Electronic Supplementary Information

for

Palladium Catalyzed Chloroethoxylation of Aromatic and Heteroaromatic Chlorides: an Orthogonal Functionalization of Chloroethoxy Linker

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S1 - General Information

Unless otherwise indicated, all starting materials were obtained from commercial suppliers, and were used without further purification. Analytical thin-layer chromatography (TLC) was performed on Merck DC precoated TLC plates with 0.25 mm Kieselgel 60 F_{254}. Visualization was performed with a 254 nm UV lamp. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 250 spectrometer, in $CDCl_3$, DMSO-d_6 and D_2O. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards (δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Coupling constants (*J*) are reported in Hz. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), the combination thereof (eg.: dd, dt, tq, etc.) and m (multiplet). All melting points were measured on Büchi 501 apparatus and are uncorrected. High-resolution mass spectra were acquired on an Agilent 6230 time-of-flight mass spectrometer equipped with a Jet Stream electrospray ion source in positive ion mode. Injections of 0.1-0.3 µl were directed to the mass spectrometer at a flow rate 0.5 ml/min (70% acetonitrile-water mixture, 0.1 % formic acid), using an Agilent 1260 Infinity HPLC system. Jet Stream parameters: drying gas (N_2) flow and temperature: 10.0 l/min and 325 °C, respectively; nebulizer gas (N_2) pressure: 10 psi; capillary voltage: 4000V; sheath gas flow and temperature: 325 °C and 7.5 l/min; TOFMS parameters: fragmentor voltage: 120 V; skimmer potential: 120V; OCT 1 RF Vpp:750 V. Full-scan mass spectra were acquired over the m/z range 100-2500 at an acquisition rate of 250 ms/spectrum and processed by Agilent MassHunter B.03.01 software.

S1.1 – Drug molecules containing alkoxy-linkers between an aryl-group and a nucleophilic center

To the best of our knowledge, the following list contains more or less all important drug molecules, currently containing an ethoxy-spacer between an aromatic core and a nucleophilic center (mostly nitrogen atom of an aliphatic heterocycle). Most of the compounds are marketed currently, or in advanced phase of clinical trials.

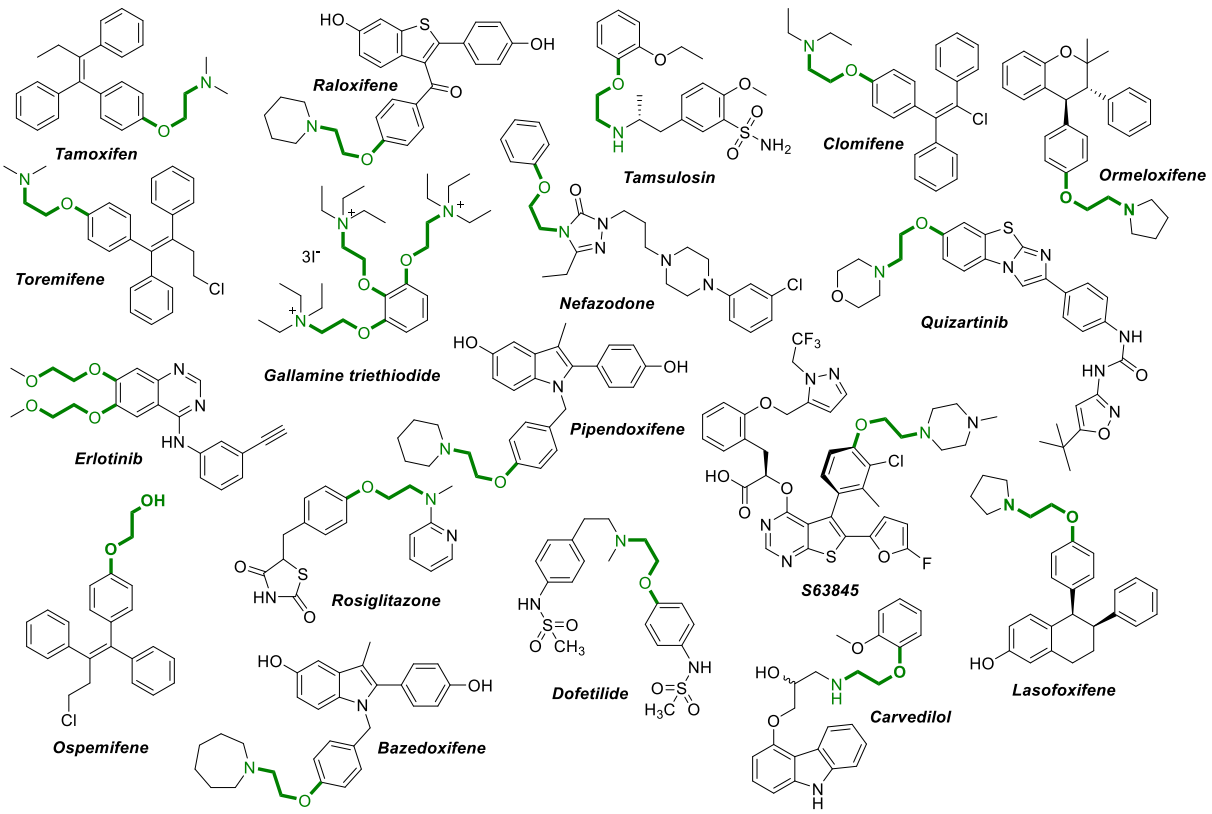


Figure 1. Pharmaceuticals containing an ethoxy-spacer

Similarly, longer alkoxy spacers are also quite frequent in pharmaceutical chemistry. Next table contains drug molecules containing propyl- or butyl-linkers.

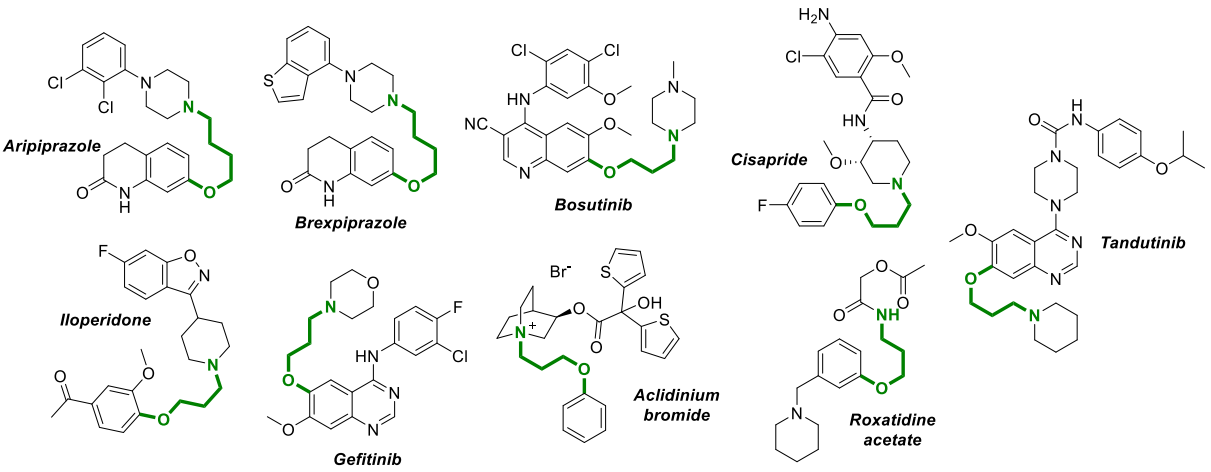
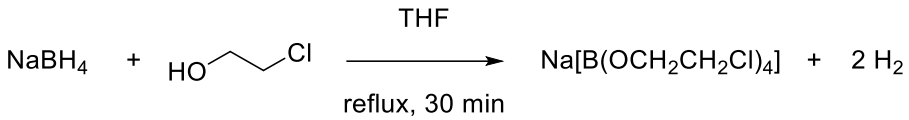


Figure 2. Pharmaceuticals containing propoxy- and butoxy-spacers

S2 - Preparation of $Na[B(OCH_2CH_2Cl)_4]$



To a 50 ml round bottom flask, sodium borohydire (946 mg, 25 mmol), and THF (25 ml) were measured in. While stirring, 2-chloroethanol (10 ml, 6 equiv) was added dropwise to the solution, evolution of H_2 gas was observed. The flask was equipped with a reflux condenser, then the mixture was heated to reflux for 30 minutes. The residual solvent was evaporated under reduced pressure, 10 ml Et_2O was added to the solution and the precipitated product was filtered, washed with 20 ml Et_2O and dried to give sodium tetrakis(2-chloroethoxy)-borate as a white solid (7.58 g, 86%). **Mp**: not determined, over 350 °C. **^{1}H NMR** (250 MHz, D_2O) δ = 3.71 (dd, *J*=6.3, 3.8, 8H), 3.55 (dd, *J*=6.1, 4.0, 8H). **^{13}C NMR** (63 MHz, D_2O) δ = 62.3, 46.5.

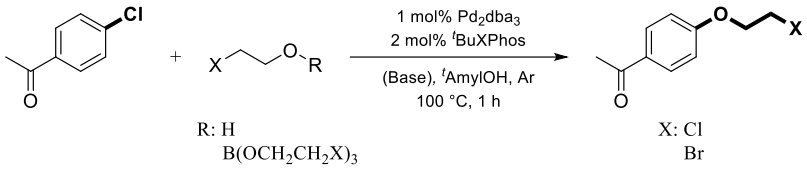
Other borate salts were prepared in a similar manner.

S3- Selected optimization results

S3.1 - Preliminary experiments for 2-haloethoxylation of 4'-chloroacetophenone

A 4 ml screw-cap vial equipped with a stirring bar was charged with Pd_2dba_3 (1.8 mg, 2 µmol, 1.0 mol%), ^{t}BuXPhos (1.7 mg, 4 µmol, 2.0 mol%), the borate salt (entries 3 and 4; 0.3 mmol, 1.5 equiv.), Cs_2CO_3 (entries 1 and 2; 0.3 mmol, 1.5 equiv.) and *tert*-amyl alcohol (500 µl). The atmosphere was changed to argon, 4′-chloroacetophenone (30.9 mg, 0.2 mmol) and 2-haloethanol (entries 1 and 2; 0.3 mmol, 1.5 equiv) was added and the mixture was stirred at 100 °C for 1 hour. Samples were taken from the mixtures, diluted with DCM, and analyzed by GC-FID.

Workup: The reaction mixture was diluted with EtOAc (10 ml), washed with water (10 ml), and the aqueous layer was extracted with EtOAc (10 ml). The combined organic layers were evaporated and purified by coloumn chromatography.

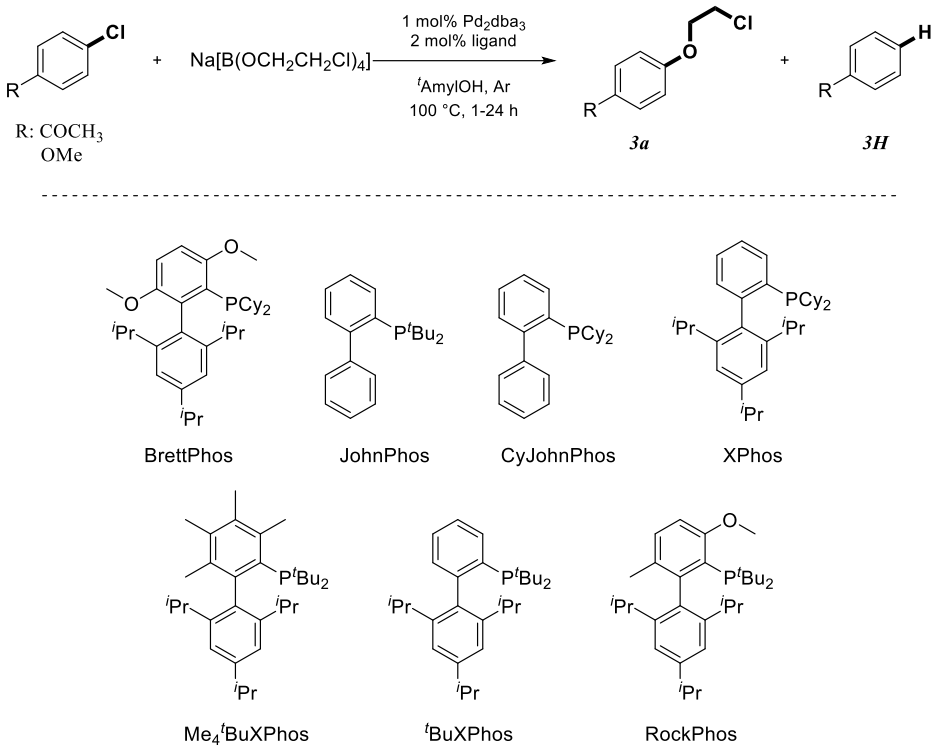


Entry	Reagent	Base additive	Conversion (%)	Isolated yield (%)
1	$BrCH_2CH_2OH$	Cs_2CO_3	100	Trace
2	$ClCH_2CH_2OH$	Cs_2CO_3	100	45
3	$Na[B(OC_2H_4Br)_4]$	-	0	0
4	$Na[B(OC_2H_4Cl)_4]$	-	100	95

Figure 1. Preliminary experiments

S3.2 – Optimization of the catalytic system

Carried out on 0.1 mmol scale, with the same protocol as S2.1. Conversions were determined by GC-FID.



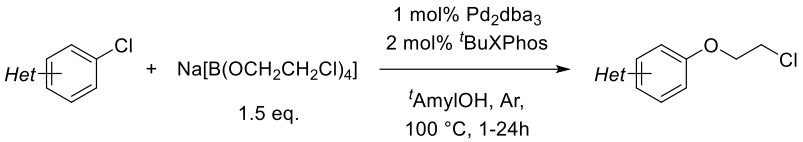
Entry	Substrate	Ligand	Conv. 3H (%)[b]	Conv. 3a (%)[b]
1	4'-chloroacetophenone	BrettPhos	1 (1)	92 (95)
2	4'-chloroacetophenone	JohnPhos	24 (24)	63 (72)
3	4'-chloroacetophenone	CyJohnPhos	1 (1)	1 (1)
4	4'-chloroacetophenone	XPhos	13 (13)	54 (64)
5	4'-chloroacetophenone	Me$_4$^{t}BuXPhos	0 (1)	86 (97)
6	4'-chloroacetophenone	^{t}BuXPhos	0 (0)	99 (100)
7	4'-chloroacetophenone	RockPhos	0 (0)	99 (100)
8	4-chloroanisole	BrettPhos	2 (2)	0 (0)
9	4-chloroanisole	Me$_4$^{t}BuXPhos	0 (1)	2 (3)
10	4-chloroanisole	^{t}BuXPhos	4 (5)	8 (9)
11	4-chloroanisole	RockPhos	1 (1)	8 (13)

Figure 4. Optimization of the catalytic system. [b] Determined by GC analysis after 1 h ; numbers in parenthesis indicates conversions after 24 h.

However, RockPhos was found to be the most active phosphine-ligand for the transformation, in the case of active, electron-poor substrates, the more affordable ^{t}BuXPhos has the same efficiency, thus it was found to be the optimal ligand.

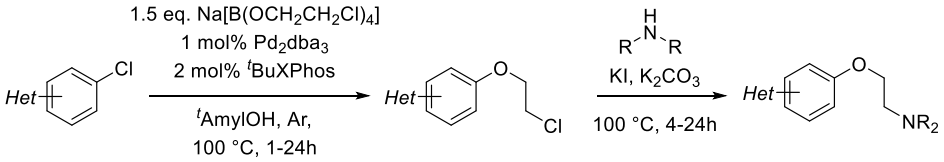
S4 - General reaction procedure

Procedure for the 2-chloroethoxylation of chloroarenes



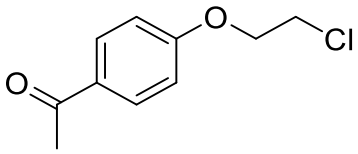
A 4 ml screw-cap vial equipped with a stirring bar was charged with Pd_2dba_3 (4.6 mg, 5 µmol, 1.0 mol%), ^{t}BuXPhos (4.2 mg, 10 µmol, 2.0 mol%) the substrate if solid (0.5 mmol, 1 equiv.), and *tert*-amyl alcohol (100 µl). The atmosphere was changed to argon, and the solution was stirred at RT for 5 minutes. The suspension of $Na[B(OCH_2CH_2Cl)_4]$ (263.9 mg, 0.75 mmol, 1.5 equiv.) in *tert*-amyl alcohol (900 µl), and the substrate (0.5 mmol, 1 equiv.) if liquid was added and the mixture was stirred at 100 °C for 1-24 hours. The mixture was allowed to cool down to room temperature, diluted with EtOAc (15 ml), and washed with brine (15 mL). The aqueous phase was extracted with EtOAc (15 ml), then the combined organic phases were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes: EtOAc eluent mixture).

Procedure for *one-pot* synthesis of 2-aminoethoxy arenes



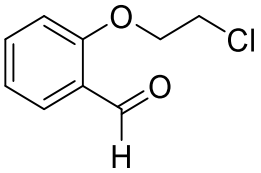
A 4 ml screw-cap vial equipped with a stirring bar was charged with Pd_2dba_3 (4.6 mg, 5 µmol, 1.0 mol%), ^{t}BuXPhos (4.2 mg, 10 µmol, 2.0 mol%) the substrate if solid (0.5 mmol, 1 equiv.), and *tert*-amyl alcohol (100 µl). The atmosphere was changed to argon, and the solution was stirred at RT for 5 minutes. The suspension of $Na[B(OCH_2CH_2Cl)_4]$ (263.9 mg, 0.75 mmol, 1.5 equiv.) in *tert*-amyl alcohol (900 µl), and the substrate (0.5 mmol) if liquid was added and the mixture was stirred at 100 °C for 1-24 hours. The mixture was allowed to cool down to room temperature, KI (166 mg, 1 mmol, 2 equiv.), K_2CO_3 (138 mg, 1 mmol, 2 equiv.) and secondary amine (eg.: piperidine, 2 ml) was added to the solution, then stirred at 100 °C for further 4-24 hours. The mixture was cooled down to room temperature, diluted with water (10 ml), and extracted with EtOAc (3X15 ml). The combined organic layers were evaporated under reduced pressure, and purified by coloumn chromatography (silica gel, DCM:MeOH eluent mixture).

1-(4-(2-chloroethoxy)phenyl)ethan-1-one (3a) [1]



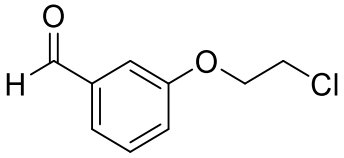
From 4′-chloroacetophenone (77.2 mg, 0.499 mmol). Reaction time: 1 h. Purification by column chromatography (20 g SiO_2, hex/EtOAc 50/1-5/1) gave 1-(4-(2-chloroethoxy)phenyl)ethan-1-one (94.3 mg, 0.475 mmol, 95 %) as white solid. **Mp**: 53-54 °C, $\mathbf{R_f}$ = 0.47 (hex/EtOAc 7/3), **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 7.87 (d, *J*=8.9, 2H), 6.87 (d, *J*=8.9, 2H), 4.22 (t, *J*=5.8, 2H), 3.76 (t, *J*=5.8, 2H), 2.48 (s, 3H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 197.1, 162.4, 131.3, 131.0, 114.6, 68.4, 42.0, 26.7. **MS** (EI, 70 eV): m/z (%): 200(9), 198(27), 185(33), 183(100), 121(68), 93(16), 77(7), 63(17).). **IR**: 833, 956, 1033, 1171, 1247, 1271, 1357, 1508, 1577, 1599, 1672 cm^{-1}.

2-(2-chloroethoxy)benzaldehyde (3b) [2]



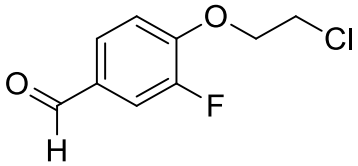
From 2-chlorobenzaldehyde (62.9 mg, 0.447 mmol). Reaction time: 1 h. Purification by column chromatography (20 g SiO_2, hex/EtOAc 50/1-25/1) gave 2-(2-chloroethoxy)benzaldehyde (65.0 mg, 0.352 mmol, 79%) as a pale yellow solid. **Mp**: 25-27 °C, $\mathbf{R_f}$ = 0.38 (hex/EtOAc 4/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 10.53 (s, 1H), 7.85 (dd, *J*=7.7, 1.9, 1H), 7.55 (ddd, *J*=8.9, 7.3, 1.9, 1H), 7.07 (t, *J*=7.5, 1H), 6.97 (d, *J*=8.4, 1H), 4.36 (t, *J*=5.6, 2H), 3.88 (t, *J*=5.6, 2H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 189.9, 160.9, 136.3, 128.9, 125.6, 121.9, 113.1, 68.9, 42.1. **MS** (EI, 70 eV): m/z (%): 186(1), 184(4), 148(20), 121(100), 104(16), 93(14), 77(17), 65(38), 63(34). **IR**: 757, 1033, 1163, 1191, 1242, 1288, 1303, 1454, 1486, 1601, 1681, 1687, 1711, 1728, 1737 cm^{-1}.

3-(2-chloroethoxy)benzaldehyde (3c)



From 3-chlorobenzaldehyde (70.0 mg, 0.498 mmol). Reaction time: 4 h. Purification by column chromatography (20 g SiO_2, hex/EtOAc 100/1-30/1) gave 3-(2-chloroethoxy)benzaldehyde (53.1 mg, 0.288 mmol, 58%) as a pale yellow oil. $\mathbf{R_f}$ = 0.34 (hex/EtOAc 5/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 9.90 (s, 1H), 7.53 – 7.37 (m, 2H), 7.36 – 7.22 (m, 1H), 7.13 (dt, *J*=6.9, 2.5, 1H), 4.22 (t, *J*=5.7, 2H), 3.77 (t, *J*=5.7, 2H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 192.3, 159.2, 138.2, 130.6, 124.6, 122.4, 113.2, 68.6, 42.1. **MS** (EI, 70 eV): m/z (%): 186(23), 184(71), 135(16), 122(66), 121(97), 77(25), 65(67), 63(100). **IR**: 682, 744, 757, 789, 1040, 1150, 1171, 1264, 1288, 1303, 1322, 1448, 1486, 1585, 1599, 1694 cm^{-1}. **HRMS** calculated for $C_9H_9ClO_2Na$ $[M+Na]^+$ 207.0189 found: 207.0182.

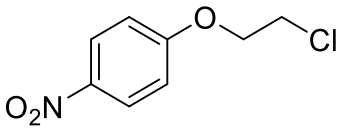
4-(2-chloroethoxy)-3-fluorobenzaldehyde (3d)



[1] M. Li, X.F. Bai, Y.J. Hou, *Z. Kristallogr. - New Cryst. Struct.* **2016**, *231*, 407-408.
[2] Katz, L.; Karger, L. S.; Schroeder, W.; Cohen, M. S. *J. Org. Chem.* **1953**, *18*, 1380-1402.

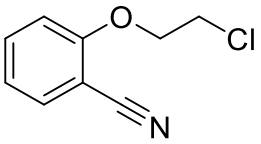
From 4-chloro-3-fluorobenzaldehyde (76.9 mg, 0.485 mmol). Reaction time: 1 h. Purification by column chromatography (20 g SiO_2, hex/EtOAc 50/1-10/1) gave 4-(2-chloroethoxy)-3-fluorobenzaldehyde (97.1 mg, 0.479 mmol, 99%) as white solid. **Mp**: 43-45 °C, $\mathbf{R_f}$ = 0.13 (hex/EtOAc 9/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 9.87 (d, *J*=2.1, 1H), 7.66 – 7.64 (m, 1H), 7.63 – 7.60 (m, 2H), 7.09 (dd, *J*=8.6, 7.7, 1H), 4.39 (t, *J*=5.9, 2H), 3.88 (t, *J*=5.9, 2H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 190.1 (d, *J*=2.1), 153.1 (d, *J*=250.5), 151.9 (d, *J*=11.1), 131.2 (d, *J*=5.1), 128.2 (d, *J*=3.3), 116.6 (d, *J*=18.7), 114.8 (d, *J*=1.6)., 69.7, 41.6. **^{19}F NMR** (235 MHz, $CDCl_3$) δ = -131.92. **MS** (EI, 70 eV): m/z (%): 204(13), 202(41), 140(42), 139(100), 111(16), 83(29), 63(66). **IR**: 746, 781, 813, 1027, 1109, 1118, 1221, 1258, 1277, 1441, 1512, 1585, 1609, 1687 cm^{-1}. **HRMS** calculated for $C_9H_9ClFO_2$ $[M+H]^+$ 203.0275 found: 203.0271.

1-(2-chloroethoxy)-4-nitrobenzene (3e) [3]



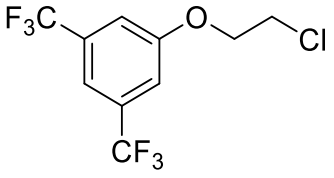
From 1-chloro-4-nitrobenzene (79.2 mg, 0.503 mmol). Reaction time: 1 h. Purification by column chromatography (20 g SiO_2, hex/EtOAc 50:1-15:1) gave 1-(2-chloroethoxy)-4-nitrobenzene (81.0 mg, 0.402 mmol, 80%) as a green solid. **Mp**: 55-56 °C, (lit: 48 °C) $\mathbf{R_f}$ = 0.35 (hex/EtOAc 4/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 8.13 (td, *J*=10.5, 9.3, 2H), 6.91 (td, *J*=10.5, 9.3, 2H), 4.26 (t, *J*=5.7, 2H), 3.79 (t, *J*=5.7, 2H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 163.5, 142.3, 126.3, 115.0, 68.9, 41.8. **MS** (EI, 70 eV): m/z (%): 202 (8), 200 (29), 152 (6), 139 (7), 109 (35), 76 (17), 63 (100). **IR**: 751, 844, 1029, 1109, 1174, 1260, 1299, 1331, 1495, 1512, 1558, 1592, 1653, 1685, 1700 cm^{-1}.

2-(2-chloroethoxy)benzonitrile (3f)



From 2-chlorobenzonitrile (70.9 mg, 0.515 mmol). Reaction time: 1 h. Purification by column chromatography (20 g SiO_2, hex/EtOAc 100/1-20/1) gave 2-(2-chloroethoxy)benzonitrile (84.9 mg, 0.467 mmol, 91%) as off-white solid. **Mp**: 59-61 °C, $\mathbf{R_f}$ = 0.35 (hex/EtOAc 4/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 7.60 – 7.49 (m, 2H), 7.04 (td, *J*=7.6, 0.9, 1H), 6.97 (d, *J*=8.5, 1H), 4.34 (t, *J*=6.0, 2H), 3.86 (t, *J*=6.0, 2H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 160.1, 134.8, 134.3, 122.0, 116.5, 112.9, 102.8, 69.2, 41.5. **MS** (EI, 70 eV): m/z (%): 183(7), 181(23), 120(9), 119(100), 91(40), 63(28). **IR**: 756, 1029, 1044, 1113, 1167, 1258, 1290, 1450, 1493, 1581, 1599, 2228 cm^{-1}. **HRMS** calculated for $C_9H_8ClNONa$ $[M+Na]^+$ 204.0192 found: 204.0184.

1-(2-chloroethoxy)-3,5-bis(trifluoromethyl)benzene (3g)

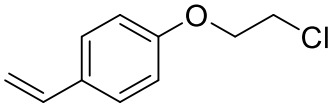


From 1-chloro-3,5-bis(trifluoromethyl)benzene (124.0 mg, 0.499 mmol). Reaction time: 1 h. Purification by column chromatography (20 g SiO_2, hex/EtOAc 10/1-20/1) gave 1-(2-chloroethoxy)-3,5-bis(trifluoromethyl)benzene (123.8 mg, 0.423 mmol, 85%) as colorless oil. $\mathbf{R_f}$ = 0.44 (hex/EtOAc 9/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 7.41 (s, 1H), 7.25 (s, 2H), 4.23 (t, *J*=5.6, 2H), 3.77 (t, *J*=5.6, 2H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 159.2, 133.4 (q, *J*=33.5), 123.4 (q, *J*=272.7), 115.49 – 115.36 (m), 115.36 – 115.18 (m)., 69.0, 41.7.

[3] V. Šukalović, D. Andrić, G. Roglić, S. Kostić-Rajačić, A. Schrattenholz, V. Šoškić, *Eur. J. Med. Chem.* **2005**, *40*, 481-493.

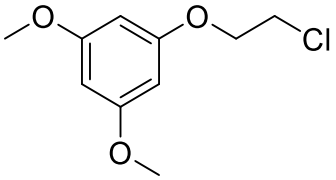
^{19}F NMR (235 MHz, $CDCl_3$) δ = -63.2. **MS** (EI, 70 eV): m/z (%): 294(5), 292(15), 275(5), 273(14), 230(20), 213(12), 163(16), 132(19), 65(28), 63(100).

1-(2-chloroethoxy)-4-vinylbenzene (3h)[4]



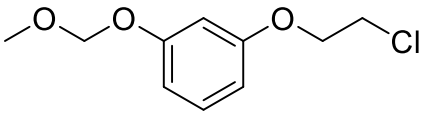
From 1-chloro-4-vinylbenzene (70.5 mg, 0.509 mmol). The starting material was added to the reaction mixture as a solution (in 500 µl *tert*-amyl alcohol) via syringe pump within 30 minutes. Reaction time: 24 h. Purification by column chromatography (25 g SiO_2, hex/EtOAc 100/1-20/1) gave 1-(2-chloroethoxy)-4-vinylbenzene (71.6 mg, 0.392 mmol, 77%) as white solid. **Mp**: 41.5-42.5 °C, $\mathbf{R_f}$ = 0.81 (hex/EtOAc 4/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 7.27 (td, *J*=9.6, 8.7, 2H), 6.80 (td, *J*=9.6, 8.7, 2H), 6.59 (dd, *J*=17.6, 10.9, 1H), 5.54 (dd, *J*=17.6, 1.0, 1H), 5.07 (dd, *J*=10.9, 1.0, 1H), 4.16 (t, *J*=5.9, 2H), 3.73 (t, *J*=5.9, 2H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 158.3, 136.4, 131.6, 127.8, 115.1, 112.4, 68.5, 42.2. **MS** (EI, 70 eV): m/z (%): 184(15), 182(45), 120(100), 91(42), 77(11), 65(25), 63(21). **IR**: 837, 1245, 1605, 2841, 2850, 2861, 2906, 2919, 2994 cm^{-1}.

1-(2-chloroethoxy)-3,5-dimethoxybenzene (3i)



From 1-chloro-3,5-dimethoxybenzene (85.6 mg, 0.496 mmol). Reaction temperature: 120 °C. Reaction time: 4 h. Purification by column chromatography (20 g SiO_2, hex/EtOAc 100/1-10/1) gave 1-(2-chloroethoxy)-3,5-dimethoxybenzene (72.7 mg, 0.336 mmol, 68%) as pale yellow oil. $\mathbf{R_f}$ = 0.44 (hex/EtOAc 9/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 6.14 – 6.08 (m, 3H), 4.19 (t, *J*=5.8, 2H), 3.81 (t, *J*=5.9, 2H), 3.77 (s, 6H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 162.0, 160.4, 94.0, 68.4, 55.7, 42.2. **MS** (EI, 70 eV): m/z (%): 218(13), 216(41), 181(7), 154(98), 126(100), 111(35), 96(19), 79(14), 69(29). **IR**: 820, 1066, 1152, 1195, 1206, 1428, 1447, 1454, 1461, 1478, 1601 cm^{-1}. **HRMS** calculated for $C_{10}H_{14}ClO_3$ $[M+H]^+$ 217.0631 found: 217.0626.

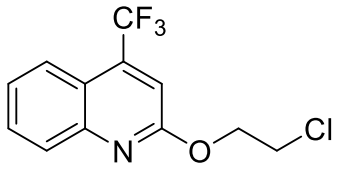
1-(2-chloroethoxy)-3-(methoxymethoxy)benzene (3j)



From 1-chloro-3-(methoxymethoxy)benzene (83.4 mg, 0.483 mmol). Reaction time: 18 h. Purification by column chromatography (20 g SiO_2, hex/EtOAc 100/1-10/1) gave 1-(2-chloroethoxy)-3-(methoxymethoxy)benzene (69.9 mg, 0.323 mmol, 67%) as a pale yellow oil. $\mathbf{R_f}$ = 0.37 (hex/EtOAc 9/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 7.34 – 7.07 (m, 1H), 6.79 – 6.38 (m, 3H), 5.17 (s, 2H), 4.22 (t, *J*=5.9, 2H), 3.81 (t, *J*=5.9, 2H), 3.48 (s, 3H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 159.7, 158.9, 130.4, 109.6, 108.4, 103.8, 94.8, 68.4, 56.4, 42.2. **MS** (EI, 70 eV): m/z (%): 218(33), 216(100), 186(10), 155(15), 124(61), 92(23), 81(17), 63(77). **IR**: 688, 768, 992, 1010, 1044, 1077, 1145, 1173, 1264, 1284, 1491, 1592, 1603 cm^{-1}. **HRMS** calculated for $C_{10}H_{14}ClO_3$ $[M+H]^+$ 217.0631 found: 217.0625.

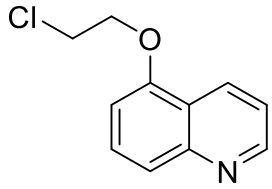
[4] C. Lee, H. K. Hall, *Macromolecules* **1989**, *22*, 21-25.

2-(2-chloroethoxy)-4-(trifluoromethyl)quinoline (3k)



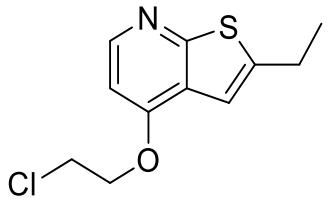
From 2-chloro-4-(trifluoromethyl)quinoline (116.5 mg, 0.503 mmol). Reaction time: 4 h. Purification by column chromatography (20 g SiO_2, hex/EtOAc 50/1-10/1) gave 2-(2-chloroethoxy)-4-(trifluoromethyl)quinoline (121.6 mg, 0.441 mmol, 88%) as white solid. **Mp**: 121-123 °C, $\mathbf{R_f}$ = 0.53 (hex/EtOAc 4/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 8.29 (dd, *J*=8.4, 1.5, 1H), 8.16 (d, *J*=8.5, 1H), 7.81 (ddd, *J*=8.5, 6.8, 1.6, 1H), 7.64 (ddd, *J*=8.1, 6.8, 1.2, 1H), 7.02 (s, 1H), 4.53 (t, *J*=5.5, 2H), 4.01 (t, *J*=5.5, 2H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 162.7, 149.28 (q, *J*=34.3), 148.6, 131.5, 130.0, 128.1, 122.3, 121.9, 121.84 (q, *J*=275.5), 97.04 (q, *J*=2.2), 69.0, 41.6. **^{19}F NMR** (235 MHz, $CDCl_3$) δ = -67.8. **MS** (EI, 70 eV): m/z (%): 277(20), 275(59), 256(8), 226(25), 213(98), 184(18), 165(11), 144(51), 134(21), 116(15), 101(18), 89(20), 75(17), 65(30), 63(100). **IR**: 720, 757, 777, 789, 846, 928, 990, 1096, 1118, 1135, 1169, 1193, 1240, 1255, 1284, 1368, 1411, 1594 cm^{-1}. **HRMS** calculated for $C_{12}H_{10}ClNOF_3$ $[M+H]^+$ 276.0403 found: 276.0407.

5-(2-chloroethoxy)quinoline (3l) [5]



From 5-chloroquinoline (82.0 mg, 0.501 mmol). Reaction time: 24 h. Purification by column chromatography (20 g SiO_2, hex/EtOAc 50/1-10/1) gave 5-(2-chloroethoxy)quinoline (195.4 mg, 0.410 mmol, 82%) as a yellow oil. $\mathbf{R_f}$ = 0.13 (hex/EtOAc 4/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 8.78 (dd, *J*=4.3, 1.7, 1H), 8.05 (dd, *J*= 9.0, 1.6, 2H), 7.50 – 7.31 (m, 2H), 7.07 (d, *J*=2.8, 1H), 4.34 (t, *J*=5.9, 2H), 3.88 (t, *J*=5.9, 2H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 156.7, 148.4, 144.6, 135.5, 131.3, 129.6, 122.8, 121.9, 106.8, 68.6, 42.1. **MS** (EI, 70 eV): m/z(%): 209(11), 207(36), 167(11), 145(100), 128(9), 116(37), 89(28), 63(23). **IR**: 671, 727, 762, 826, 1003, 1025, 1050, 1230 cm^{-1}.

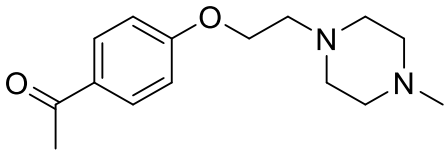
4-(2-chloroethoxy)-2-ethylthieno[2,3-b]pyridine (3m)



From 4-chloro-2-ethylthieno[2,3-b]pyridine (98.8 mg, 0.500 mmol). Reaction time: 24 h. Purification by column chromatography (25 g SiO_2, hex/EtOAc 4/1-1/1) gave 4-(2-chloroethoxy)-2-ethylthieno[2,3-b]pyridine (76.9 mg, 0.318 mmol, 64%) as a yellow oil. $\mathbf{R_f}$ = 0.17 (hex/EtOAc 4/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 8.35 (d, *J*=5.6, 1H), 7.10 (t, *J*=1.2, 1H), 6.67 (d, *J*=5.6, 1H), 4.42 (t, *J*=5.8, 2H), 3.91 (t, *J*=5.8, 2H), 2.94 (qd, *J*=7.5, 1.2, 2H), 1.39 (t, *J*=7.5, 3H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 162.4, 159.2, 147.5, 147.1, 124.9, 114.1, 101.9, 68.4, 41.7, 24.8, 15.6. **MS** (EI, 70 eV): m/z (%): 243(23), 241(65), 228(31), 226(85), 178(33), 164(100), 150(12), 135(15), 77(10), 65(14), 63(28). **IR**: 673, 809, 831, 1040, 1079, 1132, 1249, 1288, 1322, 1337, 1452, 1476, 1529, 1564, 1585 cm^{-1}. **HRMS** calculated for $C_{11}H_{13}NOSCl$ $[M+H]^+$ 242.0406 found: 242.0405.

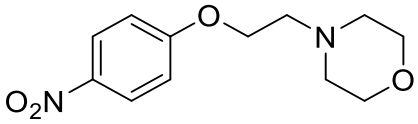
[5] Mewshaw, R. E.; Zhou, D.; Zhou, P.; Shi, X.; Hornby, G.; Spangler, T.; Scerni, R.; Smith, D.; Schechter, L. E.; Andree, T. H. *J. Med. Chem.* **2004**, *47*, 3823-3842.

1-(4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)ethan-1-one (4a)



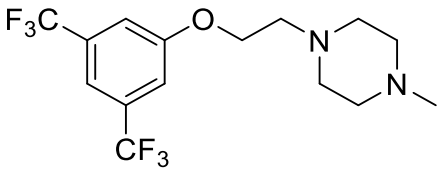
From 1-(4-chlorophenyl)ethan-1-one (76.7 mg, 0.496 mmol). Reaction time: 1h (first step) + 24h (second step). Purification by column chromatography (20 g SiO_2, DCM/MeOH 20/1-10/1) gave 1-(4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)ethan-1-one (93.3 mg, 0.356 mmol, 72%) as off-white solid. **Mp**: 70 °C, $\mathbf{R_f}$ = 0.33 (DCM/MeOH 5/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 7.90 (dt, *J*=9.0, 2.7, 1.9, 2H), 6.91 (dt, *J*=8.8, 2.7, 1.8, 2H), 4.14 (t, *J*=5.8, 2H), 2.82 (t, *J*=5.8, 2H), 2.75 – 2.57 (m, 4H), 2.55 – 2.41 (m, 4H), 2.29 (s, 3H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 197.1, 163.0, 130.9, 130.7, 114.6, 66.6, 57.3, 55.3, 53.8, 46.3, 26.7. **IR**: 798, 837, 958, 1010, 1152, 1171, 1255, 1275, 1305, 1359, 1575, 1599, 1672, 2809, 2921, 2932 cm^{-1}. **HRMS** calculated for $C_{15}H_{23}N_2O_2$ $[M+H]^+$ 263.1760 found: 263.1759.

4-(2-(4-nitrophenoxy)ethyl)morpholine (4b) [6]



From 1-chloro-4-nitrobenzene (78.9 mg, 0.500 mmol). Reaction time: 1h (first step) + 24h (second step). The second step was carried out in EtOH solvent (2 ml), with morpholine (0.75 mmol, 1.5 eq), NaI (0.5 mmol, 1eq.) and K_2CO_3 (1 mmol, 2 eq.). Purification by column chromatography (20 g SiO_2, DCM/MeOH 50/1-20/1) gave 4-(2-(4-nitrophenoxy)ethyl)morpholine (69.5 mg, 0.276 mmol, 55%) as a brown solid. **Mp**: 74 °C, $\mathbf{R_f}$ = 0.30 (DCM/MeOH 20/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 8.12 (dt, *J*=9.2, 3.3, 1.9, 2H), 6.90 (dt, *J*=9.2, 3.2, 2.0, 2H), 4.15 (t, *J*=5.6, 2H), 3.68 (t, *J*=4.6, 4H), 2.80 (t, *J*=5.6, 2H), 2.55 (t, *J*=4.6, 4H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 164.0, 142.0, 126.3, 114.9, 67.1, 66.9, 57.6, 54.4. **IR:** 753, 846, 859, 1113, 1174, 1260, 1299, 1340, 1501, 1512, 1594, 1607 cm^{-1}.

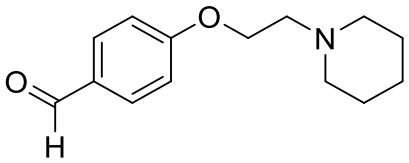
1-(2-(3,5-bis(trifluoromethyl)phenoxy)ethyl)-4-methylpiperazine (4c)



From 1-chloro-3,5-bis(trifluoromethyl)benzene (137.4 mg, 0.553 mmol). Reaction time: 1h (first step) + 22h (second step). Purification by column chromatography (20 g SiO_2, EtOAc/MeOH 20/1-5/1) gave 1-(2-(3,5-bis(trifluoromethyl)phenoxy)ethyl)-4-methylpiperazine (86.4 mg, 0.242 mmol, 44%) as a yellow oil. $\mathbf{R_f}$ = 0.21 (EtOAc/MeOH 5/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 7.38 (s, 1H), 7.26 (s, 2H), 4.10 (t, *J*=5.6, 2H), 2.78 (t, *J*=5.6, 2H), 2.65 – 2.48 (m, 4H), 2.48 – 2.31 (m, 4H), 2.23 (s, 3H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 159.7, 133.12 (q, *J*=33.3), 123.51 (q, *J*=272.7), 115.32 (q, *J*=3.5), 114.69 (dt, *J*=8.0, 4.2), 67.2, 57.2, 55.3, 53.9, 46.3. **^{19}F NMR** (235 MHz, $CDCl_3$) δ = -63.09. **IR**: 682, 703, 729, 871, 926, 969, 1014, 1036, 1126, 1169, 1277, 1355, 1368, 1378, 1461 cm^{-1}. **HRMS** calculated for $C_{15}H_{19}F_6N_2O$ $[M+H]^+$ 357.1402 found: 357.1401.

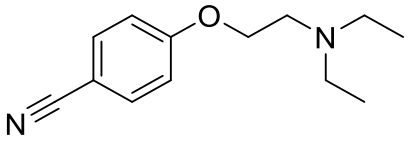
[6] Kaye, I. A.; Burlant, W. J.; Price, L. *J. Org. Chem.* **1951**, *16*, 1421-1426.

4-(2-(piperidin-1-yl)ethoxy)benzaldehyde (4d) [7]



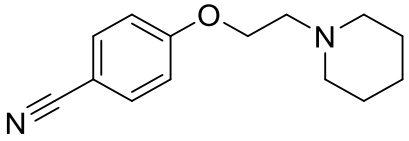
From 4-chlorobenzaldehyde (70.6 mg, 0.502 mmol). Reaction time: 1h (first step) + 22h (second step). Purification by column chromatography (20 g SiO_2, DCM/MeOH 50/1-25/1) gave 4-(2-(piperidin-1-yl)ethoxy)benzaldehyde (90.4 mg, 0.387 mmol, 77%) as a brown oil. $\mathbf{R_f}$ = 0.22 (DCM/MeOH 20/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 9.81 (s, 1H), 7.75 (d, *J*=8.7, 2H), 6.94 (d, *J*=8.7, 2H), 4.14 (t, *J*=5.9, 2H), 2.77 (t, *J*=5.9, 2H), 2.49 (t, *J*=5.4, 4H), 1.73 – 1.49 (m, 4H), 1.47 – 1.29 (m, 2H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 191.2, 164.1, 132.3, 130.3, 115.2, 66.6, 58.0, 55.4, 26.1, 24.4. **IR**: 811, 831, 856, 1033, 1111, 1133, 1156, 1215, 1253, 1309, 1510, 1577, 1599, 1687, 2929 cm^{-1}.

4-(2-(diethylamino)ethoxy)benzonitrile (4e) [8]



From 4-chlorobenzonitrile (69.5 mg, 0.505 mmol). Reaction time: 1h (first step) + 22h (second step). Purification by column chromatography (20 g SiO_2, DCM/MeOH 50/1-10/1) gave 4-(2-(diethylamino)ethoxy)benzonitrile (97.5 mg, 0.447 mmol, 88%) as a brownish oil. $\mathbf{R_f}$ = 0.38 (DCM/MeOH 10/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 7.56 (td, *J*=9.4, 2.0, 2H), 6.94 (td, *J*=9.4, 2.0, 2H), 4.09 (t, *J*=6.1, 2H), 2.89 (t, *J*=6.1, 2H), 2.65 (q, *J*=7.1, 4H), 1.07 (t, *J*=7.1, 6H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 162.5, 134.3, 119.6, 115.6, 104.3, 67.4, 51.9, 48.3, 12.1 **IR**: 707, 835, 1020, 1038, 1171, 1258, 1301, 1508, 1605, 2226, 2932, 2971 cm^{-1}.

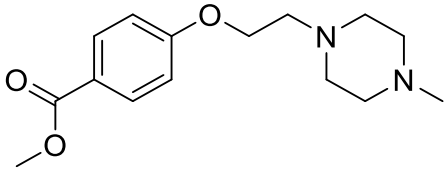
4-(2-(piperidin-1-yl)ethoxy)benzonitrile (4f) [9]



From 4-chlorobenzonitrile (68.8 mg, 0.500 mmol). Reaction time: 1h (first step) + 22h (second step). Purification by column chromatography (20 g SiO_2, DCM/MeOH 20/1-10/1) gave 4-(2-(piperidin-1-yl)ethoxy)benzonitrile (98.9 mg, 0.429 mmol, 86%) as a brown oil. $\mathbf{R_f}$ = 0.27 (DCM/MeOH 5/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 7.50 (td, *J*=9.0, 2.2, 2H), 6.89 (td, *J*=8.9, 2.0, 2H), 4.11 (t, *J*=5.9, 2H), 2.76 (t, *J*=5.9, 2H), 2.49 (t, *J*=5.4, 4H), 1.68 – 1.48 (m, 4H), 1.46 – 1.27 (m, 2H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 162.4, 134.3, 119.6, 115.7, 104.4, 66.5, 57.8, 55.4, 26.0, 24.3. **IR**: 837, 1033, 1173, 1258, 1303, 1454, 1508, 1605, 2226, 2936 cm^{-1}.

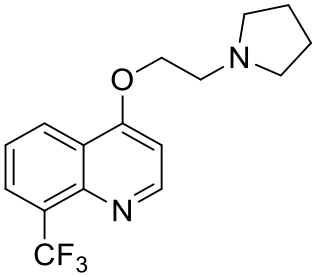
[7] Patel, M. R.; Bhatt, A.; Steffen, J. D.; Chergui, A.; Murai, J.; Pommier, Y.; Pascal, J. M.; Trombetta, L. D.; Fronczek, F. R.; Talele, T. T. *J. Med. Chem.* **2014**, *57*, 5579-5601.
[8] Campbell, L. J.; Borges, L. F.; Heldrich, F. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2627-2630.
[9] Marquet, J.; Cayon, E.; Martin, X.; Casado, F.; Gallardo, I.; Moreno, M.; Lluch, J. M. *J. Org. Chem.* **1995**, *60*, 3814-3825.

4-(2-(4-methylpiperazin-1-yl)ethoxy)benzoate (4g)



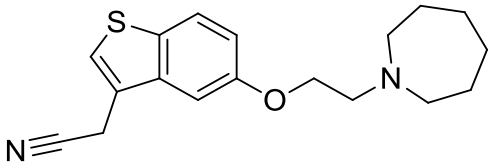
From methyl 4-chlorobenzoate (85.0 mg, 0.498 mmol). Reaction time: 5h (first step) + 21h (second step). Purification by column chromatography (20 g SiO_2, DCM/MeOH 20/1-10/1) gave methyl 4-(2-(4-methylpiperazin-1-yl)ethoxy)benzoate (98.3 mg, 0.353 mmol, 71%) as a brown oil. $\mathbf{R_f}$ = 0.35 (DCM/MeOH 5/1). **^{1}H NMR** (250 MHz, DMSO-d_6) δ = 7.88 (dt, *J*=9.0, 2.8, 2.0, 2H), 7.02 (dt, *J*=8.9, 2.7, 2.0, 2H), 4.12 (t, *J*=5.8, 2H), 3.79 (s, 3H), 2.67 (t, *J*=5.8, 2H), 2.57 – 2.41 (m, 4H), 2.38 – 2.23 (m, 4H), 2.14 (s, 3H). **^{13}C NMR** (63 MHz, DMSO-d_6) δ = 166.2, 162.7, 131.5, 122.1, 114.8, 66.2, 56.7, 55.0, 53.2, 52.1, 46.0. **IR**: 697, 772, 800, 850, 1010, 1105, 1169, 1253, 1283, 1316, 1435, 1512, 1605, 1711 cm^{-1}. **HRMS** calculated for $C_{15}H_{23}N_2O_3$ $[M+H]^+$ 279.1709 found: 279.1700.

4-(2-(pyrrolidin-1-yl)ethoxy)-8-(trifluoromethyl)quinoline (4h)



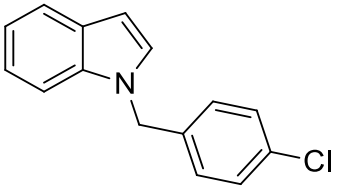
From 4-chloro-8-(trifluoromethyl)quinoline (114.4 mg, 0.494 mmol). Reaction time: 1h (first step) + 4h (second step). Purification by column chromatography (20 g SiO_2, DCM/MeOH 50/1-10/1) gave 4-(2-(pyrrolidin-1-yl)ethoxy)-8-(trifluoromethyl)quinoline (113.3 mg, 0.365 mmol, 74%) as a pale brown oil. $\mathbf{R_f}$ = 0.28 (DCM/MeOH 10/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 8.74 (d, *J*=5.2, 1H), 8.25 (d, *J*=8.4, 1H), 7.90 (d, *J*=7.3, 1H), 7.39 (dd, *J*=7.9, 1H), 6.71 (d, *J*=5.3, 1H), 4.39 (t, *J*=5.4, 2H), 3.15 (t, *J*=5.4, 2H), 2.95 – 2.51 (m, 4H), 2.02 – 1.58 (m, 4H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 161.0, 152.7, 146.1, 128.75 (q, *J*=5.7), 127.74 (q, *J*=29.5), 126.6, 124.8, 124.44 (q, *J*=263.2), 122.2, 102.1, 66.5, 55.2, 54.4, 23.8. **^{19}F NMR** (235 MHz, $CDCl_3$) δ = -60.25. **IR**: 729, 768, 816, 1008, 1025, 1081, 1133, 1279, 1299, 1512, 1586, 1594 cm^{-1}. **HRMS** calculated for $C_{16}H_{18}N_2OF_3$ $[M+H]^+$ 311.1371 found: 311.1364.

2-(5-(2-(azepan-1-yl)ethoxy)benzo[b]thiophen-3-yl)acetonitrile (4i)



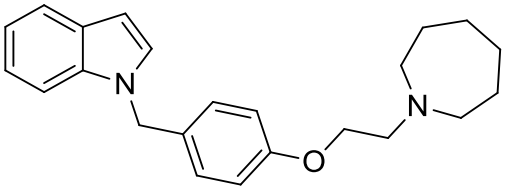
From 2-(5-chlorobenzo[b]thiophen-3-yl)acetonitrile (102.4 mg, 0.493 mmol), with Pd2dba(4.6 mg, 1 mol%) and 2-Di(tert-butyl)phosphino-2′,4′,6′-triisopropyl-3-methoxy-6-methylbiphenyl (RockPhos; 4.7 mg, 2 mol%). Reaction time: 22h (first step) + 4h (second step). Purification by column chromatography (20 g SiO_2, DCM/MeOH 100/1-20/1) gave 2-(5-(2-(azepan-1-yl)ethoxy)benzo[b]thiophen-3-yl)acetonitrile (37.4 mg, 0.119 mmol, 24%) as yellow oil, and 68.2 mg (0.329 mmol) starting material was regained. Yield calculated based upon consumed starting material is 72%. $\mathbf{R_f}$ = 0.40 (DCM/MeOH 10/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 7.74 (d, *J*=8.8, 1H), 7.49 (s, 1H), 7.16 (d, *J*=2.4, 1H), 7.06 (dd, *J*=8.9, 2.4, 1H), 4.34 (t, *J*=5.7, 2H), 3.88 (s, 2H), 3.19 (t, *J*=5.7, 2H), 3.04 (t, *J*=5.4, 4H), 1.93 – 1.74 (m, 4H), 1.74 – 1.53 (m, 4H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 156.8, 138.5, 133.6, 126.7, 124.3, 123.9, 117.3, 115.8, 104.8, 66.0, 56.5, 56.0, 27.4, 26.4, 18.2. **IR**: 1225, 1443, 1601, 2852, 2899, 2927 2955 cm^{-1}. **HRMS** calculated for $C_{18}H_{23}N_2OS$ $[M+H]^+$ 315.1531 found: 315.1528.

1-(4-chlorobenzyl)-1*H*-indole (5a)[10]



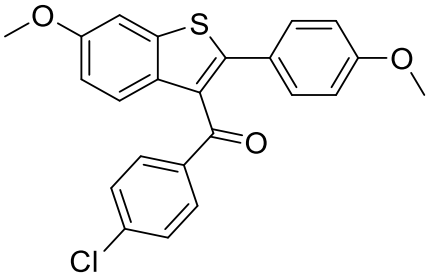
The starting material was prepared from indole and 1-(bromomethyl)-4-chlorobenzene, following a literature example.[11] In a 50 ml round bottom flask indole (117.2 mg, 1 mmol), was solved in DMSO (10 ml). KOH (224 mg, 4 mmol) was added and the mixture was stirred at RT for 30 minutes. 1-(bromomethyl)-4-chlorobenzene (215.8 mg, 1.05 mmol) was added, and the reaction was stirred for 16 hours at RT. Then, 20 ml water was added, the mixture was extracted with EtOAc (2X20 ml), the organic layers were concentrated under reduced pressure, to give the 1-(4-chlorobenzyl)-1*H*-indole (204.5 mg, 0.846 mmol, 85%) as green solid. $\mathbf{R_f}$ = 0.49 (Hex/EtOAc 4/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 7.57 (d, *J*=6.9, 1H), 7.27 – 6.98 (m, 6H), 6.92 (d, *J*=8.1, 2H), 6.47 (d, *J*=3.2, 1H), 5.17 (s, 2H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 136.6, 136.5, 133.8, 129.3, 129.2, 128.5, 128.5, 122.3, 121.5, 120.1, 110.0, 102.4, 49.9.

1-(4-(2-(azepan-1-yl)ethoxy)benzyl)-1H-indole (5b)



The coupling reaction was started from 1-(4-chlorobenzyl)-1*H*-indole **5a** (120.9 mg, 0.500 mmol). Reaction time: 4h (first step) + 24h (second step). Purification by column chromatography (20 g SiO_2, DCM/MeOH 100/1-15/1) gave 1-(4-(2-(azepan-1-yl)ethoxy)benzyl)-1H-indole (121.7 mg, 0.349 mmol, 70%) as brown oil. $\mathbf{R_f}$ = 0.32 (DCM/MeOH 10/1). **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 7.71 (d, *J*=7.2, 1H), 7.35 (d, *J*=7.9, 1H), 7.28 – 6.99 (m, 5H), 6.88 (d, *J*=8.6, 2H), 6.60 (d, *J*=3.2, 1H), 5.26 (s, 2H), 4.07 (t, *J*=6.2, 2H), 2.99 (t, *J*=6.2, 2H), 2.82 (t, *J*=5.2, 4H), 1.78 – 1.55 (m, 8H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 158.8, 136.7, 129.9, 129.2, 128.6, 128.5, 122.0, 121.4, 119.9, 115.2, 110.2, 101.9, 66.9, 56.7, 56.3, 50.0, 28.3, 27.5. **IR**: 716, 738, 762, 1012, 1031, 1174, 1245, 1305, 1316, 1443, 1463, 1512, 1612, 2919 cm^{-1}. **HRMS** calculated for $C_{23}H_{29}N_2O$ $[M+H]^+$ 349.2280 found: 349.2270.

(4-chlorophenyl)(6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)methanone (6b)

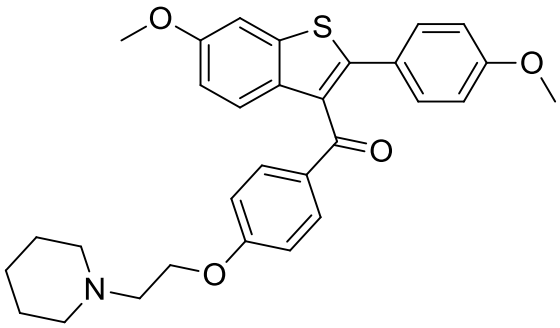


To a 50 ml round bottom flask 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (270 mg, 1 mmol) was added, and dissolved in 10 ml DCM. While stirring at RT, 4-chlorobenzoyl chloride (0.192 ml, 1.5 mmol), and $AlCl_3$ (800 mg, 6 mmol) in small portions were added. The mixture was heated to reflux for 2 hours, then poured onto

[10] H. Mao, R. Xu, J. Wan, Z. Jiang, C. Sun, Y. Pan *Chem. Eur. J.* **2010**, *16*, 13352-13355.
[11] Zs. Gonda, Sz. Kovács, Cs. Wéber, T. Gáti, A. Mészáros, A. Kotschy, Z. Novák, *Org. Lett.* **2014**, *16*, 4268-4271

15 g crushed ice. The aqueous phase was washed with DCM (15 ml), then the combined organic phases were washed with 1M NaOH (10 ml) and brine (10 ml). The organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (Hex/EtOAc 50/1-15/1) to give(4-chlorophenyl)(6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)methanone as a yellow solid (217.6 mg, 0.532 mmol, 53%). **Mp**: 53 °C $\mathbf{R_f}$ = 0.52 (Hex/EtOAc 4/1). **^{1}H NMR** (250 MHz, DMSO-d_6) δ = 7.61 (dt, *J*=8.6, 2.4, 1.9, 2H), 7.55 (d, *J*=8.9, 1H), 7.24 (d, *J*=2.4, 1H), 7.20 (d, *J*=8.8, 2H), 7.14 (d, *J*=8.6, 2H), 6.92 (dd, *J*=8.9, 2.4, 1H), 6.66 (dt, *J*=8.8, 2.8, 2.0, 2H), 3.81 (s, 3H), 3.67 (s, 3H). **^{13}C NMR** (63 MHz, DMSO-d_6) δ = 193.4, 160.4, 158.1, 145.0, 140.5, 139.8, 136.2, 134.0, 131.6, 130.9, 130.0, 129.0, 126.1, 124.5, 115.4, 114.5, 104.8, 56.0, 55.7. **HRMS** calculated for $C_{23}H_{18}N_2ClO_3S$ $[M+H]^+$ 409.0665 found: 409.0667.

(6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(piperidin-1-yl)ethoxy)phenyl)methanone (6c) [12]

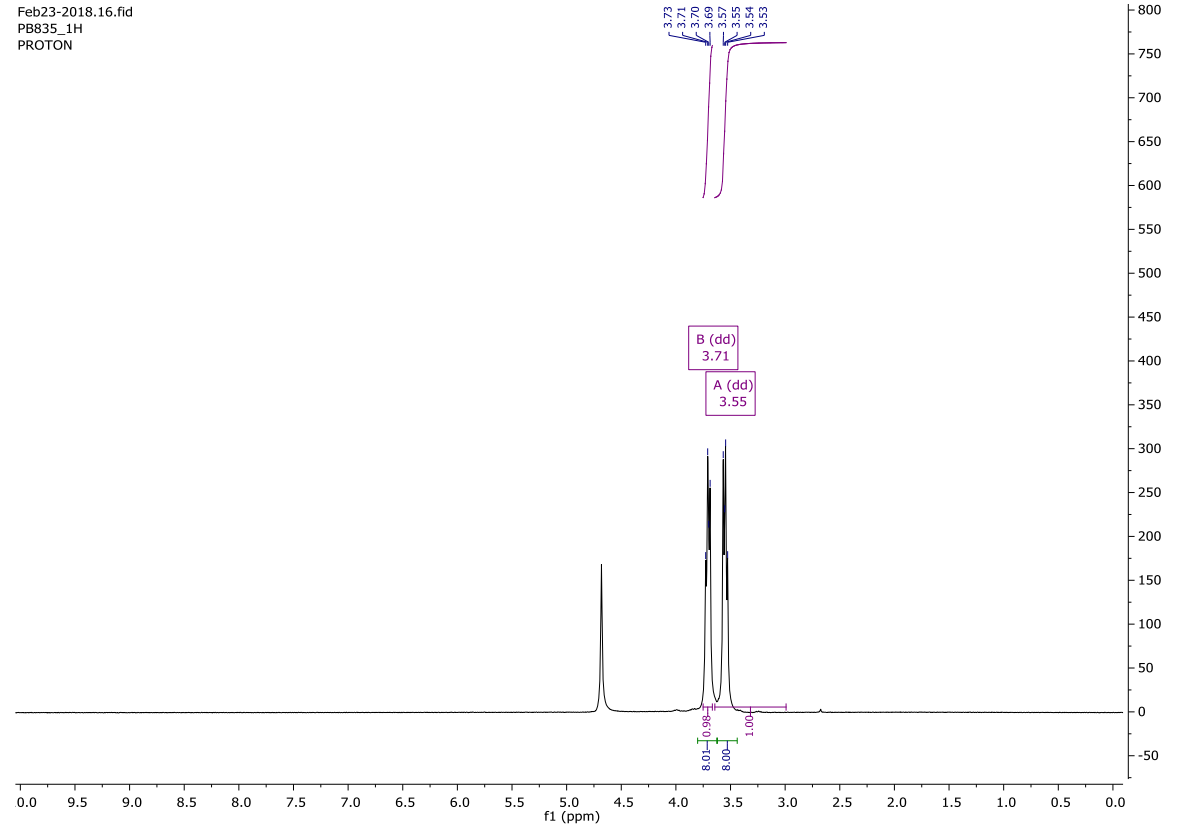


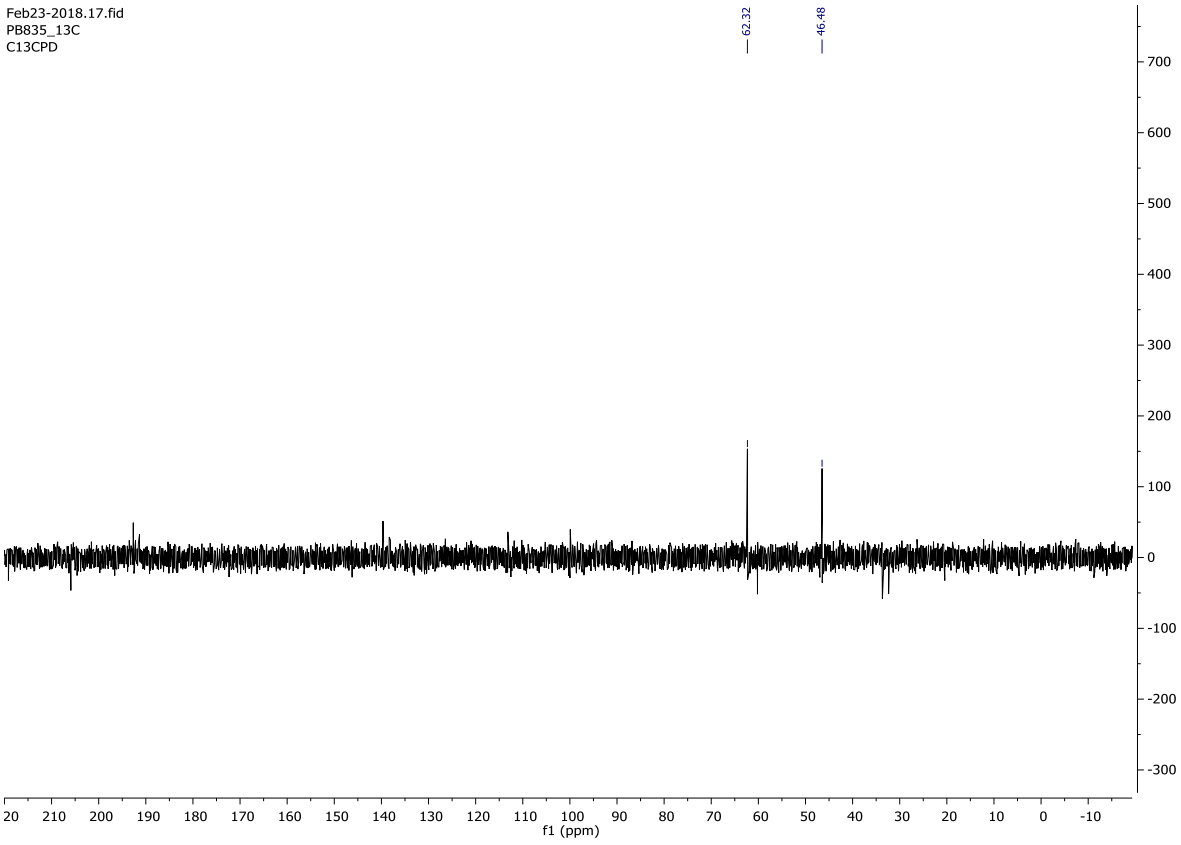
Prepared from (4-chlorophenyl)(6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)methanone (140.7 mg, 0.345 mmol) using general procedure. Reaction time: 1h (first step) + 4h (second step). Purification by column chromatography (20 g SiO_2, EtOAc/MeOH 20/1) gave (6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(piperidin-1-yl)ethoxy)phenyl)methanone (172.7 mg, 0.344 mmol, 99%) as brown oil. $\mathbf{R_f}$ = 0.25 (EtOAc/MeOH 5/1). **^{1}H NMR** (250 MHz, $CDCl_3$) 7.69 (d, *J*=8.8, 2H), 7.44 (d, *J*=8.9, 1H), 7.33 – 7.13 (m, 3H), 6.87 (dd, *J*=8.9, 2.4, 1H), 6.68 (dd, *J*=8.8, 2.0, 4H), 4.02 (t, *J*=5.9, 2H), 3.80 (s, 3H), 3.66 (s, 3H), 2.68 (t, *J*=5.9, 2H), 2.43 (t, *J*=5.3, 4H), 1.53 (dq, *J*=10.8, 5.1, 4H), 1.37 (q, *J*=5.9, 2H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 193.6, 163.3, 160.1, 158.0, 142.8, 140.4, 134.3, 132.7, 130.9, 130.7, 130.6, 126.3, 124.4, 115.2, 114.6, 114.4, 104.8, 66.4, 57.9, 56.0, 55.6, 55.4, 26.1, 24.4.

[12] Jones, C. D.; Jevnikar, M. G.; Pike, A. J.; Peters, M. K.; Black, L. J.; Thompson, A. R.; Falcone, J. F.; Clemens, J. A. *J. Med. Chem.* **1984**, *27*, 1057-1066.

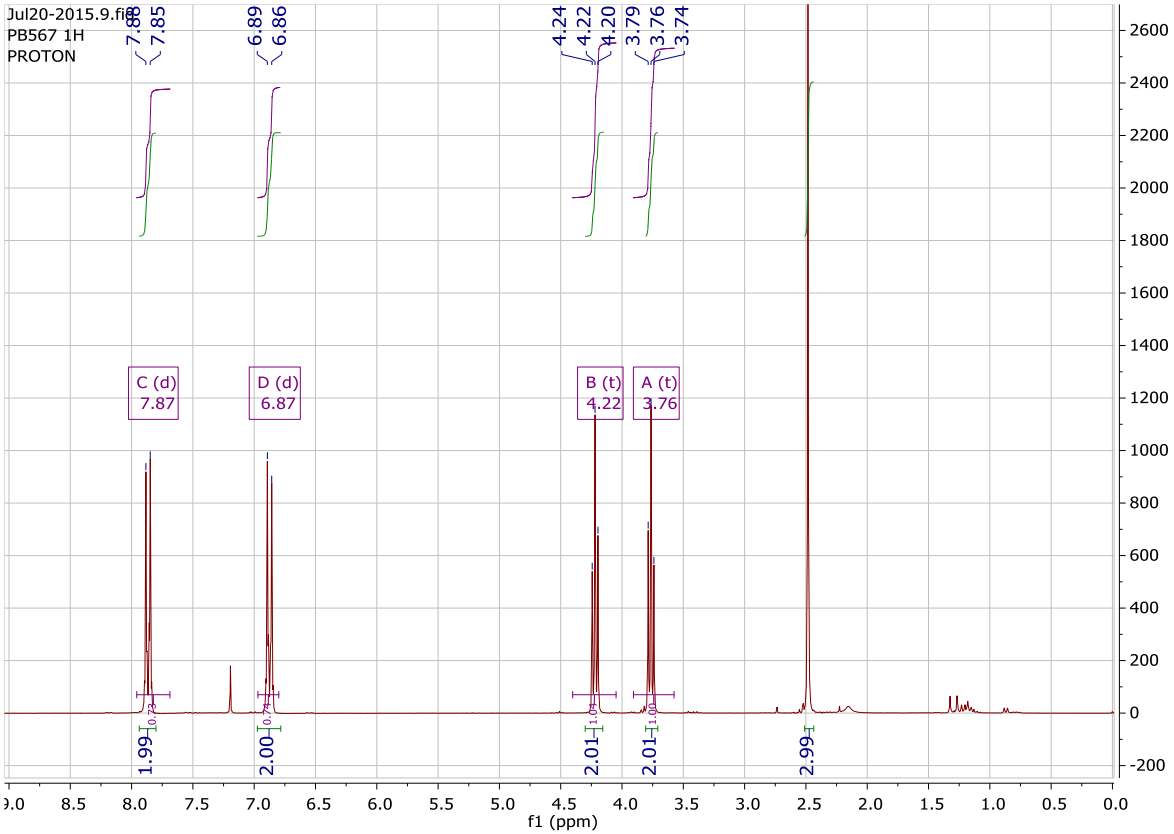
S5 - Experimental spectra

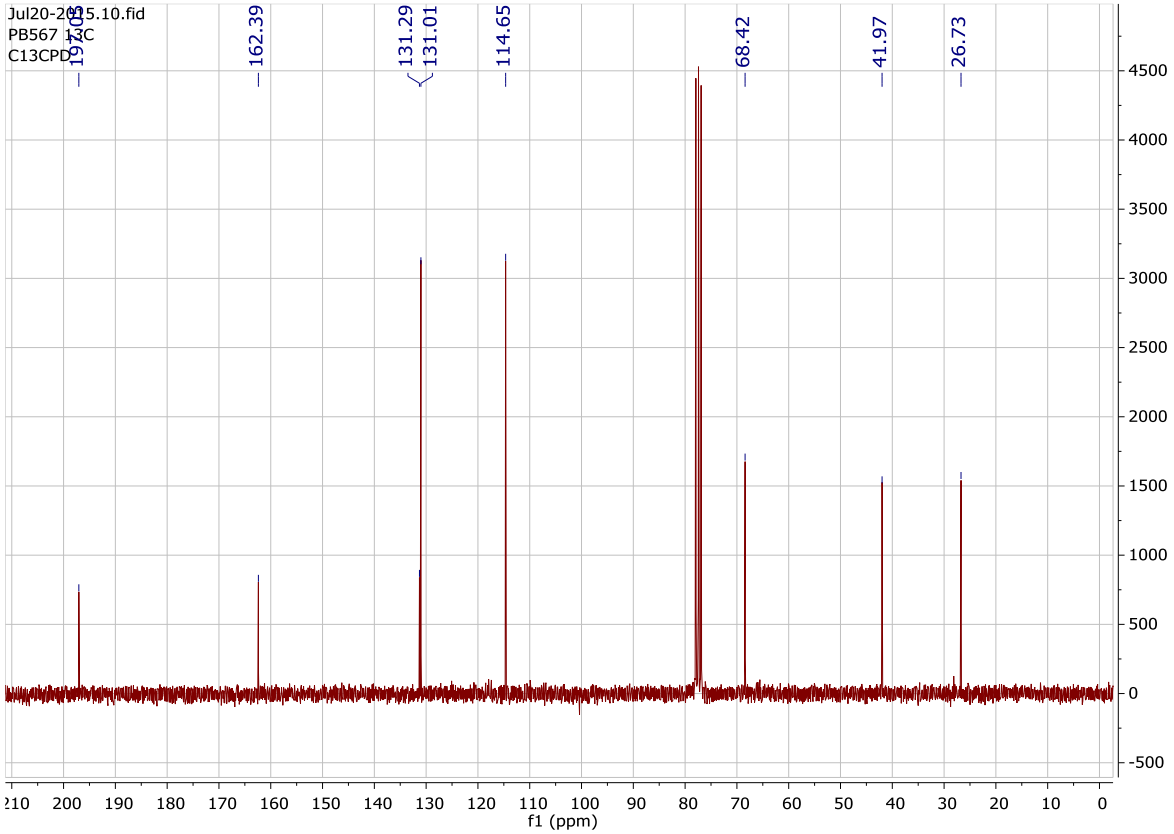
Sodium tetrakis(2-chloroethoxy)-borate (2a)



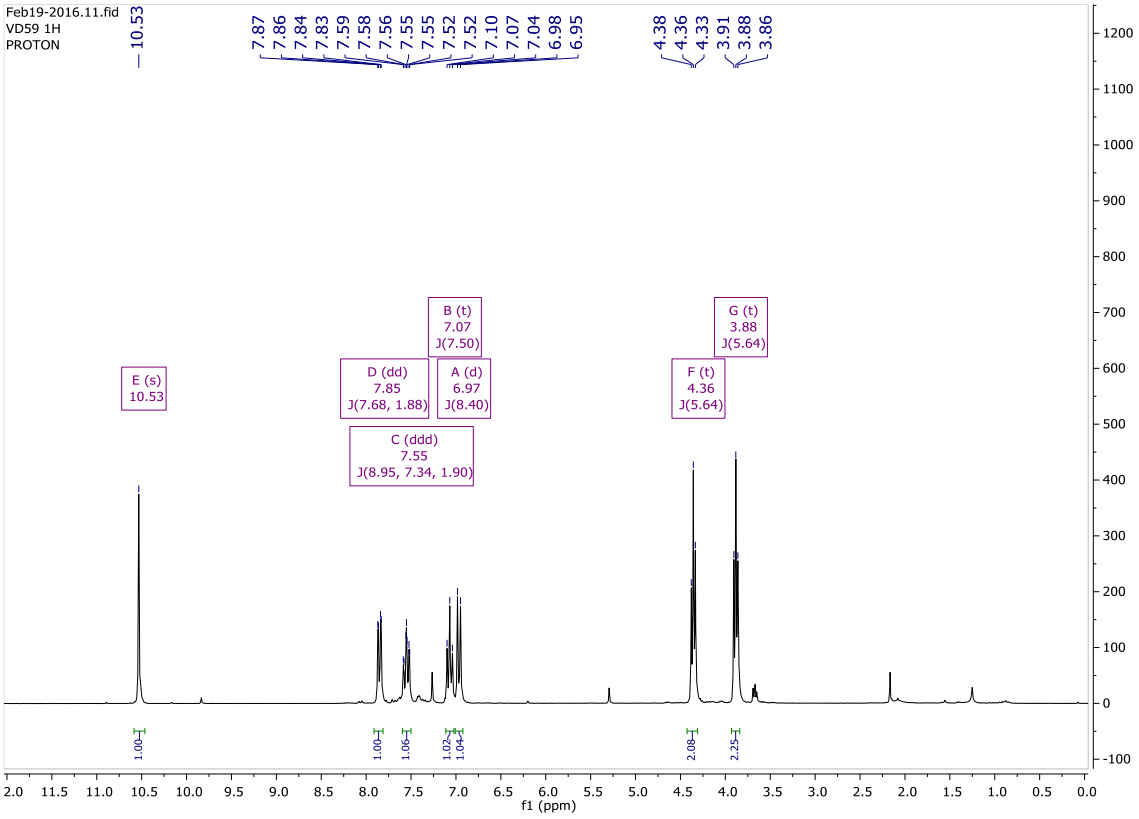


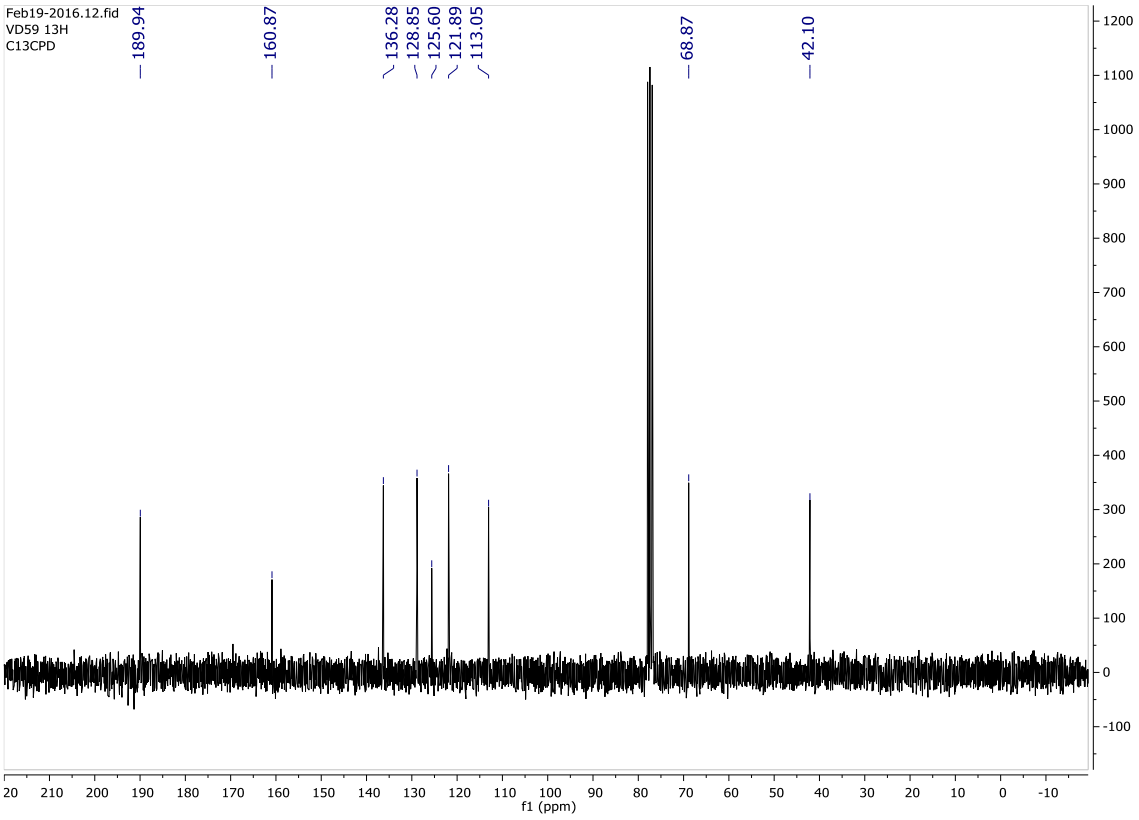
1-(4-(2-chloroethoxy)phenyl)ethan-1-one (3a)



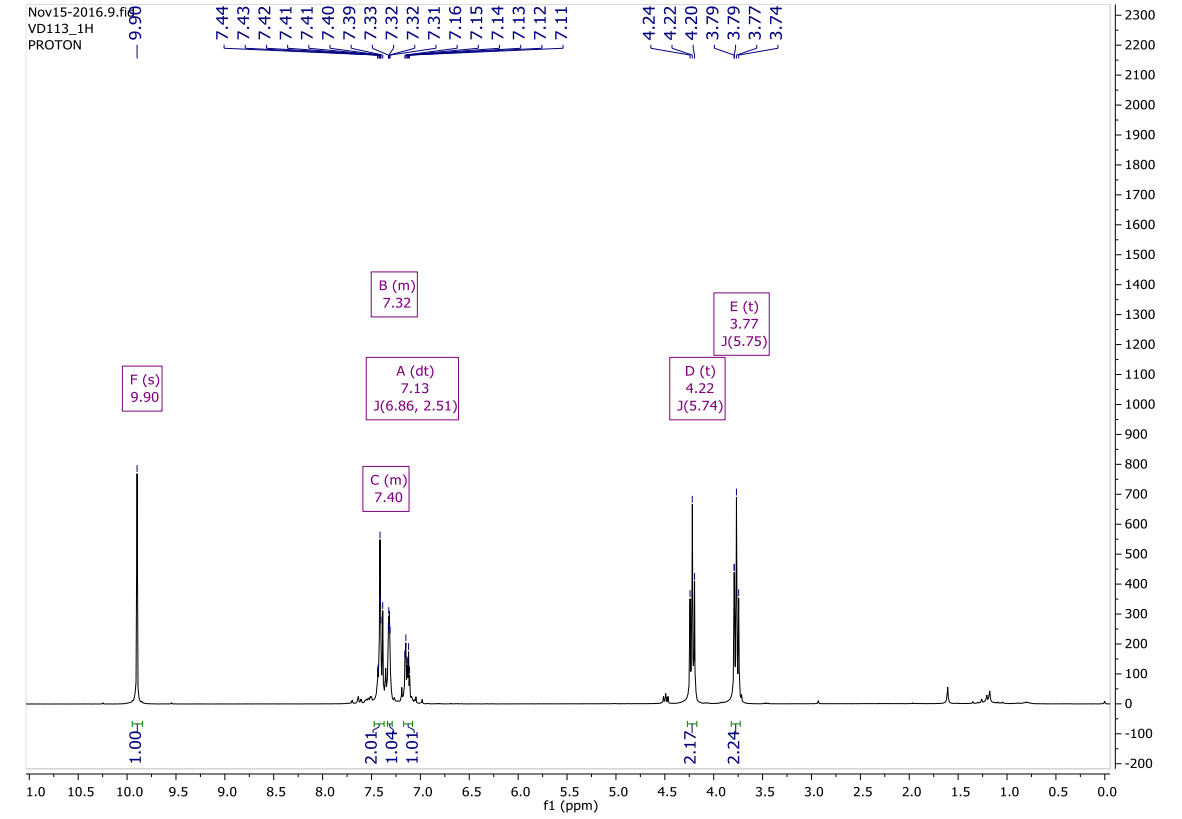


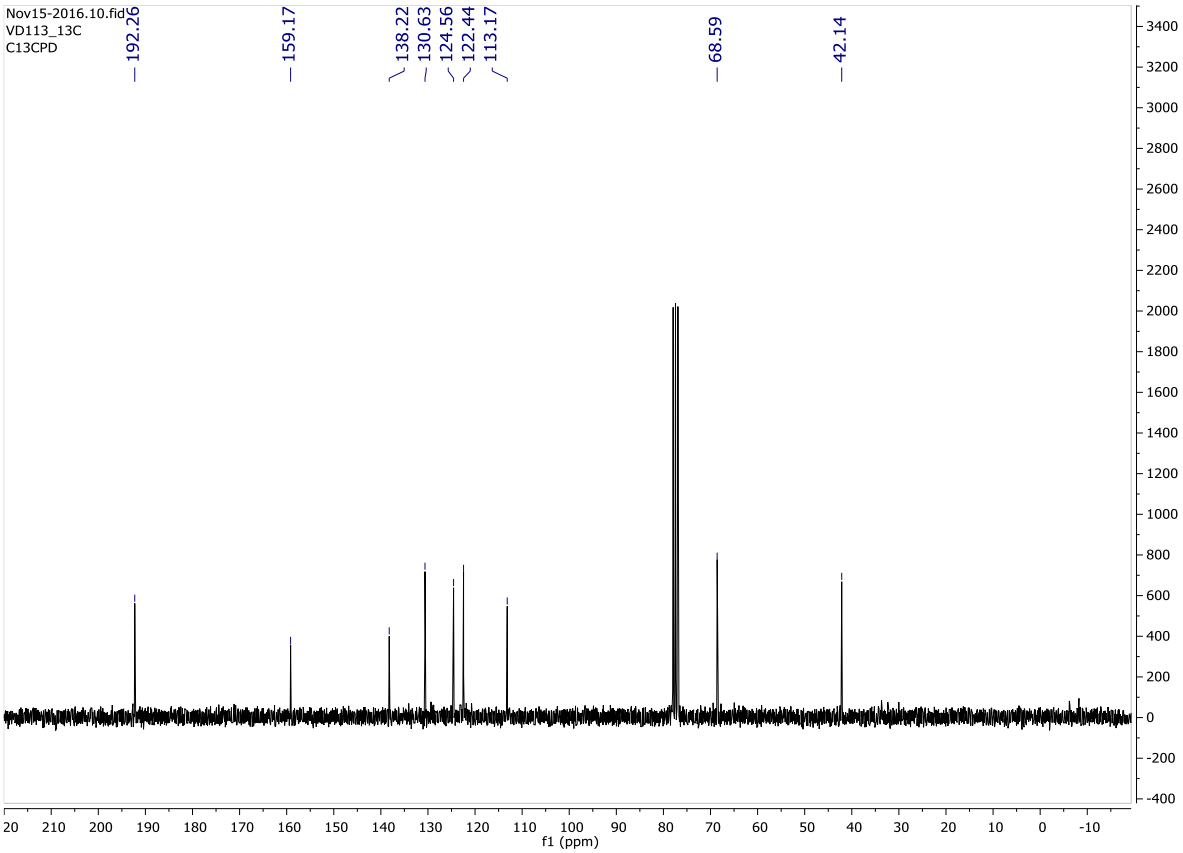
2-(2-chloroethoxy)benzaldehyde (3b)



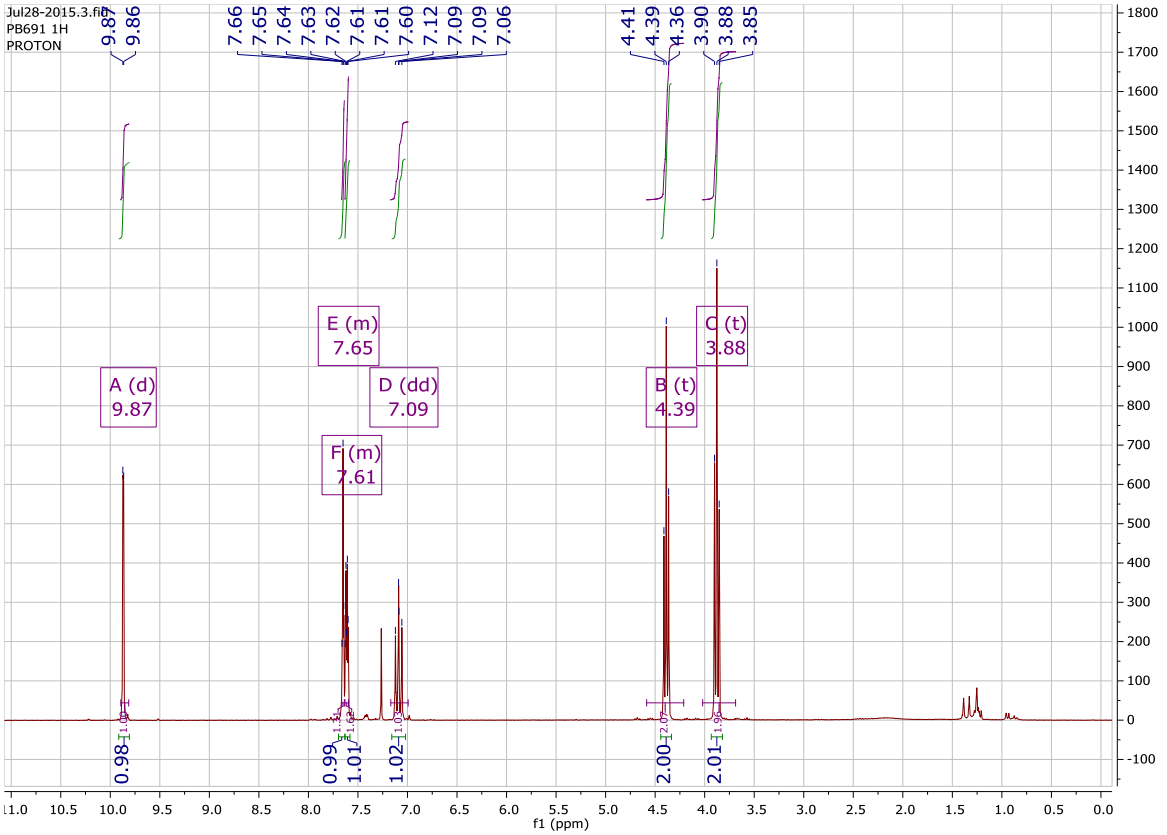


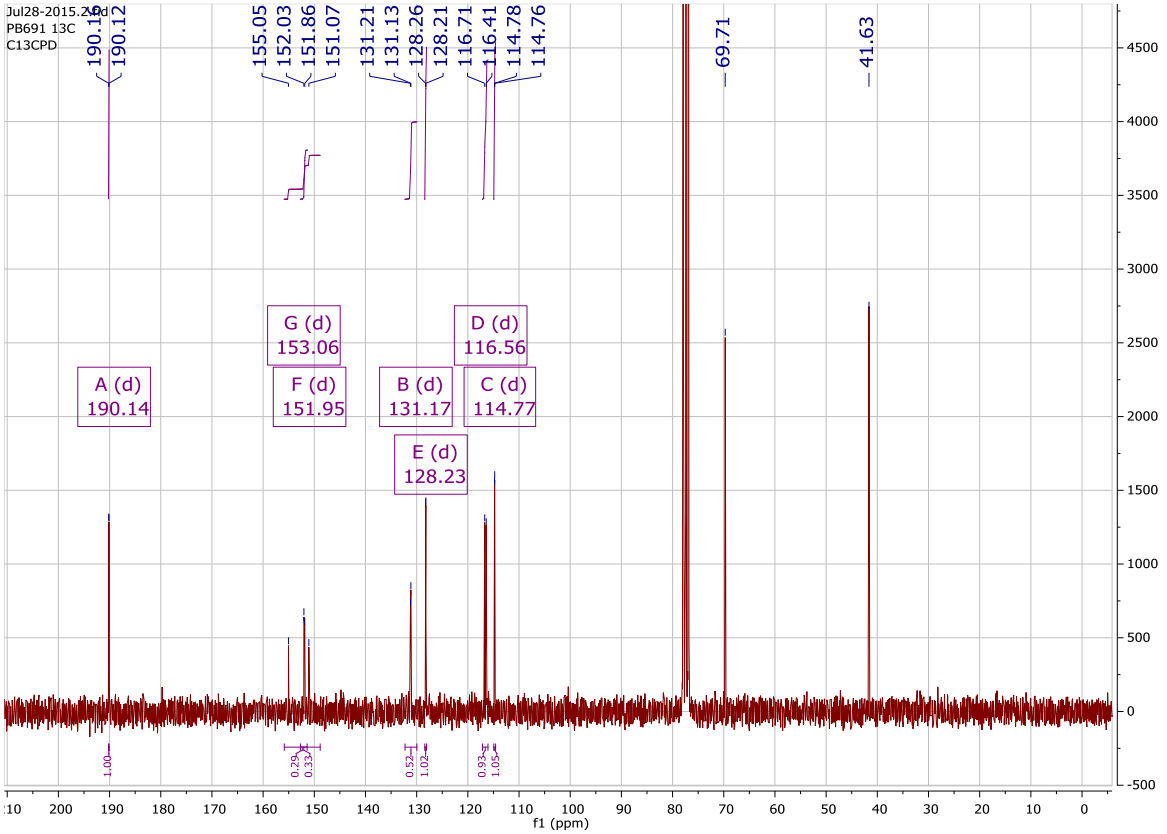
3-(2-chloroethoxy)benzaldehyde (3c)

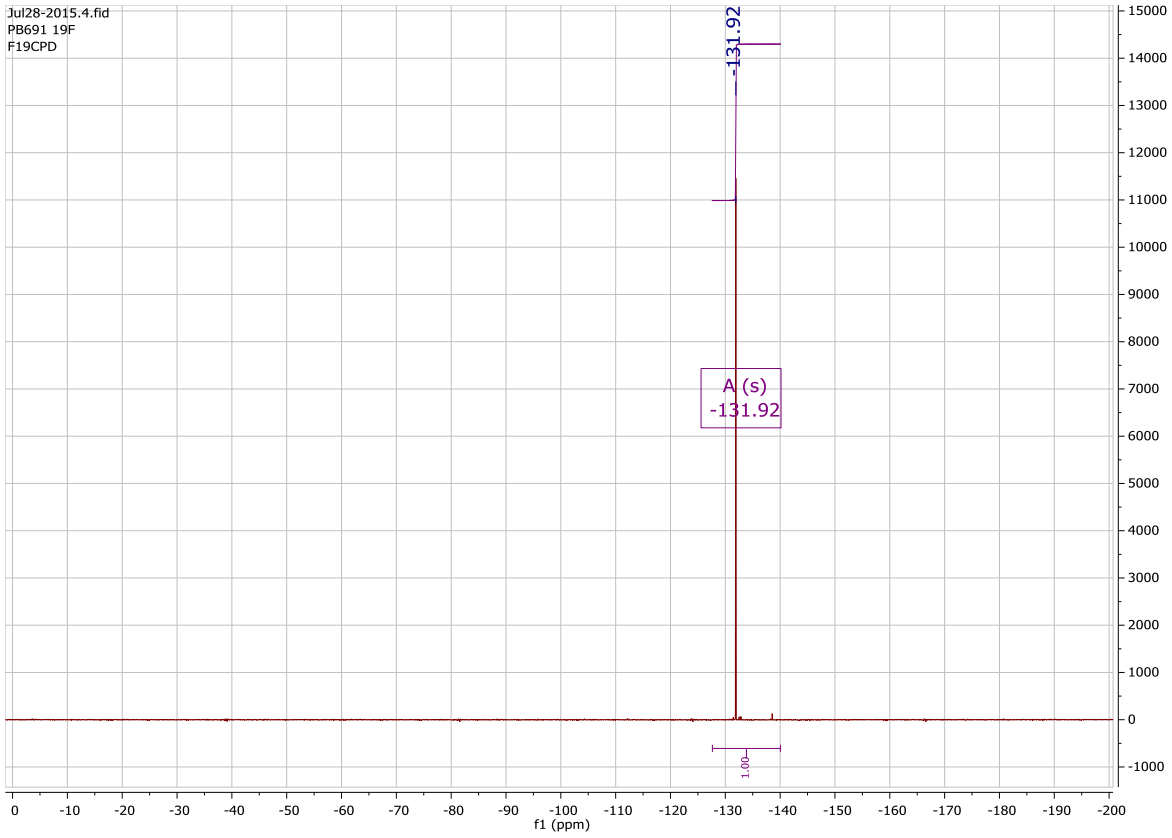




4-(2-chloroethoxy)-2-fluorobenzaldehyde (3d)



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A (s)
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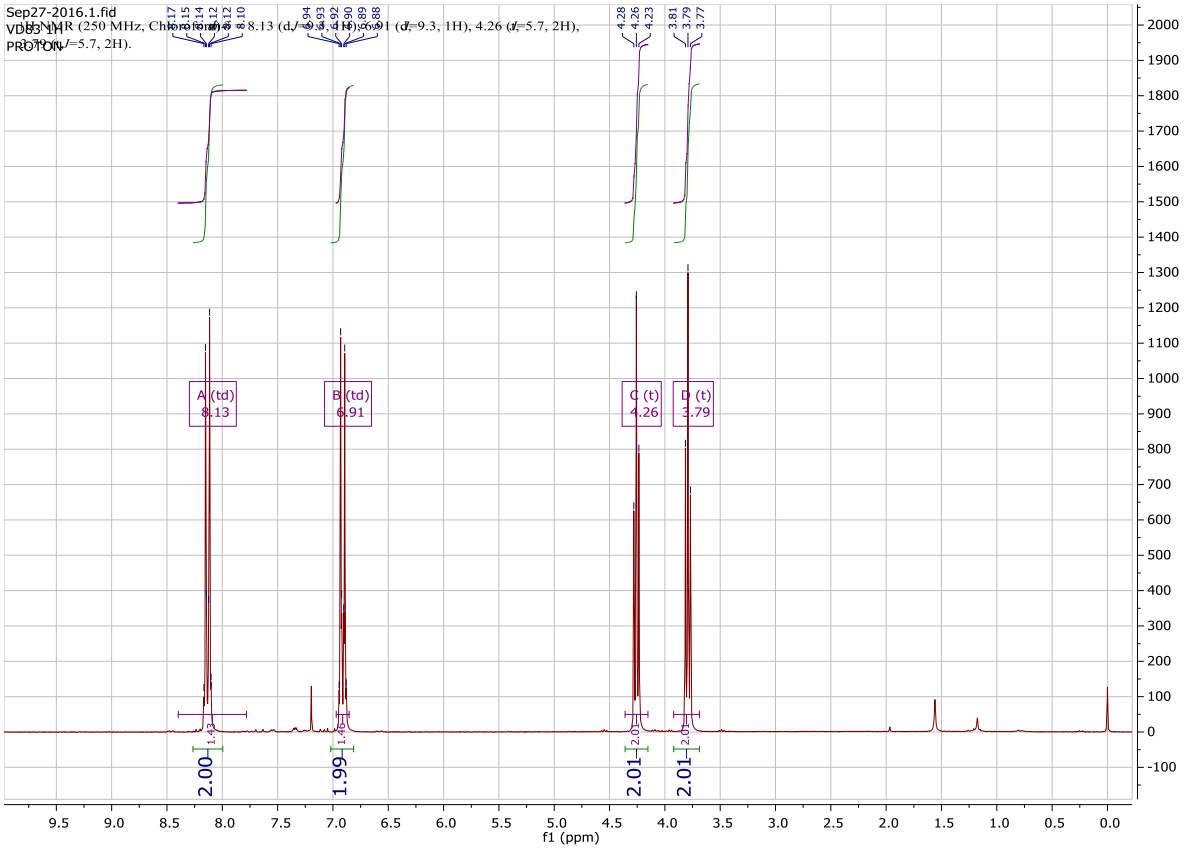
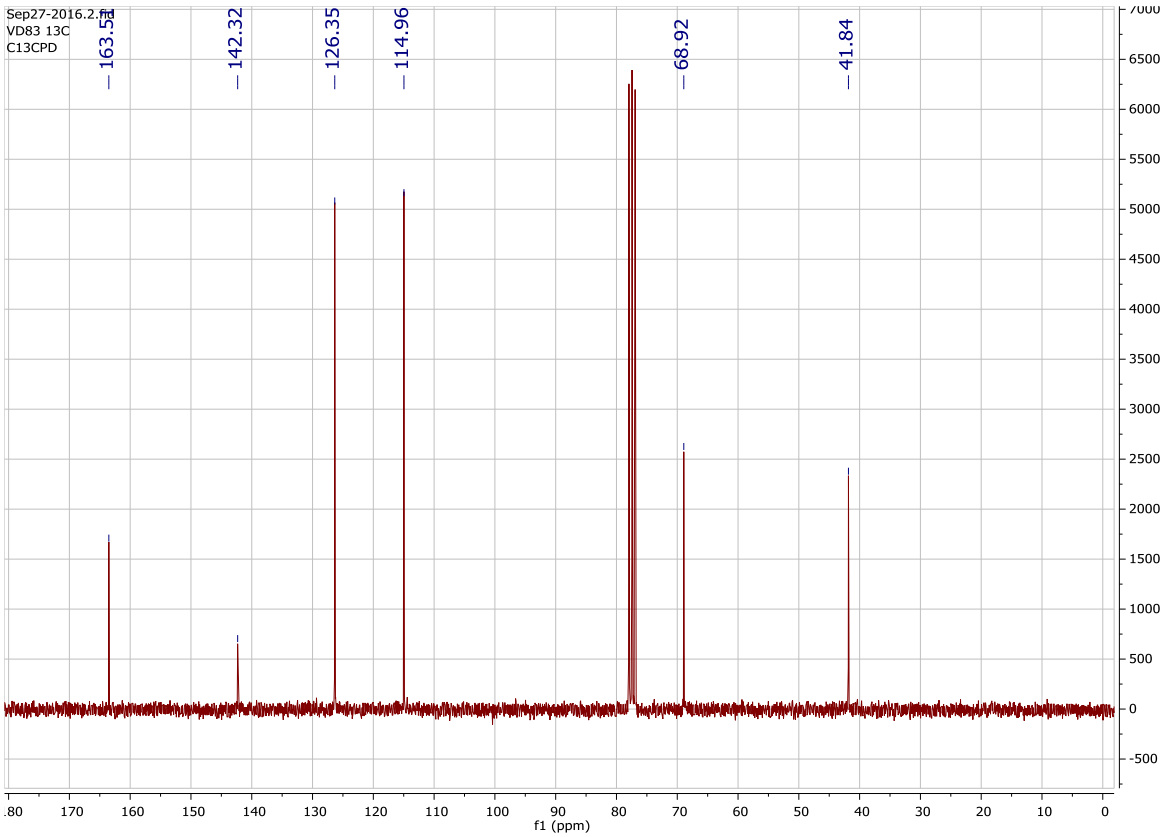
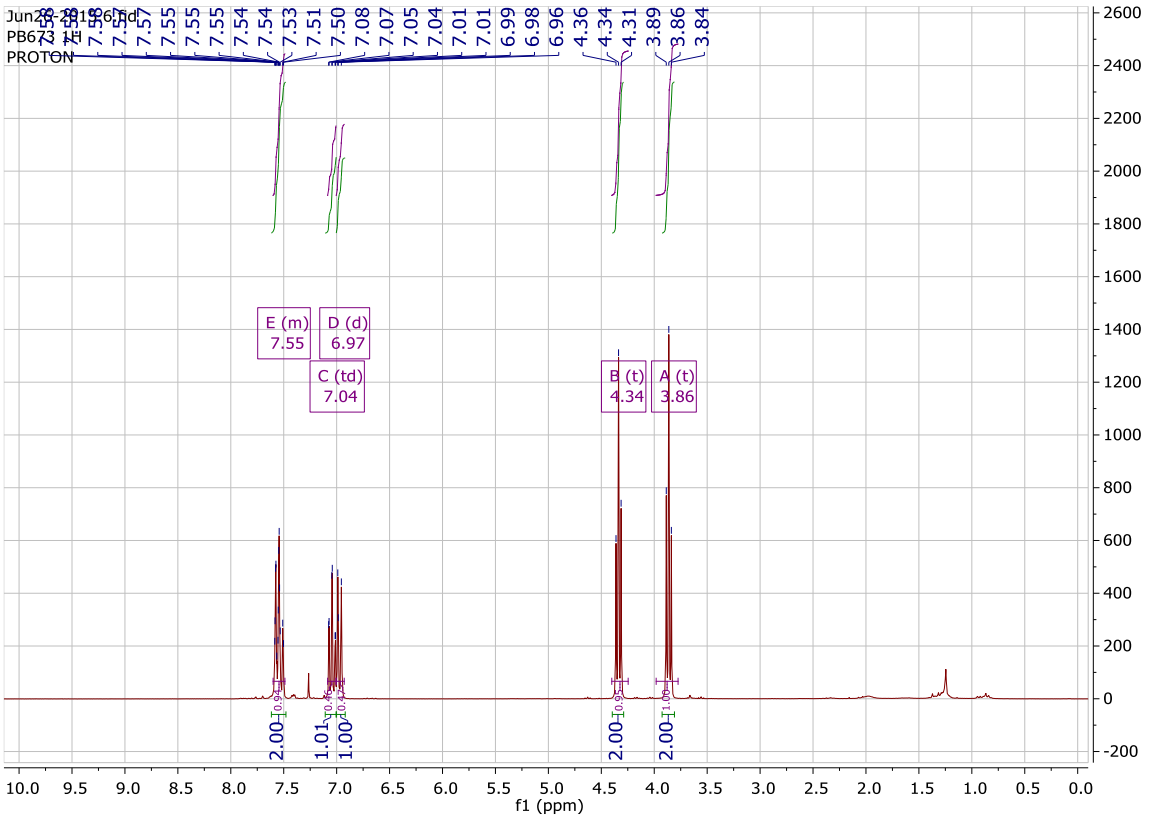
1.00
f1 (ppm)

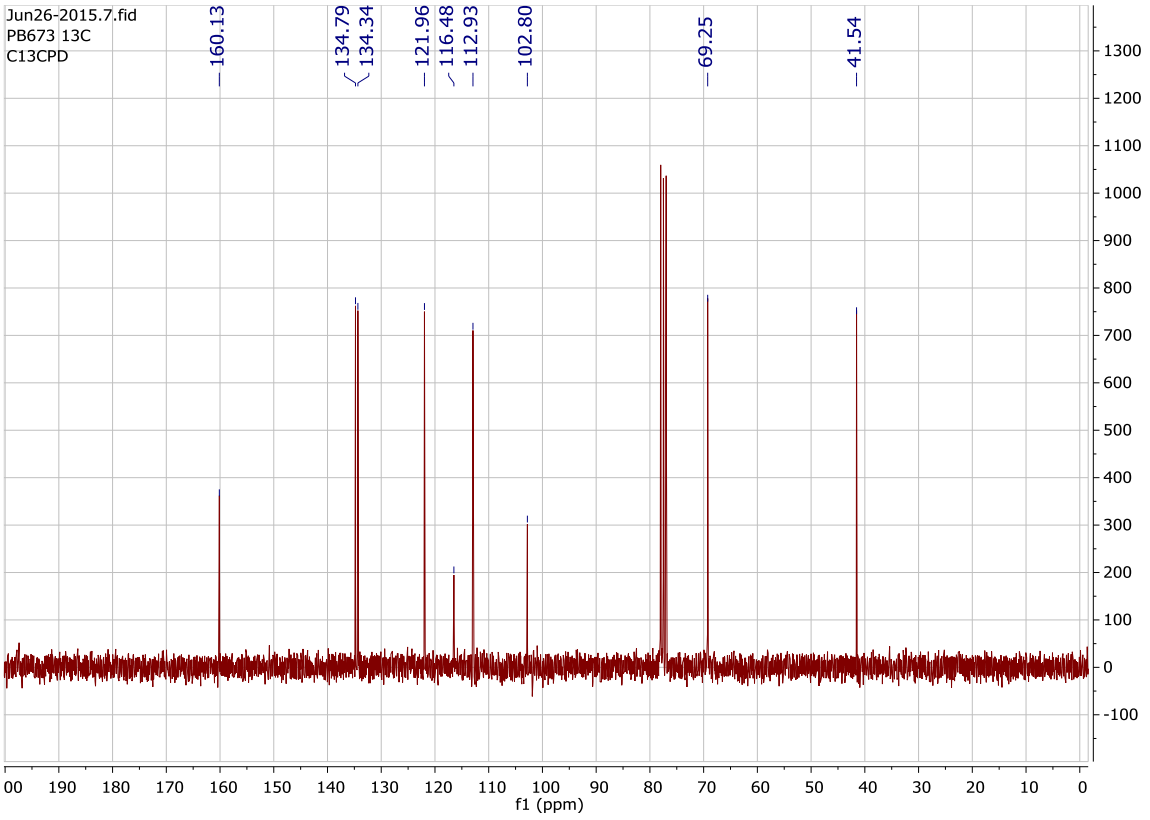
1-(2-chloroethoxy)-4-nitrobenzene (3e)



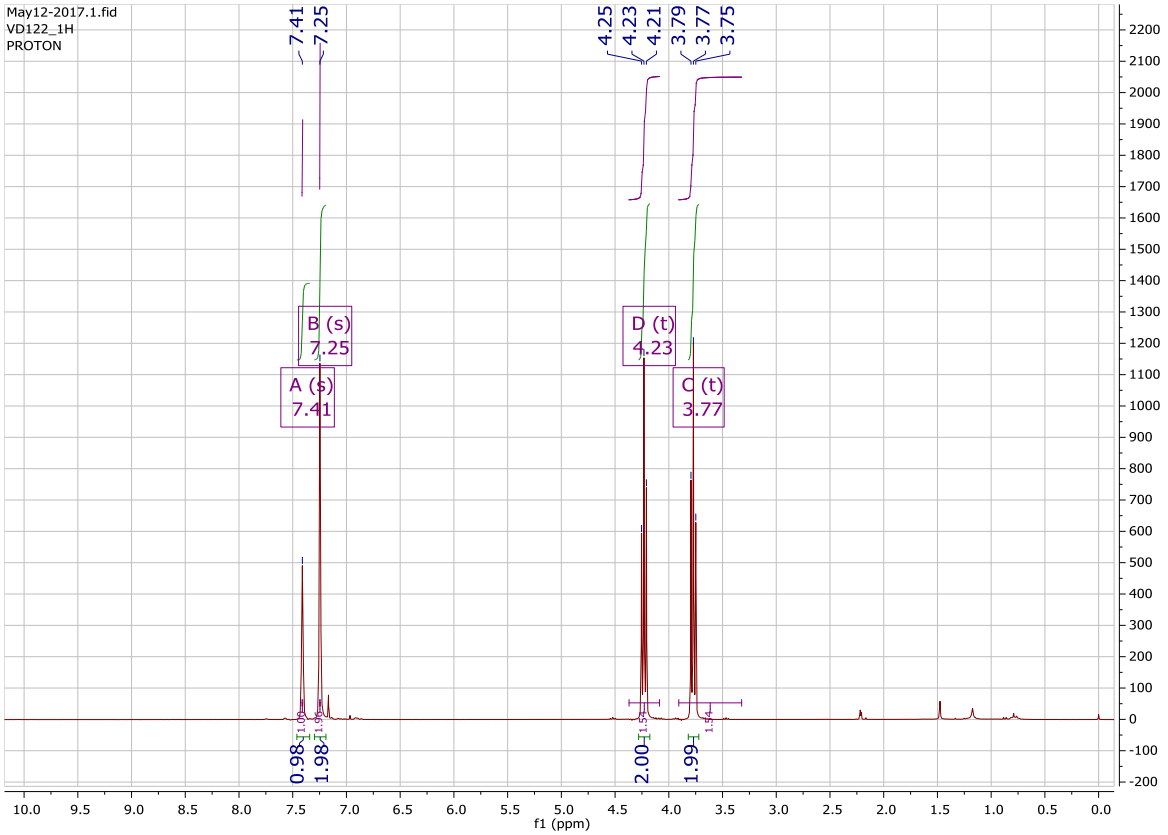


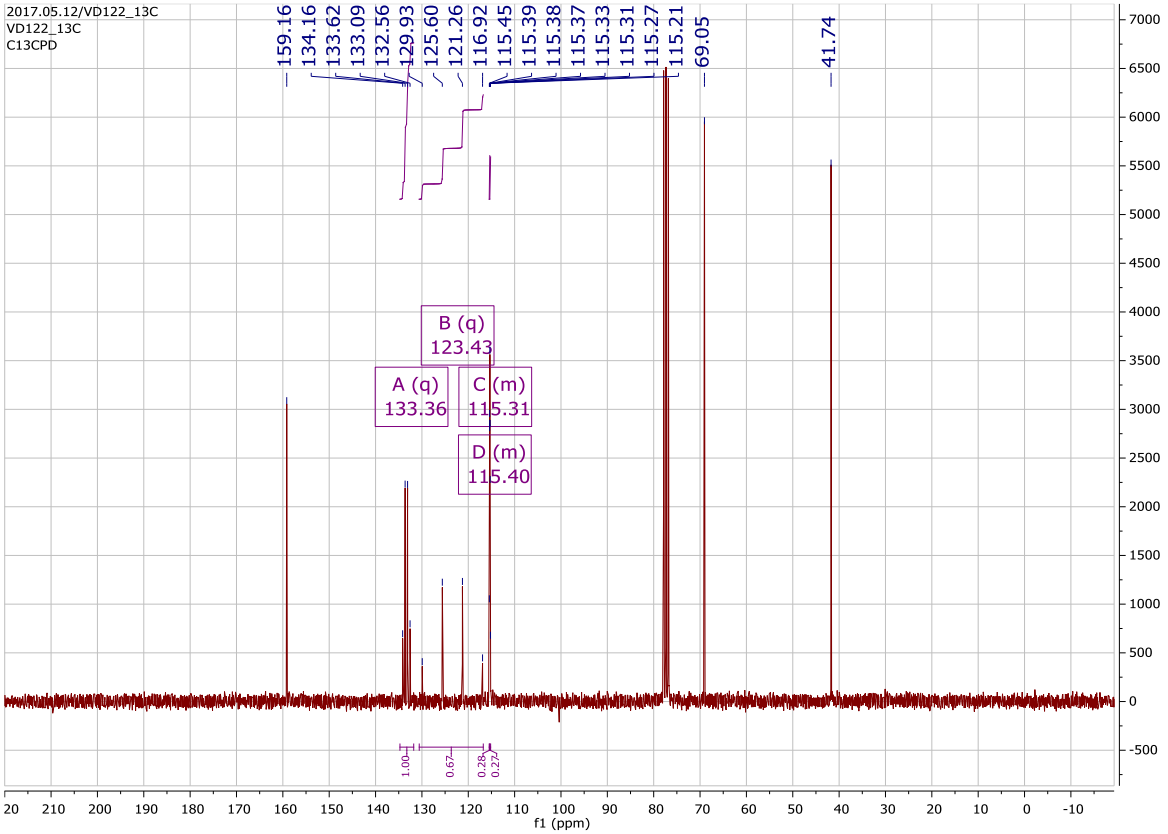
2-(2-chloroethoxy)benzonitrile (3f)

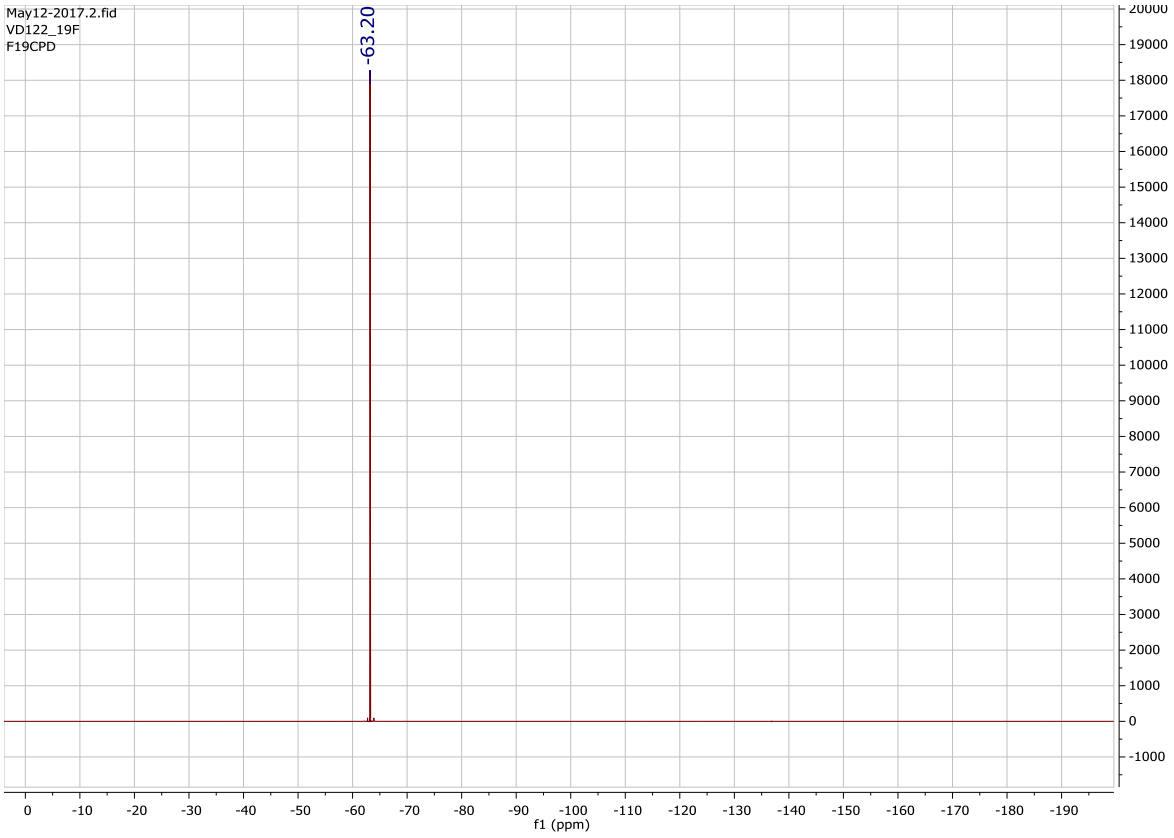




1-(2-chloroethoxy)-3,5-bis(trifluoromethyl)benzene (3g)



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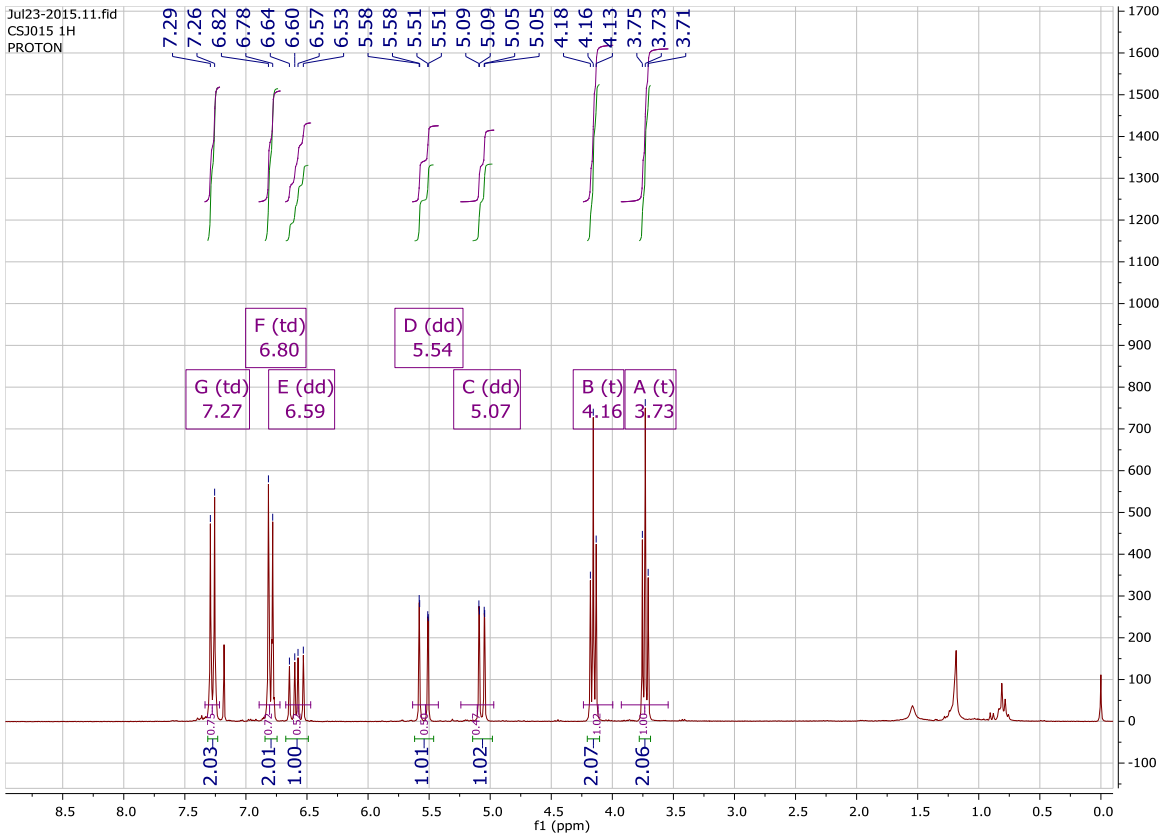
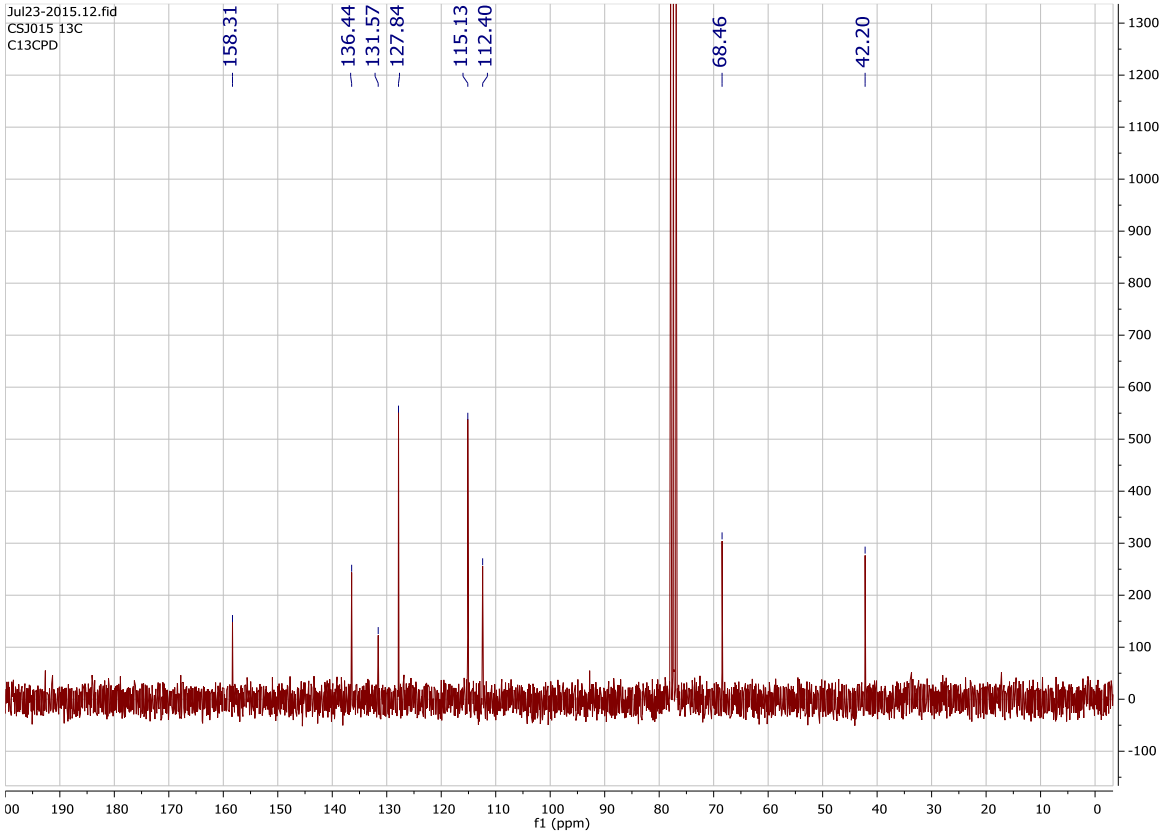
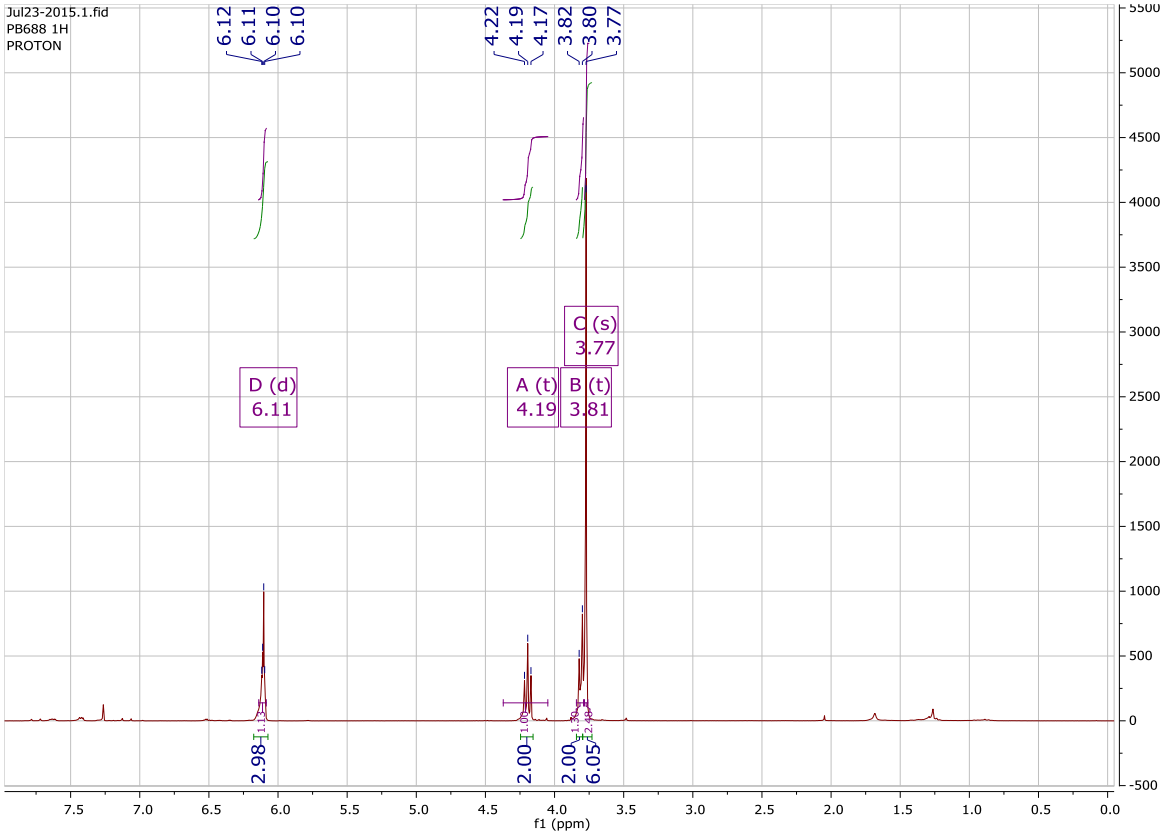
f1 (ppm)

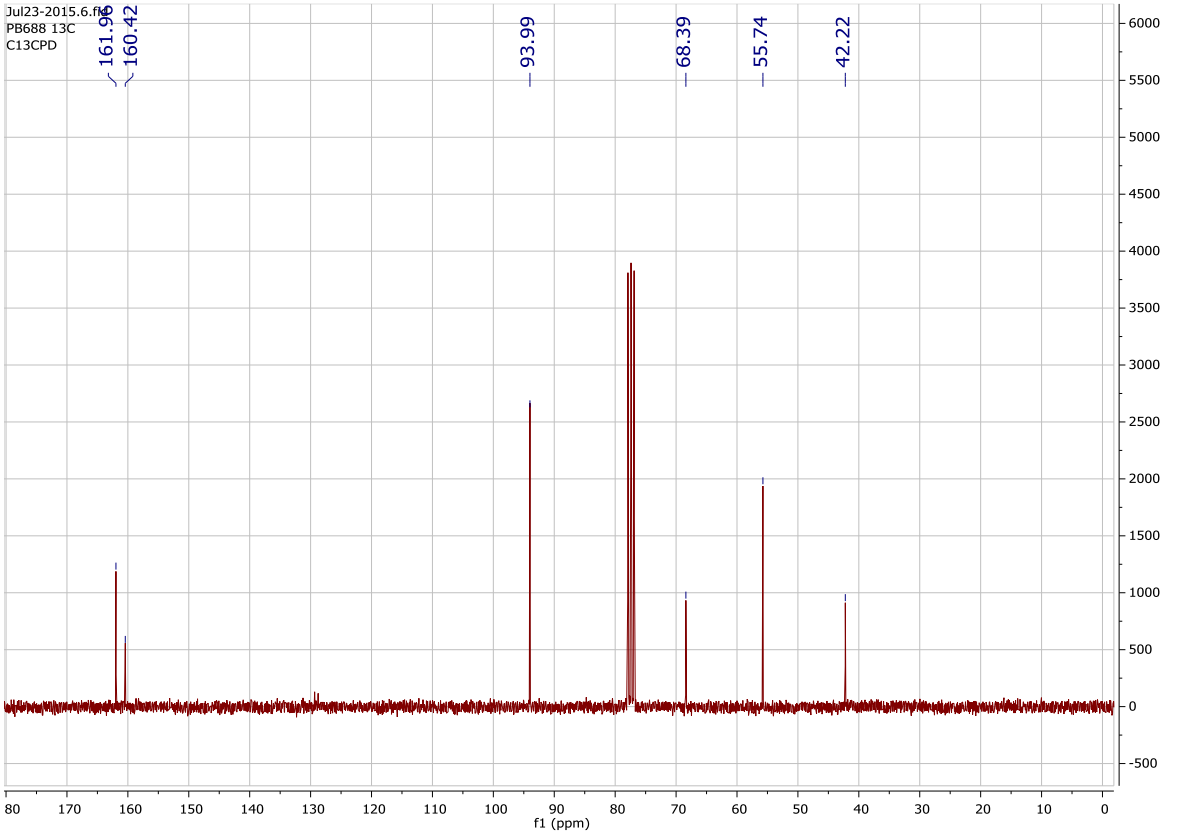
1-(2-chloroethoxy)-4-vinylbenzene (3h)



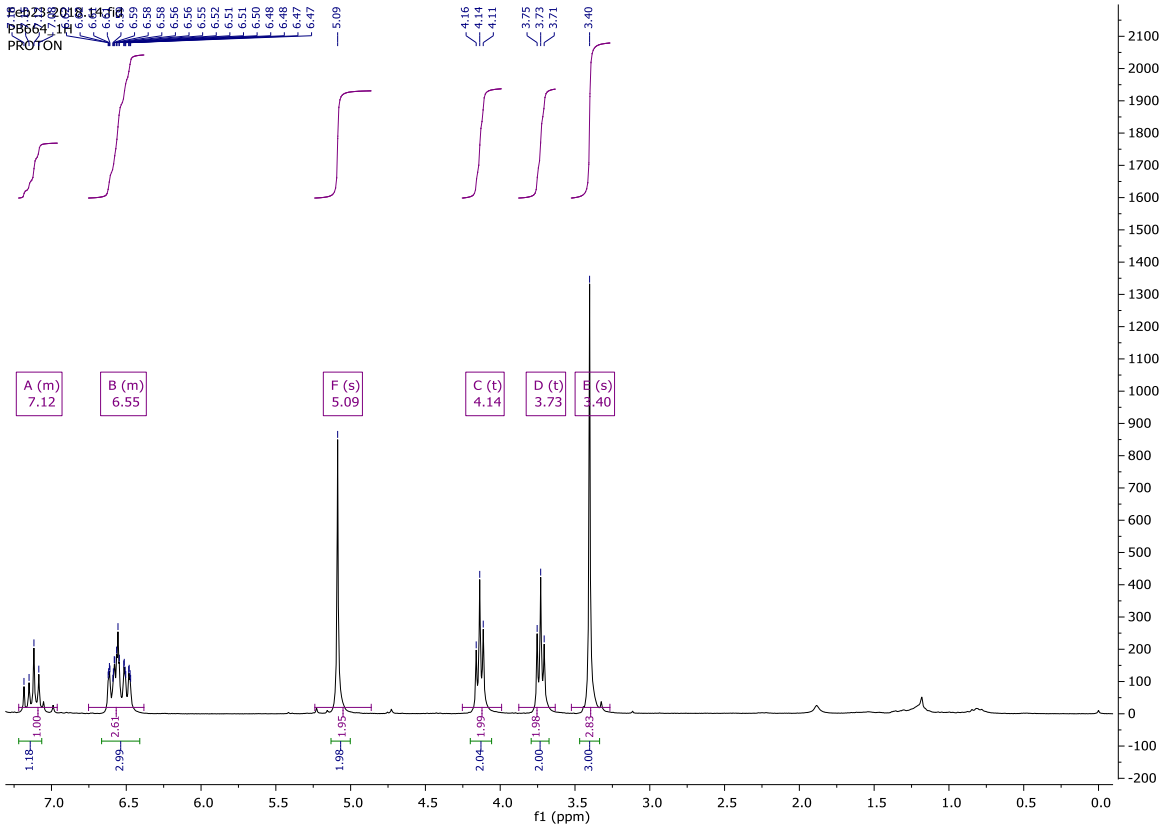


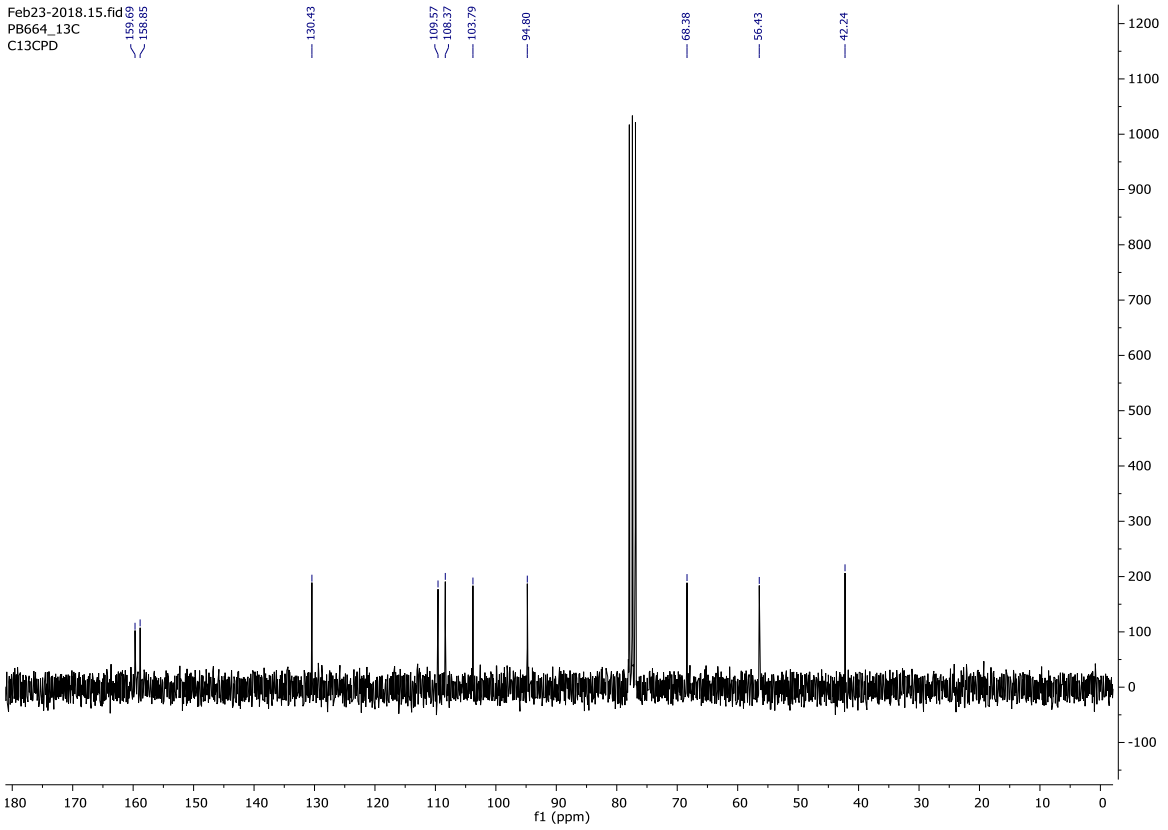
1-(2-chloroethoxy)-3,5-dimethoxybenzene (3i)



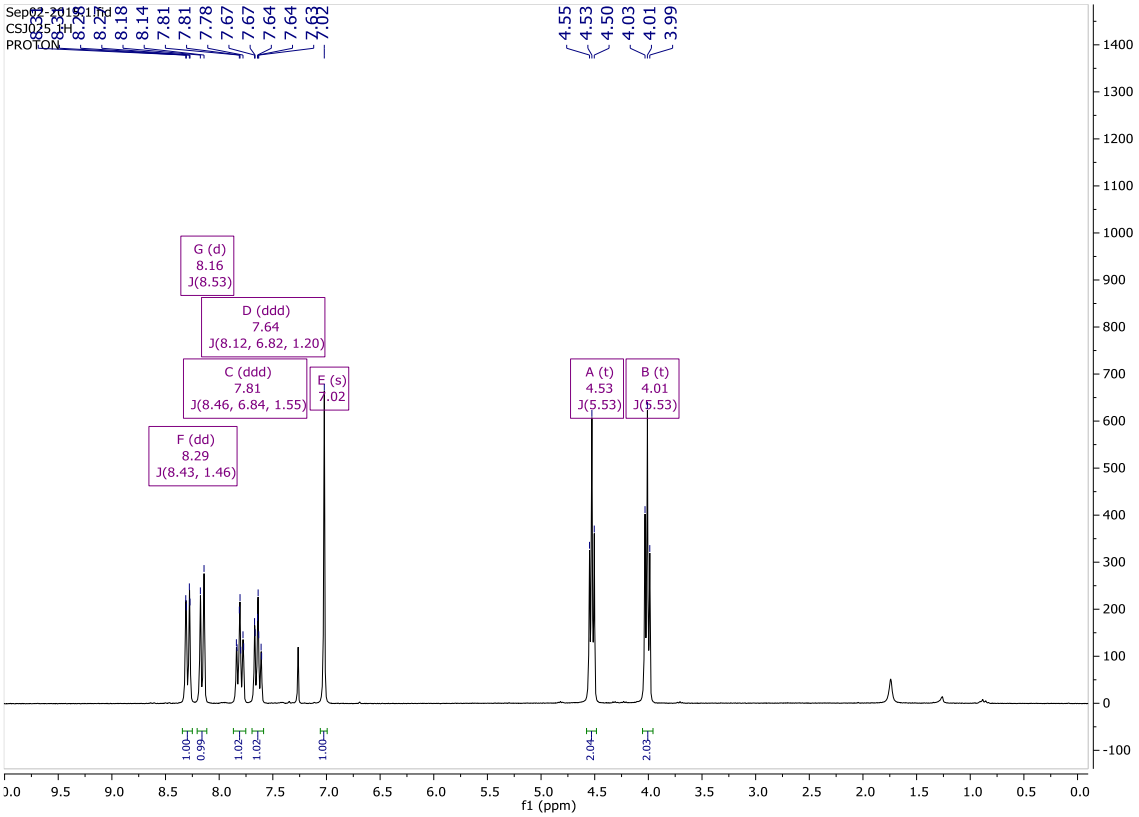


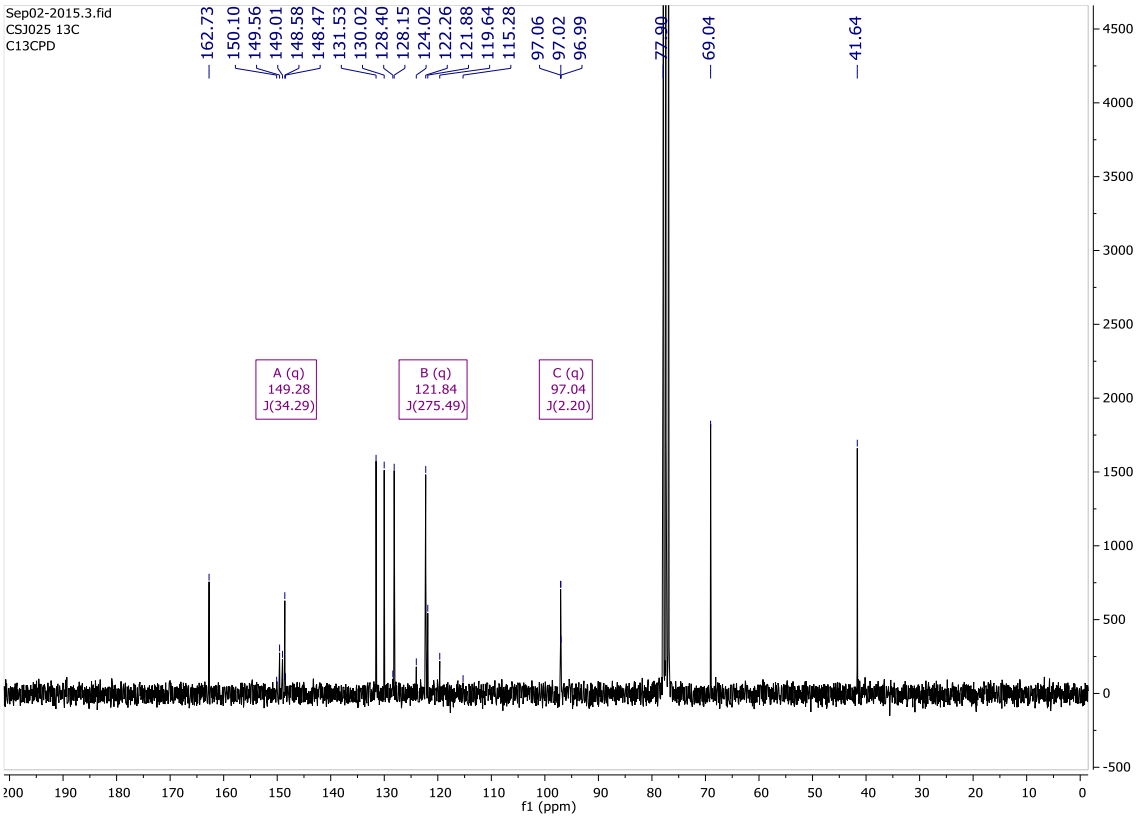
1-(2-chloroethoxy)-3-(methoxymethoxy)benzene (3j)

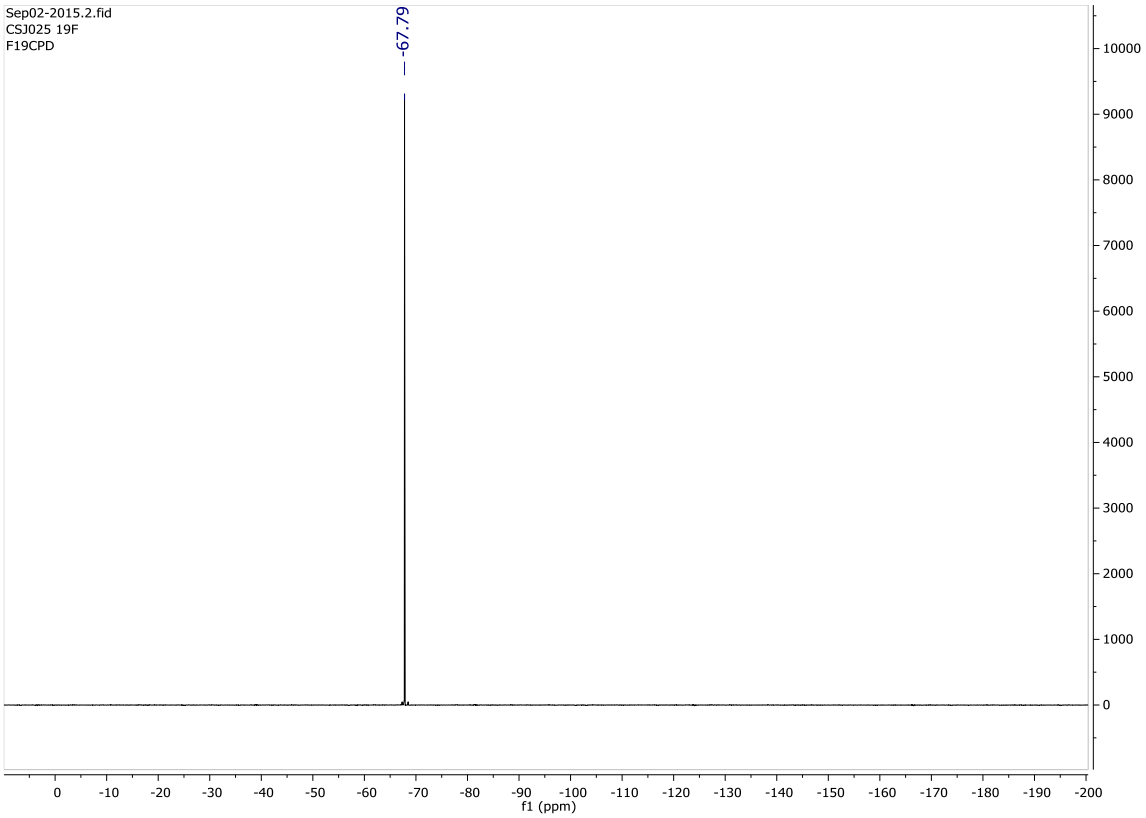




2-(2-chloroethoxy)-4-(trifluoromethyl)quinoline (3k)



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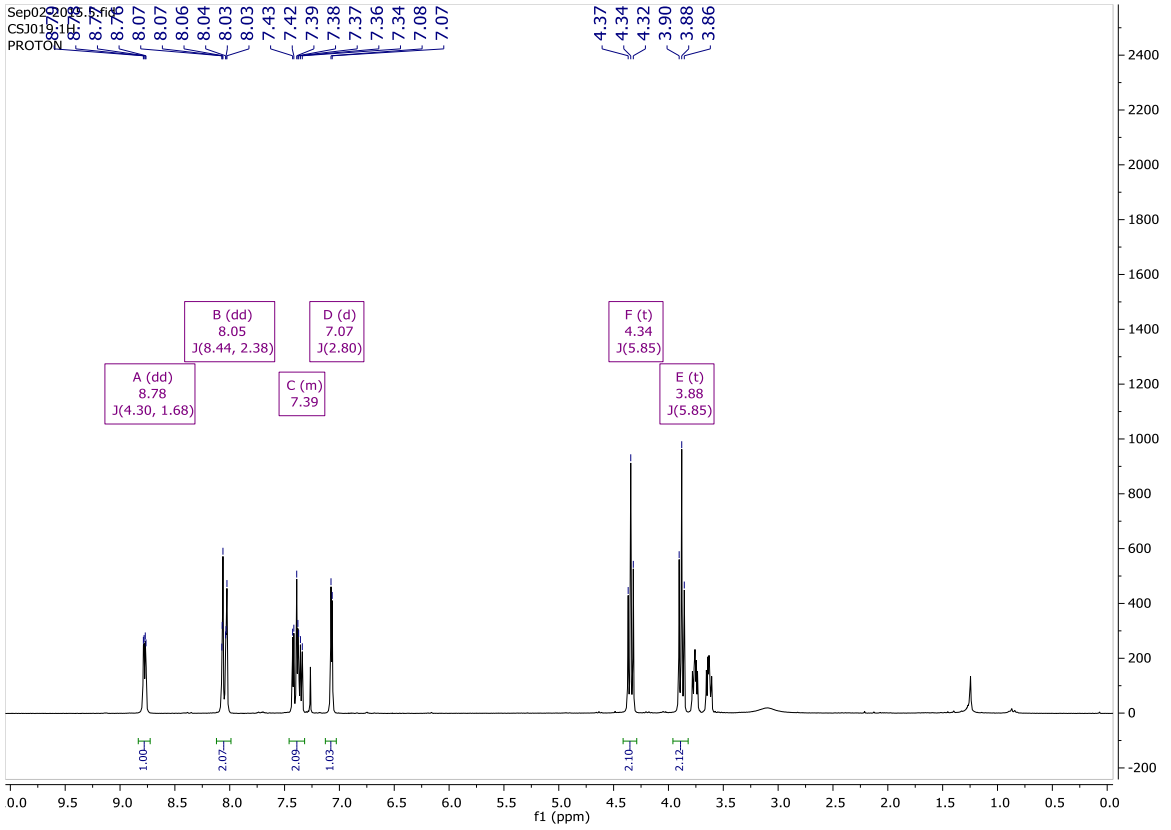
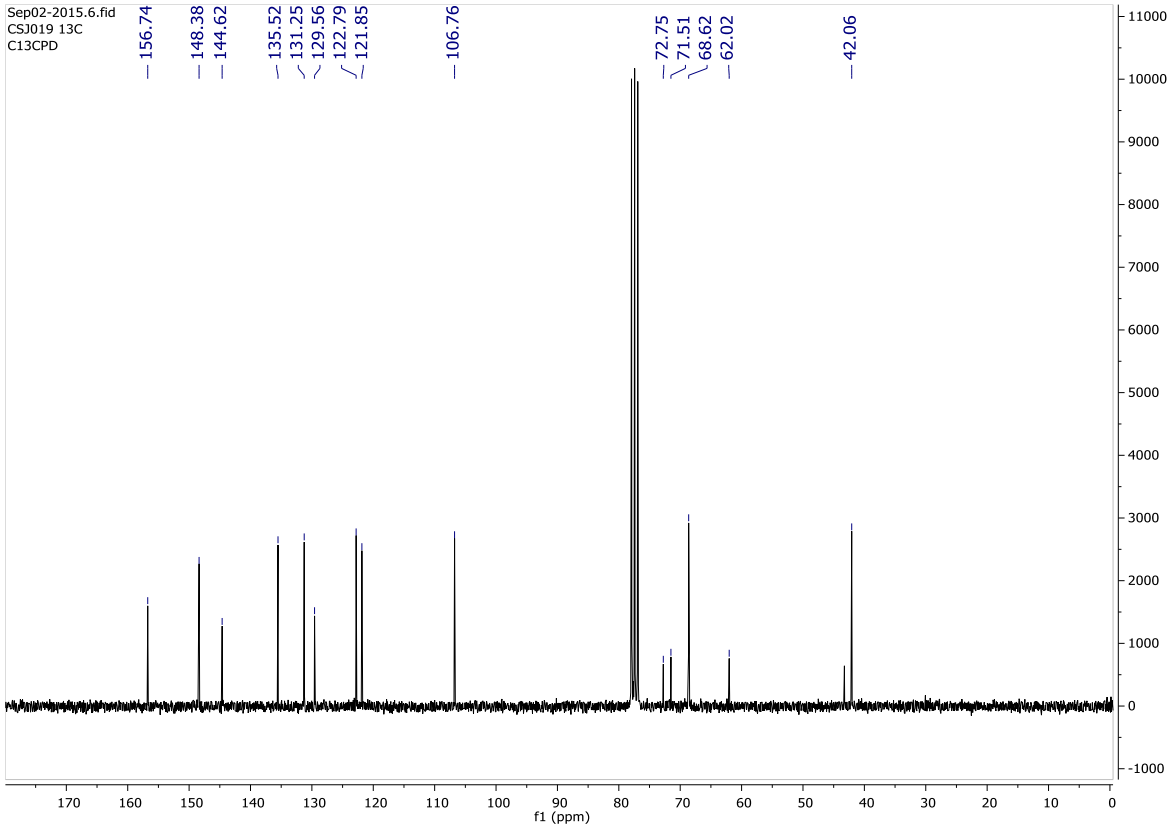
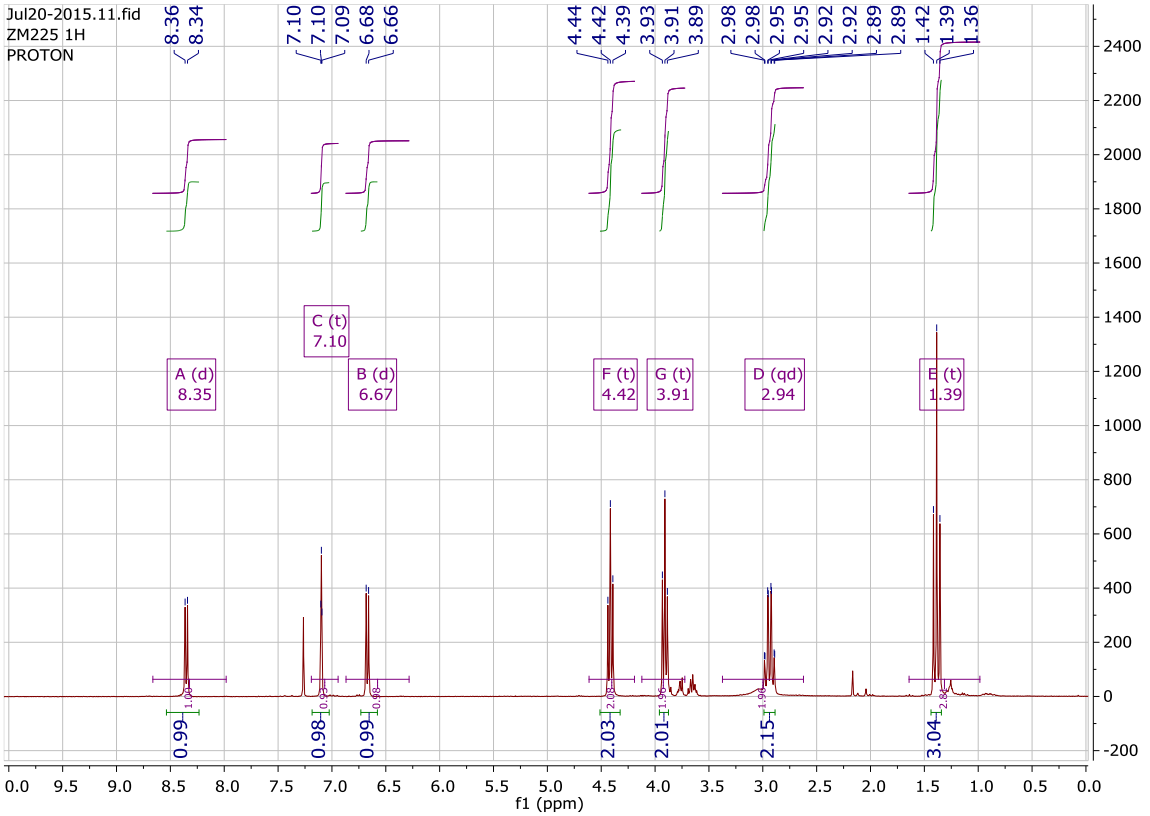
f1 (ppm)

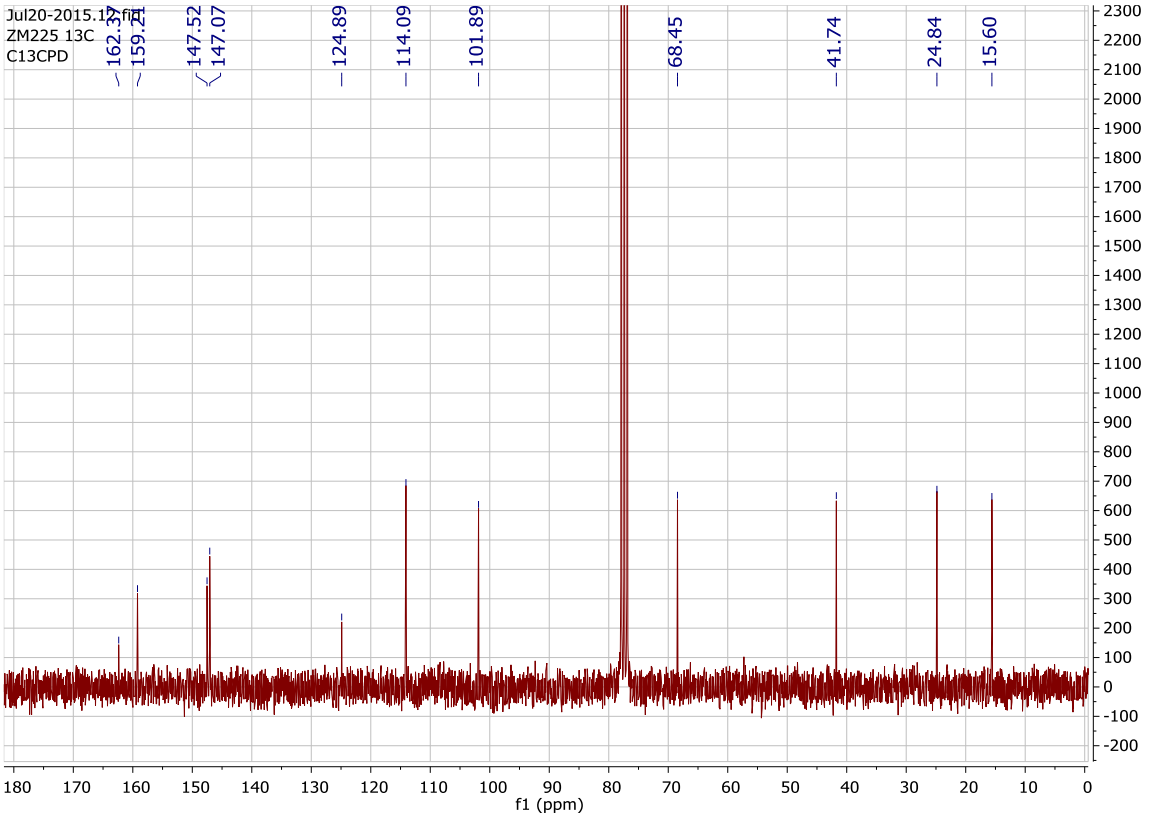
5-(2-chloroethoxy)quinoline (3l)



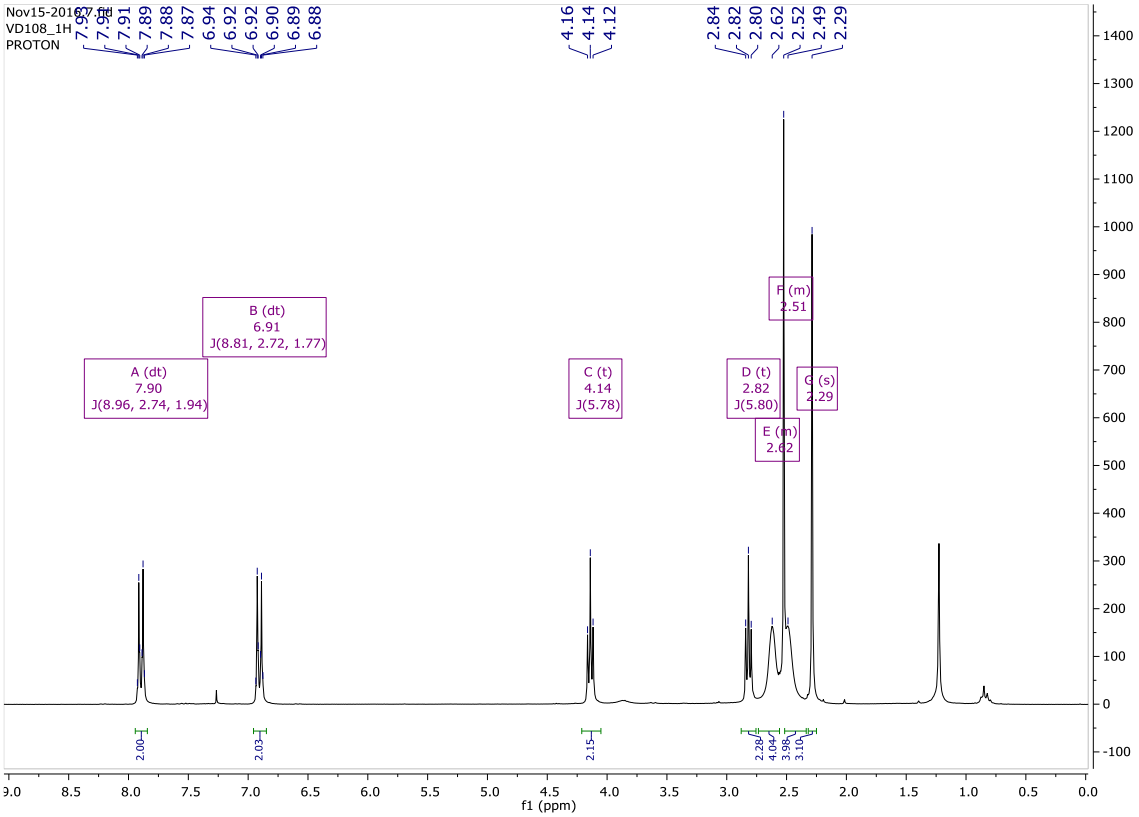


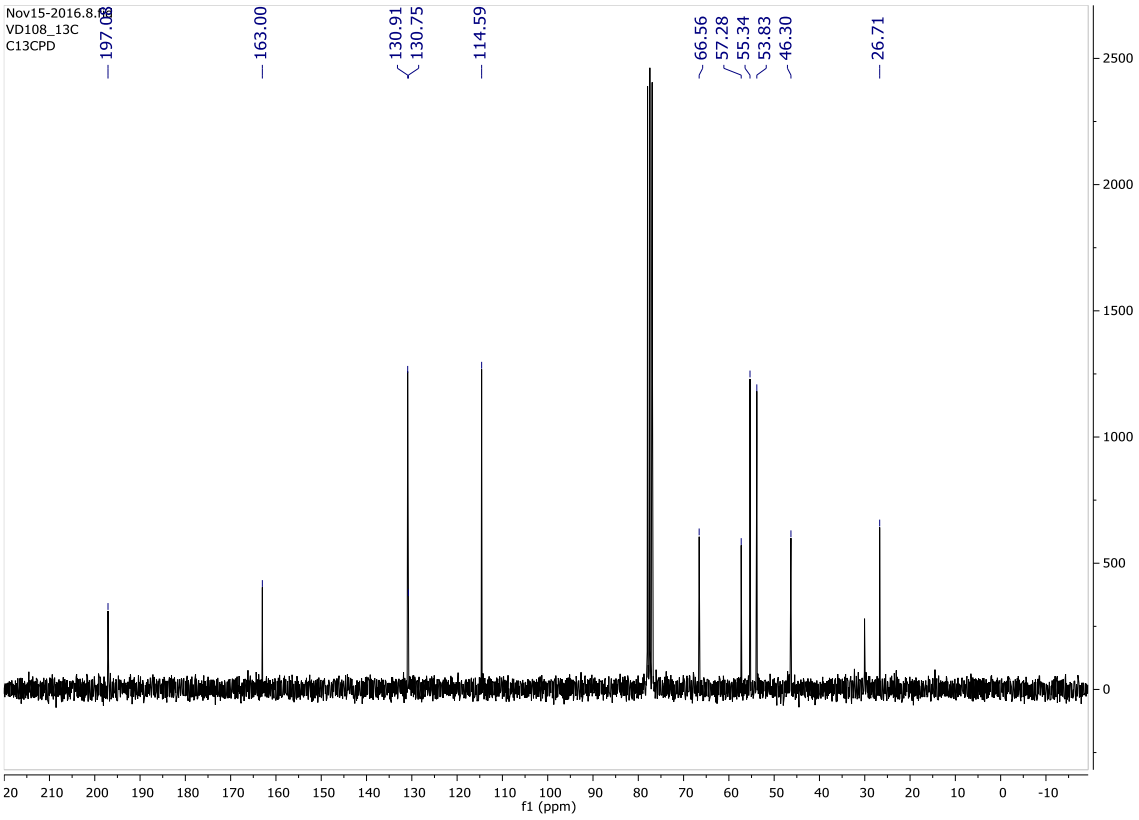
4-(2-chloroethoxy)-2-ethylthieno[2,3-b]pyridine (3m)



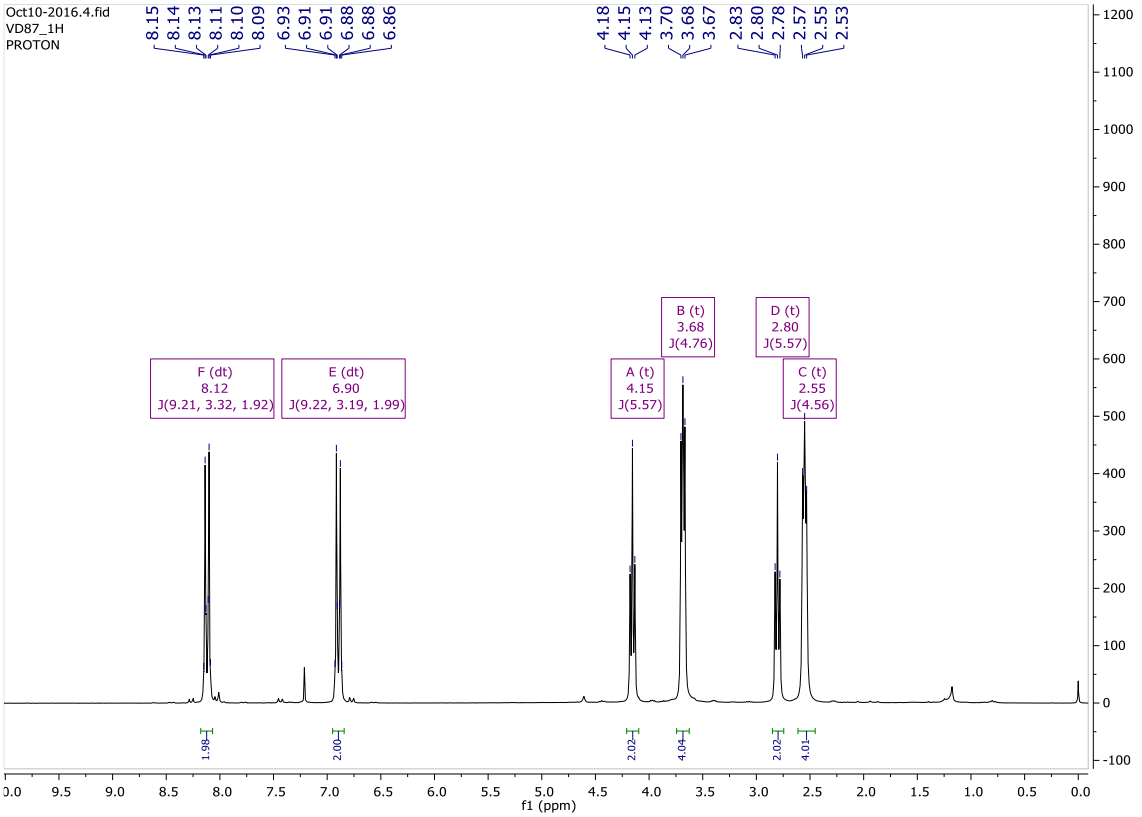


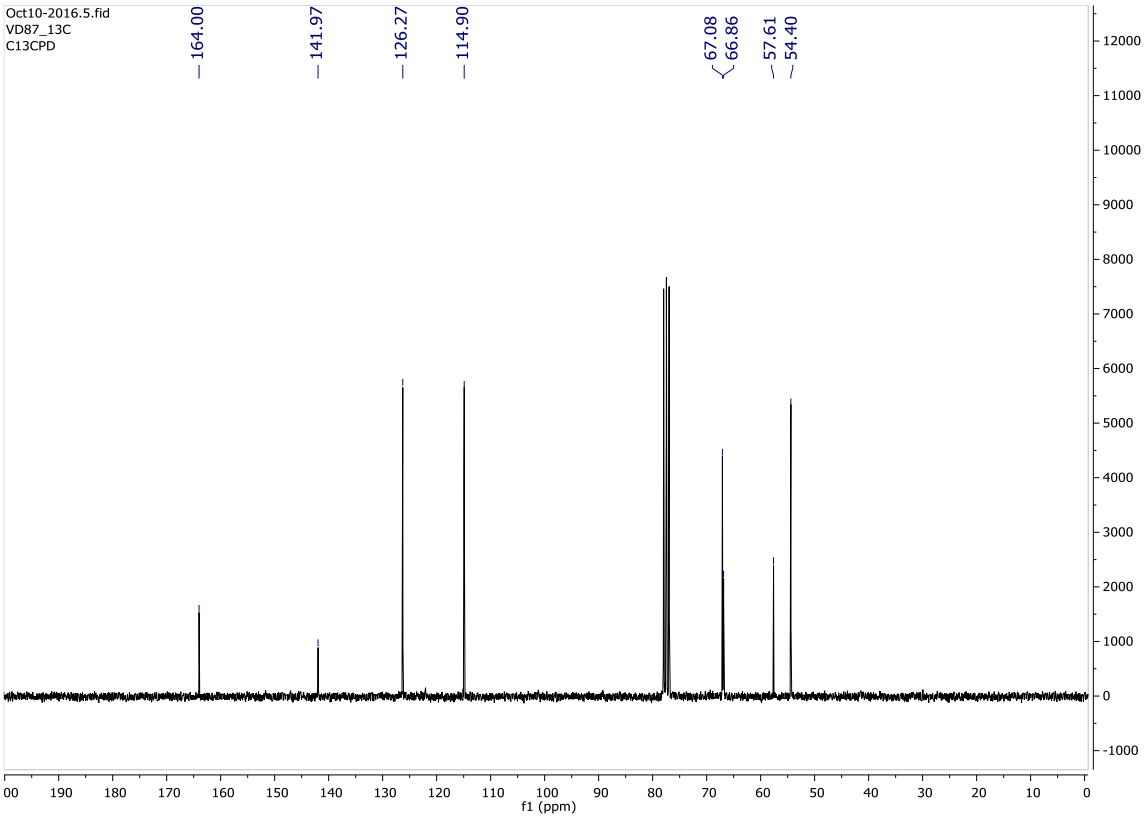
1-(4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)ethan-1-one (4a)



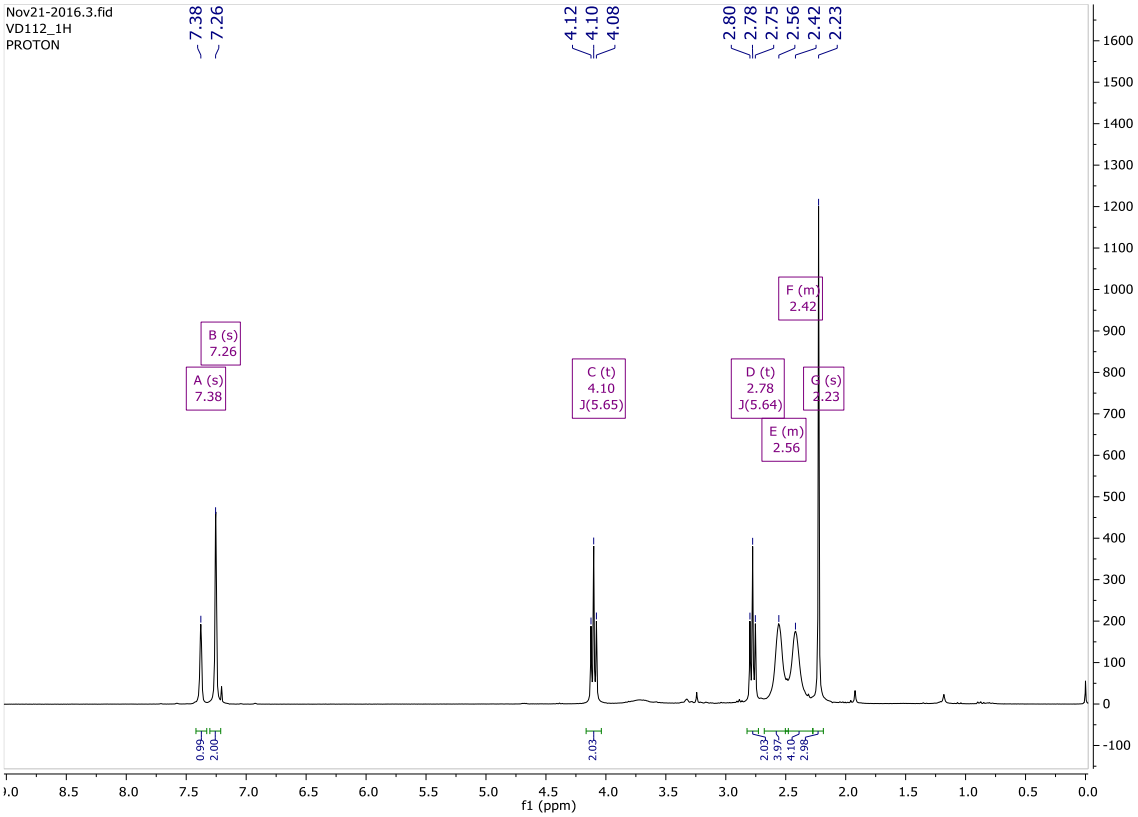


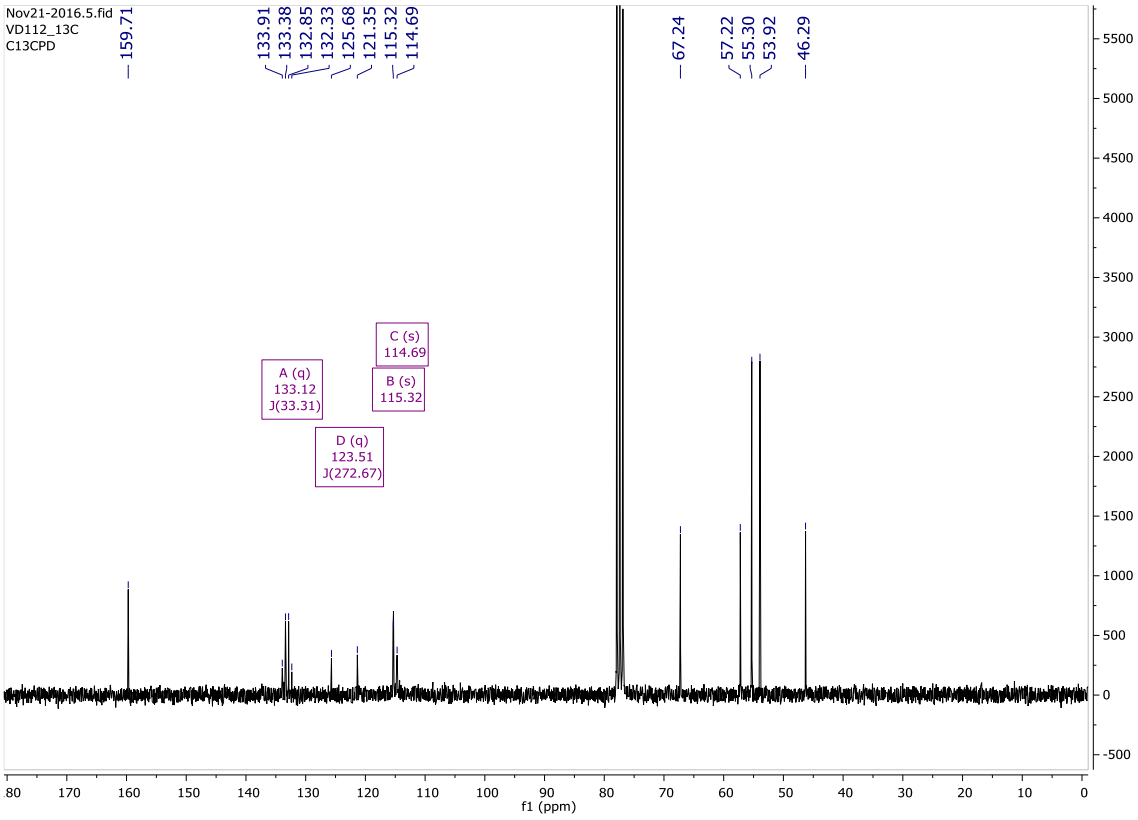
4-(2-(4-nitrophenoxy)ethyl)morpholine (4b)

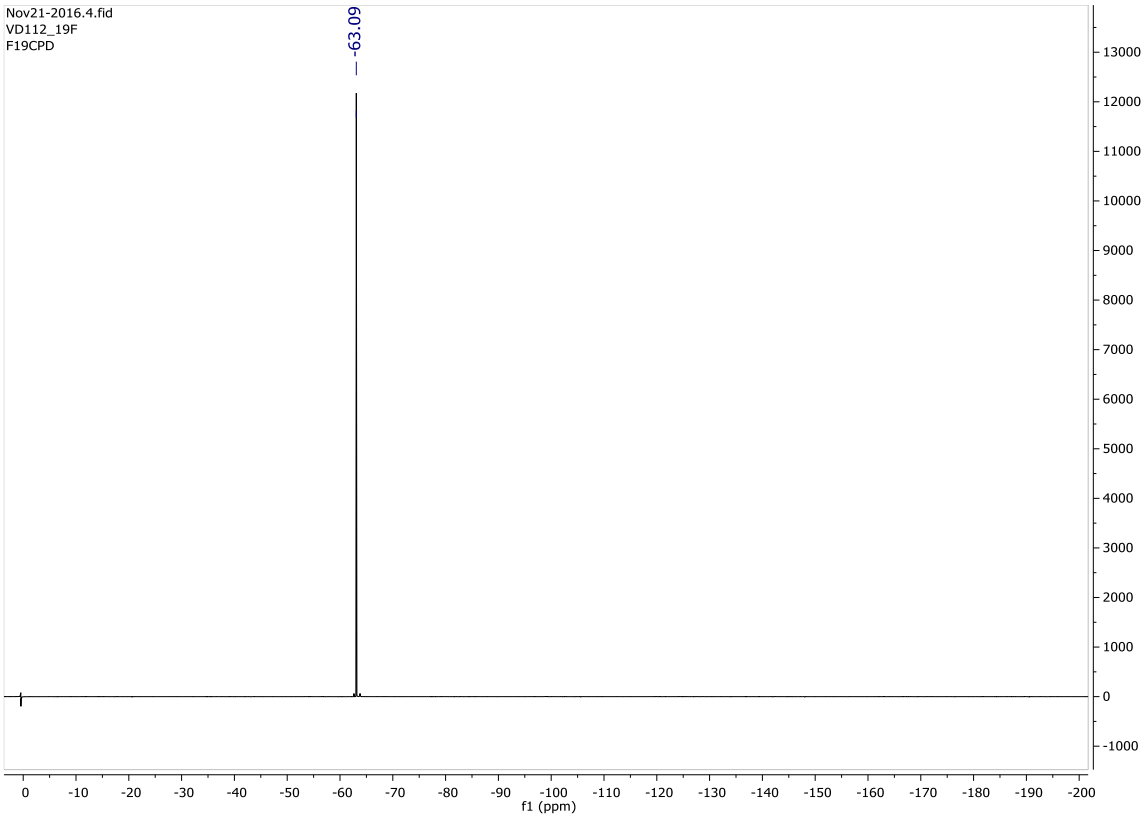




1-(2-(3,5-bis(trifluoromethyl)phenoxy)ethyl)-4-methylpiperazine (4c)



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-60
-70
-80
-90
-100
-110
-120
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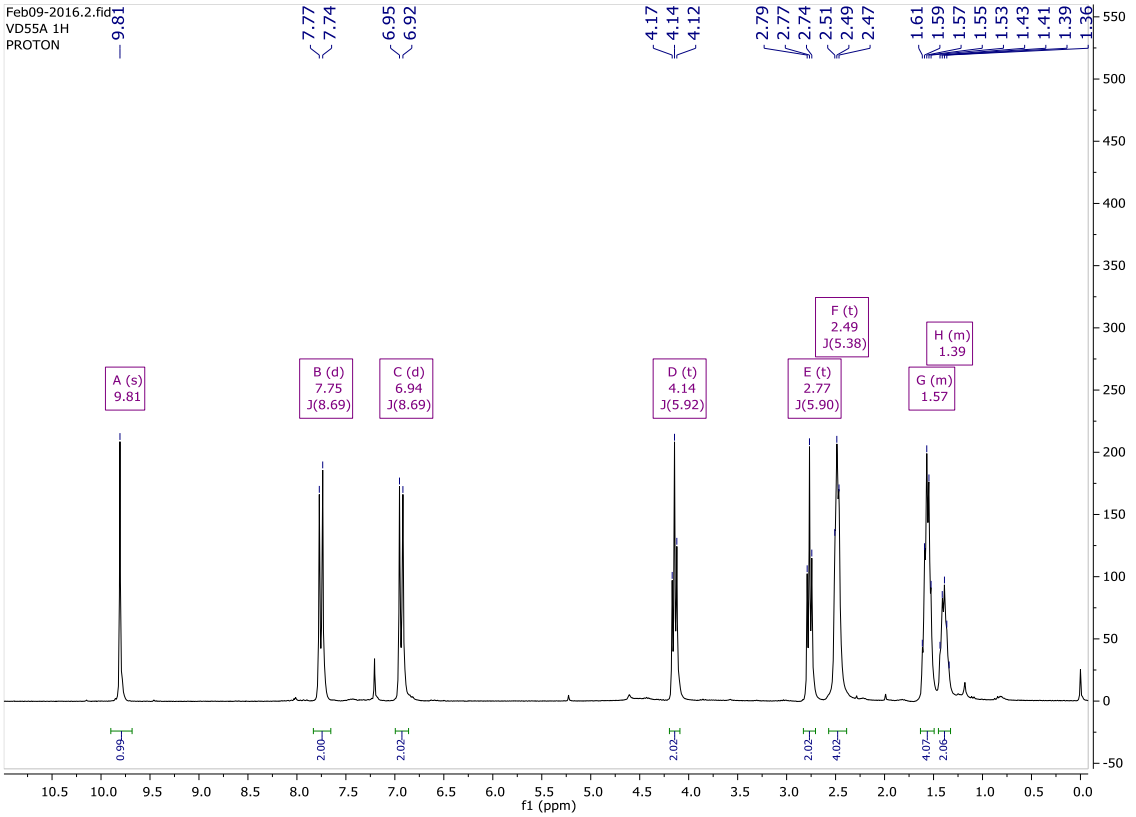
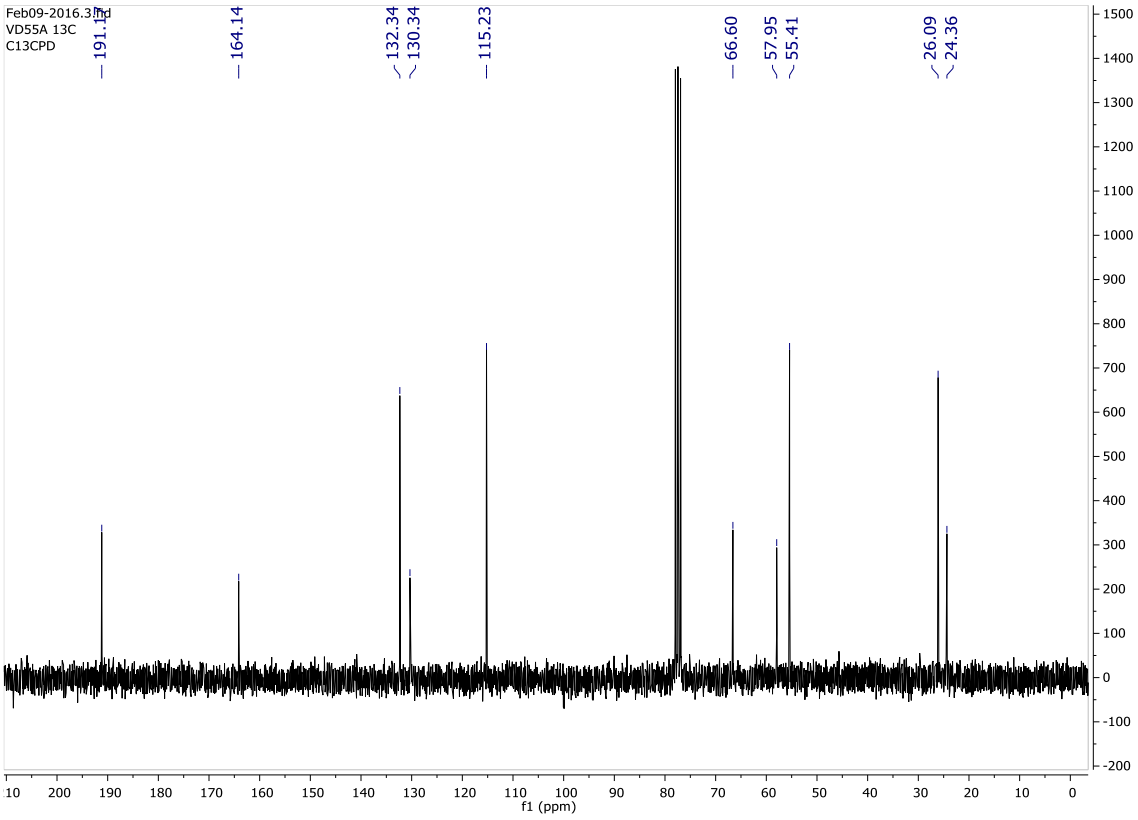
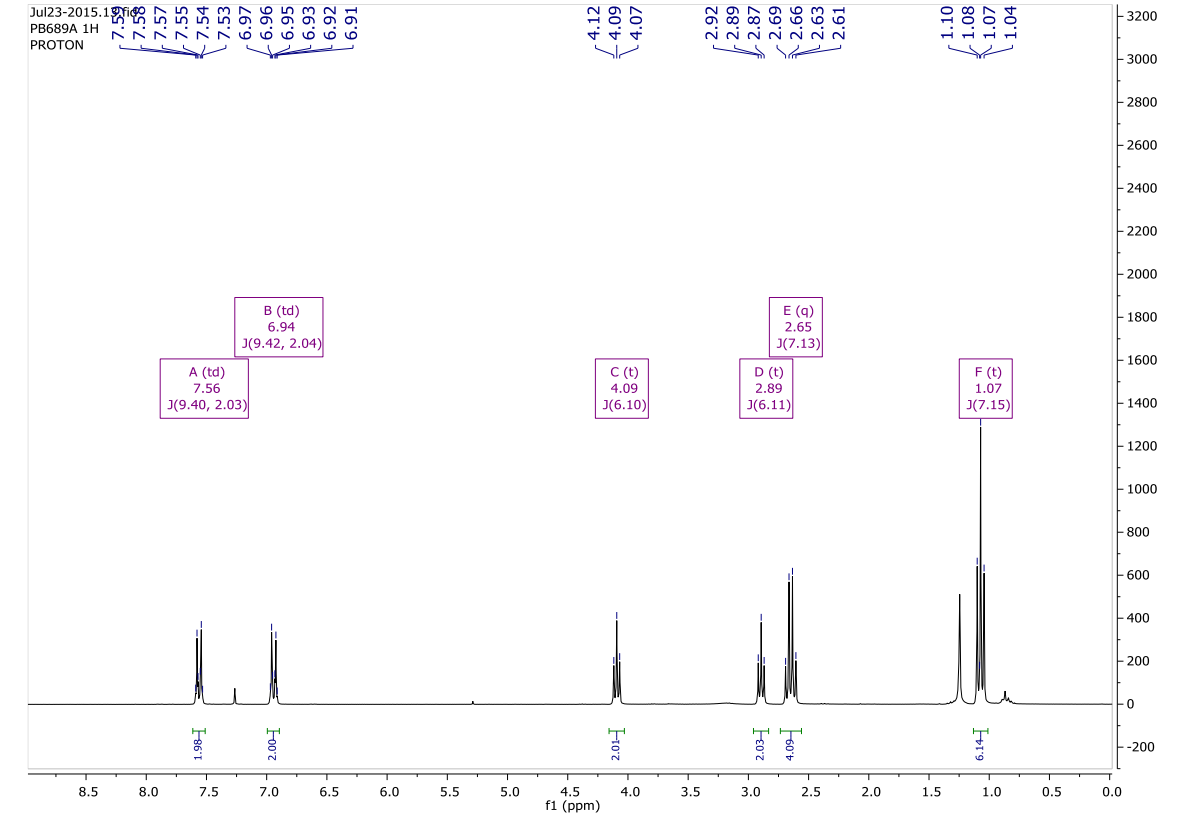
-170
-180
-190
-200
f1 (ppm)

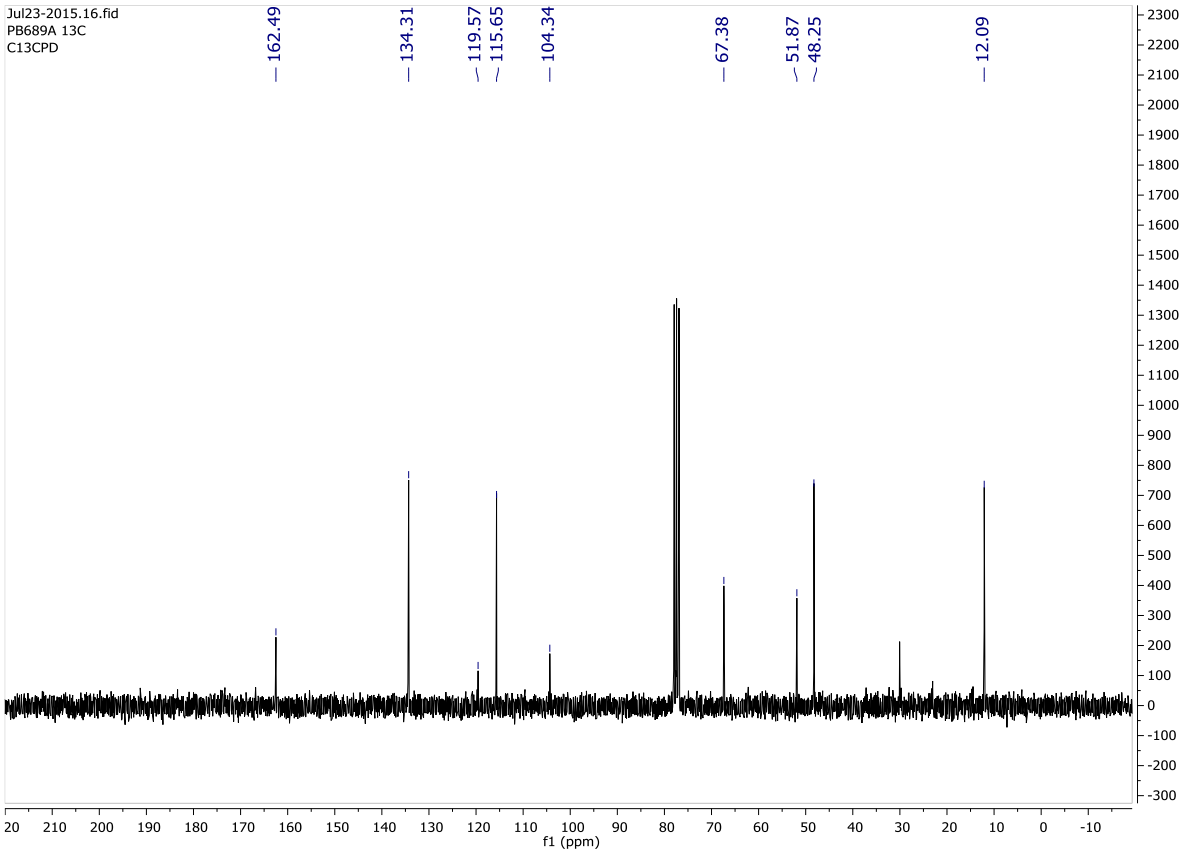
4-(2-(piperidin-1-yl)ethoxy)benzaldehyde (4d)



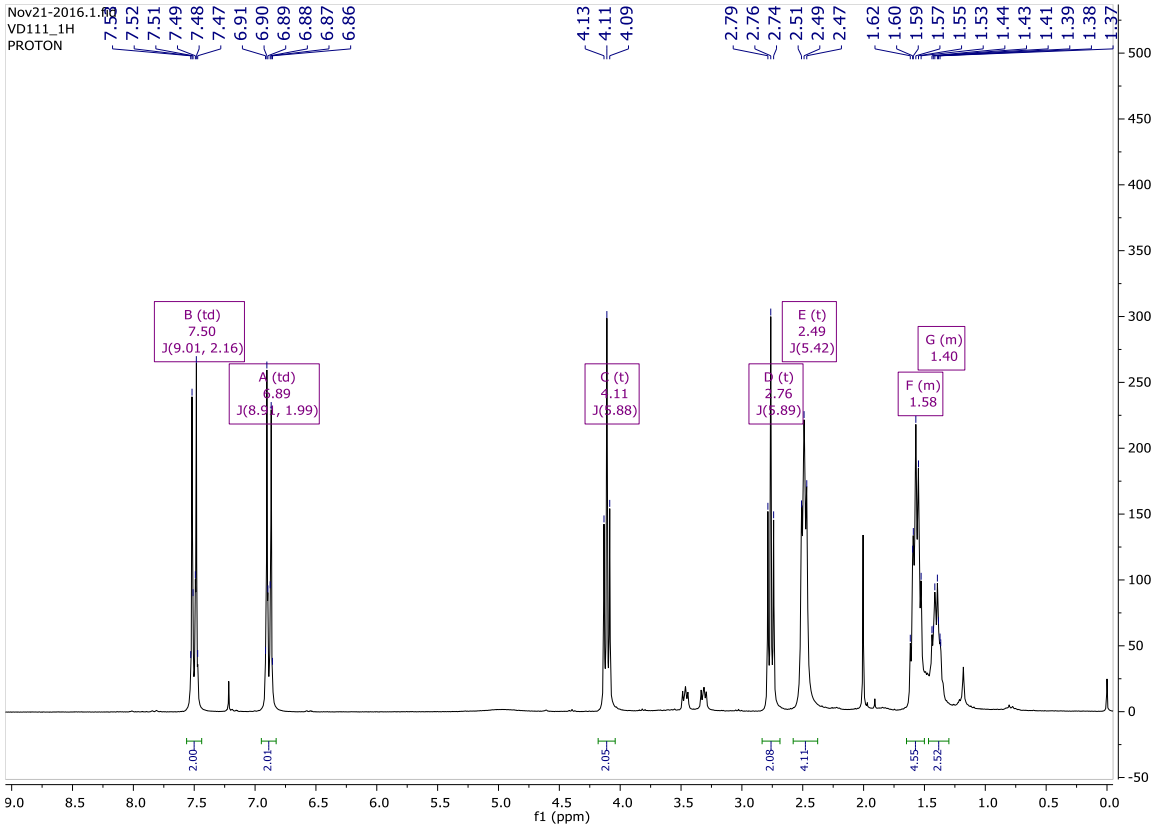


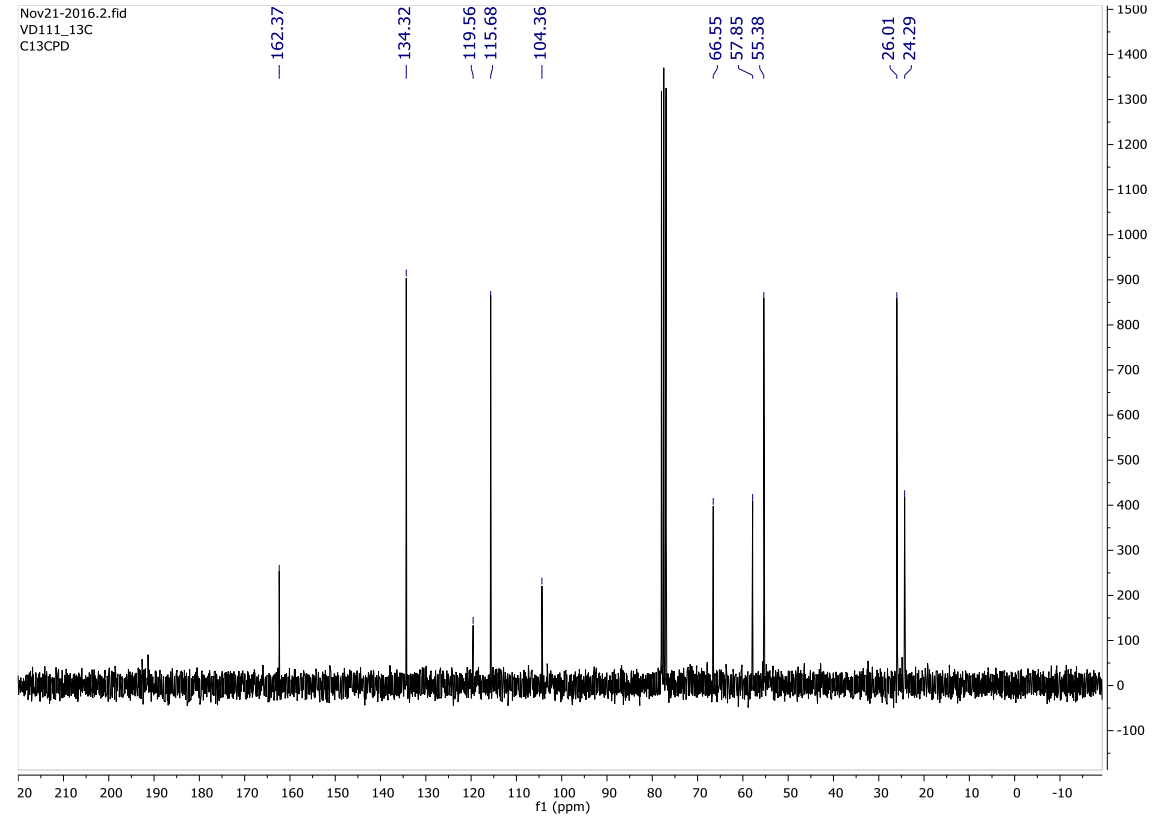
4-(2-(diethylamino)ethoxy)benzonitrile (4e)



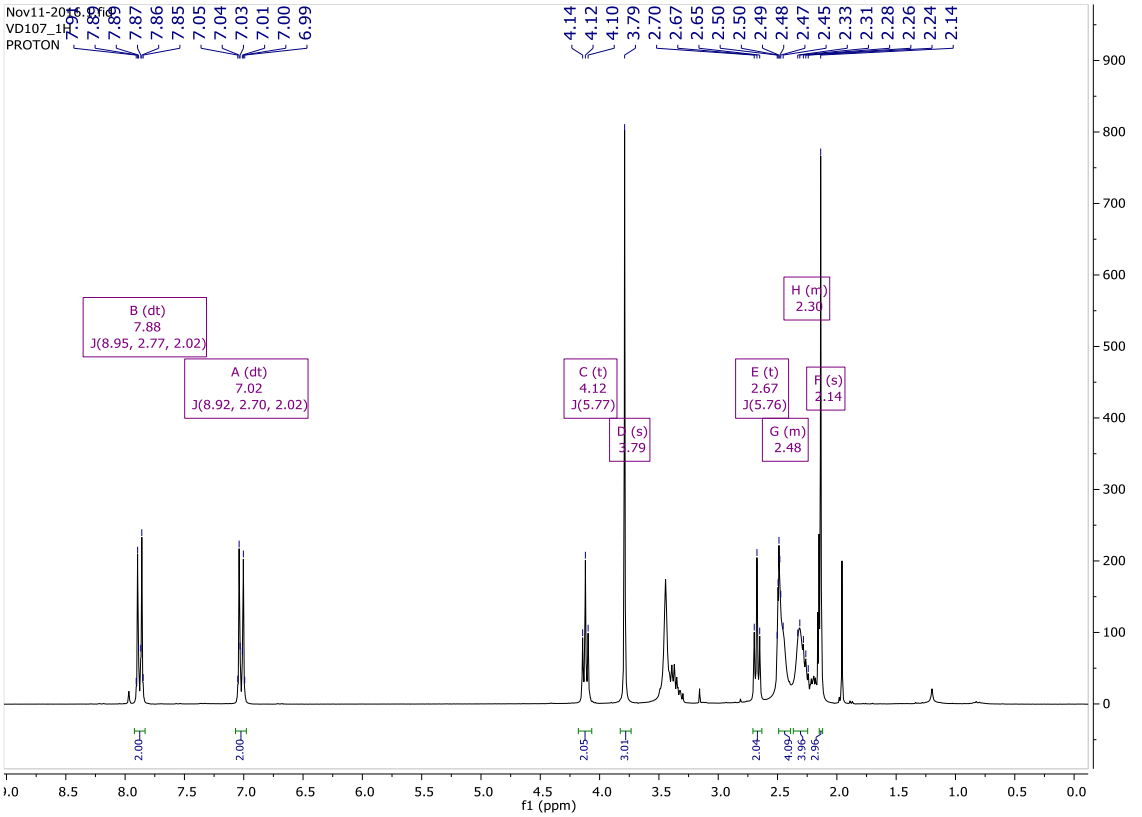


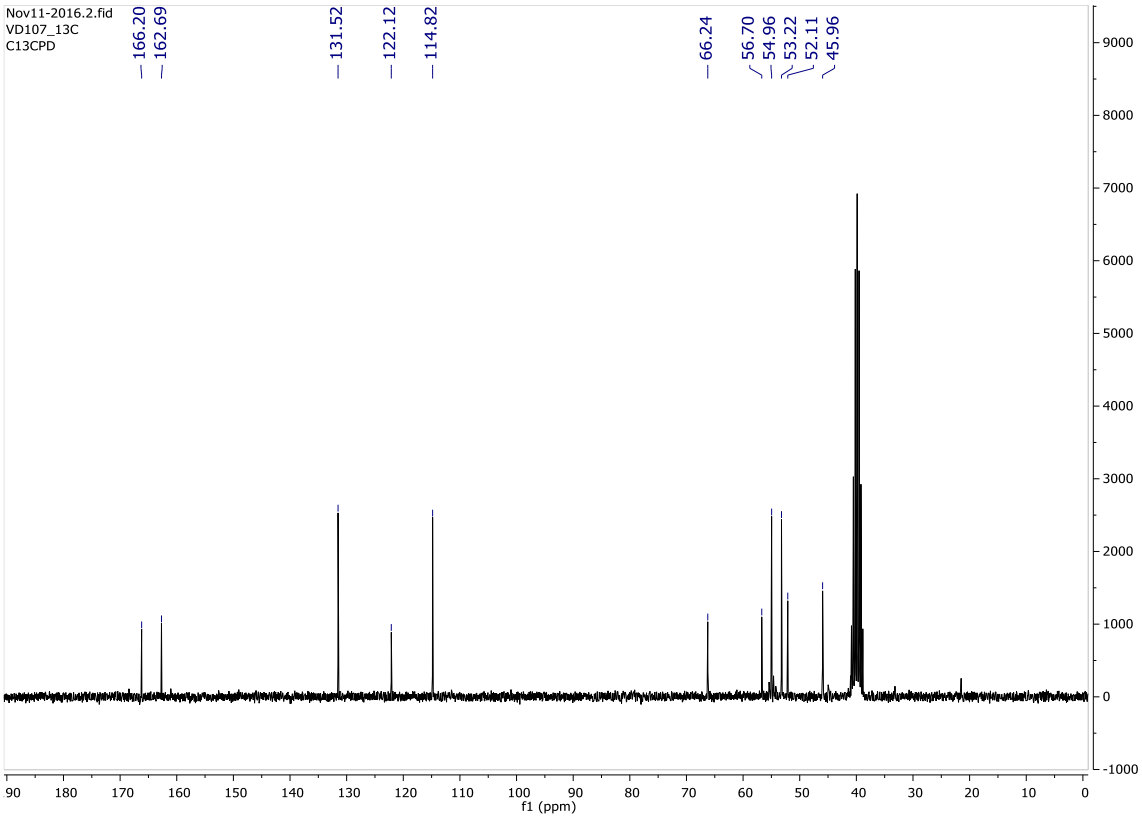
4-(2-(piperidin-1-yl)ethoxy)benzonitrile (4f)



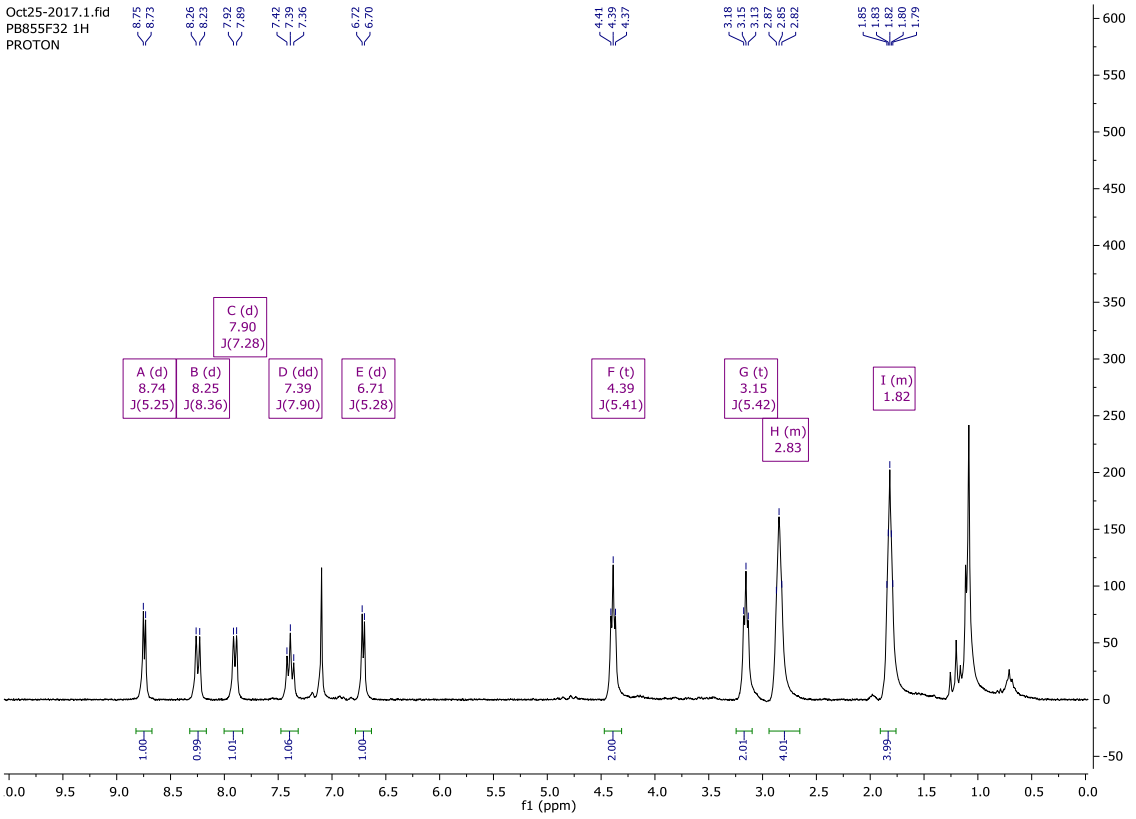


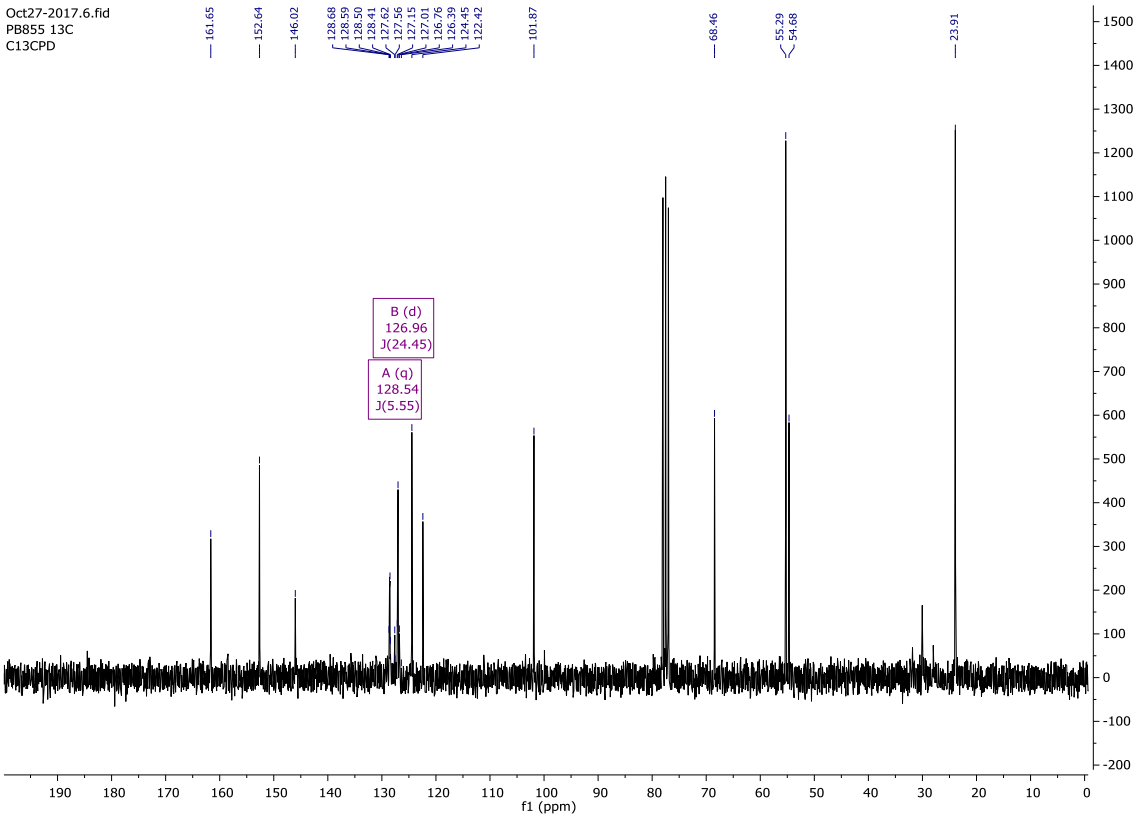
4-(2-(4-methylpiperazin-1-yl)ethoxy)benzoate (4g)

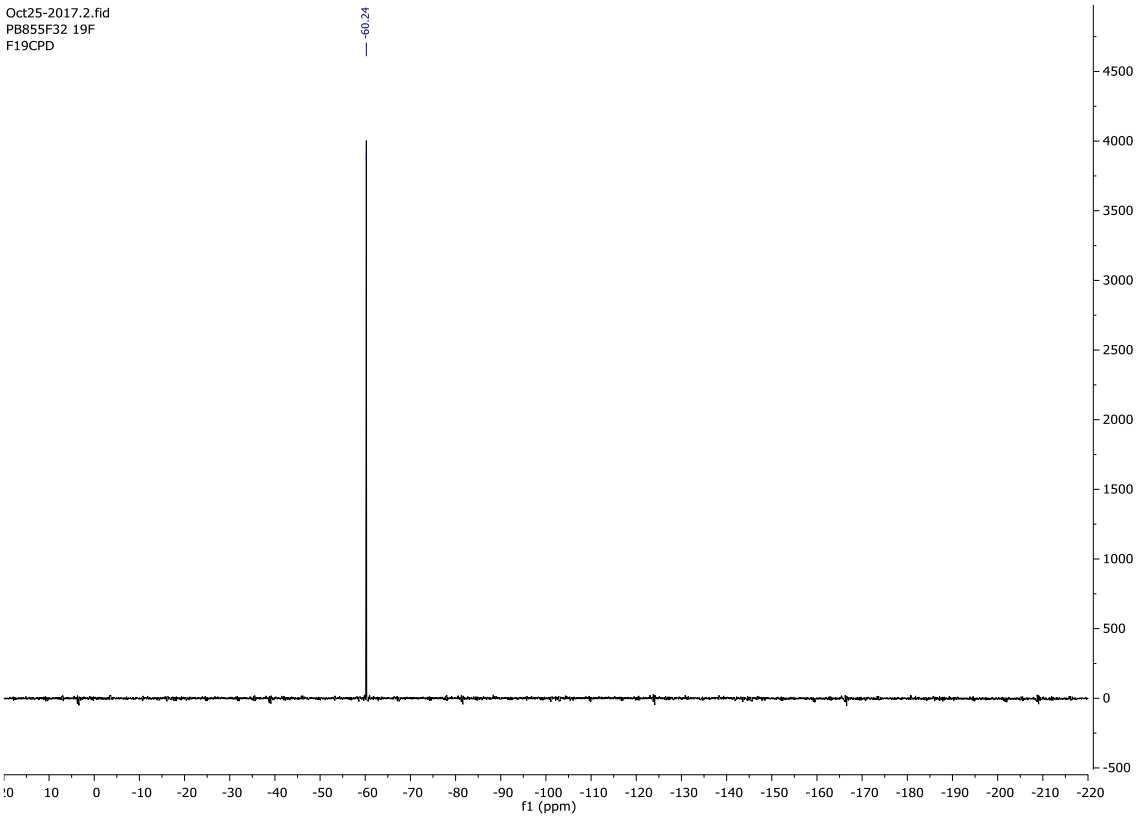




4-(2-(pyrrolidin-1-yl)ethoxy)-8-(trifluoromethyl)quinoline (4h)



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500
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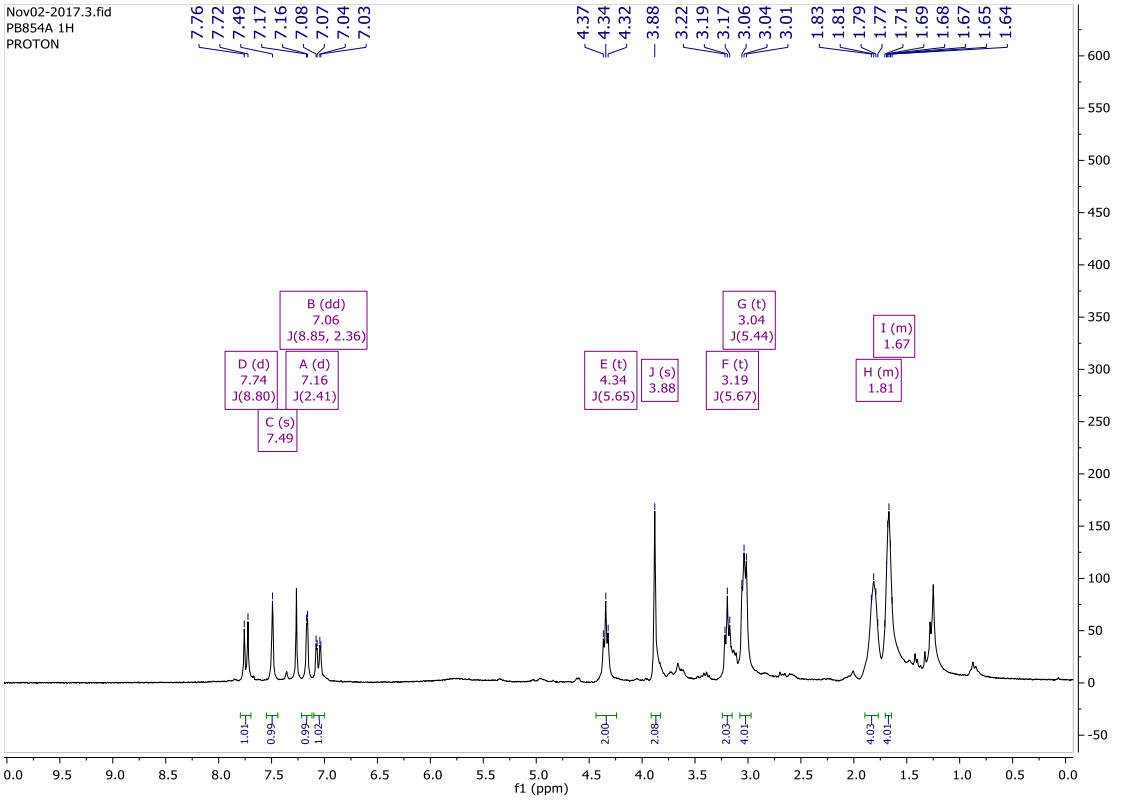
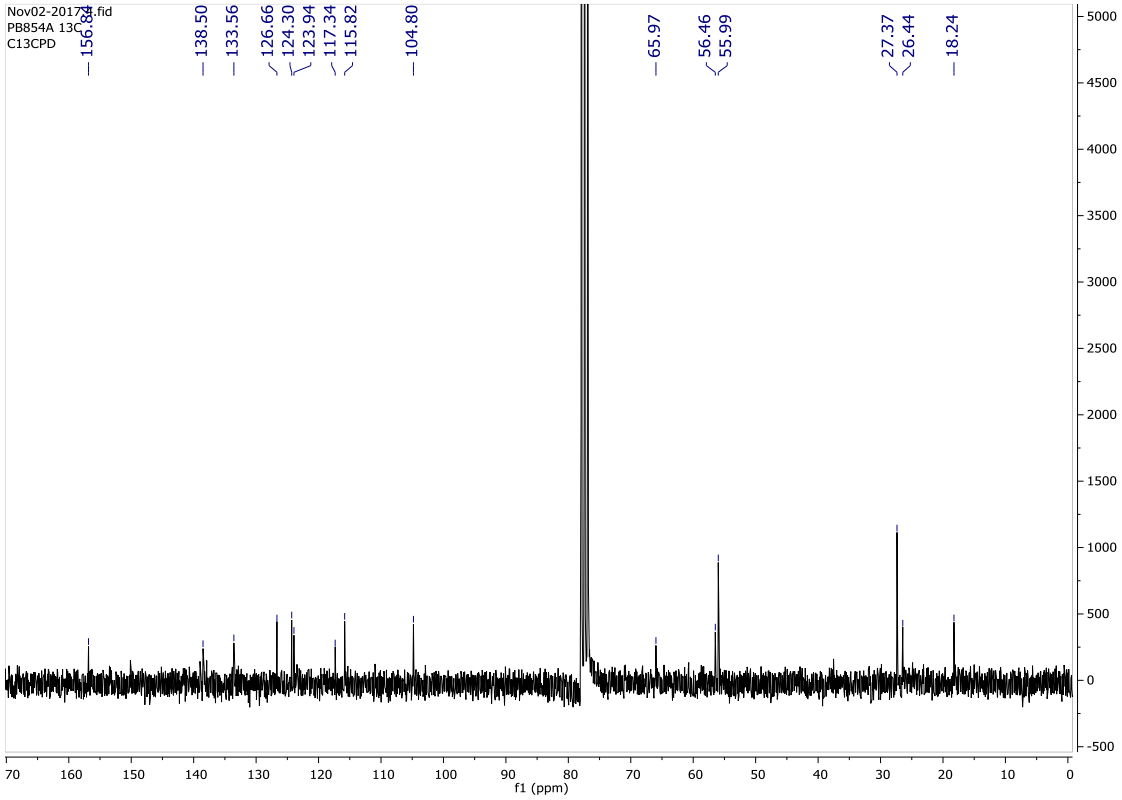
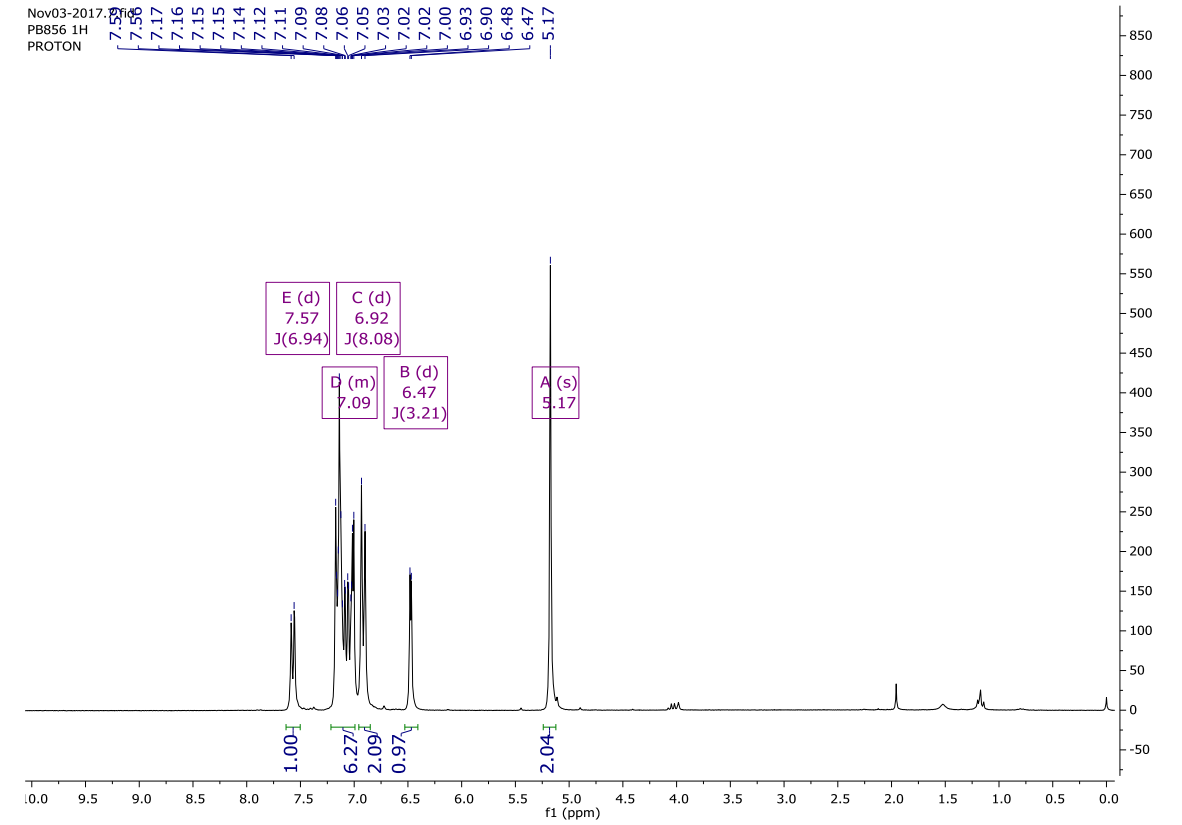
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)

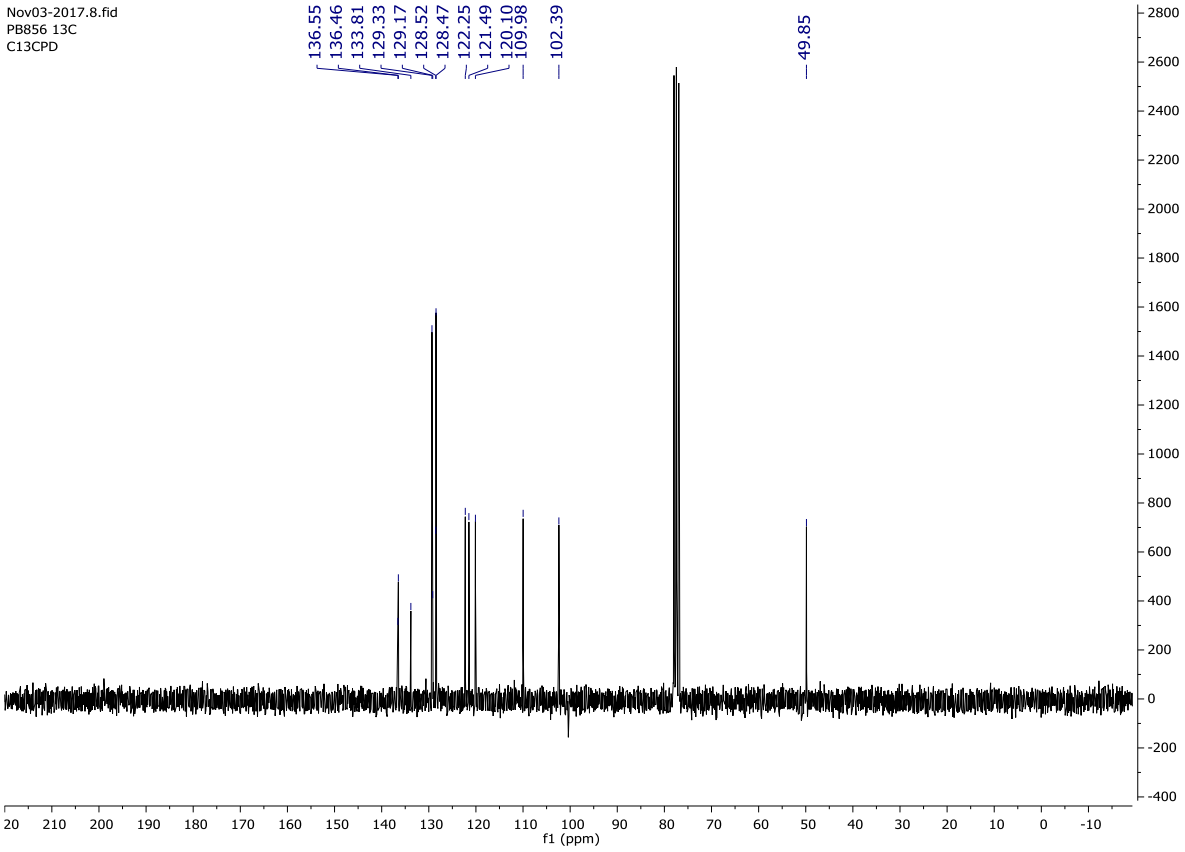
2-(5-(2-(azepan-1-yl)ethoxy)benzo[b]thiophen-3-yl)acetonitrile (4i)



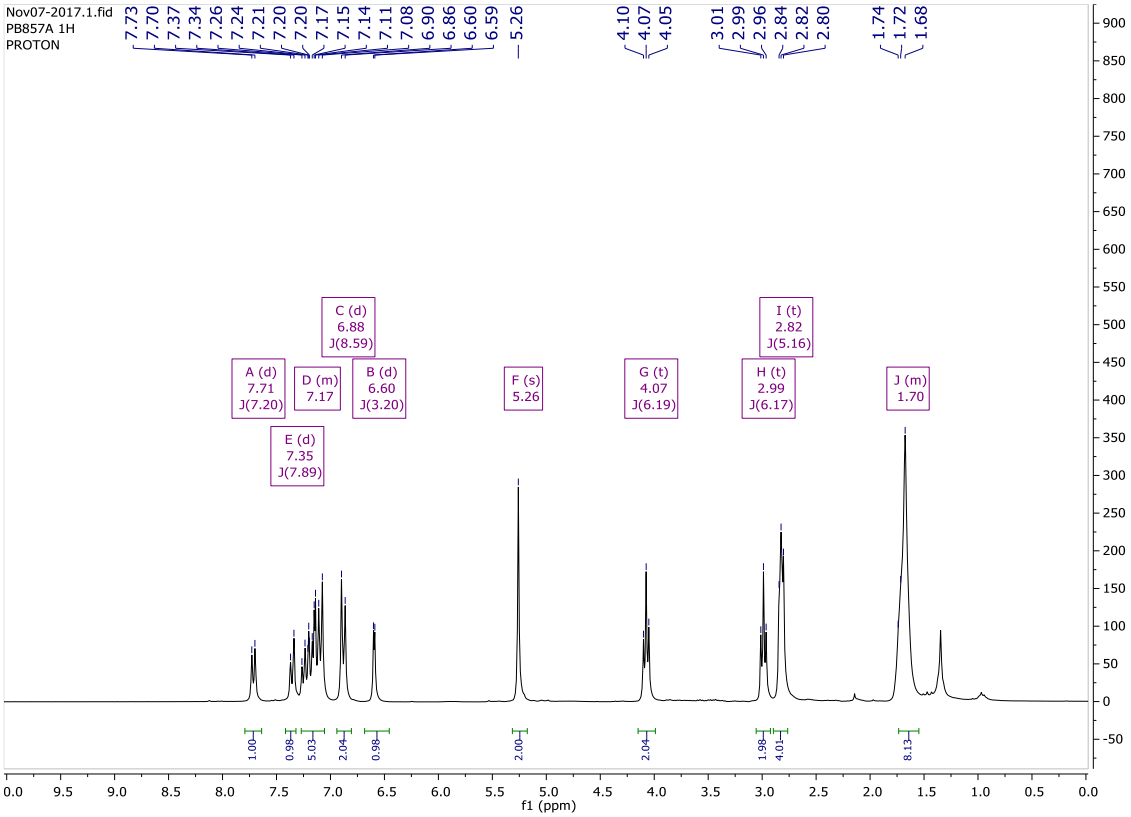


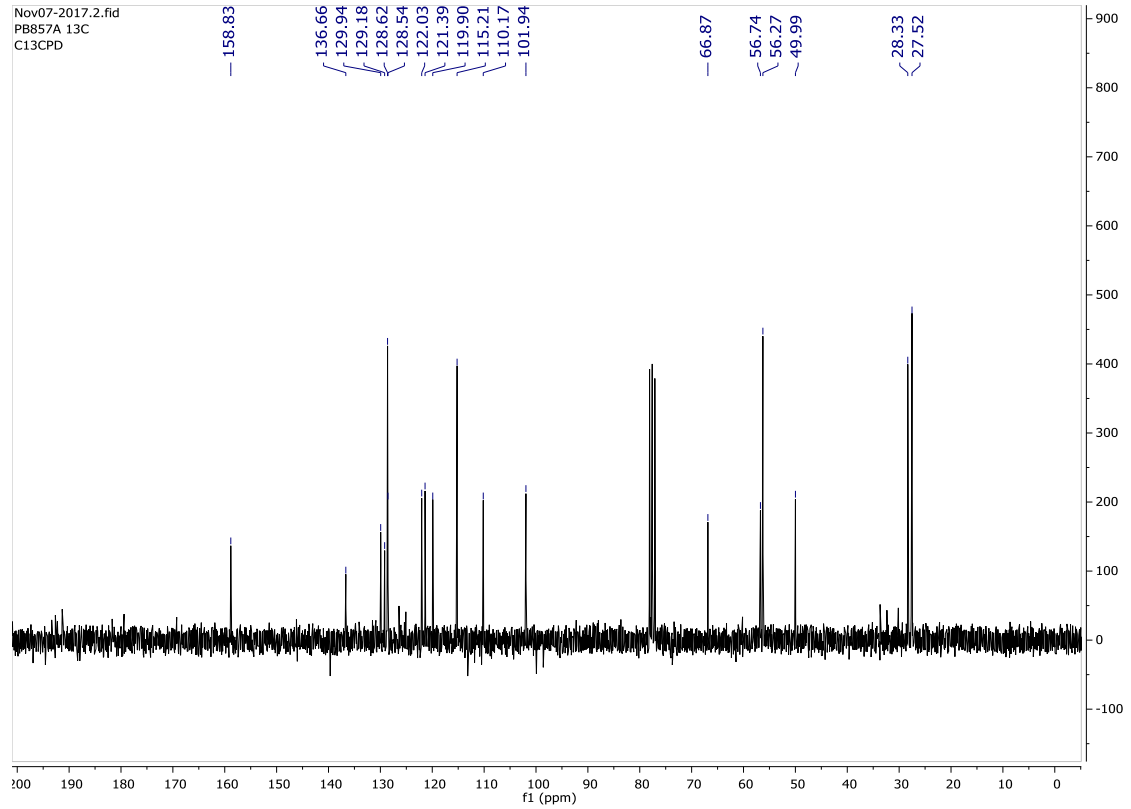
1-(4-chlorobenzyl)-1*H*-indole (5a)



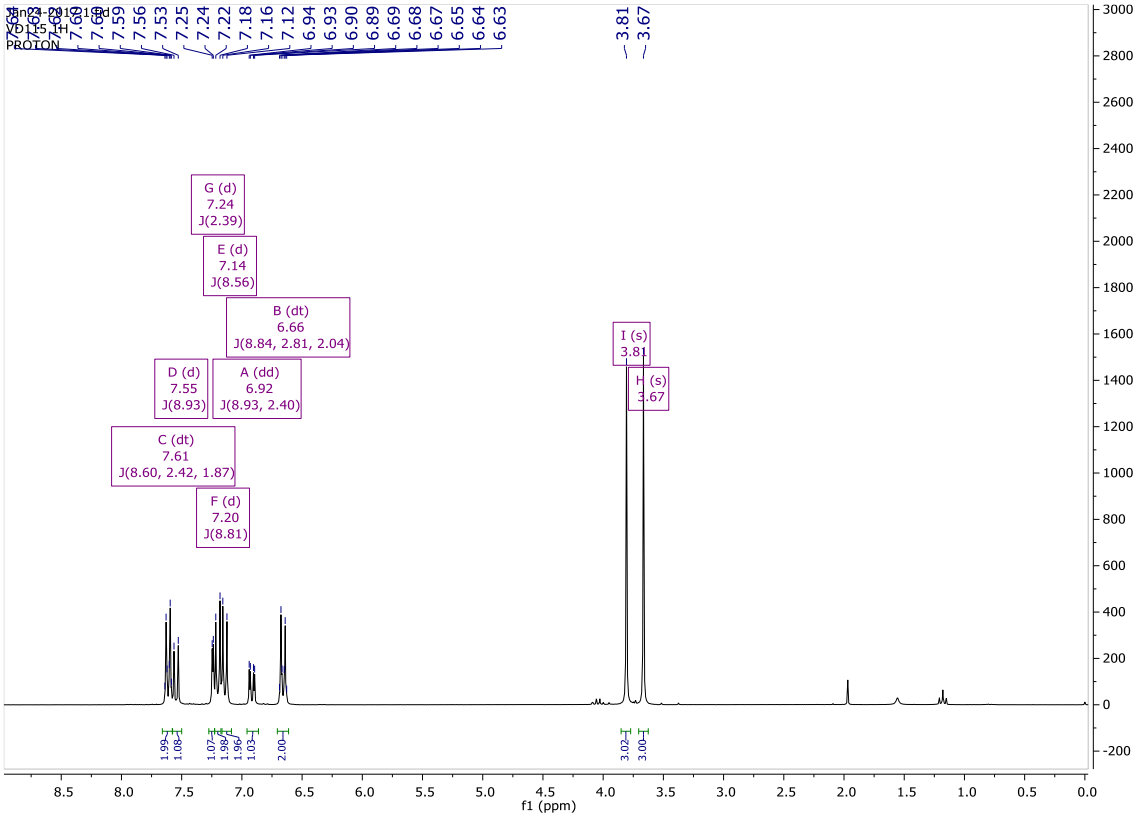


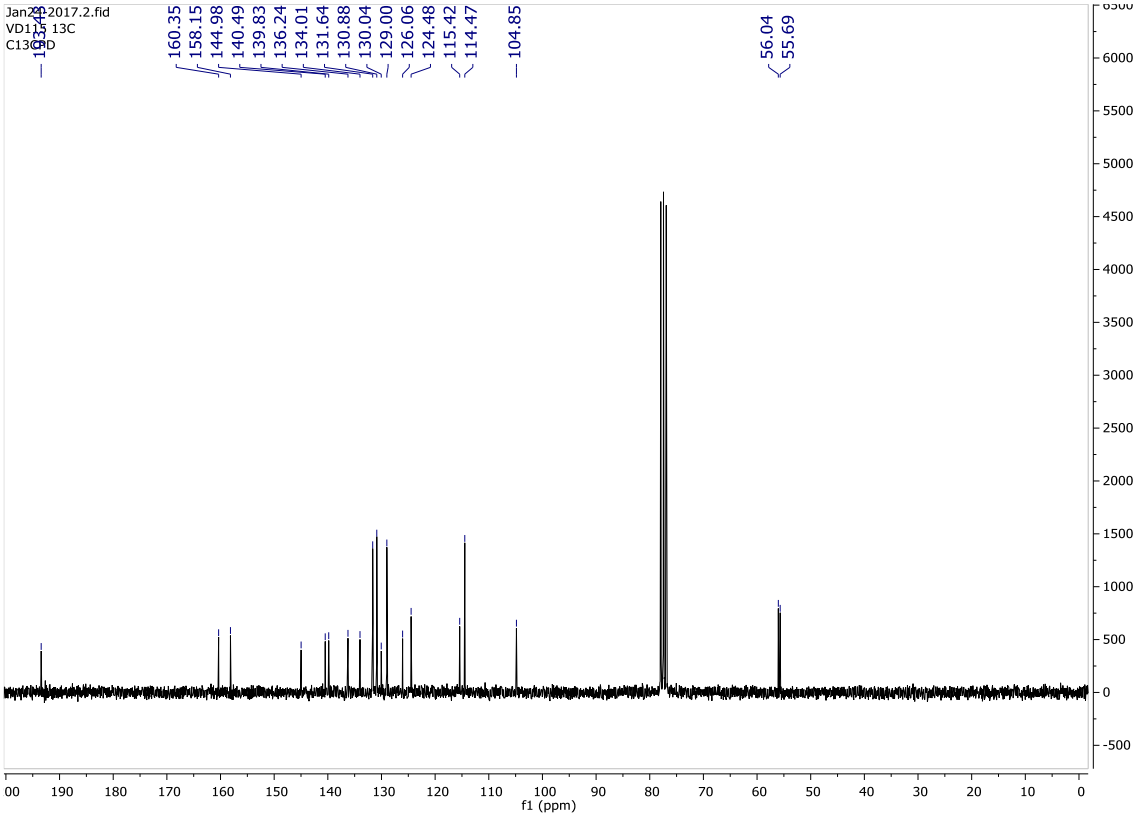
1-(4-(2-(azepan-1-yl)ethoxy)benzyl)-1H-indole (5b)





(4-chlorophenyl)(6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)methanone (6b)





(6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophen-3-yl)(4-(2-(piperidin-1-yl)ethoxy)phenyl)methanone (6c)