν_{max} 3196, 3157, 3055, 2918, 2849, 1625, 1595, 1509, 1459, 1437, 1354, 1318, 1116, 994, 953, 844, 764; **HRMS (ESI)** calculated for $C_{14}H_{11}N_2F_2$, $[M+H]^+$ is 245.0885 (100%), 246.0918 (15%), found 245.0885 (100%), 246.0919 (15%).

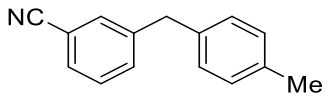
4-(4-(Tert-butyl)benzyl)-1H-indazole (6bm)



General Procedure G was followed, using 4-*tert*-butylbenzyl bromide (55 µL, 0.30 mmol, 1.5 equiv.), 4-bromo-1H-indazole (39.4 mg, 0.20 mmol, 1.0 equiv.) and β-nitrile sulfinate (46.6 mg, 0.33 mmol, 1.65 equiv.). The crude residue was first purified by column chromatography (10 – 30% EtOAc in petrol) to give the product as an impure yellow oil (32.8 mg). This resulting solid was resubmitted to column chromatography (20 – 40% Et_2O in petrol) to give the product as a pale yellow solid (24.2 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H, N*H*), 8.13 (s, 1H, Het-*H*), 8.05 (s, 1H, Het-*H*), 7.36 (d, *J* = 6.5 Hz, 1H, Het-*H*), 7.32 – 7.29 (m, 2H, 2 × Ar-*H*), 7.18 (d, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 6.98 (dd, *J* = 6.5, 1.0 Hz, 1H, Het-*H*), 4.28 (s, 2H, C*H*$_2$), 1.30 (s, 9H, 3 × C*H*$_3$); **^{13}C NMR (**101 MHz, $CDCl_3$) δ 149.3, 137.1, 134.9, 128.6, 127.9, 127.4, 125.6, 124.1, 121.3, 109.1, 108.0, 39.2, 34.5, 31.5; **MP** (CH_2Cl_2) 106 – 110 °C; **IR** (neat)/ν_{max} 3175, 2962, 2905, 2866, 1619, 1515, 1390, 1356, 1203, 947, 918, 841, 776, 749; **HRMS (ESI)** calculated for $C_{18}H_{20}N_2$, $[M+H]^+$ is 265.1699, found 265.1700.

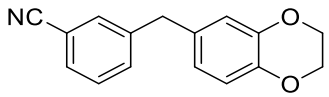
3-(4-Methylbenzyl)benzonitrile (6bn)



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), 4-bromotoluene (34.2 mg, 0.20 mmol, 1.0 equiv.) and β-nitrile sulfinate (46.6 mg, 0.33 mmol, 1.65 equiv.). The crude residue was purified by column chromatography (10 – 30% EtOAc in petrol) to give the product as a white crystalline solid (34.2 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.34 (m, 4H, 4 × Ar-*H*), 7.14 (d, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 7.06 (d, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 3.97 (s, 2H, Ar-C*H*$_2$-Ar), 2.34 (s, 3H, Ar-C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1, 136.5, 136.4, 133.5, 132.4, 130.0, 129.6, 129.3, 128.9, 119.1, 112.6, 41.1, 21.1; **MP** (CH_2Cl_2) 49 – 50 °C; **IR** (neat)/ν_{max} 3023, 2922, 2229, 1600, 1583, 1514, 1483, 1436, 793, 751, 688; **HRMS (ESI)** calculated for $C_{15}H_{14}N$, $[M+H]^+$ is 208.1121 (100%), found 208.1122 (100%).

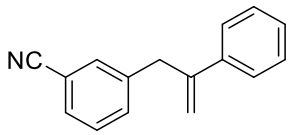
3-((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)methyl)benzonitrile (6bo)



General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), 6-Bromo-1,4-benzodioxane (27 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude residue was purified by column chromatography (5 – 30% EtOAc in petrol) to give the product as a clear oil (50.2 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dt, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.46 – 7.34 (m, 3H, 3 × Ar-*H*), 6.80 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.66 – 6.59 (m, 2H, 2 × Ar-*H*), 4.24 (s, 4H, 2 × Ar-OCH_2), 3.89 (s, 2H, Ar-CH_2-Ar); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1, 136.5, 136.4, 133.5, 132.4, 130.0, 129.6, 129.3, 128.9, 119.1, 112.6, 41.1, 21.1; **IR** (neat)/ν_{max} 3023, 2922, 2229, 1600, 1583, 1514, 1483, 1436, 793, 751, 688; **HRMS (ESI)** calculated for $C_{15}H_{14}N$, $[M+H]^+$ is 208.1121 (100%), found 208.1122 (100%).

3-(2-Phenylallyl)benzonitrile (6bp)

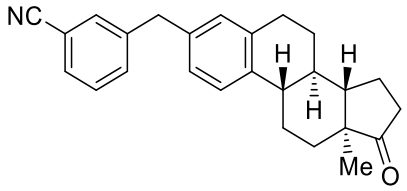


General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), α-bromostyrene (26 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude residue was purified by column chromatography (5 – 20% EtOAc in pentane) to give the title product as a yellow oil (14.7 mg, 34%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 1.5 Hz, 1H, Ar-*H*), 7.49 – 7.44 (m, 2H, 2 × Ar-*H*), 7.41 – 7.27 (m, 6H, 6 × Ar-*H*), 5.54 (d, *J* = 1.5 Hz, 1H, C*H*H'), 5.06 (q, *J* = 1.5 Hz, 1H, CH*H*'), 3.87 (s, 2H, Ar-CH_2-R); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.9, 141.2, 140.0, 133.5, 132.5, 130.2, 129.3, 128.6, 128.0, 126.2, 119.1, 115.6, 112.6, 41.3; **IR** (neat)/ν_{max} 3062, 2917, 2849, 2230, 1600, 1484, 1448, 1261, 800, 763, 701.

The data is consistent with the literature.[266]

3-(((8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)methyl)benzonitrile (6bq)

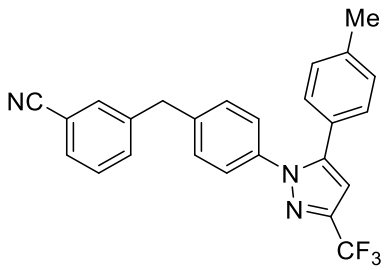


Desulfinative cross-couplings

General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.) and estrone triflate (3-trifluoromethylsulfonate-estra-1,3,5(10)-triene-17-one) (80.5 mg, 0.20 mmol, 1.0 equiv.) and β-nitrile sulfinate (42.3 mg, 0.30 mmol, 1.5 equiv.). The crude residue was purified by column chromatography (10 – 40% Et_2O in petrol) to give the title product as a colourless oil (72.2 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dt, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.45 (dd, *J* = 6.0, 1.5 Hz, 2H, 2 × Ar-*H*), 7.38 (dd, *J* = 8.5, 7.5 Hz, 1H, Ar-*H*), 7.24 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.95 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar-*H*), 6.89 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 3.94 (s, 2H, Ar-*CH_2*-Ar), 2.89 (dd, *J* = 8.5, 4.0 Hz, 2H, Ar-*CH_2*-CH_2-), 2.56 – 2.45 (m, 1H, -CO-*C(H')*H-), 2.46 – 2.37 (m, 1H, Ar-*CH*(CHR_2)CH_2-), 2.29 (dq, *J* = 10.5, 4.5 Hz, 1H, -CO-*C*H'*(H")*-), 2.21 – 1.89 (m, 4H, -CO-CH'(H")-*CH'(H")*, Ar-CH(CHR_2)CH-*C*H'*(H")*-*C*H'*(H")*-), 1.71 – 1.37 (m, 6H, Ar-CH(CHR_2)CH-*CH'*(H")-*CH'*(H")-, Ar--CH_2-*CH_2*-, CO-CH'(H")-CH'(H")-*CH*R-*CH*R-), 0.92 (s, 3H, Alk-*CH_3*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 220.9, 142.9, 138.3, 137.1, 137.0, 133.5, 132.5, 130.0, 129.6, 129.3, 126.4, 125.9, 119.1, 112.6, 50.6, 48.1, 44.4, 41.1, 38.2, 36.0, 31.7, 29.5, 26.6, 25.8, 21.7, 14.0; **IR** (neat)/ν_{max} 2928, 2859, 2228, 1736, 1500, 1482, 1454, 1435, 1259, 1084, 1053, 1008, 735, 690; **HRMS (ESI)** calculated for $C_{26}H_{28}ON$, $[M+H]^+$ is 370.2165, found 370.2166; **$[\alpha]_D^{25}$** = +110.7° (*c* = 1.0, $CHCl_3$).

3-(4-(5-(*p*-Tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)benzonitrile (6br)

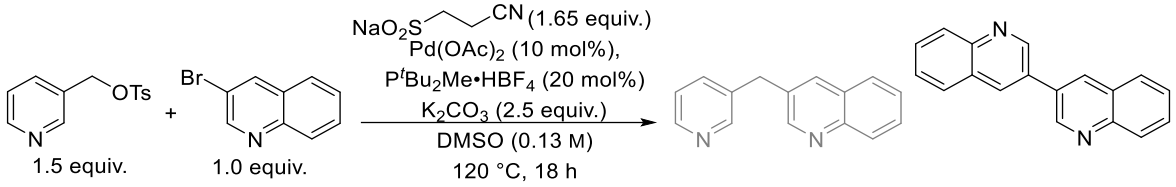


General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.) and 1-(4-bromophenyl)-4-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazole (76.2 g, 0.20 mmol, 1.0 equiv.) and β-nitrile sulfinate (42.3 mg, 0.30 mmol, 1.5 equiv.). The crude reaction mixture was purified by column chromatography (10 – 50% Et_2O in petrol) to give the title product as a colourless oil (82.5 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 1H, Ar-*H*), 7.42 (*app.* s, 1H, Ar-*H*), 7.41 – 7.37 (m, 2H, 2 × Ar-*H*), 7.27 (app. d, *J* = 8.5 Hz, 2H, 2 × Ar-*H*), 7.16 – 7.09 (m, 6H, 6 × Ar-*H*), 6.71 (s, 1H, Het-*H*), 4.02 (s, 2H, Ar-*CH_2*-Ar), 2.36 (s, 3H, Ar-*CH_3*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.9, 143.3 (q, *J* = 38.0 Hz), 141.9, 139.9, 139.3, 138.1, 133.5, 132.4, 130.3, 129.7, 129.53, 129.49, 128.7, 126.3, 125.9, 121.4 (q, *J* = 268.5 Hz), 118.9, 112.8, 105.4 (q, *J* = 2.0 Hz), 40.9, 21.4; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.16; **IR** (neat)/ν_{max} 3000, 2910, 2230, 1746, 1509, 1473, 1235, 1160, 1131, 1097, 978, 809, 791; **HRMS (ESI)** calculated for $C_{25}H_{19}N_3F_3$, $[M+H]^+$ is 418.1526, found 418.1523.

7.4.3. Side-products

3,3'-Biquinoline (9a)

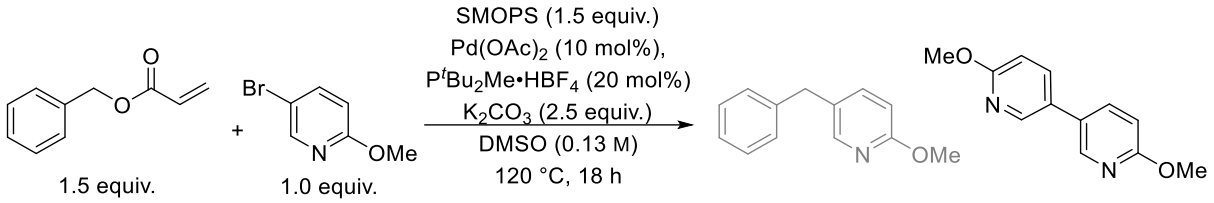


General Procedure G was followed, using 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), pyridin-3-ylmethyl 4-methylbenzenesulfonate (79.0 mg, 0.30 mmol, 1.5 equiv.) and β-nitrile sulfinate (46.6 mg, 0.33 mmol, 1.65 equiv.). The crude reaction mixture was purified by column chromatography (10 – 30% EtOAc in petrol) to give the title product as a pale yellow solid (21.5 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (d, *J* = 2.5 Hz, 2H, 2 × Het-*H*), 8.47 (d, *J* = 2.5 Hz, 2H, 2 × Het-*H*), 8.19 (d, *J* = 8.5 Hz, 2H, 2 × Het-*H*), 7.96 (d, *J* = 8.5 Hz, 2H, 2 × Het-*H*), 7.79 (t, *J* = 7.5 Hz, 2H, 2 × Het-*H*), 7.64 (t, *J* = 7.5 Hz, 2H, 2 × Het-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.6, 147.8, 134.0, 130.9, 130.2, 129.5, 128.3, 128.1, 127.6; **LRMS** (ESI, *m/*z) calculated for $C_{18}H_{13}N_2$ $[M+H]^+$ is 257.1, found 257.1.

Data is in accordance with the literature.[267]

6,6'-Dimethoxy-3,3'-bipyridine (9b)

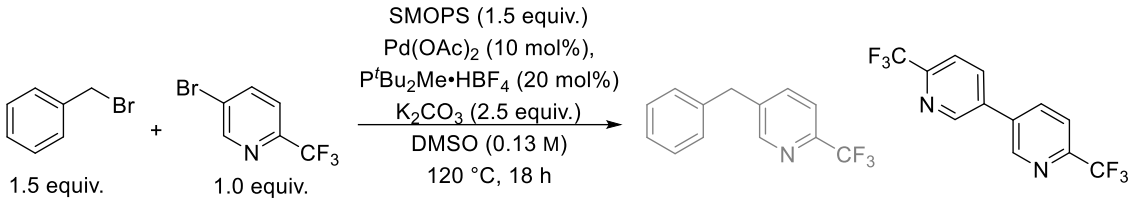


General Procedure G was followed, using benzyl acrylate (46 µL, 0.30 mmol, 1.5 equiv.), 5-bromo-2-methoxypyridine (26 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude reaction mixture was purified by column chromatography (2 – 10% EtOAc in petrol) to give the title product as a white solid (22.4 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 2.5, 1.0 Hz, 2H, 2 × Het-*H*), 7.72 (dd, *J* = 8.5, 2.5 Hz, 2H, 2 × Het-*H*), 6.83 (dd, *J* = 8.5, 1.0 Hz, 2H, 2 × Het-*H*), 3.98 (s, 6H, 2H, 2 × O*C*H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.8, 144.6, 137.3, 127.1, 111.3, 53.8; **LRMS** (ESI, *m/*z) calculated for $C_{12}H_{13}O_2N_2$ $[M+H]^+$ is 217.1 found 217.0.

Data is in accordance with the literature.[268]

6,6'-Bis(trifluoromethyl)-3,3'-bipyridine (9c)

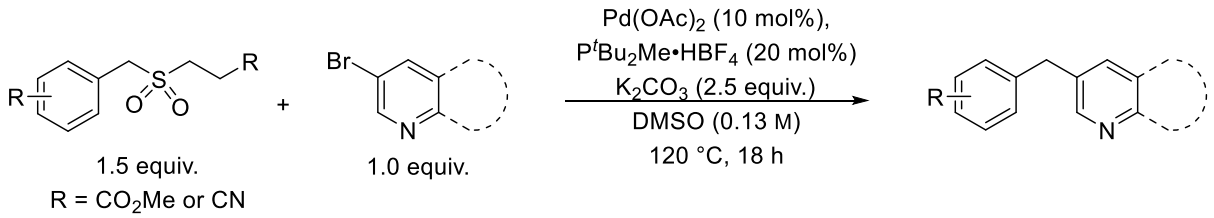


General Procedure G was followed, using benzyl bromide (36 µL, 0.30 mmol, 1.5 equiv.), 5-bromo-2-(trifluoromethyl)pyridine (45.2 mg, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude reaction mixture was purified by column chromatography (5 – 10% EtOAc in petrol) to give the title product as a white solid (4.3 mg, 15%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, *J* = 2.0 Hz, 2H, 2 × Het-*H*), 8.13 – 8.08 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 2H, 2 × Het-*H*), 7.86 (dd, *J* = 8.0, 1.0 Hz, 2H, 2 × Het-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.7 (q, *J* = 35.0 Hz), 148.6, 136.2, 135.2, 121.0 (q, *J* = 3.0 Hz), 120.9 (q, *J* = 273.5 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -67.95; **LRMS** (ESI, *m/*z) calculated for $C_{12}H_7F_6N_2$ $[M+H]^+$ is 293.1 found 293.0.

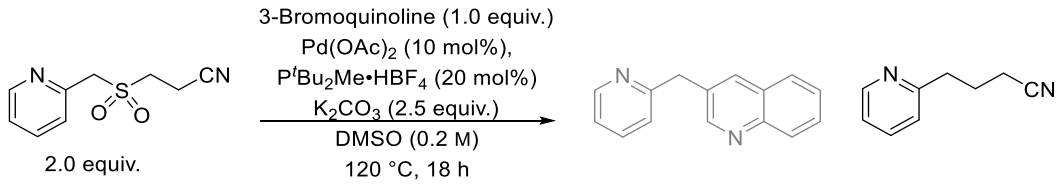
Data is in accordance with the literature.[269]

General Procedure H



To a 10 mL microwave vial equipped with a stirrer bar was added, benzyl sulfone (0.30 mmol, 1.5 equiv.), potassium carbonate (69.1 mg, 0.50 mmol, 2.5 equiv.), $Pd(OAc)_2$ (4.5 mg, 10 mol%) and $P^tBu_2Me{\cdot}HBF_4$ (9.9 mg, 20 mol%). The vial was sealed with a microwave vial cap, evacuated under vacuum (<1 mbar) and back-filled with nitrogen gas. This cycle was repeated a further two times. Addition of 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and DMSO (1.5 mL, 0.13 M) followed. The reaction was heated to 120 °C for 18 h before being cooled to room temperature. The reaction mixture was filtered through a pad of celite, rinsed thoroughly with EtOAc (50 mL) and the solvents were removed under reduced pressure. If the product was highly polar, 15 mL EtOAc was added to the crude residue and this was then washed with 5% aqueous LiCl solution (3 × 8 mL) to draw the DMSO into the aqueous layer. The aqueous washings were discarded. The organic layer was dried over $MgSO_4$, before removal of the solvents under reduced pressure. The resulting crude material was purified by silica gel chromatography to give the desired cross-coupled product.

4-(Pyridin-2-yl)butanenitrile (10a)

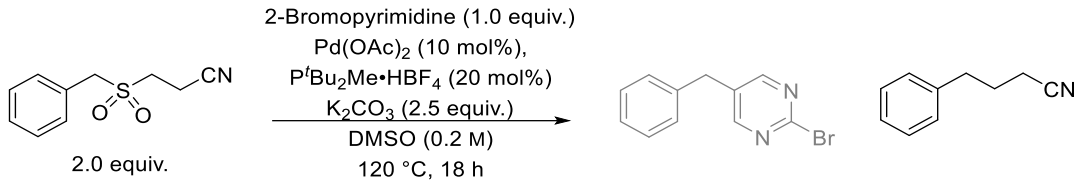


General Procedure H was followed, using 3-((pyridin-2-ylmethyl)sulfonyl)propanenitrile (84.1 mg, 0.40 mmol, 2.0 equiv.) and DMSO (1.0 mL, 0.2 M). The crude reaction mixture was purified by silica gel column chromatography (10 – 30% EtOAc in petrol) to give the title product as a yellow oil (4.5 mg, 15%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, Het-*H*), 7.62 (td, *J* = 7.5, 2.0 Hz, 1H, Het-*H*), 7.18 (d, *J* = 8.5 Hz, 1H, Het-*H*), 7.16 – 7.13 (m, 1H, Het-*H*), 2.95 (t, *J* = 7.5 Hz, 2H, C*H*$_2$), 2.40 (t, *J* = 7.0 Hz, 2H, C*H*$_2$), 2.19 – 2.10 (tt, *J* = 7.5, 7.0 Hz, 2H, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.7, 149.7, 136.8, 123.35, 122.0, 121.8, 36.6, 25.1, 16.7; **LRMS** (ESI, *m/*z) calculated for $C_{19}H_{11}N_2$ $[M+H]^+$ is 147.1 found 147.0.

Data is in accordance with the literature.[270]

4-Phenylbutanenitrile (10b)

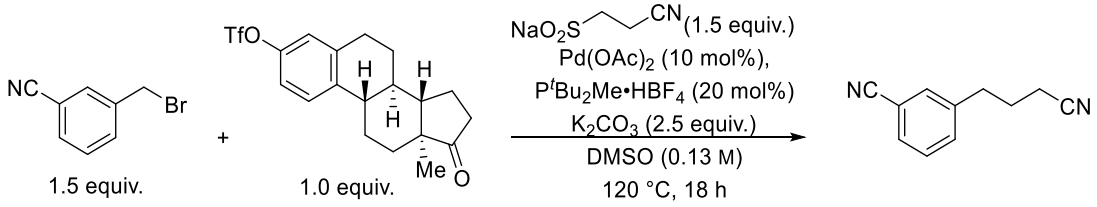


General Procedure H was followed, using 3-(benzylsulfonyl)propanenitrile (83.7 mg, 0.40 mmol, 2.0 equiv.), 2-bromopyrimidine (31.8 mg, 0.20 mmol, 1.0 equiv.), potassium carbonate (41.5 mg, 0.30 mmol, 1.5 equiv.), and DMSO (1.0 mL, 0.2 M). The crude reaction mixture was purified by silica gel column chromatography (10 – 50% EtOAc in petrol) to give the title product as a colourless oil (6.8 mg, 11% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H, 2 × Ar-*H*), 7.26 – 7.16 (m, 3H, 3 × Ar-*H*), 2.78 (t, *J* = 7.5 Hz, 2H, C*H*$_2$), 2.32 (t, *J* = 7.5 Hz, 2H, C*H*$_2$), 1.99 (p, *J* = 7.5 Hz, 2H, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.9, 128.8, 128.6, 126.7, 119.6, 34.5, 27.1, 16.5.

Data is in accordance with the literature.[271]

3-(3-Cyanopropyl)benzonitrile (10c)

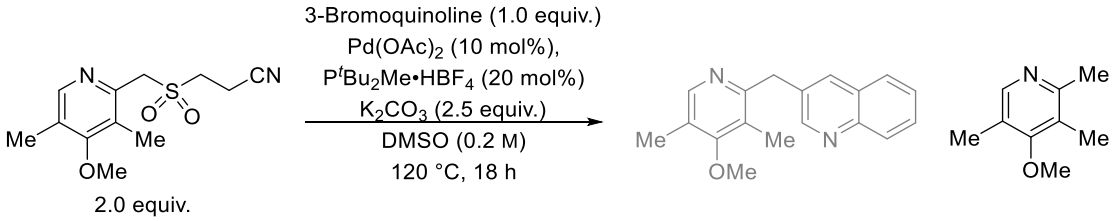


General Procedure G was followed, using 3-(bromomethyl)benzonitrile (58.8 mg, 0.30 mmol, 1.5 equiv.), estrone triflate (3-trifluoromethylsulfonate-estra-1,3,5(10)-triene-17-one) (80.5 mg, 0.20 mmol, 1.0 equiv.) and β-nitrile sulfinate (42.3 mg, 0.30 mmol, 1.5 equiv.). The crude residue was purified by column chromatography (10 – 40% Et_2O in petrol) to give the title product as a yellow oil (8.2 mg, 16% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.52 (m, 1H, Ar-*H*), 7.50 – 7.48 (m, 1H, Ar-*H*), 7.47 – 7.42 (m, 2H, 2 × Ar-*H*), 2.84 (t, *J* = 7.5 Hz, 2H, C*H*$_2$), 2.36 (t, *J* = 7.0 Hz, 2H, C*H*$_2$), 2.00 (tt, *J* = 7.5, 7.0 Hz, 2H, C*H*$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.3, 133.2, 132.0, 130.6, 129.7, 119.1, 118.8, 113.0, 34.1, 26.7, 16.7; **LRMS** (ESI, *m/*z) calculated for $C_{11}H_{11}N_2$ $[M+H]^+$ is 171.1 found 171.0.

Data is in accordance with the literature.[271]

4-Methoxy-2,3,5-trimethylpyridine (11a)

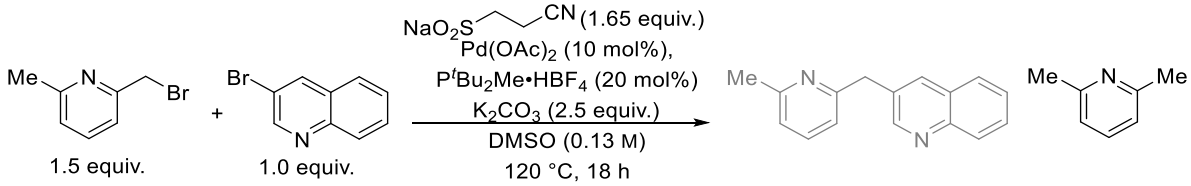


General Procedure H was followed, using 3-(((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)sulfonyl)propanenitrile (107 mg, 0.40 mmol, 2.0 equiv.) and DMSO (1.0 mL, 0.2 M). The crude reaction mixture was purified by silica gel column chromatography (10 – 40% EtOAc in petrol) to give the title product as a yellow oil (45.7 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H, Het-*H)*, 3.72 (s, 3H, OC*H*$_3$), 2.44 (s, 3H, C*H*$_3$), 2.20 (s, 3H, C*H*$_3$), 2.17 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.8, 157.0, 148.5, 124.4, 124.0, 59.9, 22.5, 13.3, 11.7; **LRMS** (ESI, *m/*z) calculated for $C_9H_{14}NO$ $[M+H]^+$ is 152.1 found 152.2.

Data is in accordance with the literature.[272]

2,6-Dimethylpyridine (11b)

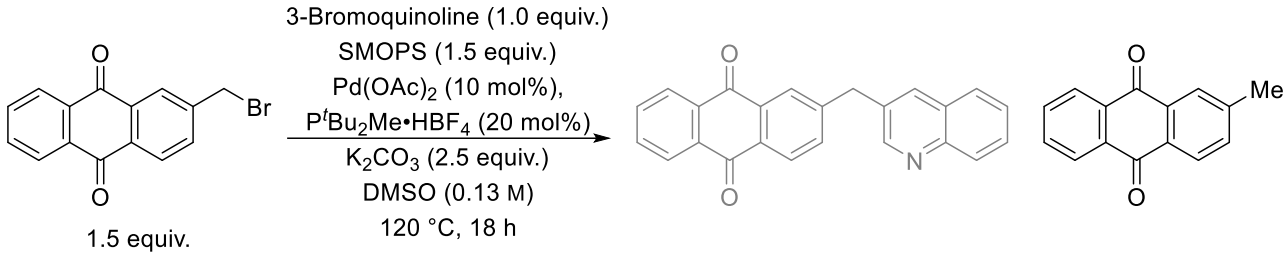


General Procedure G was followed, using 2-(bromomethyl)-6-methylpyridine (55.8 mg, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and β-nitrile sulfinate (46.6 mg, 0.33 mmol, 1.65 equiv.). The crude reaction mixture was purified by column chromatography (10 – 30% EtOAc in petrol) to give the title product as a colourless oil (5.6 mg, 17%).

^{1}H NMR (400 MHz, $CDCl_3$) δ7.45 (t, *J* = 7.5 Hz, 1H, Het-*H*), 6.95 (d, *J* = 7.5 Hz, 2H, 2 × Het-*H*), 2.52 (s, 6H, 2 × C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.7, 136.8, 120.3, 24.5; **LRMS** (ESI, *m/*z) calculated for $C_7H_{10}N$ $[M+H]^+$ is 108.1 found 108.2.

Data is in accordance with the literature.[273]

2-Methylanthracene-9,10-dione (11c)

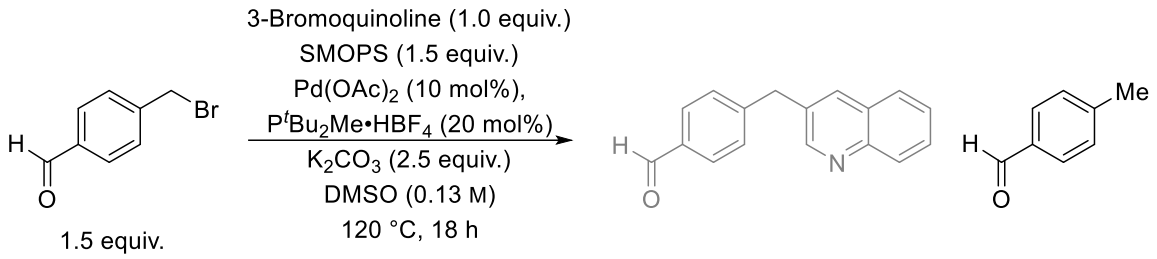


General Procedure G was followed, using 2-bromomethyl-anthraquinone (90.3 mg, 0.30 mmol, 1.5 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude residue was purified by column chromatography (5 – 40% EtOAc in petrol) to give the title product as a yellow solid (62.6 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.23 (m, 2H, 2 × Ar-*H*), 8.17 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.07 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.80 – 7.75 (m, 2H, 2 × Ar-*H*), 7.57 (ddd, *J* = 8.0, 4.0, 1.5 Hz, 1H, Ar-*H*), 2.51 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 183.5, 183.1, 145.4, 137.7, 135.0, 134.1, 134.0, 133.70, 133.66, 133.5, 127.6, 127.5, 127.3, 127.2, 22.0; **LRMS** (ESI, *m/*z) calculated for $C_{15}H_{11}O_2$ $[M+H]^+$ is 223.1 found 223.0.

Data is in accordance with the literature.[274]

4-Methylbenzaldehyde (11d)

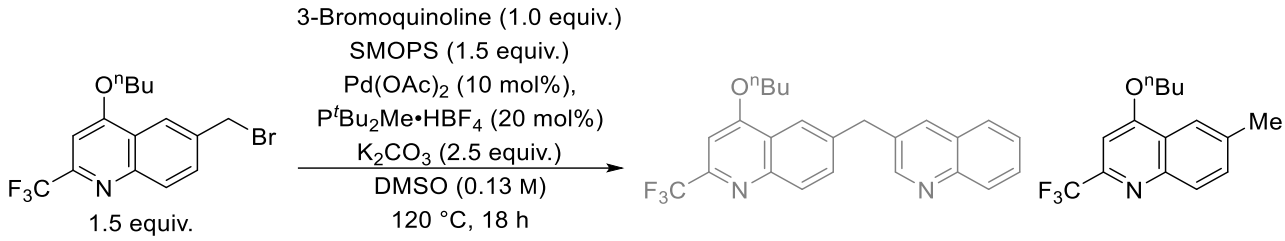


General Procedure G was followed, using 4-(Bromomethyl)benzaldehyde (59.7 mg, 0.30 mmol, 1.5 equiv.) and 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.) and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude residue was purified by column chromatography (15 – 30% EtOAc in petrol) to give the title product as a clear oil (6.7 mg, 19%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H, CO*H*), 7.78 (d, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 7.33 (d, *J* = 8.0 Hz, 2H, 2 × Ar-*H*), 2.44 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.2, 145.7, 134.4, 130.0, 129.9, 22.0; **LRMS** (ESI, *m/*z) calculated for C_8HO_2 $[M+H]^+$ is 121.1 found 121.0.

Data is in accordance with the literature.[275]

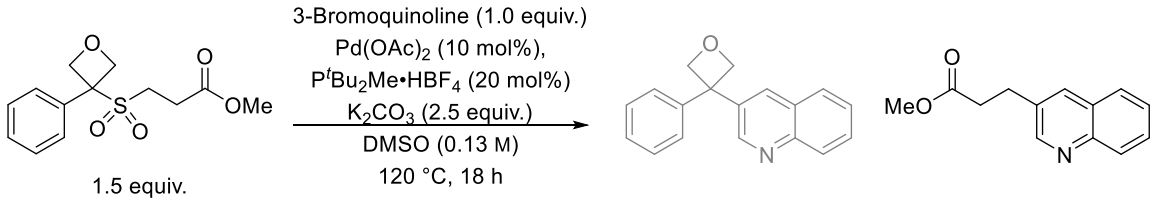
4-Butoxy-6-methyl-2-(trifluoromethyl)quinoline (11e)



General Procedure G was followed, using 6-(bromomethyl)-4-butoxy-2-(trifluoromethyl)quinoline (95 mg, 0.26 mmol, 1.3 equiv.), 3-bromoquinoline (27 µL, 0.20 mmol, 1.0 equiv.), and SMOPS (52.2 mg, 0.30 mmol, 1.5 equiv.). The crude residue was purified by column chromatography (20 – 30 % EtOAc in petrol) to give the product as a white solid (10.8 mg, 13%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.5 Hz, 1H, Het-*H*), 8.00 (s, 1H, Het-*H*), 7.62 (td, *J* = 8.5, 2.0 Hz, 1H, Het-*H*), 7.01 (s, 1H, Het-*H*), 4.26 (t, *J* = 6.5 Hz, 2H, CH_2), 2.57 (s, 3H, Ar-CH_3), 1.99 – 1.94 (m, 2H, CH_2), 1.65 – 1.59 (m, 2H, CH_2), 1.07 – 1.04 (t, *J* = 7.5 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1, 146.4 (q, *J* = 40.5 Hz), 141.2, 137.9, 133.4, 131.4 (q, *J* = 273.0 Hz), 129.3, 121.9, 120.9, 96.8, 69.0, 31.0, 22.0, 19.5, 14.0; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -67.53; **MP** (CH_2Cl_2) 70 – 72 °C; **IR** (neat)/ν_{max} 2960, 2876, 1577, 1375, 1281, 1182, 1136, 1094; **LRMS** (ESI, *m/*z) calculated for $C_{15}H_{17}NF_3O$ $[M+H]^+$ is 284.1 found 284.0; **HRMS (ESI)** calculated for $C_{15}H_{17}NF_3O$, $[M+H]^+$ is 284.1257 (100%), 285.1290 (18%), found 284.1256 (100%), 285.1291 (18%).

Methyl 3-(quinolin-3-yl)propanoate (14)



General Procedure H was followed, using methyl 3-((3-phenyloxetan-3-yl)sulfonyl)propanoate (**13d**) (85.3 mg, 0.30 mmol, 1.5 equiv.). The crude reaction mixture was purified by silica gel column chromatography (10 – 50% EtOAc in petrol) to give the title product as an impure yellow oil (3.3 mg, 8%).

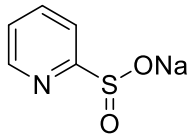
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H, Het-*H*), 8.23 (d, *J* = 8.5 Hz, 1H, Het-*H*), 8.15 (s, 1H, Het-*H*), 7.85 (dd, *J* = 8.5, 2.5 Hz, 1H, Het-*H*), 7.76 (t, *J* = 7.5 Hz, 1H, Het-*H*), 7.61 (t, *J* = 7.5 Hz, 1H, Het-*H*), 3.68 (s, 3H, OC*H*$_3$), 3.19 (t, *J* = 7.5 Hz, 2H, C*H*$_2$), 2.77 (t, *J* = 7.5 Hz, 2H, C*H*$_2$); **LRMS** (ESI, *m/*z) calculated for $C_{13}H_{14}NO_2$ $[M+H]^+$ is 216.1, found 216.1.

Data is in accordance with the literature.[276]

7.5. Chapter 5: Experimental procedures and data

7.5.1. Starting material synthesis

Sodium pyridine-2-sulfinate (15a)



A 1 L single-necked round-bottom flask is equipped with a magnetic stirrer bar (oval, Teflon-coated, 65 × 18 mm) and charged with methanol (450 mL), distilled water (56.2 mL) and sodium hydroxide (3.60 g, 90.0 mmol, 0.9 equiv.) (photo 1). The contents were stirred at ambient temperature for 25 minutes, until the Sodium hydroxide was completely dissolved, before cooling to 0 °C. 2-Mercaptopyridine (11.1 g, 100 mmol, 1.0 equiv.) was added in one portion at this temperature and the contents were stirred for 5 minutes until complete dissolution (photo 2). Hydrogen peroxide solution (17.3 mL of a 30% (w/w) aqueous solution, 180 mmol, 1.8 equiv.) was added dropwise at this temperature with constant stirring *via* dropping funnel over 30 minutes (photo 3). Once the hydrogen peroxide dropwise addition was complete, methanol (5 mL) was added to the dropping funnel. This was swirled around the funnel before being emptied into the reaction mixture (to ensure all hydrogen peroxide had been added). Stirring was continued at this temperature for 1 hour, before removal of the cooling bath. The solution was allowed to warm to ambient temperature, stoppered and stirred for a further 15 hours (photo 4). The resulting pale-yellow reaction mixture was tested with peroxide test strips, and showed complete consumption of hydrogen peroxide. Therefore, a quench step was not needed.* The solvents were removed on a rotary evaporator (bath temperature 45 °C, initially 180 mbar, then 40 mbar, 20 minutes). The resulting off-white mass was further co-evaporated

with toluene (3 × 100 mL) to remove residual water. Ethyl acetate (225 mL) was added to the residue and the mixture stirred at ambient temperature for one hour (stir bar: oval, Teflon-coated, 50 × 18 mm, photo 5). The heterogeneous mixture was vacuum filtered through a glass sintered-funnel (diameter 7 cm, depth 5 cm) into a 500 mL round-bottom flask. Any solid on the walls of the reaction flask was scraped off with a spatula, before rinsing the flask into the funnel with ethyl acetate (3 × 20 mL), ensuring complete transfer of all material to the sintered funnel. The pump was disconnected and the collected solids were stirred for 30 seconds with ethyl acetate (2 × 100 mL) before the pump was reconnected and the washings removed. The bright yellow filtrate (containing left over starting material) was discarded (photo 6). The collected solids were transferred to a 250 mL single-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar (oval, 50 × 18 mm). Isopropyl alcohol (150 mL) was added and the solids were stirred at ambient temperature for 30 minutes (photo 7). The heterogeneous mixture was vacuum filtered through a glass sintered-funnel (Porosity 3, 40 × 100 mm) into a 500 mL round-bottom flask (photo 8). The reaction flask was rinsed with isopropyl alcohol (3 × 45 mL), to ensure complete transfer of all material to the sintered funnel. The pump was then disconnected and the collected solids were stirred for 1 minute with isopropyl alcohol (100 mL) before the pump was reconnected and the washings removed. The filtrate was discarded and the solid transferred to a 50 mL tared round-bottomed flask and dried under high vacuum (<0.1 mbar) at ambient temperature until to a constant weight (overnight), to afford sodium pyridine-2-sulfinate as a white amorphous solid (14.0 g, 84.6 mmol, 94% yield, 99% ^{1}H NMR purity).

*If the peroxide test strip showed >0 ppm, then MnO_2 (5 mol%) was added to the reaction mixture. This was stirred for 30 minutes before vacuum filtration through celite. If the

reaction mixture appeared to still be contaminated with black MnO_2 particles, then the filtration was repeated through celite. The resulting reaction mixture was retested with a peroxide test strip to show that 0 ppm hydrogen peroxide remained. The next work up and purification steps followed as above.

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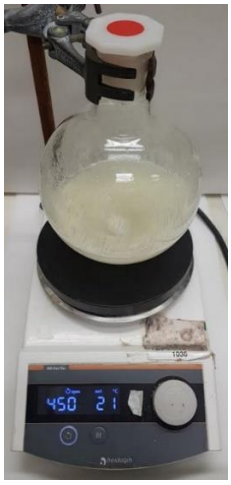
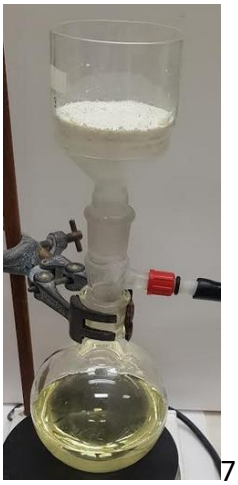
5. 
6. 
7. 
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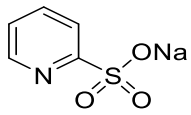
^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (ddd, *J* = 5.0, 1.5, 1.0 Hz, 1H, Het-*H*), 7.95 (td, *J* = 7.5, 1.5 Hz, 1H, Het-*H*), 7.88 (dt, *J* = 7.5, 1.0 Hz, 1H, Het-*H*), 7.41 (ddd, *J* = 7.5, 5.0, 1.5 Hz, 1H, Het-*H*); **^{13}C NMR** (101 MHz, CD_3OD) δ 174.6, 149.4, 139.4, 125.7, 118.9; **MP** (^{i}PrOH) 280 – 282 °C ; **IR** (neat)/ν_{max} 1578, 1422, 1048, 1035, 769; **LRMS** (ESI, *m/z*) calculated for $C_5H_4O_2S$, $[M-Na]^-$ is 142.0, found 142.1.

The data is consistent with the literature.[20]

Sodium pyridine-2-sulfonate (15b)



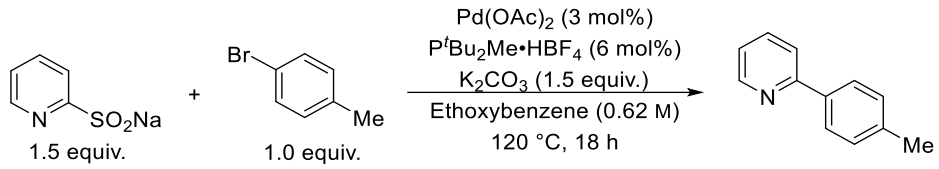
A 250 mL single-necked round-bottom flask, equipped with a magnetic stir bar, was charged with methanol (48.0 mL), distilled water (6.0 mL) and sodium hydroxide (360 mg, 9.0 mmol, 0.9 equiv.). The contents were stirred at ambient temperature for 5 minutes until complete dissolution, before cooling to 0 °C. 2-Mercaptopyridine (5.56 g, 50.0 mmol, 1.0 equiv.) was added in one portion at this temperature and the contents were stirred for 5 minutes until complete dissolution. Hydrogen peroxide solution (1.8 mL of a 30% (w/w) aqueous solution, 17.5 mmol, 1.75 equiv.) was added dropwise at this temperature with constant stirring *via* syringe over 5 minutes. Stirring was continued at this temperature for 1 hour, before removal of the cooling bath. The solution was allowed to warm to ambient temperature, stoppered and stirred for a further 15 hours. The reaction mixture was cooled to 0 °C, to control any exotherm and MnO_2 (5 mol%) was added in one portion to quench any excess hydrogen peroxide. The mixture was stirred for 30 minutes before filtration through celite. The solvents were removed on a rotary evaporator (bath temperature 45 °C, initially 100 mbar, then 40 mbar). The resulting off-white mass was further co-evaporated with toluene (3 × 40 mL) to remove residual water. Ethyl acetate (50 mL) was added to the residue and the mixture was stirred at ambient temperature for one hour. The heterogeneous mixture was vacuum filtered through a glass sintered-funnel into a 250 mL single-necked round-bottomed flask. The reaction flask was rinsed with ethyl acetate (3 × 10 mL) to ensure complete transfer of all material to the sintered funnel. The pump was disconnected and the collected solids are stirred for 1 minute in ethyl acetate (50 mL) before the pump was reconnected and the washings removed. The filtrate was discarded

and the collected solids were transferred to a 250 mL single-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar (oval, 35 × 15 mm). Isopropyl alcohol (50 mL) was added and the solids stirred at ambient temperature for 30 minutes. The heterogeneous mixture was vacuum filtered through a glass sintered-funnel (Porosity 3, 40 × 100 mm) into a 250 mL single-necked round-bottomed flask. The reaction flask was rinsed with isopropyl alcohol (3 × 10 mL) to ensure complete transfer of all material to the sintered funnel. The pump was disconnected and the collected solids were stirred for 1 minute in isopropyl alcohol (20 mL) before the pump was reconnected and the washings removed. The filtrate was discarded and the solid transferred to a tared vial and dried under high vacuum (<0.1 mbar) at ambient temperature until to a constant weight. The solid was then purified by column chromatography (dry loaded in celite, 10 – 50% methanol in acetone) to give two isolated products and one sample of mixed fractions. Sodium pyridine-2-sulfonate eluted from the column first and was given as an off-white solid (133 mg, 8% yield).

^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (d, *J* = 4.5 Hz, 1H, Het-*H*), 7.99 – 7.92 (m, 2H, 2 × Het-*H*), 7.49 (q, *J* = 4.5 Hz, 1H, Het-*H*); **^{13}C NMR** (101 MHz, CD_3OD) δ 162.5, 149.9, 139.3, 126.5, 122.2; **MP** (^{i}PrOH) 240 °C *decomp.*; **IR** (neat)/ν_{max} 1231, 1205, 1048; **LRMS** (ESI, *m/z*) calculated for $C_5H_4O_3S$, $[M\text{-}Na]^-$ is 158.0, found 158.0.

7.5.2. Desulfinative cross-couplings

2-(*p*-Tolyl)pyridine (16a)



To an oven-dried 250 mL two-neck round-bottom flask, equipped with a stirrer bar (oval, teflon coated, 18 mm × 50 mm), was added 4-bromotoluene (5.99 g, 35.0 mmol, 1.0 equiv.) (Note: melt 4-bromotoluene (MP = 26 °C to 29 °C) and directly pipette the liquid into the flask for ease when weighing out). Addition of the solid reagents followed: pyridine-2-sulfinate (8.67 g, 52.5 mmol, 1.5 equiv.), palladium(II) acetate (236 mg, 1.05 mmol, 3 mol%), di-*tert*-butyl(methyl)phosphonium tetrafluoroborate (521 mg, 2.10 mmol, 6 mol%), potassium carbonate (7.26 g, 52.5 mmol, 1.5 equiv.). The flask was placed into a 250 mL DrySyn® heating block. A condenser with a suba-seal® fitted to the top was connected to one-neck and a suba-seal® was fitted to the other. The condenser-flask joint and terminal suba-seal® were wrapped with parafilm. The flask was evacuated under vacuum (<1 mbar) for 2 minutes, then backfilled with nitrogen gas. This process was repeated two further times. Ethoxybenzene (56.5 mL) (Note: not purchased as anhydrous, so dried by 4 Å molecular sieves and degassed for a minimum of 6 hours on receipt. The solvent was degassed again for a minimum of 1 hour before use) was then added through the round-bottom flask neck fitted with a suba-seal®. A flow of nitrogen was connected through the suba-seal® at the top of the condenser. The reaction mixture was stirred at 45 °C for 15 mins, then heated to 130 °C for 20 minutes, and then 150 °C (internal reaction temperature, photo 1) for 18 hours (photo 2). Once the vessel had cooled to room temperature, the reaction mixture was filtered through a pad of celite and washed with

30% ethyl acetate in petrol (400 mL) into a 1 L round-bottom flask (photo 3). The solvents were concentrated under vacuum (bath temperature 45 °C, initially 180 mbar, then 25 mbar, 20 minutes) until just ethoxybenzene remained (photo 4). The reaction mixture was transferred to a 250 mL separating funnel and 80 mL isopropyl acetate was added. The organic layer was washed with brine (2 × 60 mL) to remove any remaining inorganic impurities (photo 5), and then the aqueous washings were discarded. The organic layer was then washed with an aqueous solution of HCl (3.0 M, 3 × 40 mL) to protonate the product and draw it into the aqueous phase, separating it from the solvent and organic impurities (photo 6). Brine was added (10 mL) after the final wash to ensure complete layer separation. The organic layer was discarded (containing ethoxybenzene and any remaining aryl bromide starting material). The acidic aqueous layers were combined into a 500 mL conical flask and an aqueous solution of sodium hydroxide was added (3.0 M, 140 mL) to basify the aqueous phase (reach pH 8 minimum, checked by pH paper), and return the product to the neutral form rather than the hydrochloride salt. The aqueous was then transferred to a 500 mL separating funnel (the conical flask was rinsed into the separating funnel with 10 mL isopropyl acetate and 10 mL water). The aqueous was extracted with isopropyl acetate (4 × 50 mL, photo 7). The organic layers were combined and transferred to a 500 mL separating funnel. The aqueous was discarded. The organic layer was then washed with 1% $CuSO_4 \cdot 5H_2O$ solution (3 × 60 mL) and the aqueous layers were discarded (photo 8). The organic layer was then washed with Na_2EDTA solution (1×10^{-4} M, 3 × 60 mL) to remove all remaining copper (photo 9). The organic layer was washed finally with brine (60 mL) and the aqueous layers were discarded. The organics were combined, dried over $MgSO_4$ before being transferred to a 500 mL round-bottom flask. The solvents were removed under reduced pressure (bath temperature 45 °C, initially 180 mbar, then 25

mbar, 20 minutes), resulting in 2-tolylpyridine as a dark-brown oil (5.57 g, 32.9 mmol, 94% yield, purity 91% by qNMR, photo 10).

Purification by column chromatography

A glass column fitted with a frit (length: 28 cm, diameter: 5 cm) was filled with a slurry of silica in petrol (90 g in 400 mL) and tightly packed by a flow of nitrogen gas (the silica filled the column up to 11 cm). To 2-tolylpyridine, as a dark-brown oil, was added 4.0 g celite and 25 mL DCM. The solvents were then removed under vacuum (40 °C, 700 mbar then 20 mbar, 20 minutes). The resulting sample was dry-loaded on the column, and a layer of sand (2.5 cm) was placed on top of the celite. The column was washed with petrol (400 mL) and the eluent was collected in a 500 mL conical flask (photo 11). The column was then washed with 15% ethyl acetate in petrol (800 mL), and the eluent was collected into 15 mL tubes (photo 12). The column was then washed with 25% ethyl acetate in petrol (400 mL, photo 13). The fractions containing the product (monitored by TLC) were combined and the tubes were rinsed out with ethyl acetate into a 1 L round-bottom flask. The solvents were removed under vacuum (45 °C, 550 mbar, 350 mbar, 100 mbar then 20 mbar, 40 minutes). The oil was transferred to a tared vial in $CHCl_3$. The solvents were removed under reduced pressure (45 °C, 350 mbar then 20 mbar, 20 minutes), followed by high vacuum (<1 mbar) until constant weight to give the product as a pale-yellow oil (5.25 g, 31.0 mmol, 89% yield, purity 99% by qNMR, photo 14).

Purification by HCl salt formation and recrystallisation

To a 100 mL round-bottom flask equipped with a stir bar was added 2-tolylpyridine (5.33 g, 31.5 mmol), given as a dark-brown oil, and methyl *tert*-butyl ether (50 mL, 10 solvent volumes) (photo 15). Hydrogen chloride solution 2.0 M in methyl *tert*-butyl ether (18.6 mL,

37.2 mmol, 1.2 equiv.) was added by syringe over 5 minutes. The mixture was stirred for 15 minutes, with the solution changing colour to a milky white (photo 16). Vacuum filtration (photo 17) of the mixture through a fritted funnel (porosity 3) followed by washes with methyl *tert*-butyl ether (50 mL) and ethyl acetate (50 mL), afforded the 2-tolylpyridine HCl salt as a light brown amorphous solid (photo 18). The filtrate was discarded. The solids were transferred to a 100 mL flask, and any remaining solvents were removed under vacuum on a rotary evaporator (45 °C, 10 mbar, 15 minutes). The salt was formed in quantitative yield (6.48 g, 31.5 mmol). A stir bar was added to the flask, isopropyl alcohol (30 mL) was added, and the vessel was placed in a heating block on a stirrer-hot plate, set to 95 °C (photo 19). Further isopropyl alcohol (10 mL, then 7 mL) was added to ensure complete dissolution of the solid. The round-bottom flask was then removed from heat, and left at room temperature for crystallisation to occur. Within 30 minutes a considerable amount of crystals had already formed (photo 20), however the flask was left for a further 12 hours before filtration to ensure completion. The white crystals were isolated by vacuum filtration, with a filter funnel fitted with a frit (porosity: 3), into a 500 mL round-bottom flask (photo 21 and 22). The crystals were washed with ethyl acetate (2 × 50 mL) before transferring them to a tared vial. The filtrate was not discarded. Instead, the solvents were removed under vacuum and, on the resulting solid, the recrystallisation process was repeated again. The crystals obtained from the second batch were darker in colour (photo 23), however, both batches were shown to have a purity of 99% by qNMR analysis. The total recrystallised 2-tolyl pyridine hydrochloride salt was 6.38 g (31.1 mmol, 99% yield).

Next, the combined crystals (6.38 g, 31.1 mmol) were transferred to a to a 100 mL separating funnel, and water was added (30 mL). Isopropyl acetate (30 mL) was added, and

then aqueous sodium hydroxide solution (3.0 M, 15.5 mL, 46.5 mmol, 1.5 equiv.) was added, to return the HCl salt to 2-tolylpyridine. The layers were separated and the organic layer was removed. The aqueous was further extracted with isopropyl acetate (2 × 30 mL) (photo 24). The organics were combined into a 250 mL conical flask and dried over $MgSO_4$. The solids were removed by gravimetric filtration into a 250 mL round-bottom flask. The solvents were removed under vacuum on a rotary evaporator (bath temperature 45 °C, 120 mbar, then 10 mbar, 30 minutes). The oil was transferred to a tared 25 mL round-bottom flask in $CHCl_3$ and the solvents were removed under vacuum (bath temperature 45 °C, 350 mbar then 10 mbar). The product was then dried under high vac (<1 mbar) until constant weight, to afford 2-tolyl pyridine as a brown oil (5.21 g, 30.8 mmol, 88% yield) (photo 25).

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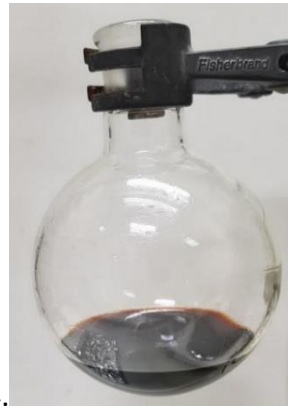
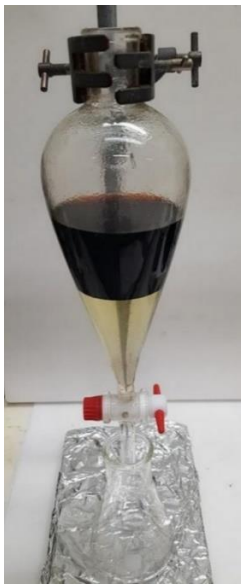
4. 

5. 
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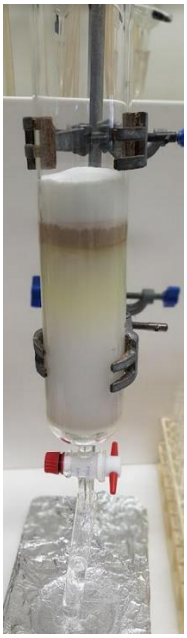
13. 
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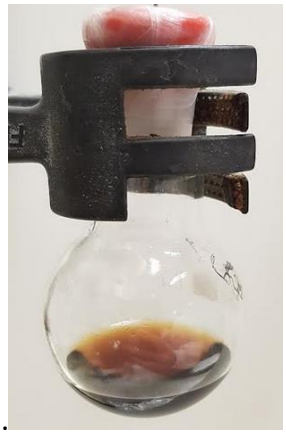
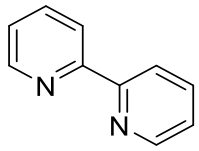
25. 

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 – 8.67 (m, 1H, Het-*H*), 7.92 – 7.89 (m, 2H, 2 × Ar-*H*), 7.76 – 7.69 (m, 2H, 2 × Het-*H*), 7.29 (dt, *J* = 7.5, 1.0 Hz, 2H, 2 × Ar-*H*), 7.20 (ddd, *J* = 6.5, 5.0, 2.0 Hz, 1H, Het-*H*), 2.41 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.5, 149.6, 139.2, 136.9, 136.6, 129.6, 126.9, 121.9, 120.4, 21.4; **BP** 310 °C; **IR** (neat)/ν_{max} 3050, 1588, 1467, 773; **LRMS** (ESI, *m/z*) calculated for $C_{12}H_{12}N$, $[M+H]^+$ is 170.1, found 170.0 $[M+H]^+$.

The data is consistent with the literature.[277]

2,2'-Bipyridine (16b)



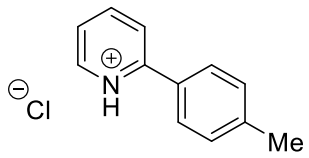
To a 50 mL two-neck round-bottom flask equipped with a stirrer bar, was added 4-bromotoluene (melted, 1.71 g, 10.0 mmol, 1.0 equiv.) by pipette. Addition of the solid reagents followed: pyridine-2-sulfinate (2.48 g, 15.0 mmol, 1.5 equiv.), palladium(II) acetate (67.4 mg, 0.3 mmol, 3 mol%), di-*tert*-butyl(methyl)phosphonium tetrafluoroborate (149 mg, 0.6 mmol, 6 mol%), potassium carbonate (2.07 g, 15.0 mmol, 1.5 equiv.). The flask was placed into a 50 mL DrySyn® heating block. A condenser with a suba-seal® fitted to the top was connected to single-neck and a suba-seal® was fitted to the other. The condenser-flask joint and terminal suba-seal® were wrapped with parafilm. The flask was evacuated under vacuum (<1 mbar) for 5 minutes, then backfilled with nitrogen gas. This process was repeated two further times. Ethoxybenzene (16.25 mL, anhydrous) was then added through the round-bottom flask neck fitted with a suba-seal®. A flow of nitrogen was connected through the suba-seal® at the top of the condenser. The reaction mixture was stirred at room temperature for 5 mins, then heated to 130 °C for 20 minutes, and then 150 °C for 20 hours. Once the vessel had cooled to room temperature, the reaction mixture was filtered through a pad of celite and washed with ethyl acetate (100 mL) into a 250 mL round-bottom flask. The solvents were concentrated under vacuum until just ethoxybenzene remained (bath temperature 45 °C, initially 180 mbar, then 25 mbar, 20 minutes). The reaction mixture was transferred to a 100 mL separating funnel and 20 mL isopropyl acetate was added. The organic layer was washed with brine (2 × 20 mL) to remove any remaining inorganic impurities, and then the aqueous washings were

discarded. The organic layer was then washed with an aqueous solution of HCl (3.0 M, 3 × 10 mL) to protonate the product and draw it into the aqueous phase, separating it from the solvent and organic impurities. Brine was added (10 mL) after the final wash to ensure complete layer separation. The organic layer was discarded (containing ethoxybenzene and any remaining aryl bromide starting material). The acidic aqueous layers were combined into a 250 mL conical flask and an aqueous solution of sodium hydroxide was added (3.0 M, 30 mL) to basify the aqueous phase (reach pH 8 minimum, checked by pH paper), and return the product to the neutral form. The aqueous was then transferred to a 100 mL separating funnel (the conical flask was rinsed into the separating funnel with 10 mL isopropyl acetate and 10 mL water). The aqueous was extracted with isopropyl acetate (3 × 20 mL). The organics were combined, dried over $MgSO_4$ and the solvents were removed under reduced pressure to give a yellow oil. The oil was purified by flash column chromatography (40 – 100% ethyl acetate in petrol) to afford bipyridine, as the key by-product, as an off-white crystalline solid (171 mg, 1.09 mmol, 15% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (q, *J* = 2.0 Hz, 2H, Het-*H*), 8.46 (d, *J* = 8.0 Hz, 2H, Het-*H*), 7.87 (td, *J* = 8.0, 2.0 Hz, 2H, Het-*H*), 7.35 (ddd, *J* = 8.0, 5.0, 1.5 Hz, 2H, Het-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.2, 149.0, 137.7, 124.2, 121.7; **MP** ($CDCl_3$) 68 – 72 °C; **IR** (neat)/ν_{max} 2923, 1457, 758; **LRMS** (ESI *m/z*) calculated for $C_{10}H_9N_2$, $[M+H]^+$ is 157.1 found 157.0.

The data is consistent with the literature.[278]

2-(*p*-Tolyl)pyridin-1-ium chloride (16c)



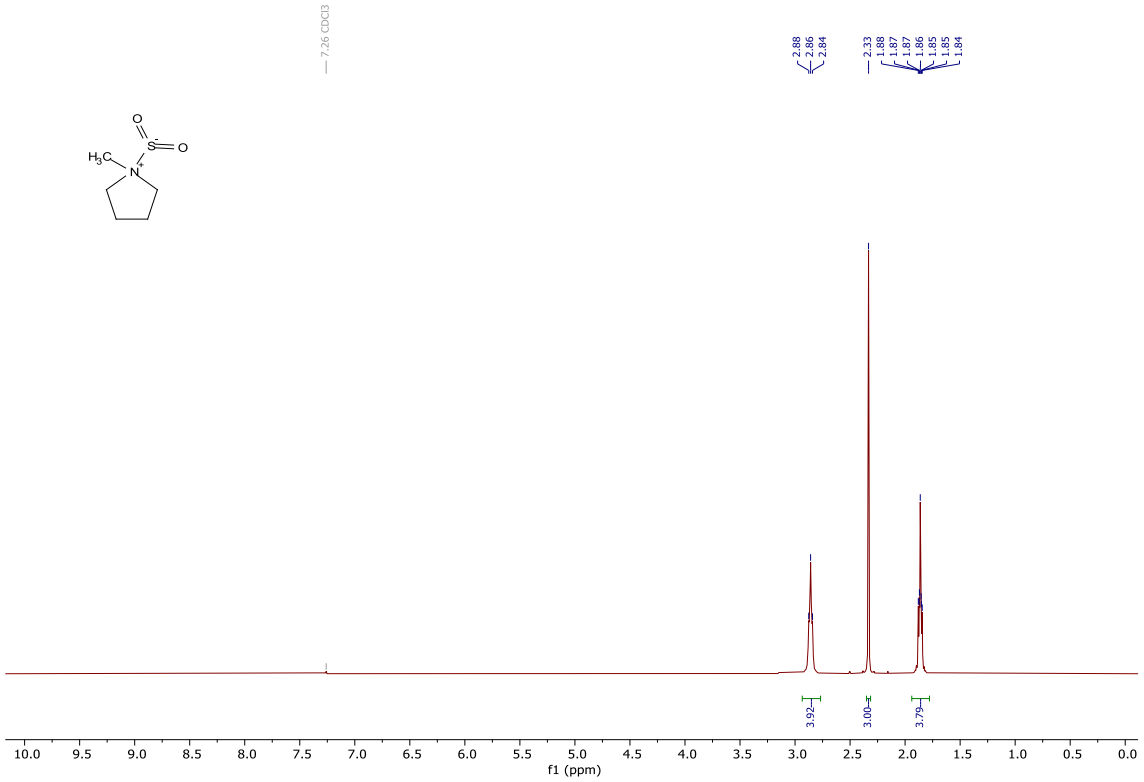
To a 100 mL round-bottom flask equipped with a stirrer bar, was added crude 2-(*p*-tolyl)pyridine (5.24 g, 31.0 mmol), given as a dark-brown oil, in methyl *tert*-butyl ether (50 mL, 10 solvent volumes). Hydrogen chloride solution (2.0 M in methyl *tert*-butyl ether, 18.6 mL, 37.2 mmol, 1.2 equiv.) was added by syringe over 5 minutes, at room temperature. The mixture was stirred for 15 minutes. Vacuum filtration of the mixture through a fritted funnel (porosity 3) followed by washes with methyl *tert*-butyl ether (50 mL) and ethyl acetate (50 mL), gave the title hydrochloride salt product as an off-white amorphous solid. The solid was transferred to a 100 mL flask, and any remaining solvents removed by a rotary evaporator (45 °C, 20 mbar, 15 minutes). A stirrer bar was added to the flask, and the vessel was placed in a heating block on a stirrer-hot plate. isopropyl alcohol (30 mL) was added, and the hot-plate was heated to 95 °C. Further isopropyl alcohol (10 mL, then 7 mL) was added to ensure complete dissolution of the solid. The vessel was then removed from heat, and left at room temperature to allow crystallisation to occur (this began within 30 minutes). The crystals were isolated by filtration through a filter funnel fitted with a frit (porosity: 3) into a 500 mL round-bottom flask. The crystals were washed with cold ethyl acetate (50 mL × 2) before being transferred to a tared vial. The filtrate was retained after the filtration and the solvents were removed under vacuum. The resulting solid was transferred to a 100 mL round-bottom flask, and recrystallisation in the same manner as before was re-attempted. The recrystallised product was given as off-white needles (5.72 g, 27.9 mmol, 90% yield, purity 99% by qNMR). A sample of the 2-tolylpyridine hydrogen

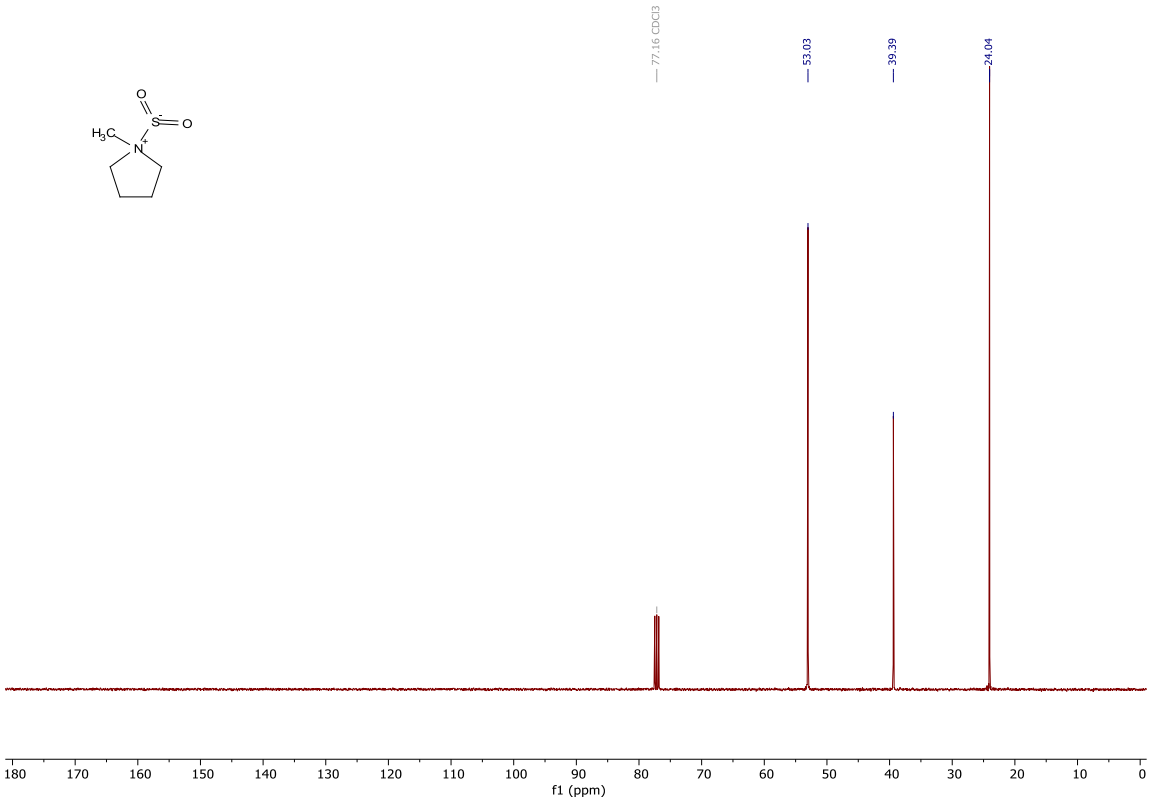
chloride was stored for a week, under air, at room temperature. Pleasingly, NMR analysis showed that no decomposition had occurred compared to the day of formation.

^{1}H NMR (400 MHz, CD_3OD) δ 8.81 (ddd, *J* = 6.0, 1.5, 1.0 Hz, 1H, Het-*H*), 8.67 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, Het-*H*), 8.39 (dt, *J* = 8.0, 1.0 Hz, 1H, Het-*H*), 8.02 (ddd, *J* = 7.5, 6.0, 1.5 Hz, 1H, Het-*H*), 7.90 – 7.86 (m, 2H, 2 × Ar-*H*), 7.54 – 7.51 (m, 2H, 2 × Ar-*H*), 2.49 (s, 3H, C*H*$_3$); **^{13}C NMR** (101 MHz, CD_3OD) δ 154.2, 148.3, 145.0, 142.7, 131.7, 129.3, 129.2, 127.1, 126.3, 21.5; **MP** (^{i}PrOH) 178 – 180 °C; **IR** (neat)/ν_{max} 3090, 1608, 1448, 783; **LRMS** (ESI, *m/z*) 170.1 $[M\text{-}Cl]^+$; **HRMS** (ESI, *m/z*) calculated for $C_{12}H_{12}N$, $[M\text{-}Cl]^+$ is 170.0964 (100%), found 170.0963 (100%).

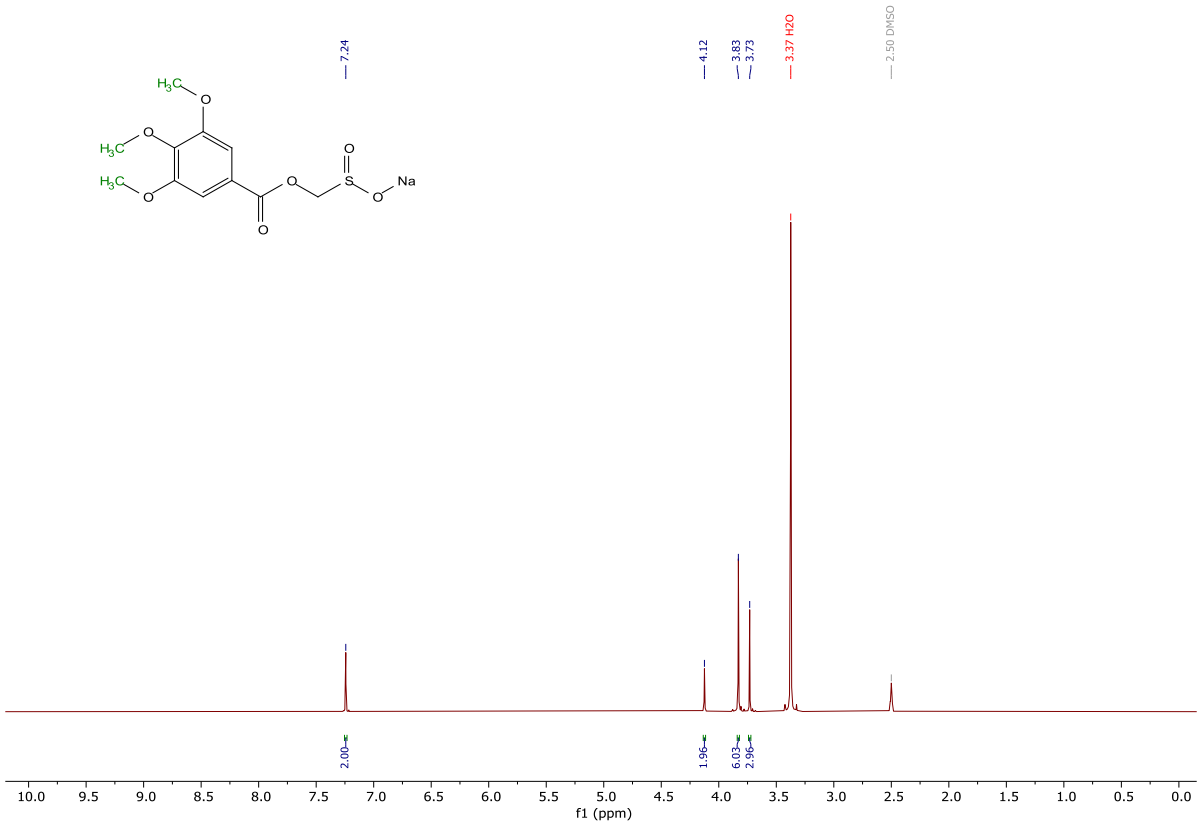
7.6. Spectra

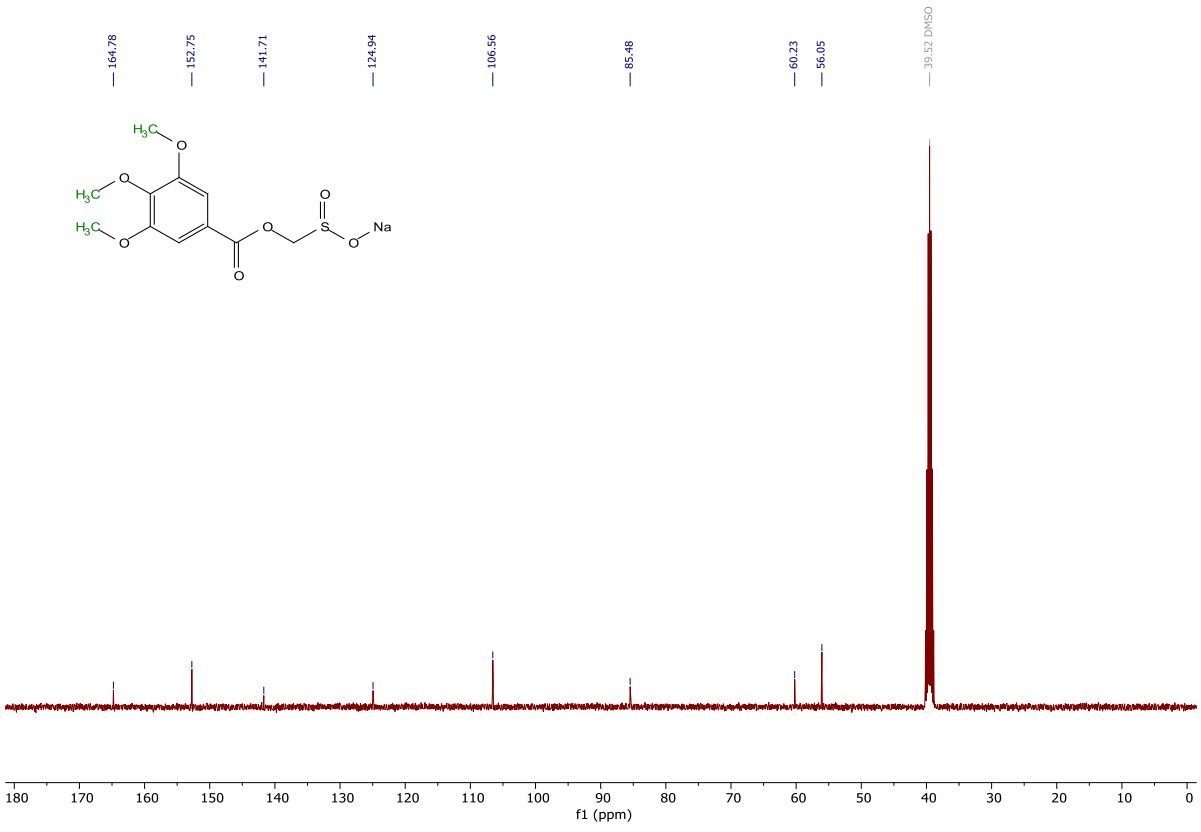
N-Methylpyrrolidine SO_2 adduct (TIMSO) (S1)



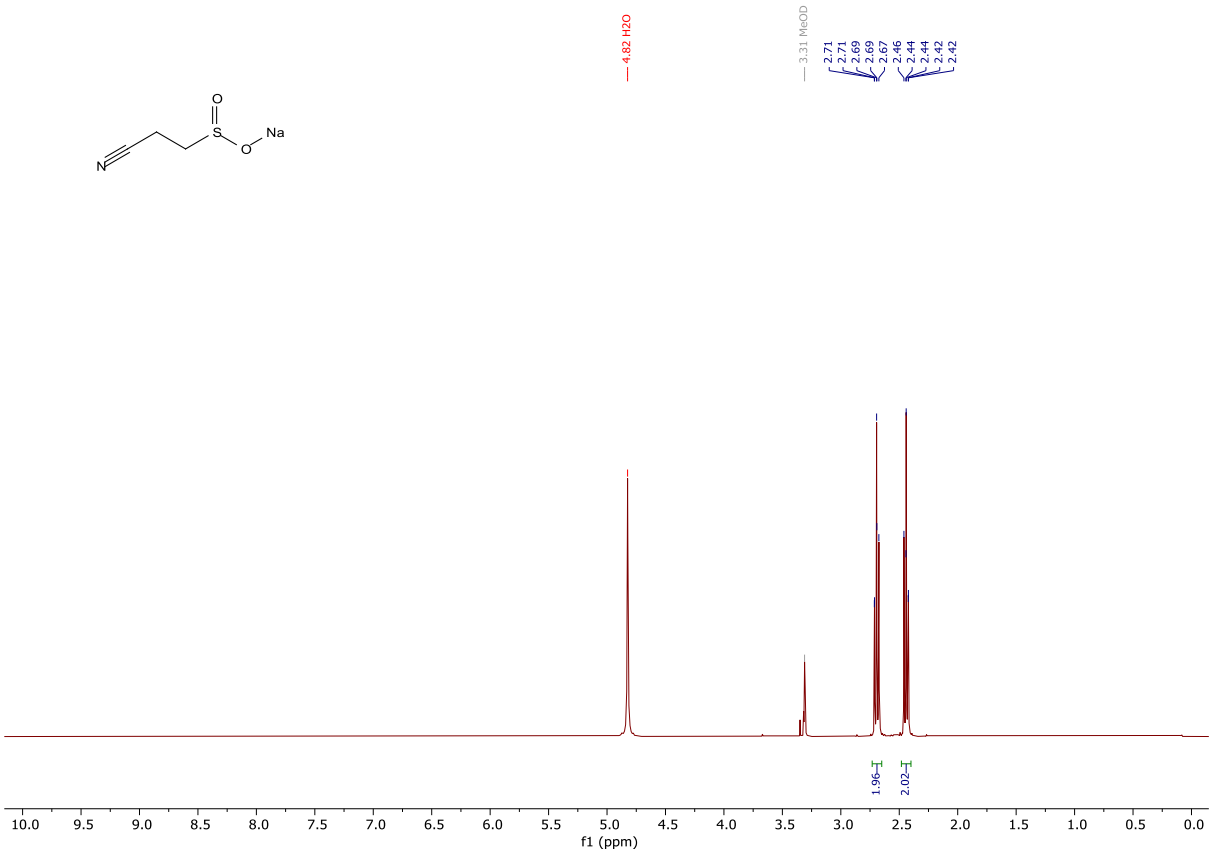


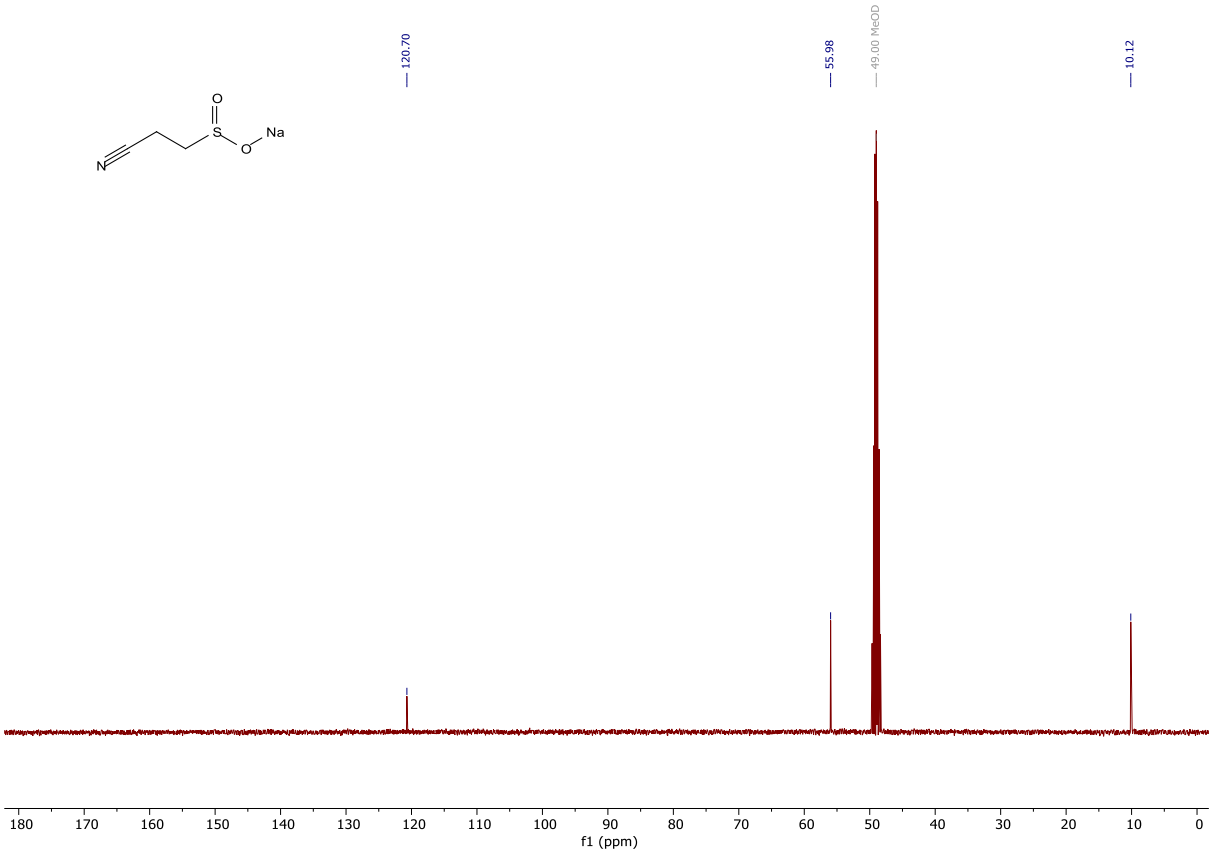
Sodium ((3,4,5-trimethoxybenzoyl)oxy)methanesulfinate (Rongacyl) (S2)



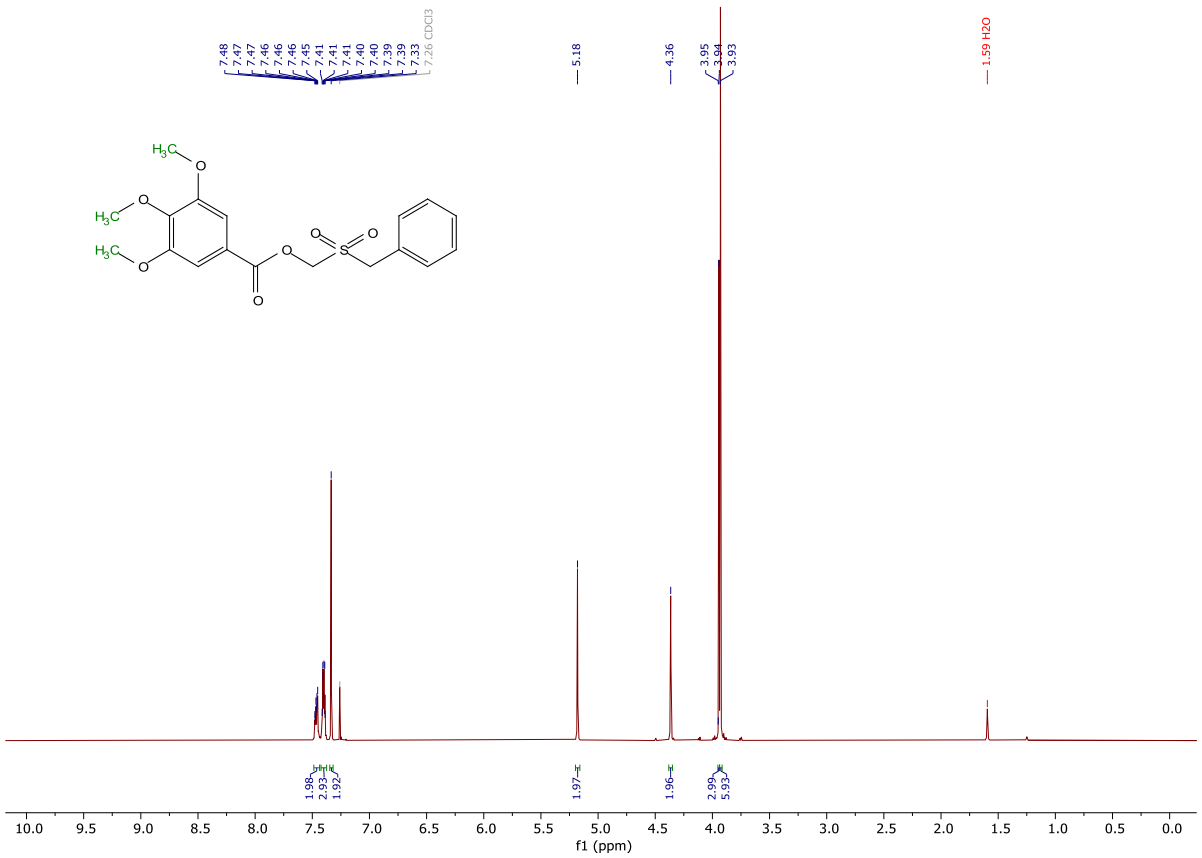


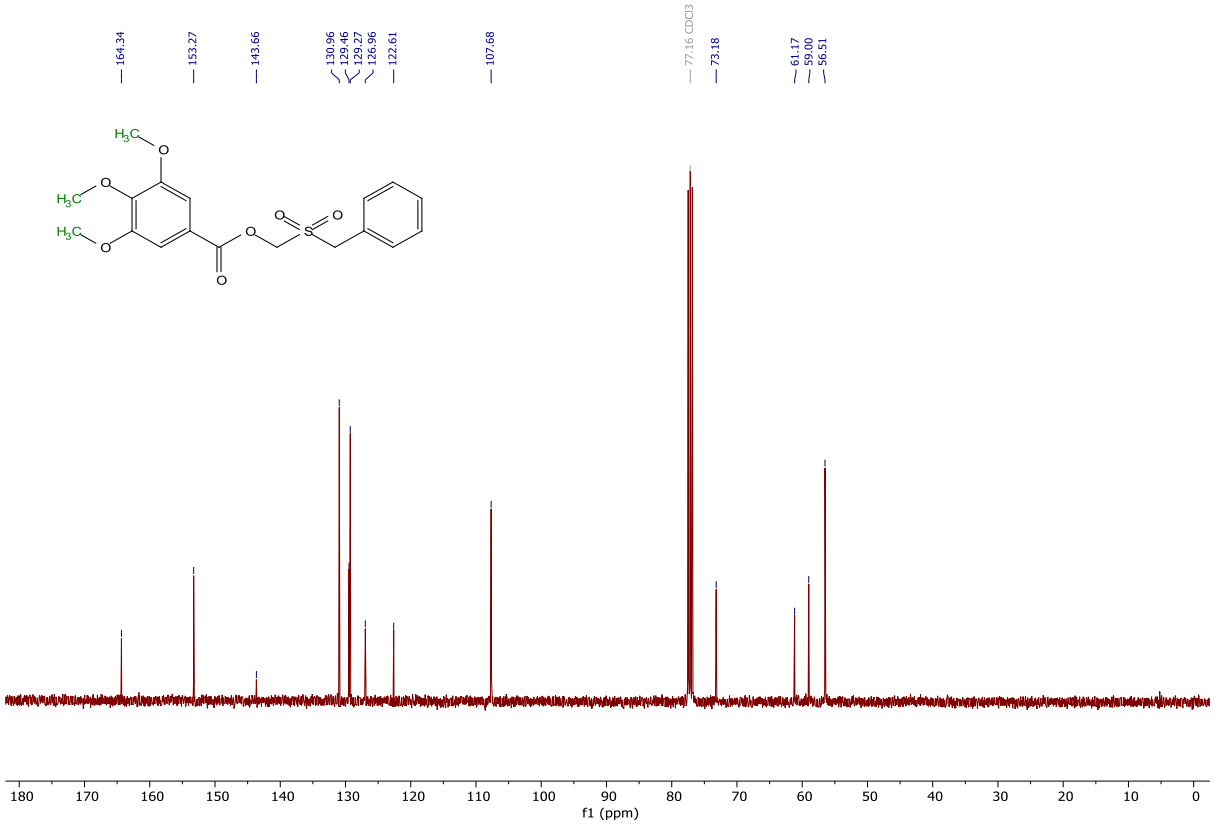
Sodium 2-cyanoethane-1-sulfinate (β-nitrile sulfinate) (S3)



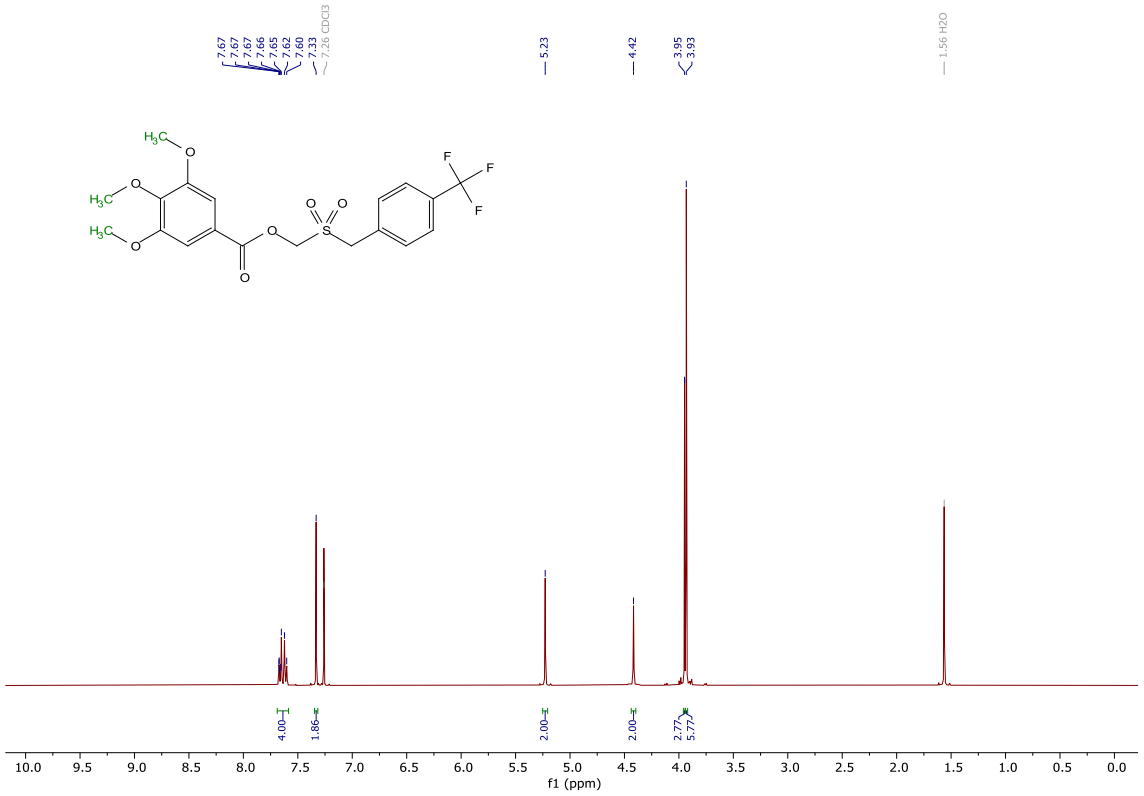


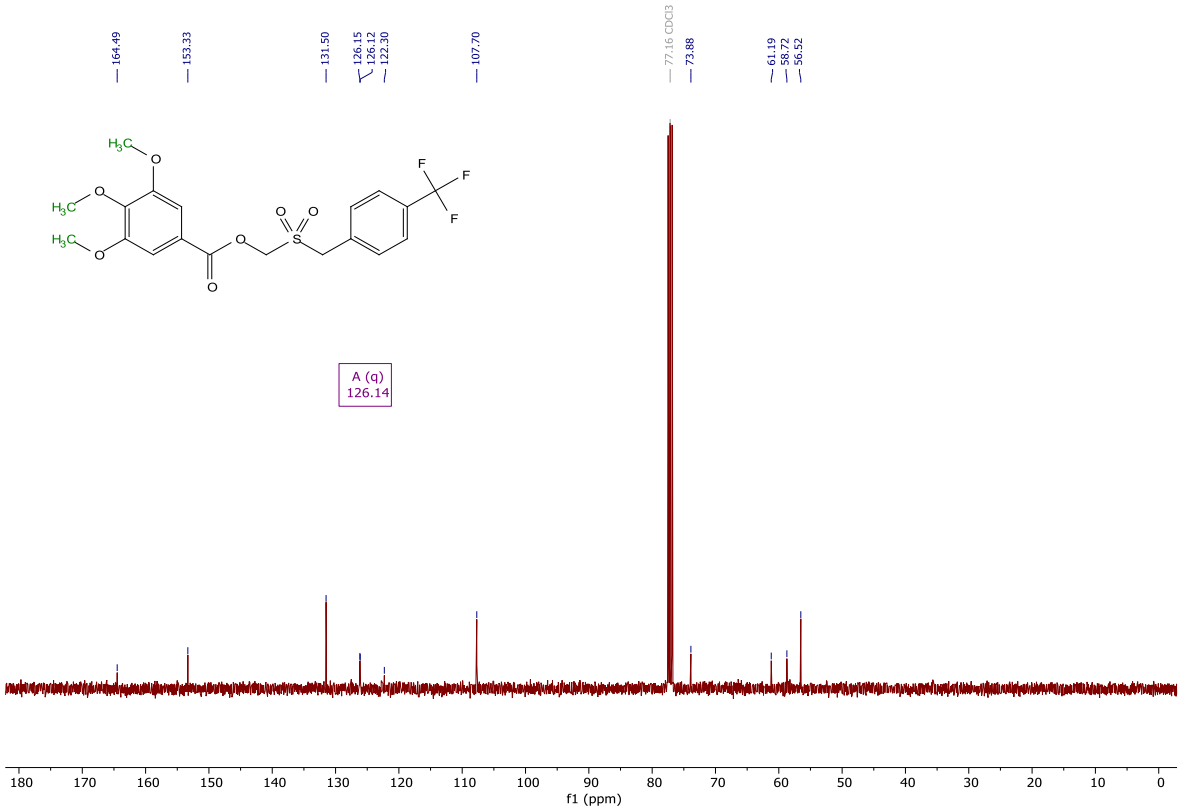
((Benzyl)sulfonyl)methyl 3,4,5-trimethoxybenzoate (2a)

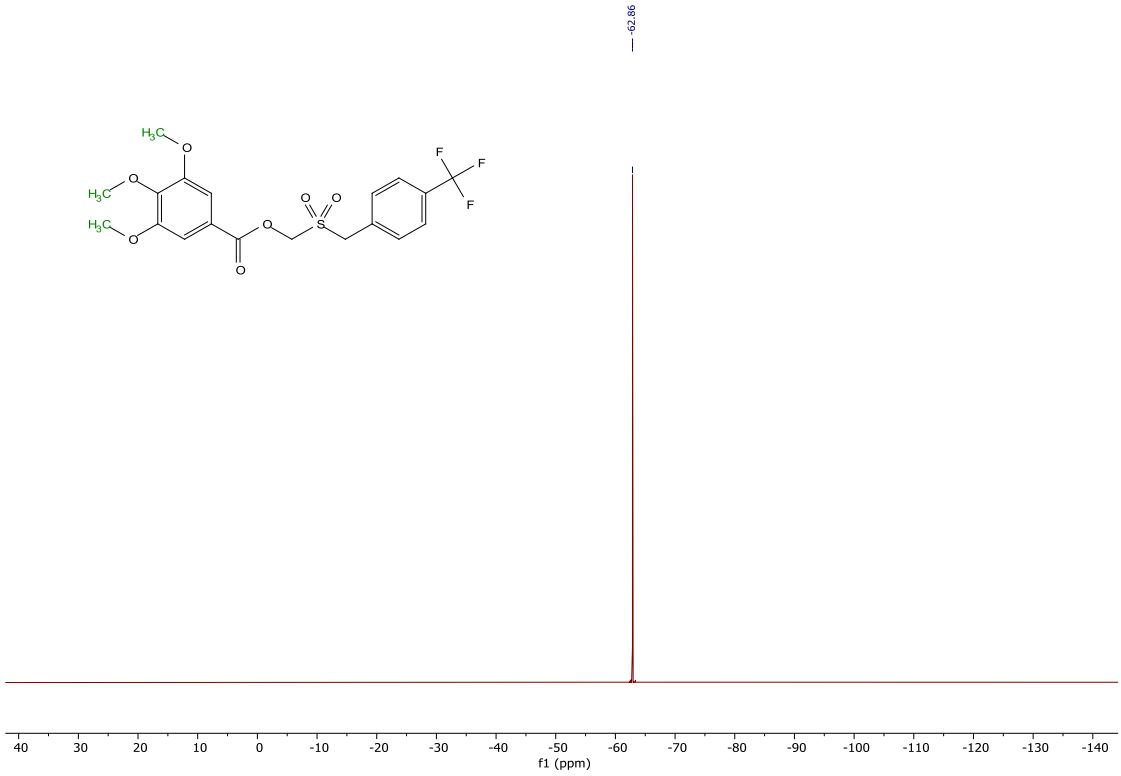




((4-(Trifluoromethyl)benzyl)sulfonyl)methyl 3,4,5-trimethoxybenzoate (2b)



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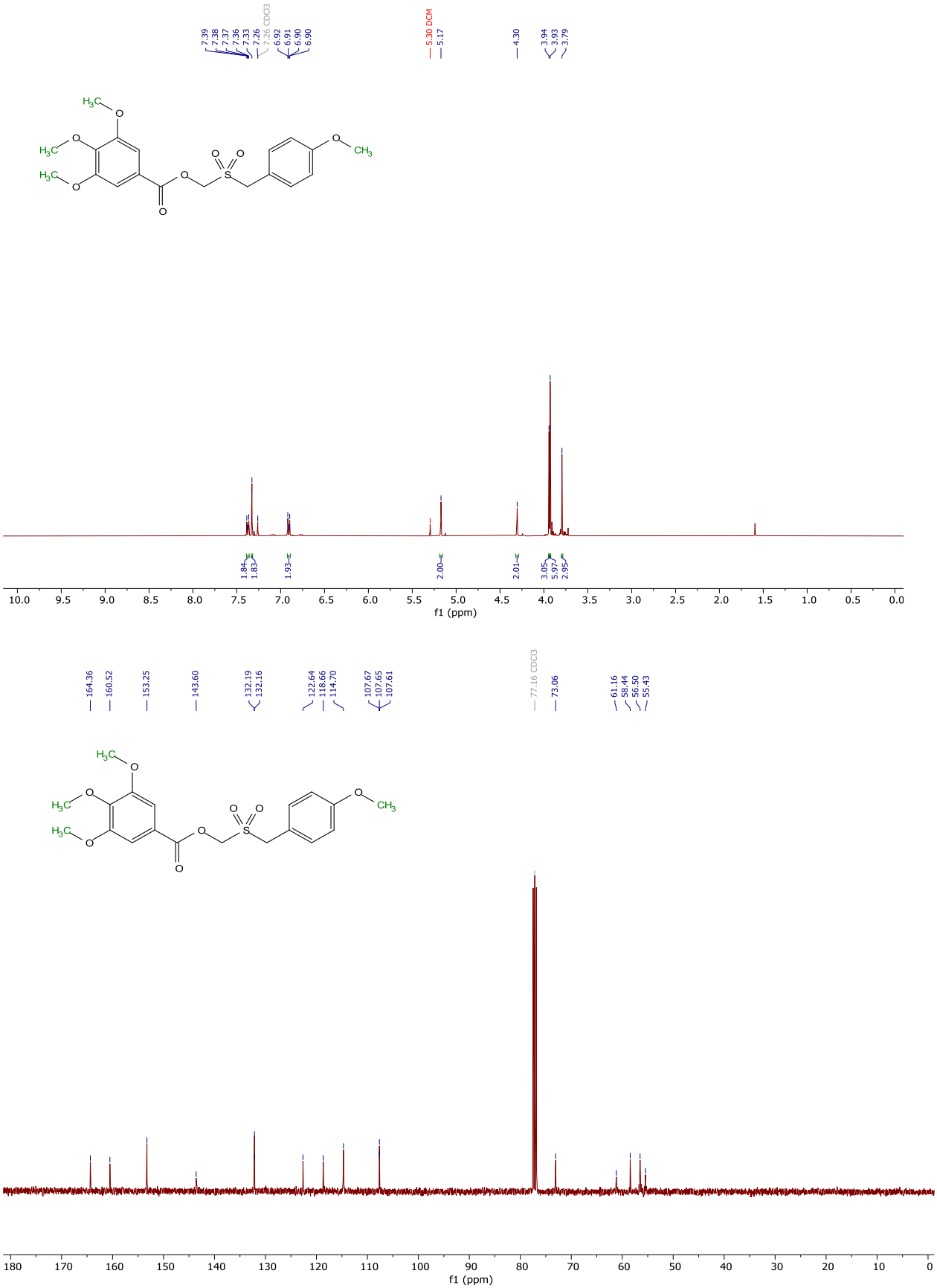
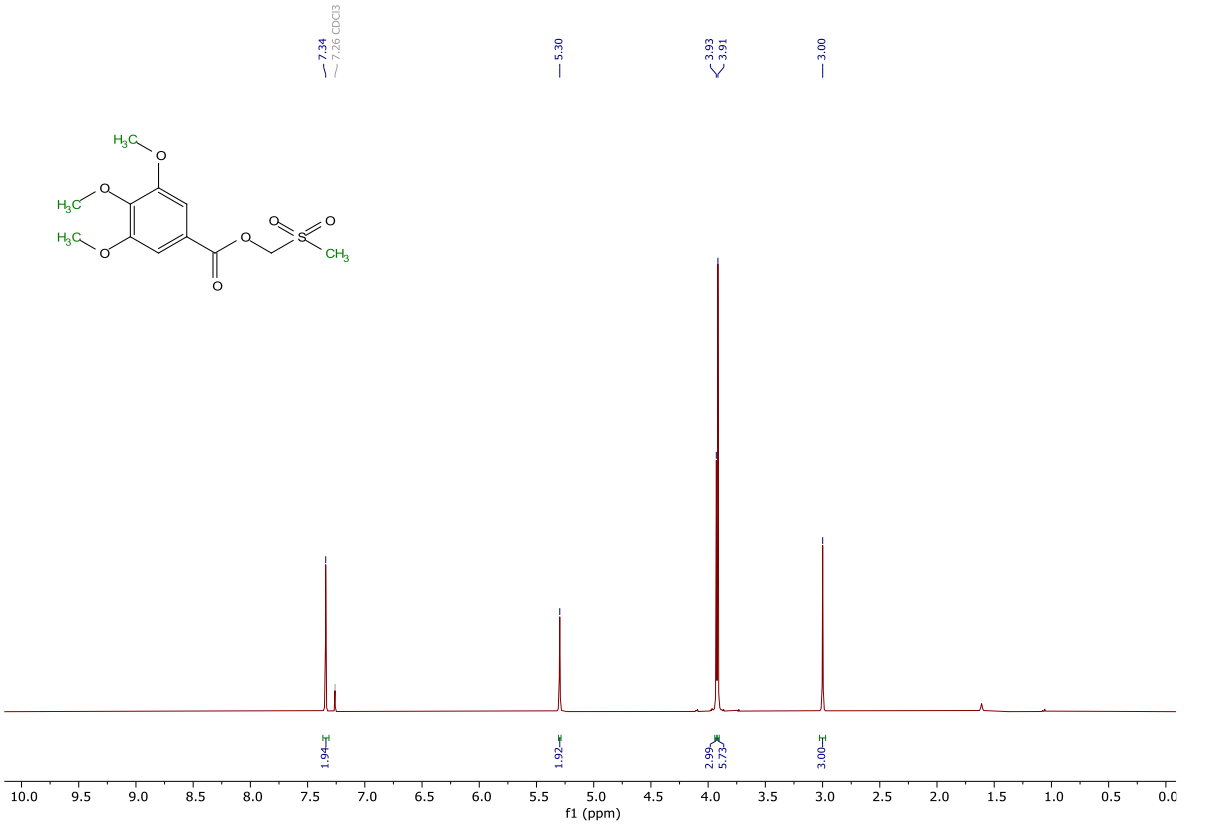
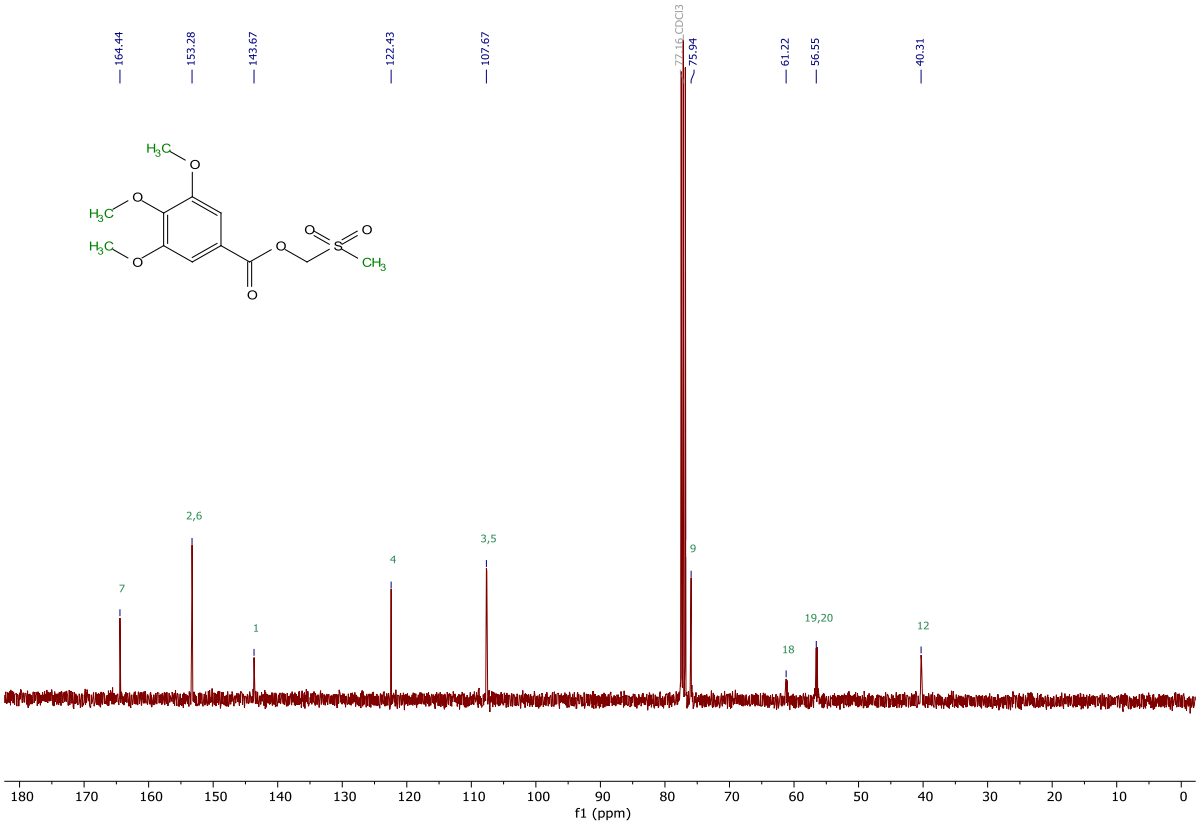
f1 (ppm)

((4-Methoxybenzyl)sulfonyl)methyl 3,4,5-trimethoxybenzoate (2c)

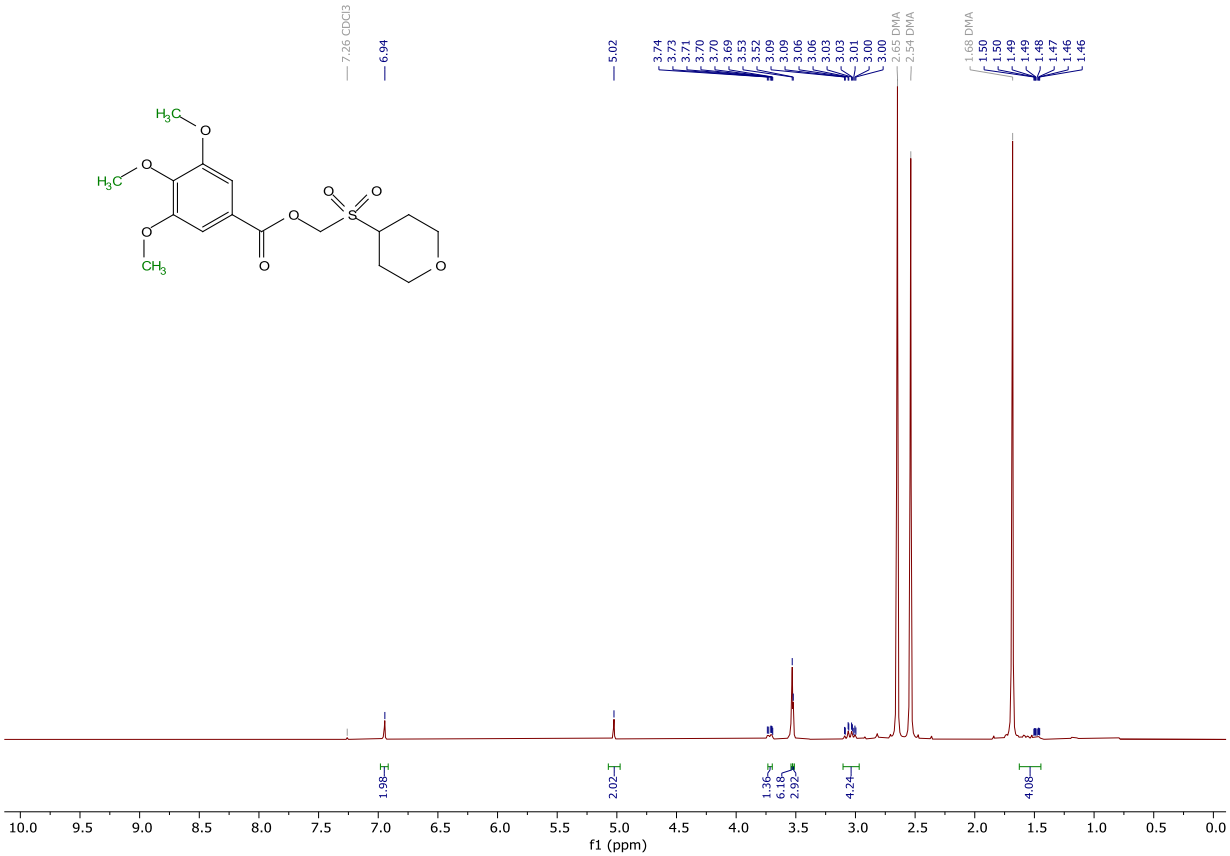


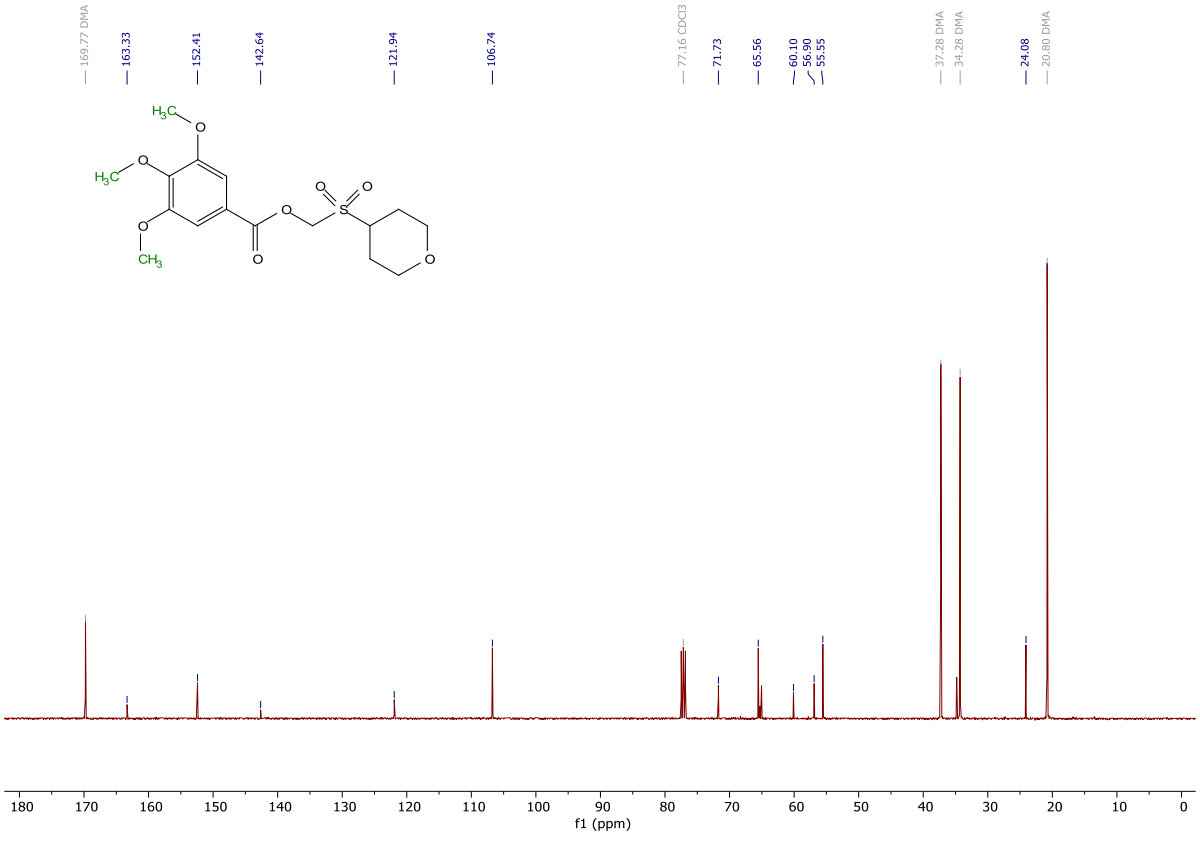
Methylsulfonyl)methyl 3,4,5-trimethoxybenzoate (2d)



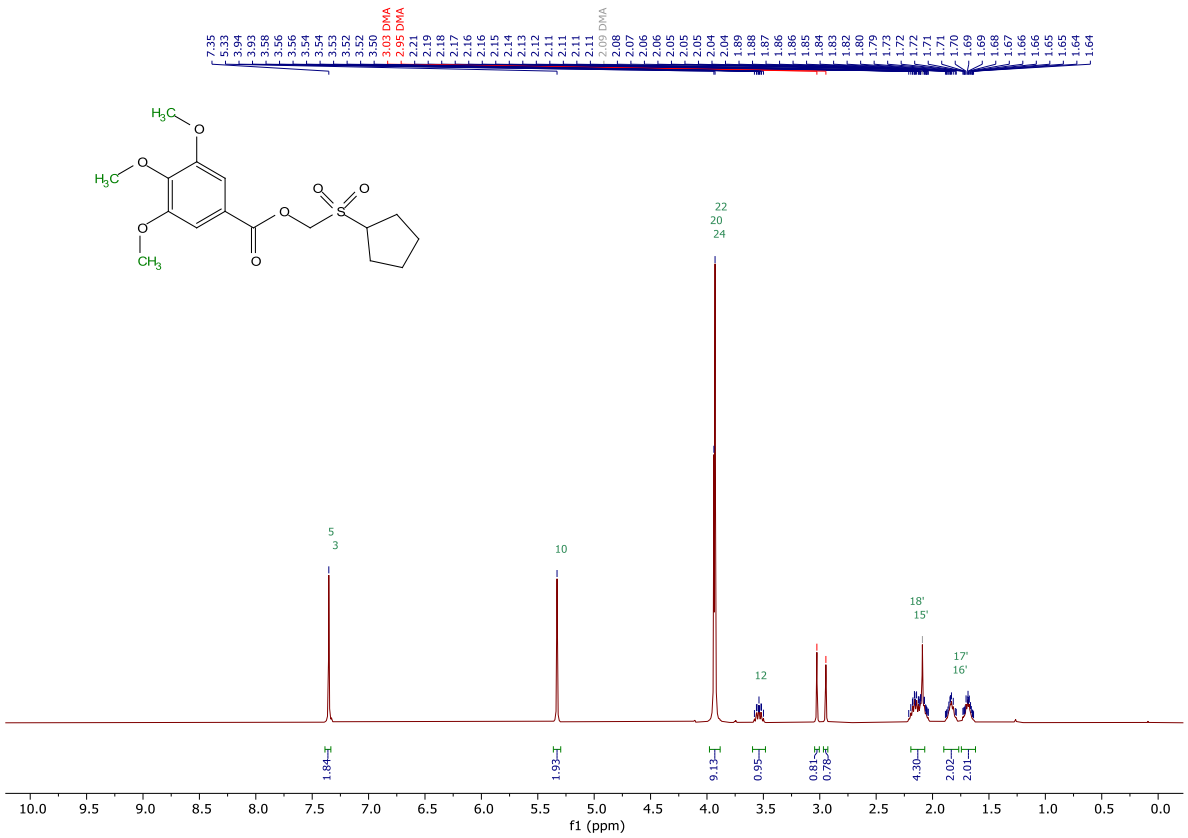


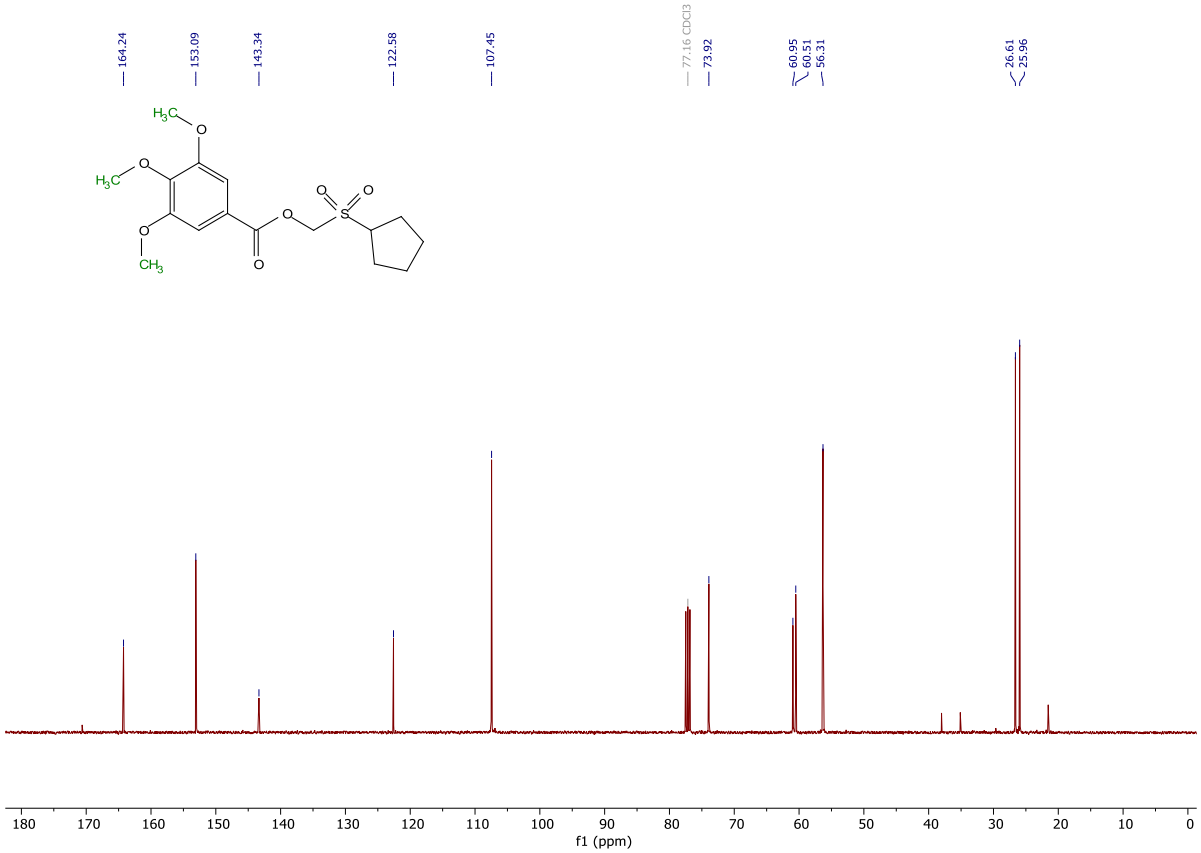
((Tetrahydro-2H-pyran-4-yl)sulfonyl)methyl 3,4,5-trimethoxybenzoate (2e)



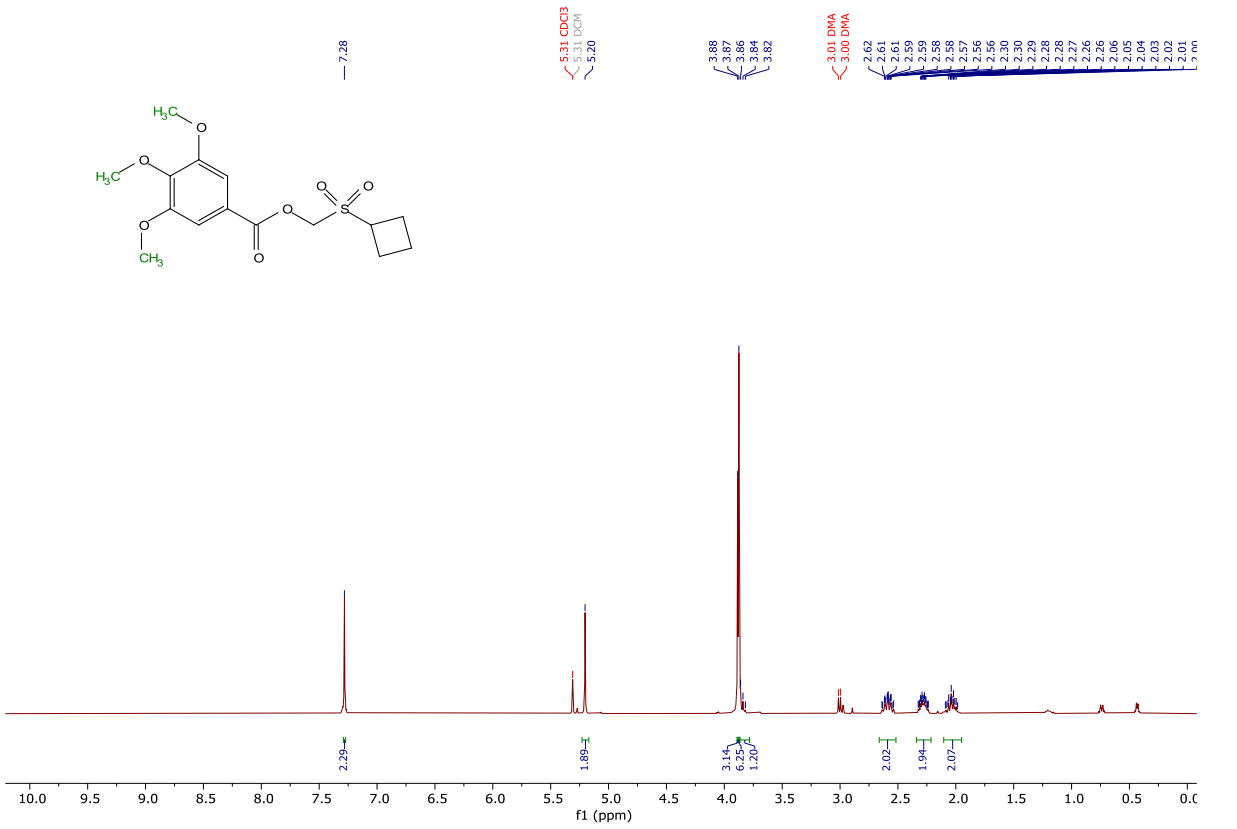


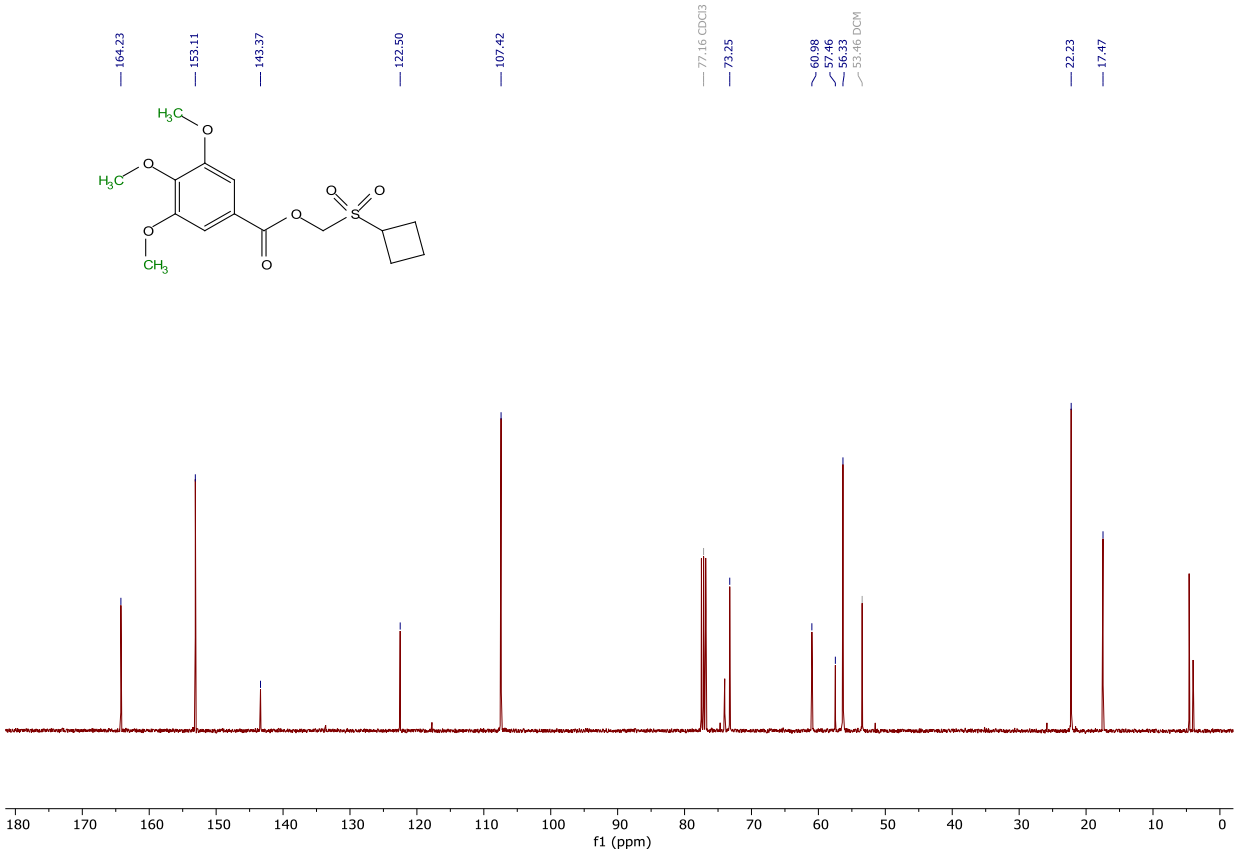
(Cyclopentylsulfonyl)methyl 3,4,5-trimethoxybenzoate (2f)



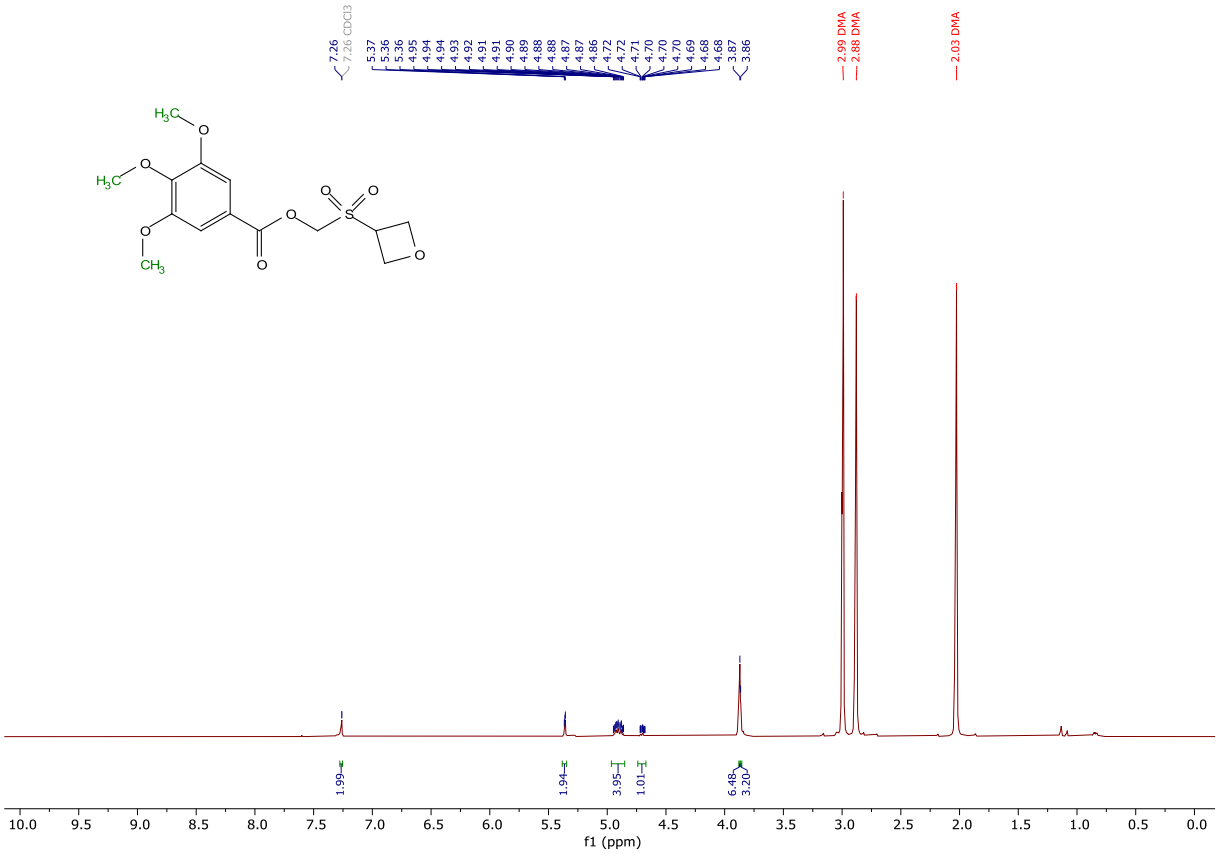


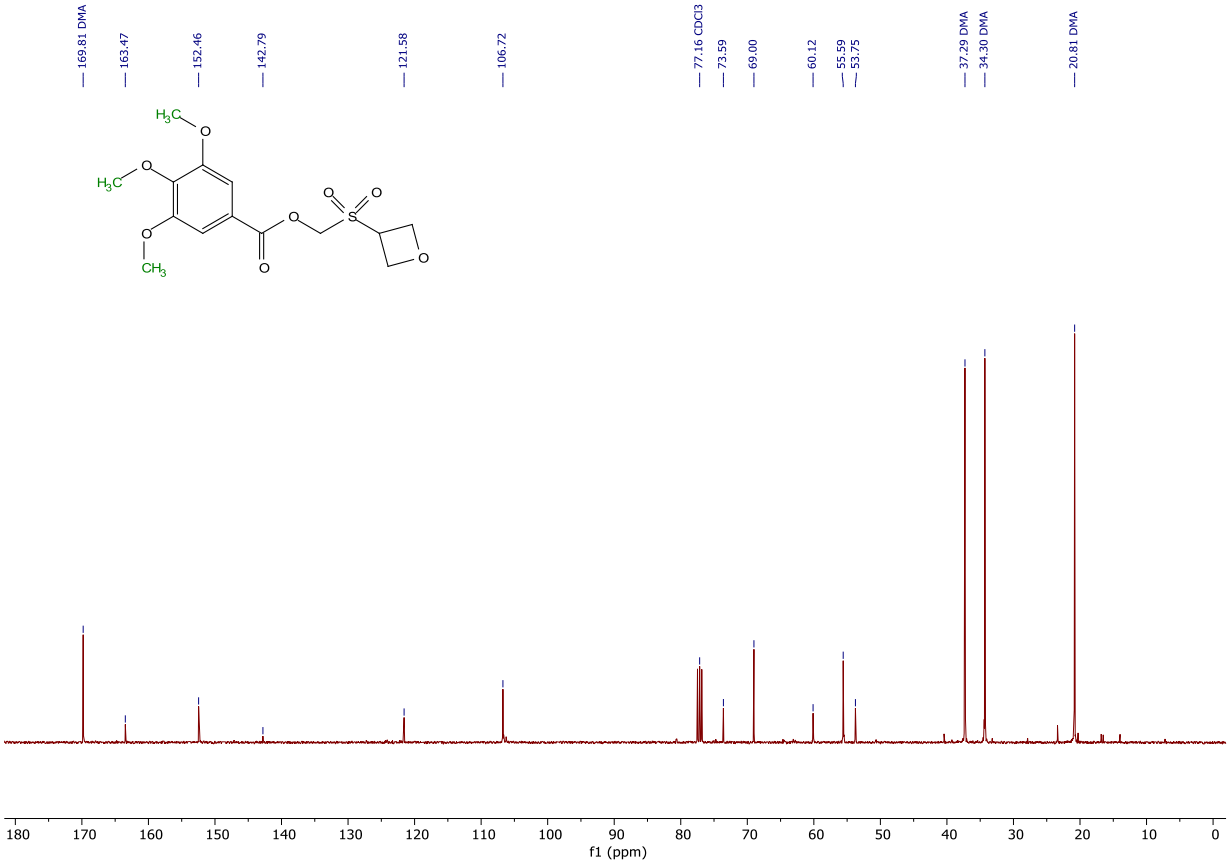
(Cyclobutylsulfonyl)methyl 3,4,5-trimethoxybenzoate (2g)



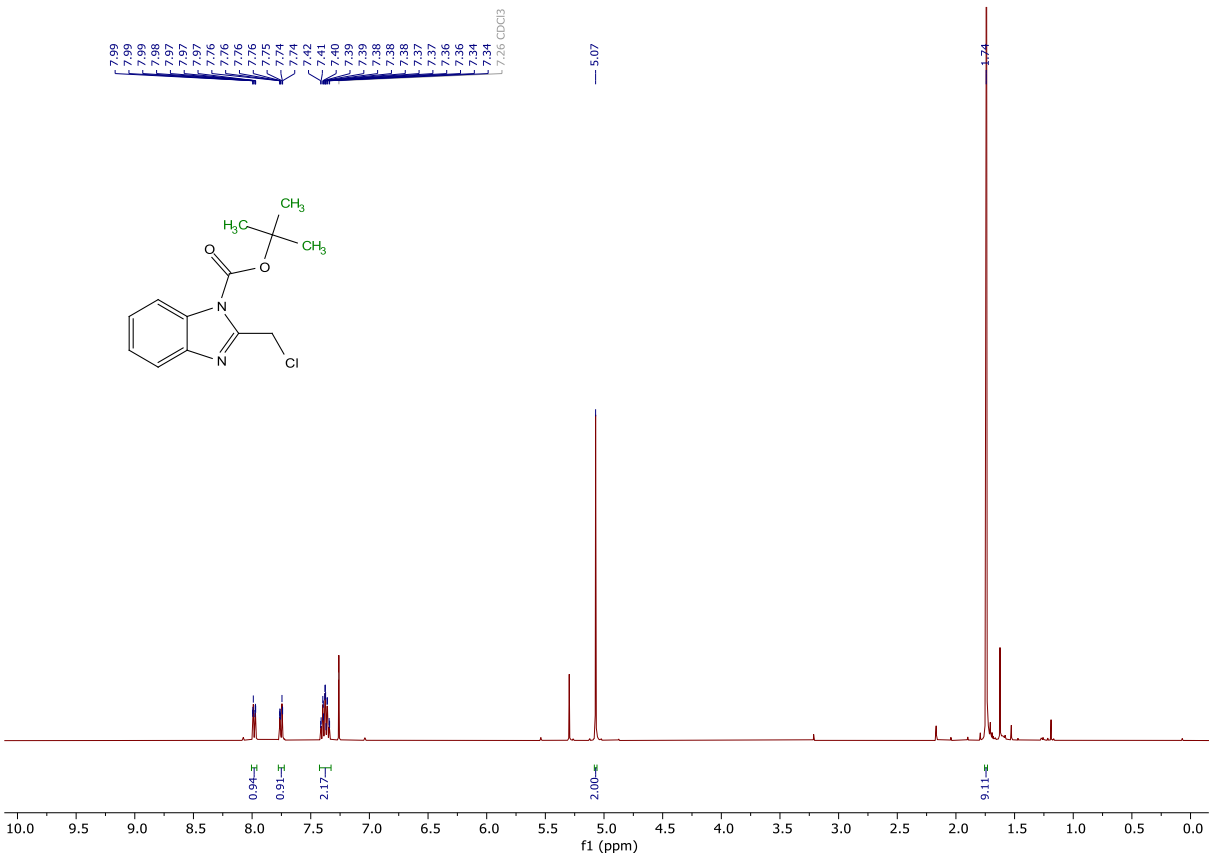


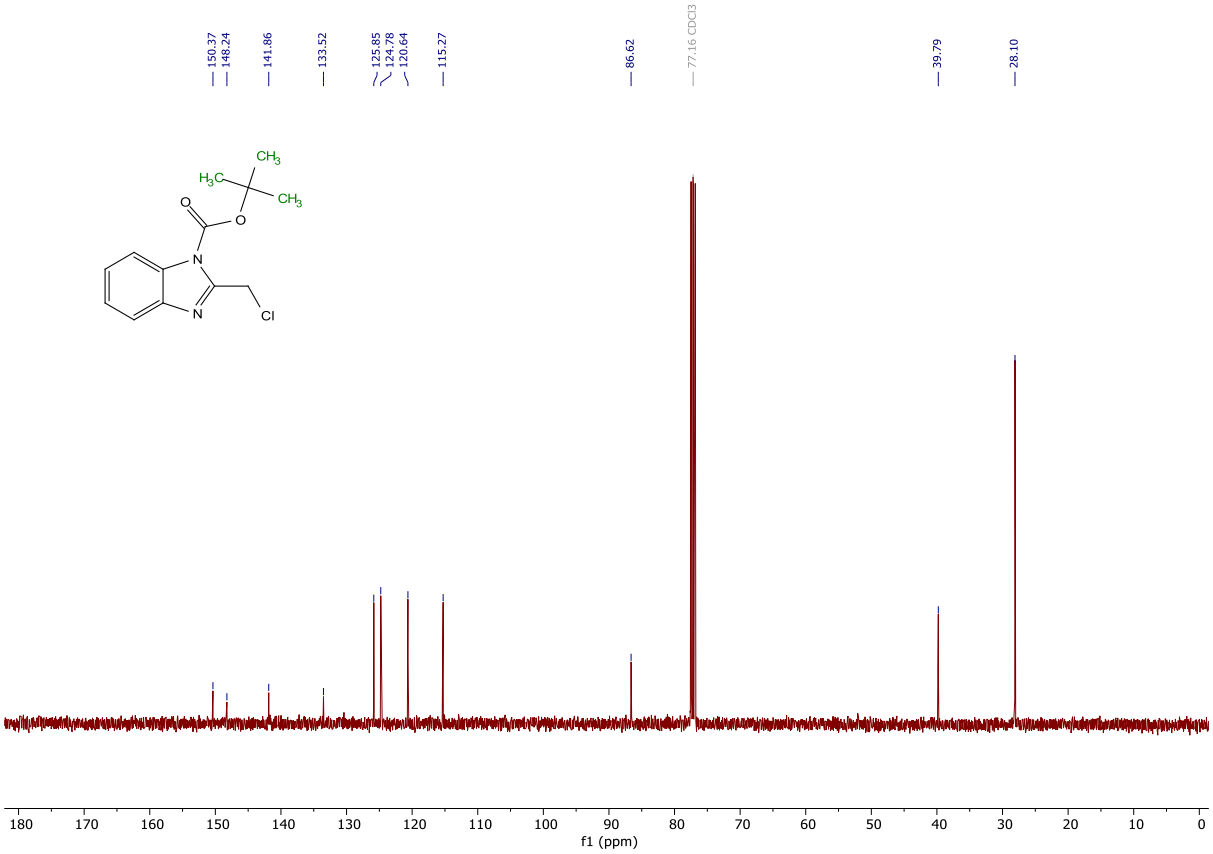
(Oxetan-3-ylsulfonyl)methyl 3,4,5-trimethoxybenzoate (2h)



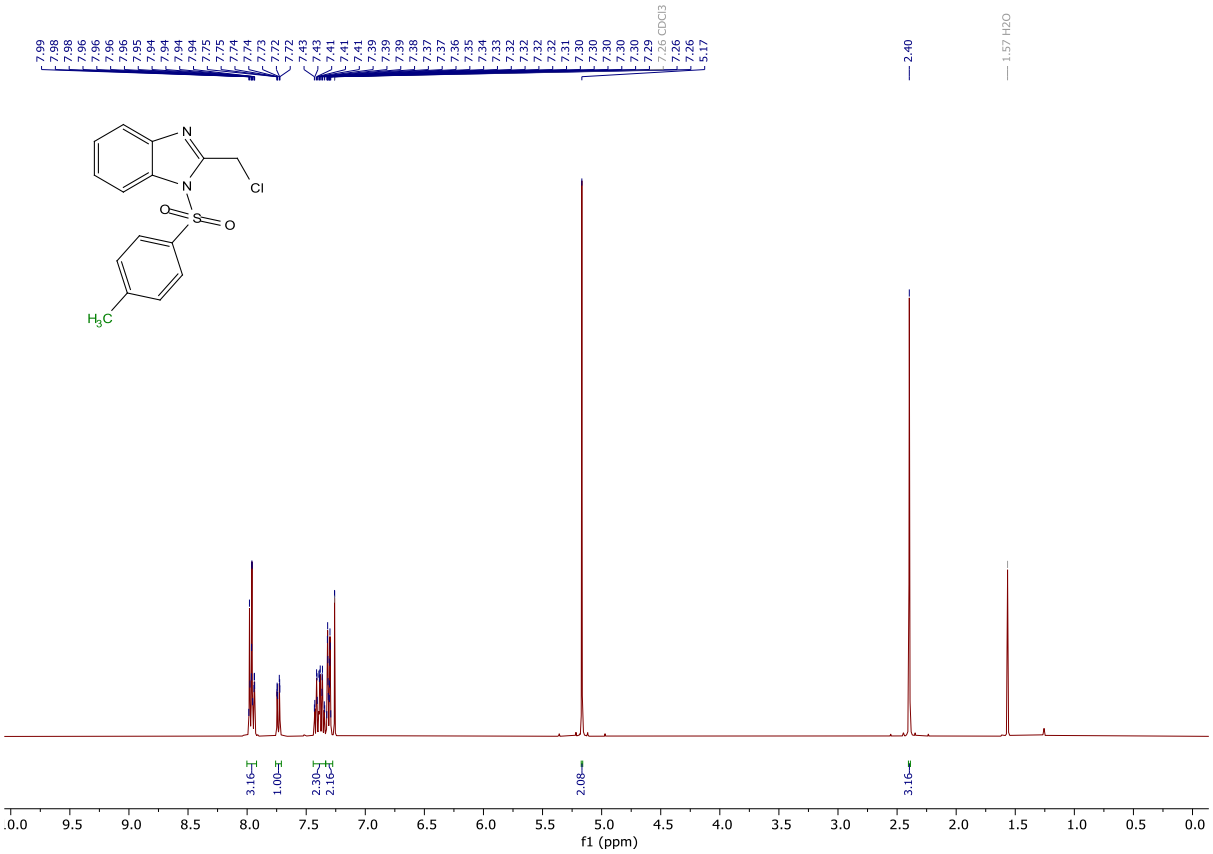


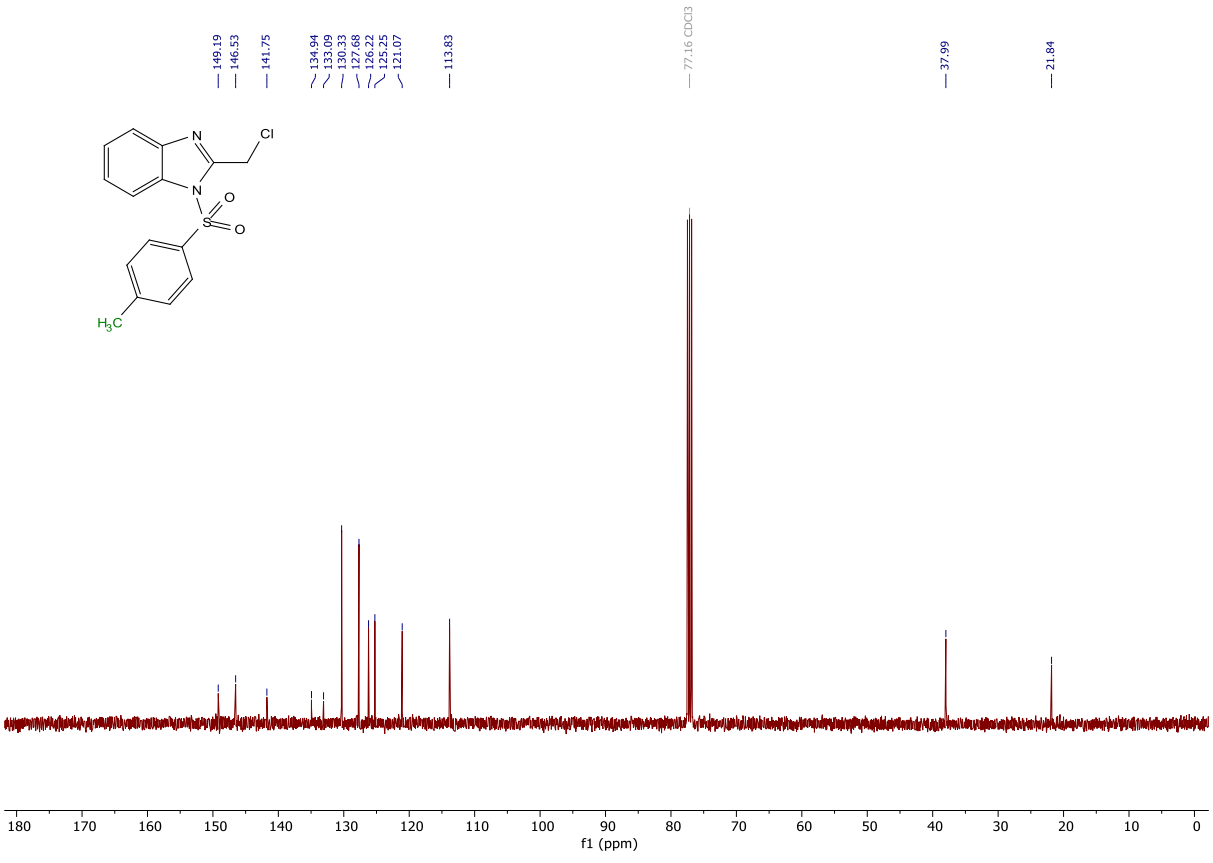
Tert-butyl 2-(chloromethyl)-1H-benzo[d]imidazole-1-carboxylate (S4)



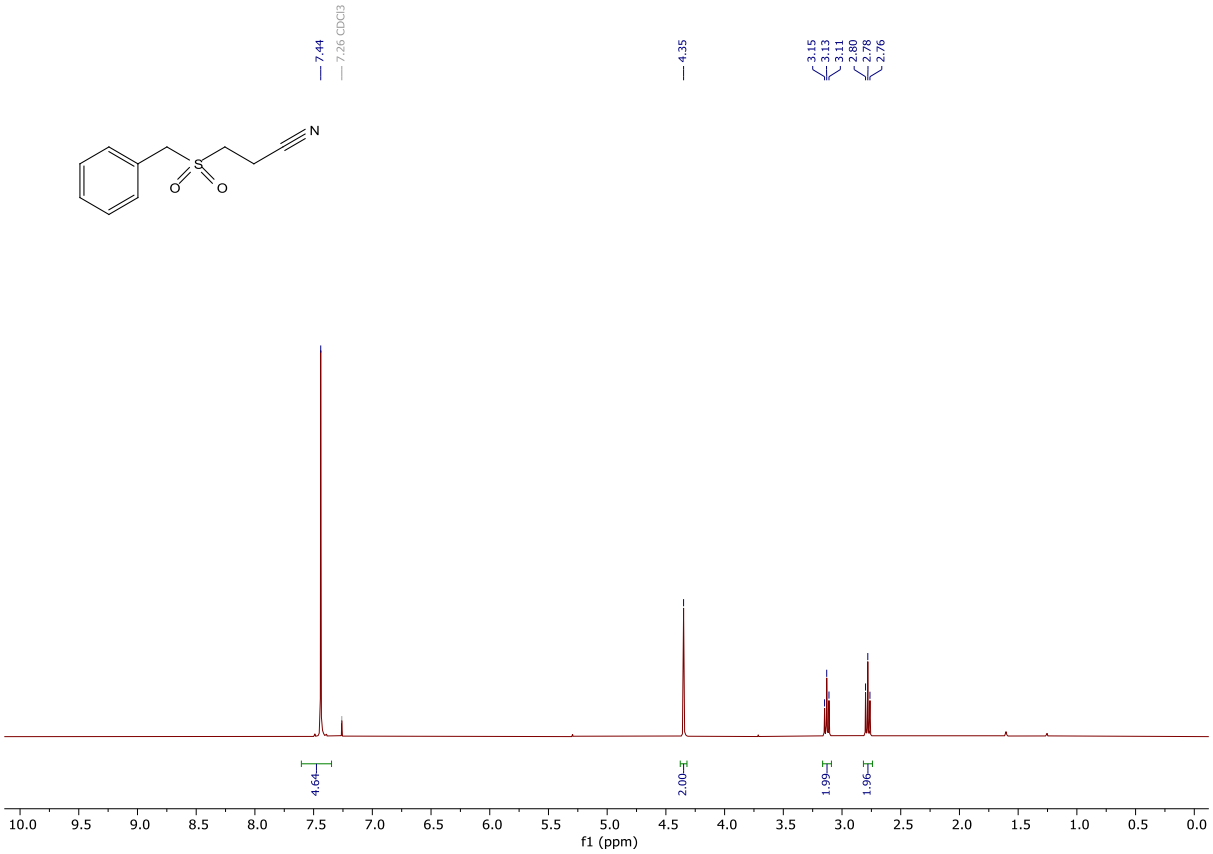


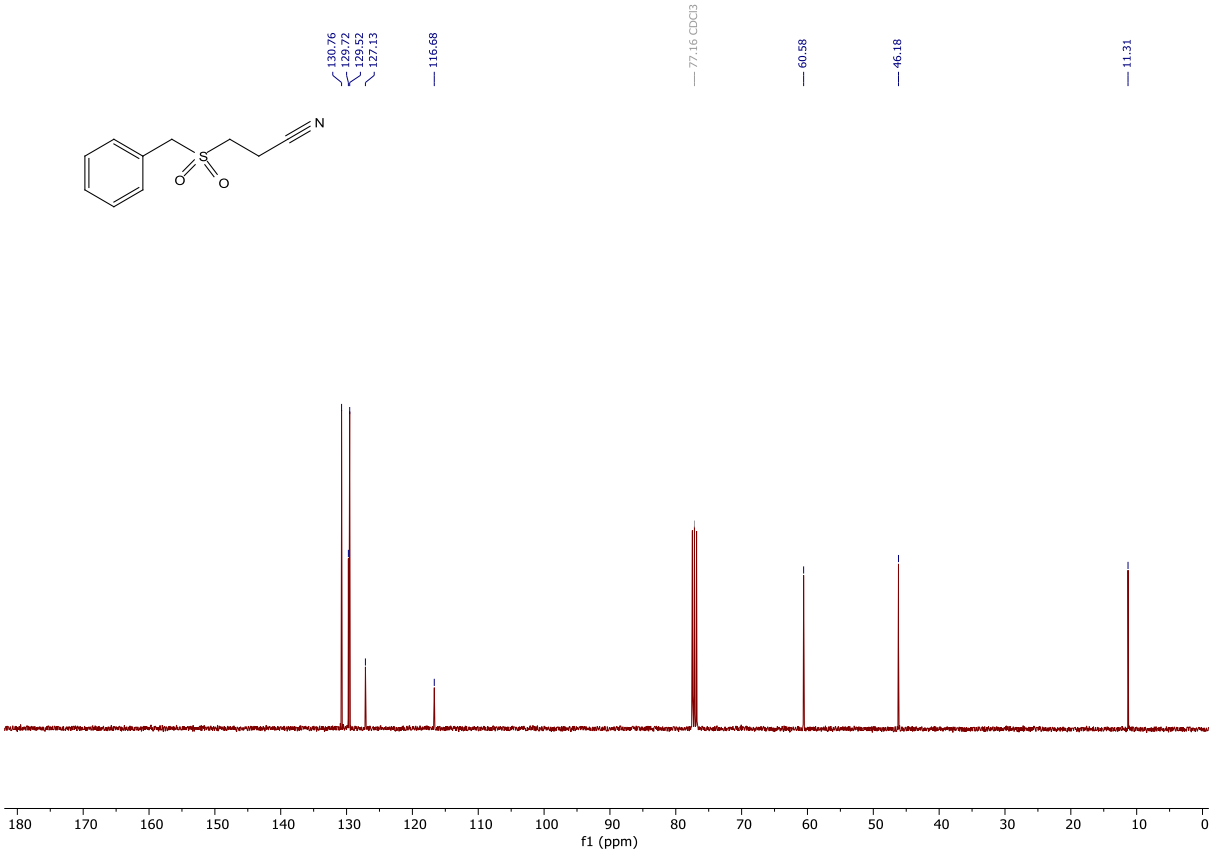
2-(Chloromethyl)-1-tosyl-1H-benzo[d]imidazole (S5)



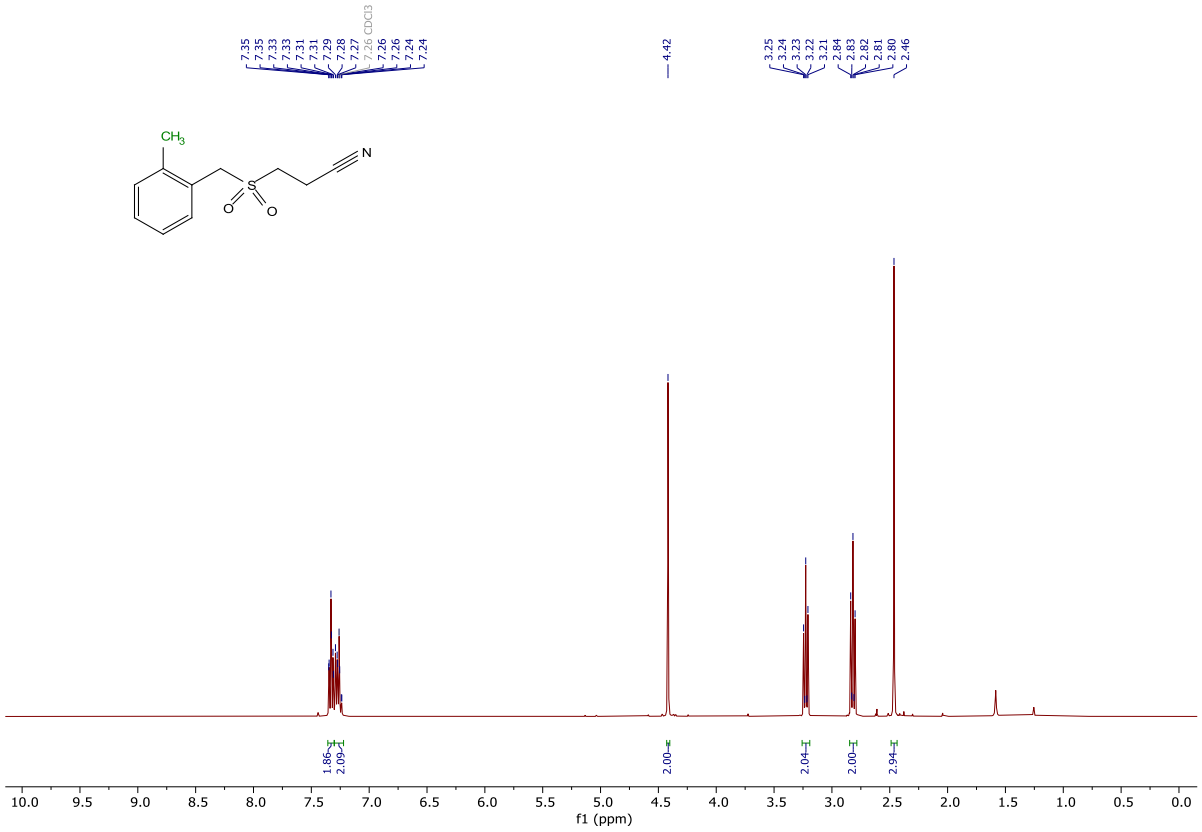


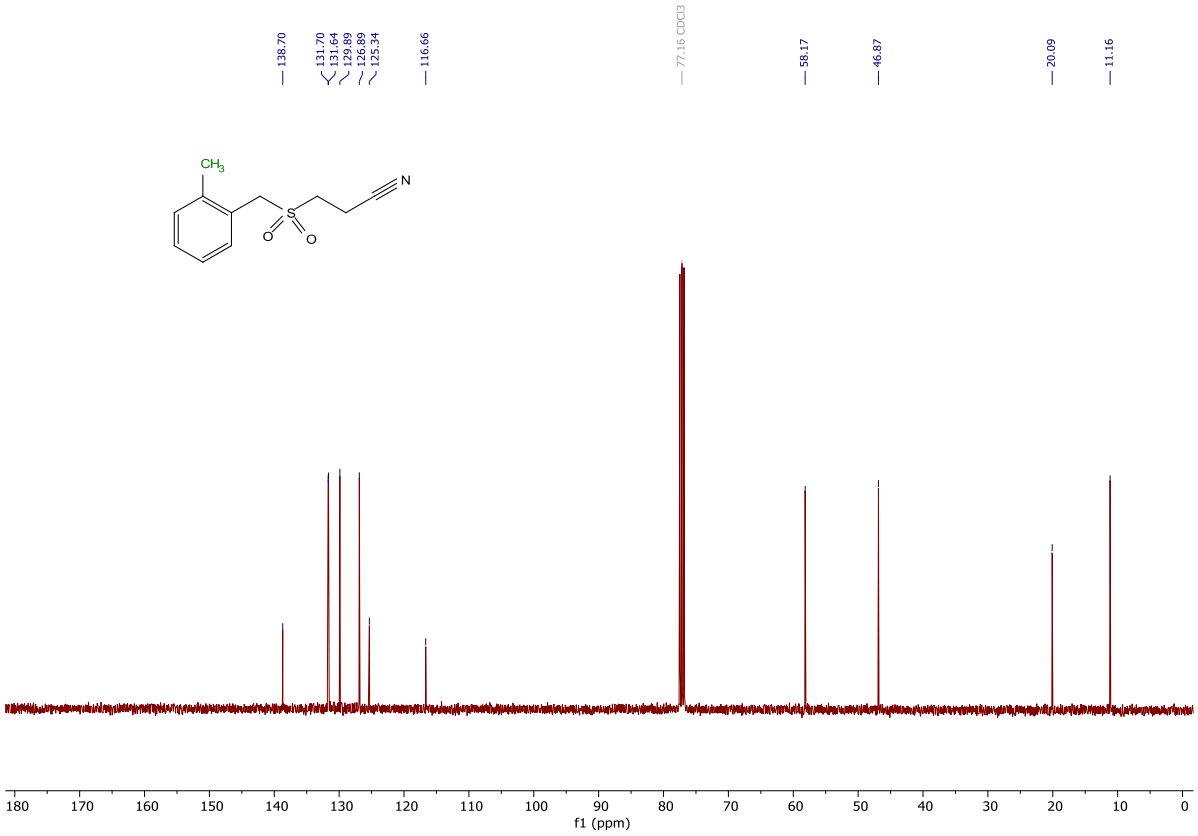
3-(Benzylsulfonyl)propanenitrile (3a)



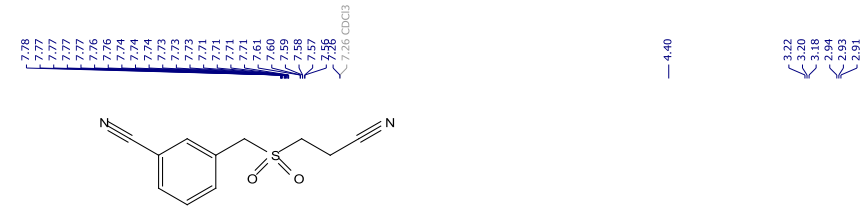


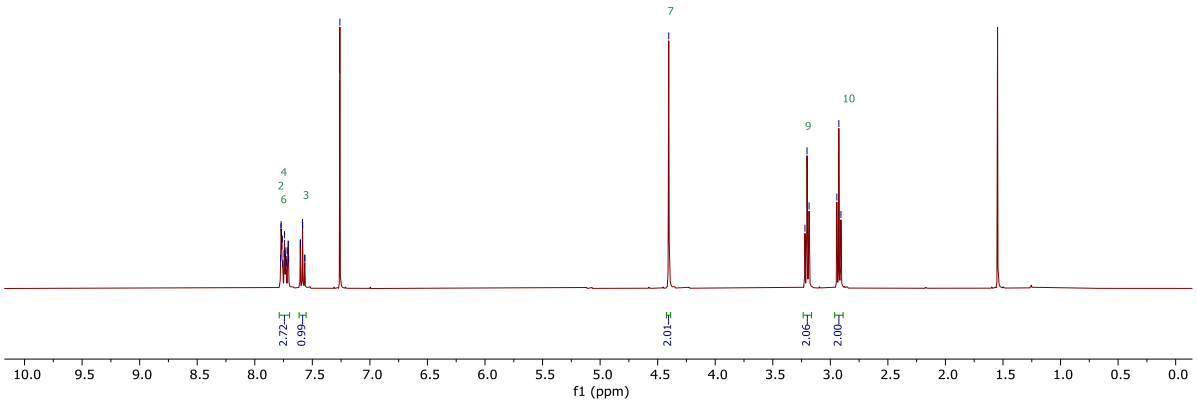
3-((2-Methylbenzyl)sulfonyl)propanenitrile (3b)

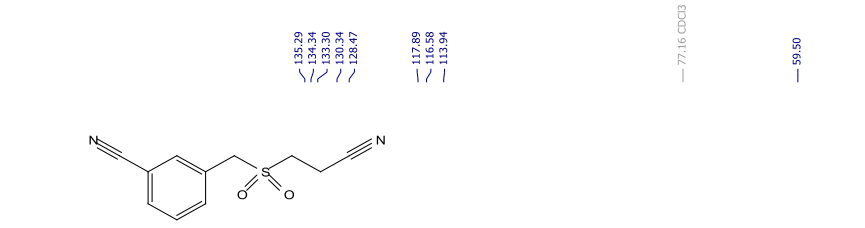


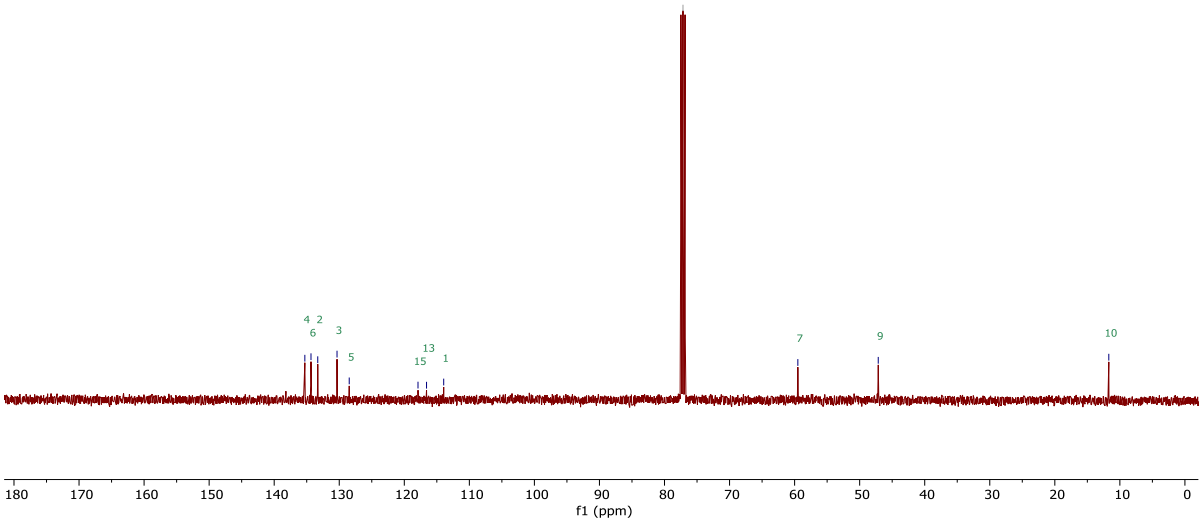


3-(((2-Cyanoethyl)sulfonyl)methyl)benzonitrile (3c)

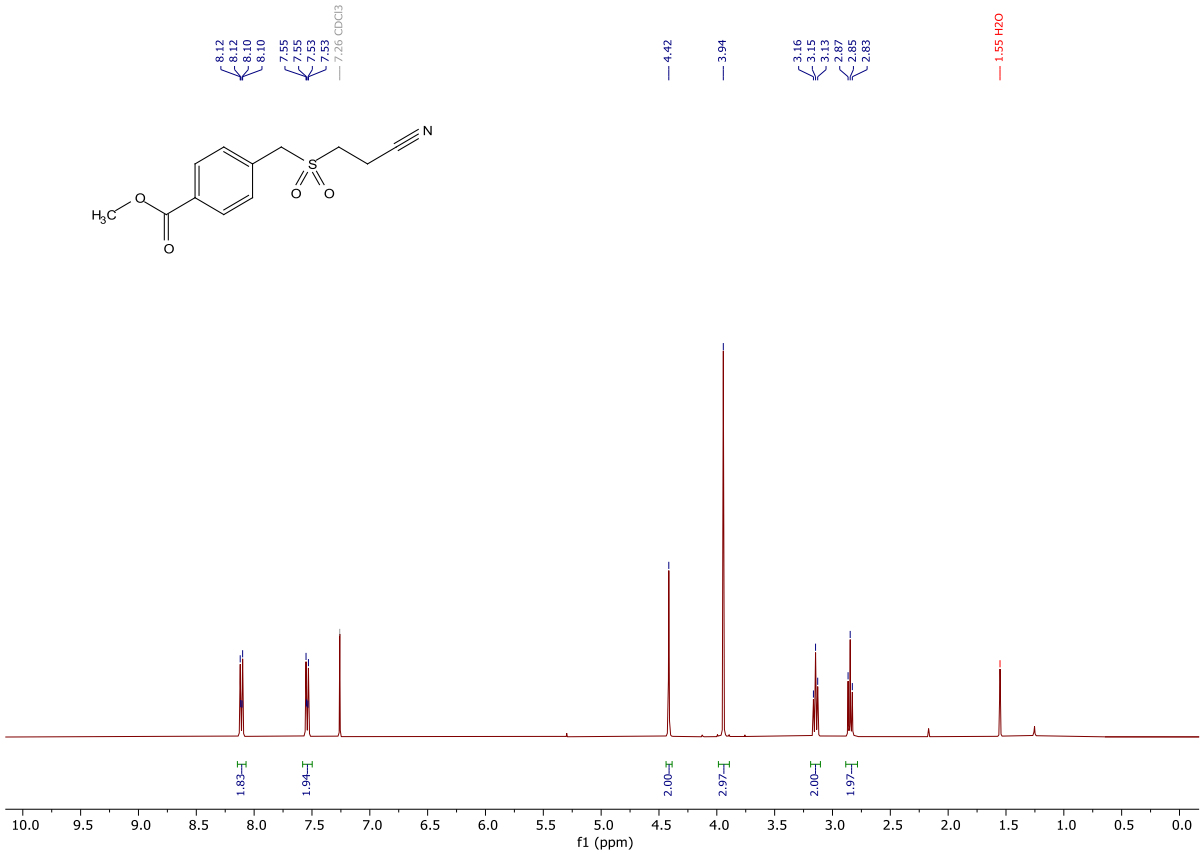


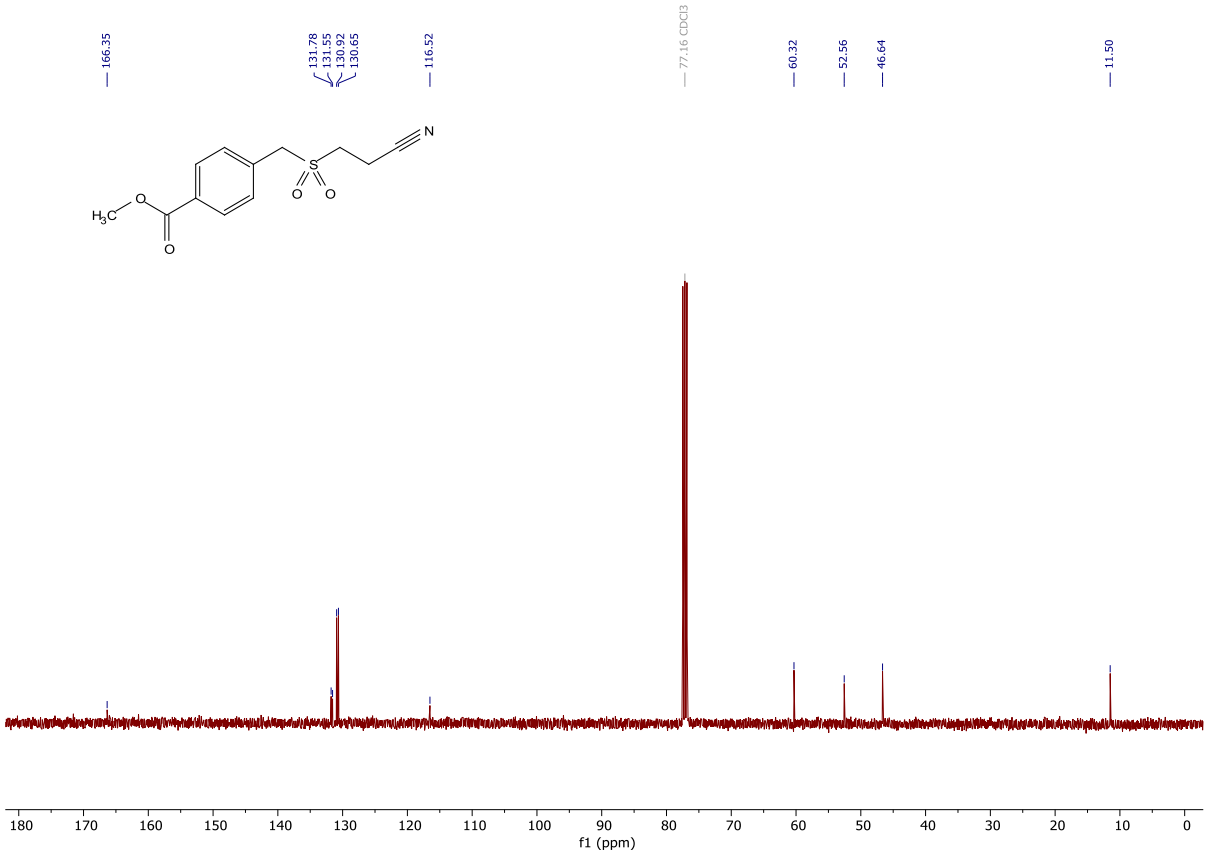




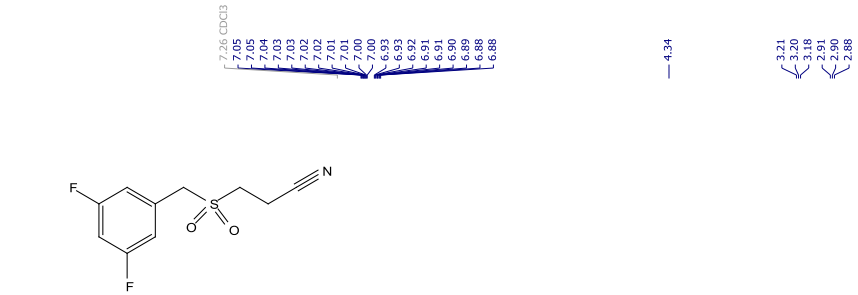


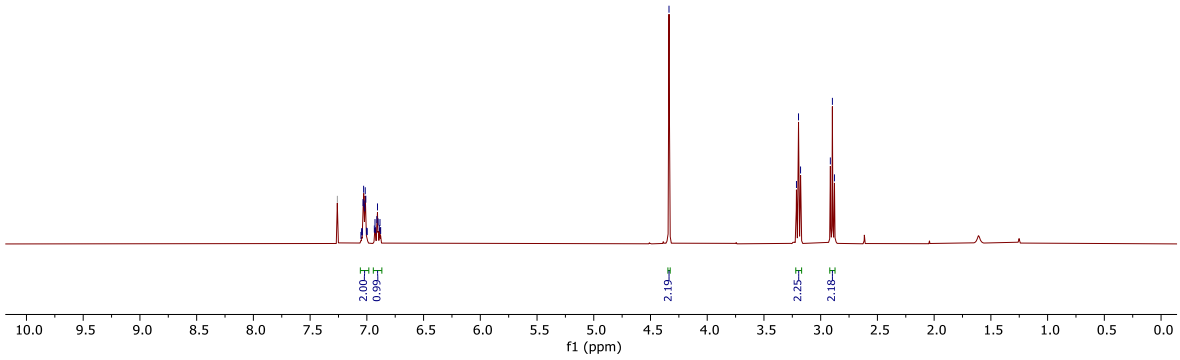
Methyl 4-(((2-cyanoethyl)sulfonyl)methyl)benzoate (3d)

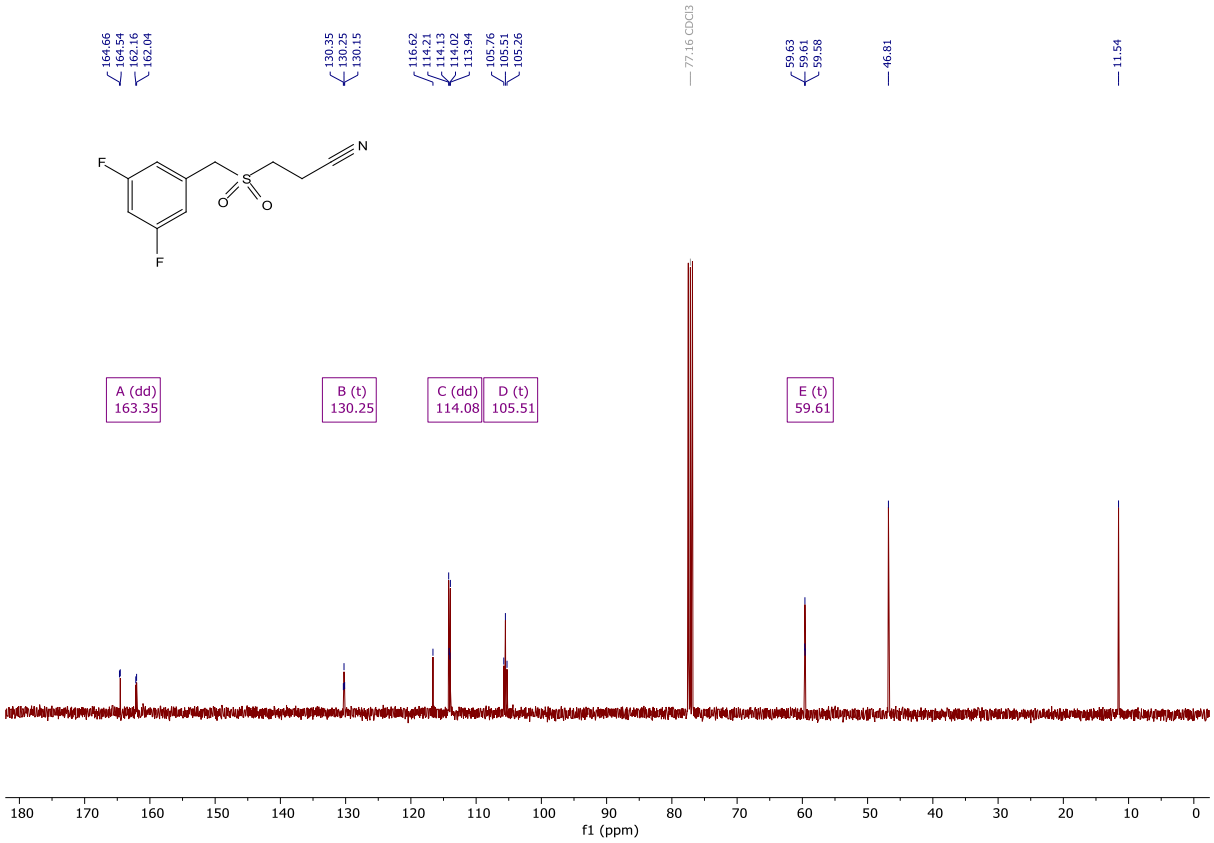


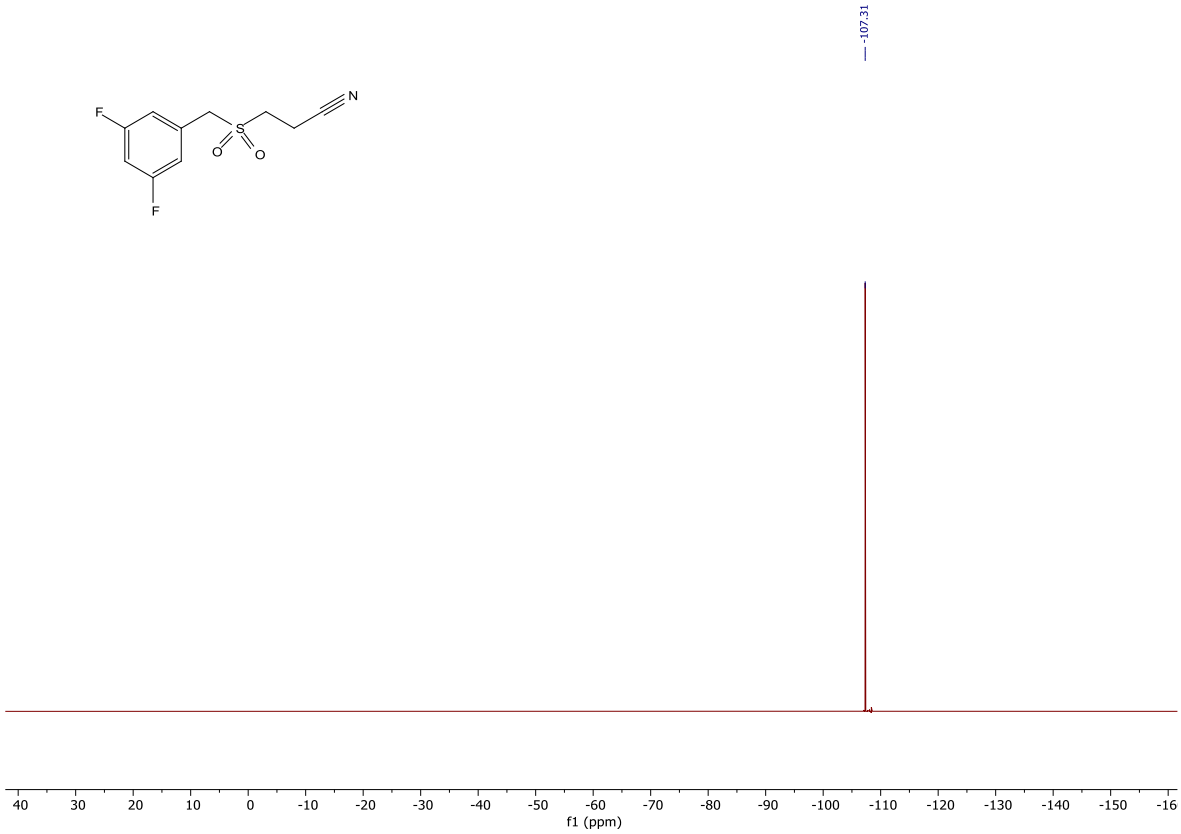


3-((3,5-Difluorobenzyl)sulfonyl)propanenitrile (3e)





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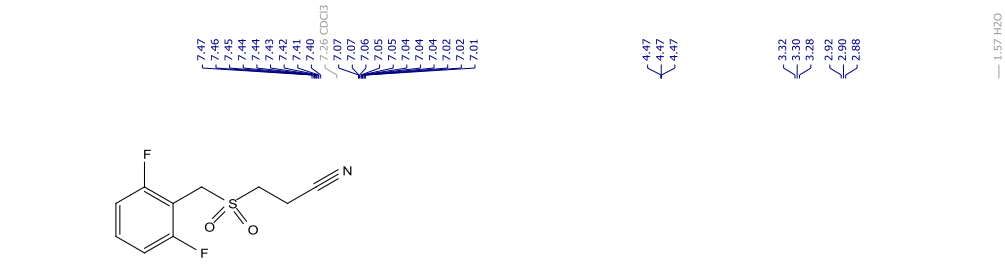
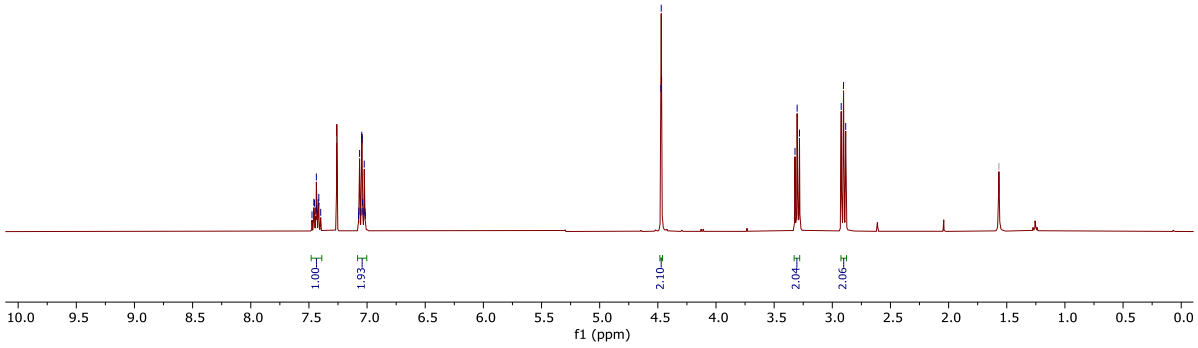
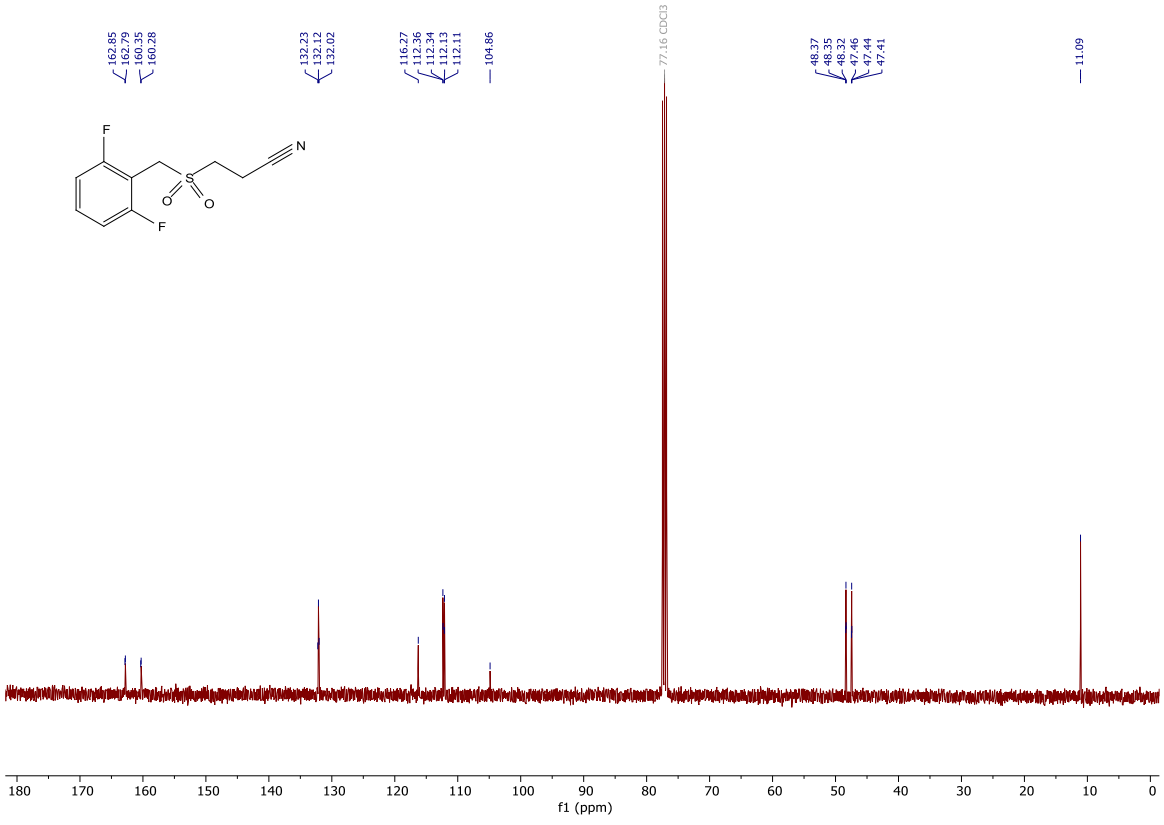
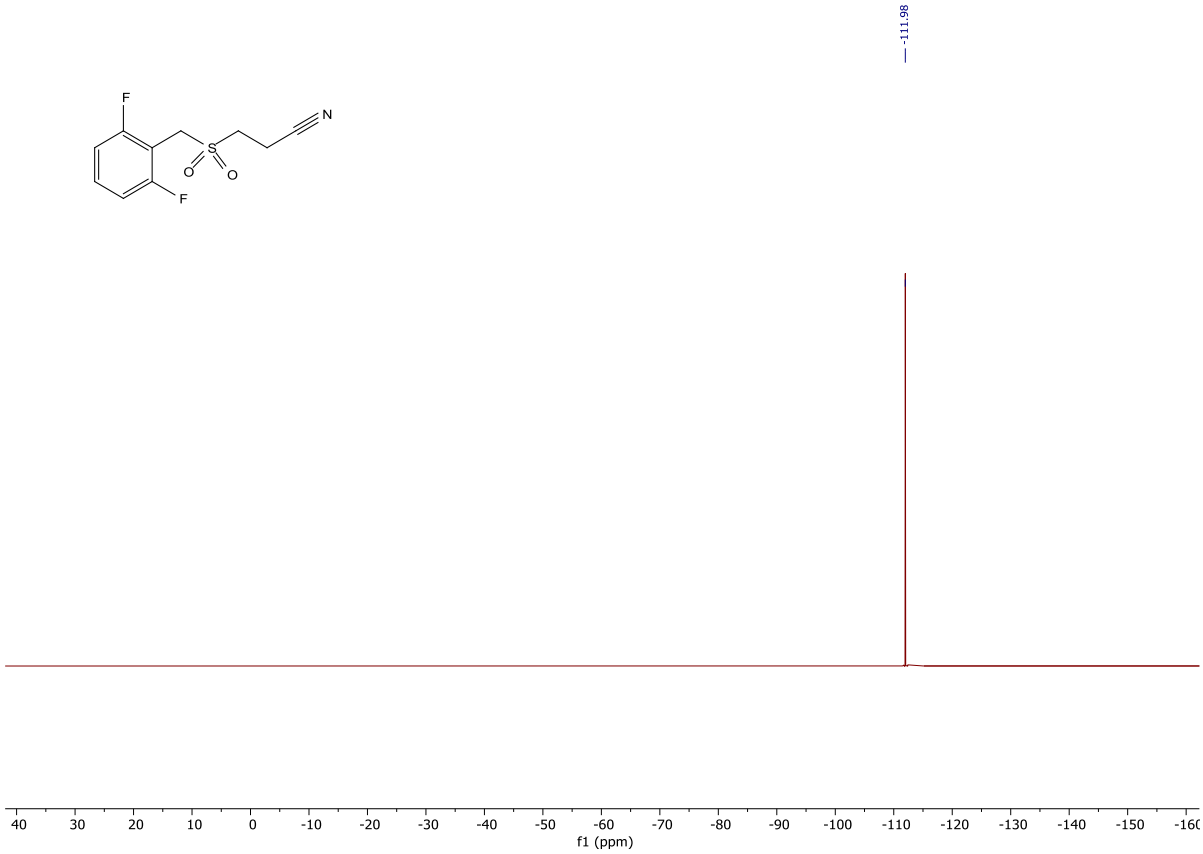
f1 (ppm)

3-((2,6-Difluorobenzyl)sulfonyl)propanenitrile (3f)





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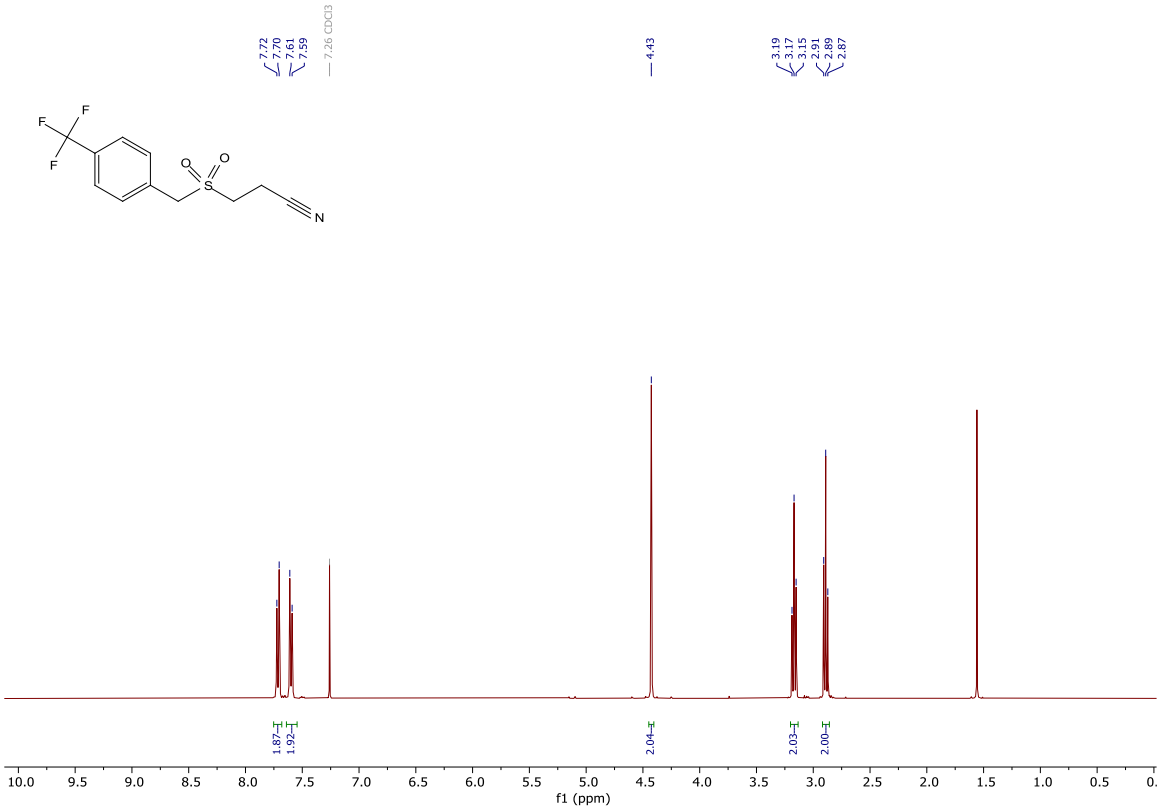
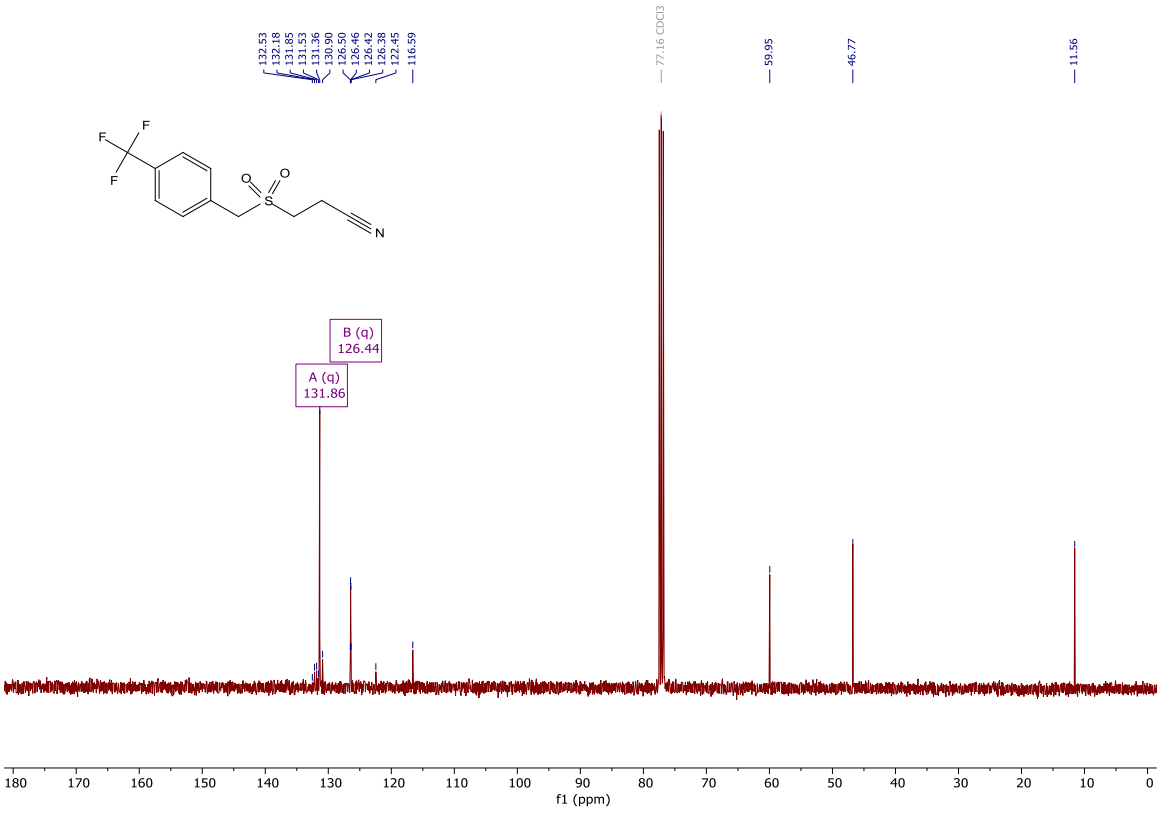
-150
f1 (ppm)

3-((4-(Trifluoromethyl)benzyl)sulfonyl)propanenitrile (3g)



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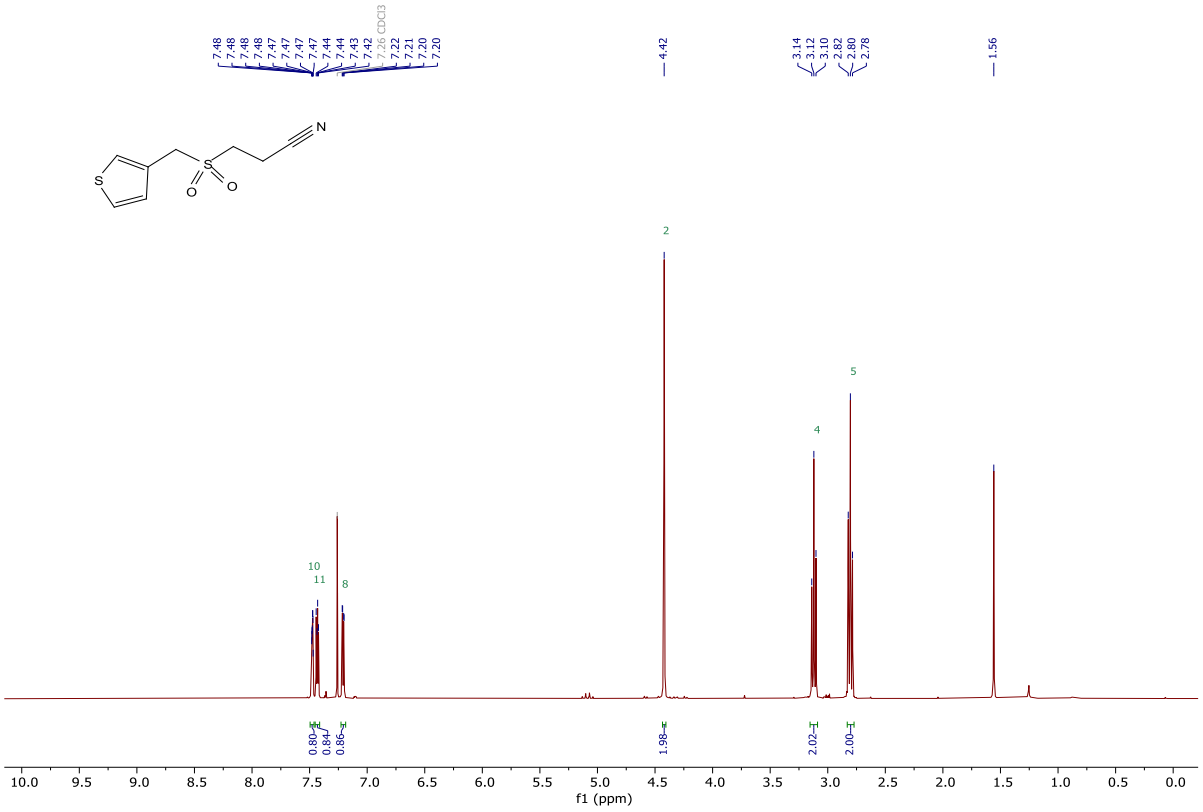
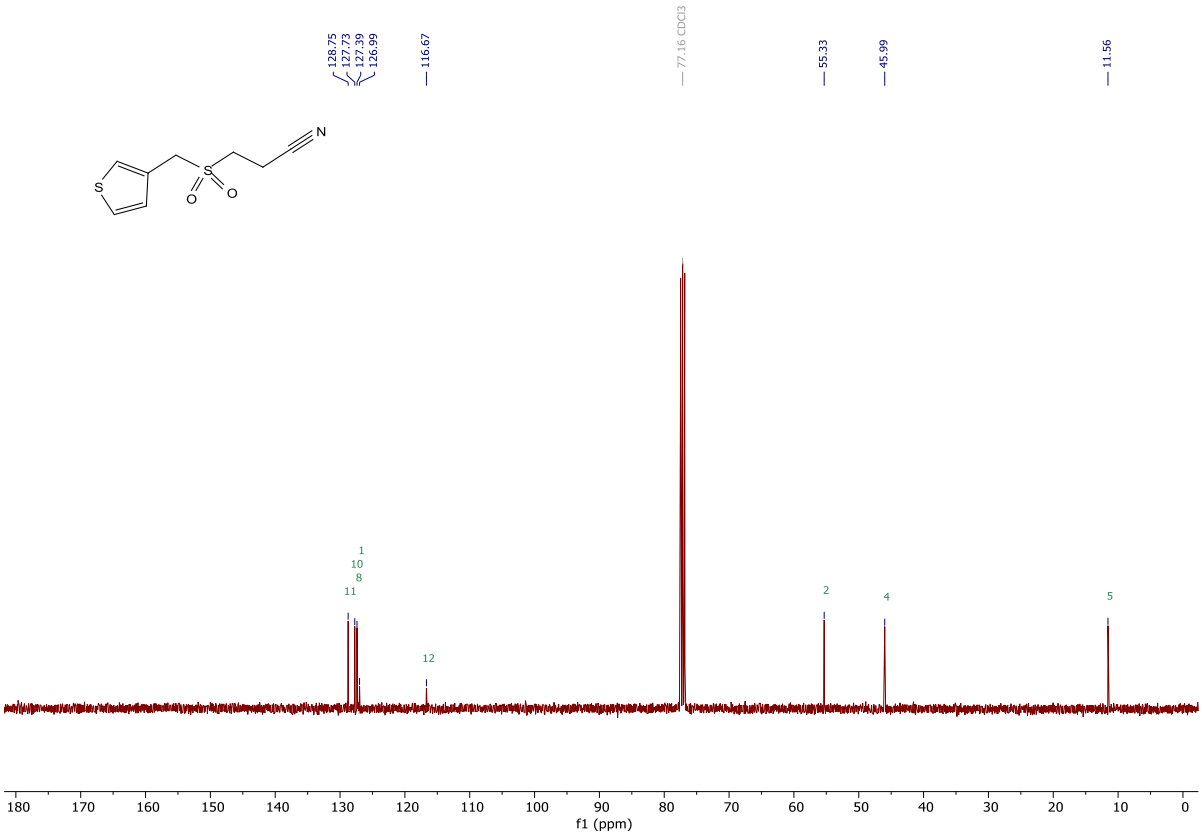
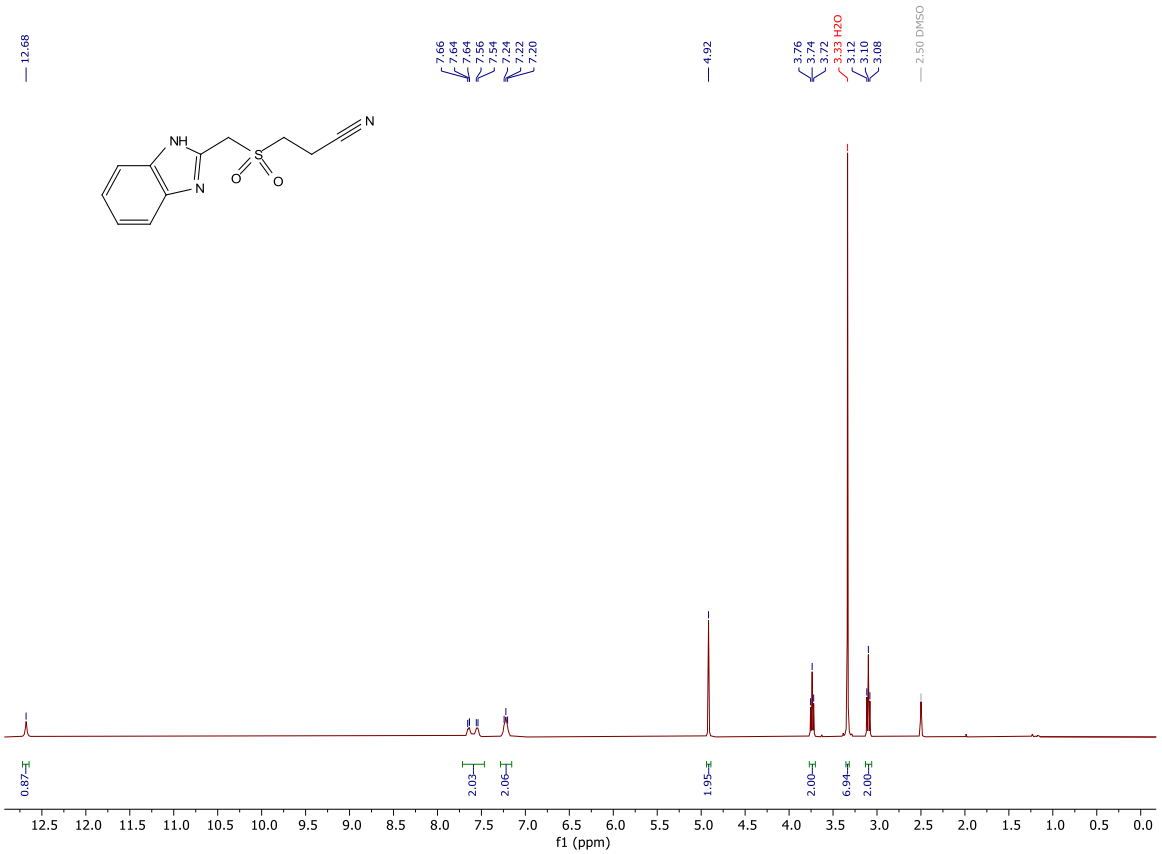
f1 (ppm)

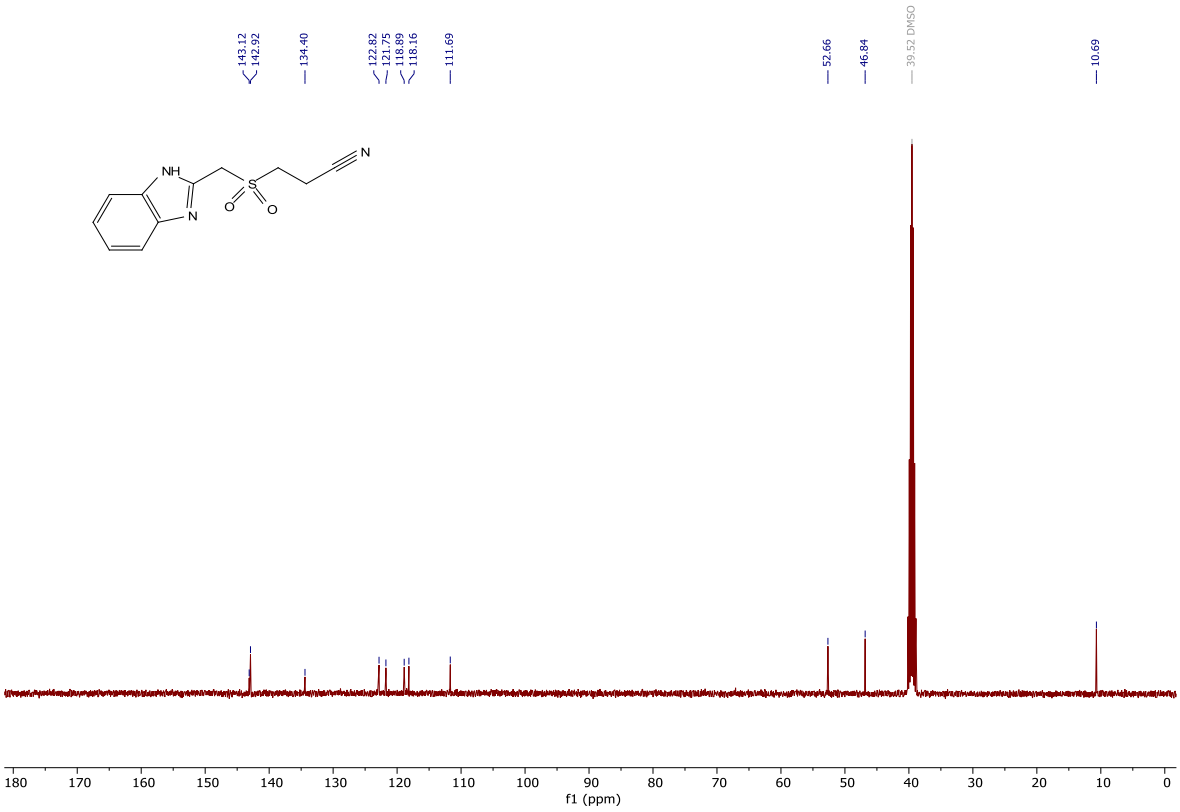
3-((Thiophen-3-ylmethyl)sulfonyl)propanenitrile (3h)



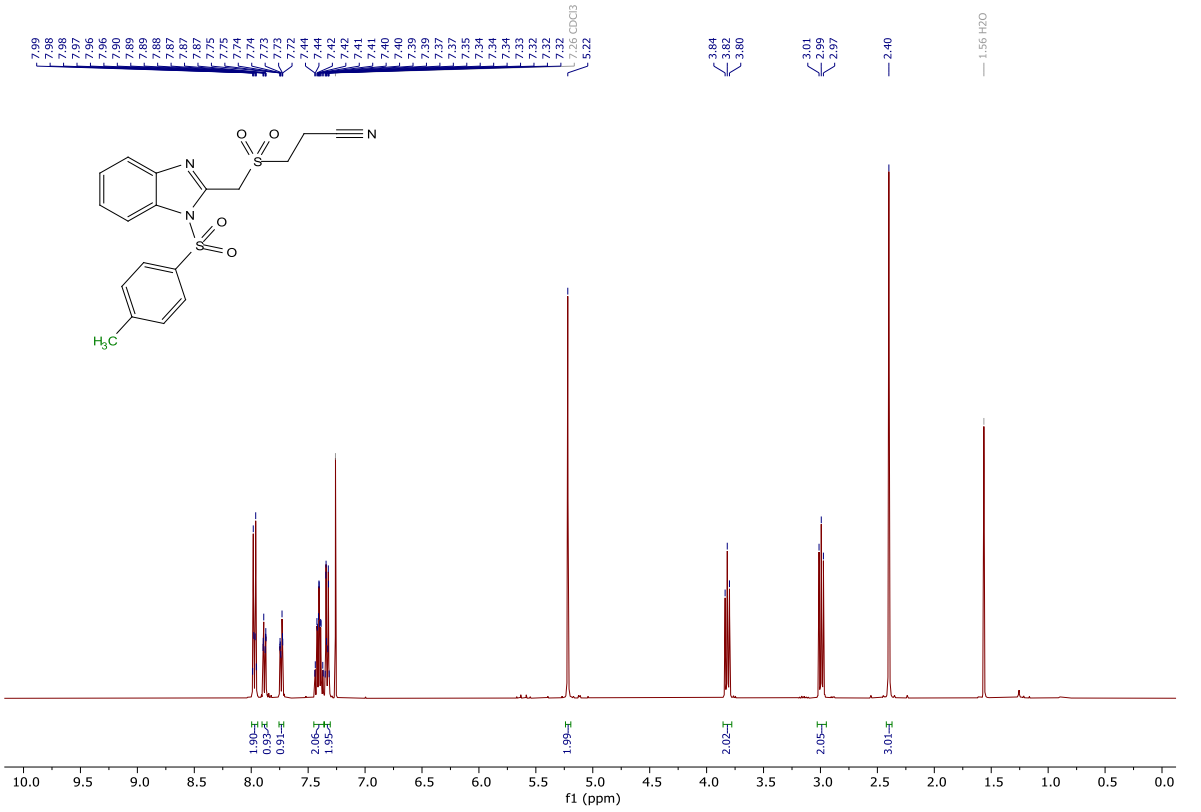


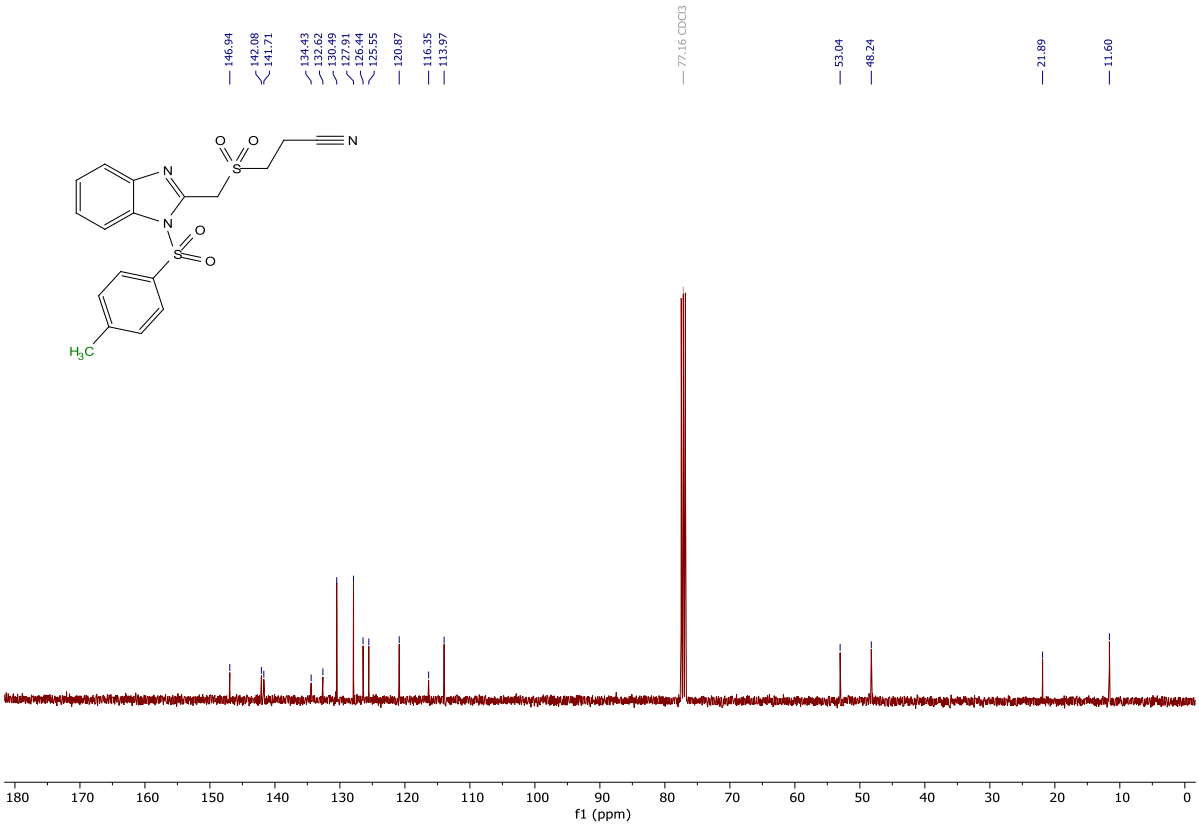
3-(((1H-Benzo[d]imidazol-2-yl)methyl)sulfonyl)propanenitrile (3i)



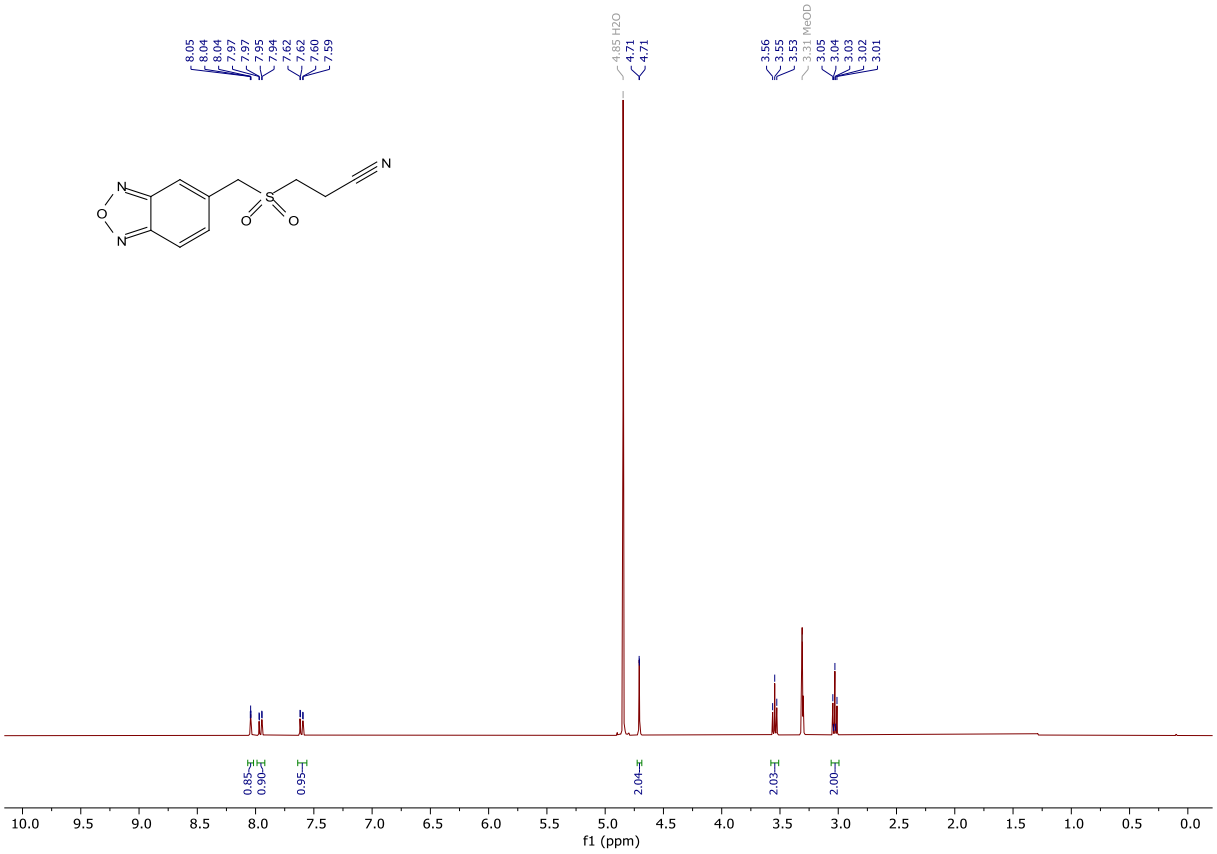


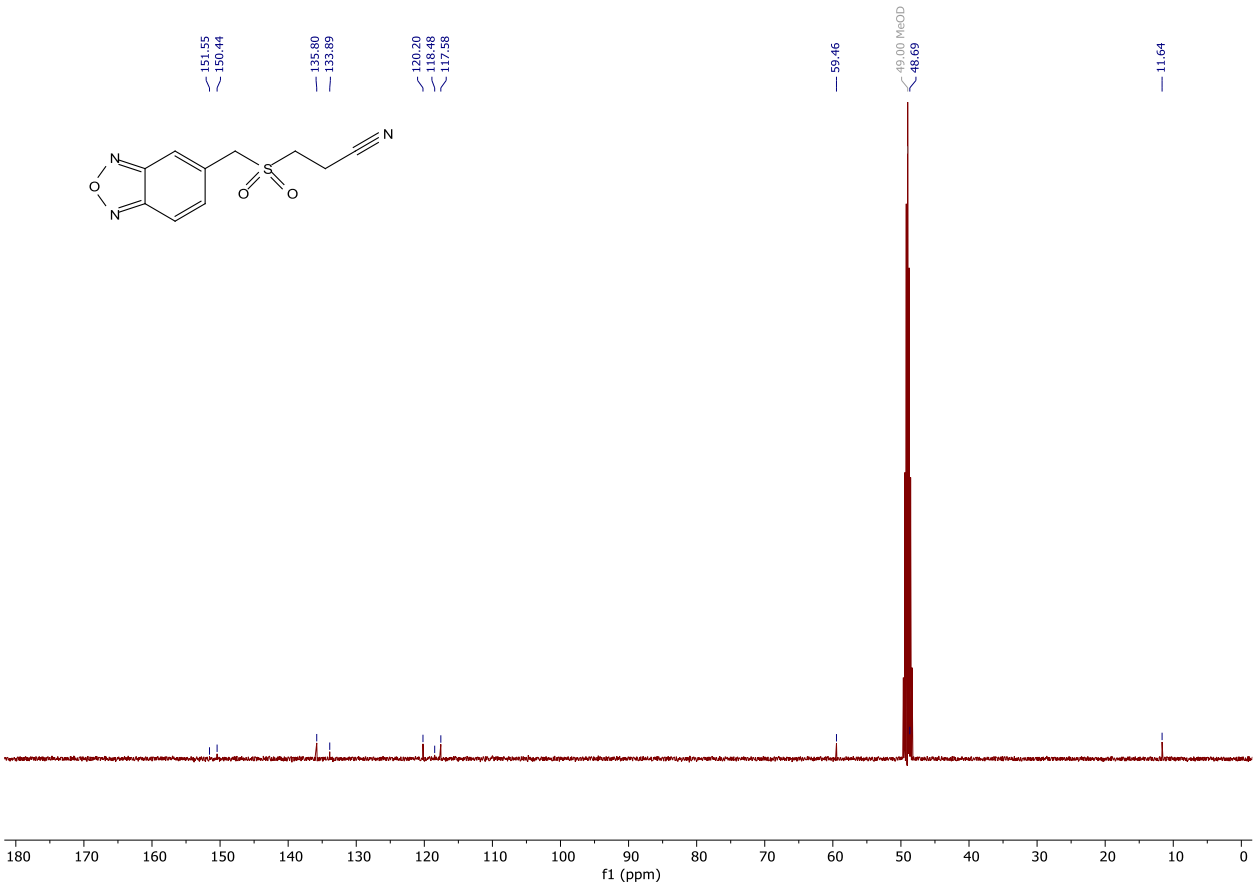
3-(((1-Tosyl-1H-benzo[d]imidazol-2-yl)methyl)sulfonyl)propanenitrile (3j)



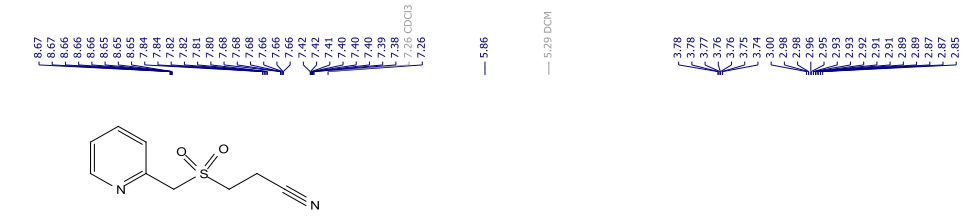


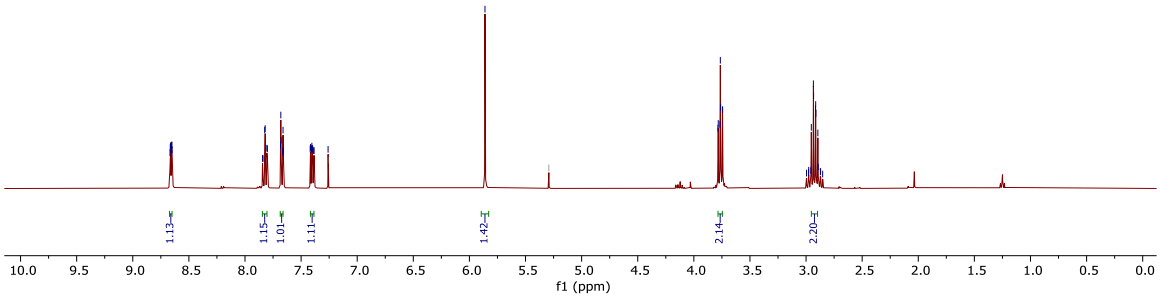
3-((Benzo[c][1,2,5]oxadiazol-5-ylmethyl)sulfonyl)propanenitrile (3k)

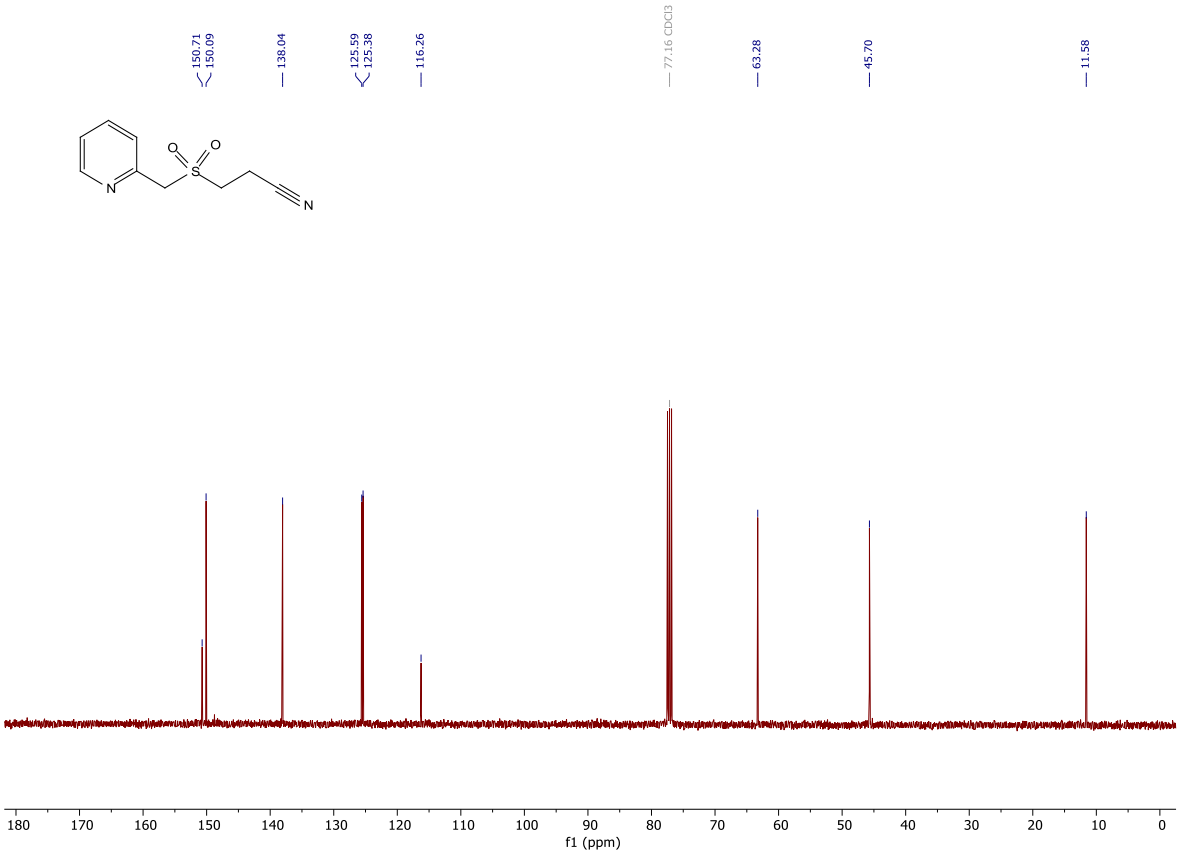




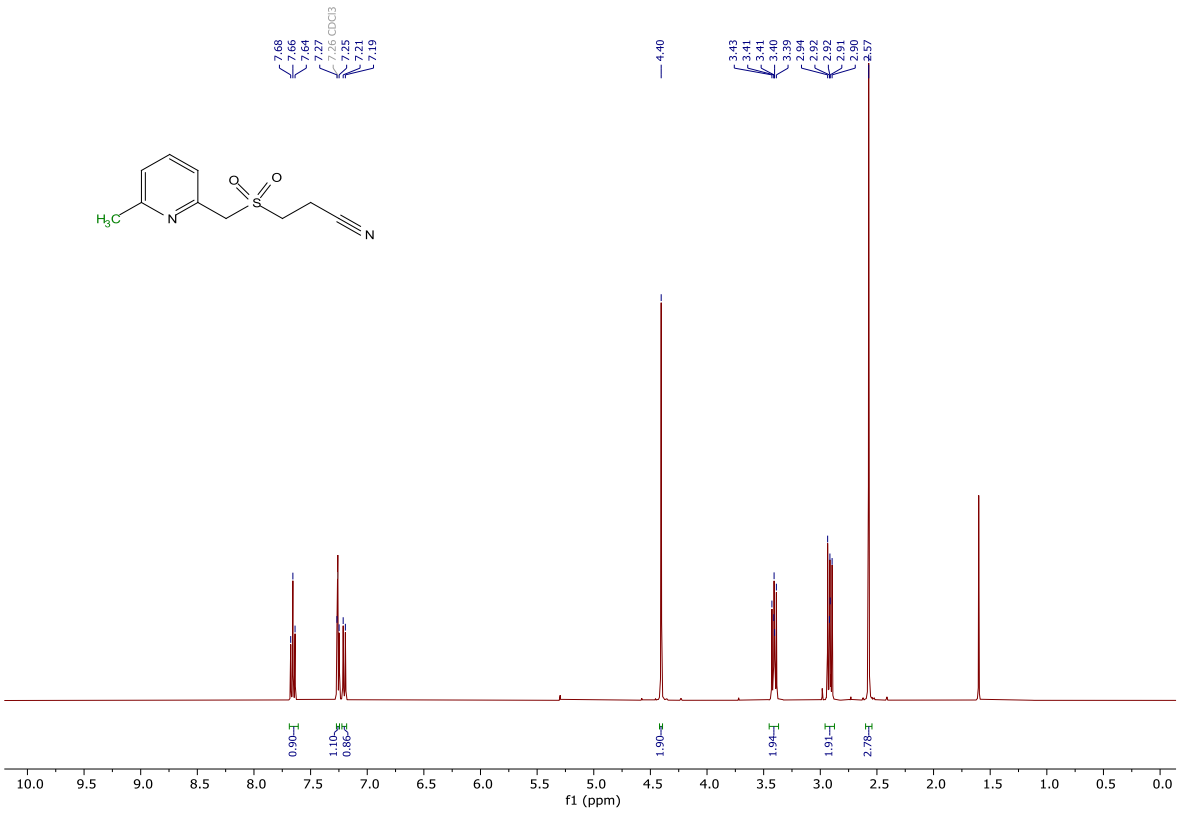
3-((Pyridin-2-ylmethyl)sulfonyl)propanenitrile (3l)

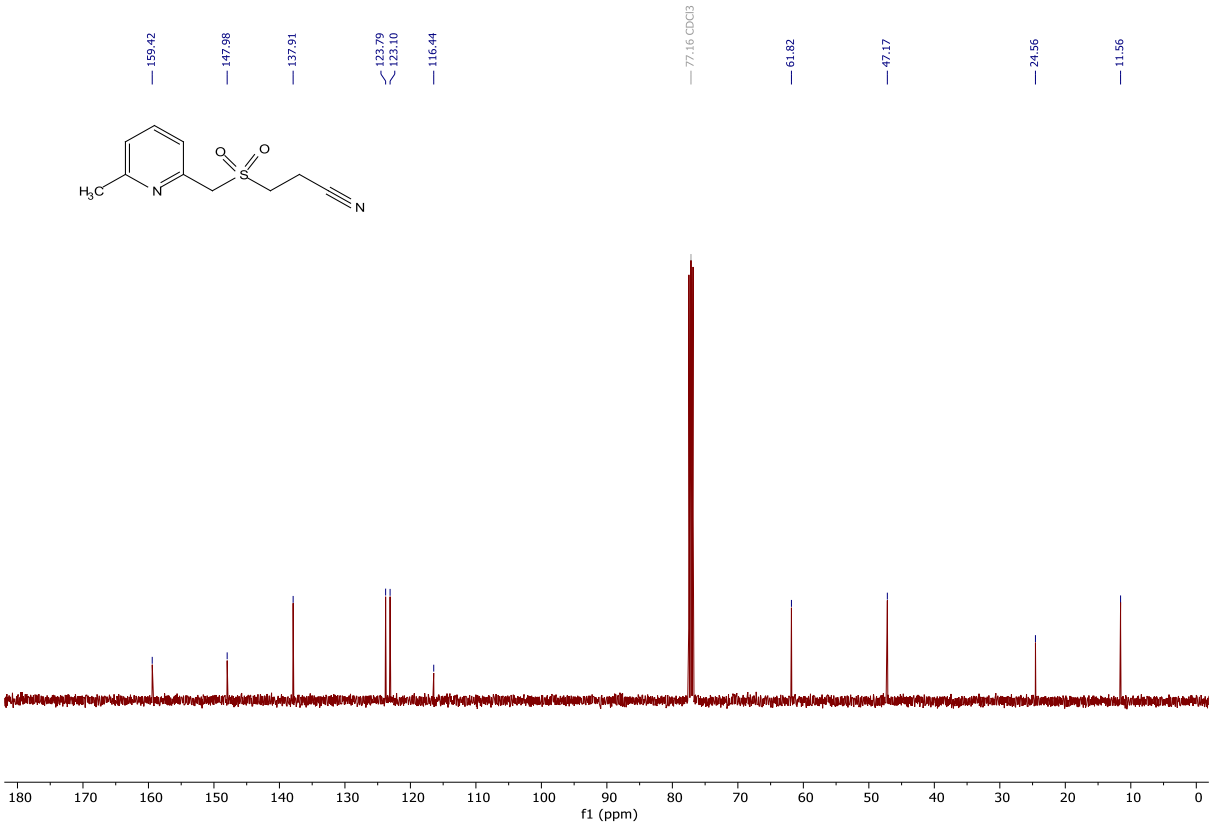




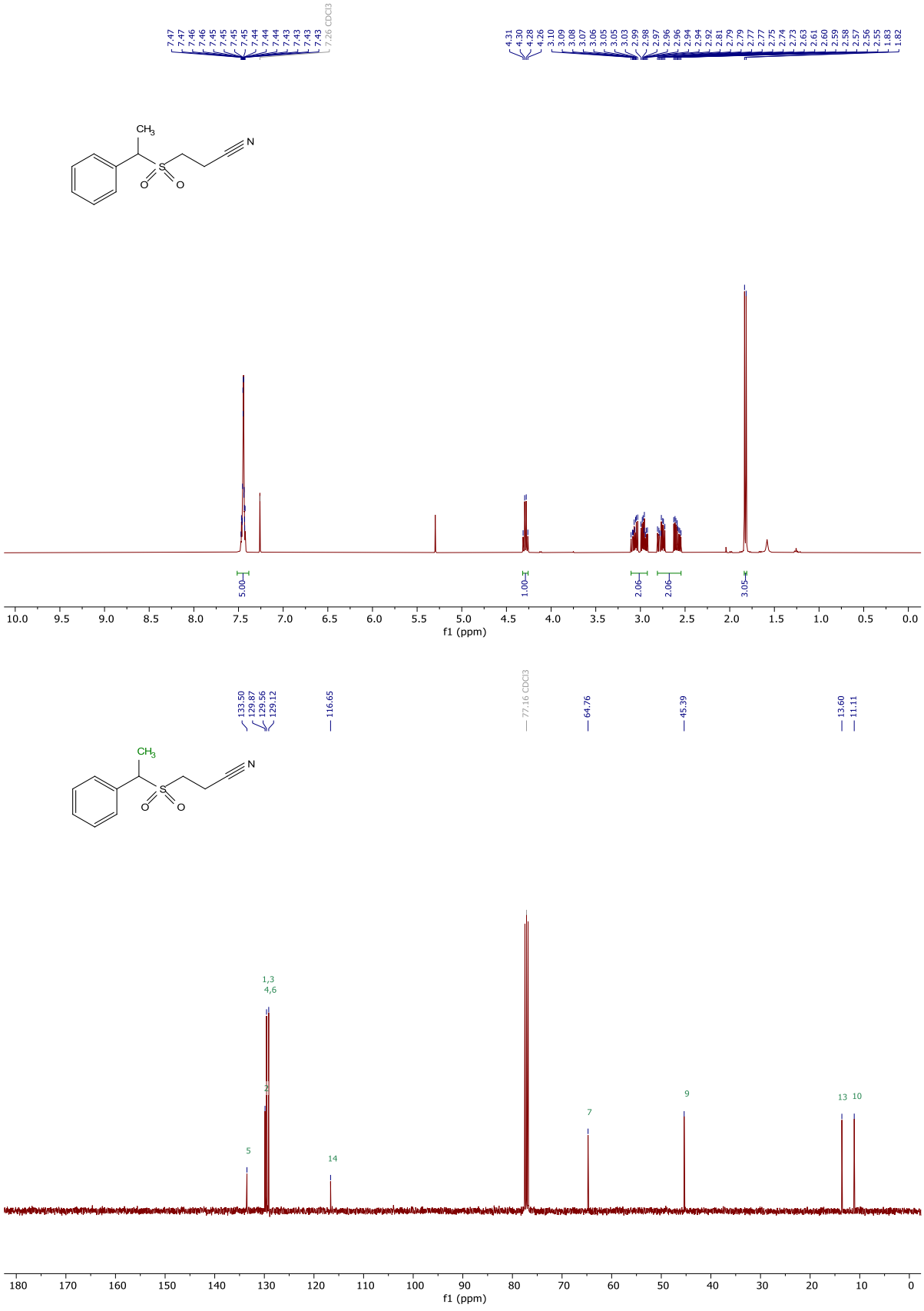


3-(((6-Methylpyridin-2-yl)methyl)sulfonyl)propanenitrile (3m)

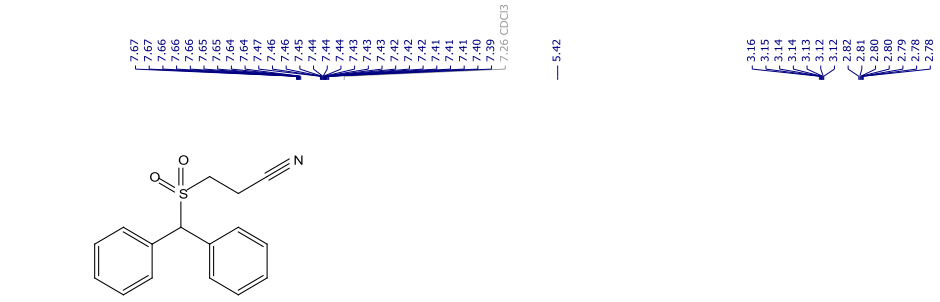


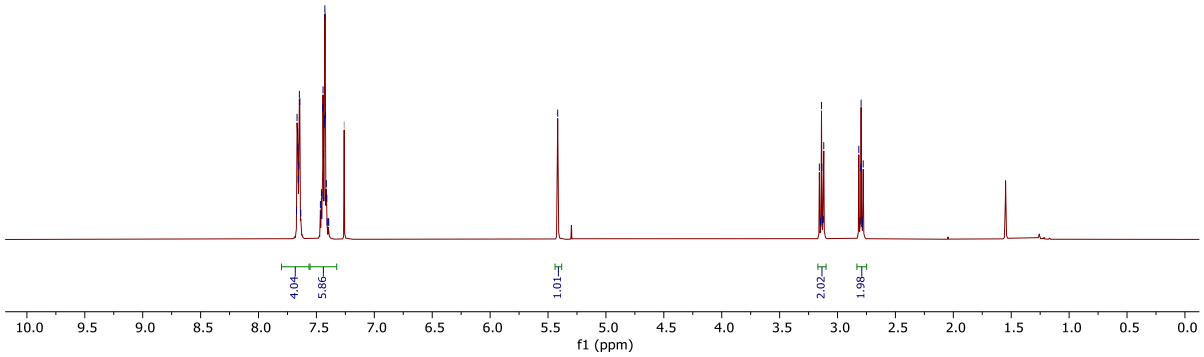


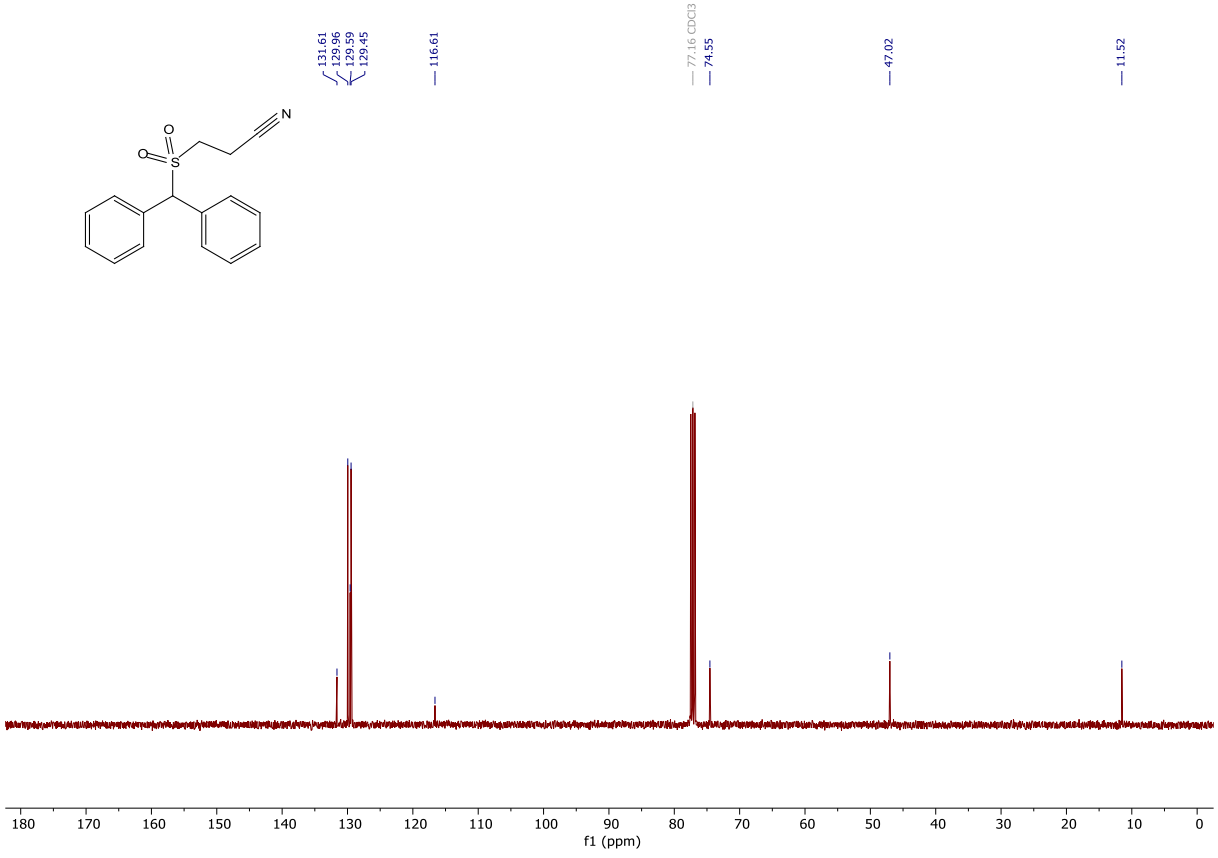
3-((1-Phenylethyl)sulfonyl)propanenitrile (3n)



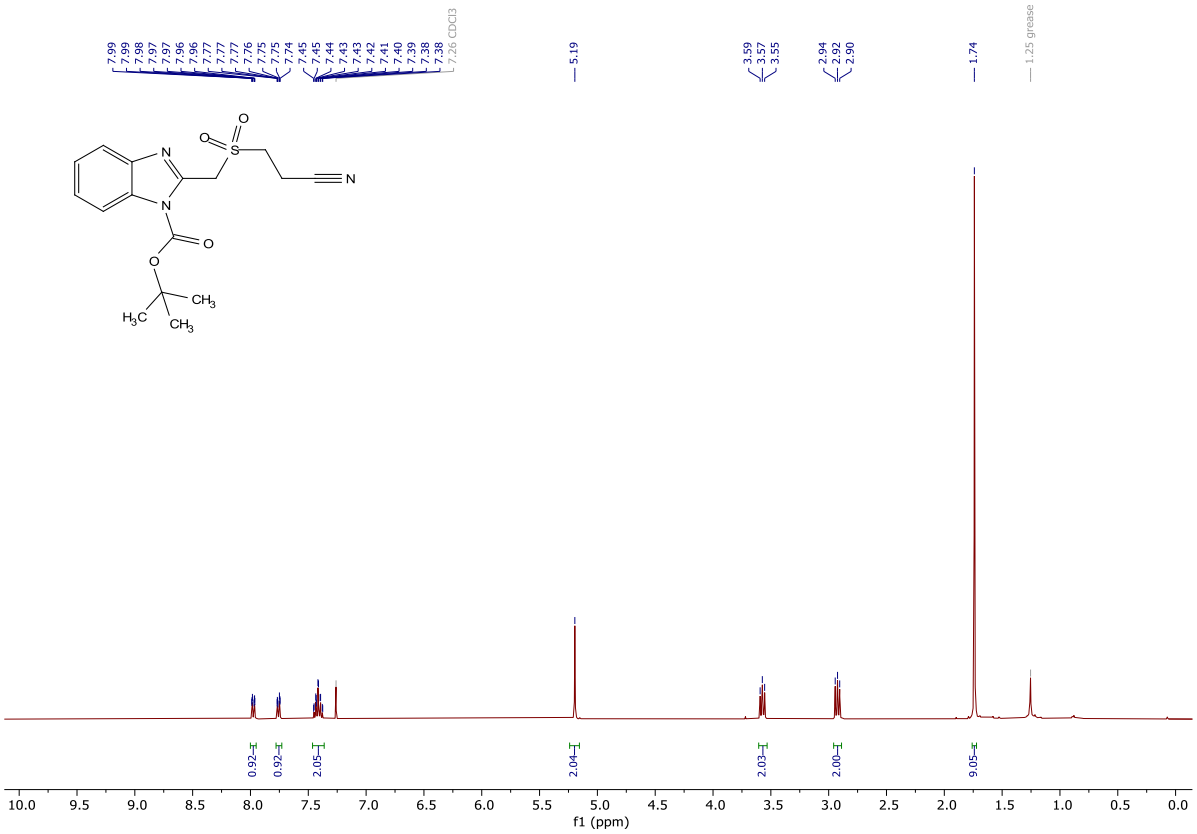
3-(Benzhydrylsulfonyl)propanenitrile (3o)

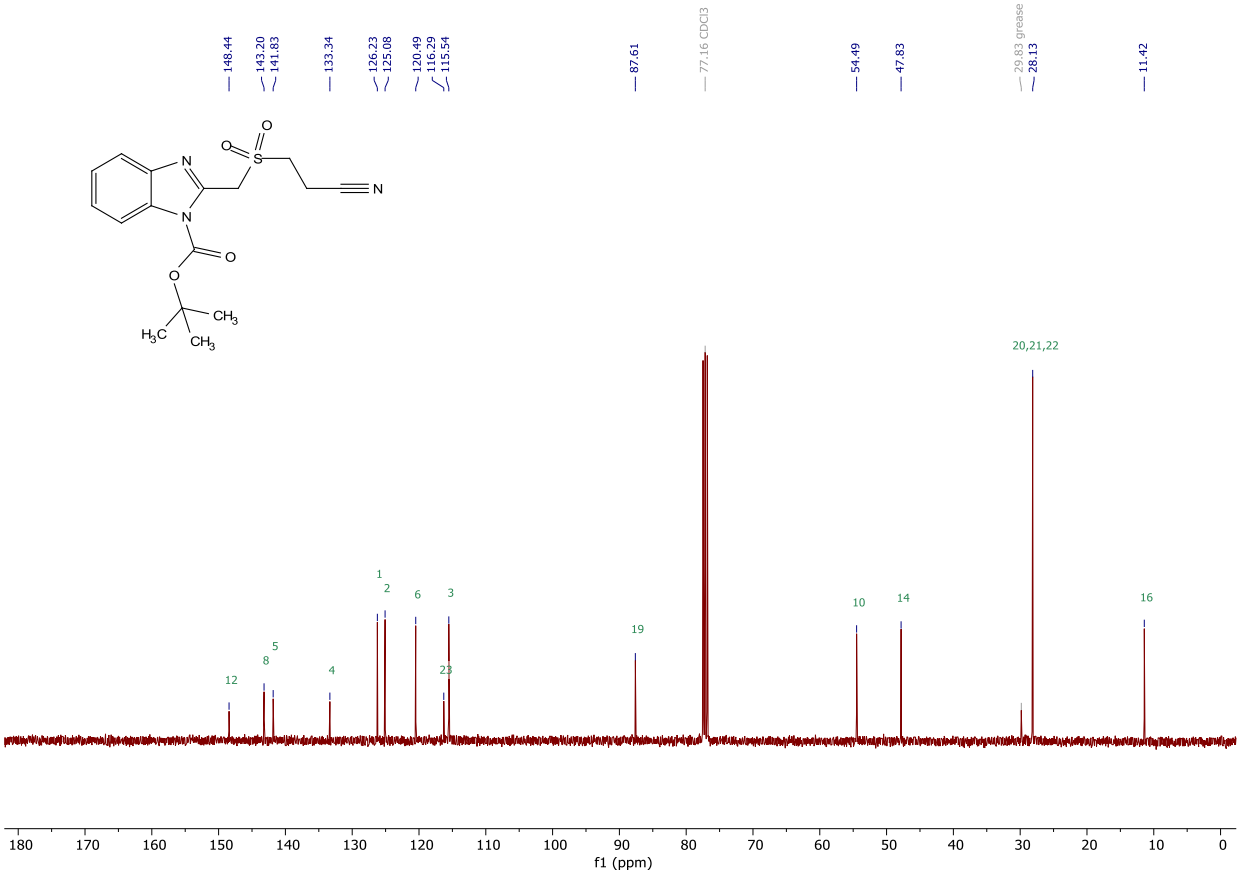




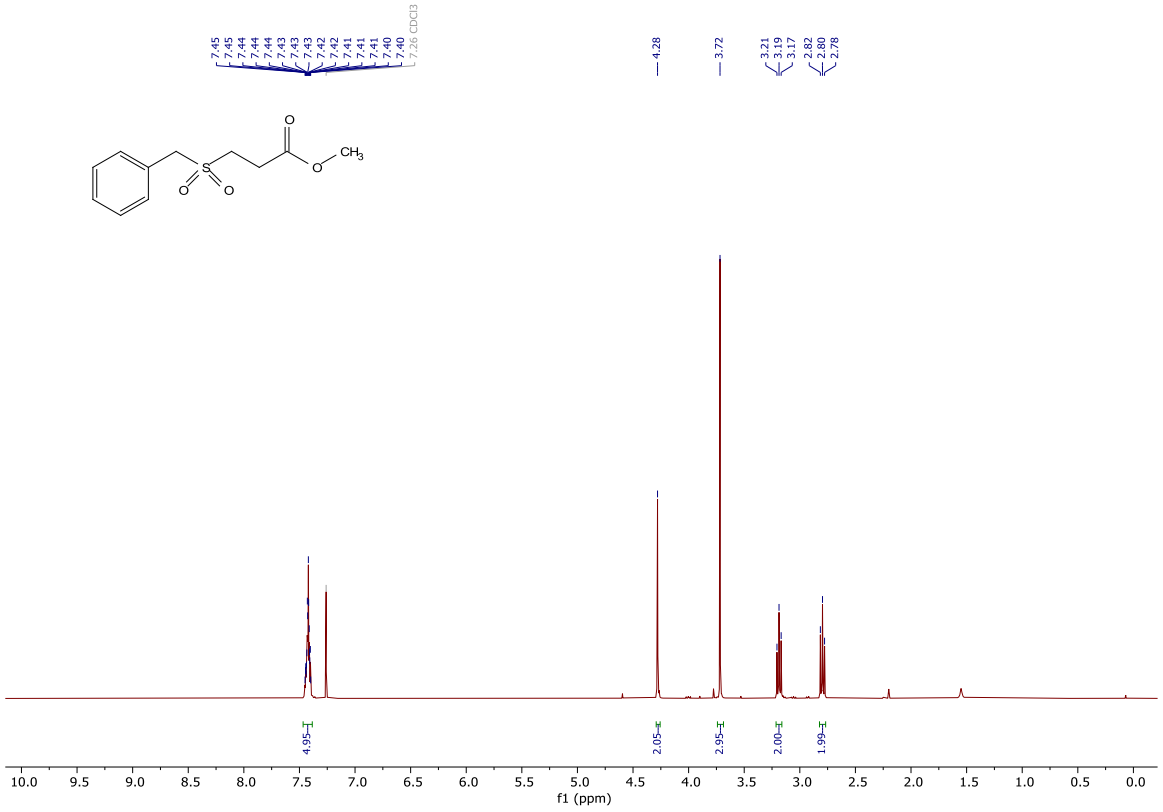


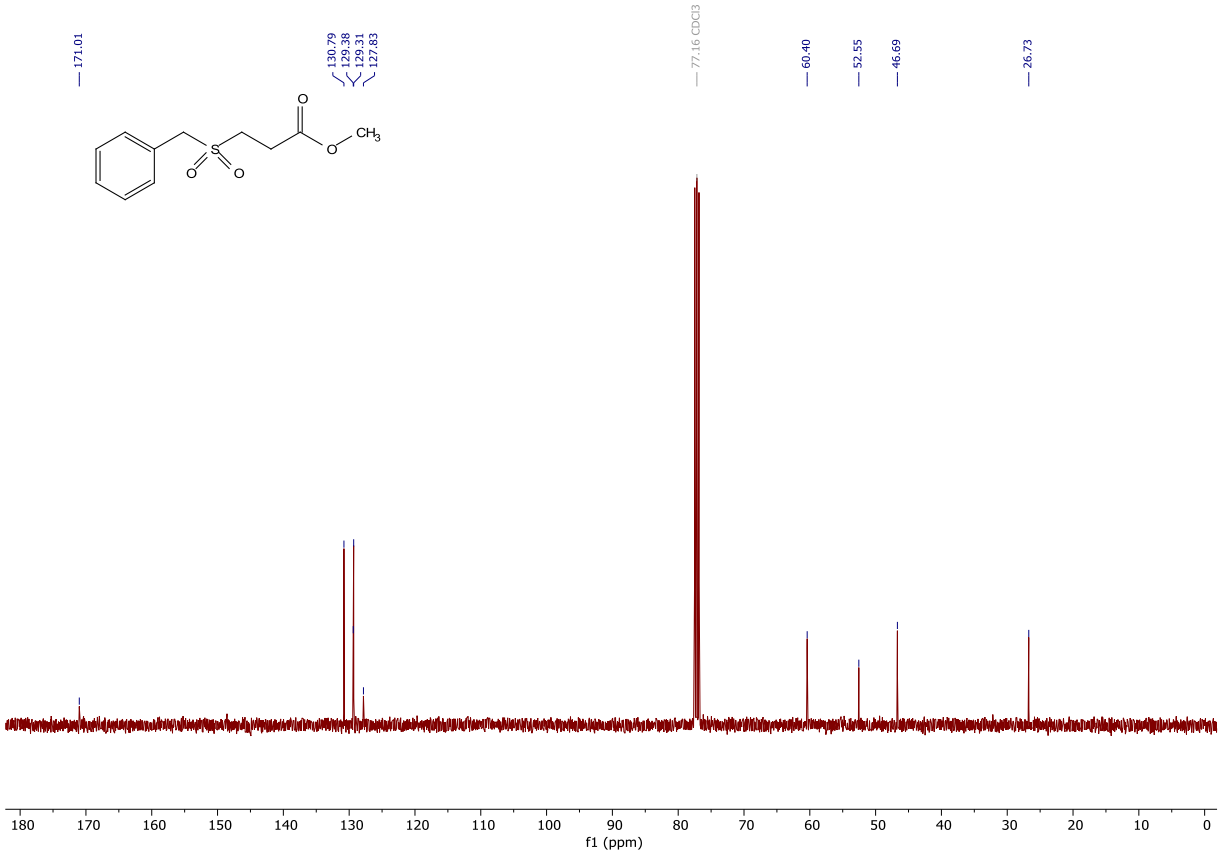
Tert-butyl 2-(((2-cyanoethyl)sulfonyl)methyl)-1H-benzo[d]imidazole-1-carboxyl (3p)



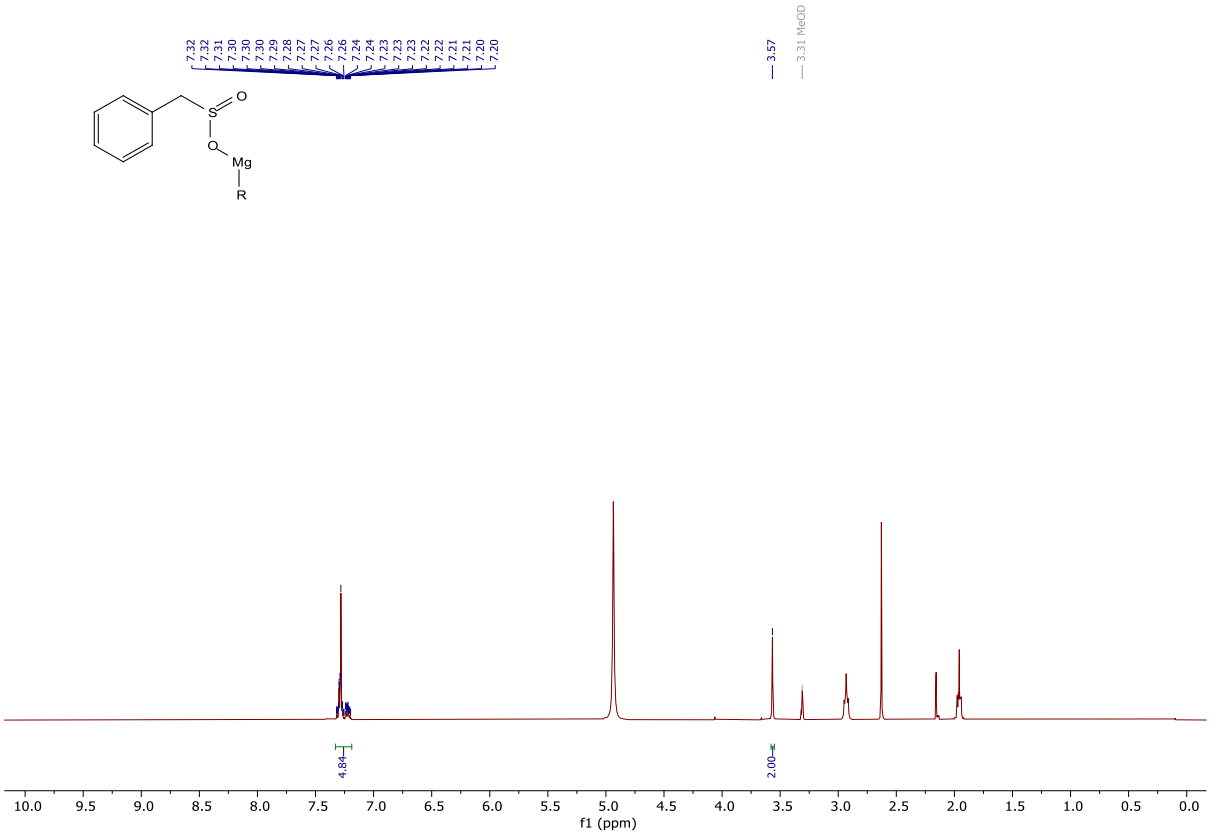


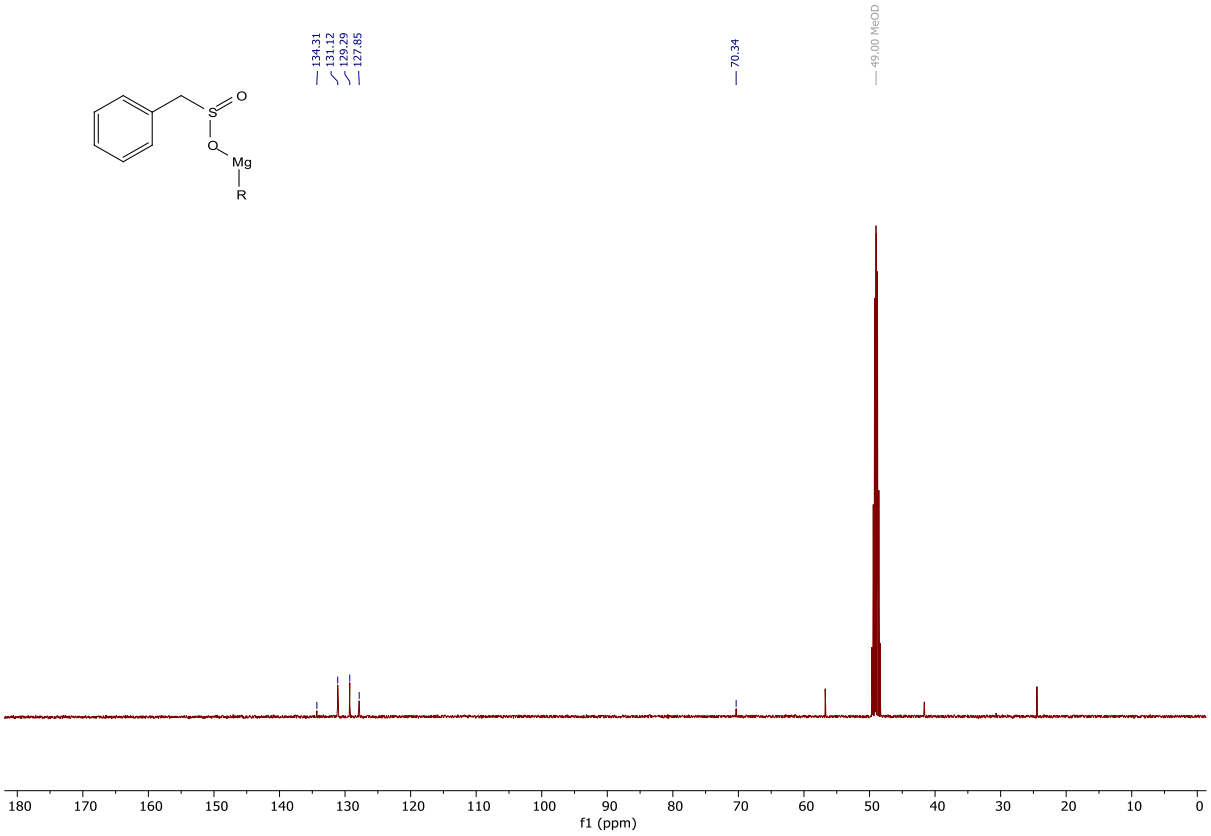
Methyl 3-(benzylsulfonyl)propanoate (3q)



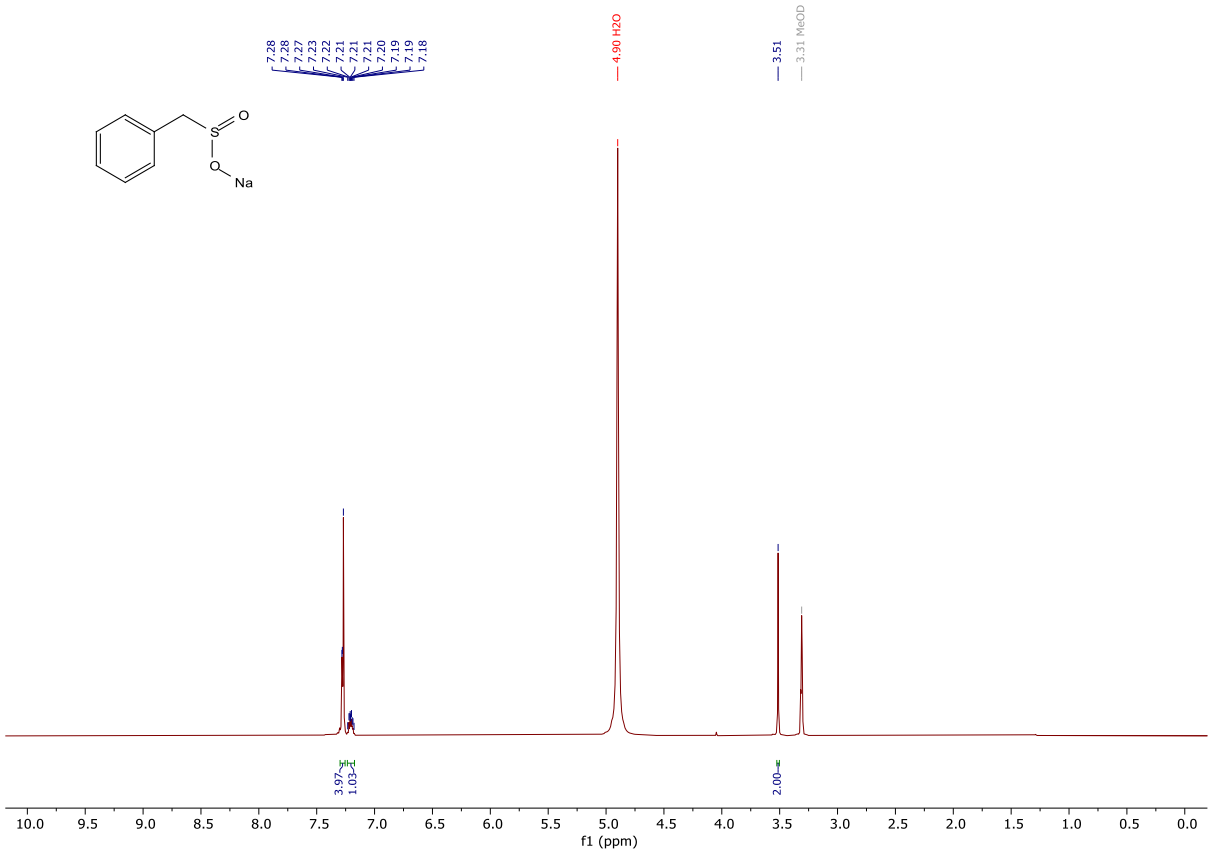


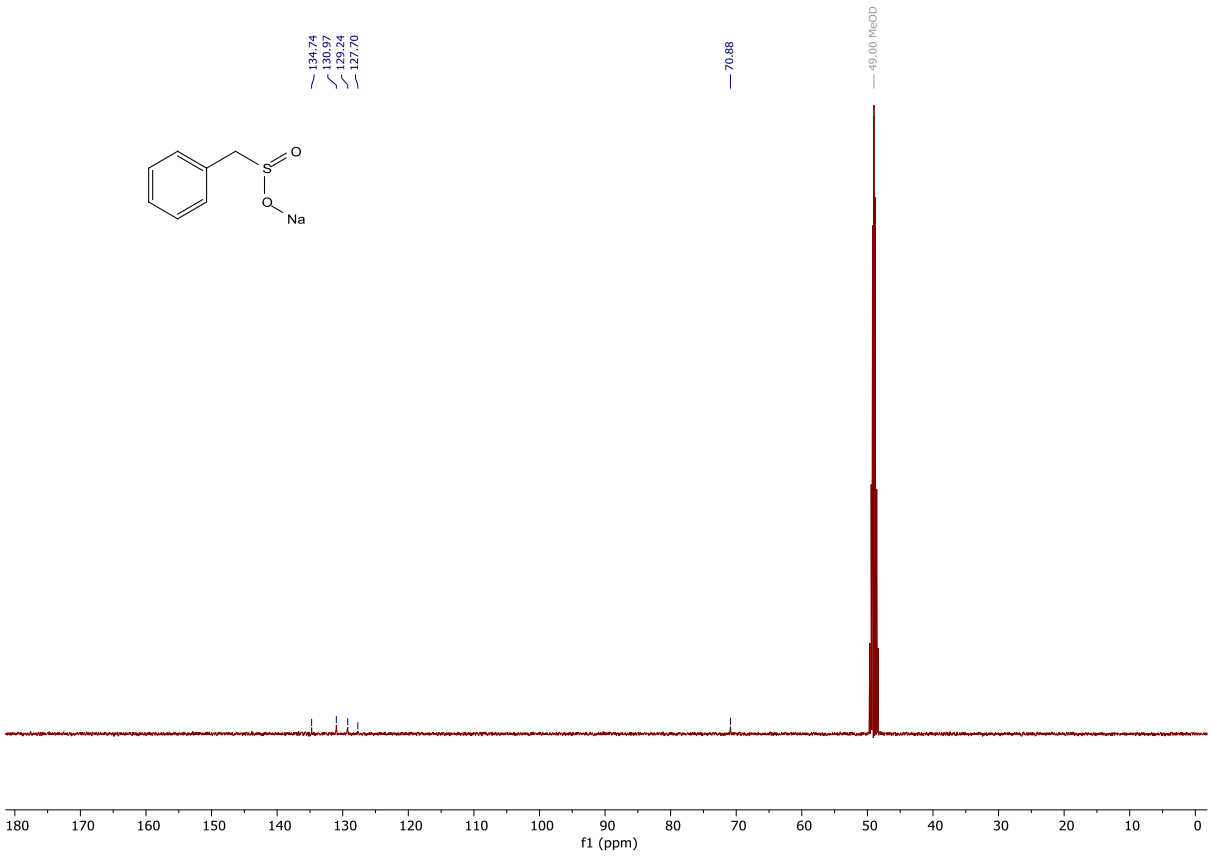
Magnesium benzylsulfinate (1b)



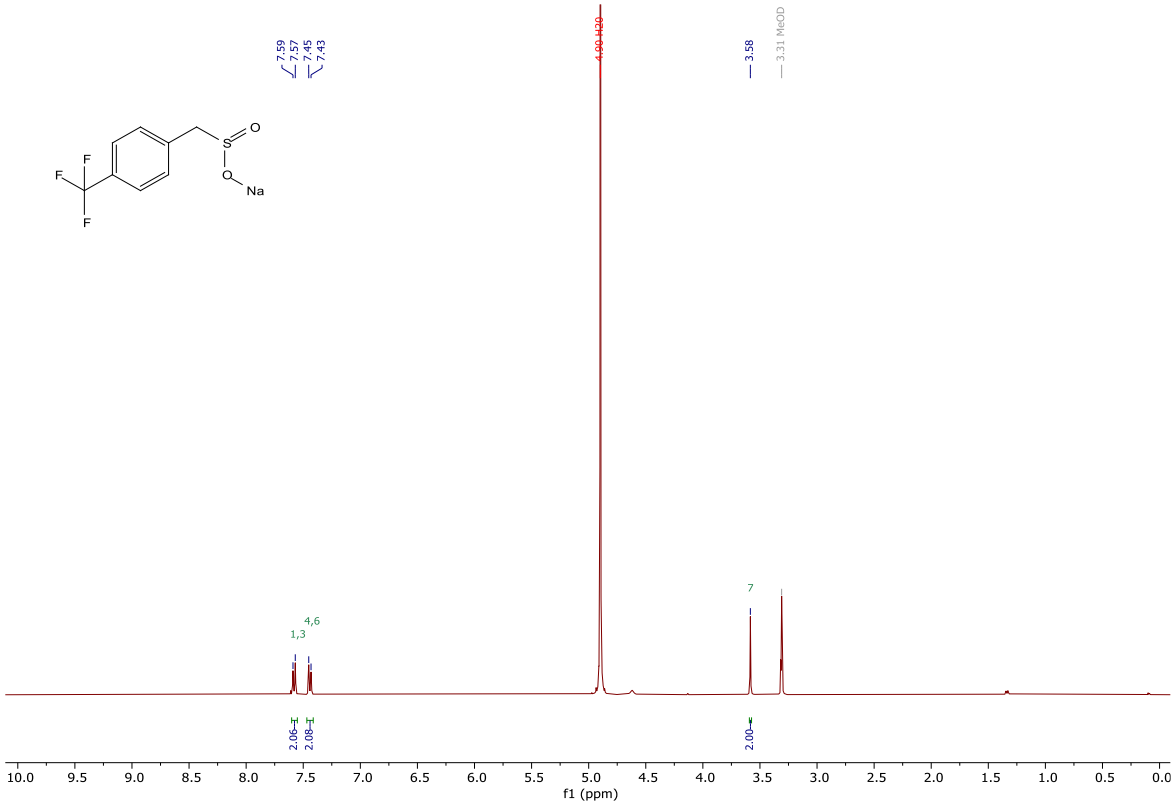


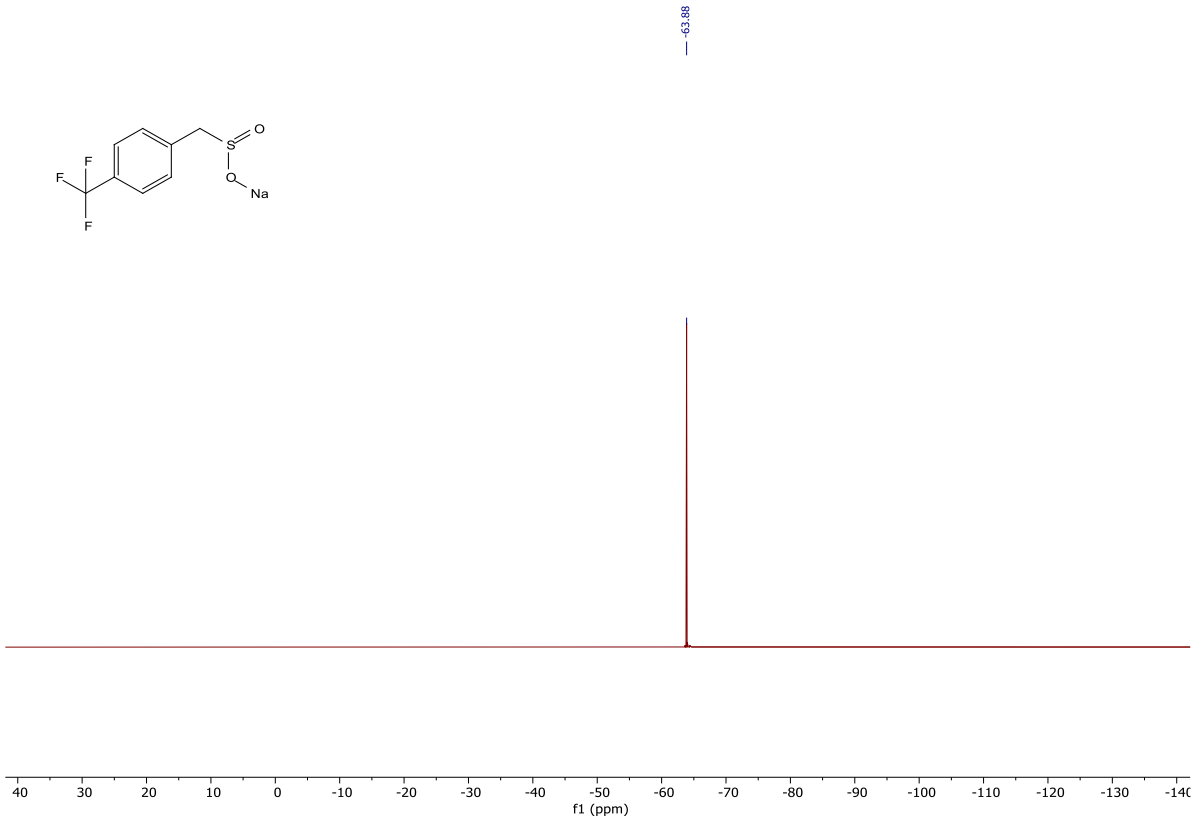
Sodium benzylsulfinate (1c)

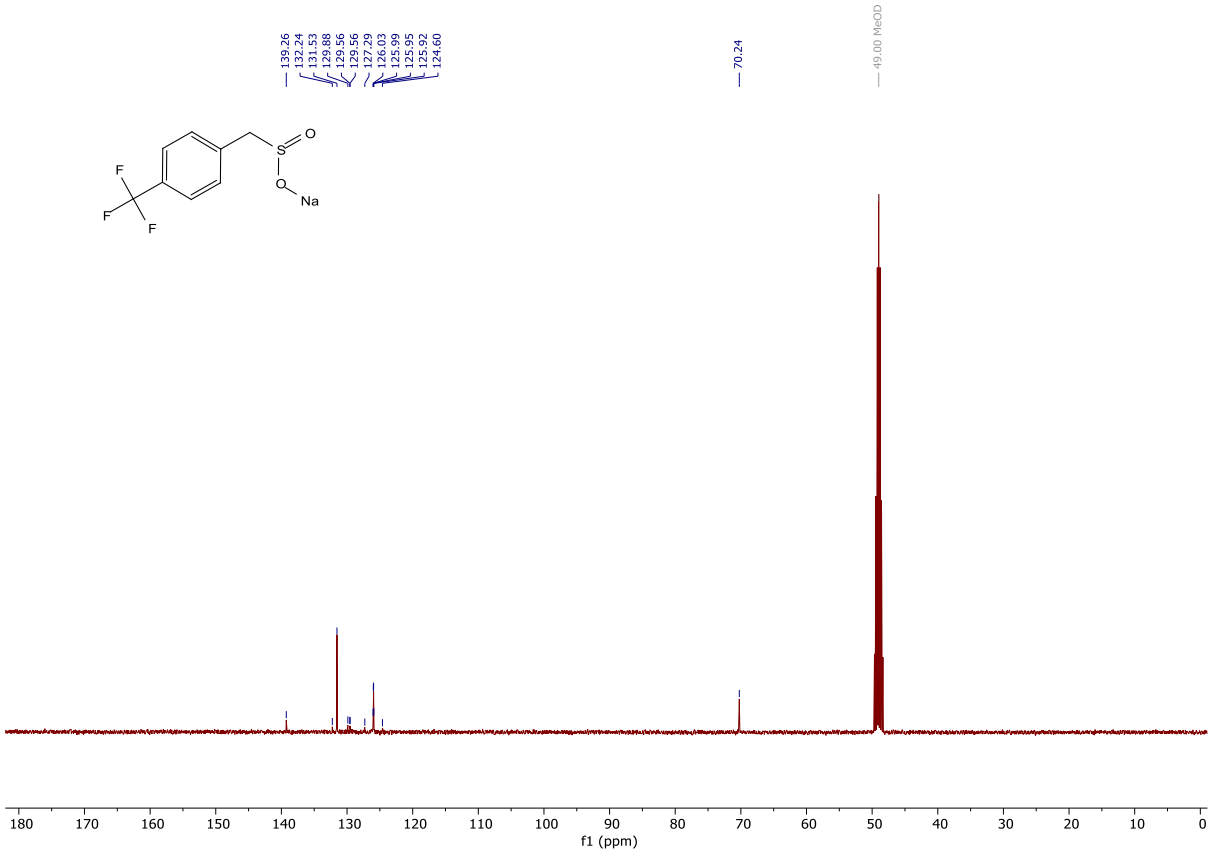




Sodium (4-(trifluoromethyl)phenyl)methanesulfinate (1d)


7.59
7.57
7.45
7.43
4.90 H2O
3.58
3.31 MeOD
F
F
F
S
O
O
Na
1,3
4,6
7
2.06
2.08
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


-63.88
F
F
F
S
O
O
Na
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140
f1 (ppm)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132.24
131.53
129.88
129.56
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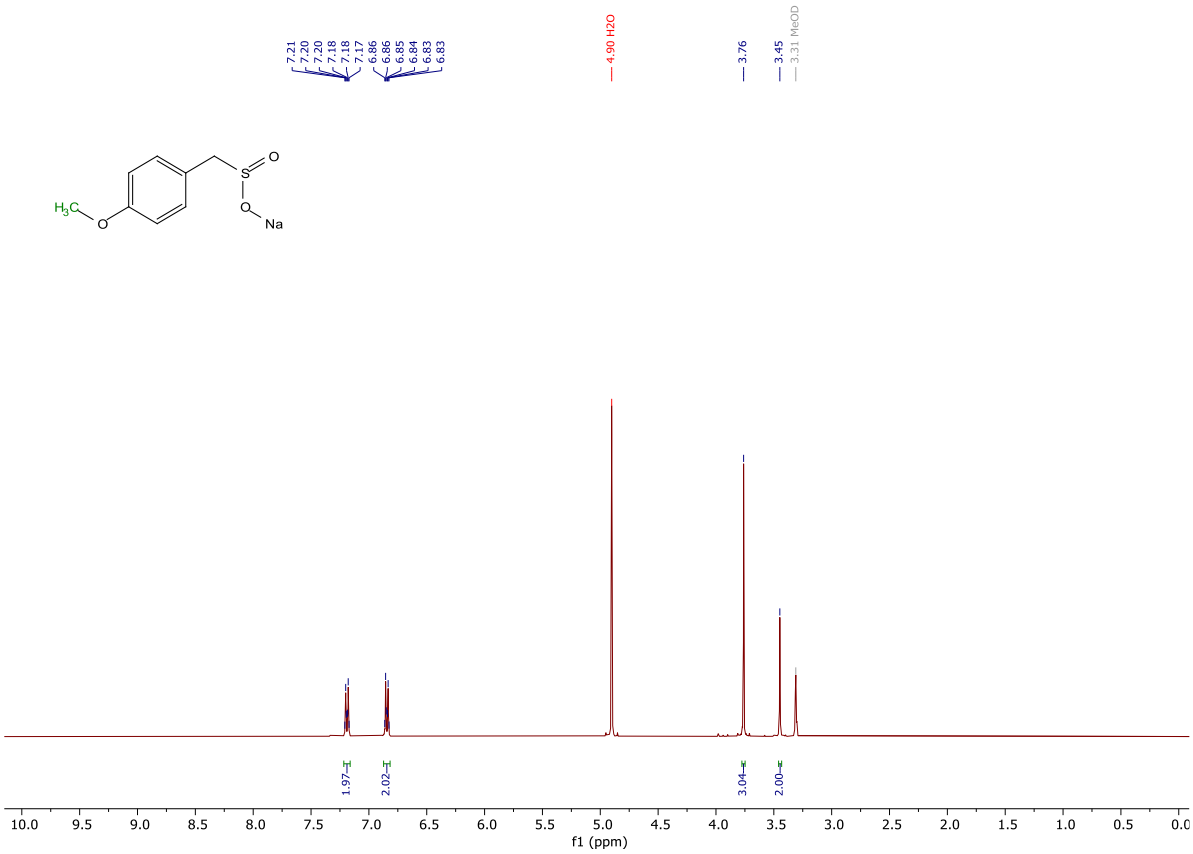
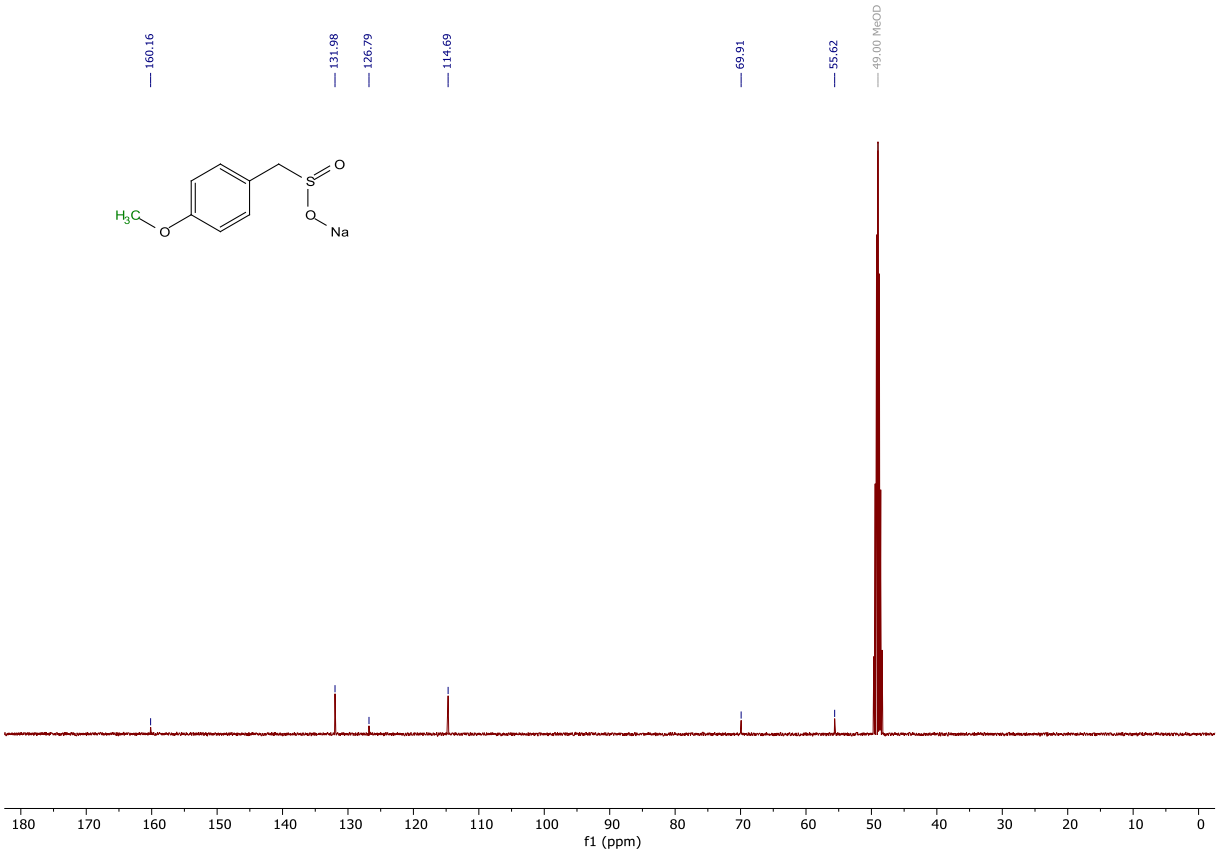
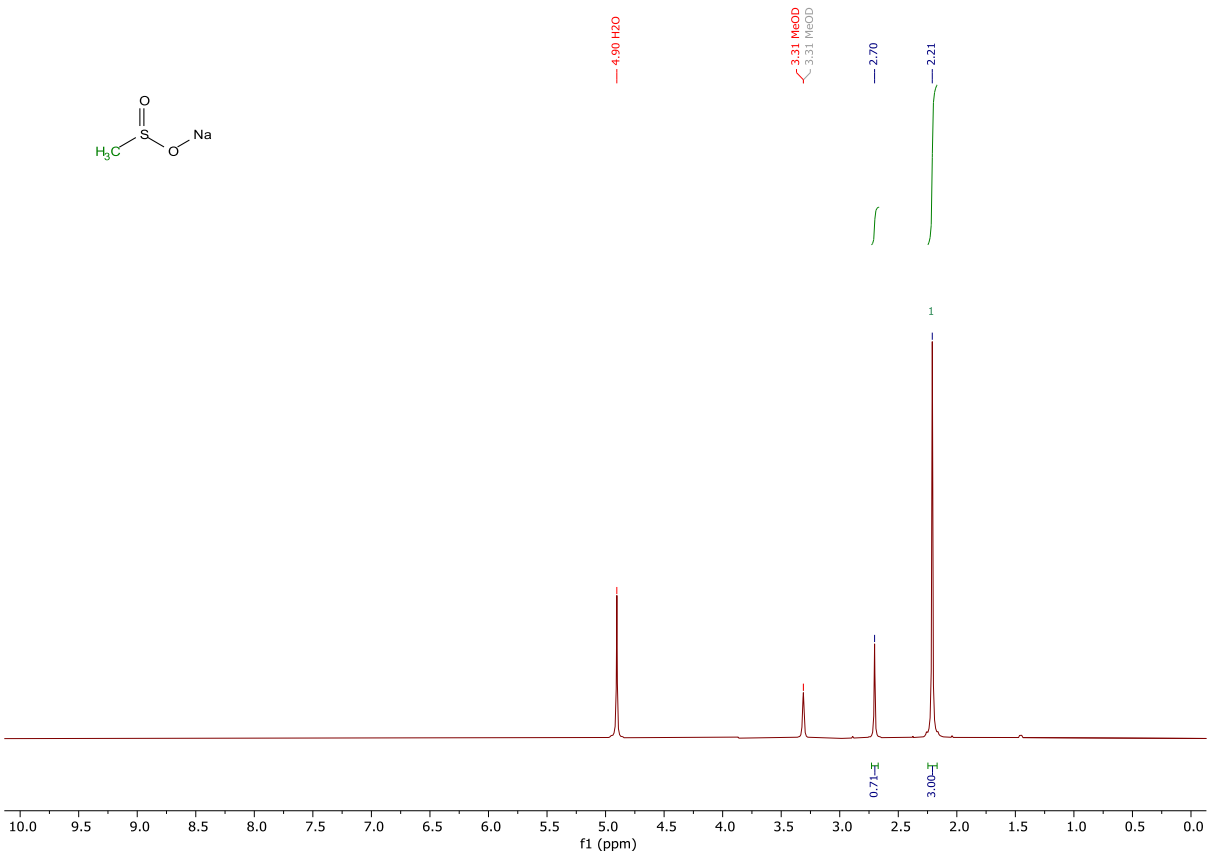
127.29
126.03
125.99
125.95
125.92
124.60
70.24
49.00 MeOD
O
S
O
Na
F
F
F
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

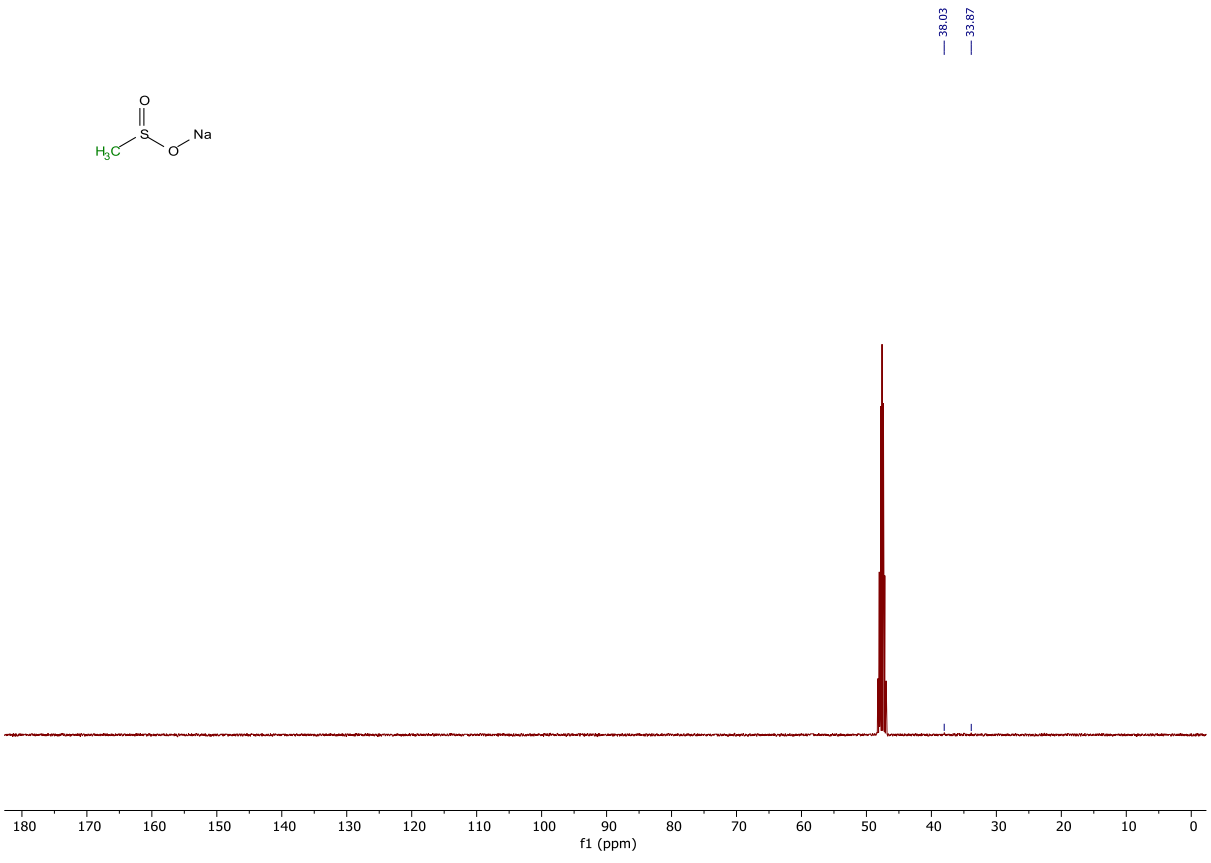
Sodium (4-methoxyphenyl)methanesulfinate (1e)



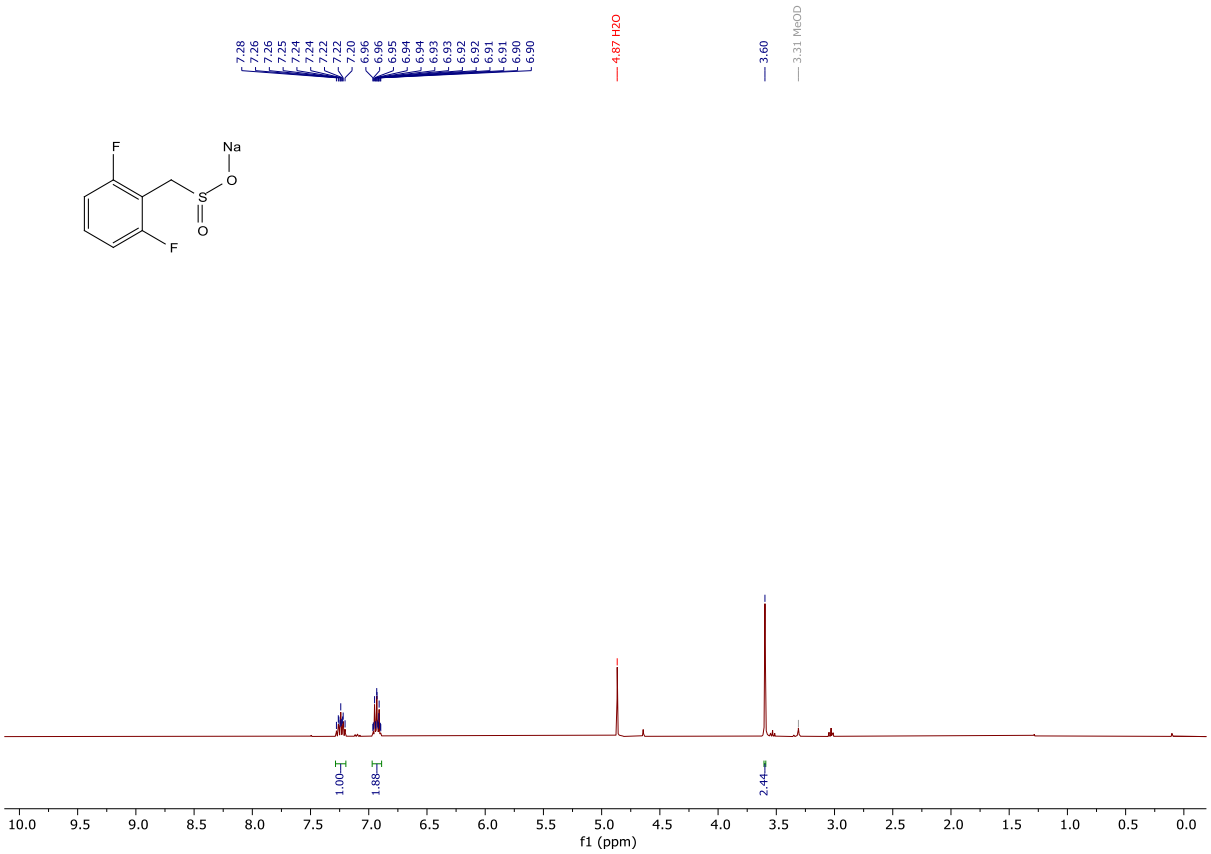


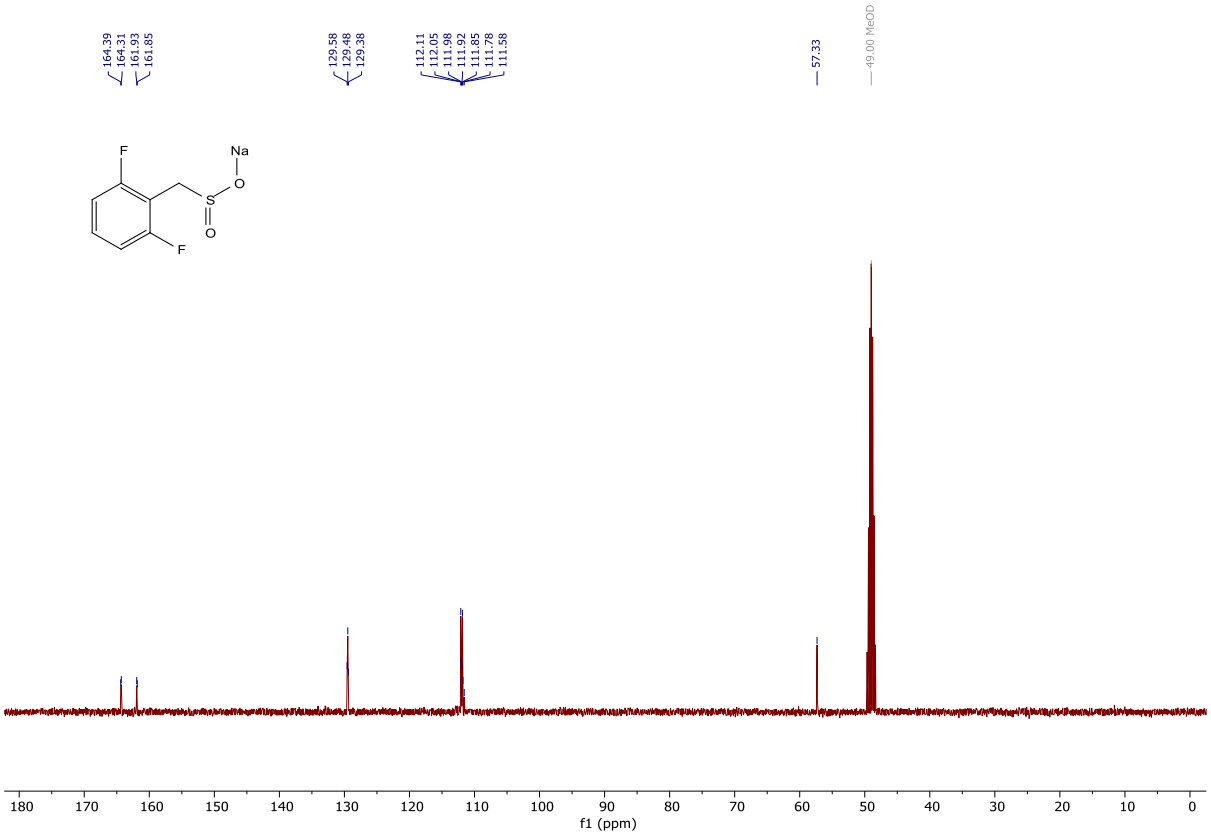
Sodium methanesulfinate (1f)





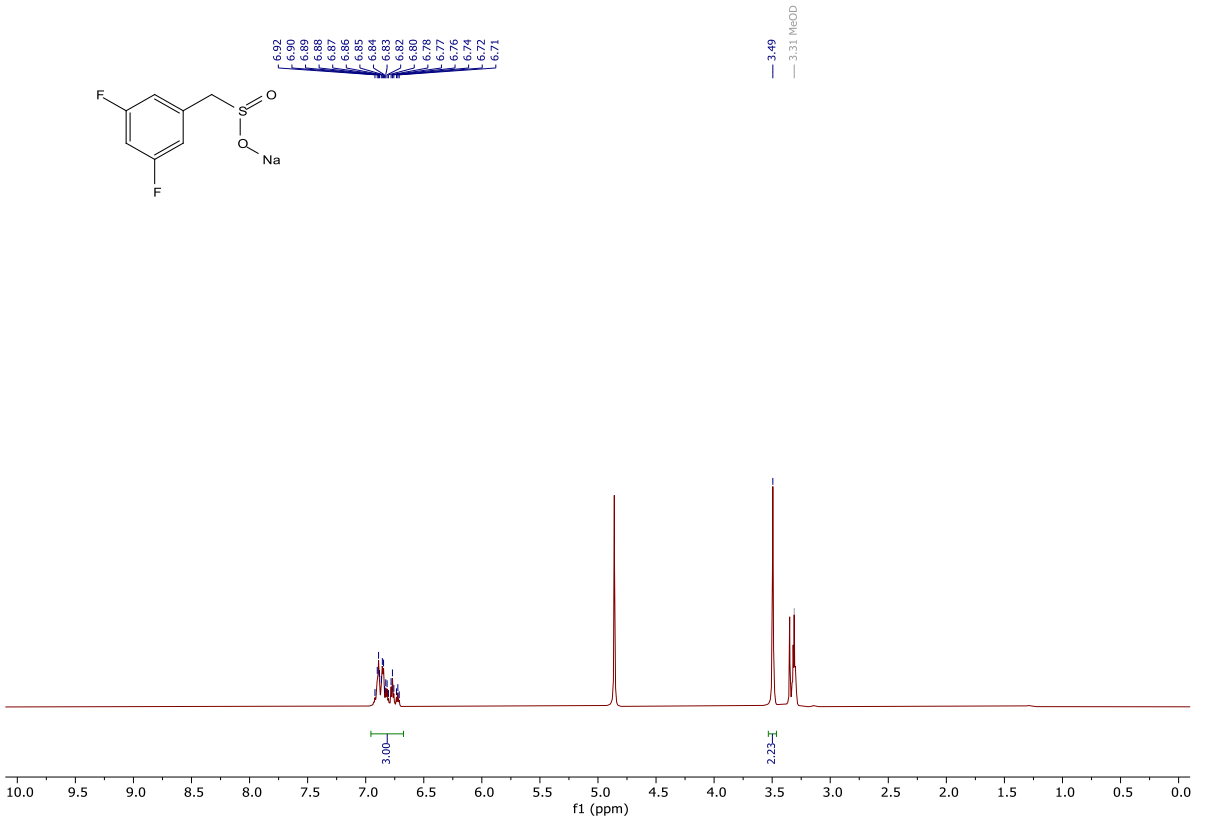
Sodium (2,6-difluorophenyl)methanesulfinate (1i)

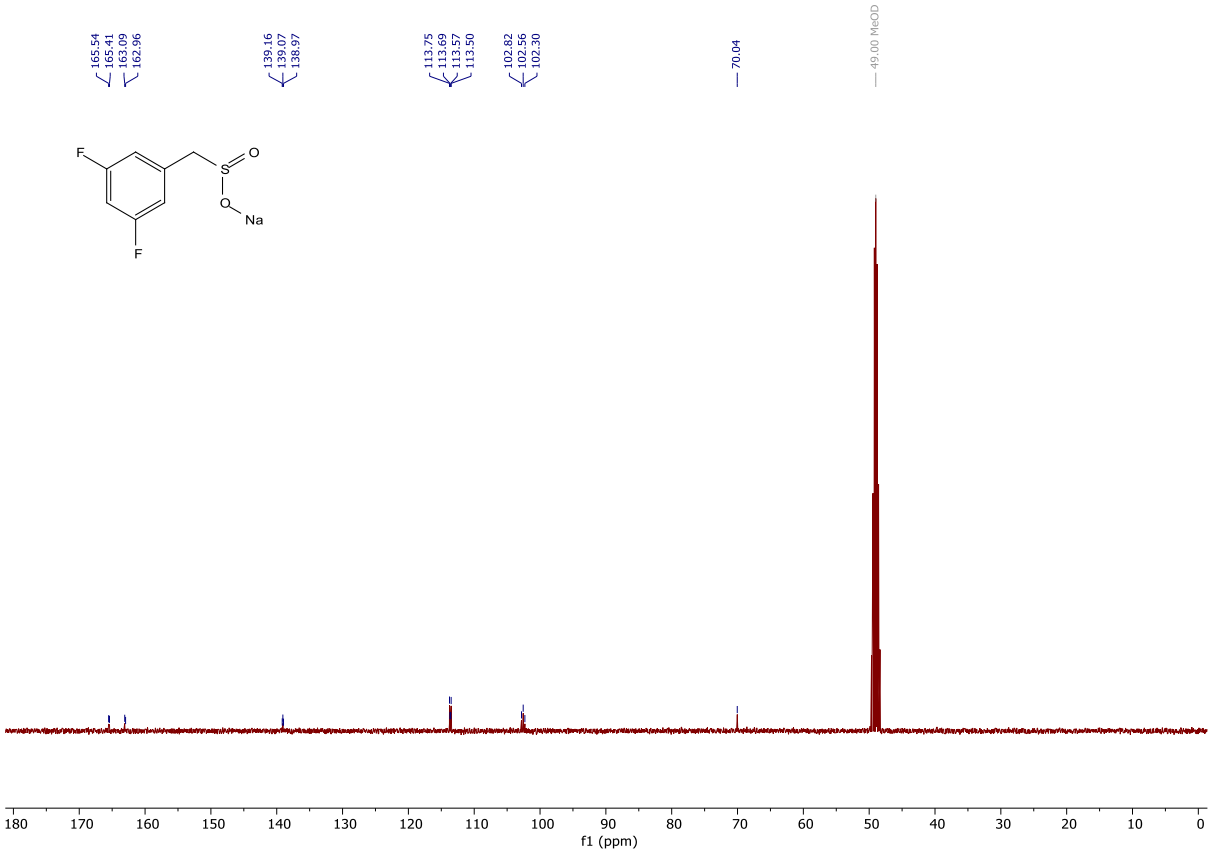


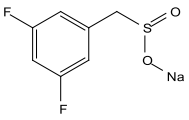



-115.10
F
Na
O
S
O
F
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-18
f1 (ppm)

Sodium (3,5-difluorophenyl)methanesulfinate (1j)

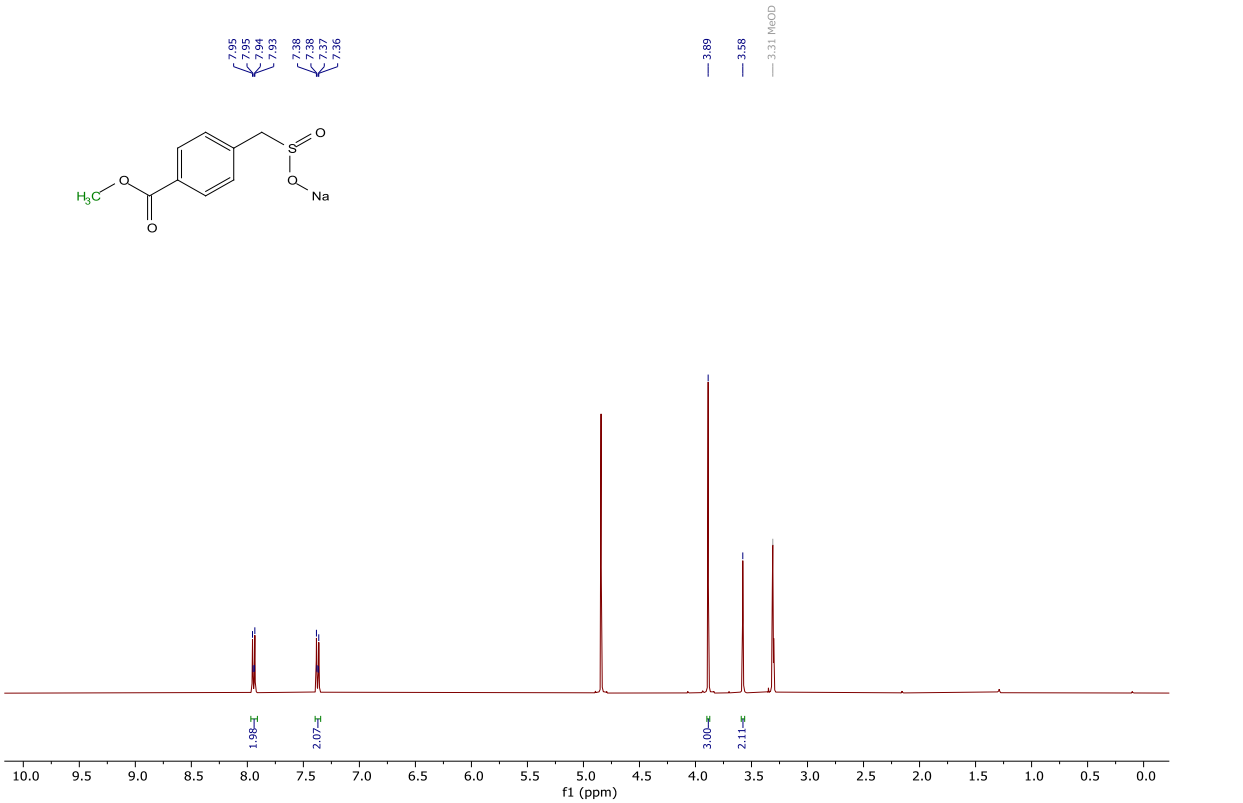


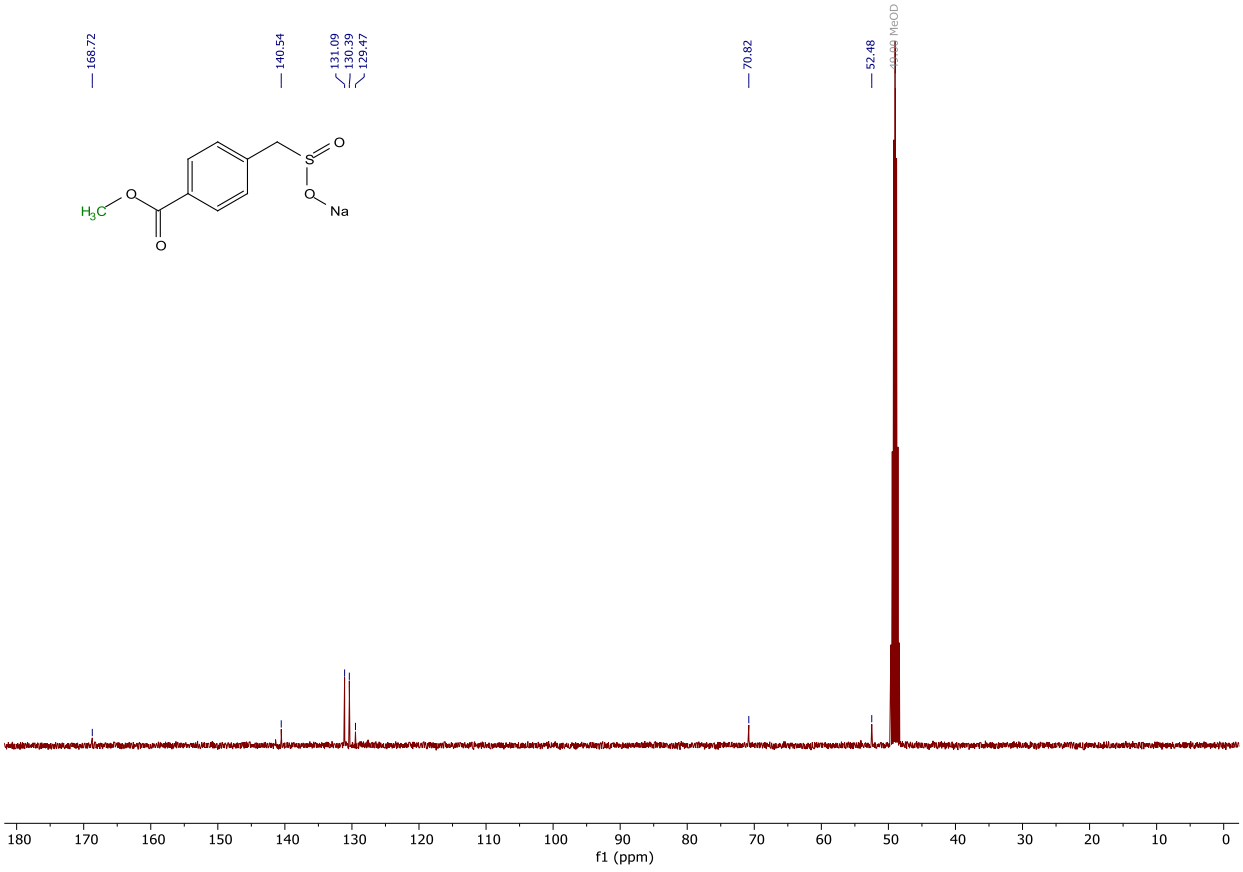



F
S
O
O
Na
F

-113.15
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
f1 (ppm)

Sodium (4-(methoxycarbonyl)phenyl)methanesulfinate (1k)

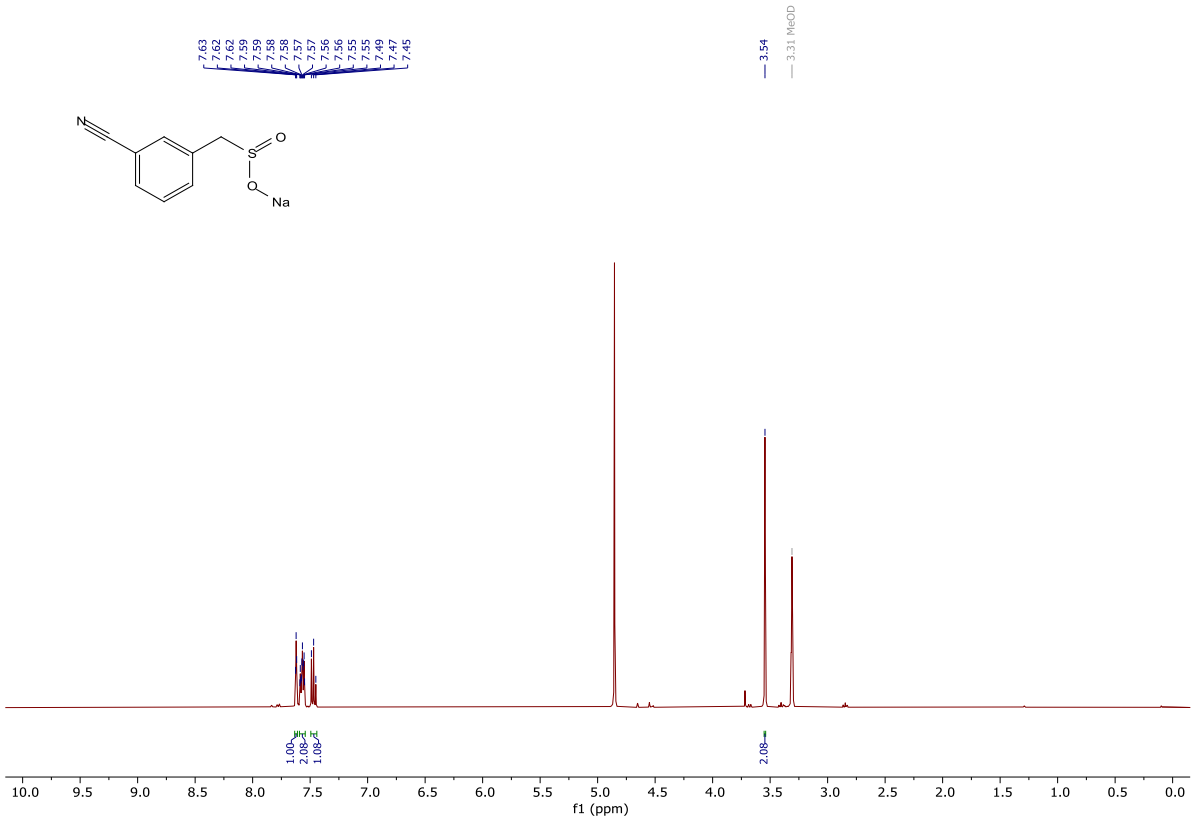


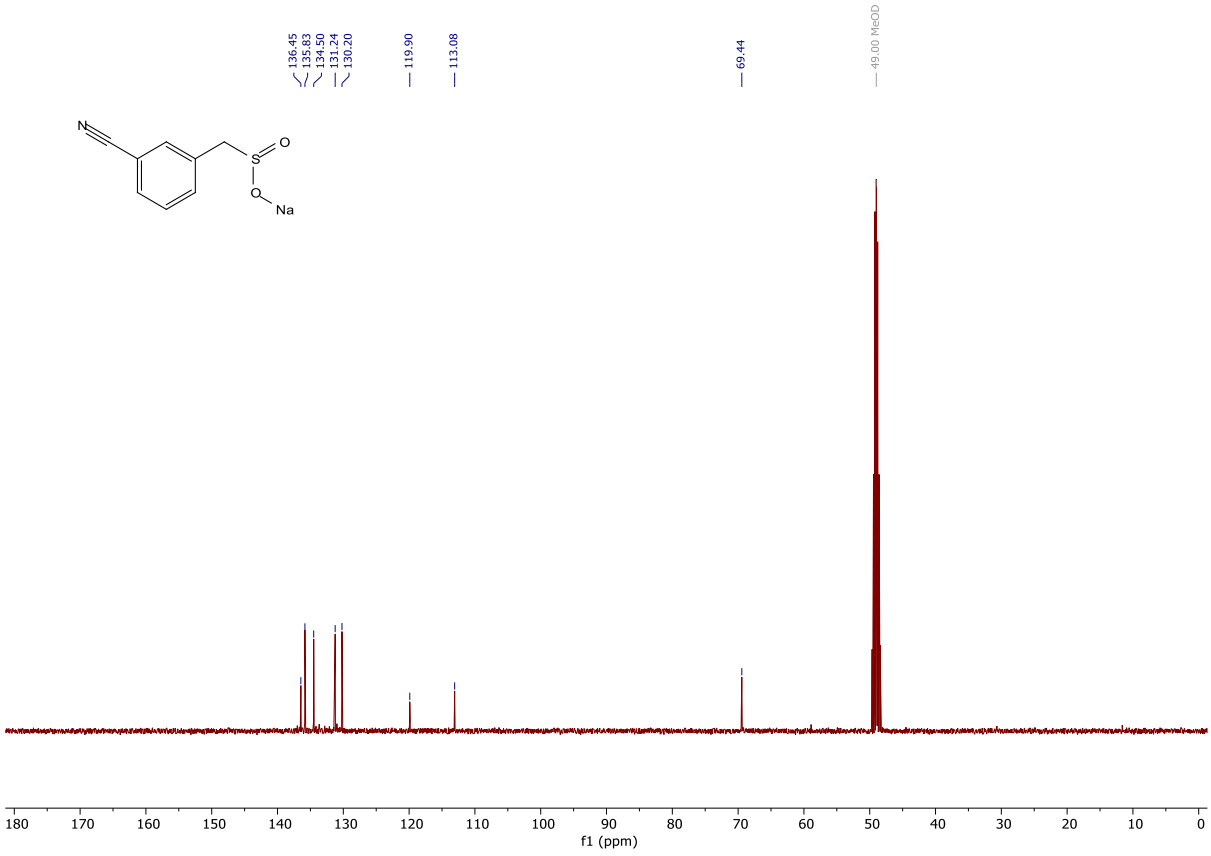


Sodium o-tolylmethanesulfinate (1l)

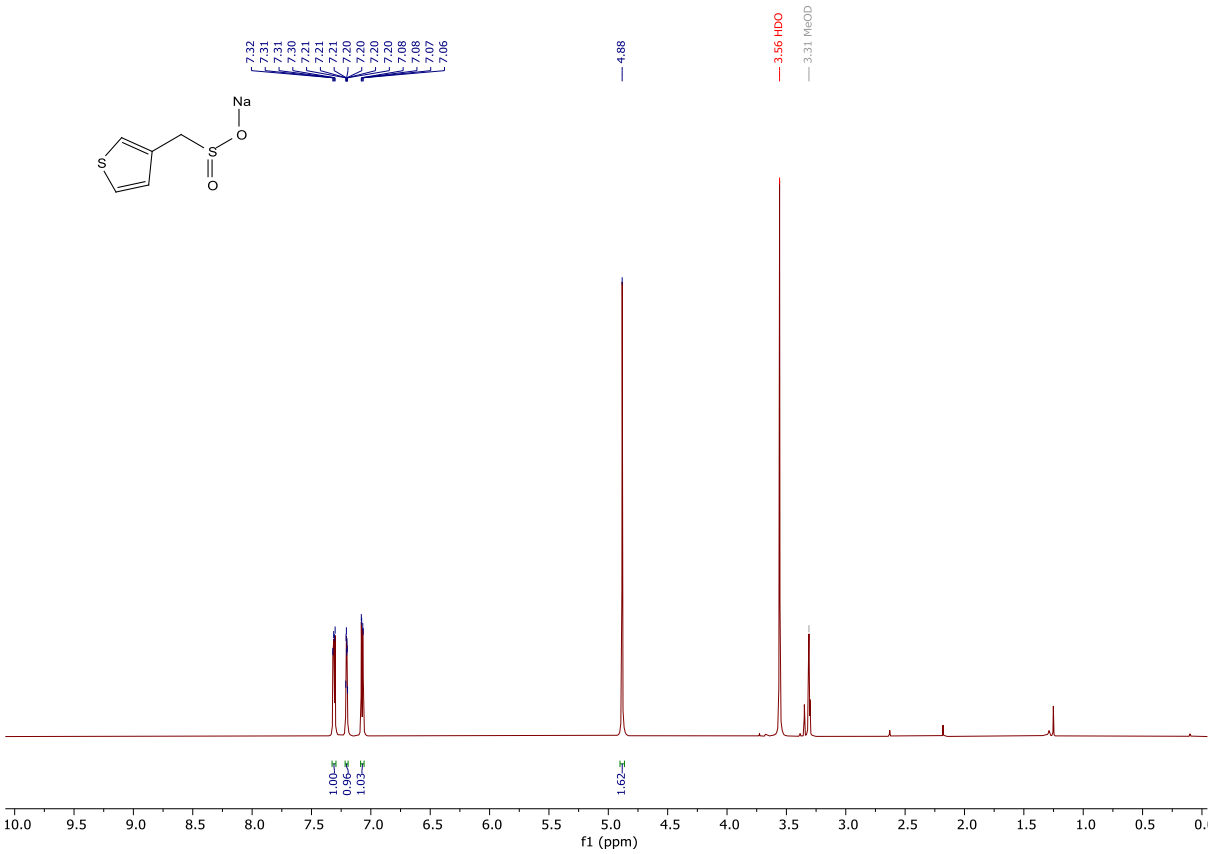


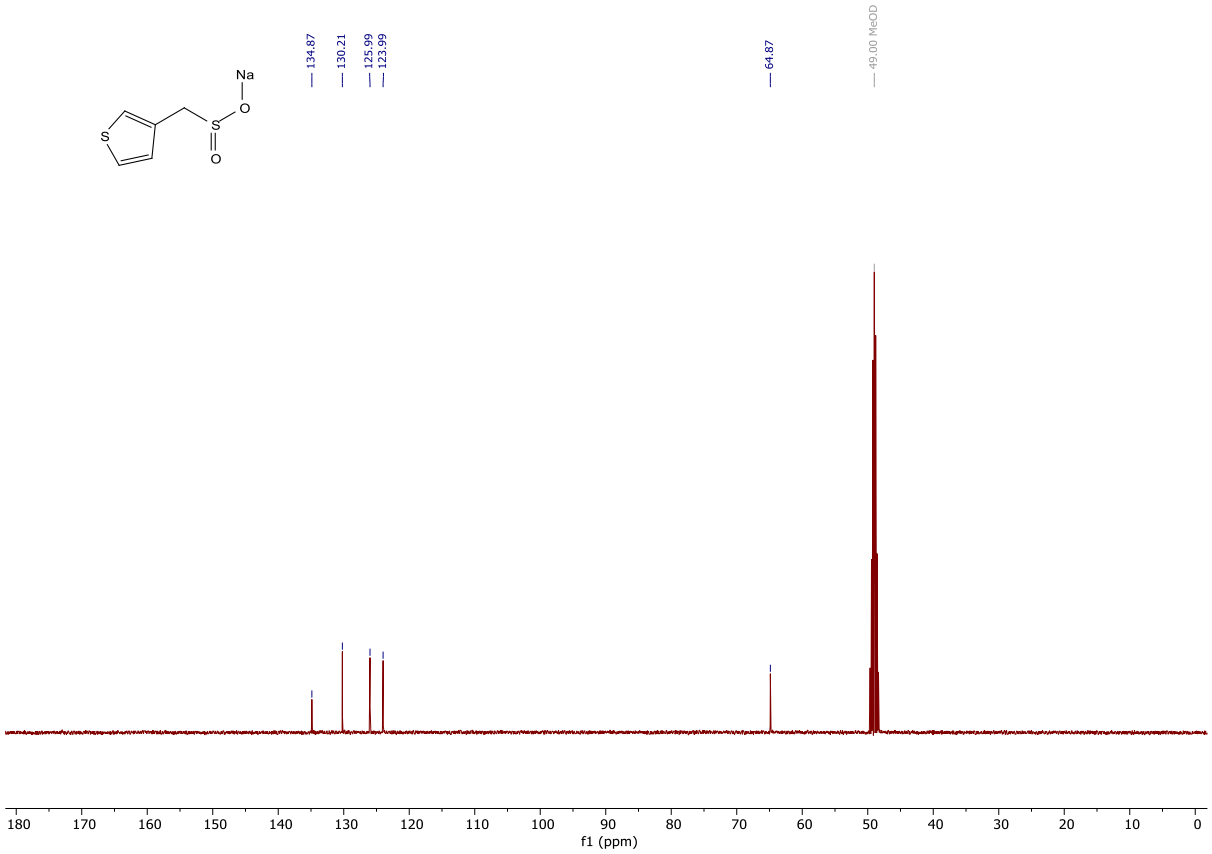
Sodium (3-cyanophenyl)methanesulfinate (1m)



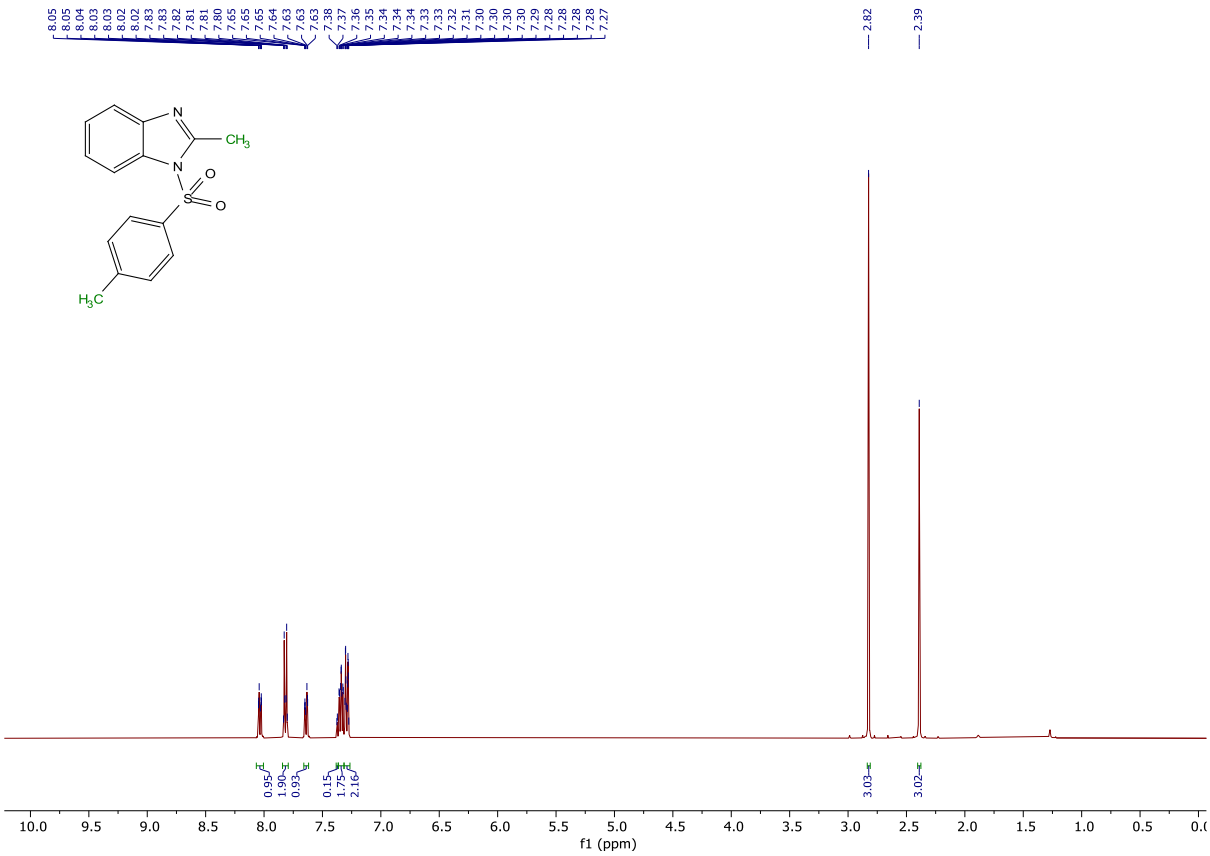


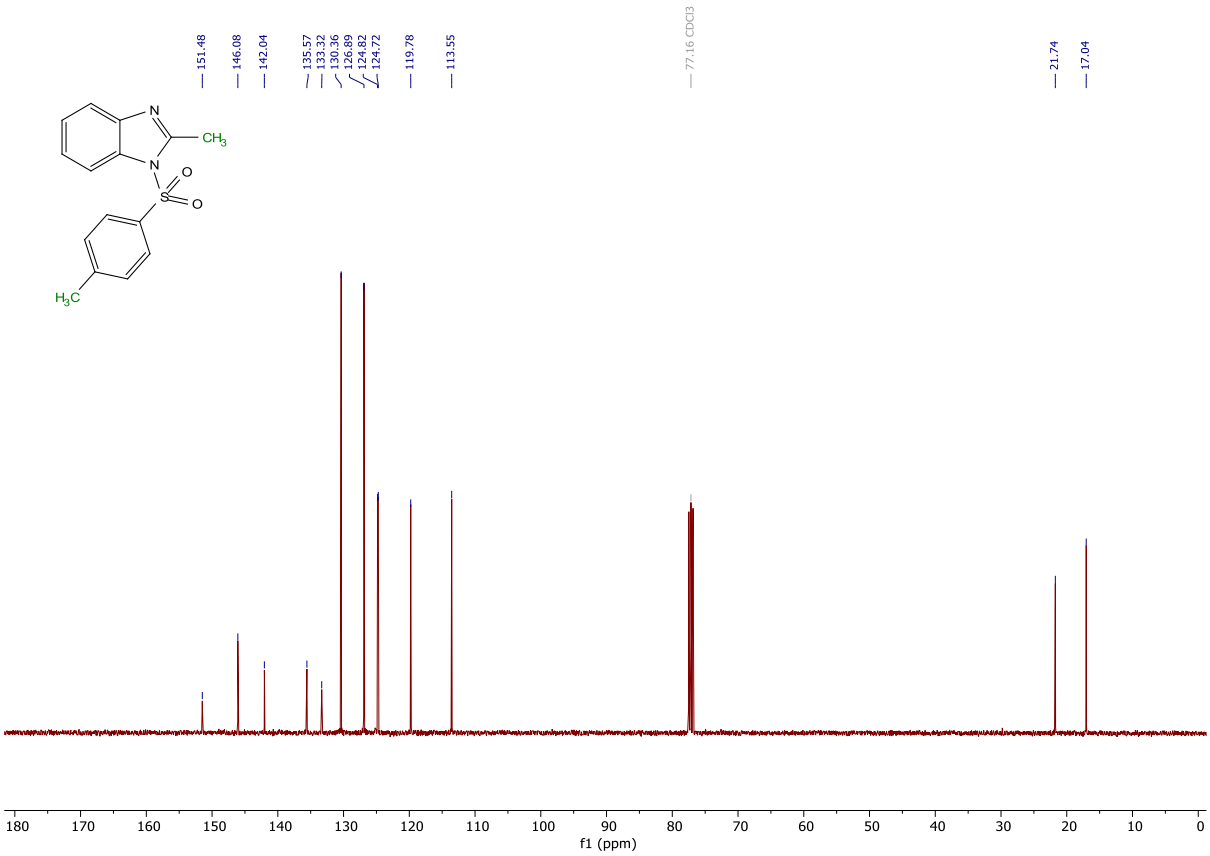
Sodium thiophen-3-ylmethanesulfinate (1n)



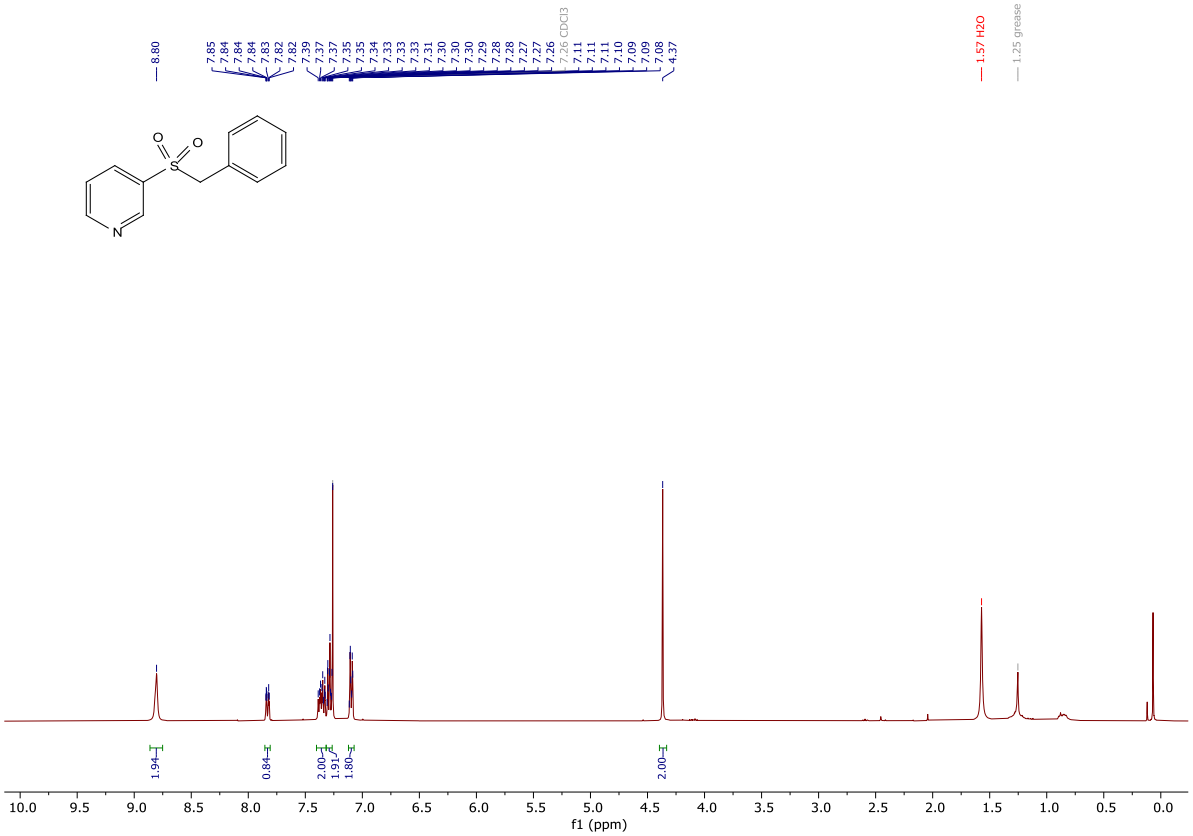


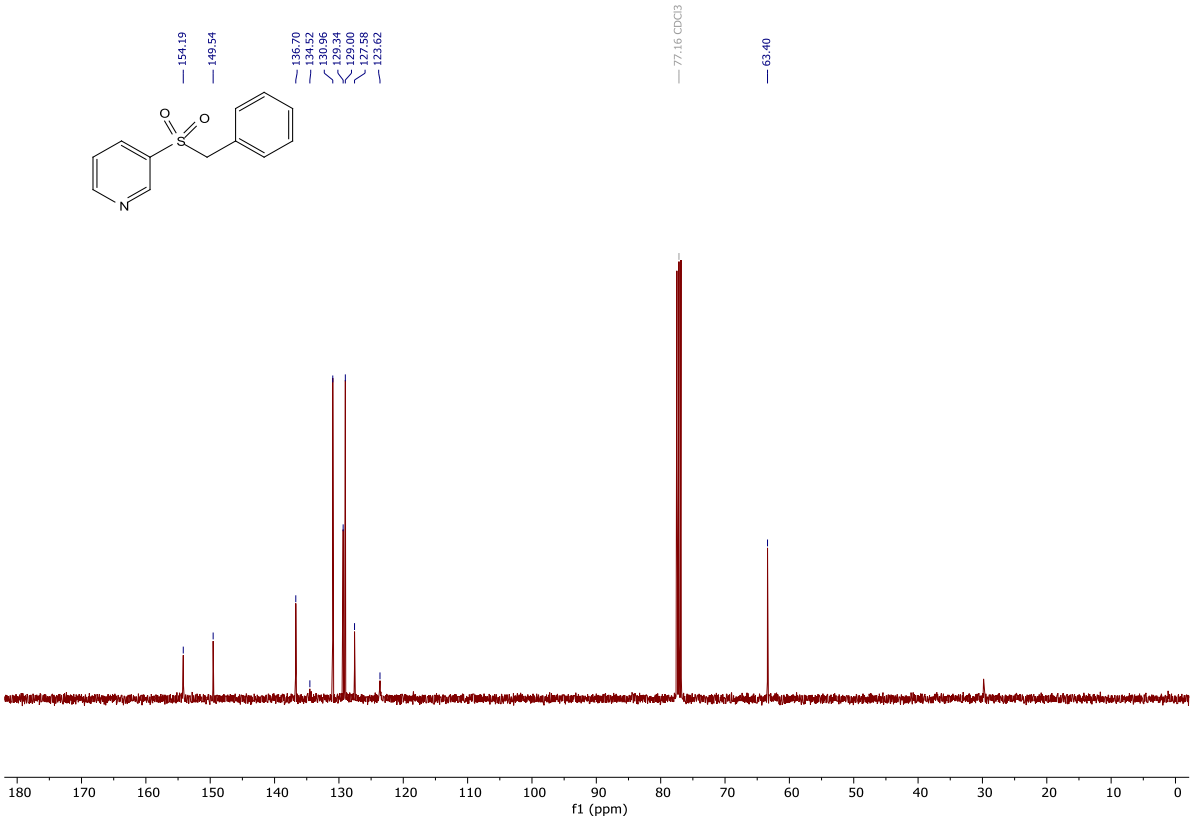
2-Methyl-1-tosyl-1H-benzo[d]imidazole (4a)



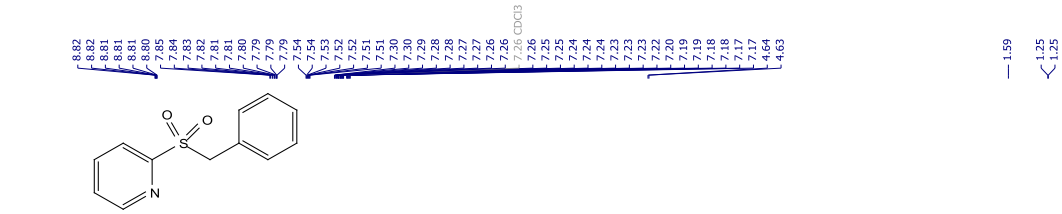


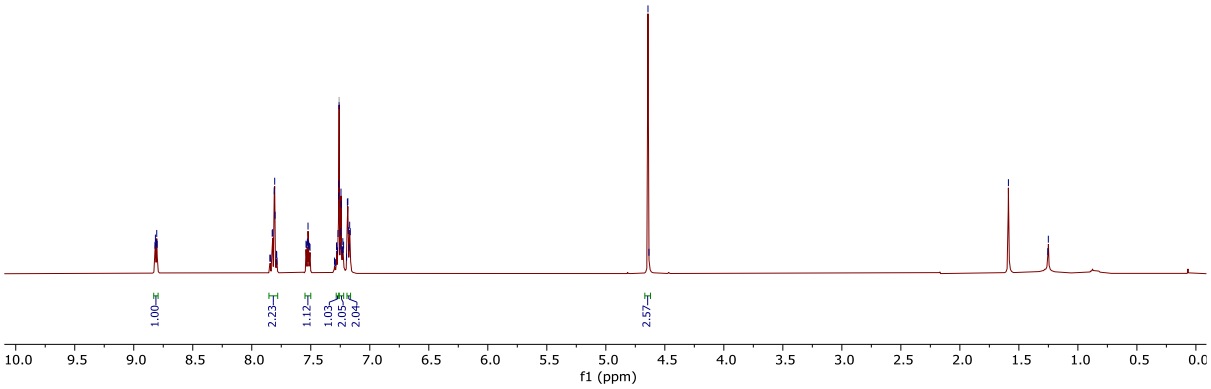
3-(Benzylsulfonyl)pyridine (5a)

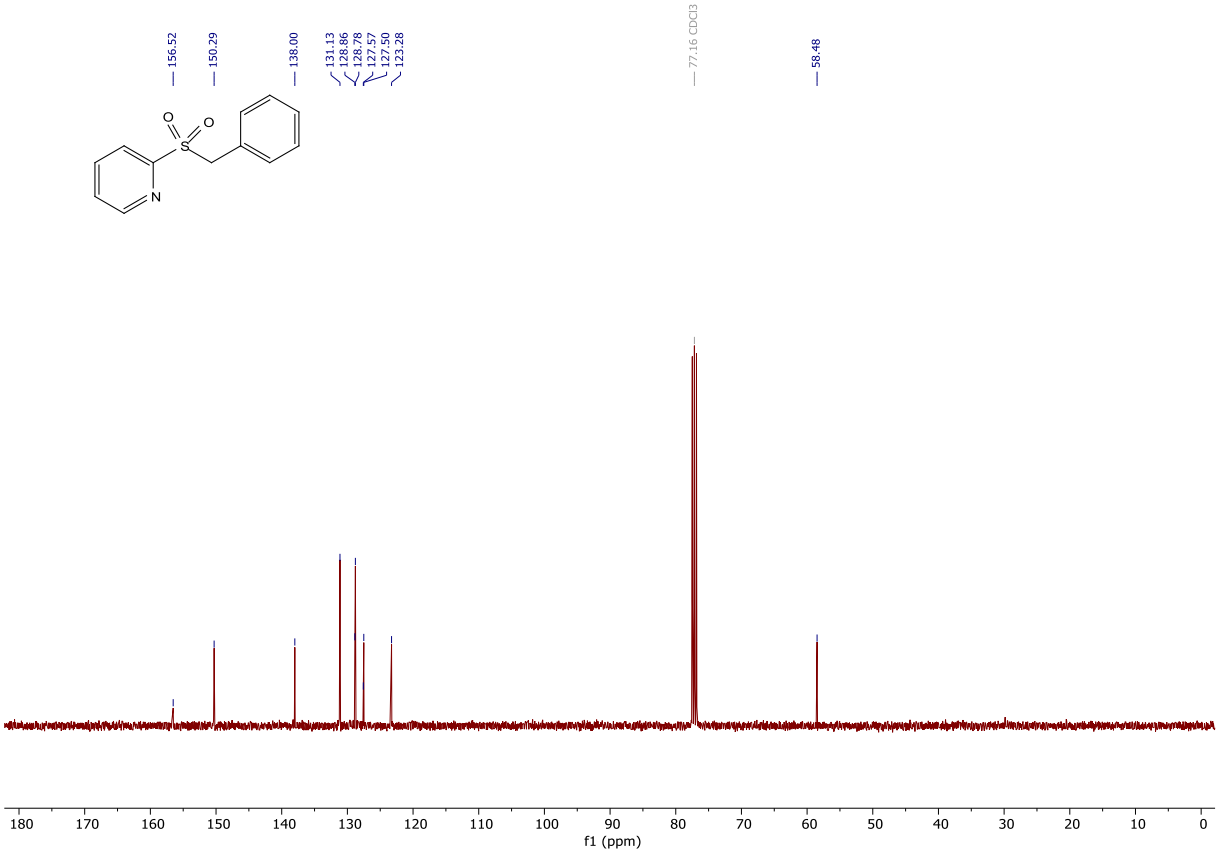




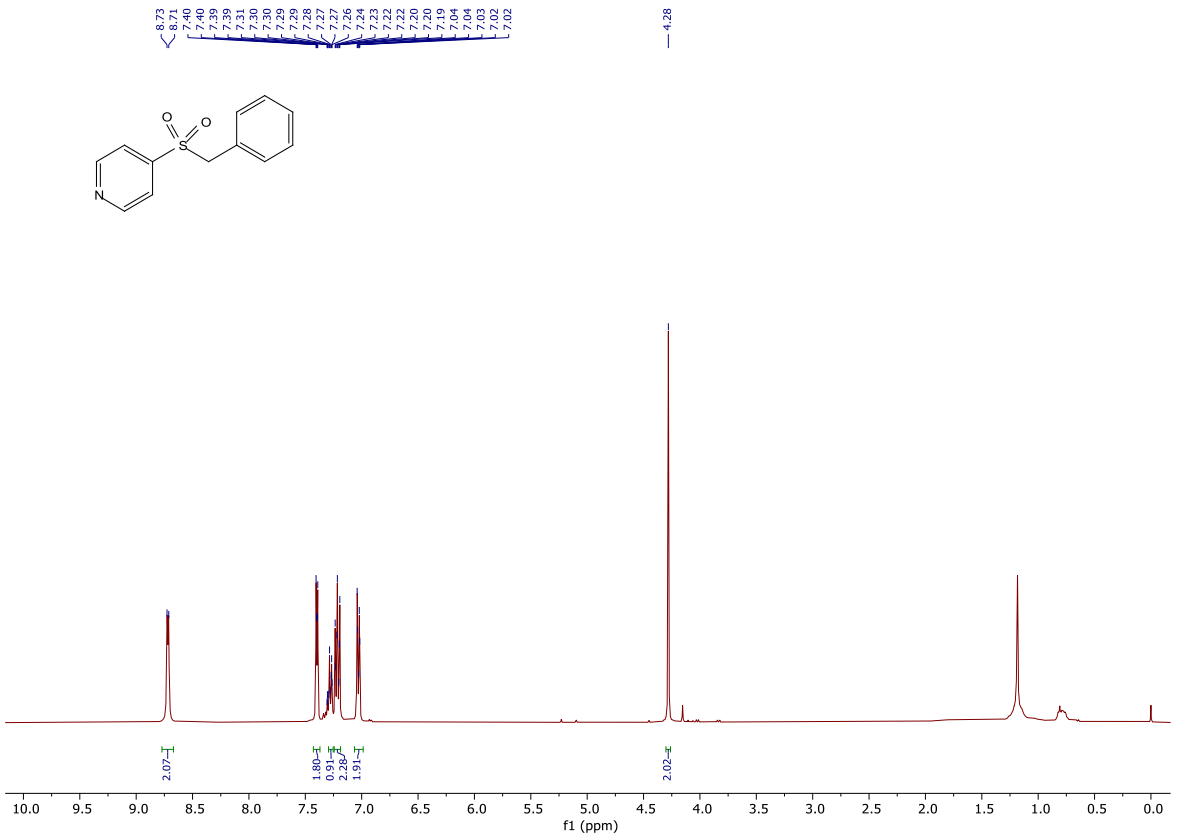
2-(Benzylsulfonyl)pyridine (5b)

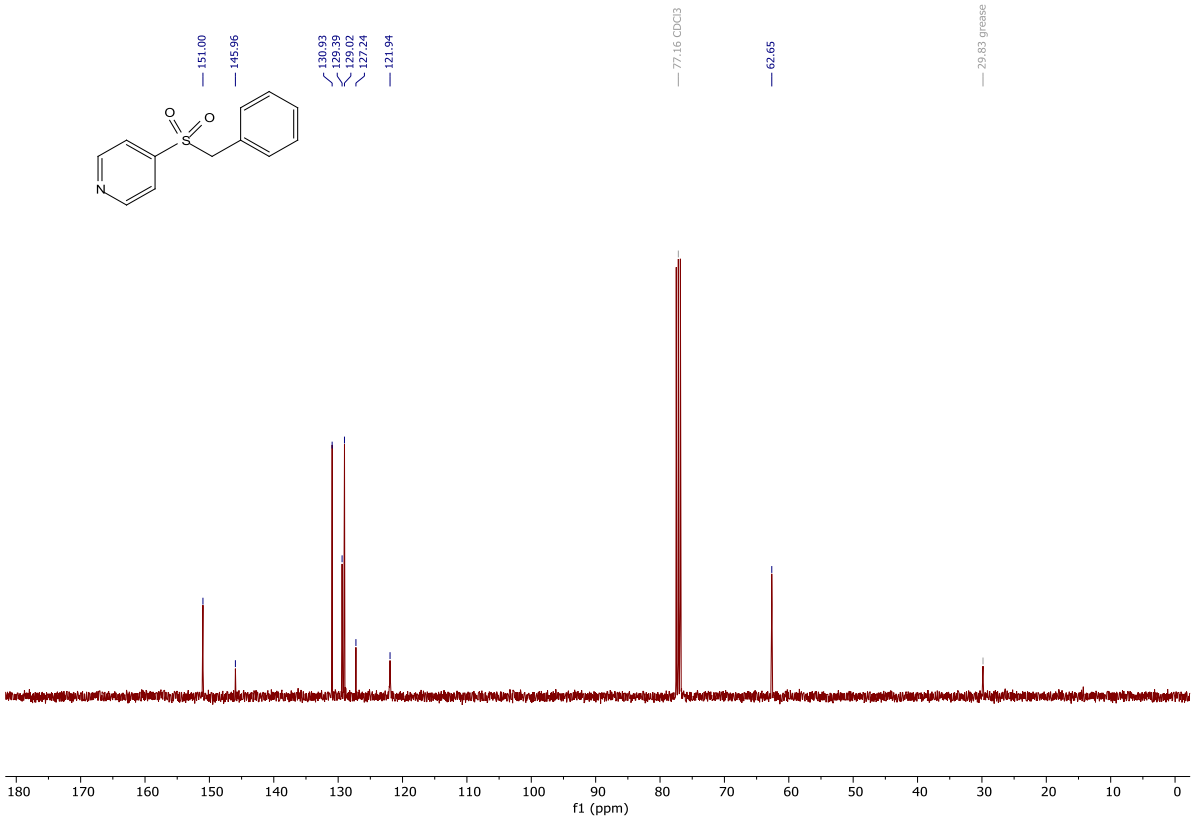




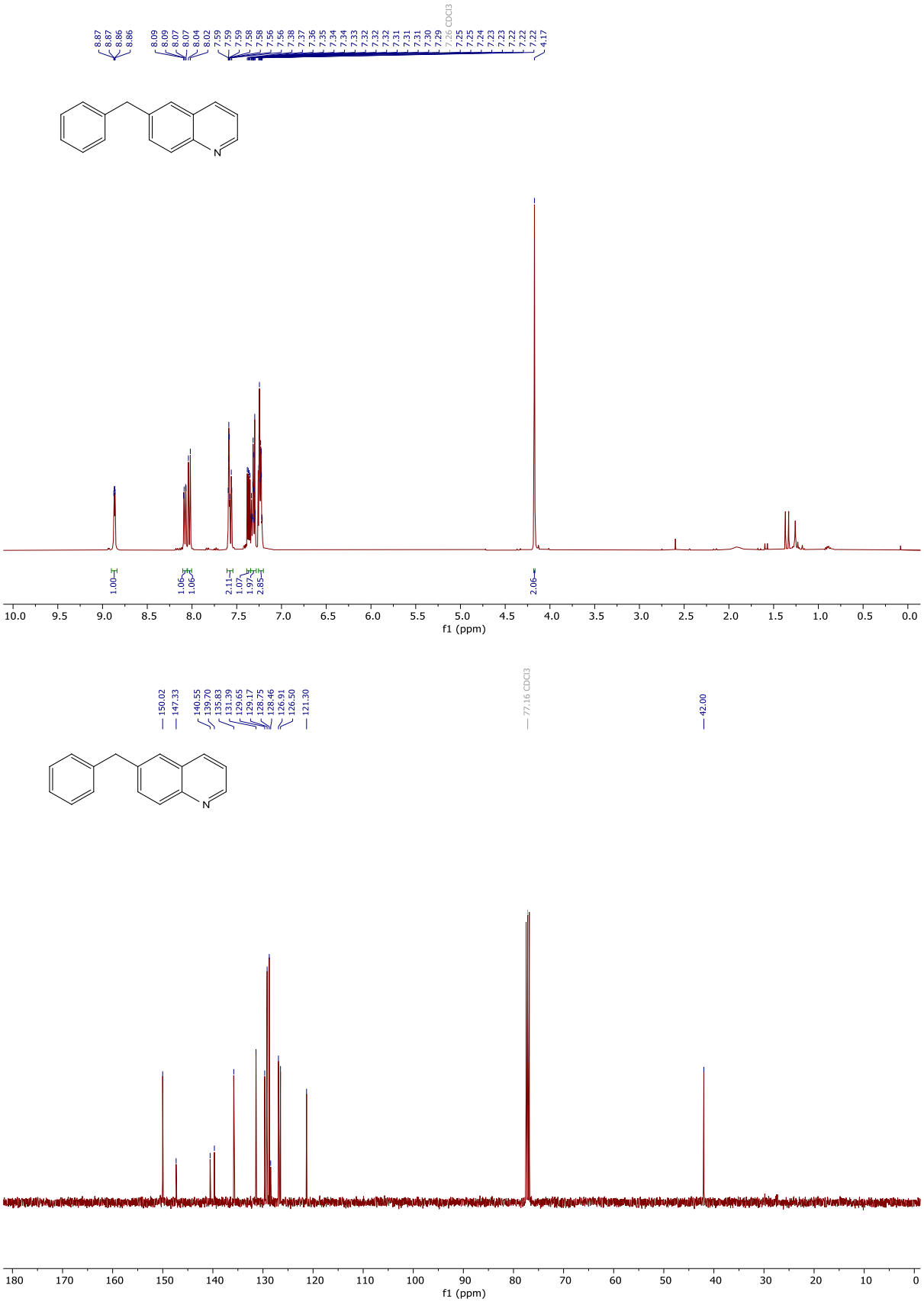


4-(Benzylsulfonyl)pyridine (5c)



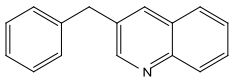


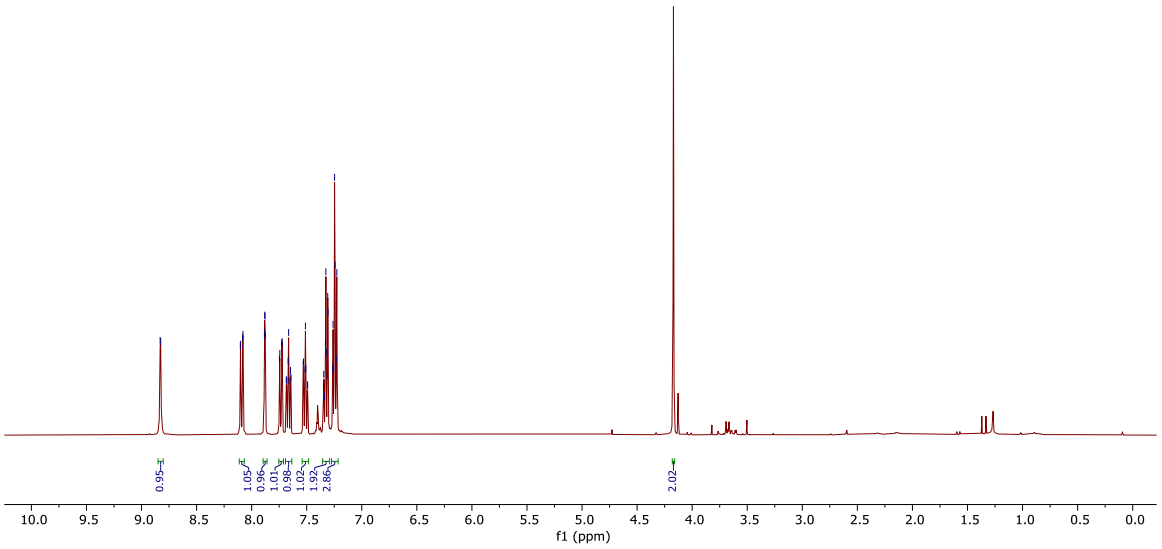
6-Benzylquinoline (6a)

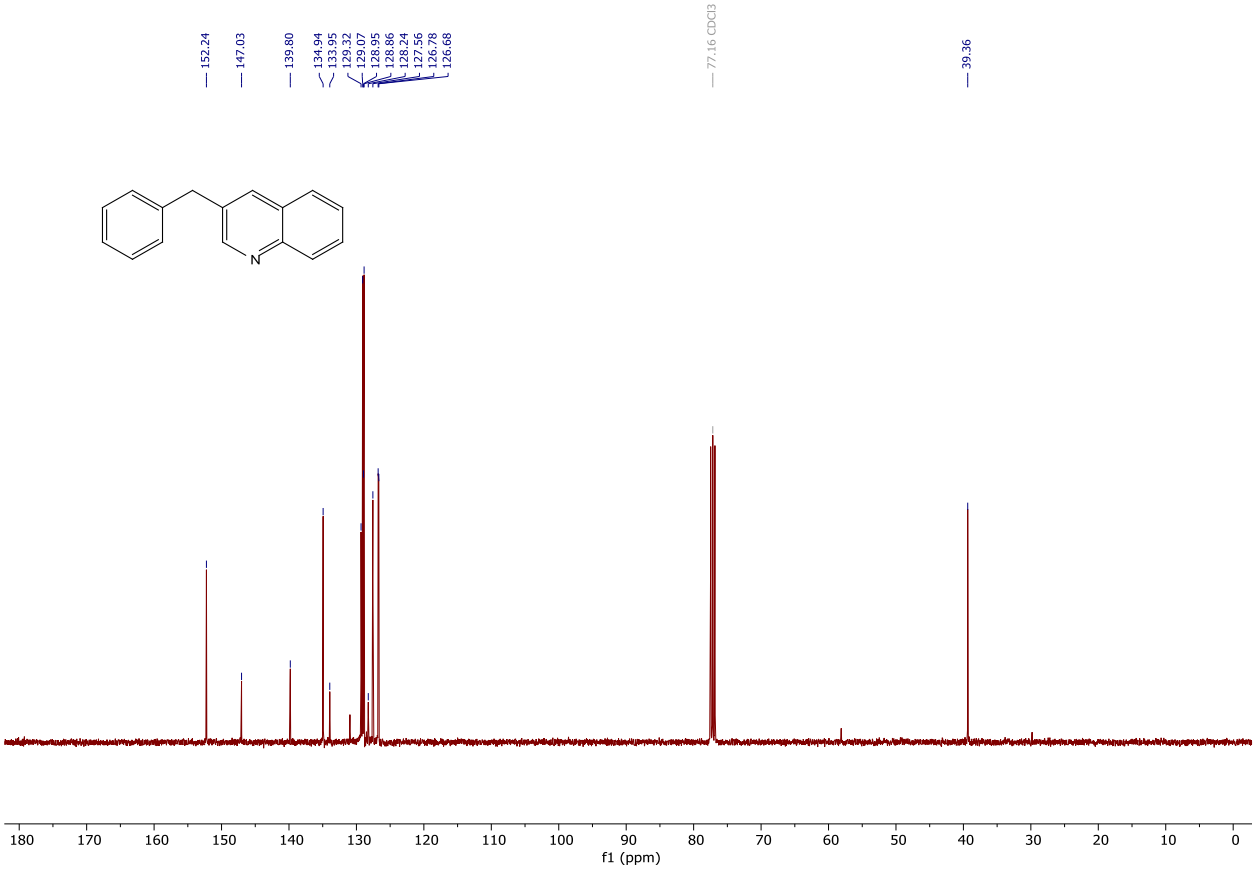


3-Benzylquinoline (6b)

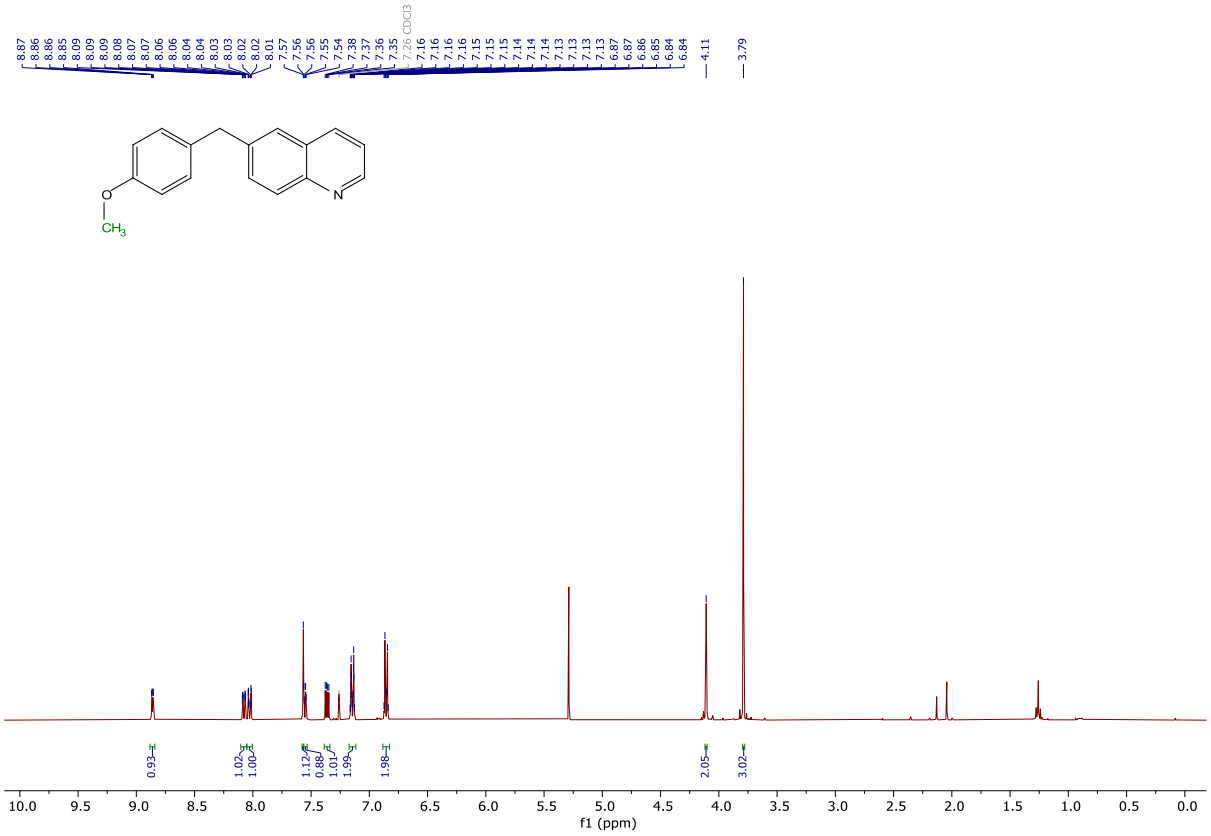


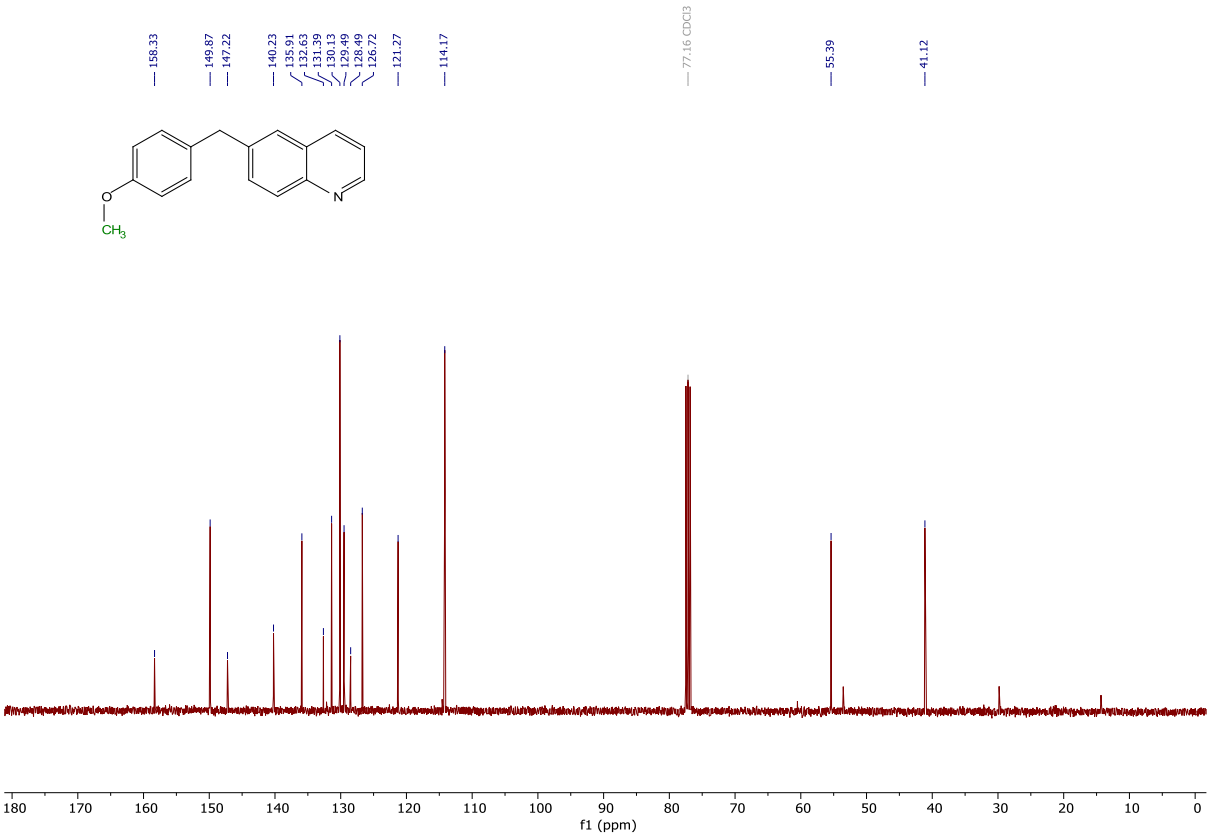




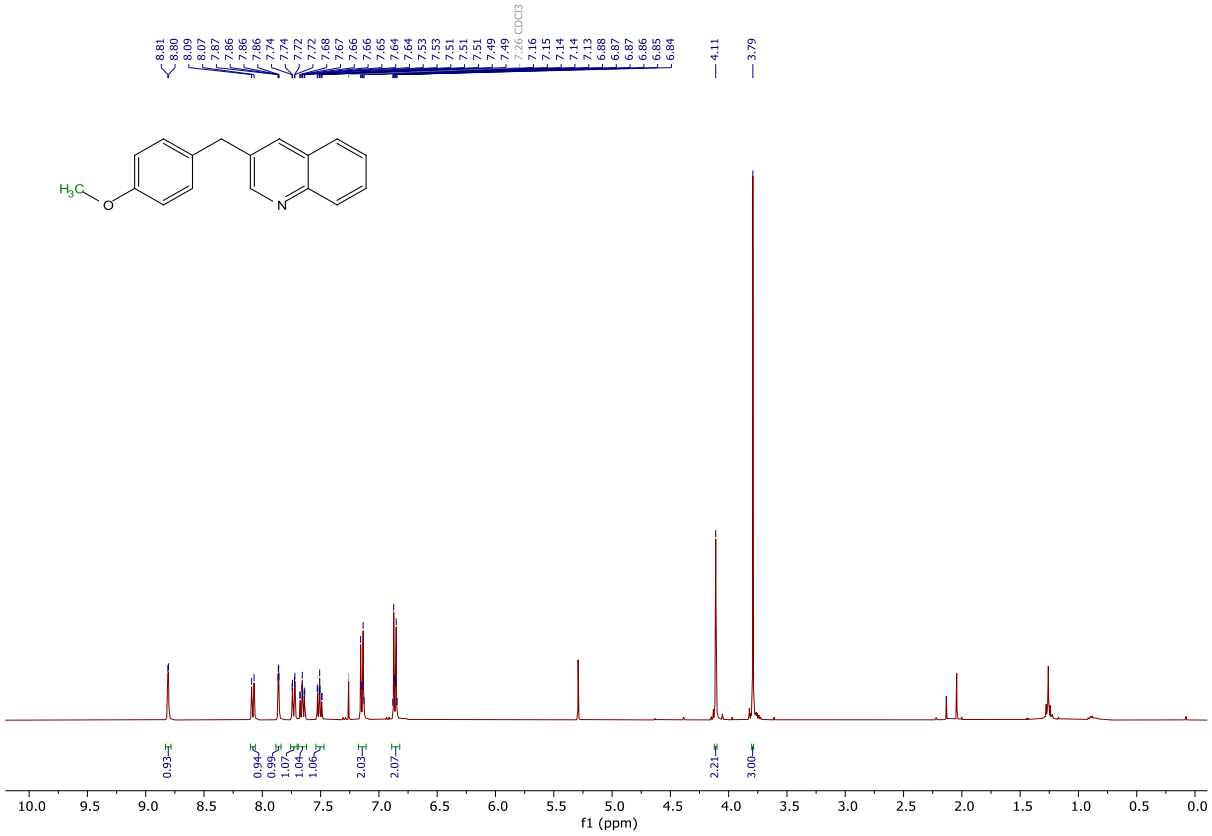


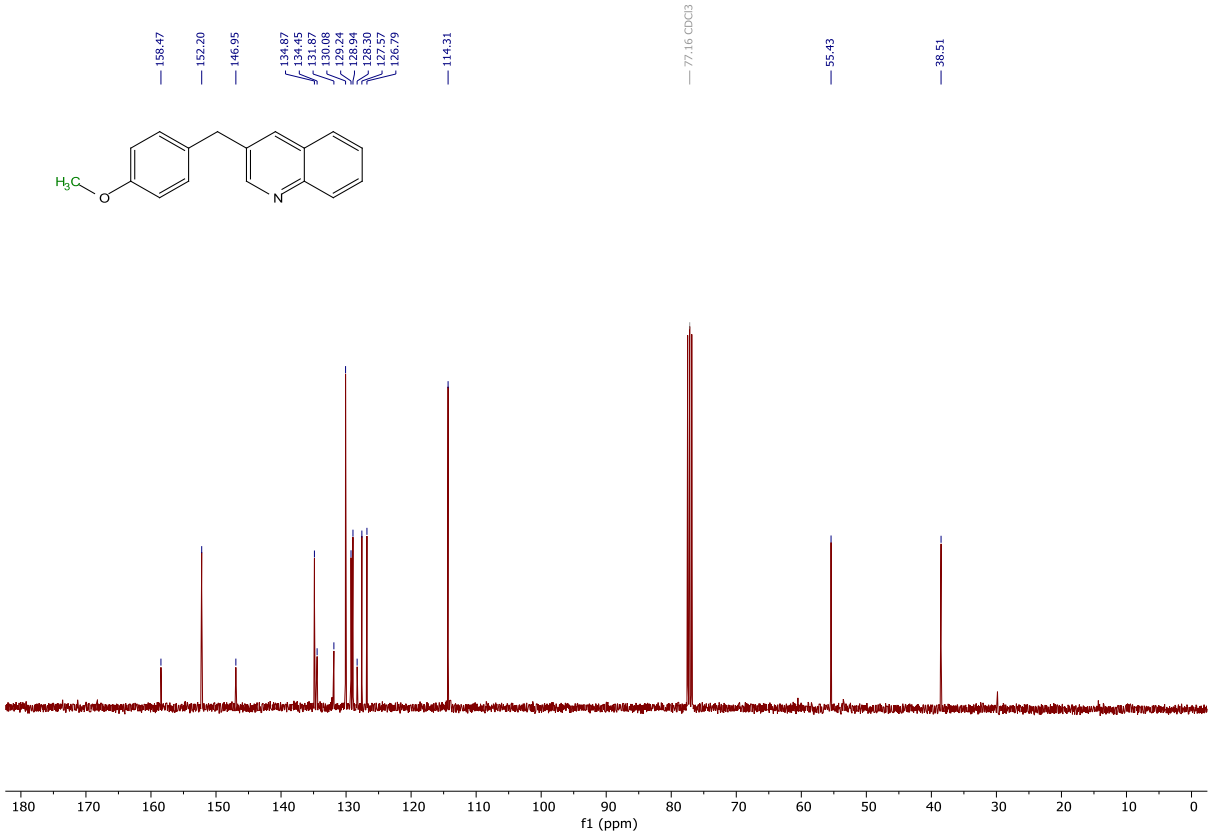
6-(4-Methoxybenzyl)quinoline (6c)



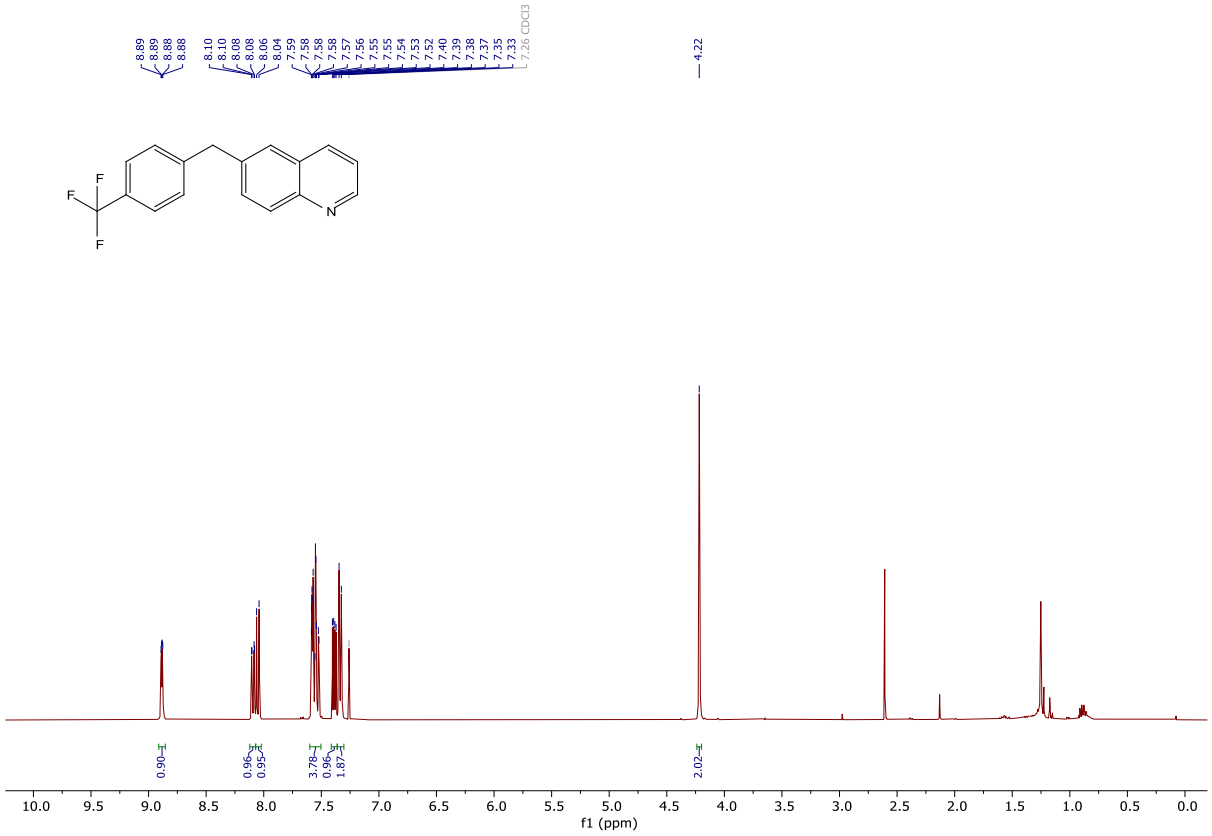


3-(4-Methoxybenzyl)quinoline (6d)





6-(4-(Trifluoromethyl)benzyl)quinoline (6e)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7.54
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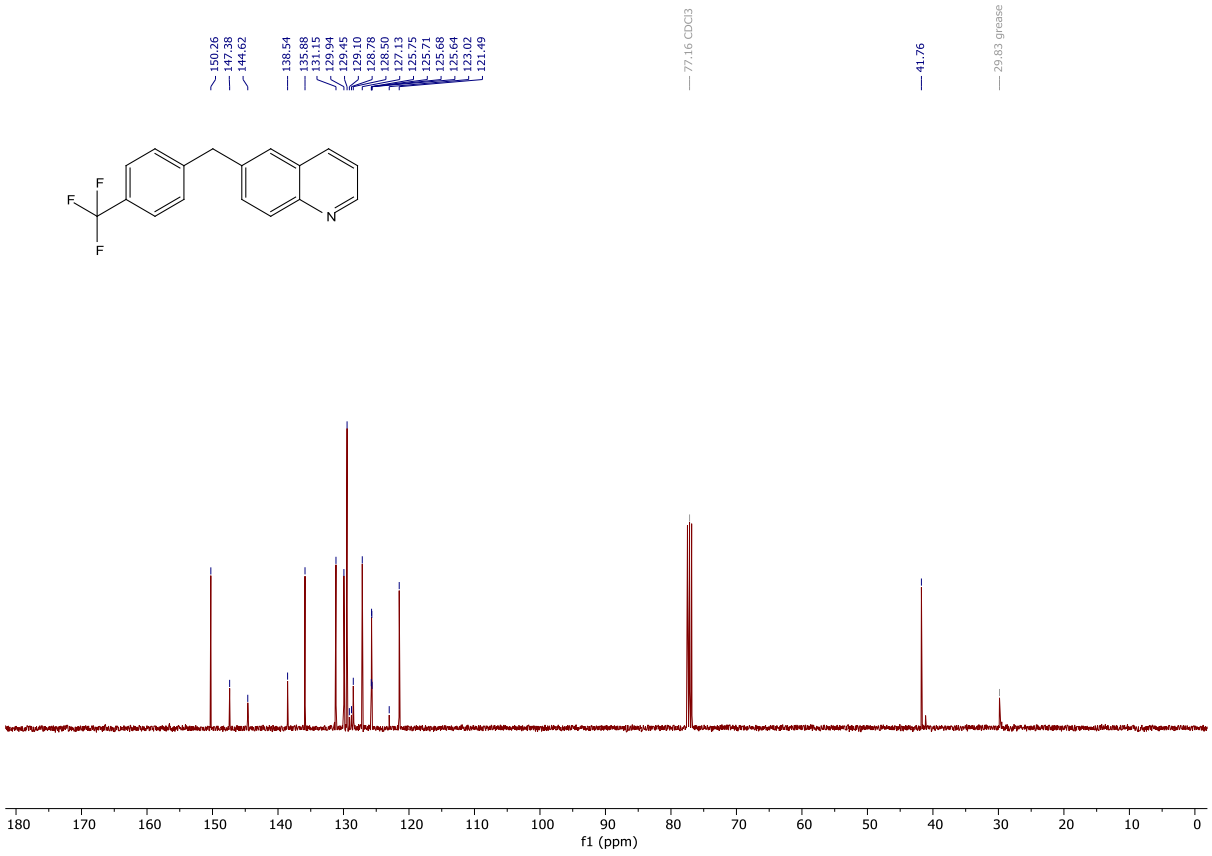
7.52
7.40
7.39
7.38
7.37
7.35
7.33
7.26 CDCl3
4.22
F
F
F
N
0.90
0.96
0.95
3.78
0.96
1.87
2.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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125.68
125.64
123.02
121.49
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29.83 grease
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F
F
N
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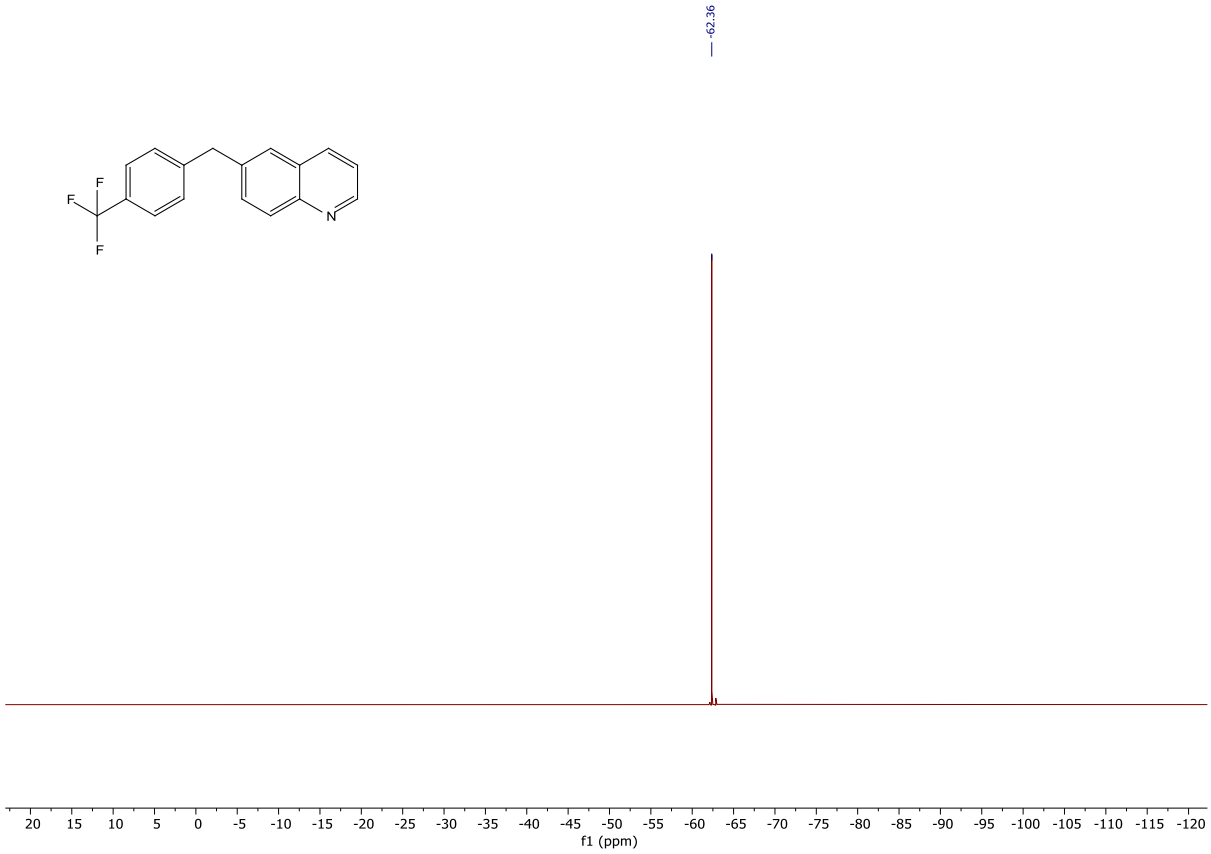
f1 (ppm)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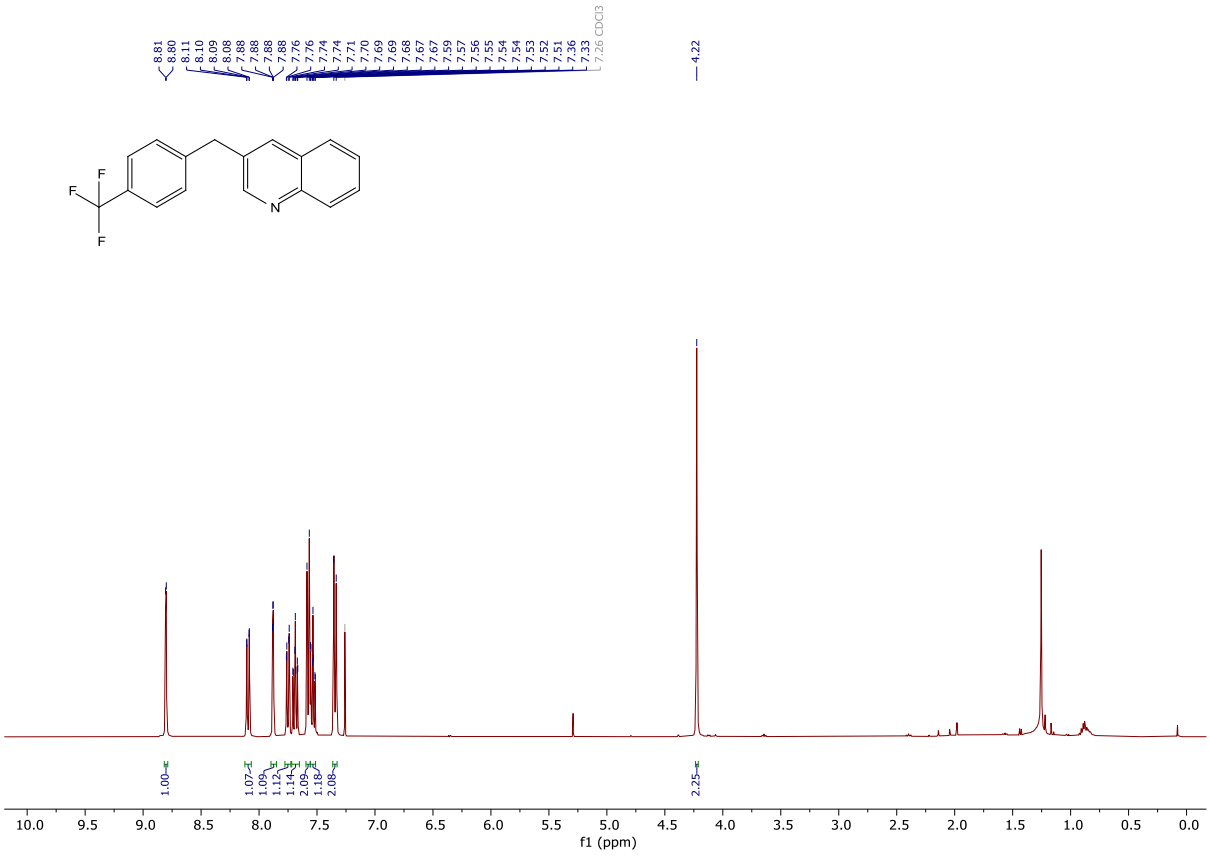
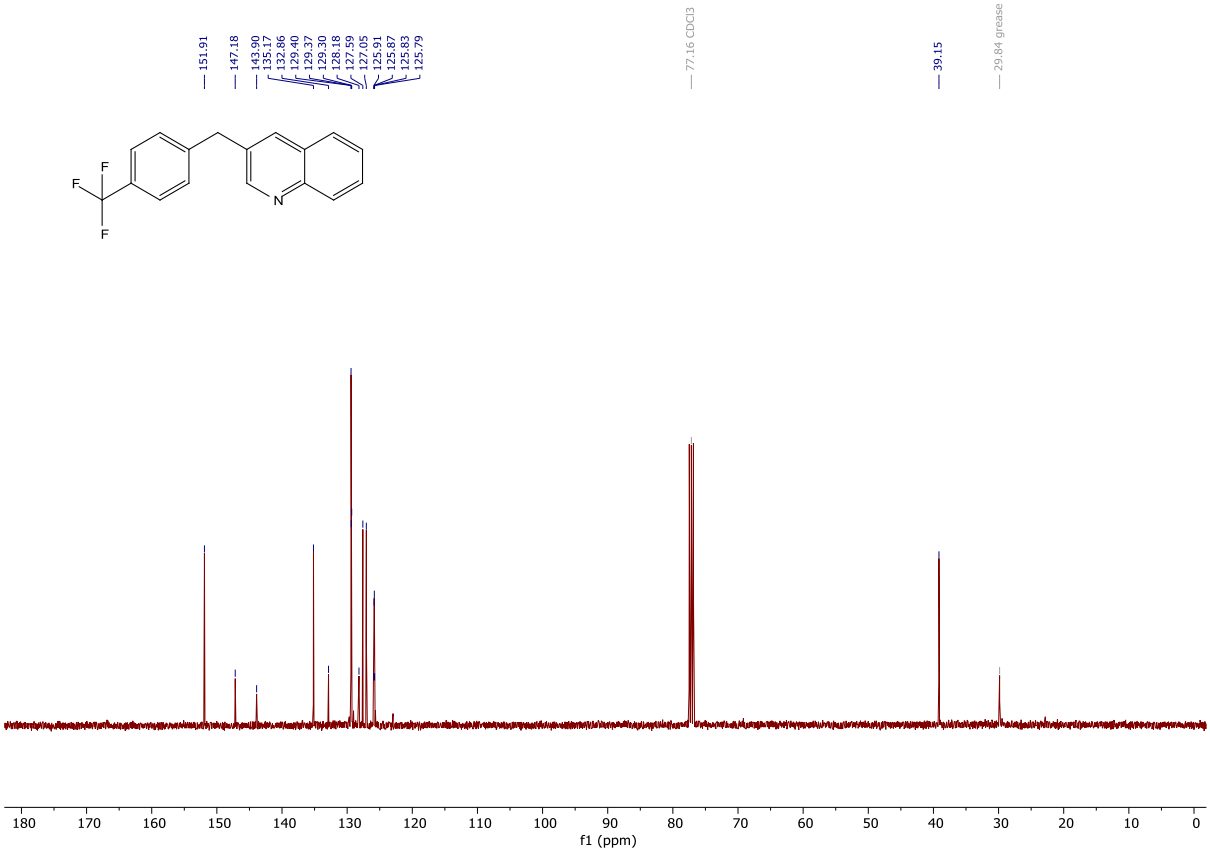
F
F
N
20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120
f1 (ppm)

3-(4-(Trifluoromethyl)benzyl)quinoline (6f)



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F
F
F
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20
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0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
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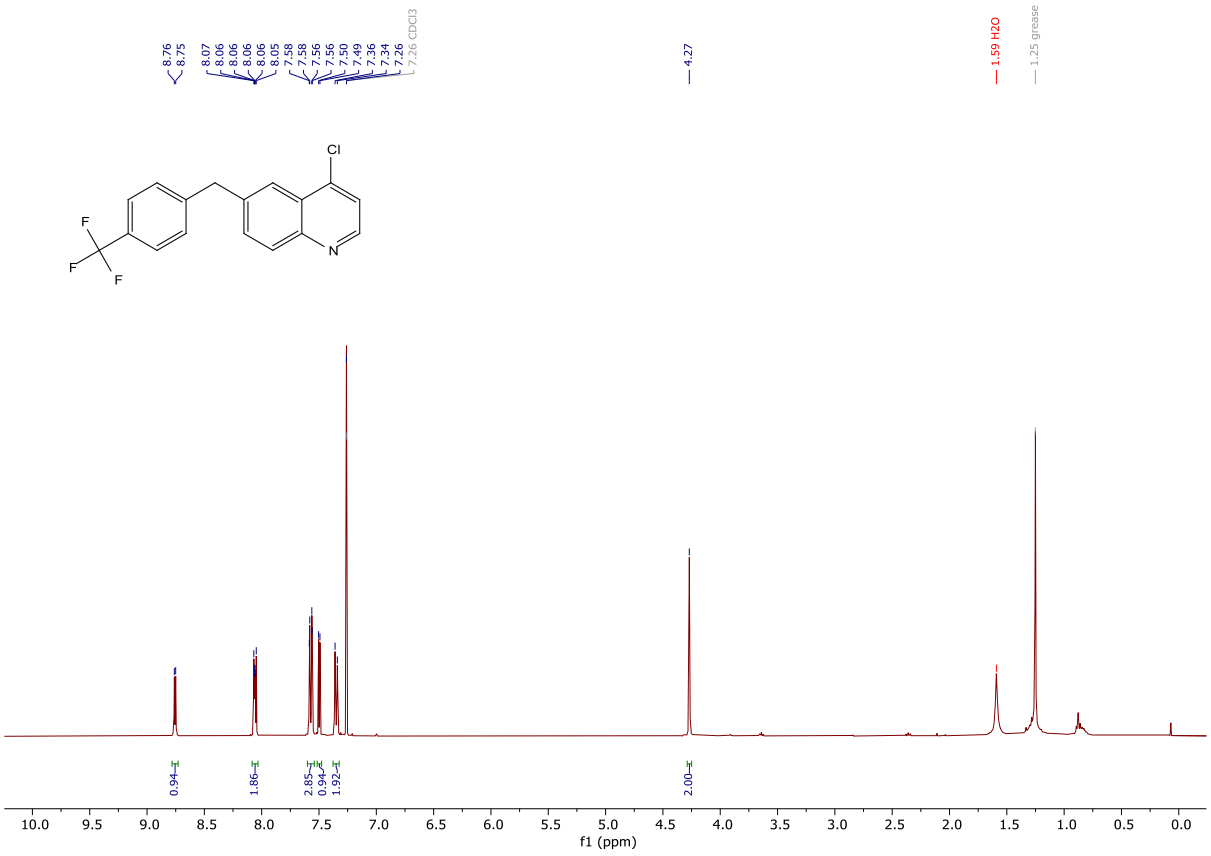
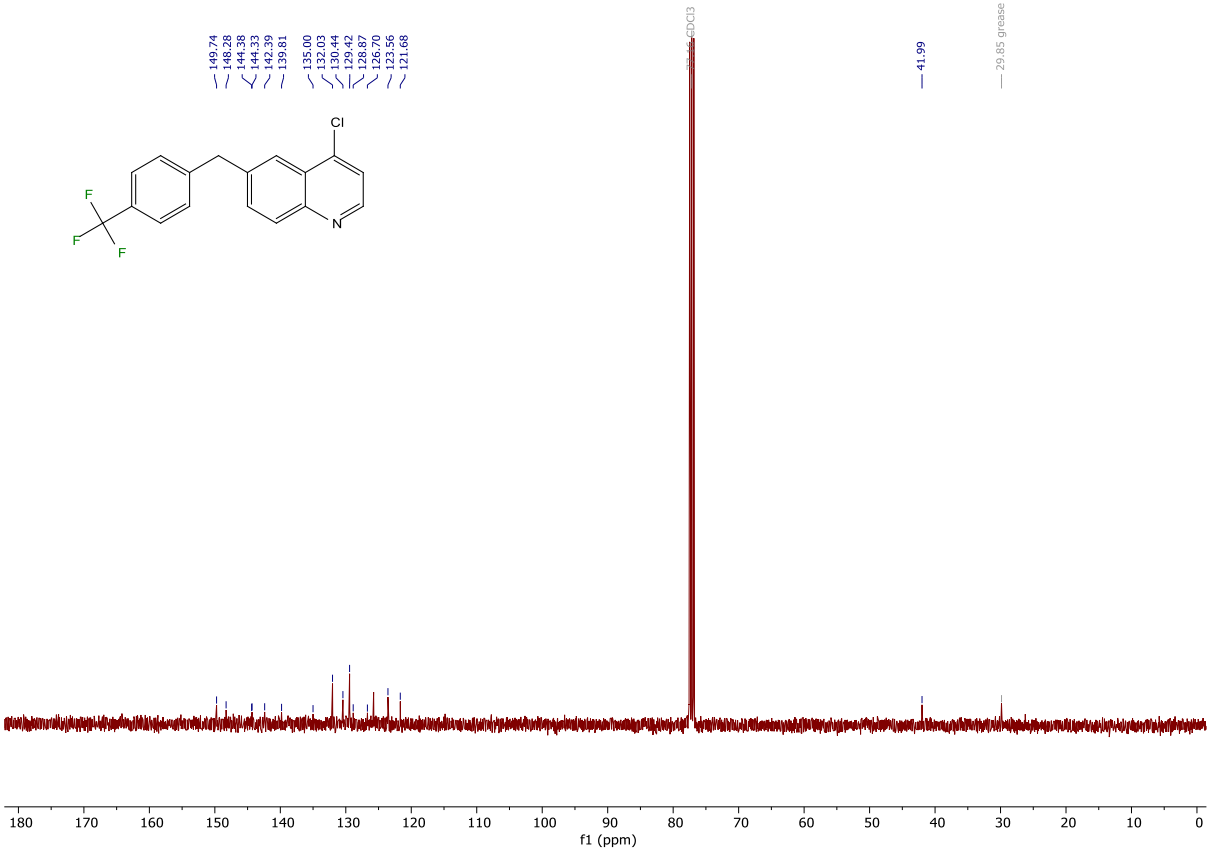
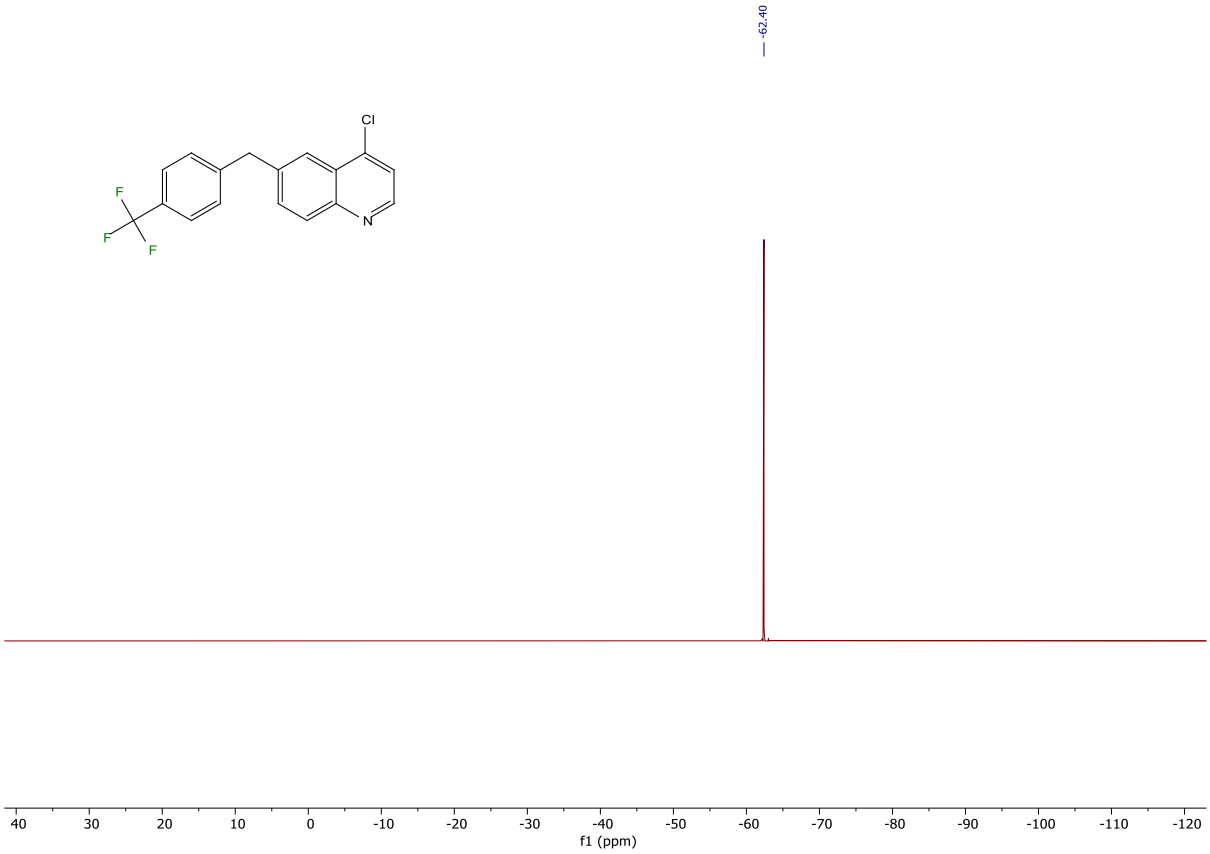
-130
-140
-150
-160
f1 (ppm)

4-Chloro-6-(4-(trifluoromethyl)benzyl)quinoline (6g)



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Cl
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F
F
N
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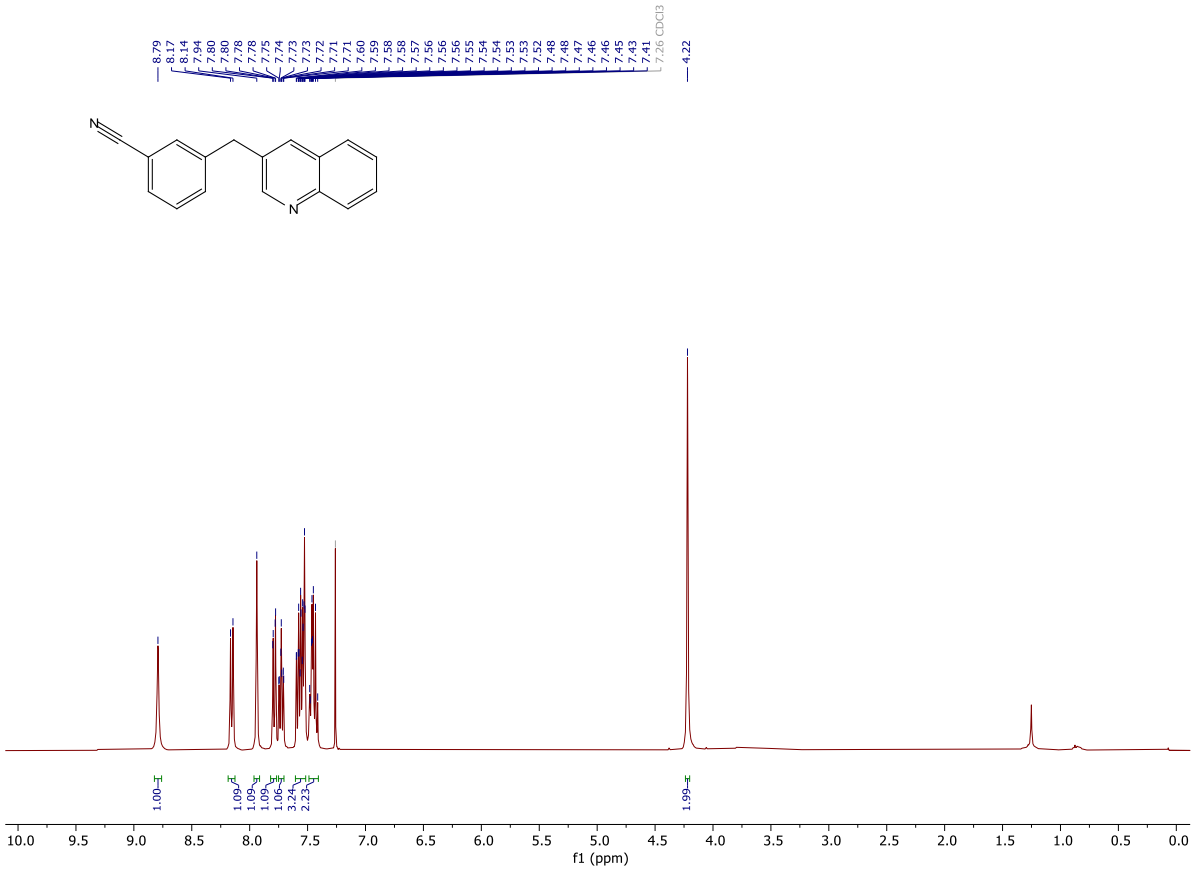
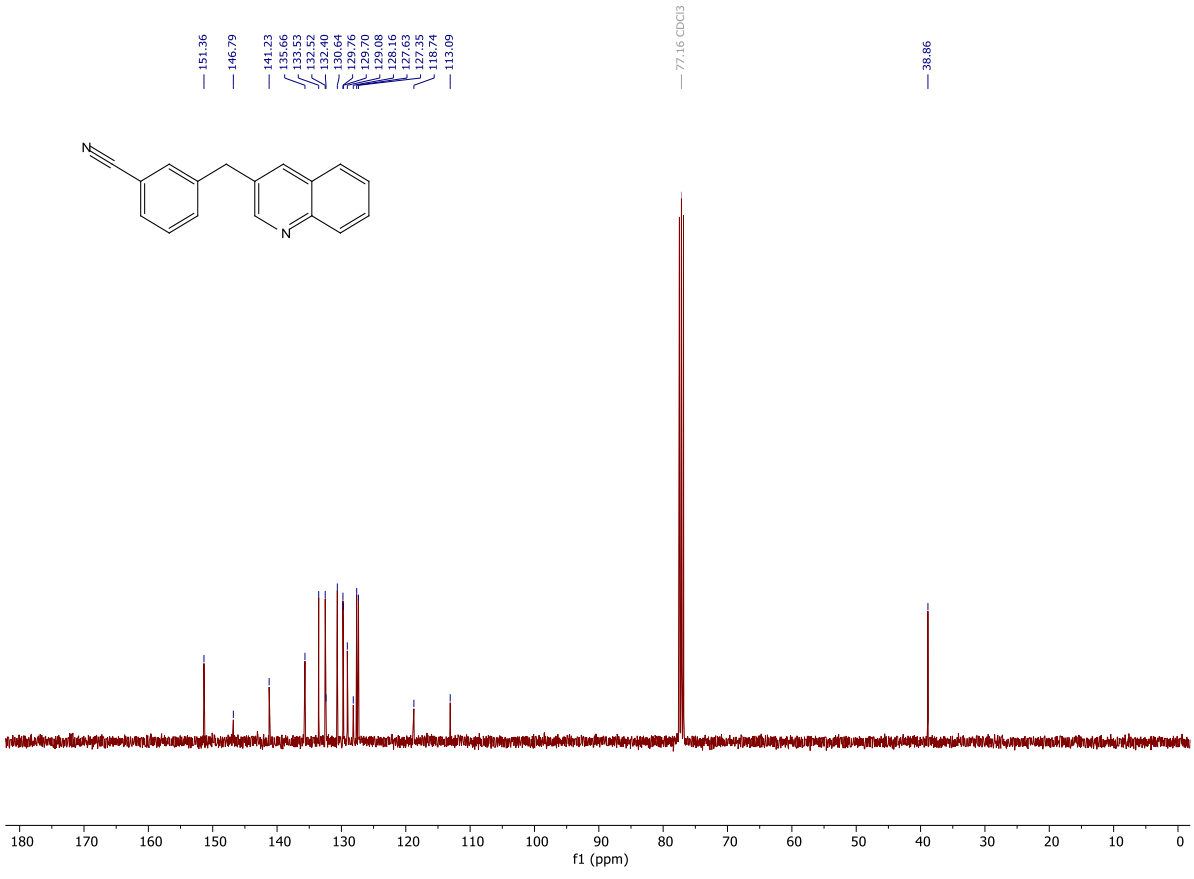
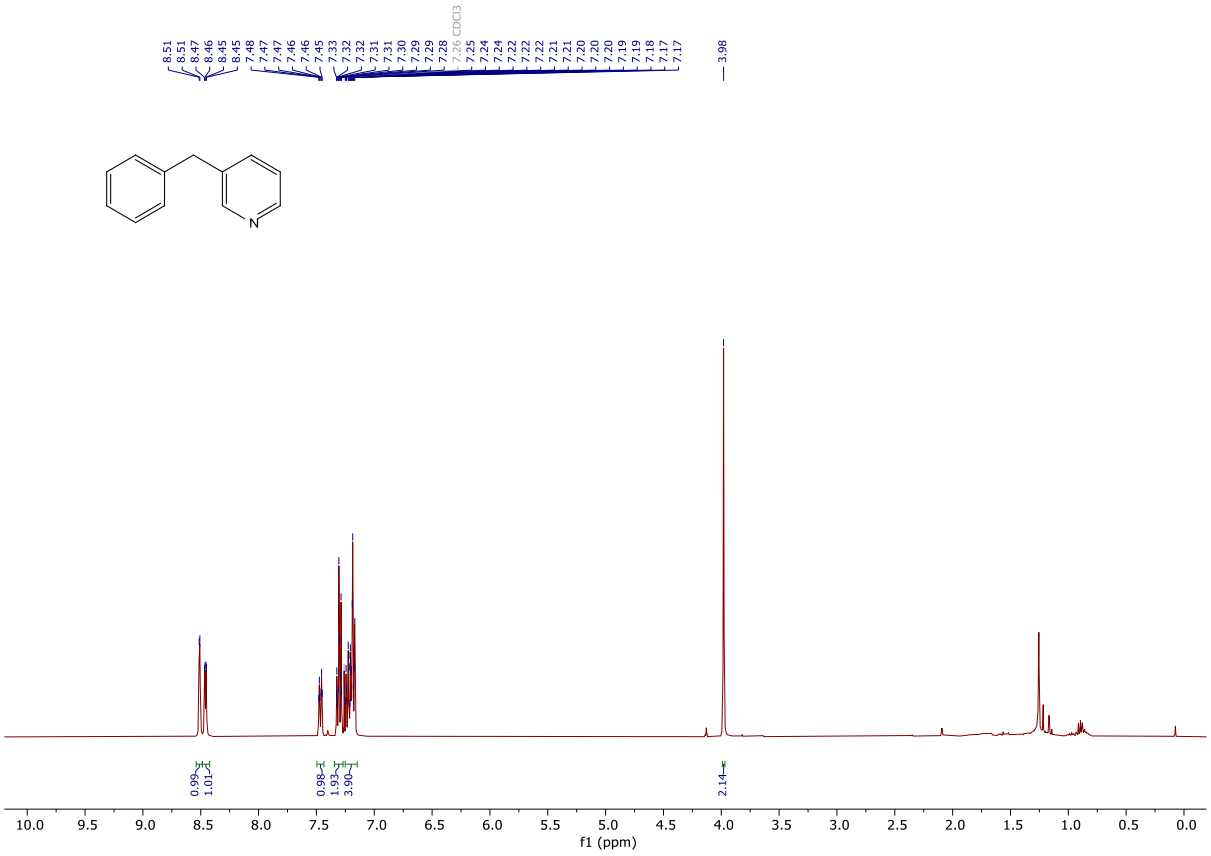
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
f1 (ppm)

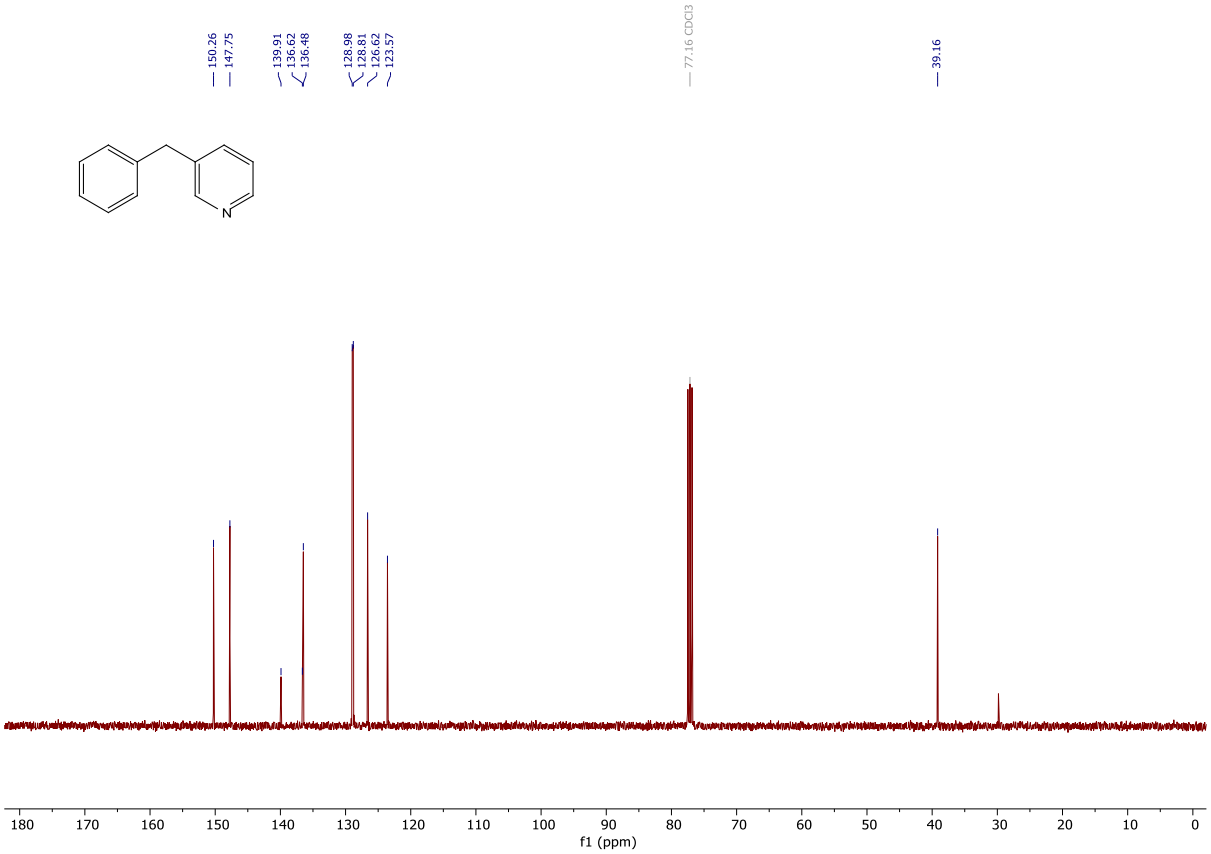
3-(Quinolin-3-ylmethyl)benzonitrile (6h)



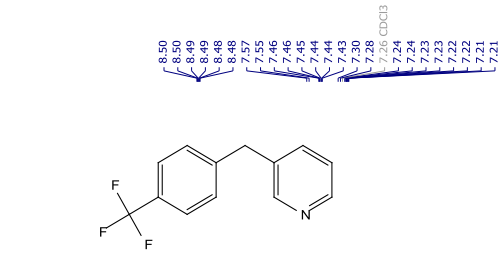


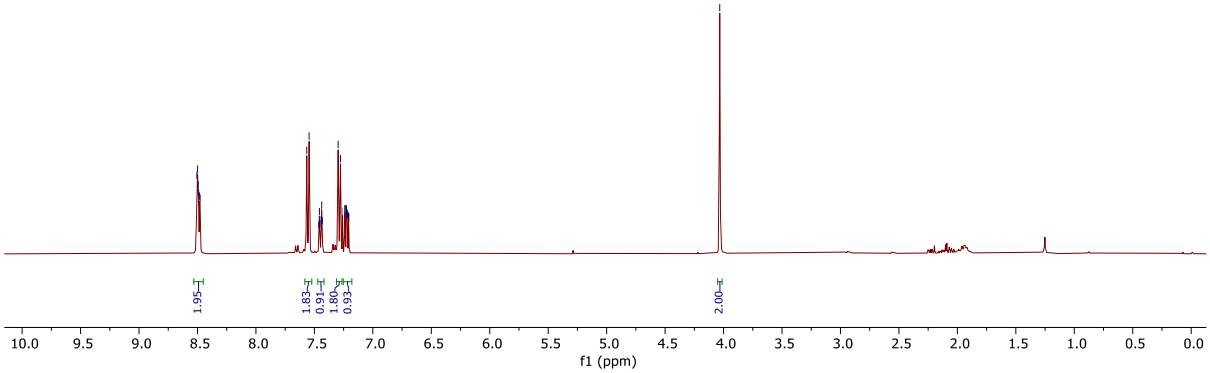
3-Benzylpyridine (6i)



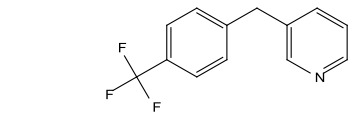


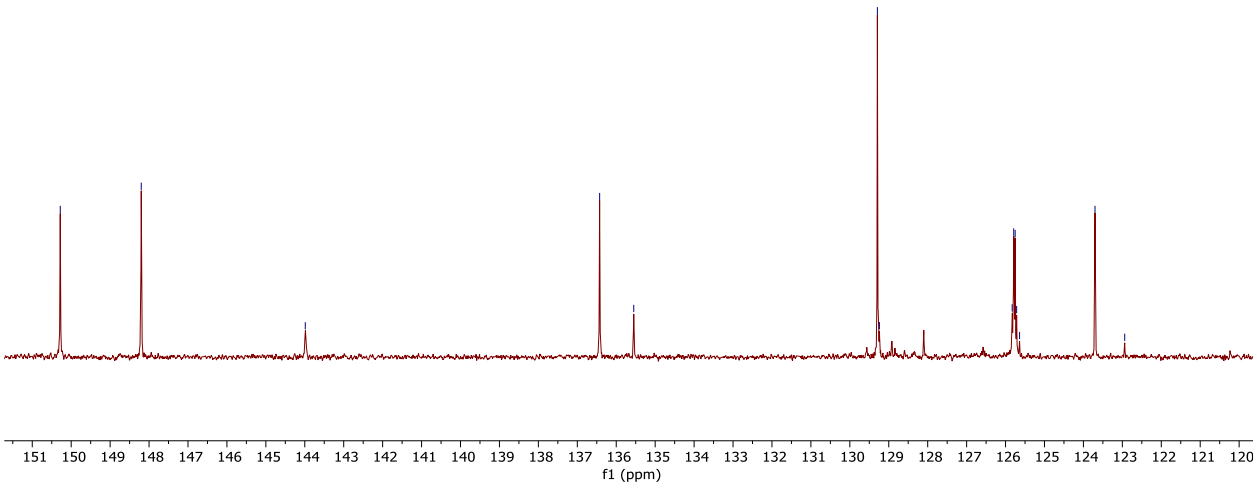
3-(4-(Trifluoromethyl)benzyl)pyridine (6j)

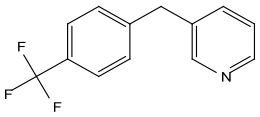








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20
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0
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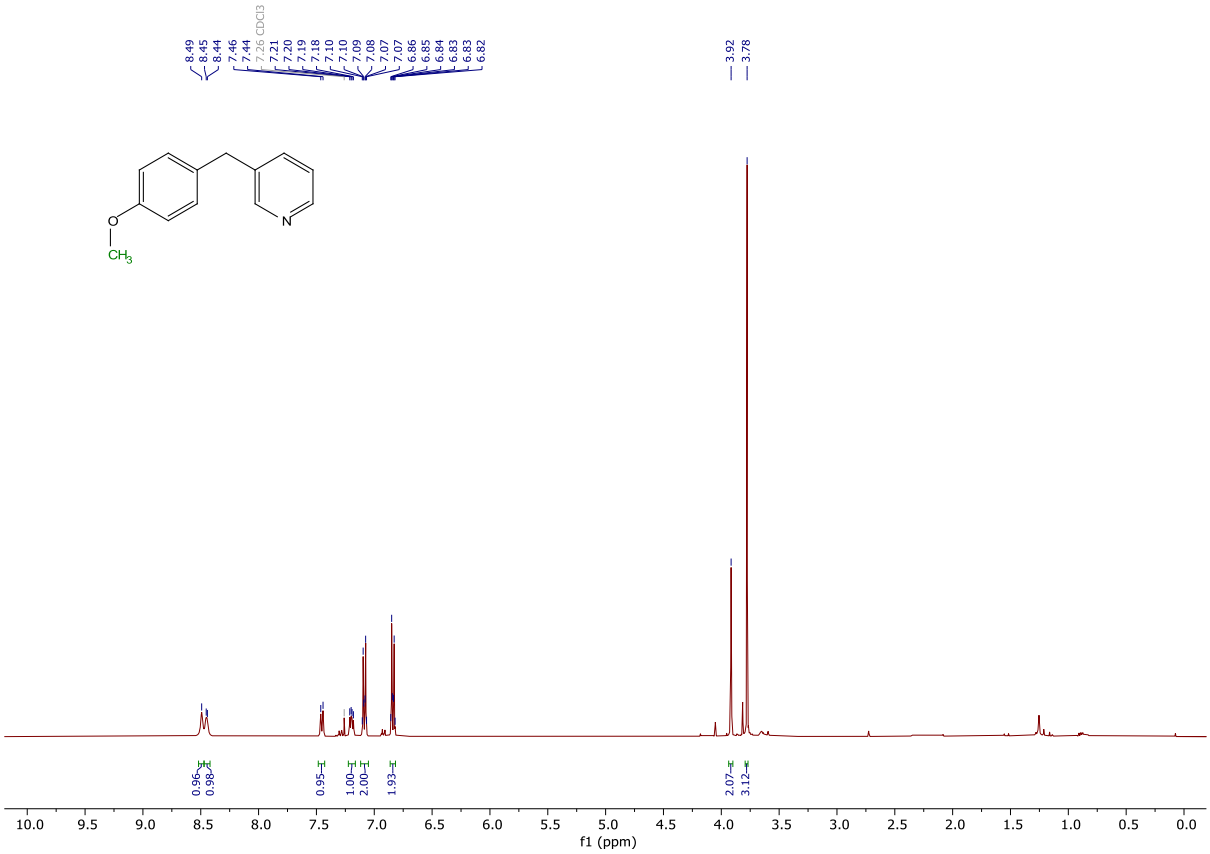
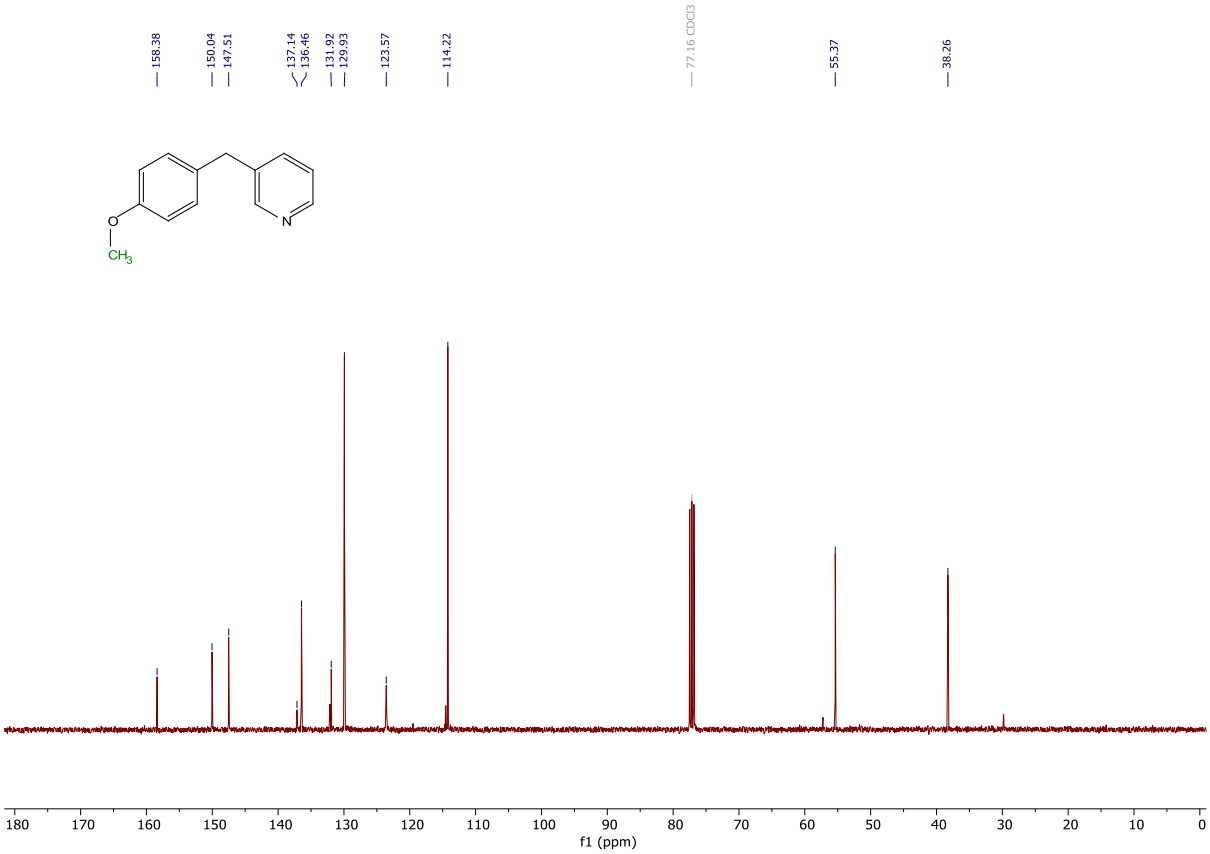
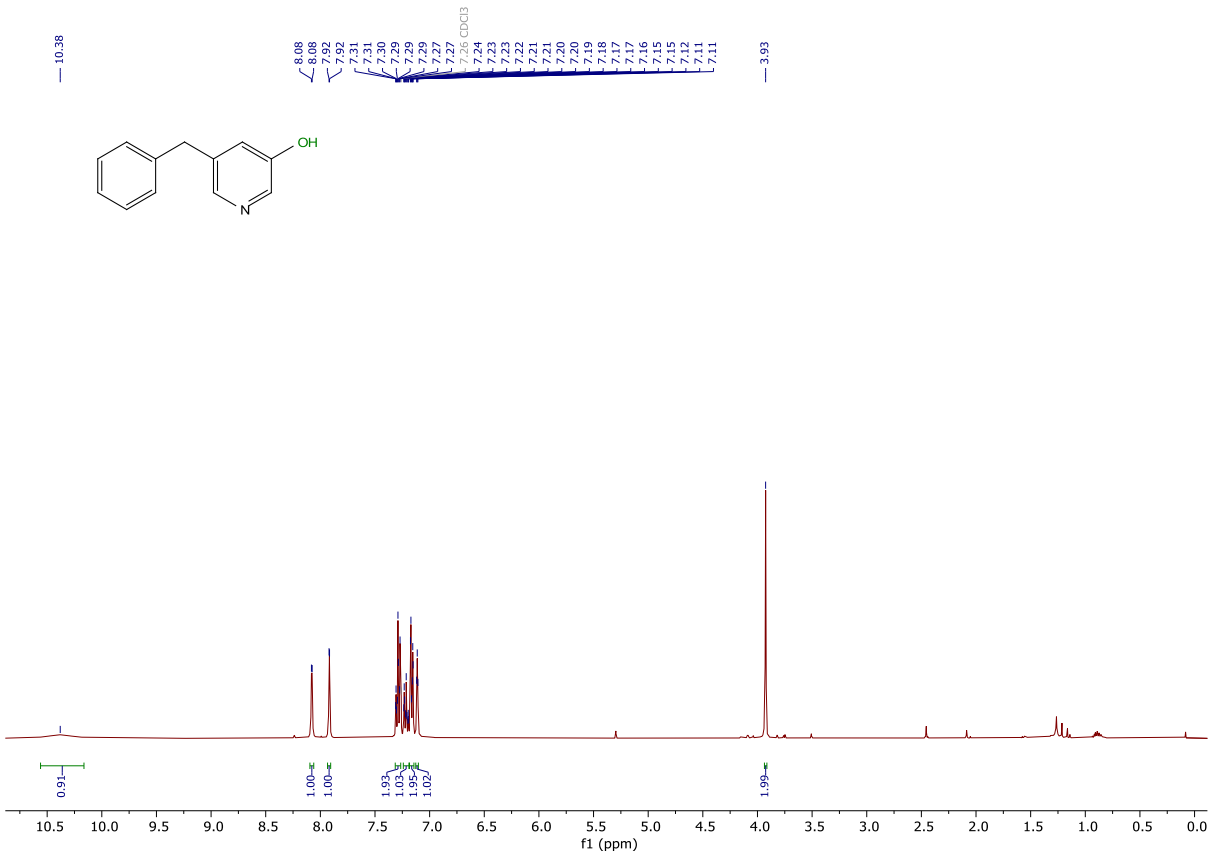
-120
f1 (ppm)

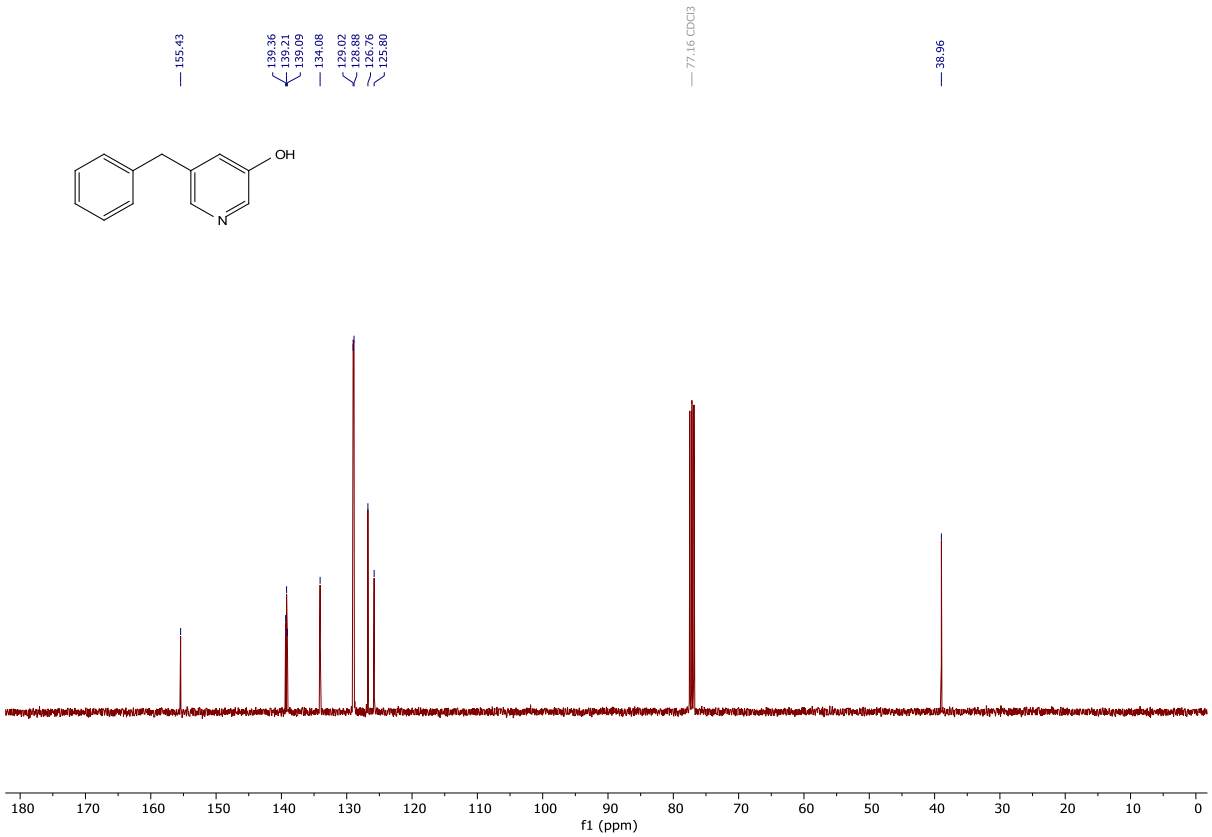
3-(4-Methoxybenzyl)pyridine (6k)



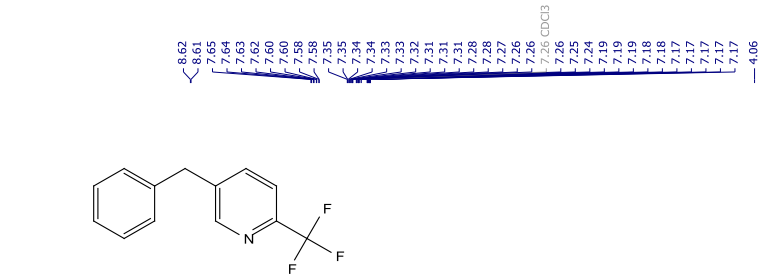


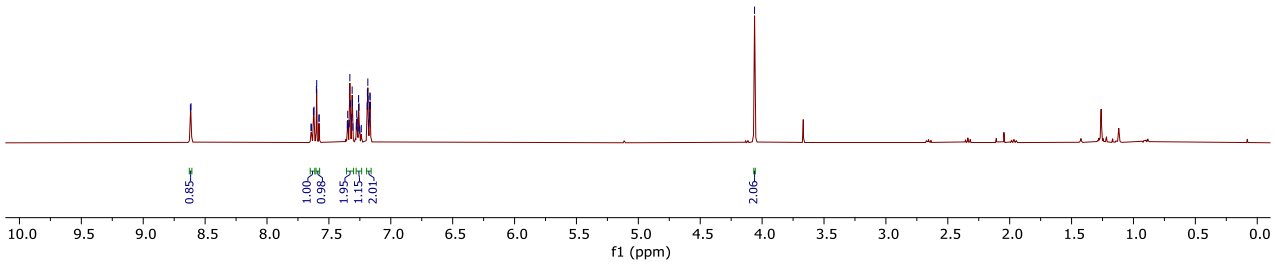
5-Benzylpyridin-3-ol (6l)

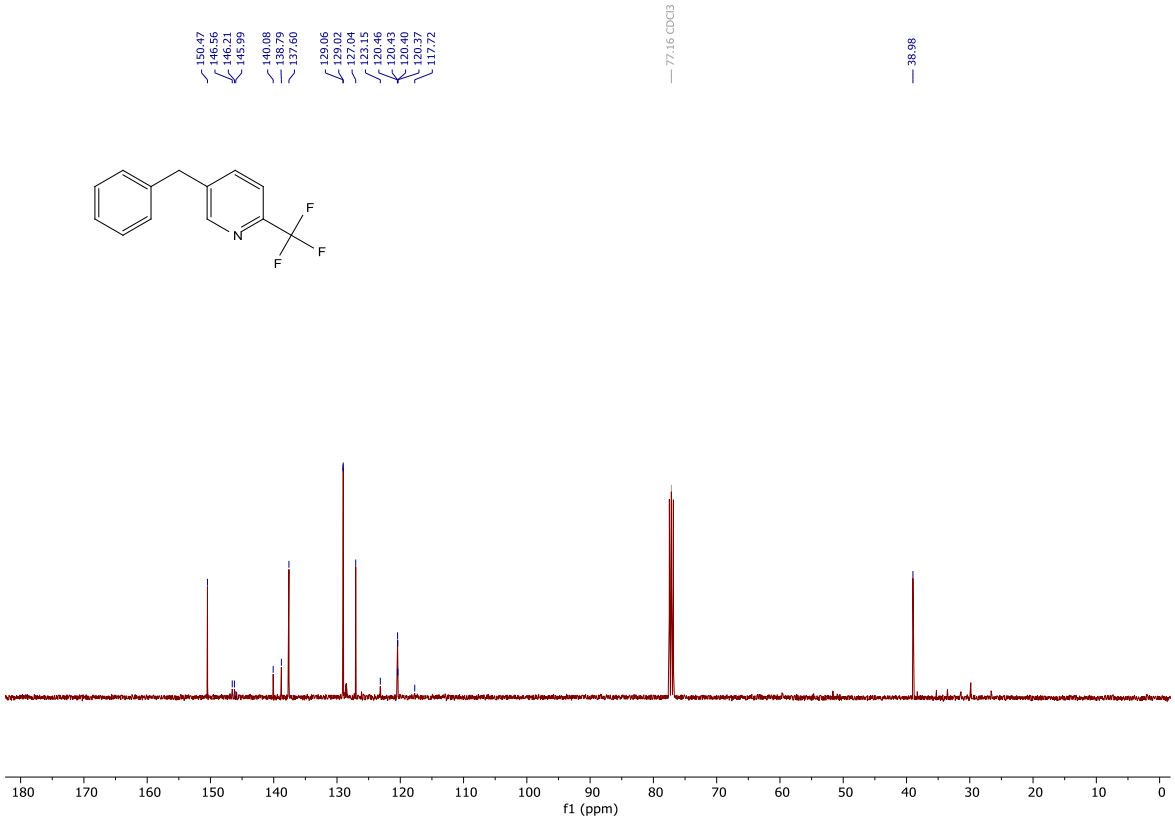


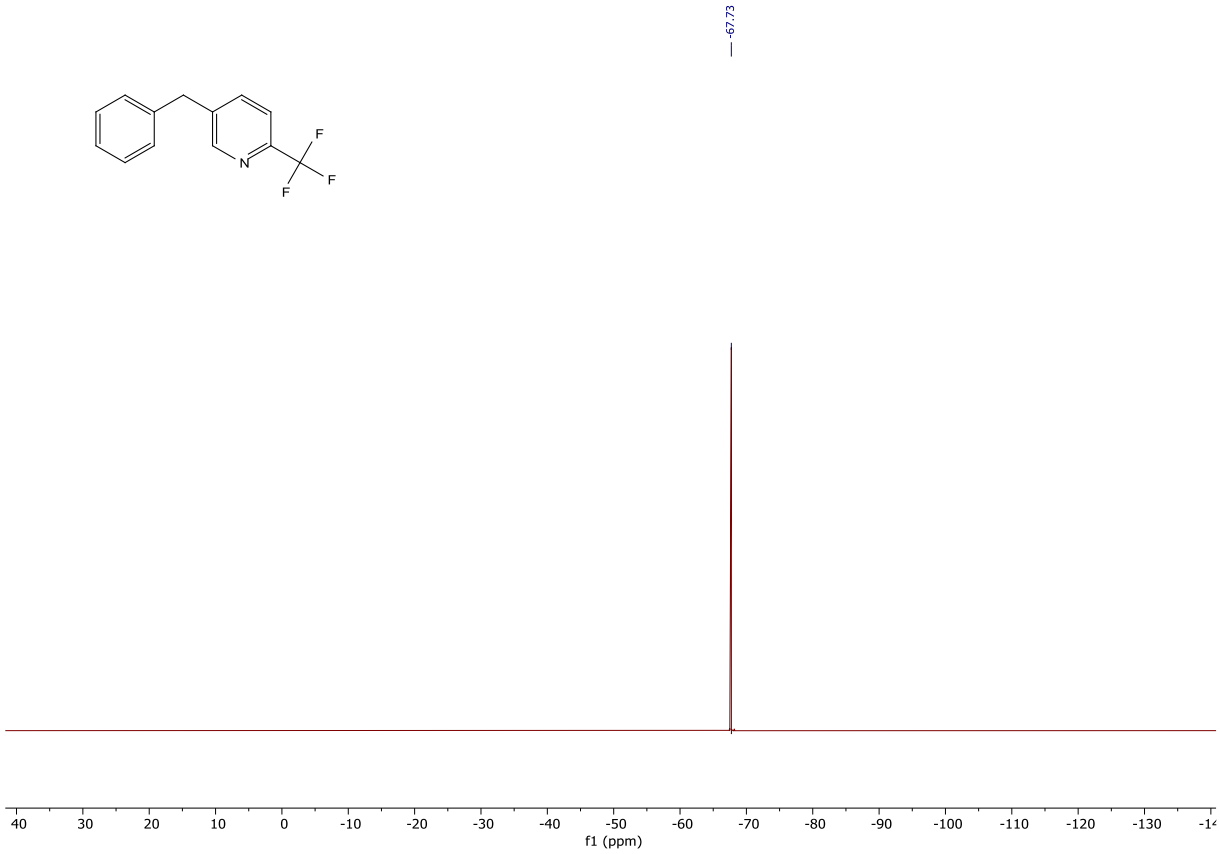


5-Benzyl-2-(trifluoromethyl)pyridine (6m)





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F
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0
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-20
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-40
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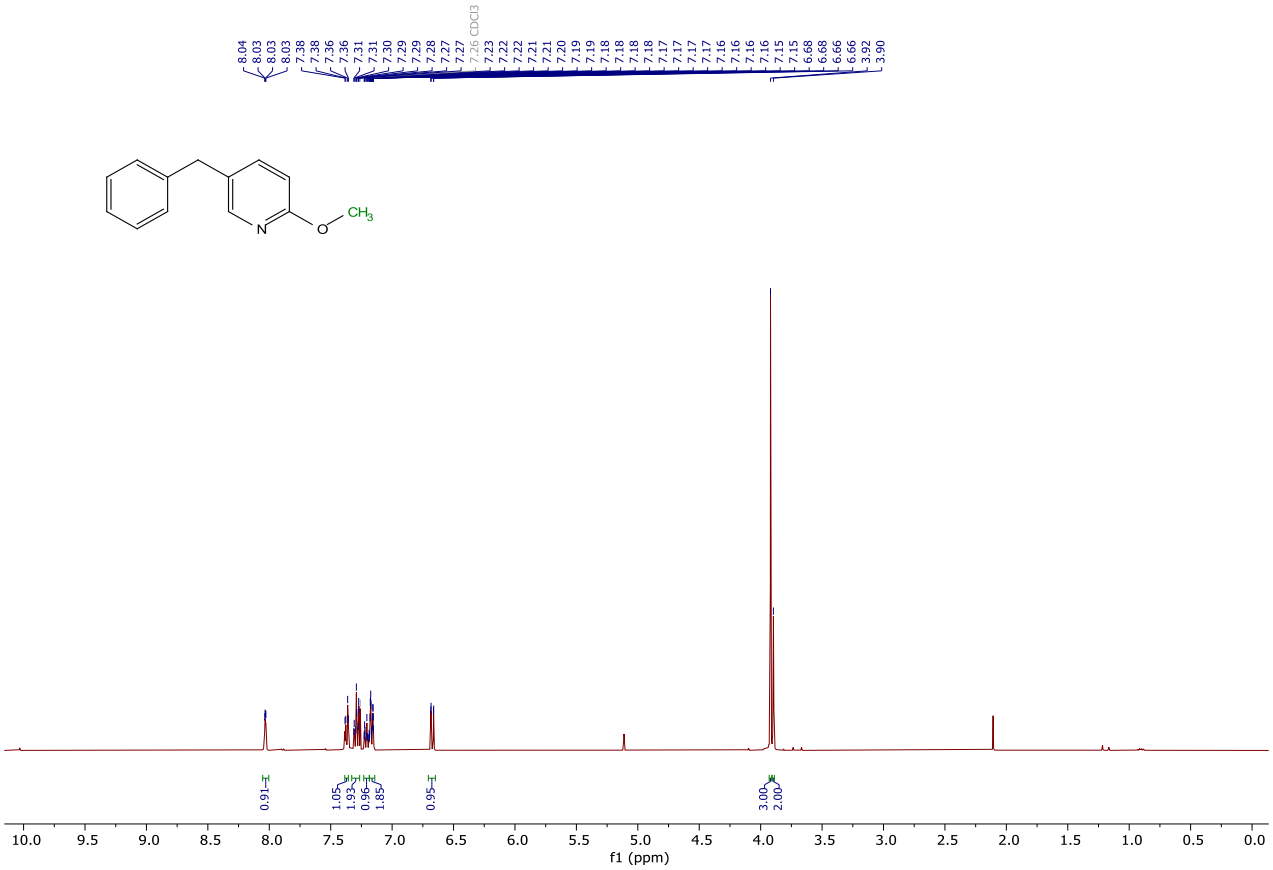
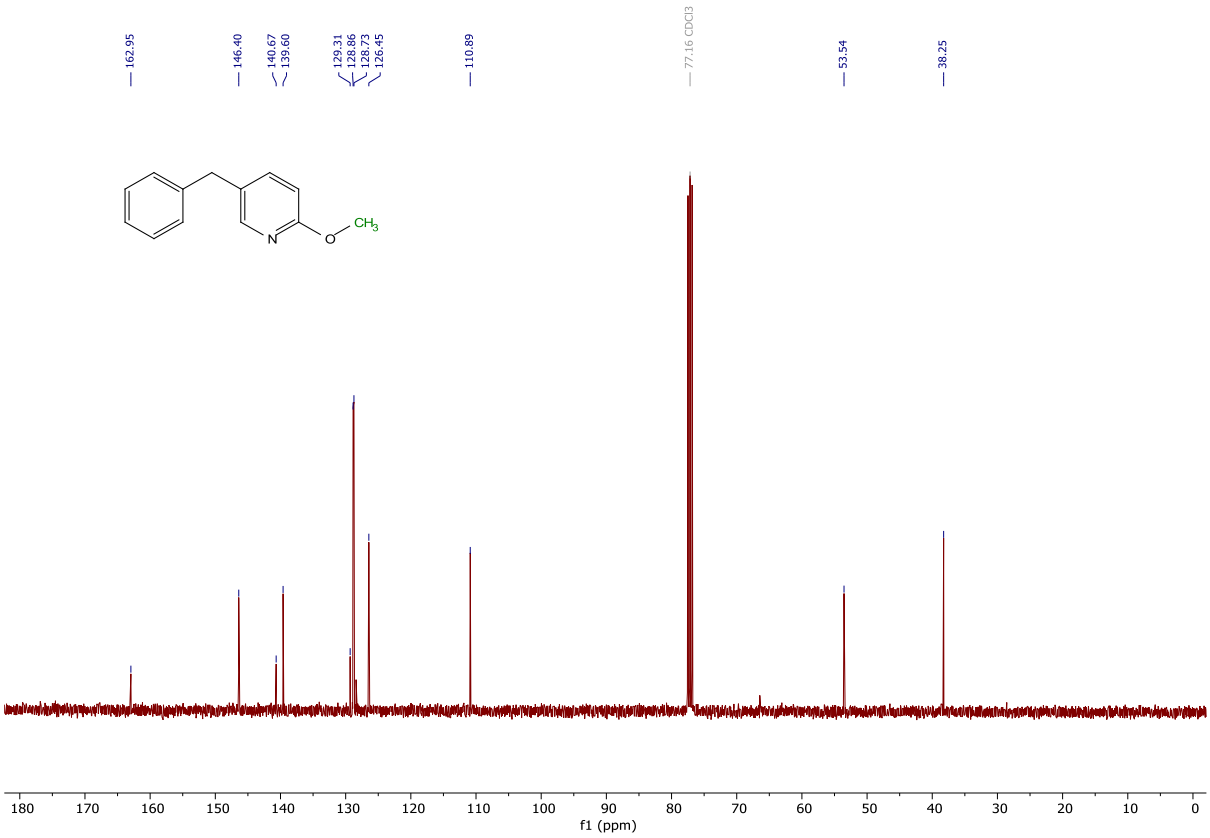
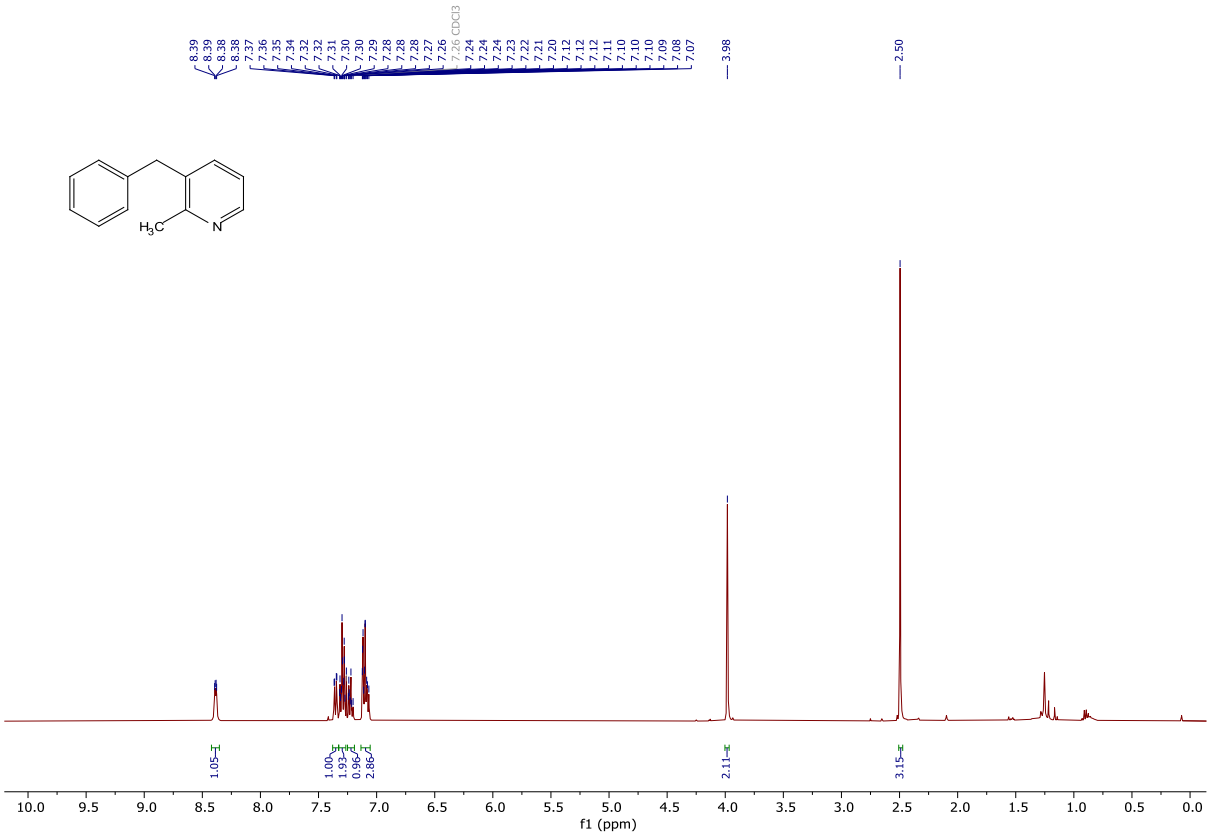
-110
-120
-130
f1 (ppm)

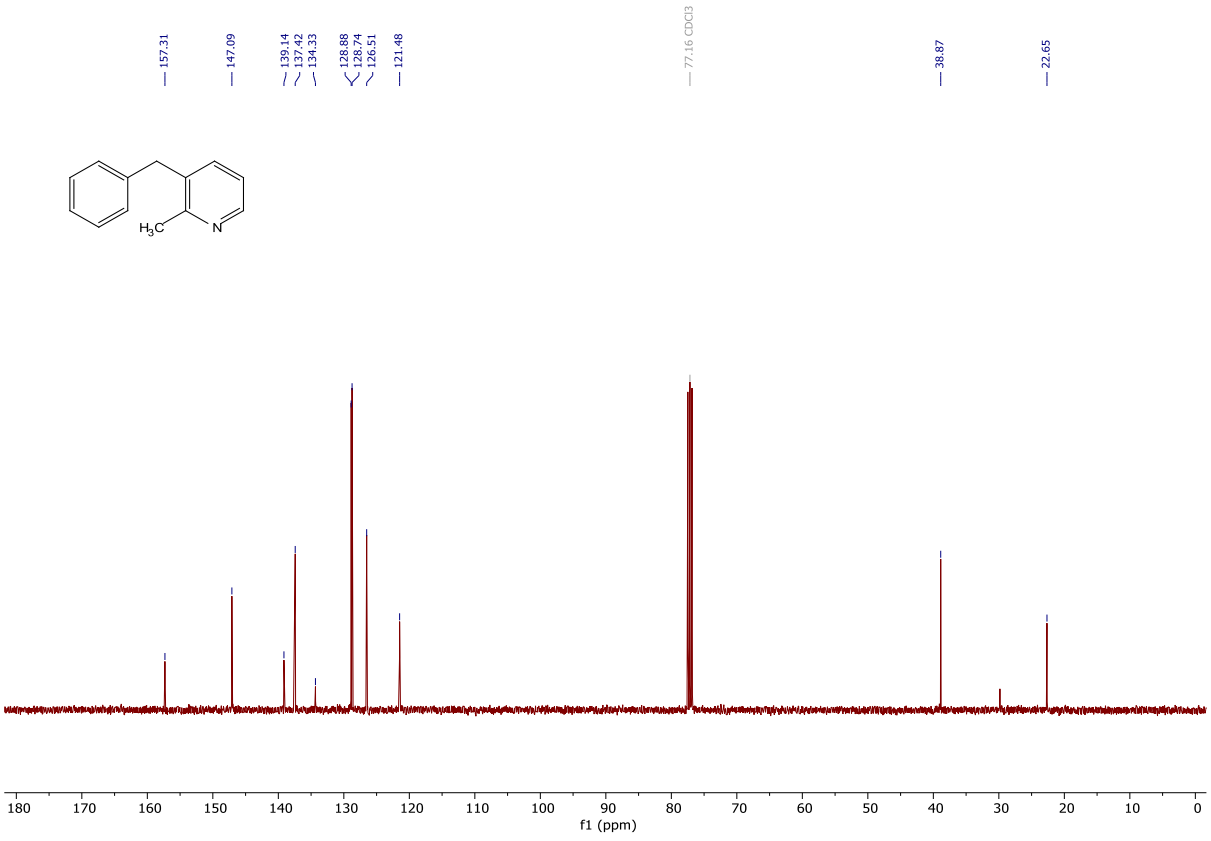
5-Benzyl-2-methoxypyridine (6n)



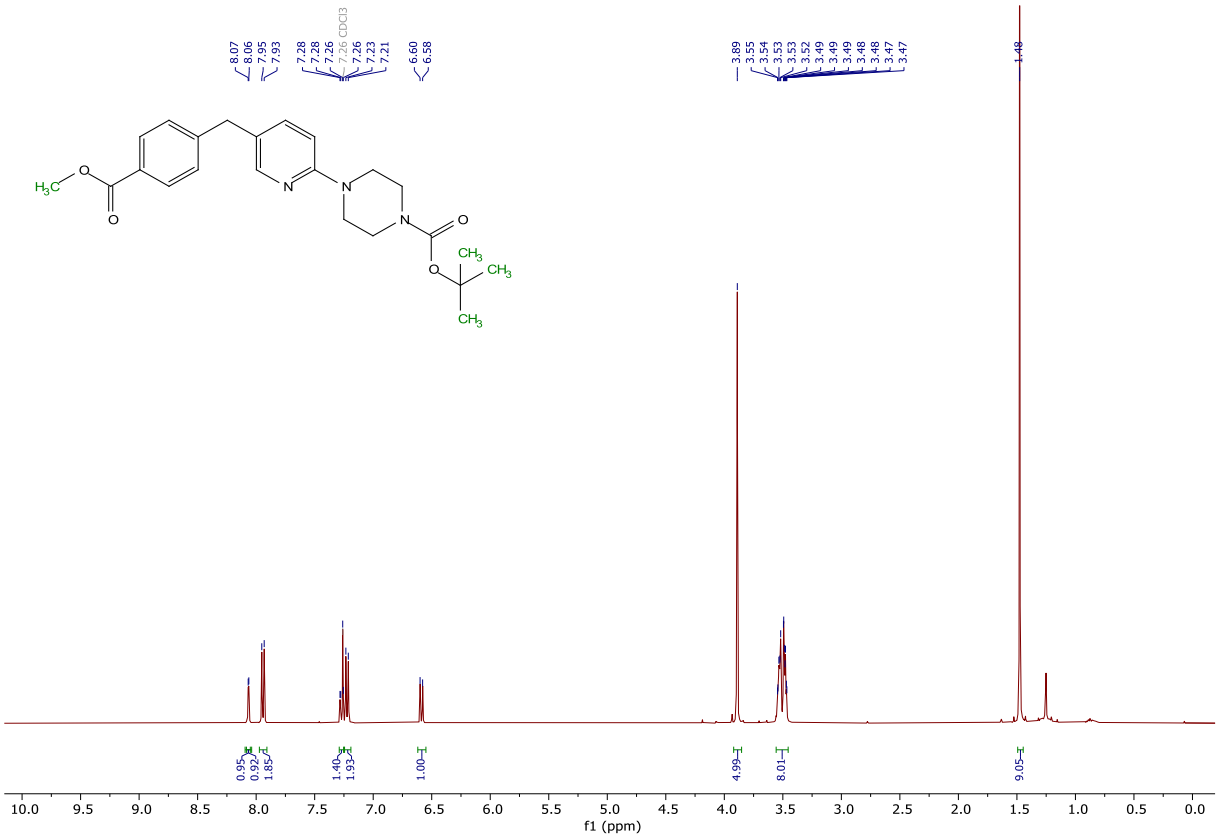


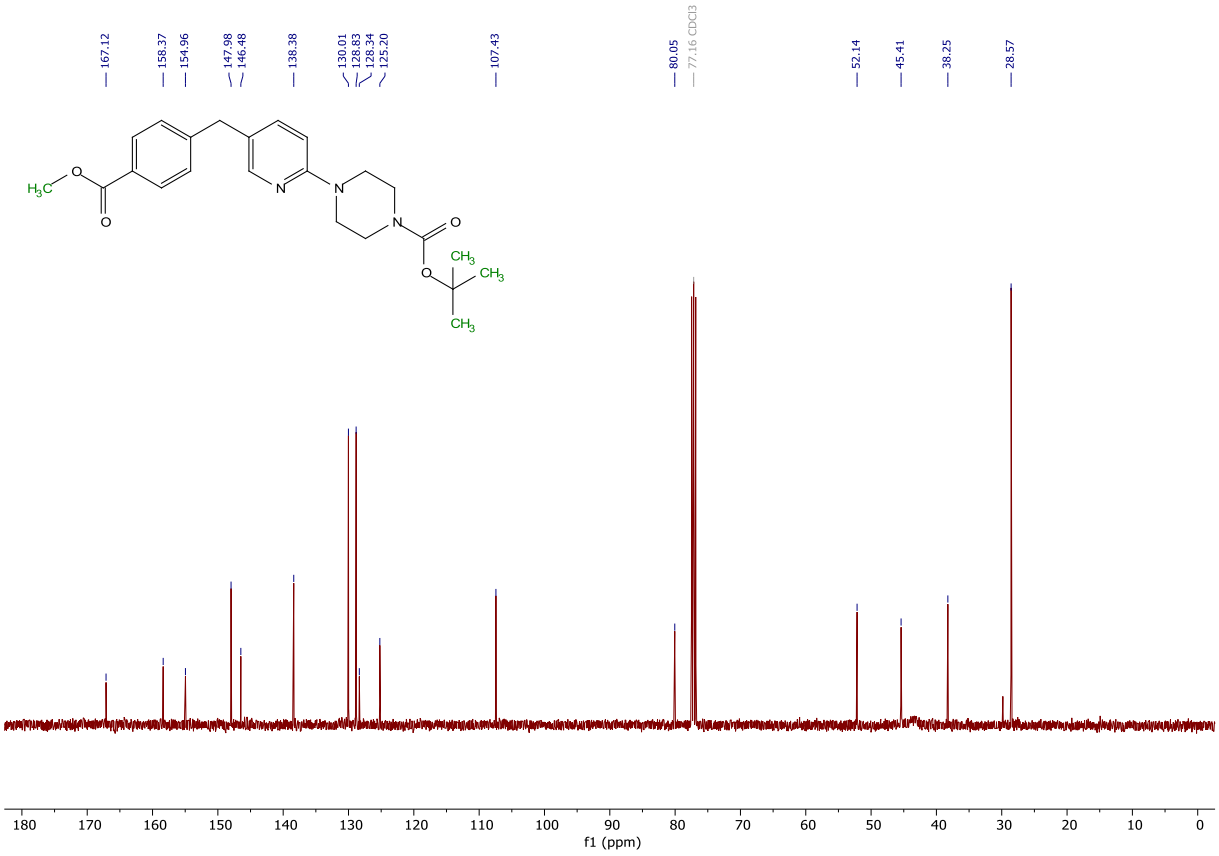
3-Benzyl-2-methylpyridine (6o)



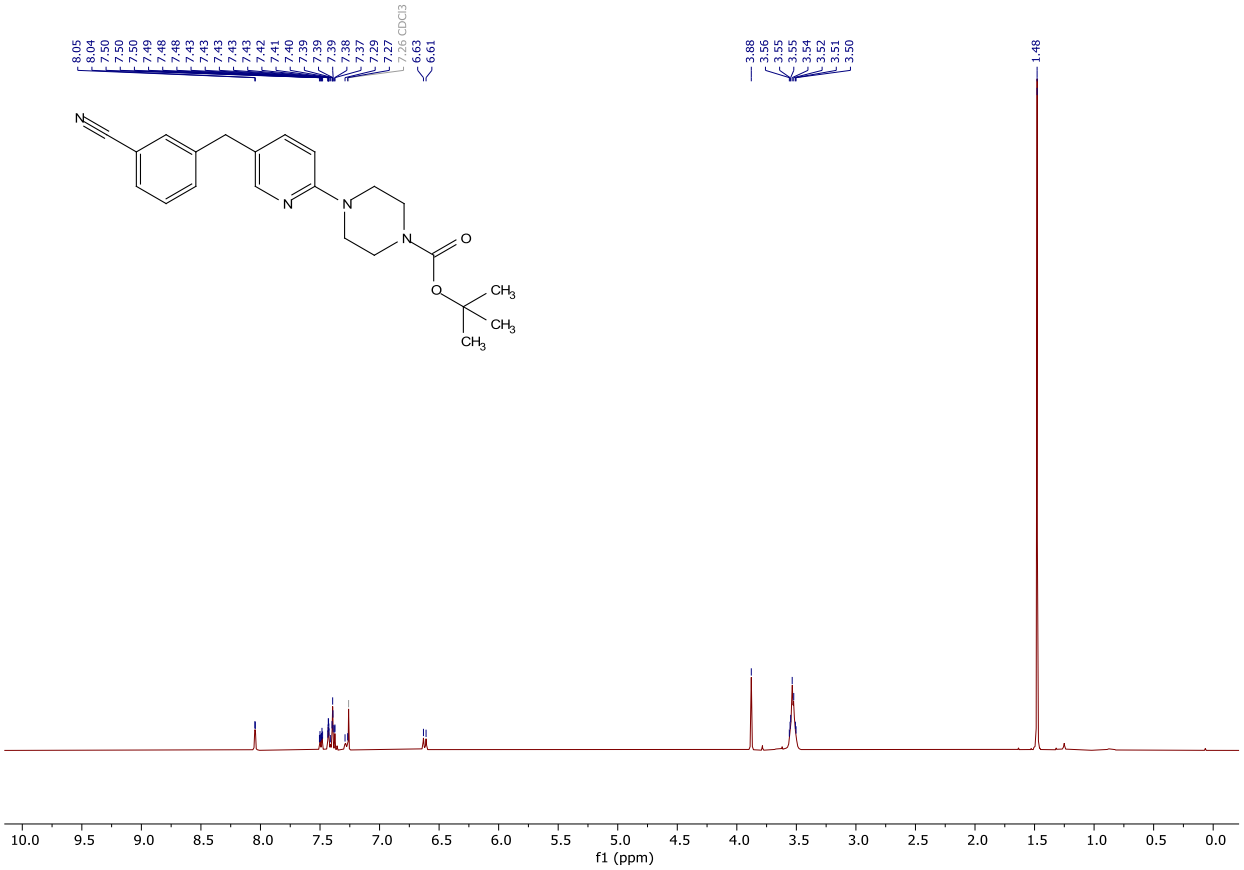


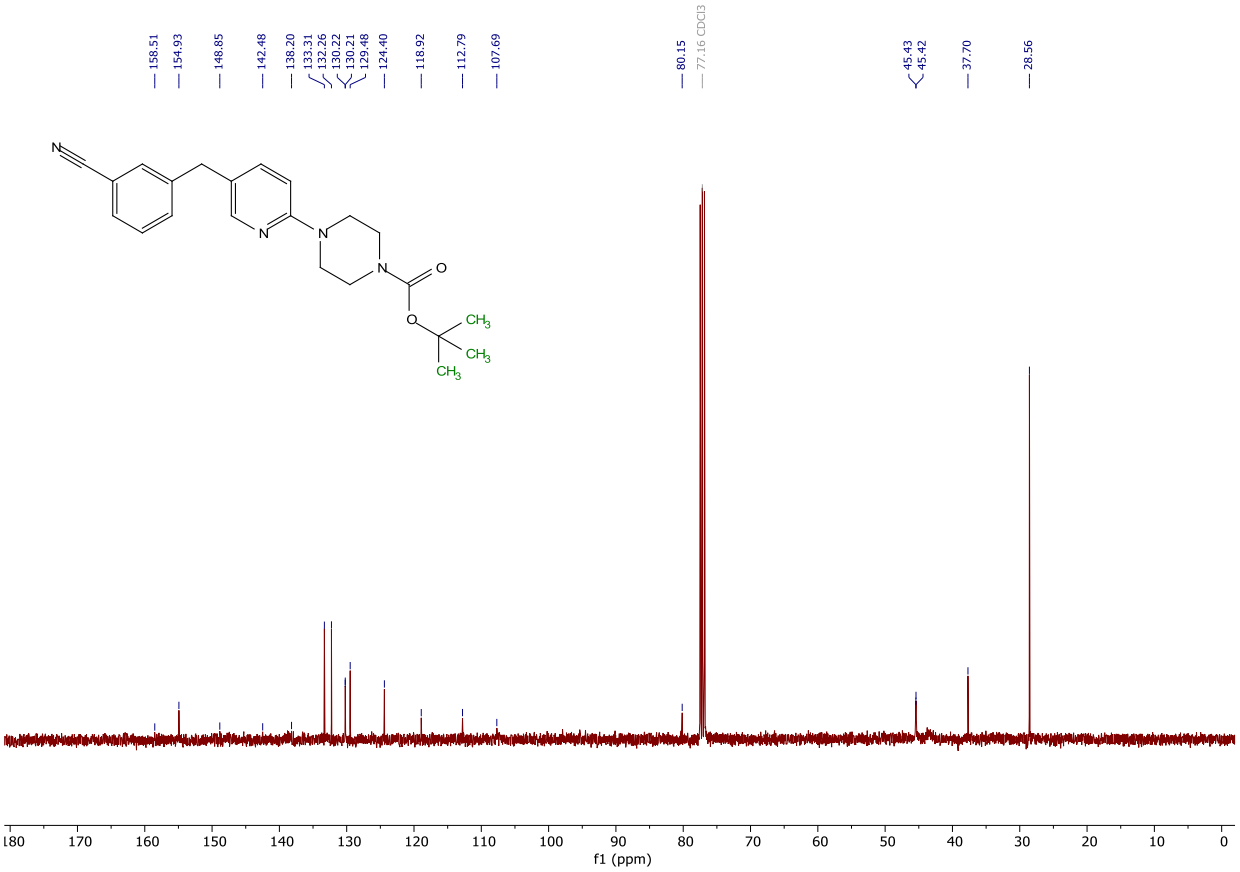
Tert-butyl 4-(5-(4-(methoxycarbonyl)benzyl)pyridin-2-yl)piperazine-1-carboxylate (6p)



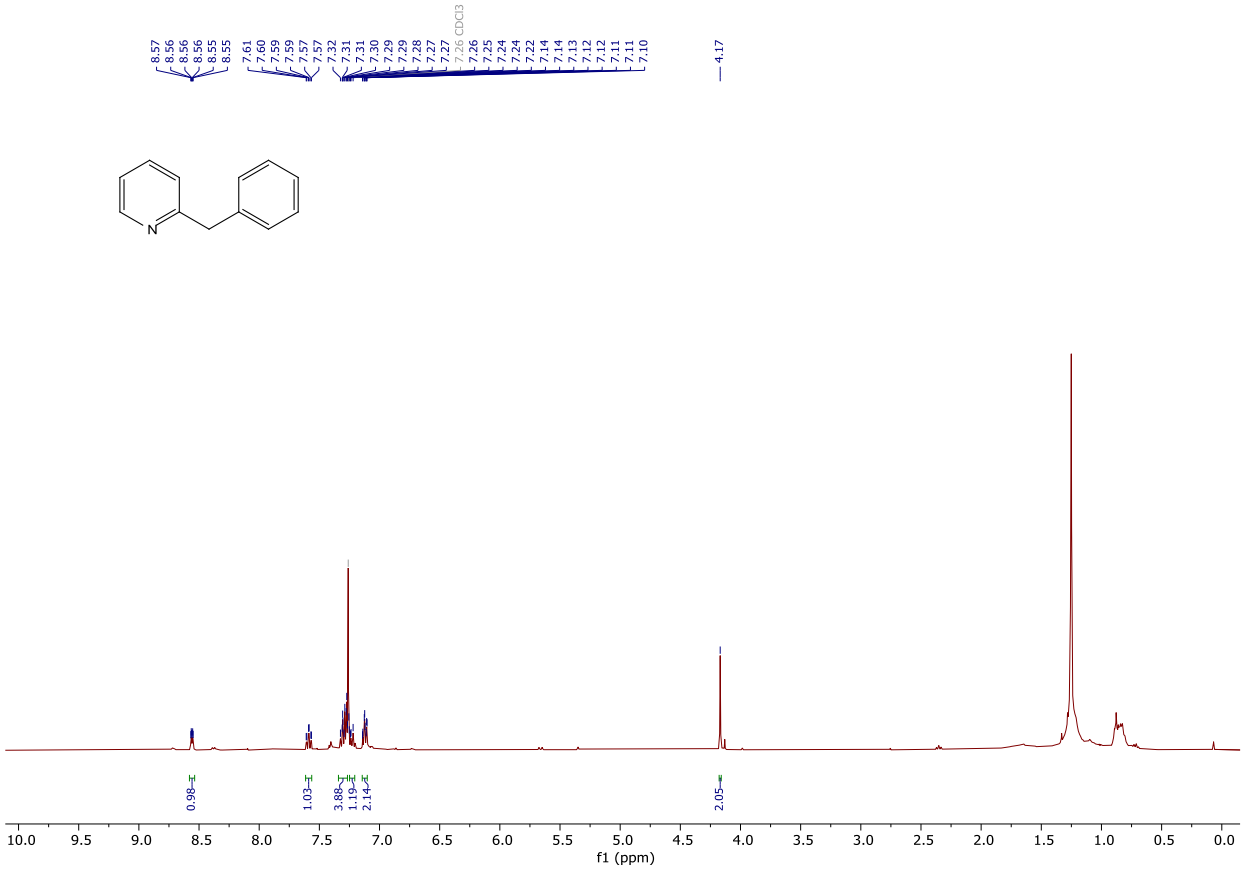


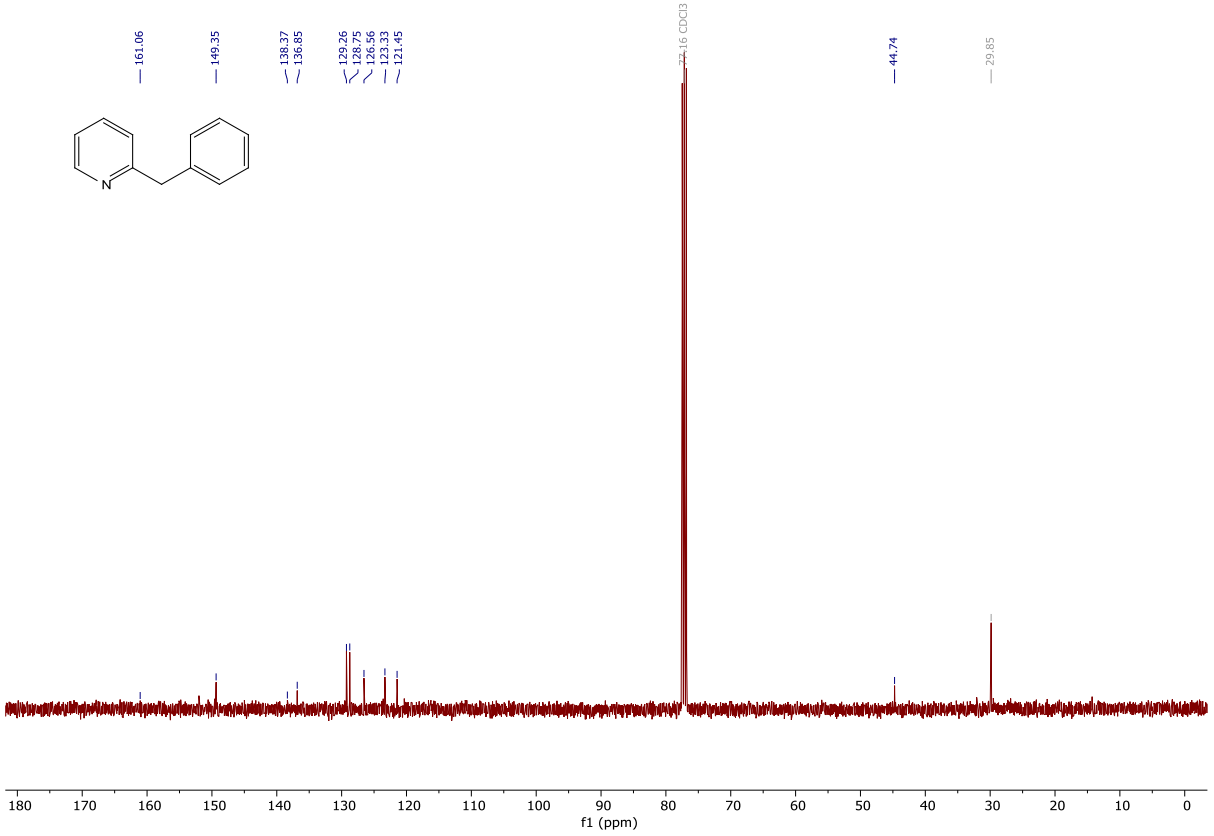
Tert-butyl 4-(5-(3-cyanobenzyl)pyridin-2-yl)piperazine-1-carboxylate (6q)



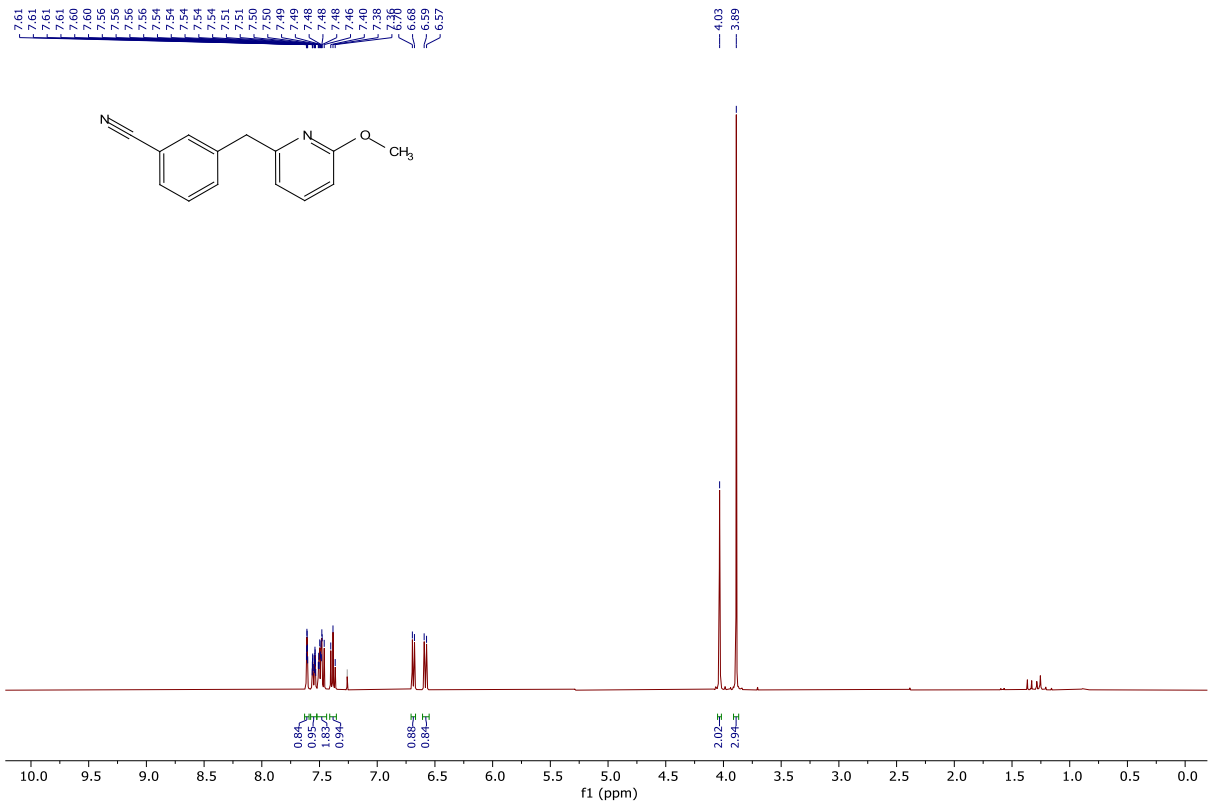


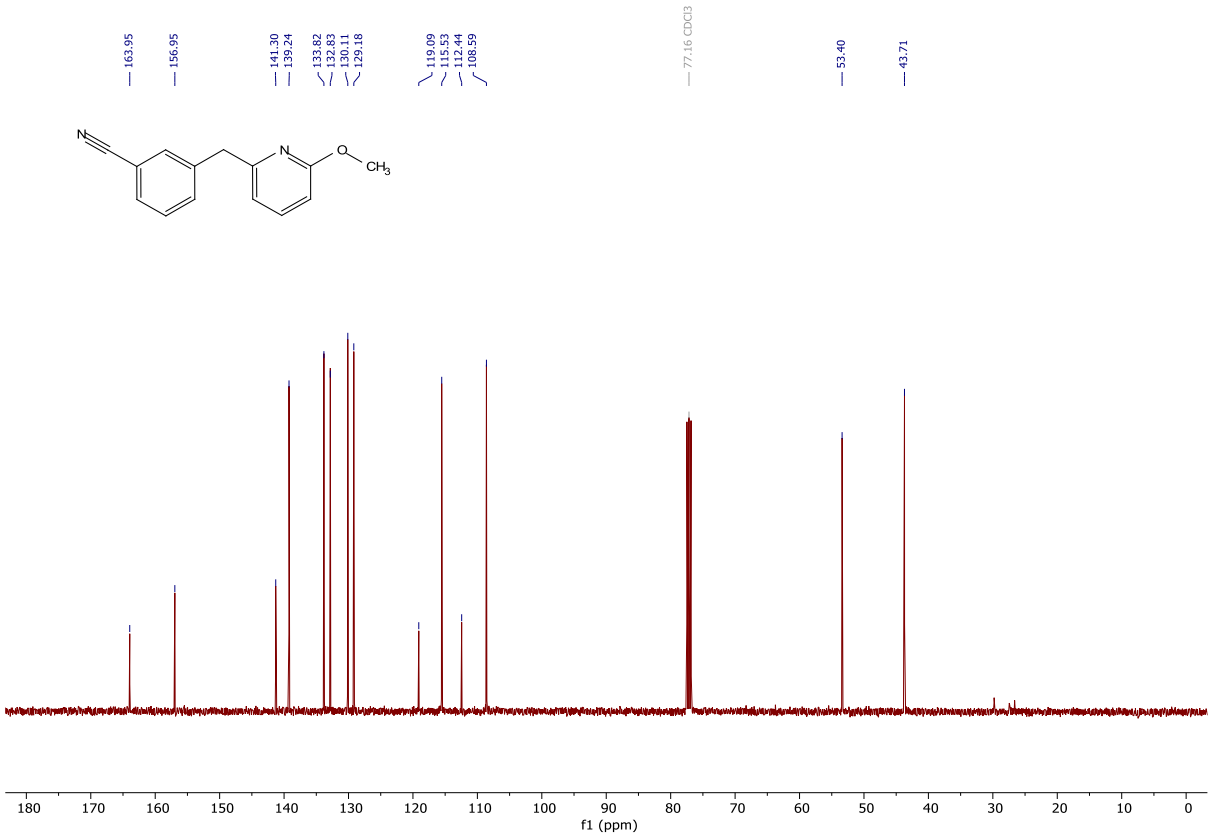
2-Benzylpyridine (6r)



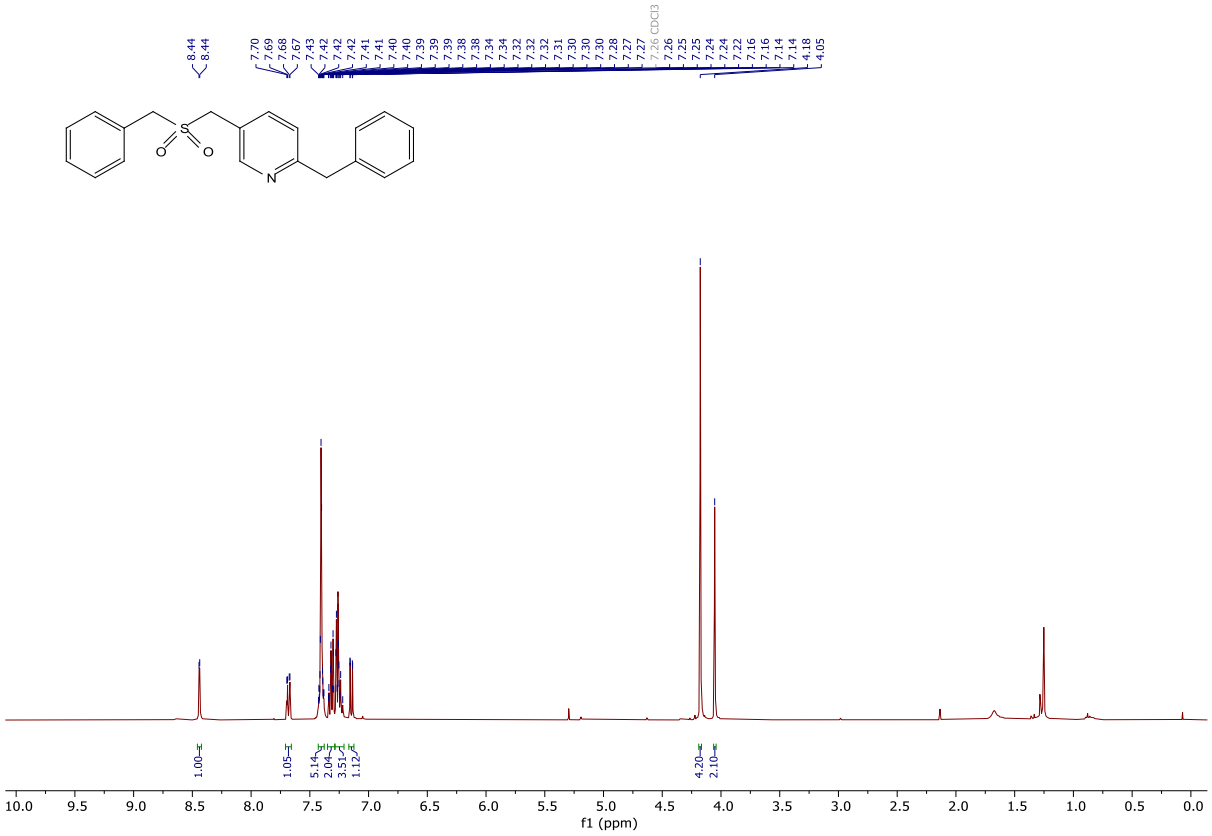


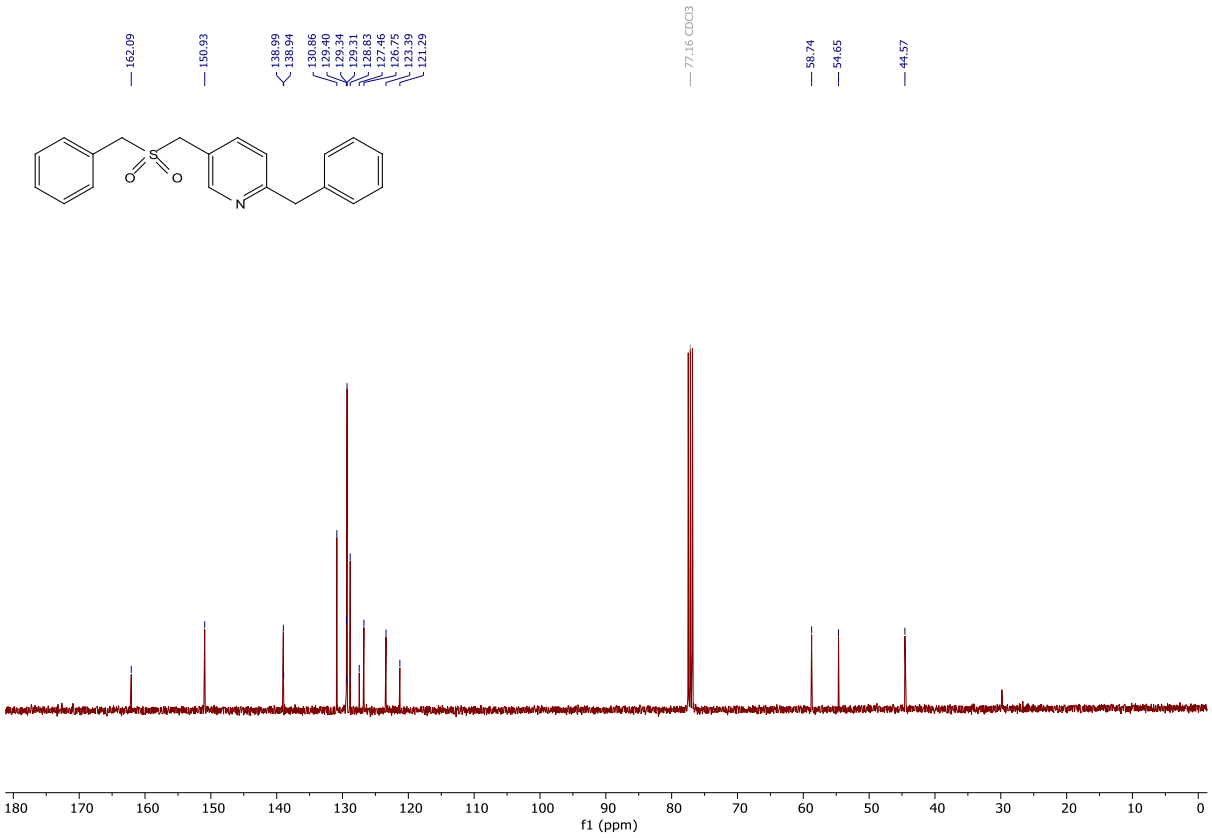
3-((6-Methoxypyridin-2-yl)methyl)benzonitrile (6s)



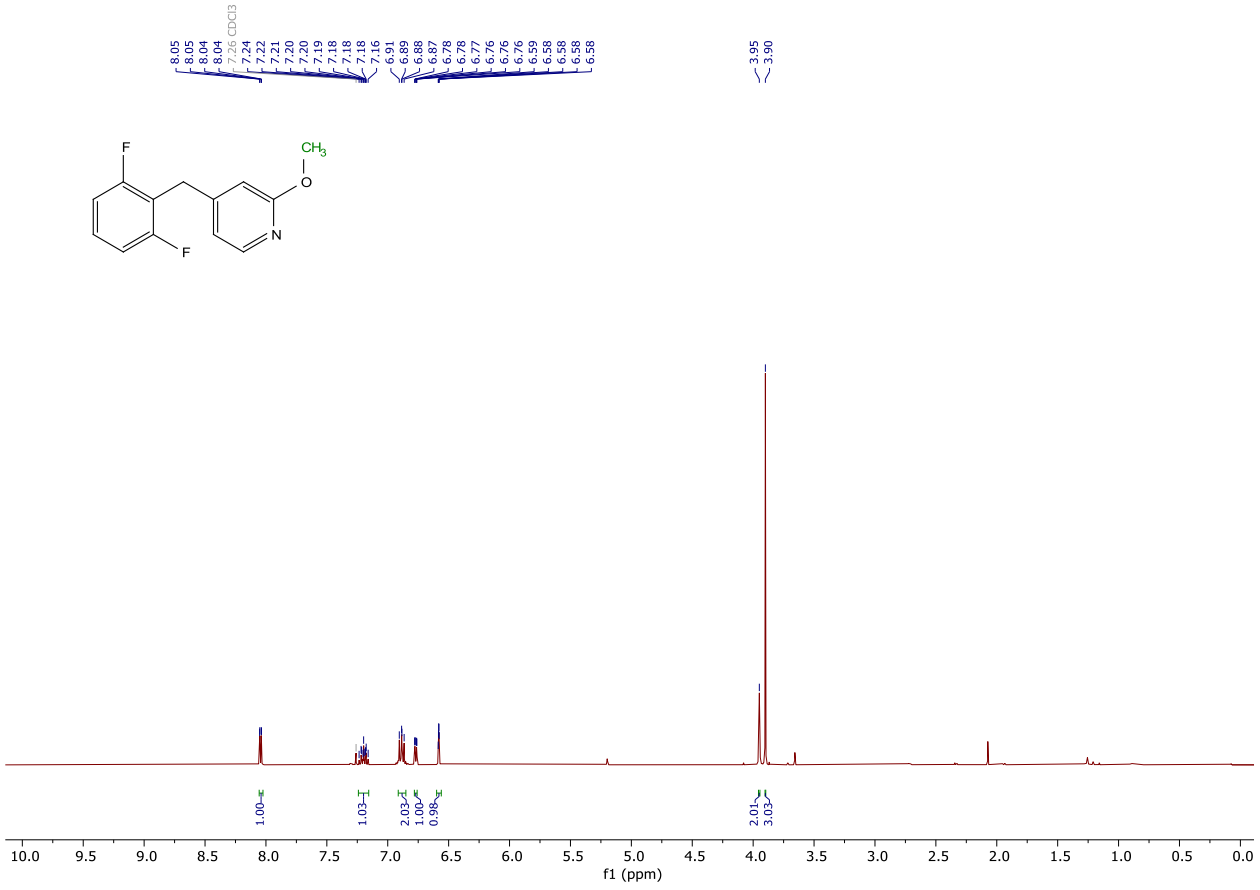


2-Benzyl-5-((benzylsulfonyl)methyl)pyridine (6t)





4-(2,6-Difluorobenzyl)-2-methoxypyridine (6u)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8.04
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3.90
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CH3
O
N
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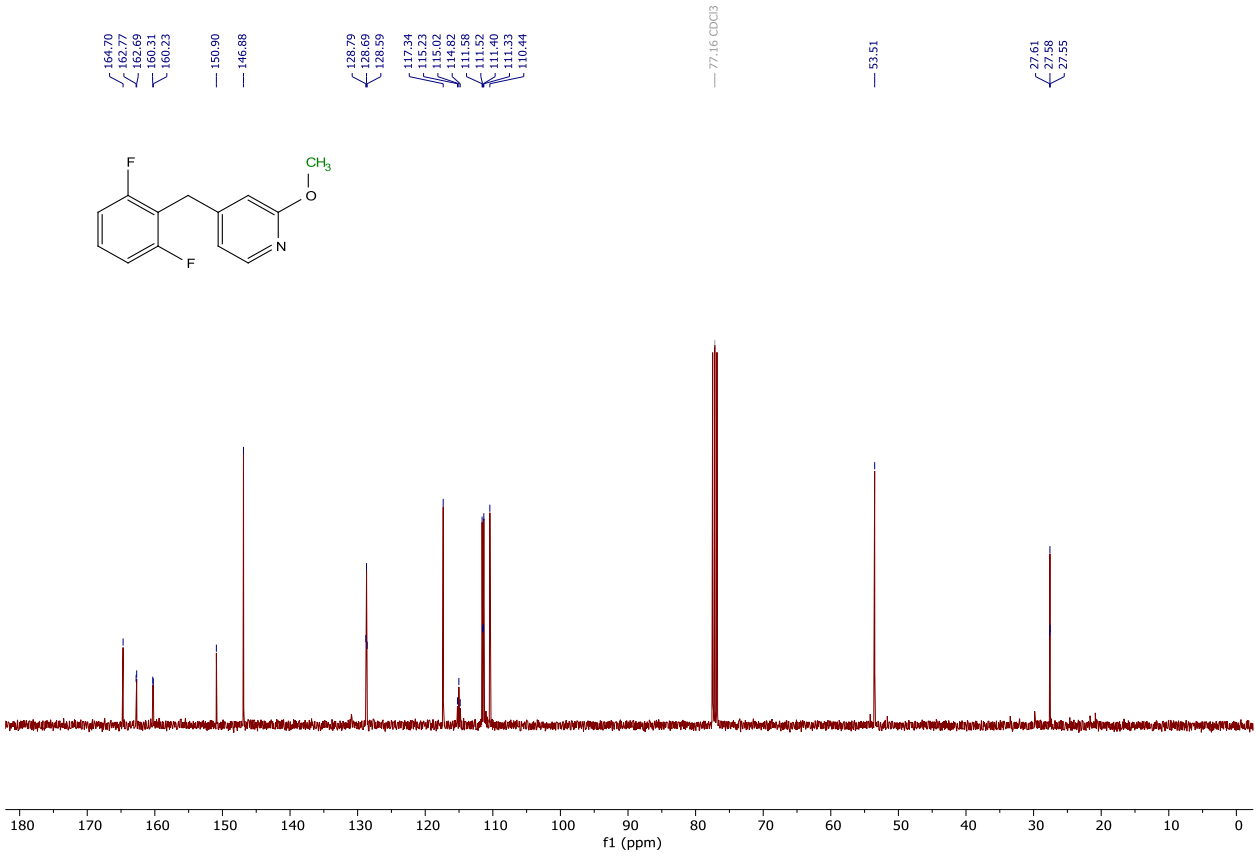
3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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111.52
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77.16 CDCl3
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27.55
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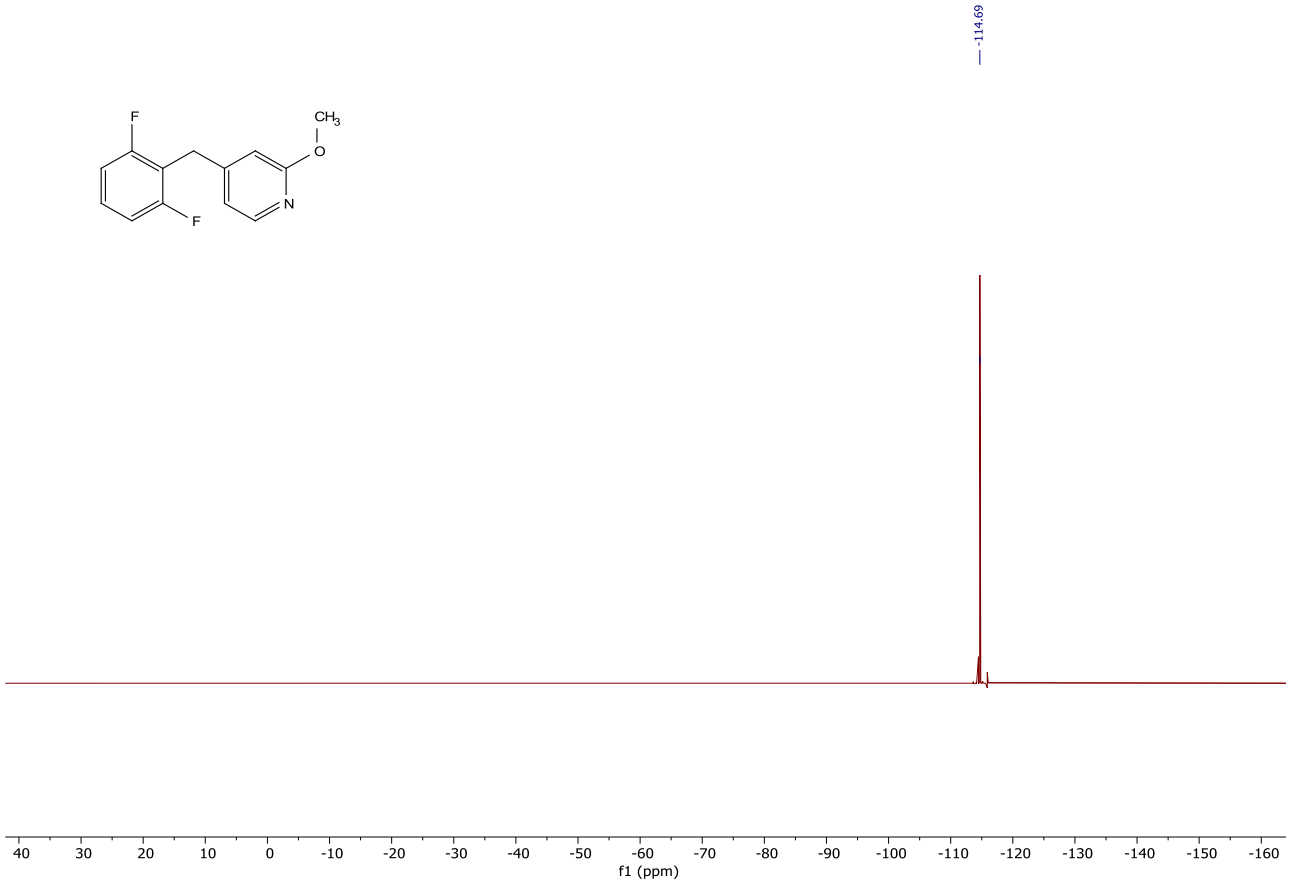
f1 (ppm)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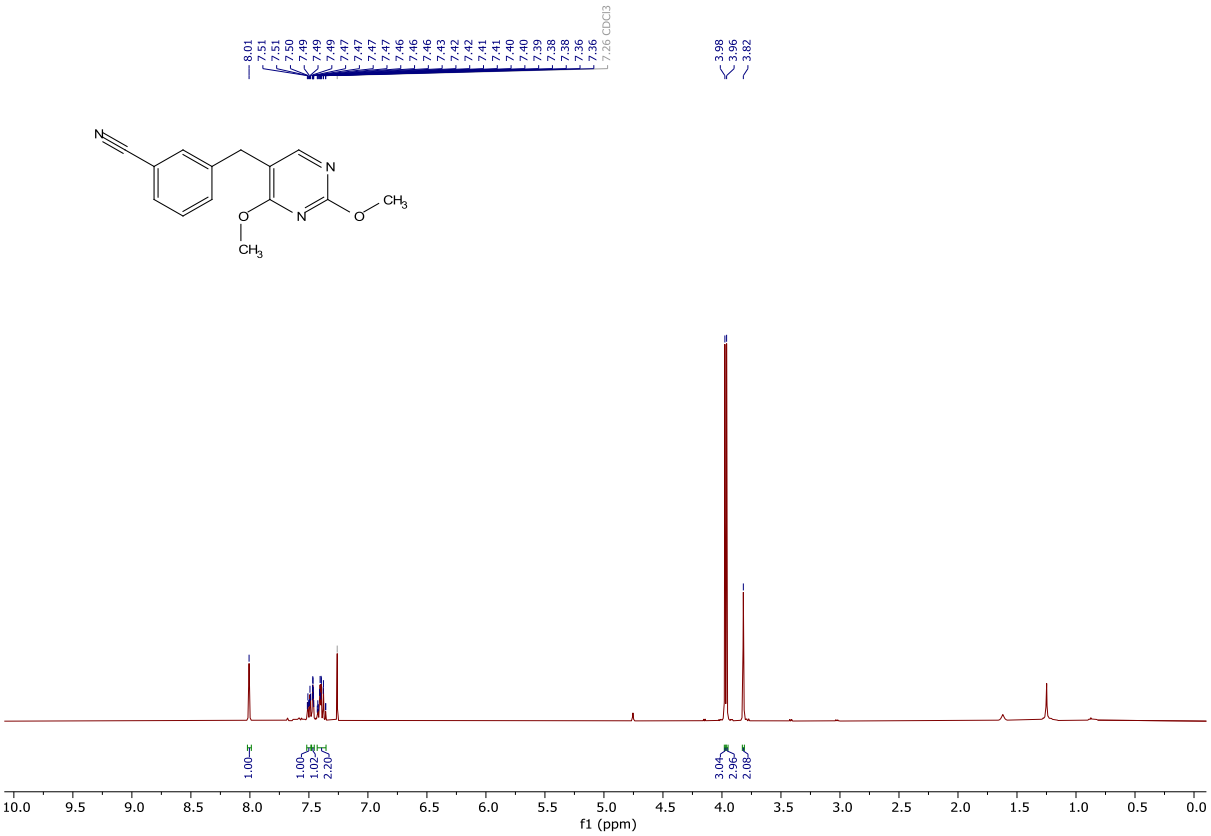
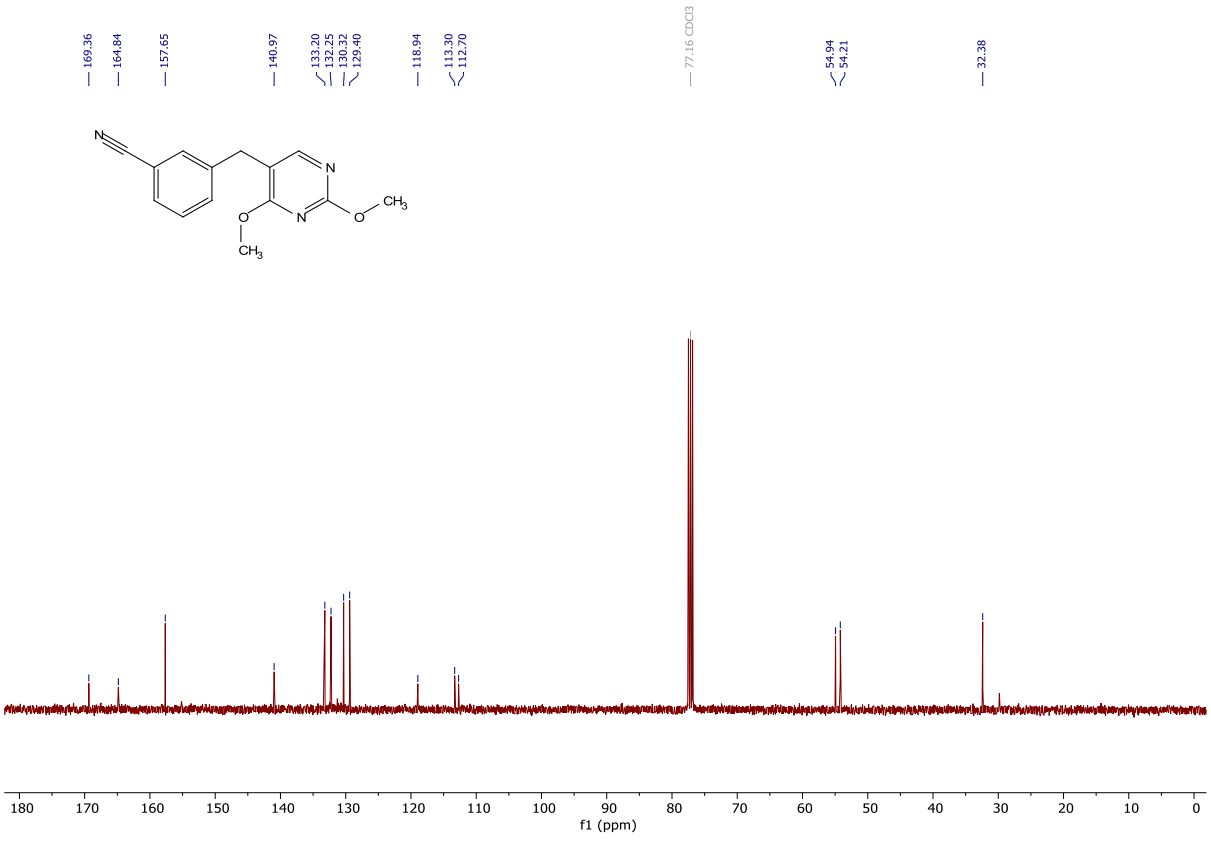
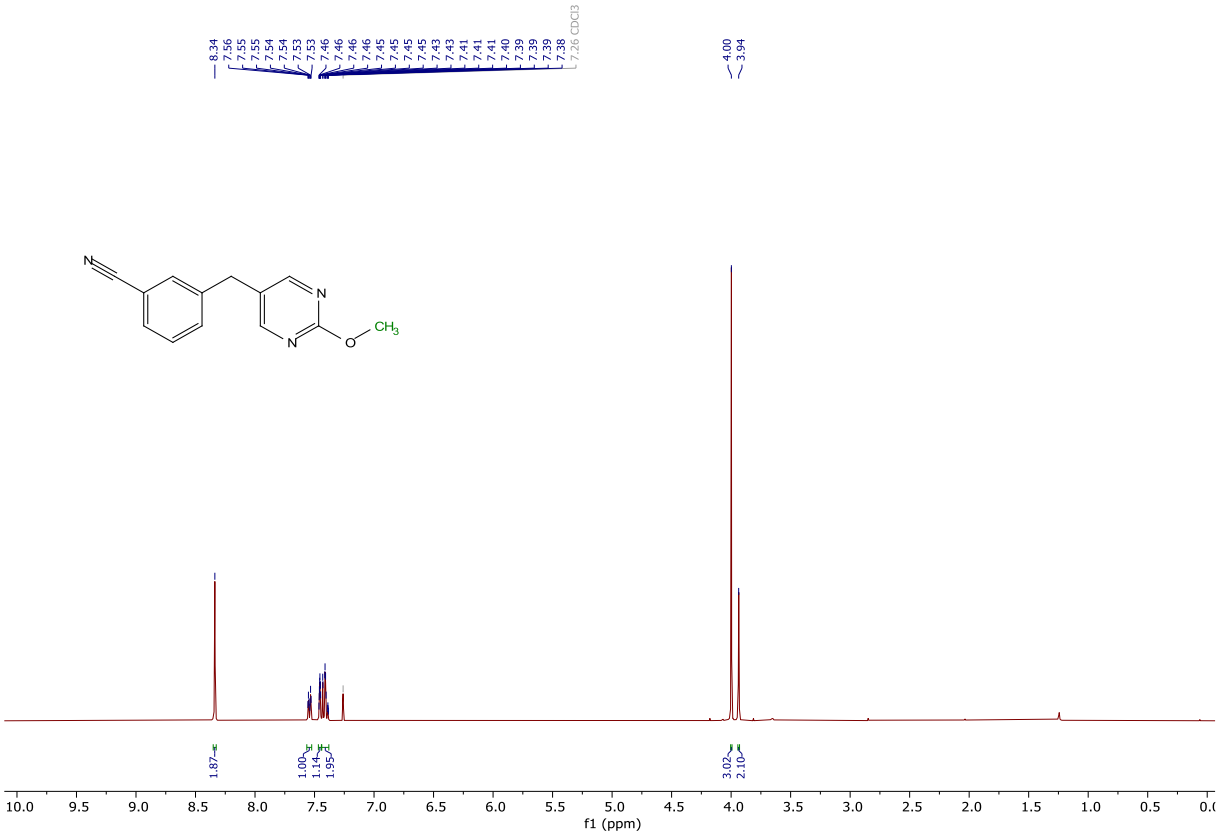
-150
-160
f1 (ppm)

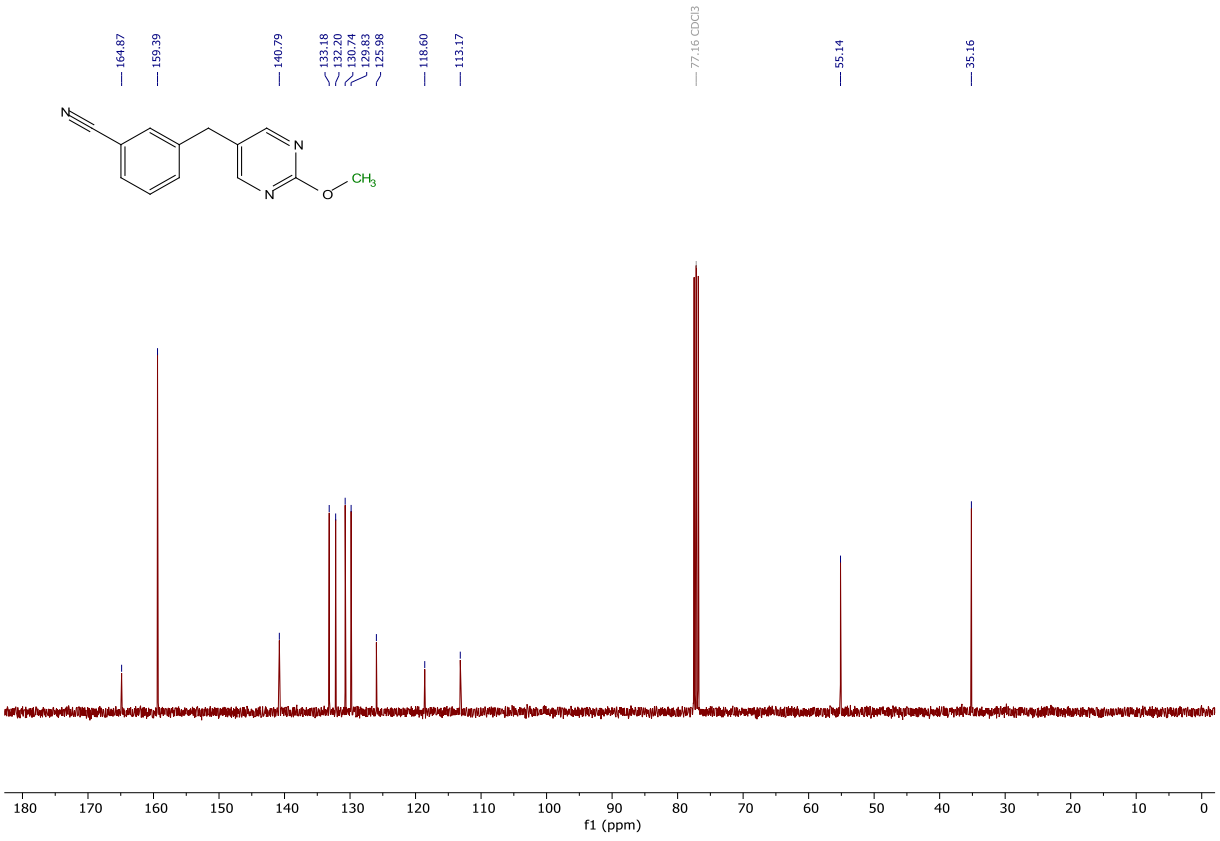
3-((2,4-Dimethoxypyrimidin-5-yl)methyl)benzonitrile (6v)



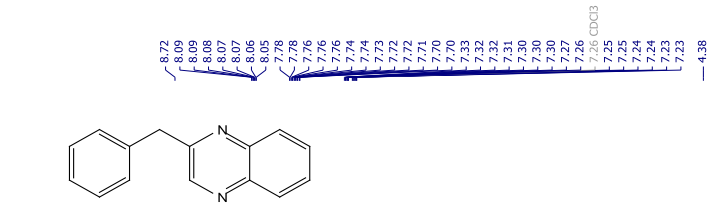


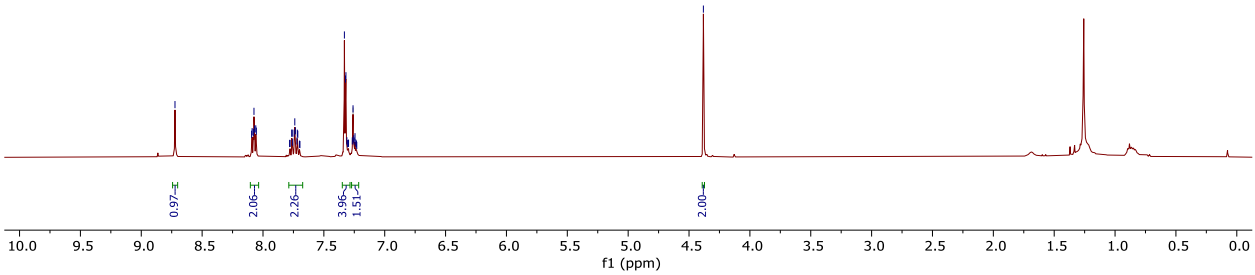
3-((2-Methoxypyrimidin-5-yl)methyl)benzonitrile (6w)

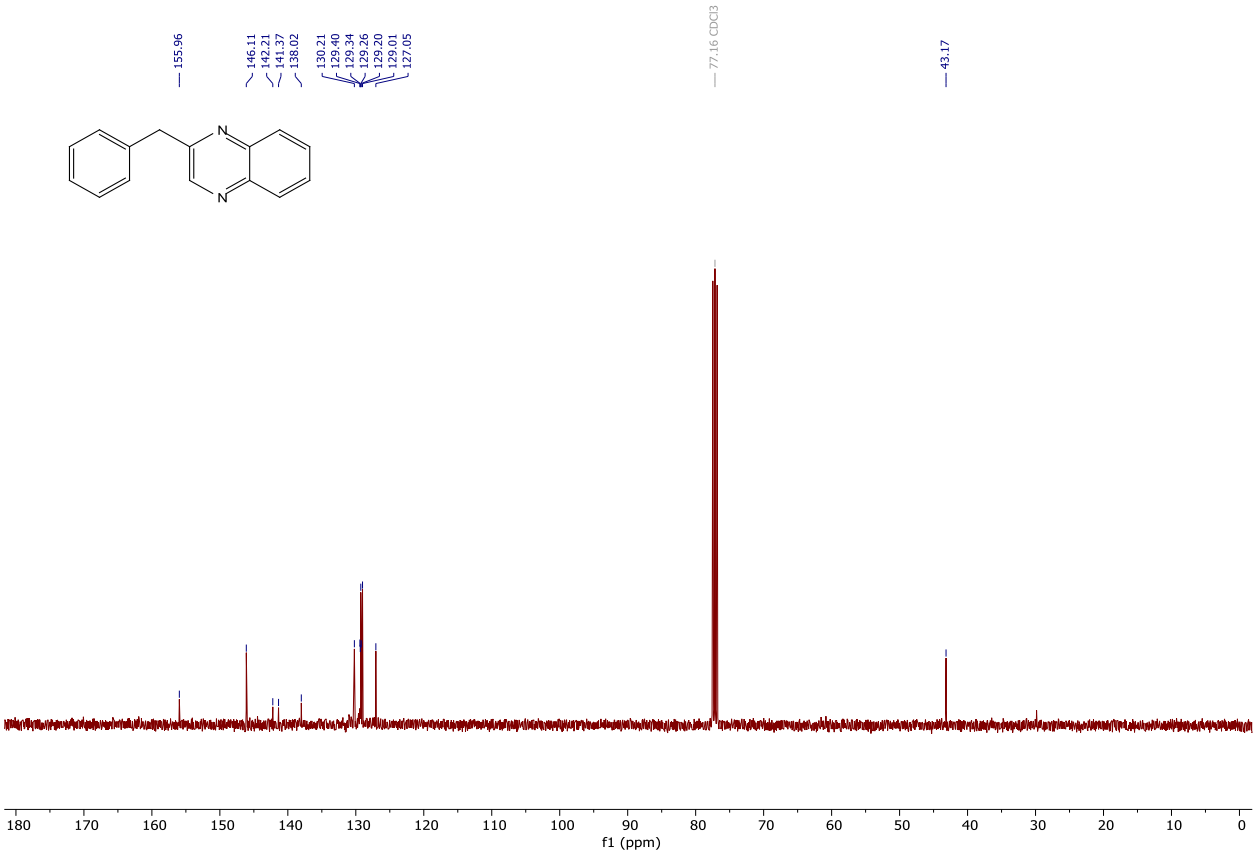




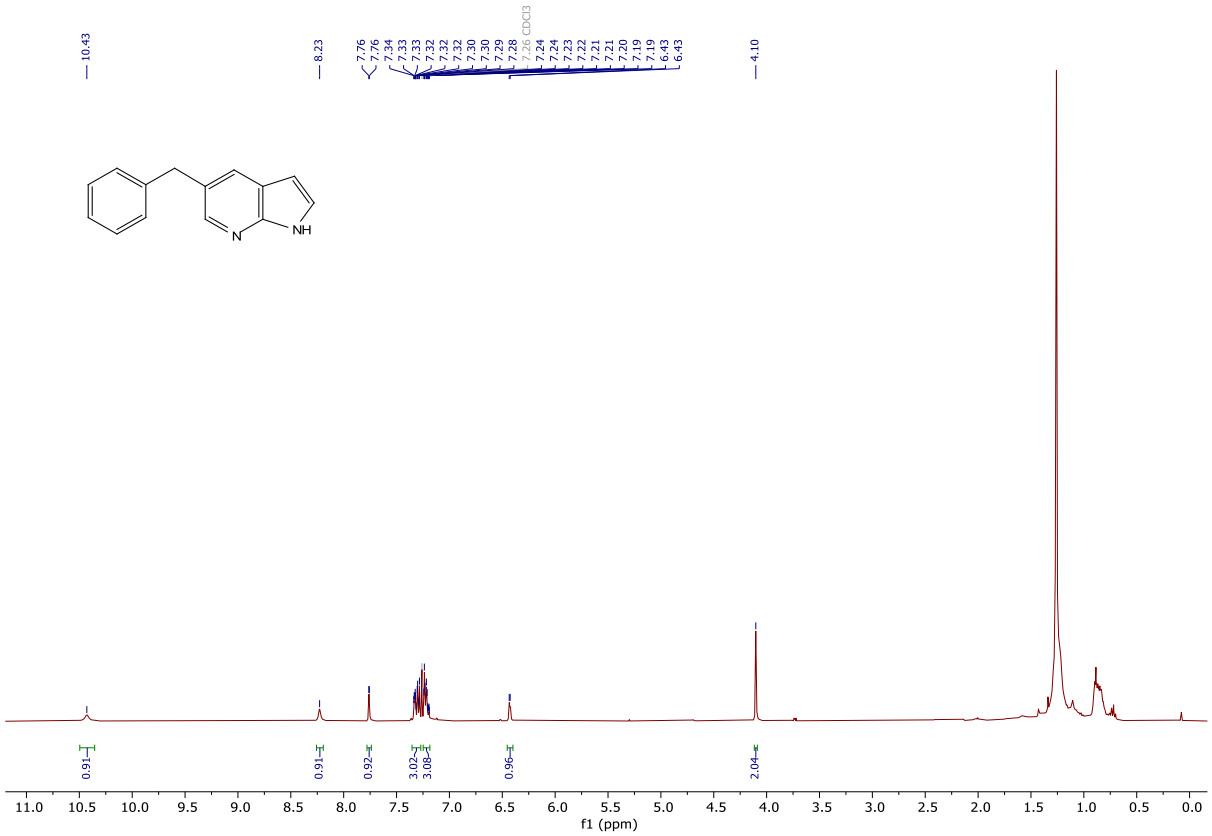
2-Benzylquinoxaline (6x)

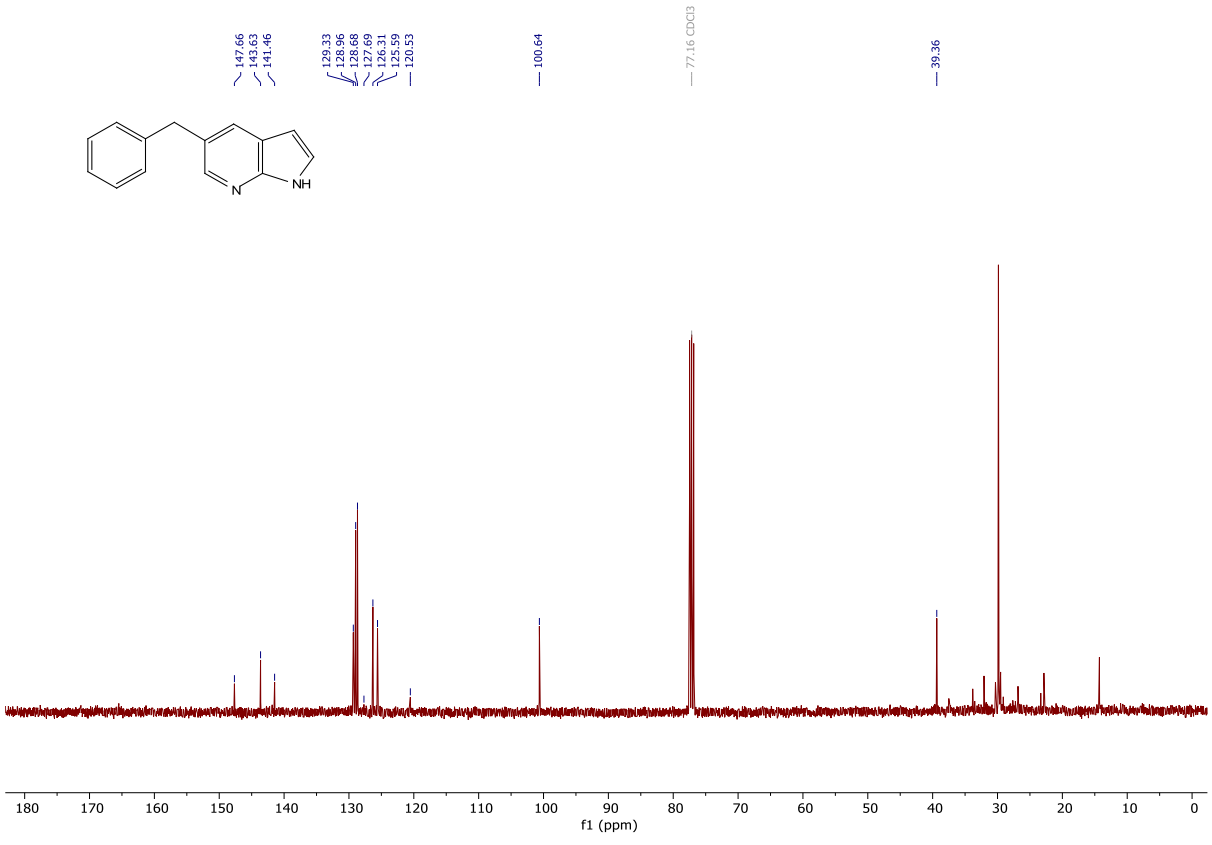




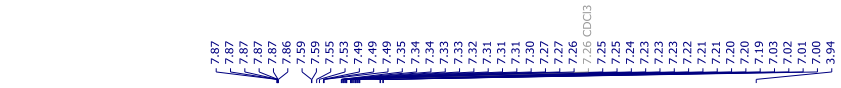


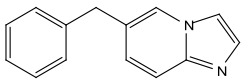
5-Benzyl-1*H*-pyrrolo[2,3-b]pyridine (6y)

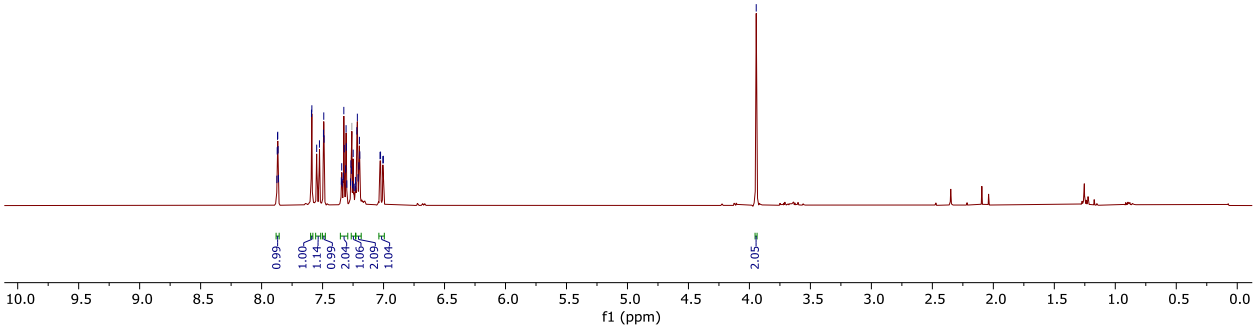




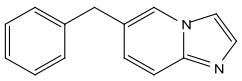
6-Benzylimidazo[1,2-a]pyridine (6z)

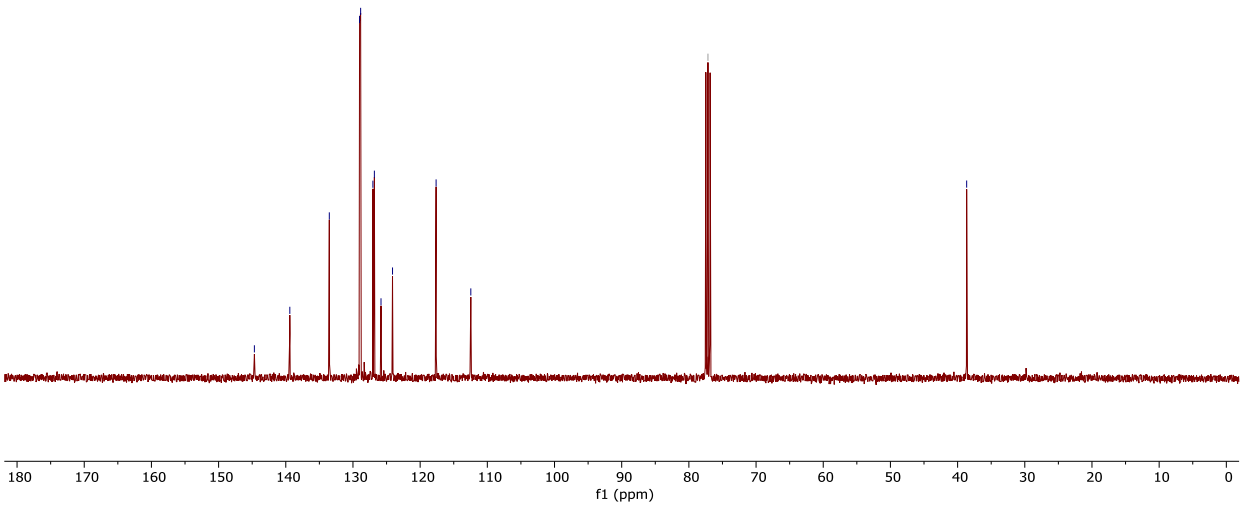






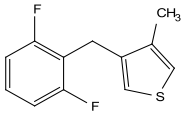


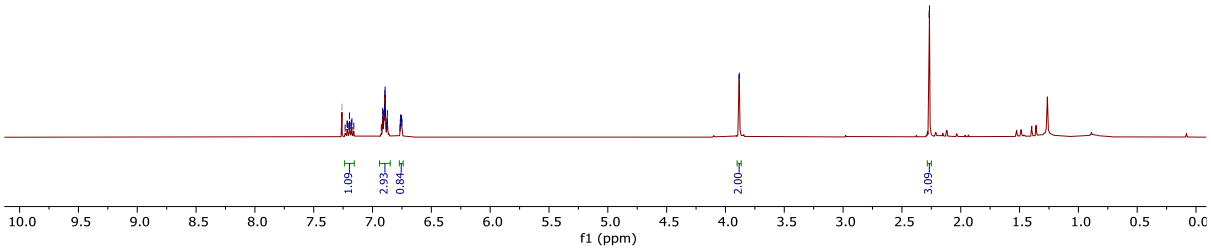


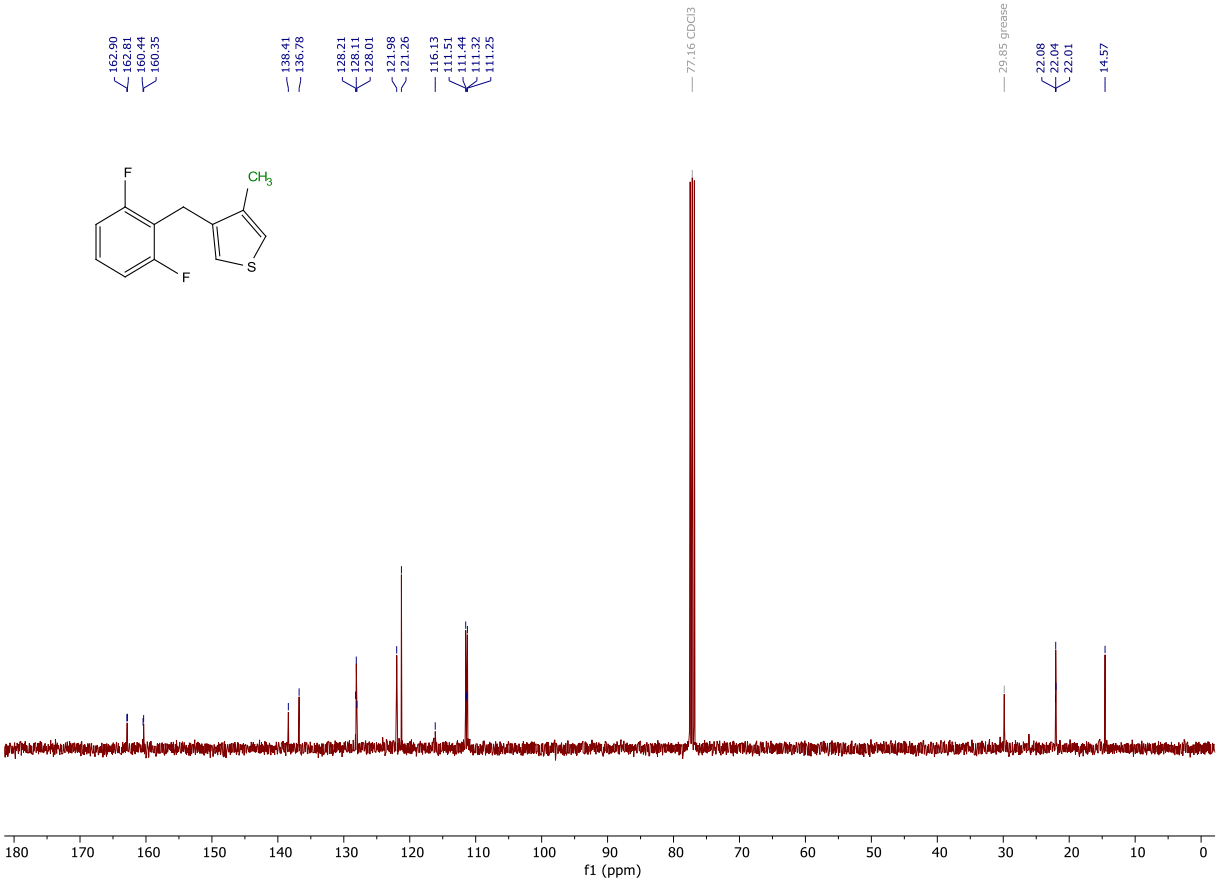


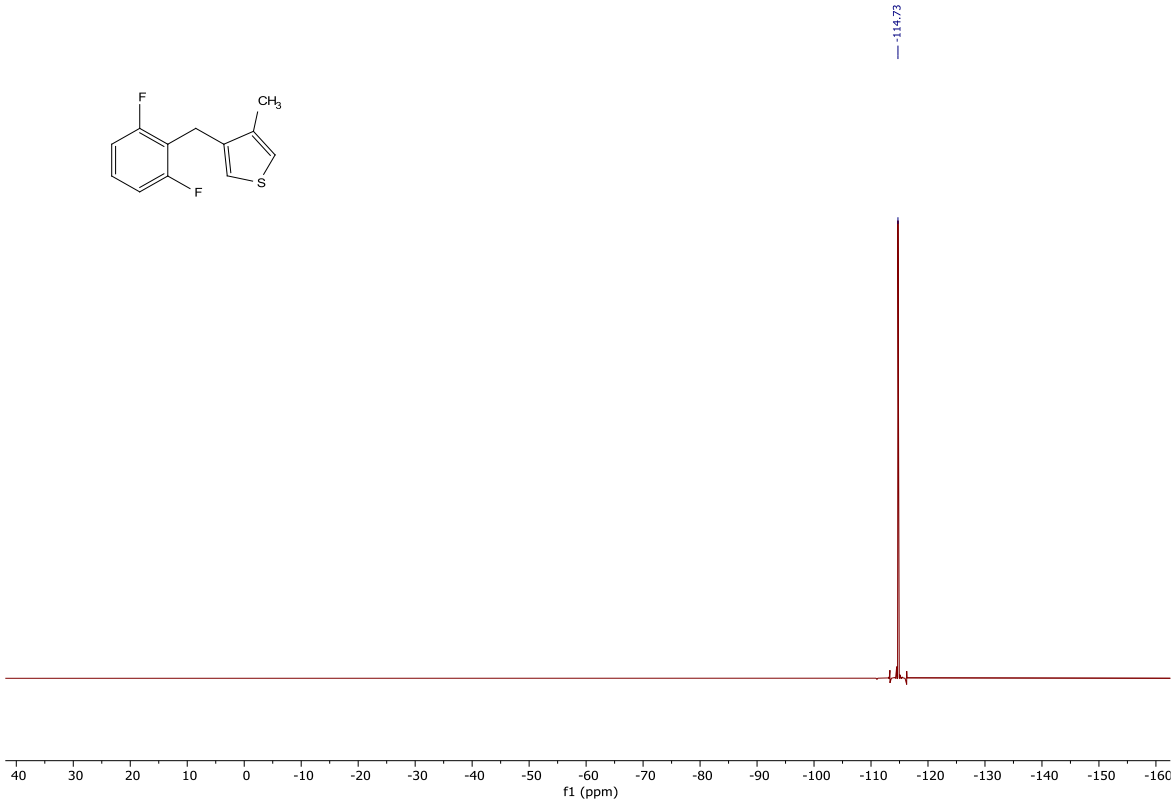
3-(2,6-Difluorobenzyl)-4-methylthiophene (6aa)



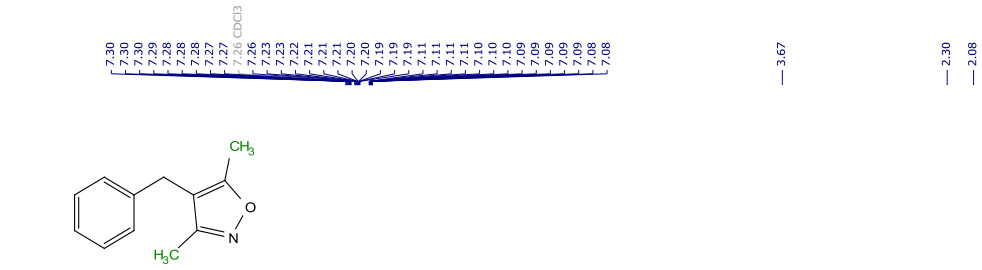


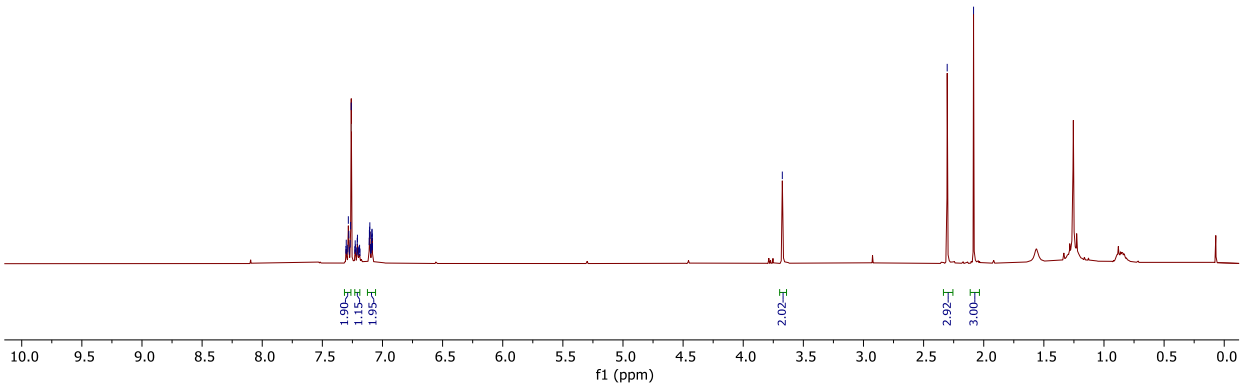


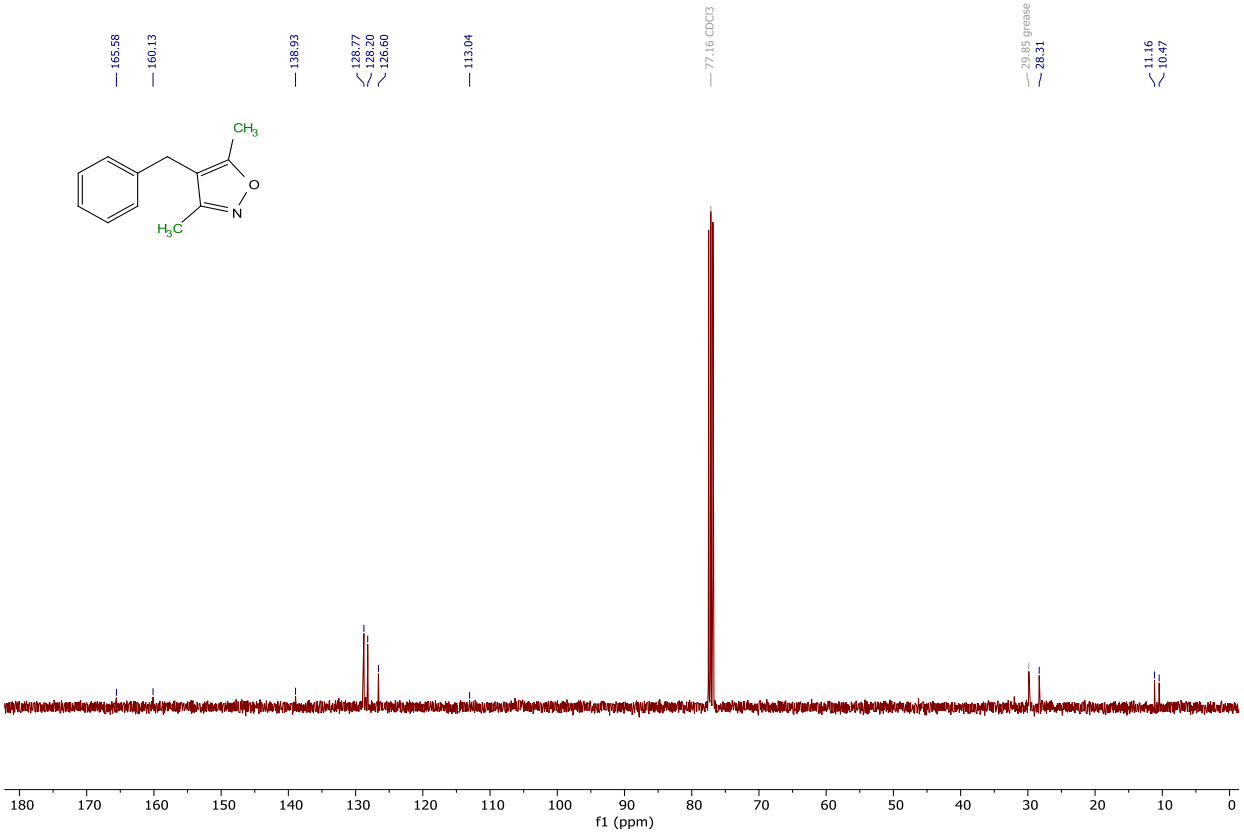



F
CH3
S
F
-114.73
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
f1 (ppm)

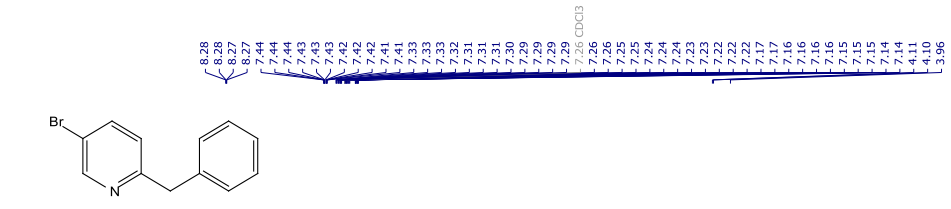
4-Benzyl-3,5-dimethylisoxazole (6ab)

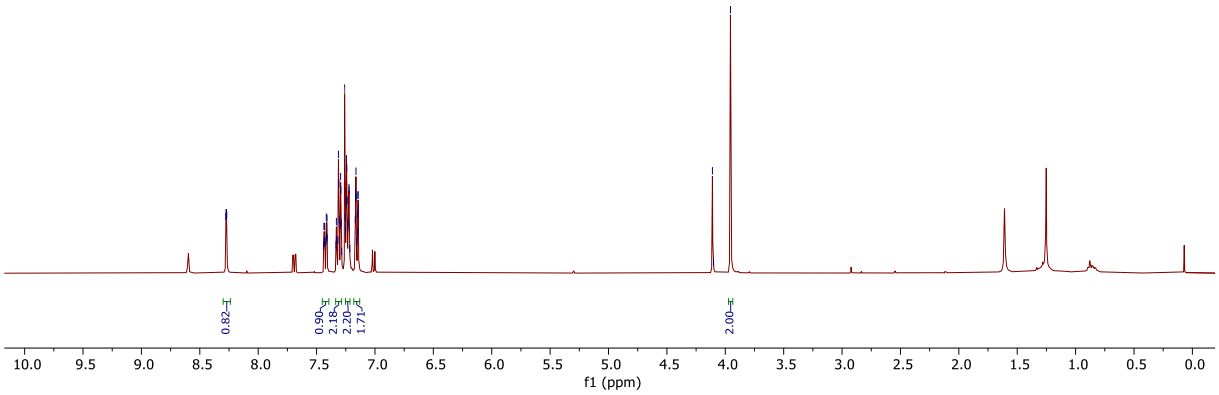


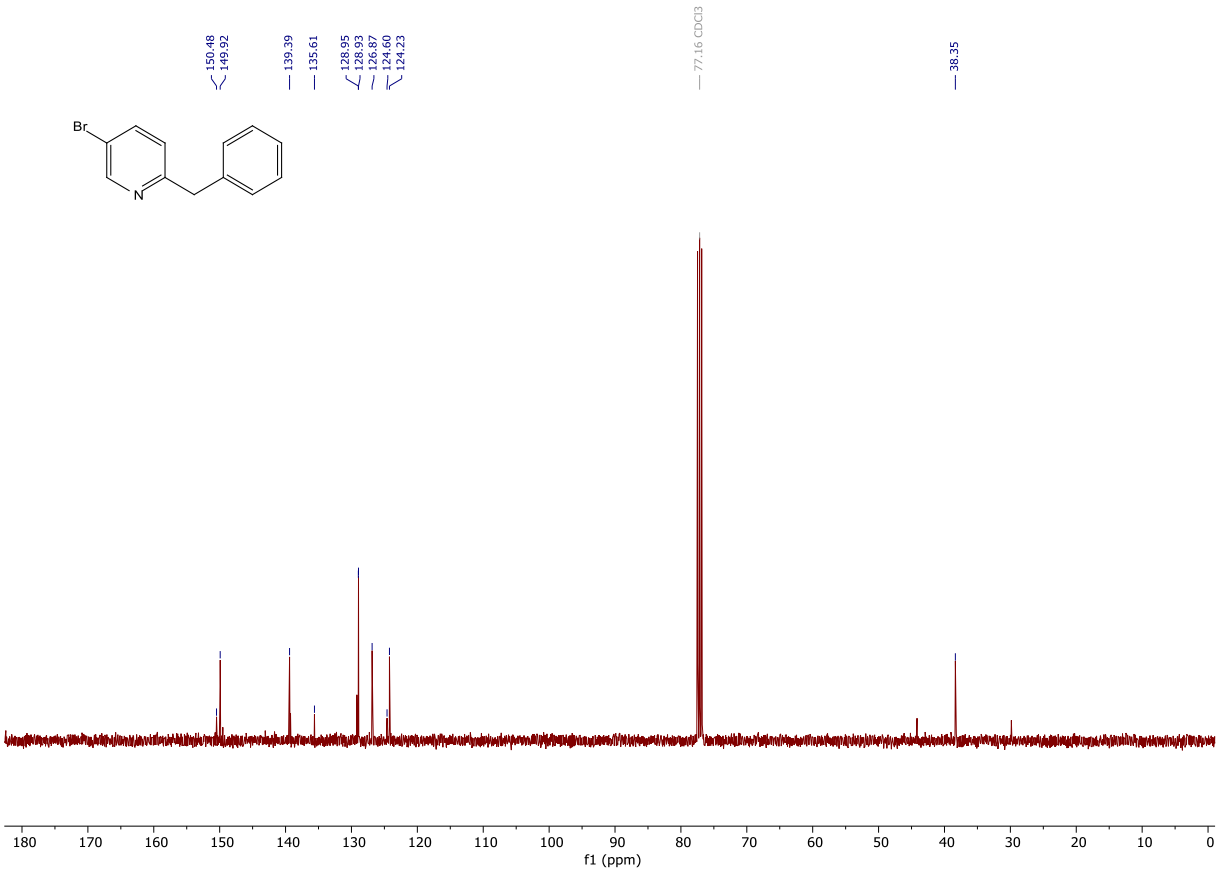




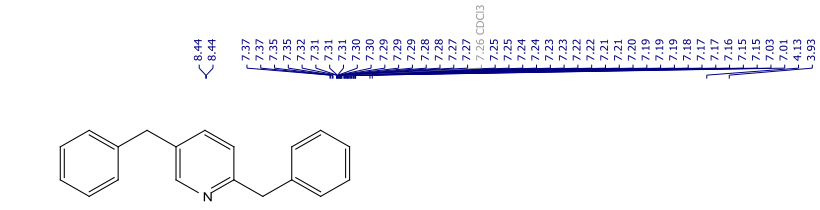
2-Benzyl-5-bromopyridine (6ac)

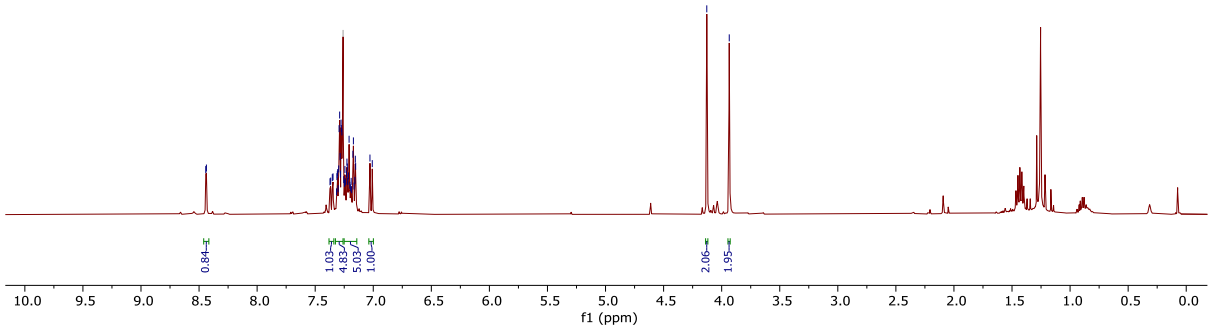


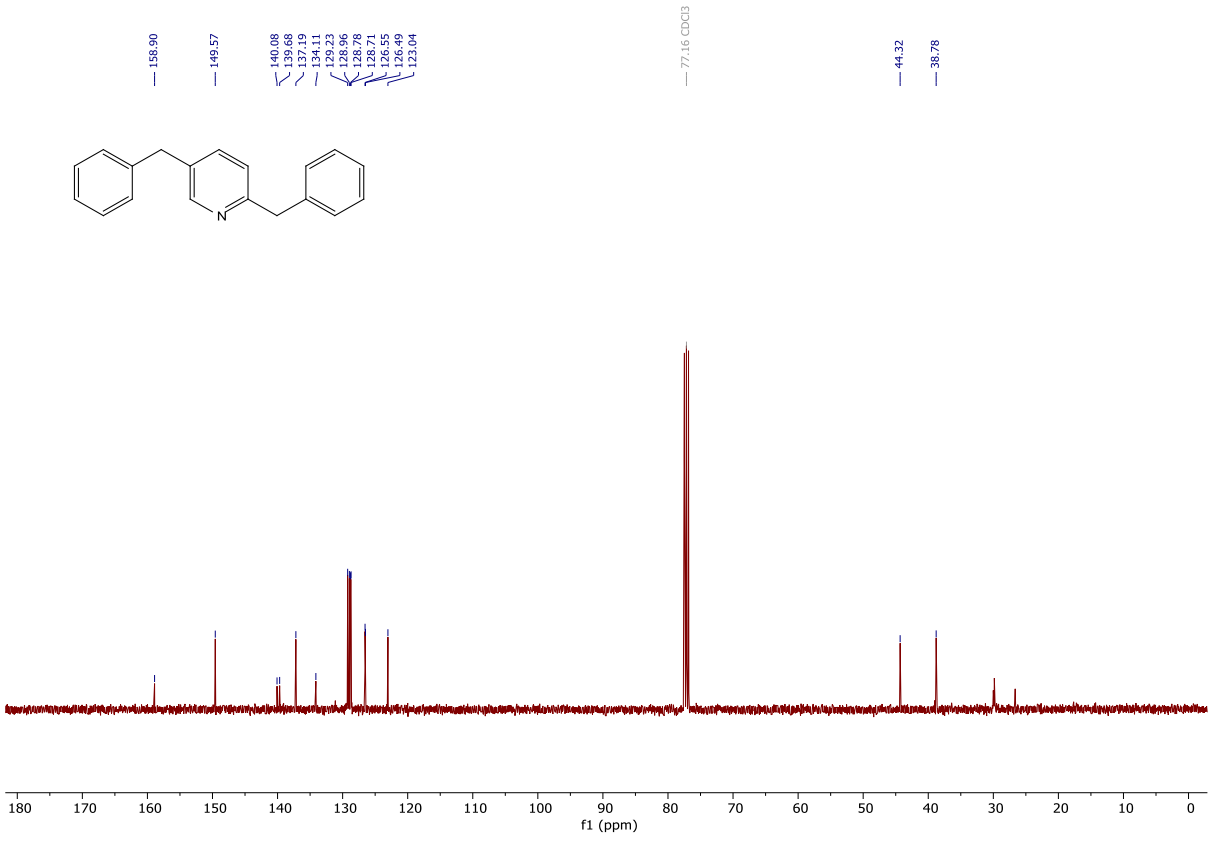




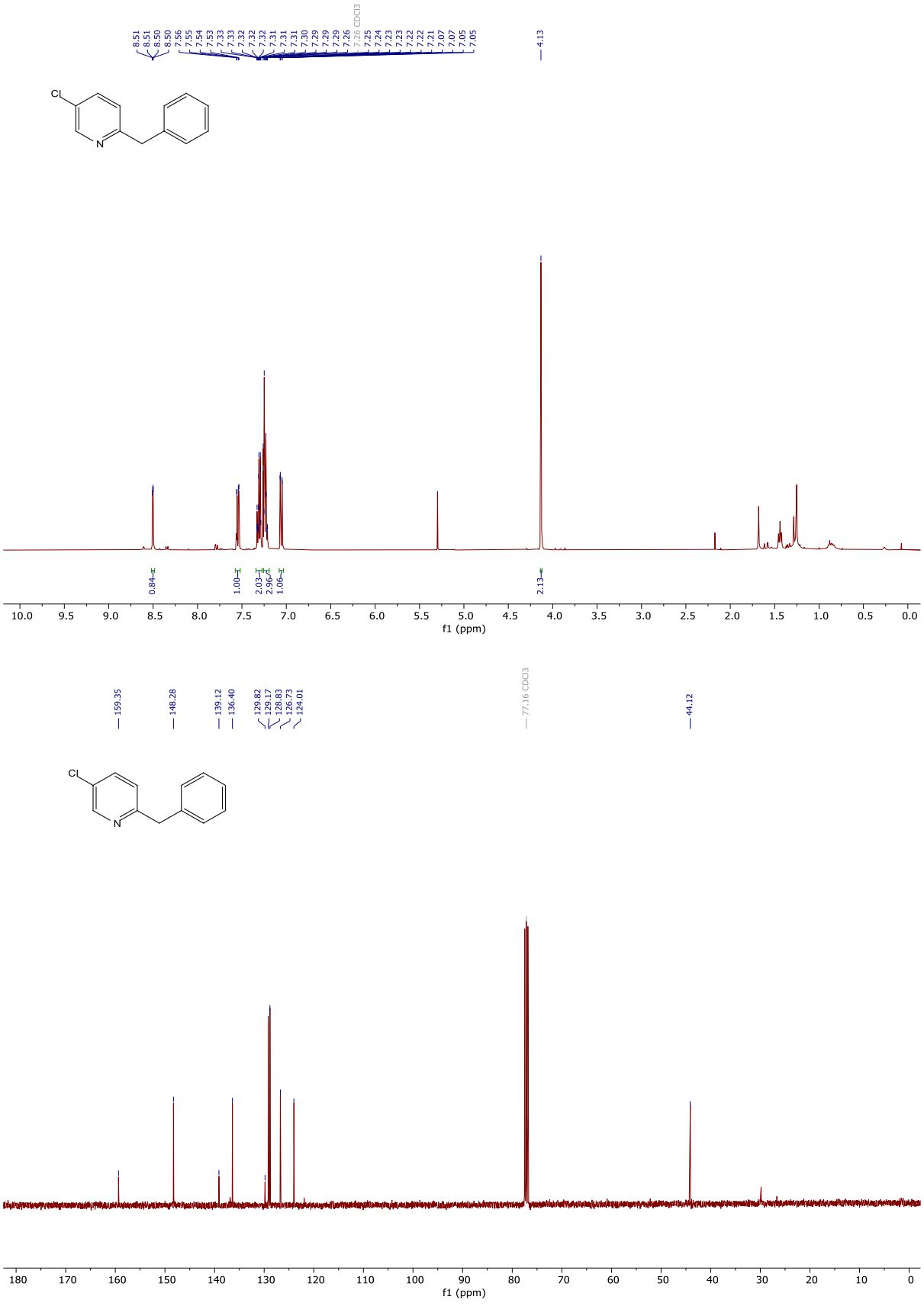
2,5-Dibenzylpyridine (6ad)



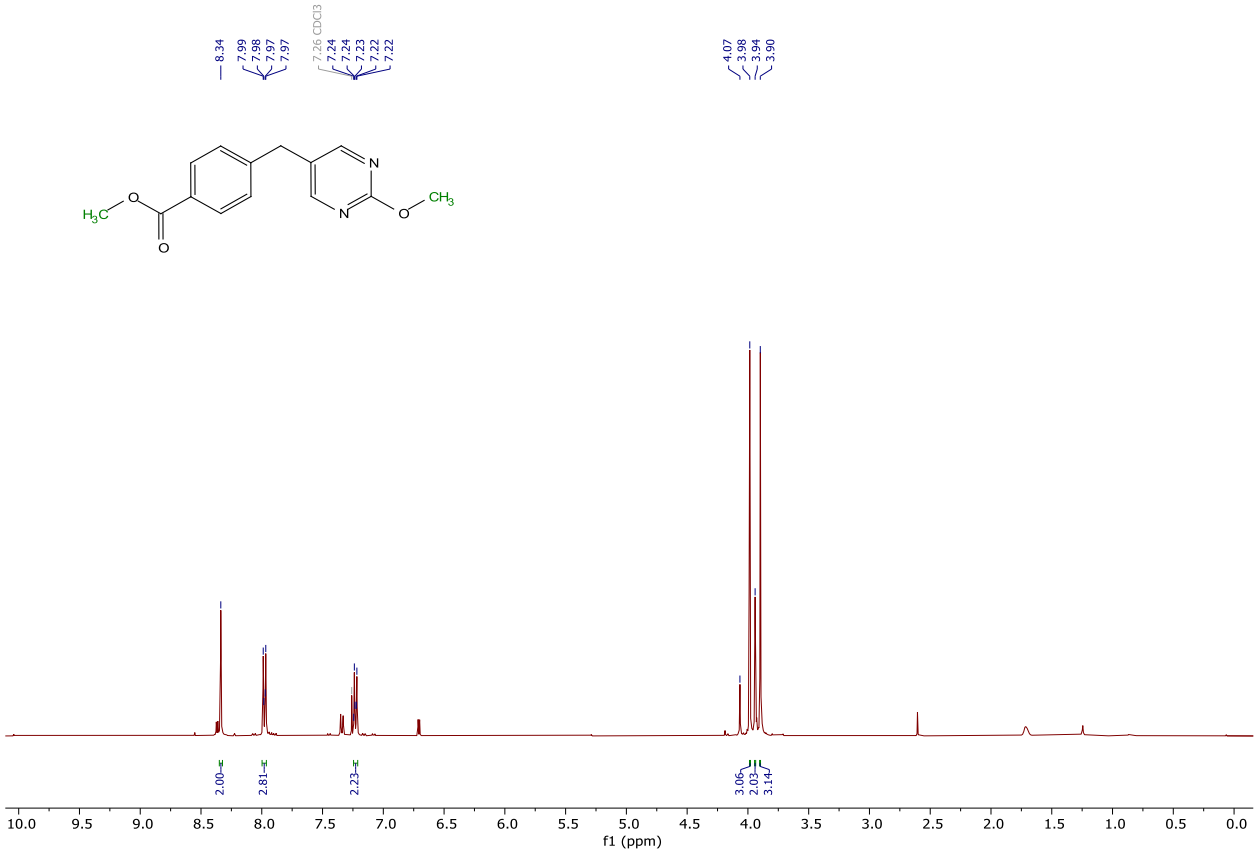


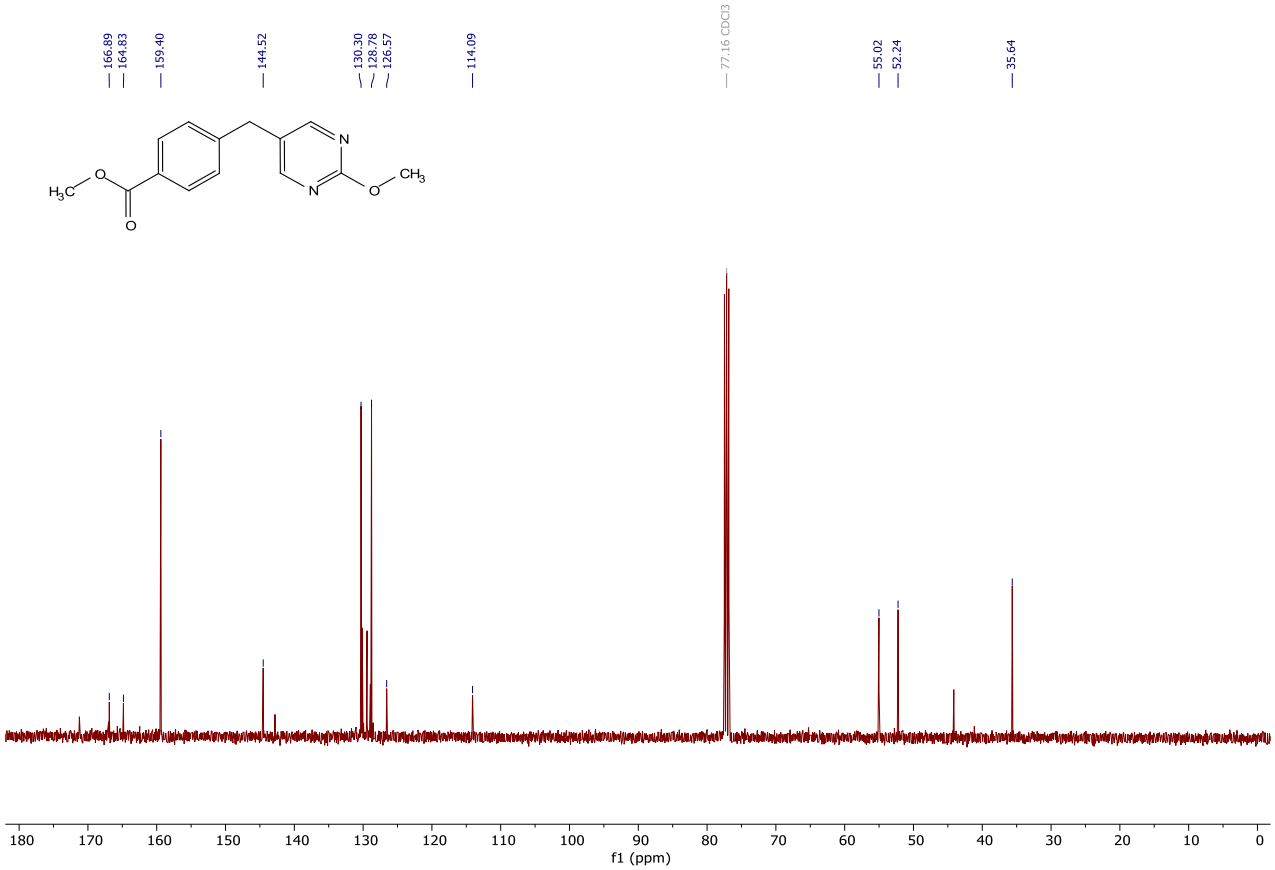


2-Benzyl-5-chloropyridine (6ae)

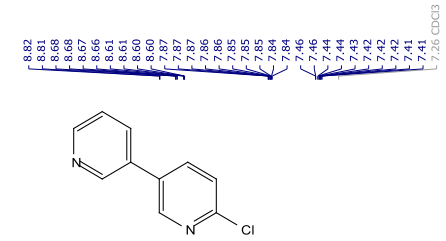


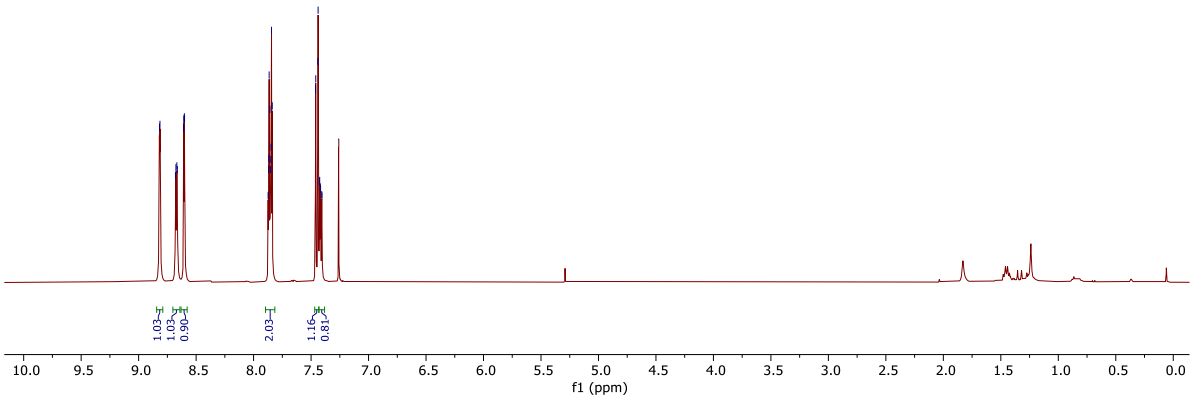
Methyl 4-((2-methoxypyrimidin-5-yl)methyl)benzoate (6af)

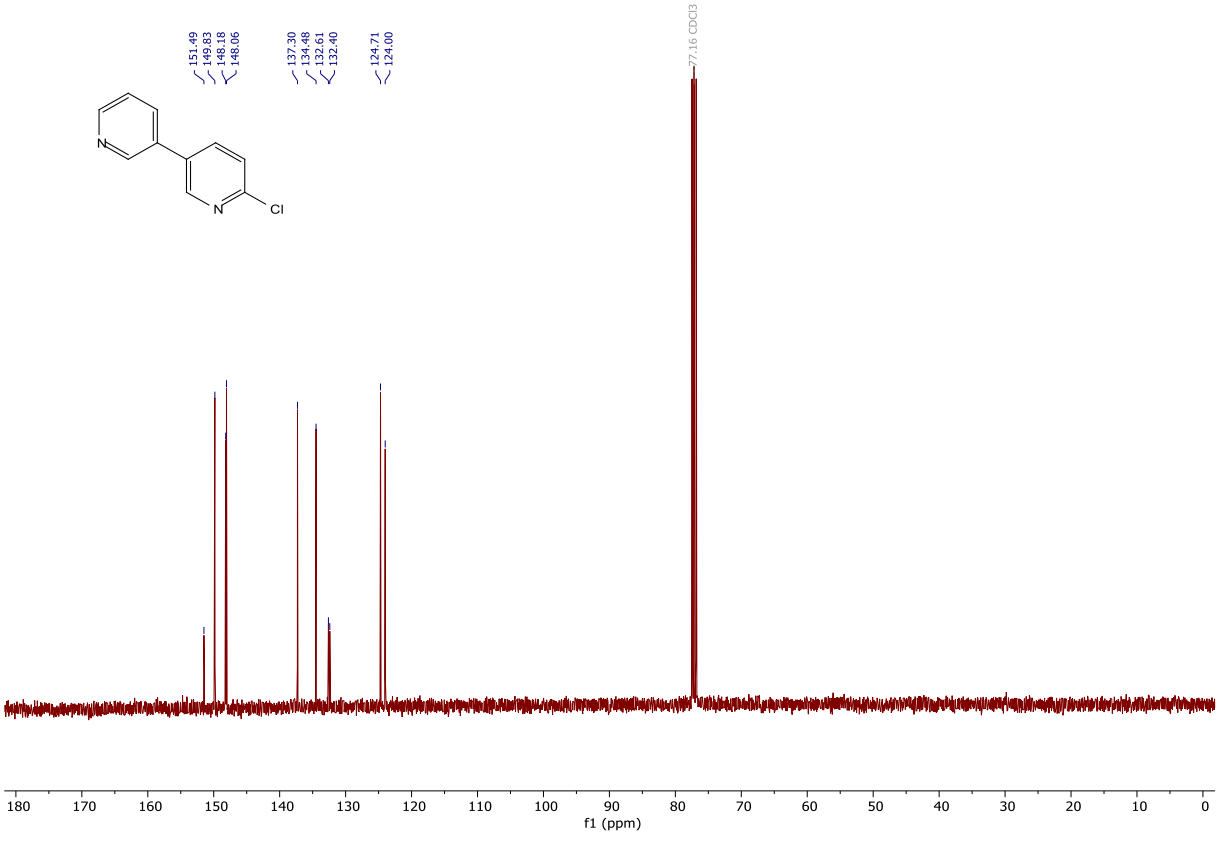




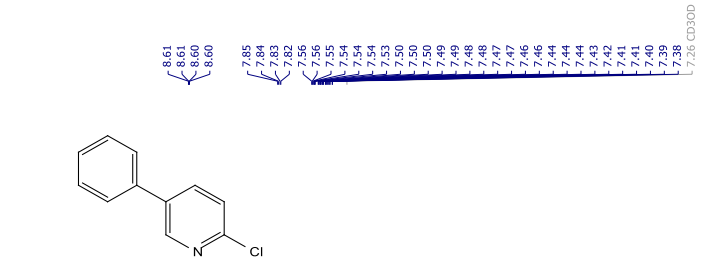
6-Chloro-3,3'-bipyridine (7a)

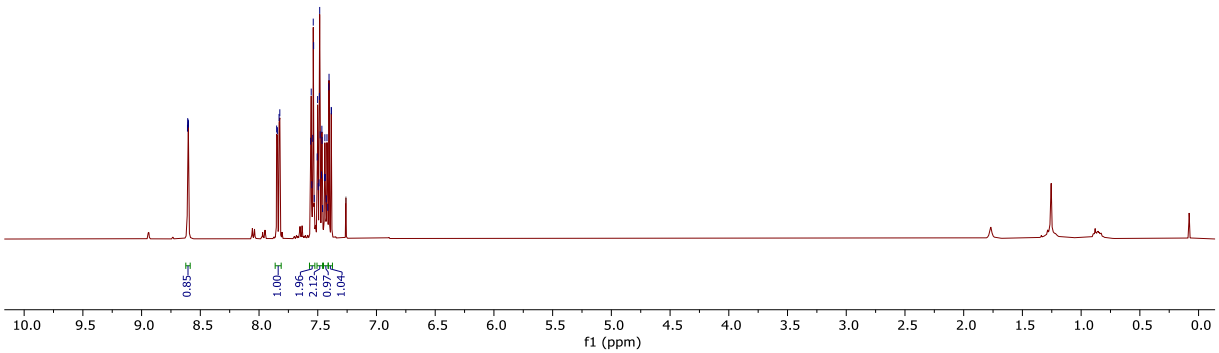


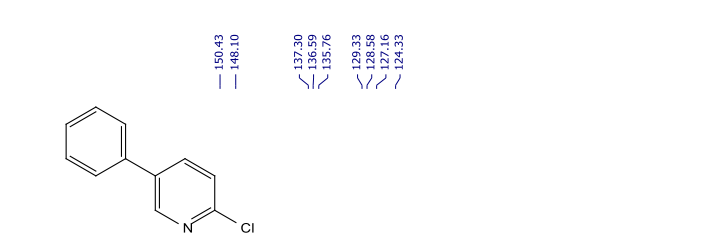


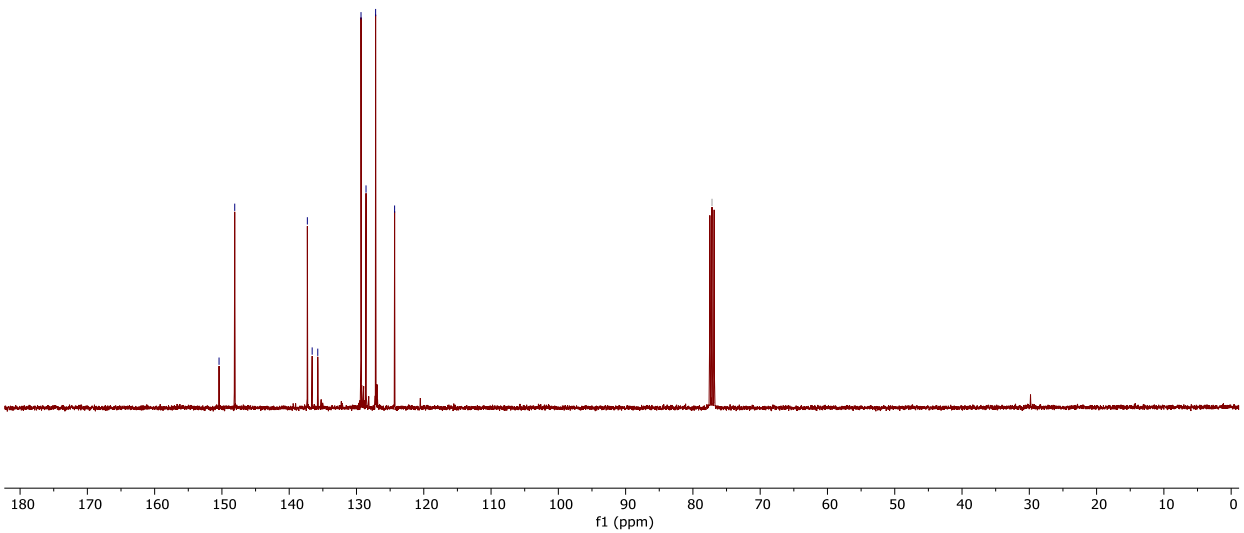


2-Chloro-5-phenylpyridine (7b)

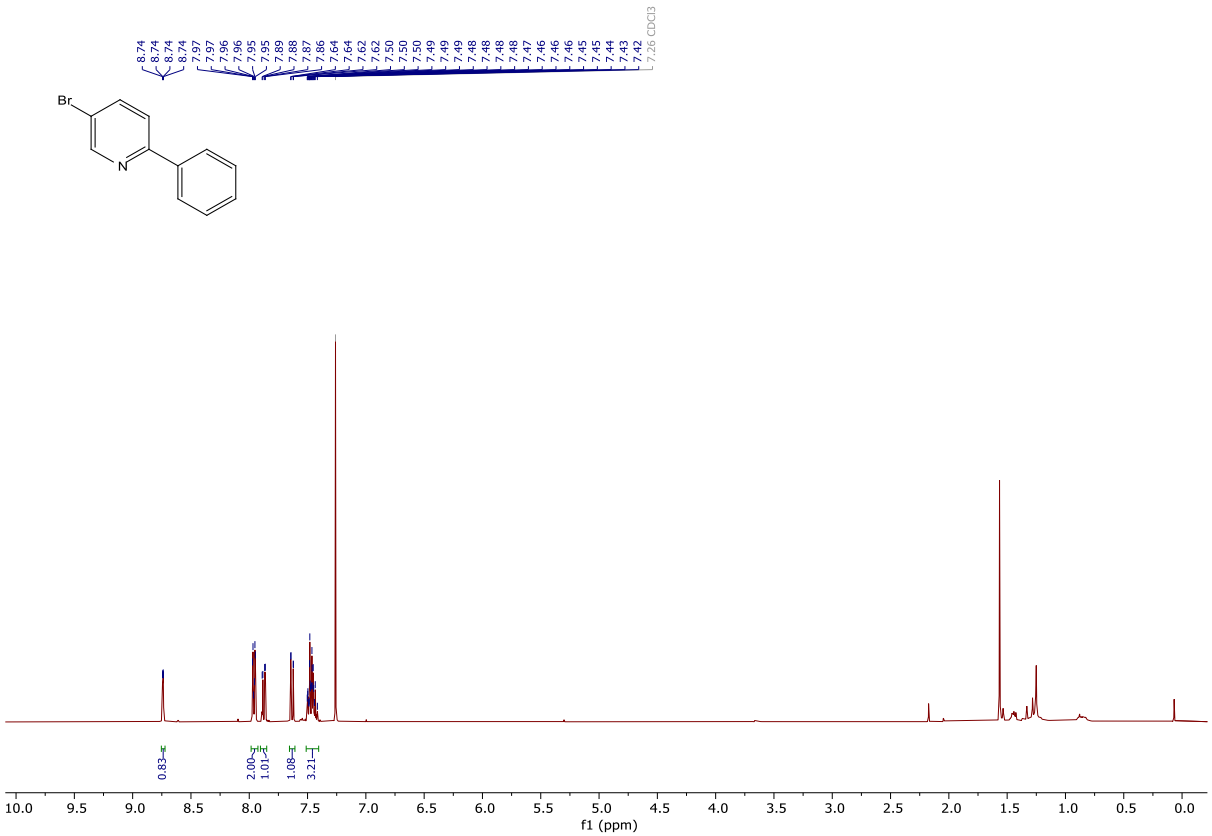


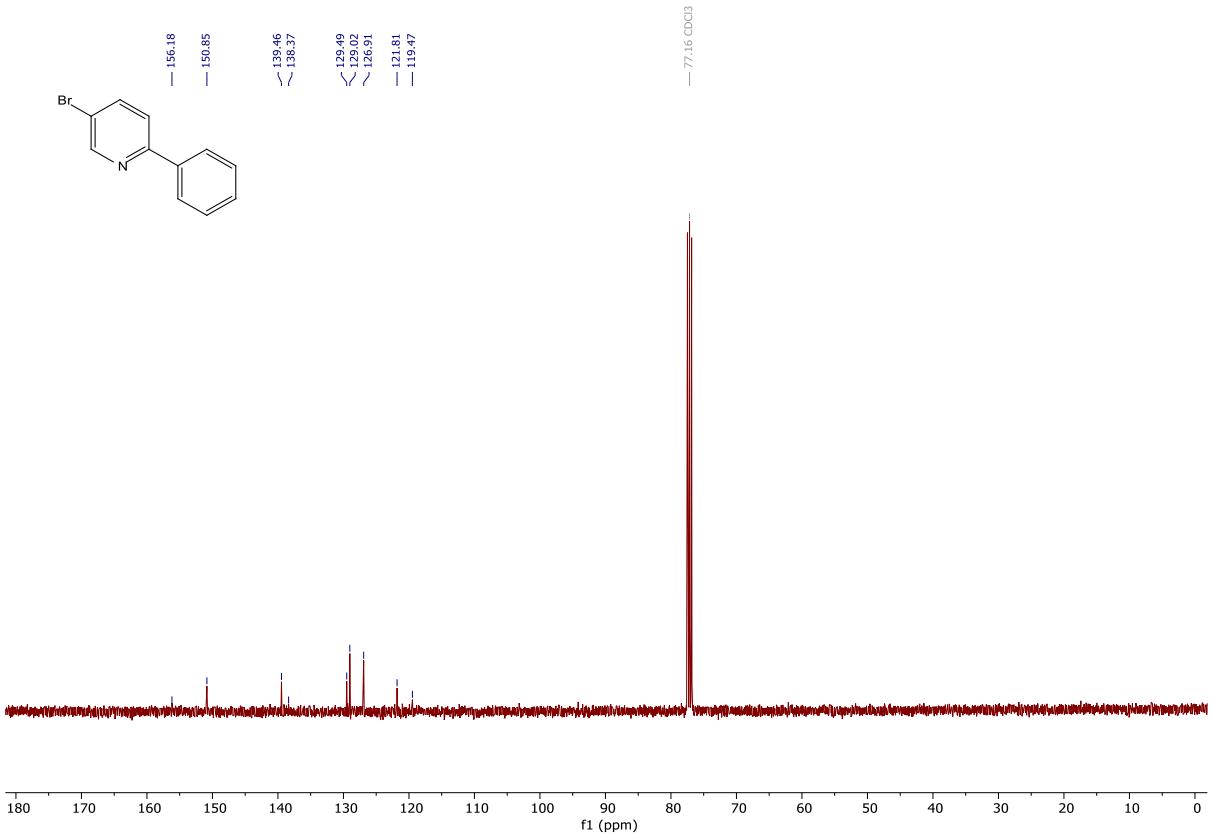




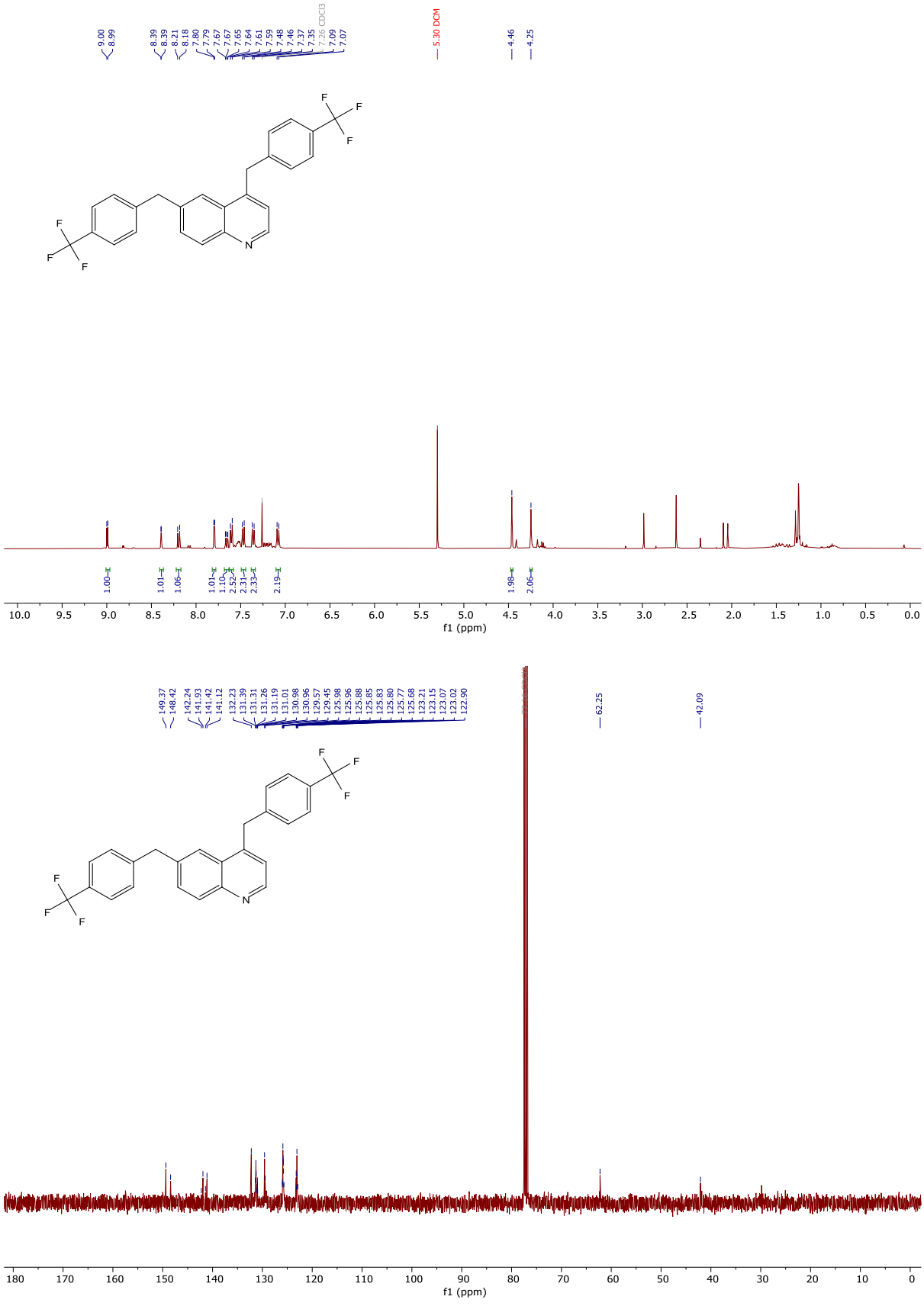


5-Bromo-2-phenylpyridine (7c)





4,6-Bis(4-(trifluoromethyl)benzyl)quinoline (S7)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7.59
7.48
7.46
7.37
7.35
7.26 CDCl3
7.09
7.07
5.30 DCM
4.46
4.25
F
F
F
F
F
F
N
1.00
1.01
1.06
1.01
1.10
2.52
2.31
2.33
2.19
1.98
2.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
149.37
148.42
142.24
141.93
141.42
141.12
132.23
131.39
131.31
131.26
131.19
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125.88
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123.02
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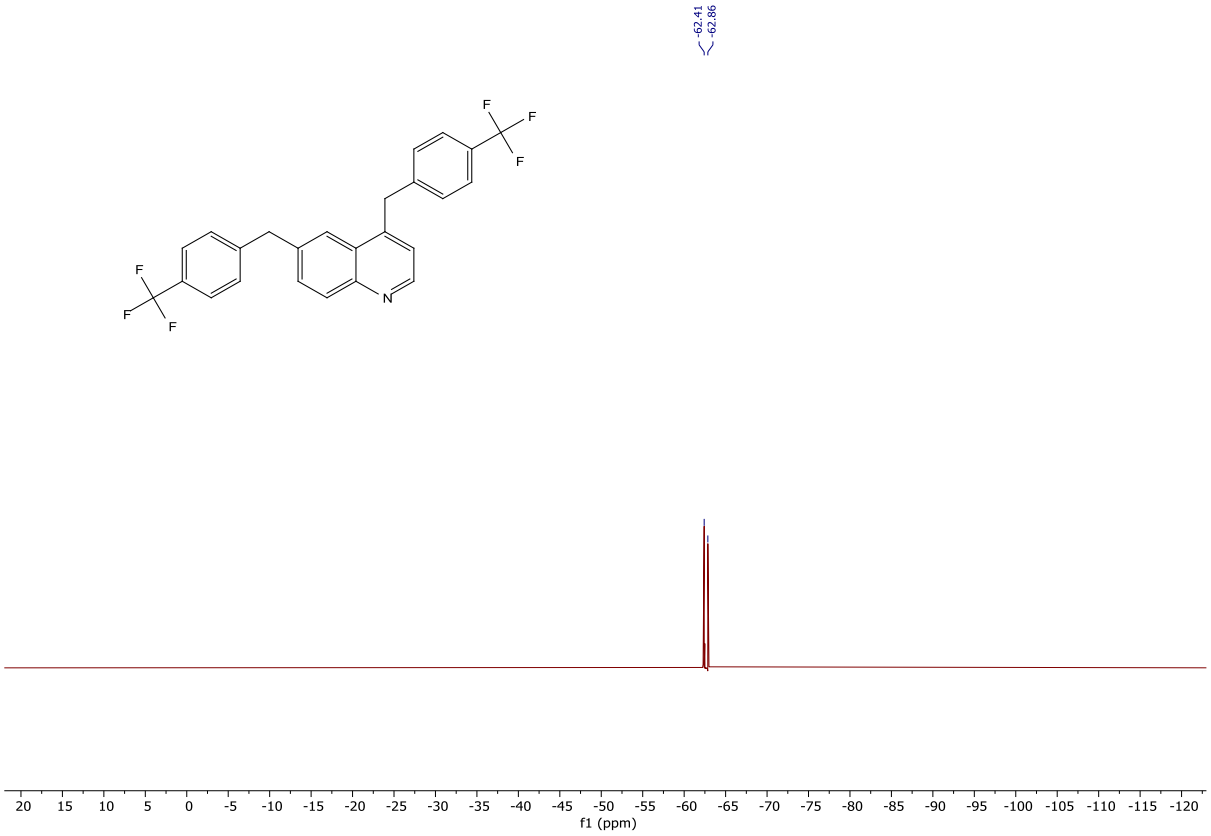
f1 (ppm)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F
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F
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F
F
N
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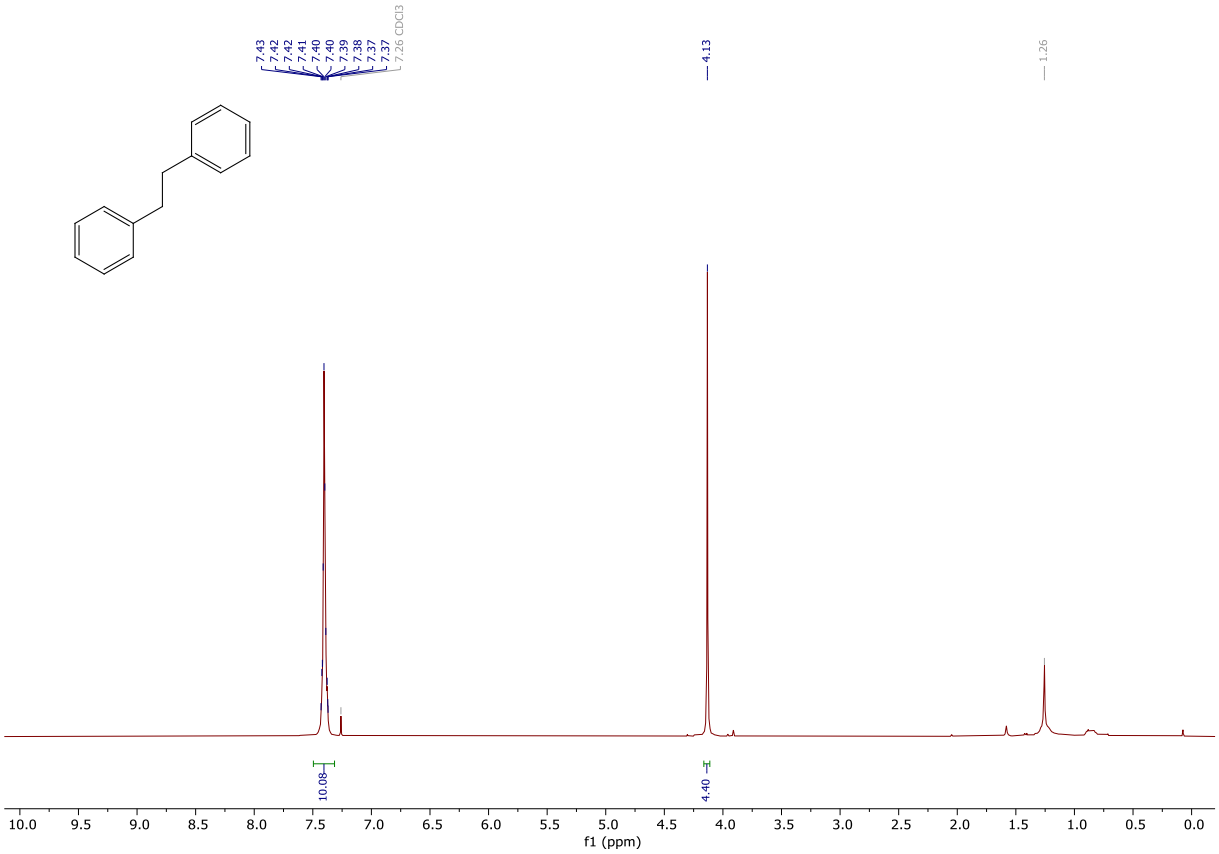
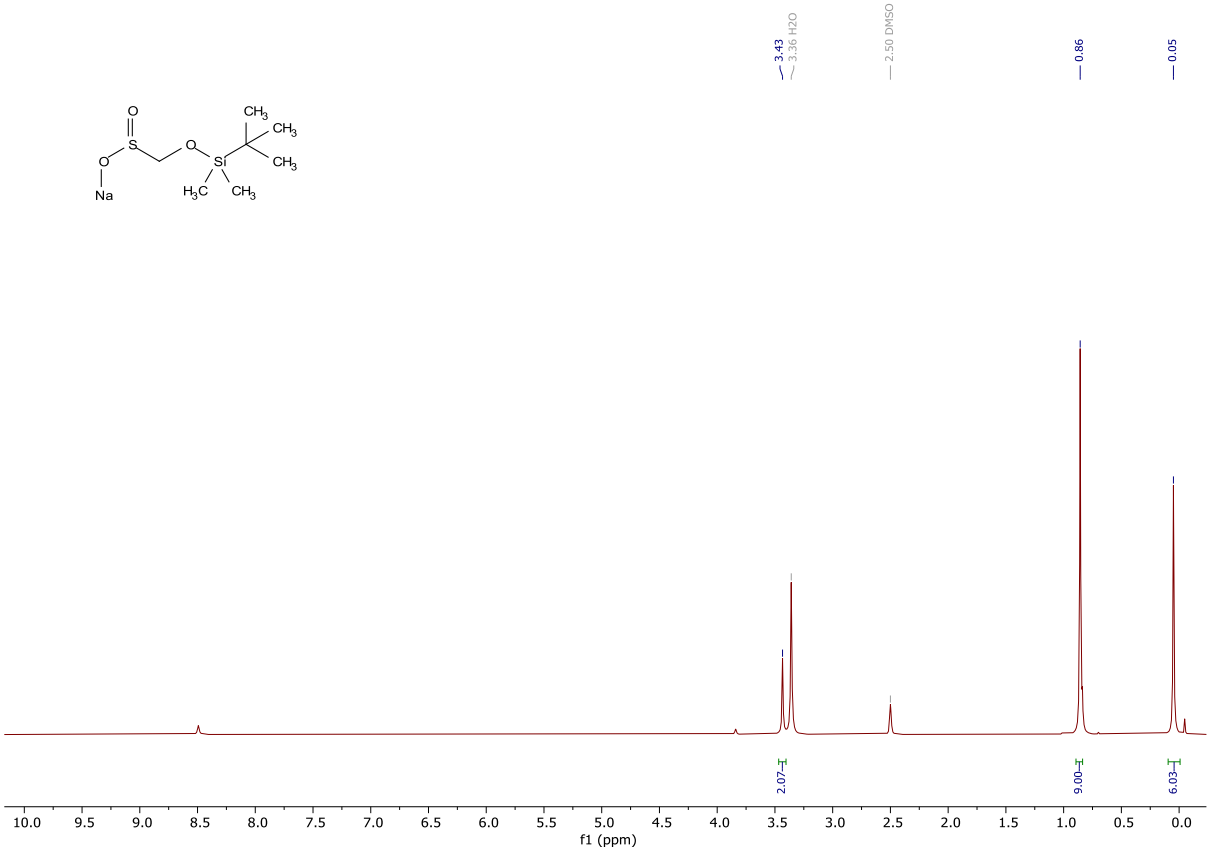
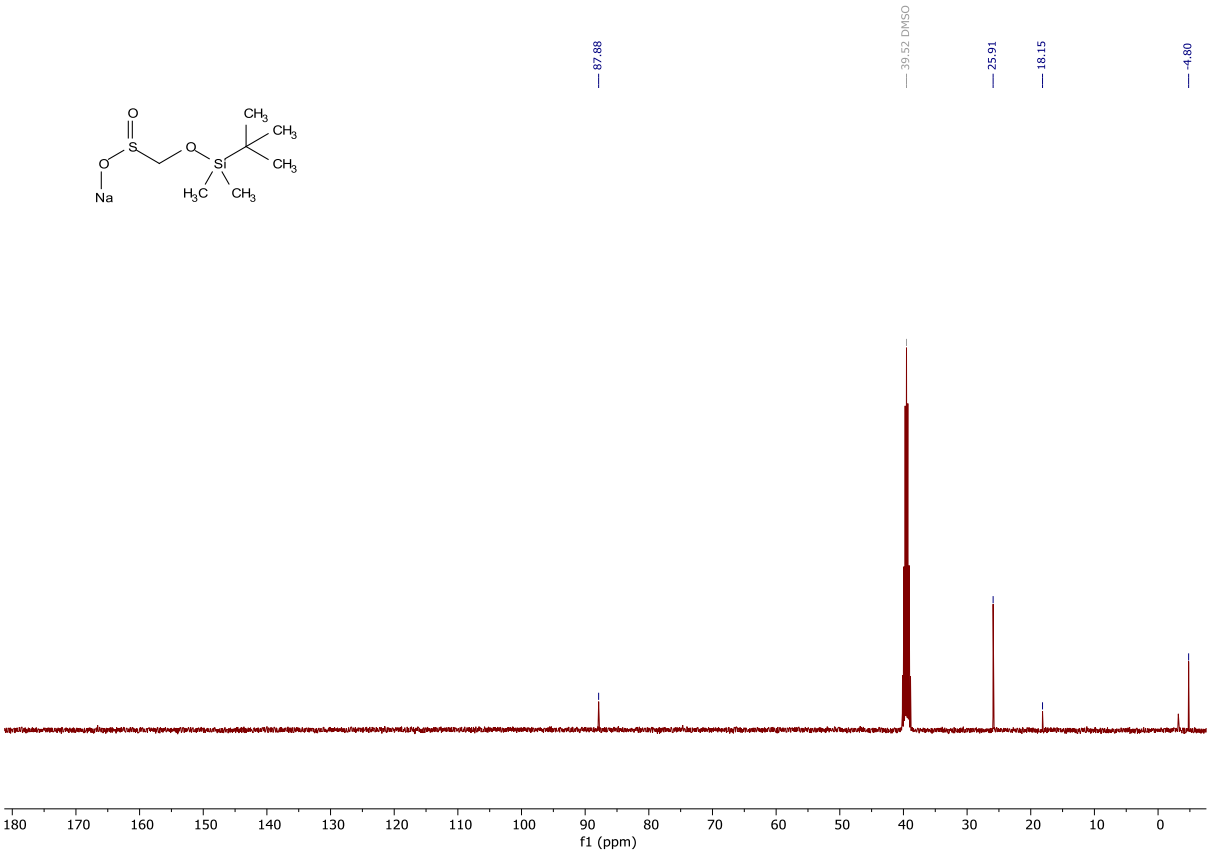
f1 (ppm)

1,2-Diphenylethane (S8)

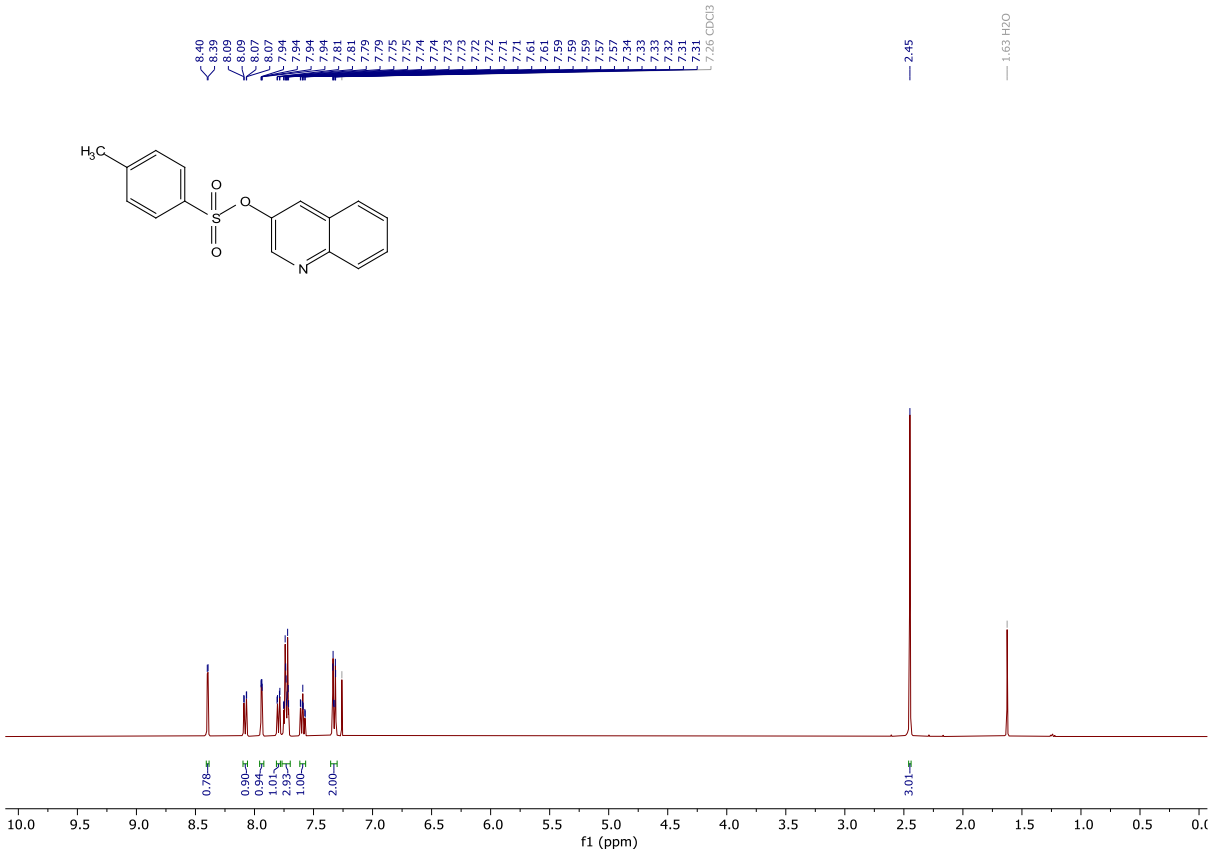


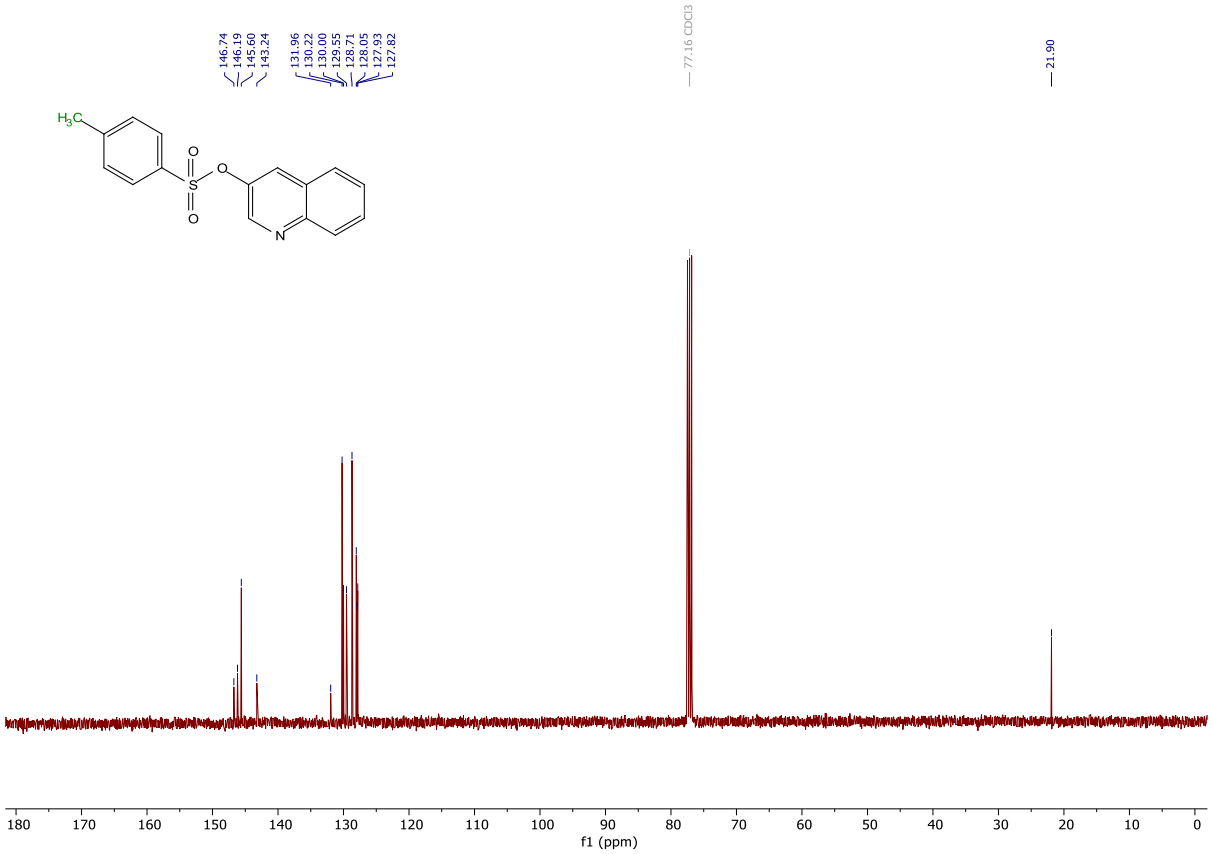
Sodium ((tert-butyldimethylsilyl)oxy)methanesulfinate (TBSOMS-Na) (S9)



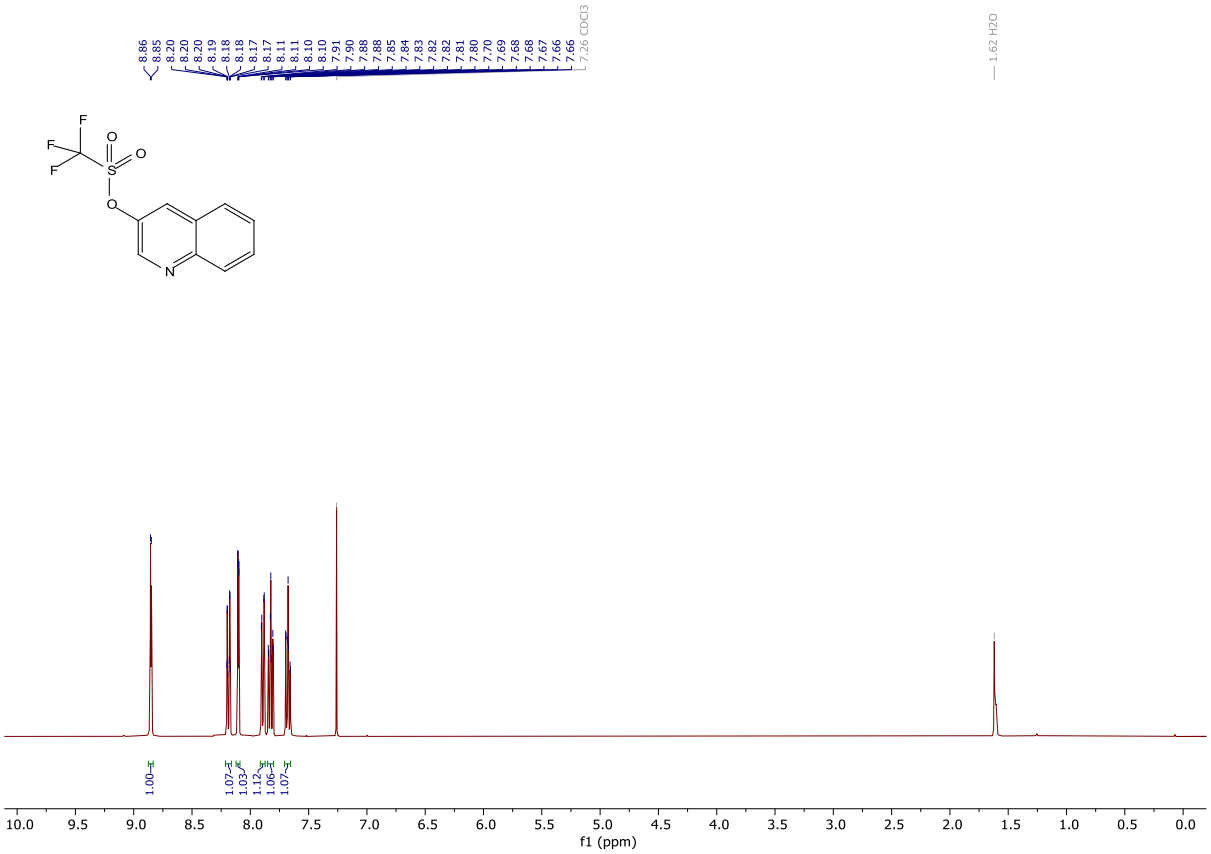


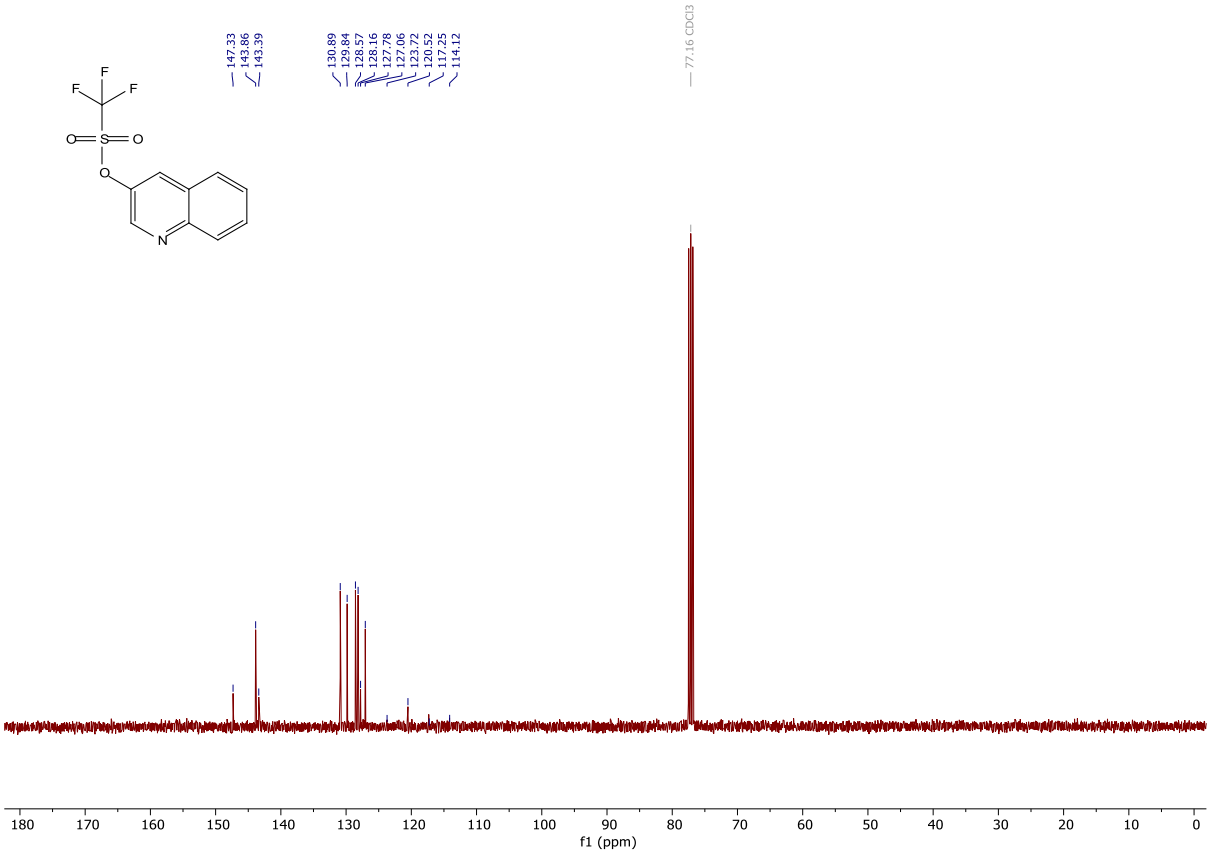
Quinolin-3-yl 4-methylbenzenesulfonate (S10)

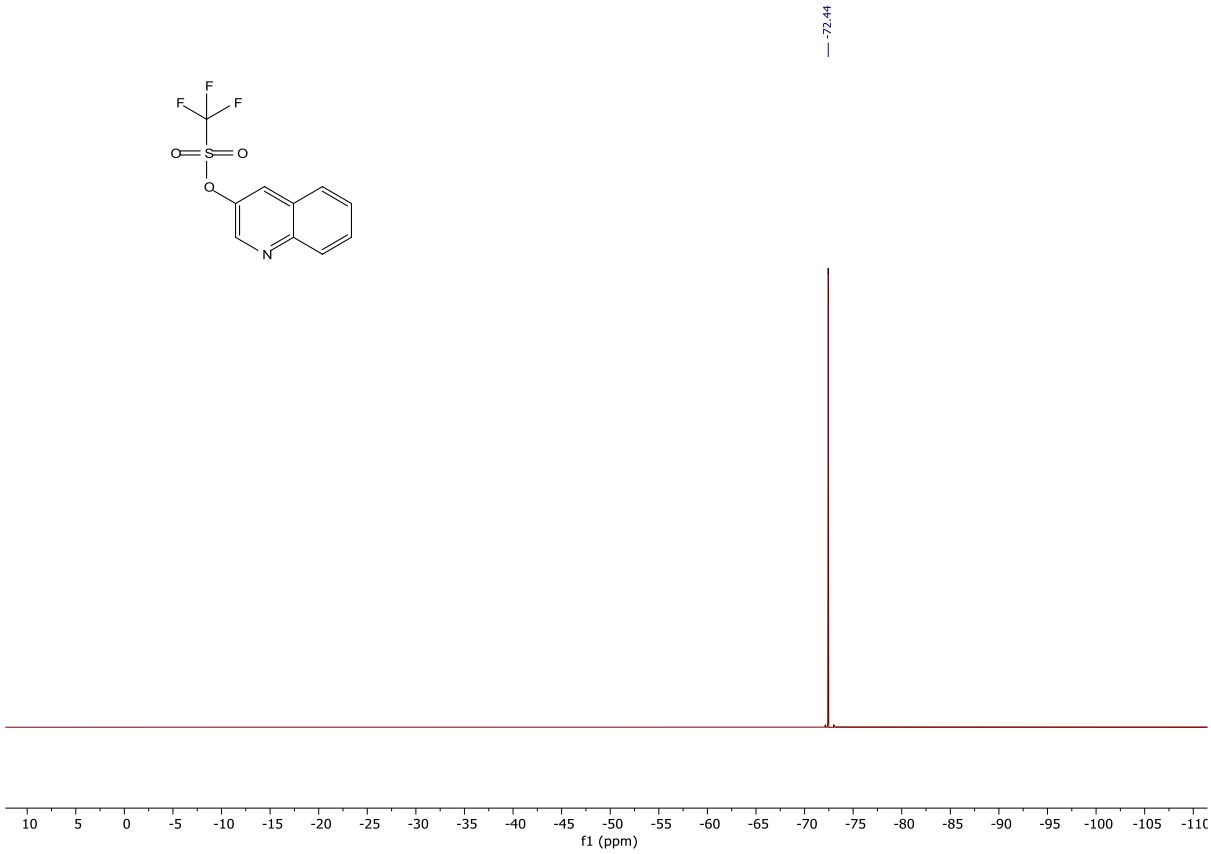




Quinolin-3-yl trifluoromethanesulfonate (S11)






-72.44
F
F
F
O
S
O
O
N
10
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0
-5
-10
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-35
-40
-45
-50
-55
-60
-65
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-90
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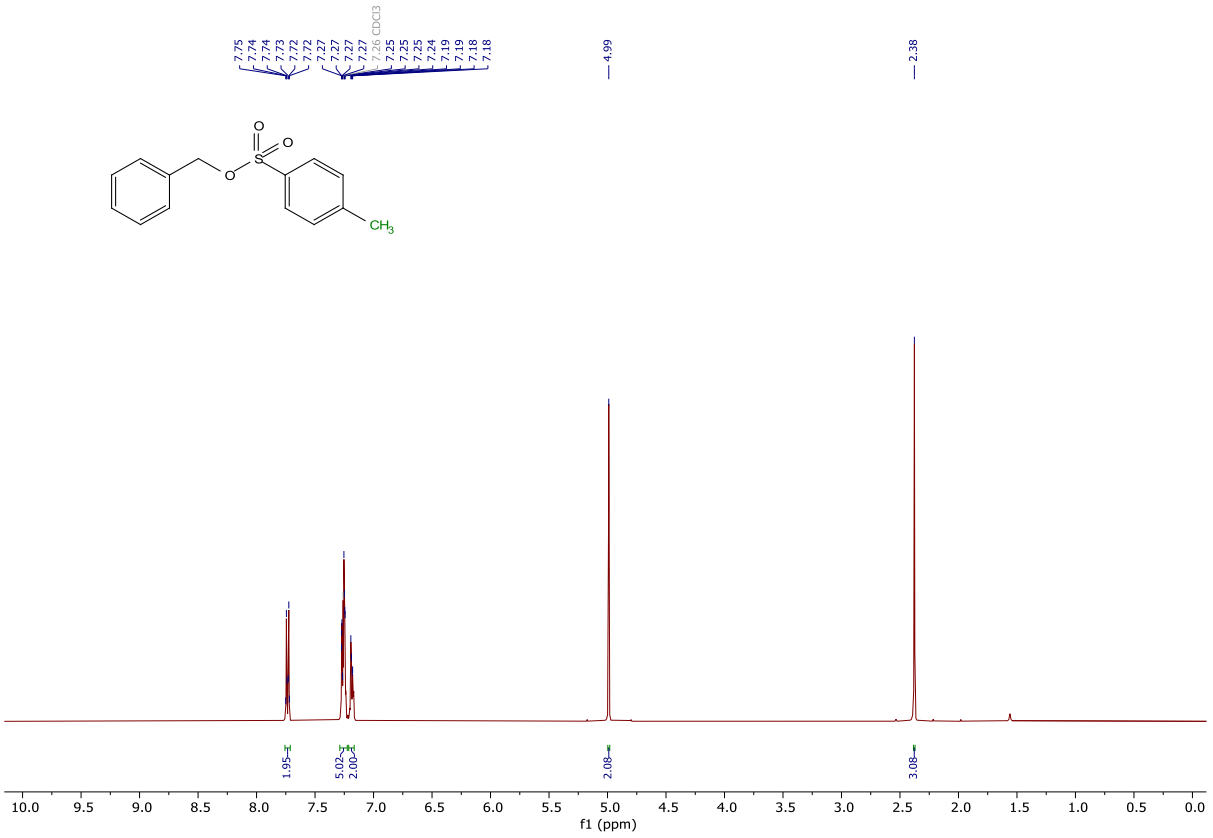
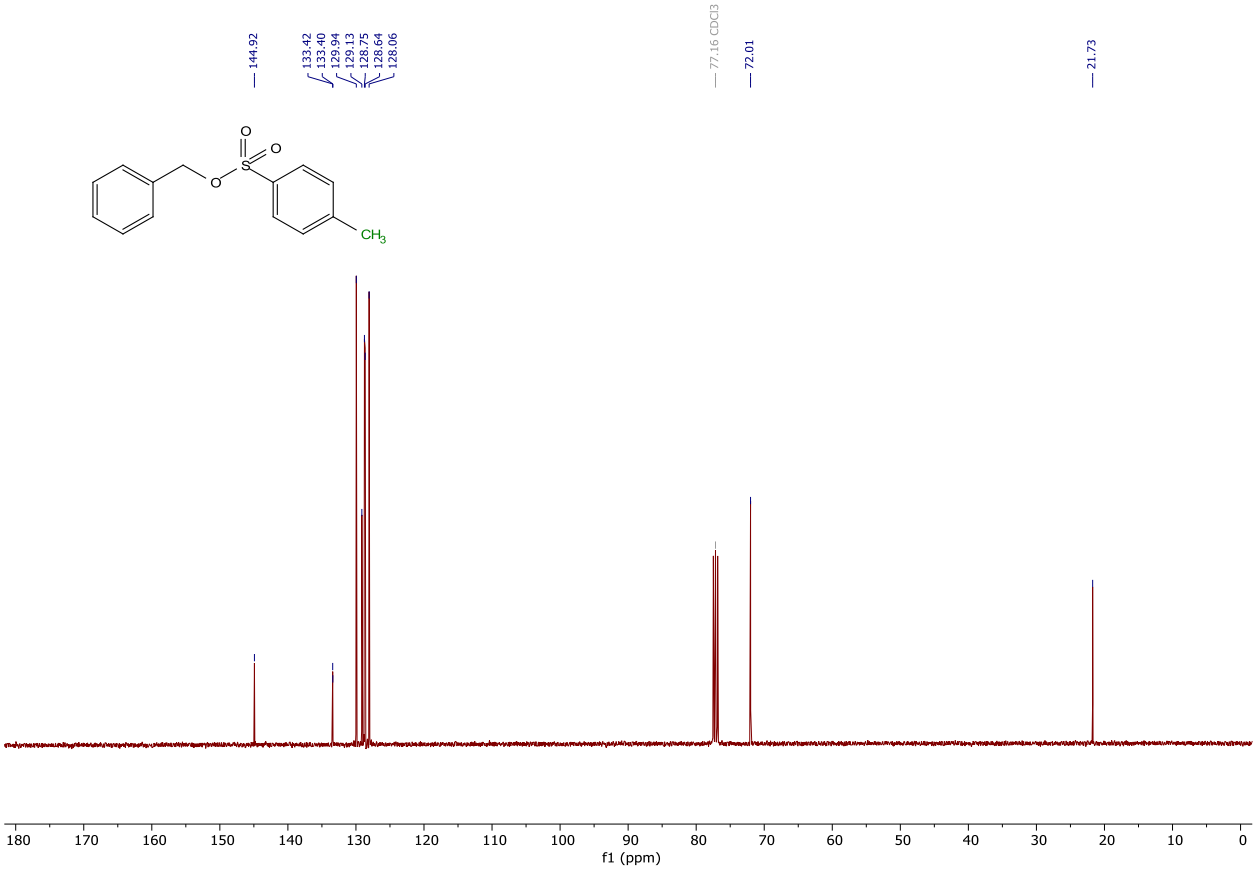
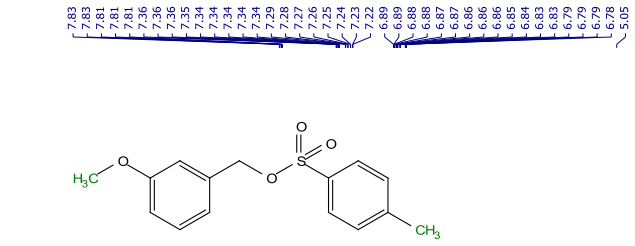
-100
-105
-110
f1 (ppm)

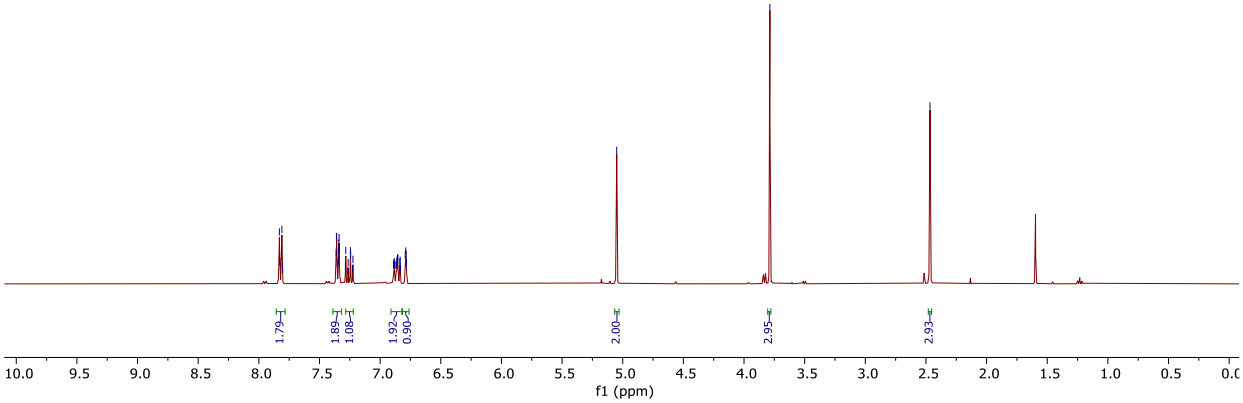
Benzyl 4-methylbenzenesulfonate (8a)

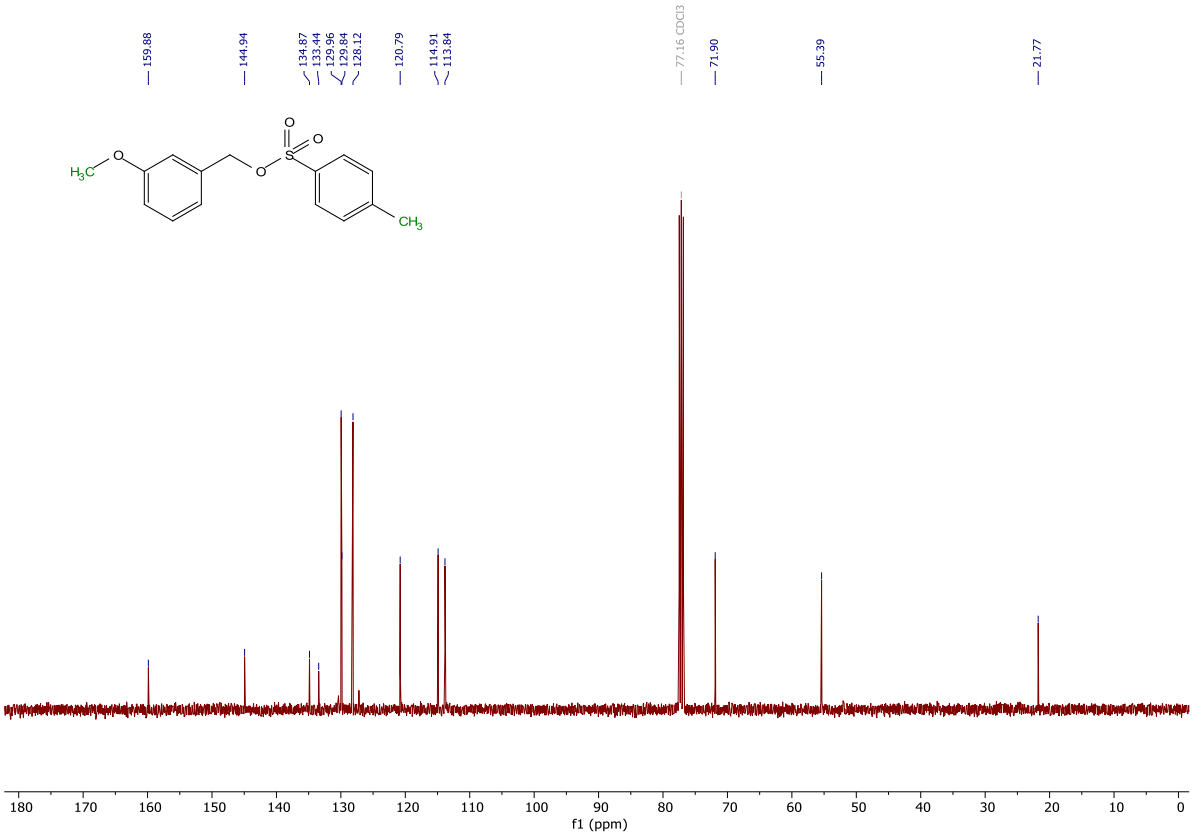




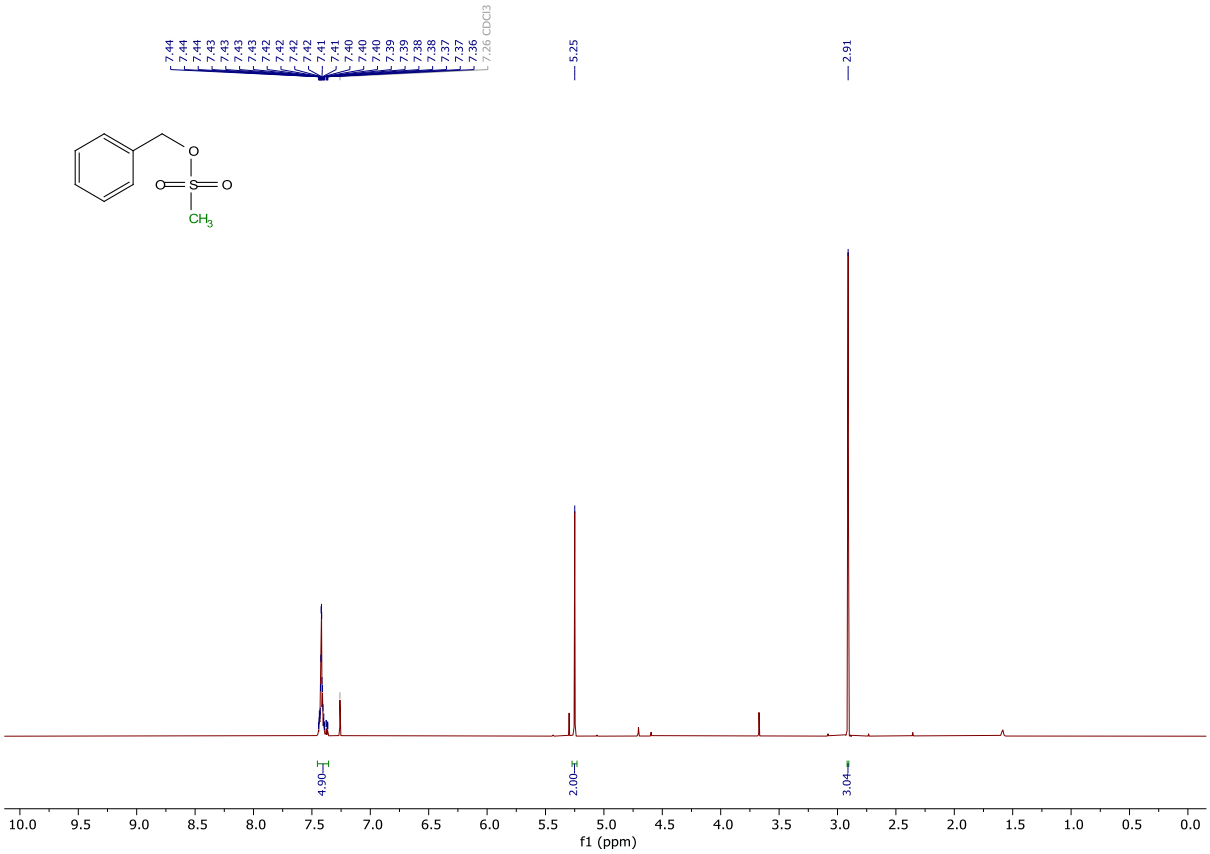
3-Methoxybenzyl 4-methylbenzenesulfonate (8b)

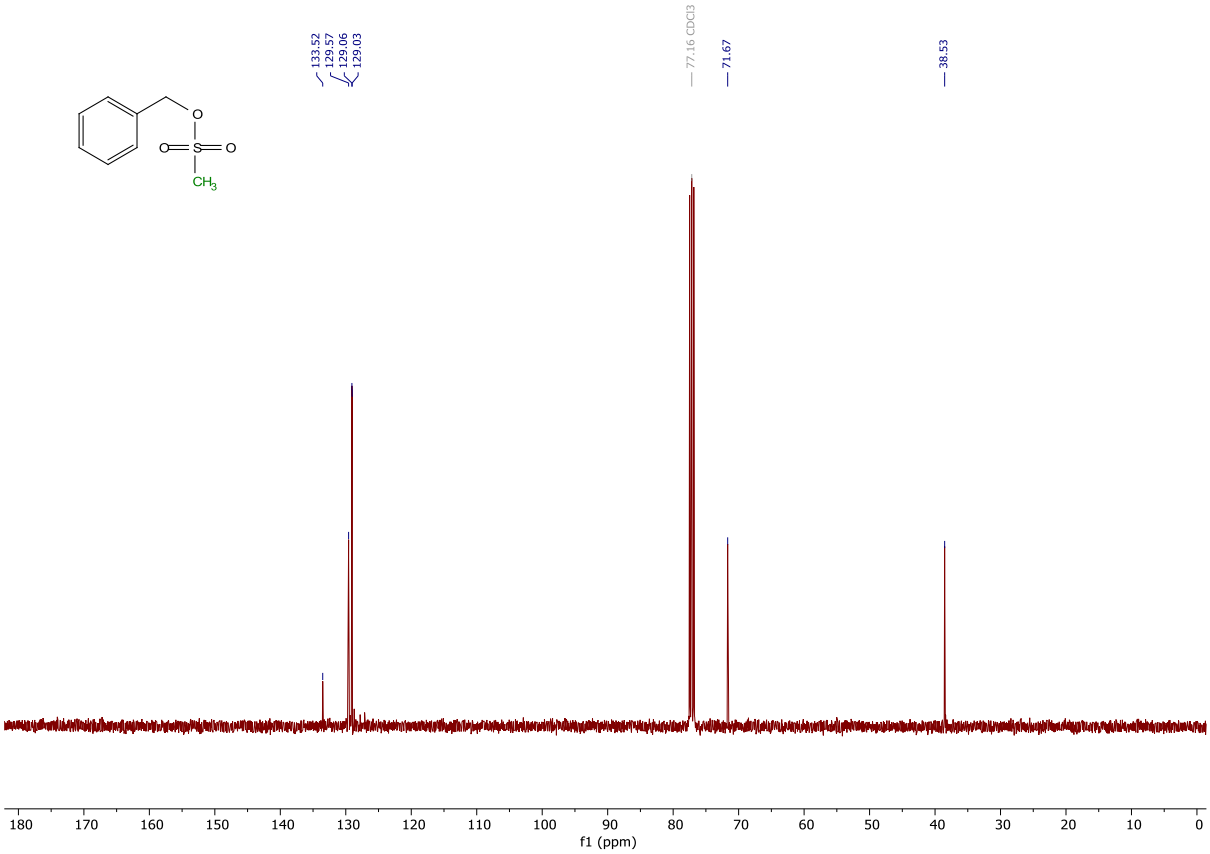




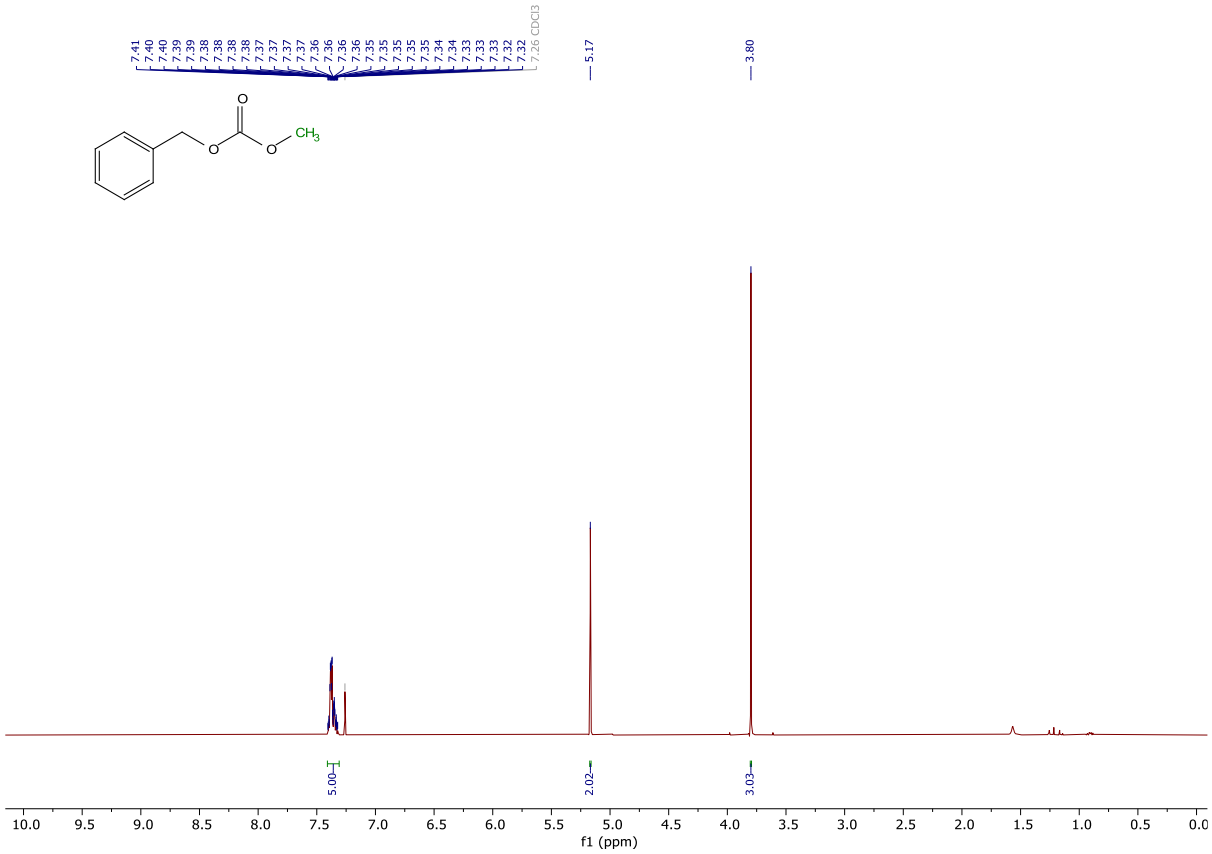


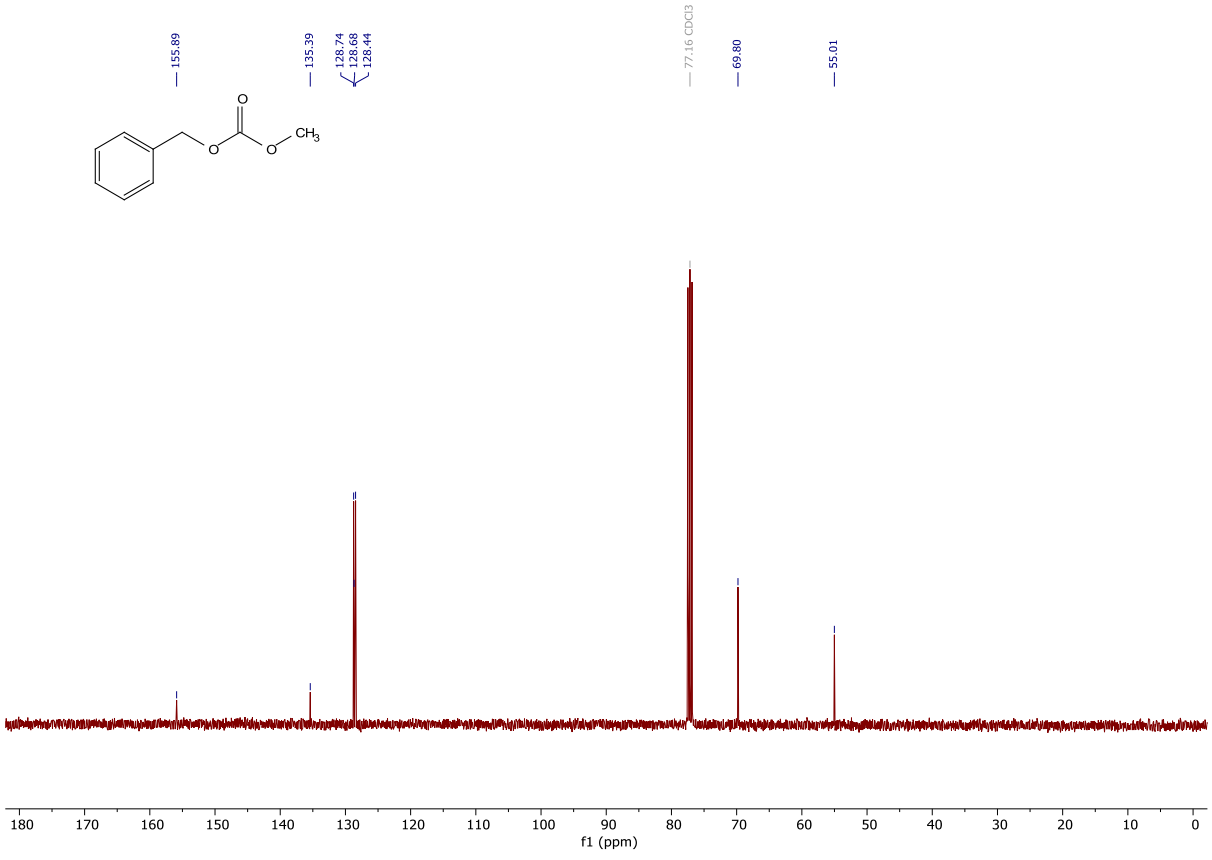
Benzyl methanesulfonate (8c)



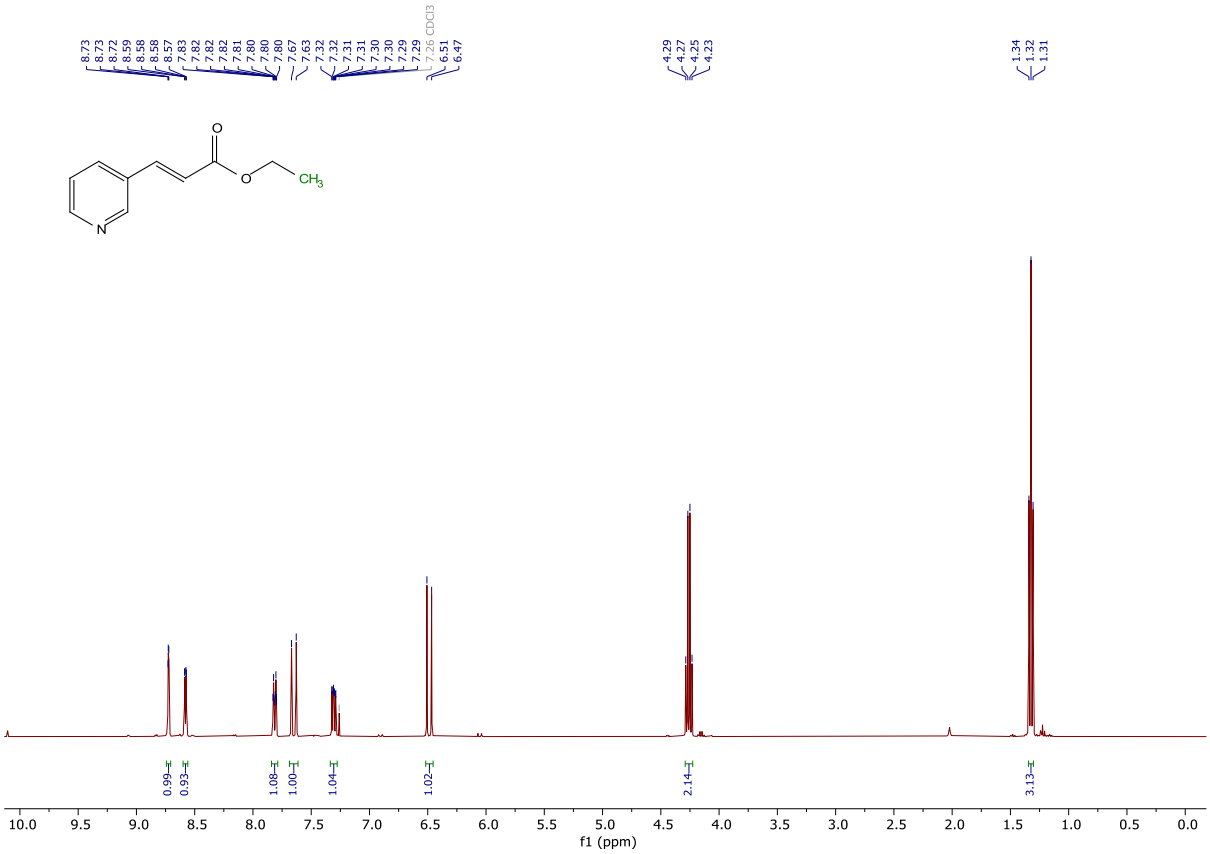


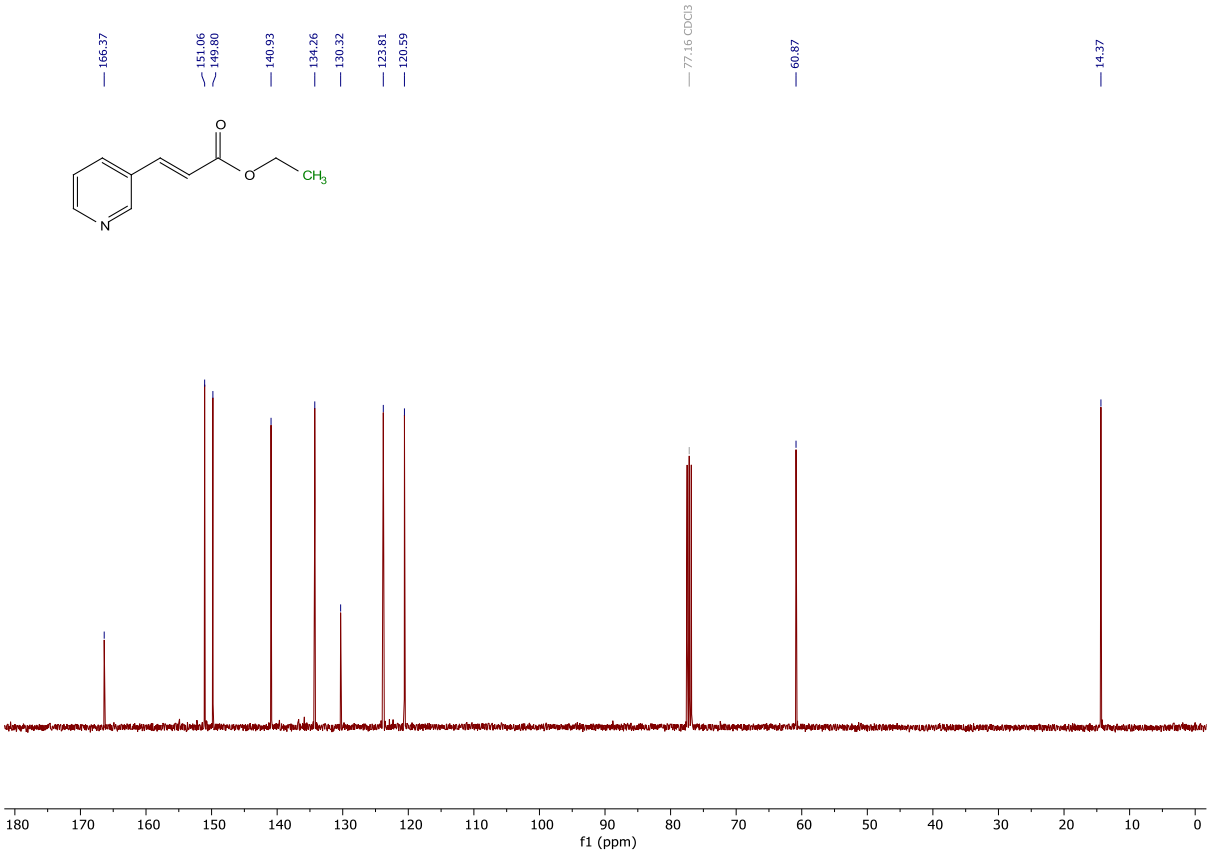
Benzyl methyl carbonate (8d)



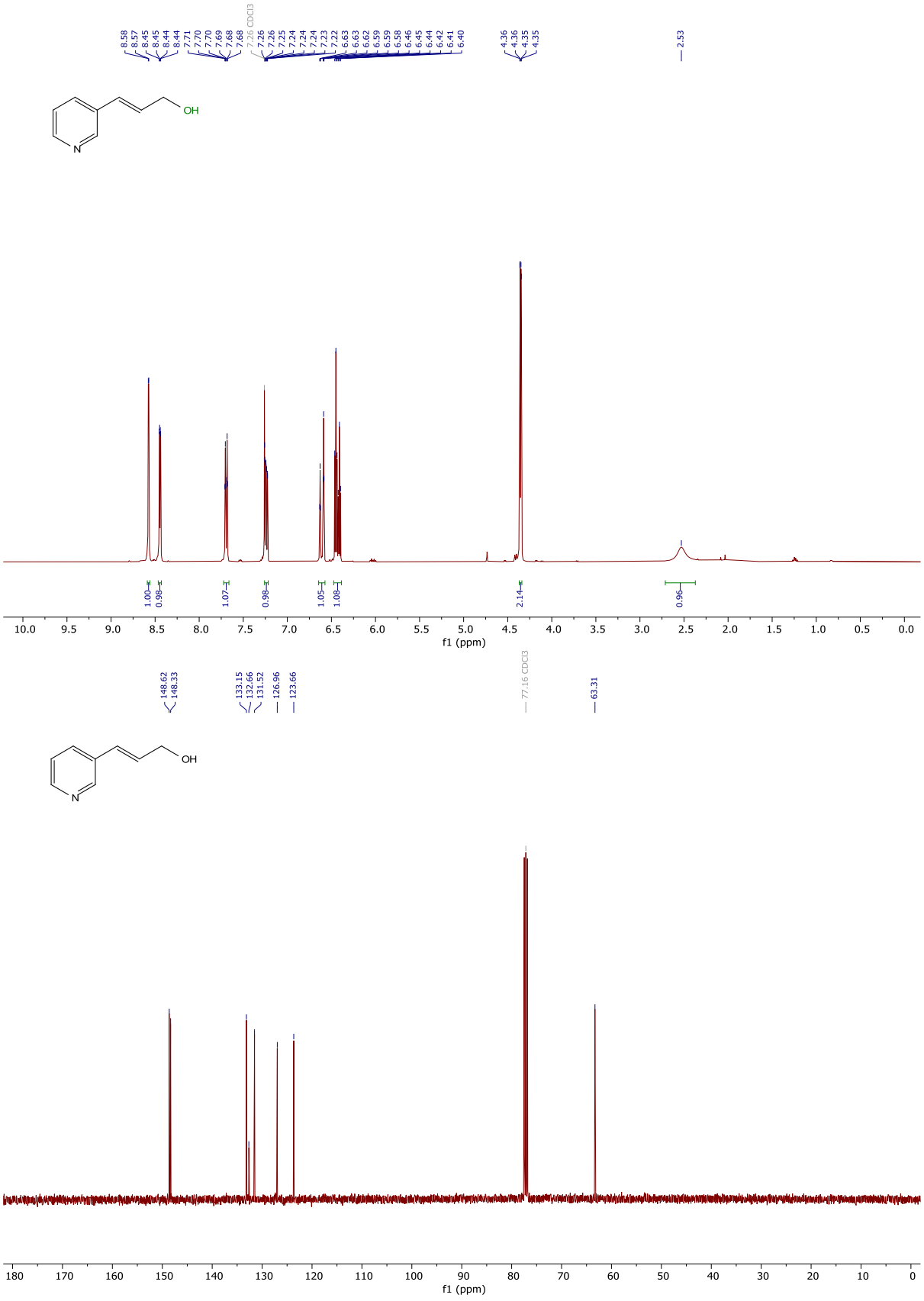


Ethyl (E)-3-(pyridin-3-yl)acrylate (12a)

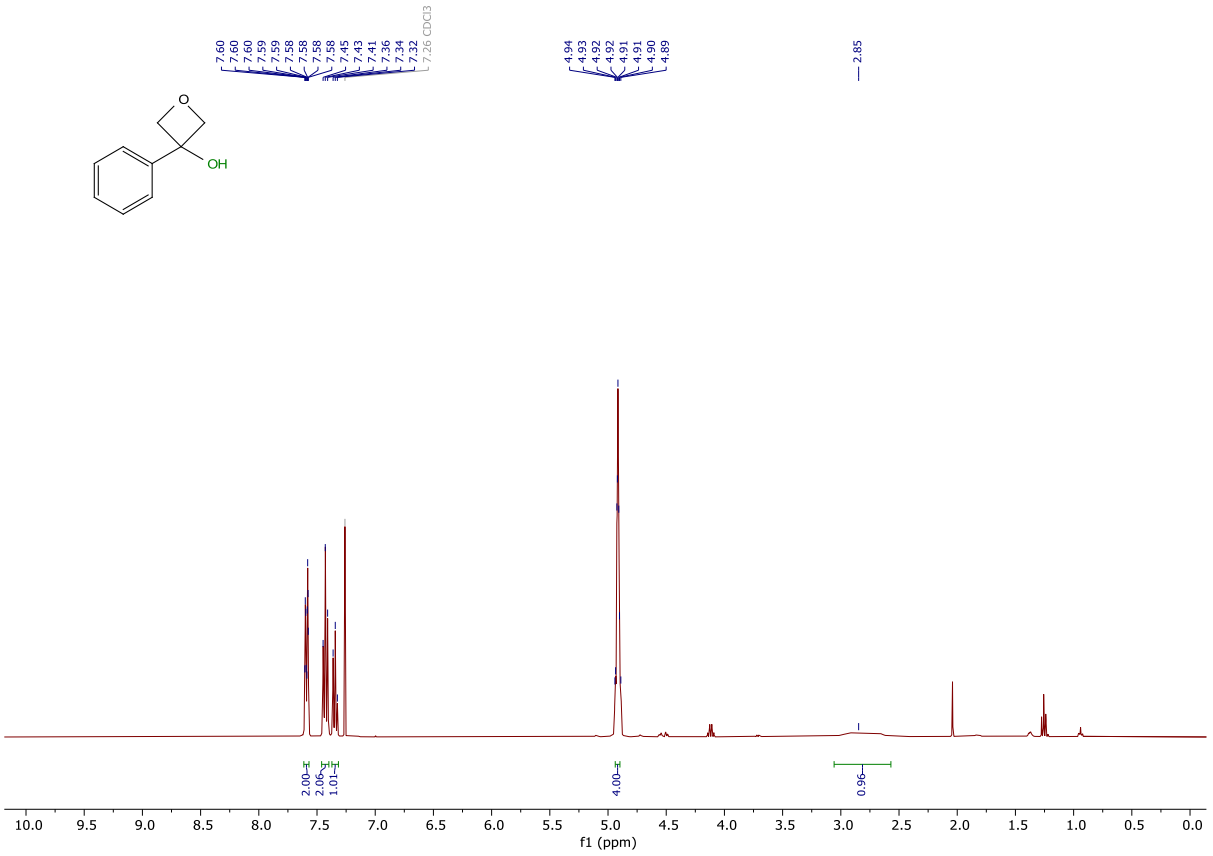


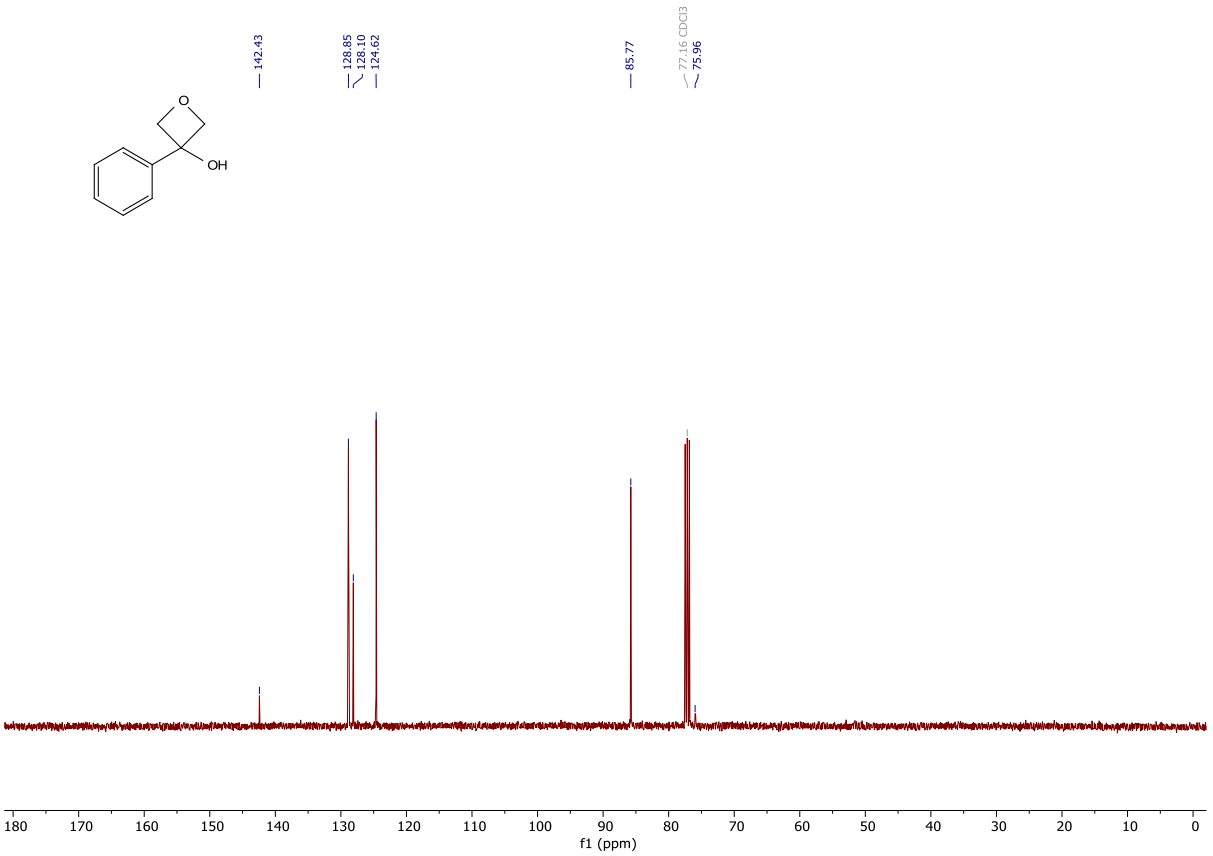


(E)-3-(Pyridin-3-yl)prop-2-en-1-ol (12b)

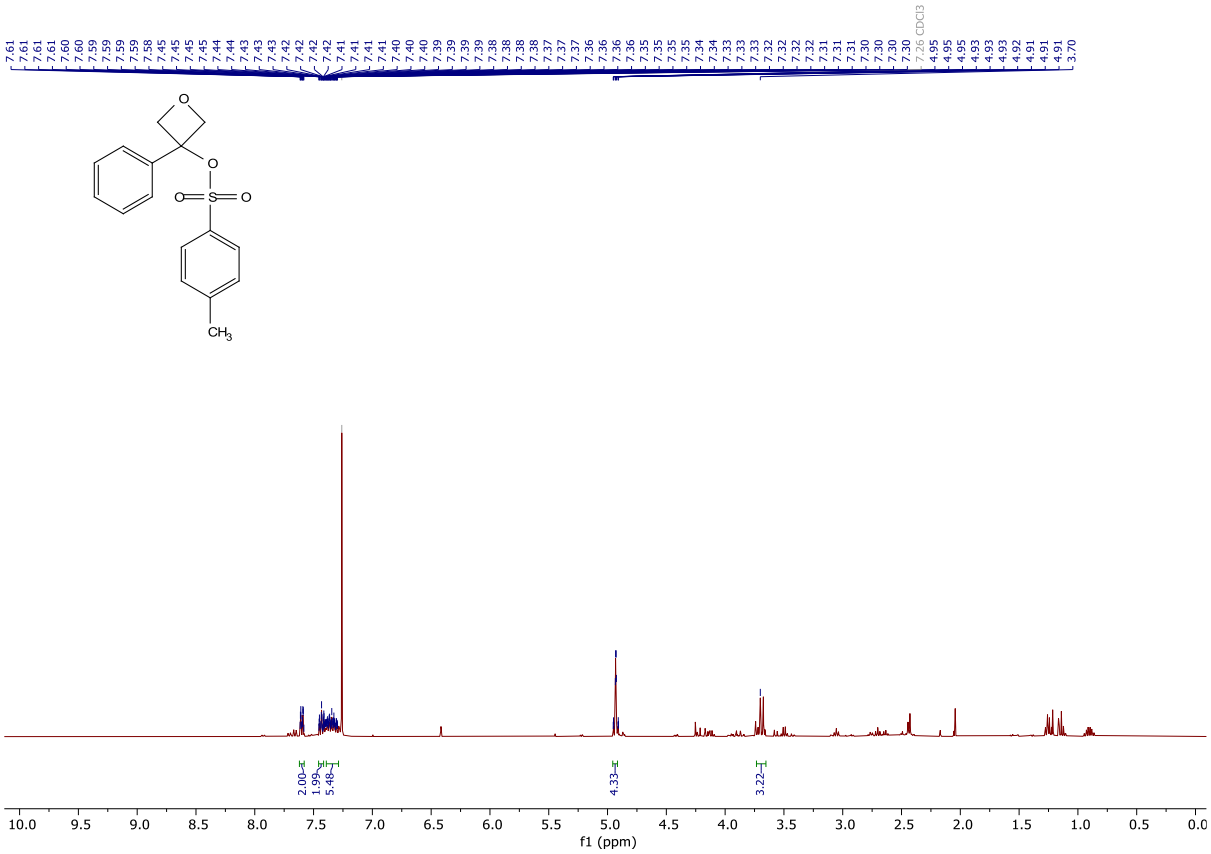


3-Phenyloxetan-3-ol (13a)

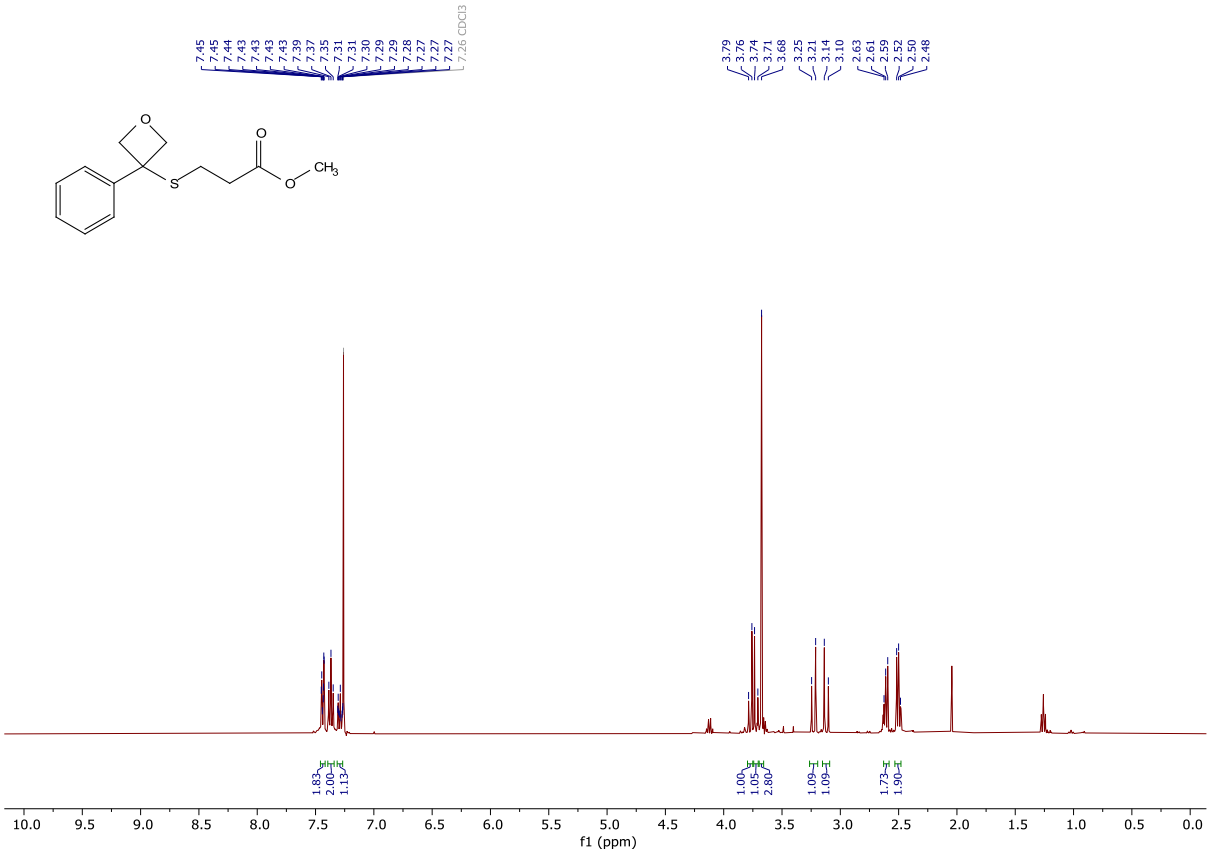


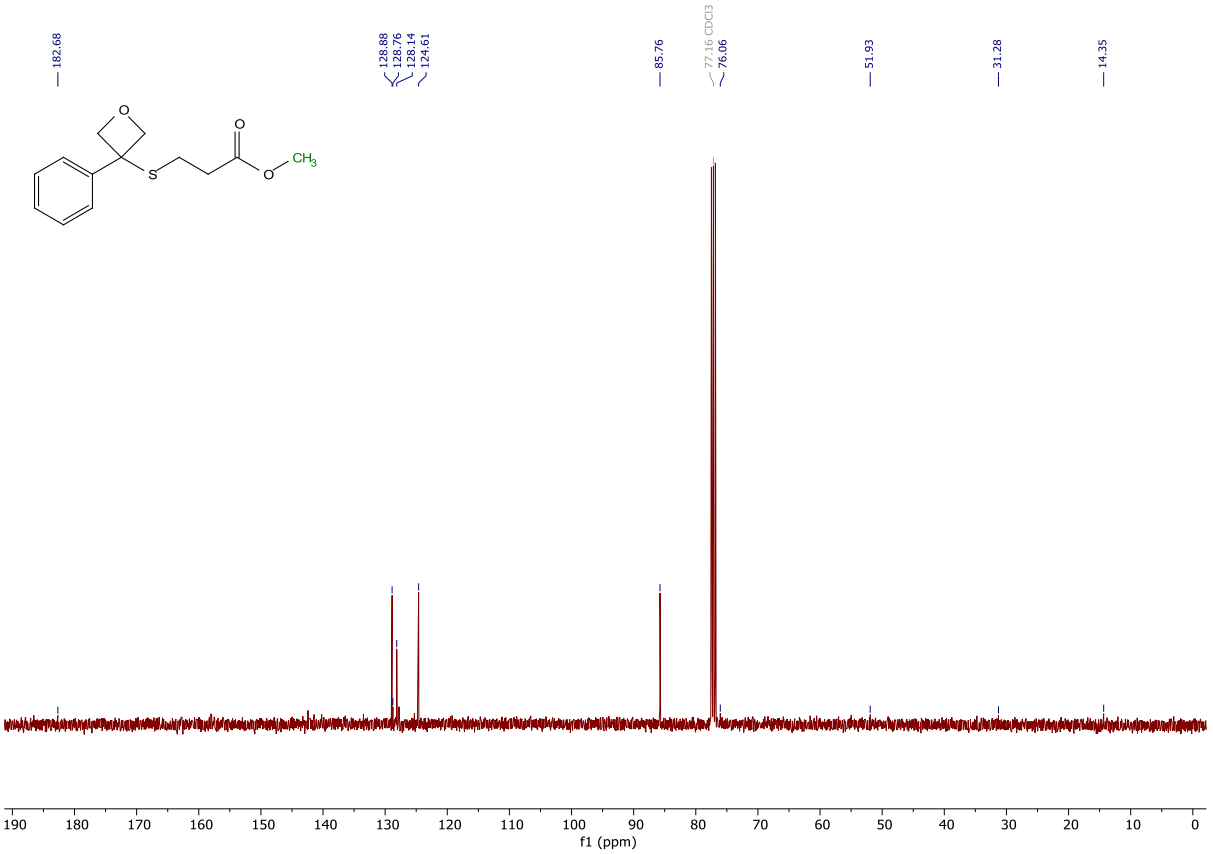


3-Phenyloxetan-3-yl 4-methylbenzenesulfonate (13b)

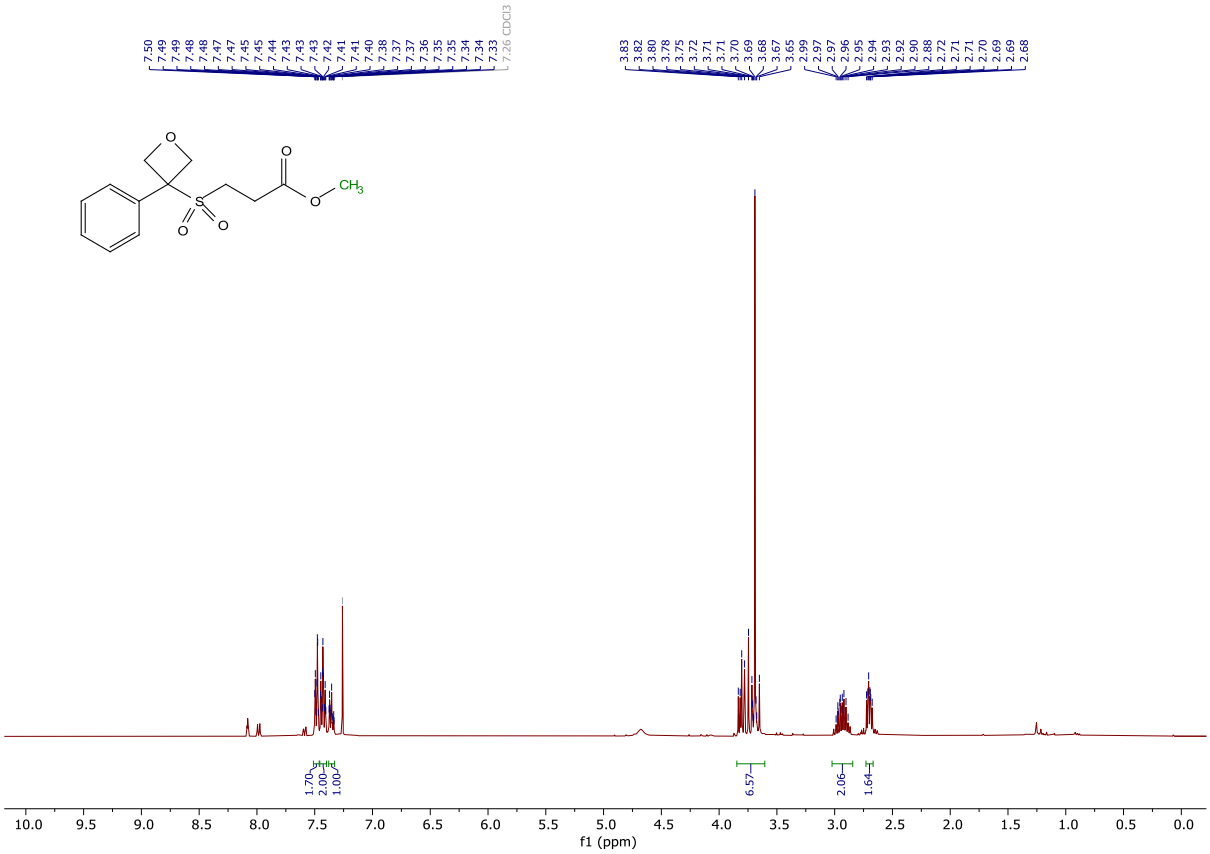


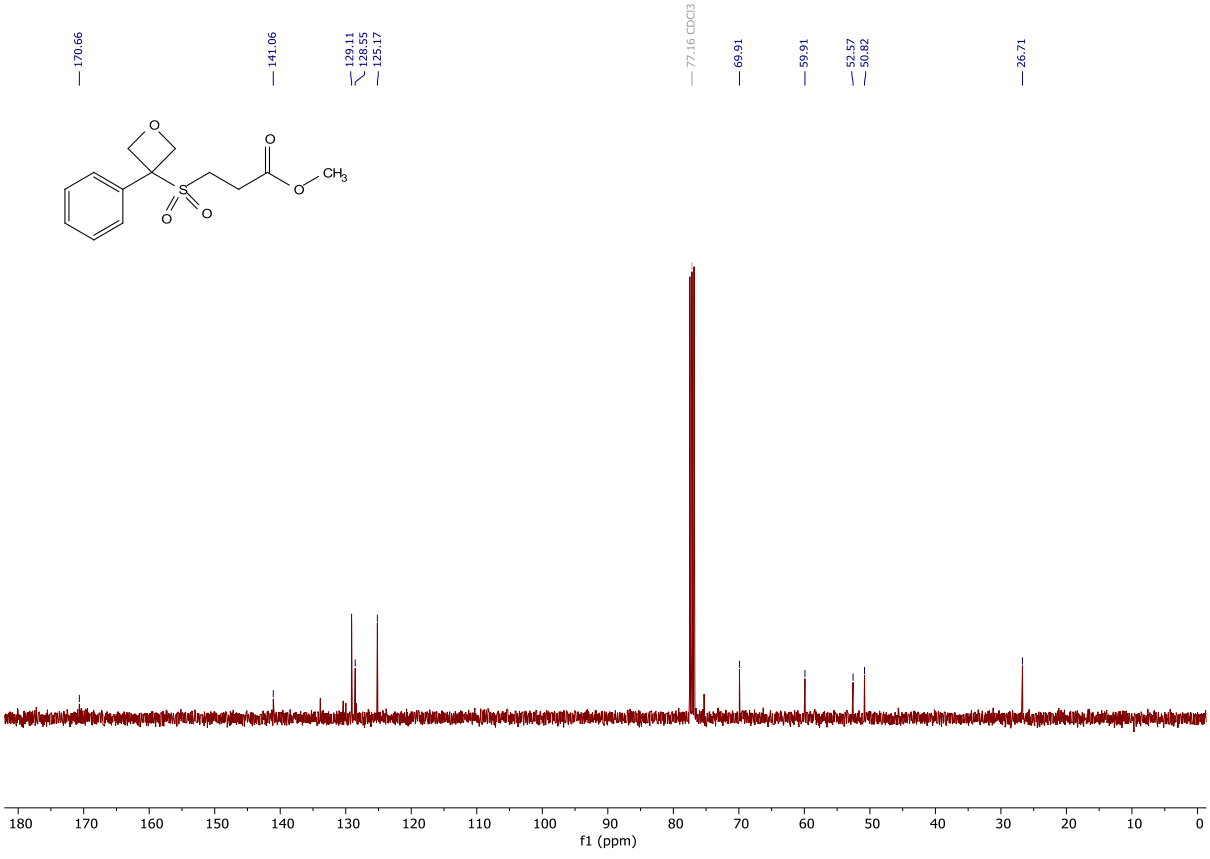
Methyl 3-((3-phenyloxetan-3-yl)thio)propanoate (13c)



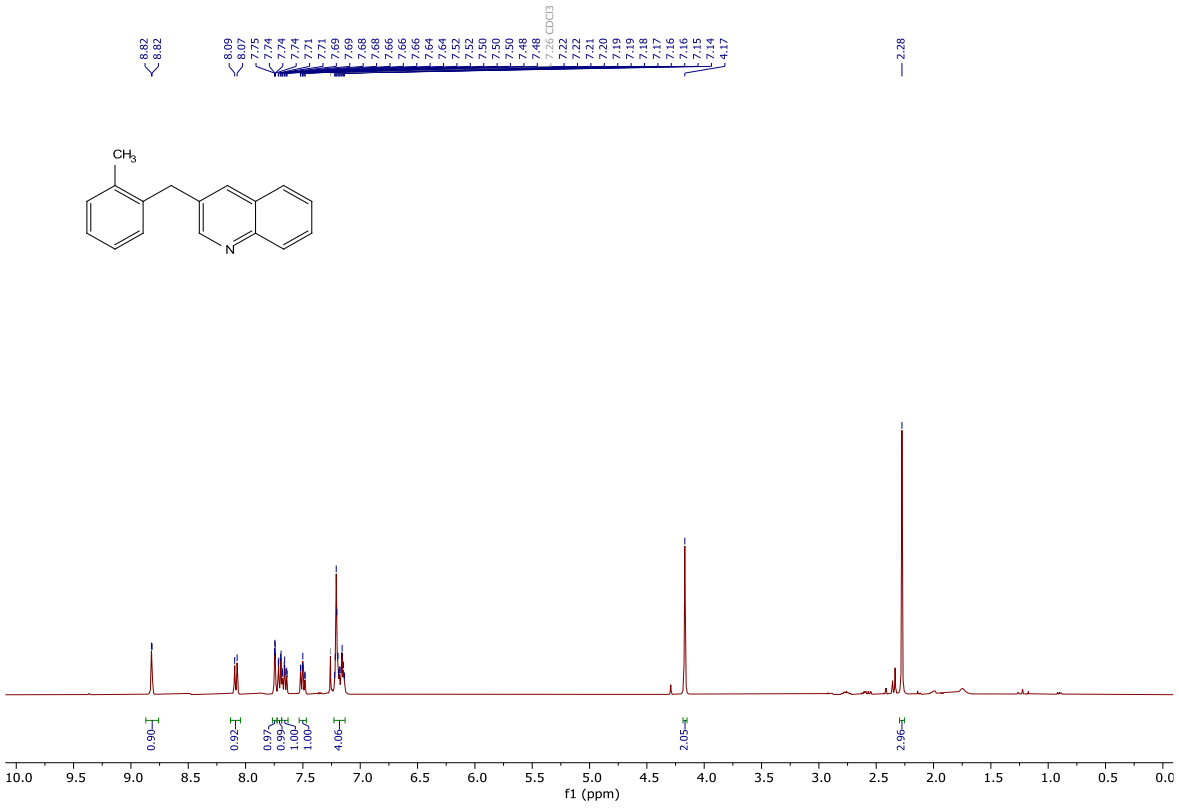


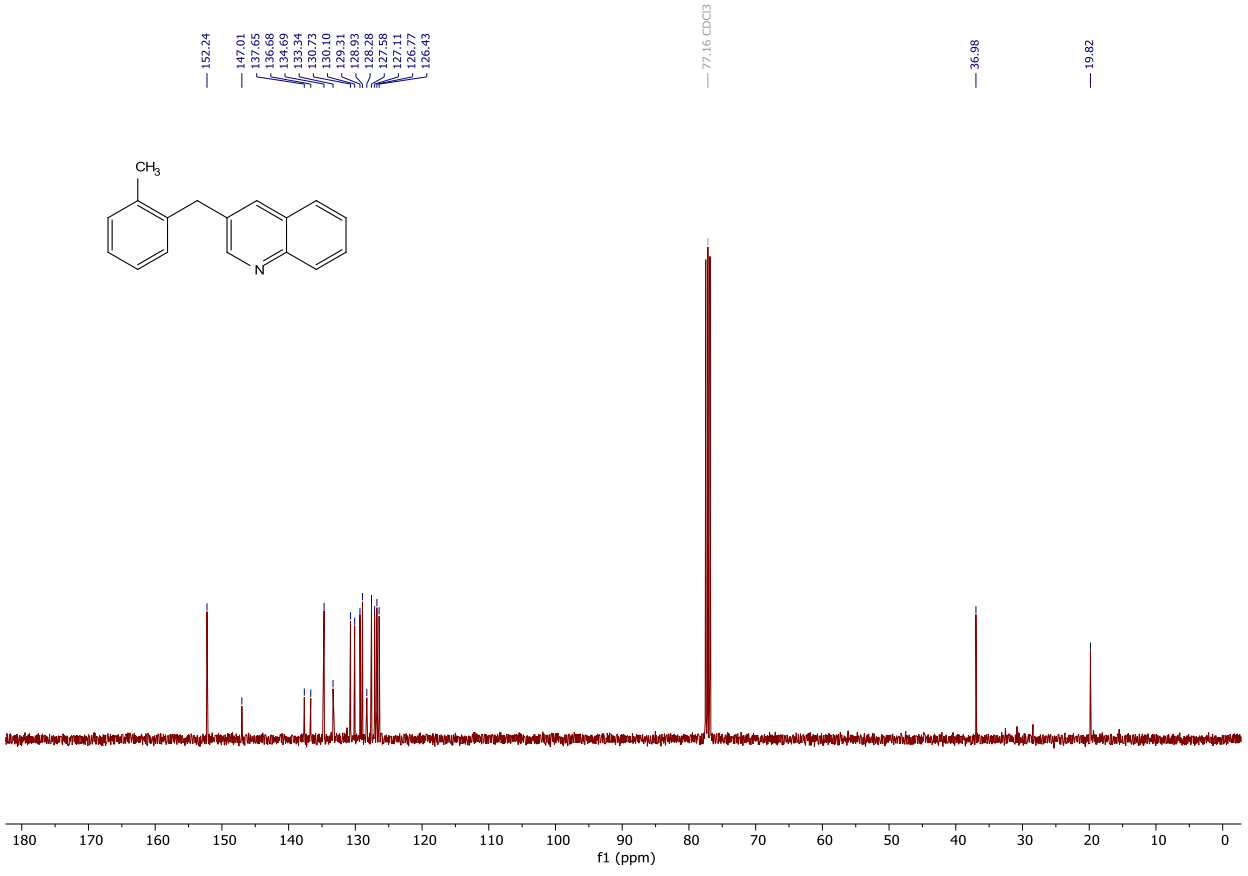
Methyl 3-((3-phenyloxetan-3-yl)sulfonyl)propanoate (13d)



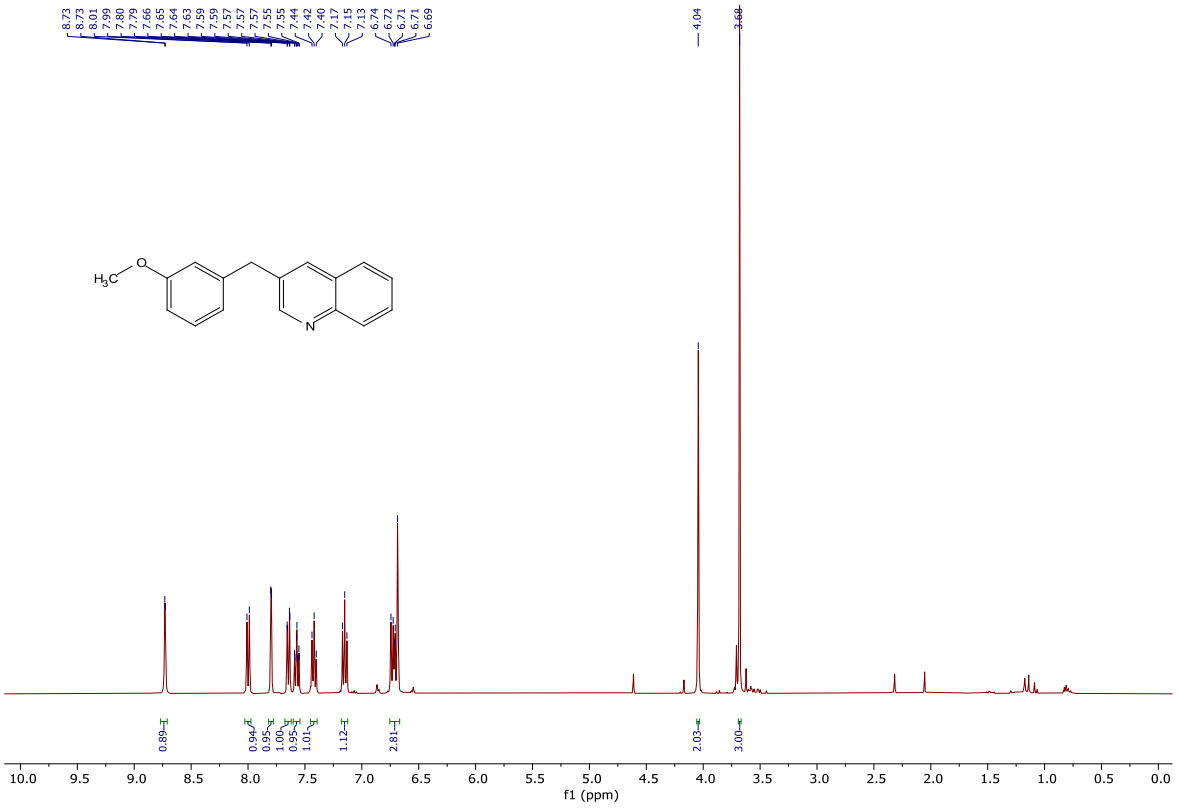


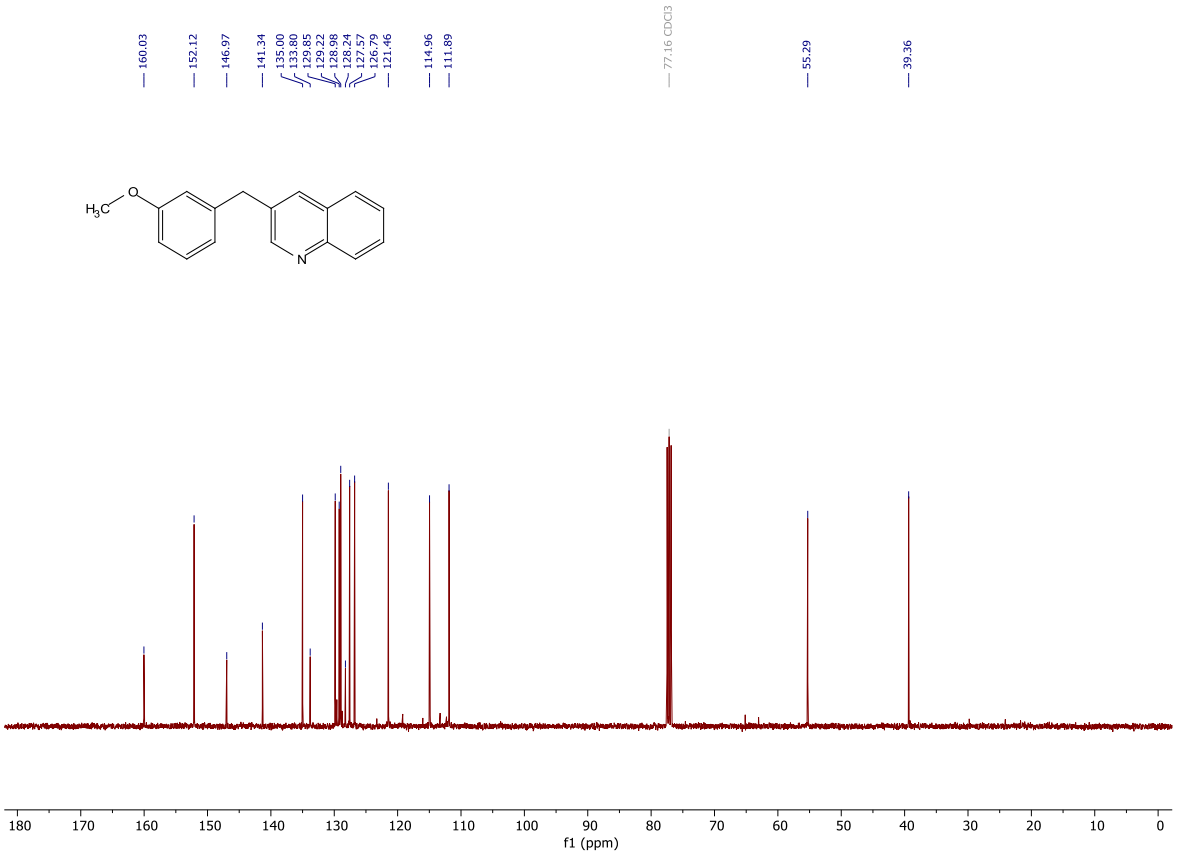
3-(2-Methylbenzyl)quinoline (6ag)



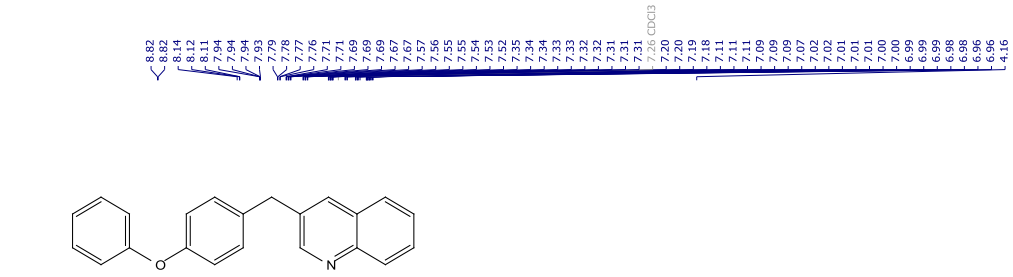


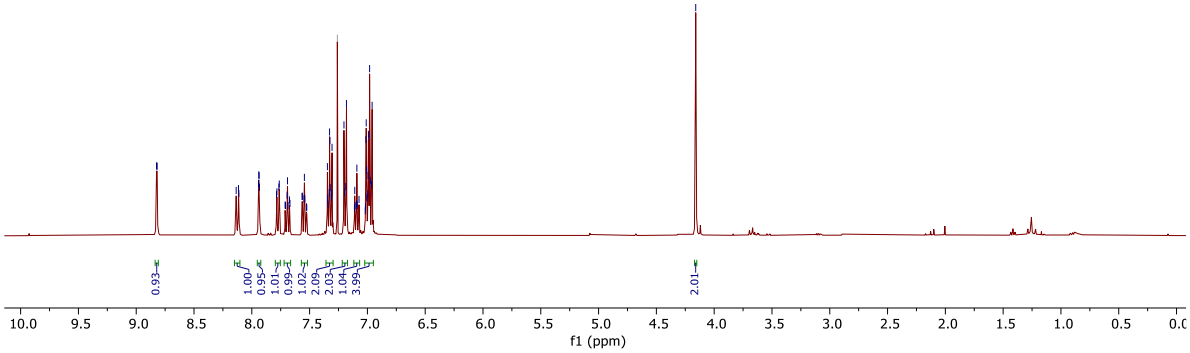
3-(3-Methoxybenzyl)quinoline (6ah)



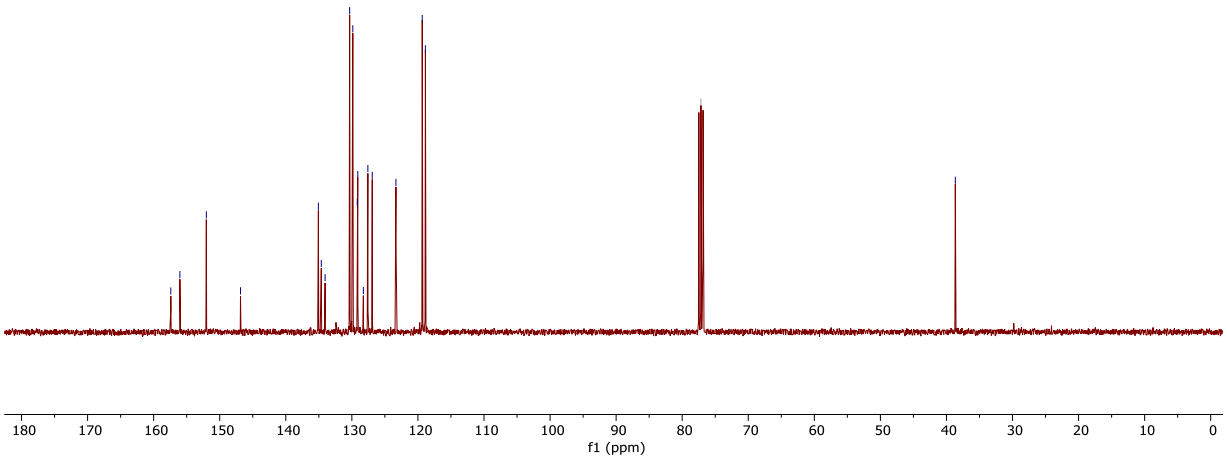


3-(4-Phenoxybenzyl)quinoline (6ai)

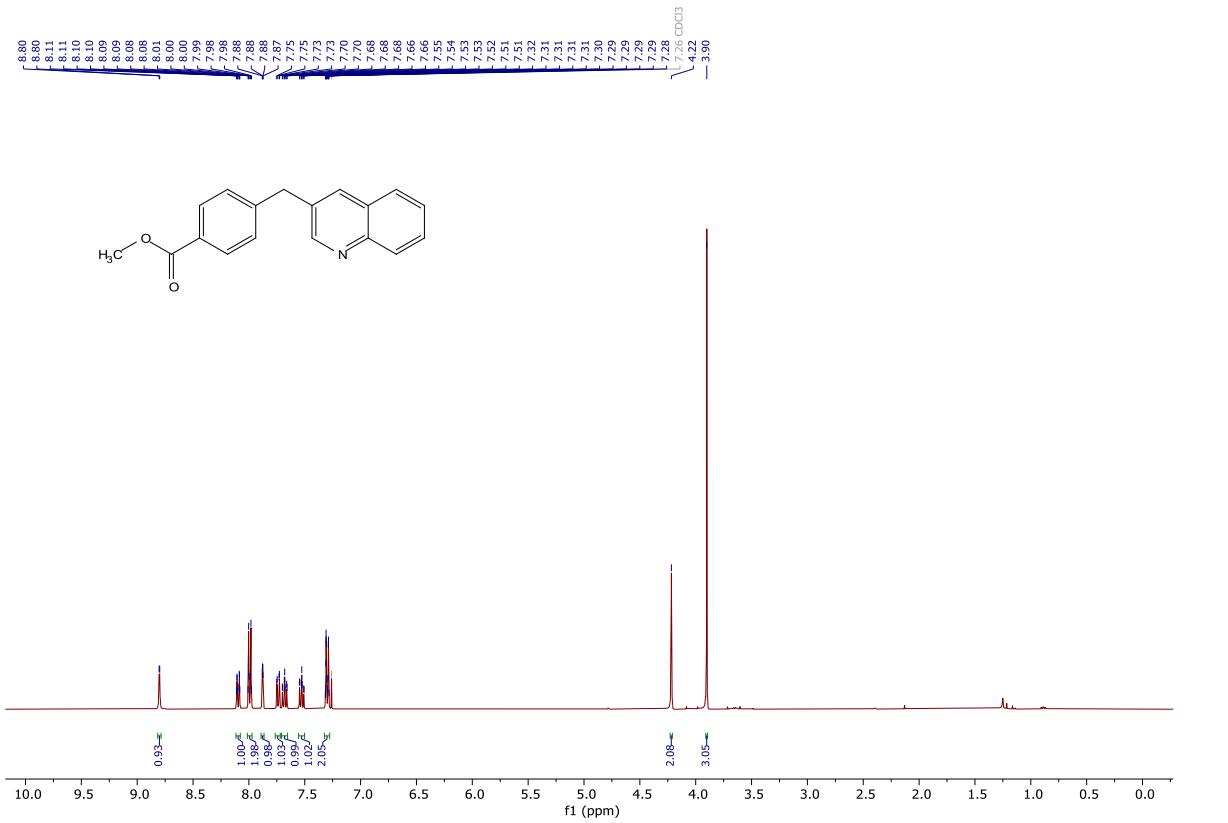


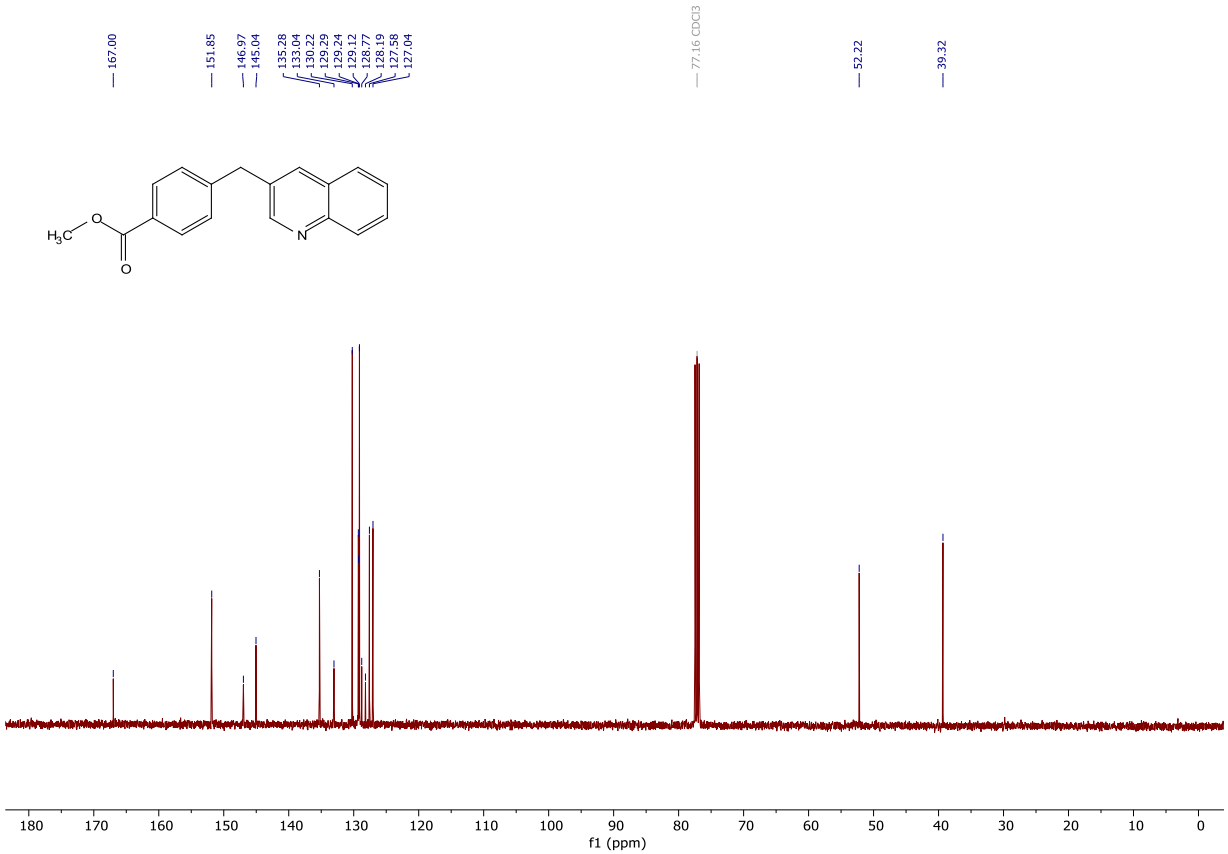




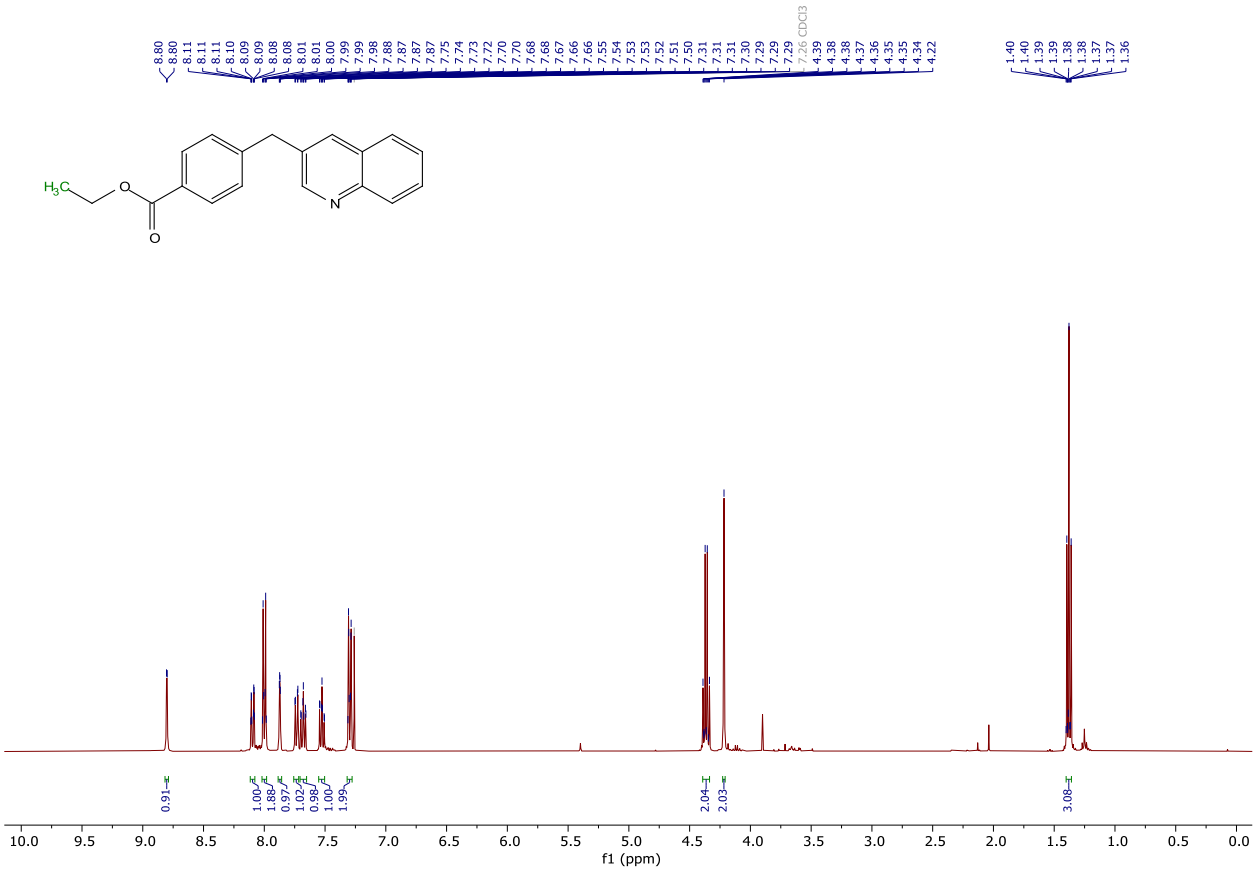


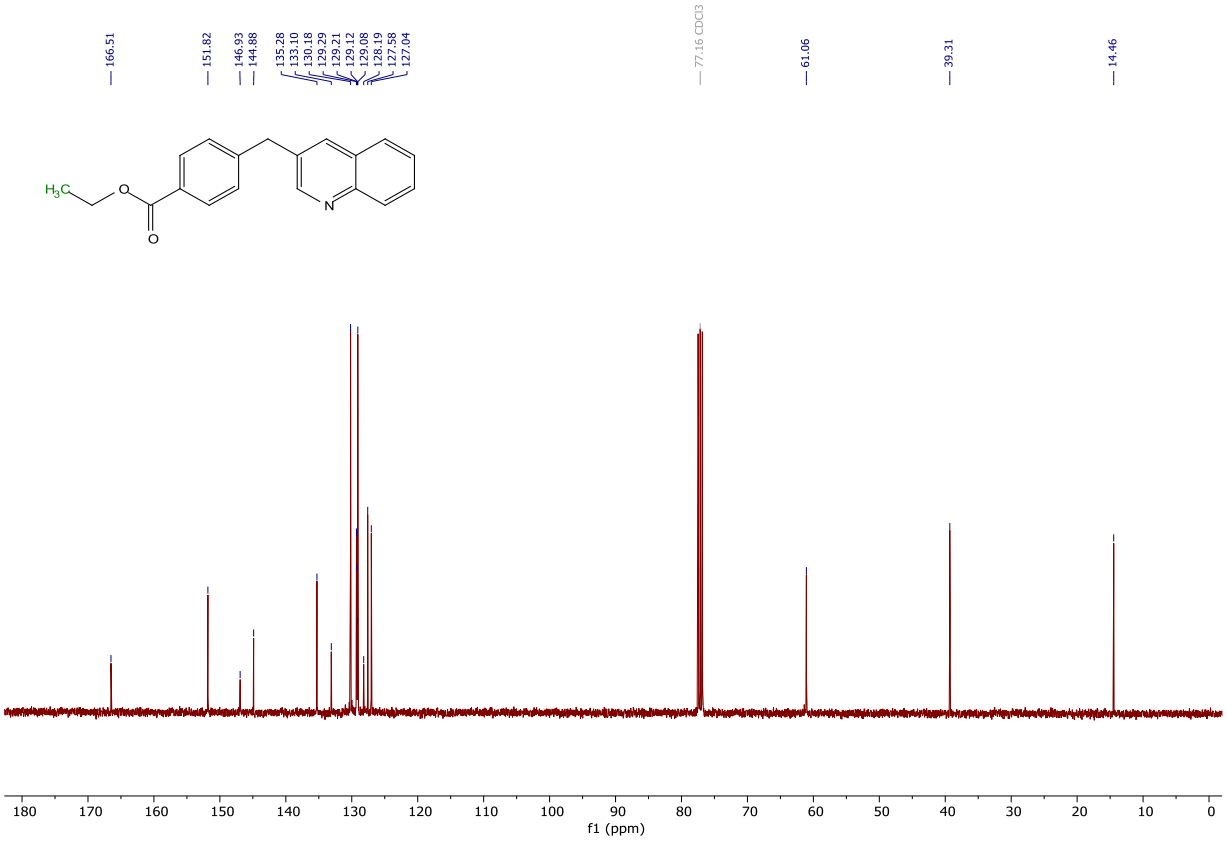
Methyl 4-(quinolin-3-ylmethyl)benzoate (6aj)





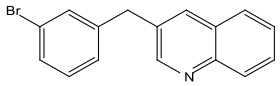
Ethyl 4-(quinolin-3-ylmethyl)benzoate (6ak)

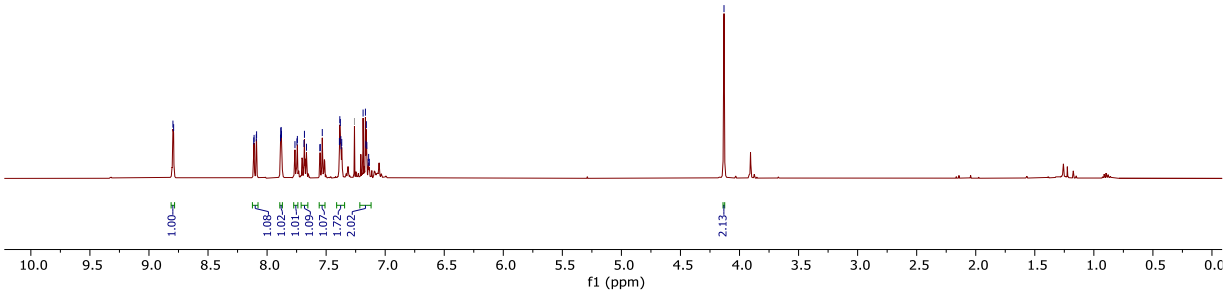




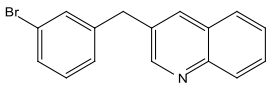
3-(3-Bromobenzyl)quinoline (6al)

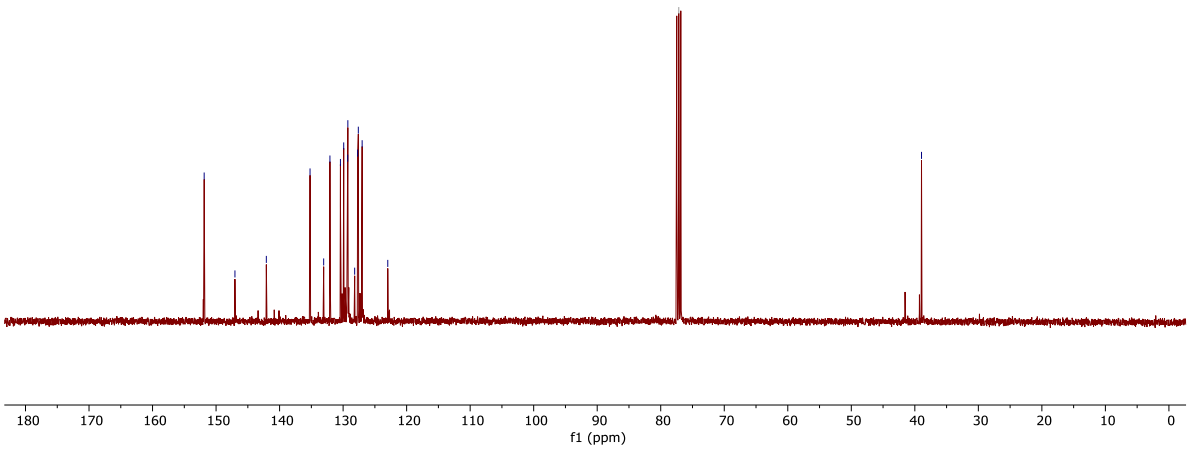




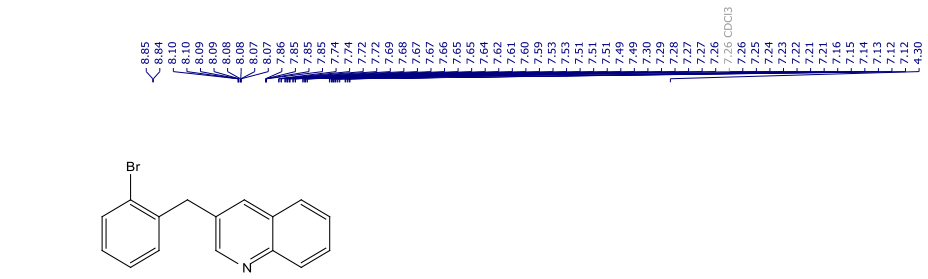


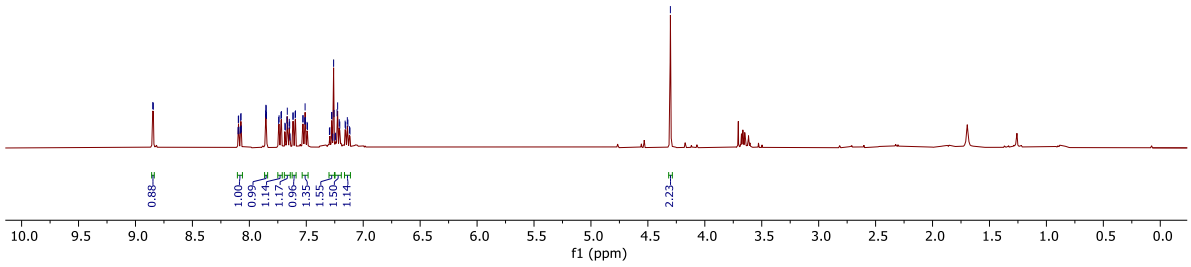


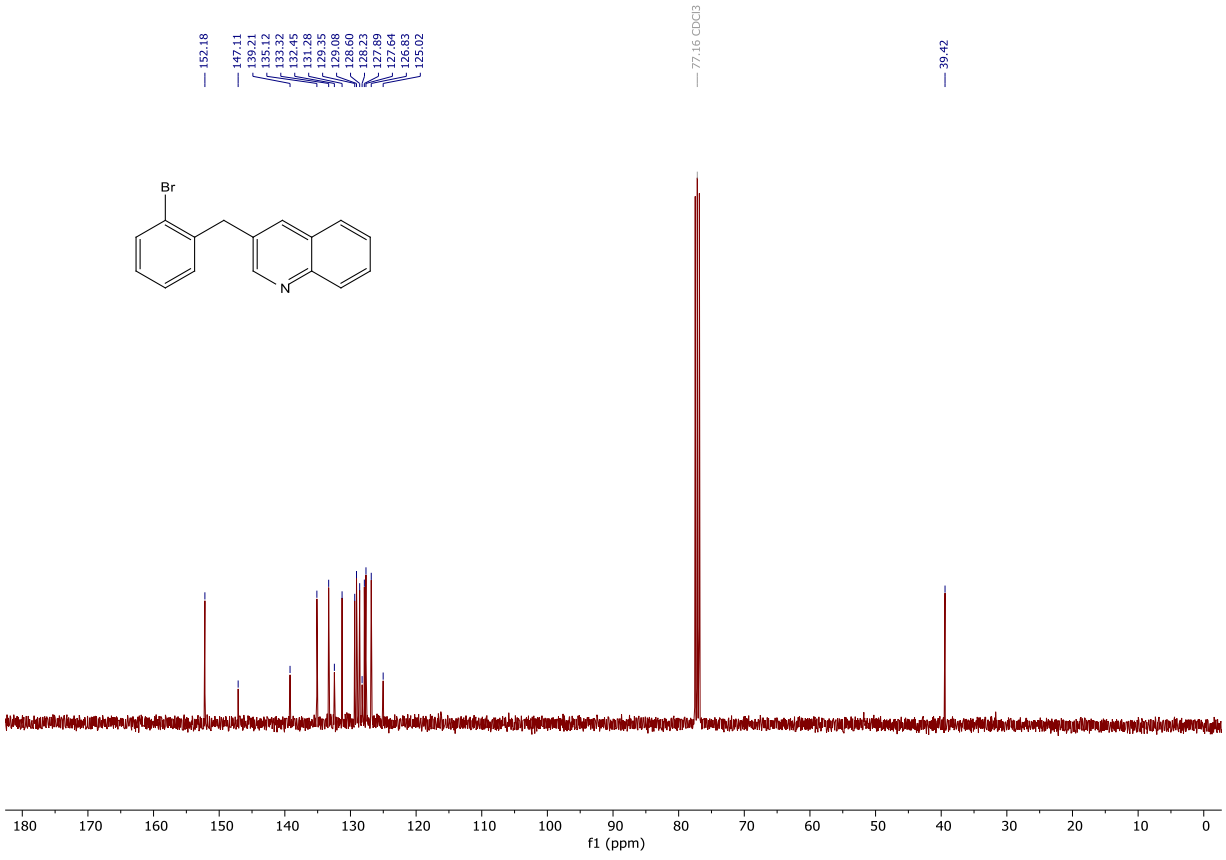




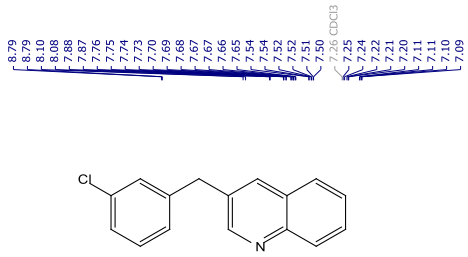
3-(2-Bromobenzyl)quinoline (6am)

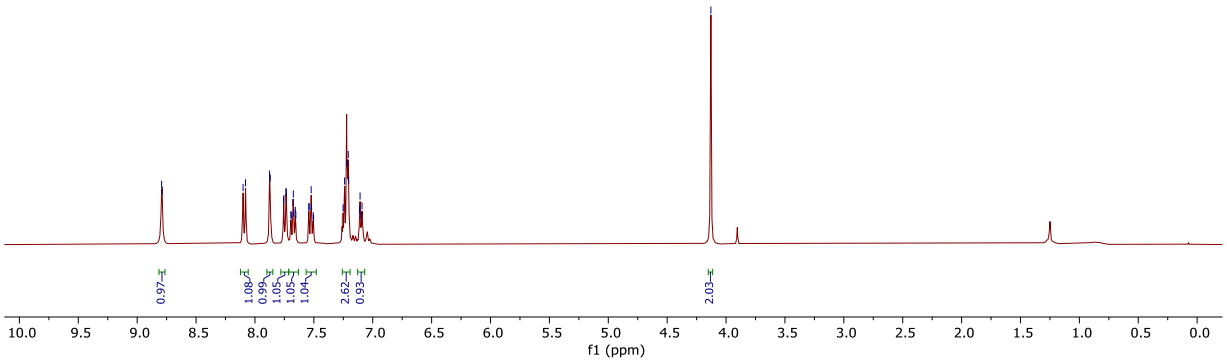


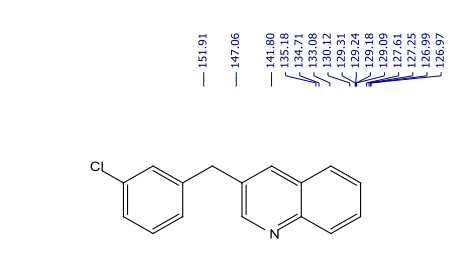


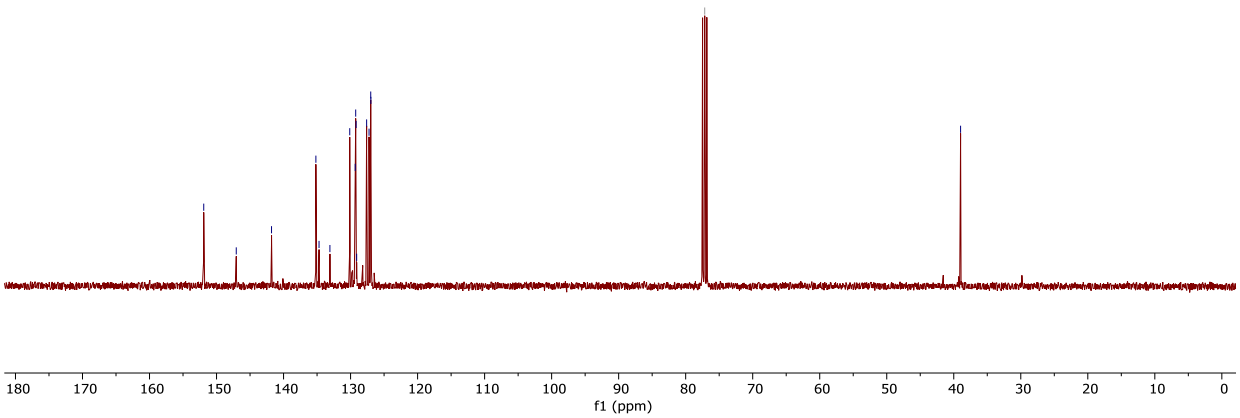


3-(3-Chlorobenzyl)quinoline (6an)

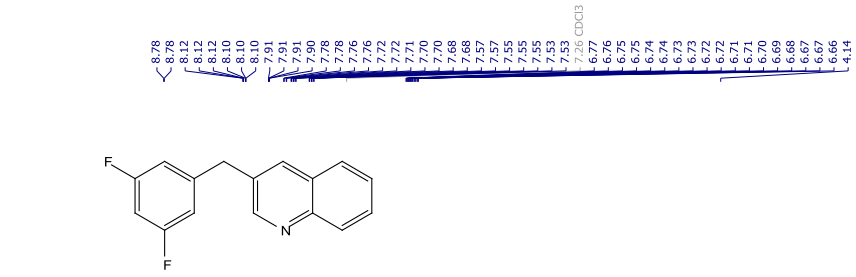


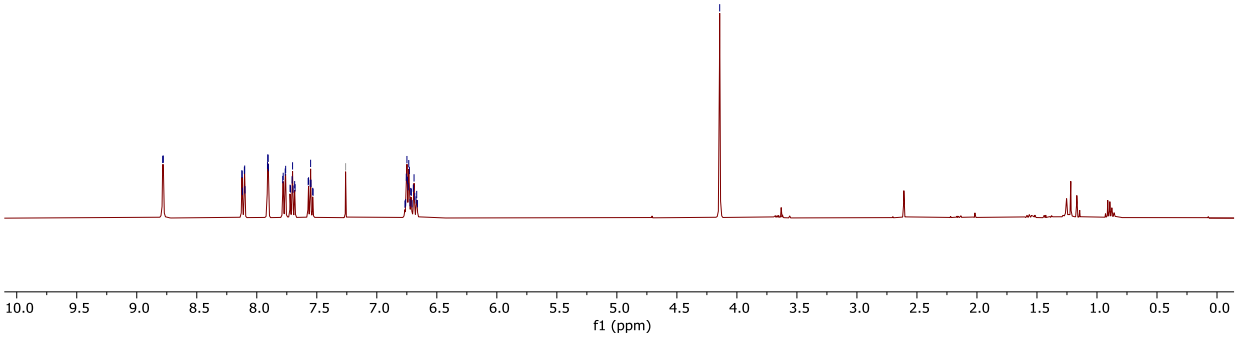


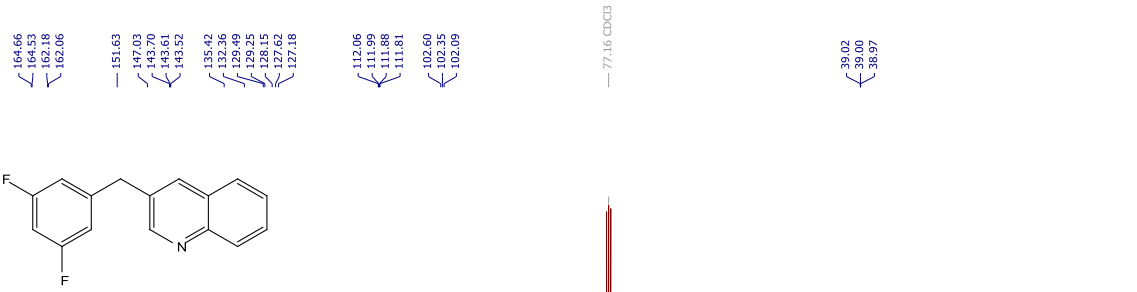


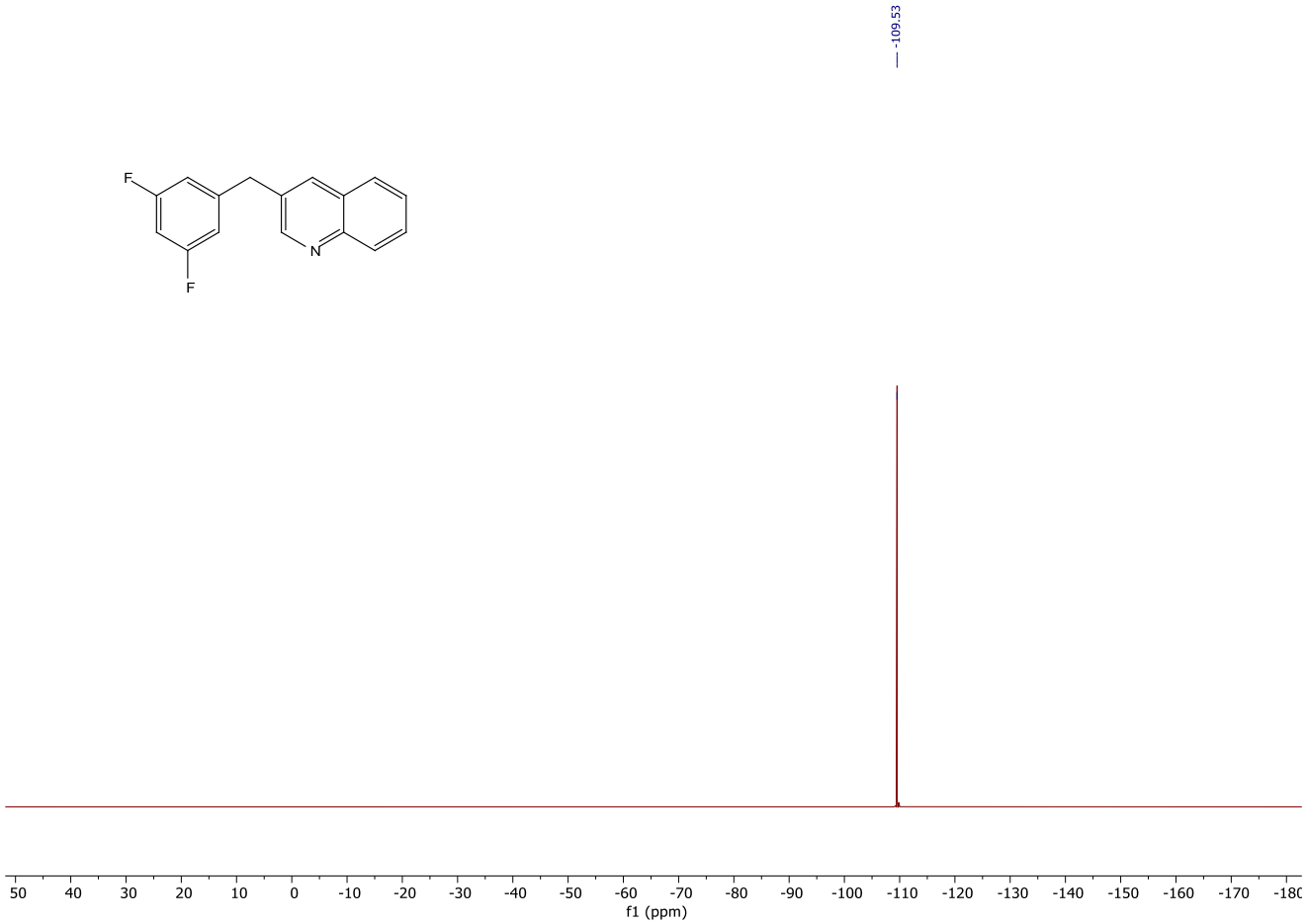


3-(3,5-Difluorobenzyl)quinoline (6ao)





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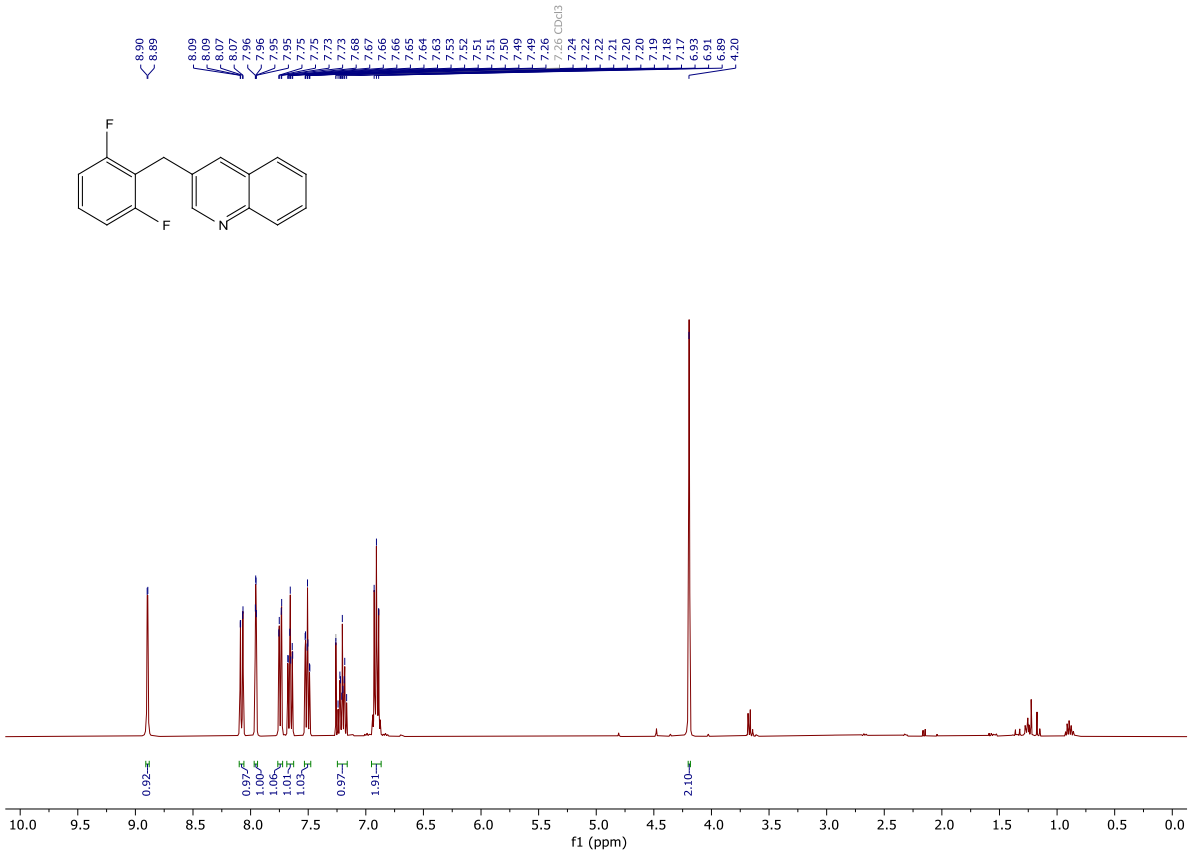
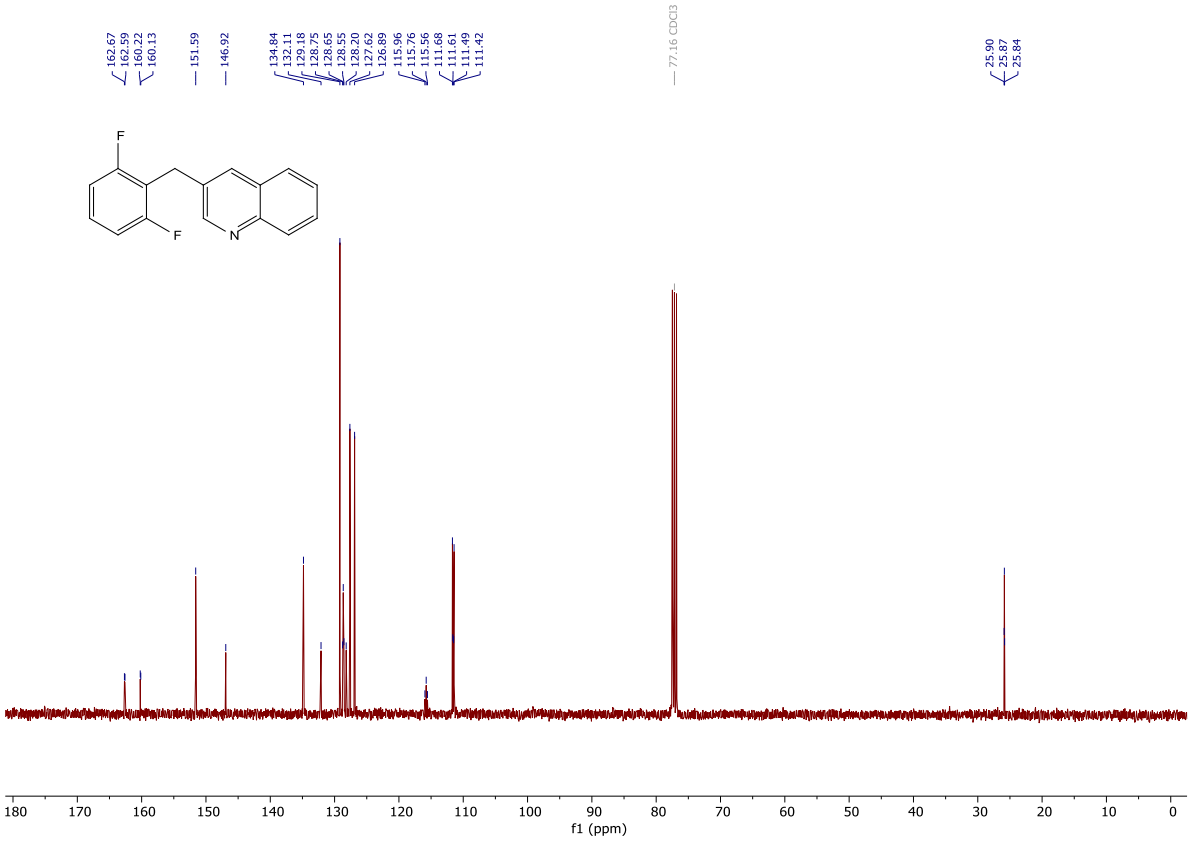
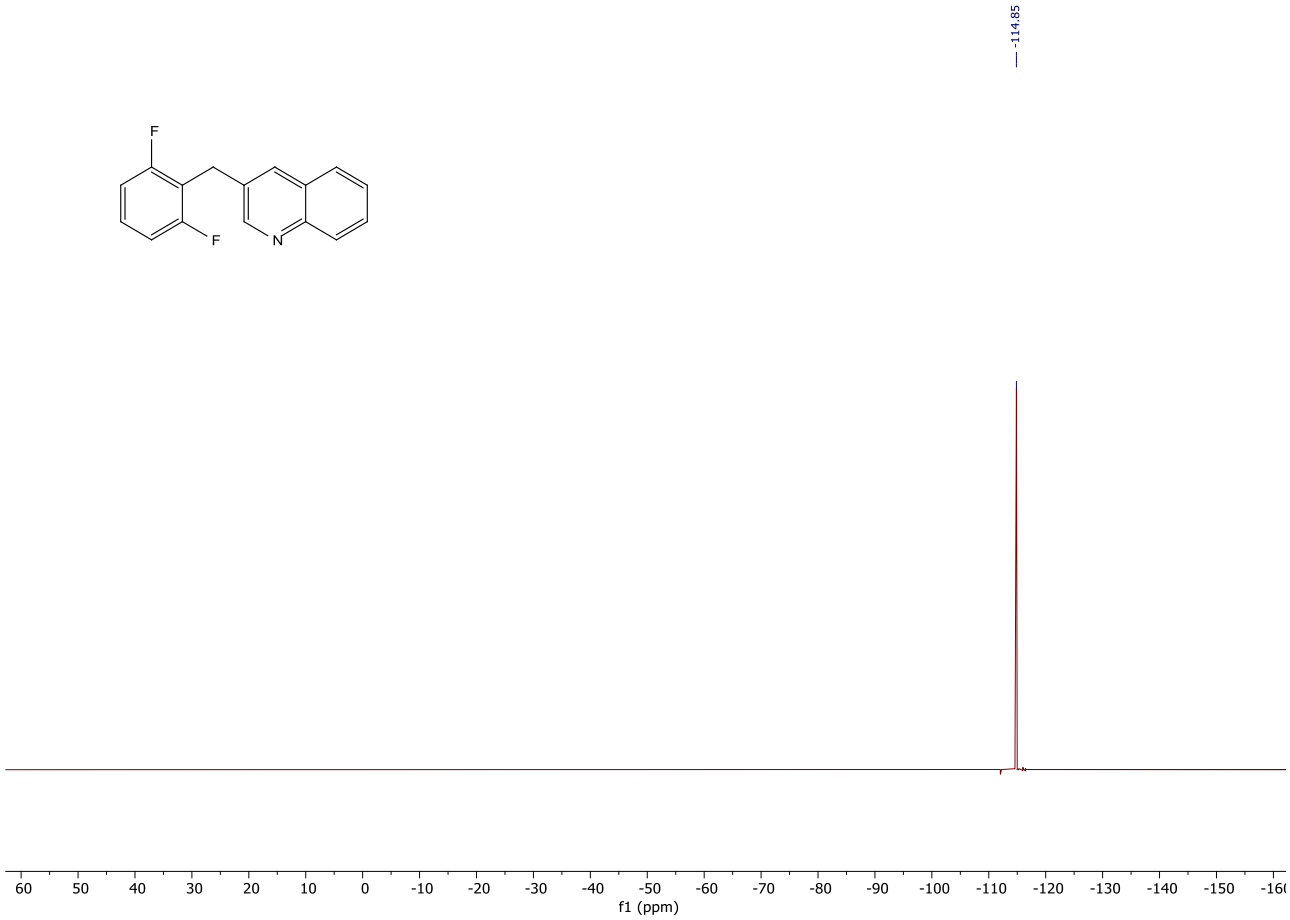
f1 (ppm)

3-(2,6-Difluorobenzyl)quinoline (6ap)



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-60
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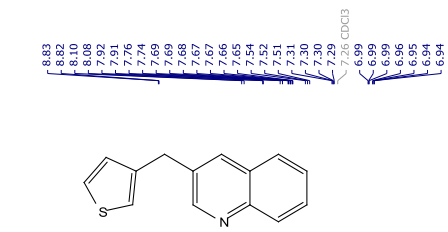
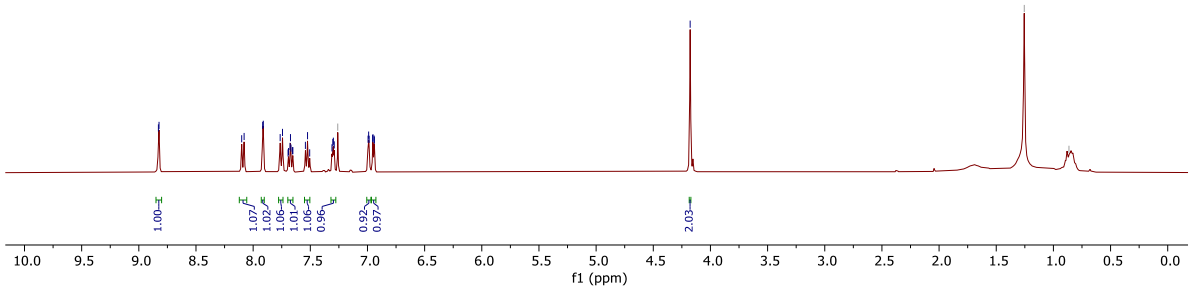
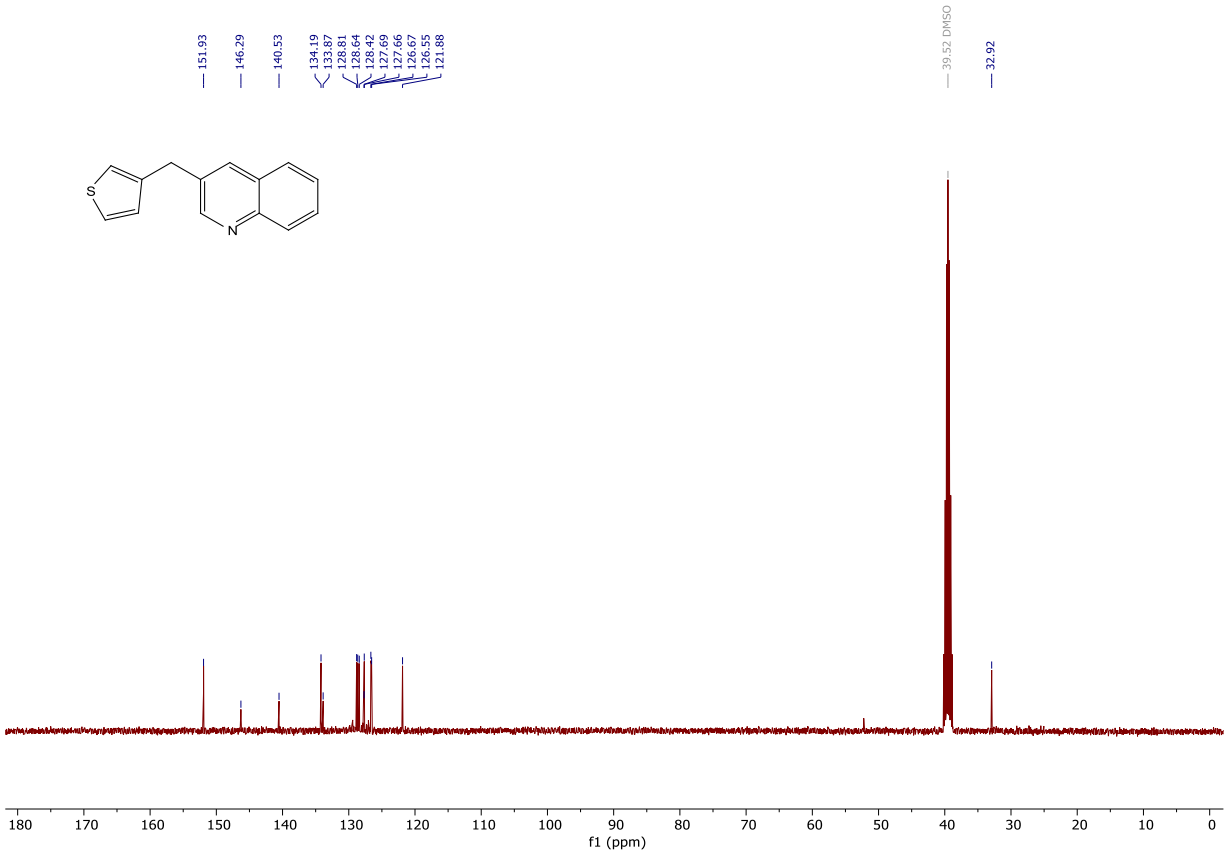
-140
-150
f1 (ppm)

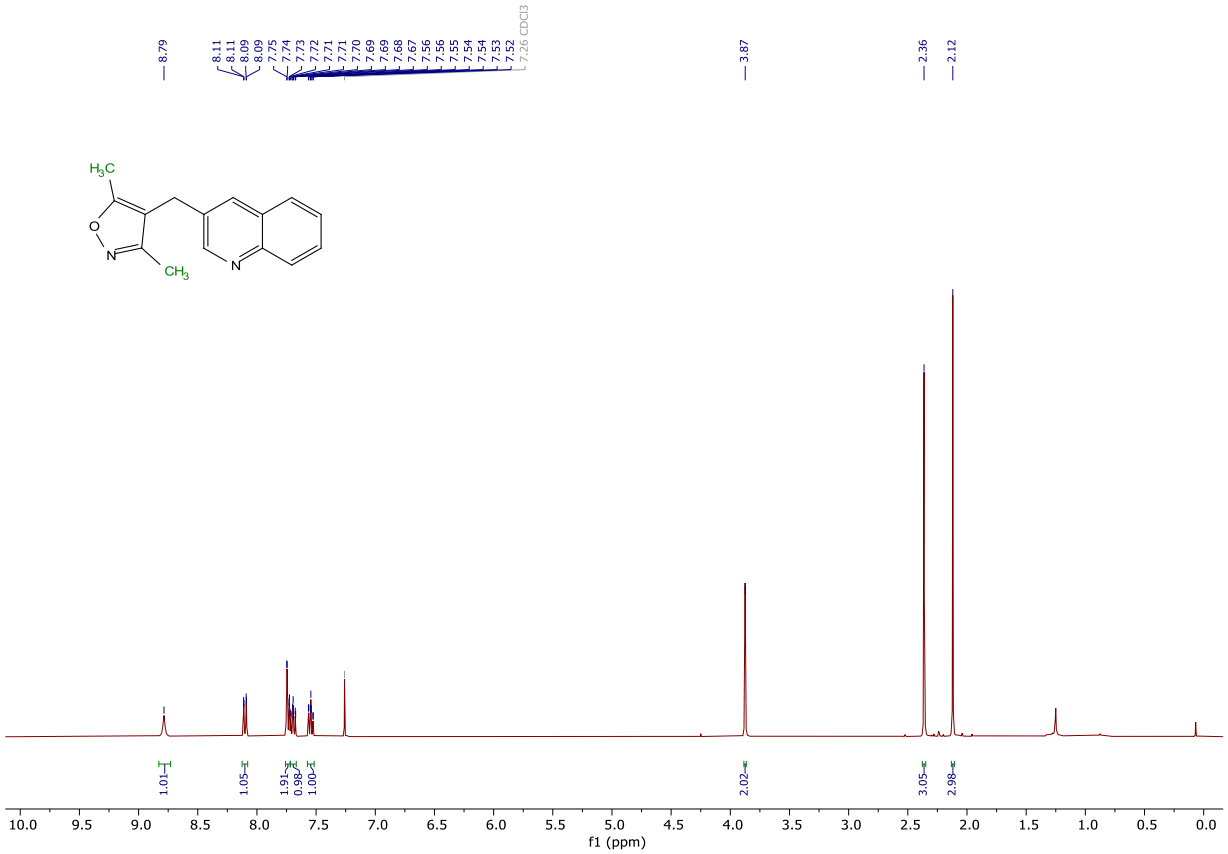
3-(Thiophen-3-ylmethyl)quinoline (6aq)

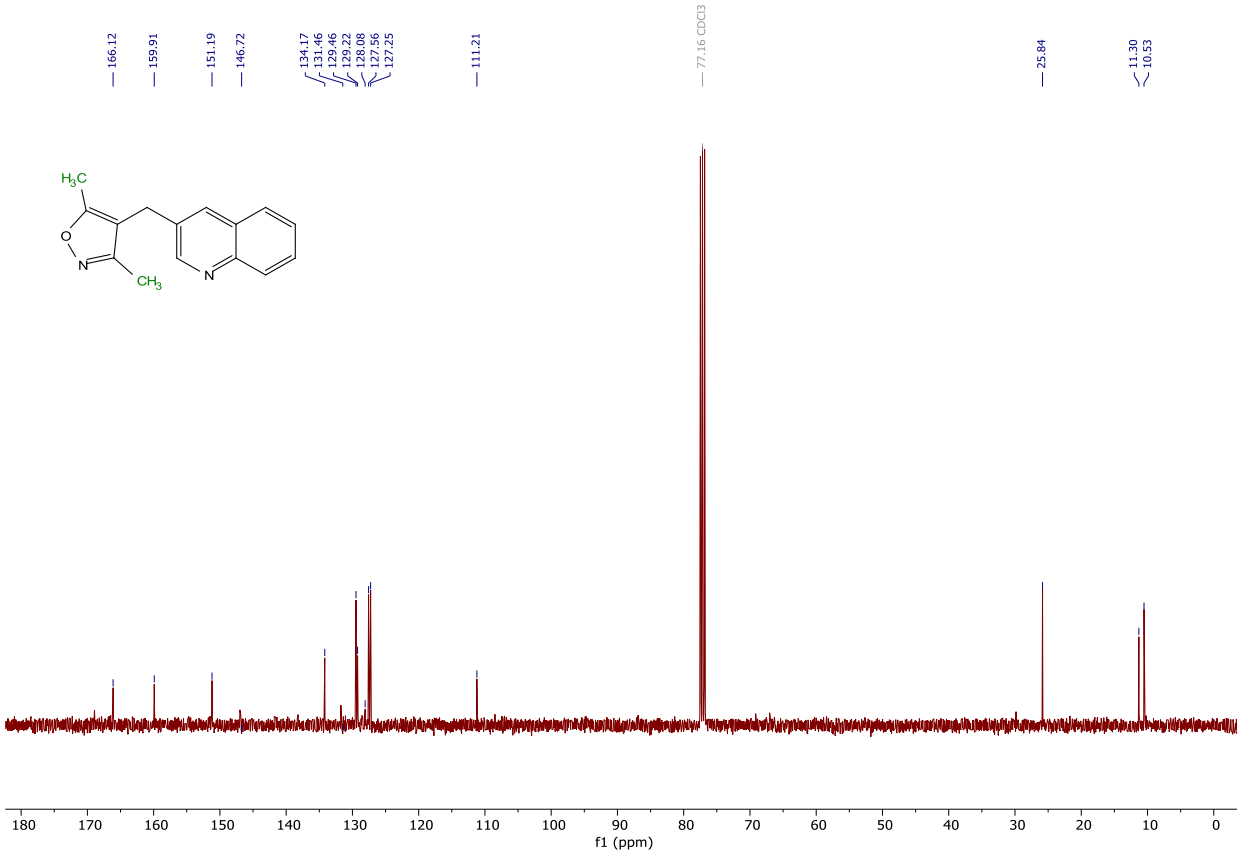




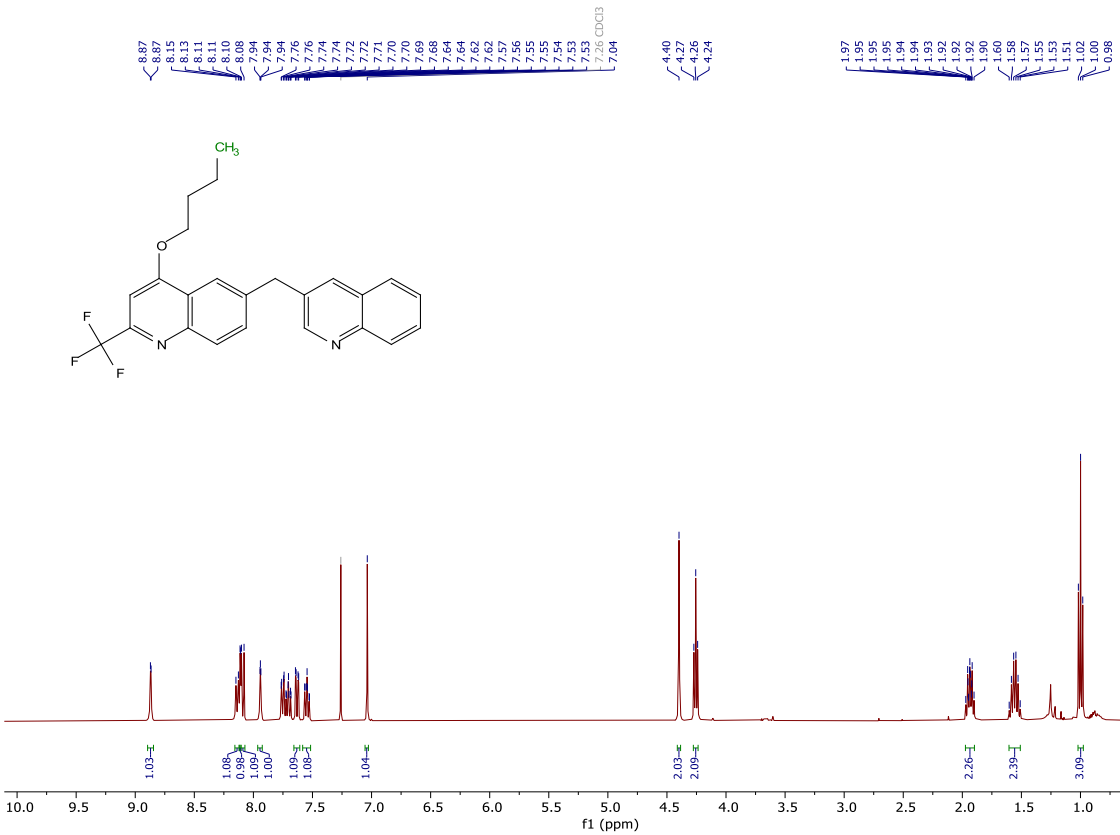


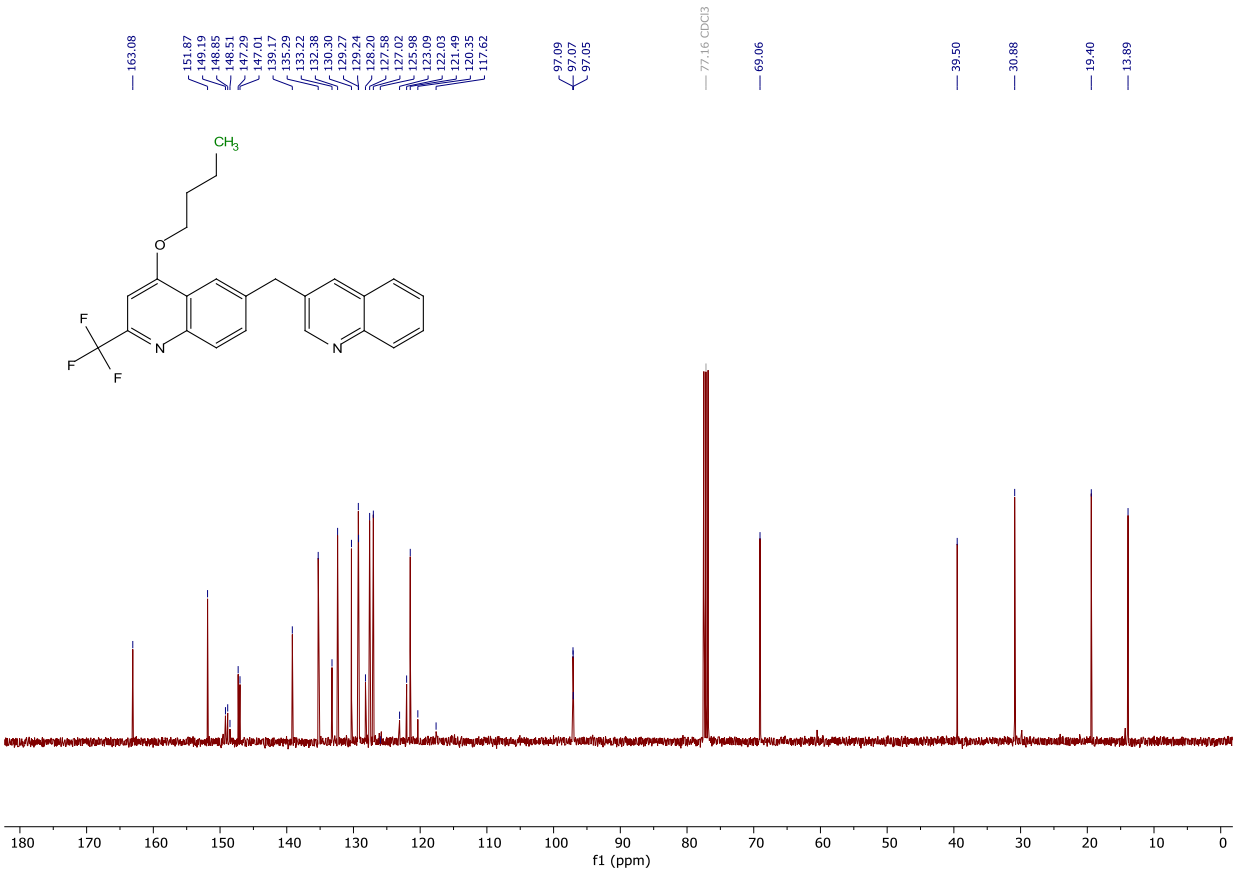
3,5-Dimethyl-4-(quinolin-3-ylmethyl)isoxazole (6ar)

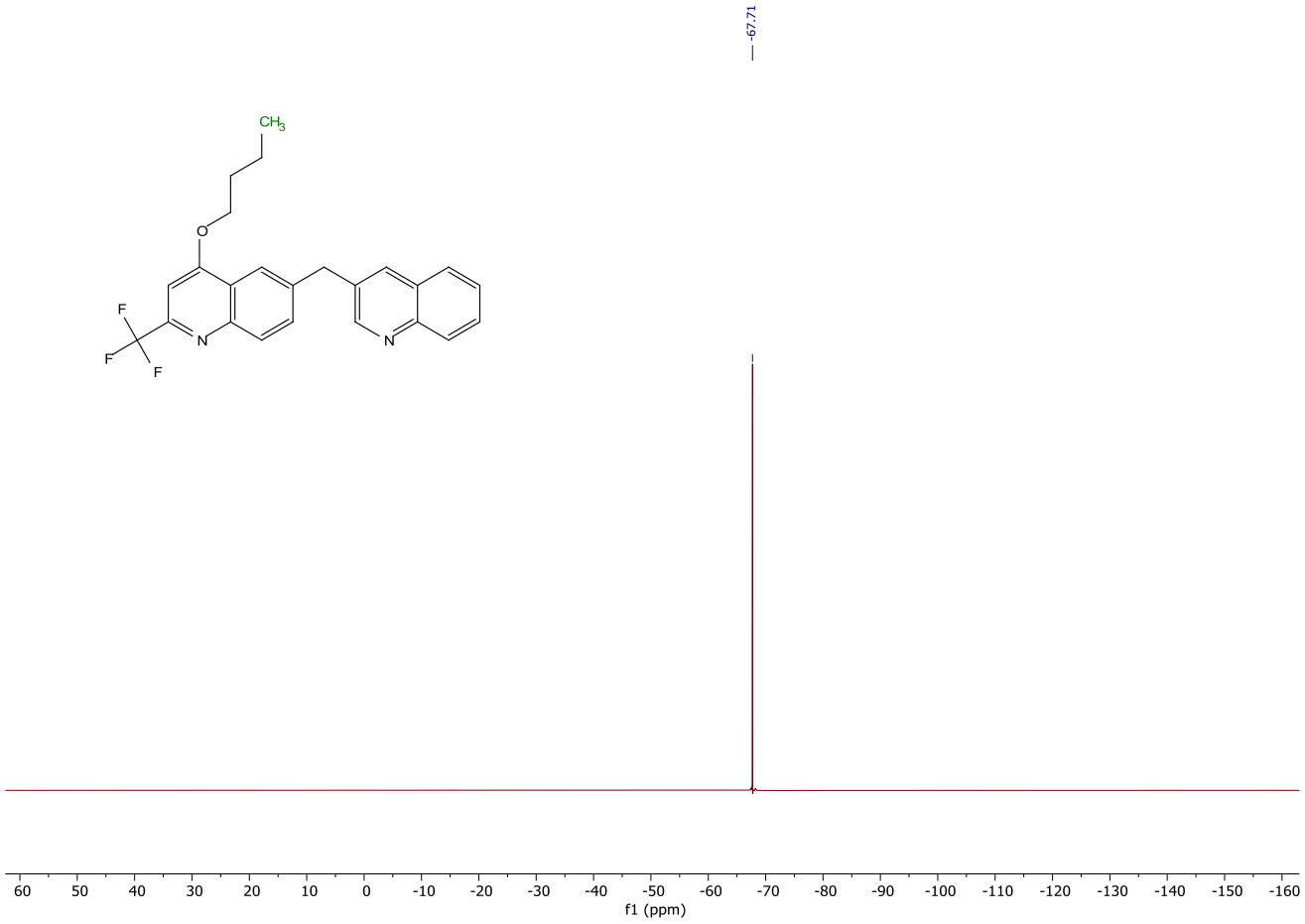




4-Butoxy-6-(quinolin-3-ylmethyl)-2-(trifluoromethyl)quinoline (6as)






-67.71
CH3
O
F
F
F
N
N
60
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40
30
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-30
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-50
-60
-70
-80
-90
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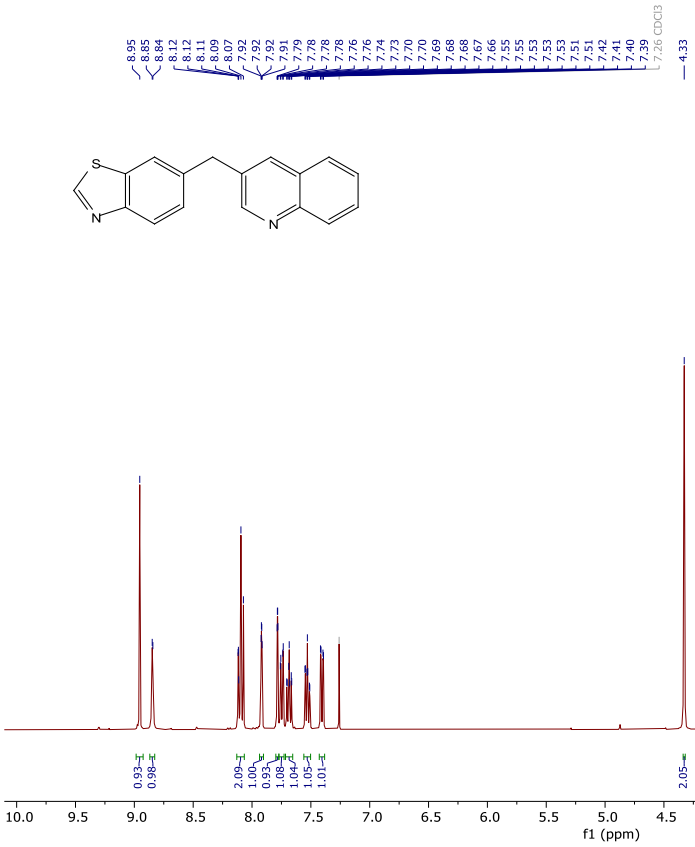
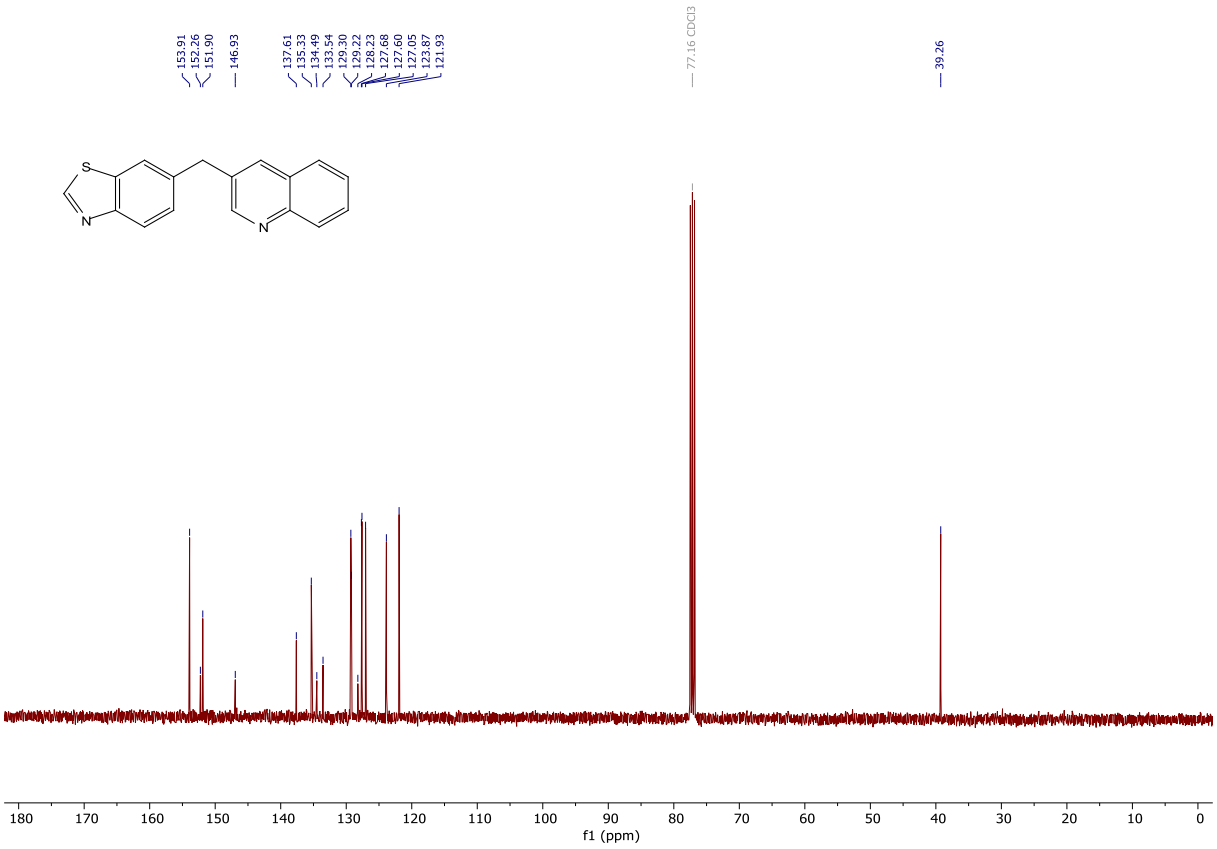
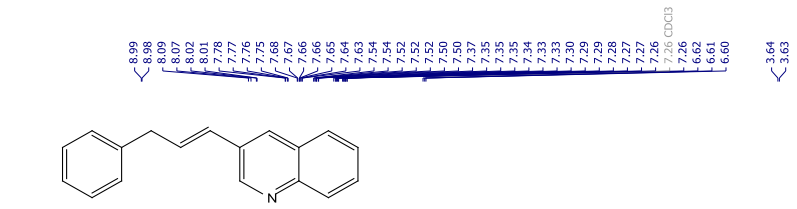
-140
-150
-160
f1 (ppm)

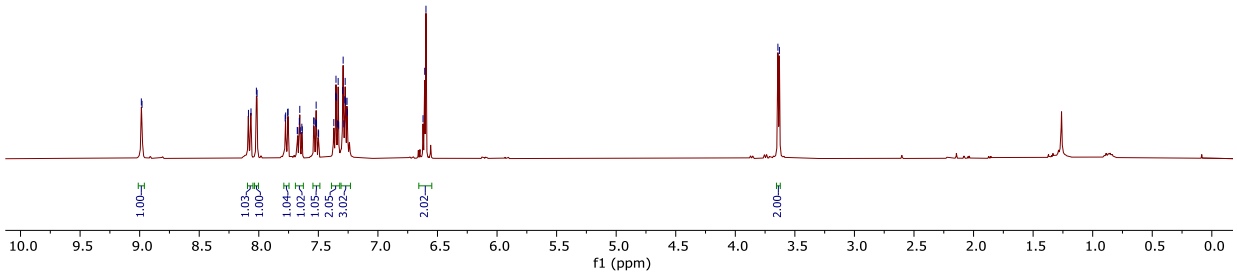
6-(Quinolin-3-ylmethyl)benzo[d]thiazole (6at)

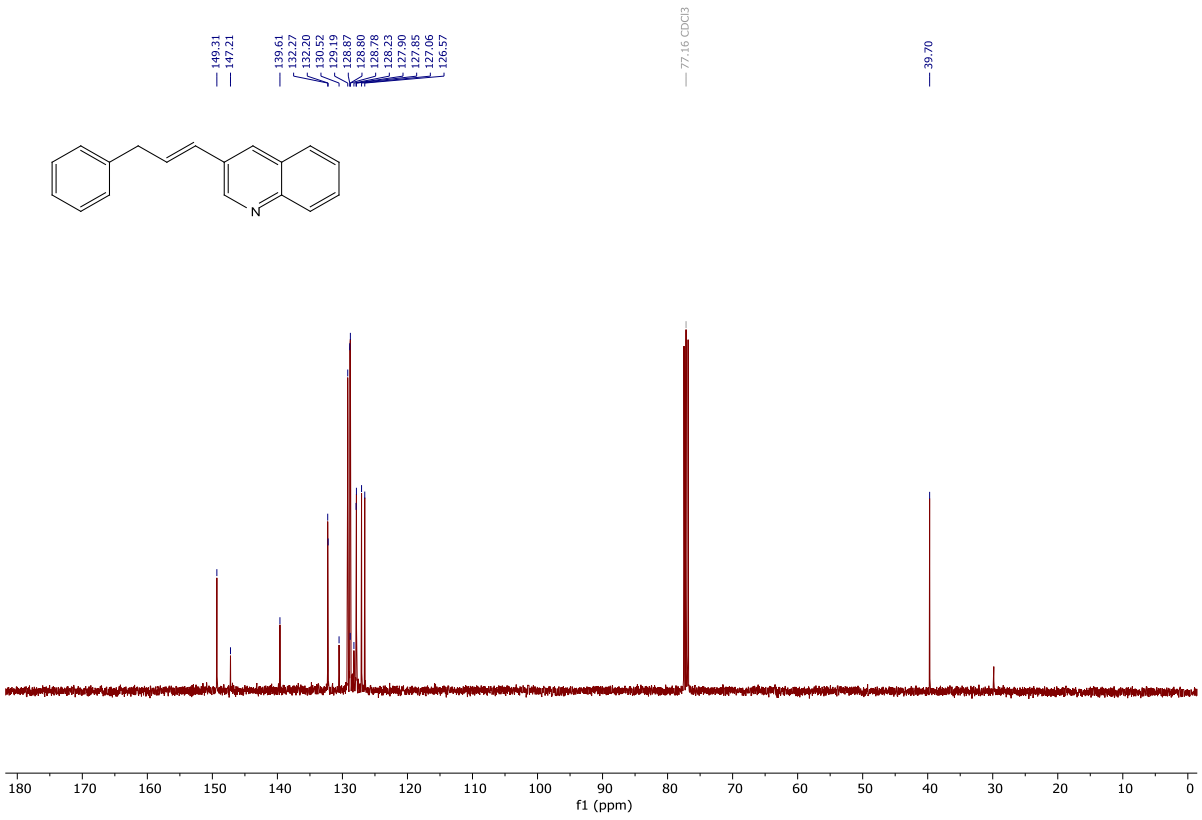




(E)-3-(3-phenylprop-1-en-1-yl)quinoline (6au’)

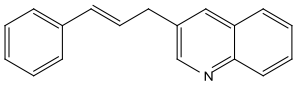


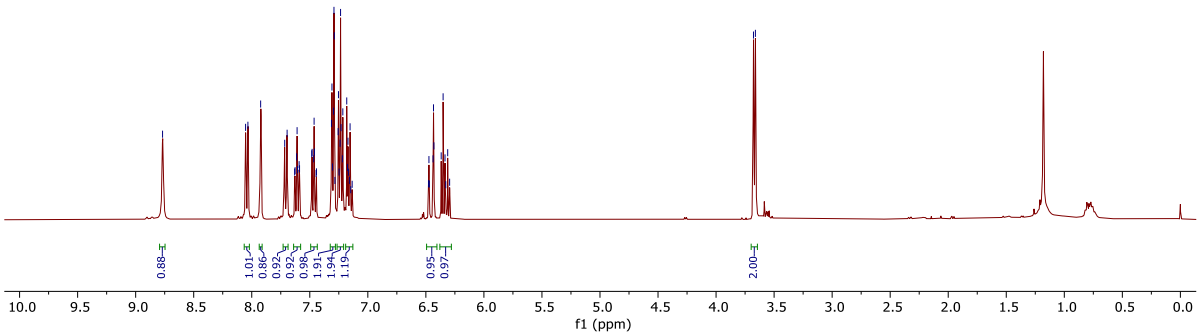




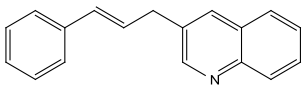
3-Cinnamylquinoline (6au”)

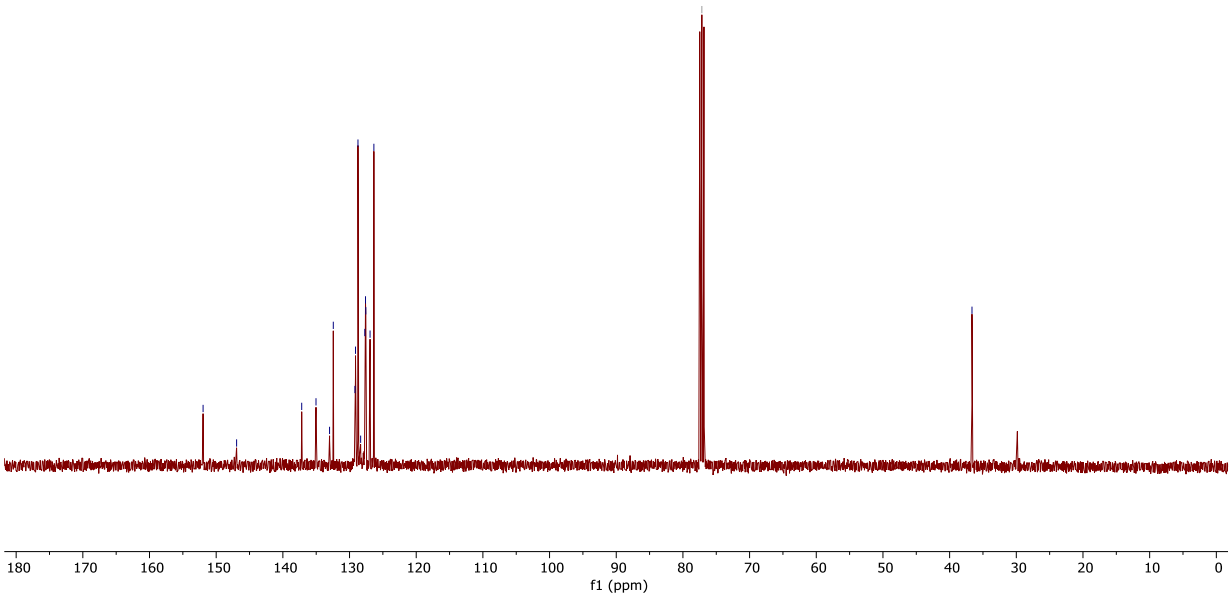




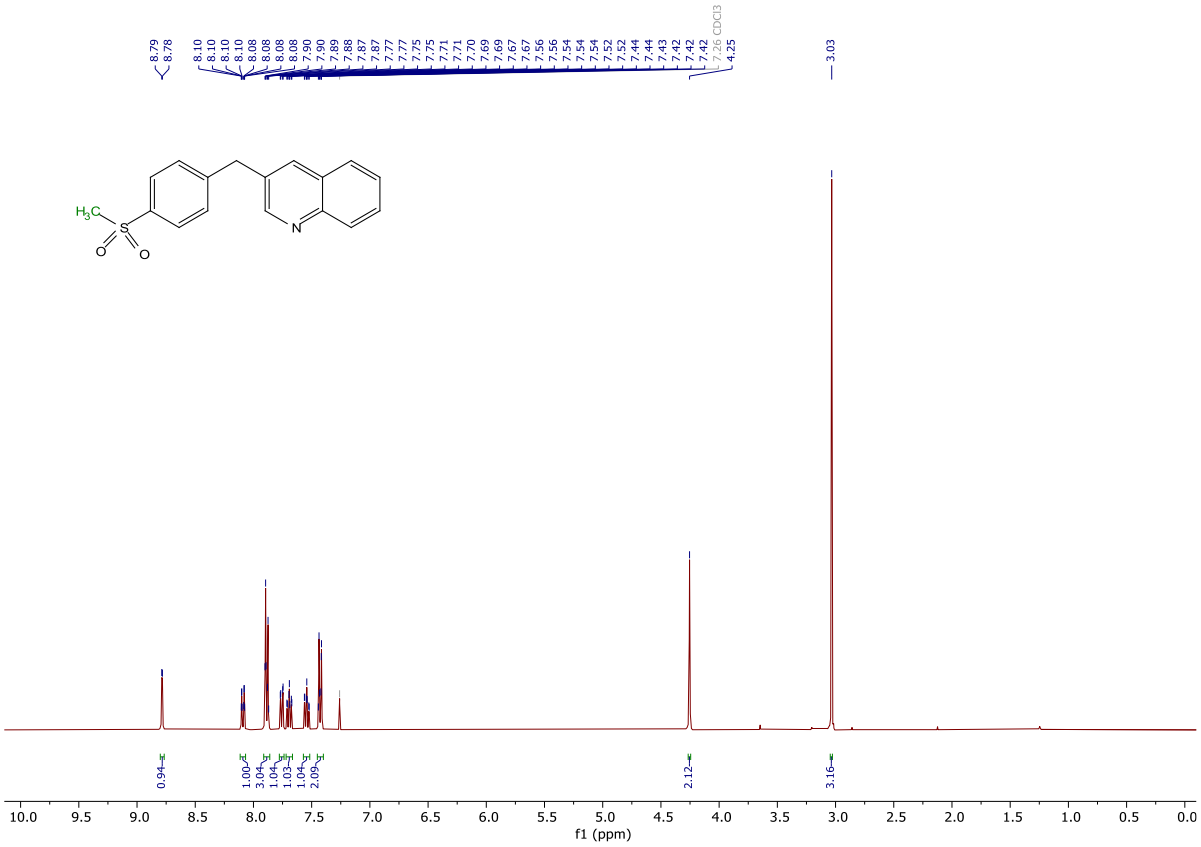


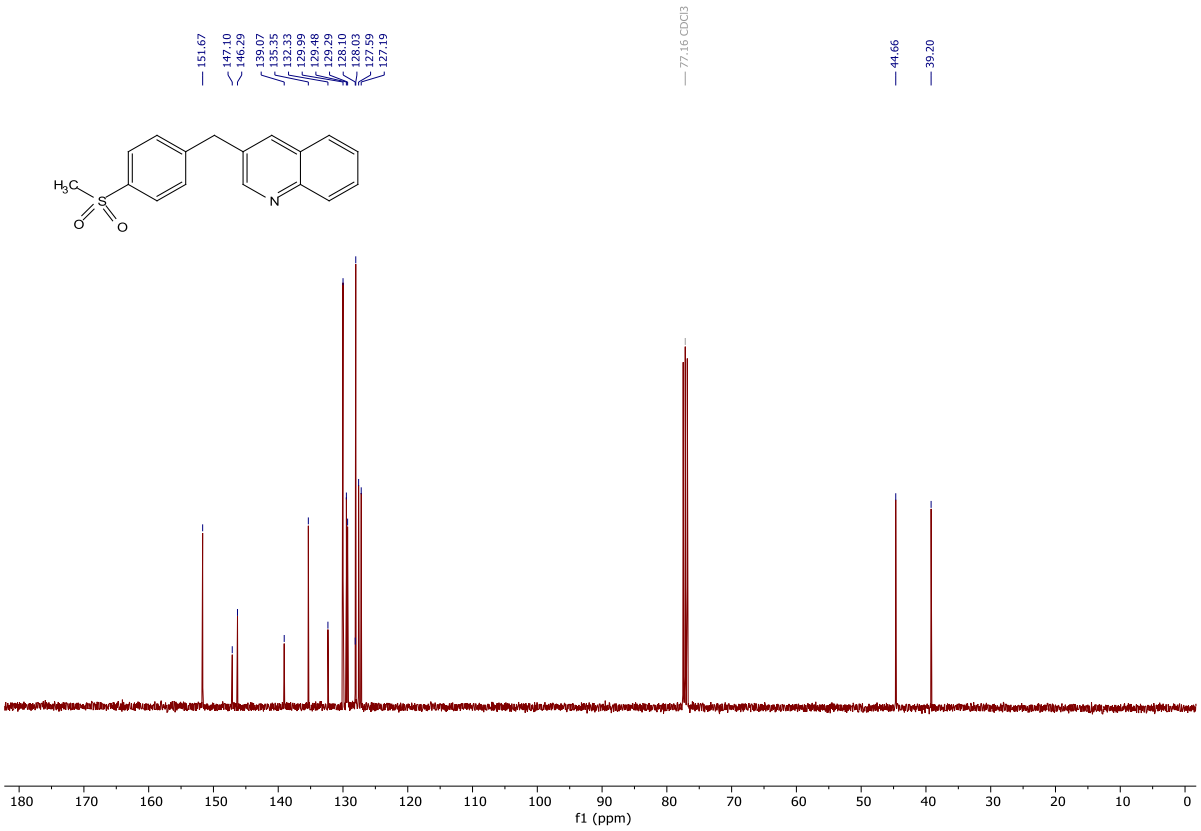




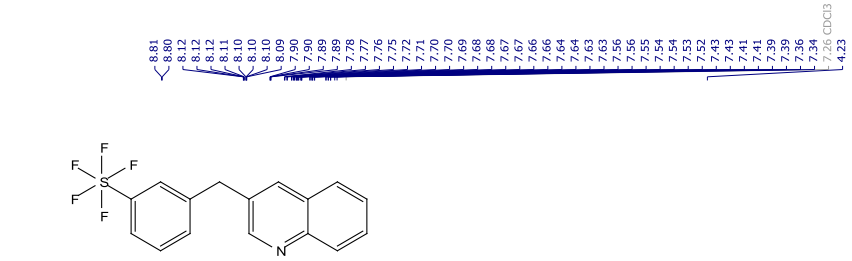


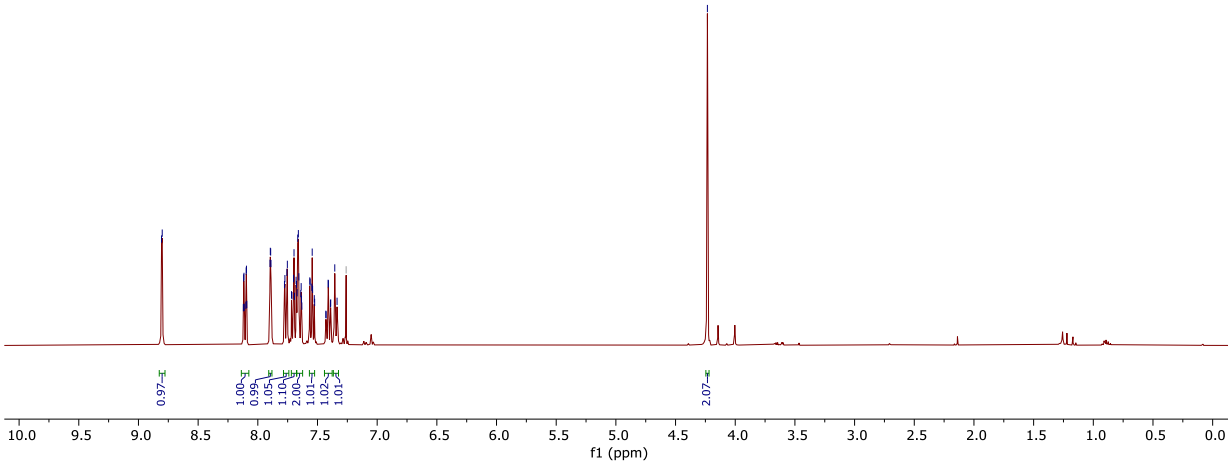
3-(4-(Methylsulfonyl)benzyl)quinoline (6av)



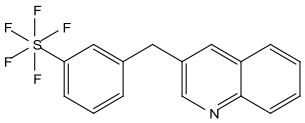


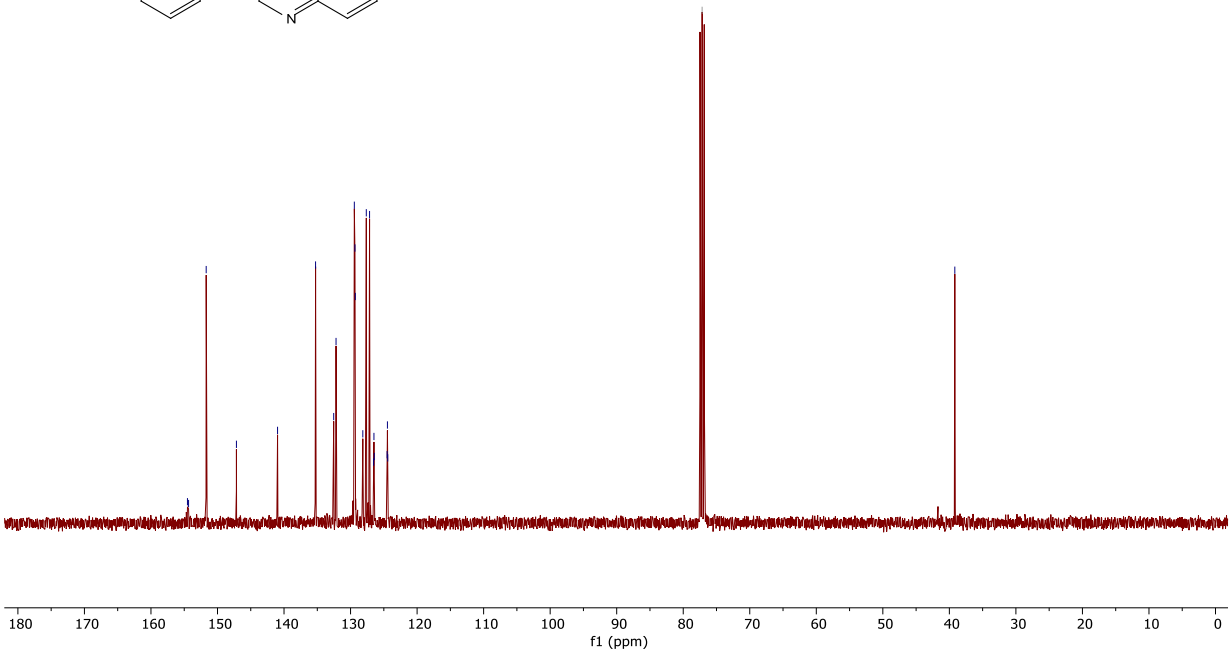
3-(3-(Pentafluorothio)benzyl)quinoline (6aw)

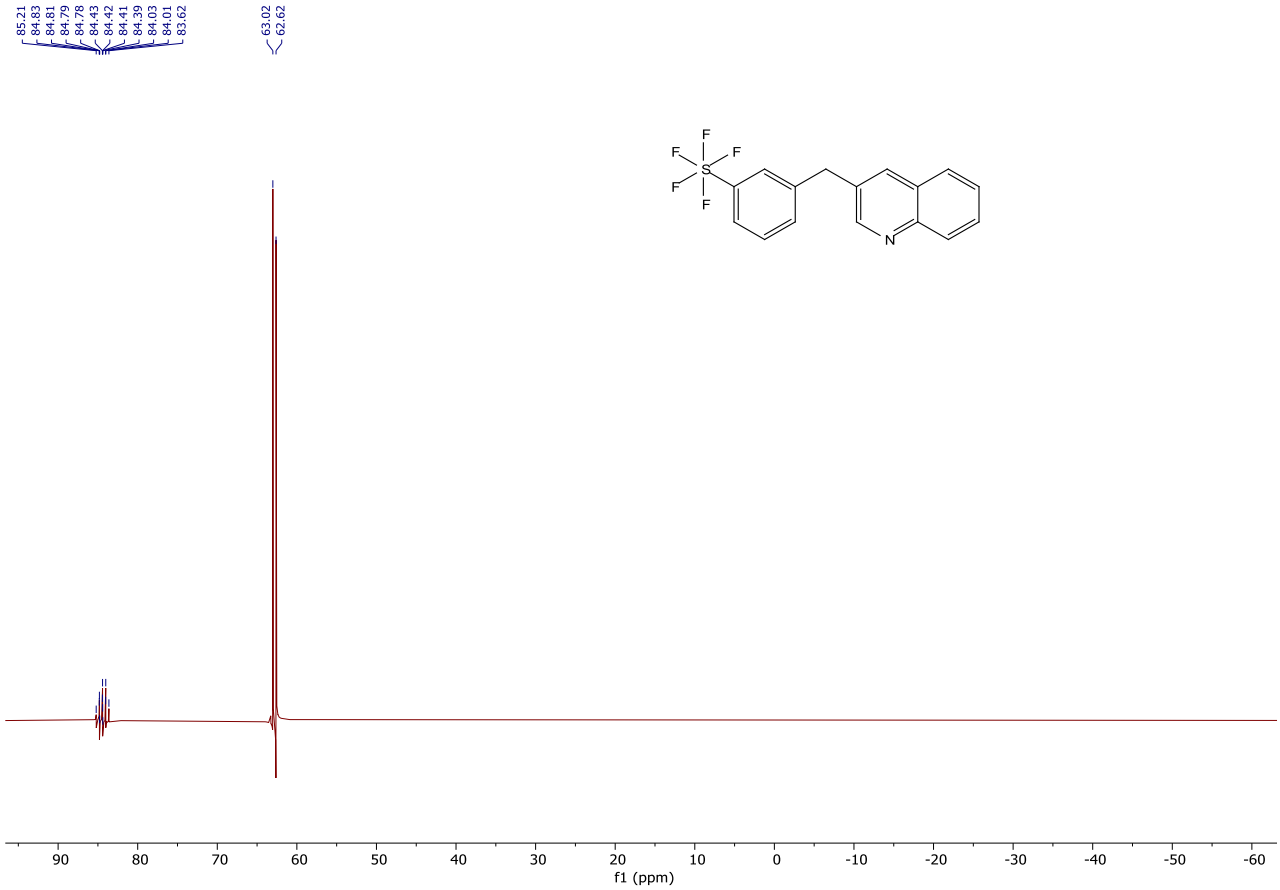








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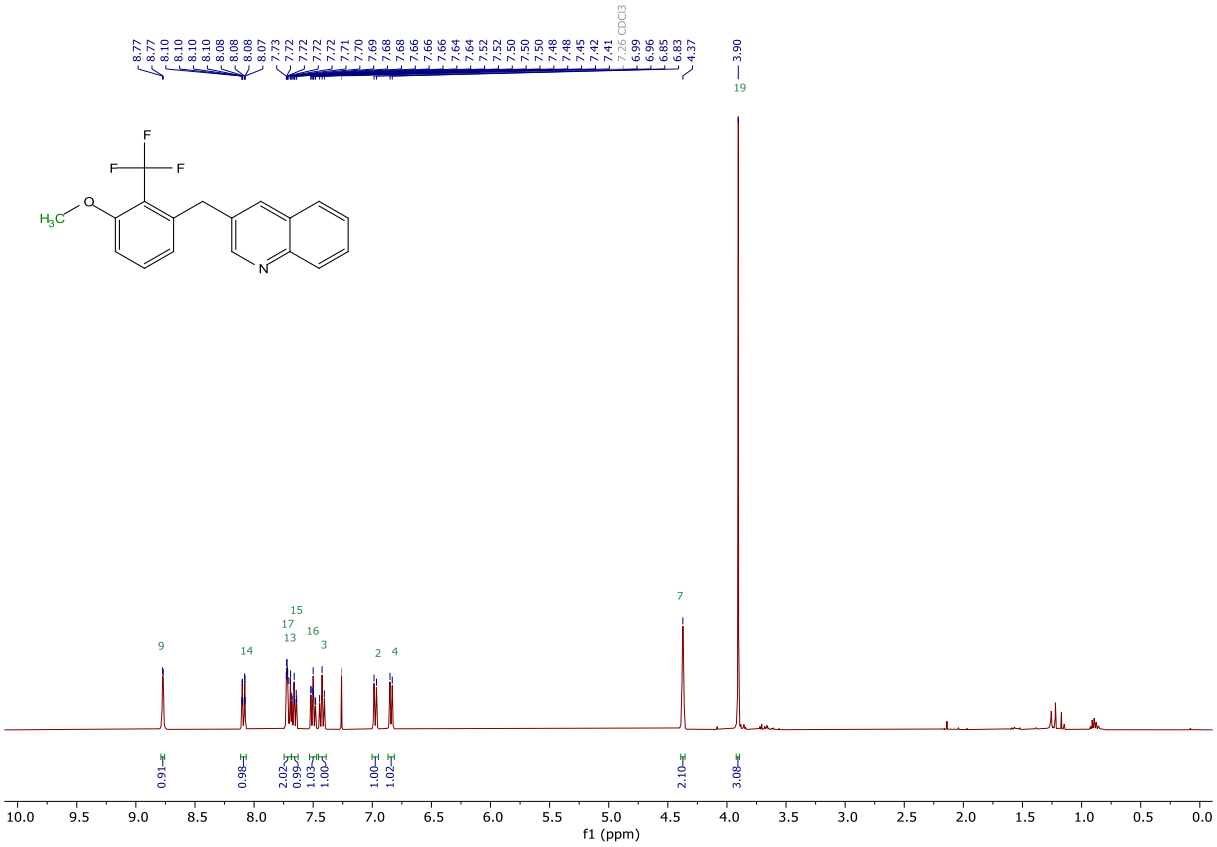
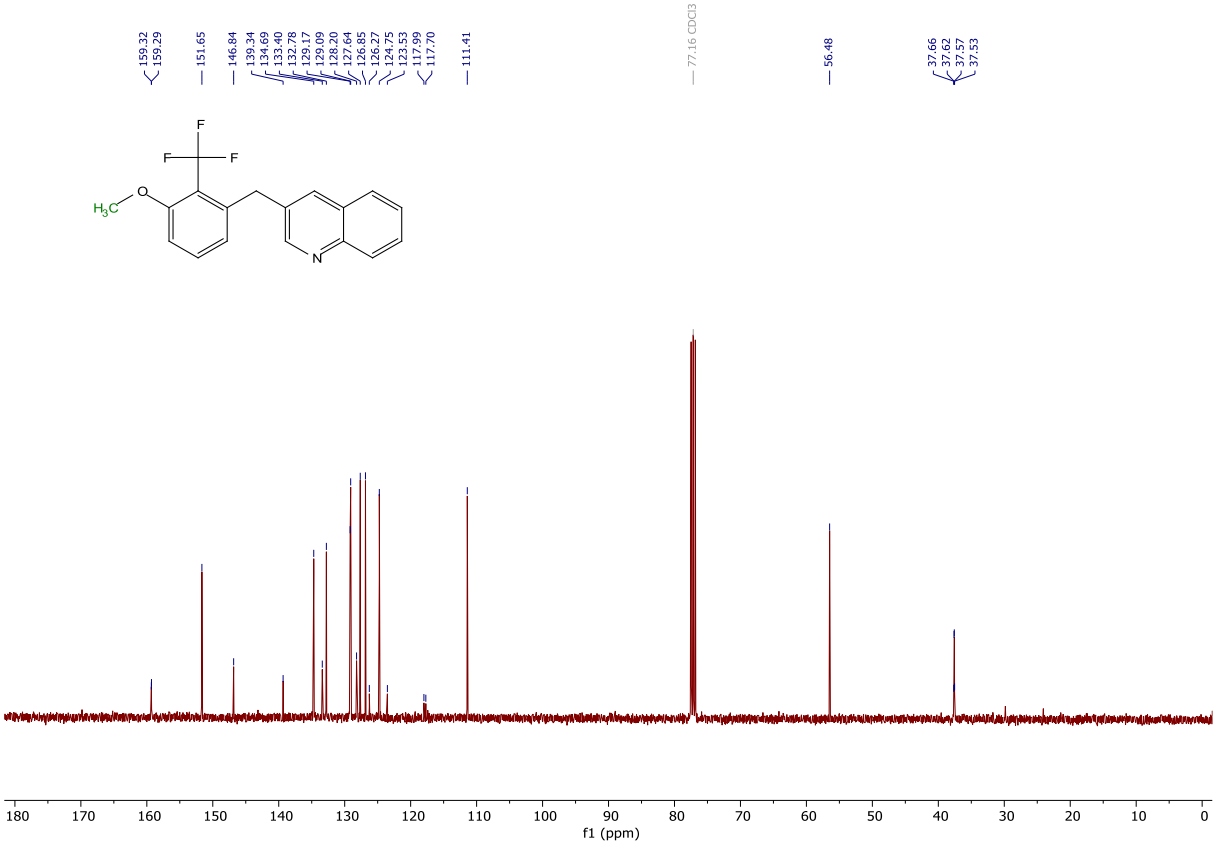
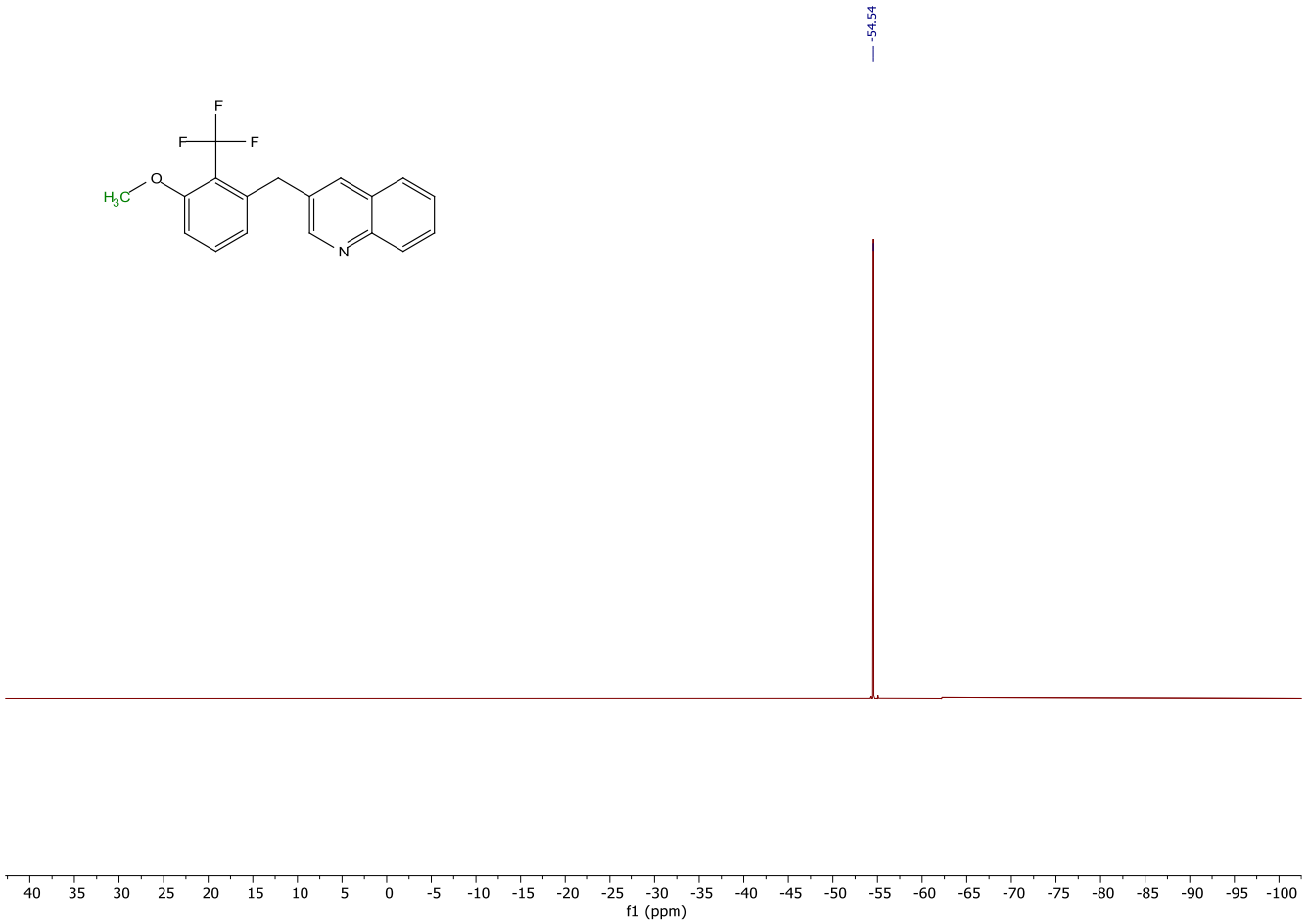
84.81
84.79
84.78
84.43
84.42
84.41
84.39
84.03
84.01
83.62
63.02
62.62
F
F
S
F
F
F
N
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
f1 (ppm)

3-(3-Methoxy-2-(trifluoromethyl)benzyl)quinoline (6ax)



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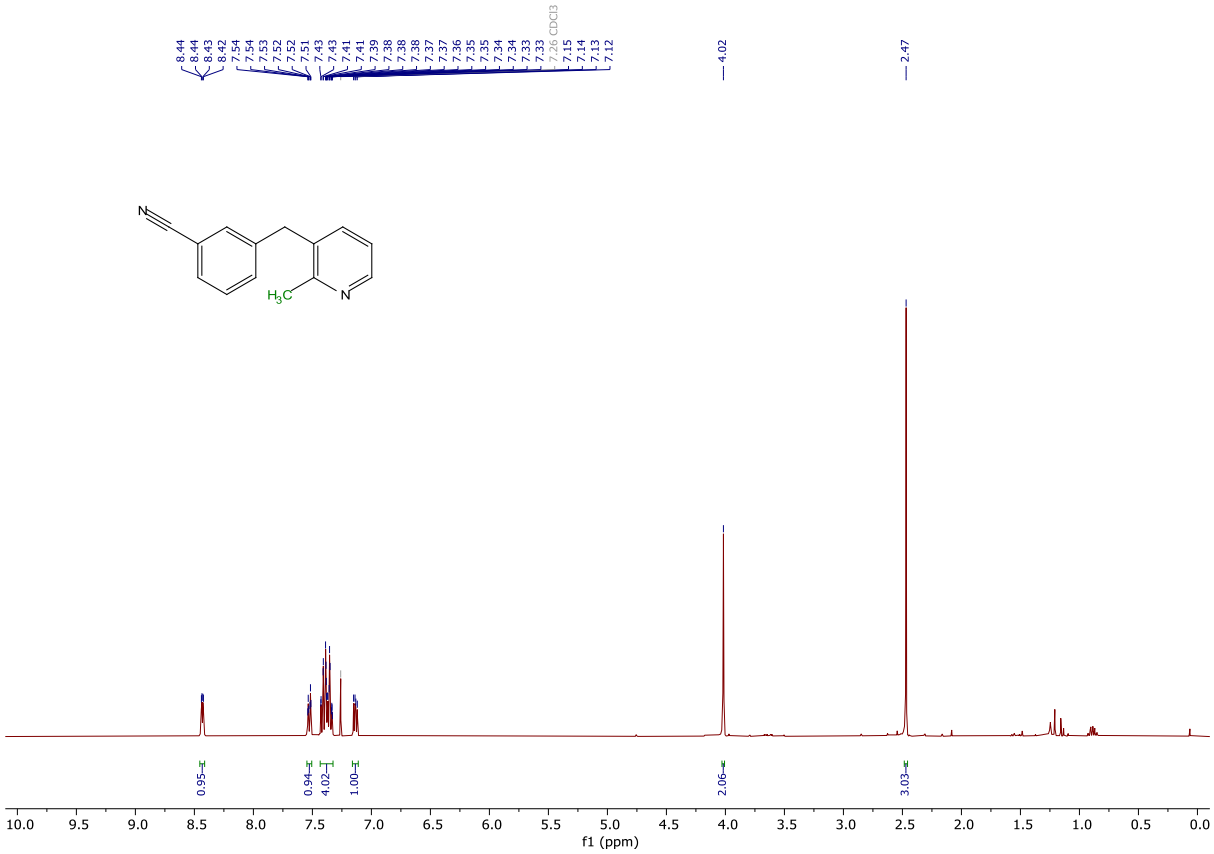
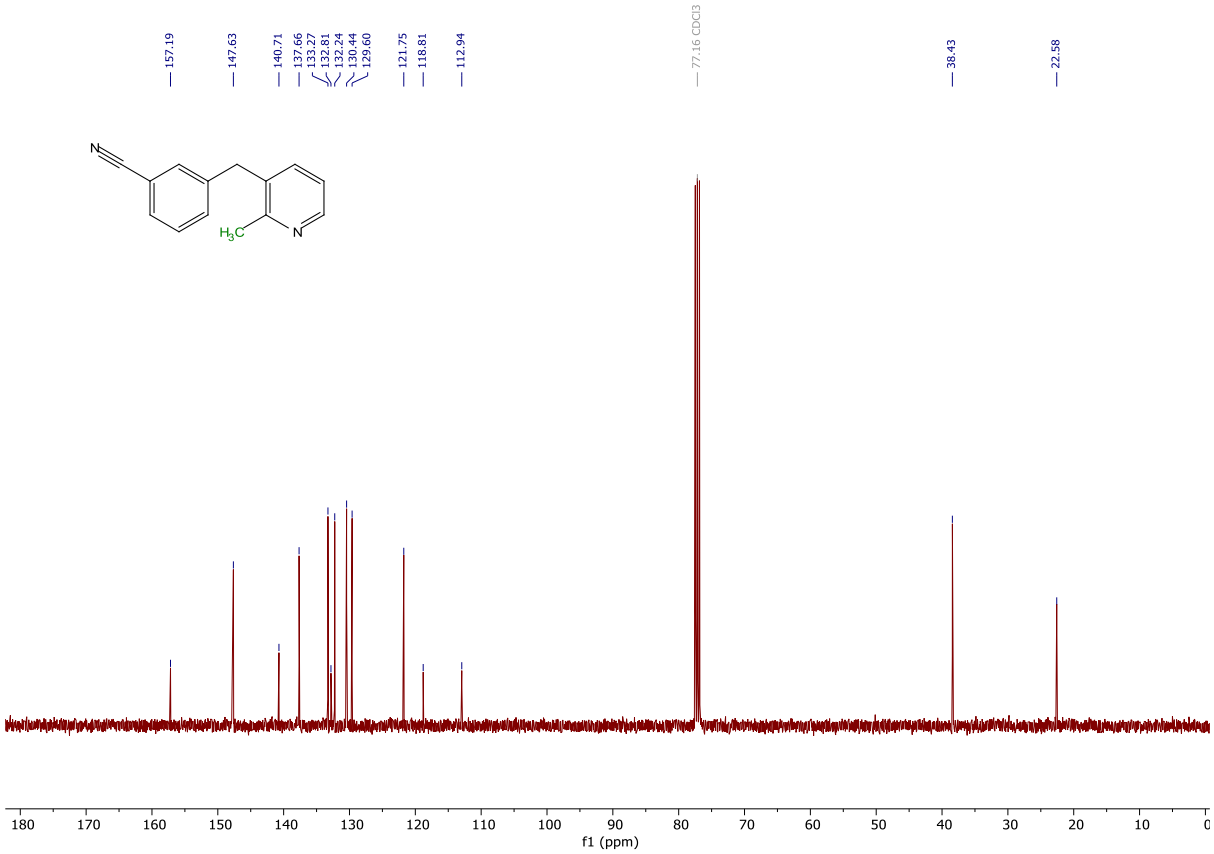
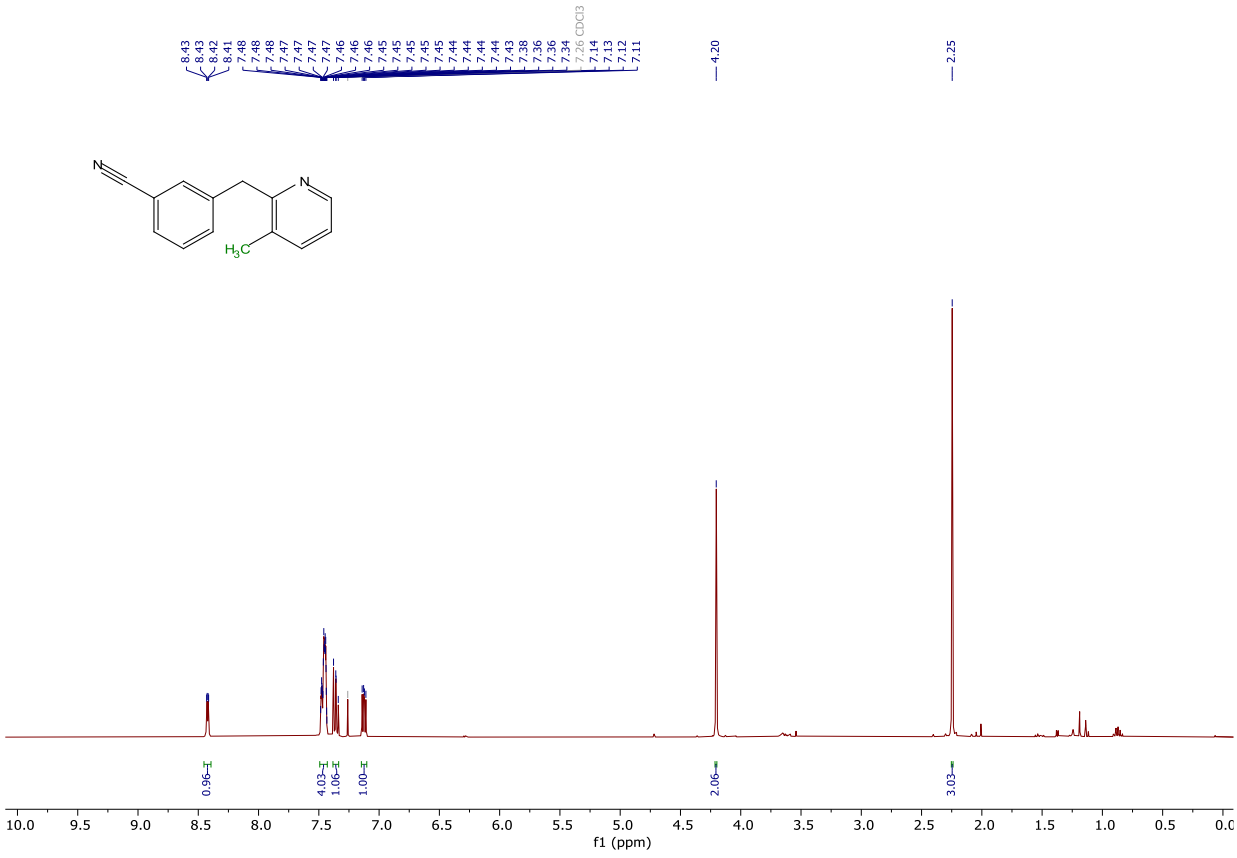
F
F
F
O
H3C
N
40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100
f1 (ppm)

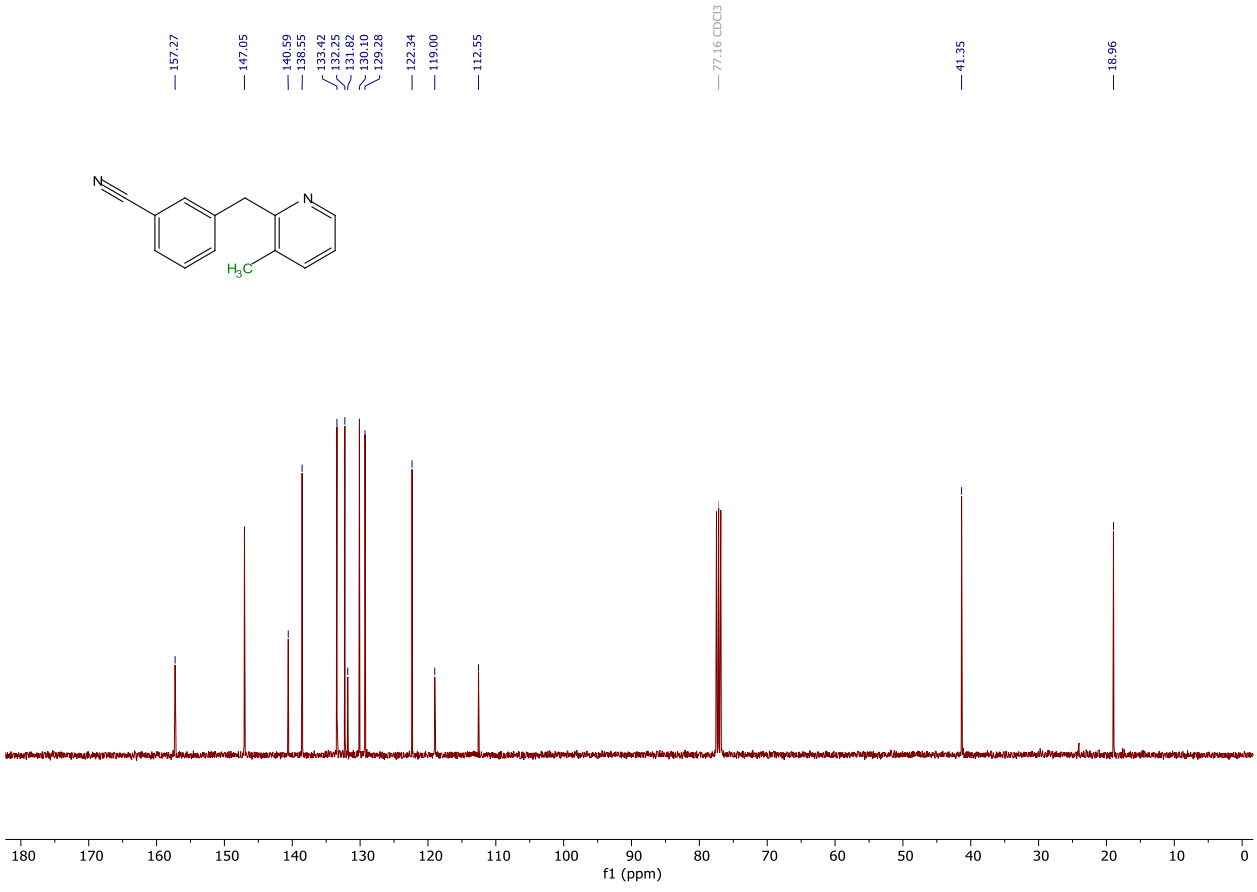
3-((2-Methylpyridin-3-yl)methyl)benzonitrile (6ay)



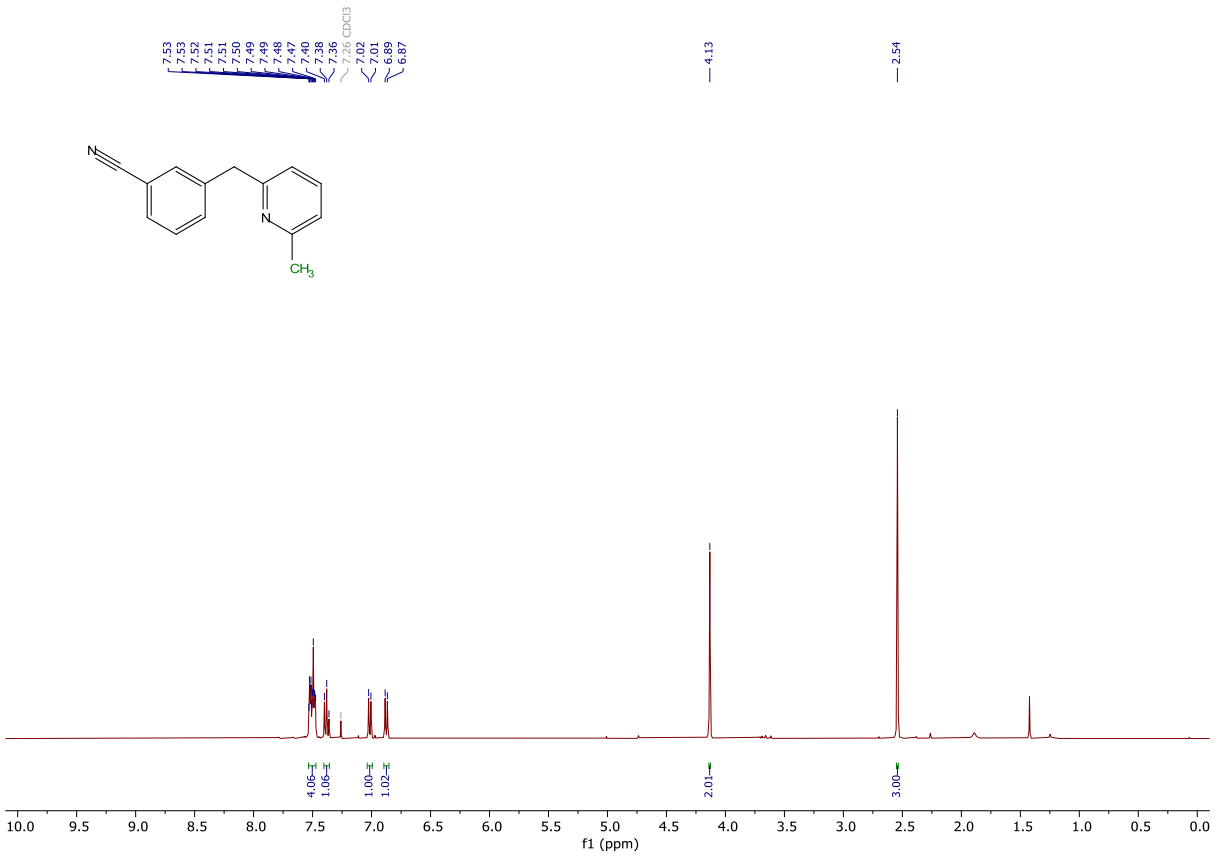


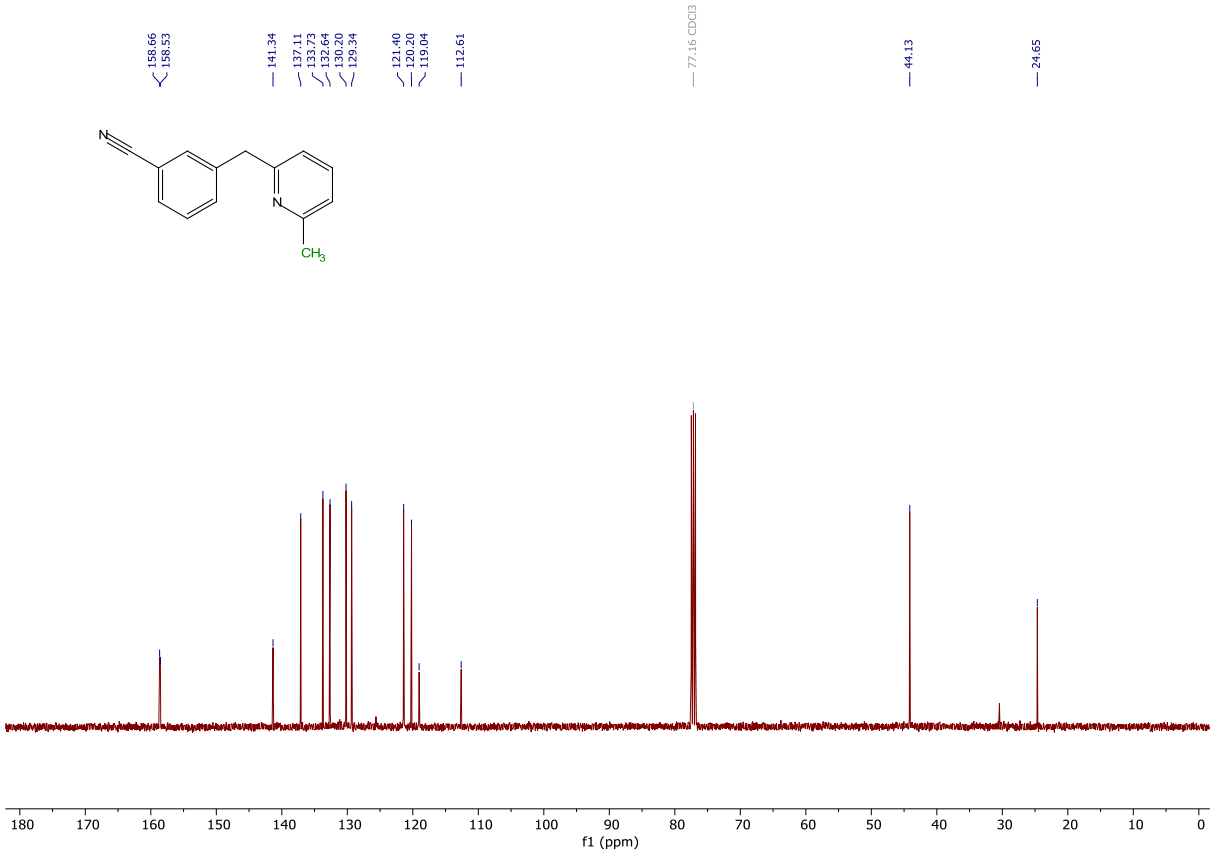
3-((3-Methylpyridin-2-yl)methyl)benzonitrile (6az)



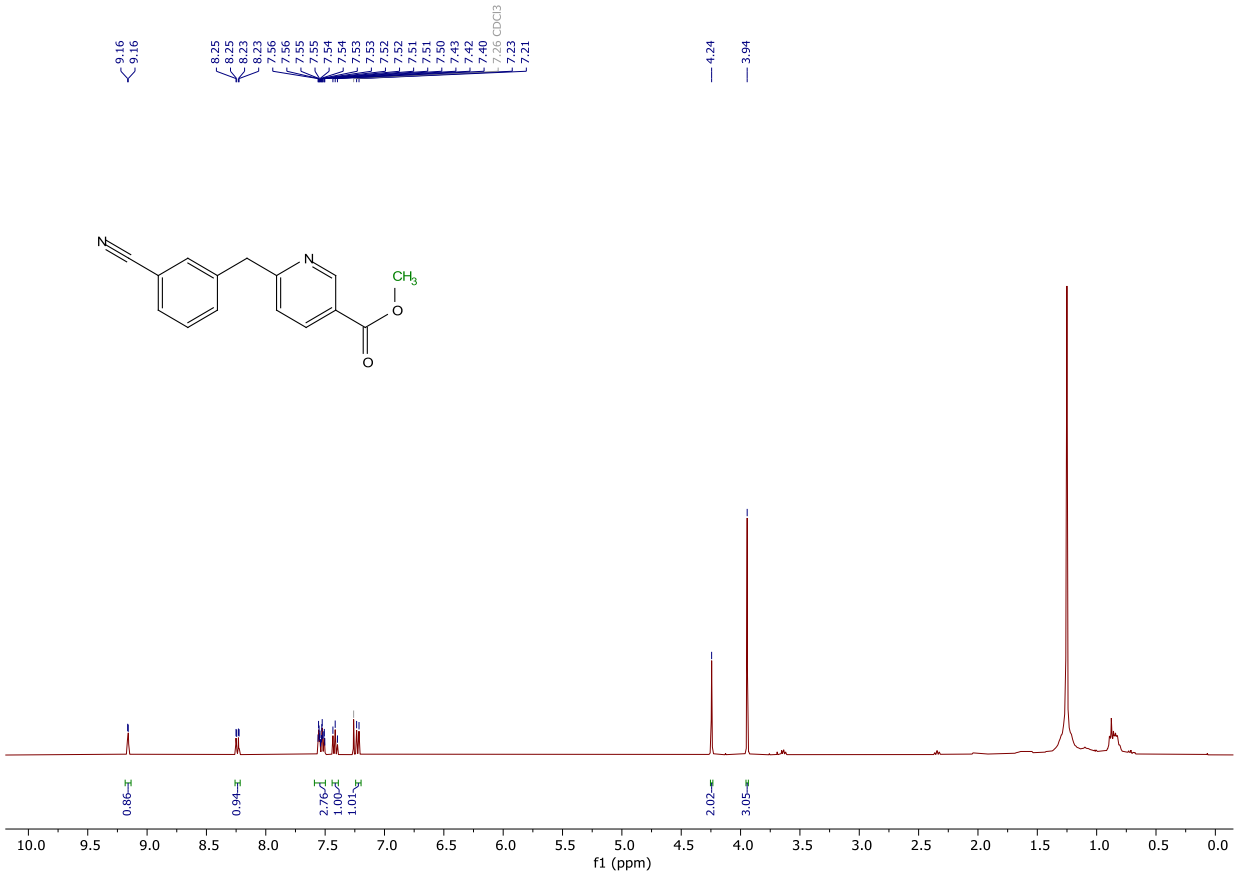


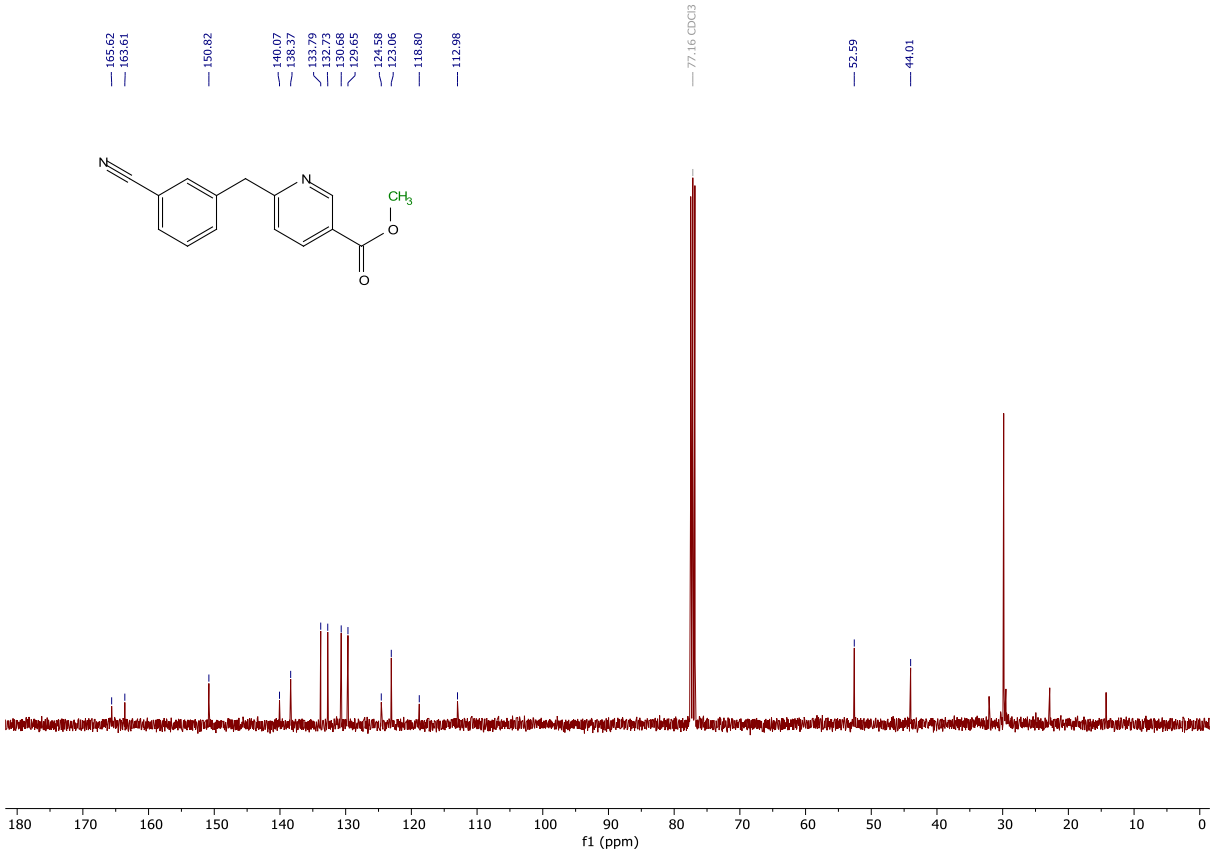
3-((6-Methylpyridin-2-yl)methyl)benzonitrile (6ba)



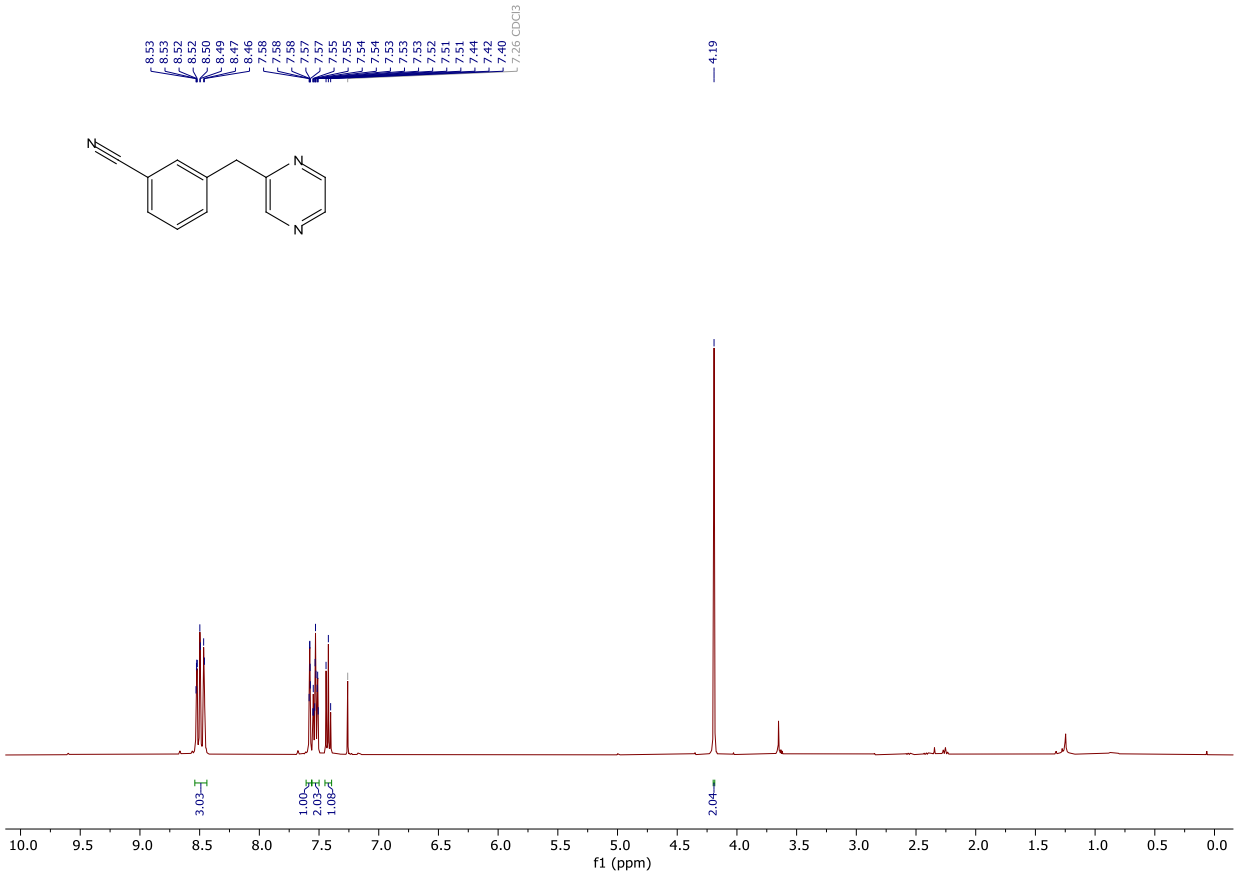


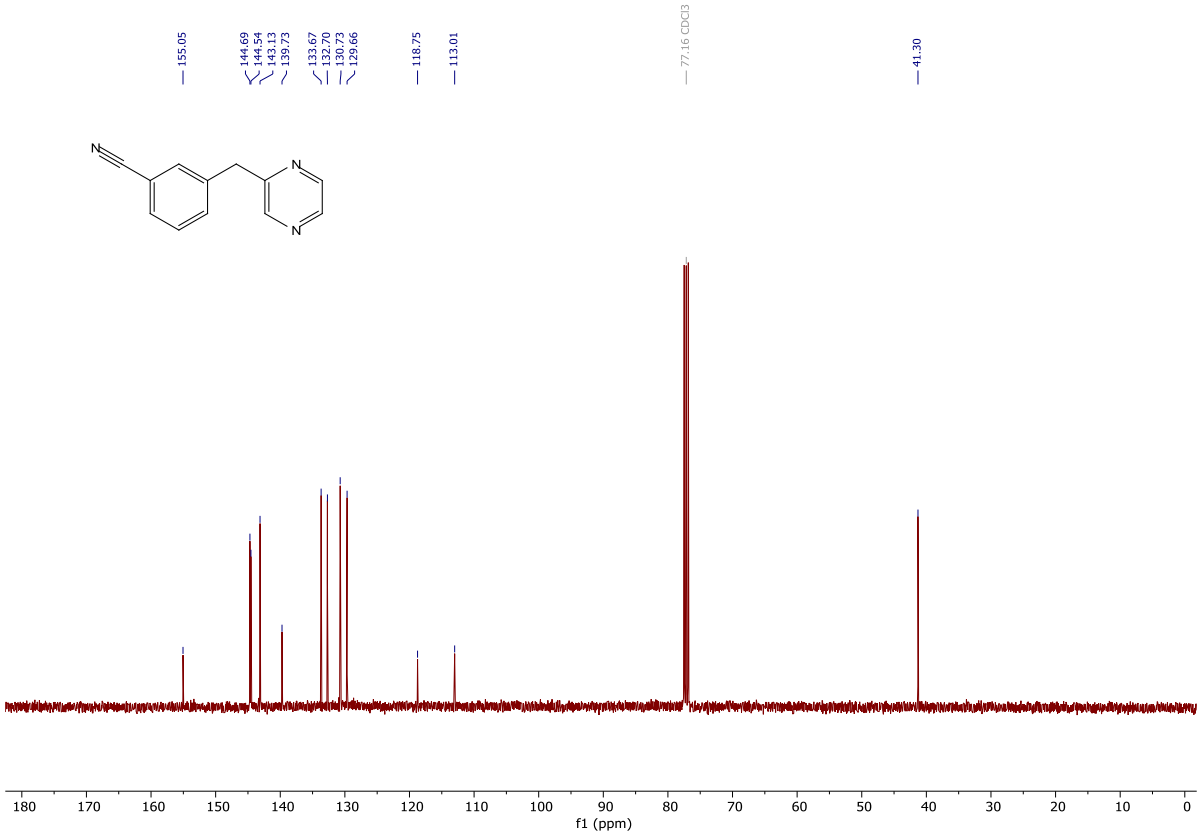
Methyl 6-(3-cyanobenzyl)nicotinate (6bb)



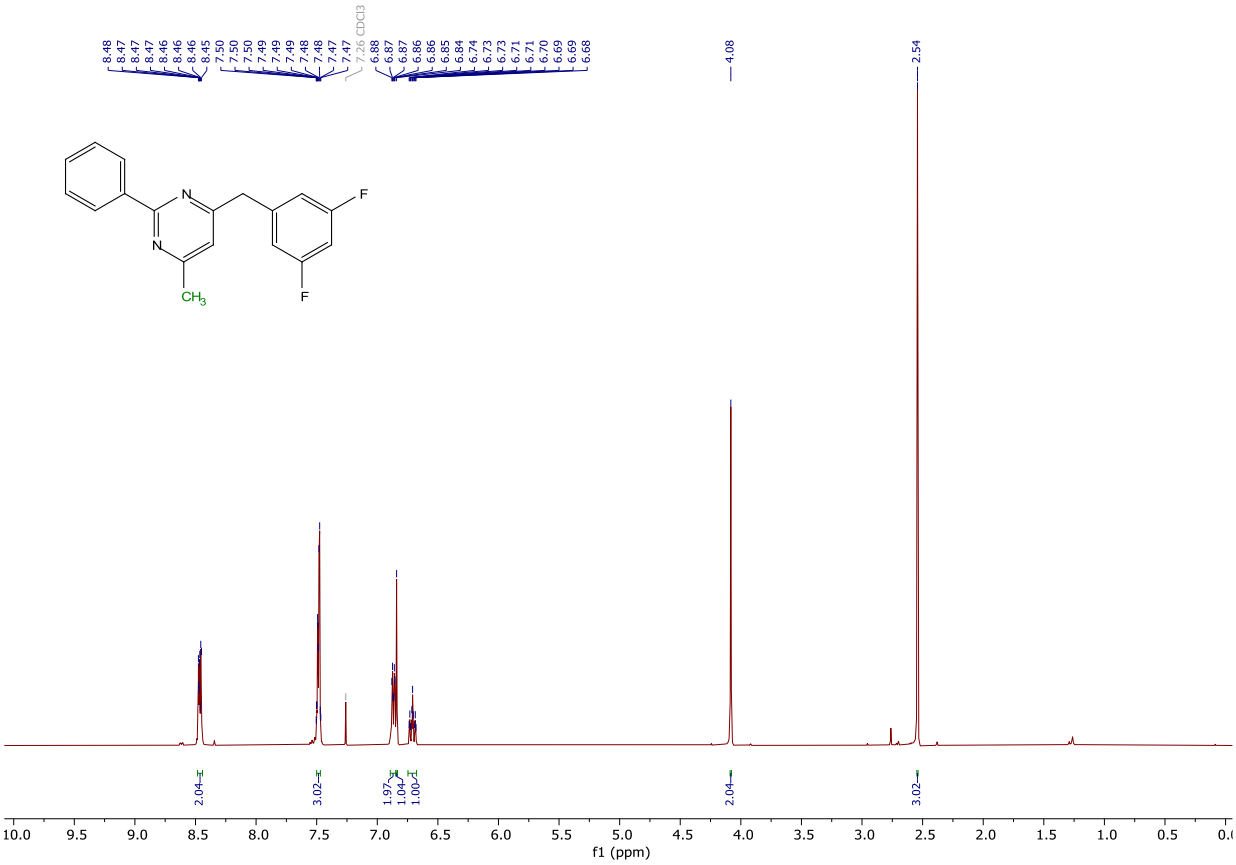


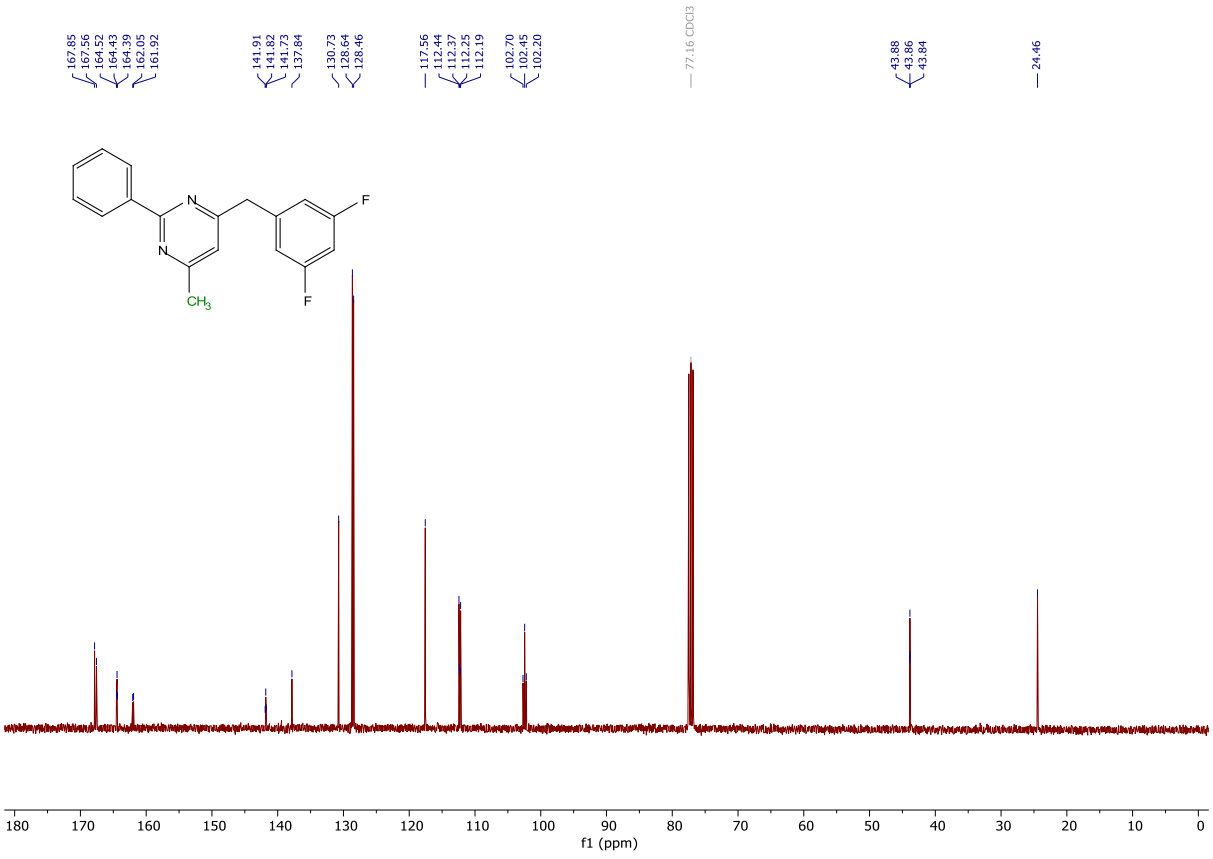
3-(Pyrazin-2-ylmethyl)benzonitrile (6bc)

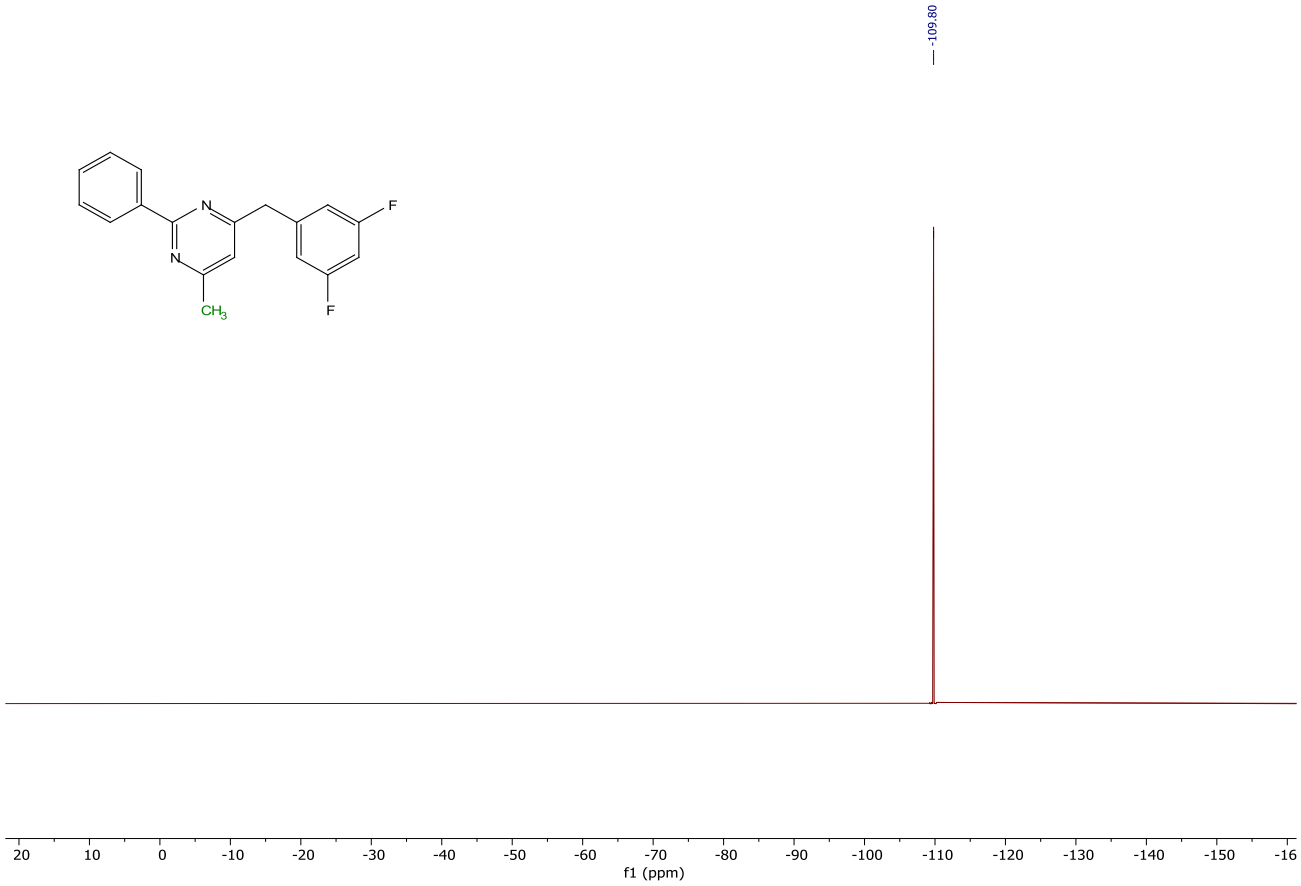




4-(3,5-Difluorobenzyl)-6-methyl-2-phenylpyrimidine (6bd)



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CH3
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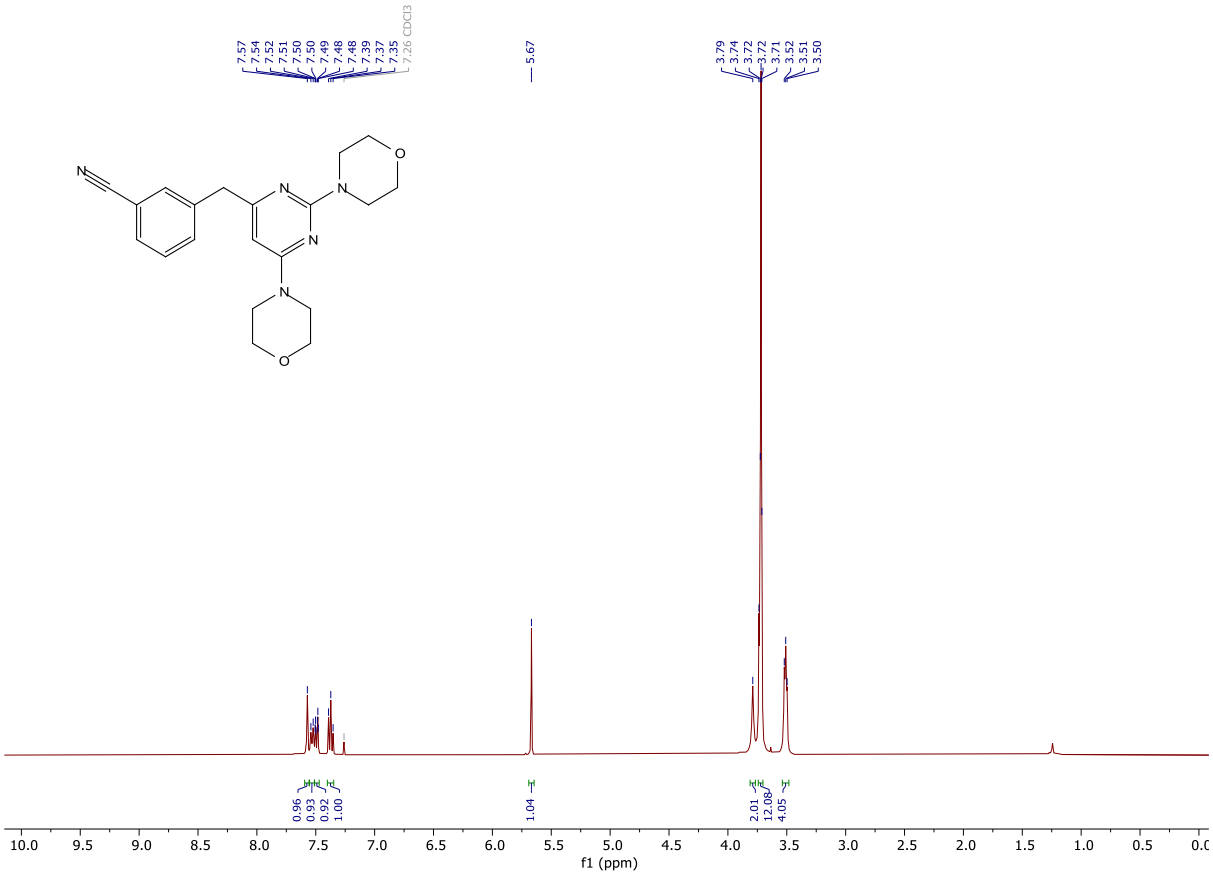
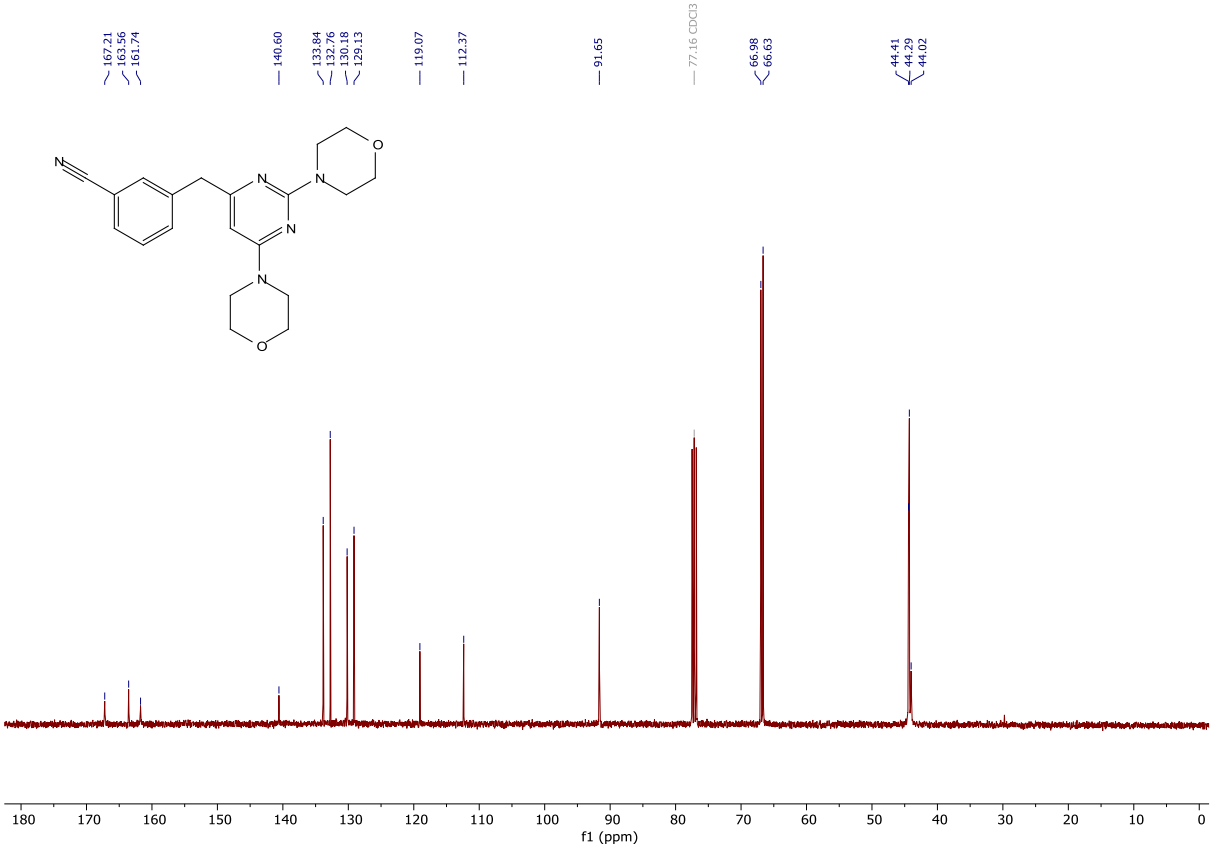
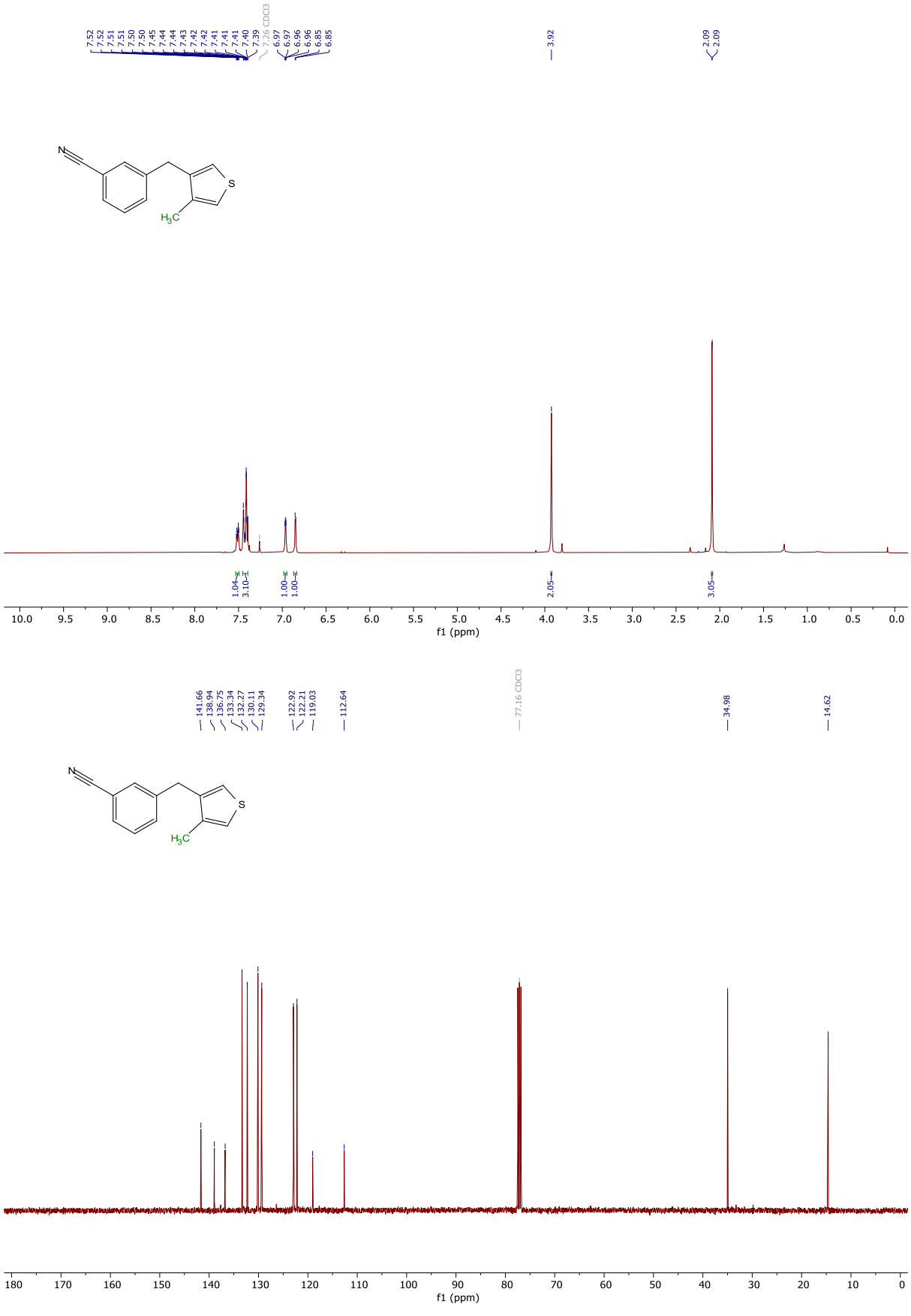
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-16
f1 (ppm)

3-((2,6-Dimorpholinopyrimidin-4-yl)methyl)benzonitrile (6be)

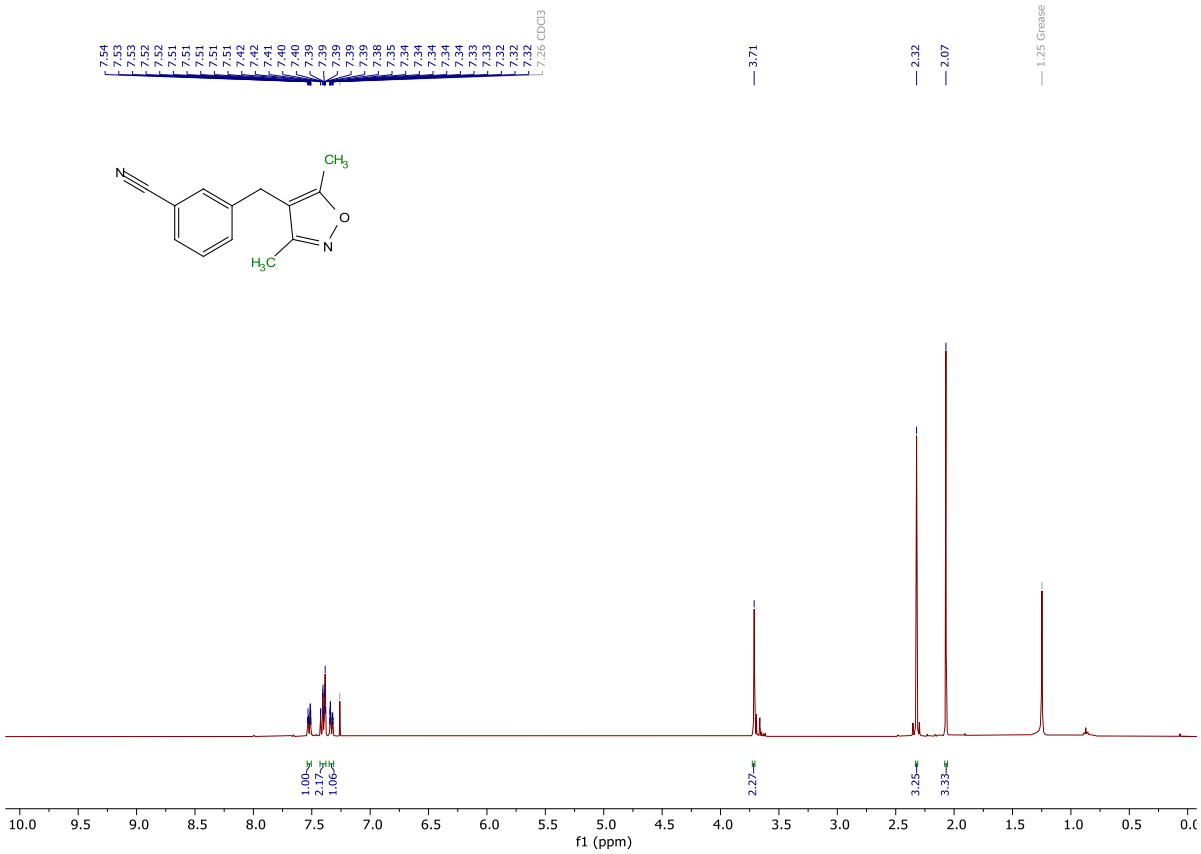


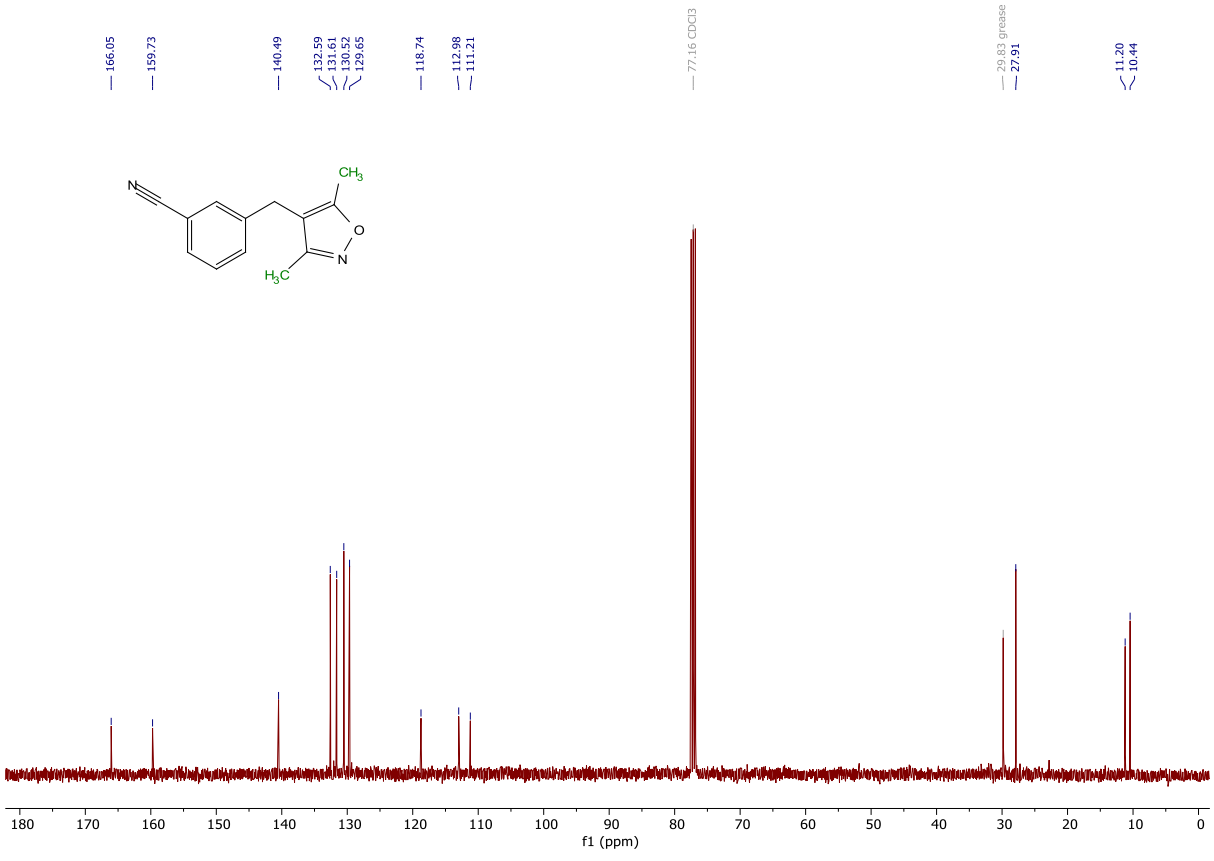


3-((4-Methyl-3-yl)methyl)benzonitrile (6bf)

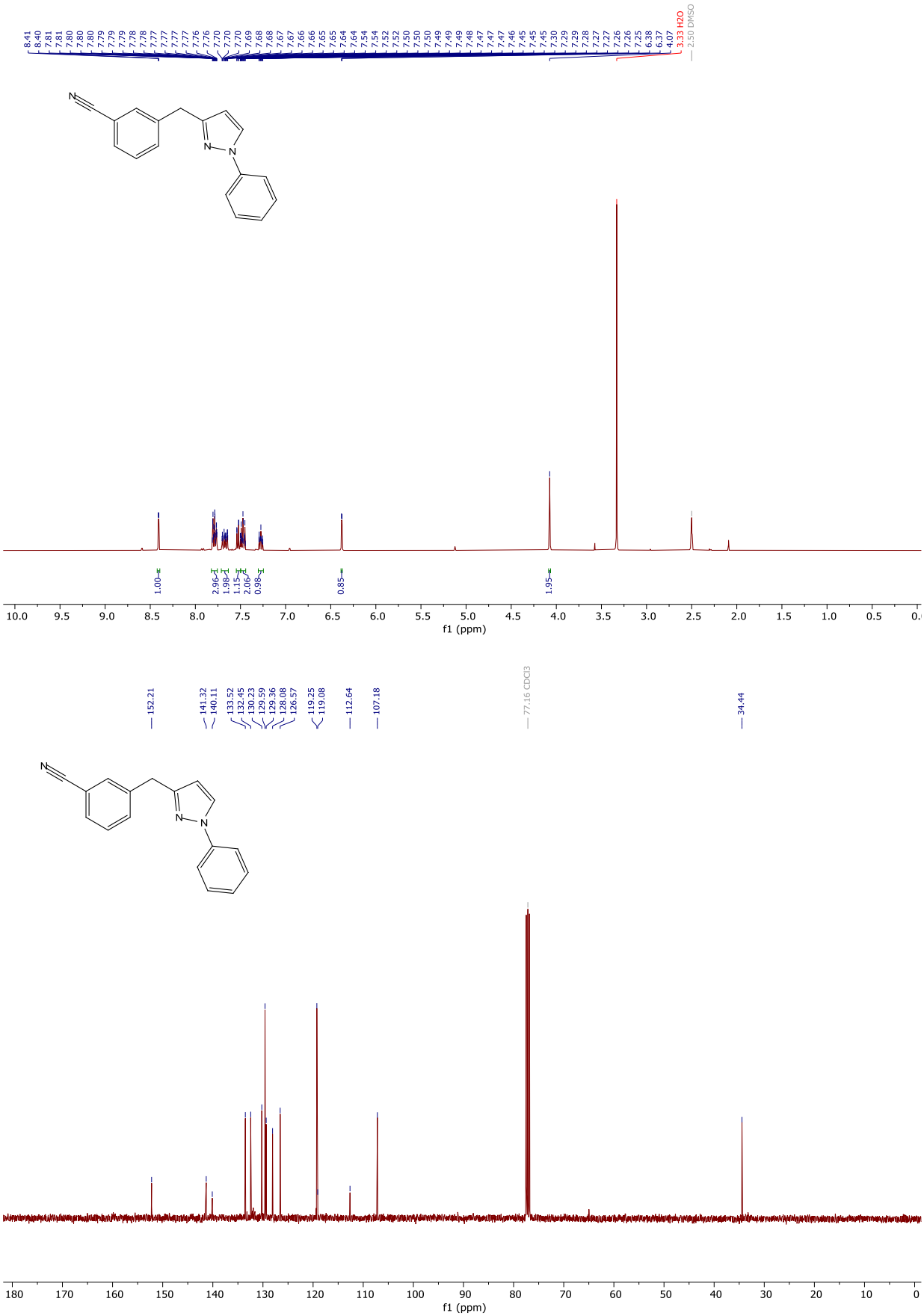


3-((3,5-Dimethylisoxazol-4-yl)methyl)benzonitrile (6bg)

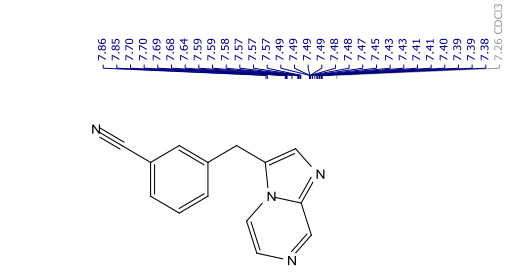


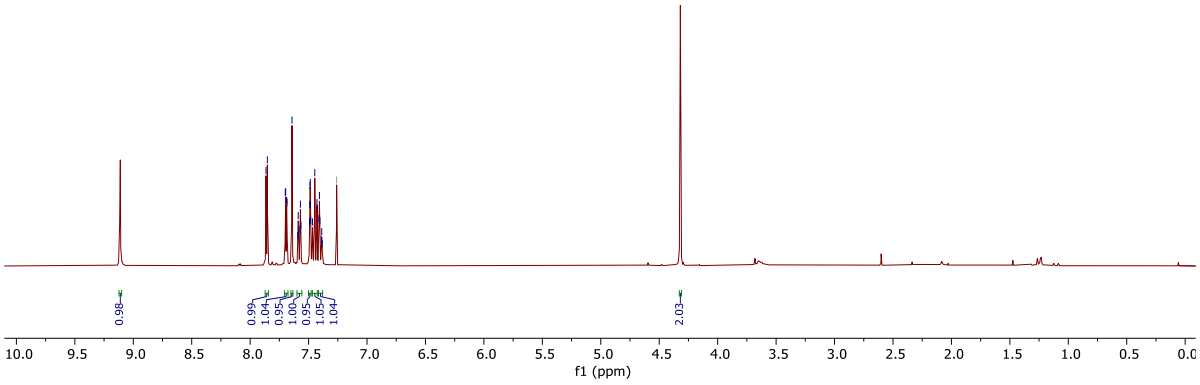


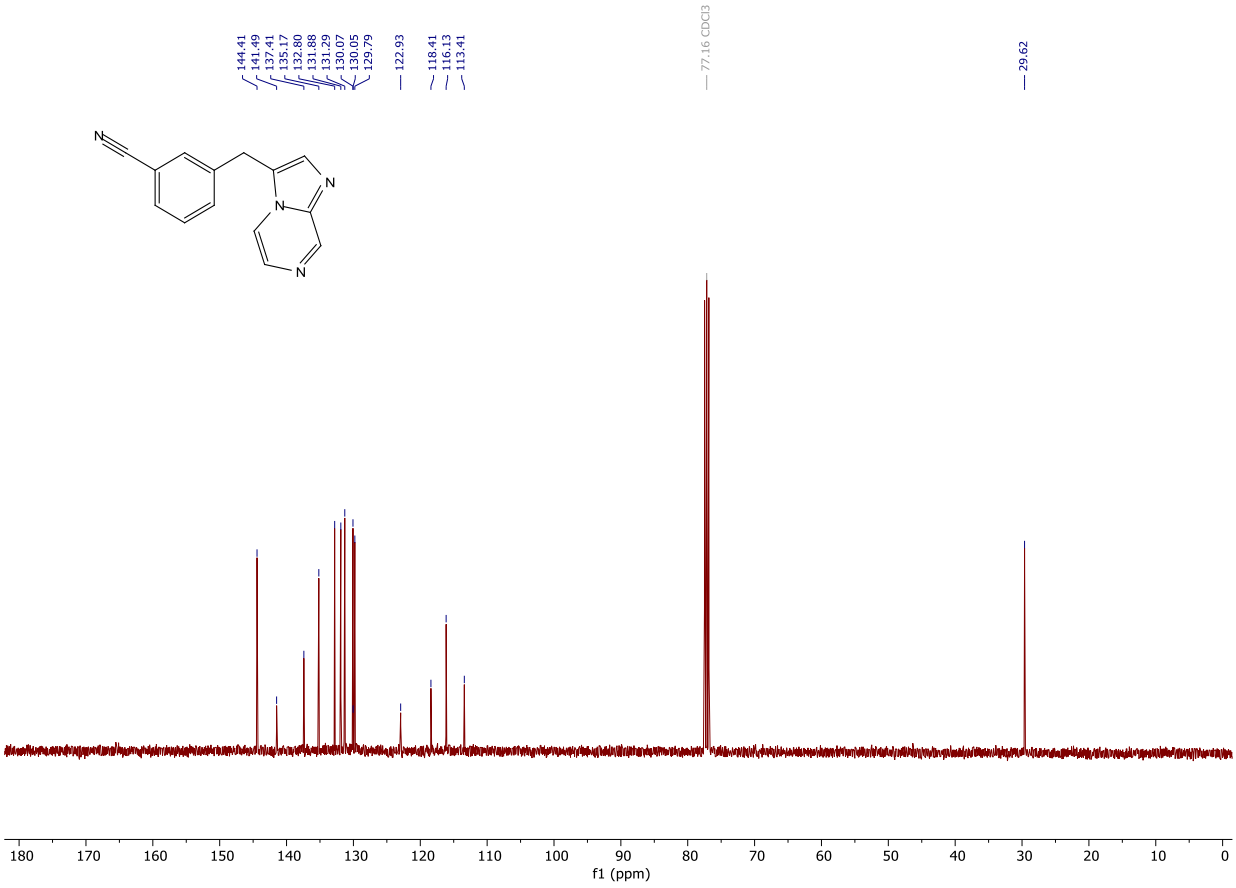
3-((1-Phenyl-1H-pyrazol-3-yl)methyl)benzonitrile (6bh)



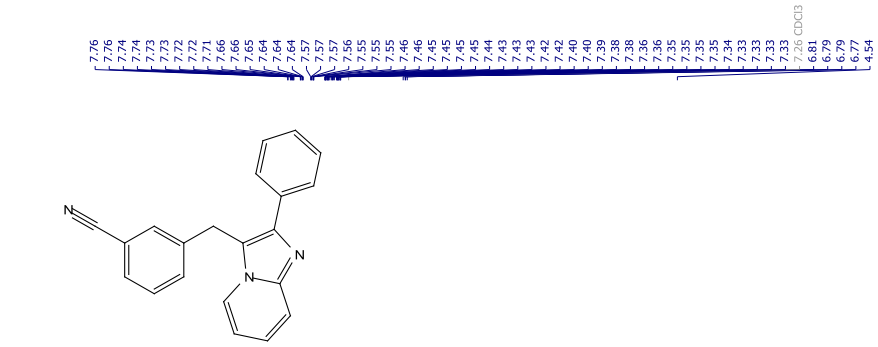
3-(Imidazo[1,2-a]pyrazin-3-ylmethyl)benzonitrile (6bl)

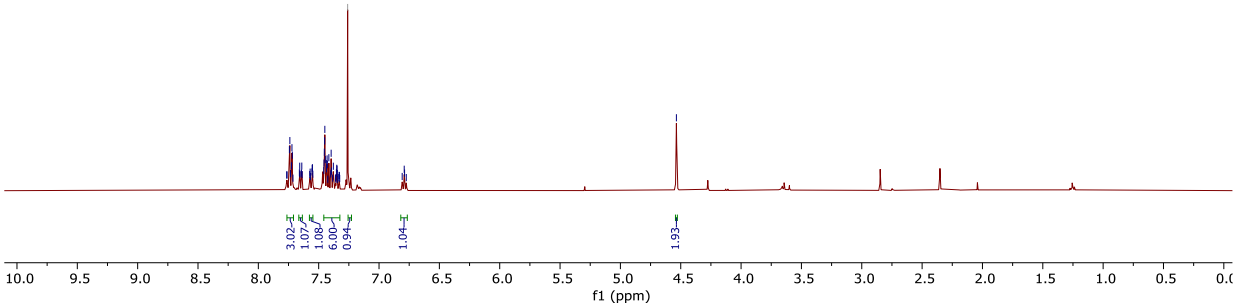


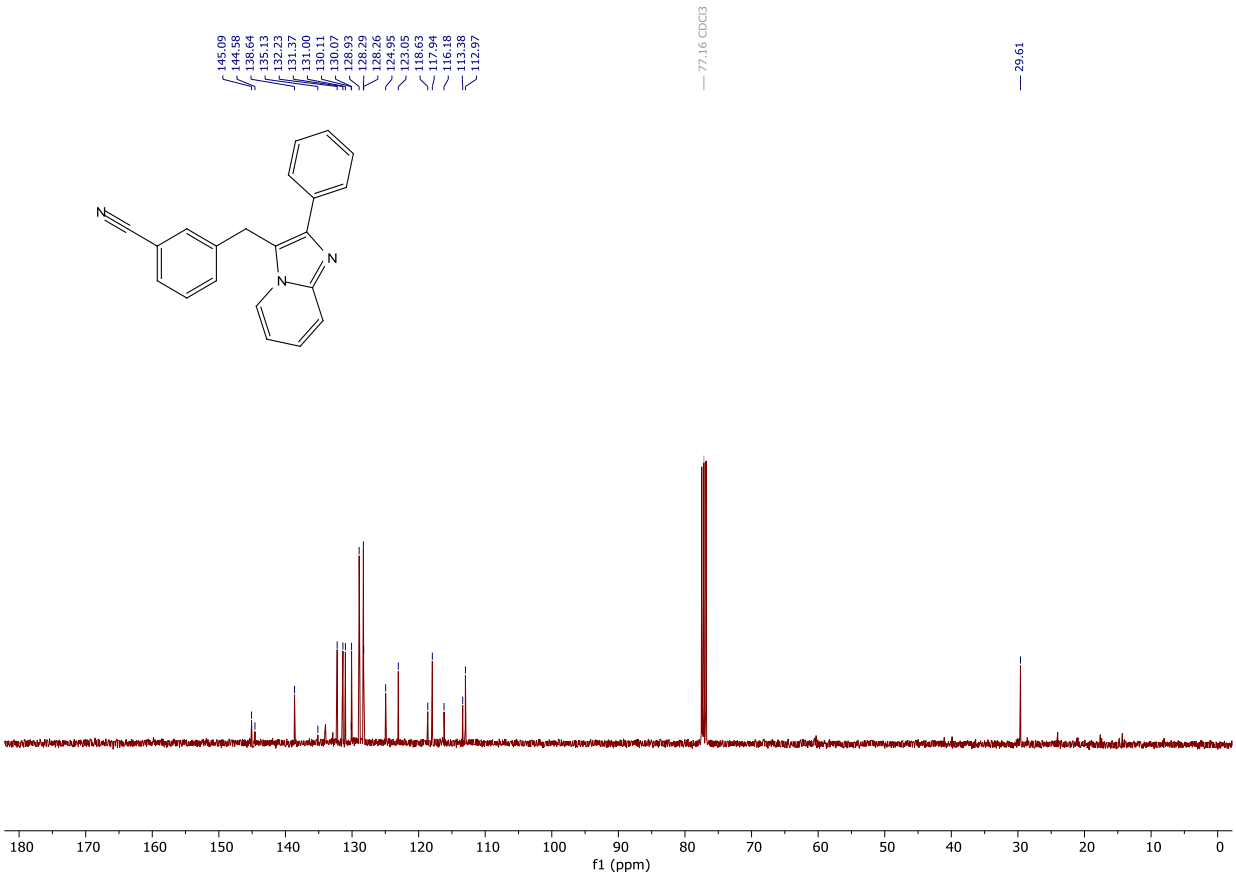




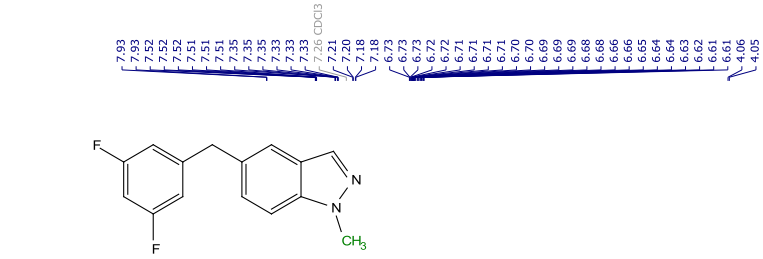
3-((2-Phenylimidazo[1,2-a]pyridin-3-yl)methyl)benzonitrile (6bj)

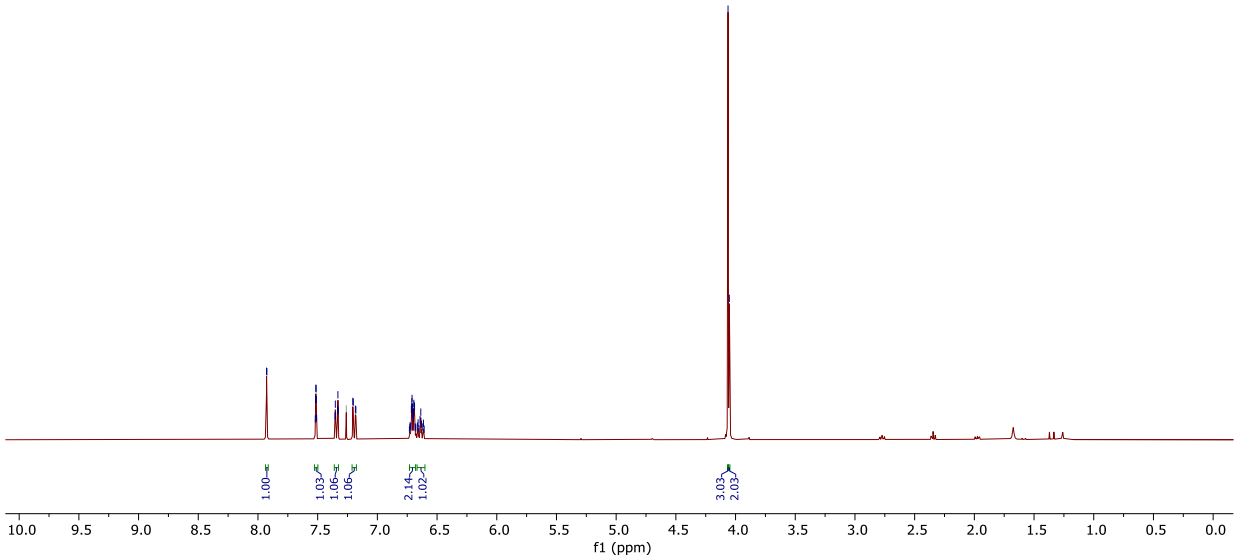


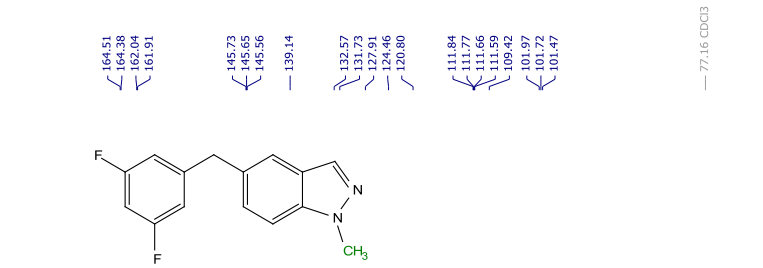


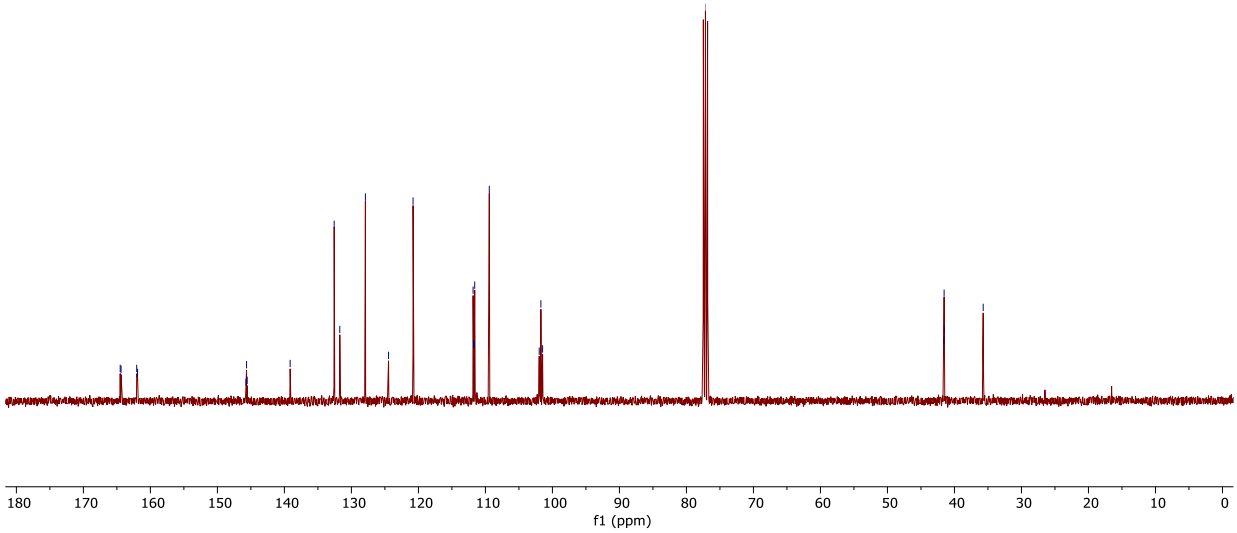


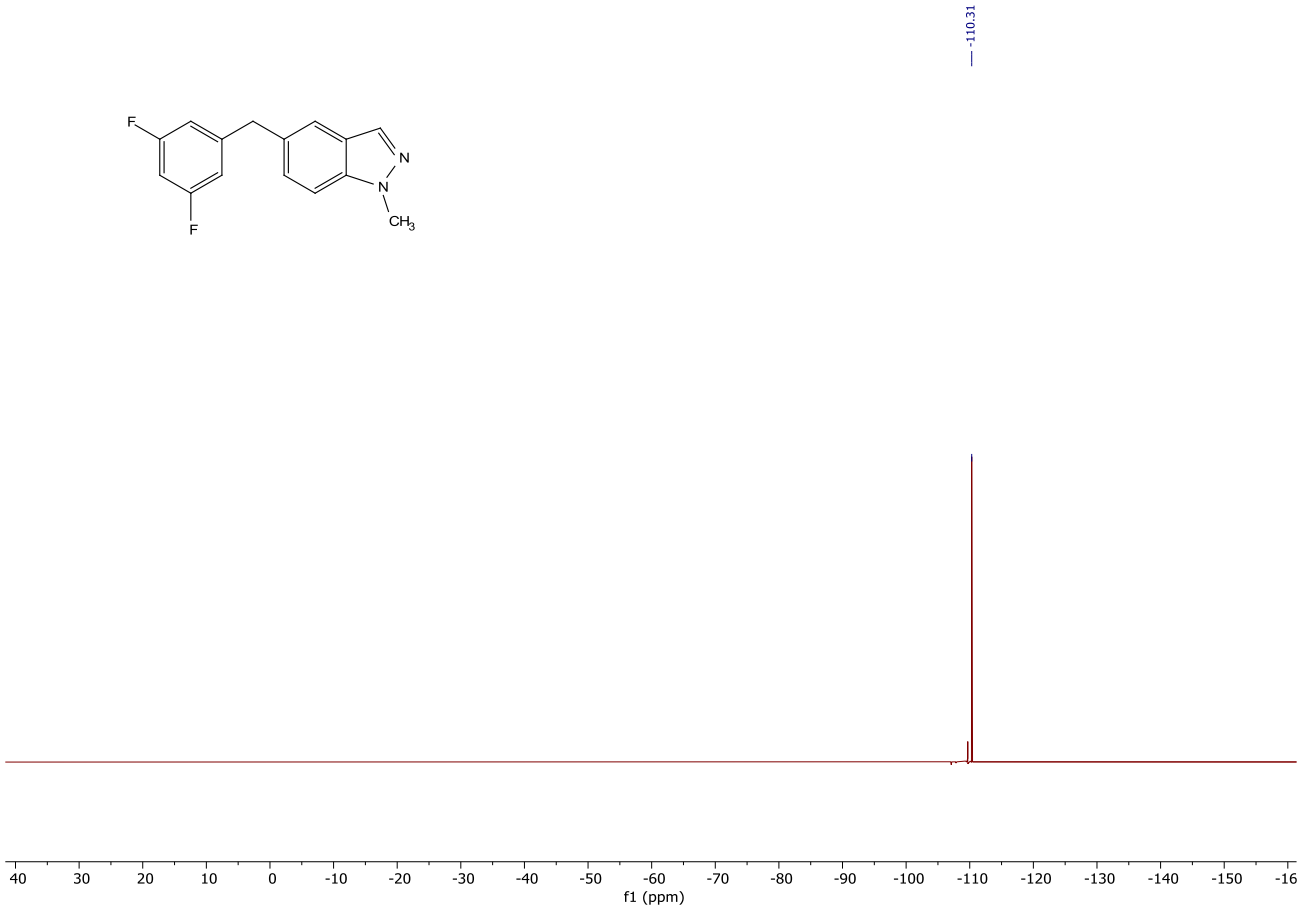
5-(3,5-Difluorobenzyl)-1-methyl-1H-indazole (6bk)







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F
N
N
CH3
40
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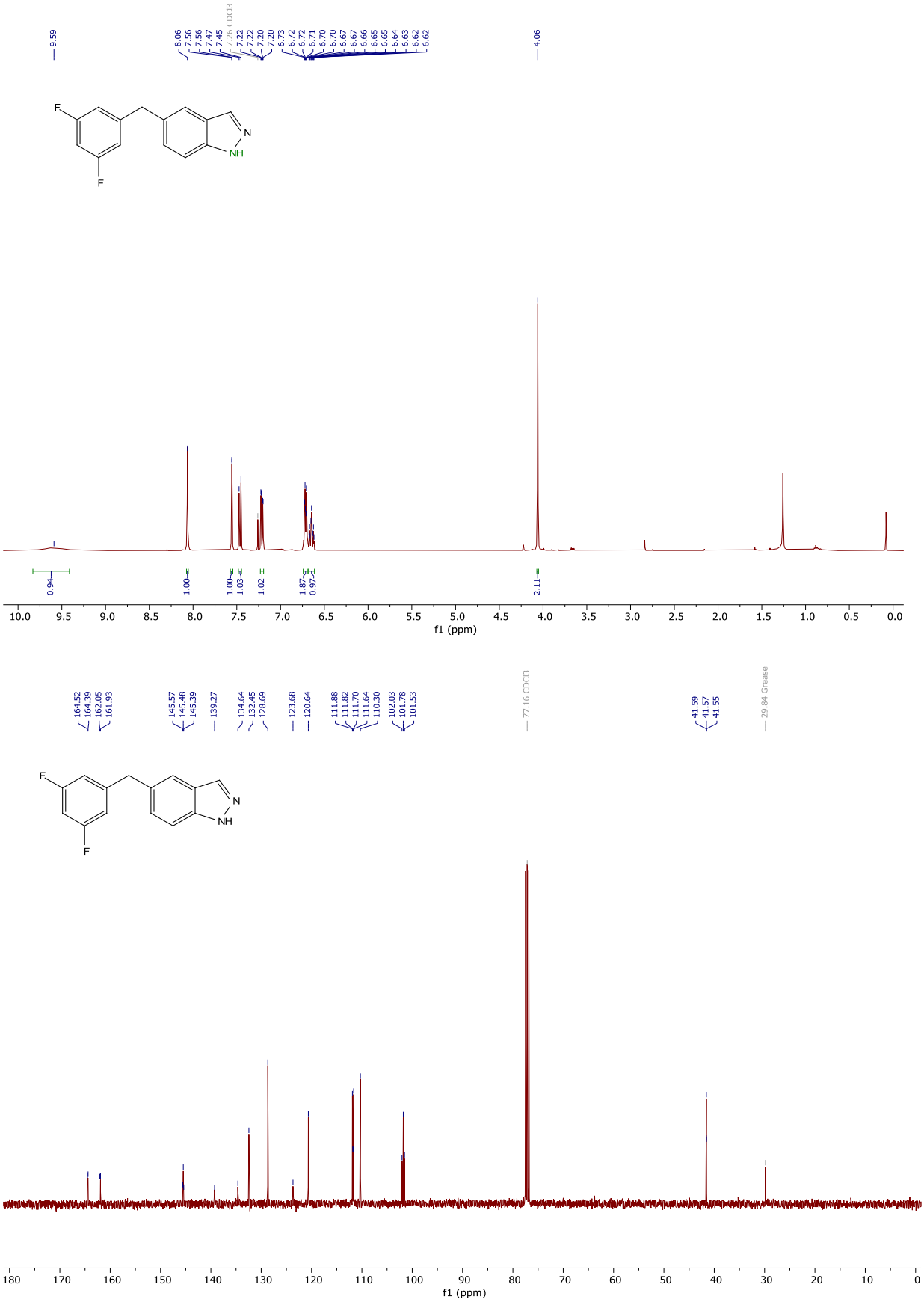
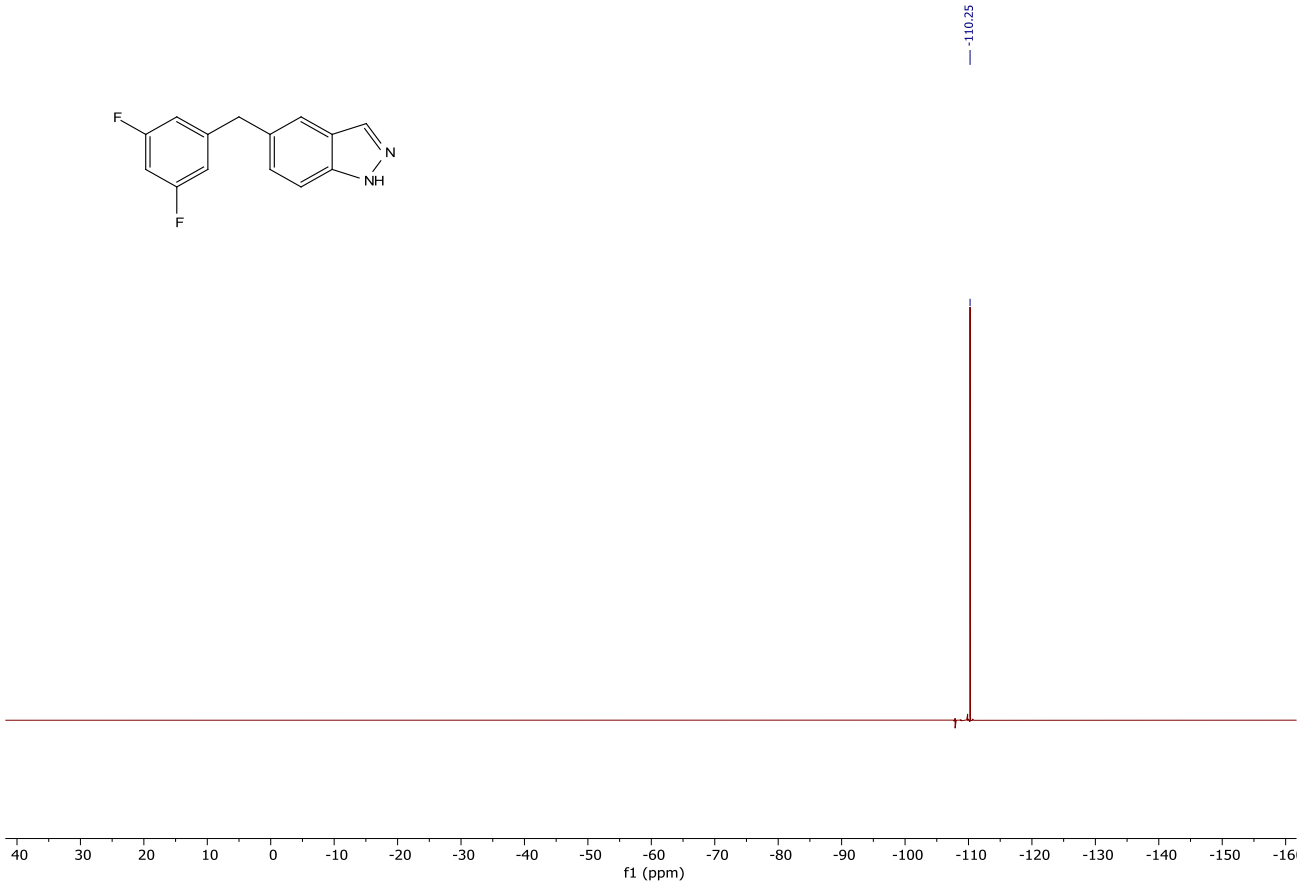
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-16
f1 (ppm)

5-(3,5-Difluorobenzyl)-1H-indazole (6bl)




-110.25
F
F
N
NH
40
30
20
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0
-10
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-40
-50
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-70
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-90
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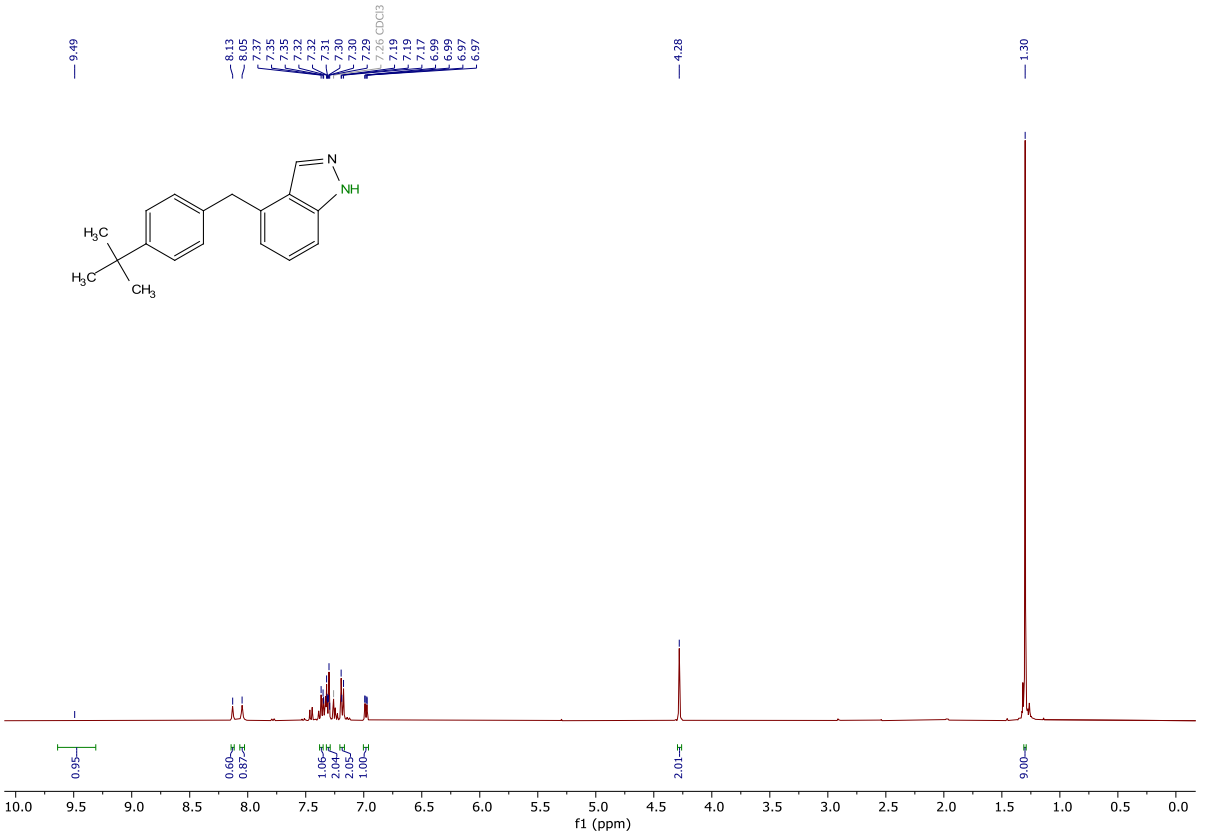
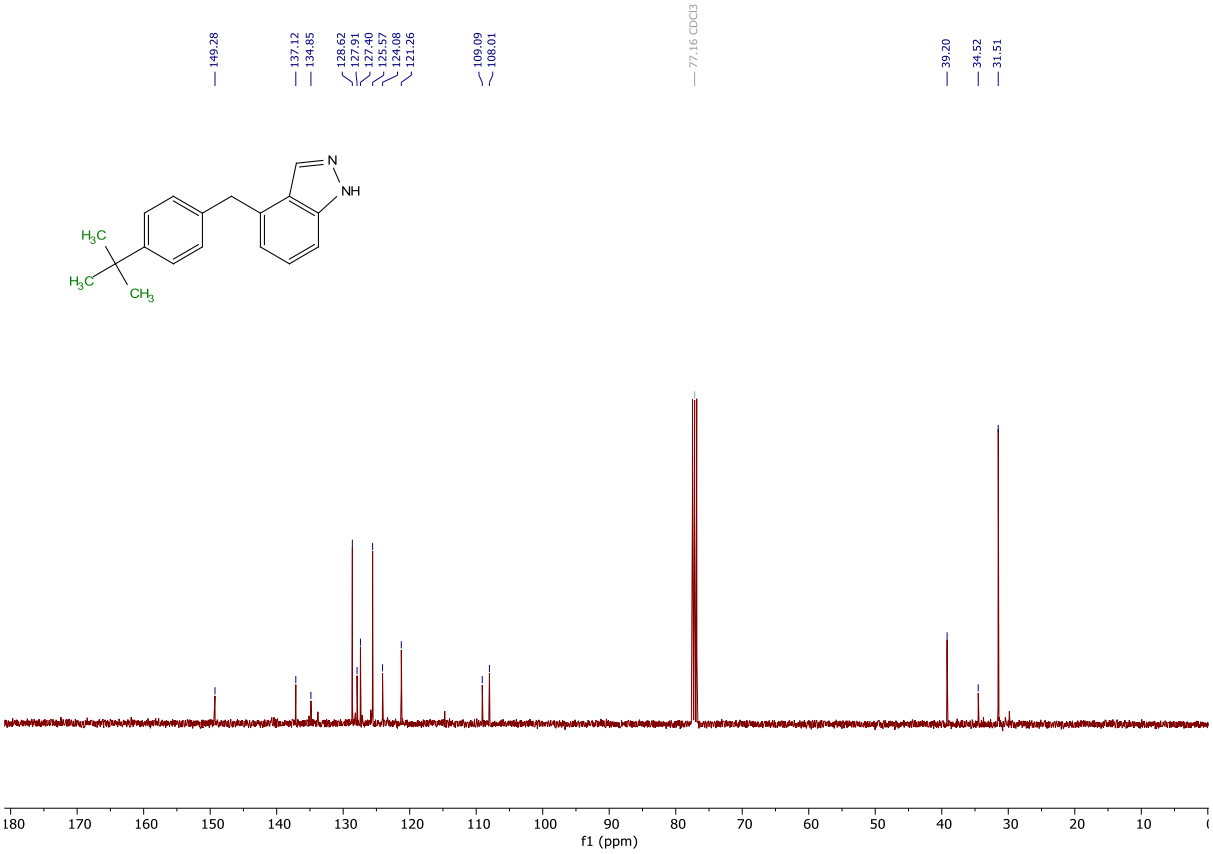
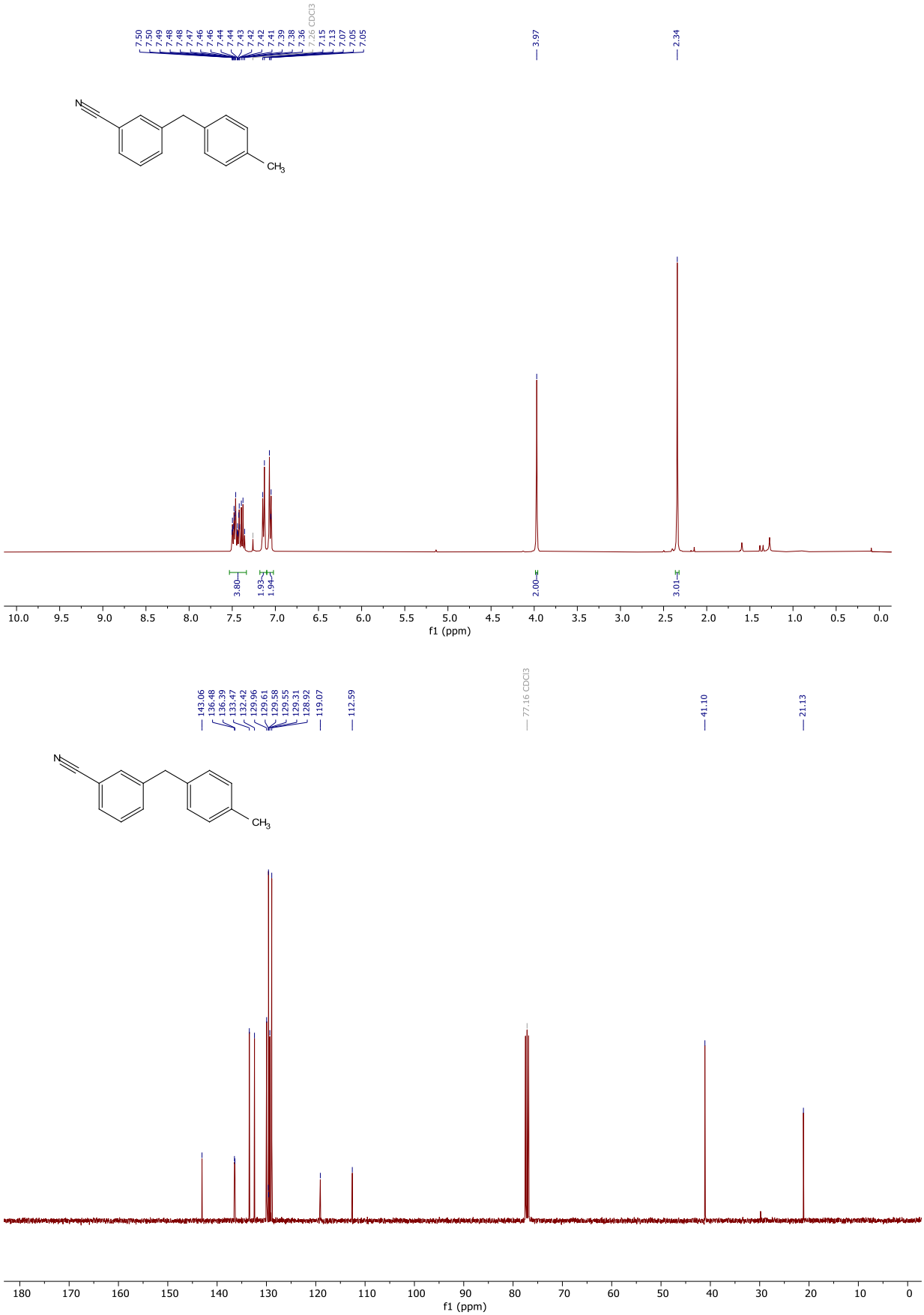
-140
-150
f1 (ppm)

4-(4-(Tert-butyl)benzyl)-1H-indazole (6bm)

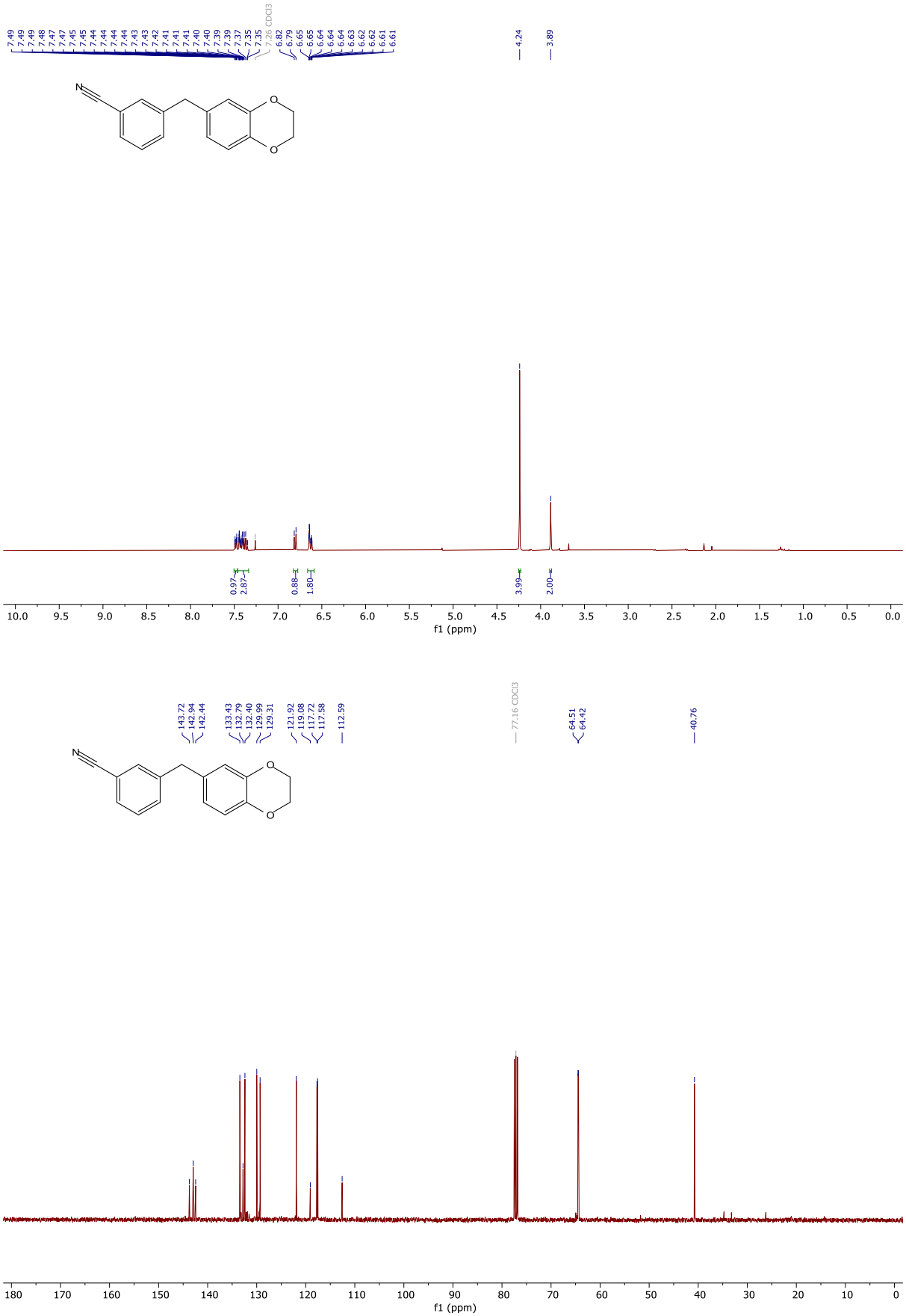




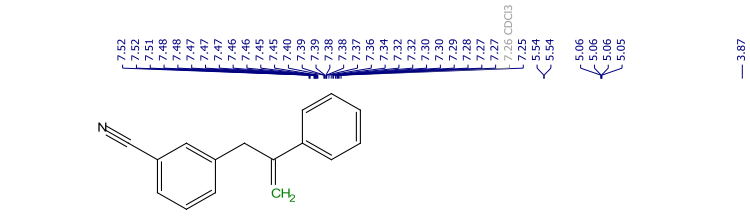
3-(4-Methylbenzyl)benzonitrile (6bn)

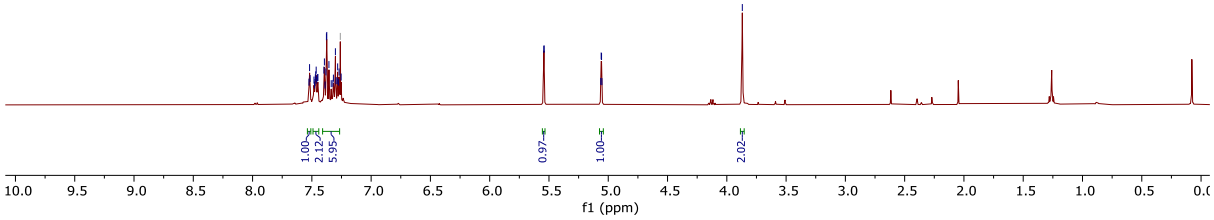


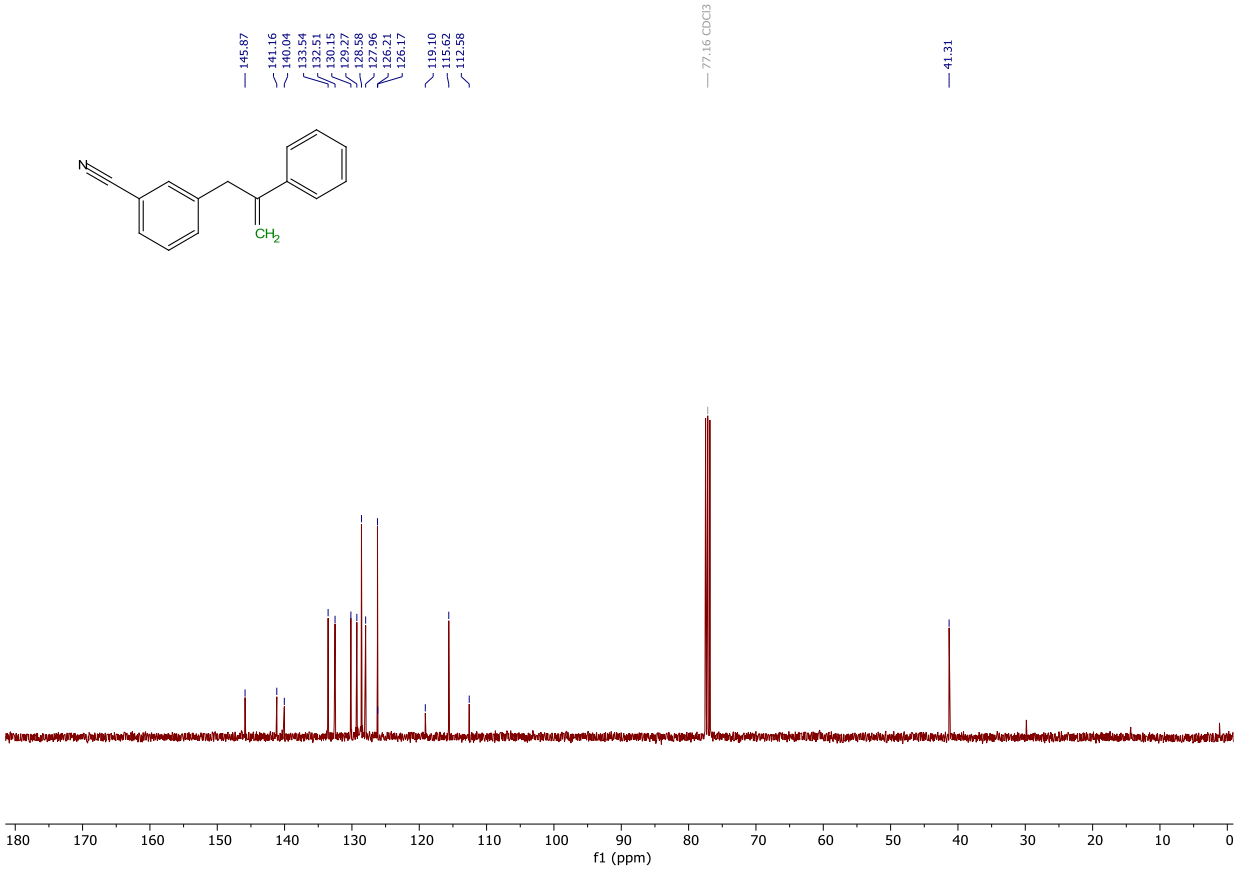
3-((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)methyl)benzonitrile (6bo)



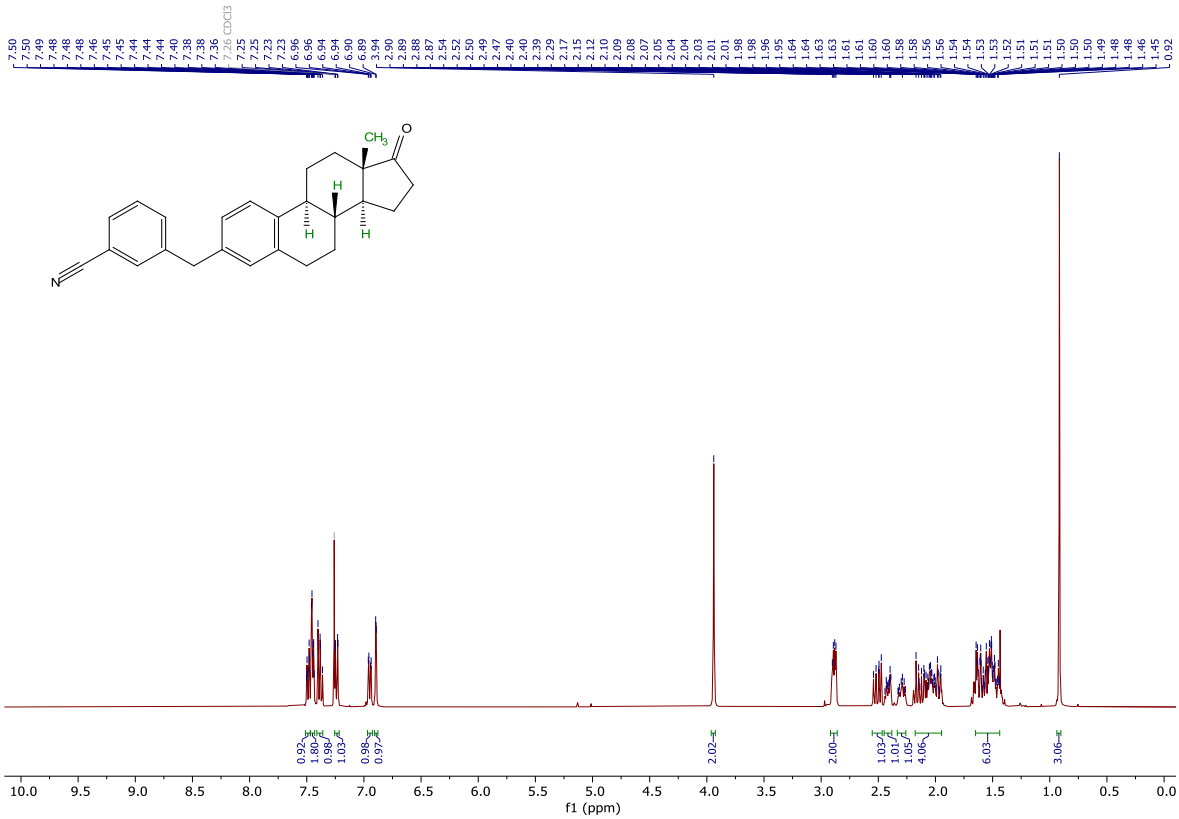
3-(2-Phenylallyl)benzonitrile (6bp)

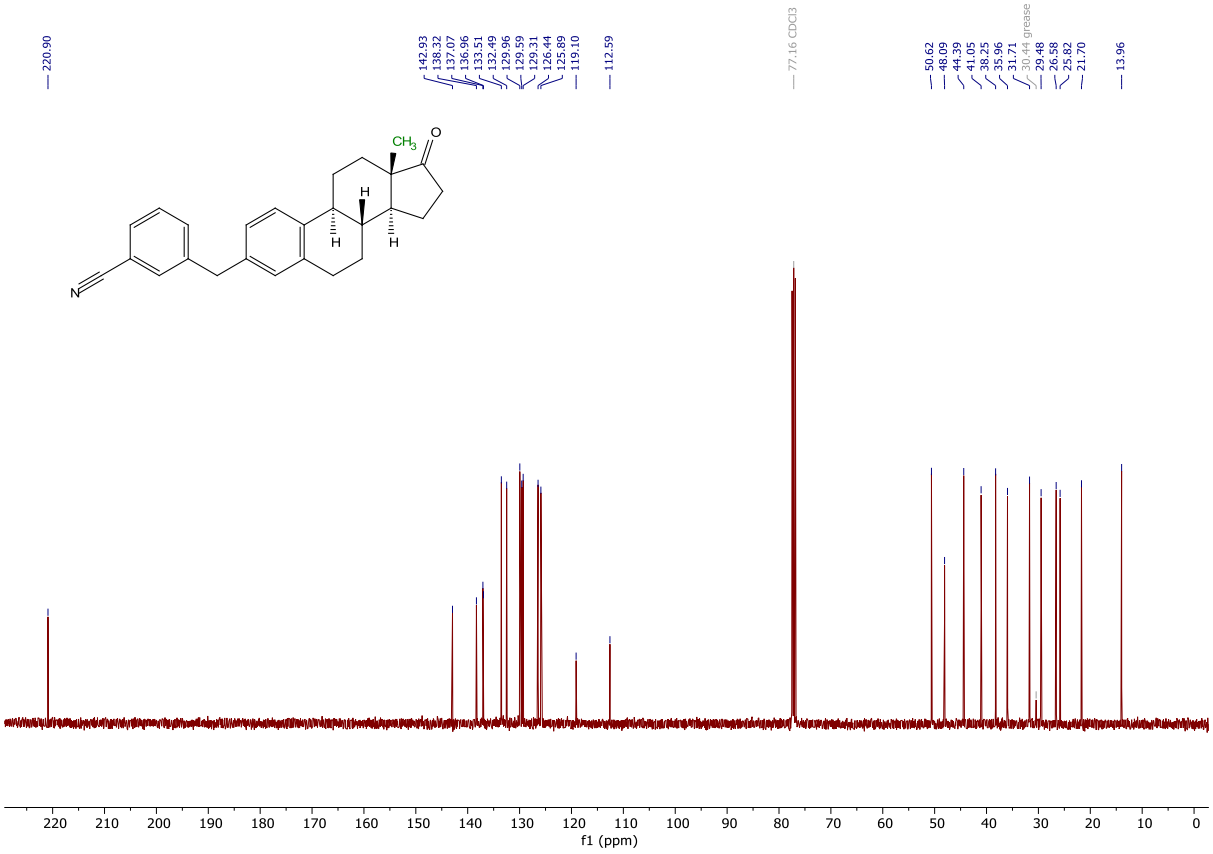




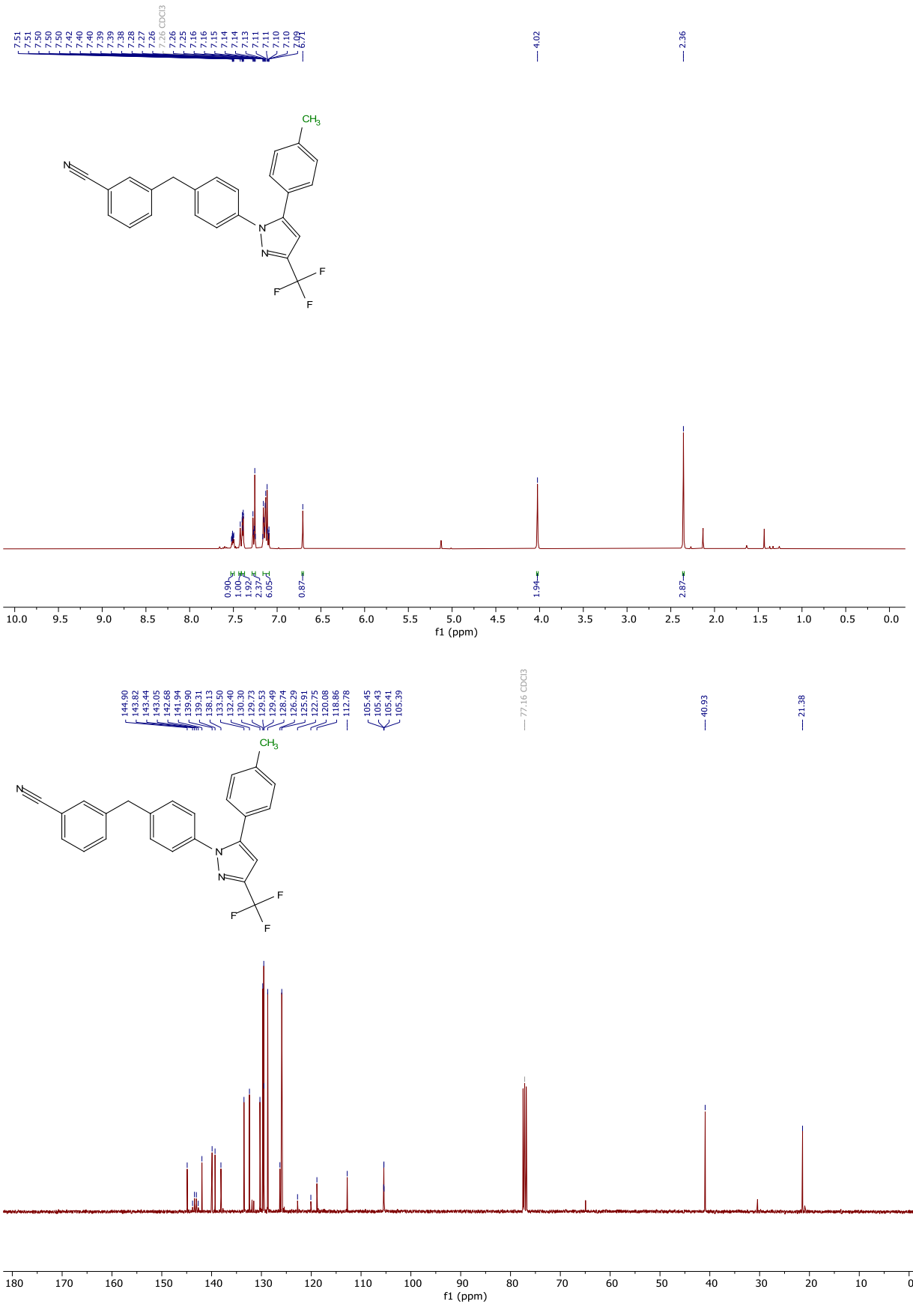


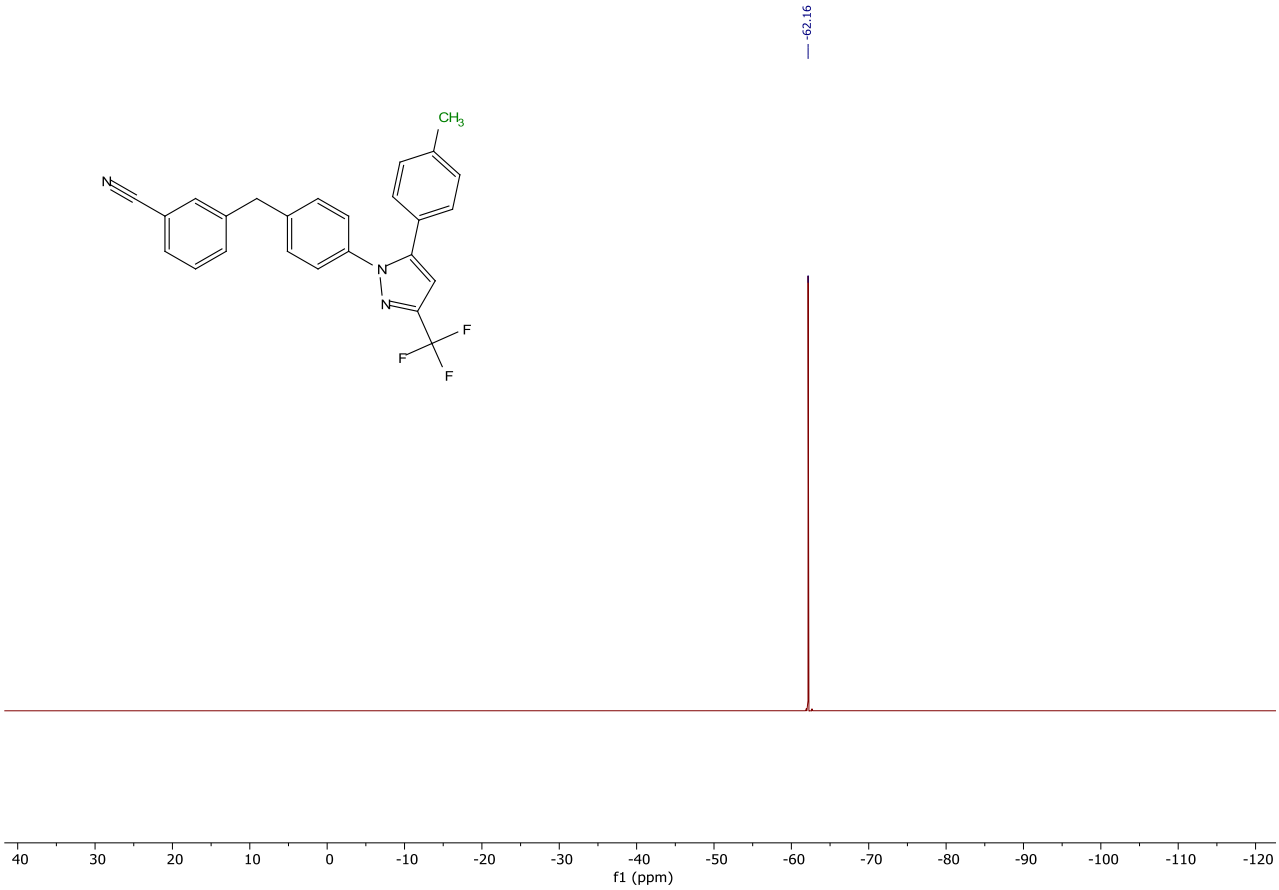
3-(((8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)methyl)benzonitrile (6bq)





3-(4-(5-(*p*-Tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)benzonitrile (6br)

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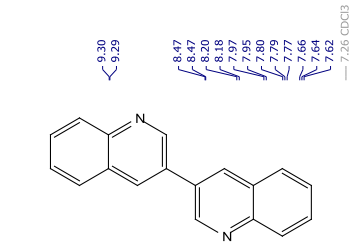
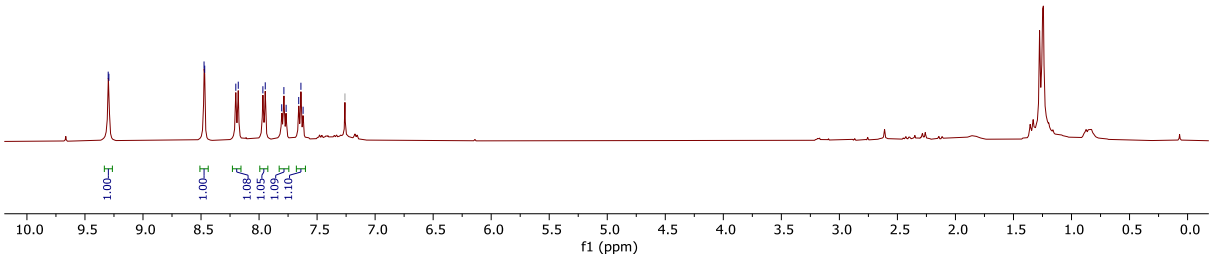
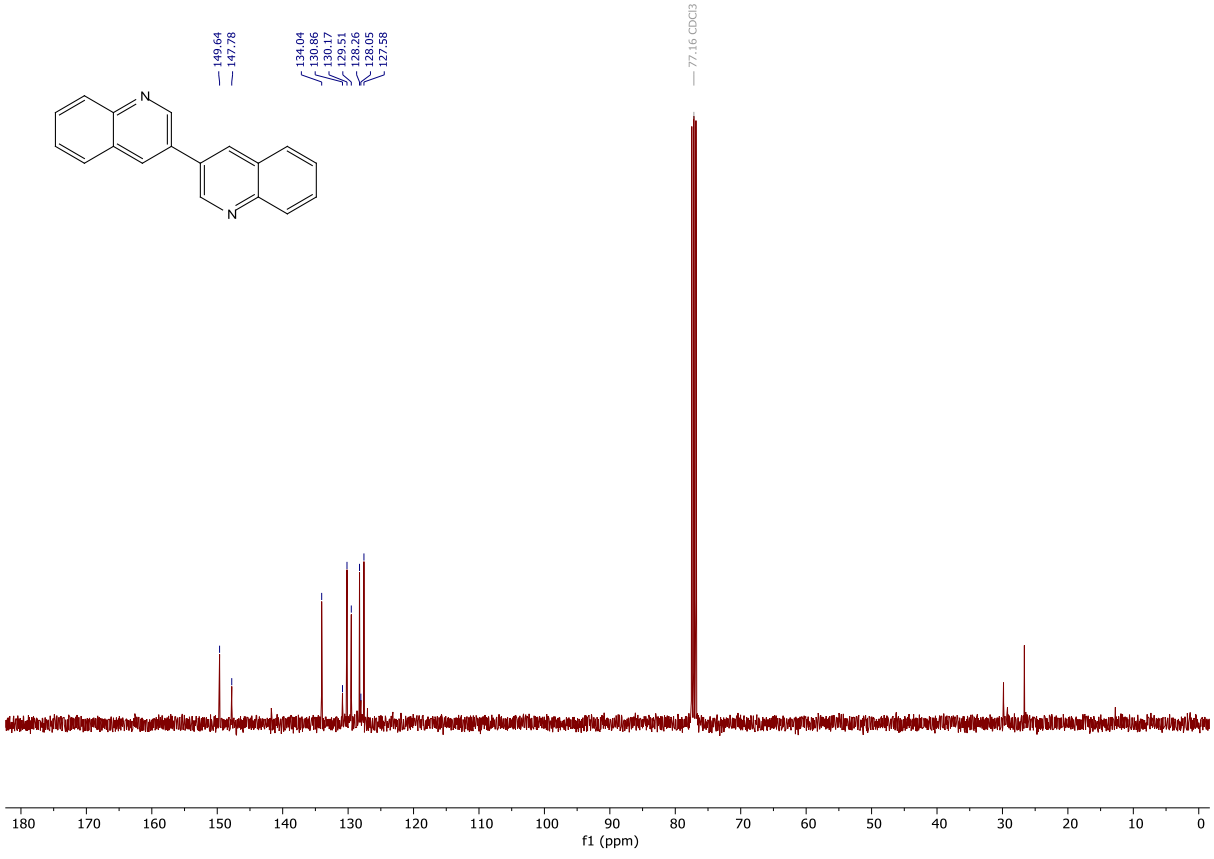
N
N
F
F
F
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
f1 (ppm)

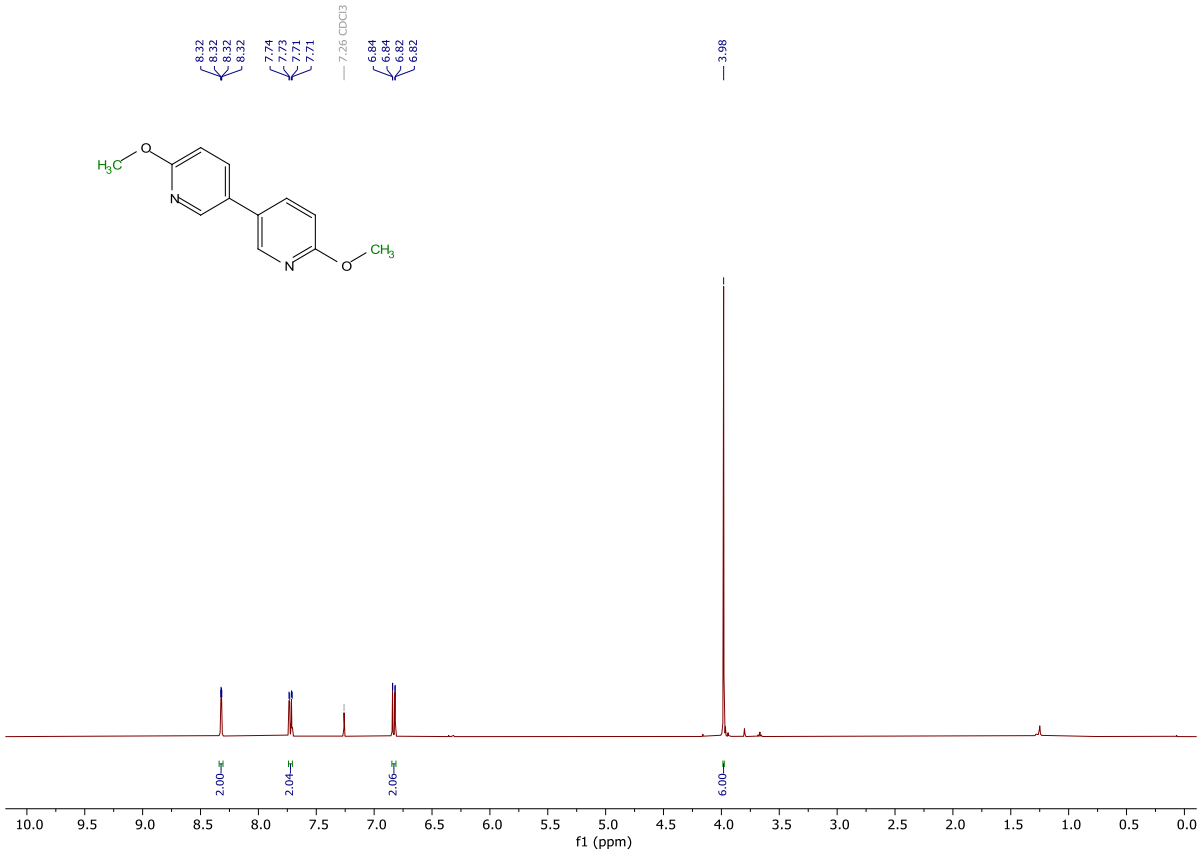
3,3'-Biquinoline (9a)

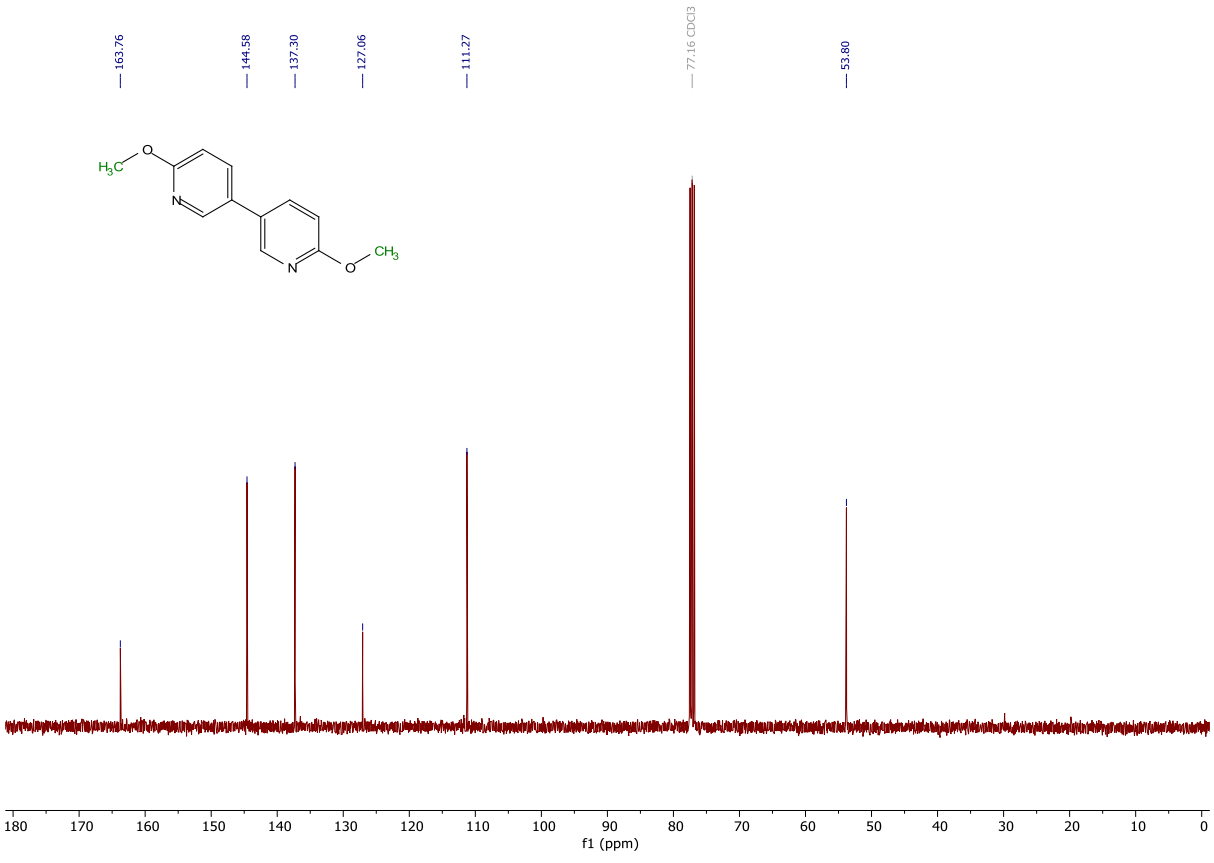




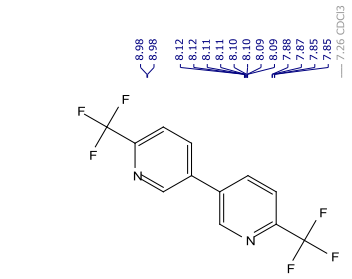


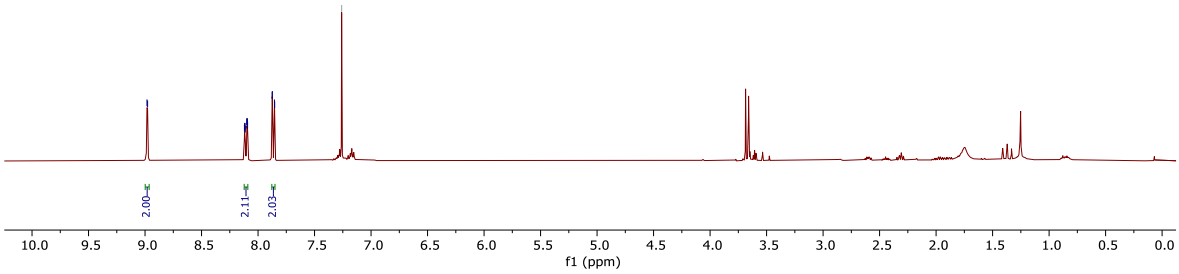
6,6'-Dimethoxy-3,3'-bipyridine (9b)

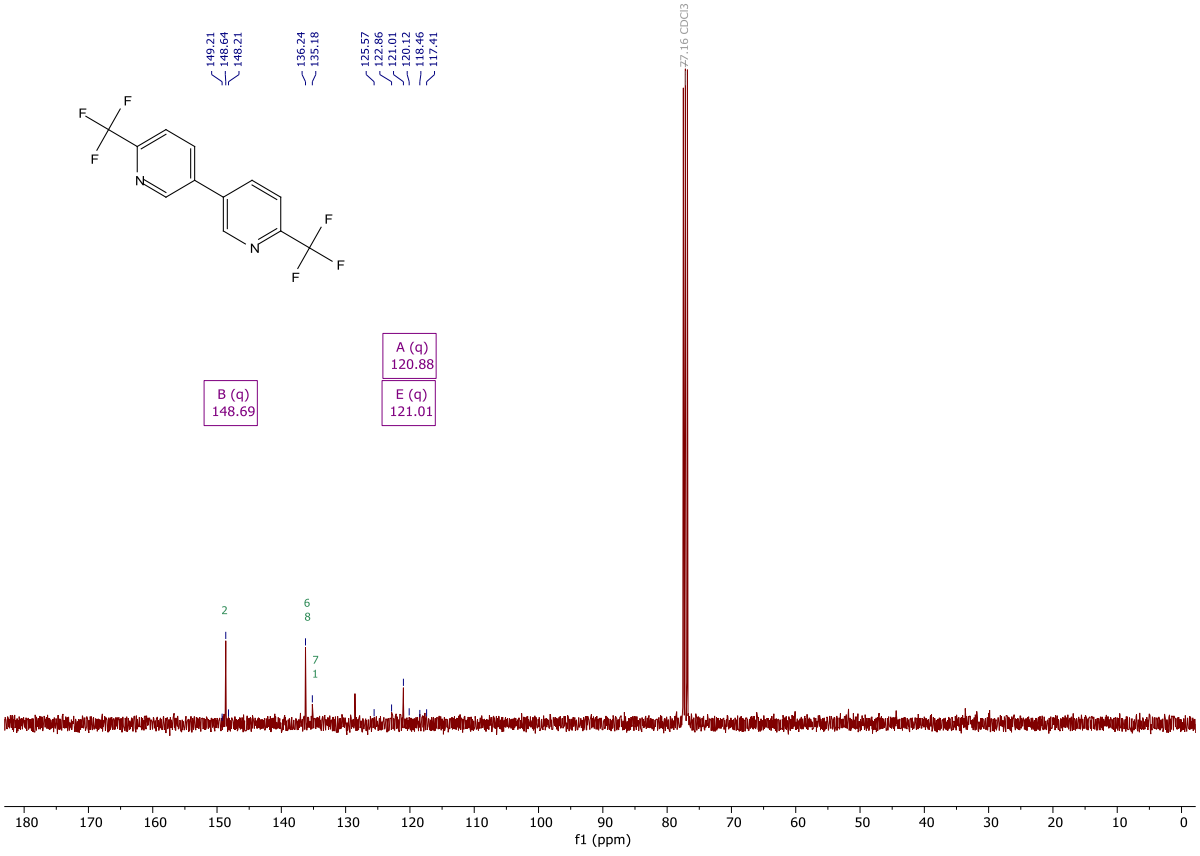


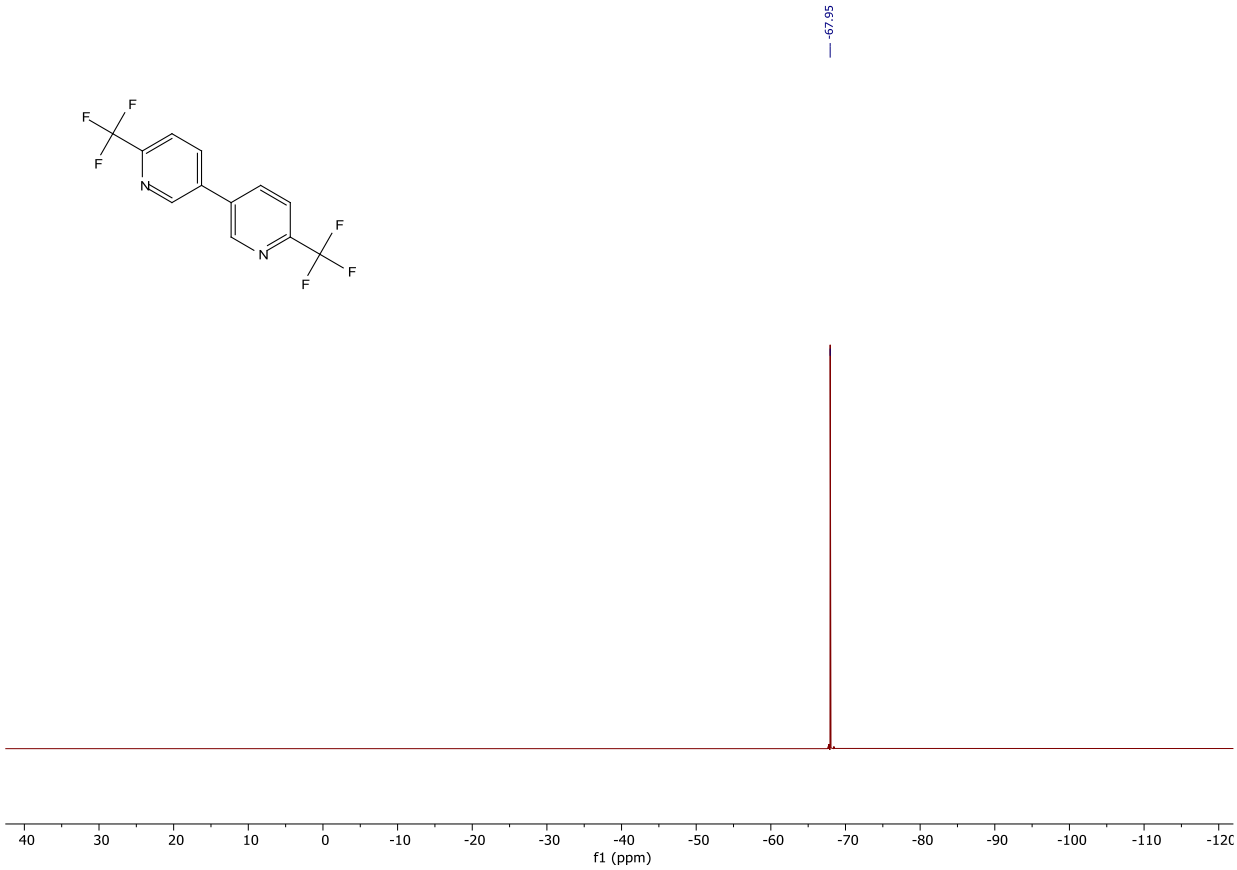


6,6'-Bis(trifluoromethyl)-3,3'-bipyridine (9c)





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F
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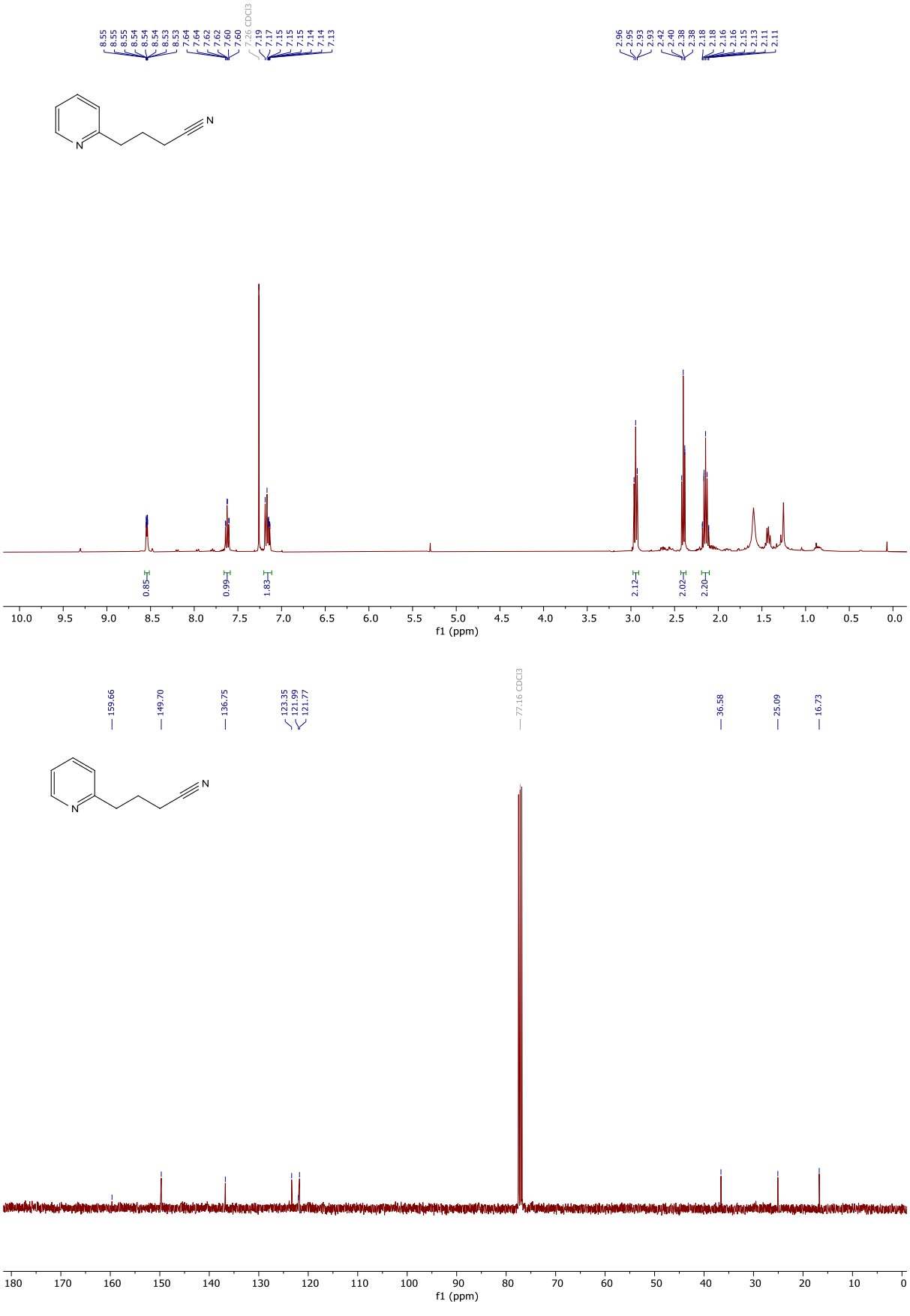
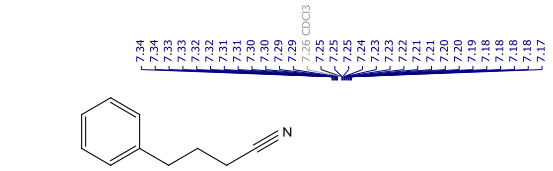
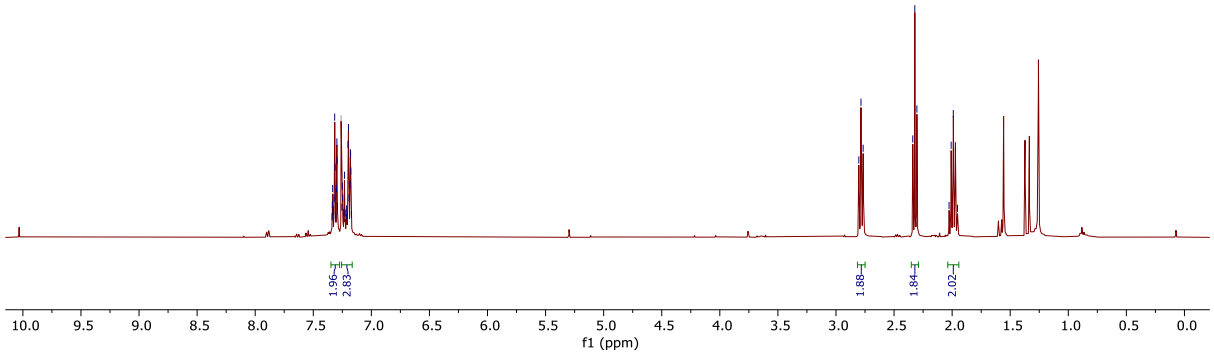
F
N
N
F
F
F
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
f1 (ppm)

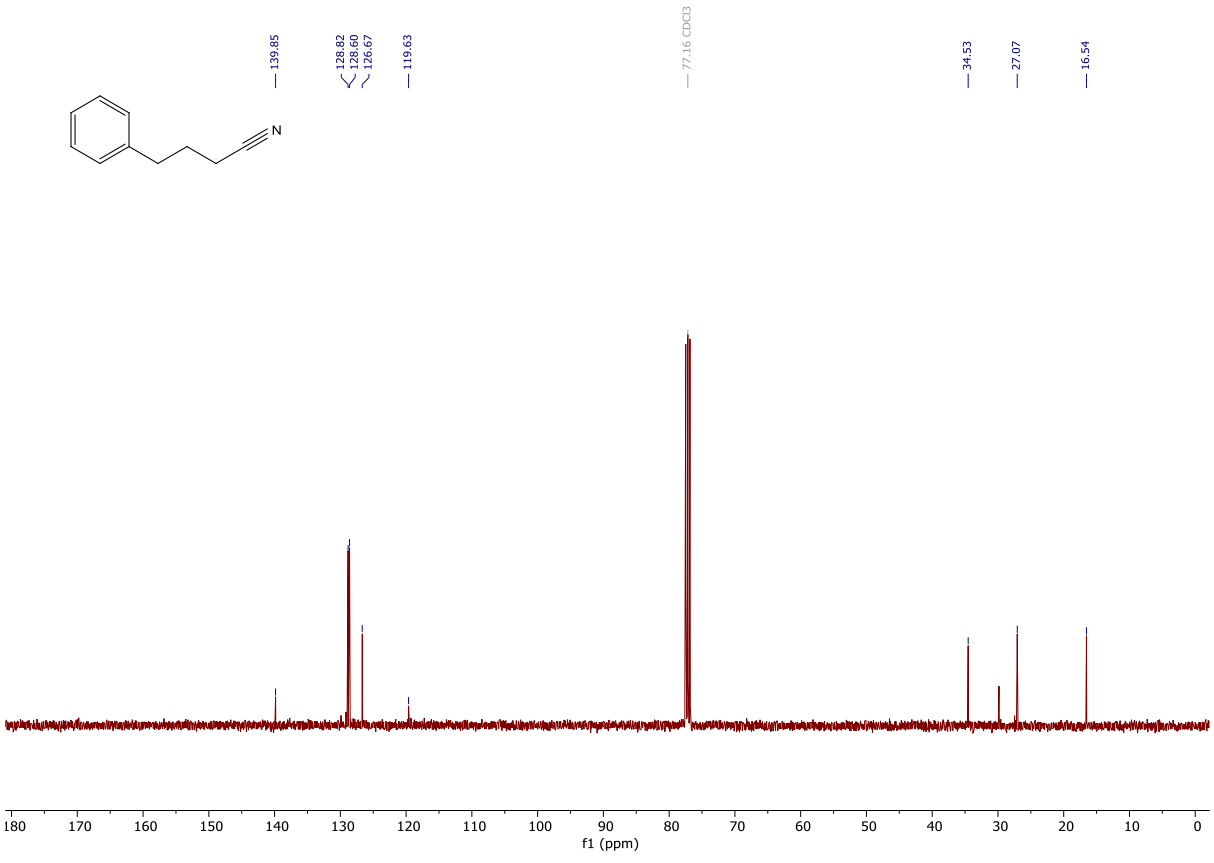
4-(Pyridin-2-yl)butanenitrile (10a)



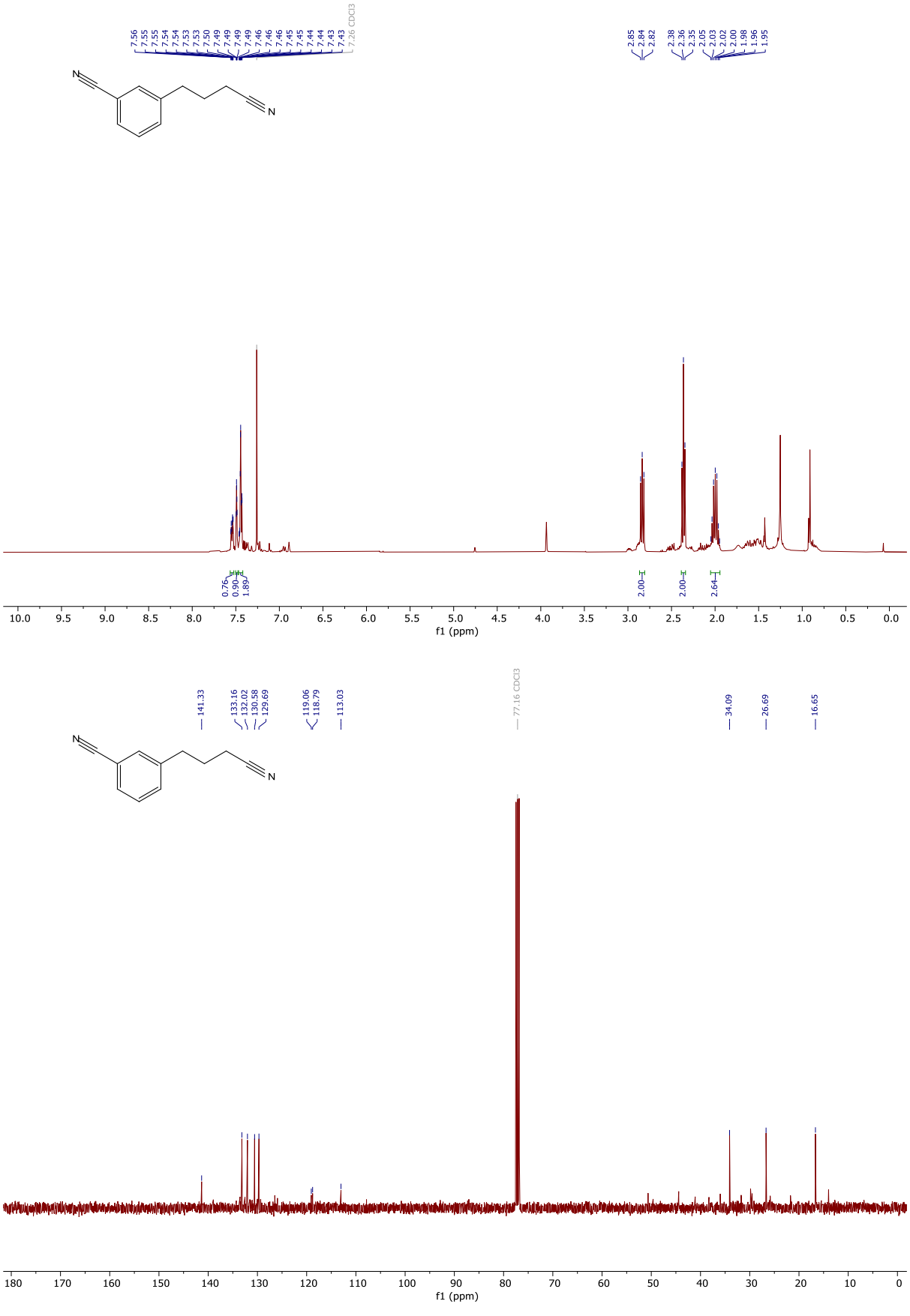
4-Phenylbutanenitrile (10b)



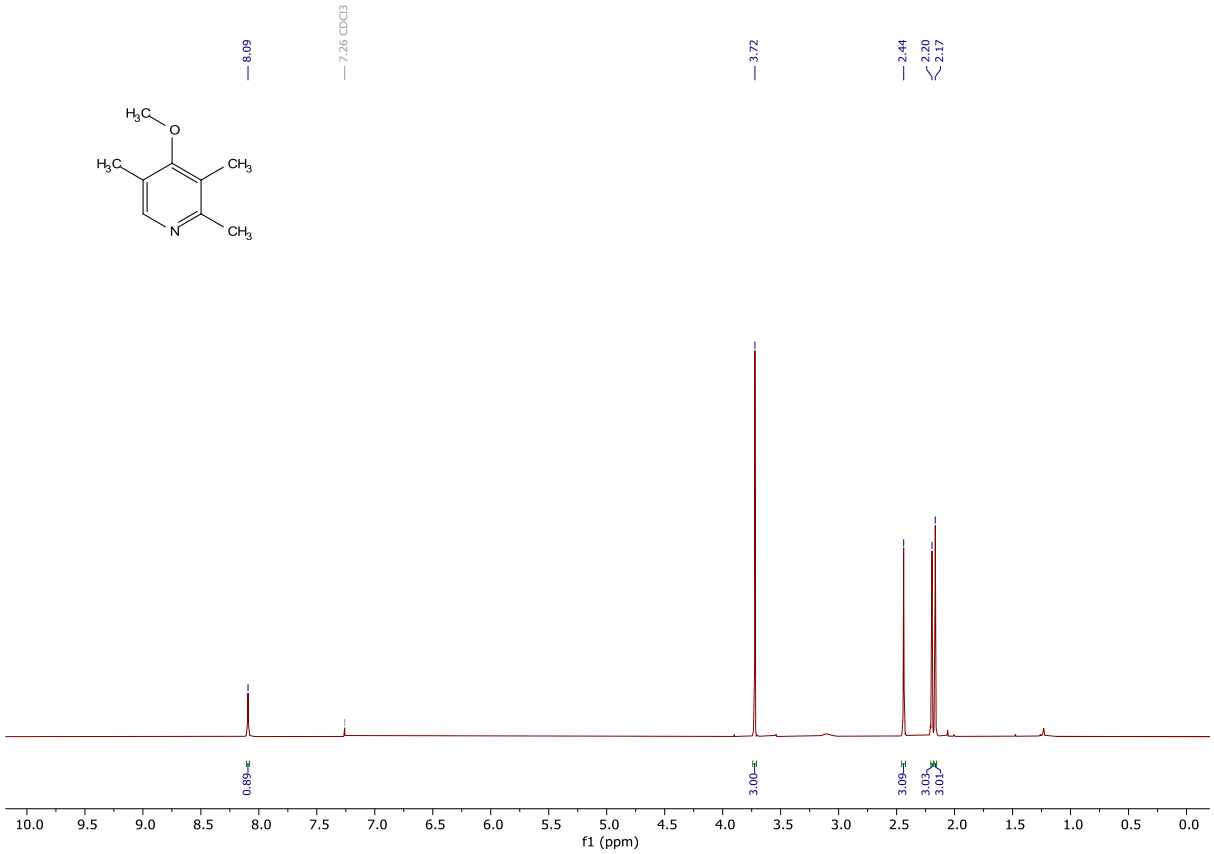


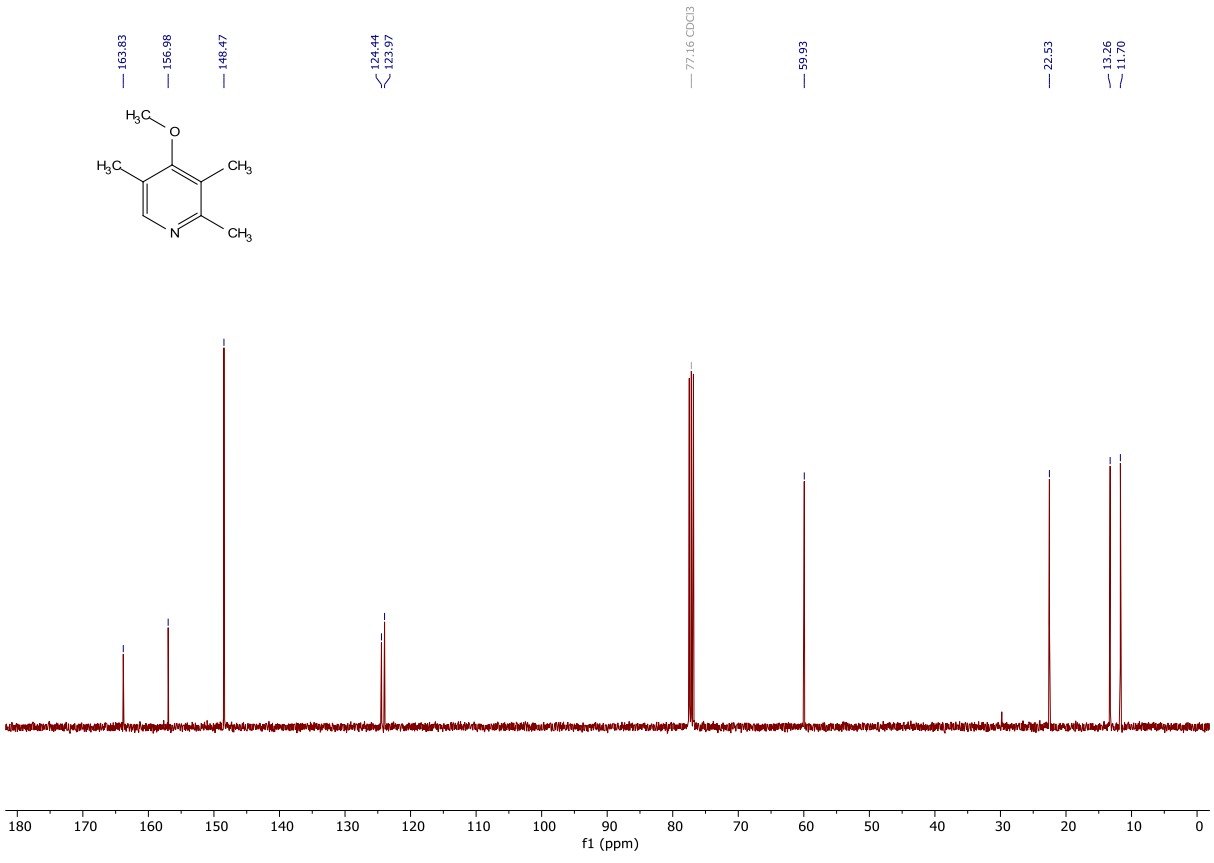


3-(3-Cyanopropyl)benzonitrile (10c)

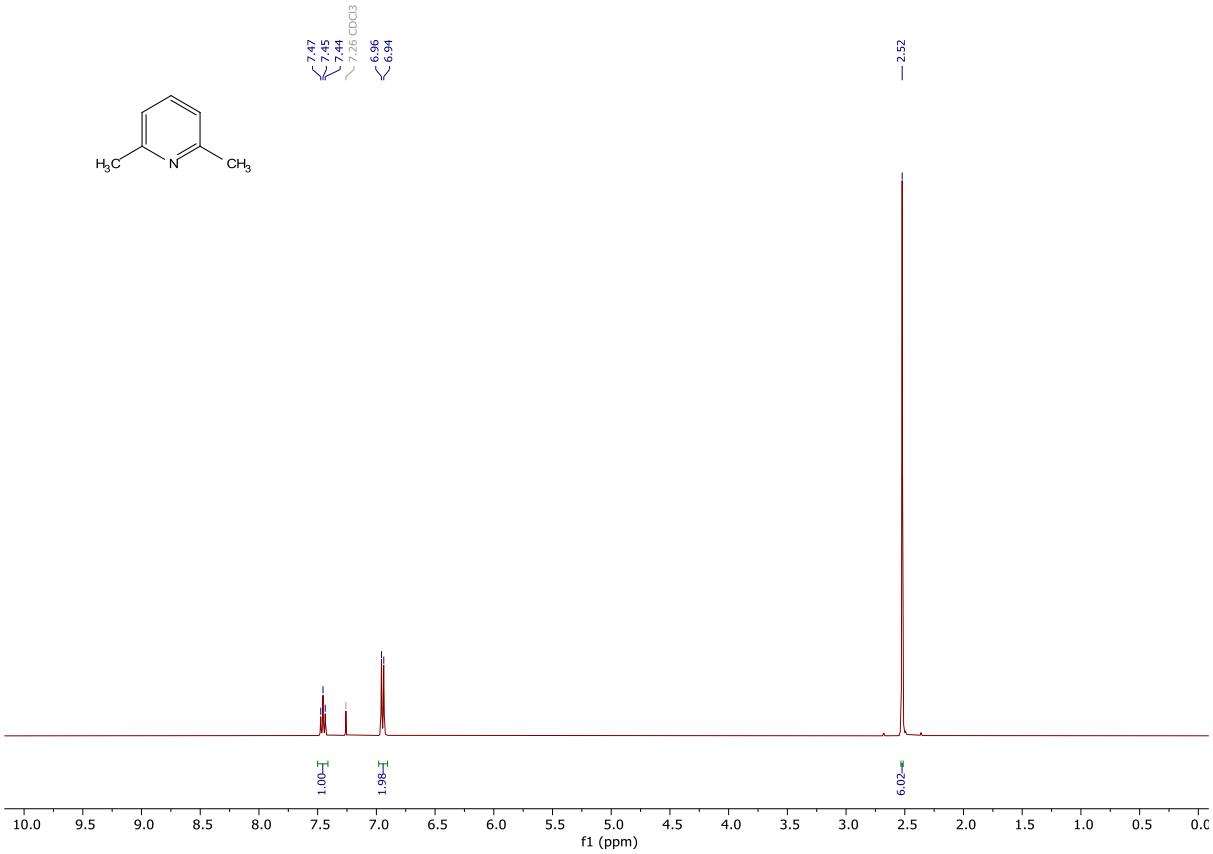


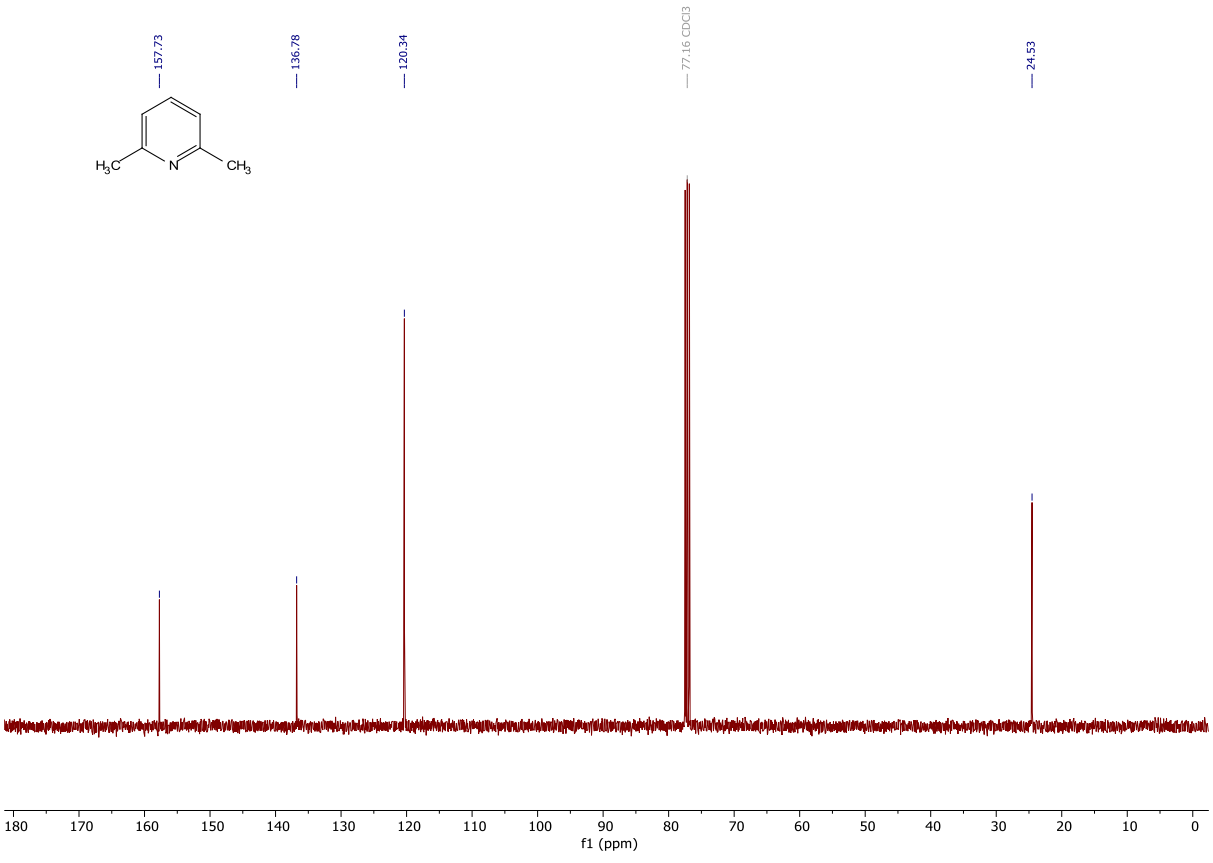
4-Methoxy-2,3,5-trimethylpyridine (11a)



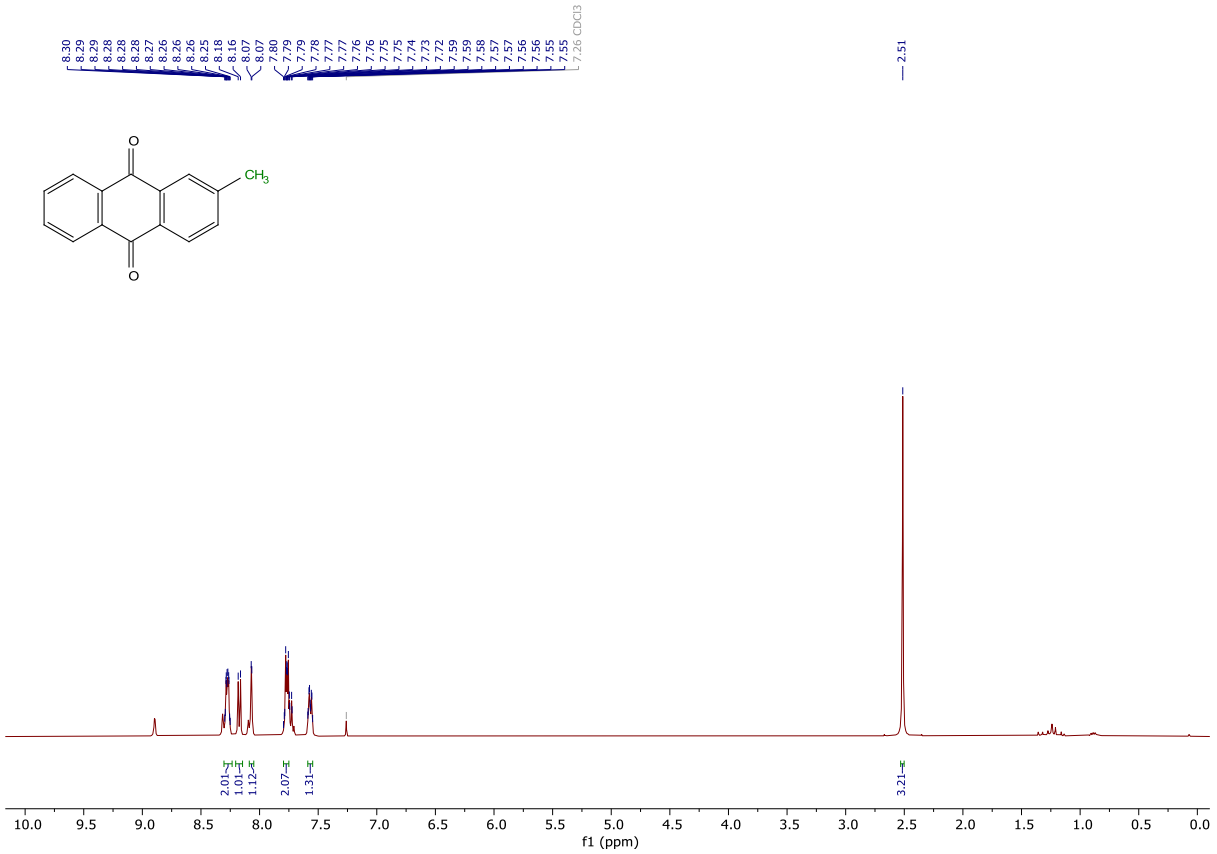


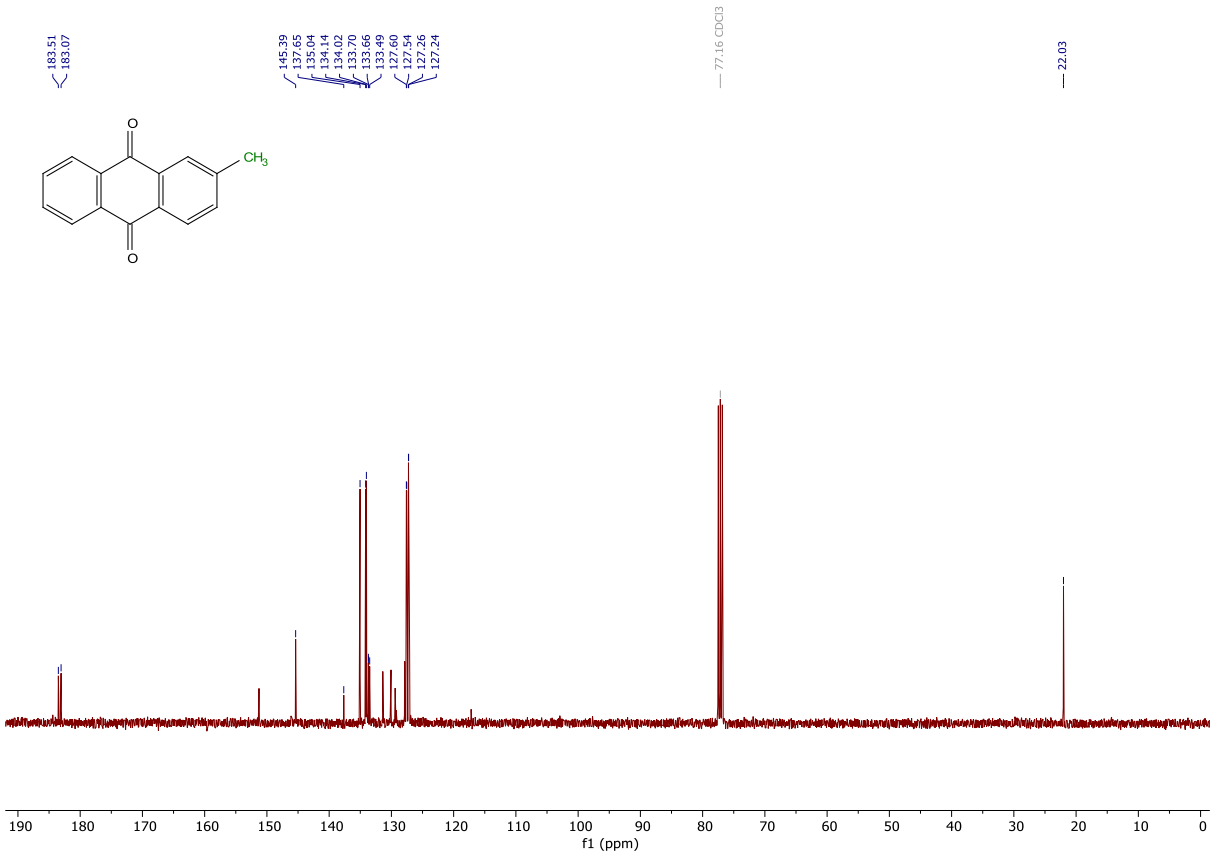
2,6-Dimethylpyridine (11b)



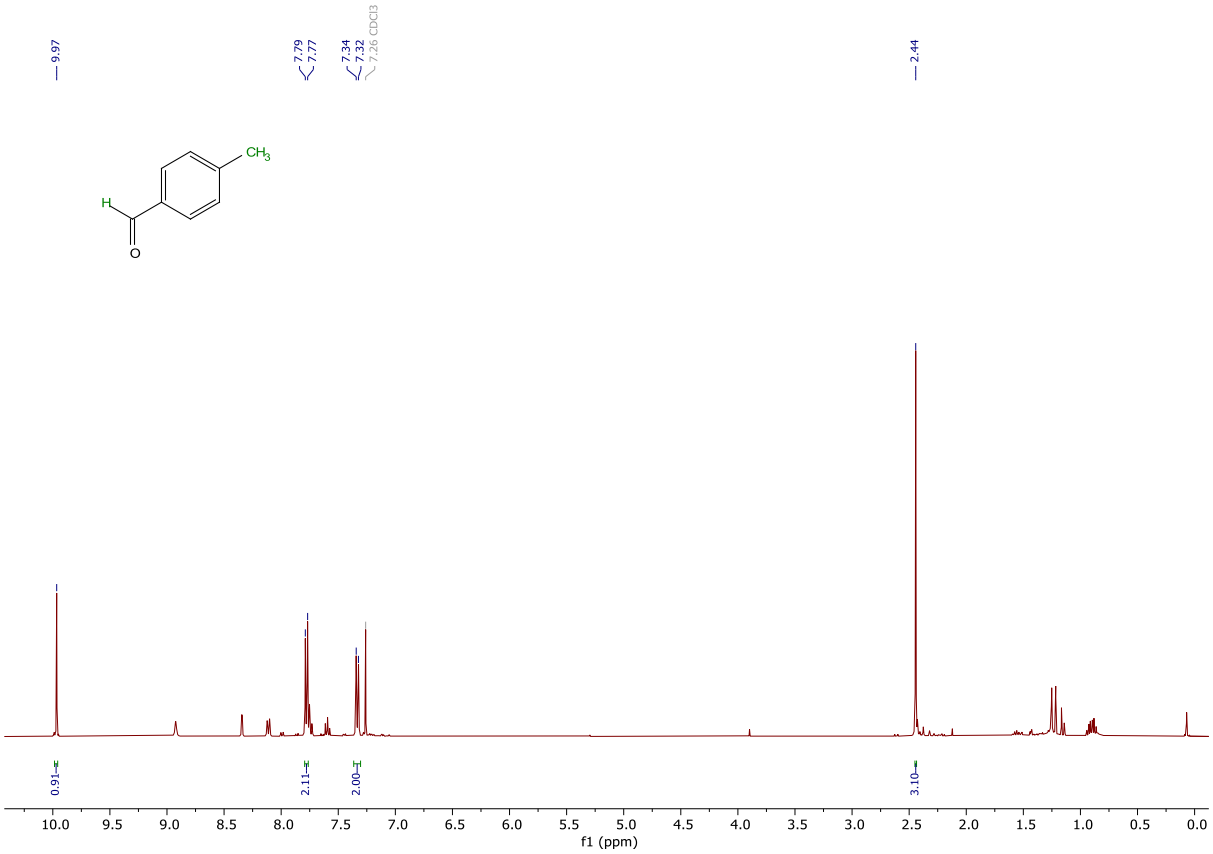


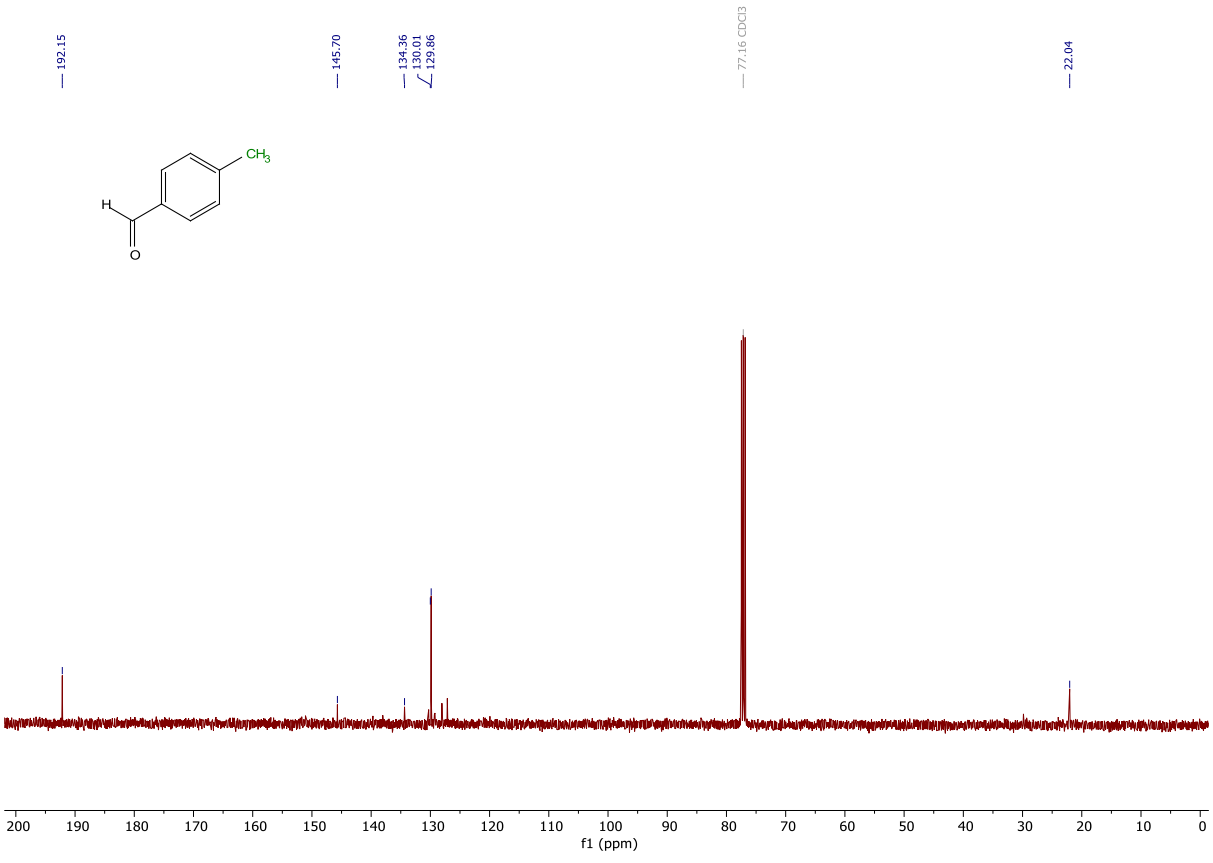
2-Methylanthracene-9,10-dione (11c)



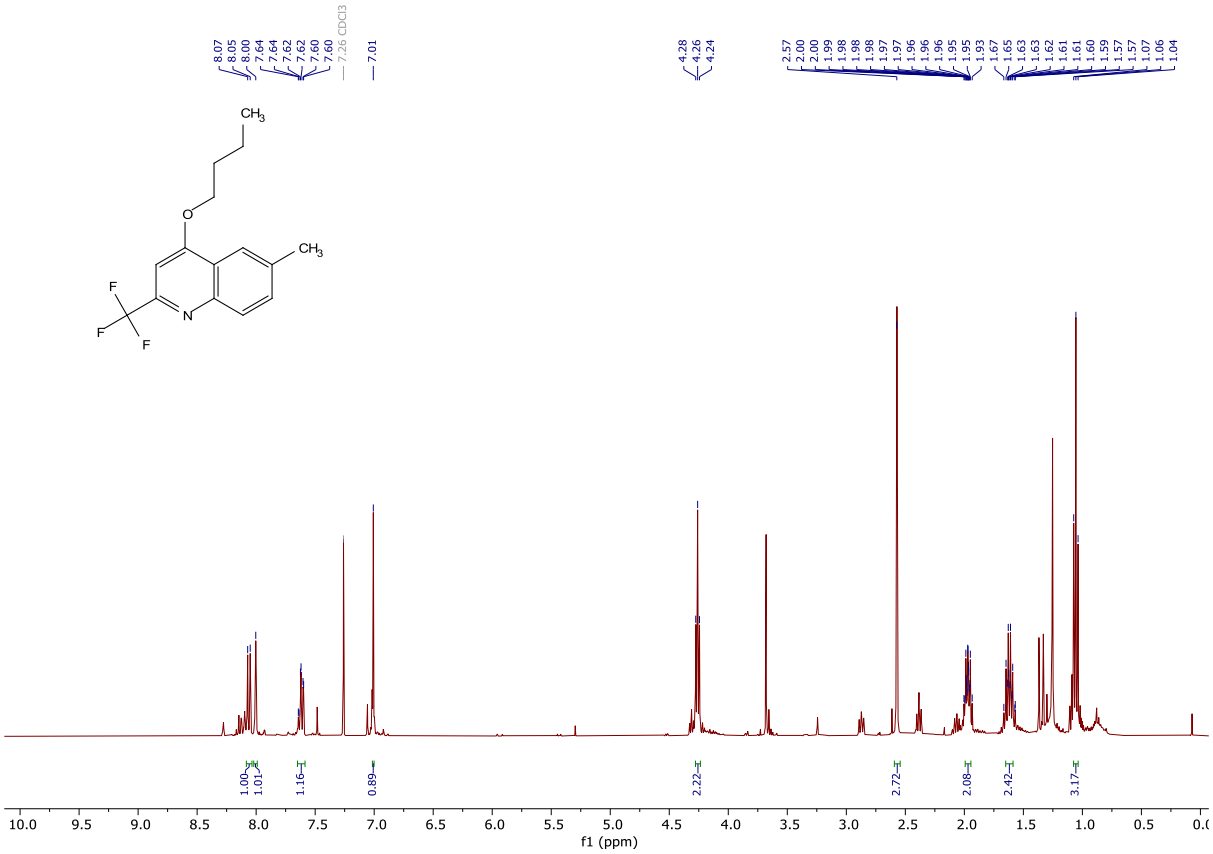


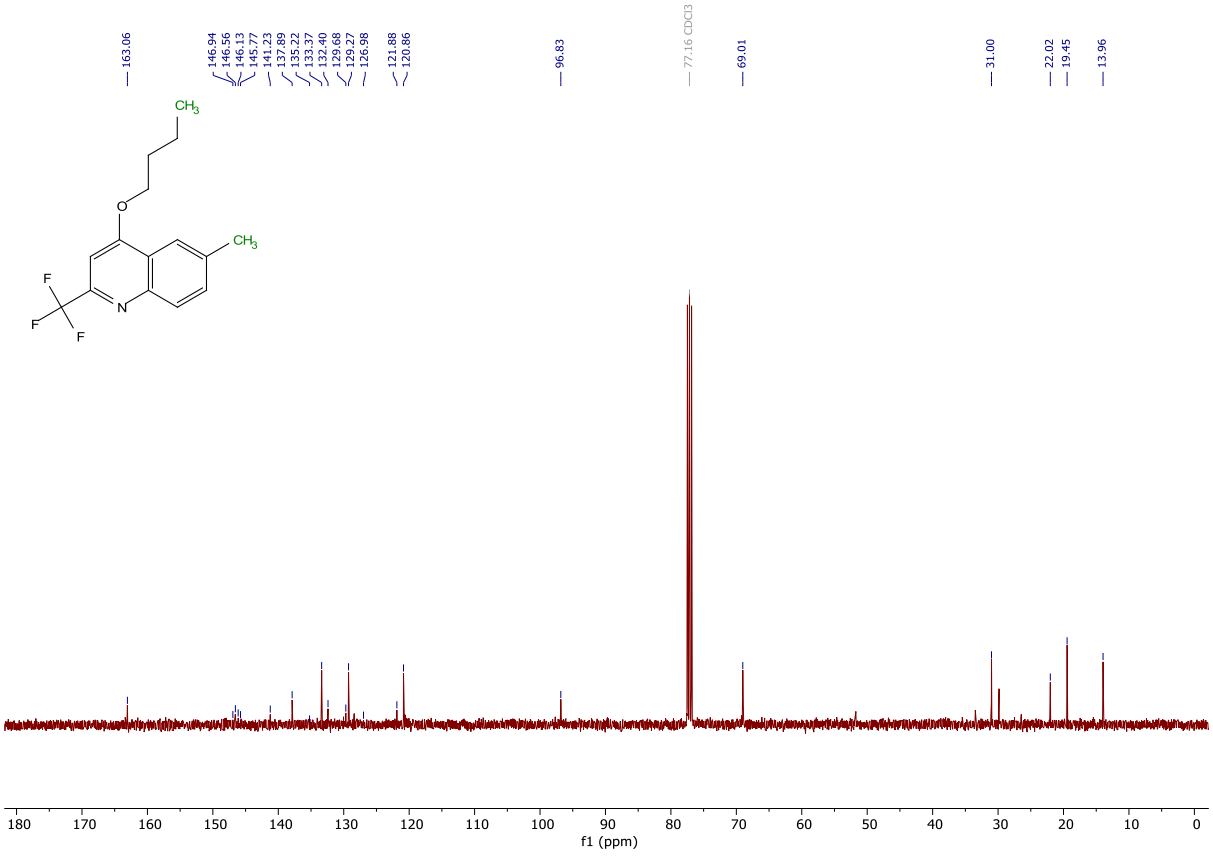
4-Methylbenzaldehyde (11d)

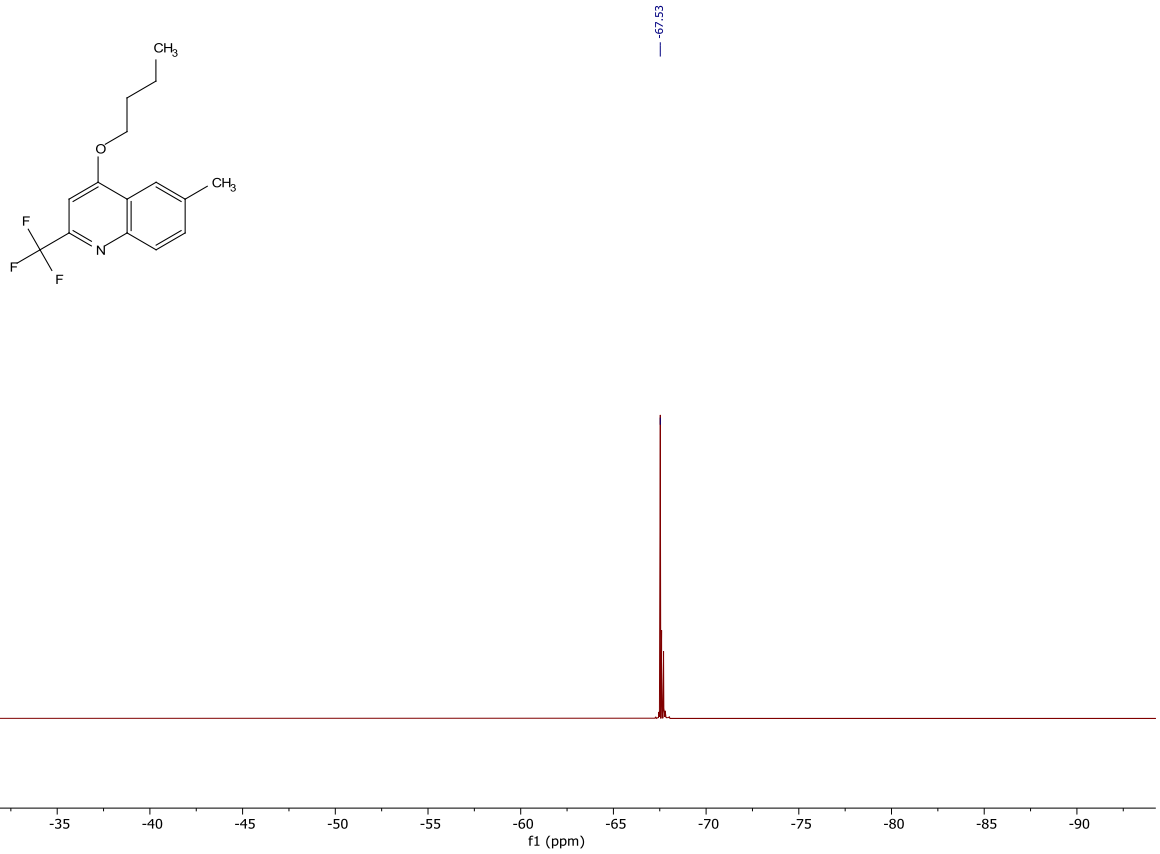




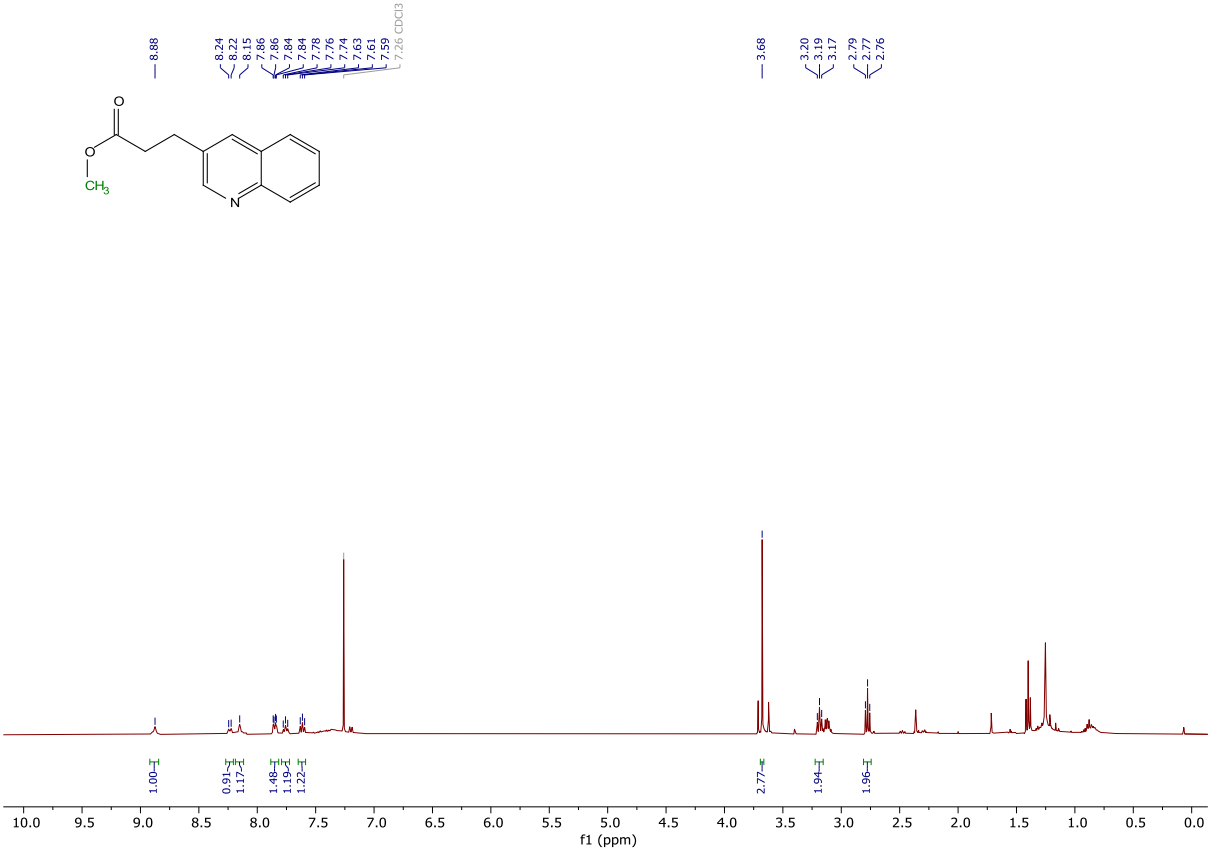
4-Butoxy-6-methyl-2-(trifluoromethyl)quinoline (11e)



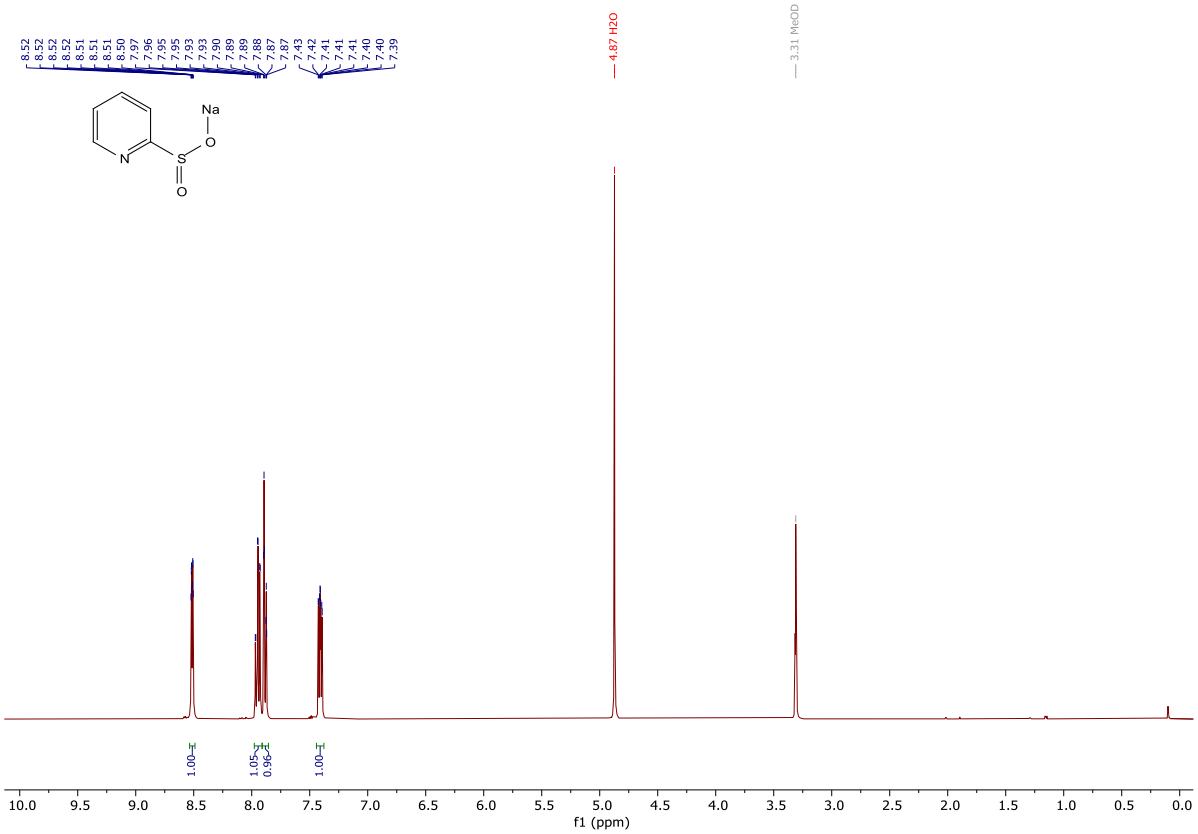


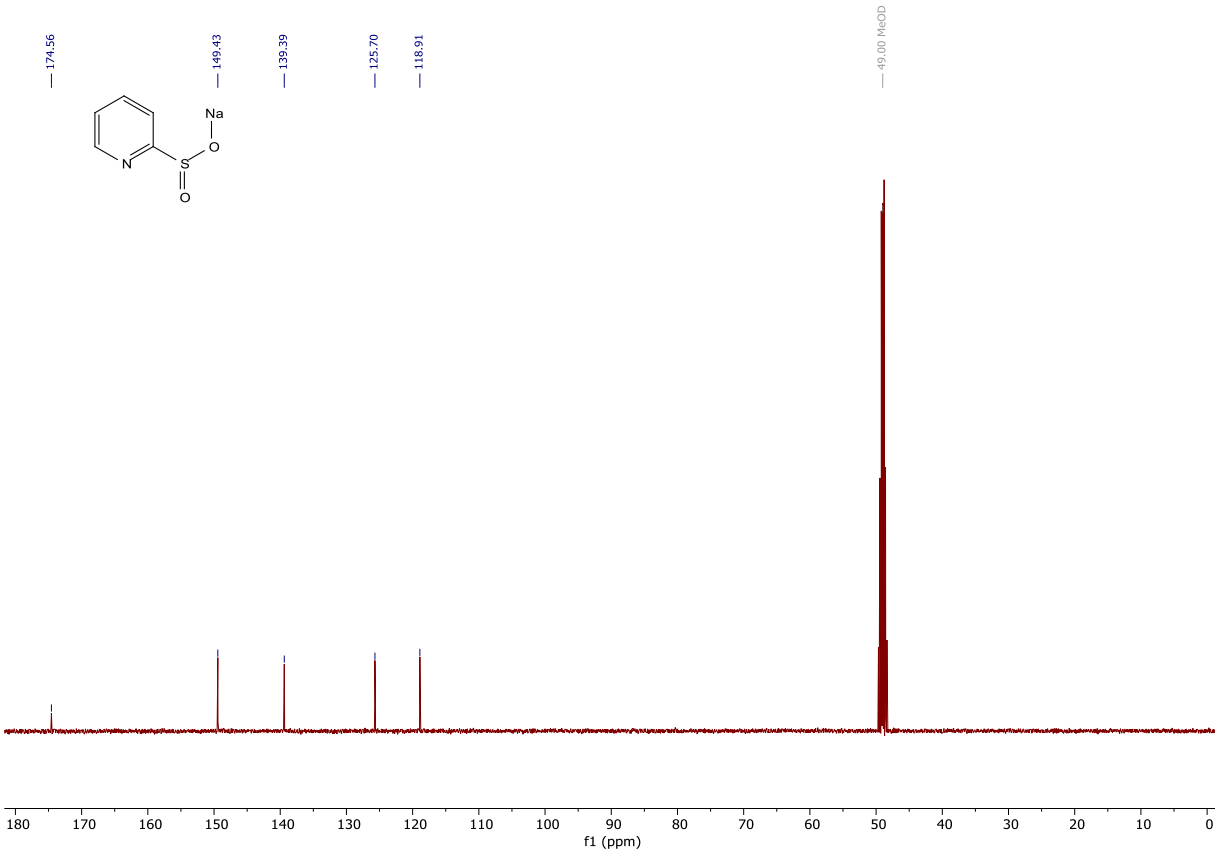


Methyl 3-(quinolin-3-yl)propanoate (14)

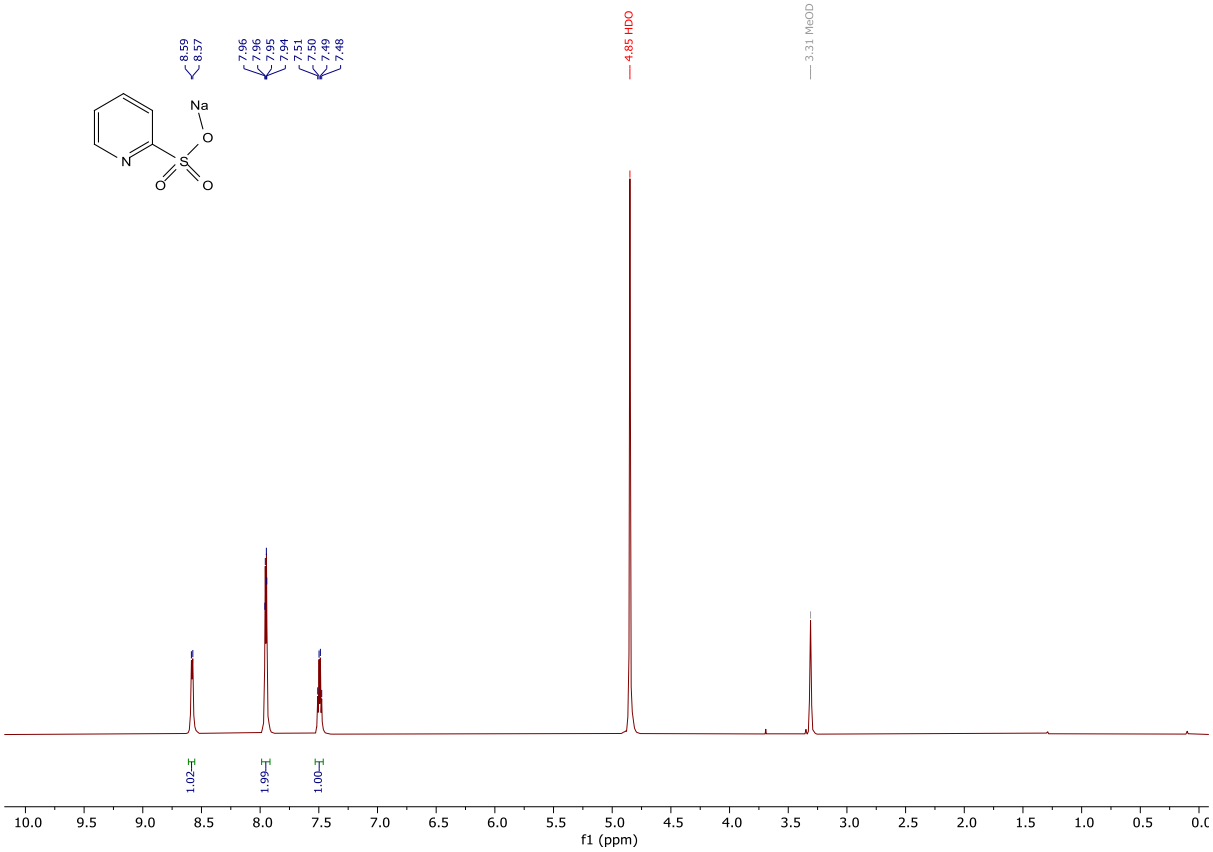


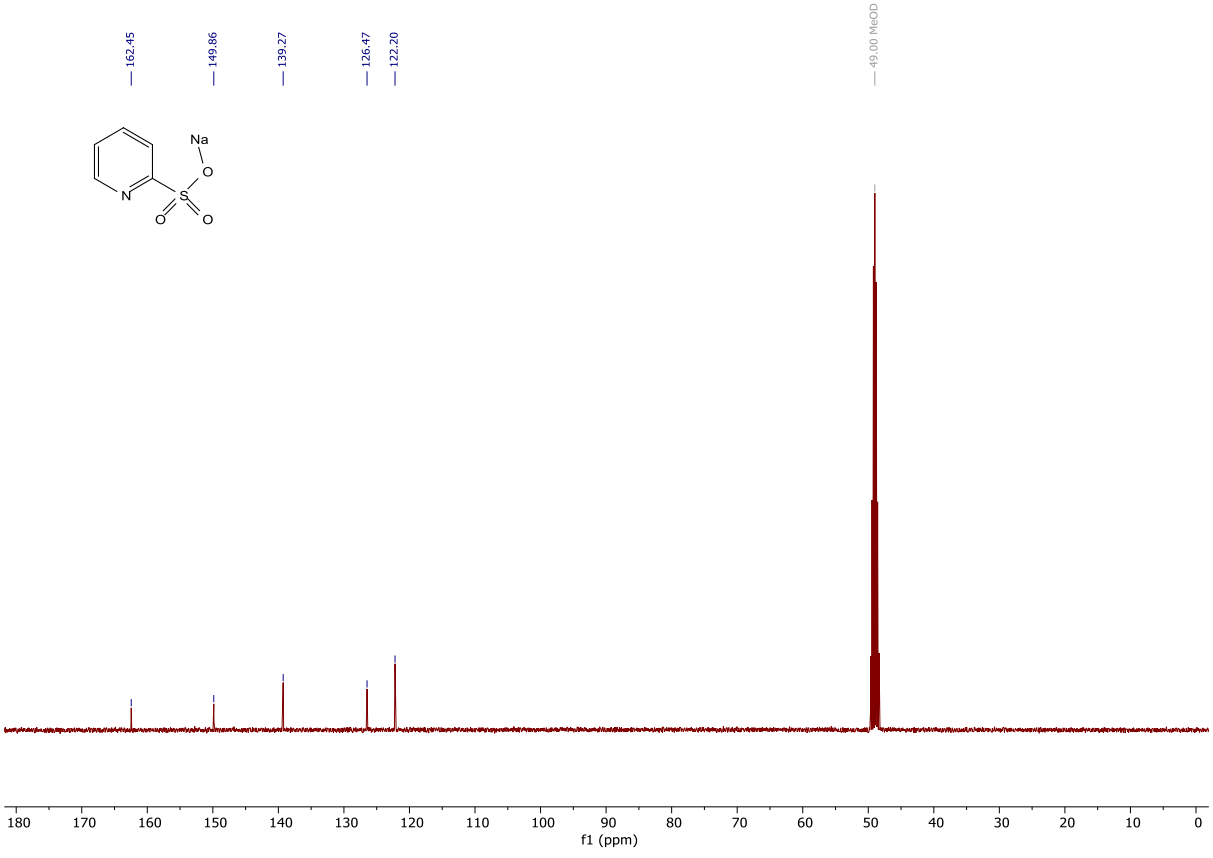
Sodium pyridine-2-sulfinate (15a)



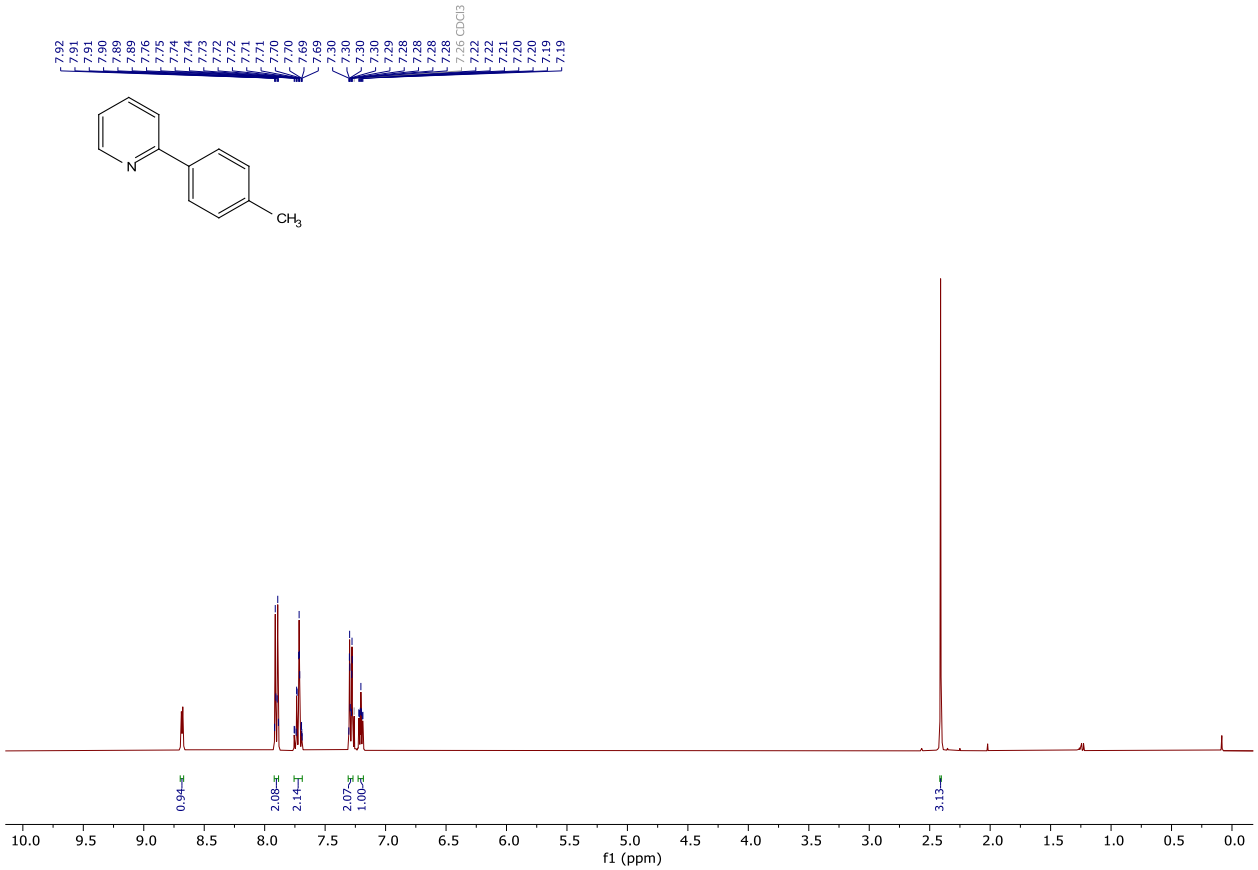


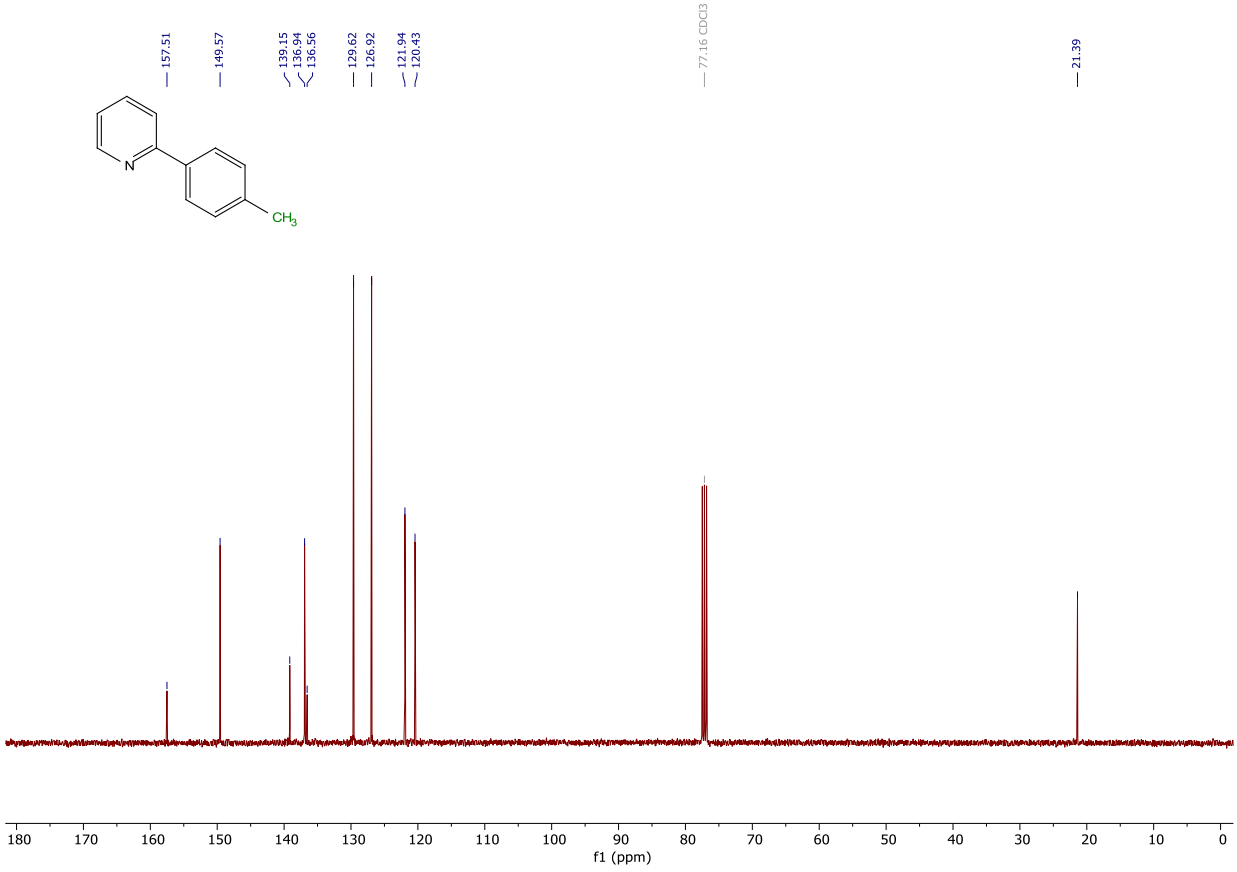
Sodium pyridine-2-sulfonate (15b)



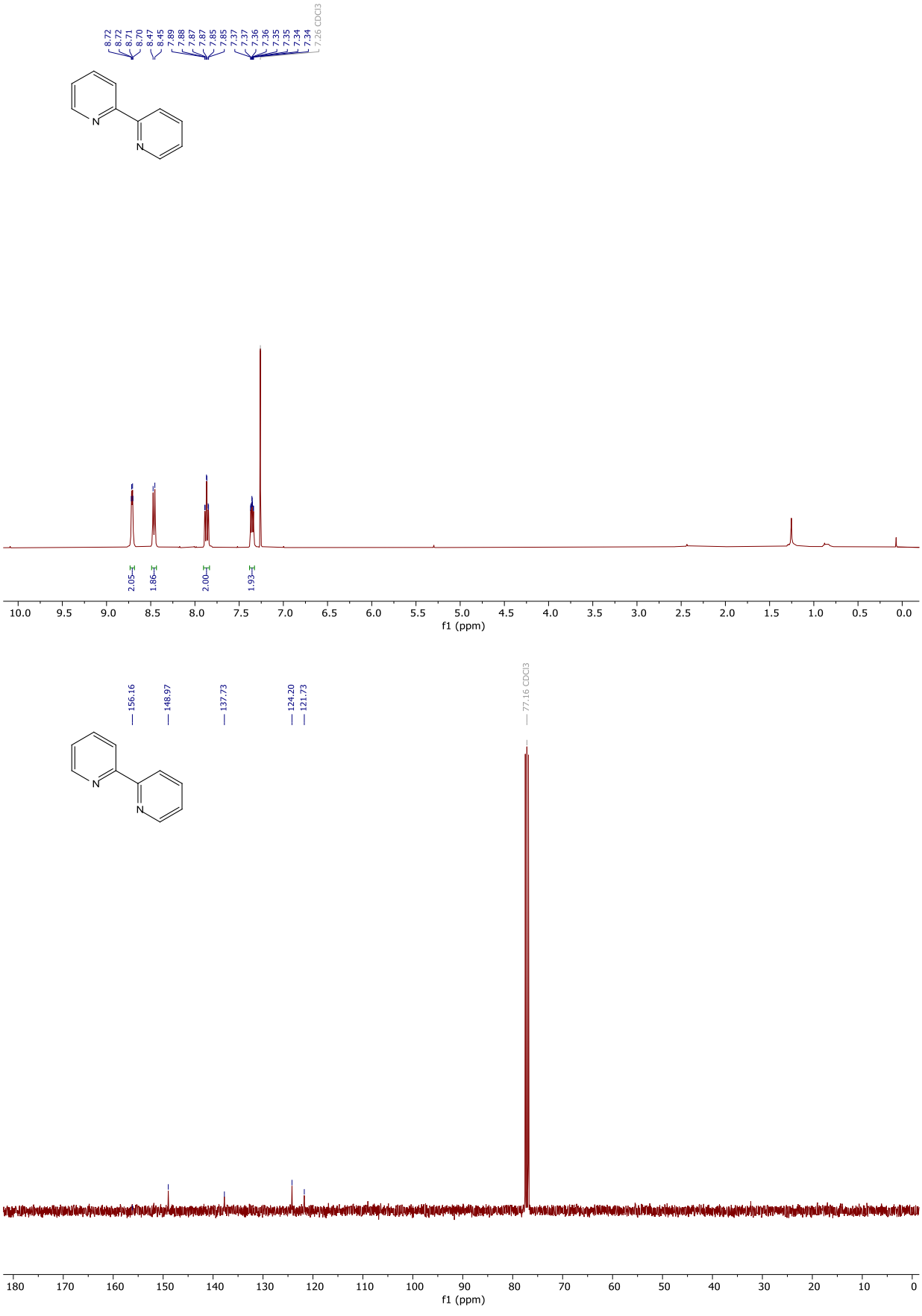


2-(*p*-Tolyl)pyridine (16a)

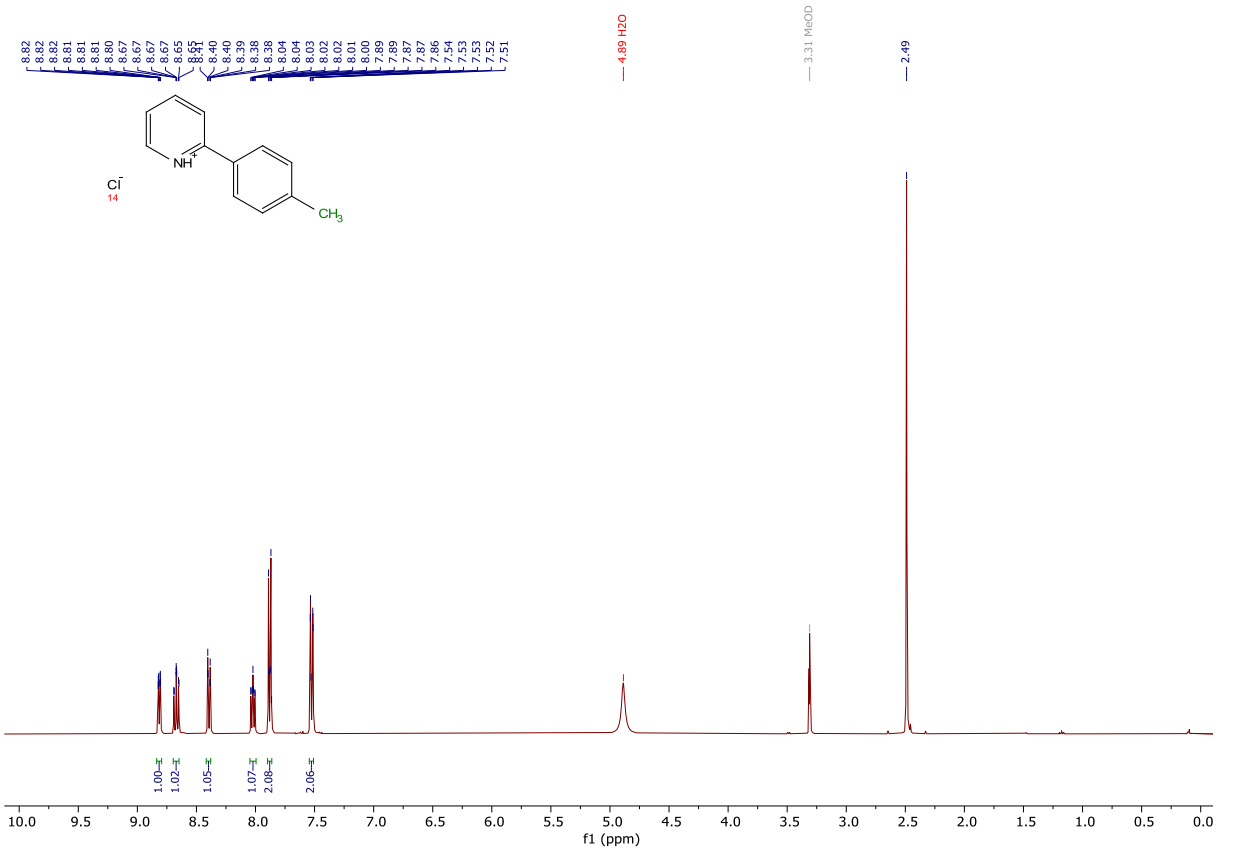


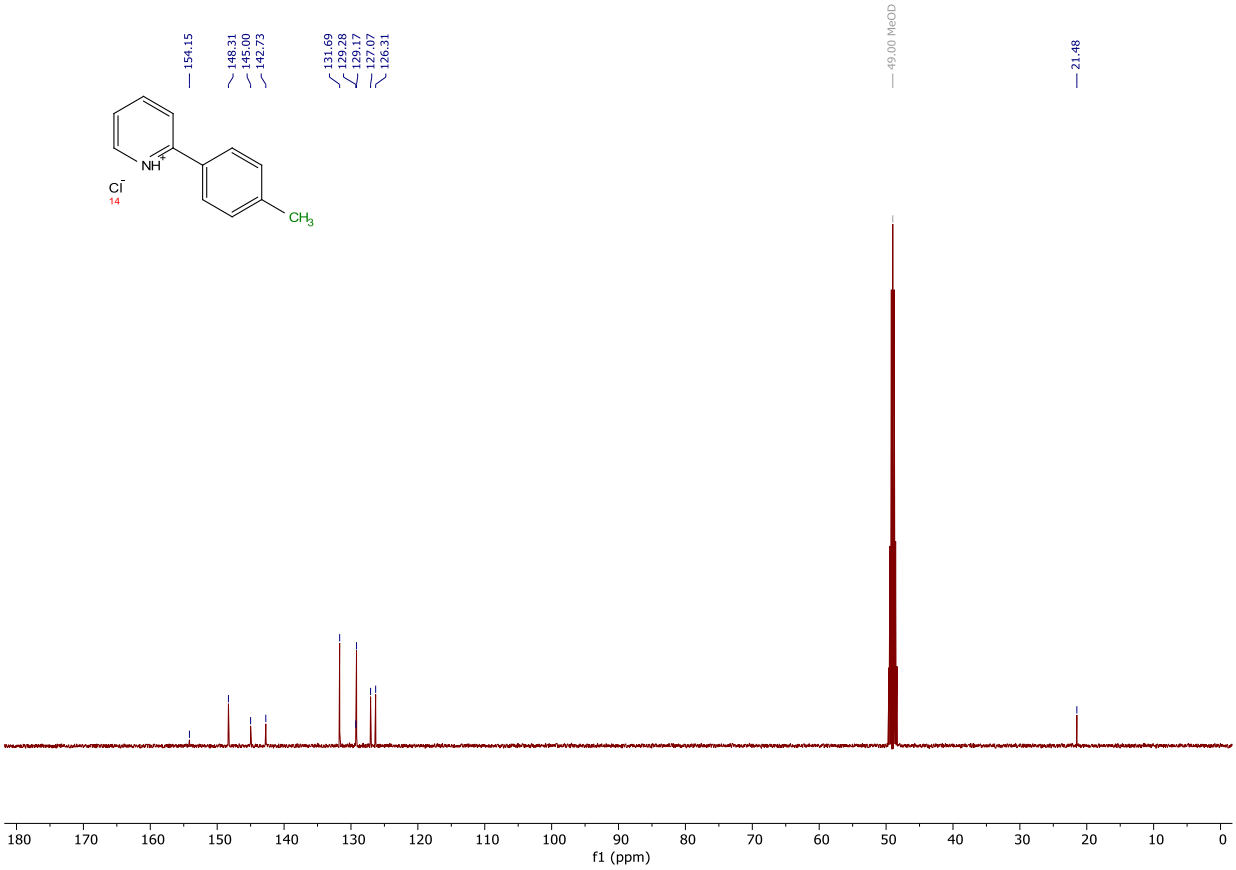


2,2'-Bipyridine (16b)



2-(*p*-Tolyl)pyridin-1-ium chloride (16c)





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