Supplementary Information

Copper-catalysed benzylic C–H coupling with alcohols via radical relay enabled by redox buffering

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Table of Content

I. General Considerations

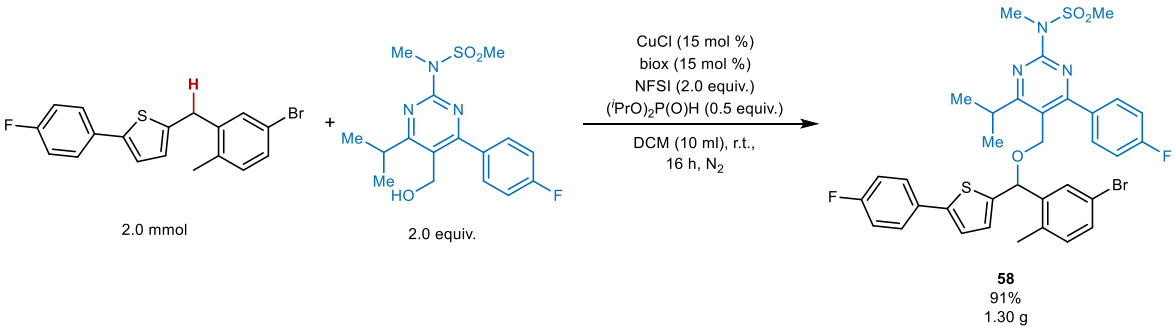
All reagents were purchased and used as received unless otherwise noted. Cu salts were purchased from Aldrich. Benzylic C–H substrates were purchased from Oakwood Chemicals, Combi-Blocks, Chem-Impex, Alfa Aesar, TCI America, Ark Pharm, Enamine, AstaTech or Aldrich. With the exception of ligand L8 (cf. Supplementary Table 3a), which was prepared by a literature protocol [1], ligands were purchased from Aldrich or TCI America. N-Fluorobenzenesulfonimide (NFSI) was purchased from Combi-Blocks and Ark Pharm. Methanol was purchased from Aldrich and Macron Fine Chemicals. Dialkyl phosphites were purchased from Aldrich, TCI America, Alfa Aesar and Oakwood Chemicals.

^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 MHz or Bruker 500 MHz spectrometers and chemical shifts are reported in parts per million (ppm). ^{1}H NMR spectra were referenced to tetramethylsilane at 0.00 ppm and ^{13}C NMR spectra were referenced to $CDCl_3$ at 77.16 ppm. Chromatography was performed using either a Combi-flash® with reusable 24 g or 12 g Combi-flash gold® cartridges, or a Biotage Isolera One® with reusable 25 g SNAP Ultra® cartridges or standard silica cartridges unless otherwise noted. Enantiomeric separation was conducted with supercritical fluid chromatography (SFC, Waters ACQUITY UPC) or chiral HPLC (Waters Alliance). UV-Vis experiments were performed with a Cary 60 UV-Vis Spectrophotometer from Agilent in quartz cuvettes. Electron paramagnetic resonance (EPR) spectra were acquired on a Bruker ELEXSYS E500 EPR spectrometer. High-resolution mass spectra were obtained using a Thermo Q Exactive™ Plus (ESI or ASAP-MS) by the mass spectrometry facility at the University of Wisconsin (funded by NIH grant: 1S10OD020022-1).

Note that the reported benzylic C–H etherification reactions involve generation of $(RO)_2P(O)F$ and/or HF, which are hazardous and have safety concerns. Appropriate standard operation procedures should be followed when handling these reactions.

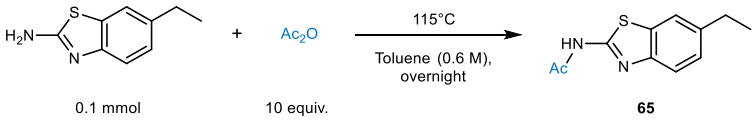
II. Experimental Procedures for Preparations of Compounds

Procedure for the gram scale experiment.



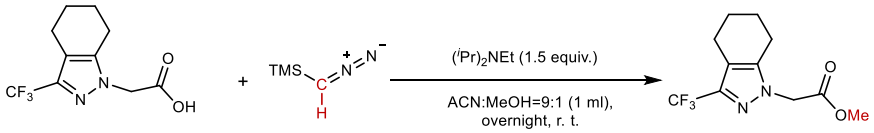
Copper(I) chloride (15 mg, 0.30 mmol), 4,4',5,5'-tetrahydro-2,2'-bioxazole (42 mg, 0.30 mmol), 4-(4-Fluorophenyl)-6-isopropyl-2-[(N-methyl-N-methylsufonyl)amino]pyrimidine-5-yl-methanol (1414 mg, 4.0 mmol), 2-(5-Bromo-2-methylbenzyl)-5-(4-fluorophenyl]thiophene (723 mg, 2.0 mmol) and NFSI (1261 mg, 4.0 mmol) were added under air to a 24 mL vial containing a magnetic stir bar. Then the vial was capped with a pierceable Teflon cap. A needle was pierced through the cap and kept in the cap to facilitate the exchange of the vial headspace with the atmosphere. The vial was transferred to a glove box, through three vacuum-nitrogen-backfill cycles. The needle was removed. Dichloromethane (10 mL) and diisopropyl phosphite (163 µL, 1.0 mmol) were added into the vial. The vial was capped, taken out of the glove box and stirred at room temperature for 16 h. When the reaction finished, triethylamine (1.4 mL, 10 mmol) was added. Then the mixture was evaporated under vacuum and the crude mixture was purified by flash chromatography (silica gel, eluted by pentane/ethyl acetate = 9:1). 1.30 g (91%) of pale-yellow liquid was obtained.

Procedure for the preparation of the substrate 65.



The synthetic protocol for the preparation of **59** was adapted from a literature procedure[2]. 6-ethyl-1,3-benzothiazol-2-amine (446 mg, 2.5 mmol) was weighed into 15 mL glass vial containing a Teflon coated magnetic stir bar. Toluene (15 ml) and acetic anhydride (94.5 µL, 10.0 equiv.) were added into the flask in sequence. The vial was then capped with a pierceable Teflon cap and the reaction mixture was stirred at 115 °C overnight. The reaction was concentrated under vacuum and the residue was triturated with 5 mL of ethyl acetate and 50 mL of pentane. The product was filtered out and dried. Trituration and filtration were repeated three times and 473 mg off-white non-crystalline powder (86% isolated yield) of **59** (the substrate of **27**) was collected.

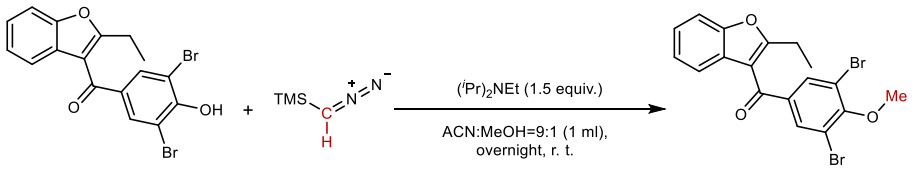
Procedure for the preparation of the substrate 66.



1.0 equiv. 1.5 equiv. **66**

The synthetic protocol for the preparation of **62** was adapted from a literature procedure[3]. 2-[3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]acetic acid (298 mg, 1.2 mmol) was weighed into 15 mL vial containing a Teflon coated magnetic stir bar. A mixture of acetonitrile and MeOH (9:1, 4.8 mL), followed diisopropylethylamine (0.43 mL, 1.5 equiv.) were added into the vial and the mixture was stirred for 10 min, at which time trimethylsilyldizaomethane (2.0 M Hexane solution, 0.9 mL, 1.5 equiv.) was added dropwise into the reaction mixture. When no obvious bubbling was observed, the vial was capped with a pierceable Teflon cap and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and the residue was purified by column chromatography (pentane:ethyl acetate = 4:1). 255 mg white non-crystalline powder (82% isolated yield) of **60** (the substrate of **28**) was collected.

Procedure for the preparation of the substrate 67.

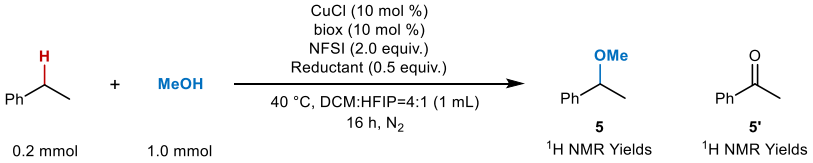


1.0 equiv. 1.5 equiv. **67**

The synthetic protocol for the preparation of **61** was adapted from a literature procedure[3]. Benzbromarone (1.70 g, 4.0 mmol) was weighed into a 50 mL round bottom flask containing a Teflon coated magnetic stir bar. A mixture of acetonitrile and MeOH (9:1, 16 mL), followed diisopropylethylamine (1.44 mL, 1.5 equiv.) was added into the flask and the mixture was stirred for 10 min, at which time trimethylsilyldizaomethane (2.0 M Hexane solution, 3 mL, 1.5 equiv.) was added dropwise into the reaction mixture. A funnel was placed upside down on top of the flask to minimize the evaporation of the solvent and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and the residue was purified by column chromatography (pentane:ethyl acetate = 4:1). 1.67 g white non-crystalline powder (95% isolated yield) of **61** (the substrate of **34**) was collected.

III. Optimization of the Reaction Conditions

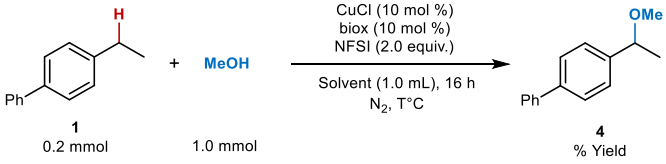
Supplementary Table 1. Investigation of various reductants with ethylbenzene as the substrate



Entry	Reductant	Conv. of EtPh (%)	Yield of **3** (%)
1	**$(MeO)_2P(O)H$**	**97**	**80**
2	$(EtO)_2P(O)H$	91	77
3	$(^iPrO)_2P(O)H$	88	73
4	$(^tBuO)_2P(O)H$	34	28
5	$(^nBuO)_2P(O)H$	94	75
6	$(MeO)_2MeSiH$	79	70
7	$(EtO)_2MeSiH$	100	62
8	PhNHNHPh	7	0
9	$EtCO_2NHNHCO_2Et$	94	62
10	$P(^nBu)_3$	37	22
11	Sodium Ascorbate	100	62

[a]Reaction yields monitored by ^1H NMR spectroscopy with 0.2 mmol mesitylene as the external standard. Conv., conversion.

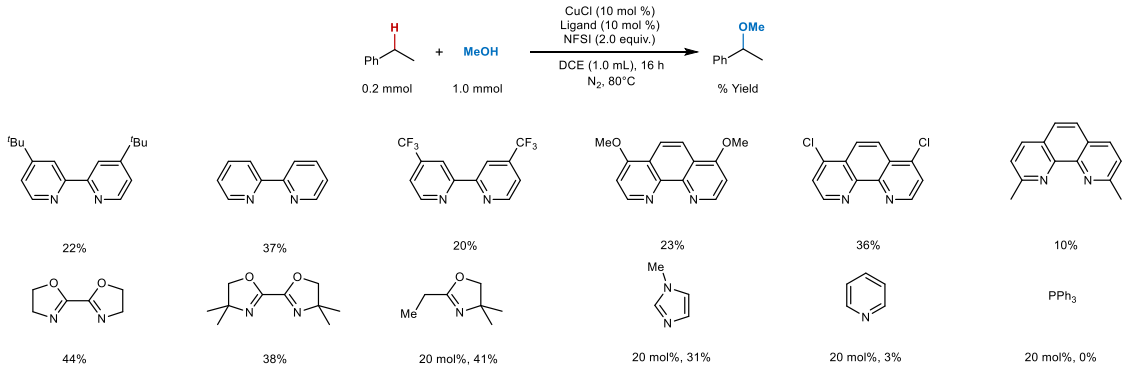
Supplementary Table 2. Investigation of dimethylphosphite with 4-ethylbiphenyl as the substrate



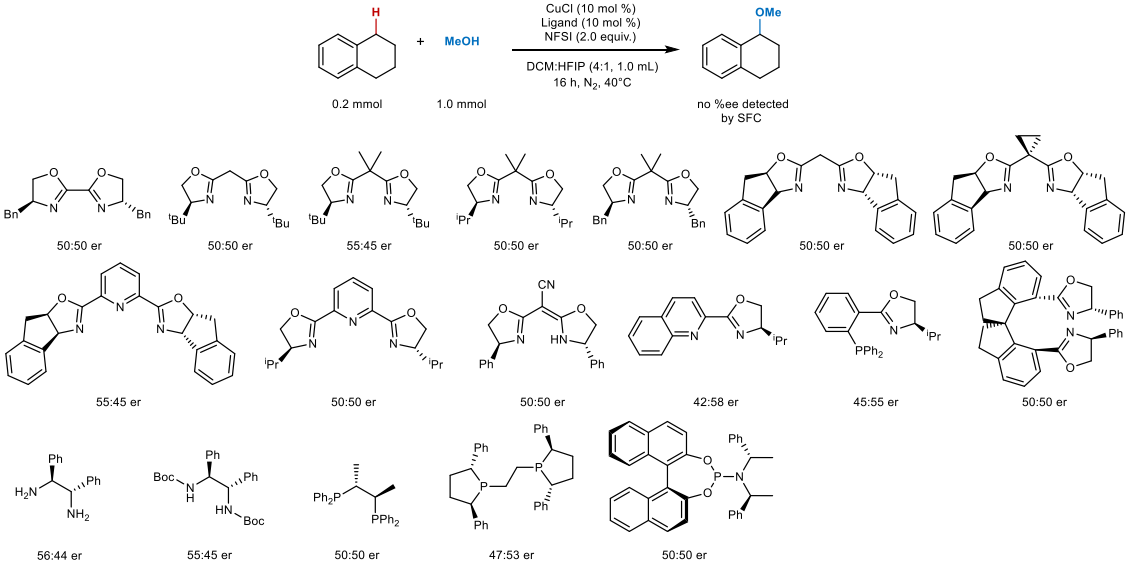
Entry	Additive (0.5 equiv.)	Solvent	T (°C)	Conv. of EtPh (%)	Yield (%)[a]
1	–	Benzene	r. t.	5	4
2	–	DCM	r. t.	9	9
3	$(MeO)_2POH$	DCM	r. t.	88	57
4	–	DCM	40	52	26
5	$(MeO)_2POH$	DCM	40	100	70
6	–	DCM : HFIP = 4 : 1	r. t.	4	5
7	$(MeO)_2POH$	DCM : HFIP = 4 : 1	r. t.	49	45
8	–	DCM : HFIP = 4 : 1	40	25	23
9	$(MeO)_2POH$	DCM : HFIP = 4 : 1	40	85	77

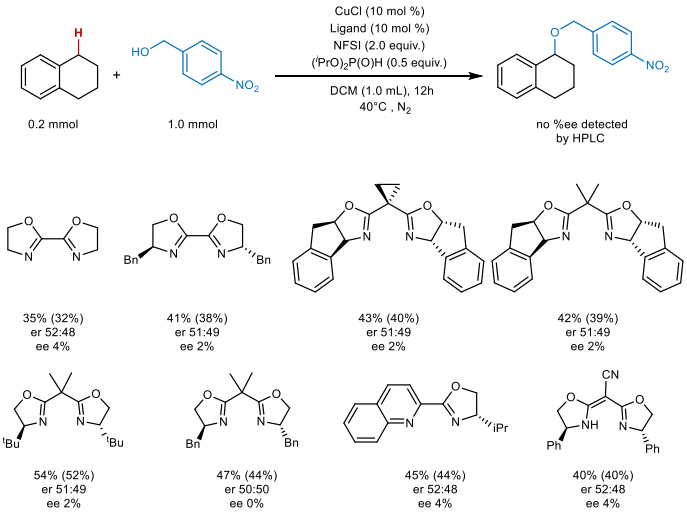
[a]Reaction yields monitored by ^1H NMR spectroscopy with 0.2 mmol mesitylene as the external standard. T, temperature; Conv., conversion.

Supplementary Table 3a. Ligand Optimization

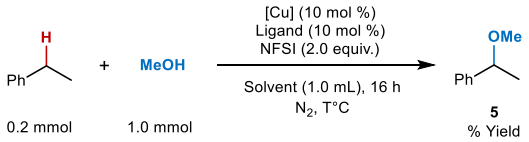


Supplementary Table 3b. Unsuccessful Ligand Testing for Enantioselective Methoxylation





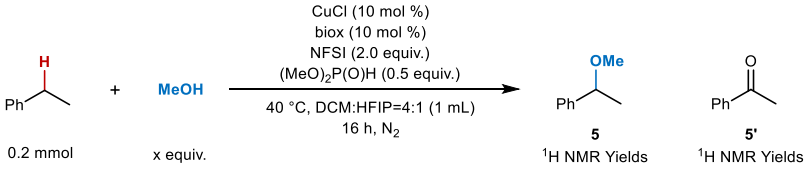
Supplementary Table 4a. Optimization of the Reaction Conditions with Various Solvents, Cu Salts and Temperature



Entry	Cu Source	Solvent	T (°C)	Conv. of EtPh (%)	Yield of **5** (%)[a]
1	CuCl	DCE	80	56	44
2	CuBr	DCE	80	64	41
3	$CuCl_2$	DCE	80	59	42
4	$[Cu(MeCN)_4]BF_4$	DCE	80	69	40
5	CuCl	DMC	80	56	33
6	CuCl	Benzene	80	59	35
7	CuCl	EtOAc	80	30	17
8	CuCl	DCM	80	67	49
9	CuCl	MeOH	80	16	16
10	CuCl	HFIP	80	85	2
11	CuCl	DCM:HFIP=4:1	40	81	72
12	CuCl	DCM	40	23	23
13[b]	**CuCl**	**DCM:HFIP=4:1**	**40**	**97**	**80**

[a]Reaction yields monitored by ^{1}H NMR spectroscopy with 0.2 mmol mesitylene as the external standard. [b]50 mol % of $(MeO)_2P(O)H$ was added. DCE, 1,2-dichloroethane; DMC, dimethyl carbonate; DCM, dichloromethane; HFIP, hexafluoroisopropanol; T, temperature; Conv., conversion.

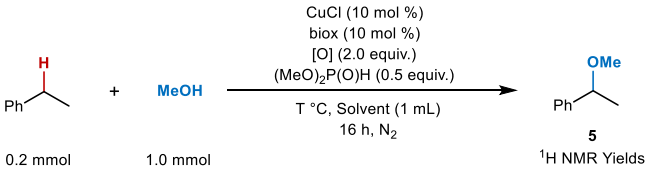
Supplementary Table 4b. Control Experiments with Various Amounts of Methanol



Entry	Equivalents (X)	Conv. of EtPh (%)	Yield of **5'** (%)	Yield of **5** (%)[a]
1	5.0	100	5	80
2	3.0	94	4	68
3	2.0	79	3	60
4	1.0	100	22	43

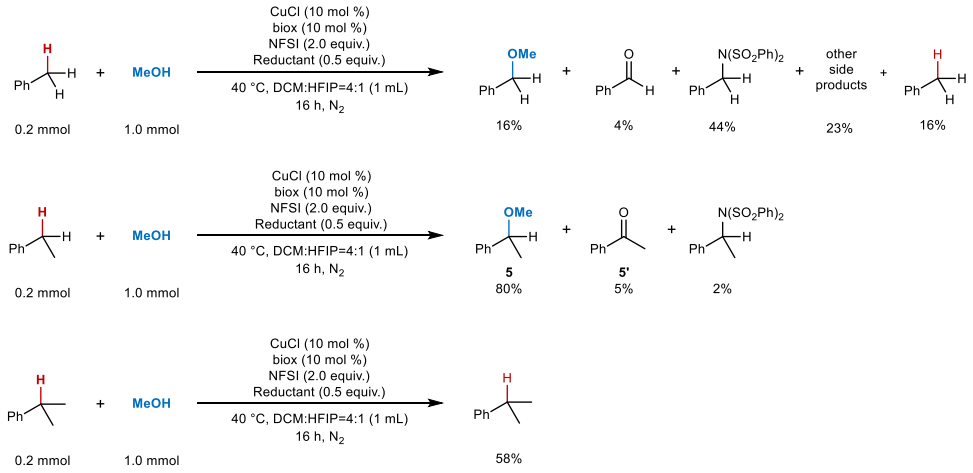
[a]Reaction yields monitored by ^{1}H NMR spectroscopy with 0.2 mmol mesitylene as the external standard. Conv., conversion.

Supplementary Table 5. Investigation of various radical initiators/oxidants



Entry	[O]	Solvent	Temperature (°C)	Conv. of EtPh (%)	Yield of **5** (%)[a]
1	NFSI	DCM:HFIP = 4:1	40	97	80
2	^{t}BuOO^{t}Bu	DCM:HFIP = 4:1	40	0	0
3	^{t}BuOOH	DCM:HFIP = 4:1	40	30	0
4	^{t}BuOOBz	DCM:HFIP = 4:1	40	15	5
5	BzOOBz	DCM:HFIP = 4:1	40	14	7
6	$K_2S_2O_8$	DCM:HFIP = 4:1	40	7	2
7	Oxone	DCM:HFIP = 4:1	40	0	0
8	$PhI(OAc)_2$	DCM:HFIP = 4:1	40	12	5
9	$PhI(OTFA)_2$	DCM:HFIP = 4:1	40	24	3
10	Selectfluor	DCM:HFIP = 4:1	40	23	11
11	NFSI	DCE	80	56	44
12	^{t}BuOO^{t}Bu	DCE	80	1	1
13	^{t}BuOOH	DCE	80	37	0
14	^{t}BuOOBz	DCE	80	16	0
15	BzOOBz	DCE	80	27	4
16	$K_2S_2O_8$	DCE	80	5	0
17	Oxone	DCE	80	6	1
18	$PhI(OAc)_2$	DCE	80	32	2
19	$PhI(OTFA)_2$	DCE	80	31	5
20	Selectfluor	DCE	80	3	0

[a]Reaction yields monitored by ^{1}H NMR spectroscopy with 0.2 mmol mesitylene as the external standard. Conv. conversion.



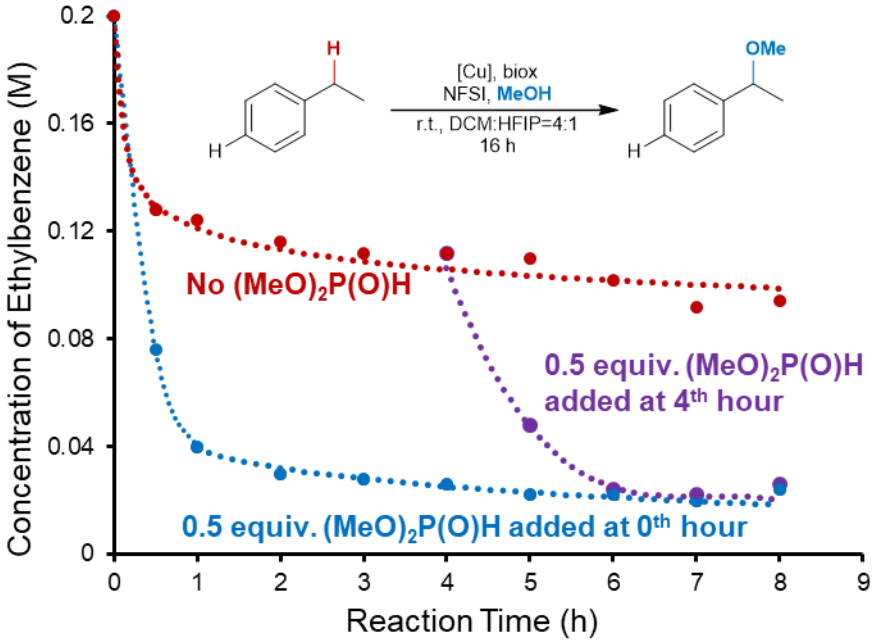
Supplementary Fig. 1 Investigation of the reactivities and chemo-selectivity of primary, secondary and tertiary benzylic C–H substrate

Reaction yields were determined by ^{1}H NMR spectroscopy with 0.2 mmol mesitylene as the external standard. Toluene shows good reactivity, but poor selectivity. The major product is the coupling product of toluene and $(PhSO_2)_2N$ fragment from NFSI, while several other side products were observed. Ethylbenzene shows good reactivity and selectivity. Cumene is much less reactive and the conversion is much lower comparing to toluene and ethylbenzene.

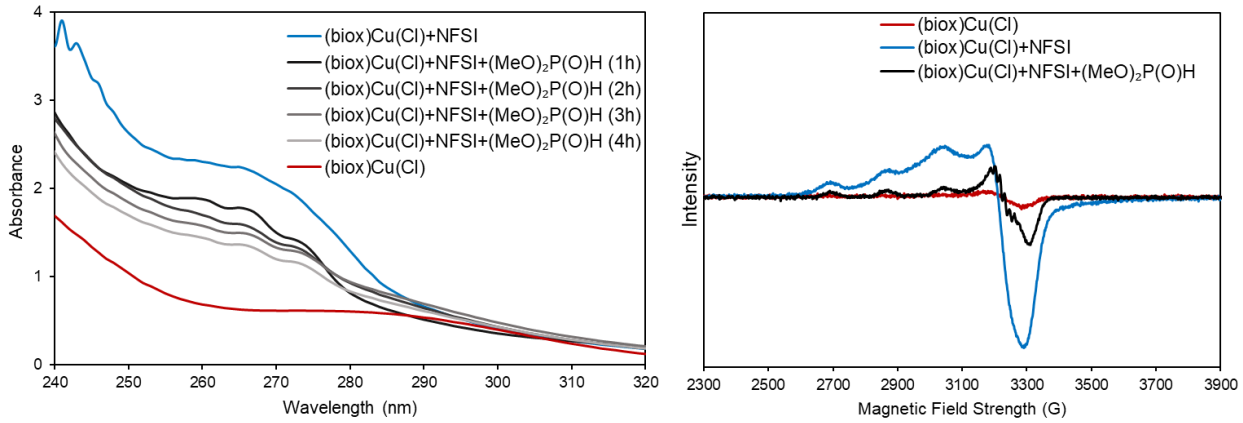
IV. Effects of Phosphite (Time course experiments, UV-Vis and EPR)

The data in Supplementary Tables 1, 2, and 4a show that phosphite can have a beneficial effect on the reaction yield; however, the magnitude of the effect appears to be substrate dependent. A moderate improvement in yield was observed with ethylbenzene (cf. Supplementary Table 4a, entries 11 and 13), while a significant improvement was observed upon adding phosphite to the reaction of 4-ethylbiphenyl (e.g., entries 8 and 9, Supplementary Table 2). In spite of the relatively modest yield improvement with ethylbenzene in the 16 h reaction, monitoring of the reaction time course clearly shows the beneficial effect of added phosphite (Supplementary Fig. 2).

To further corroborate our "redox buffering" hypothesis, we performed a series of UV-Vis and EPR experiments to investigate the copper speciation under catalysis-relevant conditions (Fig. 3). When NFSI is added to a (biox)Cu(Cl) solution, a characteristic absorption at 270 nm was observed in the UV-Vis trace (red trace, Supplementary Fig. 3a), indicating the formation of Cu^{II} species, corroborated by a Cu^{II} signal in the EPR spectrum of the same mixture (red trace, Fig. 3b). Addition of dimethyl phosphite significantly attenuates the UV absorption at 270 nm as well as the observed EPR signal after heating the mixture at 40 °C for 4 h (black and grey traces, Fig. 3a and 3b), suggesting a slow reduction of Cu^{II} to Cu^{I}. These observations in UV-Vis and EPR experiments support that dimethyl phosphite slowly reduces Cu^{II} to Cu^{I}.



Supplementary Fig. 2 Reaction time course for benzylic etherification conducted in the absence (red) and presence of 0.5 equiv. dimethyl phosphite (blue) as well as when 0.5 equiv. dimethyl phosphite was added at the 4th hour (purple). Reaction conditions: ethylbenzene (0.2 mmol), NFSI (0.4 mmol), MeOH (1.0 mmol), CuCl (0.02 mmol), 2,2'-bioxazoline (0.02 mmol), DCM:HFIP = 4:1 (1 mL), 40°C.



Supplementary Fig. 3 UV-Vis and EPR Experiments to probe the effect of additives on copper speciation. a, UV-Vis traces monitoring the reaction of Cu^{II} with dimethyl phosphite and methanol. b, EPR experiments investigating the effect of dimethyl phosphite and methanol on Cu^{II}.

Procedure for EPR experiments

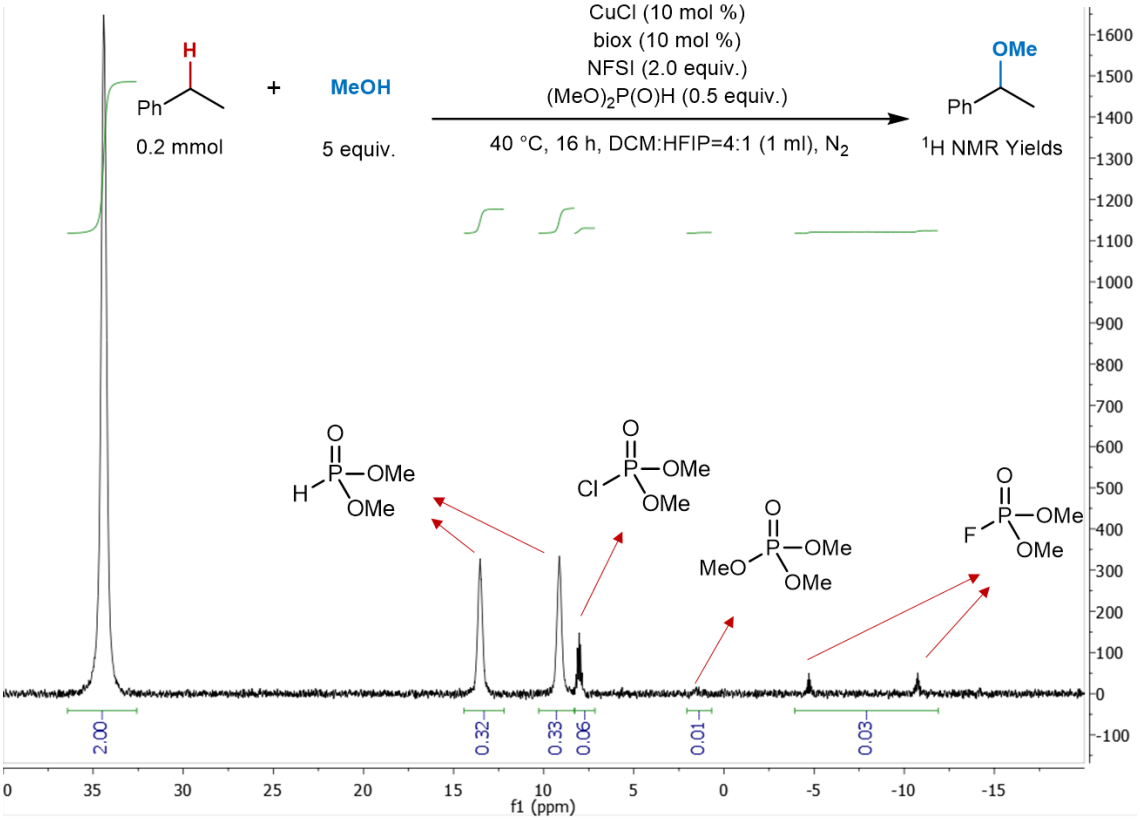
Copper(I) chloride (20.0 mg, 0.20 mmol), 4,4',5,5'-tetrahydro-2,2'-bioxazole (28.0 mg, 0.20 mmol,) were weighed into a 10 mL volumetric flask. Then DCM:HFIP = 4:1 as a solvent mixture was added to the graduation marking, followed by the addition of a magnetic stir bar to assist stirring. 1 mL of this stock solution was transferred into 4 mL glass vials containing NFSI (126.1 mg, 0.40 mmol), $(MeO)_2P(O)H$ (9.5 µL, 0.10 mmol, 0.5 equiv.), methanol (42 µL, 1.0 mmol, 5.0 equiv.) and an empty vial respectively in the glove box. Magnetic stir bars were added into each one of these four vials and the reaction mixtures were sealed, stirred and heated at 40 °C for 16 h. After that, an aliquot of each solution was transferred into a quartz EPR tube for analysis. All the EPR spectra were acquired with the following parameters:
Center: 3100 G; Sweeping width: 3000 G; Attenuation: 30 dB; Number of scans: 4; Number of points: 2048; Conversion time: 10 ms; Temperature: 105 K.

Procedure for UV-Vis experiments

Copper(I) chloride (20.0 mg, 0.20 mmol), 4,4',5,5'-tetrahydro-2,2'-bioxazole (28.0 mg, 0.20 mmol,) were weighed into a 10 mL volumetric flask. Then DCM:HFIP = 4:1 as a solvent mixture was added to the graduation marking, followed by the addition of a magnetic stir bar to assist stirring. 1 mL of this stock solution was transferred into six 4 mL glass vials containing NFSI (126.1 mg, 0.40 mmol) as well as an empty one. $(MeO)_2P(O)H$ (9.5 µL, 0.10 mmol, 0.5 equiv.) were added into five of the vials and methanol (42 µL, 1.0 mmol, 5.0 equiv.) was added to the final vial, all in the glove box. Magnetic stir bars were added into each one of these six vials and the reaction mixtures were sealed, stirred and heated at 40 °C for 1-4 h (indicated in the figures). After that, 50 µL of each solution was transferred into a quartz UV-Vis cuvette and diluted with 2.5 mL of DCM:HFIP = 4:1 solvent mixture for analysis.

V. The Fate of the Dialkyl Phosphites (^{31}P-^{1}H coupled NMR)

Dialkyl phosphites are reported to serve as single-electron reductants of Cu^{II}. Chlorinated, fluorinated and methoxylated products were observed in ^{31}P NMR spectrum from a reaction mixture run under standard conditions and worked up via filtration through a silica plug (Supplementary Fig. 4). Only 35% of the starting dimethyl phosphite was converted, consistent with the slow reduction of Cu^{II} observed in the experiments described above. Controlled experiment without ethylbenzene afforded similar product yields and distribution. The loss of P-based material(s) is attributed to retention of polar dimethyl phosphite derivatives in the silica gel. Attempts to characterise the phosphite speciation of reaction mixtures containing paramagnetic Cu salts proved unfruitful.

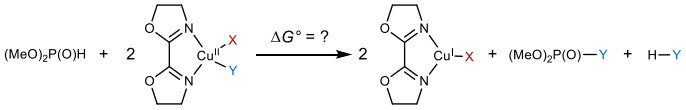


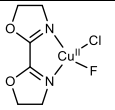
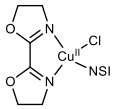
^{31}P NMR

Supplementary Fig. 4 ^{31}P-^{1}H coupled NMR spectrum of the reaction mixture of the benzylic C–H methoxylation with 0.2 mmol $Ph_3P(O)$ as the internal standard.

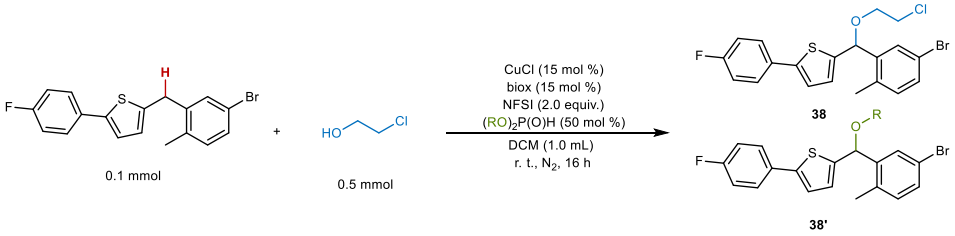
DFT calculations suggest that oxidation of $(MeO)_2P(O)H$ by $(biox)Cu^{II}(Cl)(F)$ is the most thermodynamically favorable, forming a strong P–F bond (Supplementary Table 6). Thermodynamics remains favorable when $(MeO)_2P(O)H$ reduces $(biox)Cu^{II}(Cl)(NSI)$ to form either P–N or P–Cl bonds.

Supplementary Table 6. Energetics of Cu^{II} reduction to Cu^{I} by $(MeO)_2P(O)H$



Entry	(biox)CuXY	X	Y	ΔG°(kcal/mol)
1		Cl	F	–45.2
2		F	Cl	+1.5
3		Cl	NSI	–24.5
4		NSI	Cl	–11.0

Supplementary Table 7. Investigation of various phosphites with a canagliflozin precursor

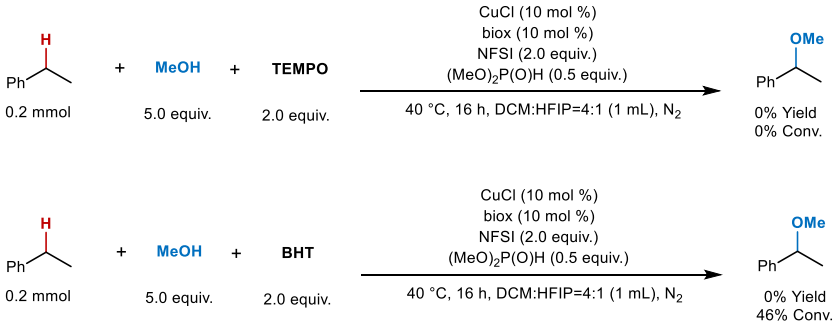


Entry	Additive	Conv. of the substrate (%)[a]	Yield of **38'** (%)[a]	Yield of **38** (%)[a]
1	$(MeO)_2P(O)H$	83	18	64
2	$(EtO)_2P(O)H$	92	8	81
3	$(^{i}PrO)_2P(O)H$	95	2	92
4	$(^{n}BuO)_2P(O)H$	94	8	84
5	$(BnO)_2P(O)H$	92	13	76
6	$(CF_3CH_2O)_2P(O)H$	69	3	59
7	$(^{t}BuO)_2P(O)H$	68	3	65
8	-	23	-	23

[a]Calibrated ^1H NMR yields using dibromomethane as the internal standard. Conv., conversion.

VI. Radical trap experiments

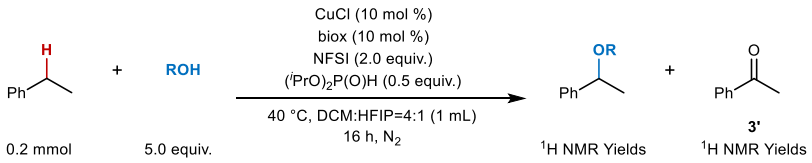
Supplementary Table 8. Control Experiments with Radical Traps



The reactions were set up following the standard procedure, with TEMPO (62.4 mg, 0.4 mmol) and BHT (88.1 mg, 0.4 mmol) weighed into the glass vials respectively before the vials were charged with nitrogen.

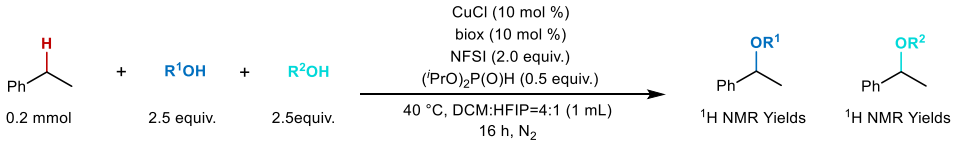
VI. Control experiments with various alcohols

Supplementary Table 9. Investigation of ethylbenzene cross-coupling with various alcohols



Entry	R	Conv. of EtPh (%)	Yield of 3' (%)	Yield of C–O^{i}Pr (%)	Yield of C–OH (%)	Yield of C–NSI (%)	Yield of C–OR (%)
1	Me	88	5	3	0	3	73
2	Et	82	4	3	0	3	47
3	^{i}Pr	82	5	-	0	9	54
4	^{t}Bu	95	6	5	14	22	0
5	$(CF_3)_2CH$	70	3	0	11	12	0

Supplementary Table 10. Competition experiments in ethylbenzene etherification

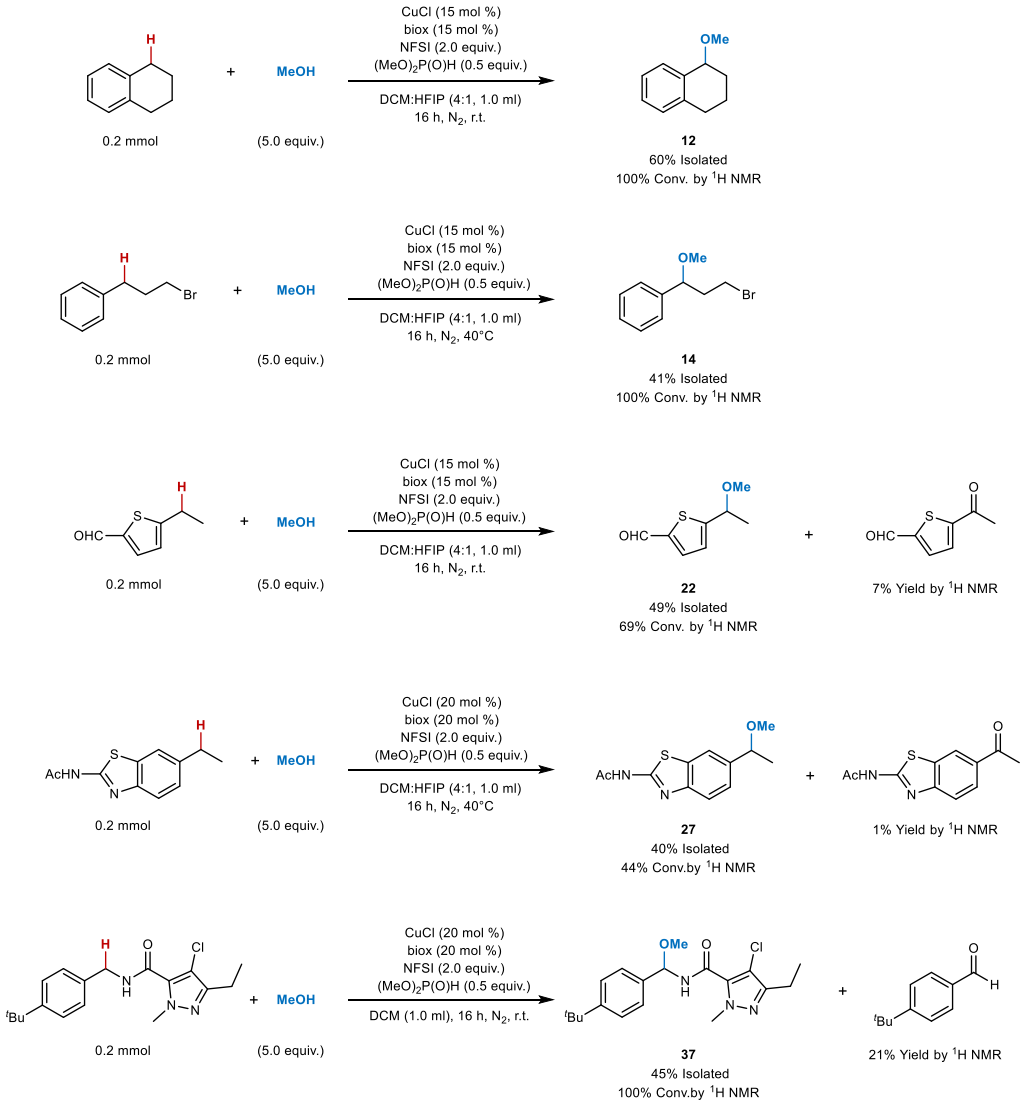


Entry	R^1	R^2	Conv. of EtPh (%)	Yield of C–NSI (%)	Yield of C–OR^1 (%)	Yield of C–OR^2 (%)
1	Me	Et	84	4	25	30
2	Me	^{i}Pr	73	6	28	19
3	Et	^{i}Pr	67	16	30	17
4	Et	CF_3CH_2	86	2	39	31
5	Et	^{i}PrCH$_2$	80	4	30	25
6	CF_3CH_2	^{i}PrCH$_2$	91	2	39	39

Alcohols with various steric bulk and electronic profiles were evaluated with ethylbenzene as the benzylic C–H substrate to probe the nature of the bond-forming step. In independent reactions, both ethanol and isopropanol gave moderate yields of the benzyl ethers, whereas *tert*-butanol failed to undergo effective coupling. Formation of sulfonimidated product becomes increasingly favorable with increased steric bulk of the alcohol coupling partner. Competitions between methanol, ethanol and isopropanol afforded similar yields of the corresponding ethers in each reaction. On the other hand, trifluoroethanol and isobutanol, with similar steric bulk but drastically different electronics, showed comparable yields. These data support a radical/polar crossover mechanism, where benzylic cations are generated via the oxidation of benzylic radicals.

VII. Further analyses of reaction outcomes of benzylic C–H etherification reactions

Supplementary Table 11. Analyses of mass balances of benzylic C–H etherification reactions

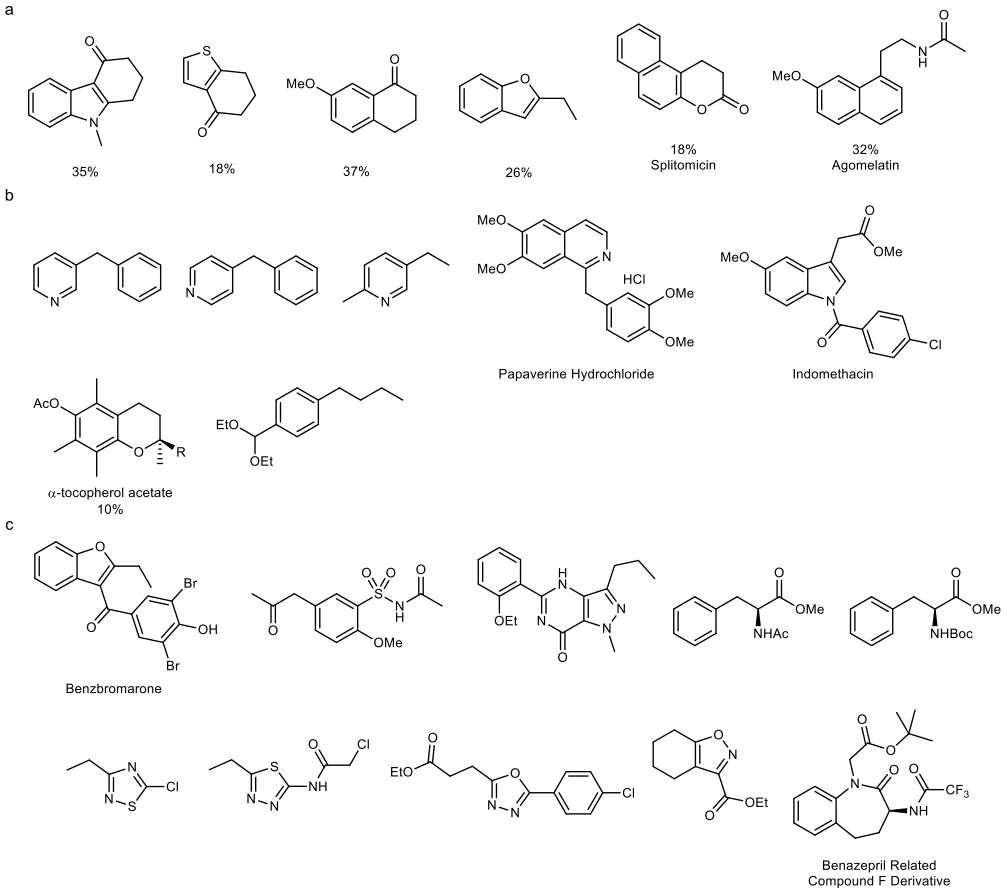


A selection of benzylic substrates were further analyzed to insight the mass balance of this benzylic C–H etherification. No undesired substitution at Br was observed with **12.** Bis-methoxylation product has not been detected with any substrate that has more than one benzylic C–H sites, for example, **14**. In the cases of **22** and **27**, significant amounts of starting materials were observed after the reactions were terminated. More forcing conditions only led to the formation of more side products, for example, ketones in the case of **22** and **27** as well as the aldehyde in the case of **37**, but not higher yields of the desired products.

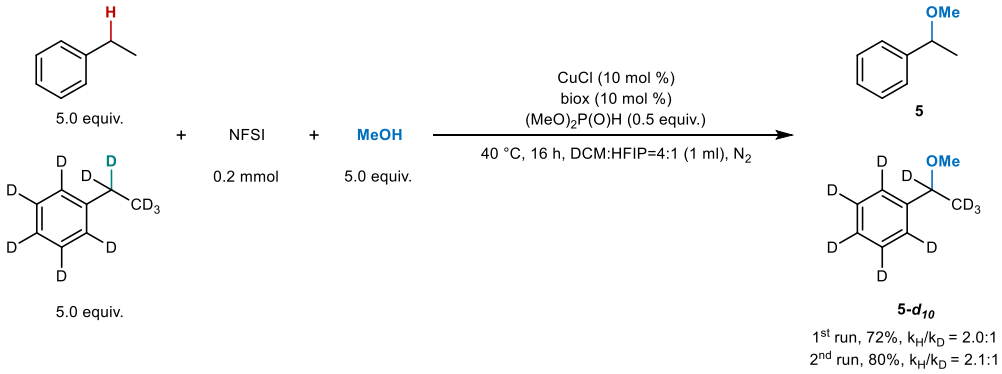
Unsuccessful Substrates.

Not all substrates tested were effective in the benzylic etherification reaction. The substrates in Supplementary Table 12 afford methyl ethers in < 40% yield, based on analysis of the crude reaction mixture by ^{1}H NMR spectroscopy (Supplementary Table 12a). An elimination product was observed in the case of splitomicin. Substrates in Supplementary Table 12b generally underwent high conversion but led to low-to-negligible yields of the desired products. Pyridines, quinoline and pyrimidine derivatives have been reported to react directly with NFSI[4] and no desirable methoxylated product was observed under all the reaction conditions tested. Substrates in Supplementary Table 12c are rather inactive, giving low conversions and low yields. Substrates with free phenols or acidic N–H groups suffered from low conversion, possibly reflecting inhibition by coordination to Cu or quenching of reactive radicals (in the case of phenols). Free carboxylic acids and amines are known to undergo side reactions[5-67] and are therefore incompatible with this reaction unless suitably modified. Sites adjacent to electron-deficient heterocycles were generally unreactive, and unreacted starting material was observed with the substrates in Supplementary Table 12c.

Supplementary Table 12. Unsuccessful substrates in benzylic C-H methoxylation

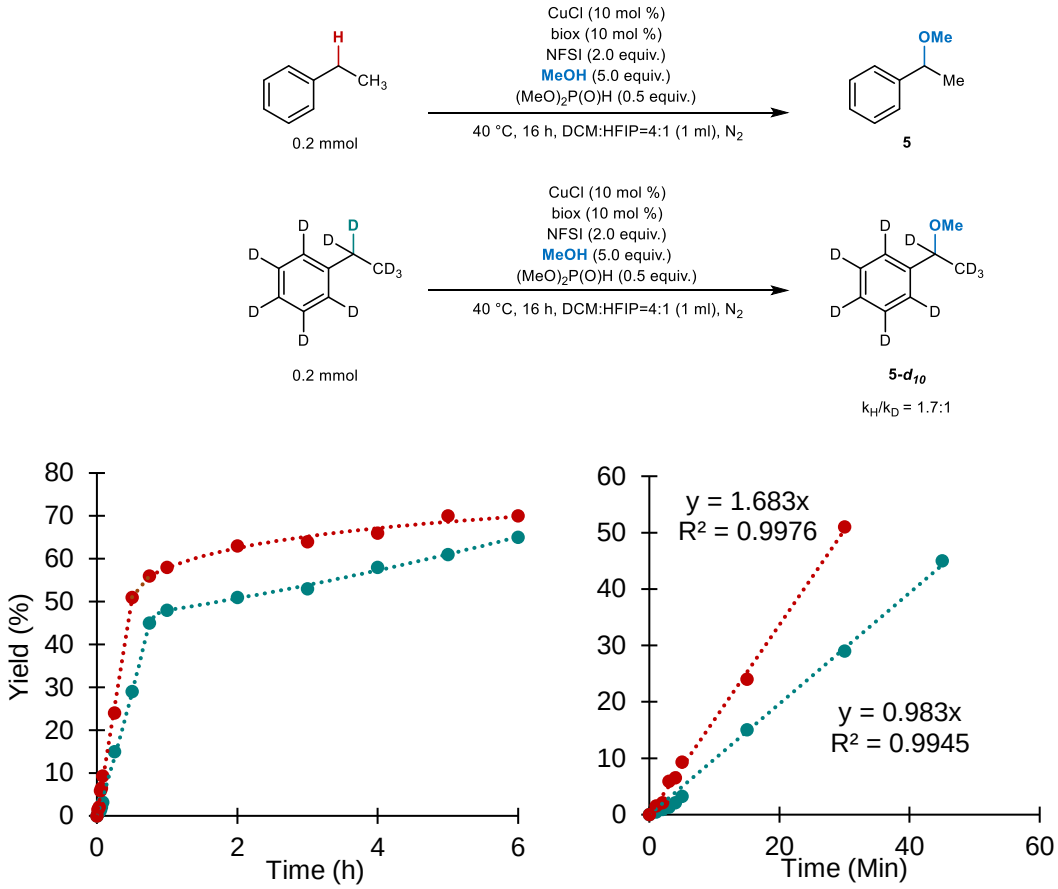


VII. KIE Experiments



Supplementary Fig. 5 Intermolecular Competition Kinetic Isotopic Effect

Procedure: Copper(I) chloride (2.0 mg, 0.020 mmol, 10 mol%), 4,4',5,5'-tetrahydro-2,2'-bioxazole (2.8 mg, 0.020 mmol, 10 mol%) and NFSI (63.6 mg, 0.20 mmol, 1.0 equiv.) were weighed into a 4 mL glass vial containing a magnetic stir bar. Then the vial was capped with a pierceable Teflon cap. A needle was pierced through the cap to facilitate exchange of the vial headspace with the atmosphere. The vial was moved into a glove box, through three vacuum-nitrogen-backfill cycles. The needle was removed, and the vial was taken out of the glove box (now sealed under an inert gas). DCM (0.8 mL), HFIP (0.2 mL), ethylbenzene-d_{10} (122.5 µL, 1.0 mmol, 5.0 equiv.), ethylbenzene (122.5 µL, 1.0 mmol, 5.0 equiv.), methanol (42 µL, 1.0 mmol, 5.0 equiv.) and dimethyl phosphonate (9.5 µL, 0.10 mmol, 0.5 equiv.) were added into the vial by injection through the cap. The sealed vial was heated at 40 °C and stirred for 16 h. When the reaction finished, the mixture was cooled down to room temperature. The mixture was quenched by a silica plug and an aliquot was taken into an NMR tube, which was diluted to the volume suitable for crude ^{1}H NMR analysis.



Supplementary Fig. 6 Intermolecular Competition Kinetic Isotopic Effect

Procedure: Copper(I) chloride (2.0 mg, 0.020 mmol, 10 mol%), 4,4',5,5'-tetrahydro-2,2'-bioxazole (2.8 mg, 0.020 mmol, 10 mol%) and NFSI (126.1 mg, 0.40 mmol, 2.0 equiv.) were weighed into a 4 mL glass vial containing a magnetic stir bar. Then the vial was capped with a pierceable Teflon cap. A needle was pierced through the cap to facilitate exchange of the vial headspace with the atmosphere. The vial was moved into a glove box, through three vacuum-nitrogen-backfill cycles. The needle was removed, and the vial was taken out of the glove box (now sealed under an inert gas). The vials were kept at 40 °C in the heating block on a hot plate. A stock solution of ethylbenzene (24.5 µL, 0.2 mmol, 1.0 equiv.), methanol (42 µL, 1.0 mmol, 5.0 equiv.) and dimethyl phosphonate (9.5 µL, 0.10 mmol, 0.5 equiv.) in DCM:HFIP = 4:1 was prepared and maintained at 40 °C in a water bath. 1 mL of the stock solution was added into each reaction vial by injection through the cap. The sealed vial was heated at 40 °C and stirred. The reaction mixture was cooled in a dry ice-isopropanol bath after the reaction has been run for a certain amount of time. The mixture was then through a silica plug and an aliquot was taken into an NMR tube, which was diluted to the volume suitable for crude ^{1}H NMR analysis. Reactions were stopped at 1, 2, 3, 4, 5, 15, 30 and 45 minutes to study the initial rates of the methoxylation of ethylbenzene and ethylbenzene-d_{10}.

VIII. Methods for HPLC/SFC Chiral Separation

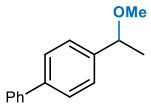
HPLC

A Daicel CHIRALPAK® AS-H column (4.6 mm × 250 mm, 5 μm PS) was used for separations. The eluent was a mixture (gradient, 95:5 to 50:50 hexanes/ ^{i}PrOH, 20 min) with a flow rate of 1 mL/min at 25 °C.

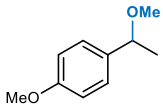
SFC

A Daicel CHIRALPAK® IA column (3 mm ID × 150 mm, 3 μm PS) was used for separations. The eluent was a mixture (99:1 CO_2/^{i}PrOH) with a flow rate of 2 mL/min at 40 °C with ABPR at 1500 psi.

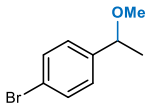
IX. Characterisation of Compounds



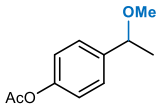
4-(1-methoxyethyl)-1,1'-biphenyl, **4**. Characterisation data matched those previously reported[8].
Reaction run at 0.4 mmol scale and 73.8 mg (87%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.62 – 7.55 (m, 4H), 7.44 (t, J = 7.5 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 4.35 (q, J = 6.5 Hz, 1H), 3.26 (s, 3H), 1.48 (d, J = 6.4 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 142.6, 141.0, 140.4, 128.8, 127.2 (2C), 127.1, 126.6, 79.4, 56.5, 23.9 ppm.



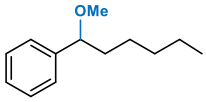
1-methoxy-4-(1-methoxyethyl)benzene, **6**. Characterisation data matched those previously reported[9].
Reaction run at 0.4 mmol scale and 45.9 mg (69%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.23 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 4.25 (q, J = 6.4 Hz, 1H), 3.80 (s, 3H), 3.19 (s, 3H), 1.42 (d, J = 6.4 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 159.0, 135.5, 127.4, 113.8, 79.1, 56.2, 55.3, 23.8 ppm.



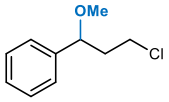
1-bromo-4-(1-methoxyethyl)benzene, **7**. Characterisation data matched those previously reported[5].
Reaction run at 0.2 mmol scale and 28.4 mg (66%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.47 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 4.26 (q, J = 6.5 Hz, 1H), 3.21 (s, 3H), 1.40 (t, J = 6.5 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 142.6, 131.6, 127.9, 121.2, 79.0, 56.5, 23.8 ppm.



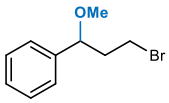
4-(1-methoxyethyl)phenyl acetate, **8**.
Reaction run at 0.4 mmol scale and 46.6 mg (60%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.31 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 4.29 (q, J = 6.5 Hz, 1H), 3.22 (s, 3H), 2.30 (s, 3H), 1.42 (d, J = 6.4 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 169.5, 149.9, 141.1, 127.2, 121.5, 79.1, 56.5, 23.9, 21.2 ppm.
HRMS Calculated for $[C_{11}H_{14}O_3+NH_4]^+$: 212.1281, Found: 212.1278.



(1-methoxyhexyl)benzene, **10.**
Reaction run at 0.4 mmol scale and 53.8 mg (70%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.38 – 7.31 (m, 2H), 7.31 – 7.24 (m, 3H), 4.07 (dd, J = 7.3, 6.0 Hz, 1H), 3.20 (s, 3H), 1.86 – 1.72 (m, 1H), 1.67 – 1.55 (m, 1H), 1.46 – 1.33 (m, 1H), 1.32 – 1.16 (m, 5H), 0.86 (t, J = 6.9 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 142.6, 128.3, 127.4, 126.7, 84.2, 56.6, 38.2, 31.8, 25.5, 22.6, 14.1 ppm.
HRMS (ASAP-MS) Calculated for $[C_{13}H_{20}O\text{-}OMe]^+$: 161.1325, Found: 161.1323.

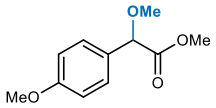


(3-chloro-1-methoxypropyl)benzene, **11.**
Reaction run at 0.4 mmol scale and 37.7 mg (51%) of colorless liquid isolated. Characterisation data matched those previously reported[10].
^{1}H NMR ($CDCl_3$, 400 MHz): 7.40 – 7.34 (m, 2H), 7.33 – 7.27 (m, 3H), 4.37 (dd, J = 8.5, 4.8, 1H), 3.71 (ddd, J = 10.8, 8.1, 5.6, 1H), 3.50 (ddd, J = 10.8, 5.9, 1H), 3.23 (s, 3H), 2.23 (ddt, J = 14.2, 8.4, 5.7 Hz, 1H), 2.01 (dddd, J = 14.3, 8.1, 6.0, 4.9 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 141.2, 128.6, 127.9, 126.6, 80.4, 56.8, 41.7, 40.9 ppm.

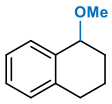


(3-bromo-1-methoxypropyl)benzene, **12**. Characterisation data matched those previously reported[11].
Reaction run at 0.4 mmol scale and 37.7 mg (41%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.40 – 7.34 (m, 2H), 7.33 – 7.27 (m, 3H), 4.35 (dd, J = 8.4, 4.8 Hz,

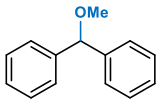
1H), 3.61 – 3.52 (m, 1H), 3.41 – 3.33 (m, 1H), 3.24 (s, 3H), 2.36 – 2.26 (m, 1H), 2.15 – 2.04 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 141.1, 128.6, 127.9, 126.6, 81.4, 56.9, 41.1, 30.3 ppm.



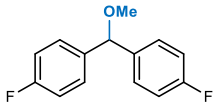
methyl 2-methoxy-2-(4-methoxyphenyl)acetate, **13**. Characterisation data matched those previously reported[12].
Reaction run at 0.4 mmol scale and 74.8 mg (89%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.36 (d J = 8.6 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.72 (s, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.38 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 171.4, 160.0, 128.6, 128.2, 114.1, 82.1, 57.1, 55.3, 52.3 ppm.



1-methoxy-1,2,3,4-tetrahydronaphthalene, **14**. Characterisation data matched those previously reported[13].
Reaction run at 0.4 mmol scale and 38.9 mg (60%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.38 – 7.31 (m, 1H), 7.22 – 7.14 (m, 1H), 7.12 – 7.06 (m, 1H), 4.31 (t, J = 4.7 Hz, 1H), 2.83 (dt, J = 16.8, 5.7 Hz, 1H), 2.71 (ddd, J = 16.7, 8.3, 6.0 Hz, 1H), 2.07 – 1.93 (m, 2H), 1.93 – 1.83 (m, 1H), 1.79 – 1.67 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 137.5, 136.6, 129.3, 129.0, 127.5, 125.7, 76.8, 56.2, 29.1, 27.4, 18.7 ppm.

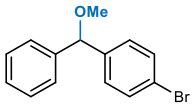


(methoxymethylene)dibenzene, **15**. Characterisation data matched those previously reported[14].
Reaction run at 0.4 mmol scale and 63.4 mg (80%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.37–7.28 (m, 8H), 7.26 – 7.21 (m, 2H), 5.24 (s, 1H), 3.38 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 142.1, 128.4, 127.5, 126.9, 85.5, 57.1 ppm.

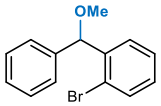


4,4'-(methoxymethylene)bis(fluorobenzene), **16**. Characterisation data matched those previously reported[15].

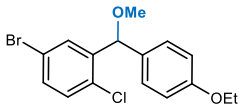
Reaction run at 0.4 mmol scale and 71.2 mg (76%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.31 – 7.24 (m, 4H), 7.05 – 6.97 (m, 4H), 5.20 (s, 1H), 3.35 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.2 (d, J = 244.3 Hz), 137.7 (d, J = 3.2 Hz), 128.5 (d, J = 8.1 Hz), 115.3 (d, J = 21.3 Hz), 84.0, 56.9 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.9 ppm.



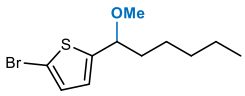
1-bromo-4-(methoxy(phenyl)methyl)benzene, **17**. Characterisation data matched those previously reported[16].
Reaction run at 0.4 mmol scale and 84.3 mg (76%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.44 (d J = 8.4 Hz, 2H), 7.35 – 7.24 (m, 5H), 7.22 (dd, J = 8.6, 0.6Hz, 2H), 5.19 (s, 1H), 3.36 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 141.5, 141.3, 131.5, 128.6, 128.6, 127.8, 126.9, 121.4, 84.7, 57.0 ppm.



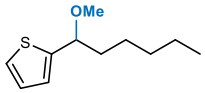
1-bromo-2-(methoxy(phenyl)methyl)benzene, **18**. Characterisation data matched those previously reported[17].
Reaction run at 0.4 mmol scale and 59.9 mg (54%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.56 – 7.50 (m, 2H), 7.42 – 7.37 (m, 2H), 7.35 – 7.29 (m, 3H), 7.28 – 7.22 (m, 1H), 7.12 (td, J = 7.6, 1.7 Hz, 1H), 5.67 (s, 1H), 3.39 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 141.0, 140.5, 132.8, 129.0, 128.5, 128.4, 127.8, 127.7, 127.4, 123.6, 83.5, 57.2 ppm.



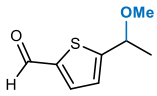
4-bromo-1-chloro-2-((4-ethoxyphenyl)(methoxy)methyl)benzene, **19.**
Reaction run at 0.2 mmol scale and 112 mg (79%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.75 (d, J = 2.4 Hz, 1H), 7.31 (dd, J = 8.5, 2.5 Hz, 1H), 7.25 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 5.52 (s, 1H), 4.01 (q, J = 7.0 Hz, 2H), 3.36 (s, 3H), 1.39 (t, J = 7.0 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 158.7, 142.0, 131.7, 131.5, 131.5, 130.9, 130.6, 128.8, 121.0, 114.4, 80.8, 63.4, 57.0, 14.8 ppm.
HRMS (ASAP-MS) Calculated for $[C_{16}H_{16}BrClO_2\text{-}OMe]^+$: 322.9833, Found: 322.9832.



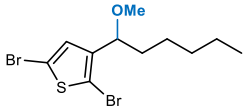
2-bromo-5-(1-methoxyhexyl)thiophene, **20**.
Reaction run at 0.4 mmol scale and 72.1 mg (65%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 6.90 (d, J = 3.7 Hz, 1H), 6.70 (d, J = 3.7 Hz, 1H), 4.25 (t, J = 6.8 Hz, 1H), 3.26 (s, 3H), 1.91 – 1.78 (m, 1H), 1.67 (m, 1H), 1.46 – 1.17 (m, 6H), 0.87 (t, J = 6.9 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 148.3, 129.0, 125.6, 111.6, 79.8, 56.5, 38.1, 31.6, 25.4, 22.5, 14.0 ppm.
HRMS Calculated for $[C_{11}H_{17}BrOS+Na]^+$: 299.0076, Found: 299.0074.



2-(1-methoxyhexyl)thiophene, **21**.
Reaction run at 0.4 mmol scale and 40.5 mg (51%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.30 – 7.23 (m, 1H), 7.01 – 6.92 (m, 2H), 4.35 (t, J = 6.8 Hz, 1H), 3.25 (s, 3H), 1.99 – 1.84 (m, 1H), 1.72 (m, 1H), 1.49 – 1.34 (m, 1H), 1.33 – 1.23 (m, 5H), 0.87 (t, J = 6.7 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 146.4, 126.2, 125.2, 124.8, 79.5, 56.4, 38.3, 31.6, 25.5, 22.6, 14.0 ppm.
HRMS Calculated for $[C_{11}H_{18}OS+Na]^+$: 221.0971, Found: 221.0969.

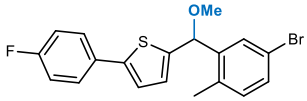


5-(1-methoxyethyl)thiophene-2-carbaldehyde, **22.**
Reaction run at 0.4 mmol scale and 33.4 mg (49%) of yellow liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 9.88 (s, 1H), 7.66 (d, J = 3.8 Hz, 1H), 7.07 (dd, J = 3.8, 0.7 Hz, 1H), 4.59 (qd, J = 6.5, 0.7 Hz, 1H), 3.33 (s, 3H), 1.55 (d, J = 6.5 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 183.0, 158.0, 142.7, 136.3, 125.1, 75.2, 56.8, 23.6 ppm.
HRMS Calculated for $[C_8H_{10}O_2S+H]^+$: 171.0474, Found: 171.0473.

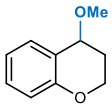


2,5-dibromo-3-(1-methoxyhexyl)thiophene, **23.**
Reaction run at 0.2 mmol scale and 52.6 mg (74%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 8.43 (d, J = 7.8 Hz, 1H), 8.24 (s, 1H), 6.88 (s, 1H), 4.23 (dd, J = 7.2,

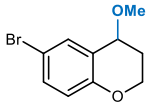
6.4 Hz, 1H), 3.20 (s, 3H), 1.76 (dddd, J = 13.4, 9.8, 7.2, 5.2 Hz, 1H), 1.57 (dddd, J = 13.4, 10.0, 6.4, 5.3 Hz, 1H), 1.42 – 1.19 (m, 6H), 0.87 (t, J = 6.8 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 143.4, 128.8, 111.5, 109.4, 78.2, 56.8, 36.2, 31.6, 25.1, 22.6, 14.1 ppm.
HRMS Calculated for $[C_{11}H_{16}Br_2OS+Na]^+$: 376.9181, Found: 376.9180.



2-((5-bromo-2-methylphenyl)(methoxy)methyl)-5-(4-fluorophenyl)thiophene, **24.**
Reaction run at 0.4 mmol scale and 65.7 mg (84%) of white non-crystalline powder isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.72 (d, J = 2.2 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.34 (dd, J = 8.1, 2.2 Hz, 1H), 7.07 – 6.99 (m, 4H), 6.75 (dd, J = 3.6, 0.8 Hz, 1H), 5.51 (s, 1H), 3.41 (s, 3H), 2.24 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.3 (d, J = 245.7 Hz), 143.8, 143.7, 141.2, 134.5, 132.3, 130.8, 130.5 (d, J = 3.4 Hz), 129.1, 127.4 (d, J = 8.0 Hz), 126.9, 122.3 (d, J = 1.2 Hz), 120.1, 115.8 (d, J = 21.7 Hz), 78.0, 57.0, 18.8 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.5 ppm.
HRMS Calculated for $[C_{19}H_{16}BrFOS+Na]^+$: 412.9982, Found: 412.9980.

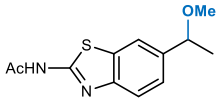


4-methoxychromane, **25.**
Reaction run at 0.4 mmol scale and 30.2 mg (46%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.24 (dd, J = 7.7, 1.7 Hz, 1H), 7.28 (td, J = 7.7, 1.7 Hz, 1H), 6.89 (td, J = 7.4, 1.2 Hz, 1H), 6.84 (dd, J = 8.2, 1.2 Hz, 1H), 4.32 – 4.21 (m, 3H), 3.44 (s, 3H), 2.18 – 2.10 (m, 1H), 2.09 – 1.98 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 154.8, 130.6, 129.7, 121.6, 119.9, 117.0, 71.8, 62.0, 55.8, 27.2 ppm.
HRMS (ASAP-MS) Calculated for $[C_{10}H_{12}O_2$-OMe$]^+$: 133.0648, Found: 133.0646.

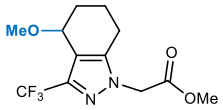


6-bromo-4-methoxychromane, **26.**
Reaction run at 0.4 mmol scale and 50.6 mg (52%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.37 (d, J = 2.4 Hz, 1H), 7.28 (dd, J = 8.8, 3.2 Hz, 1H), 6.72 (d, J = 8.7 Hz, 1H), 4.29 – 4.19 (m, 3H), 3.44 (s, 3H), 2.16 – 2.08 (m, 1H), 2.01 (dddd, J = 14.2, 9.6, 5.4, 3.8 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 153.9, 132.9, 132.5, 123.7, 118.9, 111.9, 71.5, 62.3, 56.0, 26.8 ppm.

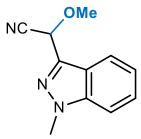
HRMS (ASAP-MS) Calculated for $[C_{10}H_{11}BrO_2\text{-}OMe]^+$: 210.9753, Found: 210.9752.



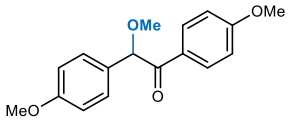
N-[6-(1-methoxyethyl)-1,3-benzothiazol-2-yl]acetamide, **27.**
Reaction run at 0.4 mmol scale and 40.3 mg (40%) of white non-crystalline powder isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 11.77 (s, 1H), 7.80 (d, J = 1.7 Hz, 2H), 7.74 (d, J = 8.3 Hz, 1H), 7.41 (dd, J = 8.4 Hz, J = 1.7 Hz, 1H), 4.43 (q, J = 6.4 Hz, 1H), 3.27 (s, 3H), 2.30 (s, 3H), 1.50 (d, J = 6.4 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 168.89, 159.91, 147.17, 139.91, 132.07, 124.80, 120.28, 119.22, 79.52, 56.59, 24.00, 23.57 ppm.
HRMS Calculated for + $[C_{12}H_{14}N_2O_2\,S+H]^+$: 251.0849, Found: 251.0846



N-[6-(1-methoxyethyl)-1,3-benzothiazol-2-yl]acetamide, **28.**
Reaction run at 0.4 mmol scale and 72.9 mg (62%) of yellow liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 4.88 (d, J = 17.5 Hz, 1H), 4.78 (d, J = 17.5 Hz, 1H), 4.43 (t, J = 3.4 Hz, 1H), 3.77 (s, 3H), 3.42 (s, 3H), 2.61 (ddd, J = 16.3 Hz, J = 5.8 Hz, J = 3.0 Hz, 1H), 2.46 (ddd, J = 16.5 Hz, J = 10.7 Hz, J = 6.1 Hz, 1H), 2.14 (ddd, J = 14.1 Hz, J = 5.4 Hz, J = 2.8 Hz, 1H), 2.00 (tdd, J = 10.5 Hz, J = 8.1 Hz, J = 5.3 Hz, 1H), 1.95-1.79 (m, 1H), 1.68-1.54 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 167.3, 142.7, 140.0 (q, J = 37.3 Hz), 121.6 (q, J = 269.4 Hz), 116.2, 69.3, 56.5, 52.8, 50.5, 26.5, 21.0, 17.0 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -61.5 ppm.
HRMS Calculated for + $[C_{12}H_{15}F_3N_2O_3+H]^+$: 293.1108, Found: 293.1102



methoxy(1-methyl-1H-indazol-3-yl)acetonitrile, **29.**
Reaction run at 0.4 mmol scale and 30.5 mg (38%) of orange to green liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.90 (d, J = 8.2 Hz, 1H), 7.43 (m, 2H), 7.24 (m, 1H), 5.63 (s, 1H), 4.08 (s, 3H), 3.57 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 141.3, 136.5, 127.1, 121.7, 121.3, 120.2, 116.2, 189.5, 66.6, 57.1, 35.8 ppm.
HRMS Calculated for + $[C_{11}H_{11}N_3O_2+H]^+$: 202.0975, Found: 202.0975



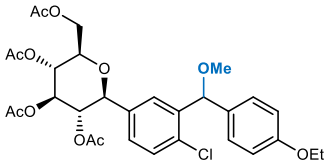
{2-methoxy-1, 2-bis(4-methoxyphenyl) ethenone}, **30**. Characterisation data matched those previously reported[18].

Reaction run at 0.4 mmol scale and 66.6 mg (58%) of colorless liquid isolated.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.99 (d, J = 8.96 Hz, 2H), 7.38 (d, J = 8.62 Hz, 2H), 6.87 (d, J = 2.85 Hz, 2H), 6.85 (d, J = 3.03 Hz, 2H), 5.45 (s, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.42 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): 195.5, 163.5, 159.7, 131.3, 129.0, 128.5, 127.9, 114.3, 113.7, 85.8, 57.2, 55.4, 55.2 ppm.

HRMS Calculated for $[C_{17}H_{18}O_4+Na]^+$: 309.1097, Found: 309.1092.



(2*R*,3*R*,4*R*,5*S*,6*S*)-2-(acetoxymethyl)-6-(4-chloro-3-((4-ethoxyphenyl)(methoxy)methyl)phenyl) tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, **31.**

Reaction run at 0.4 mmol scale and 233 mg (91%) of white non-crystalline powder was isolated. (a mixture of two diastereomers): d. r. = 1.1:1 (by ^{1}H NMR spectroscopy. Reported spectral values are of the mixture).

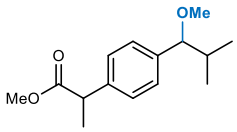
Major diastereomer: ^{1}H NMR ($CDCl_3$, 400 MHz): 7.54 (d, J = 2.1 Hz, 1H, major diastereomer), 7.48 (d, J = 2.1 Hz, 1H, minor diastereomer), 7.34 (dd, J = 10.1, 1H, minor diastereomer), 7.32 (dd, J = 10.1, 1H, major diastereomer), 7.28 – 7.17 (m, 3H), 6.88 – 6.77 (m, 2H), 5.61 (s, 1H, minor diastereomer), 5.55 (s, 1H, major diastereomer), 5.32 (t, J = 9.3 Hz, 1H, minor diastereomer), 5.31 (t, J = 9.3 Hz, 1H, major diastereomer), 5.23 (t, J = 9.7, 1H), 5.11 (t, 9.6 Hz, 1H, major diastereomer), 5.06 (t, 9.6 Hz, 1H), 4.40 (d, J = 9.8 Hz, 1H), 4.27 (dd, J = 12.4, 4.9, 1H), 4.18 (dd, J = 12.4, 2.4 Hz, 1H), 4.00 (q, J = 7.0 Hz, 2H, major diastereomer), 3.98 (q, J = 7.0 Hz, 2H), 3.82 (ddd, J = 9.9, 4.8, 2.1 Hz, 1H), 3.37 (s, 3H, minor diastereomer), 3.32 (s, 3H, major diastereomer), 2.09 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H, minor diastereomer), 1.99 (s, 3H, major diastereomer), 1.87 (s, 3H, major diastereomer) , 1.61 (s, 3H, minor diastereomer), 1.38 (t, J = 7.0, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): 170.73, 170.36, 170.34, 169.51, 168.90, 168.81, 158.53, 158.47, 139.85, 139.61, 135.57, 135.37, 133.43, 133.20, 132.42, 131.94, 129.90, 129.79, 128.81, 128.33, 126.95, 126.79, 126.72, 126.68, 114.50, 114.30, 114.24, 80.81, 80.63, 79.43, 76.15, 76.11, 74.17, 74.14, 72.66, 72.56, 68.54, 63.40, 63.38, 62.29, 57.12, 56.74, 20.79, 20.67, 20.66, 20.43, 20.19, 14.84, 14.81.

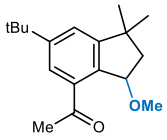
HRMS Calculated for $[C_{30}H_{35}ClO_{11}+NH_4]^+$: 624.2206, Found: 624.2203.

Methyl 2-[4-(1-methoxy-2-methylpropyl)phenyl]propanoate, **32.**

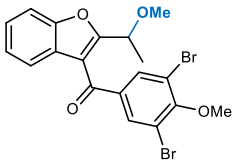
Reaction run at 0.4 mmol scale and 33.5 mg (67%) of colorless liquid was isolated.



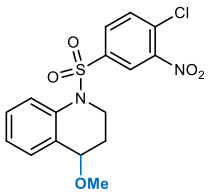
^{1}H NMR ($CDCl_3$, 400 MHz): 7.26 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 3.73 (m, 2H), 3.67 (s, 3H), 3.18 (s, 3H), 1.89 (doublet of septets, J = 6.8 Hz, 1H), 1.50 (d, J = 7.2 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 175.1, 140.0, 139.4, 127.7, 127.1, 89.4, 57.0, 52.0, 45.1, 34.7, 19.0, 18.9, 18.6 ppm.
HRMS Calculated for $[C_{15}H_{22}O_3+NH_4]^+$: 268.1907, Found: 268.1904.



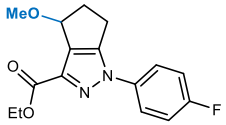
1-(6-tert-butyl-3-methoxy-1,1-dimethyl-2,3-dihydro-1H-inden-4-yl)ethan-1-one, **33.**
Reaction run at 0.4 mmol scale and 84.1 mg (77%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.66 (d, J = 1.8 Hz, 1H), 7.36 (d, J = 1.8 Hz, 1H), 5.21 (dd, J = 5.7, 3.1 Hz, 1H), 3.42 (s, 3H), 2.62 (s, 3H), 2.18 – 1.99 (m, 2H), 1.34 (s, 9H), 1.35 (s, 3H), 1.30 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 200.77, 154.23, 152.59, 137.84, 135.24, 125.05, 123.18, 81.61, 57.16, 46.12, 42.63, 34.94, 31.42, 31.19, 29.77, 28.77 ppm.
HRMS Calculated for + $[C_{17}H_{23}O_2\text{-}OCH_3]^+$: 243.1743, Found: 243.1740.



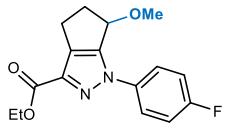
1-(6-tert-butyl-3-methoxy-1,1-dimethyl-2,3-dihydro-1H-inden-4-yl)ethan-1-one, **34.**
Reaction run at 0.4 mmol scale and 61.0 mg (65%) of white non-crystalline powder isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 8.03 (s, 2H), 7.71-7.48 (m, 1H), 7.43-7.33 (m, 2H), 7.32-7.24 (m, 1H), 4.73 (q, J = 6.6 Hz, 1H), 3.99 (s, 3H), 3.29 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 187.6, 162.5, 158.1, 154.0, 136.6, 133.8, 125.7, 125.67, 124.1, 121.3, 118.7, 117.6, 111.9, 71.3, 60.9, 57.0, 19.4 ppm.
HRMS Calculated for + $[C_{19}H_{16}Br_2O_4+H]^+$: 466.9488, Found: 466.9484.



1-(4-chloro-3-nitrobenzene-1-sulfonyl)-4-methoxy-1,2,3,4-tetrahydroquinoline, **35.**
Reaction run at 0.4 mmol scale and 36.8 mg (48%) of white solid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 8.02 (d, J = 2.1 Hz, 2H), 7.89 (d, J = 8.3 Hz, 2H), 7.65 (dd, J = 8.5 Hz, J = 2.1 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 7.36 (ddd, J = 8.4 Hz, J = 5.6 Hz, J = 2.8 Hz, 3H), 7.16 (m, 2H), 4.04 (t, J = 6.8 Hz, 1H), 3.96 (ddd, J = 12.3 Hz, J = 5.9 Hz, J = 3.0 Hz, 1H), 3.72 (td, J = 12.3 Hz, J = 4.9 Hz, 1H), 2.94 (s, 3H), 2.16 (m, 1H), 1.75 (dddd, J = 14.0 Hz, J = 12.3 Hz, J = 5.9 Hz, J = 2.9 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 147.6, 138.1, 135.3, 132.3, 131.4, 131.2, 129.9, 129.6, 129.5, 125.2, 124.4, 124.3, 73.8, 55.7, 42.3, 27.9 ppm.
HRMS Calculated for $[C_{16}H_{15}ClN_2O_5S+NH_4]^+$: 400.0729, Found: 400.0721.



Ethyl-1-(4-fluorophenyl)-4-methoxy-1,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrazole-3-carboxylate, **36a.**
Reaction run at 0.4 mmol scale and 97.7 mg (80%) of white solid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.65 (dd, J = 8.4 Hz, J = 4.3 Hz, 2H), 7.14 (t, J = 8.2 Hz, 2H), 4.84 (d, J = 5.7 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 3.22 (m, 1H), 2.83 (m, 2H), 2.63 (m, 1H), 1.40 (t, J = 7.0 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.1, 161.5 (d, J = 247.4 Hz), 152.2, 138.8, 135.7 (d, J = 3.0 Hz), 131.3, 122.3 (d, J = 8.5 Hz), 116.2 (d, J = 23.1 Hz), 76.1, 61.1, 56.6, 38.9, 24.6, 14.3 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.3 ppm.
HRMS Calculated for $[C_{16}H_{17}FN_2O_3+H]^+$: 305.1296, Found: 305.1290.



Ethyl-1-(4-fluorophenyl)-6-methoxy-1,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrazole-3-carboxylate, **36b.**

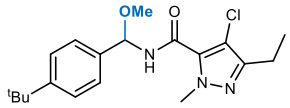
Reaction run at 0.4 mmol scale and 11.0 mg (9%) of white solid isolated.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.84 (m, 2H), 7.14 (m, 2H), 4.95 (m, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.00 (m, 1H), 2.82 (m, 2H), 2.63 (m, 1H), 1.40 (t, J = 7.1 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): 162.3, 161.6 (d, J = 247.0 Hz), 148.5, 138.0, 135.9 (d, J = 3.0 Hz), 134.7, 122.5 (d, J = 8.4 Hz), 116.1 (d, J = 22.9 Hz), 75.7, 61.0, 54.6, 36.9, 22.4, 14.4 ppm.

^{19}F NMR (377 MHz, $CDCl_3$): -114.7 ppm.

HRMS Calculated for $[C_{16}H_{17}FN_2O_3+H]^+$: 305.1296, Found: 305.1291.



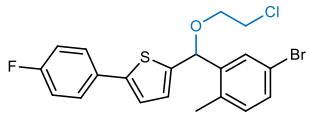
4-chloro-3-ethyl-N-[methoxy(4-tert-butylphenyl)methyl]-1-methyl-1H-pyrazole-5-carboxamide, **37.**

Reaction run at 0.2 mmol scale and 32.7 mg (45%) of white solid isolated.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 (s, 4H), 7.22 (d, J = 9.0 Hz, 1H), 6.28 (d, J = 9.1 Hz, 1H), 4.15 (s, 3H), 3.53 (s, 3H), 2.63 (q, J = 7.6 Hz, 2H), 1.32 (s, 9H), 1.23 (t, J = 7.6 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz): 158.55, 151.86, 149.71, 135.66, 130.52, 125.75, 125.70, 125.62, 125.58, 108.16, 81.63, 56.21, 40.79, 34.65, 31.30, 19.23, 12.84 ppm.

HRMS Calculated for $[C_{19}H_{26}ClN_3O_2+H]^+$: 364.1786, Found: 364.1782.



2-((5-bromo-2-methylphenyl)(2-chloroethoxy)methyl)-5-(4-fluorophenyl)thiophene, **38.**

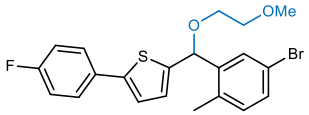
Reaction run at 0.2 mmol scale and 75.6 mg (86%) of colorless liquid isolated.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.74 (d, J = 2.2 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.35 (dd, J = 8.0, 2.2 Hz, 1H), 7.07 – 6.99 (m, 4H), 6.77 (dd, J = 3.8, 0.8 Hz, 1H), 5.71 (s, 1H), 3.81 – 3.72 (m, 2H), 3.69 (td, J = 5.8, 1.0 Hz, 1H), 2.24 (s, 3H) ppm.

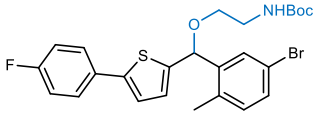
^{13}C NMR ($CDCl_3$, 100 MHz): 162.4 (d, J = 245.8 Hz), 144.1, 143.2, 140.9, 134.5, 132.3, 131.0, 130.5 (d, J = 3.4 Hz), 129.3, 127.4 (d, J = 8.0 Hz), 127.1, 122.4 (d, J = 1.2 Hz), 120.2, 115.8 (d, J = 21.7 Hz), 76.9, 69.2, 42.8, 18.8 ppm.

^{19}F NMR (377 MHz, $CDCl_3$): -114.3 ppm.

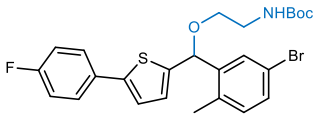
HRMS Calculated for $[C_{20}H_{18}BrClFOS+Na]^+$: 460.9748, Found: 460.9744.



2-((5-bromo-2-methylphenyl)(2-methoxyethoxy)methyl)-5-(4-fluorophenyl)thiophene, **39.**
Reaction run at 0.2 mmol scale and 62.7 mg (72%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.75 (d, *J* = 2.2 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.34 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.07 – 6.99 (m, 4H), 6.76 (dd, *J* = 3.7, 0.8 Hz, 1H), 5.72 (s, 1H), 3.73 – 3.59 (m, 4H), 3.40 (s, 3H), 2.24 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.3 (d, *J* = 245.7 Hz), 143.8, 141.4, 134.5, 132.2, 130.8, 130.6 (d, *J* = 3.4 Hz), 129.3, 127.4 (d, *J* = 8.0 Hz), 127.0, 122.32, 122.30, 120.1, 115.8 (d, *J* = 21.7 Hz), 76.6, 72.1, 68.5, 59.1, 18.8 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.6 ppm.
HRMS Calculated for $[C_{21}H_{20}BrFNO_2S+Na]^+$: 457.0244, Found: 457.0242.

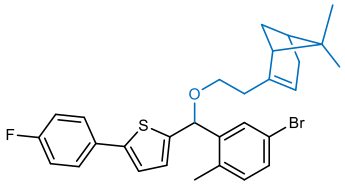


tert-butyl(2-((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methoxy)ethyl)carbamate, **40.**
Reaction run at 0.2 mmol scale and 72.7 mg (70%) of yellow liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.70 (d, *J* = 2.2 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.35 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.08 – 6.99 (m, 4H), 6.76 (dd, *J* = 3.6, 0.8 Hz, 1H), 5.63 (s, 1H), 5.03 – 4.83 (m, 1H), 3.60 (dt, *J* = 9.5, 5.1 Hz, 1H), 3.55 (dt, *J* = 9.5, 4.9 Hz, 1H), 3.40 (d, *J* = 5.5 Hz, 1H), 3.38 (d, *J* = 5.5 Hz, 1H), 2.24 (s, 3H), 1.43 (s, 9H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.4 (d, *J* = 245.8 Hz), 156.0, 144.0, 143.6, 141.2, 134.4, 132.3, 130.9, 130.5 (d, *J* = 3.4 Hz), 129.0, 127.4 (d, *J* = 8.0 Hz), 127.0, 122.3 (d, *J* = 1.2 Hz), 120.1, 115.8 (d, *J* = 21.6 Hz), 79.4, 76.5, 68.5, 40.5, 28.4, 18.8 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.4 ppm.
HRMS Calculated for $[C_{25}H_{27}BrFNO_3S+Na]^+$: 542.0771, Found: 542.0768.

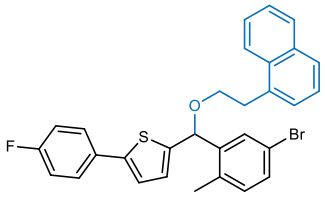


2-((5-bromo-2-methylphenyl)(pent-3-yn-1-yloxy)methyl)-5-(4-fluorophenyl)thiophene, **41.**
Reaction run at 0.2 mmol scale and 45.2 mg (51%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.75 (d, *J* = 2.2 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.34 (dd, *J* = 8.0, 2.2 Hz, 1H), 7.07 – 6.99 (m, 4H), 6.73 (dd, *J* = 3.6, 0.9 Hz, 1H), 5.69 (s, 1H), 3.60 (qt, *J* = 9.0, 6.9 Hz, 1H), 2.50 (tq, *J* = 7.2, 2.5 Hz, 1H), 2.24 (s, 3H), 1.79 (t, *J* = 2.5 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.3 (d, *J* = 245.8 Hz), 143.8, 143.8, 141.2, 134.5, 132.2, 130.8, 130.6 (d, *J* = 3.3 Hz), 129.3, 127.4 (d, *J* = 8.0 Hz), 126.9, 122.3 (d, *J* = 1.2 Hz), 120.1, 115.8 (d, *J*

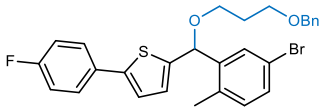
= 21.7 Hz), 77.0, 76.4, 75.7, 67.9, 20.3, 18.8, 3.6 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.5 ppm.
HRMS Calculated for $[C_{23}H_{20}BrFOS+Na]^+$: 465.0295, Found: 465.0294.



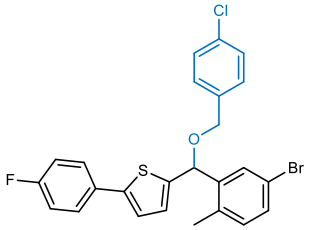
2-((5-bromo-2-methylphenyl)(2-((1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethoxy)methyl)-5-(4-fluorophenyl)thiophene, **42.**
Reaction run at 0.2 mmol scale and 35.7 mg (34%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.73 (d, *J* = 2.2 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.34 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.07 – 6.99 (m, 4H), 6.71 (dd, *J* = 3.6, 0.8 Hz, 1H), 5.60 (d, *J* = 2.0 Hz, 1H), 5.27 (ddq, *J* = 4.7, 3.2, 1.6 Hz, 1H), 3.58 – 3.45 (m, 2H), 2.42 – 2.14 (m, 8H), 2.10 – 2.02 (m, 2H), 1.26 (d, *J* = 3.7 Hz, 3H), 1.17 (d, *J* = 8.5 Hz, 1H), 0.82 (d, *J* = 1.5 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.3 (d, *J* = 245.5 Hz), 144.9, 144.3, 143.6, 141.7, 134.4, 132.2, 130.7, 130.6 (d, *J* = 3.4 Hz), 129.3, 127.3 (d, *J* = 8.0 Hz), 126.6, 122.3, 120.1, 118.1, 115.8 (d, *J* = 21.6 Hz), 76.3, 67.9, 46.0, 40.8, 38.0, 37.2, 31.7, 31.4, 26.3, 21.2, 18.8 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.6 ppm.
HRMS Calculated for $[C_{29}H_{30}BrFOS+Na]^+$: 547.1077, Found: 547.1071.



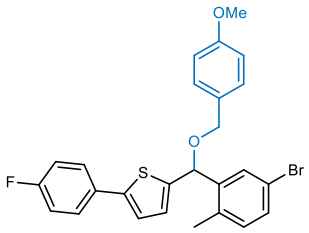
2-((5-bromo-2-methylphenyl)(2-(naphthalen-1-yl)ethoxy)methyl)-5-(4-fluorophenyl)thiophene, **43.**
Reaction run at 0.2 mmol scale and 95.7 mg (90%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 8.02 (d, *J* = 8.6 Hz, 1H), 7.84 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.75 – 7.70 (m, 2H), 7.53 – 7.43 (m, 4H), 7.43 – 7.36 (m, 2H), 7.32 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.08 – 6.95 (m, 4H), 6.67 (dd, *J* = 3.7, 0.8 Hz, 1H), 5.58 (s, 1H), 3.90 – 3.78 (m, 2H), 3.46 (t, *J* = 7.3 Hz, 2H), 2.14 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.4 (d, *J* = 245.7 Hz), 144.0, 143.7, 141.5, 134.7, 134.4, 133.9, 132.2, 132.1, 130.8, 130.6 (d, *J* = 3.4 Hz), 129.2, 128.8, 127.4 (d, *J* = 8.0 Hz), 127.2, 127.1, 126.8, 126.1, 125.6 (d, *J* = 1.5 Hz), 123.8, 122.3, 122.3, 120.1, 115.8 (d, *J* = 21.6 Hz), 76.5, 69.5, 33.6, 18.7 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.4 ppm.
HRMS Calculated for $[C_{30}H_{24}BrFOS+Na]^+$: 553.0608, Found: 553.0606.



2-((3-(benzyloxy)propoxy)(5-bromo-2-methylphenyl)methyl)-5-(4-fluorophenyl)thiophene, **44.**
Reaction run at 0.2 mmol scale and 73.7 mg (70%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.71 (d, *J* = 2.1 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.33 (dd, *J* = 8.0, 2.2 Hz, 1H), 7.32 – 7.22 (m, 5H), 7.06 – 6.99 (m, 4H), 6.70 (dd, *J* = 3.7, 0.9 Hz, 1H), 5.60 (s, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 3.69 – 3.55 (m, 4H), 2.23 (s, 3H), 1.96 (p, *J* = 6.2 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.3 (d, *J* = 245.5 Hz), 144.3, 143.6, 141.6, 138.5, 134.5, 132.2, 130.8, 130.6 (d, *J* = 3.4 Hz), 129.3, 128.4, 127.7, 127.6, 127.4 (d, *J* = 8.0 Hz), 126.7, 122.3 (d, *J* = 1.2 Hz), 120.1, 115.8 (d, *J* = 21.6 Hz), 76.5, 73.1, 67.2, 66.3, 30.2, 18.8 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.5 ppm.
HRMS Calculated for $[C_{28}H_{26}BrFO_2S+Na]^+$: 547.0713, Found: 547.0709.

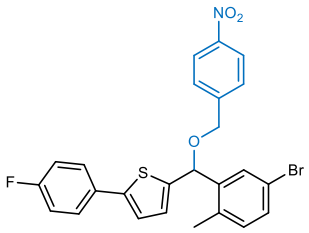


2-((5-bromo-2-methylphenyl)((4-chlorobenzyl)oxy)methyl)-5-(4-fluorophenyl)thiophene, **45.**
Reaction run at 0.2 mmol scale and 90.3 mg (90%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.77 (d, *J* = 2.2 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.39 – 7.27 (m, 5H), 7.07 – 6.99 (m, 4H), 6.72 (dd, *J* = 3.8, 0.9 Hz, 1H), 5.67 (s, 1H), 4.57 (d, *J* = 12.1 Hz, 1H), 4.51 (d, *J* = 12.1 Hz, 1H), 2.18 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.4 (d, *J* = 245.8 Hz), 144.0, 143.7, 140.9, 136.2, 134.6, 133.6, 132.4, 131.0, 130.9, 130.5 (d, *J* = 3.4 Hz), 129.5, 129.4, 129.2, 128.7, 127.4 (d, *J* = 8.0 Hz), 127.0, 122.4 (d, *J* = 1.2 Hz), 120.2, 115.8 (d, *J* = 21.7 Hz), 75.2, 69.9, 18.8 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.3 ppm.
HRMS Calculated for $[C_{25}H_{19}BrClFOS+Na]^+$: 522.9905, Found: 522.9899.

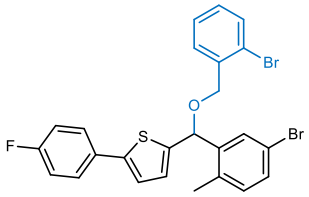


2-((5-bromo-2-methylphenyl)((4-methoxybenzyl)oxy)methyl)-5-(4-fluorophenyl)thiophene, **46.**

Reaction run at 0.2 mmol scale and 72.6 mg (73%) of yellow liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.78 (d, *J* = 2.2 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.35 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.07 – 6.98 (m, 4H), 6.69 (dd, *J* = 3.6, 0.9 Hz, 1H), 5.66 (s, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 3.81 (s, 3H), 2.17 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.3 (d, *J* = 245.7 Hz), 159.4, 144.1, 143.7, 141.2, 134.7, 132.3, 130.9, 130.6 (d, *J* = 3.4 Hz), 129.7, 129.6, 129.6, 127.4 (d, *J* = 8.0 Hz), 126.8, 122.3 (d, *J* = 1.2 Hz), 120.1, 115.8 (d, *J* = 21.6 Hz), 113.9, 74.5, 70.3, 55.3, 18.8 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.5 ppm.
HRMS Calculated for $[C_{26}H_{22}BrFO_2S+Na]^+$: 519.0400, Found: 519.0397.

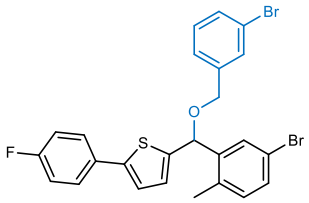


2-((5-bromo-2-methylphenyl)((4-nitrobenzyl)oxy)methyl)-5-(4-fluorophenyl)thiophene, **47.**
Reaction run at 0.2 mmol scale and 81.9 mg (79%) of yellow liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 8.23 (d, *J* = 8.7 Hz, 2H), 7.78 (d, *J* = 2.2 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.54 – 7.48 (m, 2H), 7.38 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.09 – 7.01 (m, 4H), 6.77 (dd, *J* = 3.6, 0.9 Hz, 1H), 5.73 (s, 1H), 4.69 (d, *J* = 13.1 Hz, 1H), 4.67 (d, *J* = 13.1 Hz, 1H), 2.21 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.4 (d, *J* = 245.7 Hz), 147.5, 145.3, 144.2, 143.1, 140.6, 134.6, 132.5, 131.2, 130.4 (d, *J* = 3.4 Hz), 129.2, 127.9, 127.4 (d, *J* = 8.0 Hz), 127.2, 123.8, 122.4 (d, *J* = 1.2 Hz), 120.2, 115.9 (d, *J* = 21.7 Hz), 76.2, 69.6, 18.8 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.1 ppm.
HRMS Calculated for $[C_{25}H_{19}BrFNO_3S+Na]^+$: 534.0145, Found: 534.0144.

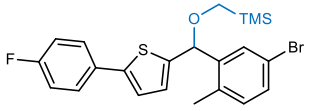


2-((5-bromo-2-methylphenyl)((2-bromobenzyl)oxy)methyl)-5-(4-fluorophenyl)thiophene}, **48.**
Reaction run at 0.2 mmol scale and 89.6 mg (82%) of white solid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.81 (d, *J* = 2.2 Hz, 1H), 7.59 – 7.46 (m, 4H), 7.39 – 7.31 (m, 2H), 7.16 (td, *J* = 7.7, 1.7 Hz, 1H), 7.06 – 6.99 (m, 4H), 6.75 (dd, *J* = 3.8, 0.9 Hz, 1H), 5.76 (s, 1H), 4.642 (d, *J* = 13.3 Hz, 1H), 4.639 (d, *J* = 13.3 Hz, 1H), 2.22 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.4 (d, *J* = 245.8 Hz), 144.0, 143.7, 141.0, 137.1, 134.7, 132.6, 132.4, 131.0, 130.6 (d, *J* = 3.4 Hz), 129.5, 129.4, 129.2, 127.6, 127.4 (d, *J* = 8.0 Hz), 127.0, 122.9,

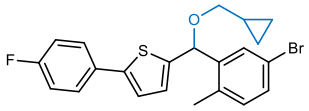
122.4 (d, J = 1.2 Hz), 120.2, 115.8 (d, J = 21.6 Hz), 76.1, 70.4, 18.8 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.4 ppm.
HRMS Calculated for $[C_{25}H_{19}Br_2FOS+Na]^+$: 566.9400, Found: 566.9396.



2-((5-bromo-2-methylphenyl)((3-bromobenzyl)oxy)methyl)-5-(4-fluoro–phenyl)thiophene, **49.**
Reaction run at 0.2 mmol scale and 99.4 mg (91%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.77 (d, J = 2.2 Hz, 1H), 7.54 – 7.48 (m, 3H), 7.44 (dt, J = 7.9, 1.6 Hz, 1H), 7.36 (dd, J = 8.1, 2.2 Hz, 1H), 7.30 (dt, J = 7.7, 1.4 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.08 – 7.00 (m, 4H), 6.73 (dd, J = 3.7, 0.9 Hz, 1H), 5.68 (s, 1H), 4.57 (d, J = 12.2 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H), 2.19 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.4 (d, J = 245.9 Hz), 144.0, 143.5, 140.8, 140.0, 134.6, 132.4, 131.0, 130.9, 130.8, 130.5 (d, J = 3.4 Hz), 130.1, 129.4, 127.4 (d, J = 8.0 Hz), 127.0, 126.3, 122.6, 122.4 (d, J = 1.2 Hz), 120.2, 115.8 (d, J = 21.7 Hz), 75.5, 69.9, 18.8 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.4 ppm.
HRMS Calculated for $[C_{25}H_{19}Br_2FNOS+Na]^+$: 566.9400, Found: 566.9399.

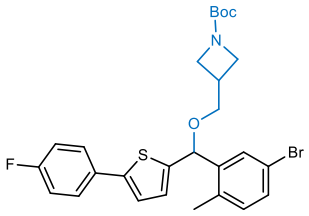


(((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methoxy)methyl)trimethylsilane, **50.**
Reaction run at 0.2 mmol scale and 76.9 mg (83%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.63 (d, J = 2.1 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.34 (dd, J = 8.1, 2.2 Hz, 1H), 7.08 – 6.99 (m, 4H), 6.66 (dd, J = 3.6, 1.0 Hz, 1H), 5.45 (s, 1H), 3.17 (d, J = 12.4 Hz, 1H), 3.10 (d, J = 12.4 Hz, 1H), 2.24 (s, 3H), 0.10 (s, 9H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.2 (d, J = 245.5 Hz), 144.8, 143.4, 141.7, 134.9, 132.2, 130.7 (d, J = 3.3 Hz), 130.6, 129.7, 127.4 (d, J = 8.0 Hz), 126.3, 122.2 (d, J = 1.2 Hz), 119.9, 115.7 (d, J = 21.6 Hz), 80.4, 63.0, 18.7, -3.0 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.7 ppm.
HRMS Calculated for $[C_{22}H_{24}BrFOSSi+Na]^+$: 485.0377, Found: 485.0377.

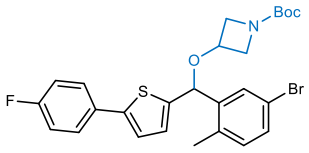


2-((5-bromo-2-methylphenyl)(cyclopropylmethoxy)methyl)-5-(4-fluoro–phenyl)thiophene, **51.**

Reaction run at 0.2 mmol scale and 75.1 mg (87%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.76 (d, J = 2.2 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.35 (dd, J = 8.1, 2.2 Hz, 1H), 7.08 – 7.00 (m, 4H), 6.74 (dd, J = 3.7, 0.8 Hz, 1H), 5.71 (s, 1H), 3.42 (dd, J = 10.1, 6.8 Hz, 1H), 3.34 (dd, J = 10.1, 6.9 Hz, 1H), 2.27 (s, 3H), 1.15 (dddd, J = 13.2, 6.8, 5.0, 2.6 Hz, 1H), 0.65 – 0.51 (m, 2H) , 0.30 – 0.17 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.3 (d, J = 245.6 Hz), 144.2, 143.6, 141.5, 134.6, 132.2, 130.7, 130.6 (d, J = 3.3 Hz), 129.4, 127.4 (d, J = 8.0 Hz), 126.7, 122.3 (d, J = 1.2 Hz), 120.1, 115.8 (d, J = 21.6 Hz), 75.7, 73.9, 18.8, 10.7, 3.25, 3.24 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.6 ppm.
HRMS Calculated for $[C_{22}H_{20}BrFOS+Na]^+$: 453.0295, Found: 453.0288.

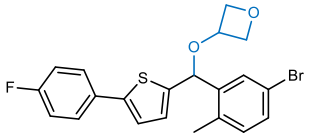


tert-butyl 3-(((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methoxy)methyl)azetidine-1-carboxylate, **52.**
Reaction run at 0.2 mmol scale and 78.7 mg (72%) of yellow liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.67 (d, J = 2.1 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.36 (dd, J = 8.1, 2.2 Hz, 1H), 7.08 – 7.01 (m, 4H), 6.73 (dd, J = 3.7, 0.8 Hz, 1H), 5.62 (s, 1H), 4.02 (td, J = 8.5, 2.1 Hz, 2H), 3.75 – 3.58 (m, 4H), 2.89 – 2.77 (m, 1H), 2.24 (s, 3H), 1.43 (s, 9H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.3 (d, J = 197.0 Hz), 156.4, 143.9, 143.6, 141.1, 134.5, 132.3, 132.2, 130.4 (d, J = 3.0 Hz), 129.2, 127.4 (d, J = 12.0 Hz), 126.8, 122.3 (d, J = 2.0 Hz), 120.1, 115.8 (d, J = 17.0 Hz), 79.4, 77.2, 76.9, 71.2, 64.6, 64.8, 28.4, 18.8 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.4 ppm.
HRMS Calculated for $[C_{27}H_{29}BrFO_3S+Na]^+$: 568.0928, Found: 568.0921.

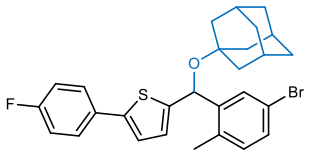


tert-butyl 3-((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methoxy)azetidine-1-carboxylate, **53.**
Reaction run at 0.2 mmol scale and 91.6 mg (86%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.76 (d, J = 2.1 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.36 (dd, J = 8.1, 2.2 Hz, 1H), 7.08 – 7.00 (m, 4H), 6.78 (dd, J = 3.7, 0.8 Hz, 1H), 5.59 (s, 1H), 4.37 (tt, J = 6.6, 4.5 Hz, 1H), 4.04 (dddd, J = 14.3, 9.4, 6.6, 1.0 Hz, 2H), 3.92 (ddd, J = 14.3, 9.3, 4.6 Hz, 2H), 2.20 (s, 3H), 1.43 (s, 9H) ppm.

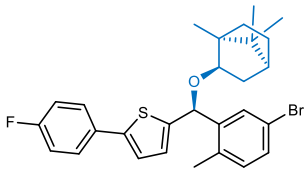
^{13}C NMR ($CDCl_3$, 100 MHz): 162.4 (d, J = 246.1 Hz), 156.3, 144.5, 142.8, 140.7, 134.2, 132.3, 131.1, 130.3 (d, J = 3.5 Hz), 129.1, 127.4 (d, J = 8.0 Hz), 127.3, 122.4 (d, J = 1.2 Hz), 120.1, 115.9 (d, J = 21.7 Hz), 79.7, 75.0, 66.4, 57.2 – 56.3 (m), 28.4, 18.8 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.2 ppm.
HRMS Calculated for $[C_{26}H_{27}BrFO_3S+Na]^+$: 554.0771, Found: 554.0767.



3-((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methoxy)oxetane, **54.**
Reaction run at 0.2 mmol scale and 39.9 mg (46%) of colorless liquid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.78 (d, J = 2.1 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.36 (dd, J = 8.1, 2.2 Hz, 1H), 7.08 – 6.99 (m, 4H), 6.77 (dd, J = 3.6, 0.8 Hz, 1H), 5.58 (s, 1H), 4.76 – 4.62 (m, 5H), 2.20 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.4 (d, J = 246.2 Hz), 144.4, 143.0, 140.8, 134.1, 132.3, 131.1, 130.3 (d, J = 3.4 Hz), 129.1, 127.4 (d, J = 8.0 Hz), 127.3, 122.4 (d, J = 1.2 Hz), 120.1, 115.9 (d, J = 21.8 Hz), 79.1, 75.3, 71.2, 18.8 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.1 ppm.
HRMS Calculated for $[C_{21}H_{18}BrFO_2S+Na]^+$: 455.0087, Found: 455.0083.



2-((((3*S*,5*S*,7*S*)-adamantan-1-yl)oxy)(5-bromo-2-methylphenyl)methyl)-5-(4-fluorophenyl)thiophene, **55.**
Reaction run at 0.2 mmol scale and 75.7 mg (74%) of white solid isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 7.83 (d, J = 2.2 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.32 (dd, J = 8.1, 2.2 Hz, 1H), 7.07 – 6.98 (m, 3H), 6.95 (d, J = 3.6 Hz, 1H), 6.42 (dd, J = 3.7, 1.0 Hz, 1H), 5.96 (s, 1H), 2.27 (s, 3H), 2.14 (q, J = 3.2 Hz, 3H), 1.83 (d, J = 11.3 Hz, 3H), 1.76(d, J = 11.3 Hz, 3H), 1.63 (d, J = 13.9 Hz, 3H), 1.60 (d, J = 13.9 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 162.2 (d, J = 245.4 Hz), 147.3, 144.5, 143.1, 133.2, 131.9, 130.4 (d, J = 3.4 Hz), 130.3, 130.2, 127.3 (d, J = 8.0 Hz), 125.8, 122.4 (d, J = 0.9 Hz), 119.8, 115.7 (d, J = 21.6 Hz), 75.0, 66.8, 42.6, 36.3, 30.7, 18.9 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -114.9 ppm.
HRMS Calculated for $[C_{28}H_{28}BrFNOS+Na]^+$: 533.0921, Found: 533.0916.



2-((*S*)-(5-bromo-2-methylphenyl)(((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)methyl)-5-(4-fluorophenyl)thiophene, **56a.**

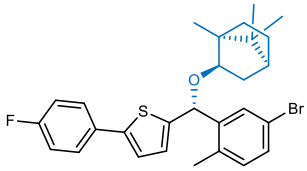
Reaction run at 0.2 mmol scale and 49.3 mg (48%) of white solid isolated.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.69 (d, J = 2.2 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.35 (dd, J = 8.0, 2.2 Hz, 1H), 7.08 – 7.01 (m, 3H), 6.99 (d, J = 3.6 Hz, 1H), 6.50 (dd, J = 3.7, 1.1 Hz, 1H), 5.62 (d, J = 1.1 Hz, 1H), 3.64 (ddd, J = 9.1, 3.3, 1.8 Hz, 1H), 2.29 – 2.20 (m, 4H), 2.17 – 2.07 (m, 1H), 1.78 (tq, J = 11.8, 4.1 Hz, 1H), 1.70 (t, J = 4.6 Hz, 1H), 1.38 (ddd, J = 11.9, 9.4, 4.4 Hz, 1H), 1.34 – 1.25 (m, 1H), 1.22 (dd, J = 12.8, 3.2 Hz, 1H), 0.86 (s, 3H), 0.85 (s, 3H), 0.76 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): 162.2 (d, J = 245.3 Hz), 146.2, 143.1, 141.5, 134.9, 132.2, 130.8 (d, J = 3.4 Hz), 130.7, 130.2, 127.4 (d, J = 7.9 Hz), 125.5, 122.3 (d, J = 1.2 Hz), 119.9, 115.7 (d, J = 21.7 Hz), 82.5, 74.6, 49.4, 47.9, 45.2, 36.0, 28.3, 26.9, 19.8, 19.0, 18.8, 13.7 ppm.

^{19}F NMR (377 MHz, $CDCl_3$): -114.8 ppm.

HRMS Calculated for $[C_{28}H_{30}BrFNOS+Na]^+$: 535.1077, Found: 535.1081.



2-((*R*)-(5-bromo-2-methylphenyl)(((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)methyl)-5-(4-fluorophenyl)thiophene, **56b.**

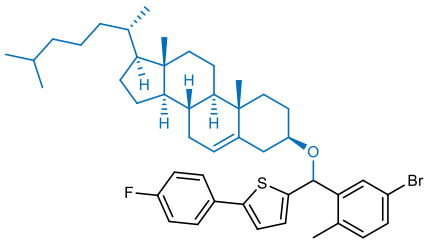
Reaction run at 0.2 mmol scale and 38.0 mg (37%) of white solid isolated.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.76 (d, J = 2.2 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.33 (dd, J = 8.1, 2.2 Hz, 1H), 7.07 – 6.98 (m, 4H), 6.64 (dd, J = 3.7, 0.9 Hz, 1H), 5.61 (s, 1H), 3.79 (ddd, J = 9.5, 3.5, 1.8 Hz, 1H), 2.23 (s, 3H), 2.22 – 2.16 (m, 1H), 2.02 (ddd, J = 13.1, 9.3, 4.1 Hz, 1H), 1.71 (tt, J = 12.2, 4.1 Hz, 1H), 1.61 (t, J = 4.6 Hz, 1H), 1.36 – 1.19 (m, 1H), 1.03 (dd, J = 13.1, 3.4 Hz, 1H), 0.95 (s, 3H), 0.85 (s, 3H), 0.79 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): 162.3 (d, J = 196.5 Hz), 145.2, 143.4, 142.8, 134.2, 132.1, 130.7 (d, J = 2.7 Hz), 130.5, 129.8, 127.3 (d, J = 6.4 Hz), 126.2 (d, J = 1.4 Hz), 122.1 (d, J = 2.4 Hz), 119.8, 115.7 (d, J = 17.3 Hz), 83.6, 76.0, 49.7, 47.7, 45.1, 35.9, 28.2, 27.1, 19.8, 19.0, 18.9, 14.1 ppm.

^{19}F NMR (377 MHz, $CDCl_3$): -114.8 ppm.

HRMS Calculated for $[C_{28}H_{30}BrFNOS+Na]^+$: 535.1077, Found: 535.1077.



2-((5-bromo-2-methylphenyl)(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methyl–heptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)methyl)-5-(4-fluorophenyl)thiophene, **57**.

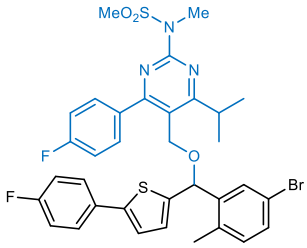
Reaction run at 0.2 mmol scale and 58.2 mg (39%) of pale-yellow liquid isolated.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.77 (d, J = 2.2 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.33 (dd, J = 8.1, 2.2 Hz, 1H), 7.07 – 6.98 (m, 4H), 6.66 (dd, J = 4.6, 0.8 Hz, 1H), 5.81 (s, 1H), 5.33 (dd, J = 12.1, 5.0 Hz, 1H), 3.31 (td, J = 10.2, 5.0 Hz, 1H), 2.50 – 2.30 (m, 2H), 2.25 (s, 3H), 2.05 – 1.75 (m, 4H), 1.70 – 0.93 (m, 22H), 1.02 (s, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.862 (d, J = 6.6 Hz, 3H), 0.857 (d, J = 6.6 Hz, 3H), 0.67 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): 163.3 (d, J = 245.4 Hz), 145.0, 143.5, 142.2, 140.7, 134.3, 132.2, 130.6 (d, J = 3.2 Hz), 129.6, 127.4 (d, J = 7.9 Hz), 126.4, 122.3, 121.88, 121.86, 120.1, 115.7 (d, J = 21.6 Hz), 73.1, 56.8, 56.1, 50.2, 42.3, 39.8, 39.5, 39.4, 39.2, 37.2, 36.9, 36.2, 35. 8, 31.9, 28.8, 28.5, 28.2, 28.0, 24.3, 23.8, 22.8, 22.6, 21.1, 19.4, 18.9, 18.7, 11.9 ppm.

^{19}F NMR (377 MHz, $CDCl_3$): -114.6 ppm.

HRMS Calculated for $[C_{45}H_{58}BrFOS\text{-}OC_{27}H_{45}]^+$ (ASAP-MS): 358.9900, Found: 358.9895.



N-(5-(((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methoxy)methyl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-*N*-methylmethanesulfonamide, **58**.

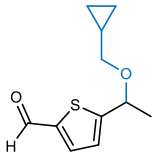
Reaction run at 0.2 mmol scale and 133 mg (93%) of pale-yellow liquid isolated.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.83 (d, J = 2.1 Hz, 1H), 7.77 – 7.70 (m, 2H), 7.54 – 7.47 (m, 2H), 7.39 (dd, J = 8.1, 2.2 Hz, 1H), 7.11 – 7.02 (m, 6H), 6.74 (dd, J = 3.6, 0.8 Hz, 1H), 5.68 (s, 1H), 4.46 (d, J = 10.2 Hz, 1H), 4.41 (d, J = 10.2 Hz, 1H), 3.58 (s, 3H), 3.51 (s, 3H), 3.34 (sept., J = 6.6 Hz, 1H), 2.22 (s, 3H), 1.34 (d, J = 6.6 Hz, 3H), 1.31 (d, J = 6.6 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): 178.3, 166.6, 163.7 (d, J = 248.4 Hz), 162.5 (d, J = 246.1 Hz), 158.2, 144.3, 143.1, 140.8, 134.3, 134.0 (d, J = 3.2 Hz), 132.4, 131.4 (d, J = 8.4 Hz), 131.2, 130.3 (d, J = 3.4 Hz), 129.2, 127.44 (d, J = 8.0 Hz), 127.37, 122.5 (d, J = 1.2 Hz), 120.1, 118.3, 115.9 (d, J = 21.7 Hz), 115.4 (d, J = 21.5 Hz), 76.6, 64.6, 42.4, 33.1, 31.7, 22.4, 22.2, 18.9 ppm.

^{19}F NMR (377 MHz, $CDCl_3$): -111.1, -114.0 ppm.

HRMS Calculated for $[C_{34}H_{32}BrF_2O_3S_2+Na]^+$: 712.1109, Found: 712.1112.



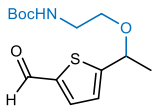
5-[1-(cyclopropylmethoxy)ethyl]thiophene-2-carbaldehyde, **59**

Reaction run at 0.4 mmol scale and 34.9 mg (42%) of pale-yellow liquid was isolated.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.87 (s, 1H), 7.65 (d, *J* = 3.8 Hz, 1H), 7.04 (d, *J* = 3.8 Hz, 1H), 4.73 (q, *J* = 6.5 Hz, 1H), 3.31 (dd, *J* = 9.9, 6.7 Hz, 1H), 3.22 (dd, *J* = 10.0, 7.1 Hz, 1H), 1.56 (d, *J* = 6.5 Hz, 3H), 1.06 (ddt, *J* = 10.8, 7.6, 3.8 Hz, 1H), 0.56 – 0.44 (m, 2H), 0.18 (dd, *J* = 4.7, 1.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 183.0, 159.8, 142.5, 136.4, 124.9, 73.9, 73.3, 24.2, 10.7, 3.2, 3.0.

HRMS Calculated for $[C_{11}H_{14}O_2S+H]^+$: 211.0787, Found: 211.0786.



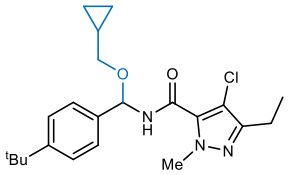
tert-butyl {2-[1-(5-formylthiophen-2-yl)ethoxy]ethyl}carbamate, **60**

Reaction run at 0.4 mmol and 36.7 mg (31%) of pale-yellow liquid was isolated.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.87 (s, 1H), 7.64 (d, *J* = 3.8 Hz, 1H), 7.04 (d, *J* = 3.8 Hz, 1H), 4.87 (b, 1H), 4.71 (q, *J* = 6.4 Hz, 1H), 3.49 (t, *J* = 5.1 Hz, 2H), 3.31 (q, *J* = 5.1 Hz, 2H), 1.55 (d, *J* = 6.4 Hz, 3H), 1.44 (s, 9H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 182.9, 158.8, 155.9, 142.8, 136.3, 125.1, 79.4, 74.0, 68.2, 40.5, 28.4, 23.8.

HRMS Calculated for $[C_{14}H_{21}NO_4S+Na]^+$: 322.1084, Found: 322.1078.



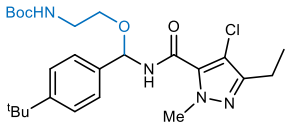
4-chloro-3-ethyl-N-[cyclopropylmethoxy(4-tert-butylphenyl)methyl]-1-methyl-1H-pyrazole-5-carboxamide, **61**

Reaction run at 0.2 mmol and 39.0 mg (40%) of pale yellow liquid was isolated.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 9.1 Hz, 1H), 6.42 (d, *J* = 9.1 Hz, 1H), 4.14 (s, 3H), 3.57 (dd, *J* = 10.2, 7.0 Hz, 1H), 3.51 (dd, *J* = 10.3, 6.9 Hz, 1H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.32 (s, 9H), 1.23 (t, *J* = 7.6 Hz, 3H), 0.55 (dq, *J* = 7.8, 2.6 Hz, 2H), 0.36 – 0.19 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.4, 151.7, 149.7, 136.1, 130.6, 129.1, 128.8, 125.7, 125.6, 108.1, 80.0, 73.4, 40.8, 34.6, 31.3, 19.2, 12.8, 10.6, 3.3, 3.0.

HRMS Calculated for $[C_{22}H_{30}ClN_3O_2+Na]^+$: 426.1919, Found: 426.1913.



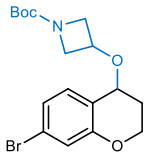
4-chloro-3-ethyl-N-[cyclopropylmethoxy(4-tert-butylphenyl)methyl]-1-methyl-1H-pyrazole-5-carboxamide, **62**

Reaction run at 0.4 mmol and 52.3 mg (27%) of pale-yellow semisolid was isolated by reverse phase column chromatography using Biotage Isolera One® with reusable 60 g SNAP C18® cartridges with H_2O:MeCN as the eluents.

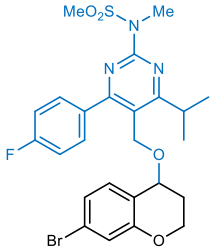
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 – 7.29 (m, 4H), 7.21 (d, J = 9.2 Hz, 1H), 6.27 (d, J = 8.9 Hz, 1H), 4.99 (br, 1H), 4.08 (s, 3H), 3.72 (dt, J = 10.4, 5.3 Hz, 1H), 3.63 (dt, J = 9.9, 5.0 Hz, 1H), 3.33 (d, J = 5.4 Hz, 2H), 2.55 (q, J = 7.6 Hz, 2H), 1.36 (s, 9H), 1.26 (s, 9H), 1.16 (t, J = 7.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 157.6, 154.9, 151.0, 148.7, 134.4, 129.4, 124.7, 124.7, 112.9, 107.2, 79.5, 66.7, 39.8, 39.4, 33.7, 30.7, 28.7, 27.4, 18.2, 11.8.

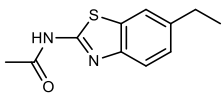
HRMS Calculated for $[C_{25}H_{37}ClN_4O_4+NH_4]^+$: 510.2842, Found: 510.2834.



tert-butyl 3-[(7-bromo-3,4-dihydro-2*H*-1-benzopyran-4-yl)oxy]azetidine-1-carboxylate, **63**
Reaction run at 0.4 mmol scale and 68.6 mg (45%) of colorless semisolid was isolated.
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.26 (d, *J* = 2.6 Hz, 1H), 6.73 (d, *J* = 8.7 Hz, 1H), 4.45 (tt, *J* = 6.6, 4.5 Hz, 1H), 4.34 (t, *J* = 3.8 Hz, 1H), 4.30 (td, *J* = 10.6, 3.8 Hz, 1H), 4.24 (dt, *J* = 11.0, 4.1 Hz, 1H), 4.15 (dd, *J* = 8.9, 7.0 Hz, 1H), 4.04 (dd, *J* = 9.0, 6.7 Hz, 1H), 3.89 (dd, *J* = 9.2, 4.5 Hz, 1H), 3.74 (dd, *J* = 9.3, 4.4 Hz, 1H), 2.03 (m, 2H), 1.44 (s, 9H) ppm.
^{13}C NMR (126 MHz) δ 156.3, 154.0, 132.9, 132.5, 122.8, 119.1, 112.0, 79.7, 69.4, 65.7, 62.1, 28.4, 27.7 ppm.
HRMS Calculated for $[C_{17}H_{22}NO_4+H]^+$: 384.0805, Found: 384.0801.

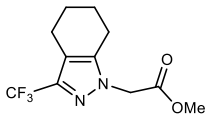


N-(5-((7-bromo-3,4-dihydro-2*H*-1-benzopyran-4-oxy)methyl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-*N*-methylmethanesulfonamide **64**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.33 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.08 (t, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 1H), 4.50 (q, *J* = 10.0 Hz, 2H), 4.43 (t, *J* = 3.7 Hz, 1H), 4.32 (m, 2H), 3.56 (s, 3H), 3.50 (s, 3H), 3.31 (hept, *J* = 6.7 Hz, 1H), 2.30 – 2.00 (m, 2H), 1.32 (t, *J* = 7.3 Hz, 6H).
^{13}C NMR ($CDCl_3$, 101 MHz) δ 178.0, 166.5, 163.7 (d, *J* = 250.2 Hz), 158.1, 153.9, 133.9, 132.8 (d, *J* = 2.4 Hz), 131.3 (d, *J* = 8.4 Hz), 126.9 (d, *J* = 275.4 Hz), 122.9, 119.2, 118.4, 115.3 (d, *J* = 21.6 Hz), 111.9, 70.6, 63.5, 62.1, 42.4, 33.1, 31.6, 27.5, 22.2, 22.1.
^{19}F NMR (377 MHz, $CDCl_3$): -110.9 ppm.
HRMS Calculated for $[C_{25}H_{27}BrFN_3O_4S+H]^+$: 564.0962, Found: 564.0964.

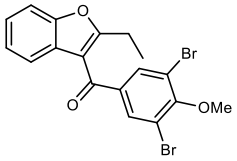


N-(6-ethyl-1,3-benzothiazol-2-yl)acetamide, **65**.
Reaction run at 2.5 mmol scale and 473 mg (86%) of off-white non-crystalline powder was isolated.

^{1}H NMR ($CDCl_3$, 400 MHz): 10.01 (s, 1H), 7.69 (m, 2H), 7.31 (m, 1H), 2.80 (q, *J* = 7.5 Hz, 2H), 2.32 (s, 3H), 1.32 (t, 3H) ppm.
^{13}C NMR ($CDCl_3$, 126 MHz): 168.8, 159.4, 145.7, 140.6, 132.0, 126.8, 120.3, 120.0, 28.9, 23.5, 15.9 ppm.
HRMS Calculated for + $[C_{11}H_{12}N_2OS+H]^+$: 221.0743, Found: 221.0737.



methyl [3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]acetate, **66.**
Reaction run at 2.0 mmol scale and 347 mg (66%) of white crystals was isolated.
Mp: 145-148°C. ^{1}H NMR ($CDCl_3$, 400 MHz): 4.82 (s, 2H), 3.76 (s, 3H), 2.56 (m, 4H), 1.80 (m, 4H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz): 167.6, 141.3, 139.2 (q, *J* = 36.7 Hz), 121.9 (q, *J* = 269.1 Hz), 115.5 (q, *J* = 1.5 Hz), 52.7, 50.5, 22.2, 22.0, 21.1, 19.9 ppm.
^{19}F NMR (377 MHz, $CDCl_3$): -61.7 ppm.
HRMS Calculated for + $[C_{11}H_{13}F_3N_2O_2+H]^+$: 263.1002, Found: 263.0999.



(3,5-dibromo-4-methoxyphenyl)(2-ethyl-1-benzofuran-3-yl)methanone, **67.**
Reaction run at 4.0 mmol scale and 1.67 g (95%) of white non-crystalline powder was isolated.
^{1}H NMR ($CDCl_3$, 400 MHz): 8.01 (s, 2H), 7.53 (dt, *J* = 8.2 Hz, *J* = 0.9 Hz, 1H), 7.44 (dt, *J* = 7.6 Hz, *J* = 0.9 Hz, 1H), 7.34 (ddd, *J* = 8.3 Hz, *J* = 7.3 Hz, *J* = 1.5 Hz, 1H), 7.27 (td, *J* = 7.5 Hz, *J* = 1.1 Hz, 1H), 4.01 (s, 3H), 2.92 (q, *J* = 7.5 Hz, 2H), 1.38 (t, *J* = 7.5 Hz, 3H)
^{13}C NMR ($CDCl_3$, 100 MHz):188.1, 166.9, 157.7, 153.7, 137.2, 133.6, 126.4, 124.7, 123.9, 121.0, 118.5, 115.3, 111.2, 60.9, 22.1, 12.2.
HRMS Calculated for + $[C_{19}H_{16}Br_2O_4+H]^+$: 436.9383, Found: 436.9380.

X. Details of DFT Calculations

1. Computational details

All density functional theory (DFT) calculations were performed with the Gaussian 16 (rev. A.03) electronic structure program suite.[19] As noted in the text, geometry optimization and frequency calculations were done at the B3LYP-D3(BJ)/basis-I level of theory,[20–23] where basis-I is the 6-31G(d,p)[24] basis set for non-metal atoms and the Stuttgart/Dresden effective core potential with its associated basis set (SDD) for Cu.[25] An "ultrafine" grid was used for numerical integration in DFT, together with an integral accuracy set to 10^{-12}. The natures of all stationary points were verified by calculating vibrational frequencies at the same level of theory; frequencies below 50 cm^{-1} were replaced with a value of 50 cm^{-1} in the vibrational partition function when computing thermal contributions to free energies (T = 313.15 K). For a best estimate of Gibbs free energies, single-point electronic energies were recomputed for the B3LYP-D3(BJ)/basis-I geometries using the M06-L[26] density functional and the def2-TZVP basis set[27] for non-metals and def2-TZVP basis /SDD pseudo potential for Cu (basis-II). All geometry optimizations, frequency calculations and single-point electronic energies employed the SMD continuum solvation model.[28] To mimic the 4:1 mixture of DCM:HFIP (DCM = Dichloromethane; ε=8.93 and HFIP = Hexafluoro-2-propanol; ε=16.75[29]) used experimentally, solvent parameters for 5-nonanone having ε = 10.6 ($\approx \frac{4}{5}\varepsilon$(DCM)+ $\frac{1}{5}\varepsilon$(HFIP)) were employed. In some cases, transition-state (TS) geometries were located on the broken-symmetry (BS) singlet surface (e.g., TS1 and TS3, where the substrates pass from two closed-shell singlet species to two open-shell doublet species), and in those instances, the final electronic energies were spin-purified using the scheme proposed by Yamaguchi et al.[30]

2. Cartesian coordinates of structures

Cartesian coordinates of all DFT-optimized structures are assembled in a separate coordinate file (.xyz).

3. Energetics for reactivity calculations

Single point electronic energies employing SMD solvation effects, E(sol), spin-purified electronic energies for broken-symmetry singlet TS structures, E'(sol), and the absolute solution-phase Gibbs free energies, G(sol) of all relevant species are presented in Supplementary Tables 13.

Supplementary Table 13. Solution phase electronic energies, E(sol)/E_h, spin-purified electronic energies, E'(sol)/E_h and absolute solution-phase Gibbs free energies, G(sol)/E_h (at 313.15K) computed at the M06-L/basis-II/SMD(ε = 10.6)//B3LYP-D3(BJ)/basis-I/SMD(ε = 10.6) level of theory.

File Description	***E*(sol)/a.u.**	***E*'(sol)/a.u. (Spin-purified)**	***G*(sol)/a.u. (*T* = 313.15 K)**
$LCu^{I}(Cl)$	-1149.73773		-1149.632618
F-NSI	-1715.320927		-1715.158911
H-NSI	-1616.142953		-1615.96973
NSI(•)	-1615.471227		-1615.313321
NSI(–)	-1615.679538		-1615.51786
TS-1	-2865.063999	-2865.067714	-2864.776992
$LCu^{II}(Cl)(F)$	-1249.609784		-1249.502365
$LCu^{II}(Cl)(NSI)$	-2765.28316		-2764.989907
$LCu^{II}(Cl)(OMe)$	-1264.869513		-1264.726259
Ph-CH_2-Me	-310.9473752		-310.8210522
Ph-CH(•)-Me	-310.3031632		-310.1918802
Ph-CH(+)-Me (**E**)	-310.1371506		-310.0212886
TS-2	-1926.426694		-1926.119146
TS-3	-1575.185323	-1575.188874	-1574.910157
LCu^{III}-(Cl)(OMe)(CH(Me)(Ph)) (**E'**)	-1575.199976		-1574.919569
TS-4	-1575.184034		-1574.905885
MeO-CH(Me)(Ph) (**F**)	-425.4950085		-425.3395945
MeOH	-115.7529859		-115.7226519
HF	-100.4762		-100.481249
HCl	-460.8148911		-460.8240061
H-P(O)$(OMe)_2$	-647.6170277		-647.5485837
Cl-P(O)$(OMe)_2$	-1107.263576		-1107.20508
F-P(O)$(OMe)_2$	-746.9396785		-746.8789075
NSI-P(O)$(OMe)_2$	-2262.578236		-2262.333056

*Minimum has a very small imaginary frequency ($10i$ cm^{-1}) assigned to numerical uncertainty in the integration grid and replaced with 50 cm^{-1} in the vibrational partition function.

XI. References

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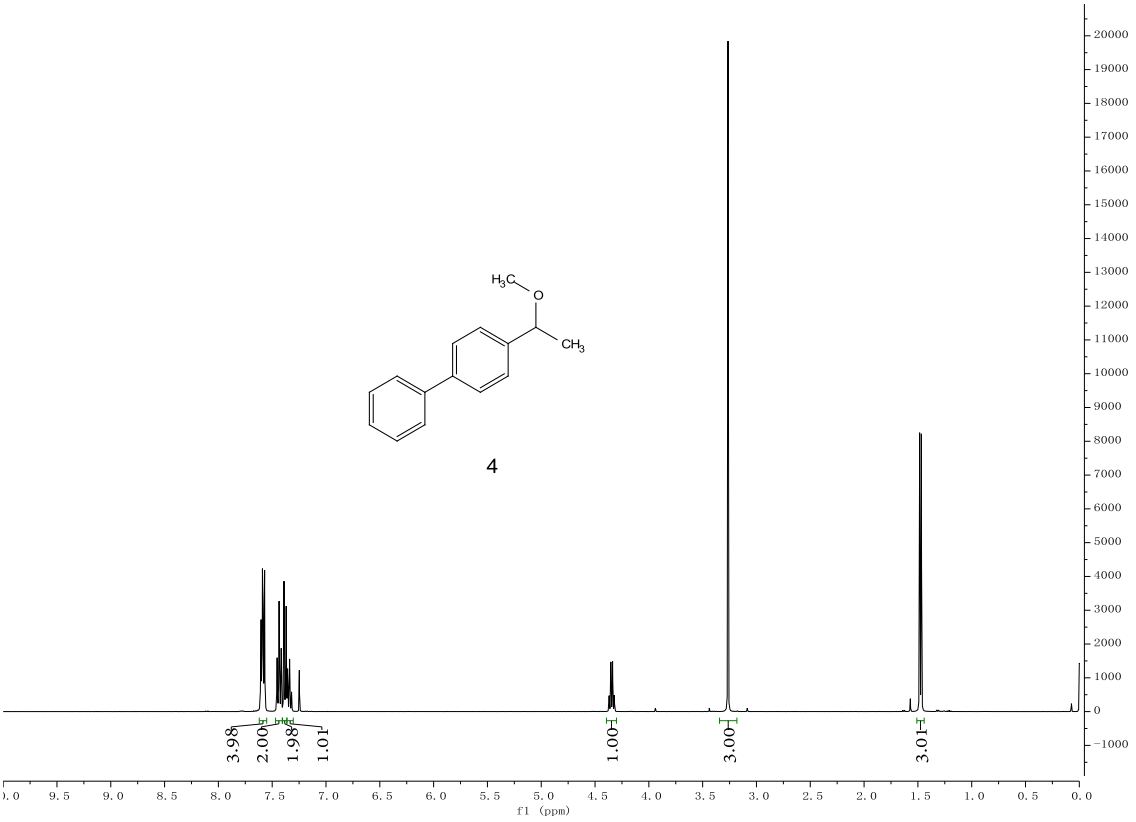
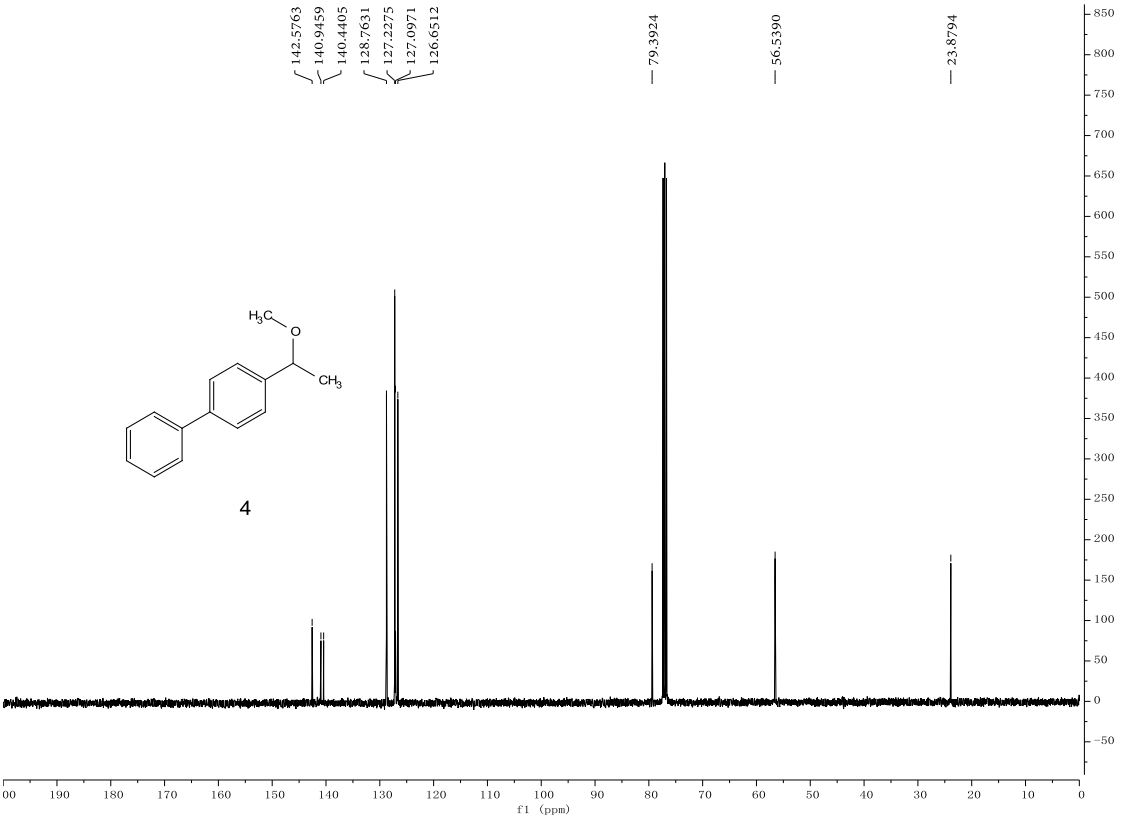
XII. NMR spectral Data

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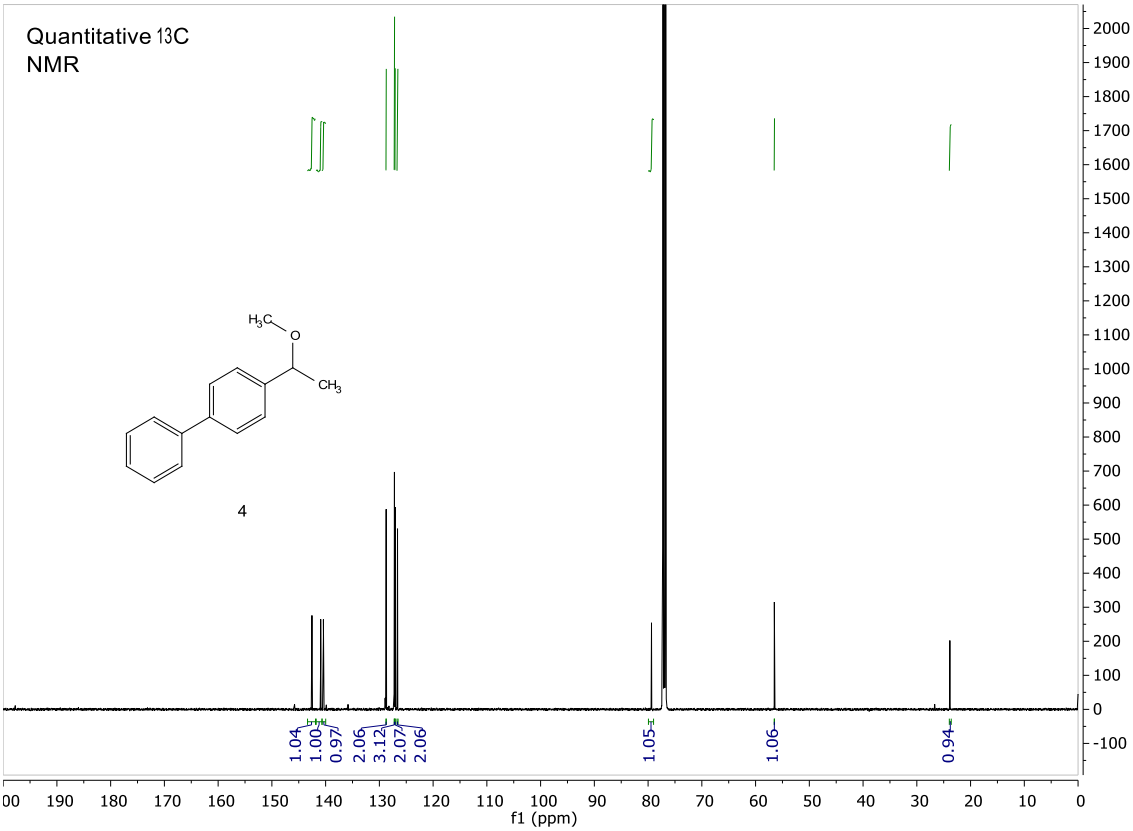
CH3
4
f1 (ppm)


Quantitative 13C
NMR
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O
CH3
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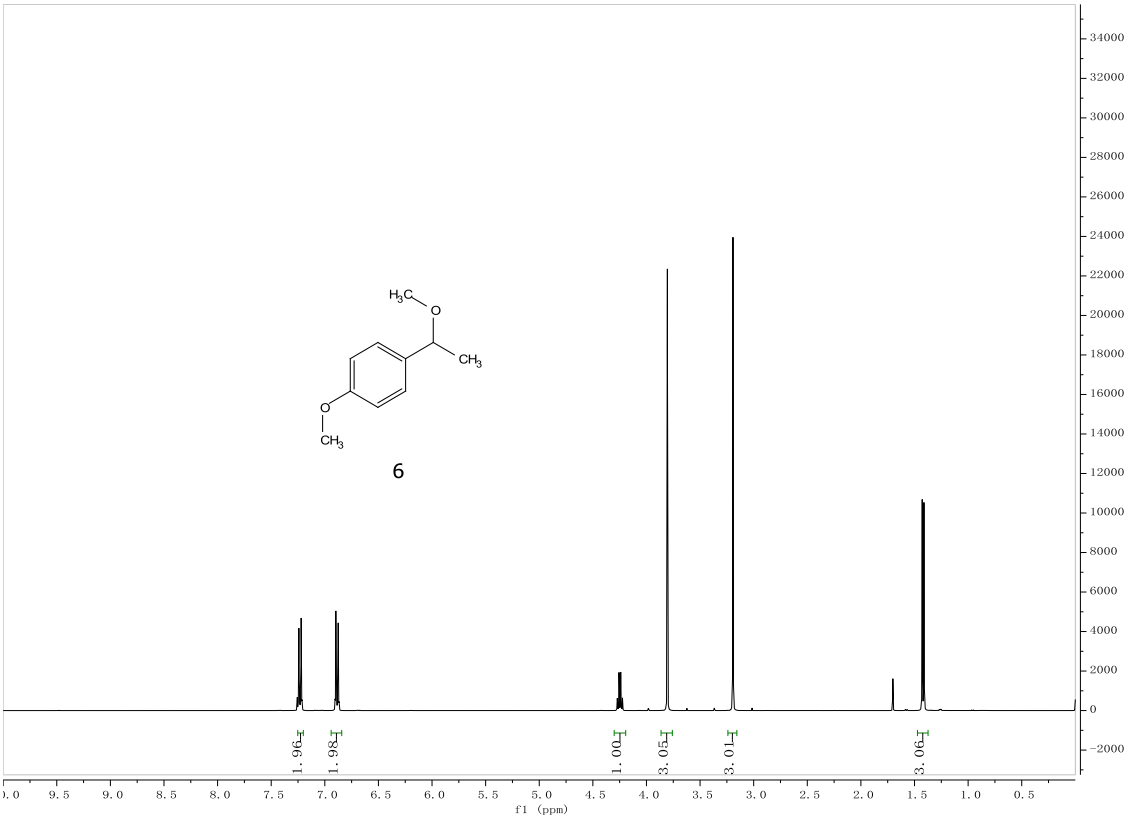
1.06
0.94
f1 (ppm)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3.06
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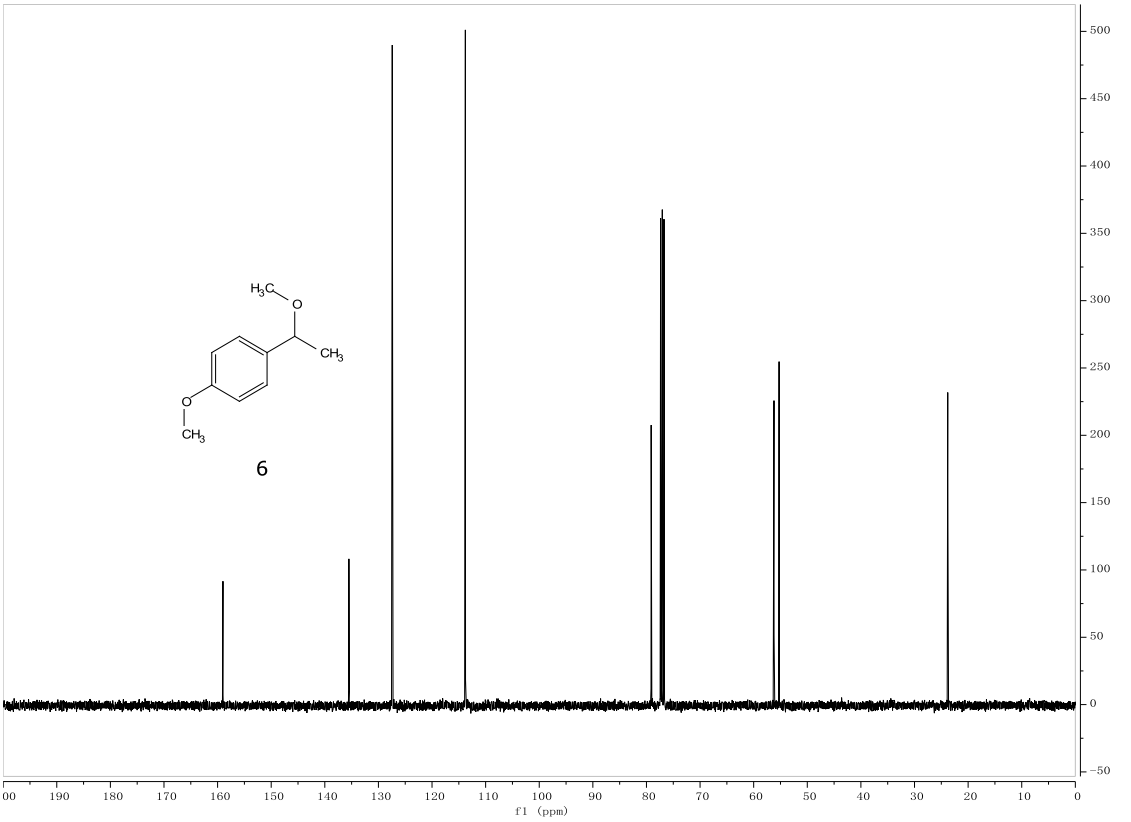
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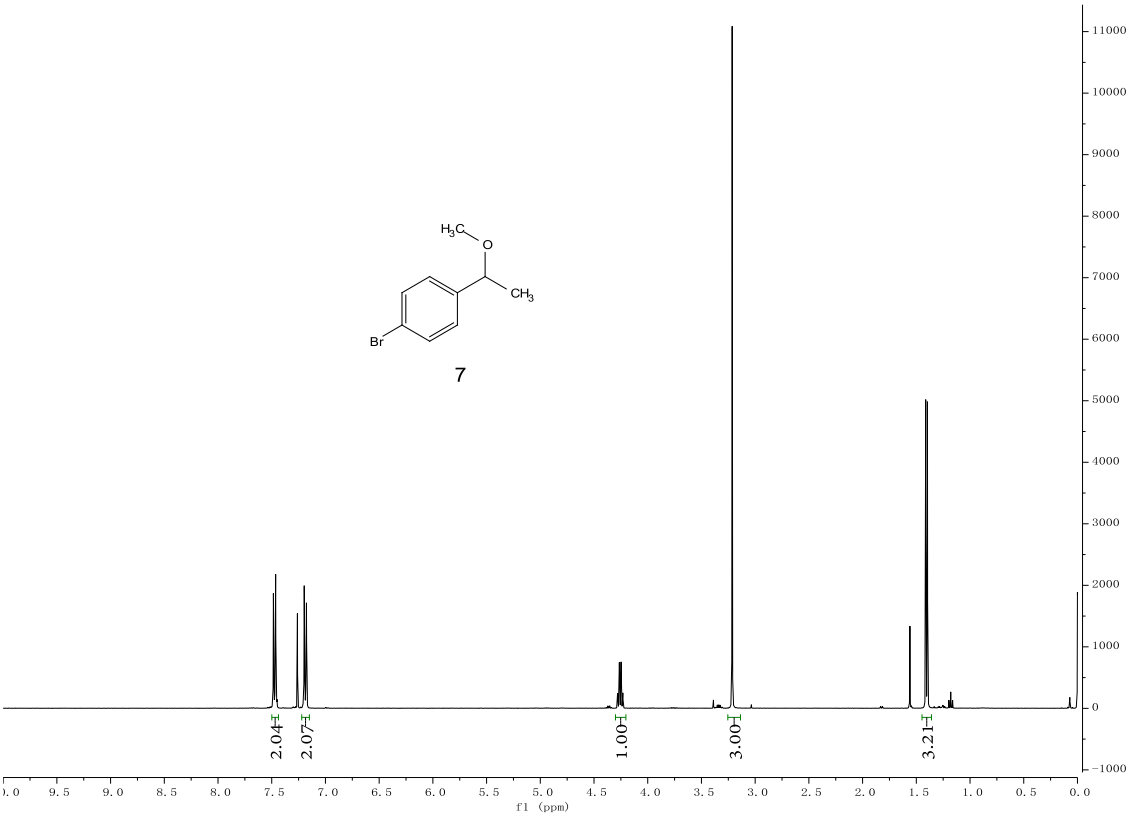
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Br
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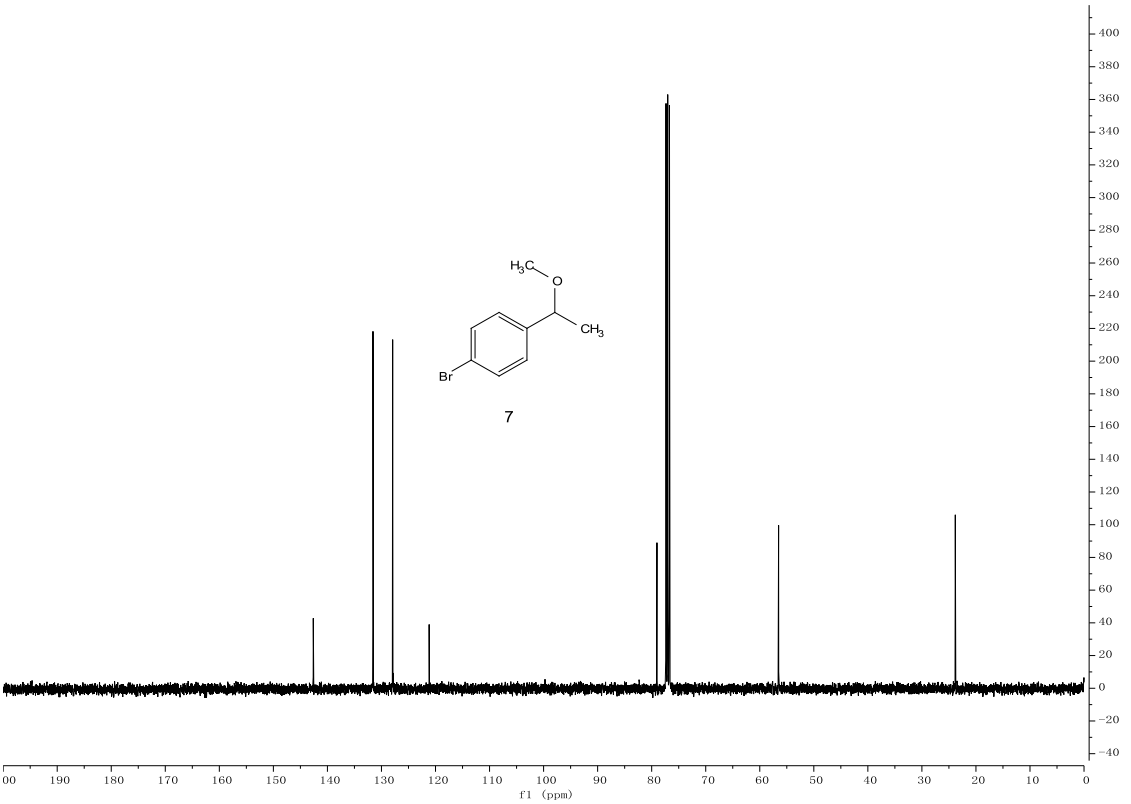
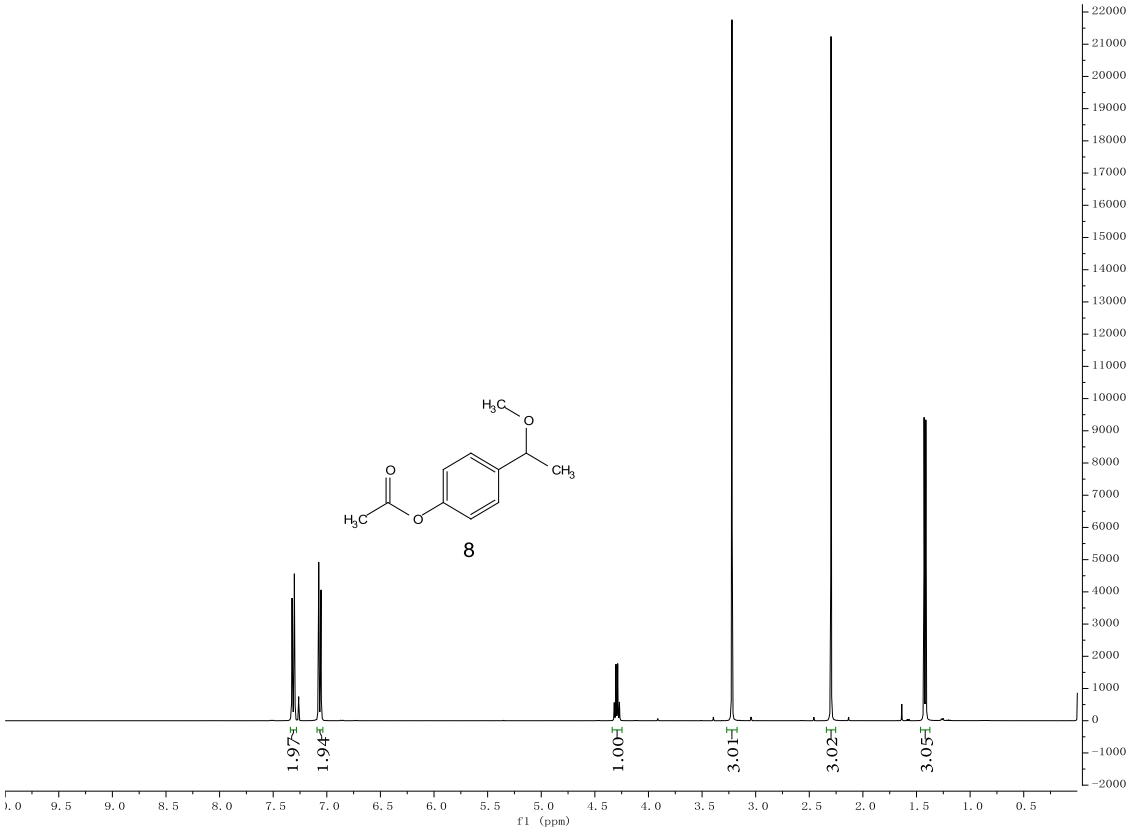
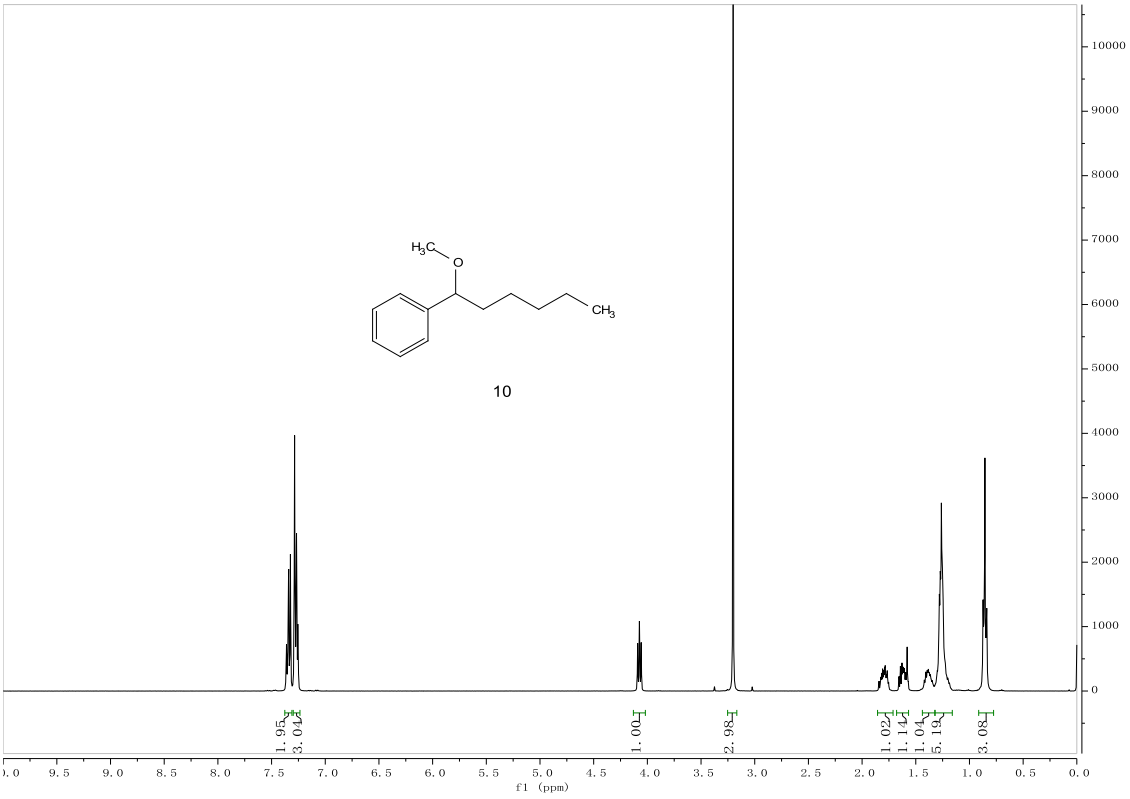
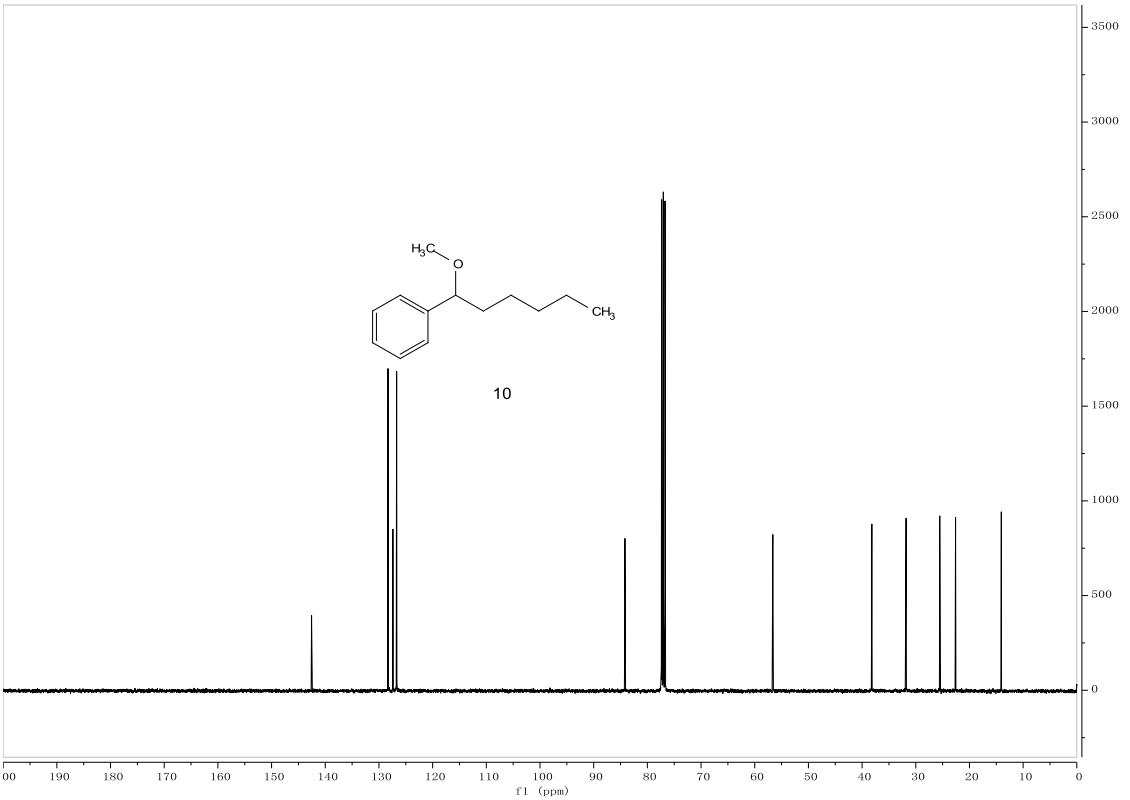
3.21
f1 (ppm)

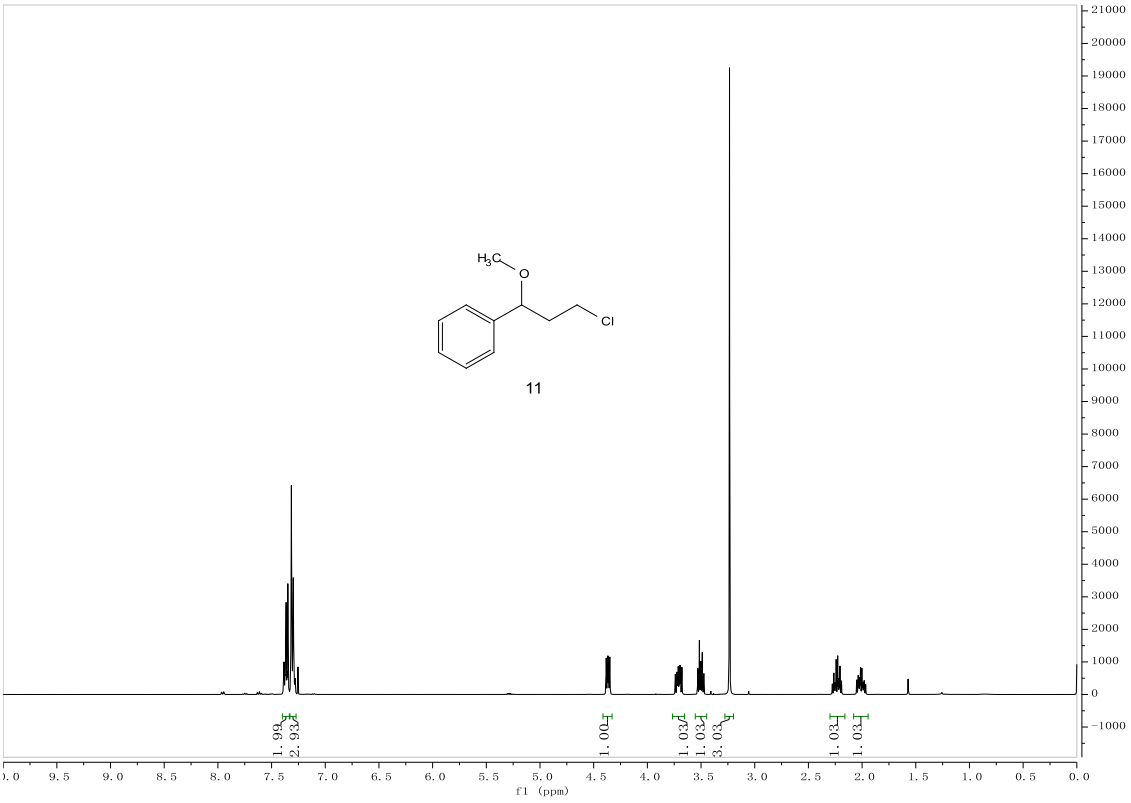

H3C
O
CH3
Br
7
f1 (ppm)

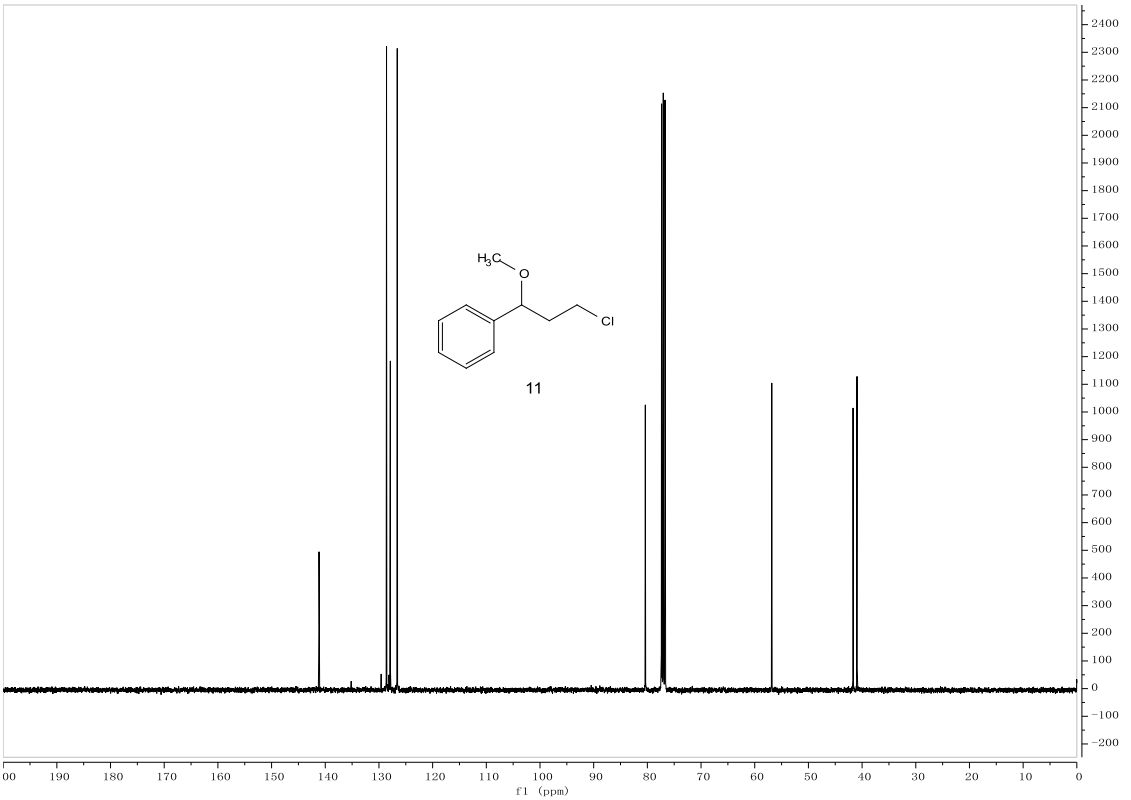

H3C
O
CH3
O
H3C
O
8
1.97
1.94
1.00
3.01
3.02
3.05
f1 (ppm)

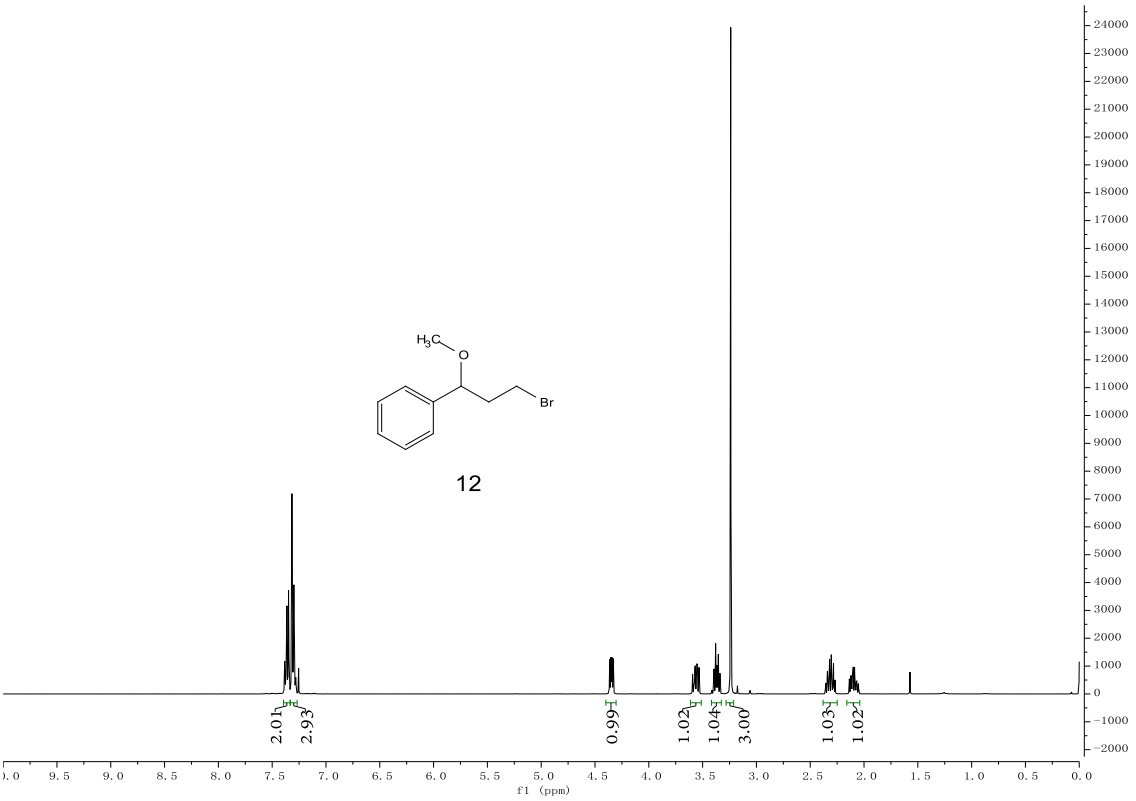

H3C
O
CH3
O
H3C
O
8
f1 (ppm)

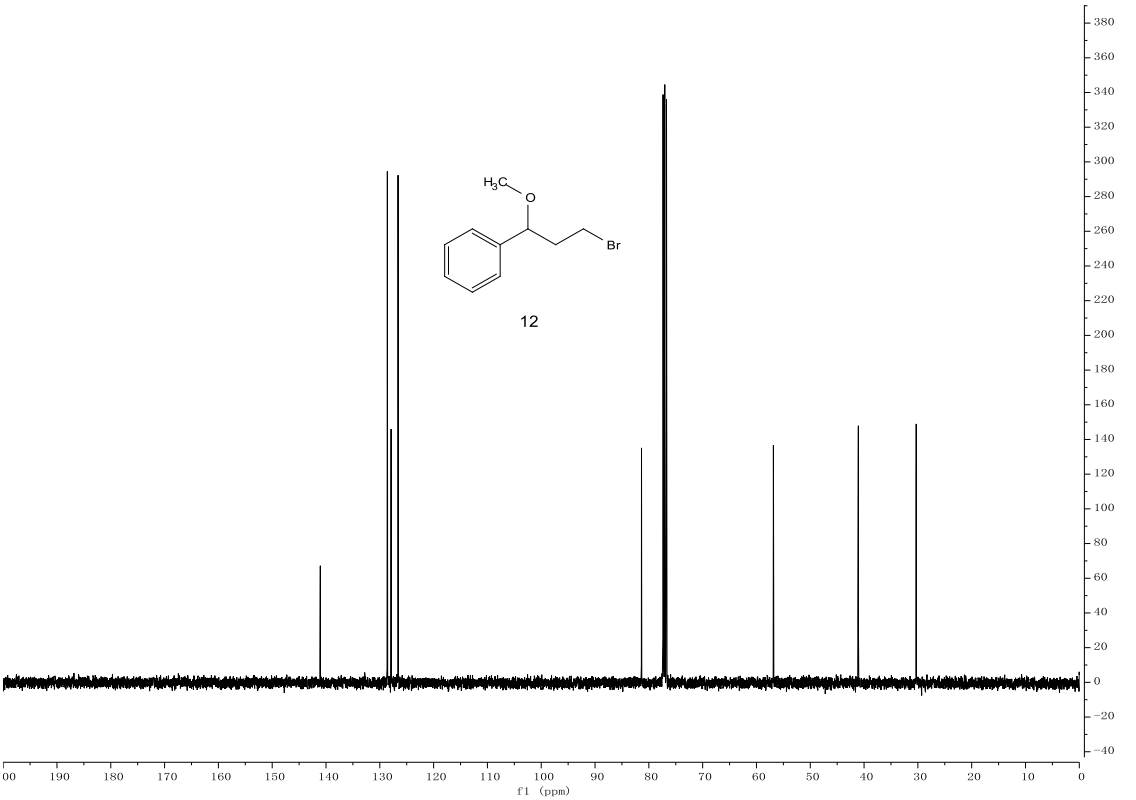

H3C
O
CH3
10
1.95
3.04
1.00
2.98
1.02
1.14
1.04
5.19
3.08
f1 (ppm)

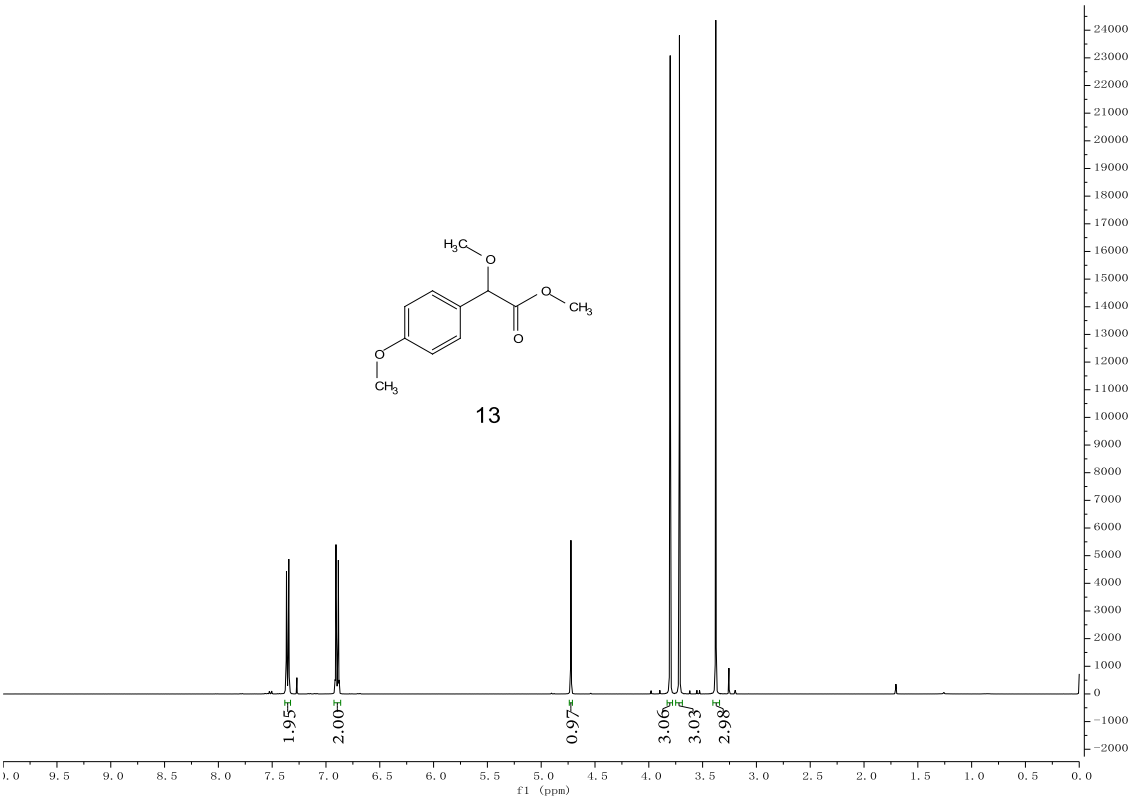

H3C
O
CH3
10
f1 (ppm)

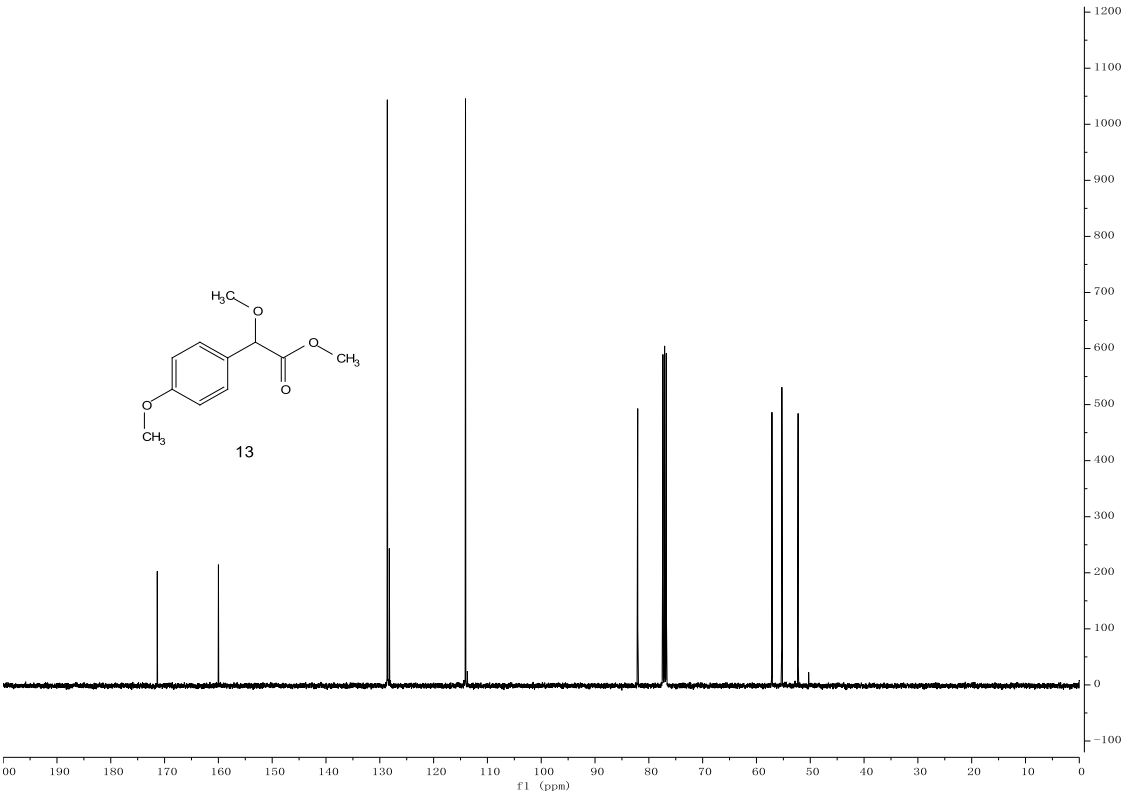

H3C
O
Cl
11
1.99
2.93
1.00
1.03
1.03
3.03
1.03
1.03
f1 (ppm)

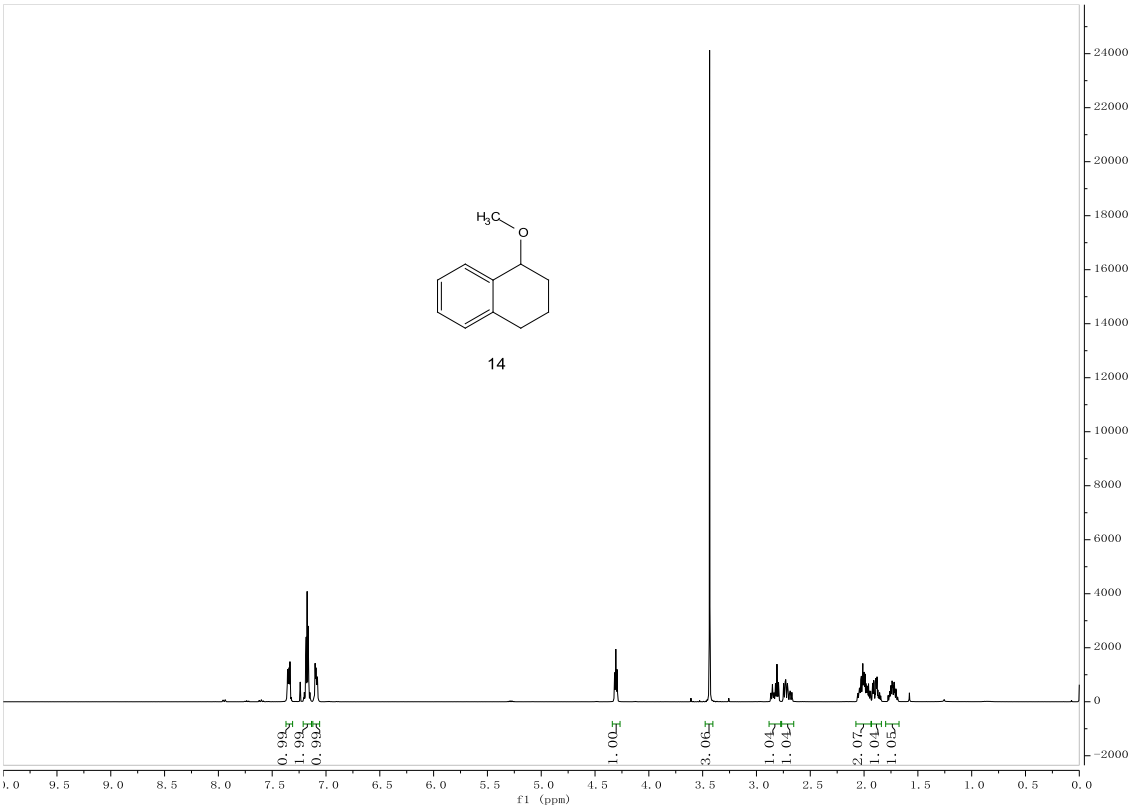

H3C
O
Cl
11
f1 (ppm)

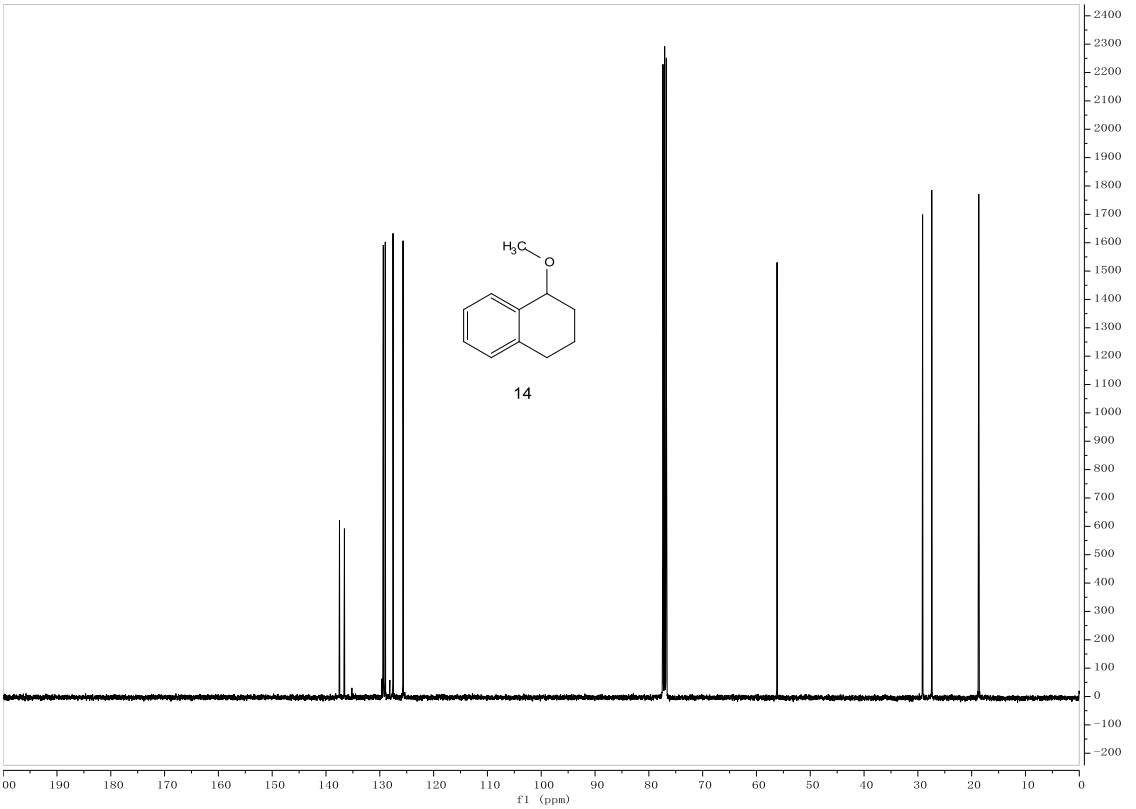

H3C
O
Br
12
2.01
2.93
0.99
1.02
1.04
3.00
1.03
1.02
f1 (ppm)

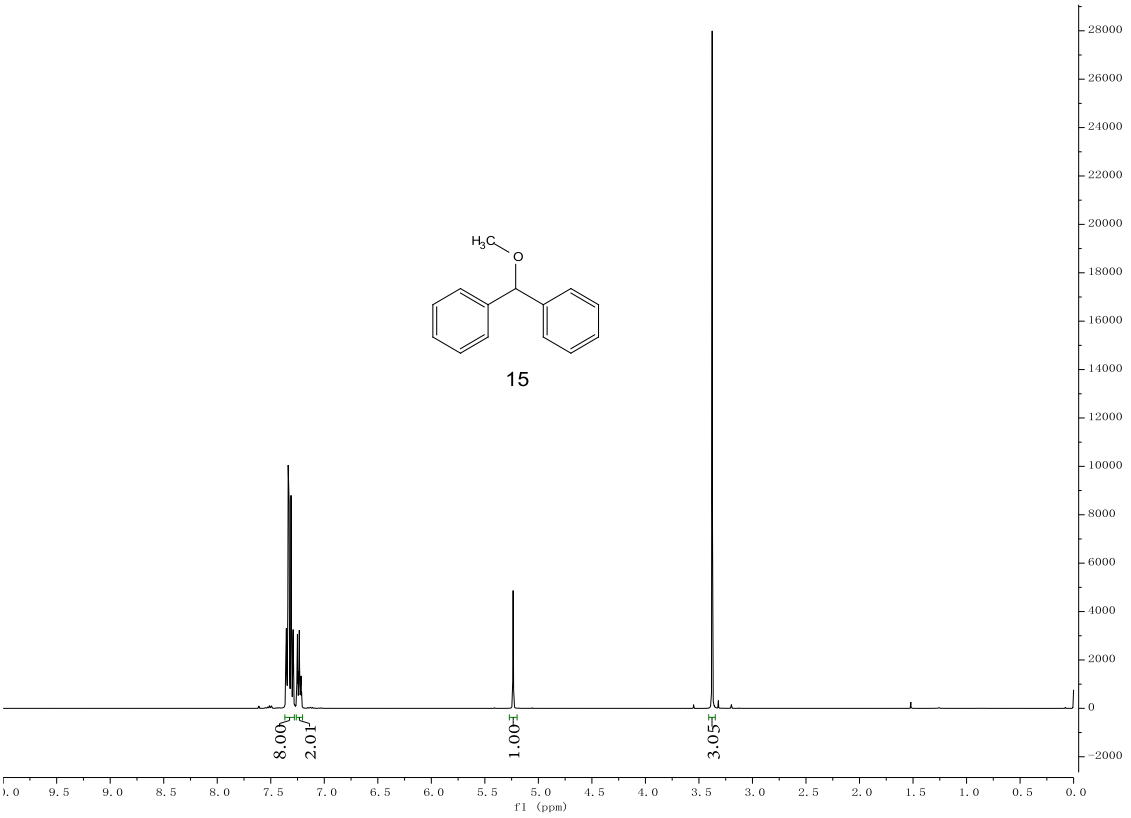

H3C
O
Br
12
f1 (ppm)


13
1.95
2.00
0.97
3.06
3.03
2.98
f1 (ppm)

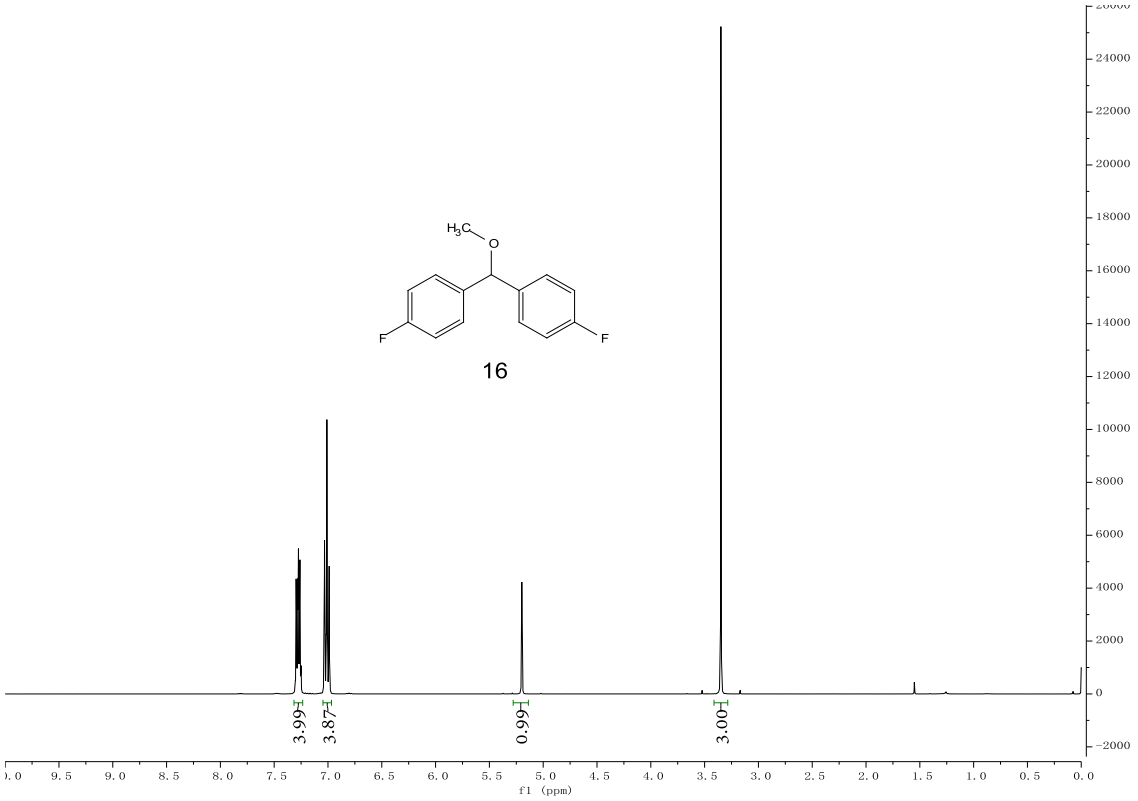

13
f1 (ppm)

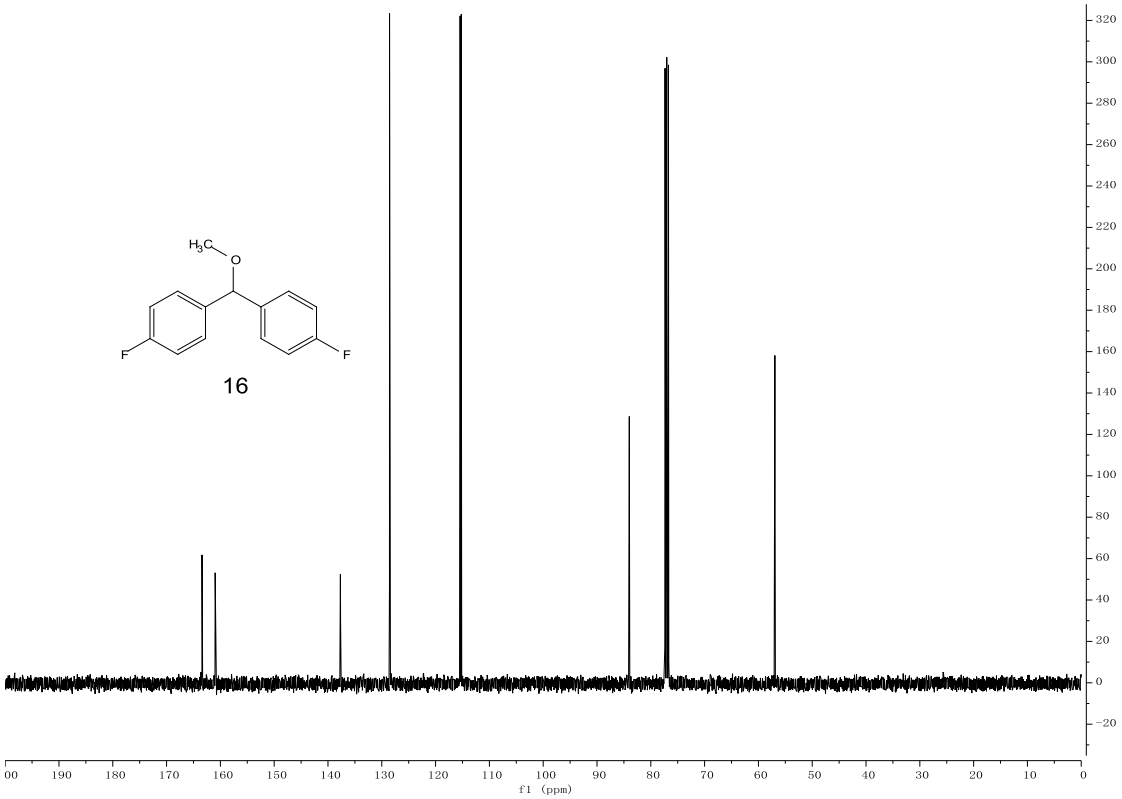

H3C
O
14
0.99
1.99
0.92
1.00
3.06
1.04
1.04
2.07
1.04
1.05
f1 (ppm)

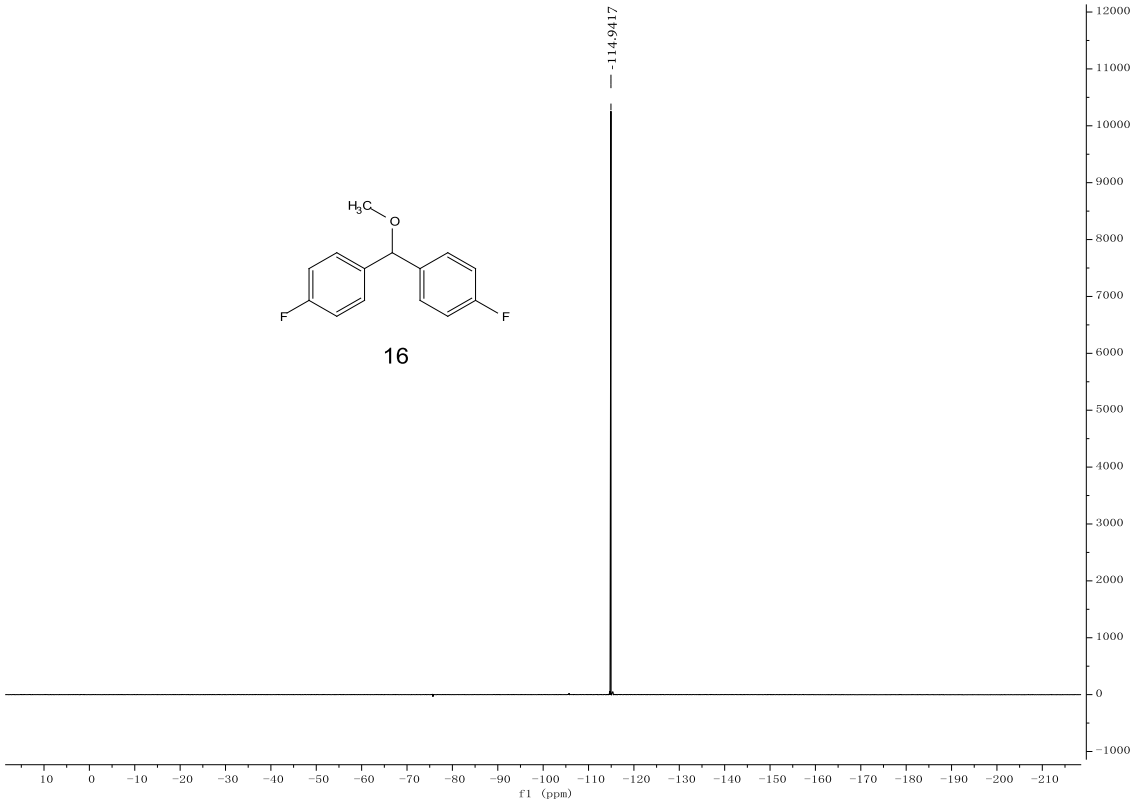

H3C
O
14
f1 (ppm)

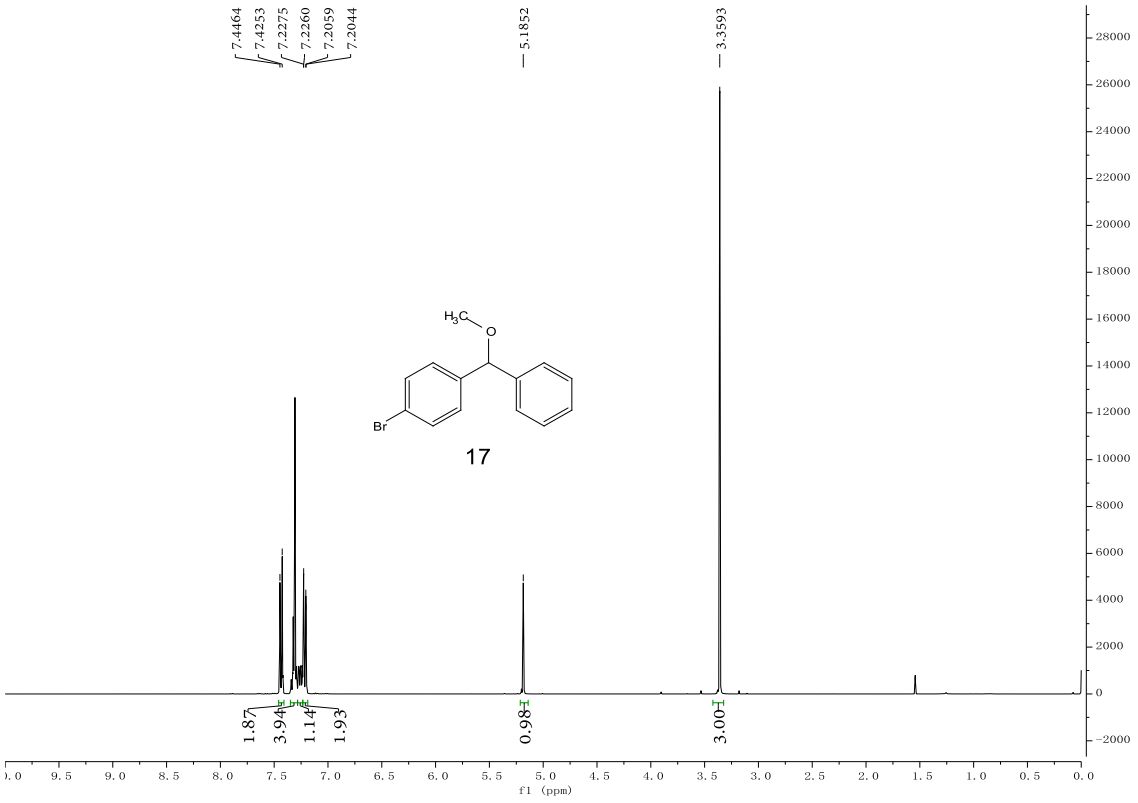

H3C
O
15
8.00
2.01
1.00
3.05
f1 (ppm)

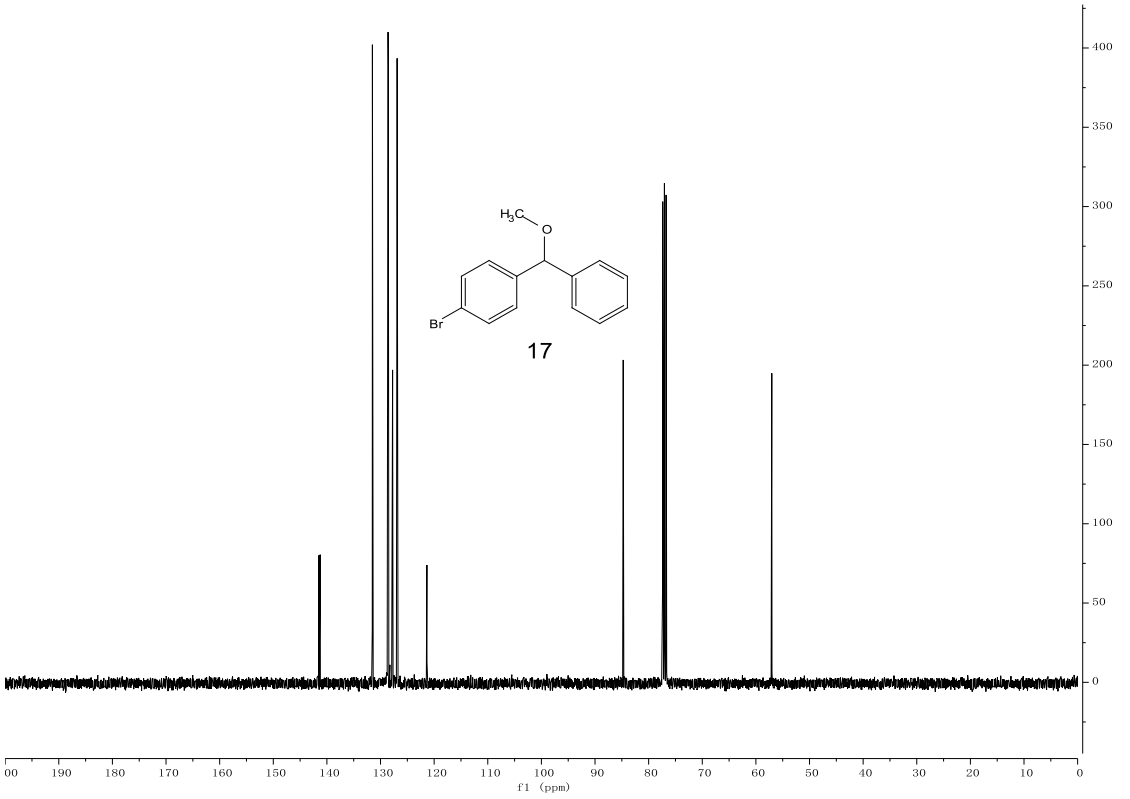

H3C
O
15
f1 (ppm)

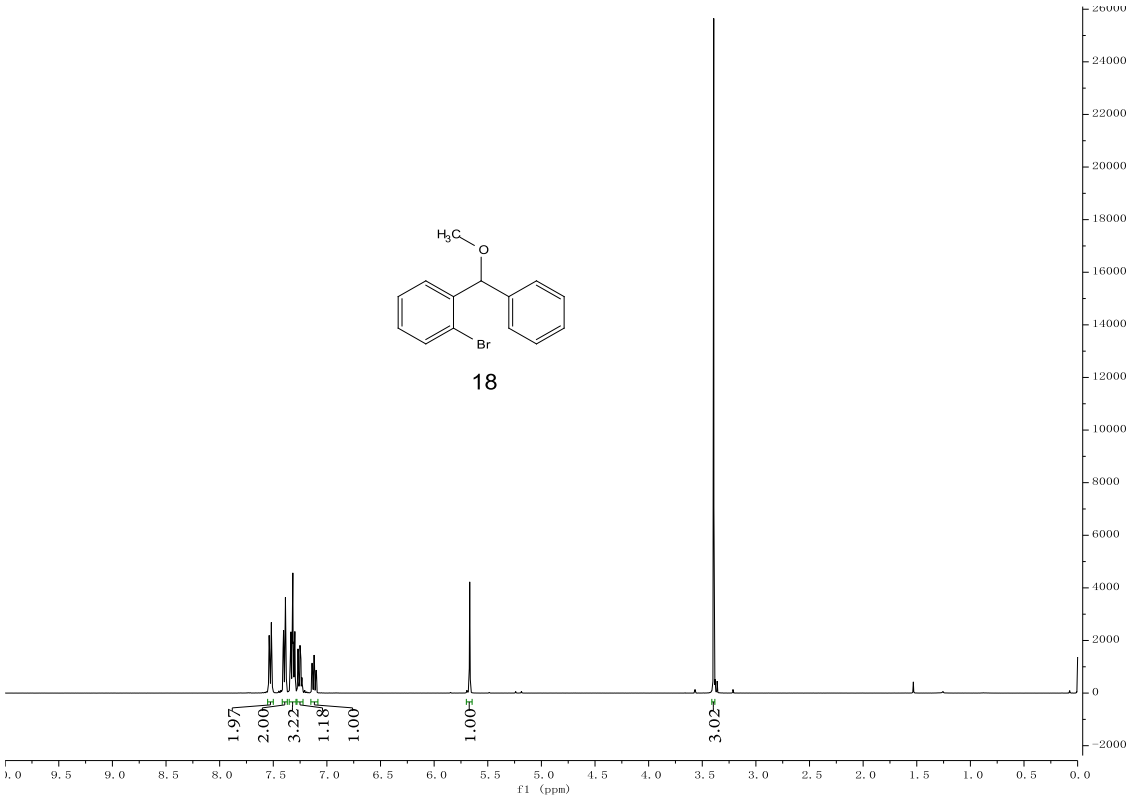

H3C
O
F
F
16
3.99
3.87
0.99
3.00
f1 (ppm)

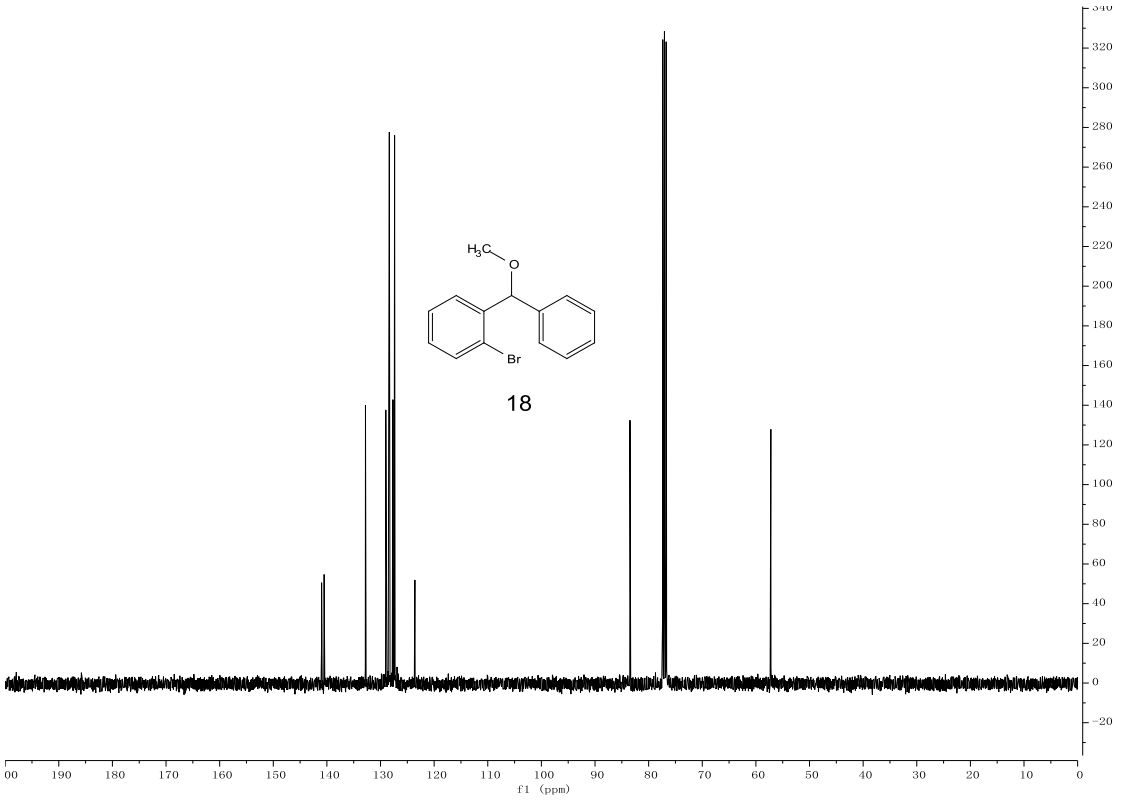

H3C
O
F
F
16
f1 (ppm)


-114.9417
H3C
O
F
F
16
f1 (ppm)


7.4464
7.4253
7.2275
7.2260
7.2059
7.2044
5.1852
3.3593
H3C
O
Br
17
1.87
3.94
1.14
1.93
0.98
3.00
f1 (ppm)


H3C
O
Br
17
f1 (ppm)

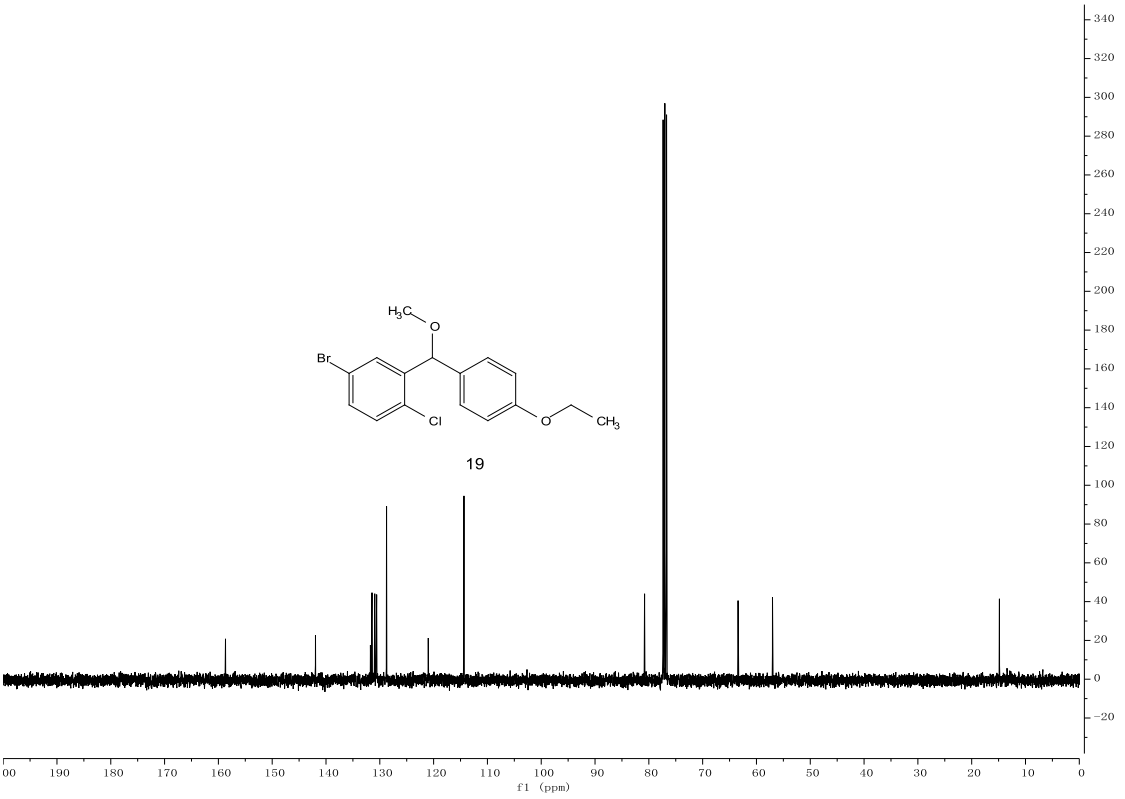

H3C
O
Br
18
1.97
2.00
3.22
1.18
1.00
1.00
3.02
f1 (ppm)

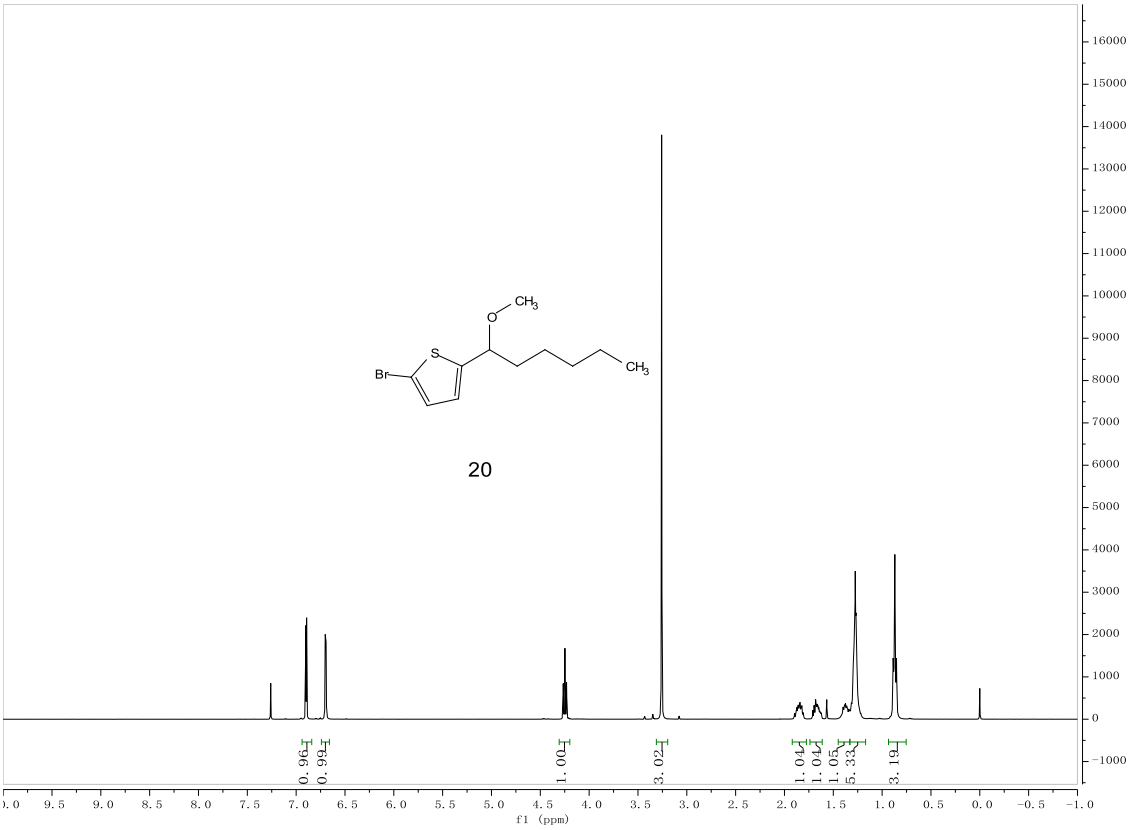

H3C
O
Br
f1 (ppm)

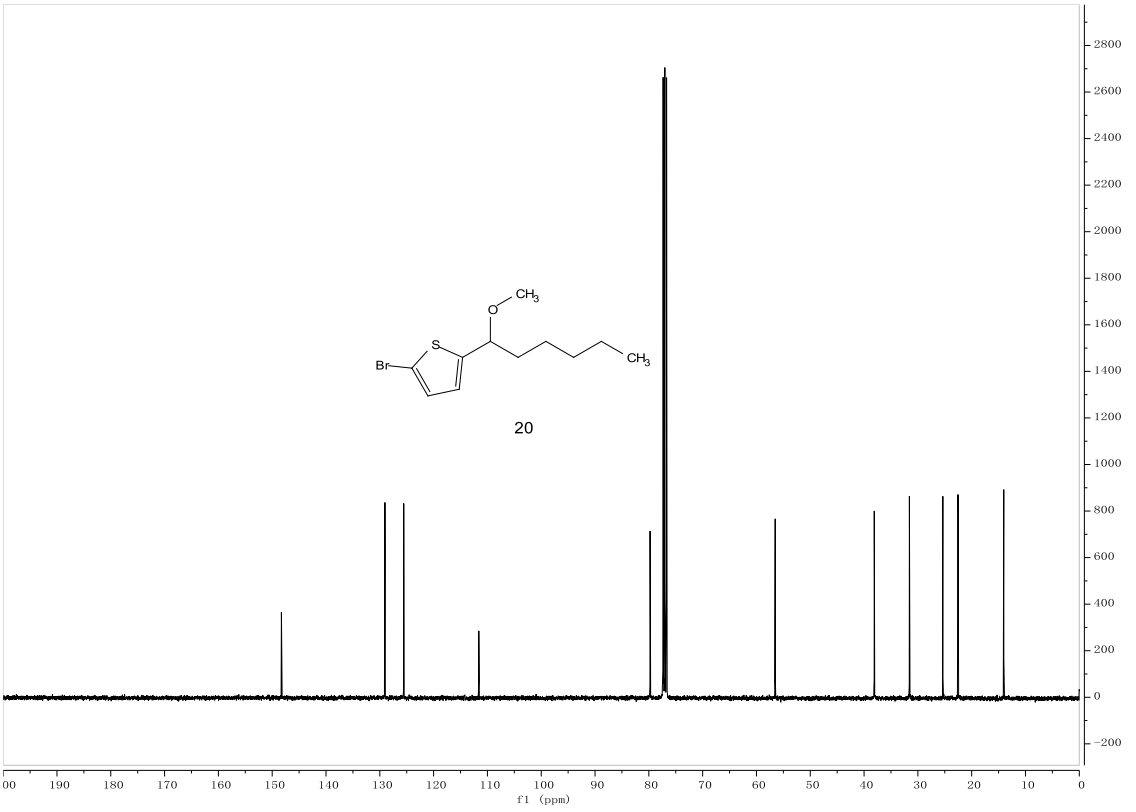
18

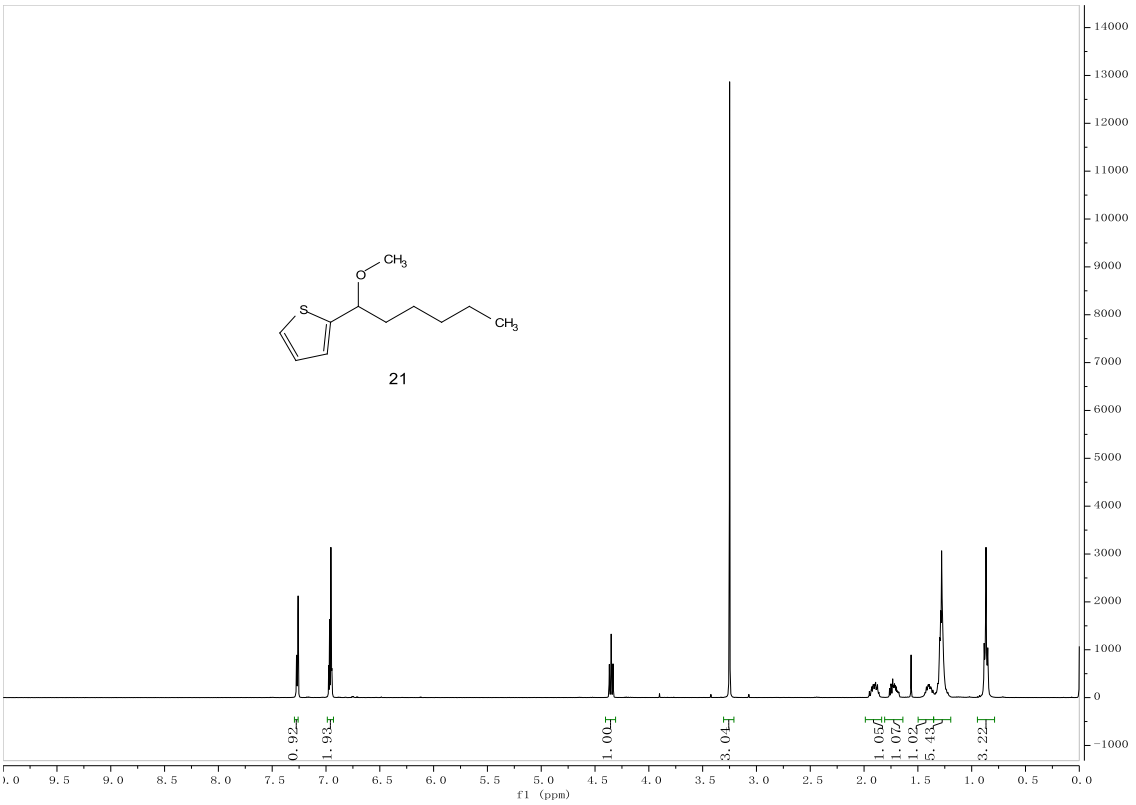

H3C
O
Br
Cl
O
CH3
1.03
1.08
2.51
0.99
2.12
1.00
2.18
3.00
3.24
f1 (ppm)

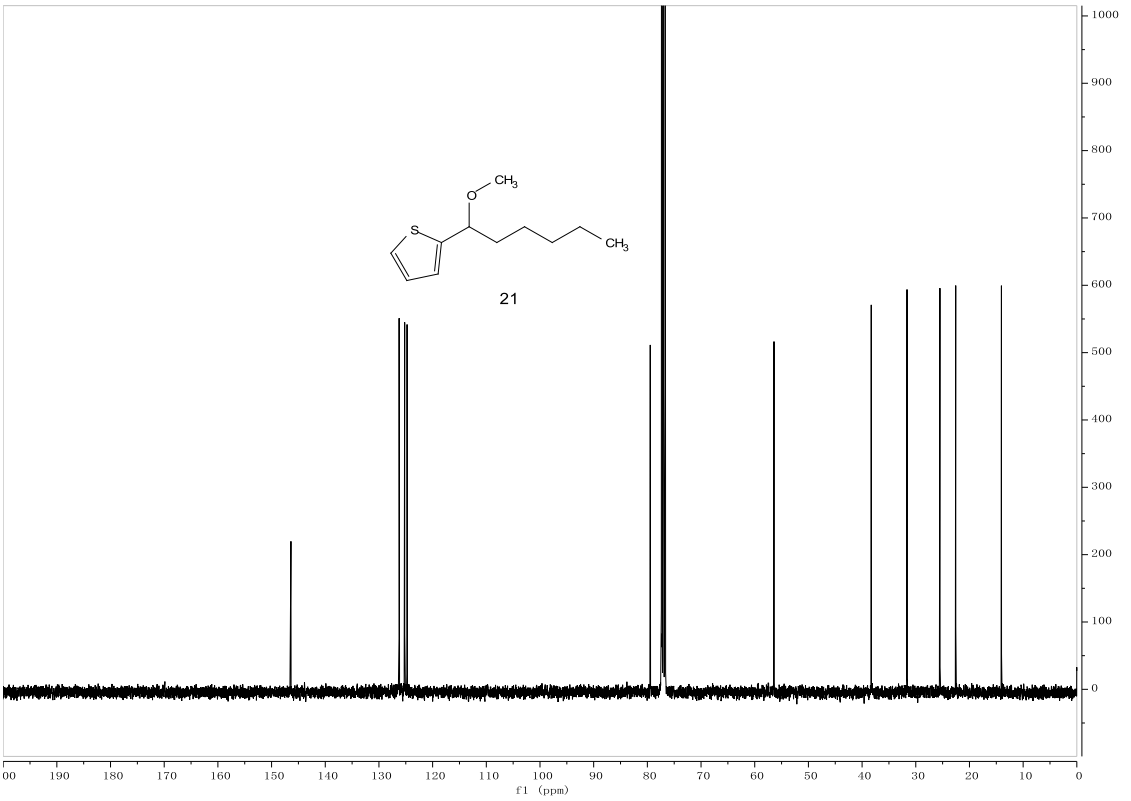
19

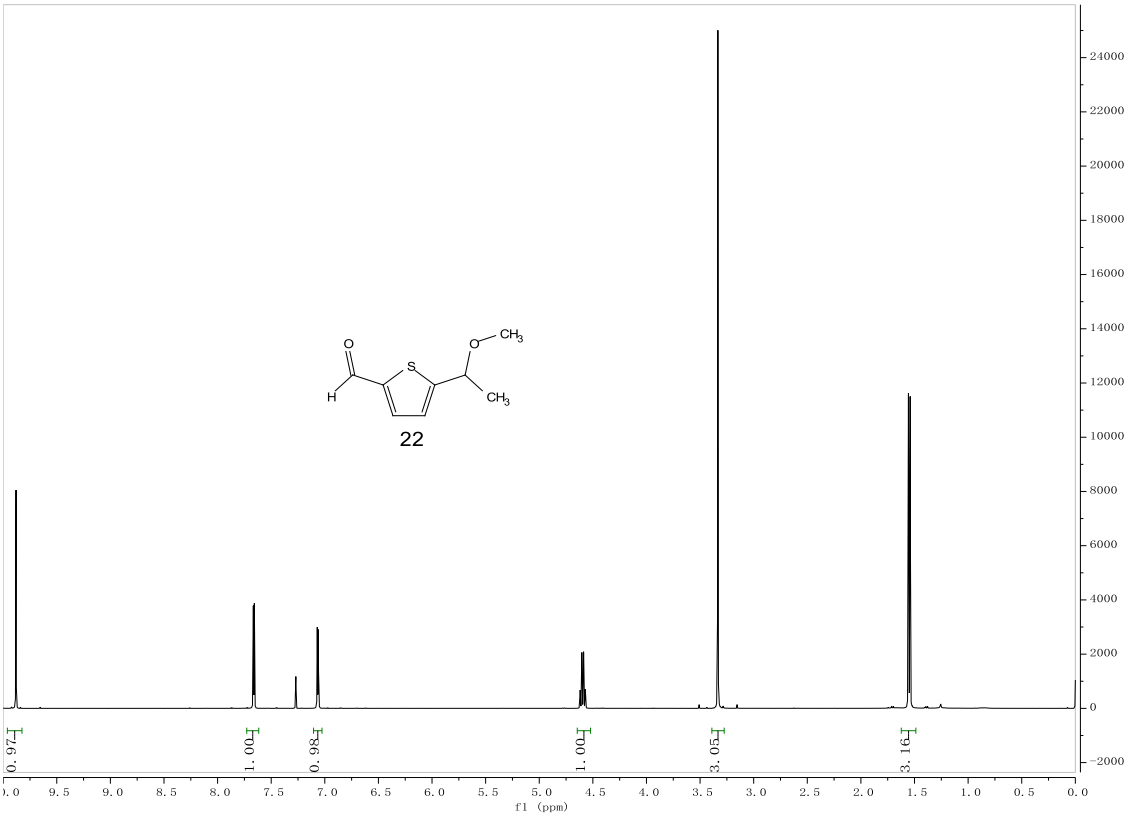

H3C
O
Br
Cl
O
CH3
19
f1 (ppm)


CH3
O
S
Br
CH3
20
0.96
0.99
1.00
3.02
1.04
1.04
1.05
5.33
3.19
f1 (ppm)


CH3
O
S
Br
CH3
20
f1 (ppm)

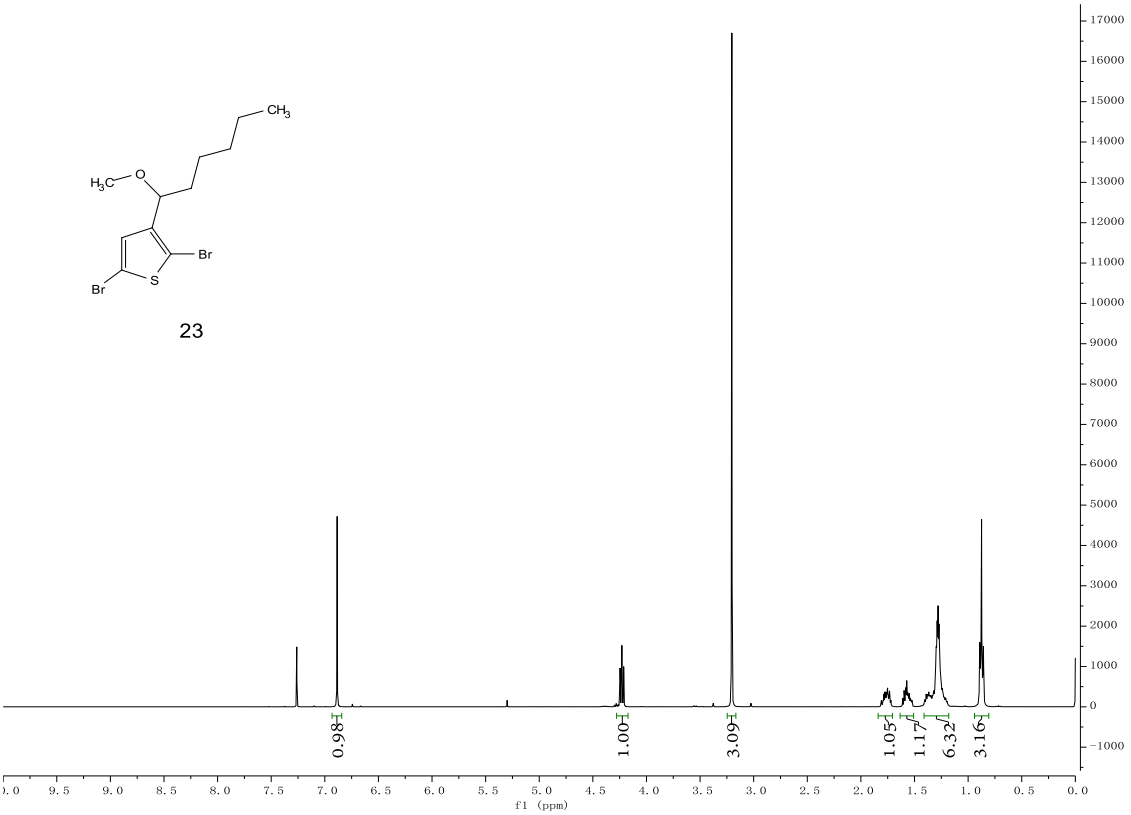

CH3
O
S
CH3
21
0.92
1.93
1.00
3.04
1.05
1.07
1.02
5.43
3.22
f1 (ppm)


CH3
O
S
CH3
21
f1 (ppm)

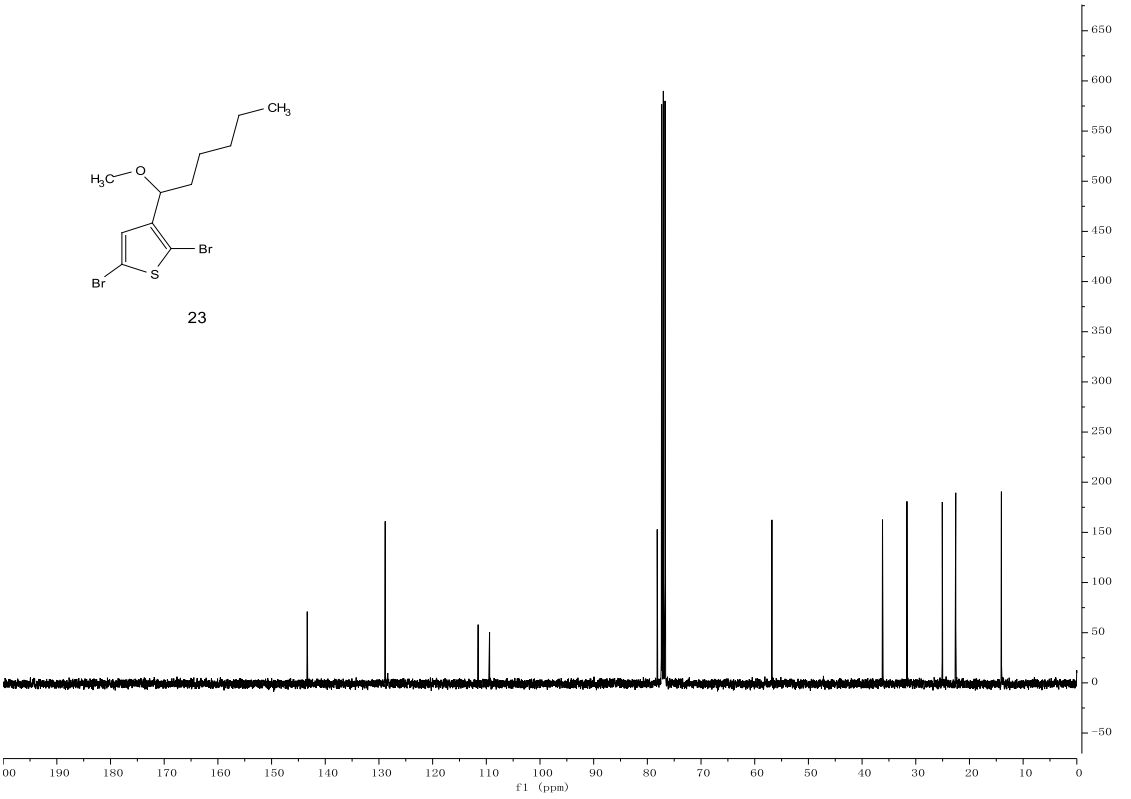

O
O
CH3
S
H
CH3
22
0.97
1.00
0.98
1.00
3.05
3.16
f1 (ppm)


O
S
O
CH3
H
CH3
f1 (ppm)

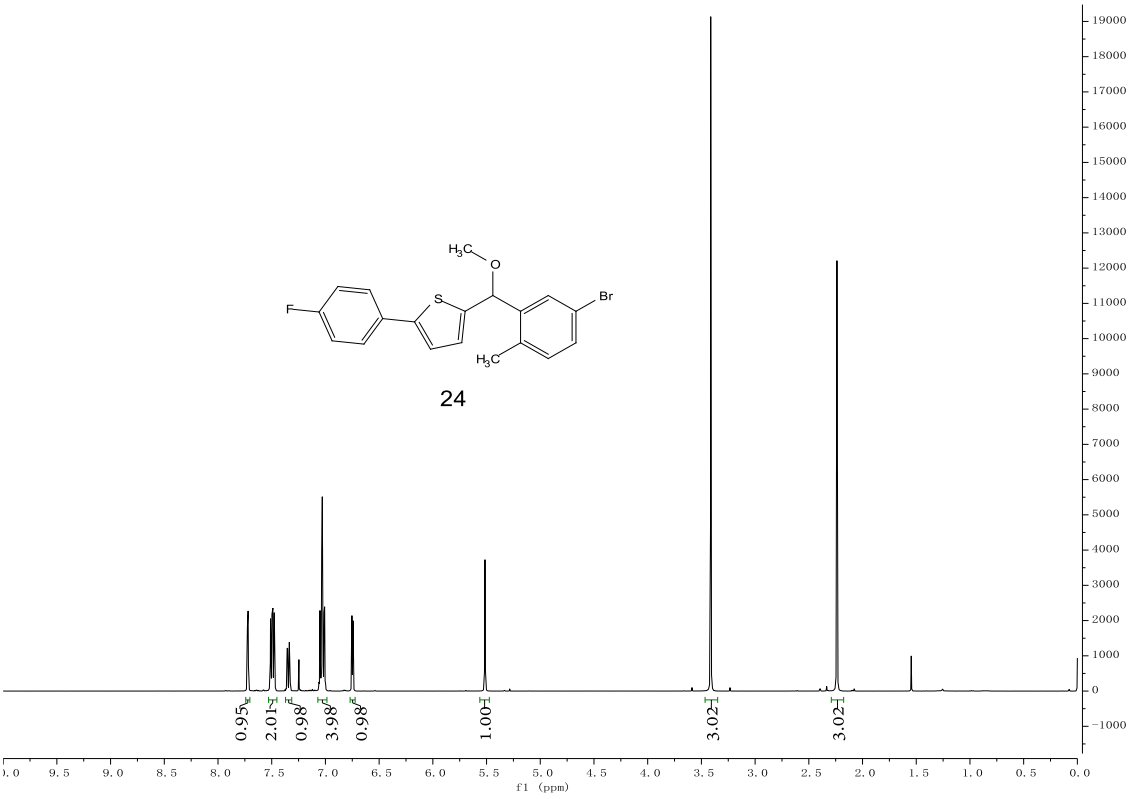
22


CH3
H3C
O
Br
Br
S
0.98
1.00
3.09
1.05
1.17
6.32
3.16
f1 (ppm)

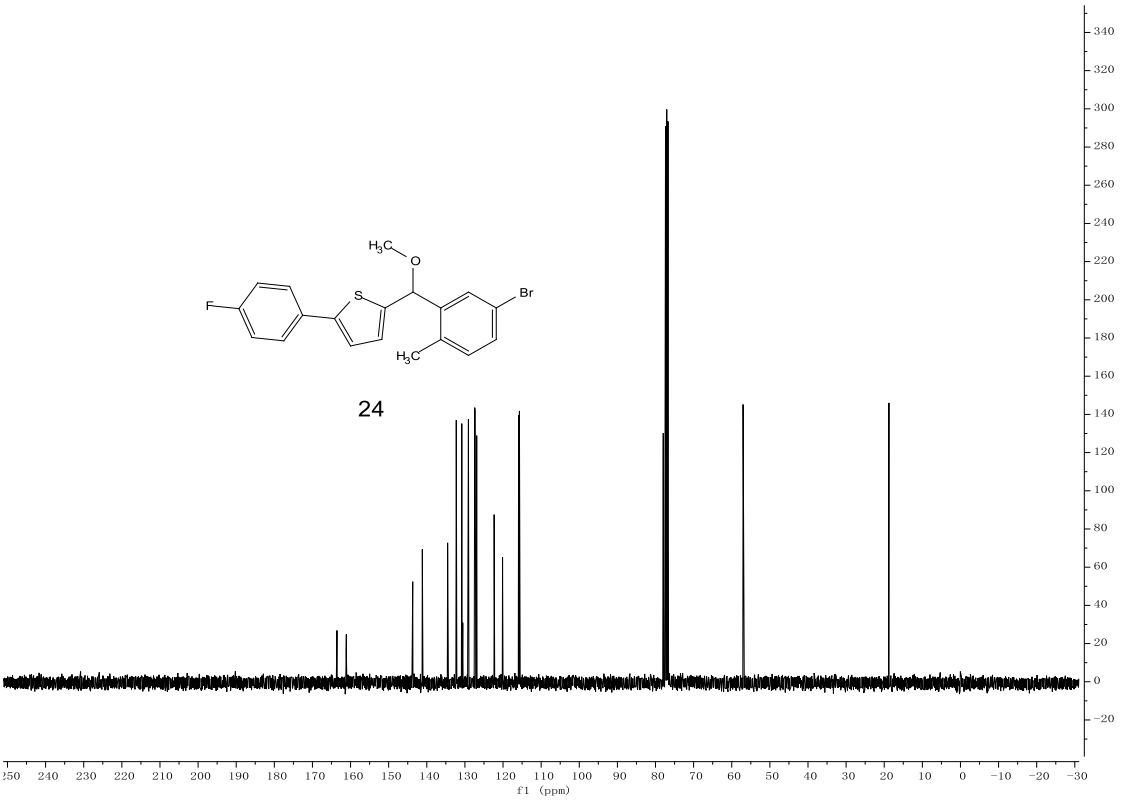
23

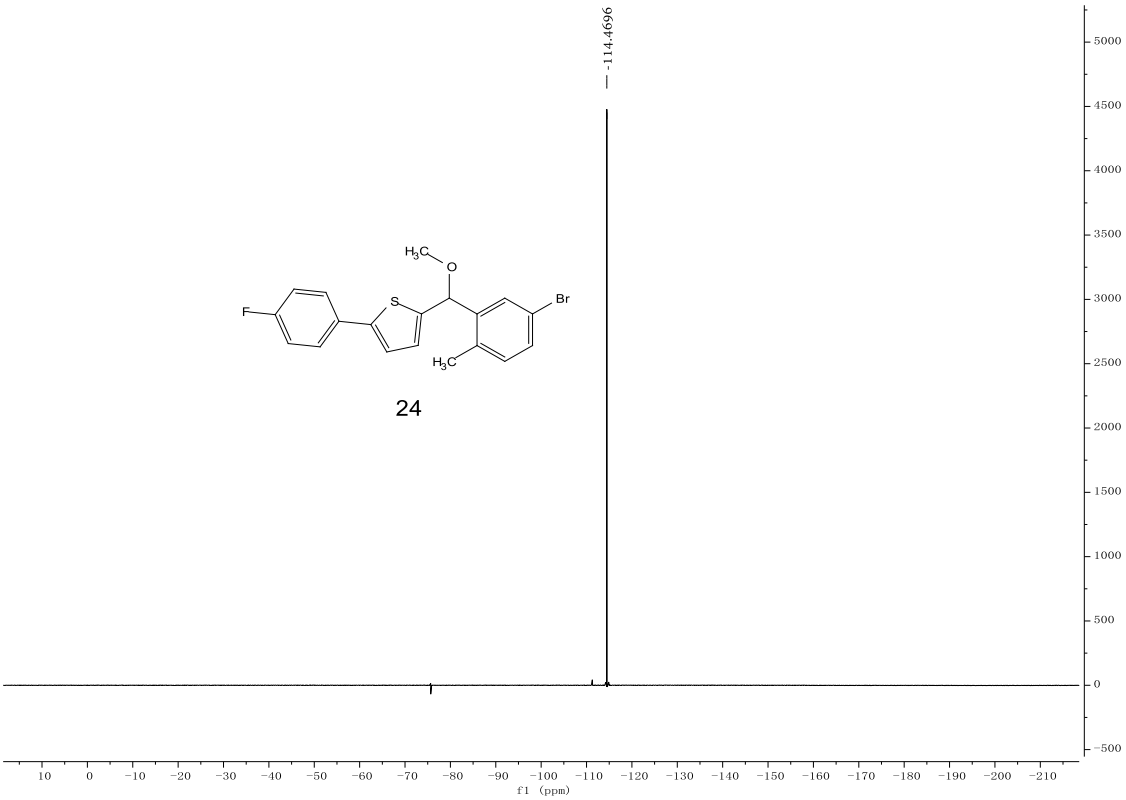

CH3
H3C
O
Br
Br
S
f1 (ppm)

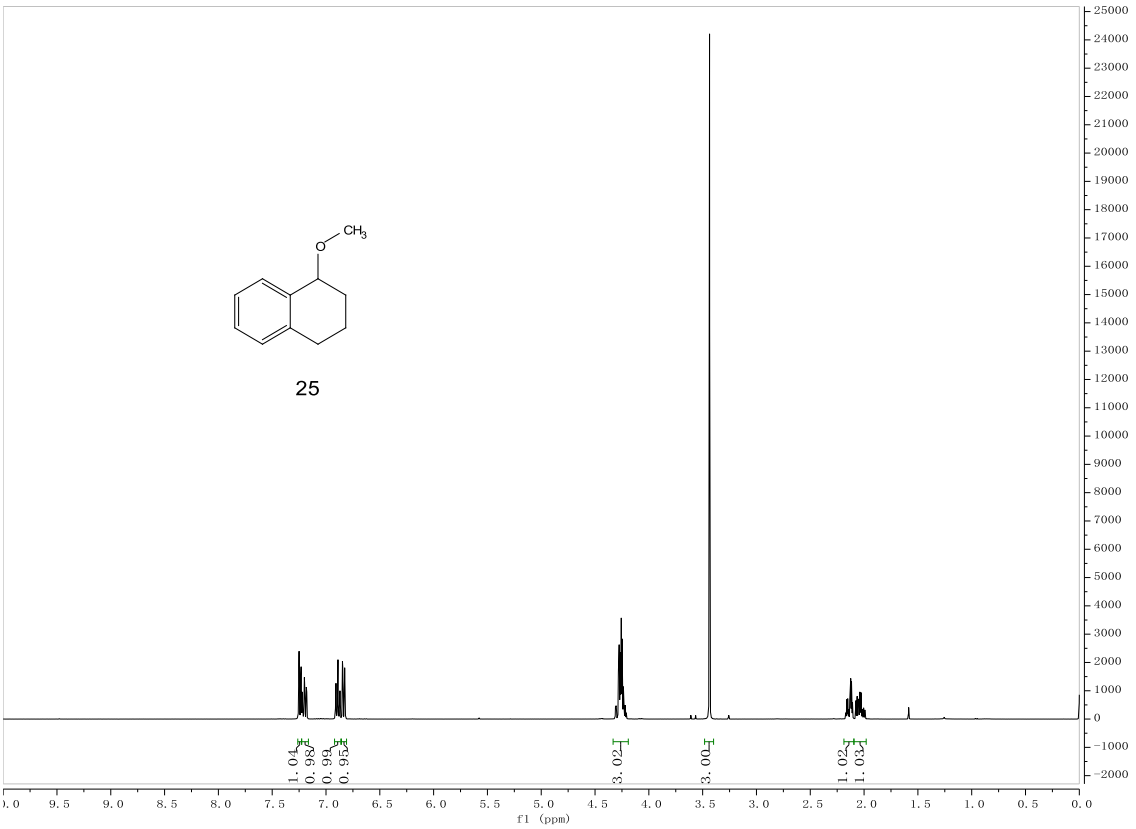
23

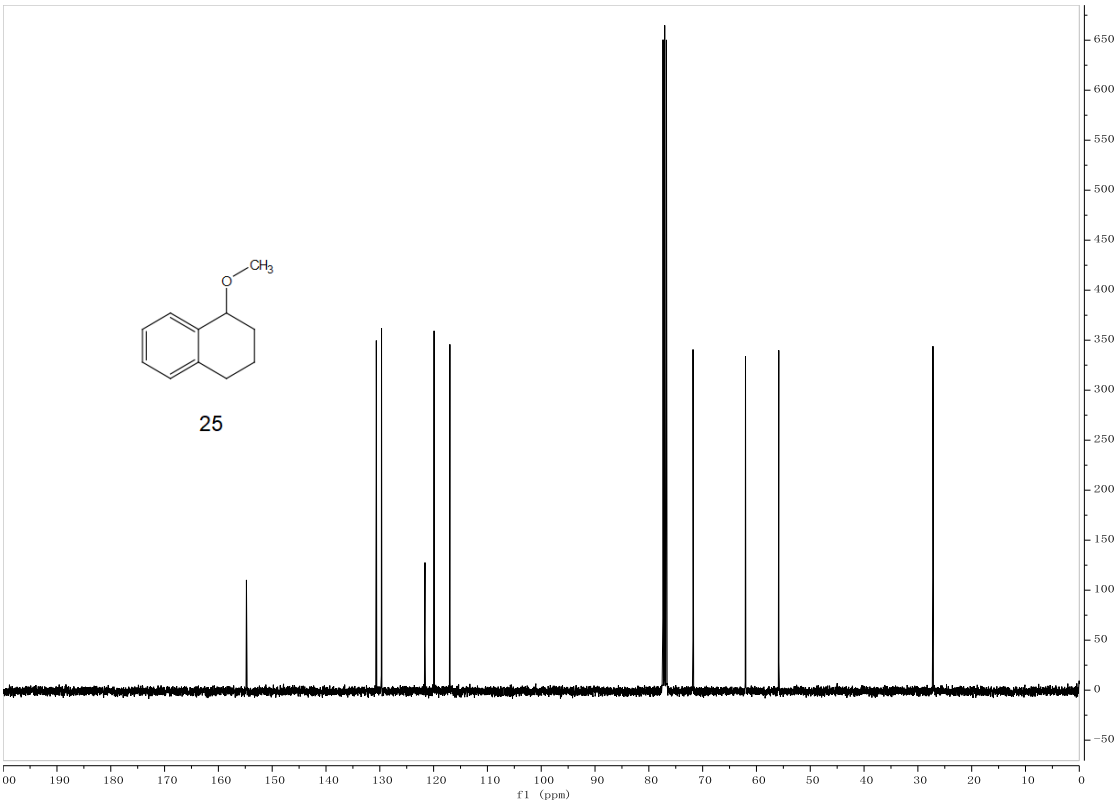

H3C
O
F
S
Br
H3C
0.95
2.01
0.98
3.98
0.98
1.00
3.02
3.02
f1 (ppm)

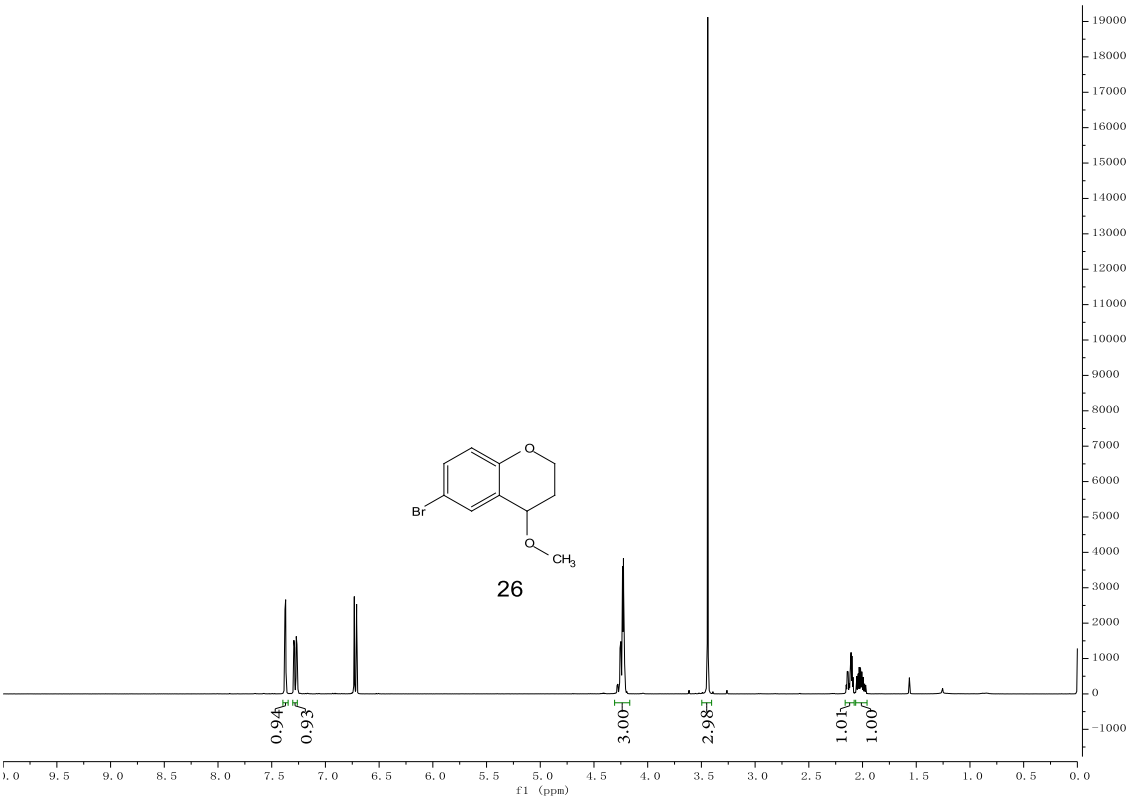
24

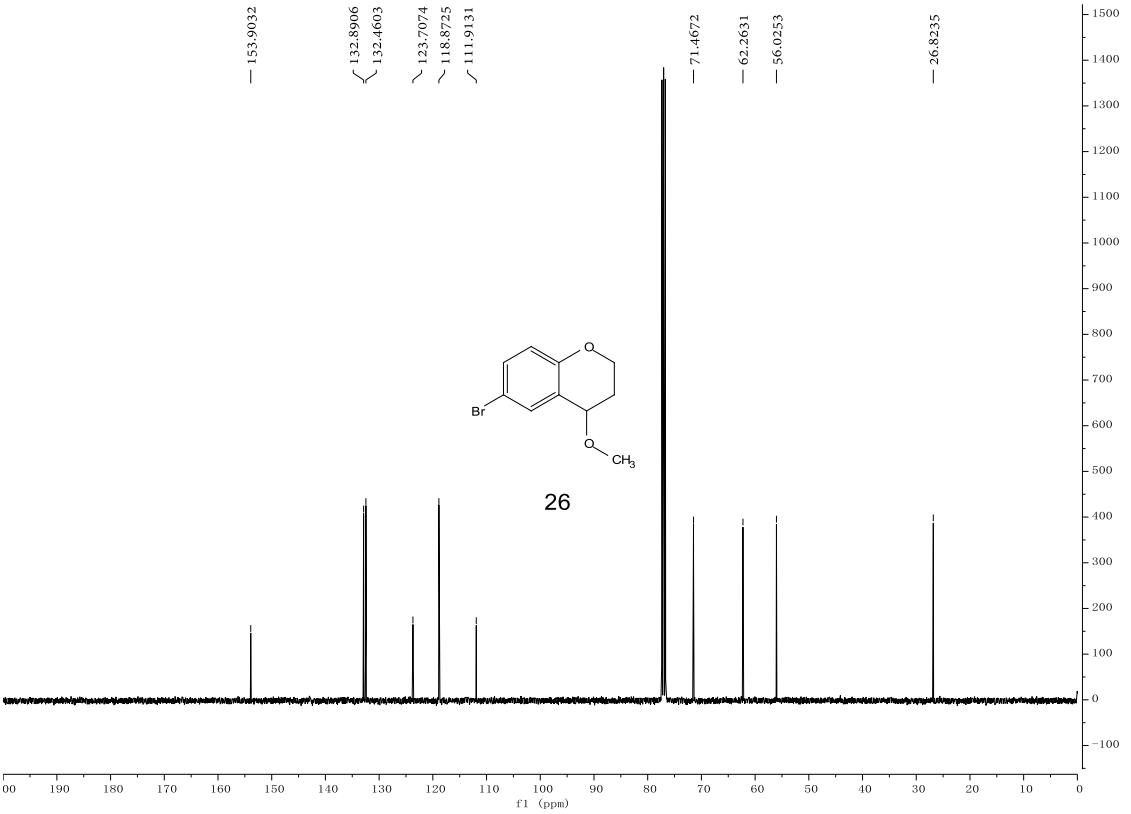

H3C
O
S
F
Br
H3C
24
f1 (ppm)

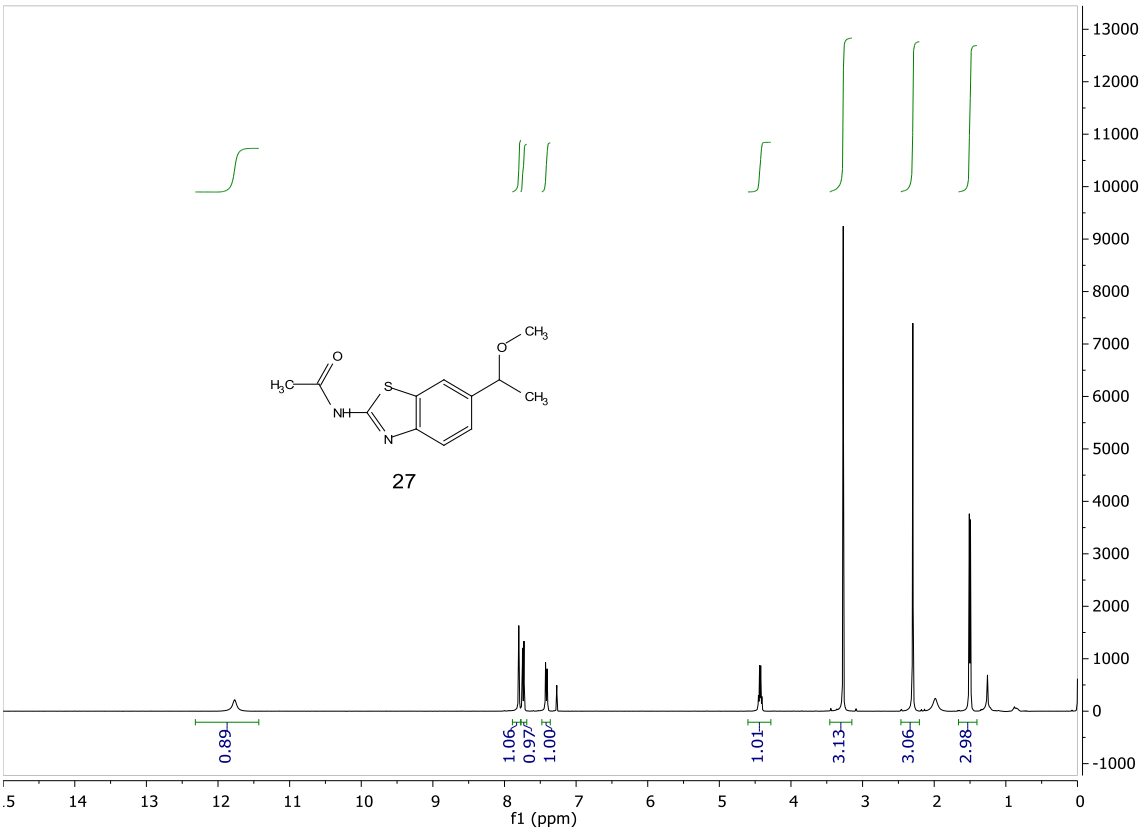

-114.4696
H3C
O
S
F
Br
H3C
24
f1 (ppm)

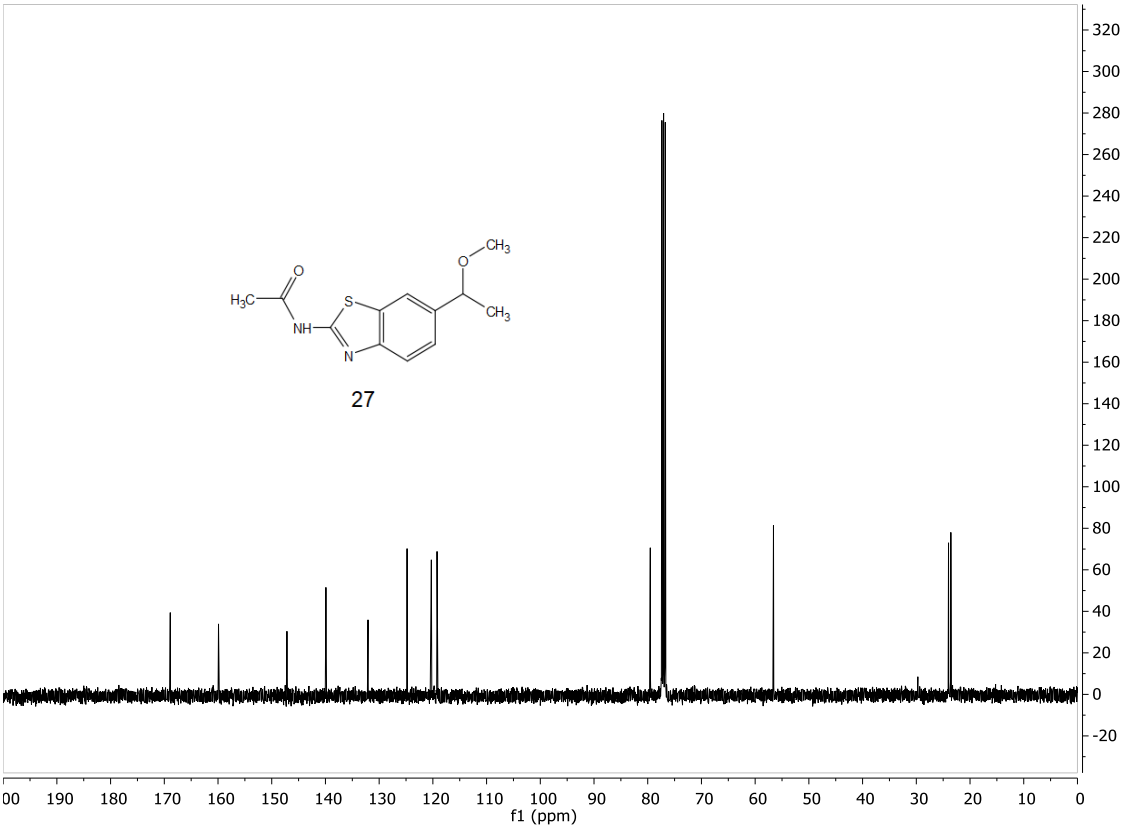

CH3
O
25
1.04
0.98
0.99
0.95
3.02
3.00
1.02
1.03
f1 (ppm)

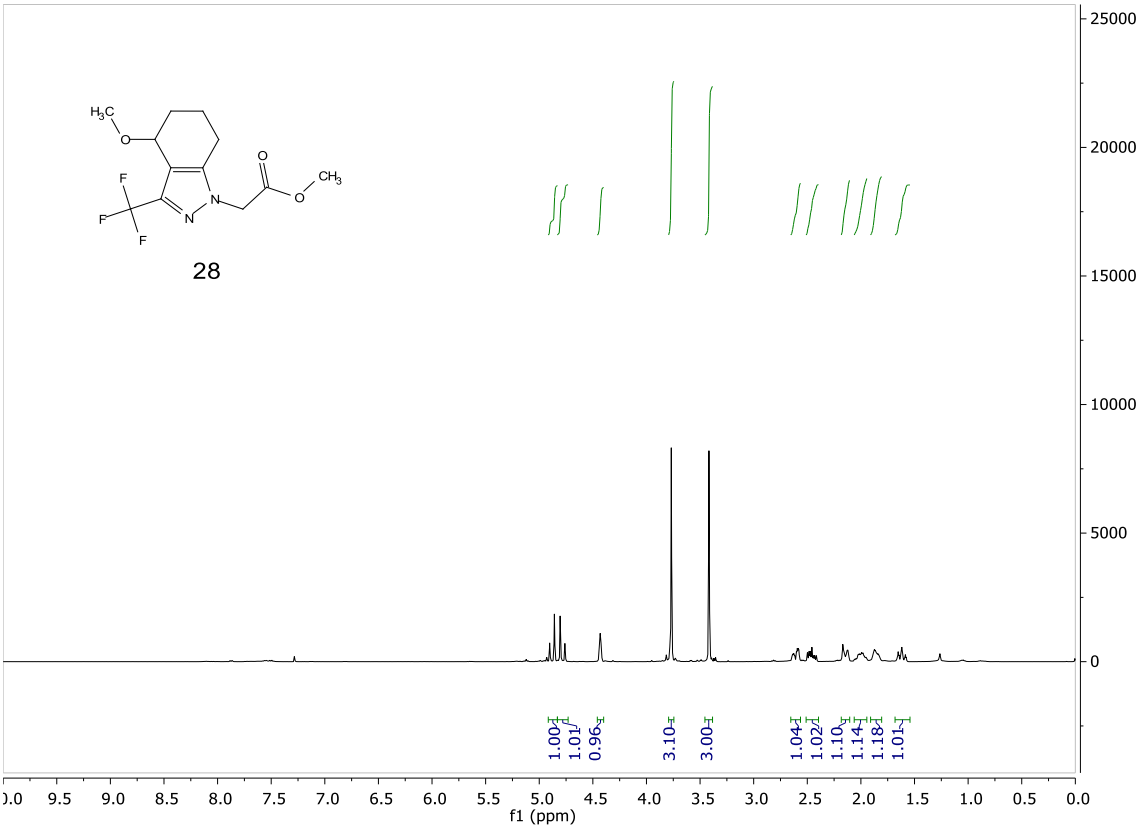

CH3
O
25
f1 (ppm)

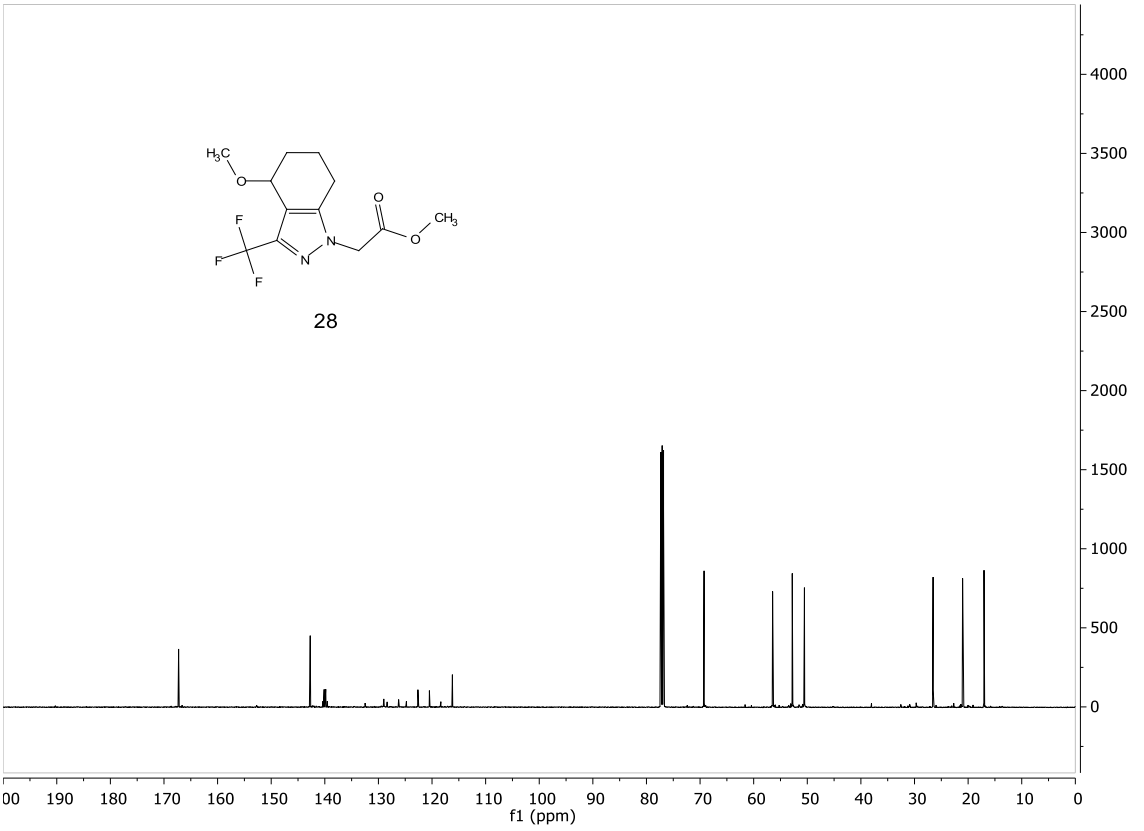

Br
O
O
CH3
26
0.94
0.93
3.00
2.98
1.01
1.00
f1 (ppm)

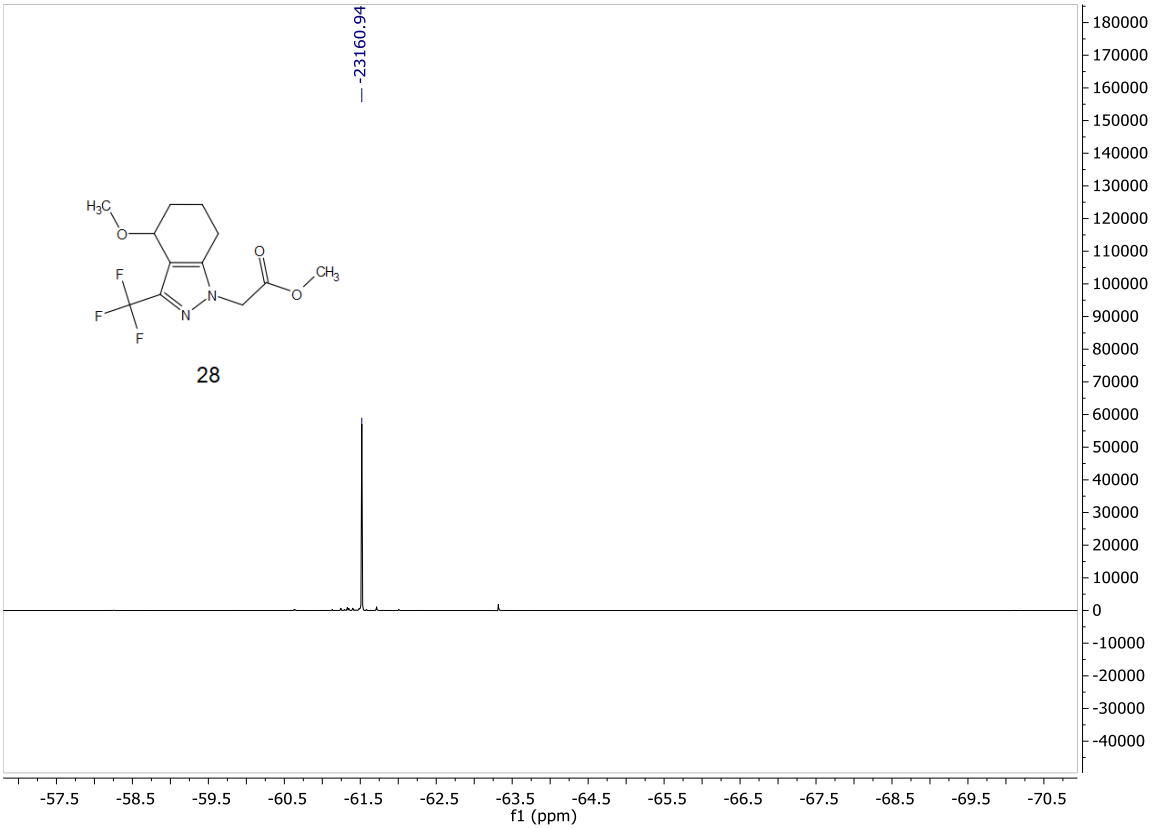

153.9032
132.8906
132.4603
123.7074
118.8725
111.9131
71.4672
62.2631
56.0253
26.8235
Br
O
O
CH3
26
f1 (ppm)

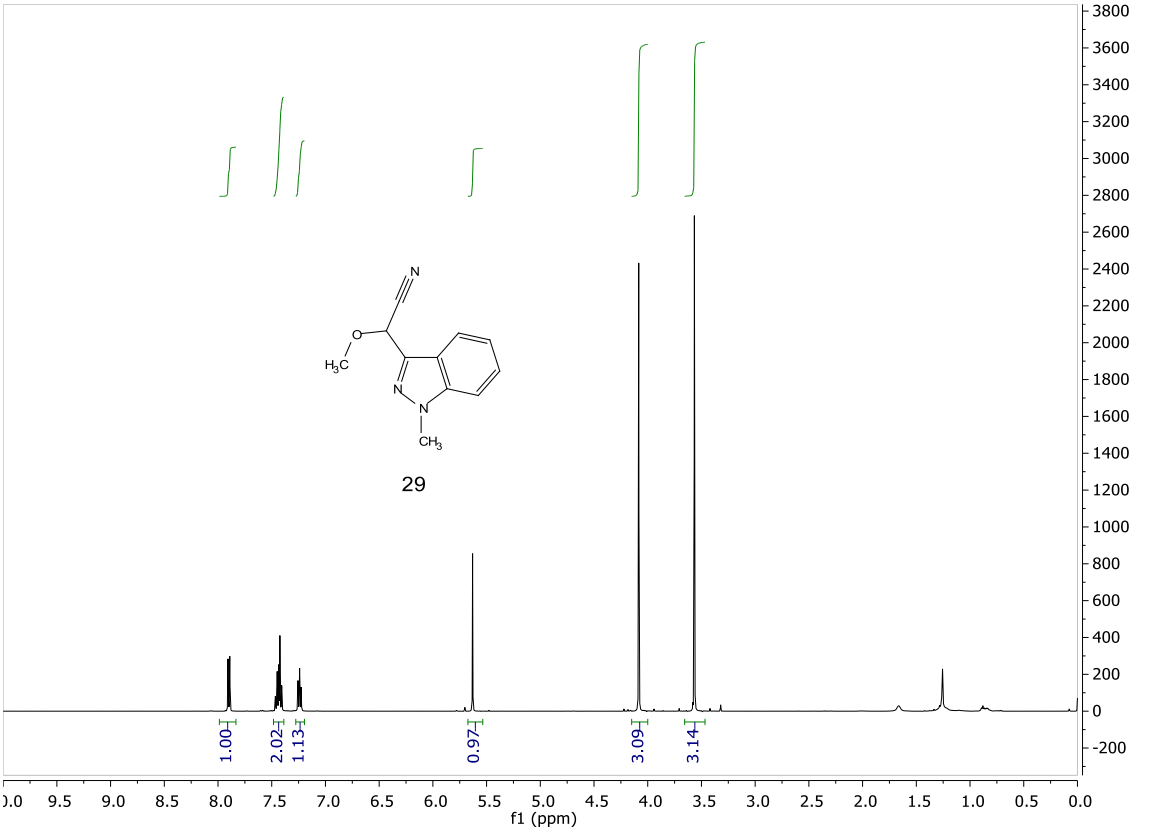

27
0.89
1.06
0.97
1.00
1.01
3.13
3.06
2.98
f1 (ppm)

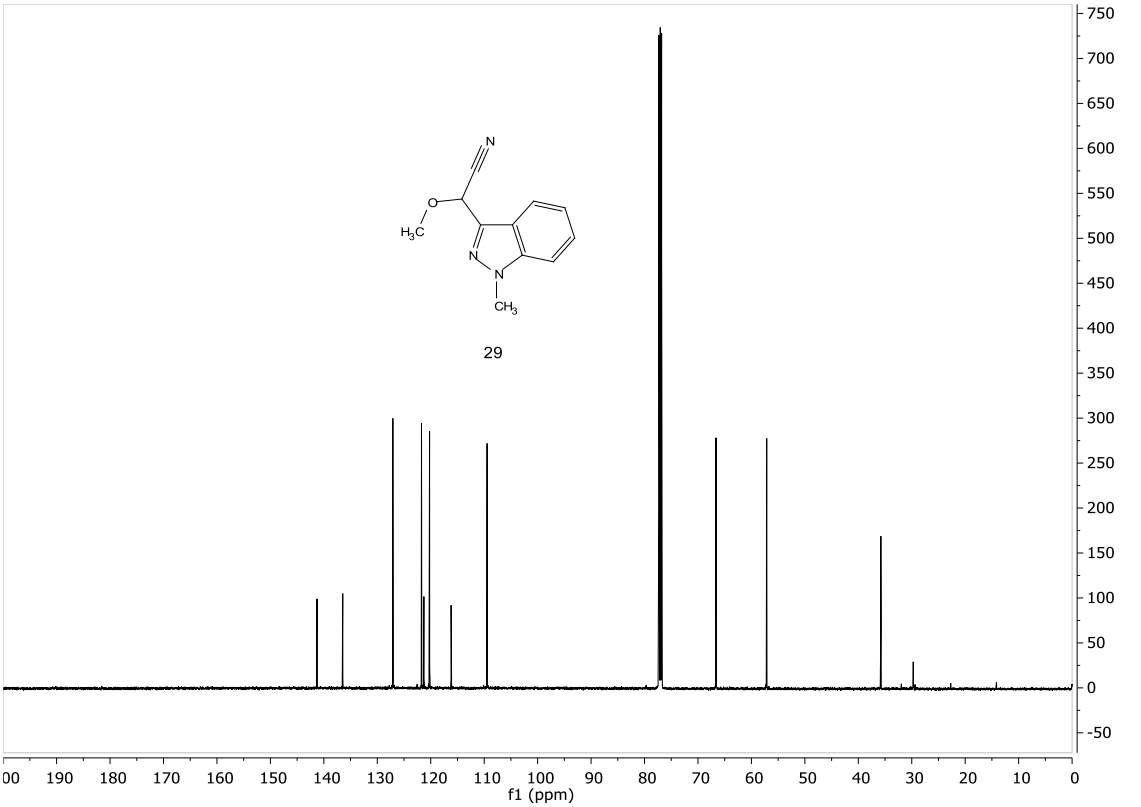

27
f1 (ppm)

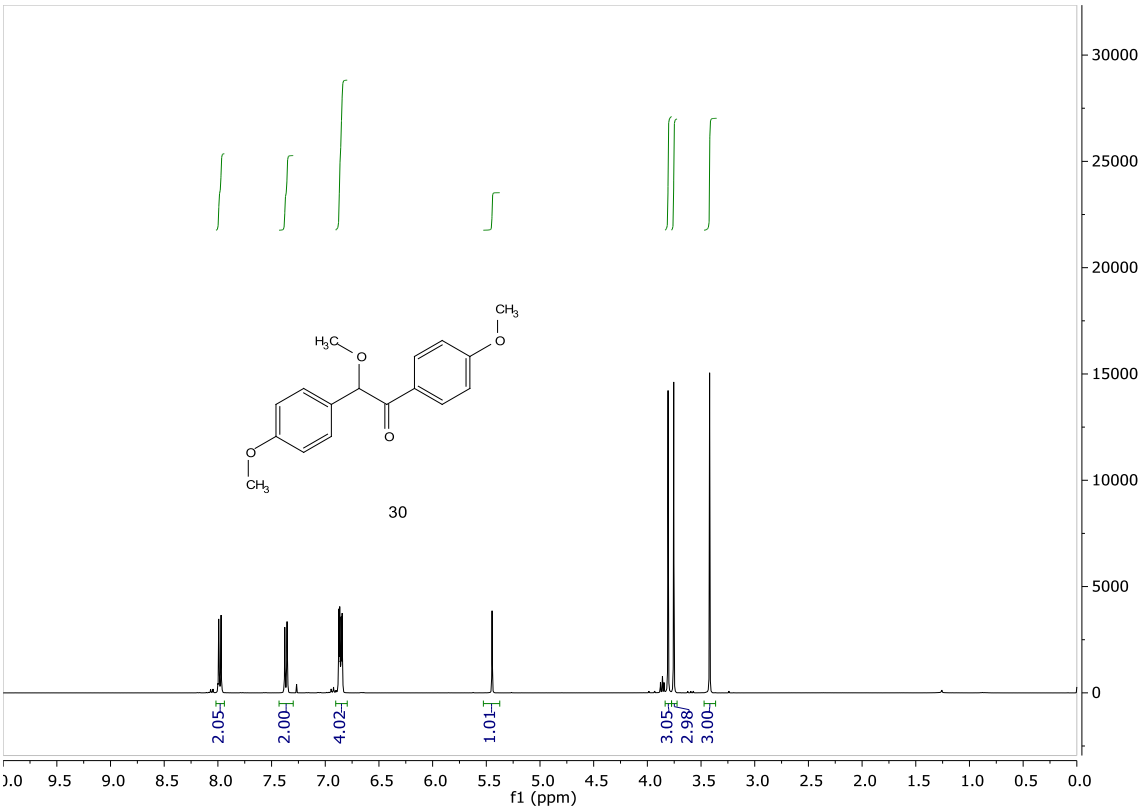

28
1.00
1.01
0.96
3.10
3.00
1.04
1.02
1.10
1.14
1.18
1.01
f1 (ppm)

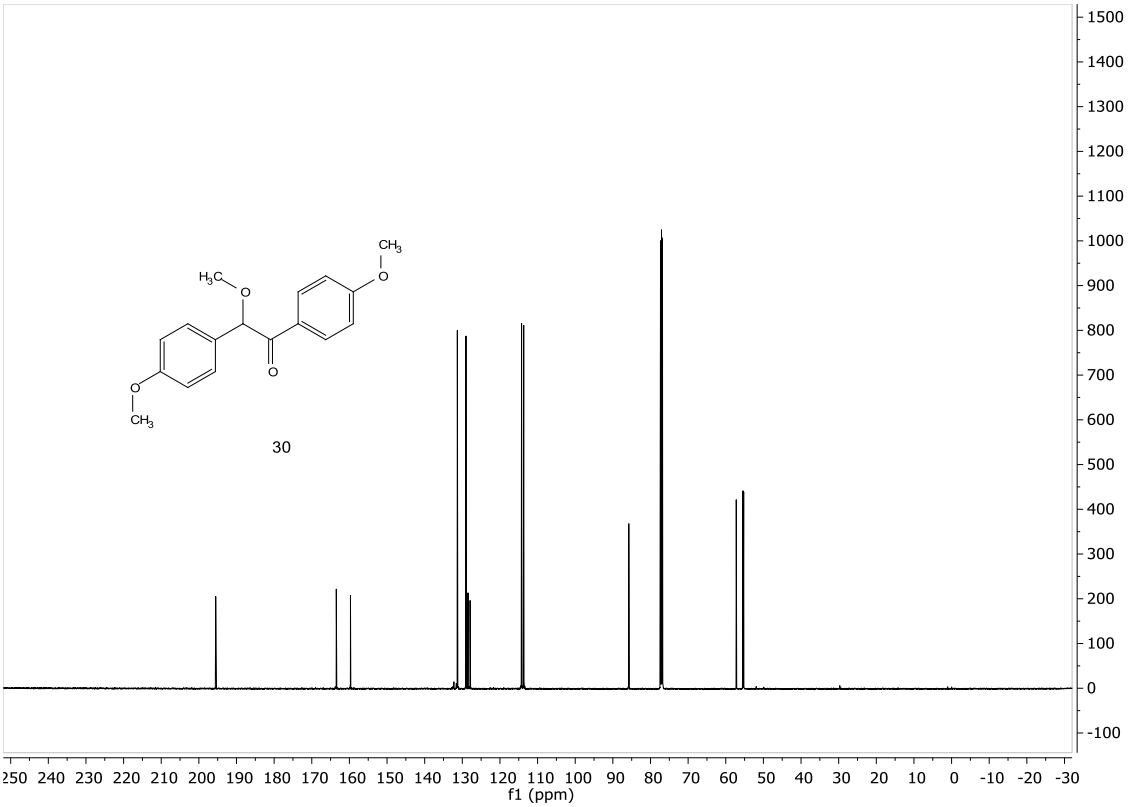

28
f1 (ppm)

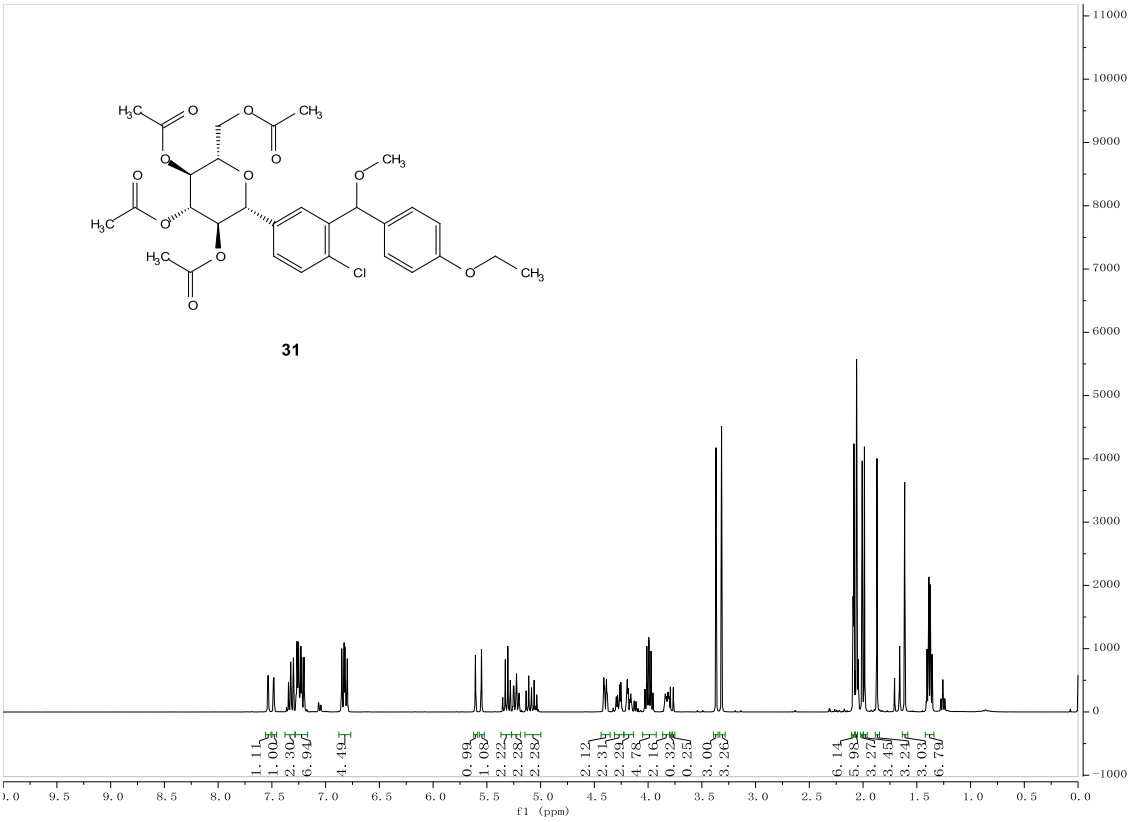

-23160.94
28
180000
170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
-20000
-30000
-40000
-57.5
-58.5
-59.5
-60.5
-61.5
-62.5
-63.5
-64.5
-65.5
-66.5
-67.5
-68.5
-69.5
-70.5
f1 (ppm)

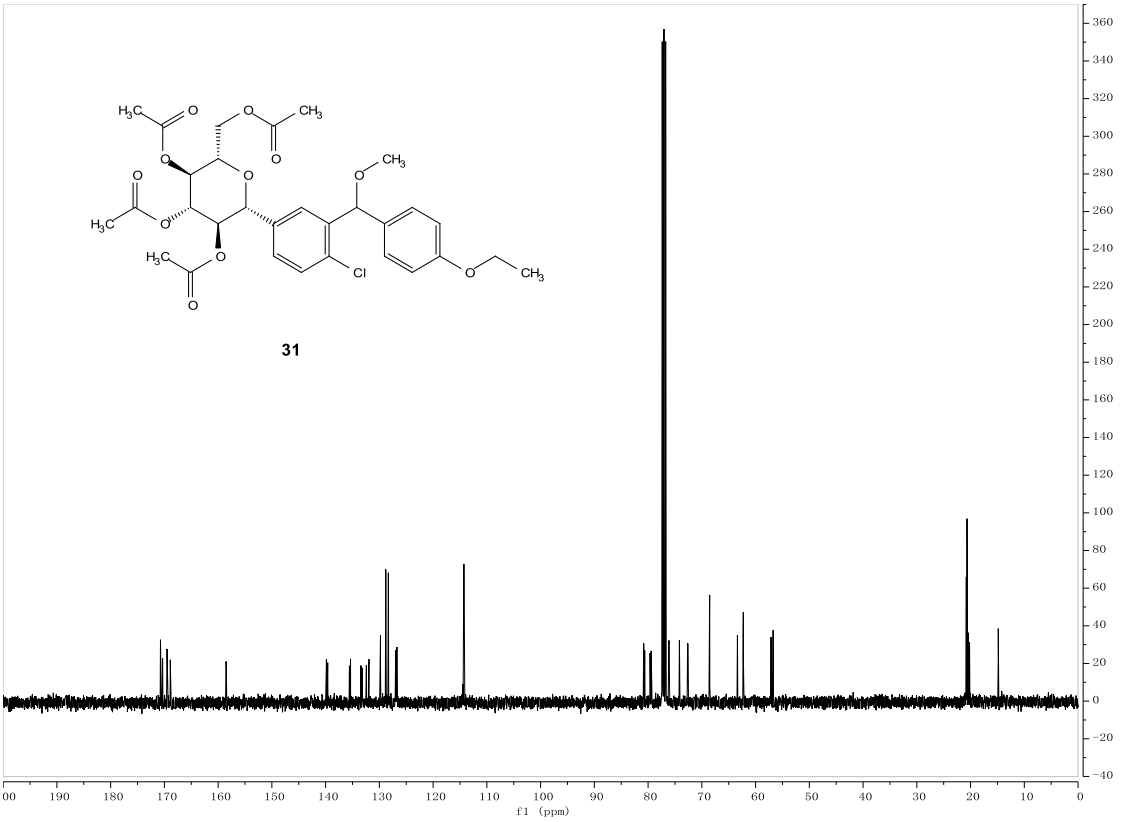

29
1.00
2.02
1.13
0.97
3.09
3.14
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

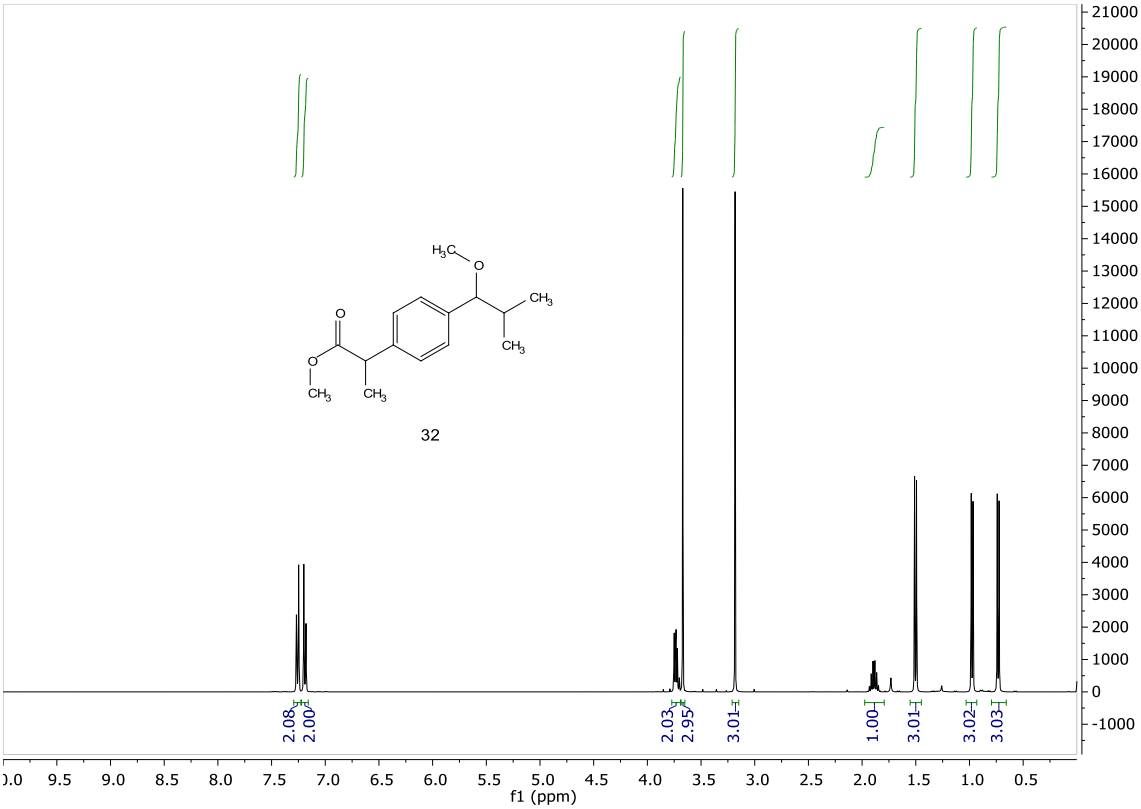

N
O
H3C
N
N
CH3
29
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

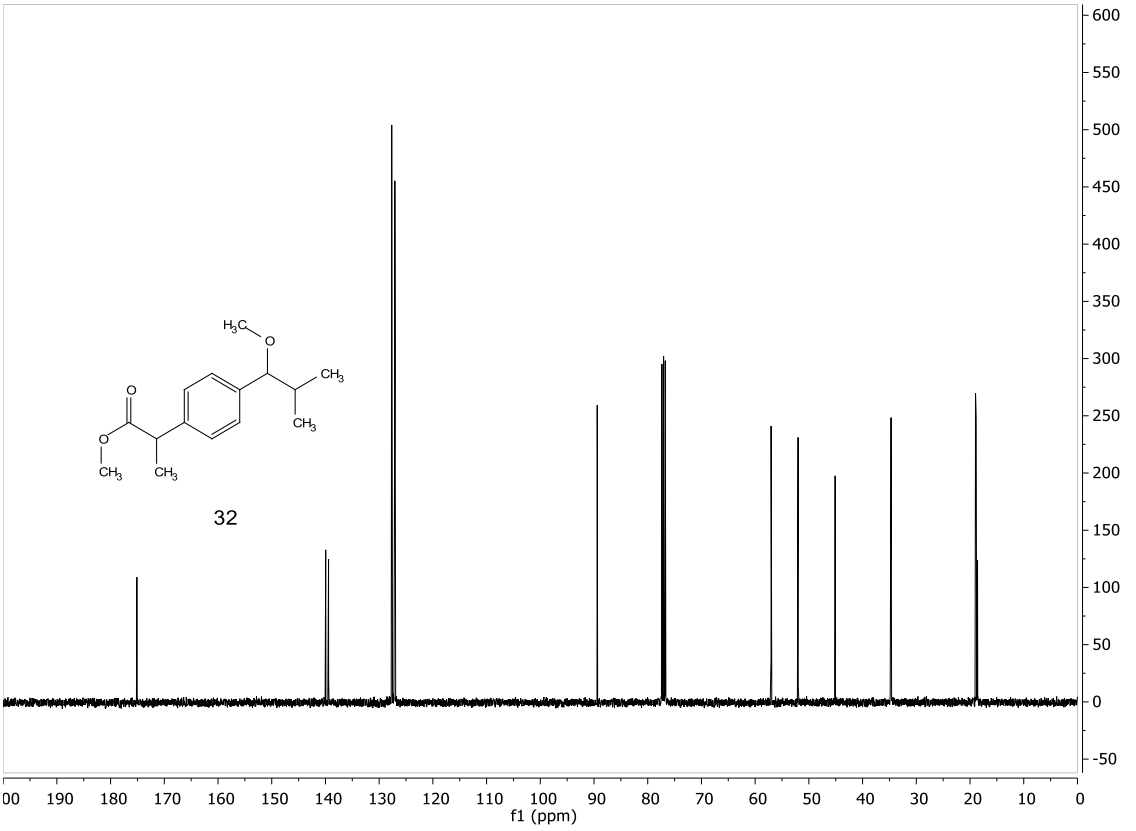

CH3
H3C
O
O
O
O
CH3
30
30000
25000
20000
15000
10000
5000
0
2.05
2.00
4.02
1.01
3.05
2.98
3.00
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


30
f1 (ppm)

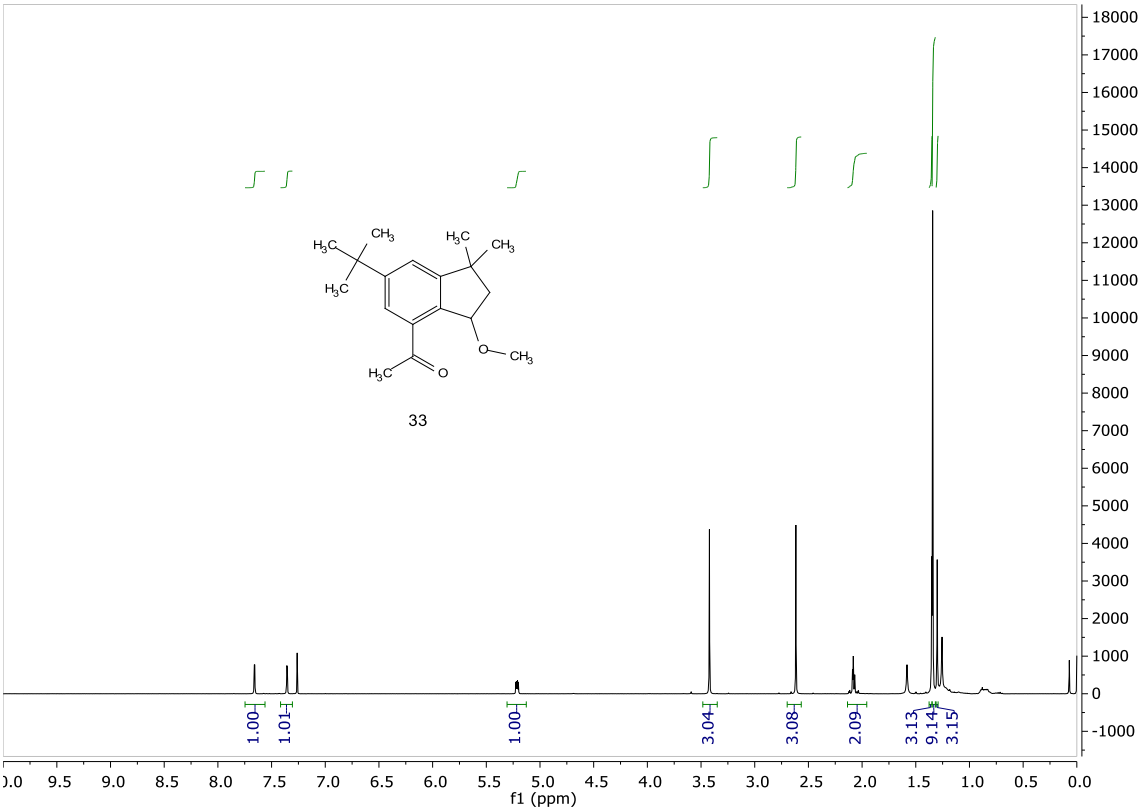

31
f1 (ppm)


31
f1 (ppm)

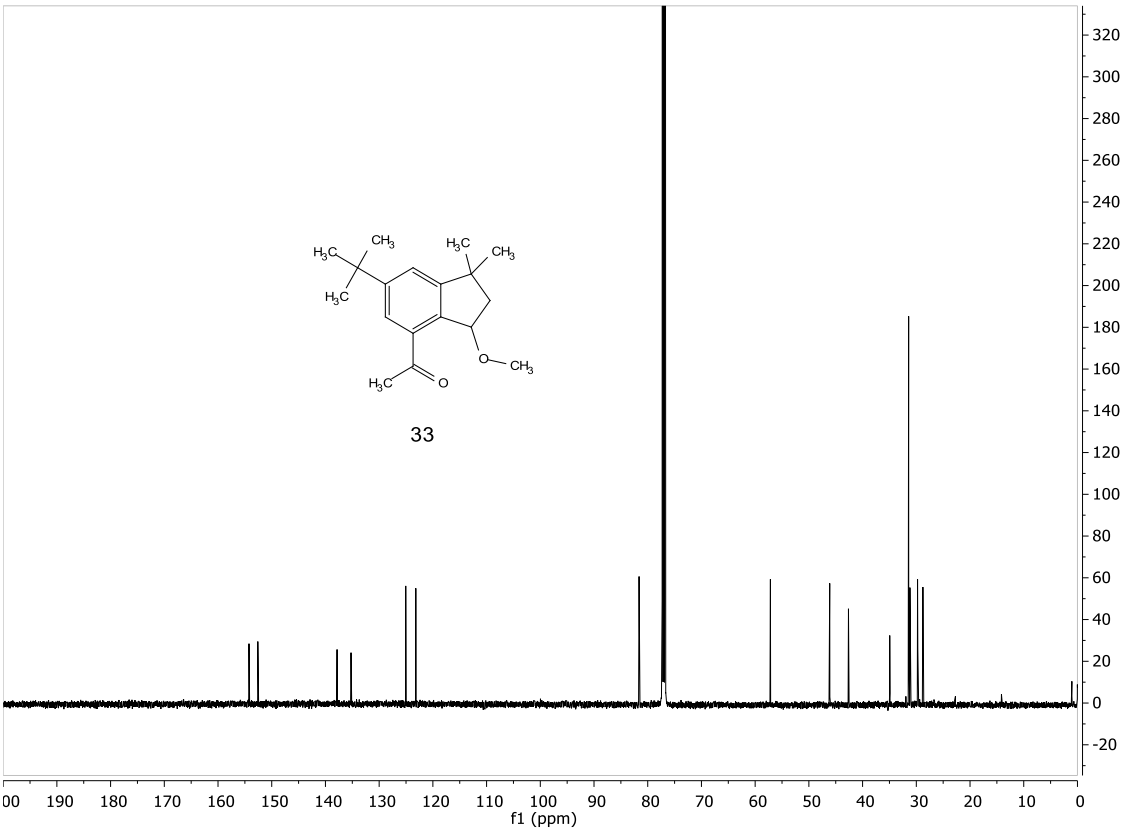

32
2.08
2.00
2.03
2.95
3.01
1.00
3.01
3.02
3.03
f1 (ppm)

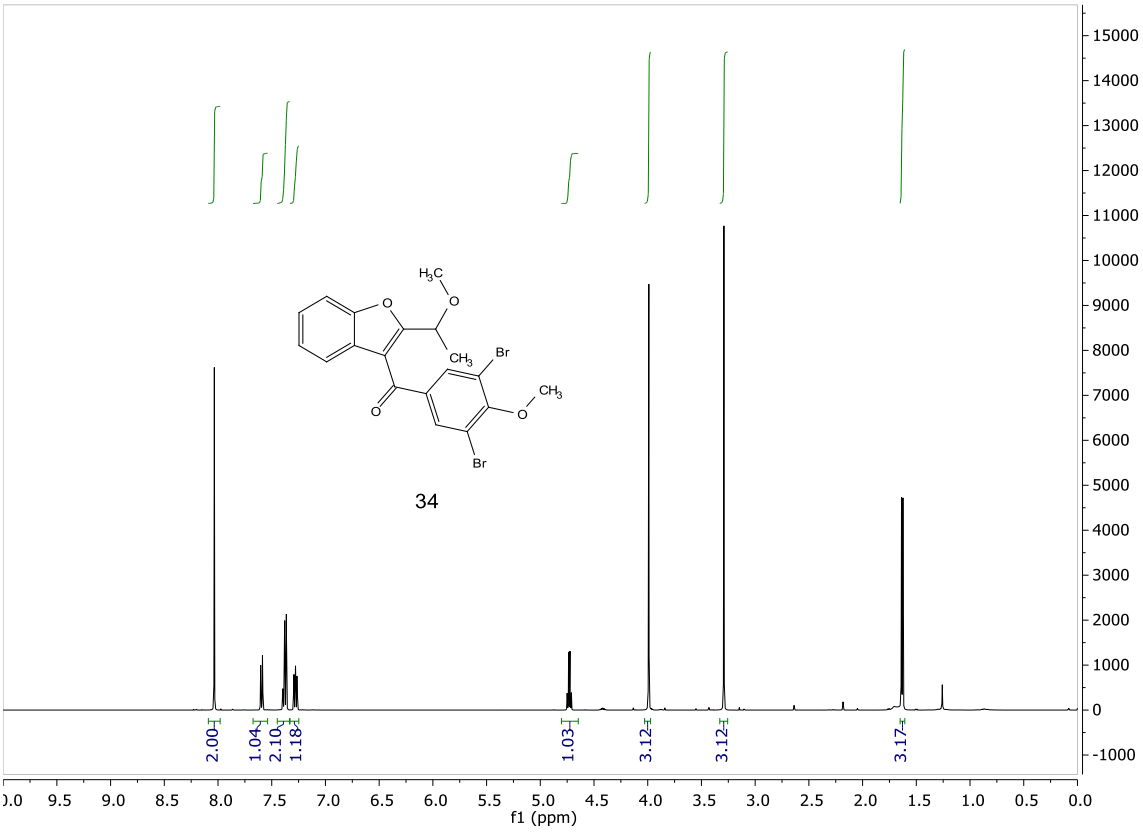


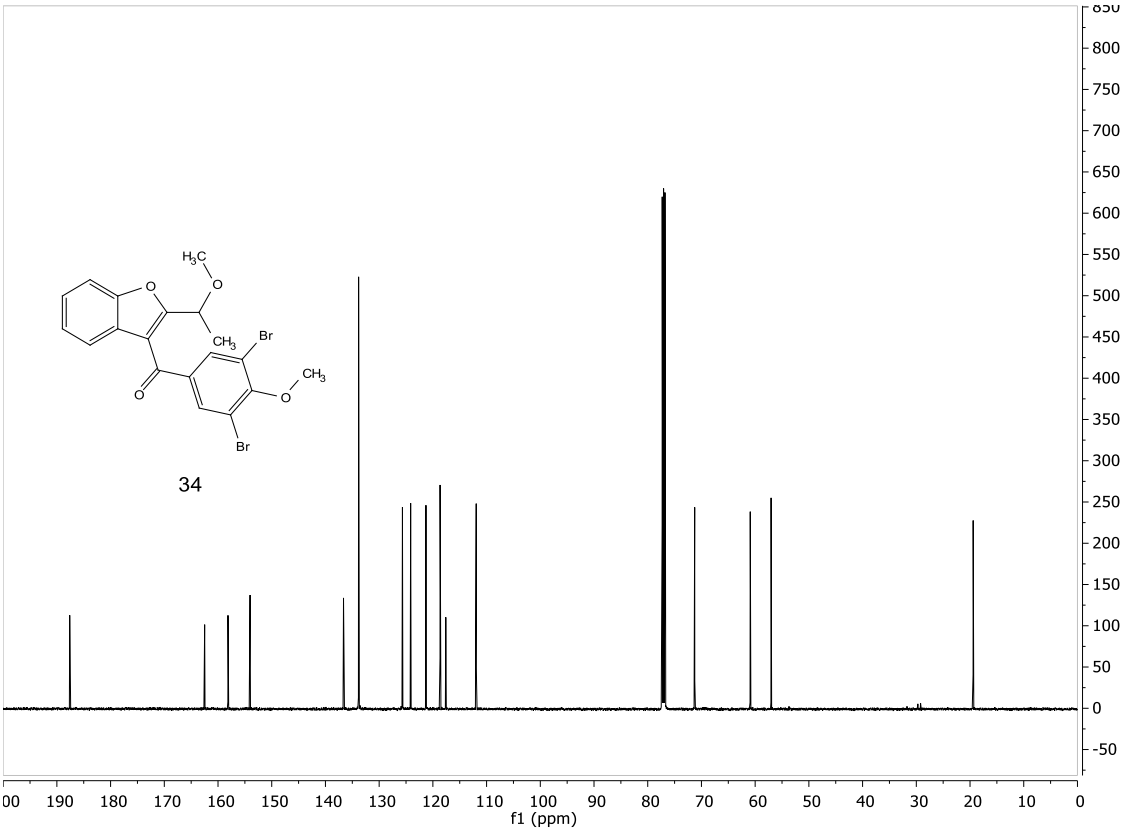
32

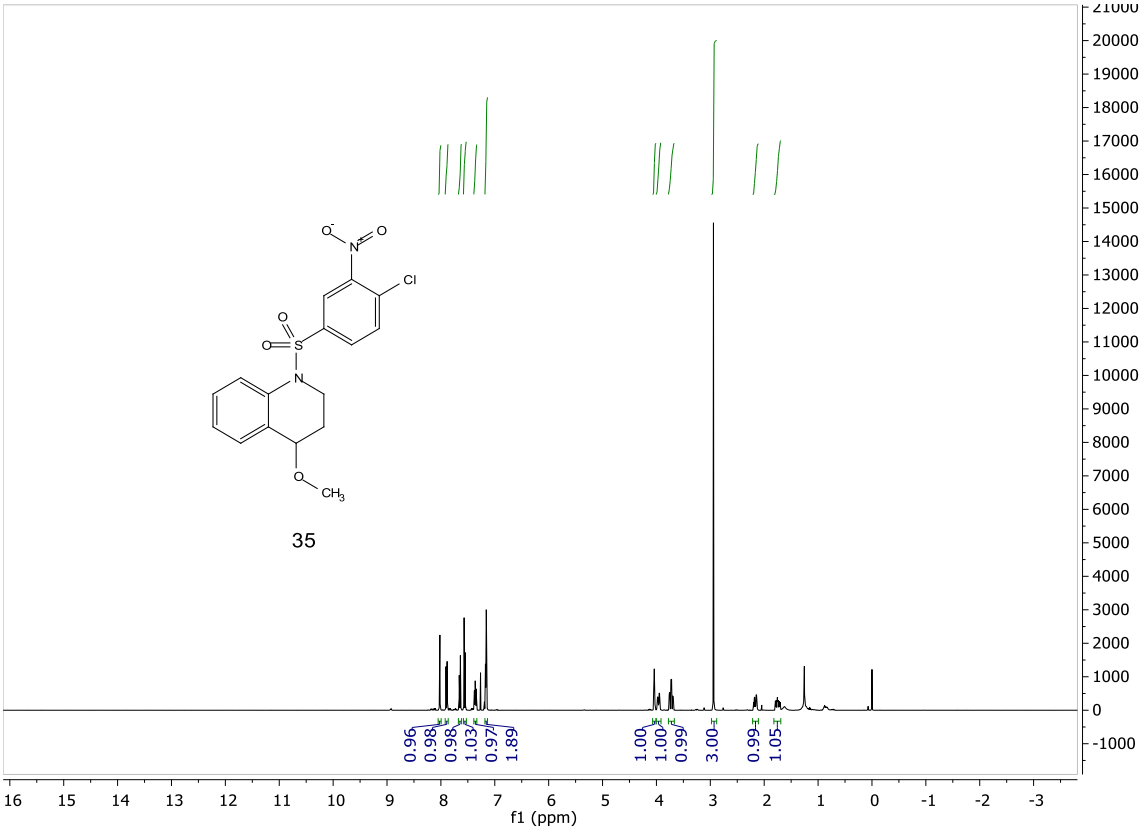


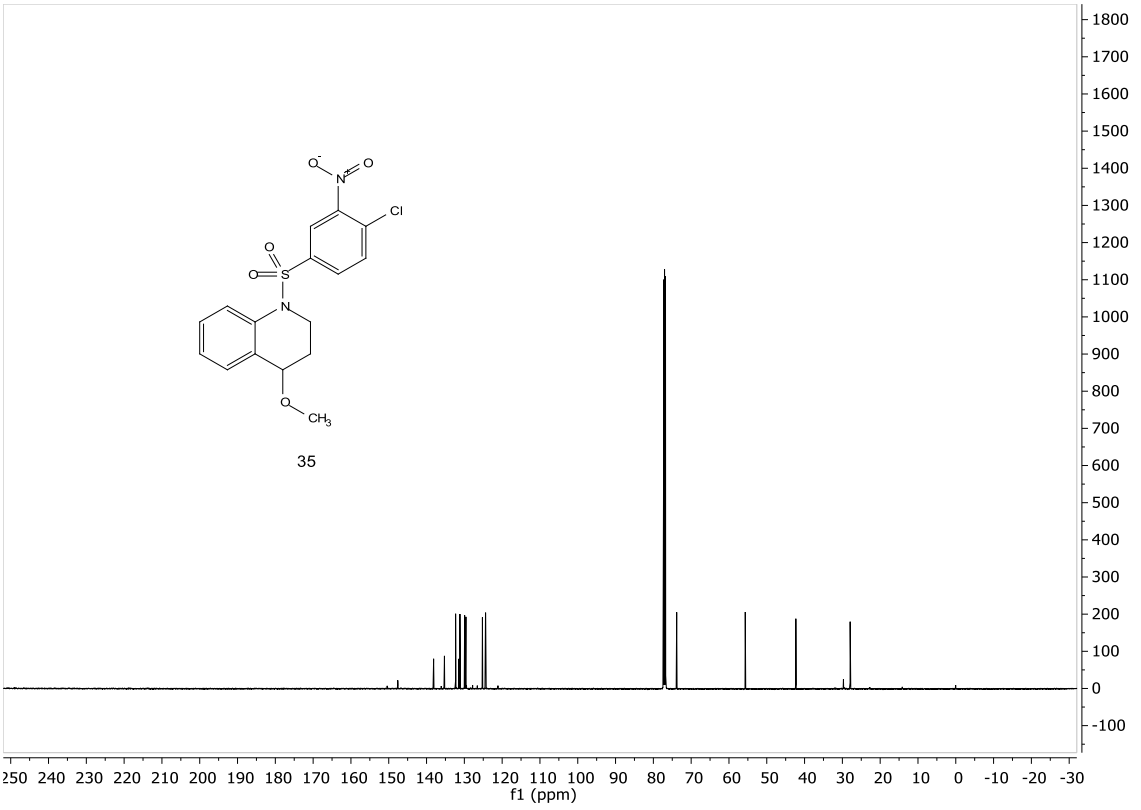
33

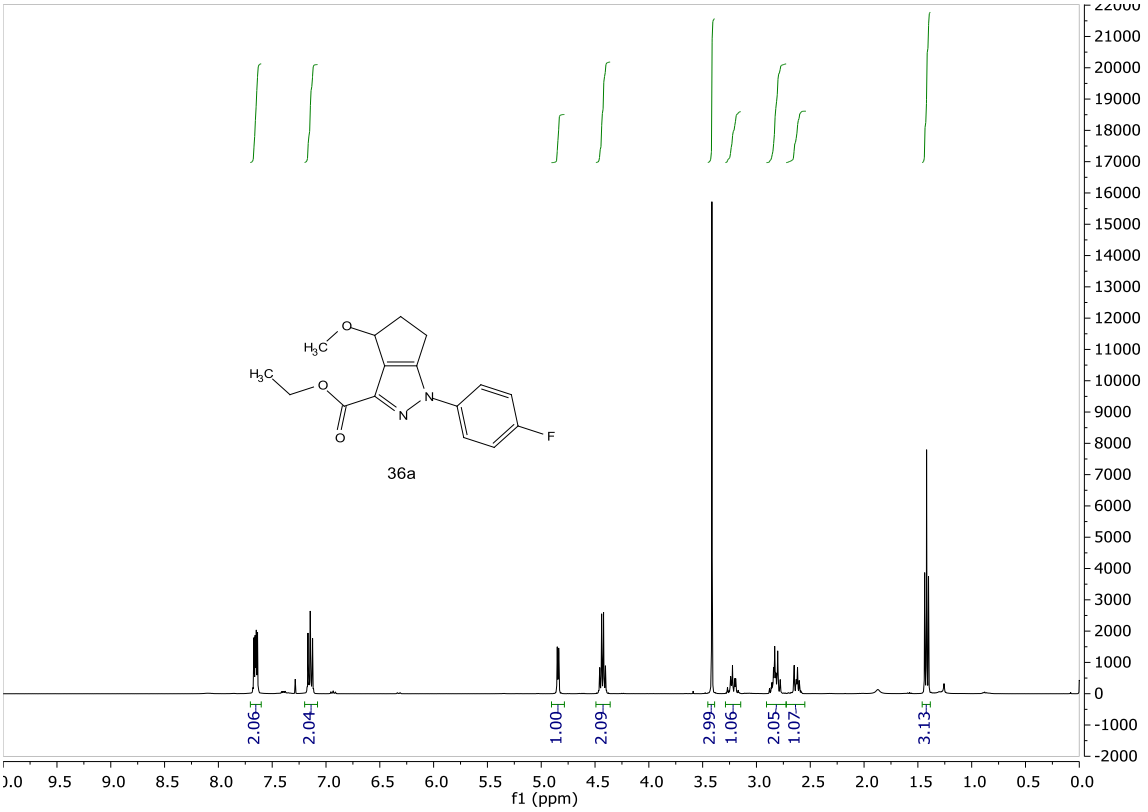

33
f1 (ppm)

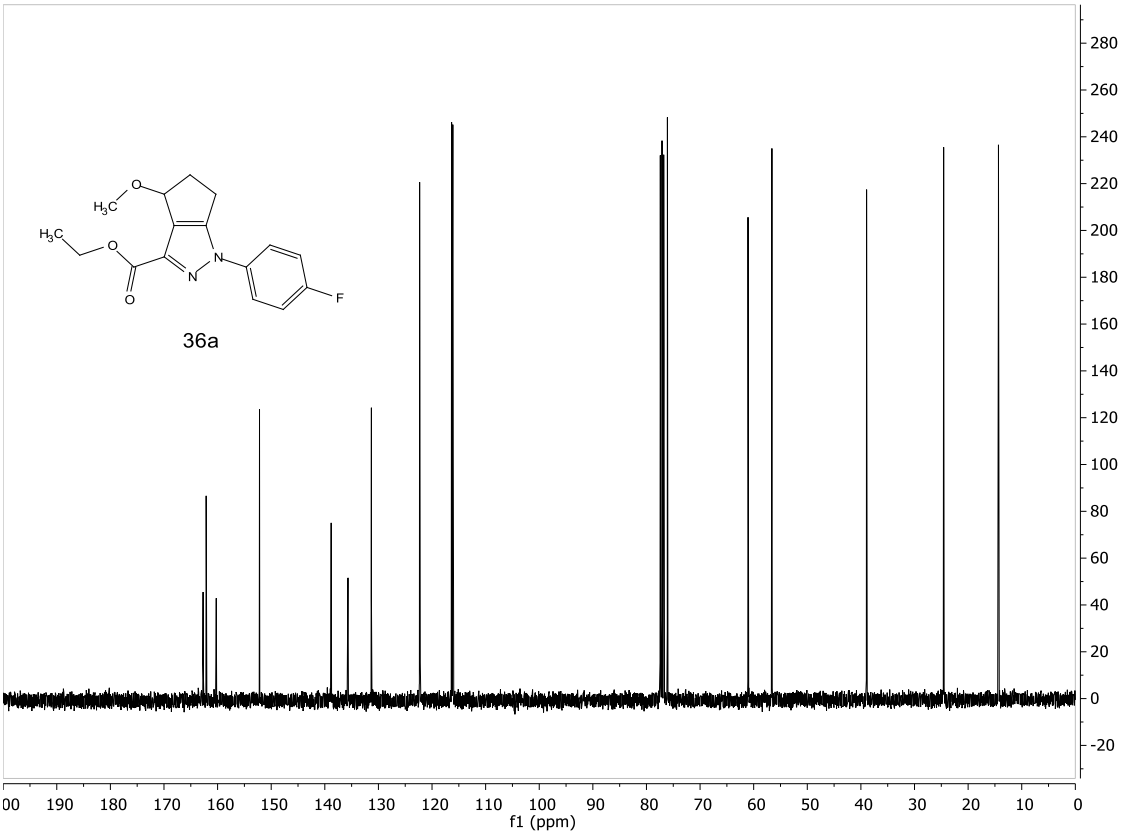

34
2.00
1.04
2.10
1.18
1.03
3.12
3.12
3.17
f1 (ppm)

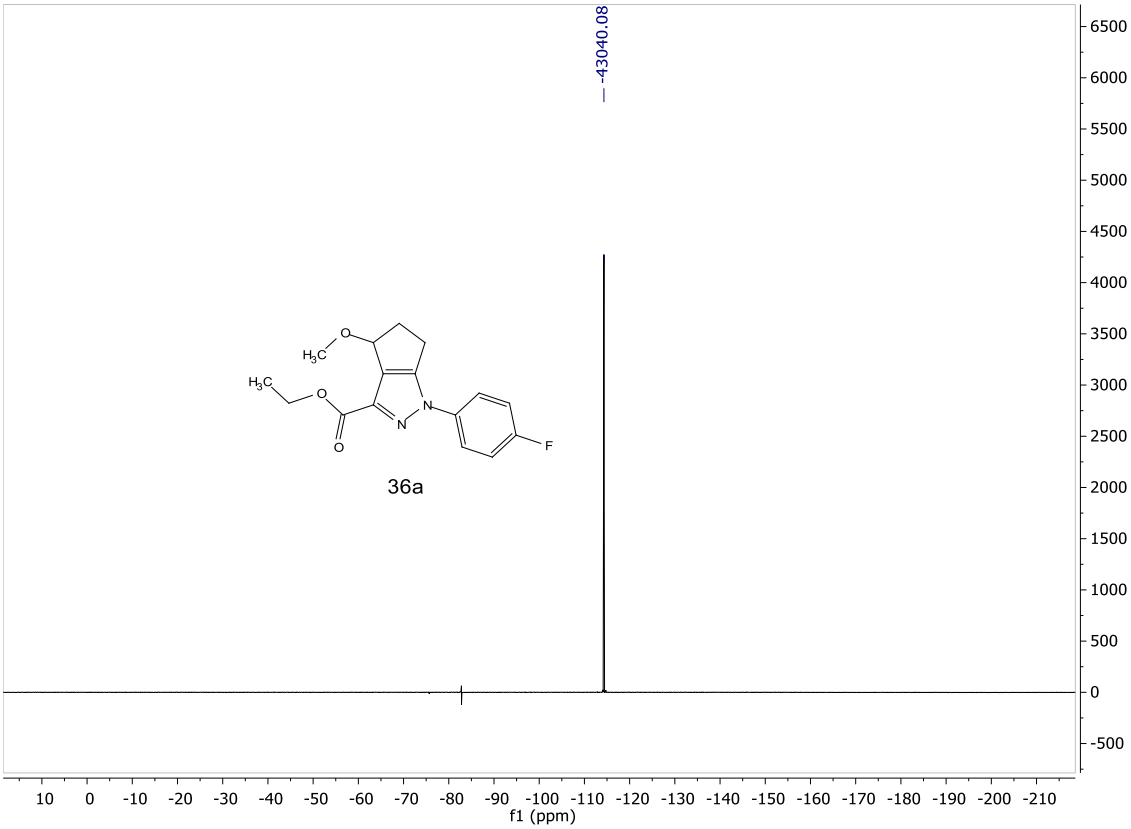

H3C
O
O
CH3
Br
CH3
O
O
Br
34
f1 (ppm)

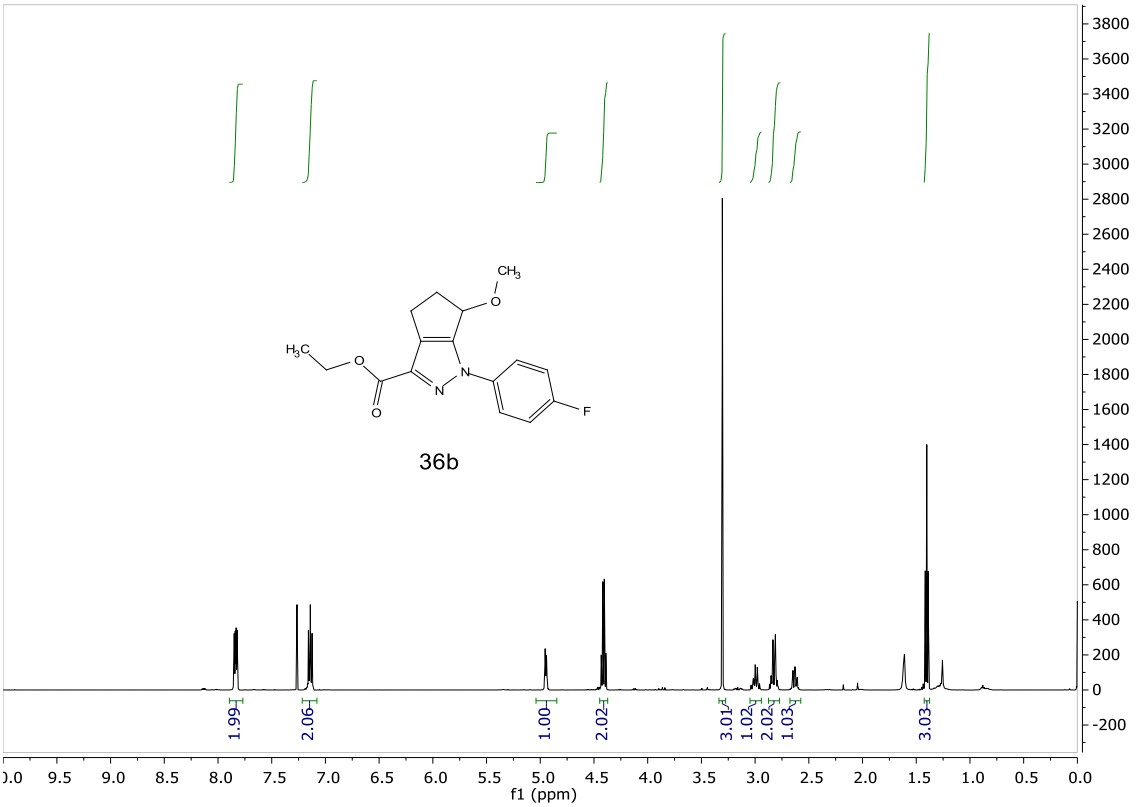

O
N
O
Cl
O
O
S
N
O
CH3
35
0.96
0.98
0.98
1.03
0.97
1.89
1.00
1.00
0.99
3.00
0.99
1.05
f1 (ppm)

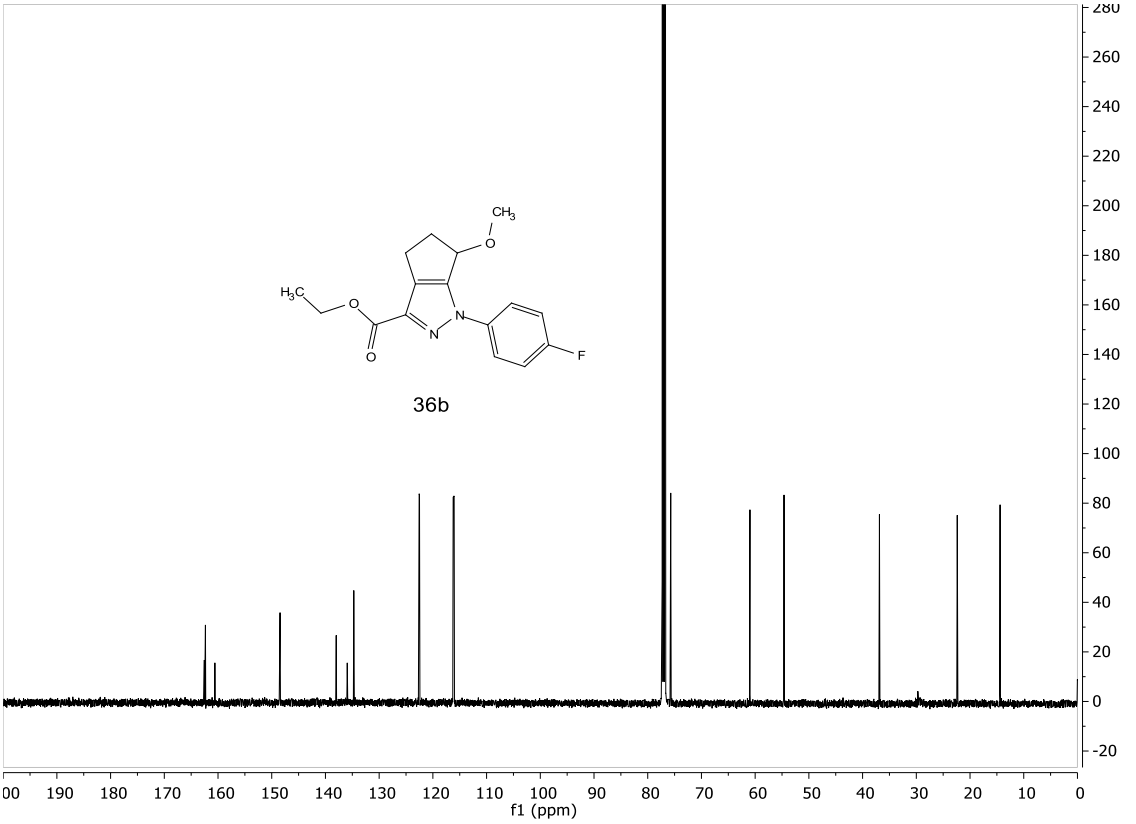

35
f1 (ppm)

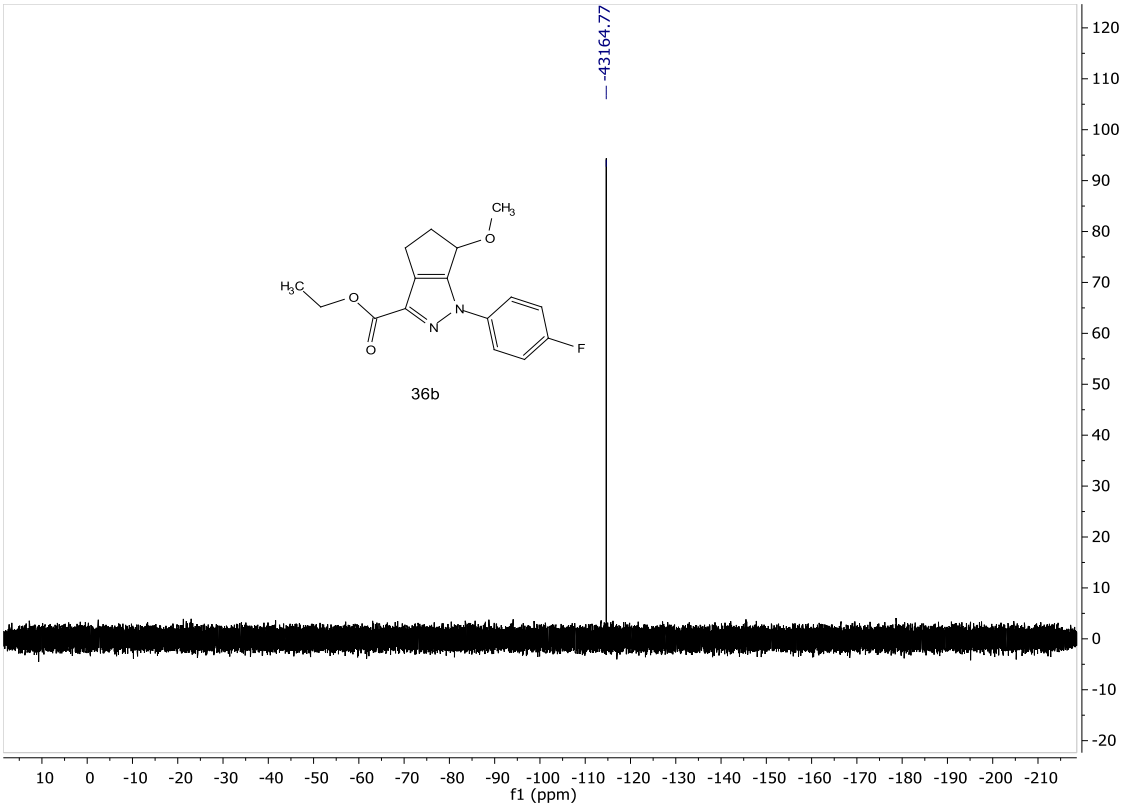

36a
2.06
2.04
1.00
2.09
2.99
1.06
2.05
1.07
3.13
f1 (ppm)

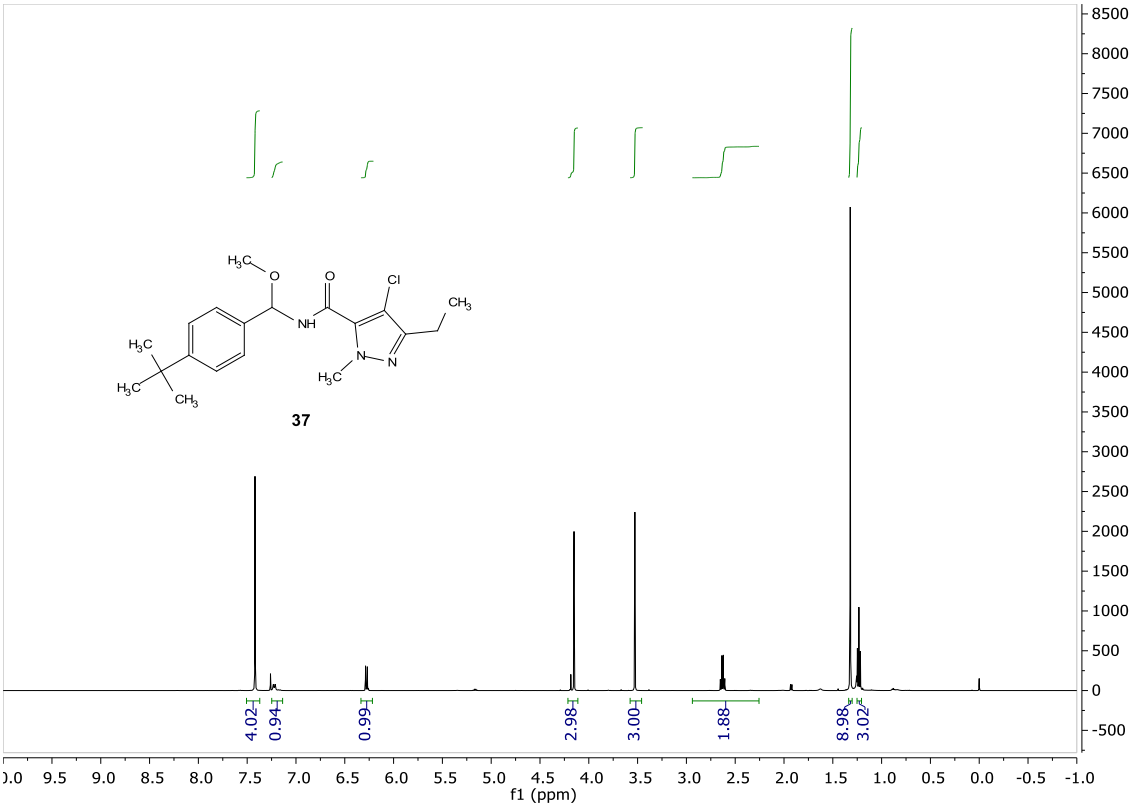

36a
f1 (ppm)

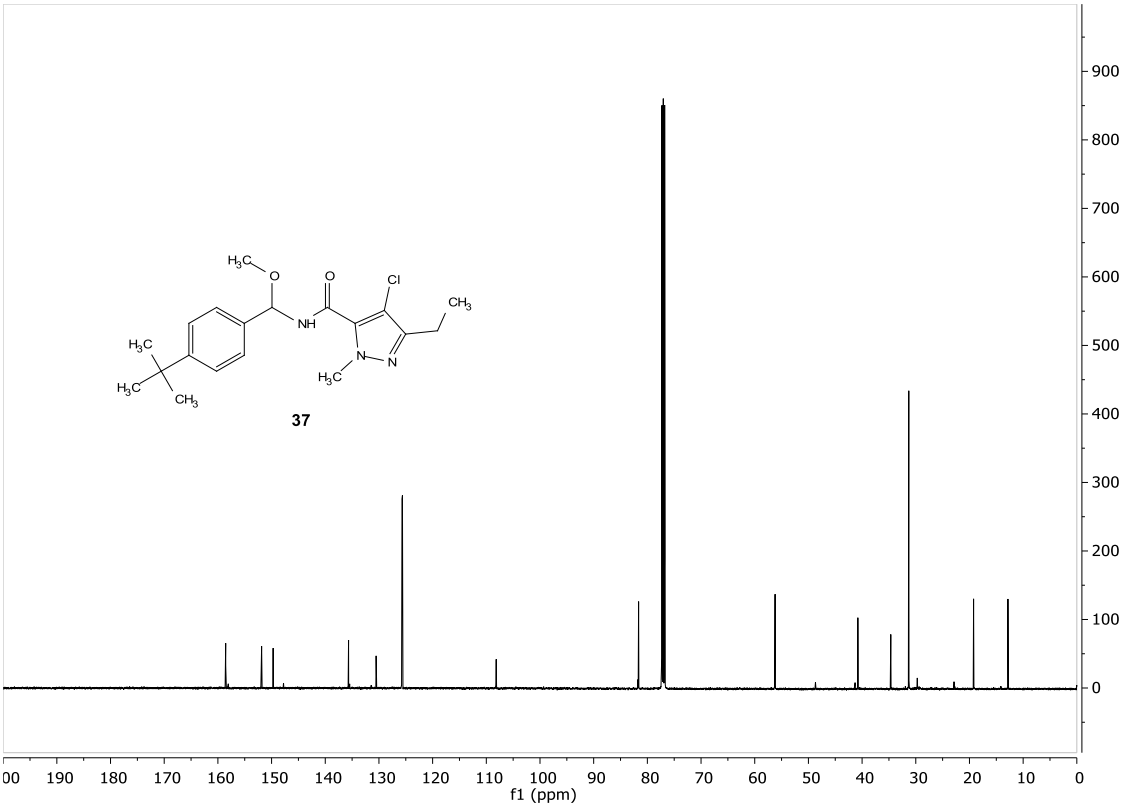

-43040.08
36a
f1 (ppm)

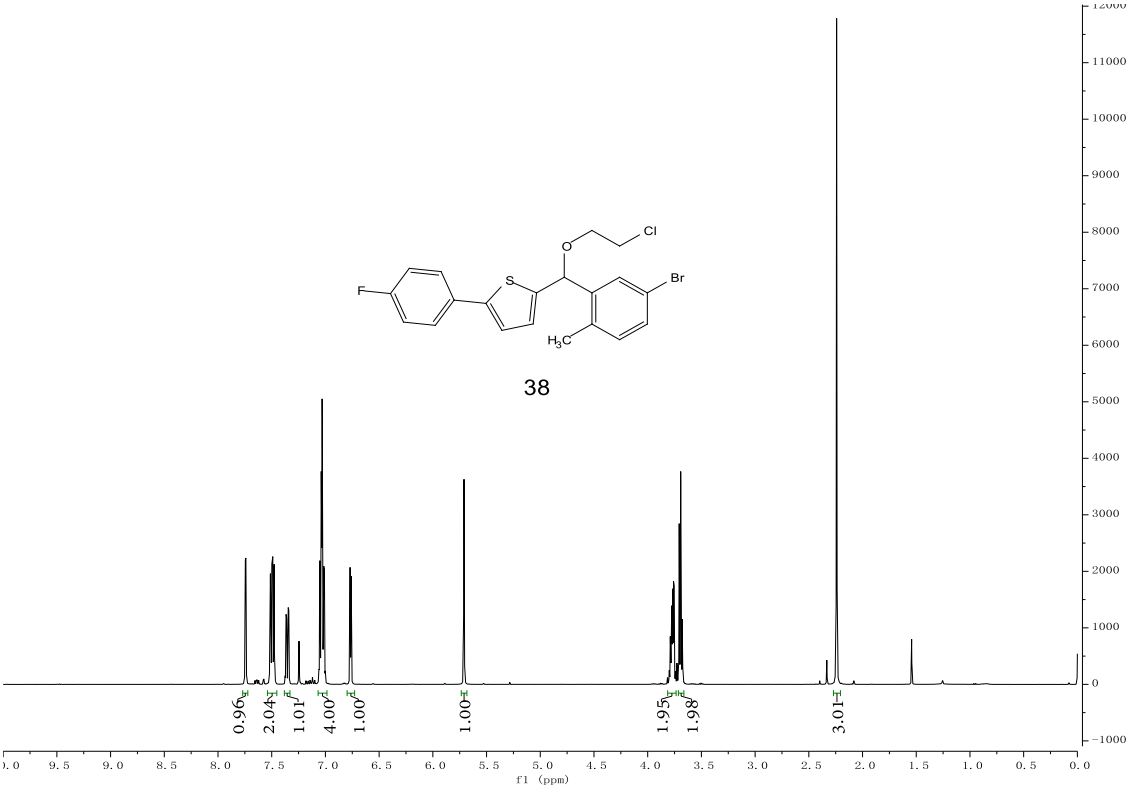

CH3
O
H3C
O
N
N
O
F
36b
1.99
2.06
1.00
2.02
3.01
1.02
2.02
1.03
3.03
f1 (ppm)

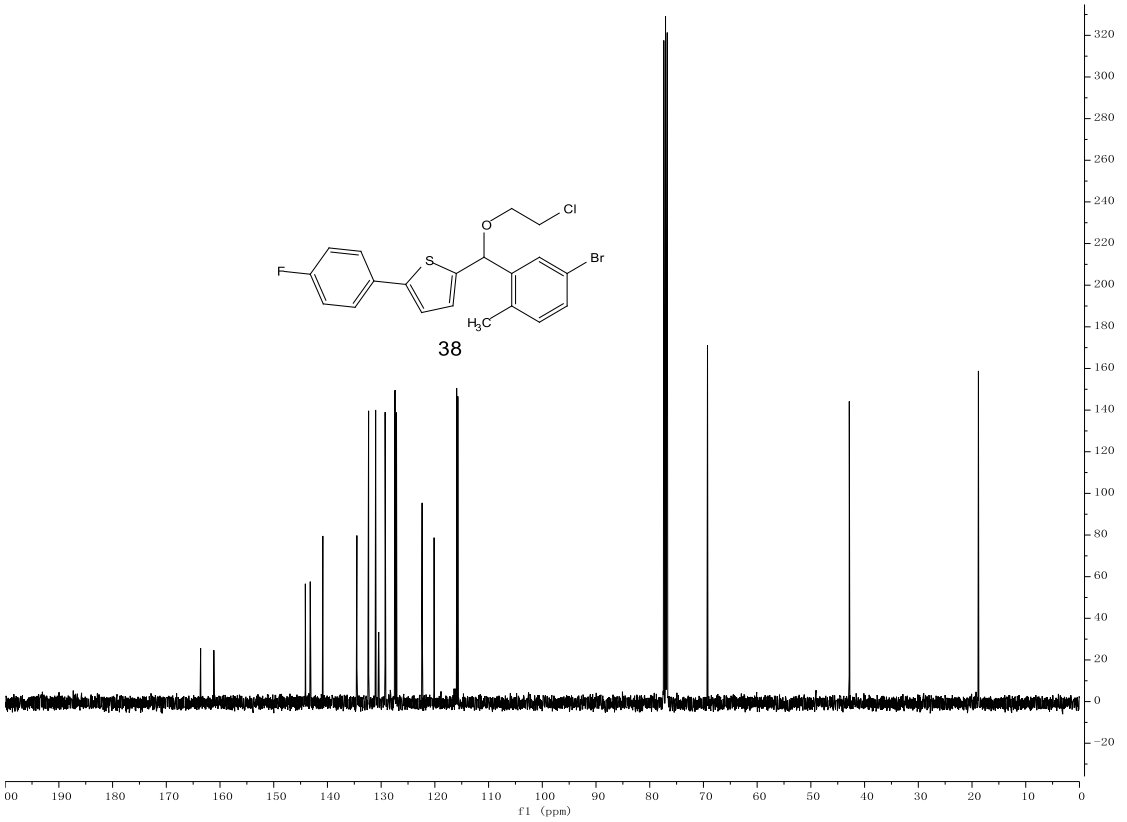

CH3
O
H3C
O
N
N
O
F
36b
f1 (ppm)


-43164.77
36b
f1 (ppm)

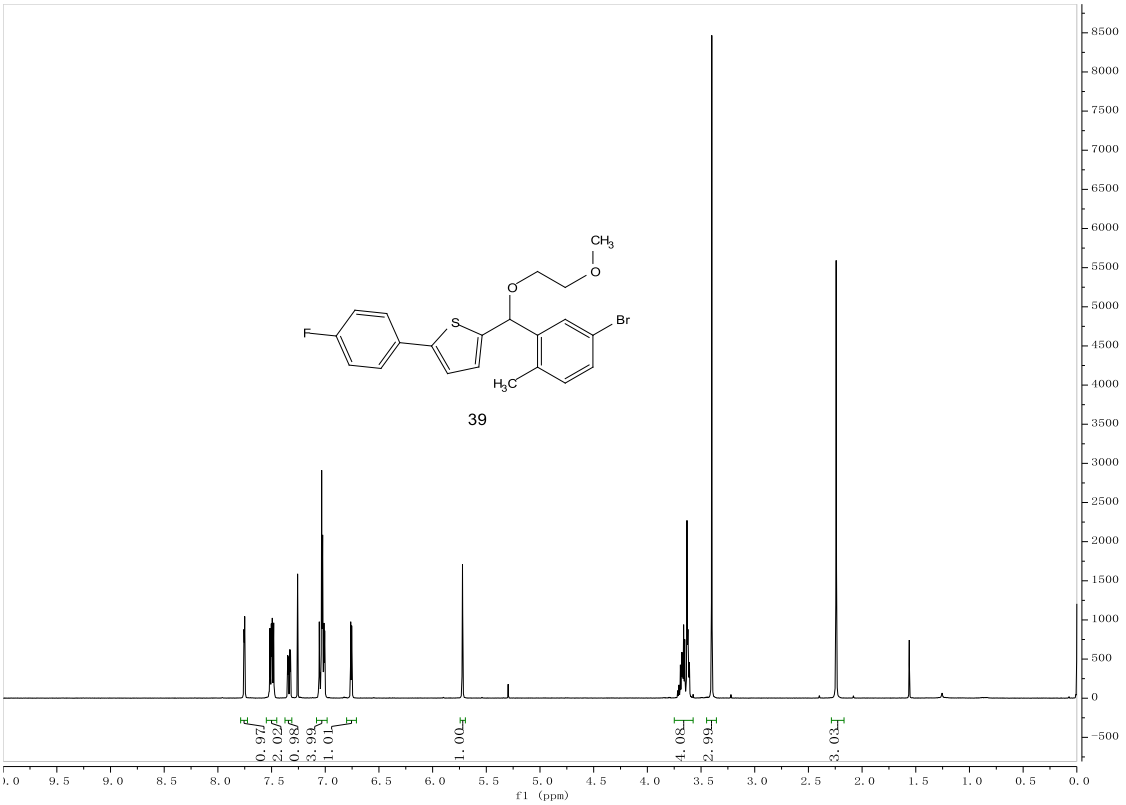

37
4.02
0.94
0.99
2.98
3.00
1.88
8.98
3.02
f1 (ppm)

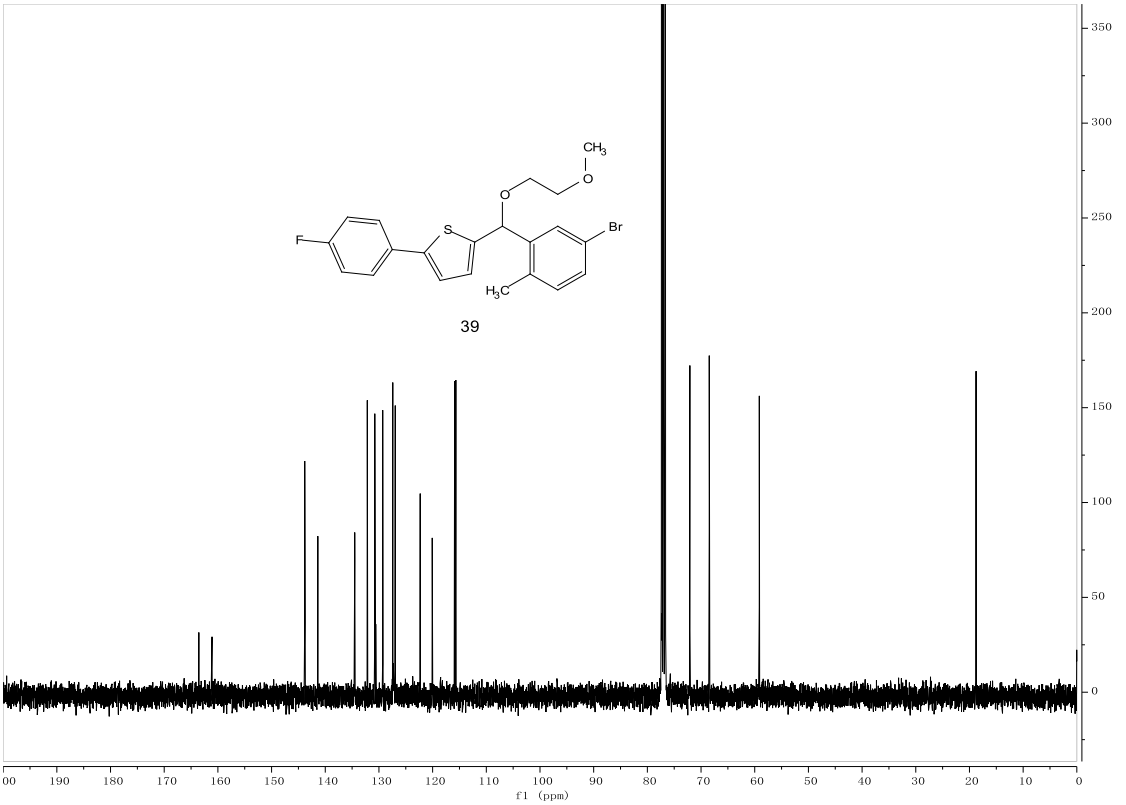

37
f1 (ppm)


38
f1 (ppm)

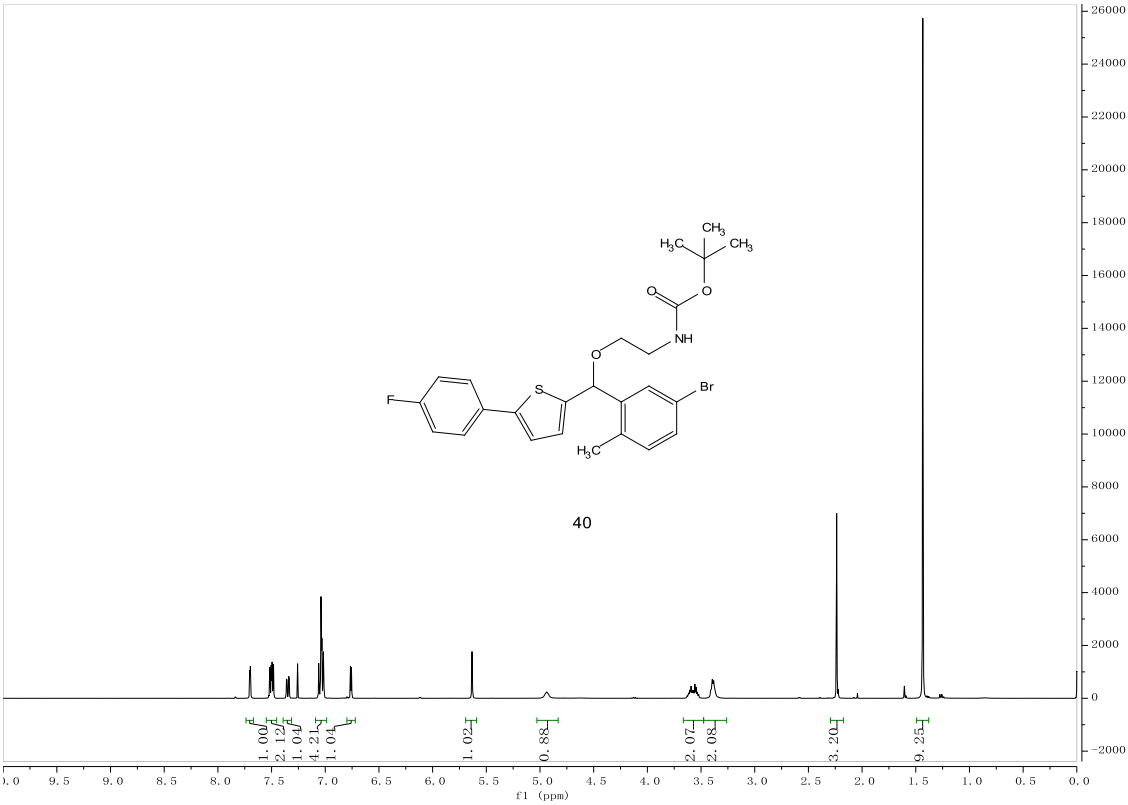

Cl
O
S
Br
F
H_3C
38
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
−20
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

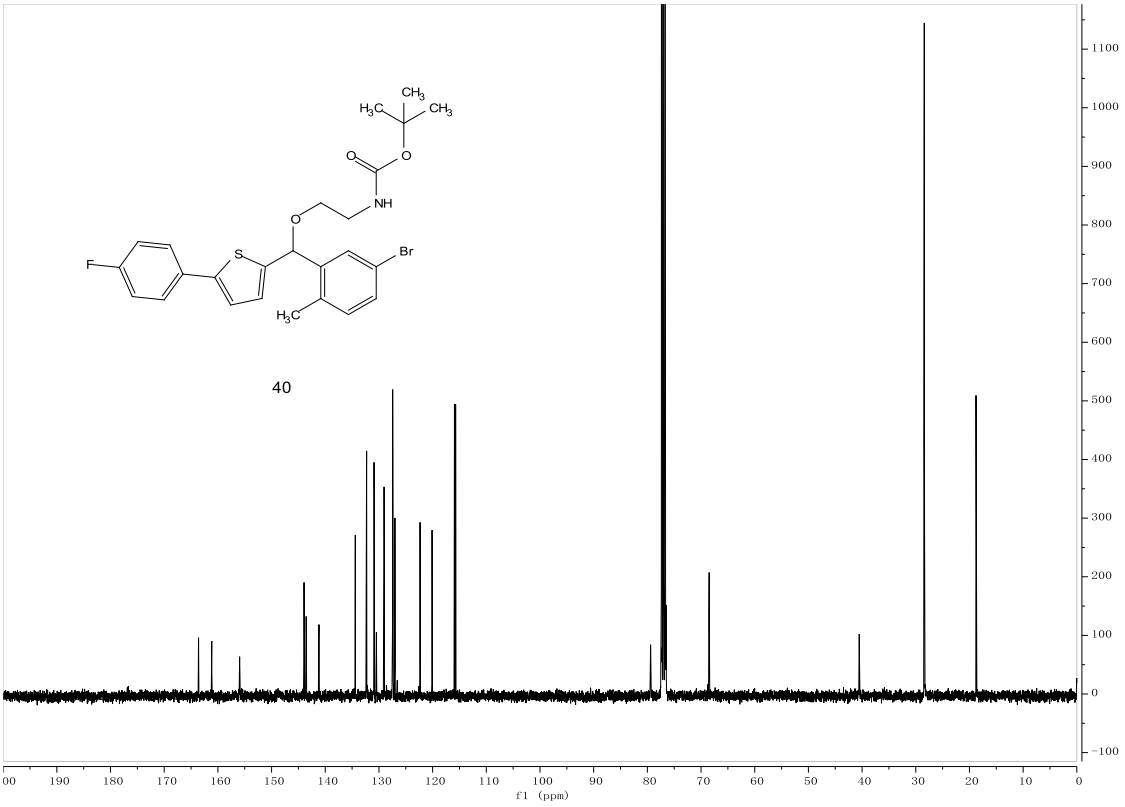

-114.3155
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
Cl
O
S
Br
F
H_3C
38
10 0 −10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110 −120 −130 −140 −150 −160 −170 −180 −190 −200 −210
f1 (ppm)

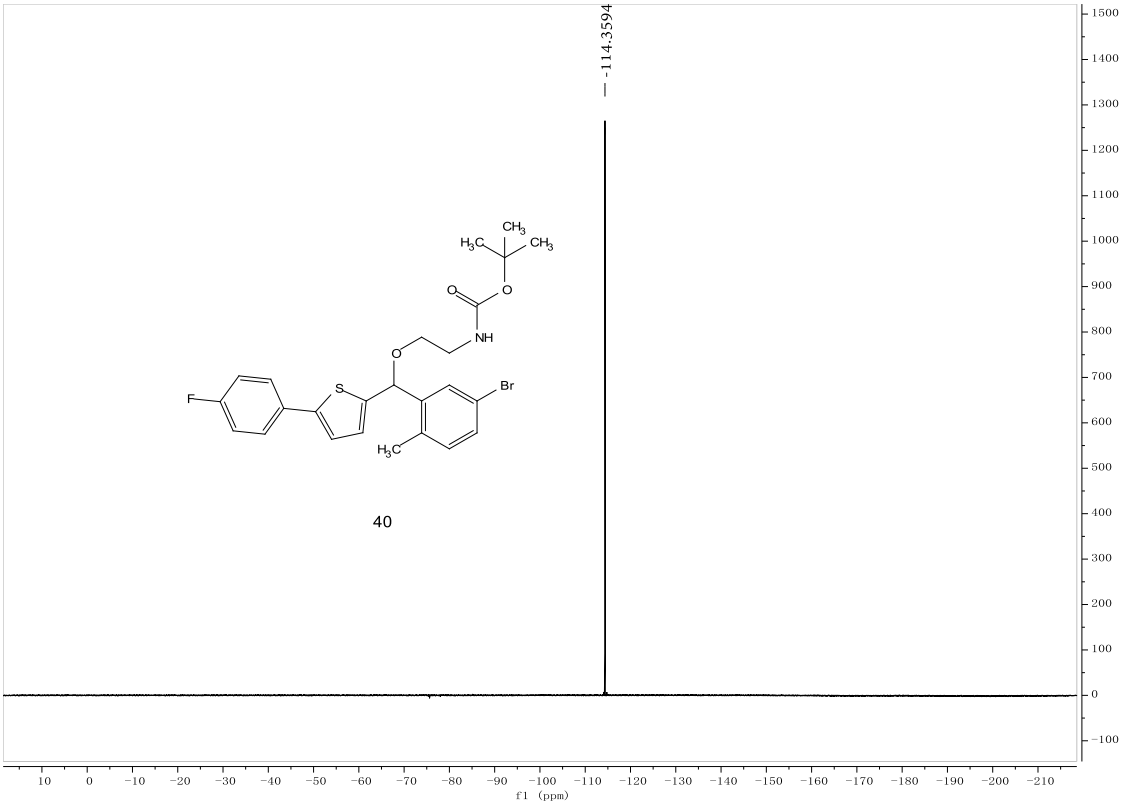

CH3
O
O
S
F
Br
H3C
39
0.97
2.02
0.98
3.99
1.01
1.00
4.08
2.99
3.03
f1 (ppm)

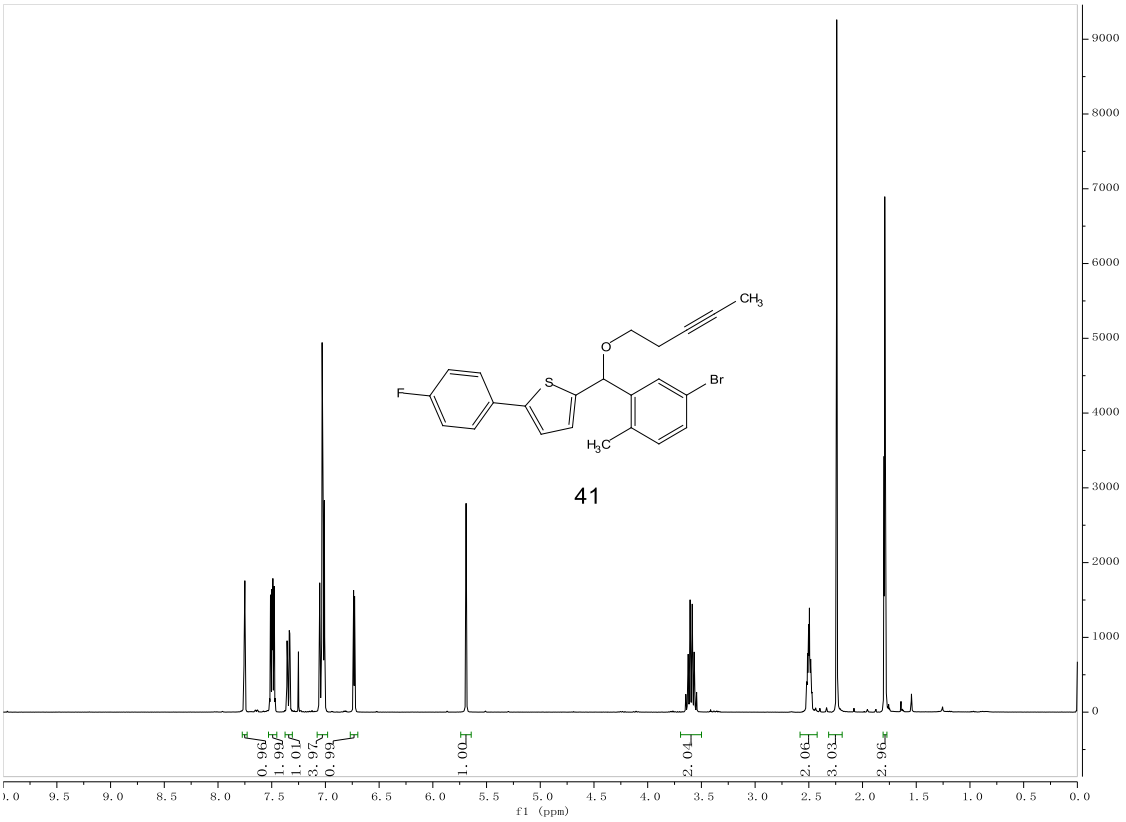

CH3
O
O
S
F
Br
H3C
39
f1 (ppm)

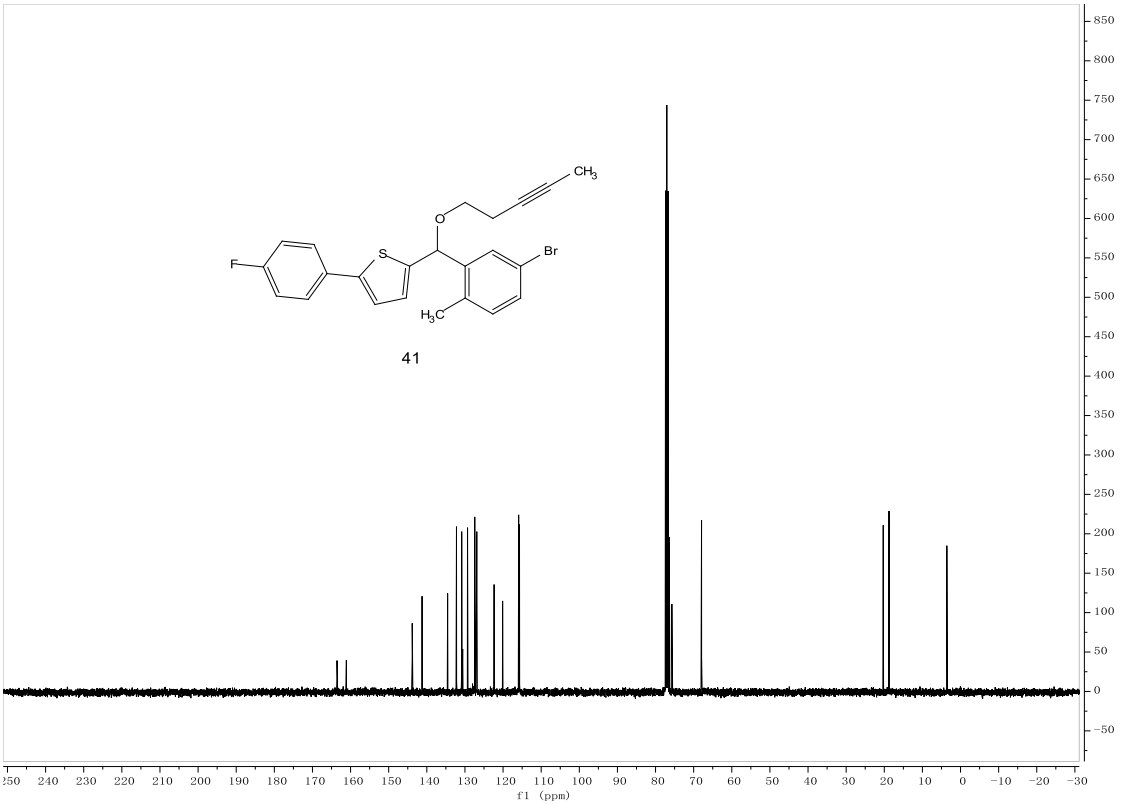

-114.5688
CH3
O
O
S
F
Br
H3C
39
f1 (ppm)

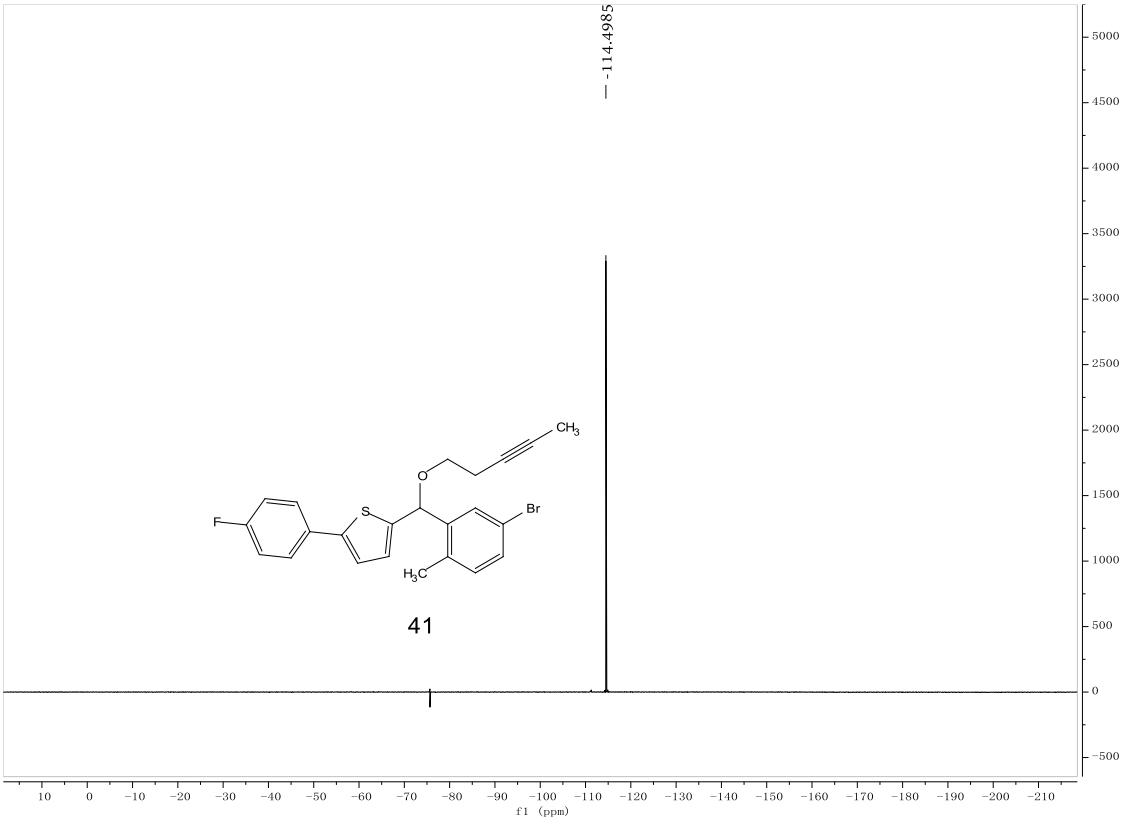

CH3
H3C
CH3
O
O
NH
O
S
F
Br
H3C
40
1.00
2.12
1.04
4.21
1.04
1.02
0.88
2.07
2.08
3.20
9.25
f1 (ppm)

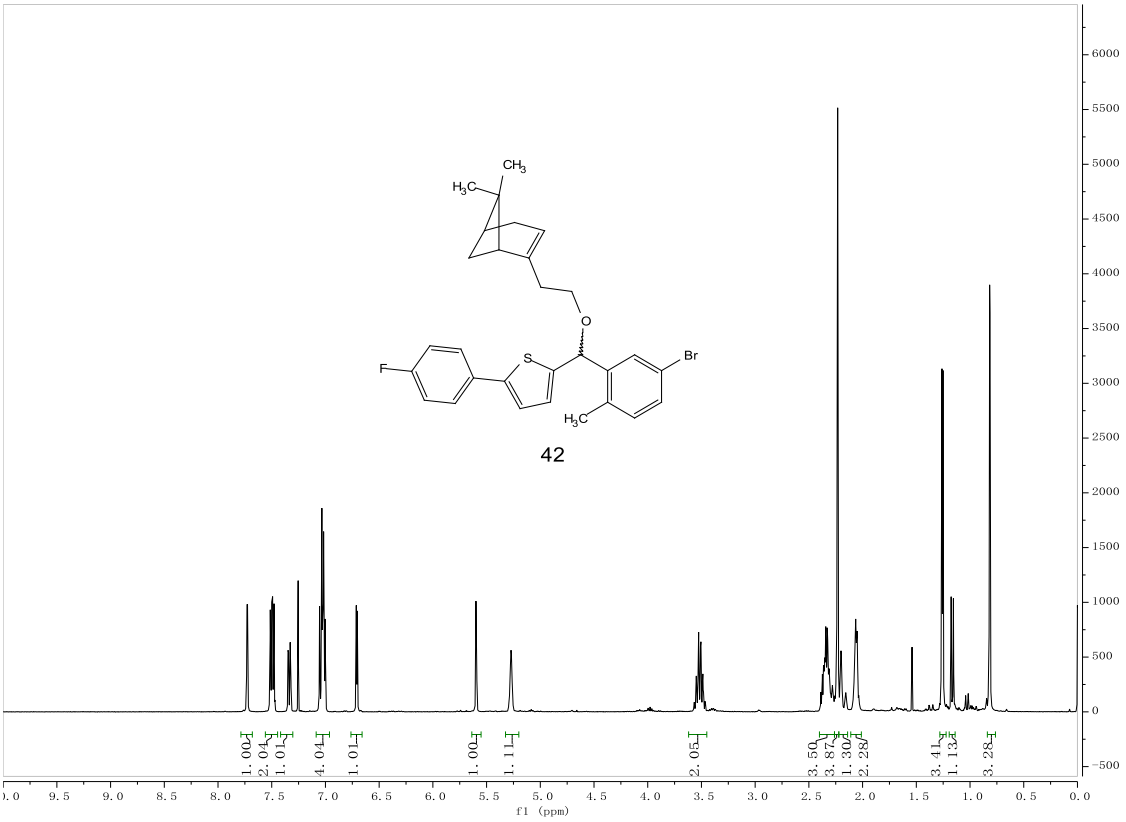

CH3
H3C
CH3
O
O
NH
O
F
S
Br
H3C
40
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

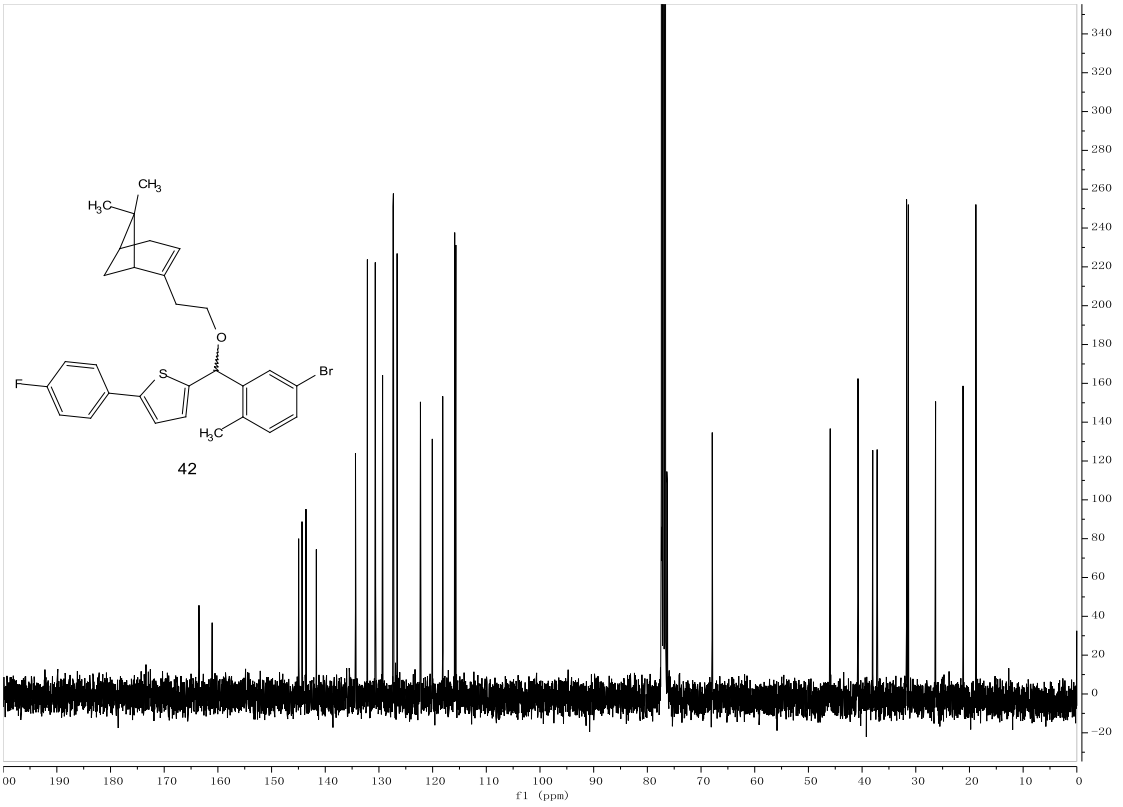

-114.3594
CH3
H3C
CH3
O
O
NH
O
F
S
Br
H3C
40
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

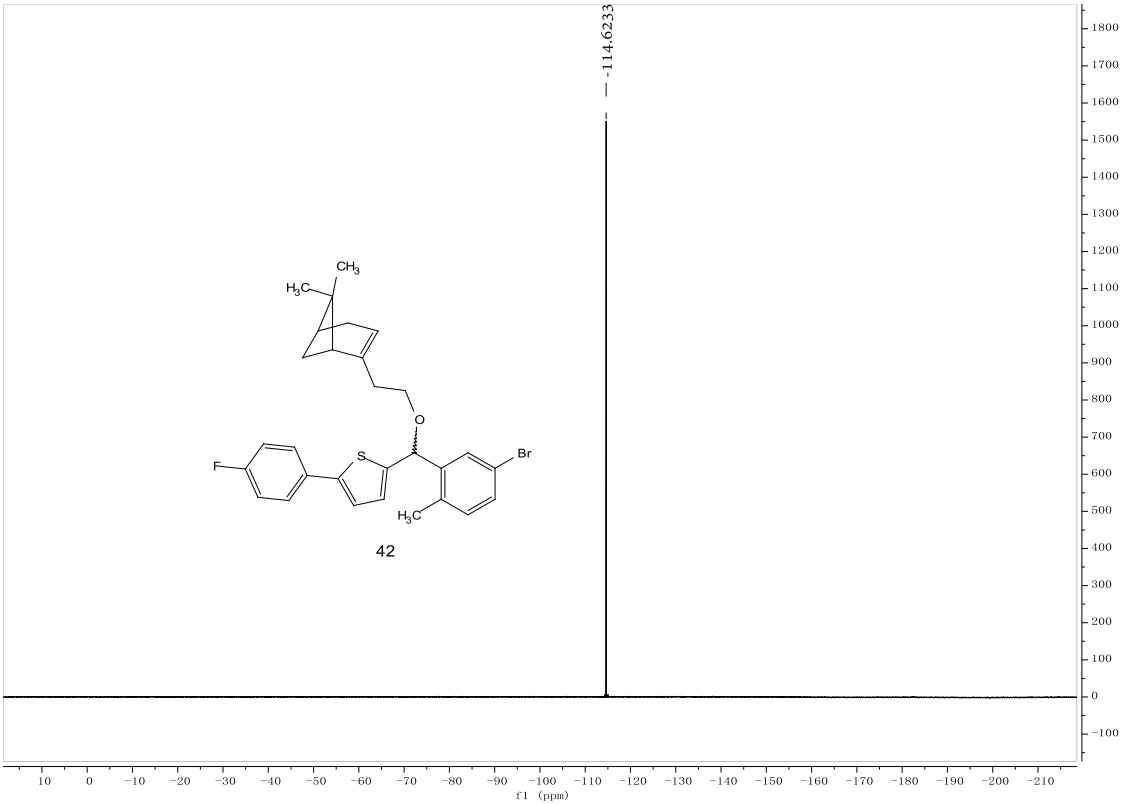

CH3
O
S
Br
F
H3C
41
0.96
1.99
1.01
3.97
0.99
1.00
2.04
2.06
3.03
2.96
f1 (ppm)

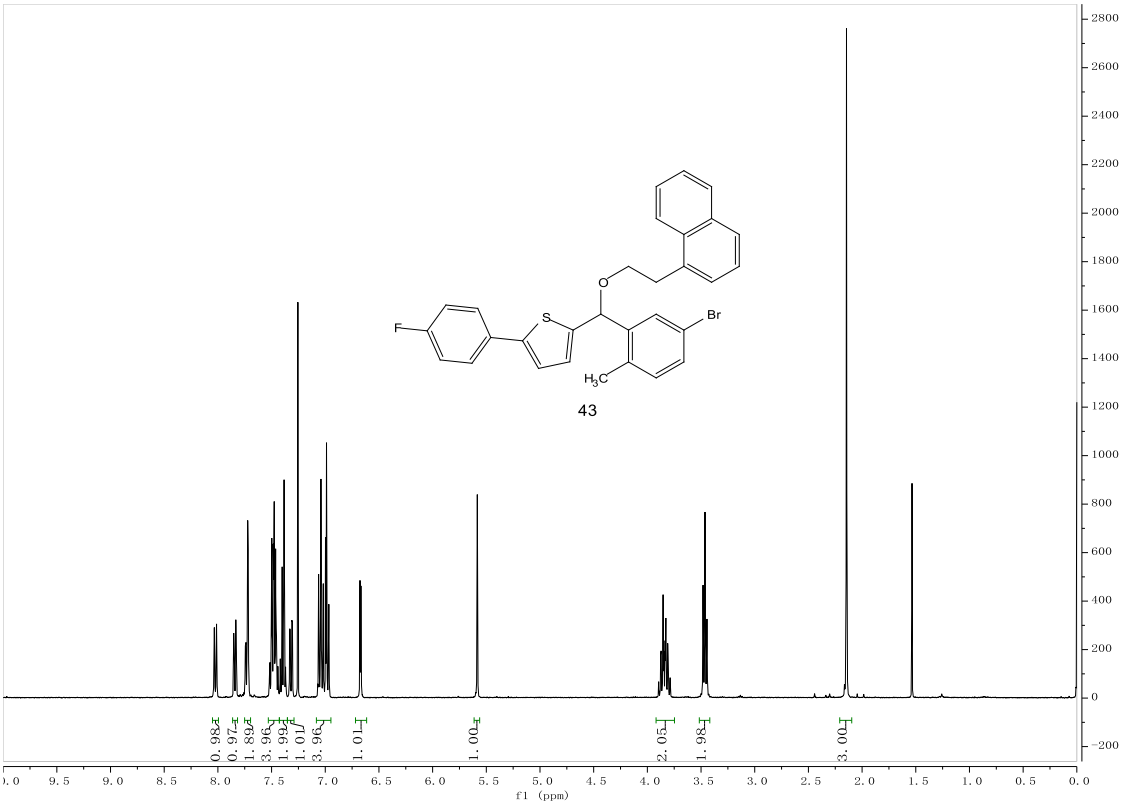

CH3
O
S
Br
F
H3C
41
f1 (ppm)

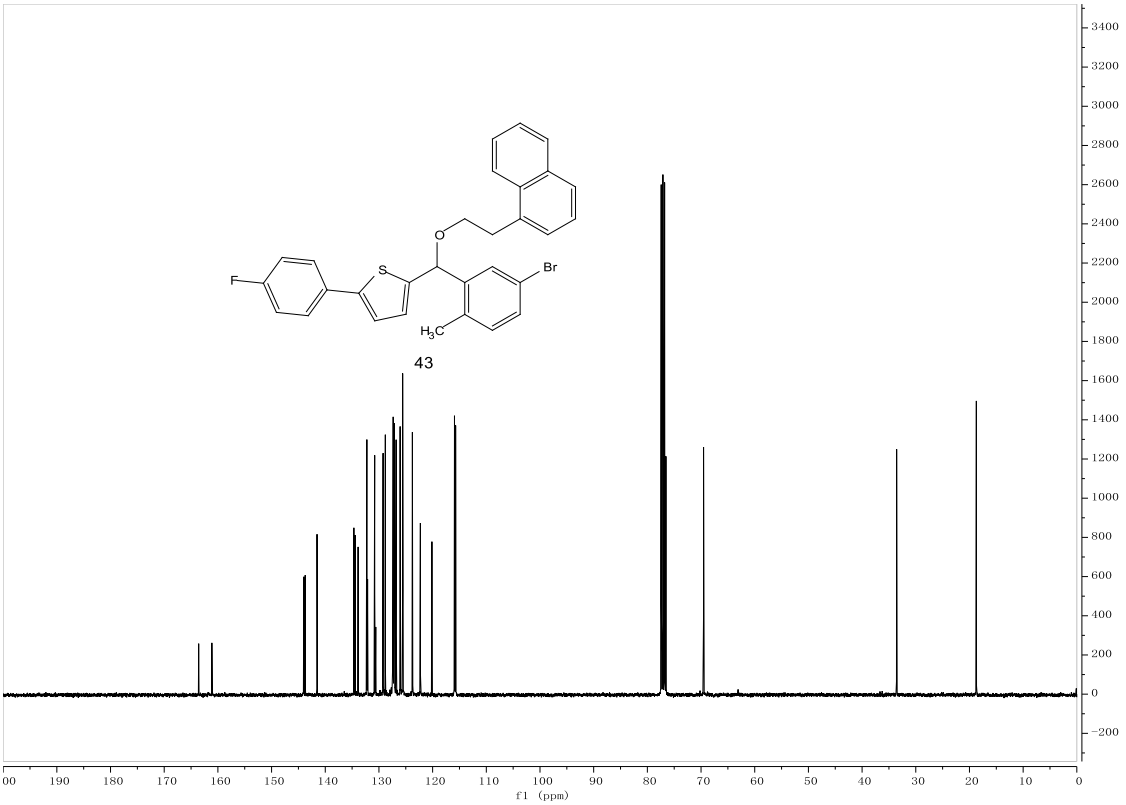

-114.4985
CH3
O
S
F
Br
H3C
41
f1 (ppm)

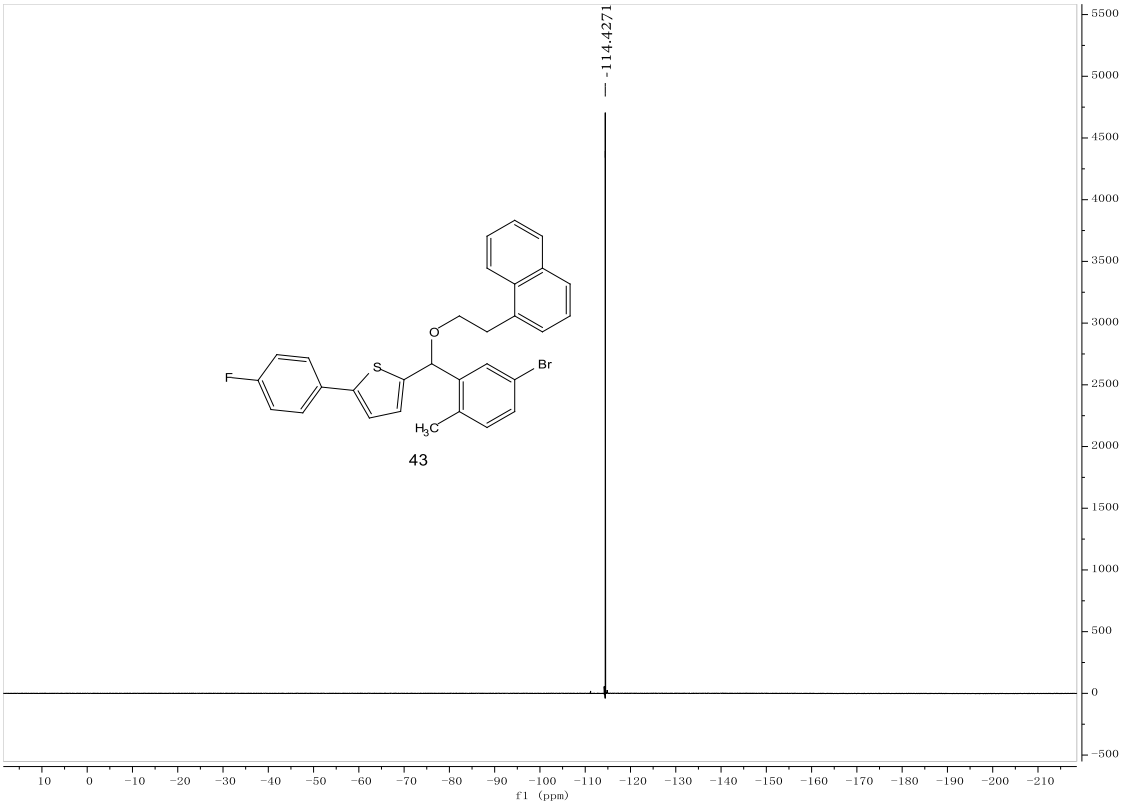

CH3
H3C
O
S
F
Br
H3C
42
1.00
2.04
1.01
4.04
1.01
1.00
1.11
2.05
3.50
3.87
1.30
2.28
3.41
1.13
3.28
f1 (ppm)

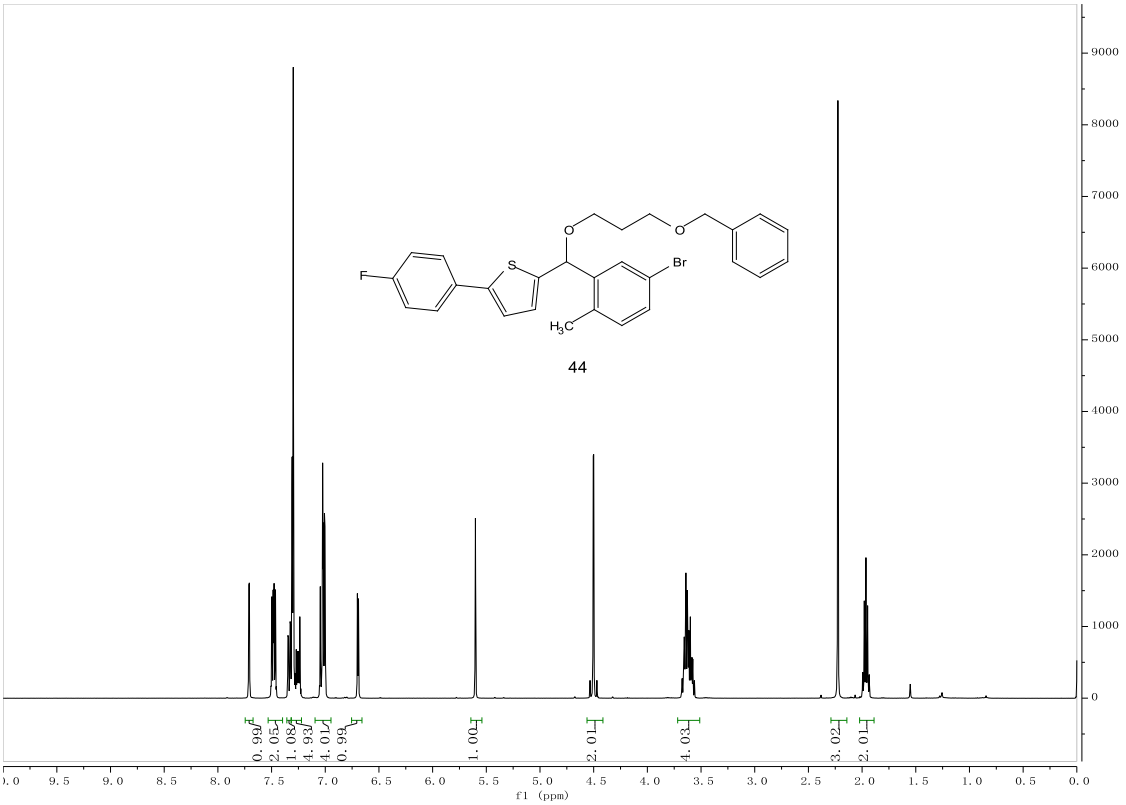

CH3
H3C
O
S
F
Br
H3C
42
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

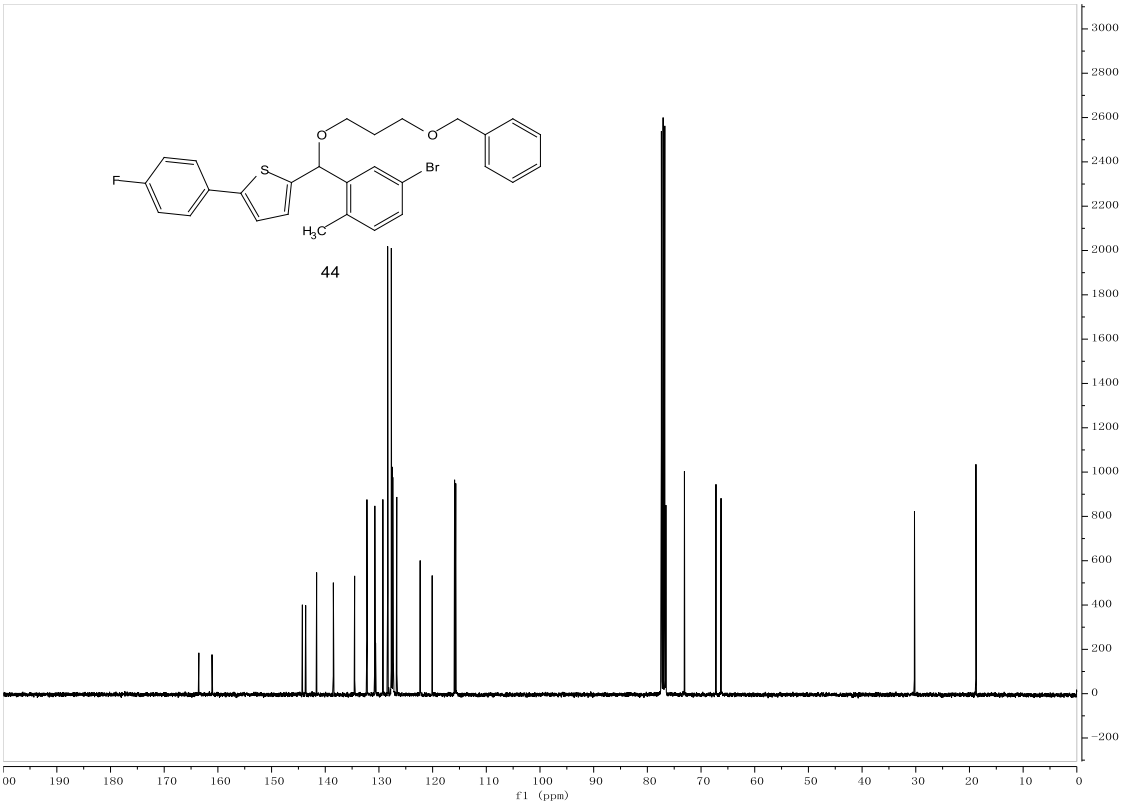

-114.6233
CH3
H3C
O
S
F
Br
H3C
42
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

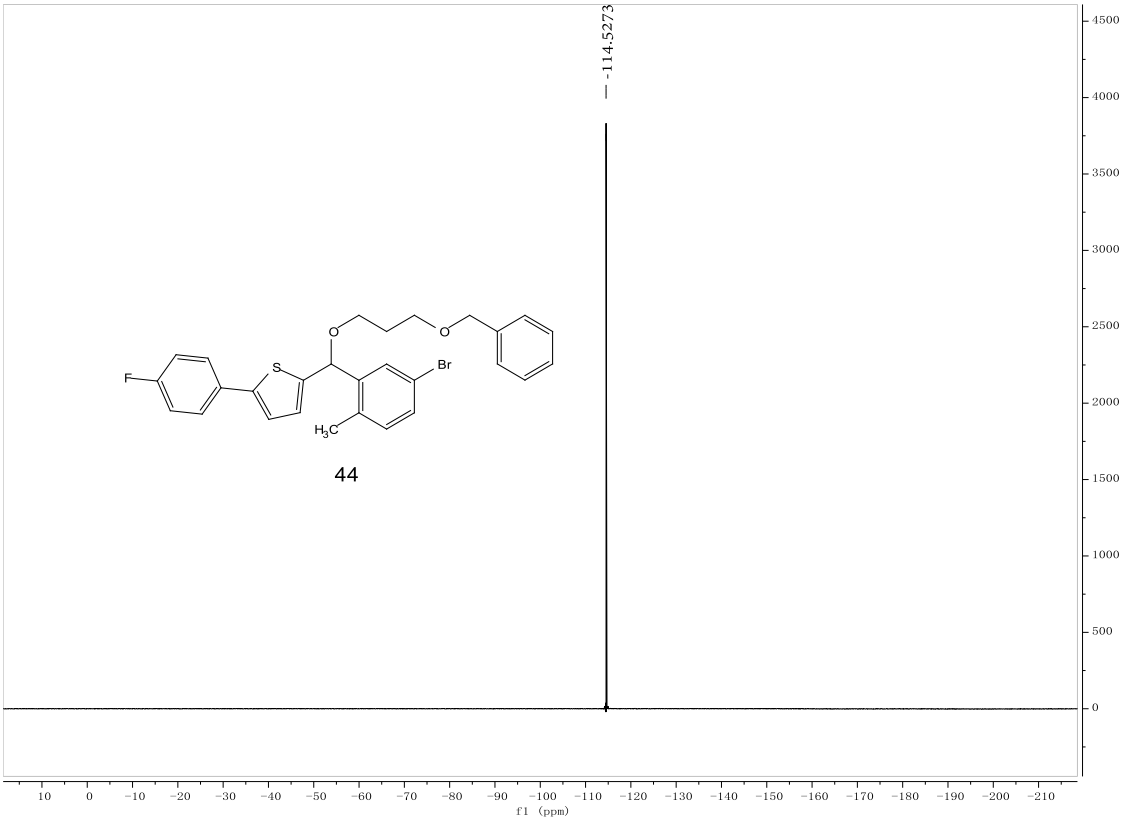

F
S
O
Br
H3C
43
0.98
0.97
1.89
3.96
1.99
1.01
3.96
1.01
1.00
2.05
1.98
3.00
f1 (ppm)

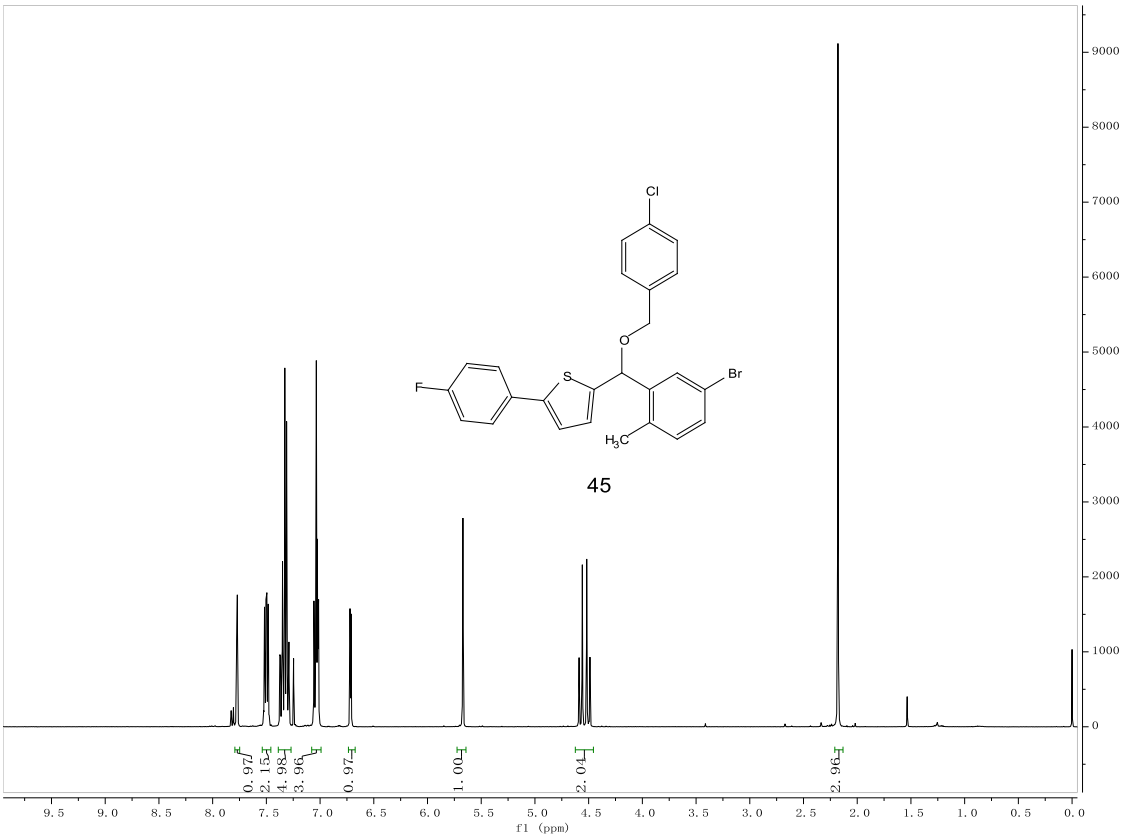

F
S
O
Br
H3C
43
f1 (ppm)

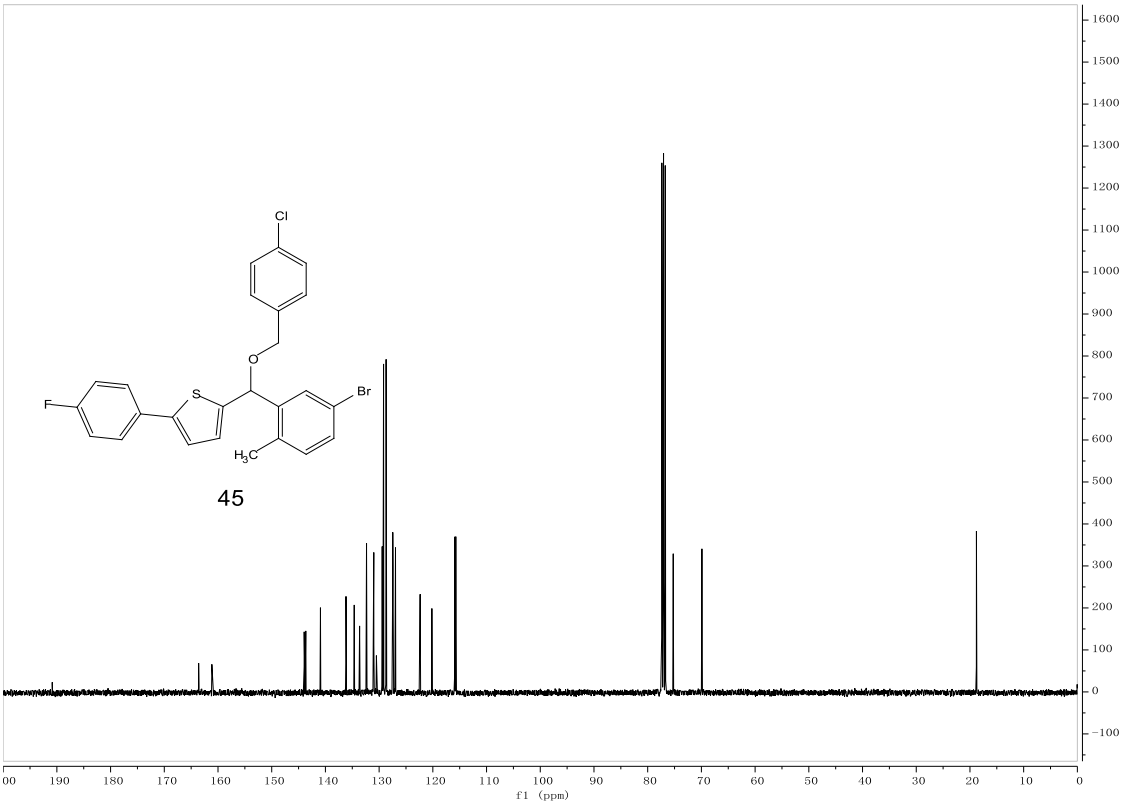

-114.4271
F
S
O
Br
H_3C
43
f1 (ppm)

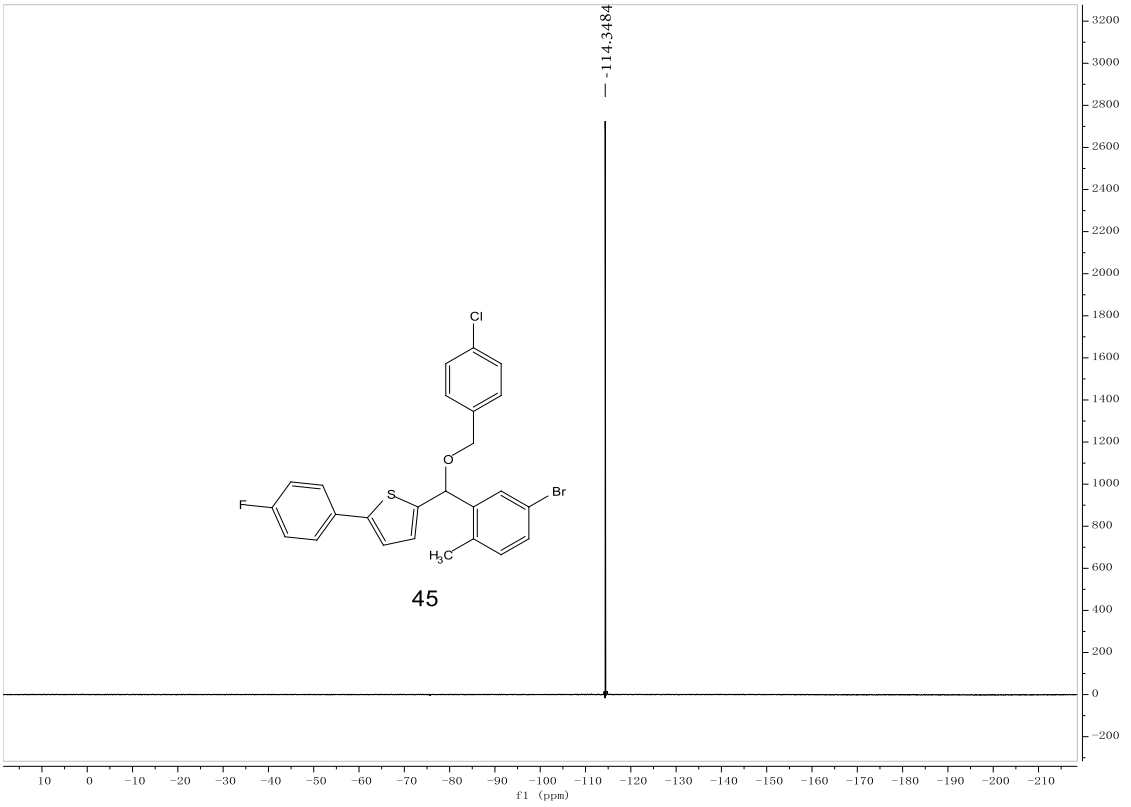

F
S
O
O
Br
H_3C
44
0.99
2.05
1.08
4.93
4.01
0.99
1.00
2.01
4.03
3.02
2.01
f1 (ppm)

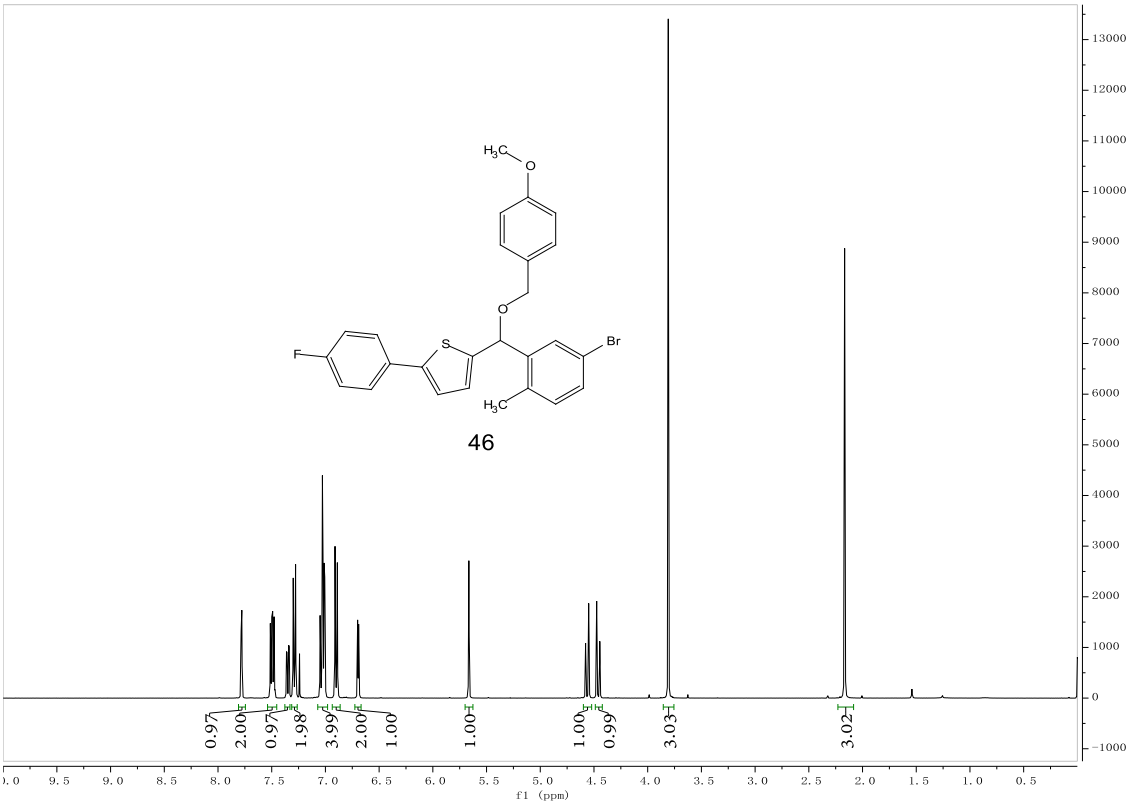

O
O
F
S
Br
H_3C
44
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

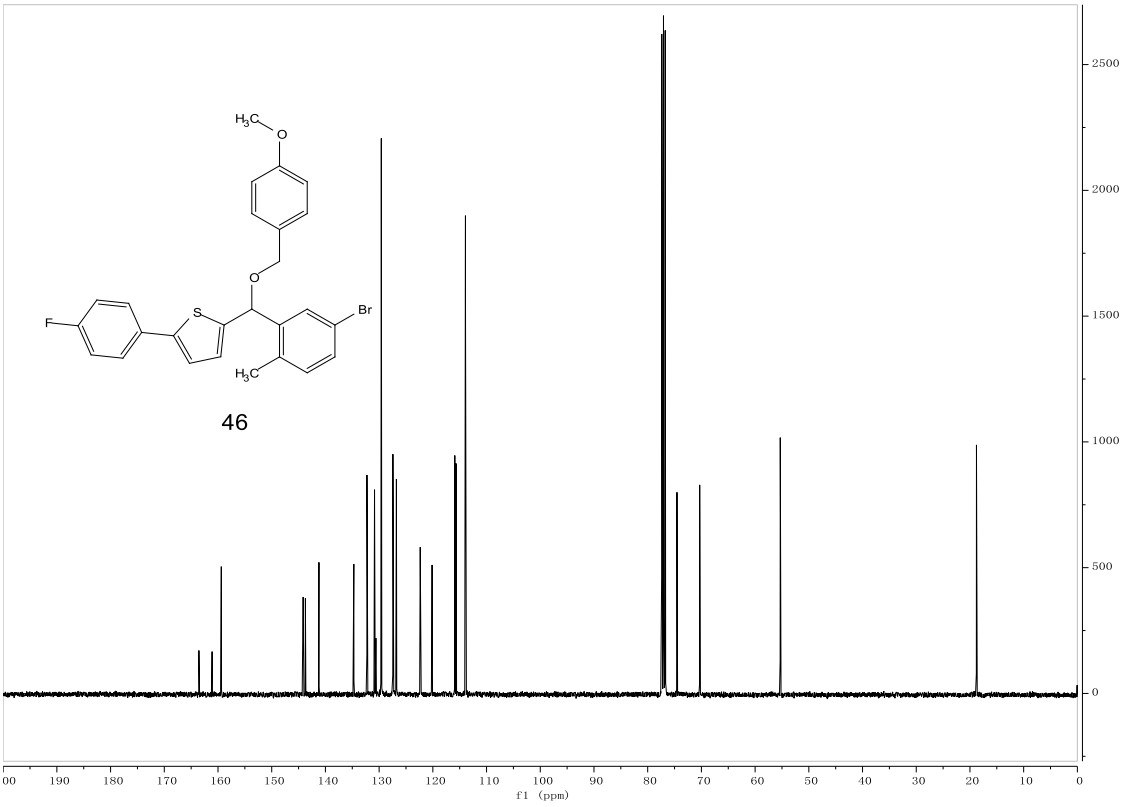

-114.5273
O
O
F
S
Br
H_3C
44
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

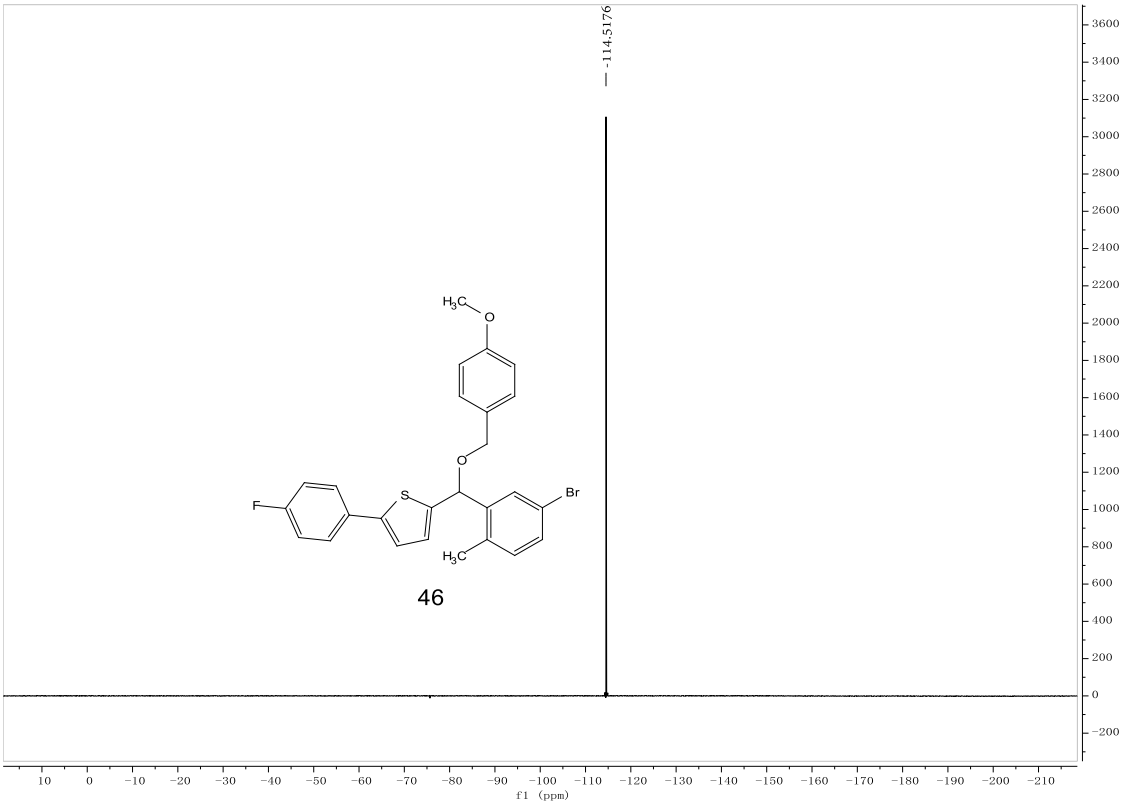

Cl
O
S
F
Br
H_3C
45
0.97
2.15
4.98
3.96
0.97
1.00
2.04
2.96
f1 (ppm)

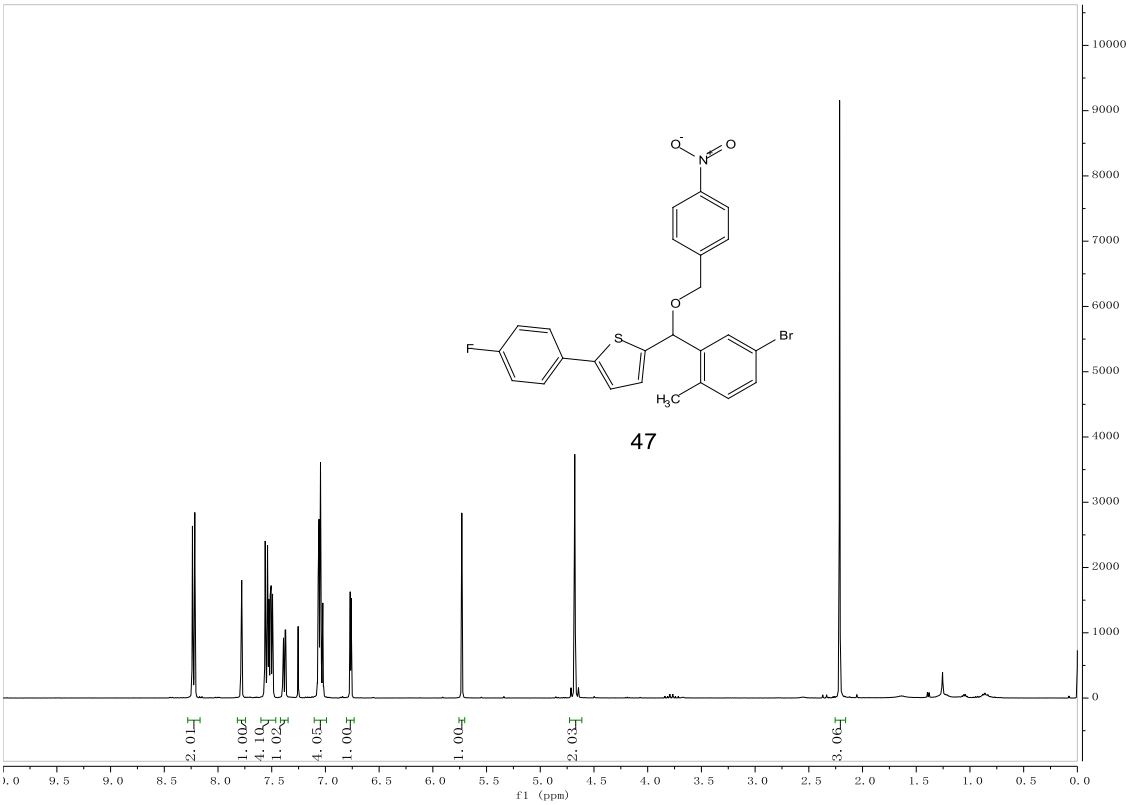

Cl
O
S
F
Br
H_3C
45
f1 (ppm)

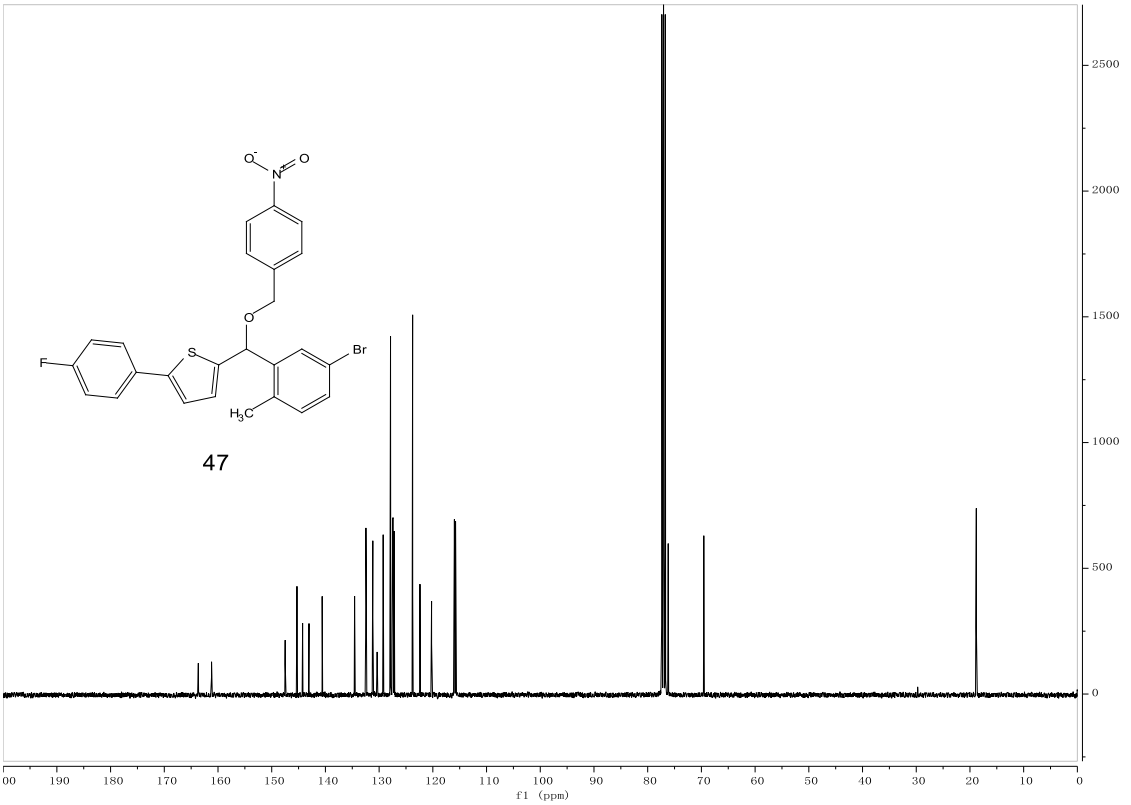

-114.3484
Cl
O
S
F
Br
H_3C
45
f1 (ppm)

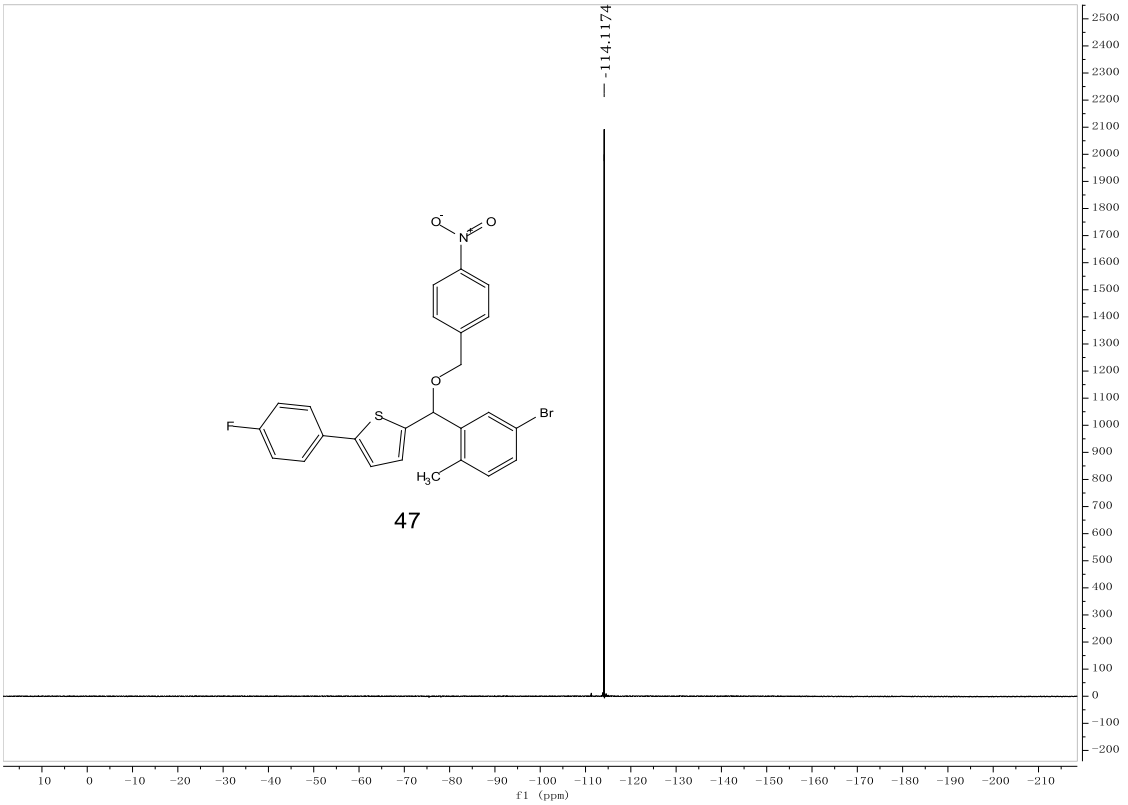

H_3C
O
O
S
F
Br
H_3C
46
0.97
2.00
0.97
1.98
3.99
2.00
1.00
1.00
1.00
0.99
3.03
3.02
f1 (ppm)

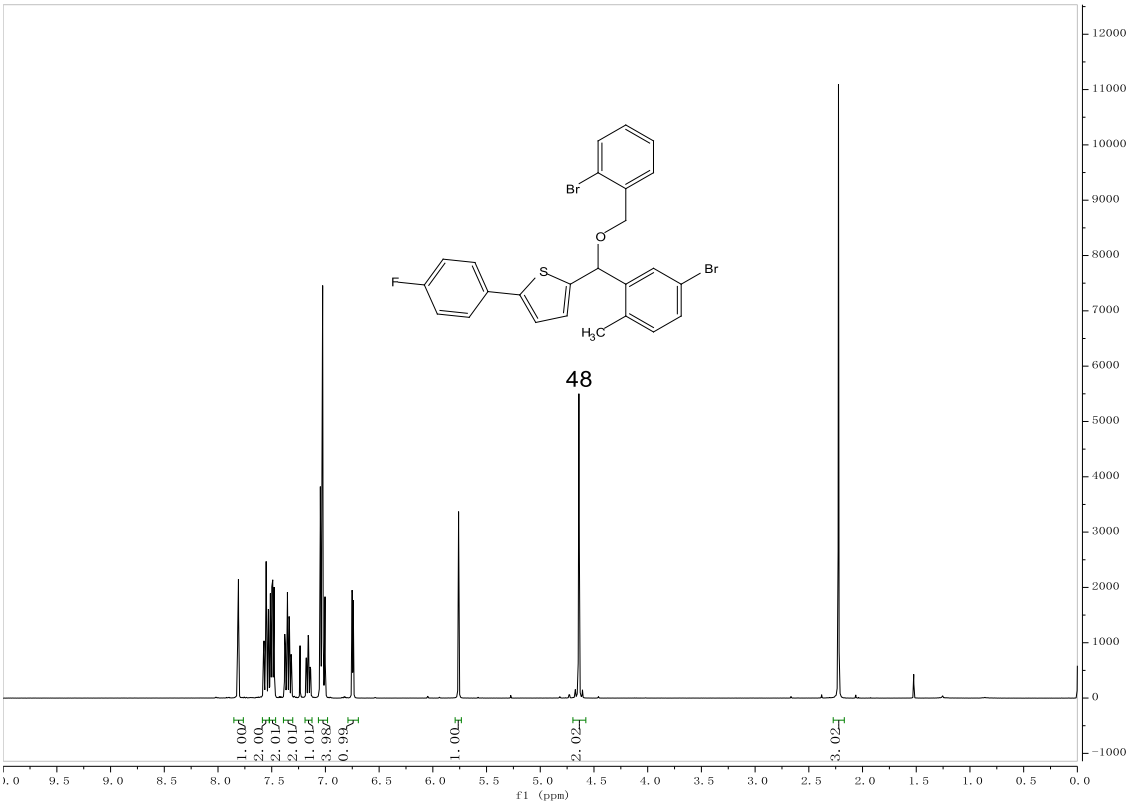

H3C
O
O
S
F
Br
H3C
46
2500
2000
1500
1000
500
0
f1 (ppm)

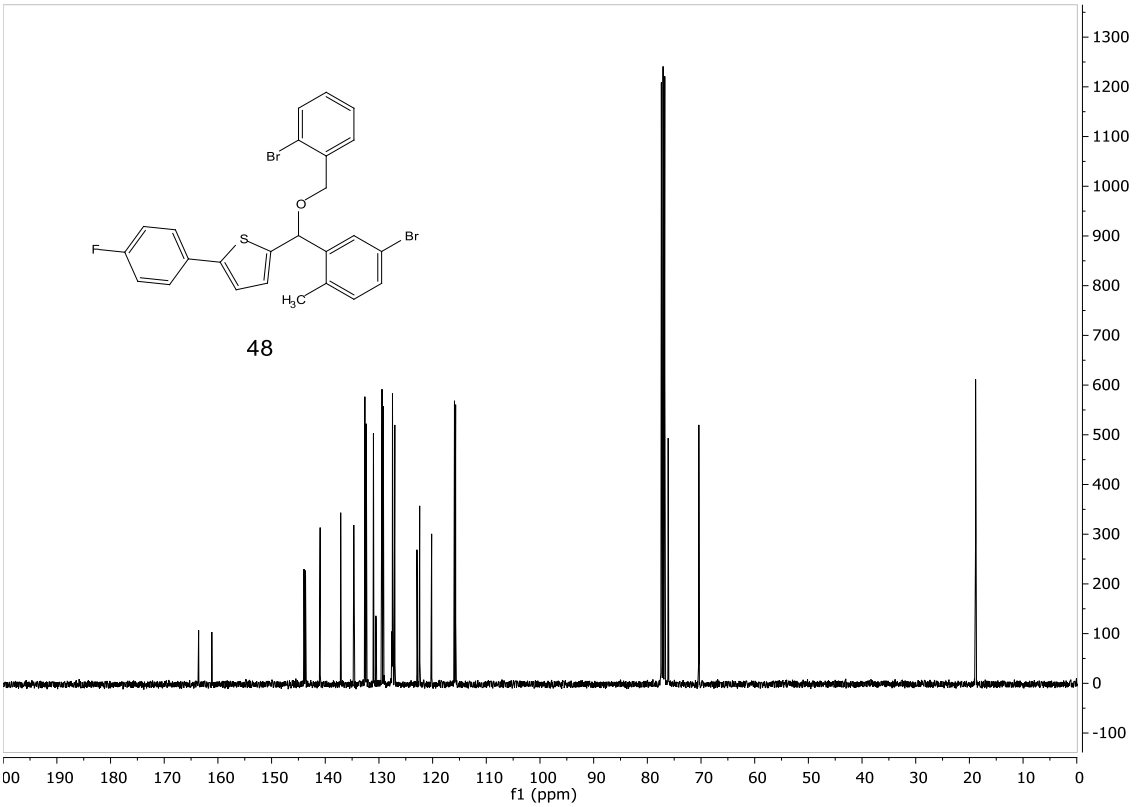

-114.5176
H3C
O
O
S
F
Br
H3C
46
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
f1 (ppm)

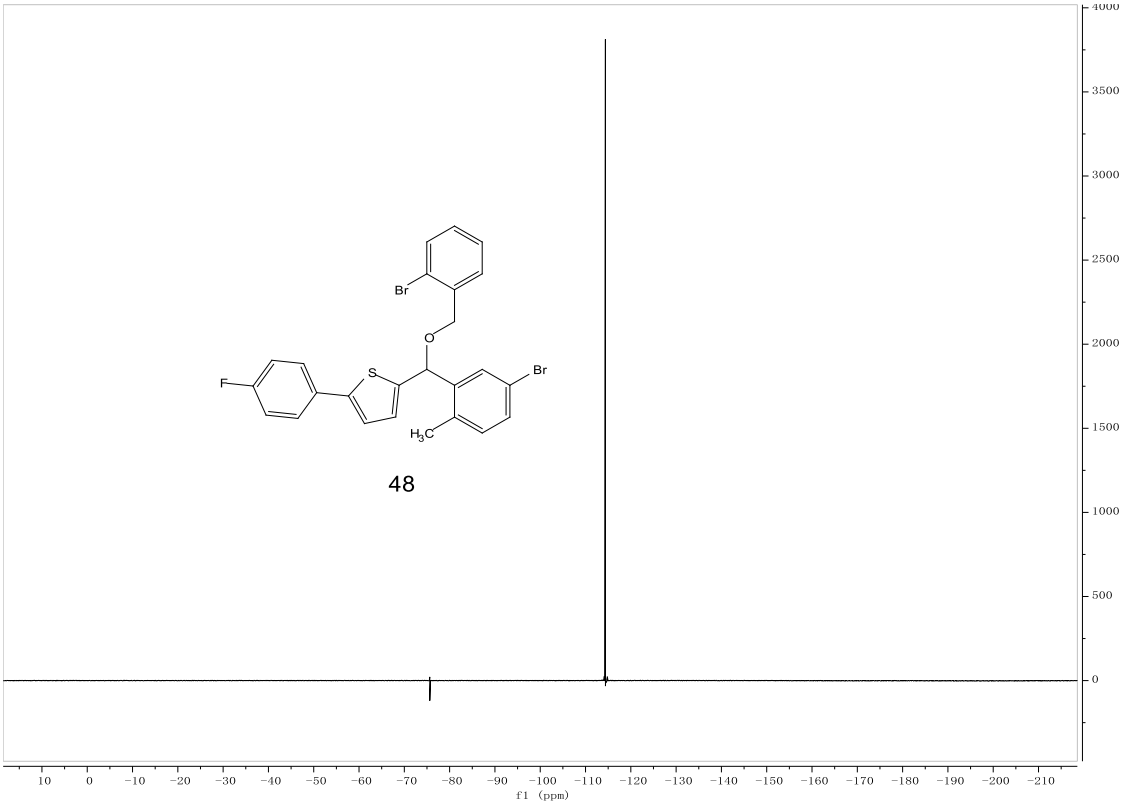

47
2.01
1.00
1.10
1.02
4.05
1.00
1.00
2.03
3.06
f1 (ppm)

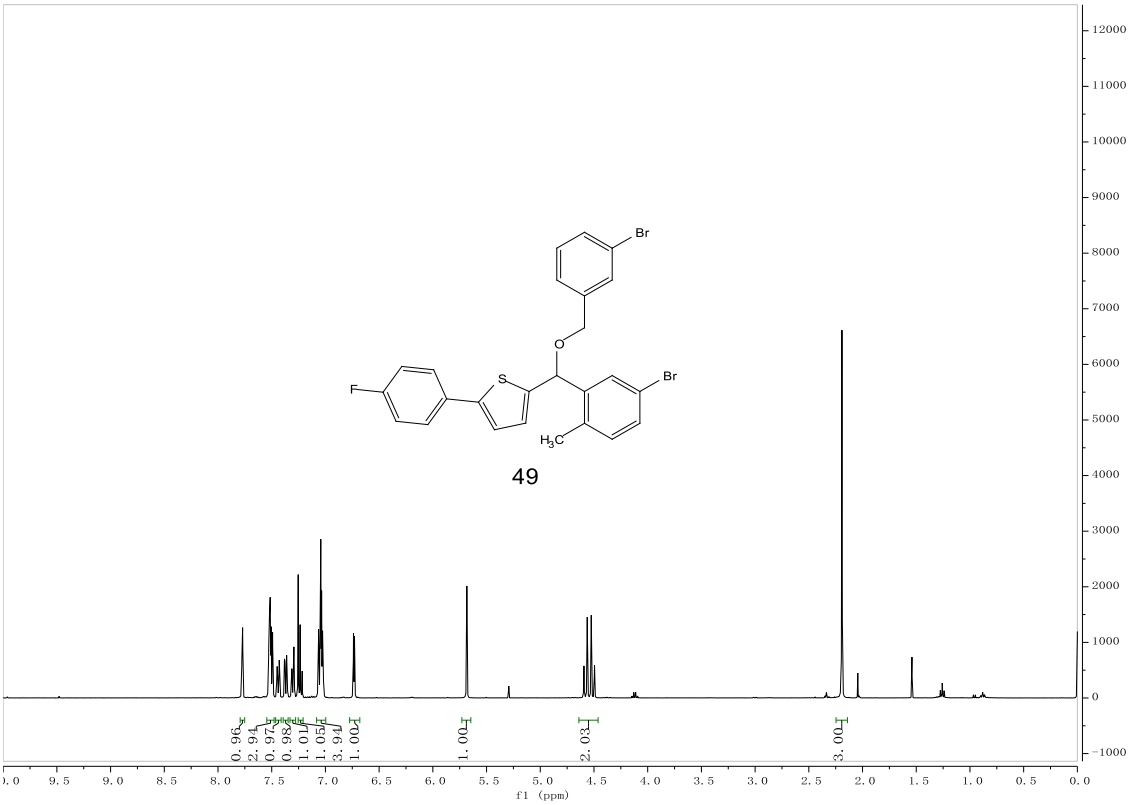

47
f1 (ppm)

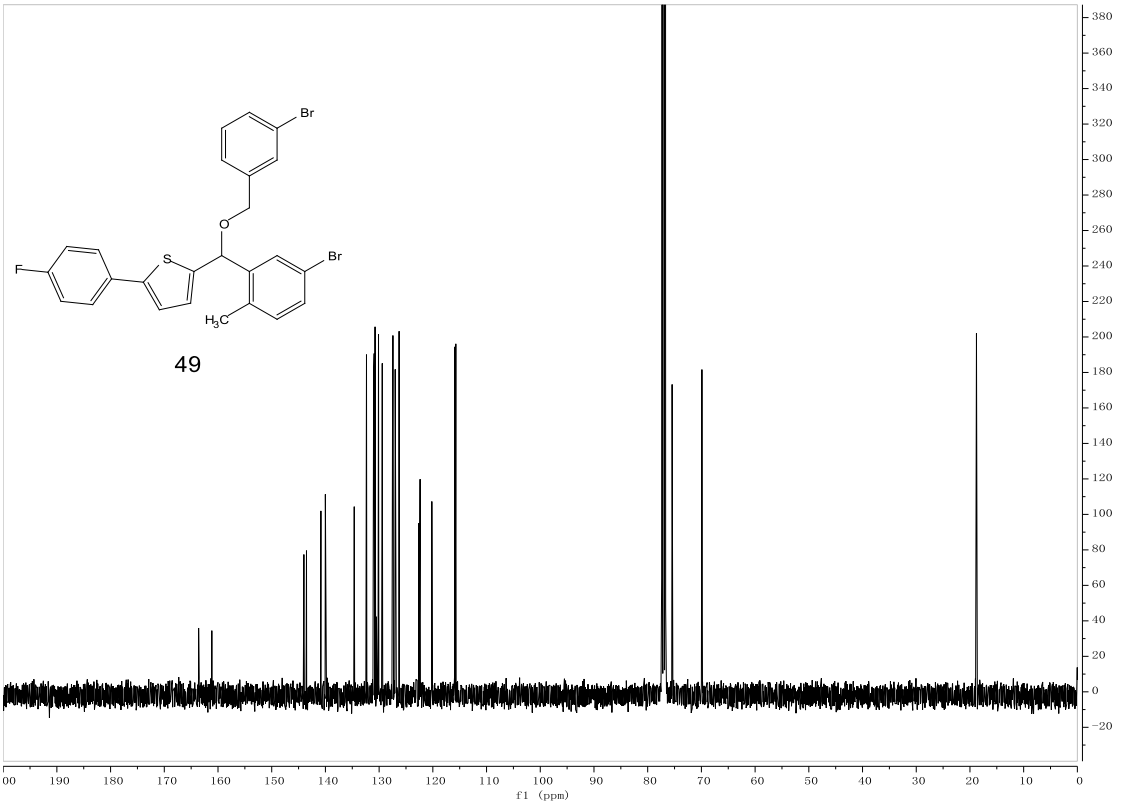

-114.1174
F
S
O
Br
H_3C
47
f1 (ppm)


Br
O
F
S
Br
H_3C
48
1.00
2.00
2.01
2.01
1.01
3.98
0.99
1.00
2.02
3.02
f1 (ppm)


Br
O
S
F
Br
H3C
48
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

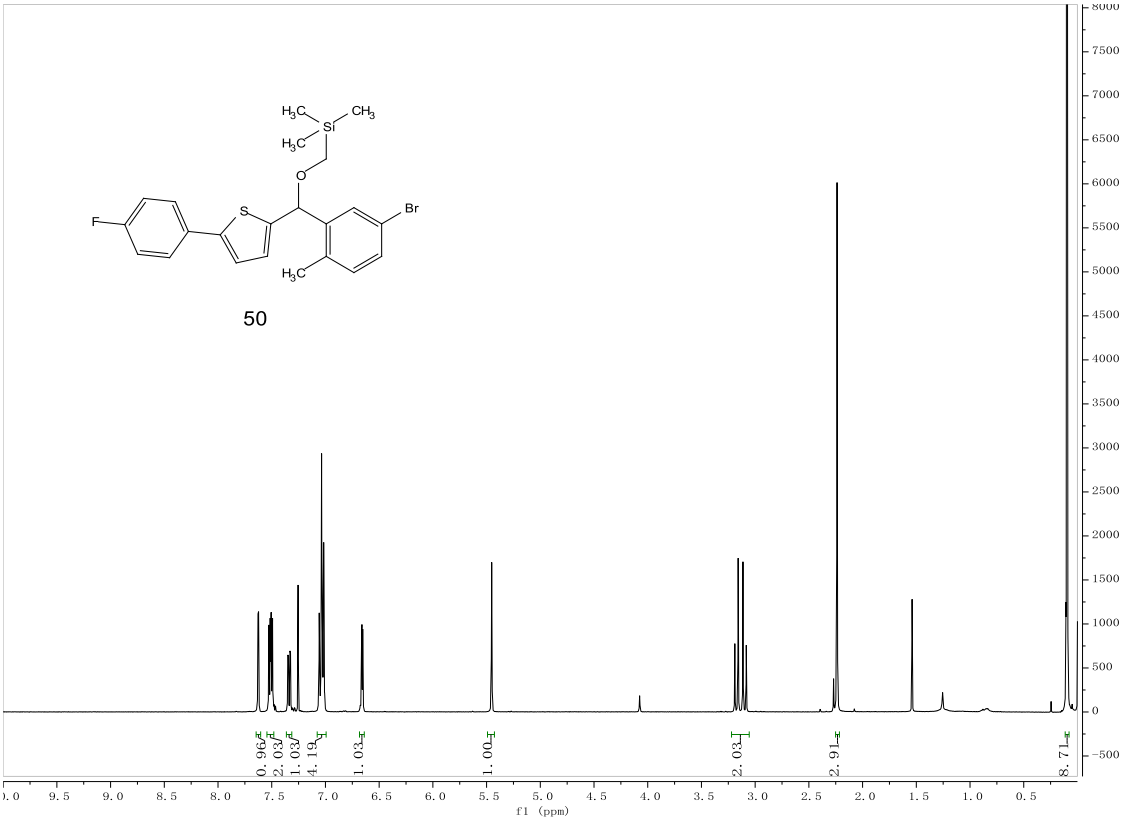

Br
O
S
F
Br
H3C
48
4000
3500
3000
2500
2000
1500
1000
500
0
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


Br
O
S
F
Br
H3C
49
0.96
2.94
0.97
0.98
1.01
1.05
3.94
1.00
1.00
2.03
3.00
f1 (ppm)

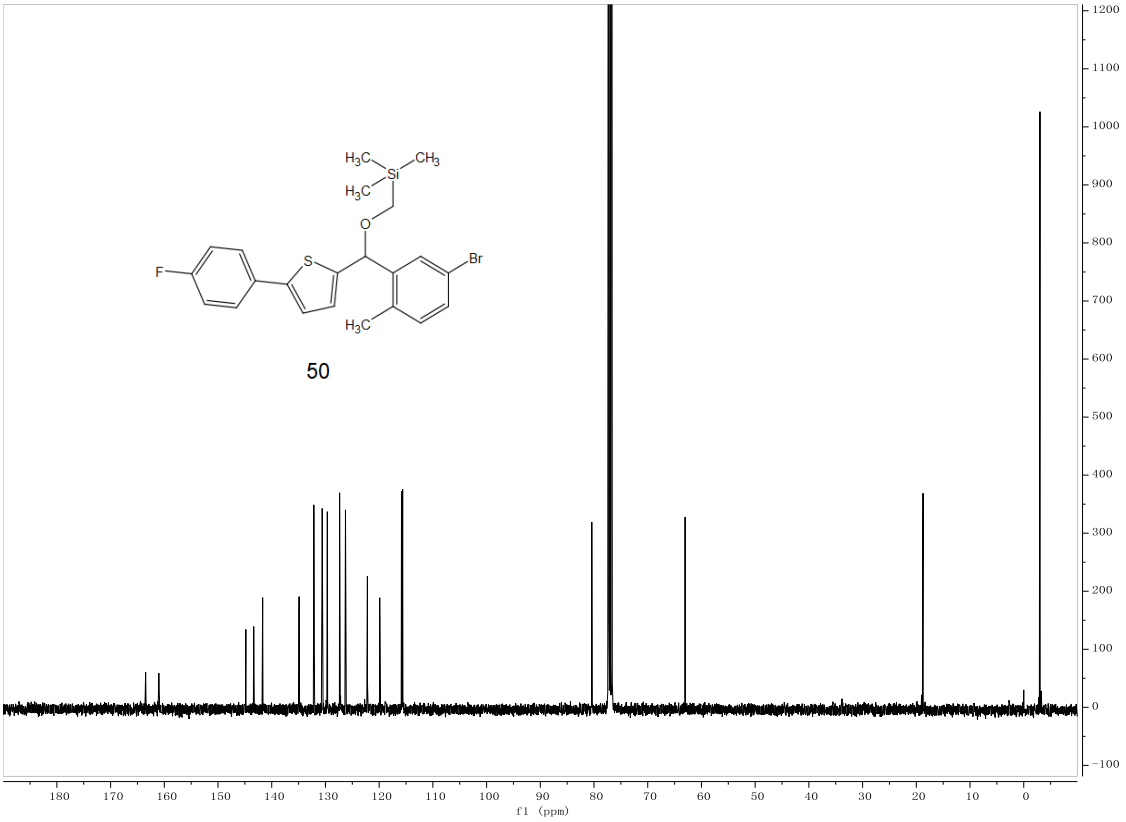

Br
O
S
F
Br
H3C
49
f1 (ppm)


-114.3791
Br
O
S
F
Br
H3C
1.00
f1 (ppm)

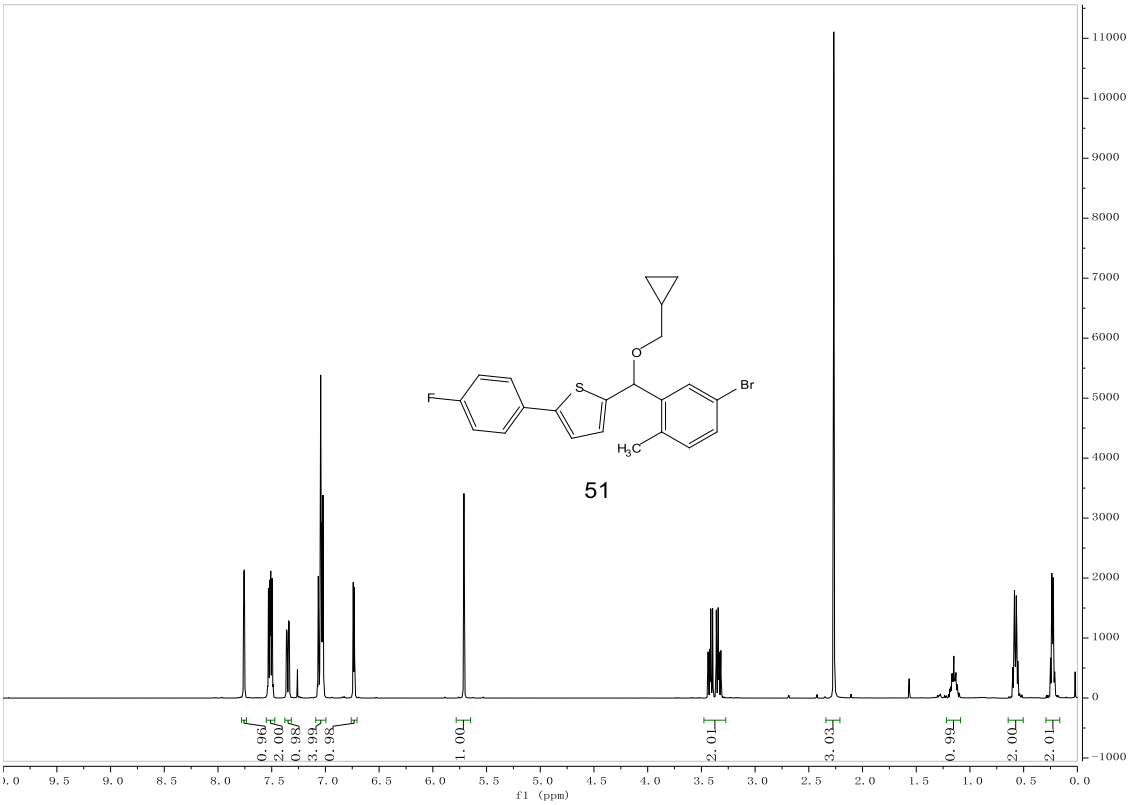
49


H3C
Si
CH3
H3C
O
S
F
Br
H3C
0.96
2.03
1.03
4.19
1.03
1.00
2.03
2.91
8.71
f1 (ppm)

50

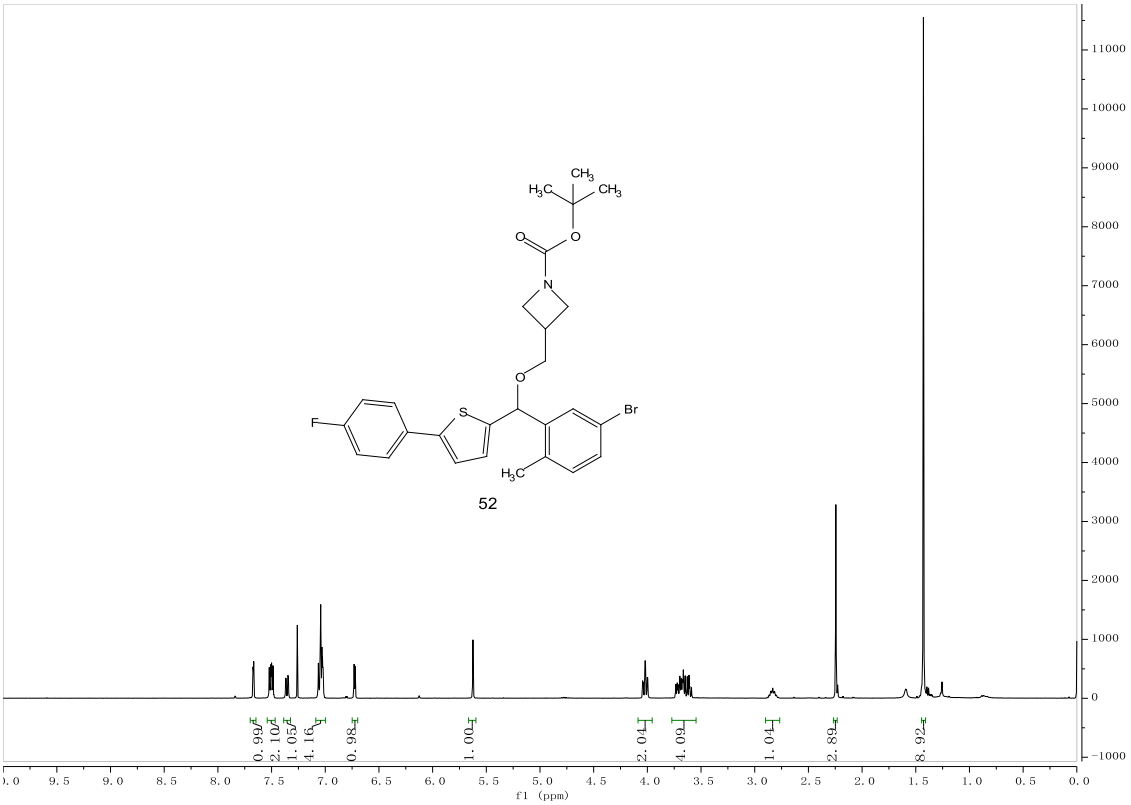

H3C
CH3
Si
H3C
O
F
S
Br
H3C
50
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

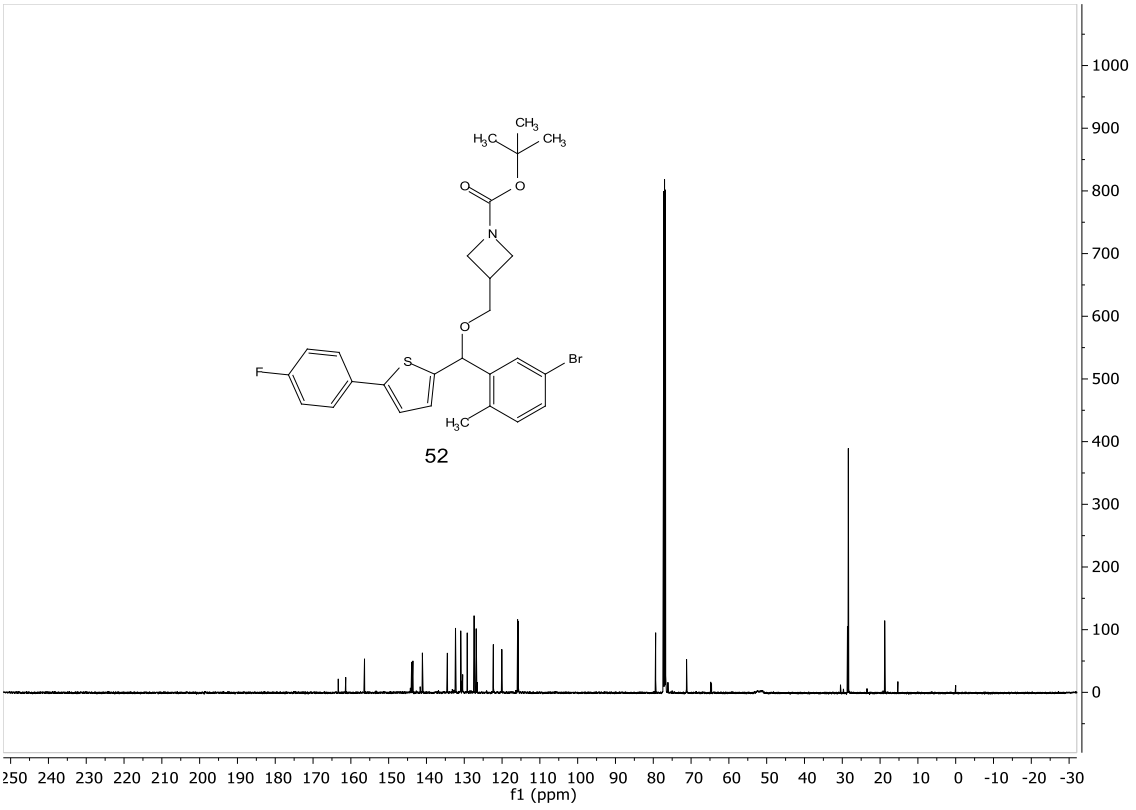

-114.7463
H3C
CH3
Si
H3C
O
F
S
Br
H3C
50
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10 0 −10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110 −120 −130 −140 −150 −160 −170 −180 −190 −200 −210
f1 (ppm)

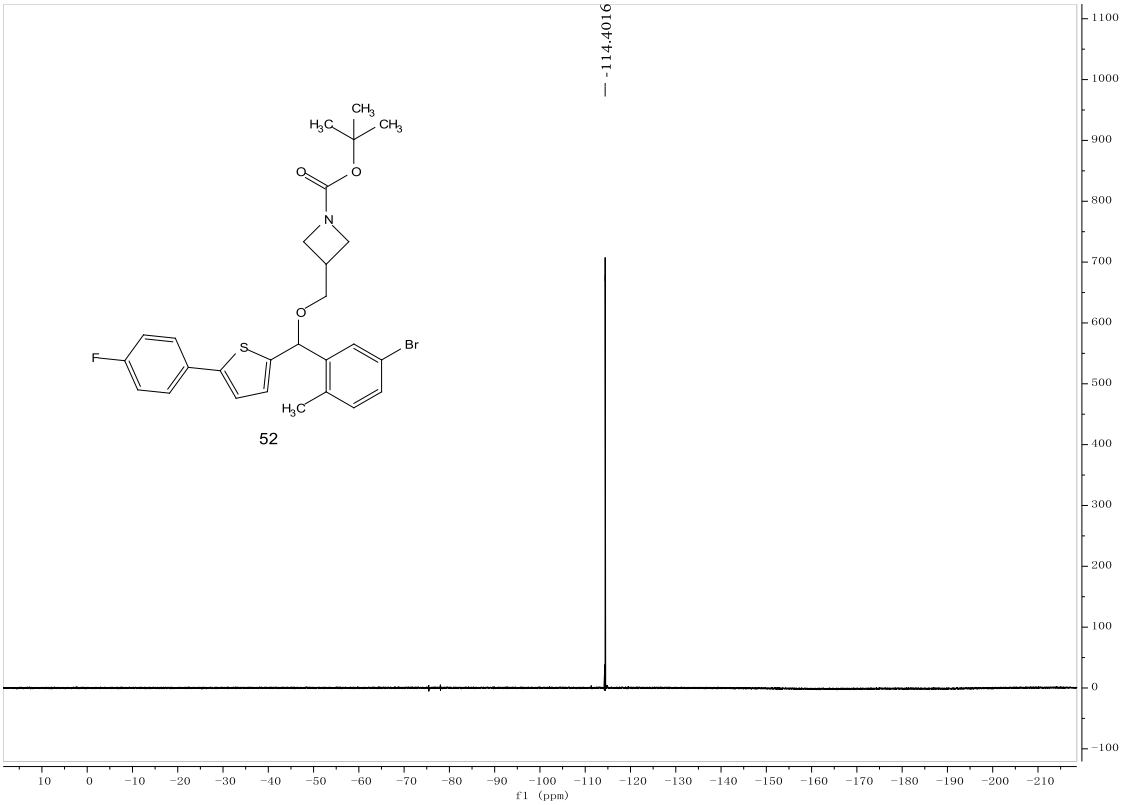

O
S
F
Br
H3C
51
0.96
2.00
0.98
3.99
0.98
1.00
2.01
3.03
0.99
2.00
2.01
f1 (ppm)

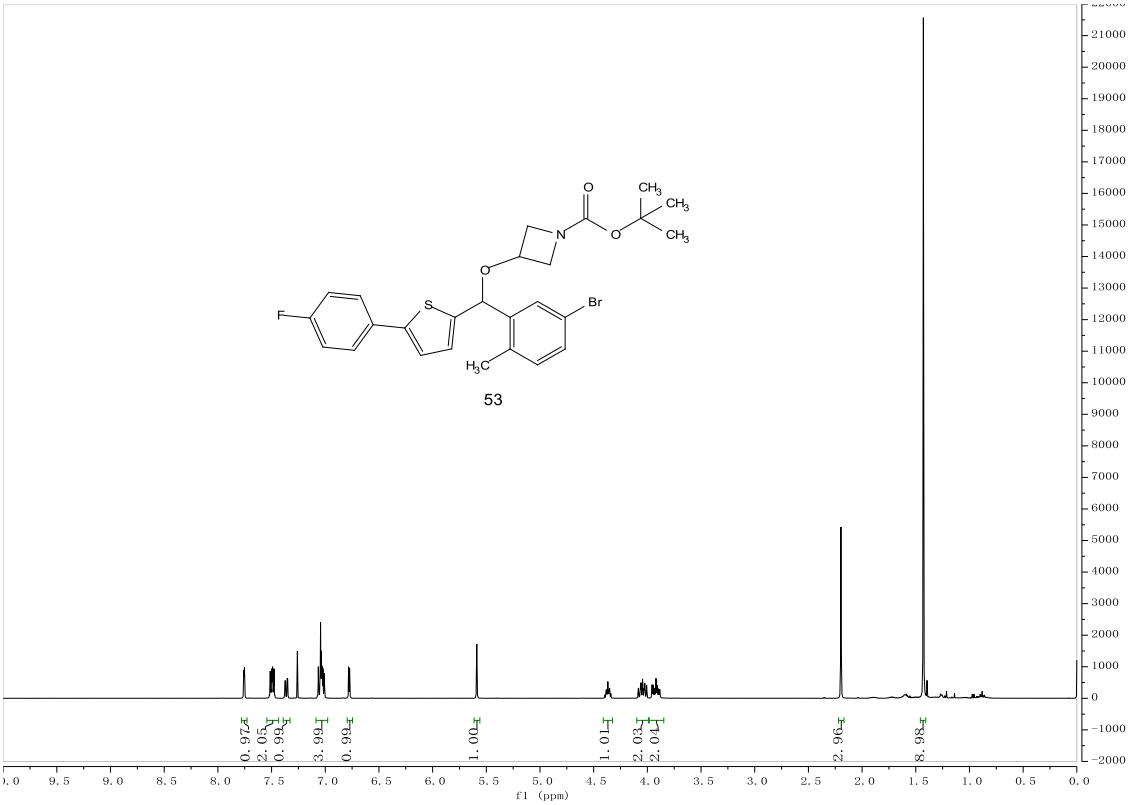

O
S
F
Br
H3C
51
f1 (ppm)

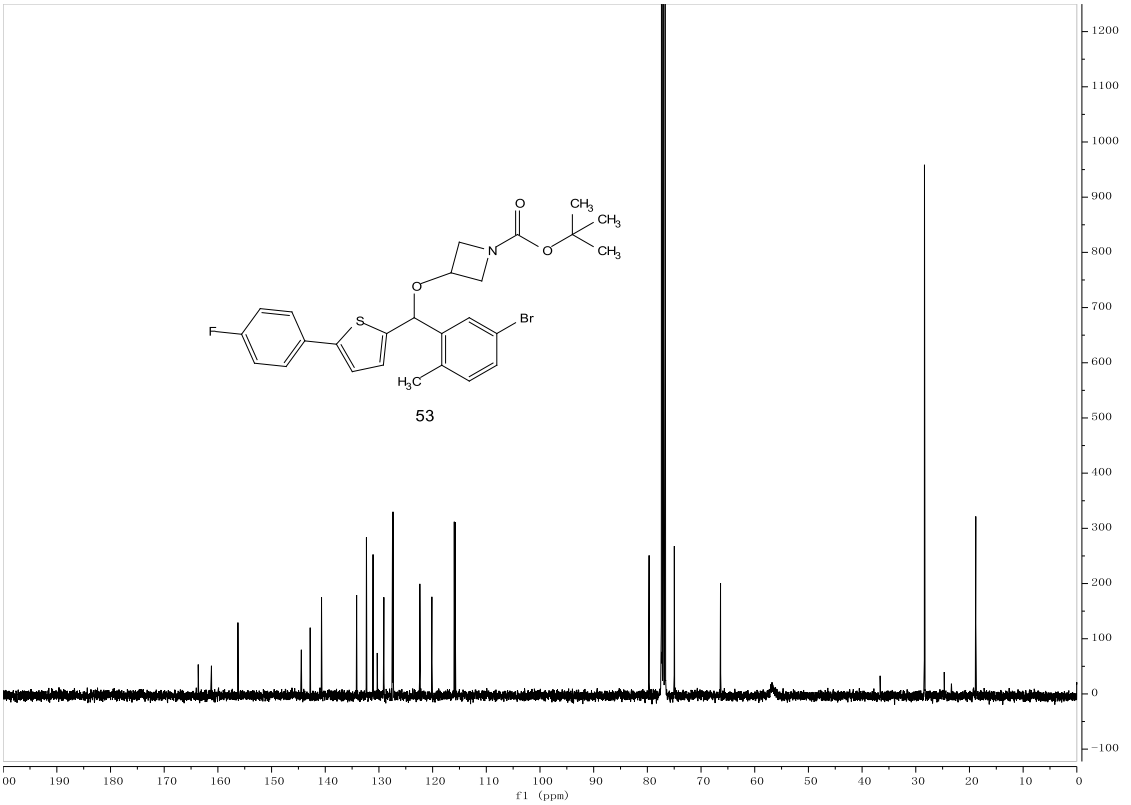

-114.5618
F
S
O
Br
H3C
51
f1 (ppm)

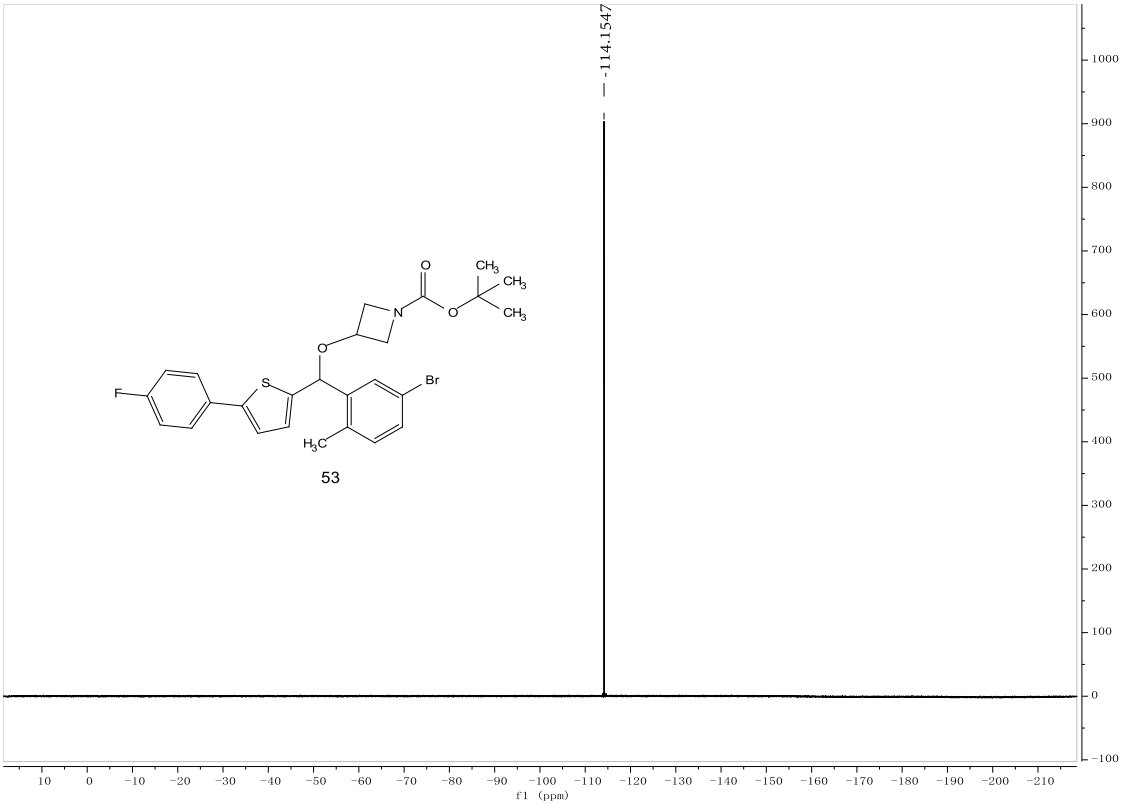

CH3
H3C
CH3
O
O
N
O
F
S
Br
H3C
52
0.99
2.10
1.05
4.16
0.98
1.00
2.04
4.09
1.04
2.89
8.92
f1 (ppm)


52
f1 (ppm)

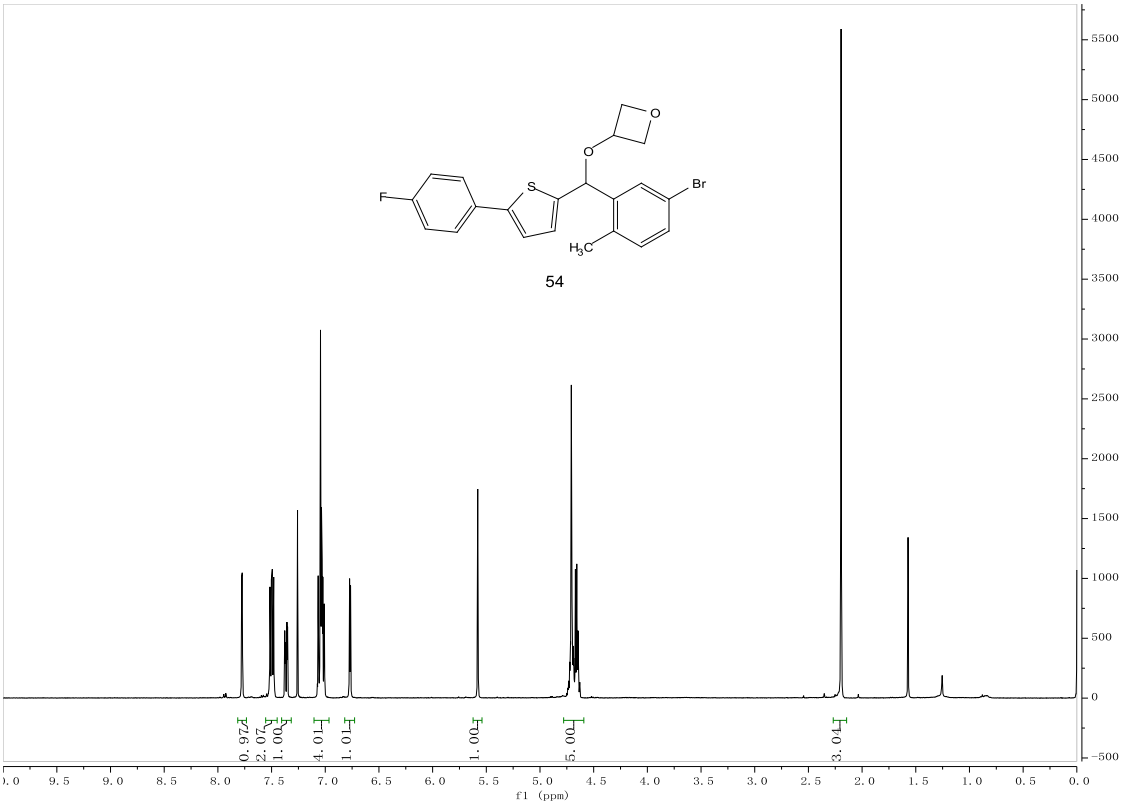

-114.4016
52
f1 (ppm)


53
0.97
2.05
0.99
3.99
0.99
1.00
1.01
2.03
2.04
2.96
8.98
f1 (ppm)

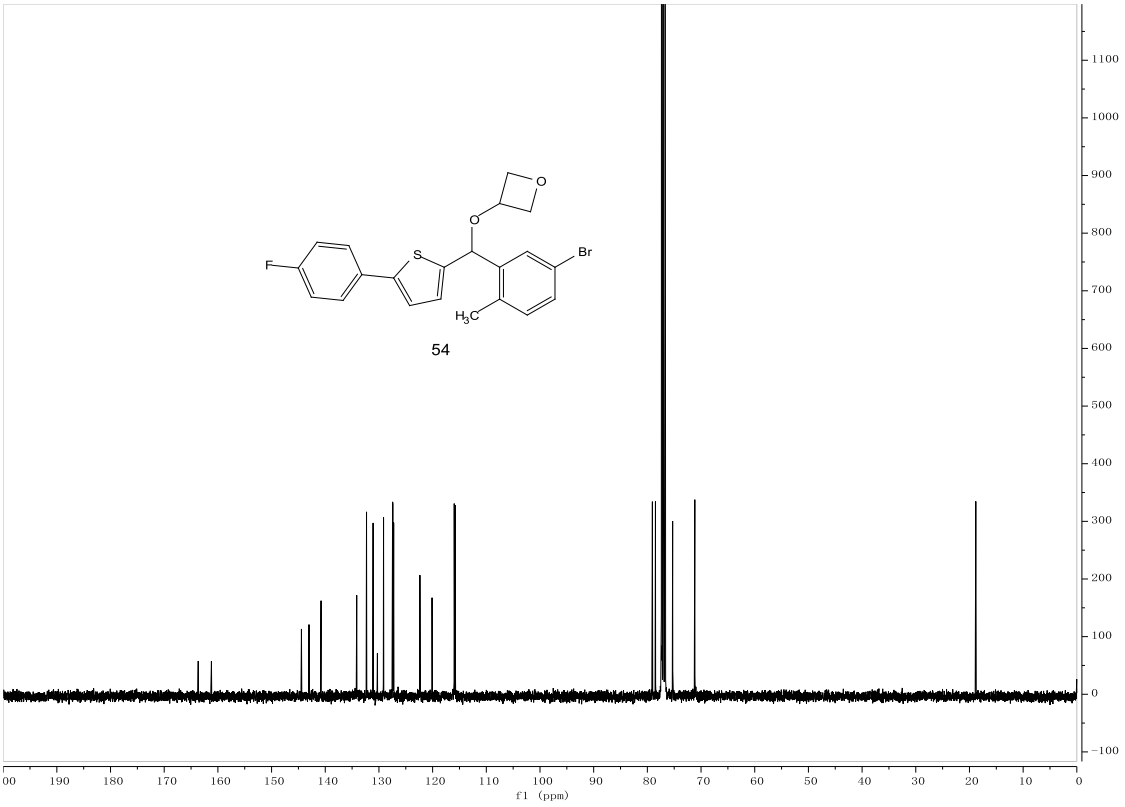

53
f1 (ppm)

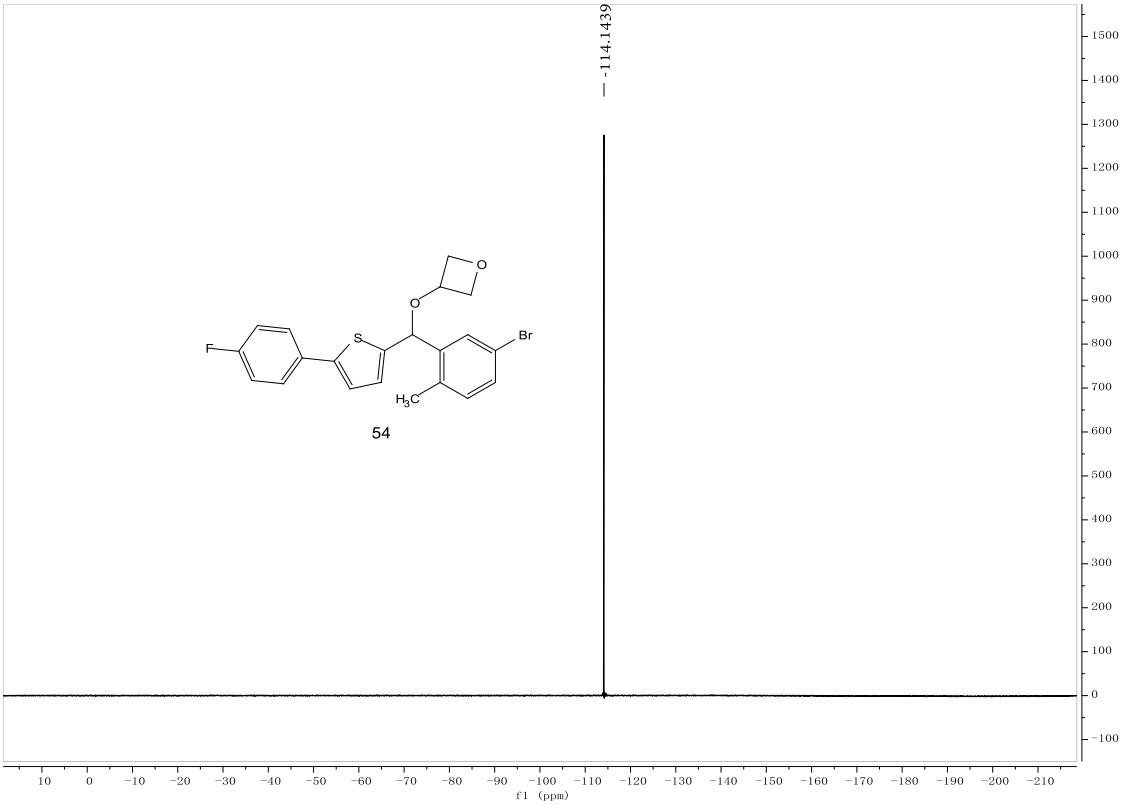


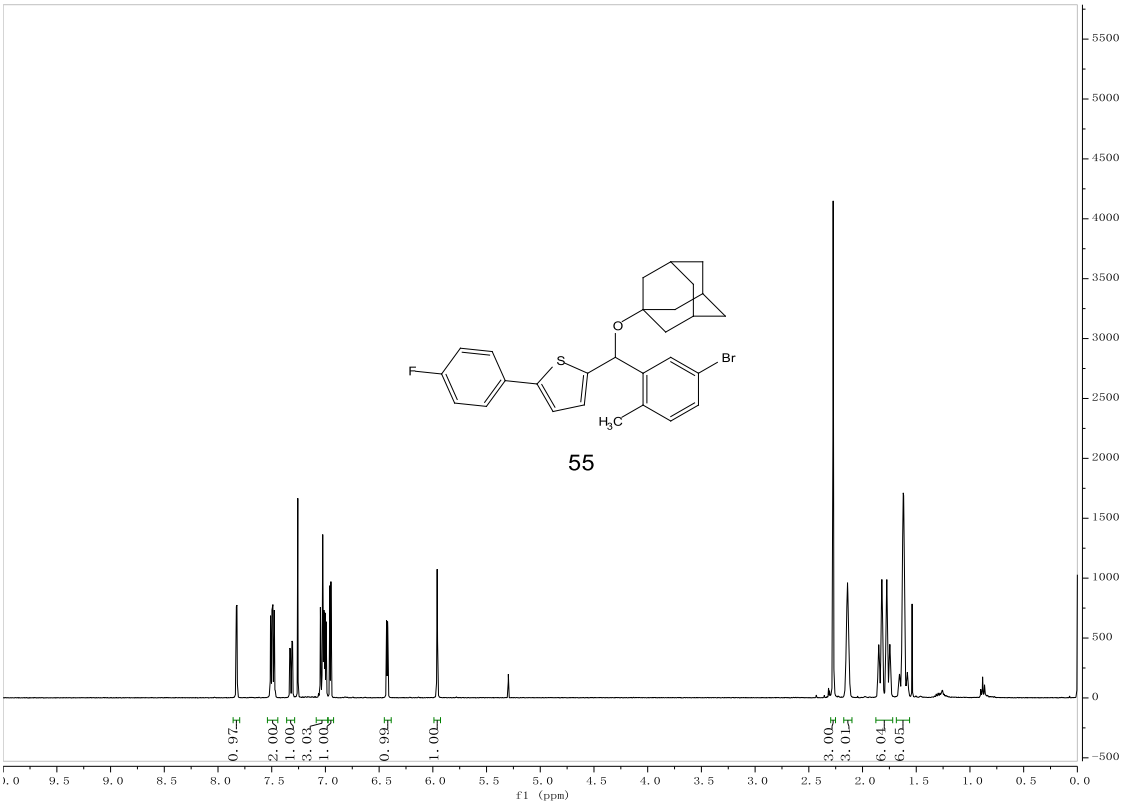
53

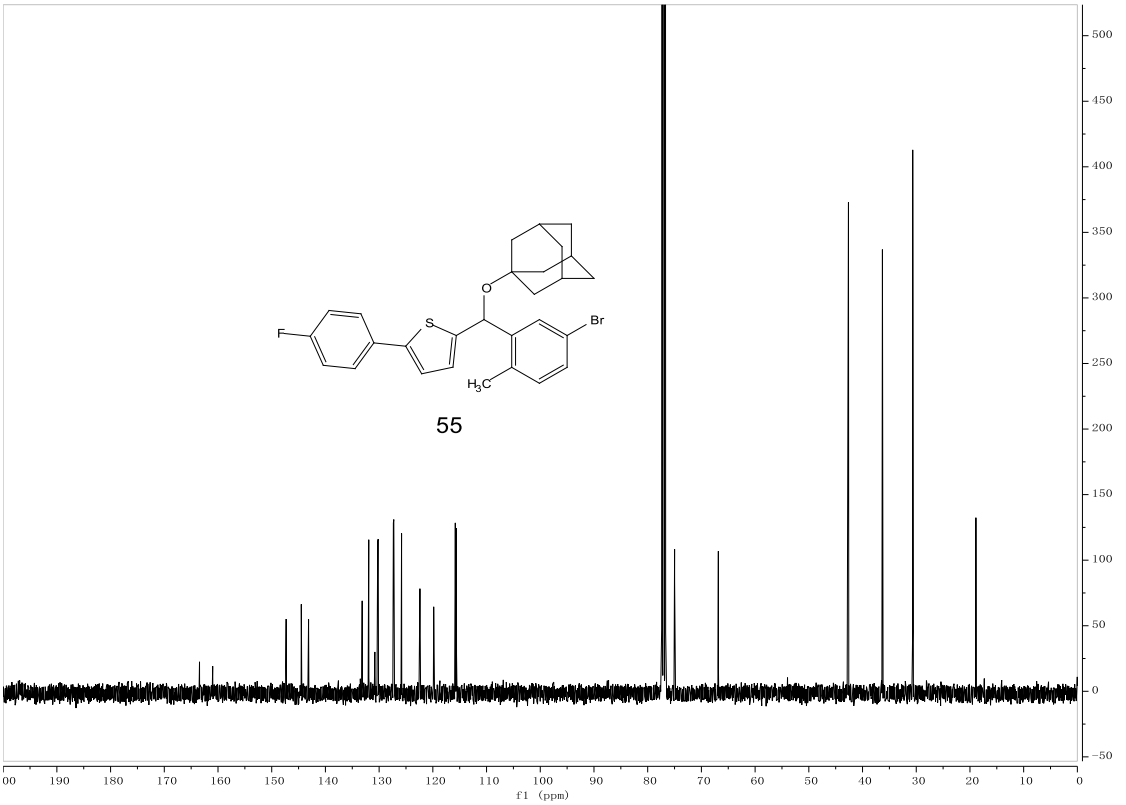


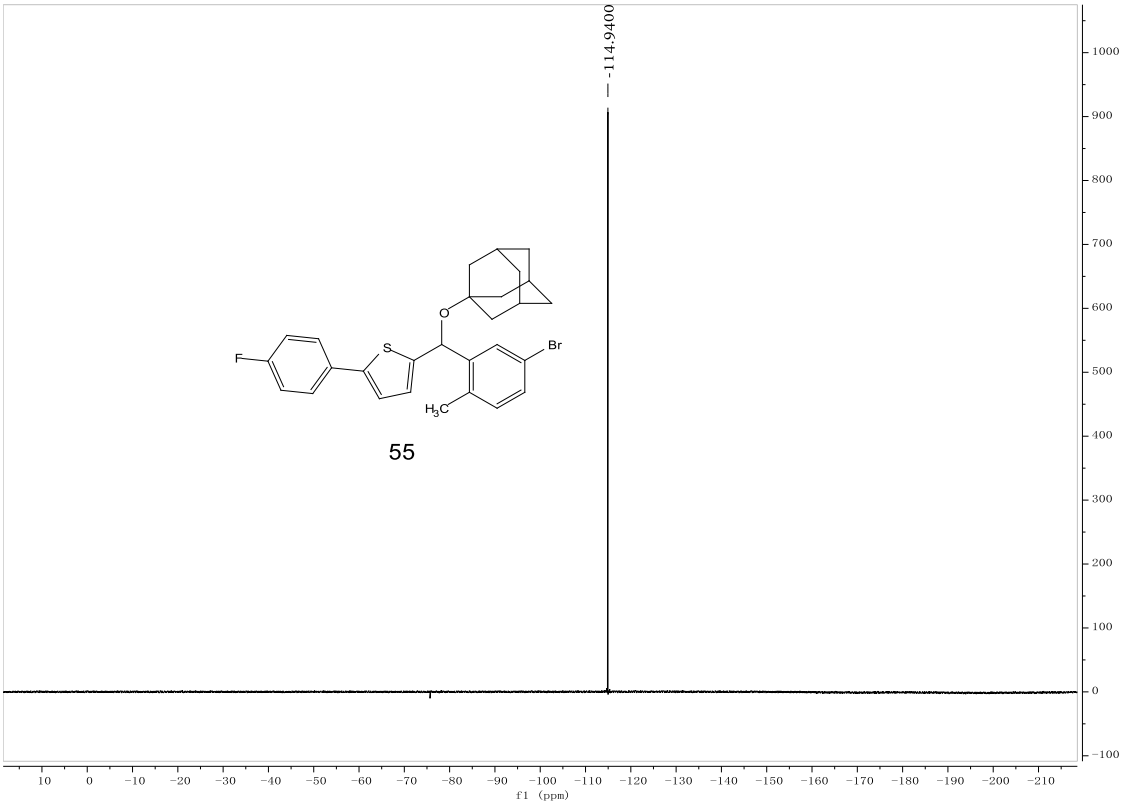
54

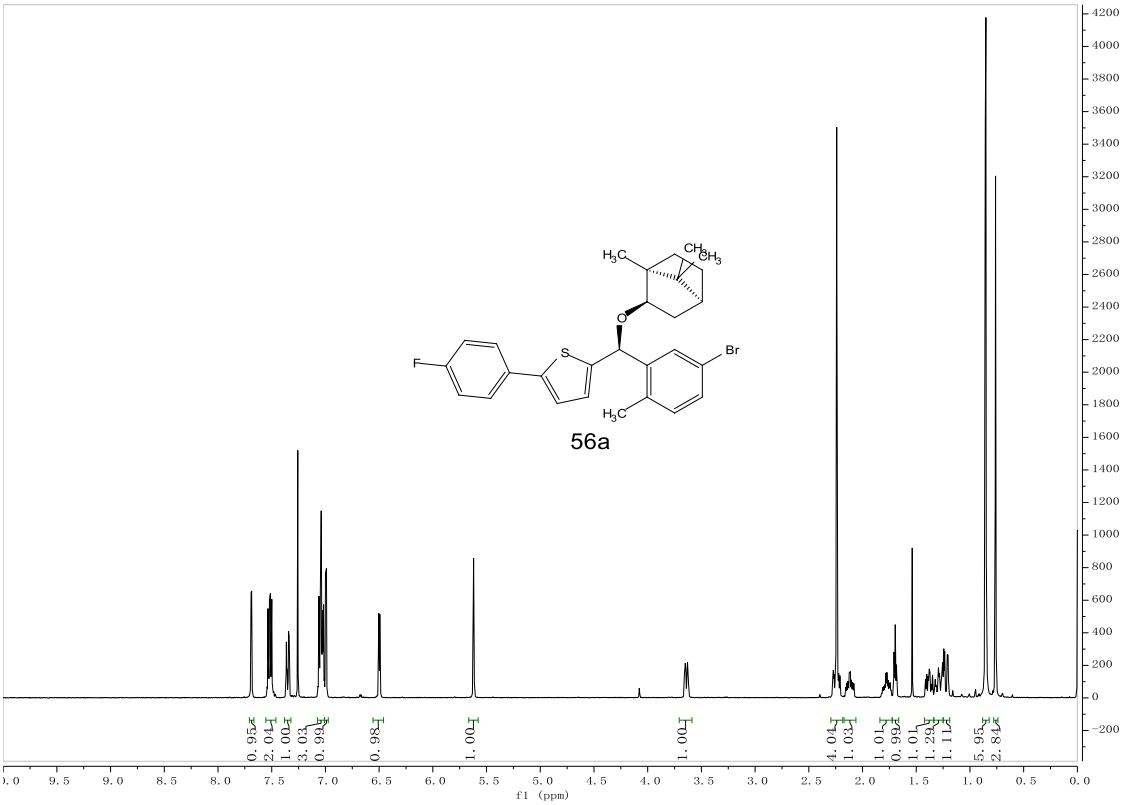

O
O
S
F
Br
H_3C
54
f1 (ppm)

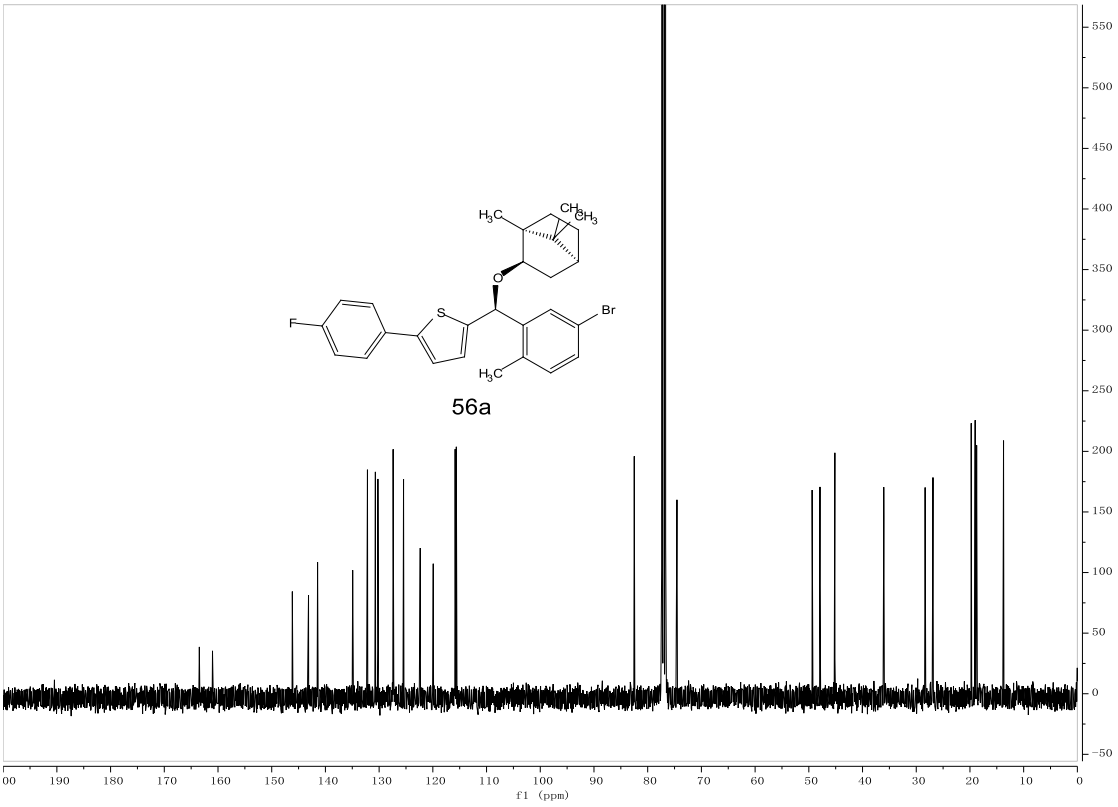

-114.1439
O
O
S
F
Br
H_3C
54
f1 (ppm)

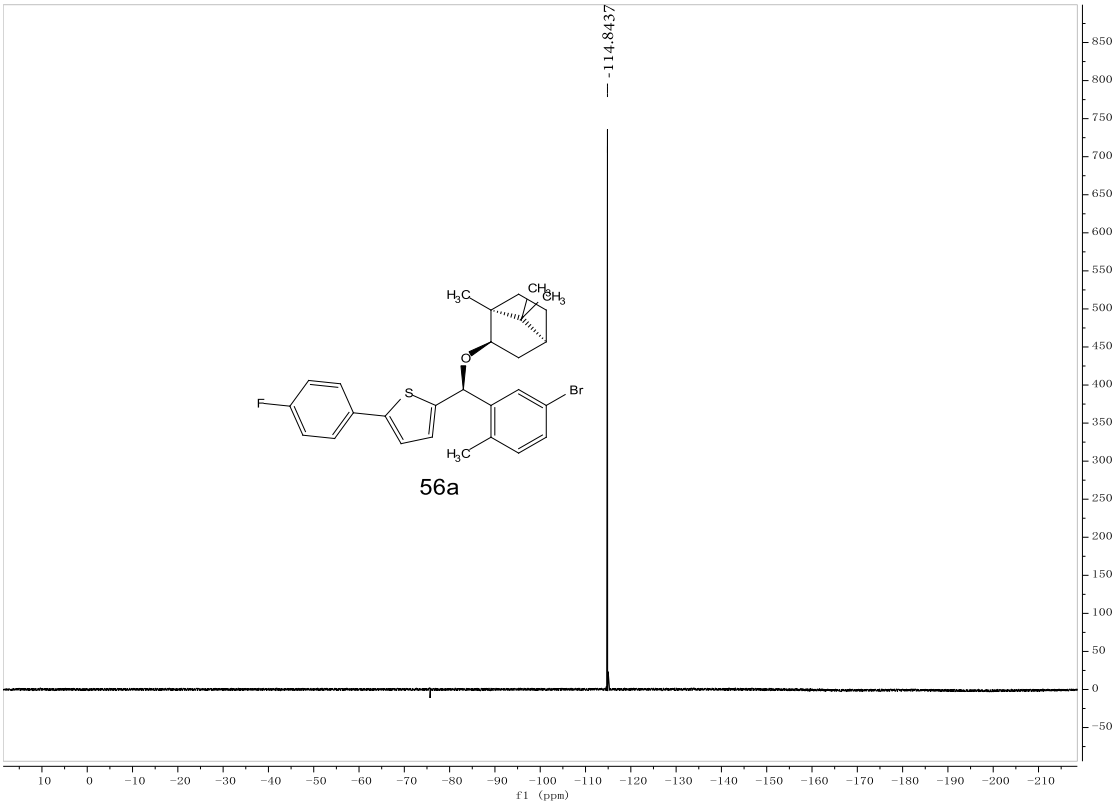

F
S
O
Br
H3C
55
0.97
2.00
1.00
3.03
1.00
0.99
1.00
3.00
3.01
6.04
6.05
f1 (ppm)

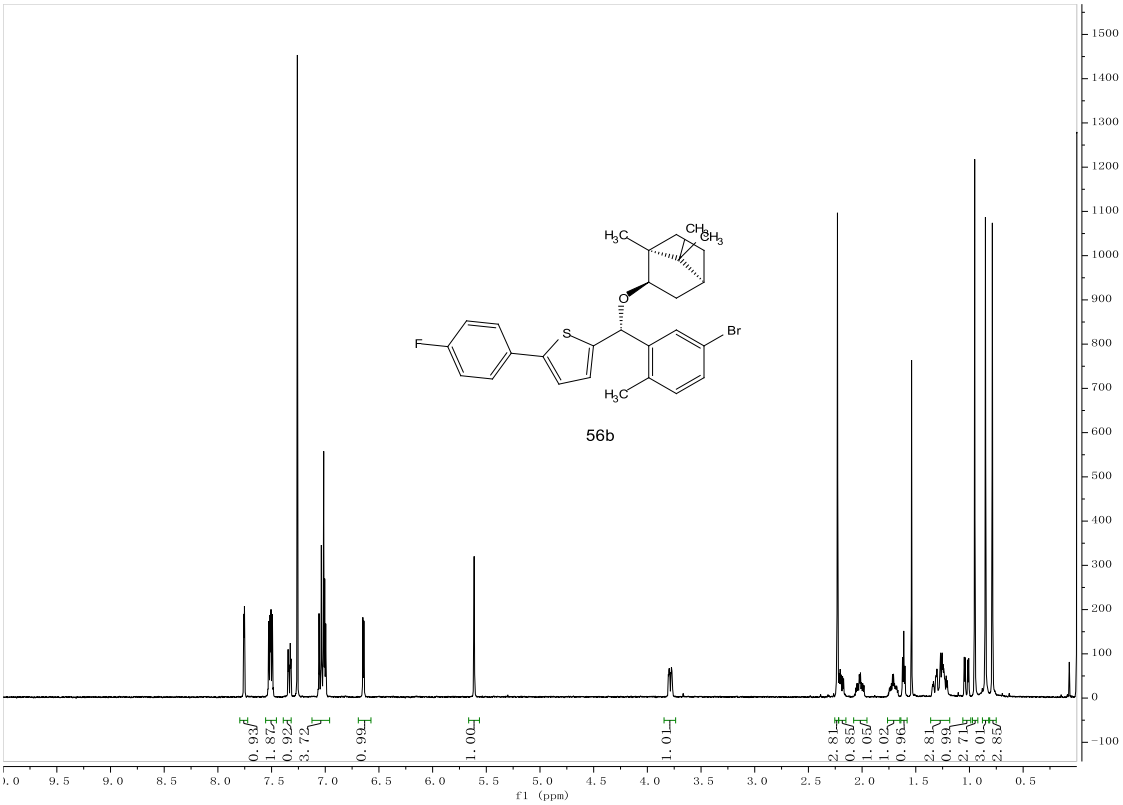

F
S
O
Br
H3C
55
f1 (ppm)

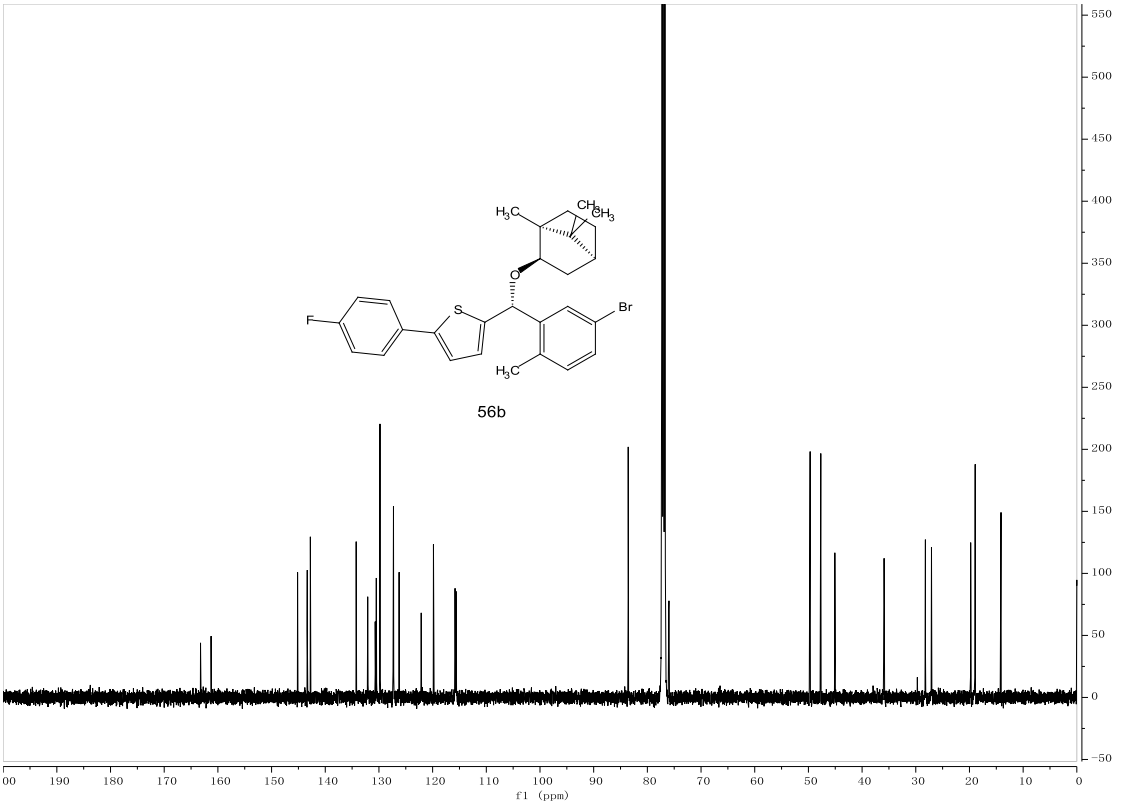

-114.9400
F
S
O
Br
H3C
55
f1 (ppm)

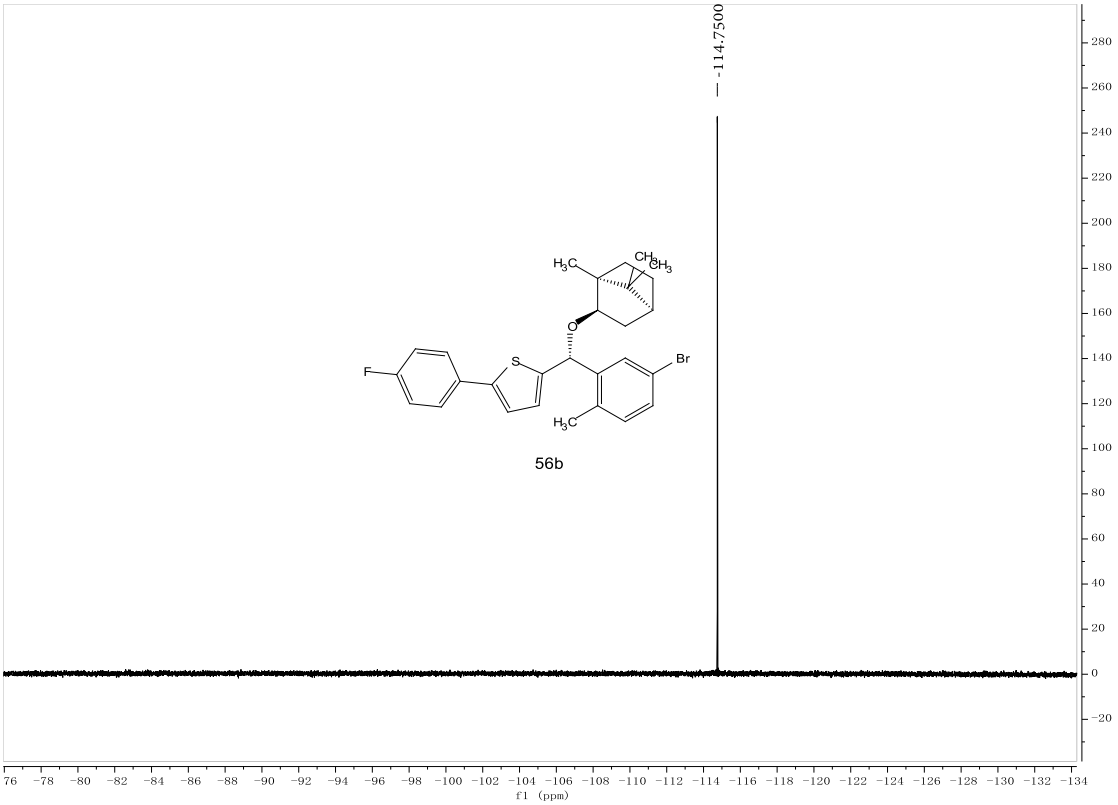

H3C
CH3
O
F
S
Br
H3C
56a
0.95
2.04
1.00
3.03
0.99
0.98
1.00
1.00
4.04
1.03
1.01
0.99
1.01
1.29
1.11
5.95
2.84
f1 (ppm)

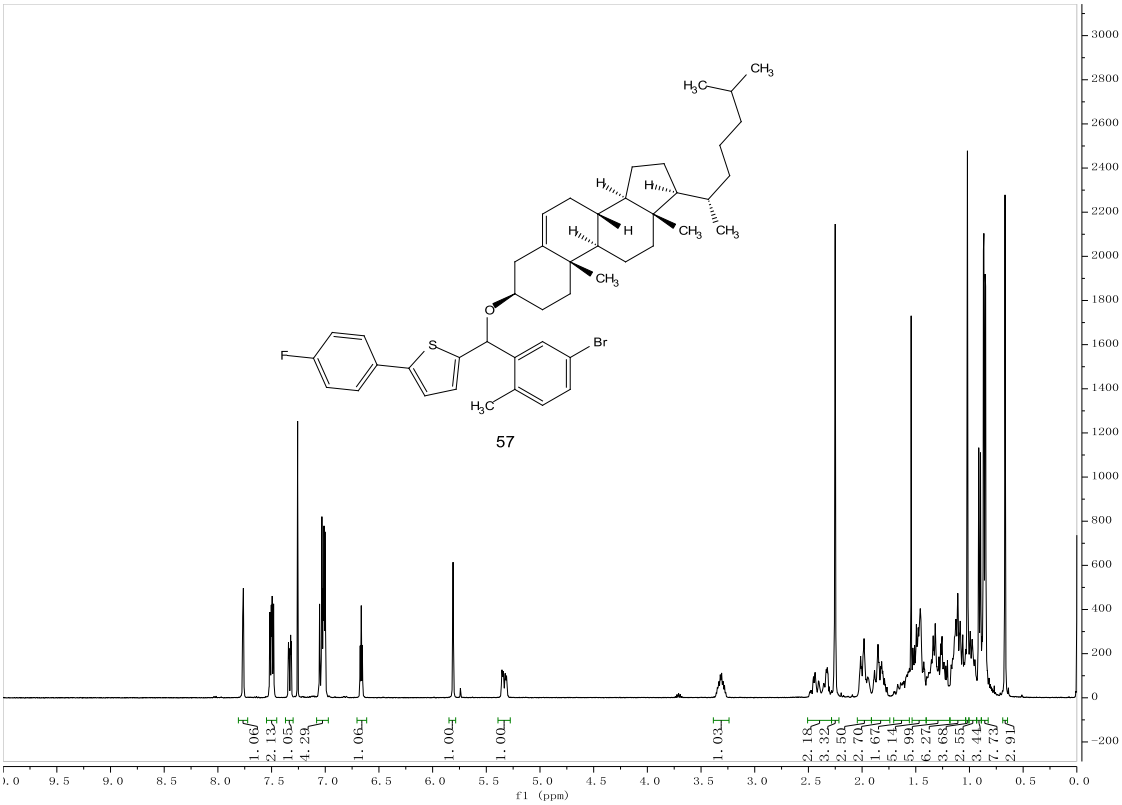

H3C
CH3
CH3
O
S
F
Br
H3C
56a
f1 (ppm)

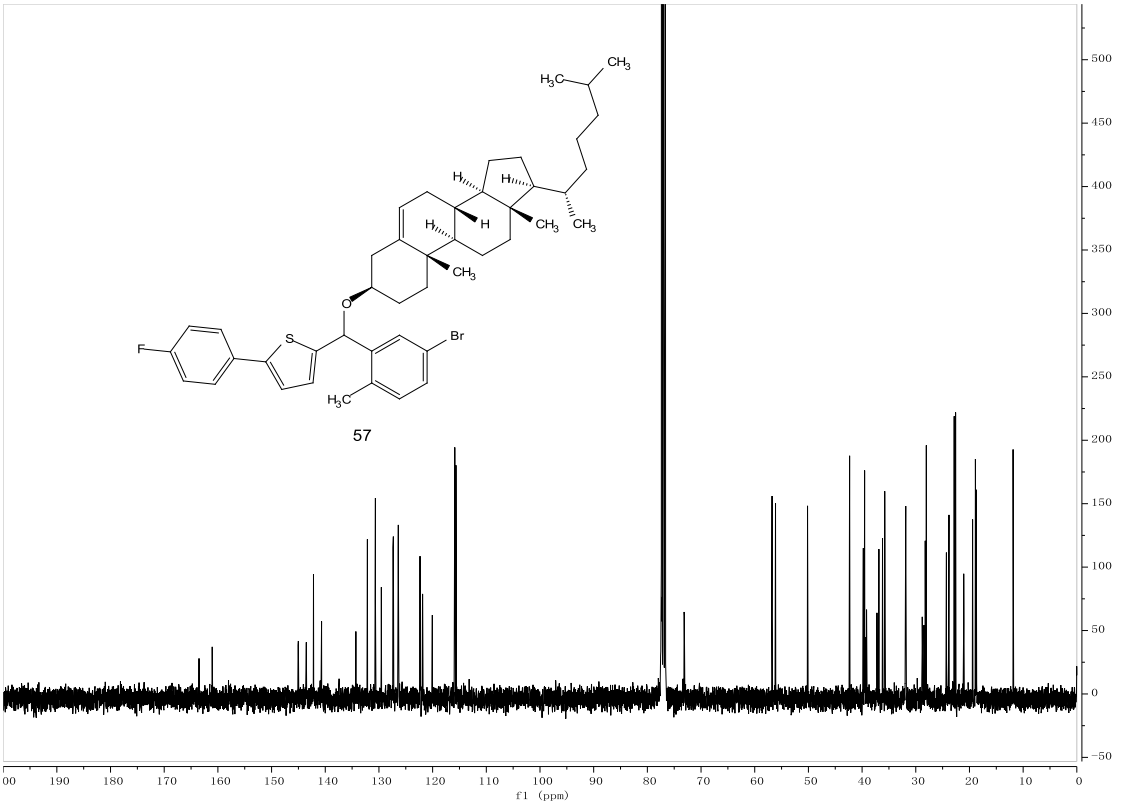

-114.8437
H3C
CH3
CH3
O
S
F
Br
H3C
56a
f1 (ppm)

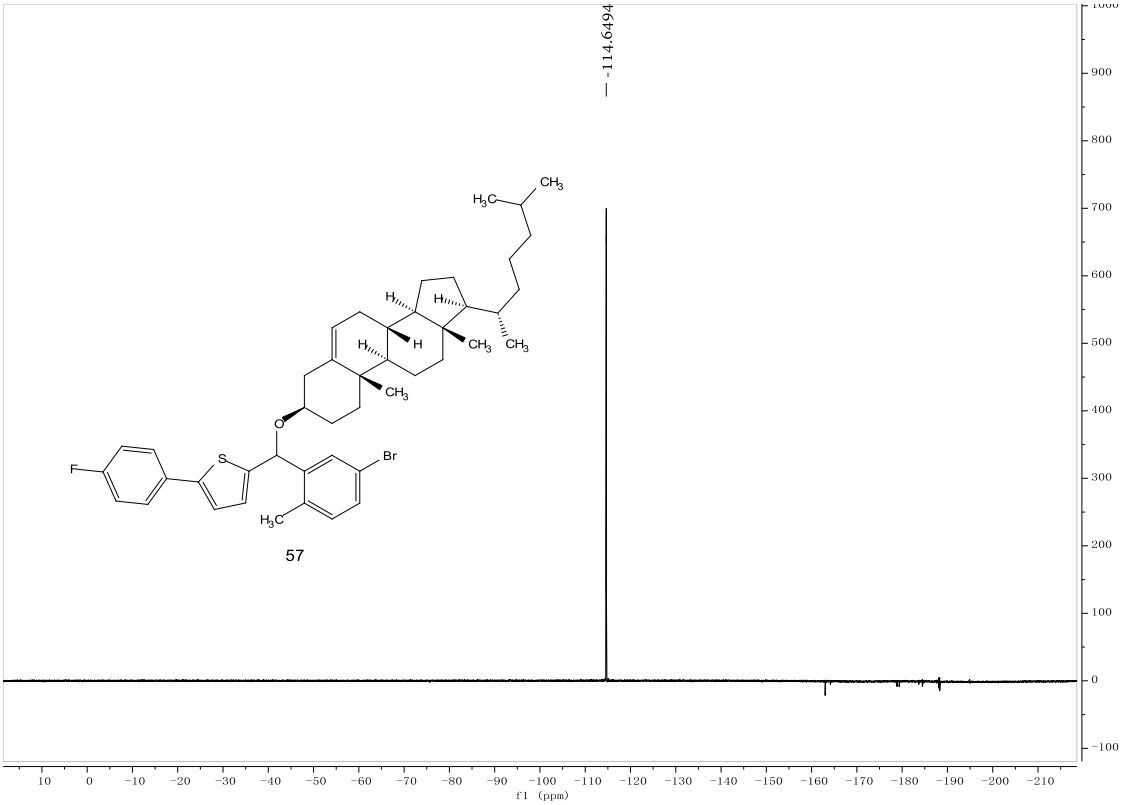

56b
f1 (ppm)

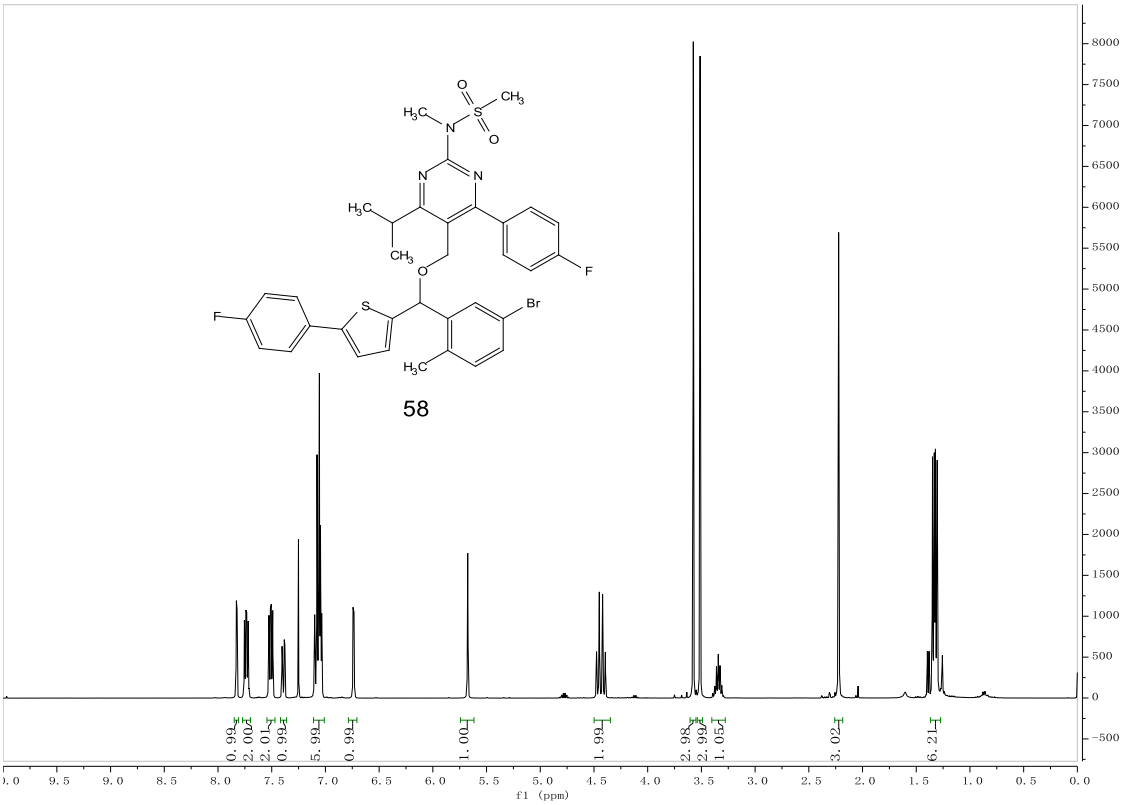

56b
f1 (ppm)

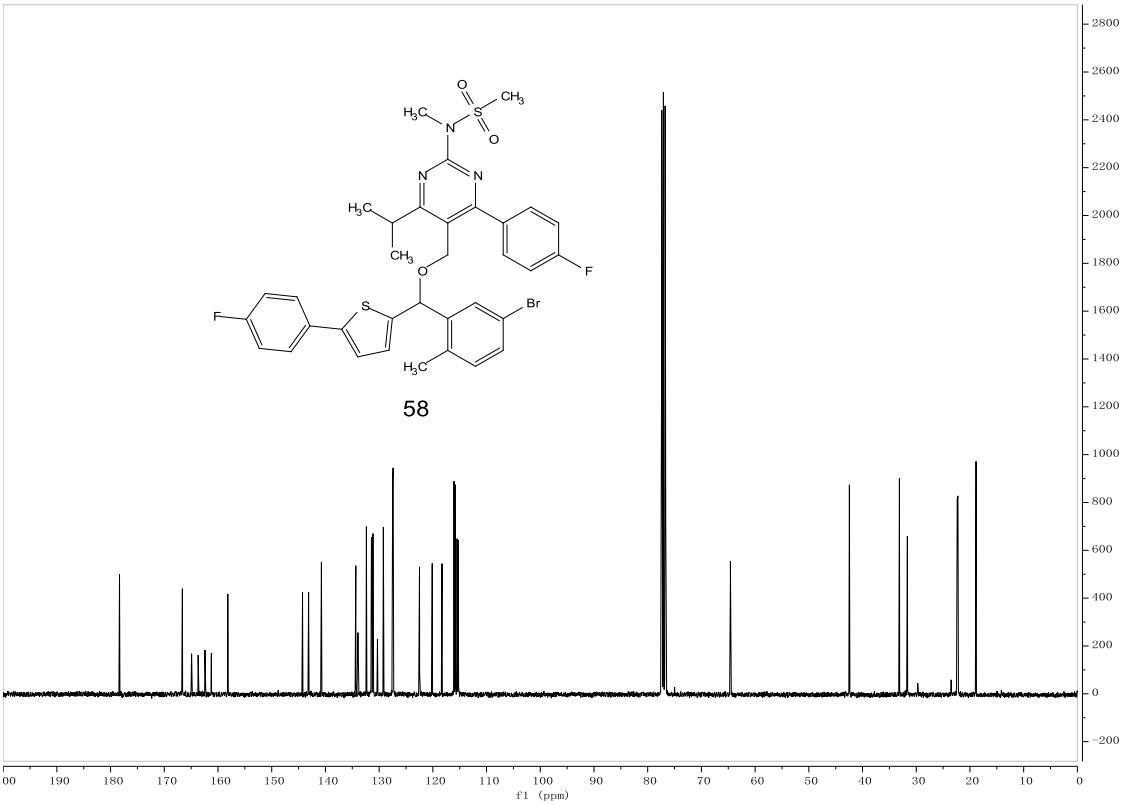

-114.7500
F
S
O
Br
H_3C
CH_3
CH_3
H_3C
56b
f1 (ppm)


H_3C
CH_3
H
H
H
H
CH_3
CH_3
CH_3
O
F
S
Br
H_3C
57
1.06
2.13
1.05
4.29
1.06
1.00
1.00
1.03
2.18
3.32
2.50
2.70
1.67
5.14
5.99
6.27
3.68
2.55
3.44
7.73
2.91
f1 (ppm)

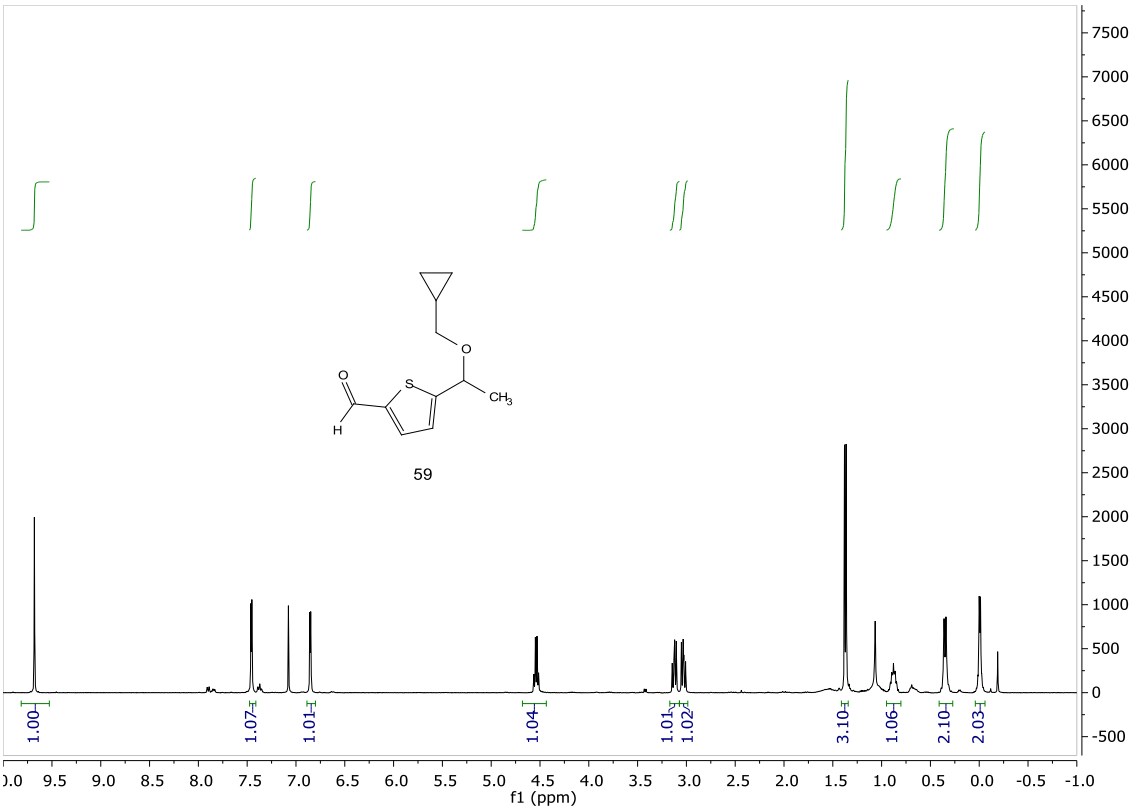

57
f1 (ppm)

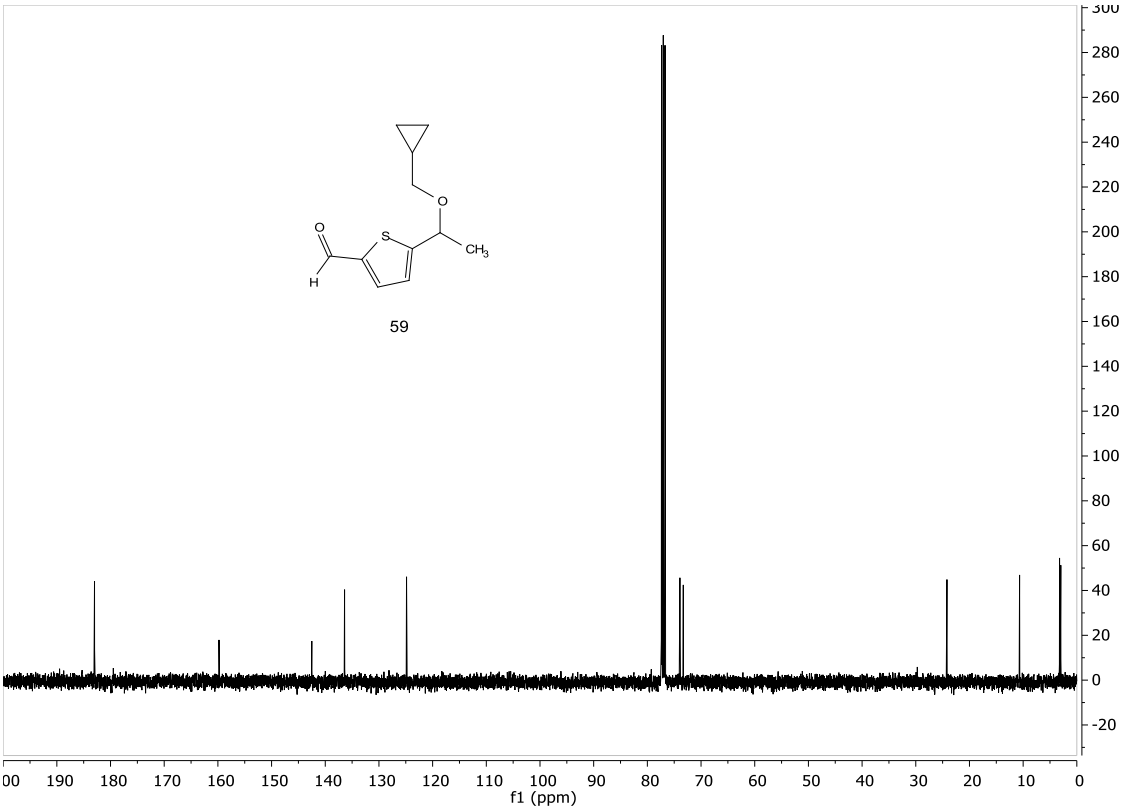

-114.6494
57
f1 (ppm)

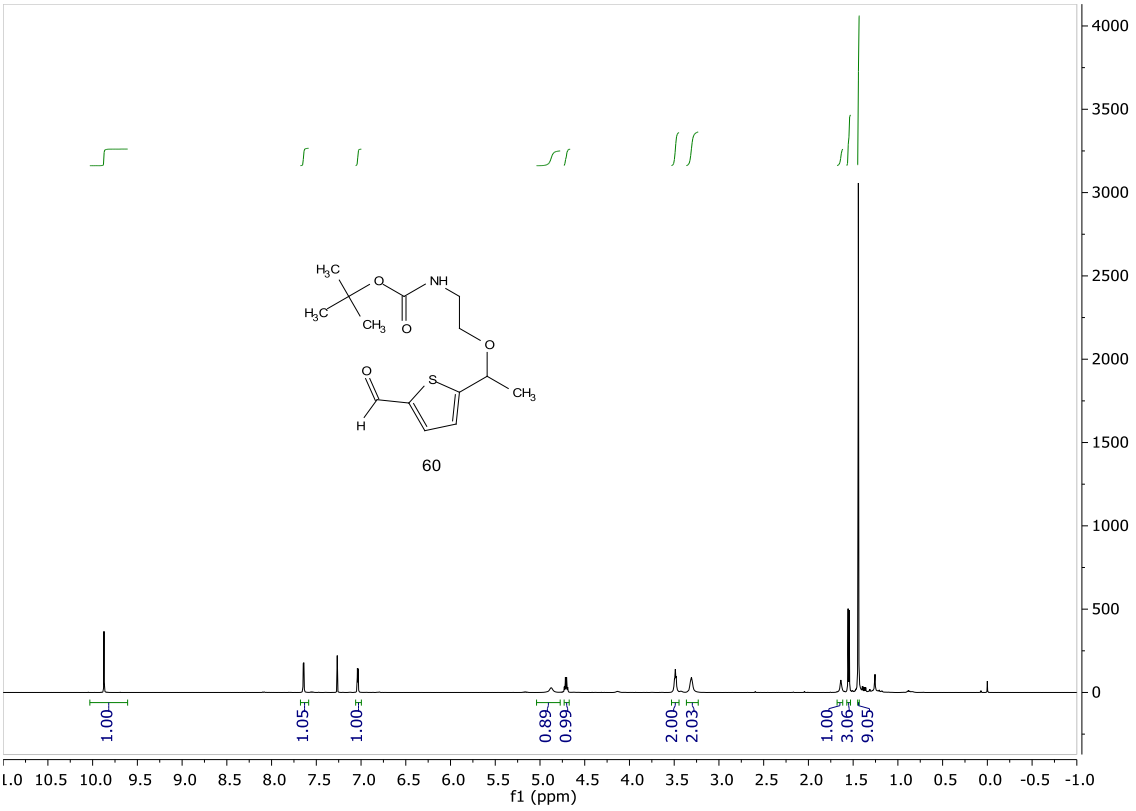

58
0.99
2.00
2.01
0.99
5.99
0.96
1.00
1.99
2.98
2.99
1.05
3.02
6.21
f1 (ppm)

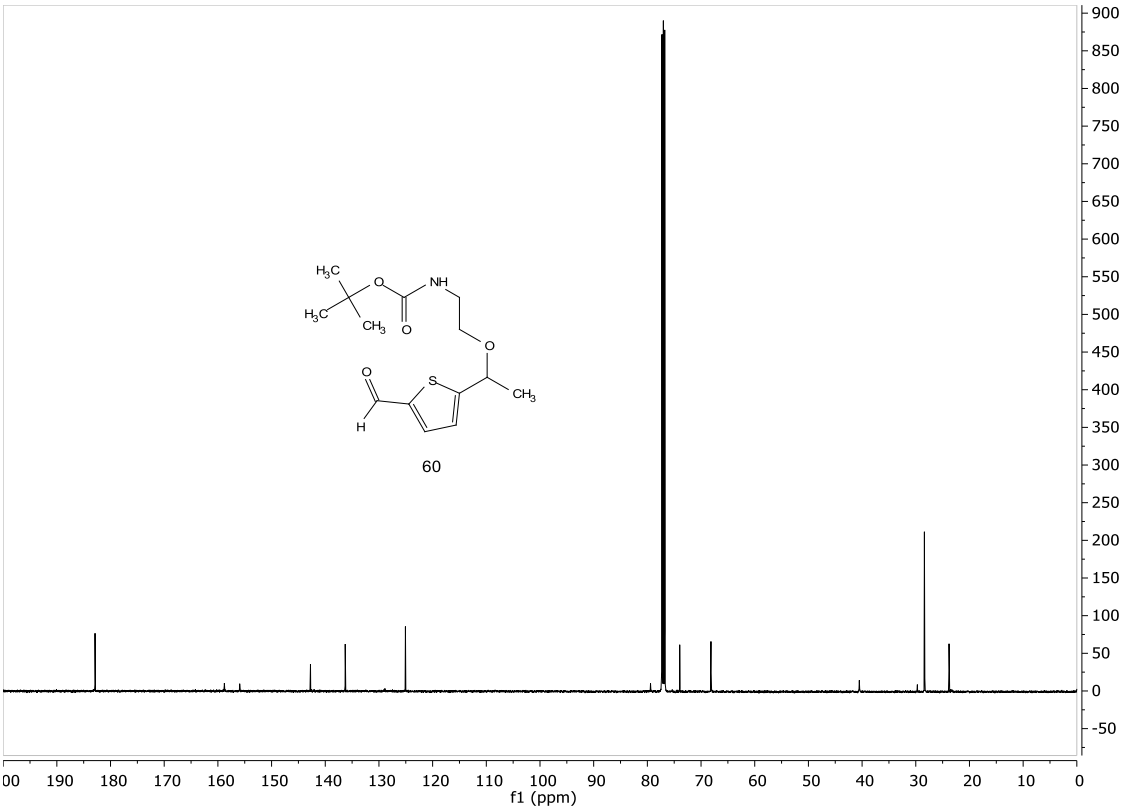

58
f1 (ppm)

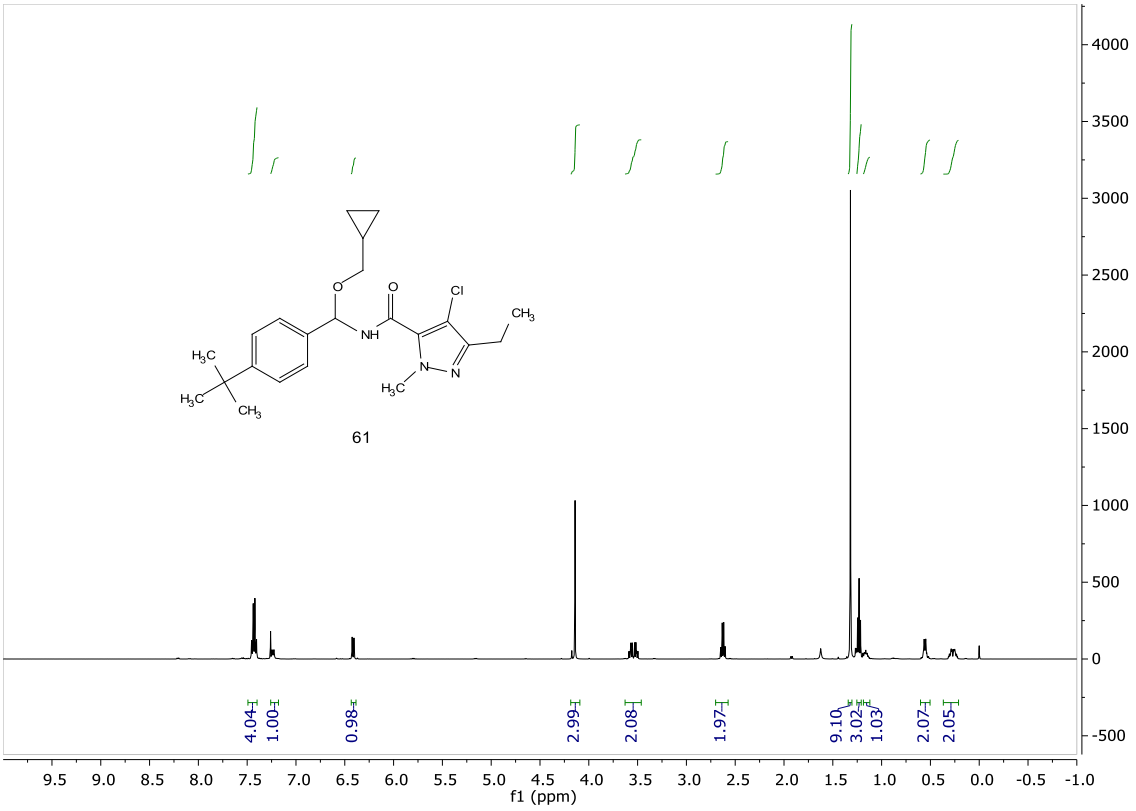

-111.1023
-114.0010
58
f1 (ppm)

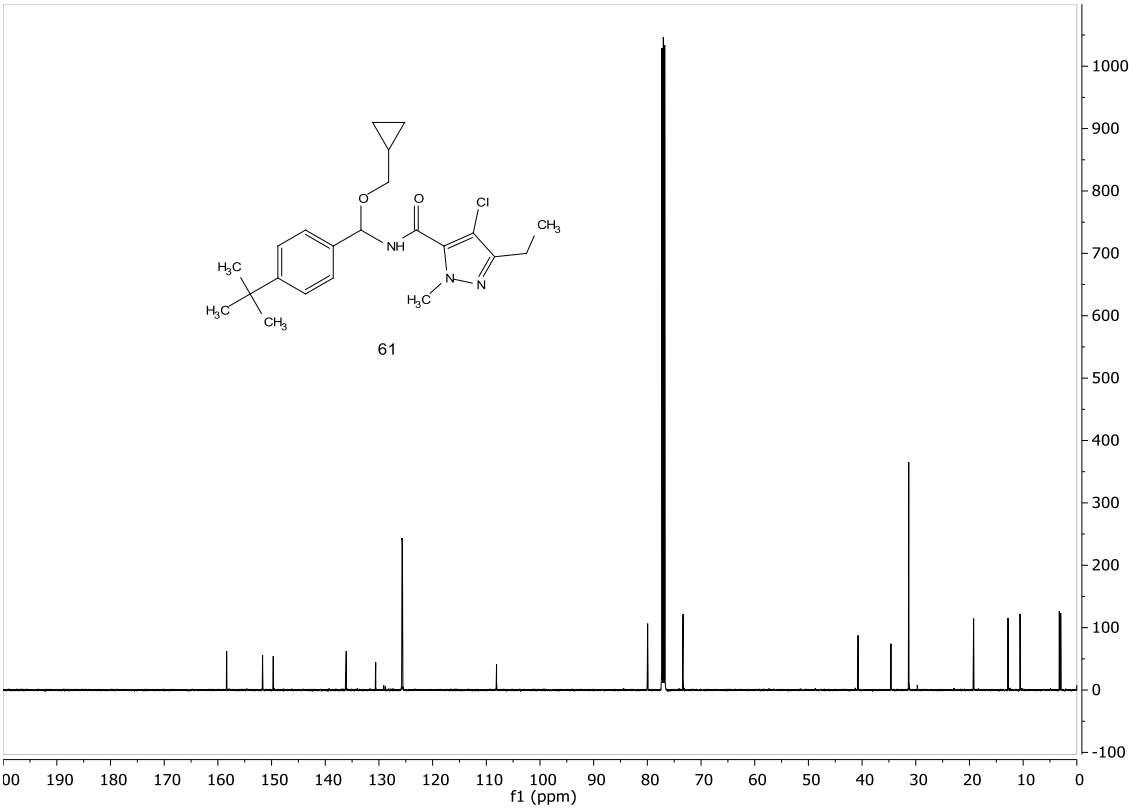

59
1.00
1.07
1.01
1.04
1.01
1.02
3.10
1.06
2.10
2.03
f1 (ppm)

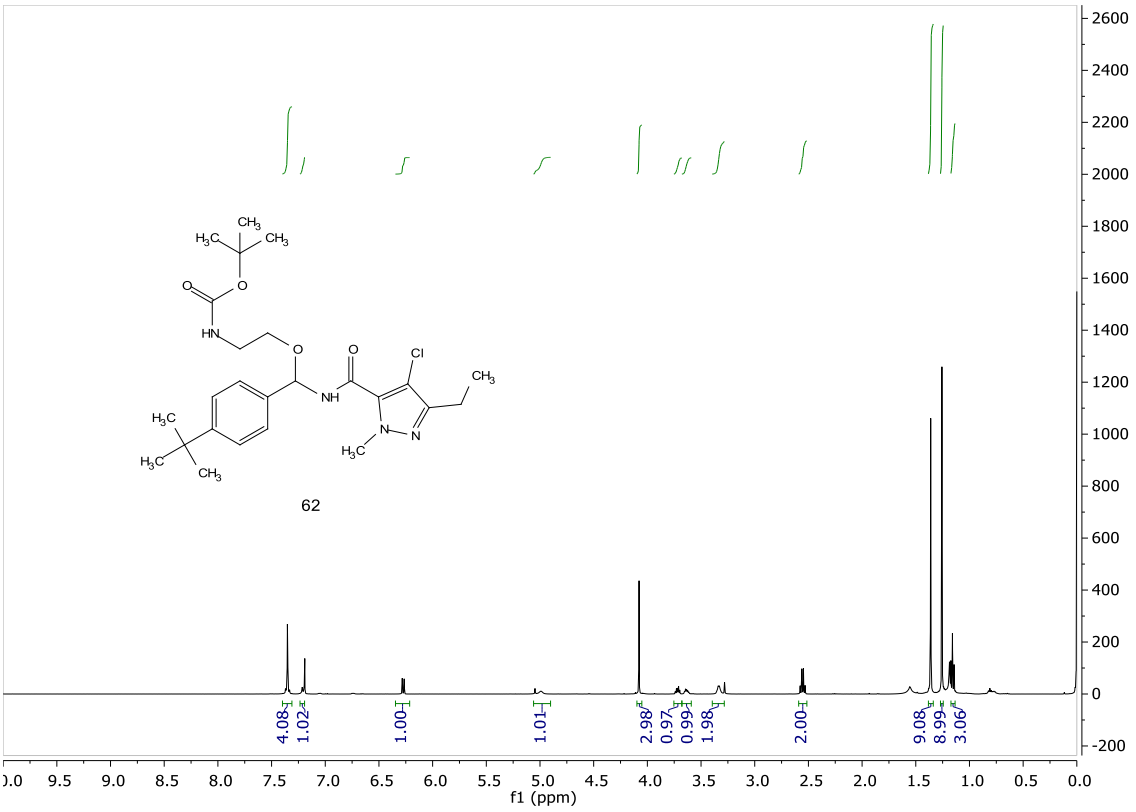

59
f1 (ppm)

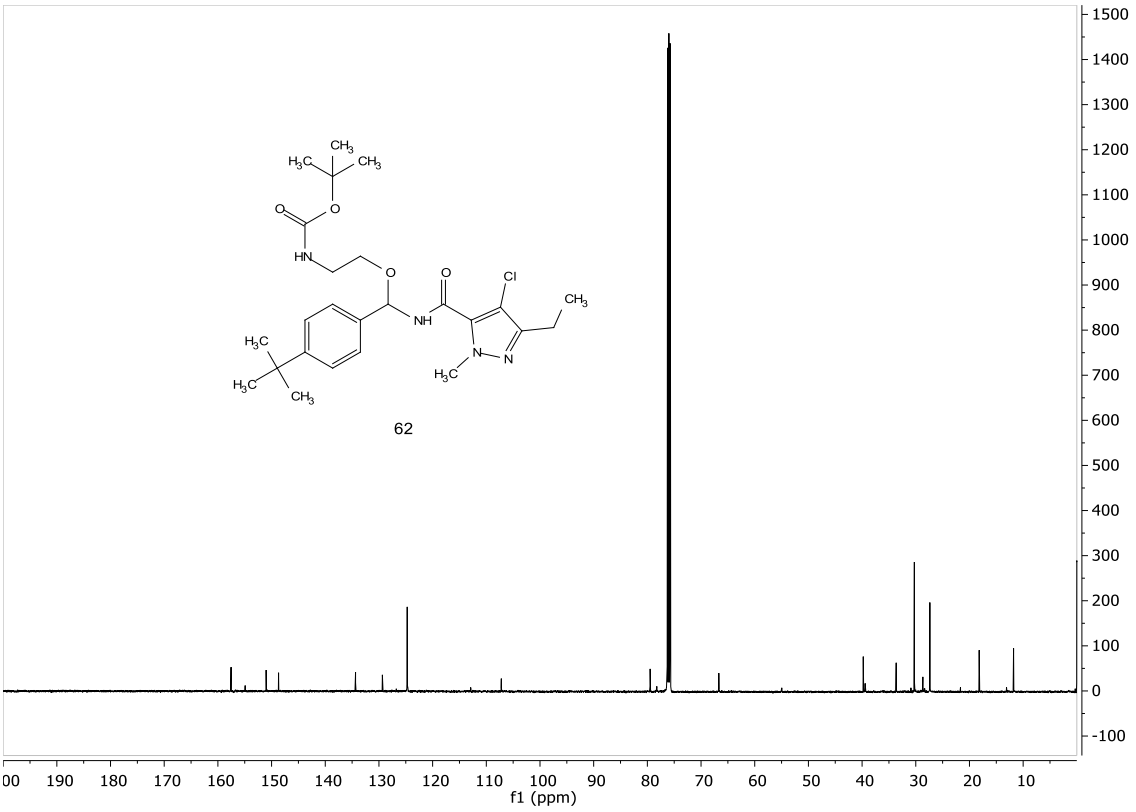

60
1.00
1.05
1.00
0.89
0.99
2.00
2.03
1.00
3.06
9.05
f1 (ppm)

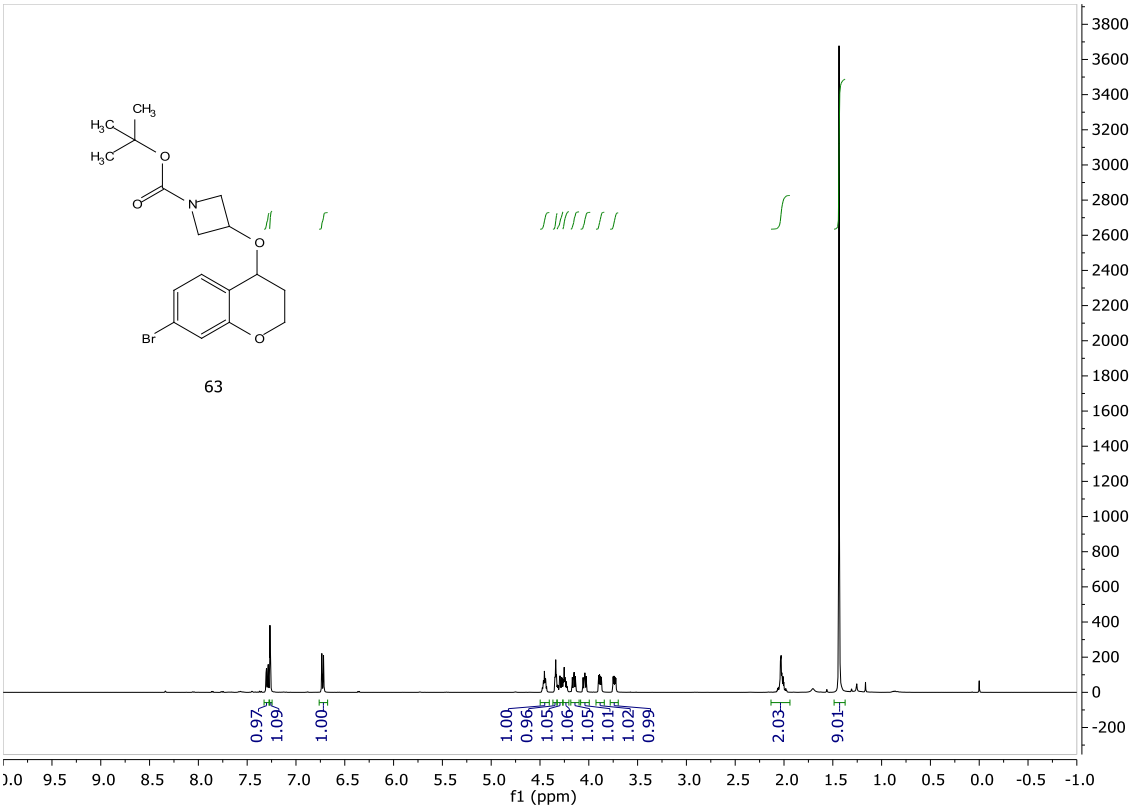

60
f1 (ppm)

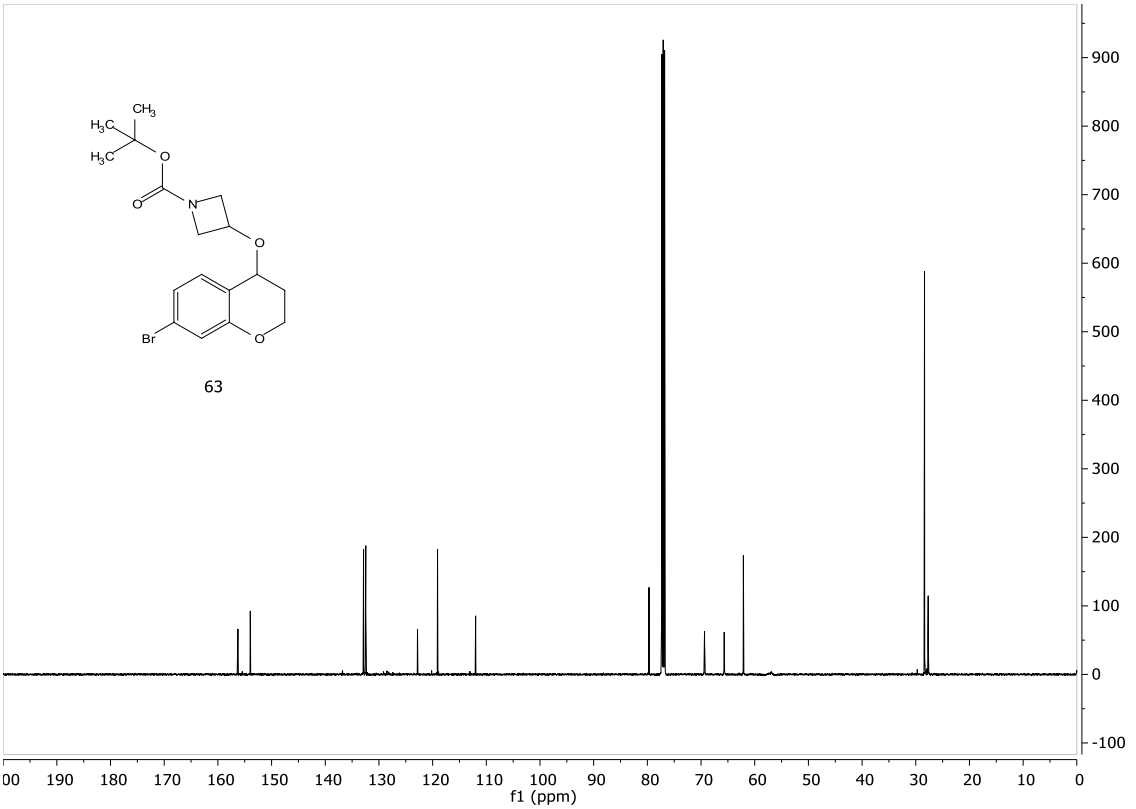

61
4.04
1.00
0.98
2.99
2.08
1.97
9.10
3.02
1.03
2.07
2.05
f1 (ppm)

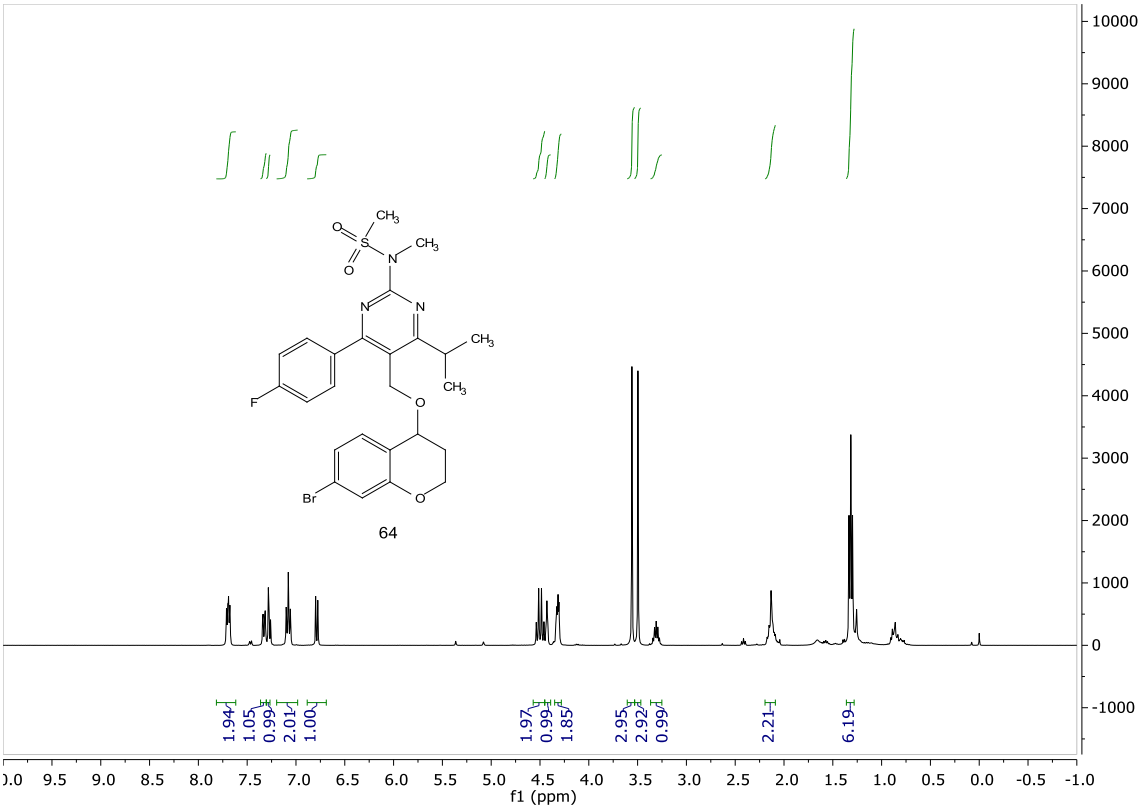

61
f1 (ppm)

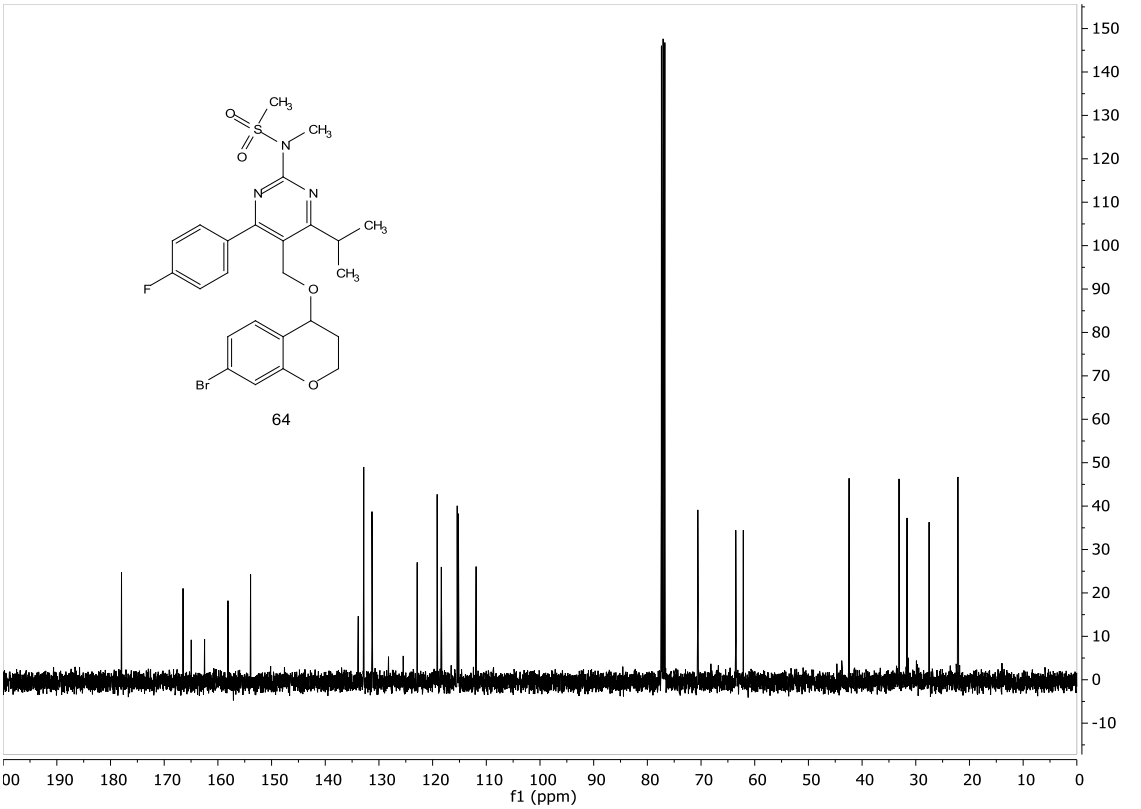

62
4.08
1.02
1.00
1.01
2.98
0.97
0.99
1.98
2.00
9.08
8.99
3.06
f1 (ppm)

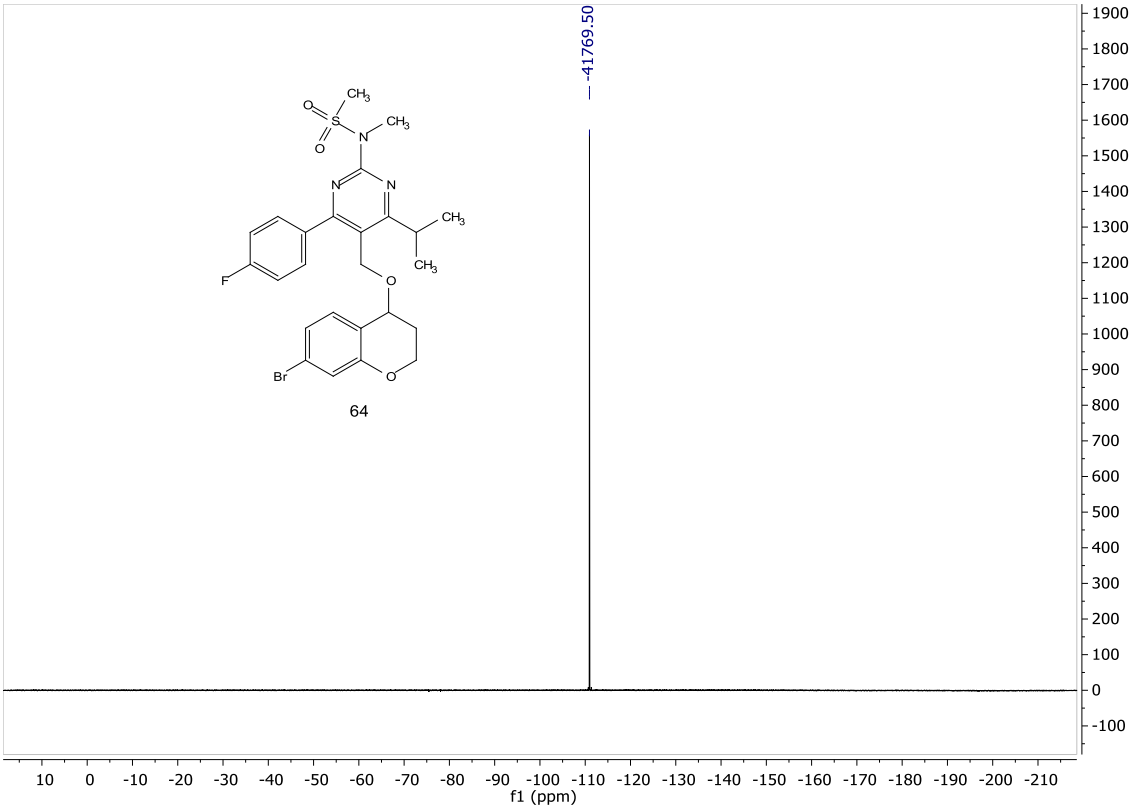

62
f1 (ppm)

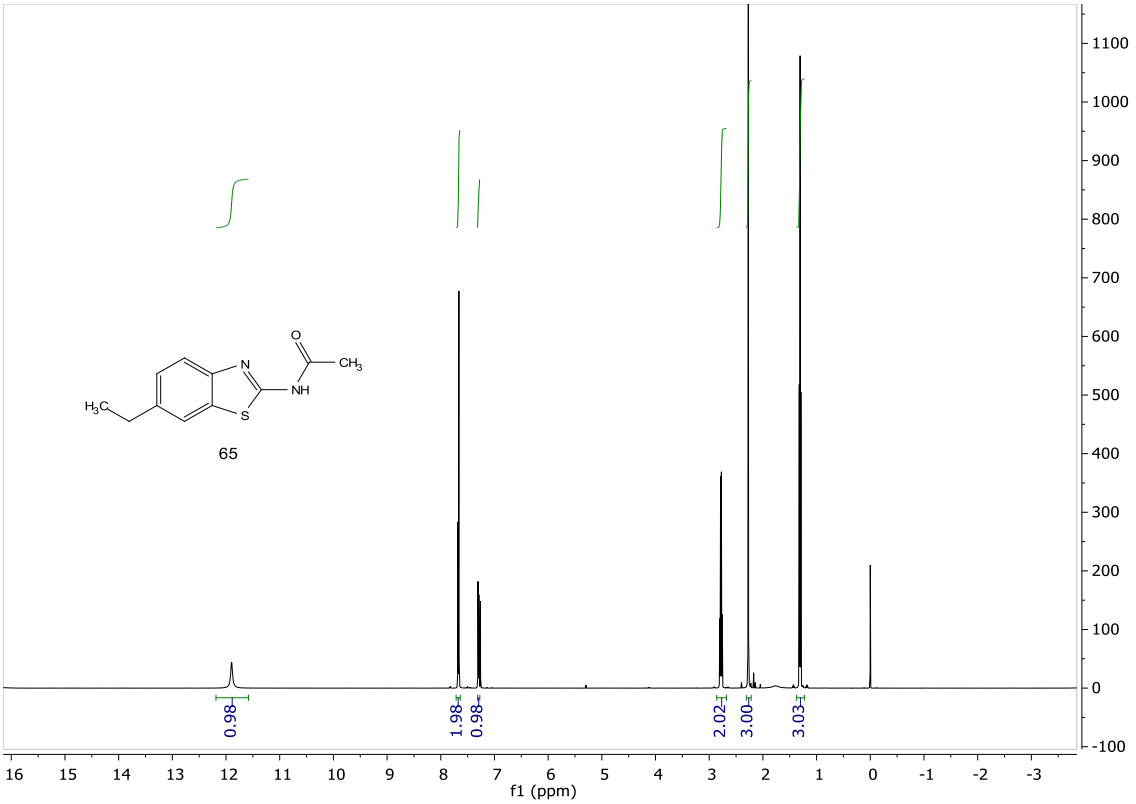

63
0.97
1.09
1.00
1.00
0.96
1.05
1.06
1.05
1.01
1.02
0.99
2.03
9.01
f1 (ppm)

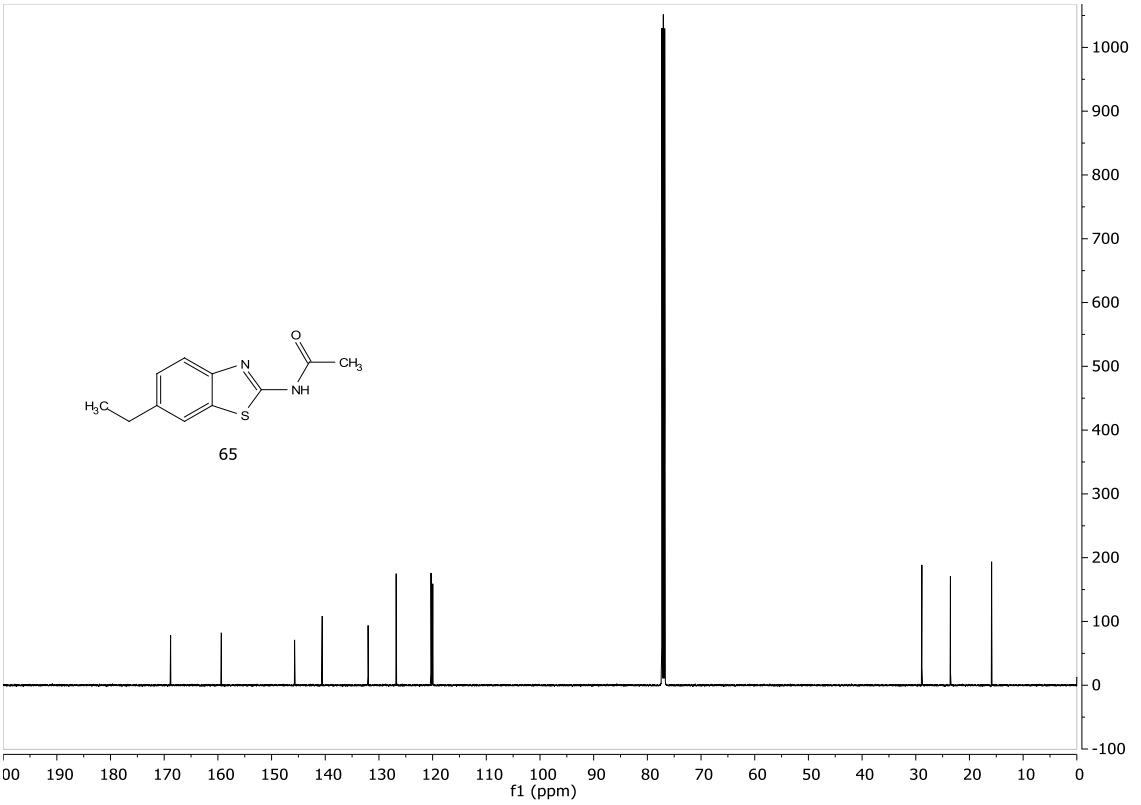

63
f1 (ppm)

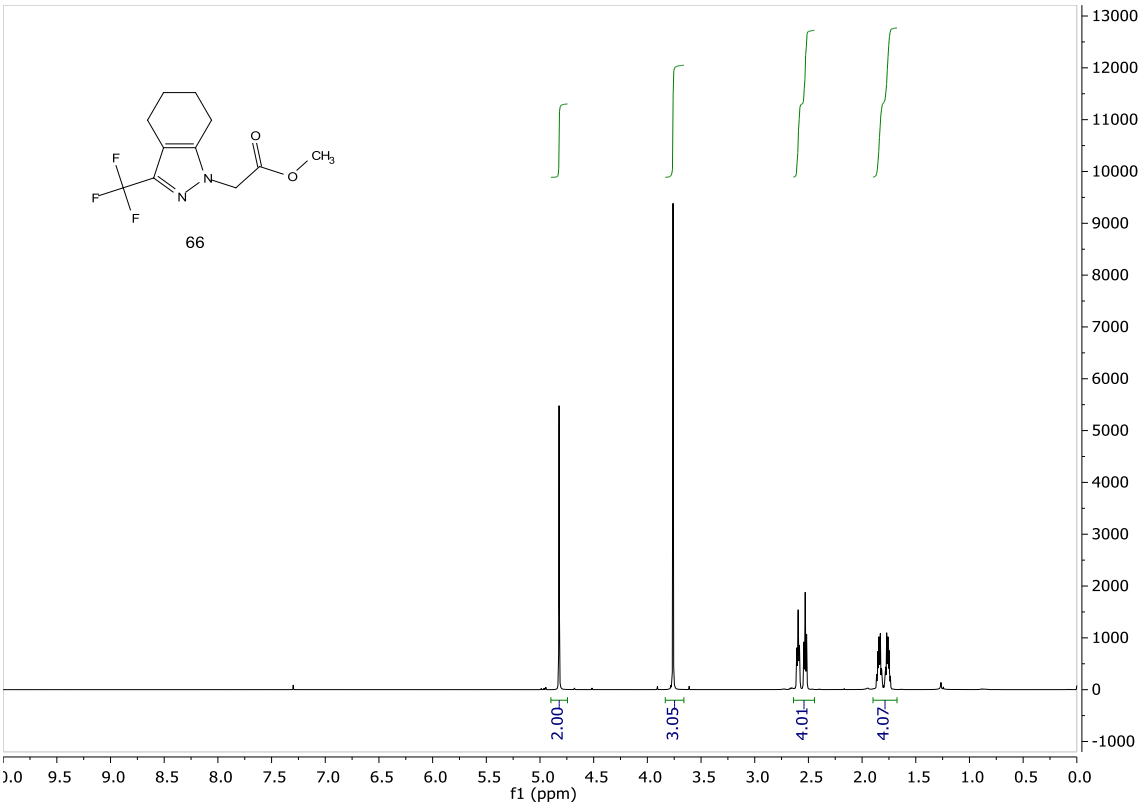

64
1.94
1.05
0.99
2.01
1.00
1.97
0.99
1.85
2.95
2.92
0.99
2.21
6.19
f1 (ppm)

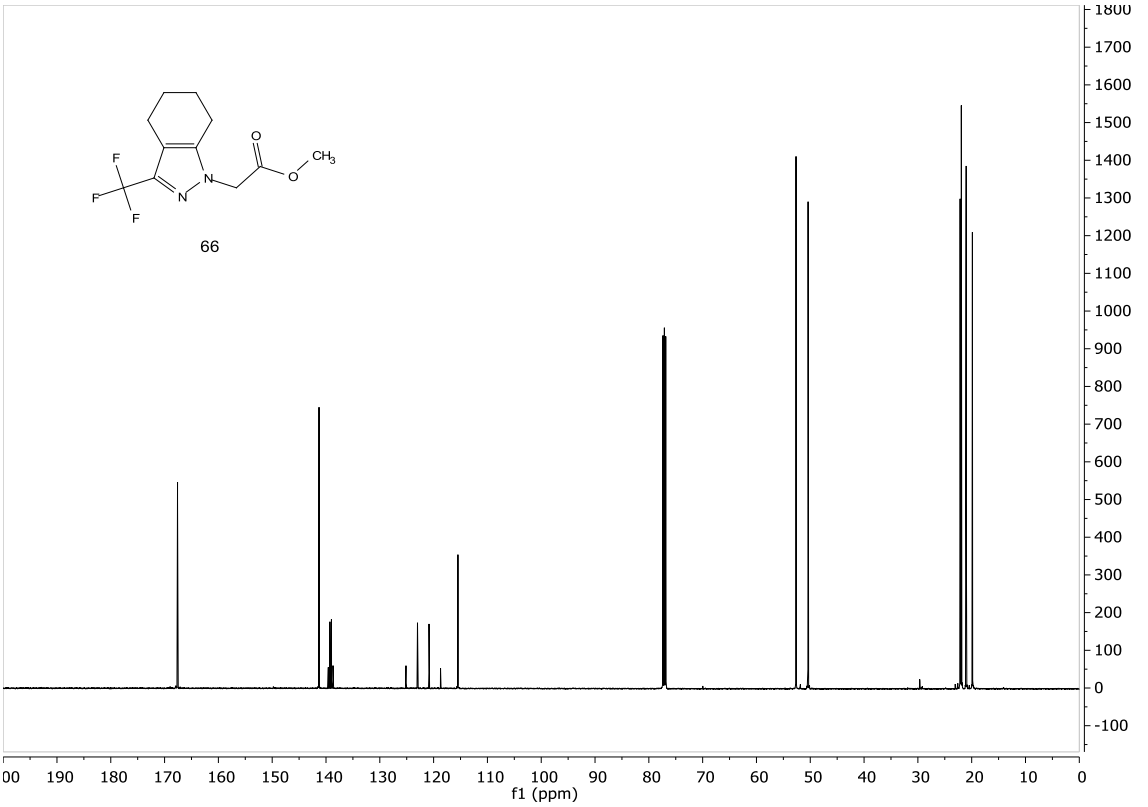

64
f1 (ppm)

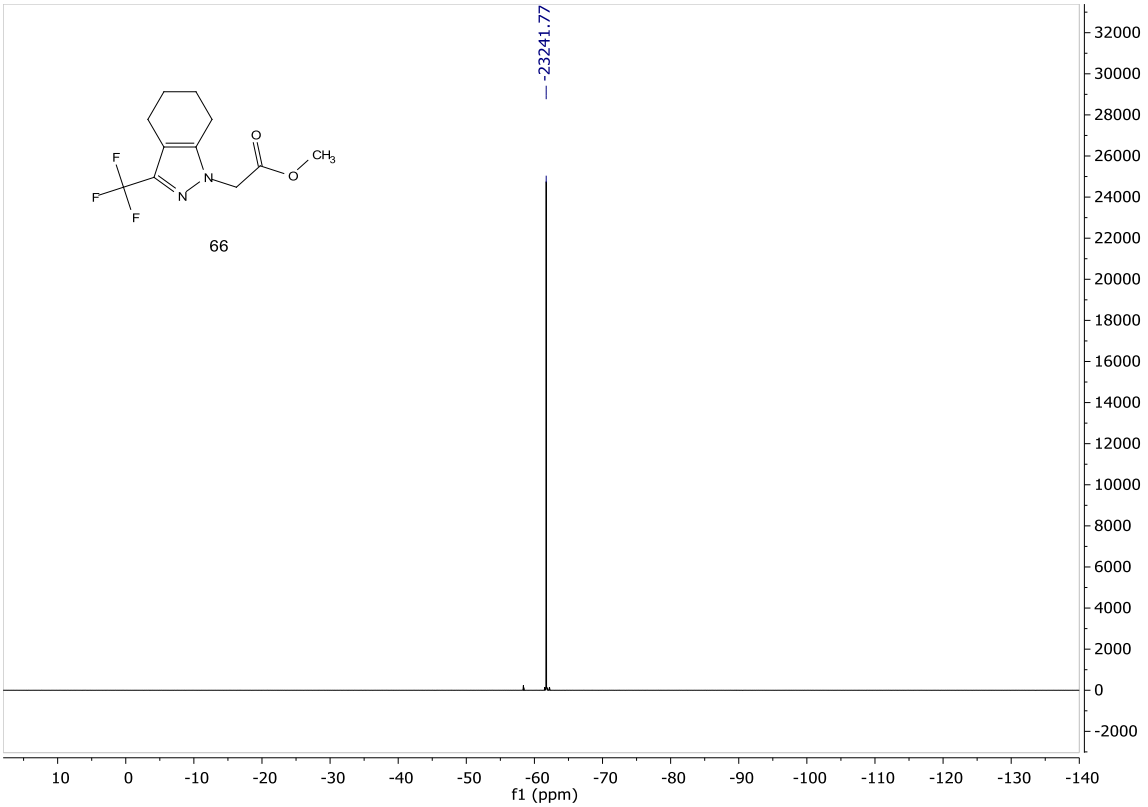

-41769.50
64
f1 (ppm)

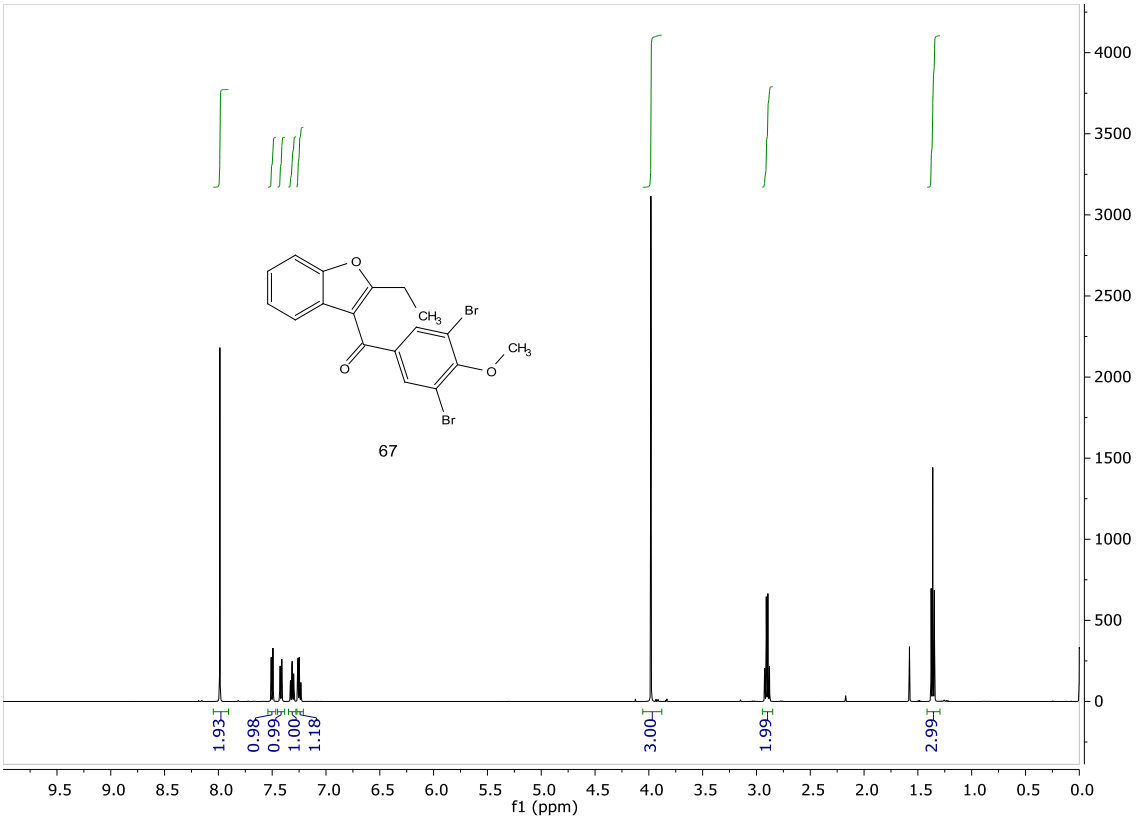

65
0.98
1.98
0.98
2.02
3.00
3.03
f1 (ppm)

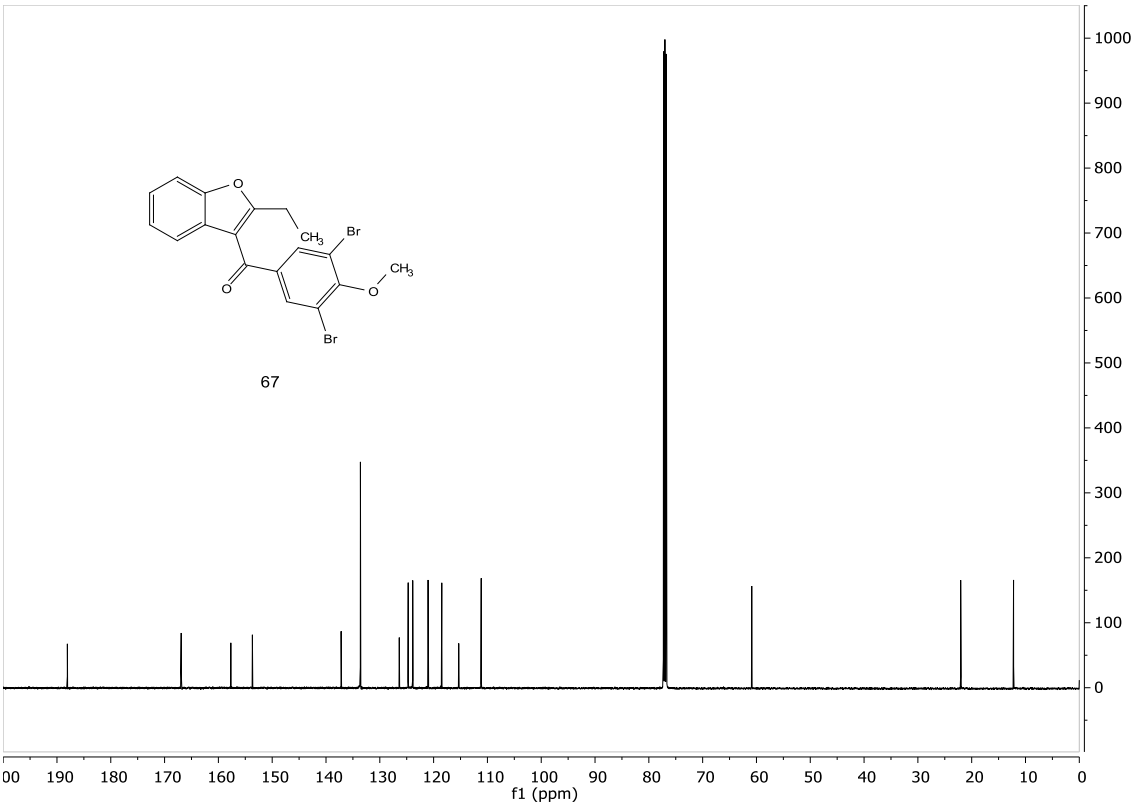

O
CH3
N
NH
S
H3C
65
1000
900
800
700
600
500
400
300
200
100
0
-100
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


F
F
F
N
N
O
O
CH3
66
2.00
3.05
4.01
4.07
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


66
f1 (ppm)


-23241.77
66
f1 (ppm)


67
1.93
0.98
0.99
1.00
1.18
3.00
1.99
2.99
f1 (ppm)


67
f1 (ppm)