UNIVERSIDADE DE SÃO PAULO

FACULDADE DE CIÊNCIAS FARMACÊUTICAS DE RIBEIRÃO PRETO

Development of new selective synthetic methods en route to privileged scaffolds of pharmaceutical relevance

Desenvolvimento de novos métodos sintéticos seletivos visando estruturas privilegiadas de relevância farmacêutica

Thiago dos Santos

Ribeirão Preto
2022

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Doctoral thesis presented to the Graduate Program of School of Pharmaceutical Sciences of Ribeirão Preto/USP for the degree of Doctor in Sciences.

Concentration Area: Natural and synthetic products.

Supervisor: Prof. Dr. Giuliano Cesar Clososki

Co-supervisor: Prof. Dr. Till Opatz

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1. Nitriles. 2. Metalation. 3. Building blocks. 4. Glucose. 5. 2,3-dihydroquinazolin-4(1*H*)-ones.

APPROVAL PAGE

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RESUMO

DOS SANTOS, T. **Desenvolvimento de novos métodos sintéticos seletivos visando estruturas privilegiadas de relevância farmacêutica**. 2021. 262f. Tese (Doutorado). Faculdade de Ciências Farmacêuticas de Ribeirão Preto – Universidade de São Paulo, Ribeirão Preto, 2021.

Desde os pioneiros trabalhos de Gilman e Bebb, e Wittig e Furhmann seguidos por importantes contribuições incluindo Snieckus, a metalação *orto*-dirigida (D*o*M) tem sido empregada na funcionalização de diversos sistemas. Particularmente, os amidetos de 2,2,6,6-tetrametilpiperidil de Knochel e colaboradores apresentam excelente solubilidade em THF e tolerância a grupos funcionais além de boa estabilidade térmica. O grupo ciano é de grande interesse em D*o*Ms seguido do fluoro como destacado no trabalho de Schlosser. Considerando a viabilidade do emprego das bases de Knochel em D*o*Ms e a potencial aplicação de nitrilas fluoradas como blocos construtores, o primeiro projeto compreendeu a metalação regiosseletiva e funcionalização de diversas nitrilas fluoradas e posterior aplicação no preparo de 4-aminoquinazolinas. Cerca de 47 nitrilas funcionalizadas (45-90%) foram preparadas via TMPMgCl·LiCl ou $(TMP)_2Zn\cdot 2MgCl_2\cdot 2LiCl$ com a exploração de novos e insuficientemente estudados sítios de metalação. Adicionalmente, uma estratégia de difuncionalização foi possível e os blocos construtores funcionalizados aplicados na síntese de relevantes heterociclos. A 2,3-diidroquinazolin-4(1*H*)-ona (DHQ) é uma estrutura privilegiada e presente em várias moléculas bioativas incluindo fármacos e candidatos a fármacos. A glicose, como um recurso renovável, pode ser facilmente obtida de biomassa lignocelulósica e empregada em processos redutivos sob condições alcalinas. O único método direto disponível para a obtenção de DHQs a partir de 2-nitrobenzonitrila demanda excesso de ácido borônico e cobre como catalizador. Assim, o segundo projeto visou o uso de glicose como um agente redutor sustentável em solução aquosa de carbonato de potássio para a síntese de DHQs derivadas da 2-nitrobenzonitrila de maneira *one-pot*. Um protocolo *one-pot* baseado em ciano-hidratação, nitro redução, formação de imina e ciclização empregando glicose em meio aquoso alcalino foi estabelecido fornecendo DHQs em rendimentos de 18-90%. A competição entre a função aldeído da glicose com o carbonílico adicionado não foi verificada e as DHQs podem ser convertidas em suas respectivas quinazolinonas encontrando mais ampla aplicação em química medicinal. Adicionalmente, um estudo de reposicionamento do fármaco Tenofovir foi efetuado.

Palavras-chave: Regiosseletividade; Metalação; TMP-bases; Nitrilas; 4-aminoquinazolinas; Glicose; 2,3-diidroquinazolin-4(1*H*)-ona; Eco-friendly; Química Verde.

ABSTRACT

DOS SANTOS, T. **Development of new selective synthetic methods en route to privileged scaffolds of pharmaceutical relevance**. 2021. 262p. Thesis (Doctoral). Faculdade de Ciências Farmacêuticas de Ribeirão Preto – Universidade de São Paulo, Ribeirão Preto, 2021.

Since the pioneering works of Gilman and Bebb, and Wittig and Furhmann accompanied by important contributions including Snieckus, directed *ortho*-metalation reactions (D*o*M) have found great application in the functionalization of diverse systems. Particularly, the 2,2,6,6-tetramethylpiperidyl bases by Knochel and co-workers show excellent solubility in THF, functional group tolerance, and great stability at room and higher temperatures. The cyano group is of great interest in *Do*Ms followed by fluoro as highlighted by the work of Schlosser. Therefore, considering the feasibility of Knochel bases in D*o*Ms and the potential application of fluorinated nitriles as building blocks, the first project comprised the regioselective metalation-functionalization of diverse fluorinated nitriles and their application in the synthesis of 4-aminoquinazolines. About 47 diverse functionalized nitriles (45-90%) with the exploration of new and scarcely investigated metalation sites were prepared by metalation with TMPMgCl·LiCl or $(TMP)_2Zn\cdot 2MgCl_2\cdot 2LiCl$. Besides, a difunctionalization strategy was possible and the building blocks were applied to construct relevant heterocycles. The 2,3-dihydroquinazolin-4(1*H*)-one (DHQ) is a privileged scaffold in a multitude of biologically active molecules including marketed pharmaceuticals and potential drug candidates. Glucose, as a renewable source, can be easily obtained from lignocellulosic biomass and applied in reduction processes under alkaline conditions. The only available method to directly access DHQs from 2-nitrobenzonitrile requires an excess of diboronic acid and copper as a catalyst in a water/methanol mixture. Thus, the second project envisioned the use of glucose as an eco-friendly reductant in an aqueous solution of potassium carbonate for the synthesis of DHQs from 2-nitrobenzonitrile in a one-pot fashion. A one-pot protocol based on nitrile hydration, nitro-reduction, imine formation, and cyclization with glucose in alkaline water was successfully established affording DHQs in yields 18-90%. No competition of the aldehyde from glucose with the externally added carbonyl compound was verified, and the synthesized DHQs in this work can be further converted to the corresponding quinazolinones finding even wider application in Medicinal Chemistry. Additionally, a study on the repositioning of the drug Tenofovir was performed.

Keywords: Regioselectivity; Metalation; TMP-bases; Nitriles; 4-aminoquinazoline; Glucose; 2,3-dihydroquinazolin-4(1*H*)-one; Eco-friendly; Green Chemistry.

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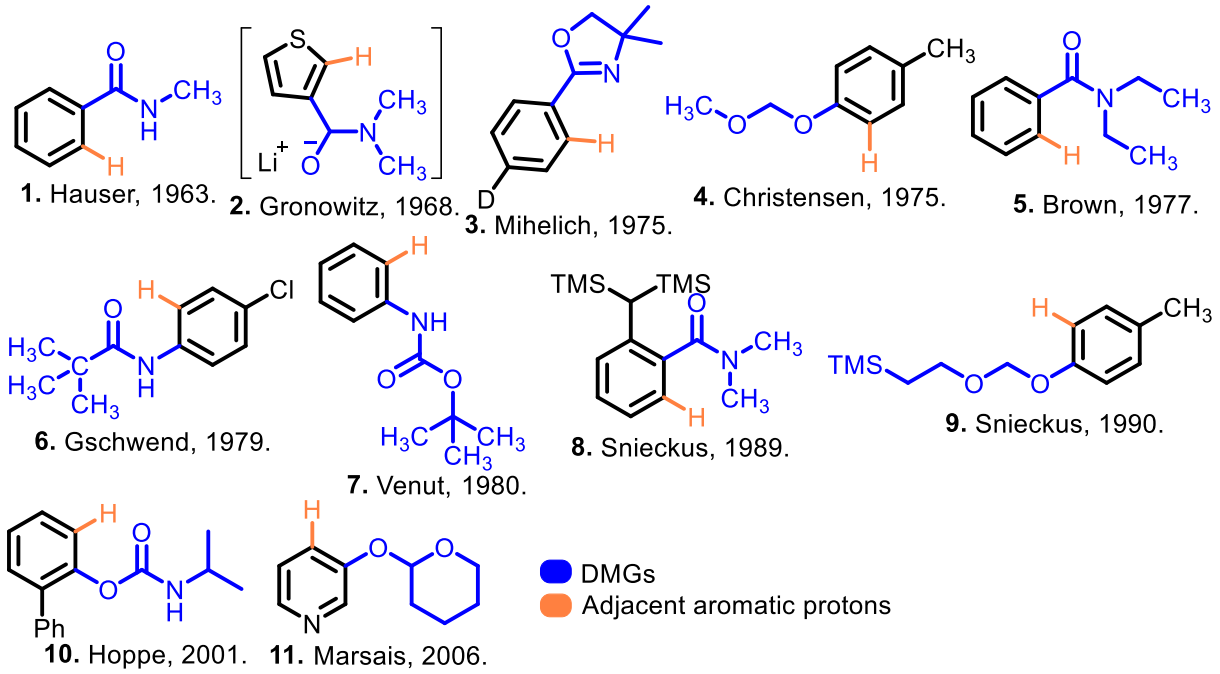
1. INTRODUCTION

1.1 DIRECTED *ORTHO*-METALATION

The first reports of directed *ortho*-metalation reactions (D*o*M) come from Gilman and Bebb[1] in 1939 and Wittig and Furhmann[2] in 1940, the *ortho*-lithiation of methoxy-bearing substrates such as 2-methoxydibenzofuran and anisole with *n*-Butyllithium or phenyl lithium, respectively. The scope of directed *ortho* metalation groups (DMGs) was later expanded[3] including the work of Hauser,[4] Gronowitz,[5] Gschwend,[6] Mihelich,[7] Brown,[8] Snieckus,[9] Christensen,[10] Venut,[11] Hoppe,[12] Marsais,[13] and their co-workers (**Figure 1**).

Figure 1. Some DMGs explored in the literature.



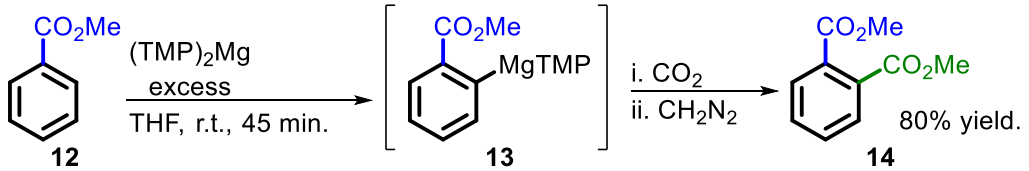
Source: GREEN; CHAUDER; SNIECKUS, 1999;[3b] MIAH *et al*., 2018.[3d]

The *ortho*-directing properties of DMGs can either relate to the establishment of a complex-induced proximity effect (CIPE) with the coordination of a heteroatom to the metal of a base with simultaneous proton transfer (e.g., Lithium in the case of LDA - Lithium diisopropylamide)[14] or the reduction in pK_a for the adjacent aromatic protons through inductive effect.[15]

Although lithium bases have been extensively applied to the deprotometalation of aromatic and heteroaromatic systems via D*o*Ms, there are important drawbacks: they normally demand low temperatures or the *in-situ* generation before metalation, and the organolithium intermediates are highly reactive and may lead to side products in the presence of some sensitive groups such as esters.[16]

As alternative methods, Hauser and co-workers developed diethyl- and diisopropylaminomagnesium bromides to promote the self-condensation of esters in the synthesis of β-keto esters.[17] In 1989, Eaton, Lee, and Xiong prepared the sterically hindered TMP-bases (2,2,6,6-tetramethylpiperidyl), TMPMgBr, and $(TMP)_2Mg$, for the *ortho*-magnesiation of aromatics as depicted in **Scheme 1**.[18] Later, Mulzer and co-workers reported the synthesis of TMPMgCl with the regioselective metalation of pyridinylcarbamates and pyridinecarboxamides.[19]

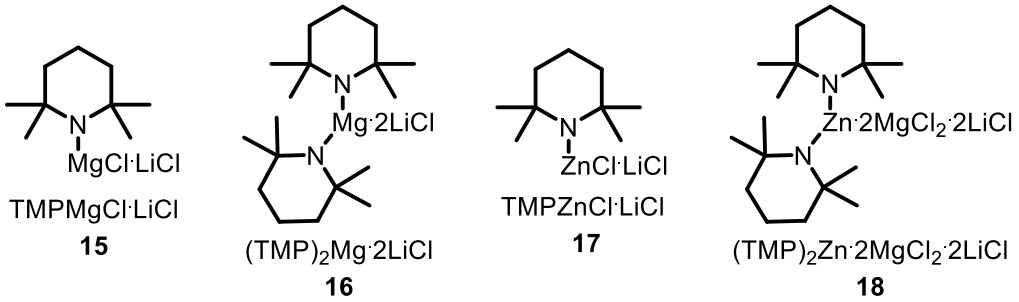
Scheme 1. The regioselective magnesiation of methyl benzoate with $(TMP)_2Mg$.



Source: EATON; LEE; XIONG, 1989.[18]

However, these magnesium-based bases displayed low solubility in common solvents and needed to be employed in excess (2-12 Equiv.)[20] in order to achieve great substrate conversions. To solve such problems, Knochel and co-workers developed the mixed Mg/Li, Zn/Li, and Zn/Mg/Li amides TMPMgCl·LiCl,[20] $(TMP)_2Mg{\cdot}2LiCl$,[21] TMPZnCl·LiCl,[22] $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[23] (**Figure 2**) with excellent solubility in THF and functional group tolerance, and great stability at room and higher temperatures. These TMP-bases have been successfully employed for the regioselective magnesiation and zincation of diverse heteroaromatic and aromatic systems, such as 1,5-naphthyridine scaffold,[24] quinolines,[25] indolizines,[26] oxazolines,[16b,27] 1,3,4-oxadiazoles and 1,2,4-triazoles,[28] 2-pyridones and 2,7-naphthyridones,[29] pyrazolo[1,5-*a*]pyridines,[30] 2- and 4-pyrones,[31], pyridines,[32] and 1*H*-imidazo[1,2-*b*]pyrazoles.[33]

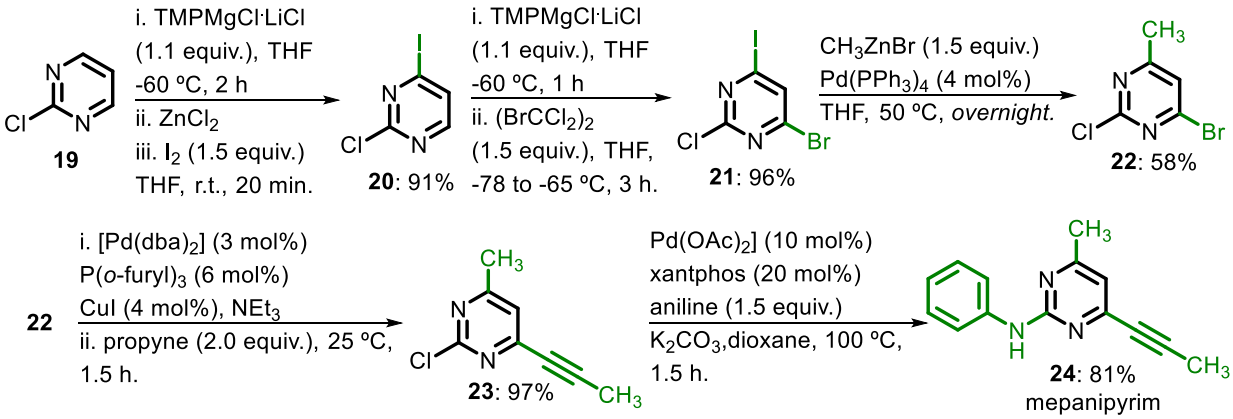
Figure 2. Developed TMP-bases by Knochel and co-workers.



Source: KRASOVSKIY; KRASOVSKAYA; KNOCHEL, 2006;[20] CLOSOSKI; ROHBOGNER; KNOCHEL, 2007;[21] UNSINN; FORD; KNOCHEL, 2013;[22] WUNDERLICH; KNOCHEL, 2007.[23]

Furthermore, the Knochel bases find direct application in the synthesis of valuable building blocks for the construction of natural products and drugs.[34] For example, Mosrin and Knochel obtained the fungicide mepanipyrim (**24**) in 40% overall yield from 2-chloropyrimidine **19** after two consecutive magnesiations with TMPMgCl·LiCl, followed by a Negishi cross-coupling with CH_3ZnBr, a Sonogashira reaction with propyne, and a Buchwald-Hartwig amination with aniline (**Scheme 2**).[35]

Scheme 2. Employment of TMPMgCl·LiCl in the synthesis of Mepanipyrim.

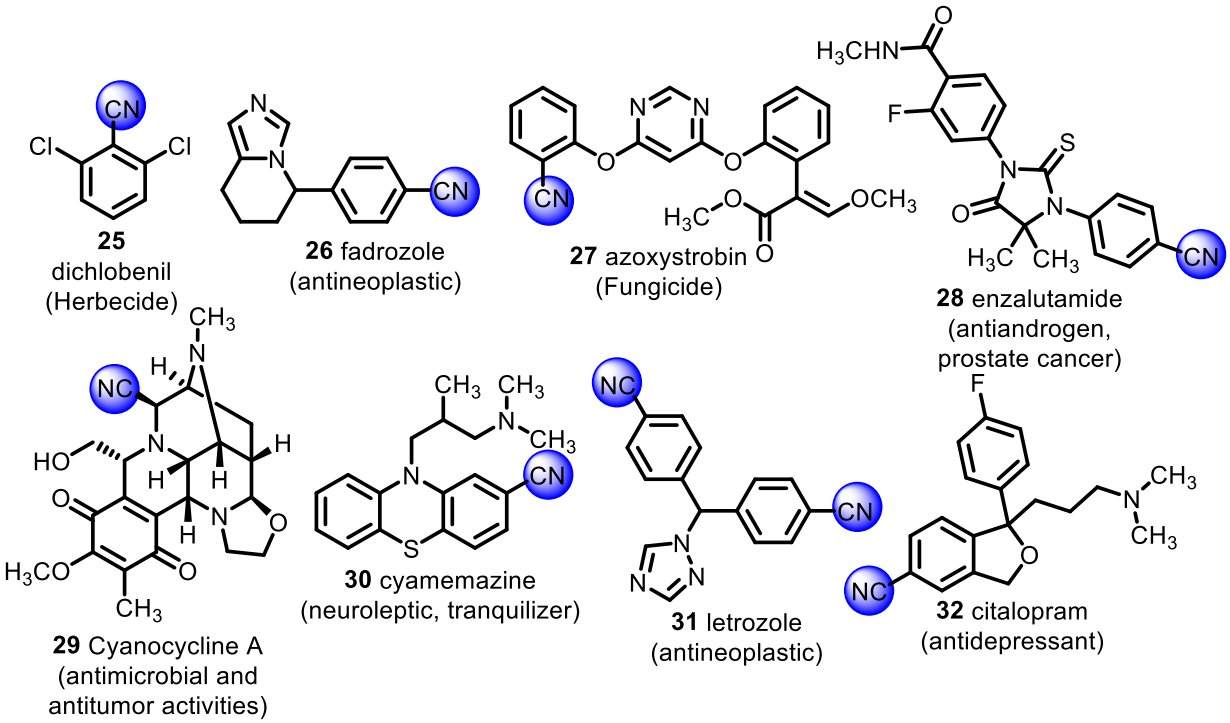


Source: MOSRIN; KNOCHEL, 2009.[35]

1.2 CYANO AND FLUORINE AS DIRECTING GROUPS

The cyano group is of great interest in organic synthesis and can be easily converted into various functional moieties, such as amines, aldehydes, amides, acids, esters, tetrazoles, triazoles, oxazoles, and thiazoles.[36] It is also present in agrochemicals, pharmaceuticals, and natural products as illustrated in **figure 3**.[37]

Figure 3. Some bioactive molecules bearing the cyano group.

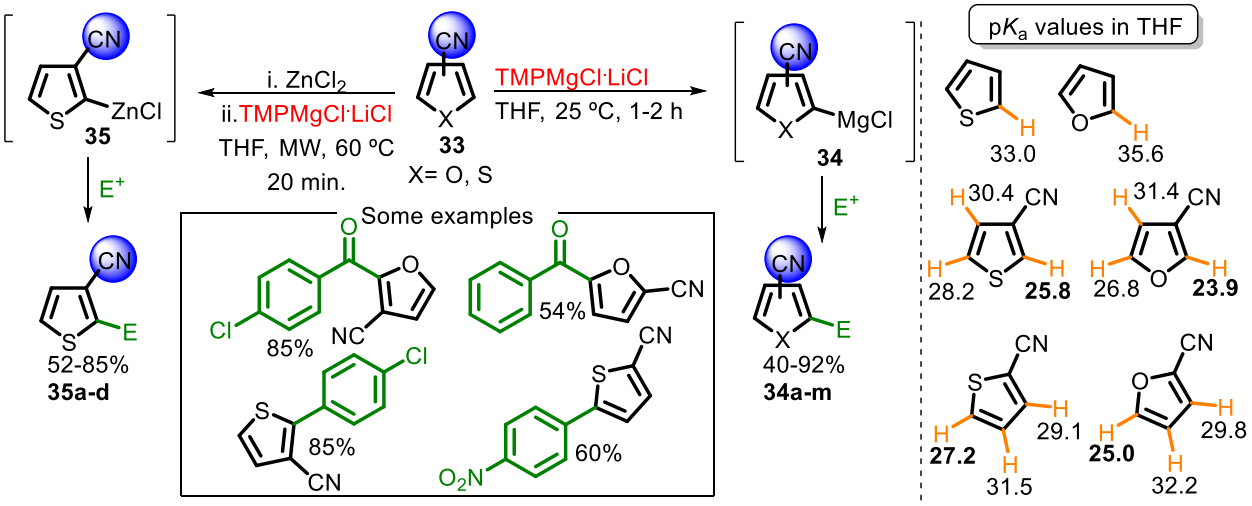


Source: ANBARASAN; SCHAREINA; BELLER, 2011;[37a] CHAITANYA; ANBARASAN, 2018;[37b] GRUNDKE; VIERENGEL; OPATZ, 2020.[37c]

Given the importance of nitriles, D*o*Ms involving the cyano as a directing group (electron-withdrawing effect and coordination properties)[38] has become an interesting strategy to access functionalized nitrile-based systems. Our research group has performed the directed metalation of cyano-substituted thiophenes and furans with TMPMgCl·LiCl (**Scheme 3**).[39] The cyano group led to a decrease in pK_a[40] for C2-H or C5-H in all the studied substrates favoring the deprotometalations at these positions. However, the regioselectivity control for thiophene-3-carbonitrile (**35**) was more challenging requiring a pre-complexation with $ZnCl_2$ followed by the magnesiation at 60

ºC in a microwave reactor to avoid a mixture of products, regioisomers, and difunctionalized ones.

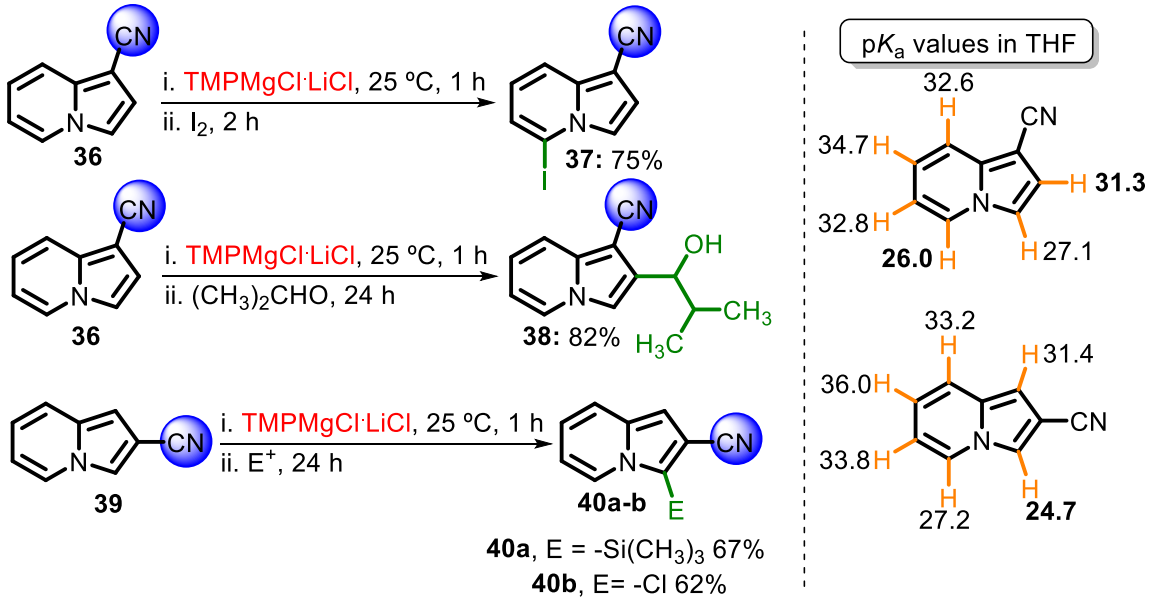
Scheme 3. Directed functionalization of cyano-substituted furans and thiophenes plus pK_a values.



Source: DOS SANTOS *et al*., 2015;[39] FRASER; MANSOUR; SAVARD, 1985.[40]

Additionally, TMPMgCl·LiCl allowed us to access position C2 for 1-cyanoindolizine **36** with isobutyraldehyde and C5 with iodine as the electrophiles, respectively (**Scheme 4**).[26b] It is expected that the observed regioselectivity for the latter electrophile relies on the disruption of a base-cyano chelate by the generated iodide leading to anion isomerization, C2 to C5. In the case of 2-cyanoindolizine **39**, the metalation took place at C3, the most acidic site.

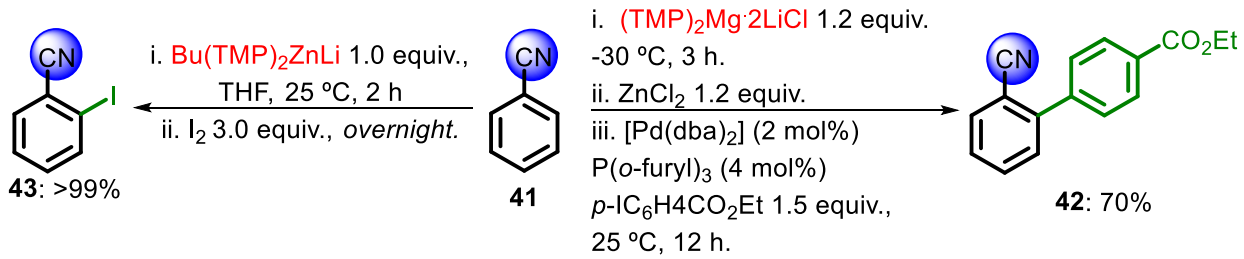
Scheme 4. Regioselective functionalization of cyano-substituted indolizines **36** and **39** and pK_a values.



Source: BERTALLO *et al*., 2019.[26b]

Knochel and co-workers have reported the direct magnesiation of benzonitrile (**41**) with the bisamide **16** $(TMP)_2Mg{\cdot}2LiCl$ at -30 ºC for 3 hours with further transmetalation with $ZnCl_2$, and a Pd-catalyzed Negishi cross-coupling reaction to afford biaryl **42** in 70%.[21] The same position, C2, was explored by Mongin and co-workers upon the use of a mixture of $ZnCl_2{\cdot}TMEDA$ (TMEDA=*N*,*N*,*N'*,*N'*-tetramethylethylenediamine), LiTMP (Lithium 2,2,6,6-tetramethylpiperidide), and *n*-BuLi (Butyllithium) to putatively obtain $Bu(TMP)_2ZnLi$ in the synthesis of aromatic **43** (**Scheme 5**).[41]

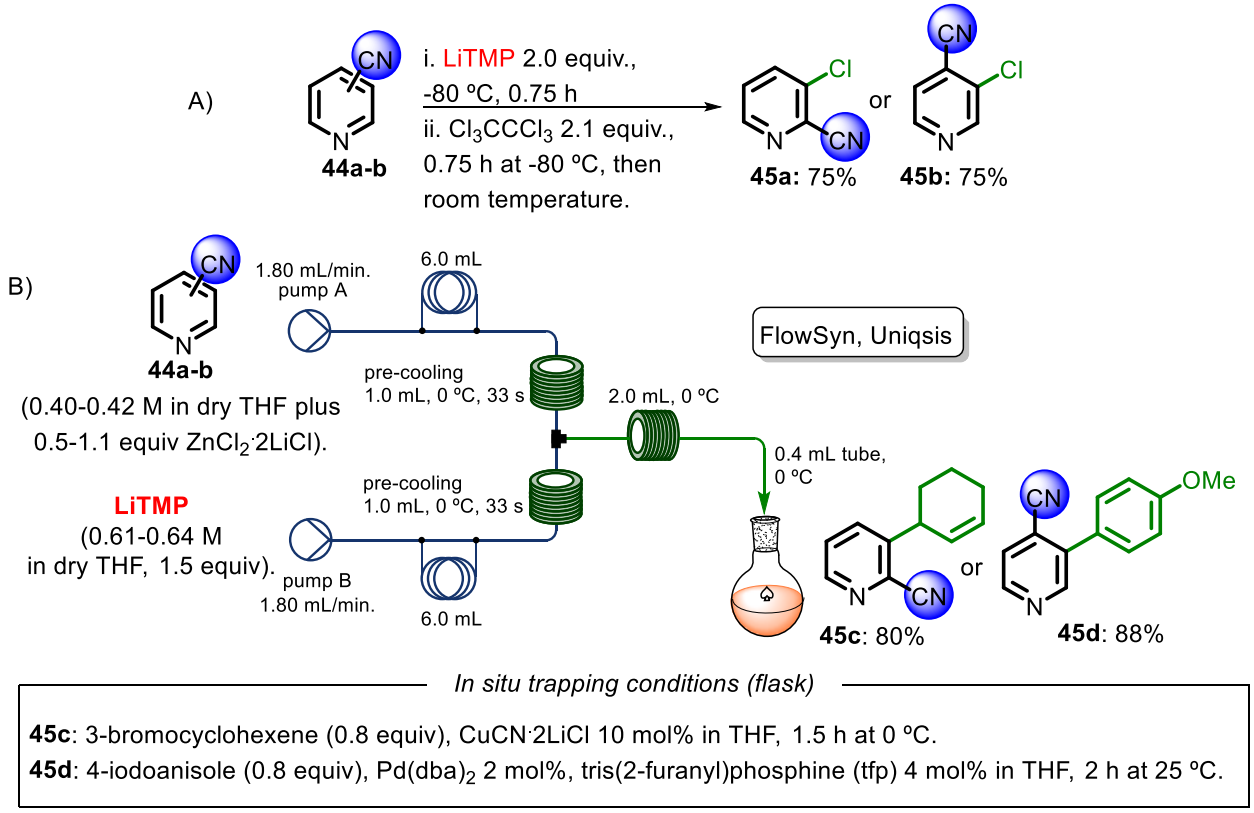
Scheme 5. Metalation and functionalization of benzonitrile.



Source: CLOSOSKI; ROHBOGNER; KNOCHEL, 2007; SNÉGAROFF *et al*., 2010.[41]

Regarding the regioselective metalation of cyano-substituted pyridines, such as 2-cyanopyridine (**44a**) and 4-cyanopyridine (**44b**), Mongin and co-workers applied a mixed lithium-cadmium base, $(TMP)_3CdLi$, but mixtures of di-, tri-, and four-substituted pyridines were obtained.[42] LiTMP, differently, can be considered for the regiocontrolled-lithiation under a low temperature of the same substrates affording **45a** and **45b** in 75% yield after reaction with hexachloroethane (**Scheme 6A**).[43] Besides, a wise approach developed by Knochel and co-workers, an *in situ* trapping transmetalation via $ZnCl_2$, allowed the metalation of **44a-b** to take place at 0 ºC (40 s) under flow conditions with the same base resulting in the disubstituted pyridines **45c** and **45d** in great yields (**Scheme 6B**). [44]

Scheme 6. Regioselective lithiation of pyridines **44a-b** and their functionalization.

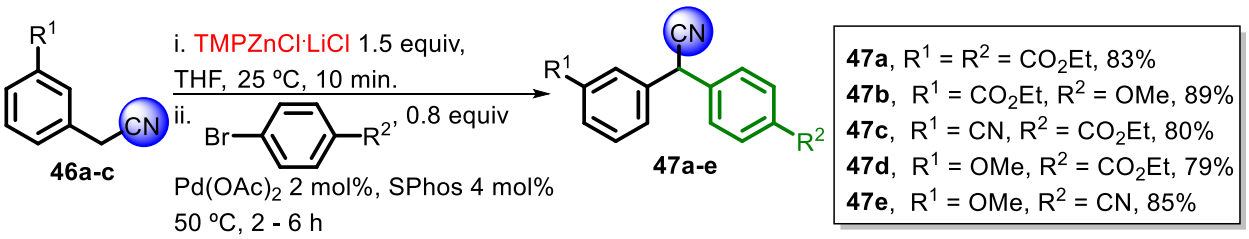


Source: CAILLY; FABIS; RAULT, 2006;[43] BECKER; KNOCHEL, 2015.[44]

Expanding the scope of functionalized nitriles via deprotometalation, TMPZnCl·LiCl was remarkably suitable for the mono-α-arylation of benzylic nitriles at room temperature

even in the presence of *ortho*-directing groups, such as methoxy, cyano, and ethyl ester in the aromatic moiety (**Scheme 7**).[45]

Scheme 7. The α-arylation of benzylic nitriles **46a-c** with TMPZnCl·LiCl.

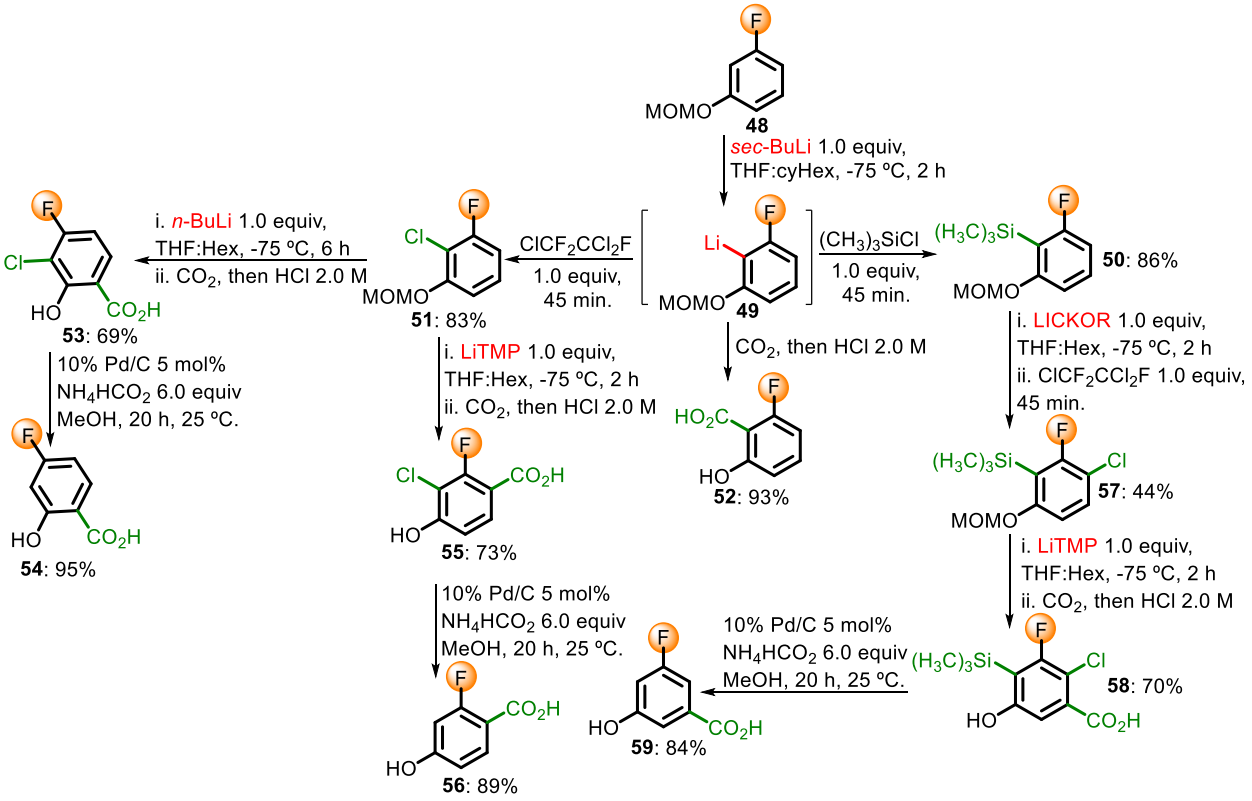


Source: DUEZ *et al.*, 2011.[45]

The fluoro group has been of great importance as an *ortho*-directing group in aromatic and heteroaromatic metalations due to its electron-withdrawing properties.[15] Prof. Dr. Manfred Schlosser has made a huge contribution in this area with the concept of regiochemically exhaustive functionalization of readily available organofluorines to furnish valuable building blocks. For instance, the treatment of the *O*-methoxymethyl-protected 3-fluorophenol **48** with sec-Butyllithium afforded the lithiated species **49** which were further reacted with 1,2,2-trichloro-1,2,2-trifluoroethane to obtain **51** (83%), carbon dioxide to synthesize **52** (92%), and chlorotrimethylsilane to prepare **50** (86%) (**Scheme 8**).[46] Regioselective lithiation of the tri-substituted aromatic **51** by *n*-Butyllithium (position C4) and subsequent carboxylation with deprotection of the phenolic methoxymethyl (MOM) ether under acidic conditions furnished the 3-chloro-4-fluoro-2-hydroxybenzoic acid **53** in 69% yield. Blocking the acidic position C2 in **50** and **51** favored the regioselective metalation with LiTMP and LICKOR at C6 in the synthesis of 3-chloro-2-fluoro-4-hydroxybenzoic acid **55** in 73% and (3-chloro-2-fluoro-6-(methoxymethoxy)phenyl)trimethylsilane **57** in 44%, respectively. LICKOR, also known as Schlosser's base, is comprised of *n*-butyllithium and potassium *tert*-butoxide in a one-to-one ratio. Furthermore, LiTMP was useful to promote the *ortho*-deprotometalation to the chlorine group in **57** giving **58** in 70% after treatment with an excess of carbon dioxide followed by acidic conditions. Therefore, using chlorine and trimethylsilyl groups to switch off metalation positions or considering directed lithiation with *sec*-BuLi for the MOM ether **48**, all the available functionalization sites were accessed: after removal of

trimethylsilyl group with tetra-butylammonium fluoride and chlorine by catalytic hydrogenation, carboxylic acids derived from 3-fluorophenol, **52**, **54**, **56**, and **59**, were prepared.

Scheme 8. The regiochemically exhaustive functionalization of 3-fluorophenol by Schlosser and co-workers.

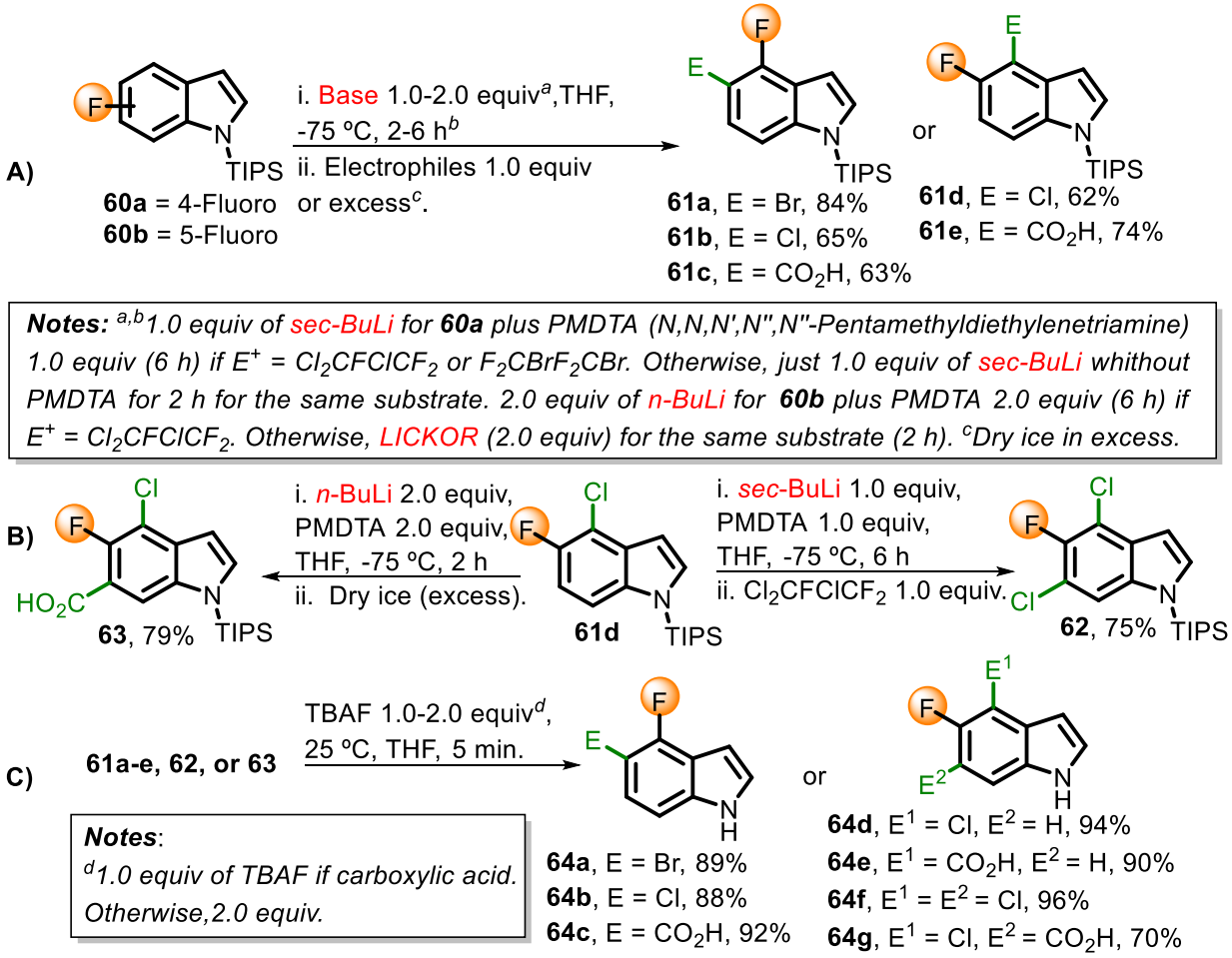


Source: MARZI *et al*., 2005.[46]

In a similar manner, Schlosser an co-workers have explored the functionalization of fluorinated pyridines (3-fluoropyridine,[46,47] 2-fluoropyridine, 2,3-difluoropyridine, and 2,5-difluoropyridine,[47,48] 2,4-difluoropyridine and 2,4,6-trifluoropyridine,[47,49] 2,6-difluoropyridine,[47,50] 2,3,5-trifluoropyridine and 3,5-difluoropyridine[47,51]), phenols (2,4-difluorophenol, 2,5-difluorophenol, 2,3-difluorophenol, 3,5-difluorophenol, 3,4-difluorophenol, 2,4,5-trifluorophenol, and 2,3,4-trifluorophenol),[52] and indoles.[53] For the latter substrate, an interesting strategy was devised in order to avoid metalation at position C2 of the indole system: its nitrogen was protected with a bulky group,

triisopropylsilyl (TIPS). The treatment of 4-fluoro-1-(triisopropylsilyl)indole **60a** with *sec*-BuLi at -75 ºC and subsequent trapping with 1,2-dibromo-1,1,2,2-tetrafluoroethane, 1,1,2-trichloro-1,2,2-trifluoroethane or carbon dioxide led to C5-functionalized indoles **61a-c** with yields up to 84%. For 5-fluoro-1-(triisopropylsilyl)indole **60b**, *n*-BuLi and LICKOR were suitable to functionalize C4 position affording **61d** (62%) and **61e** (74%) after chlorination and carboxylation, respectively (**Scheme 9A**). Interestingly, **61d** was subjected to a second metalation with *n*-BuLi or *sec*-BuLi to obtain the tri-substituted indoles **62** and **63** in great yields (**Scheme 9B**). Tetrabutylammonium fluoride was successfully applied to all substrates at 25 ºC for 5 minutes to remove the TIPS groups (**Scheme 9C**).[53]

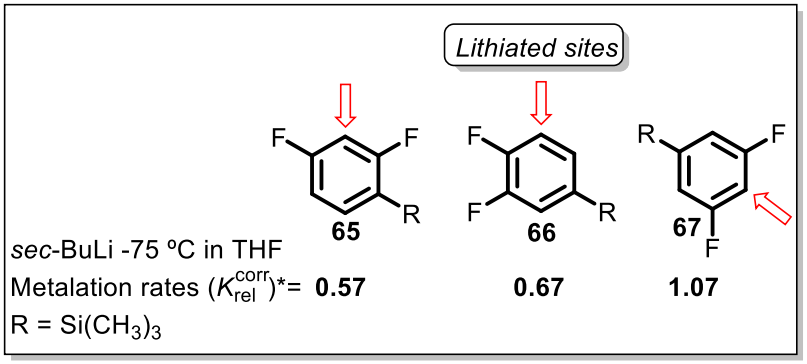
Scheme 9. The metalation and functionalization of 5-fluoro and 4-fluoro -1-(triisopropylsilyl)indoles with lithium bases.



Source: SCHLOSSER; GINANNESCHI; LEROUX, 2006.[53]

Complementing the study of the influence of a bulky alkyl-silyl group on metalation selectivity for fluorinated compounds, it was found that trimethylsilyl group (TMS) can affect kinetic acidity due to a buttressing effect when occupying a fluoro-neighboring position, and therefore, deprotometalation rates (**Figure 4**). The steric pressure exerted by TMS as pointed by Schlosser is less pronounced in **67** at position C4 because of the *meta* disposition of both fluoro groups. On the other hand, the *meta* position to TMS is available in both **66** and **65** favoring the transmission of the buttressing effect that is greatly enhanced by an adjacent fluoro group in the latter scenario.[54]

Figure 4. Metalation rates (2,4-difluorophenyl)- **65**, (3,4-difluorophenyl)- **66**, and (3,5-difluorophenyl)trimethylsilane **67.**



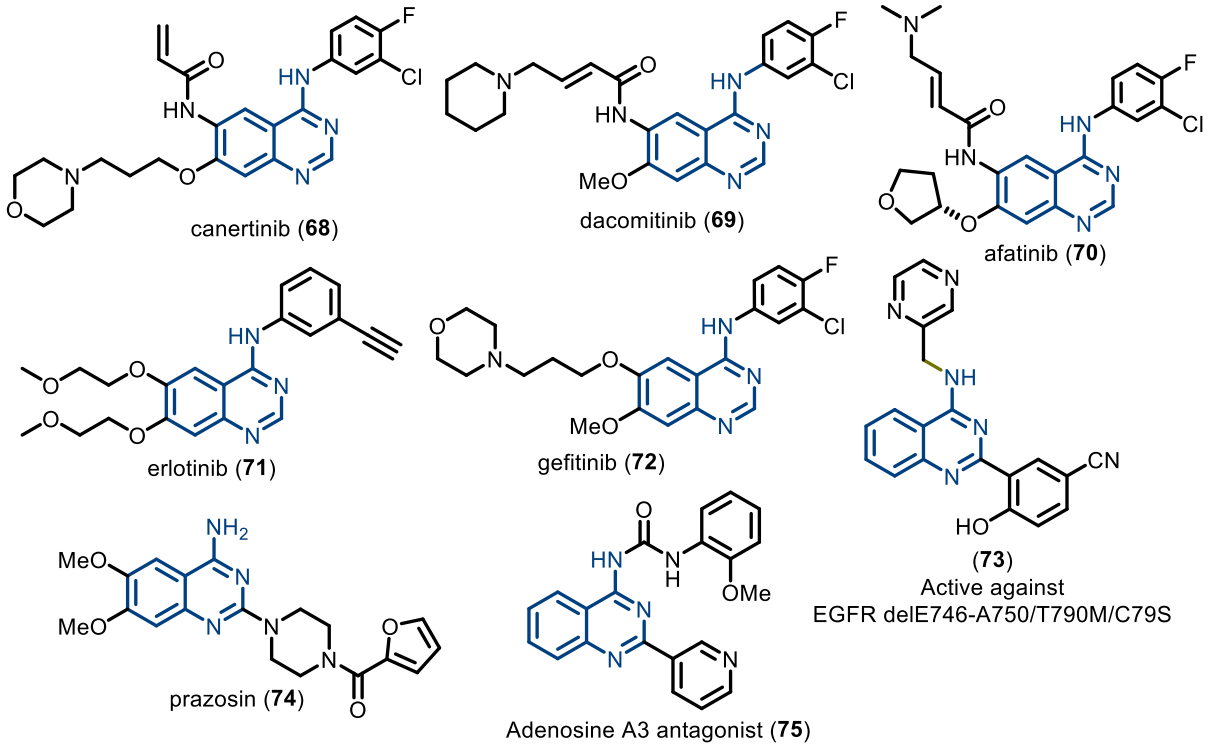
*(K_{rel}^{corr})(= $K^{R = Si(CH3)3}/K^{R = H}$).

Source: HEISS *et al*., 2007.[54]

1.3 4-AMINOQUINAZOLINES: BIOLOGICAL IMPORTANCE AND SYNTHESIS

Heterocyclic systems account for more than 85% of bioactive molecules with special mention to *N*-heterocyclic rings which represent more than 75% of the drugs approved by the FDA (The Food and Drug Administration).[55] Among them, 4-aminoquinazoline is a privileged scaffold present in bioactive molecules of high pharmaceutical importance, such as the epidermal growth factor receptor (EGFR) inhibitors **68**-**73**, the antihypertensive agent prazosin **74**, and the human adenosine A_3 receptor antagonist **75** (**Figure 5**).[56]

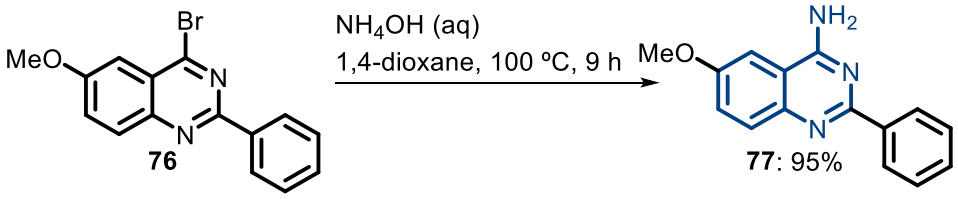
Figure 5. Some bioactive 4-aminoquinazolines.



Source: JIA *et al*., 2015; CHEN *et al*., 2018.[56]

Because of their great relevance, preparation protocols to access diverse 4-aminoquinazolines are a prevailing demand. A common method involves the nucleophilic aromatic substitution of 4-haloquinazolines[57] as verified for the synthesis of **77** in 95% by Ahmad, Hill, and Movassaghi (**Scheme 10**).[58]

Scheme 10. The synthesis of 6-methoxy-2-phenylquinazolin-4-amine **77**.

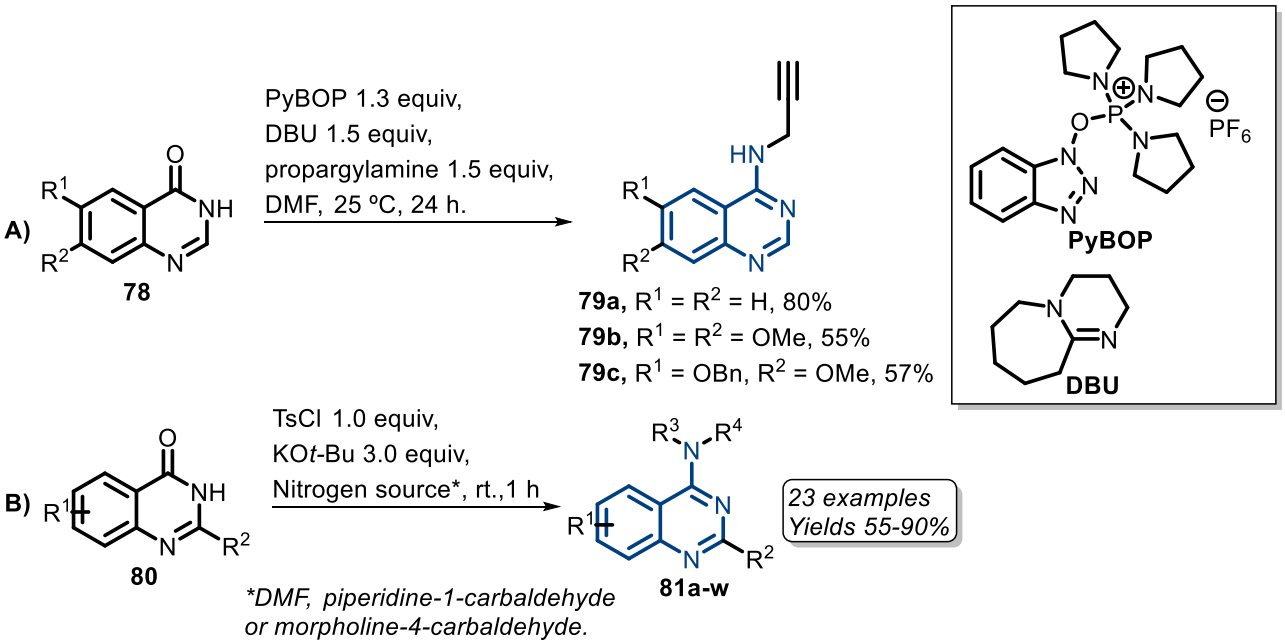


Source: AHMAD; HILL; MOVASSAGHI, 2009.[58]

PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate) in the presence of DBU (2,3,4,6,7,8,9,10-octahydropyrimidol[1,2-*a*]azepine) can be

employed for the *in situ* activation of the carbonyl group of quinazolinones[59] as in **78** with further substitution by propargylamine in DMF in the synthesis of **79a-c** (**Scheme 11A**).[60] Another strategy by Peng and co-workers employed 4-toluenesulfonyl chloride in conjunction with potassium *tert*-butoxide in DMF to generate a tosylate intermediate prone to substitution affording 4-dimethylaminoquinazolines **81a-w** (**Scheme 11B**).[61]

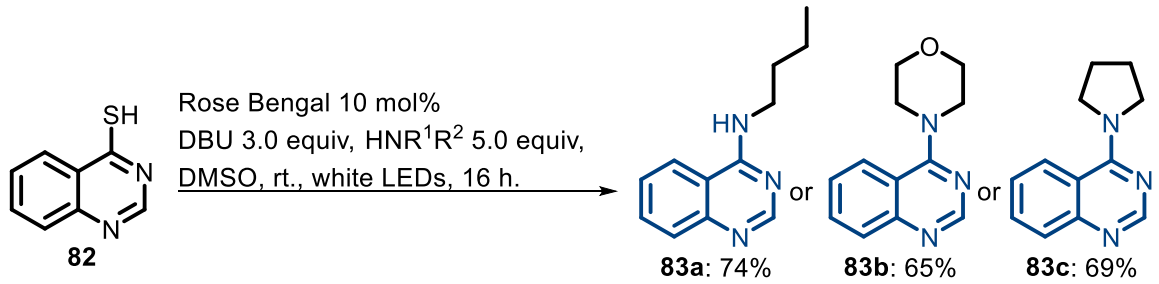
Scheme 11. Some protocols for the synthesis of 4-aminoquinazolines from quinazolinones.



Source: NUNES *et al*., 2021;[60] CHEN *et al.*, 2015.[61]

In addition to the S_NAr-based protocols, the organic dye Rose Bengal under irradiation of visible light enabled the amination of 4-mercaptoquinazoline **82** with different amines leading to **83a-c** in good yields (**Scheme 12**).[62]

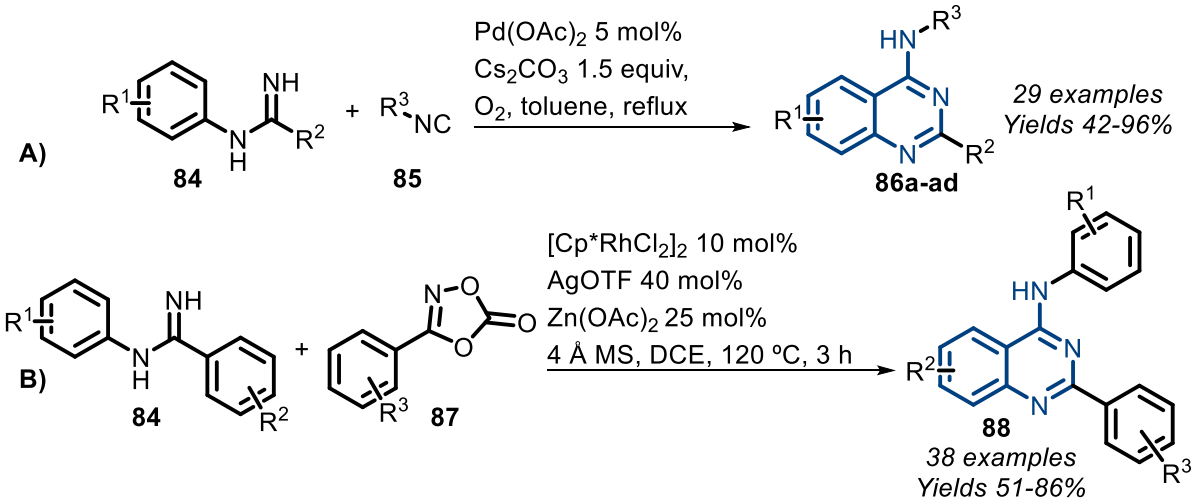
Scheme 12. Visible light enabled S_NAr of 4-mercaptoquinazoline **82** to afford 4-aminoquinazolines **83a-c**.



Source: RATTANANGKOOL; SUKWATTANASINITT; WACHARASINDHU, 2017.[62]

About the cyclization reactions based on a specific C(sp^2)-H activation bond to access 4-aminoquinazolines, palladium(II) and rhodium(III) have found application in intramolecular C-H amidinations involving isonitrile and 1,4,2-dioxazol-5-ones migratory insertion, respectively. $Pd(OAc)_2$ with Cs_2CO_3 in toluene under aerobic and reflux conditions catalyzed the conversion of *N*-arylamidines in quinazolines **86a-ad** with yields up to 96% (**Scheme 13A**).[63] For the rhodium-catalyzed annulation, $[Cp^*RhCl_2]_2$ (pentamethylcyclopentadienyl rhodium dichloride dimer) was used with AgOTf and $Zn(OAc)_2$ as additives in dichloroethane (DCE) at 120 ºC for 3 hours (**Scheme 13B**).[64]

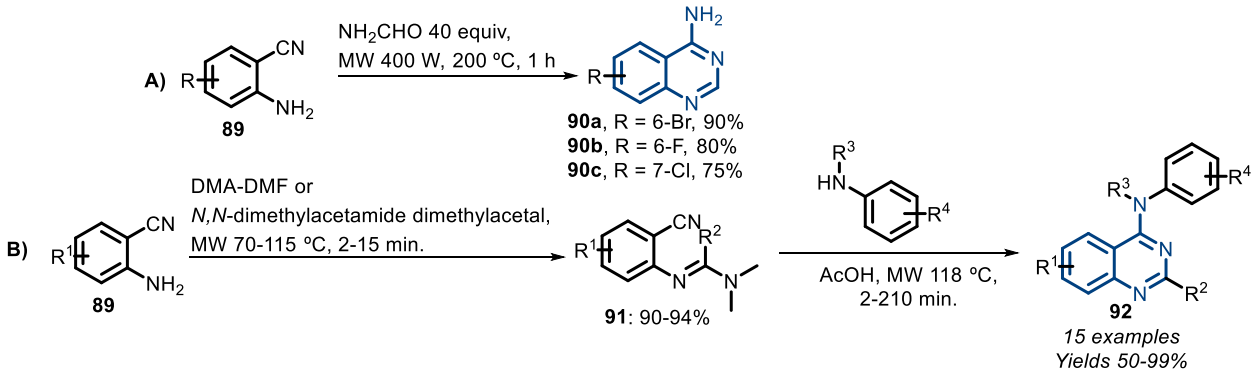
Scheme 13. Metal-catalyzed synthesis of 4-aminoquinazolines from *N*-arylamidines.



Source: WANG *et al.*, 2011;[63] REN *et al.*, 2021.[64]

Some other annulation protocols include the use of anthranilonitriles. Loidreau and Besson have applied formamide as an NH_3 and CO source under thermal decomposition in the presence of halogenated anthranilonitriles **89** for the preparation of 4-aminoquinazolines of type **90a-c** in good yields (**Scheme 14A**).[65] Moreover, anthranilonitriles can be converted into formamidines **91** which under acidic and microwave irradiation conditions react with amines through Dimroth rearrangement to afford 4-aminoquinazolines of type **92** (**Scheme 14B**).[66]

Scheme 14. Preparation of 4-aminoquinazolines from anthranilonitriles.

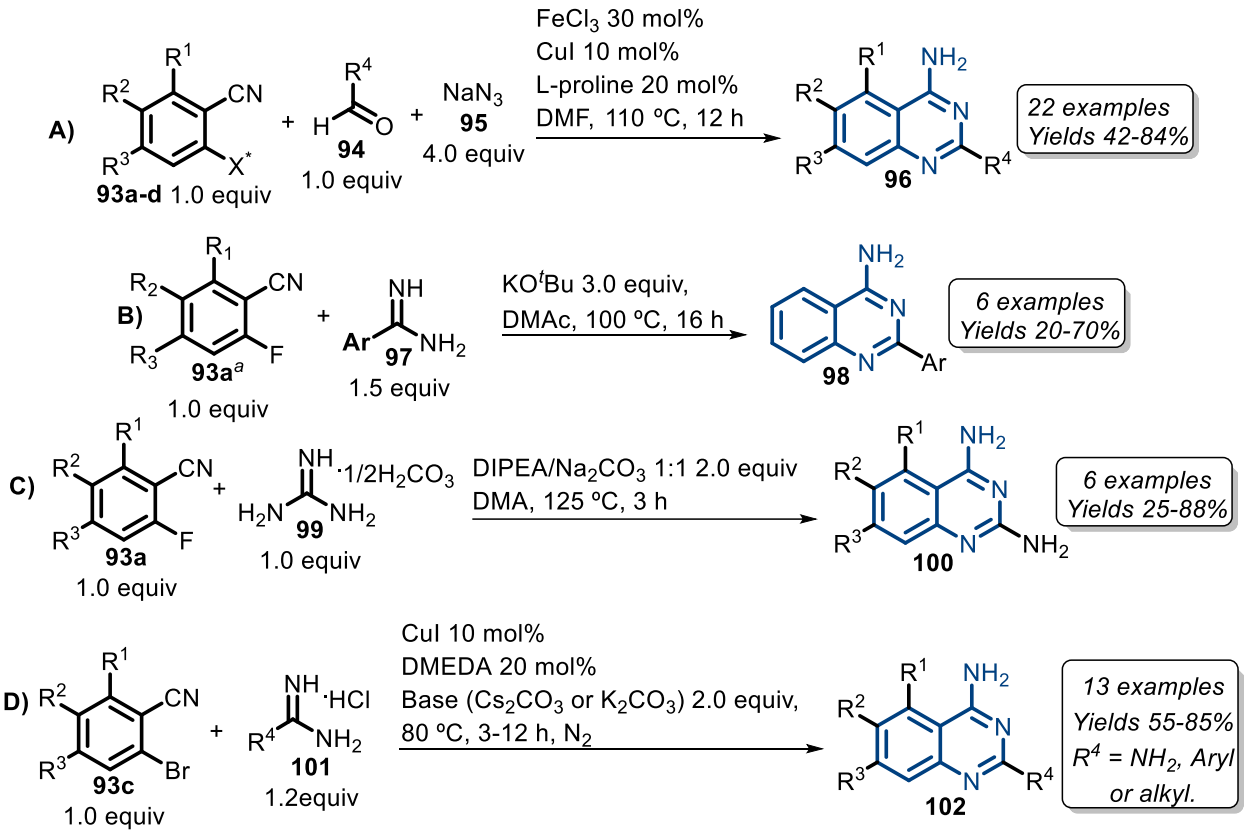


Source: LOIDREAU; BESSON, 2011;[65] FOUCOURT *et al.*, 2010.[66]

Concerning the use of *ortho*-halogenated benzonitriles, distinct protocols have been developed towards the synthesis of 2-substituted 4-aminoquinazolines. For instance, Wu and co-workers devised a domino strategy with consecutive iron-mediated [3+2] cycloaddition, copper-catalyzed S_NAr, reduction, cyclization, oxidation, and copper-catalyzed denitrogenation processes for 2-F-, 2-Cl-, 2-Br-, and 2-I-substituted benzonitriles with varied aldehydes and sodium azide as the nitrogen source (**Scheme 15A**).[56e] Another procedure includes the reaction of amidines with 2-flurobenzonitriles in the presence of potassium *t*-butoxide at 100 ºC for 16 hours by a base-assisted S_NAr followed by the attack of the amino group to the cyano carbon (**Scheme 15B**).[67] Furthermore, under basic conditions, guanidine salts cyclize well with 2-fluorobenzonitriles at 125 ºC in *N,N*-dimethylacetamide (DMAc) (**Scheme 15C**)[68] and CuI plus *N,N'*-dimethylethylenediamine (DMEDA) is suitable for the Ullmann-type

coupling of 2-bromobenzonitriles with amidine or guanidine salts in DMF at 80 ºC (**Scheme 15D**).[69]

Scheme 15. Synthesis of 4-aminoquinazolines from *ortho*-halogenated benzonitriles.



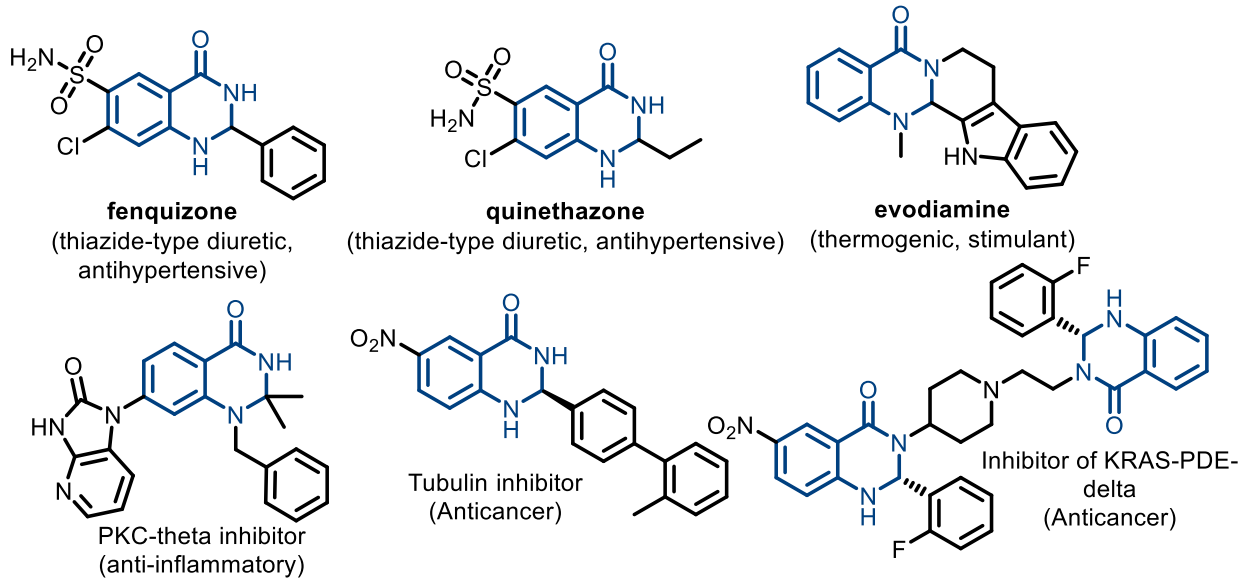
*X group: **93a*** = F, **93b** = Cl, **93c** = Br, or **93d** = I. [a]R^1=R^2=R^3 = H

Source JIA *et al*., 2015;[56e] FENG; WU, 2015;[67] SHELKE *et al*., 2015;[68] YANG *et al*., 2010.[69]

1.4 2,3-DIHYDROQUINAZOLIN-4(1*H*)-ONES: BIOLOGICAL IMPORTANCE AND SYNTHESIS

The 2,3-dihydroquinazolin-4(1*H*)-one (DHQ), a nitrogen-based heterocycle and a privileged scaffold, is present in a multitude of biologically active molecules including marketed pharmaceuticals and potential drug candidates as depicted in **figure 6**.[70] Hence, its synthesis mainly targeting 2-substituted derivatives has aroused great interest, and a vast number of synthetic protocols has been reported in the literature.

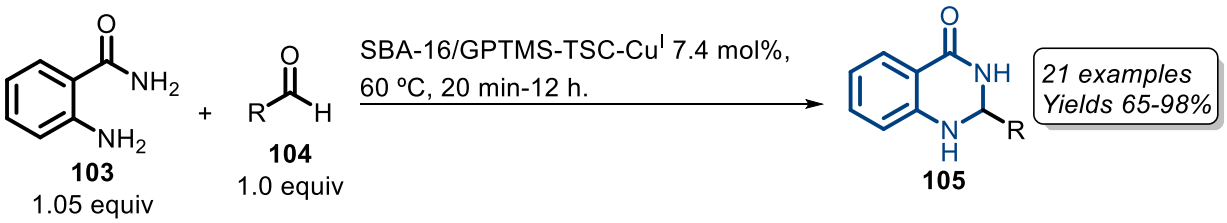
Figure 6. Some bioactive molecules containing the DHQ core.



Source: BADOLATO; AIELLO; NEAMATI, 2018;[70a] JIANG *et al*., 2017;[70d] CHINIGO *et al*., 2008.[70b]

The most common synthetic protocols comprise the use of 2-aminobenzamides to construct the central bicyclic ring system.[71] For example, a recent approach by Ghodsinia and co-workers reported the use of the heterogenous catalyst SBA-16/GPTMS-TSC-Cu^{I} to promote the cyclocondensation of 2-aminobenzamide **103** with aldehydes under solvent-free conditions furnishing twenty-one 2,3-dihydroquinazolin-4(1*H*)-ones in great to excellent yields (**Scheme 16**). For such, mesoporous silica SBA-16 was functionalized by aminated 3-glycidyloxypropyltrimethoxysilane with thiosemicarbazide and further treated with Cu^{I}.[71a]

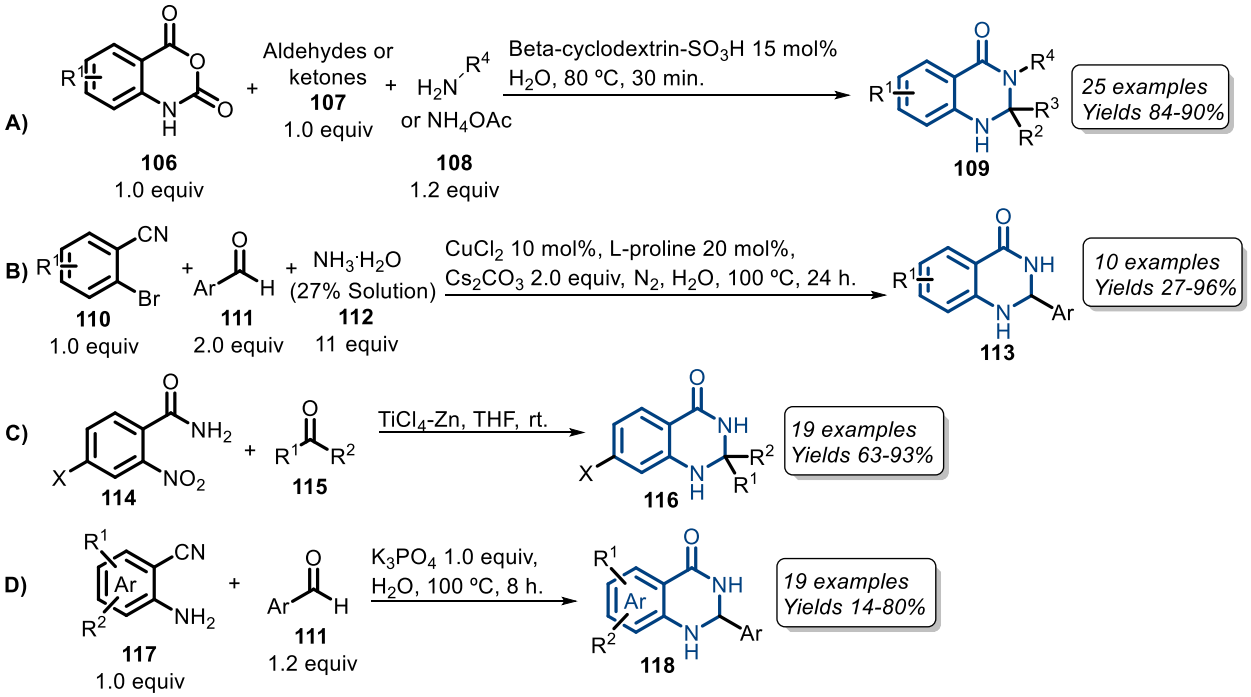
Scheme 16. Catalyzed synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by SBA-16/GPTMS-TSC-Cu^{I} catalyst.



Source: ERFAN; AKHLAGHINIA; GHODSINIA, 2020.[71a]

Other suitable substrates for the synthesis of this scaffold are isatoic anhydrides,[72] *o*-bromobenzonitriles,[73] 2-nitrobenzamides,[74] and 2-aminobenzonitriles or 2-aminonicotinonitrile.[75] β-cyclodextrin-SO_3H, a recyclable acid catalyst, applied to the one-pot condensation of isatoic anhydrides **106** with primary amines or ammonium acetate and aldehydes or ketones **107** in aqueous media at 80 ºC. Twenty-five 2,3-dihydroquinazolin-4(1*H*)-ones were obtained with yields varying from 84 to 90% (**Scheme 17A**).[72a] In the case of 2-bromobenzonitriles **110**, their treatment with benzaldehydes and aqueous ammonia under copper catalysis, nitrogen, and basic aqueous conditions gave 2,3-dihydro-2-aryl quinazolin-4(1*H*)-ones with yields up to 96% (**Scheme17B**).[73] Besides, *o*-nitrobenzamides **114** undergo reductive cyclization in the presence of carbonyl compounds with the aid of $TiCl_4$/Zn in dry THF (**Scheme 17C**),[74] and 2-aminobenzonitriles **117** favorably react with aromatic aldehydes in K_3PO_4 aqueous solution (**Scheme 17D**).[75]

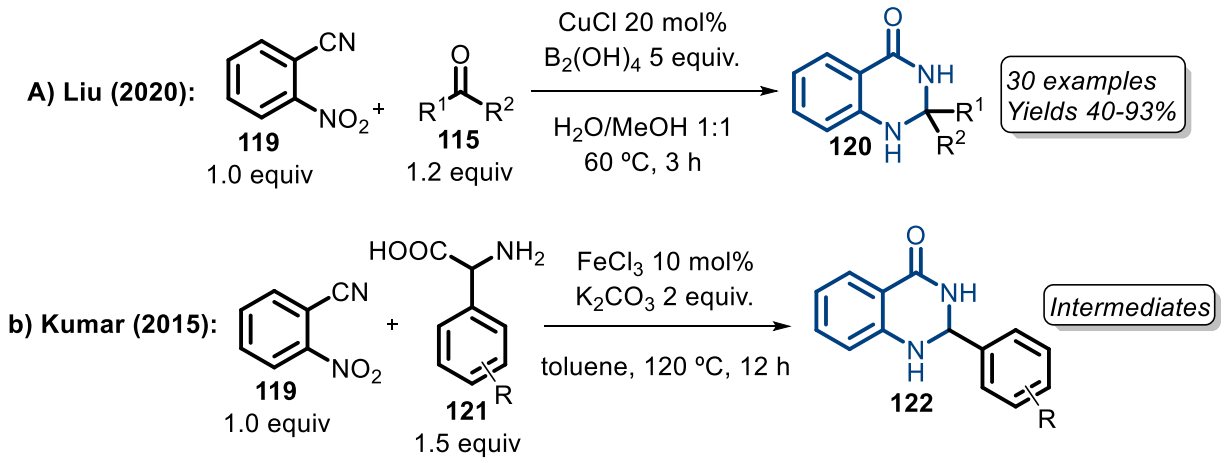
Scheme 17. Synthesis of DHQs from isatoic anhydrides, *o*-bromobenzonitriles, 2-nitrobenzamides, and 2-amino- benzonitriles or nicotinonitrile.



Source: WU *et al*., 2014;[72a] LIU *et al*., 2018;[73] SHI *et al*., 2003;[74] WU *et al*., 2014.[75]

Regarding the use of 2-nitrobenzonitrile as a precursor of DHQs, Liu and co-workers have recently reported a combined reduction/hydration/cyclocondensation approach requiring an excess of diboronic acid and copper as a catalyst in a water/methanol mixture.[76] DHQs were also observed by Kumar and co-workers from the reaction of the same substrate with phenylglycine in the presence of $FeCl_3$ and K_2CO_3 but only as intermediates.[77]

Scheme 18. Synthetic procedures for the synthesis of DHQs from 2-nitrobenzonitrile.



Source: LIU *et al*., 2020;[76] KUMAR *et al*., 2015.[77]

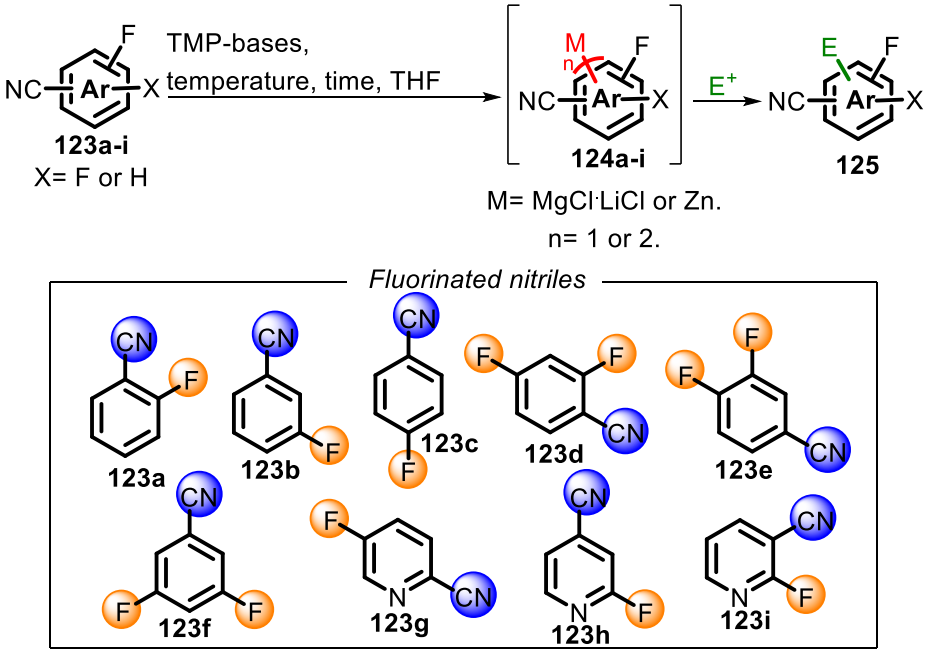
2. OBJECTIVES

In the first project, it was aimed at the regioselective metalation of fluorinated nitriles with 2,2,6,6-tetramethylpiperidyl bases (TMP-bases) to explore new and scarcely investigated metalation positions (**Scheme 19**). The subsequent trapping of the generated aromatic and heteroaromatic organometallic species with diverse electrophiles was investigated to afford functionalized building blocks. Besides, the following specific goals were settled:

- to reproduce the metalation with a TMP-base and further functionalization at gram scale for at least one substrate;
- to study sequential difunctionalization to achieve tetrasubstituted derivatives;

- to exemplify the potential of the functionalized fluorinated nitriles as building blocks in the synthesis of 4-aminoquinazolines and other heterocycles of pharmaceutical importance as synthetic applications.

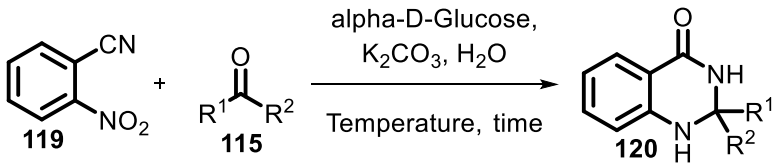
Scheme 19. The main goal from the first project and chosen substrates for study.



Source: The author.

In the second project, it was envisioned the use of glucose as an eco-friendly reductant with an aqueous solution of potassium carbonate for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from 2-nitrobenzonitrile in a one-pot manner (**Scheme 20**). In this scenario, the study of optimal conditions including time and temperature variation, the influence of concentration on reaction outcome, and the scope of carbonyl compounds were planned.

Scheme 20. Synthesis of DHQs with glucose as an eco-friendly reductant.



Source: The author.

3. CHAPTER 01 - REGIOSELECTIVE FUNCTIONALIZATION OF FLUORINATED NITRILES WITH 2,2,6,6-TETRAMETHYLPIPERIDYL BASES

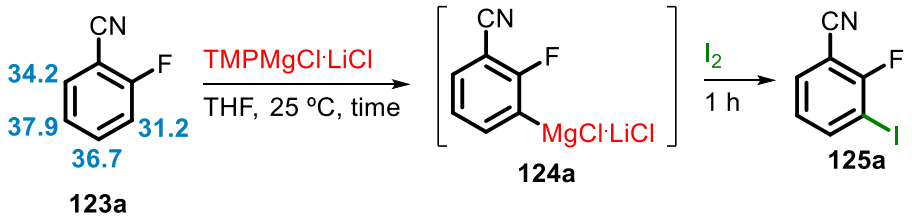
3.1 RESULTS AND DISCUSSIONS

3.1.1 Metalation studies and reaction scope

As standard procedures regarding characterization, nuclear magnetic resonance spectroscopy (NMR), high-resolution mass spectrometry (HRMS), and gas chromatography-mass spectrometry (CG-MS) analyses plus the determination of melting points were considered for the obtained molecules. Based on the observations for the metalation of the first studied substrate 2-fluorobenzonitrile (**123a**), 1.1 equivalents of the employed TMP-base at room temperature were defined as a reference point for the development of the synthetic protocols. Adjustments involving base equivalent, temperature, type of TMP-base, and transmetalation strategy with $ZnCl_2$ were made along with the study depending on the reactivity of explored substrates and stability of organometallic intermediates with the observation of side products/regioisomers or degradation.

We initiated our investigation with the selective magnesiation of C3 (pK_a = 31.2) for 2-fluorobenzonitrile (**123a**) by TMPMgCl·LiCl. When 1.1 equivalents of the base were employed for 1 hour at 25 ºC followed by reaction with molecular iodine as the test electrophile, **125a** was verified at a 6.7:1 ratio (**Table 1, entry 1**). Extending the metalation time to 2 hours did not favor the reaction outcome, but 1.3 equivalents of TMPMgCl·LiCl in 1 hour led to the almost complete substrate-magnesiation affording 2-fluoro-3-iodobenzonitrile **125a** in 96% isolated yield after iodination and purification (**Entries 2 and 3, respectively**).

Table 1. Metalation study of 2-fluorobenzonitrile with TMPMgCl·LiCl.



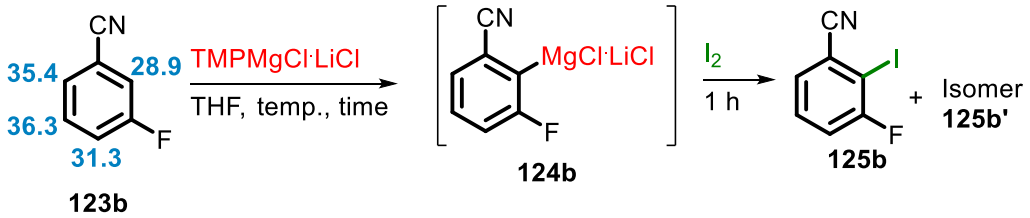
Entry	TMP-base	Equiv.	Time (h)	123a (%)[a]	125a:123a ratio
1	TMPMgCl·LiCl	1.1	1	13	6.7:1
2	TMPMgCl·LiCl	1.1	2	31	2.2:1
3**	TMPMgCl·LiCl	1.3	1	1	99[b]:1

[a]Remaining starting material: percent composition – Gas chromatography (GC-FID). [b]Isolated Yield = 96%. **Defined as the standard condition.

The reaction regioselectivity can be associated with the NMR data of **125a**: its ^{1}H spectrum shows two doublets of doublet of doublets (δ 8.01 and 7.61 ppm) with respective coupling constants of $^{4}J_{H\text{-}F}$ = 6.0 and 5.8 Hz, $^{3}J_{H\text{-}H}$ = 7.8 and 7.6 Hz, and $^{4}J_{H\text{-}H}$ = 1.6 and 1.6 Hz. The triplet-like signal at 7.03 ppm is attributed to C5-H with $^{3}J_{H\text{-}H}$ = 7.8 Hz. Another observation that corroborates with metalation at C3 is the duplet at 82.1 ppm with a characteristic $^{2}J_{C\text{-}F}$ = 24.0 Hz (^{13}C NMR spectrum) for the non-hydrogenated carbon C3-I as supported by HSQC analysis (Heteronuclear Single-Quantum Coherence).

TMPMgCl·LiCl was also suitable for the magnesiation of 3-fluorobenzonitrile **123b** (**Table 2**). The treatment of this benzonitrile with 1.2 equivalents of the base at 25 ºC with subsequent iodination afforded almost full conversion and two isomers (**Entry 1**) (**Figure 7**). The major one, C2-functionalized, was isolated in 68% yield. The loss in yield throughout purification refers to the challenging separation of the isomers due to similar retention factors on TLC. As an attempt to reduce or eliminate the other isomer, the reaction was both performed at -70 and 0 ºC, but no conversion was possible (**Entries 2 and 3**).

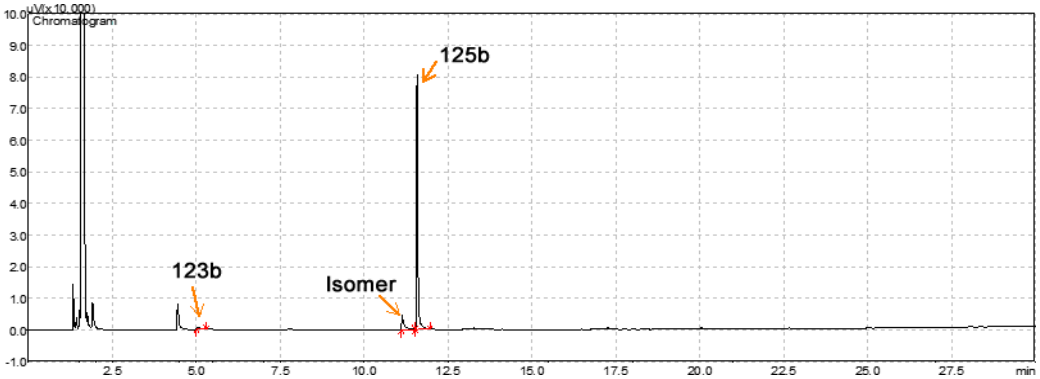
Table 2. Metalation study of 3-fluorobenzonitrile with TMPMgCl·LiCl.



Entry	Base Equiv.	Time (h)	Temp. (ºC)	123b (%)[a]	125b:125b':123b ratio
1**	1.2	0.5	25	2	44:5:1
2	1.2	1	0	>99	-
3	1.3	1	- 70	>99	-

[a]Remaining starting material: percent composition – Gas chromatography (GC-FID). [b]Isolated Yield = 68%. **Defined as the standard condition.

Figure 7. Chromatogram for the selective metalation and functionalization of **123b**.



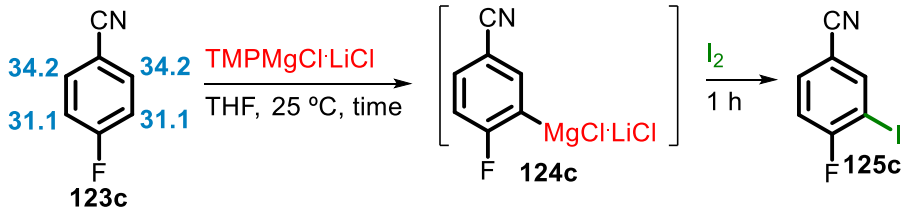
Source: The author.

Analyzing the ^{13}C NMR spectrum of **125b**, the duplets at 119.9 ppm ($^{2}J_{C\text{-}F}$ = 24.3 Hz) and 87.1 ppm ($^{2}J_{C\text{-}F}$ = 29.1 Hz), respectively, are correlated with the two *ortho* carbons to C3-F. While the second signal is attributed to the iodinated carbon (C2-I), the first one refers to C4 whose hydrogen signal appears as a multiplet at 7.31 – 7.25 ppm in the ^{1}H NMR spectrum. Besides, the two other duplets at 130.8 ($J_{C\text{-}F}$ = 8.1 Hz), and 130.4 ppm ($J_{C\text{-}F}$ = 3.7 Hz) refer to C5 and C6, respectively. In the case of 3-fluoro-4-iodobenzonitrile, three separated signals should be expected in the ^{1}H NMR spectrum, two duplets and one triplet.[78]

Complementing the studied group of monofluorinated benzonitriles, 1.3 equivalents of TMPMgCl·LiCl worked well for the practically complete conversion of 4-flurobenzonitrile

(**123c**) at room temperature (25 ºC) furnishing the aromatic **125c** in 82% yield after trapping with I_2 (**Table 3**, **entry 2**).

Table 3. Metalation study of 4-fluorobenzonitrile with TMPMgCl·LiCl.



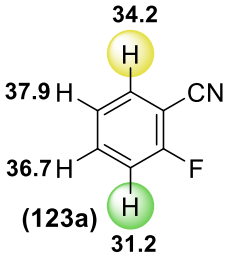
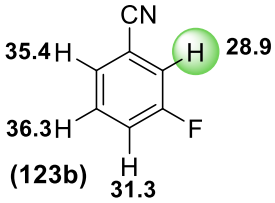
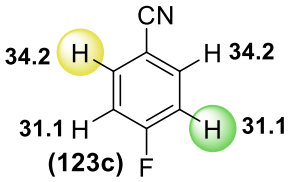
Entry	TMP-base	Equiv.	Time (h)	123c (%)[a]	125c:123c ratio
1	TMPMgCl·LiCl	1.2	1	6	15.7:1
2**	TMPMgCl·LiCl	1.3	1	trace	>99[b]:1

[a]Remaining starting material: percent composition – Gas chromatography (GC-FID). [b]Isolated Yield = 82%. **Defined as the standard condition.

The nitrile **123c** has two adjacent metalation sites to the fluorine group with expected coupling constants of type $^{2}J_{C\text{-}F}$. For the **125c** ^{13}C NMR spectrum, a duplet at 82.3 ppm ($^{2}J_{C\text{-}F}$ = 27.3 Hz) is attributed to a non-hydrogenated carbon (HSQC), the iodinated carbon C3. Moreover, its ^{1}H NMR spectrum shows a doublet of doublets at 8.07 ppm ($^{4}J_{C\text{-}F}$ = 5.7 Hz and $^{4}J_{H\text{-}H}$ = 2.0 Hz) for C2-H. This hydrogen couples with C6-H which is correlated with the doublet of doublet of doublets at 7.65 ppm ($^{3}J_{H\text{-}H}$ = 8.5 Hz, $^{4}J_{C\text{-}F}$ = 4.6 Hz, and $^{4}J_{H\text{-}H}$ = 2.0 Hz). For C5-H, another doublet of doublets is shown at 7.17 ppm ($^{3}J_{H\text{-}H}$ = 8.5 Hz and $^{3}J_{C\text{-}F}$ = 7.4 Hz).

Most synthetic strategies concerning the metalation of fluorinated nitriles **123a–c** involve the C2 or C6 positions. About **123b**, Knochel and co-workers were able to directly zincate[79] and ferrate[80] the same position achieved with TMPMgCl·LiCl, C2, but longer metalation times were required, 12 and 9 hours, respectively. The regioselective functionalization of C3 has only been accomplished by lithiation with LiTMP[82] for **123a** and sodiation with *i*Pr$_2$NNa[87], lithiation with LDA[86] or ferration with [(dioxane)$_{0.5}$NaFe{N(SiMe$_3$)$_2$}$_3$][88] for **123c** including important drawbacks, such as long metalation times, need for low or high temperatures, and limited scope (**Table 4**).

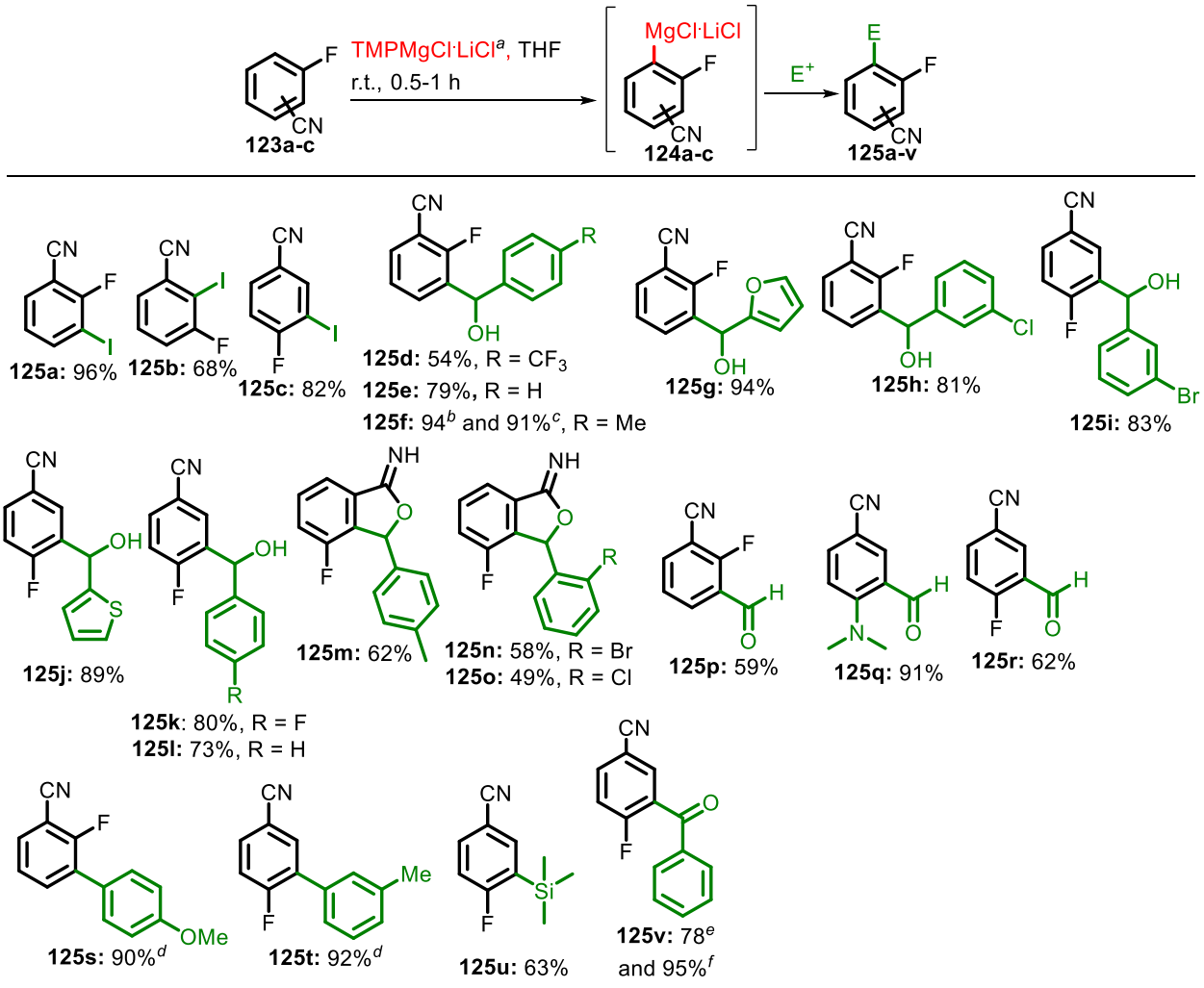
Table 4. Metalation sites of **123a–c** explored in this work and the literature.

Substrates*	H[a]	H[b]
	a. $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$, 12 h, 0 ºC to rt.[79] b. $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$, 3 h, 80 ºC.[80] c. $[t\text{Bu}(i\text{Pr})N]_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ 140 ºC, 2 h.[81]	a. LiTMP, -50 ºC, 0.5 h.[82] b. **TMPMgCl·LiCl 1 h, rt. (This work)**
	-	a. $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$, 12 h, 0 ºC to r.t.[79] b. $(TMP)_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$, 25 ºC, 9 h.[83] c. **TMPMgCl·LiCl 0.5 h, rt. (This work).**
	a. $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$, 3 h, 80 ºC.[80] b. $[t\text{Bu}(i\text{Pr})N]_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ 100 ºC, 2 h.[81] c. $(TMP)_2Fe{\cdot}2MgCl_2{\cdot}4LiCl$, 25 ºC, 18 h.[83] d. $(TMP)_2Mn{\cdot}2MgCl_2{\cdot}4LiCl$ 25 ºC, 2 h.[84] e. $(TMP)_3La{\cdot}3MgCl_2{\cdot}5LiCl$, 0 ºC, 1 h.[85]	a. LDA, -75 ºC, 1 h.[86] b. *i*PrNNa (NaDA), 0.5 s, -78 ºC (Flow reactor).[87] c. $[(\text{dioxane})_{0.5}NaFe\{N(SiMe_3)_2\}_3]$, 2 days at 50 ºC.[88] d. **TMPMgCl·LiCl 1 h, rt. (This work).**

*pK_a values are listed. [a]Yellow = literature. [b]Light-green = both, literature and this work.

With the established optimal conditions for the metalation of nitriles **123a–c**, the reactivity of the derived organomagnesium species were investigated with varied electrophiles (**Table 5**).

Table 5. Magnesiation of **123a–c** with TMPMgCl·LiCl followed by trapping with diverse electrophiles.*



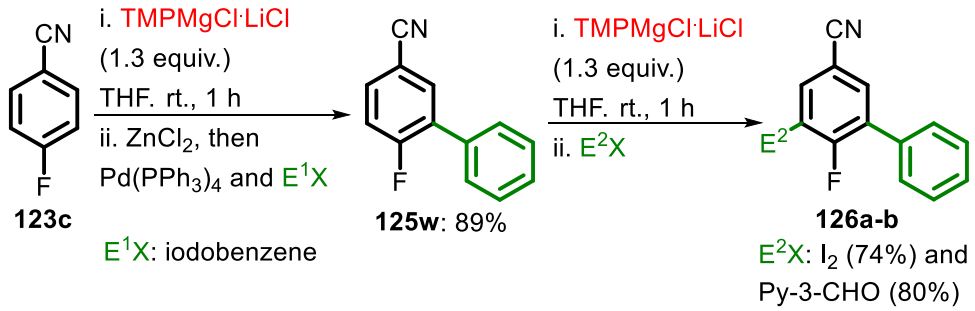
*Isolated yields. [a]1.2 equiv. for **123a** (0.5 h) and 1.3 equiv. for **123b**,**c** (1 h). [b]0.5 mmol scale. [c]5.5 mmol scale (1.21 g). [d]$ZnCl_2$ (1 M in THF) followed by Negishi cross-coupling with $Pd(PPh_3)_4$. [e]Transmetalation with CuCl·2LiCl (0.5 M in THF) followed by reaction with BzCl. [f]$ZnCl_2$ (1 M in THF) followed by $Pd(PPh_3)_4$ catalyzed benzoylation.

Treating **124a**,**c** with electron-rich and -deficient aldehydes, provided a library of alcohols (**125d**–**l**) in yields up to 94%. Notably, the synthesis of **125f** was performed at gram scale without meaningful loss in yield (91%). On the other hand, treatment of the 3-fluorobenzonitrile-derived Grignard species (**124b**) with aldehydes afforded fluorinated isobenzofuran-1(3*H*)-imines **125m**–**o** in 49-62% yields. Furthermore, while the reaction of **124a** with dimethylformamide provided aldehyde **125p** in 59% yield, **124c** underwent fluorine substitution by the *in situ* generated magnesium dimethylamide and resulted in

tertiary amine **125q** in 91% yield under the same formylation conditions. Nonetheless, when *N*-methylformanilide was employed as the electrophile, aldehyde **125r** was obtained in 62% yield. After transmetalation of **124a**,**c** with $ZnCl_2$ and subsequent addition of $Pd(PPh_3)_4$ and iodoarenes, Negishi cross-couplings were performed for **125s** and **125t**, in high yields (90% and 92%, respectively). The reaction of **124c** with trimethylsilyl chloride gave the silylated aromatic **125u** in 63% yield. Transmetalation of **124c** with CuCl·2LiCl with the subsequent addition of benzoyl chloride afforded the ketone **125v** in 78% yield. As an alternative, the synthesis of the same ketone was possible by palladium-catalyzed benzoylation with an even higher yield (**125v**: 95%).

Aiming at the synthesis of tetrasubstituted derivatives, the biaryl **125w** was prepared from **123c** and subjected to metalation via the same base, TMPMgCl·LiCl, to provide **126a**–**b** in great yields after reaction with I_2 and 3-pyridinecarbaldehyde (**Scheme 21**).

Scheme 21. Synthesis of tetrasubstituted aromatics **126a**–**b** through consecutive metalation-functionalization sequences.

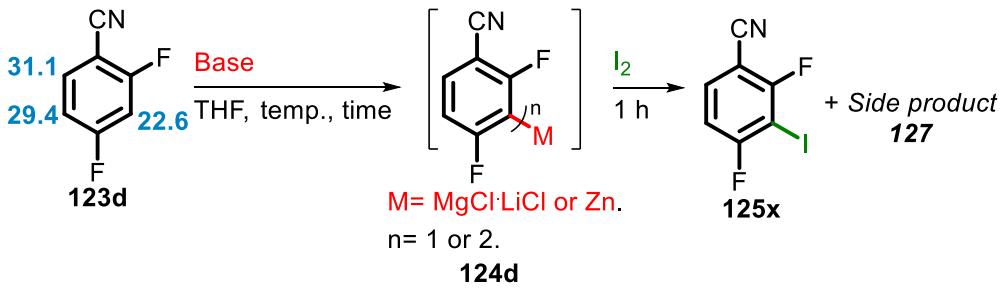


Source: The author.

Considering the suitability of TMPMgCl·LiCl in the magnesiation of fluorinated nitriles **123a**–**c**, this base was then explored for the metalation of nitriles of difficult selectivity control, the difluorinated nitriles **123d–f**. For the metalation of 2,4-difluorobenzonitrile **123d**, increasing the amount of base at 25 ºC led to better conversion rates (**Table 6, entries 1**–**3**). Although 1.3 equivalents of TMPMgCl·LiCl afforded the best conversion profile to this point, **125x** was isolated in only 63% (**Entry 3**). Besides the observation of a side product, a putative dimer, the reaction medium always turned black in 1 hour suggesting some sort of degradation not detected by gas

chromatography. To overcome this issue, the reaction was performed at 0 ºC instead, leading to the full conversion of **123d** (**Figure 8**) with an isolated yield of 80% for **125x** (**Entry 4**). Notably, $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ allowed the metalation-functionalization of the same position at 25 ºC, C3, furnishing **125x** in a higher yield (93%) and establishing a great alternative to the direct zincation of **123d** (**Entry 5**).

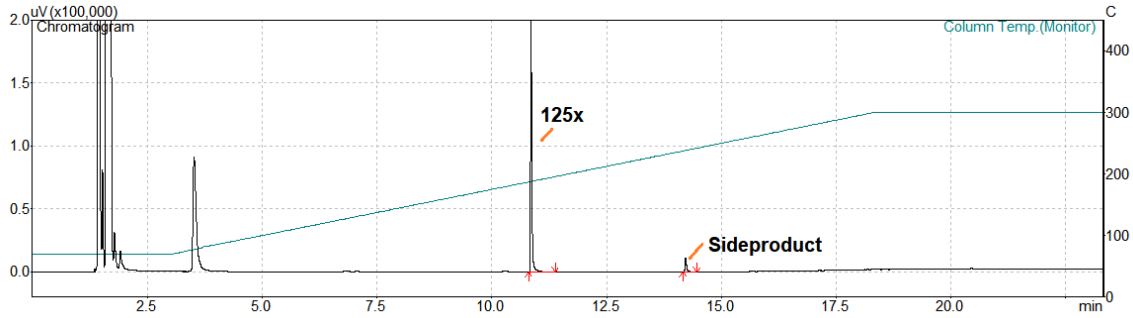
Table 6. Metalation study of 2,4-difluorobenzonitrile **123d** with TMP-bases.



Entry	TMP-base	Equiv.	Time (h)	Temp. (ºC)	123d (%)[a]	125x:127:123d ratio
1	TMPMgCl·LiCl	1.04	1	25	16	4.4:0.8:1
2	TMPMgCl·LiCl	1.20	1	25	13	5.7:1:1
3	TMPMgCl·LiCl	1.30	1	25	2	47.5[b]:1.5:1
4**	TMPMgCl·LiCl	1.30	1	0	none	(15.7[c]:1)[d]
5**	$(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$	0.65	1	25	4	(24[e]:1)[f]

[a]Remaining starting material: percent composition – Gas chromatography (GC-FID). [b]Isolated Yield = 63%. [c]Isolated Yield = 80%. [d]Full conversion. Ratio = 125x:127. [e]Isolated Yield = 93%. [f]125x:123d ratio. No side product was observed. **Defined as the standard conditions.

Figure 8. Chromatogram for the selective metalation and functionalization of **123d**.

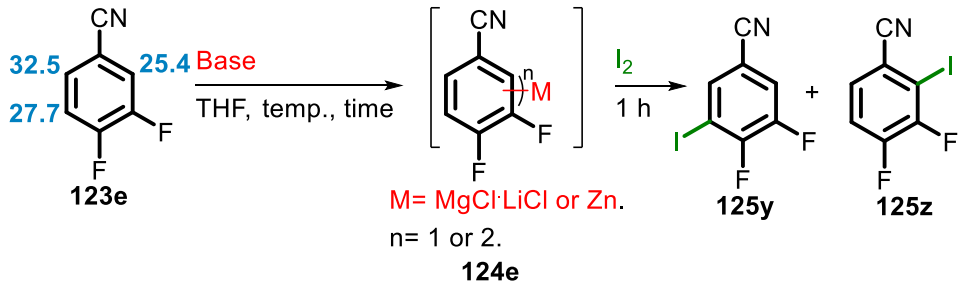


Source: The author.

The ^{1}H NMR spectrum of **125x** shows a doublet of doublet of doublets at 7.65 ppm with a coupling constant $^{3}J_{H\text{-}H}$ = 8.7 Hz which is consistent with an H-H *ortho* coupling and $^{4}J_{H\text{-}F}$ = 7.1 and 5.7 Hz due to coupling between C6-H and the two fluoro groups (C2-F and C4-F). Besides, $^{3}J_{H\text{-}F}$ = 6.8 Hz and $^{5}J_{H\text{-}F}$ = 1.5 Hz for the doublet of doublet of doublets at 7.02 ppm are compatible with C5-H and the same fluoro groups. The functionalization of C3 is also sustained by the duplet at 72.7 ppm ($^{2}J_{C\text{-}F}$ = 30.7 and 27.9 Hz) which is attributed to the non-hydrogenated carbon C3-I in its ^{13}C NMR spectrum.

When 3,4-difluorobenzonitrile **123e** was treated with 1.2 equivalents of TMPMgCl·LiCl at 25 ºC, the conversion rate was poor, the reaction medium immediately turned black, and the tetrasubstituted nitrile **125z** was detected (**Table 7, Entry 1**). Interestingly, working at 0 ºC afforded the regioisomer **125y** as the major one with a better conversion profile (**Entry 2**). Increasing the base amount to 1.5 equivalents but keeping the temperature led to almost full consumption of the starting material (**Entry 4**). Notwithstanding this result, **125y** was isolated in only 51% yield. As an attempt to surpass this obstacle, the metalation temperature was decreased to -70 ºC, but the yield slightly increased to 63% (**Entry 5**). Although no side products were detected by gas chromatography analysis, additional compounds were spotted via TLC. Thinking of it to be a high reactivity-related subject of the generated organomagnesium species even at -70 ºC, transmetalation with $ZnCl_2$ was considered to generate more stable organometallic species. As a result, **125y** was isolated in 75% yield after iodination (**Entry 6**). On the other hand, application of $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ at 25 ºC exclusively furnished **125z** in 76% with the functionalization of position C2 (**Entry 7**).

Table 7. Metalation study of 3,4-difluorobenzonitrile **123e** with TMP-bases.



Entry	TMP-base	Equiv.	Time (h)	Temp. (ºC)	123e (%)[a]	125y:125z:123e ratio
1	TMPMgCl·LiCl	1.20	1	25	88	0.14:1[b]
2	TMPMgCl·LiCl	1.20	1	0	18	3.8:0.7:1
3	TMPMgCl·LiCl	1.30	1	0	13	5.6:1.1:1
4	TMPMgCl·LiCl	1.50	1	0	2	39[c]:10:1
5	TMPMgCl·LiCl	1.50	1	-70	2	41.5[e]:7.5:1
6[d**]	TMPMgCl·LiCl	1.50	1	-70	3	27.7[f]:4.7:1
7**	$(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$	0.75	1	25	9	0.33:9.7[g]:1

[a]Remaining starting material: percent composition – Gas chromatography (GC-FID). [b]125z:123e ratio. No 125y was verified. [c]Isolated Yield = 51%. [d]After metalation at -70 ºC, 1.5 equiv. of $ZnCl_2$ were added to the mixture prior iodination at 25 ºC. [e]Isolated yield = 63%. [f]Isolated yield = 75%. [g]Isolated yield = 76%. **Defined as the standard conditions.

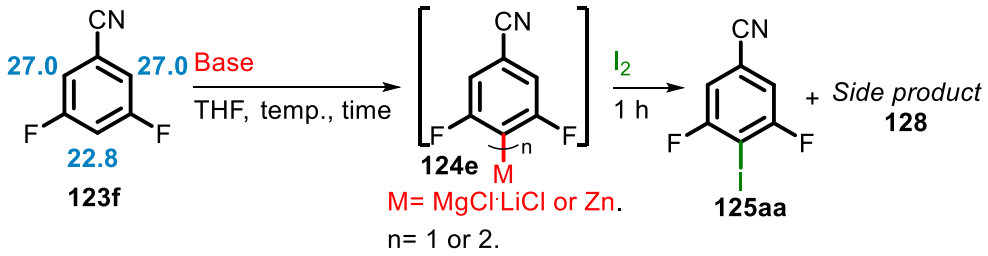
Regarding the ^{1}H NMR spectrum of **125y**, the coupling constant J = 1.9 Hz for both the doublet of triplets at 7.85 ppm and a doublet of doublet of doublets at 7.49 ppm is consistent with a *meta* H-H coupling ($^4J_{H\text{-}H}$). For the **125y** ^{13}C NMR spectrum, a duplet at 83.7 ppm ($^2J_{C\text{-}F}$ = 23.9 Hz) is attributed to a non-hydrogenated carbon (HSQC), the iodinated carbon C5. Moreover, the coupling constant J = 20.6 Hz for the doublet of doublets at 121.6 ppm is characteristic of $^2J_{C\text{-}F}$ being correlated with C2-H and C3-F coupling. For the other hydrogenated carbon, C6-H, a doublet of doublets is shown at 138.4 ppm with $^3J_{C\text{-}F}$ = 4.0 Hz.

In the case of **125z** ^{1}H NMR spectrum, the coupling constant J = 8.8 Hz for both the doublet of doublet of doublets at 7.40 ppm and the triplet of doublets at 7.29 ppm is compatible with an *ortho* H-H coupling ($^3J_{H\text{-}H}$). Its ^{13}C NMR spectrum shows a duplet at 89.1 ppm (d, $^2J_{C\text{-}F}$ = 25.3 Hz) for C2-I while a doublet of doublets at 118.6 ppm refers to C5-H with a coupling constant $^2J_{C\text{-}F}$ = 18.9 Hz.

As observed for the metalation of **123e** at 25 ºC, the reaction medium for **123f** turned black as soon as TMPMgCl·LiCl was added to the system, and a complex mixture was obtained after transference of I_2 solution in THF (**Table 8, Entry 1**). However, the product **125aa** was detected plus a side product via gas chromatography when **123f** was deprotometalated at 0 ºC (**Entry 2**). Then, it was decided to investigate the reaction outcome at a lower temperature (-30 ºC) with 1.3

equivalents of the base. Remarkably, under these conditions, no side product was produced and practically full conversion was achieved with an isolated yield for **125aa** of 75% (**Entry 3**). Complementing the metalation strategies towards **123e**, $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ allowed the metalation of the same position, C4, but at 25 ºC, furnishing **125aa** in excellent yield (91%) (**Entry 4**).

Table 8. Metalation study of 3,5-difluorobenzonitrile **123f** with TMP-bases.

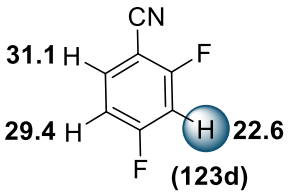
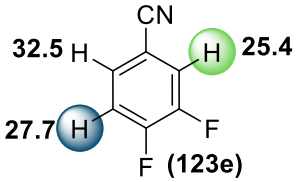
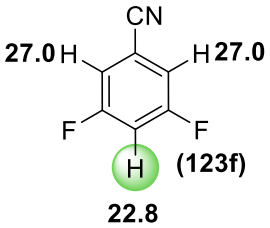


Entry	TMP-base	Equiv.	Time (h)	Temp. (ºC)	123f (%)[a]	125aa:128:123f ratio
1	TMPMgCl·LiCl	1.20	1	25	none	*
2	TMPMgCl·LiCl	1.20	1	0	14	2.5:3.6:1
3**	TMPMgCl·LiCl	1.30	1	-30	1	(99[b]:1)[c]
4**	$(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$	0.65	1	25	1	(99[d]:1)[c]

[*]A complex mixture was obtained. [a]Remaining starting material: percent composition – Gas chromatography (GC-FID). [b]Isolated Yield = 75%. [c]**125aa:123f** ratio. No side product was formed. [d]Isolated Yield = 91%. **Defined as the standard conditions.

The two hydrogens from **125aa** are assigned to a multiplet at 7.20 – 7.16 ppm (^{1}H NMR spectrum). Although these two hydrogens are chemically equivalent, they can be considered magnetically inequivalent. Therefore, one hydrogen would couple with the other hydrogen (^4J) in addition to coupling with the different fluorine atoms (^3J and ^5J, respectively). The triplet at 79.1 ppm ($^2J_{C\text{-}F}$ = 29.4 Hz) stands for C4-I (^{13}C NMR spectrum).

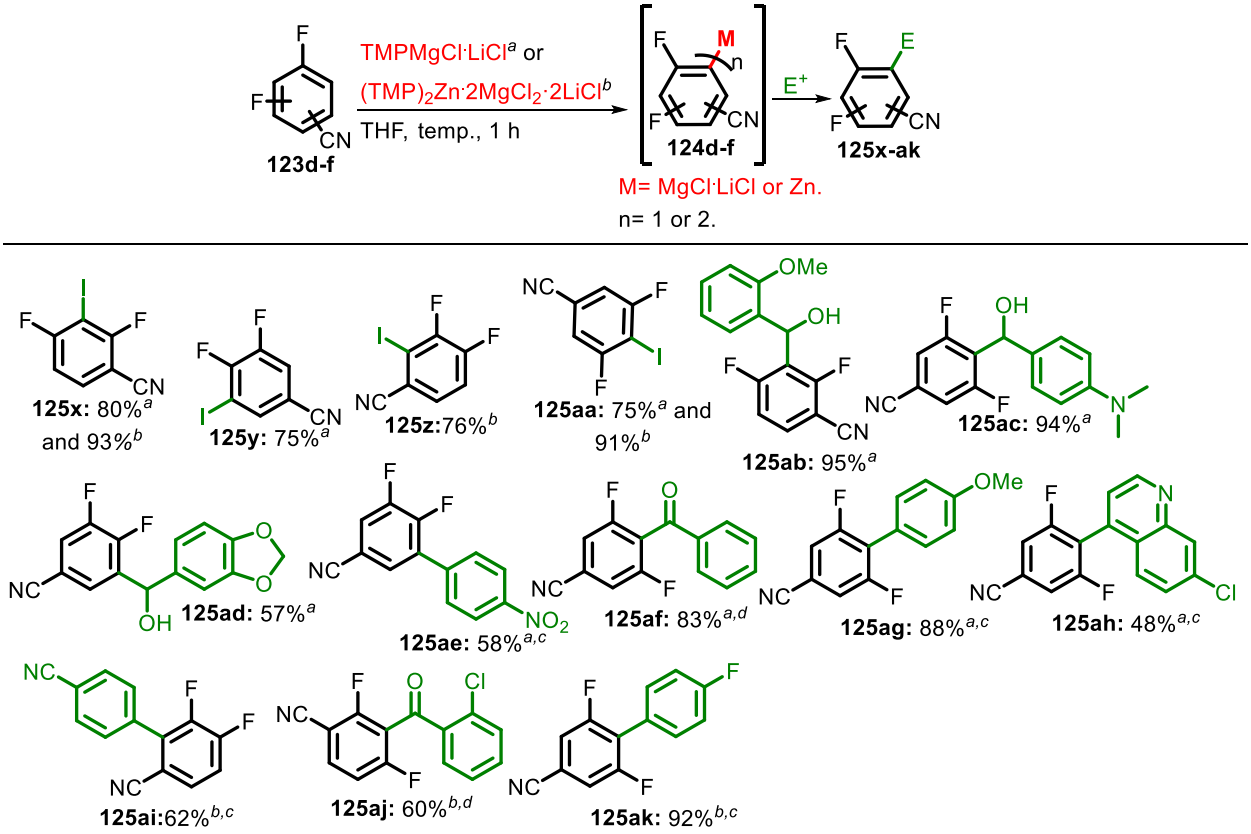
Table 9. Metalation sites of **123d–f** explored in this work and the literature.

Substrates*	H[a]	H[b]
	**a. TMPMgCl·LiCl 1 h, 0 ºC (This work).** **b. $(TMP)_2Zn·2MgCl_2·2LiCl$, 1 h, rt. (This work).**	-
	**TMPMgCl·LiCl 1 h, -70 ºC (This work).**	a.TMPZnCl·LiCl, 80 ºC, 12 h.[89] b. **$(TMP)_2Zn·2MgCl_2·2LiCl$, 1 h, r.t. (This work).**
	-	a. LDA, - 78 ºC, 1 h.[90] b.**TMPMgCl·LiCl 1 h, -30 ºC (This work).** c. **$(TMP)_2Zn·2MgCl_2·2LiCl$, 1 h, rt. (This work).**

*pK_a values are listed. [a]Blue = only this work. [b]Light-green = both, literature and this work.

Regarding the literature, only positions C2 for **123e** and C4 for **123f** have been metalated with TMPZnCl·LiCl in 12 h at 80 ºC[89] and by LDA in 1 h at -78 ºC,[90] respectively (**Table 9**). As advantages of the developed methodologies over these protocols, $(TMP)_2Zn·2MgCl_2·2LiCl$ allows the metalation to be performed in 1 hour at 25 ºC, and TMPMgCl·LiCl makes it possible to access position C5, a new metalation site for **123e**.

Table 10. Metalation and functionalization of difluorobenzonitriles **123d–f** with TMP-bases.*



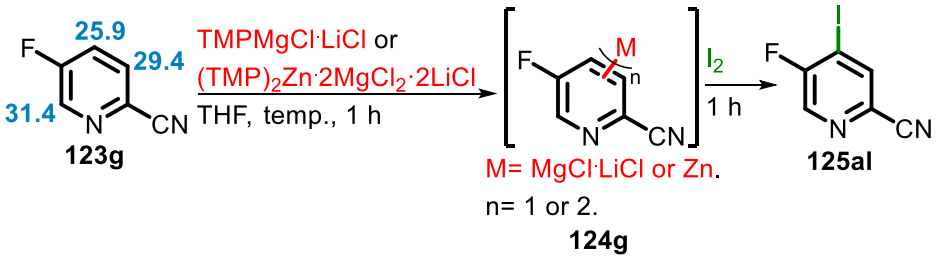
*Isolated yields. [a]1.3 equiv. for both 2,4-difluorobenzonitrile (**123d**) at 0 ºC and 3,5-difluorobenzonitrile (**123f**) at -30 ºC, and 1.5 equiv. for 3,4-difluorobenzonitrile (**123e**) at -70 ºC. [b]0.65 equiv. for both **123d** and **123f**, and 0.75 equiv. for **123e** at room temperature. [c]$ZnCl_2$ (1 M in THF) except for **125ai** followed by Negishi cross-coupling with $Pd(PPh_3)_4$. [d]$ZnCl_2$ (1 M in THF) except for **125aj** followed by $Pd(PPh_3)_4$ catalyzed benzoylation.

After metalation optimization studies for nitriles **123d–f**, their organomagnesium or organozinc derived species **124d–f** were reacted with diverse electrophiles (**Table 10**). Their treatment with iodine gave iodides **125x–aa** in yields up to 93%. The reaction of the organomagnesium species **124d–f** with 2-methoxybenzaldehyde, 4-(dimethylamino)benzaldehyde, and benzo[*d*][1,3]dioxole-5-carbaldehyde yielded alcohols **125ab–ad** in 57–95% yields. After transmetalation with $ZnCl_2$, the obtained aromatic zincates were suitable for both palladium-catalyzed Negishi cross-coupling affording systems **125ae**, **125ag**, and **125ah** in 58%, 88%, and 48% yields, respectively, and palladium-catalyzed benzoylation leading to **125af** in 83% yield. Moreover, the base $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ was used for the direct zincation at the C2 position of **123e** with

subsequent use in the synthesis of biaryl products **125ai** (62% yield) and **125ak** (92% yield), and the ketone **125aj** (60% yield) under palladium catalysis.

Lastly, the metalation of fluorinated pyridinecarbonitriles **123g–l** was assayed with the TMP-bases successfully employed before. Considering the need for low temperatures in the metalation of deactivated pyridines (e.g. 3-fluoropyridine) by TMPMgCl·LiCl[32], it was initially decided to treat 5-fluoropicolinonitrile **123g** with 1.2 equivalents of this base at -30 ºC. Favorably, the aryl iodide **125al** was observed with a tiny amount left of the starting material (**Table 11**, **Entry 1**). Increasing the base amount to 1.3 equivalents at the same temperature in 1 hour led to the full conversion of nitrile **123g** in the desired product after reaction with iodine (70% isolated yield) (**Entry 2**). When $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ was considered at 25 ºC, a mixture of **125al** with a side product, a putative regioisomer, was obtained at a 1.3:1 ratio.

Table 11. Metalation study of 5-fluoropicolinonitrile **123g** with TMP-bases.



Entry	TMP-base	Equiv.	Time (h)	Temp. (ºC)	123g (%)[a]	125al:123g ratio
1	TMPMgCl·LiCl	1.20	1	-30	10	9:1
2**	TMPMgCl·LiCl	1.30	1	-30	none	>99[b]:1
3	$(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$	0.65	1	25	1	*

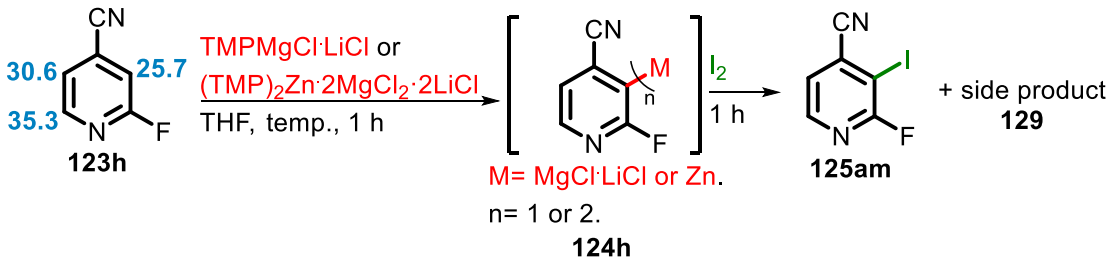
[a]Remaining starting material: percent composition – Gas chromatography (GC-FID). [b]Isolated Yield = 70%. *Not selective: a mixture of 125al:side product at 1.3:1 ratio was obtained. Not isolated. **Defined as the standard condition.

The deprotometalation for **123g** at 4-position is consistent with the two coupling constants of type $^{2}J_{C\text{-}F}$ (34.1 Hz for the duplet at 139.1 ppm and 24.8 Hz for the duplet at 93.1 ppm) in its ^{13}C NMR spectrum. The first duplet is assigned to C6 and the second one to the halogenated carbon (C4) in **125al**. In the case of a C6

functionalization, a hydrogen-hydrogen coupling ($^3J_{H4-H3}$) and a hydrogen-fluorine coupling ($^3J_{H4-F}$) would be expected with different signals in the 1H NMR spectrum, a possible triplet and a doublet of doublets. Additionally, there are correlations between carbon C4-I and hydrogens C3-H and C6-H which are separated by 2 and 3 bonds, respectively, in the HMBC (Heteronuclear Multiple Bond Correlation) correlation map. In the case of C6 functionalization, these two correlations would probably not be verified.

When 2-fluoroisonicotinonitrile **123h** was treated with 1.3 equiv. of TMPMgCl·LiCl at -30 ºC, the reaction medium turned black from the very beginning, and decomposition was observed (**Table 12**, **entry 1**). Performing the metalation at -70 ºC instead led to a light orange colored medium and a mixture of iodide **125am** (57% isolated yield) and a side product (**Entry 2**). Supposing the reaction of organomagnesium species of type **124h** with remaining non-metalated **123h**, transmetalation by $ZnCl_2$ was done after magnesiation at -70 ºC (0.5 h) followed by iodination at 25 ºC. Surprisingly, no side product was detected under these conditions and more **123h** (percent composition – GC/FID) was left non-functionalized (**Entry 3**). Increasing the base amount to 1.5 and 1.8 equivalents afforded **125am** in 68% and 69%, respectively, with no significant difference (**Entries 4 and 5**). Gratifyingly, 0.9 equiv. of $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ allowed the metalation-functionalization of the same position, C3, but at room temperature furnishing **125am** in 76% after reaction with I_2.

Table 12. Metalation study of 2-fluoroisonicotinonitrile **123h** with TMP-bases.



Entry	TMP-base	Equiv.	Time (h)	Temp. (ºC)	123h (%)[a]	125am:129:123h ratio
1	TMPMgCl·LiCl	1.30	1	-30	trace	*
2	TMPMgCl·LiCl	1.30	1	-70	8	9.8[c]:1.8:1

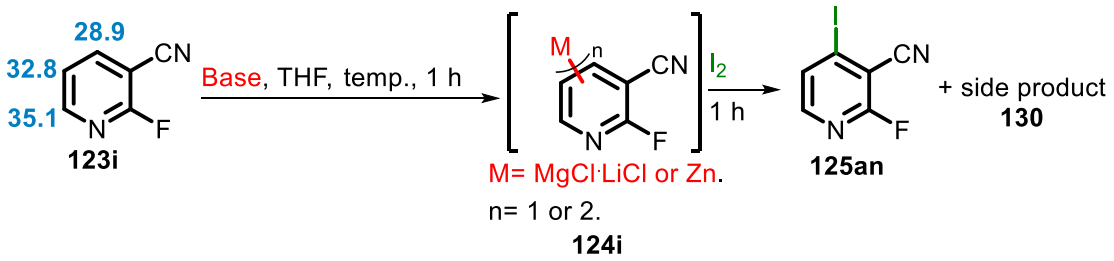
3[b]	TMPMgCl·LiCl	1.30	1	-70	29	(2.4:1)[d]
4[b]	TMPMgCl·LiCl	1.50	1	-70	26	(2.8[e]:1)[d]
5[b]	TMPMgCl·LiCl	1.80	1	-70	13	(6.7[f]:1)[d]
6**	$(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$	0.90	1	25	15	(5.7[g]:1)[d]

*Decomposition. [a]Remaining starting material: percent composition – Gas chromatography (GC-FID). [b]$ZnCl_2$ 1.3 equiv. (entry 3) or 1.5 equiv. (entries 4 and 5) at -70 ºC for 0.5 h after magnesiation. [c]Isolated yield = 57%. [d]Ratio = **125am:123h**. No side product was verified. [e]Isolated yield = 68%. [f]Isolated yield = 69%. [g]Isolated yield = 76%. **Defined as the standard condition.

The metalation-functionalization at C3 for **123h** is sustained by the coupling constant J = 5.0 Hz which is consistent with an H-H *ortho* coupling between the hydrogens assigned to the doublet of doublets at 8.33 and 7.40 ppm (^{1}H NMR of **125am**, C6-H and C5-H, respectively). Besides, the duplet at 81.8 Hz in the ^{13}C NMR spectrum is attributed with C3-I with a characteristic $^2J_{C\text{-}F}$ = 47.1 Hz and there is a correlation between this carbon and hydrogen C5-H over 3 bonds in the HBMC correlation map.

For the metalation of 2-fluoronicotinonitrile **123i**, 1.3 equivalents of TMPMgCl·LiCl was initially employed at -30 ºC followed by quenching with I_2. Similar to what was observed for the metalation of **123h**, the reaction medium turned black with a moderate conversion and the observation of a side product in a significant proportion (**Table 13**, **entry 1**). Increasing the base amount to 1.5 equivalents but working at -70 ºC greatly improved the conversion, the reaction color remained light orange, and no side product was produced. After trapping with I_2, the iodide **125an** was isolated in 85% (**Entry 2**). As an attempt to access other metalation sites, **123i** was treated with TMPZnCl·LiCl with no conversion (**Entry 3**). Besides, $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ led to a mixture of **125an** (minor) and a regioisomer (major) at a 1:2.8 ratio (**Entry 4**). Performing the same reaction but at 60 ºC in a microwave reactor or at -20ºC both for 1 h afforded only traces of **125an** and traces of the regioisomer, respectively (**Entries 5 and 6**).

Table 13. Metalation study of 2-fluoronicotinonitrile **123i** with TMP-bases.



Entry	TMP-base	Equiv.	Time (h)	Temp. (ºC)	123i (%)[a]	125an:130:123i ratio
1	TMPMgCl·LiCl	1.30	1	-30	30	1.5:0.8:1
2**	TMPMgCl·LiCl	1.50	1	-70	9	(10.1[b]:1)[c]
3	TMPZnCl·LiCl	1.50	1	25	>99	None[d]
4	$(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$	0.80	1	25	85	Regioisomers[e]
5	$(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$	0.80	1	60[g]	94	(0.06:1)[c]
6	$(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$	0.80	1	-20	97	Regioisomer[f]

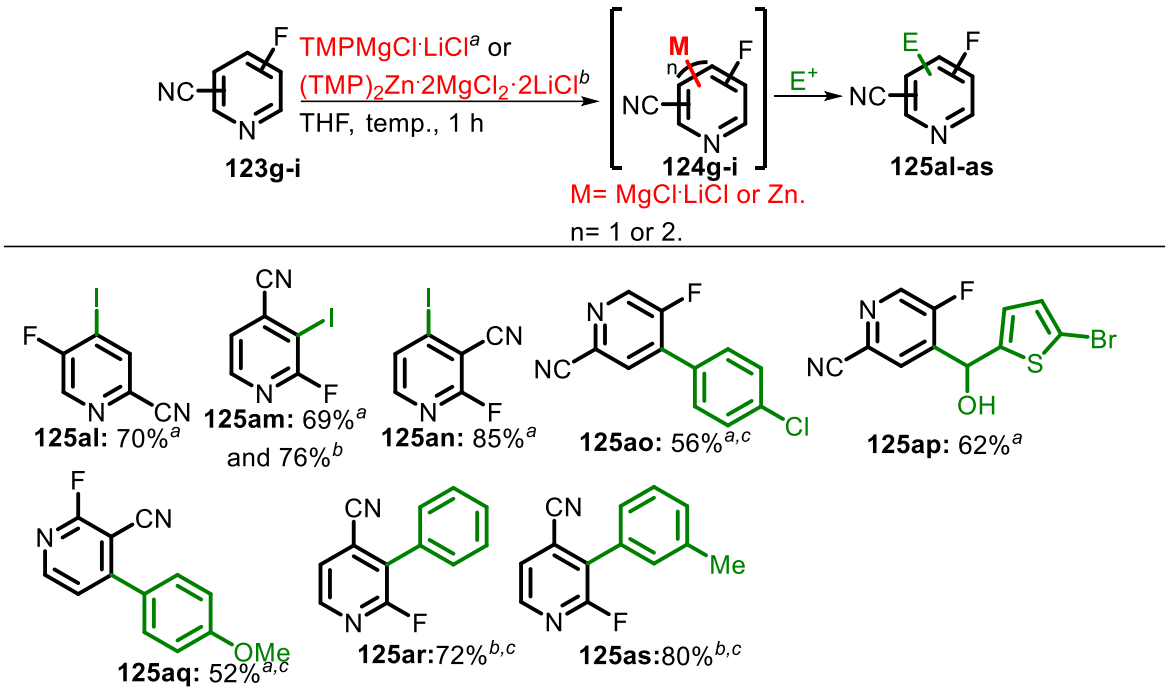
[a]Remaining starting material: percent composition – Gas chromatography (GC-FID).[b]Isolated yield = 85%. [c]Ratio = **125an:123i**. No side product was verified. [d]No products were detected. [e]A mixture of regioisomers (Ratio **125an**:regioisomer = 1:2.8) was furnished with a poor conversion rate. [f]The non-isolated regioisomer was detected (Ratio regioisomer:**123i** = 0.03:1). [g]Microwave reactor. **Defined as the standard condition.

The ^{1}H NMR spectrum of **125an** displays two doublets of doublets (8.08 and 7.80 ppm) with a coupling constant J = 5.3 Hz, which is suggestive of an *ortho* coupling involving C6-H and C5-H. Concerning its ^{13}C NMR, the duplet at 106.4 ppm ($^2J_{C\text{-}F}$ = 32.7 Hz) is assigned to C3-CN which only correlates with C5-H over 3 bonds by HMBC analysis corroborating with the scenario of a C4 metalation-functionalization.

Interestingly, no metalation reports have been found in the literature for the three studied pyridinecarbonitriles **123g-i**. To illustrate the application of the regioselectively generated organomagnesium and organozinc species by the developed metalation protocols, electrophiles including the 5-bromo-2-thiophenecarboxaldehyde and iodoarenes (1-chloro-4-iodobenzene and 4-methoxyiodobenzene) for palladium-catalyzed Negishi cross-couplings were employed in the synthesis of **125ao–aq** (52 - 62%). Moreover, zincates from 2-fluoroisonicotinonitrile **123h** were directly accessed by

$(TMP)_2Zn.2MgCl2\cdot 2LiCl$ at 25 ºC in one hour and subsequently used in the preparation of biaryls **125ar,as** in great yields, 72 and 80%, respectively.

Table 14. Metalation and functionalization of difluorobenzonitriles **123g–i** with TMP-bases.*



*Isolated Yields. [a]1.3 equiv. for 5-fluoropicolinonitrile (**123g)** at -30 ºC, and 1.5 equiv. at -70 ºC for both 2-fluoronicotinonitrile (**123i**) and 2-fluoroisonicotinonitrile (**123h**). [b]$(TMP)_2Zn\cdot 2MgCl_2\cdot 2LiCl$ (0.9 equiv. for **123h**). [c]$ZnCl_2$ (1 M in THF) followed by Negishi cross-coupling with $Pd(PPh_3)_4$.

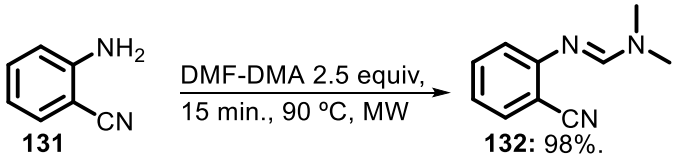
The great influence of electron-withdrawing properties of the fluoro group on the acidity of adjacent aromatic hydrogens for the studied nitriles is noticeable when the predicted pK_a values in THF by DFT (Density-functional theory) calculations are compared to the benzonitrile (Page 99). Interestingly, except for **123e** where the most acidic hydrogen was selectively abstracted by $(TMP)_2Zn\cdot 2MgCl_2\cdot 2LiCl$, TMPMgCl·LiCl mostly abstracted the most acidic hydrogens for the other nitriles, which are often located *ortho* to the fluoro group. It is known that this magnesium amide is prone to undergo kinetic driven metalations[91] instead of the thermodynamically based ones observed for the TMP-zinc base TMPZnCl·LiCl.[92] The thermodynamic control for the deprotonation at C2 in **123e** by $(TMP)_2Zn\cdot 2MgCl_2\cdot 2LiCl$ can benefit from -CN and -F

electron-withdrawing properties and their effect in acidity and stabilization of the generated anion as noticed by Otsuka and coworkers for the same substrate via TMPZnCl.LiCl.[89] Notably, despite the coordinating capability of nitrogen from pyridines to the metal center in TMPMgCl·LiCl as explored by Knochel and co-workers,[32] the directing properties of fluoro and cyano groups implied the observed regioselectivity for the studied pyridines **123g-i**.

3.1.2 Synthesis of 4-aminoquinazolines and other heterocycles as synthetic applications

Initially, the 2-aminobenzonitrile **131** was reacted with 1,1-dimethoxy-*N,N*-dimethylmethylamine (DMF-DMA) under microwave irradiation for 15 minutes to afford (*E*)-*N'*-(2-cyanophenyl)-*N,N*-dimethylformimidamide **132** in 98% (**Scheme 22**).[66]

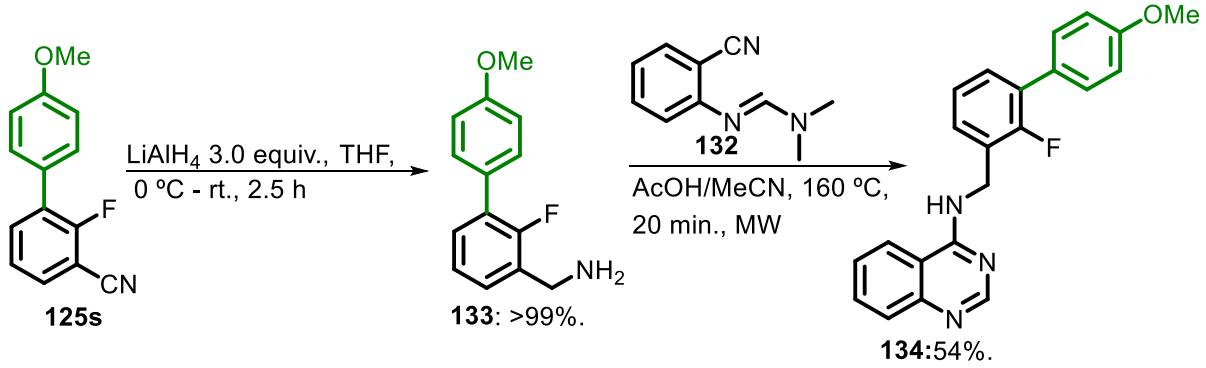
Scheme 22. Synthesis of (*E*)-*N'*-(2-cyanophenyl)-*N,N*-dimethylformimidamide **132**.



Source: The author.

Then, to illustrate the potential application of the functionalized building blocks in the construction of heterocyclic systems of pharmaceutical relevance, a 4-aminoquinazoline, **125s** was reduced to the respective benzylamine **133** in quantitative yield[127] and subsequently applied without purification to the preparation of *N*-((2-fluoro-4'-methoxy-[1,1'-biphenyl]-3-yl)methyl)quinazolin-4-amine **134** in 54% as a white solid (**Scheme 23**). The desired cyclization through Dimroth rearrangement was performed under microwave irradiation at 160 ºC for 20 minutes as an adaptation of the work of Besson and co-workers.[66]

Scheme 23. Synthesis of 4-aminoquinazoline **134**.



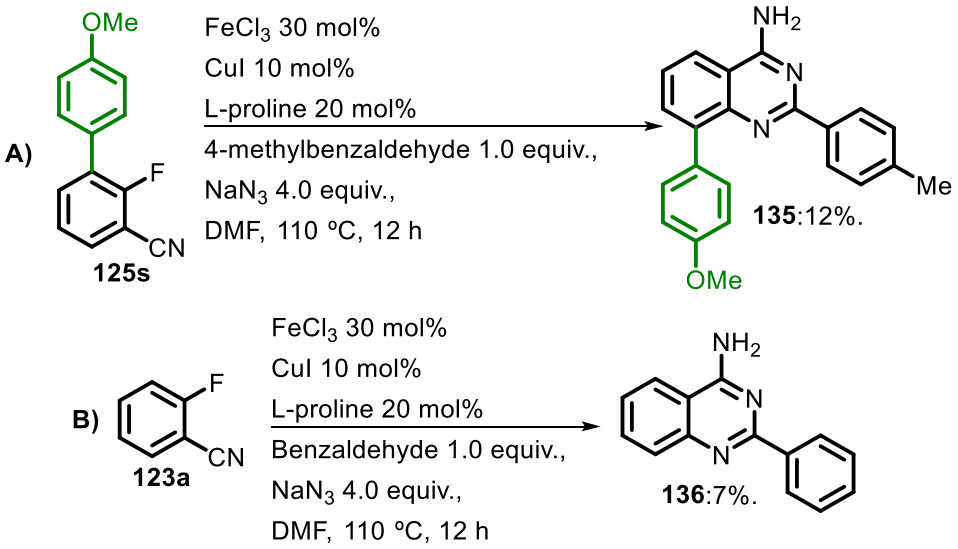
Source: The author.

Besides, based on the successful Fe(III) and Cu(I) catalyzed conversion of 2-fluorobenzonitrile in 2-phenylquinazolin-4-amine by Wu and co-workers,[56e] their domino protocol was investigated for **125s** with 4-methylbenzaldehyde (**Scheme 24A**). After 12 hours at 110 ºC and under air, **135** was spotted via TLC in conjunction with very polar yellow substances (Hexanes:AcOEt 7:3). Unfortunately, **135** was isolated in low yield (12%). The other fractions from column chromatography were sent to NMR analysis but no conclusion was possible about their identity. By facing this matter, it was decided to reproduce the exact reaction done by Wu and co-workers (**Scheme 24B**). However, a low yield (7%) was also obtained for 4-aminoquinazoline **136**.

Trying to reason the observed low yields, it was noticed that the employed DMF by the researchers was distilled from magnesium sulfate before use and, therefore, still contained traces of water. The used DMF, however, was dried with CaH_2, distilled, and stored over 4Å molecular sieves. Since water is expected to aid copper reduction (Cu^{III} to Cu^{I}) as pointed out by the authors in the general mechanism, this must have been the issue.

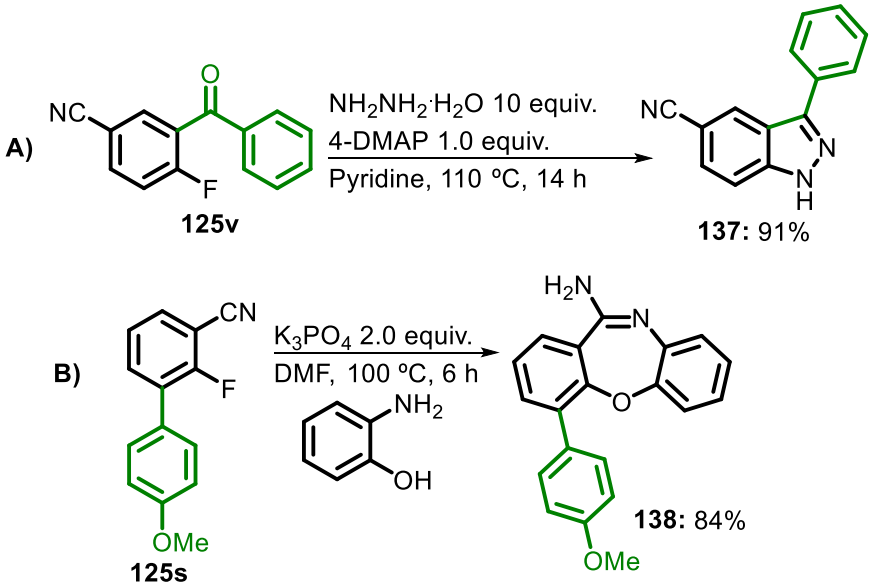
Afterward, DMF was treated as in their procedure and the model reaction (**Scheme 14B**) was repeated. Nonetheless, **136** was furnished in only 10%. An extra attempt was made by adding water to the reaction (3.0 equiv.), but no significant change in yield was observed.

Scheme 24. Synthesis of 8-(4-methoxyphenyl)-2-(*p*-tolyl)quinazolin-4-amine **135**.



Source: The author.

Scheme 25. Synthesis of 1*H*-indazole **137** and dibenzoxazepinamine **138**.



Source: The author.

In addition to the synthesis heterocycles of great interest by employing the functionalized nitriles as building blocks, **125v** and **125s** were applied to the synthesis of 1*H*-indazole **137** and dibenzoxazepinamine **138** in 84% and 91% yields, respectively (**Scheme 25AB**). The indazole core is present in a vast number of bioactive

molecules,[93] including bendazac and benzydamine.[94] Besides, the dibenzoxazepinamine scaffold is commonly found in antidepressant pharmaceuticals like loxapine.[95]

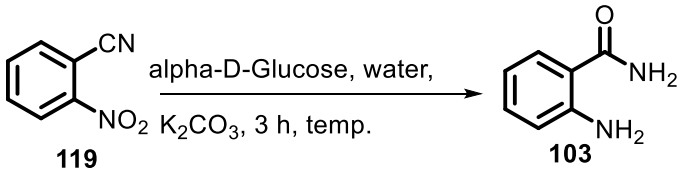
Parts of the developed work in Chapter I have been published as “Selective Metalation and Functionalization of Fluorinated Nitriles Using 2,2,6,6-Tetramethylpiperidyl Bases” in *Organic Letters*.[96]

4. CHAPTER 02 - ONE-POT SYNTHESIS OF 2,3-DIHYDROQUINAZOLIN-4(1*H*)-ONES WITH GLUCOSE AS THE REDUCTANT.

4.1 RESULTS AND DISCUSSIONS

Potassium carbonate, an eco-friendly and inexpensive base,[97] was chosen together with an aqueous glucose solution (**Table 15**) instead of the often-used strong bases potassium hydroxide and sodium hydroxide in similar reduction processes with this carbohydrate.[98] Initially, the treatment of **119** with 0.8 mmol (4 equiv.) of the base in 0.8 mL of water at 100 °C led to both nitroreduction and cyano hydration in the formation of 2-aminobenzamide **103** in 79% (**Entry 1**). Decreasing the base excess and changing the amount of glucose (**Entries 2 and 3**) improved the yield albeit running the reaction in air instead of argon did not change the outcome (**Entries 3 and 4**). Notably, by working with more diluted solutions, a higher yield was obtained (**Entries 6 and 7**) unless the amount of glucose was changed to 1 equivalent (**Entry 5**). Running the reaction at 50 °C for three hours or in the absence of glucose only afforded 2-nitrobenzamide (**Entries 8 and 9, respectively**). **Entry 6** was established as the optimum set of conditions providing 2-aminobenzamide in 92% isolated yield.

Table 15. Synthesis of 2-aminobenzamide under various conditions.[a]



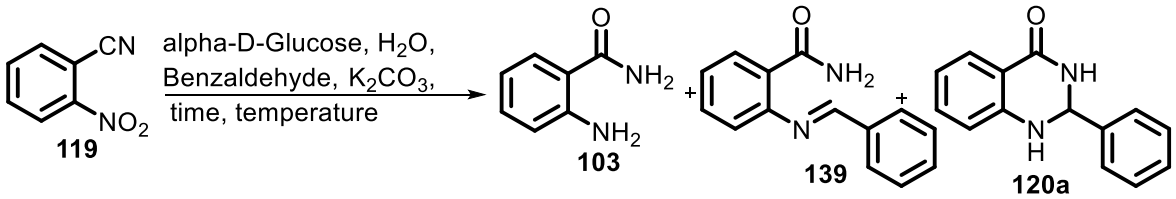
Entry	α-D-glucose	Solvent	Base amount	Yield (%)[b]
1	2 equiv.	0.8 mL	4 equiv.	79
2	1.5 equiv.	0.8 mL	3 equiv.	87
3	2 equiv.	0.8 mL	2 equiv.	91
4[c]	2 equiv.	0.8 mL	2 equiv.	90
5	1 equiv.	4 mL	2 equiv.	74
6	**2 equiv.**	**4 mL**	**2 equiv.**	**94**[d]
7	2 equiv.	4 mL	4 equiv.	95
8[e]	2 equiv.	4 mL	4 equiv.	None
9	None	4 mL	2 equiv.	None[f]

[a]The time of 3 h, temperature of 100 °C, air as atmosphere, and 0.2 mmol of 2-nitrobenzonitrile apply for all the reactions unless otherwise stated. [b]Dimethyl sulfone was employed as NMR standard for quantification. [c]Argon as atmosphere. [d]Isolated yield: 92%. [e]The temperature of 50 °C favored the formation of 2-nitrobenzamide (86% yield, NMR quantification after extraction with AcOEt 3·10 mL). [f]Only 2-nitrobenzamide was observed.

Then, it was speculated if in the presence of benzaldehyde under the established conditions to obtain 2-aminobenzamide, the respective imine would be formed with a subsequent 6-*endo*-*trig*-cyclization to yield the expected 2,3-dihydroquinazolin-4(1*H*)-one in a one-pot fashion. Gratifyingly, one equivalent of benzaldehyde at 100 °C for 16 hours (**Table 2, entry 1**) afforded 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (**120a**) in 55% yield along with 2-aminobenzamide (**103**) (**Table 16**). Increasing the aldehyde amount to 2 equivalents boosted the conversion of **119** in the imine **139** (**Entry 2**). Besides, adjusting the temperature to 120 °C with a slight excess of benzaldehyde improved the yield of **120a** (Entry 3). Keeping this temperature but working with a more concentrated medium also increased yield with the only trace of imine **139** (**Entry 4**). The variation in solvent amount was then investigated with 1.5 equivalents of

benzaldehyde (**Entries 5, 6, and 7**), and 0.8 mL of water was found to be optimal. Lastly, no increase in yield was observed by using 4 equivalents of the base (**Entry 10**), 1.5 equivalents of glucose with 3 equivalents of potassium carbonate (**Entry 9**), or with a reaction time of 24 hours (**Entry 8**). The 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one **120a** was isolated as a white solid in 75% yield (**Optimized conditions, Entry 6**).

Table 16. Optimization of the reaction conditions for the synthesis of 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one.[a]



Entry	Solvent (H_2O)	Temp. (°C)	Benzaldehyde	Time	Yield (%)[b] 103	139	120a
1	2 mL	100	1.0 equiv.	16 h	35	**	55
2	2 mL	100	2.0 equiv.	16 h	18	17	54
3	2 mL	120	1.2 equiv.	16 h	13	6	63
4	1 mL	120	1.2 equiv.	16 h	17	(trace)	72
5	1 mL	120	1.5 equiv.	16 h	7	**	75
6	**0.8 mL**	**120**	**1.5 equiv.**	**16 h**	**5**	******	**78[c]**
7	0.6 mL	120	1.5 equiv.	16 h	14	**	72
8	0.8 mL	120	1.5 equiv.	24 h	**	**	76
9[d]	0.8 mL	120	1.5 equiv.	16 h	**	**	77
10[e]	0.8 mL	120	1.5 equiv.	16 h	**	**	74

[a]0.2 mmol equiv. of 2-nitrobenzonitrile, air as atmosphere, α-D-glucose (2 equiv.) and K_2CO_3 (2 equiv.) apply for all the reactions unless otherwise stated. [b]Determined by ^{1}H-NMR using dimethyl sulfone as a standard. [c]Isolated yield: 75% (white solid). **Not detected by 1H-NMR. [d]α-D-glucose (1.5 equiv.) and K_2CO_3 (3 equiv.) were employed. [e]K_2CO_3 (4 equiv.) was employed.

The next step comprised the investigation of reaction scope including diverse aldehydes and ketones (**Table 17**). Electron-rich aldehydes, 4-substituted

benzaldehydes bearing methyl and methoxy groups afforded DHQs in good yields (**120b**, 77% and **120e**, 75%). 3,4-disubstituted benzaldehydes with similar electronic characteristics as for **120k** (90%) and **120l** (63%), were also tolerated. A lower yield was verified for the three-substituted aldehyde 3,5-bis(benzyloxy)-4-methoxybenzaldehyde for the synthesis of **120r**. For halogenated benzaldehydes (4-Cl-, 4-F-, 3-Br-, 2-I-, and 2,3-dichloro-) low to moderate yields were obtained (**120c,d,f,g,q,** 23−65%). As a synthetic limitation, the reaction with acetophenone did not provide **120s**. However, it worked well for cyclic aliphatic ketones as for cyclohexanone (**120i**, 79%) and cyclopentanone (**120n**, 61%). Extending the scope with heterocyclic aldehydes, the 2-thiophenecarboxaldehyde derivative **120h** was isolated in 59% yield while the expected products from furfural (**120u**) and 2-pyridinecarboxaldehyde (**120t**) were not observed. Furthermore, the developed protocol was suitable for a model aliphatic aldehyde, pentanal, with a moderate yield of 56% (**120j**).

Concerning the characterization of the obtained DHQs, they were subjected to nuclear magnetic resonance spectroscopy (NMR), Infrared spectroscopy, and high-resolution mass spectrometry (HRMS) analyses plus the determination of melting points. To illustrate, for the ^{1}H NMR data for **120a** (**Figure 9**), a singlet at 5.76 ppm refers to H-2 while the other singlets at 8.29 and 7.11 ppm are attributed to -CONH- and -NH-, respectively. Additionally, a doublet of doublets at 7.61 ppm (^{3}J = 7.8 Hz and ^{4}J = 1.7 Hz) is attributed to the aromatic hydrogen H-5, a multiplet from 7.51 to 7.49 ppm to H-2' and H-6', a multiplet from 7.41 to 7.32 to H-3', H-4', and H-5', a doublet of doublets of doublets at 7.24 ppm to H-7 (^{3}J = 8.5, 7.1 Hz and ^{4}J = 1.7 Hz), a duplet at 6.75 ppm to H-8 (^{3}J = 7.1 Hz), and a multiplet from 6.69 to 6.65 to H-6. The ^{13}C NMR spectrum of **120a** (**Figure 10**) shows signals at 163.6 and 66.6 ppm for -CONH- and C-2, respectively. The aromatic carbons are correlated with signals from 147.9 to 114.4 ppm. The **120a** IR spectrum shows important absorption bands including the ones at 3302 and 3178 cm-1 for -N-H stretching vibrations, at 3131, 3061, and 3035 cm^{-1} for -C-H (aromatic carbons, sp^{2} hybridized) stretching vibrations, at 1652 cm^{-1} for -C=O (amide) stretching vibration, at 1610 cm^{-1} for -N-H bending vibration, and at 1507 cm^{-1} for C-C stretching vibration.

Figure 9. Expanded ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120a**.

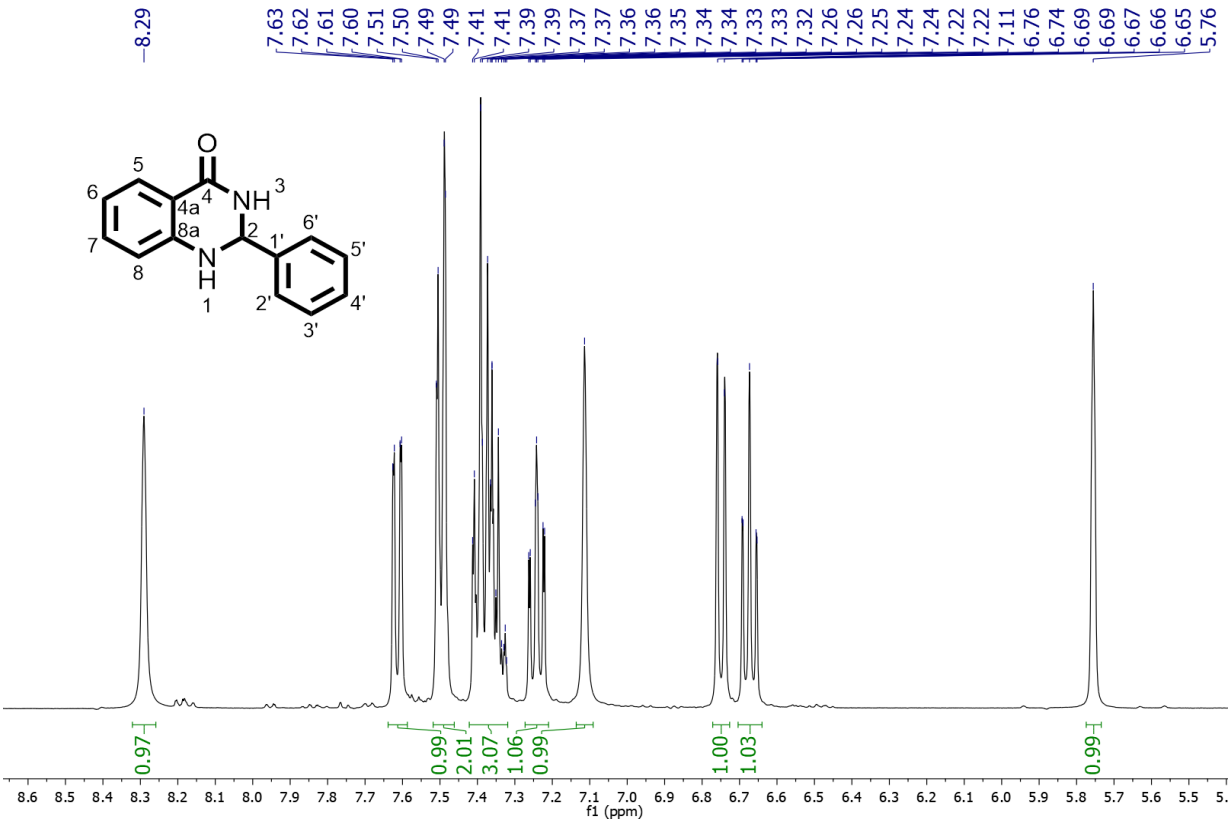


Figure 10. Expanded ^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120a**.

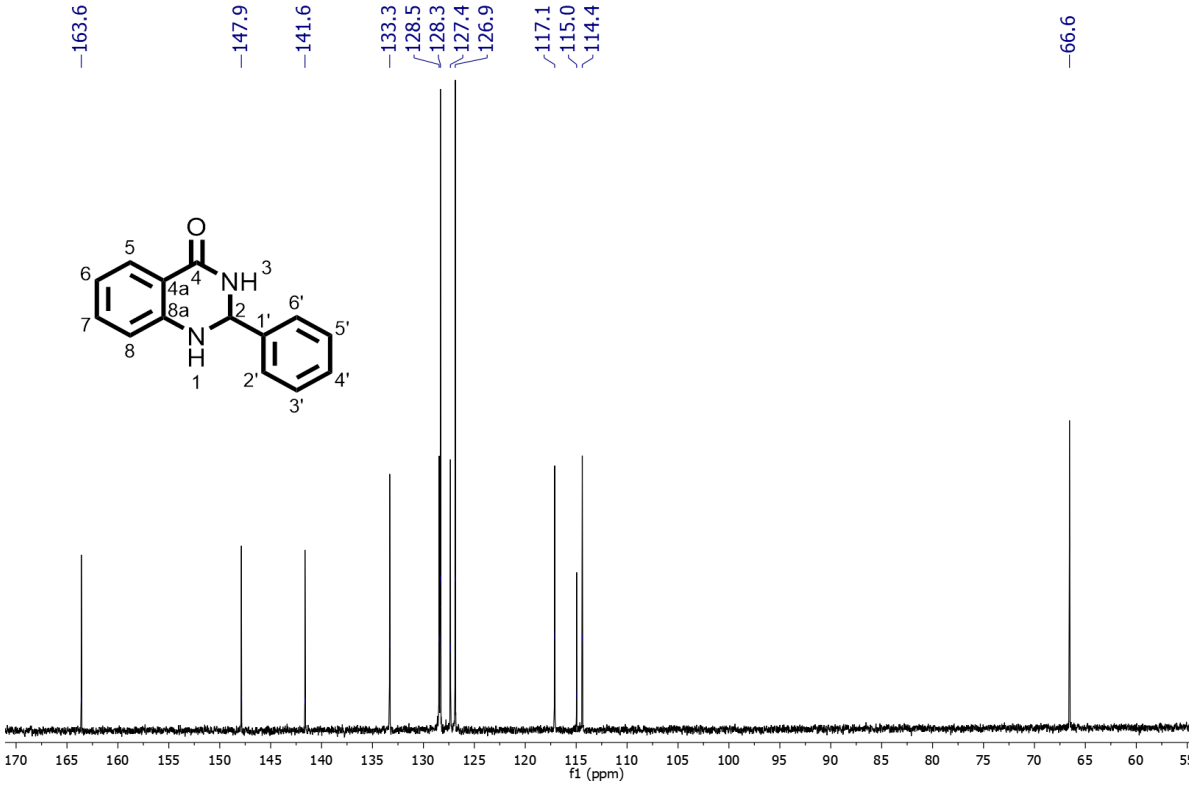
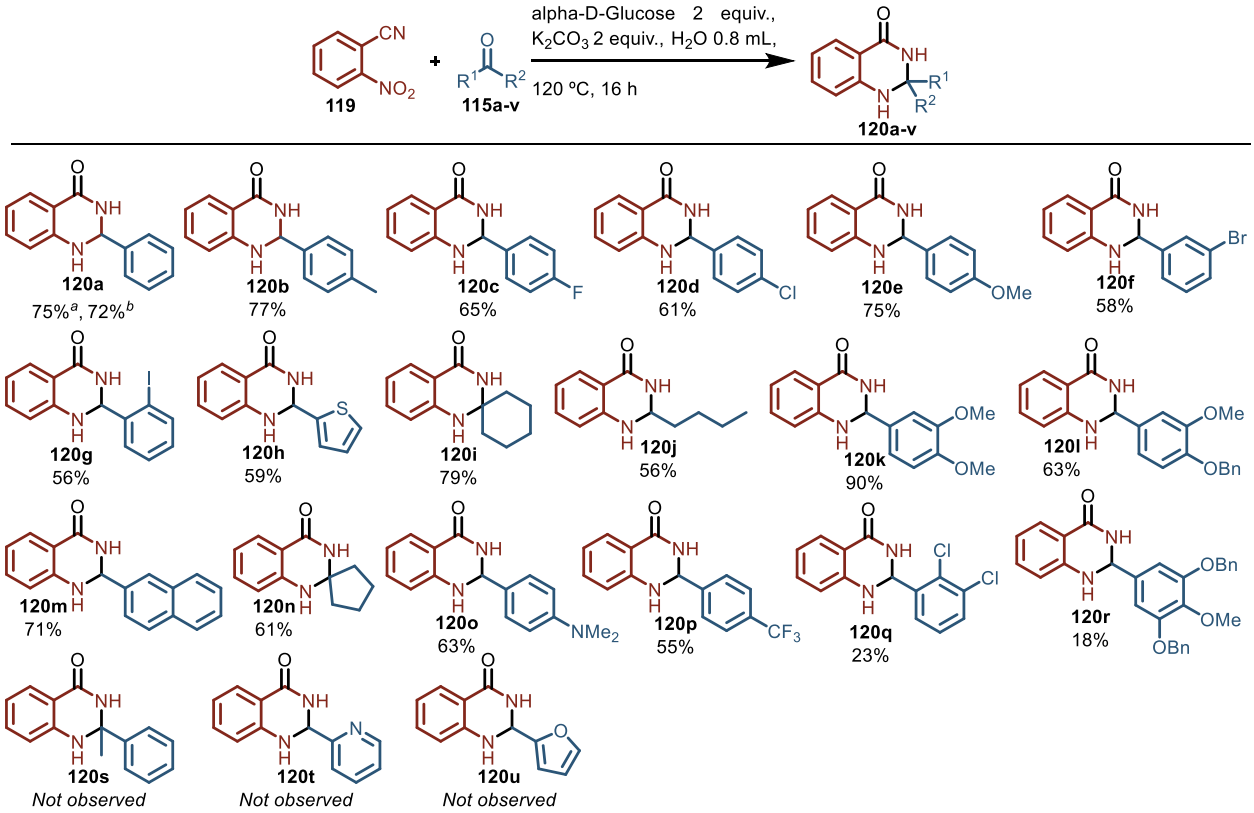


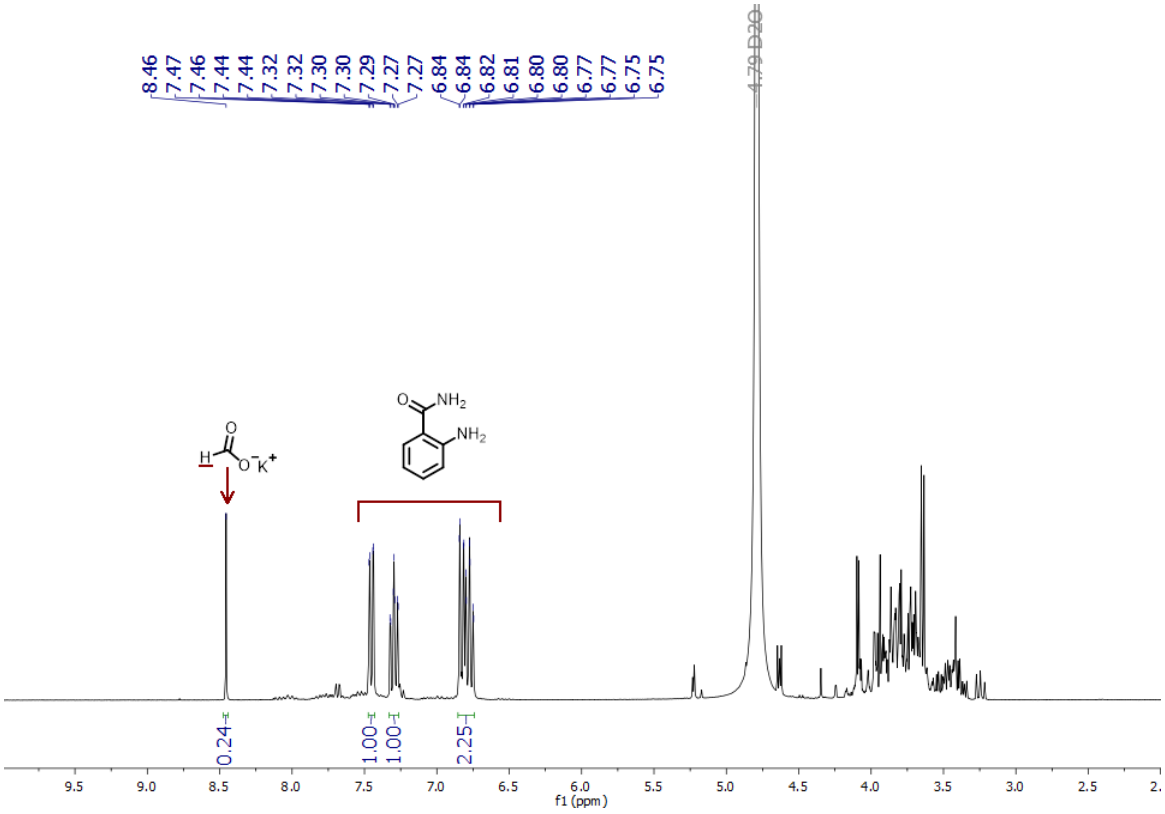
Table 17. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones with the established protocol.



Source: The author.

Regarding the mechanism underlying the devised protocol, it is known that glucose under hot alkaline conditions produces reduction equivalents ("H_2") with the aid of hydroxide anion in its decomposition into carboxylates such as formate, lactate, and glycolate.[99] The ion hydroxide can be generated by water deprotonation with potassium carbonate as explored by Tu and co-workers in the hydration of diverse nitriles.[100] Interestingly, formate was detected for the reaction performed in D_2O (**Figure 11**). Hence, it is plausible to expect hydroxide anion concomitantly acting on glucose decomposition and nitrile hydration in the preparation of 2-amizobenzamide **103** as observed in this study at temperatures equal to or above 100 °C. The facile hydration of 2-nitrobenzonitrile into 2-nitrobenzamide at 50 °C relies on the strong electron-withdrawing effect of the *ortho*-nitro group.

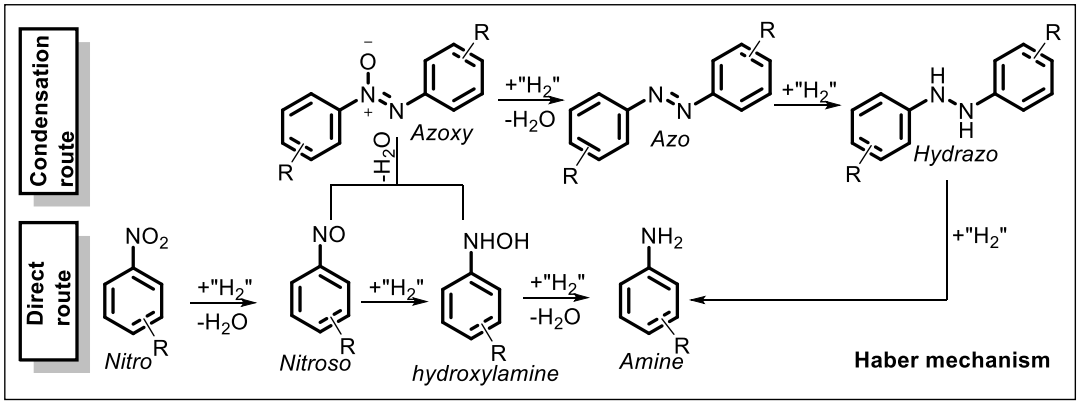
Figure 11. Observation of formate from glucose decomposition for the reaction performed in D_2O (Optimized condition, Table 16, entry 6, no benzaldehyde - ^1H NMR, 400 MHz). In accordance with the literature.[101]



Source: The author.

The nitro reduction may take two different pathways according to the Haber mechanism (**Scheme 26**),[102] one involving hydroxylamine intermediate and the other one bearing heterodimerization to azoxy and azo compounds under usually high alkaline conditions.[98c,103] Notably, no azoxy and azo species were verified by Opolonick in the nitro reduction of nitrobenzene with glucose in aqueous potassium carbonate.[104]

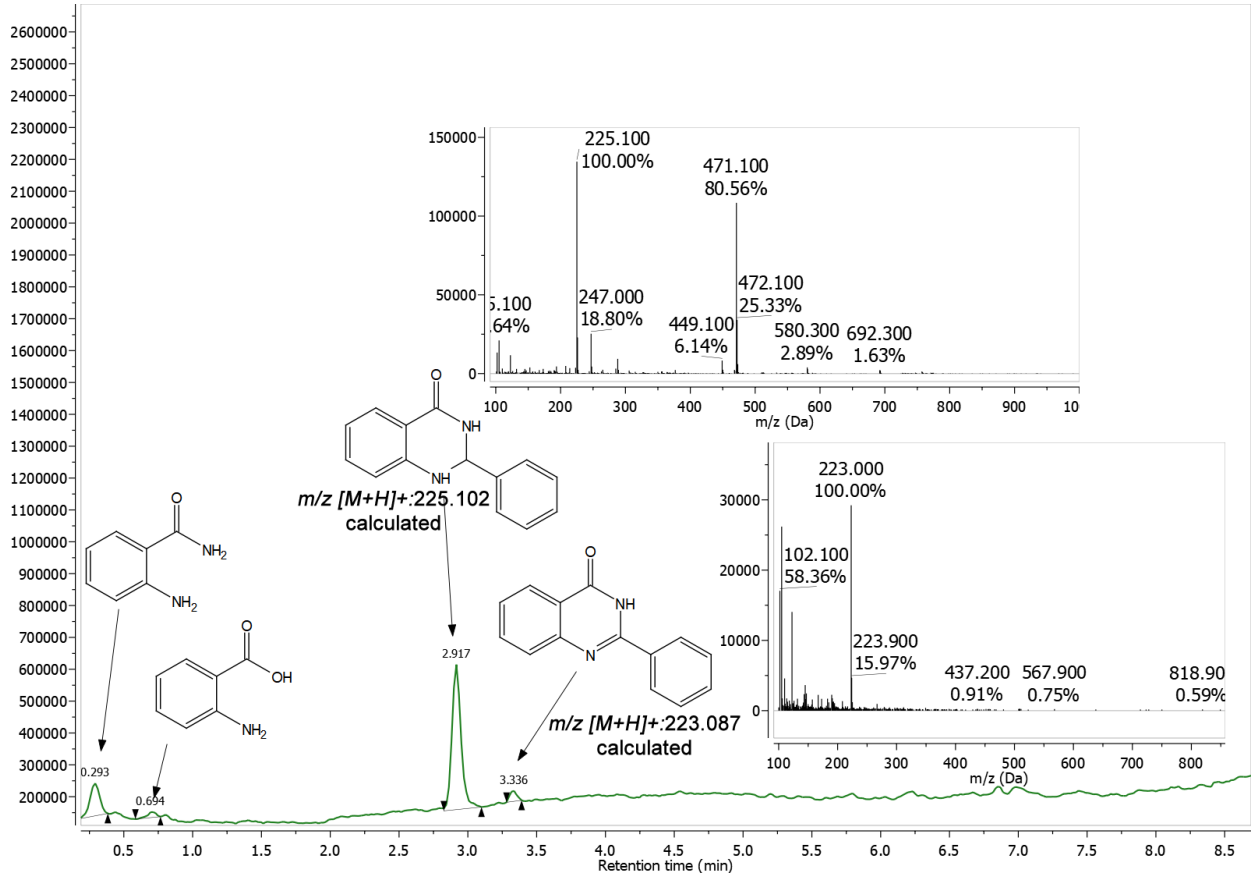
Scheme 26. Nitro reduction pathways.



Source: SERNA; CORMA, 2015.

The synthesis of azoxy compounds can be straightforwardly achieved with the addition of glucose to an aqueous solution of NaOH and the nitro compound. Besides, with the application of a second equivalent of glucose to the same reaction medium, azoxy compounds are converted in respective azo species.[98c,105] To selectively obtain the hydroxylamine instead, glucose can be employed as the reductant in an enzymatic process with a nitroreductase[106] or in fermentation with baker's yeast.[107] Concerning the potential competing reactions for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in this study, amide hydrolysis leading to carboxylic acid even with potassium carbonate and production of 2-phenylquinazolin-4(3*H*)-ones as verified via HPLC-MS (**Figure 12**) and base-induced reactions[108] of the aldehyde component cannot be ruled out.

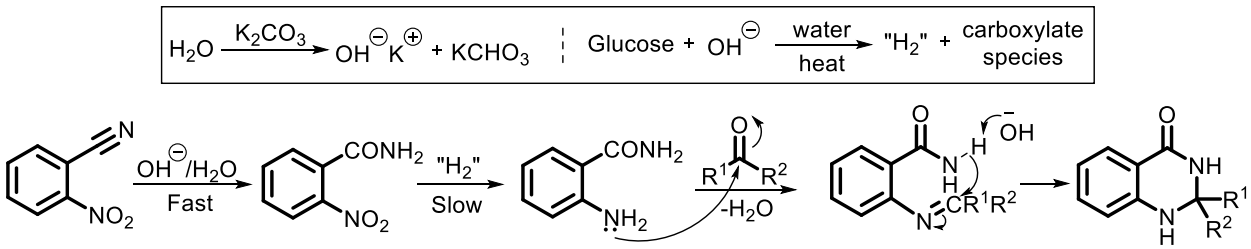
Figure 12. Recorded mass spectra and chromatogram for the optimized conditions (**Table 16, entry 6**).



Source: The author.

A plausible mechanism is depicted in **scheme 27**. Cyano hydration is the fastest step followed by nitro reduction, imine formation, and cyclization.

Scheme 27. Proposed mechanism for the developed synthesis of DHQs.



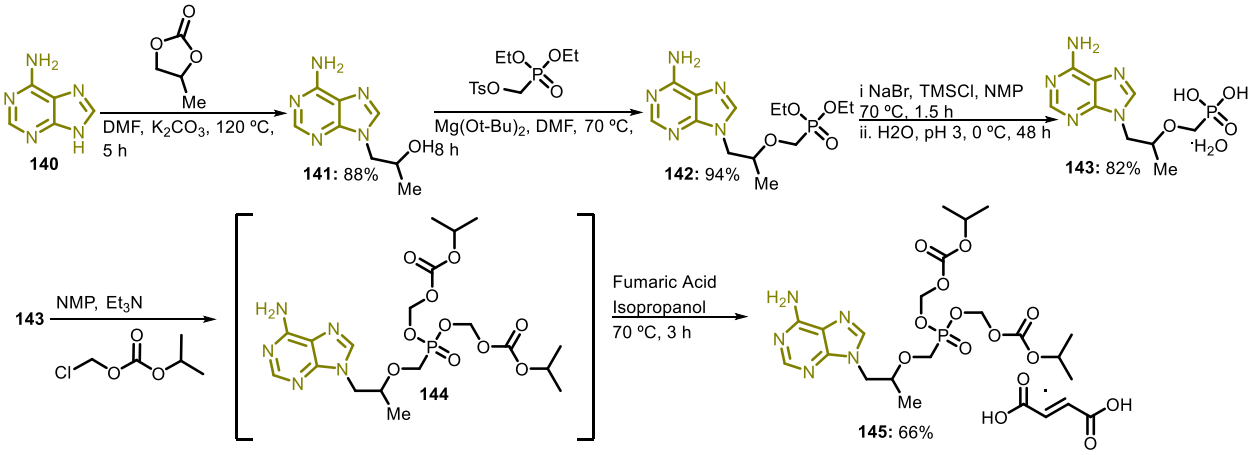
Source: The author.

This work has been published as “Glucose as an Eco-Friendly Reductant in a One-Pot Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones” in the *European Journal of Organic Chemistry*.[109]

5. CHAPTER 03 – TENOFOVIR DISOPROXIL FUMARATE AS A REPOSITIONING STRATEGY TO TACKLE SARS-COV-2

Considering the SARs-COV-2 related pandemic's huge impact on public health worldwide since the beginning of 2020,[110] our research group decided to make efforts in the search for an antiviral agent against this coronavirus using a drug repositioning approach.[111] Tenofovir disoproxil fumarate (TDF), an antiretroviral pharmaceutical used to treat acquired immune deficiency syndrome (AIDS) and hepatitis B, was synthetically obtained in a scaled-up and improved manner (**Scheme 28**) with *in situ* infrared spectroscopy monitoring and a degradation study. Subsequently, TDF was *in vitro* assayed against SARS-CoV-2 and was able to significantly reduce SARs-COV-2 viral replication (Vero CCL-81 cells were treated with TDF and further incubated with the virus).

Scheme 28. TDF improved synthetic route.



Source: The author.

Inspired by the known mechanism of action of TDF upon HIV (reverse transcriptase inhibition) and the known inhibition of the viral RNA-dependent RNA polymerase from

SARS-CoV-1 by Remdesivir, my contribution to this work relied on the computational prediction of TDF affinity toward SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) as a potential target.[112] The molecular docking studies were performed with a cryogenic electron microscopy (cryo-EM) structure of SARS-CoV-2 RdRp (PDB id = 7BV2, 2.50 Å) via via GOLD (version 2020.1 CSD release). The cryo-EM structure of SARS-CoV-2 RNA-dependent RNA polymerase was prepared via HERMES (version 2020.1 CSD release): the water molecules and the complex remdesivir-primer were removed, and the hydrogens were added. All located residues within 18 Å via GOLD (version 2020.1 CSD release) were included for the explored binding site. CHEMPLP was chosen as score function, and 50 runs per ligand were performed.

Interestingly, both drugs, TDF and Remdesivir occupied the same region in the RdRp and, therefore, a potential inhibition of this viral enzyme by TDF may not be ruled out and possibly contributed to the observed decline in viral replication. The three magnesium atoms from SARS-CoV-2 RdRp were initially kept for the docking studies given their relevant catalytic activity.[113] It is known that Tenofovir Disoproxil Fumarate undergoes enzymatic phosphorylations after oral administration leading to a triphosphate form.[114] This phosphorylated drug structure was correlated with the best predicted affinity towards the binding pocket of SARS-CoV-2 RdRp (**Table 18**) with important interactions involving residues ASN611 and ARG473 for hydrogen bonding (**Figure 13**) and some oxygens from the phosphate groups in distances less than 2.30 Å to the Mg atoms for oxygen-metal coordination. In the absence of the Mg atoms, the predicted affinity greatly decreases even with the possibility of other hydrogen bondings including the residues CYS542, LYS541, ARG473, and LYS471 (**Figure 14**).

Table 18. Obtained values of GOLD Fitness for the docking studies.

Ligand	**GOLD Fitness (ChemPLP)**	
	The Mg atoms were kept	**The Mg atoms were removed**
Tenofovir monophosphate	58.8993	-
Tenofovir diphosphate	86.0030	-
Tenofovir triphosphate	93.5799	54.3267

Figure 13. Docked TDF conformation (triphosphate form) in RdRp (PDB id = 7BV2, 2.50 Å).

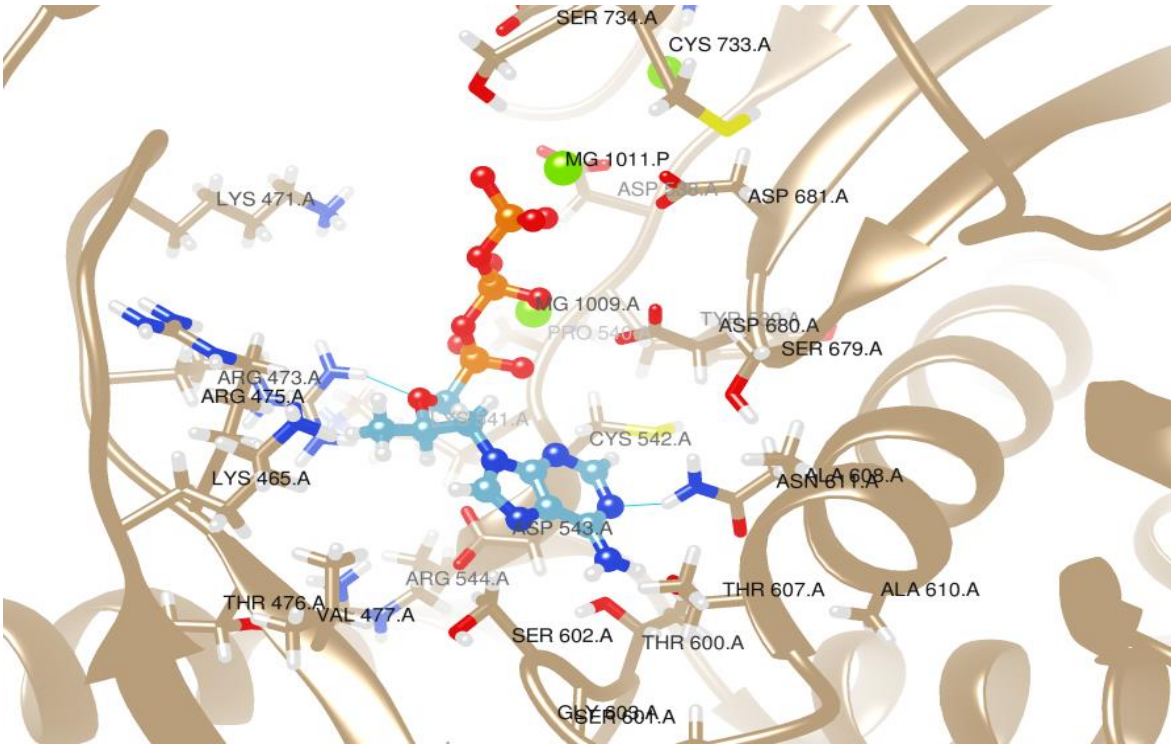
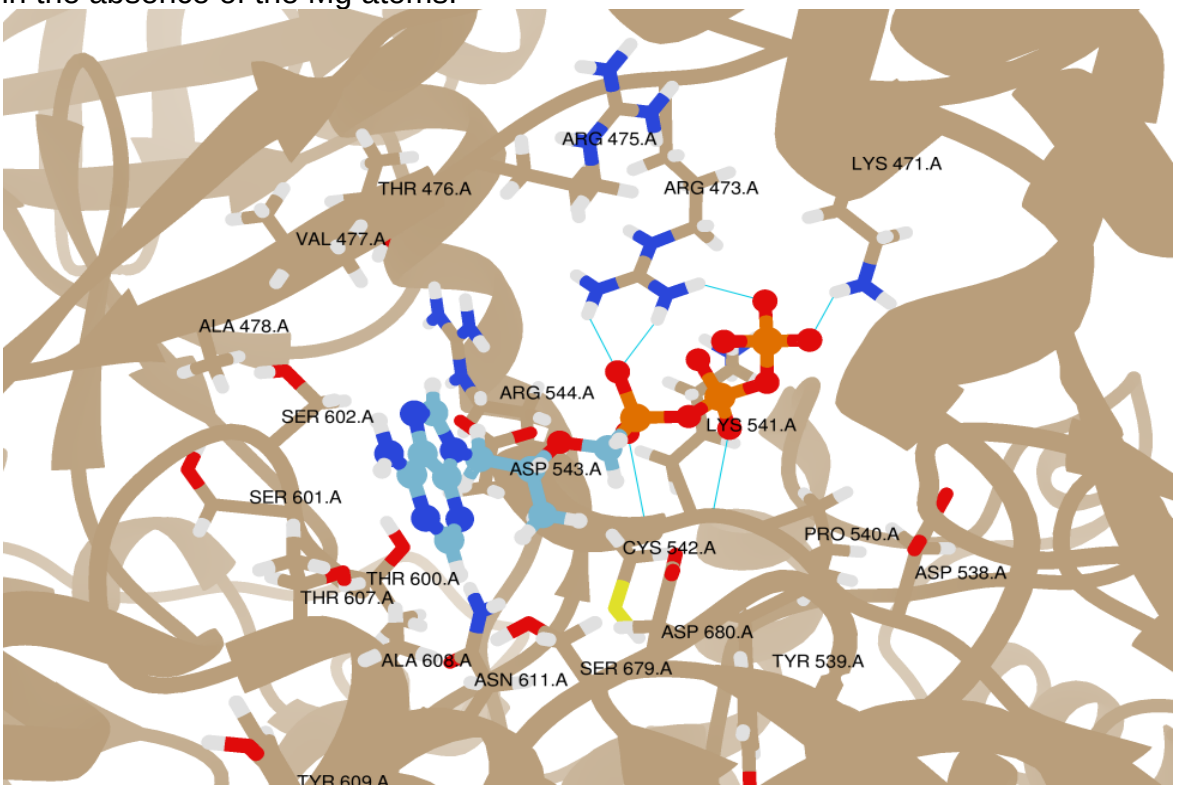


Figure 14. Docked TDF conformation (triphosphate form) in RdRp (PDB id = 7BV2, 2.50 Å) in the absence of the Mg atoms.



This work made it to the cover of the *Journal of the Brazilian Chemical Society* (JBCS) and resulted in an ongoing prospective, randomized, double-blind, placebocontrolled clinical trial coordinated by Dr. Aldo Ângelo Moreira Lima. It was approved by the Brazilian National Research Ethics Commission (no. 34 18262.00.0000.5045) and the ClinicalTrials.gov (NCT04712357) and is being carried out in the city of FortalezaCE, Brazil. Details regarding the employed biological assay, synthetic studies, and computational studies of the developed work (JBCS) can be found via http://dx.doi.org/10.21577/0103-5053.20200106.[115]

6. CONCLUSIONS

About 47 diverse functionalized nitriles with the exploration of new and scarcely investigated metalation sites were prepared in yields ranging from 48 to 95% by metalation with the TMP-bases TMPMgCl·LiCl or $(TMP)_2Zn.2MgCl_2{\cdot}2LiCl$. In the case of known metalation positions, this study has greatly contributed to the establishment of shorter metalation times at milder temperatures with a better exploration of reactivity towards varied electrophiles. Favorably, the devised methods proved to be scalable as illustrated by the synthesis of **125f** at a 5.5 mmol scale (91% isolated yield, 1.21 g). The suitability of TMPMgCl·LiCl in the difunctionalization of **123c** to access tetrasubstituted derivatives **126a-b** can be viewed as a blueprint for the development of exhaustive functionalization protocols with TMP-bases as wisely explored by prof. Manfred Schlosser with lithium-based bases.

The obtained functionalized fluorinated nitriles can be employed as building blocks in the construction of heterocyclic systems of great pharmaceutical importance as exemplified by the synthesis of 4-aminoquinazolines **134** and **135**, 1*H*-indazole **137**, and dibenzoxazepinamine **138**. Furthermore, the prepared building blocks may find application in the synthesis of other diverse important heterocycles since fluorinated nitriles have been also successfully used to access spiro[indazolo[3,2-*b*]quinazoline-7,3'-indolines,[116] indazolo-quinazolinones,[117] cyanodibenzo[1,4]dioxines,[118] dibenzo[*b,f*][1,4]oxazepines,[119] oxazepinones,[120] 11H-pyrido[2,1-b]quinazolin-11-ones,[121] and benzo[d]imidazo[2,1-b]thiazoles.[122]

In the second work, an environmentally friendly one-pot protocol based on nitrile hydration, nitro-reduction, imine formation, and cyclization with glucose in alkaline water was successfully established affording DHQs in yields 18-90%. As a transition metal-free method, it represents a great and fast alternative to access 2,3-dihydroquinazolin-4(1*H*)-ones from 2-nitrobenzonitrile. Moreover, it may ignite the general interest of the research community in applying glucose as a green reductant in the synthesis of other important heterocyclic systems.

Speaking of sustainability, glucose is a relevant renewable resource easily accessible from lignocellulosic biomass through well-established technology and was favorably employed in water as the solvent with potassium carbonate ("potash", available from plant ashes) as the base. Also important, no competition of the aldehyde from glucose with the externally added carbonyl compound was verified, and the synthesized DHQs in this work can be easily oxidized under eco-friendly conditions to the corresponding quinazolinones[123] finding even wider application in medicinal chemistry.

7. EXPERIMENTAL SECTION

7.1 CHAPTER I

7.1.1 General considerations

7.1.1.1 Solvents and reagents

Unless otherwise stated, all the solvents and reagents were obtained from commercial suppliers and used without prior purification. All fluorinated nitriles, salts ($ZnCl_2$, CuCl, LiCl, NH_4Cl, $MgSO_4$), *i*-PrMgCl·LiCl, deuterated solvents, TMPH, $PdCl_2$, PPh_3, and electrophiles were purchased from Merck. All the water-sensitive reactions were carried out with dry solvents under anhydrous conditions and a nitrogen atmosphere. The transference of the dry solvents and air-sensitive reagents was carried out through standard syringe techniques. A saturated sodium thiosulfate solution instead

of NH_4Cl was used for quenching when iodine was employed as the electrophile. $Pd(PPh_3)_4$ was prepared according to the literature.[124]

7.1.1.2 Preparation procedures of the employed TMP-bases and salt solutions

TMPMgCl·LiCl: A dry round-bottom flask equipped with a stirring bar was charged with *i*-PrMgCl·LiCl (1.3 M in THF, 14 mmol, 10.77 mL) under N_2. Then, fresh distilled 2,2,6,6-tetramethylpiperidine (1.05 equiv., 14.7 mmol, 2.48 mL) was added dropwise. The flask was wrapped in aluminum foil, and the reaction was kept at room temperature for 48 hours. The resulting base was titrated with benzoic acid, and 4-(phenylazo)-diphenylamine was used as the indicator (Base concentration range: 0.87 – 1.1 M).

TMPZnCl·LiCl: A dry round-bottom flask equipped with a stirring bar was charged with TMPH (1.1 equiv., 11 mmol, 1.86 mL) and THF (10 mL). This solution was cooled to – 30 °C, and *n*-Buli (2.35 M, 1 equiv., 10 mmol, 4.26 mL) was added dropwise. The reaction was allowed to slowly warm to – 5 °C, and $ZnCl_2$ (0.99 M solution in THF, 1 equiv., 10 mmol, 10.1 mL) was added dropwise. The resulting solution was stirred at this temperature for 30 minutes and then more 30 minutes at 25 °C before titration with benzoic acid using 4-(phenylazo)-diphenylamine as an indicator (Base concentration: 0.39 M).

CuCl·2LiCl (0.5 M in THF): A dry round-bottom flask equipped with a magnetic bar was charged with LiCl (0.85 g, 20 mmol) and heated to 140 ºC (oil bath) for 2 hours under vacuum. After cooling to room temperature, CuCl (0.99 g, 10 mmol) was added under nitrogen, and the temperature was adjusted to 140 ºC for 5 h under vacuum. After cooling, the flask was charged with dry THF (20 mL), covered in aluminum foil, and kept under vigorous stirring to obtain a yellow homogenous solution.

$ZnCl_2$ (1 M in THF): The solution was prepared by drying $ZnCl_2$ (2.73 g, 20 mmol) at 150 ºC (oil bath) for 5 h under vacuum, which was followed by the addition of dry THF (20 mL) at room temperature and vigorous stirring until all the solids were dissolved.

$(TMP)_2Zn·2MgCl_2·2LiCl$: A dry round-bottom flask equipped with a stirring bar was charged with $ZnCl_2$ (1 M, 0.53 equiv., 7.10 mmol, 7.10 mL), and TMPMgCl·LiCl (0.87 M, 13.4 mmol, 15.4 mL) was added dropwise. The flask was wrapped in aluminum foil, and

the reaction was kept at room temperature for 2.5 h. The resulting solution was titrated with benzoic acid, and 4-(phenylazo)-diphenylamine was used as the indicator (Base concentration = 0.29 M).

TMPH: TMPH was stirred overnight with NaOH beads, distilled under reduced pressure, and stored under nitrogen before use.

7.1.1.3 Analytical data and other employed equipment.

Chromatography: Chromatographic purification of the products was performed by flash column chromatography on silica gel (Sigma–Aldrich, particle size 0.040 – 0.063 nm). Thin-layer chromatography (TLC) was carried out on silica plates (TLC Silica 60 F_{254} by Merck). Gas chromatographic investigations were performed on a Shimadzu GC-2014 chromatograph equipped with a capillary column (Restek, RTX-1, 30 m × 0.25 mm) and a flame ionization detector (FID). Nitrogen gas was used as the mobile phase.

NMR spectra: NMR spectra were recorded on a Bruker DRX 400 (^{1}H-NMR: 400 MHz, ^{13}C-NMR: 101 MHz), Bruker DRX 500 (^{1}H-NMR: 500 MHz, ^{13}C-NMR: 126 MHz), or on a Bruker DRX 300 (^{19}F-NMR: 282 MHz) spectrometer. Chemical shifts are referenced to residual solvent signals (DMSO-d_6: 2.50 ppm and 39.52 ppm, and $CDCl_3$: 7.26 ppm and 77.16 ppm for ^{1}H-NMR and ^{13}C-NMR, respectively), TMS (tetramethylsilane) or using the spectrometer frequency (^{19}F-NMR, $CDCl_3$), and reported in parts per million (ppm). Coupling constants (*J*) are reported in Hz, and multiplicities of NMR signals are abbreviated as follows: bs = broad singlet, s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, td = triplet of doublets, dt = doublet of triplets, qd = quartet of dublets, sxt = sextet, m = multiplet and combinations thereof, app = apparent. NMR spectrometry analyses in conjunction with GC-MS and HRMS analyses were used to confirm compound identity. Additionally, we compared the obtained data with the literature for known molecules.

Mass spectra: Mass spectra (MS) were recorded on a Shimadzu GCMS-QP2010 mass spectrometer equipped with a DB-5 MS column from J&W Scientific. Helium was used as the mobile phase, and electron ionization (EI, 70 eV) was the ionization method. High-resolution masses (HRMS) were recorded on a Bruker Daltonics micrOTOF

QII/ESI-TOF with a suitable external calibrant or on a Waters Acquity UPLC H-Class System Xevo G2-XS Q-TOF equipped with an Acquity UPLC BEH C_{18} column (1.7 µm, 2.1x100 mm).

Melting point: Melting points were determined in open capillary tubes by using a BÜCHI Labortechnik M-560 melting point meter.

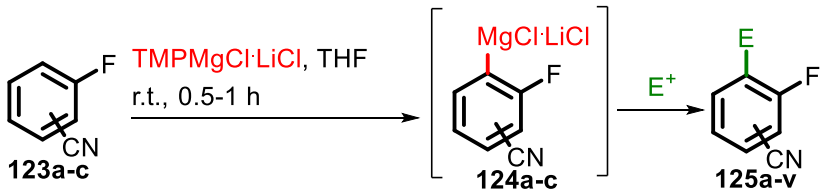
Microwave reactor: Reactions under microwave irradiation were carried out using a dedicated single-mode microwave reactor, a Monowave 300 from Anton-Paar.

7.1.2 General procedures for the functionalization of fluorinated nitriles

7.1.2.1 Reaction monitoring

Metalation of the studied nitriles was monitored by quenching reaction aliquots with an iodine solution in dry THF followed by gas chromatography analysis.

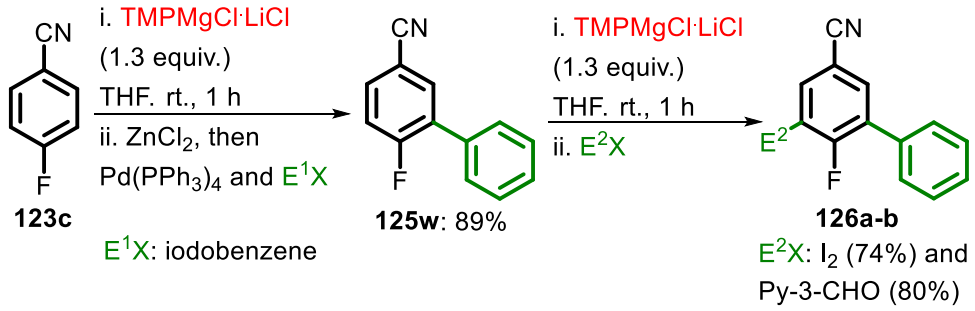
7.1.2.2 General method A (GMA): Standardized procedure for metalation of the studied fluorobenzonitriles with TMPMgCl·LiCl



A dry round-bottom flask flushed with N_2 was charged with the desired fluorobenzonitrile (0.5 mmol, 1 equiv., 0.0606 g) and dry THF (2 mL). The base, TMPMgCl·LiCl (1.3 equiv. for *ortho* **123a** and *para* fluoro-substituted **123c** benzonitriles and 1.2 equiv. for the *meta* one **123b**), was added dropwise, and the reaction was kept at room temperature for 1 h for the first two fluorobenzonitriles and 0.5 h for the latter substrate. The generated organomagnesium species were trapped with an electrophile (1.1 equiv.), and the mixture was allowed to react for 12 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under

reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/ethyl acetate).

7.1.2.2.1 Sequential difunctionalization of 4-fluorobenzonitrile

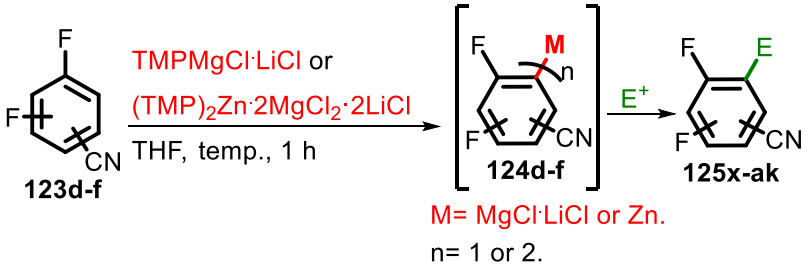


Following **GMA**, **125w** was obtained and employed in the synthesis of **126a-b** via further functionalization via the same TMP-base. The details regarding their characterization and reaction conditions are described in section 6.1.3.

*7.1.2.2.2 Gram scale synthesis of 2-fluoro-3-(hydroxy(p-tolyl)methyl)benzonitrile (**125f**)*

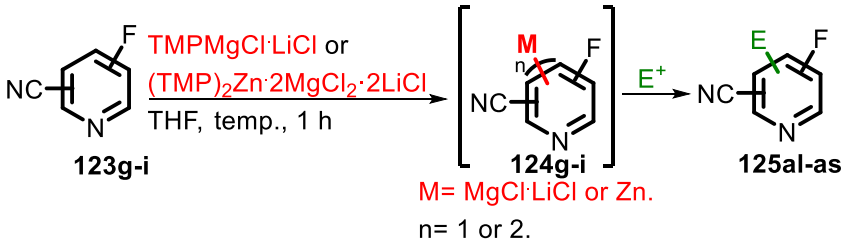
To a dry round-bottom flask flushed with N_2 and charged with 2-fluorobenzonitrile (5.5 mmol, 0.6 mL, 1 equiv.) and dry THF (22 mL), TMPMgCl·LiCl (1.3 equiv., 1.09 M, 6.6 mL) was added dropwise, and the reaction was kept at room temperature for 1 h. The generated organomagnesium species were trapped with *p*-tolualdehyde (1.1 equiv., 0.78 mL)., and the mixture was allowed to react for 12 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography (silica gel, Hexanes/AcOEt 7:3) to afford a white solid (1.21 g, 91% yield).

7.1.2.3 General method B (GMB): Standardized procedure for metalation of the studied difluorobenzonitriles **123d-f** with TMPMgCl·LiCl or $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$



A dry round-bottom flask flushed with N_2 was charged with the desired difluorobenzonitrile (0.5 mmol, 1 equiv., 0.0696 g) and dry THF (2 mL), and the mixture was kept at the specified temperature. The base, TMPMgCl·LiCl (1.3 equiv. for 2,4-difluorobenzonitrile and 3,5-difluorobenzonitrile, and 1.5 equiv. for 3,4-difluorobenzonitrile) or $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.65 equivalents for 2,4-difluorobenzonitrile and 3,5-difluorobenzonitrile, and 0.75 equivalents for 3,4-difluorobenzonitrile), was added dropwise, and the reaction was kept at the same temperature for 1 h. The generated organomagnesium or organozinc species were trapped with an electrophile (1.1 equiv.), and the mixture was allowed to slowly reach room temperature in the case of the metalations performed under reduced temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/ethyl acetate).

7.1.2.4 General method C (GMC): Standardized procedure for metalation of the studied heterocyclic nitriles **123g-i** with TMPMgCl·LiCl or $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$



A dry round-bottom flask flushed with N_2 was charged with the desired fluorinated pyridinecarbonitrile (0.5 mmol, 1 equiv., 0.0611 g) and dry THF (2 mL), and the mixture was kept at the specified temperature. The base, TMPMgCl·LiCl (1.3 equiv. for 5-

fluoropicolinonitrile **123g**, and 1.5 equiv. for 2-fluoroisonicotinonitrile **123h** and 2-fluoronicotinonitrile **123i**) or $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.9 equiv. for 2-fluoroisonicotinonitrile **123h**), was added dropwise, and the reaction was kept at the same temperature for 1 h. The generated organomagnesium or organozinc species were trapped with an electrophile (1.1 equiv.), and the mixture was allowed to slowly reach room temperature in the case of metalation performed under reduced temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/ethyl acetate). Observation: The base TMPZnCl·LiCl (1.5 equivalents) was exclusively investigated for 2-fluoronicotinonitrile **123i** at 25 ºC for 1 hour followed by iodination (1.1 equiv. of I_2).

7.1.2.5 Metalation followed by Negishi cross-coupling

After the magnesiation step (**GMA**), a solution of $ZnCl_2$ (1 M in THF) was added dropwise at room temperature, and the reaction was kept under stirring for 0.5 h. For the direct zincation via **GMB** or **GMC**, the organozinc species were direct considered for the next step. Then, $Pd(PPh_3)_4$ (5 mol%) and the desired iodoarene (1.2 equiv.) in THF (1 mL) were transferred, and the reaction was warmed to 50 ºC (oil bath) and kept under stirring for 12 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/ethyl acetate).

7.1.2.6 Metalation followed by transmetalation with copper salt

After the magnesiation step (**GMA**), the temperature was set to -40 ºC. Then, a solution of CuCl·2LiCl (0.5 M in THF, 1 equiv.) was added, and the reaction was kept at this temperature for 20 min. Next, the temperature was increased to -30 ºC, the acyl chloride was added, and the reaction was kept under stirring for 2 h. The reaction was

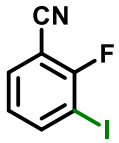
quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/ethyl acetate).

7.1.2.7 Metalation followed by palladium-catalyzed benzoylation

To the organomagnesium and organozinc species obtained via **GMA**, $ZnCl_2$ (1 M in THF) was added, and the reaction was kept at room temperature for 20 min. Then, $Pd(PPh_3)_4$ (5 mol%) and the desired acyl chloride (1 equiv.) were added. For the direct zincation via **GMB**, the organozinc species were directly employed with the palladium catalyst and an acyl chloride for the benzoylation. After 12 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/ethyl acetate).

7.1.3 Reaction scope and characterization data

1. 2-Fluoro-3-iodobenzonitrile (**125a**)



2-fluoro-3-iodobenzonitrila was obtained from **123a** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and iodine (1.1 equiv., 0.55 mmol, 139.6 mg). Purification via column chromatography (Hexanes/AcOEt 9.5:0.5) afforded the product as a yellow solid (0.48 mmol, 119.0 mg, 96%). **CAS**: 211943-27-0.

Mp: 44 – 47 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.01 (ddd, *J* = 7.8, 6.0, 1.6 Hz, 1H), 7.61 (ddd, *J* = 7.6, 5.8, 1.6 Hz, 1H), 7.03 (t-like, 1H).

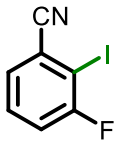
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ [ppm] = 162.3 (d, J_{C-F} = 256.7 Hz), 144.5, 133.6, 126.3 (d, J_{C-F} = 4.3 Hz) 113.1, 102.1 (d, J_{C-F} = 18.3 Hz), 82.1 (d, J_{C-F} = 24.0 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -85.98 (t, J = 5.9 Hz, 1F).

HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for C_7H_3FINNa 269.9186; Found 269.9184.

The reported characterization data is in accordance with the literature.[82]

2. 3-Fluoro-2-iodobenzonitrile (**125b**)



3-fluoro-2-iodobenzonitrile was obtained from **123b** via **GMA** using TMPMgCl·LiCl (1 M, 1.2 equiv., 0.60 mL) and iodine (1.1 equiv., 0.55 mmol, 139.6 mg). Purification via column chromatography (Hexanes/AcOEt 9.5:0.5) afforded the product as a yellow solid (0.34 mmol, 84 mg, 68%). **CAS**: 916792-62-6.

Mp: 86 – 88 °C.

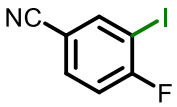
^1H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.49 – 7.43 (m, 2H), 7.31 – 7.25 (m, 1H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ [ppm] = 162.6 (d, J_{C-F} = 248.6 Hz), 130.8 (d, J_{C-F} = 8.1 Hz), 130.4 (d, J_{C-F} = 3.7 Hz), 122.7, 119.9 (d, J_{C-F} = 24.3 Hz), 118.5 (d, J_{C-F} = 3.5 Hz), 87.1 (d, J_{C-F} = 29.1 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -87.24 – -87.33 (m, 1F).

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for C_7H_4FIN 247.9367; Found 247.9366.

3. 4-Fluoro-3-iodobenzonitrile (**125c**)



4-fluoro-3-iodobenzonitrile was obtained from **123c** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and iodine (1.1 equiv., 0.55 mmol, 139.6 mg). Purification via column chromatography (Hexanes/AcOEt 9.5:0.5) afforded the product as a yellow solid (0.41 mmol, 101.3 mg, 82%). **CAS**: 159719-57-0.

Mp: 55 – 58 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.07 (dd, *J* = 5.7, 2.0 Hz, 1H), 7.65 (ddd, *J* = 8.5, 4.6, 2.0 Hz, 1H), 7.17 (dd, *J* = 8.5, 7.4 Hz, 1H).

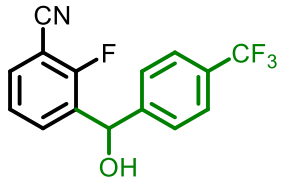
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 164.6 (d, $J_{C\text{-}F}$ = 255.0 Hz), 143.5, 134.5 (d, $J_{C\text{-}F}$ = 8.9 Hz), 116.9, 116.6, 110.5 (d, $J_{C\text{-}F}$ = 4.1 Hz), 82.3 (d, $J_{C\text{-}F}$ = 27.3 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -83.16 – -83.23 (m, 1F).

GC-MS (EI, 70 eV) m/z: 246.95 (100%), 120.05 (58%), 100.05 (21%), 93.00 (10%), 247.95 (8%).

The reported characterization data is in accordance with the literature.[125]

4. 2-Fluoro-3-(hydroxy(4-(trifluoromethyl)phenyl)methyl)benzonitrile (**125d**)



2-fluoro-3-(hydroxy(4-(trifluoromethyl)phenyl)methyl)benzonitrile was obtained from **123a** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and 4-(trifluoromethyl)benzaldehyde (1.1 equiv., 0.55 mmol, 75 µL). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a yellow solid (0.27 mmol, 80 mg, 54%).

Mp: 112 – 114 °C.

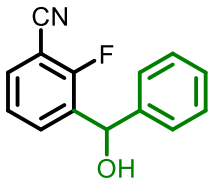
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.86 – 7.82 (m, 1H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.57 – 7.52 (m, 3H), 7.32 – 7.28 (m, 1H), 6.22 (s, 1H), 2.78 (bs, 1H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ [ppm] = 160.1 (d, J_{C-F} = 258.7 Hz), 145.6, 133.0, 132.8 (d, J_{C-F} = 4.6 Hz), 132.2 (d, J_{C-F} = 12.1 Hz), 130.6 (q, J_{C-F} = 32.4 Hz), 126.7 (2C), 125.9 (q, J_{C-F} = 11.6 Hz, 2C), 125.4 (d, J_{C-F} = 4.6 Hz), 124.1 (q, J_{C-F} = 273.3 Hz), 113.8, 101.8 (d, J_{C-F} = 15.3 Hz), 68.8 (d, J_{C-F} = 2.8 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -62.62 (s, 3F), -111.78 (t, J = 6.5 Hz, 1F).

HRMS (ESI-TOF) m/z: $[M+H-H_2O]^+$ Calcd for $C_{15}H_8F_4N$ 278.0587; Found 278.0585.

5. 2-Fluoro-3-(hydroxy(phenyl)methyl)benzonitrile (**125e**)



2-fluoro-3-(hydroxy(phenyl)methyl)benzonitrile was obtained from **123a** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and benzaldehyde (1.1 equiv., 0.55 mmol, 56 µL). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a yellow oil (0.40 mmol, 90 mg, 79%).

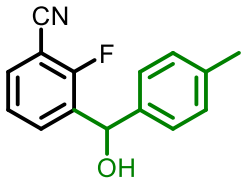
^1H-NMR (400 MHz, $CDCl_3$): δ [ppm] = *δ* 7.90 – 7.86 (m, 1H), 7.51 (ddd, J = 7.7, 6.0, 1.8 Hz, 1H), 7.38 – 7.25 (m, 6H), 6.13 (s, 1H), 2.67 (s, 1H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ [ppm] = 160.2 (d, J_{C-F} = 258.9 Hz), 141.8, 132.9 (d, J_{C-F} = 10.6 Hz), 132.8 (d, J_{C-F} = 4.5 Hz), 132.5, 128.9 (2C), 128.5, 126.5 (2C), 125.1 (d, J_{C-F} =4.2 Hz), 114.0, 101.5 (d, J_{C-F} = 15.9 Hz), 69.5 (d, J_{C-F} = 2.9 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -111.54 (t, J = 6.6 Hz, 1F).

HRMS (ESI-TOF) m/z: $[M+H-H_2O]^+$ Calcd for $C_{14}H_9FN$ 210.0714; Found 210.0711.

6. 2-Fluoro-3-(hydroxy(p-tolyl)methyl)benzonitrile (**125f**)



2-fluoro-3-(hydroxy(phenyl)methyl)benzonitrile was obtained from **123a** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and 4-methylbenzaldehyde (1.1 equiv., 0.55 mmol, 65 µL). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a white solid (0.47 mmol, 113.4 mg, 94%).

Mp: 76 – 79 °C.

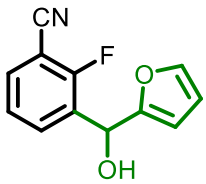
^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.91 – 7.88 (m, 1H), 7.52 – 7.49 (m, 1H), 7.28 – 7.24 (m, 3H), 7.16 (d, *J* = 7.9 Hz, 2H), 6.09 (s, 1H), 2.54 (s, 1H), 2.33 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 160.2 (d, $J_{C\text{-}F}$ =259.0 Hz), 139.0, 138.4, 133.0 (d, $J_{C\text{-}F}$ =11,9 Hz), 132.7 (d, $J_{C\text{-}F}$ =5.0 Hz), 132.4, 129.6 (2C), 126.4 (2C), 125.0 (d, $J_{C\text{-}F}$ =4.3 Hz), 114.0, 101.6 (d, $J_{C\text{-}F}$ =15.7 Hz), 69.5 (d, $J_{C\text{-}F}$ =2.8 Hz), 21.2.

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -111.52 (t, *J* = 6.6 Hz, 1F).

HRMS (ESI-TOF) m/z: $[M+H-H_2O]^+$ Calcd for $C_{15}H_{11}FN$ 224.0870; Found 224.0869.

7. 2-Fluoro-3-(furan-2-yl(hydroxy)methyl)benzonitrile (**125g**)



2-fluoro-3-(furan-2-yl(hydroxy)methyl)benzonitrile was obtained from **123a** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and 2-furaldehyde (1.1 equiv., 0.55 mmol, 46 µL). Purification via column chromatography (Hexanes/AcOEt 7:3) afforded the product as an orange oil (0.47 mmol, 103.2 mg, 94%).

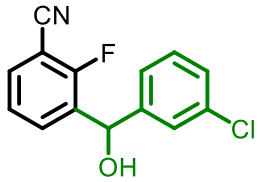
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.94 – 7.90 (m, 1H), 7.59 (ddd, *J* = 7.8, 6.0, 1.8 Hz, 1H), 7.39 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 6.34 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.17 (d, *J* = 3.3 Hz, 1H), 6.14 (s, 1H), 2.86 (s, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 160.3 (d, J_{C-F} =259.7 Hz), 153.6, 143.2, 133.5 (d, J_{C-F} =4,7 Hz), 133.1, 129.9 (d, J_{C-F} =11.6 Hz), 125.1 (d, J_{C-F} =3.9 Hz), 113.9, 110.6, 108.1, 101.6 (d, J_{C-F} =15.3 Hz), 63.4 (d, J_{C-F} =3.3 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -112.03 (t, *J* = 6.5 Hz, 1F).

HRMS (ESI-TOF) m/z: $[M+H-H_2O]^+$ Calcd for $C_{12}H_7FNO$ 200.0506; Found 200.0504.

8. 3-((3-Chlorophenyl)(hydroxy)methyl)-2-fluorobenzonitrile (**125h**)



3-((3-chlorophenyl)(hydroxy)methyl)-2-fluorobenzonitrile was obtained from **123a** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and 3-chlorobenzaldehyde (1.1 equiv., 0.55 mmol, 62 µL). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a yellow oil (0.40 mmol, 106 mg, 81%).

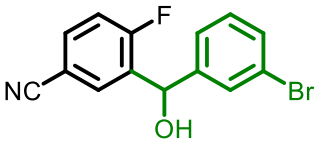
^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.86-7.82 (m, 1H), 7.54 (ddd, *J* = 7.8, 6.0, 1.8 Hz, 1H), 7.38 (s, 1H), 7.31 – 7.24 (m, 4H), 6.11 (s, 1H), 2.79 (s, 1H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 160.1 (d, J_{C-F} =259.1 Hz), 143.8, 134.9, 132.9, 132.8 (d, J_{C-F} =4.7 Hz), 132.3 (d, J_{C-F} =12.0 Hz), 130.2, 128.6, 126.6, 125.3 (d, J_{C-F} =4.4 Hz), 124.6, 113.8, 101.7 (d, J_{C-F} =15.9 Hz), 68.8 (d, J_{C-F} =2.9 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -111.67 (t, *J* = 6.5 Hz, 1F).

HRMS (ESI-TOF) m/z: $[M+H-H_2O]^+$ Calcd for $C_{14}H_8ClFN$ 244.0324; Found 244.0327.

9. 3-((3-Bromophenyl)(hydroxy)methyl)-4-fluorobenzonitrile (**125i**)



3-((3-bromophenyl)(hydroxy)methyl)-4-fluorobenzonitrile was obtained from **123c** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and 3-bromobenzaldehyde (1.1 equiv., 0.55 mmol, 64 µL). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a white solid (0.41 mmol, 127.0 mg, 83%).

Mp: 111 – 114 °C.

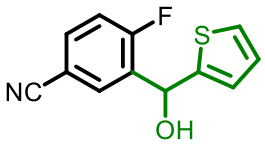
^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.93 (dd, *J* = 6.6, 2.2 Hz, 1H), 7.59 (ddd, *J* = 8.5, 4.8, 2.2 Hz, 1H), 7.53 (s, 1H), 7.44 – 7.42 (m, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.13 (t-like, *J* = 8.5 Hz, 1H), 6.07 (s, 1H), 2.39 (bs, 1H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 162.0 (d, $J_{C\text{-}F}$ =256.8 Hz), 144.0, 133.9 (d, $J_{C\text{-}F}$ =9.7 Hz), 132.7 (d, $J_{C\text{-}F}$ =14.5 Hz), 132.3 (d, $J_{C\text{-}F}$ =5.5 Hz), 131.6, 130.5, 129.6, 125.1, 123.1, 118.1, 117.0 (d, $J_{C\text{-}F}$ =23.3 Hz), 109.1 (d, $J_{C\text{-}F}$ =3.8 Hz), 68.9 (d, $J_{C\text{-}F}$ =2.7 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -107.77 – -107.85 (m, 1F).

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{10}BrFNO$ 305.9925; Found 305.9921.

10. 4-Fluoro-3-(hydroxy(thiophen-2-yl)methyl)benzonitrile (**125j**)



4-fluoro-3-(hydroxy(thiophen-2-yl)methyl)benzonitrile was obtained from **123c** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and 2-thiophenecarboxaldehyde (1.1 equiv., 0.55 mmol, 51 µL). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a yellow solid (0.44 mmol, 104.0 mg, 89%). **CAS**: 2237249-90-8.

Mp: 60 – 62 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 8.01 (dd, *J* = 6.7, 2.2 Hz, 1H), 7.61 (ddd, *J* = 8.5, 4.7, 2.2 Hz, 1H), 7.30 (dd, *J* = 4.2, 2.2 Hz, 1H), 7.14 (dd, *J* = 9.4, 8.5 Hz, 1H), 6.97 – 6.96 (m, 2H), 6.34 (s, 1H), 2.85 (s, 1H).

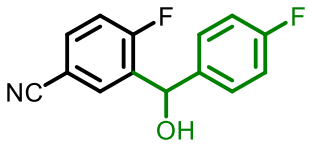
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 162.1 (d, J_{C-F} =257.0 Hz), 145.6, 133.9 (d, J_{C-F} =9.6 Hz), 132.8 (d, J_{C-F} =14.3 Hz), 132.2 (d, J_{C-F} =5.3 Hz), 127.1, 126.2, 125.4, 118.1, 117.0 (d, J_{C-F} =23.2 Hz), 109.0 (d, J_{C-F} =3.9 Hz), 65.6 (d, J_{C-F} =3.7 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -108.19 – -108.27 (m, 1F).

HRMS (ESI-TOF) m/z: $[M-H]^-$ Calcd for $C_{12}H_7FNOS$ 232.0238; Found 232.0235.

The reported characterization data is in accordance with the literature.[126]

11. 4-Fluoro-3-((4-fluorophenyl)(hydroxy)methyl)benzonitrile (**125k**)



4-fluoro-3-((4-fluorophenyl)(hydroxy)methyl)benzonitrile was obtained from **123c** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and 4-fluorobenzaldehyde (1.1 equiv., 0.55 mmol, 59 µL). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a white solid (0.40 mmol, 98.1 mg, 80%). **CAS**: 1519447-09-6.

Mp: 82 – 84 °C.

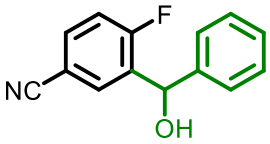
^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.96 (dd, *J* = 6.8, 2.2 Hz, 1H), 7.58 (ddd, *J* = 8.5, 4.7, 2.2 Hz, 1H), 7.35 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.11 (dd, *J* = 9.7, 8.5 Hz, 1H), 7.06 – 7.02 (m, 2H), 6.09 (s, 1H), 2.61 (d, *J* = 2.6 Hz, 1H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 162.7 (d, J_{C-F} =247.4 Hz), 162.0 (d, J_{C-F} =256.4 Hz), 137.6 (d, J_{C-F} =3.1 Hz), 133.7 (d, J_{C-F} =9.7 Hz), 133.2 (d, J_{C-F} =14.5 Hz), 132.1 (d, J_{C-F} =5.6 Hz), 128.4 (d, J_{C-F} =8.3 Hz, 2C), 118.2, 117.6, (d, J_{C-F} =23.1 Hz), 115.9 (d, J_{C-F} =21.9 Hz, 2C), 109.0 (d, J_{C-F} =3.9 Hz), 69.0 (d, J_{C-F} =2.8 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -107.84 – -107.92 (m, 1F), -113.27 – -113.37 (m, 1F).

HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_9F_2NNaO$ 268.0544; Found 268.0546.

12. 4-Fluoro-3-(hydroxy(phenyl)methyl)benzonitrile (**125l**)



4-fluoro-3-(hydroxy(phenyl)methyl)benzonitrile was obtained from **123c** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and benzaldehyde (1.1 equiv., 0.55 mmol, 56 µL). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a white solid (0.36 mmol, 83 mg, 73%). **CAS**: 1499388-65-6.

Mp: 101 – 103 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.96 (dd, *J* = 6.8, 2.2 Hz, 1H), 7.56 (ddd, *J* = 8.5, 4.8, 2.2 Hz, 1H), 7.39 – 7.35 (m, 4H), 7.35 – 7.29 (m, 1H), 7.10 (dd, *J* = 9.6, 8.5 Hz, 1H), 6.10 (s, 1H), 2.40 (s, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 162.1 (d, $J_{C\text{-}F}$ =256.6 Hz), 141.7, 133.5 (d, $J_{C\text{-}F}$ =9.6 Hz), 133.2 (d, $J_{C\text{-}F}$ =14.6 Hz), 132.2 (d, $J_{C\text{-}F}$ =5.6 Hz), 129.0 (2C), 128.5, 126.5 (2C), 118.3, 116.9 (d, $J_{C\text{-}F}$ =23.3 Hz), 108.8 (d, $J_{C\text{-}F}$ =3.8 Hz), 69.6 (d, $J_{C\text{-}F}$ =2.7 Hz).

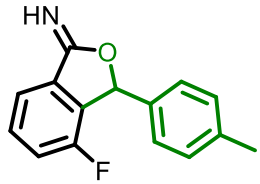
^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -107.68 – -107.75 (m, 1F).

GC-MS (EI, 70 eV) m/z: 227.00 (100%), 79.05 (96%), 148.00 (68%), 78.05 (37%), 77.00 (37%).

HRMS (ESI-TOF) m/z: $[M+FA-H]^-$ Calcd for $C_{15}H_{11}FNO_3$ 272.0728; Found 272.0701.

The reported characterization data is in accordance with the literature.[87]

13. 4-Fluoro-3-(*p*-tolyl)isobenzofuran-1(3*H*)-imine (**125m**)



4-fluoro-3-(*p*-tolyl)isobenzofuran-1(3*H*)-imine was obtained from **123b** via **GMA** using TMPMgCl·LiCl (1 M, 1.2 equiv., 0.6 mL) and 4-methylbenzaldehyde (1.1 equiv., 0.55 mmol, 65 µL). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a white solid (0.31 mmol, 75 mg, 62%).

Mp: 121 – 125 °C.

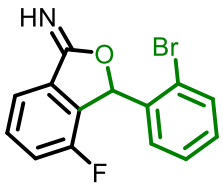
^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.74 (d, *J* = 6.9 Hz, 1H), 7.49 (td, *J* = 7.9, 4.5 Hz, 1H), 7.20 – 7.16 (m, 5H), 6.46 (s, 1H), 2.35 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 157.2 (d, J_{C-F} =251.4 Hz), 139.4, 133.6, 133.5 (d, J_{C-F} =17.8 Hz), 131.5 (d, J_{C-F} =6.3 Hz), 129.6 (2C), 127.1 (2C), 120.0 (2C), 119.1 (d, J_{C-F} =19,6 Hz, 2C), 82.9, 21.3.

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -118.29 (dd, *J* = 8.8, 4.6 Hz, 1F).

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{12}FO_2$ 243.0816; Found 243.0815. * Under the analysis conditions (MeCN: H_2O mixture, formic acid) the 3-substituted-isobenzofuran-1(3*H*)-imine was converted into the respective isobenzofuran-1(3*H*)-one. The hydrolysis under acidic conditions is already mentioned in the literature.[127]

14. 3-(2-Bromophenyl)-4-fluoroisobenzofuran-1(3*H*)-imine (**125n**)



3-(2-bromophenyl)-4-fluoroisobenzofuran-1(3*H*)-imine was obtained from **123b** via **GMA** using TMPMgCl·LiCl (1 M, 1.2 equiv., 0.6 mL) and 2-bromobenzaldehyde (1.1 equiv.,

0.55 mmol, 64 µL). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a yellow solid (0.29 mmol, 89 mg, 58%).

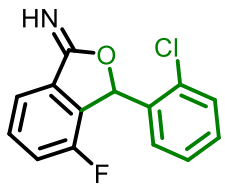
Mp: 112 – 115 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.77 (d, *J* = 7.6 Hz, 1H), 7.67 – 7.65 (m, 1H), 7.53 (td, *J* = 7.9, 4.5 Hz, 1H), 7.27 – 7.21 (m, 3H), 6.98 (s, 1H), 6.95 (dd, *J* = 7.2, 2.5 Hz, 1H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 157.1 (d, $J_{C\text{-}F}$ =253.0 Hz), 135.4, 133.6, 132.6 (d, $J_{C\text{-}F}$ =17.9 Hz), 131.9 (d, $J_{C\text{-}F}$ =6.6 Hz), 131.0, 128.9, 128.1, 124.3, 120.2, 120.1, 119.3 (d, $J_{C\text{-}F}$ =19.1 Hz, 2C), 81.9.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_9BrFO_2$ 306.9765; Found 306.9765. * Under the analysis conditions (MeCN: H_2O mixture, formic acid) the 3-substituted-isobenzofuran-1(3*H*)-imine was converted into the respective isobenzofuran-1(3*H*)-one. The hydrolysis under acidic conditions is already mentioned in the literature.[127]

15. 3-(2-Chlorophenyl)-4-fluoroisobenzofuran-1(3*H*)-imine (**125o**)



3-(2-chlorophenyl)-4-fluoroisobenzofuran-1(3*H*)-imine was obtained from **123b** via **GMA** using TMPMgCl·LiCl (1 M, 1.2 equiv., 0.6 mL) and 2-chlorobenzaldehyde (1.1 equiv., 0.55 mmol, 62 µL). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a white solid (0.24 mmol, 64 mg, 49%).

Yield: 49% (white solid, 64 mg).

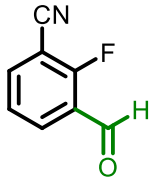
Mp: 110 – 113 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.76 (d, *J* = 7.6 Hz, 1H), 7.52 (td, *J* = 8.0, 4.5 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.29 (m, 1H), 7.23 – 7.20 (m, 2H), 6.99 – 6.97 (m, 2H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 157.1 (d, J_{C-F} =252.1 Hz), 134.3, 133.8, 132.5 (d, J_{C-F} =17.7 Hz), 131.9 (d, J_{C-F} =6.6 Hz), 130.7, 130.3, 128.7, 127.4, 120.1 (2C), 119.2 (d, J_{C-F} =19.4 Hz, 2C), 79.5.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_9ClFO_2$ 263.0270; Found 263.0266. *Under the analysis conditions (MeCN: H_2O mixture, formic acid) the 3-substituted-isobenzofuran-1(3*H*)-imine was converted into the respective isobenzofuran-1(3*H*)-one. The hydrolysis under acidic conditions is already mentioned in the literature.[127]

16. 2-Fluoro-3-formylbenzonitrile (**125p**)



2-fluoro-3-formylbenzonitrile was obtained from **123a** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and *N,N*-dimethylformamide (2.0 equiv., 1.0 mmol, 77 µL). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a yellow solid (0.29 mmol, 44 mg, 59%). **CAS**: 1261823-31-7.

Mp: 46 – 48 °C.

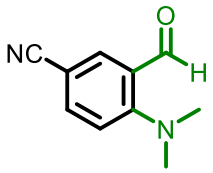
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 10.36 (s, 1H), 8.13 (ddd, *J* = 7.9, 6.7, 1.9 Hz, 1H), 7.90 (ddd, *J* = 7.8, 6.1, 1.9 Hz, 1H), 7.44 (t-like, *J* = 7,8 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 184.9 (d, J_{C-F} =6.3 Hz), 164.9 (d, J_{C-F} =270.0 Hz), 139.1, 133.5, 125.6 (d, J_{C-F} =4.6 Hz), 124.8 (d, J_{C-F} =7.4 Hz), 112.7, 103.2 (d, J_{C-F} =14.9 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -116.08 (t, *J* = 6.4 Hz, 1F).

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for C_8H_5FNO 150.0350; Found 150.0351.

17. 4-(Dimethylamino)-3-formylbenzonitrile (**125q**)



4-(dimethylamino)-3-formylbenzonitrile was obtained from **123c** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and *N,N*-dimethylformamide (2.0 equiv., 1.0 mmol, 77 µL). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a yellow solid (0.45 mmol, 79.3 mg, 91%). **CAS**: 1289200-50-5.

Mp: 62 – 64 °C.

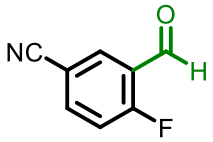
^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 9.97 (s, 1H), 7.96 (d, *J* = 2.2 Hz, 1H), 7.57 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 3.06 (s, 6H).*

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 188.2, 155.9, 137.9, 136.6, 124.4, 119.0, 116.9, 101.0, 44.5 (2C).

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_{11}N_2O$ 175.0866; Found 175.0863.

*Previously reported in the literature.[128]

18. 4-Fluoro-3-formylbenzonitrile (**125r**)



4-fluoro-3-formylbenzonitrile was obtained from **123c** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and *N*-methylformanilide (2.0 equiv., 1.0 mmol, 123 µL). Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as a white solid (0.31 mmol, 46.2 mg, 62%). **CAS**: 146137-79-3.

Yield: 62% (white solid, 46.2 mg).

Mp: 68 – 71 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 10.34 (s, 1H), 8.20 (ddd, *J* = 6.3, 2.3, 0.4 Hz, 1H), 7.91 (ddd, *J* = 8.7, 4.8, 2.3 Hz, 1H), 7.38 – 7.33 (m, 1H).

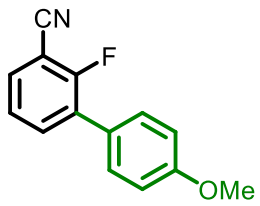
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 185.0 (d, *J* = 6.2 Hz), 166.4 (d, J_{C-F} = 267.5 Hz), 139.6 (d, J_{C-F} = 10.4 Hz), 133.6 (d, J_{C-F} = 3.3 Hz), 125.0 (d, J_{C-F} = 9.8 Hz), 118.5 (d, J_{C-F} = 22.3 Hz), 117.0, 109.9 (d, J_{C-F} = 3.9 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -112.19 – -112.27 (m, 1F).

GC-MS (EI, 70 eV) m/z: 148.05 (100%), 149.05 (64%), 120.05 (36%), 94.00 (15%), 100.00 (14%).

The reported characterization data is in accordance with the literature.[129]

19. 2-Fluoro-4'-methoxy-[1,1'-biphenyl]-3-carbonitrile (**125s**)



After applying **GMA** [TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL)] for **123a** followed by transmetalation with $ZnCl_2$ (1 M in THF, 1.3 equiv., 0.65 mL), the Negishi cross-coupling was performed using $Pd(PPh_3)_4$ (5 mol%, 29 mg) and 4-methoxyiodobenzene (1.2 equiv., 0.6 mmol, 140.4 mg) at 50 ºC (oil bath). Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as a beige solid (0.45 mmol, 102.3 mg, 90%).

Mp: 106 – 108 °C.

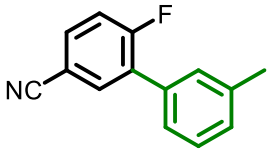
^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.66 (t-like, *J* = 7.8 Hz, 1H), 7.55 (t-like, *J* = 7.1 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 3.86 (s,3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 160.3 (d, J_{C-F} =259.6 Hz), 160.1, 135.5 (d, J_{C-F} =4.1 Hz), 131.8, 130.3 (d, J_{C-F} =14.0 Hz), 130.2 (d, J_{C-F} =3.1 Hz, 2C), 125.9, 125.1 (d, J_{C-F} =4.3 Hz), 114.4 (2C), 114.3, 102.4 (d, J_{C-F} =17.0 Hz), 55.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -111.52 (t, *J* = 6.6 Hz, 1F).

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{11}FNO$ 228.0819; Found 228.0818.

20. 6-Fluoro-3'-methyl-[1,1'-biphenyl]-3-carbonitrile (**125t**)



After applying **GMA** [TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL)] for **123c** followed by transmetalation with $ZnCl_2$ (1 M in THF, 1.3 equiv., 0.65 mL), the Negishi cross-coupling was performed using $Pd(PPh_3)_4$ (5 mol%, 29 mg) and 1-iodo-3-methylbenzene (1.2 equiv., 0.6 mmol, 77 µL) at 50 ºC (oil bath). Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as a white solid (0.46 mmol, 97.2 mg, 92%). **CAS**: 1267960-92-8.

Mp: 57 – 59 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.66 (dd, *J* = 7.0, 2.2 Hz, 1H), 7.53 (ddd, *J* = 8.6, 4.5, 2.2 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.23 – 7.21 (m, 2H), 7.18 – 7.14 (m, 2H), 2.33 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 162.2 (d, J_{C-F} =257.7 Hz), 138.7, 135.2 (d, J_{C-F} =5.1 Hz), 133.5, 133.1 (d, J_{C-F} =9.6 Hz), 131.2 (d, J_{C-F} =15.1 Hz), 129.7, 129.6, 128.8, 126.1 (d, J_{C-F} =3.0 Hz), 118.2, 117.7 (d, J_{C-F} =24.6 Hz), 109.0 (d, J_{C-F} =4.0 Hz), 21.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -107.55 – -107.64 (m, 1F).

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{11}FN$ 212.0870; Found 212.0869.

21. 4-Fluoro-3-(trimethylsilyl)benzonitrile (**125u**)

4-fluoro-3-(trimethylsilyl)benzonitrile was obtained from **123c** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) and fresh distilled chlorotrimethylsilane (1.1 equiv., 0.55 mmol, 70 µL). Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as a yellow solid (0.31 mmol, 61 mg, 63%).

Mp: 49 – 51 °C.

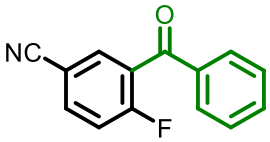
^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.70 (dd, *J* = 4.9, 2.2 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.08 (t, *J* = 8.2 Hz, 1H), 0.34 (s, 9H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 169.5 (d, J_{C-F} =250.9 Hz), 140.0 (d, J_{C-F} =13.4 Hz), 135.6 (d, J_{C-F} =10.0 Hz), 129.1 (d, J_{C-F} =32.9 Hz), 118.6, 116.1 (d, J_{C-F} =27.9 Hz), 108.7 (d, J_{C-F} =3.4 Hz), -1.2 (3C).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -90.55 – -90.61 (m, 1F).

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_{13}FNSi$ 194.0796; Found 194.0793.

22. 3-Benzoyl-4-fluorobenzonitrile (**125v**)



After applying **GMA** [TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL)] for **123c** followed by transmetalation with $ZnCl_2$ (1 M in THF, 1.3 equiv., 0.65 mL), the benzoylation was performed using $Pd(PPh_3)_4$ (5 mol%, 29 mg) and benzoyl chloride (1.0 equiv., 0.5 mmol, 58 µL) at room temperature. Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as a white solid (0.47 mmol, 107 mg, 95%). Applying **GMA** at the same conditions followed by transmetalation with CuCl·2LiCl (0.5 M in THF, 1 equiv.) at -40 ºC and the reaction of organocopper species with benzoyl chloride (1.0 equiv., 0.5 mmol, 58 µL), furnished the same ketone in 78%. **CAS**: 217498-80-1.

Mp: 92 – 95 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.87 – 7.78 (m, 4H), 7,65 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.31 (t, *J* = 8.8 Hz, 1H).

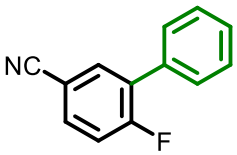
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 190.8, 162.1 (d, J_{C-F} =261.3 Hz), 136.7 (d, J_{C-F} =9.5 Hz), 136.3, 135.1 (d, J_{C-F} =4.4 Hz), 134.2, 129.8 (2C), 128.8 (2C), 128.6 (d, J_{C-F} =16.3 Hz), 118.0 (d, J_{C-F} =23.4 Hz), 117.2, 109.3 (d, J_{C-F} =4.2 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -101.35 – -101.42 (m, 1F).

HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_8FNNaO$ 248.0482; Found 248.0482.

The reported characterization data is in accordance with the literature.[130]

23. 6-Fluoro-[1,1'-biphenyl]-3-carbonitrile (**125w**)



After applying **GMA** [TMPMgCl·LiCl (1 M, 1.3 equiv., 3.7 mL) and 4-fluorobenzonitrile (**123c**) (1.0 equiv., 2.84 mmol, 344 mg)] followed by transmetalation with $ZnCl_2$ (1 M in THF, 1.3 equiv., 3.7 mL), the Negishi cross-coupling was performed using $Pd(PPh_3)_4$ (5 mol%, 164.1 mg) and iodobenzene (1.2 equiv., 3.41 mmol, 0.38 mL) at 50 ºC (oil bath). Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as a white solid (2.52 mmol, 497 mg, 89%). **CAS**: 1214331-73-3.

Mp: 83 – 84 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.77 (dd, *J* = 7.1, 2.2 Hz, 1H), 7.64 (ddd, *J* = 8.6, 4.5, 2.2 Hz, 1H), 7.53 – 7.42 (m, 5H), 7.27 (app t, *J* = 8.6 Hz, 1H).

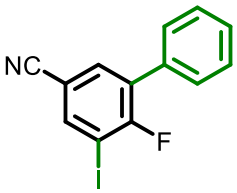
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 162.2 (d, J_{C-F} = 257.9 Hz), 135.2 (d, J_{C-F} = 5.2 Hz), 133.5, 133.2 (d, J_{C-F} = 9.6 Hz), 131.1 (d, J_{C-F} = 15.2 Hz), 129.0 (d, J_{C-F} = 2.9 Hz, 2C), 128.9 (2C), 128.9, 118.2, 117.7 (d, J_{C-F} = 24.6 Hz), 109.1 (d, J_{C-F} = 4.2 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -107.71 – -107.79 (m, 1F).

GC-MS (EI, 70 eV) m/z: 197.05 (100%), 196.05 (28%), 198.05 (18%), 169.00 (14%), 170.00 (11%).

The reported characterization data is in accordance with the literature.[131]

24. 6-Fluoro-5-iodo-[1,1'-biphenyl]-3-carbonitrile (**126a**)



6-fluoro-5-iodo-[1,1'-biphenyl]-3-carbonitrile was obtained from **125w** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL), 6-fluoro-[1,1'-biphenyl]-3-carbonitrile (1.0 equiv., 0.5 mmol, 99 mg) and iodine (1.1 equiv., 0.55 mmol, 139.6 mg). Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as a white solid (0.37 mmol, 119.5 mg, 74%).

Mp: 103 – 105 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.03 (dd, *J* = 5.1, 2.1 Hz, 1H), 7.71 (dd, *J* = 6.5, 2.1 Hz, 1H), 7.49 – 7.45 (m, 5H).

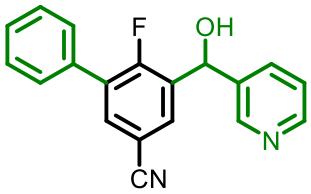
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 161.3 (d, $J_{C\text{-}F}$ = 255.6 Hz), 141.8 (d, $J_{C\text{-}F}$ = 3.1 Hz), 135.1 (d, $J_{C\text{-}F}$ = 4.5 Hz), 133.0 (d, $J_{C\text{-}F}$ = 1.9 Hz), 131.2 (d, $J_{C\text{-}F}$ = 17.8 Hz), 129.3, 129.0 (2C), 129.0 (2C), 116.7, 110.6 (d, $J_{C\text{-}F}$ = 4.7 Hz), 83.4 (d, $J_{C\text{-}F}$ = 29.3 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -86.97 (t, *J* = 5.8 Hz, 1F).

GC-MS (EI, 70 eV) m/z: 322.95 (100%), 195.00 (26%), 169.00 (25%), 323.95 (15%), 195.95 (14%).

HRMS (ESI-TOF) m/z: $[M+CH_3OH+H]^+$ Calcd for $C_{14}H_{12}FINO$ 355.9942; Found 355.9950.

25. 6-Fluoro-5-(hydroxy(pyridin-3-yl)methyl)-[1,1'-biphenyl]-3-carbonitrile (**126b**)



6-fluoro-5-(hydroxy(pyridin-3-yl)methyl)-[1,1'-biphenyl]-3-carbonitrile was obtained from **125w** via **GMA** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL), 6-fluoro-[1,1'-biphenyl]-3-carbonitrile (1.0 equiv., 0.5 mmol, 99 mg) and 3-pyridinecarboxaldehyde (1.1 equiv., 0.55 mmol, 52 µL). Purification via column chromatography (Hexanes/AcOEt 7:3) afforded the product as a white solid (0.40 mmol, 121.6 mg, 80%).

Mp: 127 – 130 °C.

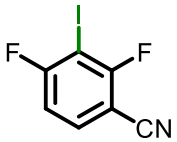
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.58 (d, *J* = 1.5 Hz, 1H), 8.42 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.00 (dd, *J* = 6.0, 2.1 Hz, 1H), 7.82 (app dt, *J* = 8.0, 1.9 Hz, 1H), 7.66 (dd, *J* = 6.8, 2.1 Hz, 1H), 7.46 – 7.39 (m, 5H), 7.35 (dd, *J* = 8.0, 4.9 Hz, 1H), 6.20 (s, 1H), 5.03 (s, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 158.8 (d, J_{C-F} = 257.4 Hz), 147.8, 147.0 (d, J_{C-F} = 1.7 Hz), 139.1, 135.9, 134.4 (d, J_{C-F} = 5.1 Hz), 133.2 (d, J_{C-F} = 16.1 Hz), 133.1, 131.0 (d, J_{C-F} = 15.5 Hz), 130.6 (d, J_{C-F} = 5.4 Hz), 129.0 (d, J_{C-F} = 4.4 Hz, 2C), 129.0, 128.9 (2C), 124.4, 118.1, 109.2 (d, J_{C-F} = 4.3 Hz), 67.2 (d, J_{C-F} = 3.8 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -113.41 (t, *J* = 6.5 Hz, 1F).

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{14}FN_2O$ 305.1085; Found 305.1070.

26. 2,4-Difluoro-3-iodobenzonitrile (**125x**)



2,4-difluoro-3-iodobenzonitrile was obtained from **123d** via **GMB** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) at 0 ºC or $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.29 M in THF, 0.65 equiv., 1.1 mL) at room temperature followed by trapping with iodine (1.1 equiv., 0.55 mmol,

139.6 mg). Purification via column chromatography (Hexanes/AcOEt 9.7:0.3) afforded the product as a white solid (106 mg - 80%[a] and 123.2 mg - 93%[b]). **CAS**: 1804885-55-9.

Mp: 58 – 59 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.65 (ddd, *J* = 8.7, 7.1, 5.7 Hz, 1H), 7.02 (ddd, *J* = 8.7, 6.8, 1.5 Hz, 1H).

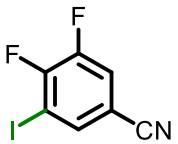
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 165.9 (dd, J_{C-F} = 257.2, 5.5 Hz), 164.0 (dd, J_{C-F} = 258.2, 6.7 Hz), 134.7 (dd, J_{C-F} = 10.3, 1.6 Hz), 112.7 (dd, J_{C-F} = 25.6, 3.8 Hz), 112.5 (d, J_{C-F} = 3.4 Hz), 98.3 (dd, J_{C-F} = 18.2, 4.0 Hz), 72.7 (dd, J_{C-F} = 30.7, 27.9 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -79.96 – -80.03 (m, 1F), -82.90 (dt, *J* = 6.9, 1.4 Hz, 1F).

GC-MS (EI, 70 eV) m/z: 264.90 (100%), 138.05 (46%), 88.00 (30%), 265.90 (9%), 87.00 (6%).

Note: HRMS analysis of compound **125x** was not possible due to low stability.

27. 3,4-Difluoro-5-iodobenzonitrile (**125y**)



3,4-difluoro-5-iodobenzonitrile was obtained from **123e** via **GMB** using TMPMgCl·LiCl (1 M, 1.5 equiv., 0.75 mL) at -70 ºC followed by transmetalation with $ZnCl_2$ (1 M in THF, 1.5 equiv., 0.75 mL) during 20 minutes and quenching with iodine (1.1 equiv., 0.55 mmol, 139.6 mg). Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as a white solid (0.37 mmol, 99 mg, 75%). **CAS**: 1439903-28-2.

Mp: 71 – 73 °C.

[a] Metalation via TMPMgCl·LiCl

[b] Metalation via $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.85 (dt, *J* = 4.7, 1.9 Hz, 1H), 7.49 (ddd, *J* = 8.8, 6.6, 1.9 Hz, 1H).

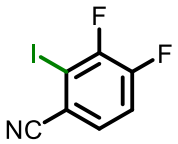
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 154.0 (dd, $J_{C\text{-}F}$ = 256.2, 13.4 Hz), 149.6 (dd, $J_{C\text{-}F}$ = 258.2, 15.6 Hz), 138.4 (dd, $J_{C\text{-}F}$ = 4.0, 1.4 Hz), 121.6 (dd, $J_{C\text{-}F}$ = 20.6, 1.5 Hz), 115.6, 110.7 (dd, $J_{C\text{-}F}$ = 8.1, 5.1 Hz), 83.7 (d, $J_{C\text{-}F}$ = 23.9 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -106.06 – -106.18 (m, 1F), -129.90 – -130.02 (m, 1F).

GC-MS (EI, 70 eV) m/z: 264.90 (100%), 138.00 (56%), 88.05 (31%), 265.90 (9%), 87.00 (8%).

Note: HRMS analysis of compound **125y** was not possible due to low stability.

28. 3,4-Difluoro-2-iodobenzonitrile (125z)



3,4-difluoro-2-iodobenzonitrile was obtained from **123e** via **GMB** using $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.29 M in THF, 0.75 equiv., 1.3 mL) at room temperature and iodine (1.1 equiv., 0.55 mmol, 139.6 mg). Purification via column chromatography (Hexanes/AcOEt 9.5:0.5) afforded the product as a white solid (0.38 mmol, 101 mg, 76%). **CAS**: 1803847-48-4.

Mp: 67 – 69 °C.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ [ppm] = 7.47 (ddd, *J* = 8.8, 4.6, 1.8 Hz, 1H), 7.29 (td, *J* = 8.8, 7.2 Hz, 1H).

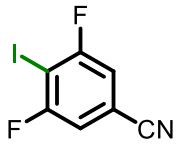
^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$): δ [ppm] = 152.4 (dd, $J_{C\text{-}F}$ = 263.6, 15.1 Hz), 151.6 (dd, $J_{C\text{-}F}$ = 250.0, 14.0 Hz), 131.0 (dd, $J_{C\text{-}F}$ = 7.6, 4.3 Hz), 118.6 (dd, $J_{C\text{-}F}$ = 18.9, 0.9 Hz), 117.9, 117.8 (dd, $J_{C\text{-}F}$ = 4.1, 1.3 Hz), 89.1(d, $J_{C\text{-}F}$ = 25.3 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -109.65 (ddd, *J* = 23.0, 7.2, 1.7 Hz, 1F), -123.99 (ddd, *J* = 23.0, 9.0, 4.6 Hz, 1F).

GC-MS (EI, 70 eV) m/z: 264.90 (100%), 138.05 (50%), 88.05 (33%), 265.90 (9%), 87.00 (7%).

Note: HRMS analysis of compound **125z** was not possible due to low stability.

29. 3,5-Difluoro-4-iodobenzonitrile (**125aa**)



3,5-difluoro-4-iodobenzonitrile was obtained from **123f** via **GMB** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) at -30 ºC or $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.29 M in THF, 0.65 equiv., 1.1 mL) at room temperature followed by iodine (1.1 equiv., 0.55 mmol, 139.6 mg). Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as a white solid (93 mg - 75%[c] and 120.6 mg - 91%[d]). **CAS**: 1487337-76-7.

Mp: 127 – 130 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.20 – 7.16 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 163.0 (dd, J_{C-F} = 250.6, 6.3 Hz, 2C), 116.3 (t, J_{C-F} = 3.4 Hz), 115.2-114.9 (m, 2C), 114.4 (t, J_{C-F} = 11.1 Hz), 79.1 (t, J_{C-F} = 29.4 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -87.41 – -87.47 (m, 2F).

GC-MS (EI, 70 eV) m/z: 264.90 (100%), 138.05 (43%), 88.00 (31%), 265.90 (9%), 87.00 (7%).

The reported characterization data is in accordance with the literature.[90]

30. 2,4-Difluoro-3-(hydroxy(2-methoxyphenyl)methyl)benzonitrile (**125ab**)

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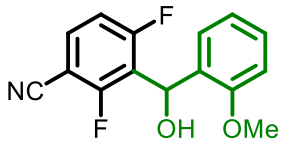
[c] Metalation via TMPMgCl·LiCl.

[d] Metalation via $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$.



2,4-difluoro-3-(hydroxy(2-methoxyphenyl)methyl)benzonitrile was obtained from **123d** via **GMB** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) at 0 ºC and 2-methoxybenzaldehyde (1.1 equiv., 0.55 mmol, 75 mg). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a white solid (0.47 mmol, 130.7 mg, 95%).

Mp: 120 – 121 °C.

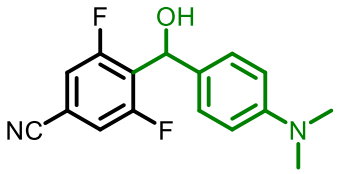
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.55 – 7.48 (m, 2H), 7.30 (td, *J* = 8.1, 1.7 Hz, 1H), 7.01 (td, *J* = 7.5, 0.9 Hz, 1H), 6.97 (td, *J* = 9.3, 1.3 Hz, 1H), 6.86 (app dd, *J* = 8.1, 0.7 Hz, 1H), 6.38 (s, 1H), 3.79 (s, 3H), 2.78 (bs, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 164.0 (dd, $J_{C\text{-}F}$ = 260.7, 8.5 Hz), 162.4 (dd, $J_{C\text{-}F}$ = 262.6, 9.1 Hz), 156.3, 133.3 (dd, $J_{C\text{-}F}$ = 11.6, 2.3 Hz), 129.4, 128.5, 126.8 (t, $J_{C\text{-}F}$ = 2.0 Hz), 120.9 (dd, $J_{C\text{-}F}$ = 16.9, 14.7 Hz), 120.7, 113.6, 113.3 (dd, $J_{C\text{-}F}$ = 24.4, 3.8 Hz), 110.5, 98.3 (dd, $J_{C\text{-}F}$ = 17.0, 3.9 Hz), 64.3 (t, $J_{C\text{-}F}$ = 2.8 Hz), 55.4.

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -101.26 – -101.35 (m, 1F), -104.96 (dd, *J* = 11.2, 7.0 Hz, 1F).

HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{11}F_2NNaO_2$ 298.0650; Found 298.0640.

31.4-((4-(Dimethylamino)phenyl)(hydroxy)methyl)-3,5-difluorobenzonitrilebenzo--nitrile (**125ac**)



4-((4-(dimethylamino)phenyl)(hydroxy)methyl)-3,5-difluorobenzonitrilebenzonitrile was obtained from **123f** via **GMB** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) at -30 ºC

and 4-(dimethylamino)benzaldehyde (1.1 equiv., 0.55 mmol, 82 mg) as the electrophile. Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a beige solid (0.47 mmol, 135.5 mg, 94%).

Mp: 150 – 151 °C.

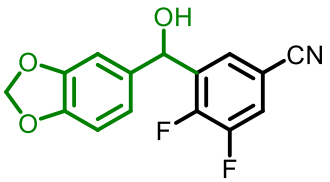
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.24 (app d, *J* = 8.4 Hz, 2H), 7.21 (app d, *J* = 7.7 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.16 (s, 1H), 2.95 (s, 6H), 2.73 (bs, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 160.6 (dd, J_{C-F} = 252.4, 9.1 Hz, 2C), 150.4, 126.9 (2C), 126.1 (t, J_{C-F} = 16.2 Hz), 116.6 (t, J_{C-F} = 3.5 Hz), 116.3 – 116.0 (m, 2C), 112.7 (t, J_{C-F} = 12.4 Hz), 112.7 (2C), 111.1, 68.0, 40.7 (2C).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -110.00 – -110.08 (m, 2F).

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{15}F_2N_2O$ 289.1147; Found 289.1135.

32. 3-(Benzo[d][1,3]dioxol-5-yl(hydroxy)methyl)-4,5-difluorobenzonitrile (**125ad**)



3-(benzo[d][1,3]dioxol-5-yl(hydroxy)methyl)-4,5-difluorobenzonitrile was obtained from **123e** via **GMB** using TMPMgCl·LiCl (1 M, 1.5 equiv., 0.75 mL) at -70 ºC and 1,3-benzodioxole-5-carboxaldehyde (1.1 equiv., 0.55 mmol, 82.6 mg) as the electrophile. Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a yellow oil (0.28 mmol, 82.4 mg, 57%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.78 – 7.76 (m, 1H), 7.39 (ddd, *J* = 9.1, 6.9, 2.1 Hz, 1H), 6.86 – 6.81 (m, 2H), 6.78 (d, *J* = 7.9 Hz, 1H), 6.03 (s, 1H), 5.96 (d, *J* = 1.4 Hz, 1H), 5.95 (d, *J* = 1.4 Hz, 1H), 2.31 (bs, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 150.6 (dd, J_{C-F} = 258.6, 12.9 Hz), 150.2 (dd, J_{C-F} = 253.4, 13.5 Hz), 148.3, 147.9, 135.8 (d, J_{C-F} = 11.2 Hz), 135.2, 127.0 (t, J_{C-F} = 3.8

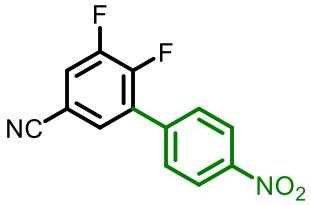
Hz), 120.2 (dd, J_{C-F} = 20.3, 1.3 Hz), 120.2 (d, J_{C-F} = 0.9 Hz), 117.2, 108.6, 108.6 (dd, J_{C-F} = 8.1, 5.1 Hz) 106.9, 101.5, 69.3.

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -132.50 (dt, *J* = 21.1, 6.2 Hz, 1F), -134.19 – -134.30 (m, 1F).

GC-MS (EI, 70 eV) m/z: 289.05 (100%), 123.05 (86%), 93.05 (65%), 151.00 (42%), 165.95 (31%).

HRMS (ESI-TOF) m/z: $[M+FA-H]^-$ Calcd for $C_{16}H_{10}F_2NO_5$ 334.0533; Found 334.0521.

33. 5,6-Difluoro-4'-nitro-[1,1'-biphenyl]-3-carbonitrile (**125ae**)



5,6-difluoro-4'-nitro-[1,1'-biphenyl]-3-carbonitrile was obtained from **123e** via **GMB** using TMPMgCl·LiCl (1 M, 1.5 equiv., 0.75 mL) at -70 ºC followed by transmetalation with $ZnCl_2$ (1 M in THF, 1.5 equiv., 0.75 mL) during 20 minutes and Negishi cross-coupling catalyzed by $Pd(PPh_3)_4$ (5 mol%, 29 mg) in the presence of 1-iodo-4-nitrobenzene (1.2 equiv., 0.6 mmol, 149.4 mg) at 50 ºC (oil bath). Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as an orange solid (0.29 mmol, 75.5 mg, 58%).

Mp: 162 – 164 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.39 – 8.35 (m, 2H), 7.73 – 7.70 (m, 2H), 7.61 – 7.56 (m, 2H).

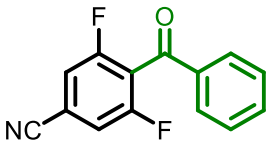
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 151.2 (dd, J_{C-F} = 256.6, 15.8 Hz), 151.0 (dd, J_{C-F} = 264.0, 15.8 Hz), 148.4, 138.7, 130.9 (dd, J_{C-F} = 11.2, 0.8 Hz), 130.1 (d, J_{C-F} = 3.1 Hz, 2C), 130.0 (t, J_{C-F} = 3.0 Hz), 124.3 (2C), 121.4 (dd, J_{C-F} = 20.0, 2.4 Hz), 116.6, 109.4 (dd, J_{C-F} = 8.5, 5.4 Hz).

GC-MS (EI, 70 eV) m/z: 260.00 (100%), 202.00 (46%), 213.00 (44%), 214.00 (38%), 187.00 (33%).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -131.74 – -131.85 (m, 1F), -131.93 – -132.05 (m, 1F).

HRMS (ESI-TOF) m/z: $[M+CH_3OH+H]^+$ Calcd for $C_{14}H_{11}F_2N_2O_3$ 293.0732; Found 293.0741.

34. 4-Benzoyl-3,5-difluorobenzonitrile (**125af**)



4-benzoyl-3,5-difluorobenzonitrile was obtained from **123f** via **GMB** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) at -30 ºC followed by transmetalation with $ZnCl_2$ (1 M in THF, 1.3 equiv., 0.65 mL) for 20 minutes and palladium catalyzed benzoylation using $Pd(PPh_3)_4$ (5 mol%, 29 mg) and benzoyl chloride (1.0 equiv., 0.5 mmol, 58 µL) at room temperature. Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as a white solid (0.41 mmol, 100.9 mg, 83%).

Mp: 104 – 105 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.83 (app d, *J* = 7.7 Hz, 2H), 7.68 (tt, *J* = 7.1, 1.3 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.37 – 7.32 (m, 2H).

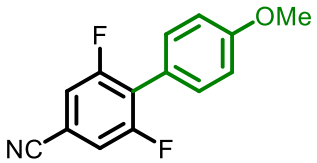
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 186.9, 159.7 (dd, J_{C-F} = 255.5, 8.5 Hz, 2C), 135.9, 135.2, 129.7 (2C), 129.2 (2C), 122.1 (t, J_{C-F} = 22.7 Hz), 116.4 - 116.1 (m, 2C), 116.1 (t, J_{C-F} = 3.5 Hz), 115.5 (t, J_{C-F} = 11.4 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -107.68 – -107.73 (m, 2F).

GC-MS (EI, 70 eV) m/z: 105.05 (100%), 243.00 (74%), 77.00 (54%), 165.95 (30%), 51.00 (18%).

HRMS (ESI-TOF) m/z: $[M+CH_3OH+H]^+$ Calcd for $C_{15}H_{12}F_2NO_2$ 276.0831; Found 276.0839.

35. 2,6-Difluoro-4'-methoxy-[1,1'-biphenyl]-4-carbonitrile (**125ag**)



2,6-difluoro-4'-methoxy-[1,1'-biphenyl]-4-carbonitrile was obtained from **123f** via **GMB** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) at -30 ºC followed by transmetalation with $ZnCl_2$ (1 M in THF, 1.3 equiv., 0.65 mL) and Negishi cross-coupling catalyzed by $Pd(PPh_3)_4$ (5 mol%, 29 mg) in the presence of 4-methoxyiodobenzene (1.2 equiv., 0.6 mmol, 140.4 mg) at 50 ºC (oil bath). Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as a white solid (0.44 mmol, 107.9 mg, 88%). **CAS**: 2222566-95-0.

Mp: 150 – 151 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.44 – 7.39 (m, 2H), 7.33 – 7.26 (m, 2H), 7.03 – 7.00 (m, 2H), 3.87 (s, 3H).

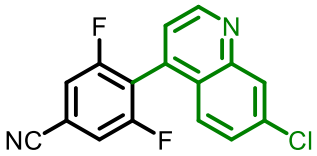
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 160.5, 160.0 (dd, J_{C-F} = 251.8, 8.0 Hz, 2C), 131.6 (t, J_{C-F} = 2.3 Hz, 2C), 124.1 (t, J_{C-F} = 18.3 Hz), 119.3, 116.9 (t, J_{C-F} = 3.4 Hz), 116.2 - 115.9 (m, 2C), 114.2 (2C), 111.7 (t, J_{C-F} = 12.3 Hz), 55.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -110.59 – -110.66 (m, 2F).

GC-MS (EI, 70 eV) m/z: 245.05 (100%), 202.00 (59%), 230.00 (25%), 175.95 (19%), 246.05 (17%).

The reported characterization data is in accordance with the literature.[132]

36. 4-(7-Chloroquinolin-4-yl)-3,5-difluorobenzonitrile (**125ah**)



4-(7-chloroquinolin-4-yl)-3,5-difluorobenzonitrile was obtained from **123f** via **GMB** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) at -30 ºC followed by transmetalation with $ZnCl_2$ (1 M in THF, 1.3 equiv., 0.65 mL) and Negishi cross-coupling catalyzed by $Pd(PPh_3)_4$ (5 mol%, 29 mg) in the presence of 7-chloro-4-iodoquinoline (1.2 equiv., 0.6 mmol, 173.7 mg) at 50 ºC (oil bath). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a white solid (0.24 mmol, 72.2 mg, 48%).

Mp: 142 – 144 °C.

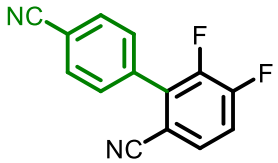
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 9.05 (d, *J* = 4.5 Hz, 1H), 8.27 (d, *J* = 2.1 Hz, 1H), 7.53 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.47 – 7.42 (m, 3H), 7.41 (d, *J* = 4.5 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 160.1 (dd, J_{C-F} = 254.6, 7.2 Hz, 2C), 150.4, 148.3, 136.6, 134.8, 129.1, 128.8, 126.1, 124.7, 123.0, 119.6 (t, J_{C-F} = 20.3 Hz), 116.4 – 116.1 (m, 2C), 116.2 (t, J_{C-F} = 3.4 Hz), 115.0 (t, J_{C-F} = 11.7 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -106.24 – -106.30 (m, 2F).

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_8ClF_2N_2$ 301.0339; Found 301.0352.

37. 5,6-Difluoro-[1,1'-biphenyl]-2,4'-dicarbonitrile (125ai)



5,6-difluoro-[1,1'-biphenyl]-2,4'-dicarbonitrile was obtained from **123e** via **GMB** using $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.29 M in THF, 0.75 equiv., 1.3 mL) at room temperature and subsequent Negishi cross-coupling catalyzed by $Pd(PPh_3)_4$ (5 mol%, 29 mg) in the presence of 4-iodobenzonitrile (1.2 equiv., 0.6 mmol, 137.4 mg) at 50 ºC (oil bath).

Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a brown solid (0.31 mmol, 74.5 mg, 62%).

Mp: 160 – 162 °C.

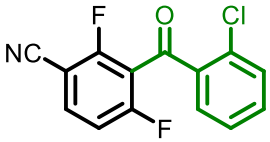
^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ [ppm] = 7.84 (app. d, *J* =8.6 Hz, 2H), 7.64 – 7.60 (m, 3H), 7.37 (td, *J* = 8.9, 7.3 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$): δ [ppm] = 153.9 (dd, J_{C-F} = 260.8, 13.4 Hz), 148.1 (dd, J_{C-F} = 253.3, 13.7 Hz), 135.0 (d, J_{C-F} = 2.5 Hz), 133.8 (dd, J_{C-F} = 14.2, 1.1 Hz), 132.7, 130.7 (d, J_{C-F} = 1.9 Hz), 130.6 (dd, J_{C-F} = 8.0, 4.8 Hz), 118.5 (d, J_{C-F} = 18.6 Hz), 118.2, 116.3 (app. dd, J_{C-F} = 3.3, 1.9 Hz), 113.9, 109.2 (app. dd, J_{C-F} = 3.7, 2.7 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -125.49 (ddd, *J* = 21.7, 9.1, 4.6 Hz, 1F), -136.50 – -136.61 (m, 1F).

HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_7F_2N_2Na$ 263.0391; Found 263.0389.

38. 3-(2-Chlorobenzoyl)-2,4-difluorobenzonitrile (125aj)



3-(2-chlorobenzoyl)-2,4-difluorobenzonitrile was obtained from **123d** via **GMB** using $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.29 M in THF, 0.65 equiv., 1.1 mL) at room temperature and subsequent palladium-catalyzed benzoylation using $Pd(PPh_3)_4$ (5 mol%, 29 mg) and 2-chlorobenzoyl chloride (1.0 equiv., 0.5 mmol, 63 µL) at the same temperature. Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as a white solid (0.30 mmol, 83.3 mg, 60%).

Mp: 69 – 72 °C.

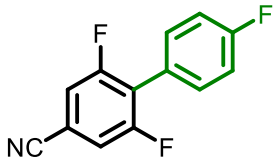
^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ [ppm] = 7.77 (ddd, *J* = 8.7, 7.0, 5.7 Hz, 1H), 7.68 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.53 (ddd, *J* = 8.2, 7.3, 1.7 Hz, 1H), 7.45 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.42 (td, *J* = 7.7, 1.3 Hz, 1H), 7.12 (td, *J* = 8.7, 1.4 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$): δ [ppm] = 185.9, 162.9 (dd, J_{C-F} = 264.6, 6.7 Hz), 161.5 (dd, J_{C-F} = 266.4, 7.7 Hz), 136.7, 136.5 (dd, J_{C-F} = 11.1, 1.9 Hz), 134.2, 132.9, 131.3, 131.1, 127.5, 119.7 (dd, J_{C-F} = 19.8, 17.5 Hz), 113.8 (dd, J_{C-F} = 23.2, 4.0 Hz), 112.6 (d, J_{C-F} = 1.2 Hz), 99.0 (dd, J_{C-F} = 16.2, 4.2 Hz).

^{19}F NMR (282 MHz, CDCl$_3$): δ [ppm] = -100.10 (td, *J* = 8.5, 5.7 Hz, 1F), -103.68 – -103.74 (m, 1F).

HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_6ClF_2NNaO$ 299.9998; Found 300.0022.

39. 2,4',6-Trifluoro-[1,1'-biphenyl]-4-carbonitrile (125ak)



2,4',6-trifluoro-[1,1'-biphenyl]-4-carbonitrile was obtained from **123f** via **GMB** using $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.29 M in THF, 0.65 equiv., 1.1 mL) at room temperature and subsequent Negishi cross-coupling catalyzed by $Pd(PPh_3)_4$ (5 mol%, 29 mg) in the presence of 4-fluoroiodobenzene (1.2 equiv., 0.6 mmol, 69 µL) at 50 ºC (oil bath). Purification via column chromatography (Hexanes/AcOEt 9.5:0.5) afforded the product as a white solid (0.46 mmol, 107.3 mg, 92%).

Mp: 195 – 196 °C.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ [ppm] = 7.47 – 7.44 (m, 2H), 7.35 – 7.29 (m, 2H), 7.22 – 7.17 (m, 2H).

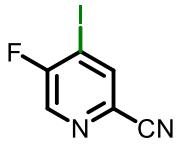
^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.4 (d, J_{C-F} = 250.1 Hz), 160.0 (dd, J_{C-F} = 252.5, 7.7 Hz, 2C), 132.2 (dt, J_{C-F} = 8.5, 2.1 Hz, 2C), 123.3 (t, J_{C-F} = 18.3 Hz), 123.1 (d, J_{C-F} = 3.4 Hz), 116.7 (t, J_{C-F} = 3.5 Hz), 116.3 – 115.9 (m, 2C), 116.0 (d, J_{C-F} = 21.9 Hz, 2C), 112.6 (t, J_{C-F} = 12.3 Hz).

^{19}F NMR (282 MHz, CDCl$_3$): δ [ppm] = -110.32 – -110.39 (m, 2F), -110.98 – -111.07 (m, 1F).

GC-MS (EI, 70 eV) m/z: 233.00 (100%), 234.05 (18%), 213.00 (14%), 232.05 (10%), 116.55 (9%).

HRMS (ESI-TOF) m/z: $[M+CH_3OH+H]^+$ Calcd for $C_{14}H_{11}F_3NO$ 266.0787; Found 266.0797.

40. 5-Fluoro-4-iodopicolinonitrile (**125al**)



5-fluoro-4-iodopicolinonitrile was obtained from **123g** via **GMC** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) at -30 ºC and iodine (1.1 equiv., 0.55 mmol, 139.6 mg). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a white solid (0.35 mmol, 86.8 mg, 70%). **CAS**: 1807159-50-7.

Mp: 130 – 133 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.41 (s, 1H), 8.14 (d, *J* = 4.6 Hz, 1H).

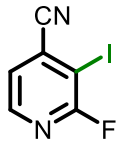
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 161.4 (d, J_{C-F} = 264.2 Hz), 139.3 (d, J_{C-F} = 5.7 Hz), 139.1 (d, J_{C-F} = 34.1 Hz), 130.4 (d, J_{C-F} = 5.5 Hz), 115.2, 93.1 (d, J_{C-F} = 24.8 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -99.10 (d, *J* = 4.6 Hz, 1F).

GC-MS (EI, 70 eV) m/z: 247.95 (100%), 121.00 (51%), 94.00 (24%), 69.00 (12%), 101.00 (8%).

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_6H_3FIN_2$ 248.9320; Found 248.9324.

41. 2-Fluoro-3-iodoisonicotinonitrile (**125am**)



2-fluoro-3-iodoisonicotinonitrile was obtained from **123h** via **GMC** using TMPMgCl·LiCl (1 M, 1.5 equiv., 0.75 mL) at -70 ºC followed by transmetalation with $ZnCl_2$ (1 M in THF, 1.5 equiv., 0.75 mL) or $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.29 M in THF, 0.9 equiv., 1.5 mL) at room temperature with iodine (1.1 equiv., 0.55 mmol, 139.6 mg) as the electrophile. Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as a white solid (85.6 mg - 69%[e] and 94.2 mg - 76%[f]). **CAS**: 898854-64-3.

Mp: 96 – 97 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.33 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.40 (dd, *J* = 5.0, 1.0 Hz, 1H).

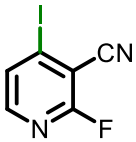
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 163.1 (d, $J_{C\text{-}F}$ = 237.6 Hz), 148.3 (d, $J_{C\text{-}F}$ = 14.4 Hz), 133.2 (d, $J_{C\text{-}F}$ = 4.2 Hz), 125.2 (d, $J_{C\text{-}F}$ = 5.5 Hz), 116.6 (d, $J_{C\text{-}F}$ = 4.9 Hz), 81.8 (d, $J_{C\text{-}F}$ = 47.1 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -48.43 (s, 1F).

GC-MS (EI, 70 eV) m/z: 247.90 (100%), 121.05 (76%), 76.00 (23%), 94.00 (13%), 101.00 (9%).

Note: HRMS analysis of compound **125am** was not possible due to low stability.

42. 2-Fluoro-4-iodonicotinonitrile (**125an**)



2-fluoro-4-iodonicotinonitrile was obtained from **123i** via **GMC** using TMPMgCl·LiCl (1 M, 1.5 equiv., 0.75 mL) at -70 ºC and iodine (1.1 equiv., 0.55 mmol, 139.6 mg) as the

[e] Metalation via TMPMgCl·LiCl.

[f] Metalation via $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$.

electrophile. Purification via column chromatography (Hexanes/AcOEt 8.5:1.5) afforded the product as a white solid (0.42 mmol, 105.4 mg, 85%). **CAS**: 898854-59-6.

Mp: 85 – 86 °C.

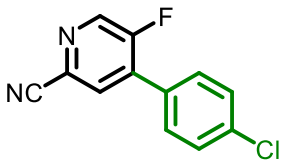
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.08 (dd, *J* = 5.3, 0.9 Hz, 1H), 7.80 (dd, *J* = 5.3, 0.9 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 163.0 (d, $J_{C\text{-}F}$ = 251.1 Hz), 150.9 (d, $J_{C\text{-}F}$ = 15.8 Hz), 132.2 (d, $J_{C\text{-}F}$ = 4.8 Hz), 114.0, 113.7 (d, $J_{C\text{-}F}$ = 6.1 Hz), 106.4 (d, $J_{C\text{-}F}$ = 32.7 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -57.27 (s, 1F).

GC-MS (EI, 70 eV) m/z: 247.95 (100%), 121.05 (77%), 76.00 (24%), 94.00 (15%), 75.00 (15%).
Note: HRMS analysis of compound **1125an** was not possible due to low stability.

43. 4-(4-Chlorophenyl)-5-fluoropicolinonitrile (**125ao**)



4-(4-chlorophenyl)-5-fluoropicolinonitrile was obtained from **123g** via **GMC** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) at -30 ºC followed by transmetalation with $ZnCl_2$ (1 M in THF, 1.3 equiv., 0.65 mL) and a Negishi cross-coupling catalyzed by $Pd(PPh_3)_4$ (5 mol%, 29 mg) in the presence of 1-chloro-4-iodobenzene (1.2 equiv., 0.6 mmol, 143.1 mg) at 50 ºC (oil bath). Purification via column chromatography (Hexanes/AcOEt 9:1) afforded the product as a white solid (0.28 mmol, 65.1 mg, 56%).

Mp: 130 – 131 °C.

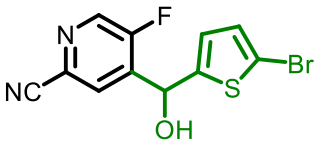
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.63 (d, *J* = 2.2 Hz, 1H), 7.82 (d, *J* = 6.0 Hz, 1H), 7.57 – 7.50 (m, 4H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ [ppm] = 157.7 (d, J_{C-F} = 266.8 Hz), 141.3 (d, J_{C-F} = 28.0 Hz), 136.9, 136.4 (d, J_{C-F} = 11.7 Hz), 130.5 (d, J_{C-F} = 5.4 Hz), 130.2 (d, J_{C-F} = 3.7 Hz, 2C), 129.7 (2C), 129.5 (d, J_{C-F} = 2.7 Hz), 129.3 (d, J_{C-F} = 1.8 Hz), 116.6.

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -123.46 – -123.49 (m, 1F).

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_7ClFN_2$ 233.0277; Found 233.0292.

44. 4-((5-Bromothiophen-2-yl)(hydroxy)methyl)-5-fluoropicolinonitrile (**125ap**)



4-((5-bromothiophen-2-yl)(hydroxy)methyl)-5-fluoropicolinonitrile was obtained from **123g** via **GMC** using TMPMgCl·LiCl (1 M, 1.3 equiv., 0.65 mL) at -30 ºC and 5-bromo-2-thiophenecarboxaldehyde (1.1 equiv., 0.55 mmol, 65 µL) as the electrophile. Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a white solid (0.31 mmol, 97.1 mg, 62%).

Mp: 113 – 115 °C.

^1H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.48 (d, *J* = 1.1 Hz, 1H), 8.08 (d, *J* = 5.6 Hz, 1H), 6.92 (d, *J* = 3.8 Hz, 1H), 6.77 (dt, *J* = 3.8, 0.7 Hz, 1H), 6.28 (d, *J* = 0.7 Hz, 1H), 2.53 (bs, 1H).

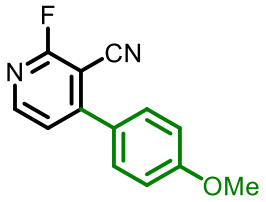
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ [ppm] = 157.5 (d, J_{C-F} = 266.0 Hz), 145.2, 140.2 (d, J_{C-F} = 25.9 Hz), 140.0 (d, J_{C-F} = 12.9 Hz), 130.4 (d, J_{C-F} = 5.2 Hz), 130.0, 127.0 (d, J_{C-F} = 2.8 Hz), 126.2 (d, J_{C-F} = 1.2 Hz), 116.6, 114.0, 64.9 (d, J_{C-F} = 2.5 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -122.56 (s, 1F).

GC-MS (EI, 70 eV) m/z: 232.95 (100%), 84.00 (24%), 313.85 (21%), 311.90 (21%), 149.00 (19%).

HRMS (ESI-TOF) m/z: $[M-H]^-$ Calcd for $C_{11}H_5BrFN_2OS$ 310.9295; Found 310.9293.

45. 2-Fluoro-4-(4-methoxyphenyl)nicotinonitrile (**125aq**)



2-fluoro-4-(4-methoxyphenyl)nicotinonitrile was obtained from **123i** via **GMC** using TMPMgCl·LiCl (1 M, 1.5 equiv., 0.75 mL) at -70 ºC followed by transmetalation with $ZnCl_2$ (1 M in THF, 1.5 equiv., 0.75 mL) and a Negishi cross-coupling reaction catalyzed by $Pd(PPh_3)_4$ (5 mol%, 29 mg) in the presence of 4-methoxyiodobenzene (1.2 equiv., 0.6 mmol, 140.4 mg) at 50 ºC (oil bath). Purification via column chromatography (Hexanes/AcOEt 8:2) afforded the product as a brown solid (0.26 mmol, 59.3 mg, 52%).

Mp: 136 – 139 °C.

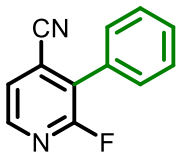
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.38 (d, *J* = 5.3 Hz, 1H), 7.65 – 7.61 (m, 2H), 7.36 (dd, *J* = 5.3, 0.9 Hz, 1H), 7.08 – 7.04 (m, 2H), 3.89 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 164.4 (d, $J_{C\text{-}F}$ = 246.1 Hz), 161.9, 157.6, 150.8 (d, $J_{C\text{-}F}$ = 16.1 Hz), 130.2 (2C), 126.8 (d, $J_{C\text{-}F}$ = 3.1 Hz), 121.7 (d, $J_{C\text{-}F}$ = 4.2 Hz), 114.9 (2C), 113.1 (d, $J_{C\text{-}F}$ = 4.5 Hz), 95.0 (d, $J_{C\text{-}F}$ = 31.0 Hz), 55.6.

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -60.42 (s, 1F).

HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{13}H_9FN_2NaO$ 251.0591; Found 251.0584.

46. 2-Fluoro-3-phenylisonicotinonitrile (**125ar**)



2-fluoro-3-phenylisonicotinonitrile was obtained from **123h** via **GMC** using $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.29 M in THF, 0.9 equiv., 1.5 mL) at room temperature and subsequent Negishi cross-coupling catalyzed by $Pd(PPh_3)_4$ (5 mol%, 29 mg) in the

presence of iodobenzene (1.2 equiv., 0.6 mmol, 67 µL) at 50 ºC (oil bath). Purification via column chromatography (Hexanes/AcOEt 9.5:0.5) afforded the product as a beige solid (0.36 mmol, 71.4 mg, 72%).

Mp: 57 – 58 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.35 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.56 (dd, *J* = 5.1, 0.8 Hz, 1H), 7.54 - 7.53 (m, 5H).

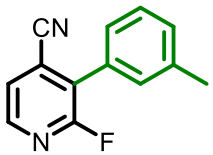
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 160.7 (d, $J_{C\text{-}F}$ = 241.7 Hz), 147.2 (d, $J_{C\text{-}F}$ = 15.5 Hz), 130.2, 129.8 (d, $J_{C\text{-}F}$ = 4.6 Hz), 129.7 (d, $J_{C\text{-}F}$ = 1.7 Hz, 2C), 129.0 (2C), 127.4 (d, $J_{C\text{-}F}$ = 33.6 Hz), 124.7 (d, $J_{C\text{-}F}$ = 5.3 Hz), 124.1 (d, $J_{C\text{-}F}$ = 5.6 Hz), 115.4 (d, $J_{C\text{-}F}$ = 5.7 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -66.01 (s, 1F).

GC-MS (EI, 70 eV) m/z: 198.00 (100%), 197.00 (29%), 199.05 (16%), 171.00 (15%), 151.00 (13%).

HRMS (ESI-TOF) m/z: $[M+CH_3OH+H]^+$ Calcd for $C_{13}H_{12}FN_2O$ 231.0928; Found 231.0934.

47. 2-Fluoro-3-(m-tolyl)isonicotinonitrile (**125as**)



2-fluoro-3-(m-tolyl)isonicotinonitrile was obtained from **123h** via **GMC** using $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.29 M in THF, 0.9 equiv., 1.5 mL) at room temperature and subsequent Negishi cross-coupling catalyzed by $Pd(PPh_3)_4$ (5 mol%, 29 mg) in the presence of 3-iodotoluene (1.2 equiv., 0.6 mmol, 77 µL) at 50 ºC (oil bath). Purification via column chromatography (Hexanes/AcOEt 9.5:0.5) afforded the product as a colorless oil (0.40 mmol, 84.9 mg, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.34 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.55 (dd, *J* = 5.1, 0.8 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.33 – 7.32 (m, 3H), 2.44 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 160.7 (d, J_{C-F} = 241.7 Hz), 147.1 (d, J_{C-F} = 15.4 Hz), 138.8, 130.9, 130.2 (d, J_{C-F} = 1.7 Hz), 129.7 (d, J_{C-F} = 3.9 Hz), 128.9, 127.5 (d, J_{C-F} = 33.8 Hz), 126.8 (d, J_{C-F} = 1.7 Hz), 124.6 (d, J_{C-F} = 5.3 Hz), 124.1 (d, J_{C-F} = 5.7 Hz), 115.5 (d, J_{C-F} = 5.6 Hz), 21.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ [ppm] = -65.90 (s, 1F).

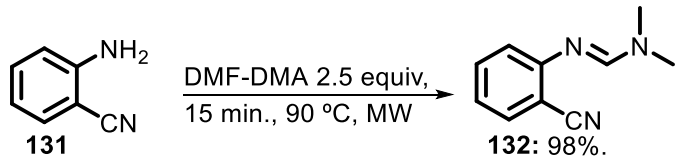
GC-MS (EI, 70 eV) m/z: 212.05 (100%), 211.05 (83%), 184.00 (30%), 185.00 (19%), 165.00 (14%).

HRMS (ESI-TOF) m/z: $[M+CH_3OH+H]^+$ Calcd for $C_{14}H_{14}FN_2O$ 245.1085; Found 245.1092.

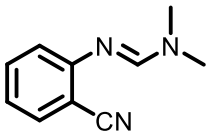
7.1.4 Examples of synthetic applications of the functionalized nitriles

7.1.4.1 Synthesis of 4-aminoquinazolines

7.1.4.1.1 Synthesis of (E)-N'-(2-cyanophenyl)-N,N-dimethylformimidamide ***132***



A microwave vessel was charged with 2-aminobenzonitrile (1.0 equiv., 2 mmol, 0.2381 g) and DMF-DMA (2.5 equiv., 5 mmol, 0.67 mL). The reaction was kept at 90 °C for 15 minutes in the microwave reactor. Then, the remaining DMF-DMA was removed under reduced pressure, and the crude material was subjected to column chromatography (hexanes/AcOEt 7:3) to afford (*E*)-*N'*-(2-cyanophenyl)-*N,N*-dimethylformimidamide as a white solid (340 mg, 98%). Note = It only became solid after staying in the freezer overnight followed by drying under high vacuum. **CAS**: 36185-83-8. Procedure according to Besson and co-workers.[66]



132

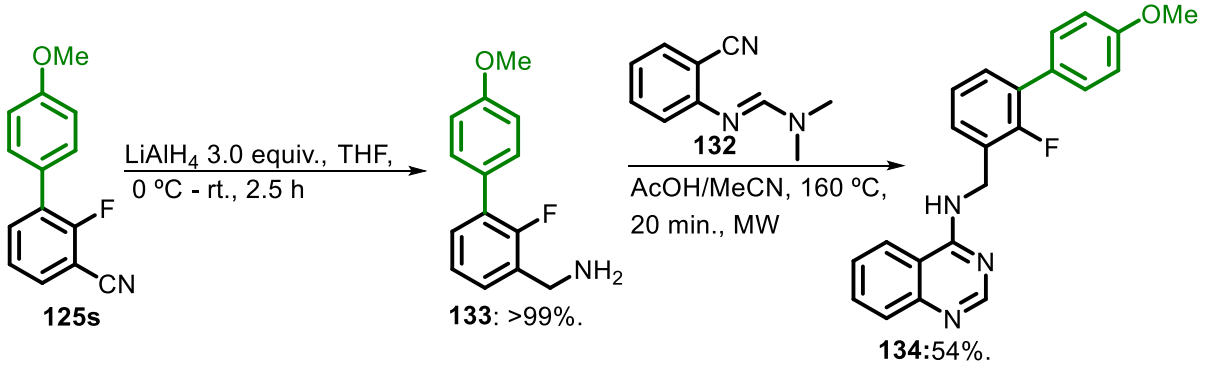
Mp: 40 – 42 ºC.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.57 (s, 1H), 7.51 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.41 – 7.37 (m, 1H), 6.98 (td, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 3.07 (s, 3H), 3.06 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 155.3, 153.8, 133.5, 133.2, 122.1, 119.9, 118.8, 106.8, 40.4, 34.7.

GC-MS (EI, 70 eV) m/z: 173 (88), 172 (23), 131 (100), 102 (37), 129 (32), 44 (55), 57 (14), 42 (13).

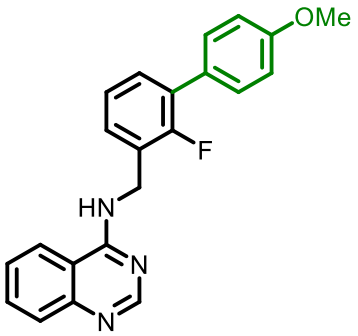
*7.1.4.1.2 Synthesis of of N-((2-fluoro-4'-methoxy-[1,1'-biphenyl]-3-yl)methyl)quinazolin-4-amine **134***



Part A: A solution of 2-fluoro-4'-methoxy-[1,1'-biphenyl]-3-carbonitrile **125s** (1.0 equiv., 0.2 mmol, 0.0454 g) in dry THF (1.5 mL) at 0 °C were gradually transferred to a round-bottom flask charged with LAH (3.0 equiv., 0.6 mmol, 0.0228 g) under nitrogen. The reaction was kept at 0 °C for 1 h and room temperature for 1h30. Then, water (10 mL) was cautiously added to the reaction mixture, and it was extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure affording the product as a brown oil in quantitative

yield. The obtained benzylamine[g] was employed for the next step without further purification. This procedure was adapted from Empfield and co-workers.[133]

Part B: A solution of (2-fluoro-4'-methoxy-[1,1'-biphenyl]-3-yl)methanamine **133** (1.0 equiv., 0.2 mmol, 0.048 g) in AcOH/MeCN 3:2 (1.2 mL – 0.72 ml of AcOH and 0.48 ml of MeCN) were transferred to a microwave vessel charged with (*E*)-*N*'-(2-cyanophenyl)-*N,N*-dimethylformimidamide **132** (0.2 mmol, 0.0346 g). The reaction was kept at 160 °C for 20 minutes. Then, the mixture was cooled and concentrated under reduced pressure prior to purification via column chromatography (Hexanes/AcOEt 6:4). The product was isolated as a white solid (0.039 g, 54% yield). This procedure was adapted from Besson and co-workers.[66]



134

Mp: 155 – 156 ºC.

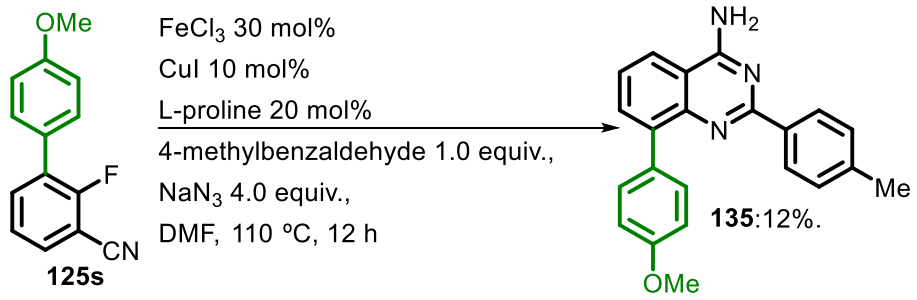
^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.85 (bs, 1H), 8.47 (s, 1H), 8.35 (d, *J* = 8.2 Hz, 1H), 7.80 (t, *J* = 7.5 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.55 (t, *J* = 7.6 Hz,1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.0 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 2H), 4.87 (d, *J* = 5.6 Hz, 2H), 3.80 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$): δ [ppm] = 159.3, 158.9, 157.0 (d, J_{C-F} = 245.8 Hz), 155.0, 149.1, 132.7, 130.0 (d, J_{C-F} = 2.9 Hz, 2C) 129.1 (d, J_{C-F} = 2.4 Hz), 127.8 (d, J_{C-F} = 21.1 Hz), 127.7 (d, J_{C-F} = 3.5 Hz), 127.5, 127.3, 126.6 (d, J_{C-F} = 15.8 Hz), 125.8, 124.3 (d, J_{C-F} = 3.9 Hz), 122.7, 114.9, 114.0 (2C), 55.1, 37.9 (d, J_{C-F} = 5.8 Hz).

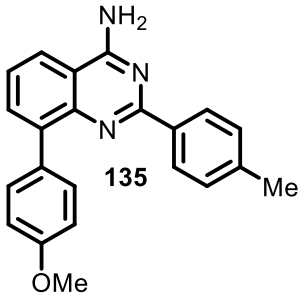
HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}FN_3O$ 360.1507; Found 360.1530.

[g] The conversion was confirmed via (GC-MS (EI, 70 eV) m/z: **231 (100),** 210 (77), 230 (51), 232 (17), 211 (16).

*7.1.4.1.3 Synthesis of 8-(4-methoxyphenyl)-2-(p-tolyl)quinazolin-4-amine **135***



A vessel was charged with 2-fluoro-4'-methoxy-[1,1'-biphenyl]-3-carbonitrile **125s** (1.0 equiv., 0.3 mmol, 0.0682 g), *p*-Tolualdehyde (1.0 equiv., 0.3 mmol, 0.035 mL), NaN_3 (4.0 equiv., 1.2 mmol, 0.0780 g), $FeCl_3$ (0.3 equiv., 0.09 mmol, 0.0146 g), CuI (0.1 equiv., 0.03 mmol, 0.0057 g), L-proline (0.2 equiv., 0.06 mmol, 0.0069 g) and dry DMF (1.8 mL). It was sealed under air and kept at 110 °C for 16 h. Then, 20 mL of water was added to the mixture, and it was extracted with EtOAc (3 × 10 mL). The extract was washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure (rotary evaporator). Column chromatography (Hexanes/AcOEt 7:3) was performed to afford the desired 4-aminoquinazoline **135** as a white solid (12 mg, 12% yield). Adapted from Wu and co-workers.[56e]



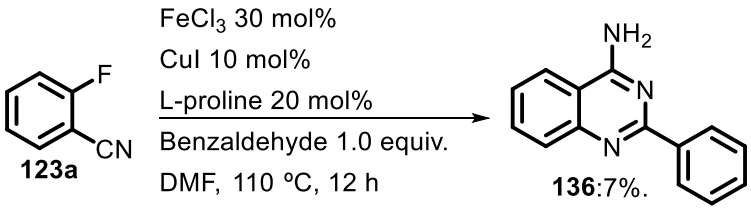
Mp: 253 – 256 ºC.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.33 (d, *J* = 8.2 Hz, 2H), 7.82 – 7.78 (m, 3H), 7.72 (d, *J* = 7.4 Hz, 1H), 7.47 (t-like, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.06 (d-like, *J* = 8.8 Hz, 2H), 5.85 (s, 2H), 3.92 (s, 3H), 2.40 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ [ppm] = 161.6, 159.1, 140.3, 139.5, 135.6, 135.4, 133.4, 133.0, 132.1 (2C), 131.1, 129.1 (2C), 128.3 (2C), 125.3, 120.5, 113.4, 113.3 (2C), 55.4, 21.5.

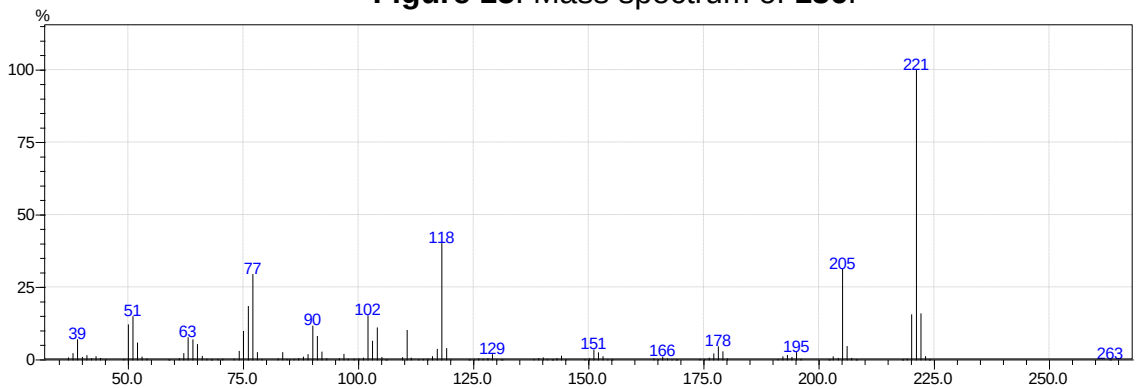
HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{20}N_3O$ 342.1601; Found 342.1605.

*7.1.4.1.4 Synthesis of 2-phenylquinazolin-4-amine **136***



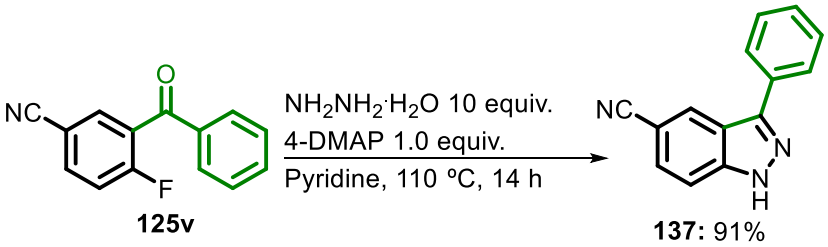
A vessel was charged with 2-fluorobenzonitrile **123a** (1.0 equiv., 0.5 mmol, 0.054 mL), benzaldehyde (1.0 equiv., 0.5 mmol, 0.051 mL), NaN_3 (4.0 equiv., 2.0 mmol, 0.1300 g), $FeCl_3$ (0.3 equiv., 0.15 mmol, 0.0243 g), CuI (0.1 equiv., 0.05 mmol, 0.0095 g), L-proline (0.2 equiv., 0.1 mmol, 0.0115 g) and dry DMF (3.0 mL). It was sealed under air and kept at 110 °C for 16 h. Then, 20 mL of water was added to the mixture, and it was extracted with EtOAc (3 × 10 mL). The extract was washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure (rotary evaporator). Column chromatography (Hexanes/AcOEt 7:3) was performed to afford the desired 4-aminoquinazoline **136** as a yellow solid (7.7 mg, 7% yield). The product was confirmed via GC-MS analysis: (GC-MS (EI, 70 eV) m/z: **221.10 (100),** 118.10 (39), 205.10 (30), 77.05 (28), 76 (18) (**Figure 15**).

Figure 15. Mass spectrum of **136**.



Source: The author.

7.1.4.2 Synthesis of 3-phenyl-1*H*-indazole-5-carbonitrile (**137**)



3-phenyl-1*H*-indazole-5-carbonitrile **137** was prepared according to a modified procedure from Zhu and coworkers.[134] A mixture of 3-benzoyl-4-fluorobenzonitrile (112.6 mg, 0.5 mmol, 1 equiv.), 4-DMAP (61.1 mg, 0.5 mmol, 1 equiv.), and hydrazine monohydrate (0.24 mL, 5 mmol, 10 equiv.) in pyridine (3.0 mL) was kept at 110 °C (oil bath) for 14 h. Then, water was added (10 mL), and the reaction was extracted with ethyl acetate (3x10 mL). After drying with $MgSO_4$, filtration, and concentration under reduced pressure, it was purified by column chromatography (silica gel, hexanes/ethyl acetate 7:3) as a colorless oil (91%, 100 mg). **CAS**: 83684-54-2.

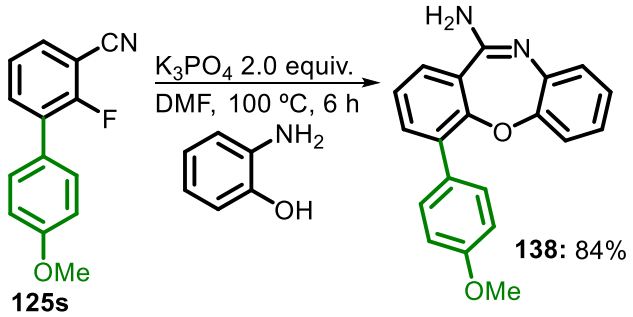
^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ [ppm] = 13.77 (s, 1H, -N<u>H</u>-), 8.69 (s, 1H), 8.06 – 8.03 (m, 2H), 7.77 (d, *J* = 8.7, 0.8 Hz, 1H), 7.73 (d, *J* = 8.7, 1.3 Hz, 1H), 7.56 – 7.52 (m, 2H), 7.47 – 7.43 (m, 1H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$): δ [ppm] = 144.6, 142.4, 132.4, 129.1 (2C), 128.4, 128.3, 127.8, 127.1 (2C), 119.8, 119.7, 112.2, 103.5.

GC-MS (EI, 70 eV) m/z: 219.05 (100%), 77.00 (26%), 218.05 (22%), 220.05 (18%), 192.00 (15%).

HRMS (ESI-TOF) m/z: $[M-H]^-$ Calcd for $C_{14}H_8N_3$ 218.0724; Found 218.0704.

7.1.4.3 Synthesis of 4-(4-methoxyphenyl)dibenzo[*b,f*][1,4]oxazepin-11-amine (**138**)



4-(4-methoxyphenyl)dibenzo[*b,f*][1,4]oxazepin-11-amine **138** was prepared according to the procedure of Wu and Feng.[135] A 5-mL pressure tube equipped with a stirring bar was charged with 2-fluoro-4'-methoxy-[1,1'-biphenyl]-3-carbonitrile (0.5 mmol, 113.6 mg), 2-aminophenol (0.75 mmol, 81.8 mg), K_3PO_4 (2 equiv., 1 mmol, 212.3 mg) and DMF (1 mL). The reaction was kept at 100 °C (oil bath) for 6 h, cooled to room temperature, quenched with distilled water, and extracted with ethyl acetate (3x 10 mL). The combined organic phases were dried with $MgSO_4$, and the product was purified by column chromatography (ethyl acetate/hexanes = 7:3) as a dark-red oil (84%, 134 mg).

^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ [ppm] = 7.67 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 6.89 – 6.85 (m, 2H), 6.85 – 6.79 (m, 2H), 6.56 (ddd, *J* = 8.8, 6.9, 2.0 Hz, 1H), 6.27 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.34 (bs, 2H), 3.76 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$): δ [ppm] = 159.6, 154.2, 146.3, 136.9, 135.8, 132.7, 130.0 (2C), 127.9, 125.8, 123.5, 119.6, 117.4, 115.7, 114.2, 114.1 (2C), 108.6, 55.4.

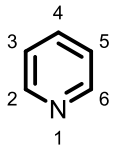
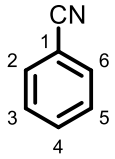
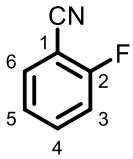
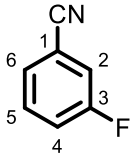
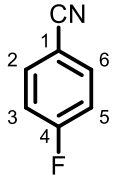
HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{17}N_2O_2$ 317.1285; Found 317.1268.

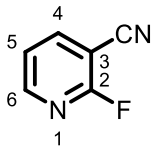
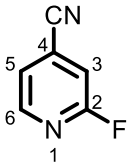
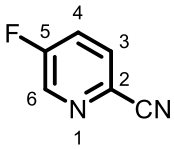
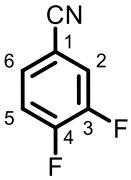
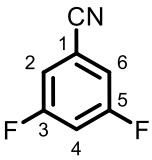
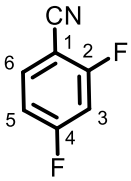
7.1.5 Computational study: p*K*$_a$ calculations

The p*K*$_a$ calculations were performed using hypothetical reactions which combine computational and experimental values, as suggested in some studies.[136] The deprotonated and neutral compounds had their geometries optimized in B3LYP/6-31+G(d,p) level in Gaussian 03 software.[137] The vibrational frequencies were calculated

with the same model[138] where all values were positive, which suggest the minimum in the potential energy surface. The solvent system (THF) was employed using the PCM model[139] at B3LYP/6-311++G(d,p) and the pyridine was the reference compound to the pK_a value (40.2 in THF).

Table 19 - Solvation Gibbs energies (G_{solv}), in Hartree, obtained by PCM/B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d,p) and pK_a values.

Compound	G_{solv}	pK_a
	Neutral (-248.355300)	H4 = 40.2
	Deprotonated **4** (-247.795888)	
	Neutral (-324.582271)	H2 = 37.4
	Deprotonated **2** (-324.028840)	H3 = 39.8
	Deprotonated **3** (-324.023759)	H4 = 39.9
	Deprotonated **4** (-324.023544)	
	Neutral (-423.846520)	H3 = 31.2
	Deprotonated **3** (-423.306607)	H4 = 36.7
	Deprotonated **4** (-423.294619)	H5 = 37.9
	Deprotonated **5** (-423.292130)	H6 = 34.3
	Deprotonated **6** (-423.299914)	
	Neutral (-423.848337)	H2 = 28.9
	Deprotonated **2** (-423.313463)	H4 = 31.3
	Deprotonated **4** (-423.308176)	H5 = 36.3
	Deprotonated **5** (-423.296727)	H6 = 35.4
	Deprotonated **6** (-423.299267)	
	Neutral (-423.849942)	H2 = 34.2
	Deprotonated **2** (-423.303580)	H3 = 31.1
	Deprotonated **3** (-423.310234)	

	Neutral (-439.893292) Deprotonated **4** (-439.358408) Deprotonated **5** (-439.349881) Deprotonated **6** (-439.344861)	H4 = 28.9 H5 = 32.8 H6 = 35.1
	Neutral (-439.893001) Deprotonated **3** (-439.365130) Deprotonated **5** (-439.354546) Deprotonated **6** (-439.344165)	H3 = 25.7 H5 = 30.6 H6 = 35.3
	Neutral (-439.884033) Deprotonated **3** (-439.348086) Deprotonated **4** (-439.355624) Deprotonated **6** (-439.343673)	H3 = 29.4 H4 = 25.9 H6 = 31.4
	Neutral (-523.108392) Deprotonated **2** (-522.581180) Deprotonated **5** (-522.576255) Deprotonated **6** (-522.565647)	H2 = 25.4 H5 = 27.7 H6 = 32.5
	Neutral (-523.112559) Deprotonated **2** (-522.581814) Deprotonated **4** (-522.590933)	H2 = 27.0 H4 = 22.8
	Neutral (-523.112488) Deprotonated **3** (-522.591403) Deprotonated **5** (-522.576637) Deprotonated **6** (-522.572945)	H3 = 22.6 H5 = 29.4 H6 = 31.1

7.2 CHAPTER II

7.2.1 General considerations

7.2.1.1 Solvents and reagents

Unless otherwise stated, all solvents and reagents were obtained from commercial suppliers and used without prior purification.

7.2.1.2 Analytical data

Chromatography: Chromatographic purification of products was performed as flash column chromatography on silica gel (35–70µm, Acros Organics) or with the automatic purification system Isolera Four (Biotage). Thin-layer chromatography (TLC) was carried out on silica plates (TLC Silica 60 F_{254} by Merck).

NMR spectra: NMR spectra were recorded on a Bruker Avance-II (^{1}H-NMR: 400MHz, ^{13}C-NMR: 100.6MHz; ^{19}F-NMR: 376 MHz) or on a Bruker Avance-III HD (^{1}H-NMR: 300 MHz, ^{13}C-NMR: 75.5 MHz) spectrometer. Chemical shifts are referenced to residual solvent signals (DMSO-d_6: 2.50 ppm and 39.52 ppm for ^{1}H-NMR and ^{13}C-NMR respectively) or using the spectrometer frequency (^{19}F-NMR, DMSO-d_6) and reported in parts per million (ppm). Coupling constants (J) are reported in Hz, and multiplicities of NMR signals are abbreviated as follows: bs = broad singlet, s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, td = triplet of doublets, m = multiplet and combinations thereof, app = apparent.

Infrared spectra: Infrared (IR) spectra were recorded on an FTIR-spectrometer (Bruker Tensor 27) equipped with a diamond ATR unit and are reported in terms of frequency of absorption ν [cm^{-1}].

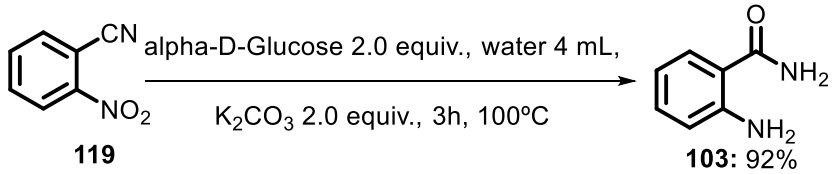
Mass spectra: Electron spray ionization (ESI) mass spectra were recorded on a 1200-series HPLC-system or a 1260-series Infinity II HPLC-system (Agilent-Technologies) with binary pump and integrated diode array detector coupled to an LC/MSDTrap-XTC-mass spectrometer (Agilent-Technologies) or an LC/MSD Infinitylab LC/MSD (G6125BLC/MSD). High-resolution masses were recorded on an Agilent 6545 QTOF instrument with a Lock Spray interface and a suitable external calibrant. Gas chromatographic investigations were carried out using an Agilent 8890 GC gas chromatograph (Agilent Technologies HP 5MS UI GC column (30 m x 0.25 mm x 0.25

µm) and helium as carrier gas with a flow rate of 1.2 mL/min) connected to a 5977 GC/MS detector and evaluated using the Mestrenova software.

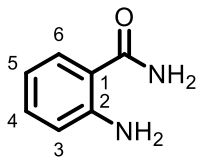
Melting point: Melting points were determined in open capillary tubes using a Krüss-OptronicKSP 1 N thermoelectric melting point meter.

7.2.2 Developed reactions

7.2.2.1 General procedure for the synthesis of 2-aminobenzamide



A test tube was charged with 2-nitrobenzonitrile (0.2 mmol, 1 equiv.), α-D-Glucose (0.4 mmol, 2.0 equiv.), K_2CO_3 (0.4 mmol, 2.0 equiv.) and 4 mL of deionized water and the reaction mixture kept at 100 ºC until total consumption of starting material (3h) checked by TLC. After extraction with AcOEt (3x10 mL), the organic phase was concentrated and the product purified by column chromatography (^{c}Hex:AcOEt 4:6) as a white solid (0.0251 g, 92%). CAS: 88-68-6.



Mp: 110-112 ºC.

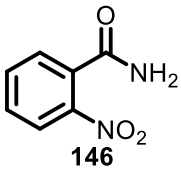
^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = δ 7.73 (bs, 1H, -CON<u>H</u>$_2$), 7.52 (dd, *J* = 8.1, 1.5 Hz, 1H, H-6), 7.12 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1H, H-4), 7.07 (s, 1H, -CON<u>H</u>$_2$), 6.67 (dd, *J* = 8.4, 1.2 Hz, 1H, H-3), 6.56 (s, 2H, -N<u>H</u>$_2$), 6.47 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H, H-5).

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 171.4 (-<u>C</u>ONH$_2$), 150.2 (C-2), 132.0 (C-4), 128.8 (C-6), 116.4 (C-3), 114.4 (C-5), 113.7 (C-1).

GC-MS: *m/z* (%) = 119.1 (100%), 136.1 (79%) [M].

Characterization data in accordance with the literature.[140]

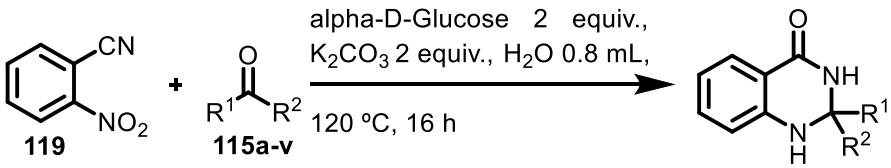
When the reaction was performed with Glucose 2 equiv., K_2CO_3 4 equiv., and 2-nitrobenzonitrile (0.2 mmol, 1 equiv.) in water (4 mL) at 50 ºC for 3h, 2-nitrobenzamide was obtained in 86% yield.



146

^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.16 (s, 1H, -CONH$_2$), 7.99 (dd, *J* = 8.1, 1.2 Hz, 1H, H-6), 7.76 (td, *J* = 7.5, 1.2 Hz, 1H, H-4), 7.69 (s, 1H, -CONH$_2$), 7.68 – 7.64 (m, 1H, H-5), 7.63 (dd, *J* = 7.5, 1.5 Hz, 1H, H-3). In accordance with the literature.[141]

7.2.2.2 General procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

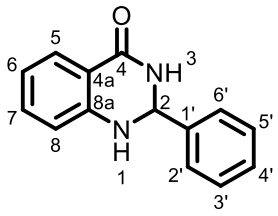


119 **115a-v** **120a-v**

A microwave reaction vial (5 mL, Biotage) was charged with 2-nitrobenzonitrile (0.5 mmol, 1 equiv.), α-D-Glucose (1.0 mmol, 2.0 equiv.), K_2CO_3 (1.0 mmol, 2.0 equiv.), 2.0 mL of deionized water and 1.5 equiv. of the respective aldehyde or ketone. The vial was sealed and the reaction mixture was kept at 120 ºC for 16 h under vigorous stirring. After removal of water in vacuo, the crude material was loaded onto silica gel for column chromatography (^{c}Hex:AcOEt 7:3 to 6:4) to afford the desired 2,3-dihydroquinazolin-4(*1H*)-one.

7.2.3 Characterization data of the synthesized 2,3-dihydroquinazolin-4(1*H*)-ones

1. 2-Phenyl-2,3-dihydroquinazolin-4(1*H*)-one (**120a**)



Yield: 72% (white solid, 0.0809g).

Rf: 0.43 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 218.8 –220.1°C (Lit.: 219 - 223°C).[71e]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3302, 3178, 3131, 3061, 3035, 1652, 1610, 1507, 1482, 808, 746, 698.

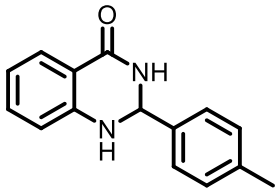
^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.29 (s, 1H, -CONH-), 7.61 (dd, *J* = 7.8, 1.6 Hz, 1H, H-5), 7.51-7.49 (m, 2H, H-2', H-6'), 7.41 – 7.32 (m, 3H, H-3', H4', H-5'), 7.24 (ddd, *J* = 8.5, 7.1, 1.7 Hz, 1H, H-7), 7.11 (s, 1H, -NH-), 6.75 (d, *J* = 7.1 Hz, 1H, H-8), 6.69-6.65 (m, 1H, H-6), 5.76 (s, 1H, H-2).

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.6 (C-4), 147.9 (C-8a), 141.69 (C-1'), 133.3 (C-7), 128.5 (C-3', C-5'), 128.3 (C-4'), 127.4 (C-5), 126.9 (C-2', C-6'), 117.1 (C-6), 115.0 (C-8), 114.4 (C-4a), 66.6 (C-2).

ESI-MS: (m/z) = 225.1 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+Na]^+$, calculated for $[C_{14}H_{12}N_2ONa]^+$ 247.0842, found 247.0843.

2. 2-(*p*-tolyl)-2,3-dihydroquinazolin-4(1*H*)-one (120b)



Yield: 77% (white solid, 0.0913g).

Rf: 0.41 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 220.4 –222.5°C (Lit.: 221 - 223°C).[142]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3311, 3190, 3132, 3053, 2918, 1670, 1656, 1606, 1506, 1483, 798, 775, 749.

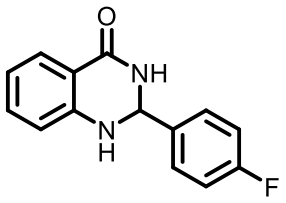
^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.23 (s, 1H, -CONH-), 7.60 (dd, *J* = 7.8, 1.6 Hz, 1H, H-5), 7.37 (d-like, *J* = 8.0 Hz, 2H, H-2', H-6'), 7.25 – 7.21 (m, 1H, H-7), 7.19 (d-like, *J* = 8 Hz, 2H, H-3', H-5'), 7.05 (s, 1H, -NH-), 6.74 (d, *J* = 7.7 Hz, 1H, H-8), 6.68 – 6.64 (m, 1H, H-6), 5.71 (s, 1H, H-2), 2.29 (s, 3H, -CH$_3$).

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.6 (C-4), 147.9 (C-8a), 138.7 (C-1'), 137.7 (C-4'), 133.3 (C-7), 128.8 (C-3', C-5'), 127.3 (C-5), 126.8 (C-2', C-6'), 117.1 (C-6), 115.0 (C-8), 114.4 (C-4a), 66.4 (C-2), 20.7 (-CH$_3$).

ESI-MS: (m/z) = 239.1 (100%, [M+H]$^+$).

ESI-HRMS (m/z): [M+Na]$^+$, calculated for [$C_{15}H_{14}N_2ONa$]$^+$ 261.0998, found 261.0995.

3. 2-(4-Fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (120c)



Yield: 65% (white solid, 0.0787g).

Rf: 0.43 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 196.2 –198.4°C (Lit.: 198 - 199°C).[143]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3298, 3180, 3125, 3067, 3042, 2936, 1665, 1651, 1604, 1504, 1481, 839, 808, 793, 756.

^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.29 (s, 1H, -CONH-), 7.62 (dd, *J* = 7.7, 1.6 Hz, 1H, H-5), 7.56-7.51 (m, 2H, H-2', H-6'), 7.27-7.20 (m, 3H, H-7, H-3', H-5'),

7.10 (s, 1H, -N<u>H</u>-), 6.75 (dd, *J* = 8.2, 1.0 Hz, 1H, H-8), 6.70-6.66 (m, 1H, H-6), 5.78 (s, 1H, H-2).

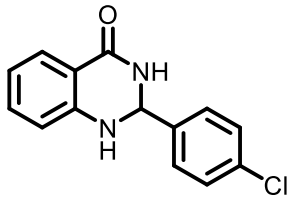
^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.6 (C-4), 162.1 (C-4', $^1J_{C-F}$ = 244.0 Hz), 147.8 (C-8a), 137.8 (C-1', $^4J_{C-F}$ = 2.9 Hz), 133.4 (C-7), 129.1 (C2', C-6', $^3J_{C-F}$ = 8.3 Hz), 127.4 (C-5), 117.3 (C-6), 115.1 (C-3', C-5', $^2J_{C-F}$ = 21.5 Hz), 115.0 (C-8), 114.4 (C-4a), 65.9 (C-2).

^{19}F NMR (376 MHz, DMSO-*d*$_6$): δ [ppm] = -115.0 (m, F).

ESI-MS: (m/z) = 243.1 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+H]^+$, calculated for $[C_{14}H_{12}FN_2O]^+$ 243.0928, found 243.0932.

4. 2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (120d)



Yield: 61% (white solid, 0.0793g).

Rf: 0.48 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 197.0 –199.6°C. (Lit.: 197 - 198°C).[144]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3307, 3184, 3129, 3066, 2937, 1666, 1652, 1607, 1506, 1482, 835, 789, 750.

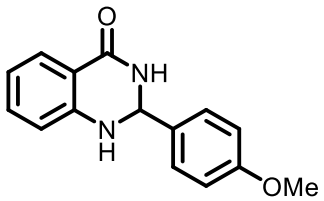
^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.34 (s, 1H, -CON<u>H</u>-), 7.61 (dd, *J* = 7.7, 1.6 Hz, 1H, H-5), 7.52 – 7.49 (m, 2H, H-2', H-6'), 7.47 – 7.45 (m, 2H, H-3', H-5'), 7.25 (ddd, *J* = 8.7, 7.2, 1.6 Hz, 1H, H-7), 7.14 (s, 1H, -N<u>H</u>-), 6.75 (dd, *J* = 8.7, 1.1 Hz, 1H, H-8), 6.70-6.66 (m, 1H, H-6), 5.77 (s, 1H, H-2).

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.5 (C-4), 147.7 (C-8a), 140.7 (C-1'), 133.4 (C-7), 133.0 (C-4'), 128.8 (C-3', C-5'), 128.3 (C2', C6'), 127.4 (C-5), 117.3 (C-6), 114.9 (C-8), 114.5 (C-4a), 65.8 (C-2).

ESI-MS: (m/z) = 259.0 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+H]^+$, calculated for $[C_{14}H_{12}ClN_2O]^+$ 259.0633, found 259.0632.

5. 2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (120e)



Yield: 75% (white solid, 0.0959g).

Rf: 0.42 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 187.4 –189.2°C. (Lit.: 185 - 187°C).[145]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3297, 3176, 3013, 2832, 1651, 1608, 1590, 1504, 1483, 834, 793, 753.

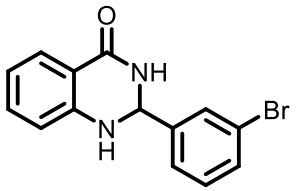
^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.19 (s, 1H, -CONH-), 7.61 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.44 – 7.40 (m, 2H, H-2', H-6'), 7.24 (ddd, *J* = 8.2, 7.2, 1.6 Hz, 1H, H-7), 7.01 (s, 1H, -NH-), 6.96 – 6.93 (m, 2H, H-3', H5'), 6.74 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.69 – 6.65 (m, 1H), 5.71 (s, 1H, H-2), 3.75 (s, 3H, -OMe).

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.7 (C-4), 159.4 (C-4'), 148.0 (C-8a), 133.5 (C-7), 133.2 (C-1'), 128.2 (C-2', C-6'), 127.3 (C-5), 117.1 (C-6), 115.0 (C-8), 114.4 (C-4a), 113.6 (C-3', C-5'), 66.3 (C-2), 55.2 (-OMe).

ESI-MS: (m/z) = 255.1 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+Na]^+$, calculated for $[C_{15}H_{14}N_2O_2Na]^+$ 277.0947, found 277.0950.

6. 2-(3-Bromophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (120f)



Yield: 58% (white solid, 0.0875g).

Rf: 0.42 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 176.4 –178.8°C. (Lit.: 184 - 185°C).[146]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3275, 3177, 3056, 1646, 1612, 1509, 1474, 745, 696, 679.

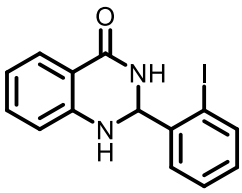
^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.39 (s, 1H, -CONH-), 7.67 (t, *J* = 1.9 Hz, 1H, H-2'), 7.60 (dd, *J* = 7.8, 1.6 Hz, 1H, H-5), 7.54 (ddd, *J* = 7.9, 2.1, 1.0 Hz, 1H, H-4'), 7.48 (d, *J* = 7.8 Hz, 1H, H-6'), 7.35 (t, *J* = 7.8 Hz, 1H, H-5'), 7.25 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H, H-7), 7.21 (s, 1H, -NH-), 6.77 – 6.75 (m, 1H, H-8), 6.70 – 6.66 (m, 1H, H-6), 5.77 (s, 1H, H-2).

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.4 (C-4), 147.5 (C-8a), 144.6 (C-1'), 133.5 (C-7), 131.2 (C-6'), 130.6 (C-5'), 129.7 (C-2'), 127.4 (C-5), 125.8 (C-4'), 121.6 (C-3'), 117.3 (C-6), 114.9 (C-8), 114.5 (C-4a), 65.5 (C-2).

ESI-MS: (m/z) = 303.0 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+H]^+$, calculated for $[C_{14}H_{12}BrN_2O]^+$ 303.0128, found 303.0128.

7. 2-(2-Iodophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (120g)



Yield: 56% (white solid, 0.0989g).

Rf: 0.55 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 178.4 –179.4°C.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3299, 3177, 3050, 2923, 2848, 1652, 1630, 1611, 1508, 1486, 1443, 745.

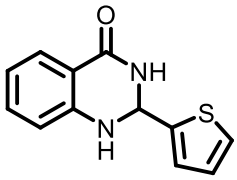
^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.17 (s, 1H, -CONH-), 7.90 (dd, *J* = 7.9, 1.2 Hz, 1H, H-3'), 7.67 (dd, *J* = 7.8, 1.7 Hz, 1H, H-5), 7.66 (dd, *J* = 7.7, 1.7 Hz, 1H, H-6'), 7.47 (app-td, *J* = 7.7, 1.2 Hz, 1H, H-5'), 7.27 (ddd, *J* = 8.8, 7.1, 1.7 Hz, 1H, H-7), 7.18 – 7.14 (m, 1H, H-4'), 6.96 (bs, 1H, -NH-), 6.77 (app-d, *J* = 8.8 Hz, 1H, H-8), 6.75 – 6.71 (m, 1H, H-6), 5.96 (s, 1H, H-2).

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.6 (C-4), 147.9 (C-8a), 141.5 (C-1'), 139.3 (C-3'), 133.4 (C-7), 131.0 (C-4'), 129.0 (C-6'), 128.7 (C-5'), 127.4 (C-5), 117.6 (C-6), 114.8 (C-8), 114.6 (C-4a), 99.0 (C-2'), 71.7 (C-2).

ESI-MS: (m/z) = 351.0 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+Na]^+$, calculated for $[C_{14}H_{11}IN_2ONa]^+$ 372.9808, found 372.9812.

8. 2-(Thiophen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (120h)



Yield: 59% (white solid, 0.0676g).

Rf: 0.33 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 198.9 –201.1°C. (Lit.: 210 - 212°C).[147]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3292, 3171, 3058, 2935, 1651, 1608, 1516, 1487, 1439, 763, 710, 683.

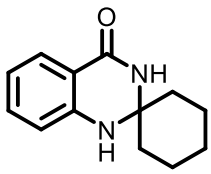
^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.45 (s, 1H, -CONH-), 7.62 (dd, *J* = 7.7, 1.6 Hz, 1H, H-5), 7.45 (dd, *J* = 5.0, 1.3 Hz, 1H, H-3'), 7.28 – 7.24 (m, 2H, -NH-, H-7), 7.13 (d, *J* = 3.5 Hz, 1H, H-5'), 6.98 (dd, *J* = 5.0, 3.5 Hz, 1H, H-4'), 6.76 (d, 1H, *J* = 8.0 Hz, H-8), 6.70 (t, 1H, *J* = 7.7 Hz, H-6), 6.02 (s, 1H, H-2).

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.1 (C-4), 147.2 (C-8a), 146.4 (C-2'), 133.4 (C-7), 127.3 (C-5), 126.5 (C-4'), 125.9 (C-3'), 125.7 (C-5'), 117.5 (C-6), 115.1 (C-8), 114.7 (C-4a), 62.6 (C-2).

ESI-MS: (m/z) = 231.0 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+Na]^+$, calculated for $[C_{12}H_{10}N_2OSNa]^+$ 253.0406, found 253.0409.

9. 1'*H*-spiro[cyclohexane-1,2'-quinazolin]-4'(3'*H*)-one (120i)



Yield: 79% (white solid, 0.0856g).

Rf: 0.29 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 220.8 –223.1°C. (Lit.: 223 - 224°C).[148]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3366, 3169, 3024, 2936, 2923, 2851, 1645, 1608, 1503, 1482, 754.

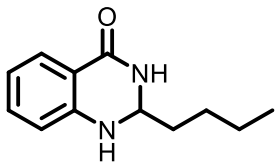
^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 7.92 (s, 1H, -CONH-), 7.56 (dd, *J* = 7.7, 1.6 Hz, 1H, H-5'), 7.21 (ddd, *J* = 8.3, 7.2, 1.6 Hz, 1H, H-7'), 6.80 (d, *J* = 8.3 Hz, 1H, H-8'), 6.63 – 6.59 (m, 2H, -NH-, H-6'), 1.76 – 1.73 (m, 2H, -CH_2-), 1.63 – 1.53 (m, 6H, -CH_2-), 1.45 – 1.23 (m, 2H, -CH_2-).

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.2 (C-4'), 146.8, (C-8a') 133.1 (C-7'), 127.1 (C-5'), 116.5 (C-6'), 114.6 (C-8'), 114.4 (C-4a'), 67.8 (C-1), 37.2 (-CH_2-), 24.6 (-CH_2-), 20.9 (-CH_2-).

ESI-MS: (m/z) = 217.1 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+Na]^+$, calculated for $[C_{13}H_{16}N_2ONa]^+$ 239.1155, found 239.1156.

10. 2-Butylquinazolin-4(3*H*)-one (120j)



Yield: 56% (white solid, 0.0598g).

Rf: 0.32 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 142.4 –144.4°C. (Lit.: 144 - 146°C).[149]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3339, 3296, 3189, 3069, 2970, 2921, 2855, 1643, 1610, 1501, 1483, 758.

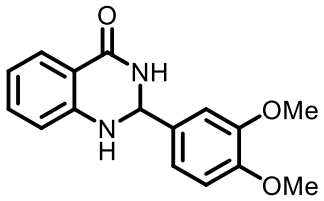
^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 7.88 (s, 1H, -CON<u>H</u>-), 7.57 (dd, *J* = 7.7, 1.6 Hz, 1H, H-5), 7.24-7.20 (m, 1H, H-7), 6.72 (d, *J* = 7.9 Hz, 1H, H-8), 6.66 – 6.63 (m, 1H, H-6), 6.56 (s, 1H, -N<u>H</u>-), 4.68 (t, 1H, *J* = 5.2 Hz, H-2), 1.65 – 1.60 (m, 2H, H-1'), 1.43 – 1.35 (m, 2H, H-2'), 1.33 – 1.24 (m, 2H, H-3'), 0.88 (t, *J* = 7.2 Hz, 3H, H-4').

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.9 (C-4), 148.5 (C-8a), 133.0 (C-7), 127.3 (C-5), 116.9 (C-6), 115.0 (C-8), 114.4 (C-4a), 64.4 (C-2), 34.7 (C-1'), 25.4 (C-2'), 22.1 (C-3'), 13.9 (C-4').

ESI-MS: (m/z) = 205.1 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+Na]^+$, calculated for $[C_{12}H_{16}N_2ONa]^+$ 227.1155, found 227.1159.

11. 2-(3,4-Dimethoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (120k)



Yield: 90% (white solid, 0.1276g).

Rf: 0.18 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 212.6 –214.8°C. (Lit.: 212 - 214°C).[150]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3354, 3333, 3177, 2967, 2935, 2836, 1667, 1609, 1497, 1481, 1460, 1142, 1017, 769, 755.

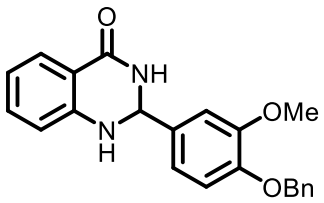
^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.18 (s, 1H, -CONH-), 7.62 (dd, *J* = 7.8, 1.6 Hz, 1H, H-5), 7.24 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H, H-7), 7.13 (d, *J* = 2.0 Hz, 1H, H-2'), 7.01 – 6.98 (m, 2H, -NH-, H-6'), 6.94 (d, *J* = 8.3 Hz, 1H, H-5'), 6.75 (d, 1H, *J* = 8.8 Hz, H-8), 6.70 – 6.66 (m, 1H, H-6), 5.70 (s, 1H, H-2), 3.75 (d, 6H, -(OCH_3)$_2$).

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.7 (C-4), 149.0 (C-4'), 148.6 (C-3'), 148.1(C-8a), 133.6 (C-7), 133.2 (C-1'), 127.3 (C-5), 119.2 (C-6'), 117.1 (C-6), 115.1 (C-8), 114.4 (C-4a), 111.3 (C-5'), 110.6 (C-2'), 66.5 (C-2), 55.6 (-OCH_3), 55.5 (-OCH_3).

ESI-MS: (m/z) = 285.1 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+Na]^+$, calculated for $[C_{16}H_{16}N_2O_3Na]^+$ 307.1053, found 307.1057.

12. 2-(4-(Benzyloxy)-3-methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (120l)



Yield: 63% (white solid, 0.1130g).

Rf: 0.35 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 155.1 –156.2°C.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3361, 3174, 3079, 3060, 2913, 2869, 1655, 1611, 1503, 1485, 1467, 1138, 747.

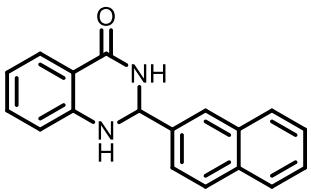
^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.18 (s, 1H, -CONH-), 7.62 (dd, *J* = 7.8, 1.6 Hz, 1H, H-5), 7.45 – 7.30 (m, 5H, -OBn, H_{Ar}), 7.24 (ddd, *J* = 8.1, 7.2, 1.6 Hz, 1H, H-7), 7.16 (d, *J* = 1.9 Hz, 1H, H-2'), 7.04 – 7.02 (m, 2H, -NH-, H-5'), 6.97 (dd, *J* = 8.3, 1.9 Hz, 1H, H-6'), 6.75 (d, *J* = 8.1 Hz, 1H, H-8), 6.70 – 6.66 (m, 1H, H-6), 5.69 (s, 1H, H-2), 5.09 (s, 2H, -CH_2-), 3.78 (s, 3H, -OCH_3).

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.7 (C-4), 149.0 (C-3'), 148.1 (C-4'), 147.9 (C-8a), 137.1 (-OBn, C_{Ar}), 134.0 (C-1'), 133.2(C-7), 128.4 (-OBn, CH_{Ar}), 127.8 (-OBn, CH_{Ar}), 127.7 (-OBn, CH_{Ar}), 127.3 (C-5), 119.2 (C-6'), 117.1 (C-6), 115.1 (C-8), 114.4 (C-4a), 113.0 (C-5`), 110.9 (C-2'), 69.8 (-CH_2-), 66.5 (C-2), 55.6 (-OCH_3).

ESI-MS: (m/z) = 361.2 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+H]^+$, calculated for $[C_{22}H_{21}N_2O_3]^+$ 361.1547, found 361.1552.

13. 2-(Naphthalen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (120m)



Yield: 71% (white solid, 0.1329g).

Rf: 0.45 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 201.4 –202.4°C. (Lit.: 224 - 225°C).[151]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3279, 3182, 3051, 3021, 1660, 1646, 1607, 1508, 1484, 1440, 1297, 742.

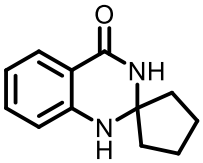
^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.38 (s, 1H, -CONH-), 7.96 – 7.91 (m, 4H, H-1', H-4', H-8', H-5'), 7.71 (dd, *J* = 8.6, 1.7 Hz, 1H, H-3'), 7.65 (dd, *J* = 7.7, 1.6 Hz, 1H, H-5), 7.56 – 7.51 (m, 2H, H-6', H-7'), 7.26 (ddd, *J* = 8.2, 7.2, 1.6 Hz, 1H, H-7), 7.20 (s, 1H, -NH-), 6.77 (dd, *J* = 8.2, 1.0 Hz, 1H, H-8), 6.71 – 6.67 (m, 1H, H-6), 5.94 (s, 1H, H-2).

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.6 (C-4), 147.9 (C-8a), 138.9 (C-2'), 133.4 (C-7), 133.0 (C-8a'), 132.5 (C-4a'), 128.1 (C-8'), 128.0 (C-5'), 127.6 (4'), 127.4 (C-5), 126.4 (C-6'), 126.4 (C7'), 125.9 (C-1'), 124.9 (C-3'), 117.2 (C-6), 115.0 (C-8), 114.4 (C-4a), 66.8 (C-2).

ESI-MS: (m/z) = 275.1 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+Na]^+$, calculated for $[C_{18}H_{14}N_2ONa]^+$ 297.0998, found 297.1000.

14. 1'*H*-spiro[cyclopentane-1,2'-quinazolin]-4'(3'*H*)-one (120n)



Yield: 61% (white solid, 0.0619).

Rf: 0.23 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 252.0 –253.4°C. (Lit.: 254 - 256°C).[152]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3289, 3162, 3001, 2972, 2941, 2877, 1635, 1613, 1542, 1516, 1459, 803, 779, 751.

^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.09 (s, 1H, -CONH-), 7.57 (dd, *J* = 7.7, 1.6 Hz, 1H, H-5'), 7.21 (ddd, *J* = 8.2, 7.3, 1.6 Hz, 1H, H-7'), 6.74 (s, 1H, -NH-), 6.69

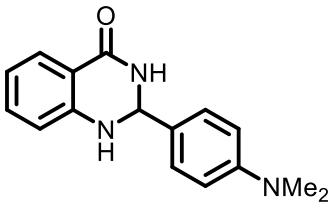
(d, *J* = 8.2 Hz, 1H, H-8'), 6.64 – 6.60 (m, 1H, H-6'), 1.82 – 1.75 (m, 4H, -C<u>H</u>$_2$-), 1.69 – 1.63 (m, 4H, -C<u>H</u>$_2$-).

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.4 (C-4'), 147.5 (C-8a'), 133.0 (C-7'), 127.2 (C-5'), 116.5 (C-6'), 114.6 (C-8'), 114.3 (C-4a'), 77.1 (C-1), 22.0 (4C, -<u>C</u>H$_2$-).

ESI-MS: (m/z) = 203.1 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+Na]^+$, calculated for $[C_{12}H_{14}N_2ONa]^+$ 225.0998, found 225.1000.

15. 2-(4-(Dimethylamino)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (120o)



Yield: 63% (white solid, 0.0848g).

Rf: 0.30 (SiO_2, ^{c}Hex/EtOAc 4:6).

Mp: 200.1 –201.6°C. (Lit.: 201 - 203°C).[153]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3291, 3187, 3052, 3031, 2980, 2891, 2803, 1665, 1650, 1609, 1509, 1483, 1436, 817, 798, 749, 730.

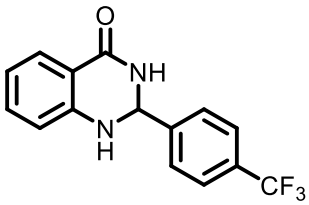
^{1}H-NMR, COSY (400 MHz, DMSO-*d*$_6$): δ [ppm] = 8.07 (s, 1H, -CON<u>H</u>-), 7.61 (dd, *J* = 7.8, 1.6 Hz, 1H, H-5), 7.30 (d-like, *J* = 8.8 Hz, 2H, H-2', H-6'), 7.22 (ddd, *J* = 8.1, 7.2, 1.6 Hz, 1H, H-7), 6.92 (s, 1H, -N<u>H</u>-), 6.74 – 6.70 (m, 3H, H-8, H-3', H-5'), 6.68 – 6.64 (m, 1H, H-6), 5.63 (s, 1H, H-2), 2.88 (s, 6H, -N(C<u>H</u>$_3$)$_2$).

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$): δ [ppm] = 163.8 (C-4), 150.7 (C-4'), 148.2 (C-8a), 133.1 (C-7), 128.6 (C-1'), 127.7 (C-2', C-6'), 127.3 (C-5), 116.9 (C-6), 115.0 (C-8), 114.4 (C-4a), 111.9 (C-3', C-5'), 66.6 (C-2), 40.2 – 39.0 (-N(<u>C</u>H$_3$)$_2$).

ESI-MS: (m/z) = 268.1 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+Na]^+$, calculated for $[C_{16}H_{17}N_3ONa]^+$ 290.1264, found 290.1267.

16. 2-(4-(Trifluoromethyl)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (120p)



Yield: 55% (white solid, 0.0798g).

Rf: 0.49 (SiO_2, ^{c}Hex/EtOAc 7:3).

Mp: 191.8 –194.1°C. (Lit.: 193 - 195°C).[154]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3297, 3184, 1666, 1651, 1613, 1514, 1487, 1325, 1129, 1163, 852, 797, 759.

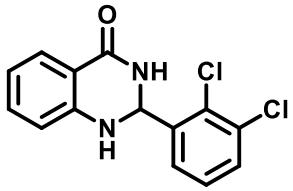
^{1}H-NMR, COSY (300 MHz, DMSO-*d*$_6$): δ [ppm] = 8.44 (s, 1H, -CON<u>H</u>-), 7.78 (d-like, *J* = 8.3 Hz, 2H, H-3', H-5'), 7.70 (d-like, *J* = 8.3 Hz, 2H, H-2', H-6'), 7.61 (dd, *J* = 7.8, 1.6 Hz, 1H, H-5), 7.28 – 7.23 (m, 2H, H-7, -N<u>H</u>-), 6.76 (d, *J* = 8.0 Hz, 1H, H-8), 6.69 (t, *J* = 7.8 Hz, 1H, H-6), 5.86 (s, 1H, H-2).

^{13}C-NMR, HSQC, HMBC (75 MHz, DMSO-*d*$_6$): δ [ppm] = 163.4 (C-4), 147.5 (C-8a), 146.4 (C-1'), 133.5 (C-7), 129.0 (q, $^2J_{C\text{-}F}$ = 32.0 Hz, C-4'), 127.7 (C-2', C6'), 127.4 (C-5), 124.2 (q, $^1J_{C\text{-}F}$ = 272.2 Hz, -<u>C</u>F$_3$), 125.4 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, C-3', C-5'), 117.4 (C-6), 114.9 (C-8), 114.5 (C-4a), 65.7 (C-2).

ESI-MS: (m/z) = 293.1 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+H]^+$, calculated for $[C_{15}H_{12}F_3N_2O]^+$ 293.0896, found 293.0898.

17. 2-(2,3-Dichlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (120q)



Yield: 23% (white solid, 0.0331g).

Rf: 0.45 (SiO_2, ^{c}Hex/EtOAc 1:1).

Mp: 227.3 –228.9°C. (Lit.: 232 - 233°C).[155]

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3274, 1656, 1613, 1509, 1487, 1449, 1415, 1381, 1325, 1158, 755, 715.

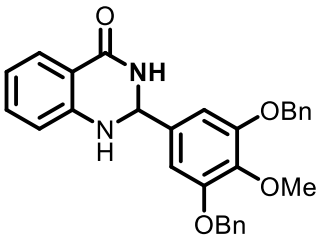
^{1}H-NMR, COSY (300 MHz, DMSO-*d*$_6$): δ [ppm] = 8.27 (s, 1H, -CONH-), 7.68 – 7.64 (m, 2H, H-5, H-4'), 7.61 (dd, *J* = 7.9, 1.5 Hz, 1H, H-6'), 7.42 (t, *J* = 7.9 Hz, 1H, H-5'), 7.27 (ddd, *J* = 8.2, 7.2, 1.6 Hz, 1H, H-7), 7.08 (s, 1H, -NH-), 6.77 – 6.69 (m, 2H, H-6, H-8), 6.18 (appt, *J* = 1.9 Hz, 1H, H-2).

^{13}C-NMR, HSQC, HMBC (75 MHz, DMSO-*d*$_6$): δ [ppm] = 163.5 (C-4), 147.4 (C-8a), 140.6 (C-1'), 133.6 (C-7), 132.0 (C-3'), 130.6 (C-4`), 129.9 (C-2'), 128.4 (C-5'), 127.4 (C-5), 127.2 (C-6'), 117.6 (C-6), 114.6 (C-8), 114.6 (C-4a), 64.3 (C-2).

ESI-MS: (m/z) = 293.1 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+Na]^+$, calculated for $[C_{14}H_{10}Cl_2N_2O]^+$ 315.0062, found 315.0062.

18. 2-(3,5-Bis(benzyloxy)-4-methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (120r)



Yield: 18% (oil, 0.0410g).

Rf: 0.41 (SiO_2, ^{c}Hex/EtOAc 1:1).

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3418, 2255, 1657, 1615, 1503, 1488, 1440, 1236, 1049, 1025, 1004, 824, 762, 700.

^{1}H-NMR, COSY (300 MHz, DMSO-*d*$_6$): δ [ppm] = 8.24 (s, 1H, -CONH-), 7.64 (dd, *J* = 7.8, 1.6 Hz, 1H, H-5), 7.47 – 7.33 (m, 10H, -OBn, H_{Ar}), 7.27 (ddd, *J* = 8.5, 7.4, 1.6 Hz, 1H, H-7), 7.08 (s, 1H, -NH-), 7.00 (s, 2H, H-2', H-6'), 6.78 (app-d, *J* = 8.5 Hz, 1H, H-8), 6.73 – 6.68 (m, 1H, H-6), 5.69 (s, 1H, H-2), 5.09 (s, 4H, -CH_2-), 3.70 (s, 3H, -OCH_3).

^{13}C-NMR, HSQC, HMBC (75 MHz, DMSO-*d*$_6$): δ [ppm] = 163.7 (C-4), 152.0 (C-5', C-3'), 147.9 (C-8a), 138.5 (C-4'), 136.9 (2C, -OBn, C*q*), 136.9 (C-1'), 133.4 (C-7), 128.5 (4C, -OBn, CH_{Ar}), 127.9 (2C, -OBn, CH_{Ar}), 127.7 (4C, -OBn, CH_{Ar}), 127.4 (C-5), 117.3 (C-6), 115.0 (C-8), 114.5 (C-4a), 106.2 (C-2', C-6'), 70.2 (2C, -CH_2-), 66.7 (C-2), 60.1 (-OCH_3).

ESI-MS: (m/z) = 467.2 (100%, $[M+H]^+$).

ESI-HRMS (m/z): $[M+H]^+$, calculated for $[C_{29}H_{27}N_2O_4]^+$ 467.1966, found 467.1964.

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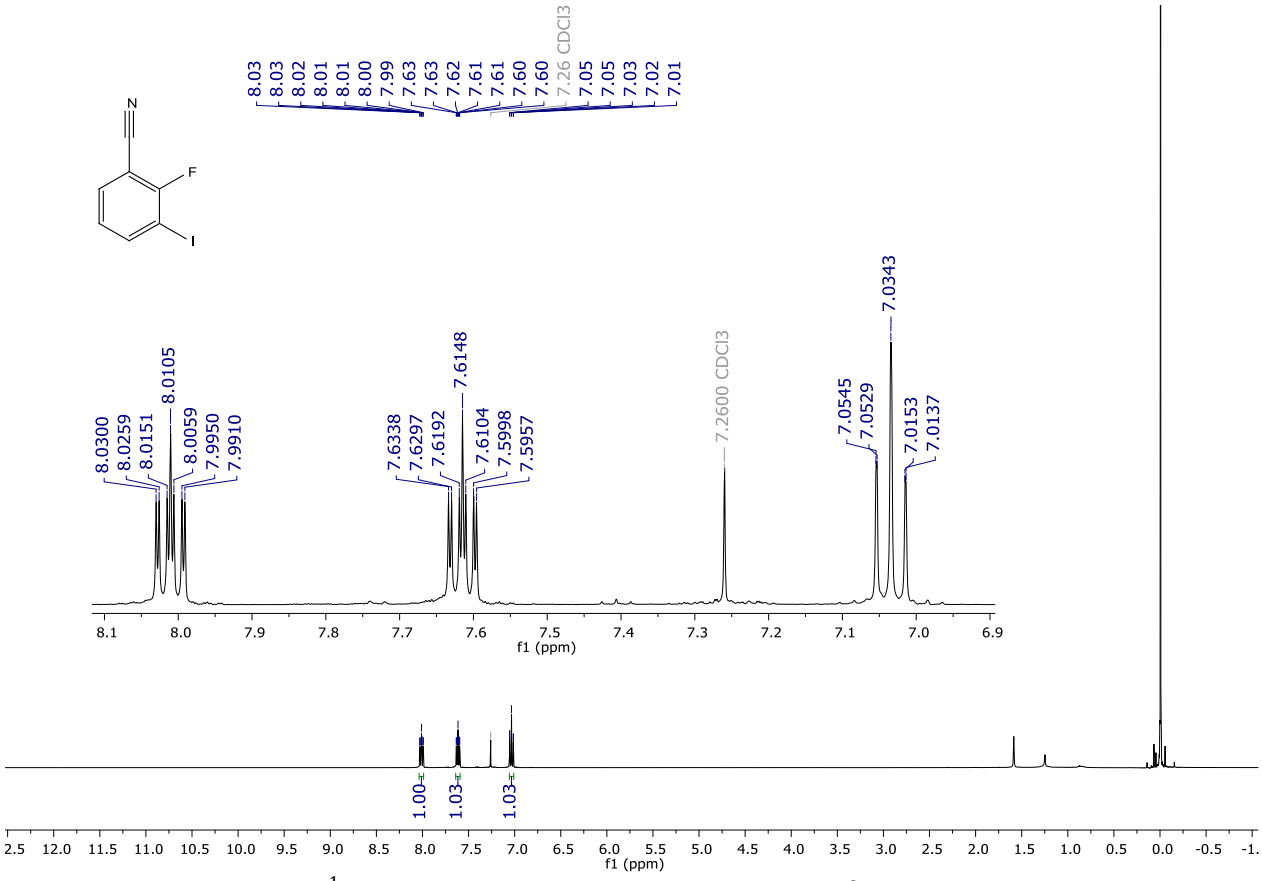
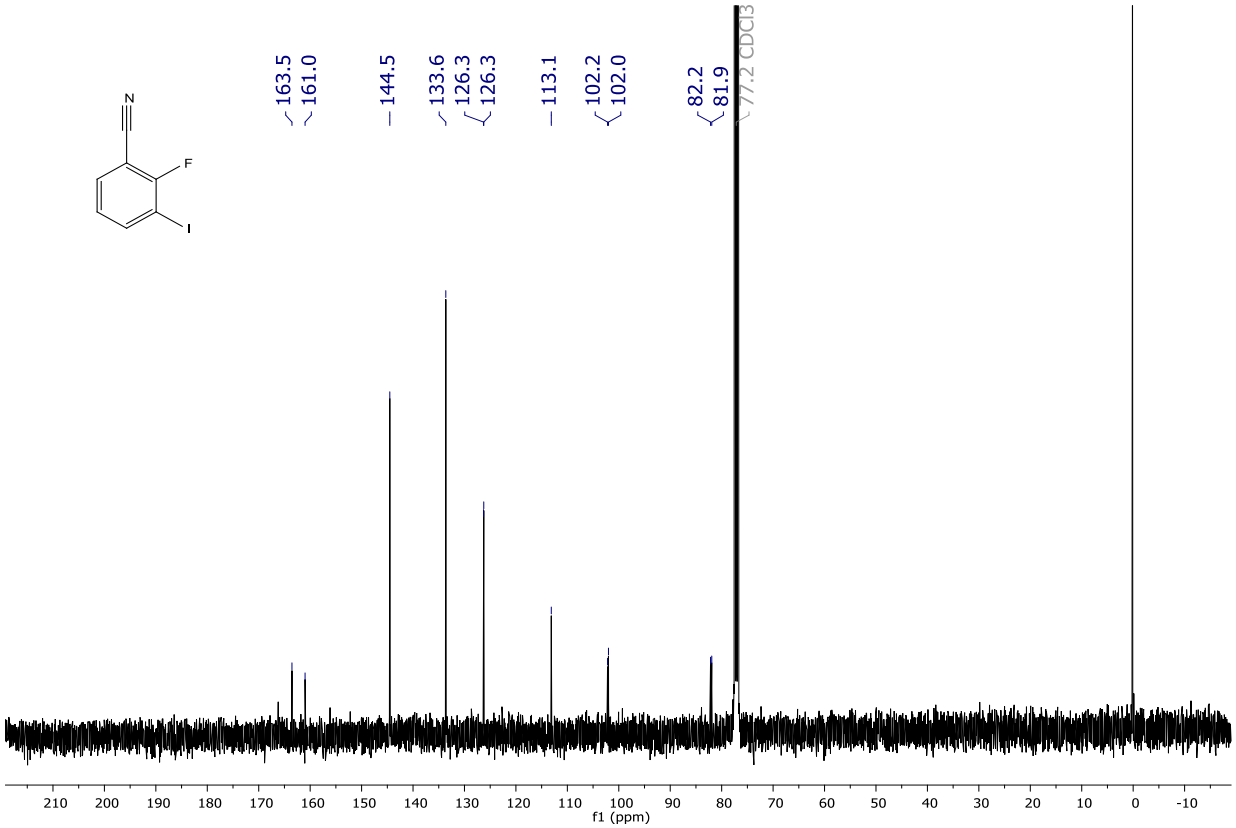
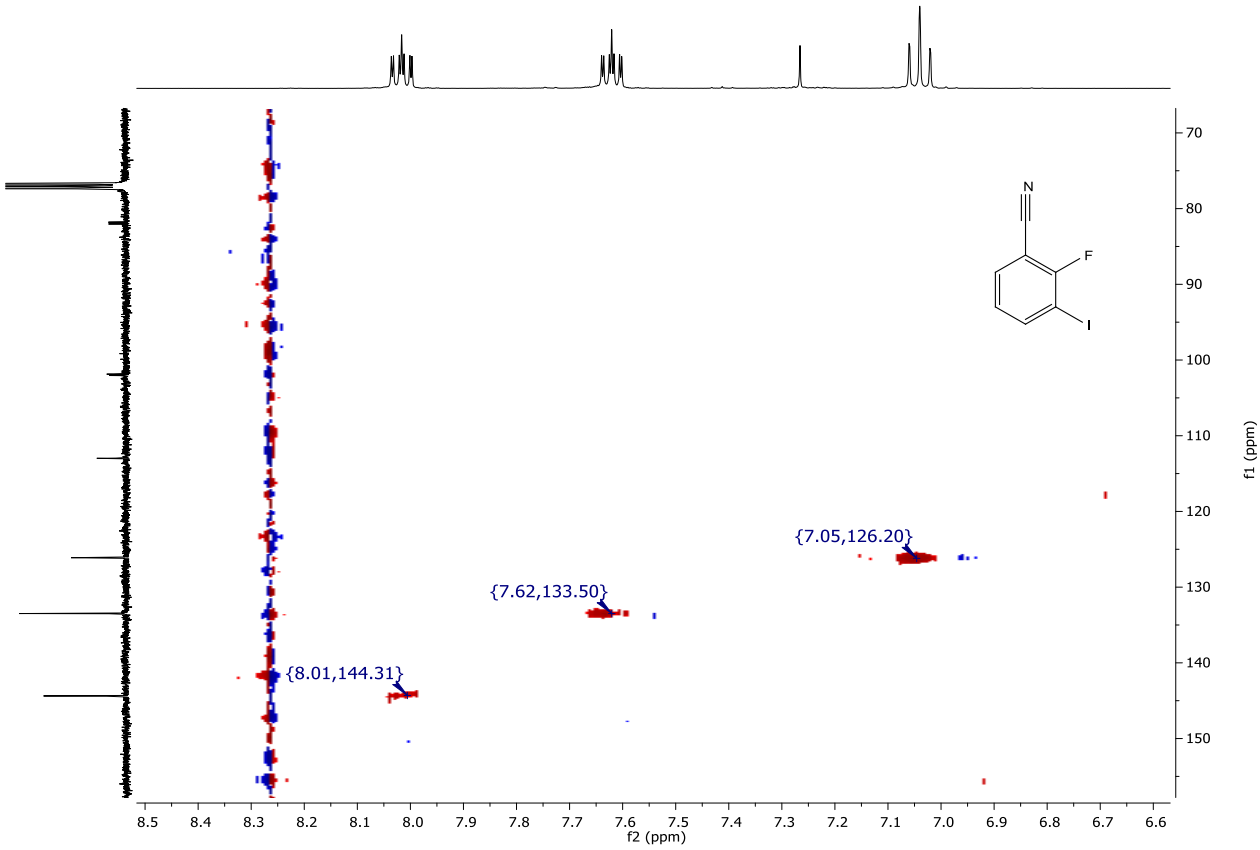
APPENDIX A - NMR SPECTRA



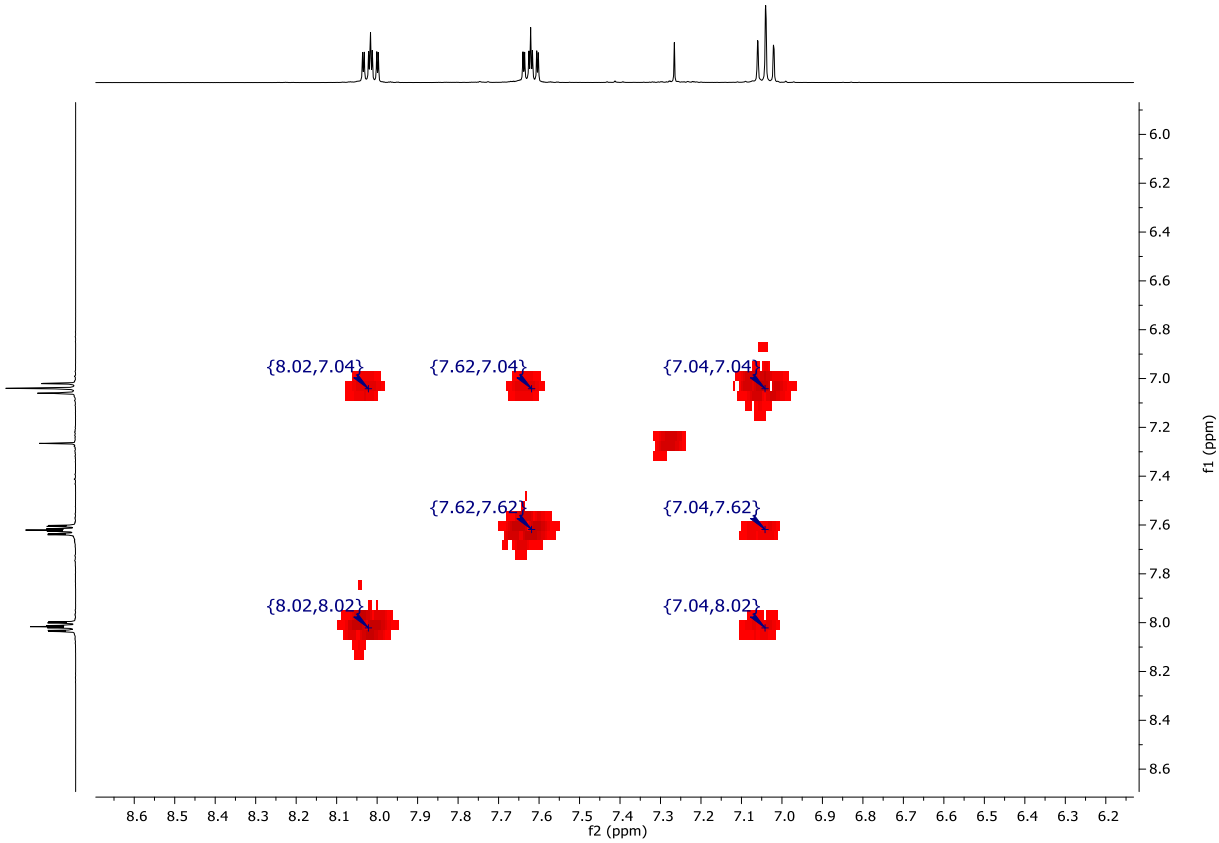
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125a.**



^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) spectrum of **125a**.

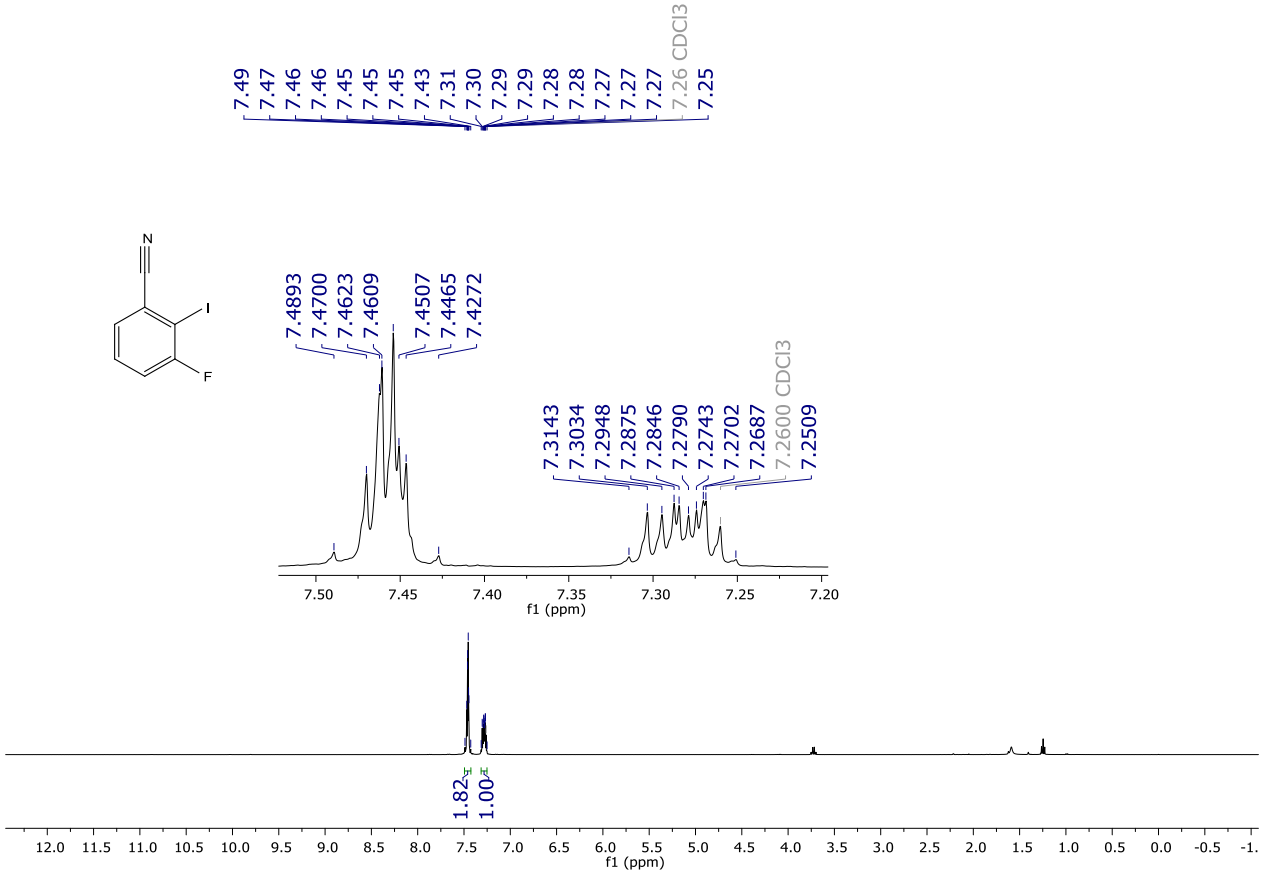


HSQC correlation map of **125a** (400 and 101 MHz, $CDCl_3$).

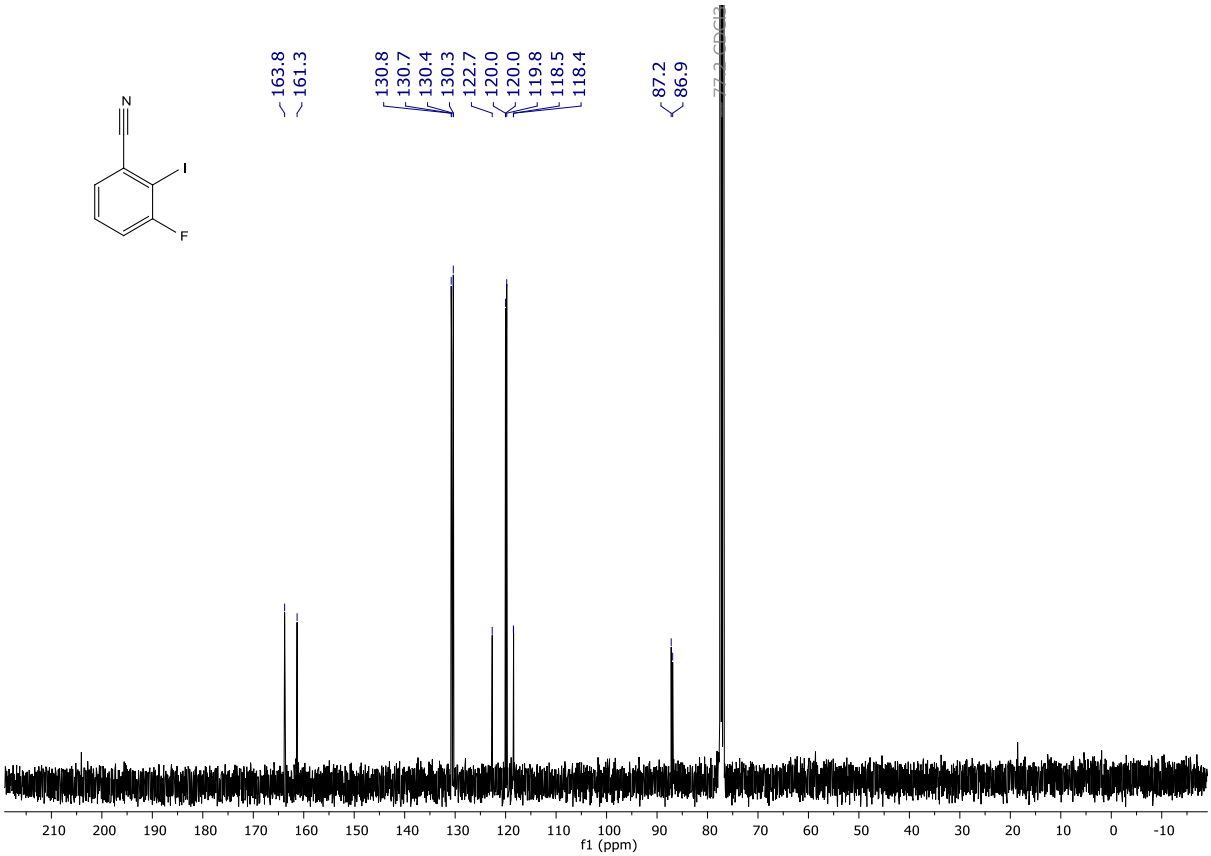


COSY correlation map of **125a** (101 MHz, $CDCl_3$).

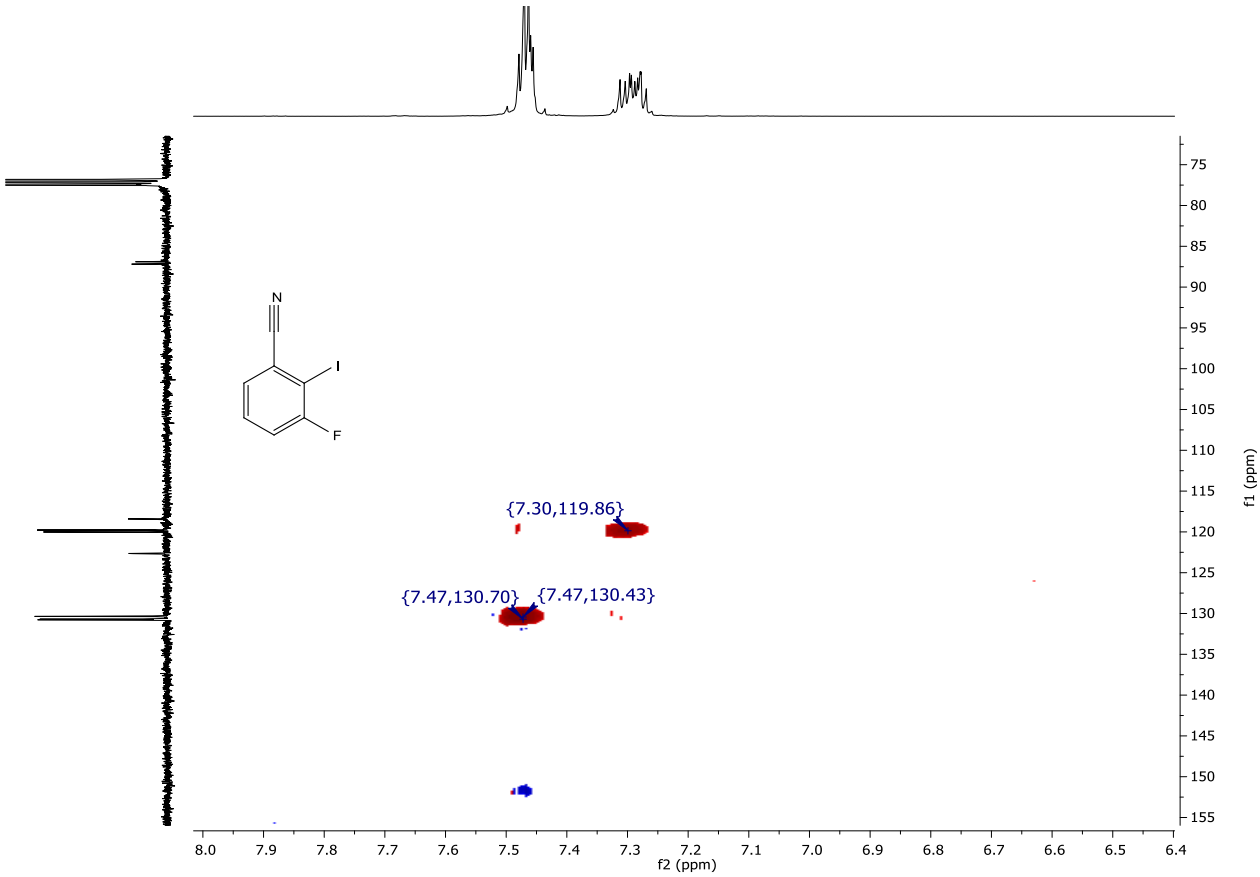
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125a**.



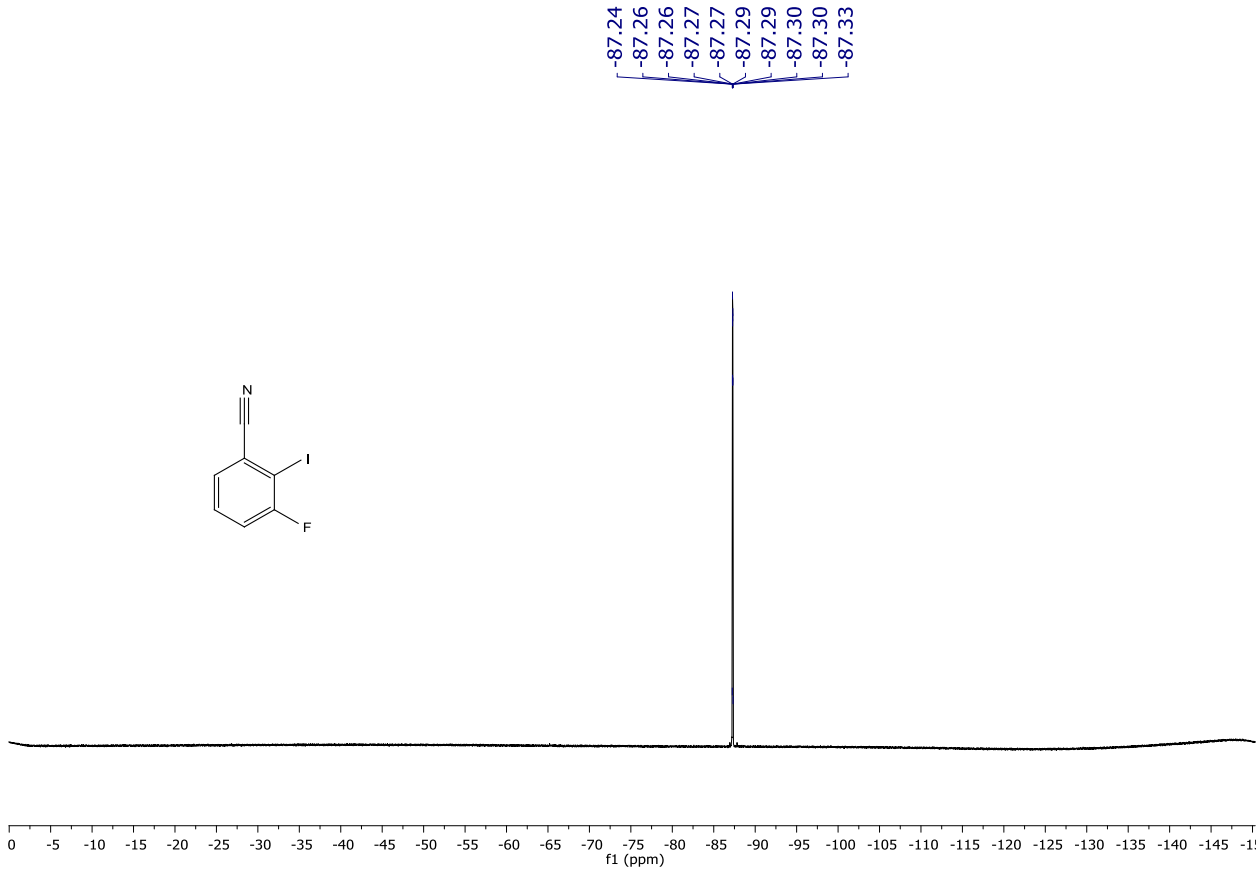
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125b.**



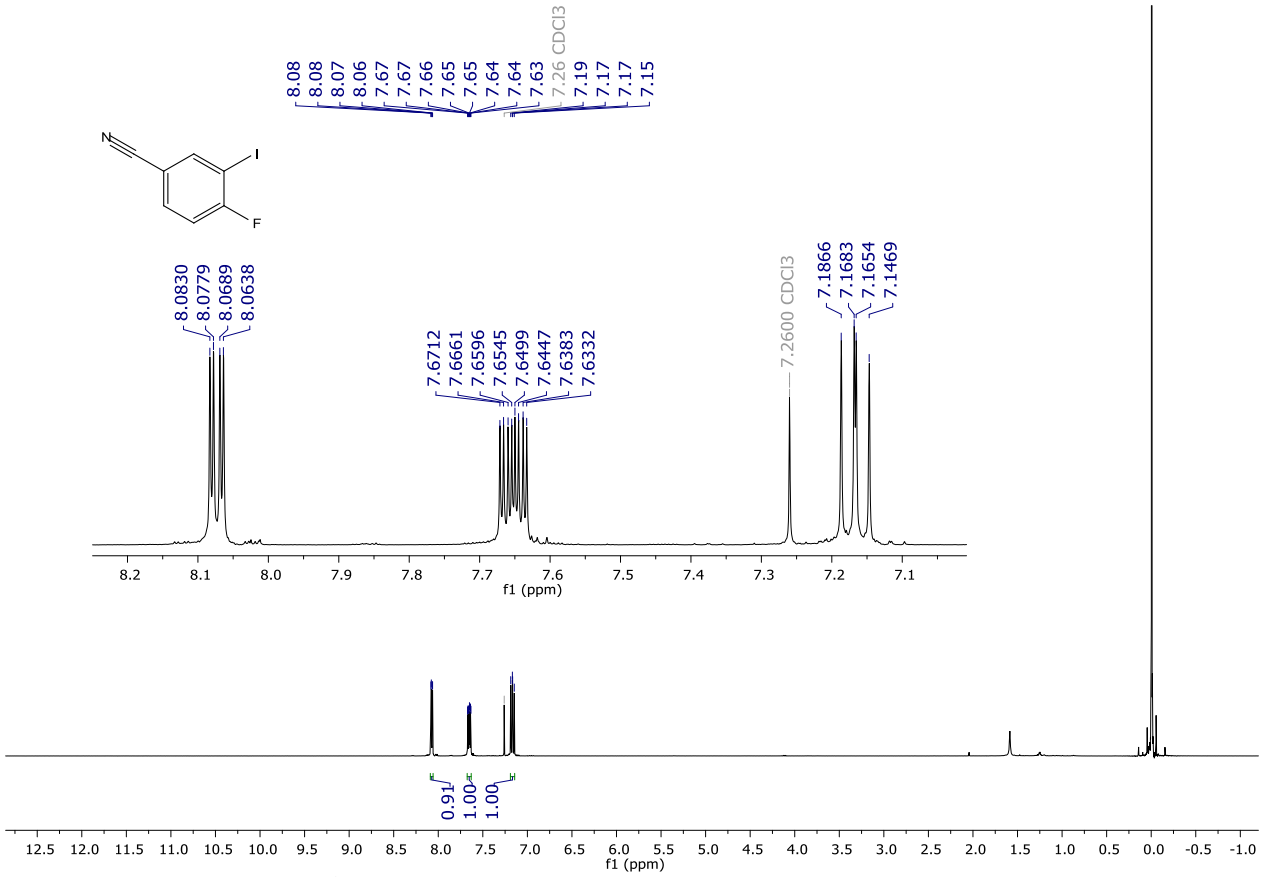
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125b**.



HSQC correlation map of **125b** (400 and 101 MHz, $CDCl_3$).



^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125b**.



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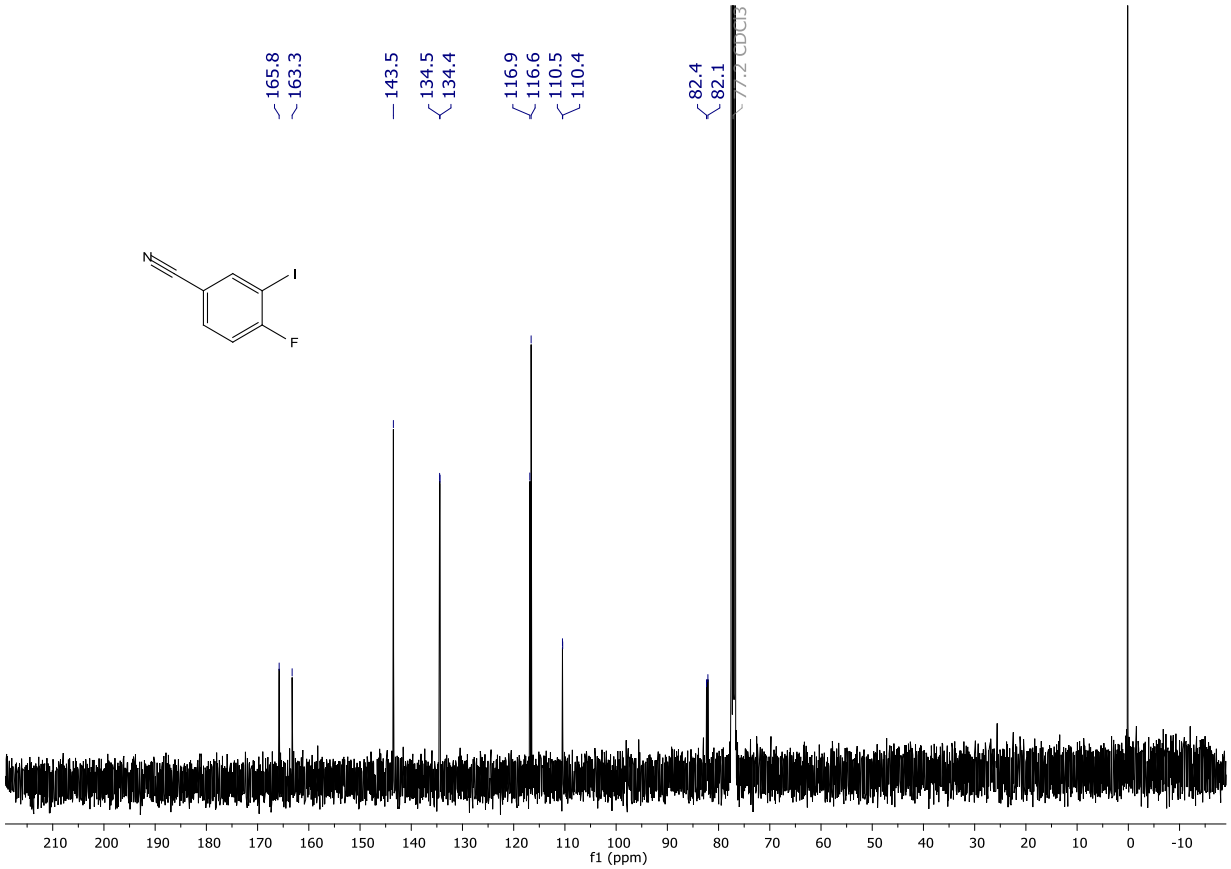
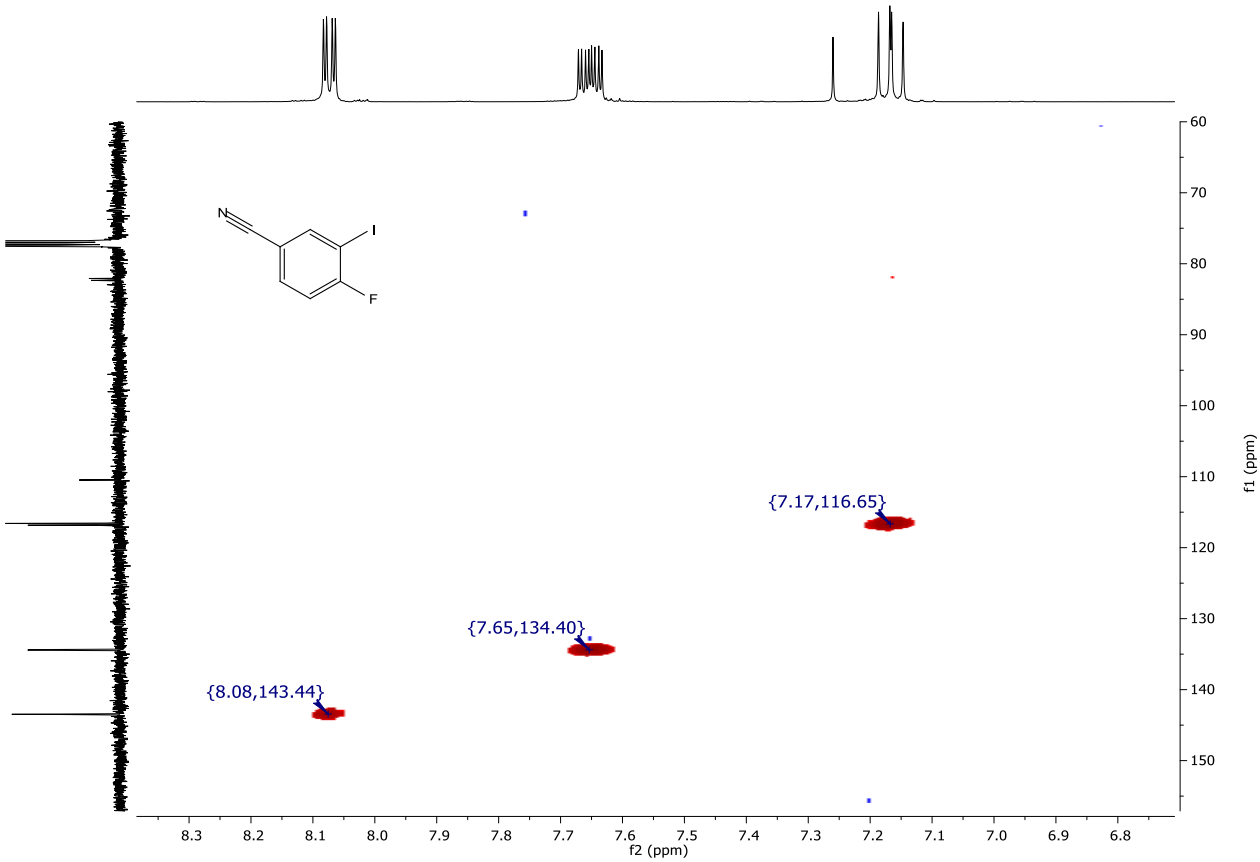
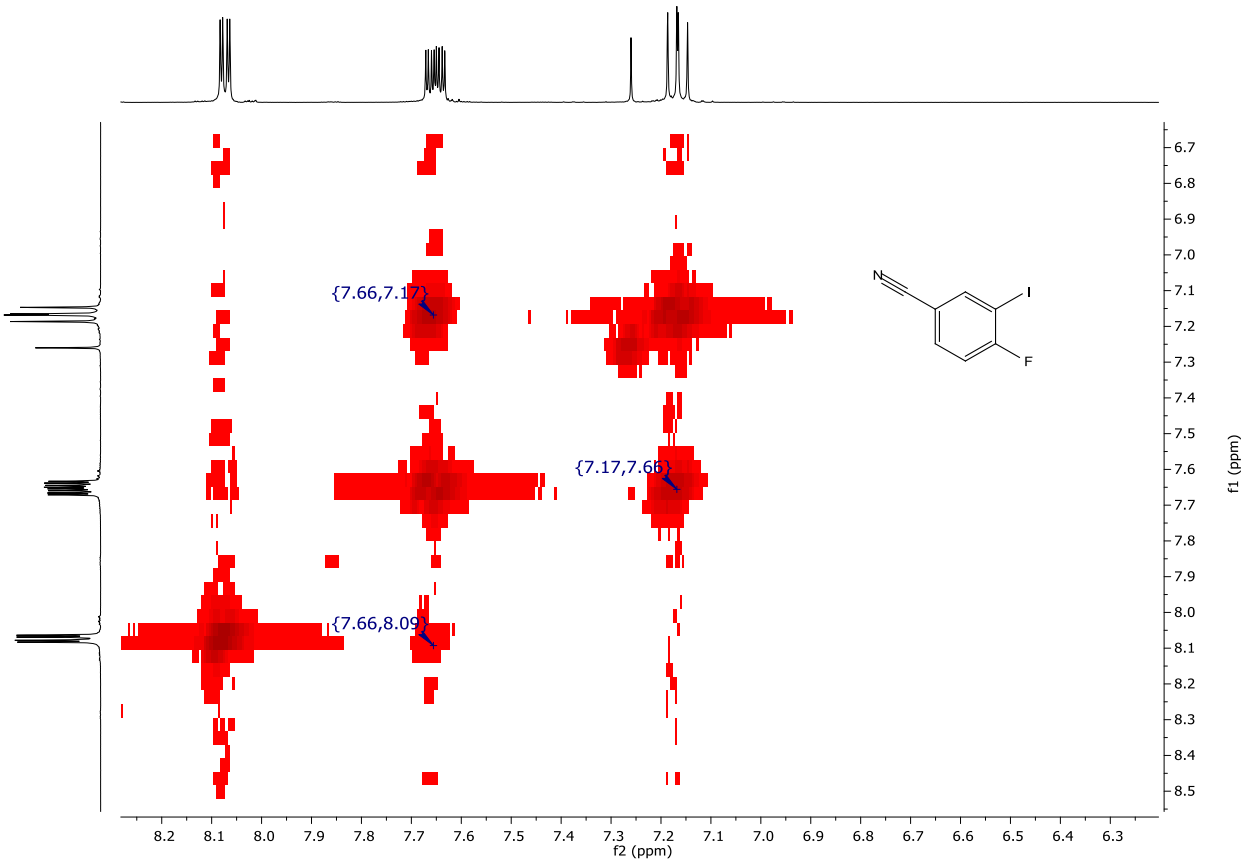


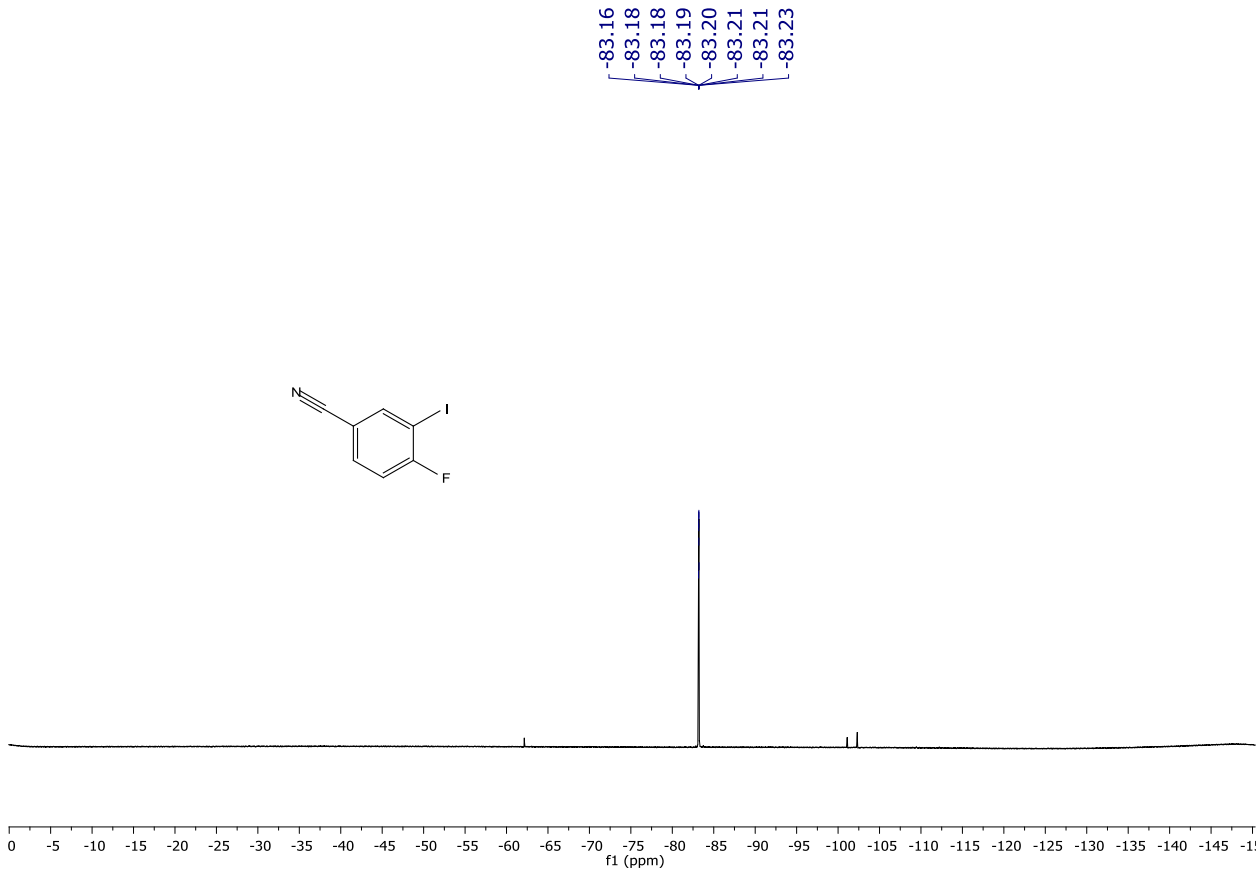
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125c**.



HSQC correlation map of **125c** (400 and 101 MHz, $CDCl_3$).



COSY correlation map of **125c** (101 MHz, $CDCl_3$).



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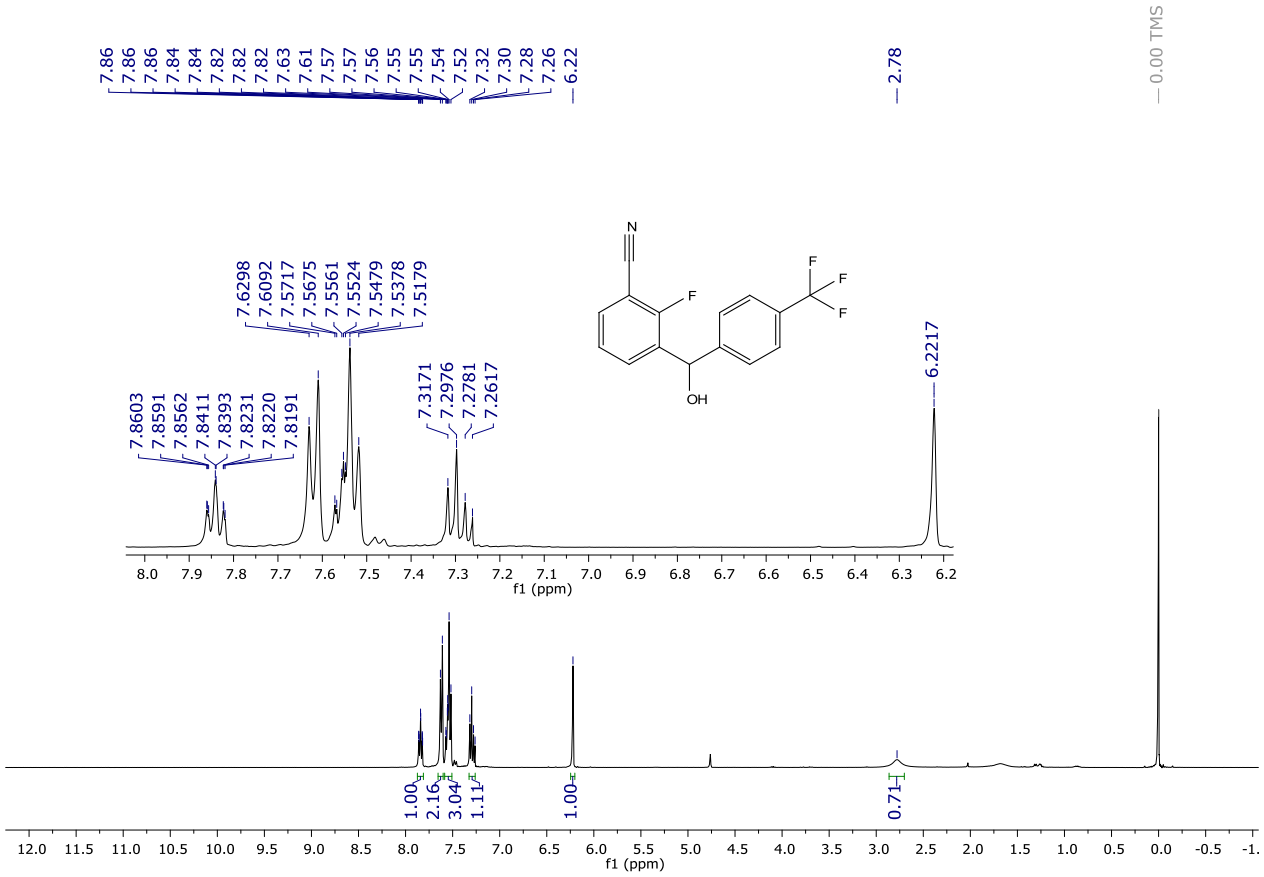

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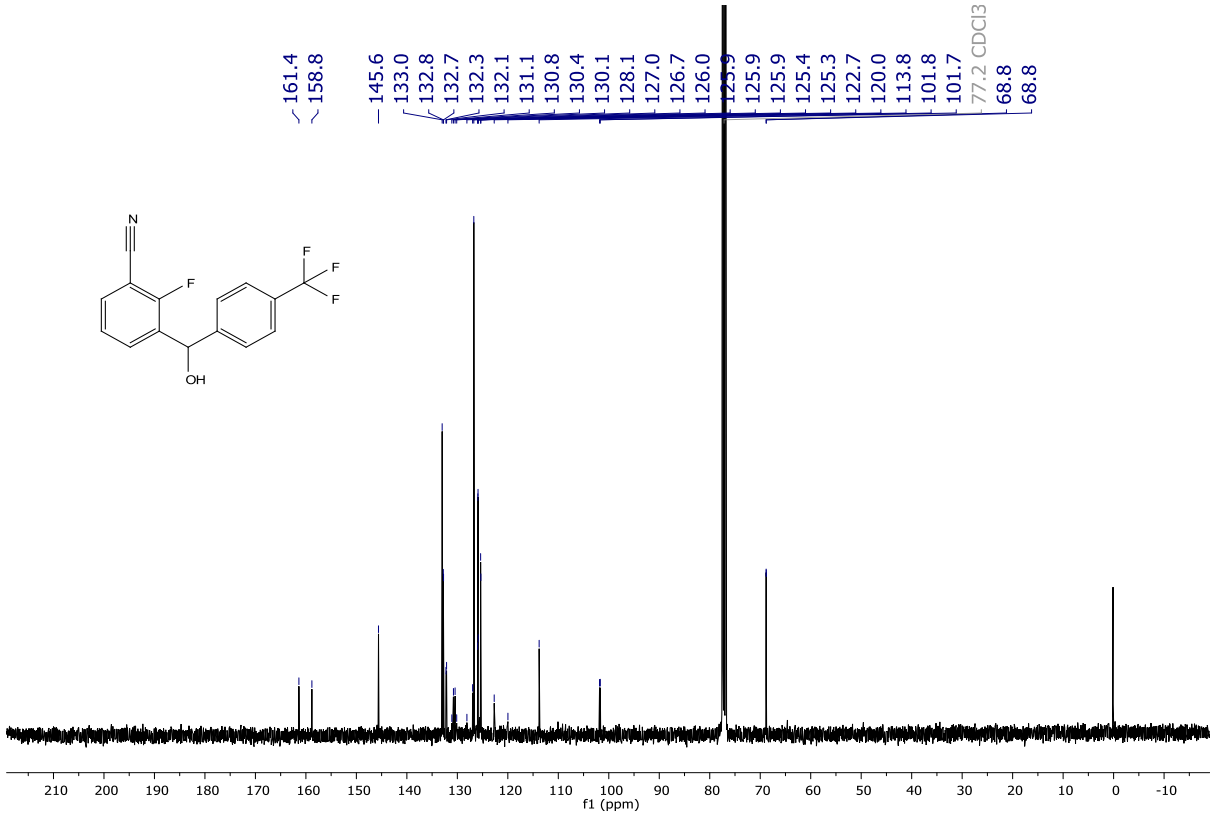

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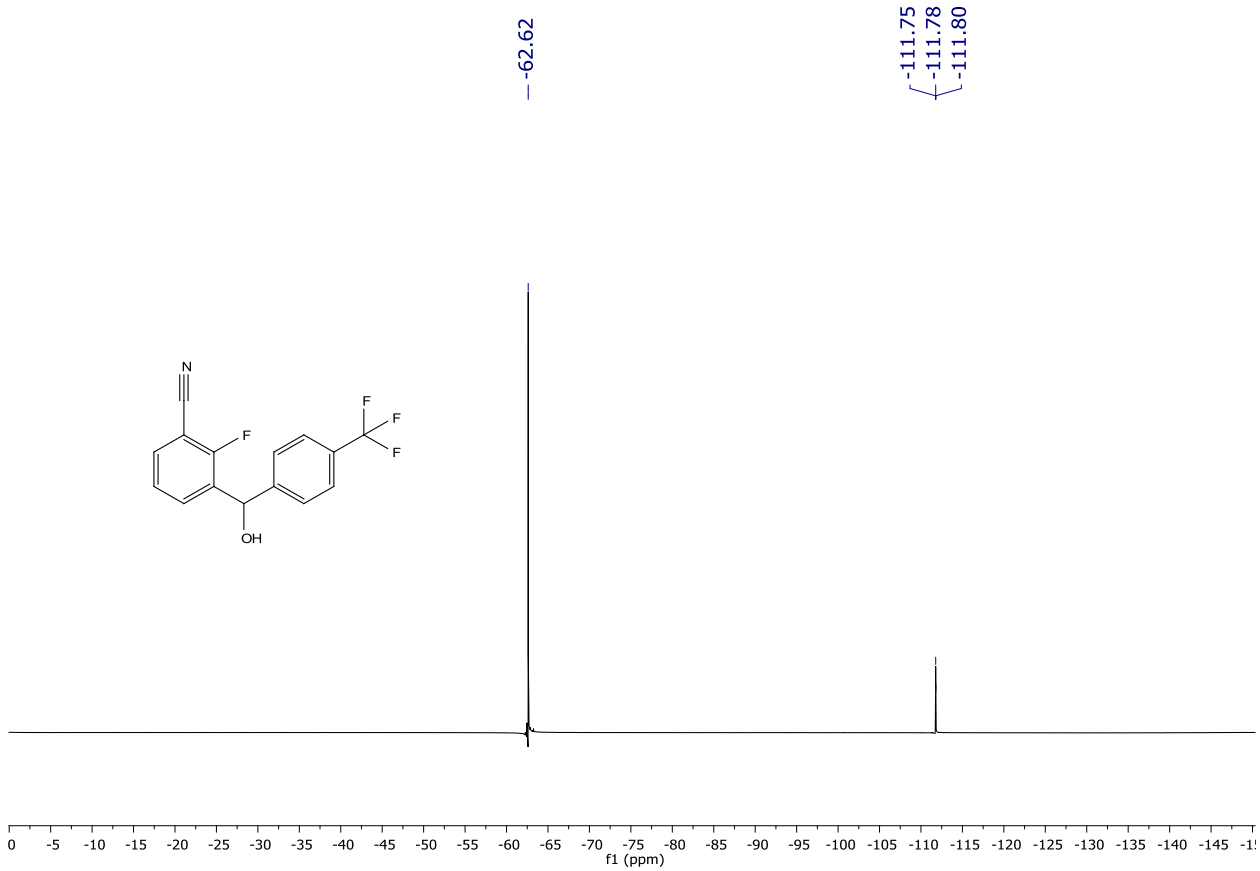

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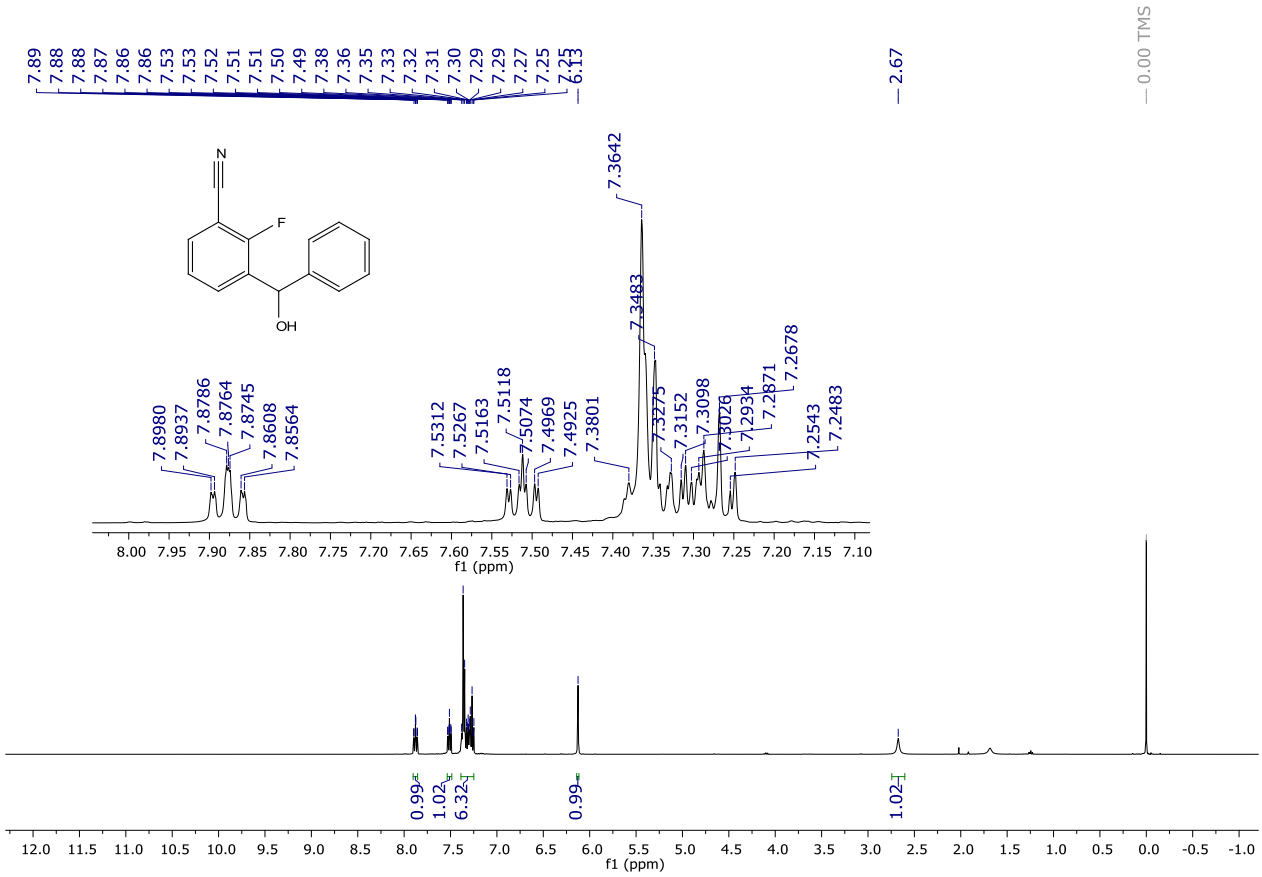

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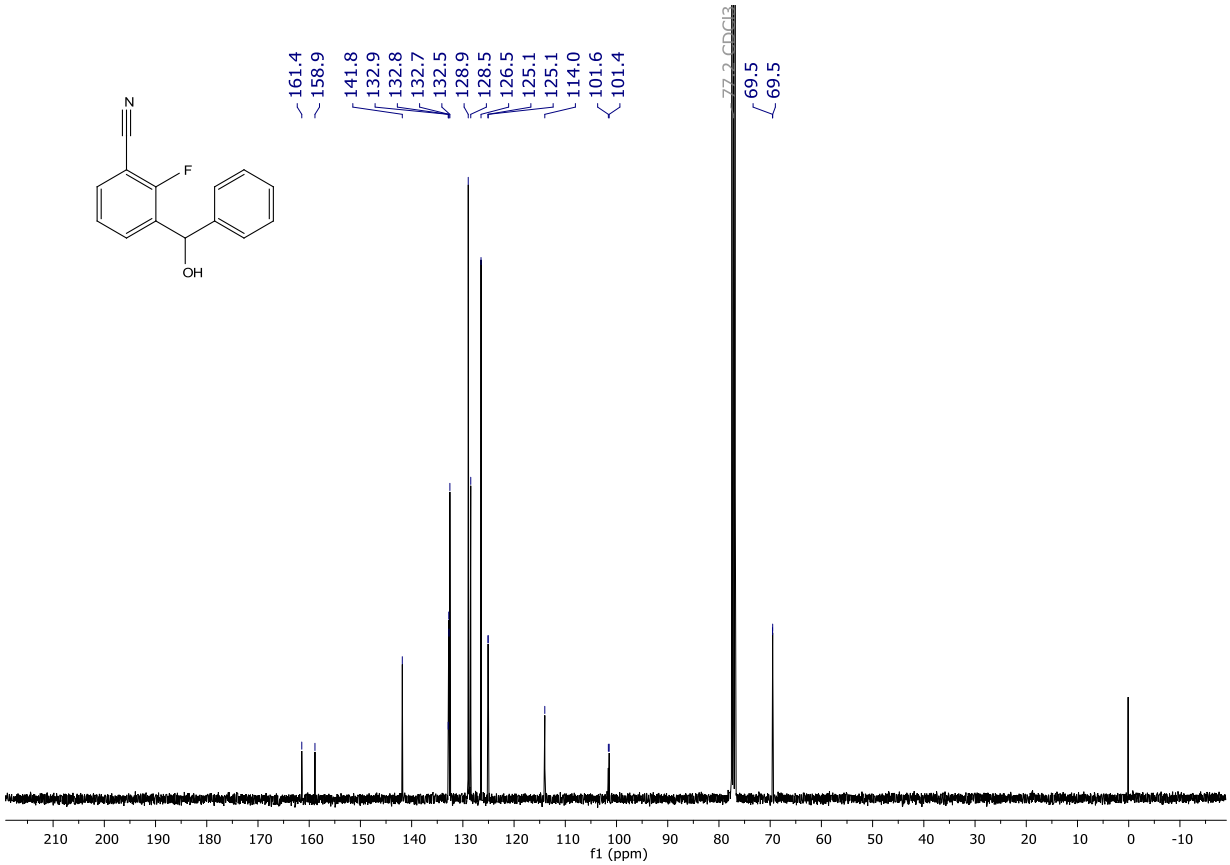

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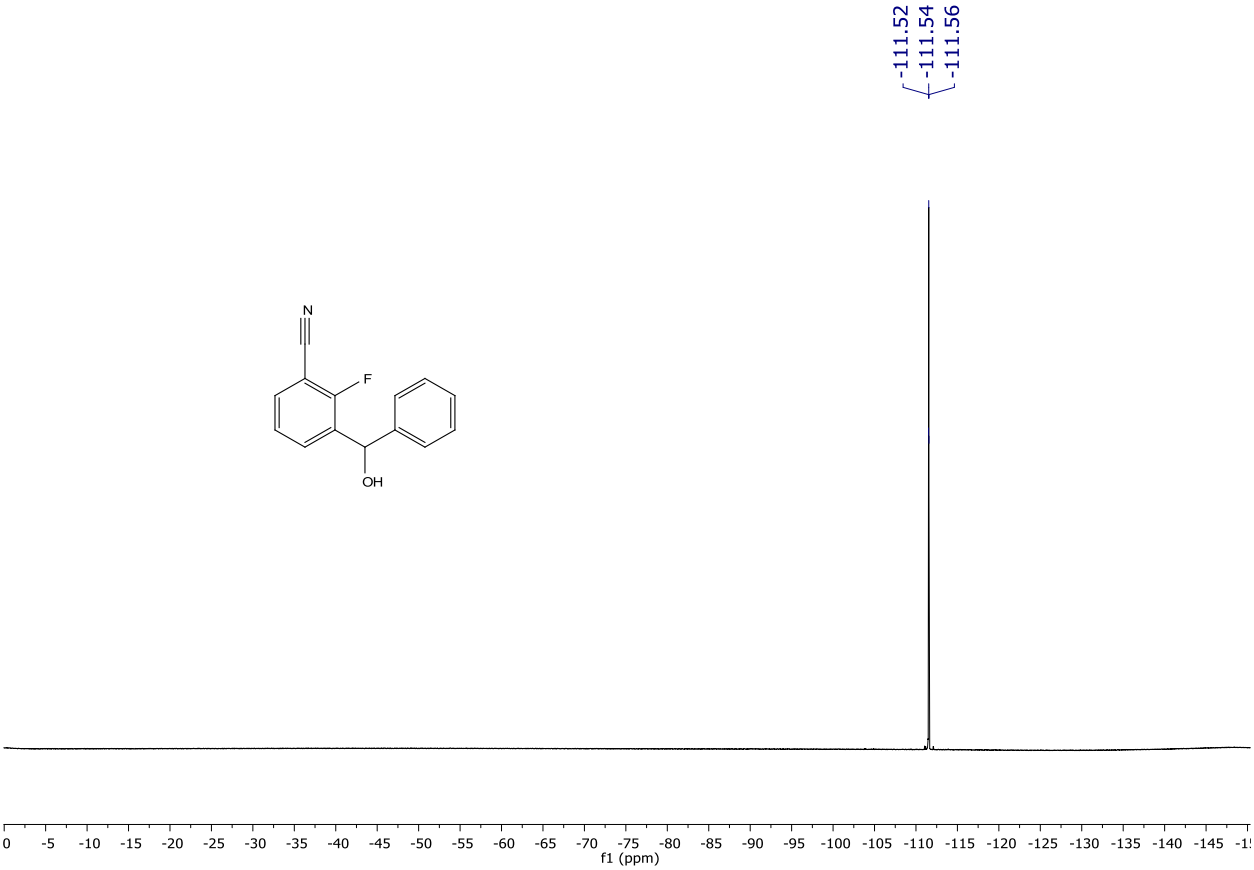

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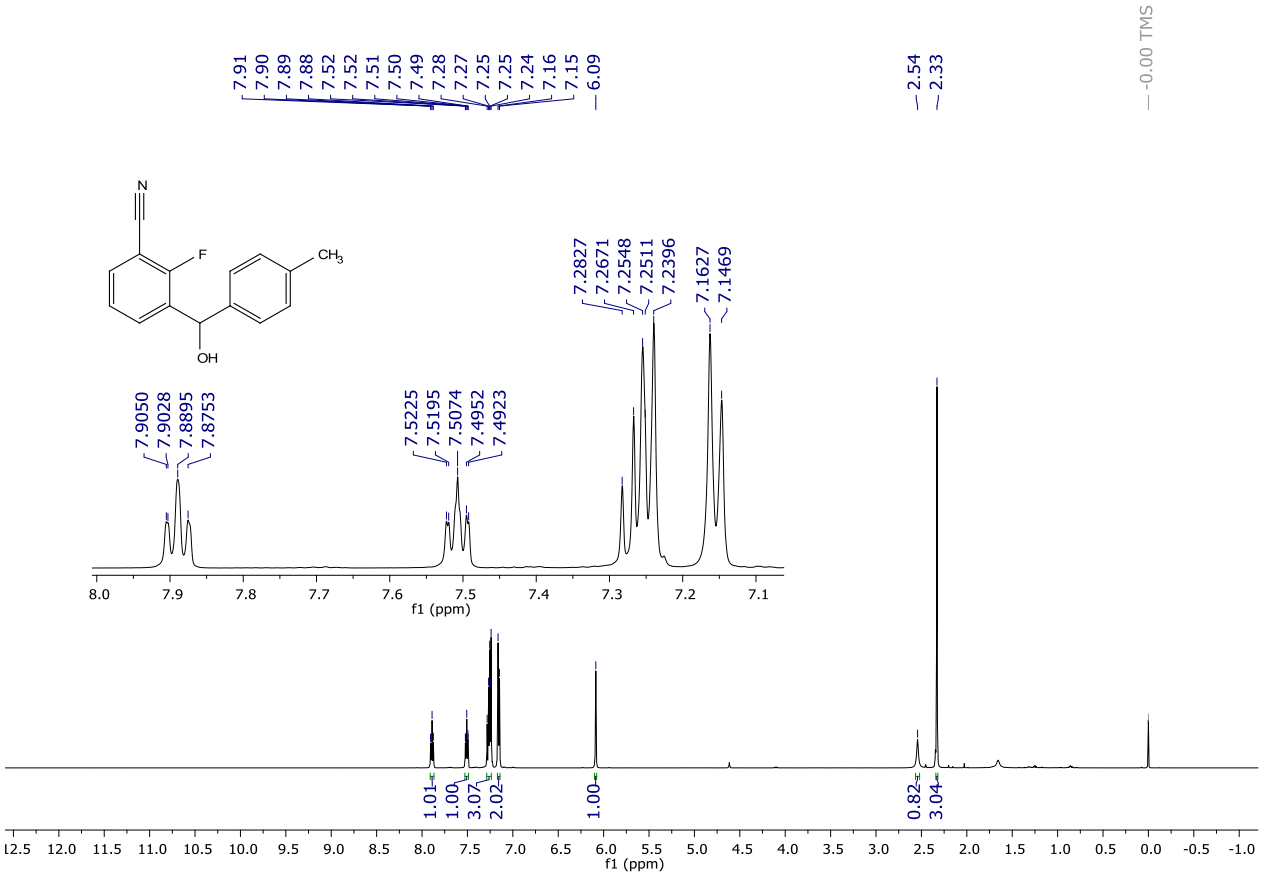
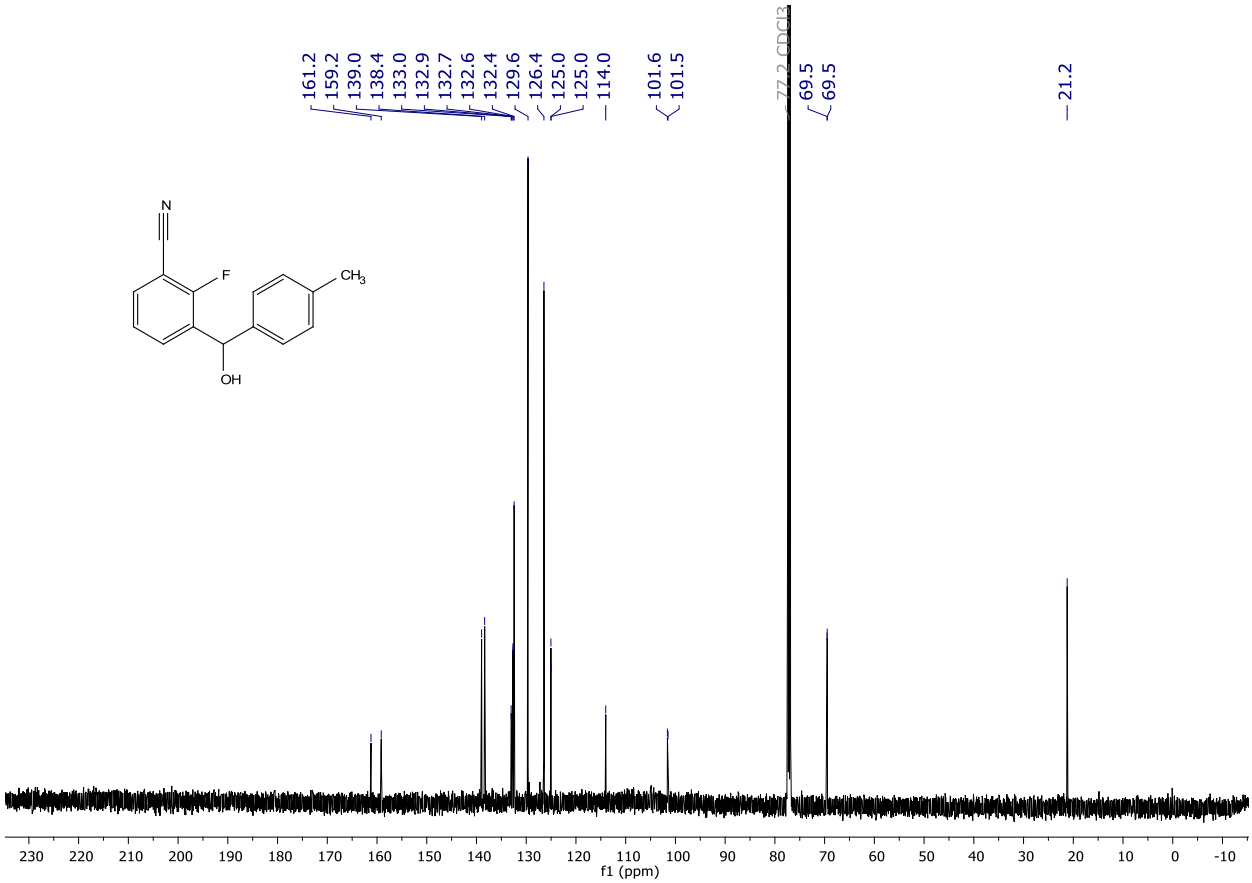
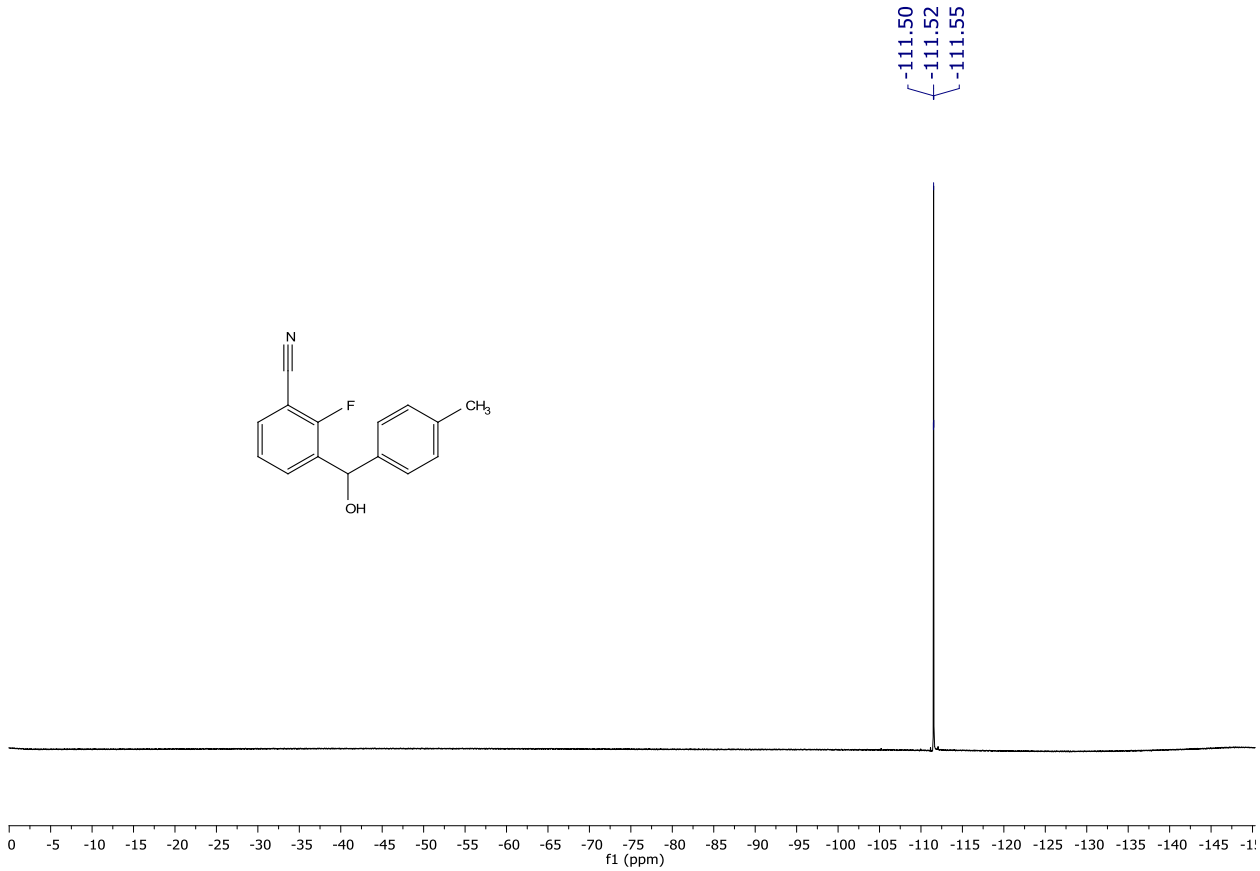


^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **125f.**



^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) spectrum of **125f**.



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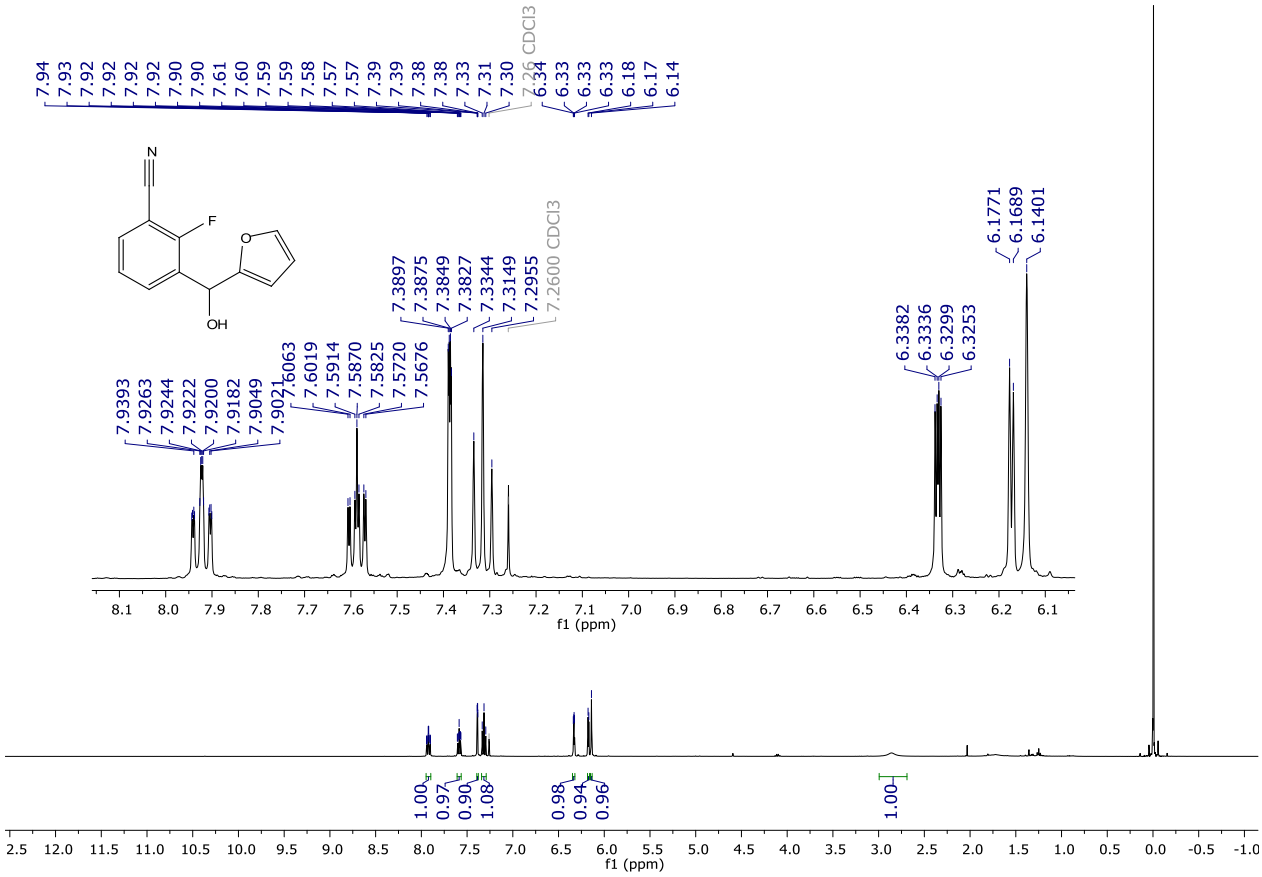

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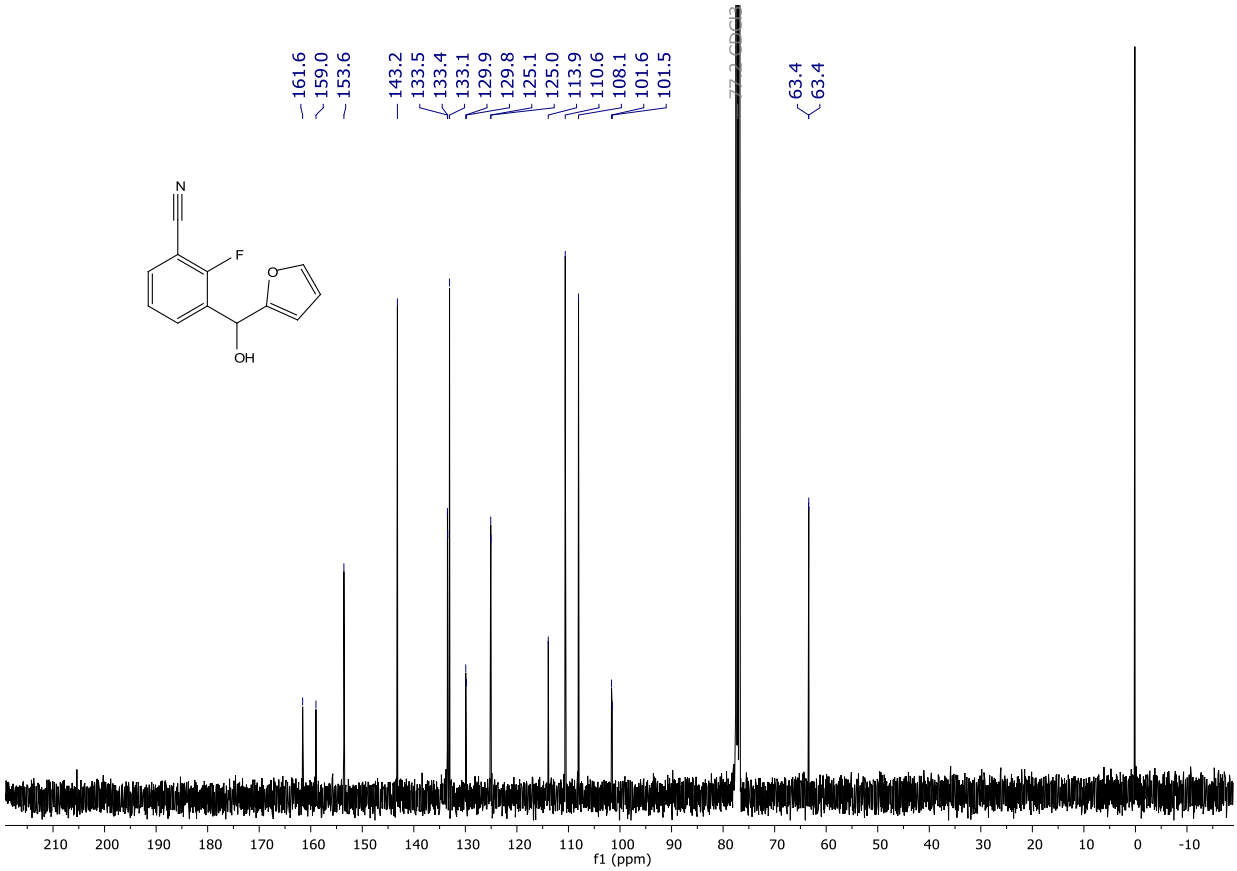

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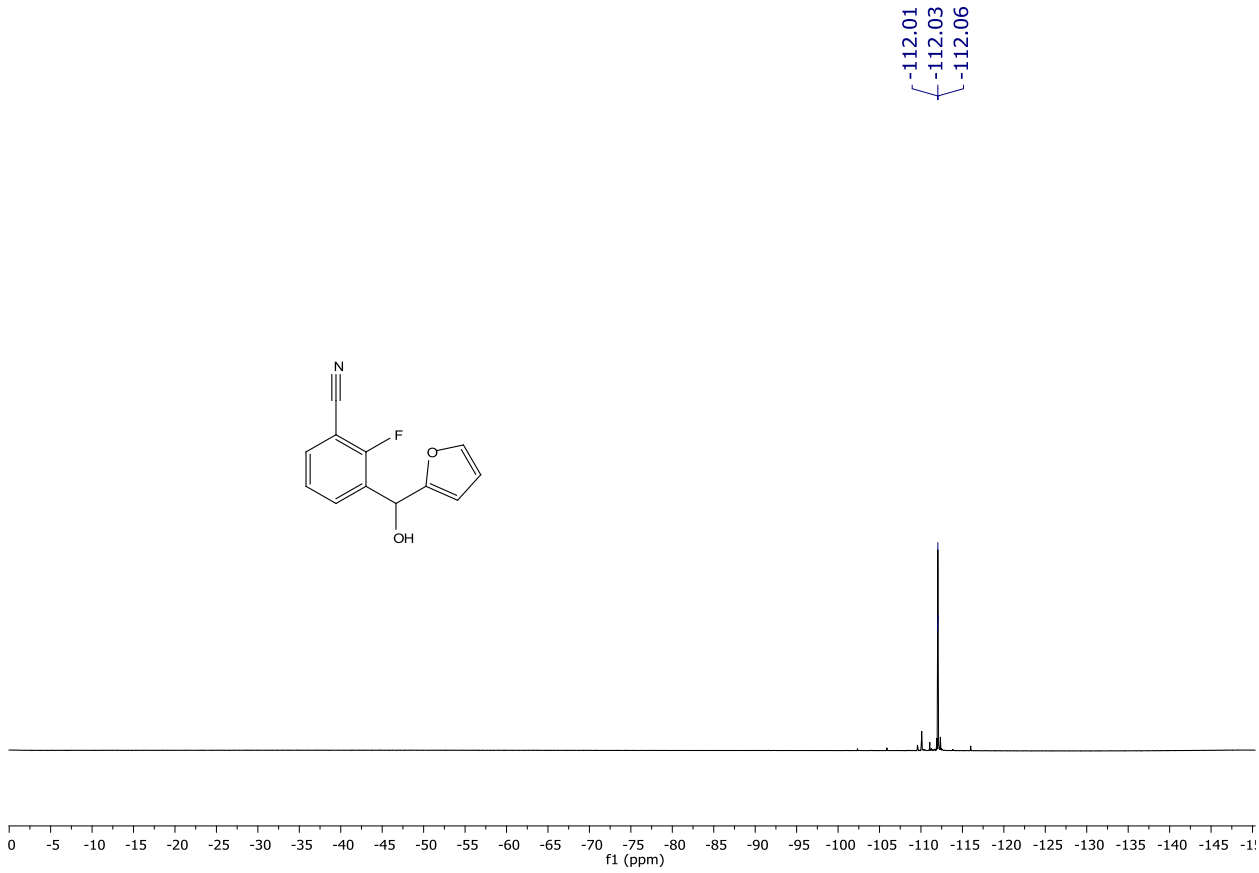

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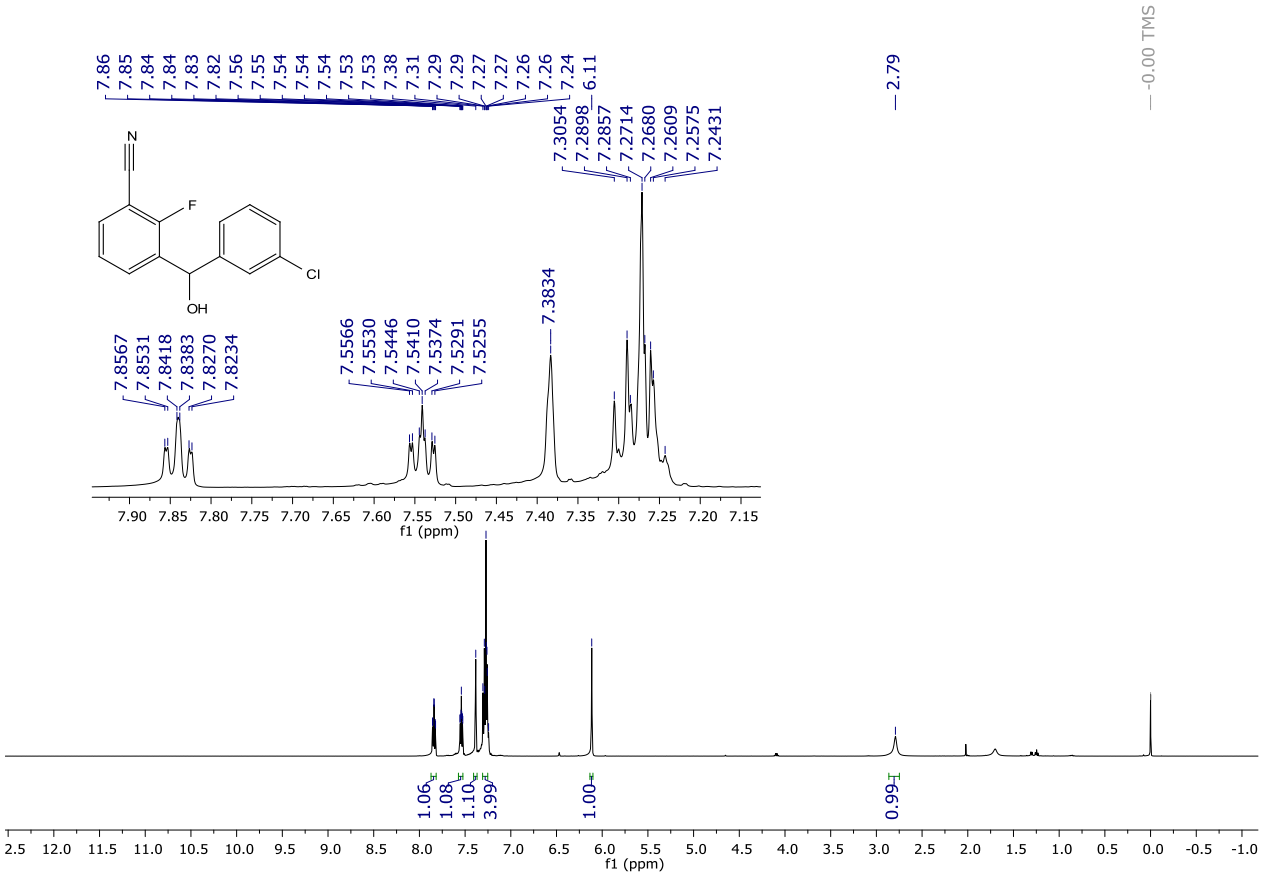

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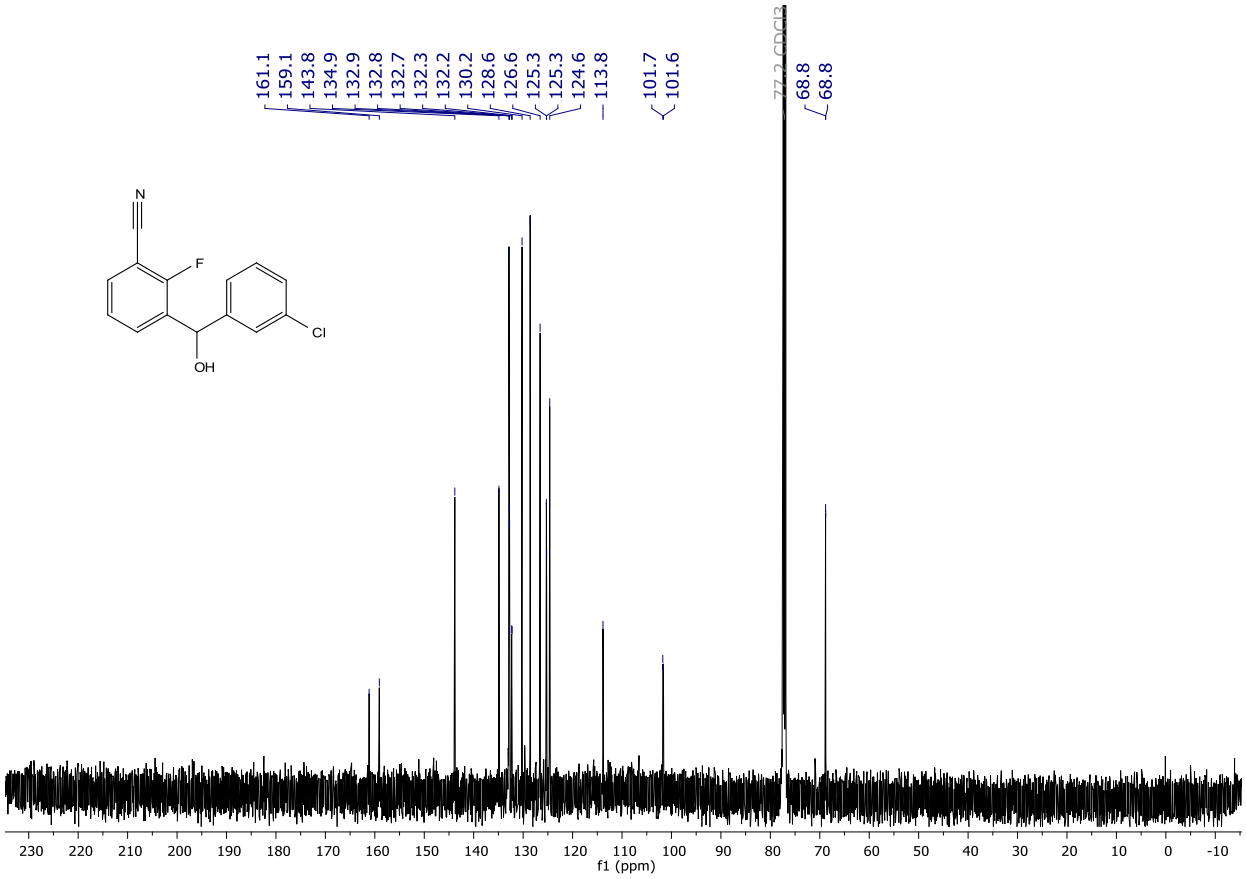

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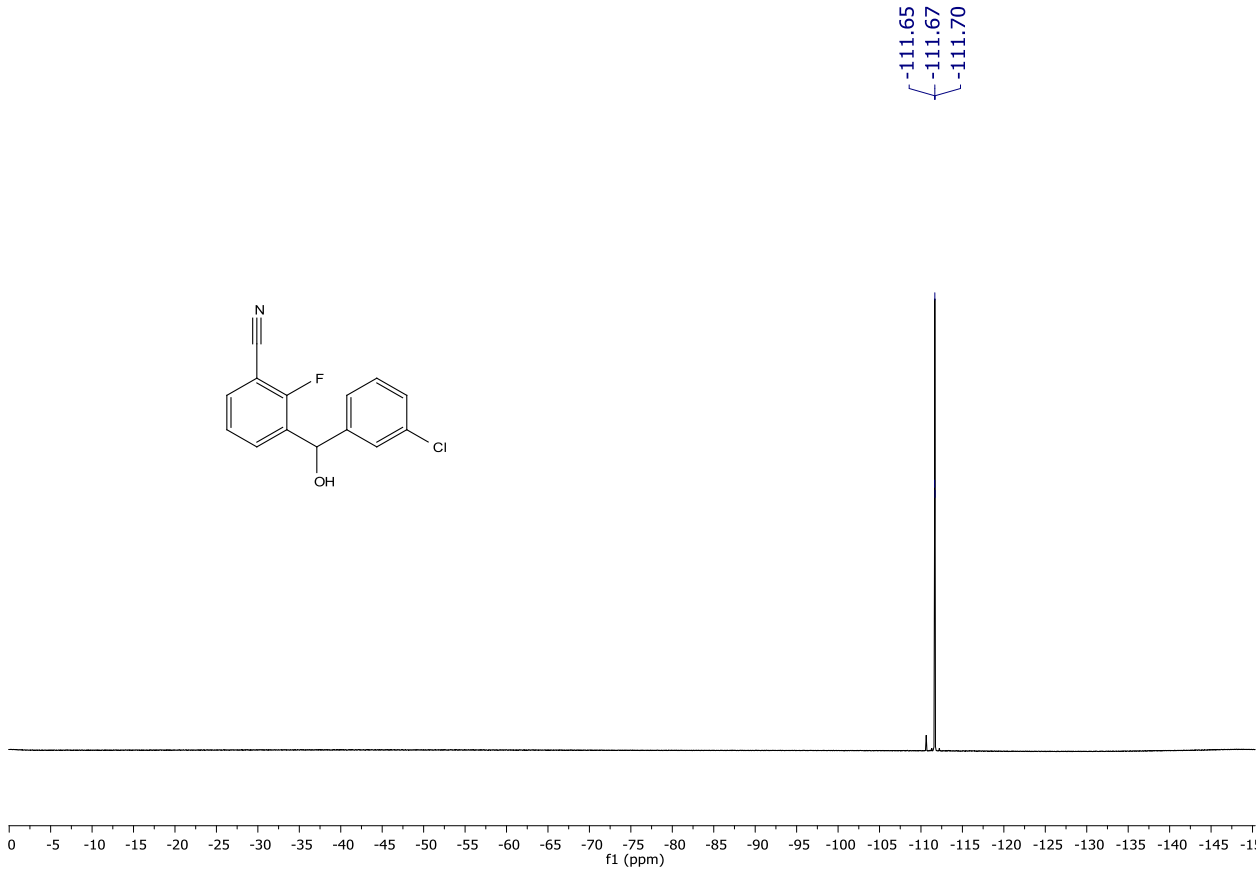

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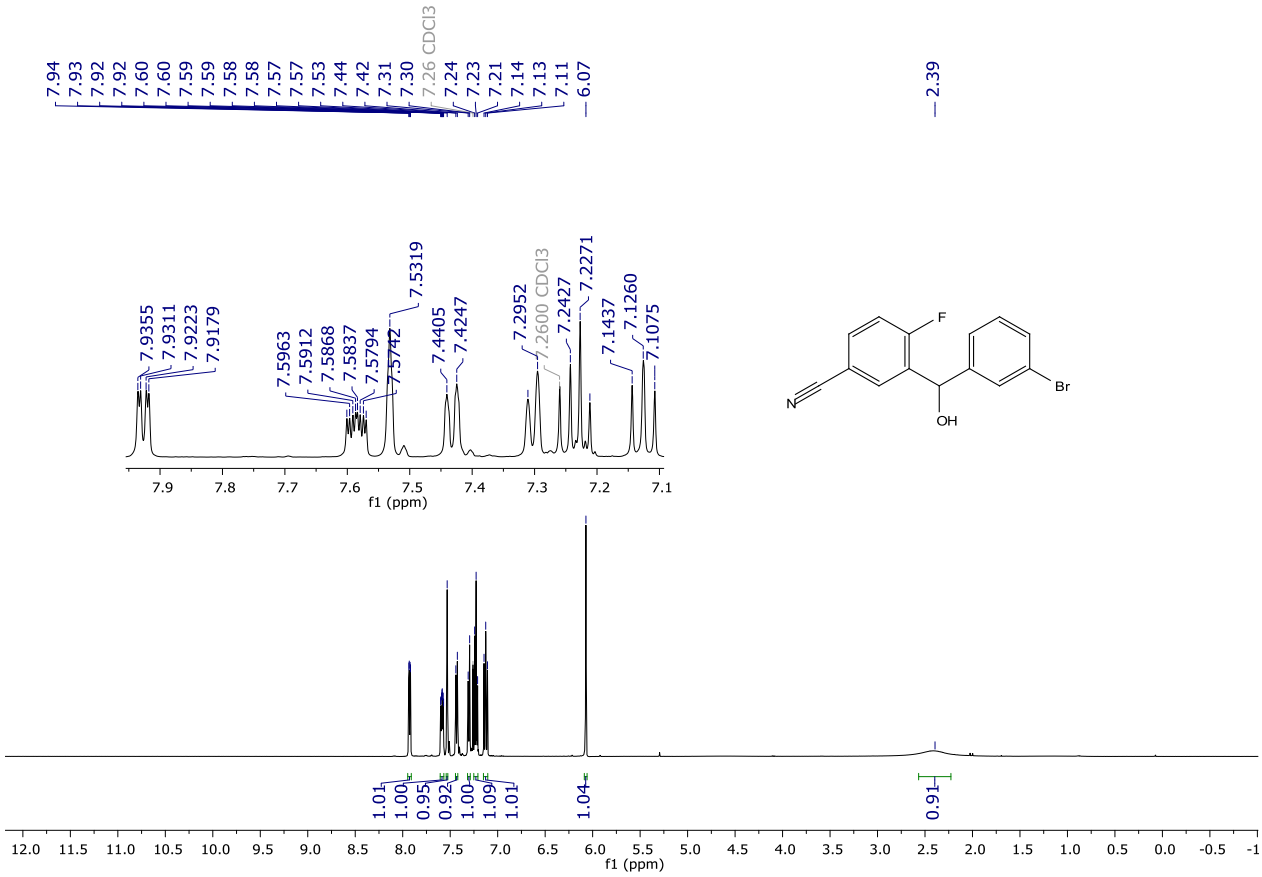

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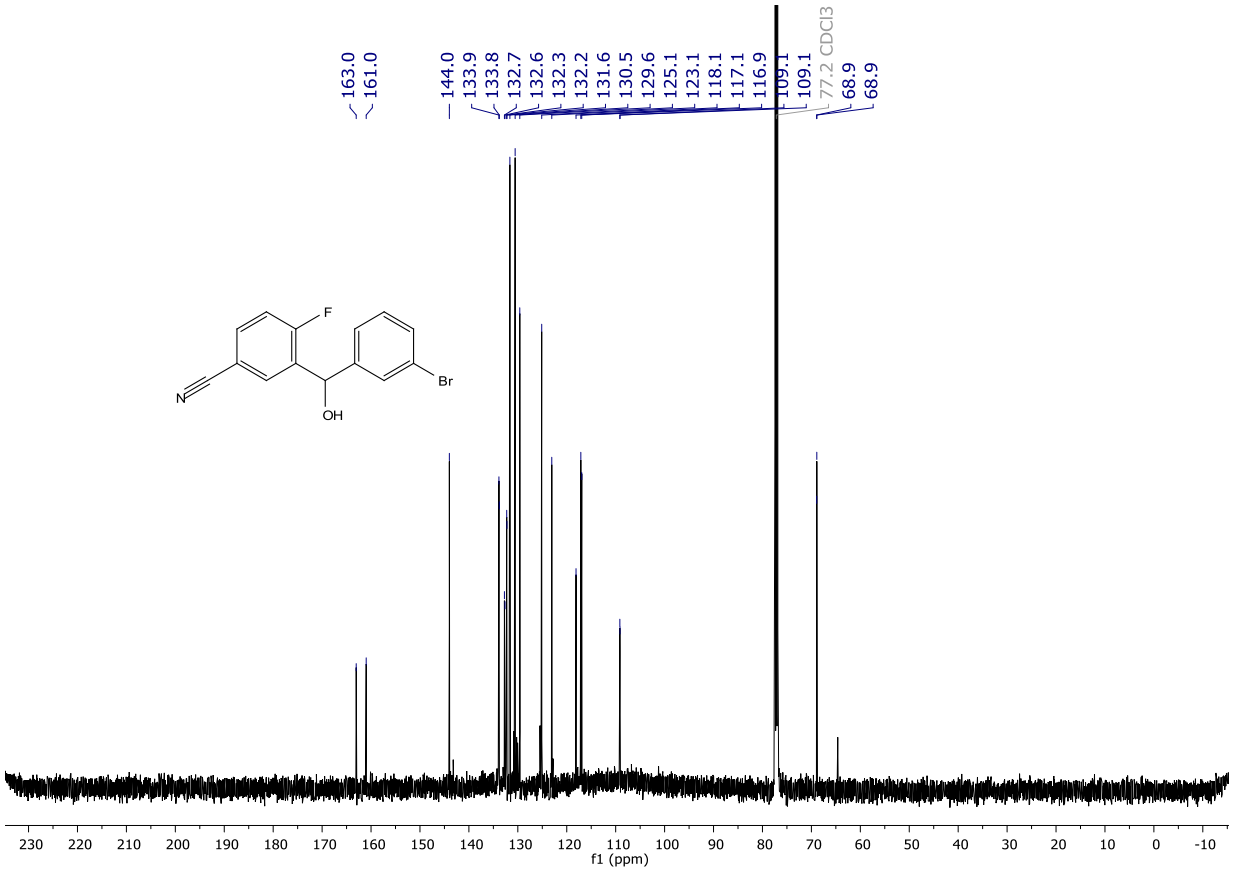

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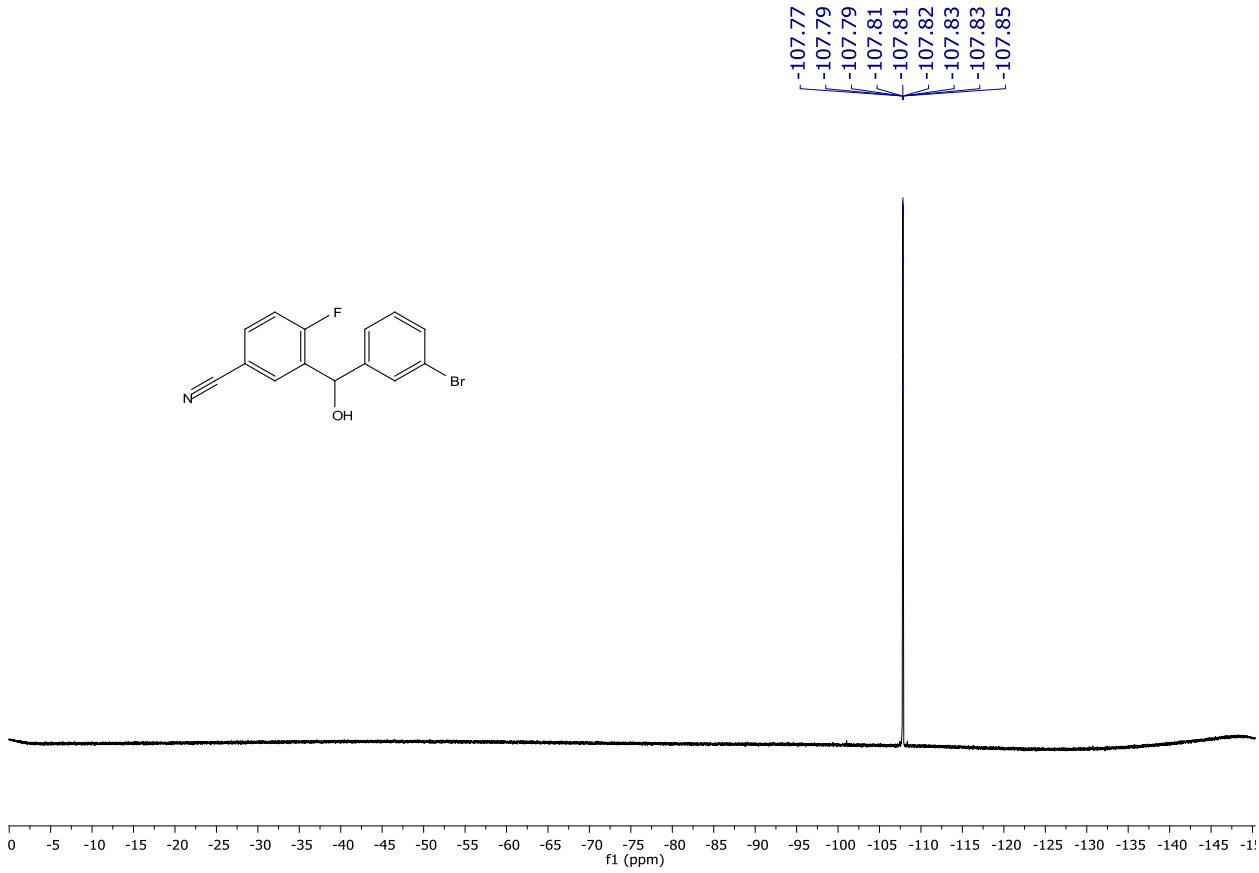

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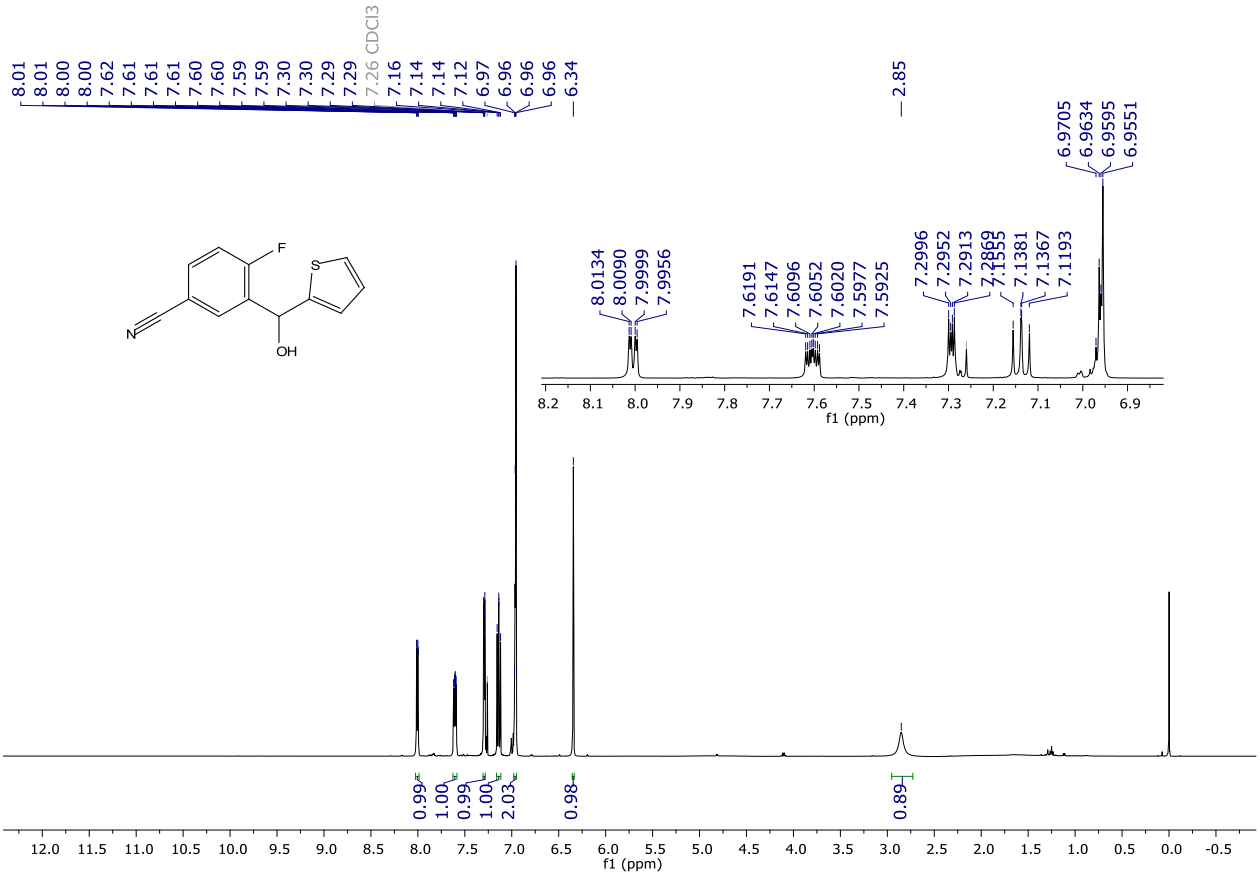

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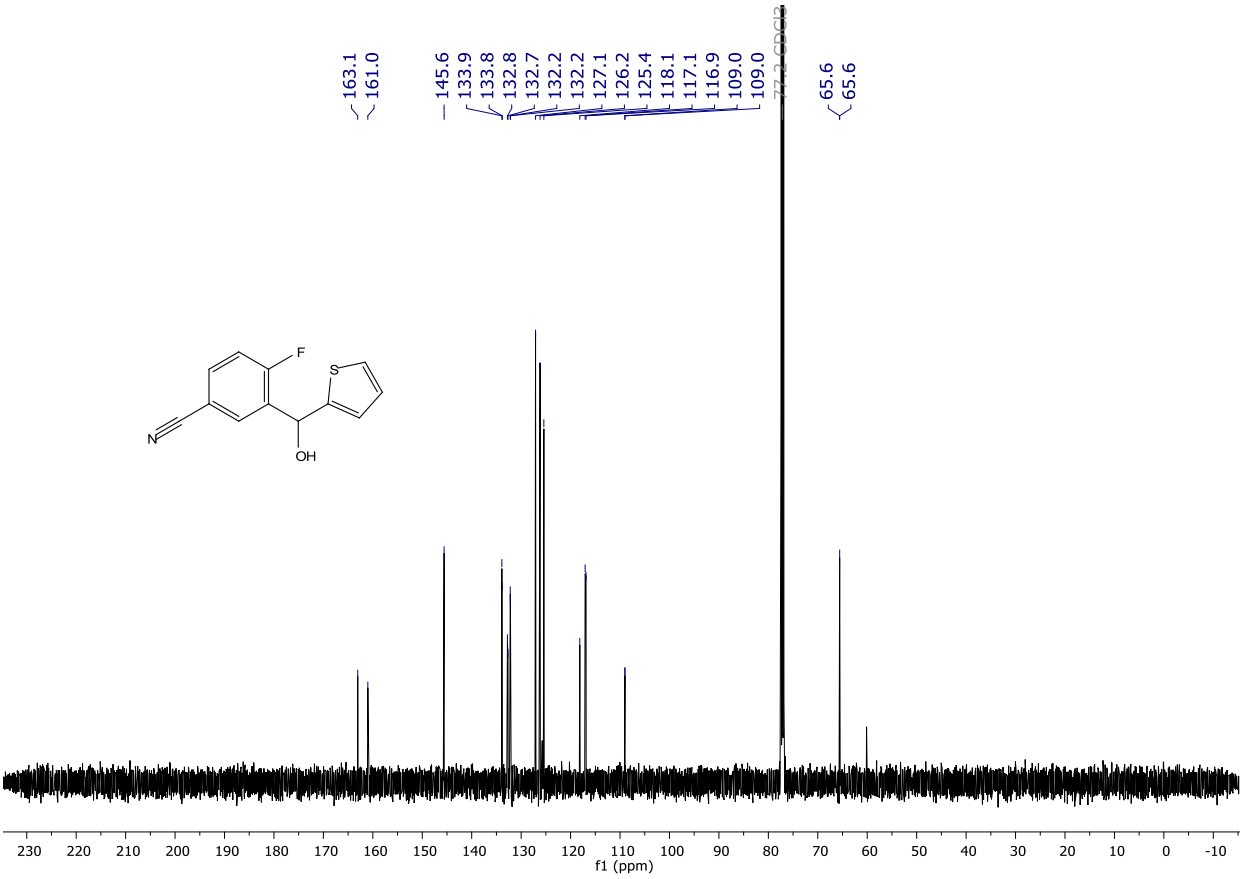

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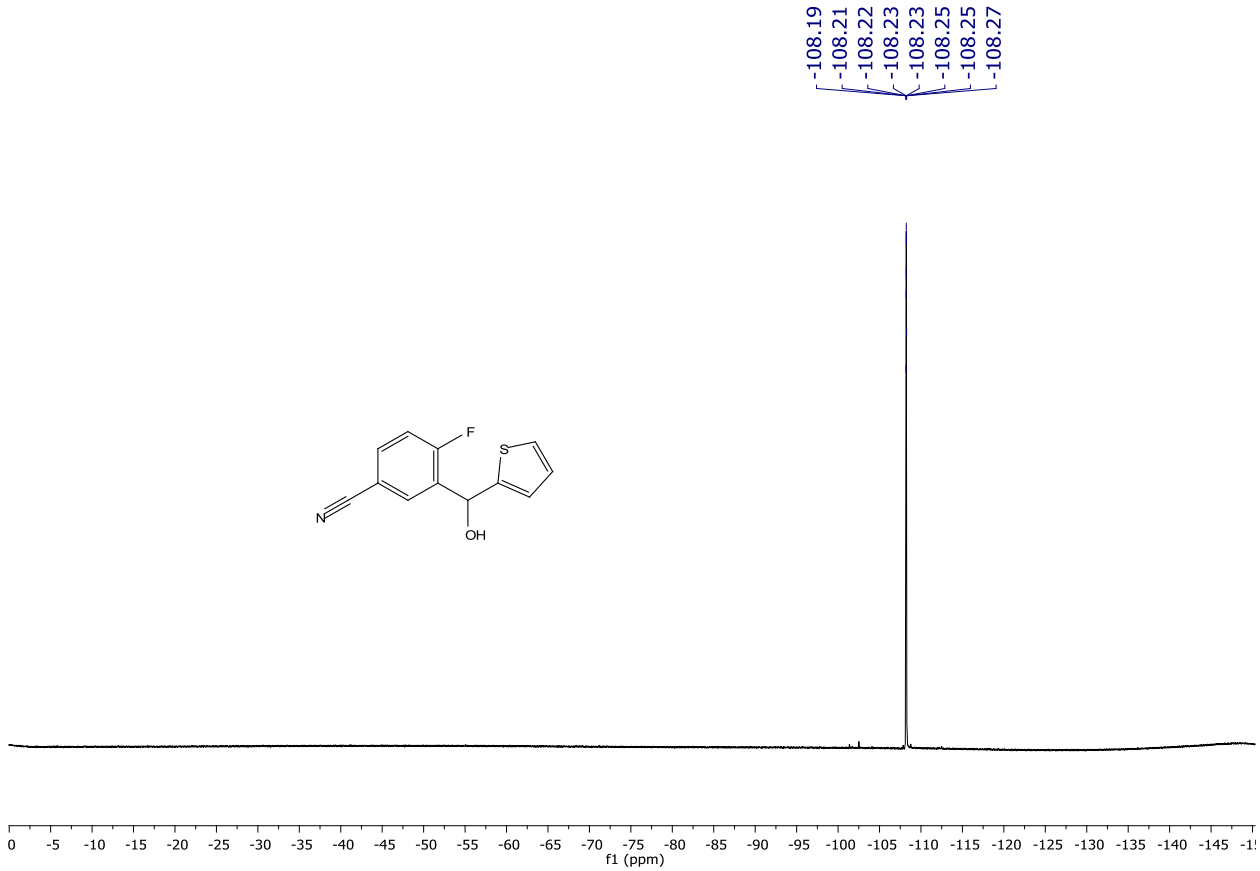

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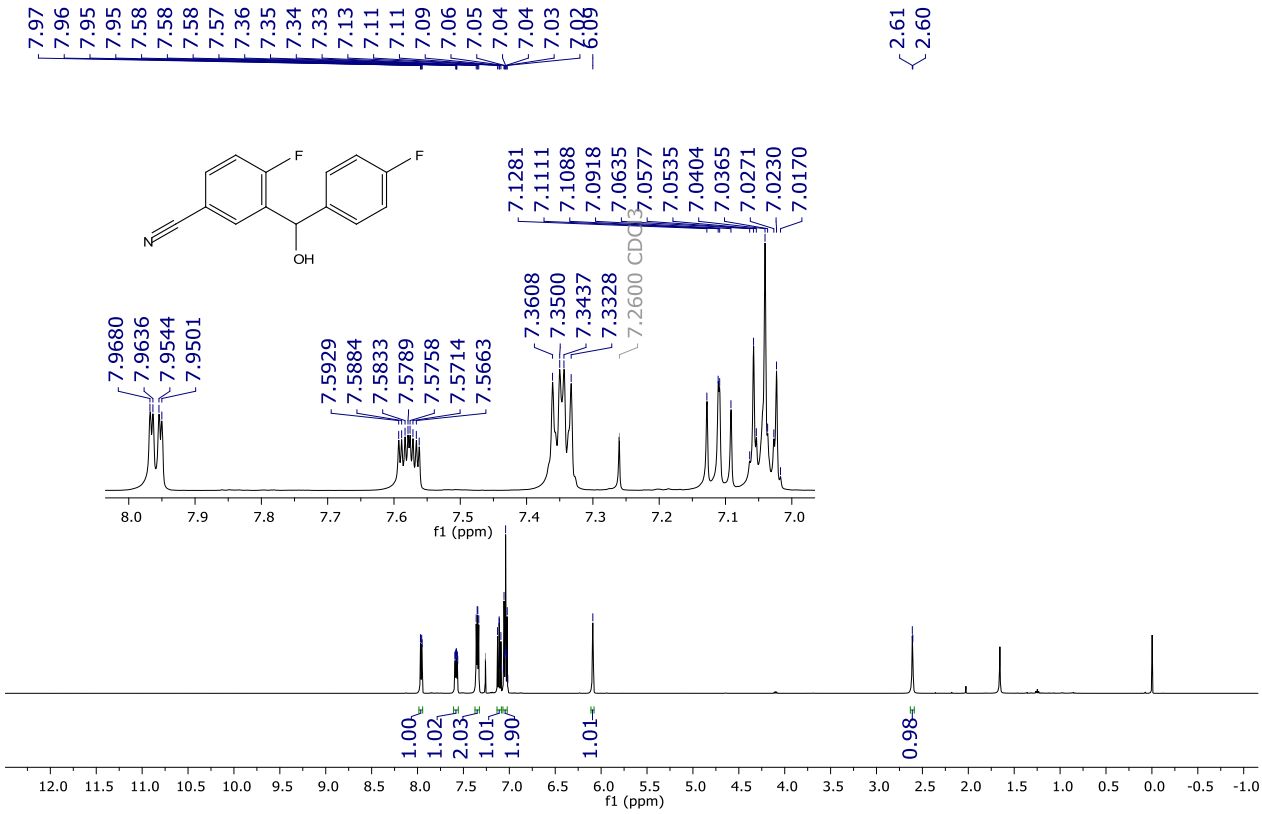

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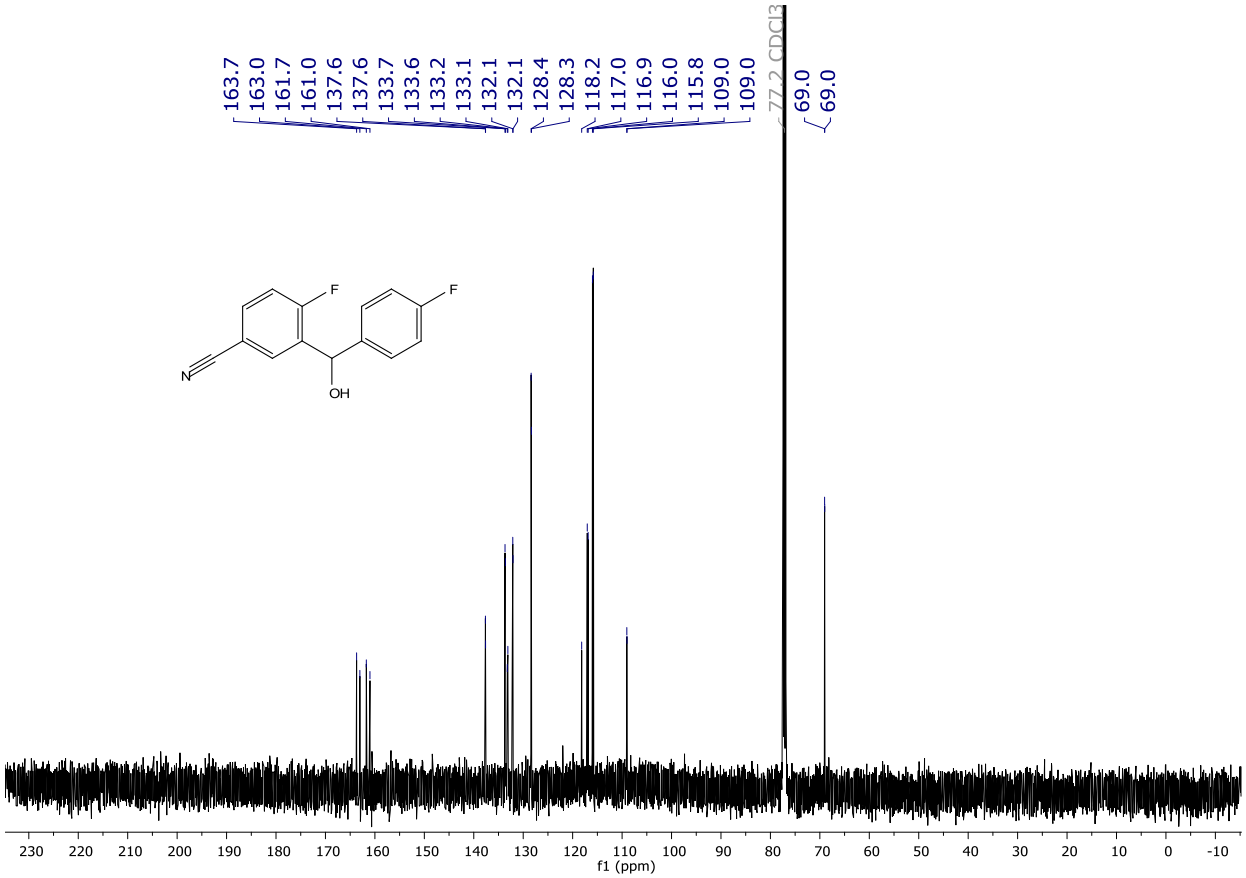

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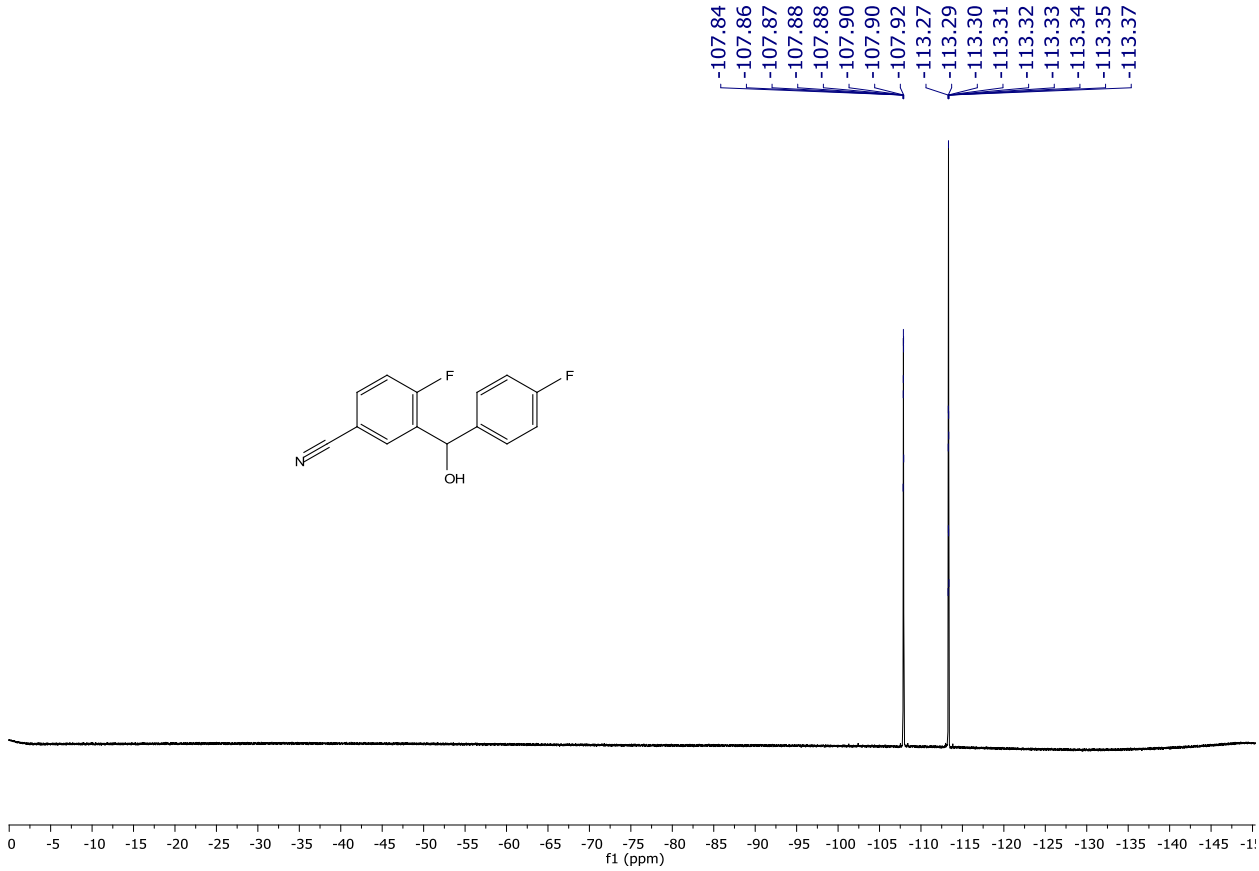
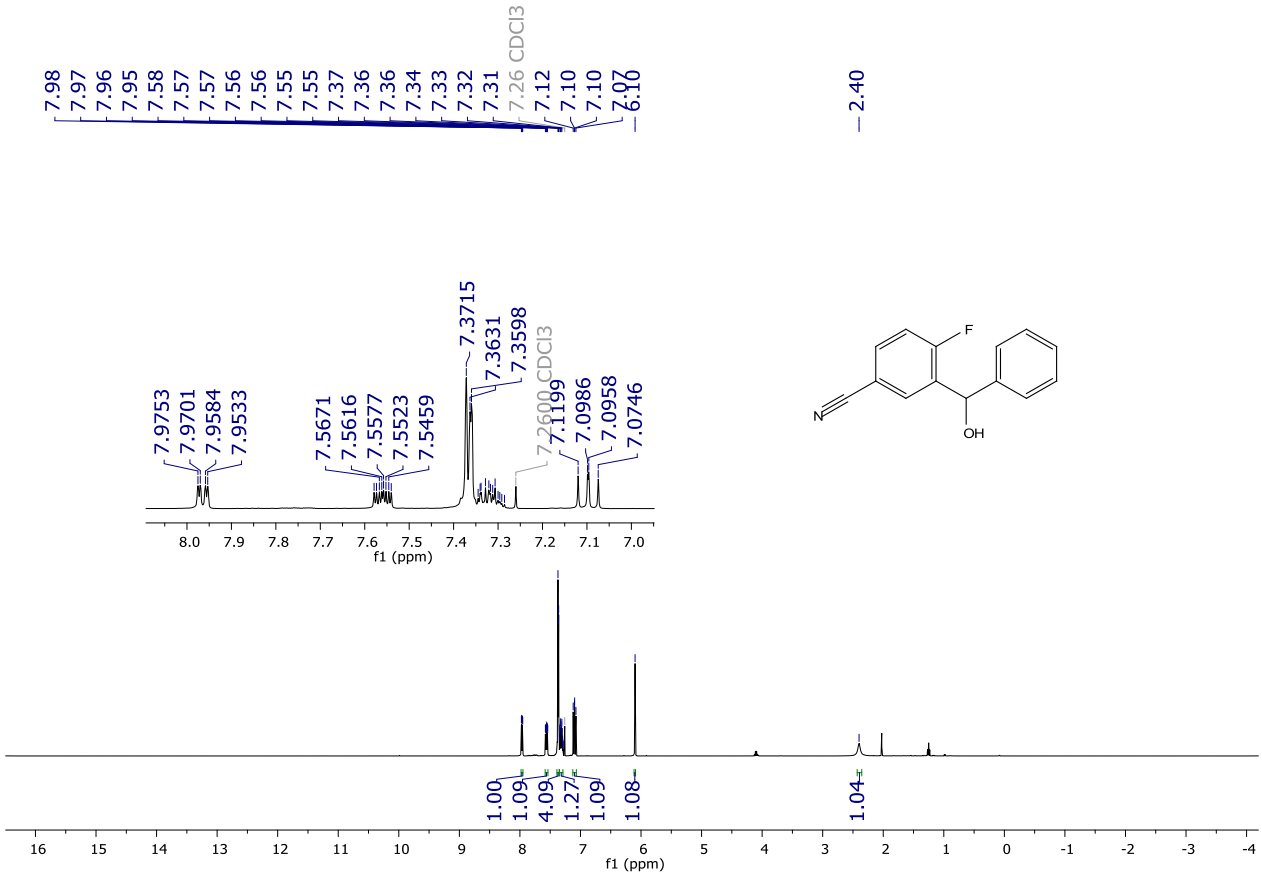
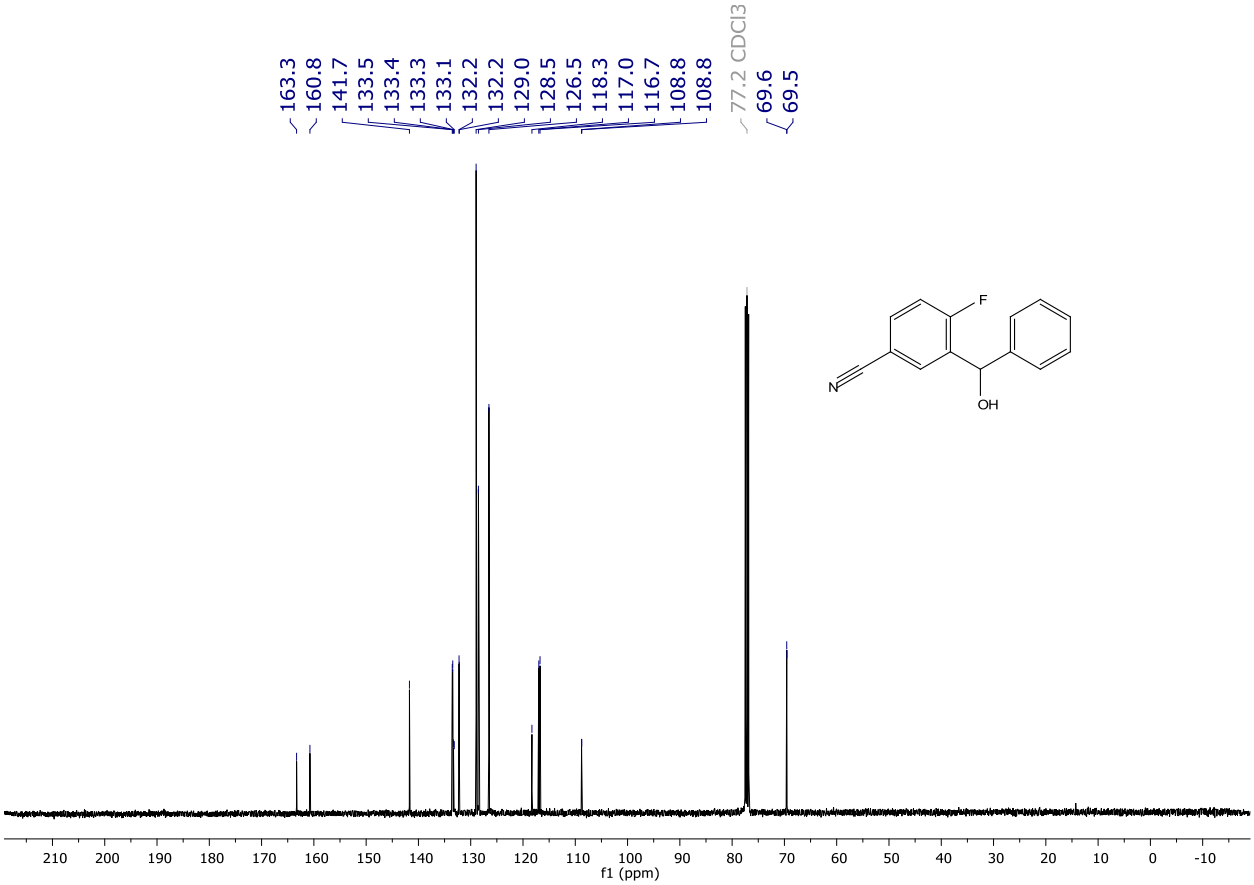


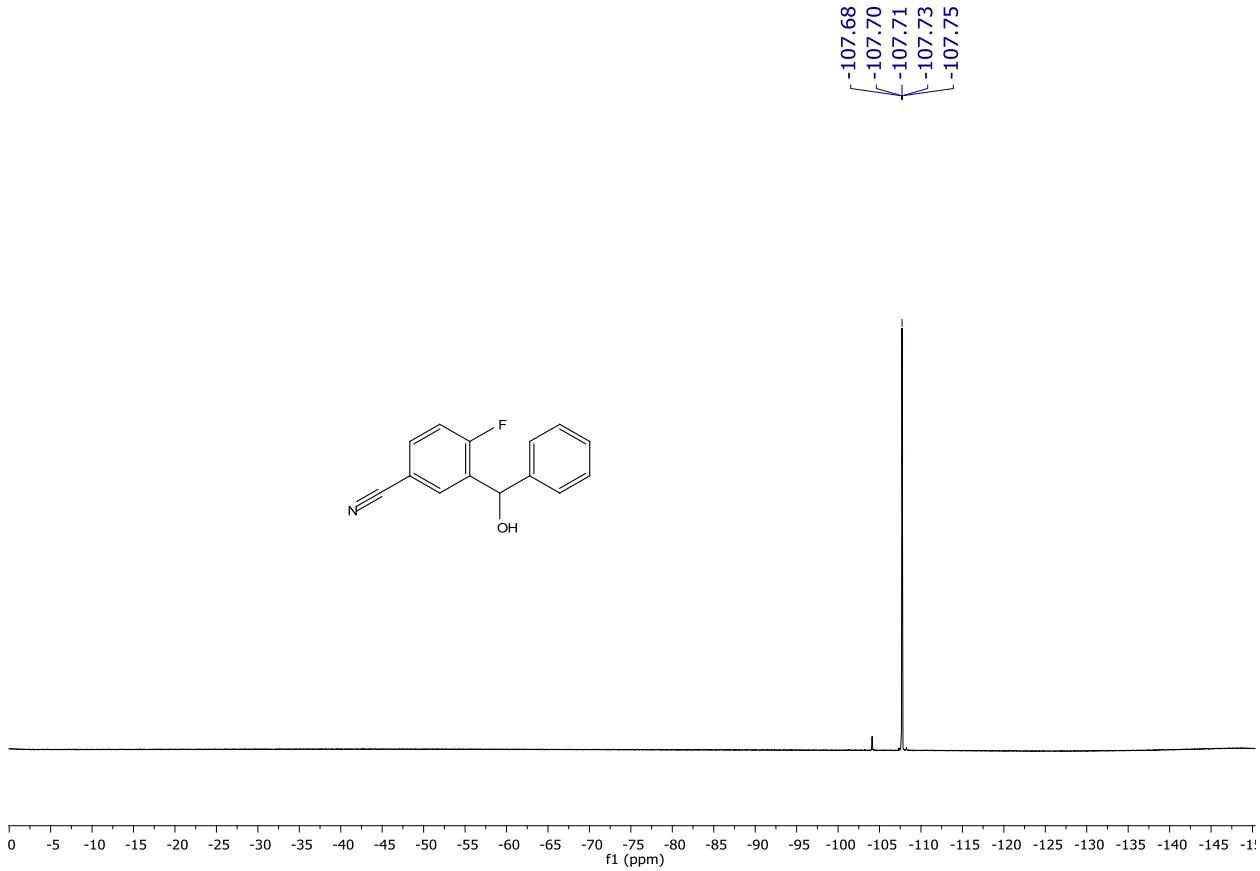
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125k**.



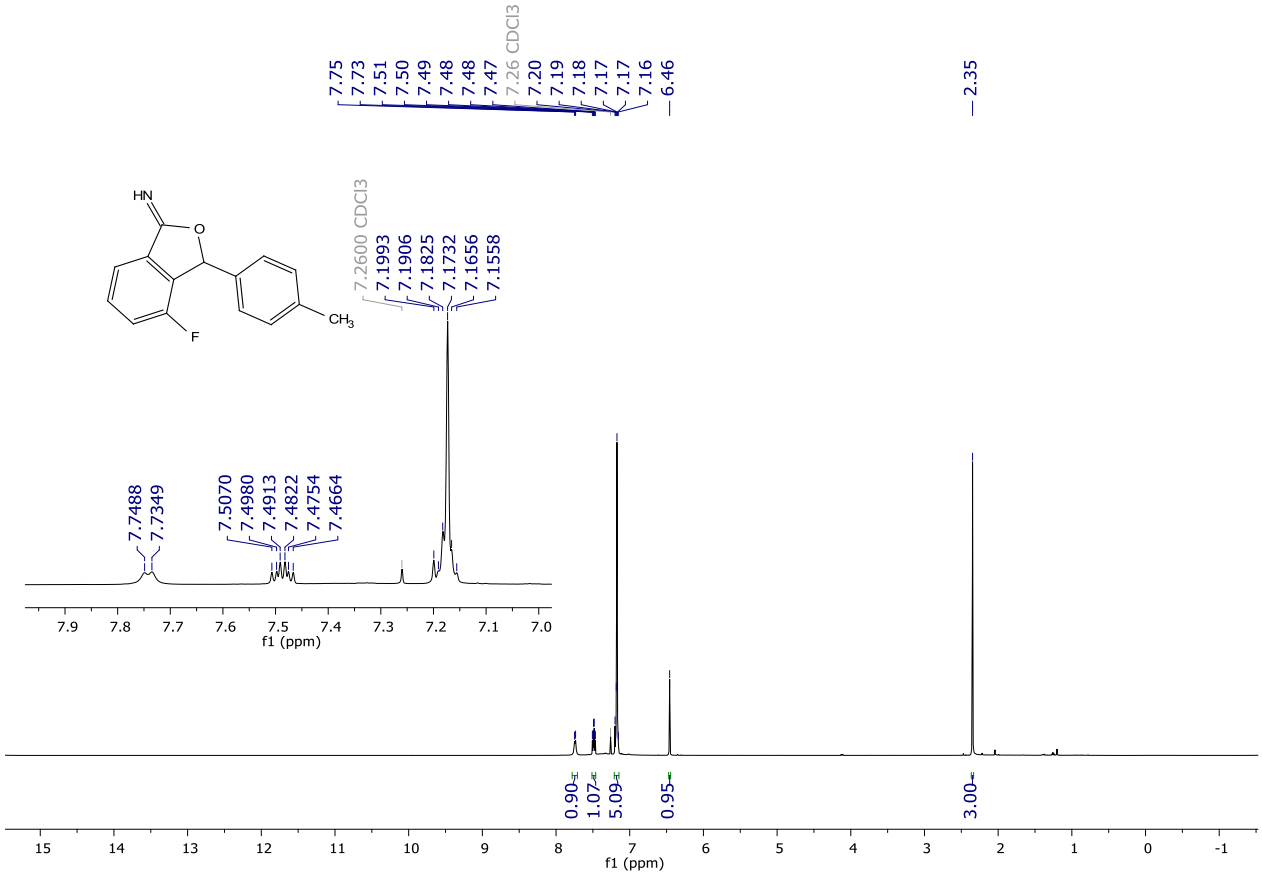
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125l.**



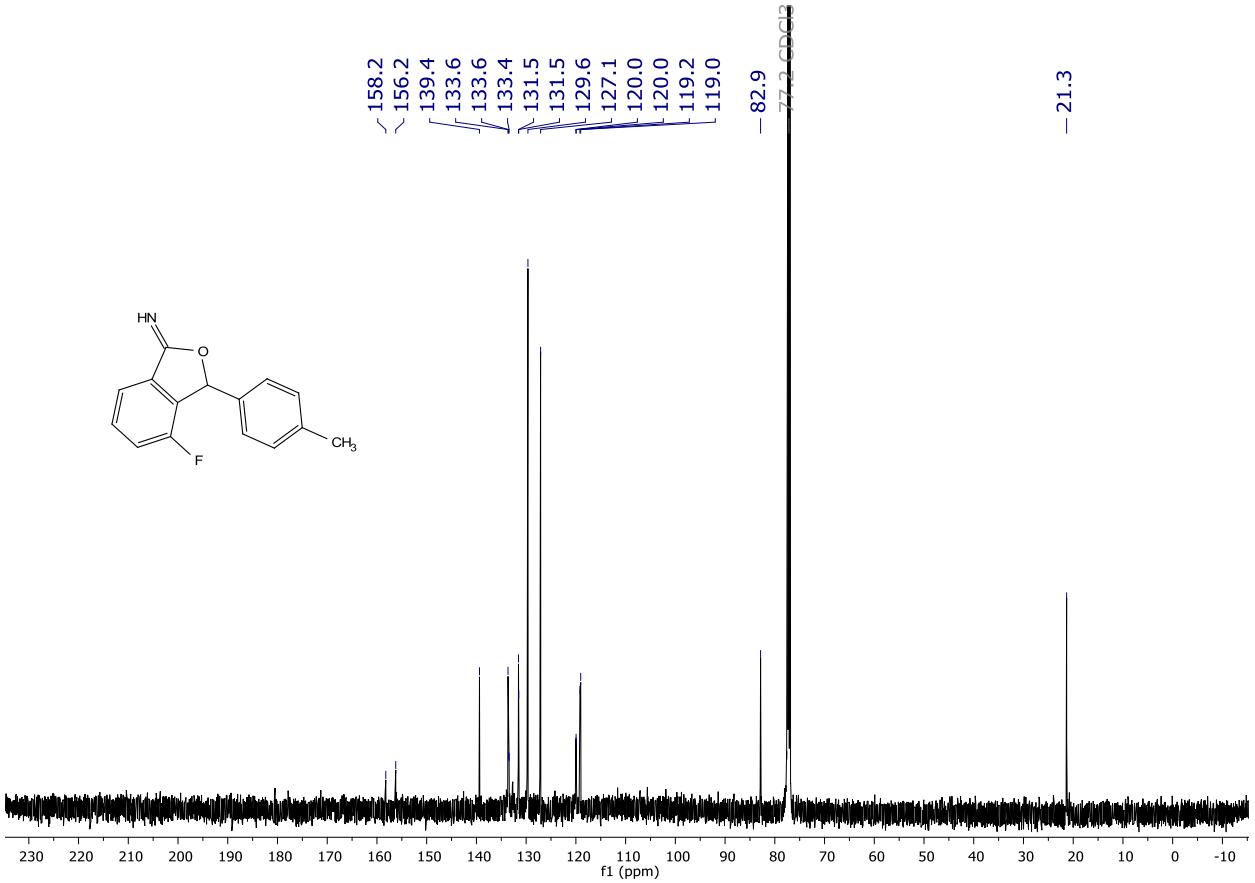
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) spectrum of **125l.**



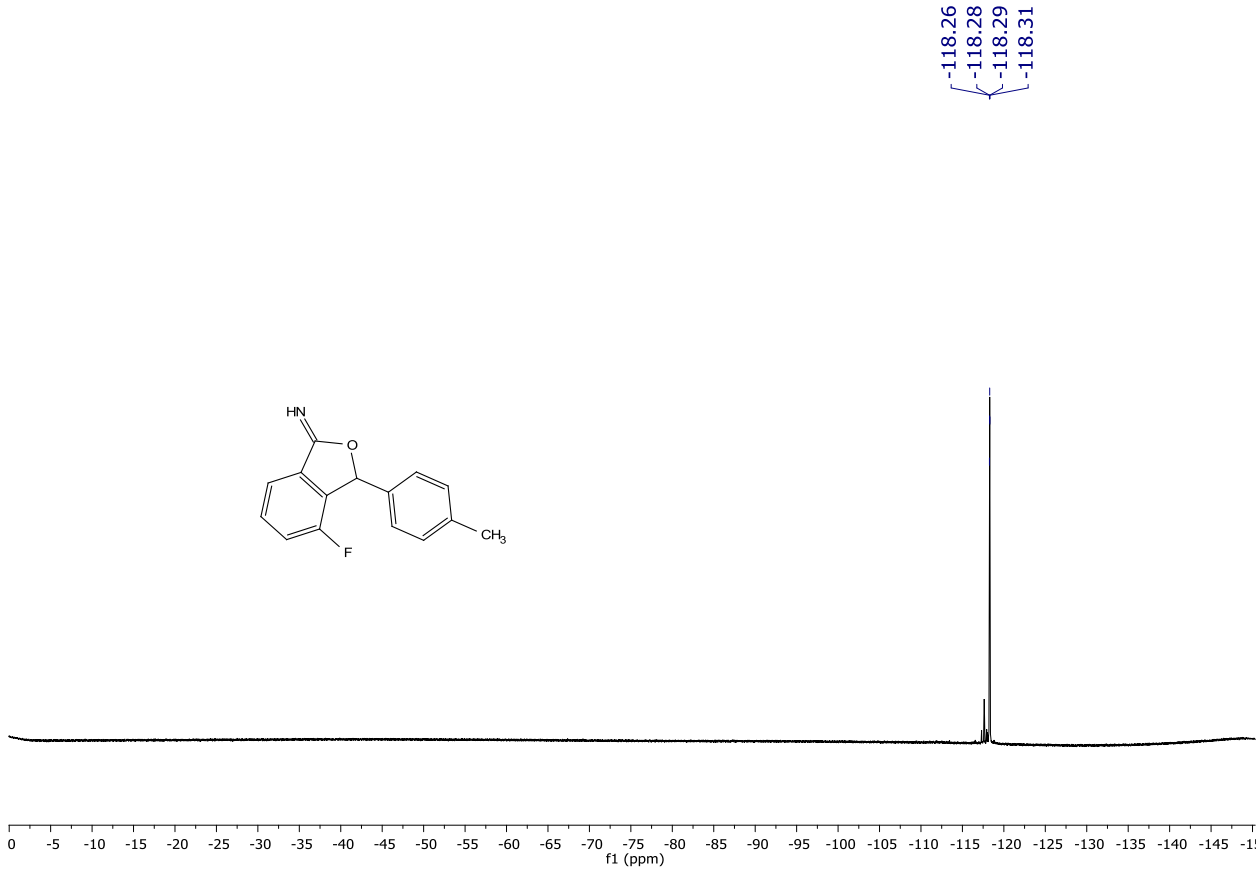
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125l.**



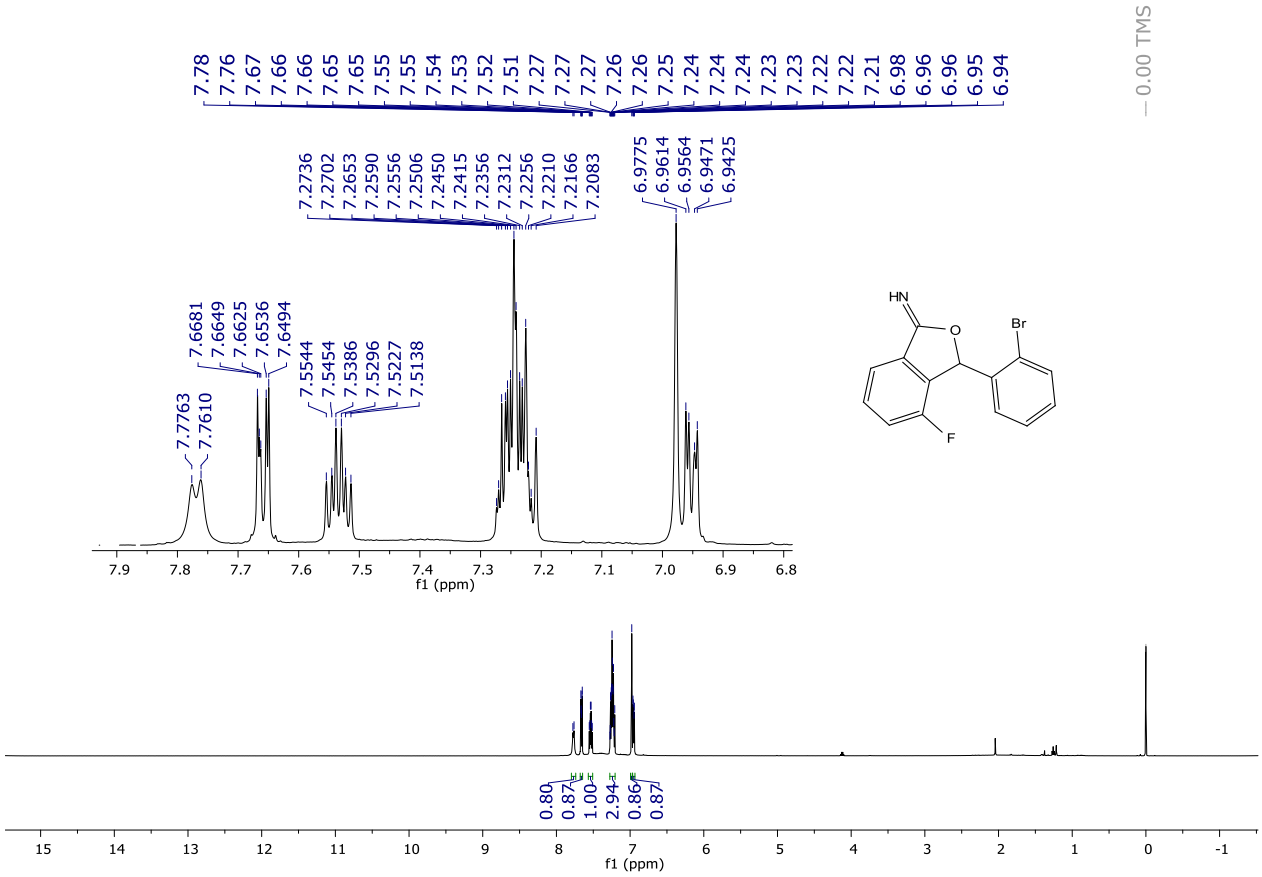
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **125m.**



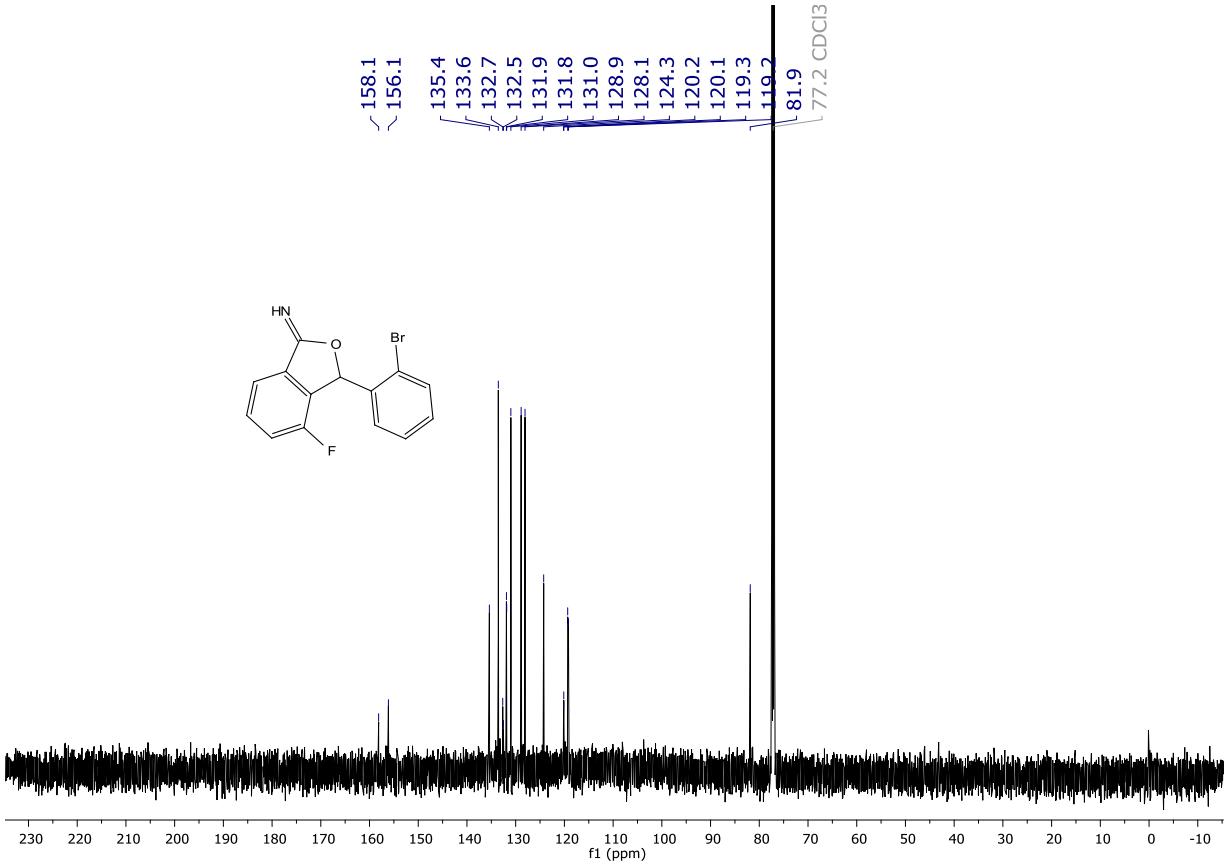
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) spectrum of **125m.**



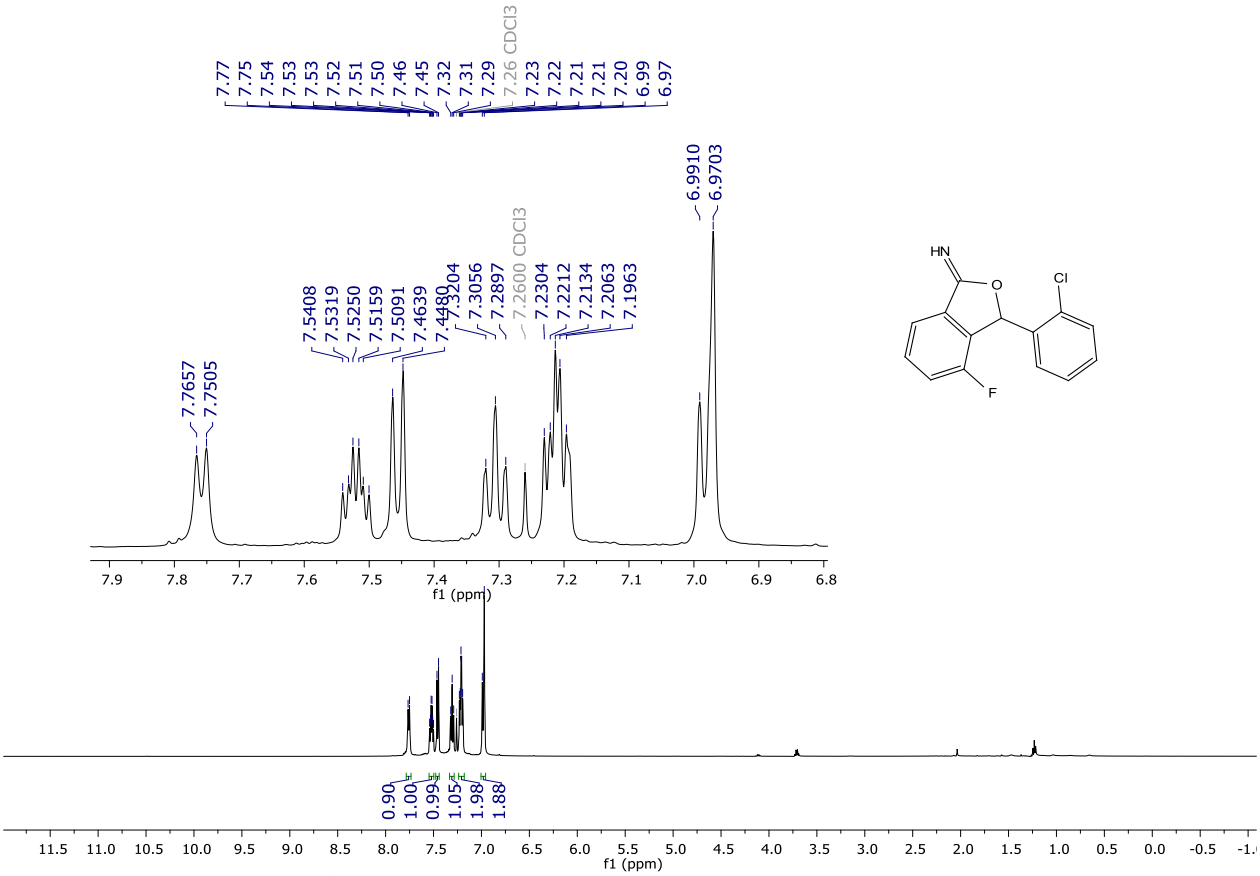
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125m.**



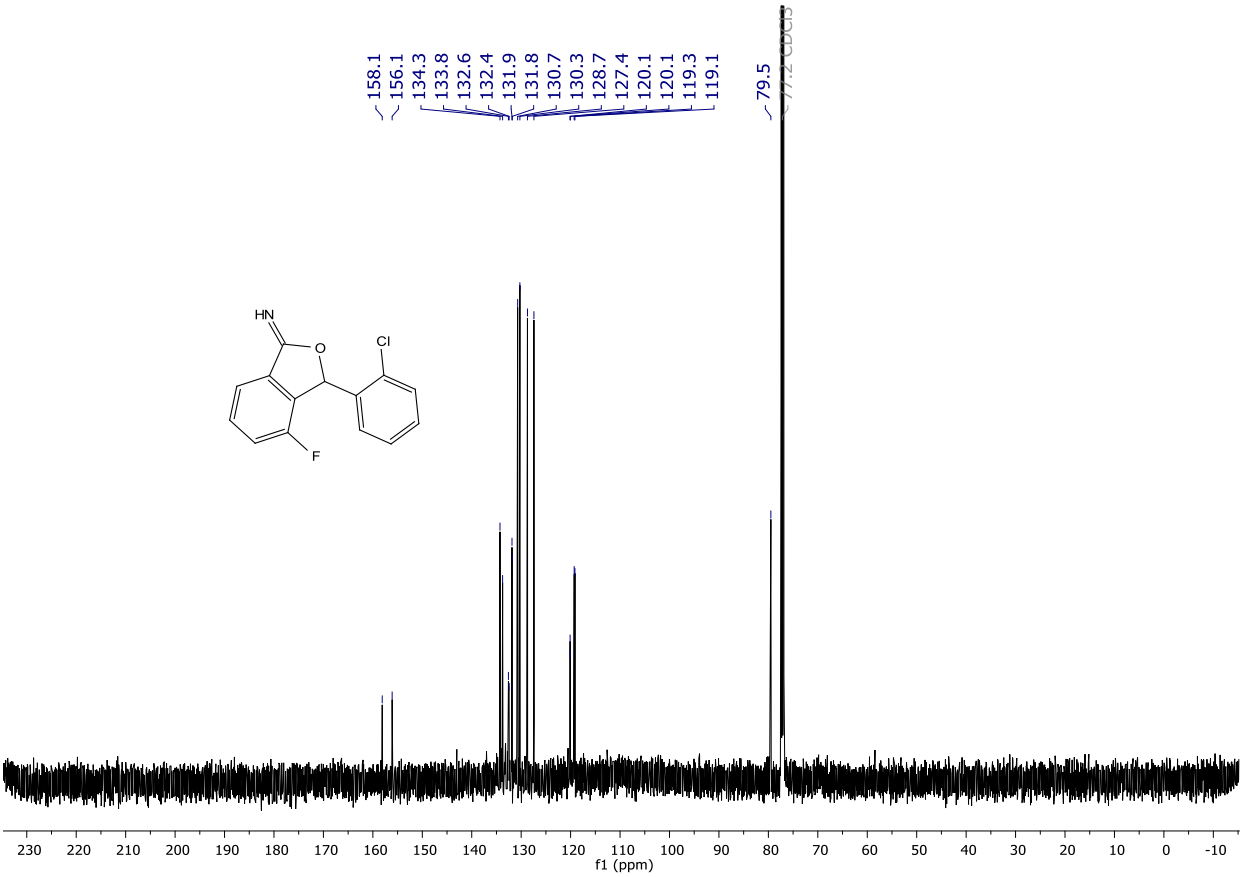
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **125n.**



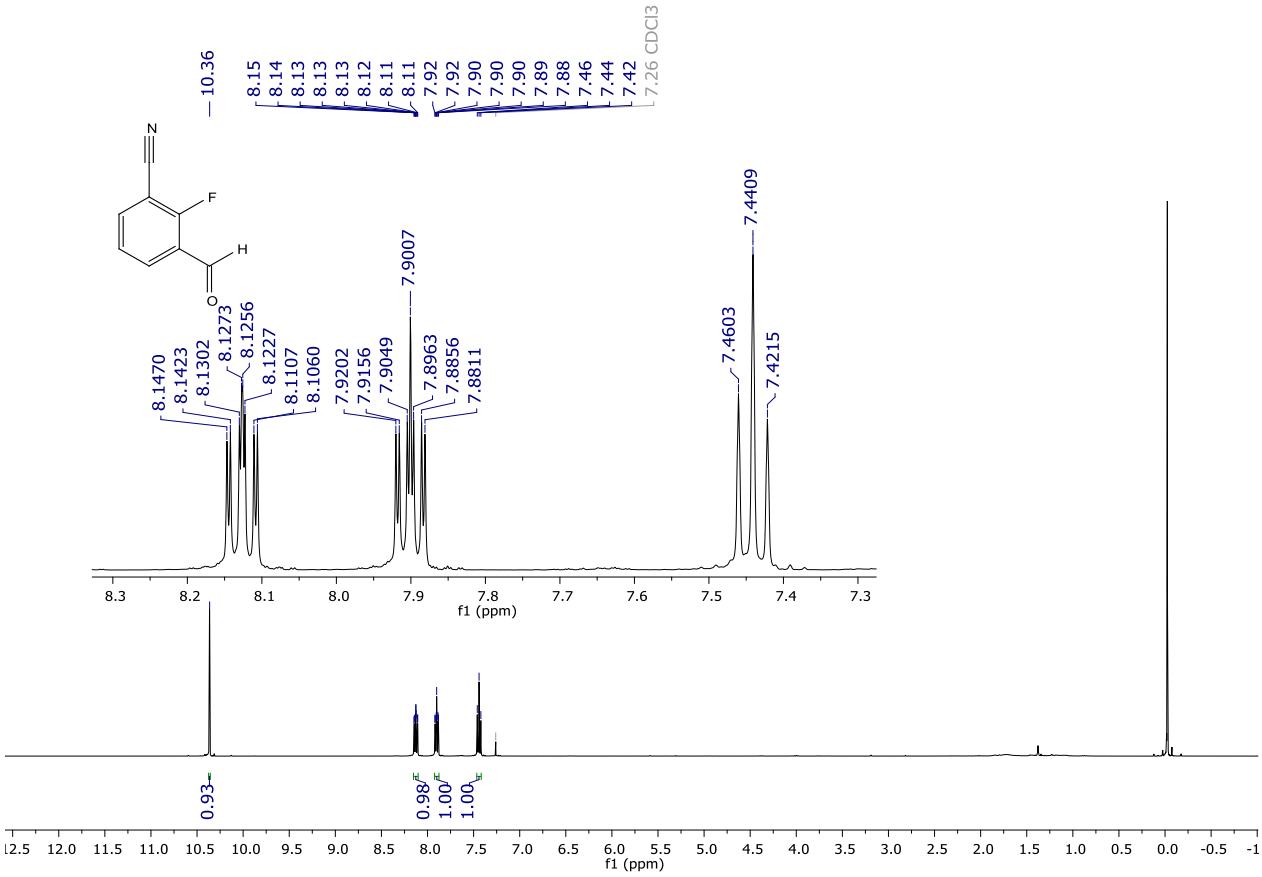
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) spectrum of **125n.**



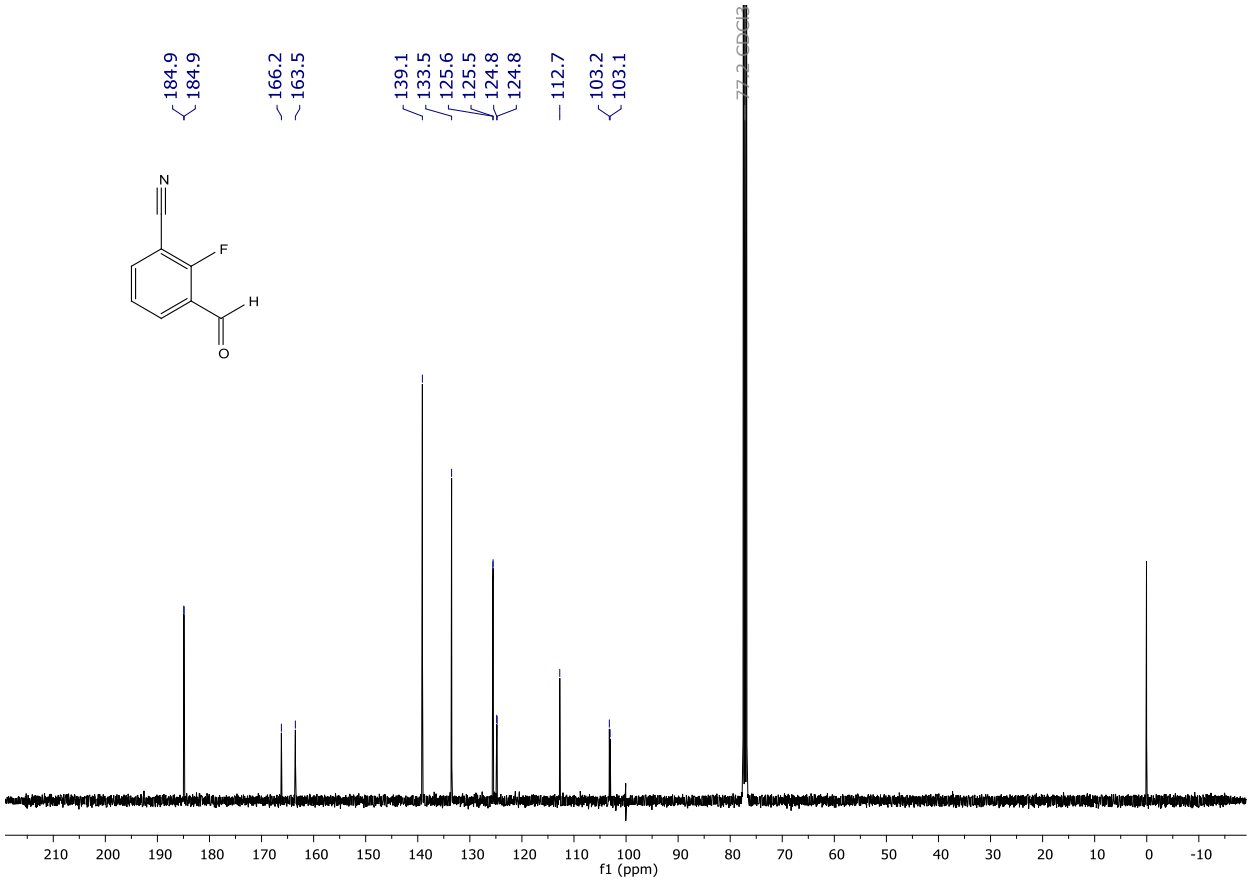
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **125o.**



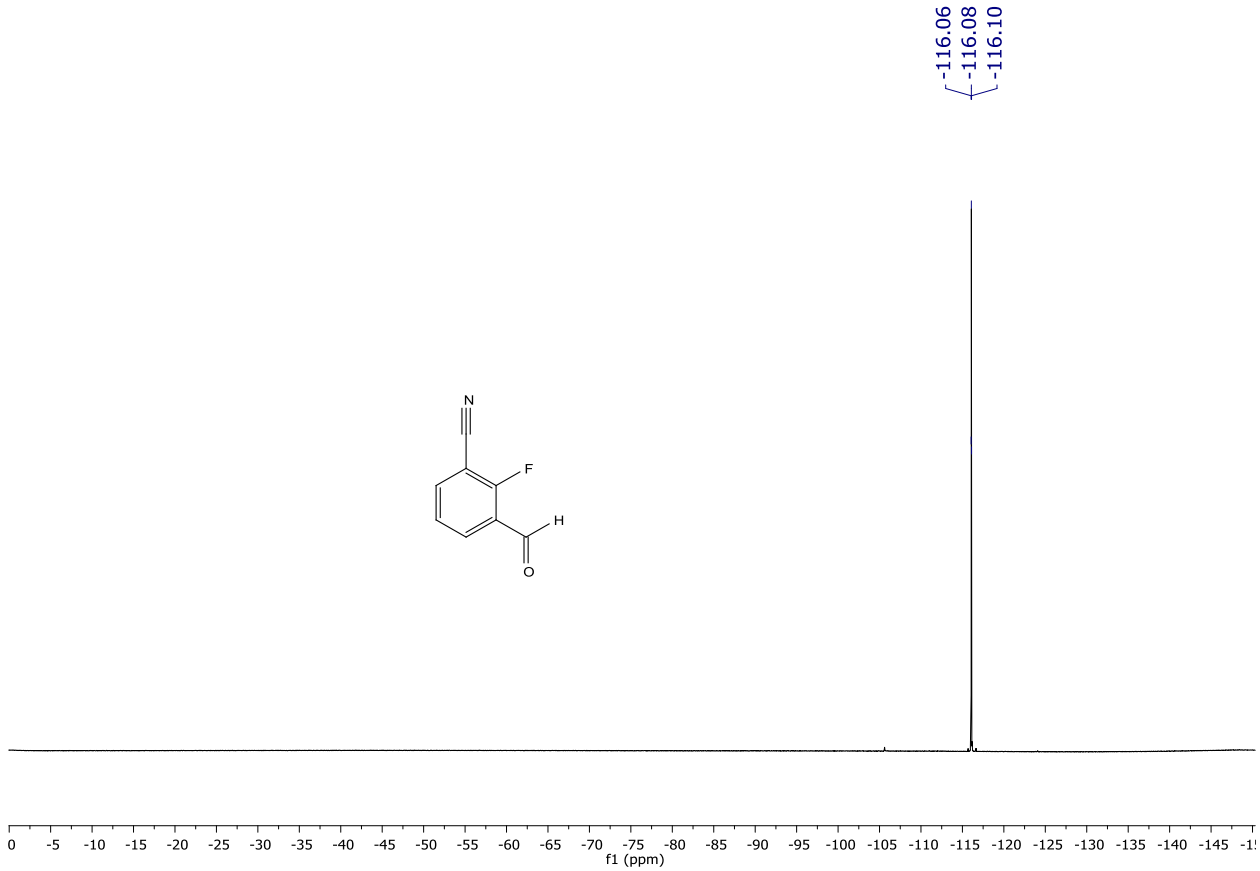
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) spectrum of **125o.**



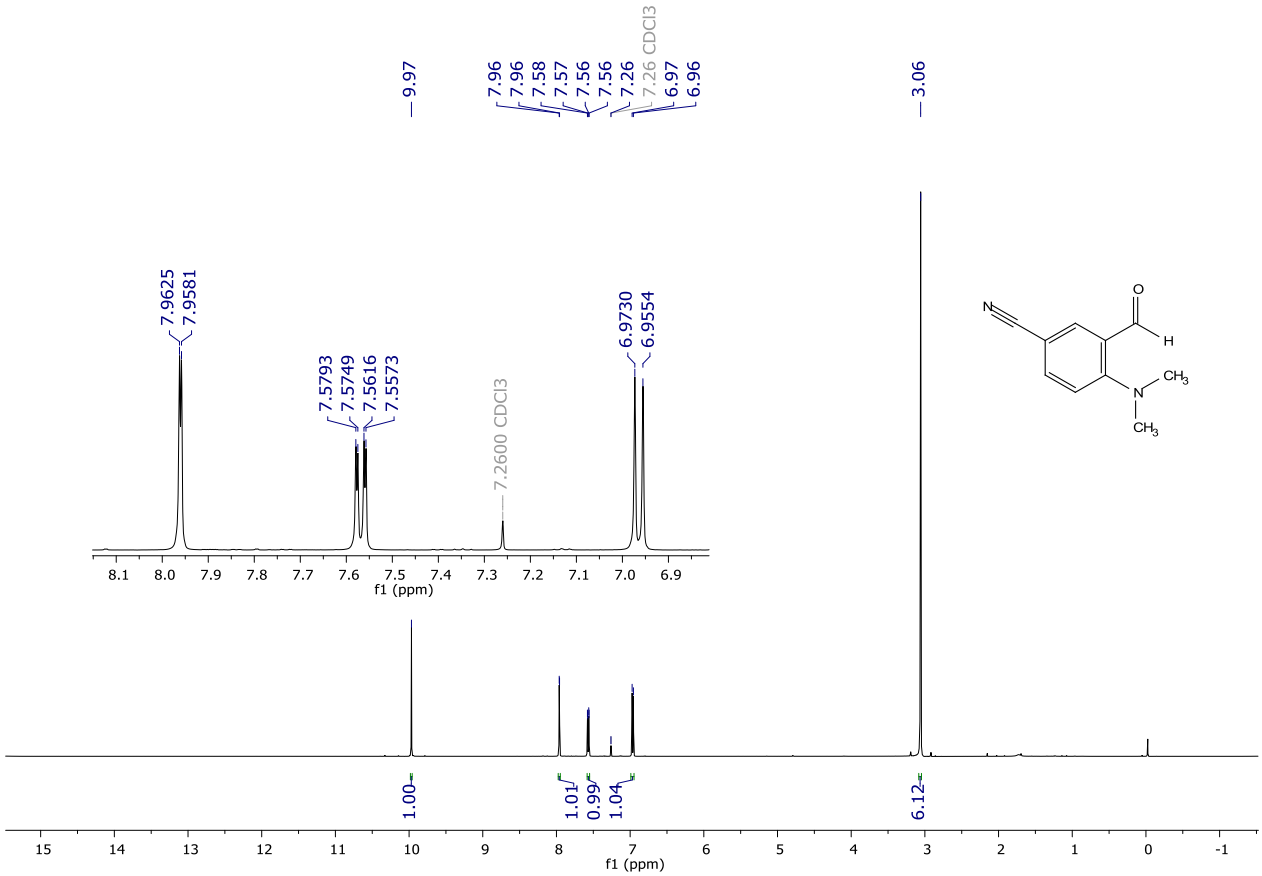
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125p.**



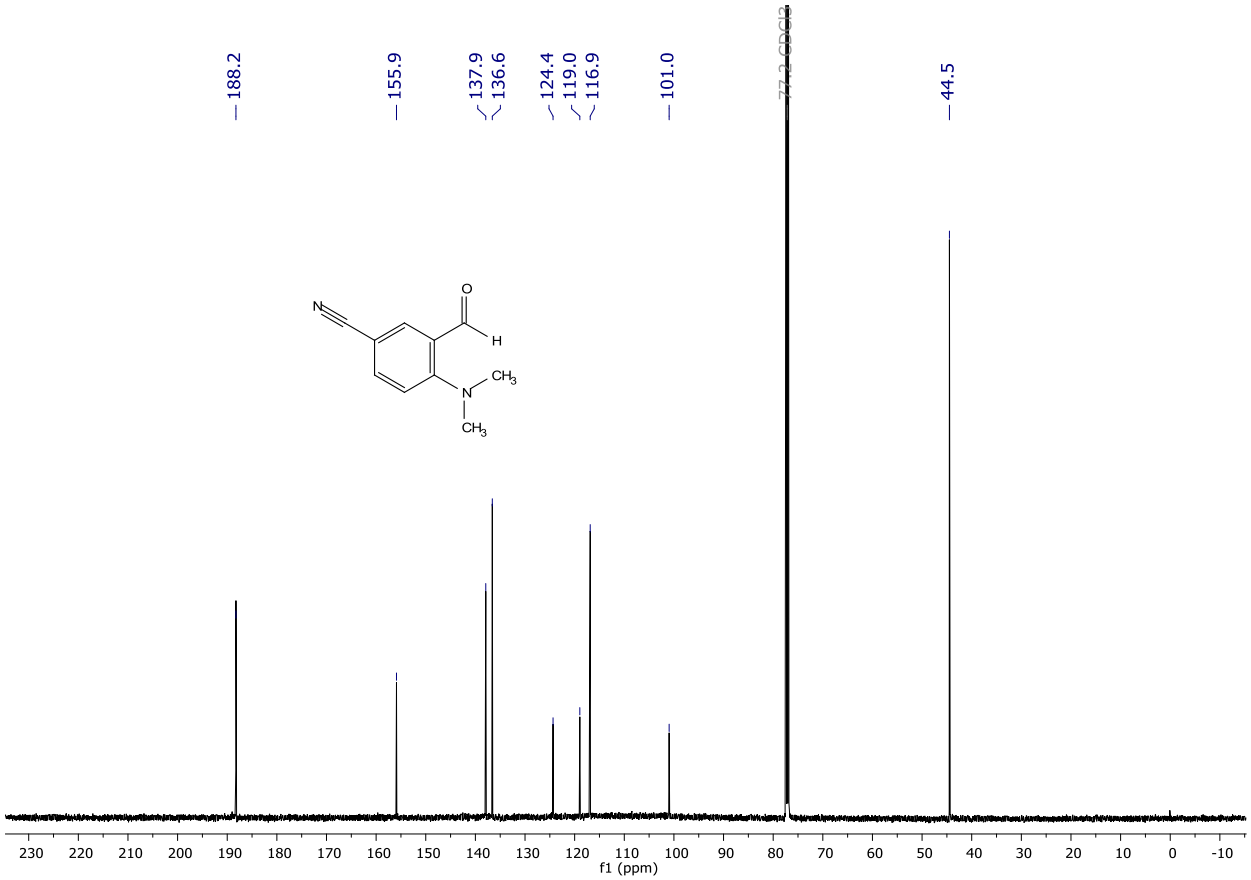
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) spectrum of **125p**.



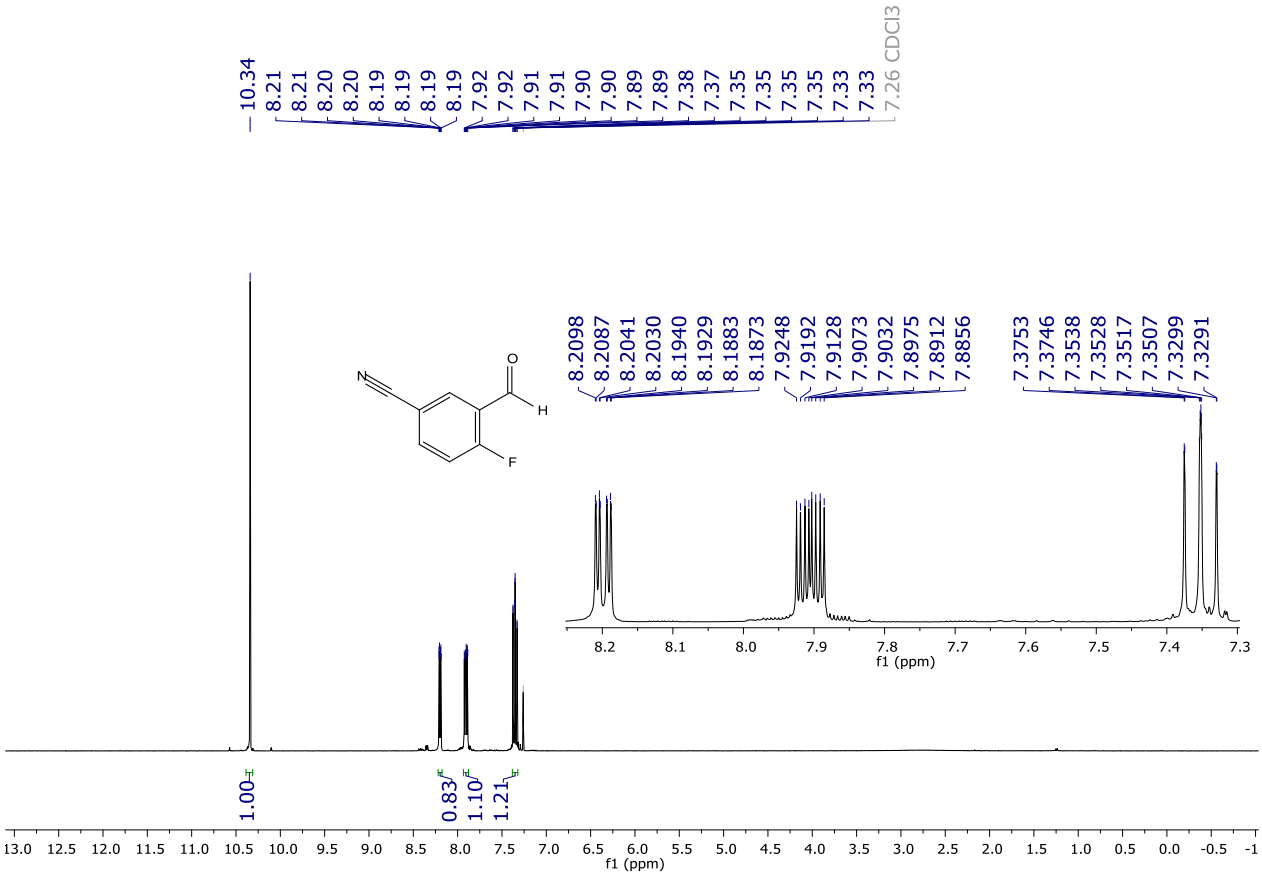
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125p**.



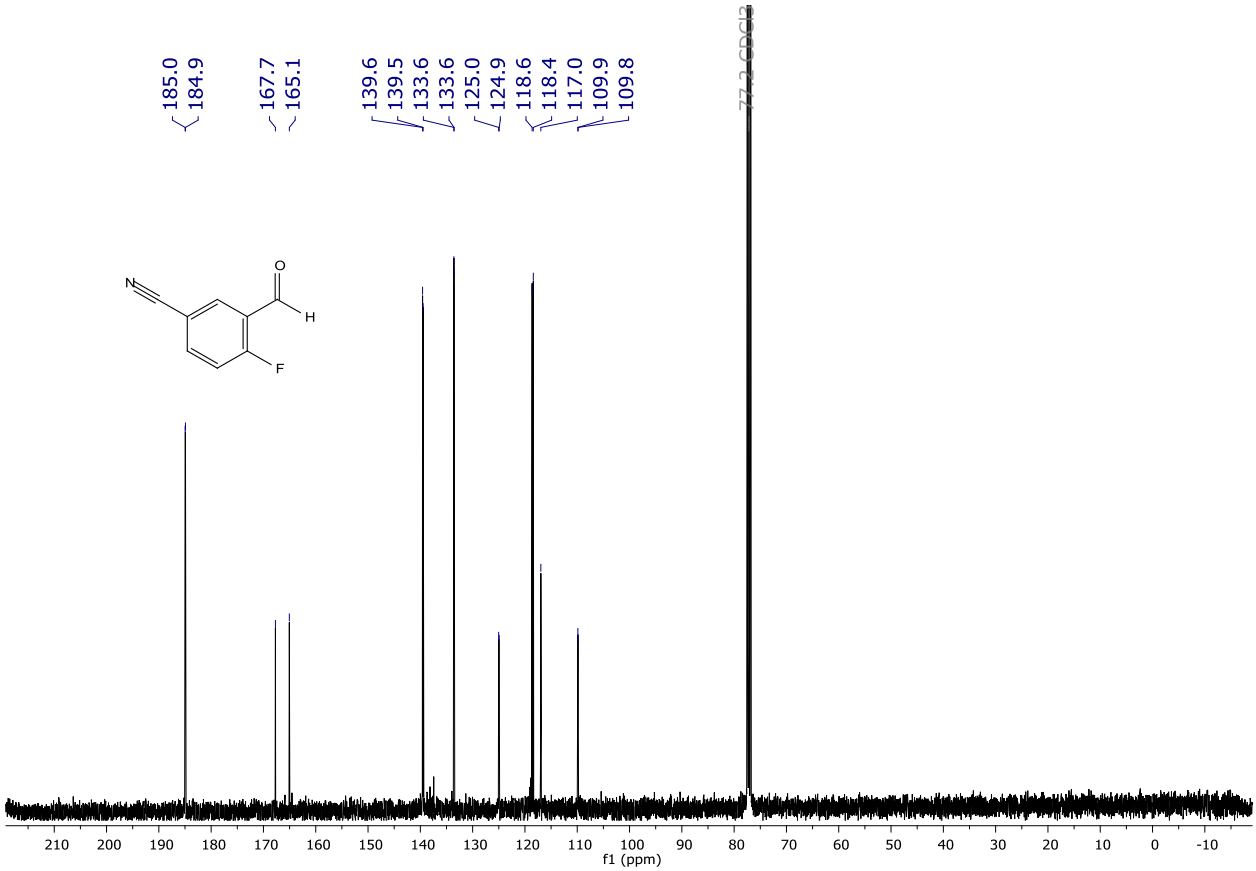
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **125q.**



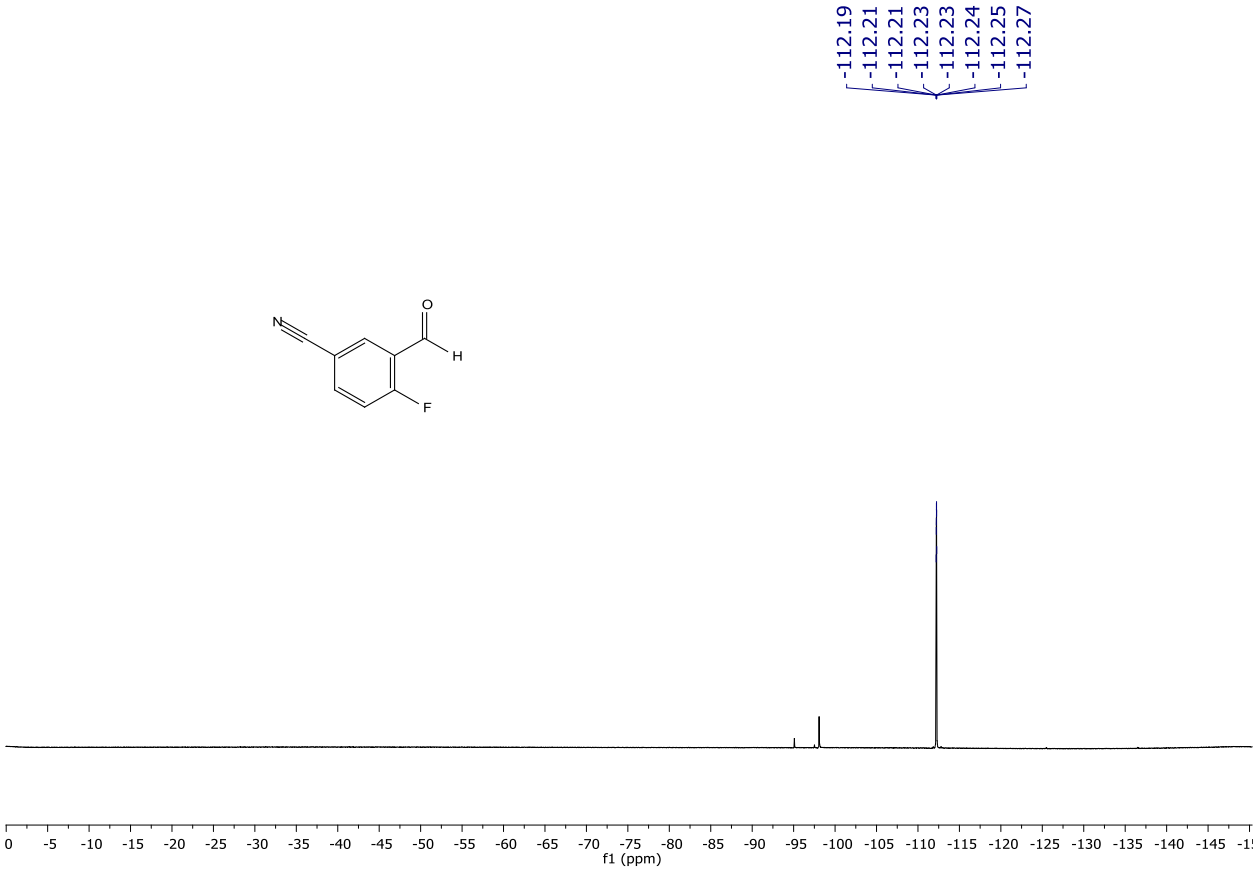
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) spectrum of **125q.**



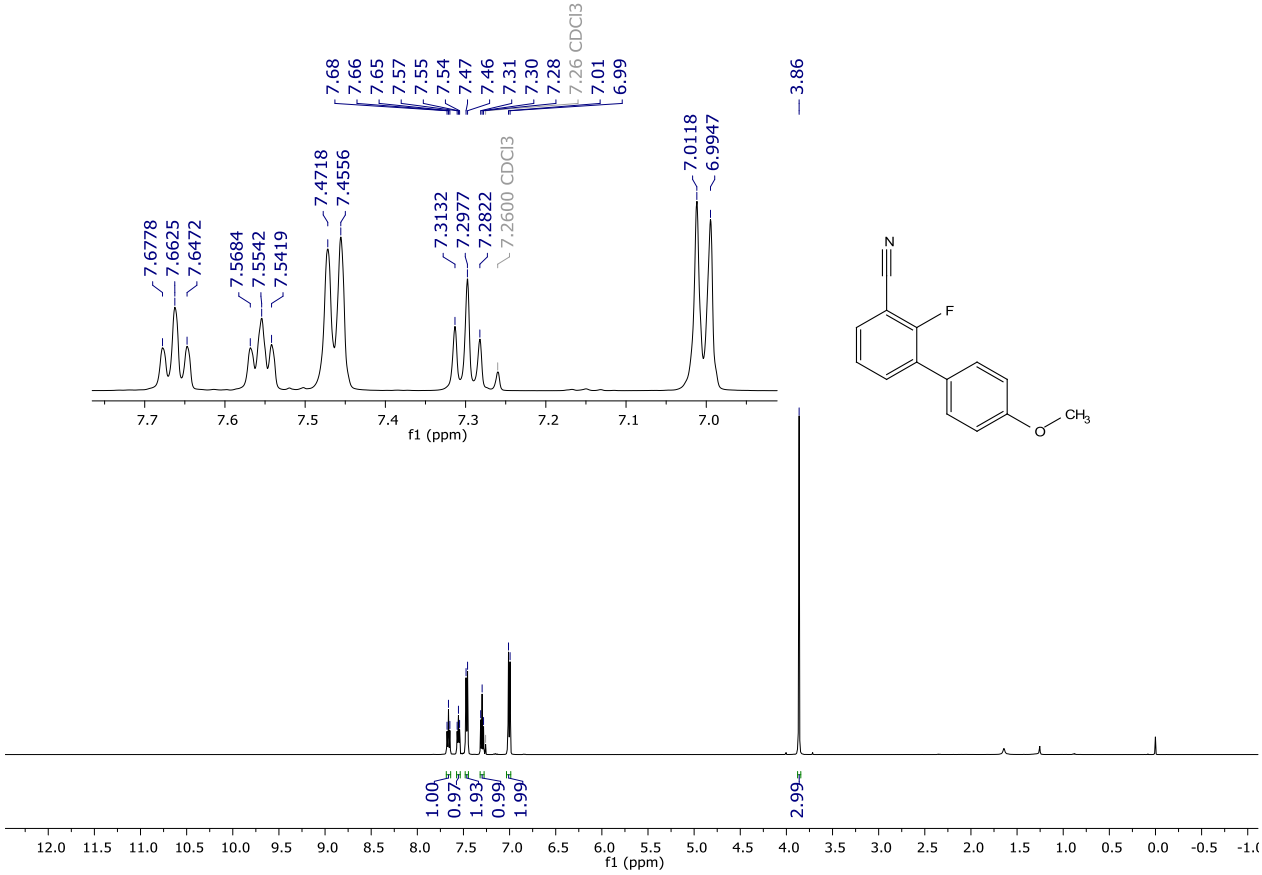
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125r.**



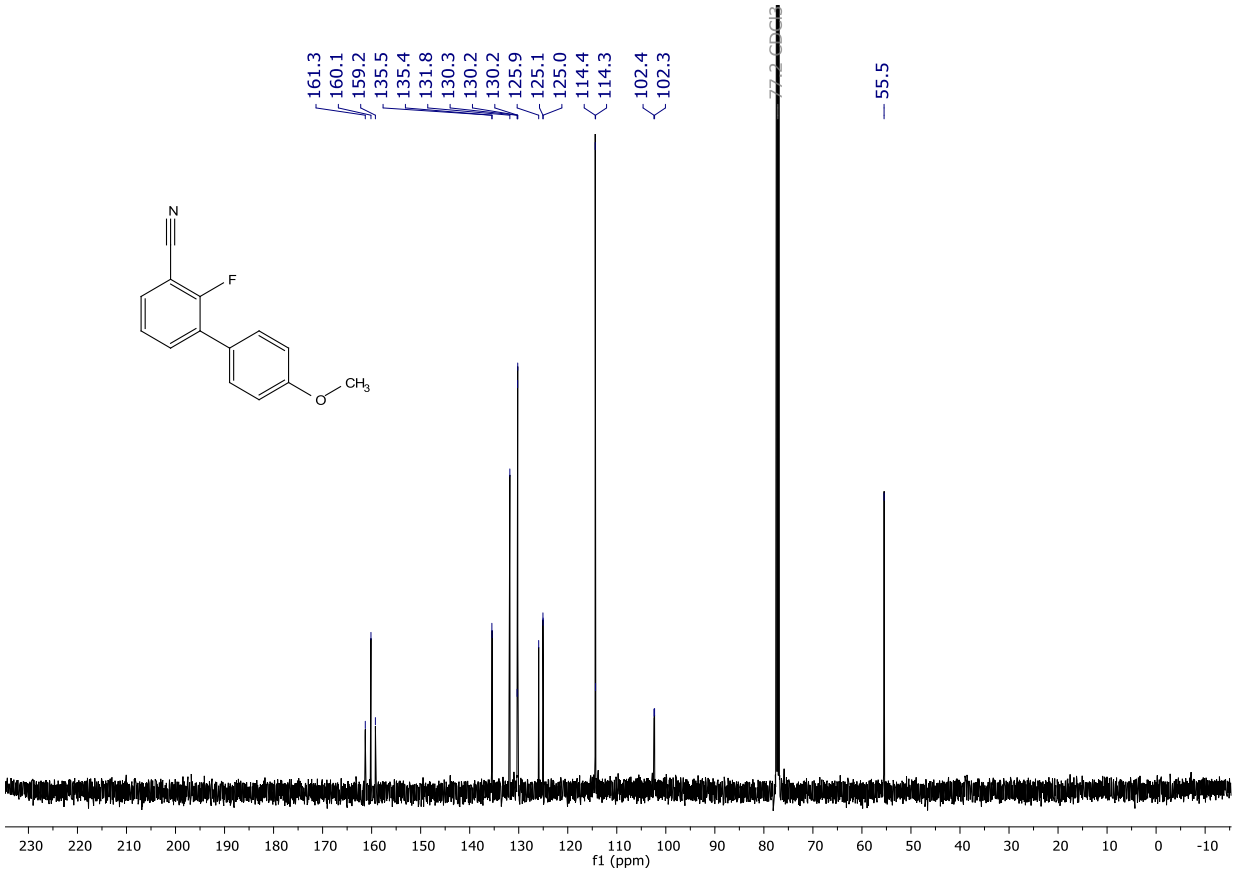
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125r.**



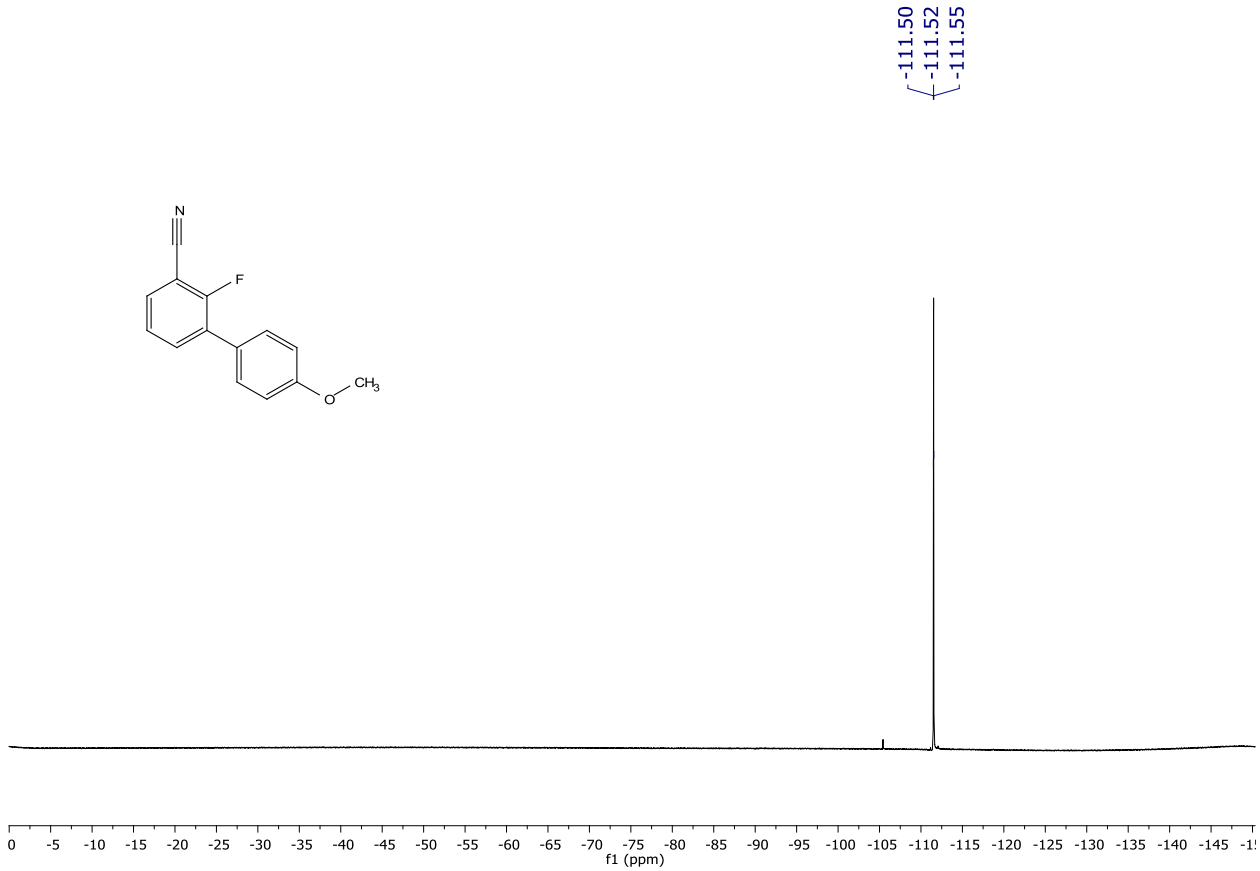
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125r.**



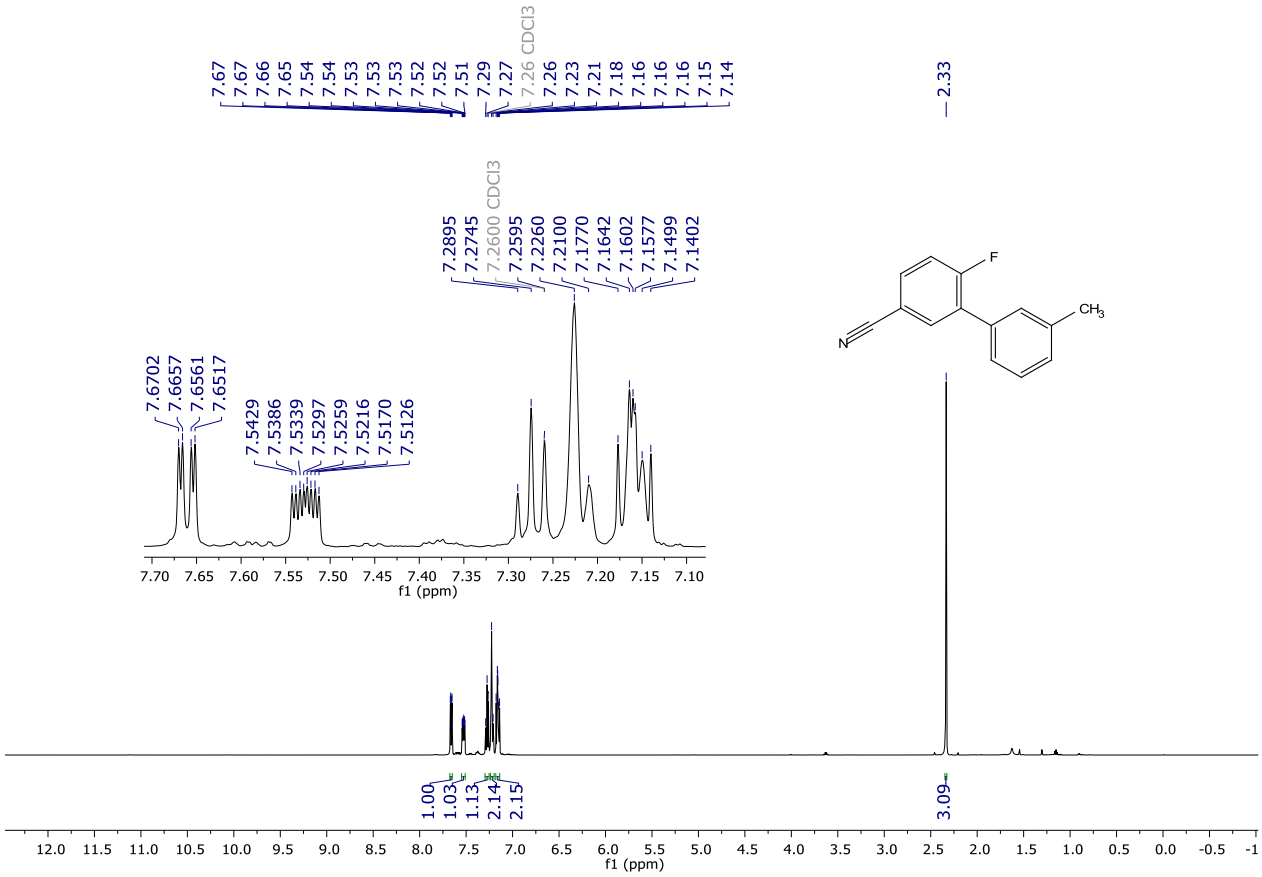
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **125s.**



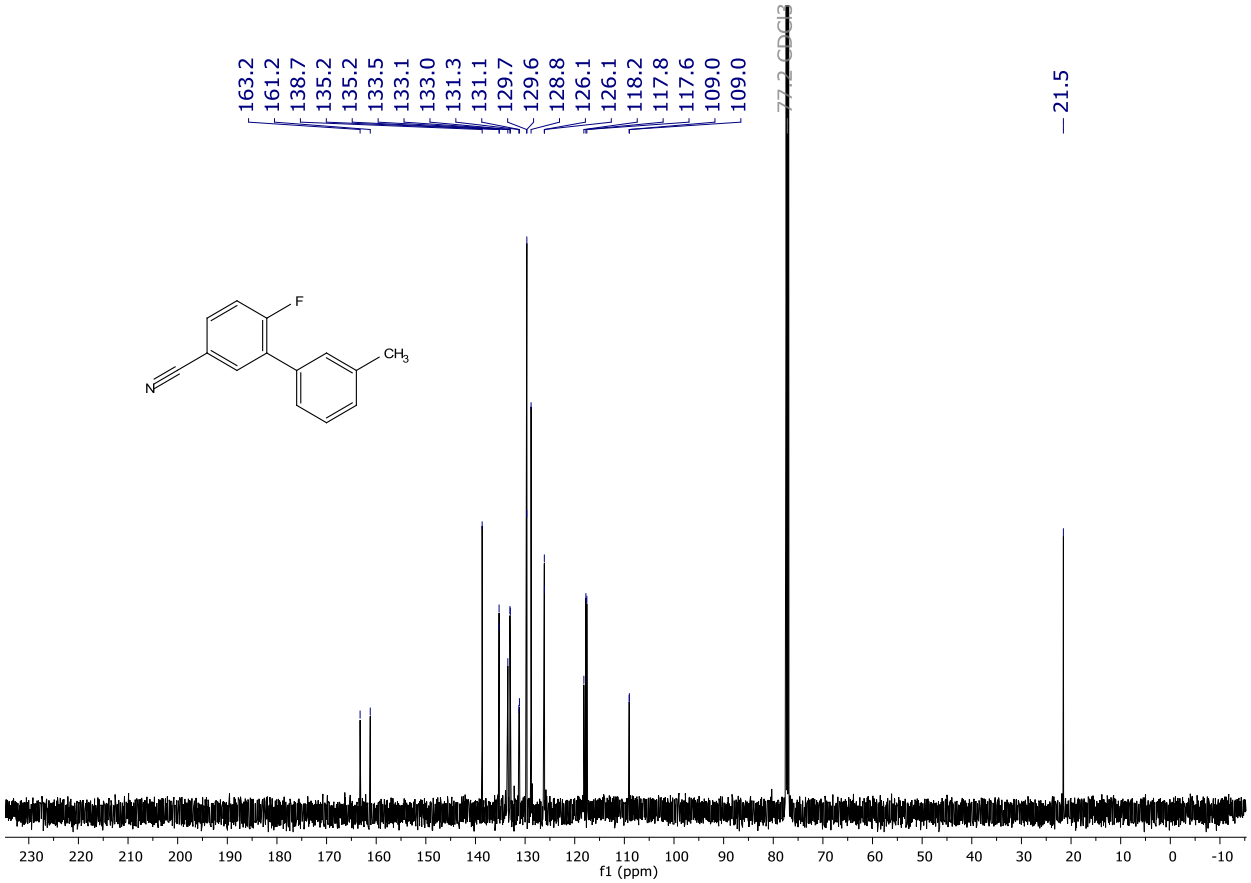
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) spectrum of **125s**.



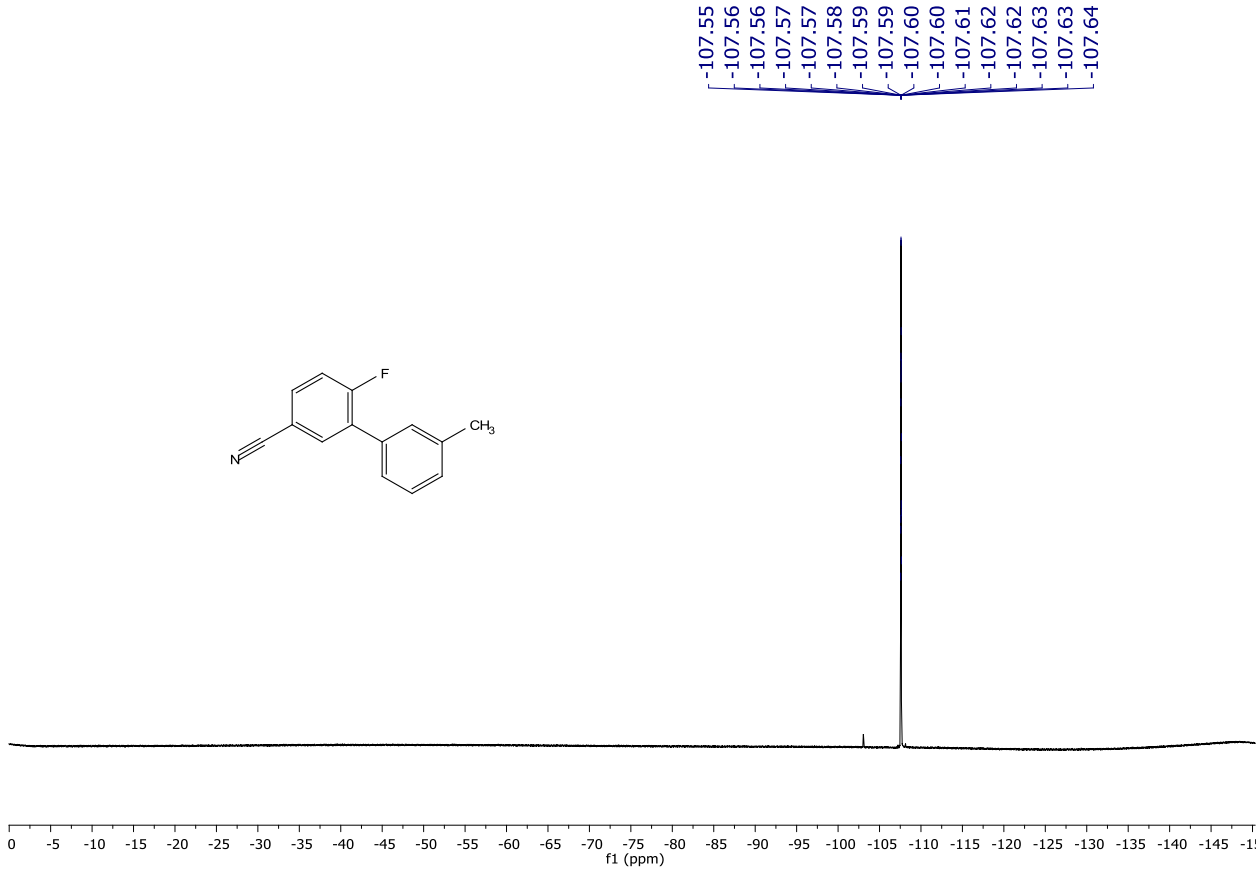
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125s**.



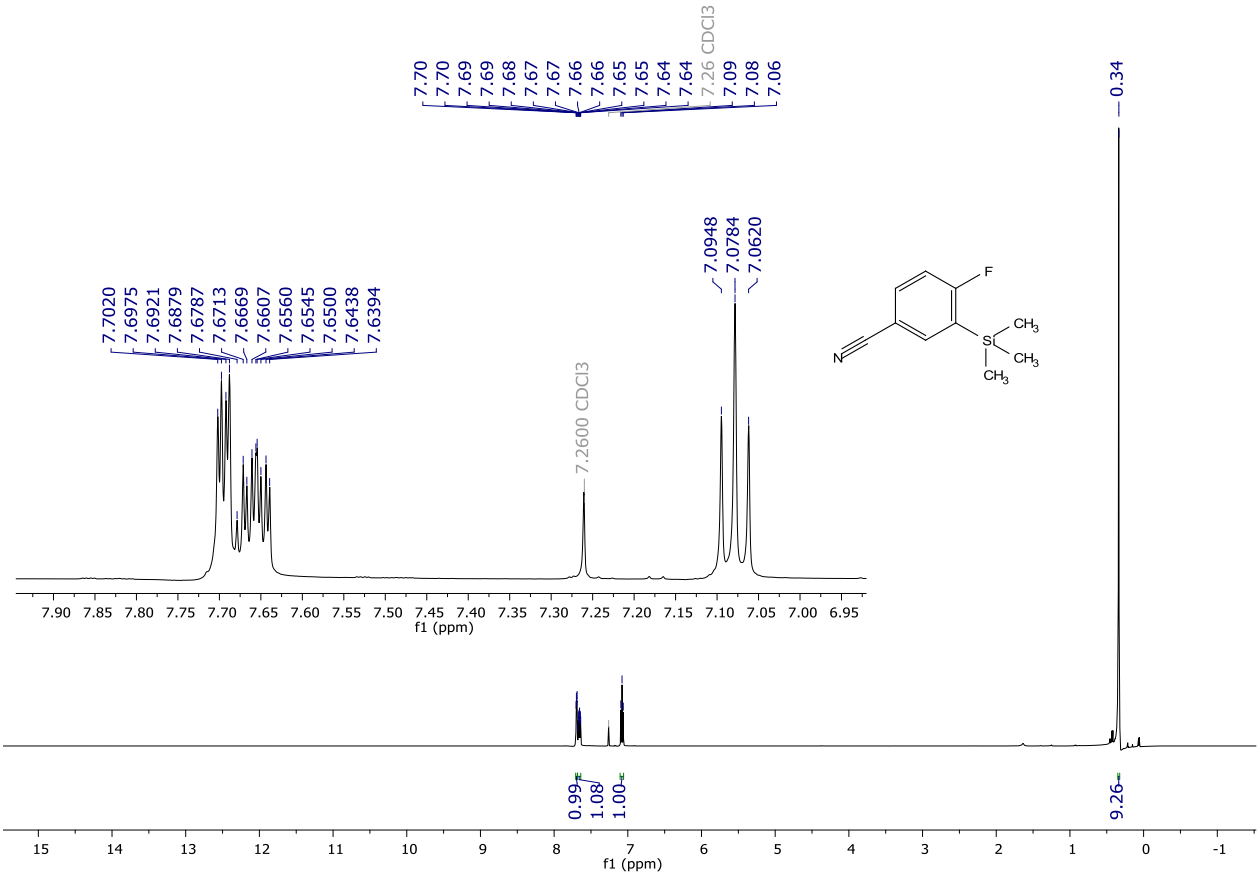
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **125t.**



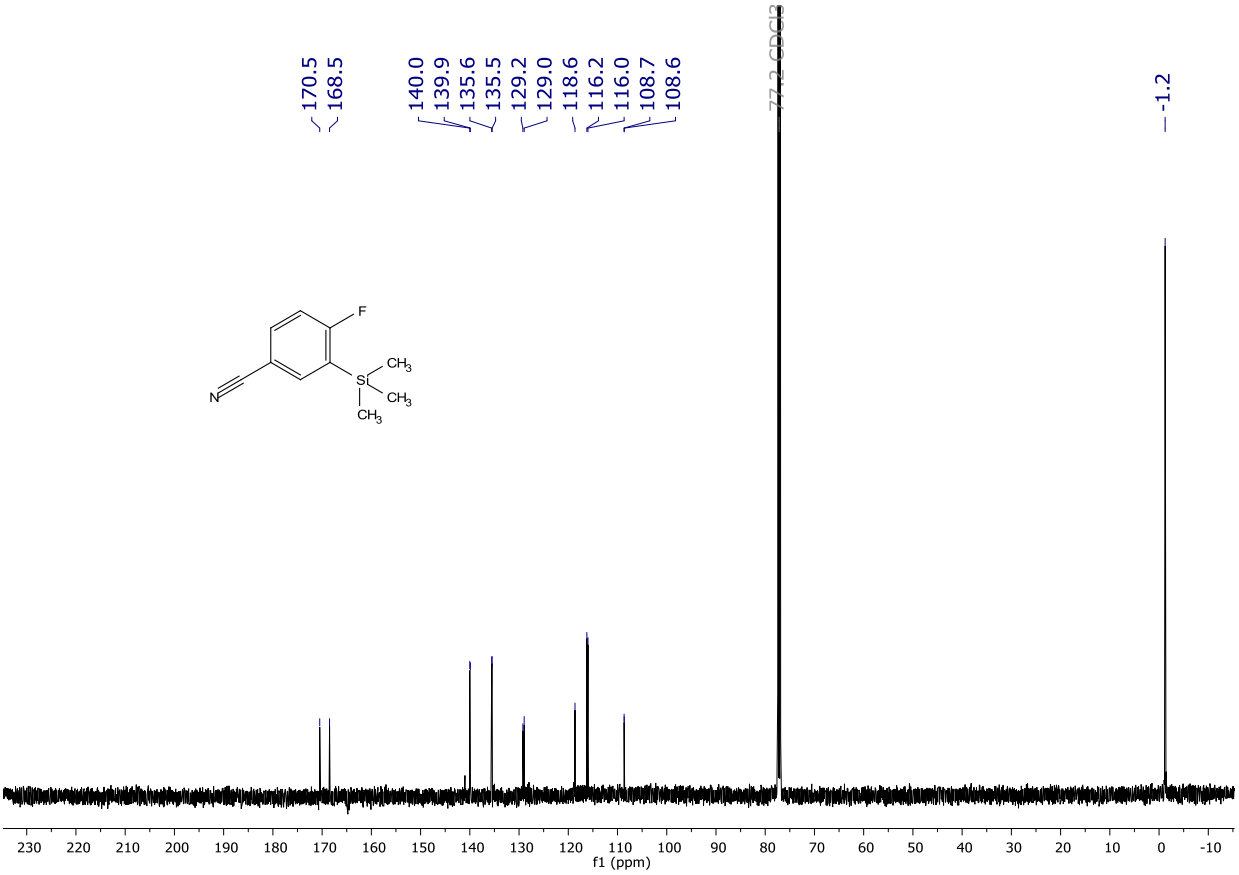
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) spectrum of **125t.**



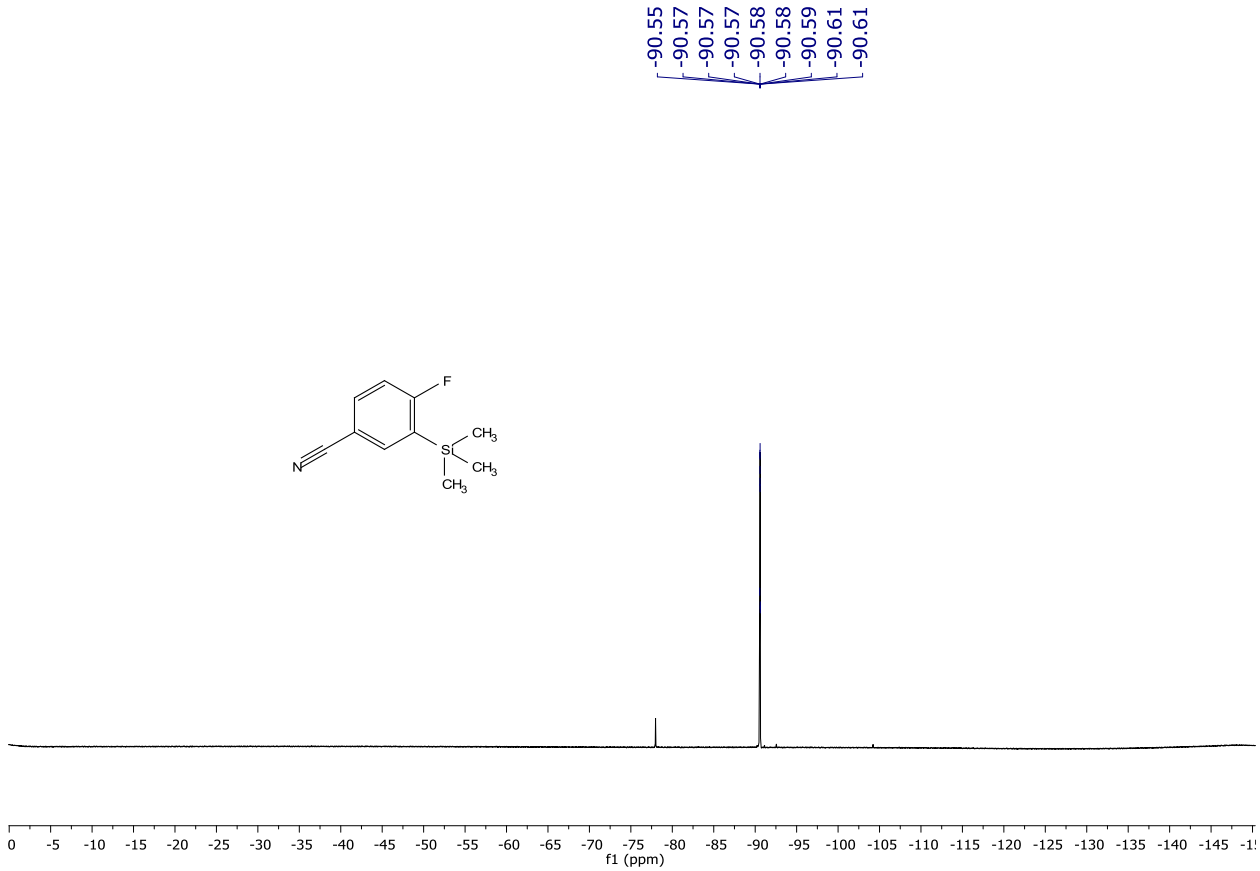
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125t.**



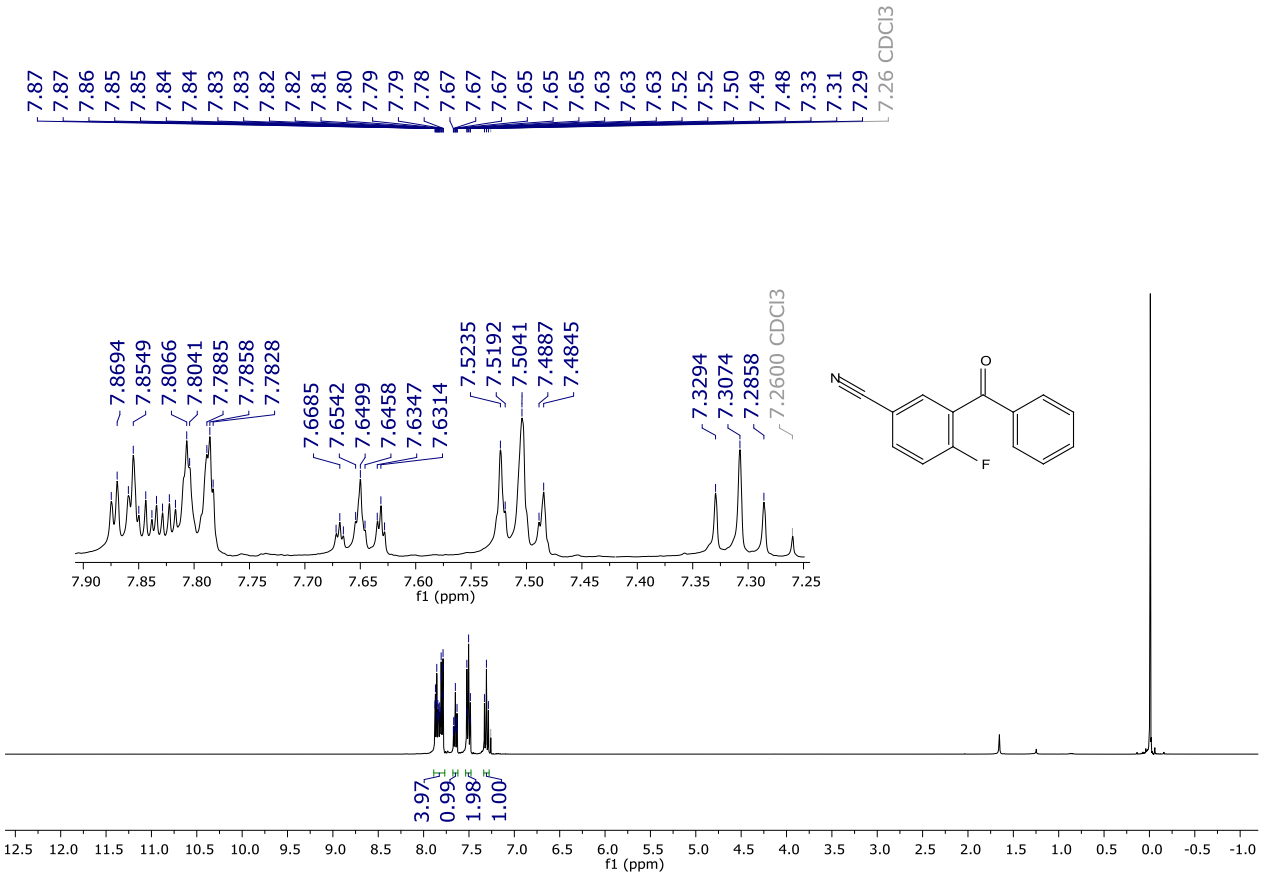
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **125u.**



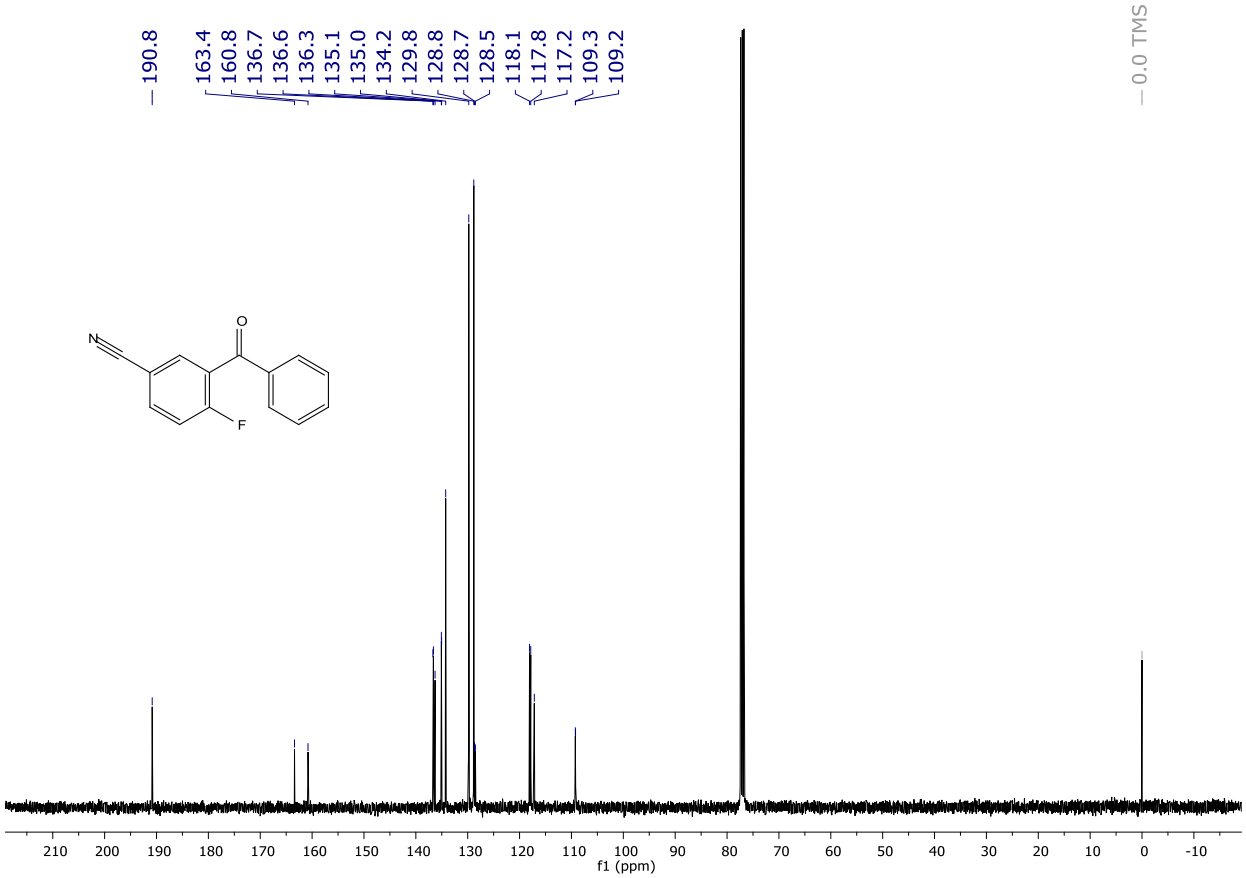
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) spectrum of **125u**.



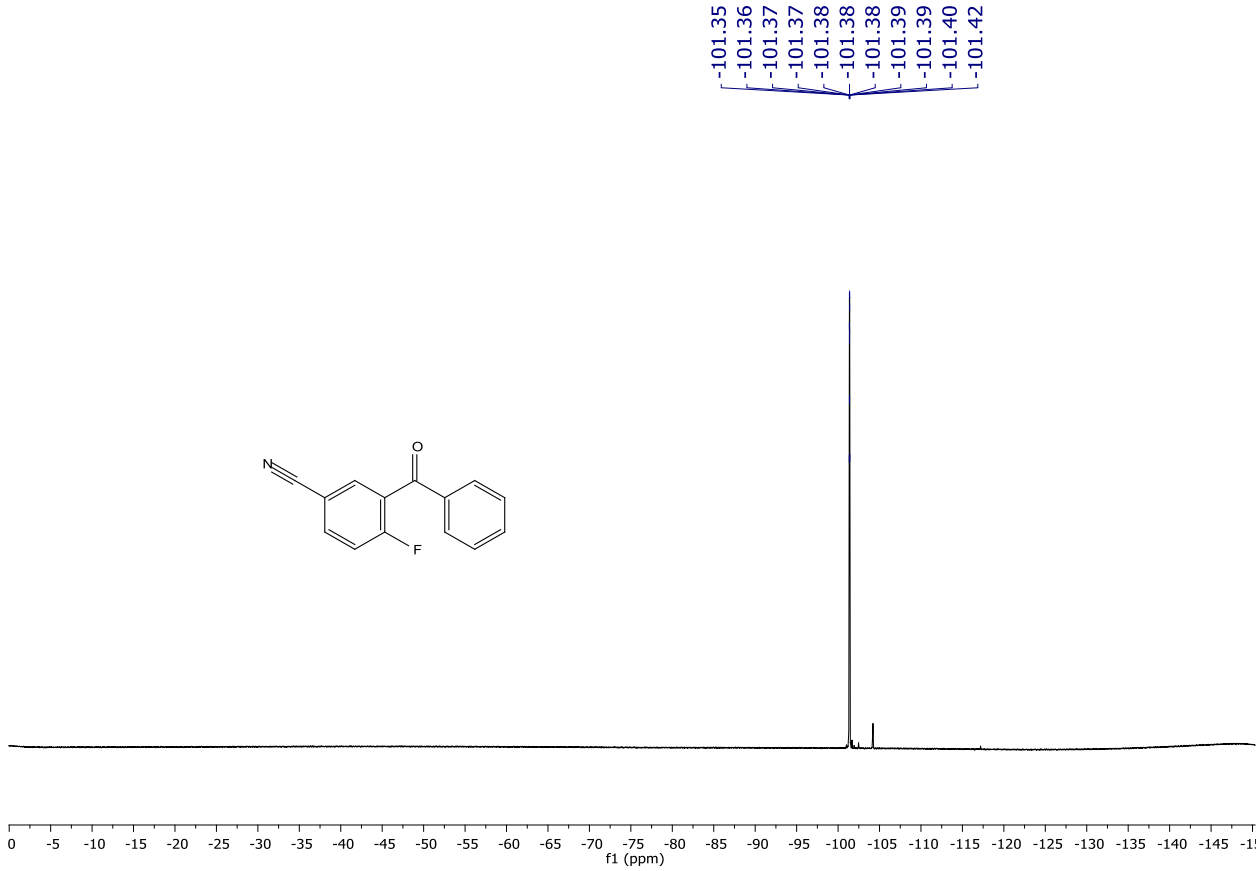
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125u**.



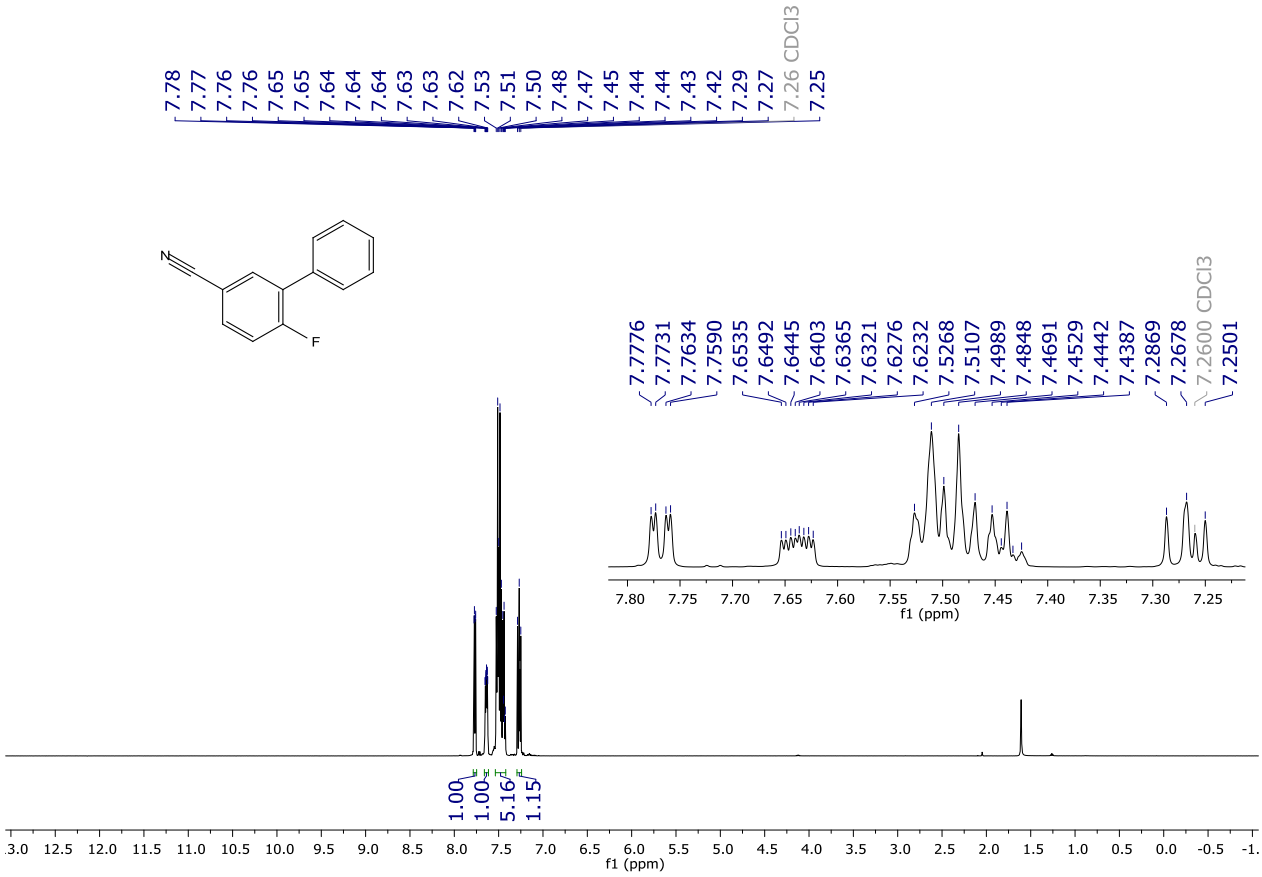
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125v.**



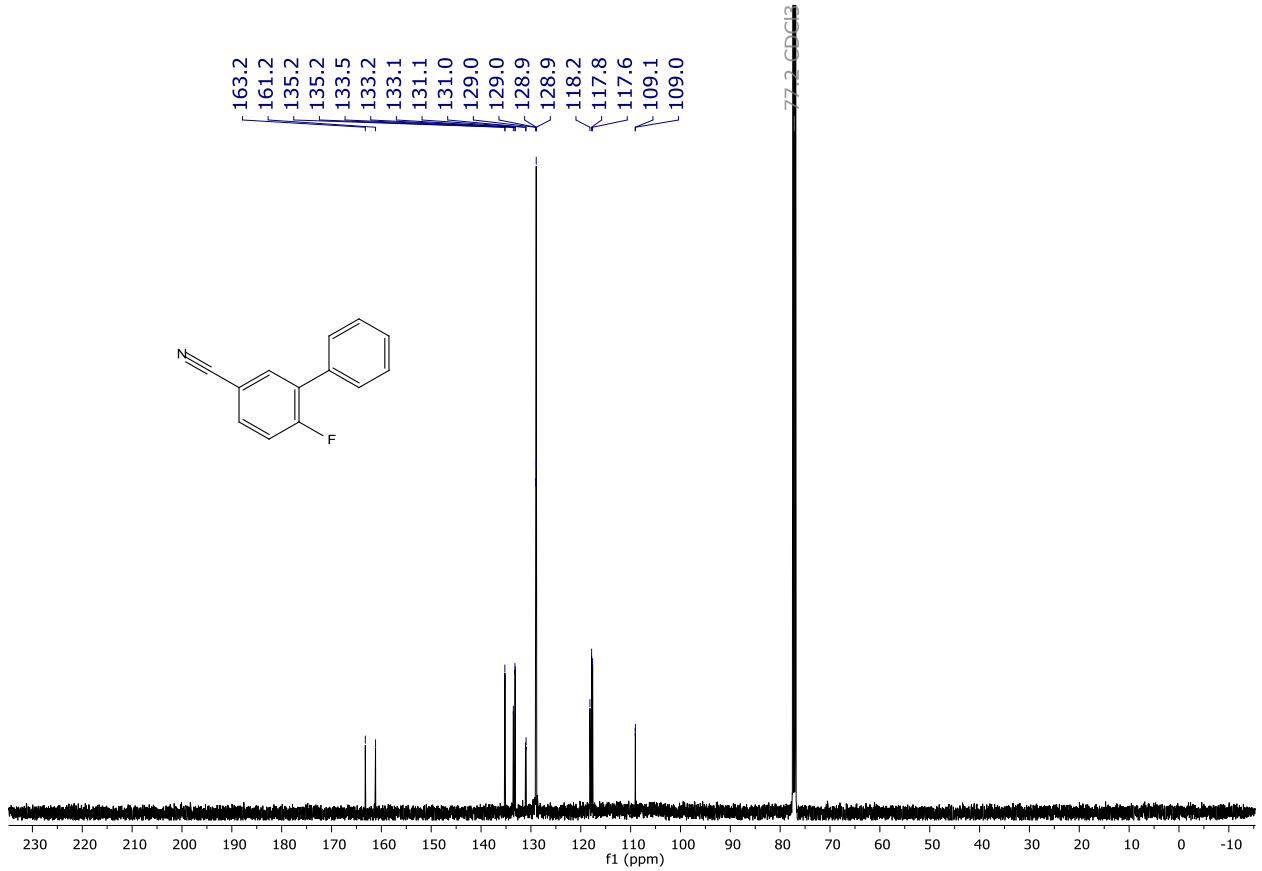
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125v**.



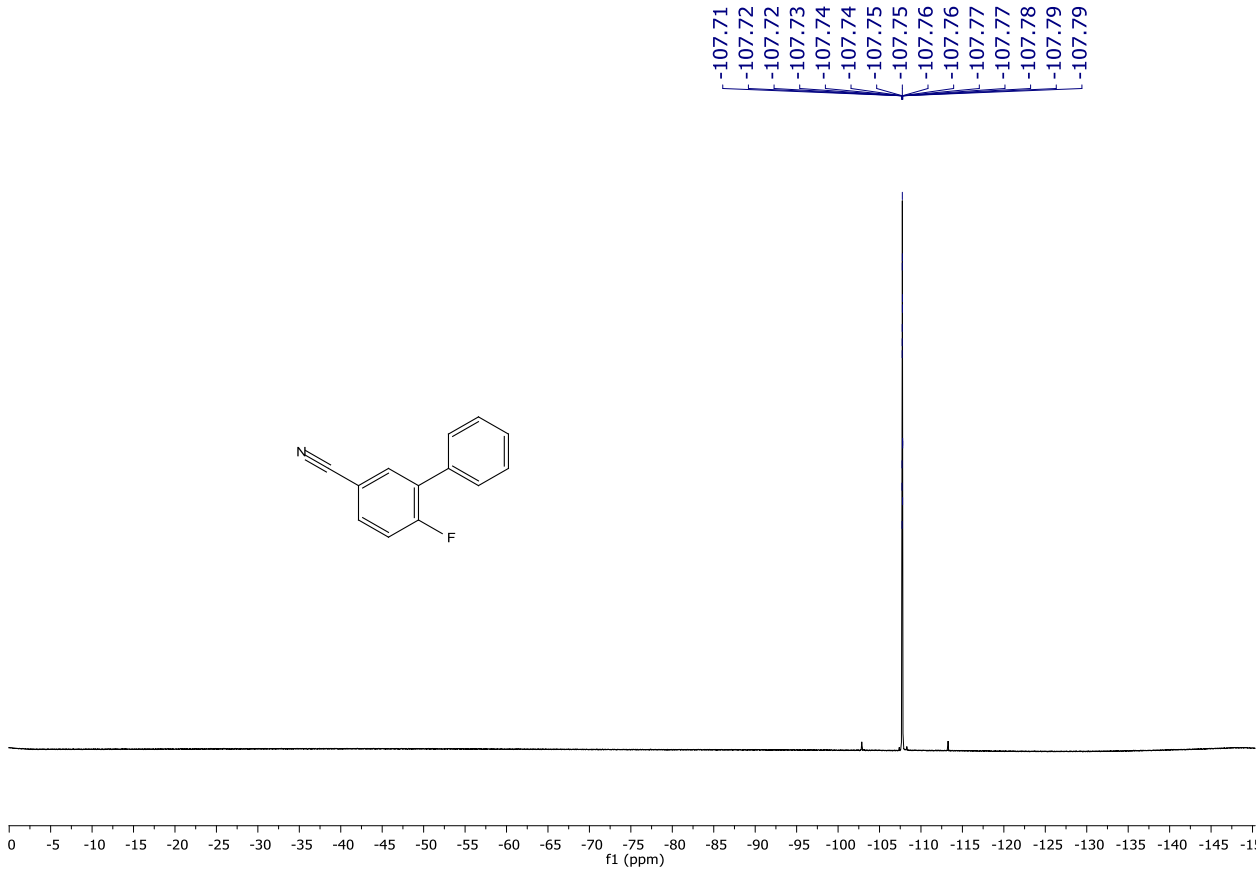
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125v**.



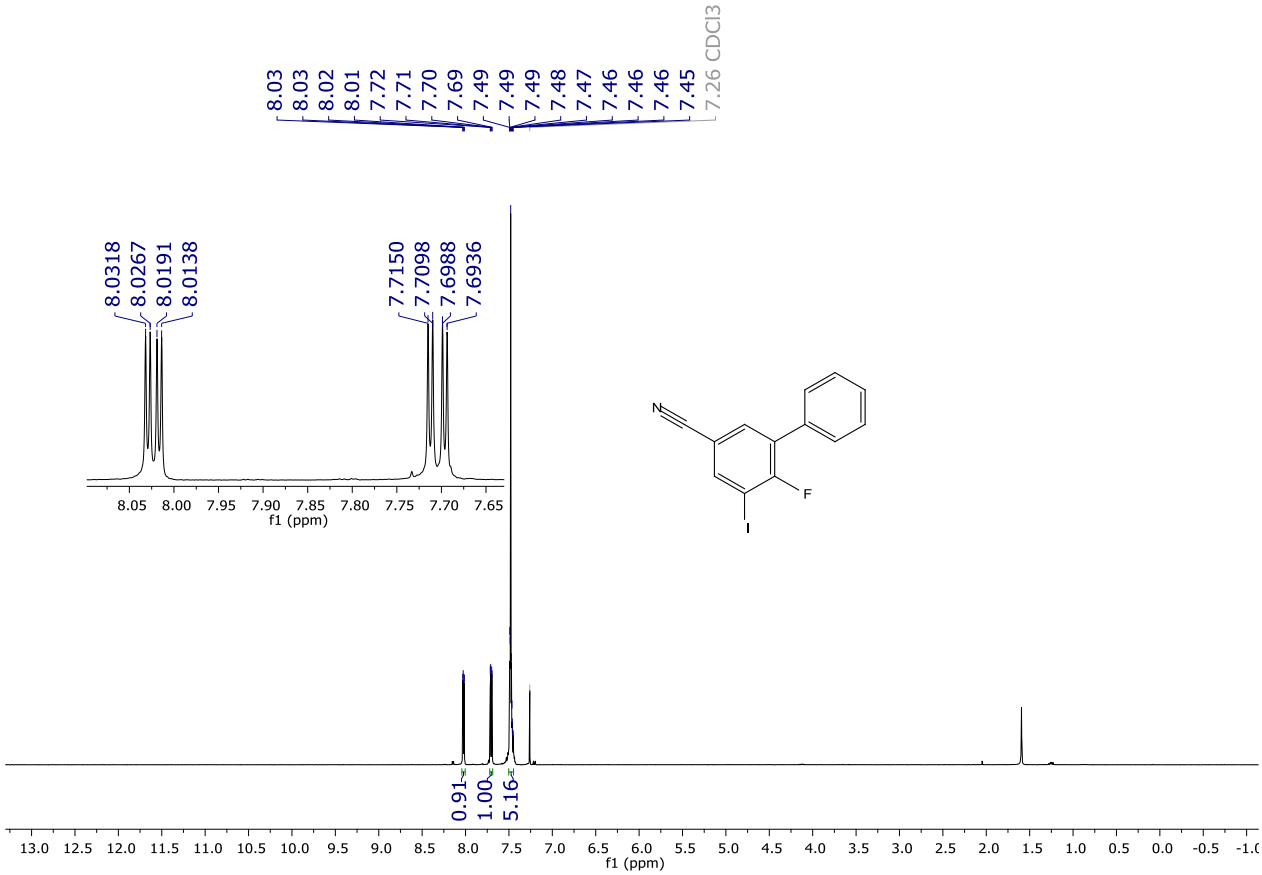
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125w.**



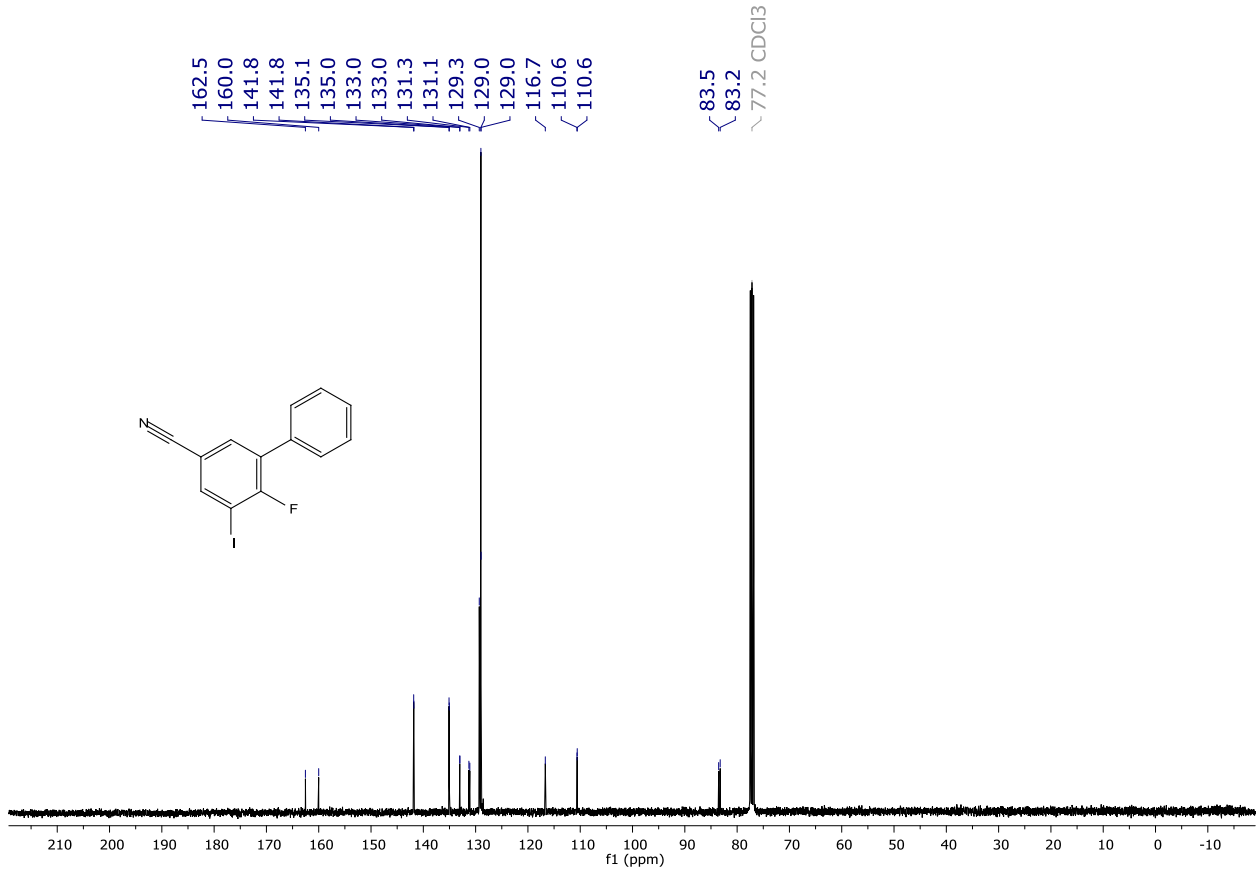
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) spectrum of **125w.**



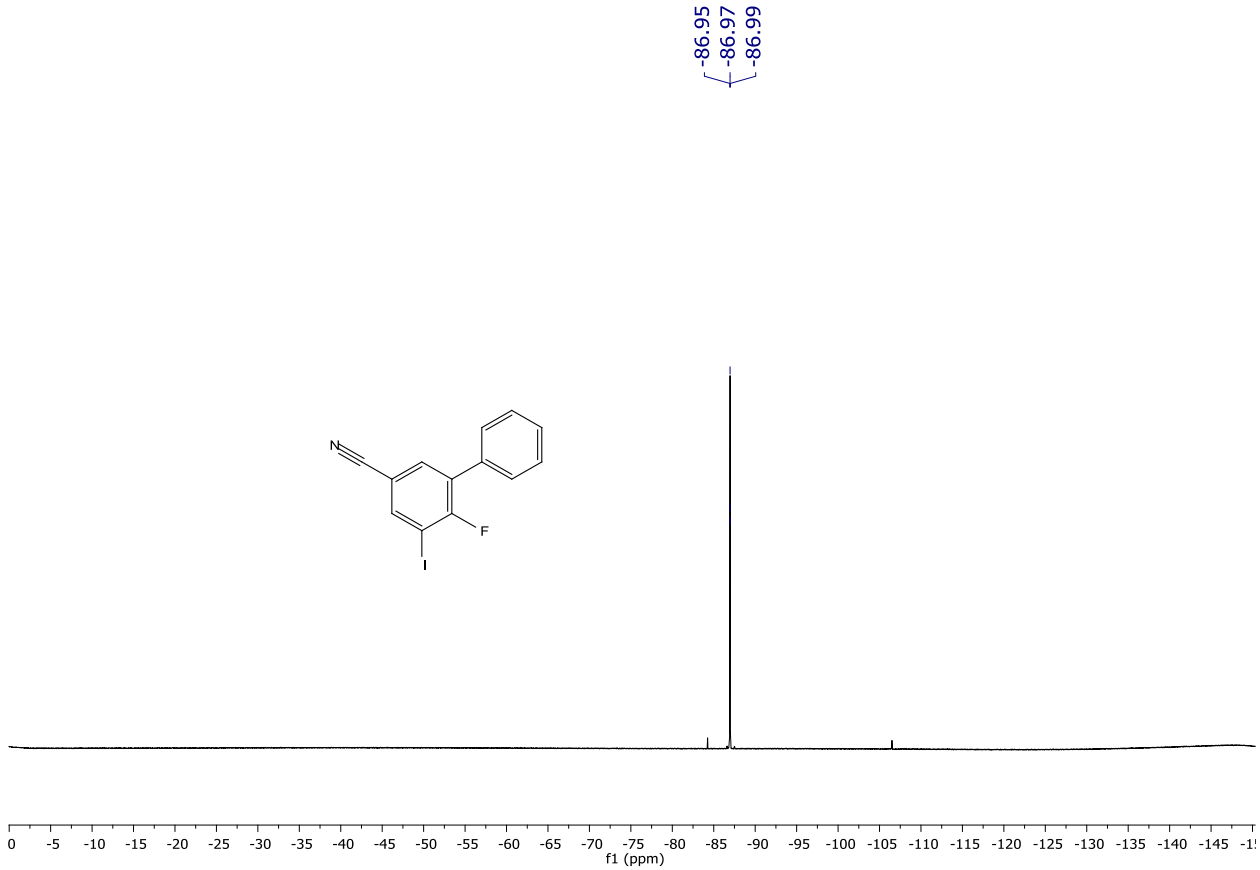
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125w.**



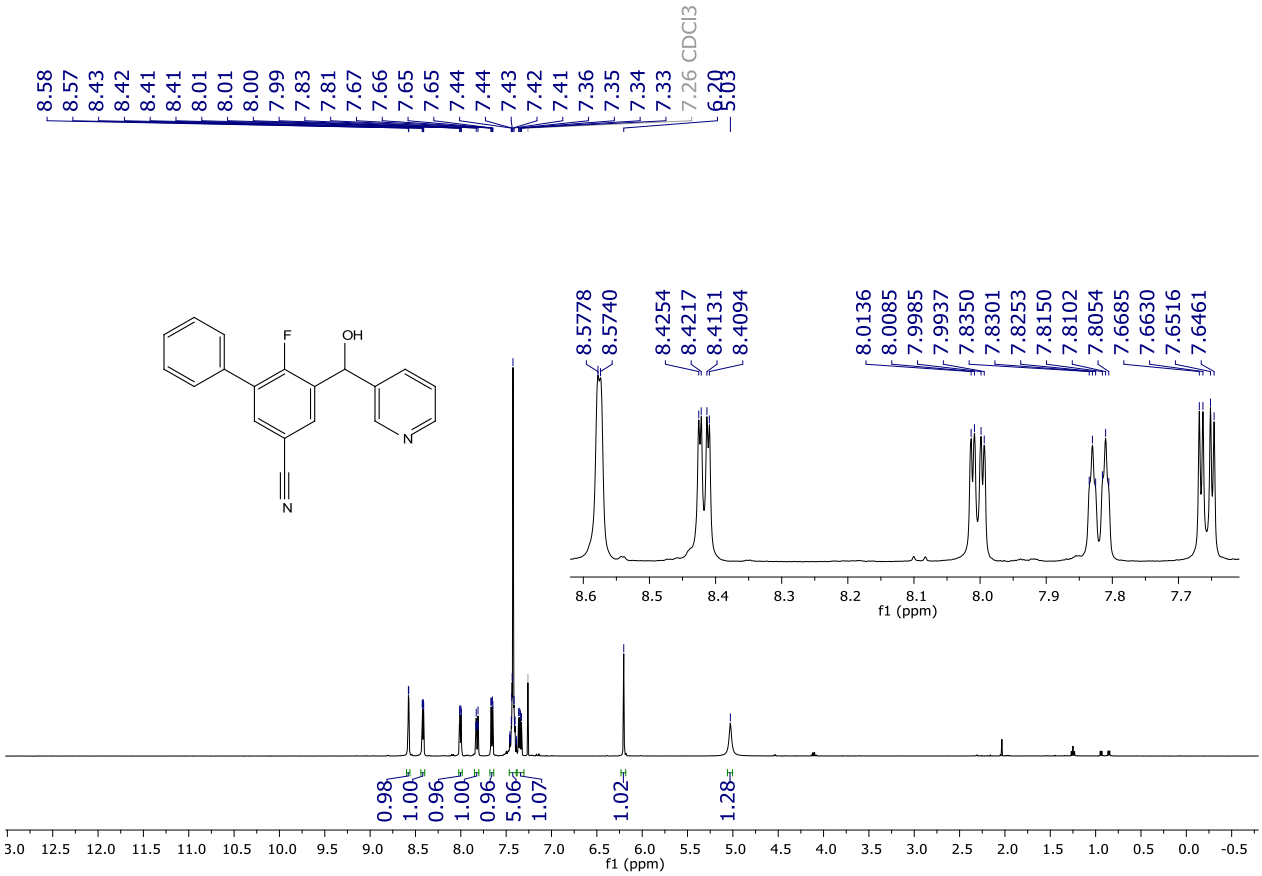
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **126a.**



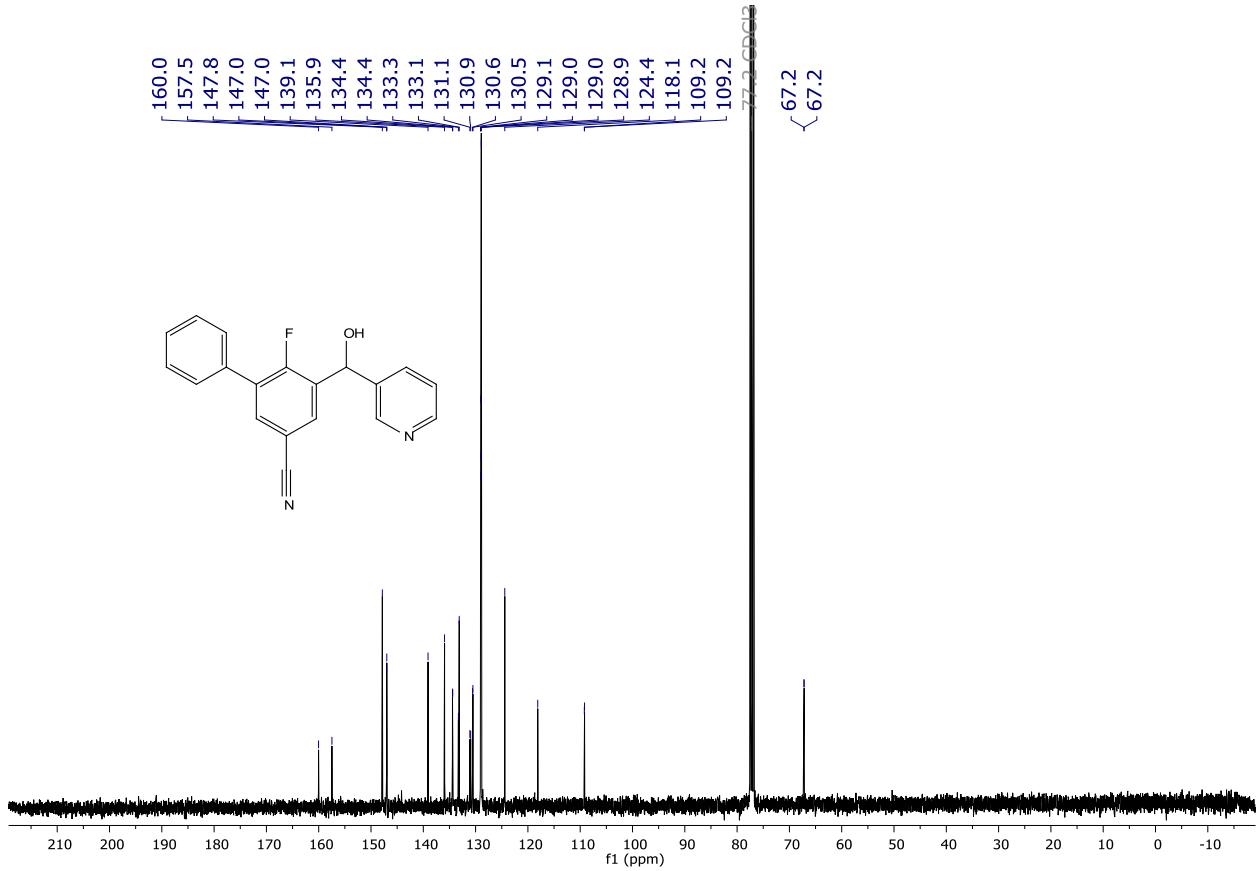
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **126a.**



^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **126a.**

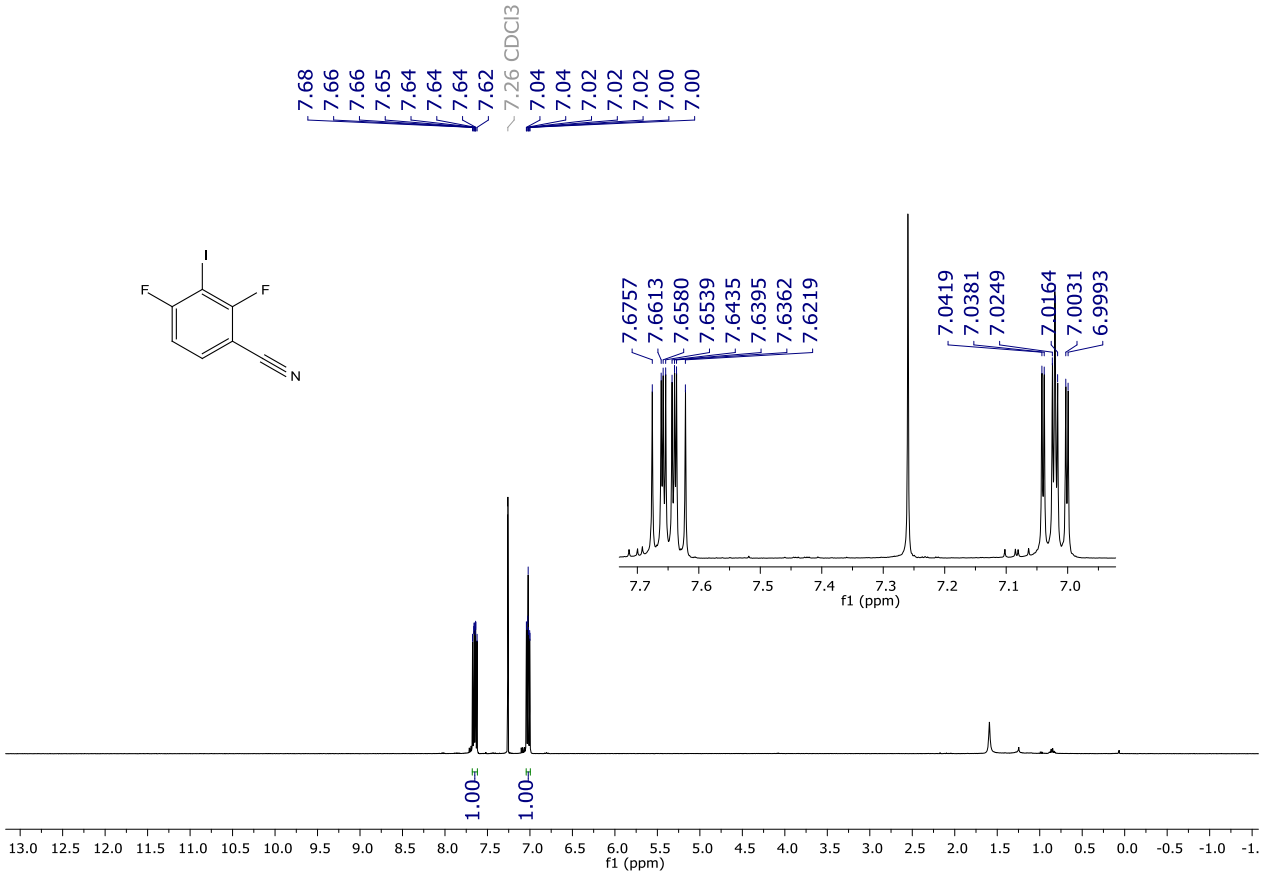


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **126b.**

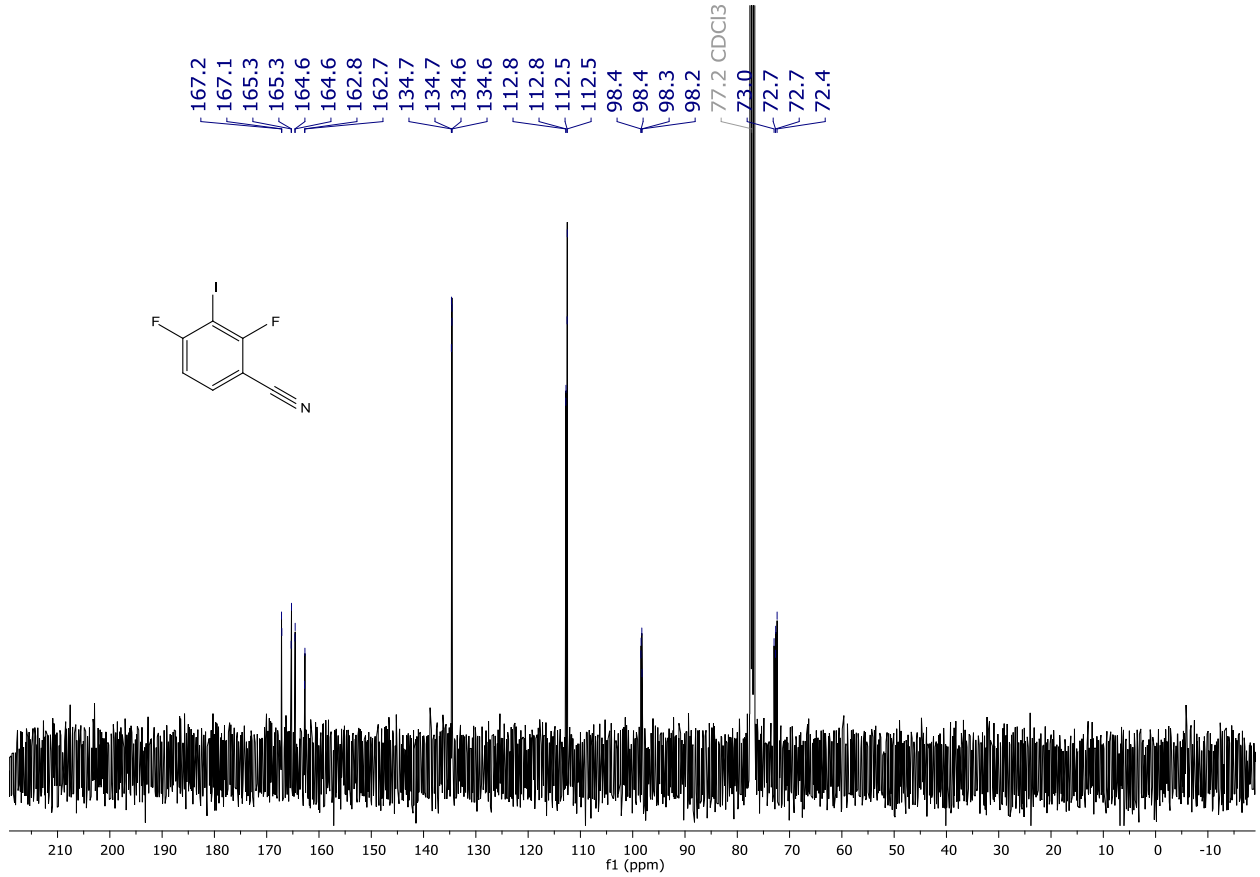


^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) spectrum of **126b.**

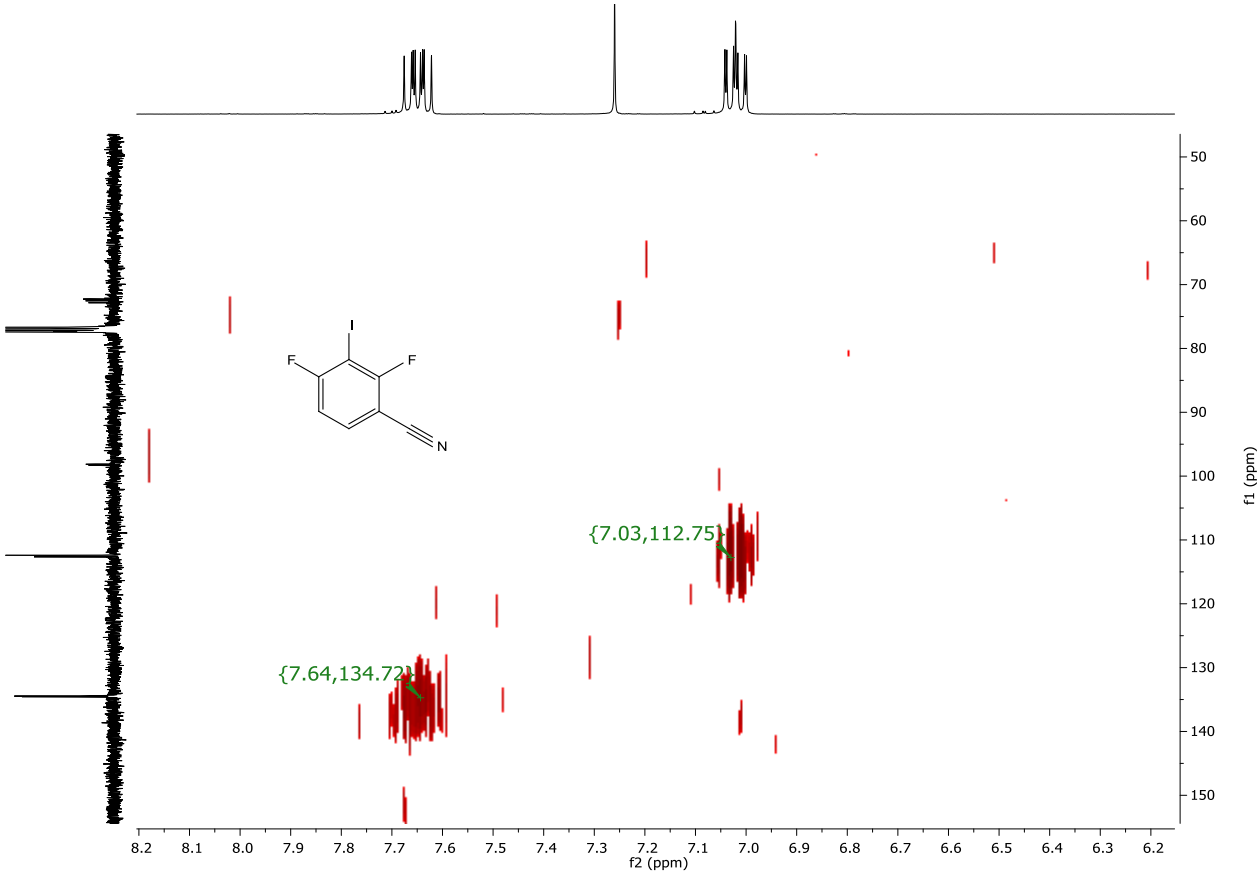
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **126b.**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125x**.

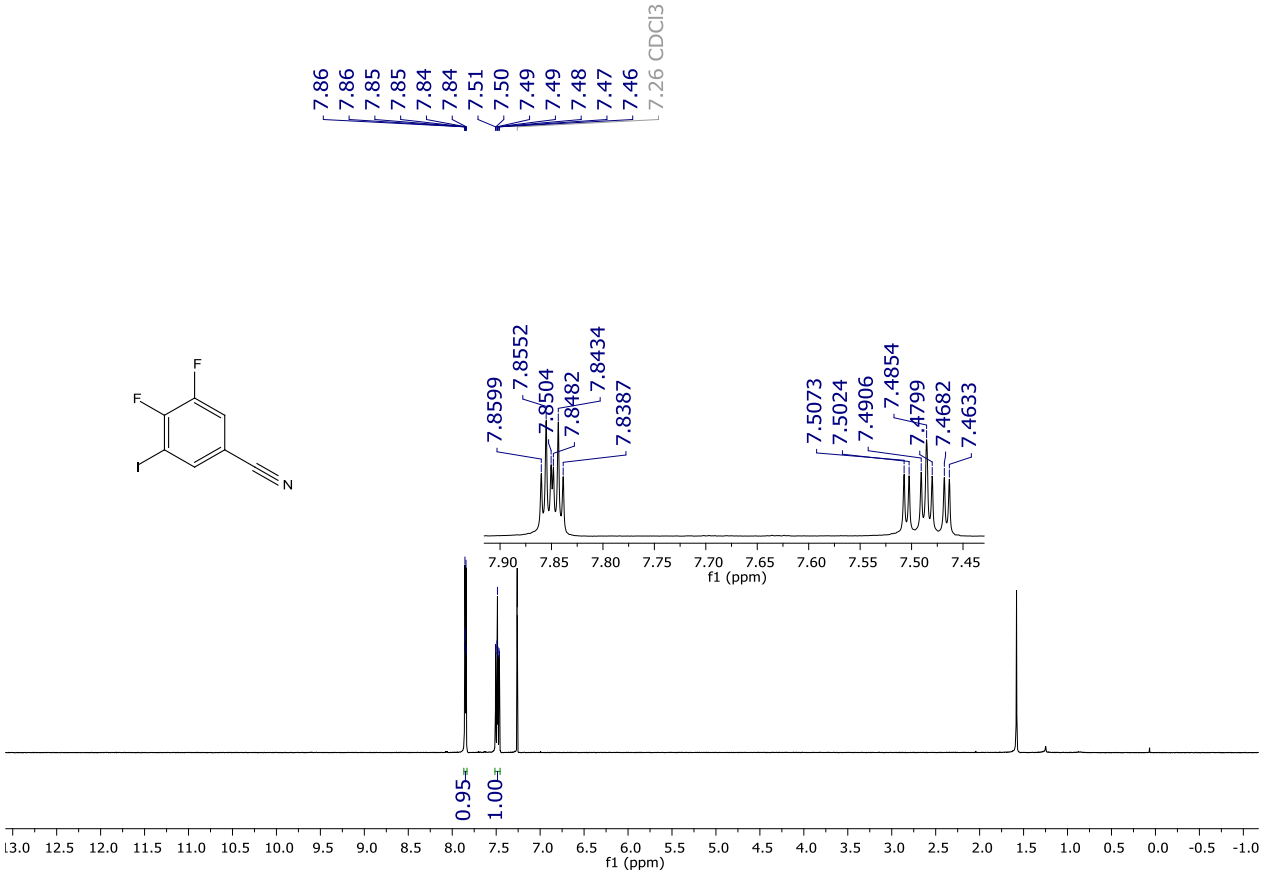


$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125x**.

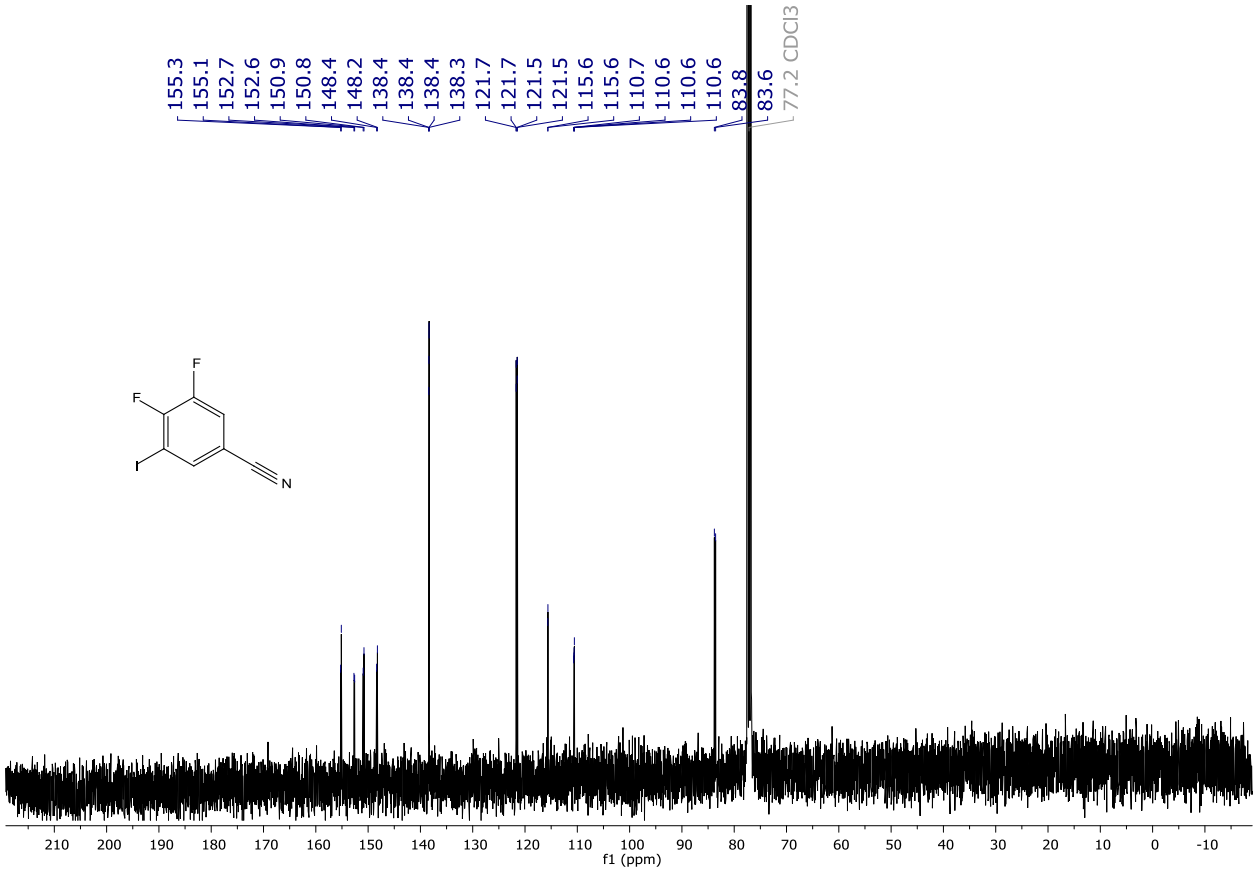


HSQC correlation map of **125x** (400 and 101 MHz, $CDCl_3$).

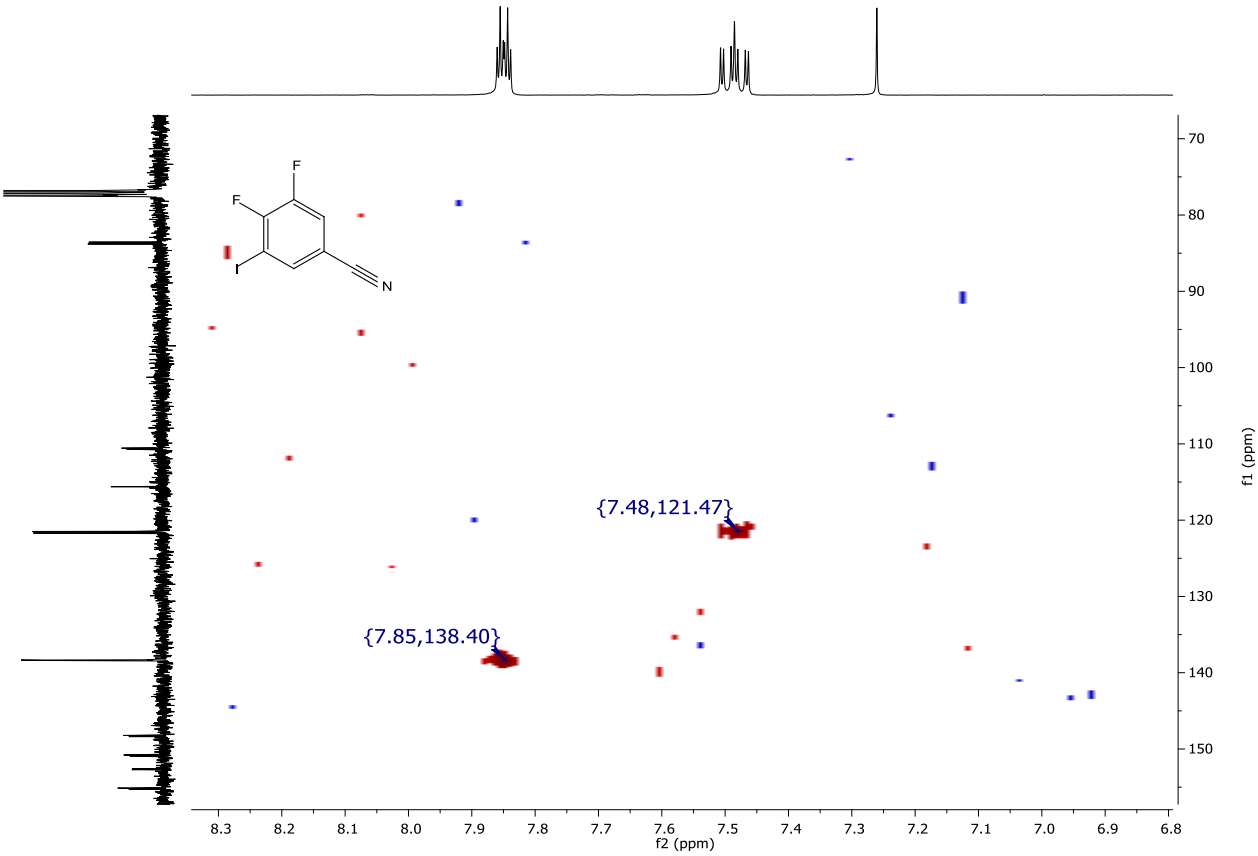
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125x**.



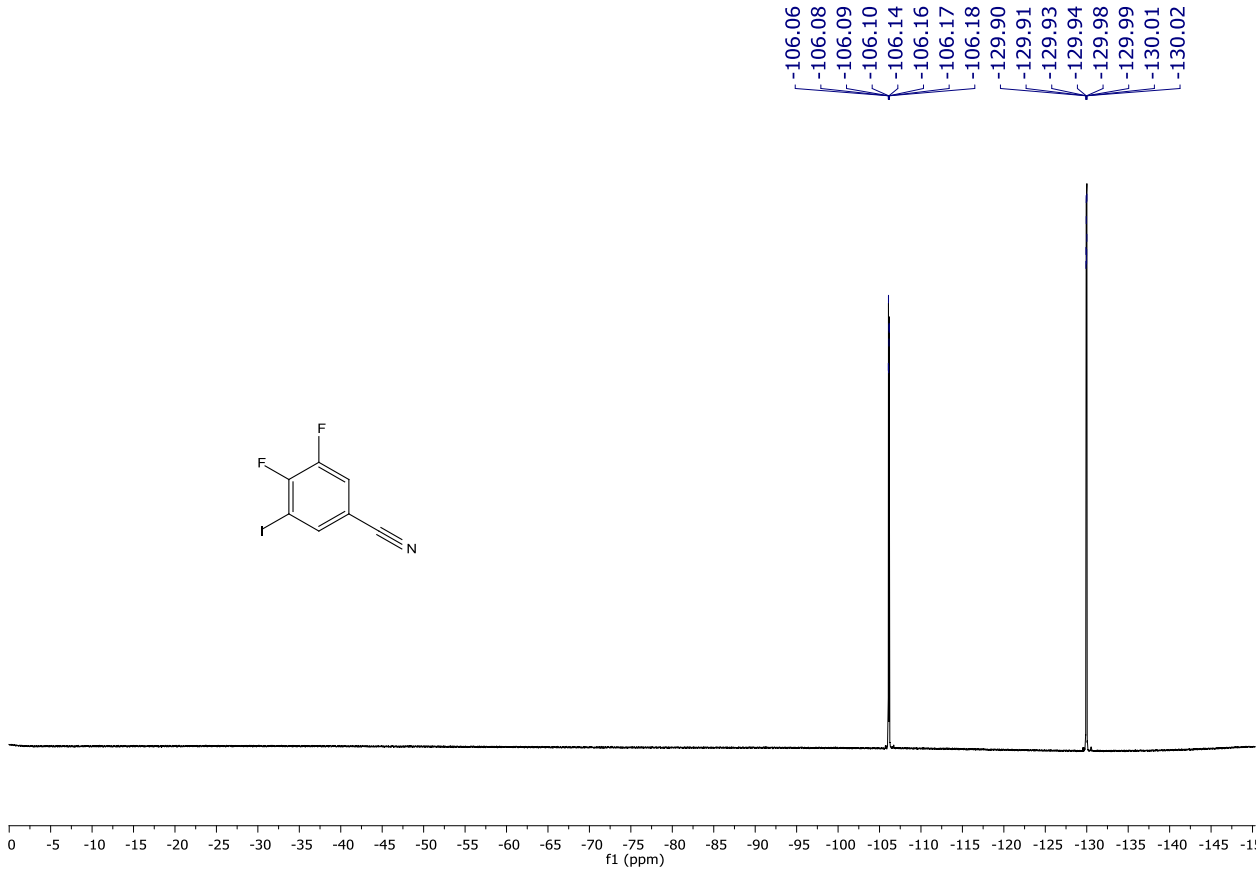
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125y**.



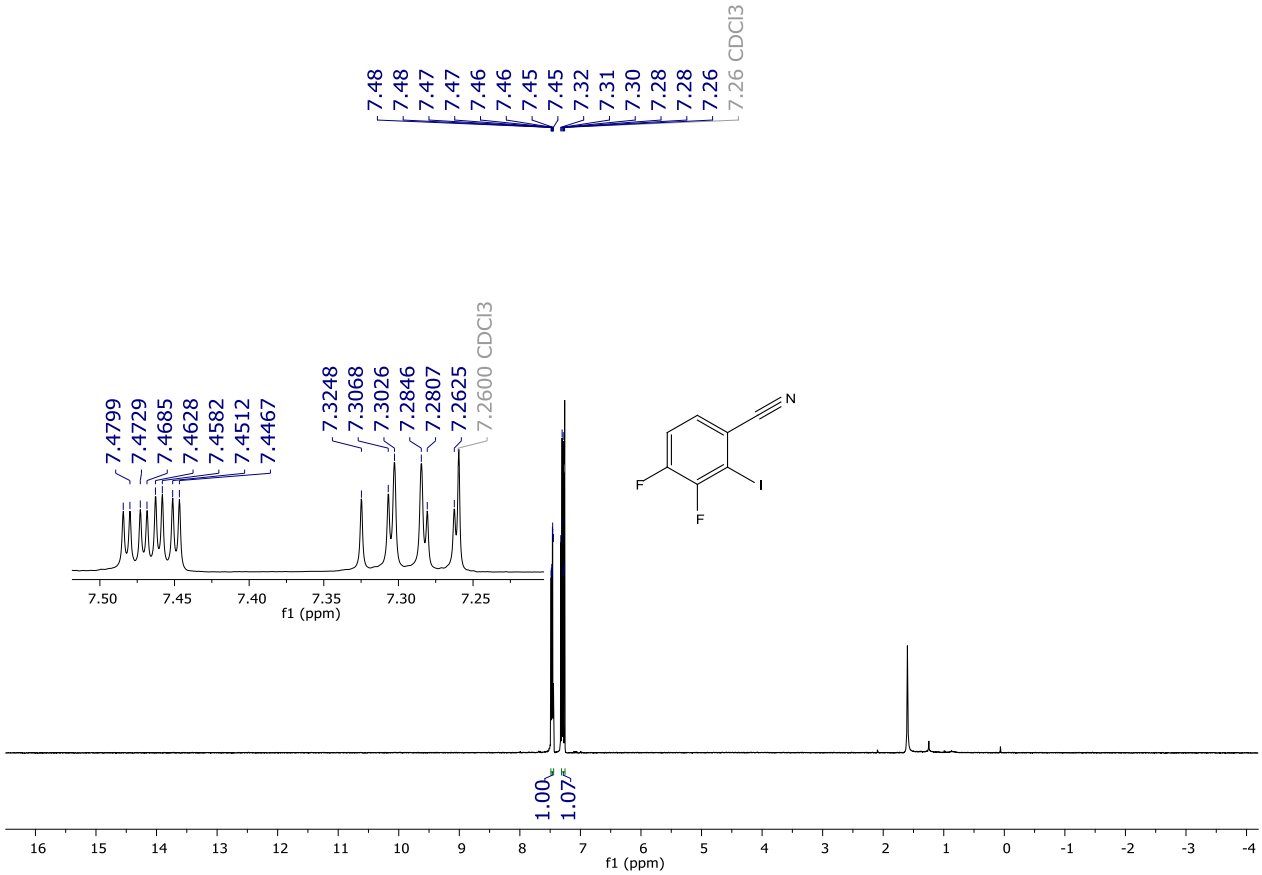
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125y**.



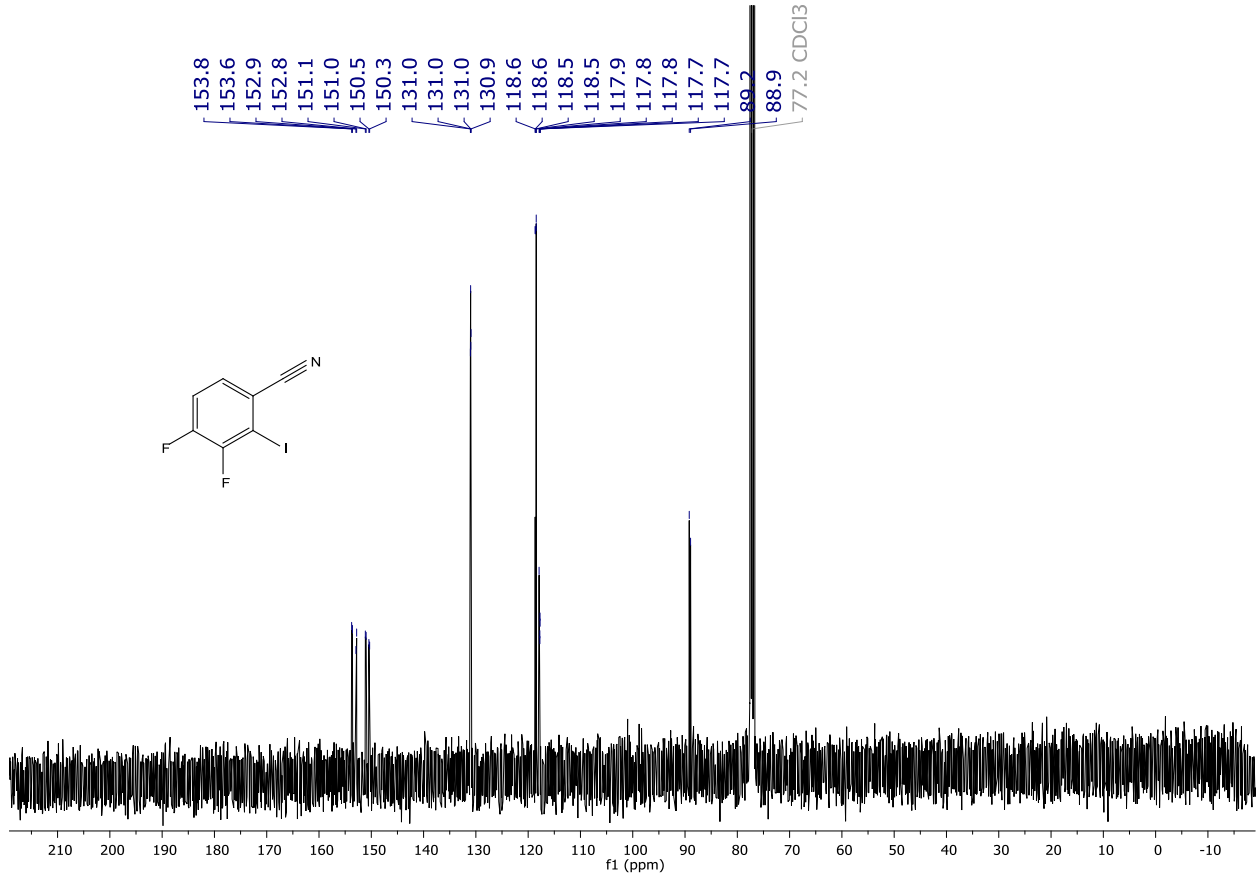
HSQC correlation map of **125y** (400 and 101 MHz, $CDCl_3$).



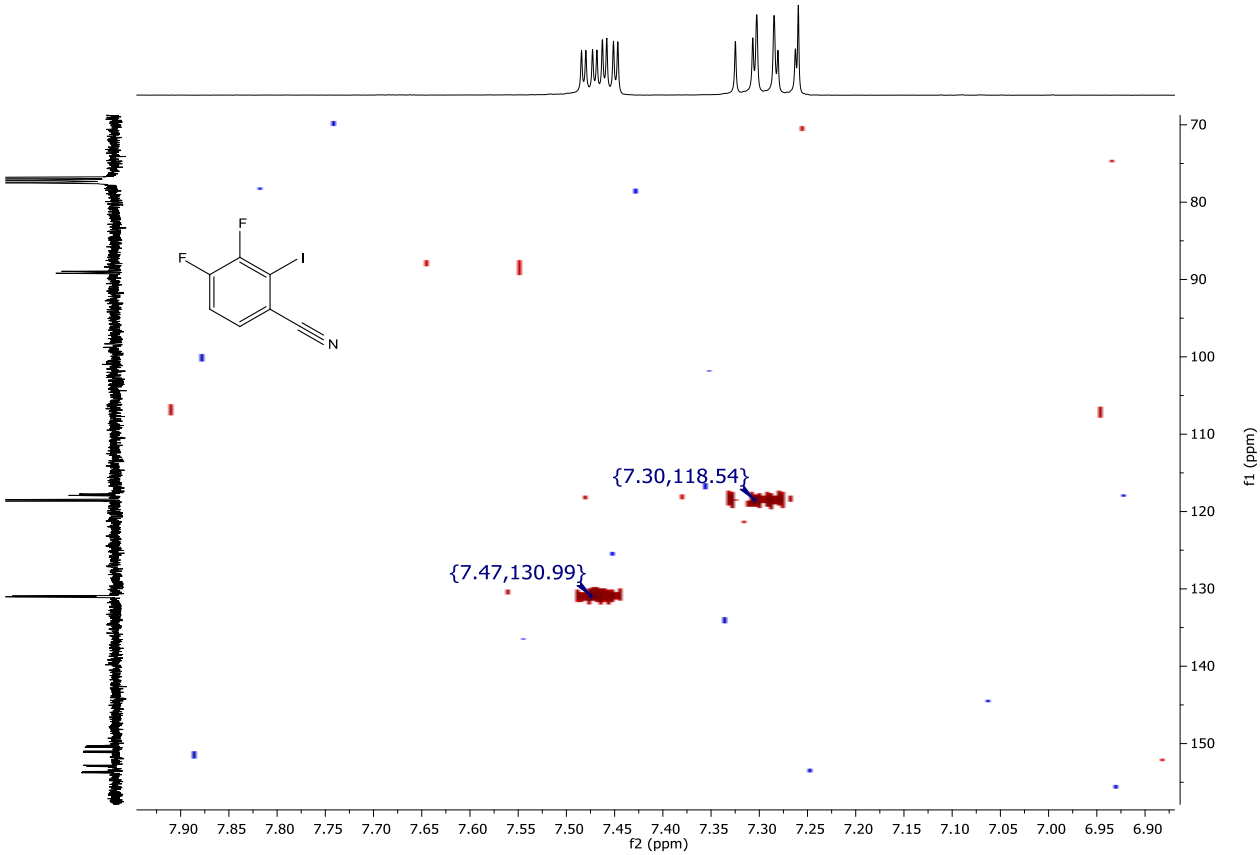
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125y**.



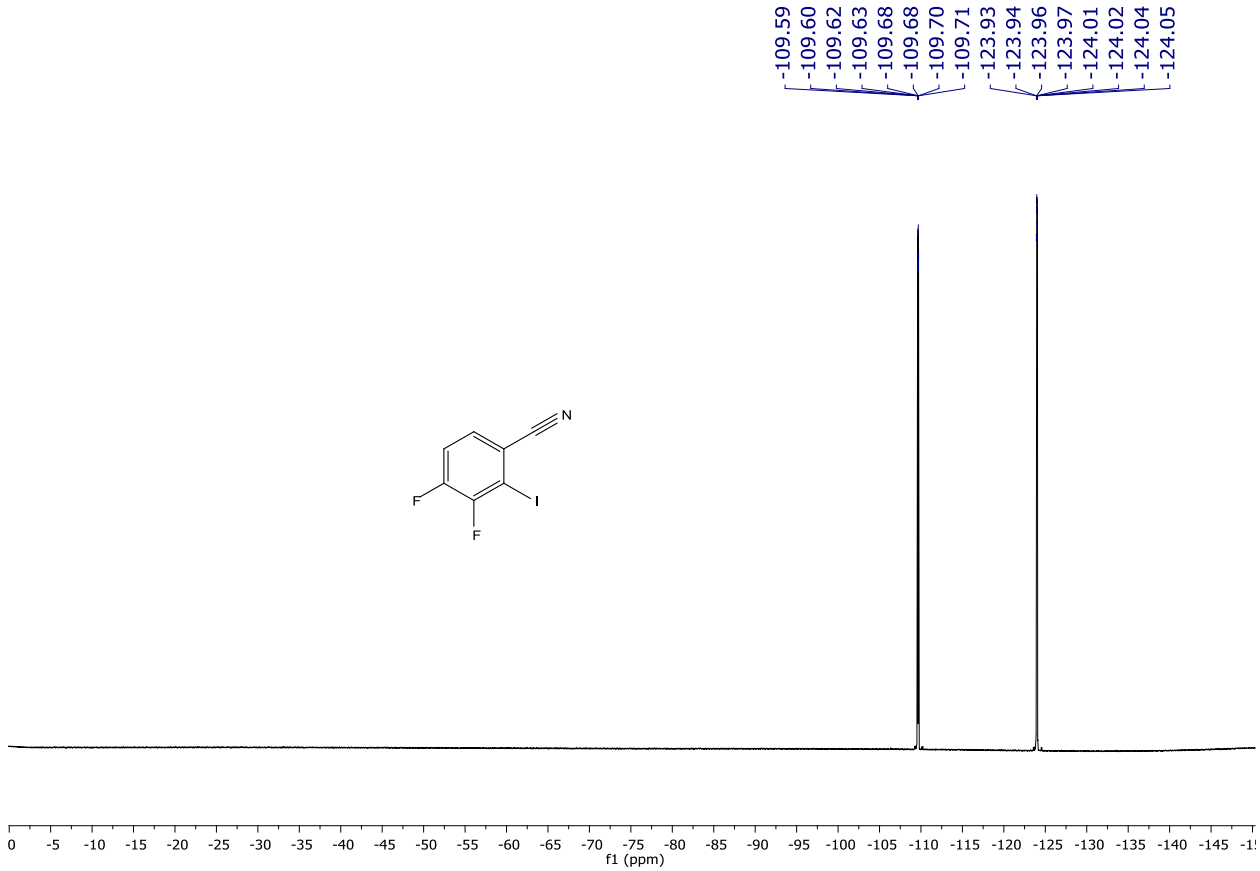
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125z**.



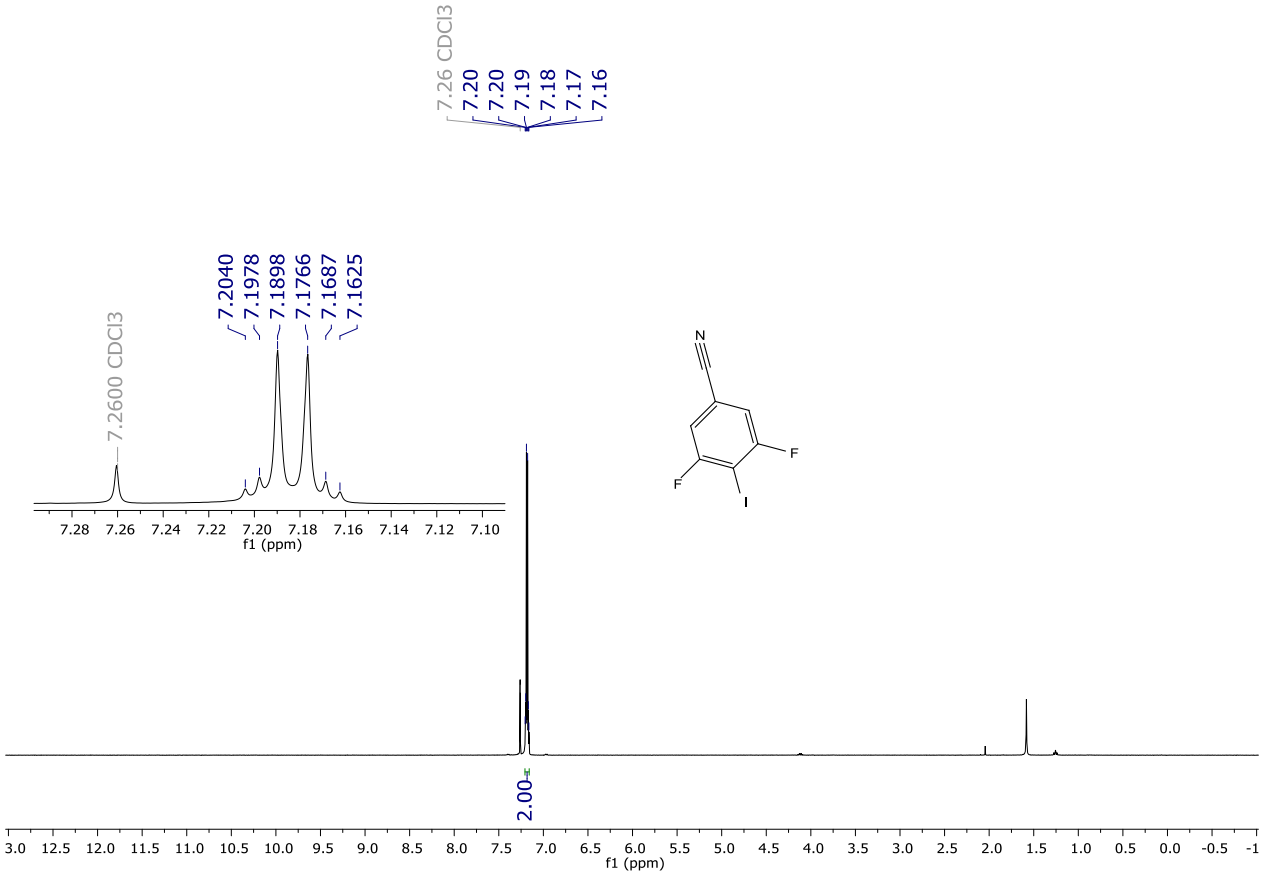
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125z**.



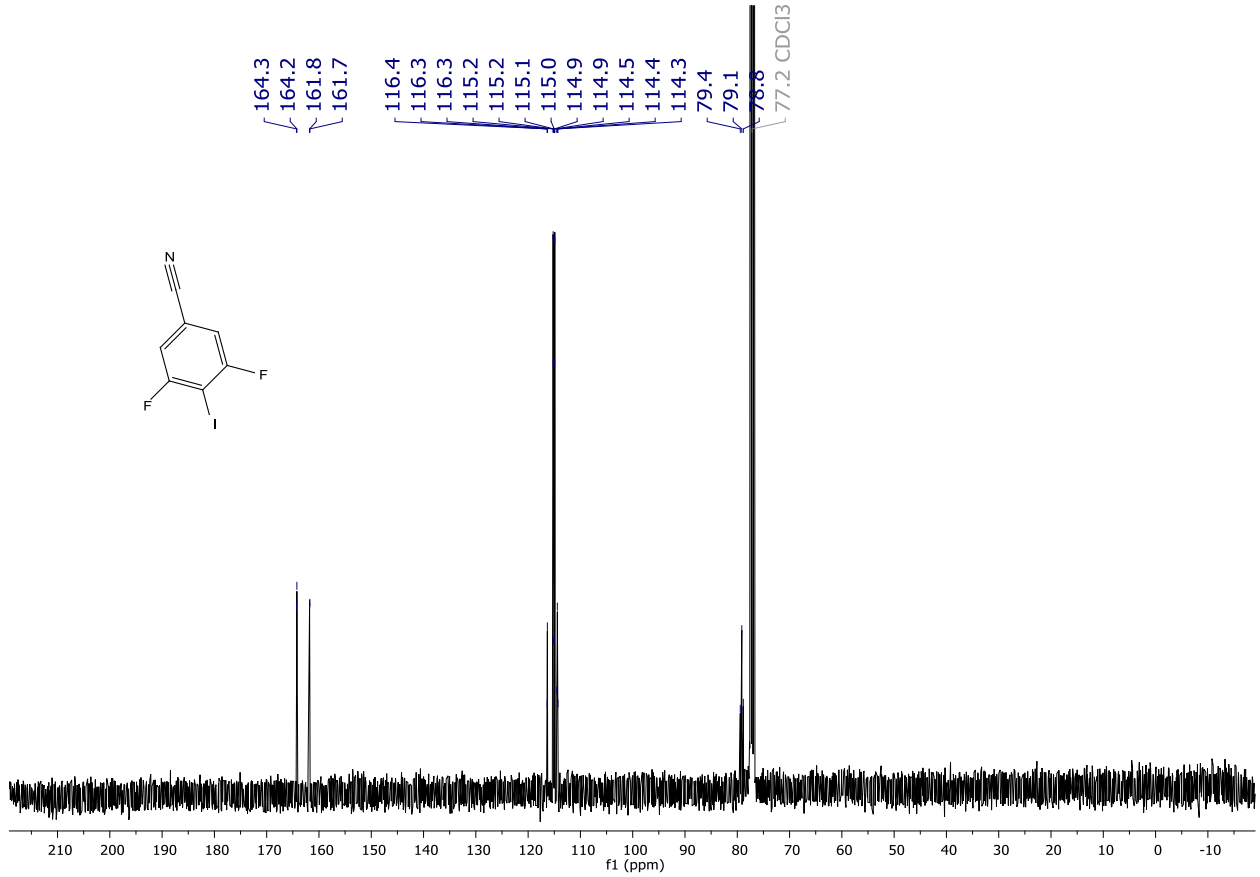
HSQC correlation map of **125z** (400 and 101 MHz, $CDCl_3$).



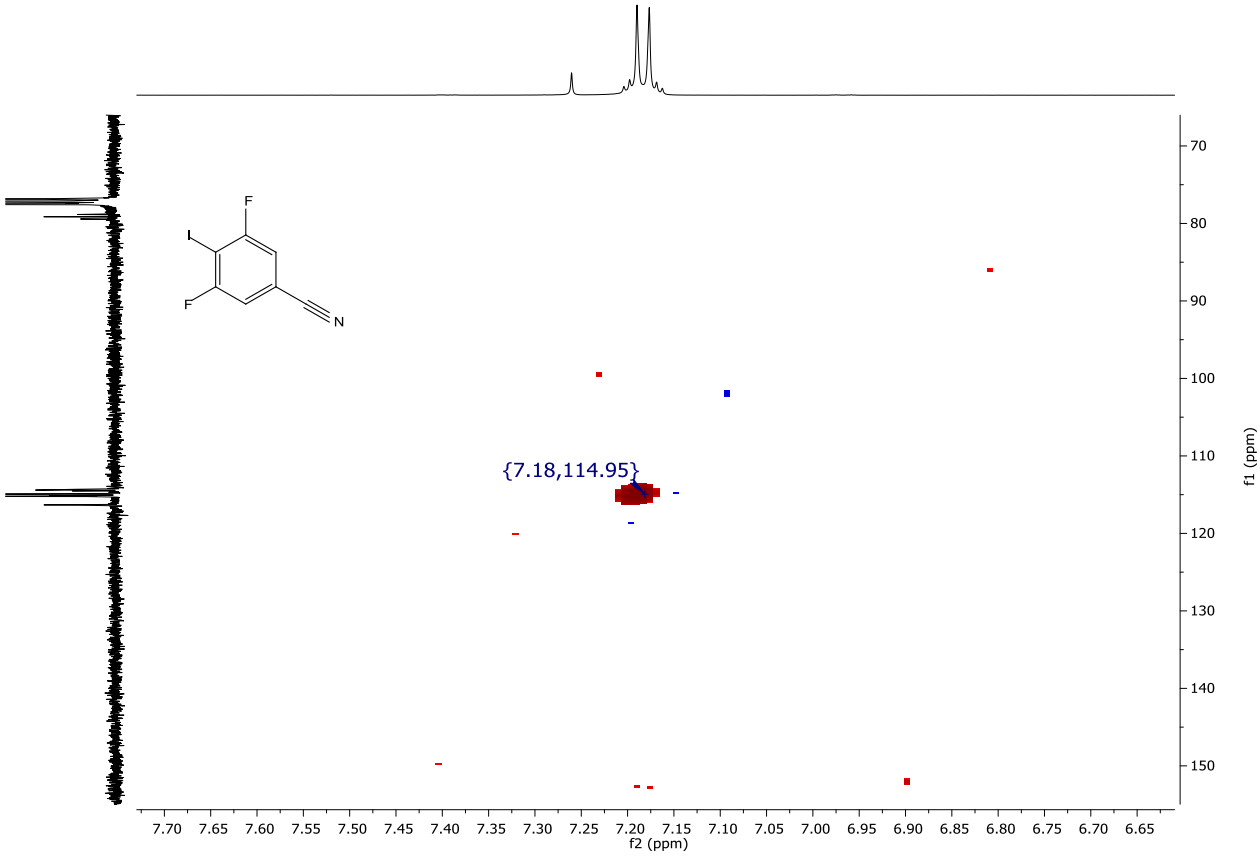
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125z**.



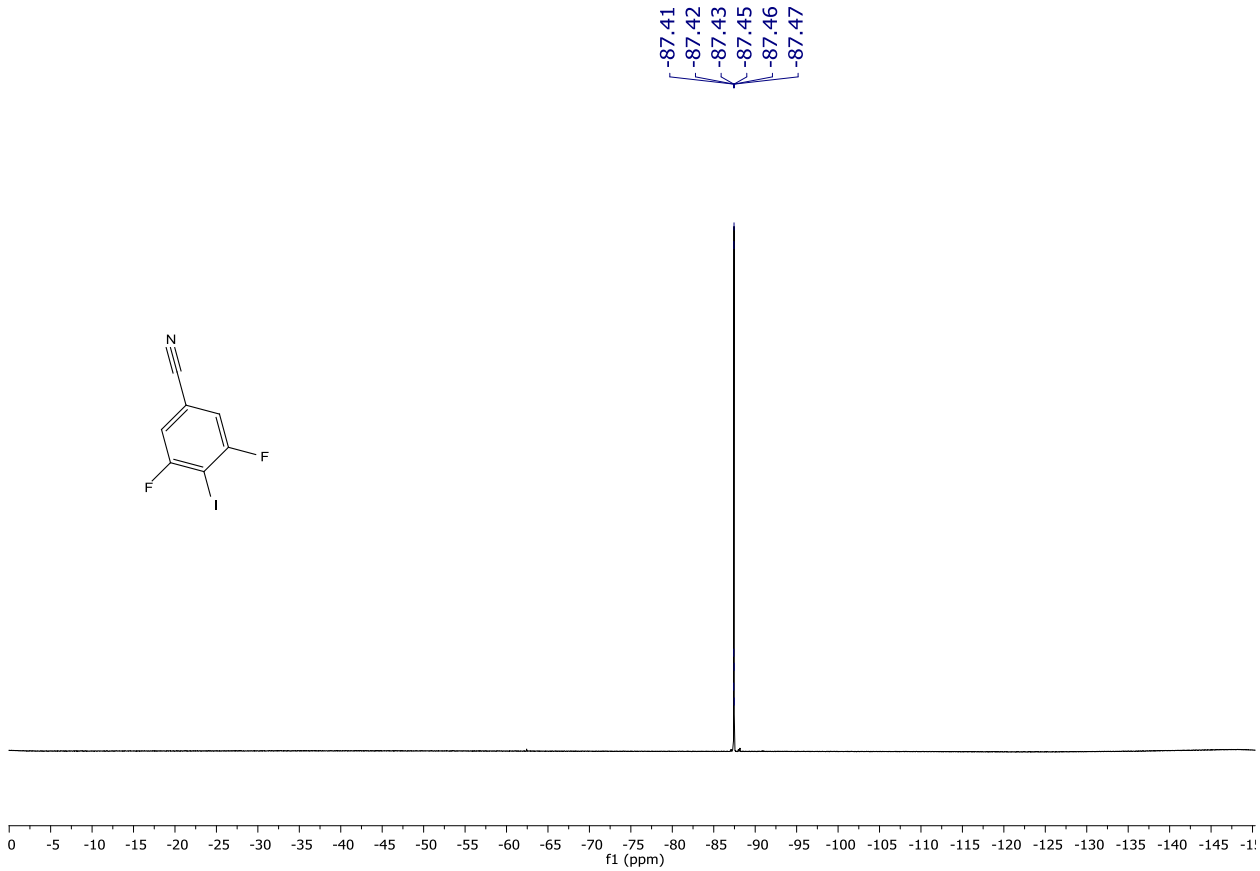
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125aa**.



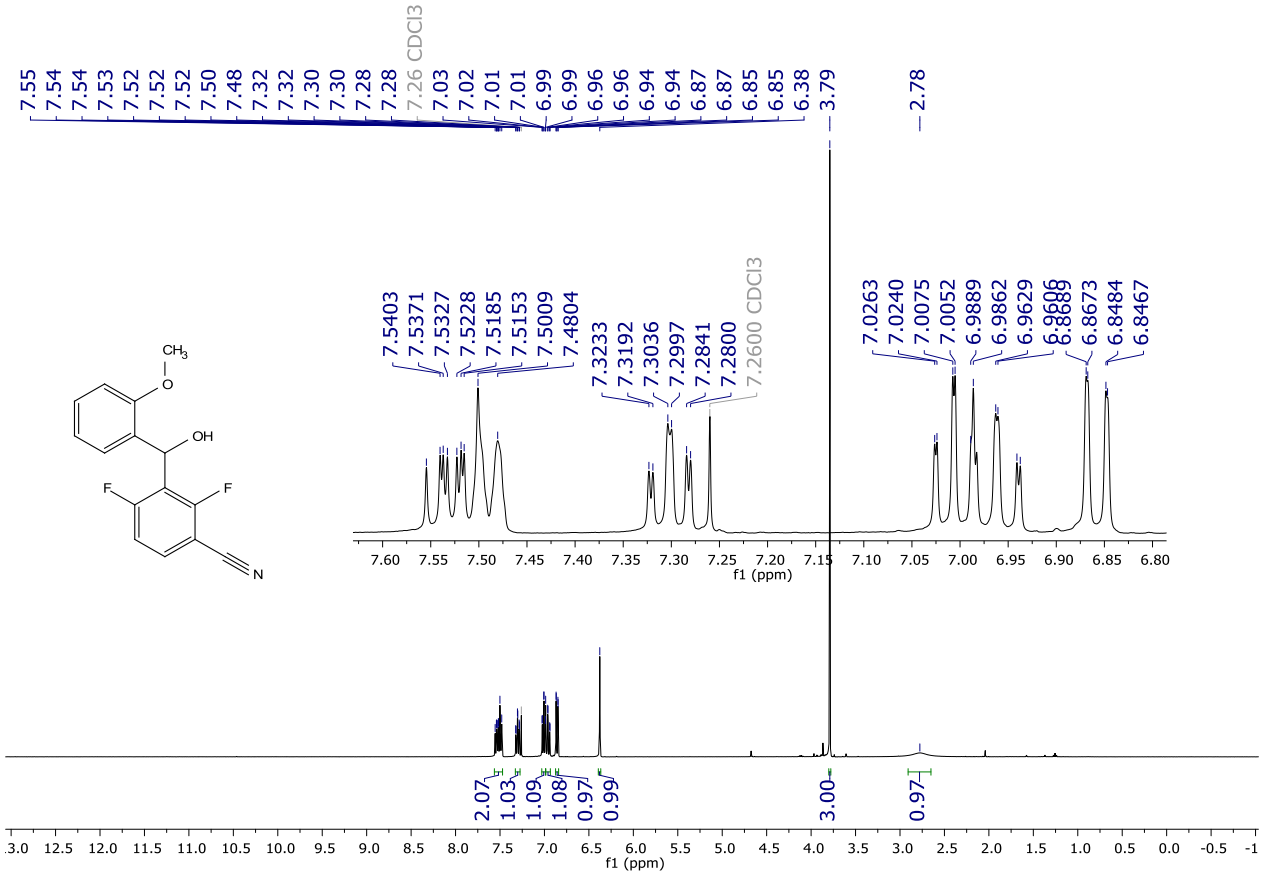
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125aa**.



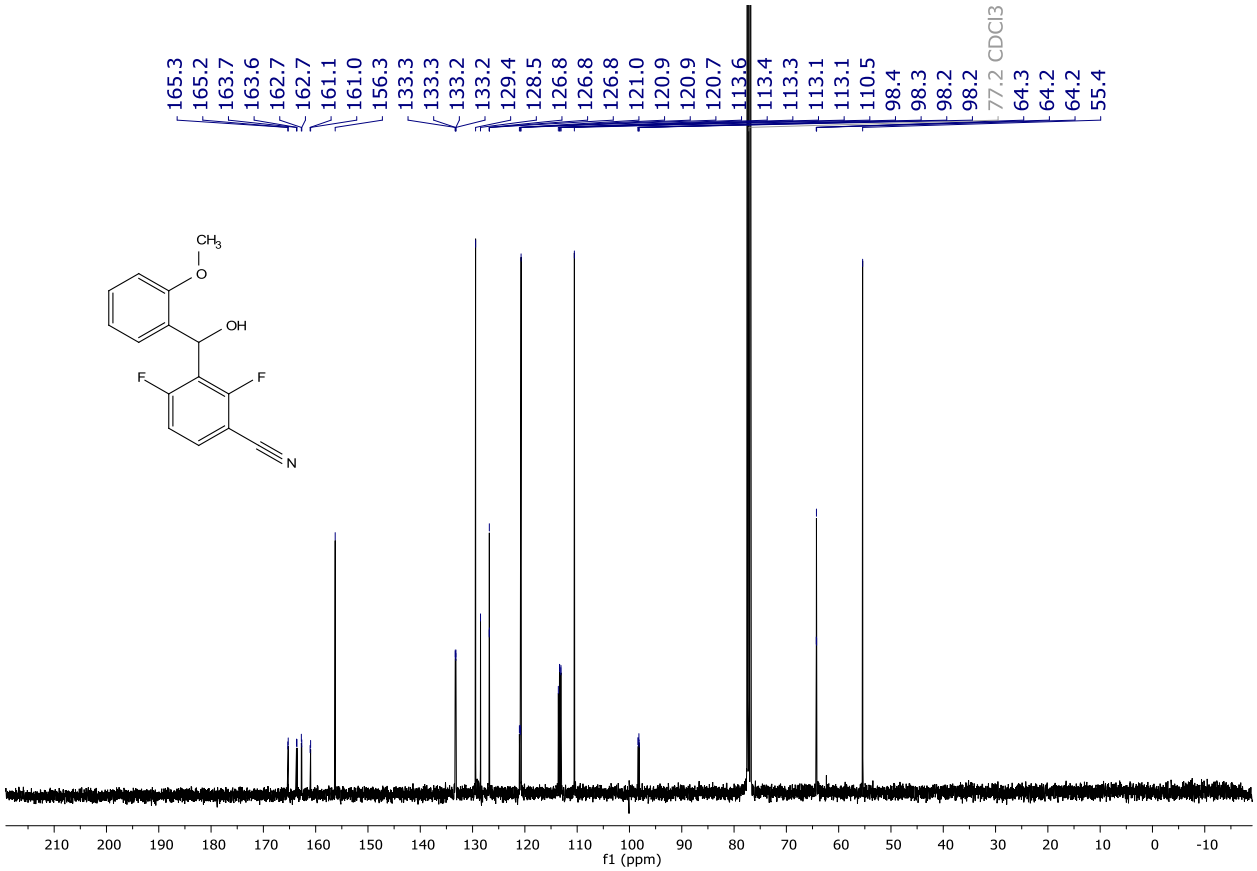
HSQC correlation map of **125aa** (400 and 101 MHz, $CDCl_3$).



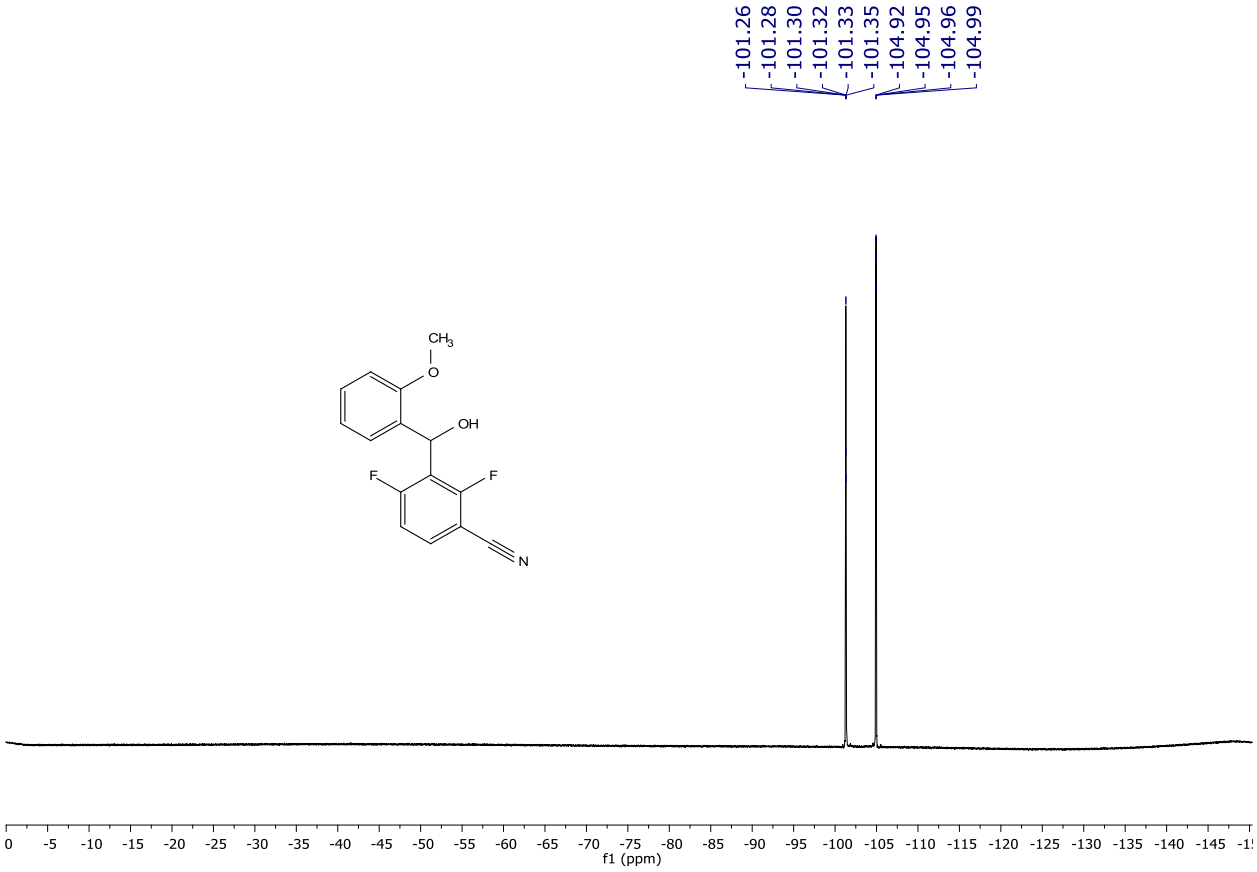
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125aa**.



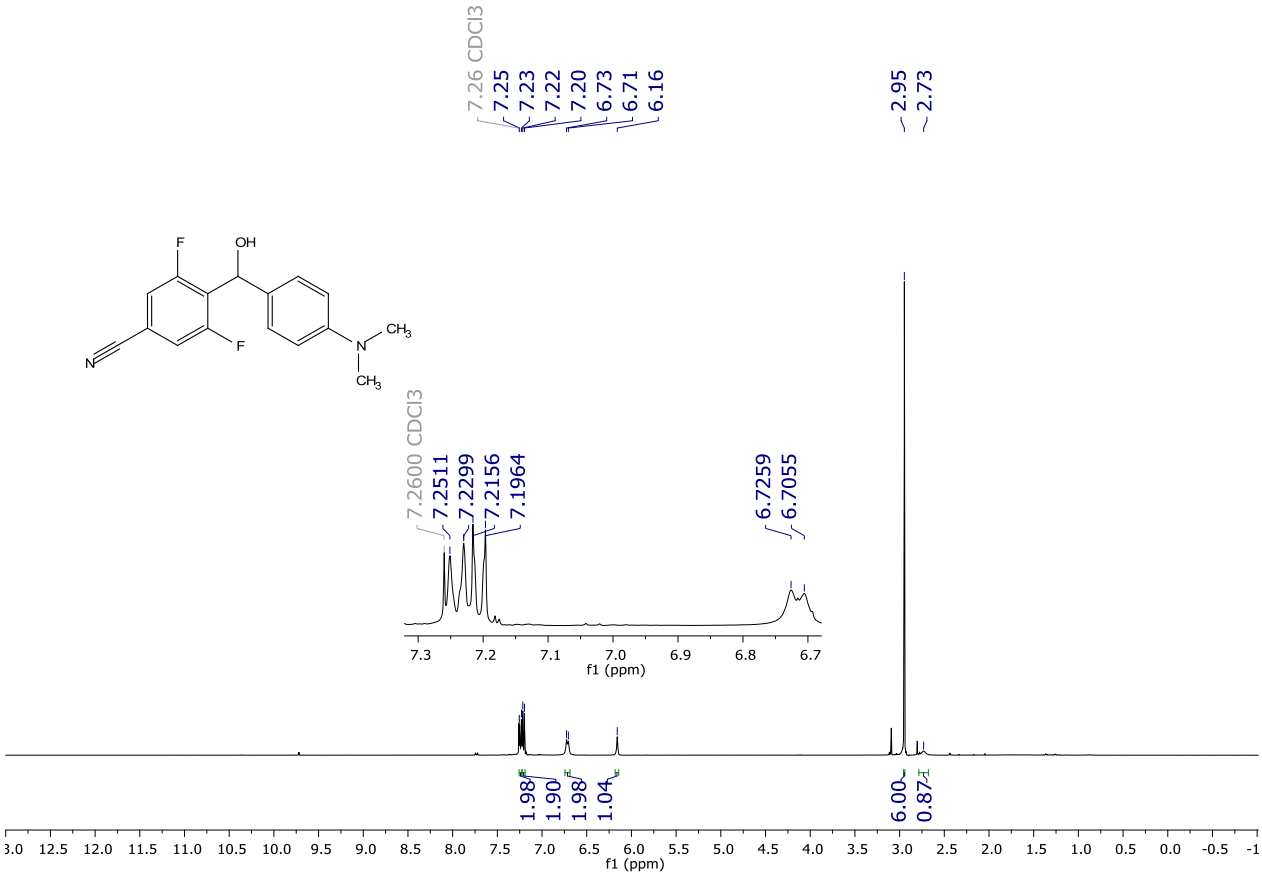
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125ab**.



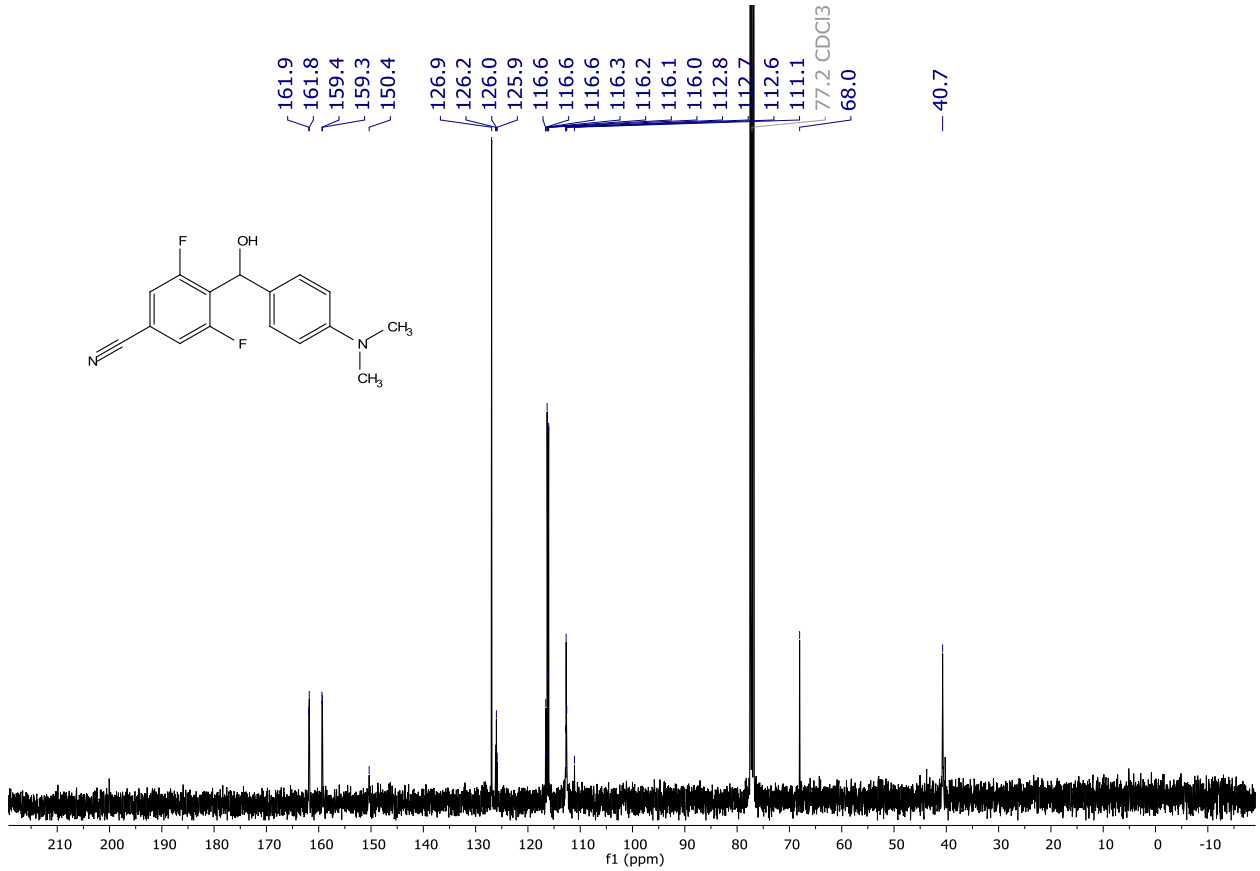
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125ab**.



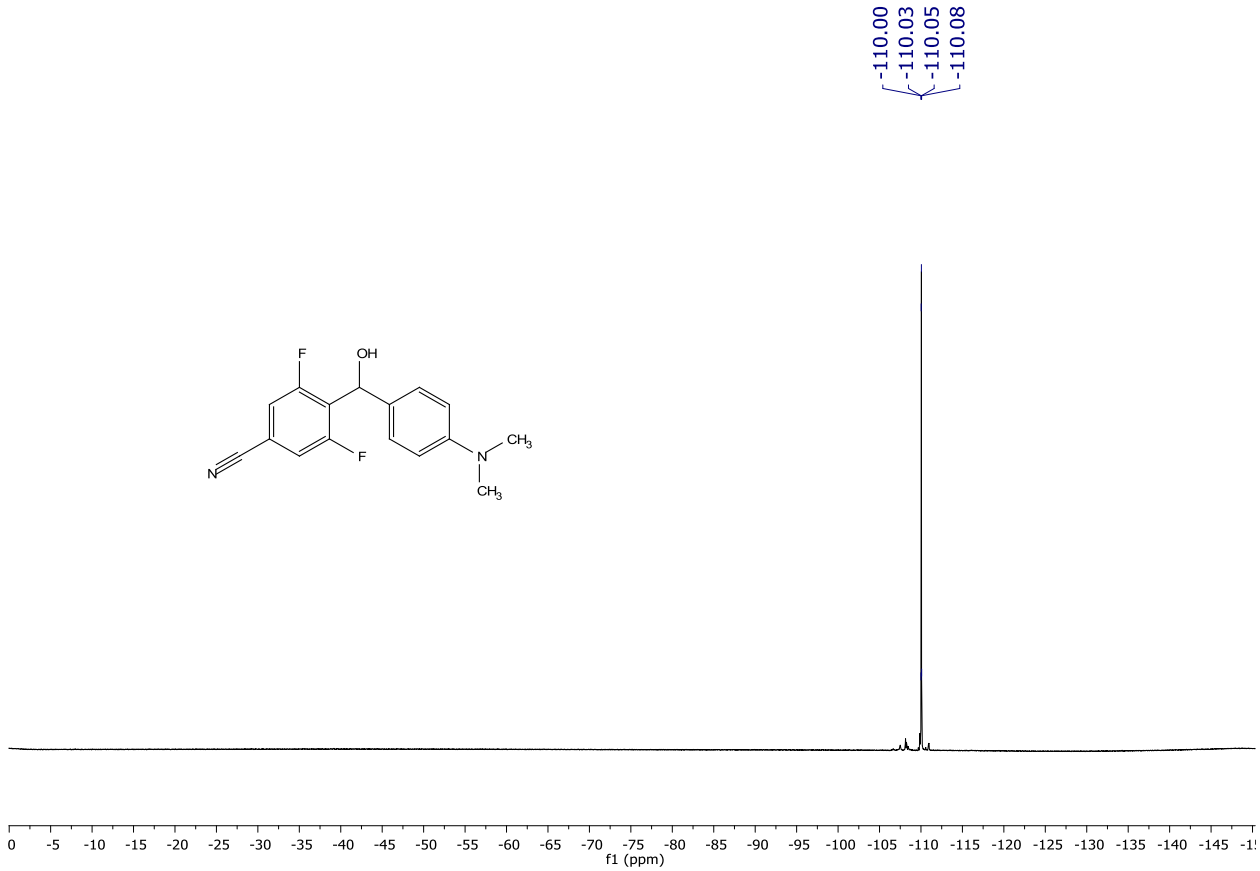
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125ab**.



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125ac**.

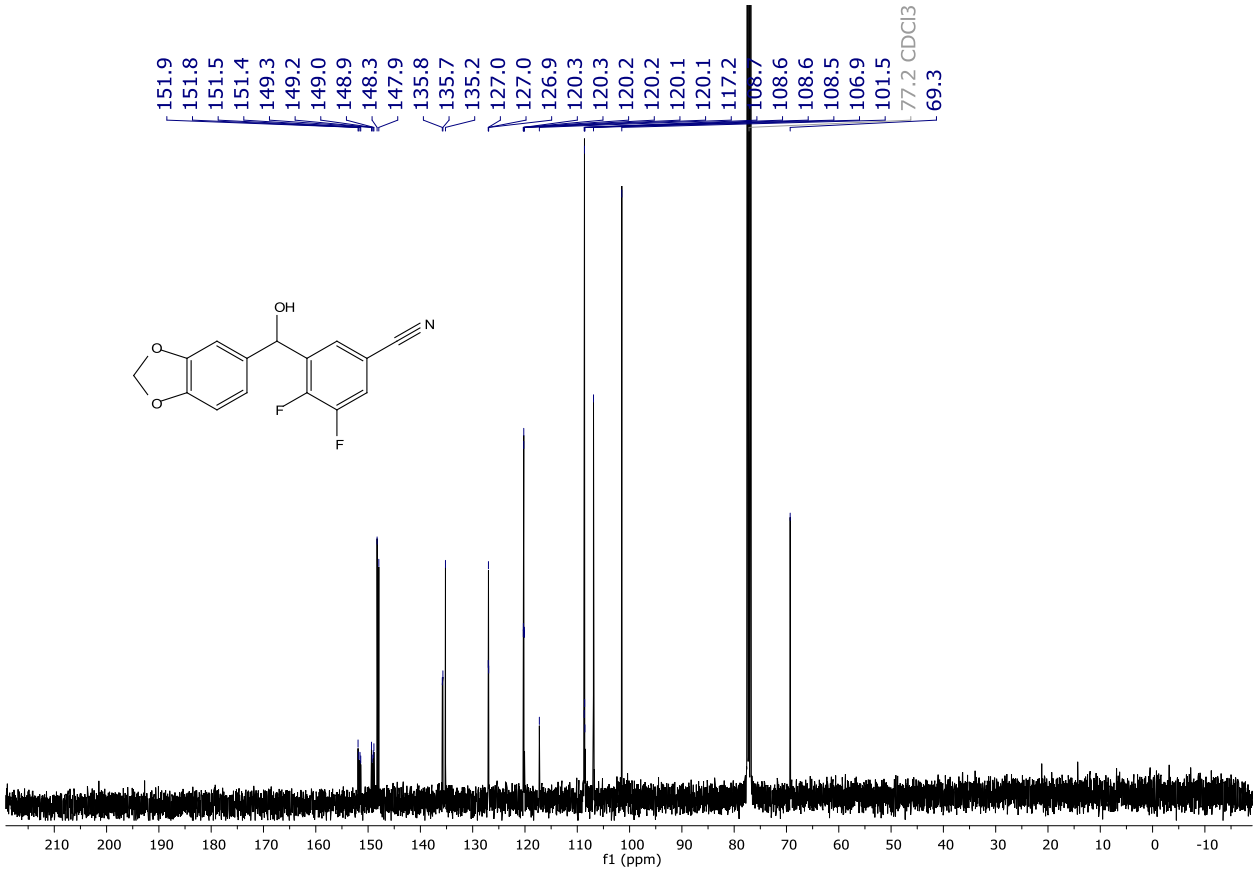


^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) spectrum of **125ac**.

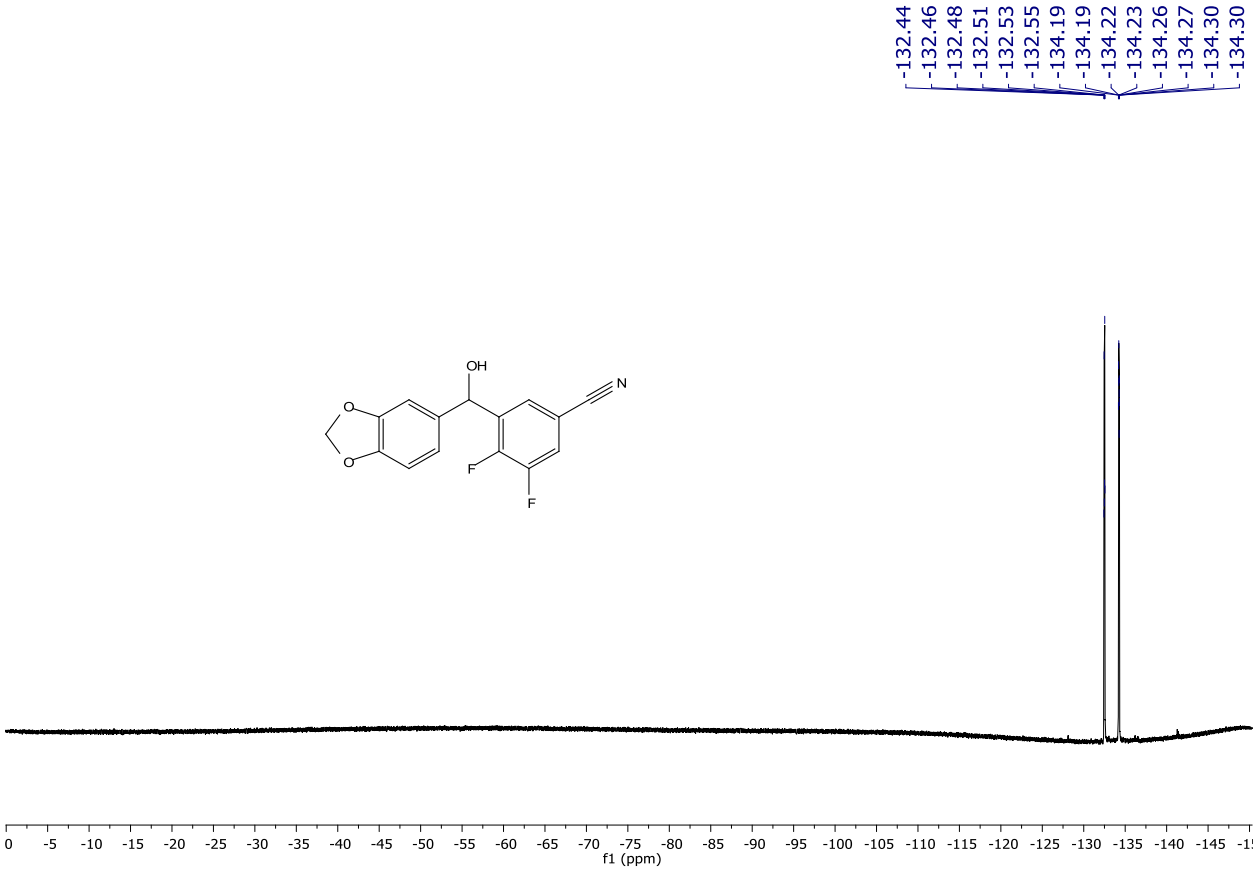


^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125ac**.

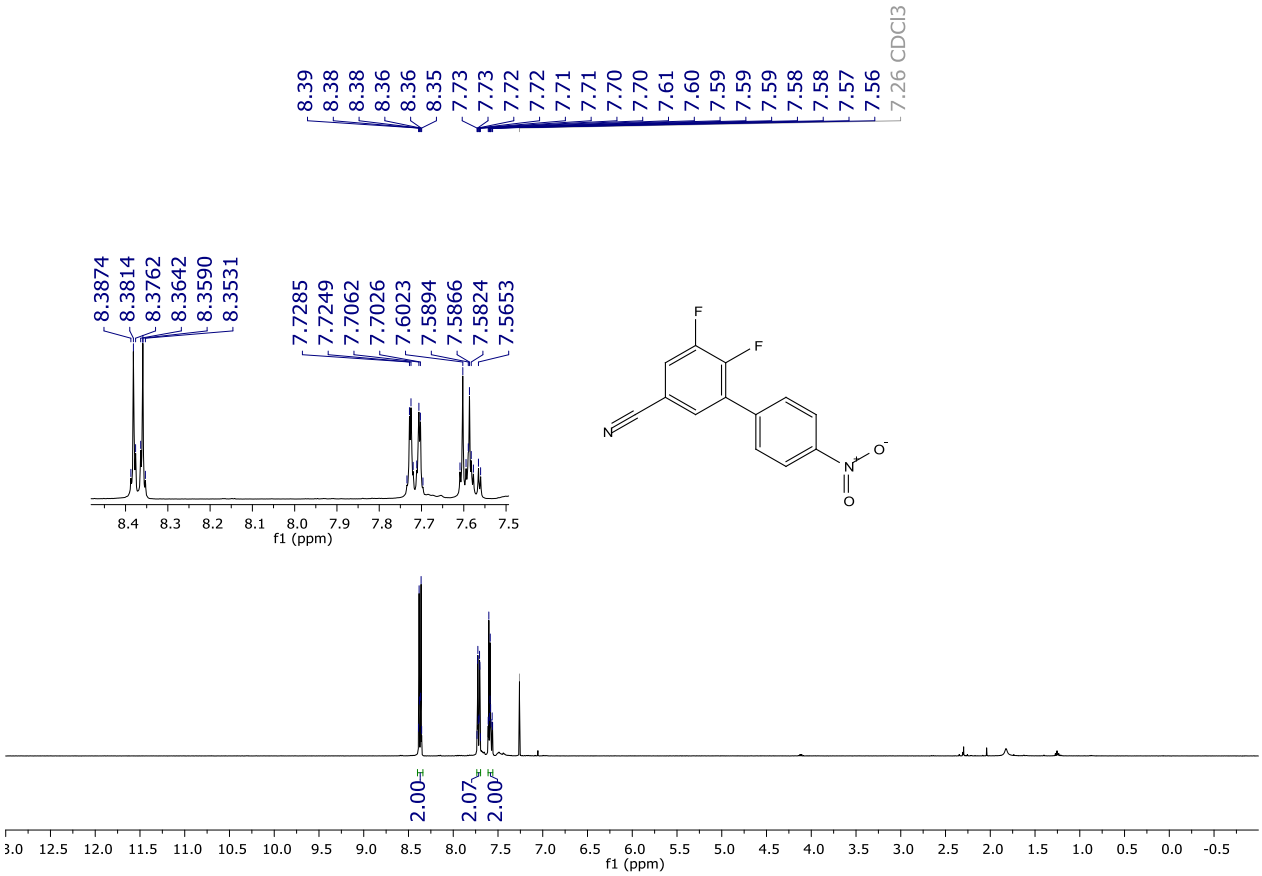
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125ad**.



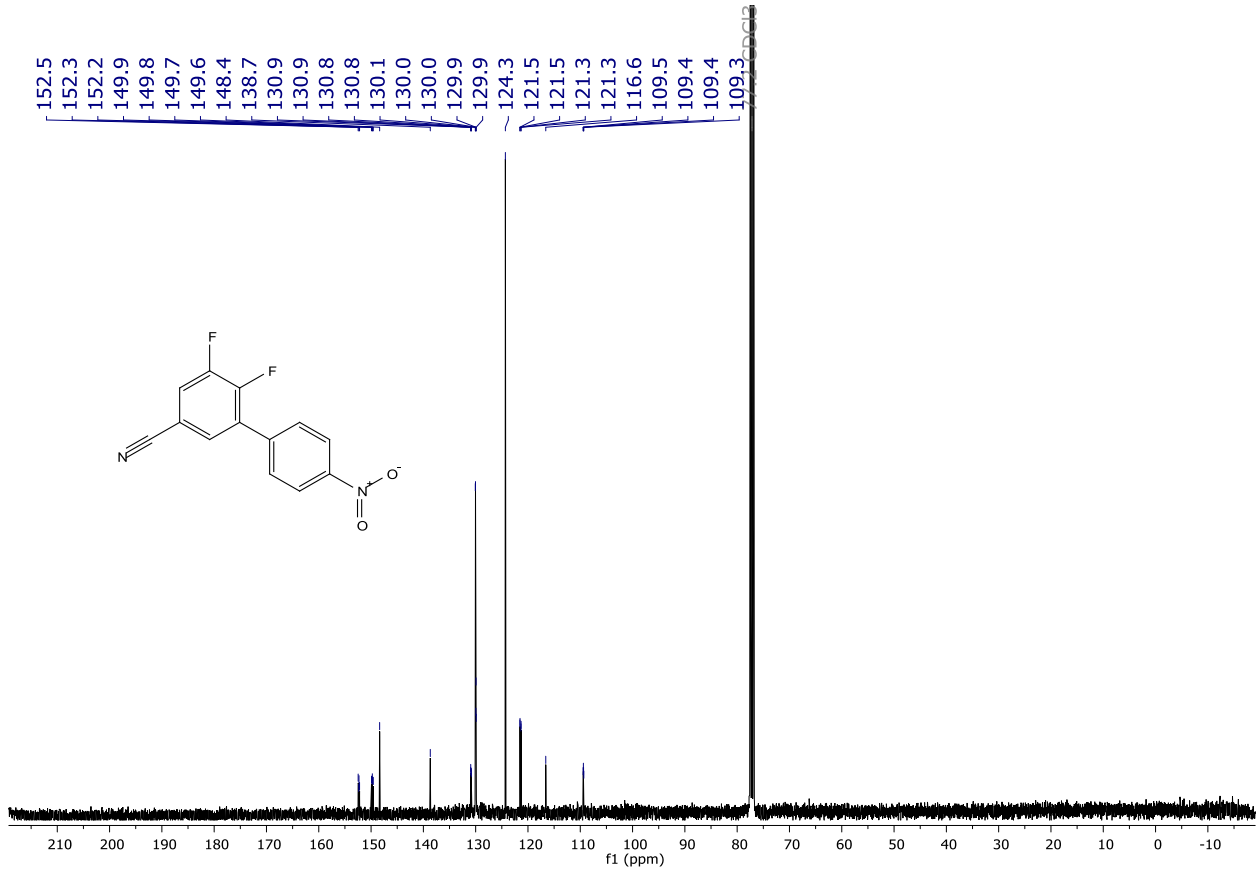
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125ad**.



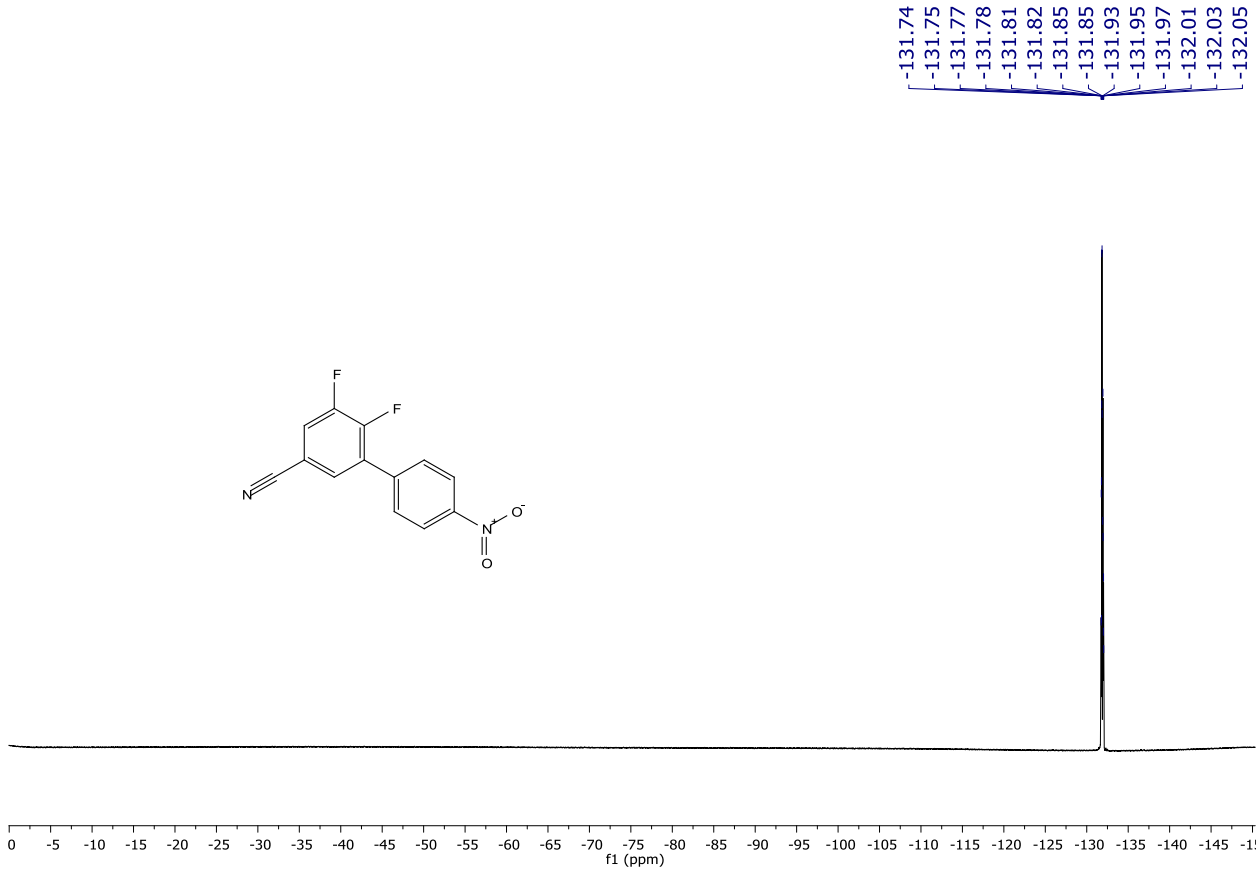
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125ad**.



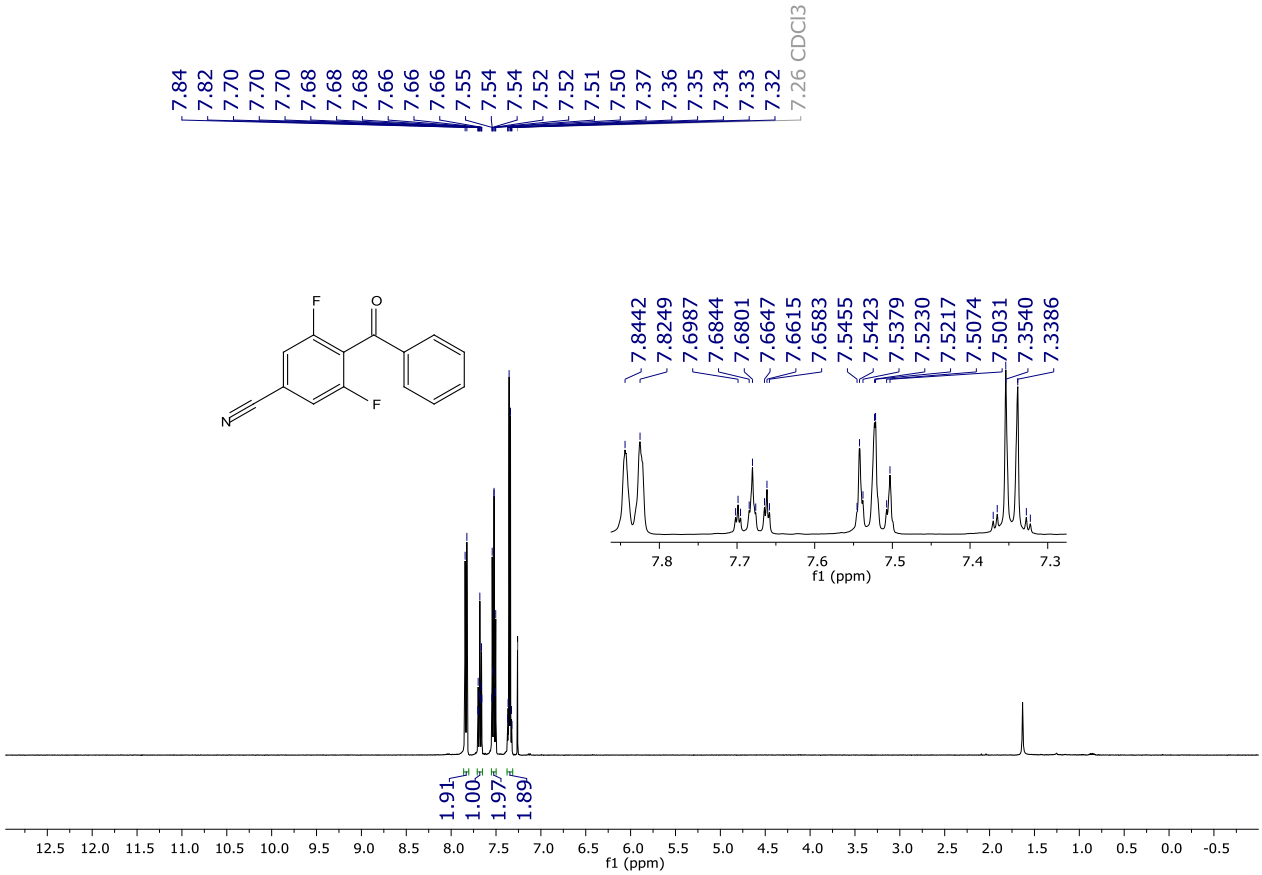
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125ae**.



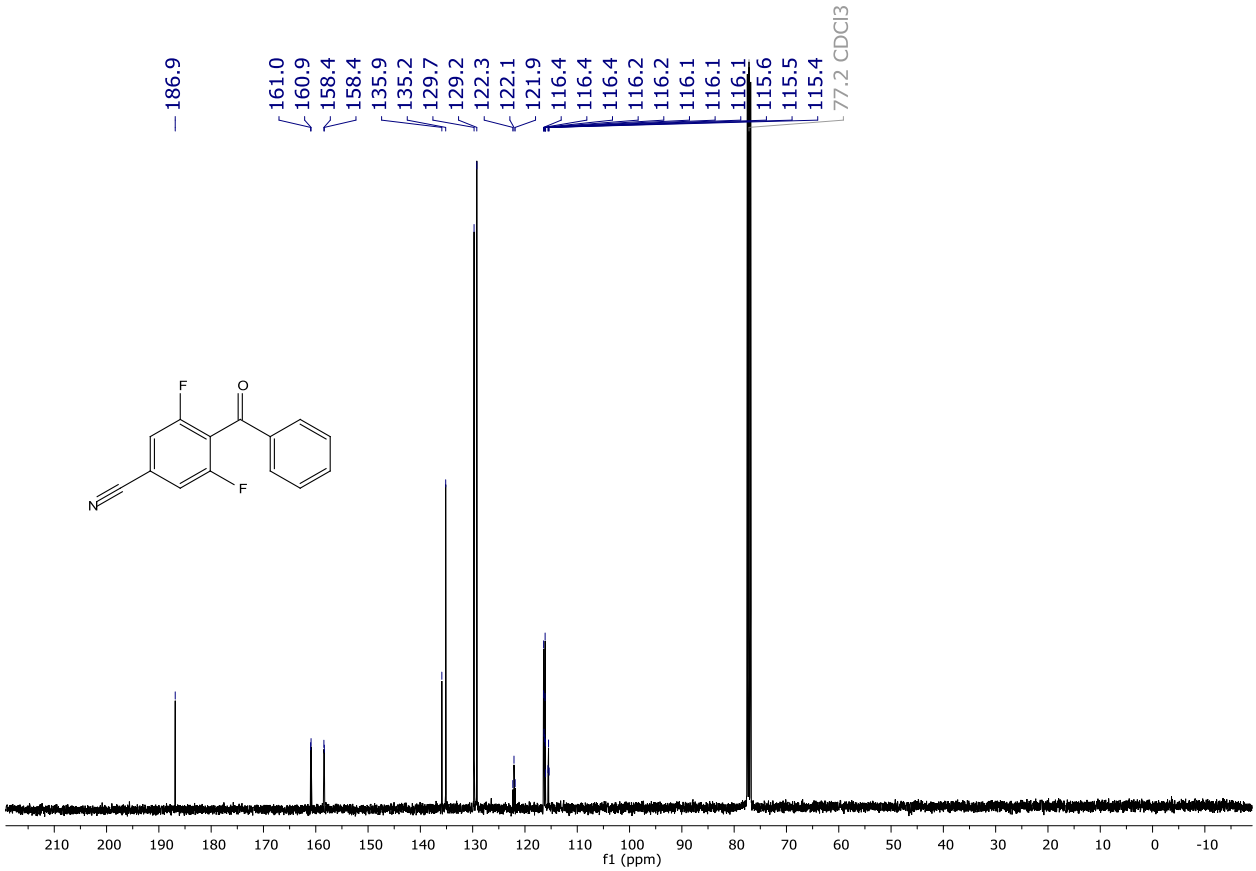
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) spectrum of **125ae.**



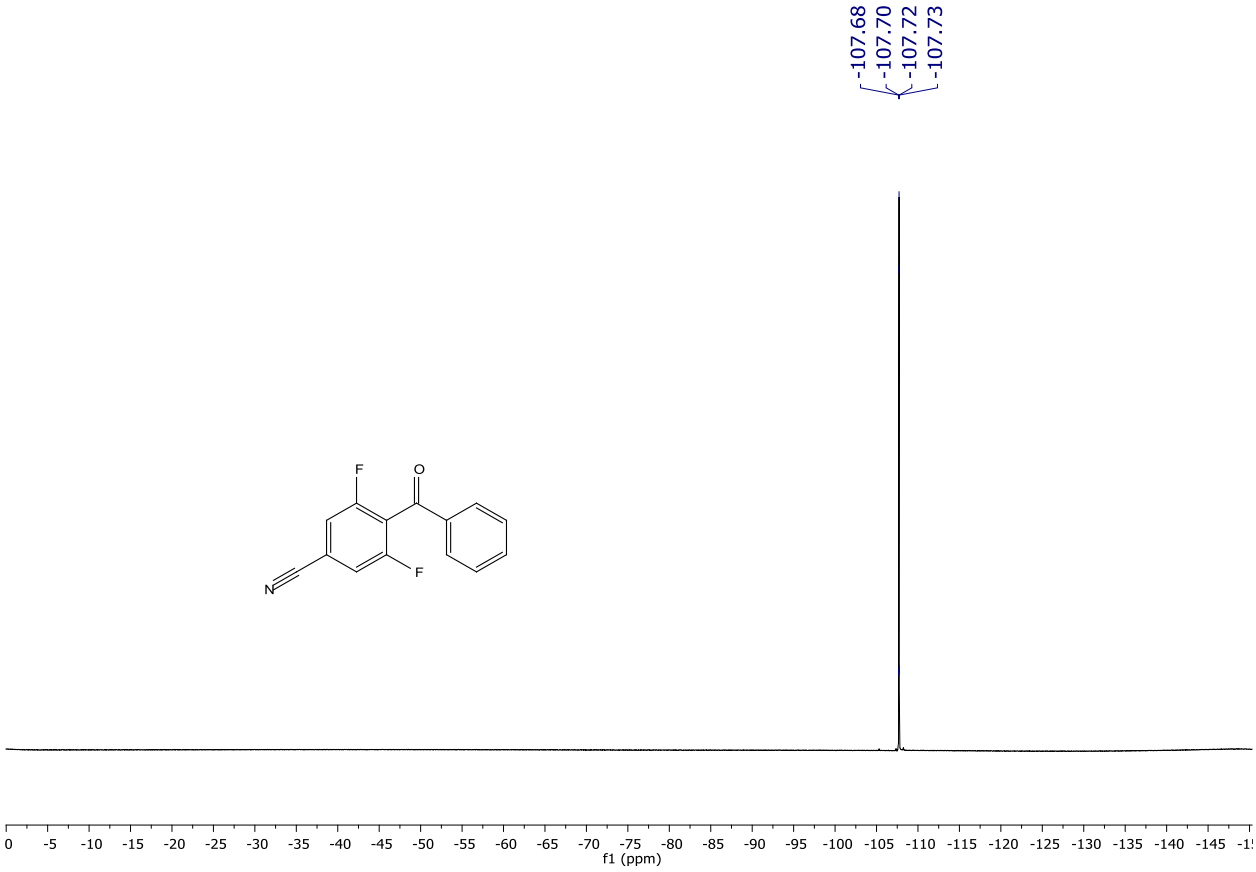
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125ae.**



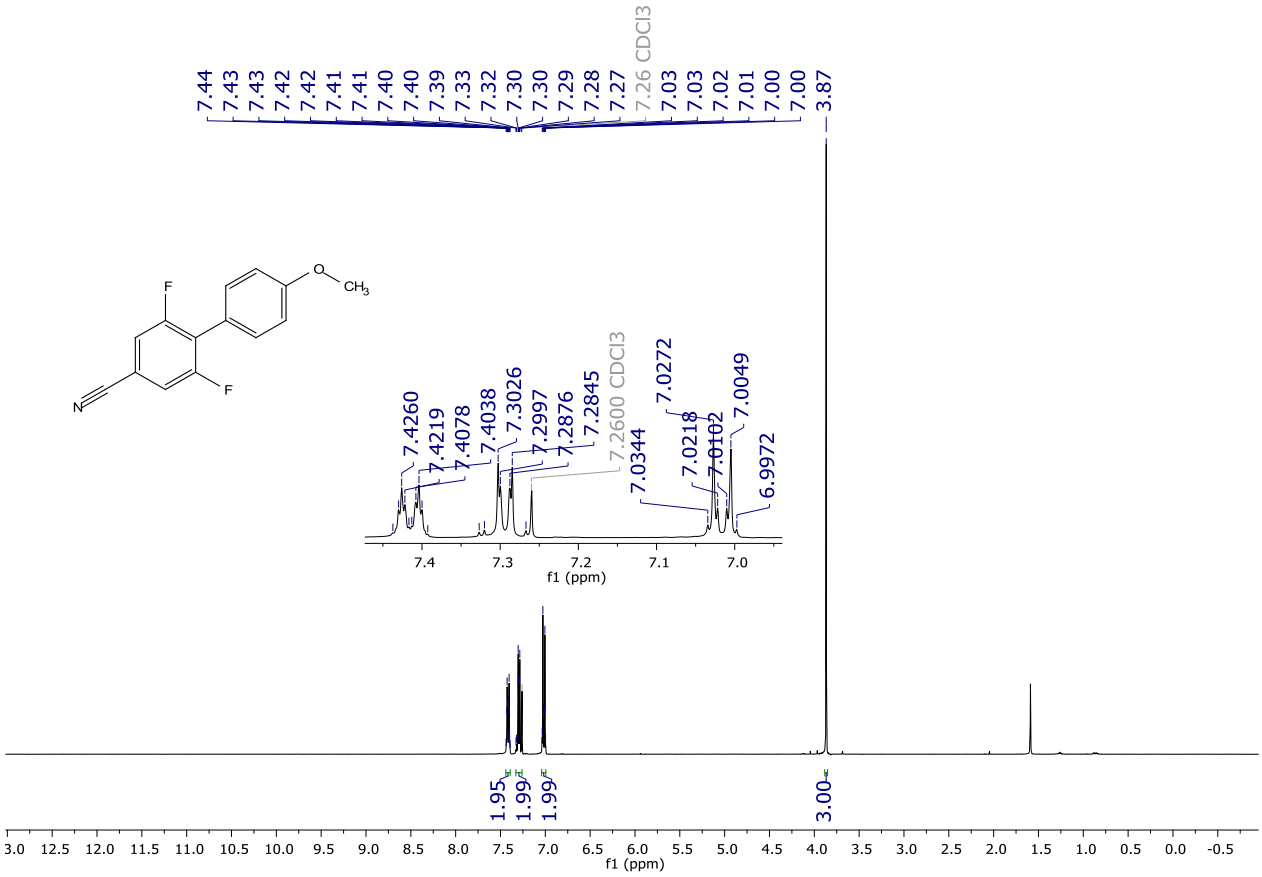
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125af**.



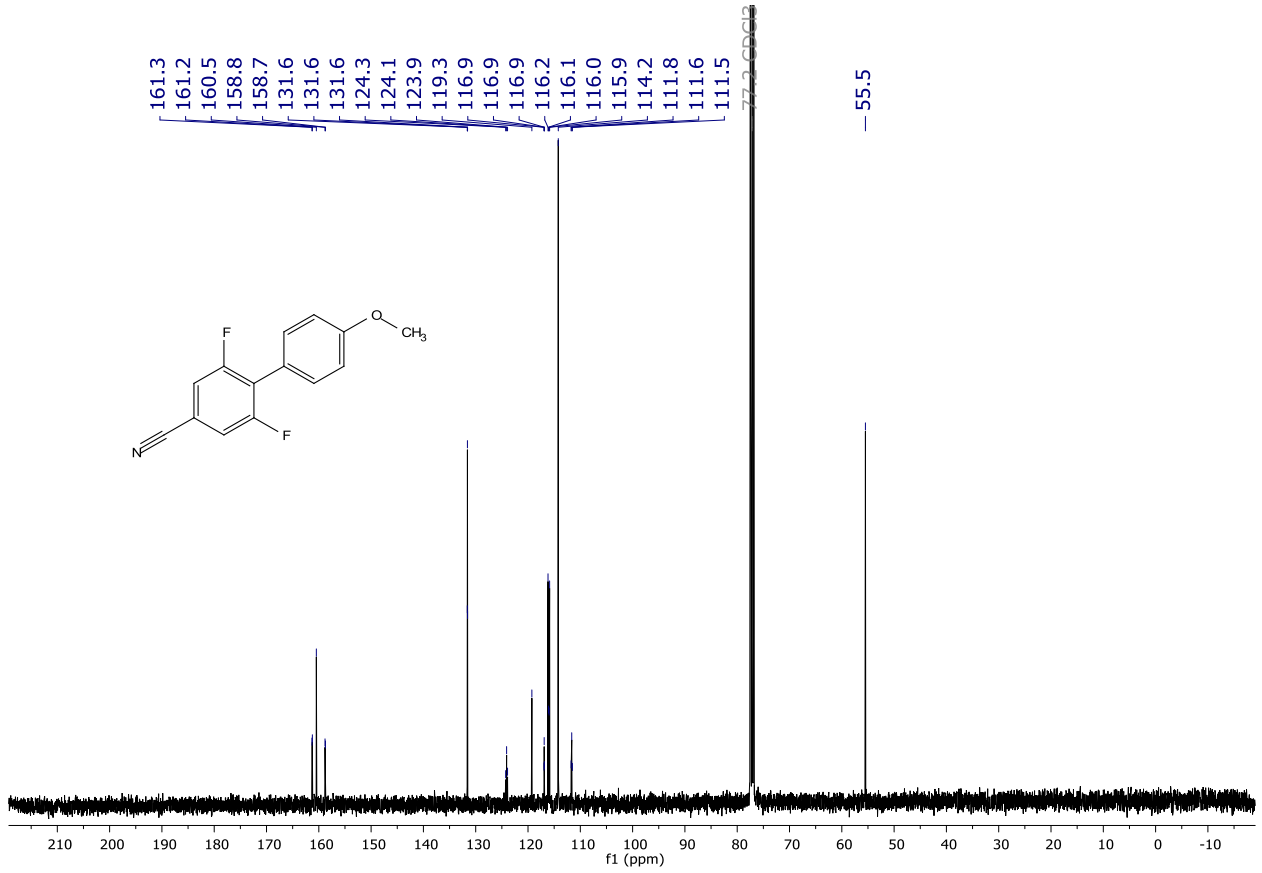
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125af.**



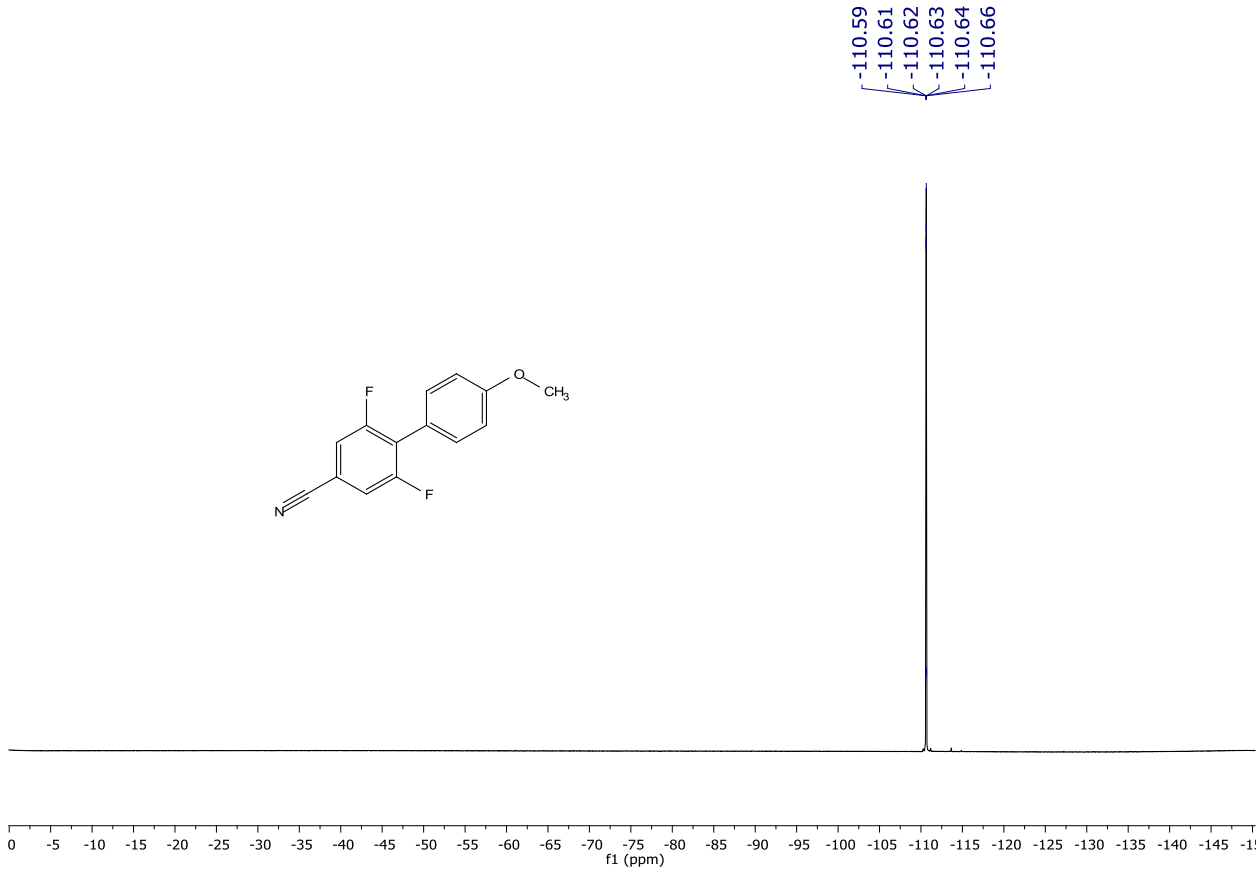
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125af.**



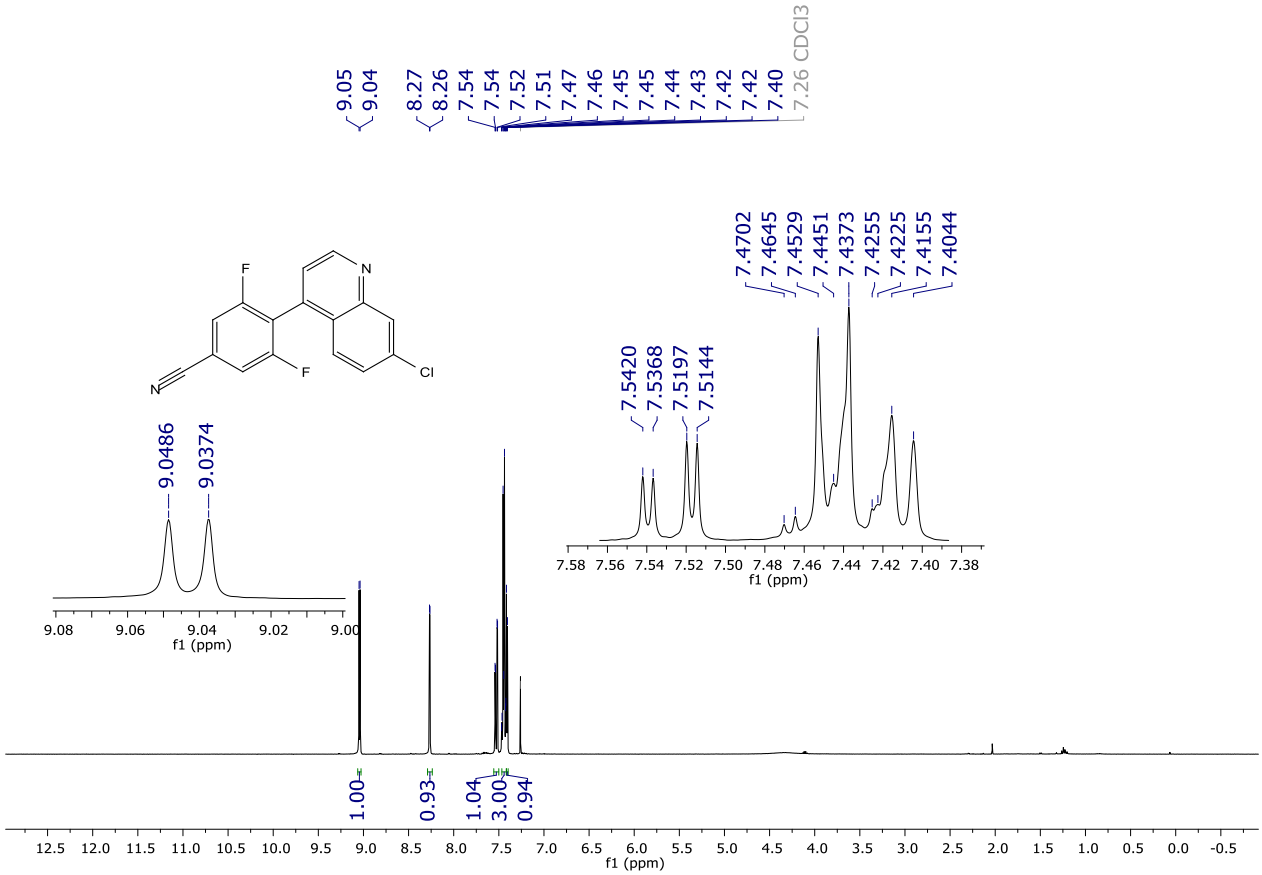
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125ag**.



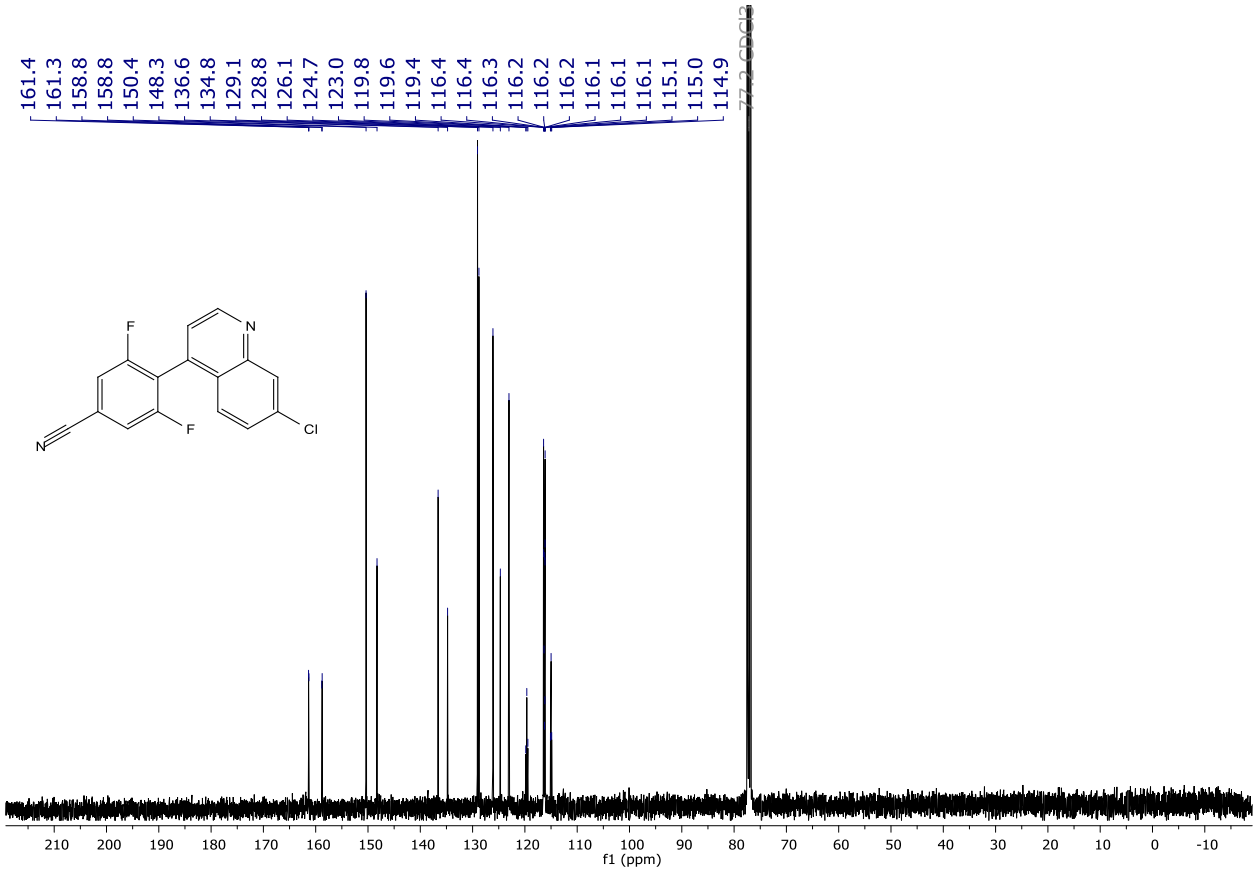
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) spectrum of **125ag.**



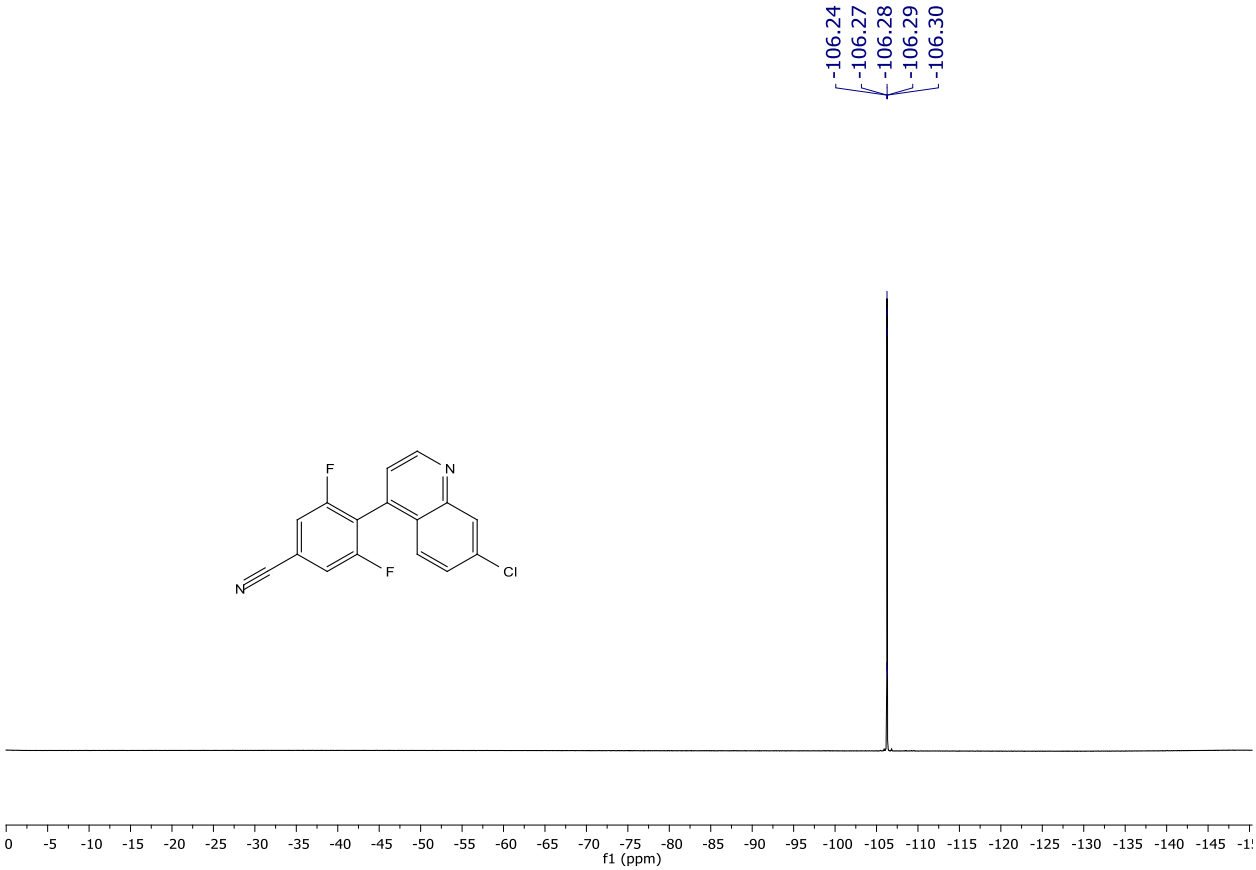
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125ag.**



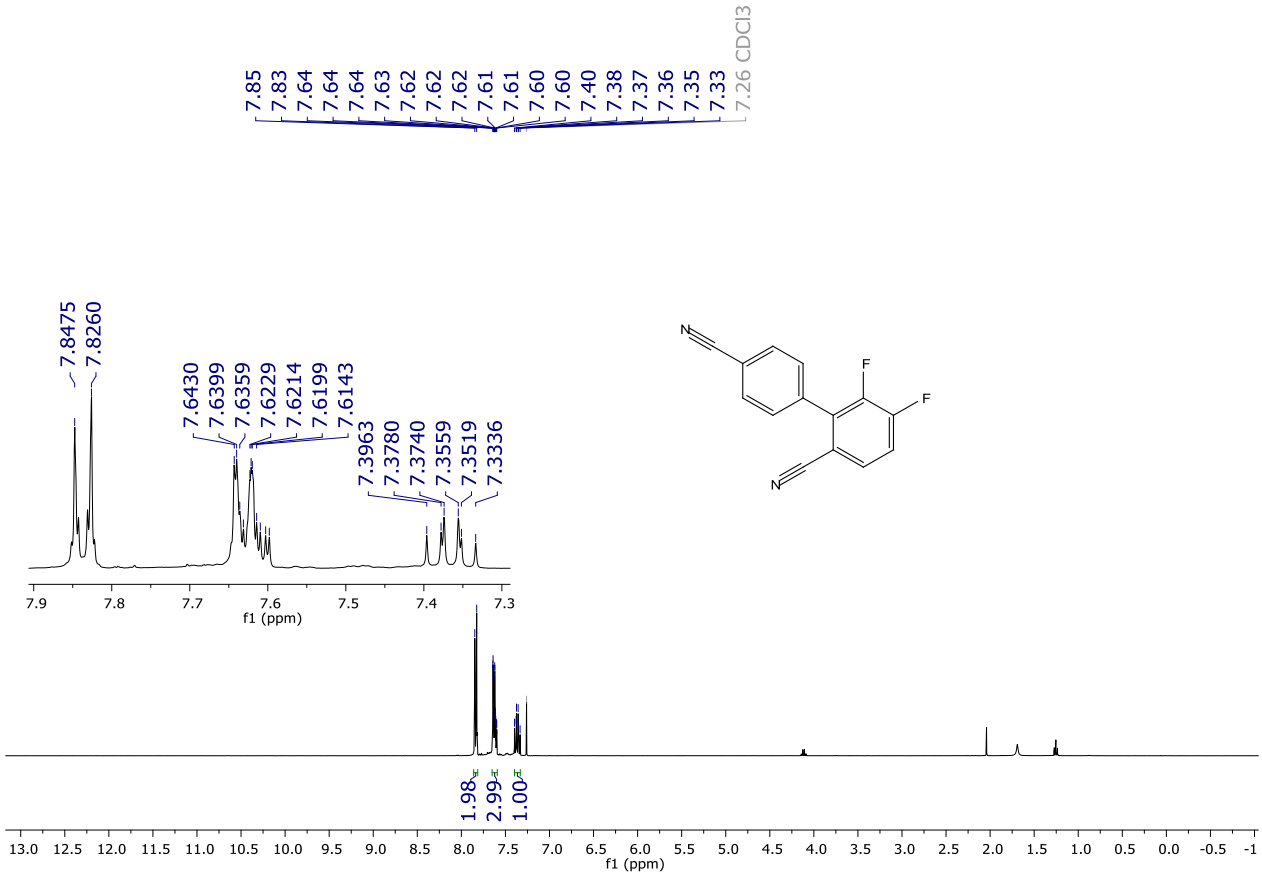
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125ah**.



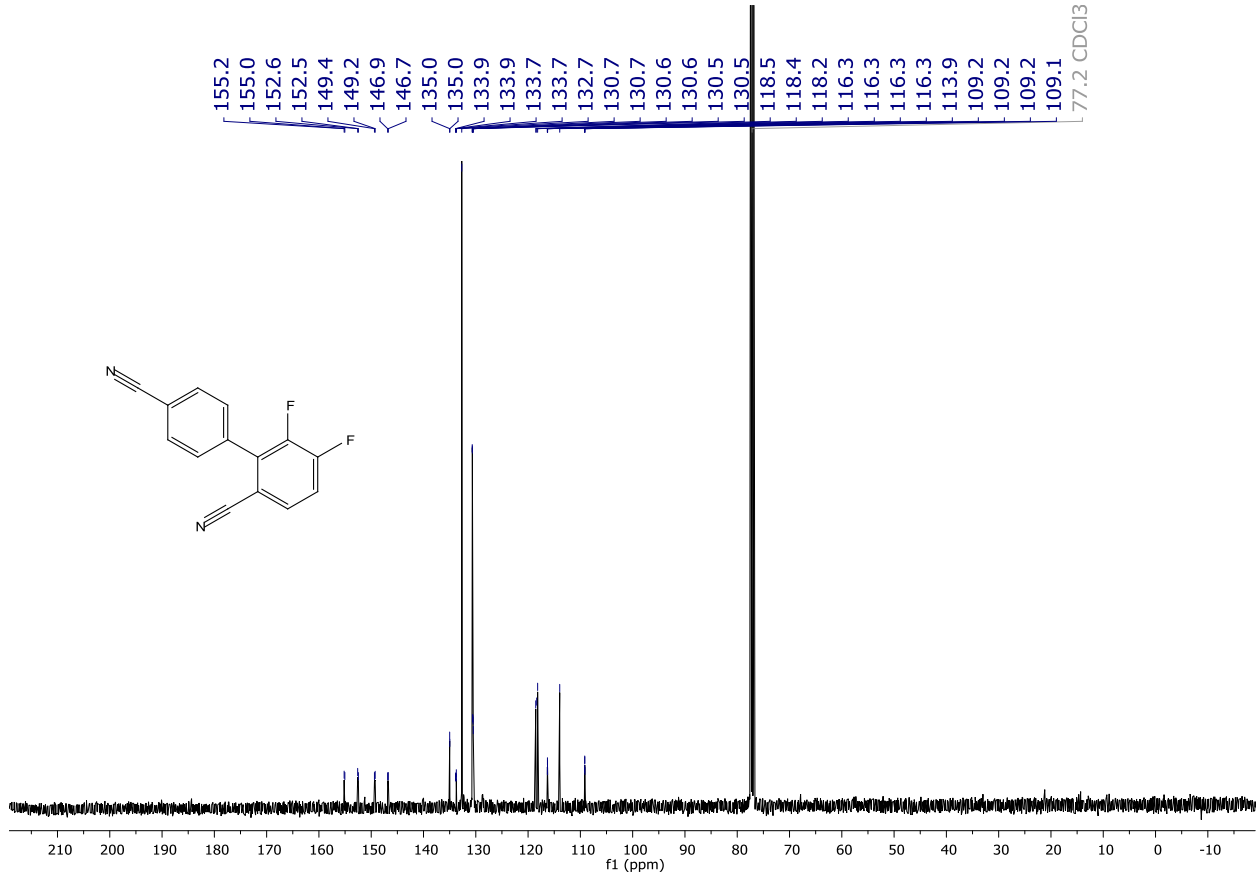
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125ah.**



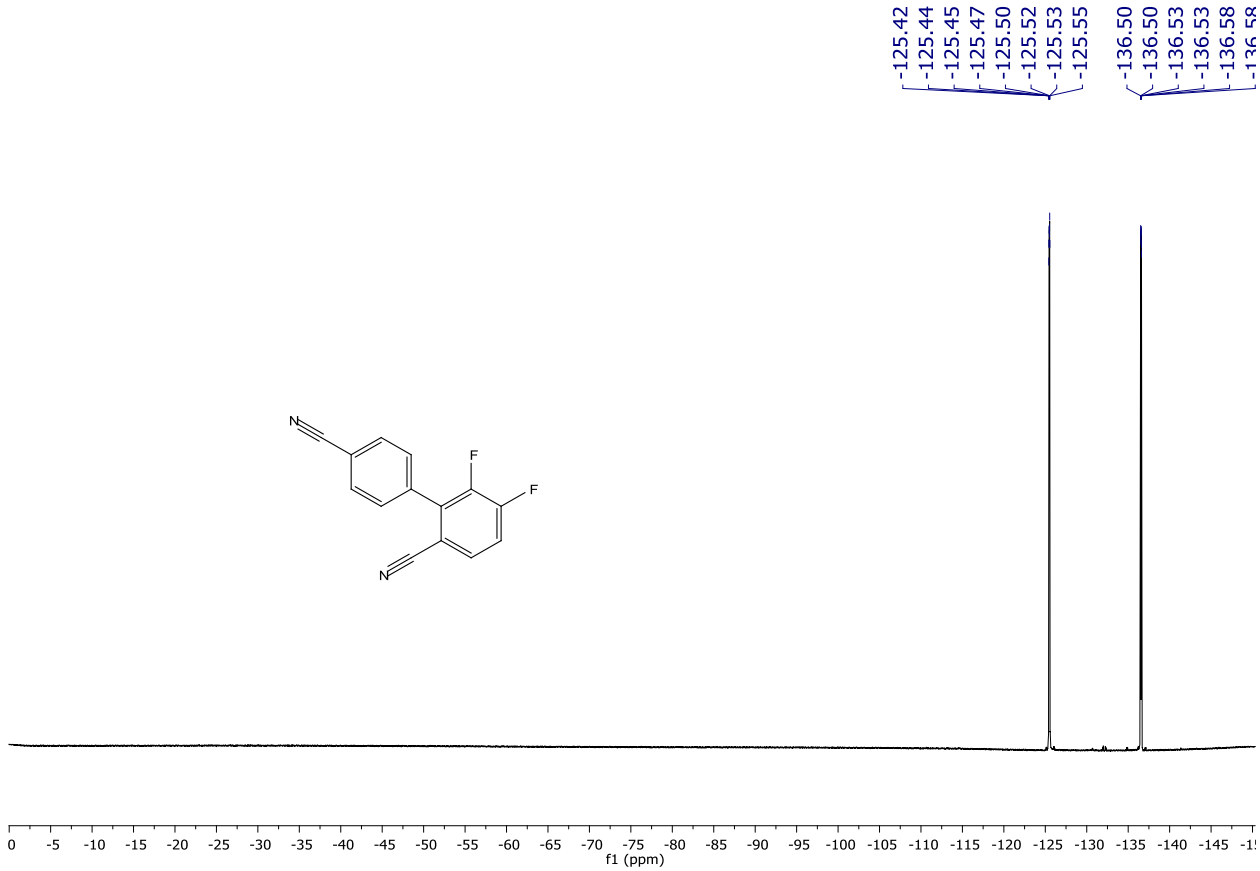
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125ah.**



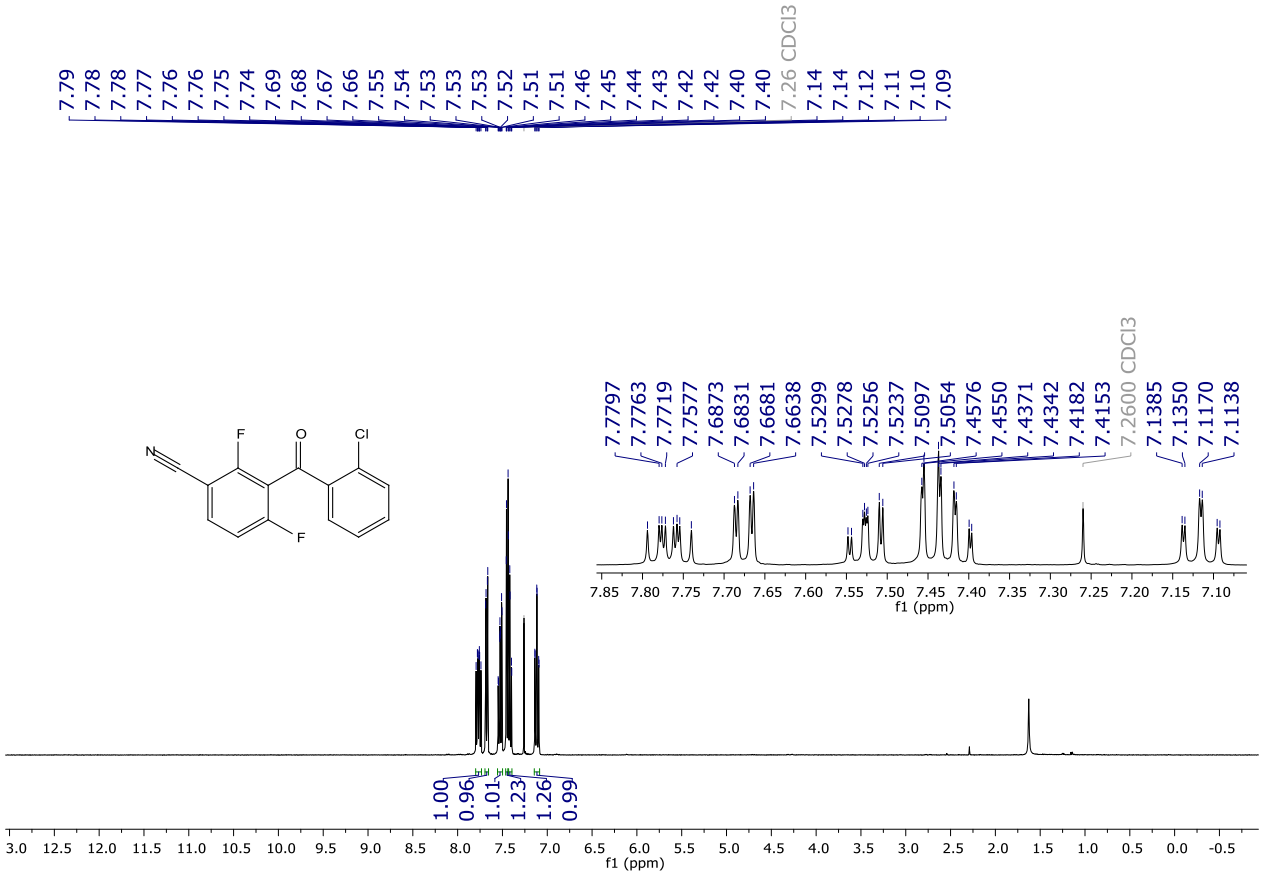
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125ai**.



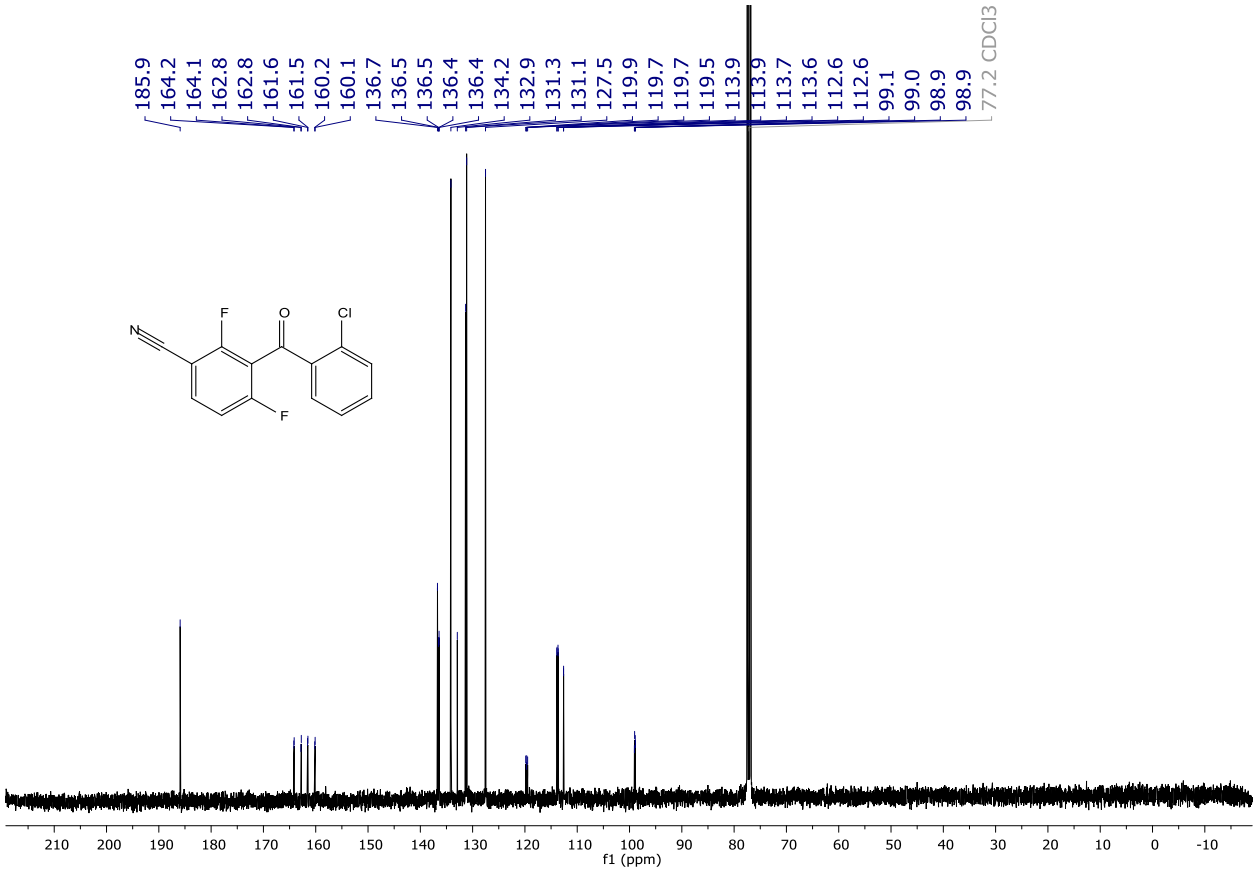
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) spectrum of **125ai**.



^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125ai**.

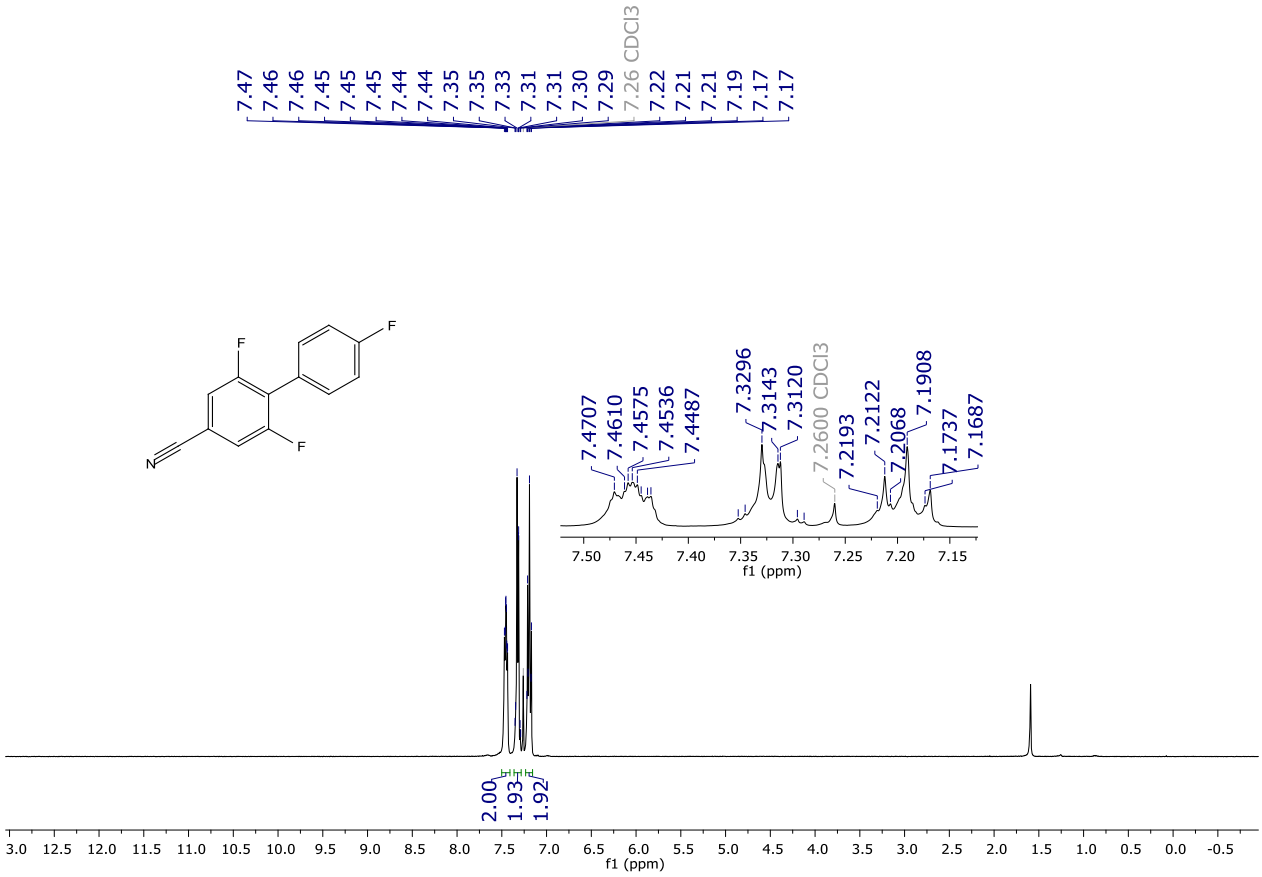


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125aj**.

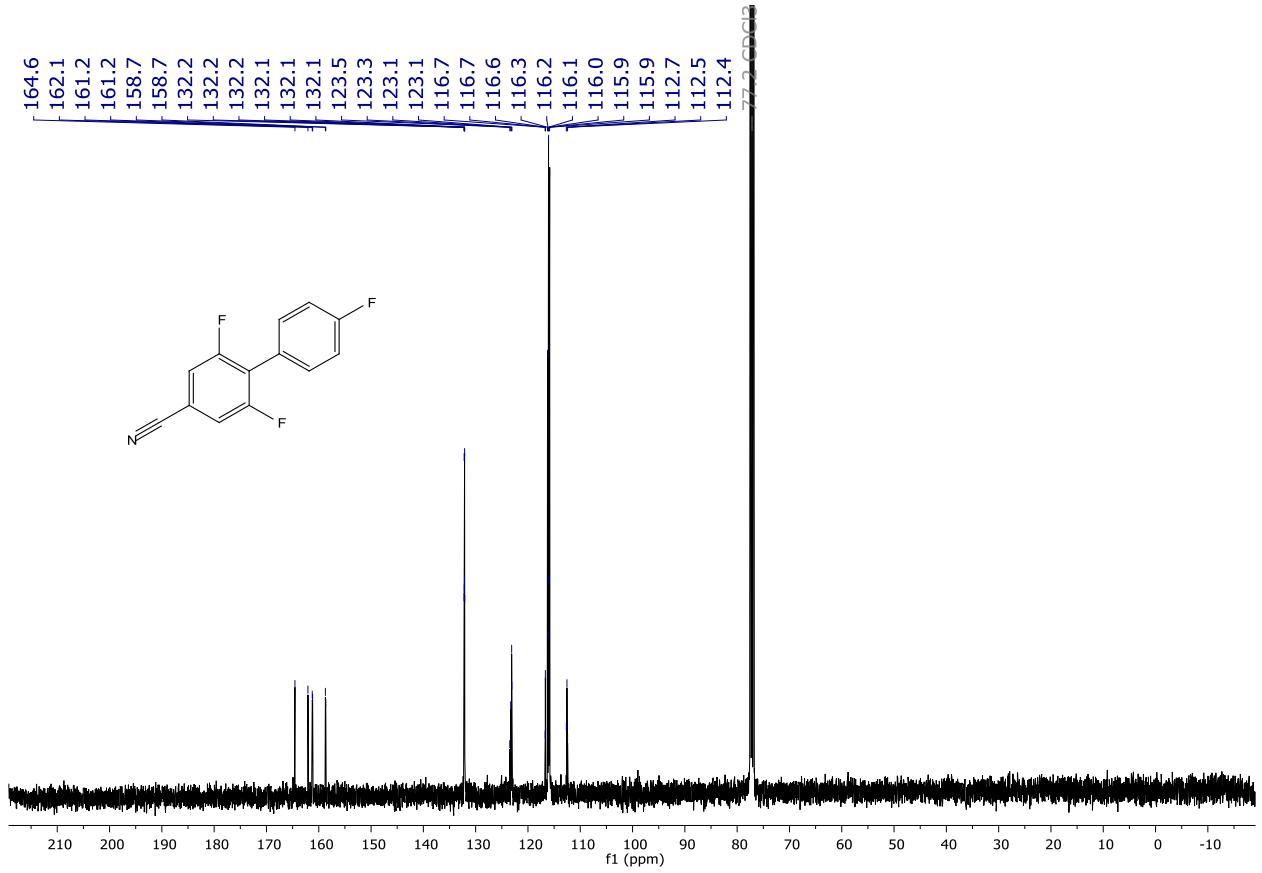


$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125aj**.

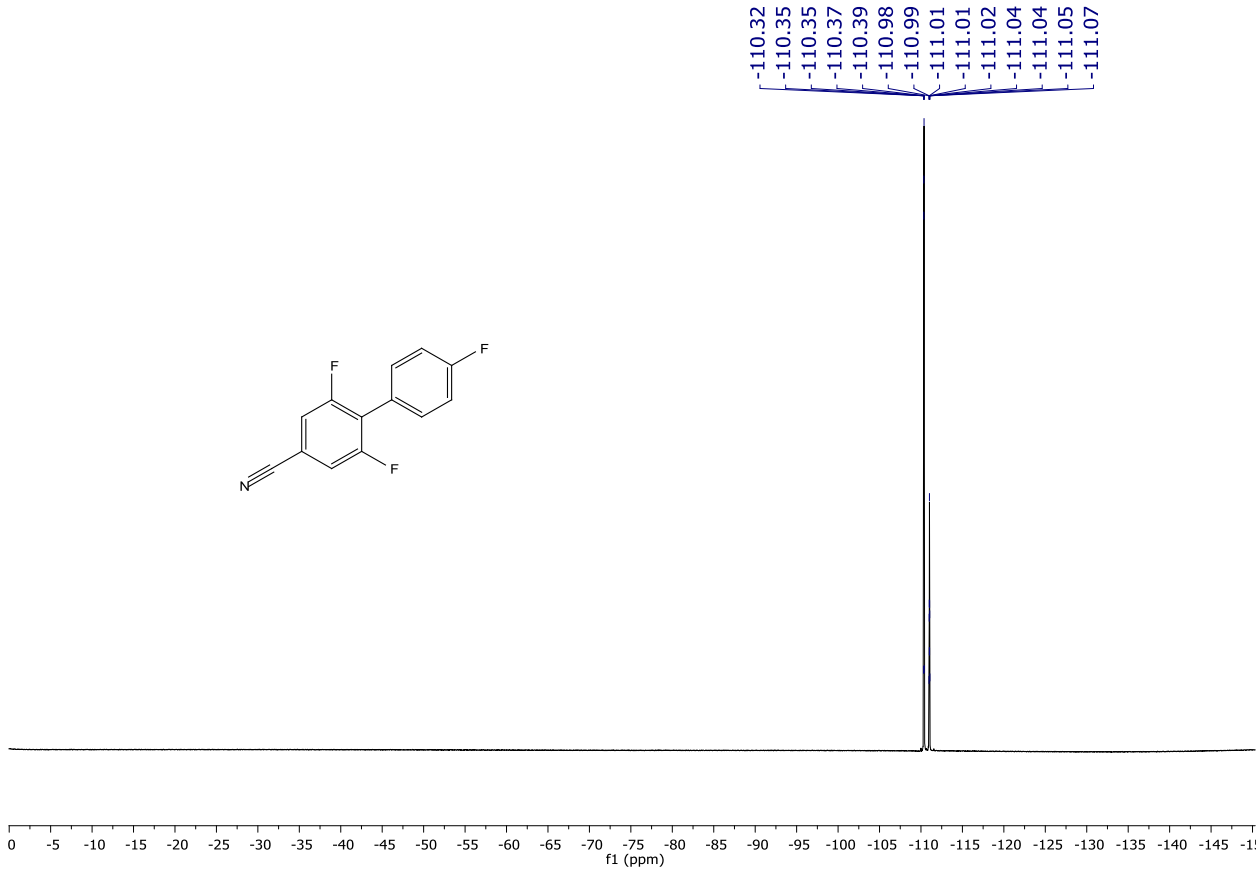
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125aj**.



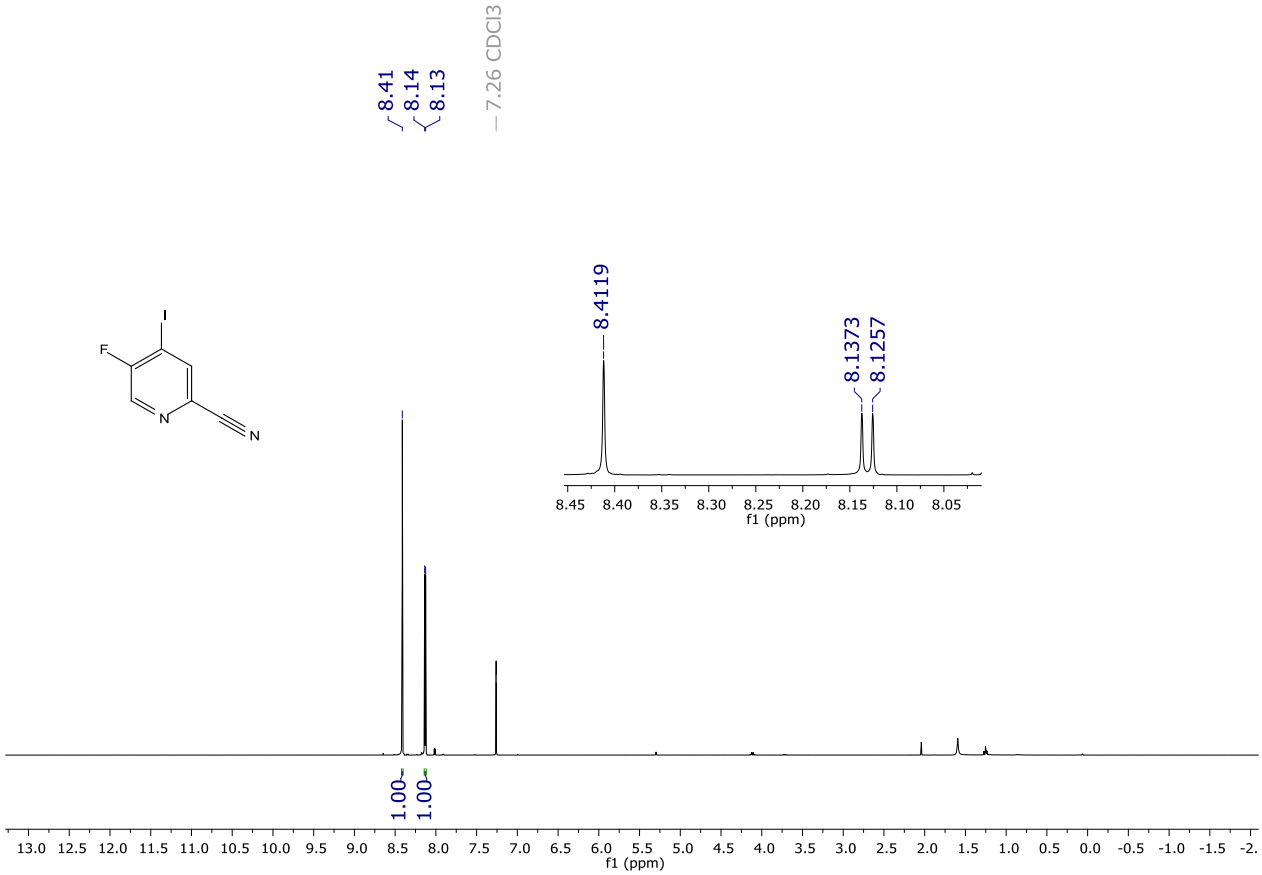
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125ak**.



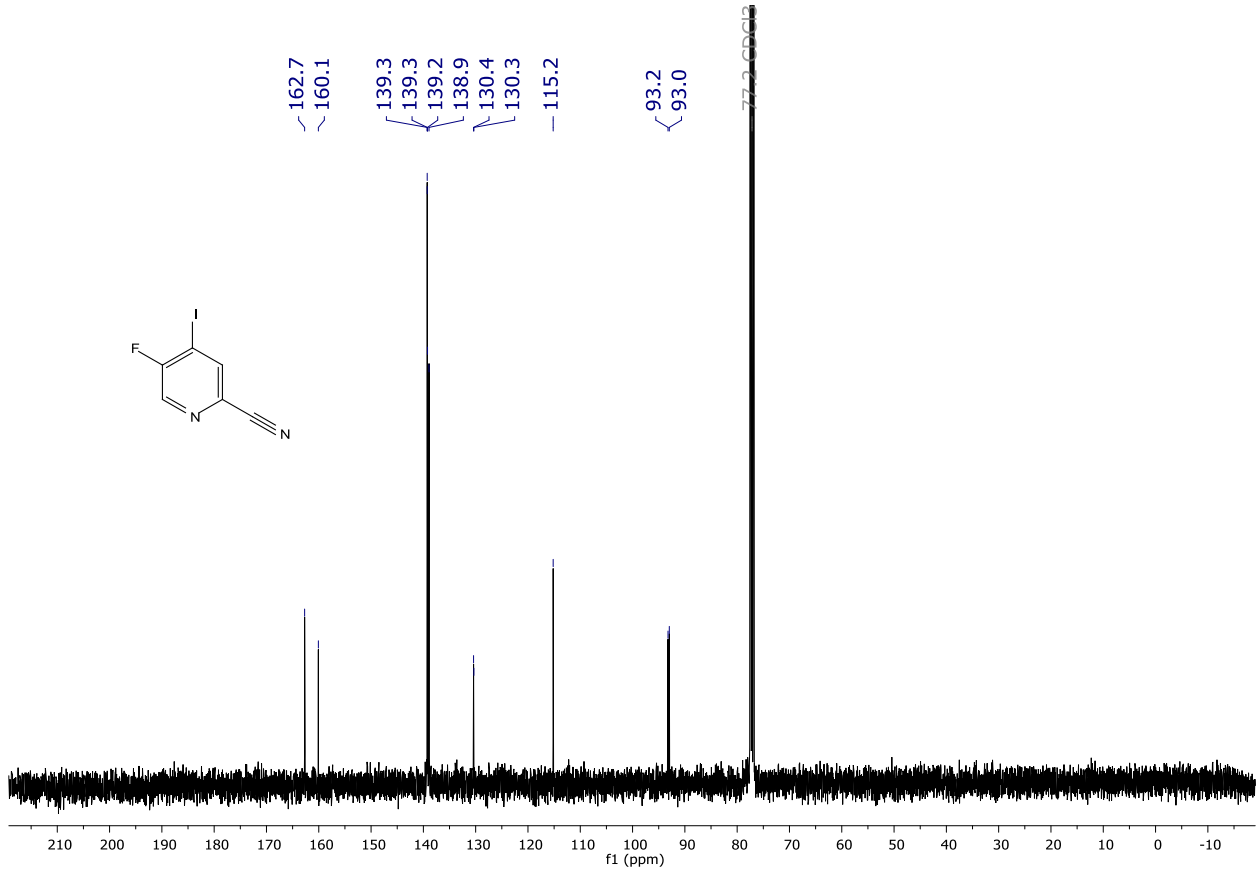
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) spectrum of **125ak**.



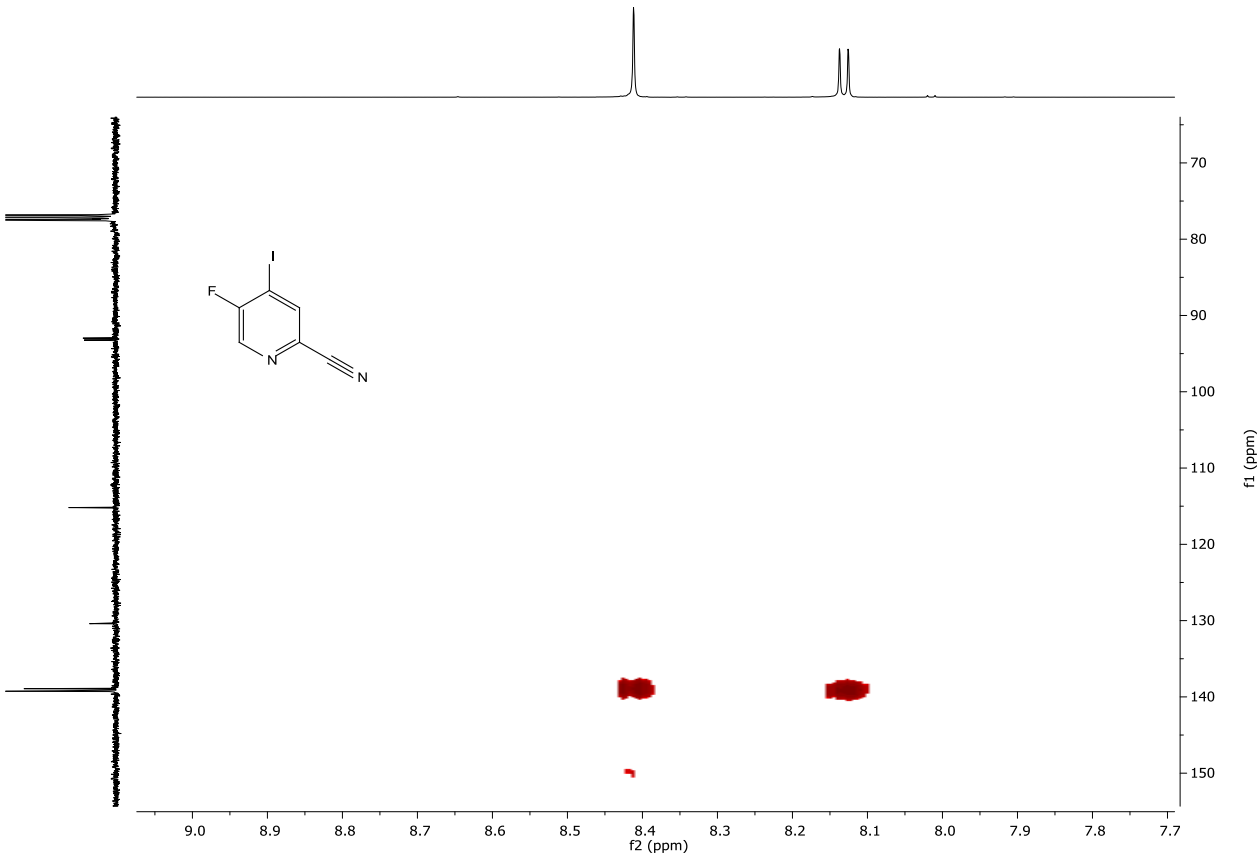
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125ak**.



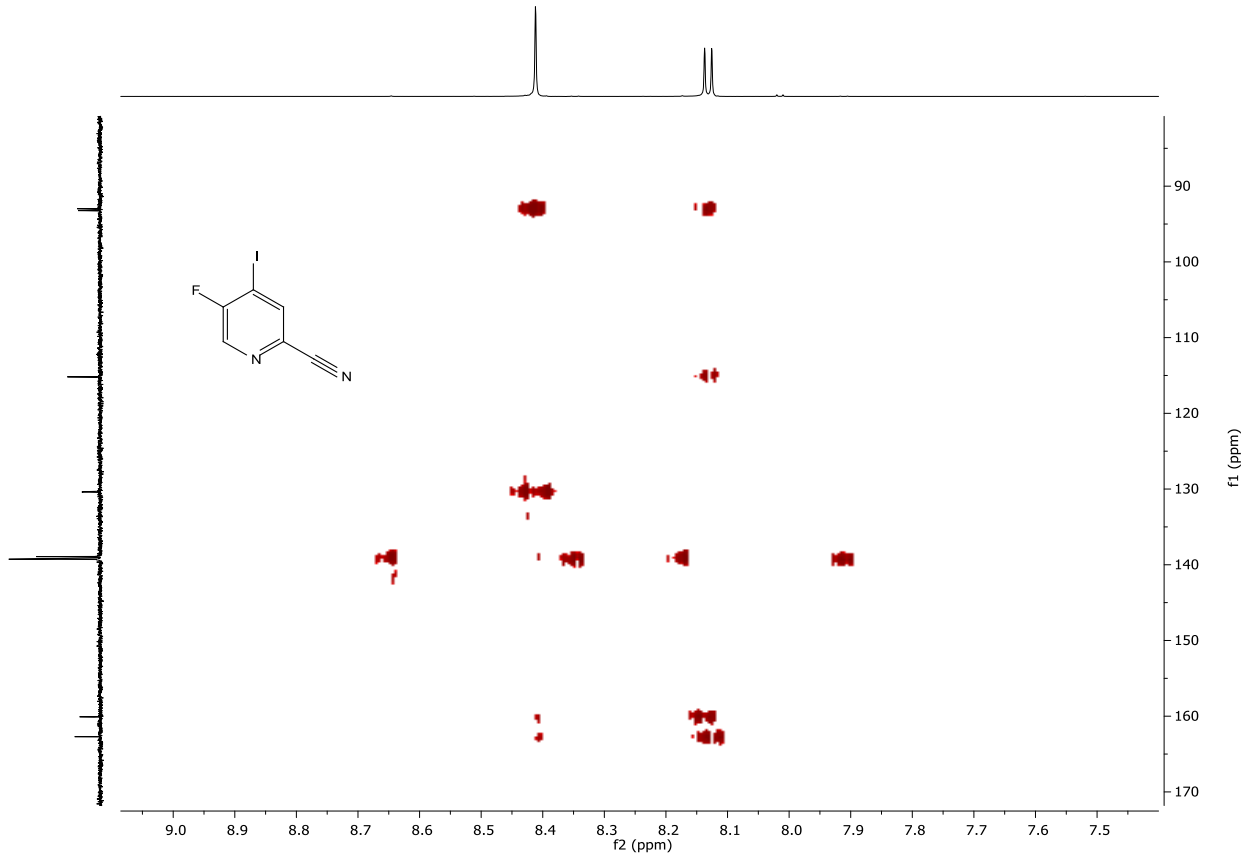
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125al**.



$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125al**.

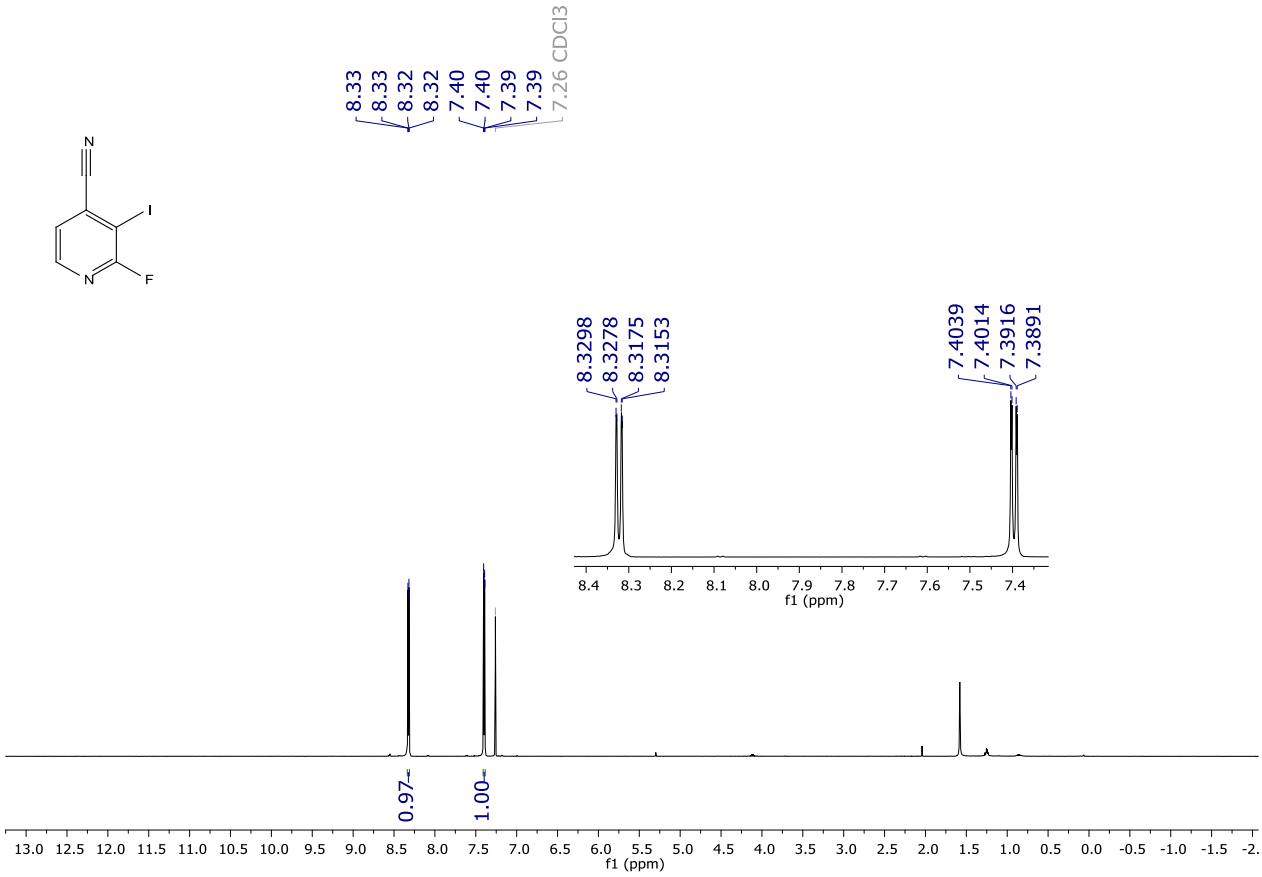


HSQC correlation map of **125al** (400 and 101 MHz, $CDCl_3$).

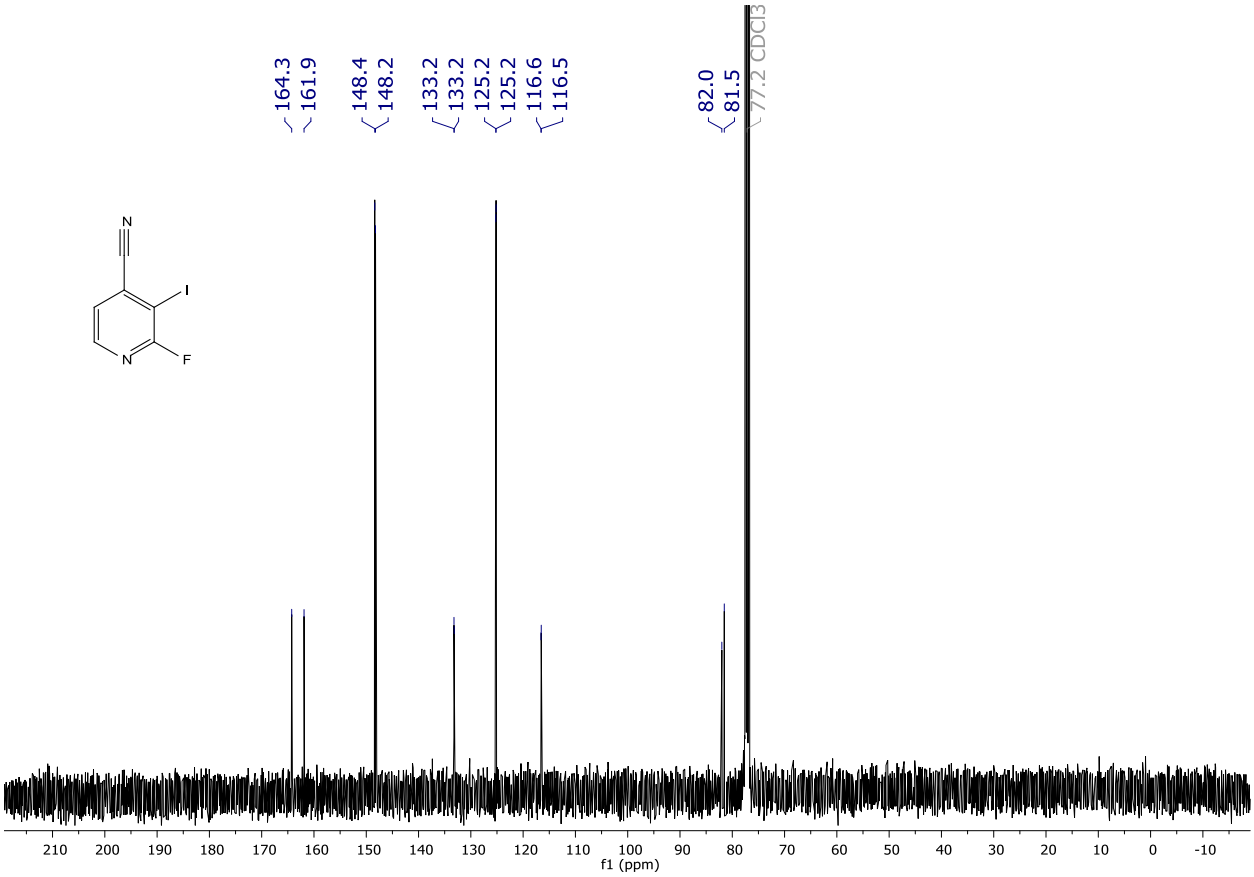


HMBC correlation map of **125al** (400 and 101 MHz, $CDCl_3$).

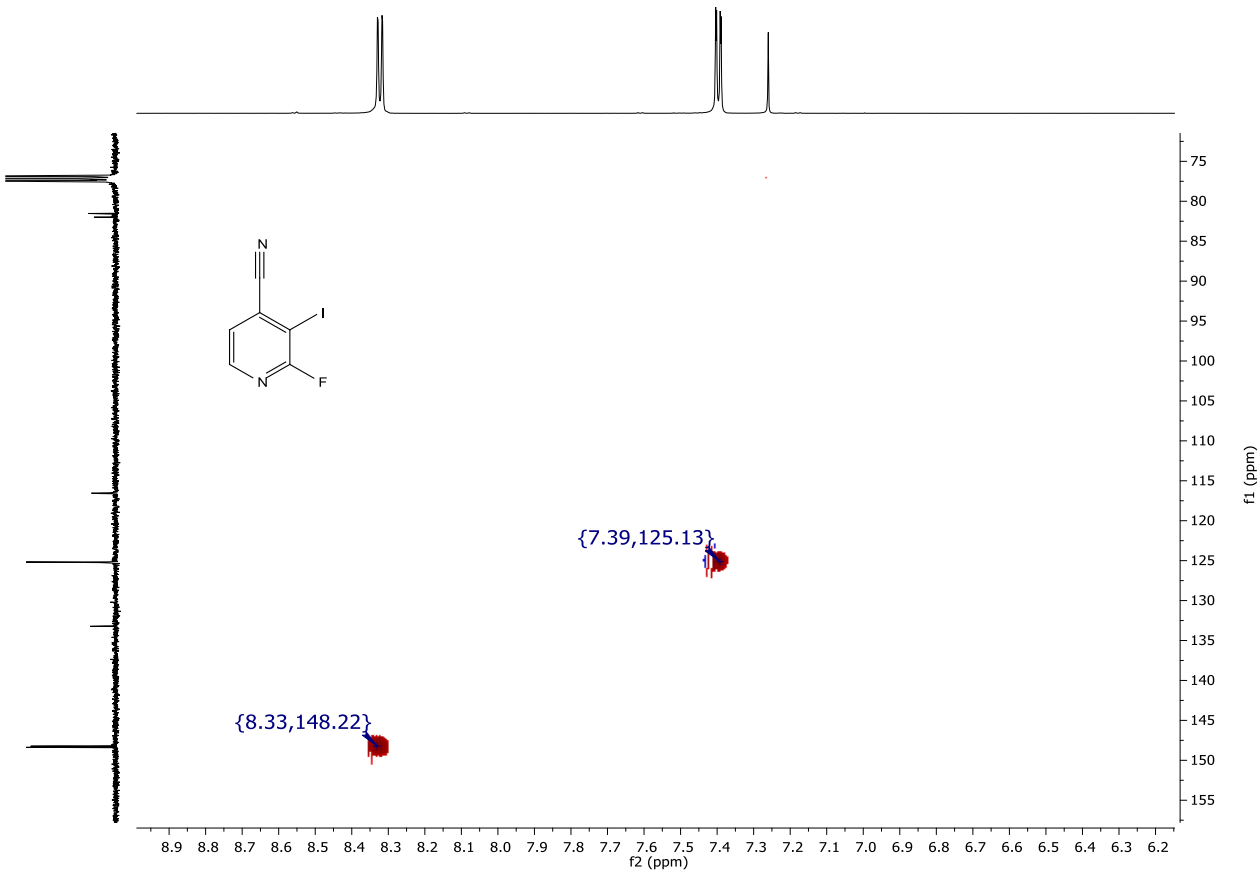
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125al**.



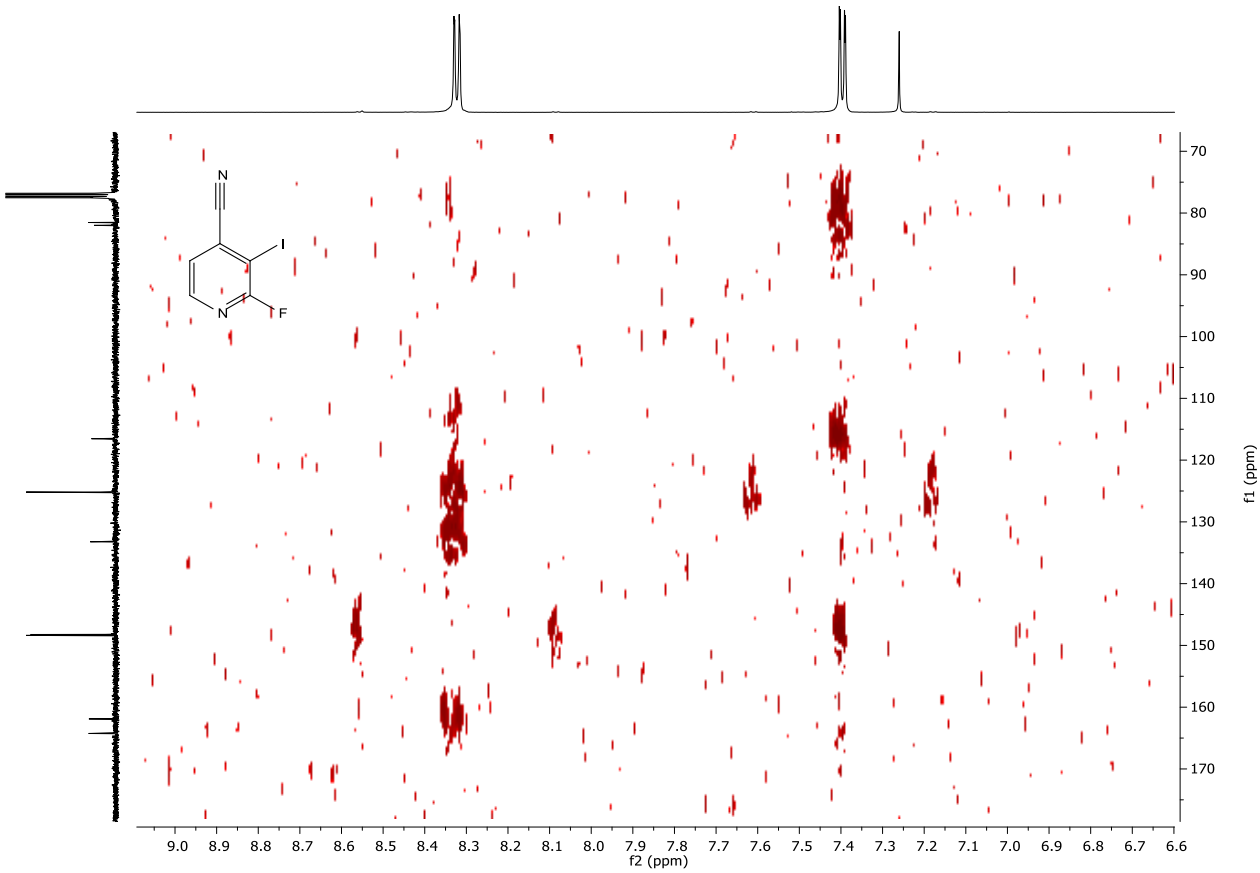
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125am**.



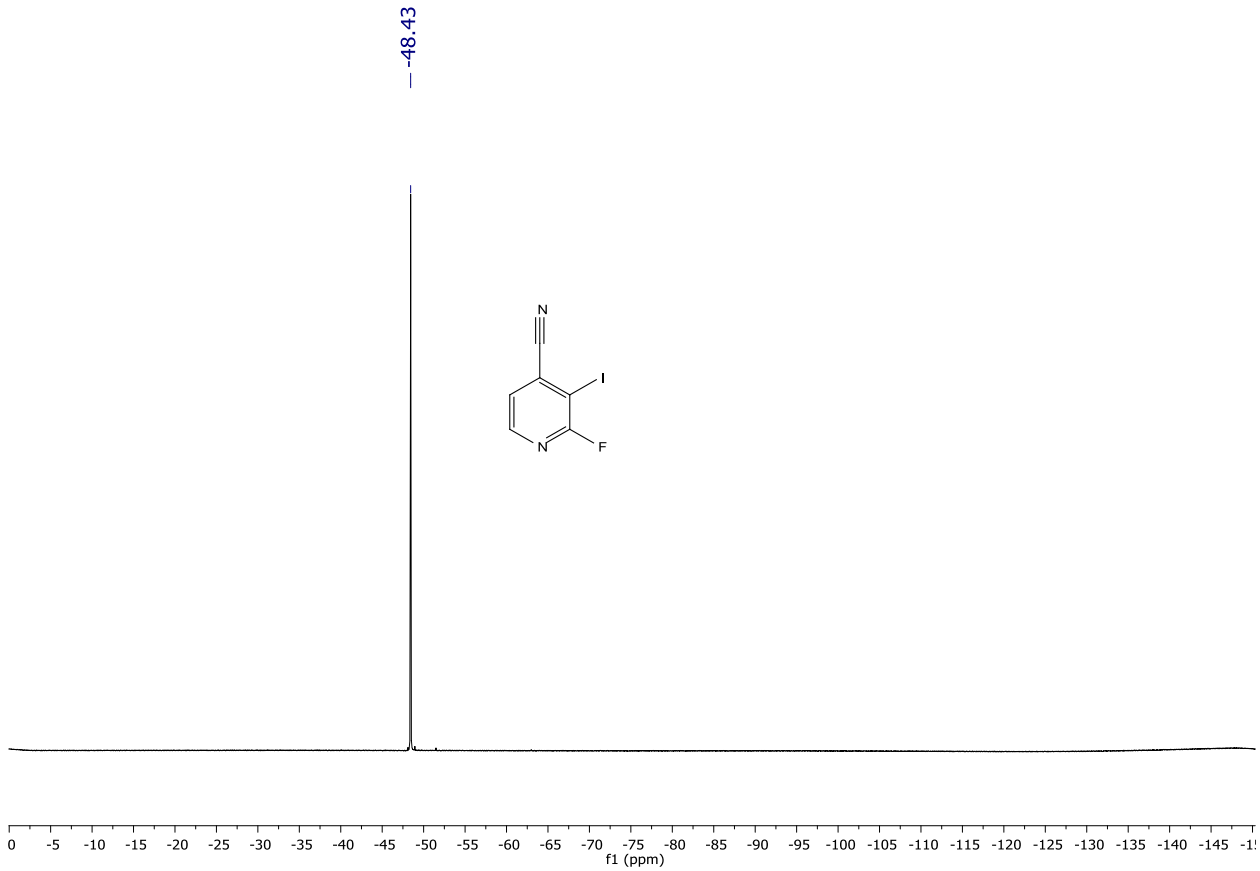
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) spectrum of **125am**.



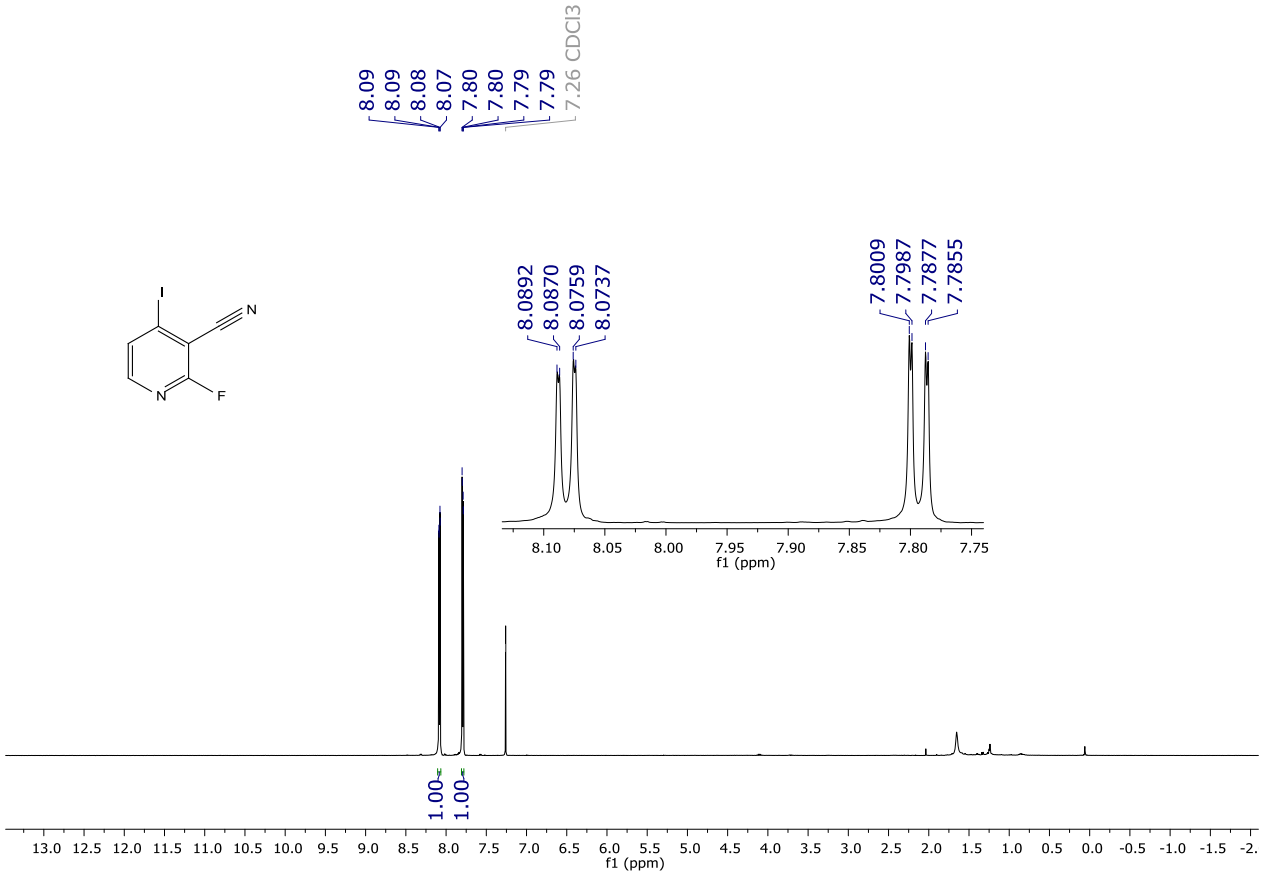
HSQC correlation map of **125am** (400 and 101 MHz, $CDCl_3$).



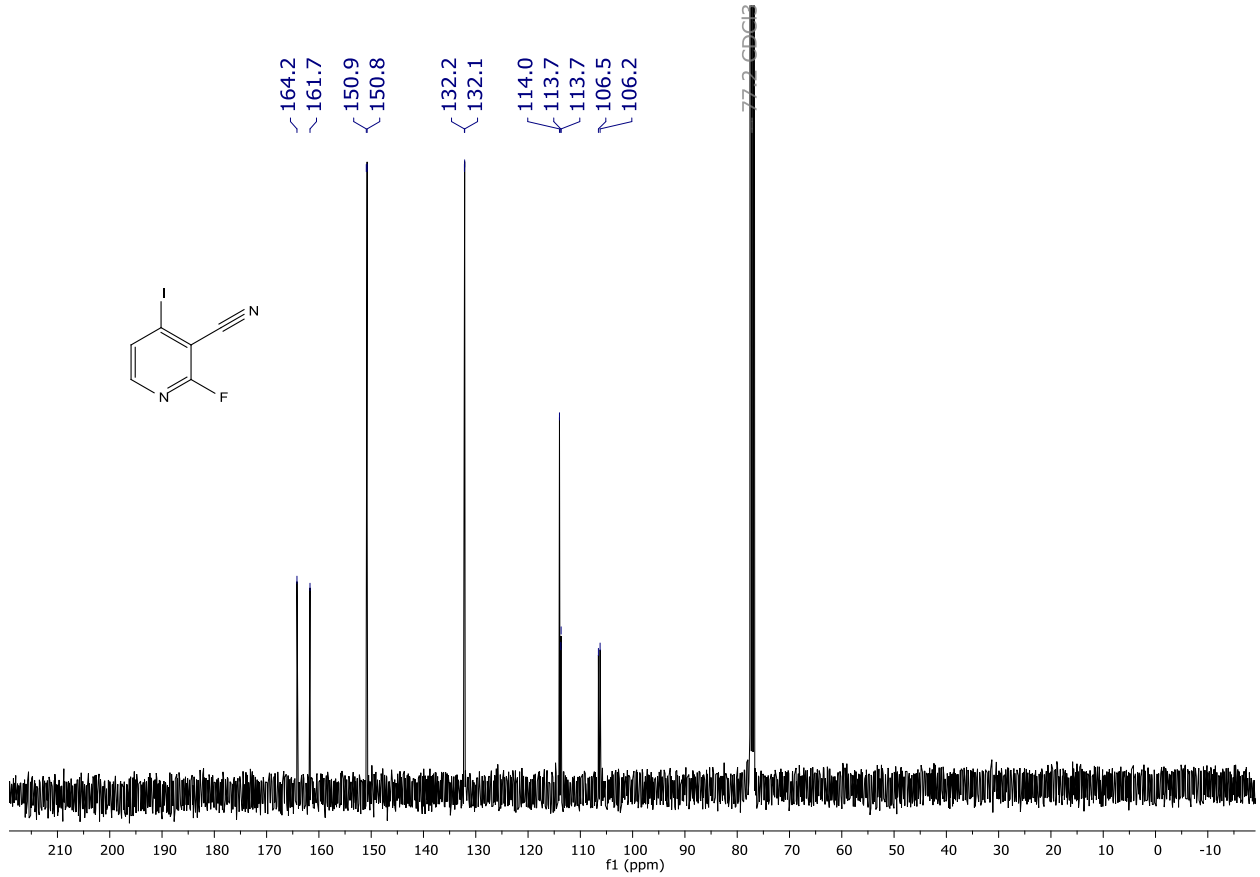
HMBC correlation map of **125am** (400 and 101 MHz, $CDCl_3$).



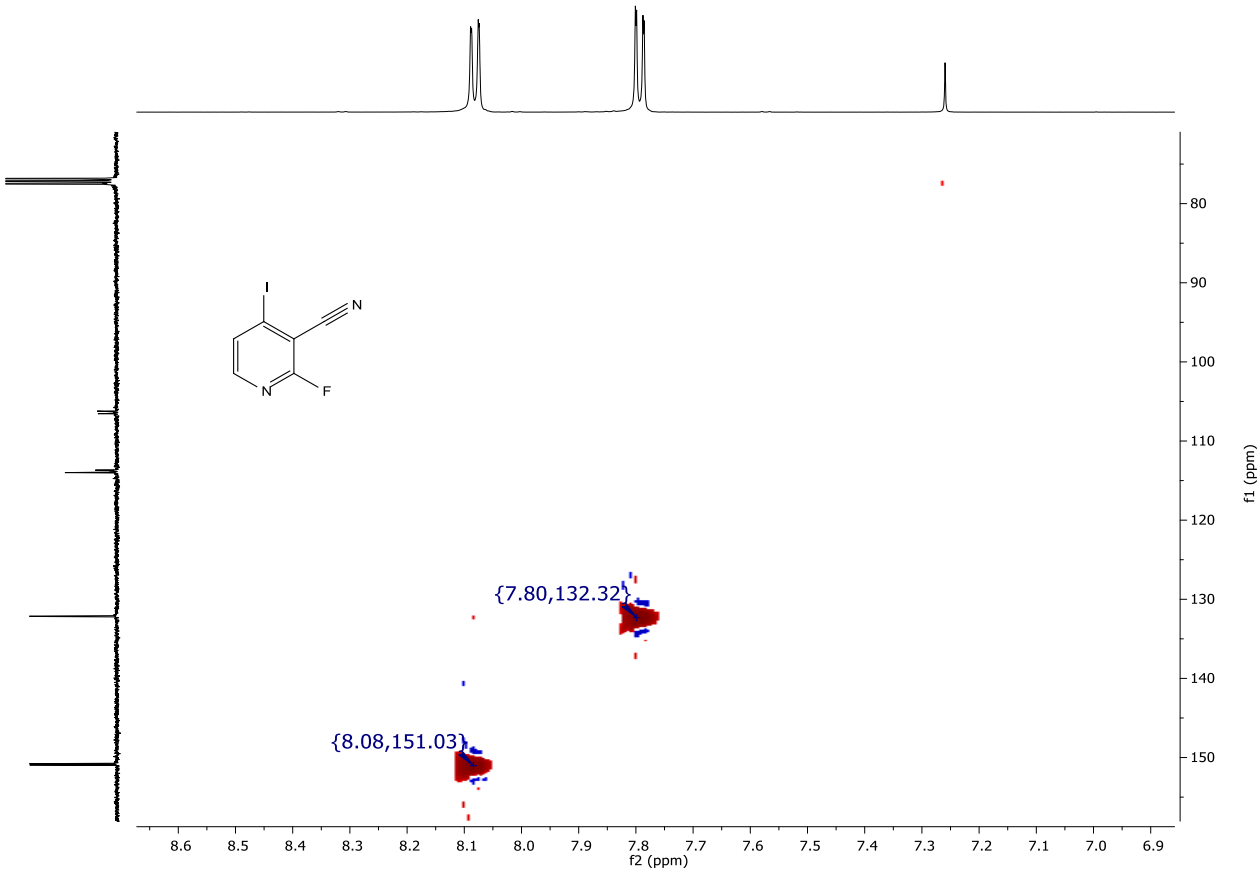
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125am**.



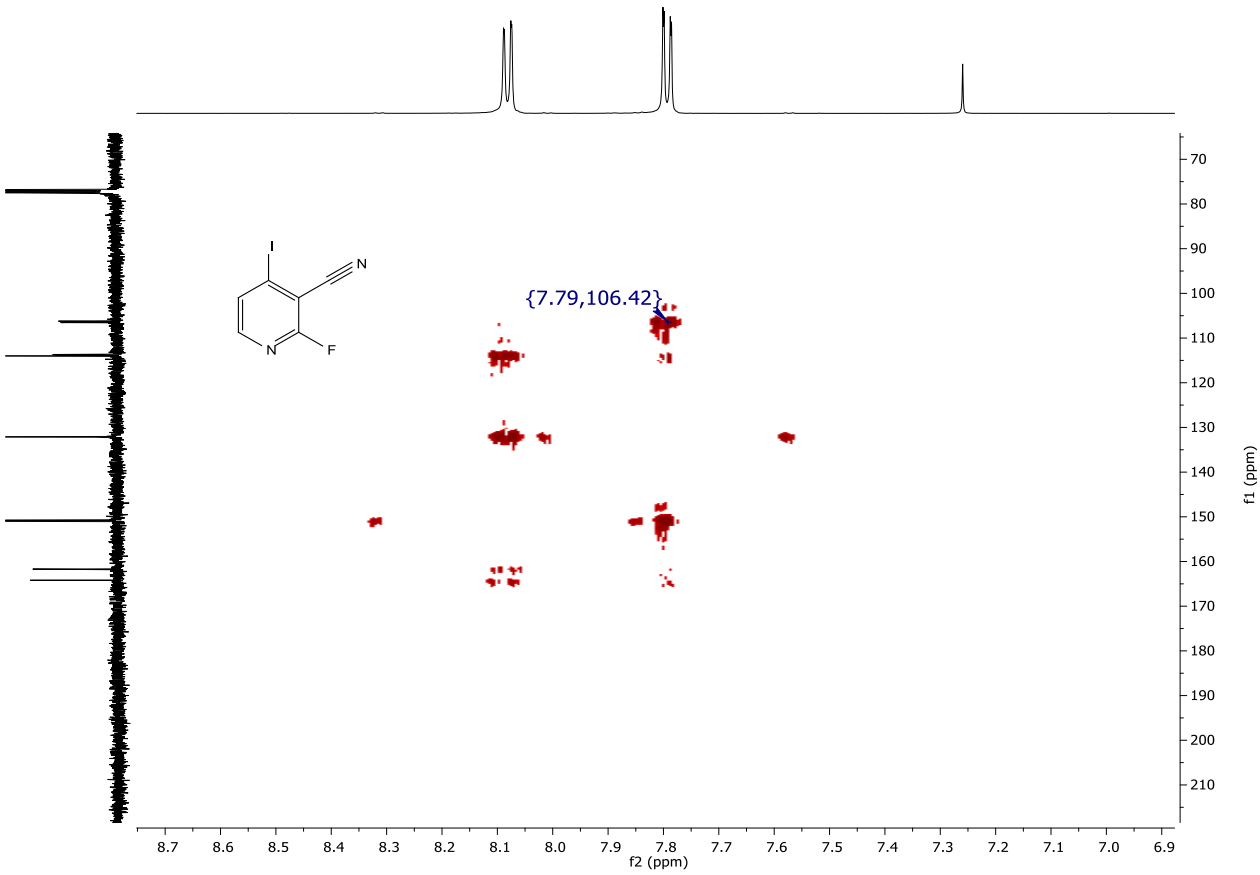
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125an**.



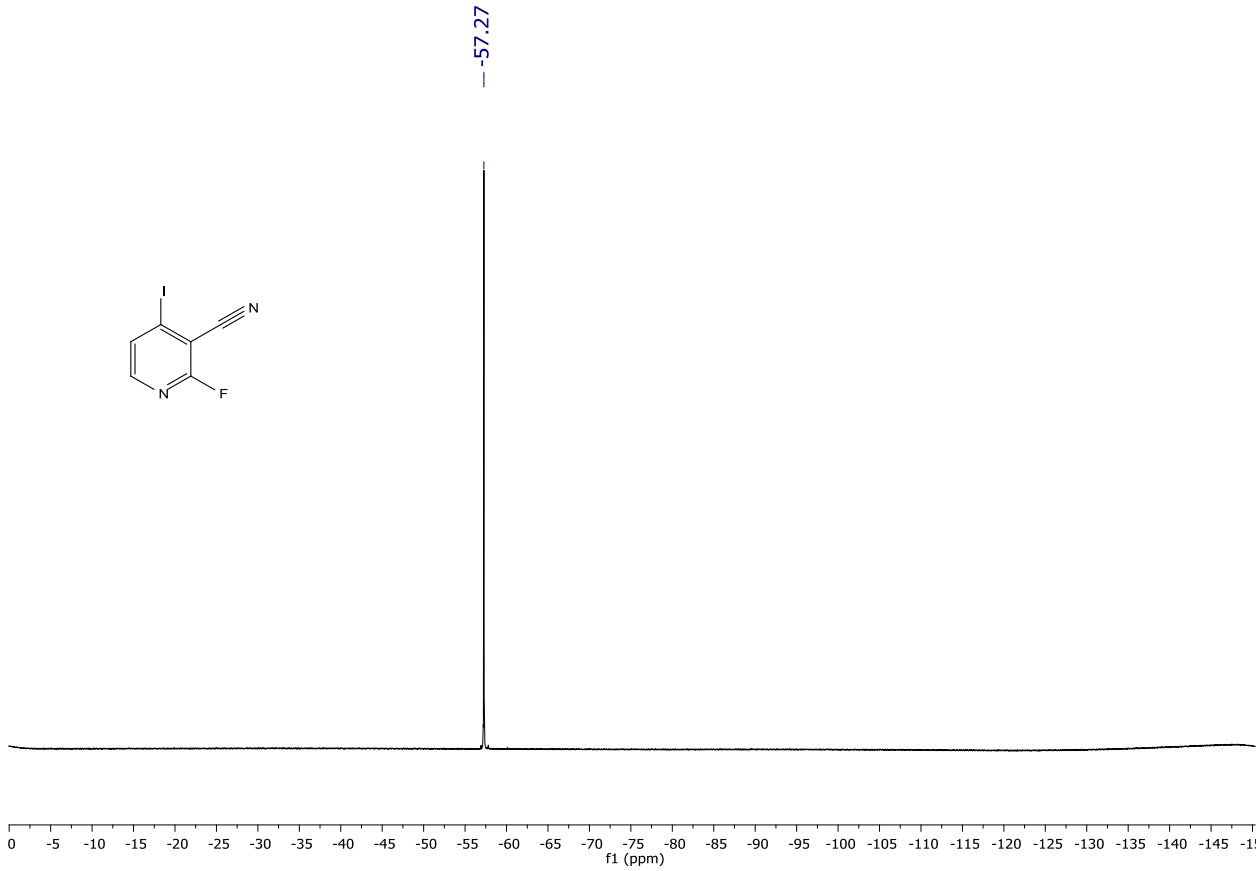
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125an**.



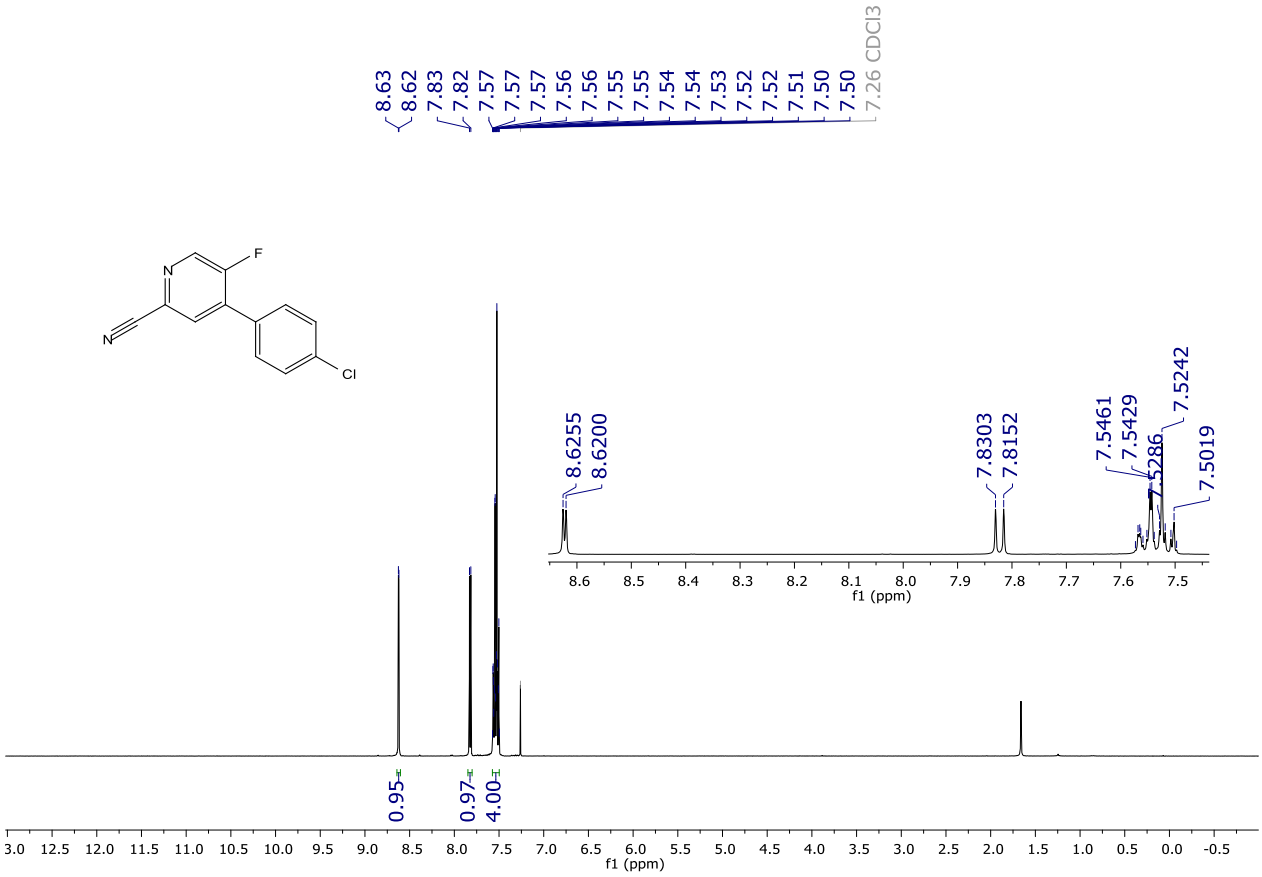
HSQC correlation map of **125an** (400 and 101 MHz, $CDCl_3$).



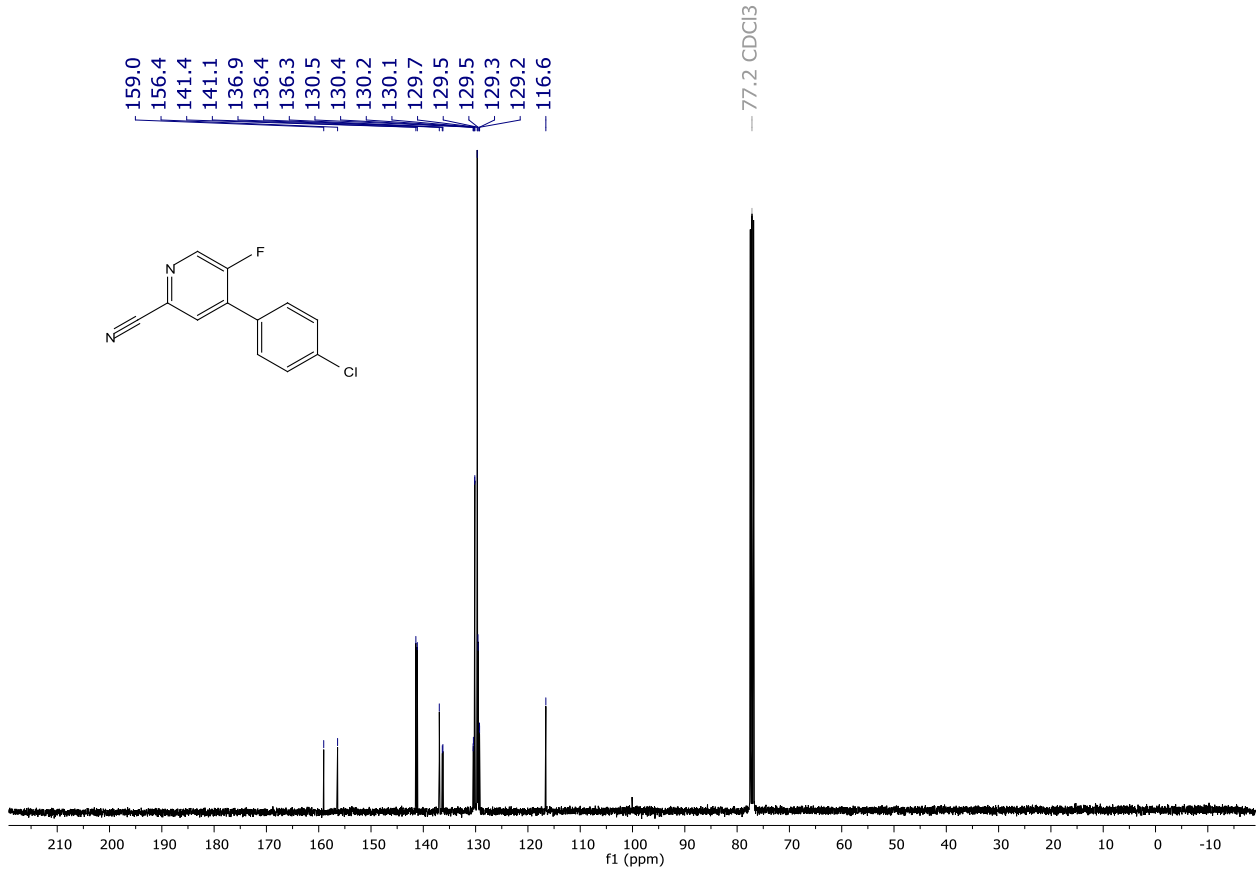
HMBC correlation map of **125an** (400 and 101 MHz, $CDCl_3$).



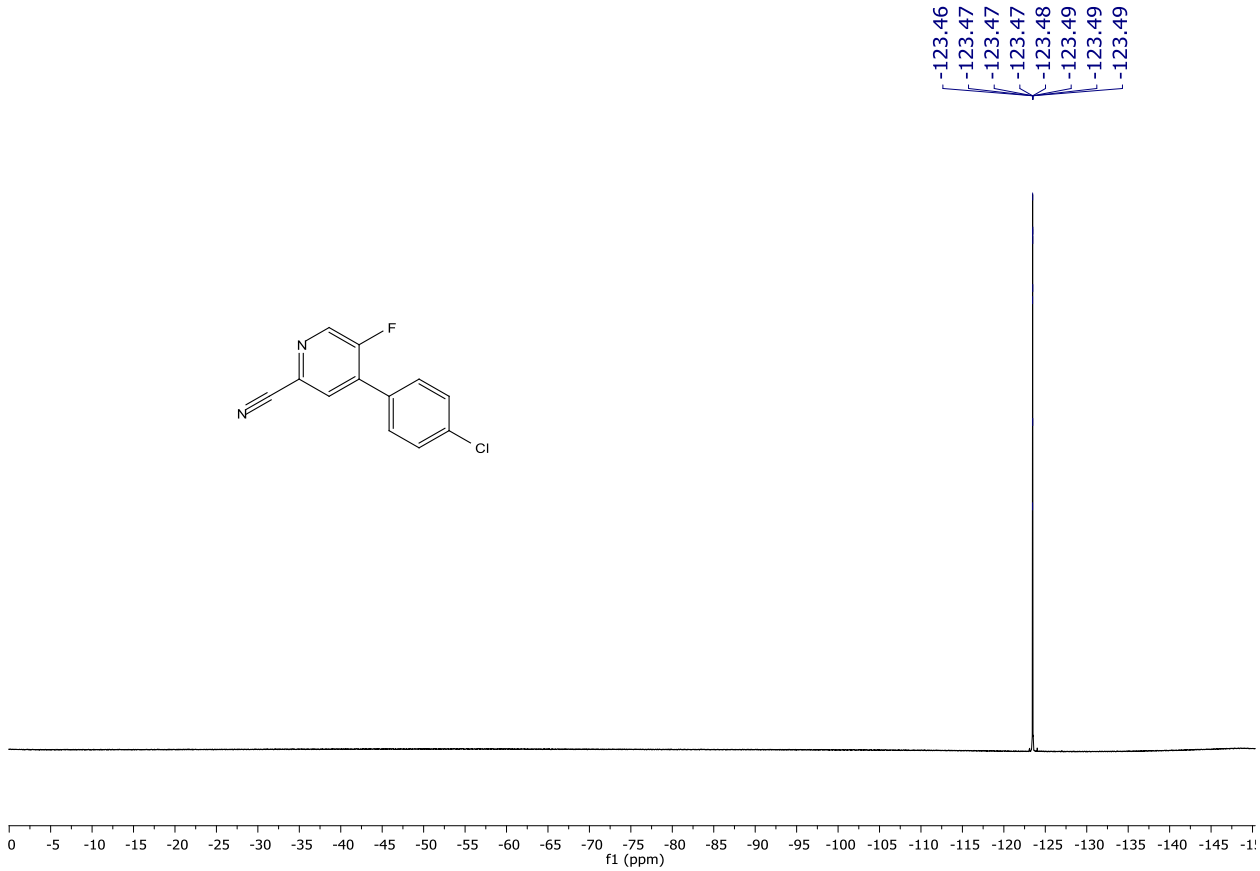
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125an**.



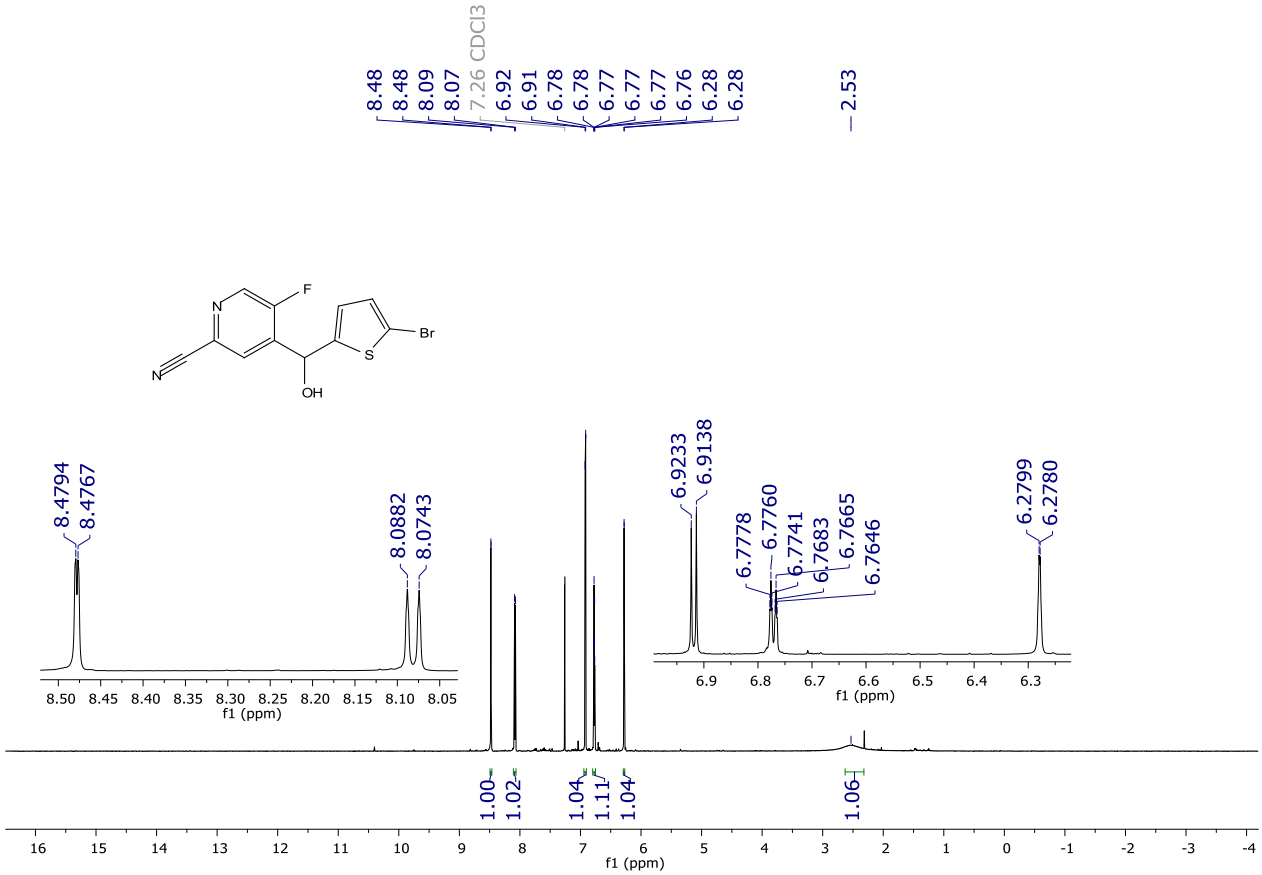
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125ao**.



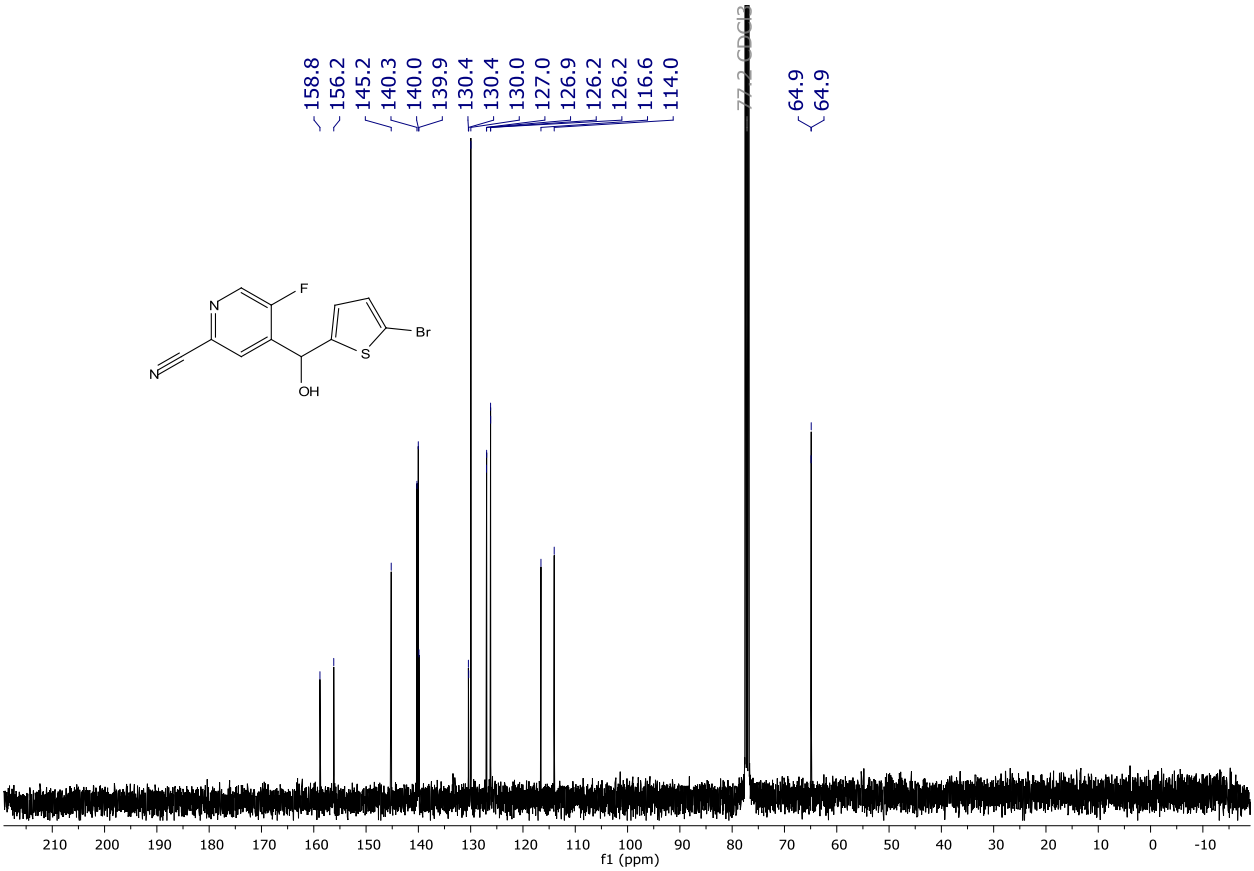
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) spectrum of **125ao**.



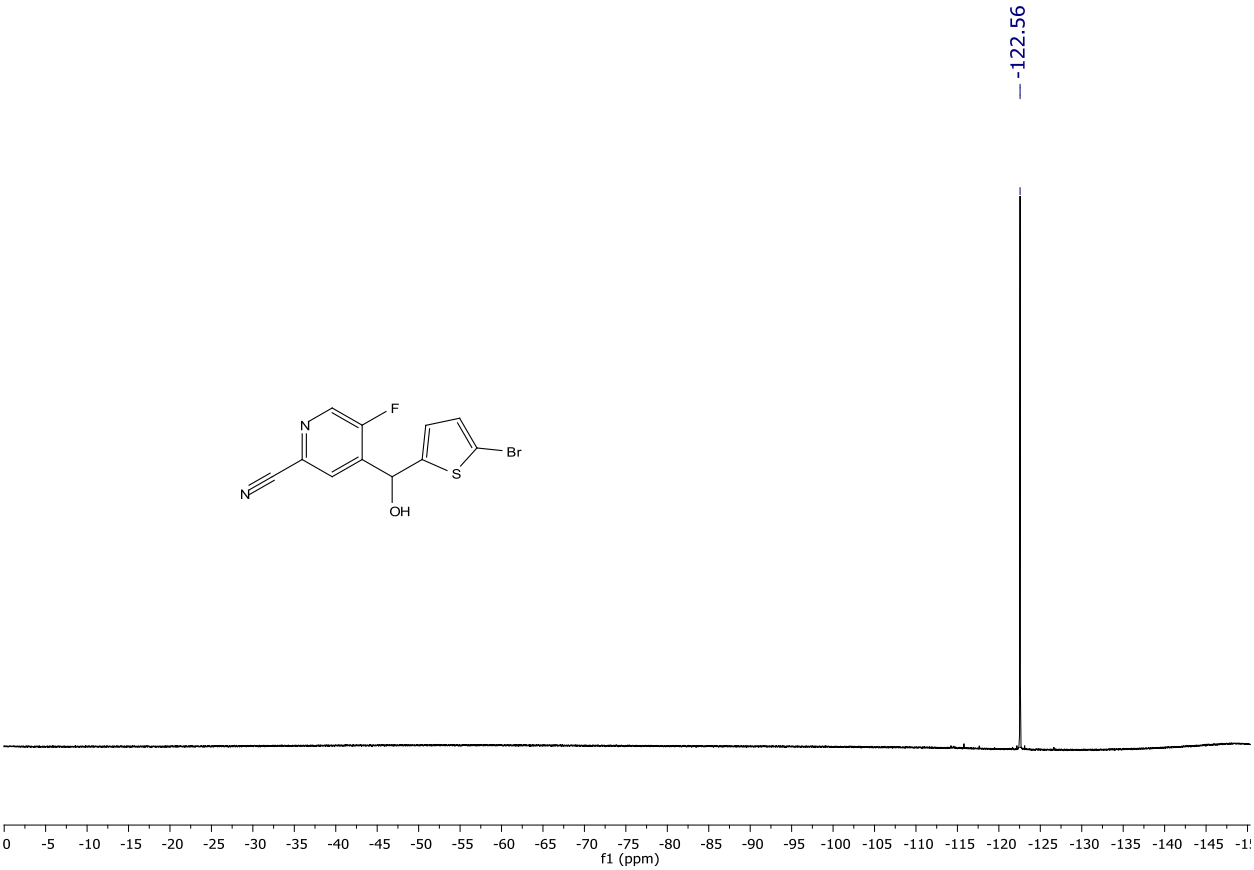
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125ao**.



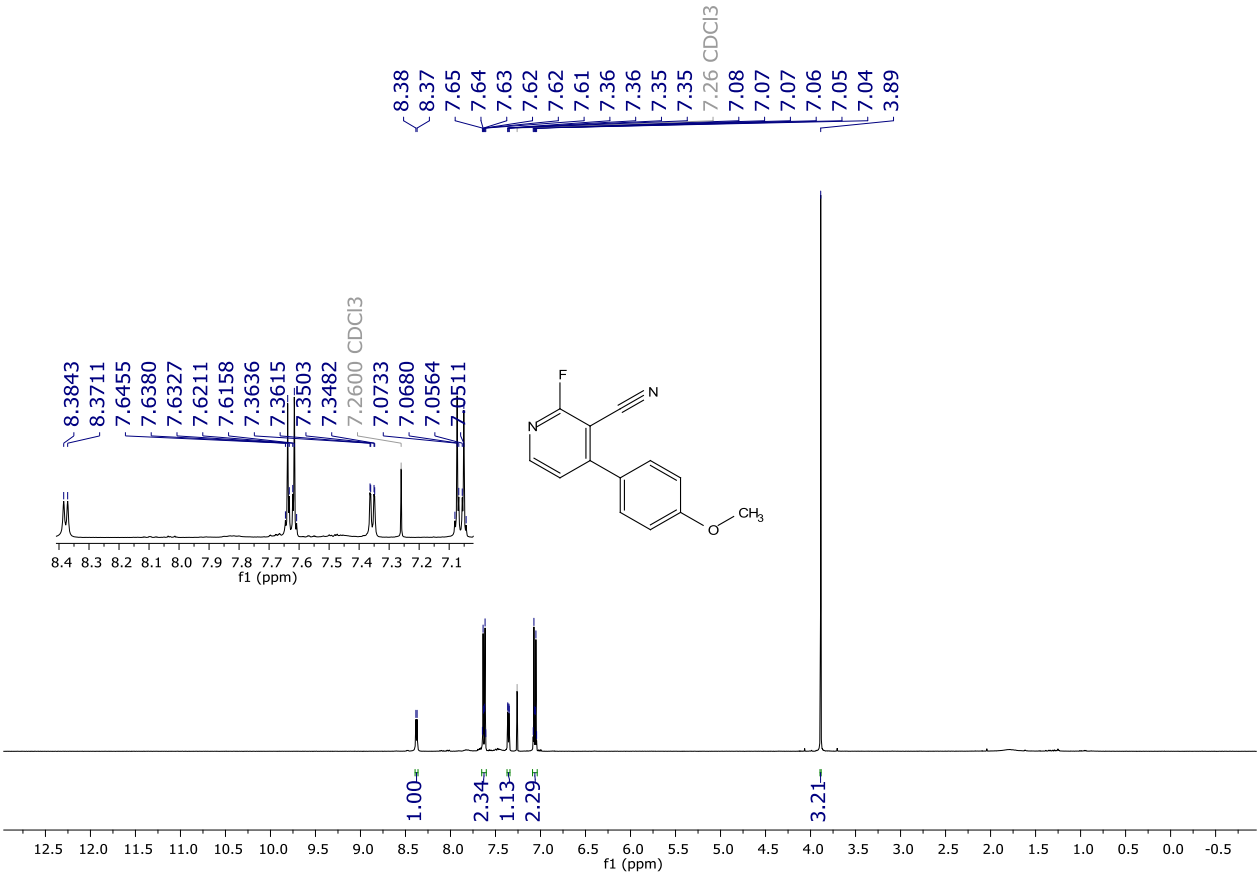
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125ap**.



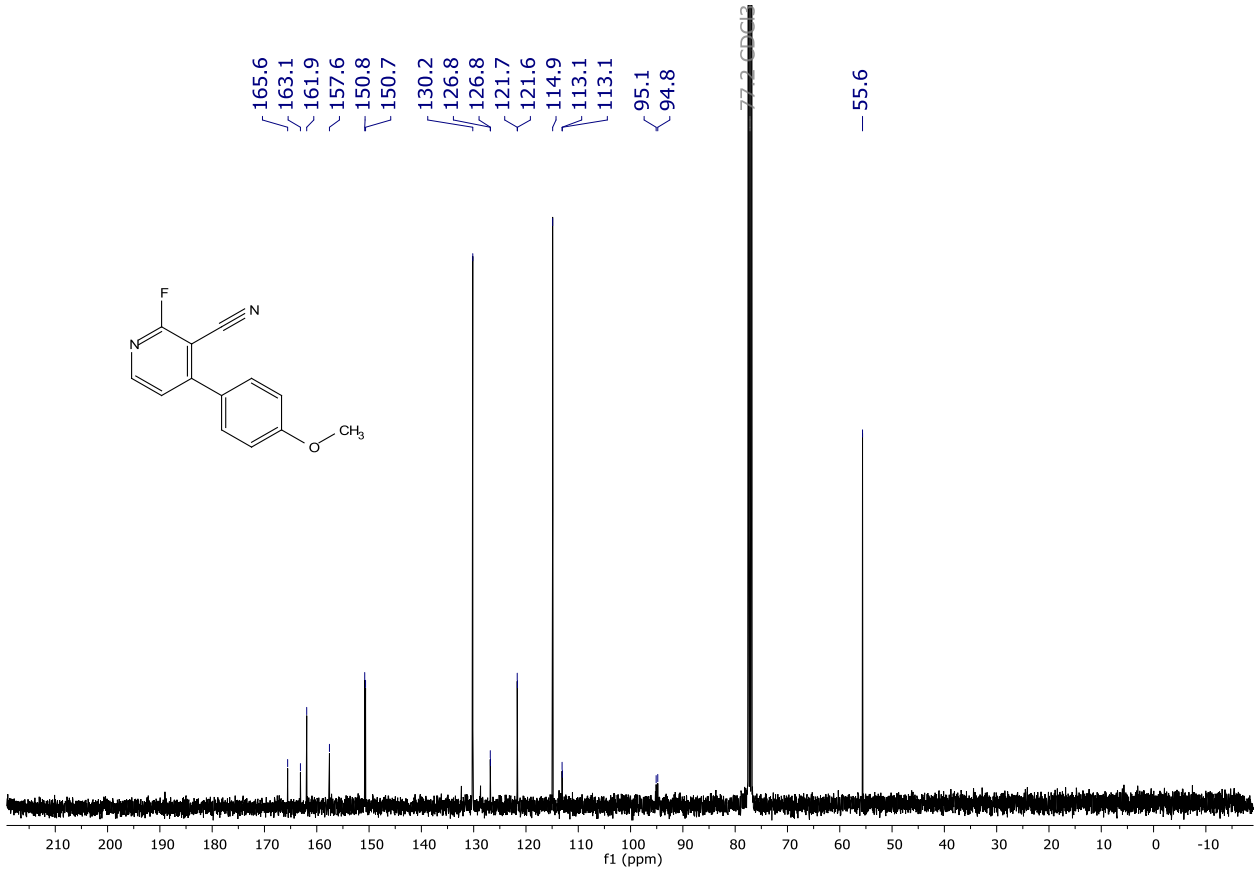
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125ap.**



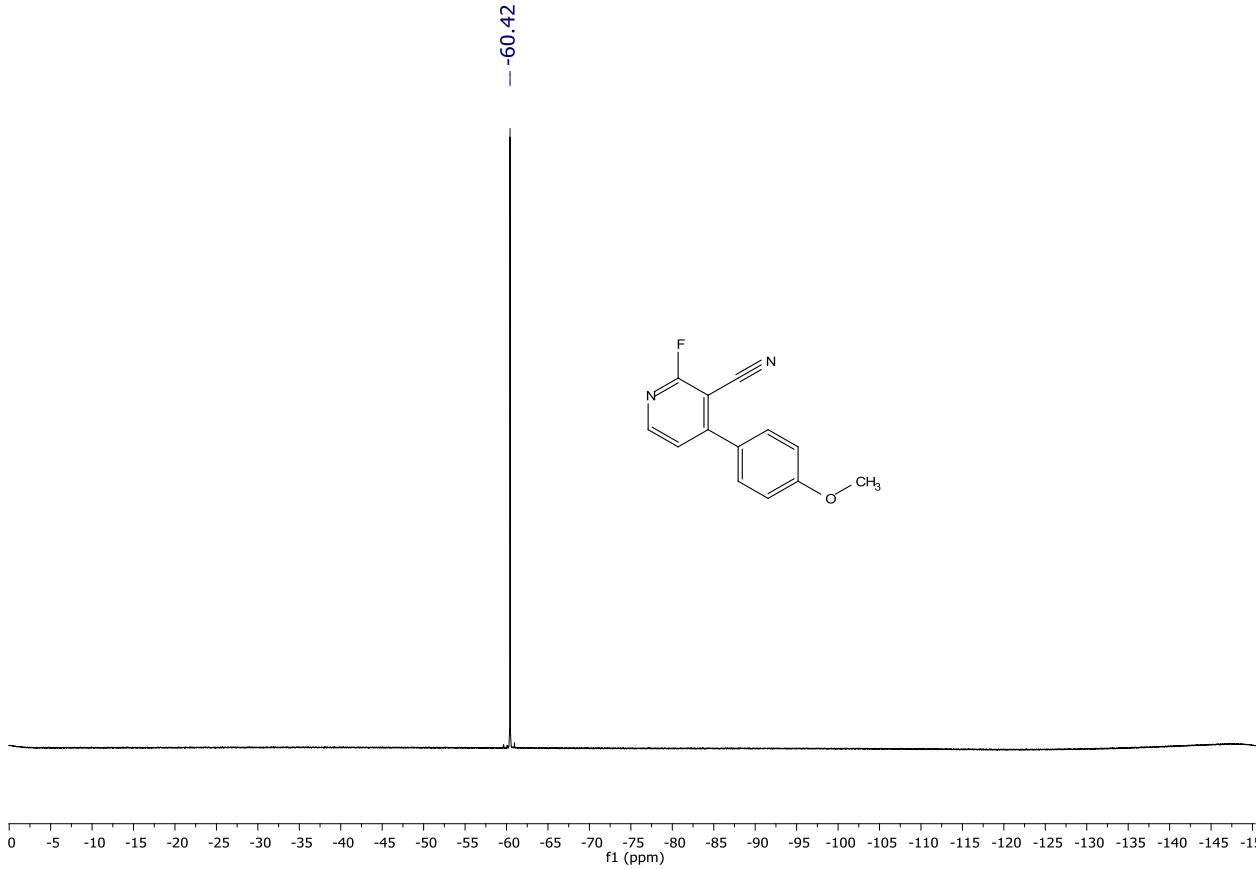
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125ap.**



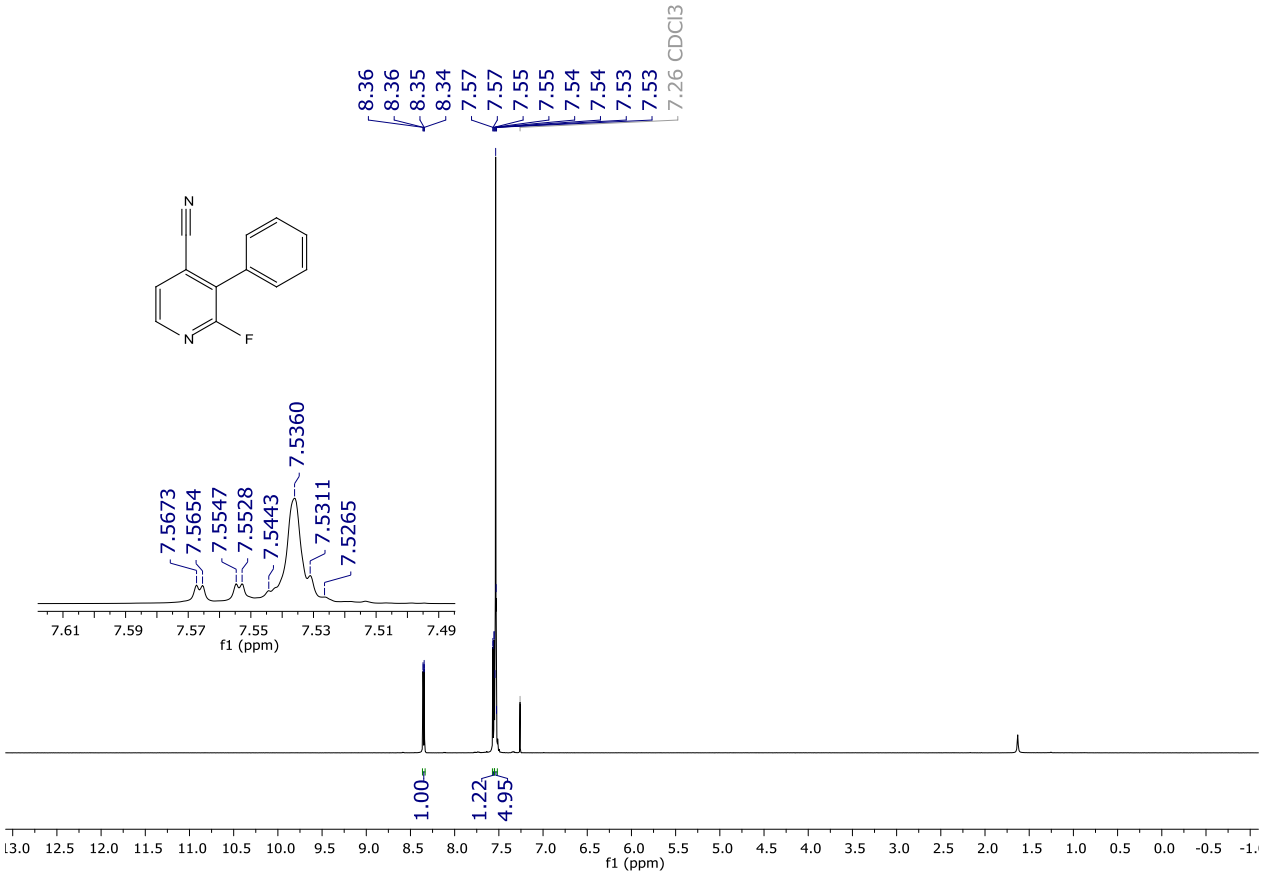
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125aq.**



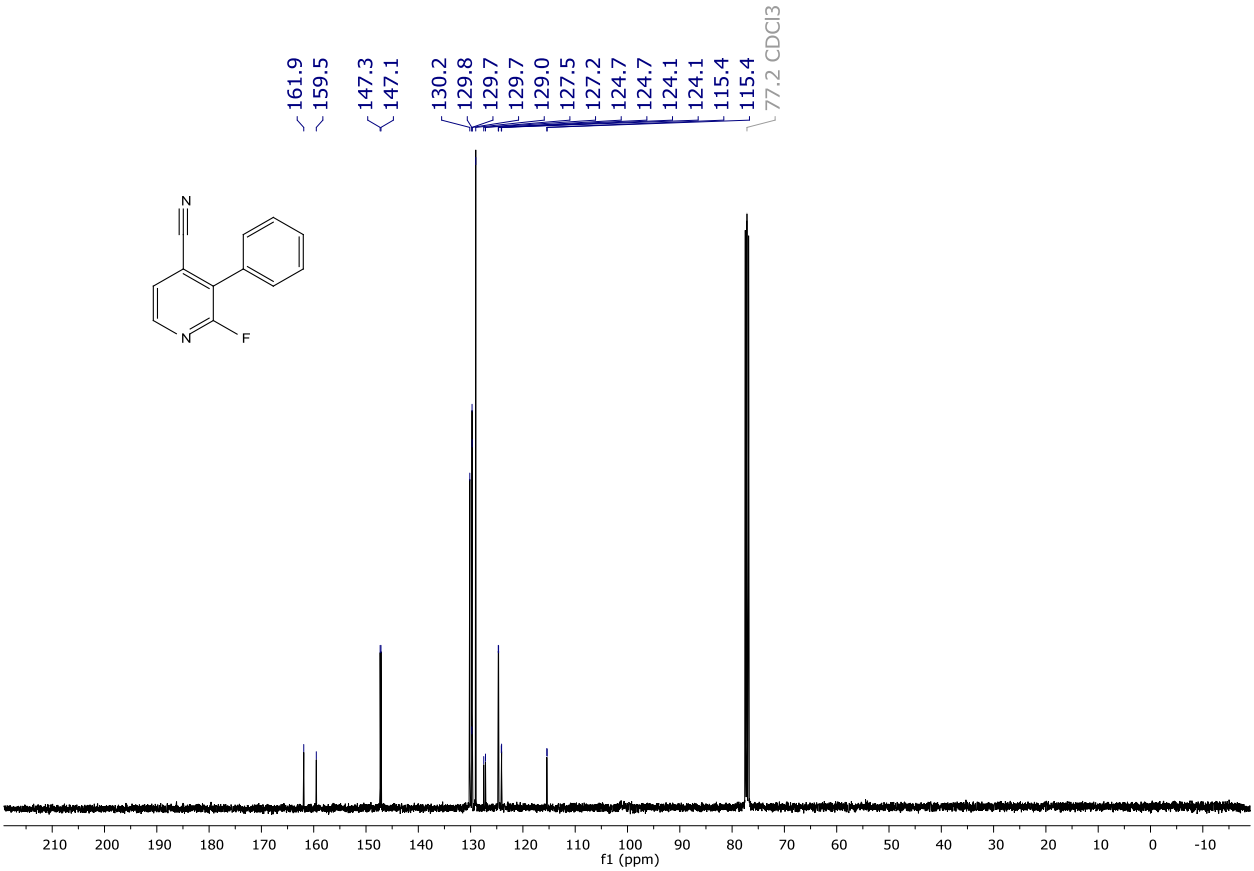
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) spectrum of **125aq.**



^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125aq.**

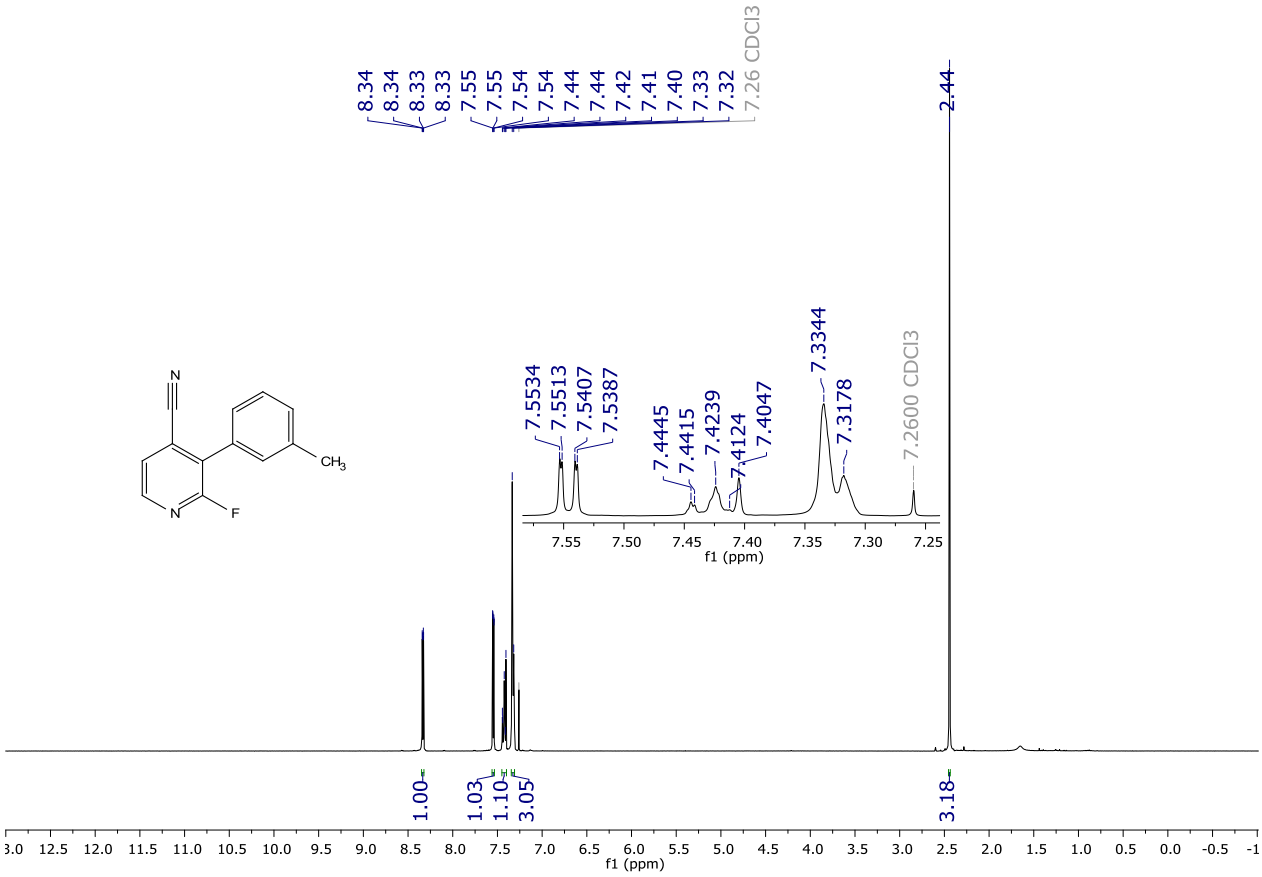


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125ar.**

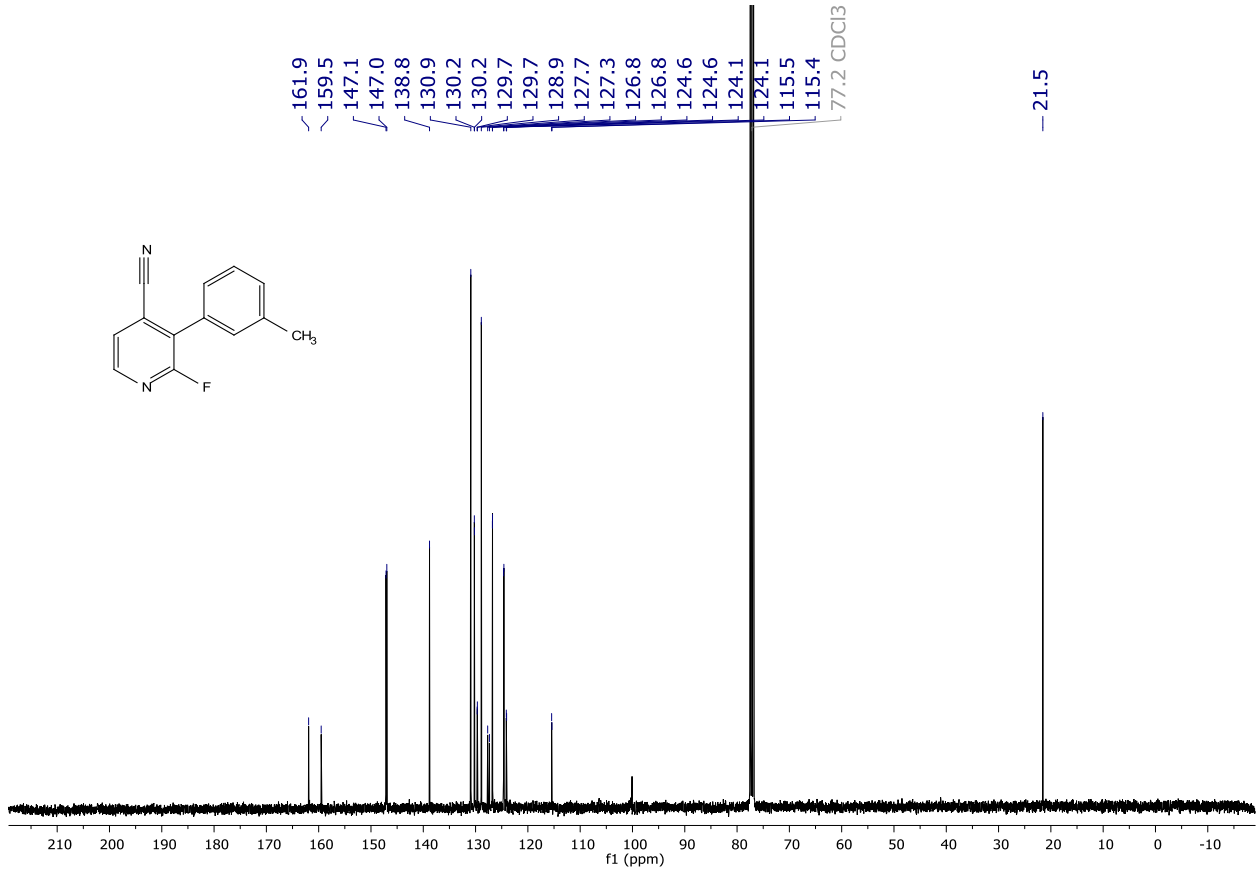


$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **125ar.**

^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125ar.**

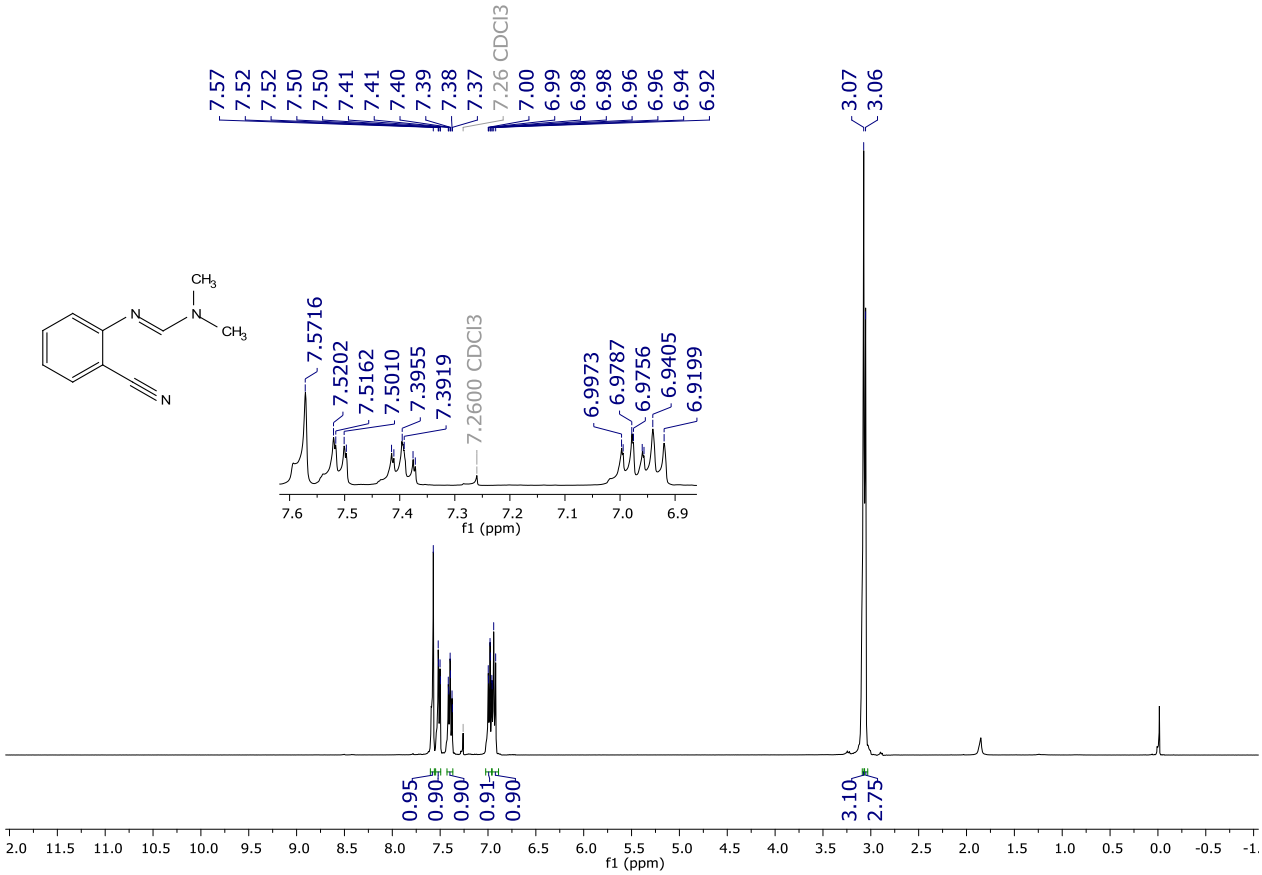


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **125as.**

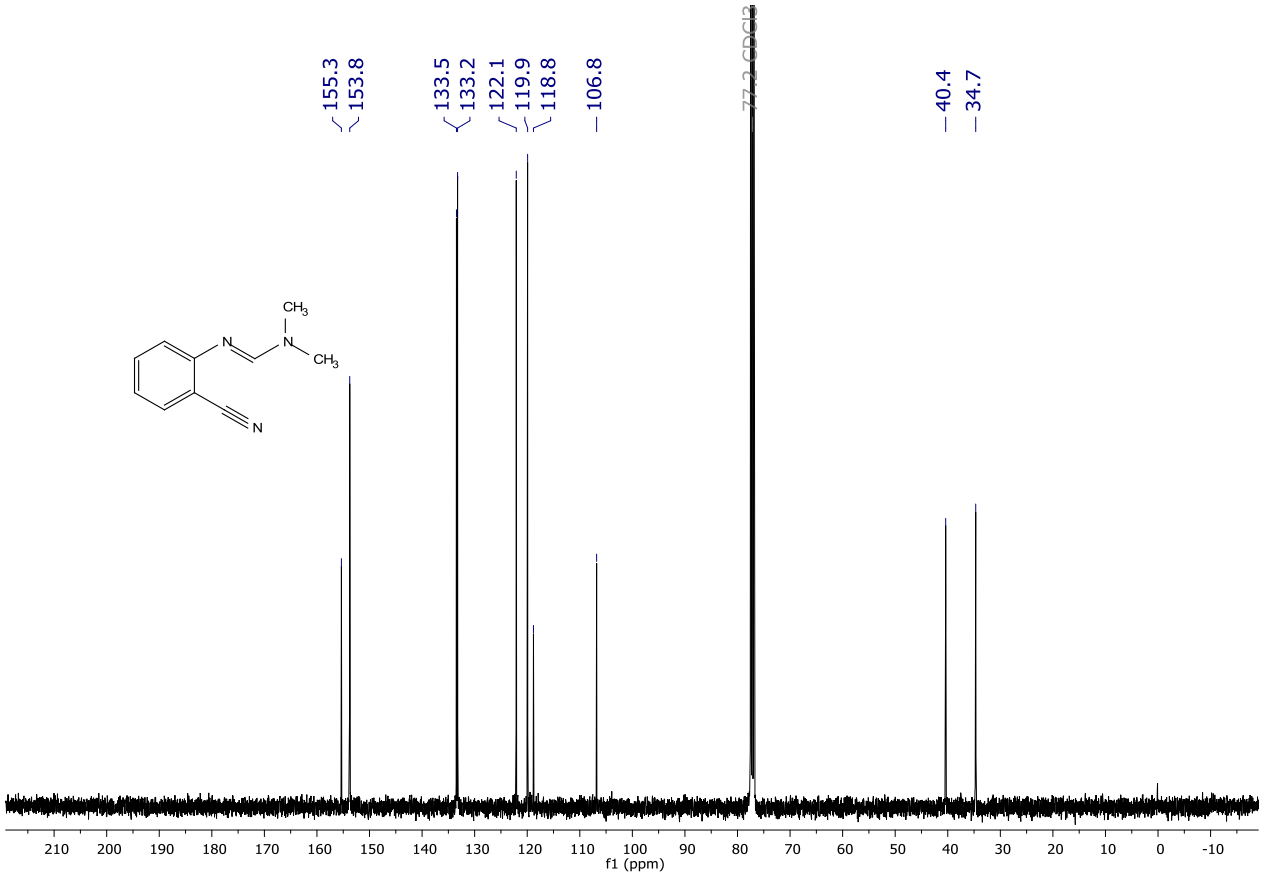


^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) spectrum of **125as.**

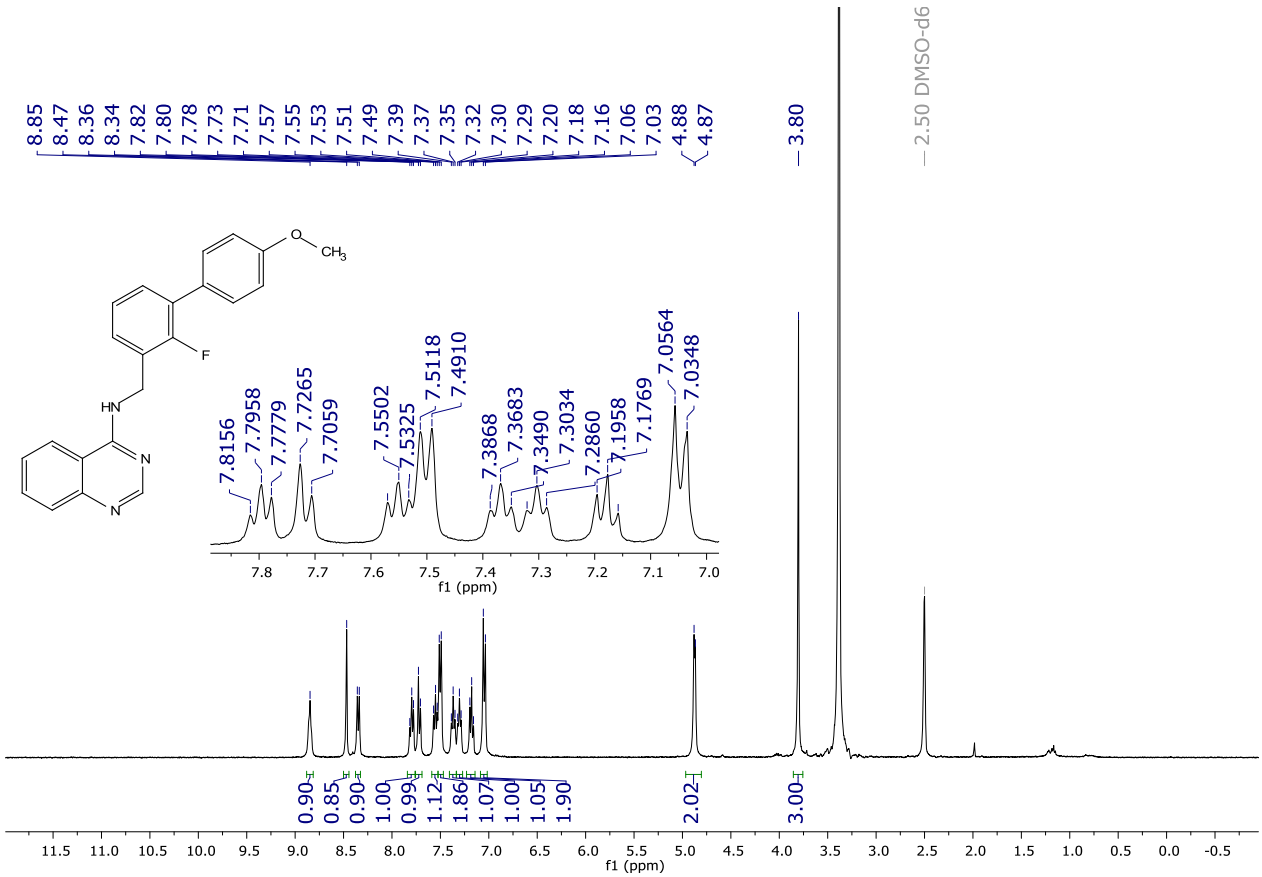
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **125as.**



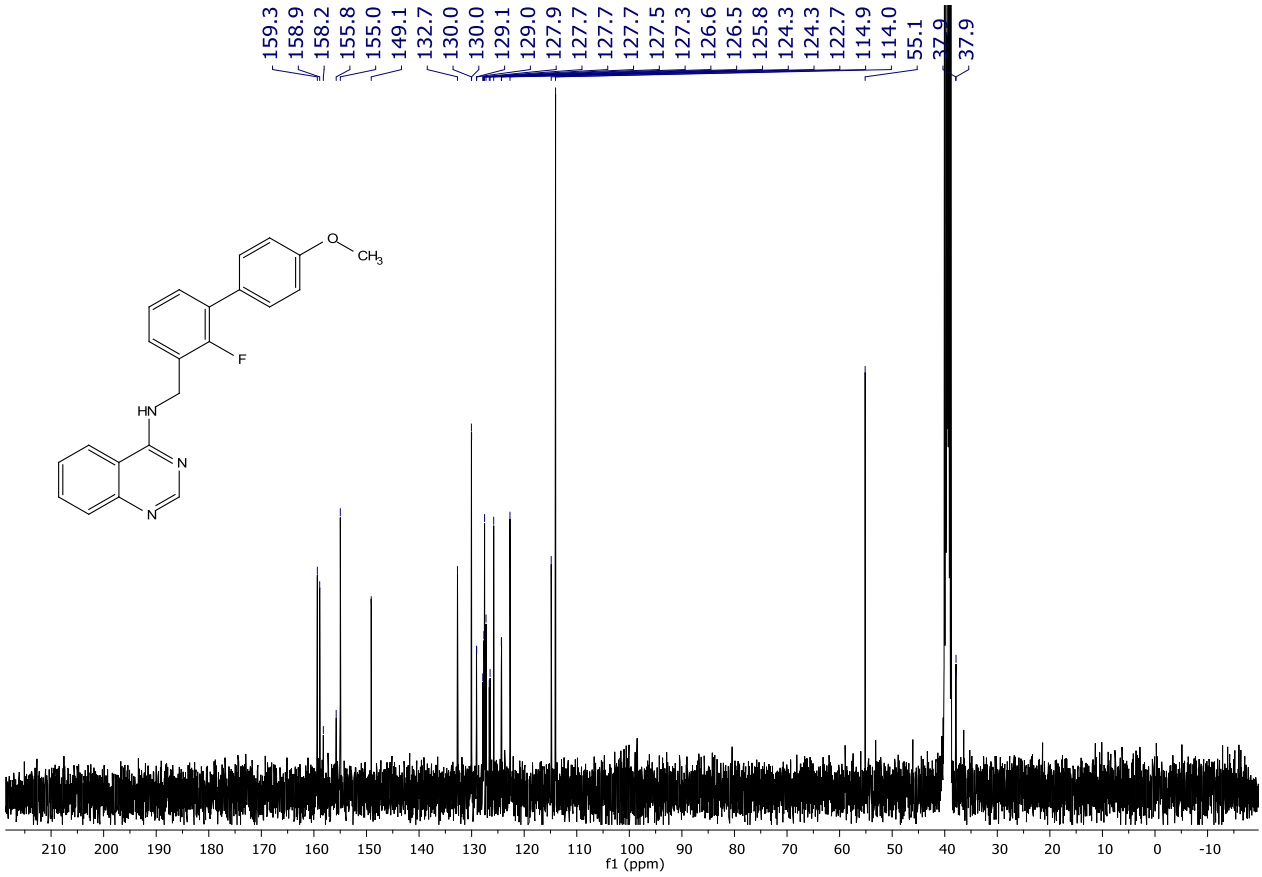
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **132**.



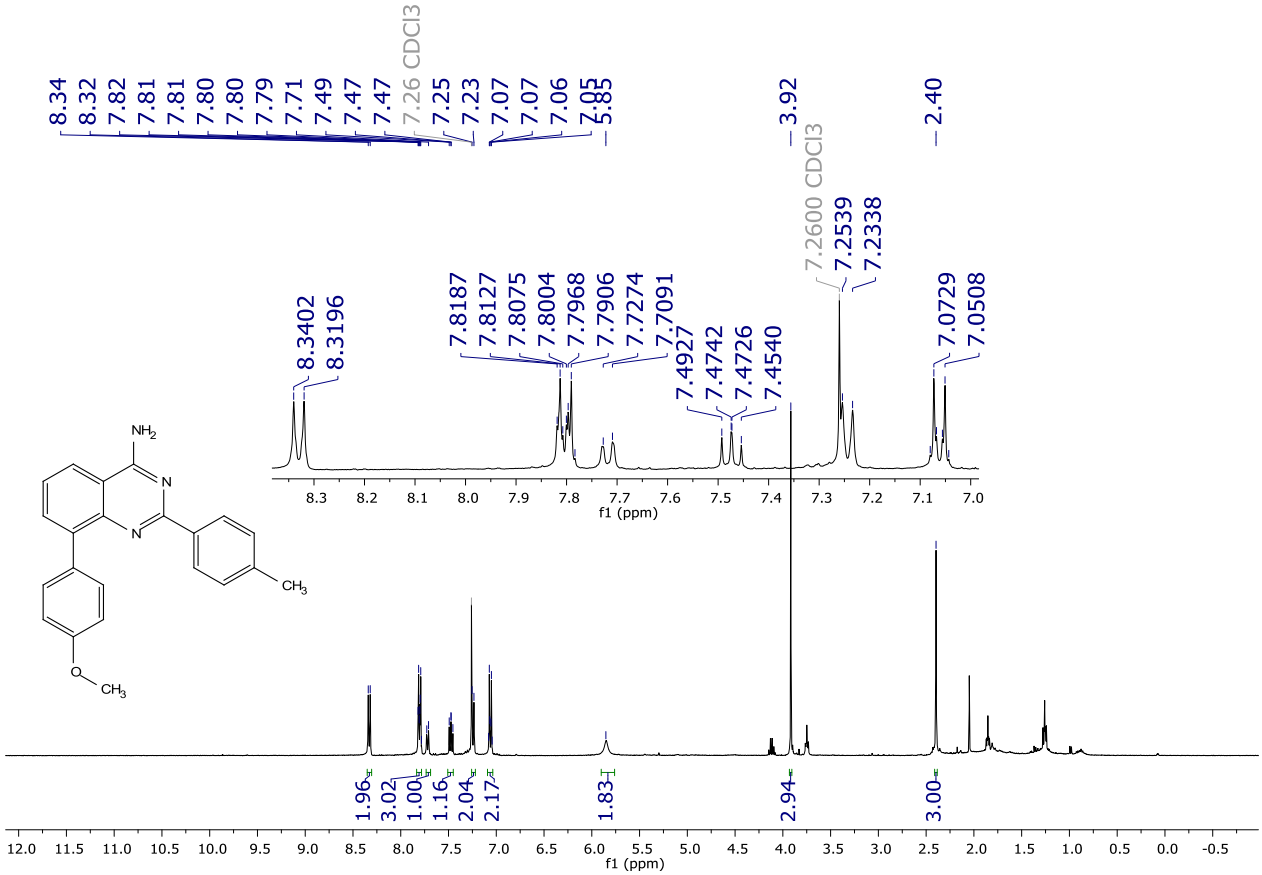
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **132**.



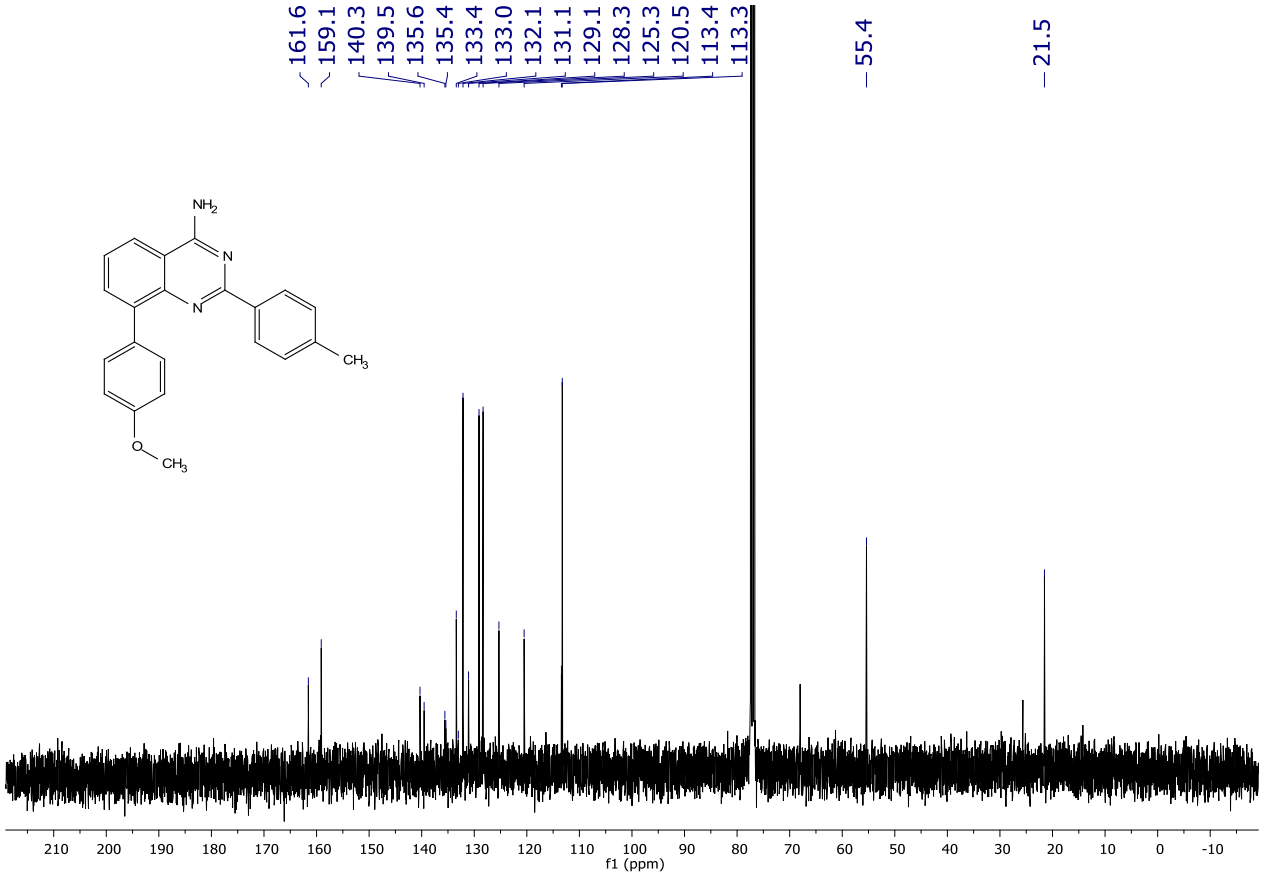
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **134**.



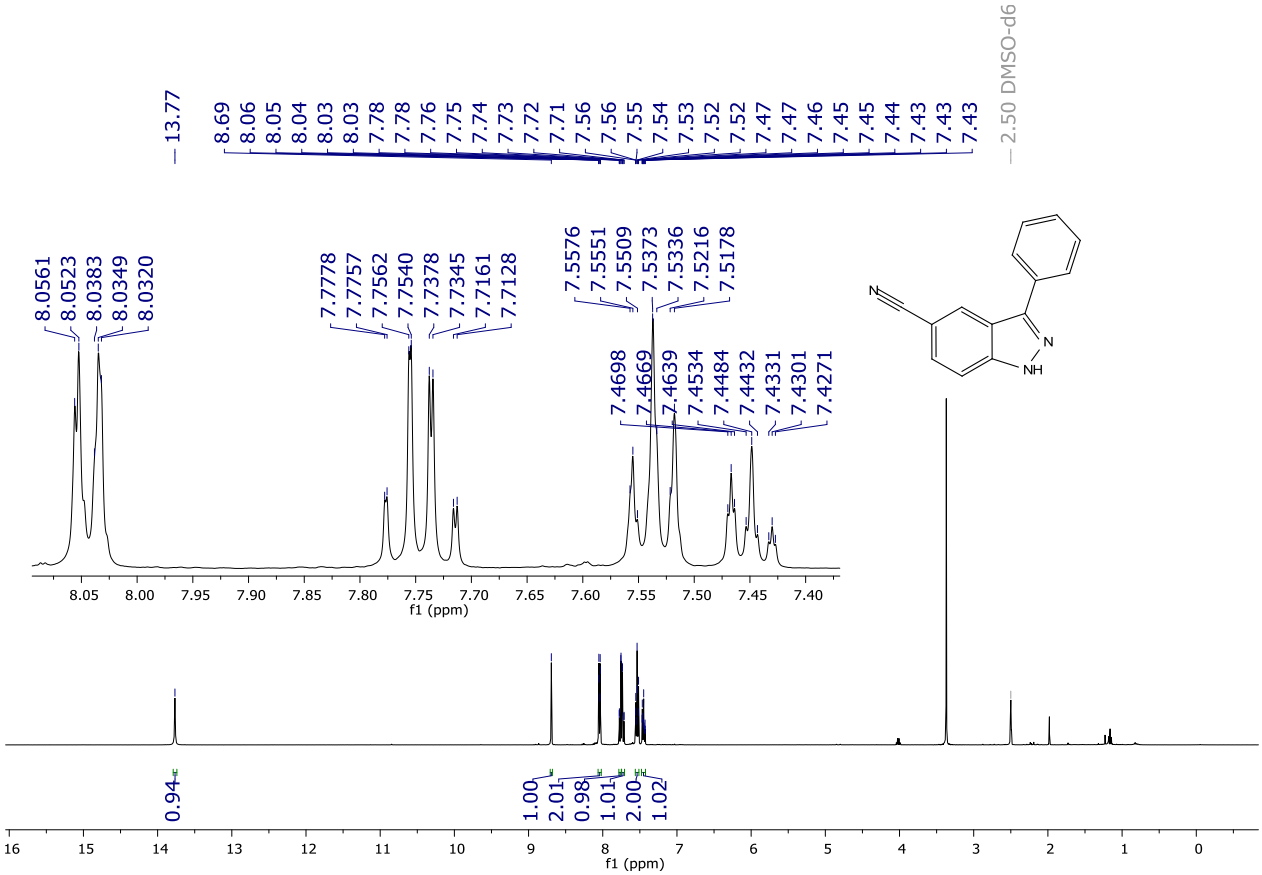
$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d*6*) spectrum of **134**.



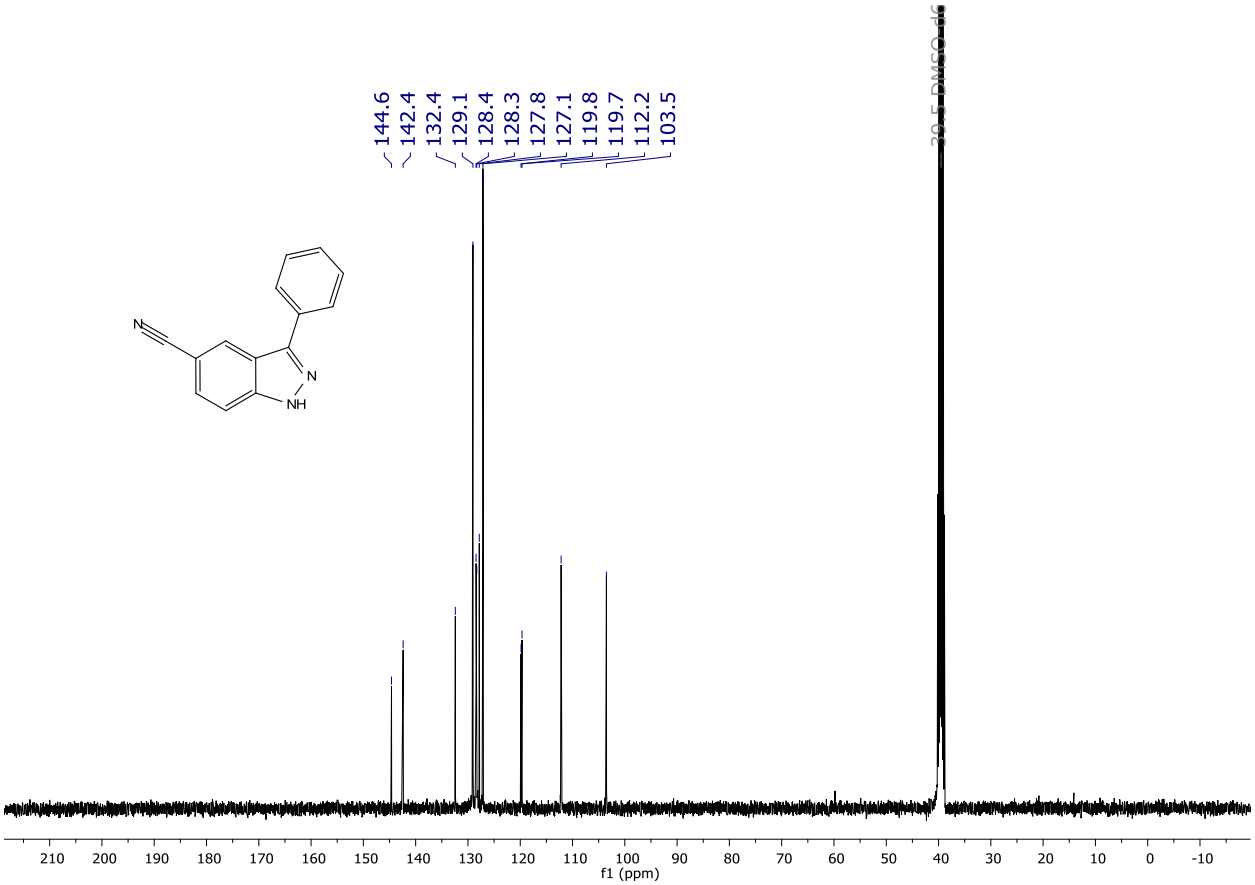
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **135**.



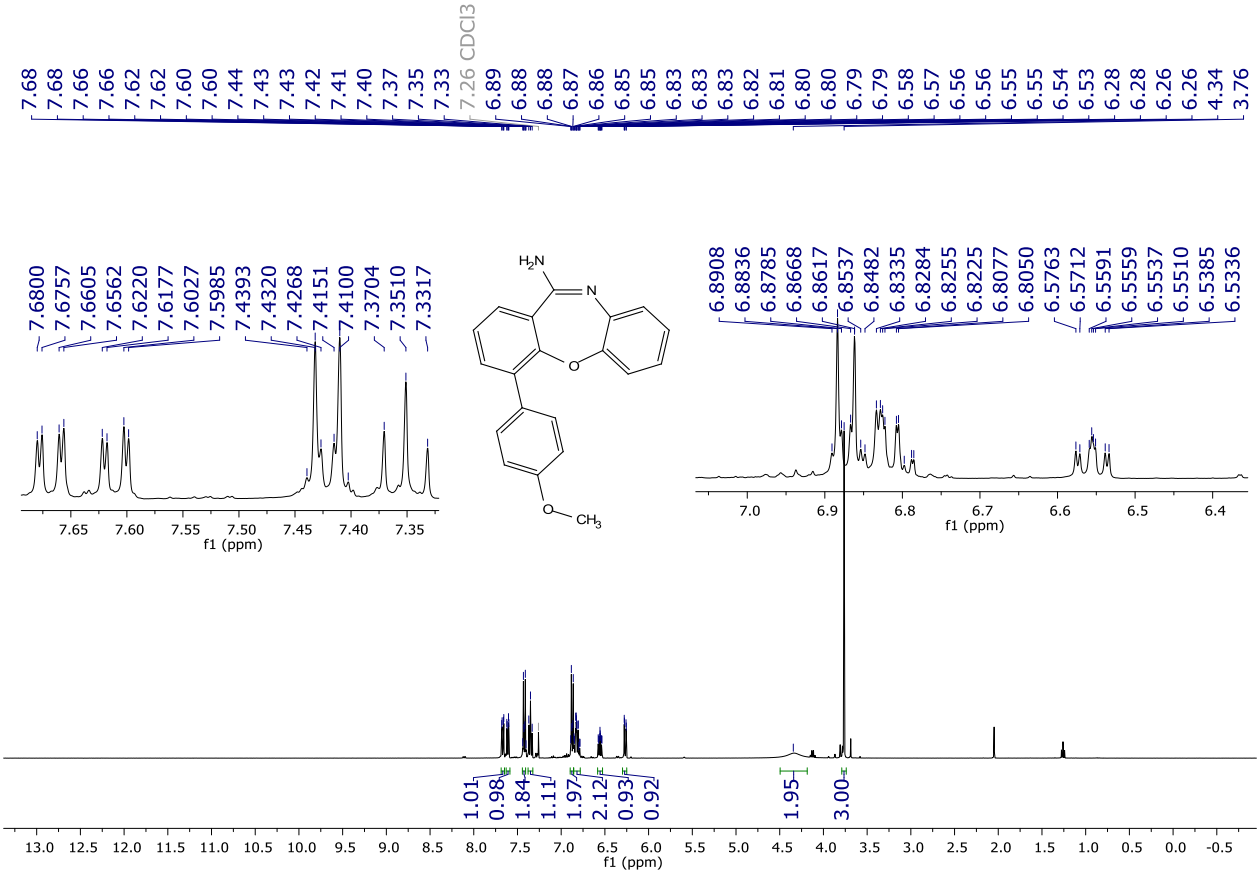
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **135**.



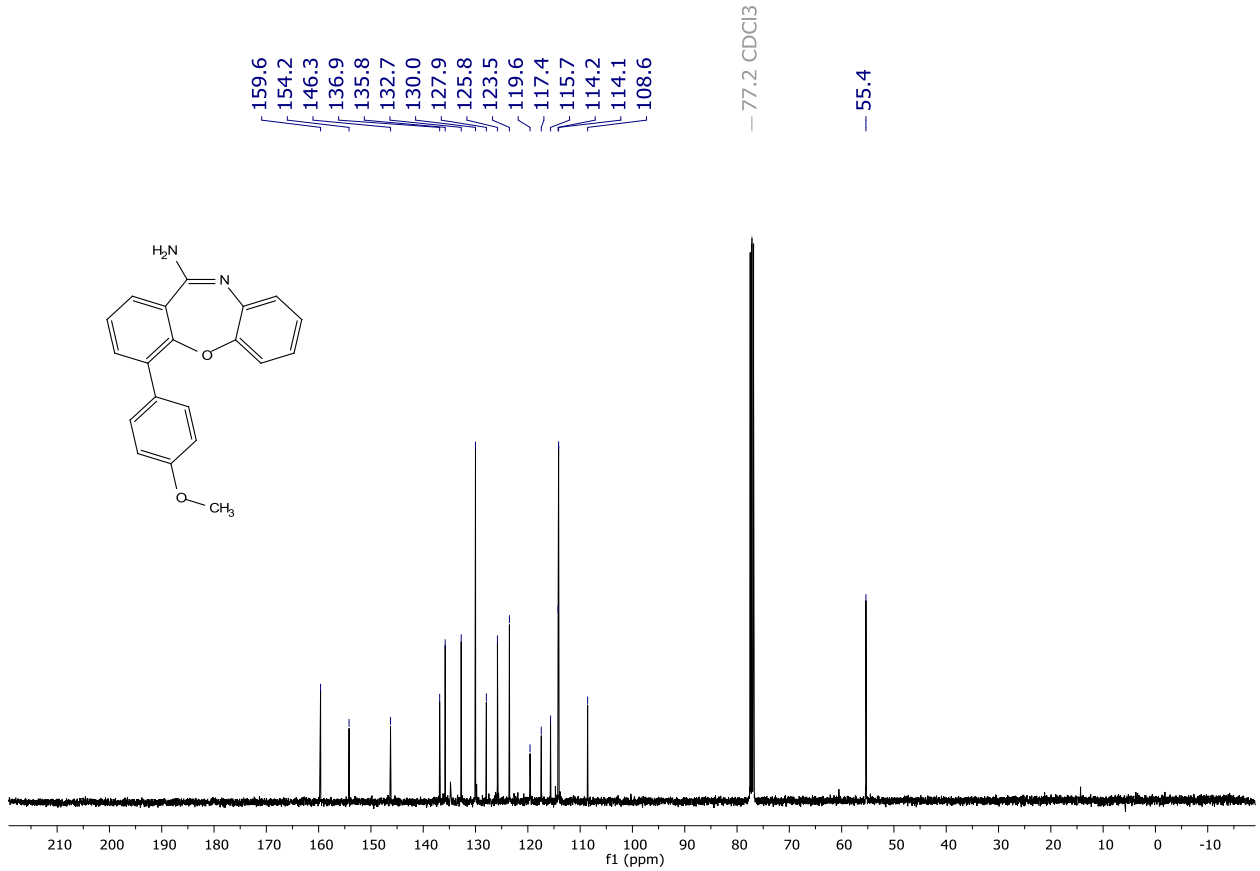
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **137**.



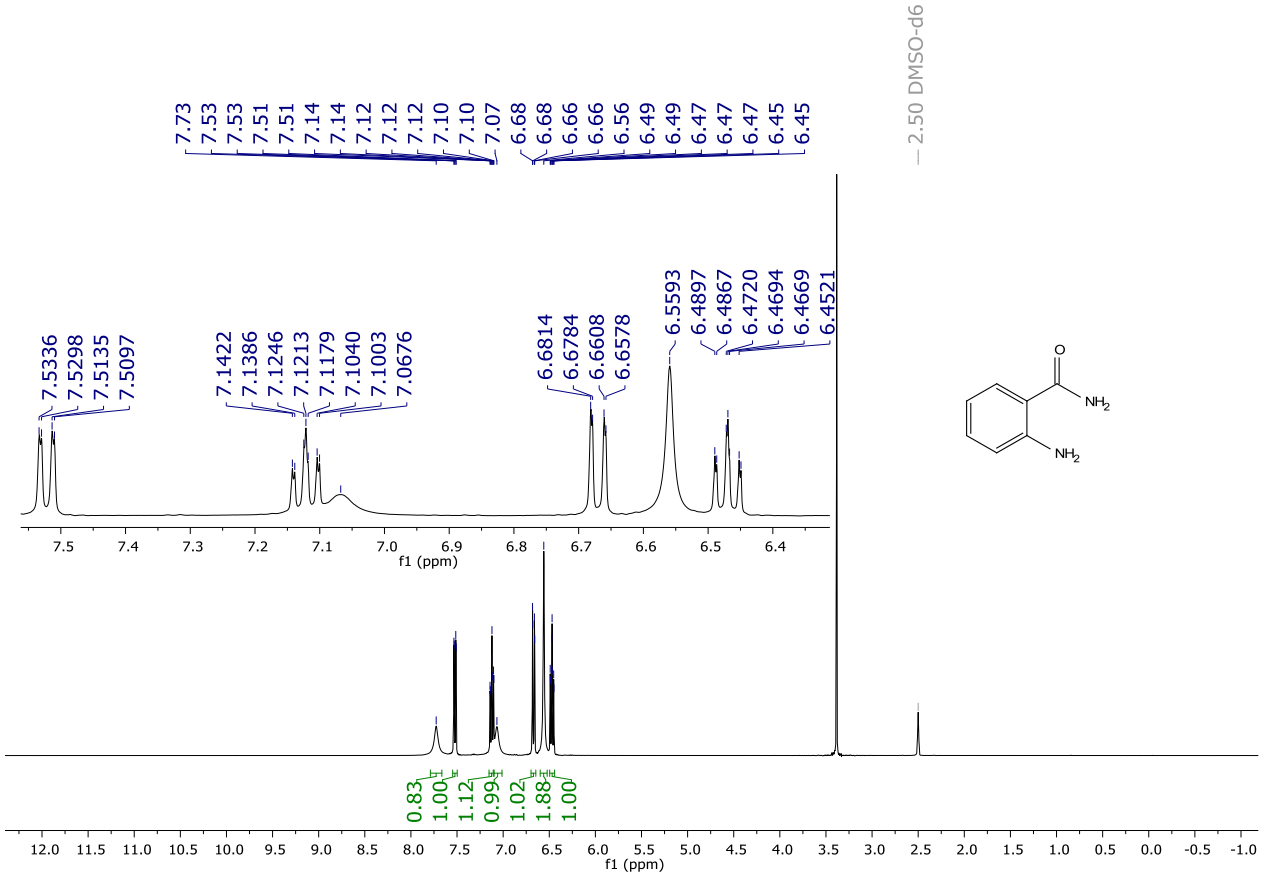
$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d*6*) spectrum of **137**.



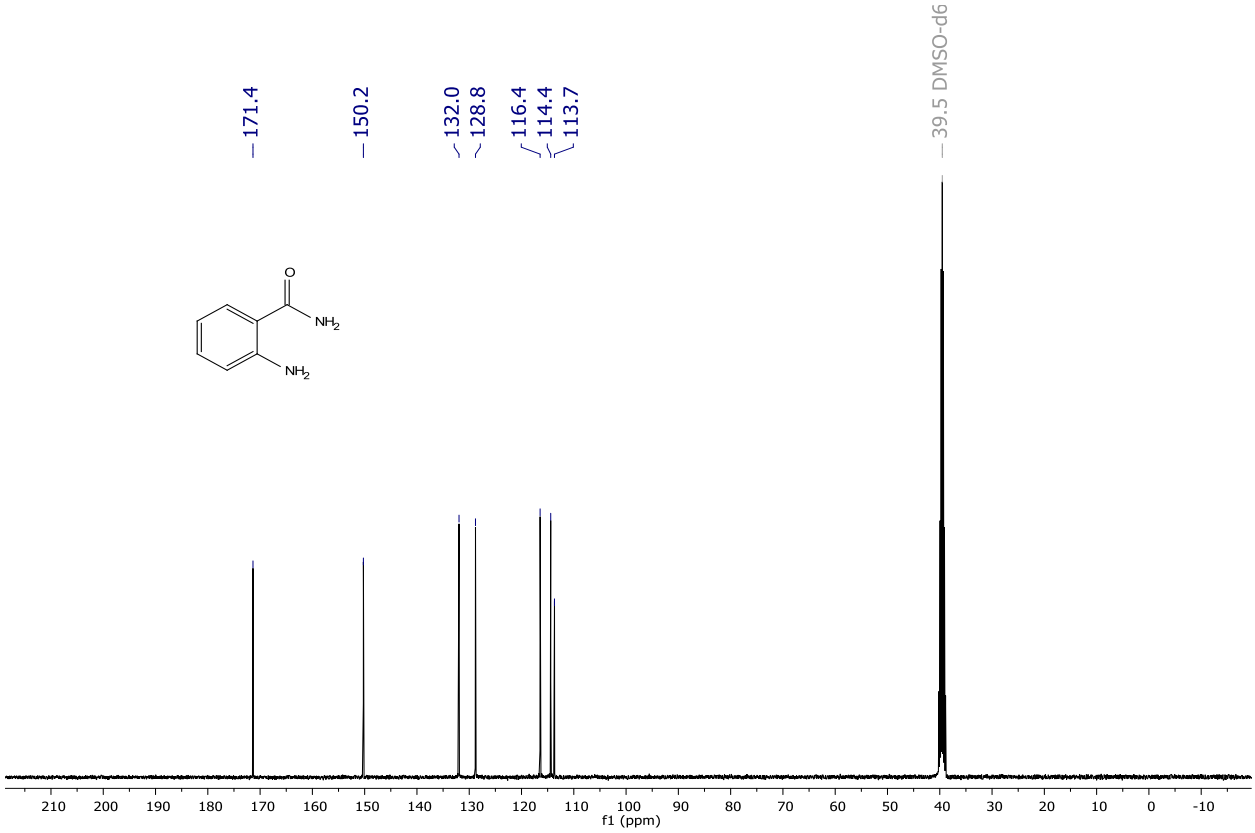
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **138.**



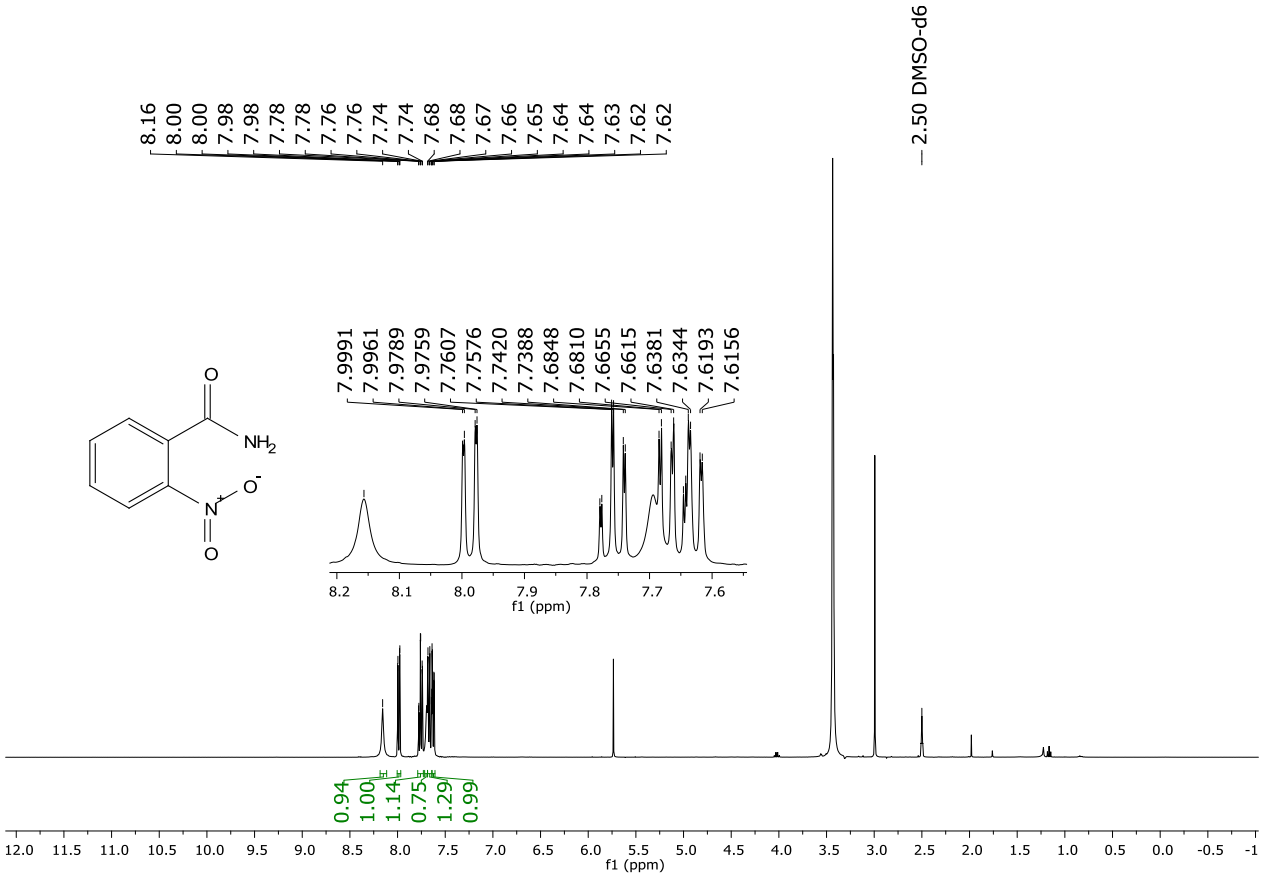
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) spectrum of **138**.



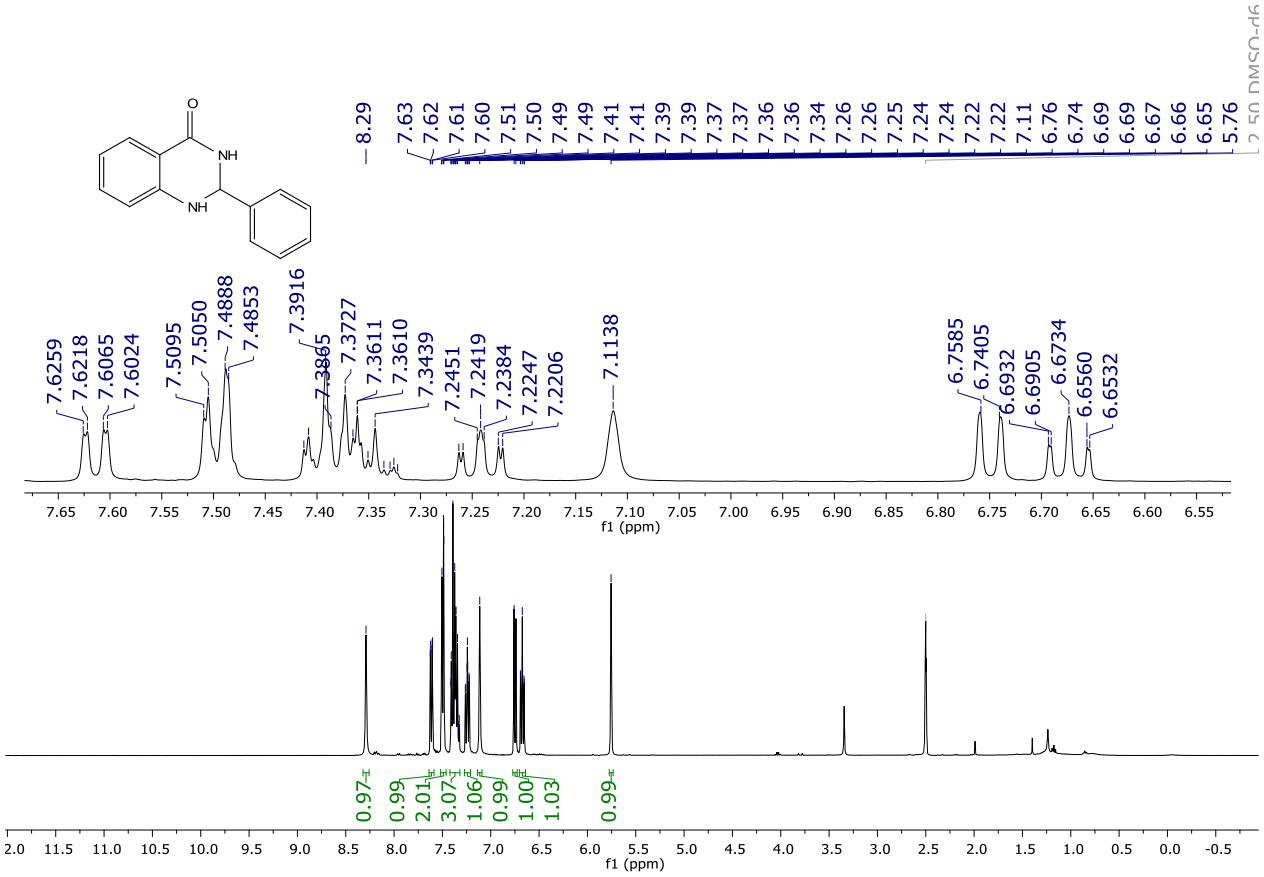
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **103**.



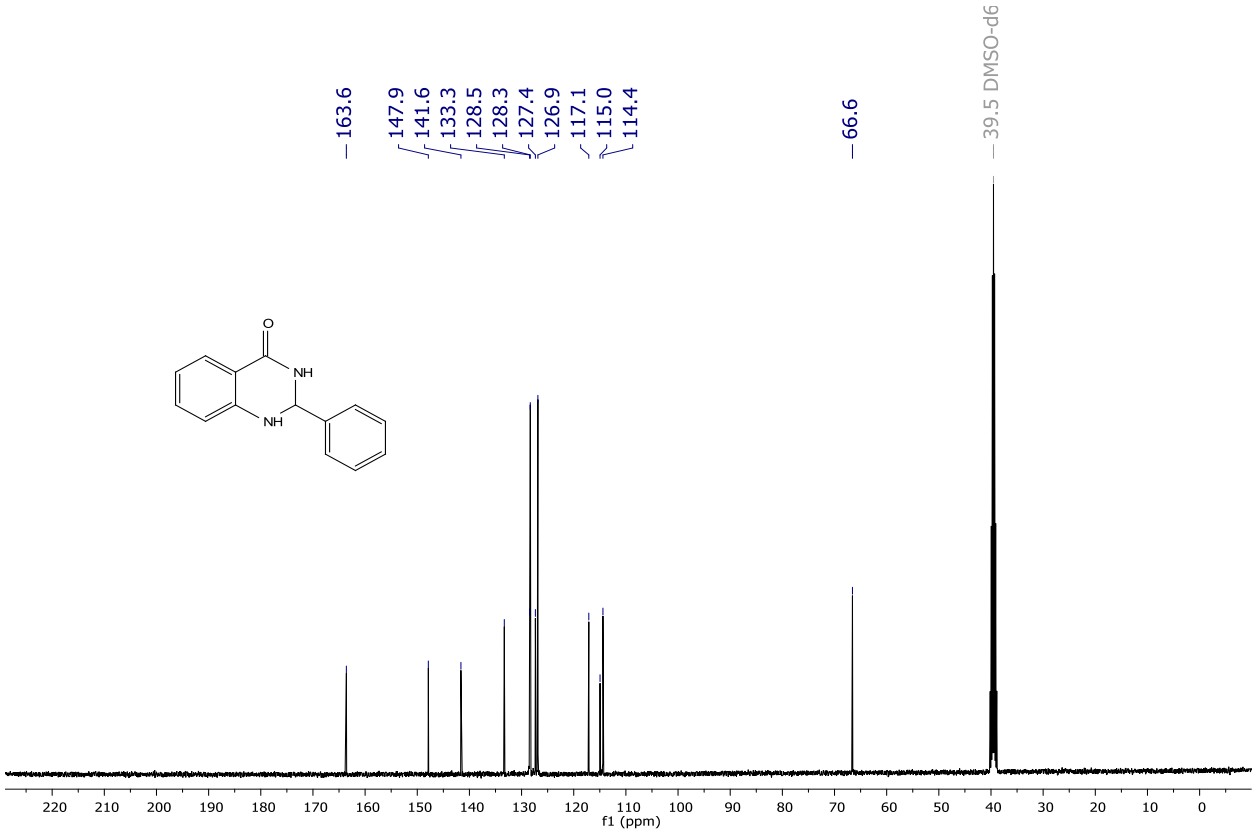
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **103**.



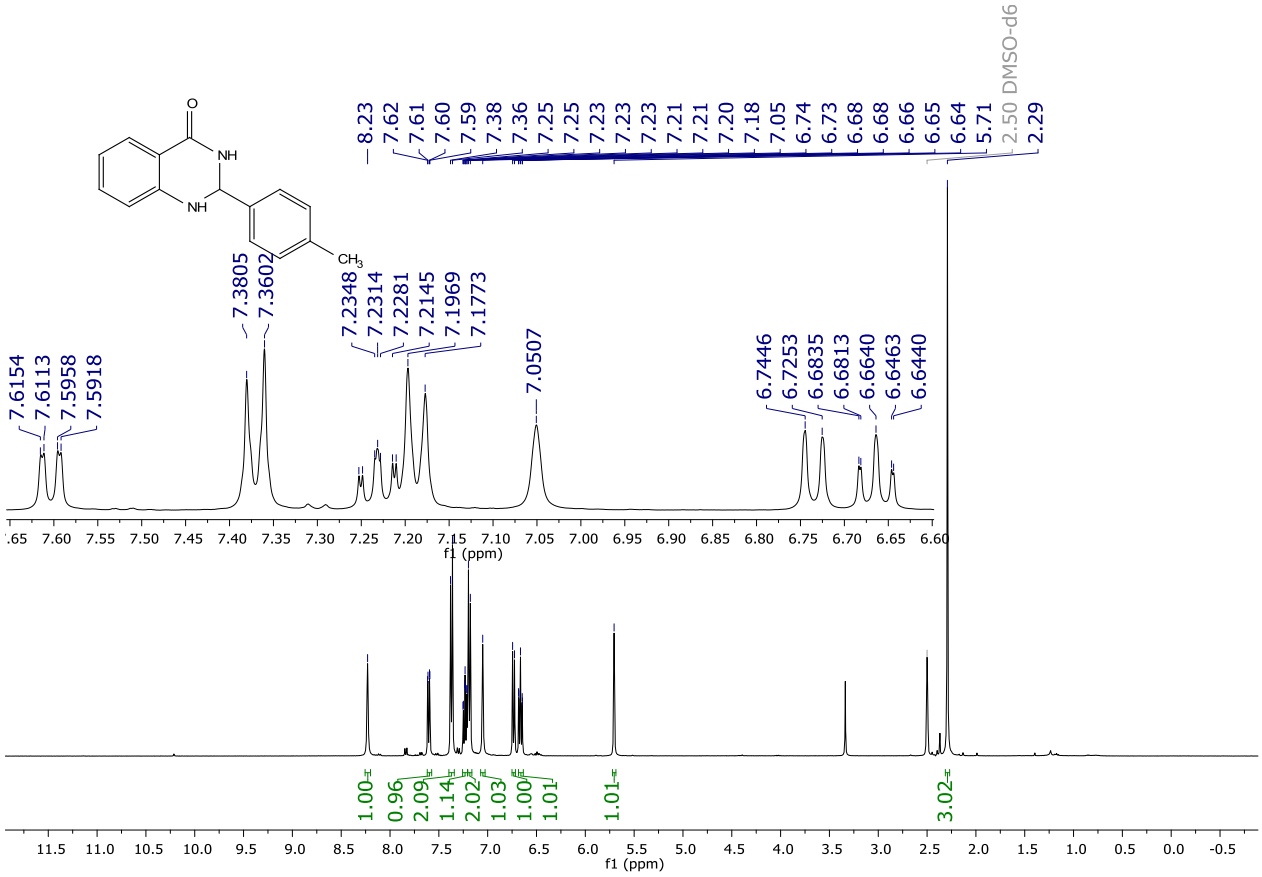
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **146**.



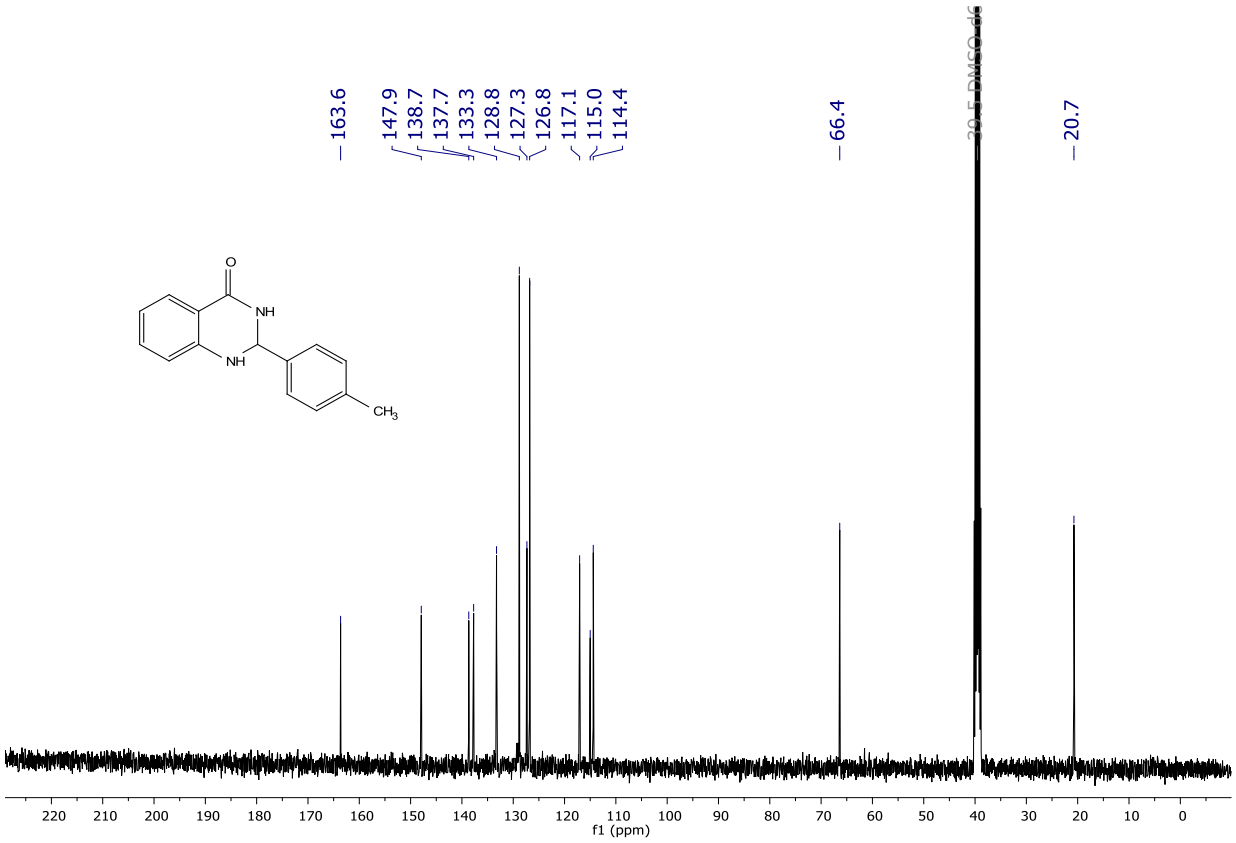
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120a**.



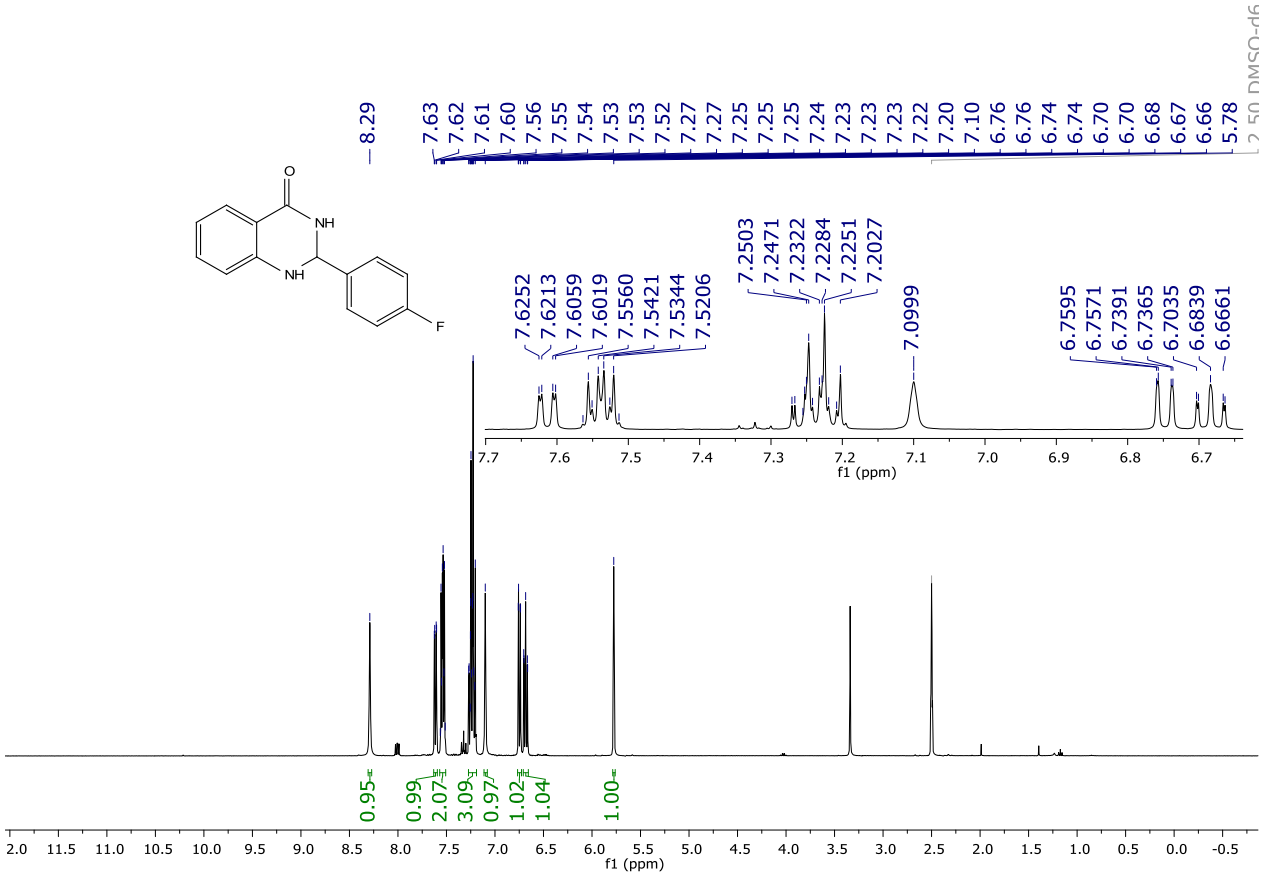
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120a**.



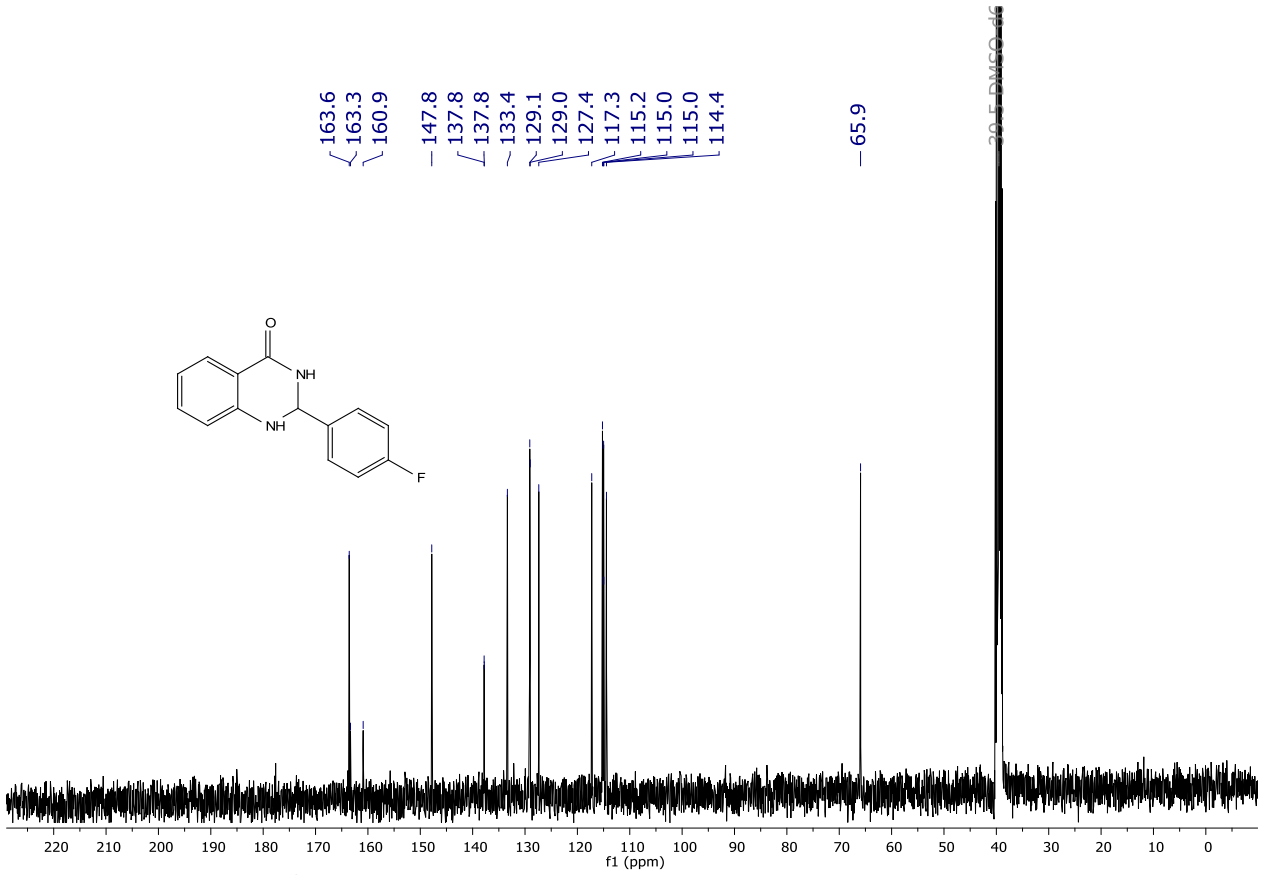
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120b**.



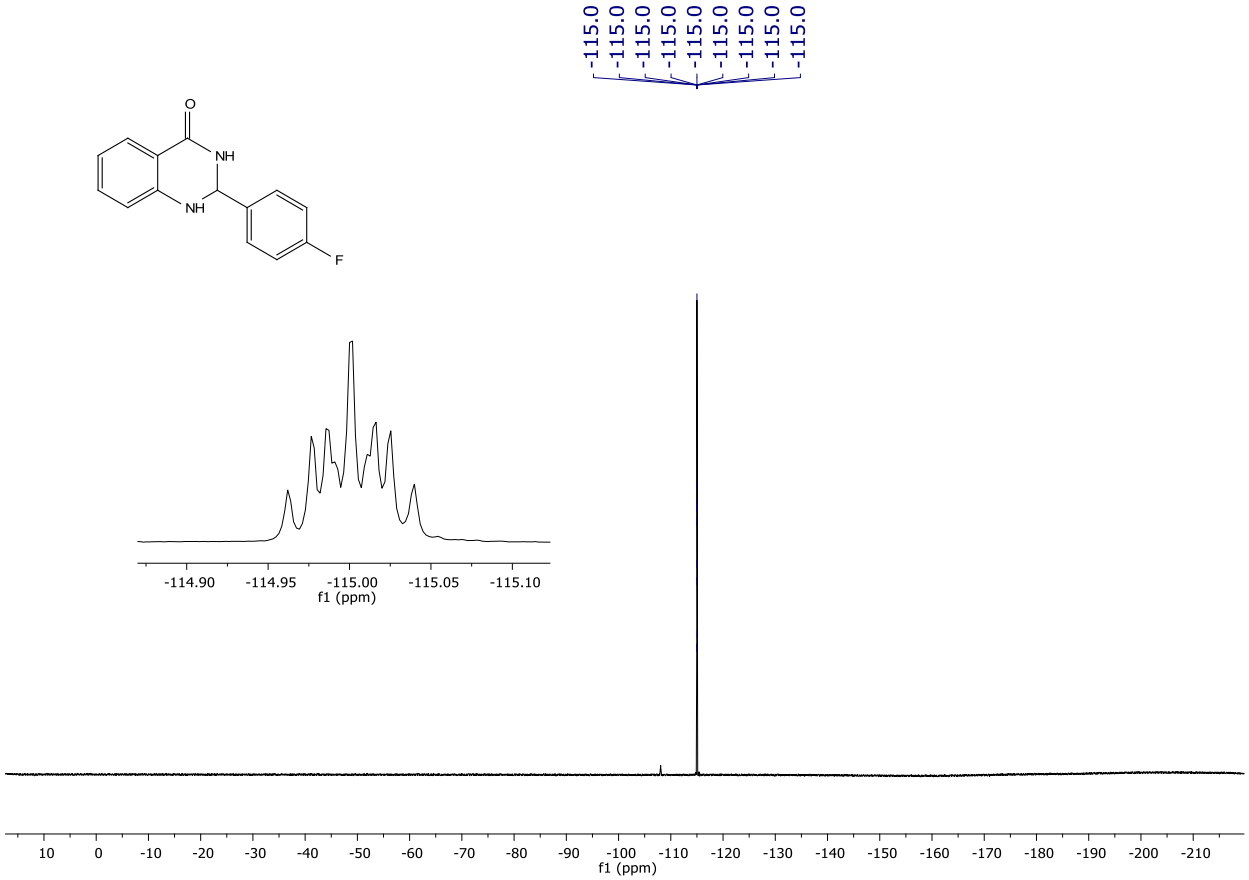
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120b**.



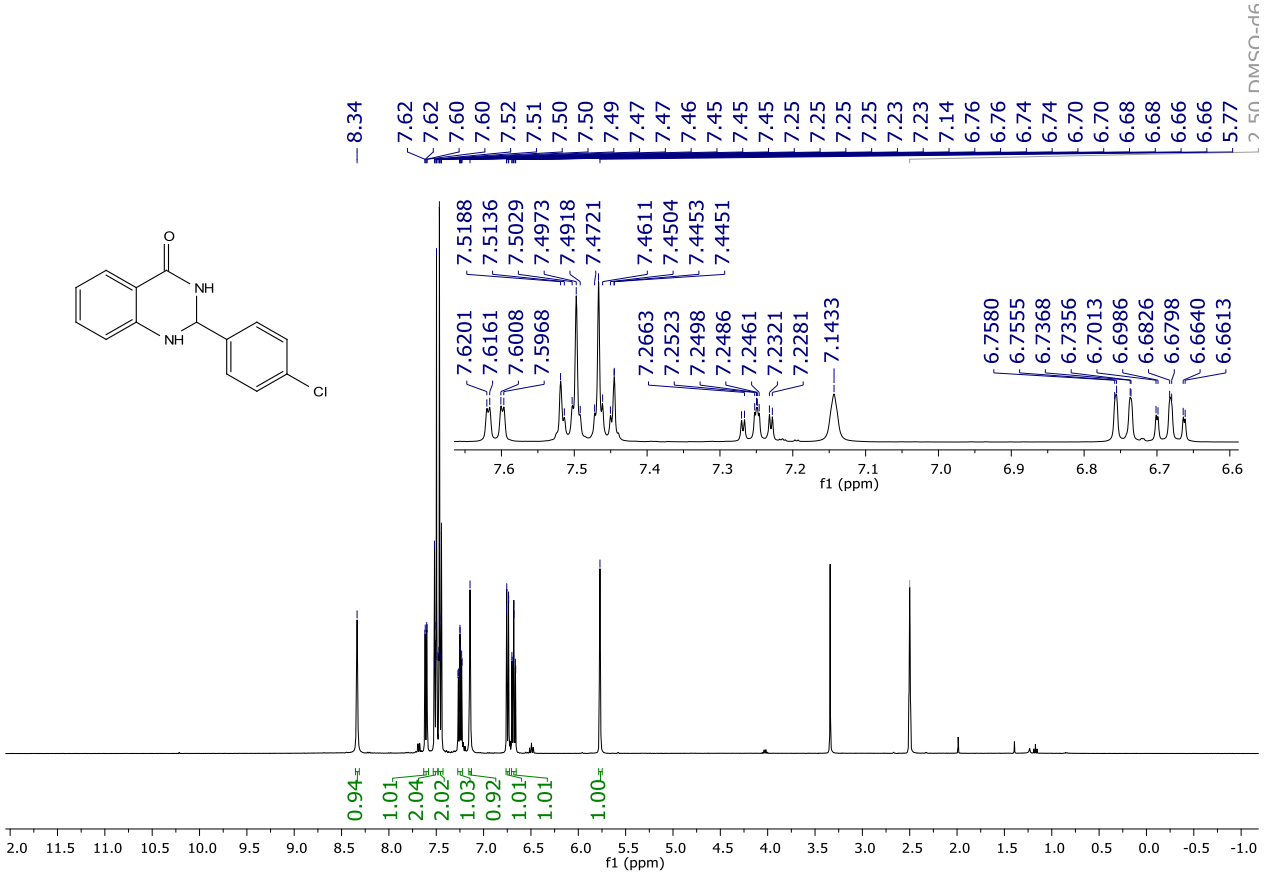
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120c**.



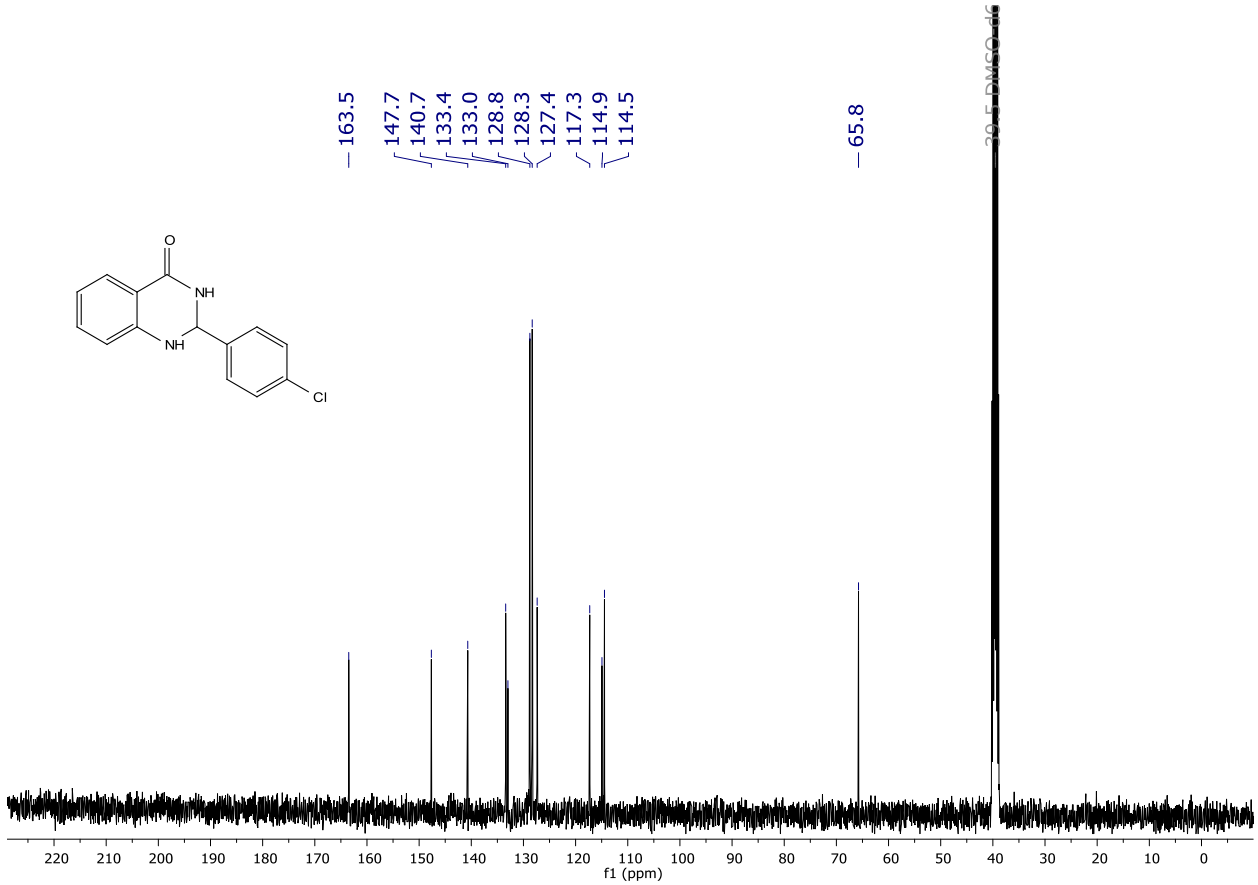
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120c**.



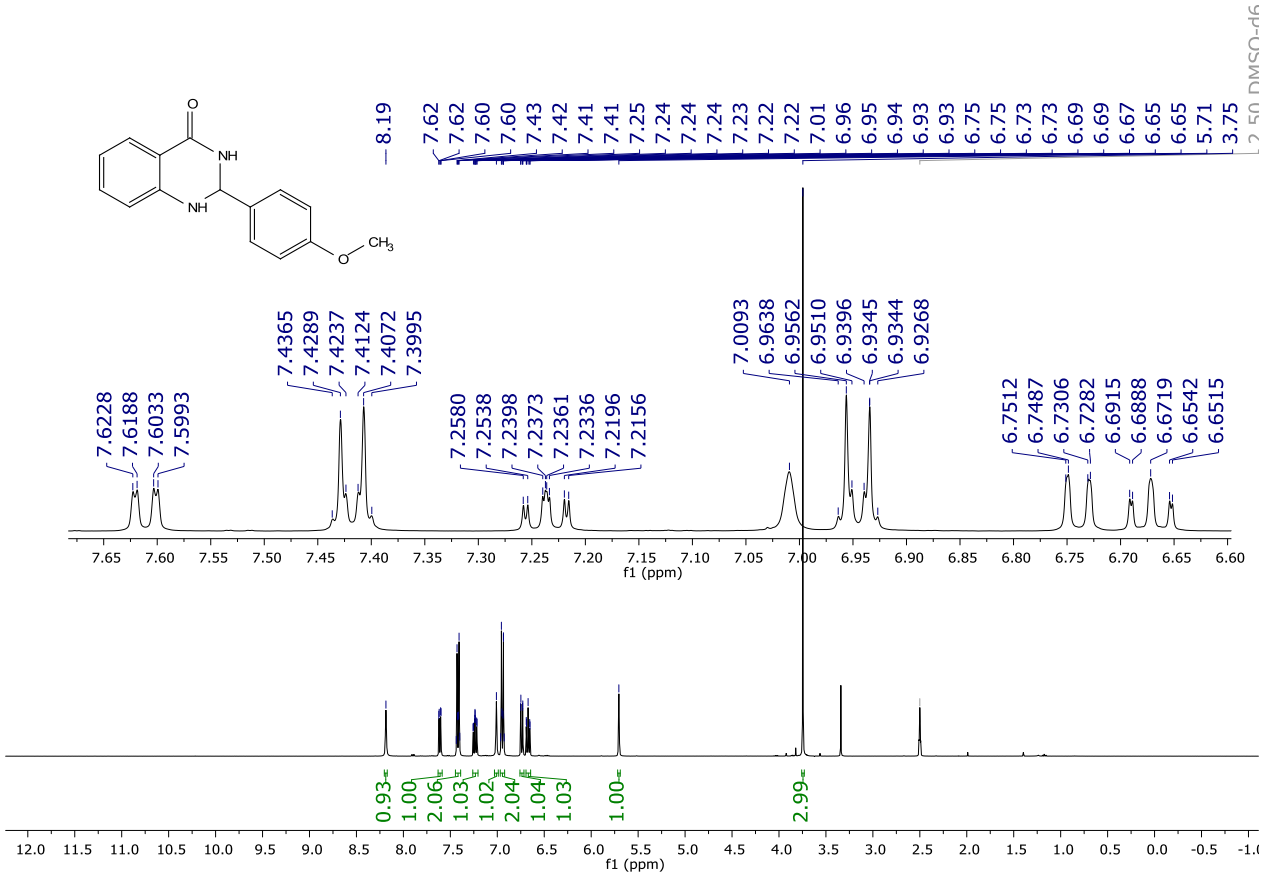
^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **120c**.



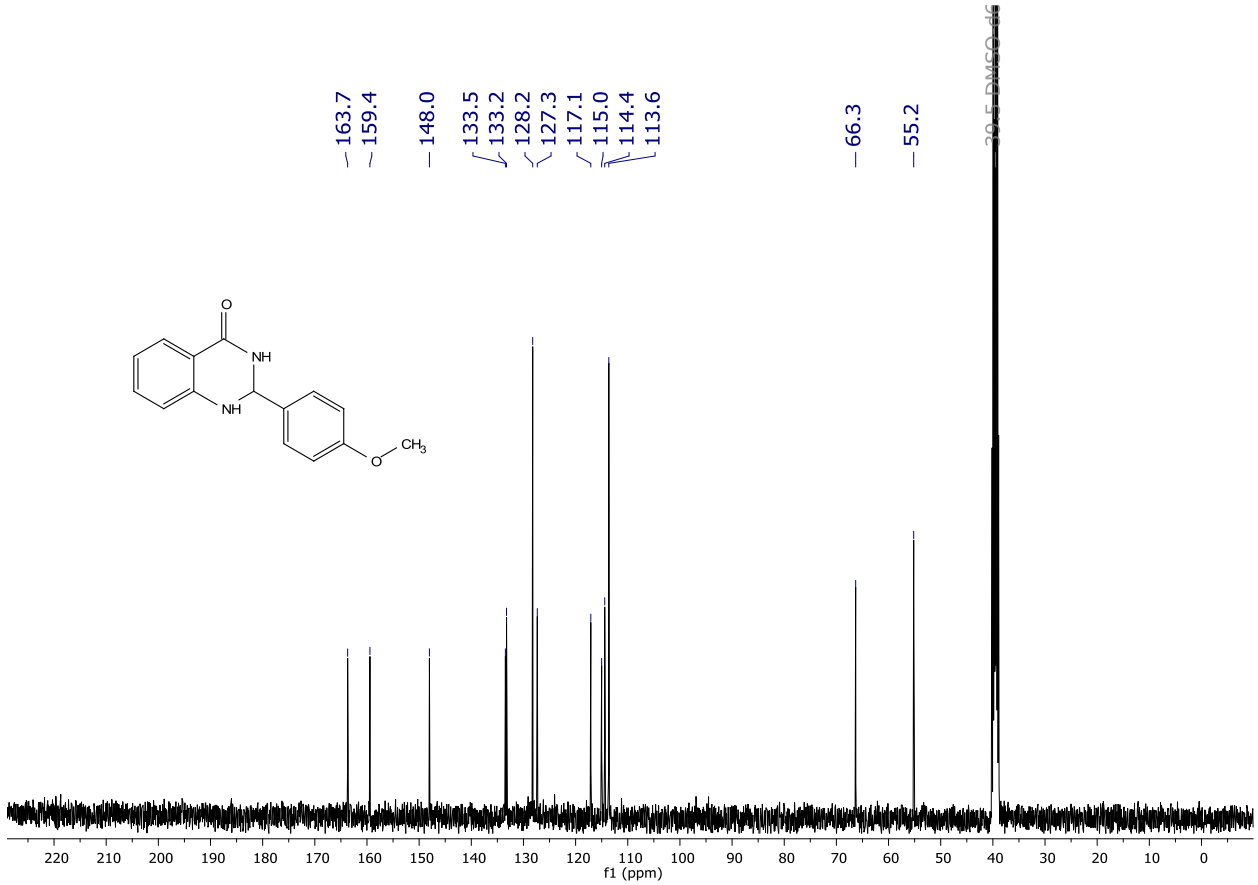
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120d**.



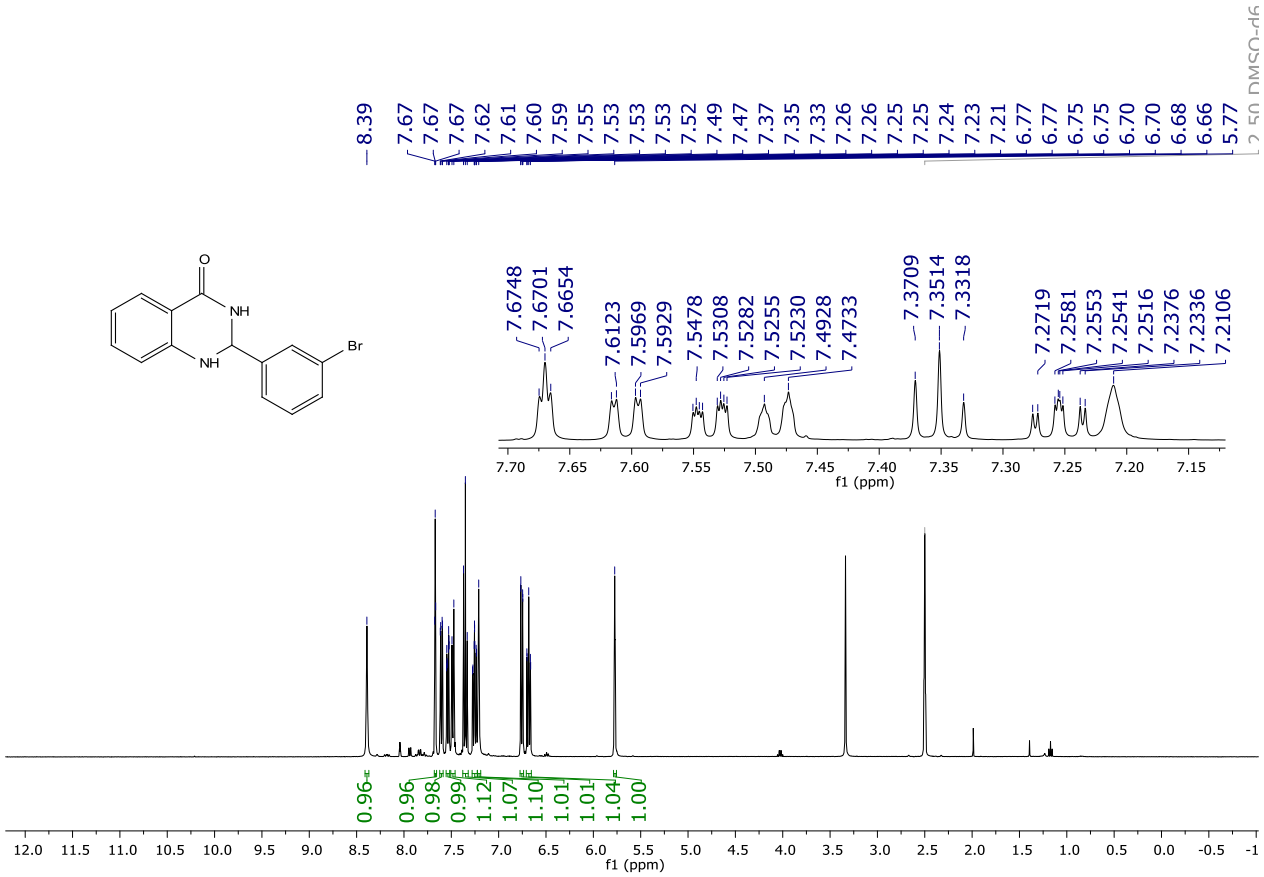
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120d**.



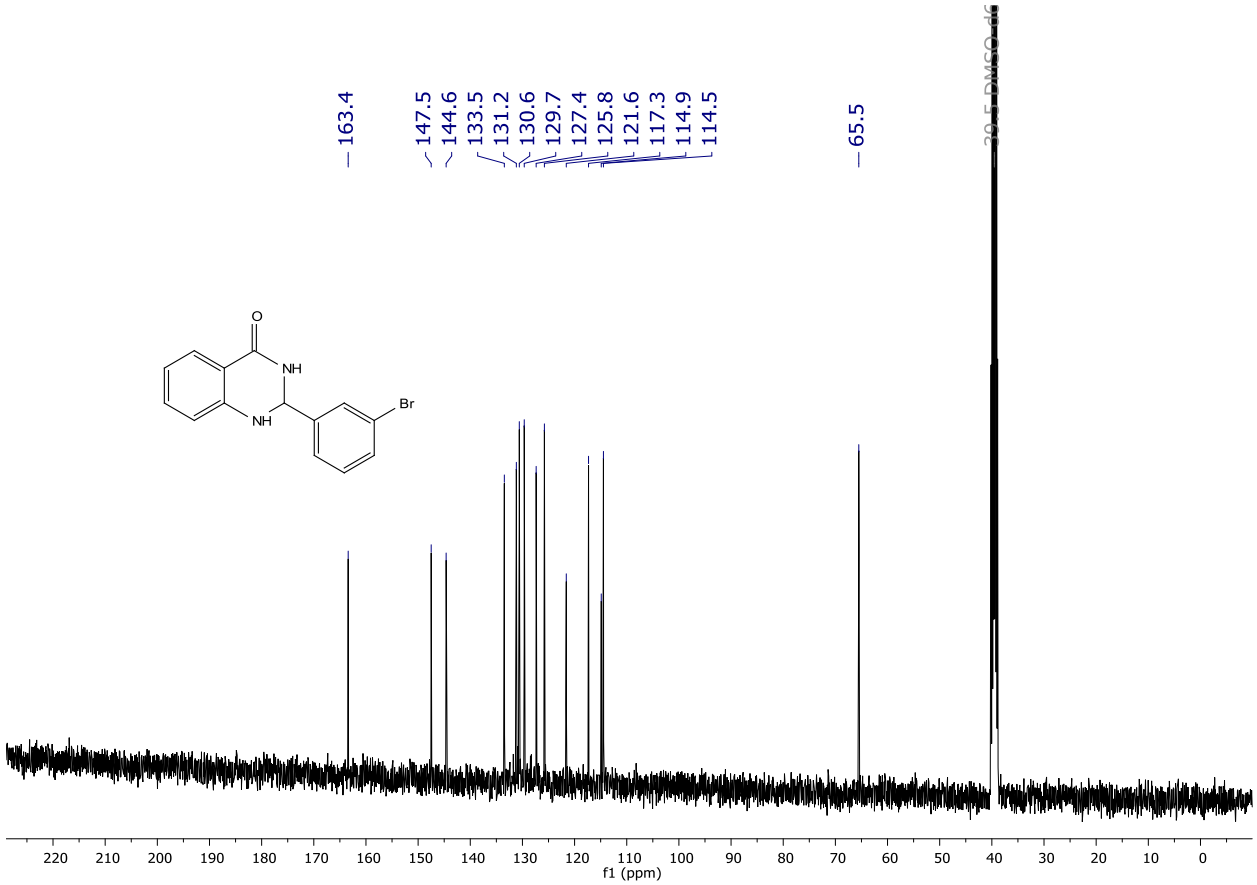
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120e**.



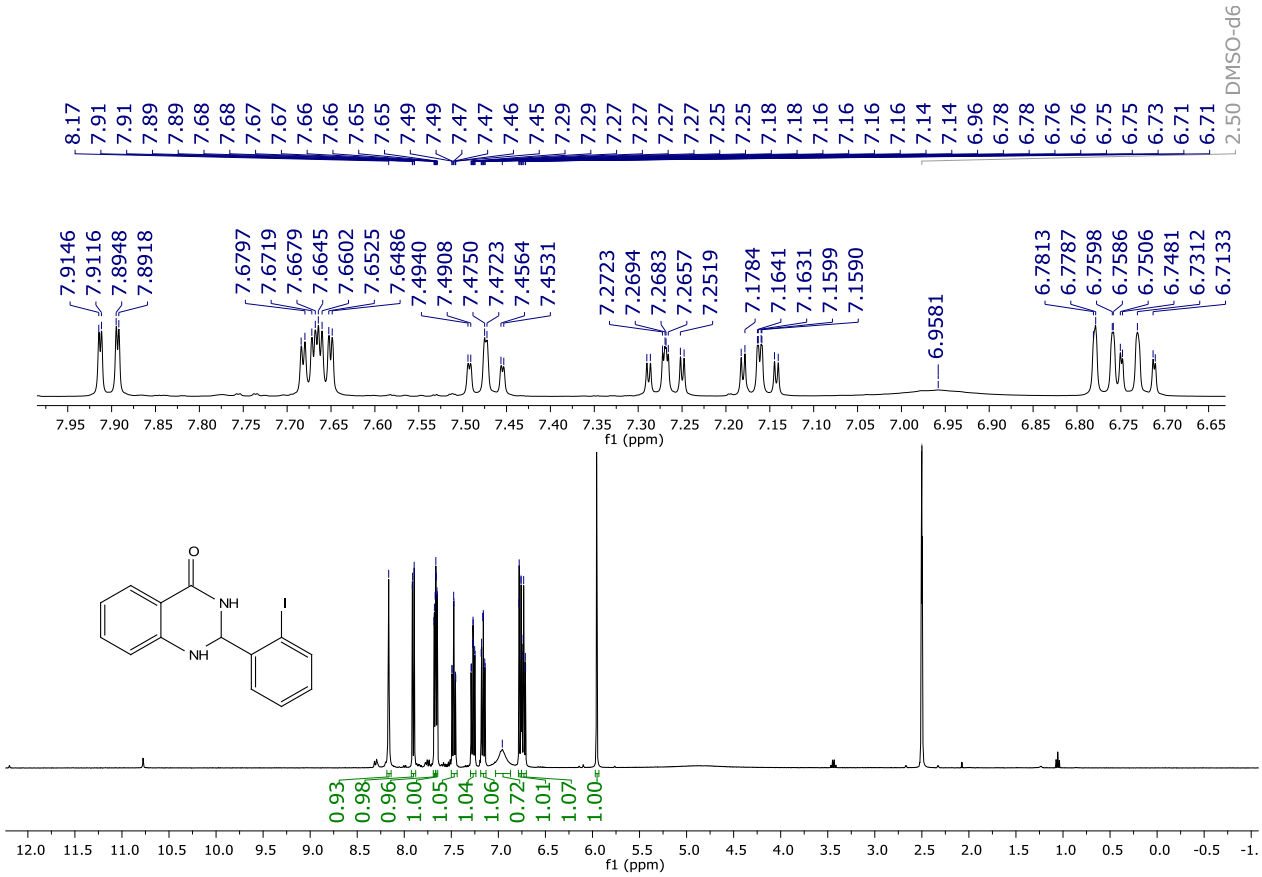
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120e**.



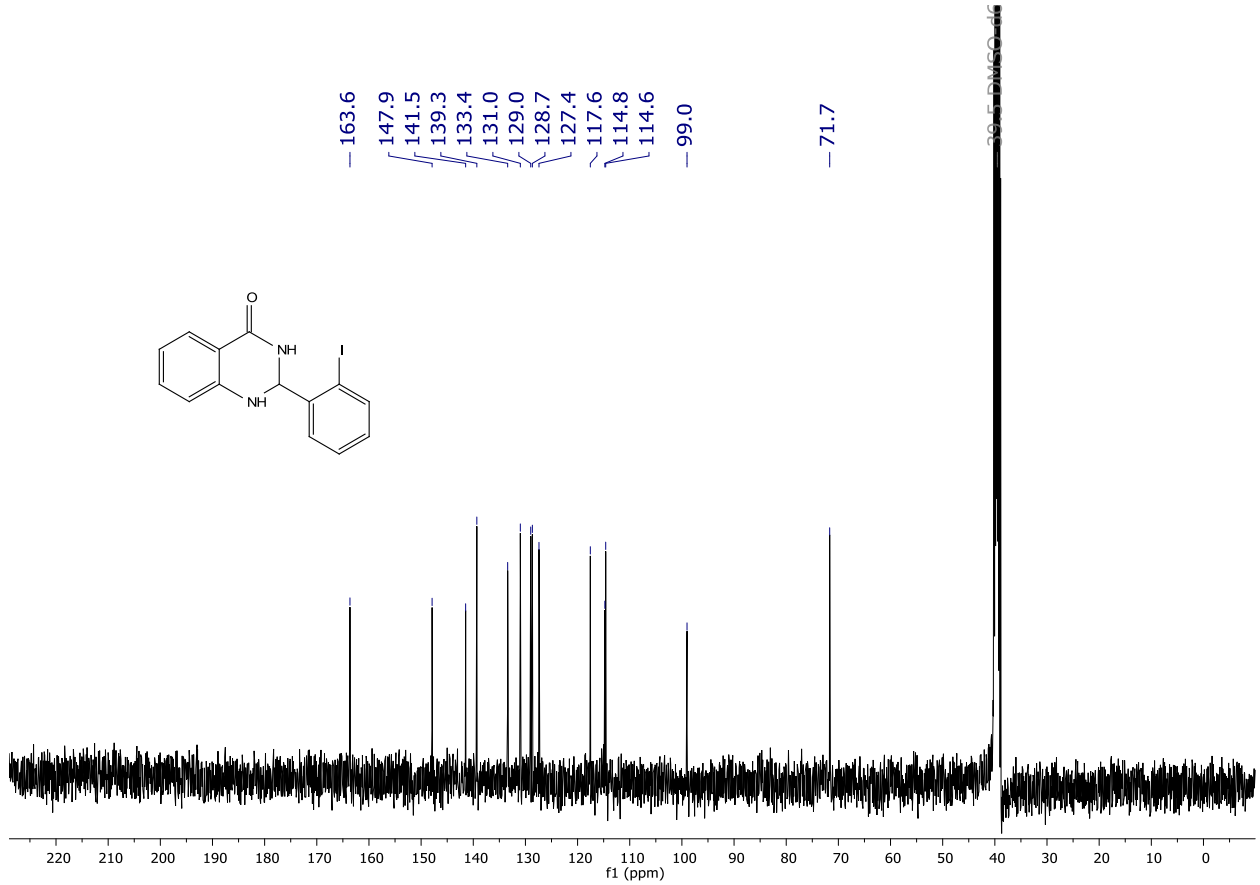
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120f**.



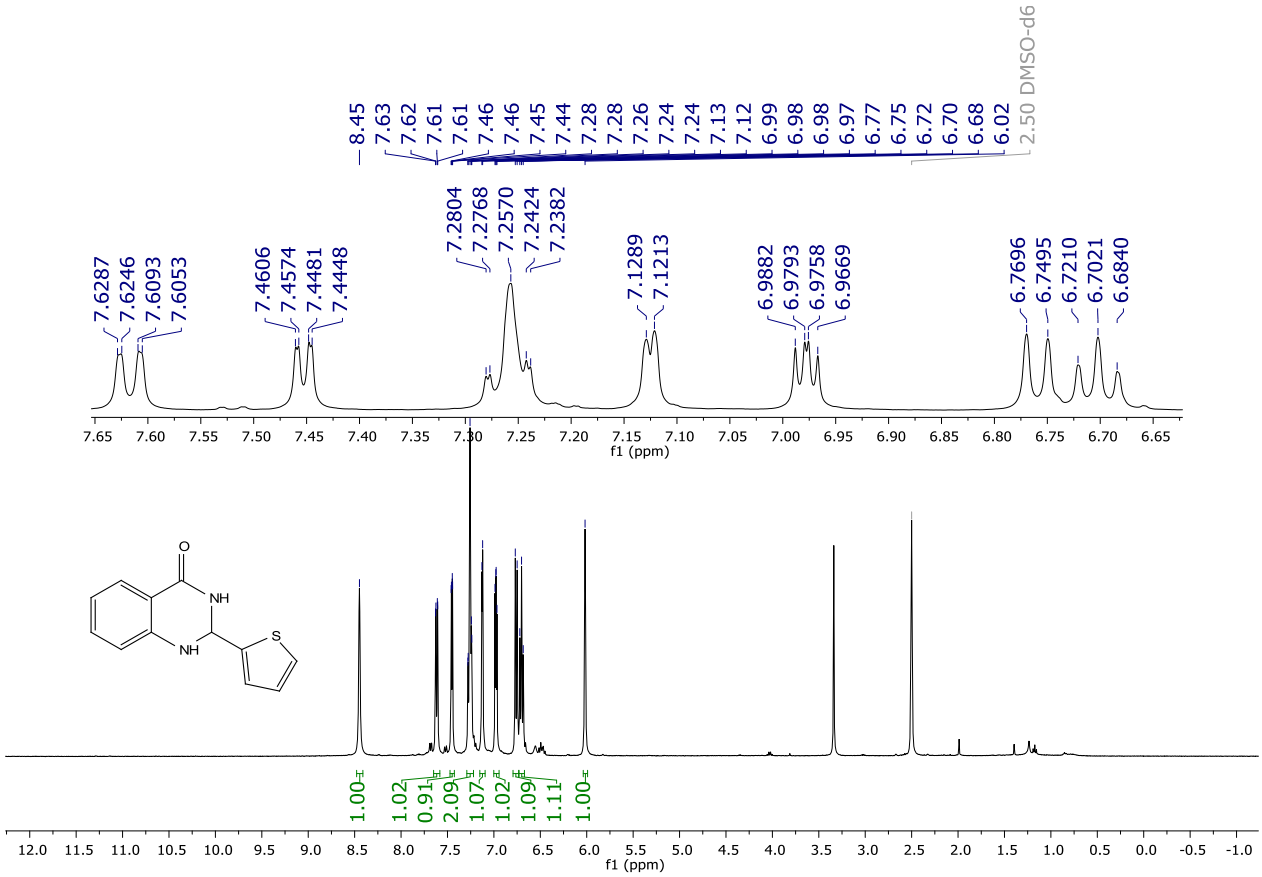
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120f**.



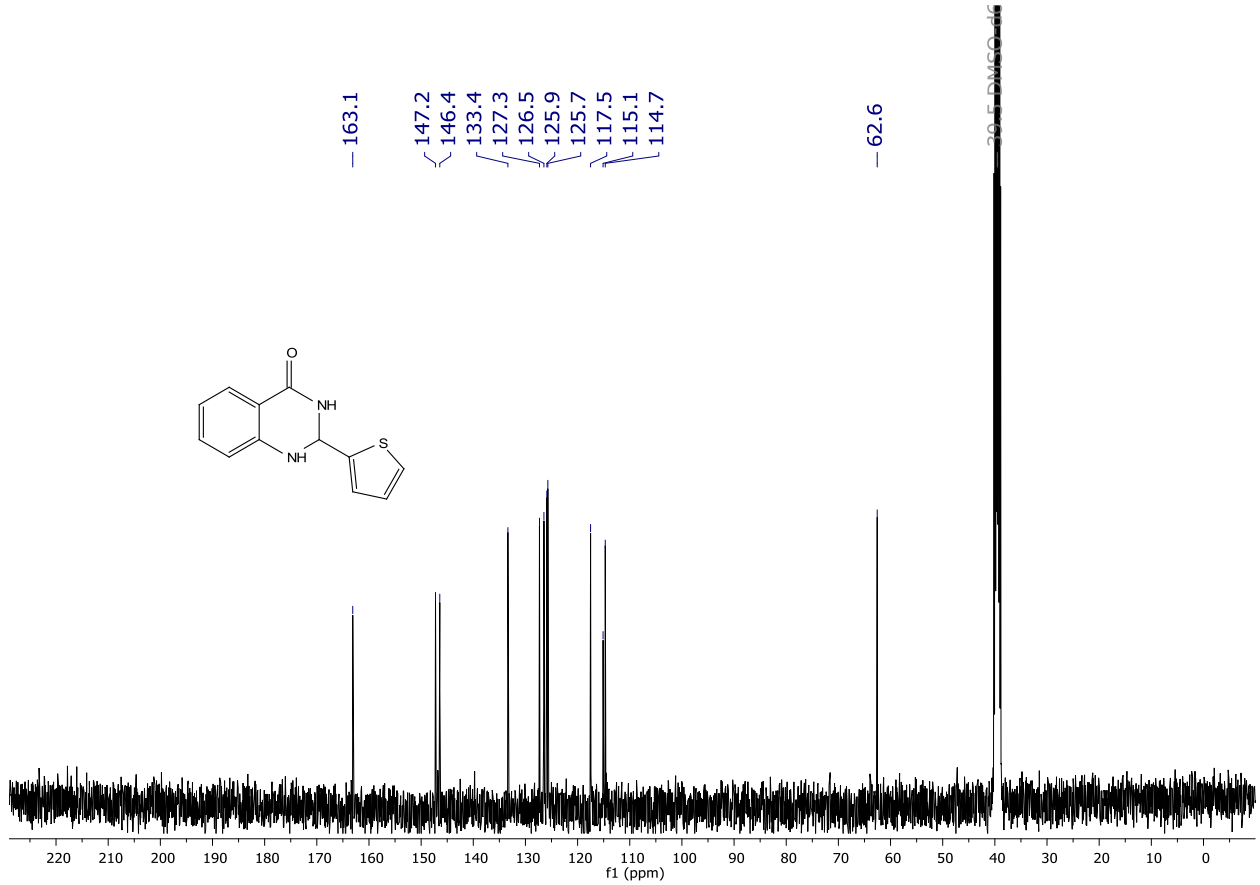
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120g**.



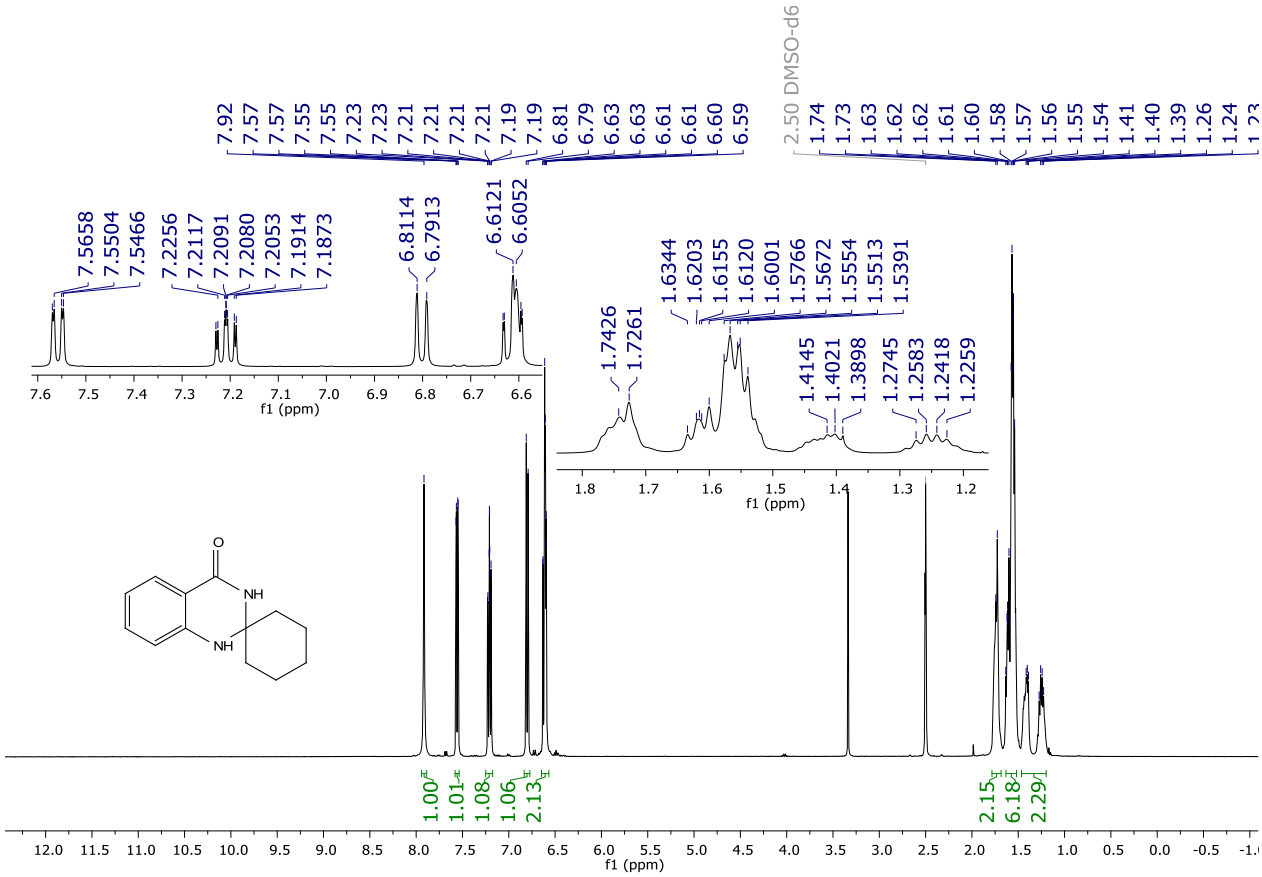
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120g**.



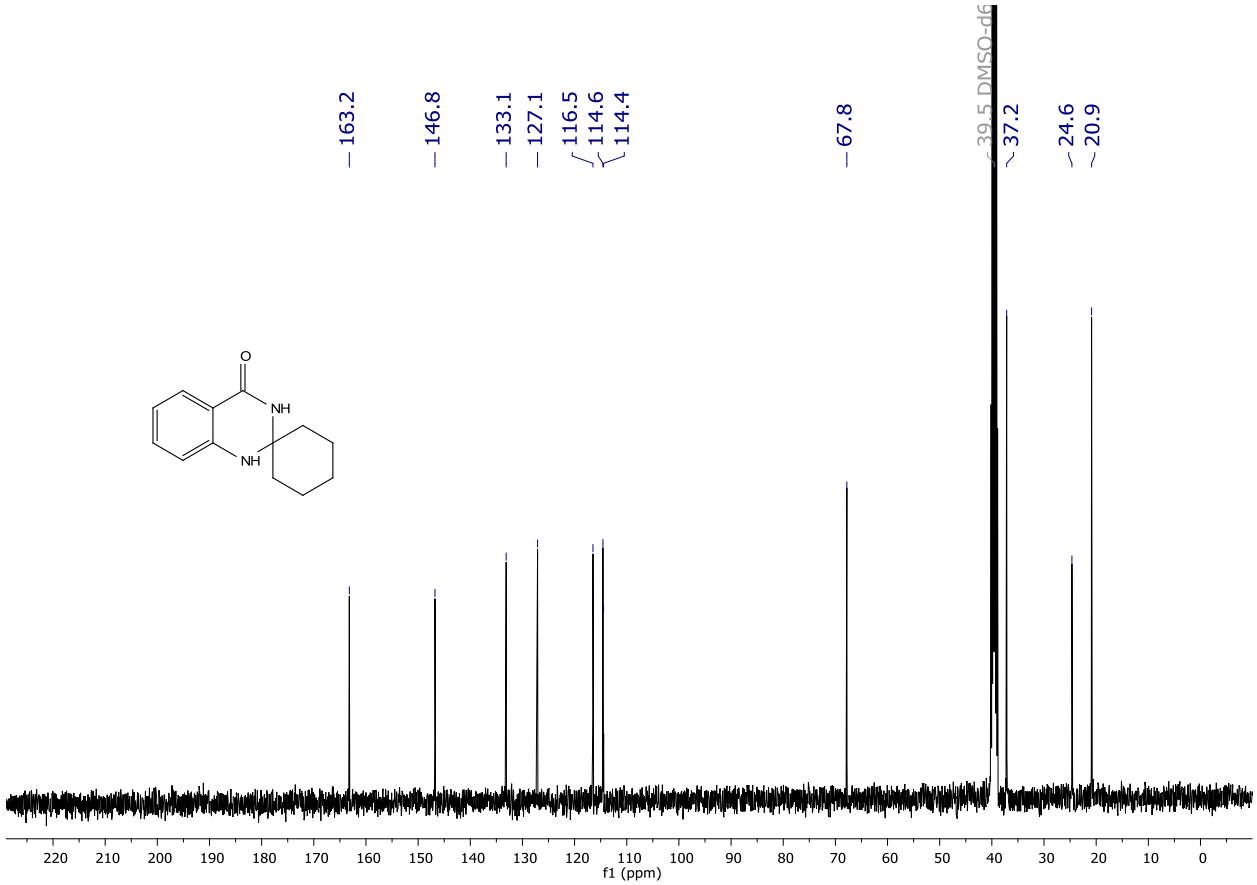
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120h**.



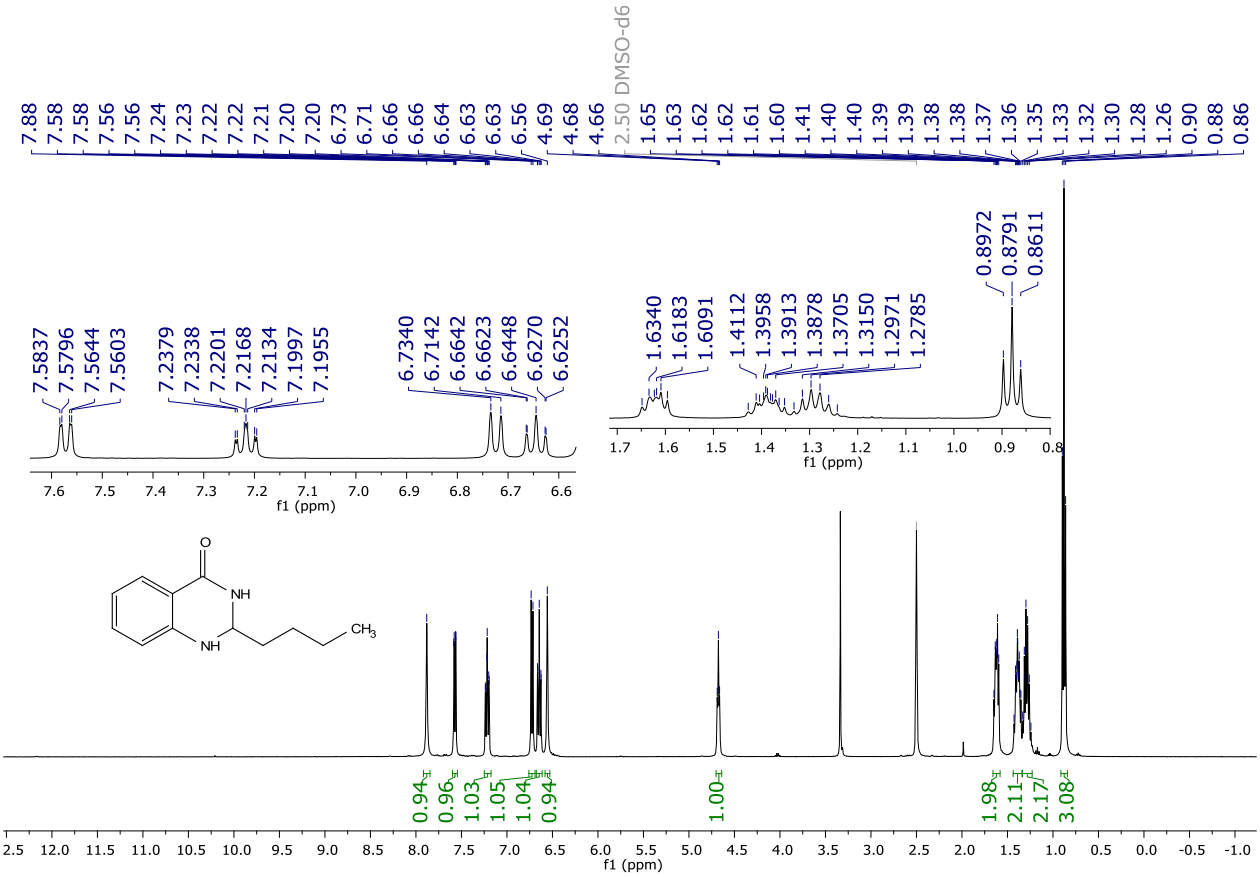
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120h**.



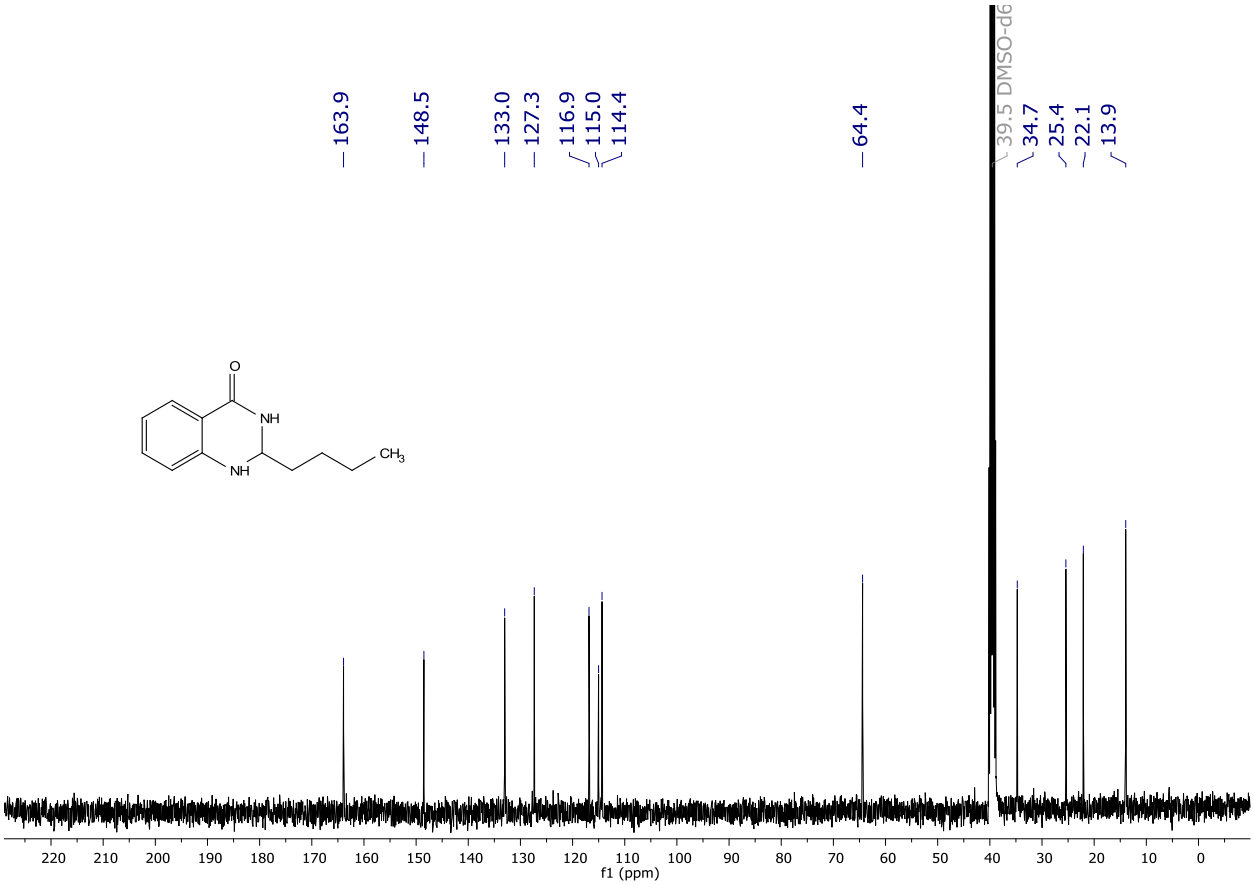
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120i**.



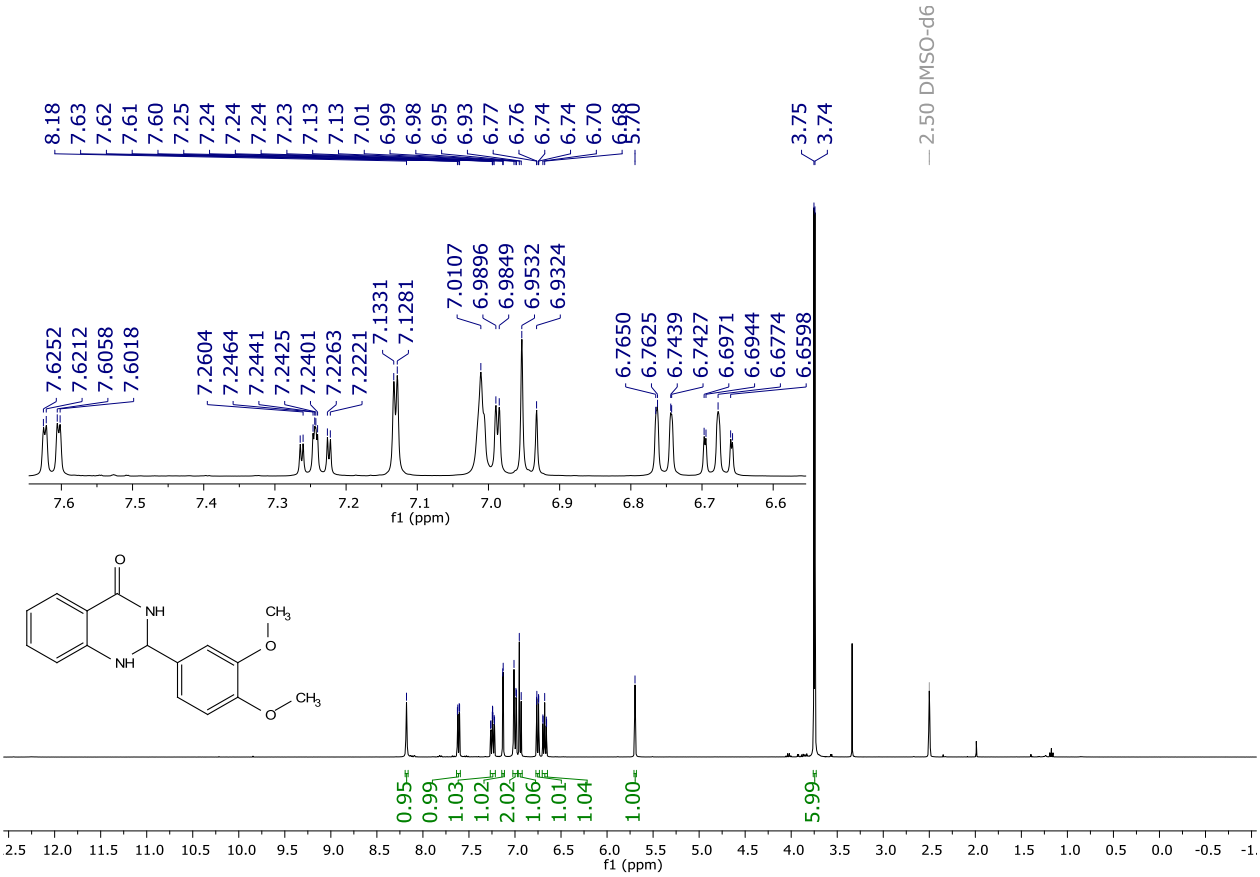
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120i**.



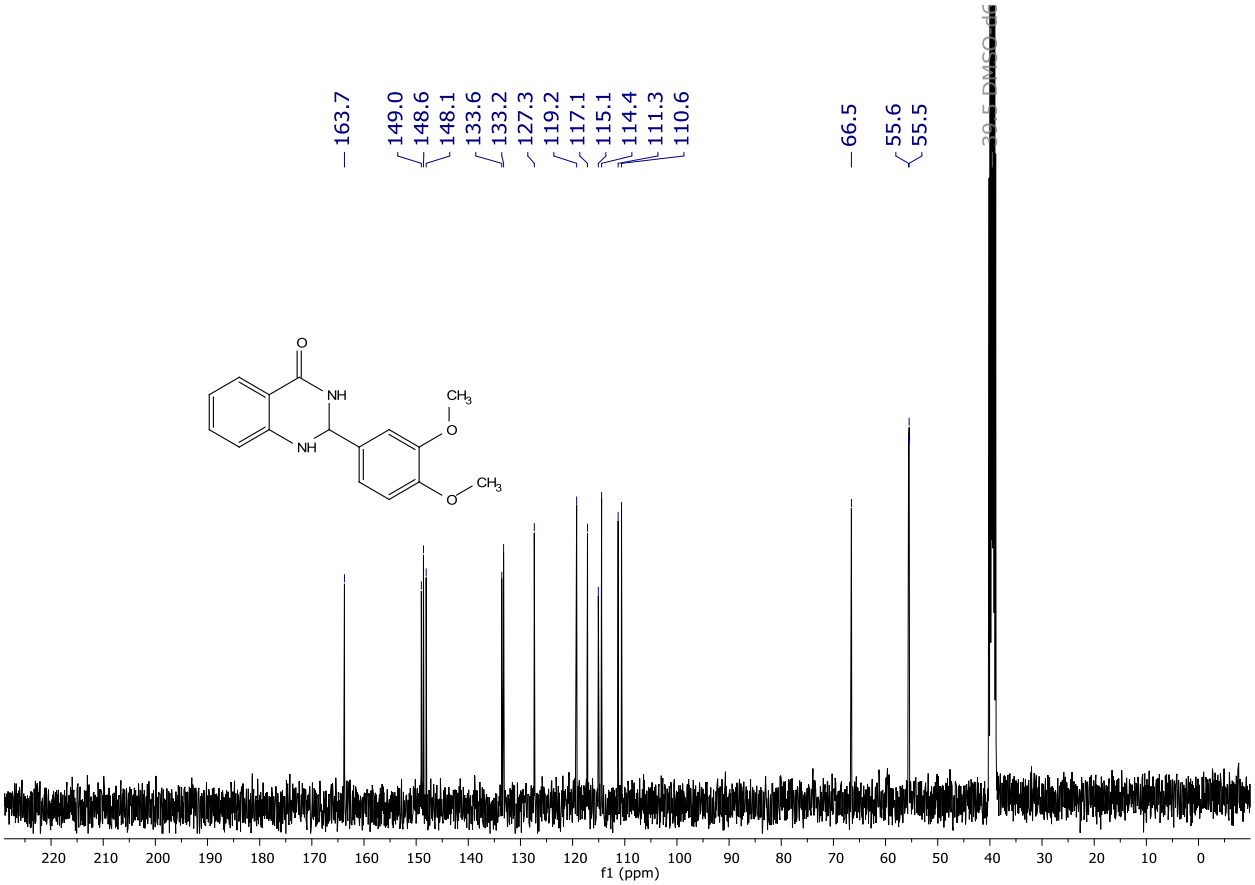
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120j**.



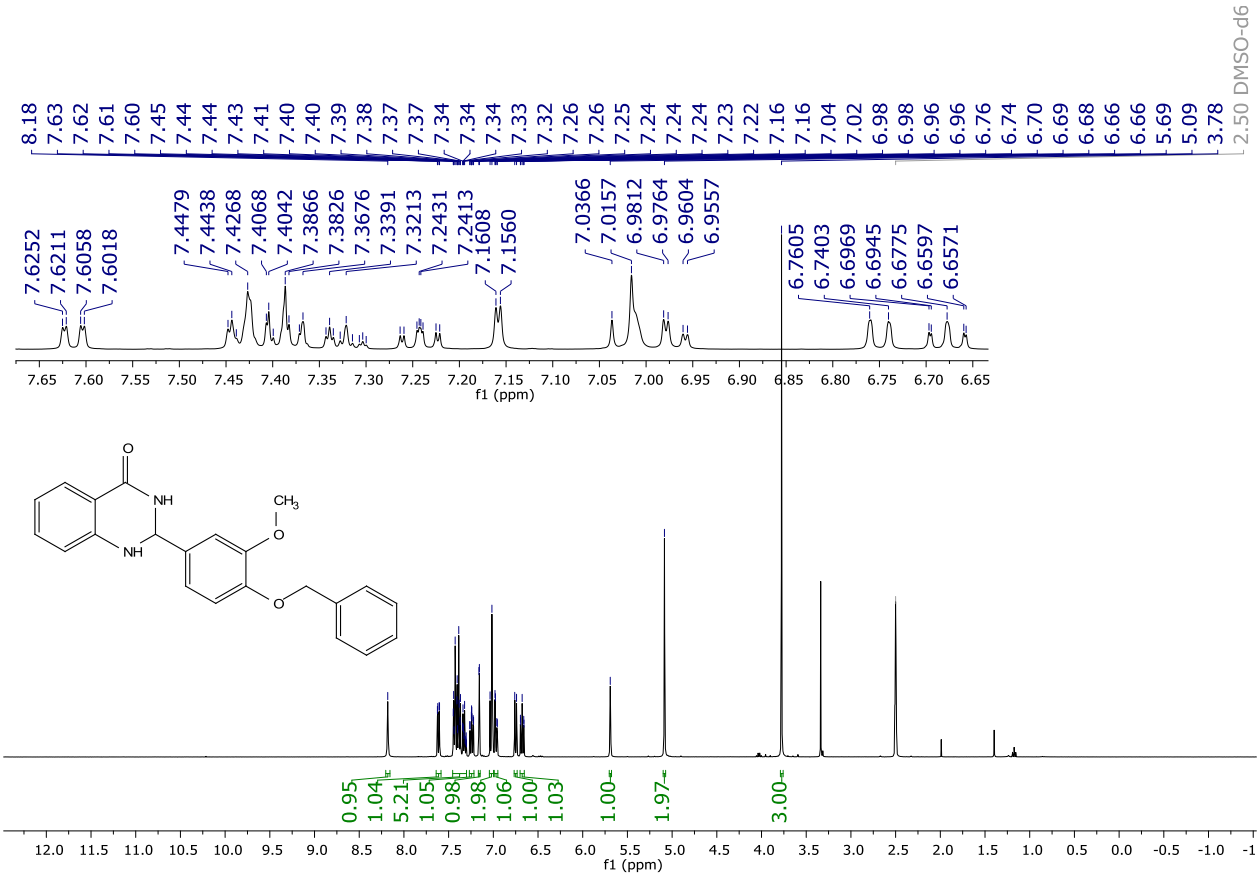
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120j**.



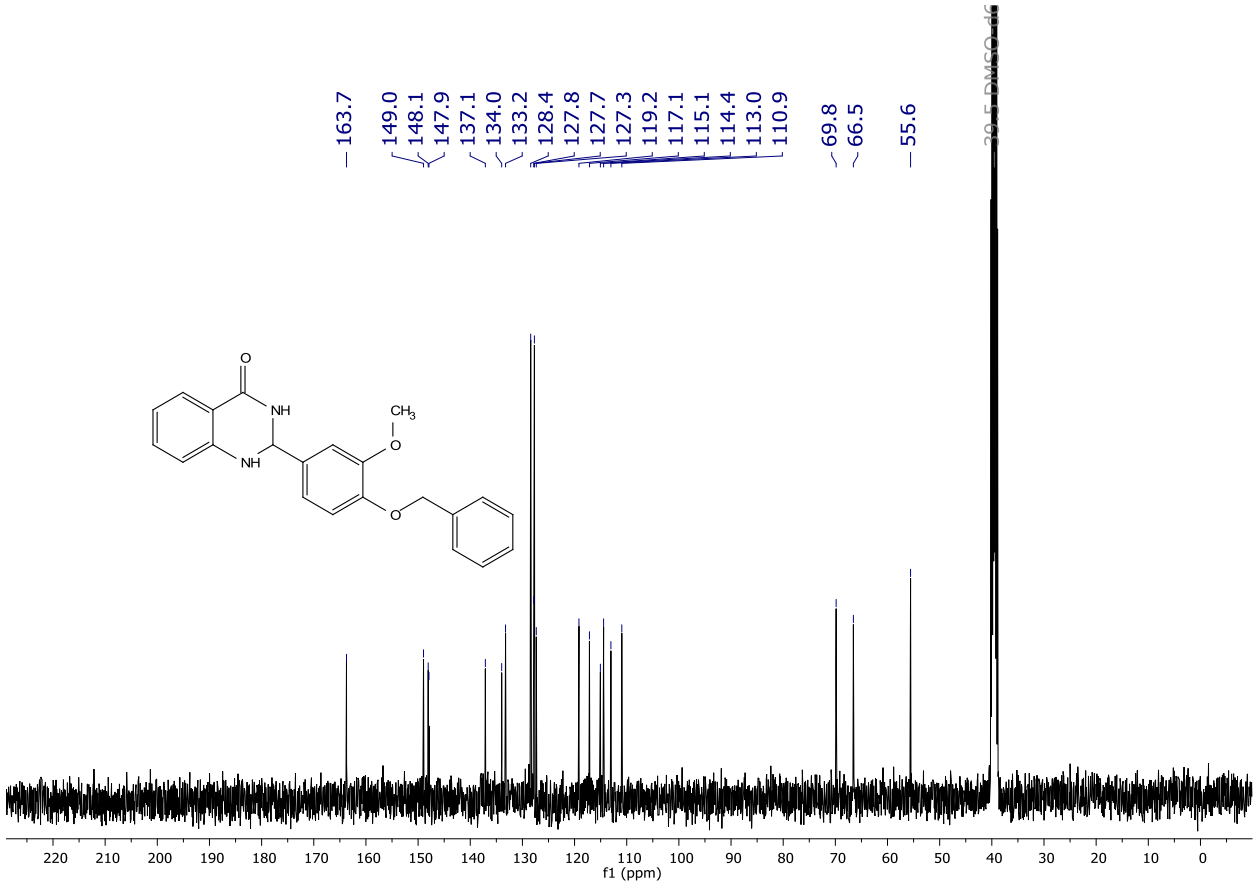
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120k**.



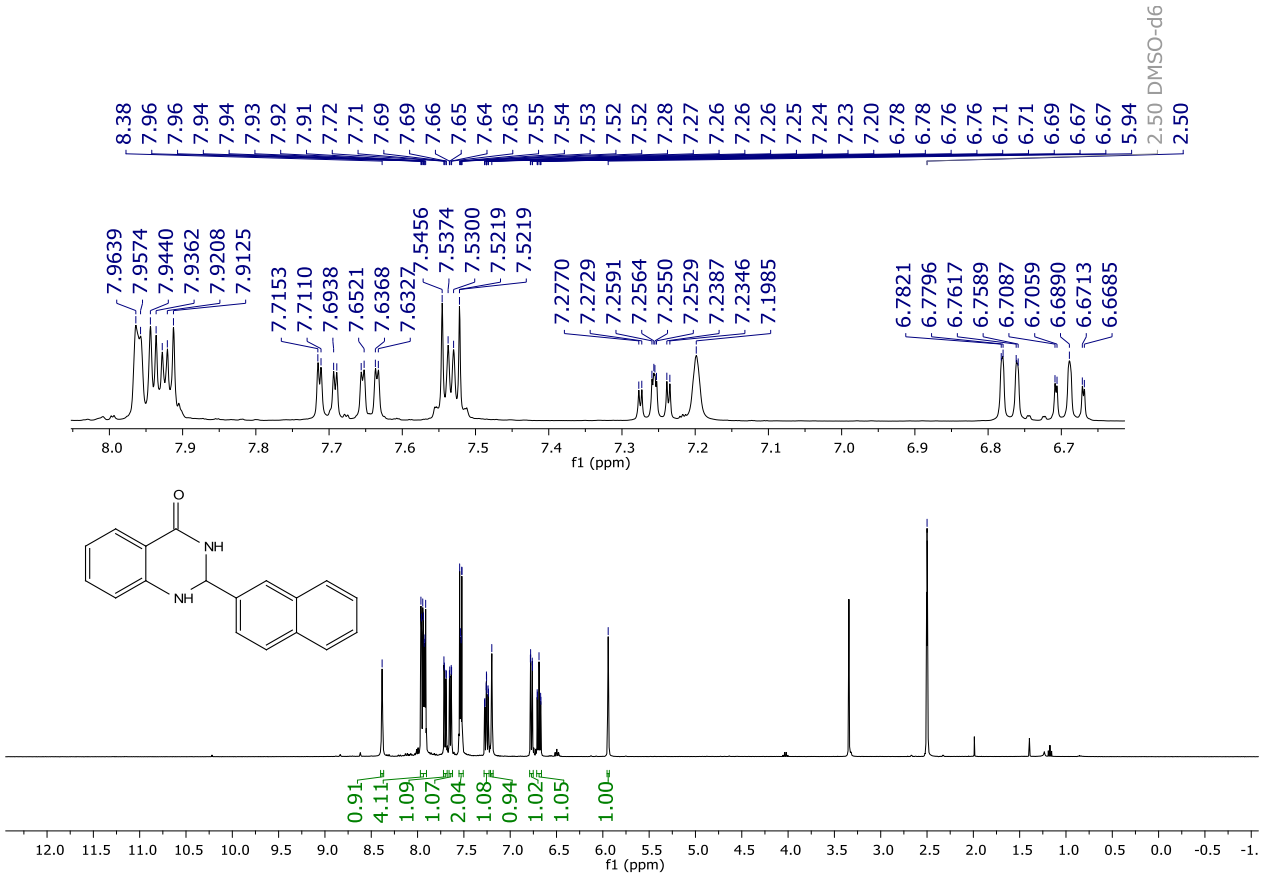
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120k**.



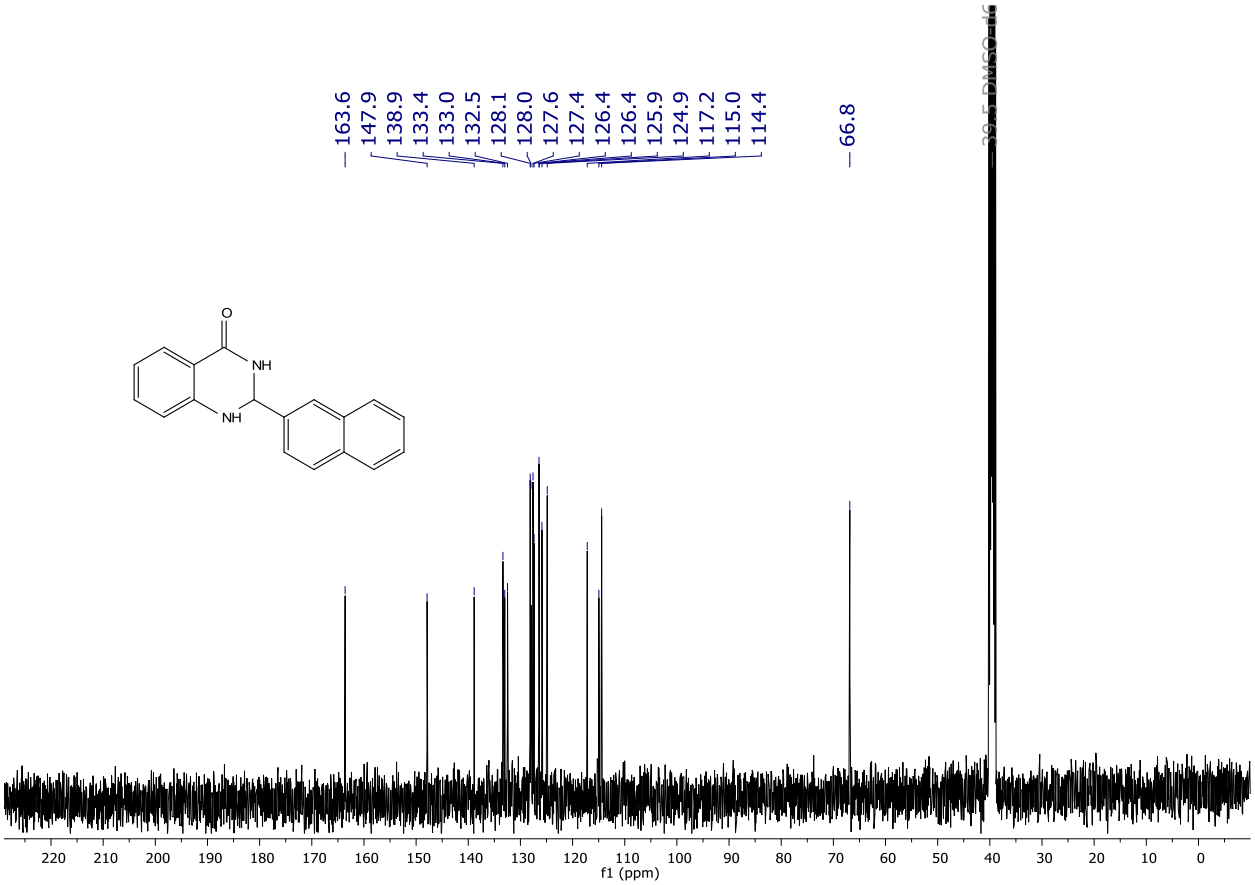
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120l**.



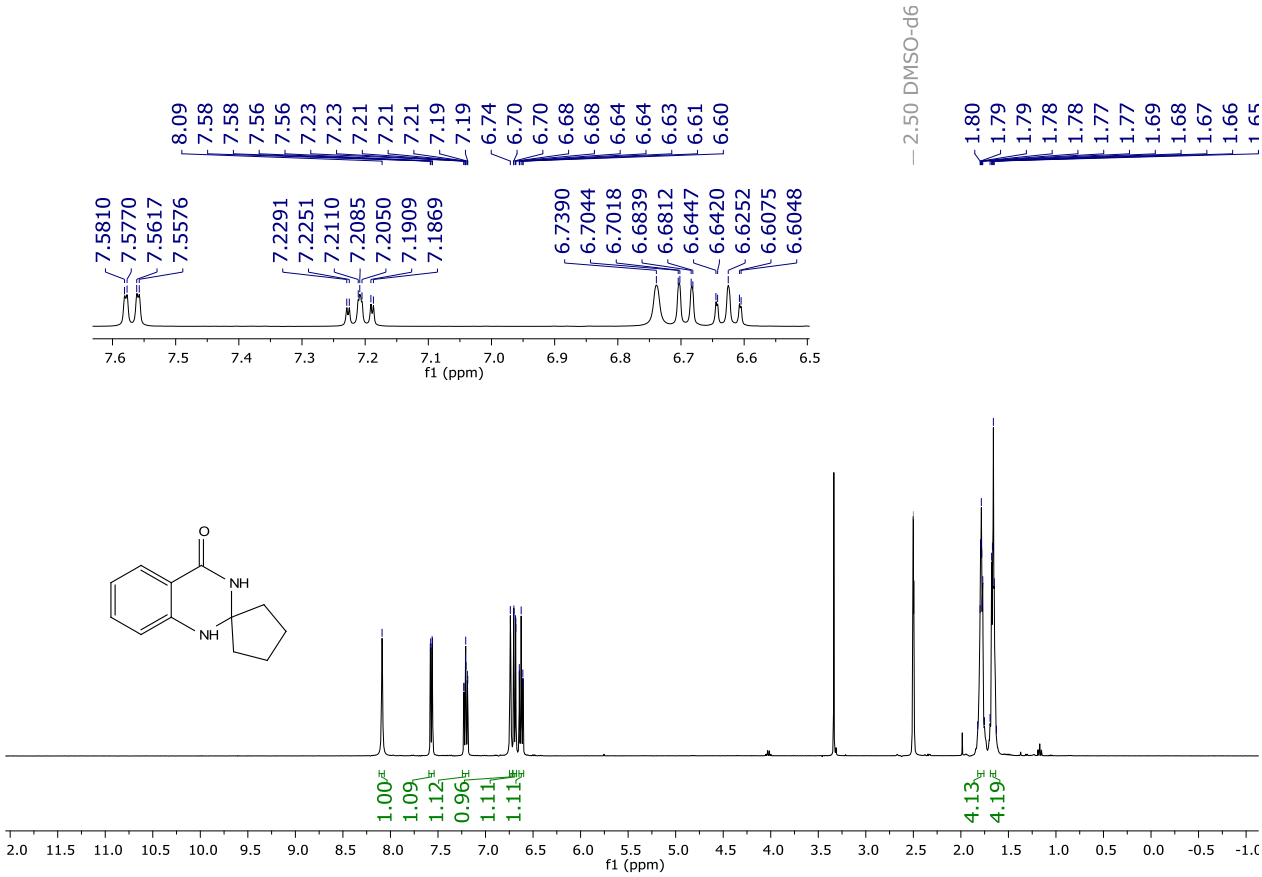
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120l**.



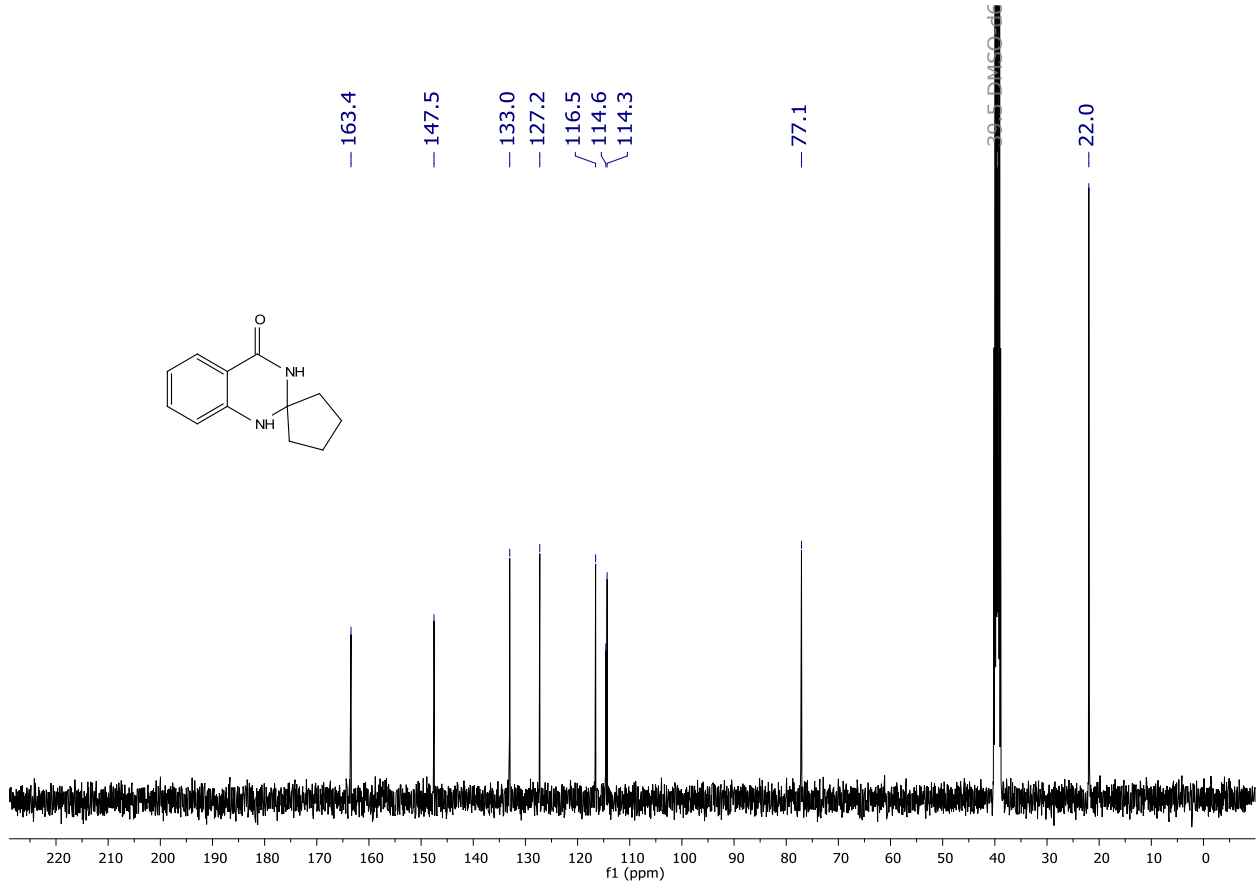
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120m**.



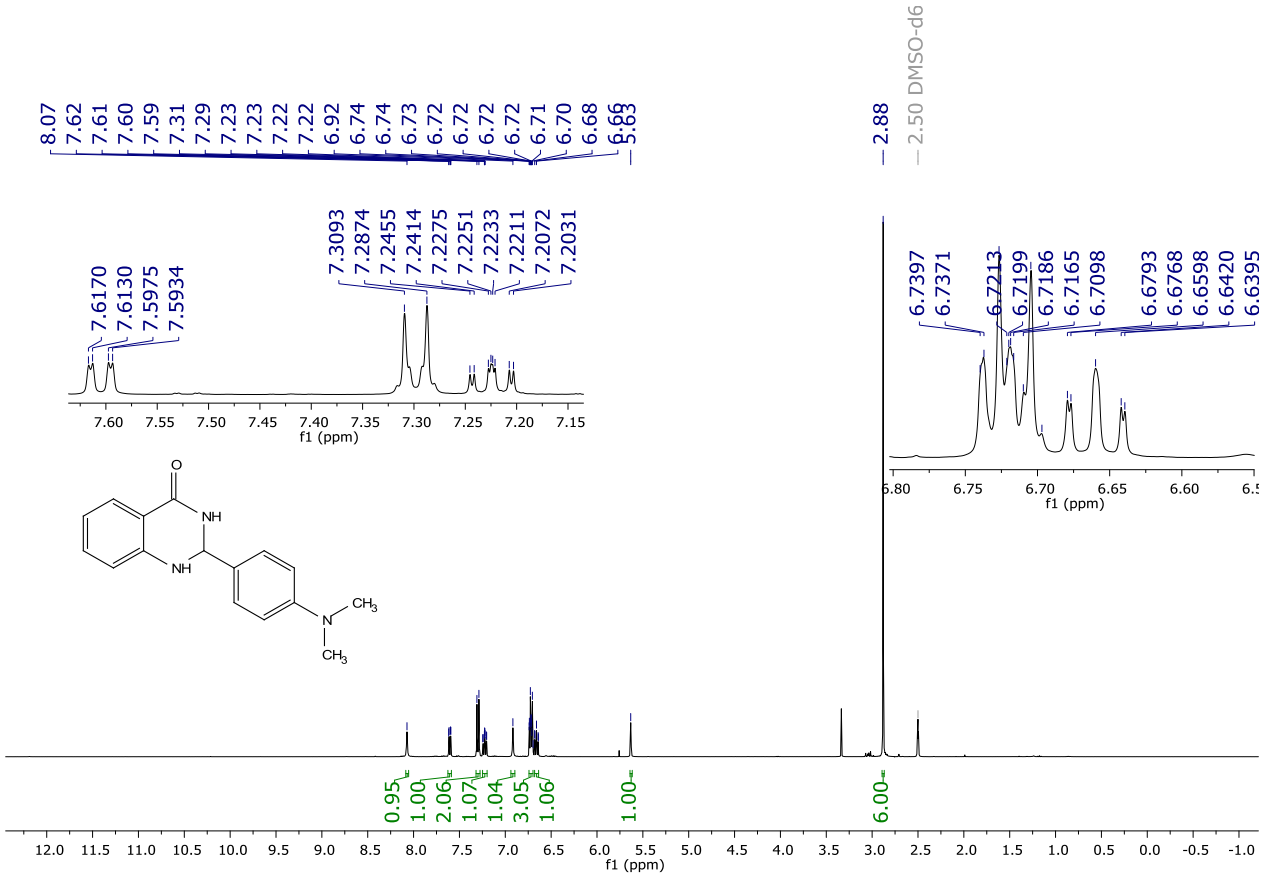
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120m**.



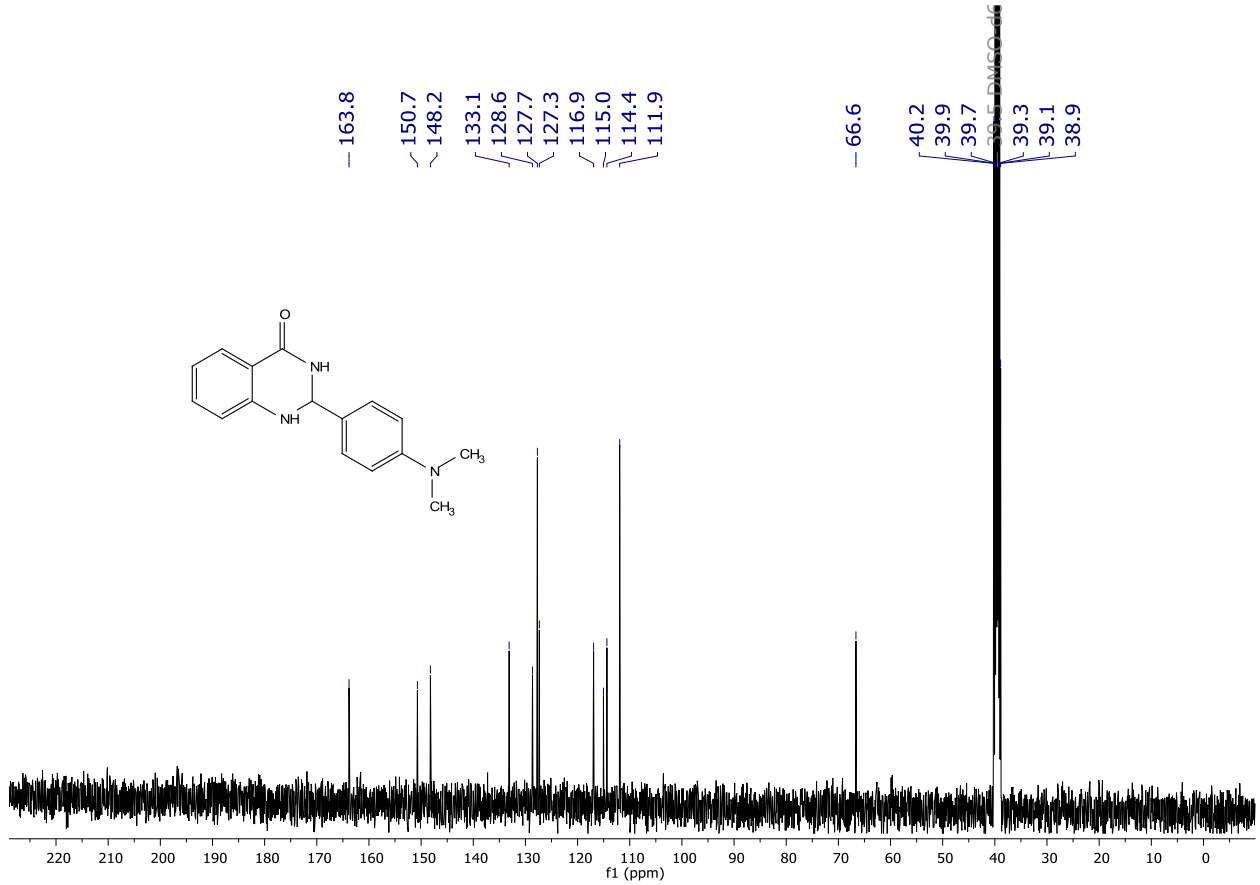
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120n**.



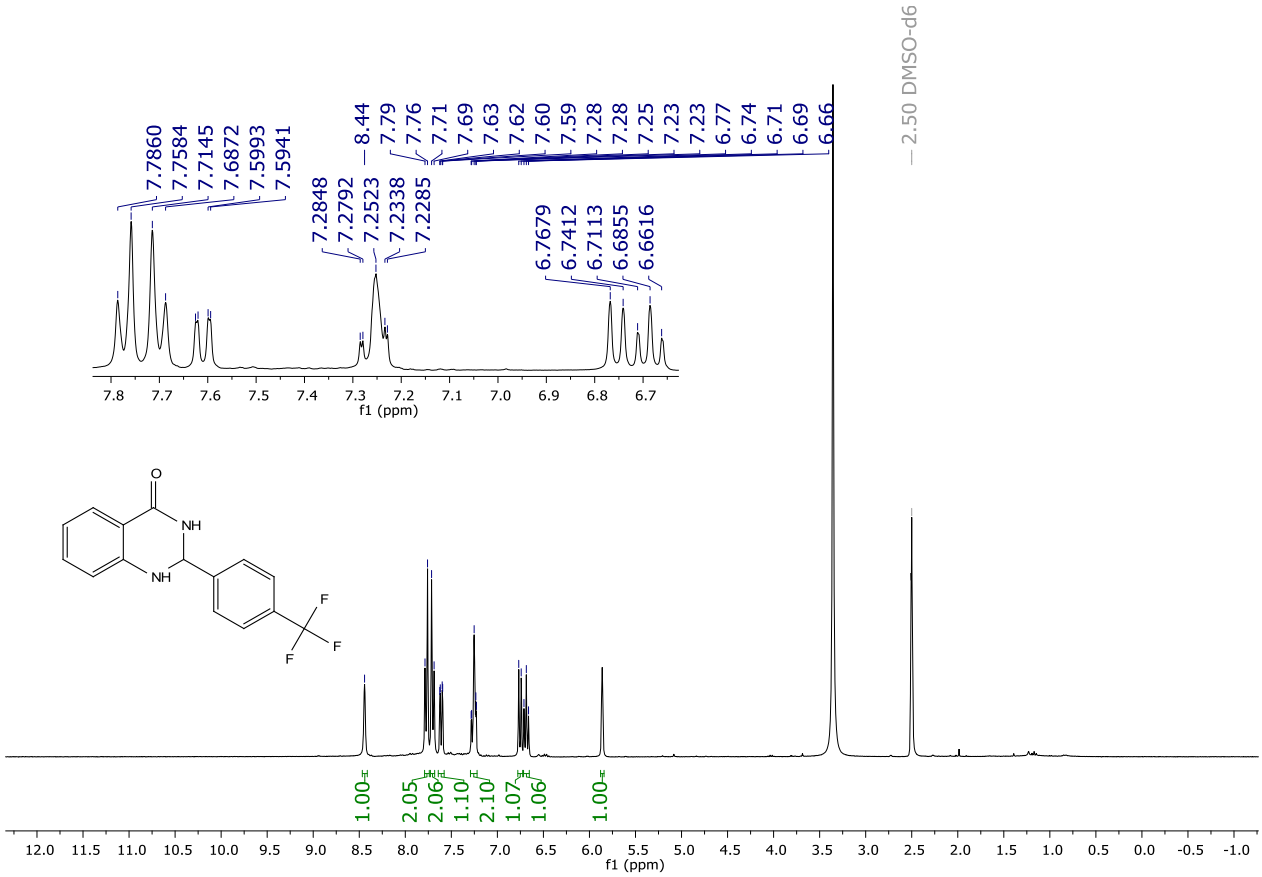
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120n**.



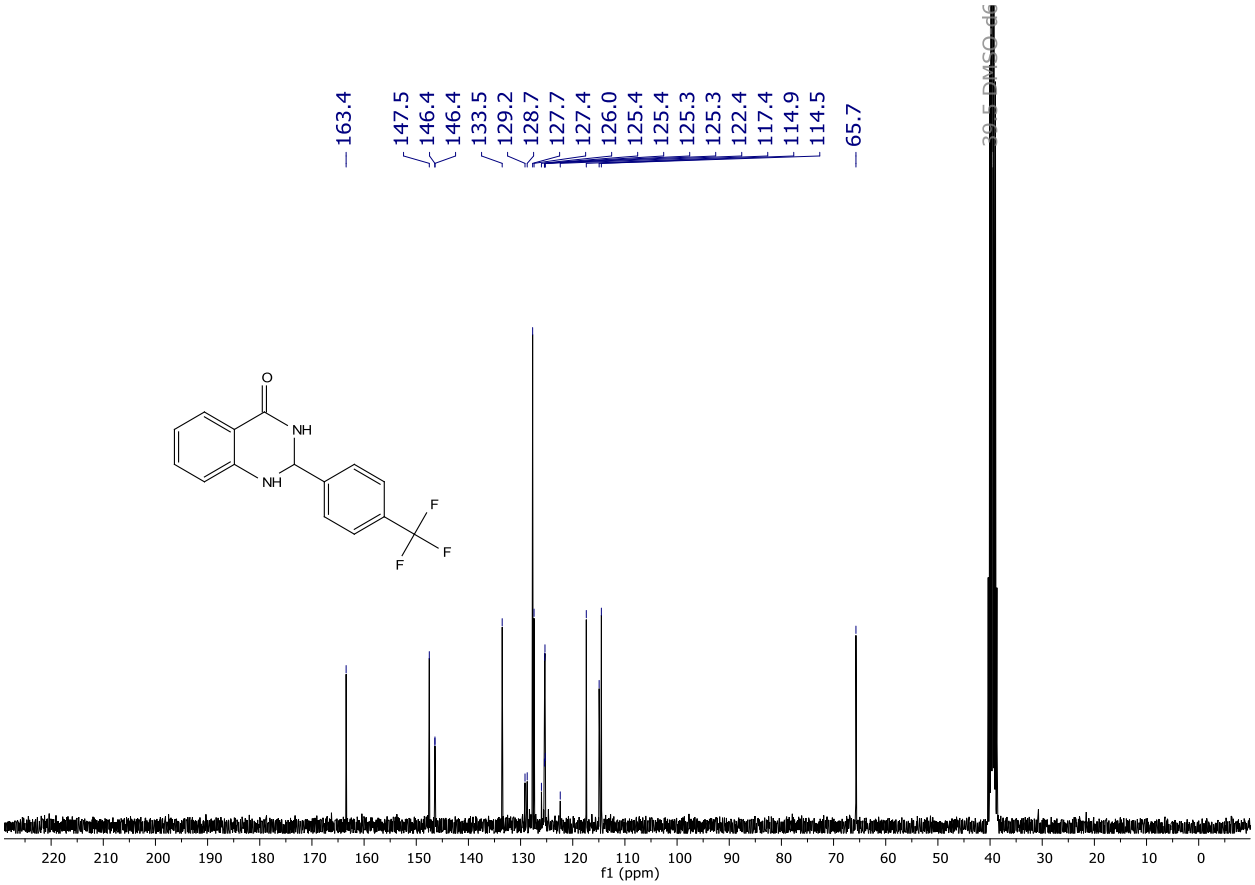
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **120o**.



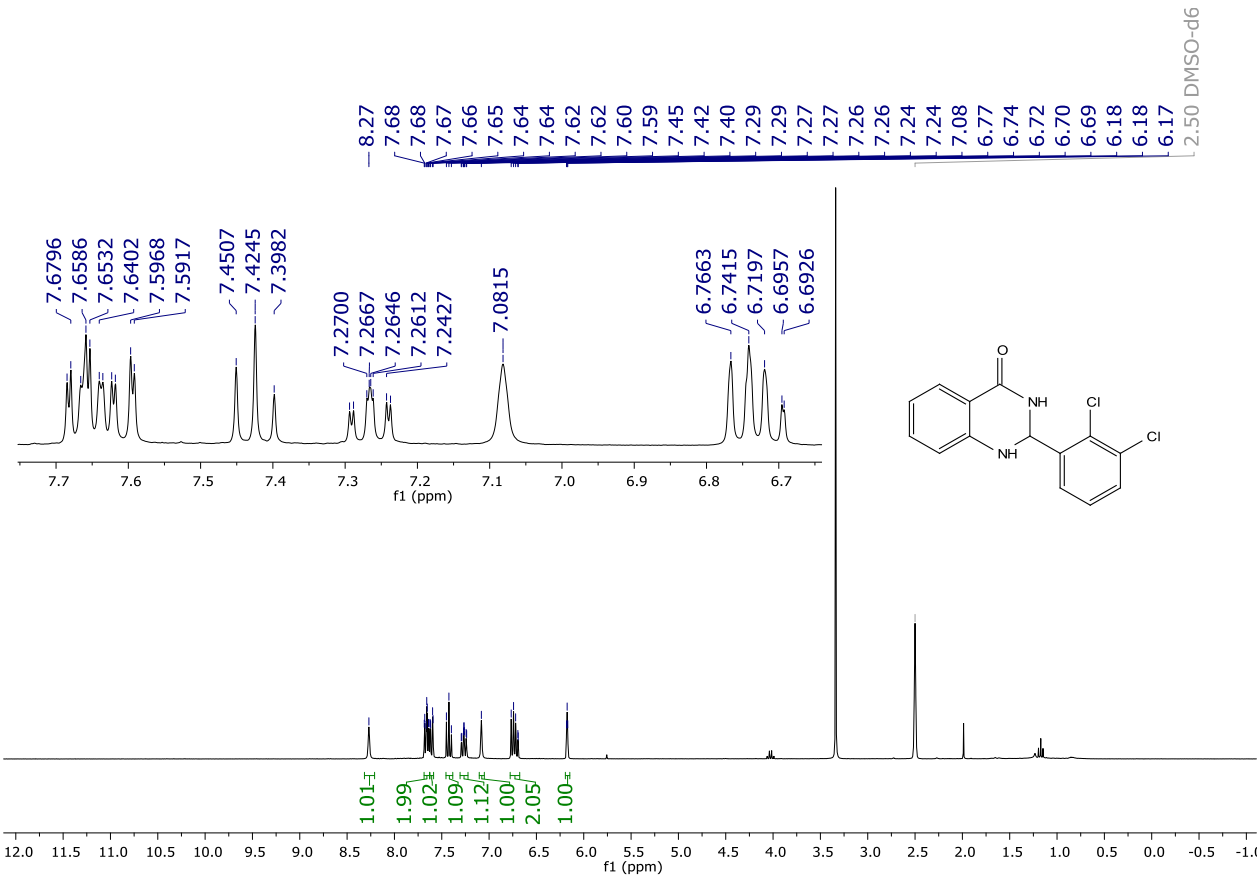
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **120o**.



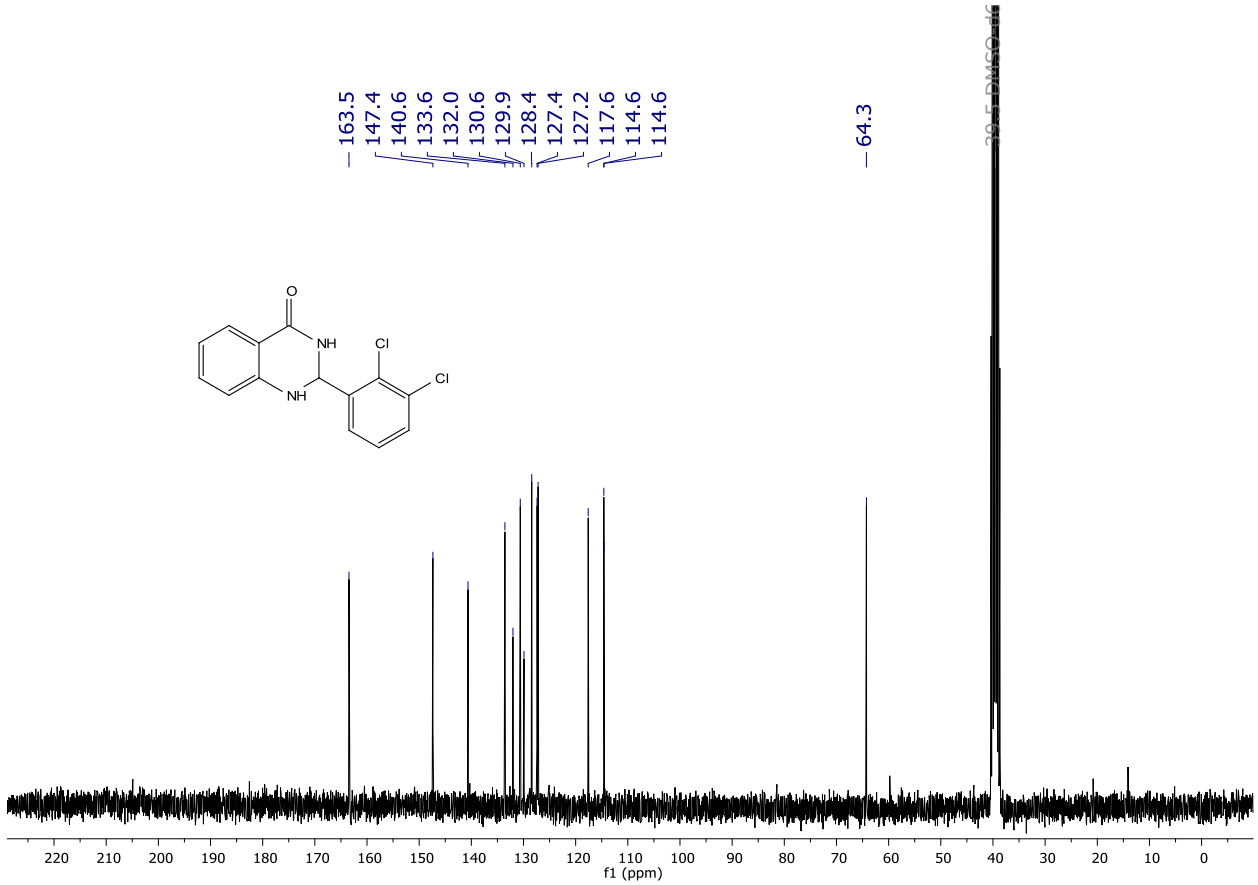
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of **120p**.



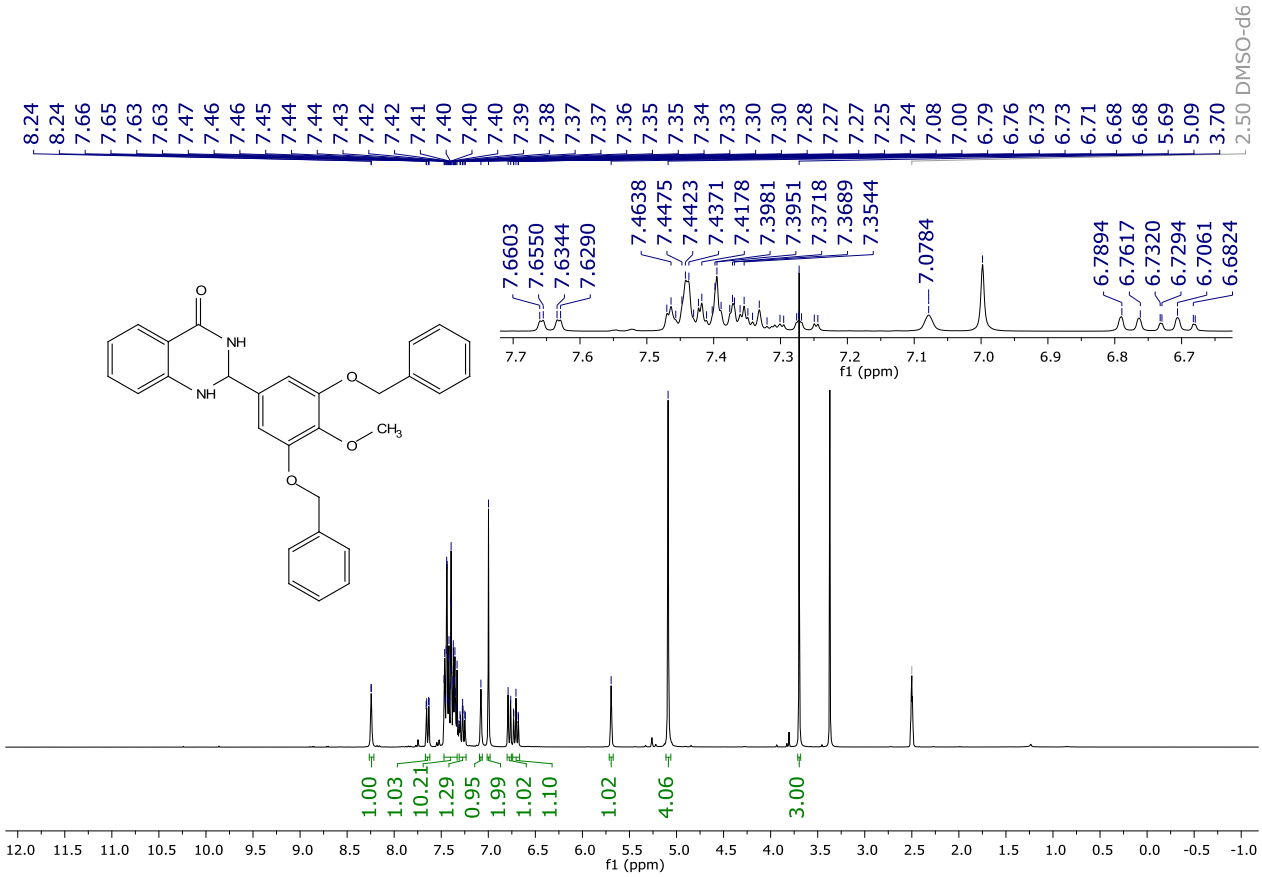
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of **120p**.



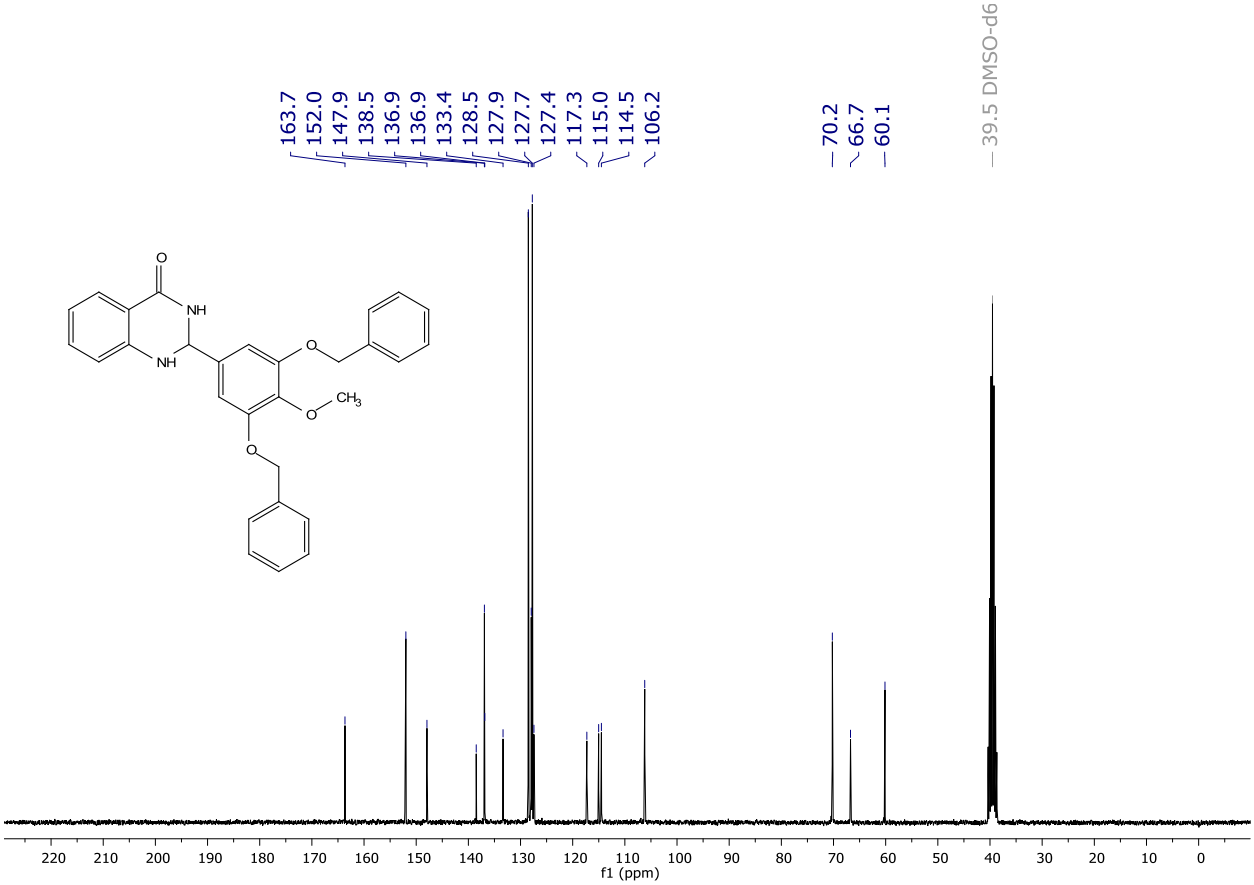
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of **120q**.



^{13}C NMR (75 MHz, DMSO-d_6) spectrum of **120q**.



^{1}H NMR (300 MHz, DMSO-d_6) spectrum of **120r**.



^{13}C NMR (75 MHz, DMSO-d_6) spectrum of **120r**.

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