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Electrophilic monofluoromethylation of O-, S-, N-, P- and Se-nucleophiles with fluoroiodomethane

verfasst von / submitted by

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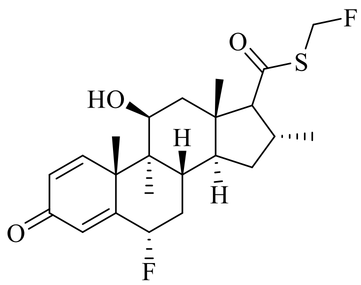
Abstract

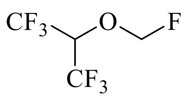
The commercially available fluoroiodomethane has shown to be a valuable electrophilic monofluoromethylating reagent toward O-, S-, N-, P-, and Se-nucleophiles. The excellent manipulability offered by its liquid physical state (bp 52 °C) allows practical and straightforward one-step nucleophilic substitutions under mild basic conditions. The optimized nucleophilic substitution is retaining the embodied chiral information and allowing to overcome the requirement for fluoromethylating agents with no immediate access. Herein, 56 examples, including drugs currently on the market show the accomplishment of the high yielding methodology.

Introduction

The introduction of fluorine atoms in pharmaceutical drugs is of great importance because of their effect on pharmacokinetics and pharmacodynamics. Fluorine atoms can increase the metabolic stability, bioavailability, lipophilicity, enhance membrane permeability as well as increased binding affinity. It is estimated that not less than 20% of all pharmaceutical drugs and 30-40% of agrochemical contain at least one fluorine atom.[1] Herein the successful electrophilic monofluoromethylation of O , S- and N-nucleophiles by using a similar method with chlorofluoromethane is reported.[2] The fluoroiodomethane is used to introduce CH2F residues into O-, S-, N-, P- and Se-nucleophiles. Compared to trifluoro- and difluoromethylation, monofluoromethylation is much less investigated. There are several pharmaceutical drugs that contain tri-, di- and monofluoromethylgroups, two of them bear a CH_2F group. As it can be seen in **Figure 1**, Sevoflurane possesses a RO-CH_2F group and is used as an inhalation anesthetic agent, while Fluticasone contains a RS-CH_2F group and is used as a glucocorticoid. Monofluoracetic acid is an inhibitor of the Krebs cycle. Moreover, [18F] structures are used as PET-diagnostics and fluoromethylated amino acids can be used as suicide inhibitors of decarboxylation reactions. [3]



Fluticasone



Sevoflurane

Figure 1 Chemical structures of Fluticasone and Sevoflurane.

The importance of monofluorination is reflected by the fact of numerous applications in drug discovery research. A research in SciFinder® for the O-, S-, and N-CH_2F moiety limited to pharmaceutical bioindicators gave the following results:

- O-CH_2F: 3107 hits covering 31 indications
- S-CH_2F: 1596 hits covering 29 indications
- N-CH_2F: 872 hits covering 25 indications.

The plethora of hits and indications reflects the importance to develop straightforward synthetic routes to O-, S-, and N-CH_2F derivatives.

In the **Figure 2** several examples of pharmaceutical active compounds containing O-, S-, and N-CH_2F moiety are shown.

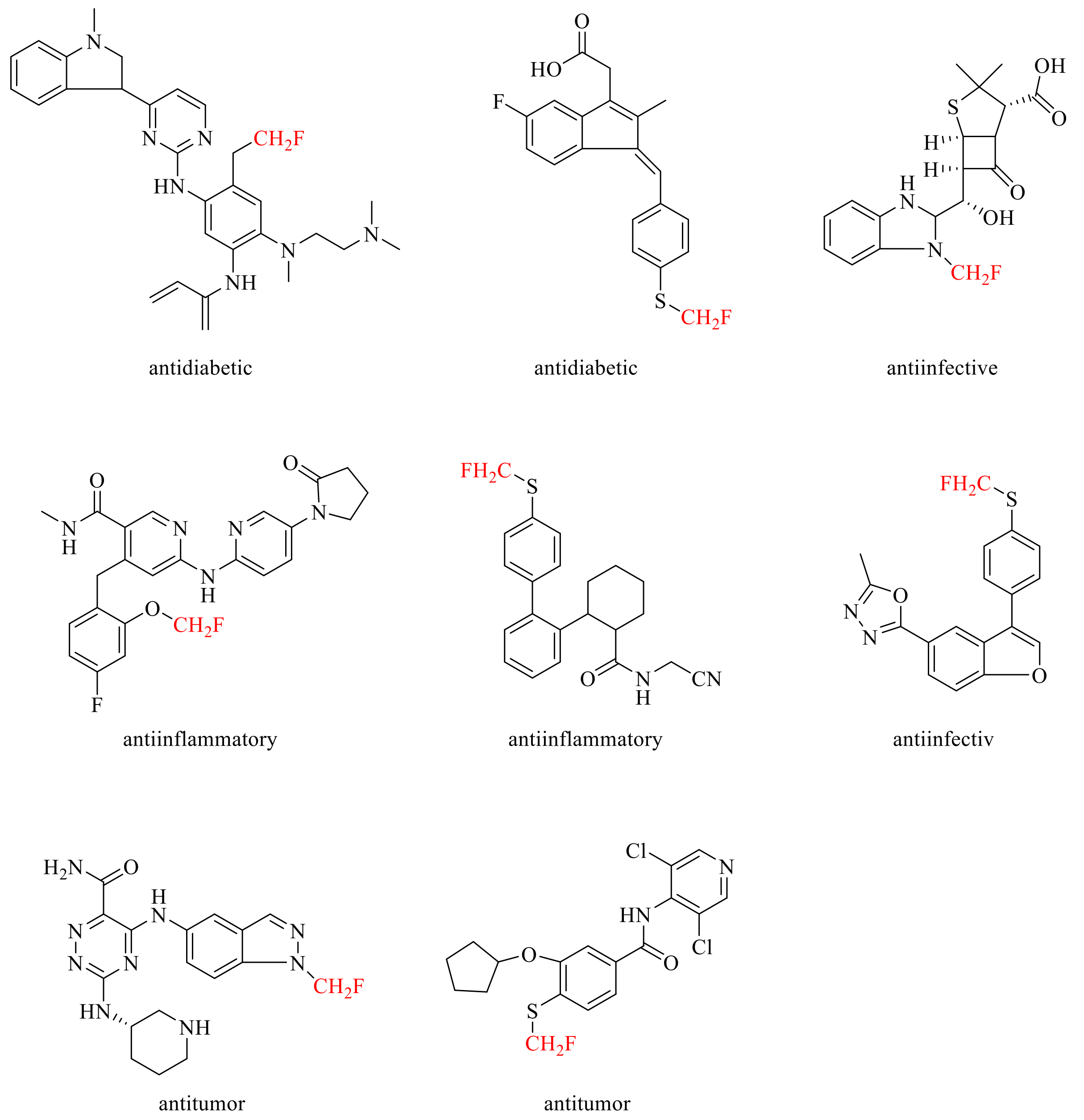


Figure 2 Examples of pharmaceutical active compounds containing O-, S-, and N-CH_2F moiety.

General methods of fluoromethylation

Trifluoromethylation

The selective introduction of Trifluoromethyl (-CF_3) units can be achieved by electrophilic, nucleophilic or free radical trifluoromethylation. Reagents can be the following: trifluoromethane[4], $FSO_2CF_2COOCH_3$ (Chen's reagent)[5], Me_3SiCF_3 (Ruppert-Prakash reagent)[6], hypervalent iodine(III)-CF_3 reagent (Togni´s reagent)[7], trifluoromethylchalcogen salts (such as Umemoto's reagent)[8], CF_3-Johnson reagent and trifluoromethyl iodine (CF_3I).[9]

Difluoromethylation

As well as trifluoromethylation, difluoromethylation can be carried out by electrophilic, nucleophilic or free radical reaction mechanism.

Nucleophilic difluoromethylation reagents such as difluoromethylcadmium, difluoromethylzinc and difluoromethylcopper[10] can be used. Other methods for nucleophilic difluoromethylation are the use of difluoromethylsilane or trifluoromethylsilane reagents[11] or $PhSO_2CFH$[12] and $PhSO_2CF_2Br$[13], as well as $HCF_2PO(OEt)_2$[14] or functionalized difluoromethylsilanes like Me_3SiCF_2H[15].

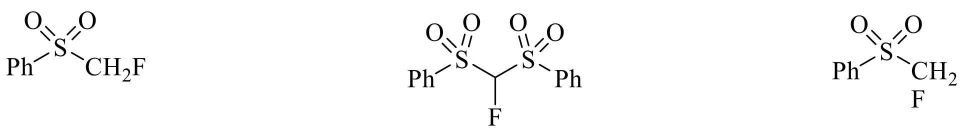
Electrophilic difluoromethylation can be achieved by using chlorodifluoromethane (F_2CHCl) into O-, S-, N-, P-nucleophiles[16]. The principles of this method are the same as in our research. Other methods of electrophilic difluoromethylation are utilizing S-difluoromethylsulfonium salt reagents[17] or Iodine(III)-CF_2SO_2Ph reagents[18].

Radical difluoromethylation can be achieved by using F_2CHI together with $Na_2S_2O_4$.[19] CHF_2Br and CHF_2Cl can be used in a two-step method using CuCl and NaH and $Na_2S_2O_4$.[20] $PhSO_2CF_2I$ reagent can also be used for radical difluoromethylation.[21]

Monofluoromethylation

The nucleophilic monofluoromethylation strategy

The selective nucleophilic monofluoromethylation can basically be realized by a direct transfer of a "CH_2F" moiety or by transfer of a fluorinated group linked to a suitable auxiliary moiety which is cleaved during the reaction. As a consequence, fluoromethyl sulfones, sulfoxidimines and bis (phenylsulfonyl) derivatives were exploited to accomplish nucleophilic monofluoromethylation (**Figure 3**).[22,23,24]



Hu 2006 Shibata, Hu 2006 Hu 2012

Figure 3 Reagents for nucleophilic monofluoromethylation

A suitable route via Mg and Li fluoromethyl carbenoids was only limited successful.

A great step forward was the first direct nucleophilic fluoromethylation strategy from Pace *et al.* **2017** via an intermediate "fleeting" lithium fluorocarbenoid ($LiCH_2F$) (**Figure 4**).[25] For this purpose 1 equiv. of fluoroiodomethane reacted with 2 equiv. of MeLi-LiBr in THF/Et_2O at -78° C with 1.5 equiv. of an electrophile. This strategy impressed by precise reaction conditions with very good yields and the versatility was showcased in more than 50 examples.

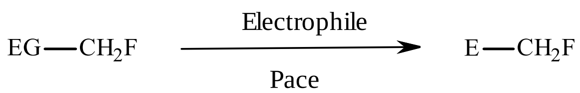


Figure 4 Direct nucleophilic fluoromethylation strategy (Pace et al., 2017).

The electrophilic monofluoromethylation strategy

For a long time, the electrophilic monofluoromethylation was more or less neglected. Since 1985 several methods of electrophilic monofluoromethylation reactions of oxygen-, sulfur-, nitrogen- and carbon-nucleophiles were studied. Nevertheless, results were not reproducible. [26]

The electrophilic monofluoromethylation was further investigated by Jinbo Hu **2007**. It was shown that FCH_2Cl is a versatile starting material and can be exploited to react with O-, S- and N-nucleophiles (**Figure 5**).[2]

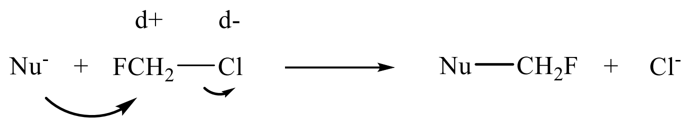


Figure 5 Electrophilic monofluoromethylation with FCH_2Cl.

Nevertheless, a further optimization of the electrophilic pathway of monofluoromethylation seems worthwhile. Especially in face of the successful experiences with fluroiodomethyllithium generated from fluoroiodomethane. It was shown that ICH_2F can easily be converted to fluroiodomethyllithium which gave access to α-fluoroepoxides and aziridines by reaction with carbonyl compounds or imines, respectively (**Figure 6**). The versatility was showcased in more than 30 examples.[27]

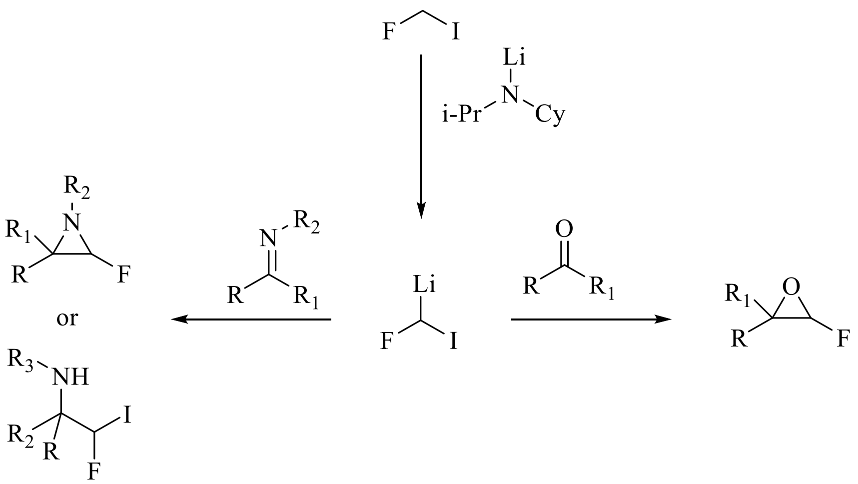


Figure 6 Monofluoromethylation with fluroiodomethyllithium generated from fluoroiodomethane.

As a consequence, the use of fluoroiodomethane to develop a new straightforward strategy for monofluoromethylation should be studied (**Figure 7**).

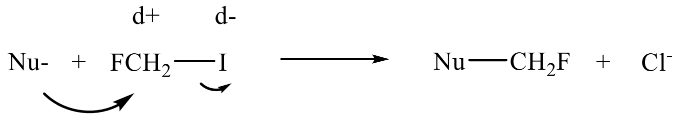


Figure 7 Monofluoromethylation with fluoroiodomethane.

Use of fluoroiodomethane

In the **Figure 8** wide range of applications of fluoroiodomethane in the case of reaction groups are shown.

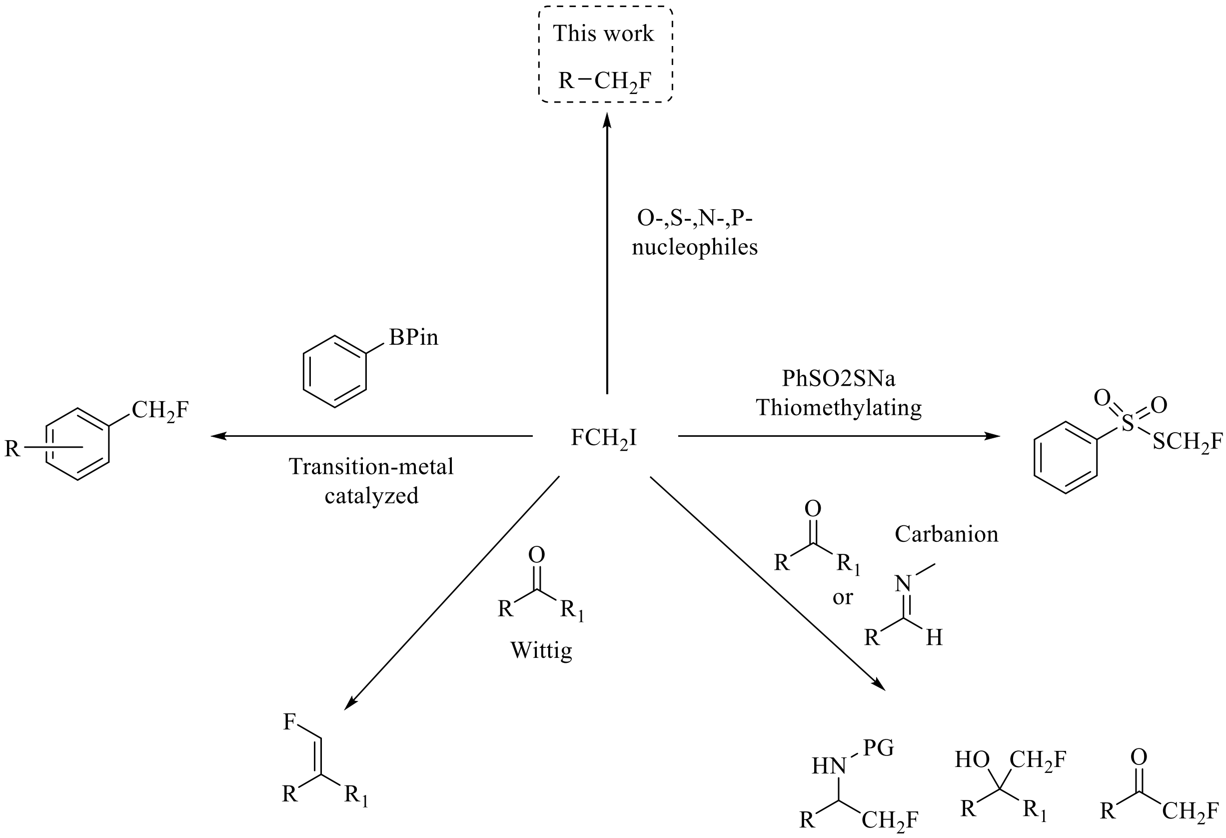


Figure 8 Possible application of fluoroiodomethane.

Results and Discussion

The reaction was performed on 1 mmol starting material in 2 mL of anhydrous acetonitrile. 1.2 equivalents of $CsCO_3$ were added and the reaction mixture was stirred under argon atmosphere at room temperature. After dropwise addition of 1.2 equivalents of ICH_2F the reaction was set for 6 hours before quenching with H_2O.

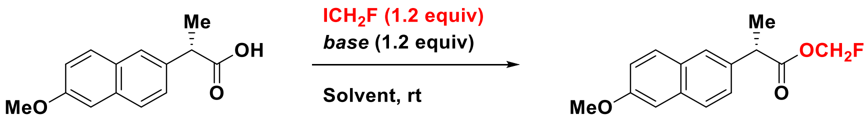
The product as well as the staring material were extracted from the water phase using diethyl ether. To remove the starting material a separating funnel was used and the organic phase was washed with 1N NaOH and brine. The fact that only the starting material gets deprotonated in basic condition and therefore moves into the water phase was exploited to enhance and facilitate work progress. A time consuming purification by column is not needed, therefore only small amounts of solvents are used, which is contributing to an ecofriendly work.

Further advantages of the method are the simple and mild reaction conditions, high yields and a broad spectrum of available nucleophiles.

Optimization

Yield ratio was examined on nonsteroidal anti-inflammatory drug Naproxen and results of optimization are shown in the **Table 1**. Polar aprotic solvents performed reasonably well under basic conditions. The presence of a base is playing a vital role. Reactions performed in the presence of NaH resulted in incomplete conversion and perceptible racemization regardless of the solvent (DMF or THF, entries 2-3). The use of Cs_2CO_3 led to a higher yield and enantiomeric ratio. The use of KF Celite25 led to a slower reaction rate. The combination of acetonitrile and Cs_2CO_3 showed to be the ideal combination for optimizing the process and allowing a completion within 6 h without any erosion of the optical purity.

Table 1 Model reactions and optimization parameters[a] of the reaction.



1
(S)-Naproxen

(*S*)-2

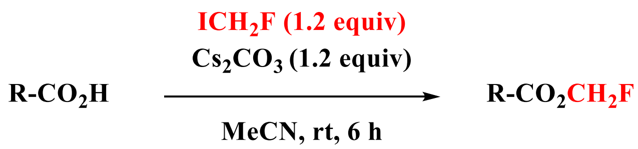
Entry	Solvent	Base	Reaction time (h)	Yield of (*S*)-2 (%)[b]	*er* of (*S*)-2
1	DMF	-	24	traces	-
2	DMF	NaH	6	71	95:5
3	THF	NaH	6	64	94:6
4	DMF	CsF	6	86	97:3
5	DMF	Cs_2CO_3	6	90	97:3
6	DMF	KF-Celite	12	72	96:4
7	MeCN	CsF	6	91	98:2
8	MeCN	KF-Celite	8	78	97:3
9	***MeCN***	***Cs_2CO_3***	***6***	***97***	***>99:1***
10[c]	MeCN	Cs_2CO_3	4	98	>99:1
11[d]	MeCN	Cs_2CO_3	6	95	>99:1
12	MeCN	DIPEA	12	61	98:2

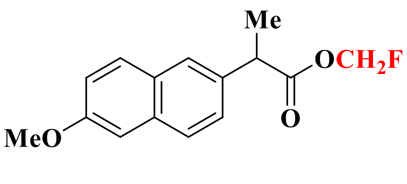
[a]Unless otherwise stated stated, a ratio of (***S***)-**1**:ICH_2F:base = 1:1.2:1.2 was employed. [b]Isolated yield. [c]ICH_2F (2.4 equiv.), Cs_2CO_3 (2.4 equiv.). [d]Reaction run at 10 mmol scale.

Stereoselectivity

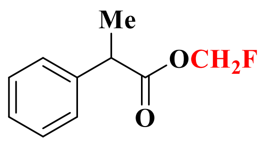
To investigate stereoselectivity of the method the scope of fluoromethylation on carboxylic acids was studied (**Scheme 1**). The full preservation of the optical purity was confirmed in the cases of α-substituted phenylacetic acid derivatives (3-4), other common anti-inflammatory agents underwent the transformation very efficiently as well: ibuprofen (5), acetylsalicylic acid (aspirin, 6) and indomethacin (7).

Scheme 1 Fluoromethylation of carboxylic acids.

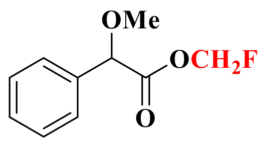




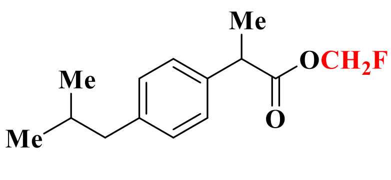
(*S*)-2 (97%, *er* > 99:1)
***rac*-2** (95%)
from Naproxen
(anti-inflammatory)



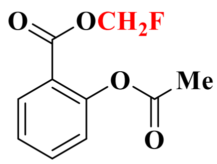
(*R*)-3 (94%, *er* > 99:1)
***rac*-3** (96%)



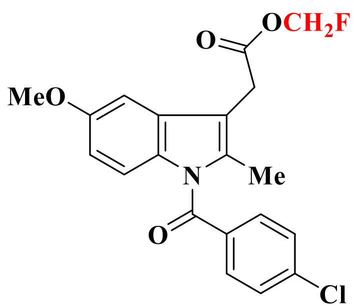
(*R*)-4 (91%, *er* > 99:1)
***rac*-4** (94%)



5 (94%)
from Ibuprofen
(anti-inflammatory)



6 (96%)
from Acetylsalicylic acid
(anti-inflammatory)



7 (93%)
from Indometacin
(anti-inflammatory)

The stereoselectivity was investigated on HPLC system (Shimazu, Japan) using a Chiralpak IG column (Daicel Group) at following conditions: λ = 254 nm, n-hexane:iso-propanol 99:1 (v:v) as eluent and at flow rate 1 mL/min. Results of chromatographic run for 2-phenylpropionic acid as racemate is shown in **Figure 9** and **Table 2**.

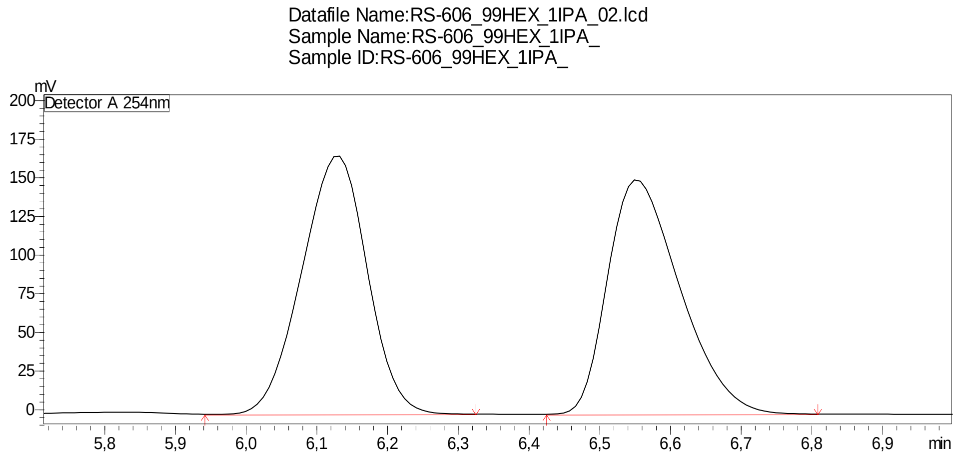


Figure 9 Chromatogram of 2-phenylpropionic acid – racemate.

Table 2 Results of chromatographic run for 2-phenylpropionic acid – racemate.

Peak	**Retention time**	**Area**	**Area %**
1	6.130	1074248	49.914
2	6.553	1077934	50.086
Total		2152182	100.000

Results of chromatographic run for 2-phenylpropionic acid as enantioenriched is shown in **Figure 10** and **Table 3**.

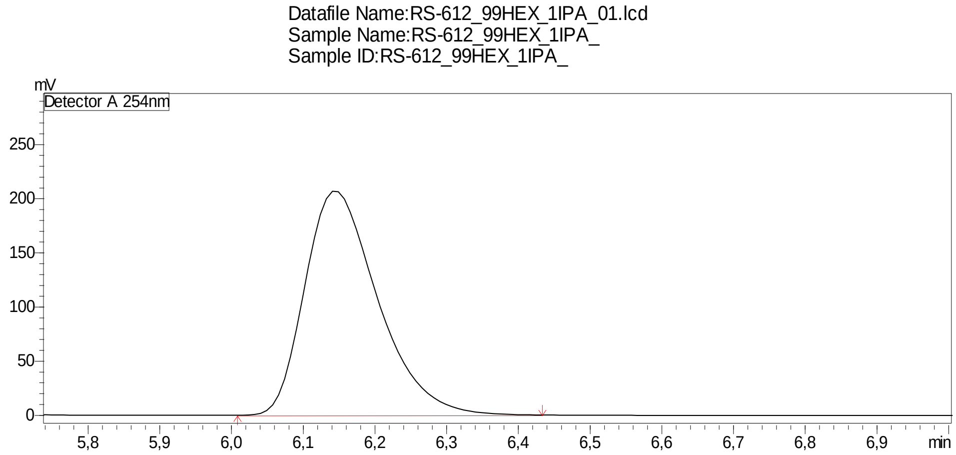


Figure 10 Chromatogram of 2-phenylpropionic acid – enantioenriched.

Table 3 Results of chromatographic run for 2-phenylpropionic acid – enantioenriched.

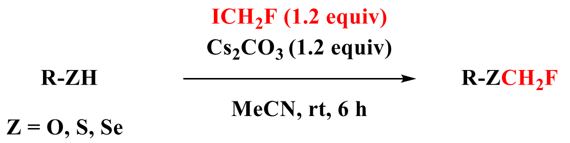
Peaks	Retention time	Area	Area %
1	6.145	1463296	100.000
Total		1463296	100.000

Fluoromethylation of O-, S-, and Se- nucleophiles

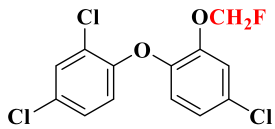
The optimized method was also investigated on a series of aromatic alcohols[28] substituted with various functional groups: halogens (8-10), ester (11), nitrile (12), ethers, ketones (13-15) and aldehydes (16-17) (**Scheme 2**). Particularly, sterically hindered (18) and (hetero)polyaromatic systems acted as competent partners for the reaction, as well as, an allyl presenting phenol (21). The method shows a clear chemoselective discrimination on the reactivity towards aromatic and aliphatic alcohols, the latter remained untouched (22-23). Attempts to perform the double fluoromethylation on both alcohol functionalities in the presence of stronger bases (KH or NaH in DMF or THF) resulted in complex mixtures. Furthermore, pyrazol-5-ones, known to manifest tautomerization phenomena to the corresponding alcoholic-forms[29], could be similarly employed for preparing fluoromethylethers, including the analogue (24) derived from the anti amyotropic lateral scelerosis (ALS) agent edavarone. Substitution across the pyrazole nucleus was uniformly permitted (25-32), being the ester- (28), ketone- (30-31) and cinnamoyl- (32) bearing systems as representative examples.

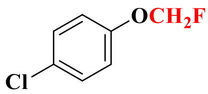
Sulfur-centered nucleophiles showed full flexibility on the reaction conditions[30], including a smooth access to the steroidal agent fluticasone (33). Thiophenol derivates (34-39) and heteroaromatic mercaptanes (41-43) reacted comparable to the aromatic alcohols discussed above. Excess of FIM and Cs_2CO_3 enabled the double functionalization on both oxygen and sulfur sites of thiosalicylic acid (45). This method proved to be modular as indicated by the synthesis of a selenium derivative (46), previously prepared through a complex sequence involving aniline diazotization – conversion into organoselenocyanate – formation of a diselenide and, finally transfer of a RSe- anion to FIM.[31]

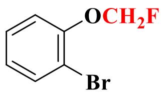
Scheme 2 Fluoromethylation of O-, S-, and Se- nucleophiles.

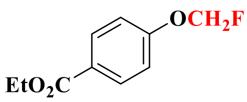


Aromatic alcohols







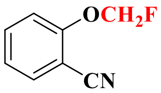


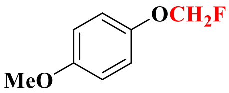
8 (96%)
from Triclosan
(antibacterial - antifungal)

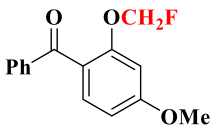
9 (92%)

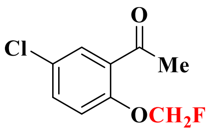
10 (95%)

11 (97%)







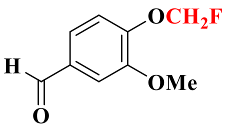


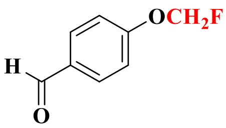
12 (94%)

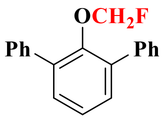
13 (97%)

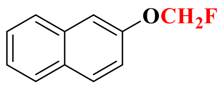
14 (92%)

15 (90%)







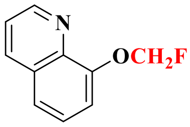


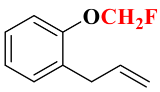
16 (96%)

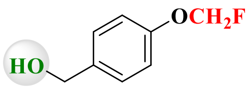
17 (95%)
10 mmol scale (91%)

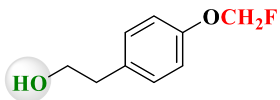
18 (91%)

19 (90%)









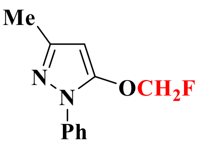
20 (88%)

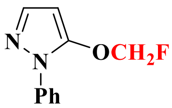
21 (85%)

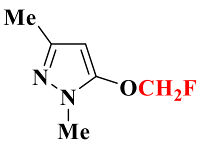
22 (96%)

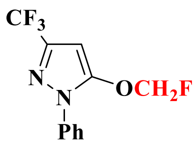
23 (98%)

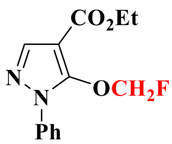
Heteroaromatic alcohols











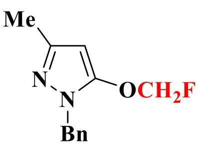
24 (91%)
from Edavarone
(used in ALS treatment)

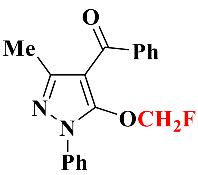
25 (87%)

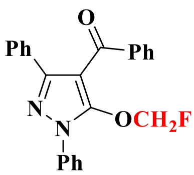
26 (88%)

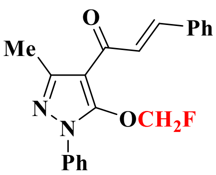
27 (90%)

28 (92%)









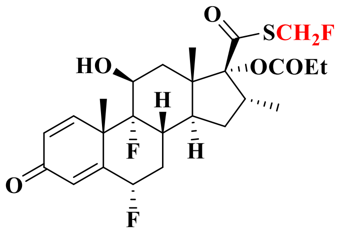
29 (88%)

30 (90%)

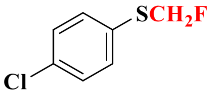
31 (95%)

32 (96%)

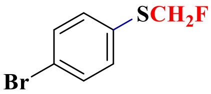
Sulfur / Selenium



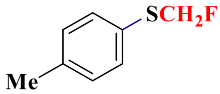
33 (82%)
Fluticasone propionate
(anti-asthmatic)
from thiocarboxylic acid



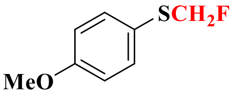
34 (86%)



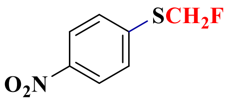
35 (91%)



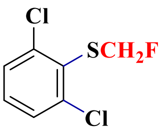
36 (89%)



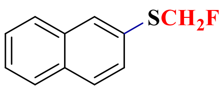
37 (96%)
15 mmol scale (92%)



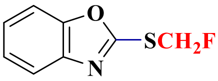
38 (97%)



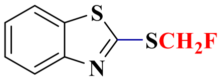
39 (93%)



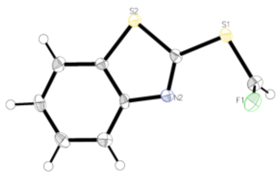
40 (93%)



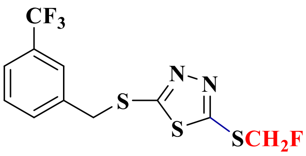
41 (92%)



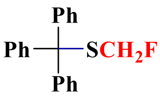
42 (94%)



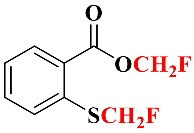
42 (CCDC 1971864)



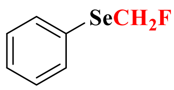
43 (90%)



44 (88%)



45 (97%)[a]



46 (77%)
from Ph-selenol

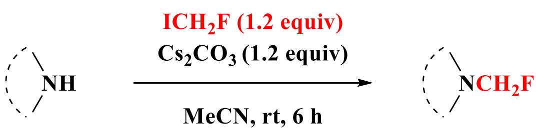
[a] ICH_2F (2.4 equiv), Cs_2CO_3 (2.4 equiv).

Fluoromethylation of N- and P-nucleophiles

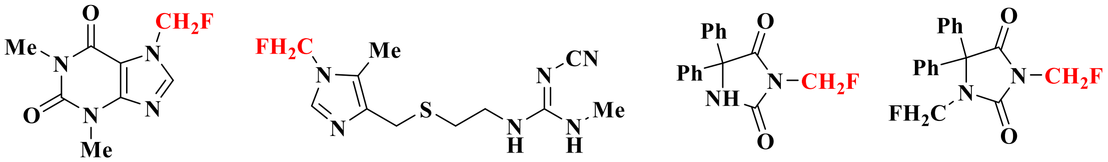
To expand the range of nucleophilic groups, the technique on medicinally important nitrogenated heterocycles was performed (**Scheme 3**). The purin base stimulant drug theophylline (47) or the prototypal histaminic-H_2 antagonist cimetidine were selectively fluoromethylated at positions 7 and 1 while the guanidine position remained untouched. Phenytoin, an anti-convulsant and class IB antiarrhythmic agent underwent mono- (49) or bis-monofluoromethylation (50) on the hydantoinic nucleus depending on the stoichiometry. Furthermore, the nitrogen atoms of imidazole, 4(1H)-quinolinone, indazole, and phthalimide represented excellent linchpins for introducing the CH_2F moiety.

To further expanding the scope of substrates suitable for this simple operation, the fluoromethylation of di-n-butylphosphine oxide (55) was also achieved in a satisfying yield.

Scheme 3 Fluoromethylation of N- and P-Nucleophiles.



Nitrogen

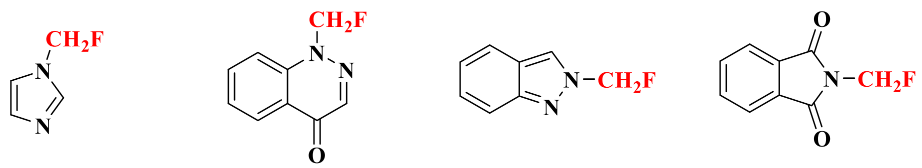


47 (96%)
from Theophylline
(anti-asthmatic)

48 (85%)
from Cimetidine
(anti-ulcer)

49 (87%)
from Phenytoin
(anti-epileptic)

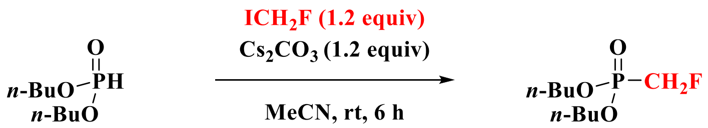
50 (92%)[a]
from Phenytoin
(anti-epileptic)



51 (83%) **52** (94%) **53** (91%) **54** (82%)

[a] ICH_2F (2.4 equiv), Cs_2CO_3 (2.4 equiv).

Phosphorus



55 (70%)

Conclusion

FIM has proven to be a suitable reagent for a convenient and effective transfer of heteroatom-centered nucleophiles under mild basic conditions. The commercially available FIM and the often chromatographic free protocol is suitable for derivatizing a wide range of common chemical functionalities including routinely used drugs.

Convincing features of this uniformly high-yielding and general methodology can be summarized as follows:

(1) remarkable stability of sensitive groups (including challenging carbonyls, ester, guanidine, amide, nitro, nitrile groups, inter alia) under these conditions

(2) complete retention of the stereochemical information contained in optically active drugs.

The results of this Master thesis were part of the following publication:

Direct and Chemoselective Electrophilic Monofluoromethylation of Heteroatoms (O-, S-, N-, P-, Se-) with Fluoroiodomethane, Organic Letters 2020, 22, 1345-1349, Raffaele Senatore, Monika Malik, Markus Spreitzer, Wolfgang Holzer and Vittorio Pace*

Instrumentation and General Analytical Methods

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Bruker maXis 4G instrument (ESI-TOF, HRMS). ^{1}H, ^{13}C, ^{19}F, ^{15}N and ^{77}Se NMR spectra were recorded with a Bruker Avance III 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 376 MHz for ^{19}F, 40 MHz for ^{15}N and 76 MHz for ^{77}Se) at 298 K using a directly detecting broadband observe (BBFO) probe. The center of the (residual) solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H in $CDCl_3$), 7.16 ppm (^{1}H in C_6D_6), 2.05 ppm (^{1}H in acetone-d_6), 2.49 ppm (^{1}H in DMSO-d_6) and δ 77.0 ppm (^{13}C in $CDCl_3$), 128.06 (^{13}C in C_6D_6), 29.84 (^{13}C in acetone-d_6), 39.5 ppm (^{13}C in DMSO-d_6). ^{19}F NMR spectra were referenced via the Ξ ratio (absolute referencing). ^{15}N NMR spectra (gs-HMBC, gs-HSQC) were referenced against neat, external nitromethane. ^{77}Se NMR spectra were referenced against diphenyldiselane (δ Ph_2Se_2 463 ppm). Spin-spin coupling constants (*J*) are given in Hz.

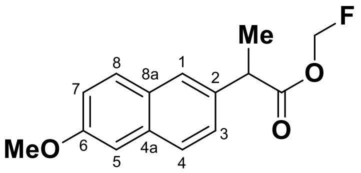
In nearly all cases, full and unambiguous assignment of all resonances was performed by combined application of standard NMR techniques, such as APT, HSQC, HMBC, HSQCTOCSY, COSY and NOESY experiments.

Fluoroiodomethane was supplied by ABCR Germany. Other chemicals were purchased from SigmaAldrich, Acros, Alfa Aesar and TCI Europe. Solutions were evaporated under reduced pressure with a rotary evaporator.

TLC was carried out on aluminium sheets precoated with silica gel 60F254 (Merchery-Nagel, Merk); the spots were visualised under UV light (λ = 254 nm) and/or $KMnO_4$ (aq.) was used as revealing system.

Characterization and Spectral Data of the Compounds

Fluoromethyl 2-(6-methoxy-2-naphthyl)propanoate (2)



By following the general procedure, starting from (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionic acid ((*S*)-naproxen) (0.230 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **2** was obtained in 97% yield (0.254 g) as a white solid.

The corresponding racemic sample has been prepared starting from racemic 2-(6-methoxy-2-naphthyl)propionic acid (naproxen) and spectroscopic data match with those ones reported below.

Scaling-up of the reaction (10 mmol) - By following the general procedure, starting from (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionic acid ((*S*)-naproxen) (2.30 g, 10.0 mmol, 1.0 equiv), Cs_2CO_3 (3.91 g, 12.0 mmol, 1.2 equiv) and fluoroiodomethane (1.92 g, 12.0 mmol, 1.2 equiv) in dry acetonitrile (20 mL), compound **2** was obtained in 95% yield (2.49 g) as a white solid. *Spectroscopic and spectrometric data match with those reported for the 1.0 mmol scale reaction.*

mp: 72 °C

^{1}H NMR (400 MHz, C_6D_6): δ 7.54 (d, ^3J = 8.5 Hz, 1H, Naph H-4), 7.52 (d, ^4J = 1.9 Hz, 1H, Naph H-1), 7.46 (d, ^3J = 8.9 Hz, 1H, Naph H-8), 7.33 (dd, ^3J = 8.5 Hz, ^4J = 1.9 Hz, 1H, Naph H-3), 7.15 (dd, ^3J = 8.9 Hz, ^4J = 2.6 Hz, 1H, Naph H-7), 6.89 (d, ^4J = 2.6 Hz, 1H, Naph H-5), 5.27 (m, $^2J_{H,F}$ = 50.9 Hz, 1H, CH_2F), 5.10 (m, $^2J_{H,F}$ = 50.9 Hz, 1H, CH_2F), 3.62 (q, ^3J = 7.1 Hz, 1H, CH), 3.38 (s, 3H, OCH_3), 1.42 (d, ^3J = 7.1 Hz, 3H, CH_3).

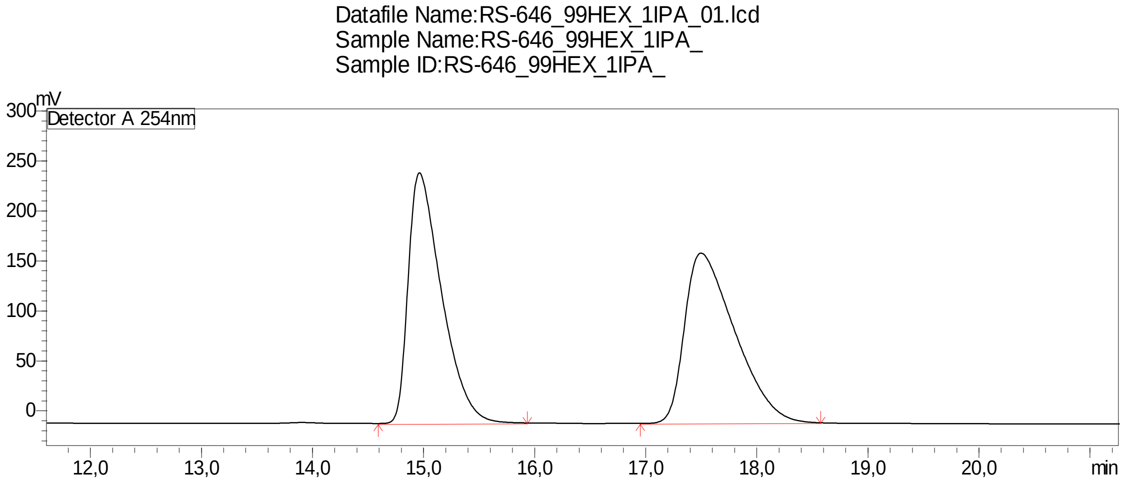
^{13}C NMR (100 MHz, C_6D_6): δ 172.7 (C=O), 158.4 (Naph C-6), 135.1 (Naph C-2,C-8a), 134.5 (Naph C-4a), 129.7 (Naph C-8), 127.7 (Naph C-4), 126.7 (Naph C-1), 126.3 (Naph C-3), 119.6 (Naph C-7), 105.9 (Naph C-5), 93.5 (d, $^1J_{C,F}$ = 220.0 Hz, CH_2F), 54.8 (OCH_3), 45.5 (CH), 18.4 (CH_3).

^{19}F NMR (376 MHz, C_6D_6): δ –156.9 (t, $^2J_{H,F}$ = 50.9 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{15}H_{16}FO_3$. 263.1078; found: 263.1085.

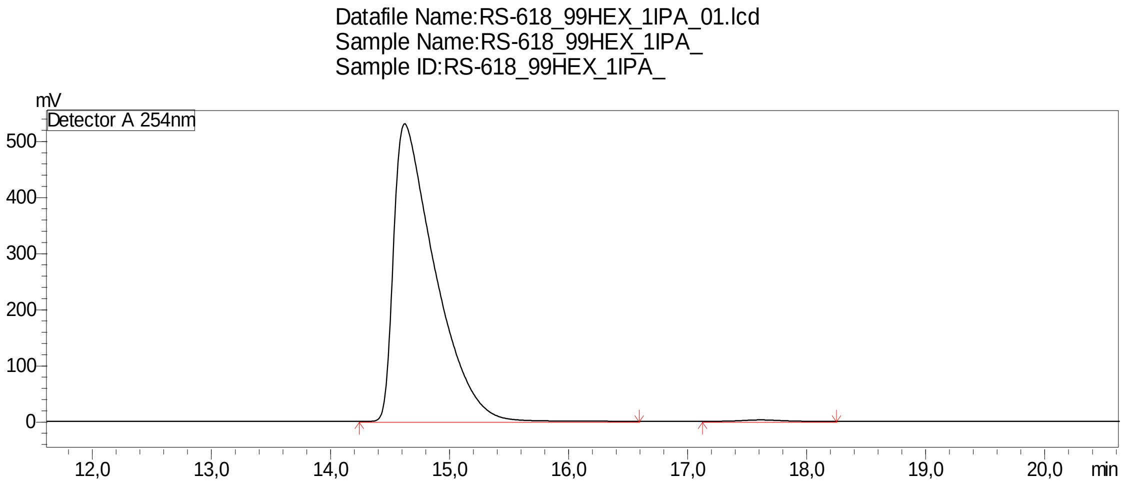
HPLC analysis: Chiralpak IG Column, λ 254 nm, eluent: *n*-hexane / *i*-propanol 99:1. Flow: 1 mL/min.

Racemate



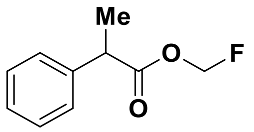
Peaks	Ret.T	Area	Area %
1	14,970	5228612	49,514
2	17,506	5331301	50,486
Total		10559913	100,000

Enantioenriched



Peaks	Ret.T	Area	Area %
1	14,630	12763124	99,589
2	17,622	52687	0,411
Total		12815811	100,000

Fluoromethyl hydratropate (3)



By following the general procedure, starting from (*R*)-2-phenyl-propionic acid (0.150 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **3** was obtained in 94% yield (0.171 g) as a colorless oil.

The corresponding racemic sample has been prepared starting from racemic 2-phenyl-propionic acid and spectroscopic data match with those ones reported below.

^{1}H NMR (400 MHz, C_6D_6): δ 7.11 (m, 2H, Ph H-2,6), 7.07 (m, 2H, Ph H-3,5), 7.01 (m, 1H, Ph H-4), 5.20 (dd, $^{2}J_{H,F}$ = 50.8 Hz, ^{2}J = 2.0 Hz, 1H, CH_2F), 5.01 (dd, $^{2}J_{H,F}$ = 51.0 Hz, ^{2}J = 2.0 Hz, 1H, CH_2F), 3.41 (q, ^{3}J = 7.1 Hz, 1H, CH), 1.29 (d, ^{3}J = 7.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 172.4 (d, $^{3}J_{C,F}$ = 1.6 Hz, C=O), 140.1 (Ph C-1), 129.0 (Ph C-3,5), 127.8 (Ph C-2,6), 127.6 (Ph C-4), 93.4 (d, $^{1}J_{C,F}$ = 220.1 Hz, CH_2F), 45.5 (CH), 18.4 (CH_3).

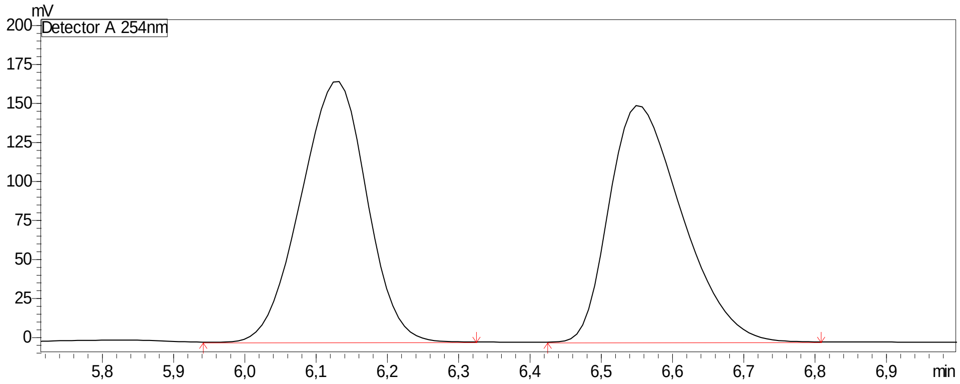
^{19}F NMR (376 MHz, C_6D_6): δ –157.1 (t, $^{2}J_{H,F}$ = 50.9 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{10}H_{12}FO_2$: 183.0816; found: 183.0818.

HPLC analysis: Chiralpak IG Column, λ 254 nm, eluent: *n*-hexane / *i*-propanol 99:1. Flow: 1 mL/min

Racemate

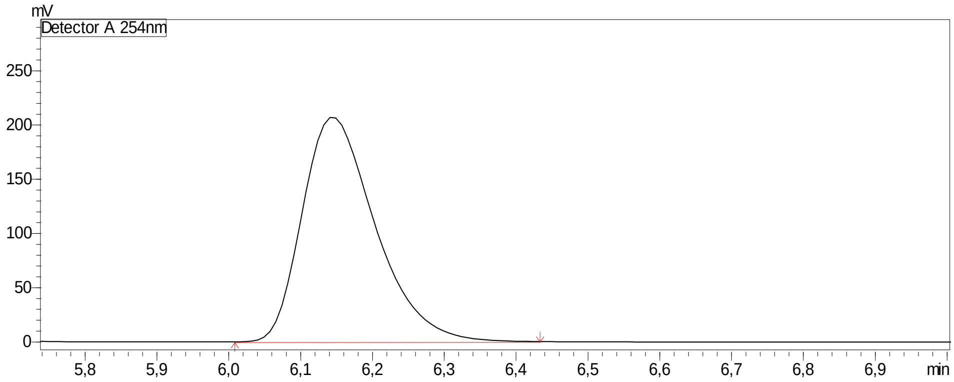
Datafile Name:RS-606_99HEX_1IPA_02.lcd
Sample Name:RS-606_99HEX_1IPA_
Sample ID:RS-606_99HEX_1IPA_



Peaks	Ret.T	Area	Area %
1	6,130	1074248	49,914
2	6,553	1077934	50,086
Total		2152182	100,000

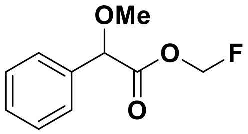
Enantioenriched

Datafile Name:RS-612_99HEX_1IPA_01.lcd
Sample Name:RS-612_99HEX_1IPA_
Sample ID:RS-612_99HEX_1IPA_



Peaks	Ret.T	Area	Area %
1	6,145	1463296	100,000
Total		1463296	100,000

Fluoromethyl methoxy(phenyl)acetate (4)



By following the general procedure, starting from (*R*)-(−)-α-Methoxyphenylacetic acid (0.166 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **4** was obtained in 91% yield (0.180 g) as a colorless oil.

The corresponding racemic sample has been prepared starting from racemic methoxy(phenyl)acetic acid and spectroscopic data match with those ones reported below.

^{1}H NMR (400 MHz, C_6D_6): δ 7.42 (m, 2H, Ph H-2,6), 7.09 (m, 2H, Ph H-3,5), 7.04 (m, 1H, Ph H-4), 5.17 (m, 1H, CH_2F), 5.05 (m, 1H, CH_2F), 4.58 (s, 1H, CH), 3.10 (s, 3H, OCH_3).

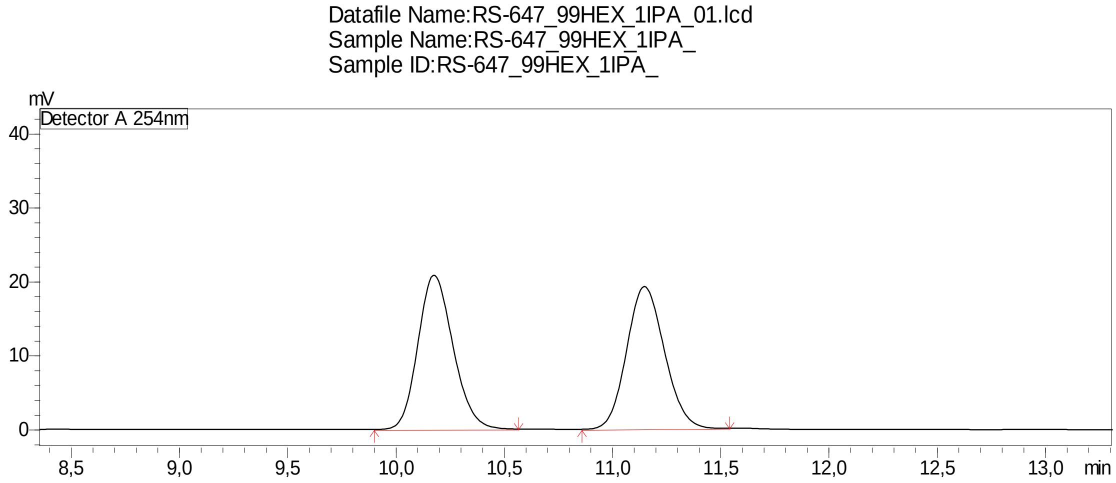
^{13}C NMR (100 MHz, C_6D_6): δ 169.1 (C=O), 136.3 (Ph C-1), 129.1 (Ph C-4), 128.9 (Ph C-3,5), 127.7 (Ph C-2,6), 93.5 (m, CH_2F), 82.5 (CH), 57.2 (OCH_3).

^{19}F NMR (376 MHz, C_6D_6): δ −157.3 (t, $^2J_{H,F}$ = 50.0 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + Na]^+$ calcd. for $C_{10}H_{11}FNaO_3$: 221.0584; found: 221.0585.

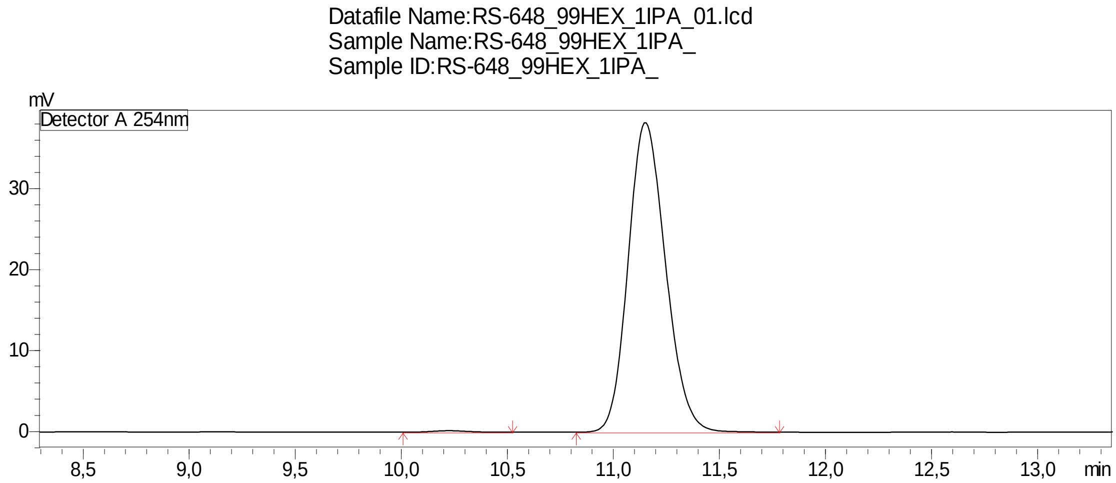
HPLC analysis: Chiralpak IG Column, λ 254 nm, eluent: *n*-hexane / *i*-propanol 99:1. Flow: 1 mL/min

Racemate



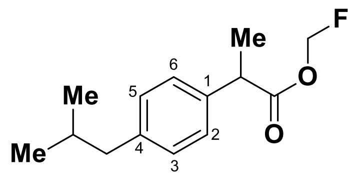
Peaks	Ret.T	Area	Area %
1	10,179	234856	50,246
2	11,151	232554	49,754
Total		467411	100,000

Enantioenriched



Peaks	Ret.T	Area	Area %
1	10,229	1976	0,419
2	11,154	469280	99,581
Total		467411	100,000

Fluoromethyl 2-(4-isobutylphenyl)propanoate (5)



By following the general procedure, starting from 2-(4-isobutylphenyl)propanoic acid (ibuprofen) (0.206 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **5** was obtained in 94% yield (0.212 g) as a colorless oil.

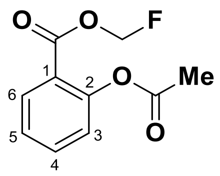
^{1}H NMR (400 MHz, C_6D_6): δ 7.13 (m, 2H, Ph H-2,6), 6.95 (m, 2H, Ph H-3,5), 5.22 (dd, $^2J_{H,F}$ = 50.9 Hz, ^2J = 2.0 Hz, 1H, CH_2F), 5.02 (dd, $^2J_{H,F}$ = 51.0 Hz, ^2J = 2.0 Hz, 1H, CH_2F), 3.46 (q, ^3J = 7.1 Hz, 1H, <u>CH</u>CH_3), 2.28 (d, ^3J = 7.2 Hz, 2H, CH_2), 1.69 (m, 1H, <u>CH</u>$(CH_3)_2$), 1.33 (d, ^3J = 7.1 Hz, 3H, CH<u>CH_3</u>), 0.80 (d, ^3J = 6.6 Hz, 6H, CH(<u>CH_3</u>)$_2$).

^{13}C NMR (100 MHz, C_6D_6): δ 172.6 (d, $^3J_{C,F}$ = 1.6 Hz, C=O), 141.0 (Ph C-4), 137.4 (Ph C-1), 129.8 (Ph C-3,5), 127.6 (Ph C-2,6), 93.4 (d, $^1J_{C,F}$ = 220.0 Hz, CH_2F), 45.22 (CH_2), 45.20 (<u>CH</u>CH_3), 30.4 (<u>CH</u>$(CH_3)_2$), 22.4 (CH(<u>CH_3</u>)$_2$), 18.5 (CH<u>CH_3</u>).

^{19}F NMR (376 MHz, C_6D_6): δ –157.0 (t, $^2J_{H,F}$ = 51.0 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + Na]^+$ calcd. for $C_{14}H_{19}FNaO_2$: 261.1261; found: 261.1271.

Fluoromethyl 2-acetoxybenzoate (6)



By following the general procedure, starting from 2-acetoxybenzoic acid (acetylsalicylic acid) (0.180 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **6** was obtained in 96% yield (0.204 g) as a colorless oil.

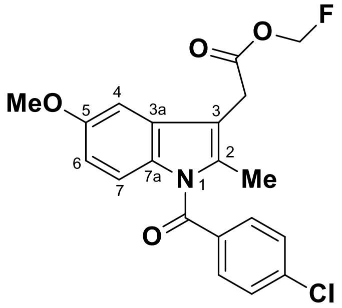
^{1}H NMR (400 MHz, C_6D_6): δ 7.80 (dd, ^3J = 7.9 Hz, ^4J = 1.7 Hz, 1H, Ph H-6), 6.99 (m, 1H, Ph H-4), 6.81 (m, 1H, Ph H-3), 6.74 (m, 1H, Ph H-5), 5.30 (d, $^2J_{H,F}$ = 50.8 Hz, 2H, CH_2F), 2.02 (s, 3H, CH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 168.9 ($CH_3\underline{C}$=O), 162.4 (d, $^3J_{C,F}$ = 1.2 Hz, Ar$\underline{C}$=O), 152.1 (Ph C-2), 134.7 (Ph C-4), 132.1 (Ph C-6), 125.9 (Ph C-5), 124.3 (Ph C-3), 122.3 (Ph C-1), 93.7 (d, $^1J_{C,F}$ = 220.8 Hz, CH_2F), 20.6 (CH_3).

^{19}F NMR (376 MHz, C_6D_6): δ −157.7 (t, $^2J_{H,F}$ = 50.8 Hz, CH_2F).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{10}H_9FNaO_4$: 235.0377; found: 235.0383.

Fluoromethyl [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetate (7)



By following the general procedure, starting from 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid (indomethacin) (0.358 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **7** was obtained in 93% yield (0.362 g) as a yellow oil.

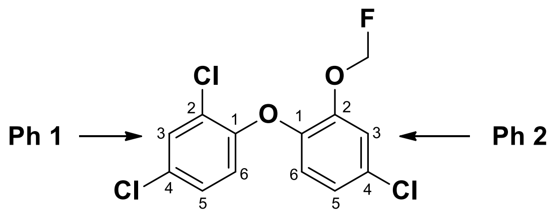
^{1}H NMR (400 MHz, C_6D_6): δ 7.10 (m, 2H, Ph H-2,6), 7.08 (d, ^4J = 2.5 Hz, 1H, H-4), 6.91 (d, ^3J = 9.0 Hz, 1H, H-7), 6.88 (m, 2H, Ph H-3,5), 6.64 (dd, ^3J = 9.0 Hz, ^4J = 2.5 Hz, 1H, Ph H-6), 5.15 (d, $^2J_{H,F}$ = 50.8 Hz, 2H, CH_2F), 3.44 (s, 3H, OCH_3), 3.34 (s, 2H, CH_2), 2.17 (s, 3H, CH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 168.9 (d, OC=O), 167.9 (NC=O), 156.9 (C-5), 139.0 (Ph C-4), 136.5 (C-2), 134.3 (Ph C-1), 131.37 (Ph C-2,6), 131.35 (C-7a), 130.9 (C-3a), 129.1 (Ph C-3,5), 115.4 (C-7), 112.1 (C-6), 111.6 (C-3), 101.7 (C-4), 93.5 (d, $^1J_{C,F}$ = 220.6 Hz, CH_2F), 55.3 (OCH_3), 30.0 (CH_2), 13.2 (CH_3).

^{19}F NMR (376 MHz, C_6D_6): δ –156.8 (t, $^2J_{H,F}$ = 50.8 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + Na]^+$ calcd. for $C_{20}H_{17}ClFNNaO_4$: 412.0722; found: 412.0728.

2,4-Dichloro-1-[4-chloro-2-(fluoromethoxy)phenoxy]benzene (8)



By following the general procedure, starting from 5-chloro-2-(2,4-dichlorophenoxy)phenol (triclosan) (0.289 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **8** was obtained in 96% yield (0.308 g) as a white solid.

mp: 56-57 °C

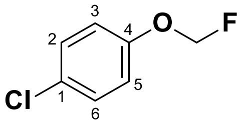
^{1}H NMR (400 MHz, C_6D_6): δ 7.15 (d, ^4J = 2.5 Hz, 1H, Ph 1 H-3), 7.10 (dd, ^4J = 2.4 Hz, $^5J_{H,F}$ = 0.9 Hz, 1-H, Ph 2 H-3), 6.67 (dd, ^3J = 8.8 Hz, ^4J = 2.5 Hz, 1H, Ph 1 H-5), 6.65 (dd, ^3J = 8.7 Hz, ^4J = 2.4 Hz, 1H, Ph 2 H-5), 6.30 (d, ^3J = 8.7 Hz, 1H, Ph 2 H-6), 6.13 (d, ^3J = 8.8 Hz, 1H, Ph 1 H-6), 4.82 (d, $^2J_{H,F}$ = 53.8 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 152.1 (Ph 1 C-1), 148.6 (d, $^3J_{C,F}$ = 2.8 Hz, Ph 2 C-2), 144.3 (Ph 2 C-1), 130.7 (Ph 1 C-3), 130.5 (Ph 2 C-4), 128.8 (Ph 1 C-4), 128.1 (Ph 1 C-5), 125.3 (Ph 1 C-2), 124.6 (Ph 2 C-5), 121.9 (Ph 2 C-6), 118.9 (d, $^4J_{C,F}$ = 1.5 Hz, Ph 2 C-3), 118.7 (Ph 1 C-6), 100.6 (d, $^1J_{C,F}$ = 222.4 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ –149.4 (t, $^2J_{H,F}$ = 53.8 Hz, CH_2F).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{13}H_9Cl_3FO_2$: 320.9647; found: 320.9647.

1-Chloro-4-(fluoromethoxy)benzene (9)[2]



By following the general procedure, starting from 4-chlorophenol (0.145 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **9** was obtained in 92% yield (0.147 g) as colorless oil.

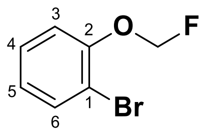
^{1}H NMR (400 MHz, C_6D_6): δ 6.93 (m, 2H, Ph H-2,6), 6.60 (m, 2H, Ph H-3,5), 4.93 (d, $^2J_{H,F}$ = 54.5 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 155.7 (Ph C-4), 129.9 (Ph C-2,6), 128.7 (Ph 1), 118.2 (d, $^4J_{C,F}$ = 1.6 Hz, Ph C-3,5), 100.4 (d, $^1J_{C,F}$ = 219.7 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ −148.9 (t, $^2J_{H,F}$ = 54.5 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for C_7H_7ClFO: 161.0164; found: 161.0164.

1-Bromo-2-(fluoromethoxy)benzene (10)[3]



By following the general procedure, starting from 2-bromophenol (0.173 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **10** was obtained in 95% yield (0.195 g) as a colorless oil.

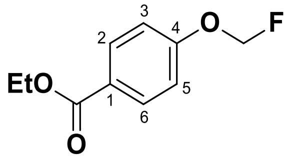
^{1}H NMR (400 MHz, C_6D_6): δ 7.29 (dd, ^{3}J = 7.9 Hz, ^{4}J = 1.5 Hz, 1H, Ph H-6), 6.81 (m, 1H, Ph H-3), 6.76 (m, 1H, Ph H-4), 6.48 (m, 1H, Ph H-5), 5.01 (d, $^{2}J_{H,F}$ = 54.2 Hz, 2H, CH_2F)

^{13}C NMR (100 MHz, C_6D_6): δ 153.9 (d, $^{3}J_{C,F}$ = 3.2 Hz, Ph C-2), 133.8 (Ph C-6), 128.7 (Ph C-4), 124.8 (Ph C-5), 117.2 (d, $^{4}J_{C,F}$ = 1.4 Hz, Ph C-3), 113.5 (d, $^{4}J_{C,F}$ = 2.1 Hz, Ph C-1), 100.8 (d, $^{1}J_{C,F}$ = 221.0 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ –149.0 (t, $^{2}J_{H,F}$ = 54.2 Hz, CH_2F).

HRMS (ESI), $[M + H]^+$ calcd. for C_7H_7BrFO: 204.9659; found: 204.9659.

Ethyl 4-(fluoromethyoxy)benzoate (11)[4]



By following the general procedure, starting from ethyl 4-hydroxybenzoate (0.166 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **11** was obtained in 97% yield (0.192 g) as a colorless oil.

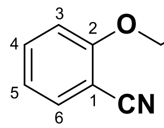
^{1}H NMR (400 MHz, C_6D_6): δ 8.10 (m, 2H, Ph H-2,6), 6.81 (m, 2H, Ph H-3,5), 4.99 (d, $^2J_{H,F}$ = 54.0 Hz, 2H, CH_2F), 4.13 (q, ^3J = 7.1 Hz, 2H, CH_2), 1.03 (t, ^3J = 7.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 165.6 (C=O), 160.3 (d, $^3J_{C,F}$ = 3.0 Hz, Ph C-4), 132.0 (Ph C-2,6), 126.3 (d, $J_{C,F}$ = 0.7 Hz, Ph C-1), 116.1 (d, $^4J_{C,F}$ = 1.5 Hz, Ph C-3,5), 99.7 (d, $^1J_{C,F}$ = 220.5 Hz, CH_2F), 60.8 (CH_2), 14.3 (CH_3).

^{19}F NMR (376 MHz, C_6D_6): δ –150.0 (t, $^2J_{H,F}$ = 54.0 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for: $C_{10}H_{12}FO_3$: 199.0765; found: 199.0765.

2-(Fluoromethoxy)benzonitrile (12)



By following the general procedure, starting from 2-hydroxybenzonitrile (0.119 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **12** was obtained in 94% yield (0.142 g) as a white solid.

mp: 38 °C

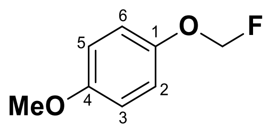
^{1}H NMR (400 MHz, C_6D_6): δ 6.93 (m, 1H, Ph H-6), 6.75 (m, 1H, Ph H-4), 6.56 (m, 1H, Ph H-3), 6.38 (m, 1H, Ph H-5), 4.84 (d, $^{2}J_{H,F}$ = 53.5 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 158.0 (d, $^{3}J_{C,F}$ = 3.0 Hz, Ph C-2), 133.9 (Ph C-4), 133.7 (Ph C-6), 123.3 (Ph C-5), 115.5 (CN), 114.9 (d, $^{4}J_{C,F}$ = 1.7 Hz, Ph C-3), 104.1 (d, $^{4}J_{C,F}$ = 1.4 Hz, Ph C-1), 99.8 (d, $^{1}J_{C,F}$ = 222.5 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ –150.5 (t, $^{2}J_{H,F}$ = 53.5 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + Na]^+$ calcd. for C_8H_6FNNaO: 174.0326; found: 174.0328.

1-(Fluoromethoxy)-4-methoxybenzene (13)[5]



By following the general procedure, starting from 4-methoxyphenol (0.124 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **13** was obtained in 97% yield (0.155 g) as a brown oil.

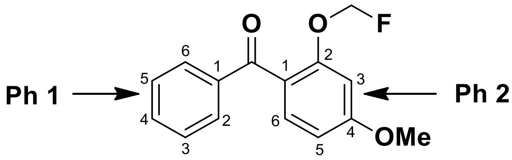
^{1}H NMR (400 MHz, C_6D_6): δ 6.91 (m, 2H, Ph H-2,6), 6.63 (m, 2H, Ph H-3,5), 5.13 (d, $^2J_{H,F}$ = 55.2 Hz, 2H, CH_2F), 3.25 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 156.4 (Ph C-4), 151.4 (d, $^3J_{C,F}$ = 3.1 Hz, Ph C-1), 118.5 (d, $^4J_{C,F}$ = 1.6 Hz, Ph C-2,6), 115.0 (Ph C-3,5), 101.7 (d, $^1J_{C,F}$ = 218.0 Hz, CH_2F), 55.1 (OCH_3).

^{19}F NMR (376 MHz, C_6D_6): δ −146.8 (t, $^2J_{H,F}$ = 55.2 Hz, CH_2F).

HRMS (ESI), $[M + H]^+$ calcd. for $C_8H_{10}FO_2$: 157.0659; found: 157.0658.

[2-(Fluoromethoxy)-4-methoxyphenyl](phenyl)methanone (14)



By following the general procedure, starting from (2-hydroxy-4-methoxyphenyl)(phenyl)methanone (0.228 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **14** was obtained in 92% yield (0.239 g) as a yellow oil.

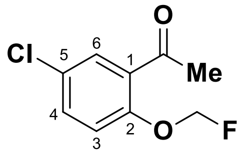
^{1}H NMR (400 MHz, C_6D_6): δ 7.88 (m, 2H, Ph 1 H-2,6), 7.31 (d, ^3J = 8.5 Hz, 1H, Ph 2 H-6), 7.13 (m, 1H, Ph 1 H-4), 7.06 (m, 2H, Ph 1 H-3,5), 6.73 (dd, ^4J = 2.3 Hz, $^5J_{H,F}$ = 1.1 Hz, 1H, Ph 2 H-3), 6.36 (dd, ^3J = 8.5 Hz, ^4J = 2.3 Hz, 1H, Ph 2 H-5), 4.92 (d, $^2J_{H,F}$ = 54.5 Hz, 2H, CH_2F), 3.22 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 194.2 (C=O), 163.2 (Ph 2 C-4), 156.6 (d, $^3J_{C,F}$ = 3.1 Hz, Ph 2 C-2), 139.1 (Ph 1 C-1), 132.6 (Ph 1 C-4), 132.1 (Ph 2 C-6), 130.1 (Ph 1 C-2,6), 128.5 (Ph 1 C-3,5), 123.7 (d, $^4J_{C,F}$ = 1.9 Hz, Ph 2 C-1), 108.9 (Ph 2 C-5), 103.3 (d, $^4J_{C,F}$ = 1.4 Hz, Ph 2 C-3), 101.1 (d, $^1J_{C,F}$ = 220.1 Hz, CH_2F), 55.1 (OCH_3).

^{19}F NMR (376 MHz, C_6D_6): δ –148.3 (t, $^2J_{H,F}$ = 54.5 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{15}H_{14}FO_3$: 261.0921; found: 261.0927.

1-[5-Chloro-2-(fluoromethoxy)phenyl]ethanone (15)



By following the general procedure, starting from 1-(5-chloro-2-hydroxyphenyl)ethanone (0.171 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **15** was obtained in 90% yield (0.151 g) as a colorless oil.

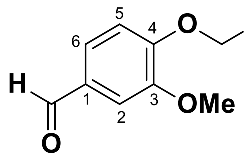
^{1}H NMR (400 MHz, C_6D_6): δ 7.70 (d, ^4J = 2.7 Hz, 1H, Ph H-6), 6.93 (dd, ^3J = 8.8 Hz, ^4J = 2.7 Hz, 1H, Ph H-4), 6.54 (d, ^3J = 8.8 Hz, 1H, Ph H-3), 4.90 (d, $^2J_{H,F}$ = 53.9 Hz, 2H, CH_2F), 2.22 (s, 3H, CH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 196.1 (C=O), 154.0 (d, $^3J_{C,F}$ = 3.1 Hz, Ph C-2), 132.9 (Ph C-4), 130.2 (Ph C-6), 131.3 (Ph C-1), 129.2 (Ph C-5), 117.5 (d, $^4J_{C,F}$ = 1.7 Hz, Ph C-3), 100.3 (d, $^1J_{C,F}$ = 221.5 Hz, CH_2F), 31.2 (CH_3).

^{19}F NMR (376 MHz, C_6D_6): δ –149.3 (t, $^2J_{H,F}$ = 53.9 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + Na]^+$ calcd. for $C_9H_8ClFNaO_2$: 225.0089; found: 225.0090.

4-(Fluoromethoxy)-3-methoxybenzaldehyde (16)[3]



By following the general procedure, starting from 4-hydroxy-3-methoxybenzaldehyde (vanillin) (0.152 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **16** was obtained in 96% yield (0.177 g) as a white solid.

mp: 77 °C

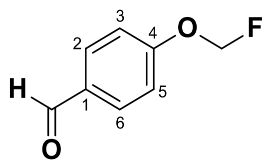
^{1}H NMR (400 MHz, C_6D_6): δ 9.61 (s, 1H, CHO), 7.25 (d, ^4J = 1.8 Hz, 1H, Ph H-2), 6.91 (dd, ^3J = 8.1 Hz, ^4J = 1.8 Hz, 1H, Ph H-6), 6.87 (dd, ^3J = 8.1 Hz, $^5J_{H,F}$ = 1.0 Hz, 1H, Ph H-5), 5.11 (d, $^2J_{H,F}$ = 54.1 Hz, 2H, CH_2F), 3.15 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 190.1 (CHO), 151.0 (d, $^3J_{C,F}$ = 3.1 Hz, Ph C-4), 151.0 (d, $^4J_{C,F}$ = 1.6 Hz, Ph C-3), 133.4 (Ph C-1), 125.4 (Ph C-6), 116.9 (d, $^4J_{C,F}$ = 1.3 Hz, Ph C-5), 110.5 (Ph C-2), 100.6 (d, $^1J_{C,F}$ = 220.9 Hz, CH_2F), 55.2 (OCH_3).

^{19}F NMR (376 MHz, C_6D_6): δ –149.4 (t, $^2J_{H,F}$ = 54.1 Hz, CH_2F).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_9H_{10}FO_3$: 185.0608; found: 185.0605.

4-(Fluoromethyoxy)benzaldehyde (17)[6]



By following the general procedure, starting from 4-hydroxybenzaldehyde (0.122 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **17** was obtained in 95% yield (0.146 g) as a yellow oil.

Scaling-up of the reaction (10 mmol) - By following the general procedure, starting from 4-hydroxybenzaldehyde (1.92 g, 10.0 mmol, 1.0 equiv), Cs_2CO_3 (3.91 g, 12.0 mmol, 1.2 equiv) and fluoroiodomethane (1.92 g, 12.0 mmol, 1.2 equiv) in dry acetonitrile (20 mL), compound **17** was obtained in 91% yield (1.40 g) as a yellow oil. *Spectroscopic and spectrometric data match with those reported for the 1.0 mmol scale reaction.*

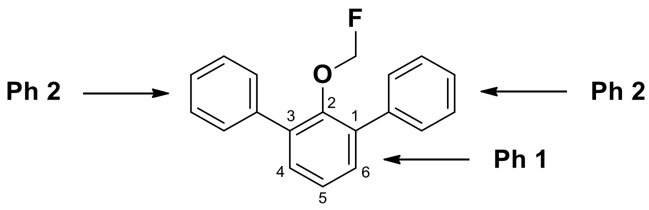
^{1}H NMR (400 MHz, C_6D_6): δ 9.58 (s, 1H, CHO), 7.44 (m, 2H, Ph H-2,6), 6.72 (m, 2H, Ph H-3,5), 4.96 (d, $^2J_{H,F}$ = 53.8 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 189.8 (CHO), 161.0 (d, $^3J_{C,F}$ = 3.0 Hz, Ph C-4), 132.6 (d, $J_{C,F}$ = 0.7 Hz, Ph C-1), 131.8 (Ph C-2,6), 116.5 (d, $^4J_{C,F}$ = 1.5 Hz, Ph C-3,5), 99.4 (d, $^1J_{C,F}$ = 221.1 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ –150.4 (t, $^2J_{H,F}$ = 53.8 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_8H_8FO_2$: 155.0503; found: 155.0502.

2’-(Fluoromethoxy)-1,1’:3’,1’’-terphenyl (18)



By following the general procedure, starting from 2,6-diphenylphenol (0.246 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **18** was obtained in 91% yield (0.253 g) as a colorless oil.

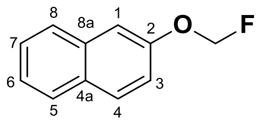
^{1}H NMR (400 MHz, C_6D_6): δ 7.53 (m, 4H, Ph 2 H-2,6), 7.22 (m, 4H, Ph 2 H-3,5), 7.20 (m, 2H, Ph 1 H-4,6), 7.12 (m, 2H, Ph 2 H-4), 7.01 (m, 1H, Ph 1 H-5), 4.72 (d, $^2J_{H,F}$ = 54.5 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 151.3 (d, $^3J_{C,F}$ = 1.5 Hz, Ph 1 C-2), 138.9 (Ph 2 C-1), 136.5 (d, $^4J_{C,F}$ = 0.7 Hz, Ph 1 C-1,3), 130.9 (Ph 1 C-4,6), 129.9 (Ph2 C-2,6), 128.6 (Ph 2 C-3,5), 127.6 (Ph 2 C-4), 125.9 (Ph 1, C-5), 103.6 (d, $^1J_{C,F}$ = 222.3 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ –150.0 (t, $^2J_{H,F}$ = 54.5 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + Na]^+$ calcd. for $C_{19}H_{15}FNaO$: 301.0999; found: 301.0998.

2-(Fluoromethoxy)naphthalene (19)[3]



By following the general procedure, starting from 2-naphthol (0.144 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **19** was obtained in 90% yield (0.158 g) as a yellow solid.

mp: 66 °C

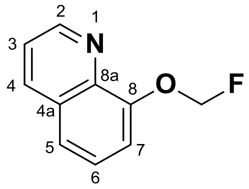
^{1}H NMR (400 MHz, C_6D_6): δ 7.54 (m, 1H, Naph H-5), 7.49 (m, 1H, Naph H-8), 7.46 (d, ^3J = 8.9 Hz, 1H, Naph H-4), 7.37 (d, ^4J = 2.5 Hz, 1H, Naph H-1), 7.23 (m, 1H, Naph H-7), 7.17 (m, 1H, Naph H-6), 7.13 (dd, ^3J = 8.9 Hz, ^4J = 2.5 Hz, 1H, Naph H-3), 5.21 (d, $^2J_{H,F}$ = 54.6 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 155.1 (d, $^3J_{C,F}$ = 3.1 Hz, Naph C-2), 134.8 (Naph C-8a), 130.7 (Naph C-4a), 130.1 (Naph C-4), 128.0 (Naph C-5), 127.6 (Naph C-8), 126.9 (Naph C-7), 125.0 (Naph C-6), 118.8 (d, $^4J_{C,F}$ = 1.5 Hz, Naph C-3), 111.5 (d, $^4J_{C,F}$ = 1.6 Hz, Naph C-1), 100.7 (d, $^1J_{C,F}$ = 219.0 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ −148.4 (t, $^2J_{H,F}$ = 54.6 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{11}H_{10}FO$: 177.0710; found: 177.0712.

8-(Fluoromethoxy)-quinoline (20)



By following the general procedure, starting from 8-quinolinol (0.145 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **20** was obtained in 88% yield (0.156 g) as a brown solid.

mp: 48 °C

^{1}H NMR (400 MHz, C_6D_6): δ 8.66 (dd, ^{3}J= 4.1 Hz, ^{4}J = 1.7Hz, 1H, H-2), 7.47 (dd, ^{3}J= 8.3 Hz, ^{4}J = 1.7 Hz, 1H, H-4), 7.31 (m, 1H, H-7), 7.11 (m, 1H, H-5), 7.02 (m, 1H, H-6), 6.74 (dd, ^{3}J = 8.3 Hz, ^{3}J = 4.1 Hz, 1H, H-3), 5.72 (d, $^{2}J_{H,F}$ = 55.0 Hz, 2H, CH_2F).

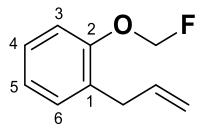
^{13}C NMR (100 MHz, C_6D_6): δ 153.2 (d, $^{3}J_{C,F}$ = 2.7 Hz, C-8), 149.9 (C-2), 141.5 (d, $^{4}J_{C,F}$ = 2.0 Hz, C-8a), 135.6 (C-4), 129.9 (C-4a), 126.6 (C-6), 123.6 (C-5), 121.6 (C-3), 117.4 (d, $^{4}J_{C,F}$ = 0.7 Hz, C-7), 102.7 (d, $^{1}J_{C,F}$ = 218.8 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ −148.1 (t, $^{2}J_{H,F}$ = 55.0 Hz, CH_2F).

^{15}N NMR (40 MHz, C_6D_6): δ −76.3 (N-1).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{10}H_9FNO$: 178.0663; found: 178.0667.

1-Allyl-2-(fluoromethoxy)benzene (21)



By following the general procedure, starting from 2-allylphenol (0.134 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **21** was obtained in 85% yield (0.141 g) as a yellow oil.

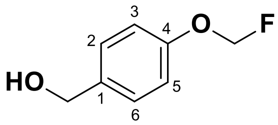
^{1}H NMR (400 MHz, C_6D_6): δ 7.03 (m, 1H, Ph H-6), 6.96 (m, 1H, Ph H-4), 6.95 (m, 1H, Ph H-3), 6.86 (m, 1H, Ph H-5), 5.91 (m, 1H, <u>CH</u>=CH_2), 5.12 (d, $^{2}J_{H,F}$ = 54.8 Hz, 2H, CH_2F), 5.01 (m, 1H, CH=<u>CH_2</u>), 4.97 (m, 1H, CH=<u>CH_2</u>), 3.35 (m, 2H, CH_2).

^{13}C NMR (100 MHz, C_6D_6): δ 155.2 (d, $^{3}J_{C,F}$ = 3.1 Hz, Ph C-2), 136.9 (<u>CH</u>=CH_2), 130.6 (Ph C-6), 130.1 (Ph C-1), 127.9 (Ph C-4), 123.8 (Ph C-5), 115.8 (CH=<u>CH_2</u>), 115.4 (d, $^{4}J_{C,F}$ = 1.5 Hz, Ph C-3), 100.9 (d, $^{1}J_{C,F}$ = 218.8 Hz, CH_2F), 34.5 (CH_2).

^{19}F NMR (376 MHz, C_6D_6): δ −147.1 (t, $^{2}J_{H,F}$ = 54.8 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{10}H_{12}FO$: 167.0867; found: 167.0867.

[4-(Fluoromethoxy)phenyl]methanol (22)[7]



By following the general procedure, starting from 4-hydroxybenzyl alcohol (0.124 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **22** was obtained in 96% yield (0.149 g) as a brown oil.

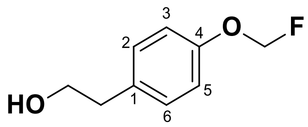
^{1}H NMR (400 MHz, C_6D_6): δ 7.03 (m, 2H, Ph H-2,6), 6.93 (m, 2H, Ph H-3,5), 5.13 (d, $^{2}J_{H,F}$ = 54.8 Hz, 2H, CH_2F), 4.24 (s, 2H, <u>CH₂</u>OH), 1.44 (br s, 1H, OH).

^{13}C NMR (100 MHz, C_6D_6): δ 156.6 (d, $^{3}J_{C,F}$ = 3.1 Hz, Ph C-4), 136.8 (Ph C-1), 128.5 (Ph C-2,6), 116.8 (d, $^{4}J_{C,F}$ = 1.5 Hz, Ph C-3,5), 100.7 (d, $^{1}J_{C,F}$ = 218.7 Hz, CH_2F), 64.4 (CH_2OH).

^{19}F NMR (376 MHz, C_6D_6): δ –148.0 (t, $^{2}J_{H,F}$ = 54.8 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_8H_{10}FO_2$: 157.0659; found: 157.0660.

[4-(Fluoromethoxy)phenyl]ethanol (23)



By following the general procedure, starting from 2-(4-hydroxyphenyl)ethanol (0.138 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **23** was obtained in 98% yield (0.167 g) as a colorless oil.

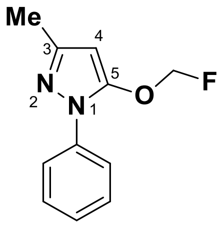
^{1}H NMR (400 MHz, C_6D_6): δ 6.92 (m, 2H, Ph H-3,5), 6.87 (m, 2H, Ph H-2,6), 5.14 (d, $^{2}J_{H,F}$ = 54.8 Hz, 2H,CH_2F), 3.45 (t, ^{3}J = 6.7 Hz, 2H, $CH_2\underline{CH_2}OH$), 2.48 (t, ^{3}J = 6.7 Hz, 2H, $\underline{CH_2}CH_2OH$), signal of OH not unambiguously identified.

^{13}C NMR (100 MHz, C_6D_6): δ 155.9 (d, $^{3}J_{C,F}$ = 3.1 Hz, Ph C-4), 134.3 (Ph C-1), 130.5 (Ph C-2,6), 117.0 (d, $^{4}J_{C,F}$ = 1.5 Hz, Ph C-3,5), 100.8 (d, $^{1}J_{C,F}$ = 218.5 Hz, CH_2F), 63.7 ($CH_2\underline{CH_2}OH$), 38.7 ($\underline{CH_2}CH_2OH$).

^{19}F NMR (376 MHz, C_6D_6): δ –147.7 (t, $^{2}J_{H,F}$ = 54.8 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_9H_{12}FO_2$: 171.0816; found: 171.0818.

5-(Fluoromethoxy)-3-methyl-1-phenyl-1*H*-pyrazole (24)



By following the general procedure, starting from 3-methyl-1-phenyl-2-pyrazolin-5-one (edavarone) (0.174 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **24** was obtained in 91% yield (0.187 g) as a yellow oil.

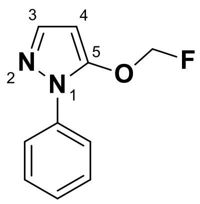
^{1}H NMR (400 MHz, C_6D_6): δ 7.78 (m, 2H, Ph H-2,6), 7.12 (m, 2H, Ph H-3,5), 6.94 (m, 1H, Ph H-4), 5.46 (d, $^5J_{H,F}$ = 1.6 Hz, 1H, H-4), 4.78 (d, $^2J_{H,F}$ = 53.2 Hz, 2H, CH_2F), 2.20 (s, 3H, CH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 152.1 (d, $^3J_{C,F}$ = 2.6 Hz, C-5), 148.8 (C-3), 139.2 (Ph C-1), 129.0 (Ph C-3,5), 126.3 (Ph C-4), 122.5 (Ph C-2,6), 101.3 (d, $^1J_{C,F}$ = 224.8 Hz, CH_2F), 89.6 (d, $^4J_{C,F}$ = 0.9 Hz, C-4), 14.6 (CH_3).

^{19}F NMR (376 MHz, C_6D_6): δ –151.9 (t, $^2J_{H,F}$ = 53.2 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{11}H_{12}FN_2O$: 207.0928; found: 207.0934.

5-(Fluoromethoxy)-1-phenyl-1*H*-pyrazole (25)



By following the general procedure, starting from 1-phenyl-1*H*-pyrazol-5-ol (0.170 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **25** was obtained in 87% yield (0.167 g) as a yellow oil.

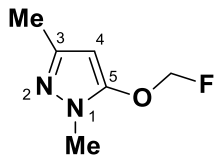
^{1}H NMR (400 MHz, C_6D_6): δ 7.73 (m, 2H, Ph H-2,6), 7.45 (d, ^3J = 1.8 Hz, 1H, H-3), 7.10 (m, 2H, Ph H-3,5), 6.94 (m, 1H, Ph H-4), 5.60 (t, ^3J = 1.8 Hz, 1H, H-4), 4.73 (d, $^2J_{H,F}$ = 53.1 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 151.9 (d, $^3J_{C,F}$ = 2.5 Hz, C-5), 139.9 (C-3), 139.1 (Ph C-1), 129.0 (Ph C-3,5), 126.8 (Ph C-4), 122.9 (Ph C-2,6), 101.4 (d, $^1J_{C,F}$ = 225.0 Hz, CH_2F), 89.6 (d, $^4J_{C,F}$ = 1.1 Hz, C-4).

^{19}F NMR (376 MHz, C_6D_6): δ –152.1 (t, $^2J_{H,F}$ = 53.1 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{10}H_{10}FN_2O$: 193.0772; found: 193.0772.

5-(Fluoromethoxy)-1,3-dimethyl-1*H*-pyrazole (26)



By following the general procedure, starting from 1,3-dimethyl-1*H*-pyrazol-5-ol (0.112 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **26** was obtained in 88% yield (0.127 g) as a yellow oil.

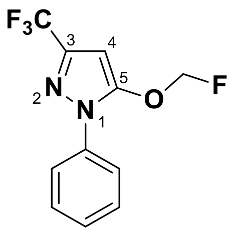
^{1}H NMR (400 MHz, C_6D_6): δ 5.34 (d, $^5J_{H,F}$ = 1.4 Hz, 1H, H-4), 4.83 (d, $^2J_{H,F}$ = 53.4 Hz, 2H, CH_2F), 3.23 (s, 3H, NCH_3), 2.18 (s, 3H, 3-CH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 152.0 (C-5), 146.9 (C-3), 101.4 (d, $^1J_{C,F}$ = 223.9 Hz, CH_2F), 87.4 (C-4), 33.4 (NCH_3), 14.6 (3-CH_3).

^{19}F NMR (376 MHz, C_6D_6): δ −151.1 (t, $^2J_{H,F}$ = 53.4 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_6H_{10}FN_2O$: 145.0772; found: 145.0775.

5-(Fluoromethoxy)-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole (27)



By following the general procedure, starting from 1-phenyl-3-trifluoromethyl-2-pyrazolin-5-one (0.228 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **27** was obtained in 90% yield (0.234 g) as a brown oil.

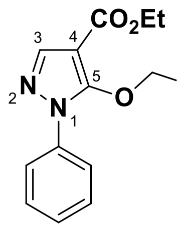
^{1}H NMR (400 MHz, C_6D_6): δ 7.44 (m, 2H, Ph H-2,6), 7.02 (m, 2H, Ph H-3,5), 6.93 (m, 1H, Ph H-4), 5.81 (s, 1H, H-4), 4.53 (d, $^2J_{H,F}$ = 52.5 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 151.9 (d, $^3J_{C,F}$ = 2.3 Hz, C-5), 142.3 (q, $^2J_{C,F}$ = 38.8 Hz, C-3), 137.8 (Ph C-1), 129.1 (Ph C-3,5), 128.0 (Ph C-4), 123.3 (Ph C-2,6), 121.9 (q, $^1J_{C,F}$ = 268.9 Hz, CF_3), 101.0 (d, $^1J_{C,F}$ = 227.4 Hz, CH_2F), 87.9 (C-4).

^{19}F NMR (376 MHz, C_6D_6): δ –152.9 (t, $^2J_{H,F}$ = 52.5 Hz, CH_2F), -62.8 (s, CF_3).

HRMS (ESI), *m/z*: $[M + H]^+$ calcd. for $C_{11}H_9F_4N_2O$: 261.0646; found: 261.0651.

Ethyl 5-(fluoromethoxy)-1-phenyl-1*H*-pyrazole-4-carboxylate (28)



By following the general procedure, starting from ethyl 5-hydroxy-1-phenyl-1*H*-pyrazole-4-carboxylate (0.232 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **28** was obtained in 92% yield (0.243 g) as a yellow oil.

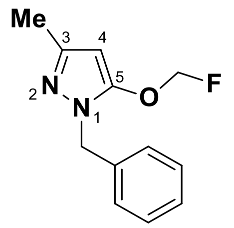
^{1}H NMR (400 MHz, C_6D_6): δ 8.06 (s, 1H, H-3), 7.70 (m, 2H, Ph H-2,6), 7.06 (m, 2H, Ph H-3,5), 6.95 (m, 1H, Ph H-4), 5.67 (d, $^{2}J_{H,F}$ = 52.7 Hz, 2H, CH_2F), 4.01 (q, ^{3}J = 7.1 Hz, 2H, CH_2), 0.96 (t, ^{3}J = 7.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 162.0 (C=O), 152.3 (C-5), 141.8 (C-3), 138.1 (Ph C-1), 129.1 (Ph C-3,5), 128.0 (Ph C-4), 124.1 (d, $J_{C,F}$ = 1.2 Hz, Ph C-2,6), 104.4 (d, $^{1}J_{C,F}$ = 227.3 Hz, CH_2F), 101.6 (d, $^{4}J_{C,F}$ = 1.3 Hz, C-4), 60.3 (CH_2), 14.2 (CH_3).

^{19}F NMR (376 MHz, C_6D_6): δ –149.4 (t, $^{2}J_{H,F}$ = 52.7 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{13}H_{14}FN_2O_3$: 265.0983; found: 265.0988.

1-Benzyl-5-(fluoromethoxy)-3-methyl-1*H*-pyrazole (29)



By following the general procedure, starting from 1-benzyl-3-methyl-1*H*-pyrazol-5-ol (0.188 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **29** was obtained in 88% yield (0.194 g) as a yellow oil.

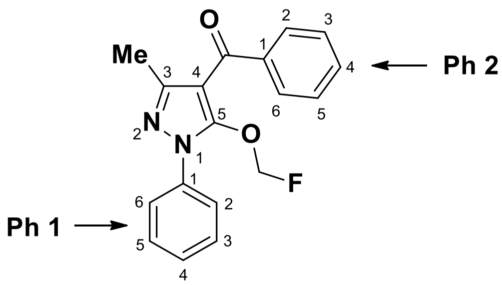
^{1}H NMR (400 MHz, C_6D_6): δ 7.14 (m, 2H, Ph H-2,6), 7.05 (m, 2H, Ph H-3,5), 6.98 (m, 1H, Ph H-4), 5.38 (d, $^5J_{H,F}$ = 1.4 Hz, 1H, H-4), 4.92 (s, 2H, CH_2), 4.77 (d, $^2J_{H,F}$ = 53.4 Hz, 2H, CH_2F), 2.18 (s, 3H, CH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 152.0 (C-5), 147.5 (C-3), 137.8 (Ph C-1), 128.8 (Ph C-3,5), 127.7 (Ph C-4), 127.6 (Ph C-2,6), 101.4 (d, $^1J_{C,F}$ = 224.3 Hz, CH_2F), 87.8 (C-4), 50.8 (CH_2), 14.7 (CH_3).

^{19}F NMR (376 MHz, C_6D_6): δ –151.2 (t, $^2J_{H,F}$ = 53.4 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{12}H_{14}FN_2O$: 221.1085; found: 221.1092.

[5-(Fluoromethoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl](phenyl) methanone (30)



By following the general procedure, starting from 4-benzoyl-5-methyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (0.278 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **30** was obtained in 90% yield (0.279 g) as a yellow oil.

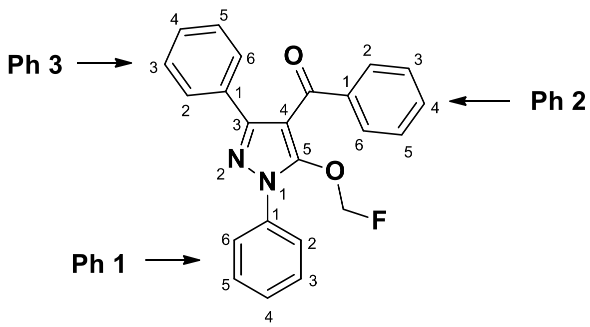
^{1}H NMR (400 MHz, C_6D_6): δ 7.77 (m, 2H, Ph 1 H-2,6), 7.68 (m, 2H, Ph 2 H-2,6), 7.11 (m, 1H, Ph 2 H-4), 7.10 (m, 2H, Ph 1 H-3,5), 7.04 (m, 2H, Ph 2 H-3,5), 6.96 (m, 1H, Ph 1 H-4), 5.00 (d, $^2J_{H,F}$ = 52.4 Hz, 2H, CH_2F), 2.27 (s, 3H, CH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 189.8 (C=O), 151.0 (C-5), 150.0 (C-3), 139.5 (Ph 2 C-1), 138.3 (Ph 1 C-1), 132.4 (Ph 2 C-4), 129.4 (Ph 2 C-2,6), 129.2 (Ph 1 C-3,5), 128.5 (Ph 2 C-3,5), 127.6 (Ph 1 C-4), 123.6 (Ph 1 C-2,6), 108.7 (C-4), 104.2 (d, $^1J_{C,F}$ = 229.1 Hz, CH_2F), 15.1 (CH_3).

^{19}F NMR (376 MHz, C_6D_6): δ –149.2 (t, $^2J_{H,F}$ = 52.4 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{18}H_{16}FN_2O_2$: 311.1190; found: 311.1201.

[5-(Fluoromethoxy)-1,3-diphenyl-1*H*-pyrazol-4-yl](phenyl)methanone (31)



By following the general procedure, starting from (5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-yl) phenyl-methanone (0.341 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **31** was obtained in 95% yield (0.353 g) as a yellow oil.

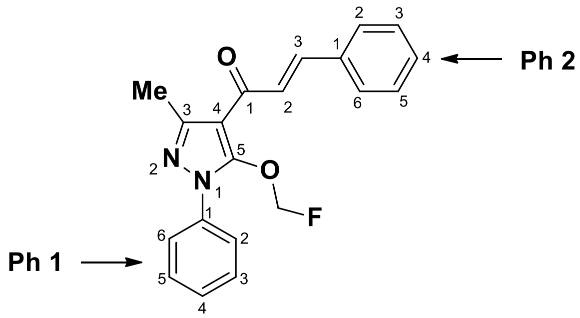
^{1}H NMR (400 MHz, C_6D_6): δ 7.83 (m, 2H, Ph 1 H-2,6), 7.75 (m, 2H, Ph 2 H-2,6), 7.67 (m, 2H, Ph 3 H-2,6), 7.13 (m, 2H, Ph 1 H-3,5), 7.00 (m, 1H, Ph 1 H-4), 6.97 (m, 2H, Ph 3 H-3,5), 6.93 (m, 2H, Ph 2 H-4, Ph 3 H-4), 6.86 (m, 2H, Ph 2 H-3,5), 5.40 (d, $^{2}J_{H,F}$ = 52.5 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 190.4 (C=O), 151.6 (C-3), 151.5 (C-5), 138.4 (Ph 2 C-1), 138.3 (Ph 1 C-1), 133.3 (Ph 3 C-1), 132.8 (Ph 2 C-4), 130.1 (Ph 2 C-2,6), 129.2 (Ph 1 C-3,5), 128.9 (Ph 3 C-2,6), 128.5 (Ph 3 C-4), 128.4 (Ph 3 C-3,5), 128.3 (Ph 2 C-3,5), 127.9 (Ph 1 C-4), 123.8 (Ph1 C-2,6), 108.2 (C-4), 104.6 (d, $^{1}J_{C,F}$ = 228.7 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ –148.0 (t, $^{2}J_{H,F}$ = 52.5 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{23}H_{18}FN_2O_2$: 373.1347; found: 373.1360.

(2E)-1-[5-(Fluoromethyoxy)-3-methyl-1-phenyl-1H-pyrazol-4-yl]-3-phenyl-propen-1-one (32)



By following the general procedure, starting from (2E)-1-(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-3-phenyl-2-propen-1-one (0.304 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **32** was obtained in 96% yield (0.323 g) as a yellow solid.

mp: 78 °C

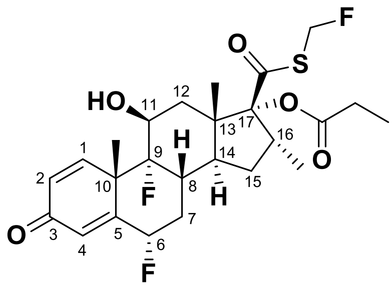
^{1}H NMR (400 MHz, C_6D_6): δ 7.93 (d, ^3J = 15.7 Hz, 1H, H-3), 7.70 (m, 2H, Ph 1 H-2,6), 7.33 (m, 2H, Ph 2 H-2,6), 7.30 (d, ^3J = 15.7 Hz, 1H, H-2), 7.09 (m, 2H, Ph 1 H-3,5), 7.06 (m, 3H, Ph 2 H-3,4,5), 6.96 (m, 1H, Ph 1 H-4), 5.07 (d, $^2J_{H,F}$ = 52.5 Hz, 2H, CH_2F), 2.61 (s, 3H, CH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 183.8 (C=O), 151.5 (pyrazole C-5), 150.5 (pyrazole C-3), 142.7 (C-3), 138.2 (Ph 1 C-1), 135.6 (Ph 2 C-1), 130.3 (Ph 2 C-4), 129.2 (Ph 1 C-3,5), 129.1 (Ph 2 C-3,5), 128.6 (Ph 2 C-2,6), 127.7 (Ph 1 C-4), 125.4 (C-2), 123.6 (Ph 1 C-2,6), 110.6 (pyrazole C-4), 104.6 (d, $^1J_{C,F}$ = 229.4 Hz, CH_2F), 16.0 (CH_3).

^{19}F NMR (376 MHz, C_6D_6): δ −149.1 (t, $^2J_{H,F}$ = 52.5 Hz, CH_2F).

HRMS (ESI), m/z $[M + H]^+$ calcd. for $C_{20}H_{18}FN_2O_2$: 337.1347; found: 337.1354.

(6α, 11β, 16α, 17α)-6,9-Difluoro-17-{[(fluoromethyl)sulfanyl]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl propionate (33)[8]



To a mixture of 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-propionyloxy-3-oxoandrosta-1,4-diene-17β-carbothioic acid[8] (0.147 g, 0.31 mmol, 1.0 equiv) and Cs_2CO_3 (0.121 g, 0.37 mmol, 1.2 equiv) in dry acetonitrile (1 mL), fluoroiodomethane (0.060 g, 0.37 mmol, 1.2 equiv) was added slowly at rt. The reaction mixture was stirred 6 h at rt and then quenched with water. The reaction mixture was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the final compound in 82% yield (0.128 g) as a white solid, after crystallization from EtOAc:EtOH, 2:1.

mp: 263-271 °C

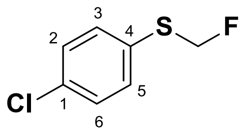
^{1}H NMR (400 MHz, C_6D_6): δ 7.24 (dd, ^3J = 10.2 Hz, $J_{H,F}$ = 1.3 Hz, 1H, H-1), 6.28 (dd, ^3J = 10.2 Hz, $J_{H,F}$ = 1.9 Hz, 1H, H-2), 6.10 (m, 1H, H-4), 5.92 (d, $^2J_{H,F}$ = 50.1 Hz, 2H, CH_2F), 5.71-5.52 (m, 1H, H-6), 4.20 (m, 1H, H-11), 3.28 (m, 1H, H-16), 2.52 (m, 1H, H-8), 2.35 (dq, $J_{H,F}$ = 1.0 Hz, ^3J = 7.6 Hz, 2H, $\underline{CH_2}CH_3$), 2.24 (m, 1H, H-7), 2.10 (m, 1H, H-12), 2.09 (m, 1H, H-14), 1.86 (m, 1H, H-15), 1.85 (m, 1H, H-12), 1.49 (m, 1H, H-7),1.47 (s, 3H, 10-CH_3), 1.25 (m, 1H, H-15), 1.0 (t, ^3J = 7.6 Hz, 3H, $CH_2\underline{CH_3}$), 0.98 (s, 3H, 13-CH_3), 0.88 (d, ^3J = 7.2 Hz, 3H, 16-CH_3), signal of OH was not unambiguously identified.

^{13}C NMR (100 MHz, C_6D_6): δ 193.2 (S-C=O), 184.3 (C-3), 172.4 (O-C=O), 162.7 (dd, $^2J_{C,F}$ = 13.7 Hz, $^3J_{C,F}$ = 1.1 Hz, C-5), 151.7 (C-1), 129.1 (C-2), 119.4 (d, $^3J_{C,F}$ = 13.0 Hz, C-4), 99.9 (d, $^1J_{C,F}$ = 177.0 Hz, C-9), 96.1 (C-17), 86.7 (d, $^1J_{C,F}$ = 180.3 Hz, C-6), 81.0 (d, $^1J_{C,F}$ = 212.0 Hz, CH_2F), 70.0 (d, $^2J_{C,F}$ = 35.6 Hz, C-11), 48.4 (C-13), 47.8 (dd, $^2J_{C,F}$ = 22.3 Hz, $^3J_{C,F}$ = 3.9 Hz, C-10), 42.8 (C-14), 35.7 (C-16), 35.1 (C-12), 33.7 (d, $^2J_{C,F}$ = 18.7 Hz, C-7), 33.3 (C-15), 31.9 (dd, $^2J_{C,F}$ = 18.3 Hz, $^3J_{C,F}$ = 10.5 Hz, C-8), 22.7 (d, $^3J_{C,F}$ = 5.3 Hz, 10-$\underline{C}H_3$), 26.9 ($\underline{CH_2}CH_3$), 16.9 (16-$\underline{C}H_3$), 15.9 (13-$\underline{C}H_3$), 8.9 ($CH_2\underline{CH_3}$).

^{19}F NMR (376 MHz, C_6D_6): δ –191.5 (t, $^2J_{H,F}$ = 50.1 Hz, CH_2F), –186.3 (dd, $^2J_{H,F}$ = 48.8 Hz, $^3J_{H,F}$ = 14.4 Hz, 6-F),
–164.2 (dd, $^3J_{H,F}$ = 29.6 Hz, $^3J_{H,F}$ = 9.0 Hz, 9-F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{25}H_{32}F_3O_5S$: 501.1917; found: 501.1919.

1-Chloro-4-[(fluoromethyl)sulfanyl]benzene (34)[9]



By following the general procedure, starting from 4-chlorothiophenol (0.145 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **34** was obtained in 86% yield (0.151 g) as a colorless oil.

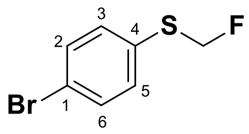
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (m, 2H, Ph H-3,5), 7.32 (m, 2H, Ph H-2,6), 5.69 (d, $^{2}J_{H,F}$ = 52.7 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1 (Ph C-1), 132.7 (d, $^{3}J_{C,F}$ = 2.9 Hz, Ph C-4), 132.1 (d, $^{4}J_{C,F}$ = 2.3 Hz, Ph C-3,5), 129.3 (Ph C-2,6), 88.4 (d, $^{1}J_{C,F}$ = 217.2 Hz, CH_2F).

^{19}F NMR (376 MHz, $CDCl_3$): δ –182.3 (t, $^{2}J_{H,F}$ = 52.7 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for C_7H_7ClFS: 176.9936; found: 176.9938.

1-Bromo-4-[(fluoromethyl)sulfanyl]benzene (35)[10]



By following the general procedure, starting from 4-bromothiophenol (0.189 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **35** was obtained in 91% yield (0.201 g) as a white solid.

mp: 60-63 °C

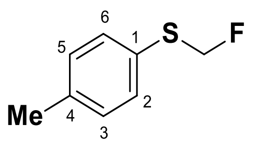
^{1}H NMR (400 MHz, C_6D_6): δ 7.02 (m, 2H, Ph H-2,6), 6.92 (m, 2H, Ph H-3,5), 4.97 (d, $^2J_{H,F}$ = 52.7 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 133.9 (d, $^3J_{C,F}$ = 2.9 Hz, Ph C-4), 132.4 (Ph C-2,6), 132.2 (d, $^4J_{C,F}$ = 2.2 Hz, Ph C-3,5), 122.1 (Ph C-1), 87.8 (d, $^1J_{C,F}$ = 217.8 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ −182.2 (t, $^2J_{H,F}$ = 52.7 Hz, CH_2F).

HRMS (ESI), $[M + H]^+$ calcd. for C_7H_7BrFS: 220.9430; found: 220.9432.

1-[(Fluoromethyl)sulfanyl]-4-methylbenzene (36)[11]



By following the general procedure, starting from *p*-toluenethiol (0.124 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **36** was obtained in 89% yield (0.139 g) as a yellow oil.

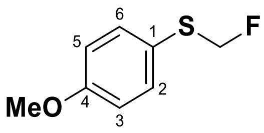
^{1}H NMR (400 MHz, C_6D_6): δ 7.33 (m, 2H, Ph H-2,6), 6.79 (m, 2H, Ph H-3,5), 5.16 (d, $^2J_{H,F}$ = 52.9 Hz, 2H, CH_2F), 1.97 (s, 3H, CH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 137.9 (Ph C-4), 131.6 (d, $^4J_{C,F}$ = 2.2 Hz, Ph C-2,6), 131.4 (d, $^3J_{C,F}$ = 2.7 Hz, Ph C-1), 130.2 (Ph C-3,5), 88.8 (d, $^1J_{C,F}$ = 216.9 Hz, CH_2F), 20.9 (CH_3).

^{19}F NMR (376 MHz, C_6D_6): δ –181.2 (t, $^2J_{H,F}$ = 52.9 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_8H_{10}FS$: 157.0482; found: 157.0485.

1-[(Fluoromethyl)sulfanyl]-4-methoxybenzene (37)[12]



By following the general procedure, starting from 4-methoxythiophenol (0.140 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **37** was obtained in 96% yield (0.165 g) as a yellow oil.

Scaling-up of the reaction (15 mmol) - By following the general procedure, starting from 4-methoxythiophenol (2.10 g, 15.0 mmol, 1.0 equiv), Cs_2CO_3 (5,87 g, 18.0 mmol, 1.2 equiv) and fluoroiodomethane (2.88 g, 18.0 mmol, 1.2 equiv) in dry acetonitrile (20 mL), compound **37** was obtained in 92% yield (2.37 g) as a yellow oil. *Spectroscopic and spectrometric data match with those reported for the 1.0 mmol scale reaction.*

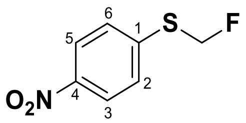
^{1}H NMR (400 MHz, C_6D_6): δ 7.36 (m, 2H, Ph H-2,6), 6.58 (m, 2H, Ph H-3,5), 5.13 (d, $^2J_{H,F}$ = 53.0 Hz, 2H, CH_2F), 3.18 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, C_6D_6): δ 160.4 (Ph C-4), 134.3 (d, $^4J_{C,F}$ = 2.1 Hz, Ph C-2,6), 125.1 (d, $^3J_{C,F}$ = 2.6 Hz, Ph C-1), 115.1 (Ph C-3,5), 89.7 (d, $^1J_{C,F}$ = 217.0 Hz, CH_2F), 54.8 (OCH_3).

^{19}F NMR (376 MHz, C_6D_6): δ −181.3 (t, $^2J_{H,F}$ = 53.0 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_8H_{10}FOS$: 173.0431; found: 173.0430.

1-[(Fluoromethyl)sulfanyl]-4-nitrobenzene (38)[10]



By following the general procedure, starting from 4-nitrobenzenethiol (0.155 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **38** was obtained in 97% yield (0.181 g) as a yellow solid.

mp: 82-83 °C

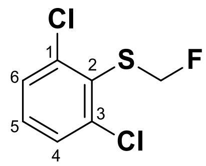
^{1}H NMR (400 MHz, C_6D_6): δ 7.59 (m, 2H, Ph H-3,5), 6.78 (m, 2H, Ph H-2,6), 4.88 (d, $^2J_{H,F}$ = 52.2 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 146.8 (Ph C-4), 143.2 (d, $^3J_{C,F}$ = 3.2 Hz, Ph C-1), 128.2 (d, $^4J_{C,F}$ = 2.4 Hz, Ph C-2,6), 124.1 (Ph C-3,5), 85.7 (d, $^1J_{C,F}$ = 218.6 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ –184.5 (t, $^2J_{H,F}$ = 52.2 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_7H_7FNO_2S$: 188.0176; found: 188.0174.

1,3-Dichloro-2-[(fluoromethyl)sulfanyl]benzene (39)[2]



By following the general procedure, starting from 2,6-dichlorobenzenethiol (0.179 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **39** was obtained in 93% yield (0.195 g) as a yellow oil.

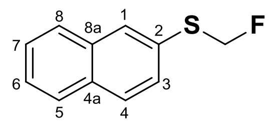
^{1}H NMR (400 MHz, C_6D_6): δ 6.85 (d, ^3J = 8.1 Hz, 2H, Ph H-4,6), 6.34 (t, ^3J = 8.1 Hz, 1H, Ph H-5), 5.13 (d, $^2J_{H,F}$ = 52.0 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 141.6 (d, $^4J_{C,F}$ = 2.0 Hz, Ph C-1,3), 131.0 (d, $^3J_{C,F}$ = 1.9 Hz, Ph C-2), 130.8 (Ph C-5), 128.8 (Ph C-4,6), 87.9 (d, $^1J_{C,F}$ = 222.1 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ –185.1 (t, $^2J_{H,F}$ = 52.0 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_7H_6Cl_2FS$: 210.9546; found: 210.9547.

2-[(Fluoromethyl)sulfanyl]naphtalene (40)[13]



By following the general procedure, starting from 2-naphthalenethiol (0.160 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **40** was obtained in 93% yield (0.179 g) as a white solid.

mp: 38 °C

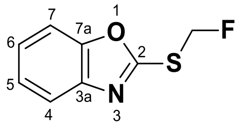
^{1}H NMR (400 MHz, C_6D_6): δ 7.87 (s, 1H, Naph H-1), 7.49 (m, 1H, Naph H-5), 7.44 (m, 1H, Naph H-8), 7.42 (m, 2H, Naph H-3,4), 7.18 (m, 1H, Naph H-6), 7.17 (m, 1H, Naph H-7), 5.22 (d, $^2J_{H,F}$ = 52.8 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 134.2 (Naph C-8a), 133.0 (Naph C-4a), 132.3 (d, $^3J_{C,F}$ = 2.9 Hz, Naph C-2), 129.9 (d, $^4J_{C,F}$ = 2.5 Hz, Naph C-1), 129.2 (Naph C-4), 128.3 (m, Naph C-3), 128.0 (Naph C-5), 127.9 (Naph C-8), 126.9 (Naph C-7), 126.6 (Naph C-6), 88.3 (d, $^1J_{C,F}$ = 217.1 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ –181.5 (t, $^2J_{H,F}$ = 52.8 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{11}H_{10}FS$: 193.0482; found: 193.0484.

2-[(Fluoromethyl)sulfanyl]-1,3-benzoxazole (41)[10]



By following the general procedure, starting from 2-mercaptobenzoxazole (0.151 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **41** was obtained in 92% yield (0.168 g) as a brown oil.

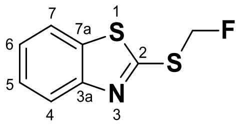
^{1}H NMR (400 MHz, C_6D_6): δ 7.53 (m, 1H, H-4), 7.00 (m, 1H, H-7), 6.93 (m, 1H, H-5), 6.83 (m, 1H, H-6), 5.40 (d, $^2J_{H,F}$ = 50.4 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 161.5 (d, $^3J_{C,F}$ = 3.3 Hz, C-2), 152.5 (C-7a), 142.2 (C-3a), 124.8 (C-5), 124.6 (C-6), 119.4 (C-4), 110.3 (C-7), 83.6 (d, $^1J_{C,F}$ = 223.8 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ −188.5 (t, $^2J_{H,F}$ = 50.4 Hz, CH_2F).

HRMS (ESI), $[M + H]^+$ calcd. for C_8H_7FNOS: 184.0227; found: 184.0229.

2-[(Fluoromethyl)sulfanyl]-1,3-benzothiazole (42)[10]



By following the general procedure, starting from 2-mercaptobenzothiazole (0.167 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **42** was obtained in 94% yield (0.187 g) as a yellow solid.

mp: 55-57 °C

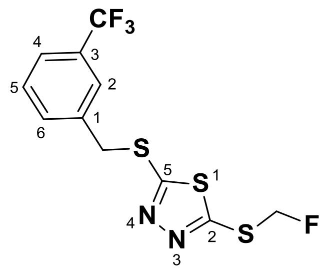
^{1}H NMR (400 MHz, C_6D_6): δ 7.88 (m, 1H, H-4), 7.18 (m, 1H, H-7), 7.05 (m, 1H, H-5), 6.89 (m, 1H, H-6), 5.52 (d, $^2J_{H,F}$ = 50.9 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 162.7 (d, $^3J_{C,F}$ = 3.7 Hz, C-2), 153.5 (C-3a), 136.1 (C-7a), 126.5 (C-5), 124.9 (C-6), 122.6 (C-4), 121.3 (C-7), 84.3 (d, $^1J_{C,F}$ = 222.7 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ –187.1 (t, $^2J_{H,F}$ = 50.9 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_8H_7FNS_2$: 199.9998; found: 199.9996.

2-[(Fluoromethyl)sulfanyl]-5-{[3-(trifluoromethyl)benzyl]sulfanyl}-1,3,4-thiadiazole (43)



By following the general procedure, starting from 5-[3-(trifluoromethyl)benzylthio]-1,3,4-thiodiatole-2-thiol (0.308 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **43** was obtained in 90% yield (0.306 g) as a yellow oil.

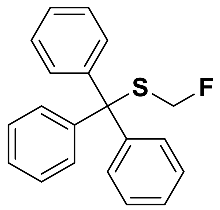
^{1}H NMR (400 MHz, C_6D_6): δ 7.40 (m, 1H, Ph H-2), 7.14 (m, 1H, Ph H-6), 7.13 (m, 1H, Ph H-4), 6.76 (m, 1H, Ph H-5), 5.07 (d, $^2J_{H,F}$ = 50.9 Hz, 2H, CH_2F), 3.94 (s, 2H, CH_2).

^{13}C NMR (100 MHz, C_6D_6): δ 166.0 (C-5), 161.3 (d, $^3J_{C,F}$ = 3.7 Hz, C-2), 137.7 (Ph C-1), 132.8 (q, $^5J_{C,F}$ = 1.3 Hz, Ph C-6), 131.1 (q, $^2J_{C,F}$ = 32.2 Hz, Ph C-3), 129.3 (Ph C-5), 126.1 (q, $^3J_{C,F}$ = 3.8 Hz, Ph C-2), 124.7 (q, $^3J_{C,F}$ = 3.8 Hz, Ph C-4), 124.7 (q, $^1J_{C,F}$ = 272.4 Hz, CF_3), 85.0 (d, $^1J_{C,F}$ = 224.0 Hz, CH_2F), 37.0 (CH_2).

^{19}F NMR (376 MHz, C_6D_6): δ –186.2 (t, $^2J_{H,F}$ = 50.9 Hz, CH_2F), -62.3 (s, CF_3).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{11}H_9F_4N_2S_3$: 340.9858; found: 340.9861.

Fluoromethyl trityl sulfide (44)



By following the general procedure, starting from triphenylmethanethiol (0.276 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **44** was obtained in 88% yield (0.271 g) as a yellow solid.

mp: 91-93 °C

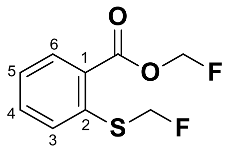
^{1}H NMR (400 MHz, C_6D_6): δ 7.49 (m, 6H, Ph H-2,6), 7.04 (m, 6H, Ph H-3,5), 6.96 (m, 3H, Ph H-4), 4.89 (d, $^2J_{H,F}$ = 53.2 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 144.9 (d, $^4J_{C,F}$ = 2.1 Hz, Ph C-1), 130.5 (d, $^5J_{C,F}$ = 0.8 Hz, Ph C-2,6), 128.2 (Ph C-3,5), 127.3 (Ph C-4), 86.0 (d, $^1J_{C,F}$ = 215.7 Hz, CH_2F), 69.5 (d, $^3J_{C,F}$ = 1.1 Hz, C-1).

^{19}F NMR (376 MHz, C_6D_6): δ –183.0 (t, $^2J_{H,F}$ = 53.2 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_{20}H_{18}FS$: 309.1108; found: 309.1109.

Fluoromethyl 2-[(fluormomethyl)sulfanyl]benzoate (45)



By following the general procedure, starting from 2-mercaptobenzoic acid (0.154 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.782 g, 2.4 mmol, 2.4 equiv) and fluoroiodomethane (0.384 g, 2.4 mmol, 2.4 equiv) in dry acetonitrile (2 mL), compound **45** was obtained in 97% yield (0.211 g) as a brown solid.

mp: 67 °C

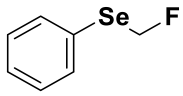
^{1}H NMR (400 MHz, C_6D_6): δ 7.75 (dd, ^3J = 7.9 Hz, ^4J = 1.6 Hz, 1H, Ph H-6), 7.43 (dd, ^3J = 8.1 Hz, ^4J = 1.2 Hz, 1H, Ph H-3), 6.92 (m, 1H, Ph H-4), 6.73 (m, 1H, Ph H-5), 5.34 (d, $^2J_{H,F}$ = 50.8 Hz, 2H, OCH_2F), 5.11 (d, $^2J_{H,F}$ = 52.4 Hz, 2H, SCH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 163.9 (d, $^3J_{C,F}$ = 1.4 Hz, C=O), 141.2 (d, $^3J_{C,F}$ = 3.5 Hz, Ph C-2), 133.7 (Ph C-4), 131.7 (Ph C-6), 127.5 (d, $^4J_{C,F}$ = 2.8 Hz, Ph C-3), 126.9 (m, Ph C-1), 125.7 (d, $J_{C,F}$ = 1.1 Hz, Ph C-5), 93.8 (d, $^1J_{C,F}$ = 221.3 Hz, OCH_2F), 85.7 (d, $^1J_{C,F}$ = 215.8 Hz, SCH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ –185.8 (t, $^2J_{H,F}$ = 52.4 Hz, SCH_2F), - 157.2 (t, $^2J_{H,F}$ = 50.8 Hz, OCH_2F).

HRMS (ESI), *m/z* $[M + Na]^+$ calcd. for $C_9H_8F_2NaO_2S$: 241.0105; found: 241.0107.

[(Fluoromethyl)selanyl]benzene (46)[14]



By following the general procedure, starting from phenylselenol (0.157 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **46** was obtained in 77% yield (0.146 g) as a colorless oil after purification by column chromatography on reverse phase silica gel (MeCN:H_2O; 8:2).

^{1}H NMR (400 MHz, C_6D_6): δ 7.45 (m, 2H, Ph H-2,6), 6.93 (m, 2H, Ph H-3,5), 6.94 (m, 1H, Ph H-4), 5.41 (d, $^2J_{H,F}$ = 52.0 Hz, 2H, CH_2F).

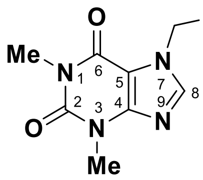
^{13}C NMR (100 MHz, C_6D_6): δ 133.3 (d, $^4J_{C,F}$ = 1.7 Hz, Ph C-2,6), 130.1 (d, $^3J_{C,F}$ = 2.4 Hz, Ph C-1), 129.5 (Ph C-3,5), 128.0 (Ph C-4), 83.6 (d, $^1J_{C,F}$ = 228.0 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ –190.4 (t, $^2J_{H,F}$ = 52.0 Hz, CH_2F).

^{77}Se NMR (76 MHz, C_6D_6): δ 408.1 (m).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for C_7H_8FSe: 190.9770; found: 190.9773.

7-(Fluoromethyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (47)



By following the general procedure, starting from 1,3-dimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (theophylline) (0.180 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **47** was obtained in 96% yield (0.205 g) as a white solid.

mp: 153-156 °C

^{1}H NMR (400 MHz, C_6D_6): δ 6.54 (d, $^4J_{H,F}$ = 1.5 Hz, 1H, H-8), 5.32 (d, $^2J_{H,F}$ = 51.3 Hz, 2H, CH_2F), 3.25 (s, 3H, N1-CH_3), 3.23 (s, 3H, N3-CH_3).

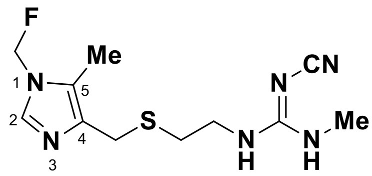
^{13}C NMR (100 MHz, C_6D_6): δ 154.7 (C-6), 151.2 (C-2), 149.1 (C-4), 141.4 (C-8), 106.2 (d, $^3J_{C,F}$ = 3.5 Hz, C-5), 81.8 (d, $^1J_{C,F}$ = 204.3 Hz, CH_2F), 29.4 (N3-CH_3), 27.7 (N1-CH_3).

^{19}F NMR (376 MHz, C_6D_6): δ –161.9 (t, $^2J_{H,F}$ = 51.3 Hz, CH_2F).

^{15}N NMR (40 MHz, C_6D_6): δ –269.4 (N-3), –230.7 (N-1), –214.3 (N-7), –143.1 (N-9).

HRMS (ESI): *m/z*: $[M + H]^+$ calcd. for $C_8H_{10}FN_4O_2$: 213.0782; found: 213.0778.

2-Cyano-1-[2-({[1-(fluoromethyl)-5-methyl-1*H*-imidazol-4-yl]methyl}sulfanyl)ethyl]-3-methylguanidine (48)



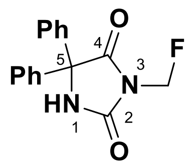
By following the general procedure, starting from 1-cyano-2-methyl-3-[2-[(5-methyl-1*H*-imidazol-4-yl)methylsulfanyl]ethyl]guanidine (cimetidine) (0.252 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **48** was obtained in 85% yield (0.241 g) as a yellow oil.

^{1}H NMR (400 MHz, acetone-d_6): δ 7.91 (s, 1H, imidazole H-2), 6.80 (br s, 1H, NH), 6.50 (br s, 1H, <u>NH</u>CH_3), 6.10 (d, $^2J_{H,F}$ = 52.7 Hz, 2H, CH_2F), 3.73 (s, 2H, SCH_2), 3.50 (m, 2H, $SCH_2\underline{CH_2}N$), 2.86 (d, ^3J = 4.6 Hz, 3H, $\underline{CH_3}NH$), 2.71 (m, 2H, $S\underline{CH_2}CH_2$), 2.30 (s, 3H, CH_3).

^{13}C NMR (100 MHz, acetone-d_6): δ 161.6 (C=N), 138.4 (imidazole C-2), 137.1 (imidazole C-4), 125.0 (imidazole C-5), 118.8 (C≡N), 83.2 (d, $^1J_{C,F}$ = 195.0 Hz, CH_2F), 42.1 ($SCH_2\underline{CH_2}N$), 30.9 ($S\underline{CH_2}CH_2$), 28.6 (CH_3NH), 27.0 (SCH_2), 7.7 (5-CH_3).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for: $C_{11}H_{18}FN_6S$: 285.1292; found: 285.1298.

3-(Fluoromethyl)-5,5-diphenyl-2,4-imidazolidinedione (49)



To a mixture of 5,5-diphenylhydantoin (phenytoin) (0.252 g, 1.0 mmol, 1.0 equiv) and Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) was added slowly at rt. The reaction mixture was stirred 6 h at rt and then quenched with water. The reaction mixture was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the final compound in 87% yield (0.247 g) as a white solid, after purification by column chromatography on silica gel (*n*-hexane:EtOAc; 8:2).

mp: 187-189 °C

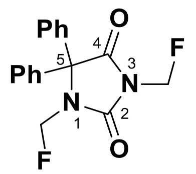
^{1}H NMR (400 MHz, C_6D_6): δ 7.33 (m, 4H, Ph H-2,6), 7.12 (s, 1H, N-H), 6.98 (m, 6H, Ph H-3,4,5), 5.12 (d, $^2J_{H,F}$ = 51.9 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 172.2 (d, $^3J_{C,F}$ = 2.5 Hz, C-4), 154.5 (d, $^3J_{C,F}$ = 2.0 Hz, C-2), 139.2 (Ph C-1), 129.1 (Ph C-3,5), 128.8 (Ph C-4), 127.2 (Ph C-2,6), 76.1 (d, $^1J_{C,F}$ = 199.5 Hz, CH_2F), 70.5 (C-5).

^{19}F NMR (376 MHz, C_6D_6): δ –175.3 (t, $^2J_{H,F}$ = 51.9 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + Na]^+$ calcd. for $C_{16}H_{13}FN_2NaO_2$: 307.0853; found: 307.0853.

1,3-Bis(fluoromethyl)-5,5-diphenyl-2,4-imidazolidione (50)



By following the general procedure, starting from 5,5-diphenylhydantoin (phenytoin) (0.252 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.782 g, 2.4 mmol, 2.4 equiv) and fluoroiodomethane (0.384 g, 2.4 mmol, 2.4 equiv) in dry acetonitrile (2 mL), compound **50** was obtained in 92% yield (0.291 g) as a colorless oil.

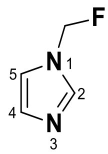
^{1}H NMR (400 MHz, C_6D_6): δ 7.19 (m, 4H, Ph H-2,6), 6.97 (m, 2H, Ph H-4), 6.99 (m, 4H, Ph H-3,5), 5.12 (d, $^2J_{H,F}$ = 51.6 Hz, 2H, 3-CH_2F), 5.04 (d, $^2J_{H,F}$ = 54.2 Hz, 2H, 1-CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 171.7 (d, $^3J_{C,F}$ = 2.7 Hz, C-4), 153.8 (t, $^3J_{C,F}$ = 2.5 Hz, C-2), 136.8 (d, $^5J_{C,F}$ = 2.0 Hz, Ph C-1), 129.4 (Ph C-4), 129.1 (Ph C-3,5), 128.6 (Ph C-2,6), 80.2 (d, $^1J_{C,F}$ = 200.6 Hz, 1-CH_2F), 76.4 (d, $^1J_{C,F}$ = 200.7 Hz, 3-CH_2F), 74.9 (d, $^4J_{C,F}$ = 2.3 Hz, C-5).

^{19}F NMR (376 MHz, C_6D_6): δ −175.8 (dt, $^2J_{H,F}$ = 51.6 Hz, $J_{F,F}$ = 1.4 Hz, 3-CH_2F), −169.5 (dt, $^2J_{H,F}$ = 54.2 Hz, $J_{F,F}$ = 1.4 Hz, 1-CH_2F).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{17}H_{14}F_2N_2NaO_2$: 339.0916; found: 339.0911.

1-(Fluoromethyl)-1*H*-Imidazole (51)[15]



By following the general procedure, starting from imidazole (0.068 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **51** was obtained in 83% yield (0.083 g) as a yellow oil.

^{1}H NMR (400 MHz, acetone-d_6): δ 8.43 (s, 1H, H-2), 7.66 (m, 1H, H-5), 7.27 (m, 1H, H-4), 6.31 (d, $^{2}J_{H,F}$ = 50.9 Hz, 2H, CH_2F).

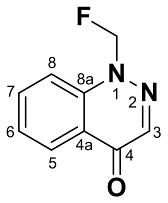
^{13}C NMR (100 MHz, acetone-d_6): δ 141.0 (C-2), 128.6 (C-4), 122.1 (C-5), 85.4 (d, $^{1}J_{C,F}$ = 198.3 Hz, CH_2F).

^{19}F NMR (376 MHz, acetone-d_6): δ – 166.2 (t, $^{2}J_{H,F}$ = 50.9 Hz, CH_2F).

^{15}N NMR (40 MHz, C_6D_6): δ –200.8 (N-1), –157.3 (N-3).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_4H_6FN_2$: 101.0510; found: 101.0510.

1-(Fluoromethyl)-4(1*H*)-cinnolinone (52)



By following the general procedure, starting from cinnolin-4(1*H*)-one (0.146 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **52** was obtained in 94% yield (0.167 g) as an orange solid, after purification by column chromatography on silica gel (*n*-hexane:EtOAc; 1:1).

mp: 118 °C

^{1}H NMR (400 MHz, C_6D_6): δ 8.28 (m, 1H, H-5), 7.62 (d, $^{5}J_{H,F}$ = 1.9 Hz, 1H, H-3), 6.96 (m, 1H, H-7), 6.80 (m, 1H, H-6), 6.70 (d, ^{3}J = 8.6 Hz, 1H, H-8), 5.30 (d, $^{2}J_{H,F}$ = 53.4 Hz, 2H, CH_2F).

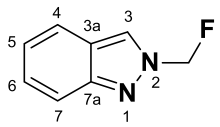
^{13}C NMR (100 MHz, C_6D_6): δ 170.9 (d, $^{5}J_{C,F}$ = 1.8 Hz, C-4), 141.7 (d, $^{4}J_{C,F}$ = 2.8 Hz, C-3), 140.4 (d, $^{3}J_{C,F}$ = 3.1 Hz, C-8a), 133.7 (C-6), 126.1 (C-5), 125.3 (C-7), 124.3 (C-4a), 114.4 (d, $^{4}J_{C,F}$ = 1.5 Hz, C-8), 91.3 (d, $^{1}J_{C,F}$ = 205.0 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ –170.0 (t, $^{2}J_{H,F}$ = 53.4 Hz, CH_2F).

^{15}N NMR (40 MHz, C_6D_6): δ –212.1 (N-1), –38.1 (N-2).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_9H_8FN_2O$: 179.0615; found: 179.0620.

2-(Fluoromethyl)-2*H*-indazole (53)



By following the general procedure, starting from indazole (0.118 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **53** was obtained in 91% yield (0.136 g) as a colorless oil, after purification by column chromatography on silica gel (*n*-hexane:EtOAc; 8:2).

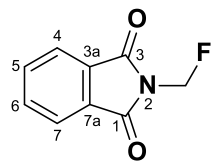
^{1}H NMR (400 MHz, C_6D_6): δ 7.80 (m, 1H, H-7), 7.37 (m, 1H, H-4), 7.10 (s, 1H, H-3), 7.05 (m, 1H, H-6), 6.89 (m, 1H, H-5), 5.43 (d, $^2J_{H,F}$ = 51.9 Hz, 2H, CH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 150.6 (d, $^4J_{C,F}$ = 1.5 Hz, C-7a), 127.4 (C-6), 124.1 (C-3), 123.0 (C-5), 122.9 (C-3a), 120.8 (C-4), 119.1 (C-7), 88.7 (d, $^1J_{C,F}$ = 203.3 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ –163.2 (t, $^2J_{H,F}$ = 51.9 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_8H_8FN_2$: 151.0666; found: 151.0668

2-(Fluoromethyl)-1*H*-isoindole-1,3(2*H*)-dione (54)[16]



By following the general procedure, starting from phthalimide (0.147 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **54** was obtained in 82% yield (0.147 g) as a white solid, after purification by column chromatography on silica gel (*n*-hexane:EtOAc; 8:2).

mp: 93 °C

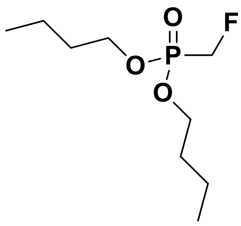
^{1}H NMR (400 MHz, C_6D_6): δ 7.32 (m, 2H, H-4,7), 6.81 (m, 2H, H-5,6), 5.29 (d, $^2J_{H,F}$ = 52.5 Hz, 2H, CH_2F)

^{13}C NMR (100 MHz, C_6D_6): δ 166.0 (d, $^3J_{C,F}$ = 2.5 Hz, C-1,3), 134.1 (C-5,6), 131.9 (C-3a,7a), 123.6 (C-4,7), 74.9 (d, $^1J_{C,F}$ = 197.7 Hz, CH_2F).

^{19}F NMR (376 MHz, C_6D_6): δ −173.8 (t, $^2J_{H,F}$ = 52.5 Hz, CH_2F).

HRMS (ESI), $[M + H]^+$ calcd. for $C_9H_7FNO_2$: 180.0455; found: 180.0456.

Dibutyl (fluoromethyl)phosphonate (55)



By following the general procedure, starting from dibutyl phosphite (0.194 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.391 g, 1.2 mmol, 1.2 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **55** was obtained in 70% yield (0.158 g) as a colorless oil, after purification by column chromatography on silica gel (*n*-hexane:EtOAc; 8:2).

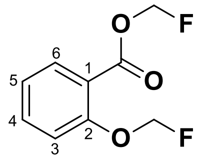
^{1}H NMR (400 MHz, C_6D_6): δ 4.34 (dd, $^{2}J_{H,F}$ = 47.1 Hz, $^{2}J_{H,P}$ = 4.7, 2H, CH_2F), 3.93 (m, 4H, $O\underline{CH_2}CH_2CH_2CH_3$), 1.40 (m, 4H, $OCH_2\underline{CH_2}CH_2CH_3$), 1.19 (m, 4H, $OCH_2CH_2\underline{CH_2}CH_3$), 0.74 (t, ^{3}J = 7.3 Hz, 6H, $OCH_2CH_2CH_2\underline{CH_3}$).

^{13}C NMR (100 MHz, C_6D_6): δ 76.8 (dd, $^{1}J_{C,F}$ = 181.0 Hz, $^{1}J_{C,P}$ = 168.5 Hz, CH_2F), 66.3 (d, $^{2}J_{C,P}$ = 6.3 Hz, $O\underline{CH_2}CH_2CH_2CH_3$), 32.8 (d, $^{3}J_{C,P}$ = 5.6 Hz, $OCH_2\underline{CH_2}CH_2CH_3$), 18.9 ($OCH_2CH_2\underline{CH_2}CH_3$), 13.6 ($OCH_2CH_2CH_2\underline{CH_3}$).

^{19}F NMR (376 MHz, C_6D_6): δ –248.6 (dt, d: $^{2}J_{P,F}$ = 61.9 Hz, t: $^{2}J_{H,F}$ = 47.1 Hz, CH_2F).

HRMS (ESI), *m/z* $[M + Na]^+$ calcd. for $C_9H_{20}FNaO_3P$: 249.1026; found: 249.1031.

Fluoromethyl 2-(fluoromethoxy)benzoate (56)



By following the general procedure, starting from 2-hydroxybenzoic acid (salicylic acid) (0.138 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.782 g, 2.4 mmol, 2.4 equiv) and fluoroiodomethane (0.384 g, 2.4 mmol, 2.4 equiv) in dry acetonitrile (2 mL), compound **56** was obtained in 91% yield (0.184 g) as a colorless oil.

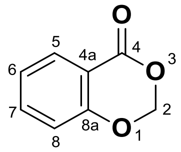
^{1}H NMR (400 MHz, C_6D_6): δ 7.70 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.7 Hz, 1H, Ph H-6), 6.92 (m, 1H, Ph H-4), 6.88 (m, 1H, Ph H-3), 6.65 (m, 1H, Ph H-5), 5.40 (d, $^{2}J_{H,F}$ = 50.9 Hz, 2H, $COOCH_2F$), 5.14 (d, $^{2}J_{H,F}$ = 54.4 Hz, 2H, OCH_2F).

^{13}C NMR (100 MHz, C_6D_6): δ 163.1 (d, $^{3}J_{C,F}$ = 1.5 Hz, C=O), 157.1 (d, $^{3}J_{C,F}$ = 3.1 Hz, Ph C-2), 134.5 (Ph C-4), 132.2 (Ph C-6), 123.6 (Ph C-5), 120.8 (d, $^{4}J_{C,F}$ = 1.8 Hz, Ph C-1), 118.2 (Ph C-3), 101.4 (d, $^{1}J_{C,F}$ = 220.5 Hz, OCH_2F), 93.7 (d, $^{1}J_{C,F}$ = 220.5 Hz, $COOCH_2F$).

^{19}F NMR (376 MHz, C_6D_6): δ –157.2 (t, $^{2}J_{H,F}$ = 50.9 Hz, $COOCH_2F$), –148.8 (t, $^{2}J_{H,F}$ = 54.4 Hz, OCH_2F).

HRMS (ESI), *m/z* $[M + Na]^+$ calcd. for $C_9H_8F_2NaO_3$: 225.0334; found: 225.0339.

4*H*-1,3-Benzodioxin-4-one (57)[17]



By following the general procedure, starting from 2-hydroxybenzoic acid (salicylic acid) (0.138 g, 1.0 mmol, 1.0 equiv), Cs_2CO_3 (0.782 g, 2.4 mmol, 2.4 equiv) and fluoroiodomethane (0.192 g, 1.2 mmol, 1.2 equiv) in dry acetonitrile (2 mL), compound **57** was obtained in 88% yield (0.132 g) as a white solid.

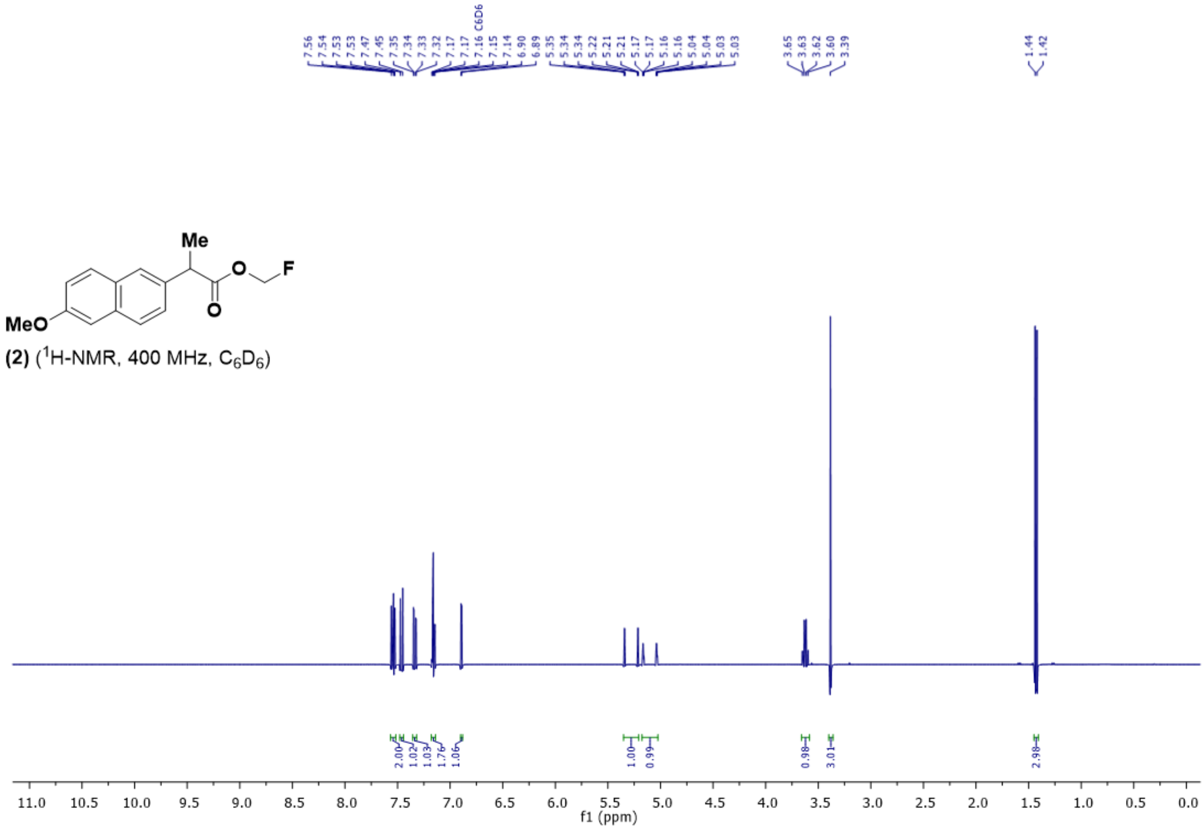
mp: 48 °C

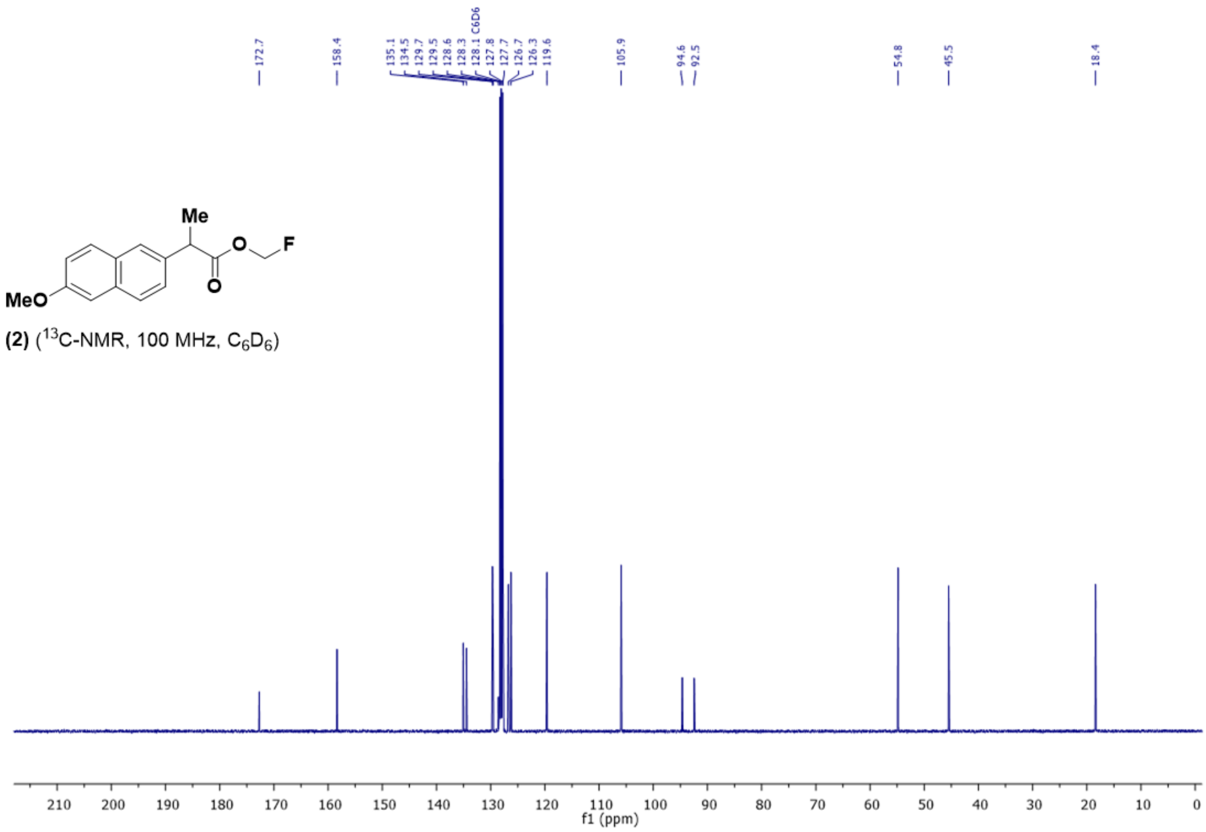
^{1}H NMR (400 MHz, C_6D_6): δ 7.92 (ddd, ^3J = 7.8 Hz, ^4J = 1.7 Hz, ^5J = 0.6 Hz, 1H, H-5), 6.85 (m, 1H, H-7), 6.57 (m, 1H, H-6), 6.54 (m, 1H, H-8), 4.70 (s, 2H, H-2).

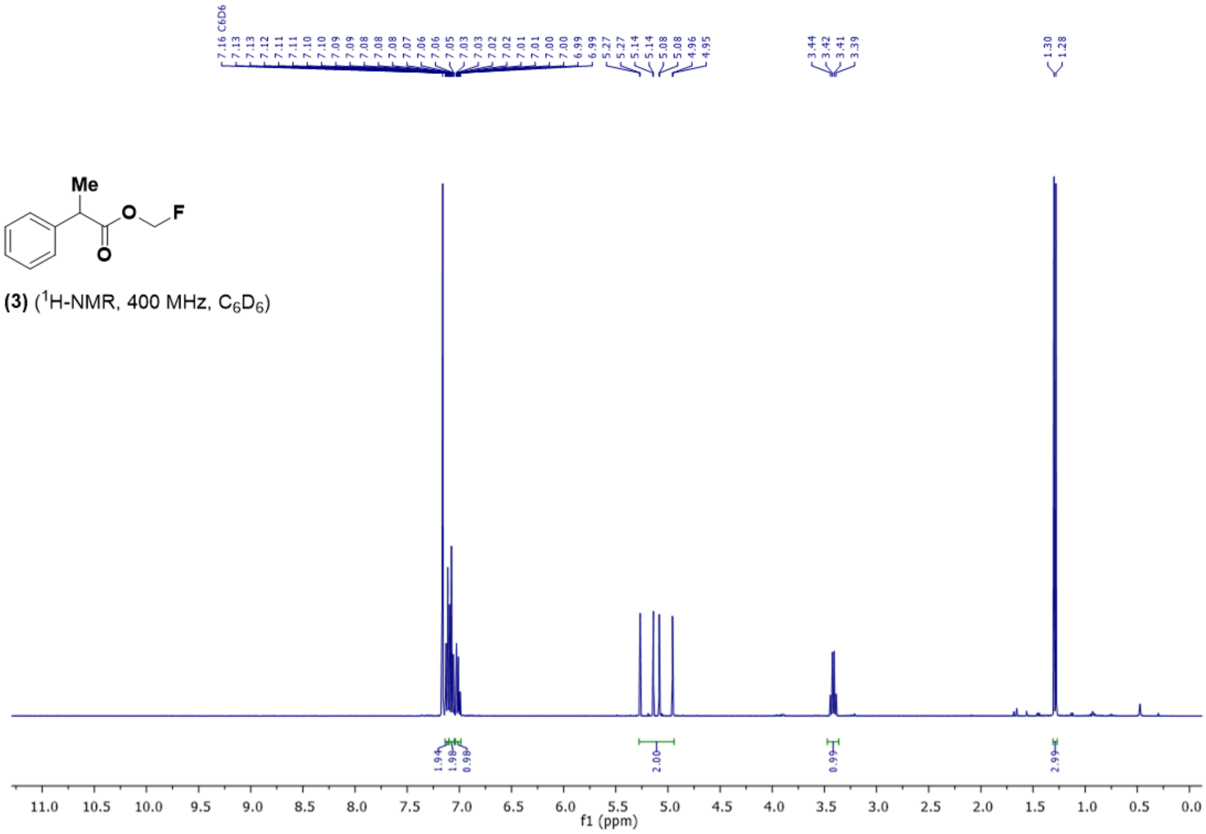
^{13}C NMR (100 MHz, C_6D_6): δ 160.7 (C-4), 158.7 (C-8a), 135.7 (C-7), 130.6 (C-5), 123.4 (C-6), 116.5 (C-8), 115.7 (C-4a), 90.8 (C-2).

HRMS (ESI), *m/z* $[M + H]^+$ calcd. for $C_8H_7O_3$: 151.0390; found: 151.0389.

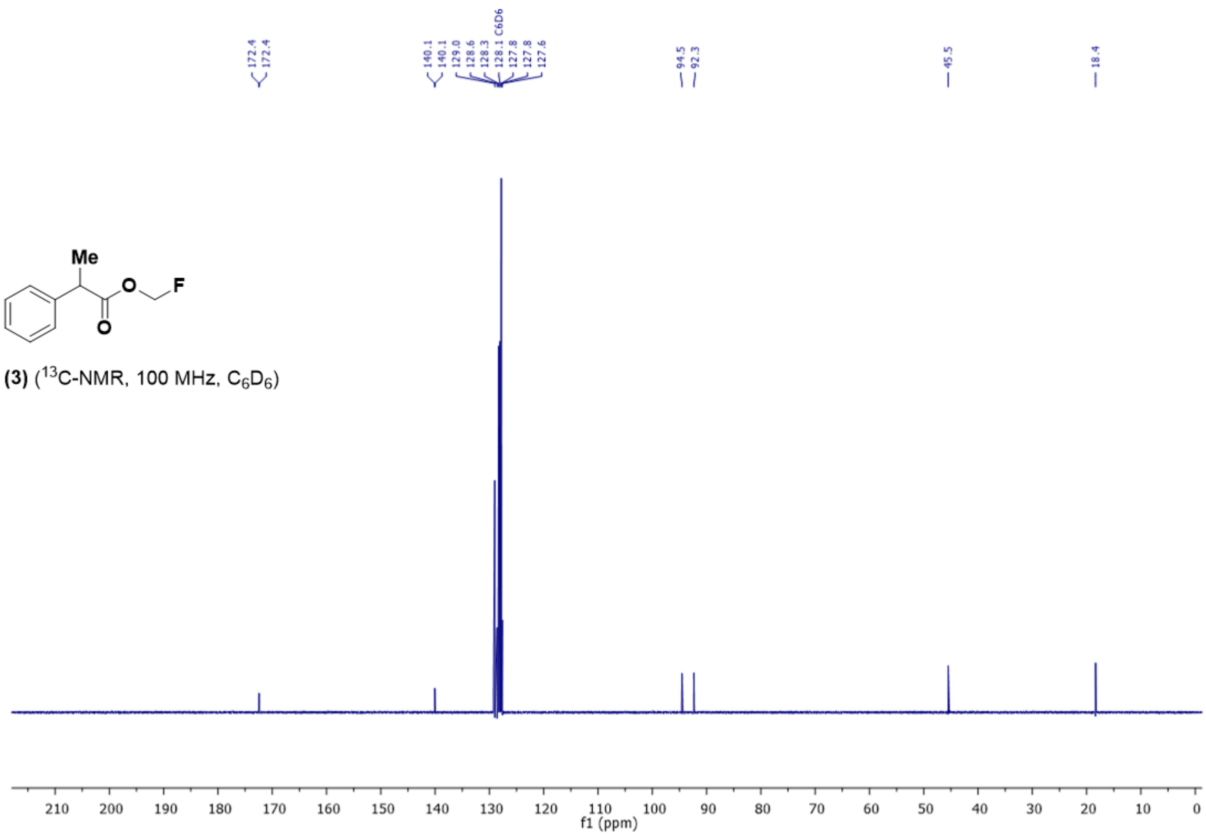
Copies of 1H- and 13C-NMR Spectra



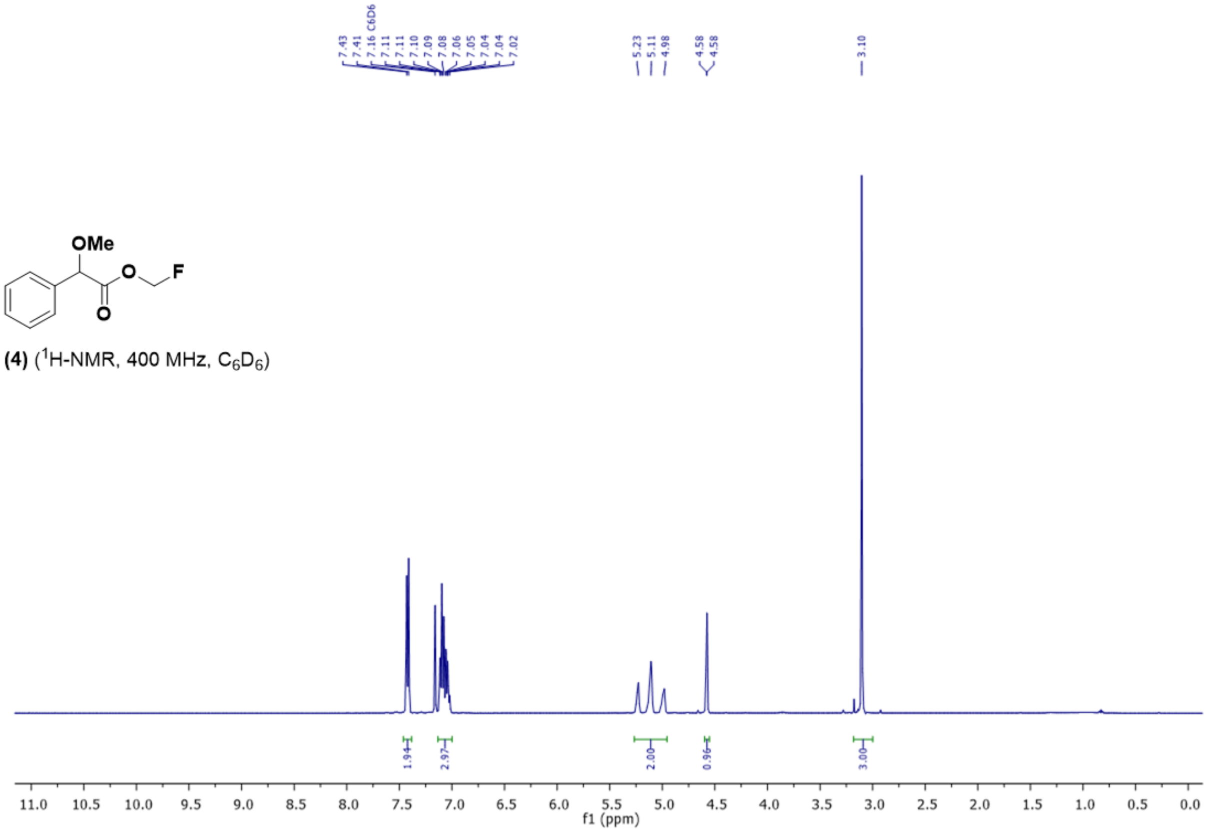




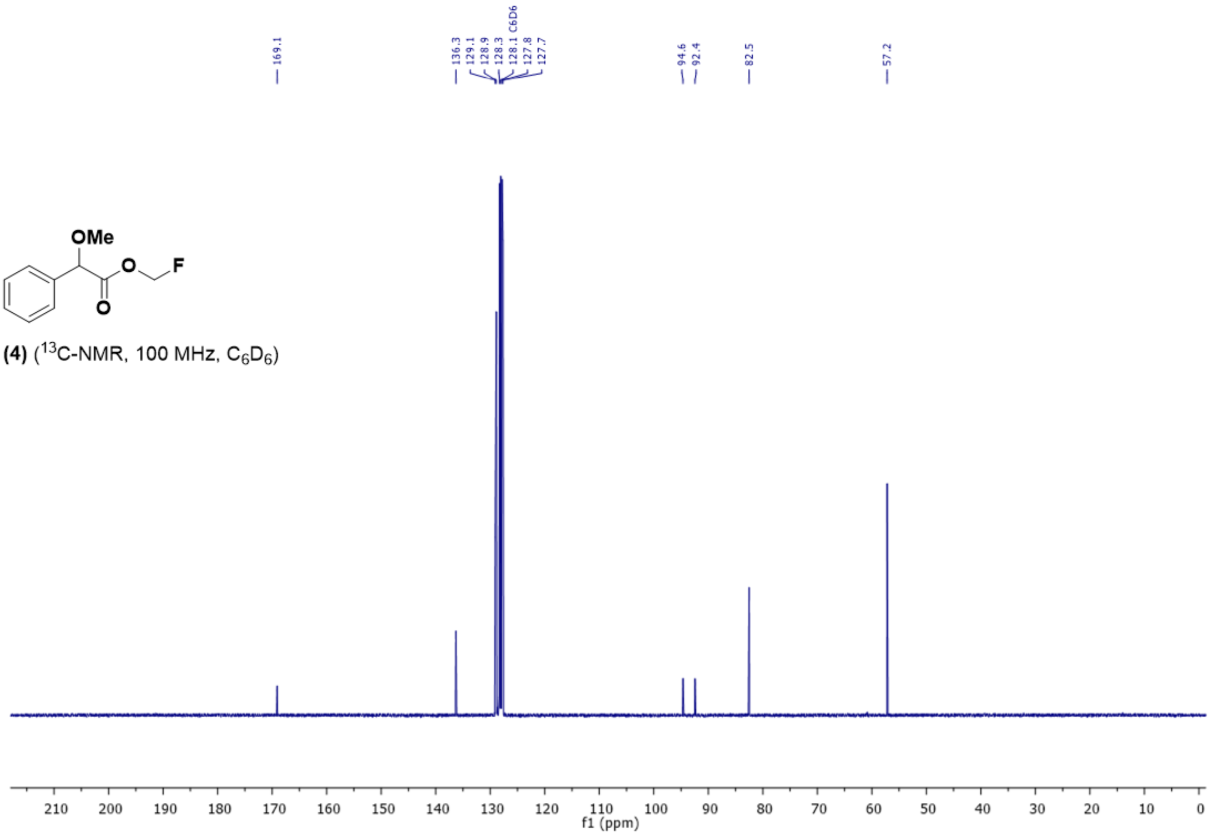
(3) (^{1}H-NMR, 400 MHz, C_6D_6)



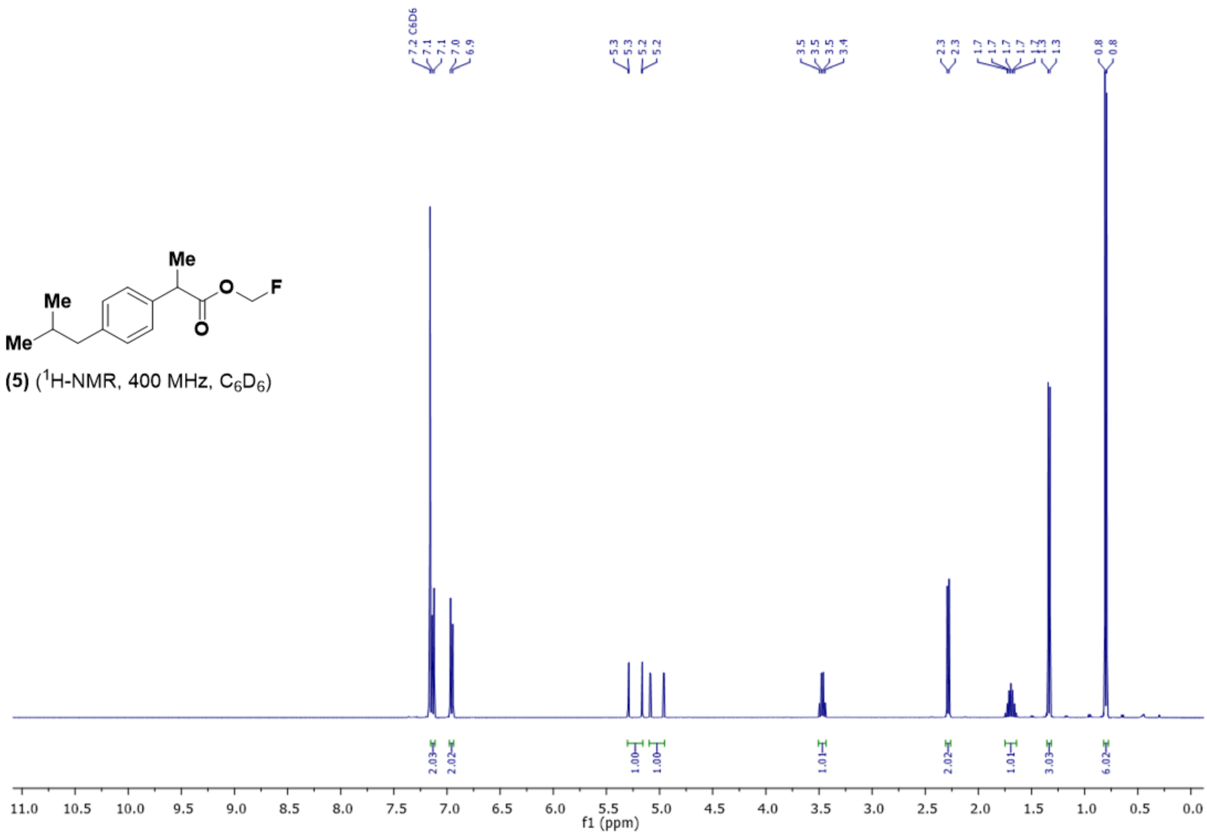
(3) (^{13}C-NMR, 100 MHz, C_6D_6)



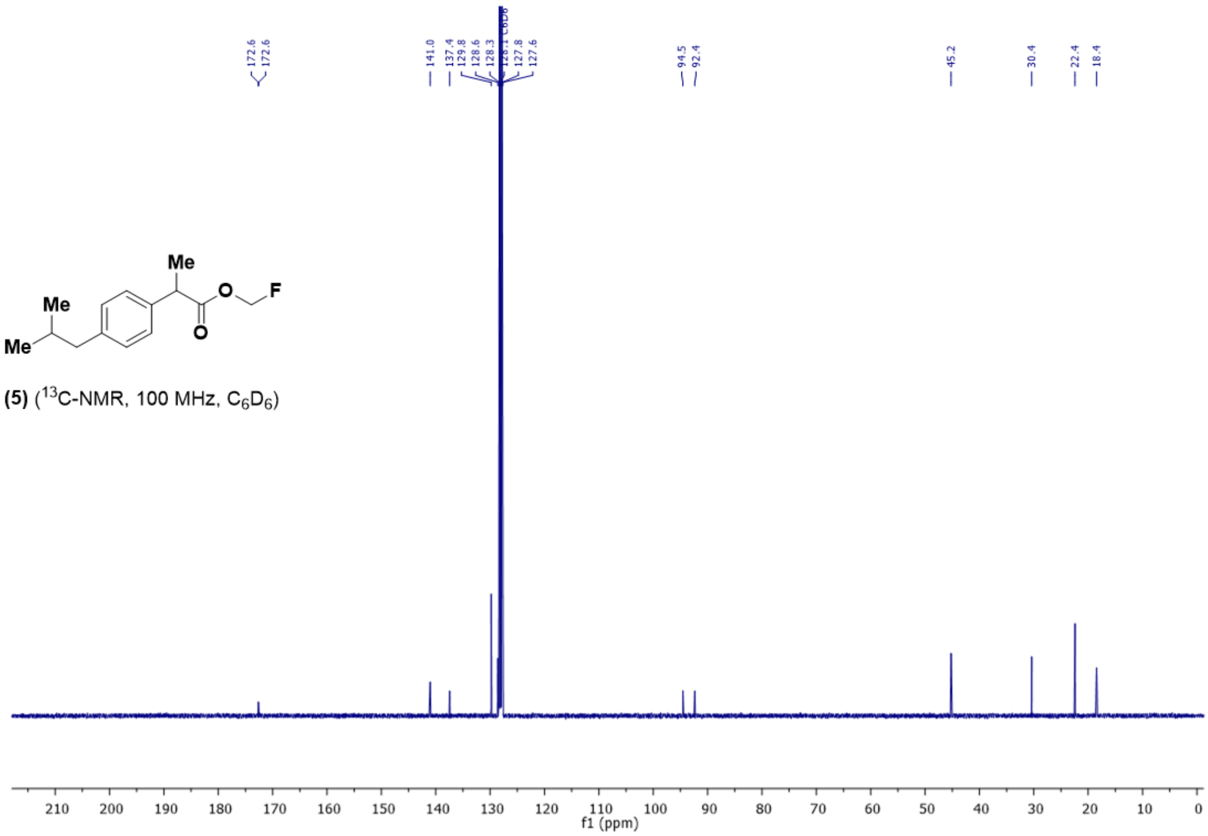
(4) (^{1}H-NMR, 400 MHz, C_6D_6)



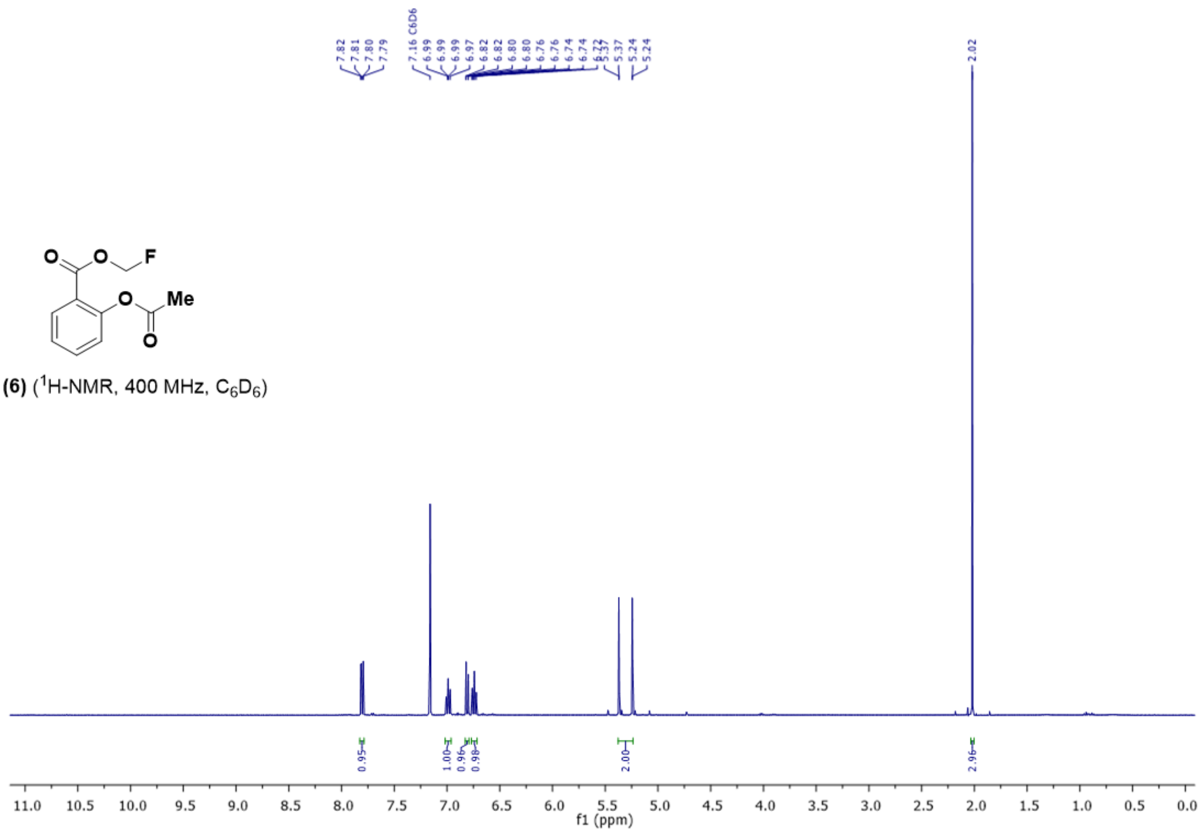
(4) (^{13}C-NMR, 100 MHz, C_6D_6)



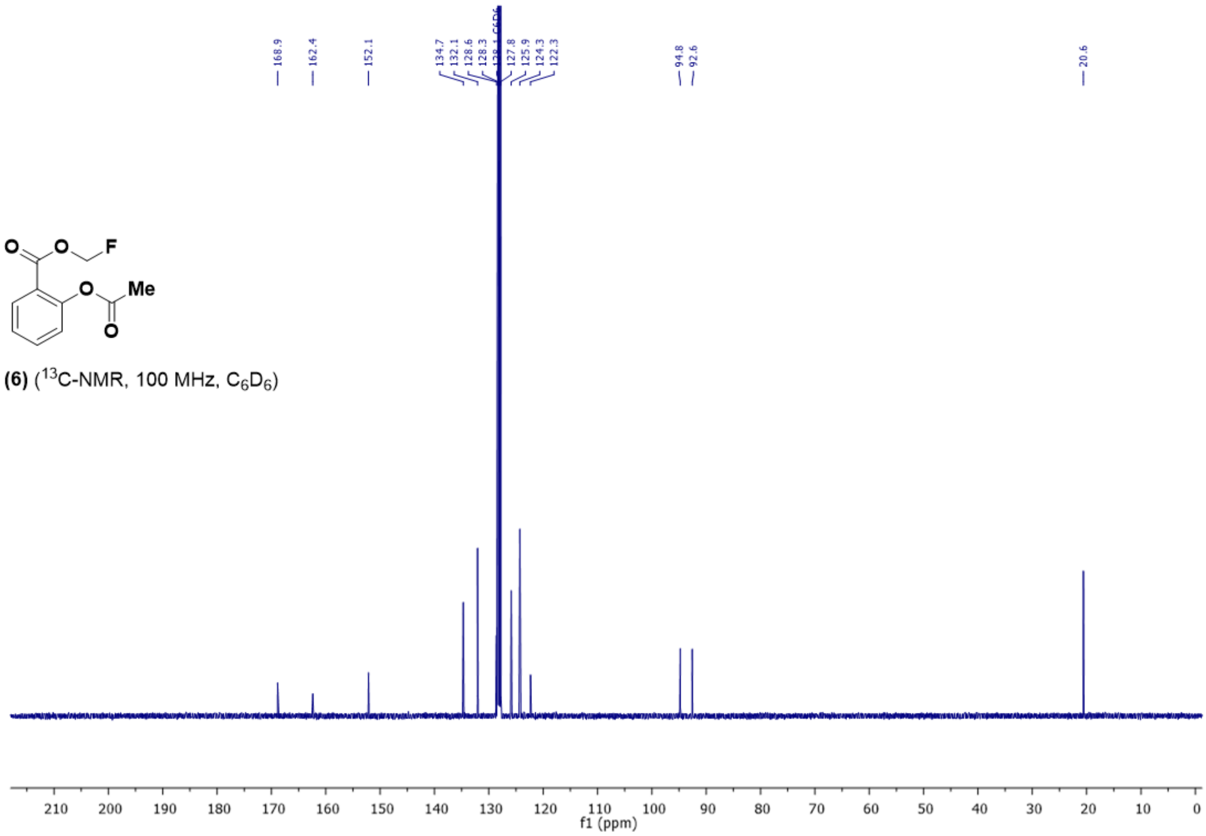
(5) (^{1}H-NMR, 400 MHz, C_6D_6)



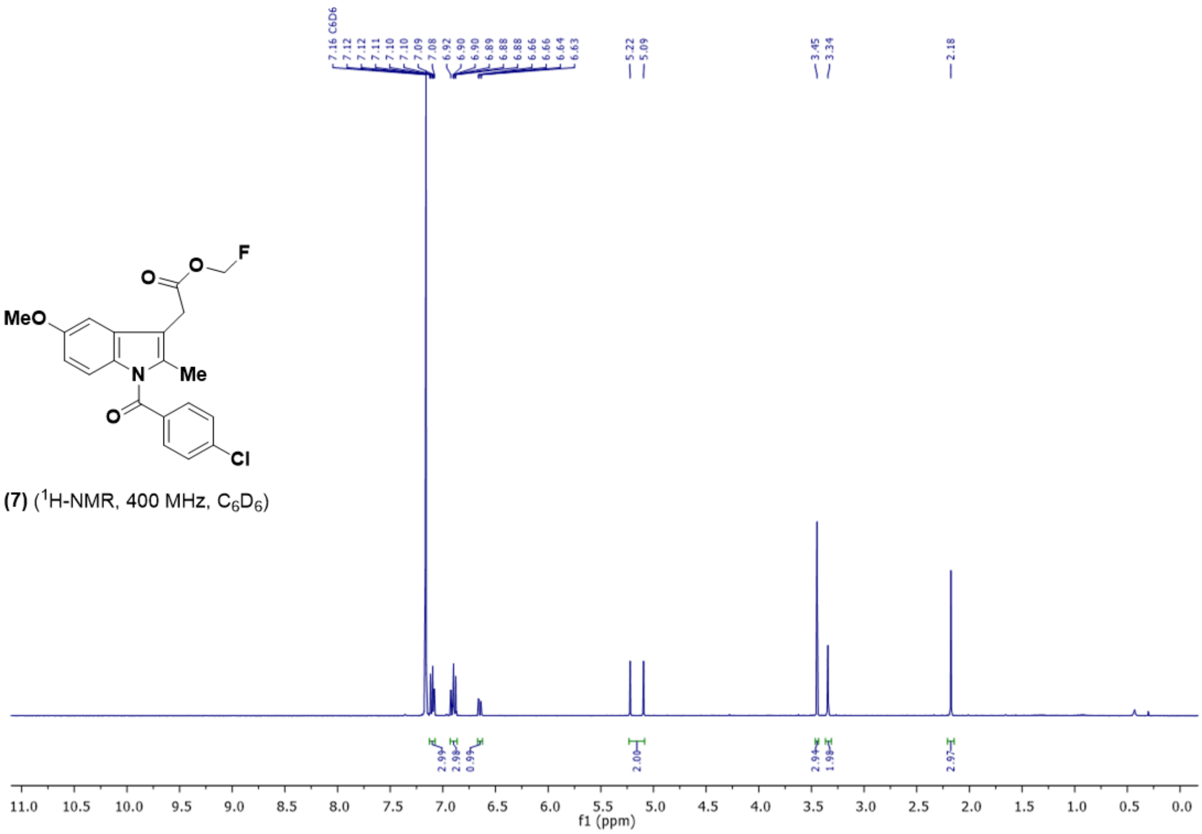
(5) (^{13}C-NMR, 100 MHz, C_6D_6)



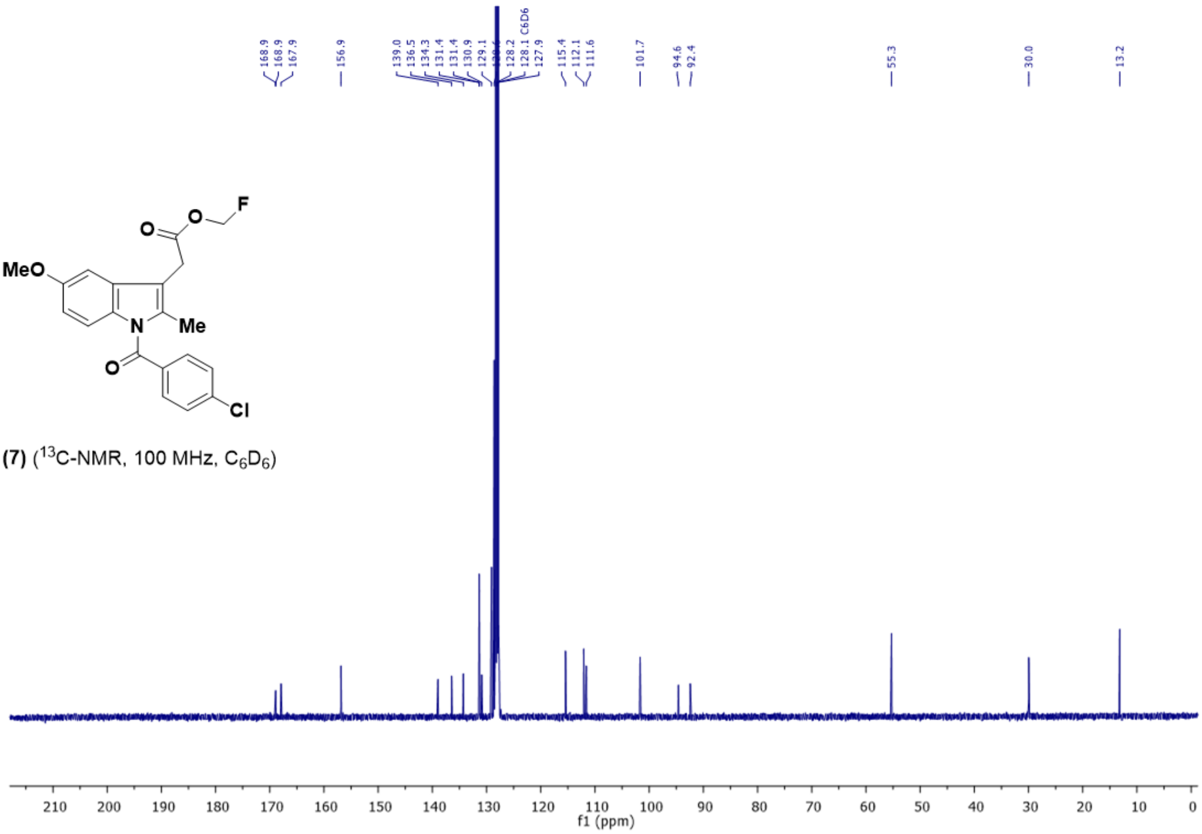
(6) (^{1}H-NMR, 400 MHz, C_6D_6)



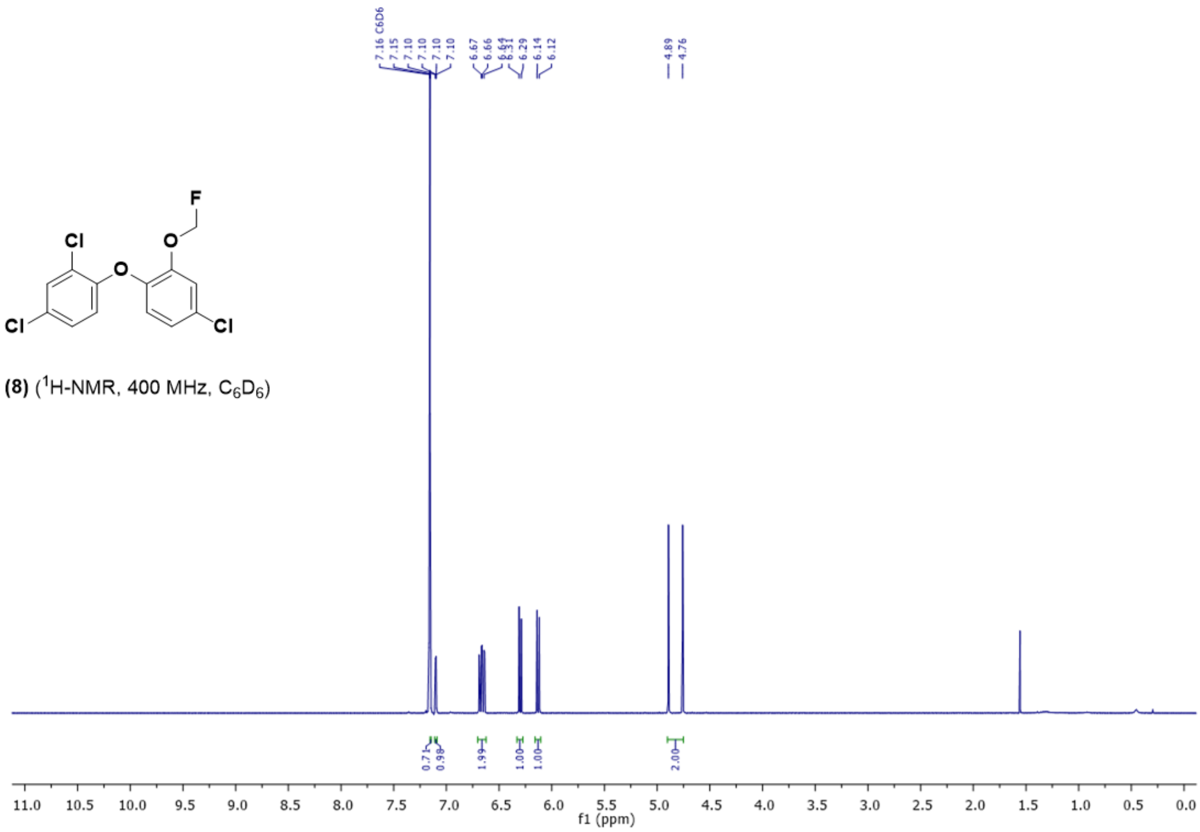
(6) (^{13}C-NMR, 100 MHz, C_6D_6)



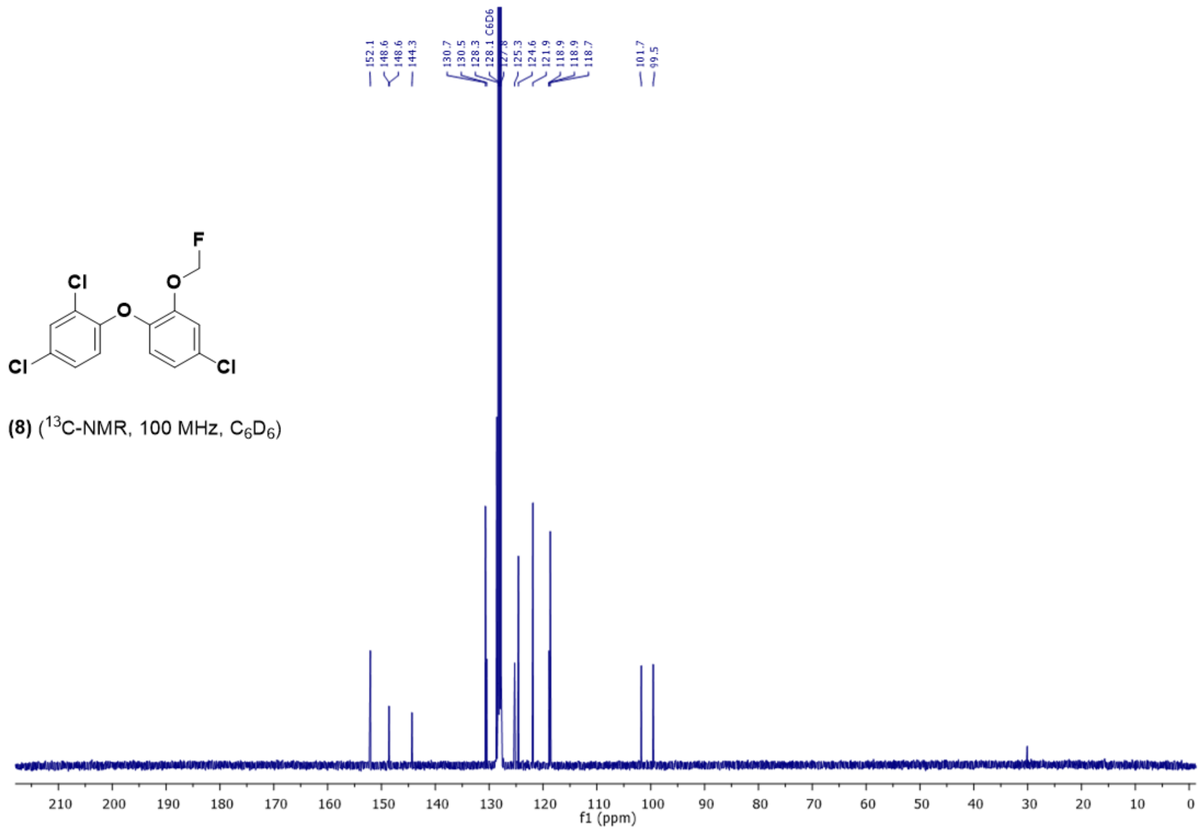
(7) (^{1}H-NMR, 400 MHz, C_6D_6)



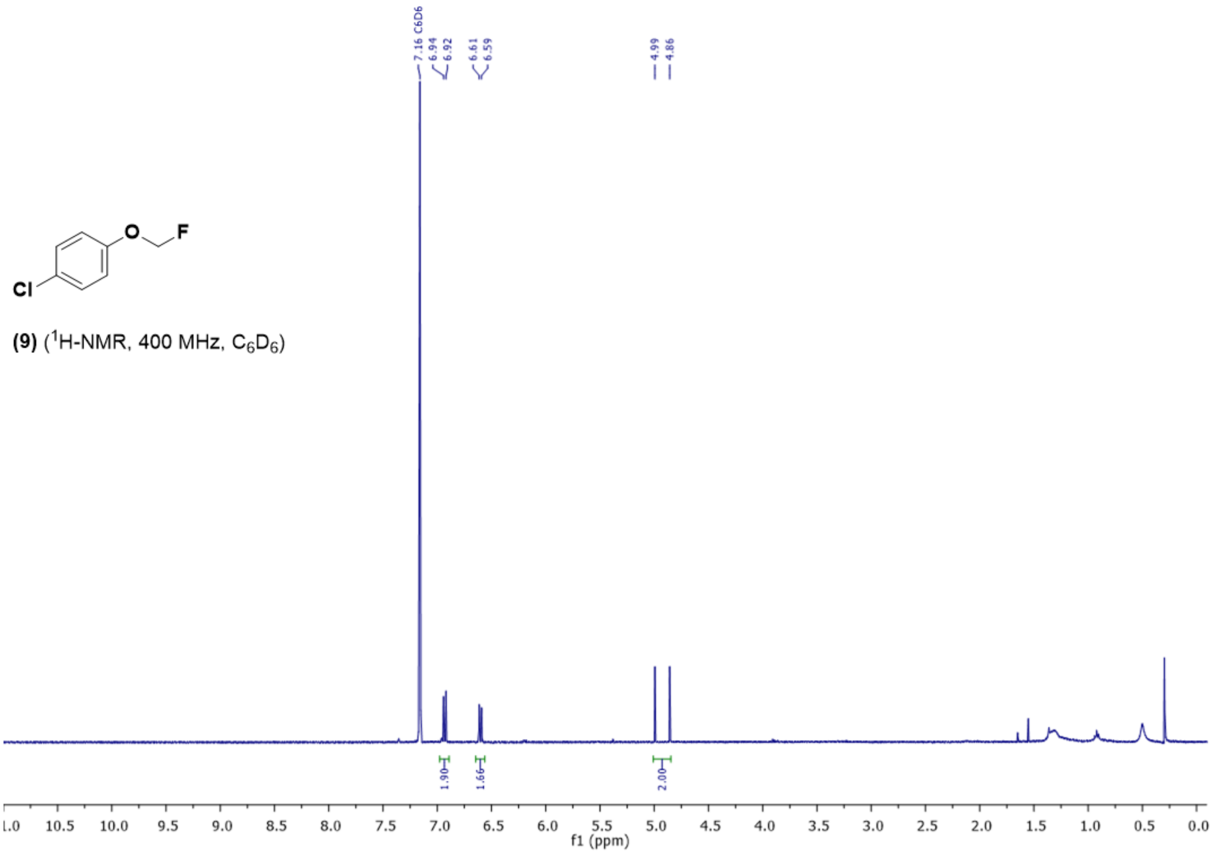
(7) (^{13}C-NMR, 100 MHz, C_6D_6)



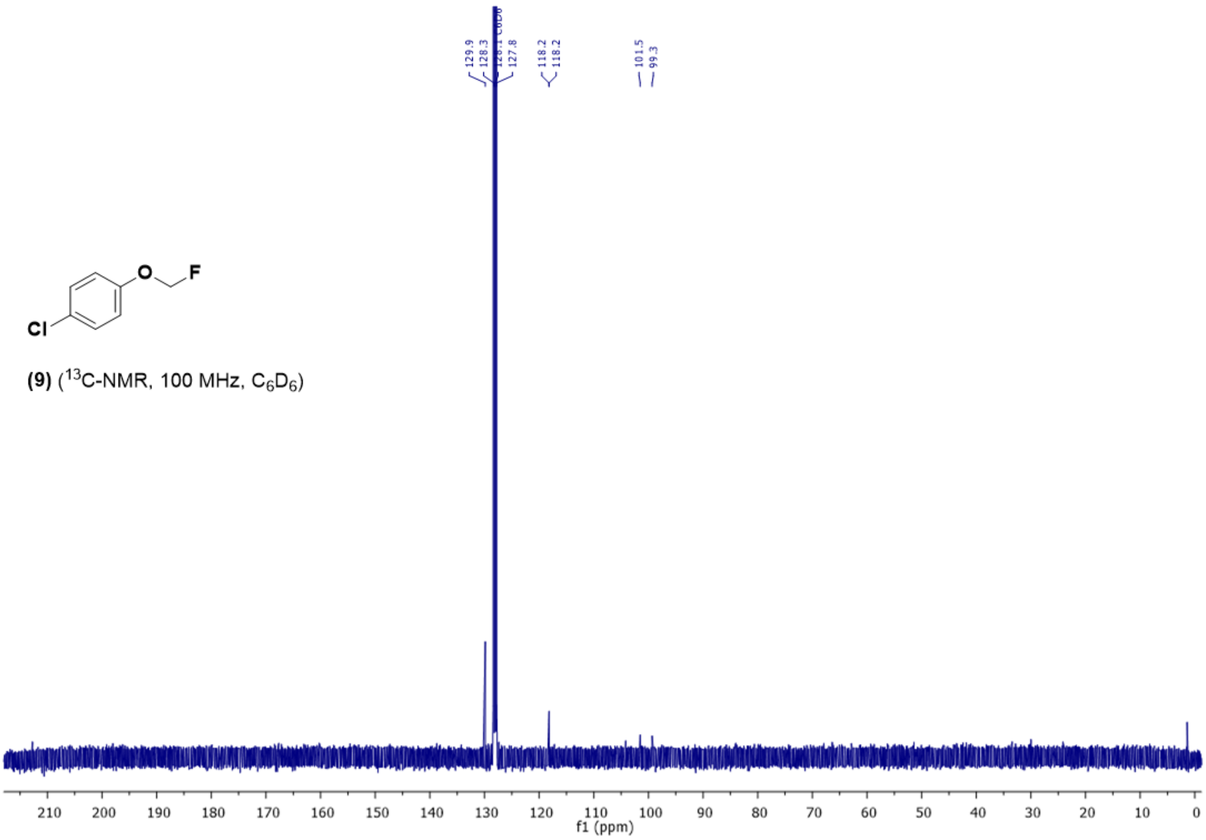
(8) (^{1}H-NMR, 400 MHz, C_6D_6)



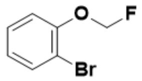
(8) (^{13}C-NMR, 100 MHz, C_6D_6)



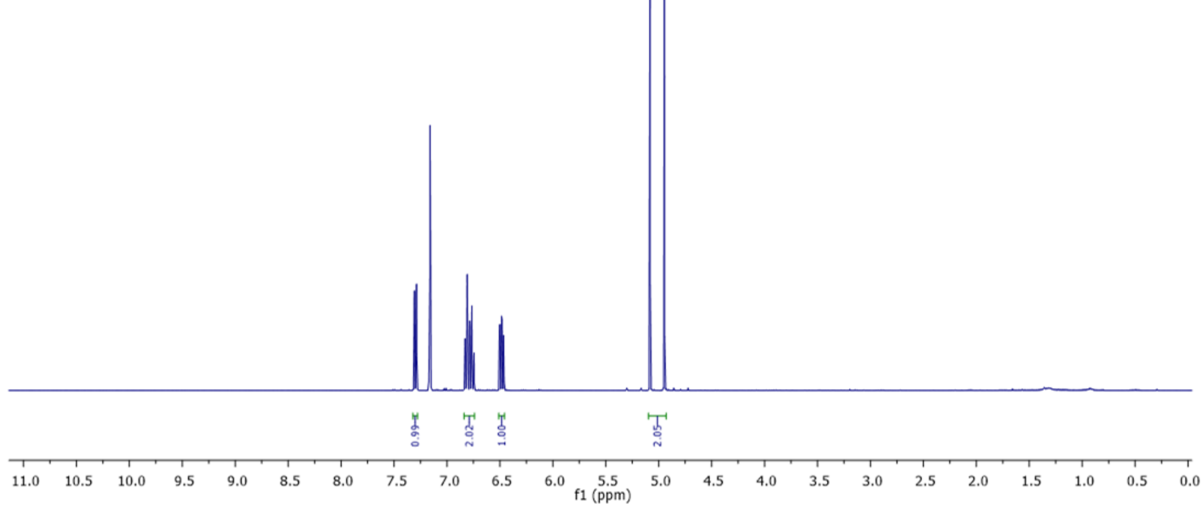
(9) (^{1}H-NMR, 400 MHz, C_6D_6)

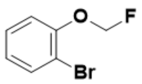


(9) (^{13}C-NMR, 100 MHz, C_6D_6)

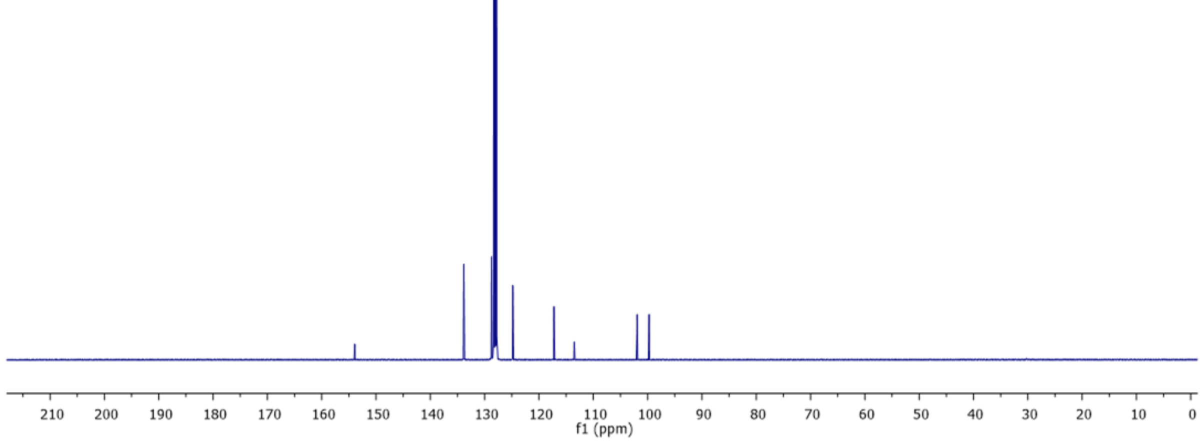


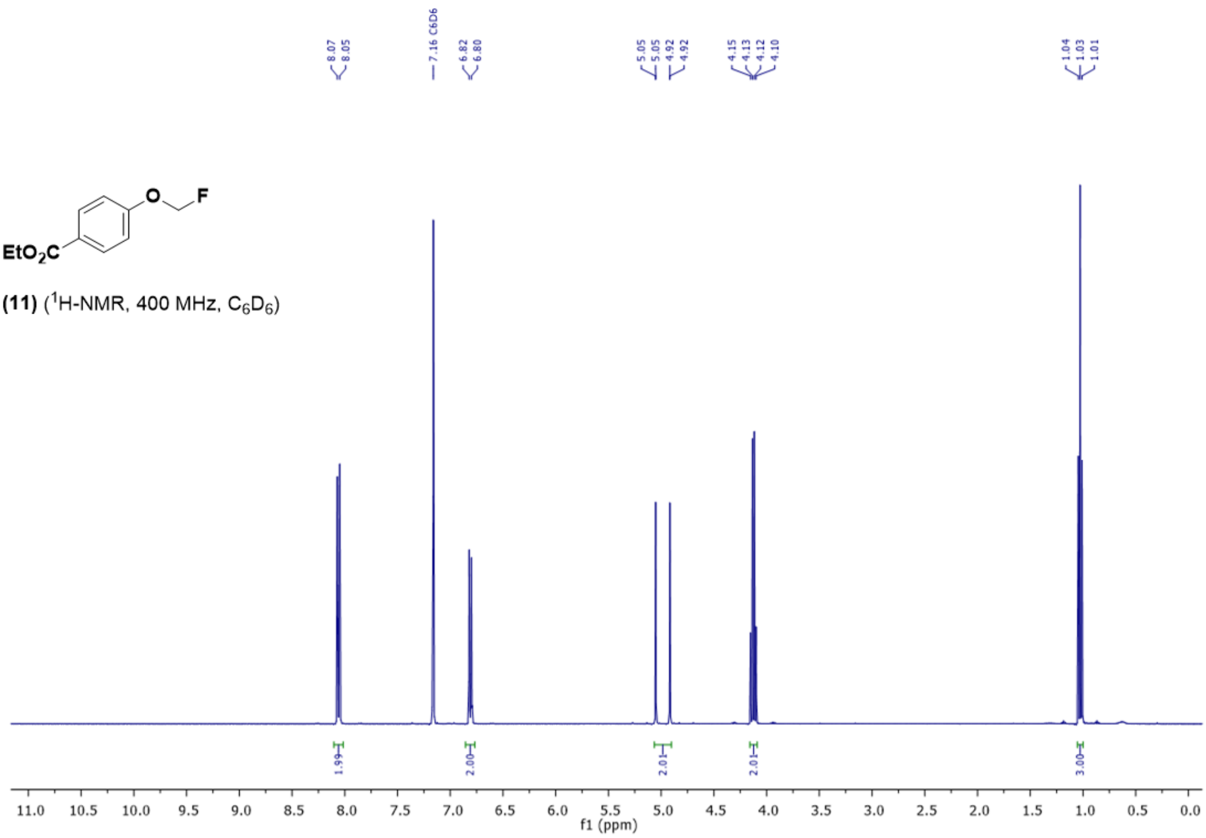
(10) (^{1}H-NMR, 400 MHz, C_6D_6)



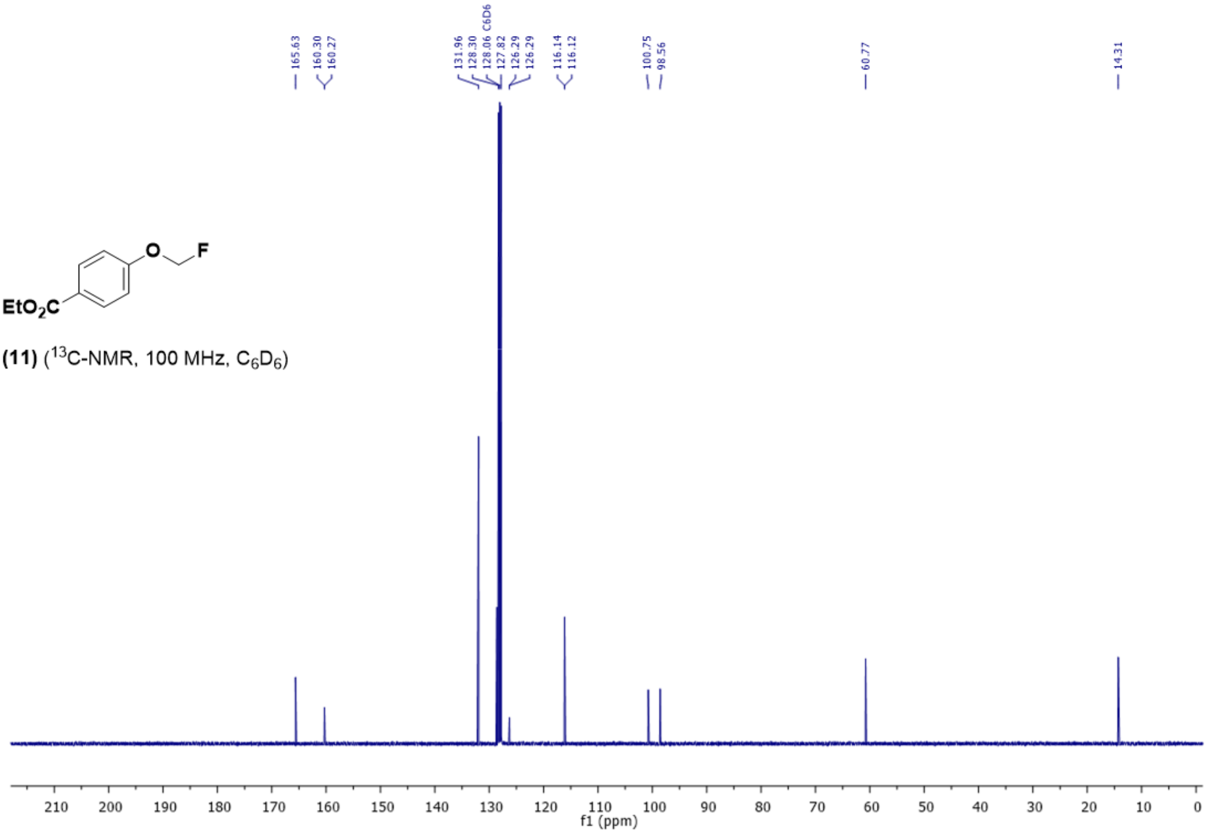


(10) (^{13}C-NMR, 100 MHz, C_6D_6)

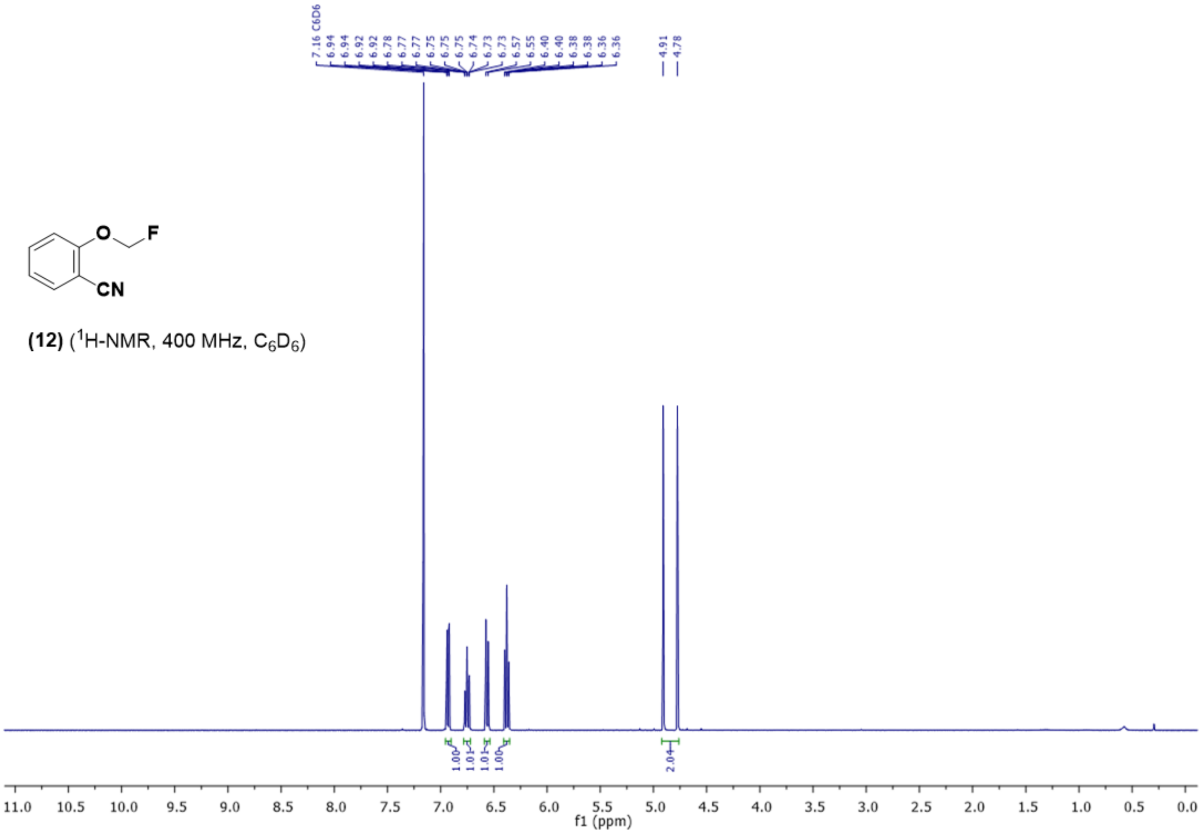




(11) (^{1}H-NMR, 400 MHz, C_6D_6)



(11) (^{13}C-NMR, 100 MHz, C_6D_6)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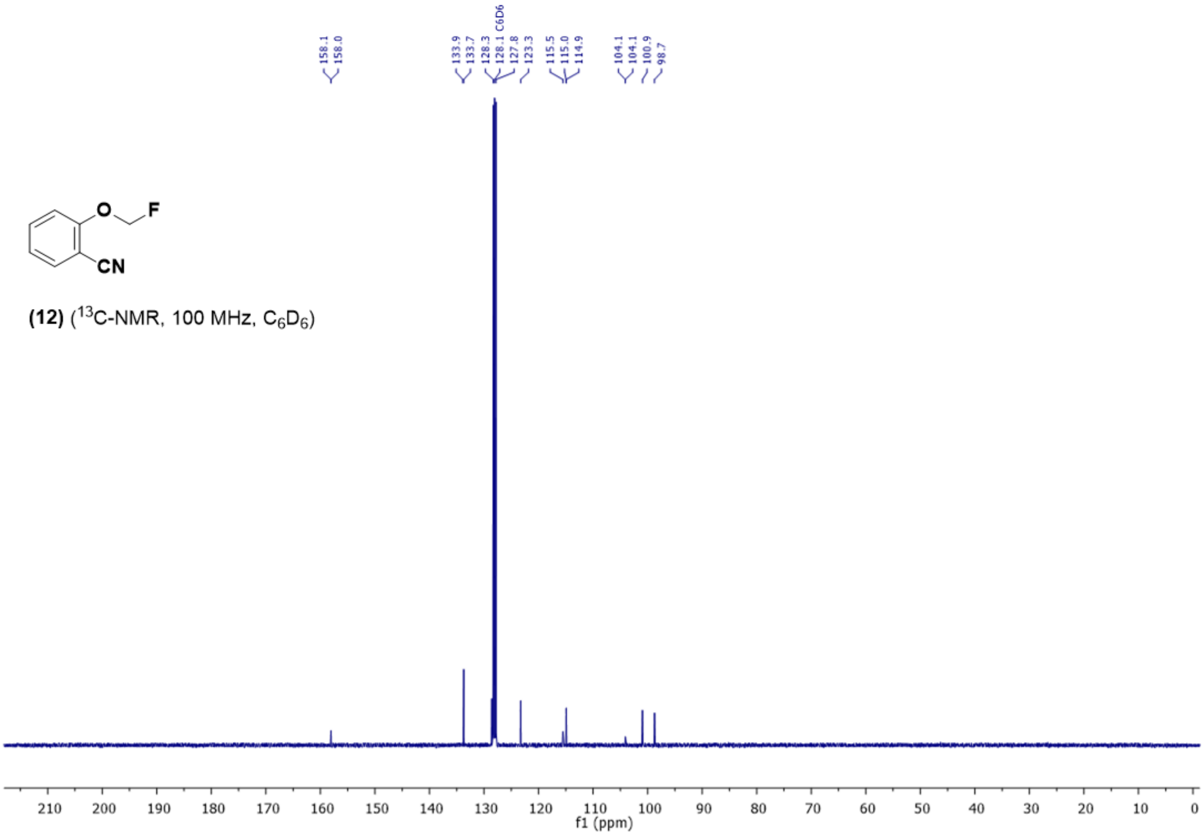
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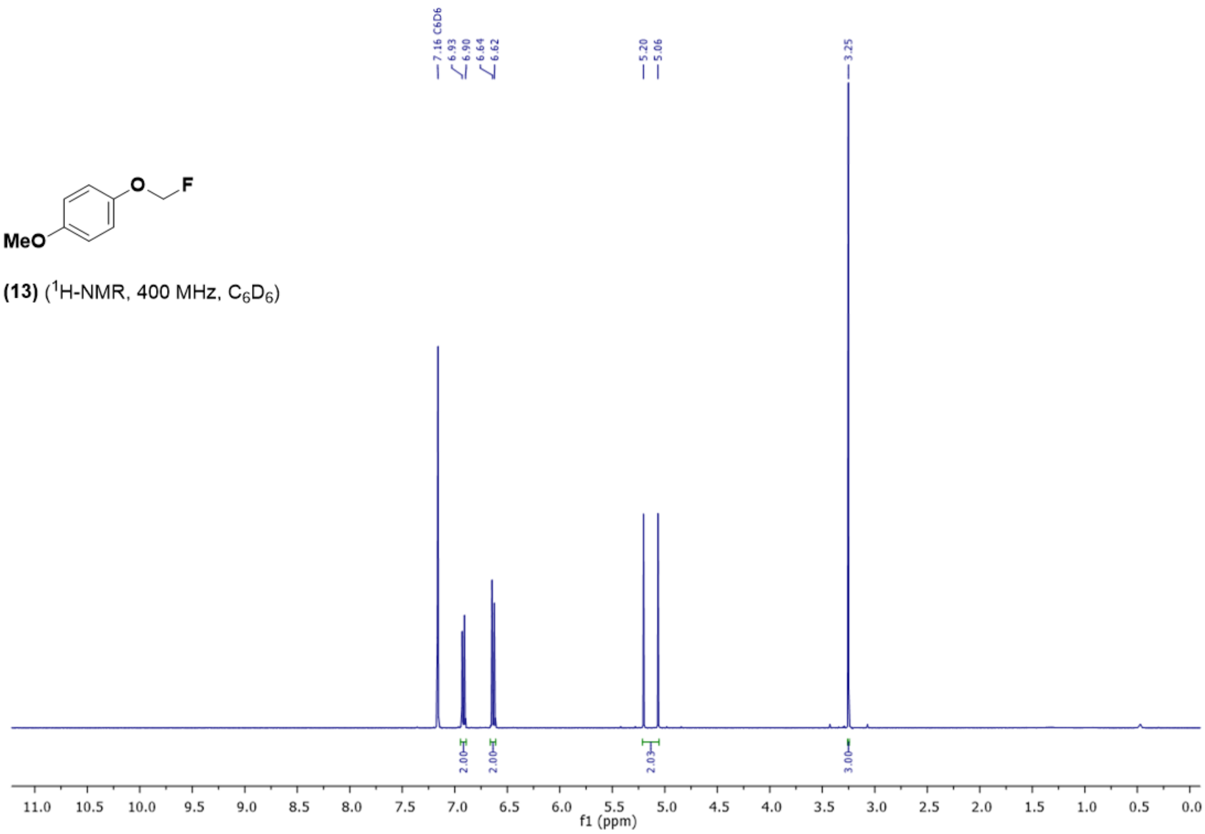
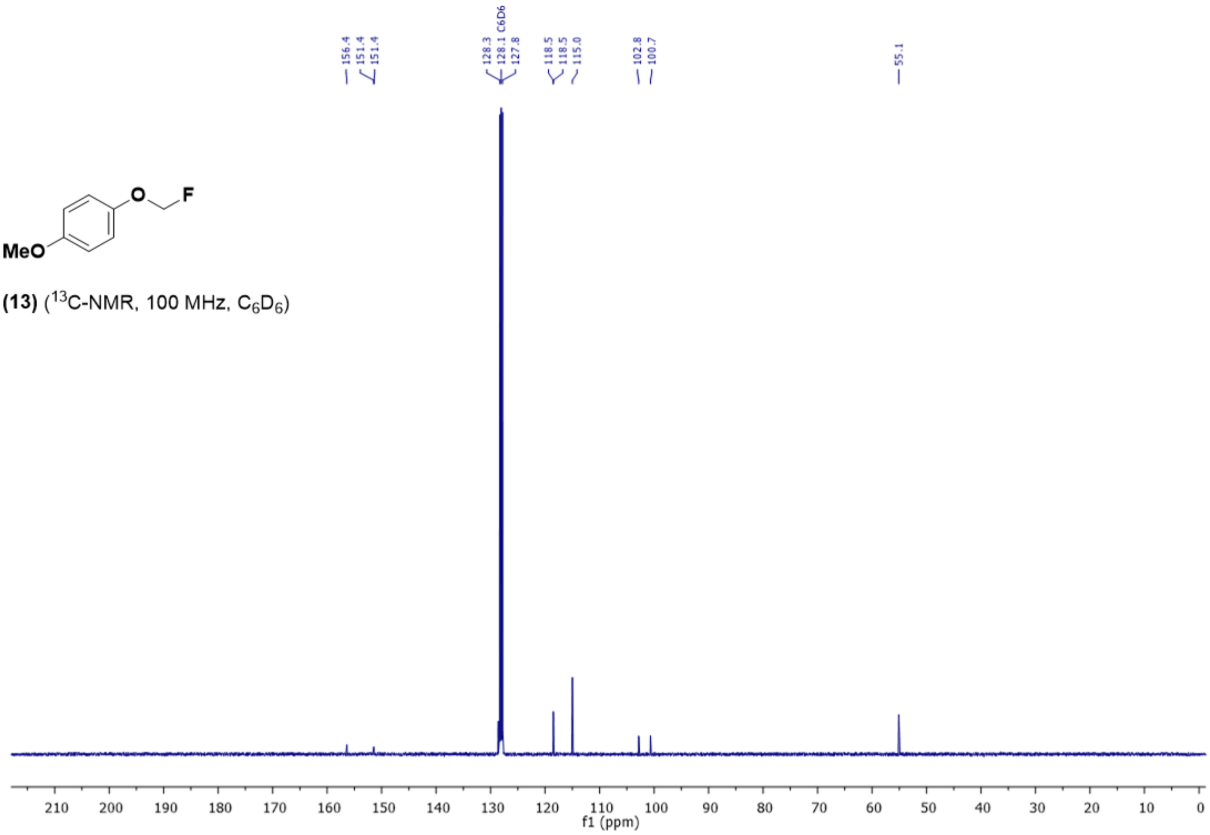
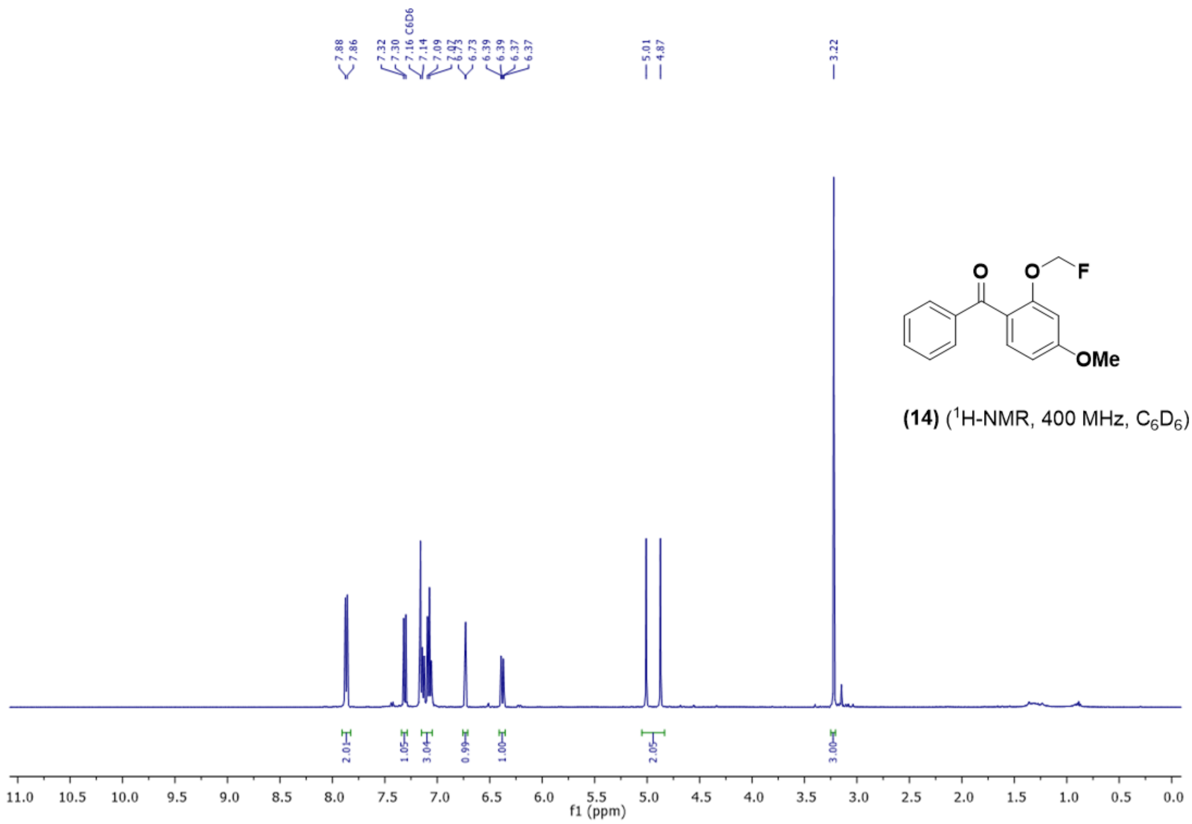


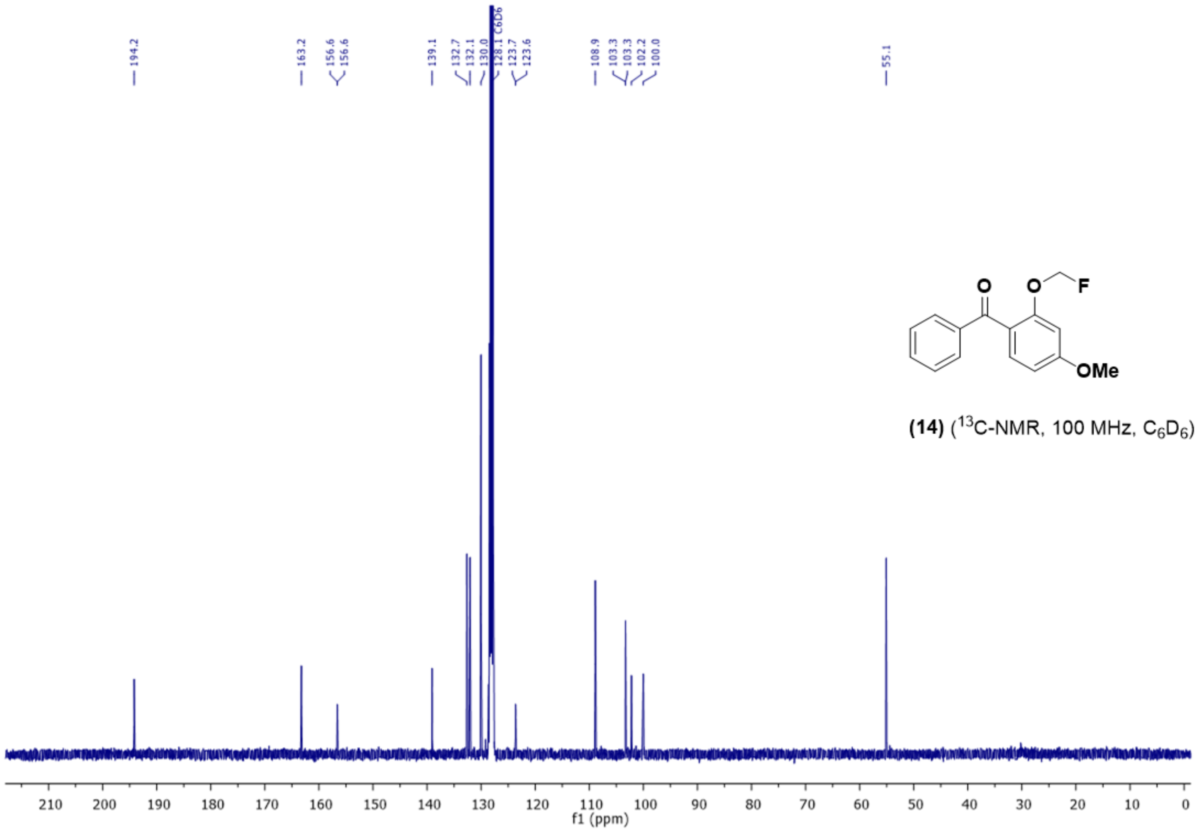
(13) (^{1}H-NMR, 400 MHz, C_6D_6)



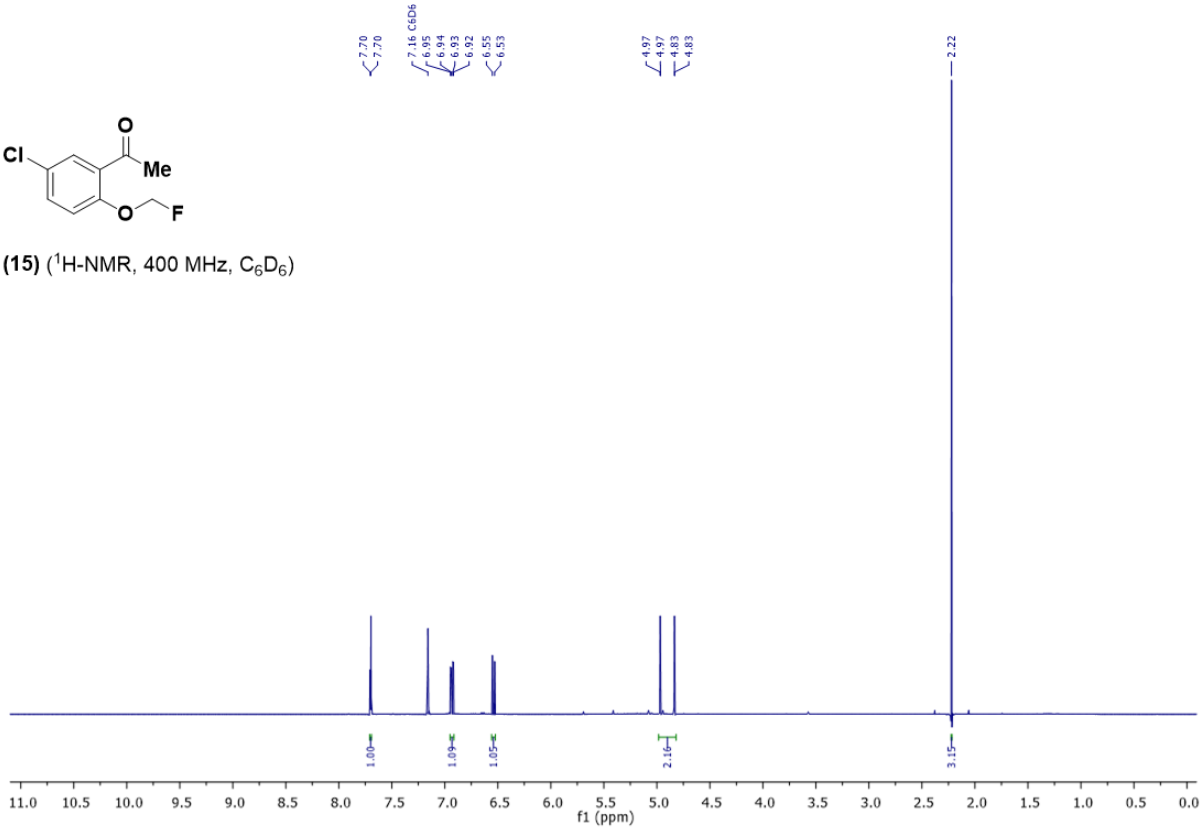
(13) (^{13}C-NMR, 100 MHz, C_6D_6)



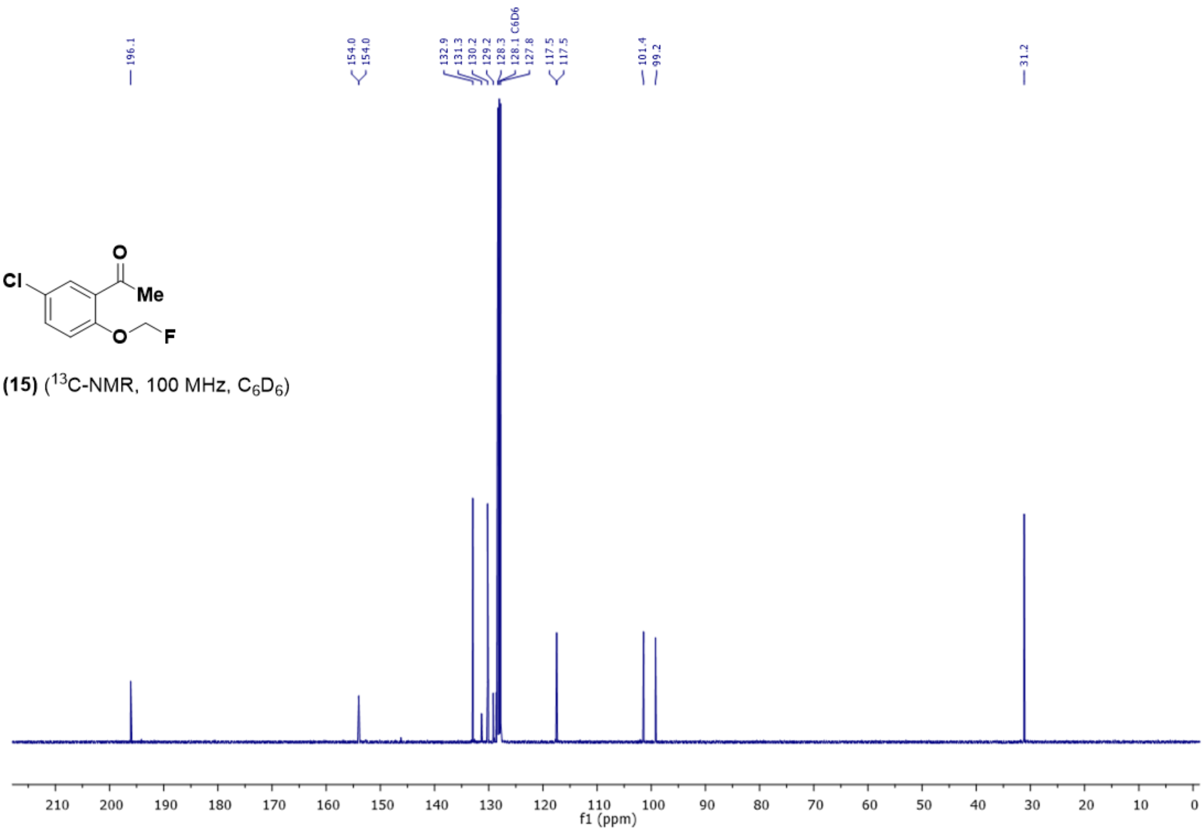
(14) (^{1}H-NMR, 400 MHz, C_6D_6)



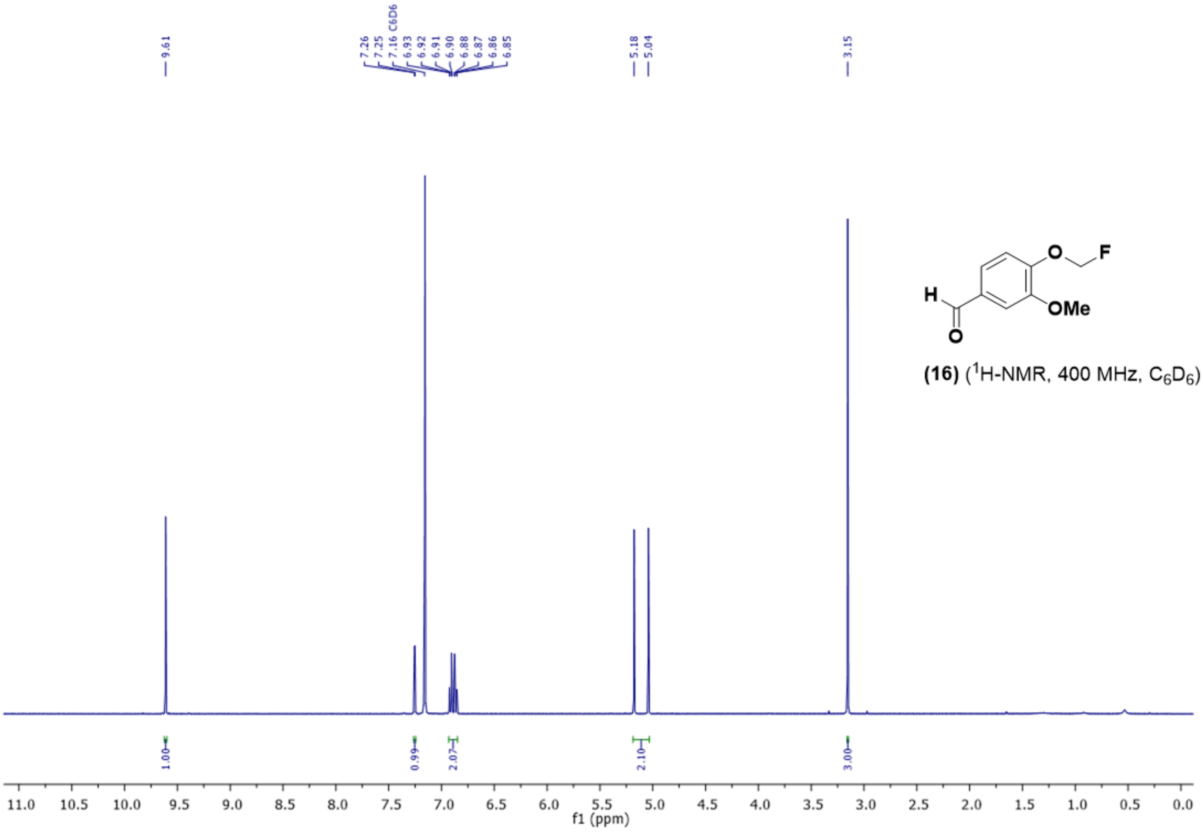
(14) (^{13}C-NMR, 100 MHz, C_6D_6)



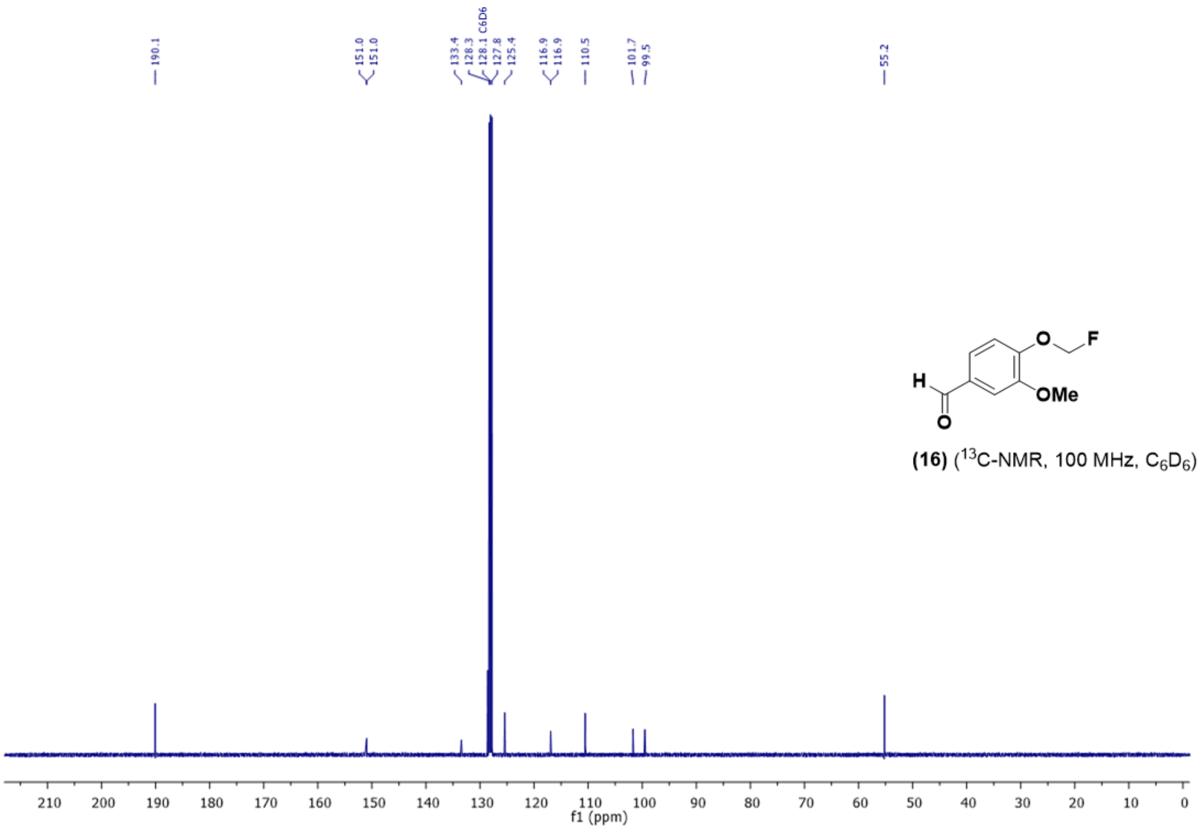
(15) (^{1}H-NMR, 400 MHz, C_6D_6)



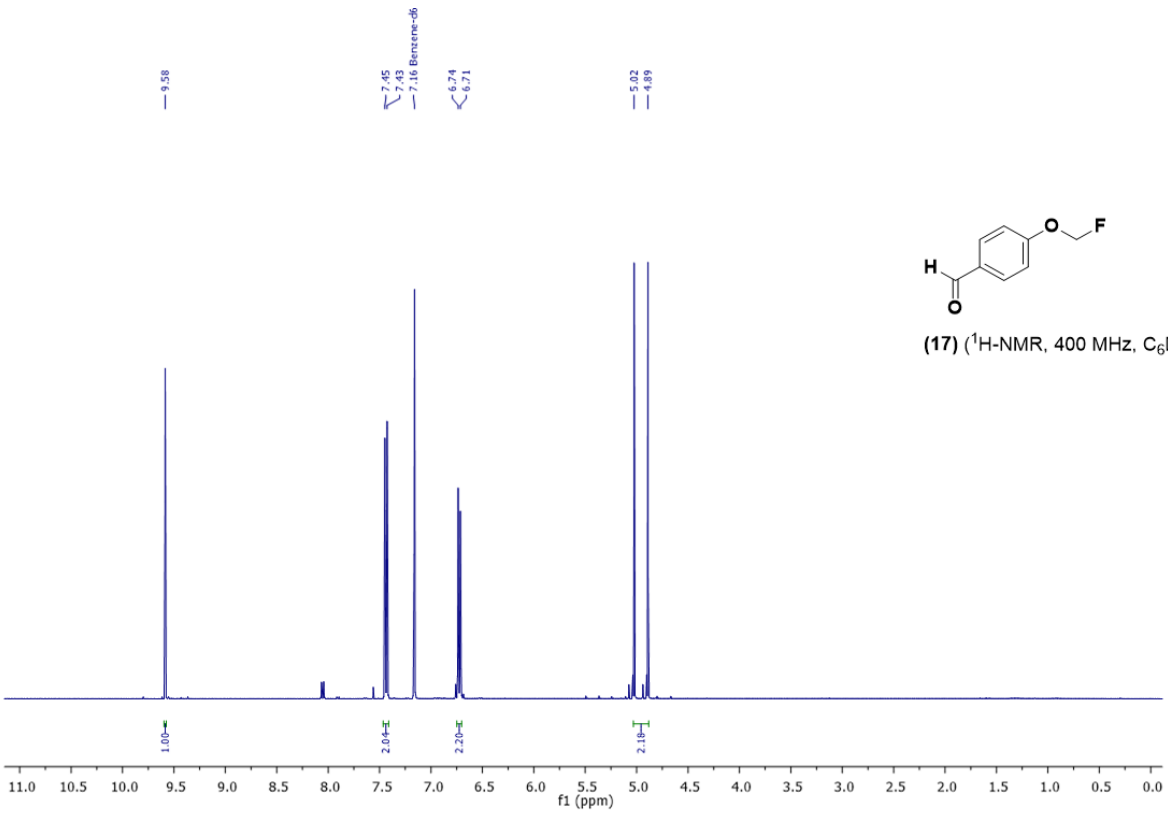
(15) (^{13}C-NMR, 100 MHz, C_6D_6)



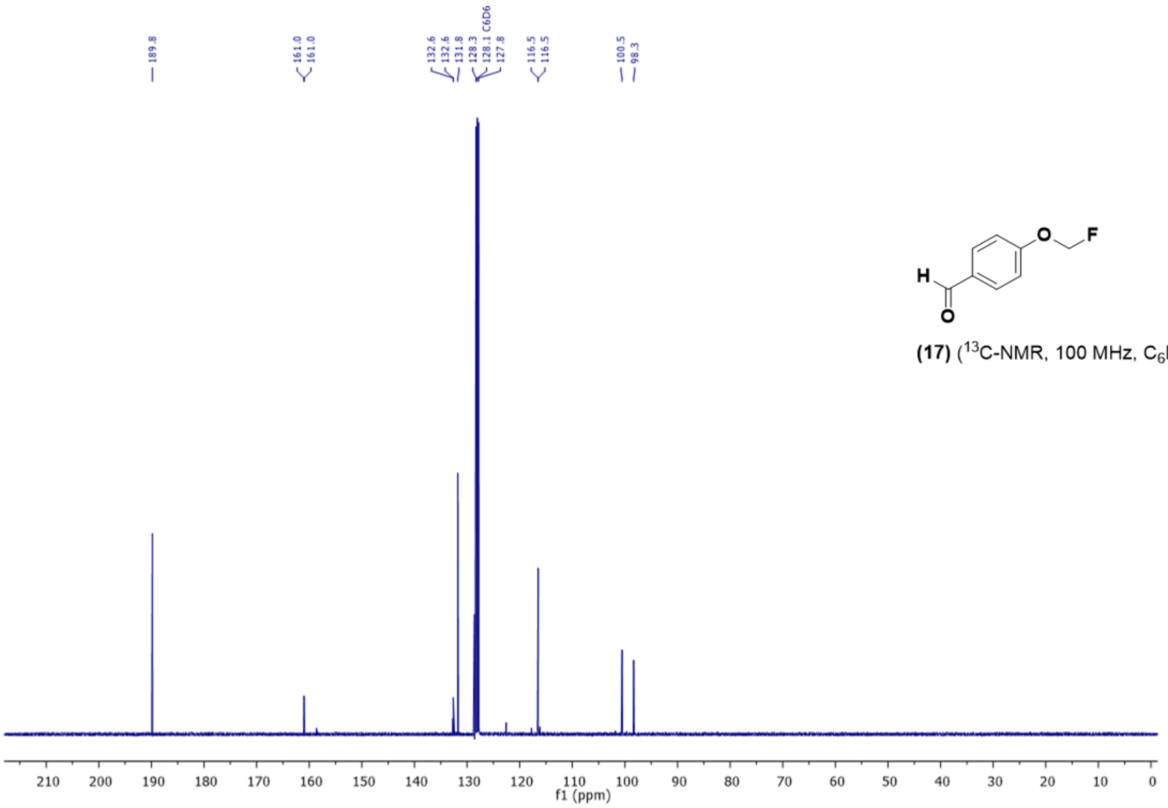
(16) (^{1}H-NMR, 400 MHz, C_6D_6)



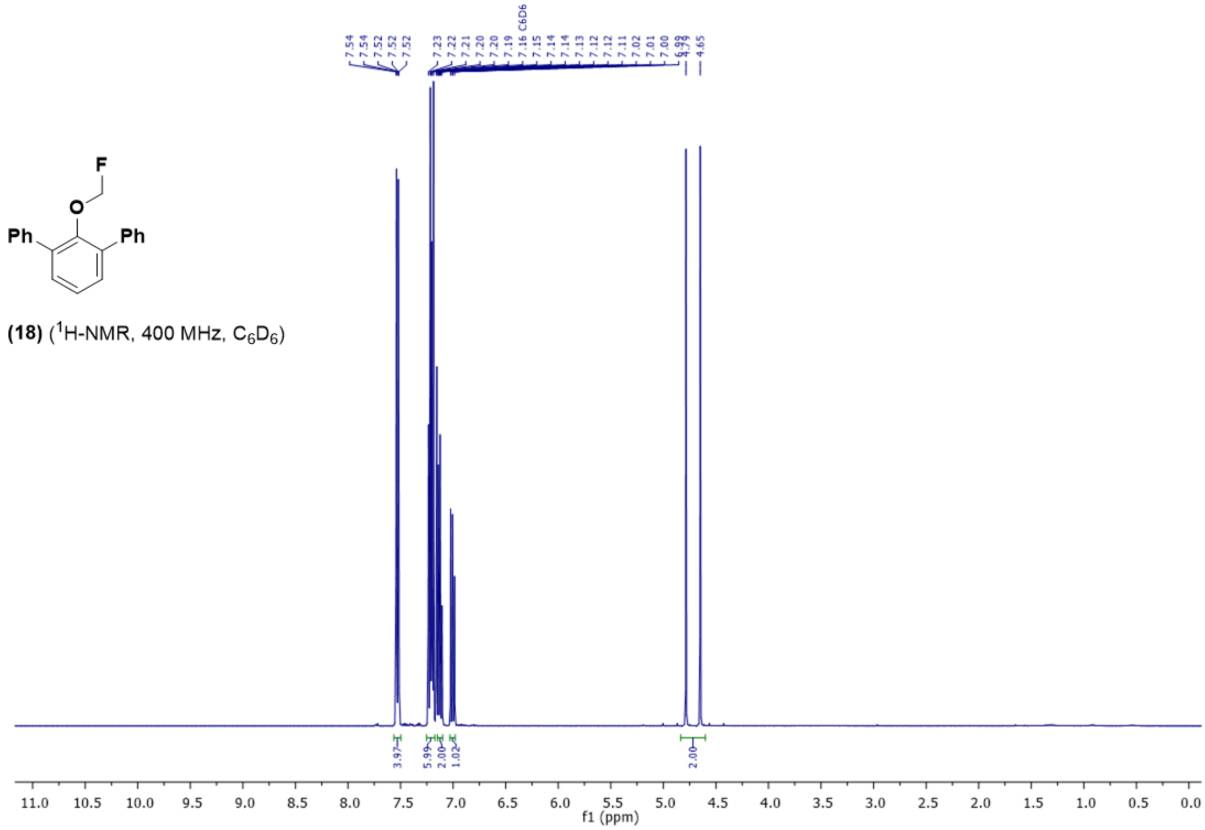
(16) (^{13}C-NMR, 100 MHz, C_6D_6)



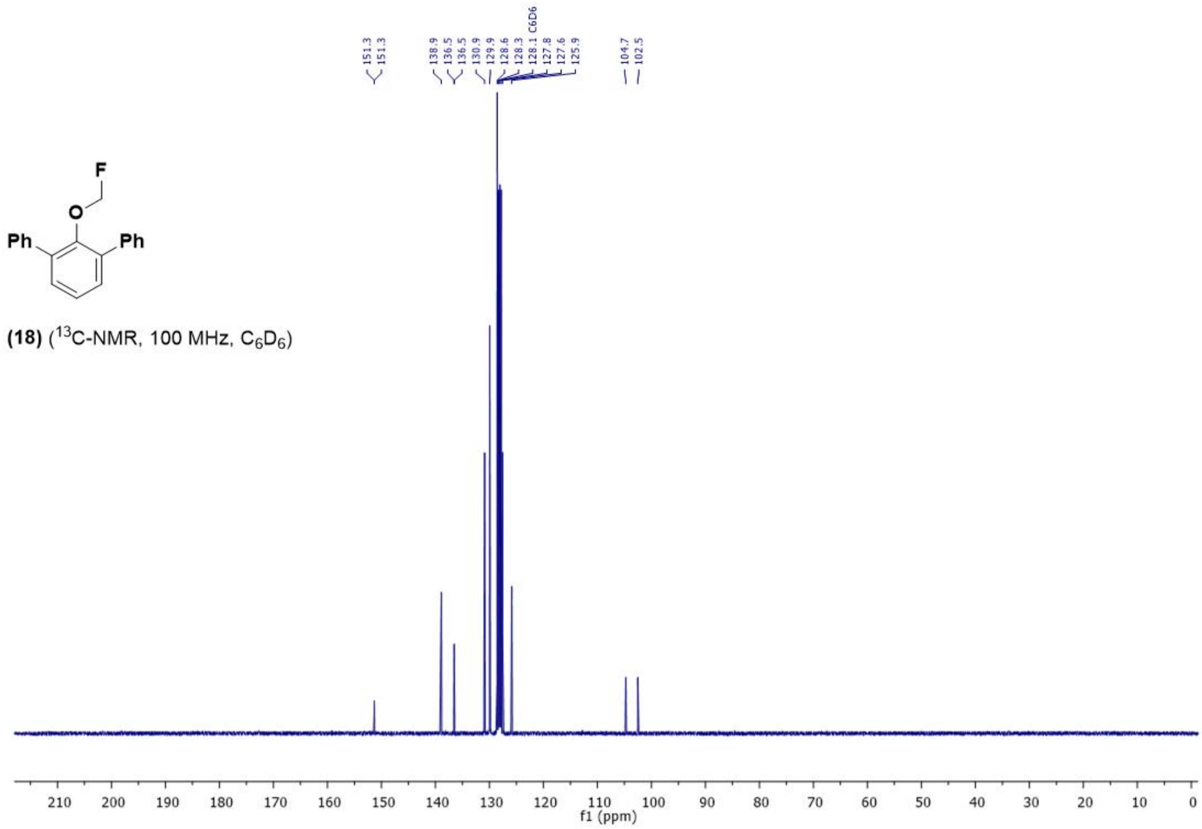
(17) (^{1}H-NMR, 400 MHz, C_6D_6)



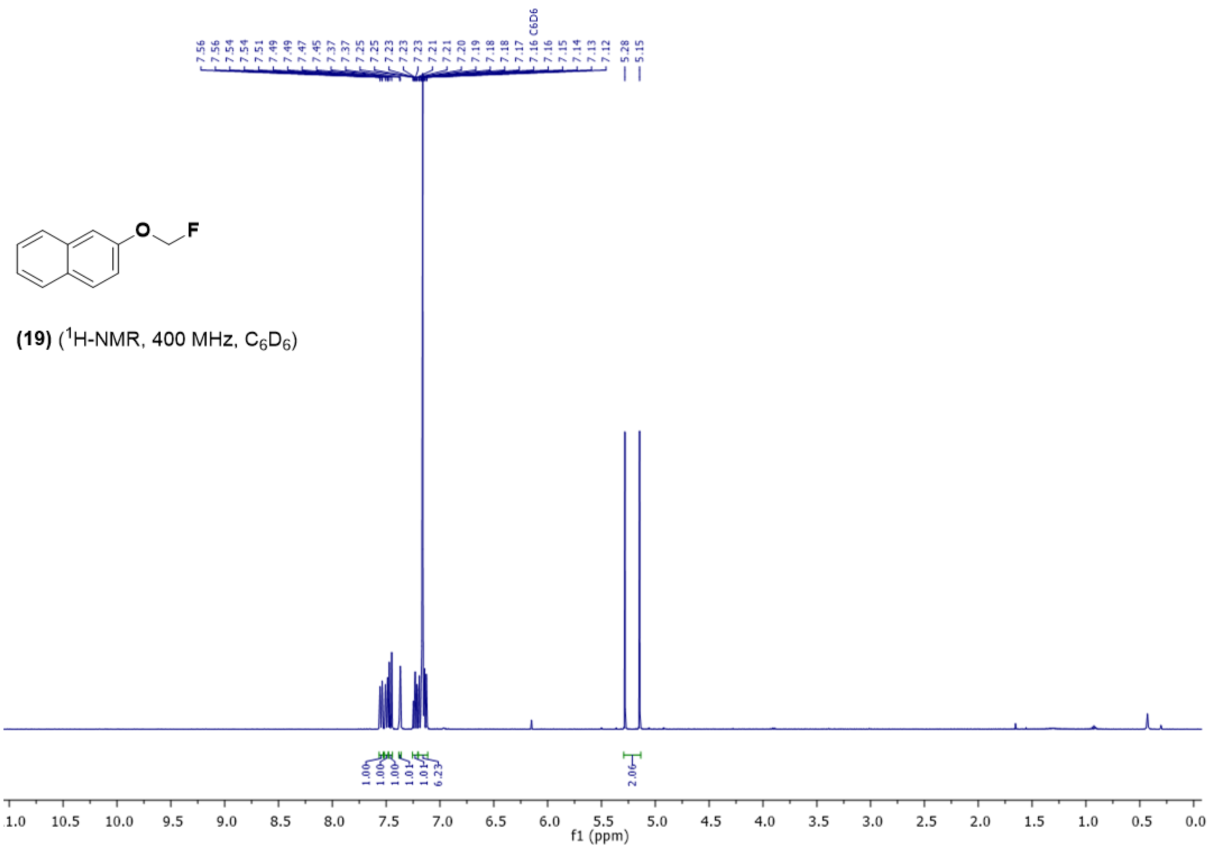
(17) (^{13}C-NMR, 100 MHz, C_6D_6)



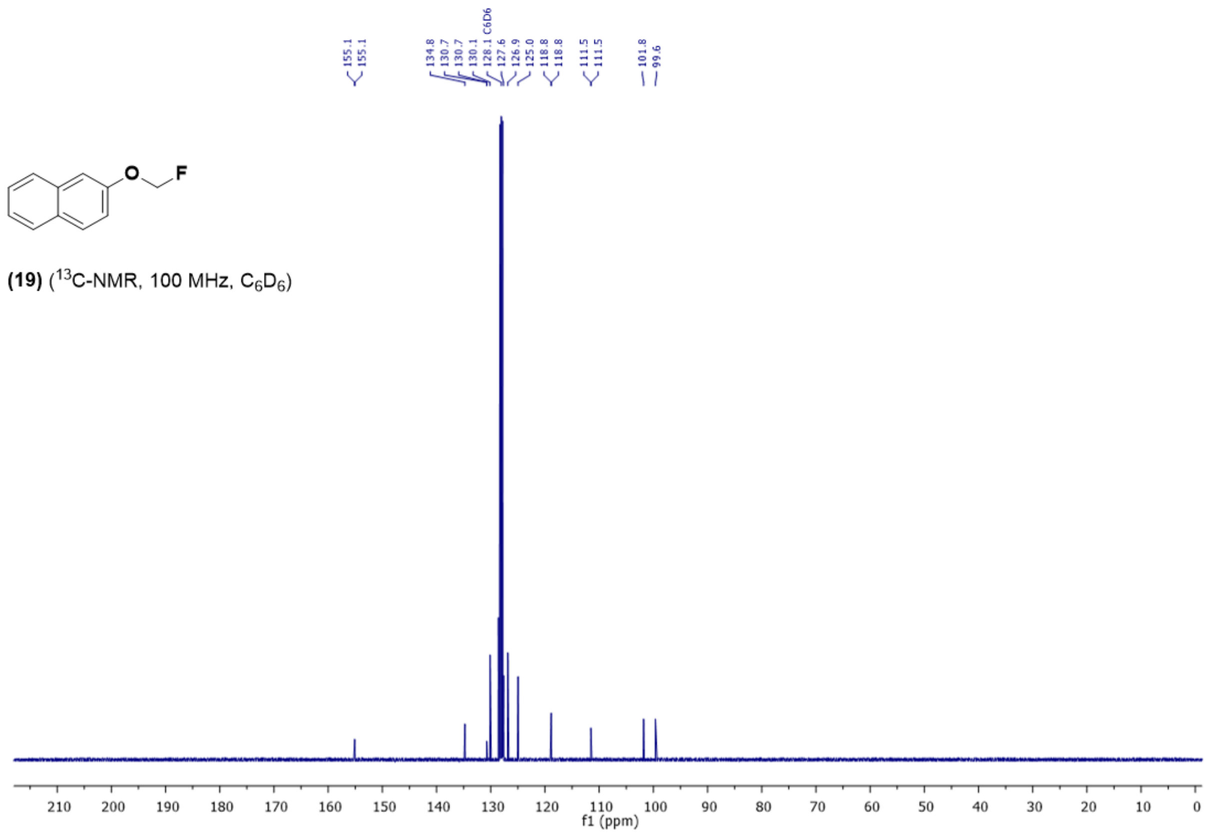
(18) (^{1}H-NMR, 400 MHz, C_6D_6)



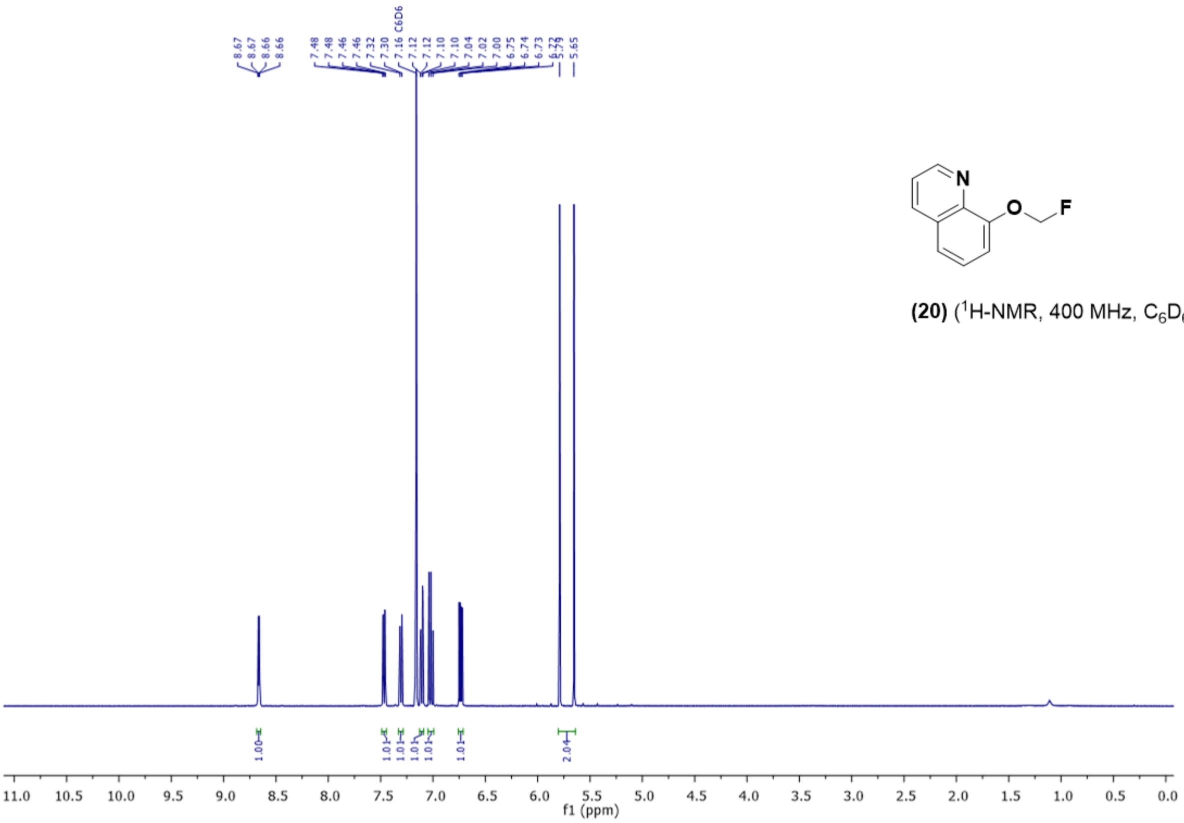
(18) (^{13}C-NMR, 100 MHz, C_6D_6)



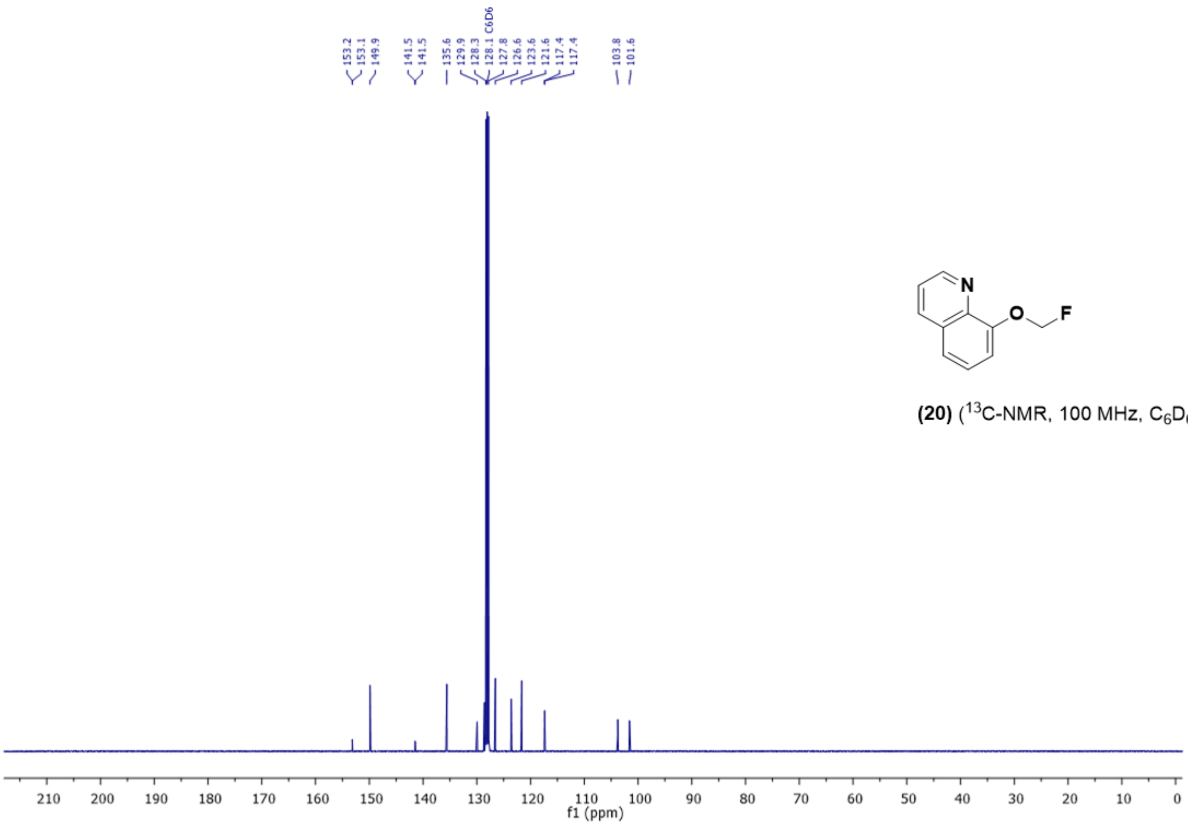
(19) (^{1}H-NMR, 400 MHz, C_6D_6)



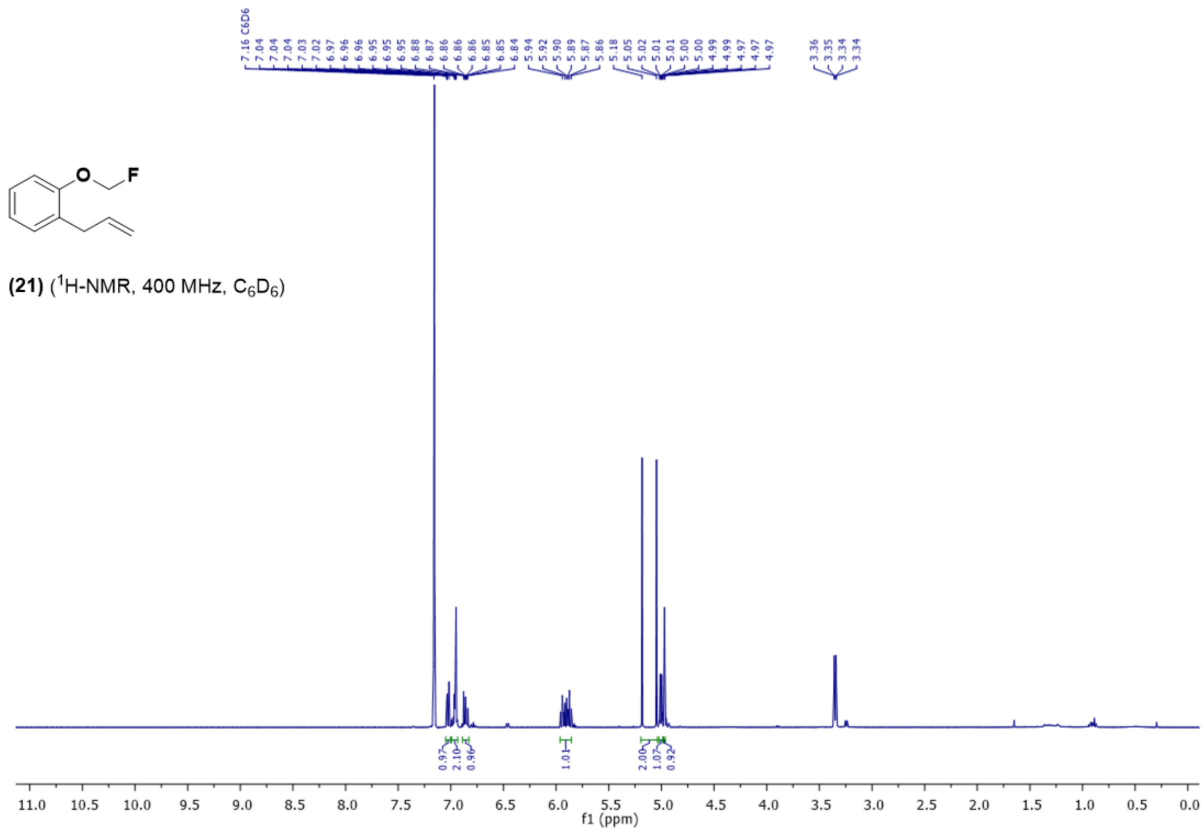
(19) (^{13}C-NMR, 100 MHz, C_6D_6)



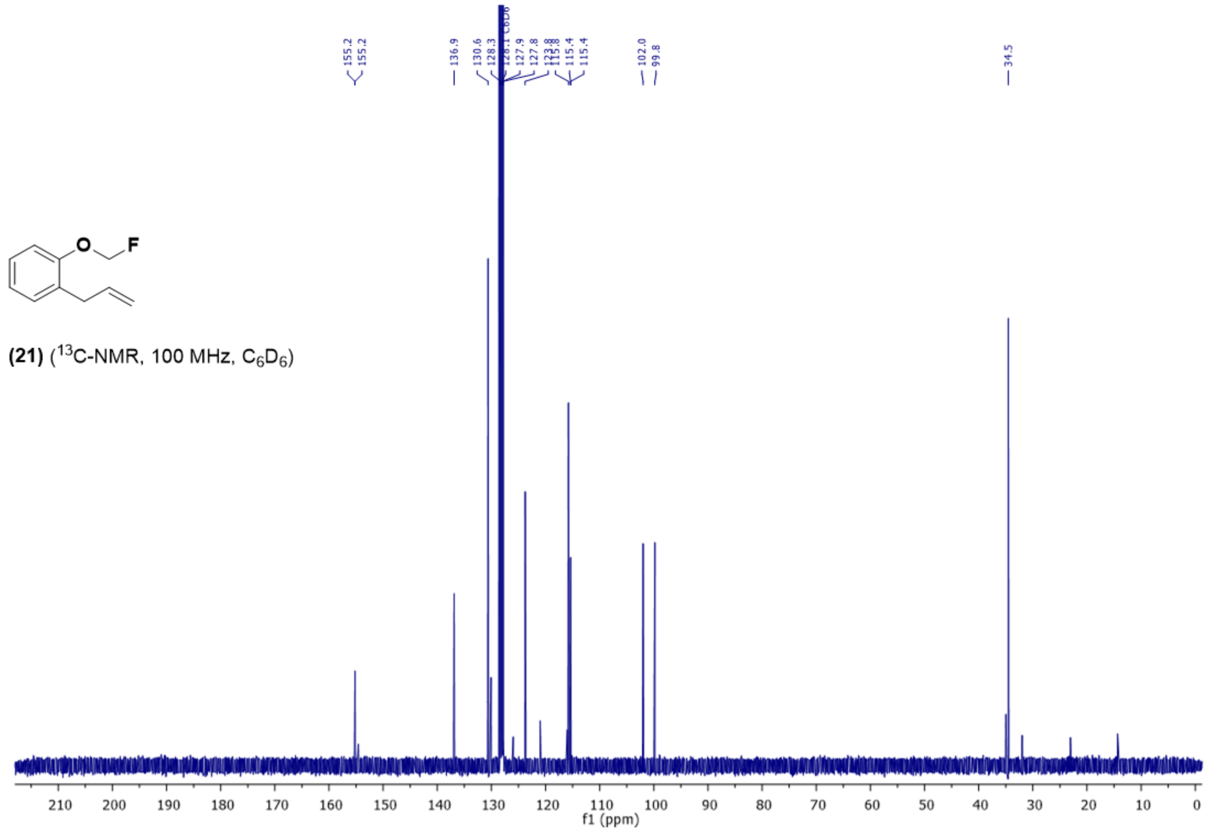
(20) (^{1}H-NMR, 400 MHz, C_6D_6)



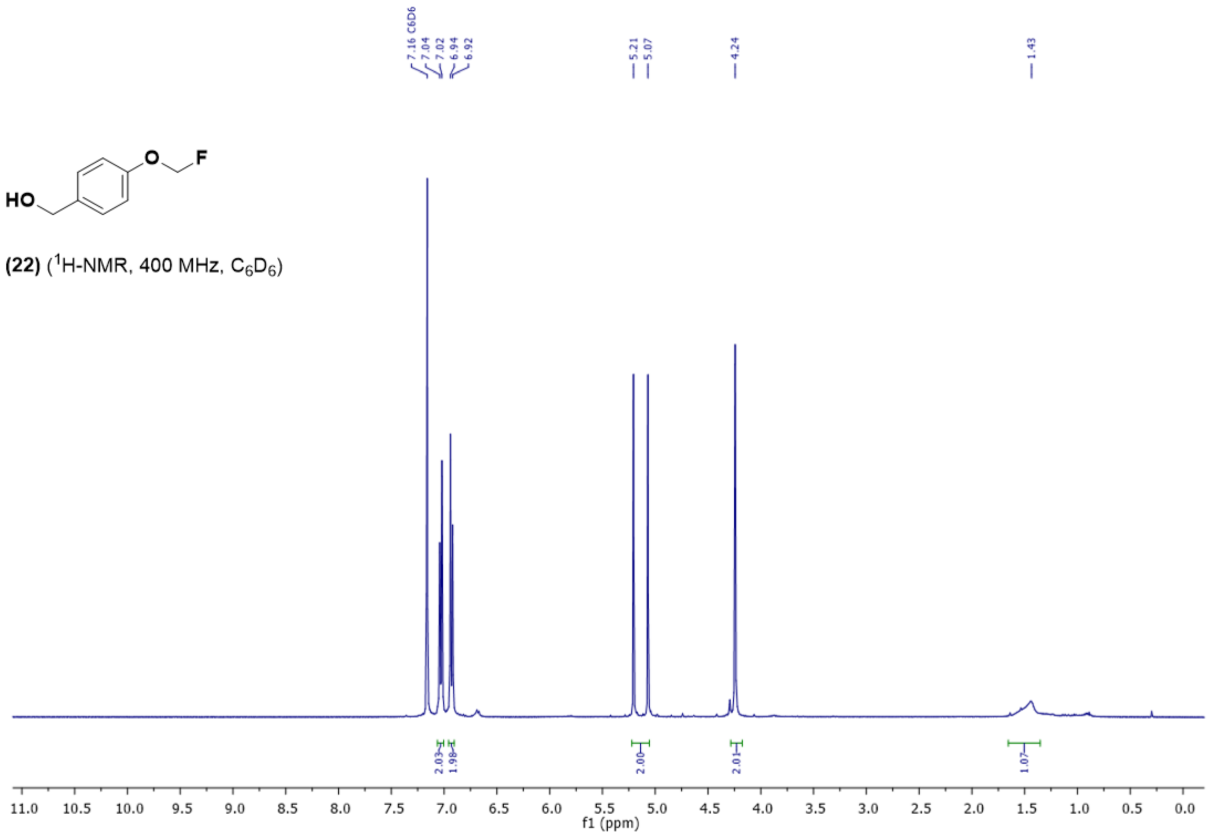
(20) (^{13}C-NMR, 100 MHz, C_6D_6)



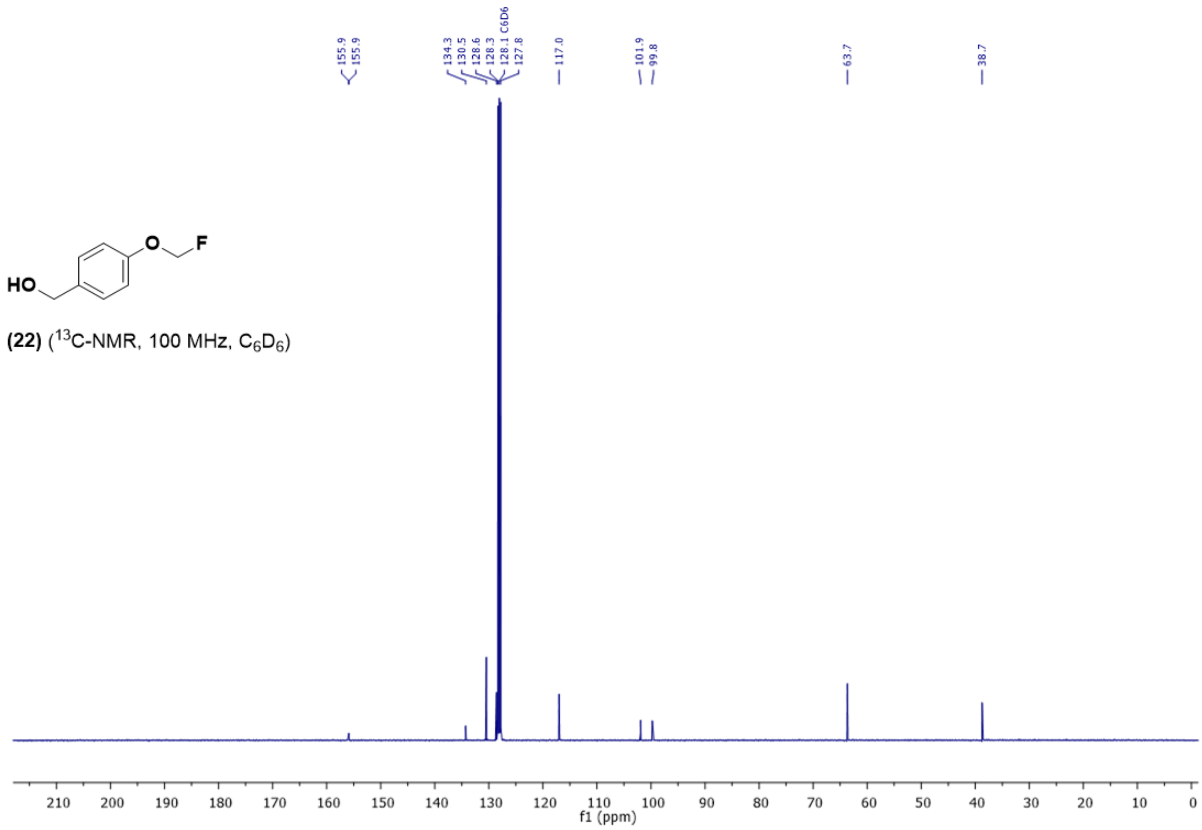
(21) (^{1}H-NMR, 400 MHz, C_6D_6)



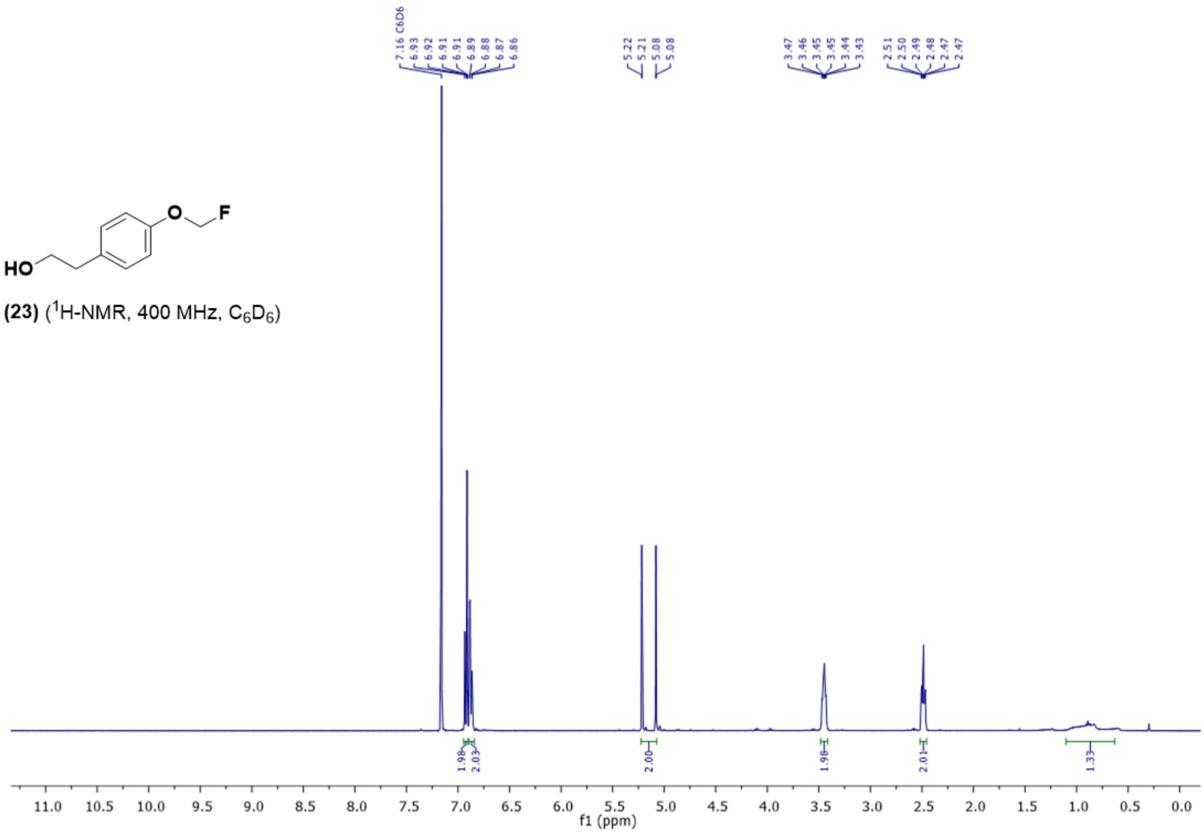
(21) (^{13}C-NMR, 100 MHz, C_6D_6)



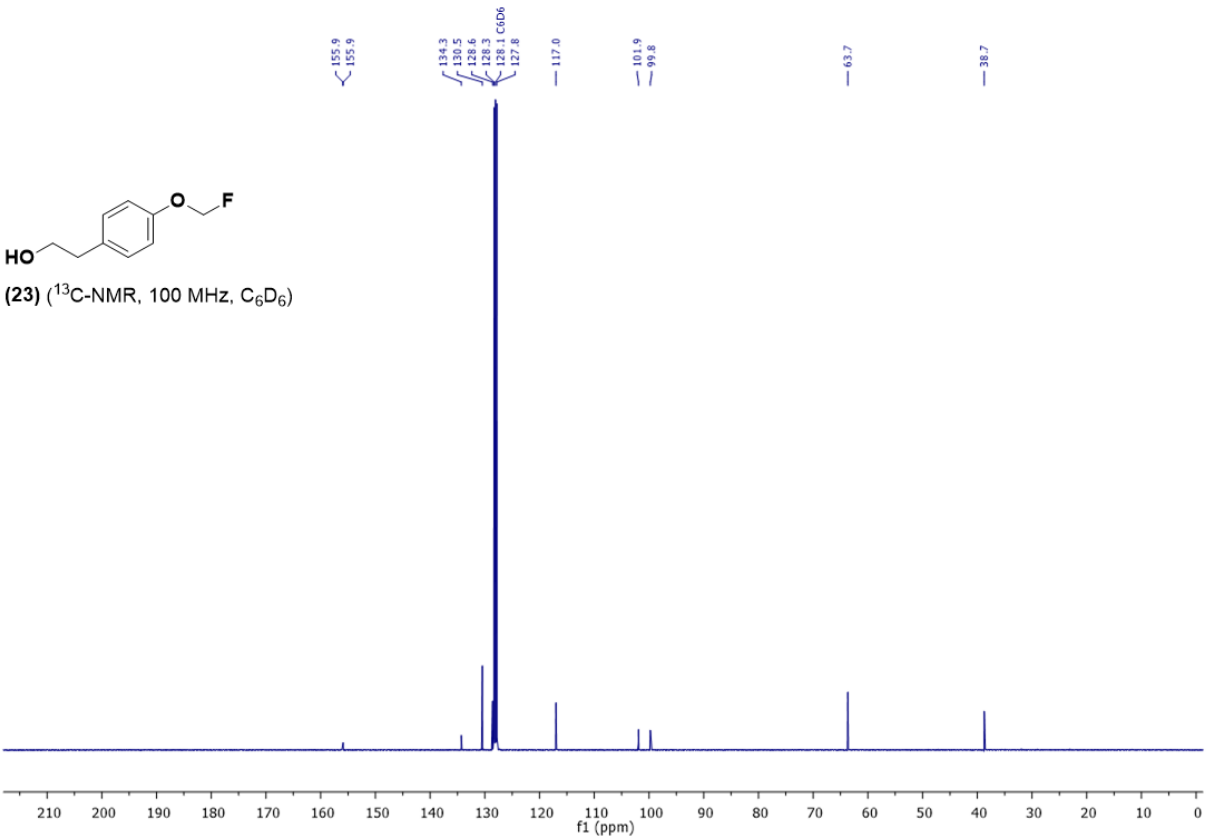
(22) (^{1}H-NMR, 400 MHz, C_6D_6)



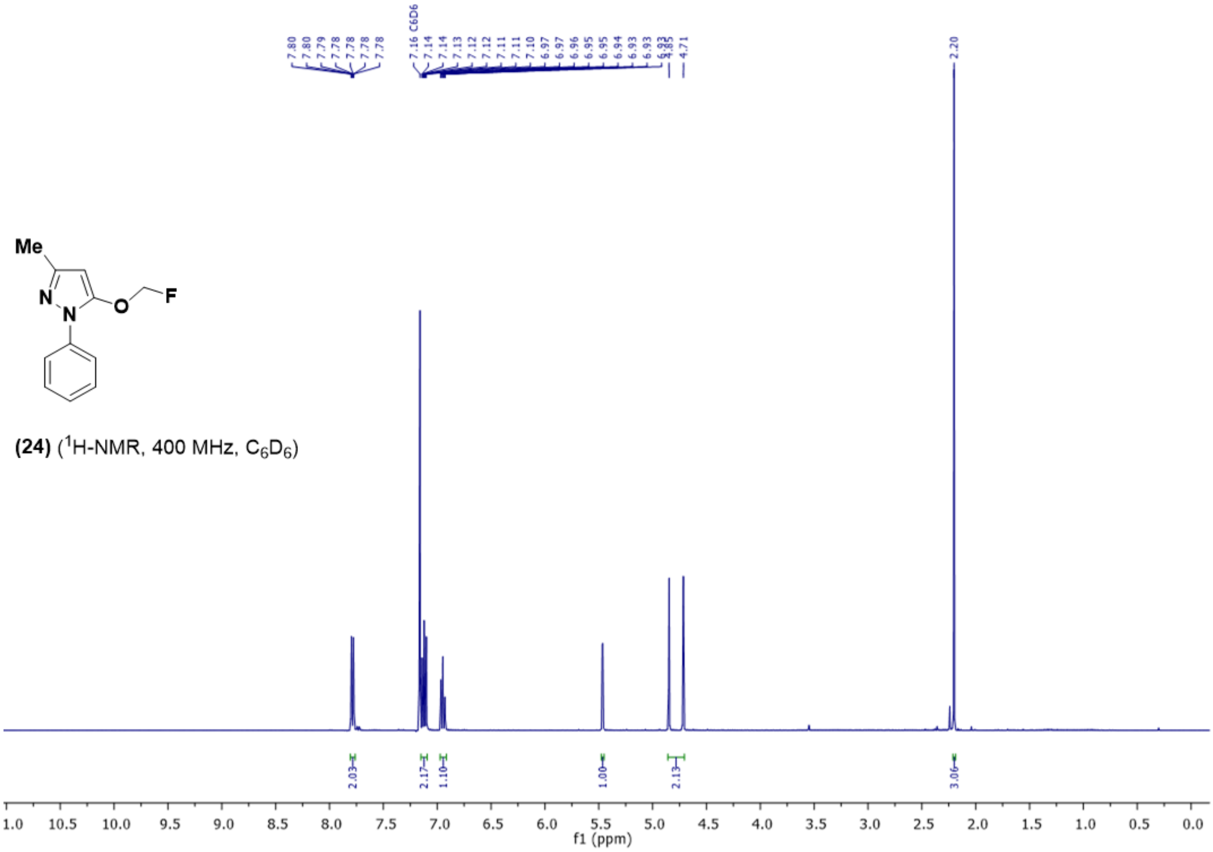
(22) (^{13}C-NMR, 100 MHz, C_6D_6)



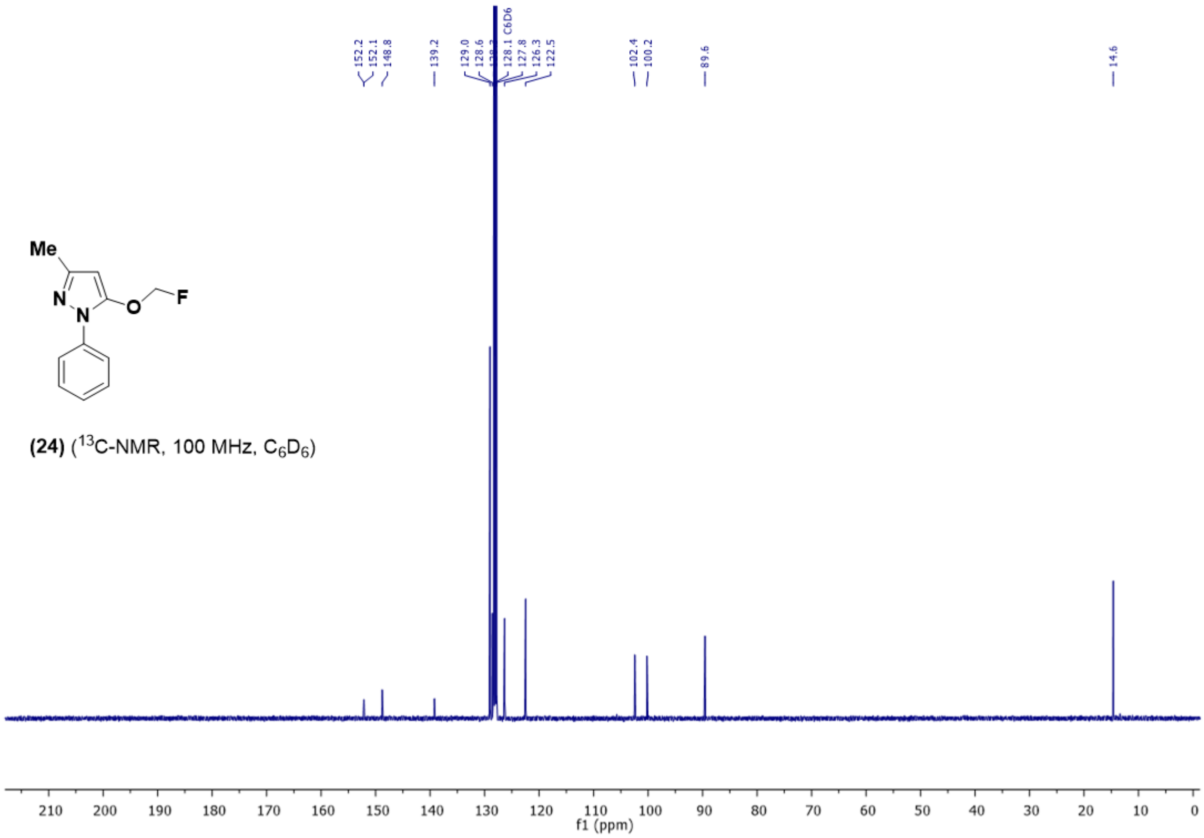
(23) (^{1}H-NMR, 400 MHz, C_6D_6)



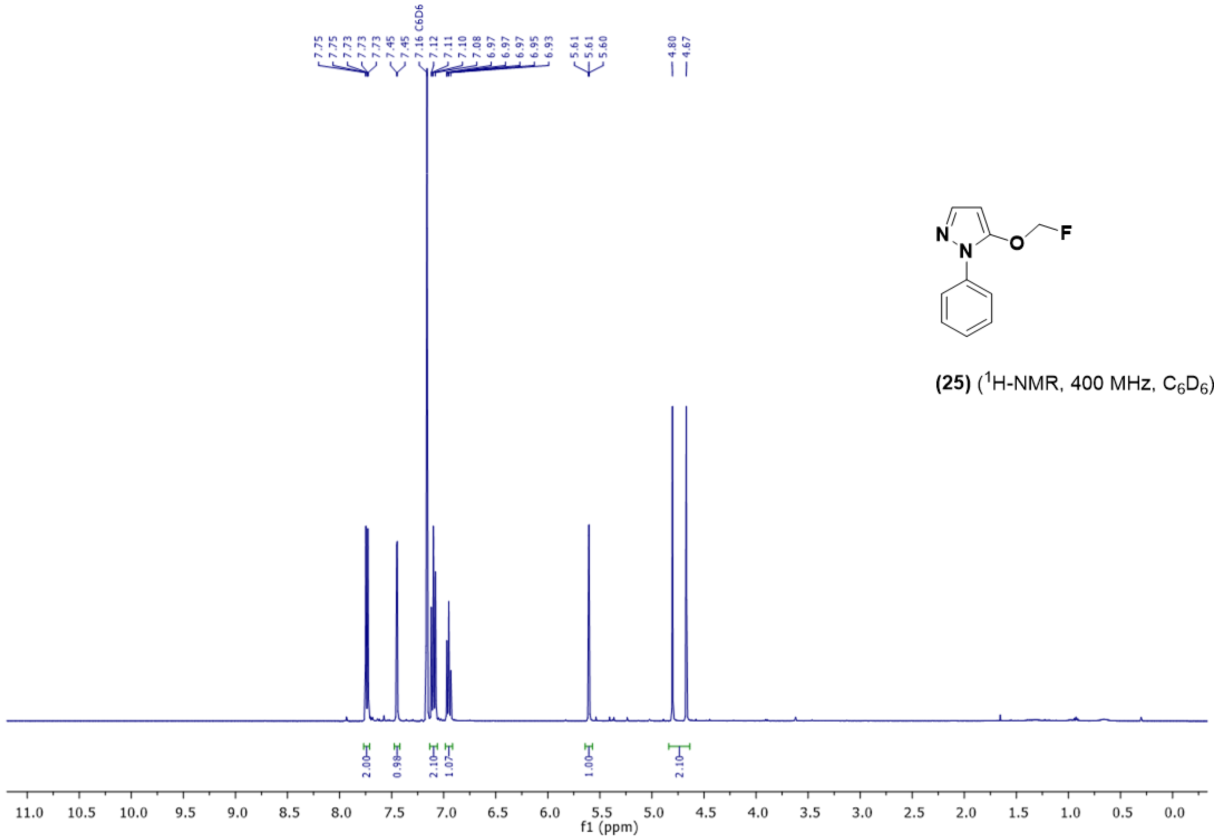
(23) (^{13}C-NMR, 100 MHz, C_6D_6)



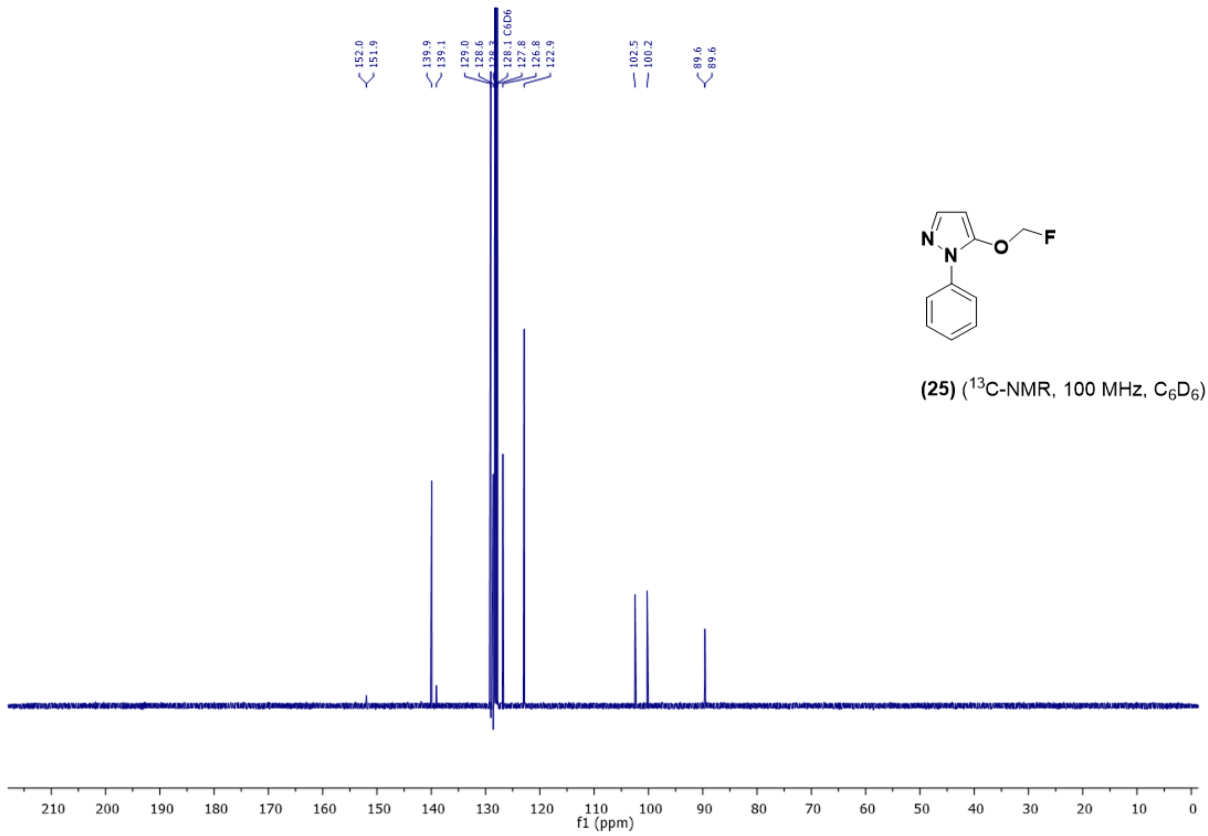
(24) (^{1}H-NMR, 400 MHz, C_6D_6)



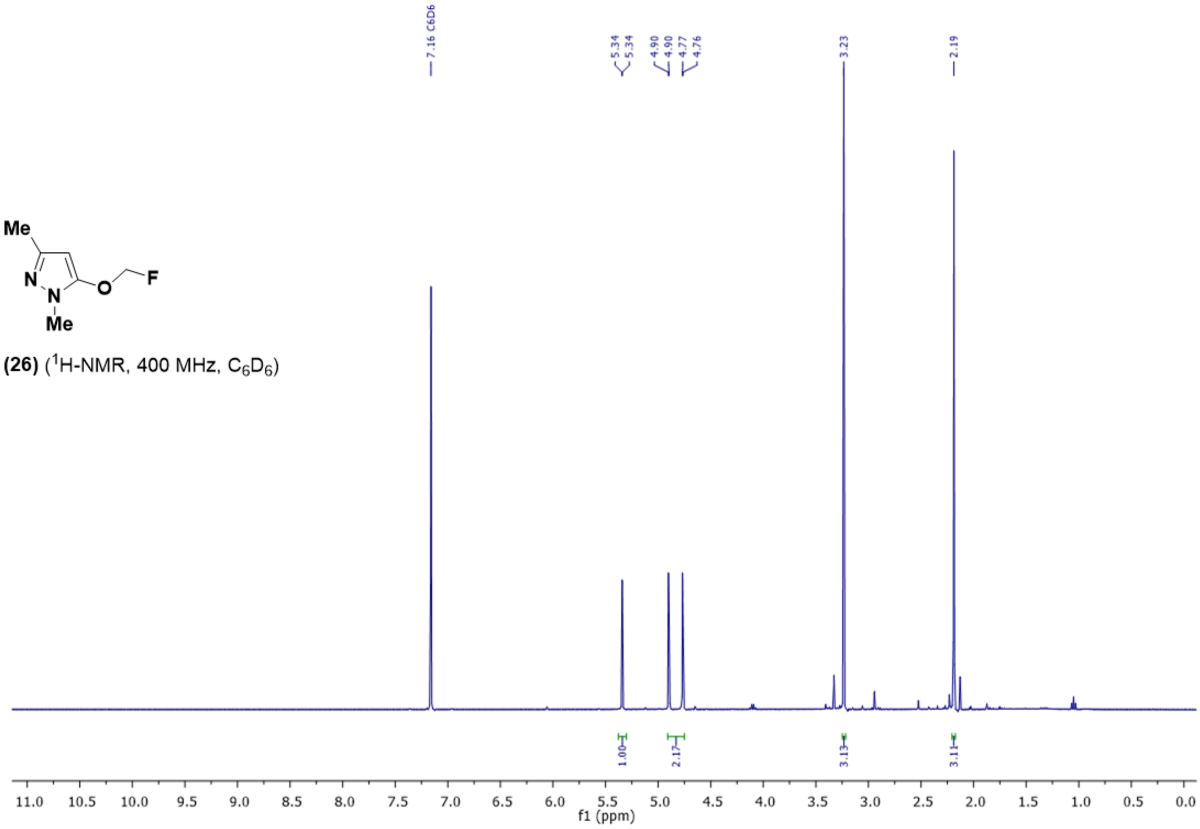
(24) (^{13}C-NMR, 100 MHz, C_6D_6)



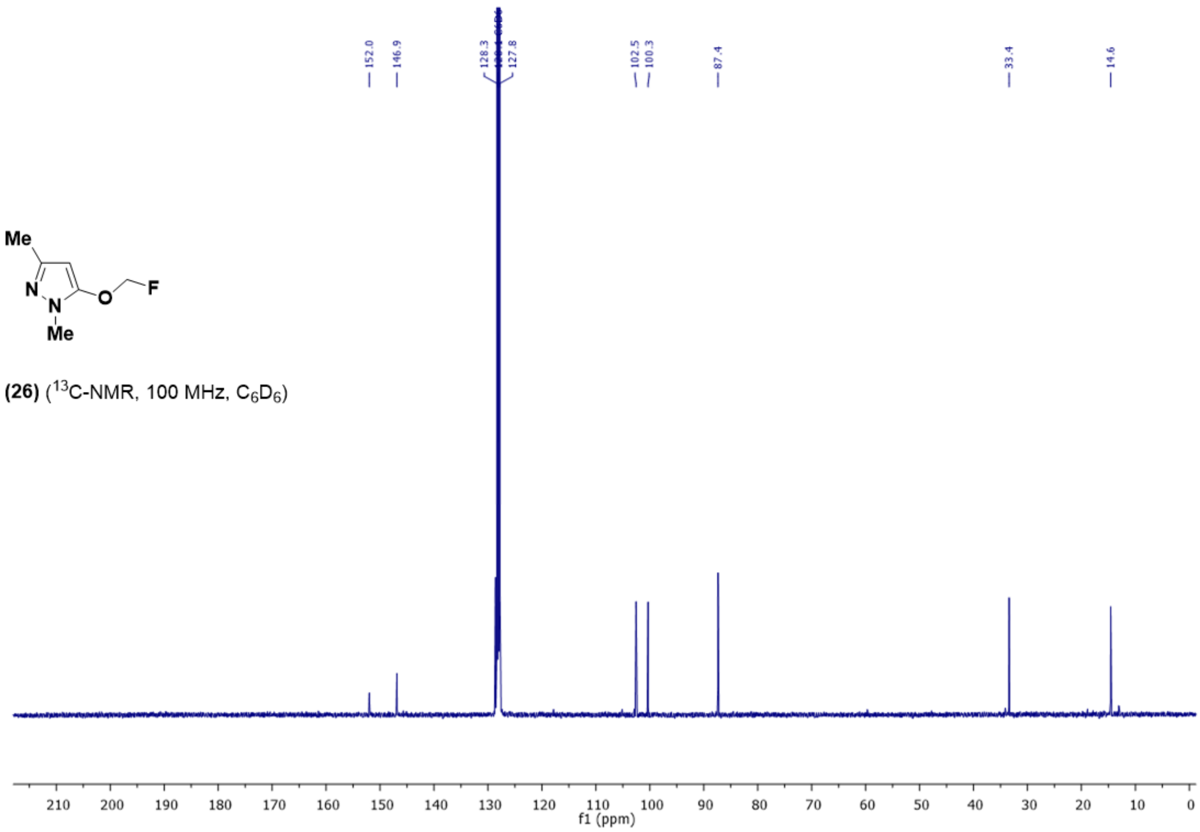
(25) (^{1}H-NMR, 400 MHz, C_6D_6)



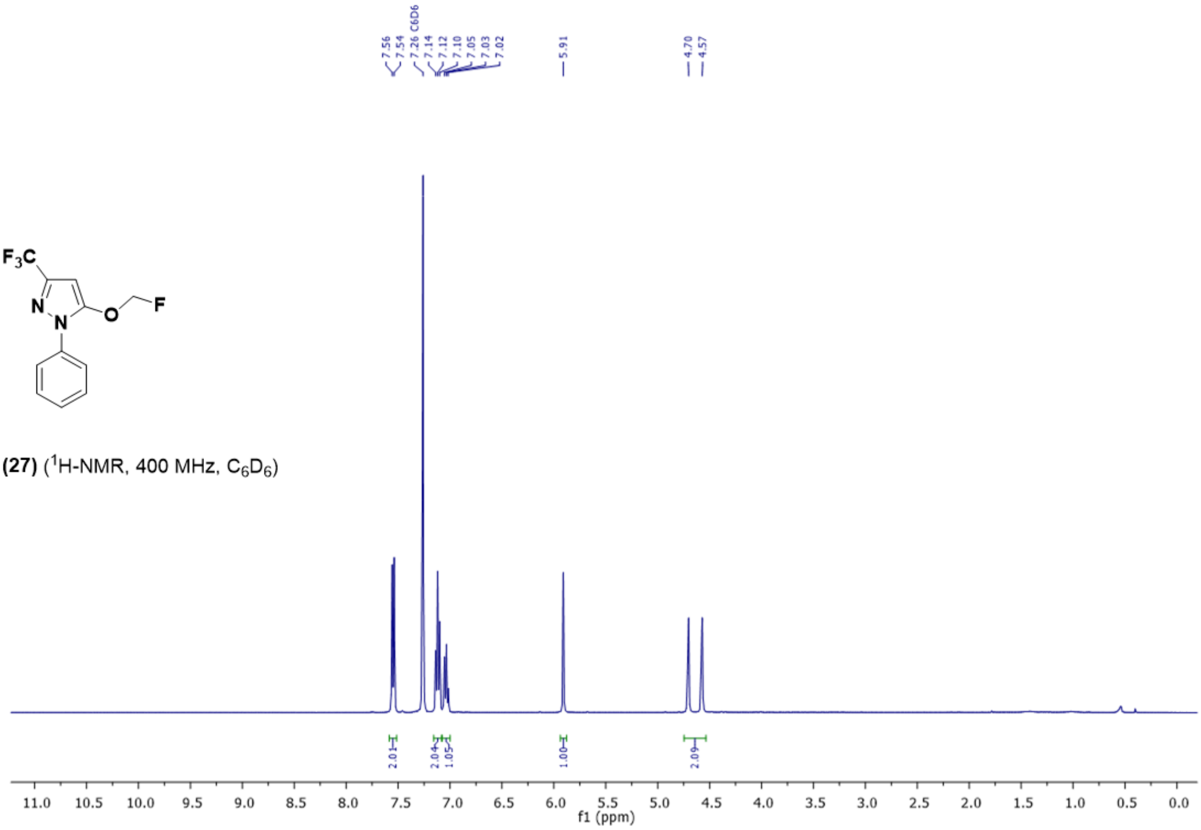
(25) (^{13}C-NMR, 100 MHz, C_6D_6)



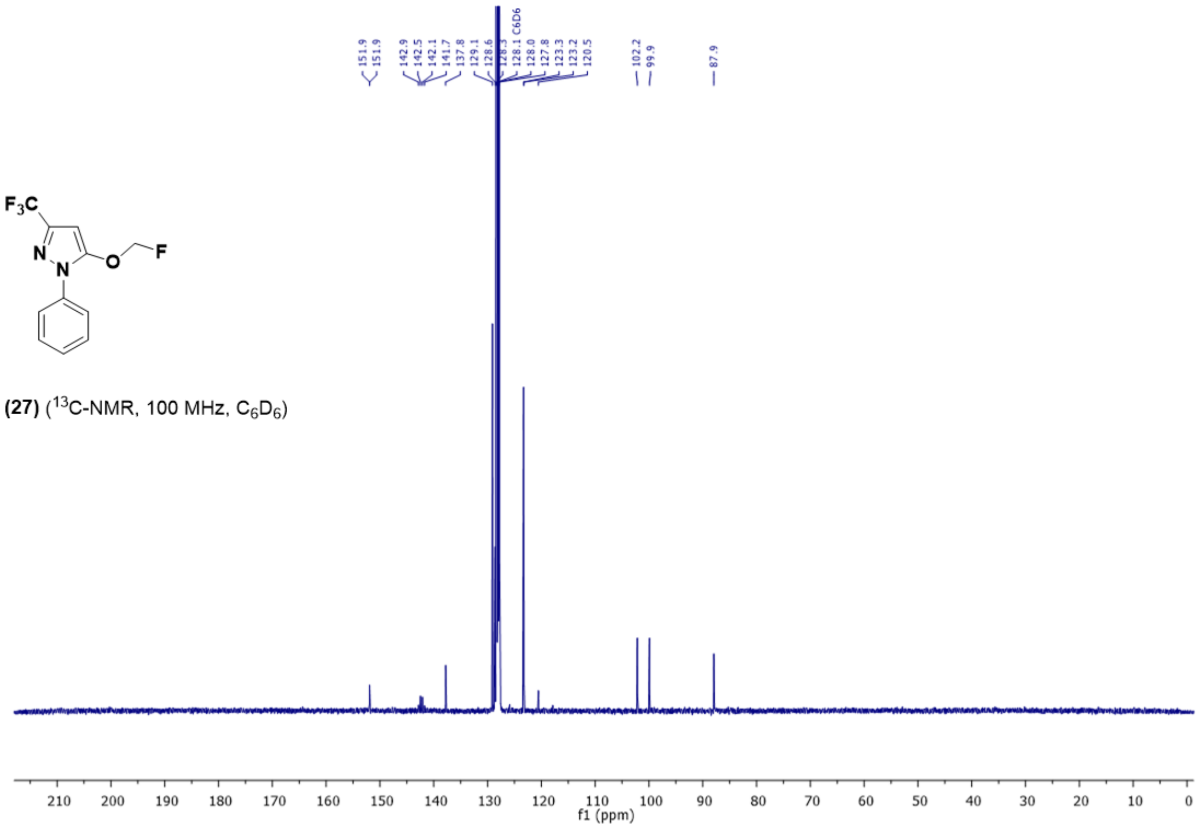
(26) (^{1}H-NMR, 400 MHz, C_6D_6)



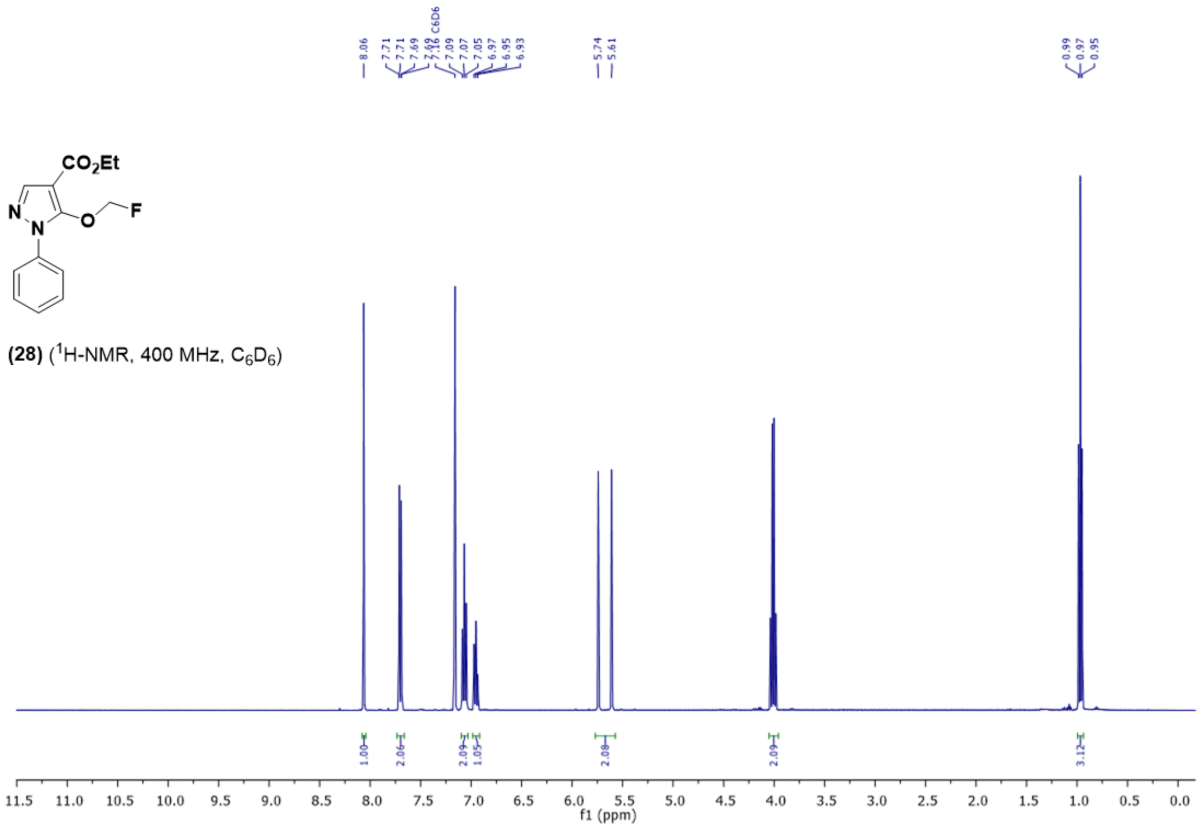
(26) (^{13}C-NMR, 100 MHz, C_6D_6)



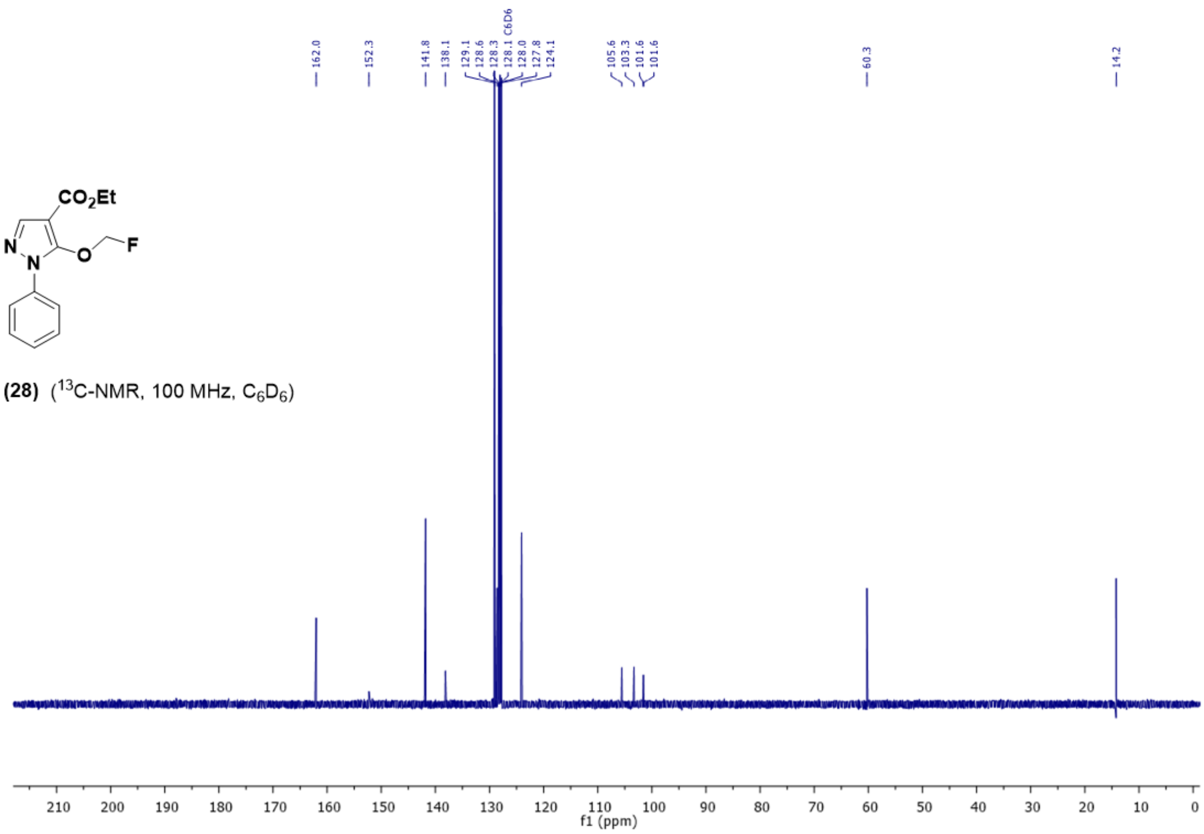
(27) (^{1}H-NMR, 400 MHz, C_6D_6)



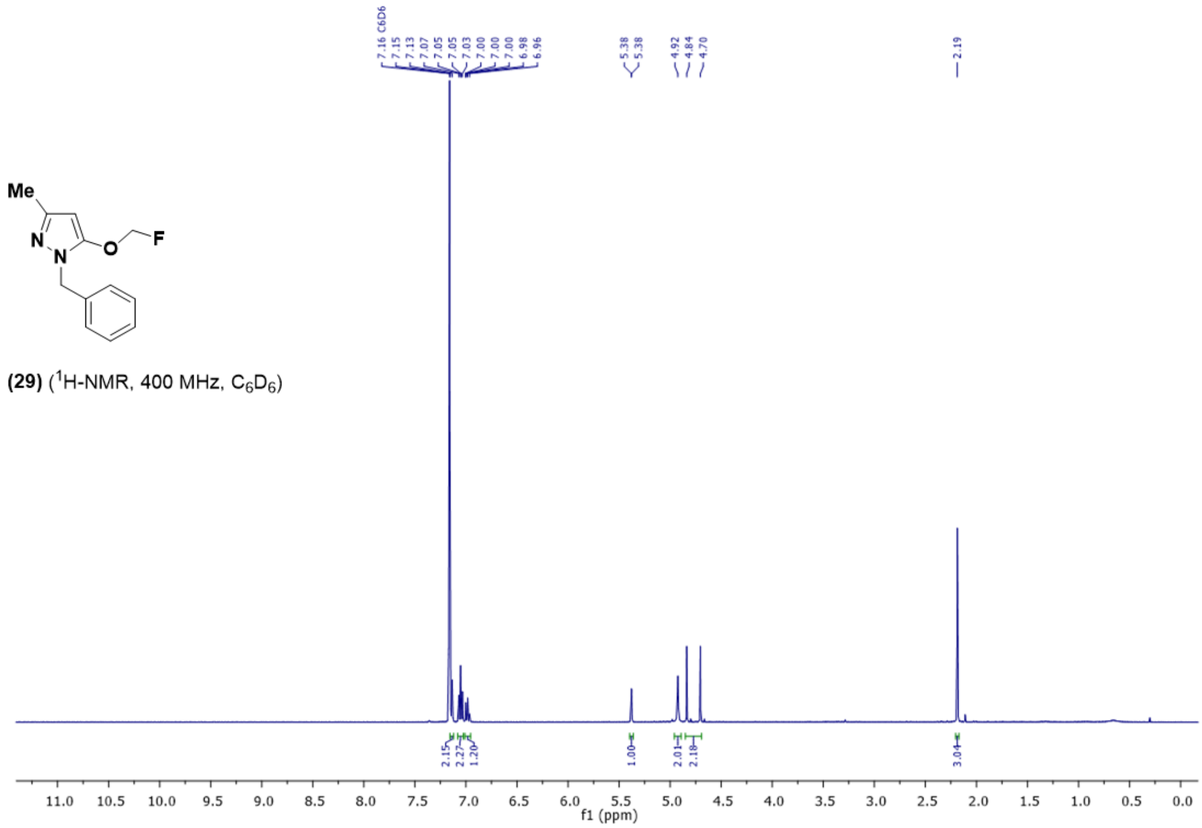
(27) (^{13}C-NMR, 100 MHz, C_6D_6)



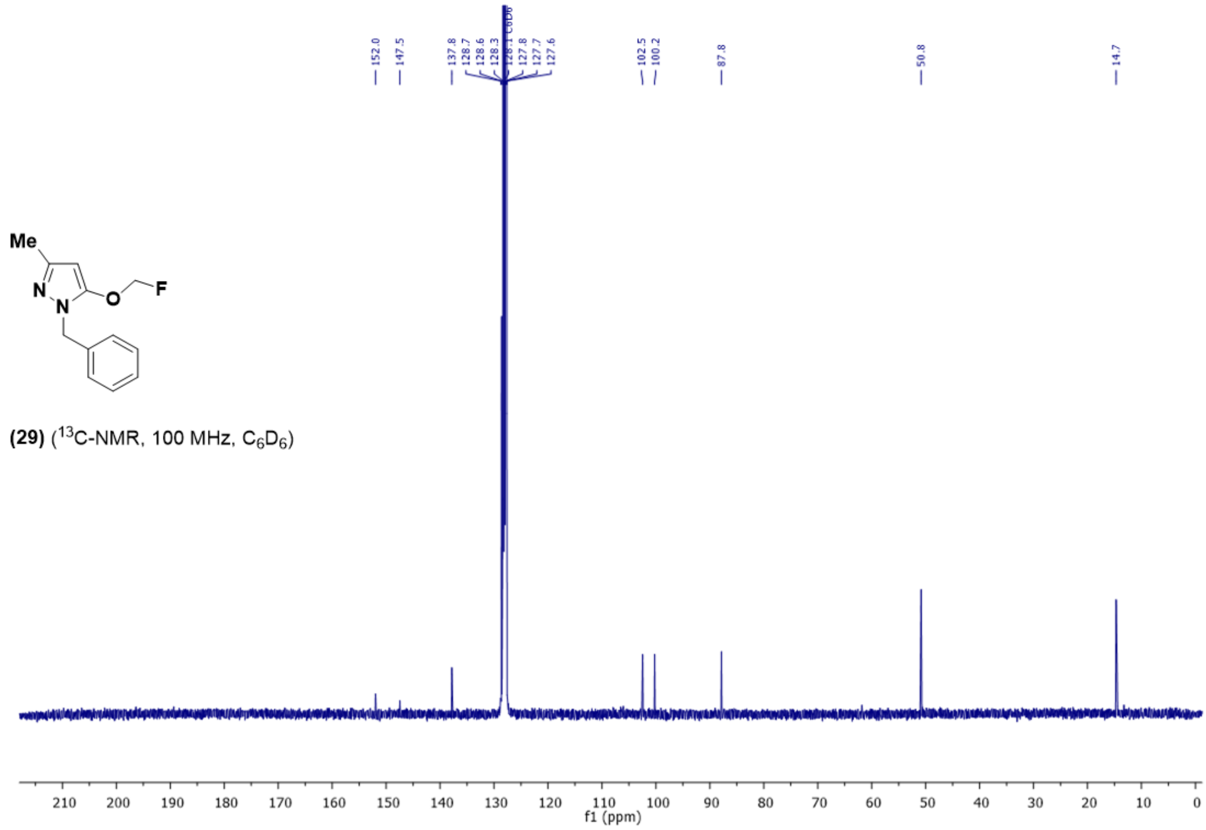
(28) (^{1}H-NMR, 400 MHz, C_6D_6)



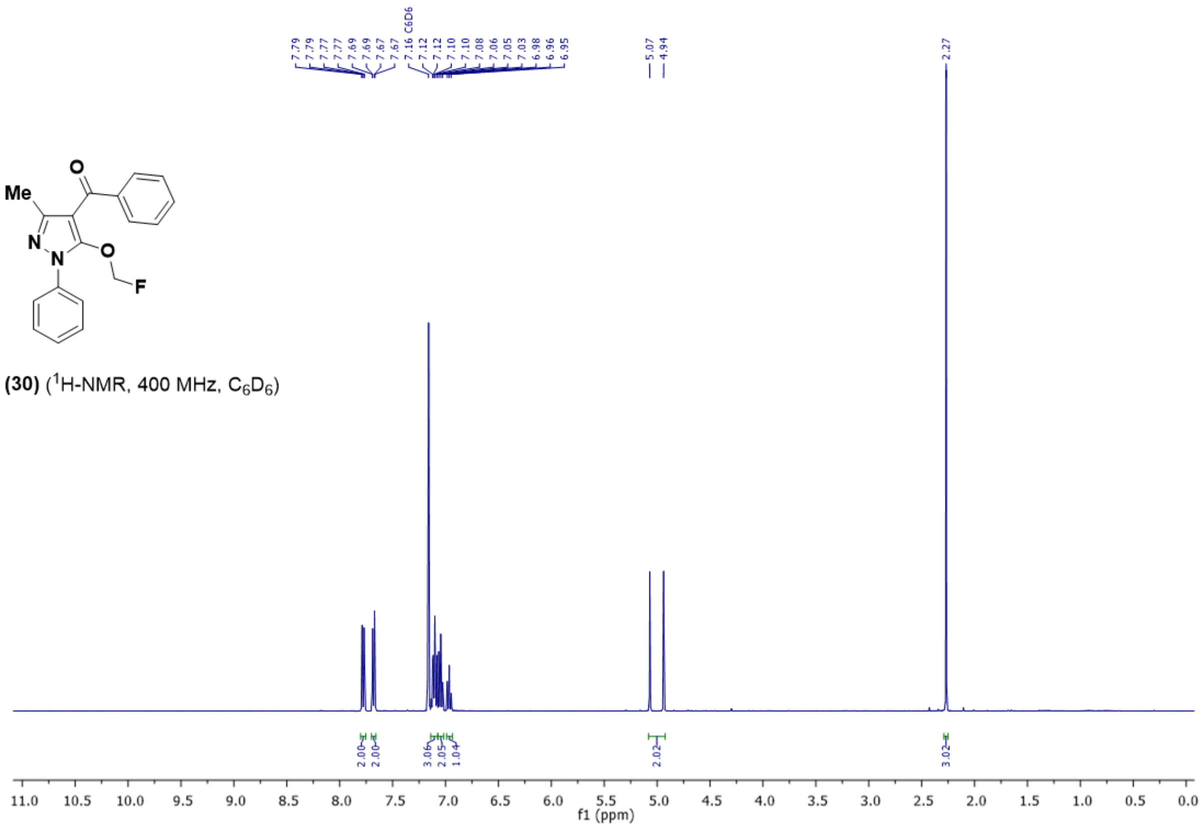
(28) (^{13}C-NMR, 100 MHz, C_6D_6)



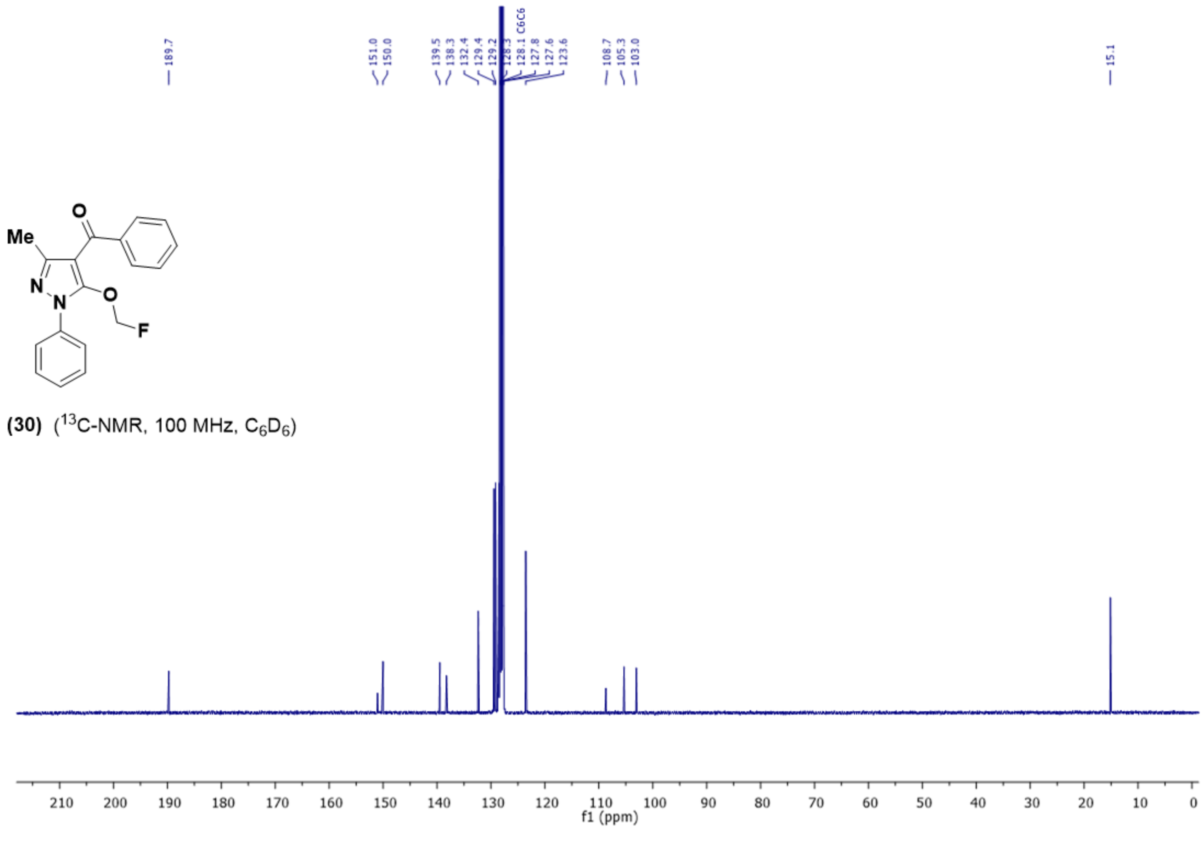
(29) (^{1}H-NMR, 400 MHz, C_6D_6)



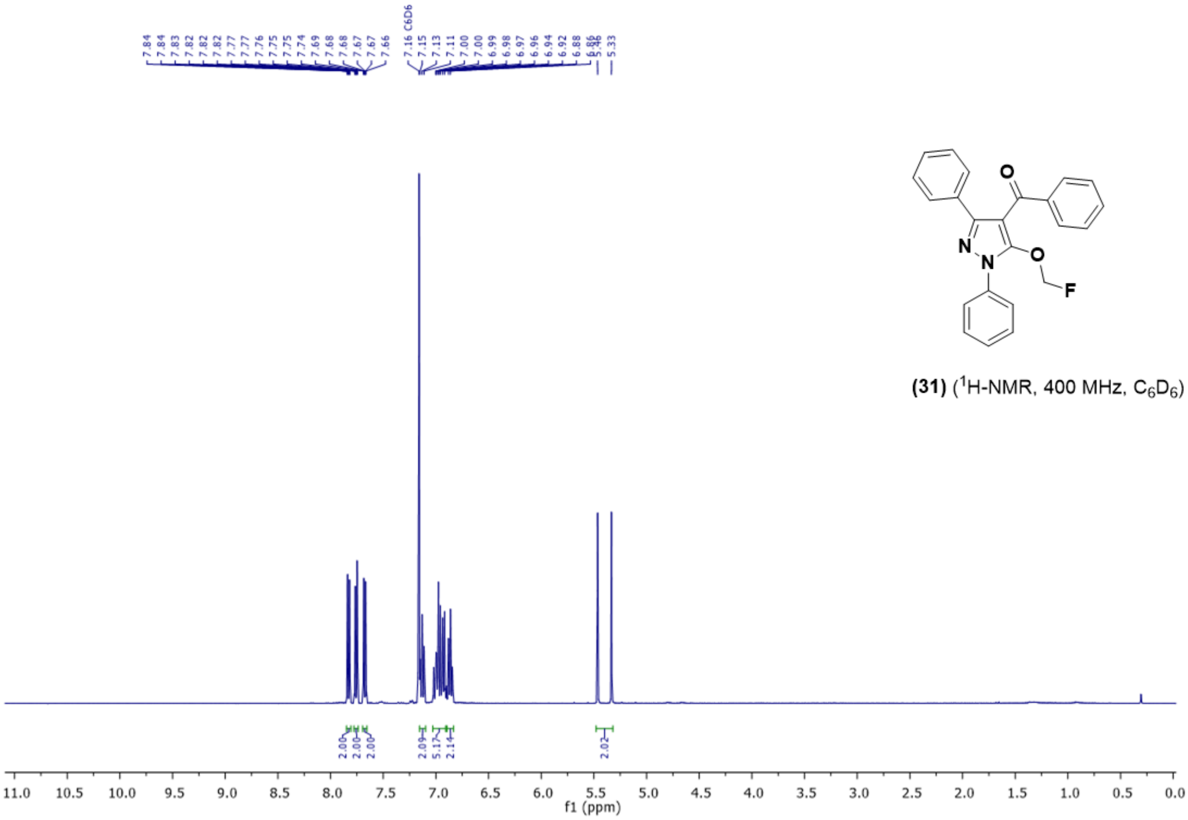
(29) (^{13}C-NMR, 100 MHz, C_6D_6)



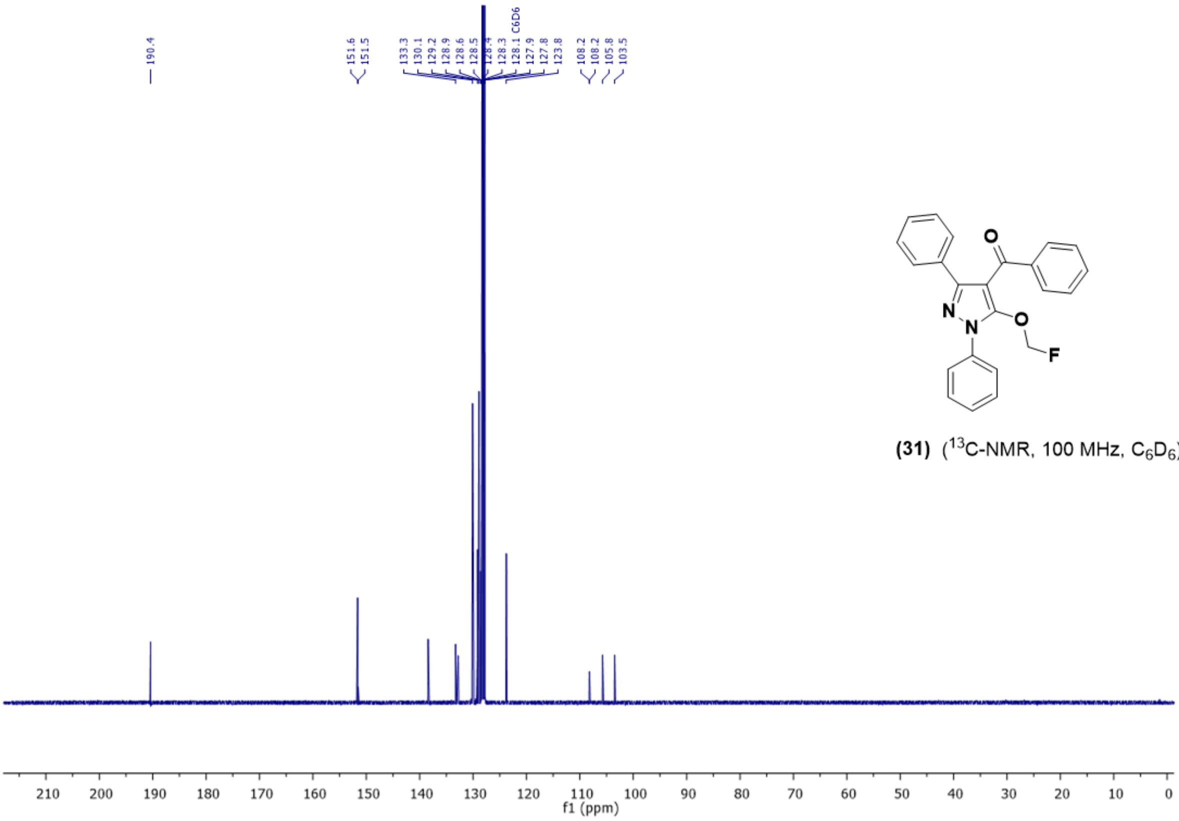
(30) (^{1}H-NMR, 400 MHz, C_6D_6)



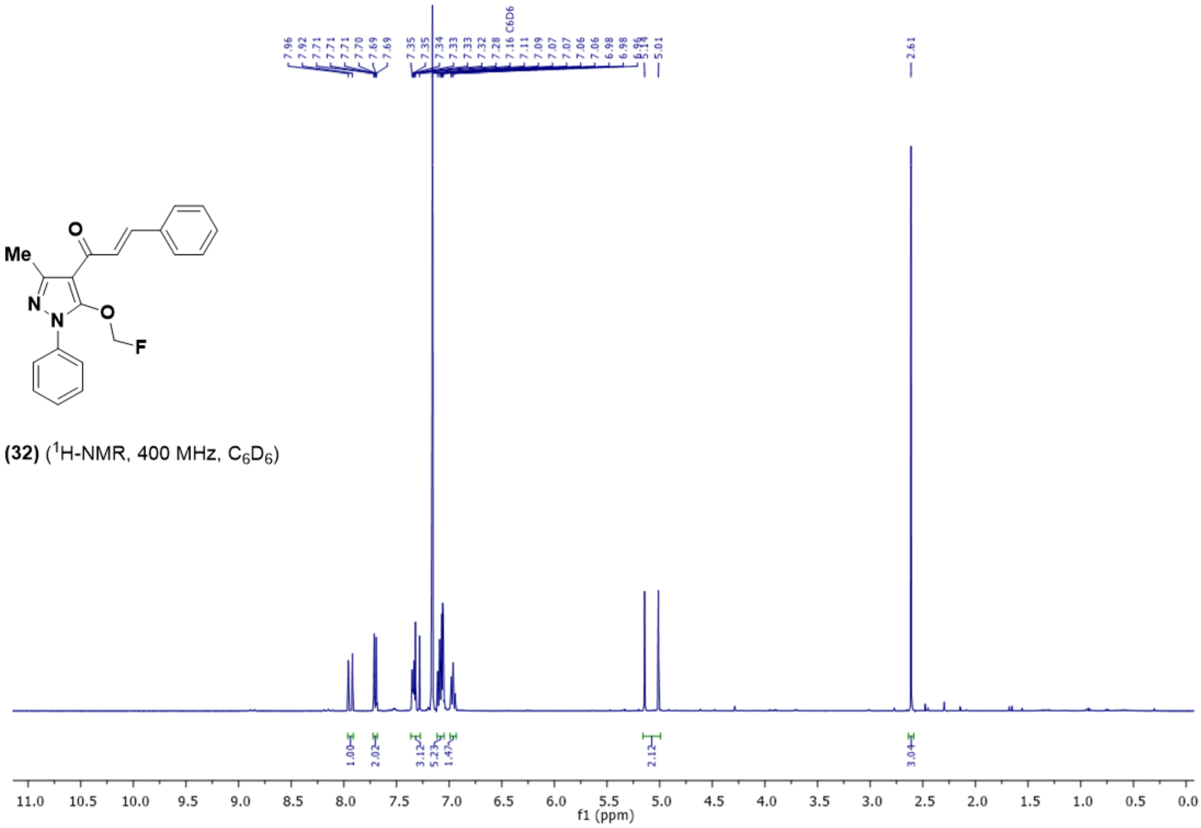
(30) (^{13}C-NMR, 100 MHz, C_6D_6)



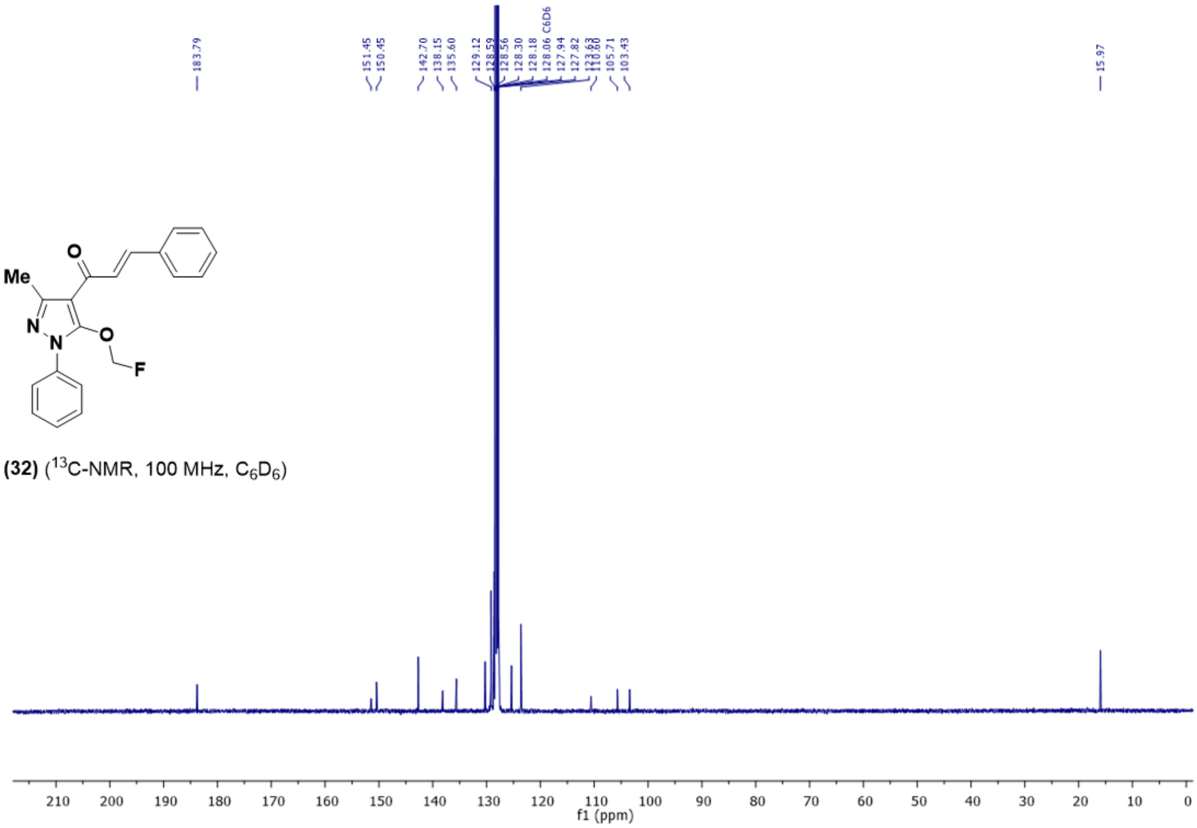
(31) (^{1}H-NMR, 400 MHz, C_6D_6)



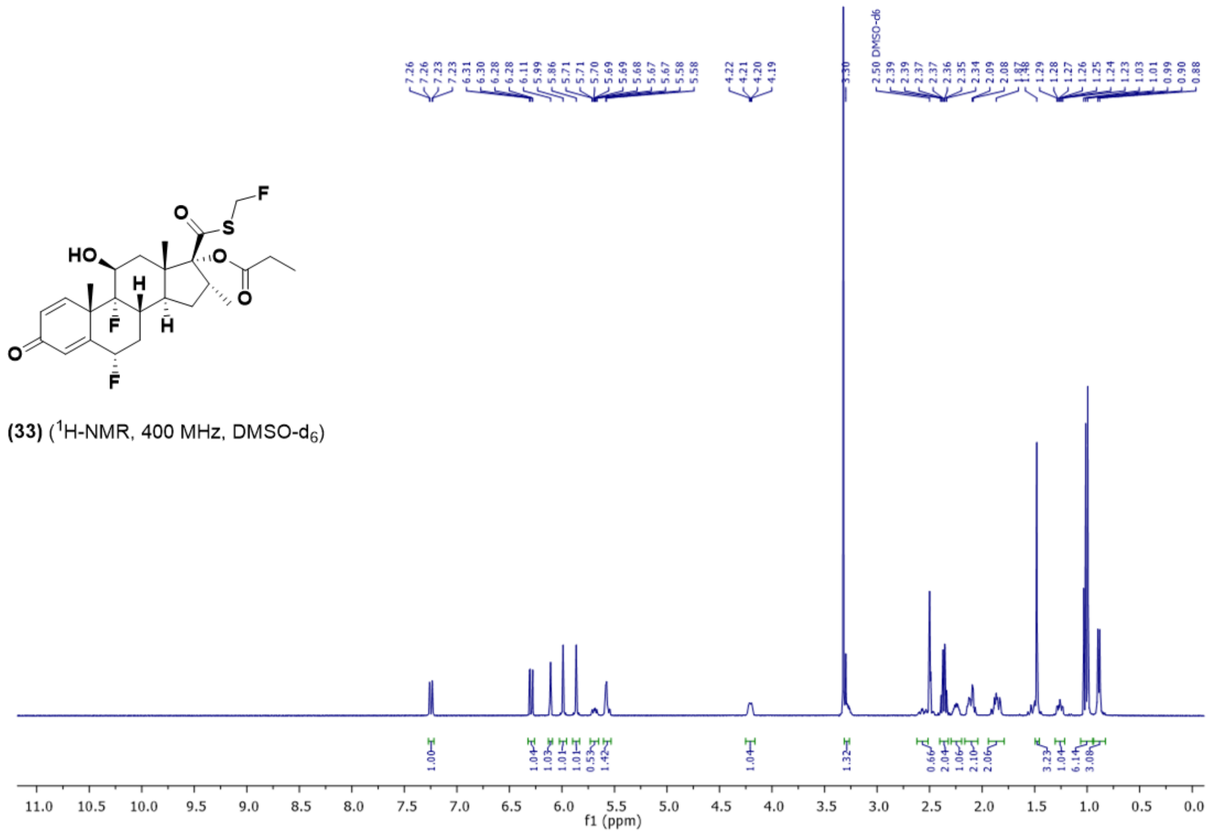
(31) (^{13}C-NMR, 100 MHz, C_6D_6)



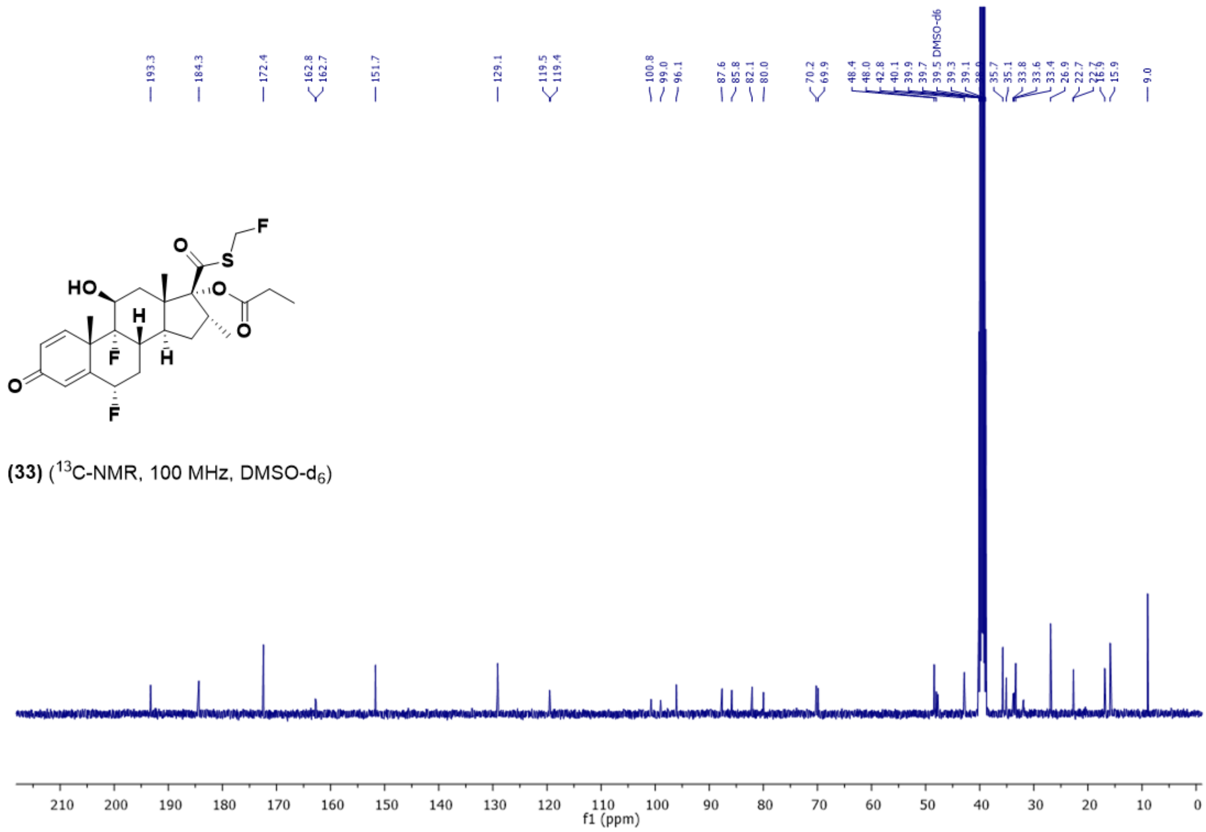
(32) (^{1}H-NMR, 400 MHz, C_6D_6)



(32) (^{13}C-NMR, 100 MHz, C_6D_6)

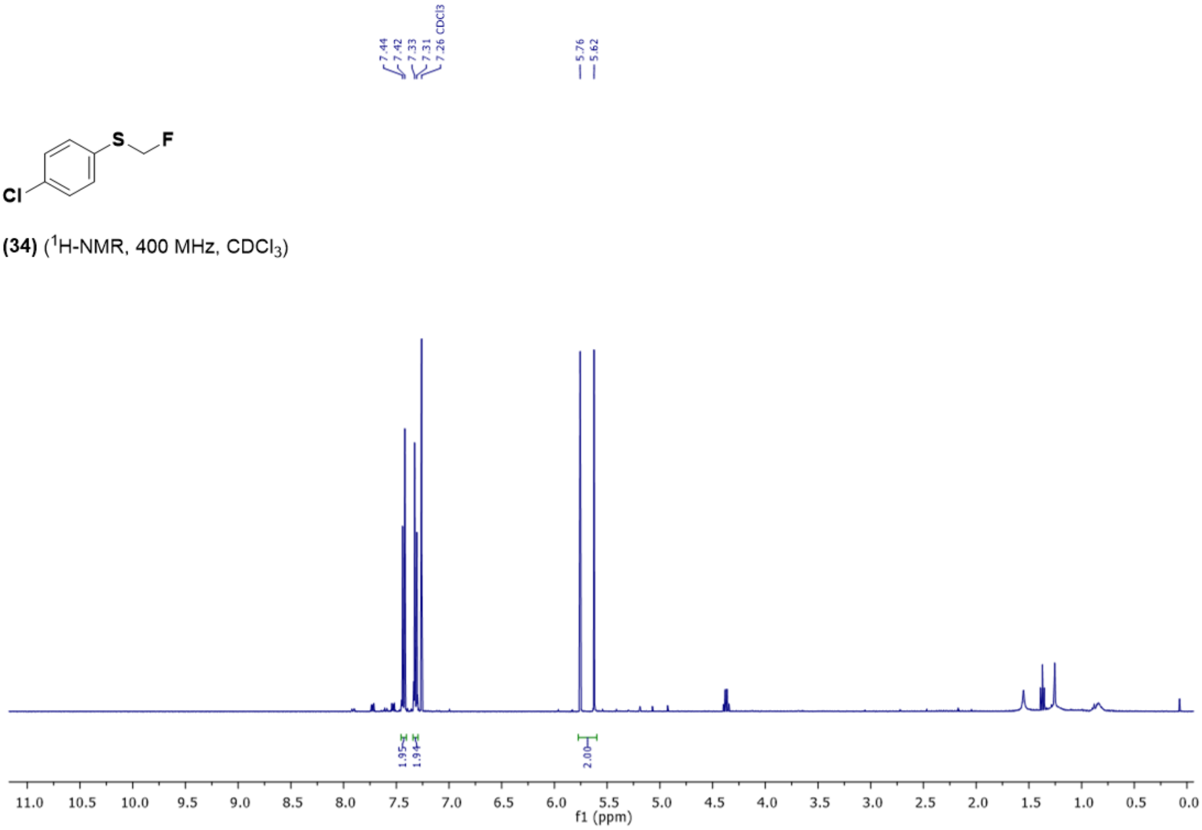


(33) (^{1}H-NMR, 400 MHz, DMSO-d_6)

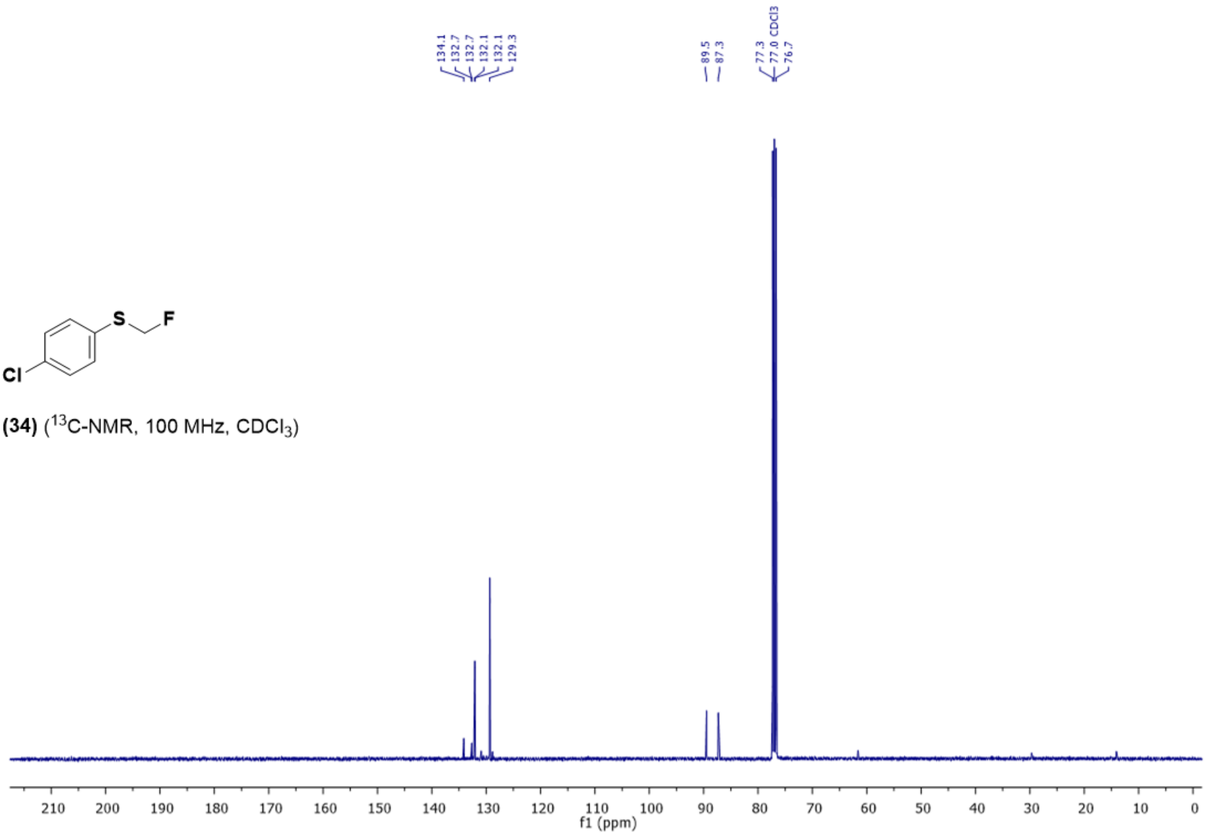


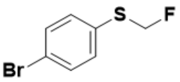
(33) (^{13}C-NMR, 100 MHz, DMSO-d_6)

(34) (^{1}H-NMR, 400 MHz, $CDCl_3$)

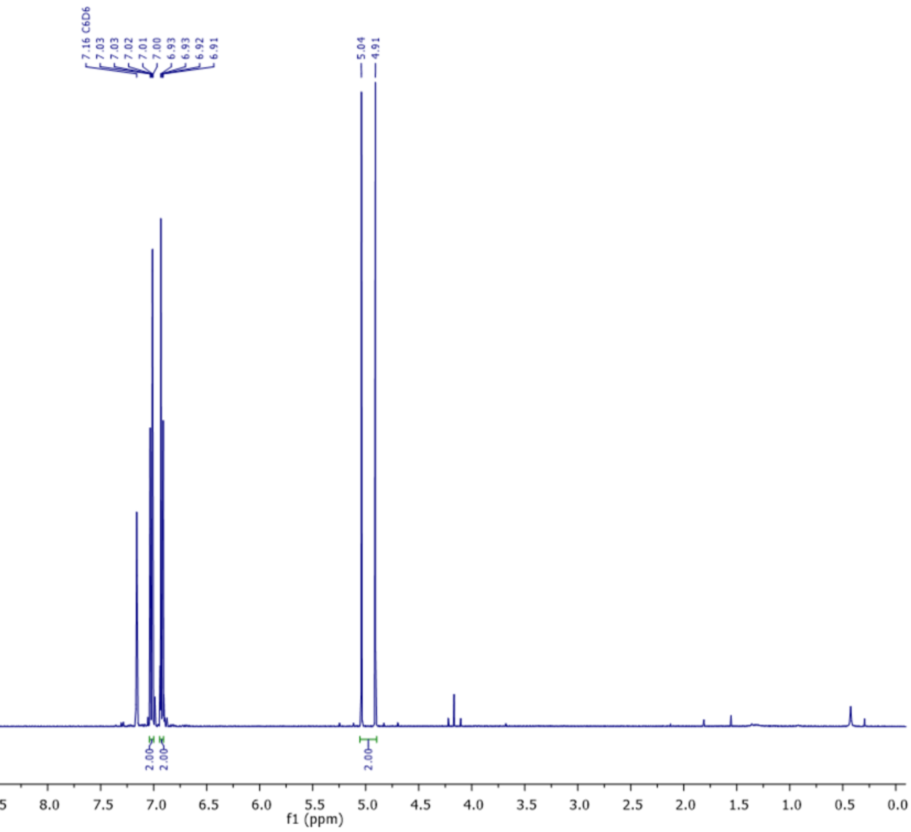


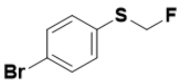
(34) (^{13}C-NMR, 100 MHz, $CDCl_3$)



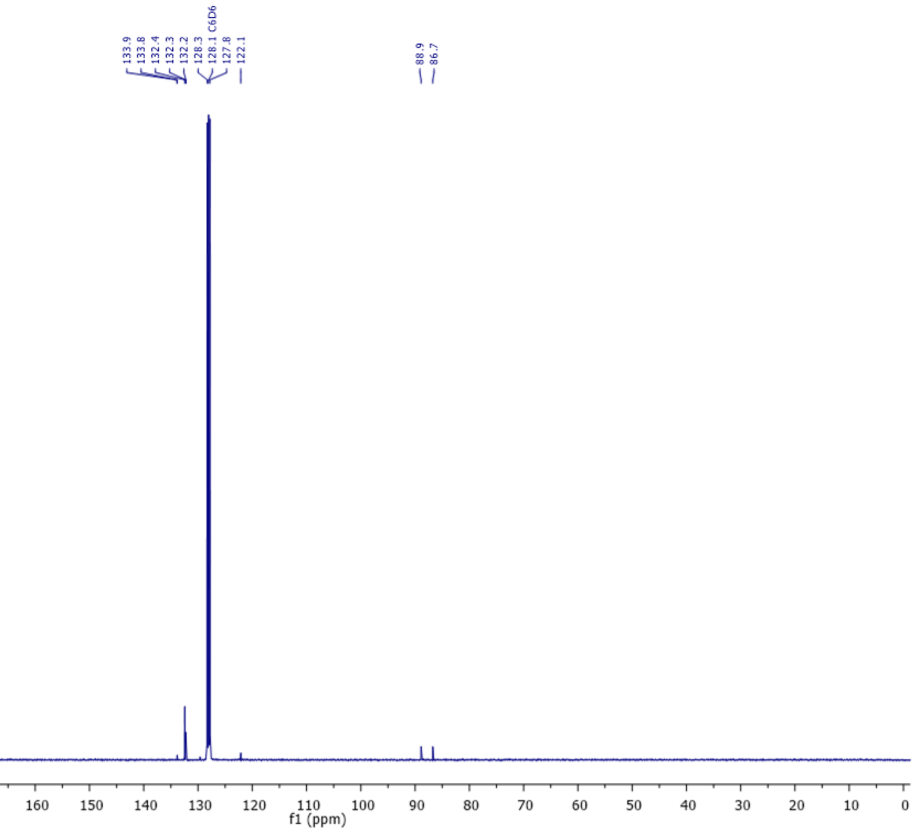


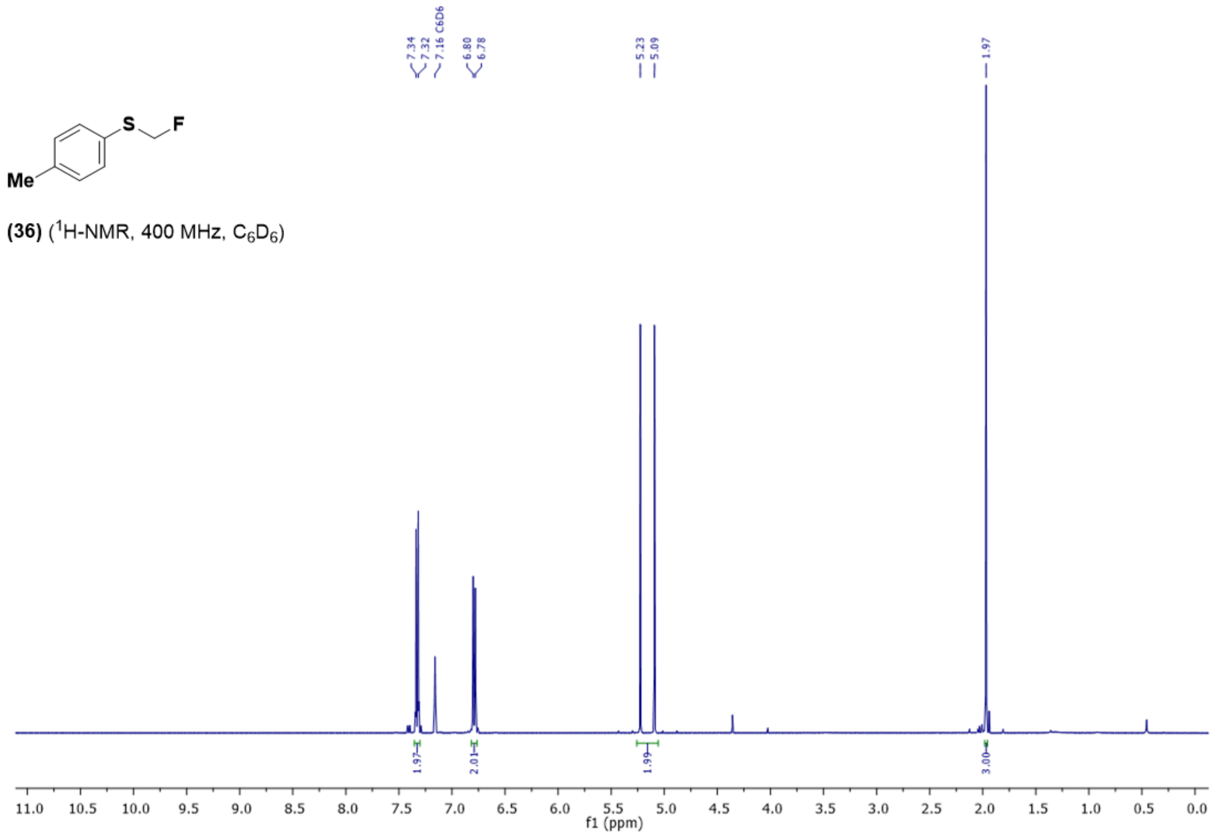
(35) (^{1}H-NMR, 400 MHz, C_6D_6)



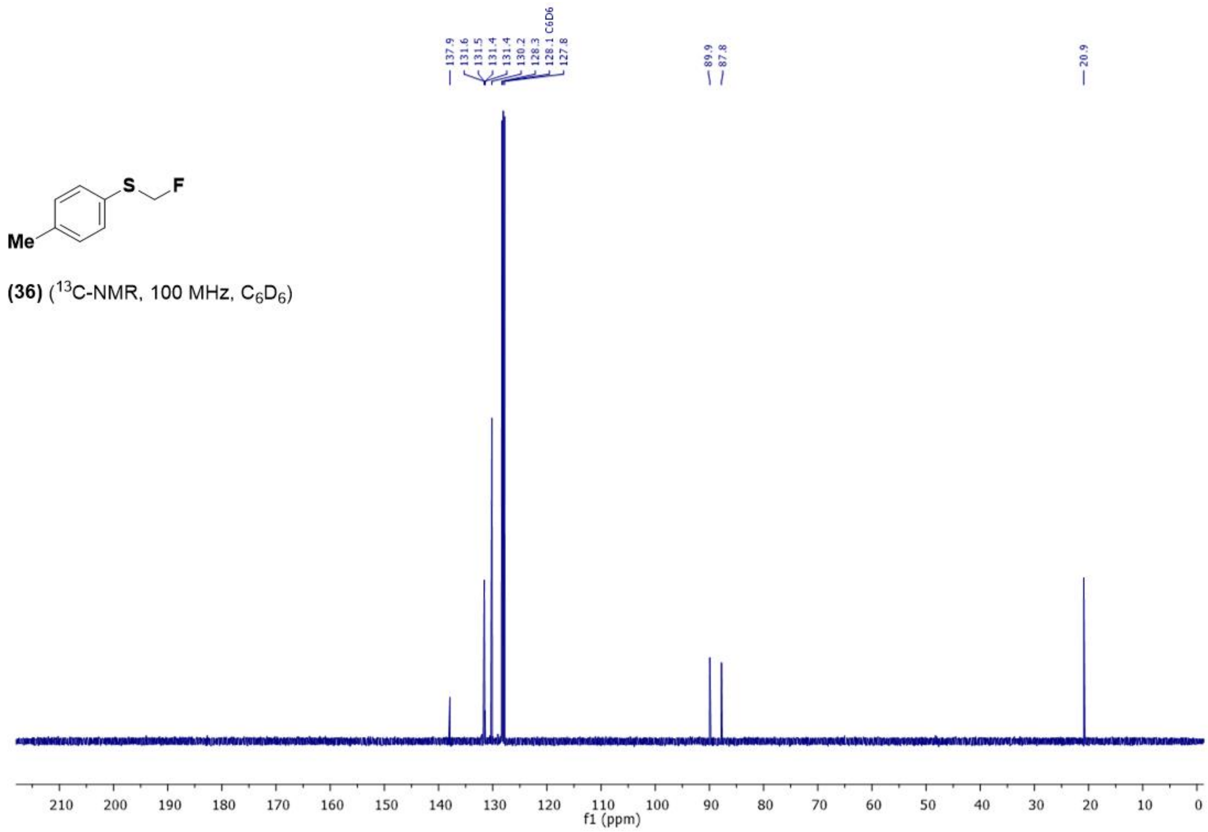


(35) (^{13}C-NMR, 100 MHz, C_6D_6)

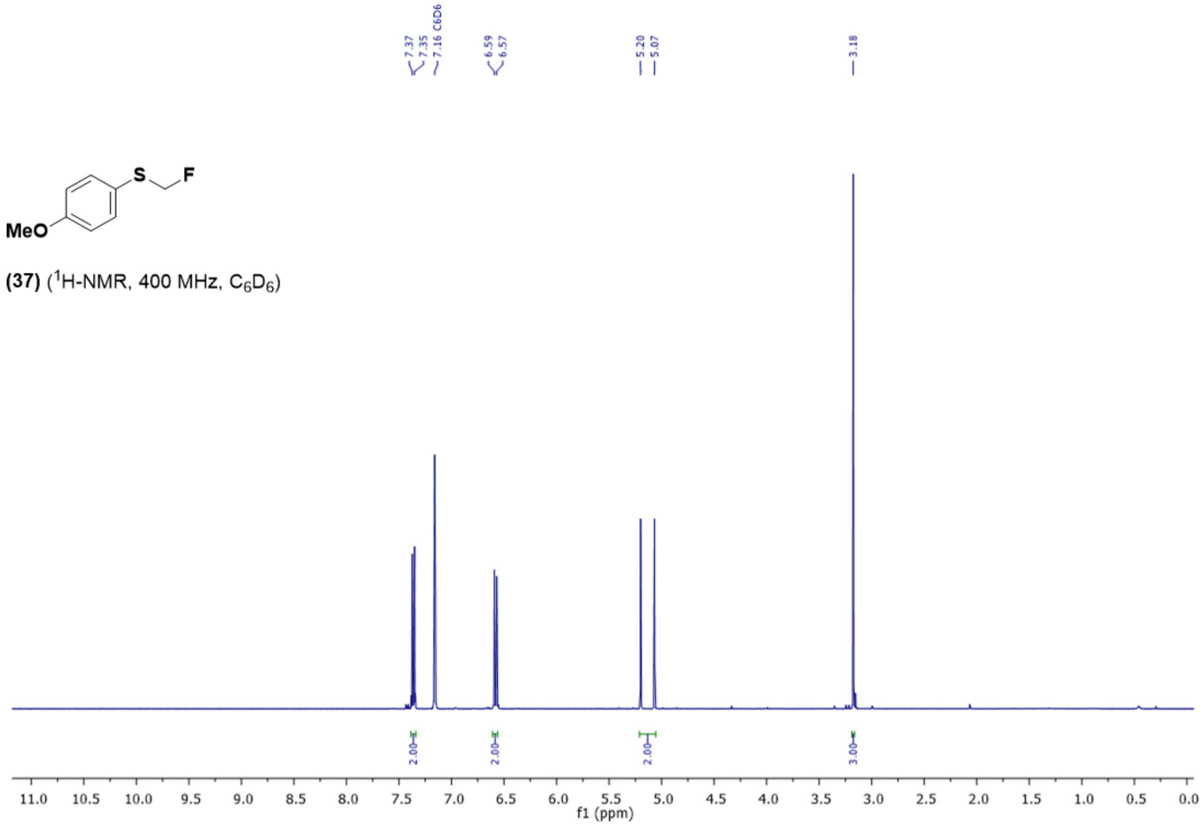




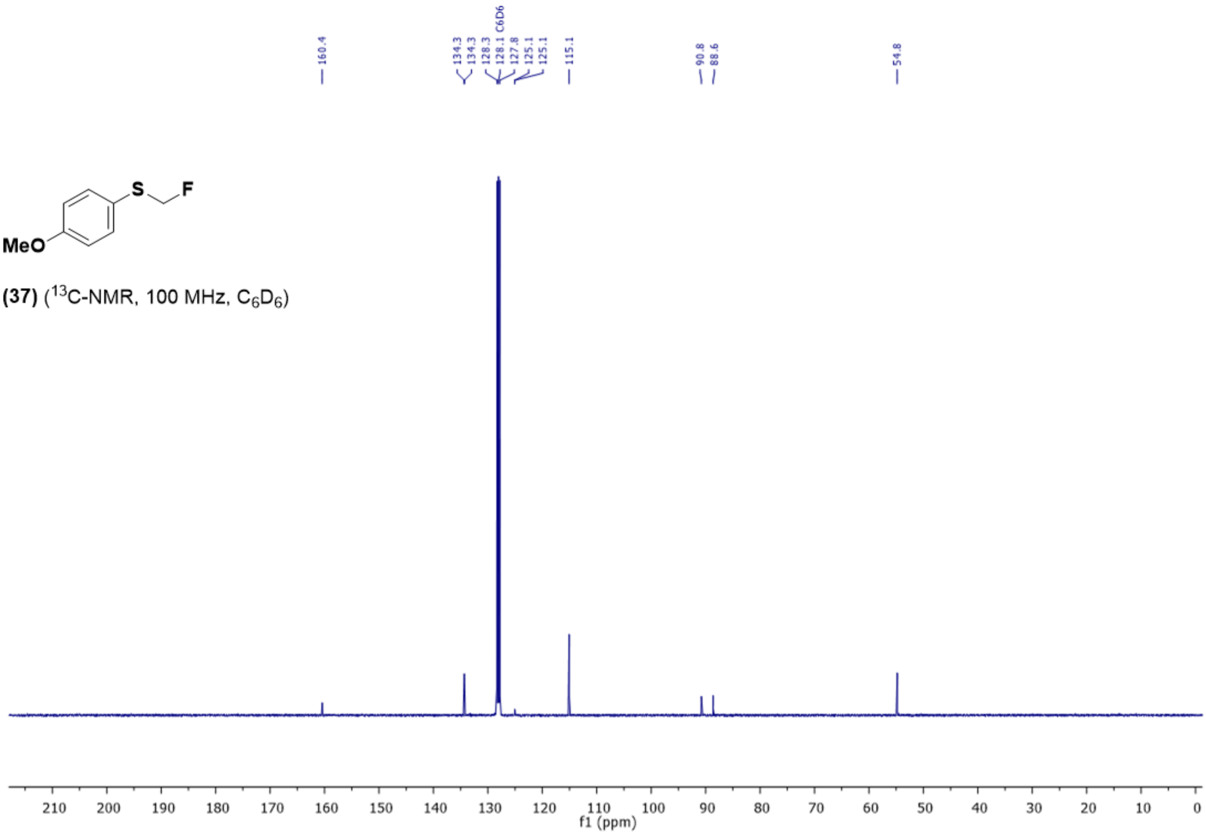
(36) (^{1}H-NMR, 400 MHz, C_6D_6)



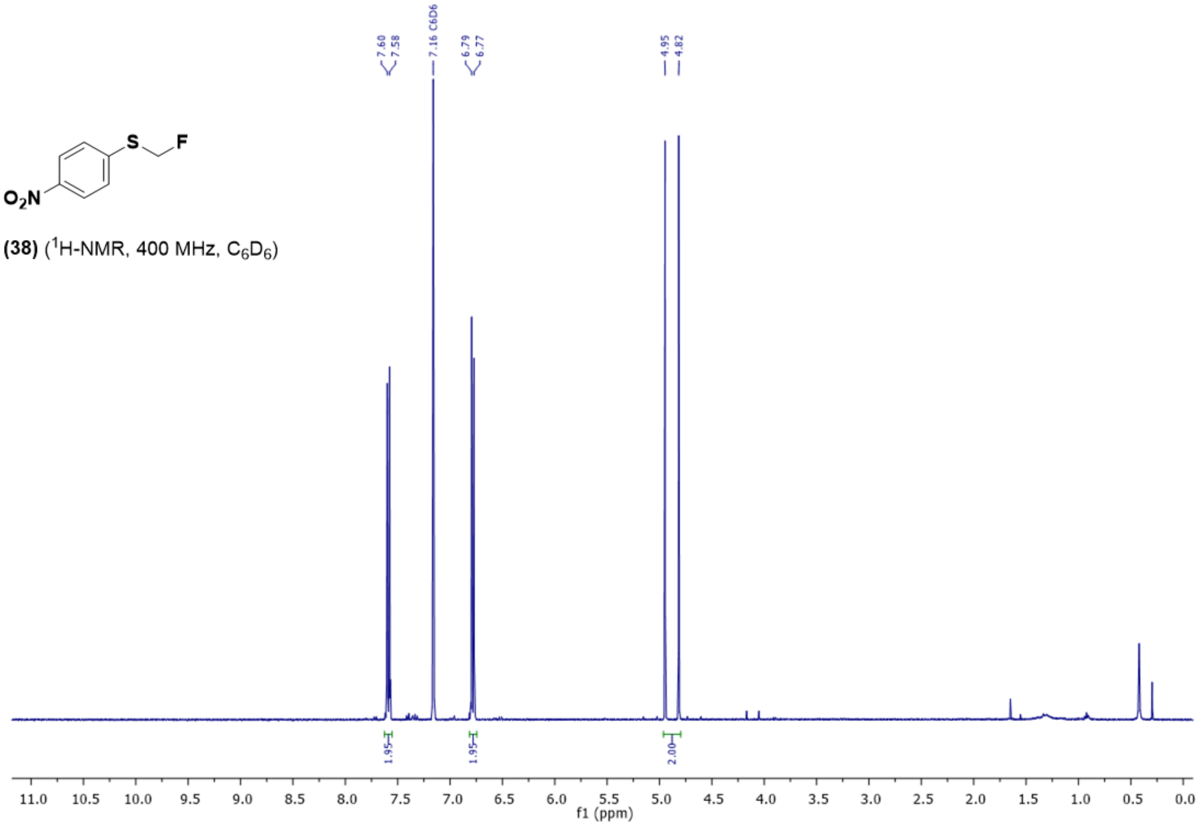
(36) (^{13}C-NMR, 100 MHz, C_6D_6)



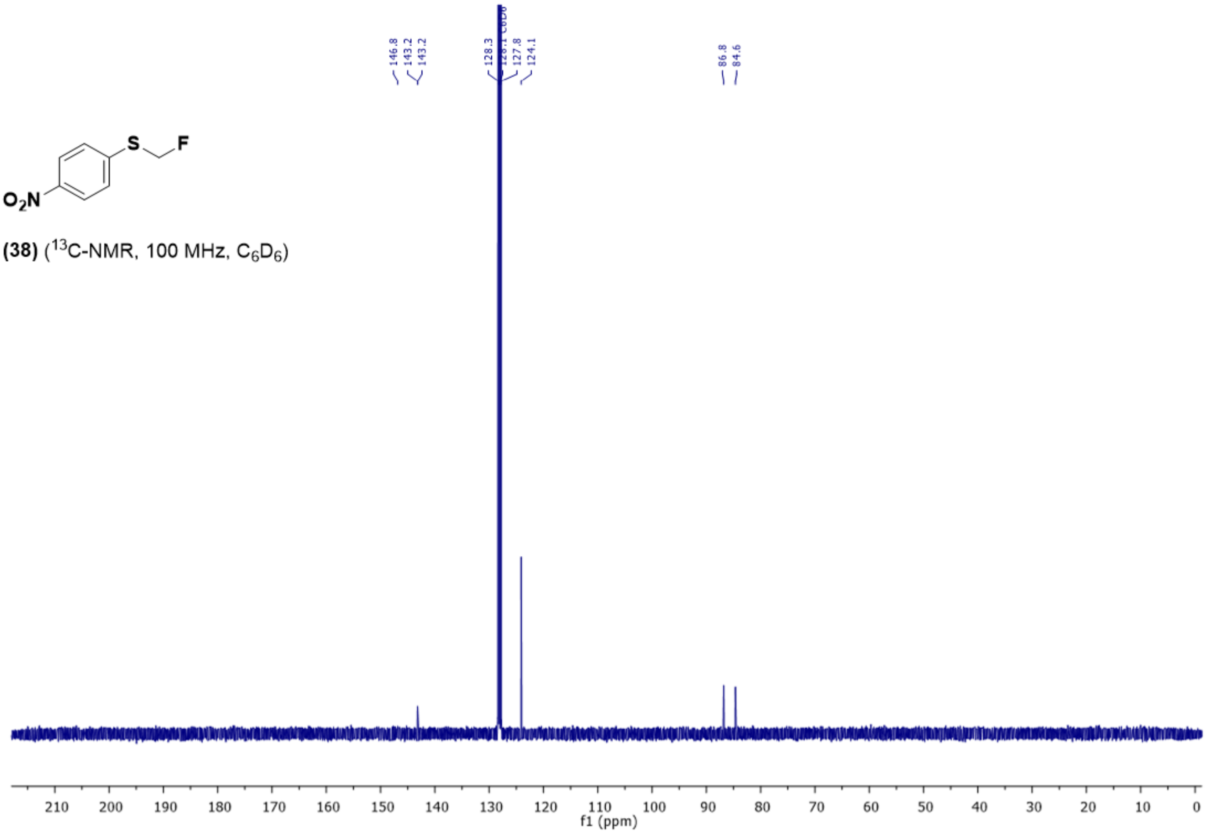
(37) (^{1}H-NMR, 400 MHz, C_6D_6)



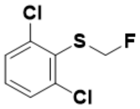
(37) (^{13}C-NMR, 100 MHz, C_6D_6)



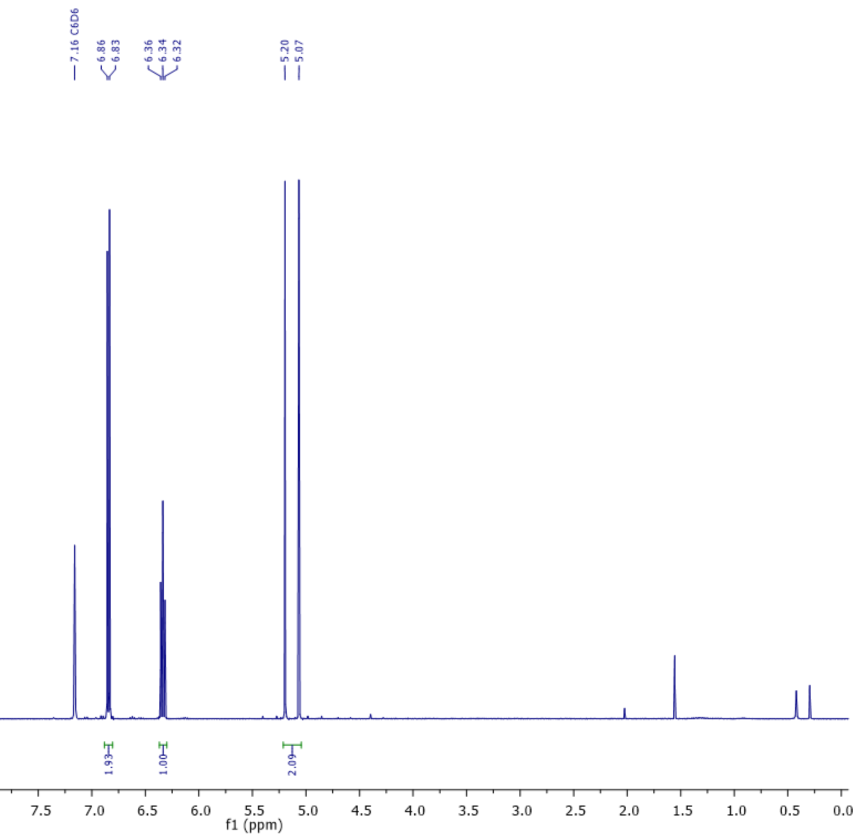
(38) (^{1}H-NMR, 400 MHz, C_6D_6)

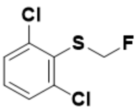


(38) (^{13}C-NMR, 100 MHz, C_6D_6)

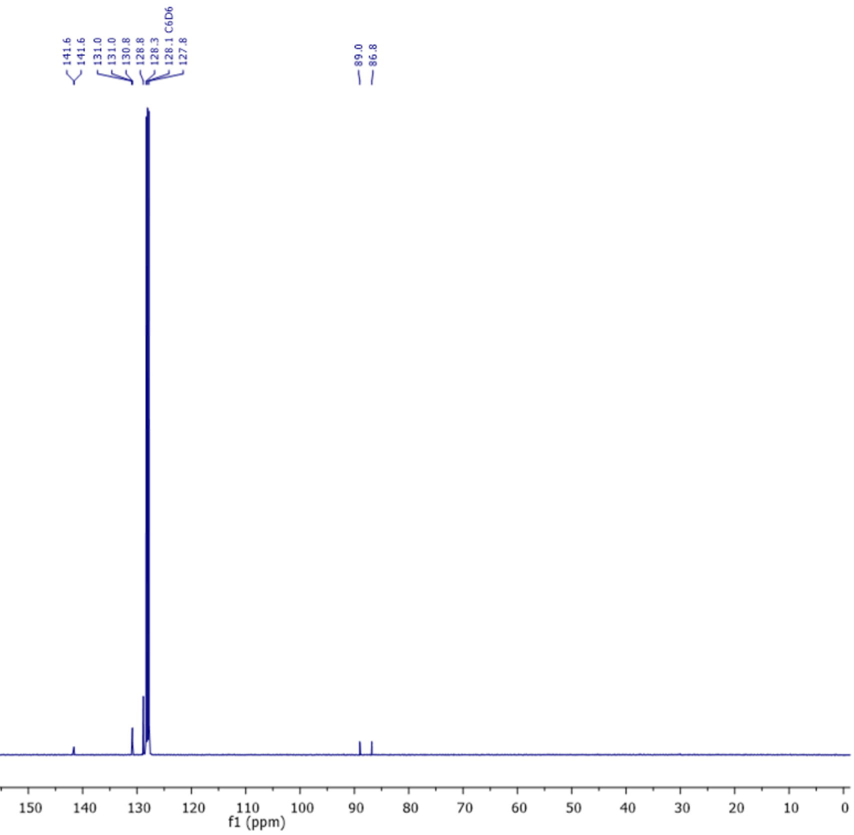


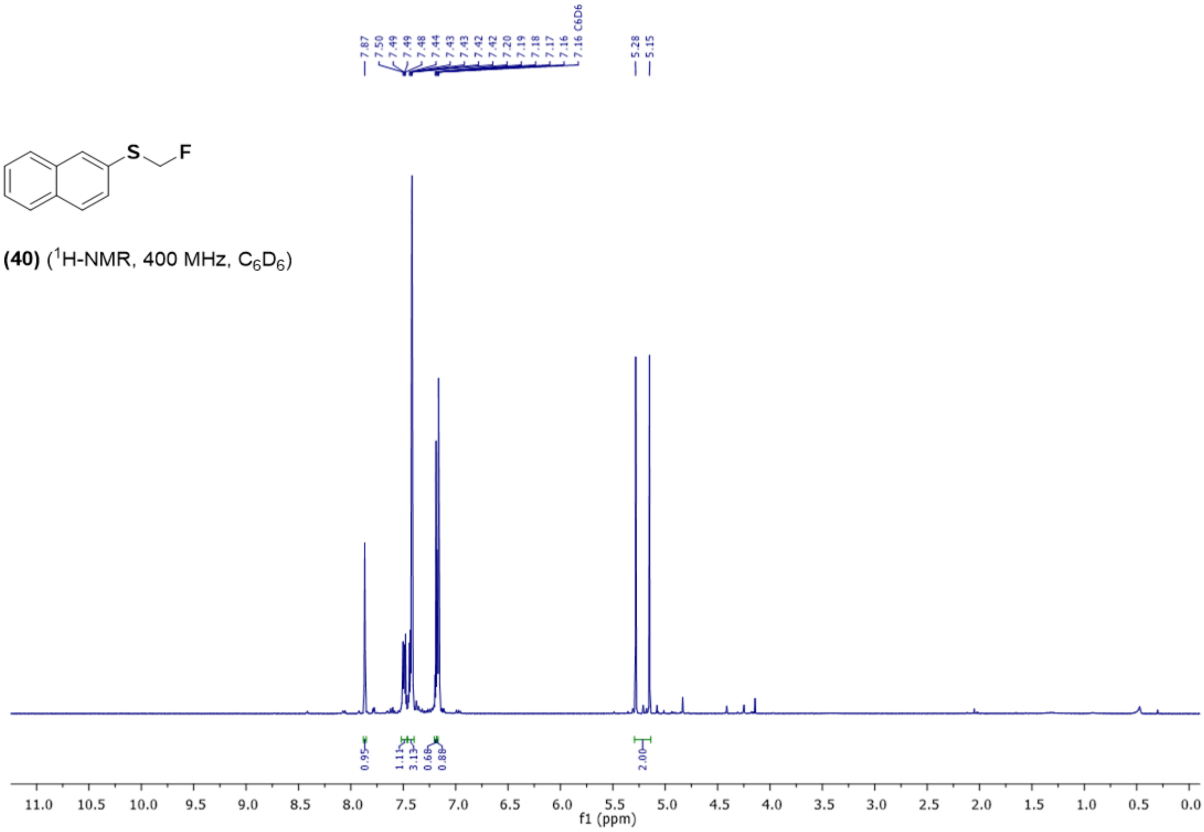
(39) (^{1}H-NMR, 400 MHz, C_6D_6)



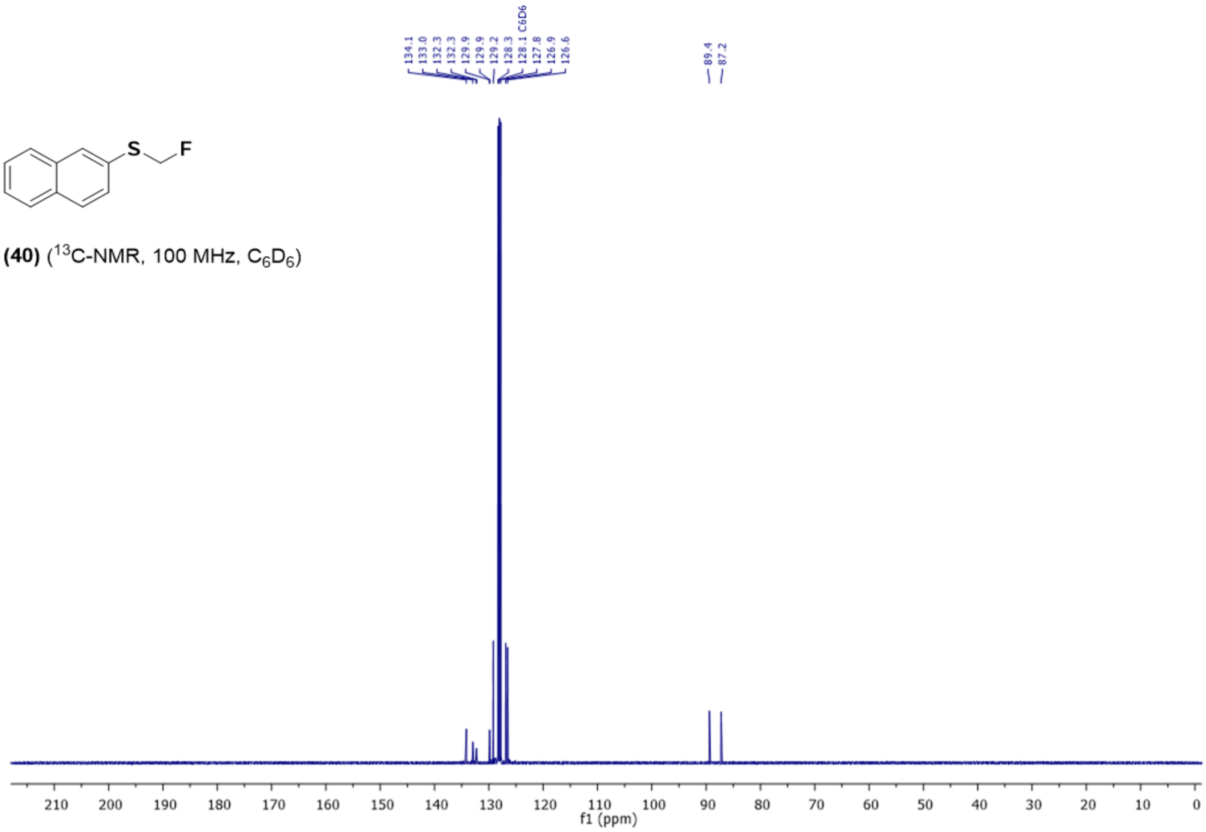


(39) (^{13}C-NMR, 100 MHz, C_6D_6)

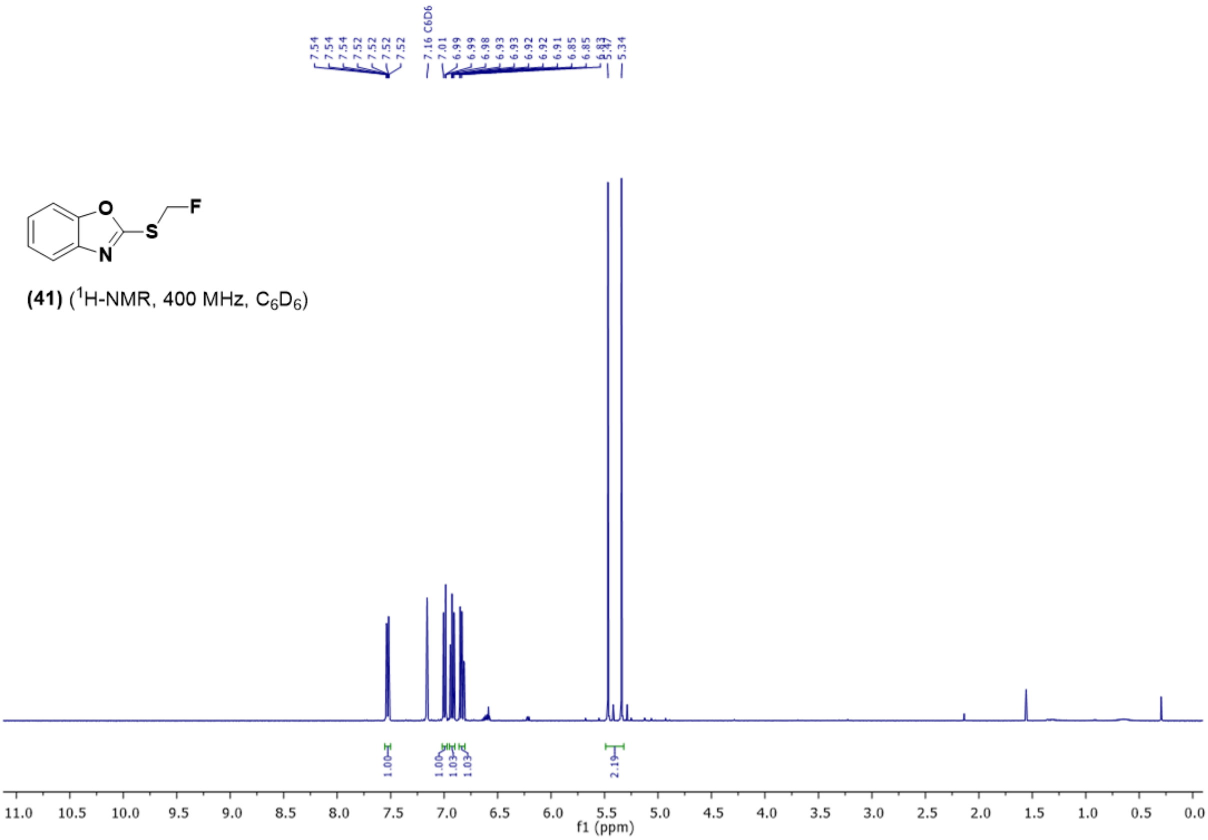




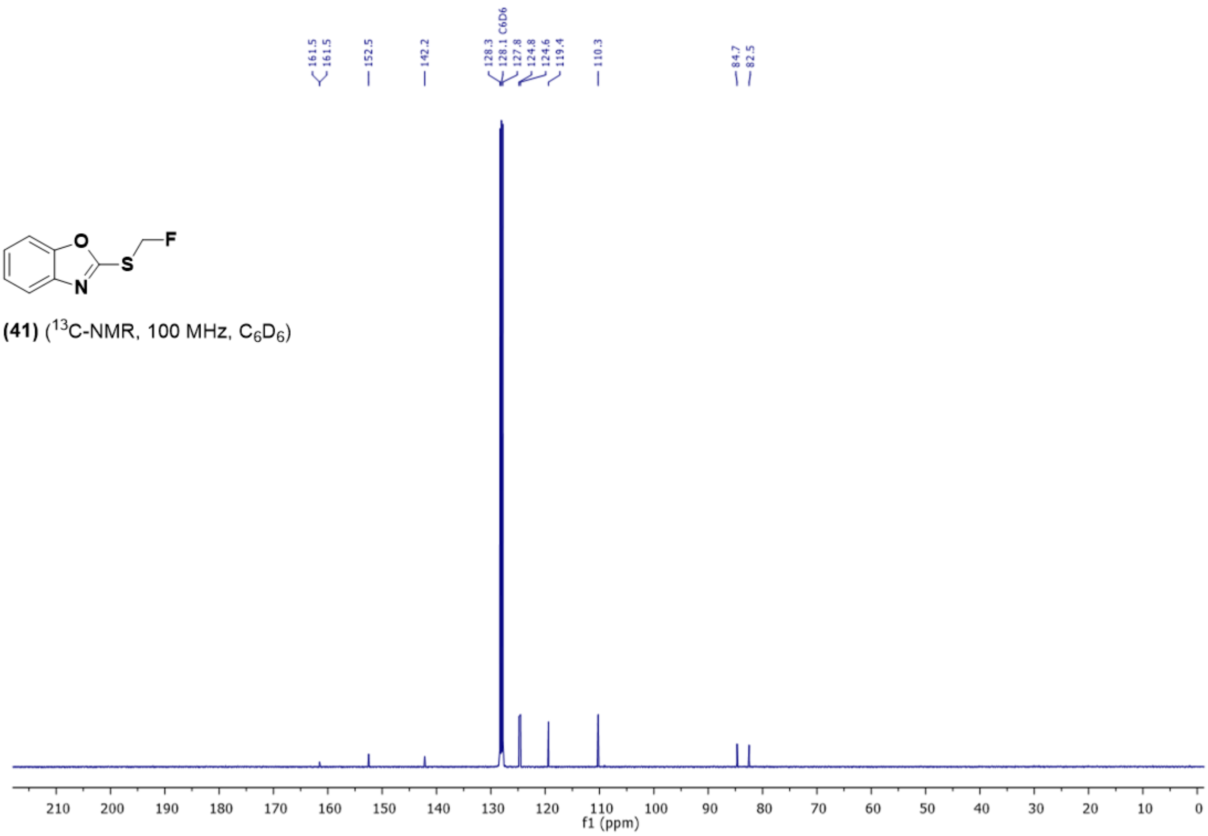
(40) (^{1}H-NMR, 400 MHz, C_6D_6)



(40) (^{13}C-NMR, 100 MHz, C_6D_6)

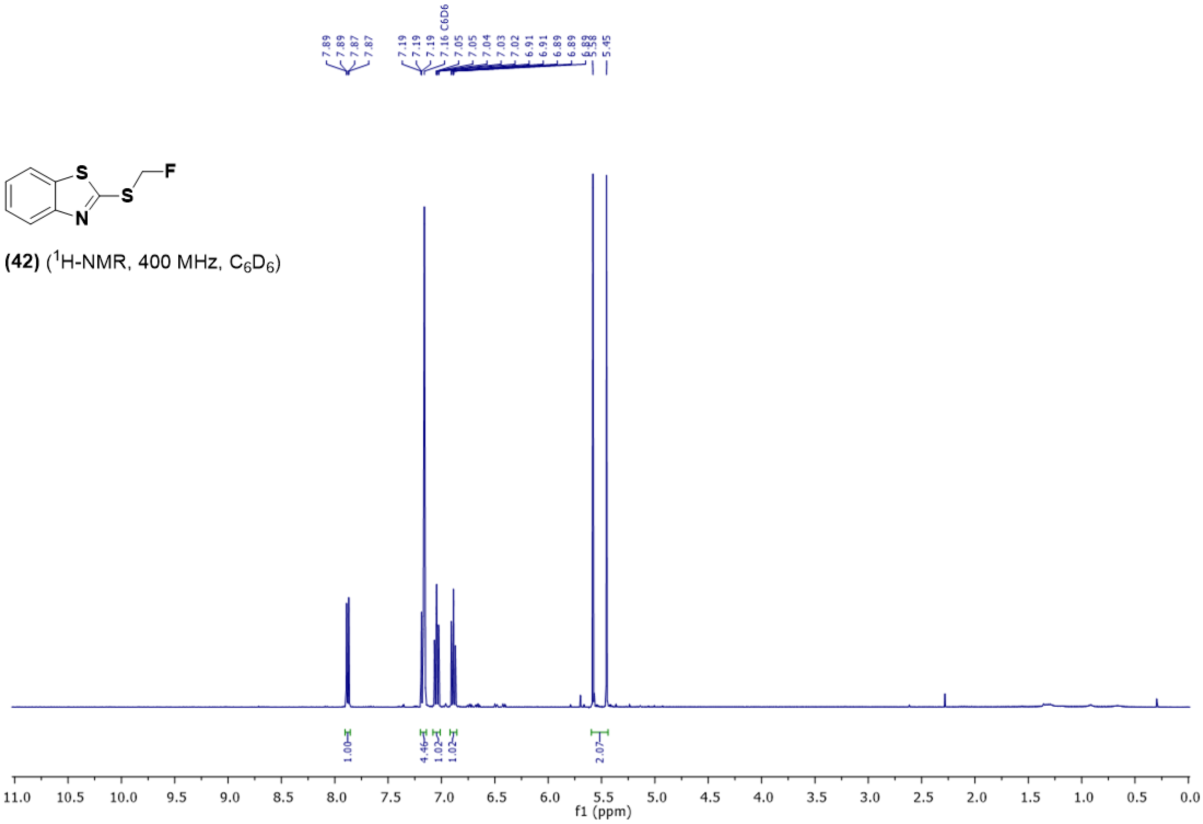


(41) (^{1}H-NMR, 400 MHz, C_6D_6)

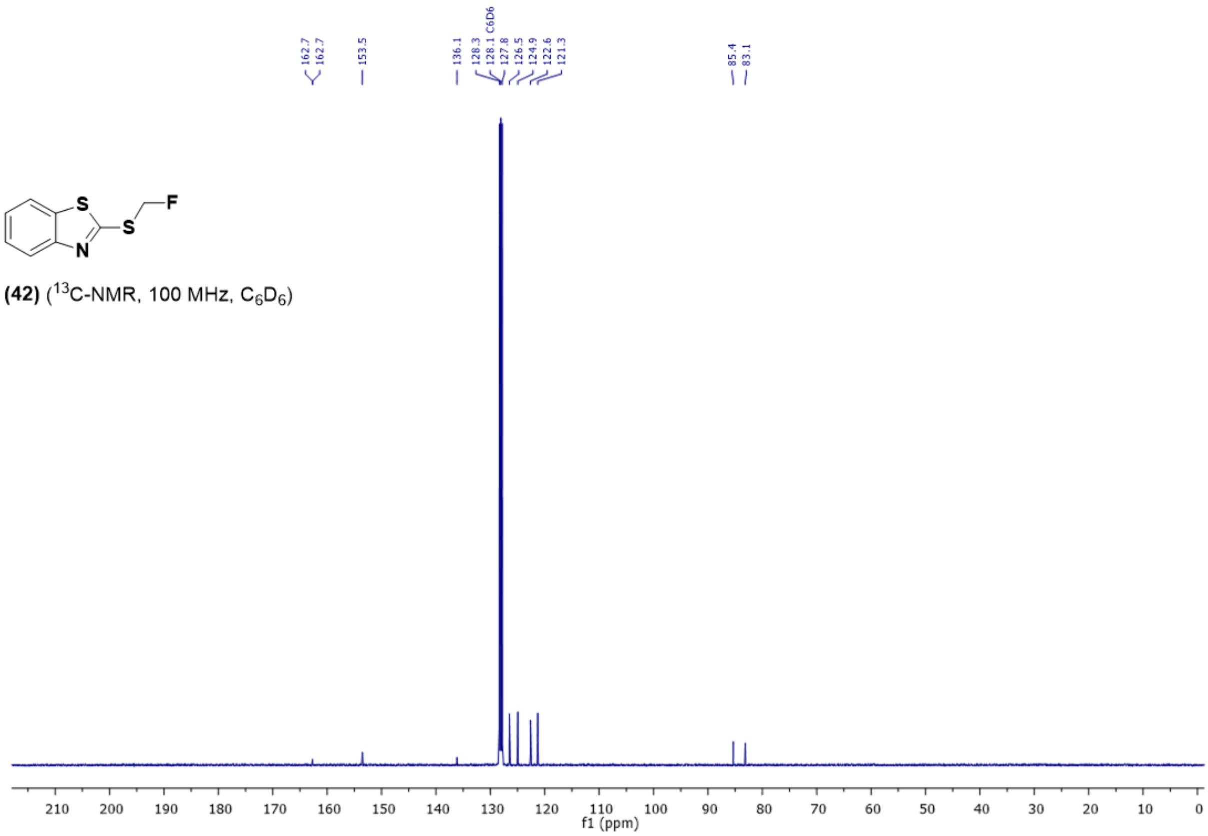


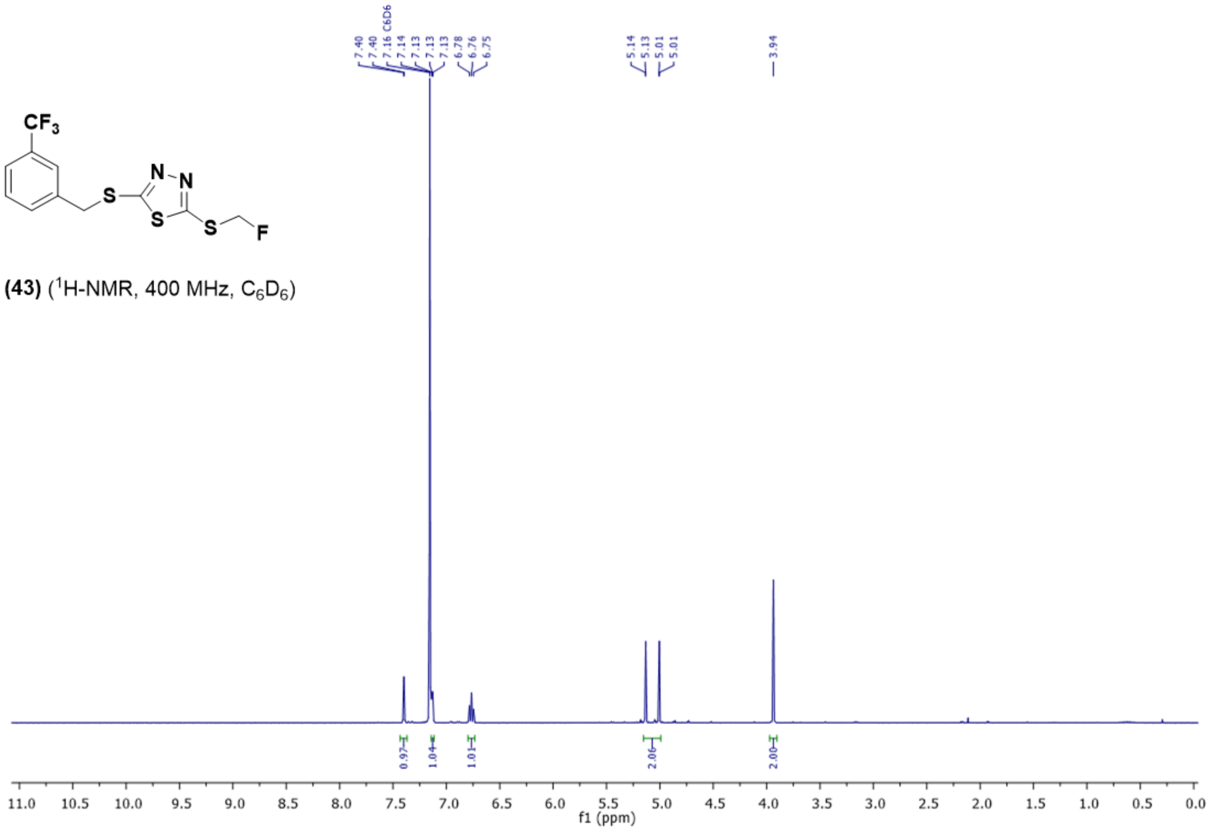
(41) (^{13}C-NMR, 100 MHz, C_6D_6)

(42) (^{1}H-NMR, 400 MHz, C_6D_6)

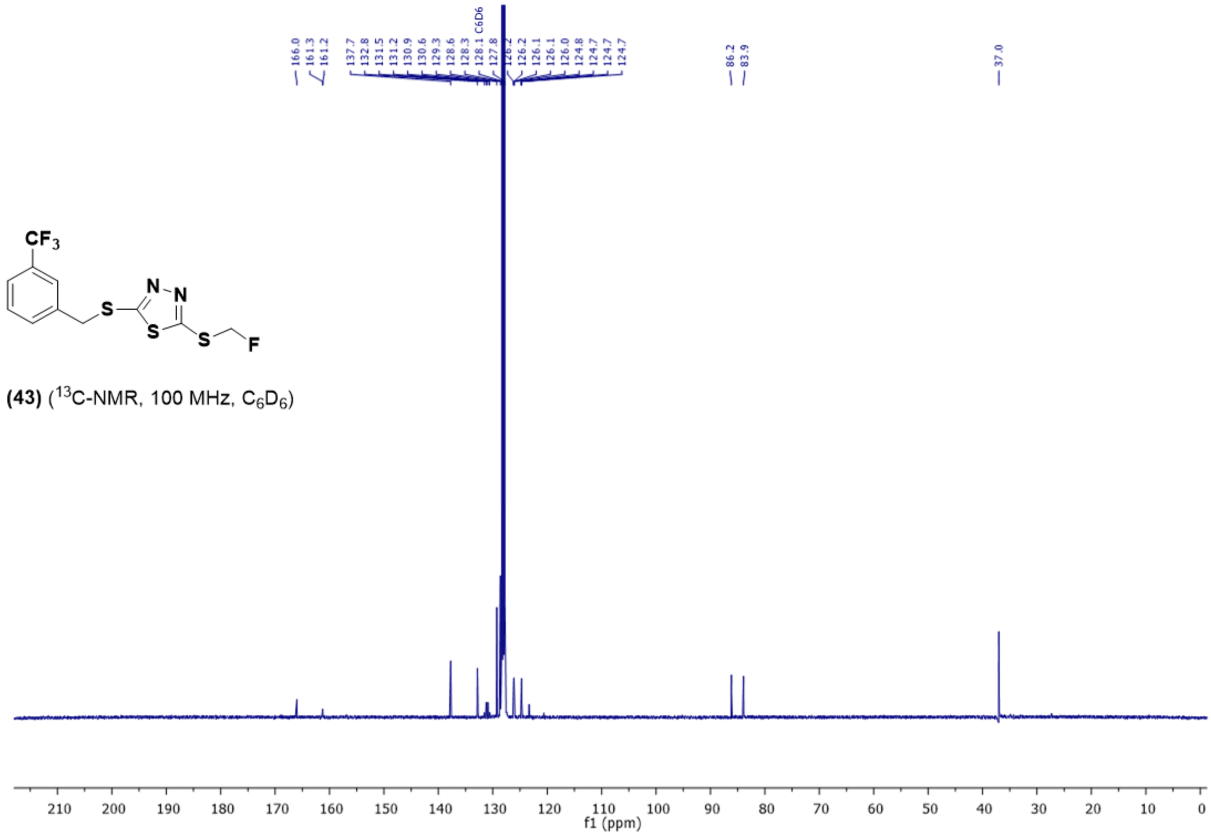


(42) (^{13}C-NMR, 100 MHz, C_6D_6)

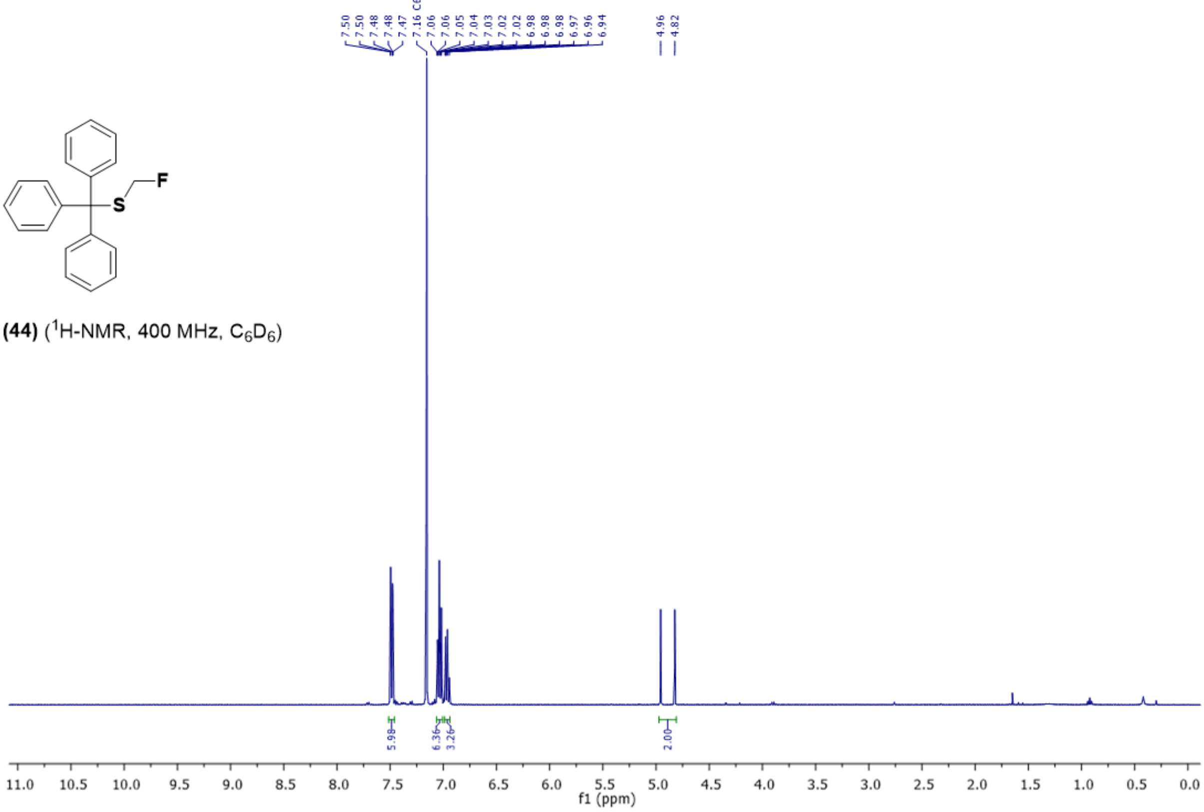




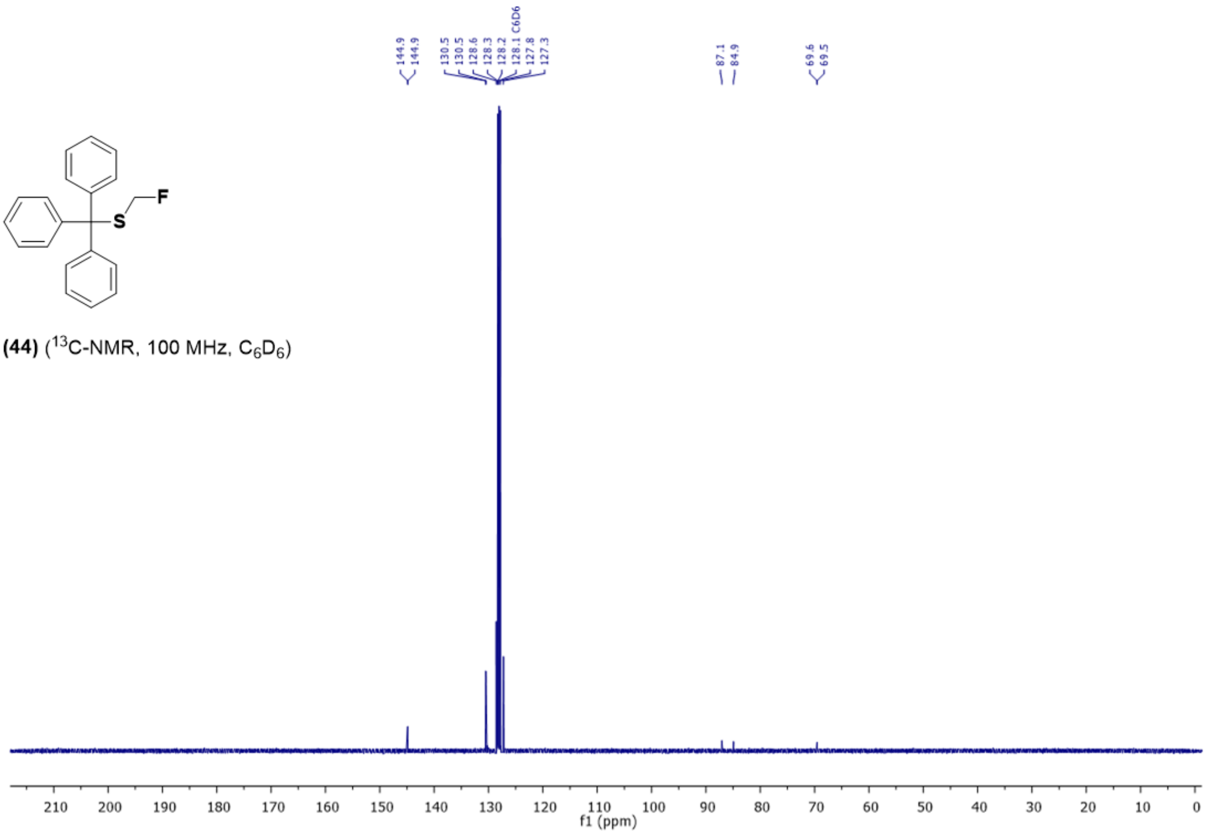
(43) (^{1}H-NMR, 400 MHz, C_6D_6)



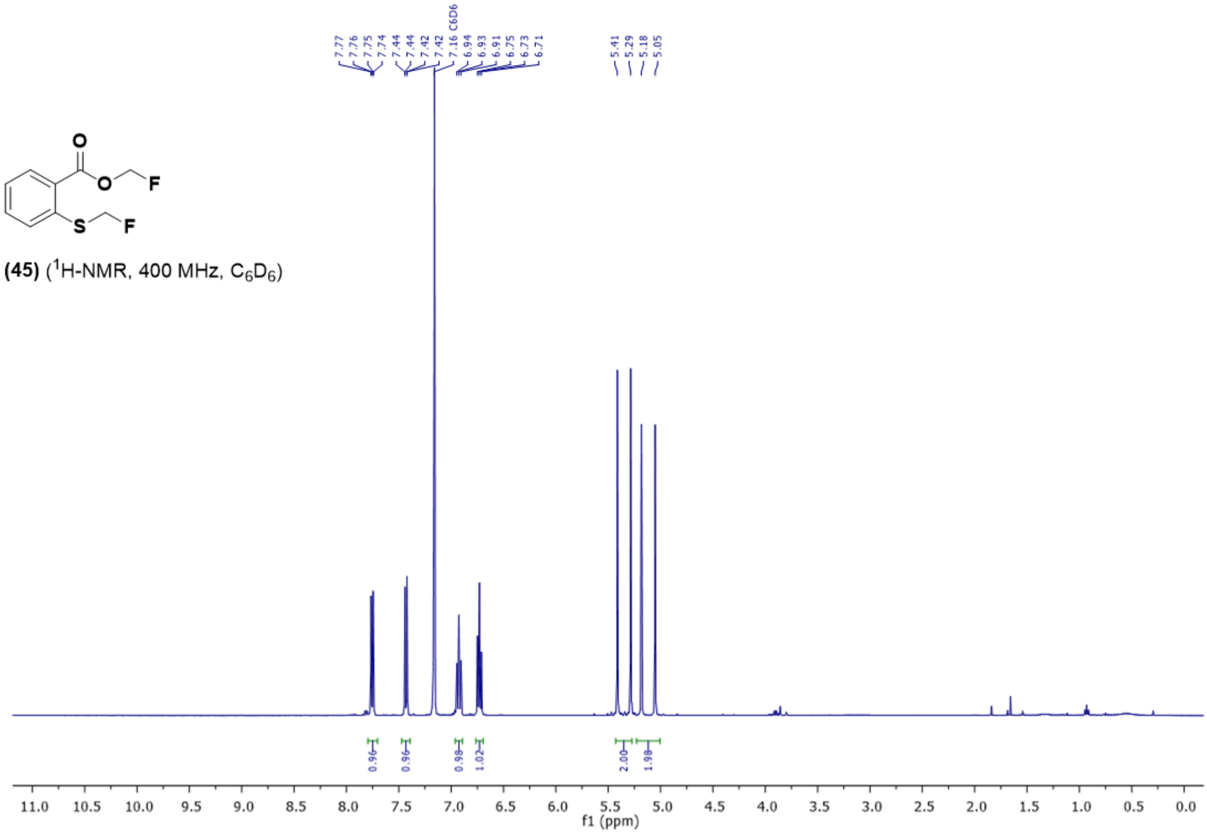
(43) (^{13}C-NMR, 100 MHz, C_6D_6)



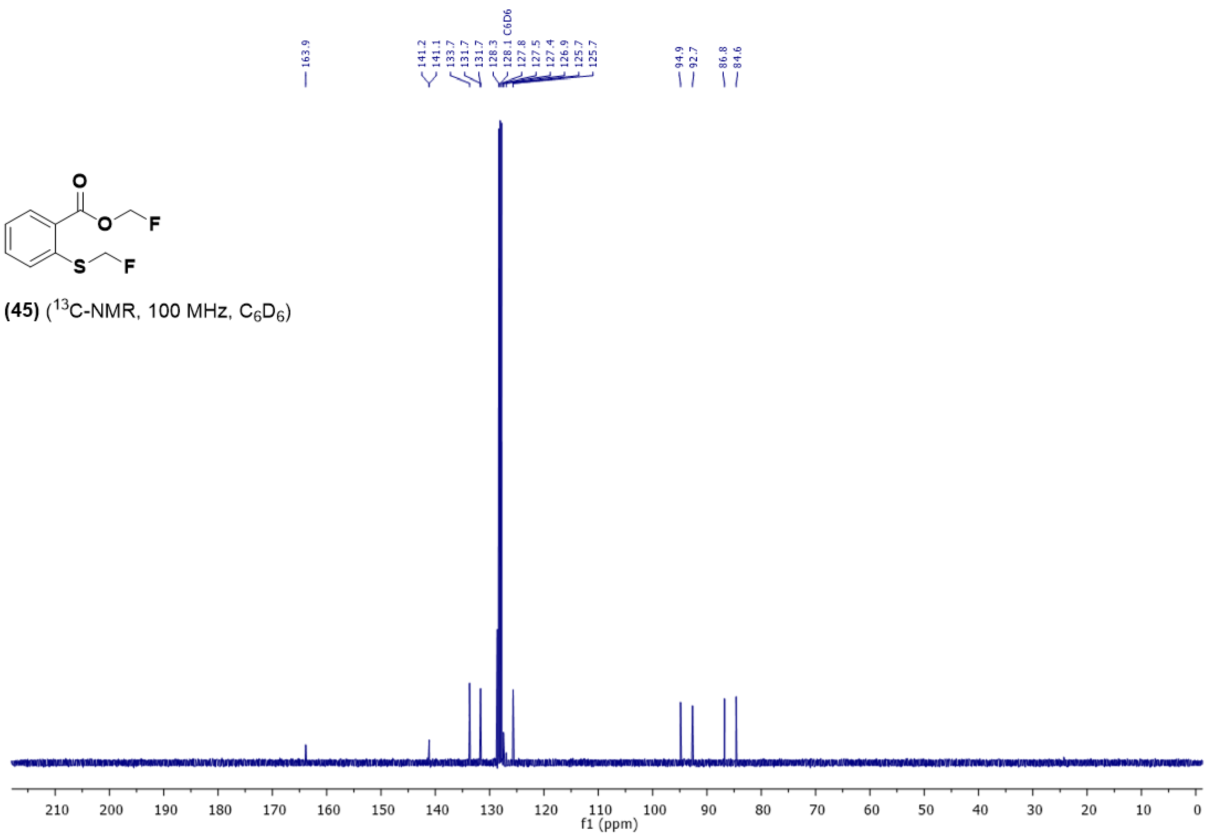
(44) (^{1}H-NMR, 400 MHz, C_6D_6)



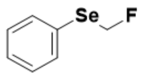
(44) (^{13}C-NMR, 100 MHz, C_6D_6)



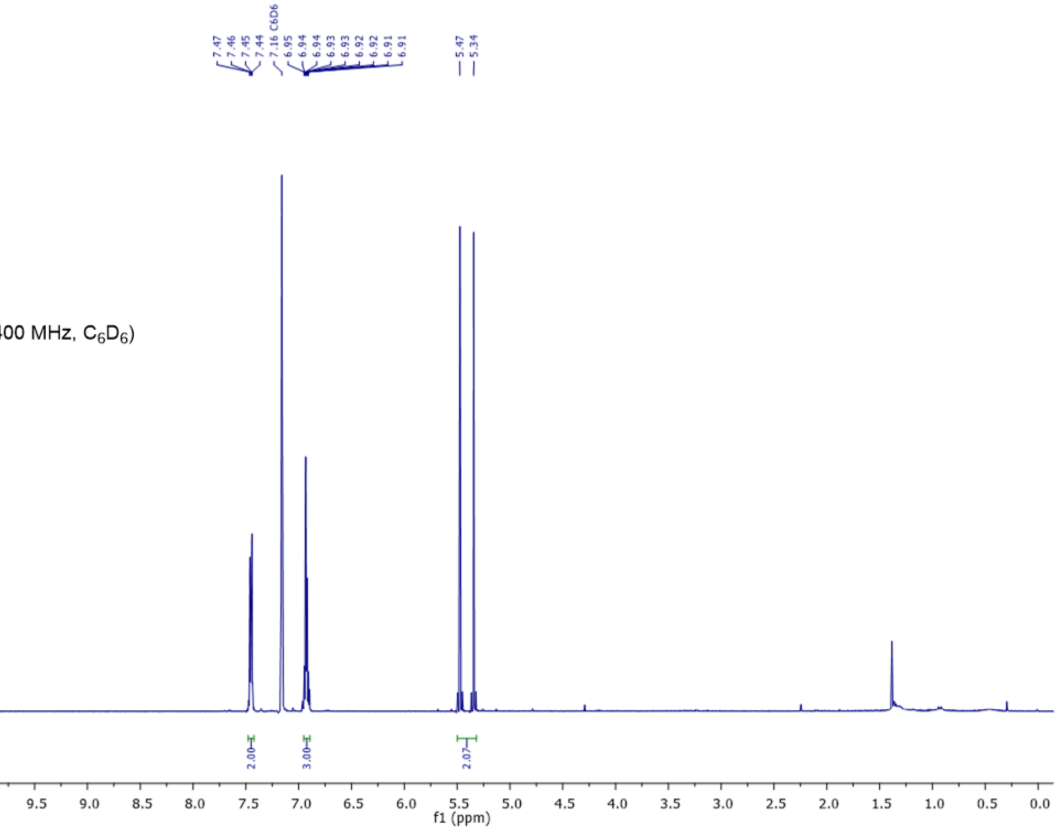
(45) (^{1}H-NMR, 400 MHz, C_6D_6)

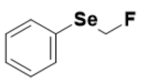


(45) (^{13}C-NMR, 100 MHz, C_6D_6)

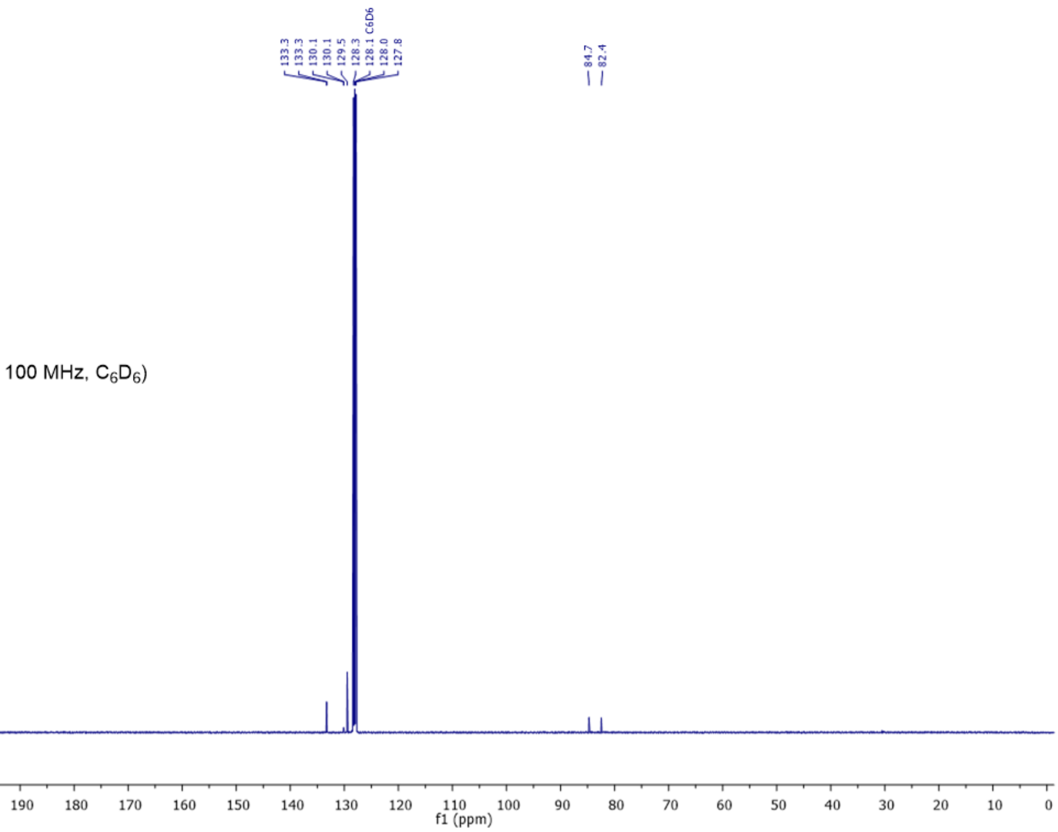


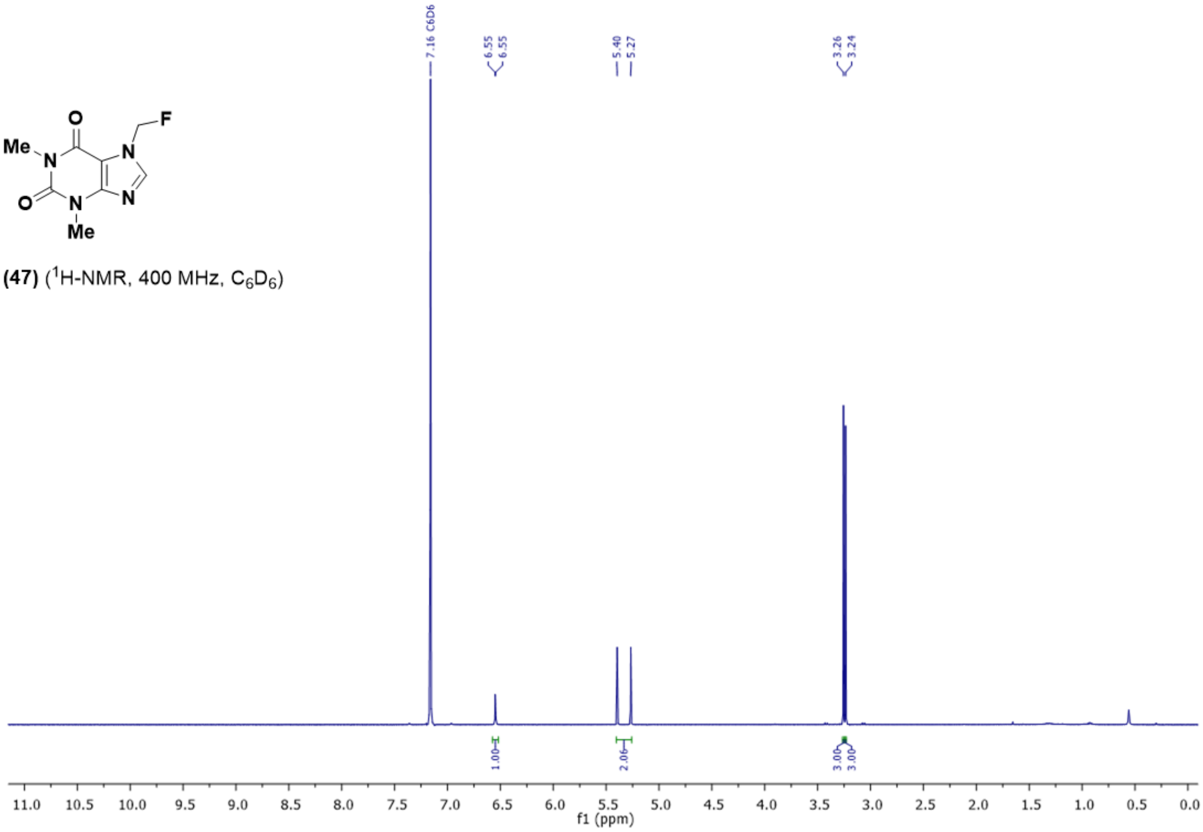
(46) (^{1}H-NMR, 400 MHz, C_6D_6)



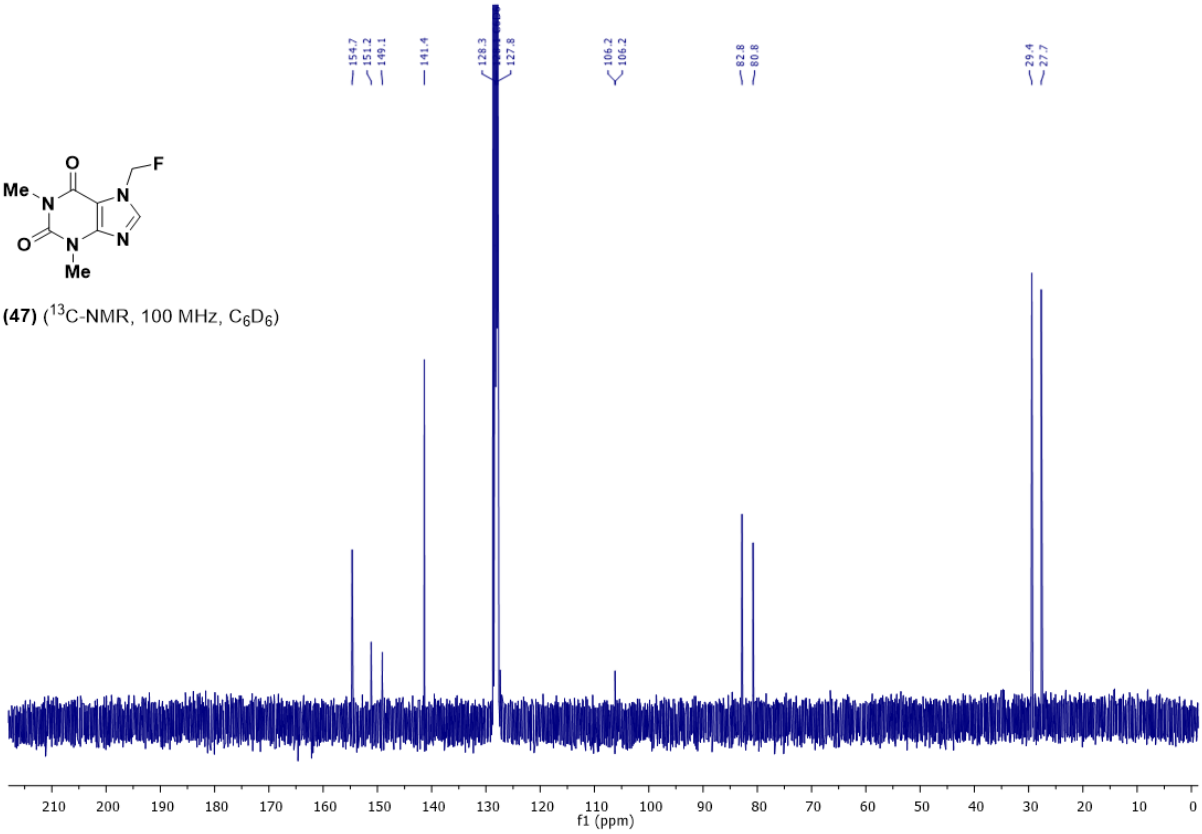


(46) (^{13}C-NMR, 100 MHz, C_6D_6)

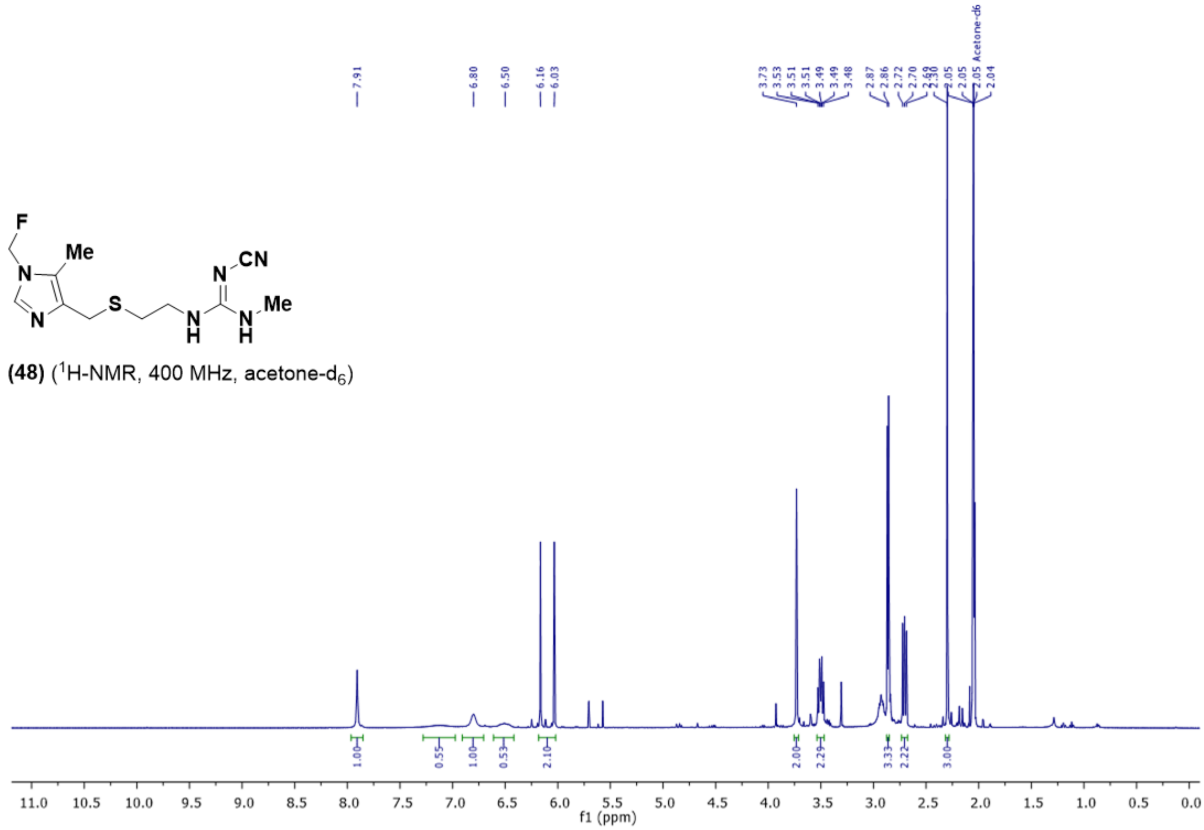




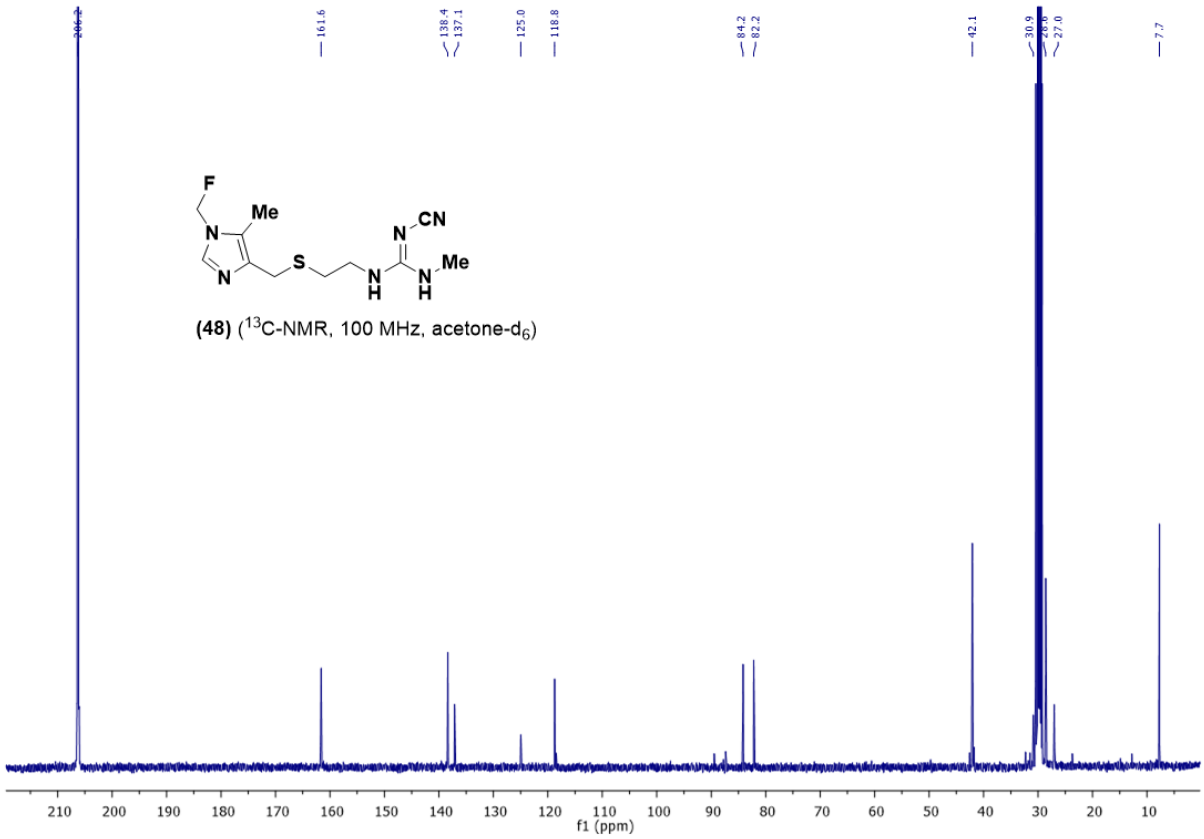
(47) (^{1}H-NMR, 400 MHz, C_6D_6)



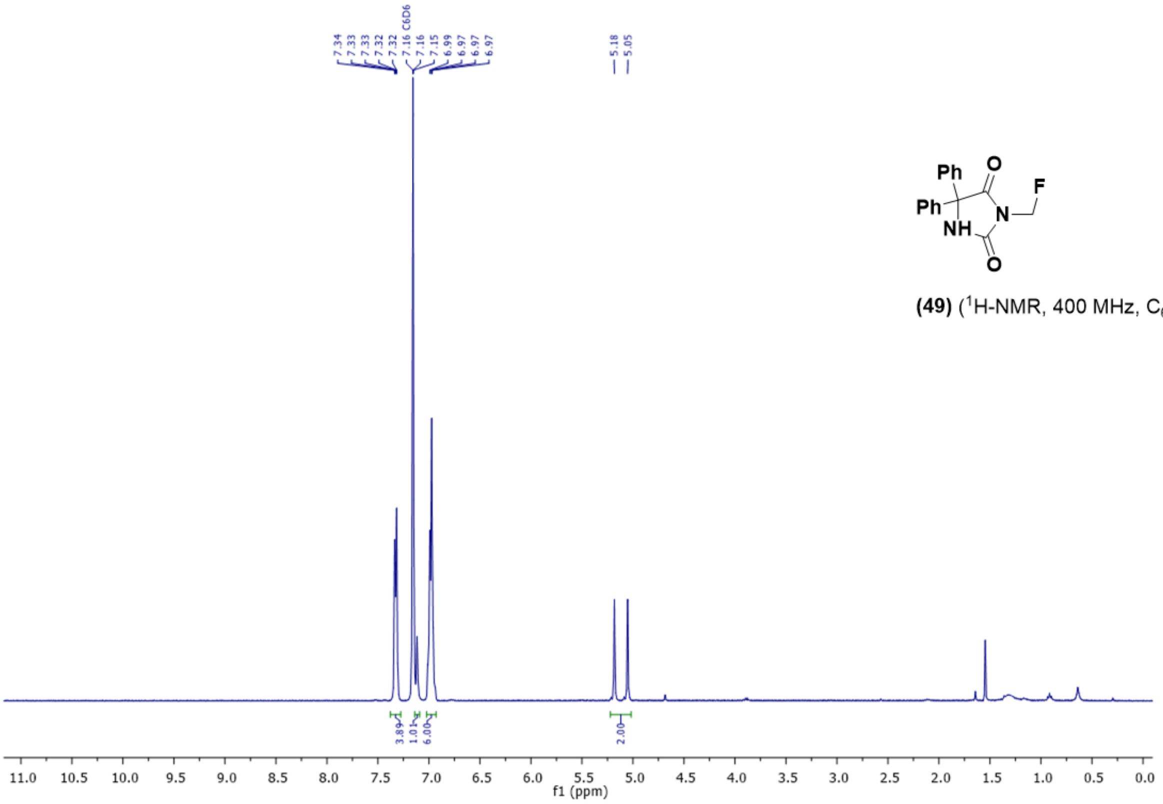
(47) (^{13}C-NMR, 100 MHz, C_6D_6)



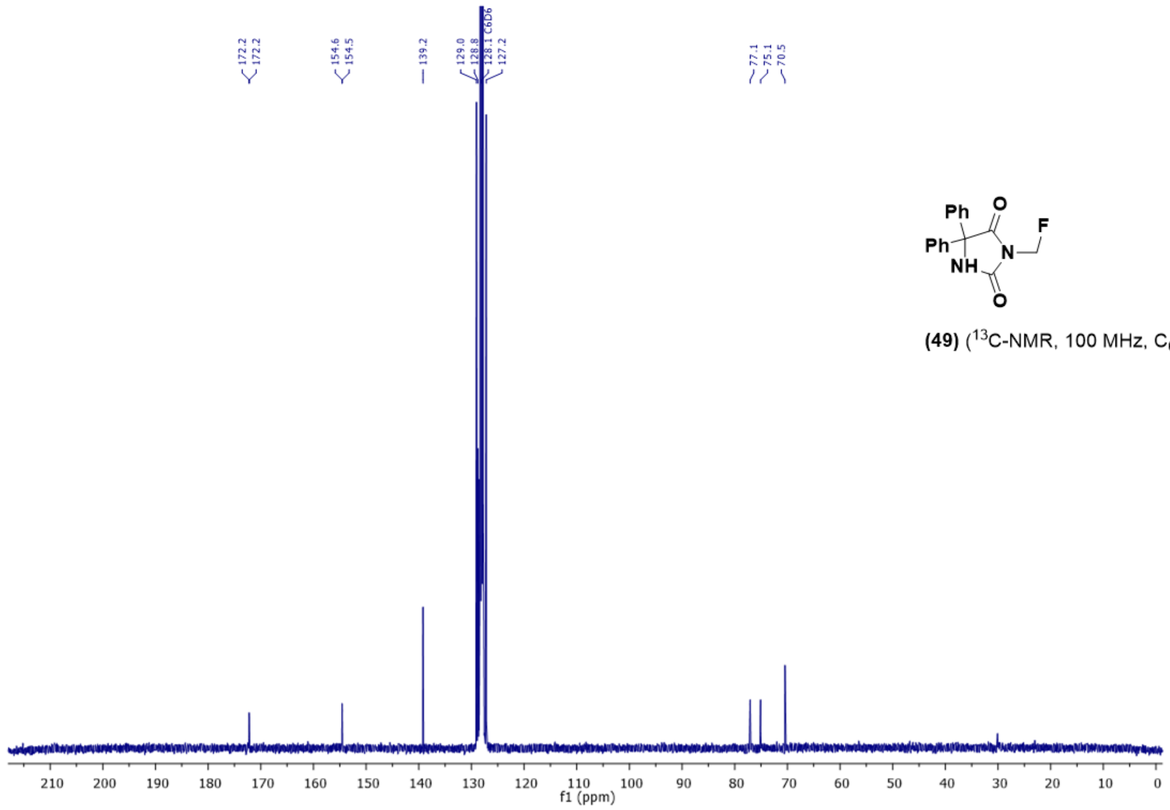
(48) (^{1}H-NMR, 400 MHz, acetone-d$_6$)



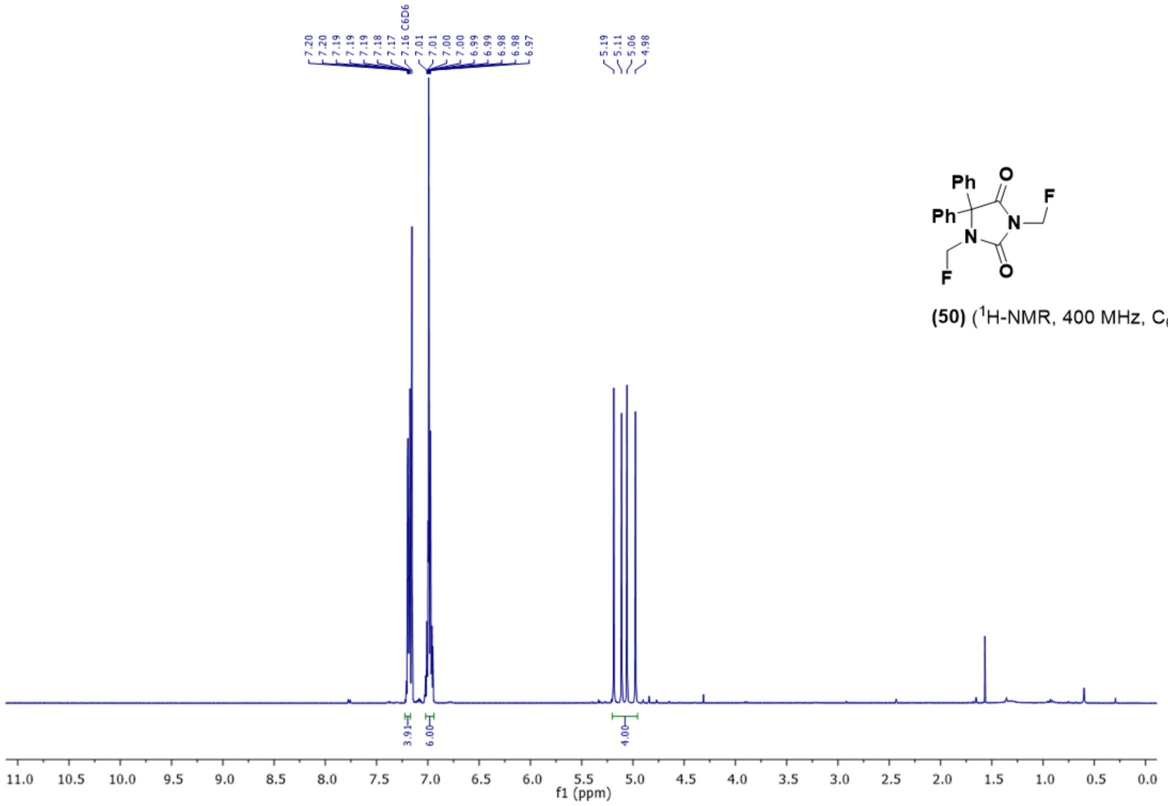
(48) (^{13}C-NMR, 100 MHz, acetone-d$_6$)



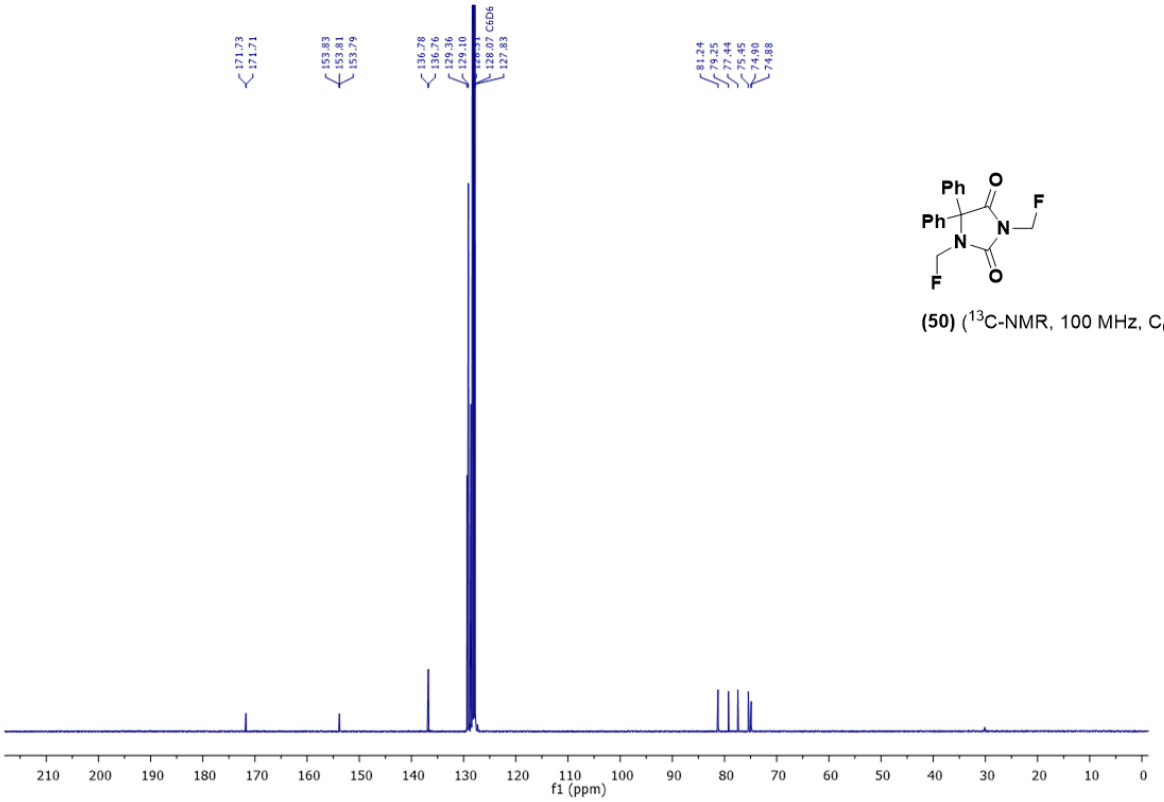
(49) (^{1}H-NMR, 400 MHz, C_6D_6)



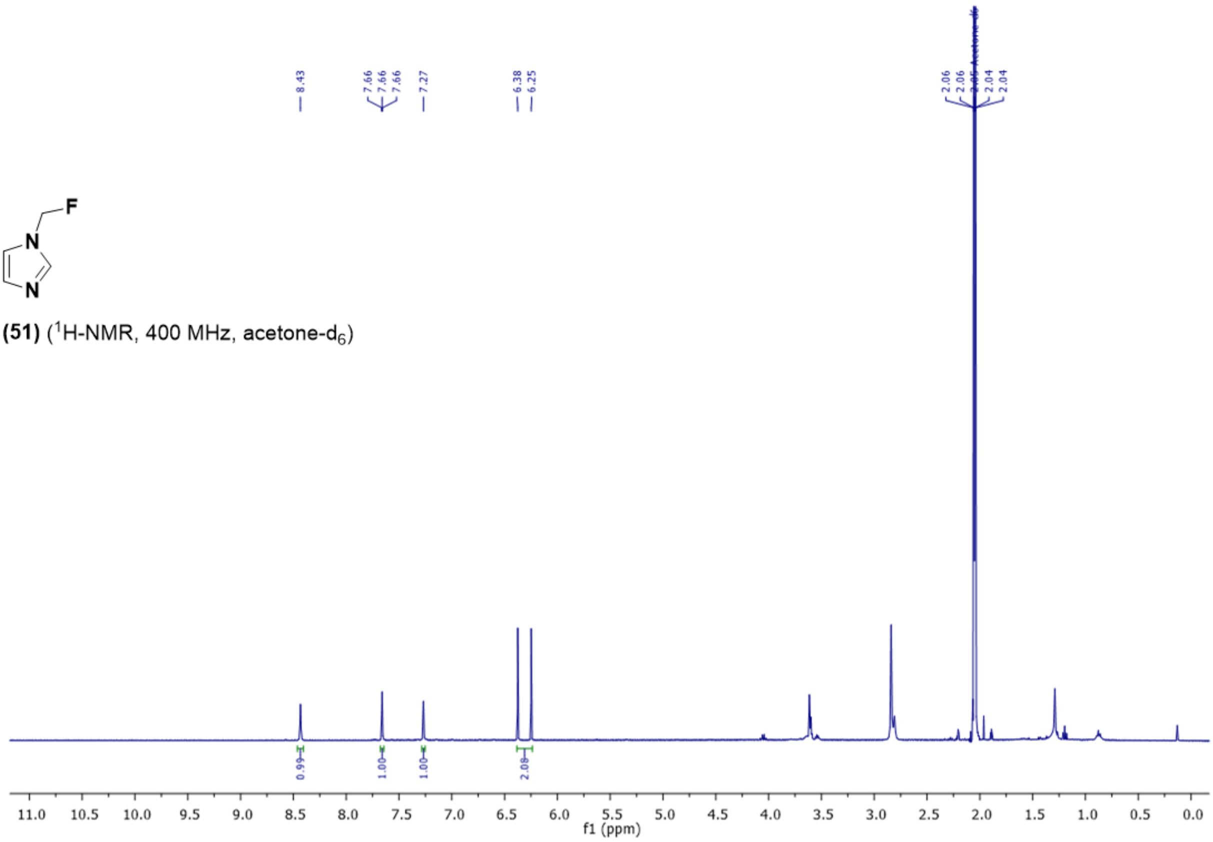
(49) (^{13}C-NMR, 100 MHz, C_6D_6)



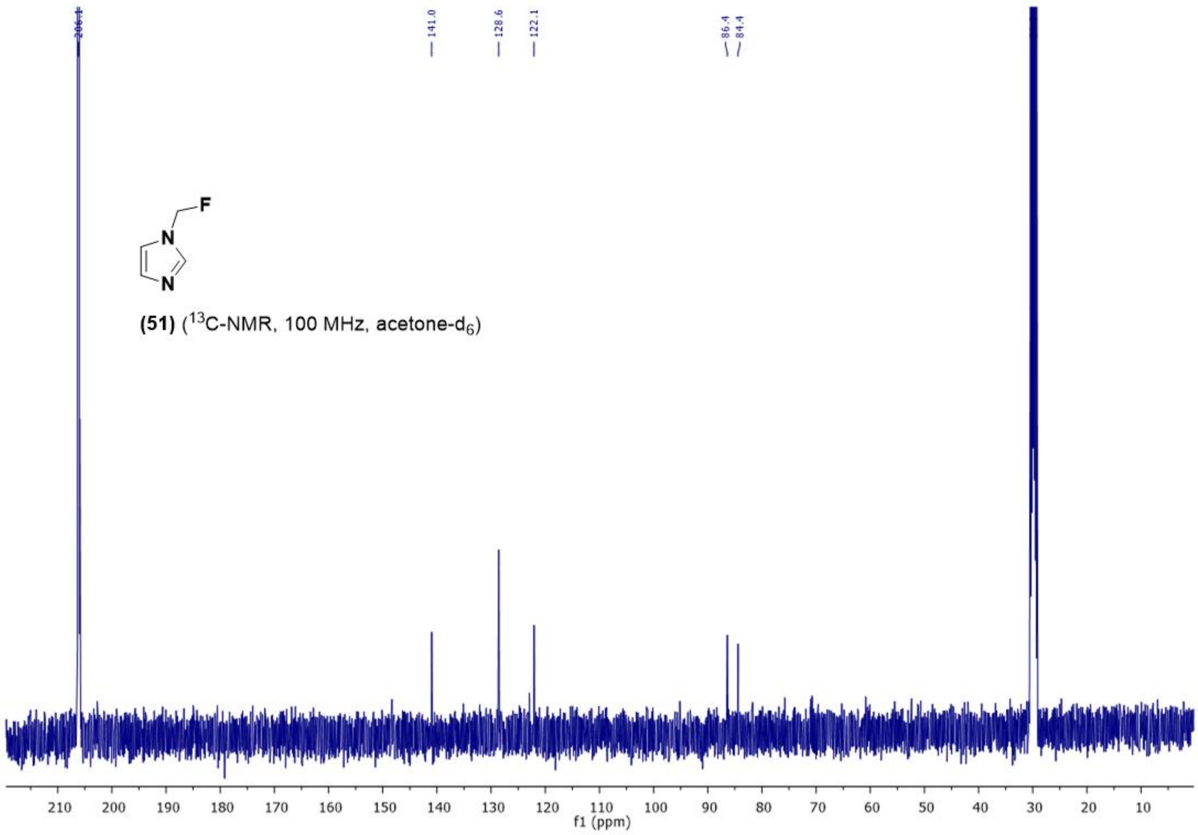
(50) (^{1}H-NMR, 400 MHz, C_6D_6)



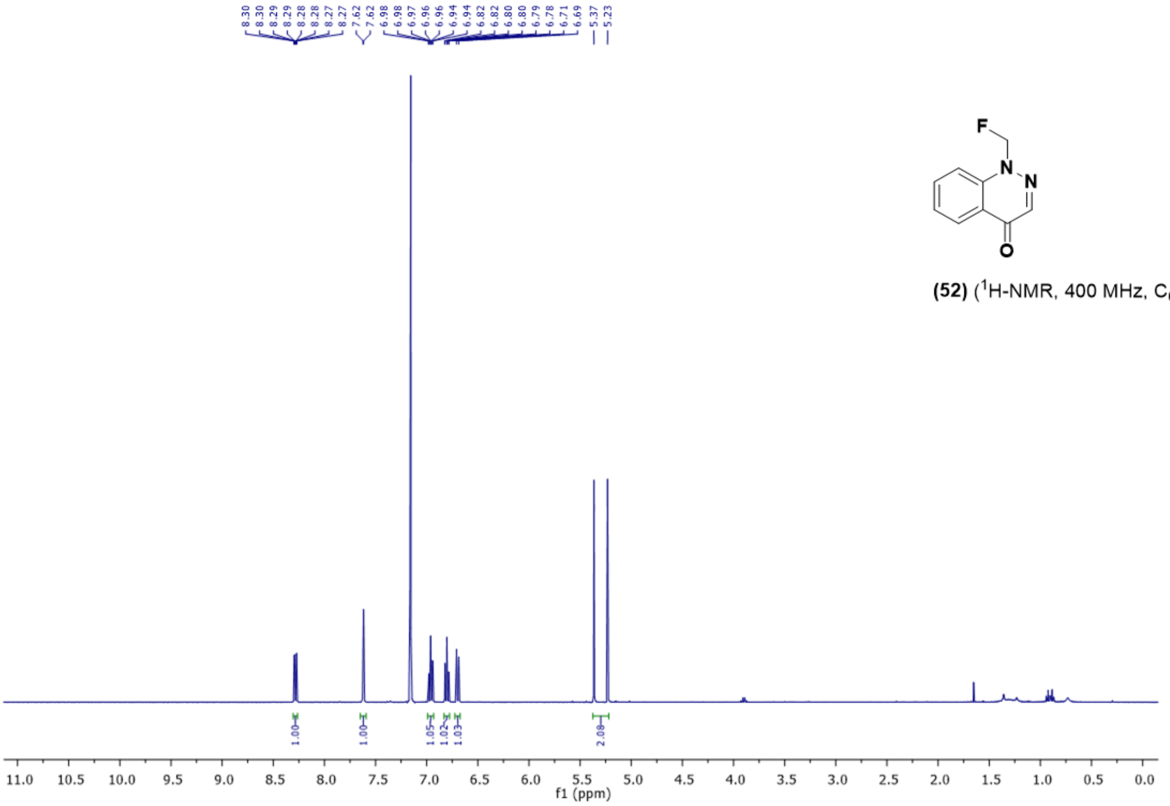
(50) (^{13}C-NMR, 100 MHz, C_6D_6)



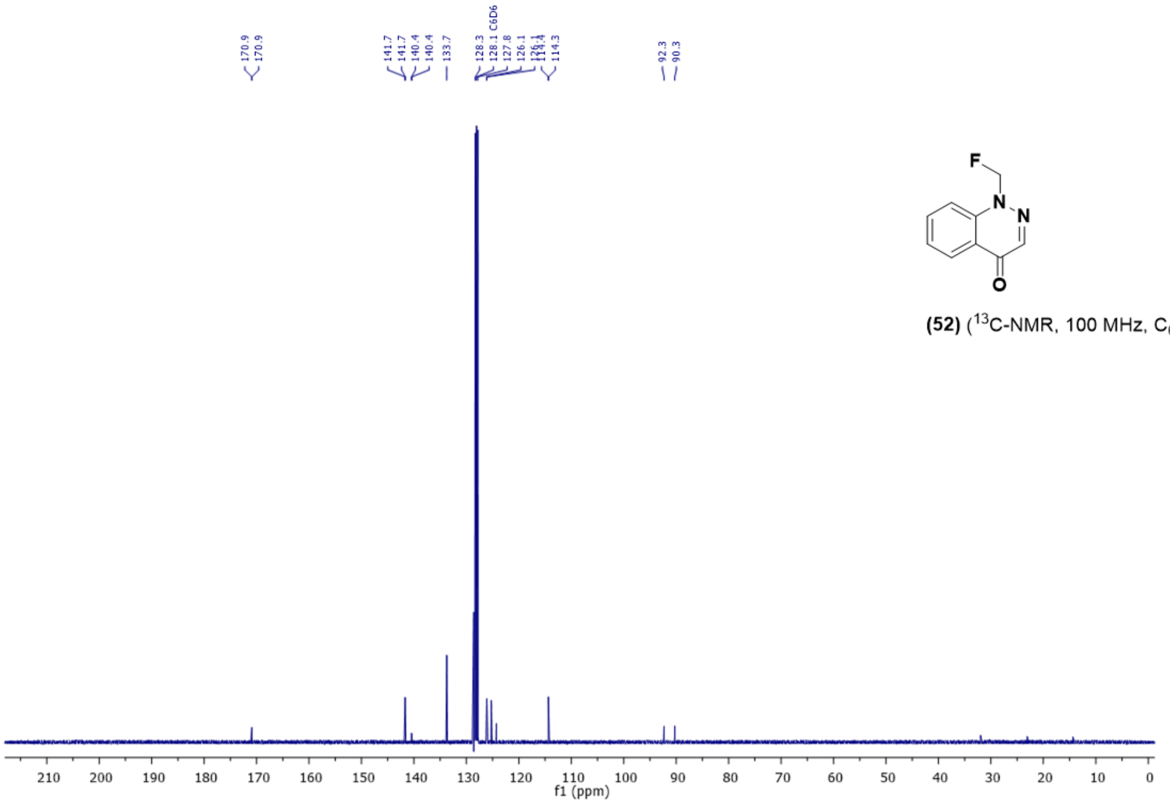
(51) (^{1}H-NMR, 400 MHz, acetone-d_6)



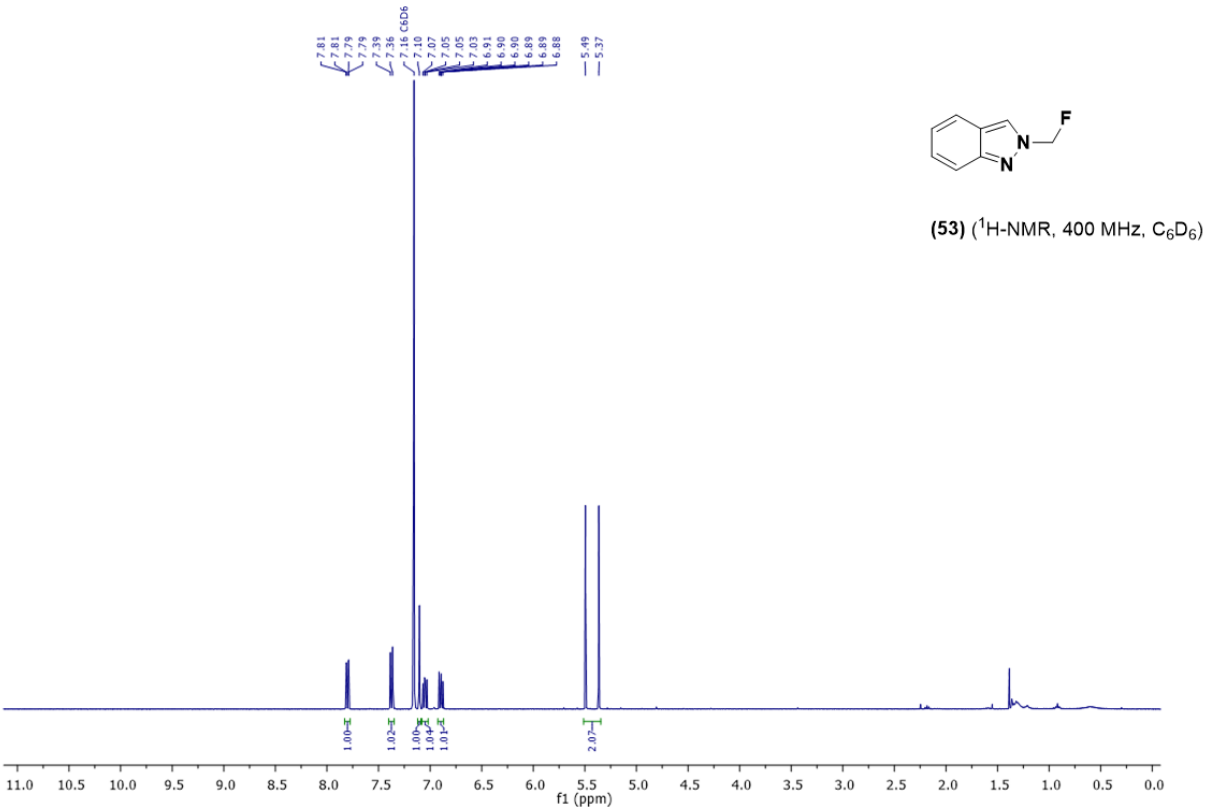
(51) (^{13}C-NMR, 100 MHz, acetone-d_6)



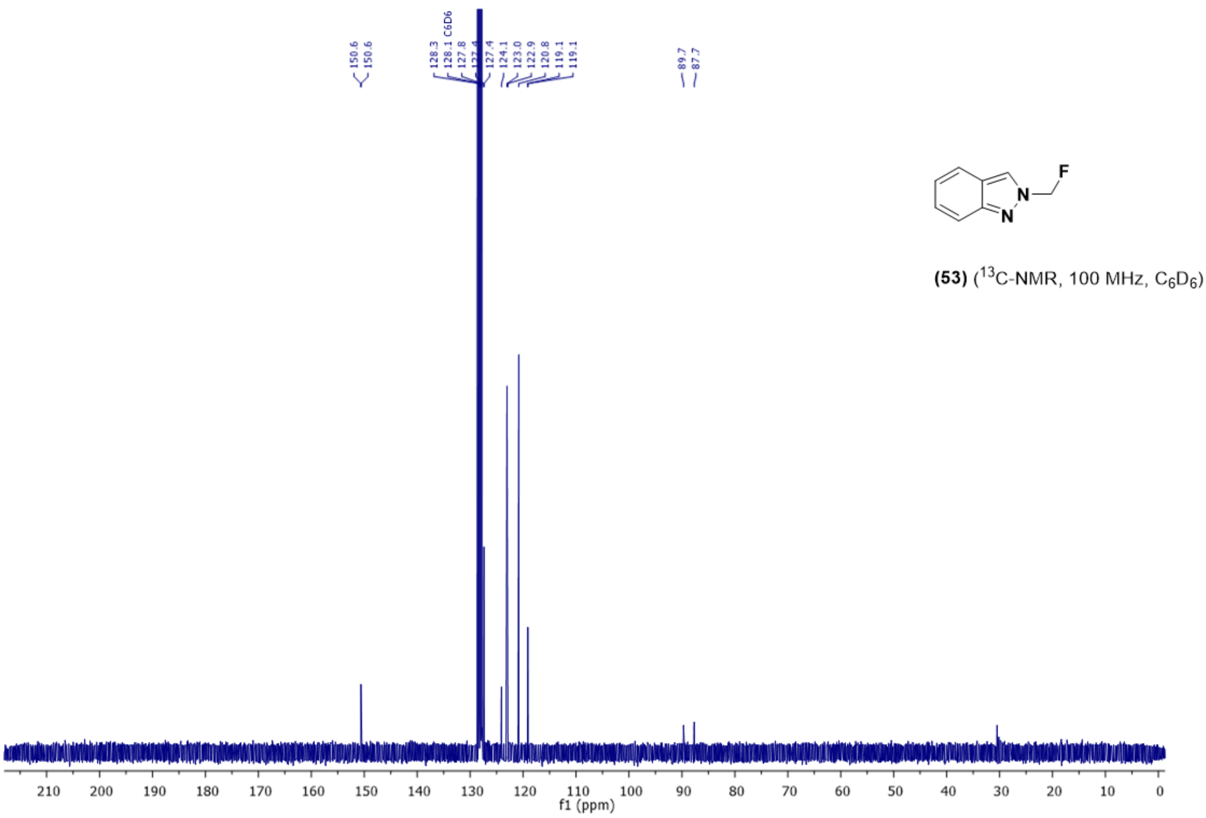
(52) (^{1}H-NMR, 400 MHz, C_6D_6)



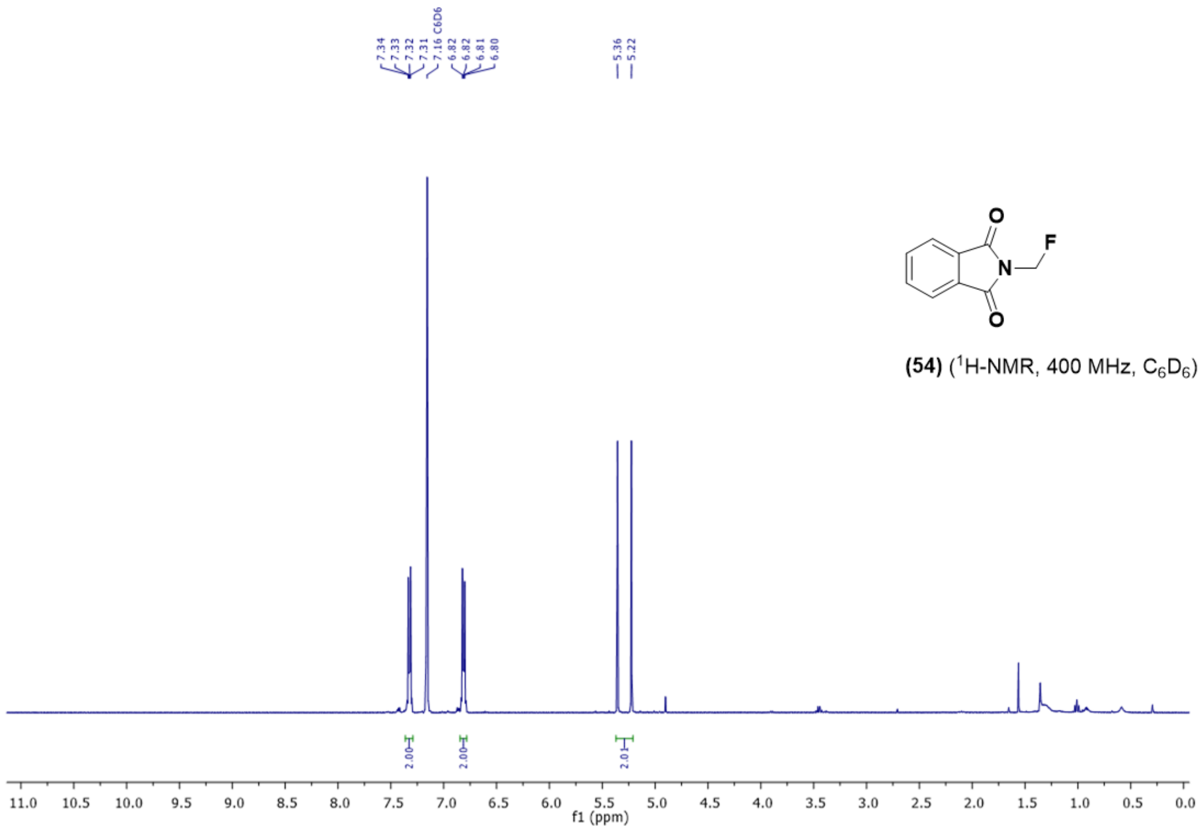
(52) (^{13}C-NMR, 100 MHz, C_6D_6)



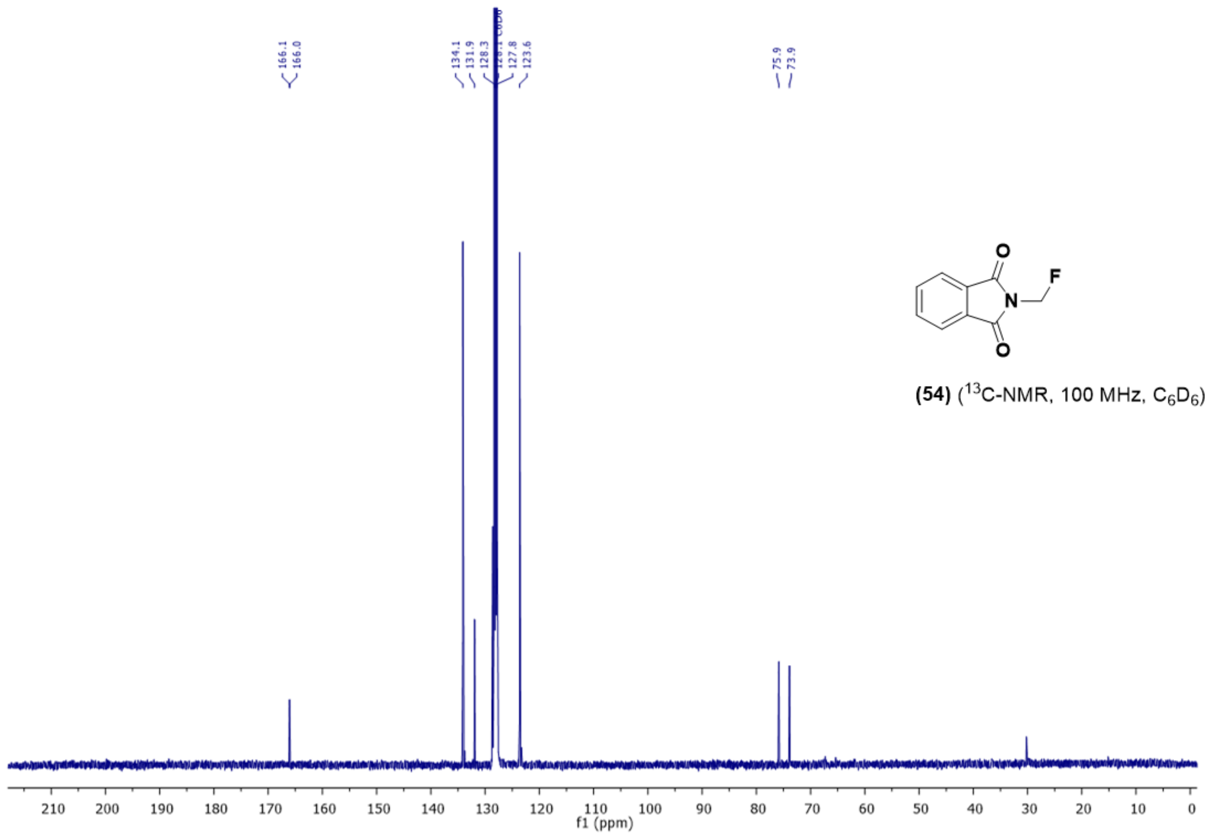
(53) (^{1}H-NMR, 400 MHz, C_6D_6)



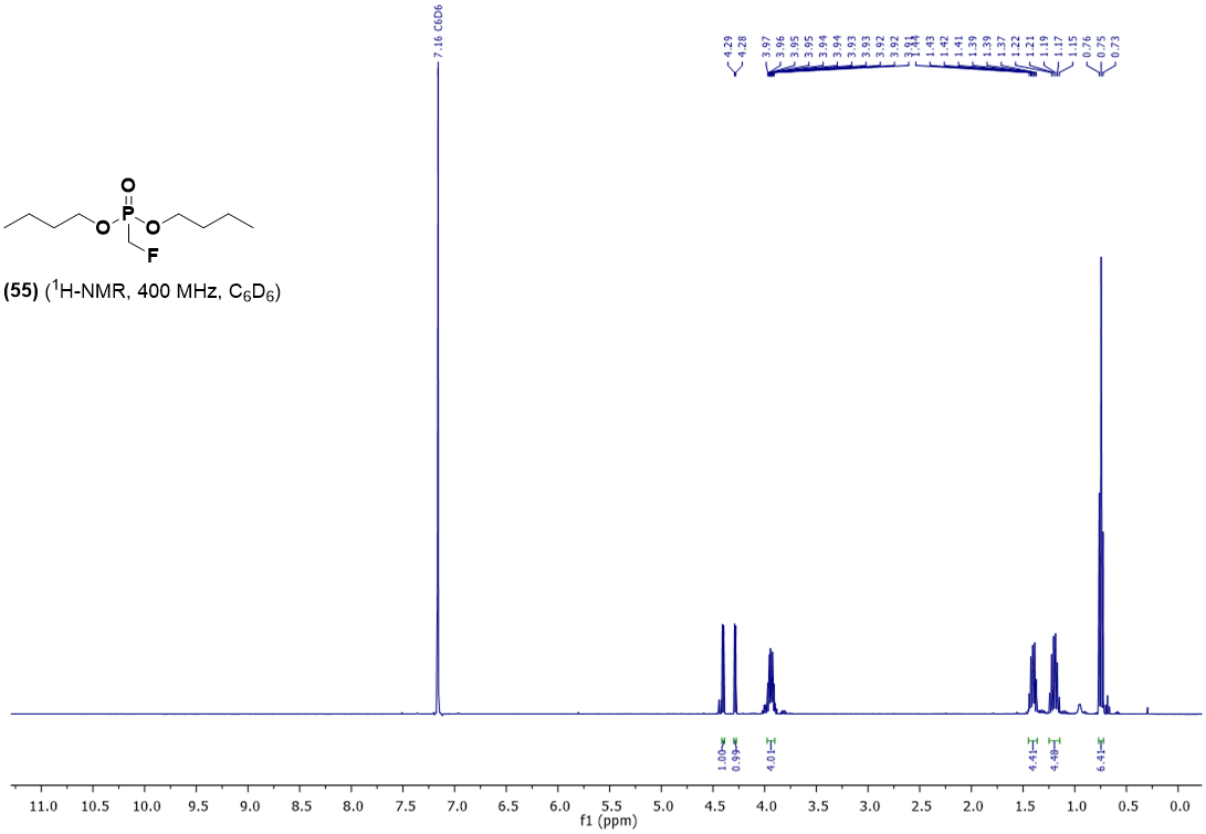
(53) (^{13}C-NMR, 100 MHz, C_6D_6)



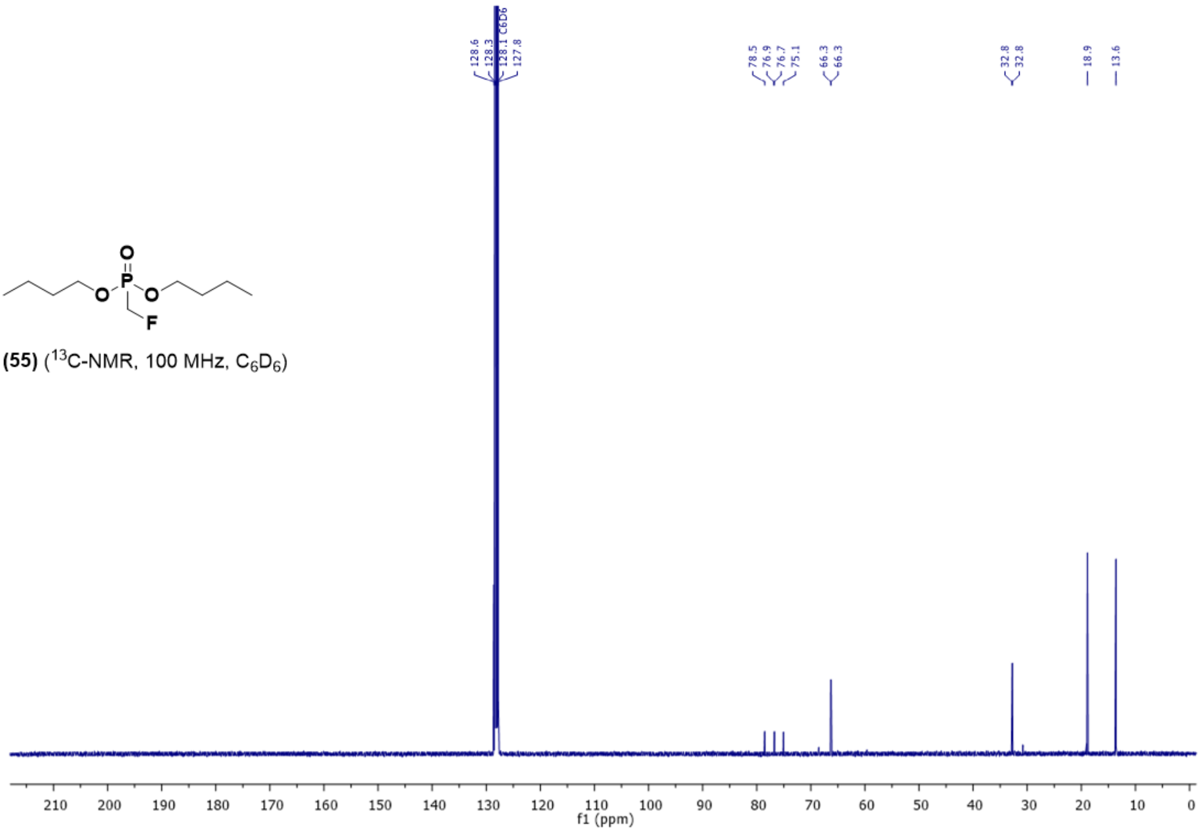
(54) (^{1}H-NMR, 400 MHz, C_6D_6)



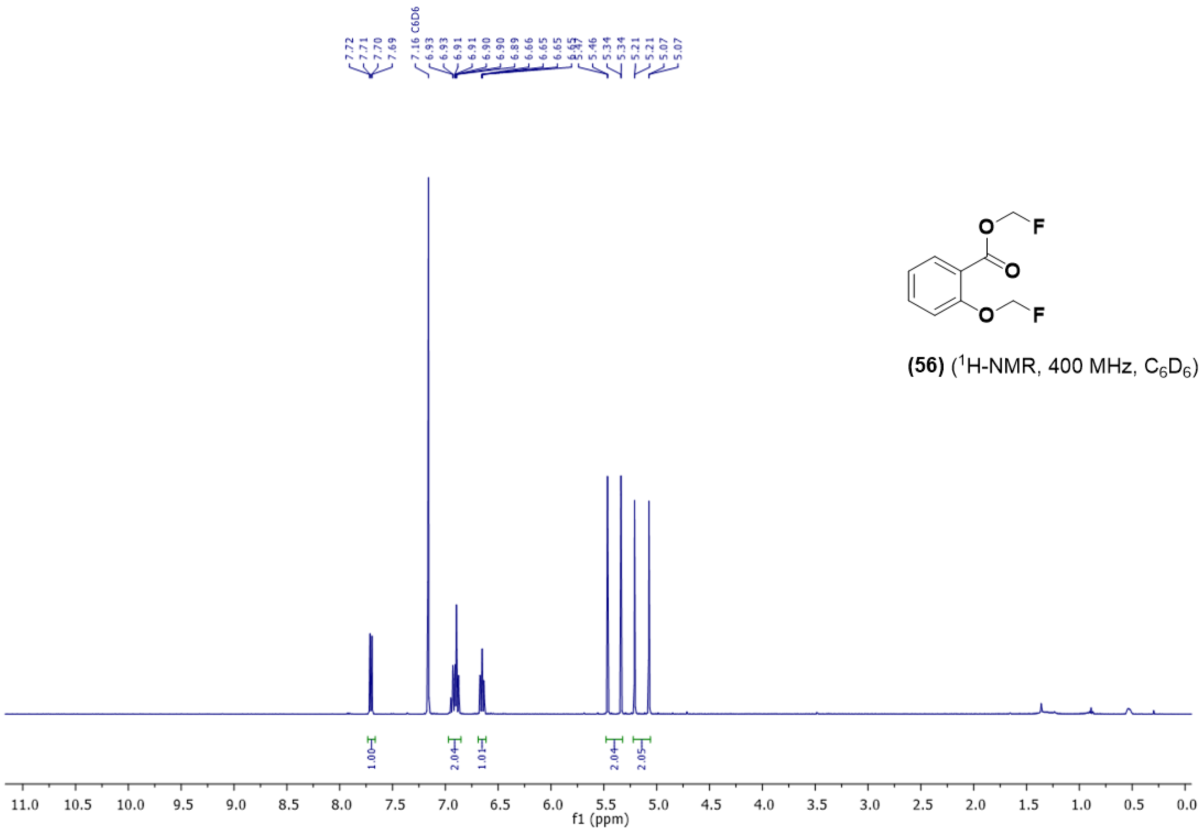
(54) (^{13}C-NMR, 100 MHz, C_6D_6)



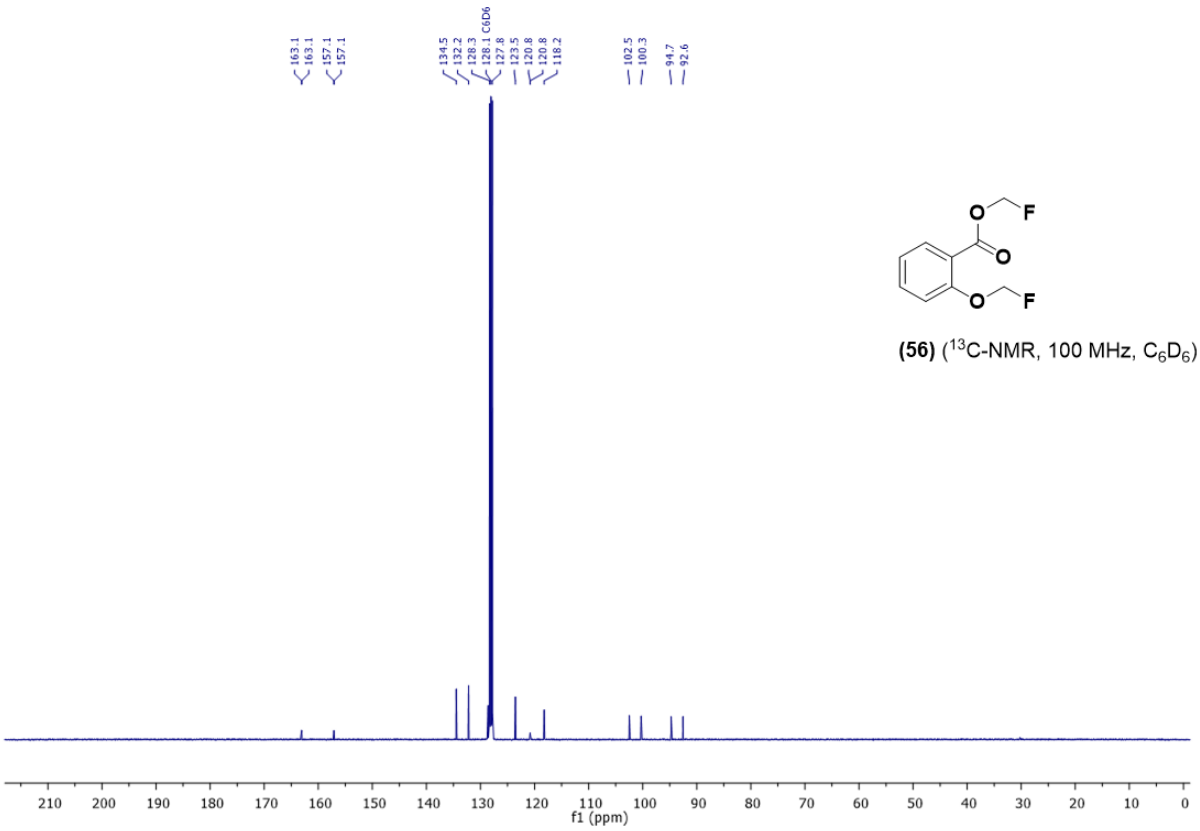
(55) (^{1}H-NMR, 400 MHz, C_6D_6)



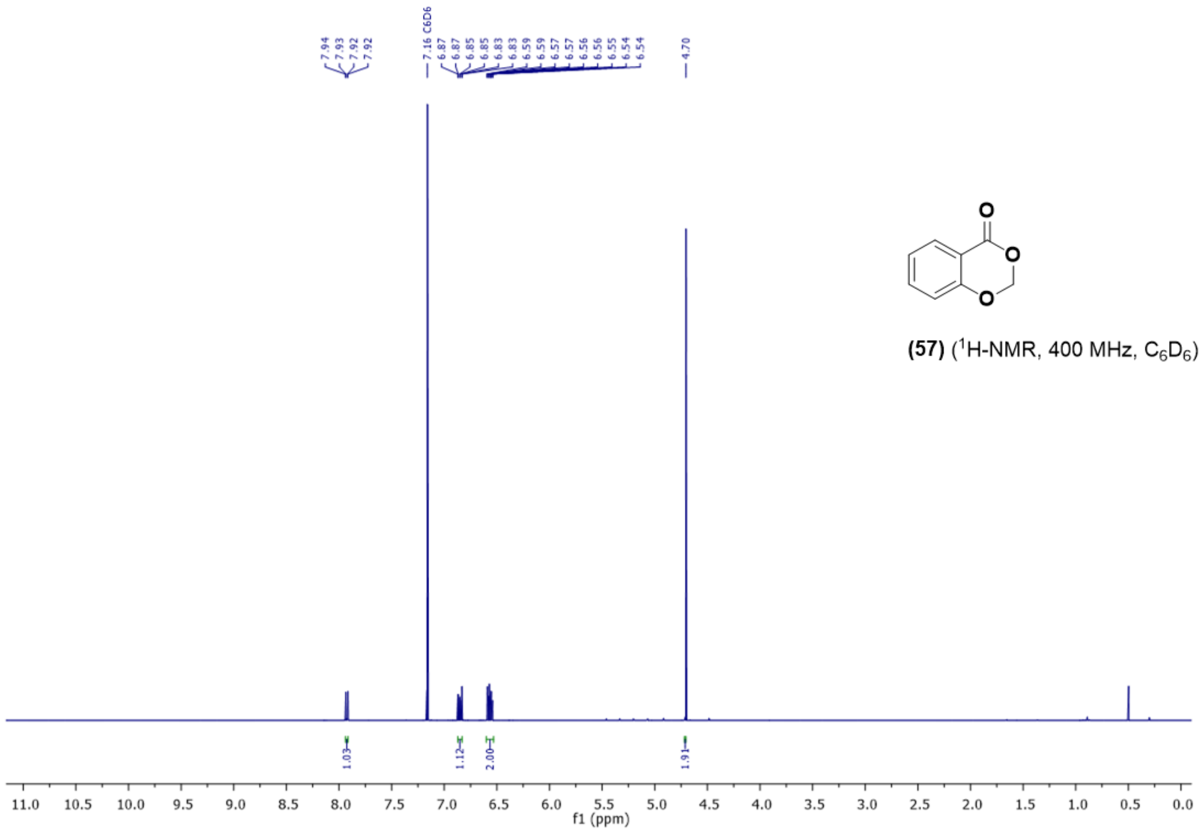
(55) (^{13}C-NMR, 100 MHz, C_6D_6)



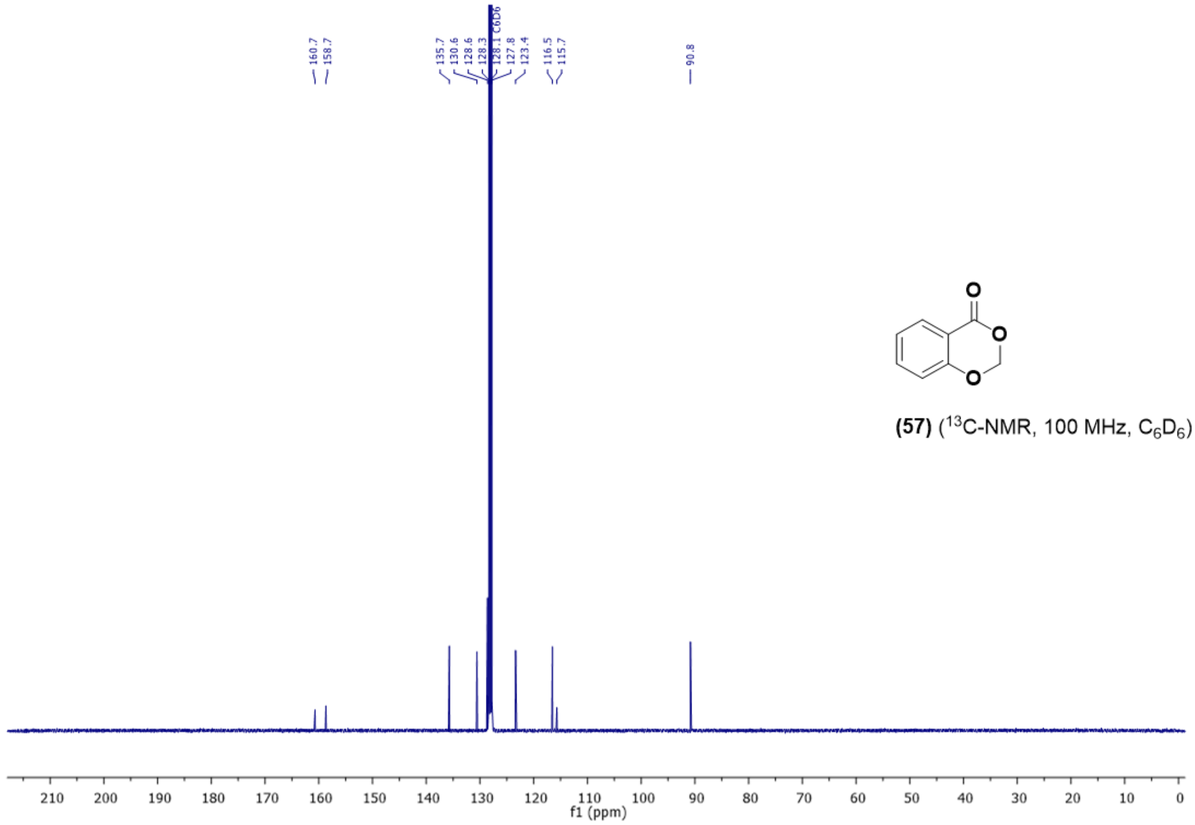
(56) (^{1}H-NMR, 400 MHz, C_6D_6)



(56) (^{13}C-NMR, 100 MHz, C_6D_6)

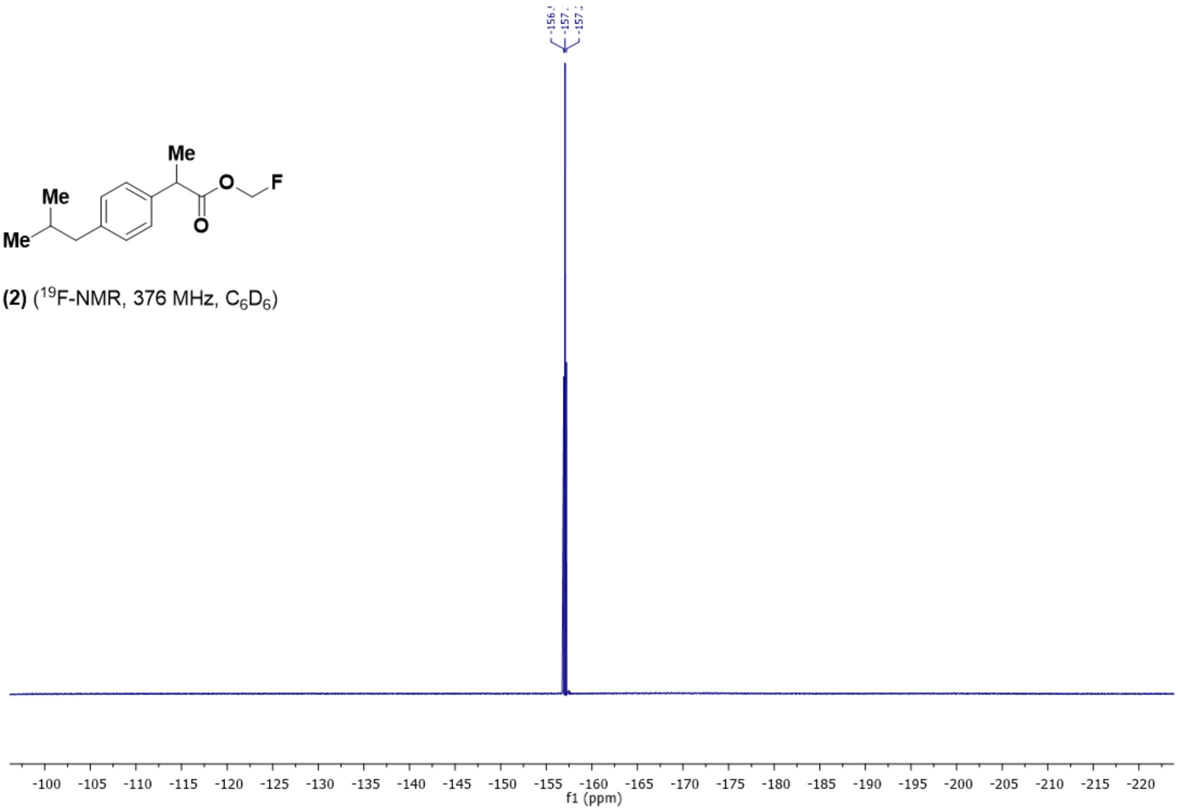


(57) (^{1}H-NMR, 400 MHz, C_6D_6)

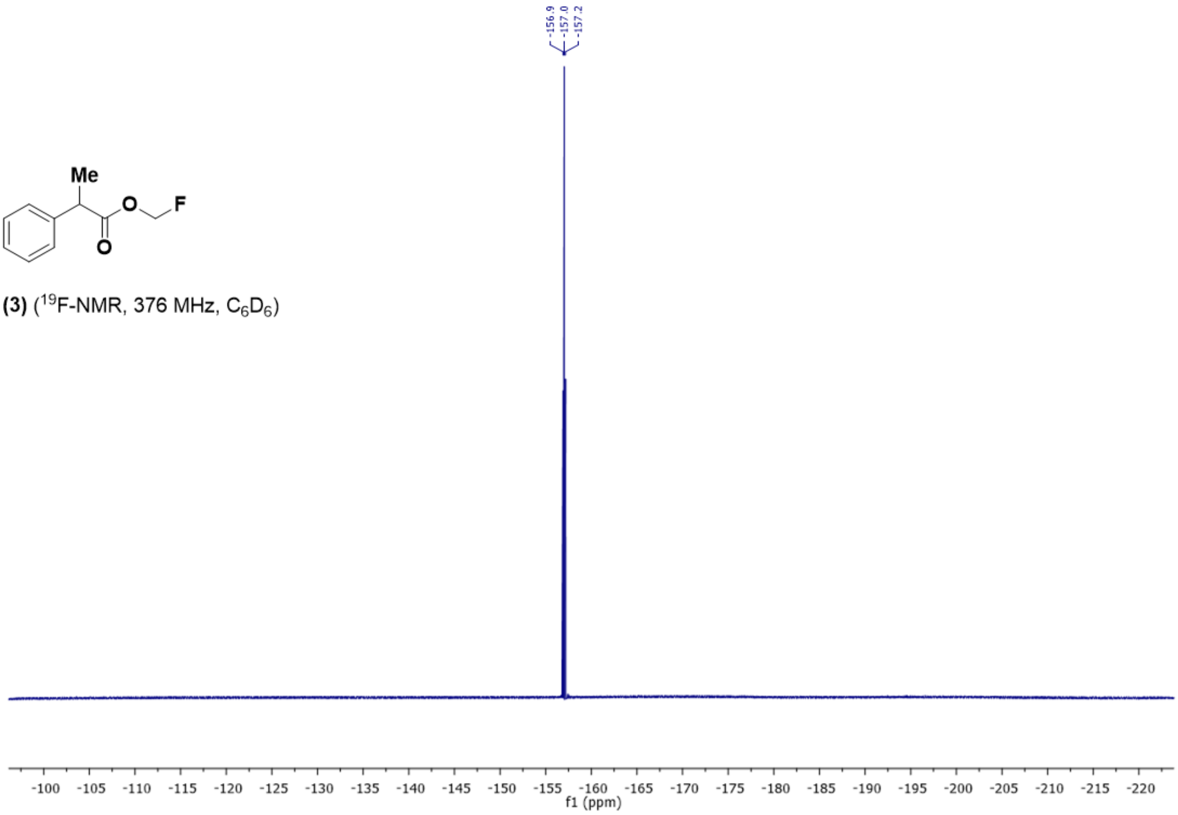


(57) (^{13}C-NMR, 100 MHz, C_6D_6)

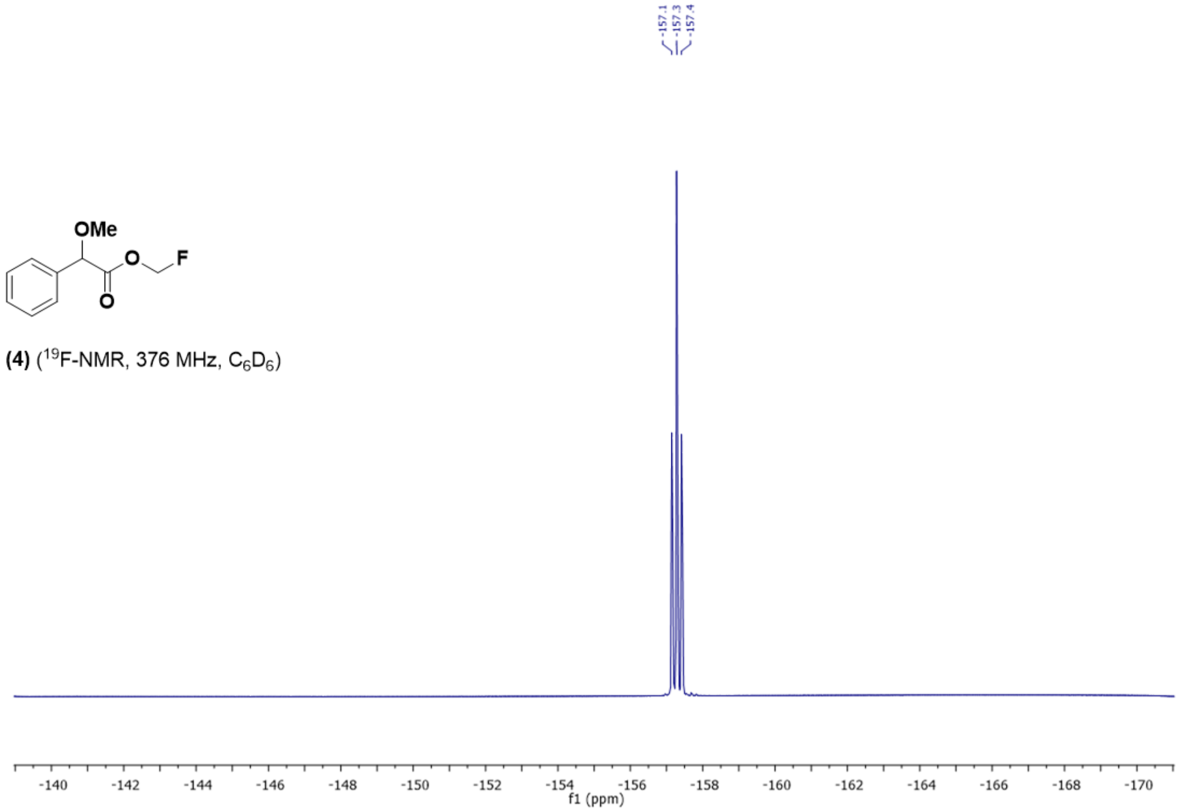
Copies of ^{19}F-NMR Spectra



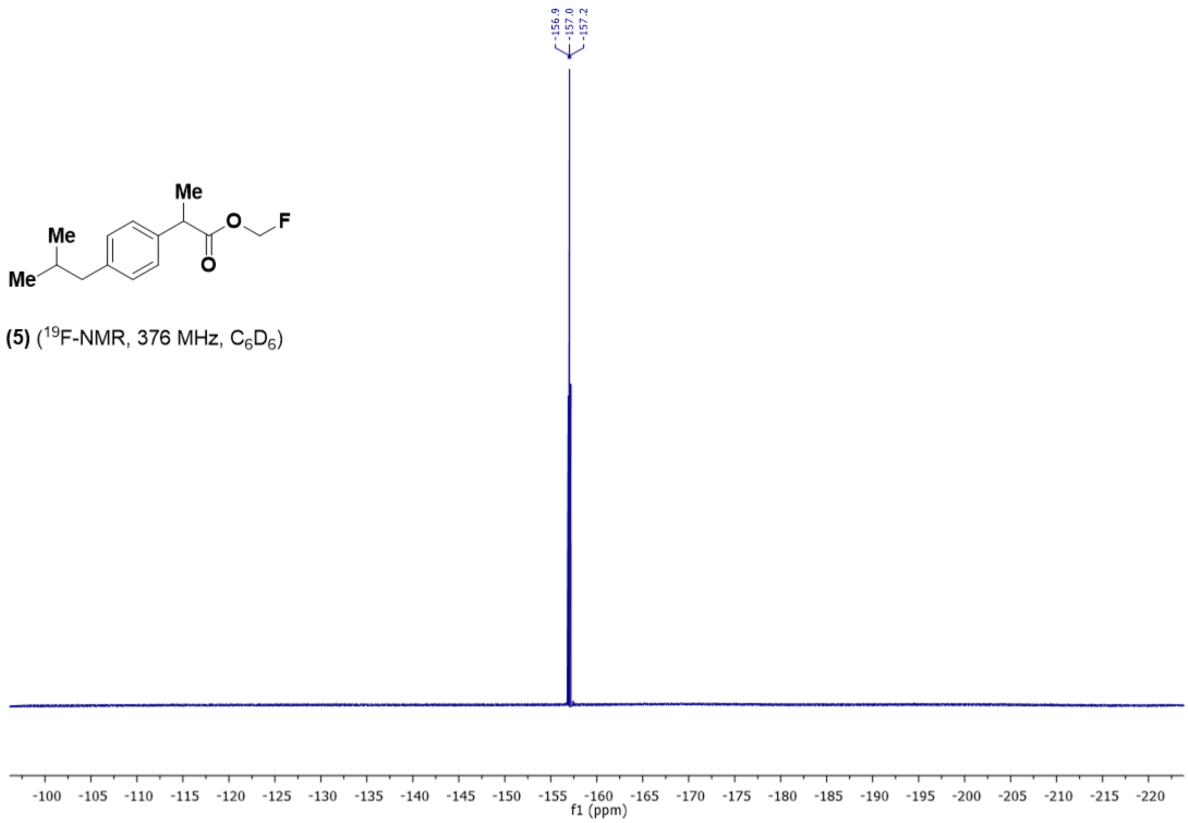
(2) (^{19}F-NMR, 376 MHz, C_6D_6)



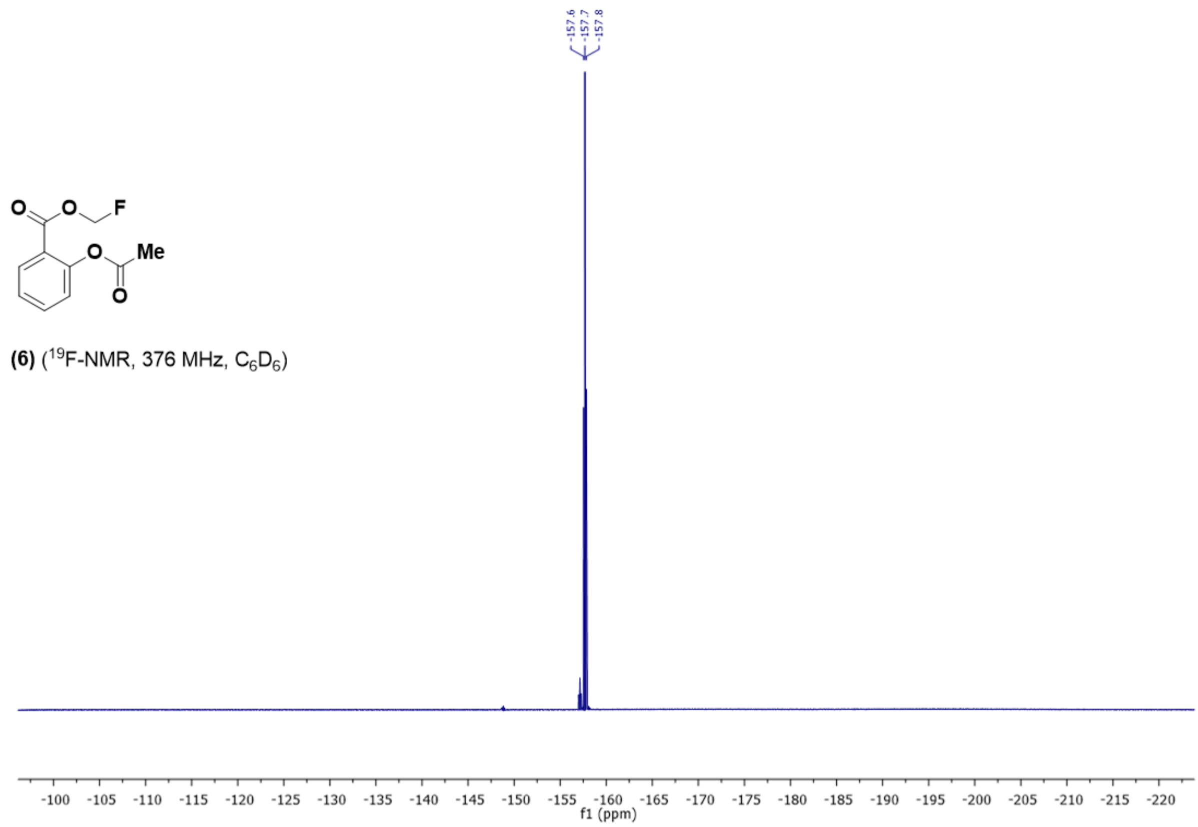
(3) (^{19}F-NMR, 376 MHz, C_6D_6)



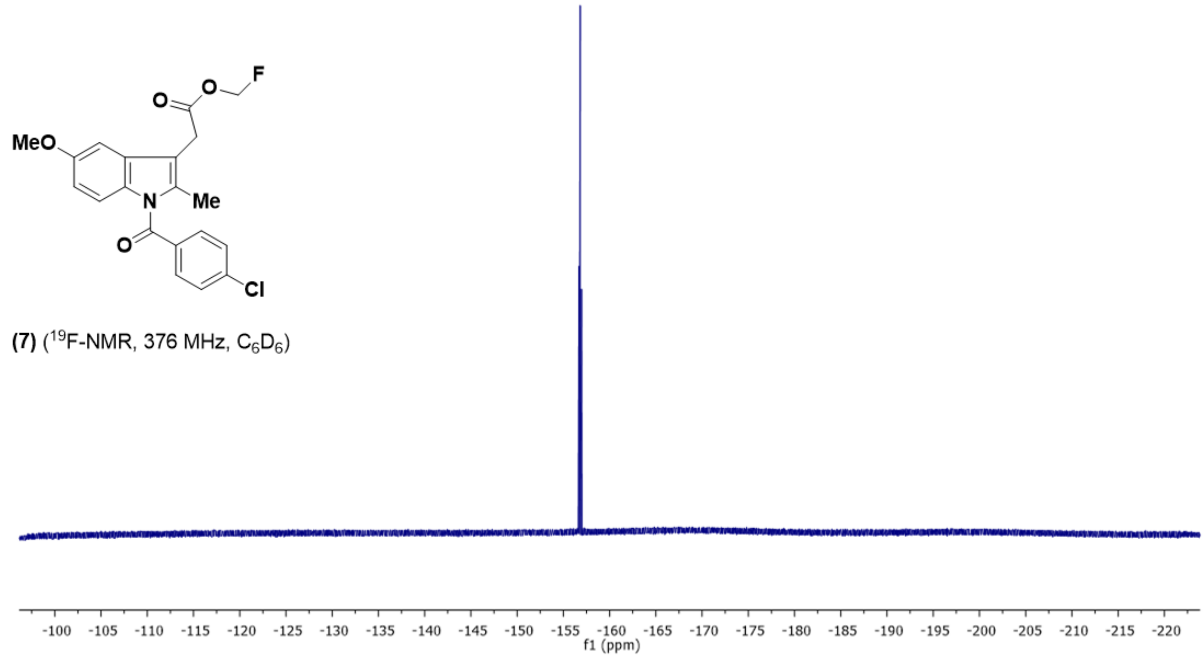
(4) (^{19}F-NMR, 376 MHz, C_6D_6)



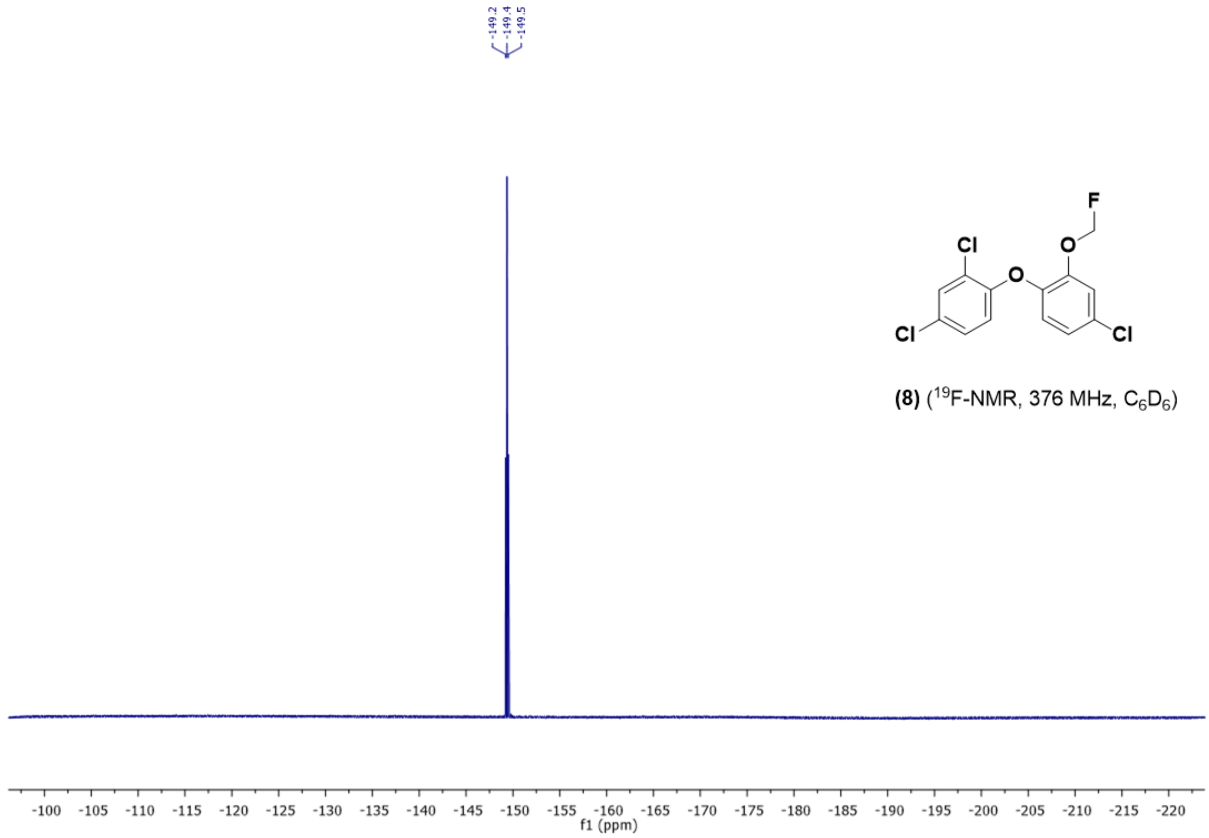
(5) (^{19}F-NMR, 376 MHz, C_6D_6)



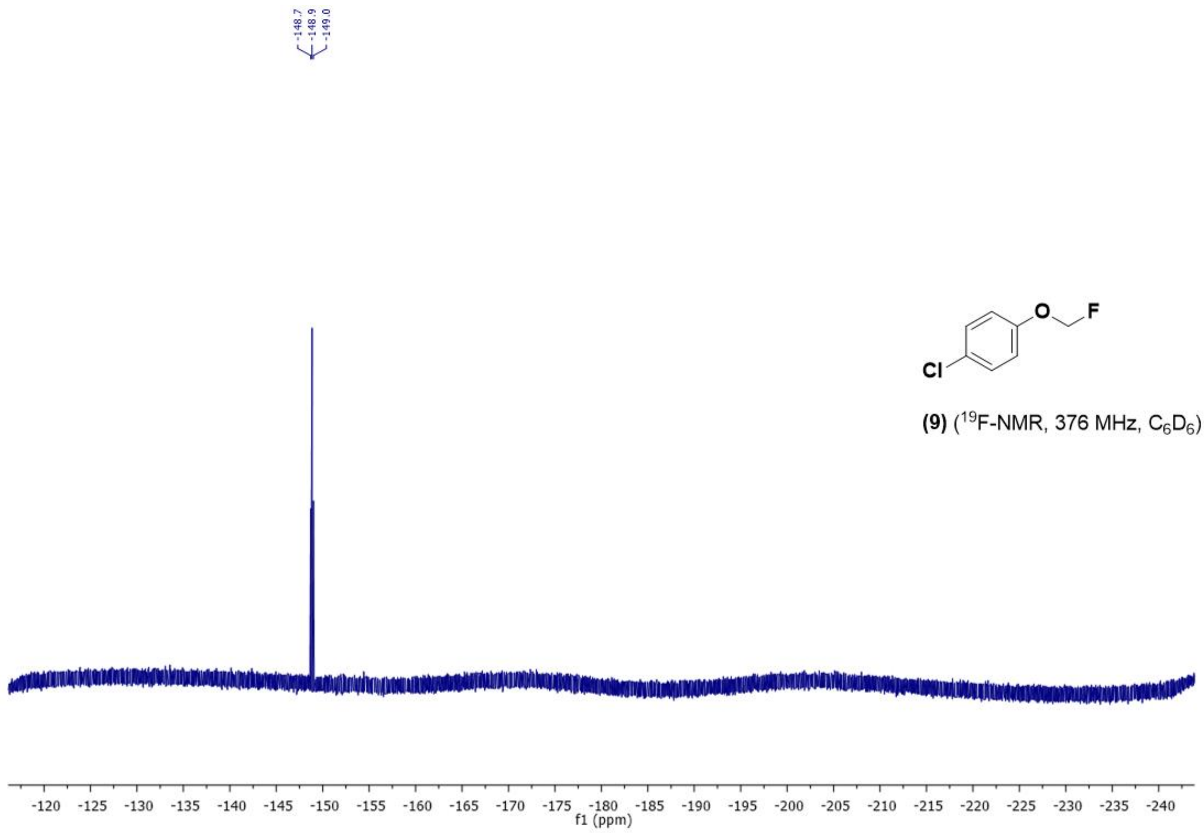
(6) (^{19}F-NMR, 376 MHz, C_6D_6)



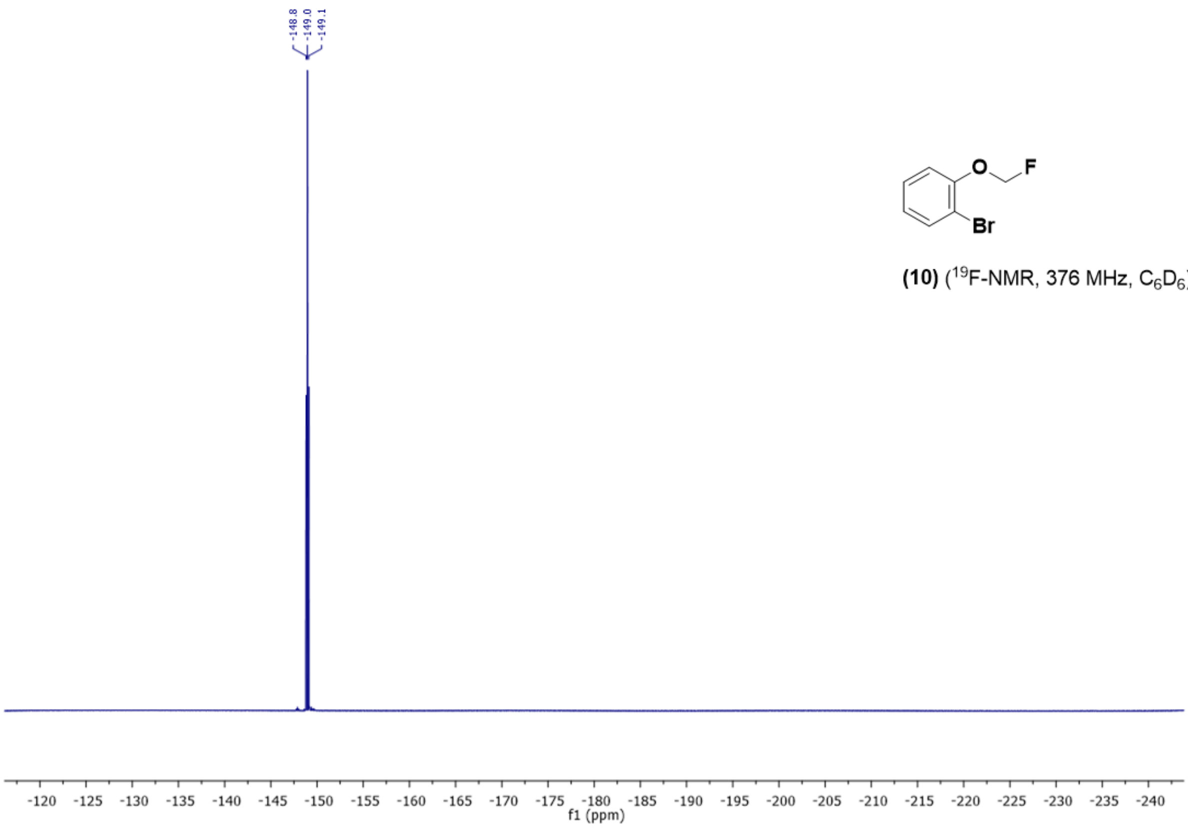
(7) (^{19}F-NMR, 376 MHz, C_6D_6)



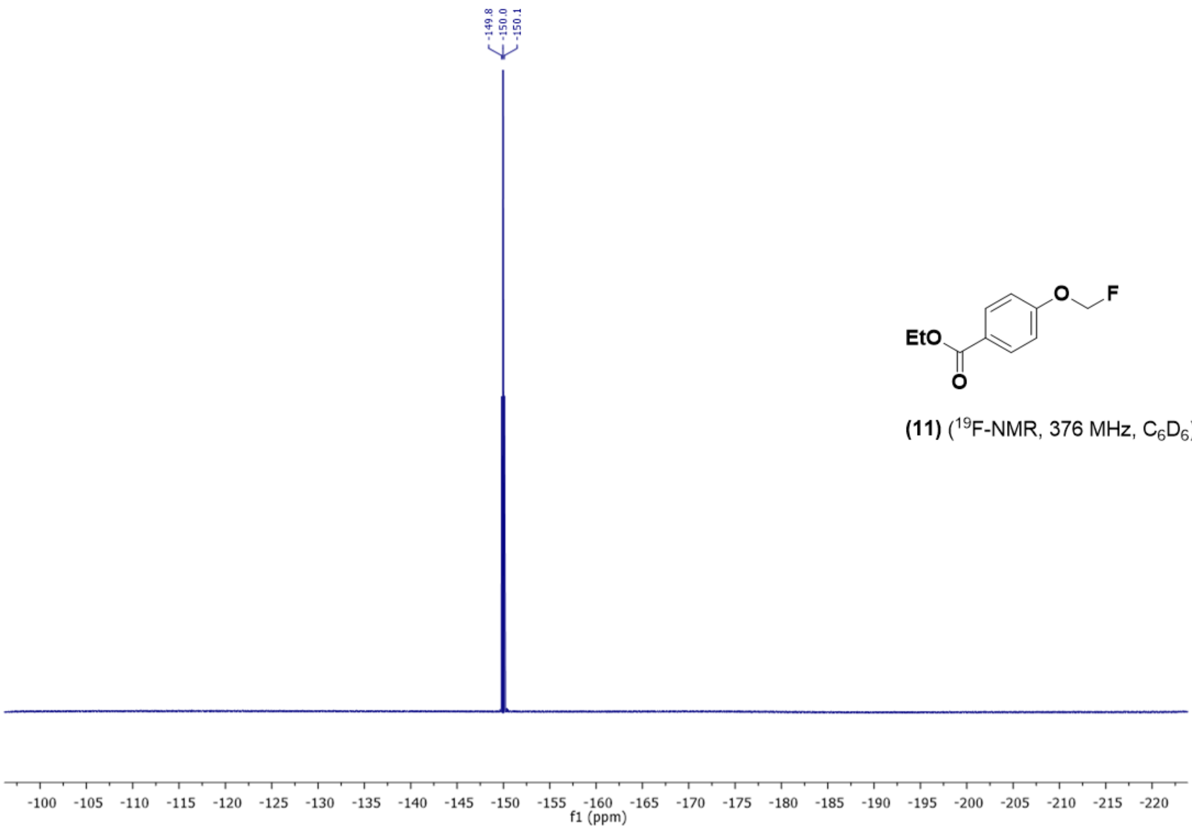
(8) (^{19}F-NMR, 376 MHz, C_6D_6)



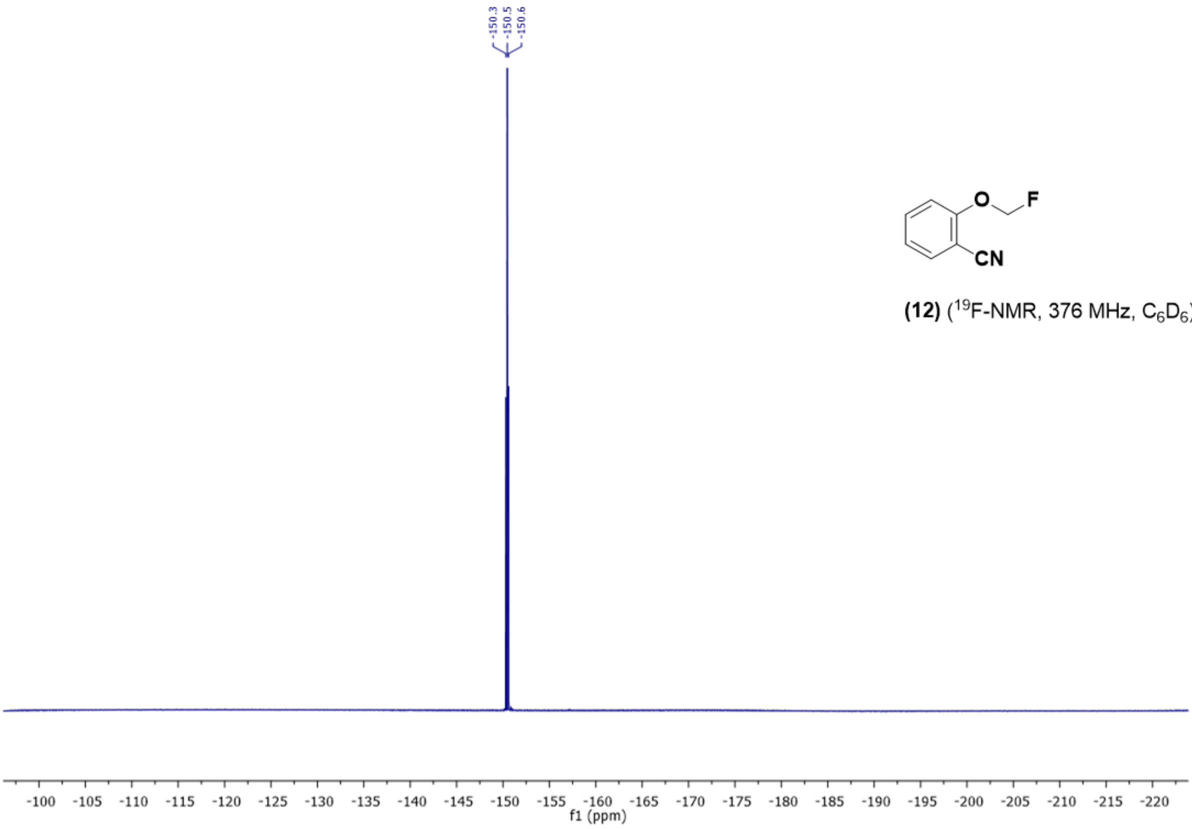
(9) (^{19}F-NMR, 376 MHz, C_6D_6)



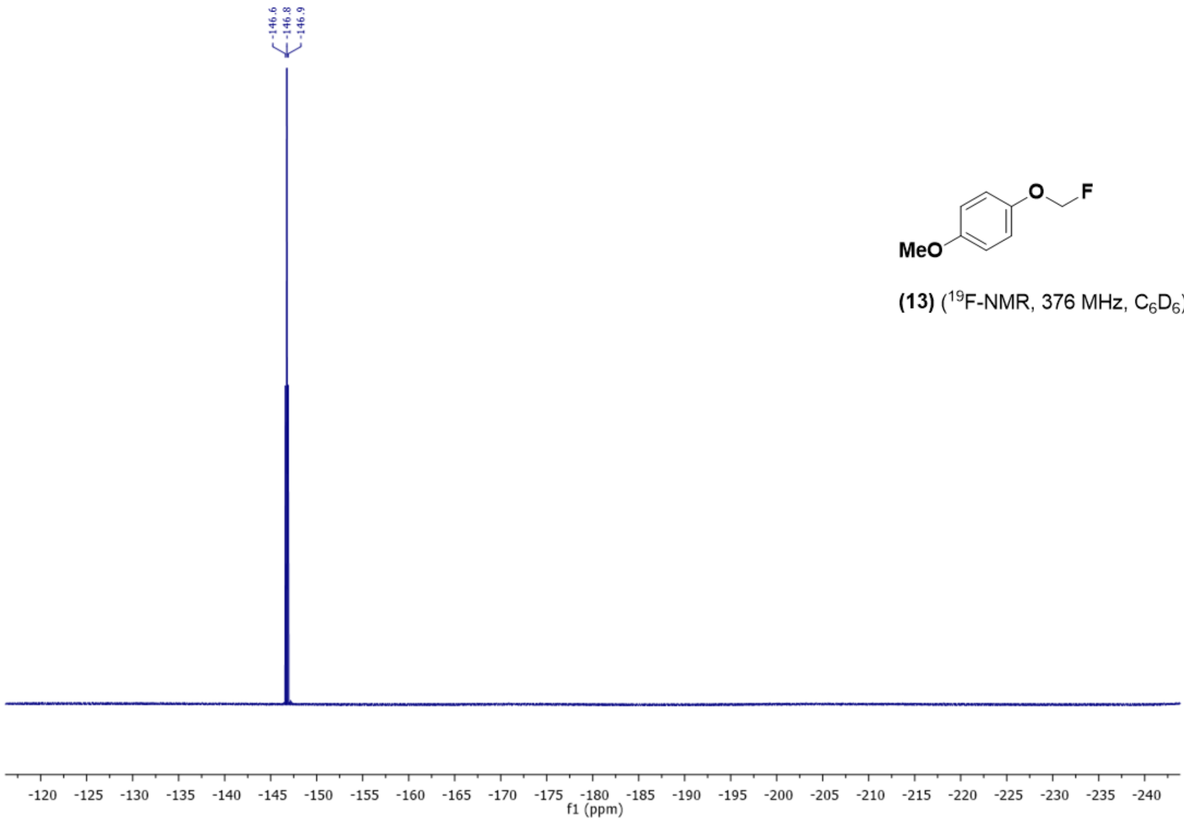
(10) (^{19}F-NMR, 376 MHz, C_6D_6)



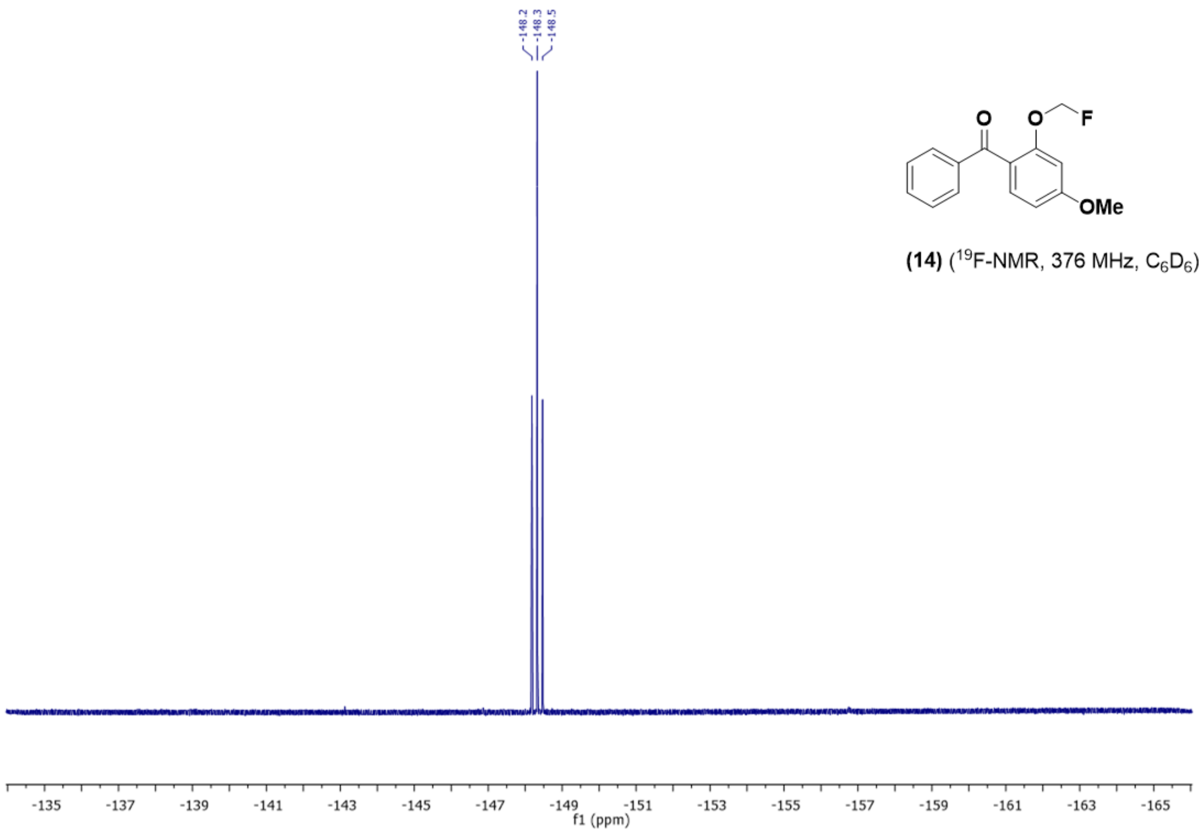
(11) (^{19}F-NMR, 376 MHz, C_6D_6)



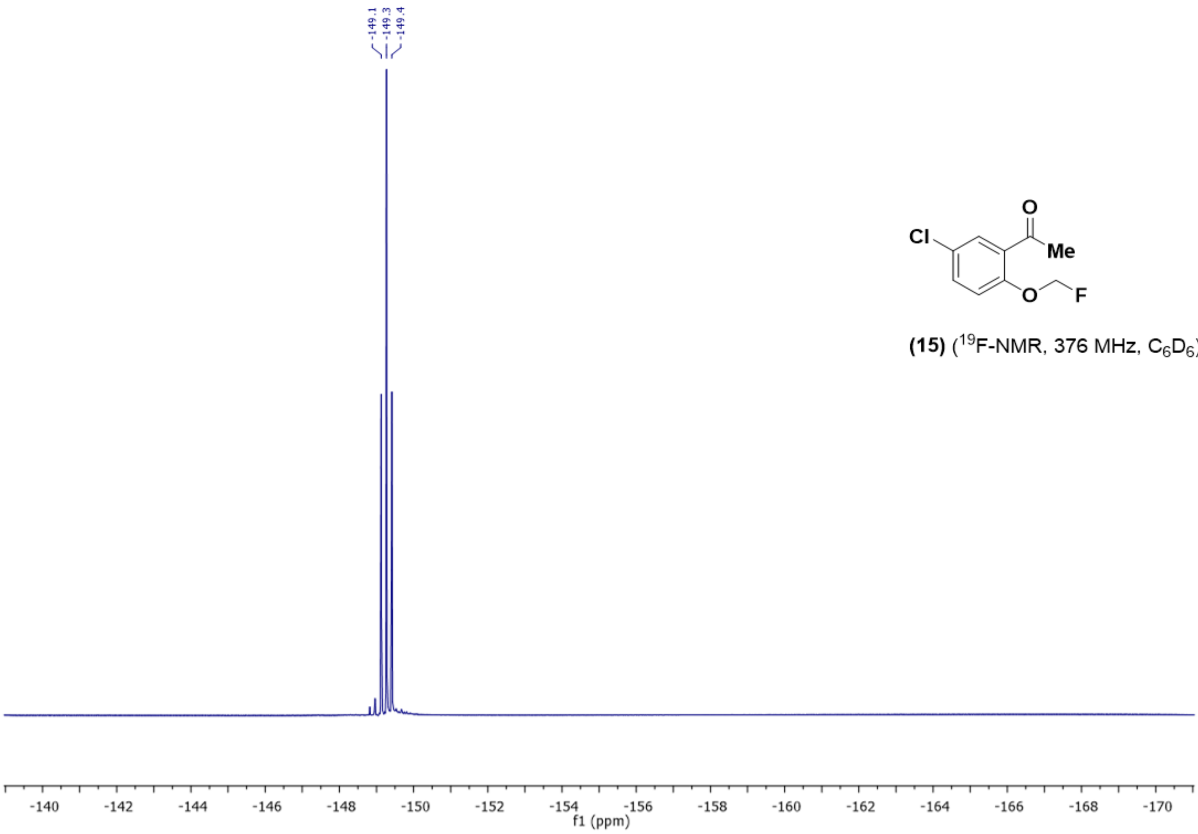
(12) (^{19}F-NMR, 376 MHz, C_6D_6)



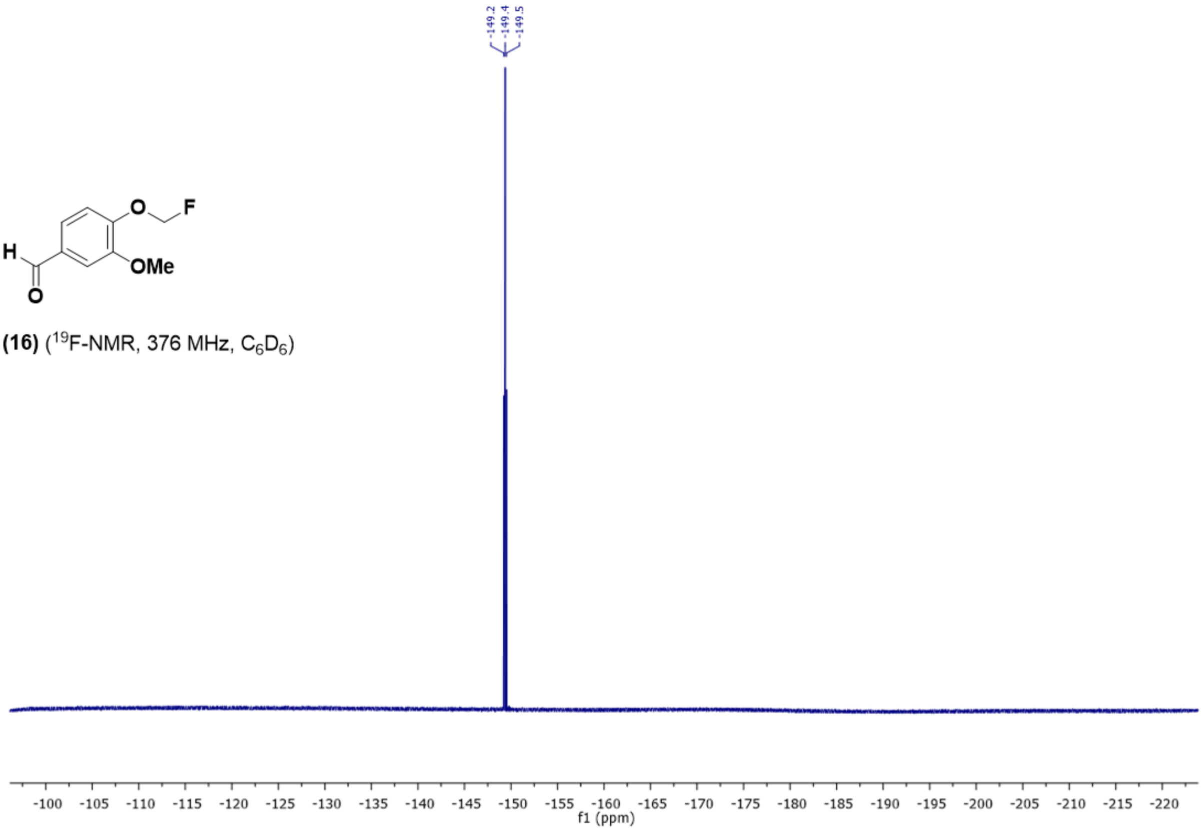
(13) (^{19}F-NMR, 376 MHz, C_6D_6)



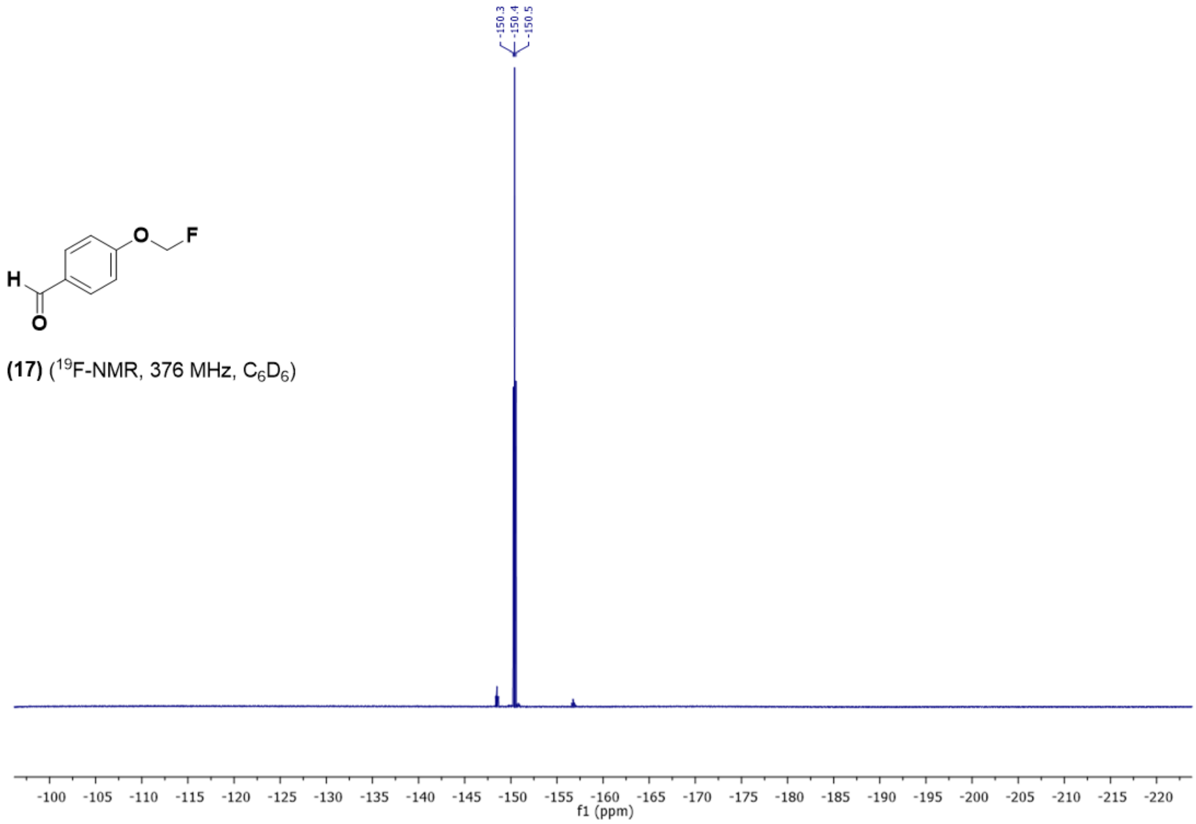
(14) (^{19}F-NMR, 376 MHz, C_6D_6)



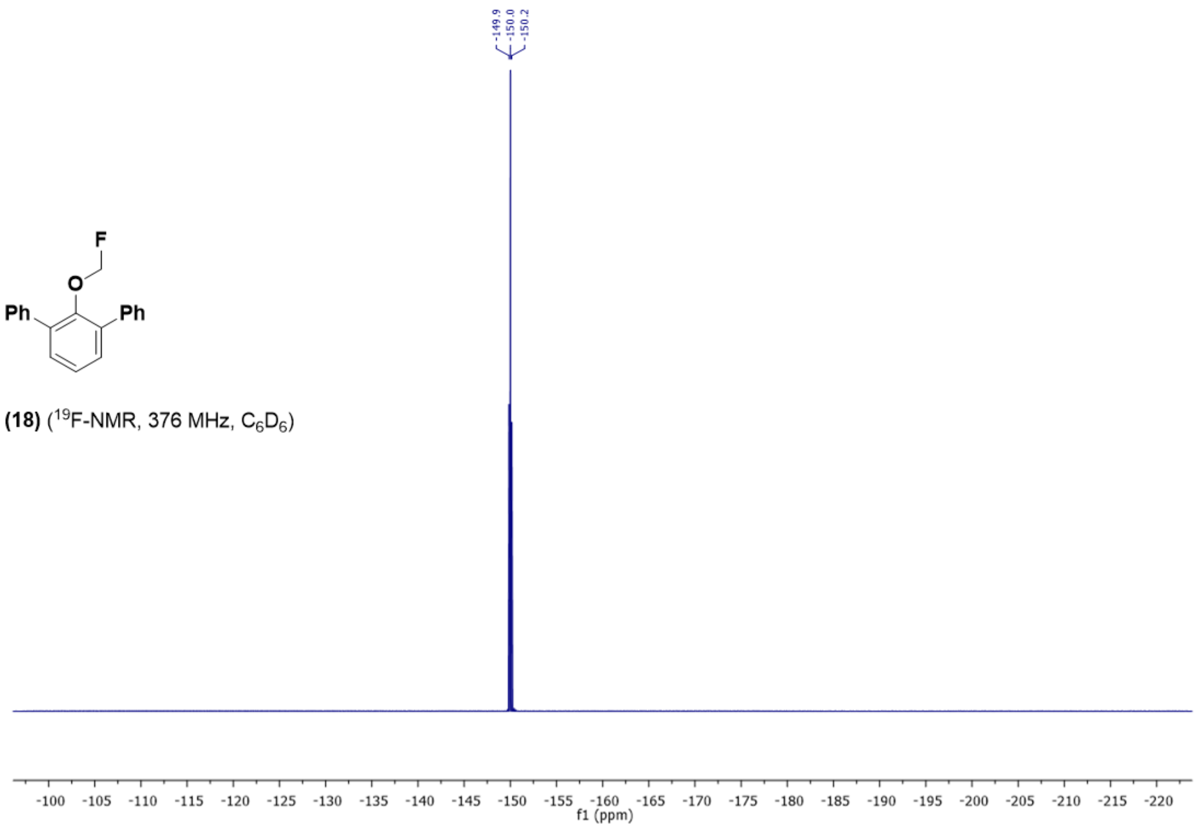
(15) (^{19}F-NMR, 376 MHz, C_6D_6)



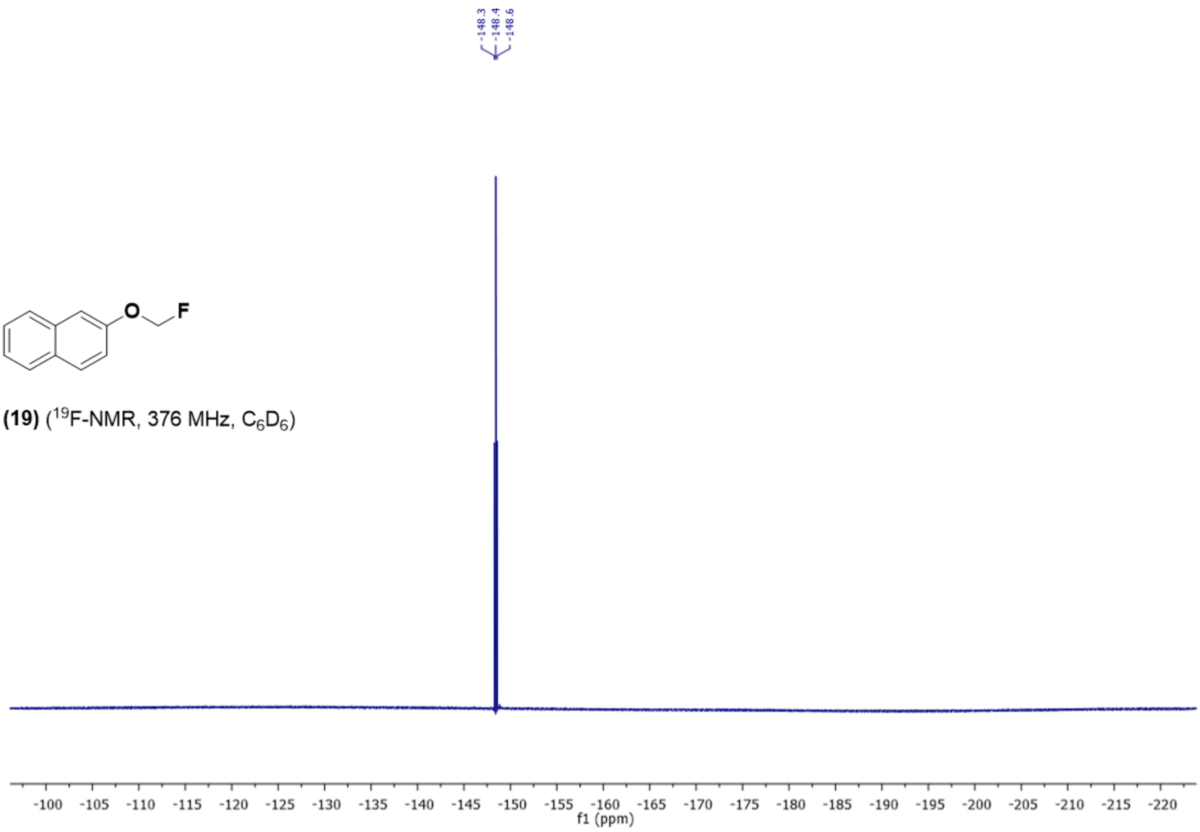
(16) (^{19}F-NMR, 376 MHz, C_6D_6)



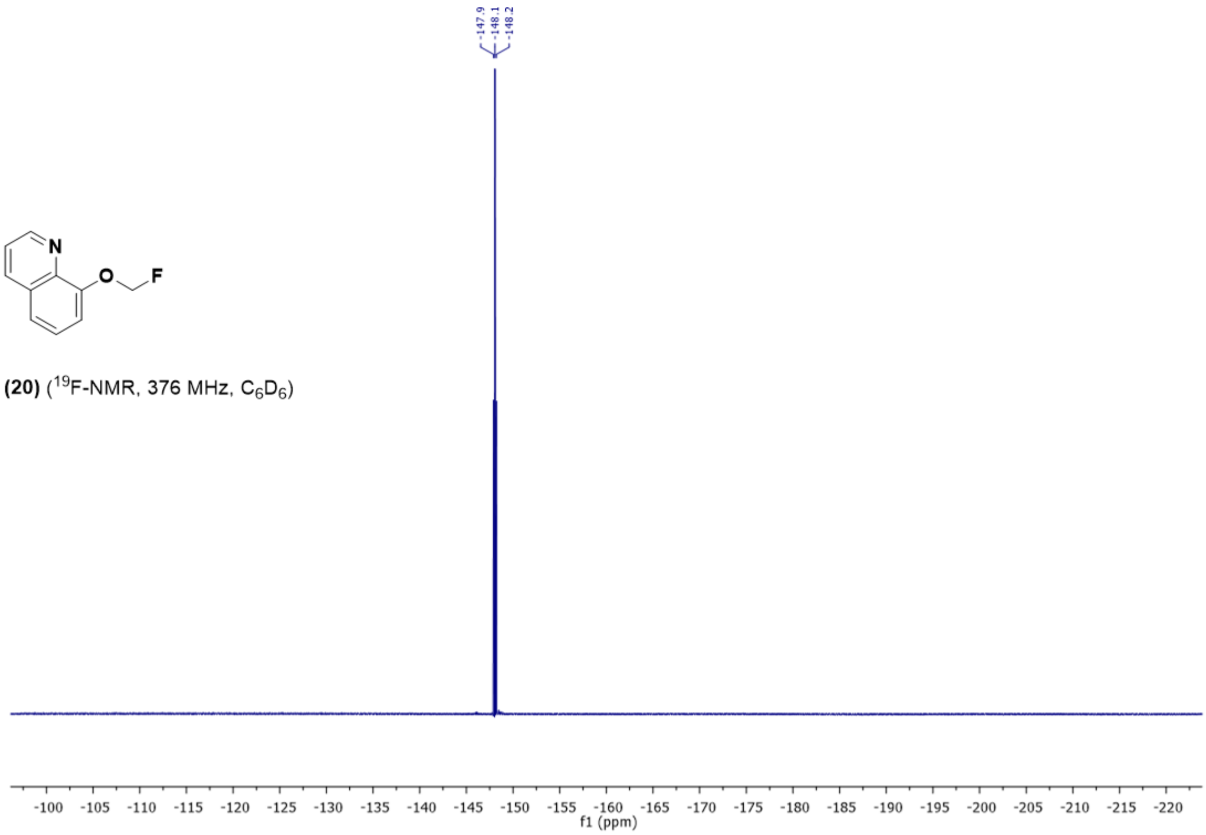
(17) (^{19}F-NMR, 376 MHz, C_6D_6)



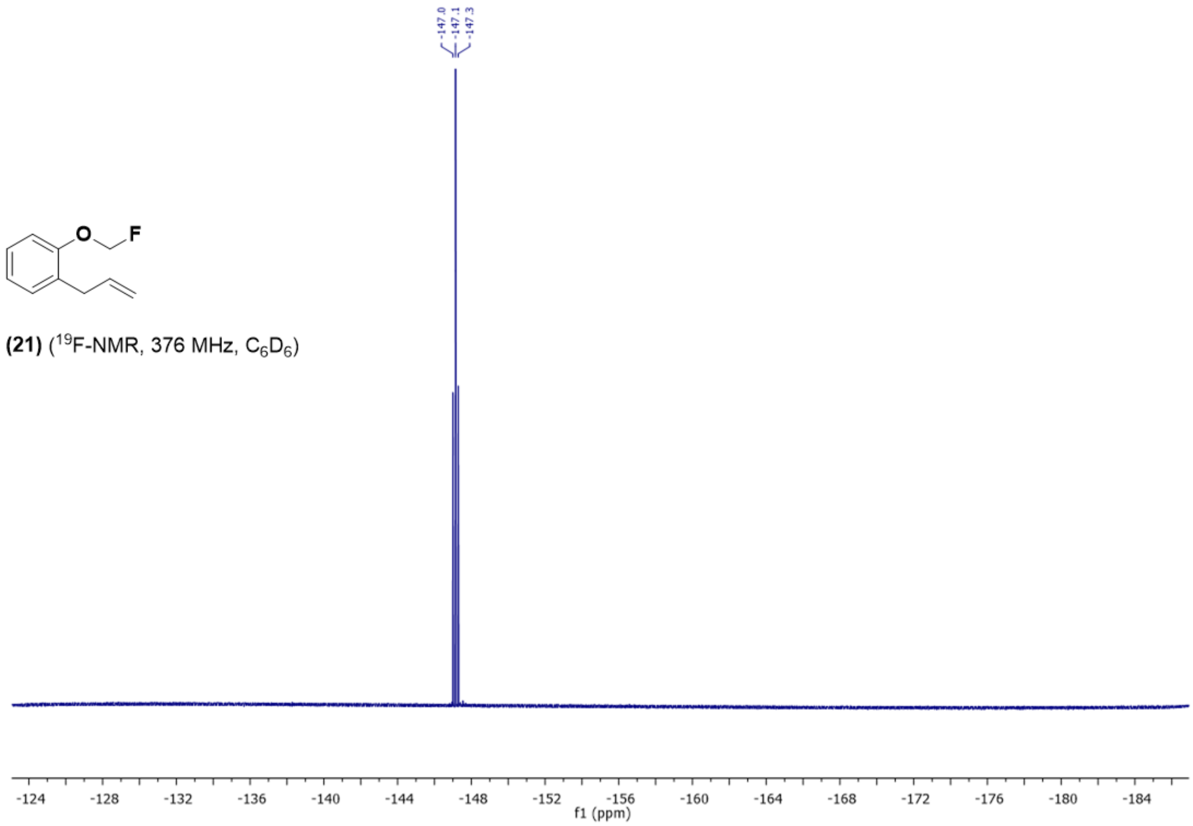
(18) (^{19}F-NMR, 376 MHz, C_6D_6)



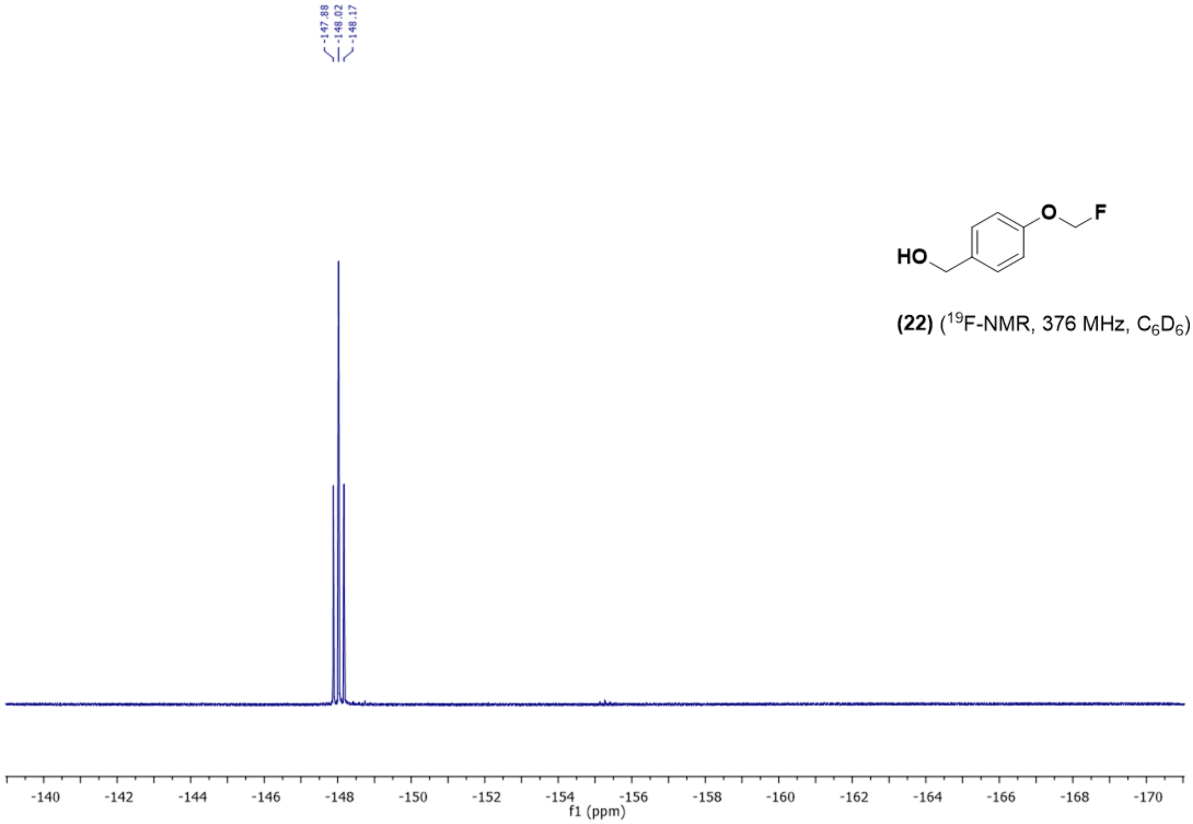
(19) (^{19}F-NMR, 376 MHz, C_6D_6)



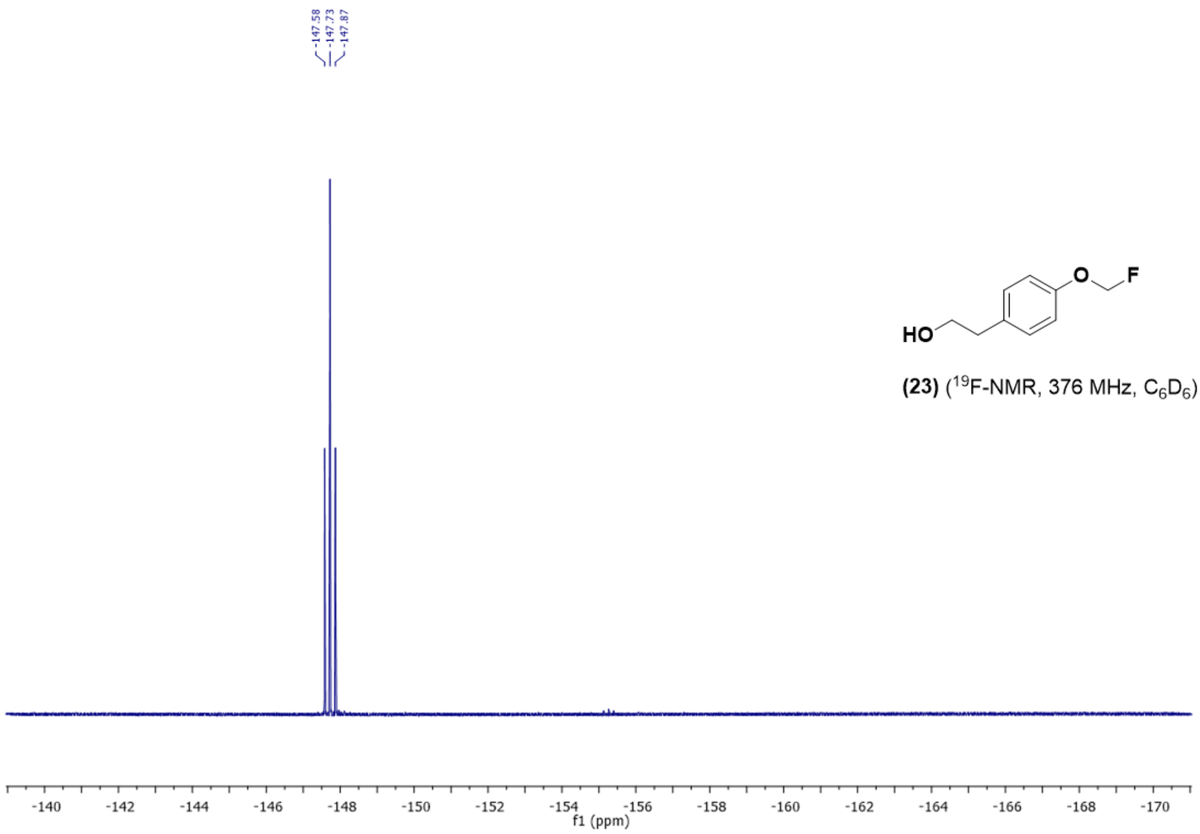
(20) (^{19}F-NMR, 376 MHz, C_6D_6)



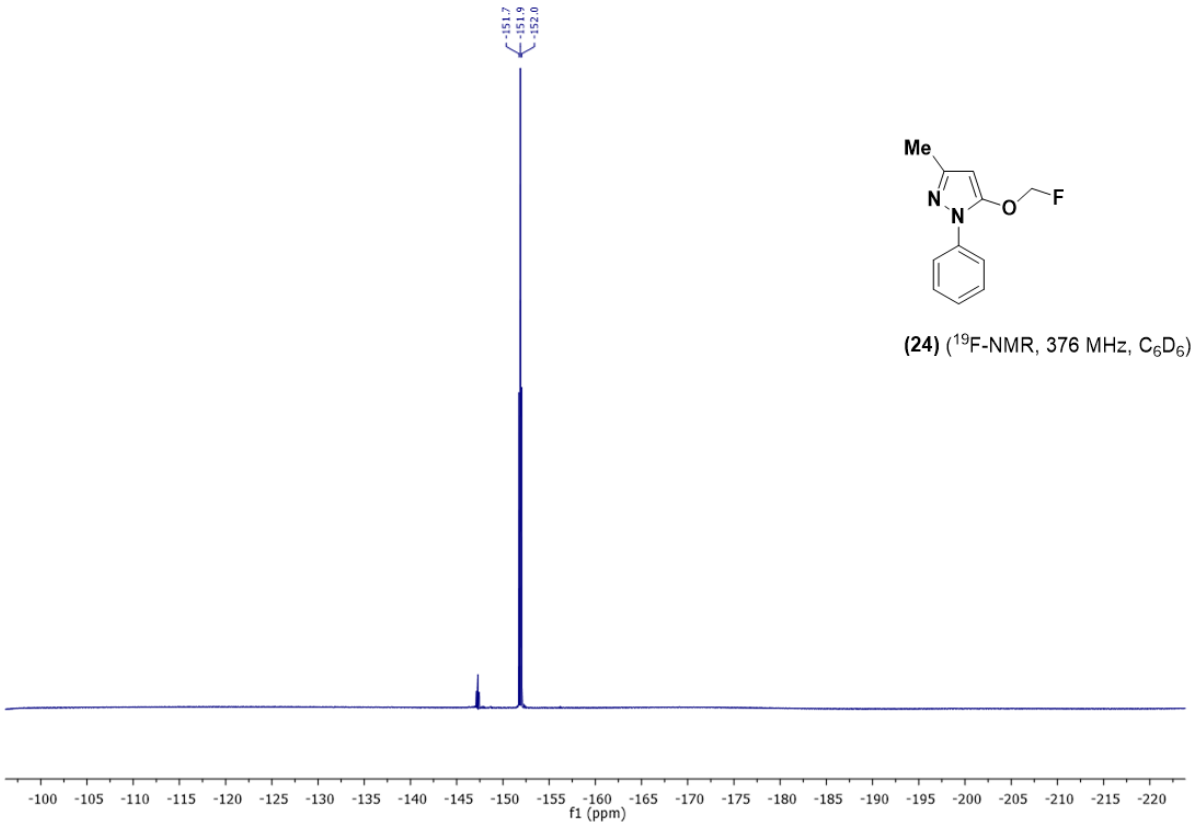
(21) (^{19}F-NMR, 376 MHz, C_6D_6)



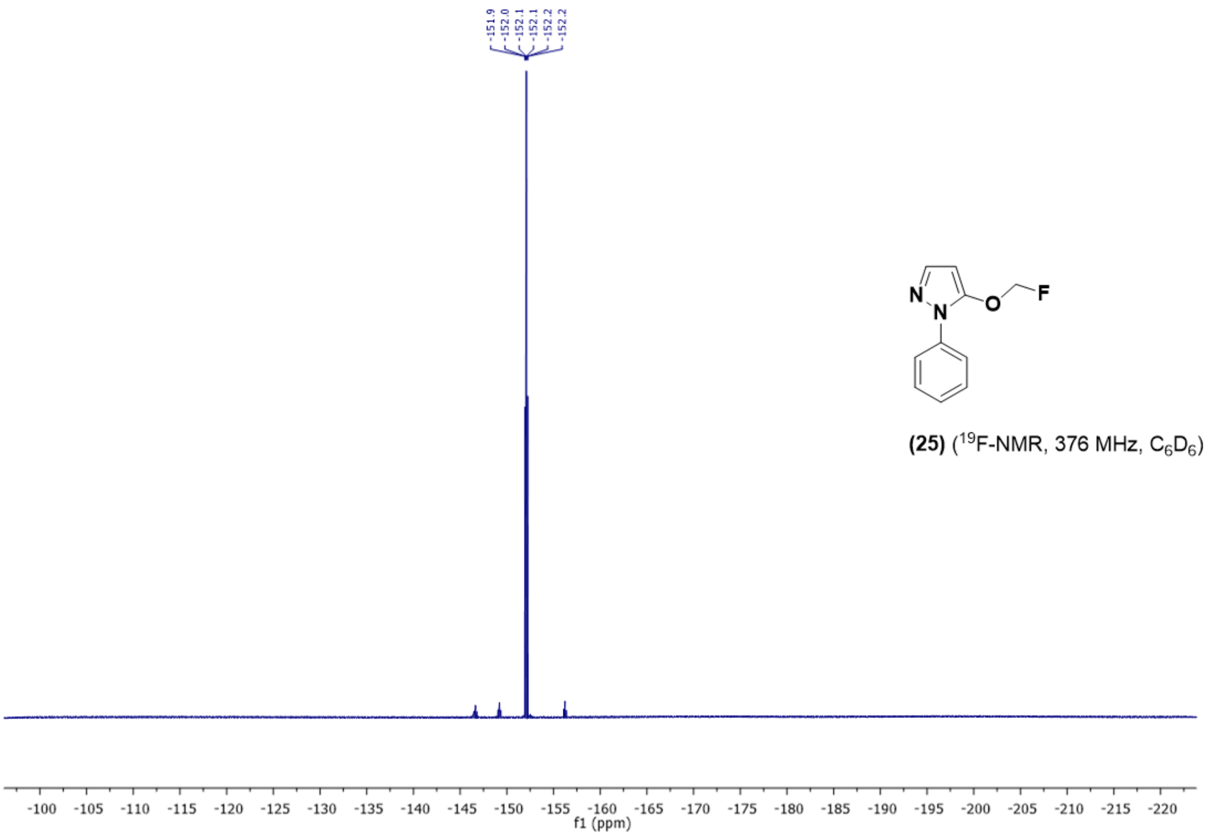
(22) (^{19}F-NMR, 376 MHz, C_6D_6)



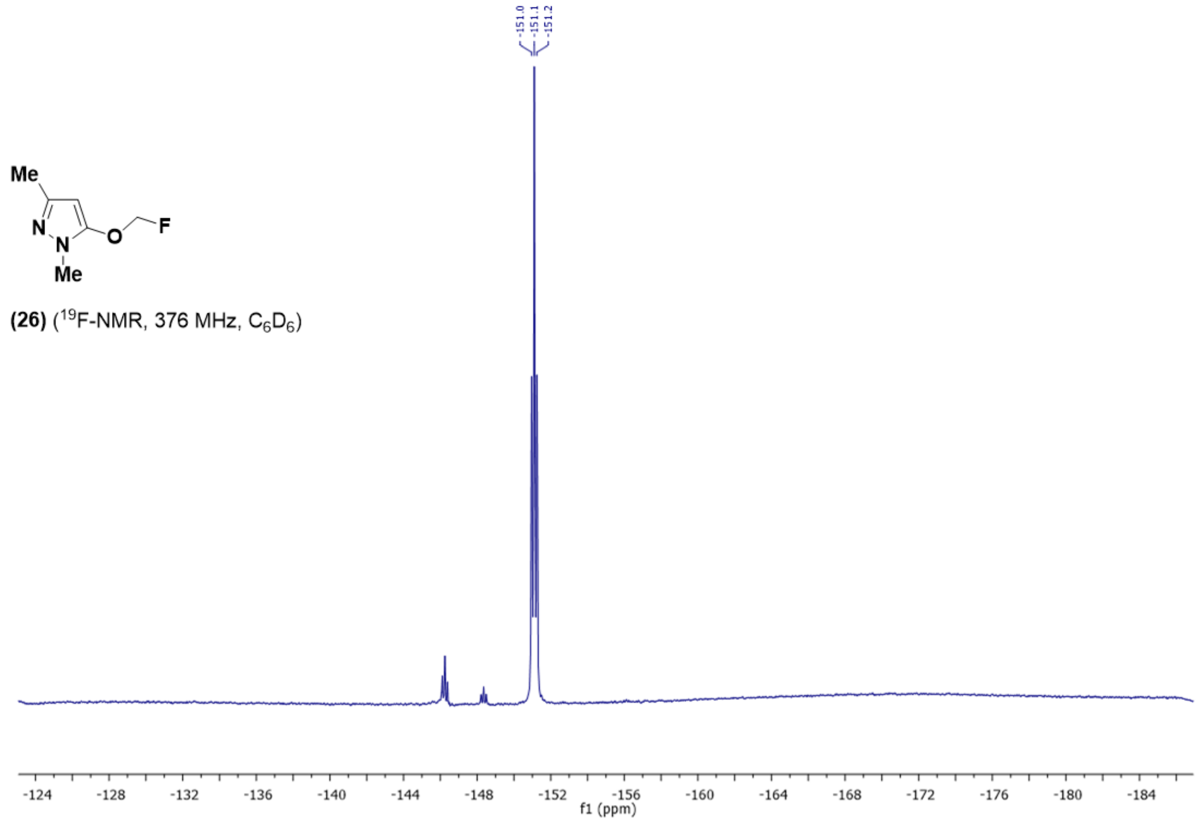
(23) (^{19}F-NMR, 376 MHz, C_6D_6)



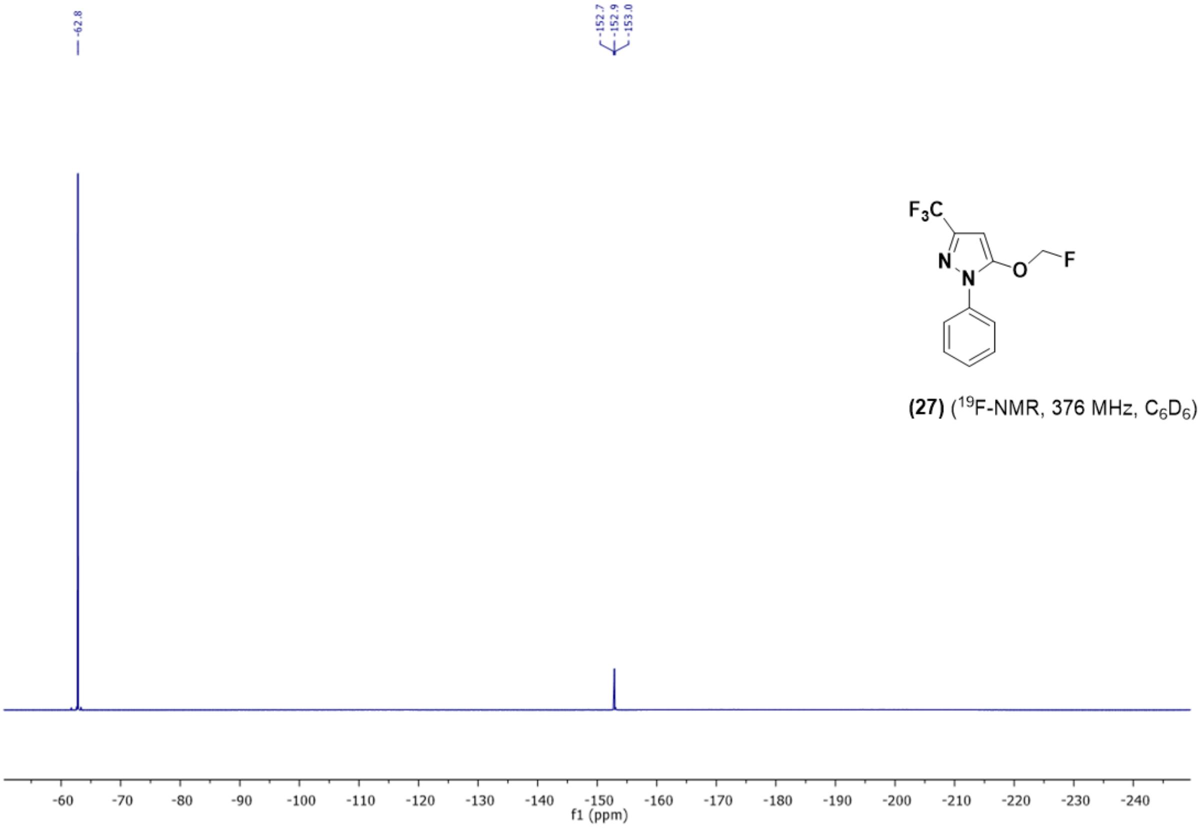
(24) (^{19}F-NMR, 376 MHz, C_6D_6)



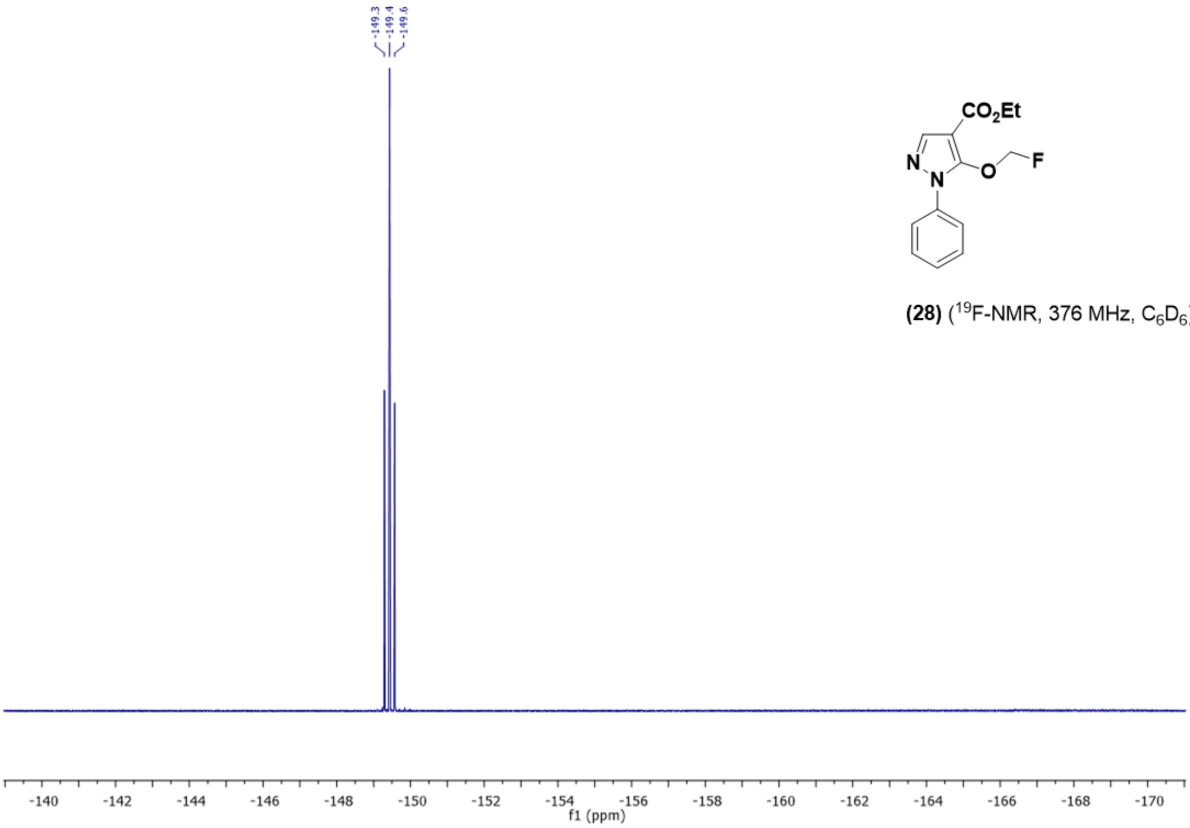
(25) (^{19}F-NMR, 376 MHz, C_6D_6)



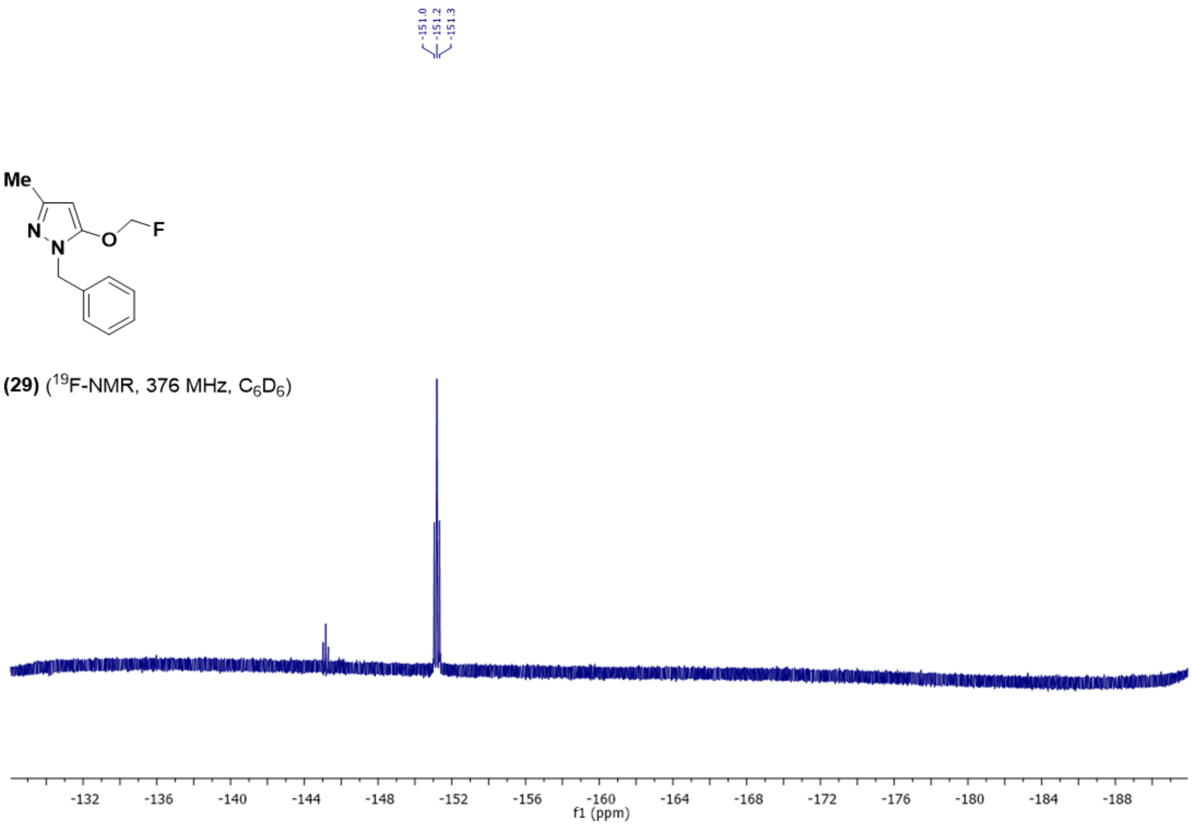
(26) (^{19}F-NMR, 376 MHz, C_6D_6)



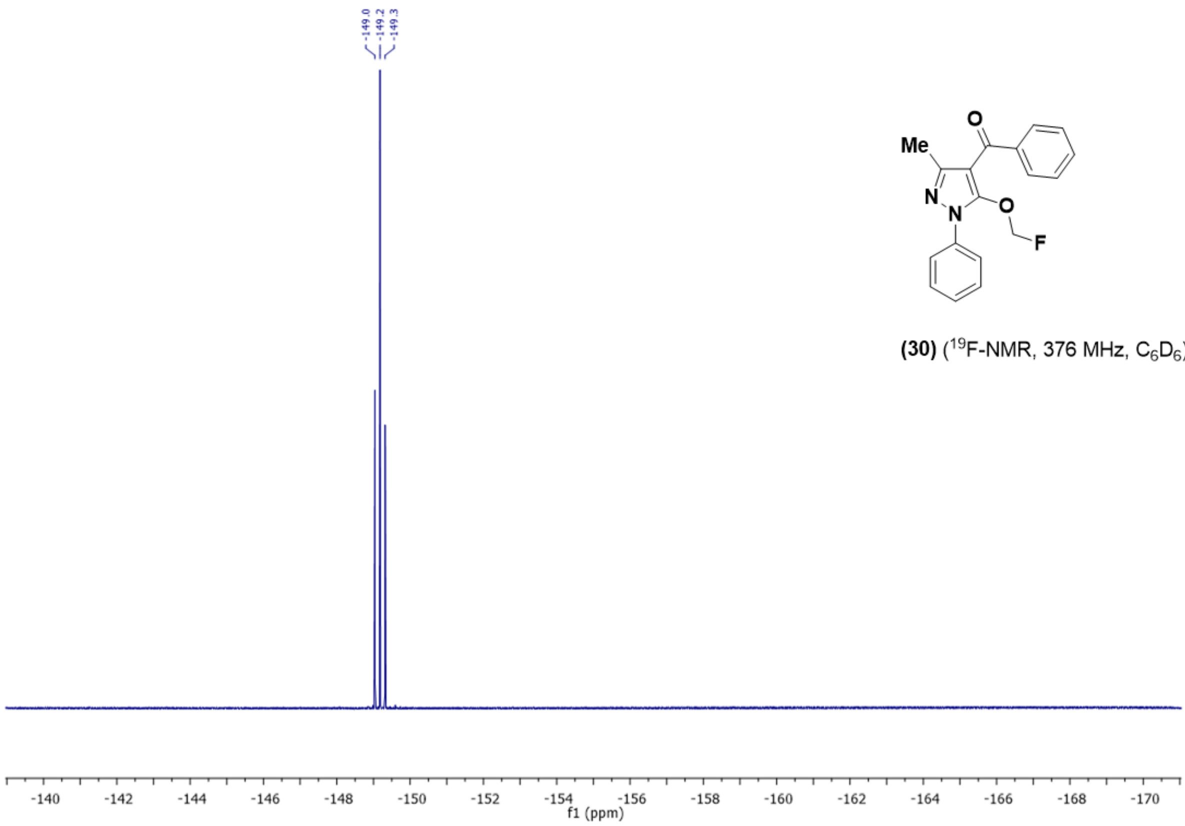
(27) (^{19}F-NMR, 376 MHz, C_6D_6)



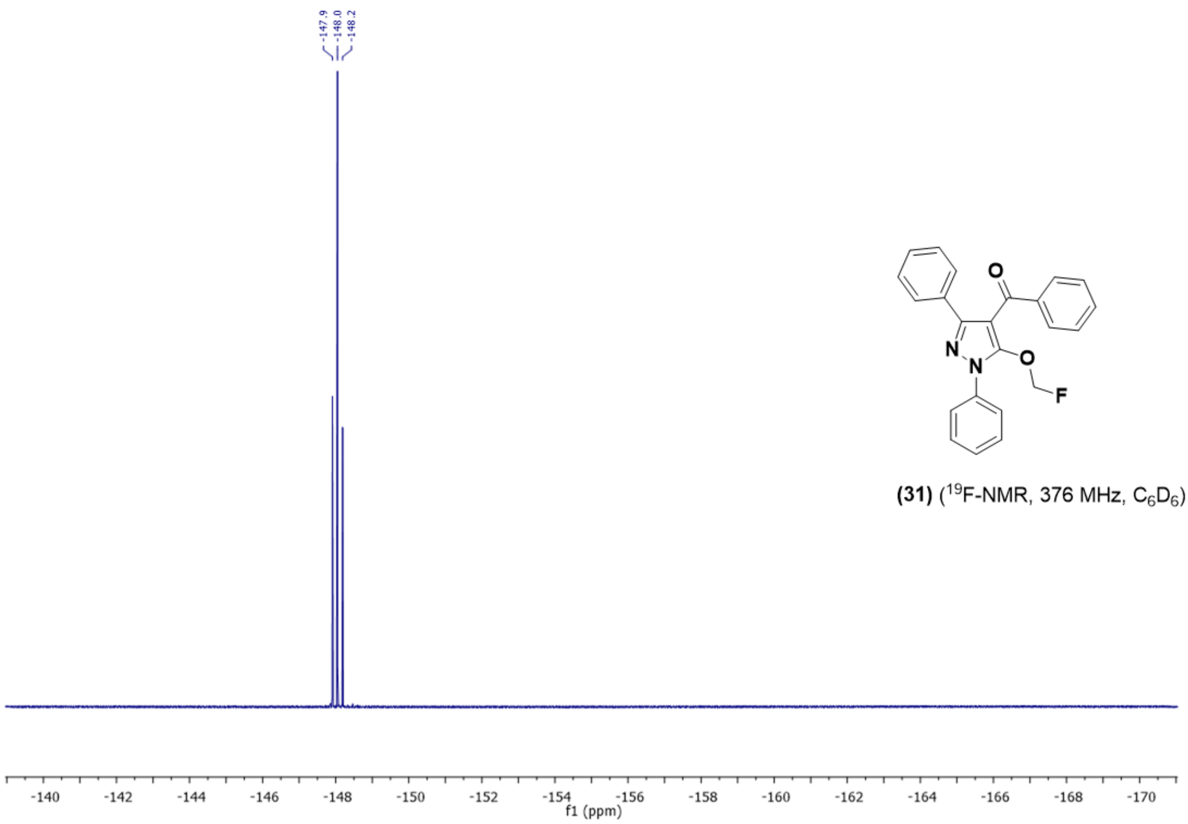
(28) (^{19}F-NMR, 376 MHz, C_6D_6)



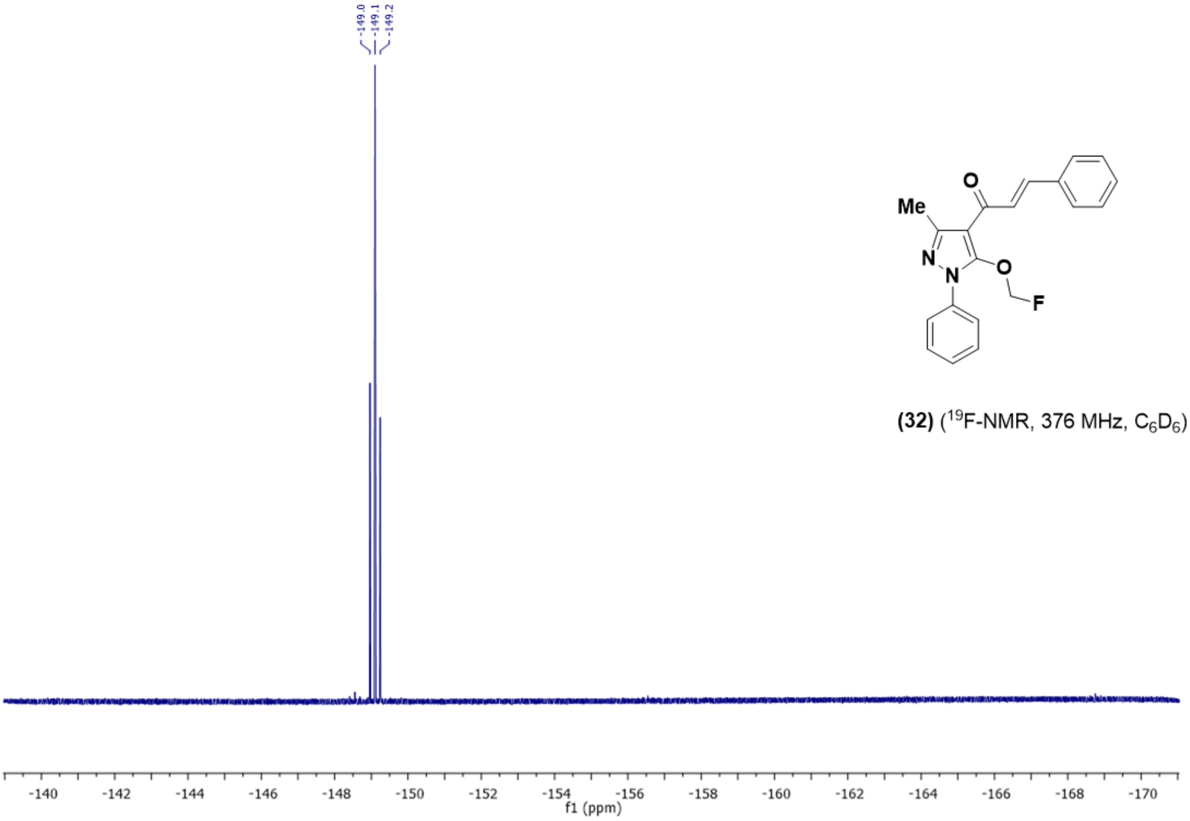
(29) (^{19}F-NMR, 376 MHz, C_6D_6)



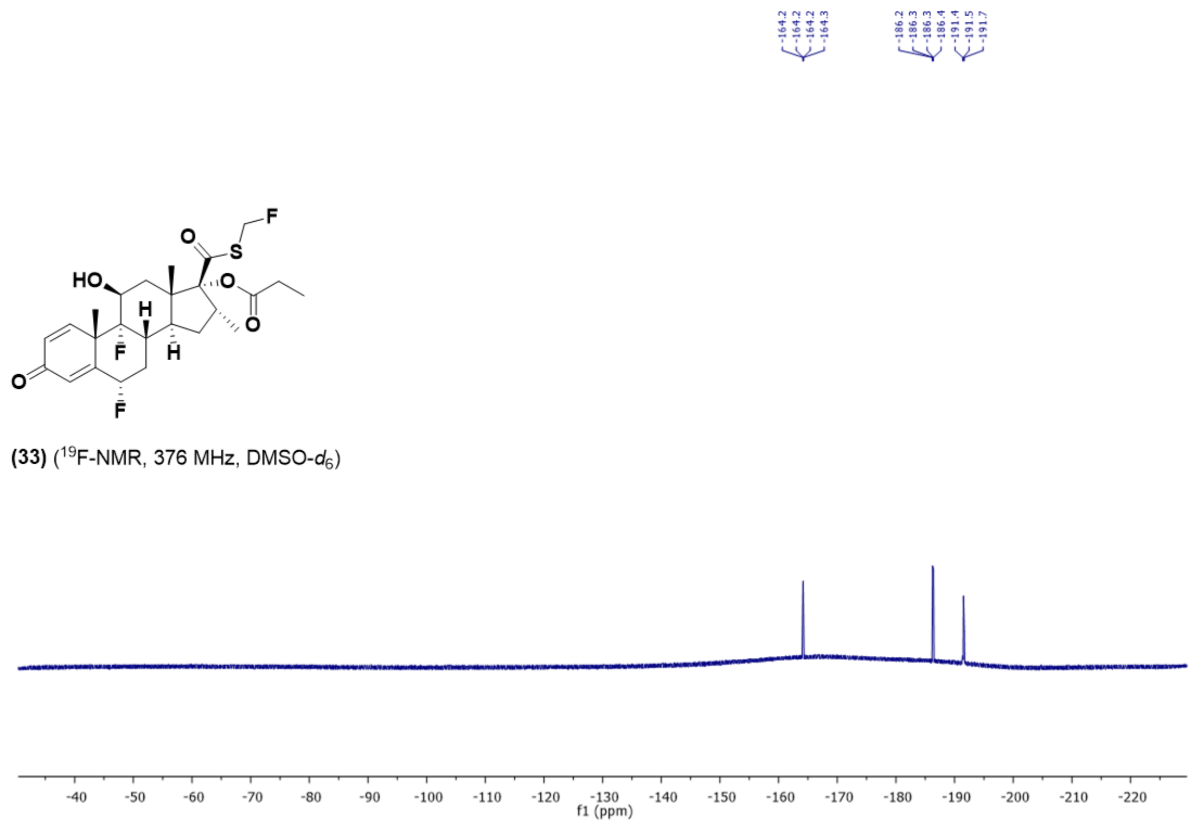
(30) (^{19}F-NMR, 376 MHz, C_6D_6)



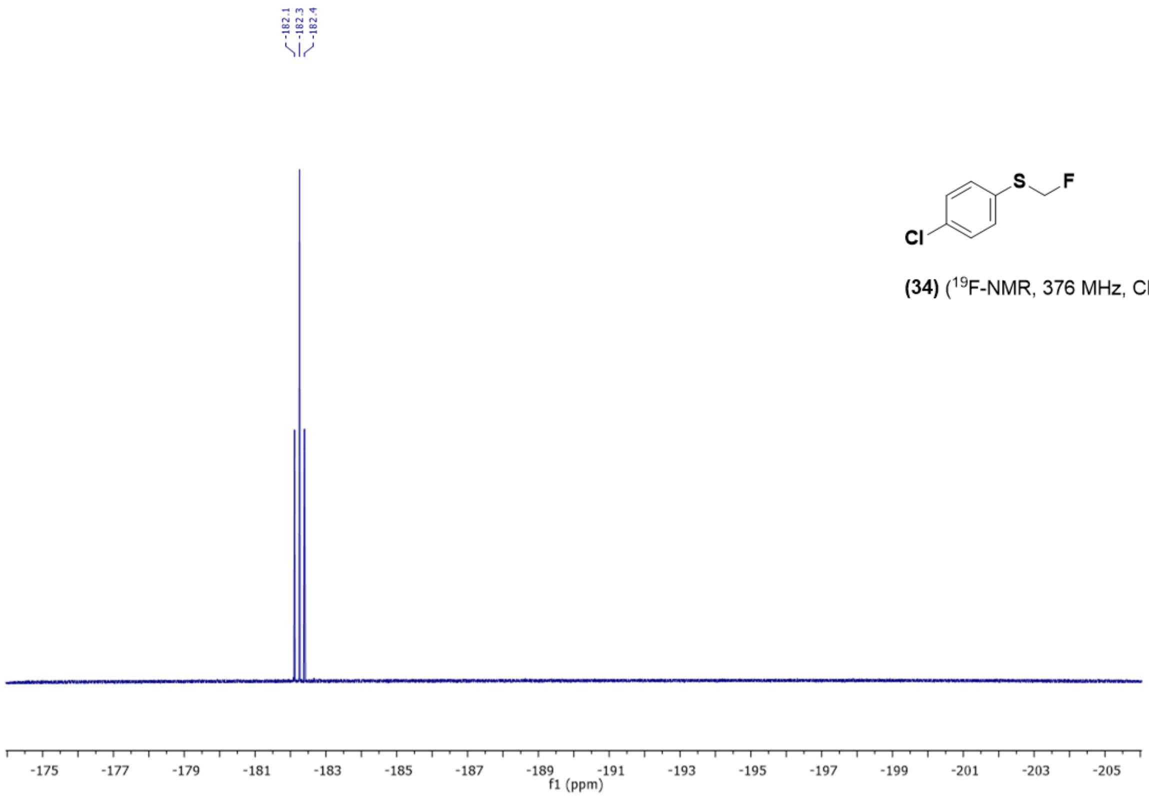
(31) (^{19}F-NMR, 376 MHz, C_6D_6)



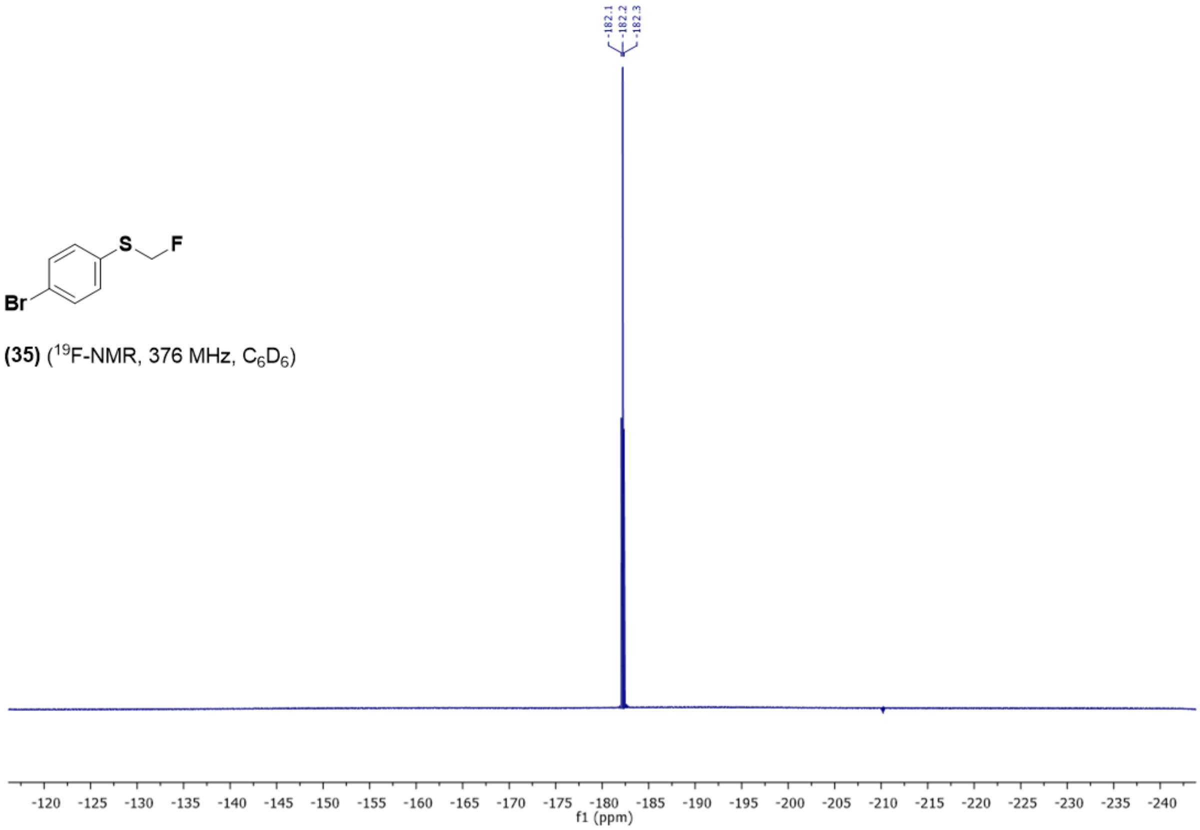
(32) (^{19}F-NMR, 376 MHz, C_6D_6)



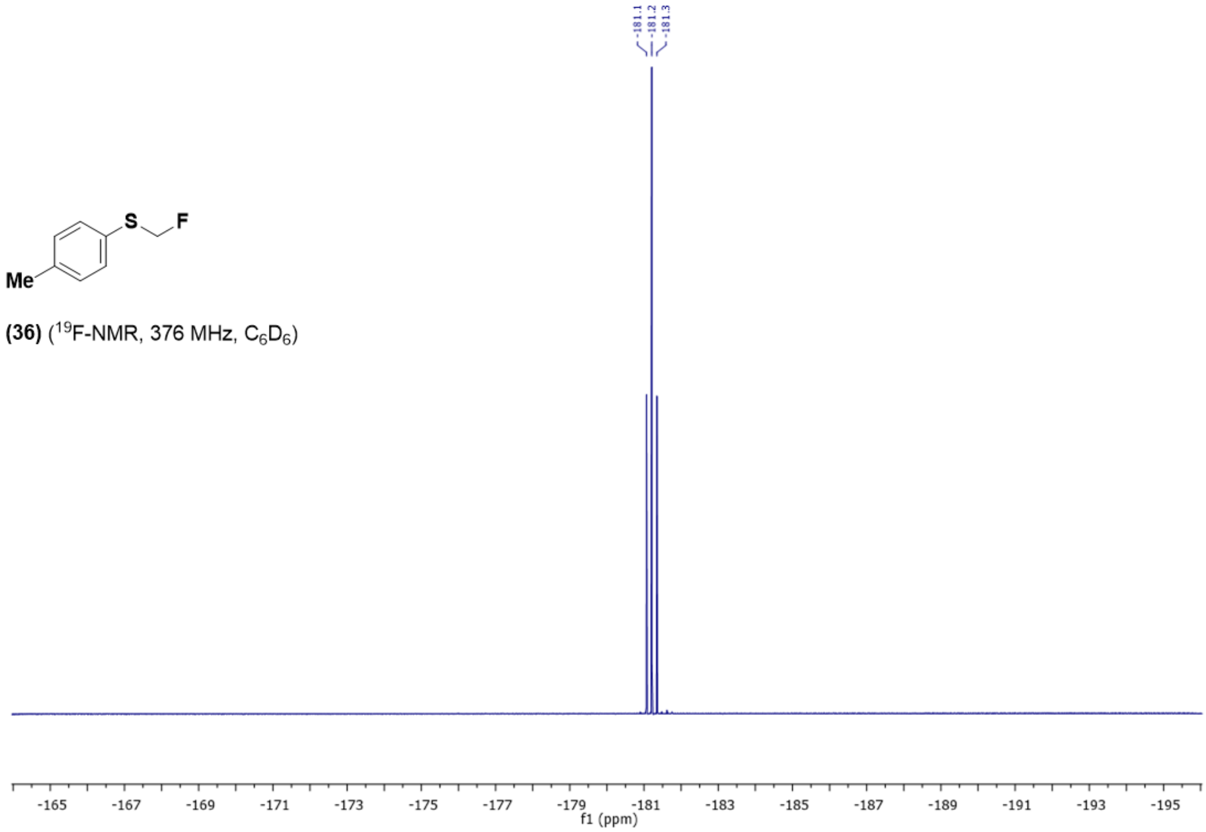
(33) (^{19}F-NMR, 376 MHz, DMSO-d_6)



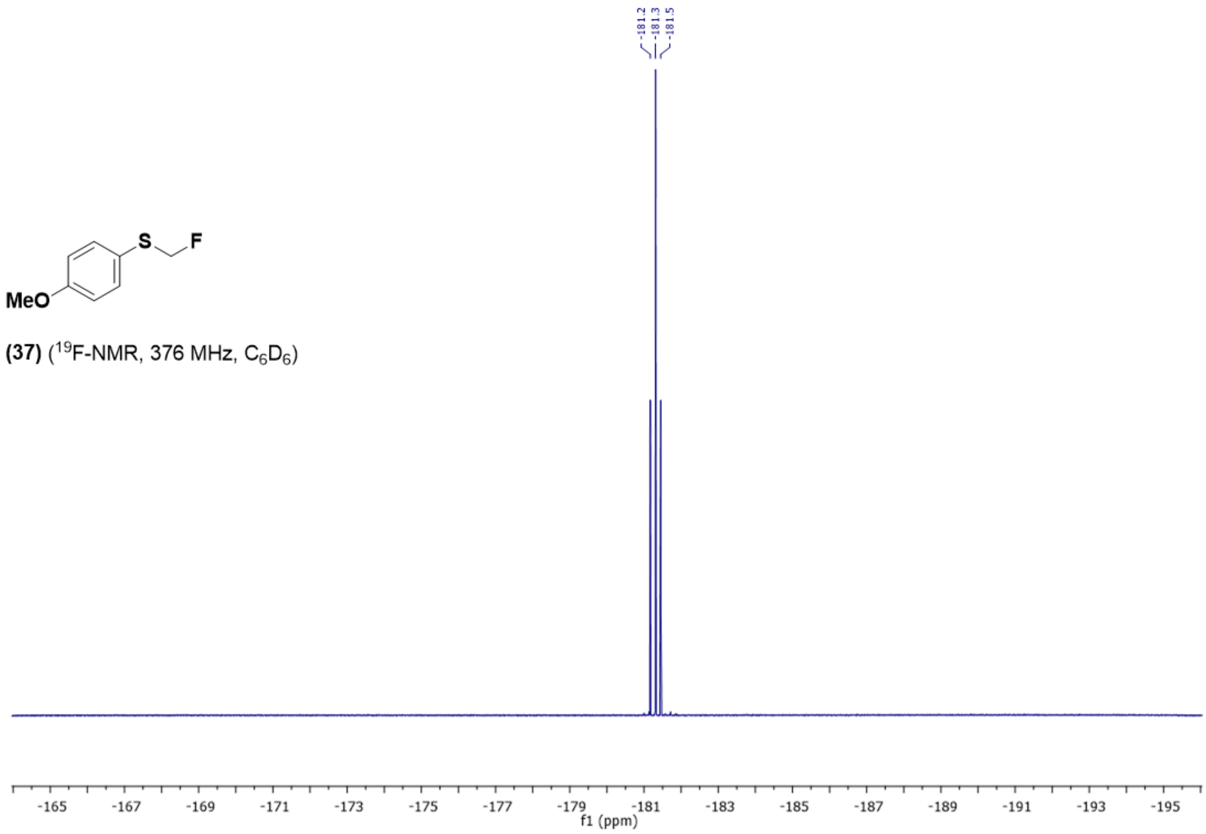
(34) (^{19}F-NMR, 376 MHz, $CDCl_3$)



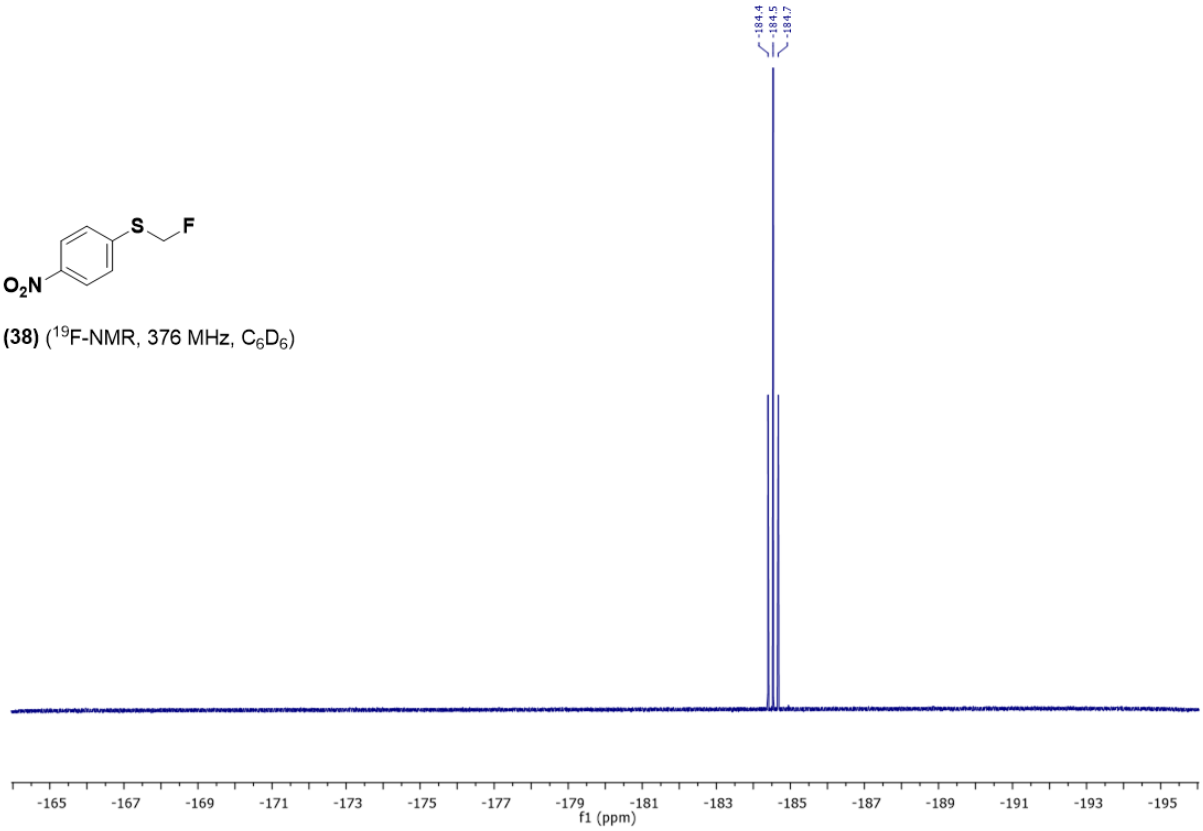
(35) (^{19}F-NMR, 376 MHz, C_6D_6)



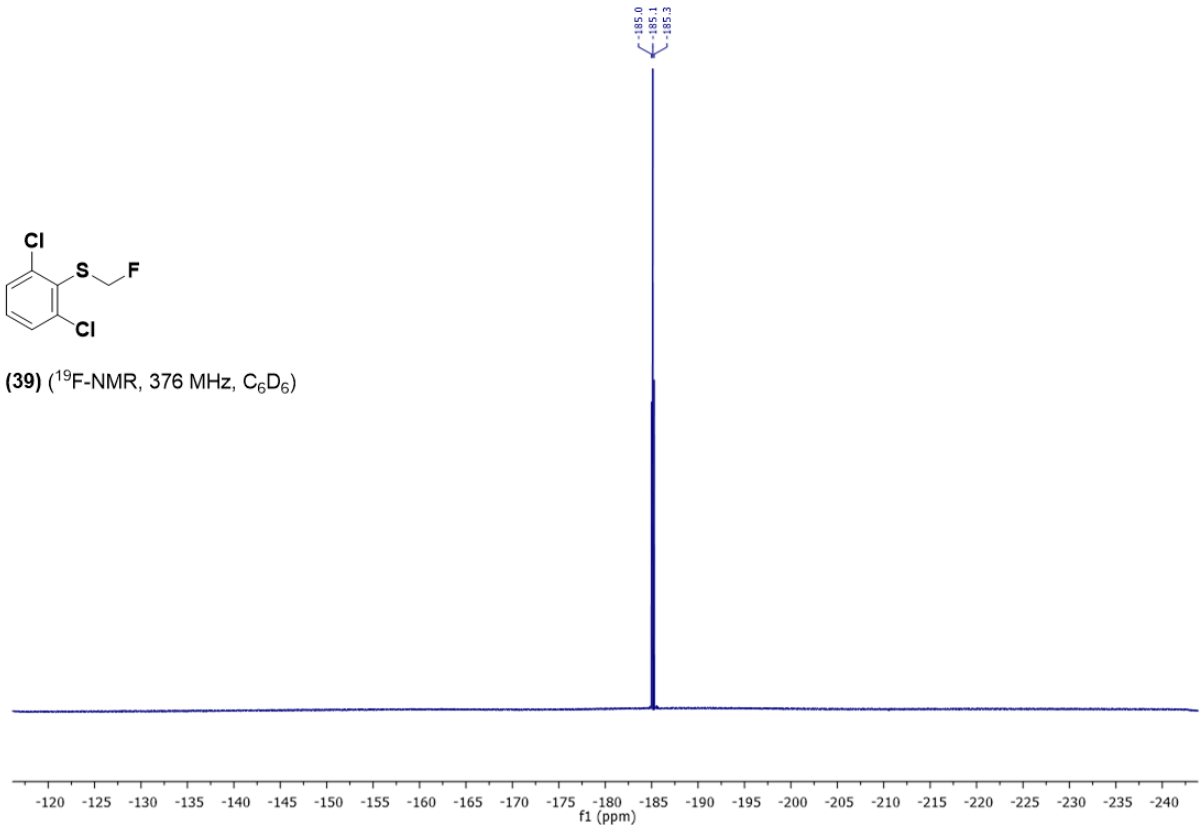
(36) (^{19}F-NMR, 376 MHz, C_6D_6)



(37) (^{19}F-NMR, 376 MHz, C_6D_6)

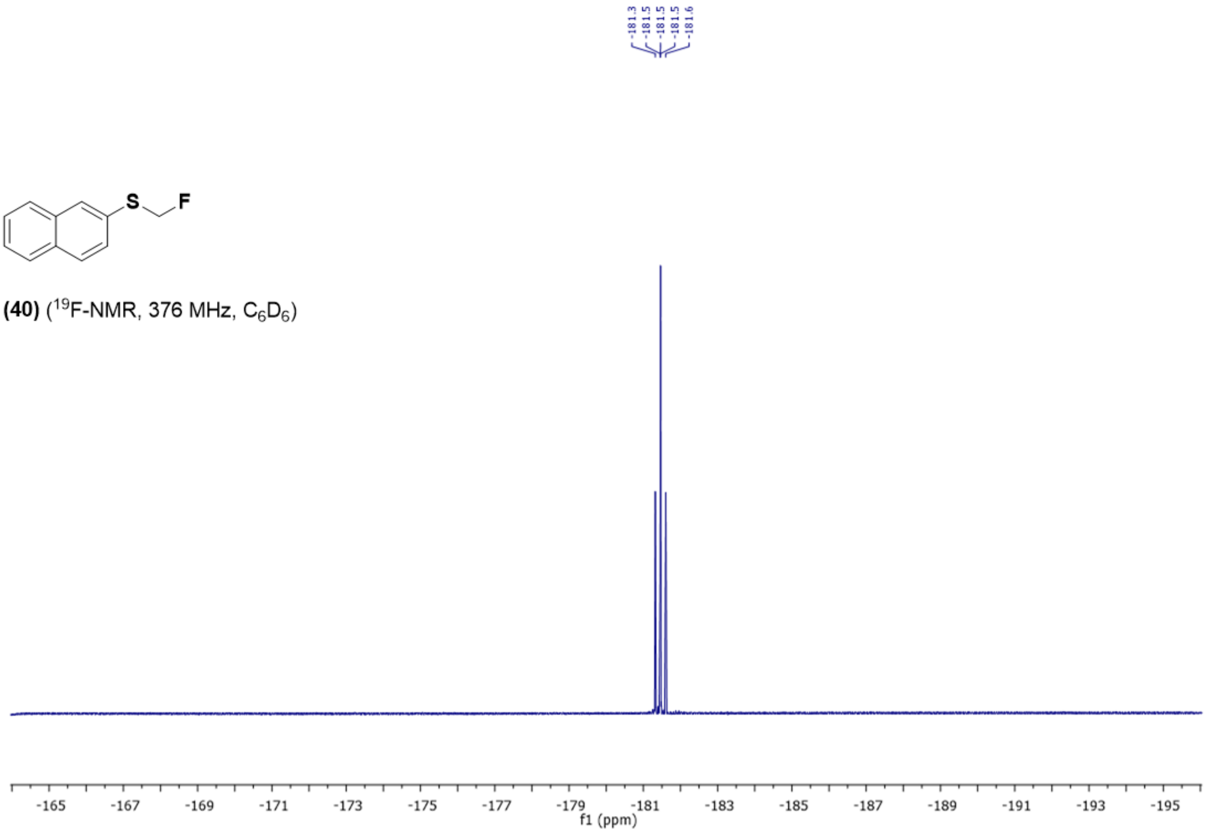


(38) (^{19}F-NMR, 376 MHz, C_6D_6)

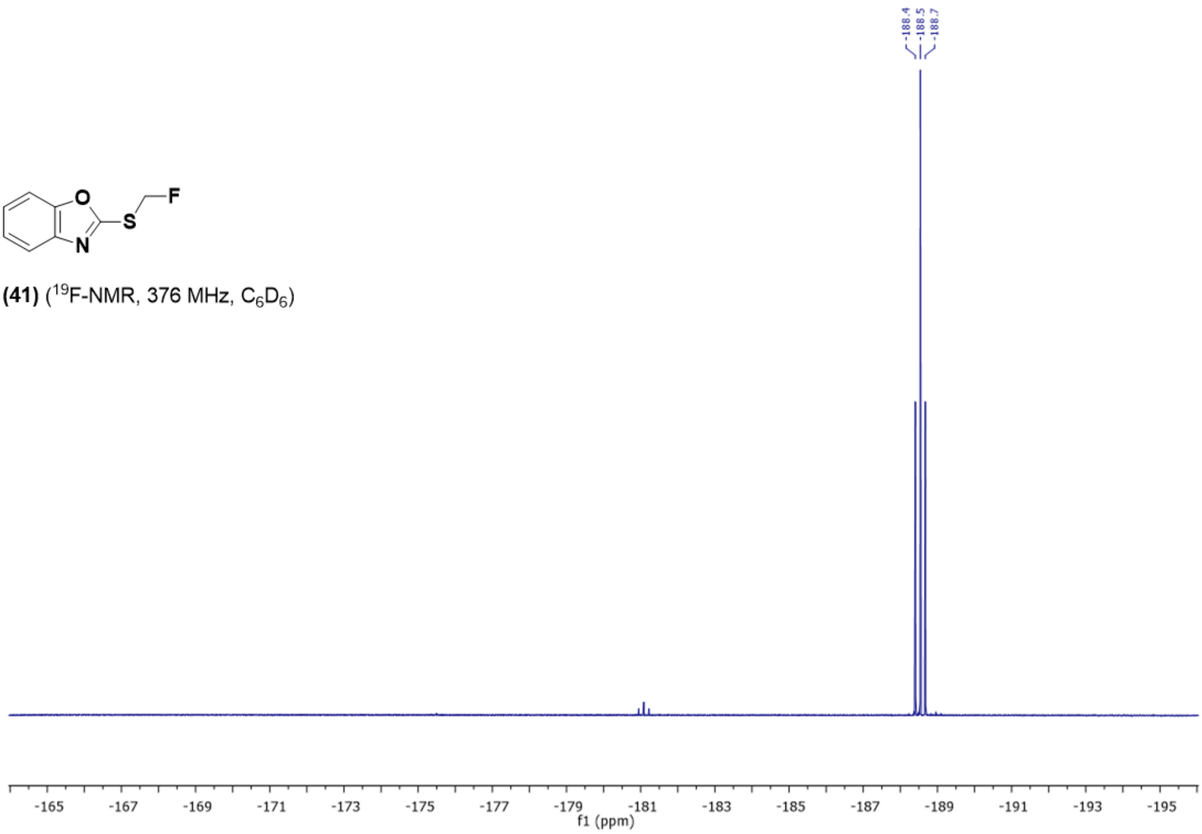


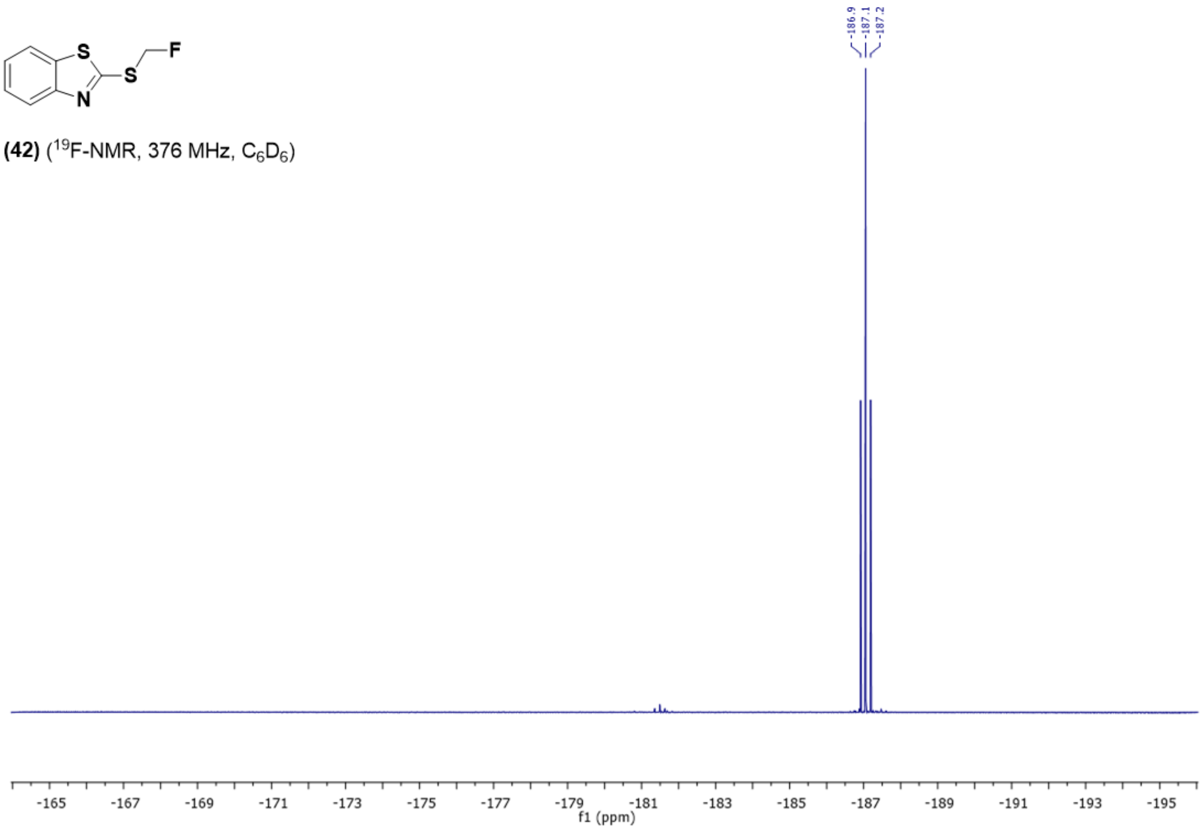
(39) (^{19}F-NMR, 376 MHz, C_6D_6)

(40) (^{19}F-NMR, 376 MHz, C_6D_6)

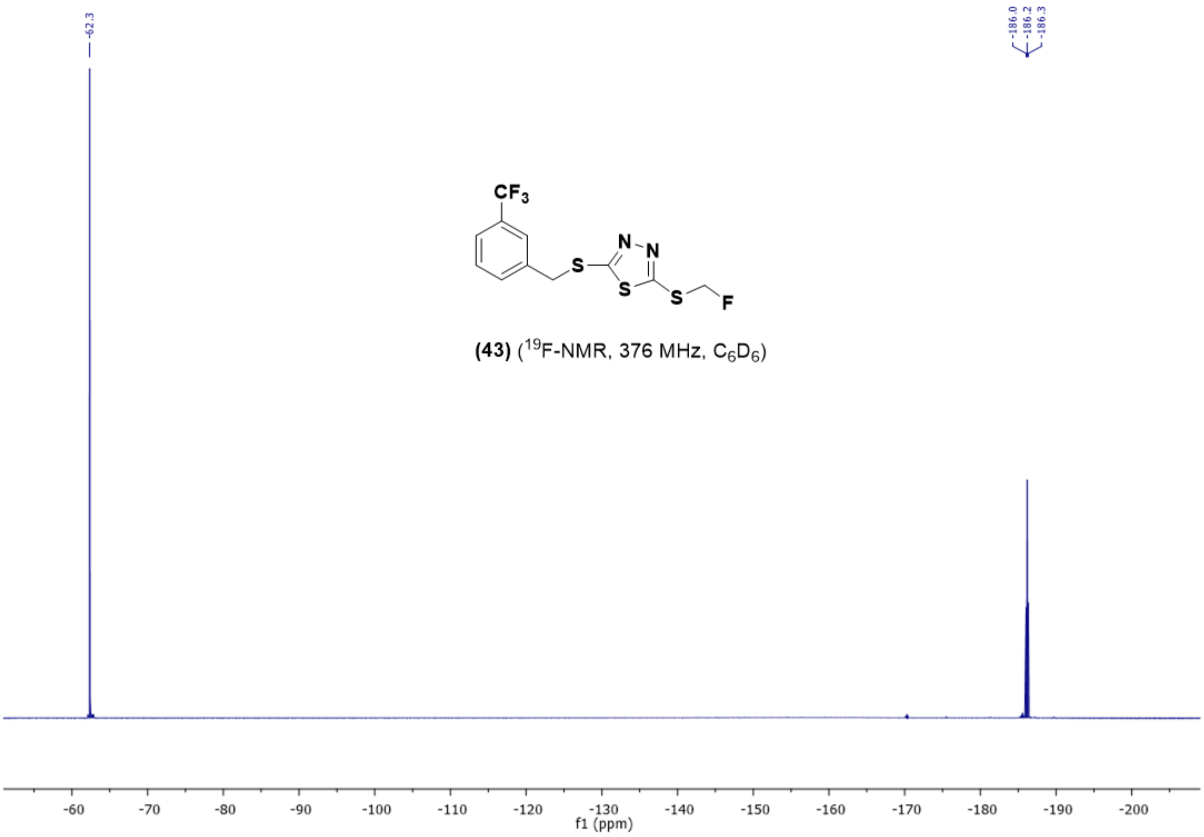


(41) (^{19}F-NMR, 376 MHz, C_6D_6)



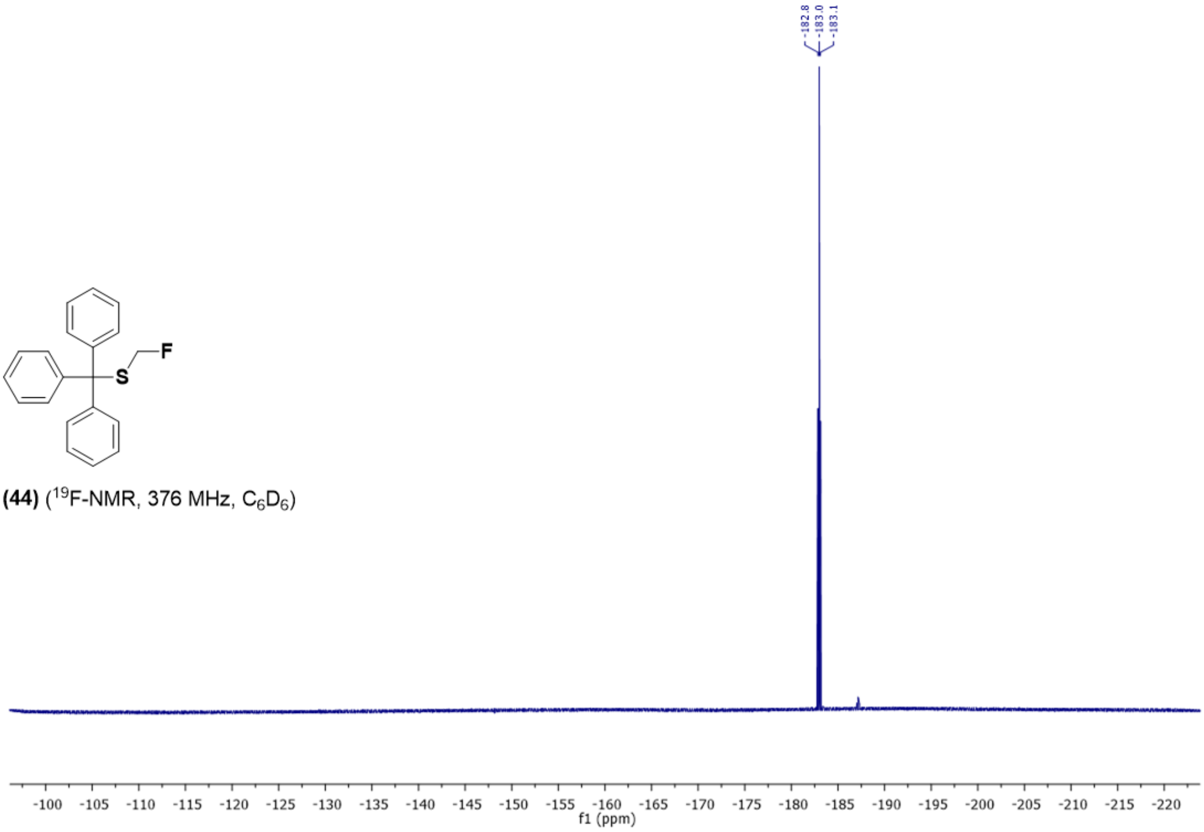


(42) (^{19}F-NMR, 376 MHz, C_6D_6)

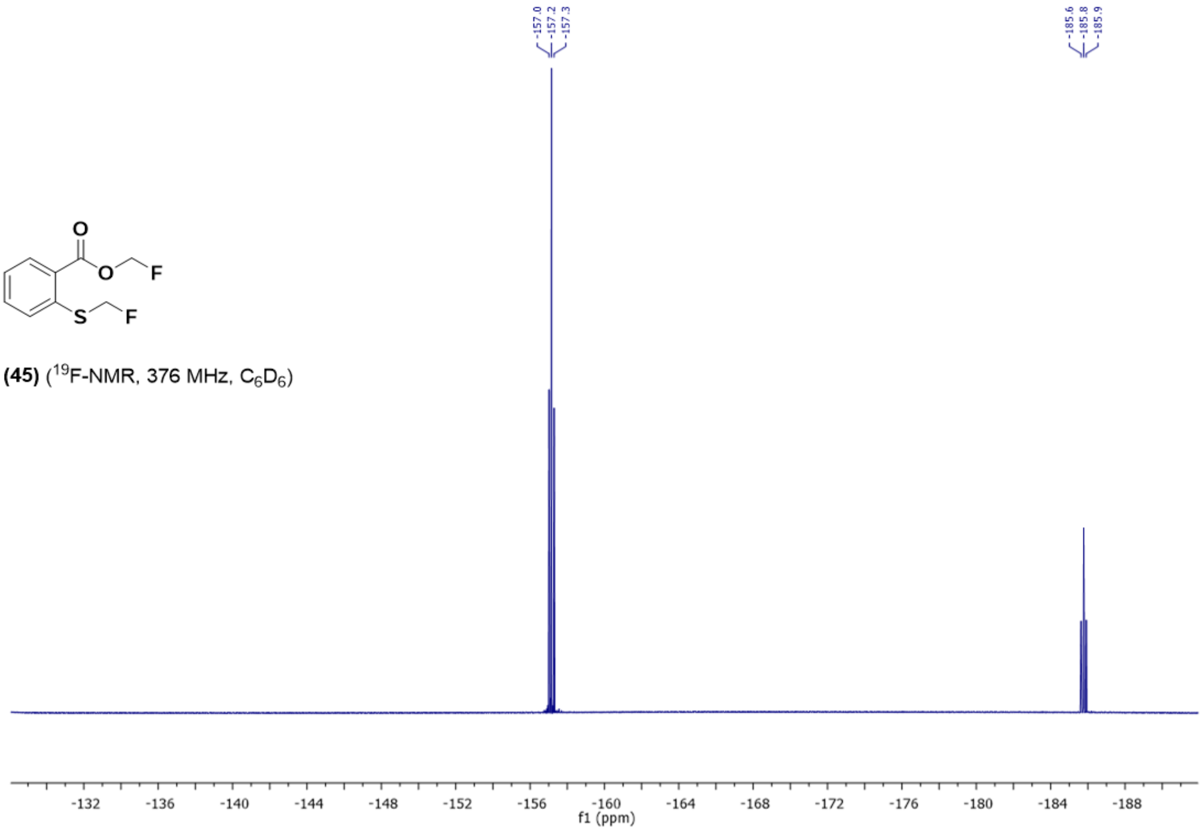


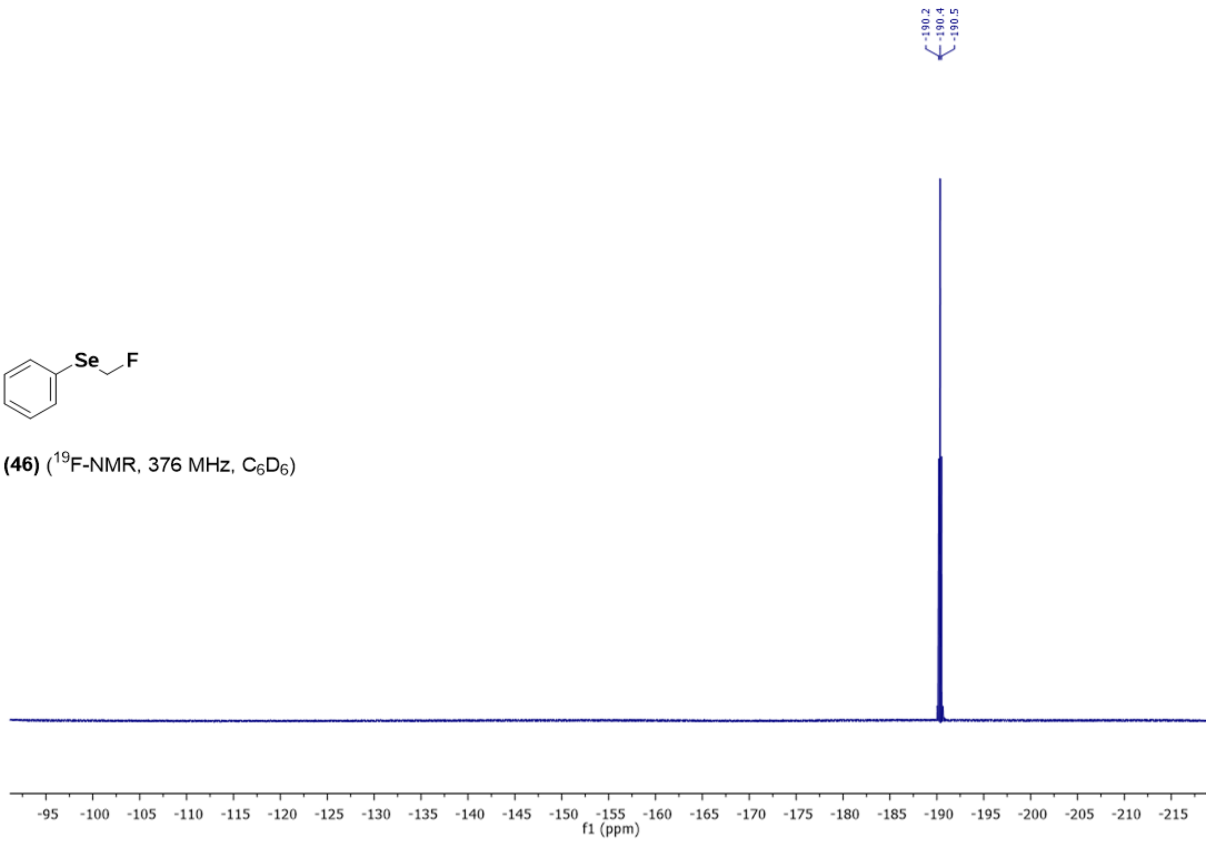
(43) (^{19}F-NMR, 376 MHz, C_6D_6)

(44) (^{19}F-NMR, 376 MHz, C_6D_6)

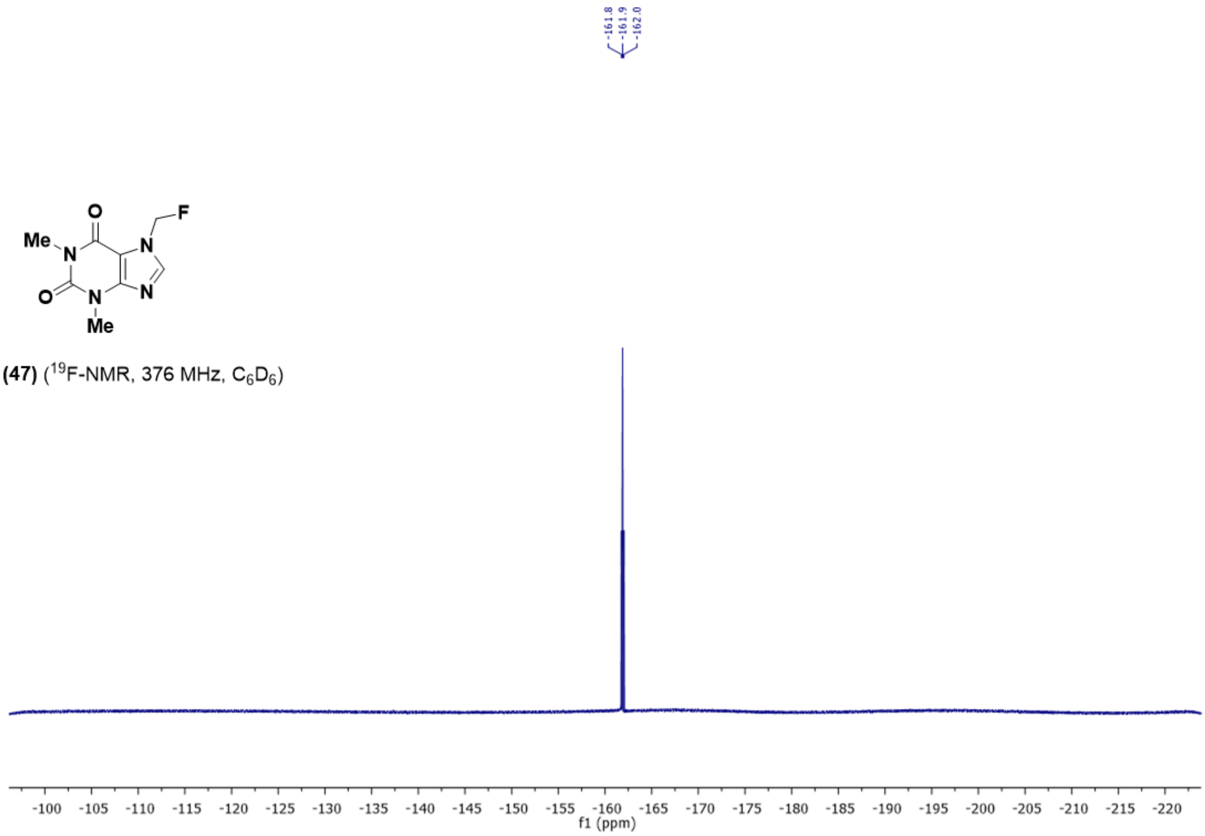


(45) (^{19}F-NMR, 376 MHz, C_6D_6)

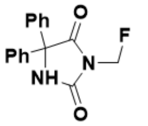




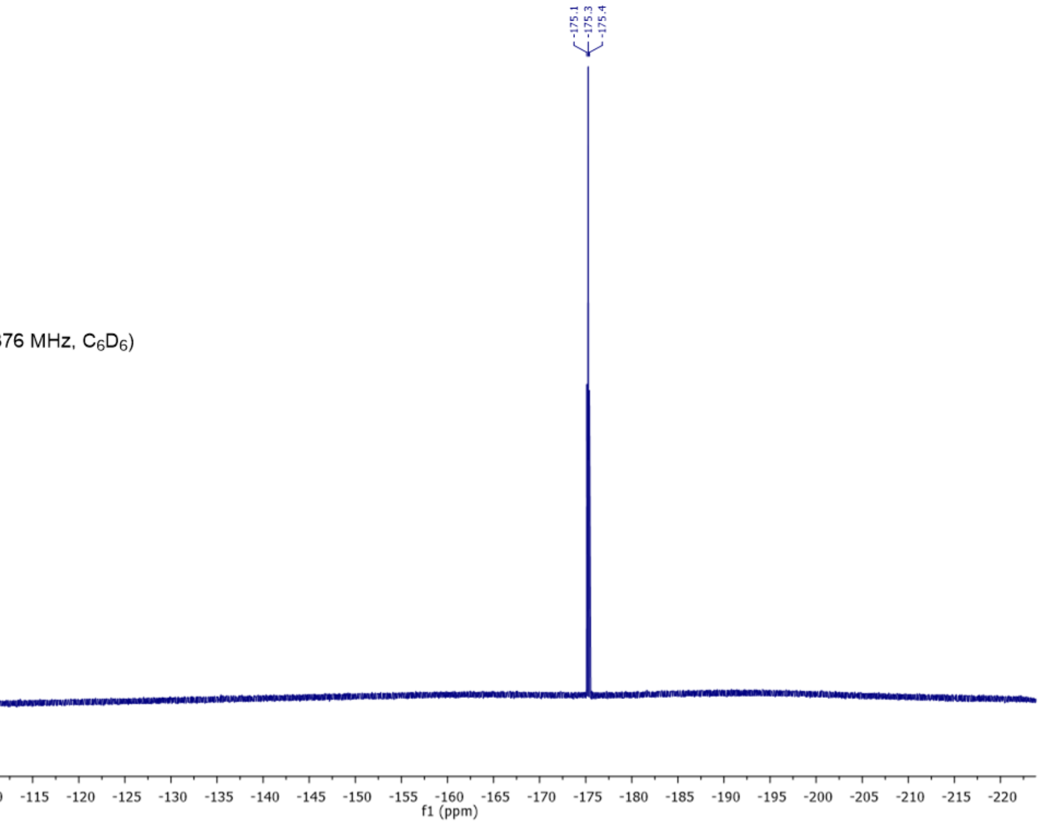
(46) (^{19}F-NMR, 376 MHz, C_6D_6)

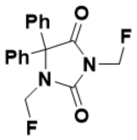


(47) (^{19}F-NMR, 376 MHz, C_6D_6)

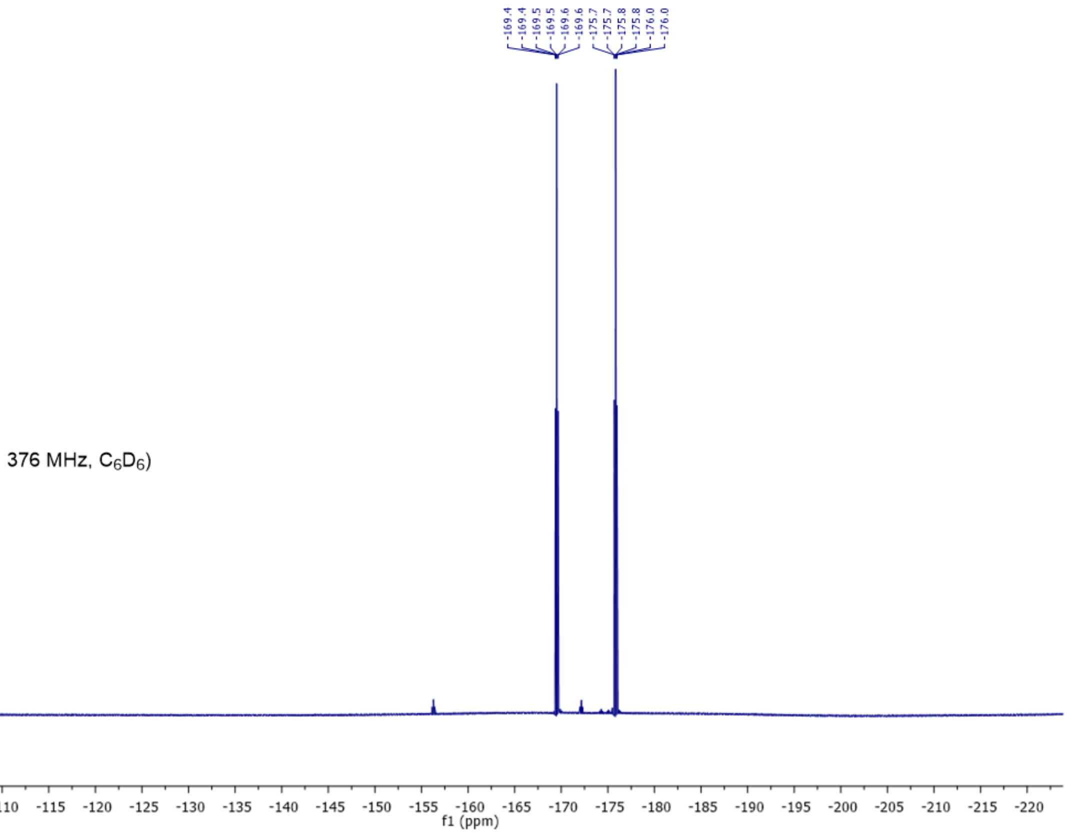


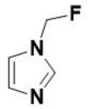
(49) (^{19}F-NMR, 376 MHz, C_6D_6)



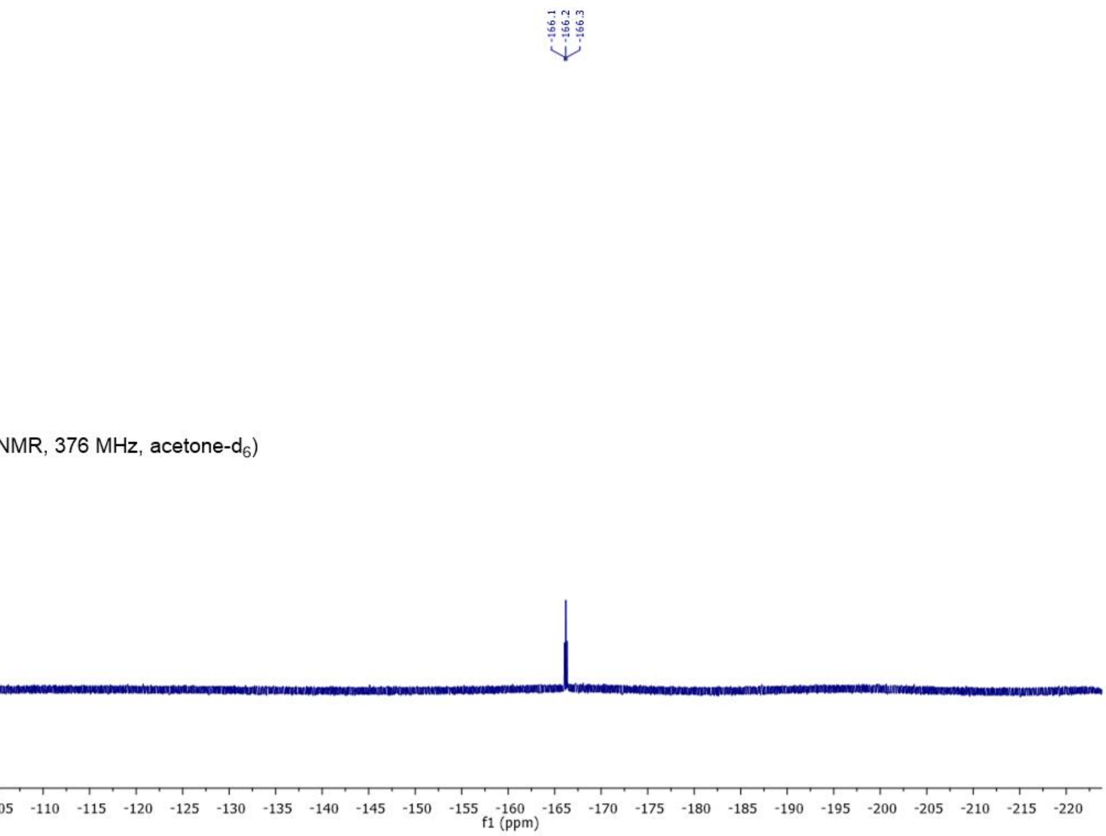


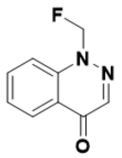
(50) (^{19}F-NMR, 376 MHz, C_6D_6)



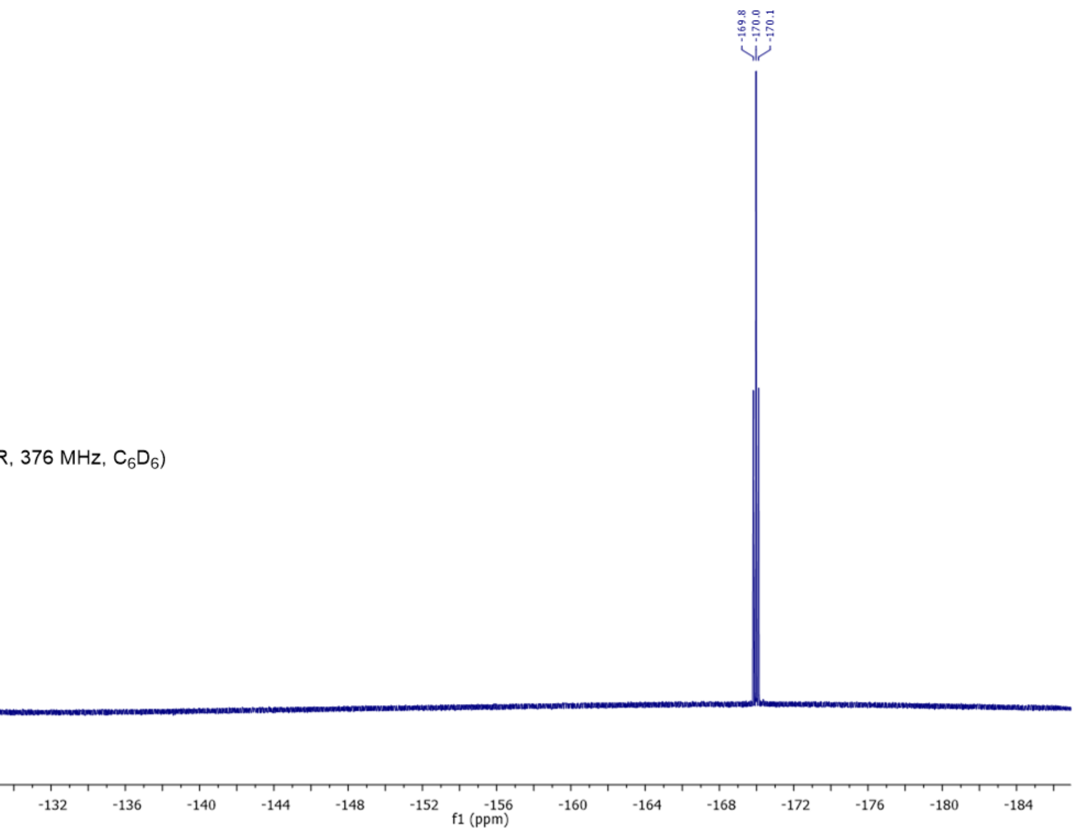


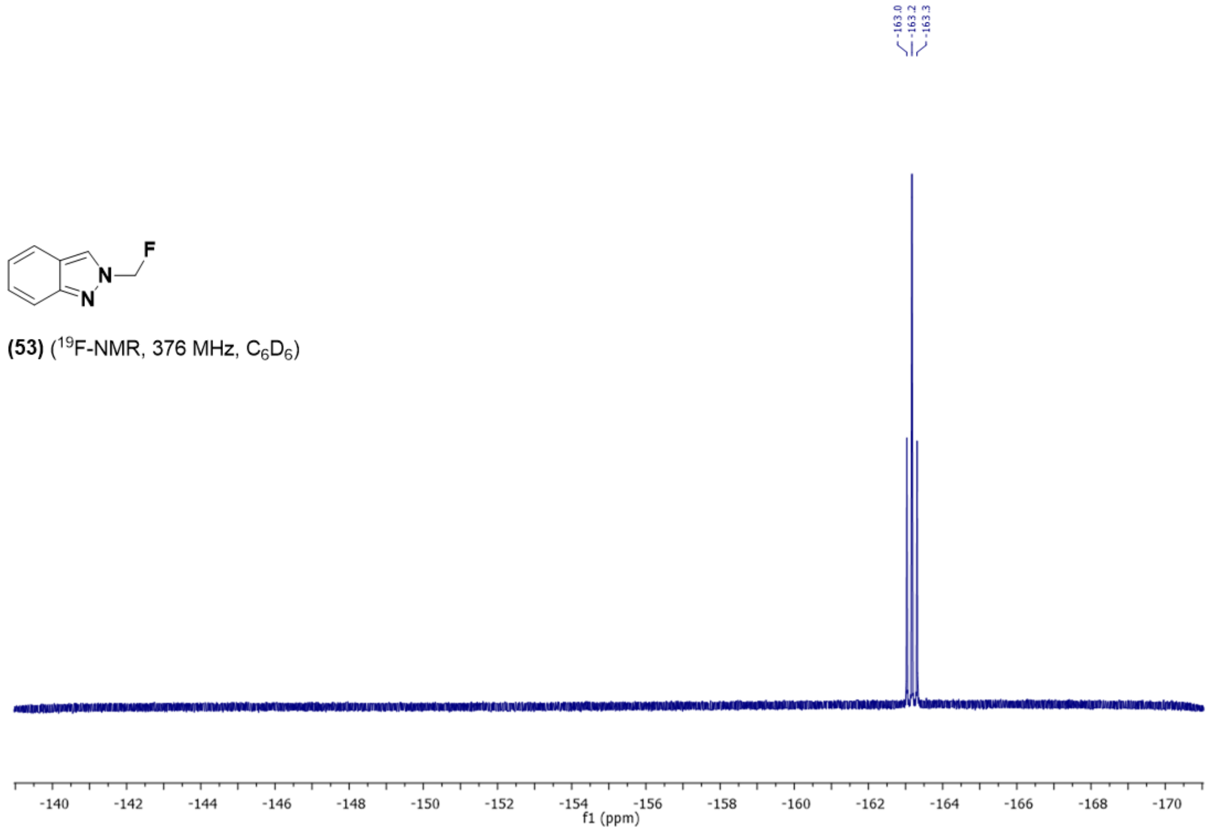
(51) (^{19}F-NMR, 376 MHz, acetone-d_6)



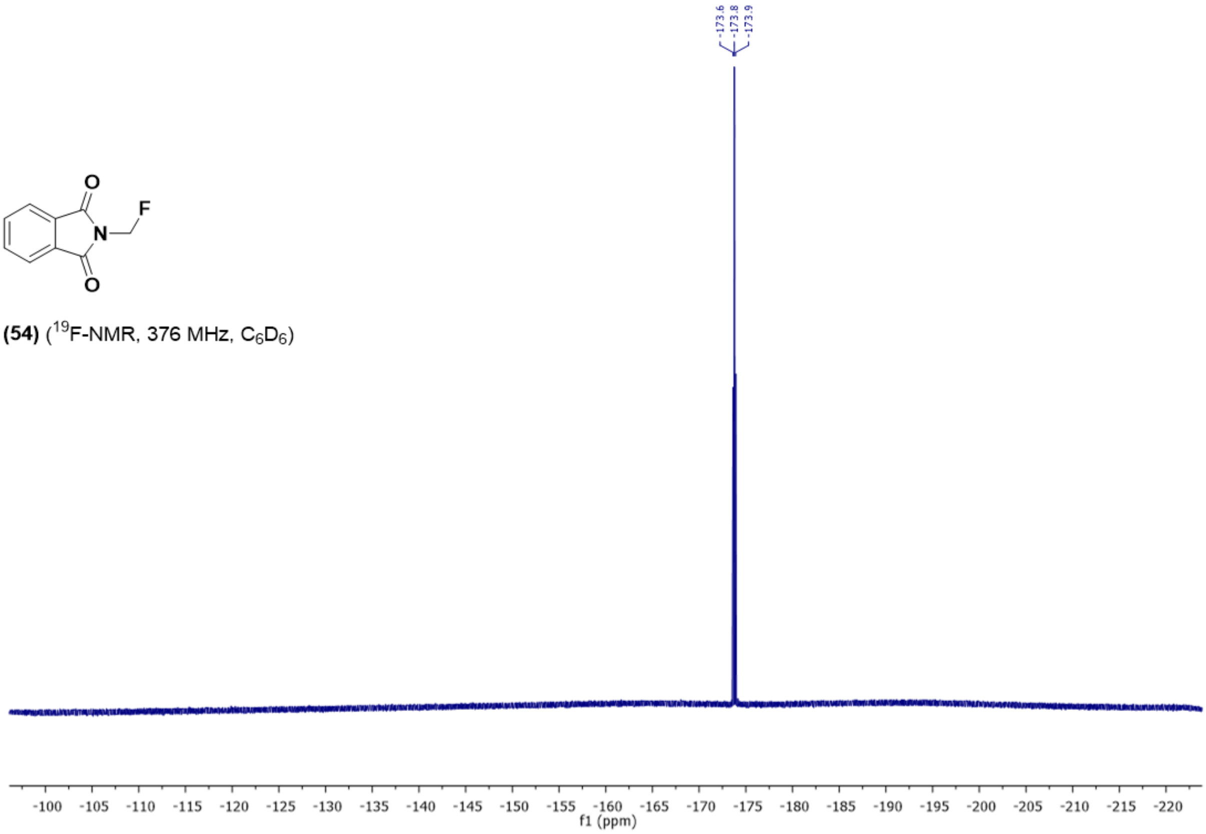


(52) (^{19}F-NMR, 376 MHz, C_6D_6)

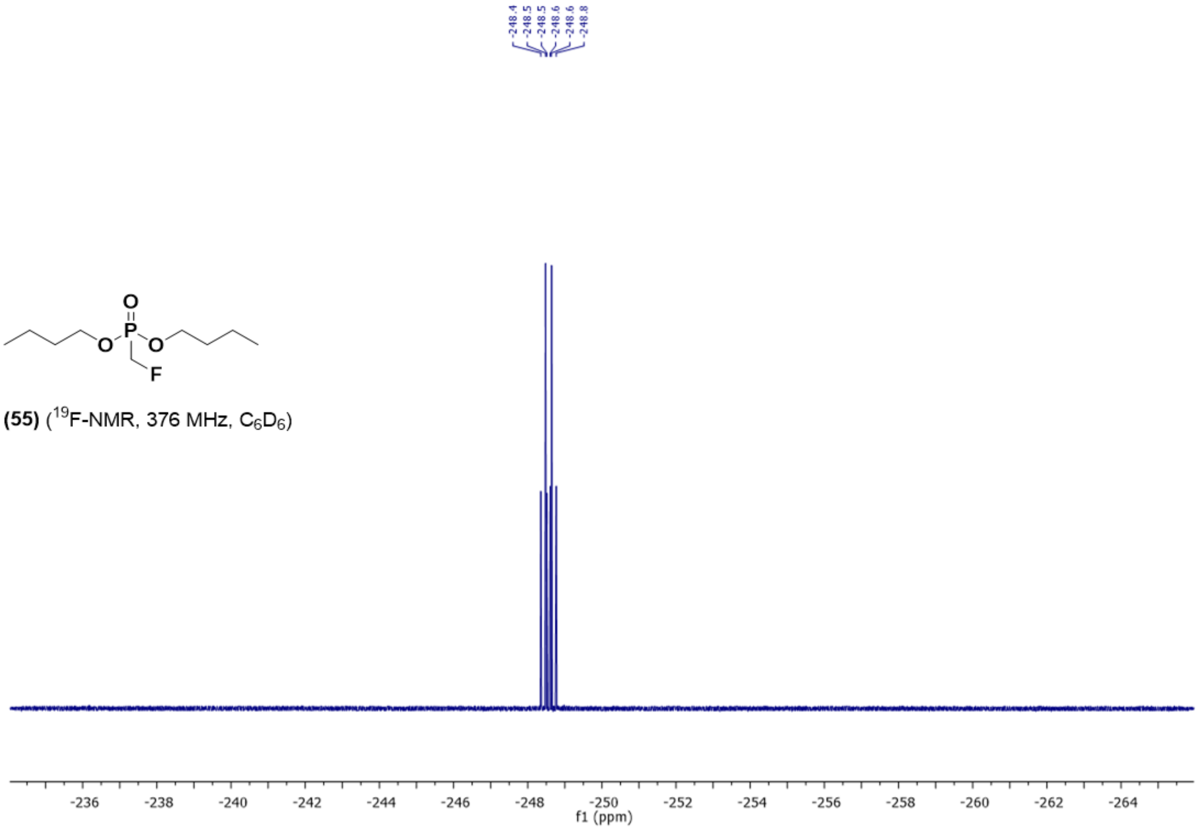




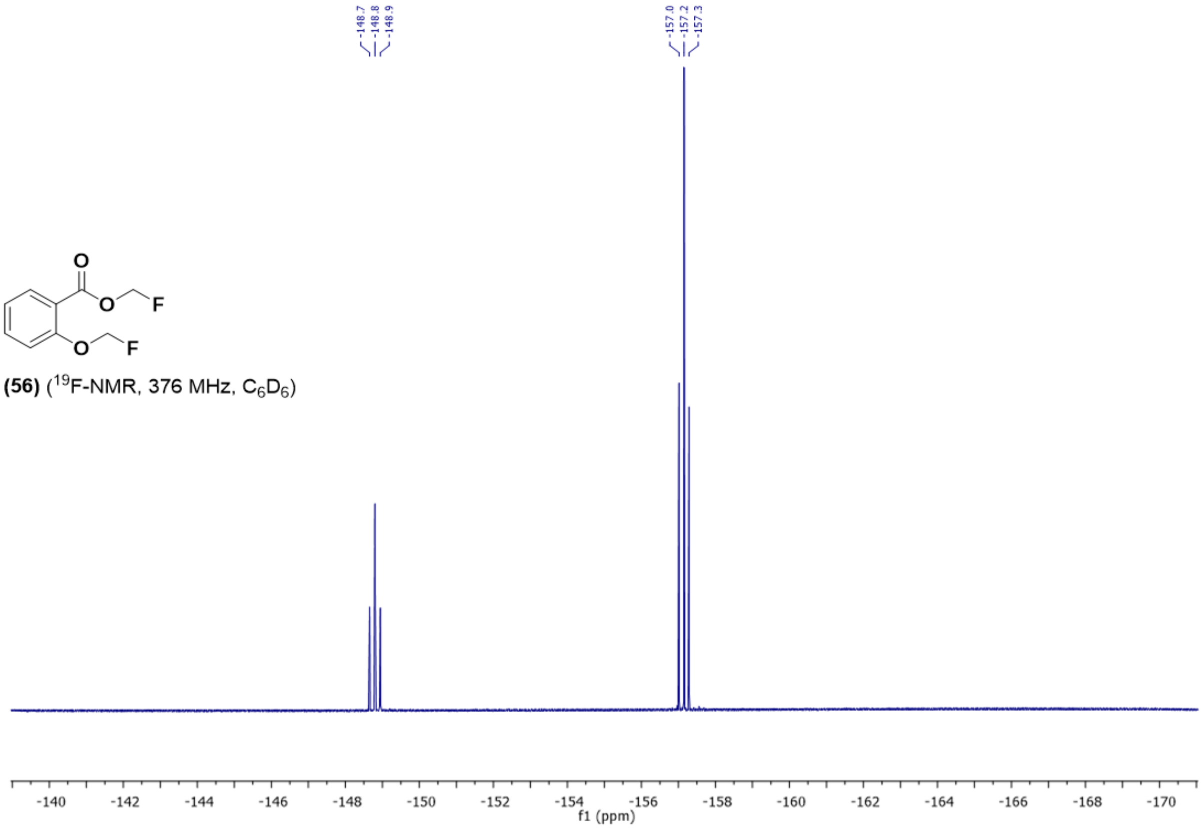
(53) (^{19}F-NMR, 376 MHz, C_6D_6)



(54) (^{19}F-NMR, 376 MHz, C_6D_6)



(55) (^{19}F-NMR, 376 MHz, C_6D_6)



(56) (^{19}F-NMR, 376 MHz, C_6D_6)

Zusammenfassung

Die vorliegende Masterarbeit zeigt die erfolgreiche Anwendung von Fluoriodmethan in einer Einstufensynthese zwecks Fluormethylierung von O-, S-, N-, P-, und Se-Nukleophilen. Die einfache Handhabung sowie der flüssige Aggregatzustand (Kp 52 °C) ermöglichen eine direkte nukleophile Substitution unter milden basischen Bedingungen. Der Erfolg dieser Methode wird an 56 Beispielen einschließlich von zugelassenen Arzneistoffen umfassend demonstriert.

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