Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Mannich reaction of trifluoroacetaldehyde hydrazones, a useful entry to trifluoromethyl substituted heterocycles

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Supporting Information

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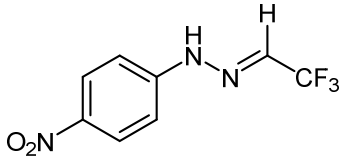
1 General Considerations

NMR spectra were recorded at 298 K using a Bruker AVANCE 400 spectrometer. ^{1}H NMR spectra were recorded at 400 MHz and residual solvent peaks were used as an internal reference ($CDCl_3$ δ 7.26). Data are reported as follows: chemical shift in ppm, apparent multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet or overlap of nonequivalent resonances), coupling constants, integration. ^{13}C NMR spectra were recorded at 100 MHz and residual solvent peaks were used as an internal reference ($CHCl_3$ δ 77.16). Data are reported as follows: chemical shift in ppm, multiplicity deduced from DEPT experiments (CH_3, CH_2, CH, Cq), apparent multiplicity, coupling constants and integration where relevant. Analytical TLC was performed with Merck silica gel plates, pre-coated with silica gel 60 F254 (0.2 mm). Visualisation was effected by quenching of UV fluorescence (λmax = 254 nm or 360 nm) and by staining with p-anisaldehyde, potassium permanganate or vanillin TLC stain solutions, followed by heating. Flash chromatography employed VWR (230–400 mesh) silica gel. Reactions were conducted under a positive pressure of dry nitrogen or argon in oven-dried or flame dried glassware, and at ambient room temperature, unless specified otherwise. Anhydrous solvents were either obtained from commercial sources or dried with a MBRAUN Solvent Purification System SPS-800. Petroleum ether refers to the 40-60 °C boiling fraction. Commercially available chemicals were used as purchased, or where specified, purified by standard techniques. IR spectra were recorded on a Perkin Elmer Spectrum 65 FT-IR Spectrometer. Melting points were measured on a Stuart SMP3 melting point apparatus and are uncorrected. High resolution mass spectra were recorded on an Agilent 1100 series LC-MS (with a 6310 ion trap) under electrospray ionization (ESI). For compounds containing bromine, the mass of 79Br was used.

2 General Procedure

2.1 Synthesis of hydrazones

Trifluoroacetaldehyde 4-nitrophenylhydrazone



$C_8H_6F_3N_3O_2$

233.15g.mol^{-1}

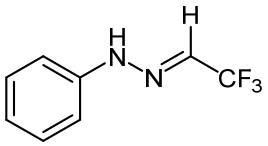
Trifluoroacetaldehyde 4-nitrophenylhydrazone was prepared by dissolving 4-nitrophenylhydrazine (380mg, 2.5mmol) in water (10ml) containing concentrated hydrochloric acid (d = 1.18, 0.2ml). Ethyl trifluoroacetaldehyde hemiacetal (0.4ml, 5mmol) was added and the solution was heated at 45^{o}C for 10 min, it was then kept at room temperature for 1.5h during which time trifluoroacetaldehyde 4-nitrophenylhydrazone separated as fine yellow solid (525mg, 90%, 210.1^{o}C-212.5^{o}C). The spectra data

are in agreement with the literature report.[1]

^{1}H NMR (400 MHz,DMSO) δ 11.80(s, 1H), 8.19 (d, *J* = 9.2 Hz, 2H),7.54 (q, *J* =4.3Hz, 1H), 7.19 (d, *J* = 9.2 Hz, 2H)

^{13}C NMR (101 MHz, DMSO) δ 149.2, 140.5, 126.8(q, *J* = 37 Hz), 126.1, 121.2(q, *J* = 267 Hz), 112.5.

Trifluoroacetaldehyde phenylhydrazone



$C_8H_7F_3N_2$

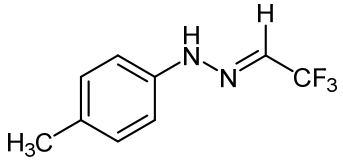
188.15 g.mol^{-1}

Trifluoroacetaldehyde phenylhydrazone was prepared by dissolving phenylhydrazine (271mg, 2.5mmol) in water (10ml) containing concentrated hydrochloric acid (d = 1.18, 0.2ml). Ethyl trifluoroacetaldehyde hemiacetal (0.4ml, 5mmol) was added and the solution was heated at 45^{o}C for 10 min, it was then kept at room temperature for 1.5h during which time trifluoroacetaldehyde phenylhydrazone separated as fine yellow solid (385mg, 82%, 68.2^{o}C-69.8^{o}C). The spectra data are in agreement with the literature report.[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.24-7.20 (m, 2H), 7.01-6.98 (m, 2H), 6.94 – 6.87 (m, 1H), 6.87 – 6.79 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 129.6, 122.4(q, *J* = 39 Hz), 122.3, 121.2(q, *J* = 268 Hz), 113.6

Trifluoroacetaldehyde 4-methylphenylhydrazone



$C_9H_9F_3N_2$

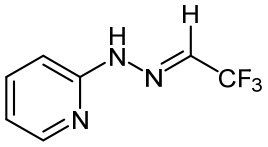
202.18 g.mol^{-1}

Trifluoroacetaldehyde 4-methylphenylhydrazone was prepared by dissolving 4-methylphenylhydrazine (306mg, 2.5mmol) in water (10ml) containing concentrated hydrochloric acid (d = 1.18, 0.2ml). Ethyl trifluoroacetaldehyde hemiacetal (0.4ml, 5mmol) was added and the solution was heated at 45^{o}C for 10 min, it was then kept at room temperature for 1.5h during which time trifluoroacetaldehyde 4-methylphenylhydrazone separated as fine yellow solid (355mg, 70%, 89.7^{o}C-90.6^{o}C). The spectra data are in agreement with the literature report.[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.15-7.13 (m, 2H), 7.04-6.98 (m, 2H), 6.90 (q, *J* =4.1Hz, 1H), 2.34(s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 131.7, 129.9, 121.7(q, *J* = 39 Hz), 121.2(q, *J* = 268 Hz), 113.6, 20.6.

(E)-2-(2-(2,2,2-trifluoroethylidene)hydrazinyl)pyridine



$C_7H_6F_3N_3$

189.14 g.mol^{-1}

A solution of 2-bromopyridine (1.42g, 9mmol) and hydrazine hydrate (20mmol) was placed in a three-necked flask fitted with mechanical stir, a dropping funnel and thermometer. The reaction mixture was stirred at reflux for 4h under an inert atmosphere of N_2. The reaction mixture was next extracted at room temperature with Et_2O (3×50ml). The organic layer was evaporated under reduced pressure to provide, in 50% yield, the 2-hydrazinepyridye as a white oil (850mg, 50%).[2]

2-hydrazinepyridye (1mmol) was added to a solution of ethyl trifluoroacetaldehyde hemiacetal (1.25mmol) in EtOH (2ml) .The stirred mixture was heated to reflux for 10h under Ar. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was washed by n-hexane (3×5ml) to afford a white solid (170mg, 90%, 159.6°C-161.9°C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.16 (d, *J* = 4.9 Hz, 1H), 7.79 – 7.67 (m, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.13 (q, *J* = 3.9 Hz, 1H), 7.02 – 6.92 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 146.4, 139.2, 124.9(q, *J* = 39 Hz), 120.9(q, *J* = 268 Hz), 117.7, 108.7.

HRMS: calculated for $C_{13}H_{15}F_3N_4O_3$: 189.0514, found: 189.0510

I.R.(thin film): 3334,1626,1599, 1580, 1519, 1446, 1354, 1301, 1290, 1266, 1136, 1092cm^{-1}.

2.2 General procedure for the formation of Mannich adducts

Hydrazone (0.5mmol) was added to a solution of secondary amine (0.5mmol) and aldehyde (0.5mmol) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford the desired product.

2.3 General procedure for the formation of dihydropyridazine derivatives.

Mannich adduct (0.5mmol) was dissolved in 3mL diketone, and the stirred mixture was heated to 130°C under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford the desired product.

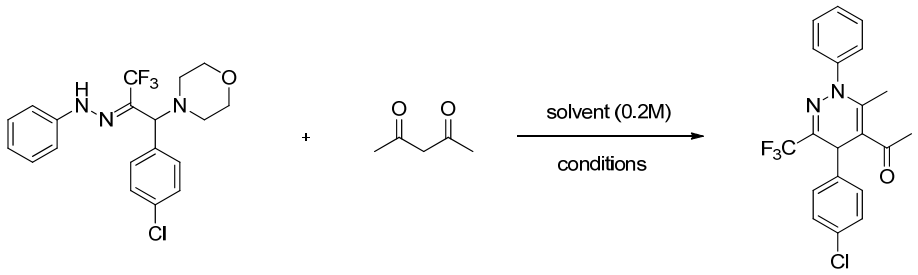
4b was dissolved in 3ml acetone and the mixture was heated to 130°C under microwave condition for 1h.

References:

[1] Wojciechowska, A.; Jasiński, M.; Kaszyński, P. *Tetrahedron*, **2015** , *71*, 2349 – 2356.

[2] Todeschini, Adriane R.; Barreiro, Eliezer J. *European Journal of Medicinal Chemistry,* **1998** , *33*, 189 – 199.

2.4 Optimization table for the preparation of dihydropyridazine derivatives.

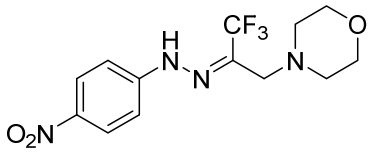


neat, 110°C,12h	45%
neat, 130°C, 12h	71%
neat, 150°C, 6h	55%
DMF, 2eq. diketone, 130°C, 12h	26%
toluene, 2eq. diketone, M.W. 150°C, 20min	no reaction
DMF, 2eq. diketone, $Zn(OTf)_2$, 20mol%, M.W. 150°C, 20min	no reaction

3 Characterization Data

Spectroscopic Data of All Compounds

Compound **4a**



$C_{13}H_{15}F_3N_4O_3$

332.28g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and formaldehyde (0.5mmol, 41mg, 37%, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=50:50) to afford the desired product **4a** (94%, 156mg).

Aspect: light yellow solid, m. p. 118.5-119.7 °C.

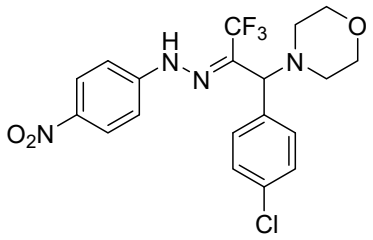
Rf: 0.43 (Et_2O:PE=50:50)

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.72 (s, 1H), 8.18 (d, *J* = 9.2 Hz, 2H), 7.12 (d, *J* = 9.2 Hz, 2H), 3.76 (bs, 4H), 3.52 (s, 2H), 2.55 (bs, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7, 141.9, 130.8(q, *J* = 34 Hz), 126.1, 121.2(q, *J* = 271 Hz), 112.8, 67.0, 54.8, 52.8.

HRMS: calculated for $C_{13}H_{15}F_3N_4O_3$: 332.1096, found: 332.1081
I.R.(thin film): 3689, 2838, 1595, 1511, 1377, 1338, 1325, 1258, 1207, 1124, 1111, 1052, 1005cm^{-1}.

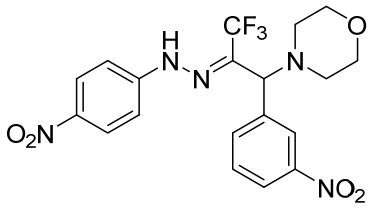
Compound **4b**



$C_{19}H_{18}ClF_3N_4O_3$
442.82$g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and p-chlorobenzaldehyde (0.5mmol, 70mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=60:40) to afford the desired product **4b** (99%, 220mg).
Aspect: light yellow solid, m. p. 88.2-90.1 °C.
Rf: 0.50 (Et_2O:PE=60:40)
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.61 (s, 1H), 8.22 (d, *J* = 9.2 Hz, 2H), 7.36-7.31 (m, 4H), 7.20 (d, *J* = 9.1 Hz, 2H), 4.22 (s, 1H), 3.74 (bs, 4H), 2.47 (bs, 4H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 142.0, 135.4, 133.4, 132.6(q, *J* = 33 Hz), 130.2, 129.8, 126.2, 121.3(q, *J* = 272 Hz), 112.8, 71.1, 67.1, 52.2.
HRMS: calculated for $C_{19}H_{18}ClF_3N_4O_3$: 442.1020, found: 442.1016
I.R.(thin film): 3691, 2973, 2853, 1595, 1511, 1494, 1337, 1256, 1209, 1159, 1122, 1112, 1016cm^{-1}

Compound **4c**



$C_{19}H_{18}F_3N_5O_5$
453.38$g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and 3-nitrobenzaldehyde (0.5mmol, 76mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: EA:PE=40:60) to afford the desired product **4c** (99%, 225mg).
Aspect: yellow solid, m. p. 155.1-156.6 °C.

Rf: 0.47 (EA:PE=40:60)

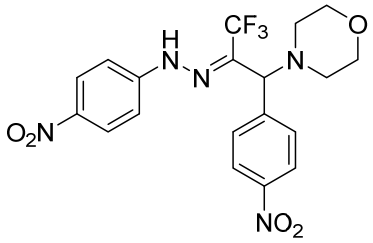
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.46 (s, 1H), 8.30 – 8.20 (m, 4H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.27 – 7.20 (m, 2H), 4.39 (s, 1H), 3.91 – 3.64 (m, 4H), 2.65 – 2.41 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8, 148.1, 142.4, 137.0, 134.6, 131.2(q, *J* = 33 Hz), 130.8, 126.2, 124.4, 123.9, 123.7(q, *J* = 272 Hz), 113.1, 70.8, 67.0, 52.3.

HRMS: calculated for $C_{19}H_{18}F_3N_5O_5$: 453.1260, found: 453.1252.

I.R.(thin film): 3692, 3094, 2973, 2854, 2258, 1595, 1536, 1513, 1351, 1338, 1257, 1249, 1210, 1160, 1123, 1123, 1112, 1035cm^{-1}

Compound **4d**



$C_{19}H_{18}F_3N_5O_5$

453.38g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and 3-nitrobenzaldehyde (0.5mmol, 76mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: EA:PE=20:80)to afford the desired product **4d** (99%, 224mg).

Aspect: yellow solid m.p. 123.5-124.6^{o}C

Rf: 0.20 (EA:PE=20:80)

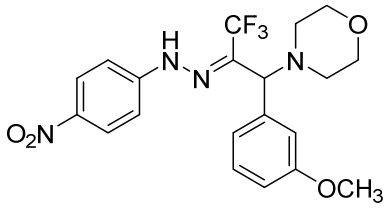
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.51 (s, 1H), 8.25-8.21 (m, 4H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 9.1 Hz, 2H), 4.38 (s, 1H), 3.90 – 3.67 (m, 4H), 2.63 – 2.41 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 148.1, 142.3, 142.0, 131.2(q, *J* = 33 Hz), 129.9, 126.2, 124.7, 121.2(q, *J* = 270 Hz), 113.0, 70.9, 67.0, 52.3.

HRMS: calculated for $C_{19}H_{18}F_3N_5O_5$:453.1260, found: 453.1269

I.R.(thin film): 2972, 2854, 1594, 1529, 1338, 1245, 1151, 1123, 1112, 1034cm^{-1}

Compound **4e**



$C_{20}H_{21}F_3N_4O_4$

438.41g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and 3-methoxybenzaldehyde (0.5mmol, 68mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=50:50) to afford the desired product **4e** (99%, 216mg).

Aspect: yellow oil

Rf: 0.38 (Et_2O:PE=50:50)

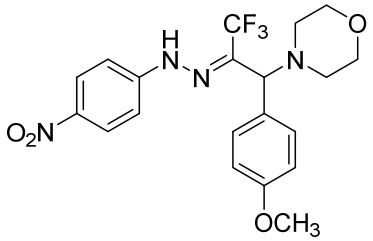
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.67 (s, 1H), 8.22 (d, *J* = 9.2 Hz, 2H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.22 – 7.15 (m, 2H), 7.00 – 6.86 (m, 3H), 4.20 (s, 1H), 3.77(s,3H), 3.75 (bs ,4H), 2.49 (bs, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 148.5, 141.9, 136.4, 133.0(q, *J* = 32 Hz), 130.6, 126.2, 121.3(q, *J* = 273 Hz) 121.0, 115.3, 113.9, 112.7, 71.7, 67.2, 55.4, 52.2.

HRMS: calculated for $C_{20}H_{21}F_3N_4O_4$: 438.1515, found: 438.1499.

I.R.(thin film): 3692, 3109, 2971, 2853, 2838, 1596, 1511, 1455, 1336, 1255, 1209, 1159, 1122, 1034cm^{-1}

Compound **4f**



$C_{20}H_{21}F_3N_4O_4$

438.41$g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and 3-methoxybenzaldehyde (0.5mmol, 68mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=50:50) to afford the desired product **4f** (82%, 179mg).

Aspect: light yellow solid, m. p. 189.9-192.1 ^oC.

Rf: 0.35 (Et_2O:PE=50:50)

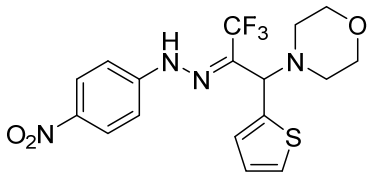
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.75 (s, 1H), 8.22 (d, *J* = 9.2 Hz, 2H), 7.29-7.18 (m, 4H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.19 (s, 1H), 3.79 (s, 3H), 3.75(bs, 4H), 2.47 (bs, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 148.6, 141.7, 133.7(q, *J* = 32 Hz), 130.2, 126.8, 126.2, 121.3(q, *J* = 273 Hz), 114.8, 112.7, 71.2, 67.2, 55.4, 52.1.

HRMS: calculated for $C_{20}H_{21}F_3N_4O_4$: 438.1515, found: 438.1520.

I.R.(thin film): 3689, 2971, 2853, 2839, 1596, 1513, 1457, 1336, 1255, 1207, 1157, 1112, 1034cm^{-1}

Compound **4g**



$C_{17}H_{17}F_3N_4O_3S$

414.40g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and thiophene-2-carbaldehyde (0.5mmol, 57mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 15h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=50:50) to afford the desired product **4g** (48%, 100mg).

Aspect: black solid, m. p. 135.1-137.2 °C.

Rf: 0.5 (Et_2O:PE=50:50)

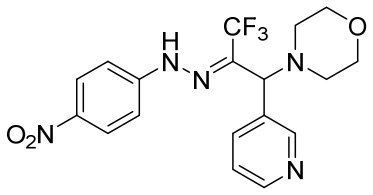
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.26 – 8.19 (m, 2H), 7.30 (dd, *J* = 4.2, 0.7 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.12 (dd, *J* = 3.5, 1.0 Hz, 1H), 6.99 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.59 (s, 1H), 3.75 (bs, 4H), 2.65 – 2.36 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 142.1, 136.2, 131.8(q, *J* = 33 Hz), 129.6, 127.2, 127.0, 126.2, 121.3(q, *J* = 272 Hz), 112.9, 67.2, 65.5, 51.9.

HRMS: calculated for $C_{17}H_{17}F_3N_4O_3S$: 414.0973, found: 414.0974.

I.R.(thin film): 3689, 1596, 1511, 1337, 1254, 1210, 1160, 1112, 1032cm^{-1}

Compound **4h**



$C_{18}H_{18}F_3N_5O_3$

409.37g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and nicotinaldehyde (0.5mmol, 54mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 15h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=50:50) to afford the desired product **4h** (99%, 201mg).

Aspect:white solid, m. p. 182.6-183.4 °C.

Rf: 0.45 (Et_2O:PE=50:50)

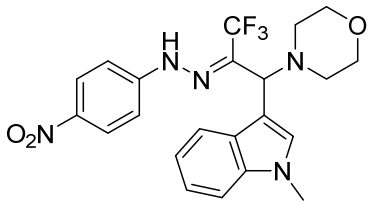
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.52 (s, 1H), 8.71 – 8.58 (m, 2H), 8.20 (d, *J* = 9.1 Hz, 2H), 7.73 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.33 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.25 – 7.15 (m, 2H), 4.28 (s, 1H), 3.76 (bs, 4H), 2.49 (bs, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 150.1, 148.2, 142.1, 136.1, 131.8(q, *J* = 33 Hz), 131.0, 126.1, 124.3, 121.1(q, *J* = 272 Hz)112.9, 69.1, 66.9, 52.2.

HRMS: calculated for $C_{18}H_{18}F_3N_5O_3$: 409.1362, found: 409.1373.

I.R.(thin film): 3689, 3039, 2973, 2916, 2895, 2854, 2836, 2768, 2446, 2233, 1595, 1513, 1456, 1337, 1264, 1209, 1159, 1123, 1112, 1035cm^{-1}

Compound **4i**



$C_{22}H_{22}F_3N_5O_3$

461.45$g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and 1-methyl-1*H*-indole-3-carbaldehyde (0.5mmol, 80mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 15h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=50:50) to afford the desired product **4i** (58%, 133mg).

Aspect: gray solid, m. p. 178.1-180.0 °C.

Rf: 0.42 (Et_2O:PE=50:50)

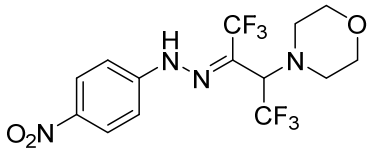
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.75 (s, 1H), 8.24 (d, *J* = 9.0 Hz, 2H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.39 – 7.10 (m, 6H), 4.64 (s, 1H), 3.77 (s, 3H), 3.72(bs, 4H), 2.60 (bs, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8, 141.6, 136.6, 135.2(q, *J* = 31 Hz), 128.1, 126.2, 122.5, 121.2(q, *J* = 273 Hz), 120.4, 118.5, 112.5, 109.9, 107.3, 67.3, 61.6, 51.9, 33.2.

HRMS: calculated for $C_{22}H_{22}F_3N_5O_3$: 461.1675, not found, fragment 373.0319

I.R.(thin film): 3689, 2971, 2853, 1596, 1509, 1425, 1334, 1297, 1256, 1207, 1154, 1113, 1071, 1034, 1005cm^{-1}

Compound **4j**



$C_{14}H_{14}F_6N_4O_3$

400.28$g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and ethyl trifluoroacetaldehyde hemiacetal (0.5mmol, 65mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=50:50) to afford the desired product **4j** (79%, 158mg).

Aspect: brown solid, m. p. 198.6-199.5 °C.

Rf: 0.44 (Et_2O:PE=50:50)

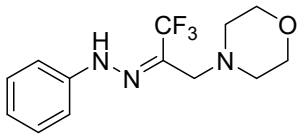
^{1}H NMR (400 MHz, MeOD) δ 8.15 (d, *J* = 9.1 Hz, 2H), 7.28 (d, *J* = 4.2 Hz, 1H), 7.15 (d, *J* = 9.1 Hz, 2H), 3.68 – 3.59 (m, 4H), 2.78 (2.82-2.73, m, 4H).

^{13}C NMR (101 MHz, MeOD) δ 150.7, 142.6, 127.4(q, *J* = 39 Hz), 126.9 (q, *J* = 291 Hz) 126.8, 122.5(q, *J* = 267 Hz) 113.4, 84.2(q, *J* = 27 Hz), 68.3, 51.0.

HRMS: calculated for $C_{14}H_{14}F_6N_4O_3$: 400.0970, not found, fragment 234.0365

I.R.(thin film): 3691, 2968, 2860, 1596, 1454, 1339, 1273, 1251, 1161, 1117, 1021cm^{-1}

Compound **4k**



$C_{13}H_{16}F_3N_3O$

287.29g.mol^{-1}

Trifluoroacetaldehyde phenylhydrazone (0.5mmol, 94mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and formaldehyde (0.5mmol, 41mg, 37%, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2:PE=50:50) to afford the desired product **4k** (95%, 136mg).

Aspect: colourless solid, m. p. 127.9-128.9 °C.

Rf: 0.41 (CH_2Cl_2:PE=50:50)

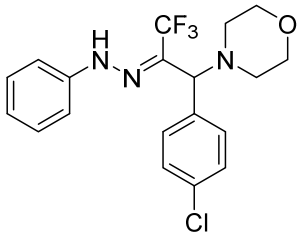
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (s, 1H), 7.36 – 6.84 (m, 5H), 3.75 (bs, 4H), 3.45 (s, 2H), 2.51 (bs, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 129.5, 126.3(q, *J* = 34 Hz), 121.9(q, *J* = 270 Hz), 121.8, 113.4, 67.1, 54.4, 52.7.

HRMS: calculated for $C_{13}H_{16}F_3N_3O$: 287.1245, found: 287.1247.

I.R.(thin film): 3172, 3107, 3030, 2973, 2858, 2833, 1601, 1523, 1496, 1456, 1376, 1346, 1296, 1251, 1155, 1119, 1053, 1005cm^{-1}

Compound **4l**



$C_{19}H_{19}ClF_3N_3O$

397.83g.mol^{-1}

Trifluoroacetaldehyde phenylhydrazone (0.5mmol, 94mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and p-chlorobenzaldehyde (0.5mmol, 70mg, 1.0eq) in 3ml toluene. The stirred

mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=40:60) to afford the desired product **4l** (85%, 169mg).

Aspect: white solid, m. p. 135.8-136.7 °C.

Rf: 0.51 (Et_2O:PE=40:60)

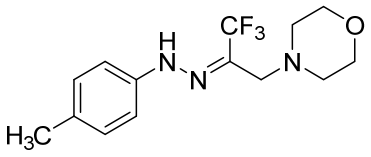
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.94 (s, 1H), 7.39-7.32(m, 6H), 7.19-7.16 (m, 2H), 7.02-6.98 (m, 1H), 4.16 (s, 1H), 3.76 (bs, 4H), 2.47 (bs, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 134.9, 134.6, 130.3, 129.6, 129.5, 127.7(q, *J* = 32 Hz), 121.9, 121.9(q, *J* = 272 Hz), 113.3, 70.7, 67.2, 52.2.

HRMS: calculated for $C_{19}H_{19}ClF_3N_3O$: 397.1169, found: 397.1172.

I.R.(thin film): 3691, 3169, 3031, 2971, 2916, 2883, 2855, 1599, 1514, 1493, 1456, 1364, 1245, 1210, 1164, 1119, 1096, 1035cm^{-1}

Compound **4m**



$C_{14}H_{18}F_3N_3O$

301.31g.mol^{-1}

Trifluoroacetaldehyde 4-methylphenylhydrazone (0.5mmol, 101mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and formaldehyde (0.5mmol, 41mg, 37%, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=40:60)to afford the desired product **4m** (95%, 143mg).

Aspect: yellow oil

Rf: 0.34 (Et_2O:PE=40:60)

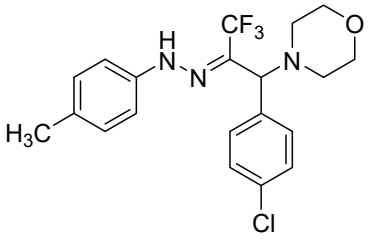
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.91 (s, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.06 – 6.98 (m, 2H), 3.74 (bs, 4H), 3.44 (s, 2H), 2.51 (bs, 4H), 2.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5, 131.2, 129.9, 125.5(q, *J* = 34 Hz), 121.9(q, *J* = 270 Hz), 113.4, 67.1, 54.3, 52.7, 20.8.

HRMS: calculated for $C_{14}H_{18}F_3N_3O$:301.1402, found: 301.1404

I.R.(thin film): 3691, 3171, 3026, 2973, 2859, 2834, 1606, 1525, 1456, 1376, 1346, 1273, 1251, 1174, 1118,1053, 1005cm^{-1}

Compound **4n**



$C_{20}H_{21}ClF_3N_3O$

411.85g.mol^{-1}

Trifluoroacetaldehyde 4-methylphenylhydrazone (0.5mmol, 101mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and p-chlorobenzaldehyde (0.5mmol, 70mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2:PE=50:50) to afford the desired product **4n** (68%, 140mg).

Aspect: yellow oil

Rf: 0.34 (DCM:PE=50:50)

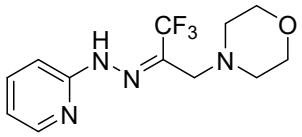
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.85 (s, 1H), 7.40-7.32 (m, 4H), 7.20 – 7.05 (m, 4H), 4.16 (s, 1H), 3.76 (bs, 4H), 2.47 (bs, 4H), 2.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2, 134.9, 134.7, 131.4, 130.3, 130.1, 129.5, 127.0(q, *J* = 32 Hz), 122.0(q, *J* = 272 Hz) , 113.3, 70.6, 67.2, 52.2, 20.8.

HRMS: calculated for $C_{20}H_{21}ClF_3N_3O$:411.1325, found: 411.1306

I.R.(thin film): 3691, 3170, 2971, 2856, 1604, 1524, 1493, 1455, 1364, 1287, 1244, 1205, 1164, 1096, 1035cm^{-1}

Compound **4o**



$C_{12}H_{15}F_3N_4O$

288.27g.mol^{-1}

(E)-2-(2-(2,2,2-trifluoroethylidene)hydrazinyl)pyridine (0.5mmol, 90mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and formaldehyde (0.5mmol, 41mg, 37%, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: EA:PE=50:50) to afford the desired product **4o** (81%, 116mg).

Aspect: yellow oil

Rf: 0.54 (EA:PE=50:50)

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 8.24 (d, *J* = 4.7 Hz, 1H), 7.66 (dd, *J* = 10.8, 4.8 Hz, 1H), 7.38 – 7.21 (m, 1H), 6.94 – 6.79 (m, 1H), 3.89 – 3.69 (m, 4H), 3.49 (s, 2H), 2.54 (bs, 4H).

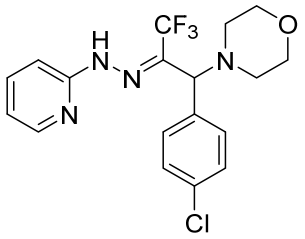
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 147.9, 138.2, 128.4(q, *J* = 34 Hz), 121.4(q, *J* = 271 Hz), 117.4, 107.6,

66.8, 54.3, 52.8.

HRMS: calculated for $C_{12}H_{15}F_3N_4O$:288.1198, found: 288.1200.

I.R.(thin film): 3172, 2972, 2899, 2863, 2830, 1597, 1577, 1515, 1444, 1375, 1345, 1296, 1268, 1178, 1146, 1058cm^{-1}

Compound **4p**



$C_{18}H_{18}ClF_3N_4O$

398.81$g.mol^{-1}$

(E)-2-(2-(2,2,2-trifluoroethylidene)hydrazinyl)pyridine (0.5mmol, 90mg, 1.0eq) was added to a solution of morpholine (0.5mmol, 44mg, 1.0eq) and p-chlorobenzaldehyde (0.5mmol, 70mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 15h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: EA:PE=40:60) to afford the desired product **4p** (47%, 93mg).

Aspect: yellow oil

Rf: 0.63(EA:PE=40:60)

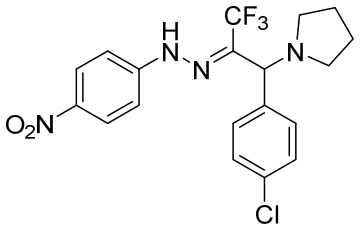
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.11 (s, 1H), 8.27 – 8.19 (m, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.26 (m, 3H), 6.89 (dd, *J* = 8.1, 4.0 Hz, 1H), 4.16 (s, 1H), 3.87 – 3.73 (m, 4H), 2.45 (bs, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 148.1, 138.4, 135.0, 134.3, 130.3, 129.6(q, *J* = 32 Hz),129.4, 121.5(q, *J* = 272 Hz), 117.6, 107.6, 70.7, 66.8, 52.3.

HRMS: calculated for $C_{18}H_{18}ClF_3N_4O$:398.1121, found: 398.1131.

I.R.(thin film): 3173, 2970, 2860, 2828, 1596, 1575, 1510, 1493, 1443, 1362, 1297, 1269, 1169, 1146, 1120, 1094, 1036cm^{-1}

Compound **4q**



$C_{19}H_{18}ClF_3N_4O_2$

426.82$g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of pyrrolidine (0.5mmol, 36mg, 1.0eq) and p-chlorobenzaldehyde (0.5mmol, 70mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the

reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2:PE = 50:50) to afford the desired product **4q** (82%, 175mg).

Aspect: yellow oil

Rf: 0.47 (CH_2Cl_2:PE=50:50)

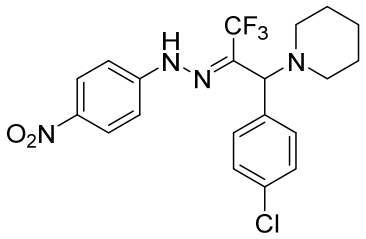
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.63 (s, 1H), 8.08 (d, *J* = 9.2 Hz, 2H), 7.25 – 7.17 (m, 4H), 7.03 (d, *J* = 9.2 Hz, 2H), 4.09 (s, 1H), 2.39 (bs, 4H), 1.91-1.84 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 141.7, 135.8, 134.9, 133.8(q, *J* = 32 Hz), 129.7, 129.5, 126.1, 121.3(q, *J* = 272 Hz), 112.8, 69.6, 53.1, 23.6.

HRMS: calculated for $C_{19}H_{18}ClF_3N_4O_2$:426.1070, found:426.1076.

I.R.(thin film): 3691, 2976, 2824, 1594, 1509, 1493, 1336, 1254, 1208, 1161, 1127, 1111, 1015cm^{-1}

Compound **4r**



$C_{20}H_{20}ClF_3N_4O_2$

440.85g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of piperidine (0.5mmol, 43mg, 1.0eq) and p-chlorobenzaldehyde (0.5mmol, 70mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2:PE = 40:60)to afford the desired product **4r** (87%, 191mg).

Aspect: light yellow solid, m.p. 192.9-194.4°C

Rf: 0.50 (DCM:PE=40:60)

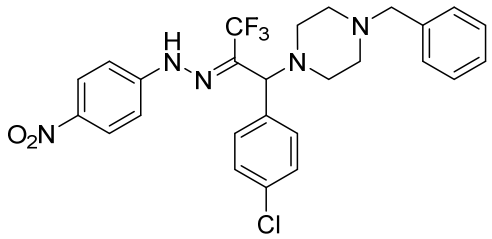
^{1}H NMR (400 MHz, $CDCl_3$) δ 13.03 (s, 1H), 8.21 (d, *J* = 9.2 Hz, 2H), 7.32 (s, 4H), 7.23 – 7.14 (m, 2H), 4.17 (s, 1H), 2.40 (bs, 4H), 1.70 – 1.50 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8, 141.7, 135.0, 134.7, 133.7(q, *J* = 32 Hz), 130.2, 129.6, 126.2, 121.3(q, *J* = 273 Hz), 112.6, 71.3, 52.8, 26.5, 24.0.

HRMS: calculated for $C_{20}H_{20}ClF_3N_4O_2$:440.1227, found: 440.1218.

I.R.(thin film): 3692, 2943, 2817, 1594, 1510, 1492, 1386, 1254, 1214, 1161, 1111, 1025, 1016cm^{-1}

Compound **4s**



$C_{26}H_{25}ClF_3N_5O_2$

531.96 g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of 1-benzylpiperazine (0.5mmol, 88mg, 1.0eq) and p-chlorobenzaldehyde (0.5mmol, 70mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=70:30) to afford the desired product **4s** (81%, 215mg).

Aspect: white solid, m. p. 84.1-85.9 °C.

Rf: 0.40 (Et_2O:PE=70:30)

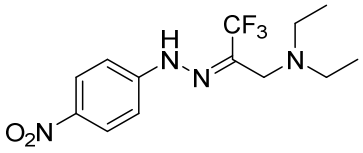
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.81 (s, 1H), 8.23 (d, *J* = 9.1 Hz, 2H), 7.39 – 7.24 (m, 9H), 7.16 (d, *J* = 8.8 Hz, 2H), 4.22 (s, 1H), 3.56 (s, 2H), 2.50 (bs, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6, 141.8, 137.2, 135.2, 134.2, 133.2(q, *J* = 33 Hz), 130.2, 129.7, 129.2, 128.4, 127.4, 126.2, 121.2(q, *J* = 272 Hz) ,112.7, 70.8, 62.7, 53.2, 51.7.

HRMS: calculated for $C_{26}H_{25}ClF_3N_5O_2$: 531.1649, found: 531.1628

I.R.(thin film): 3691, 3088, 3031, 2973, 2833, 2770, 2444, 1902, 1595, 1510, 1494, 1458, 1373, 1336, 1297, 1254, 1208, 1159, 1127, 1111, 1095, 1037cm^{-1}

Compound **4t**



$C_{13}H_{17}F_3N_4O_2$

318.30g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of diethylamine (0.5mmol, 37mg, 1.0eq) and formaldehyde (0.5mmol, 41mg, 37%, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2:PE=50:50) to afford the desired product **4t** (89%, 141mg).

Aspect: yellow solid, m. p. 78.2-79.6 °C.

Rf: 0.43 (CH_2Cl_2:PE=50:50)

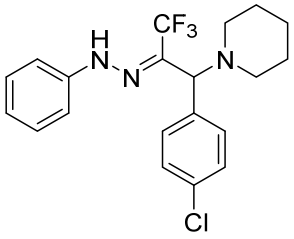
^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) = 12.32 (s, 1H), 8.16 (d, *J* = 9.0 Hz, 2H), 7.07 (d, *J* = 9.0 Hz, 2H), 3.56 (s, 2H), 2.60 (q, *J* = 7.1 Hz, 4H), 1.12 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ (ppm) = 149.0, 141.5, 132.4(q, *J* = 33 Hz), 126.1, 121.3(q, *J* = 271 Hz), 112.5, 50.6, 46.7, 11.5.

HRMS: calculated for $C_{13}H_{17}F_3N_4O_2$: 318.1304, found: 318.1305

I.R.(thin film): 3691, 3105, 2976, 2938, 2878, 2843, 2444, 1918, 1596, 1528, 1509, 1458, 1438, 1427, 1383, 1335, 1298, 1258, 1206, 1158, 1111, 1065, 1041cm^{-1}

Compound **4u**



$C_{20}H_{21}ClF_3N_3$

395.85$g.mol^{-1}$

Trifluoroacetaldehyde phenylhydrazone (0.5mmol, 94mg, 1.0eq) was added to a solution of piperidine (0.5mmol, 43mg, 1.0eq) and p-chlorobenzaldehyde (0.5mmol, 70mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2:PE=10:90) to afford the desired product **4u** (75%, 148mg).

Aspect: yellow oil

Rf: 0.78 (DCM:PE=10:90)

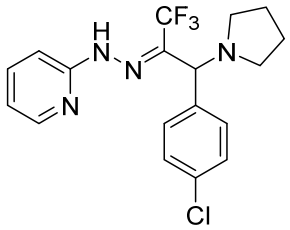
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.29 (s, 1H), 7.39-7.33 (m, 6H), 7.21 (d, *J* = 7.3 Hz, 2H), 7.03-7.00 (m, 1H), 4.14 (d, *J* = 4.4 Hz, 1H), 2.42 (bs, 4H), 1.78 – 1.42 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 135.9, 134.5, 130.2, 129.5, 129.3, 128.8(q, *J* = 32 Hz), 122.0(q, *J* = 271 Hz),121.5, 71.0, 52.8, 26.5, 24.2.

.**HRMS:** calculated for $C_{20}H_{21}ClF_3N_3$:395.1376, found: 395.1363.

I.R.(thin film): 3692, 2942, 1600, 1492, 1247, 1164, 1114, 1095, 1016cm^{-1}

Compound **4v**



$C_{18}H_{18}ClF_3N_4$

382.82$g.mol^{-1}$

(E)-2-(2-(2,2,2-trifluoroethylidene)hydrazinyl)pyridine (0.5mmol, 90mg, 1.0eq) was added to a solution of pyrrolidine (0.5mmol, 36mg, 1.0eq) and p-chlorobenzaldehyde (0.5mmol, 70mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 15h. After completion of present reaction, the

reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=30:70) to afford the desired product **4v** (58%, 111mg).

Aspect: yellow oil

Rf: 0.56 (Et_2O:PE=30:70)

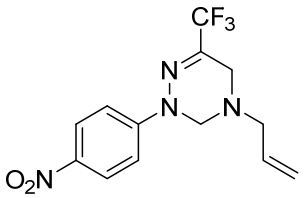
^{1}H NMR (400 MHz, $CDCl_3$)δ 12.24 (s, 1H), 8.30 – 8.23 (m, 1H), 7.67 (td, *J* = 8.2, 1.8 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.31-7.28(m, 3H), 6.92 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 4.21 (s, 1H), 2.55 (bs, 4H), 2.01 – 1.88 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 148.0, 138.3, 136.5, 134.4, 131.1(q, *J* = 32 Hz), 129.8, 129.2, 121.6(q, *J* = 273 Hz), 117.3, 107.7, 69.4, 53.2, 23.6.

HRMS: calculated for $C_{18}H_{18}ClF_3N_4$:382.1172, found: 382.1172.

I.R.(thin film): 3691, 2976, 2817, 1597, 1575, 1511, 1492, 1442, 1359, 1295, 1268, 1169, 1124, 1093, 1016cm^{-1}

Compound **5a**



$C_{13}H_{13}F_3N_4O_2$

314.27$g.mol^{-1}$

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of aqueous formaldehyde (1mmol, 82mg, 37%, 2.0eq) and allylamine (0.5mmol, 57mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: PE:Et_2O=60:40)to afford the desired product **5a** (98%, 154mg).

Aspect: white solid m.p. 86.3^{o}C-87.5^{o}C

Rf: 0.39 (PE:Et_2O=60:40)

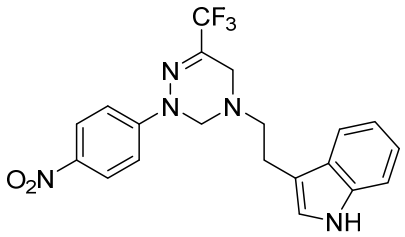
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 9.4 Hz, 2H), 7.23 (d, *J* = 9.4 Hz, 2H), 5.86 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.29 – 5.09 (m, 2H), 4.62 (s, 2H), 3.57 (s, 2H), 3.17 (d, *J* = 6.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 141.8, 133.4, 133.0(q, *J* = 35 Hz), 125.6, 120.6(q, *J* = 271 Hz), 120.3, 113.1, 63.0, 56.7, 45.4.

HRMS: calculated for $C_{13}H_{13}F_3N_4O_2$:314.0991, found: 314.0987

I.R.(thin film): 3086, 2928, 2846, 1593, 1506, 1422, 1405, 1337, 1281, 1222, 1205, 1179, 1132, 1132, 1068, 1022cm^{-1}

Compound **5b**



$C_{20}H_{18}F_3N_5O_2$

417.39 g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of aqueous formaldehyde (1mmol, 82mg, 37%, 2.0eq) and tryptamine (0.5mmol, 80mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: PE:Et_2O=50:50)to afford the desired product **5b** (36%, 75mg).

Aspect: yellow solid m.p. 198.6°C-199.5°C

Rf: 0.47 (PE:CH_2Cl_2=50:50)

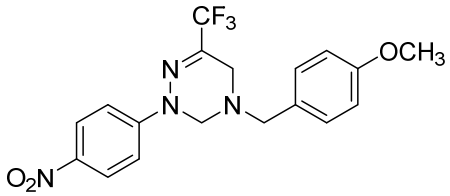
^{1}H NMR (400 MHz, $CDCl_3$) δ11.96 (s, 1H), 8.10 (dd, *J* = 8.0, 2.9 Hz, 2H), 7.85 (s, 1H), 7.53 (s, 1H), 7.41 – 7.30 (m, 1H), 7.29 – 7.10 (m, 2H), 7.09 – 6.94 (m, 2H), 3.80 (bs, 4H), 3.03-2.97 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ148.7, 141.7, 136.2, 131.0(q, *J* = 34 Hz), 129.9, 126.8, 126.0, 122.2, 121.3(q, *J* = 273 Hz), 119.9, 118.2, 112.9, 111.1, 107.9, 54.0, 50.5, 50.0, 21.3.

HRMS: calculated for $C_{20}H_{18}F_3N_5O_2$:417.1413, found: 417.1428

I.R.(thin film): 2840, 1592, 1513, 1336, 1284, 1259, 1205, 1175, 11131, 1111, 1067, 1021cm^{-1}

Compound **5c**



$C_{18}H_{17}F_3N_4O_3$

394.35 g.mol^{-1}

Trifluoroacetaldehyde 4-nitrophenylhydrazone (0.5mmol, 117mg, 1.0eq) was added to a solution of aqueous formaldehyde (1mmol, 82mg, 37%, 2.0eq) and para-methoxybenzylamine (0.5mmol, 69mg, 1.0eq) in 3ml toluene. The stirred mixture was heated to reflux under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: PE:Et_2O=50:50)to afford the desired product **5b** (98%, 193mg).

Aspect: yellow oil

Rf: 0.38 (PE:Et_2O=50:50)

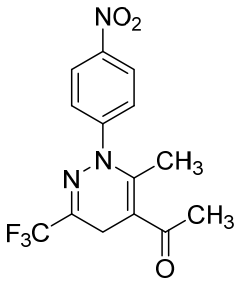
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 9.2 Hz, 2H), 7.23 – 7.12 (m, 4H), 6.86 (d, *J* = 8.3 Hz, 2H), 4.55 (s, 2H), 3.80 (s, 3H), 3.68-3.65 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 149.7, 141.8, 132.9(q, *J* = 35 Hz), 130.5, 128.1, 125.6, 120.6(q, *J* = 272 Hz), 114.2, 113.1, 62.5, 57.1, 55.4, 45.6.

HRMS: calculated for $C_{18}H_{17}F_3N_4O_3$:394.1253, found: 394.1265

I.R.(thin film): 3470, 1595, 1529, 1509, 1386, 1337, 1326, 1258, 1168, 1158, 1130, 1112, 1068cm^{-1}

Compound **7a**



$C_{14}H_{12}F_3N_3O_3$

327.26g.mol^{-1}

Mannich adduct **4a** (0.5mmol, 166mg) was dissolved in 2.5mL pentane-2,4-dione, and the stirred mixture was heated to 130°C under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=50:50) to afford the desired product **7a** (58%, 95mg).

Aspect: yellow solid, m.p. 159.6-161.2°C

Rf: 0.29 (Et_2O:PE=50:50)

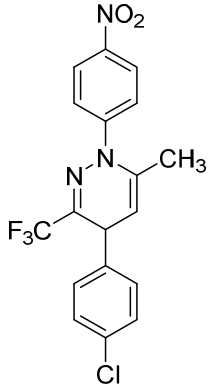
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 9.2 Hz, 2H), 7.49 (d, *J* = 9.2 Hz, 2H), 3.29 (s, 2H), 2.36 (s, 3H), 2.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0, 147.3, 145.7, 144.8, 137.7(q, *J* = 36 Hz), 124.9, 124.7, 120.5(q, *J* = 272 Hz),106.9, 30.2, 23.0, 18.3.

HRMS: calculated for $C_{14}H_{12}F_3N_3O_3$:327.0831, found: 327.0821.

I.R.(thin film): 1675, 1595, 1572, 1524, 1349, 1310, 1251, 1221, 1201, 1137, 1040cm^{-1}

Compound **7b**



$C_{18}H_{13}ClF_3N_3O_2$

395.77g.mol^{-1}

Mannich adduct **4b** (0.5mmol, 221mg) was dissolved in 2.5mL acetone, and the stirred mixture was heated to 130°C under microwave for 1h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=50:50) to afford the desired product **7b** (34%, 67mg).

Aspect: yellow oil

Rf: 0.7(Et_2O:PE=50:50)

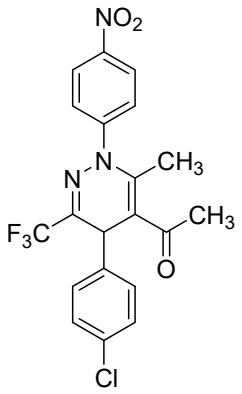
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.2 Hz, 2H), 7.47 (d, *J* = 9.1 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 5.11 (dd, *J* = 6.3, 1.1 Hz, 1H), 4.41 (d, *J* = 6.2 Hz, 1H), 1.93 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8, 145.1, 140.2, 134.7(q, *J* = 34 Hz), 134.4, 133.7, 129.4, 128.6, 124.7, 123.7, 121.2(q, *J* = 273 Hz), 104.5, 37.4, 19.5.

HRMS: calculated for $C_{18}H_{13}ClF_3N_3O_2$:395.0648, found: 395.0652.

I.R.(thin film): 2932, 1668, 1595, 1522, 1491, 1387, 1346, 1257, 1214, 1189, 1113, 1095, 1016cm^{-1}

Compound **7c**



$C_{20}H_{15}ClF_3N_3O_3$

437.80g.mol^{-1}

Mannich adduct **4b** (0.5mmol, 221mg) was dissolved in 2.5mL pentane-2,4-dione, and the stirred mixture was heated to 130°C under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=50:50) to afford the desired product **7c** (80%, 175mg).

Aspect: yellow oil

Rf: 0.37 (Et_2O:PE=50:50)

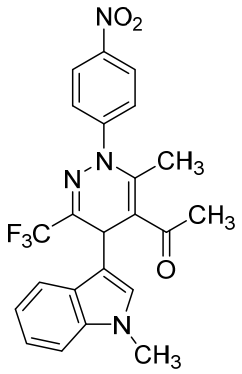
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.9 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 5.14 (s, 1H), 2.42 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8, 146.9, 146.1, 143.2, 139.0(q, *J* = 35 Hz), 137.7, 134.2, 129.5, 128.4, 125.1, 125.0, 120.7(q, *J* = 273 Hz), 113.4, 37.3, 30.4, 18.8.

HRMS: calculated for $C_{20}H_{15}ClF_3N_3O_3$:437.0754, found: 437.0734.

I.R.(thin film): 1674, 1595, 1526, 1492, 1349, 1310, 1292, 1221, 1198, 1142, 1039, 1015cm^{-1}

Compound **7d**



$C_{23}H_{19}F_3N_4O_3$

456.43g.mol^{-1}

Mannich adduct **4i** (0.5mmol, 231mg) was dissolved in 2.5mL pentane-2,4-dione, and the stirred mixture was heated to 130°C under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=50:50) to afford the desired product **7d** (92%, 210mg).

Aspect: yellow oil

Rf: 0.29 (Et_2O:PE=50:50)

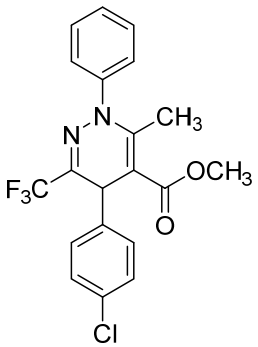
^{1}H NMR (400 MHz, $CDCl_3$) δ8.38 – 8.29 (m, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.32 – 7.20 (m, 2H), 7.17-7.13 (m, 1H), 6.78 (s, 1H), 5.33 (s, 1H), 3.71 (s, 3H), 2.37 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 147.4, 145.8, 142.2, 140.1(q, *J* = 34 Hz), 137.1, 127.6, 126.0, 125.9, 125.0, 124.8, 122.3, 120.9(q, *J* = 273 Hz), 120.0, 118.9, 114.2, 113.3, 112.9, 109.8, 33.0, 30.1, 29.6, 18.9.

HRMS: calculated for $C_{23}H_{19}F_3N_4O_3$:456.1409, found: 456.1409.

I.R.(thin film): 2939, 1672, 1595, 1524, 1495, 1348, 1310, 1293, 1221, 1197, 1139, 1111, 1040cm^{-1}

Compound **7e**



$C_{20}H_{16}ClF_3N_2O_2$

408.80g.mol^{-1}

Mannich adduct **4l** (0.5mmol, 199mg) was dissolved in 2.5mL methyl 3-oxobutanoate, and the stirred mixture was heated to 130°C under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=40:60) to afford the desired product **7e** (90%, 184mg).

Aspect: yellow oil

Rf: 0.52 (Et_2O:PE=40:60)

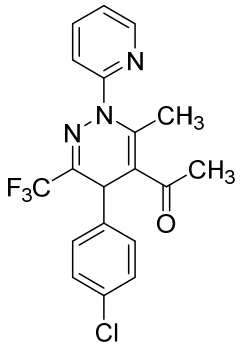
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.42 (m, 2H), 7.40 – 7.34 (m, 1H), 7.33 – 7.26 (m, 4H), 7.21 – 7.15 (m, 2H), 5.04 (s, 1H), 3.76 (s, 3H), 2.26 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 146.8, 142.3, 139.7, 136.9(q, *J* = 35 Hz), 133.6, 129.5, 129.2, 128.6, 128.0, 126.1, 121.0(q, *J* = 273 Hz), 100.9, 51.8, 36.5, 17.8.

HRMS: calculated for $C_{20}H_{16}ClF_3N_2O_2$:408.0852, found: 408.0838.

I.R.(thin film): 2953, 1701, 1595, 1491, 1436, 1384, 1221, 1199, 1138, 1093, 1035, 1016cm^{-1}

Compound **7f**



$C_{19}H_{15}ClF_3N_3O$

393.79$g.mol^{-1}$

Mannich adduct **4p** (0.5mmol, 199mg) was dissolved in 2.5mL pentane-2,4-dione, and the stirred mixture was heated to 130°C under Ar for 12h. After completion of present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=50:50) to afford the desired product **7f** (56%, 110mg).

Aspect: yellow oil

Rf: 0.41 (Et_2O:PE=50:50)

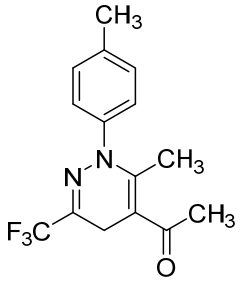
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (ddd, *J* = 4.9, 1.9, 0.7 Hz, 1H), 7.87 (ddd, *J* = 8.2, 7.4, 1.9 Hz, 1H), 7.66 (dd, *J* = 7.4, 0.8 Hz, 1H), 7.32 – 7.22 (m, 5H), 5.09 (s, 1H), 2.43 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0, 154.6, 148.0, 144.5, 138.8, 138.6, 138.0(q, *J* = 34 Hz), 133.9, 129.3, 129.0, 122.0 ,120.9(q, *J* = 273 Hz), 118.5, 113.1, 37.4, 30.9, 18.7.

HRMS: calculated for $C_{19}H_{15}ClF_3N_3O$:393.0856, found: 393.0847.

I.R.(thin film): 3063, 3014, 1671, 1581, 1490, 1470, 1439, 1381, 1360, 1317, 1292, 1222, 1199, 1140, 1093, 1041cm^{-1}

Compound **7g**



$C_{15}H_{15}F_3N_2O$

296.29g.mol^{-1}

Mannich adduct **4m** (0.5mmol, 151mg) was dissolved in 2.5mL pentane-2,4-dione, and the stirred mixture was heated to 130°C under Ar for 12h. After completion of the reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=10:90) to afford **7g** (77%, 114mg).

Aspect: yellow oil

Rf: 0.33 (Et_2O:PE=20:80)

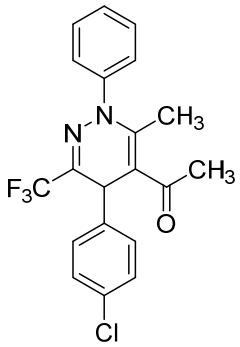
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.21 (m, 2H), 7.19 – 7.14 (m, 2H), 3.27 (s, 2H), 2.38 (s, 3H), 2.31 (s, 3H), 2.12 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0, 147.1, 140.1, 137.8, 135.0 (q, *J* = 35 Hz), 130.0, 126.1, 120.9(q, *J* = 271 Hz), 102.8, 30.3, 22.4, 21.2, 18.0

HRMS: calculated for $C_{15}H_{15}F_3N_2O$: 296.1136, found: 296.1122.

I.R.(thin film): 3039, 2924, 1664, 1562, 1512, 1420, 1393, 1381, 1360, 1319, 1243, 1219, 1190, 1111, 1039, 1018cm^{-1}

Compound **7h**



$C_{20}H_{16}ClF_3N_2O$

392.81g.mol^{-1}

Mannich adduct **4l** (0.5mmol, 199mg) was dissolved in 2.5mL pentane-2,4-dione, and the stirred mixture was heated to 130°C under Ar for 12h. After completion of the reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=20:80) to afford the desired product **7h** (71%, 140mg).

Aspect: yellow oil

Rf: 0.36 (Et_2O:PE=30:70)

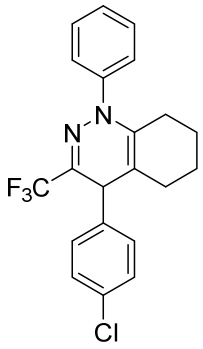
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.44 (m, 2H), 7.40 – 7.34 (m, 1H), 7.32 – 7.25 (m, 4H), 7.17-7.15 (m, 2H), 5.05 (s, 1H), 2.34 (s, 3H), 2.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7, 145.3, 142.1, 138.9, 137.1(q, *J* = 35 Hz), 133.8, 129.6, 129.3, 128.6, 128.2, 126.1, 121.0(q, *J* = 273 Hz), 110.0, 36.7, 30.6, 18.7

HRMS: calculated for $C_{20}H_{16}ClF_3N_2O$: 392.0903, found: 392.0901.

I.R.(thin film): 2969, 1667, 1637, 1592, 1557, 1489, 1382, 1350, 1243, 1214, 1189, 1122, 1091, 1037, 1024, 1013cm^{-1}

Compound **7i**



$C_{21}H_{18}ClF_3N_2$

390.83g.mol^{-1}

Mannich adduct **4l** (0.5mmol, 199mg) was dissolved in 2.5mL cyclohexanone and the stirred mixture was heated to 130°C under Ar for 12h. After completion of the reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=20:80) to afford the desired product **7i** (68%, 132mg).

Aspect: gray oil

Rf: 0.80 (Et_2O:PE=40:60)

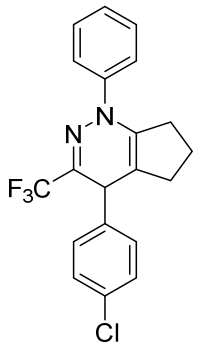
^{1}H NMR (400 MHz, $CDCl_3$)δ 7.40-7.36 (m, 2H), 7.32 – 7.22 (m, 5H), 7.19 – 7.12 (m, 2H), 4.11 (s, 1H), 2.27 – 2.05 (m, 2H), 2.00 – 1.87 (m, 1H), 1.80 – 1.46 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0, 140.8, 133.3, 131.6, 129.9(q, *J* = 34 Hz), 129.1, 129.0, 128.9, 126.6, 125.5, 121.9(q, *J* = 273 Hz), 109.9, 41.7, 27.1, 26.7, 22.9, 22.3

HRMS: calculated for $C_{21}H_{18}ClF_3N_2$: 390.1111, found: 390.1120.

I.R.(thin film): 3043, 2933, 2904, 2887, 2834, 1674, 1607, 1593, 1490, 1386, 1315, 1265, 1216, 1179, 1149, 1115, 1105, 1074, 1032, 1015, 1002cm^{-1}

Compound **7j**



$C_{20}H_{16}ClF_3N_2$

376.81g.mol^{-1}

Mannich adduct **4l** (0.5mmol, 199mg) was dissolved in 2.5mL cyclopentanone and the stirred mixture was heated to 130°C under Ar for 12h. After completion of the reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: Et_2O:PE=20:80) to afford the desired product **7j** (90%, 169mg).

Aspect: brown oil

Rf: 0.80 (Et_2O:PE=40:60)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.35 (m, 2H), 7.33 – 7.25 (m, 4H), 7.24-7.18 (m, 1H), 7.15 – 7.13 (m, 2H), 4.48 (s, 1H), 2.79-2.72 (m, 1H), 2.38 – 2.14 (m, 3H), 1.98 – 1.80 (m, 2H).

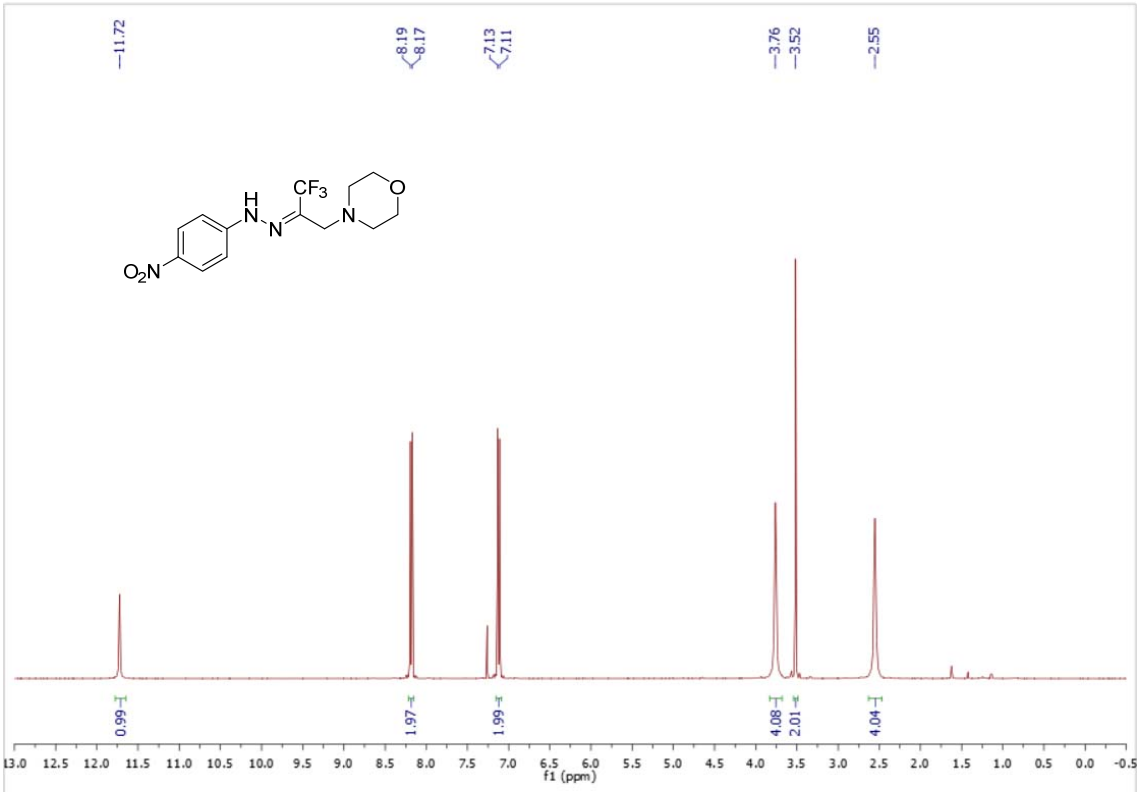
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 140.5, 135.1, 133.3, 130.7(q, *J* = 33 Hz), 129.1, 129.0, 129.0, 125.8, 122.6, 120.1(q, *J* = 273 Hz),115.0, 40.6, 32.1, 31.5, 21.2

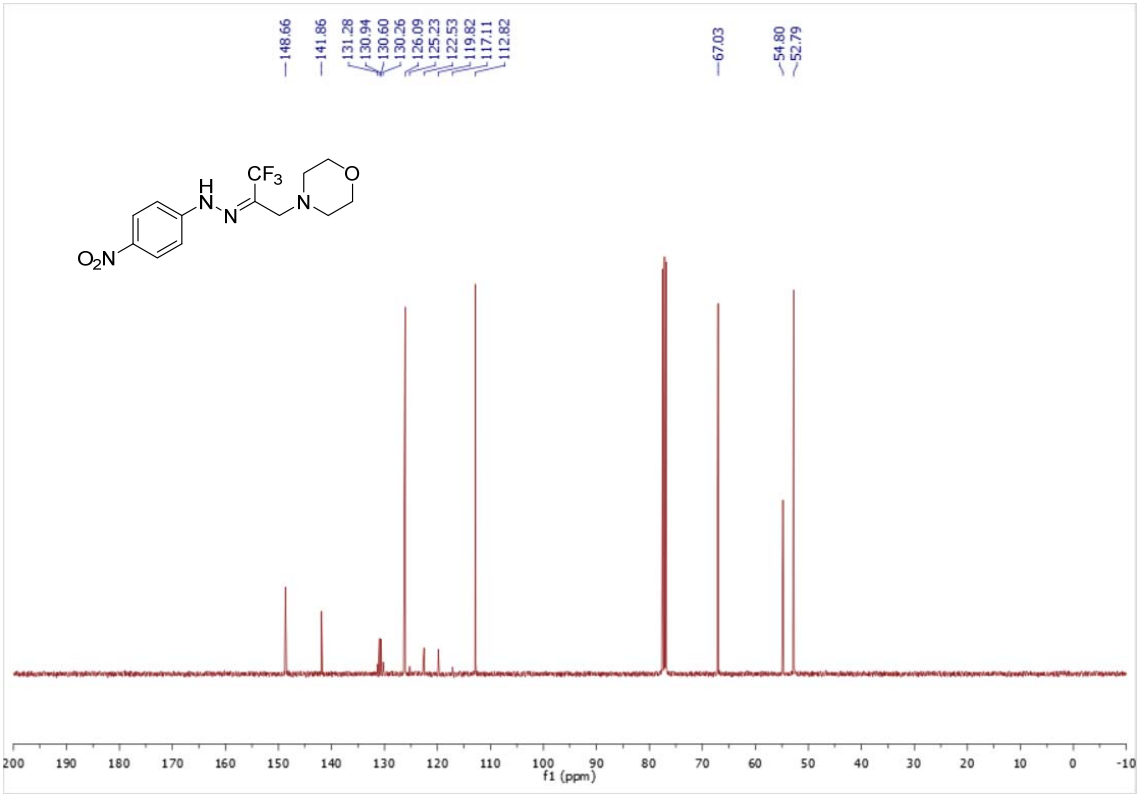
HRMS: calculated for $C_{20}H_{16}ClF_3N_2$: 376.0954, found:376.0941.

I.R.(thin film): 3042, 2956, 2850, 1679, 1594, 1584, 1496, 1489, 1379, 1329, 1294, 1225, 1186, 1160, 1117, 1090, 1077, 1014cm^{-1}

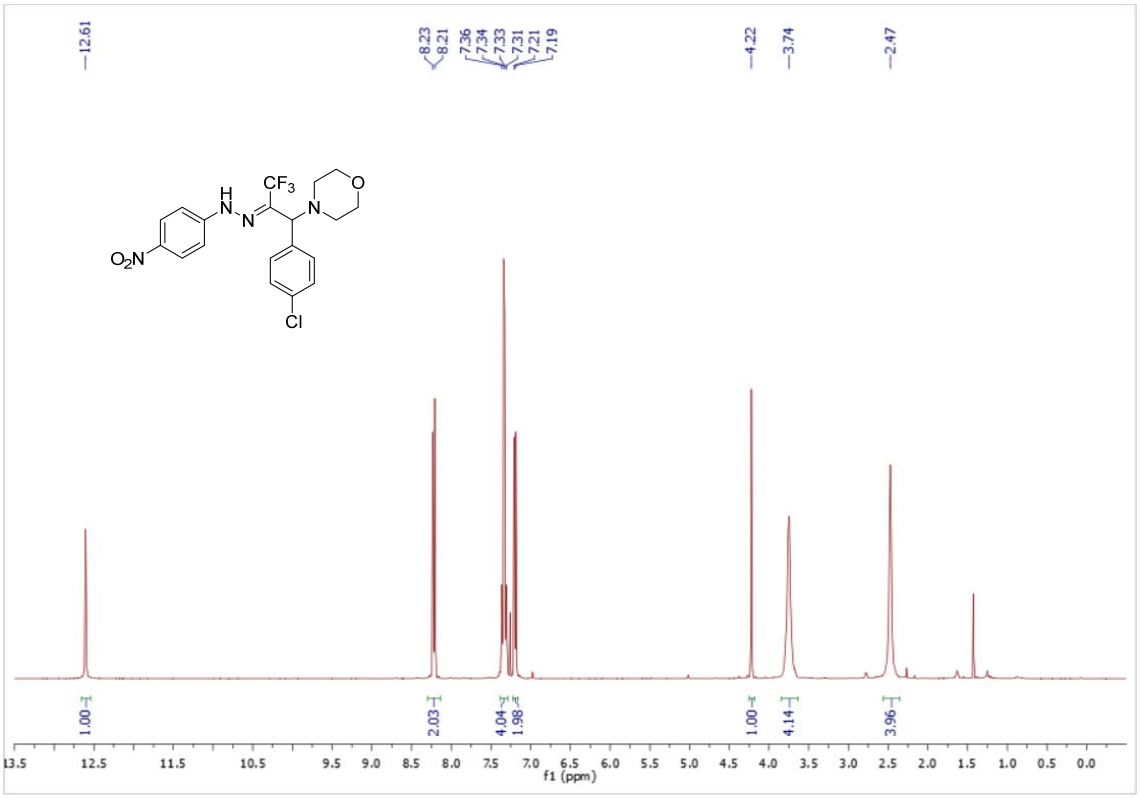
4 ^{1}H NMR and ^{13}C NMR Spectra of All Compounds

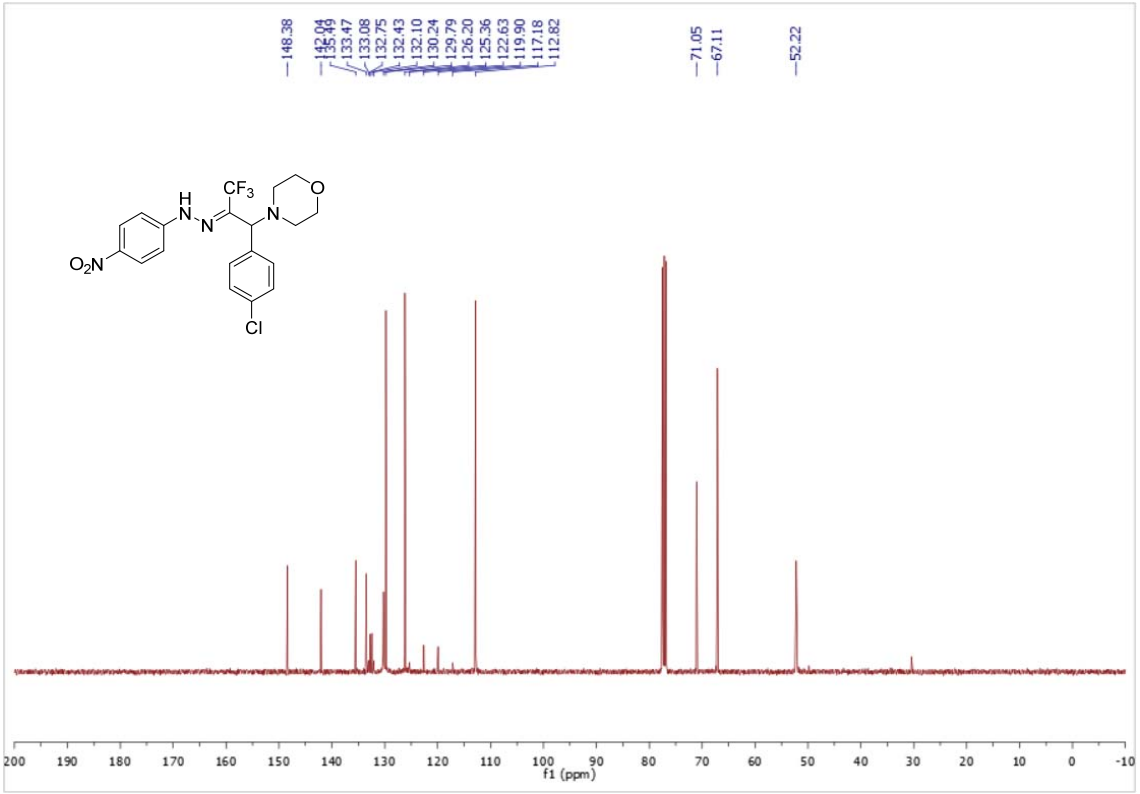
Compound 4a



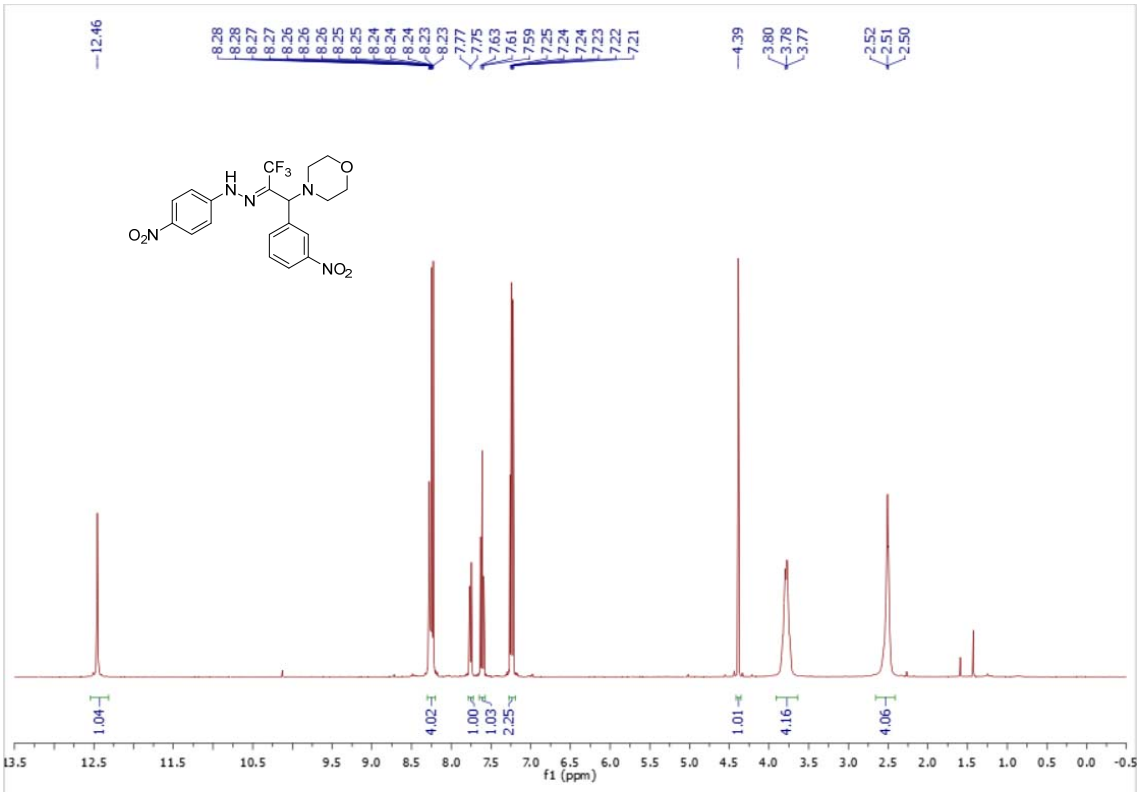


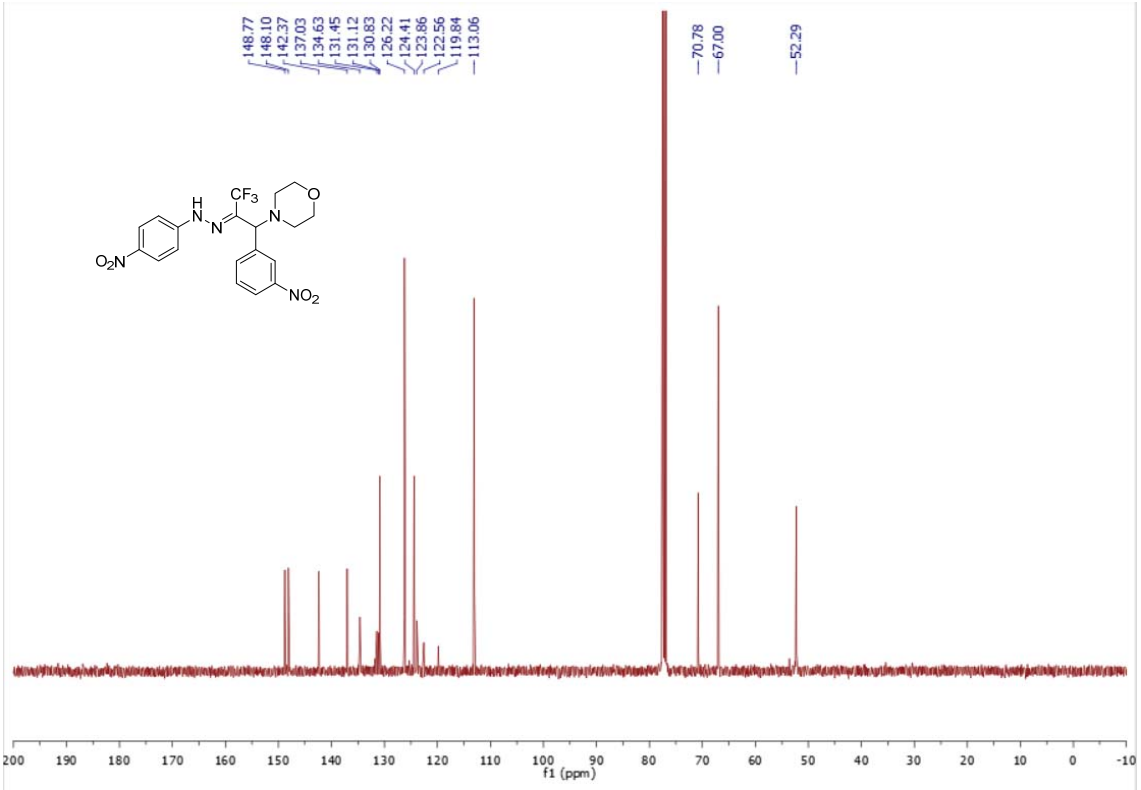
Compound 4b


12.61
8.23
8.21
7.36
7.34
7.33
7.31
7.21
7.19
4.22
3.74
2.47
1.00
2.03
4.04
1.98
1.00
4.14
3.96
f1 (ppm)

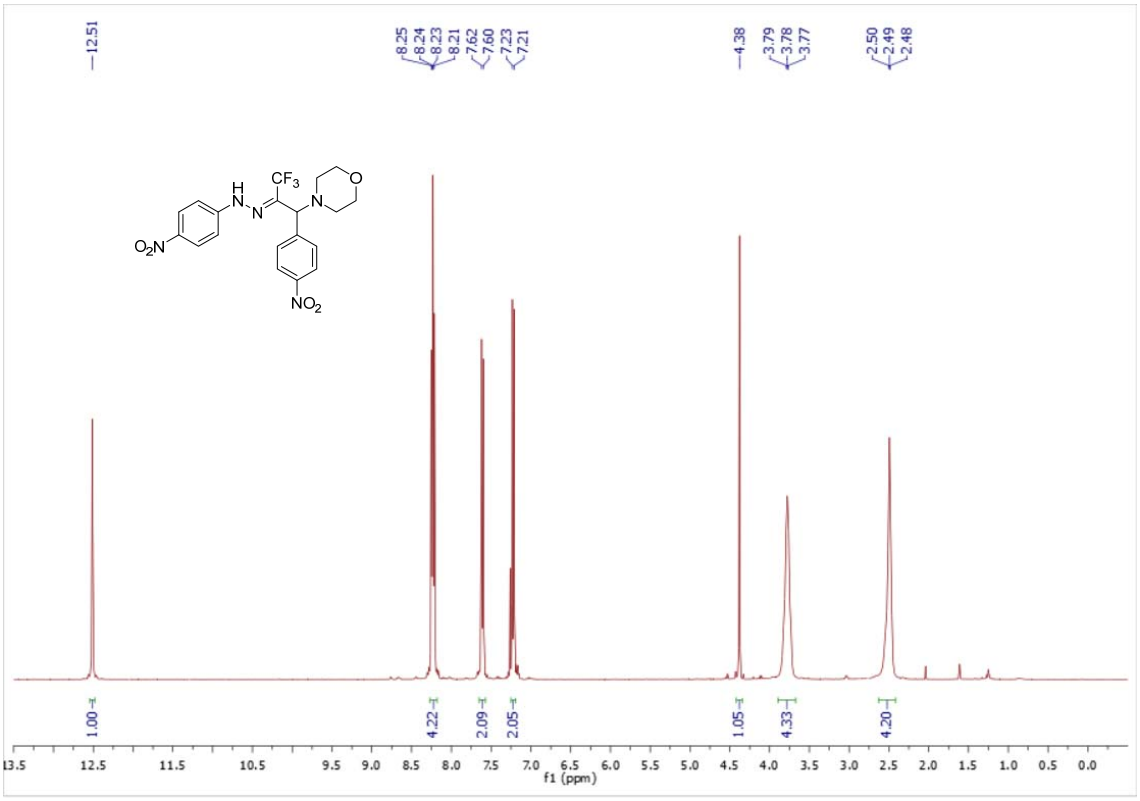

148.38
142.04
135.49
133.47
133.08
132.75
132.43
132.10
130.24
129.79
126.20
125.36
122.63
119.90
117.18
112.82
71.05
67.11
52.22
f1 (ppm)

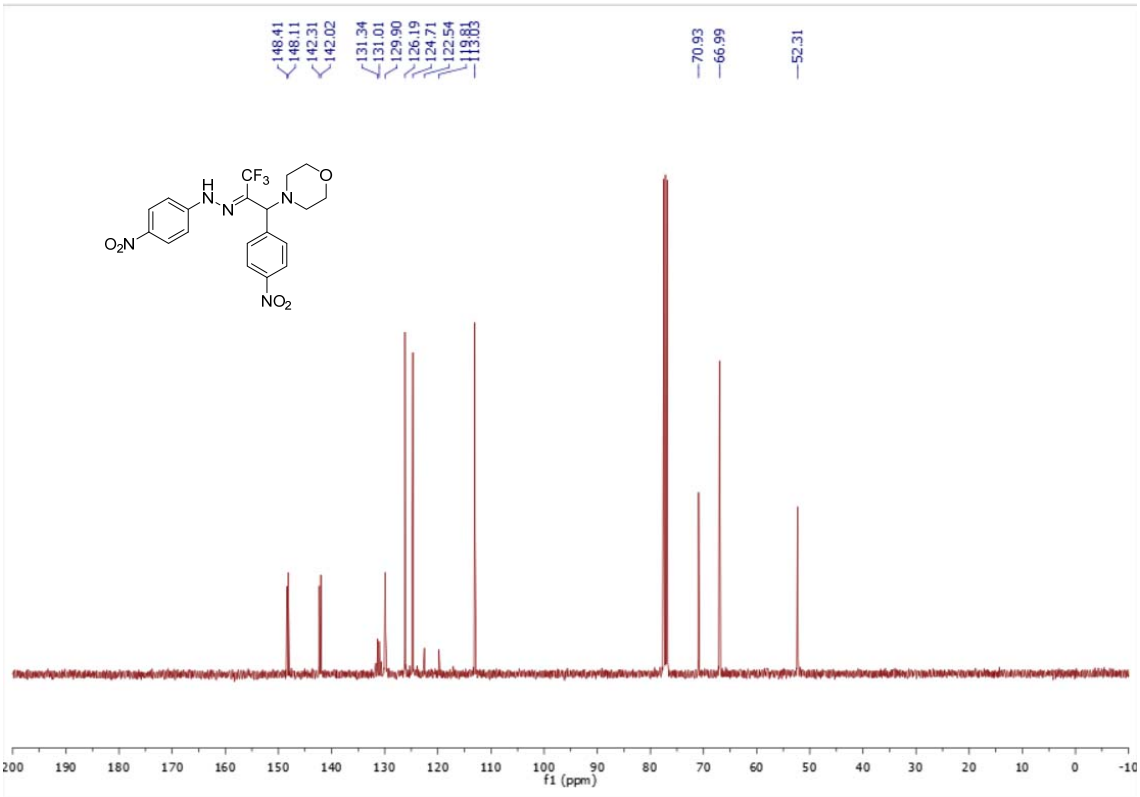
Compound 4c


12.46
8.28
8.28
8.27
8.27
8.26
8.26
8.26
8.25
8.25
8.24
8.24
8.24
8.23
8.23
7.77
7.75
7.63
7.61
7.59
7.25
7.24
7.24
7.23
7.22
7.21
4.39
3.80
3.78
3.77
2.52
2.51
2.50
1.04
4.02
1.00
1.03
2.25
1.01
4.16
4.06
f1 (ppm)

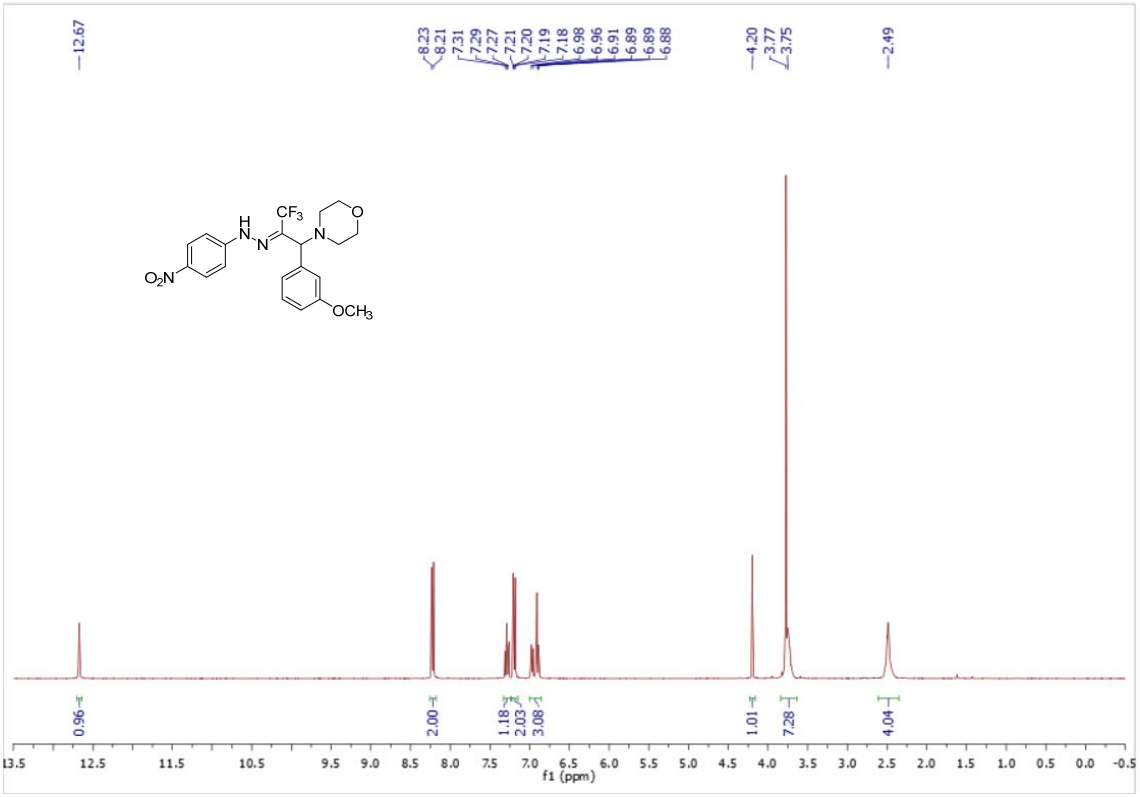

148.77
148.10
142.37
137.03
134.63
131.45
131.12
130.83
126.22
124.41
123.86
122.56
119.84
113.06
70.78
67.00
52.29
f1 (ppm)

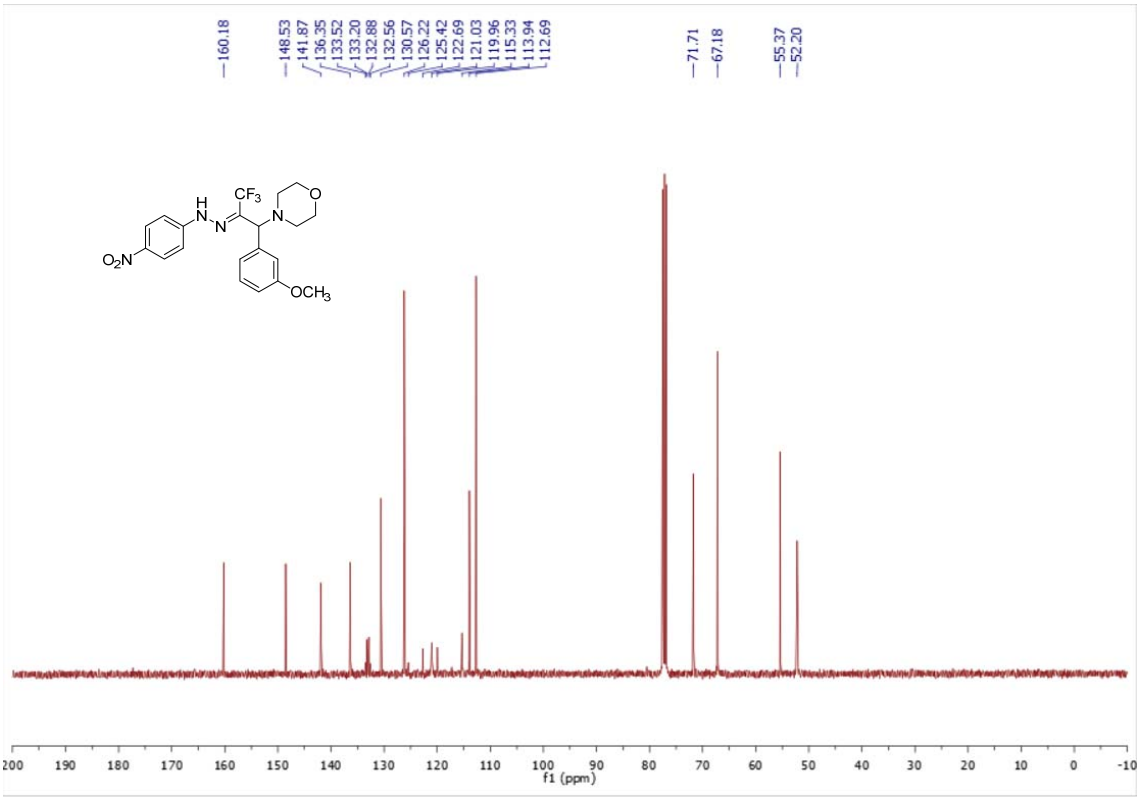
Compound 4d


12.51
8.25
8.24
8.23
8.21
7.62
7.60
7.23
7.21
4.38
3.79
3.78
3.77
2.50
2.49
2.48
1.00
4.22
2.09
2.05
1.05
4.33
4.20
f1 (ppm)

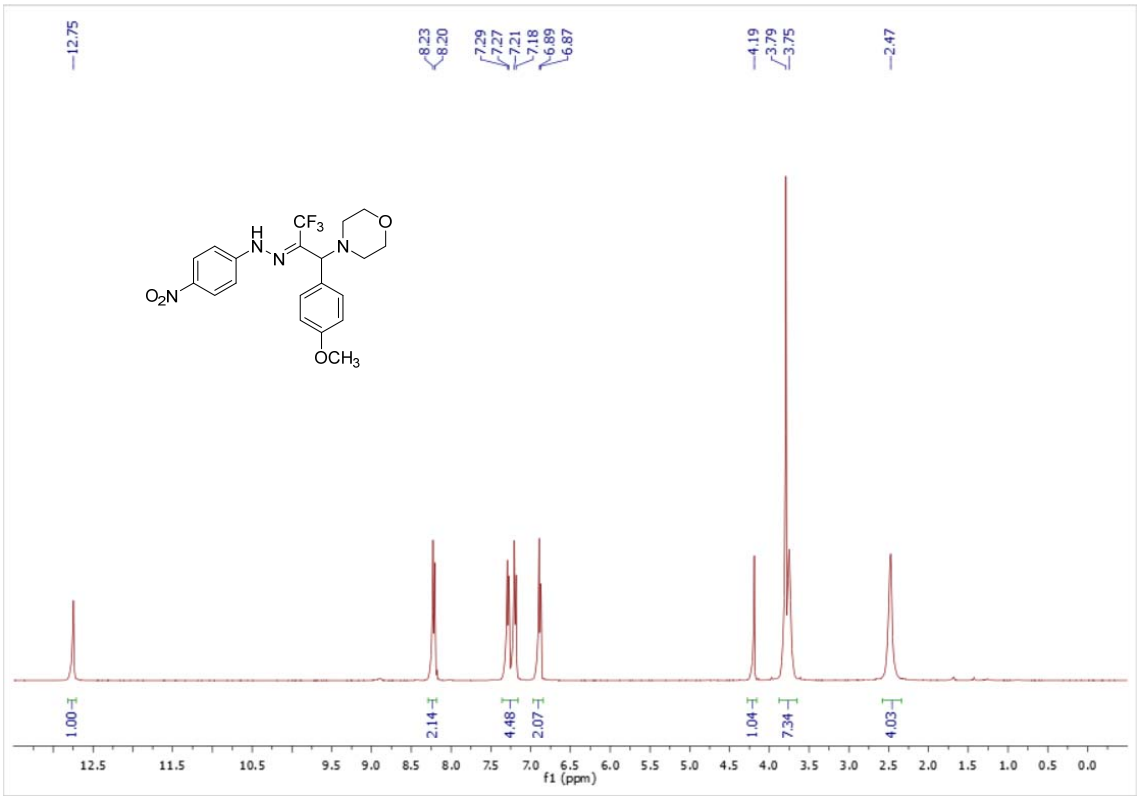

148.41
148.11
142.31
142.02
131.34
131.01
129.90
126.19
124.71
122.54
119.81
113.03
70.93
66.99
52.31
f1 (ppm)

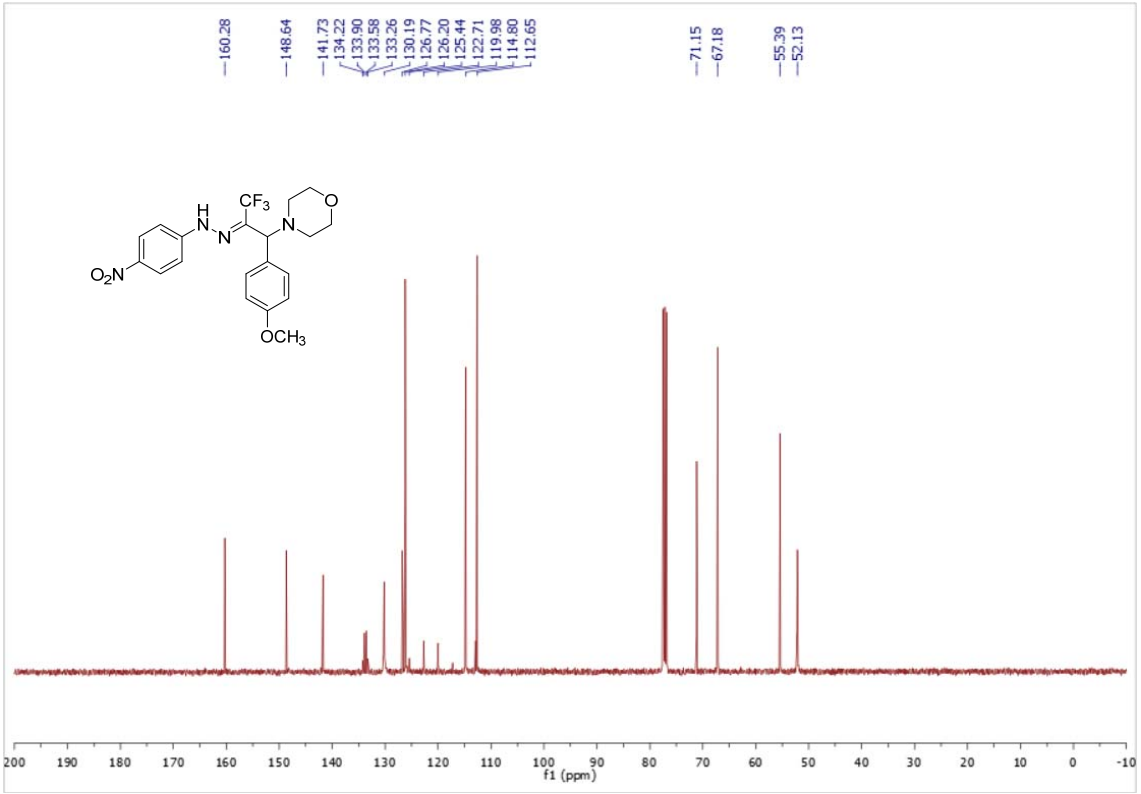
Compound 4e


12.67
8.23
8.21
7.31
7.29
7.27
7.21
7.20
7.19
7.18
6.98
6.96
6.91
6.89
6.89
6.88
4.20
3.77
3.75
2.49
0.96
2.00
1.18
2.03
3.08
1.01
7.28
4.04
f1 (ppm)

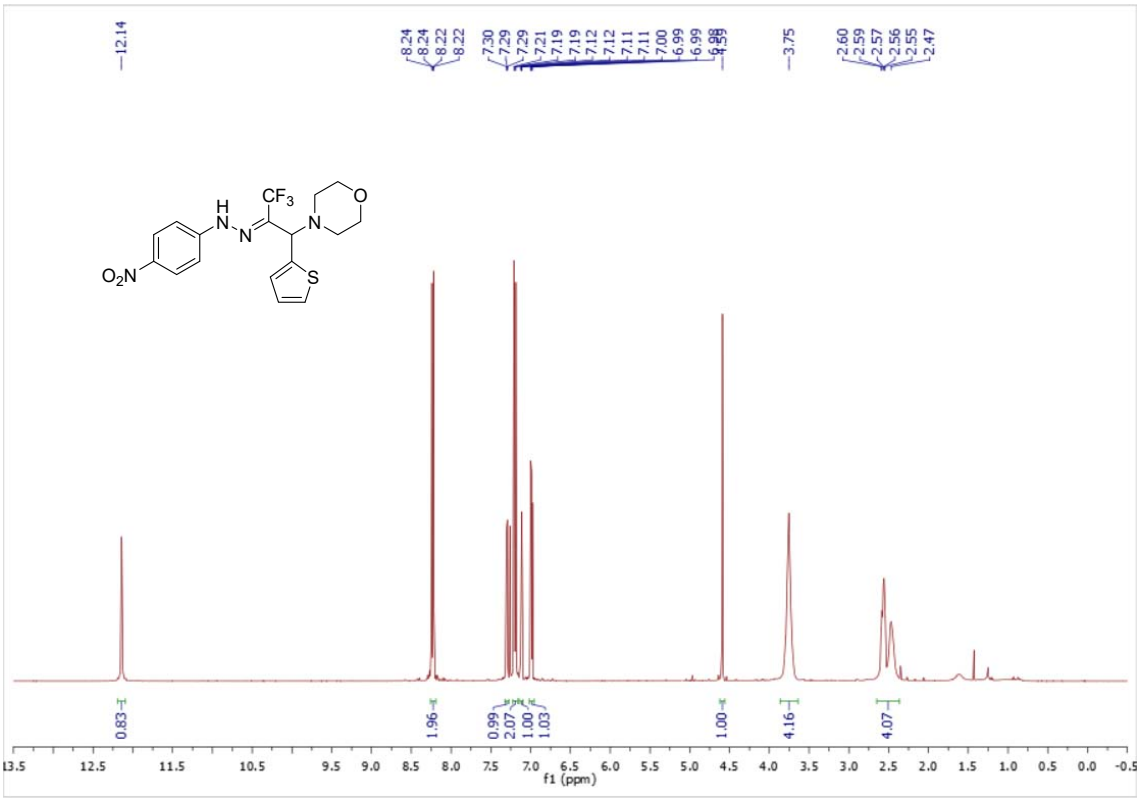

160.18
148.53
141.87
136.35
133.52
133.20
132.88
132.56
130.57
126.22
125.42
122.69
121.03
119.96
115.33
113.94
112.69
71.71
67.18
55.37
52.20
f1 (ppm)

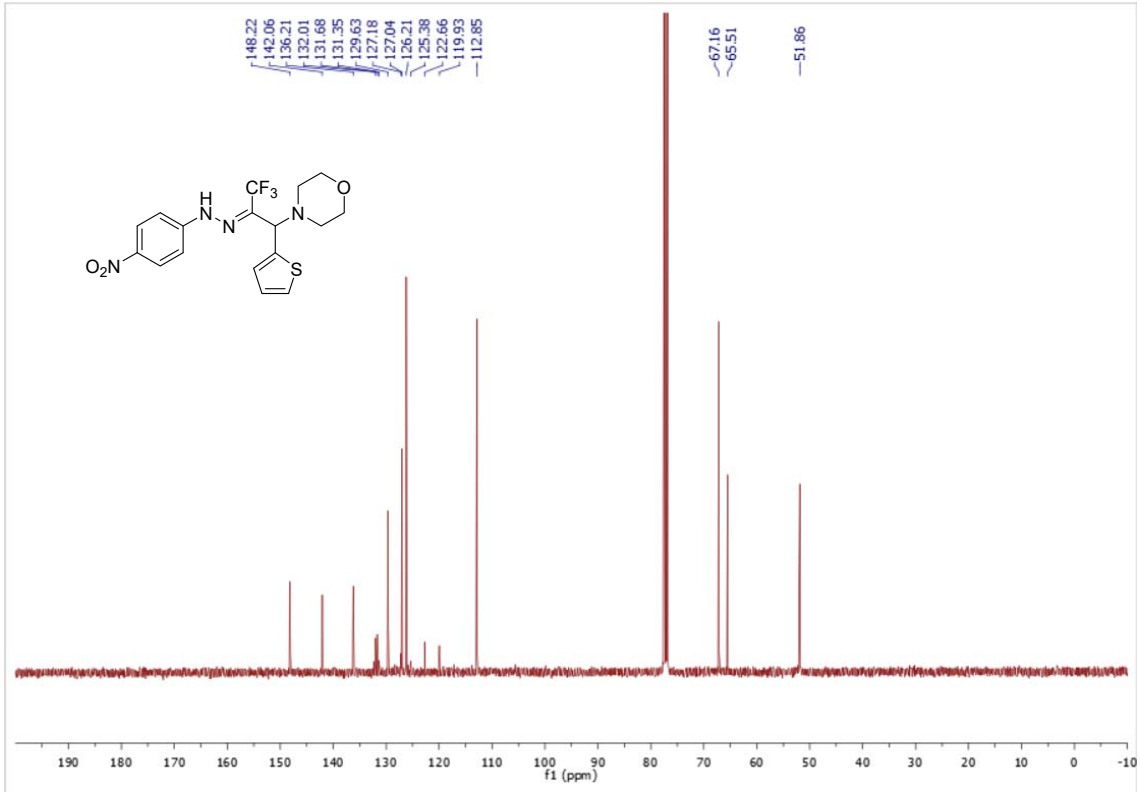
Compound 4f


12.75
8.23
8.20
7.29
7.27
7.21
7.18
6.89
6.87
4.19
3.79
3.75
2.47
1.00
2.14
4.48
2.07
1.04
7.34
4.03
f1 (ppm)

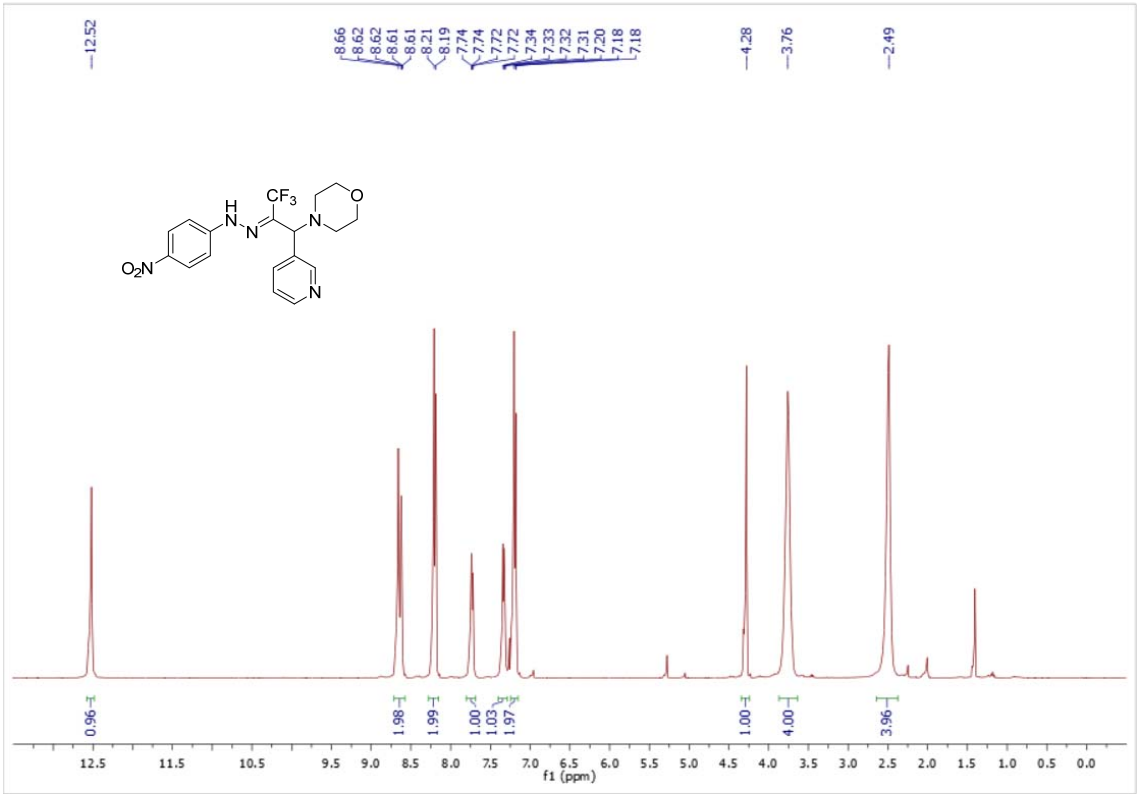

160.28
148.64
141.73
134.22
133.90
133.58
133.26
130.19
126.77
126.20
125.44
122.71
119.98
114.80
112.65
71.15
67.18
55.39
52.13
f1 (ppm)

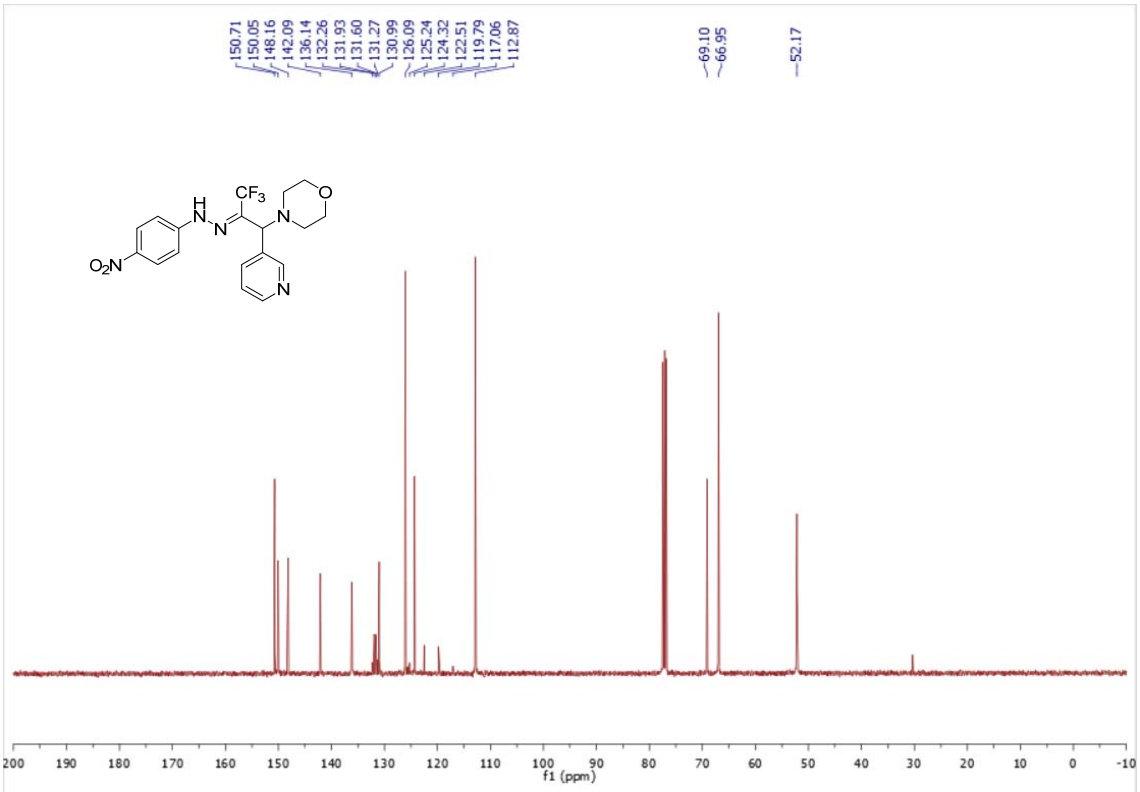
Compound 4g


12.14
8.24
8.24
8.22
8.22
7.30
7.29
7.29
7.21
7.19
7.19
7.12
7.12
7.11
7.11
7.00
6.99
6.99
4.59
3.75
2.60
2.59
2.57
2.56
2.55
2.47
0.83
1.96
0.99
2.07
1.00
1.03
1.00
4.16
4.07
f1 (ppm)

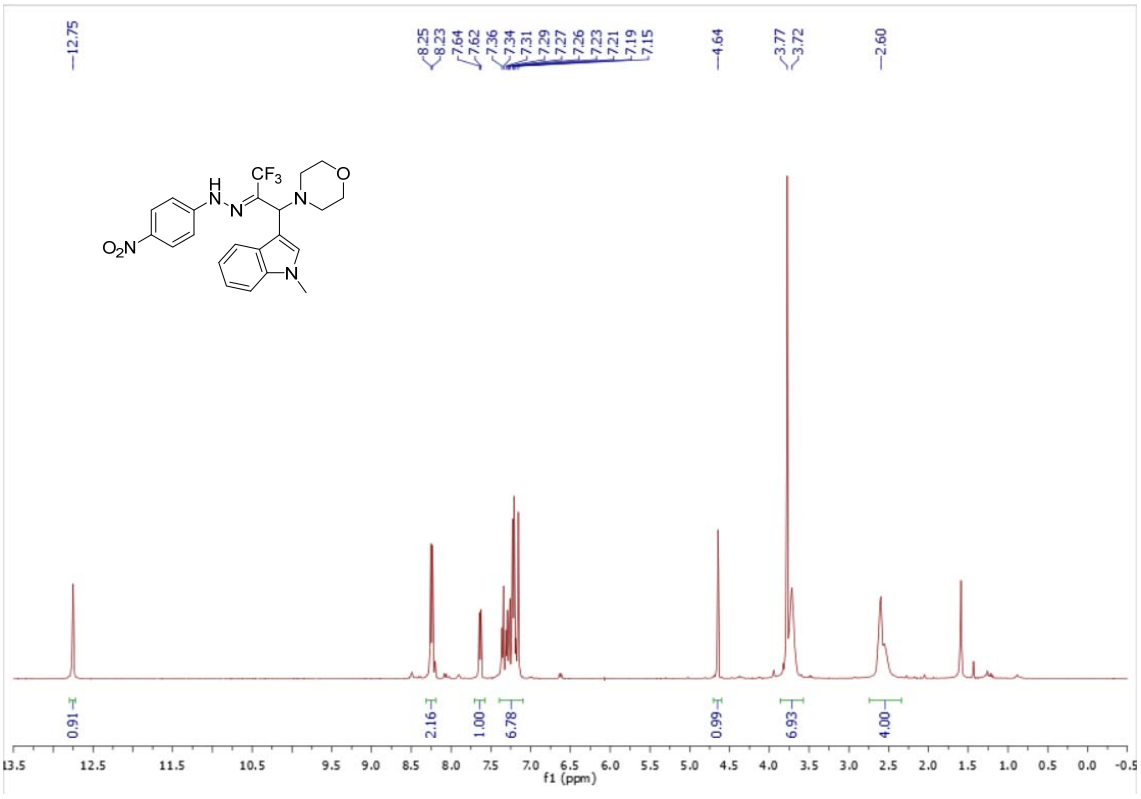

148.22
142.06
136.21
132.01
131.68
131.35
129.63
127.18
127.04
126.21
125.38
122.66
119.93
112.85
67.16
65.51
51.86
f1 (ppm)

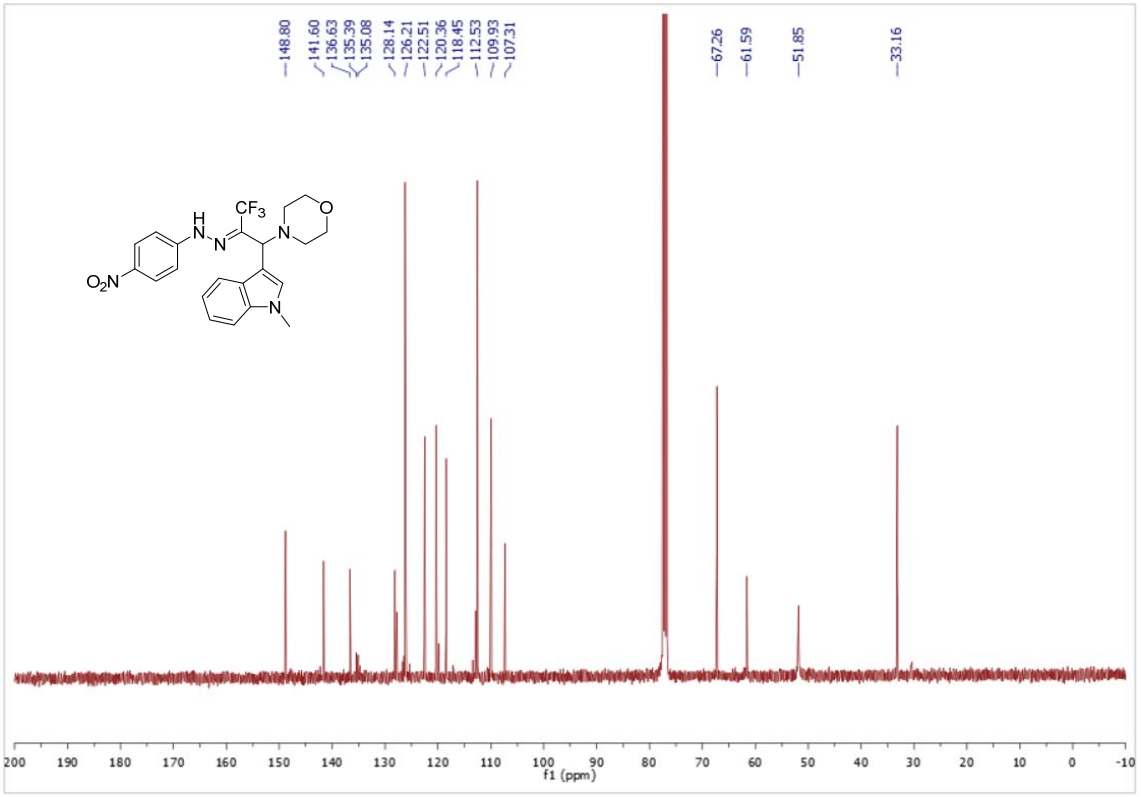
Compound 4h


12.52
8.66
8.62
8.62
8.61
8.61
8.21
8.19
7.74
7.74
7.72
7.72
7.34
7.33
7.32
7.31
7.20
7.18
7.18
4.28
3.76
2.49
0.96
1.98
1.99
1.00
1.03
1.97
1.00
4.00
3.96
f1 (ppm)

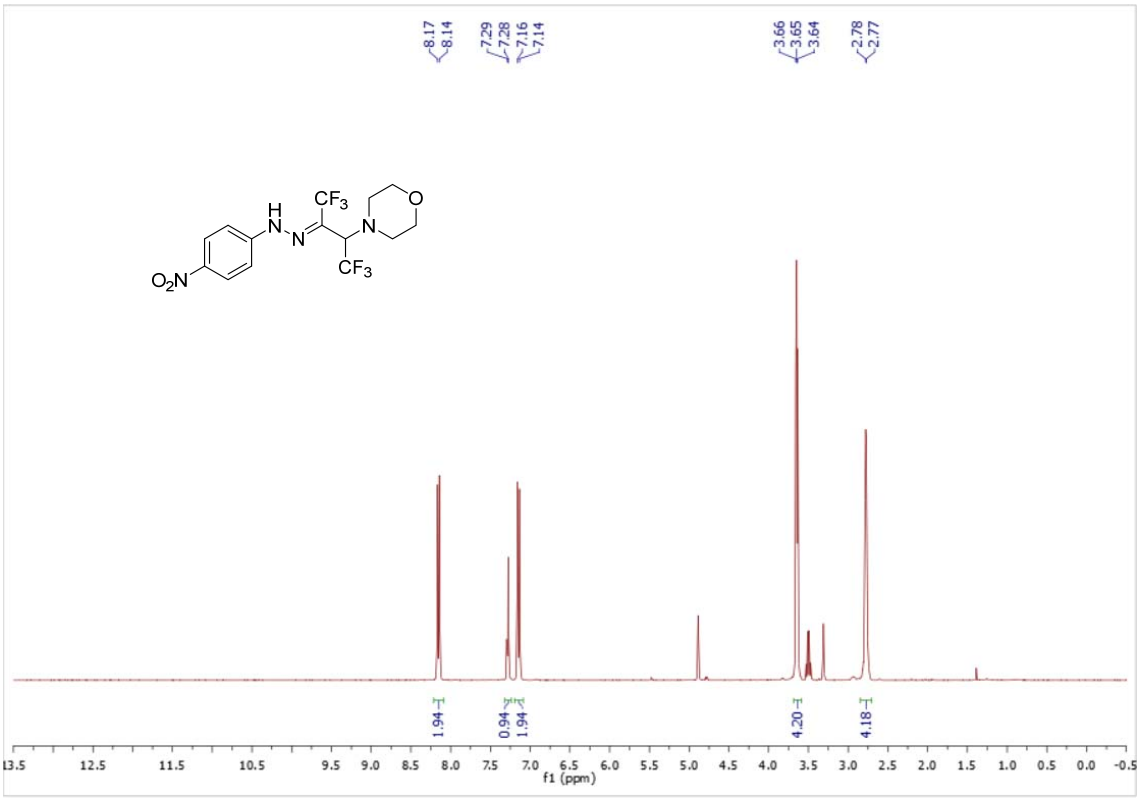

150.71
150.05
148.16
142.09
136.14
132.26
131.93
131.60
131.27
130.99
126.09
125.24
124.32
122.51
119.79
117.06
112.87
69.10
66.95
52.17
f1 (ppm)

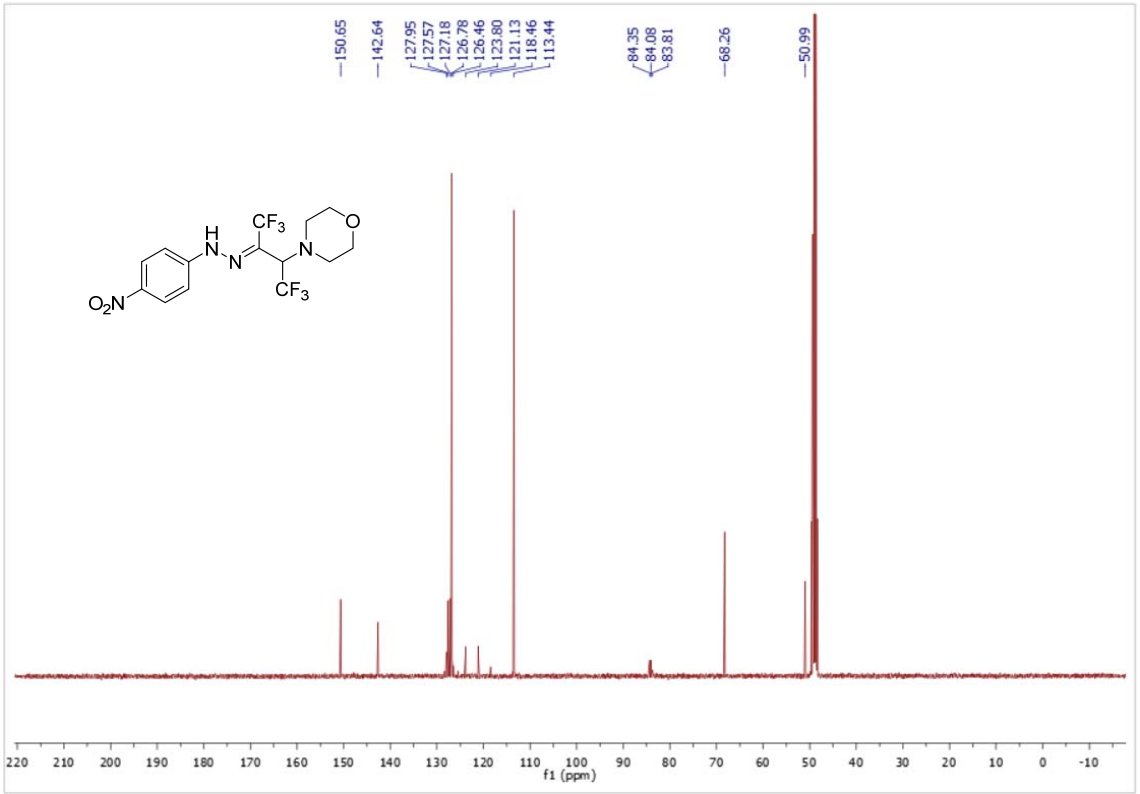
Compound 4i


12.75
8.25
8.23
7.64
7.62
7.36
7.34
7.31
7.29
7.27
7.26
7.23
7.21
7.19
7.15
4.64
3.77
3.72
2.60
0.91
2.16
1.00
6.78
0.99
6.93
4.00
f1 (ppm)

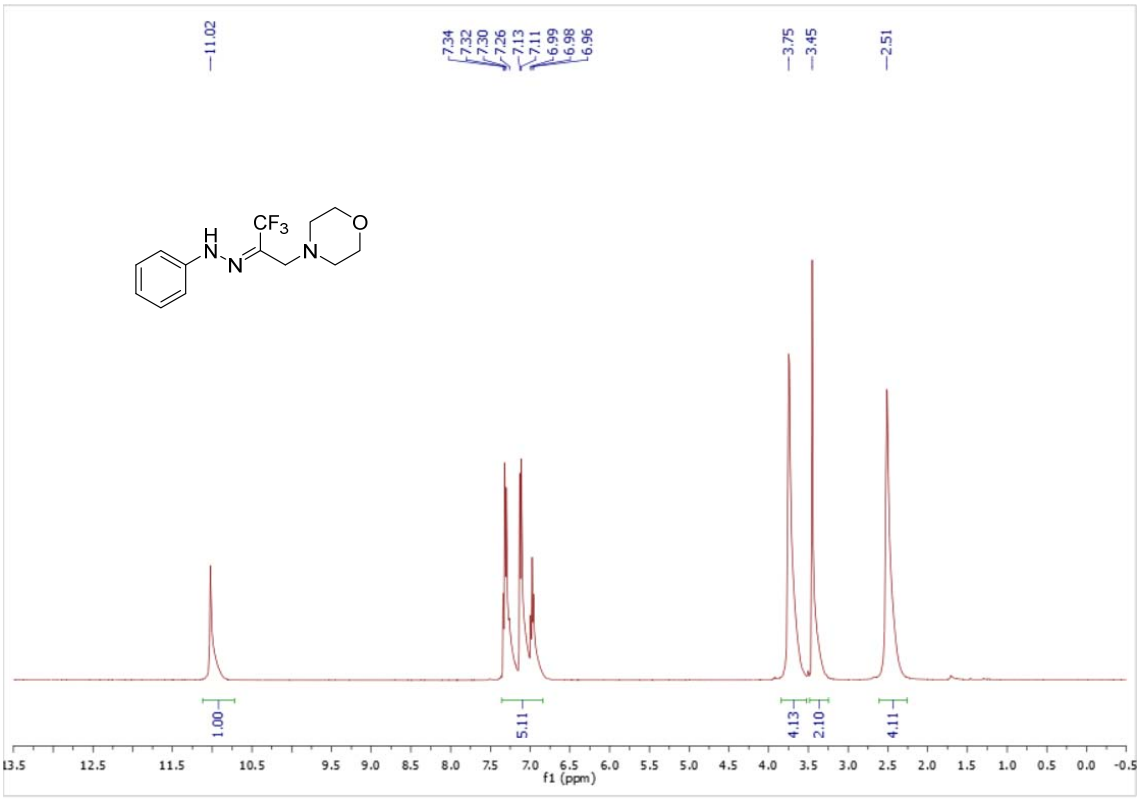

148.80
141.60
136.63
135.39
135.08
128.14
126.21
122.51
120.36
118.45
112.53
109.93
107.31
67.26
61.59
51.85
33.16
f1 (ppm)

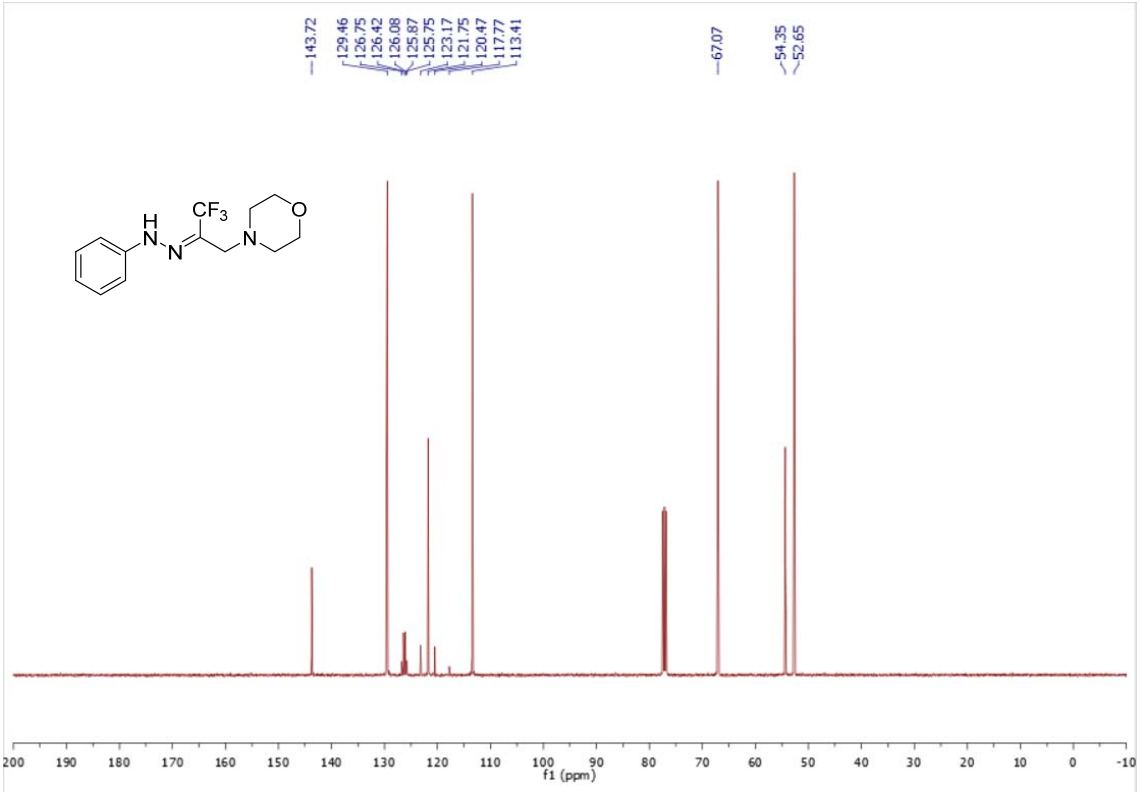
Compound 4j


8.17
8.14
7.29
7.28
7.16
7.14
3.66
3.65
3.64
2.78
2.77
1.94
0.94
1.94
4.20
4.18
f1 (ppm)

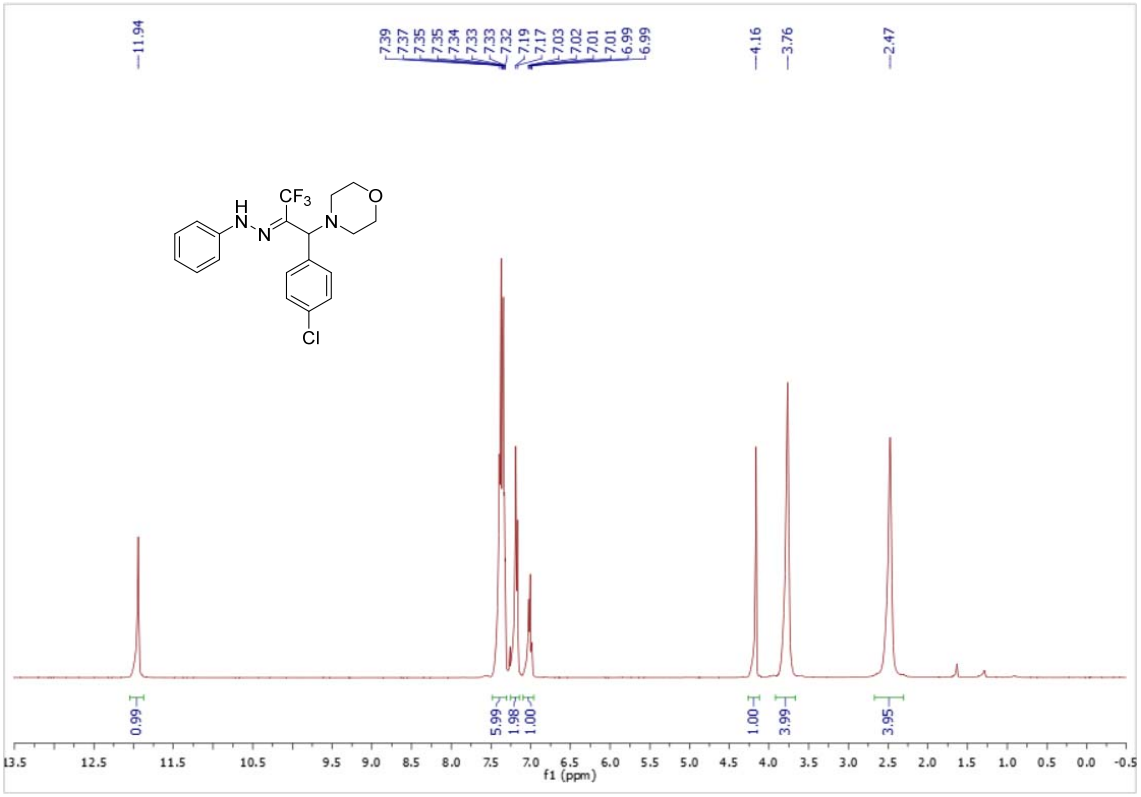

150.65
142.64
127.95
127.57
127.18
126.78
126.46
123.80
121.13
118.46
113.44
84.35
84.08
83.81
68.26
50.99
f1 (ppm)

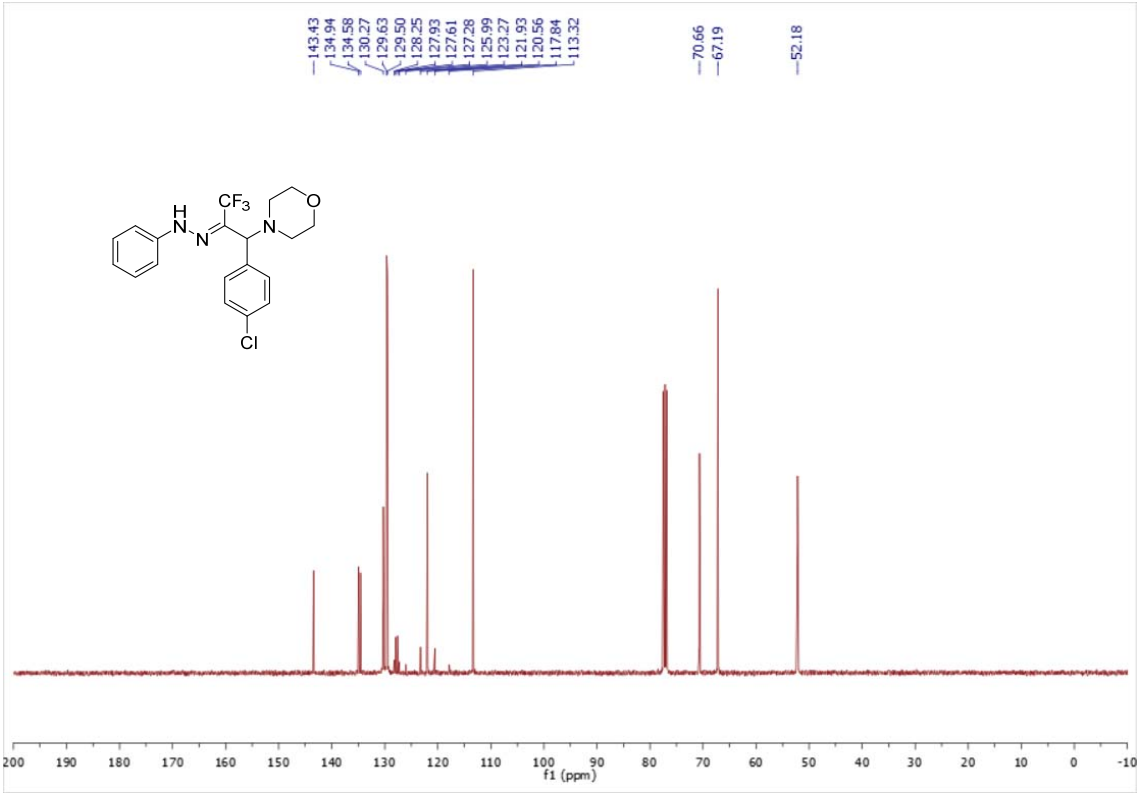
Compound 4k


11.02
7.34
7.32
7.30
7.26
7.13
7.11
6.99
6.98
6.96
3.75
3.45
2.51
CF3
H
N
N
O
N
1.00
5.11
4.13
2.10
4.11
f1 (ppm)


143.72
129.46
126.75
126.42
126.08
125.87
125.75
123.17
121.75
120.47
117.77
113.41
67.07
54.35
52.65
CF3
H
N
N
O
N
f1 (ppm)

Compound 4l


11.94
7.39
7.37
7.35
7.35
7.34
7.33
7.33
7.32
7.19
7.17
7.03
7.02
7.01
7.01
6.99
6.99
4.16
3.76
2.47
CF3
H
N
N
O
N
Cl
0.99
5.99
1.98
1.00
1.00
3.99
3.95
f1 (ppm)


143.43
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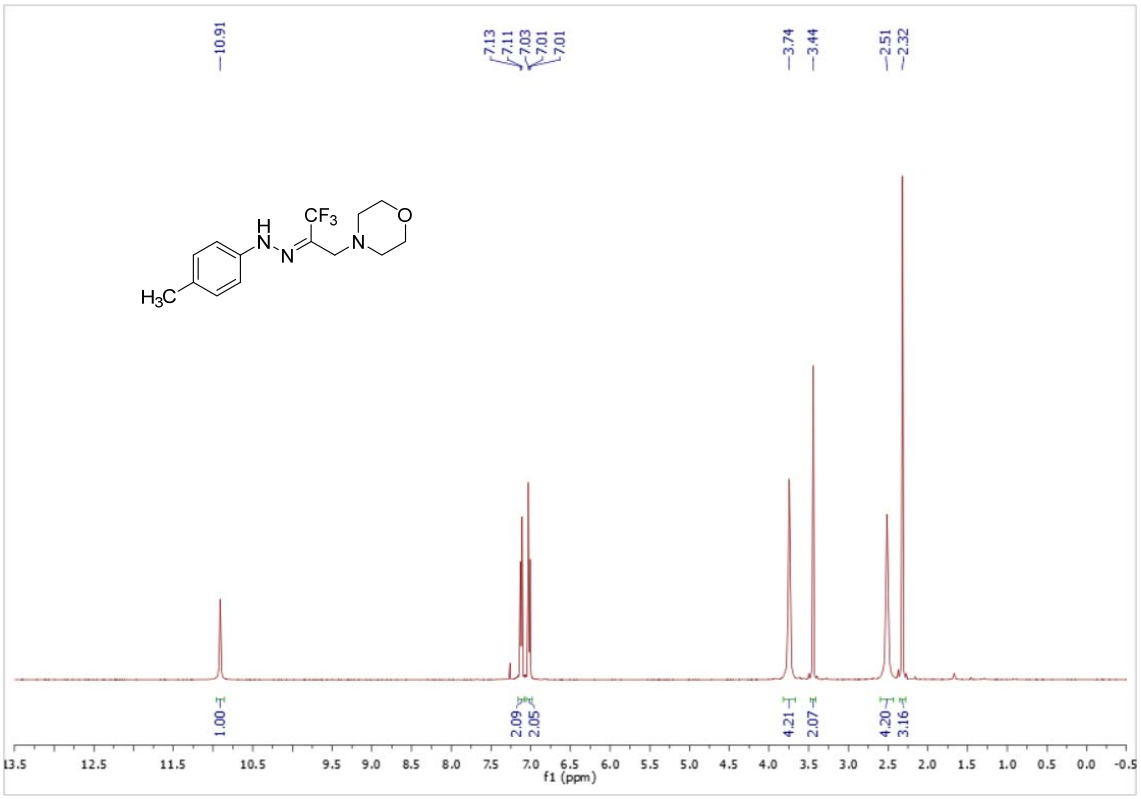
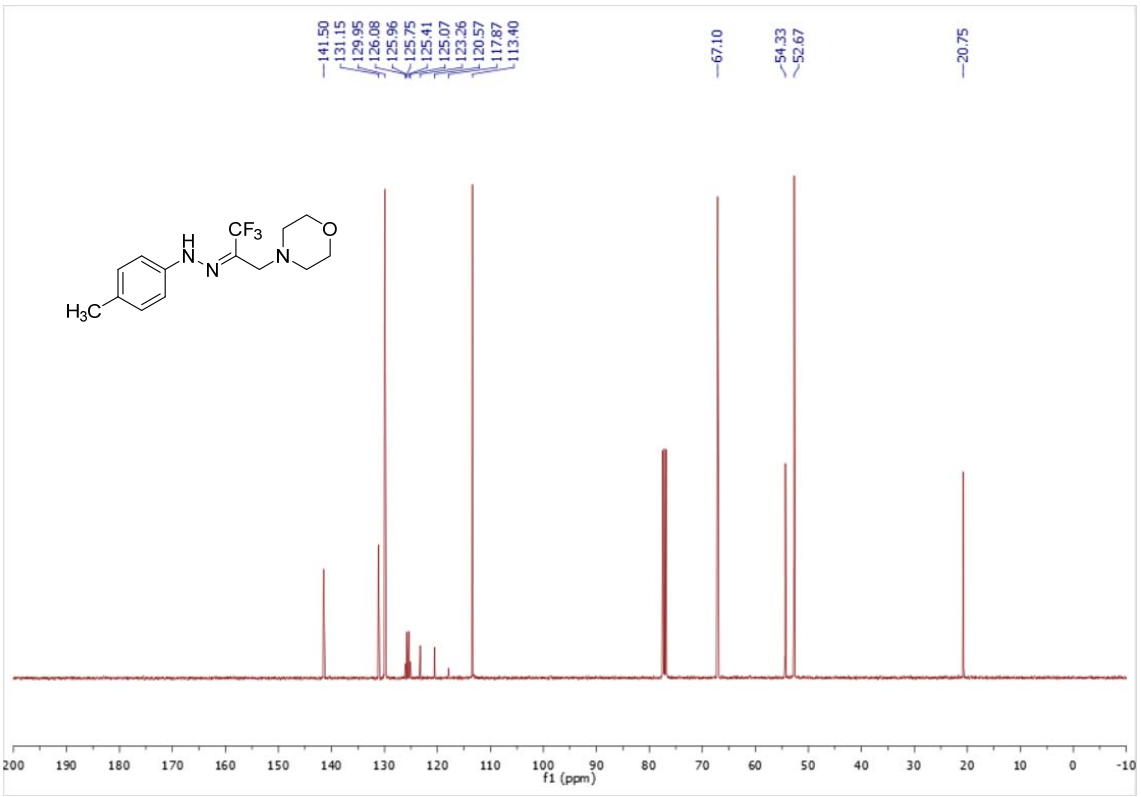
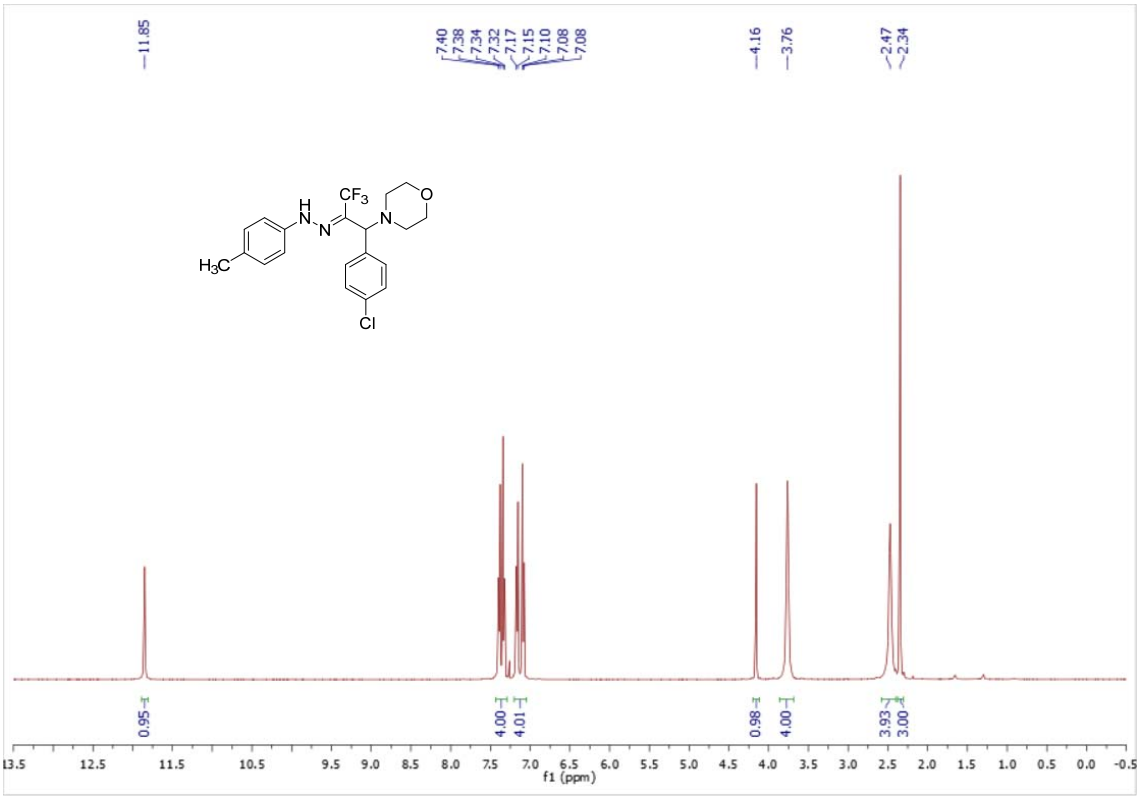
134.58
130.27
129.63
129.50
128.25
127.93
127.61
127.28
125.99
123.27
121.93
120.56
117.84
113.32
70.66
67.19
52.18
CF3
H
N
N
O
N
Cl
f1 (ppm)

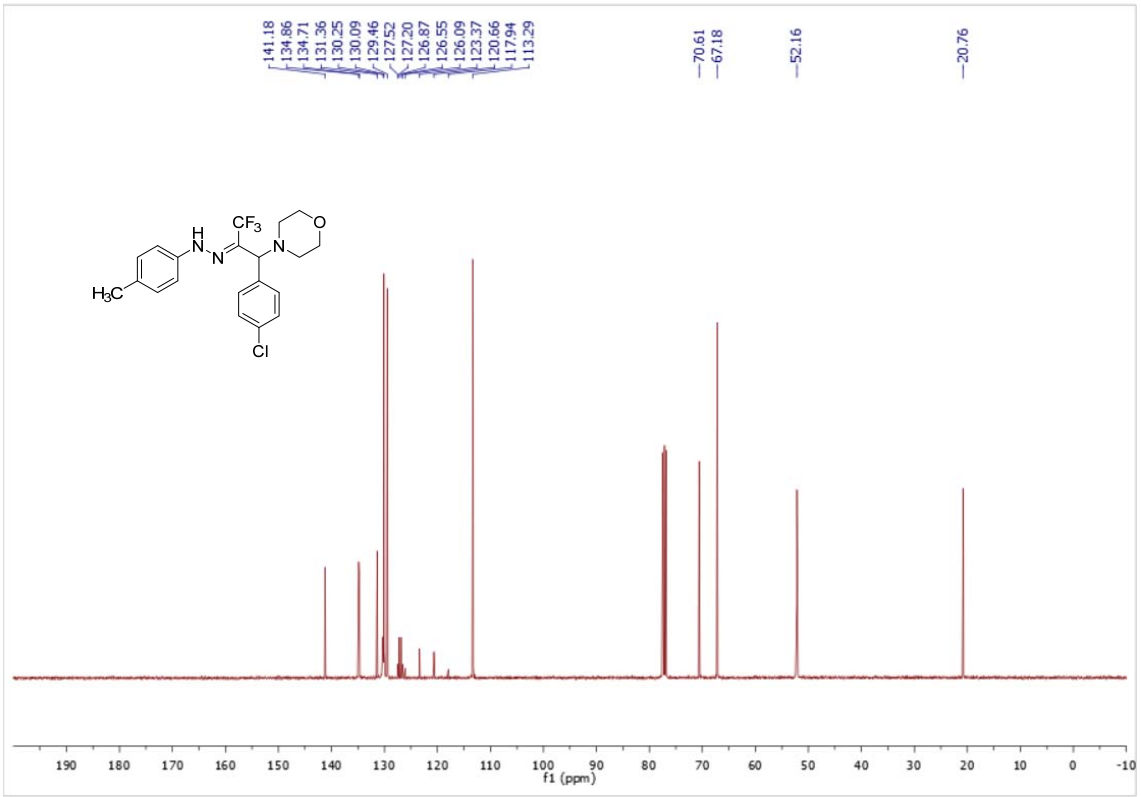
Compound 4m


10.91
7.13
7.11
7.03
7.01
7.01
3.74
3.44
2.51
2.32
1.00
2.09
2.05
4.21
2.07
4.20
3.16
f1 (ppm)

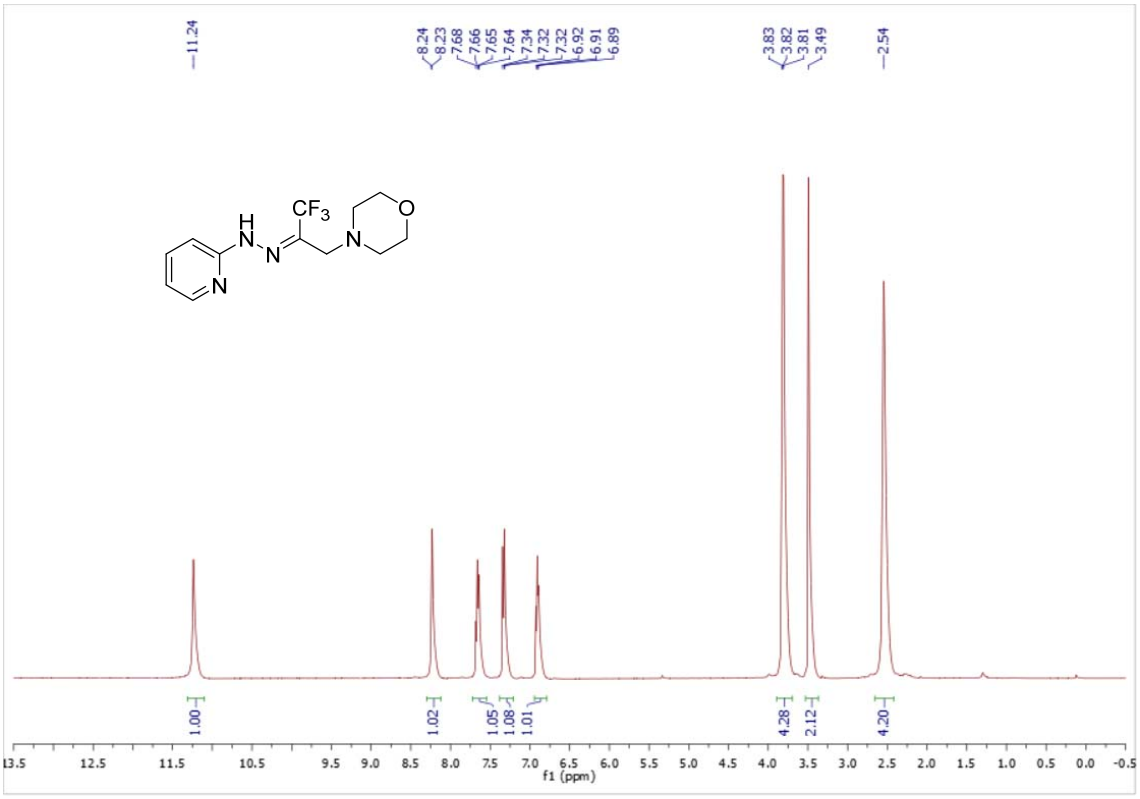

141.50
131.15
129.95
126.08
125.96
125.75
125.41
125.07
123.26
120.57
117.87
113.40
67.10
54.33
52.67
20.75
f1 (ppm)

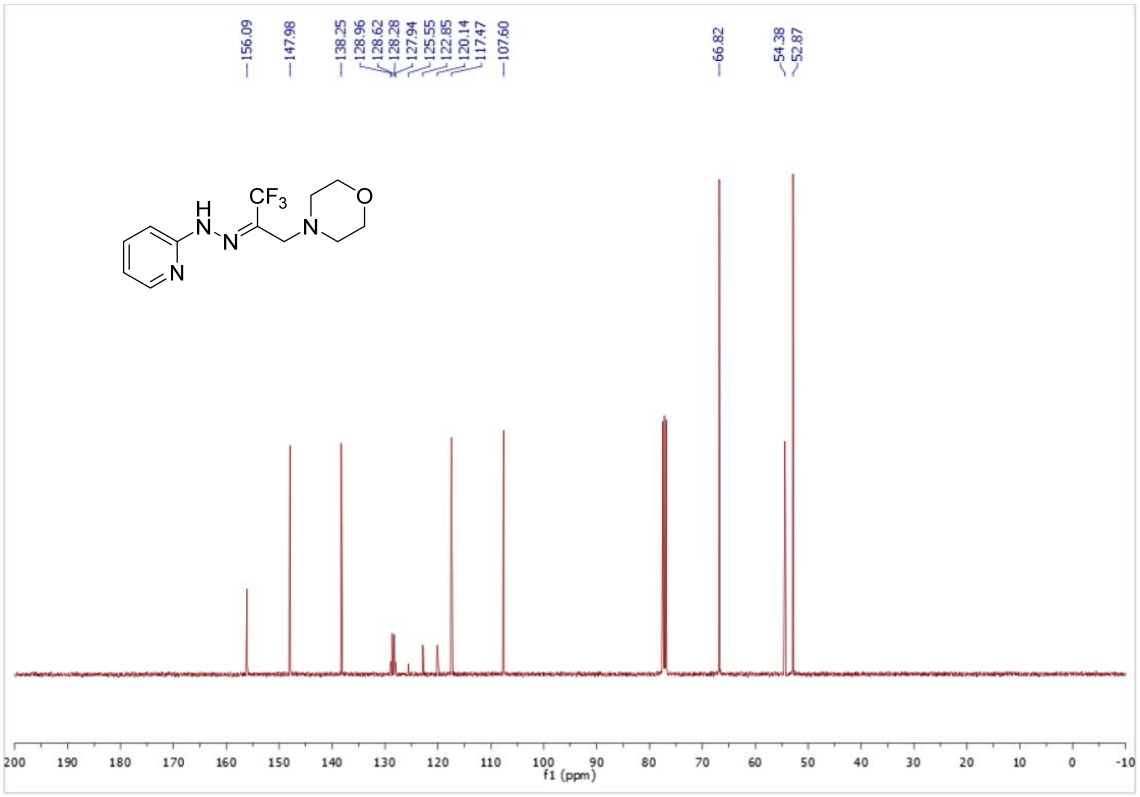
Compound 4n


11.85
7.40
7.38
7.34
7.32
7.17
7.15
7.10
7.08
7.08
4.16
3.76
2.47
2.34
0.95
4.00
4.01
0.98
4.00
3.93
3.00
f1 (ppm)

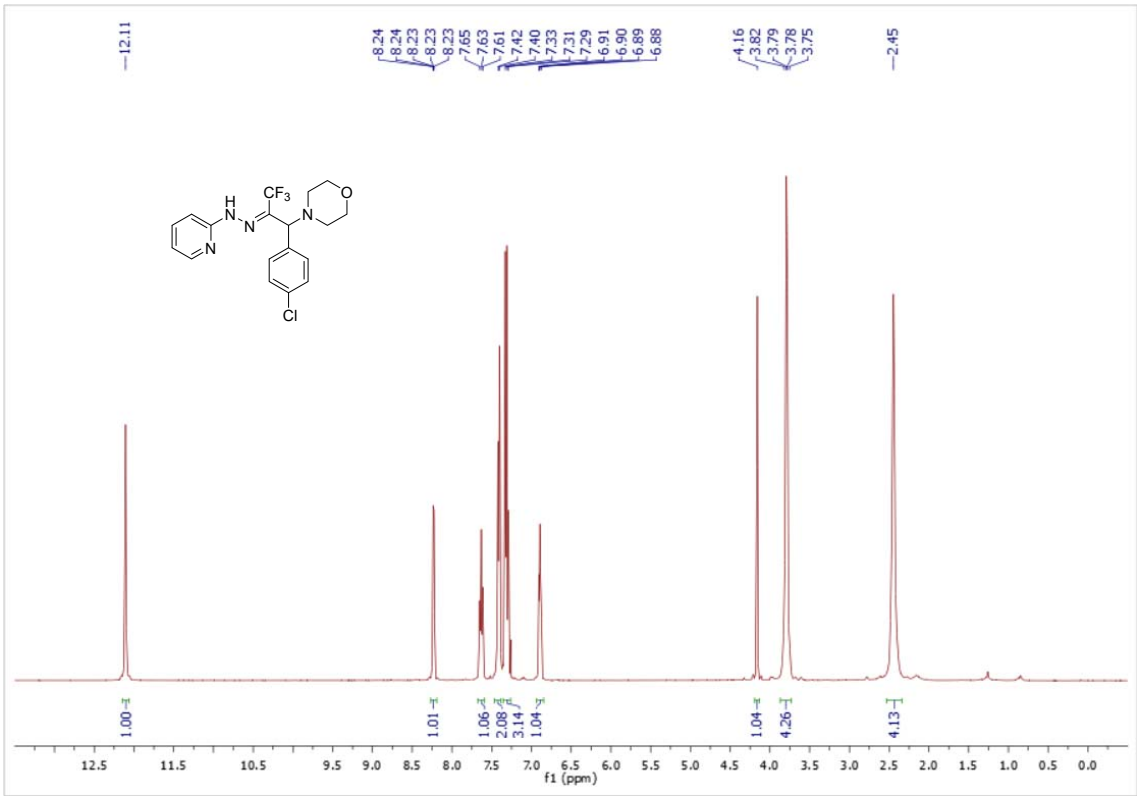

141.18
134.86
134.71
131.36
130.25
130.09
129.46
127.52
127.20
126.87
126.55
126.09
123.37
120.66
117.94
113.29
70.61
67.18
52.16
20.76
f1 (ppm)

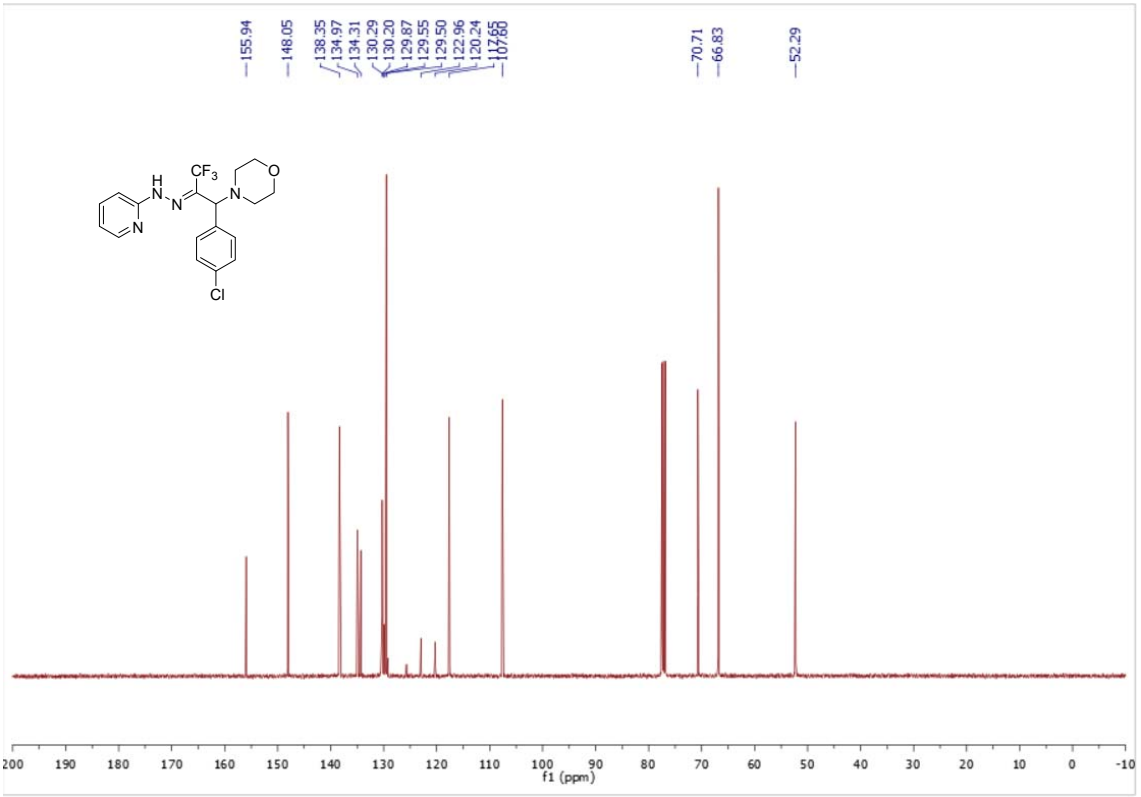
Compound 4o


11.24
8.24
8.23
7.68
7.66
7.65
7.64
7.34
7.32
7.32
6.92
6.91
6.89
3.83
3.82
3.81
3.49
2.54
1.00
1.02
1.05
1.08
1.01
4.28
2.12
4.20
f1 (ppm)

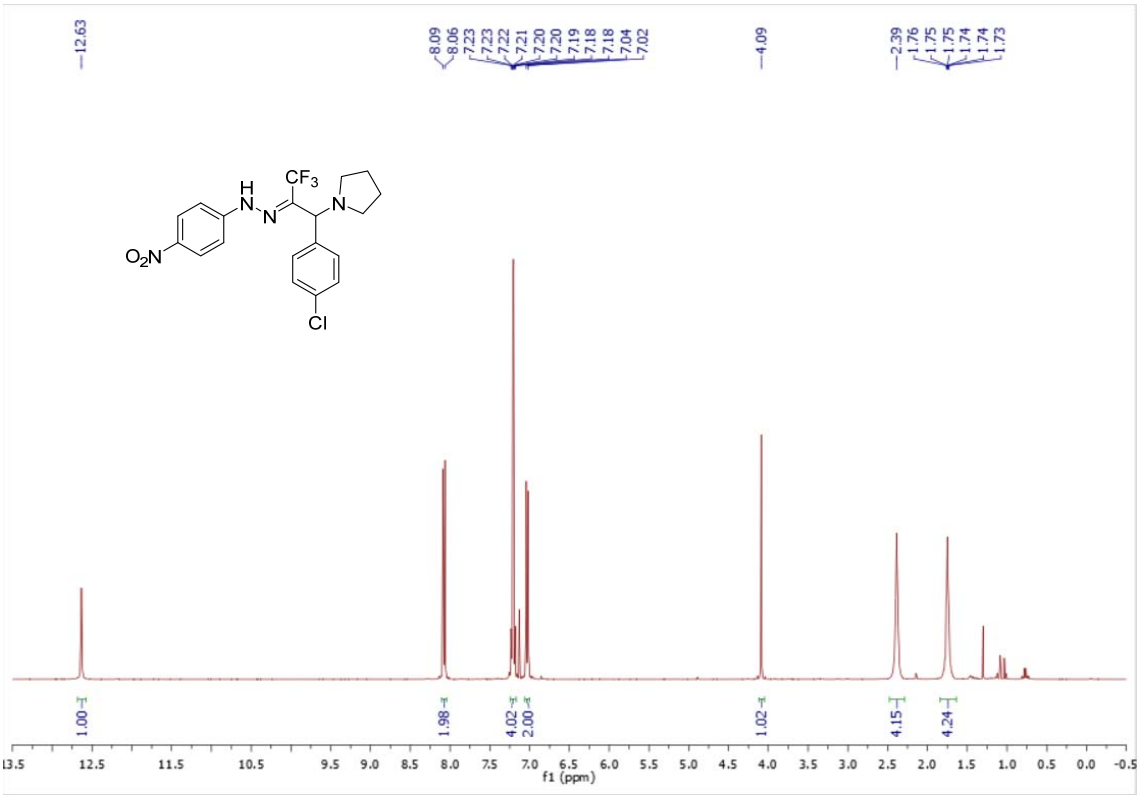

156.09
147.98
138.25
128.96
128.62
128.28
127.94
125.55
122.85
120.14
117.47
107.60
66.82
54.38
52.87
f1 (ppm)

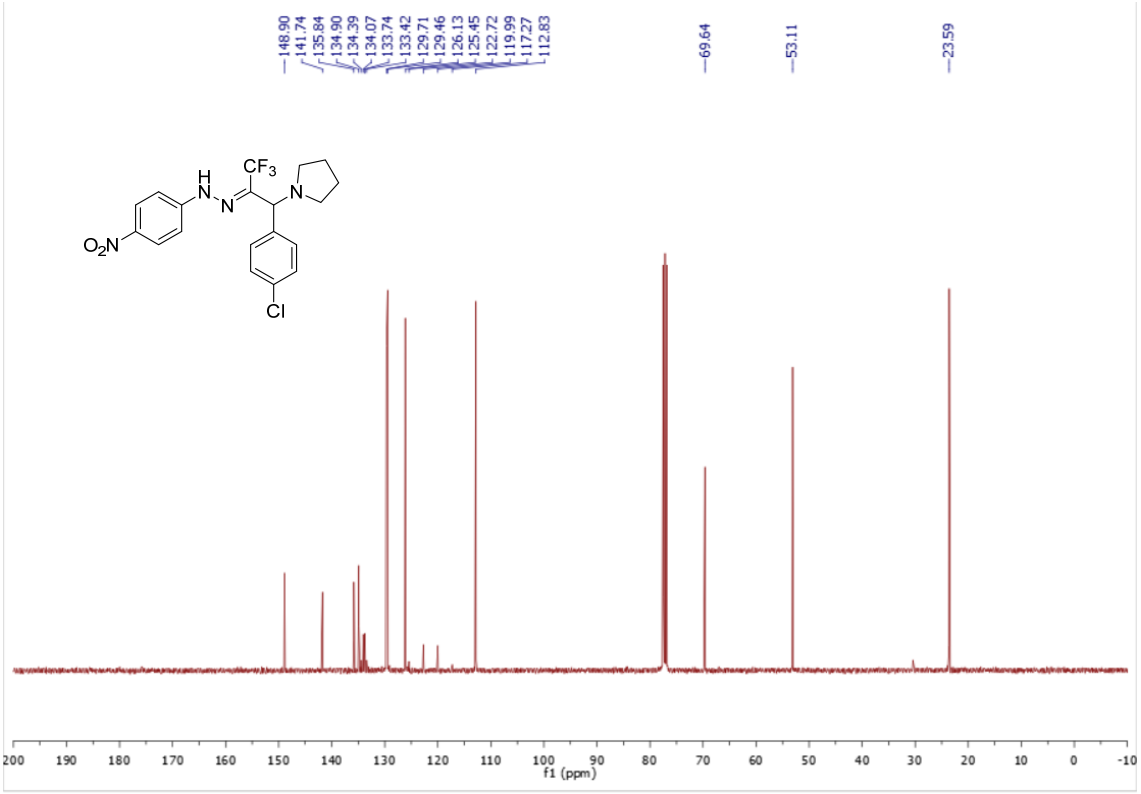
Compound 4p


12.11
8.24
8.24
8.23
8.23
7.65
7.63
7.61
7.42
7.40
7.33
7.31
7.29
6.91
6.90
6.89
6.88
4.16
3.82
3.79
3.78
3.75
2.45
1.00
1.01
1.06
2.08
3.14
1.04
1.04
4.26
4.13
f1 (ppm)

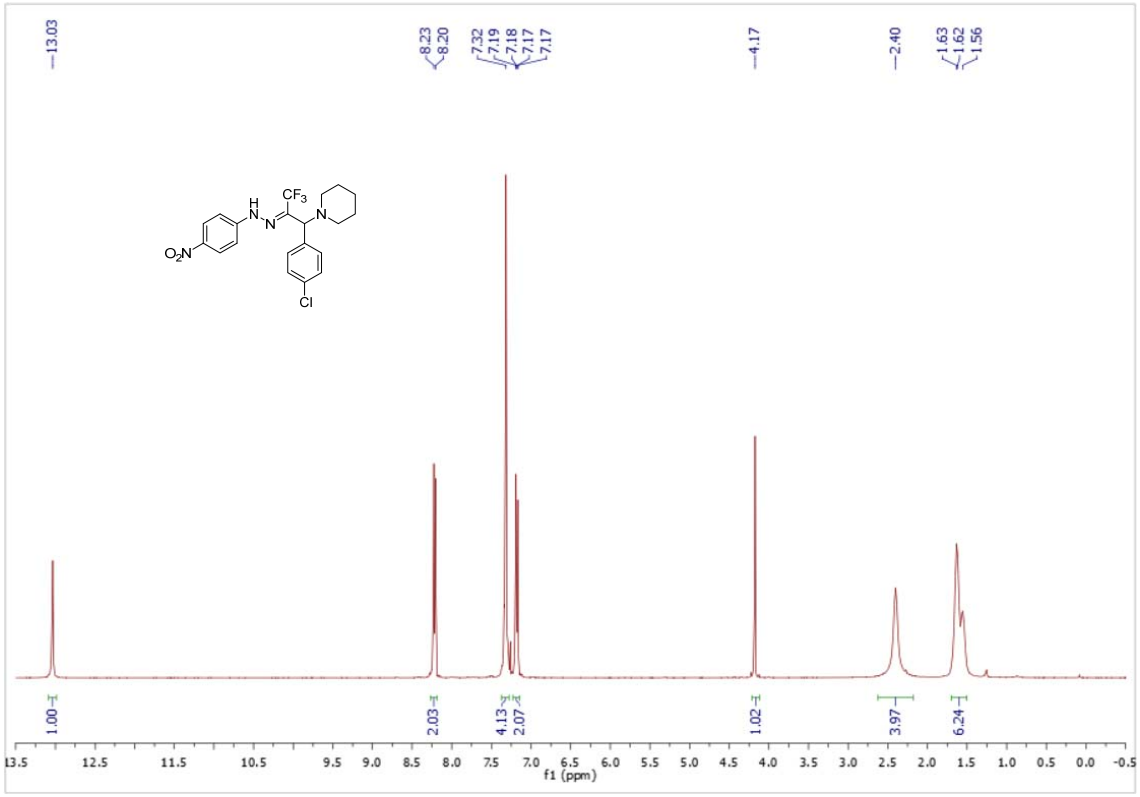

155.94
148.05
138.35
134.97
134.31
130.29
130.20
129.87
129.55
129.50
122.96
120.24
117.65
107.60
70.71
66.83
52.29
f1 (ppm)

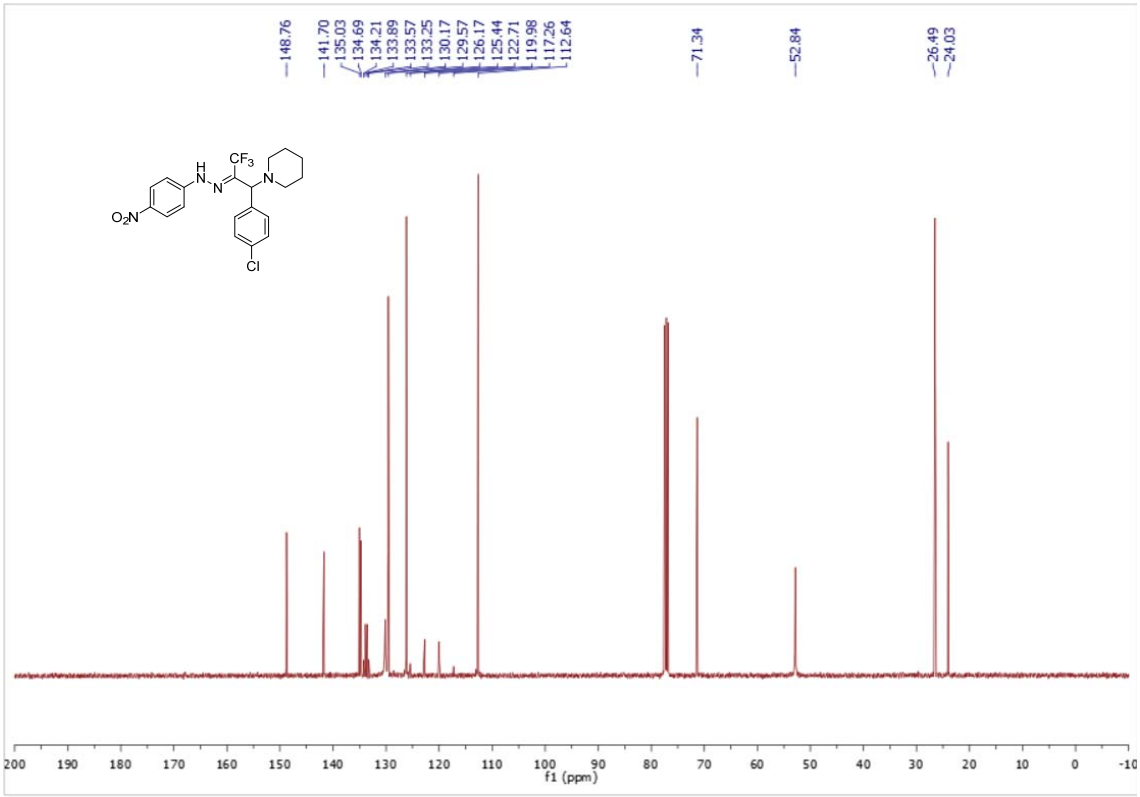
Compound 4q


12.63
8.09
8.06
7.23
7.22
7.21
7.20
7.19
7.18
7.04
7.02
4.09
2.39
1.76
1.75
1.74
1.73
1.00
1.98
4.02
2.00
1.02
4.15
4.24
f1 (ppm)

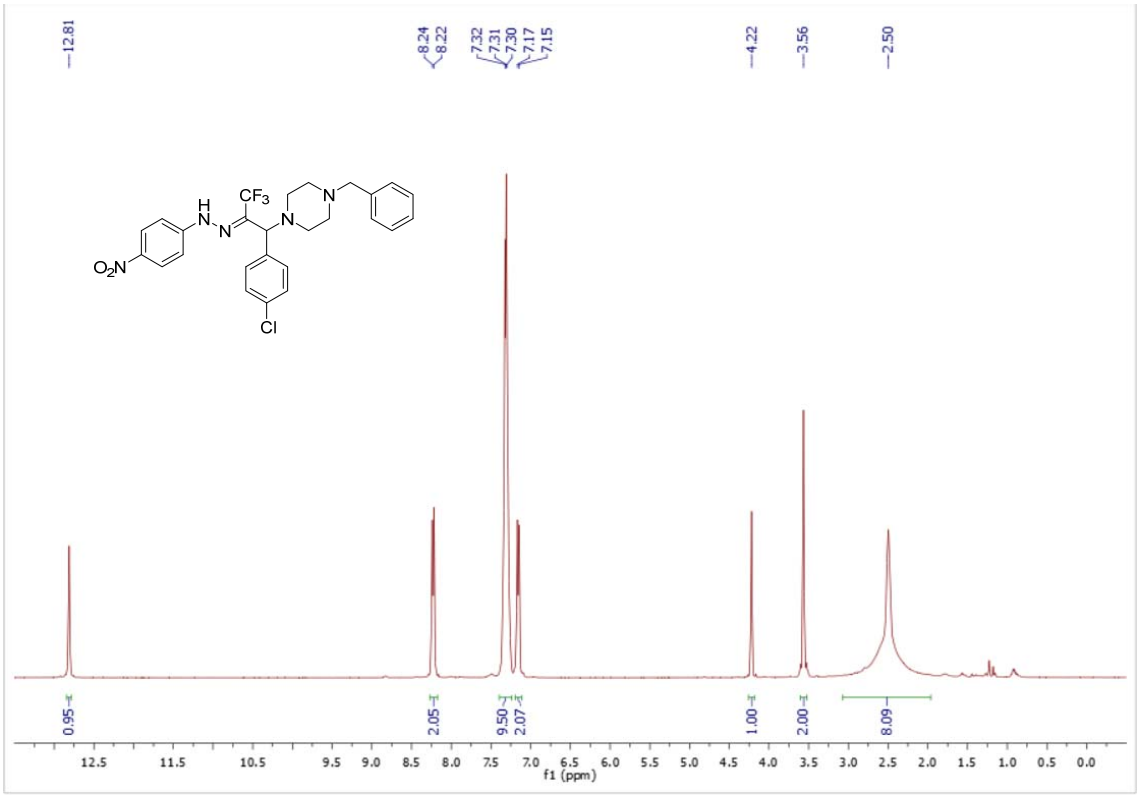

148.90
141.74
135.84
134.90
134.39
134.07
133.74
133.42
129.71
129.46
126.13
125.45
122.72
119.99
117.27
112.83
69.64
53.11
23.59
f1 (ppm)

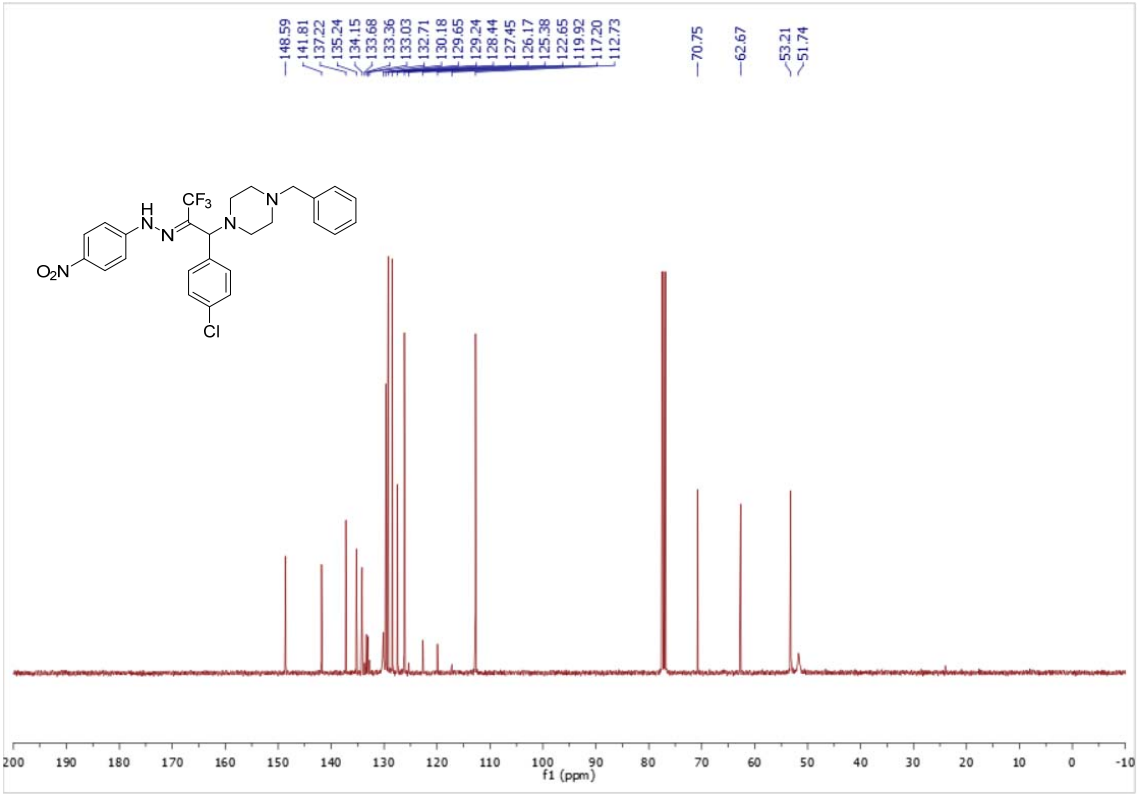
Compound 4r


13.03
8.23
8.20
7.32
7.19
7.18
7.17
7.17
4.17
2.40
1.63
1.62
1.56
1.00
2.03
4.13
2.07
1.02
3.97
6.24
f1 (ppm)

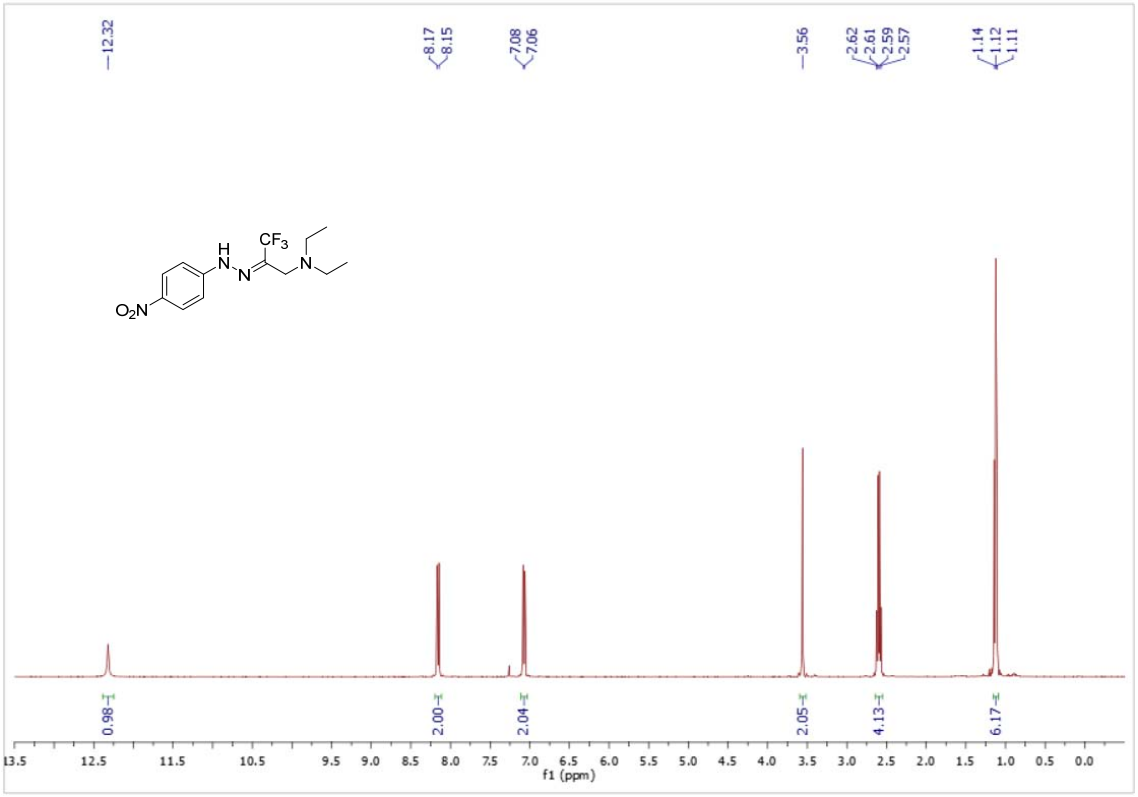

148.76
141.70
135.03
134.69
134.21
133.89
133.57
133.25
130.17
129.57
126.17
125.44
122.71
119.98
117.26
112.64
71.34
52.84
26.49
24.03
f1 (ppm)

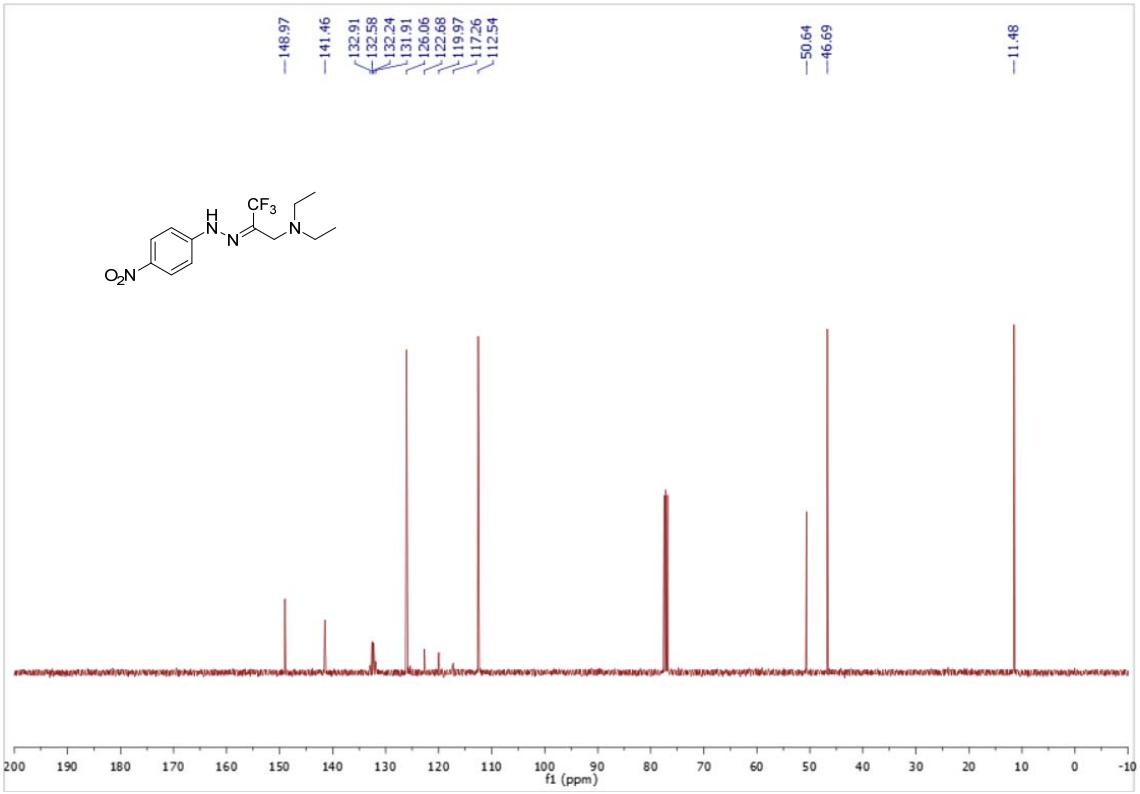
Compound 4s


12.81
8.24
8.22
7.32
7.31
7.30
7.17
7.15
4.22
3.56
2.50
0.95
2.05
9.50
2.07
1.00
2.00
8.09
f1 (ppm)

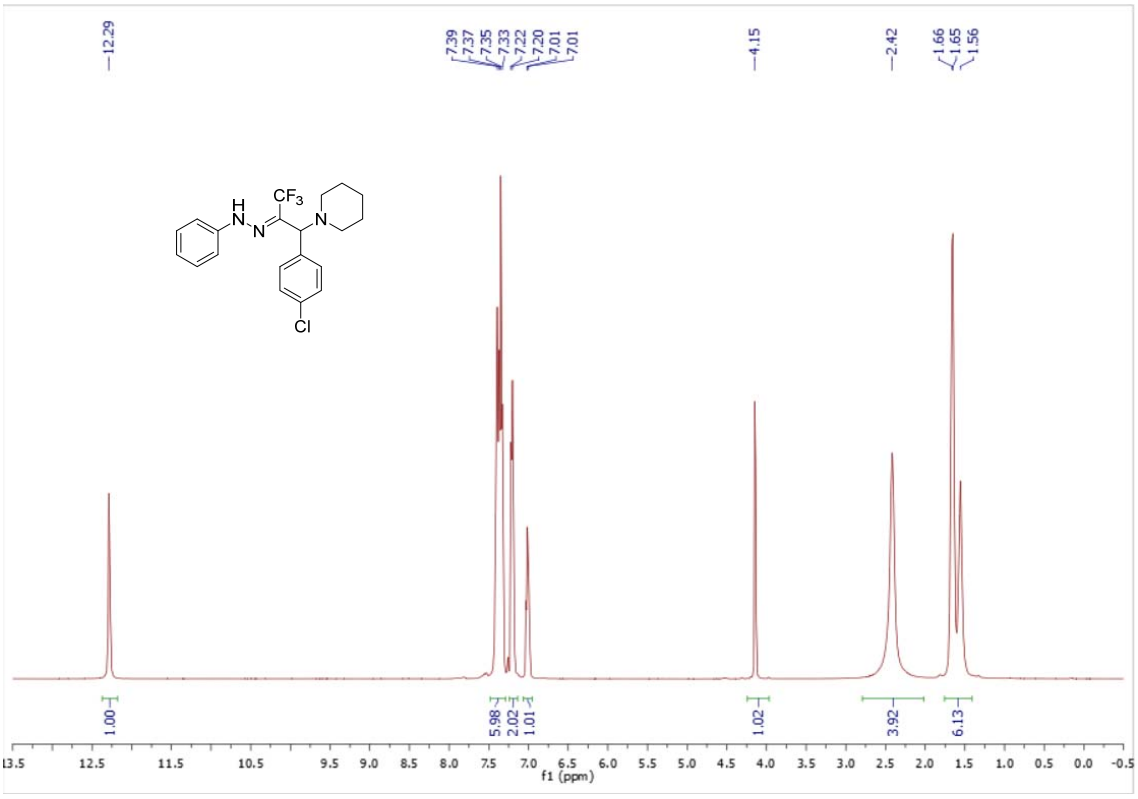

148.59
141.81
137.22
135.24
134.15
133.68
133.36
133.03
132.71
130.18
129.65
129.24
128.44
127.45
126.17
125.38
122.65
119.92
117.20
112.73
70.75
62.67
53.21
51.74
f1 (ppm)

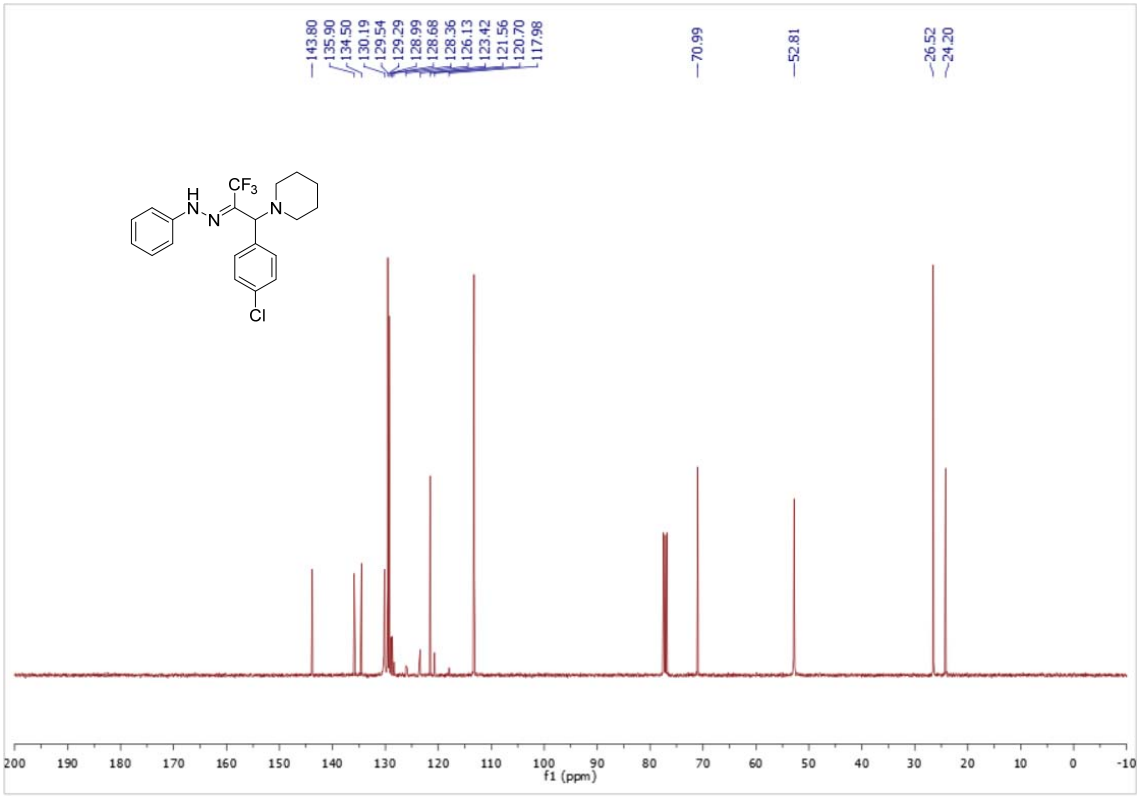
Compound 4t


12.32
8.17
8.15
7.08
7.06
3.56
2.62
2.61
2.59
2.57
1.14
1.12
1.11
0.98
2.00
2.04
2.05
4.13
6.17
f1 (ppm)

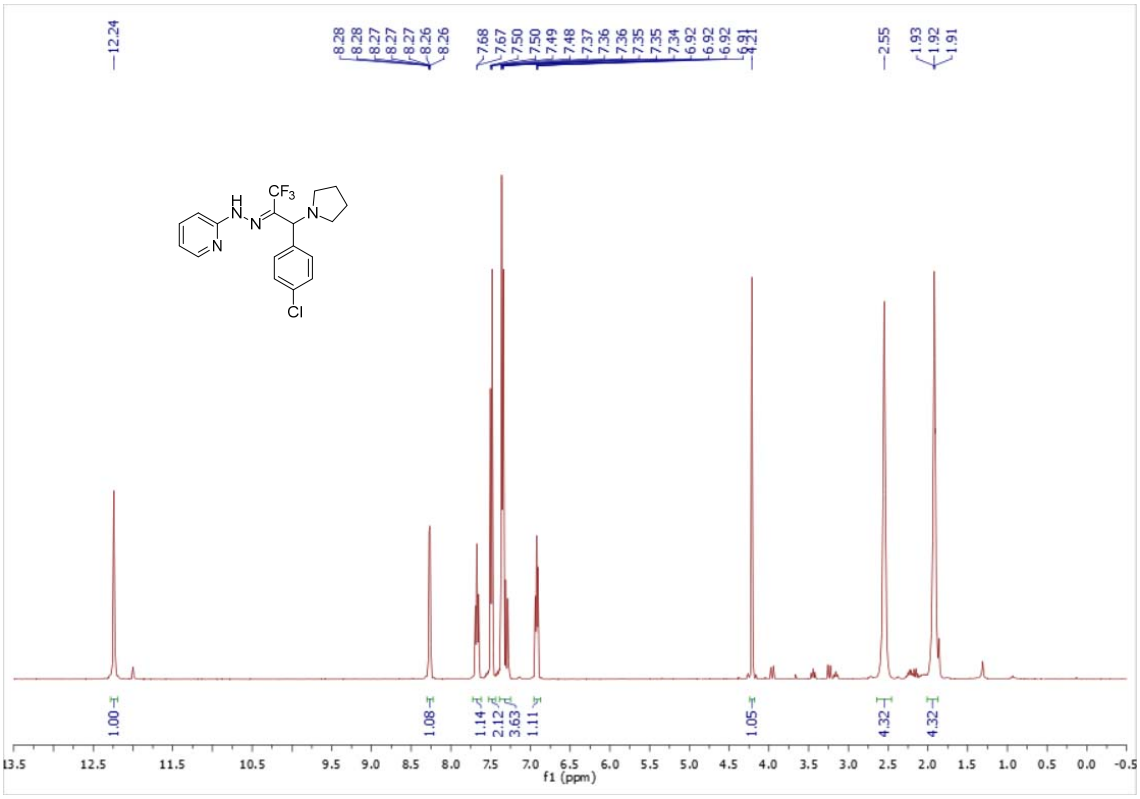

148.97
141.46
132.91
132.58
132.24
131.91
126.06
122.68
119.97
117.26
112.54
50.64
46.69
11.48
f1 (ppm)

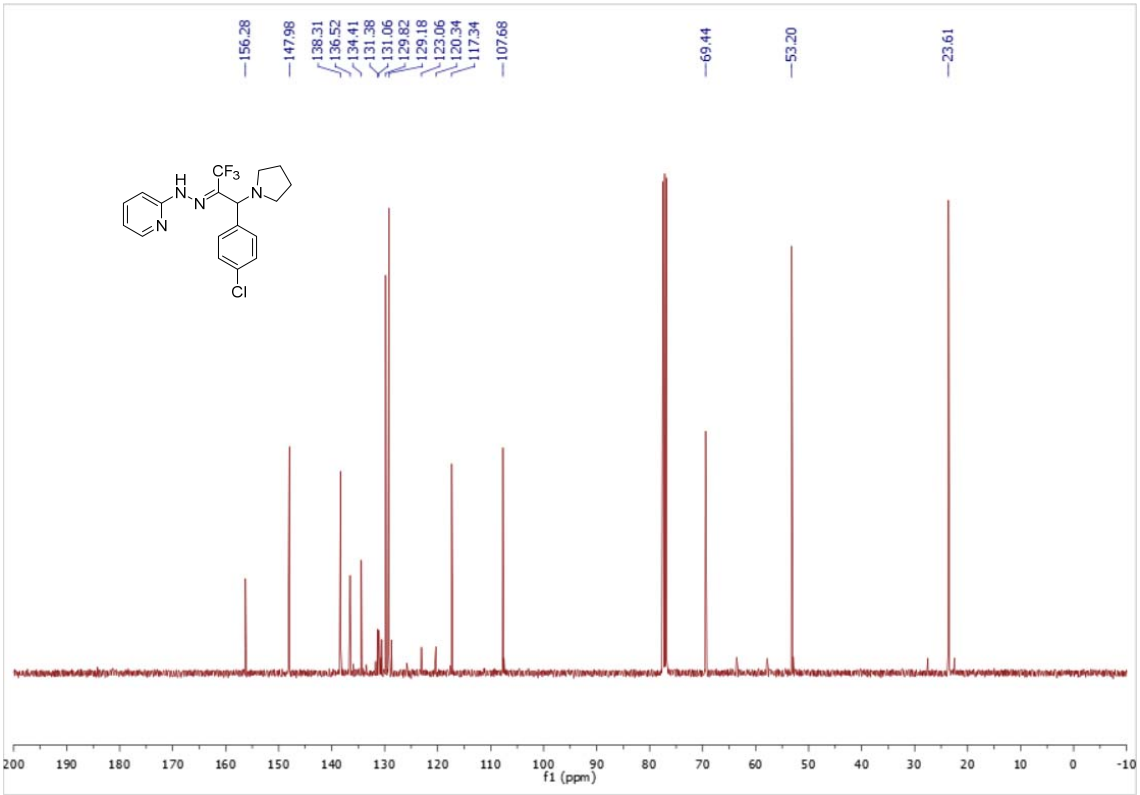
Compound 4u


12.29
7.39
7.37
7.35
7.33
7.22
7.20
7.01
7.01
4.15
2.42
1.66
1.65
1.56
1.00
5.98
2.02
1.01
1.02
3.92
6.13
f1 (ppm)

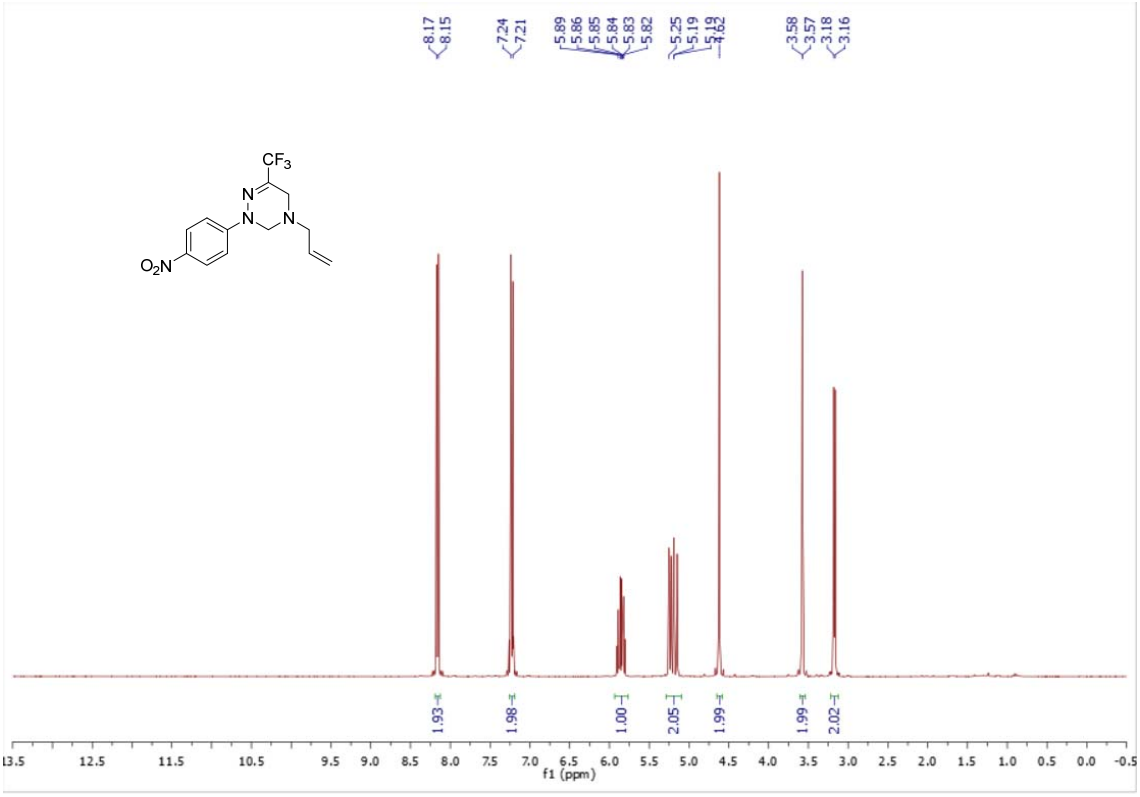

143.80
135.90
134.50
130.19
129.54
129.29
128.99
128.68
128.36
126.13
123.42
121.56
120.70
117.98
70.99
52.81
26.52
24.20
f1 (ppm)

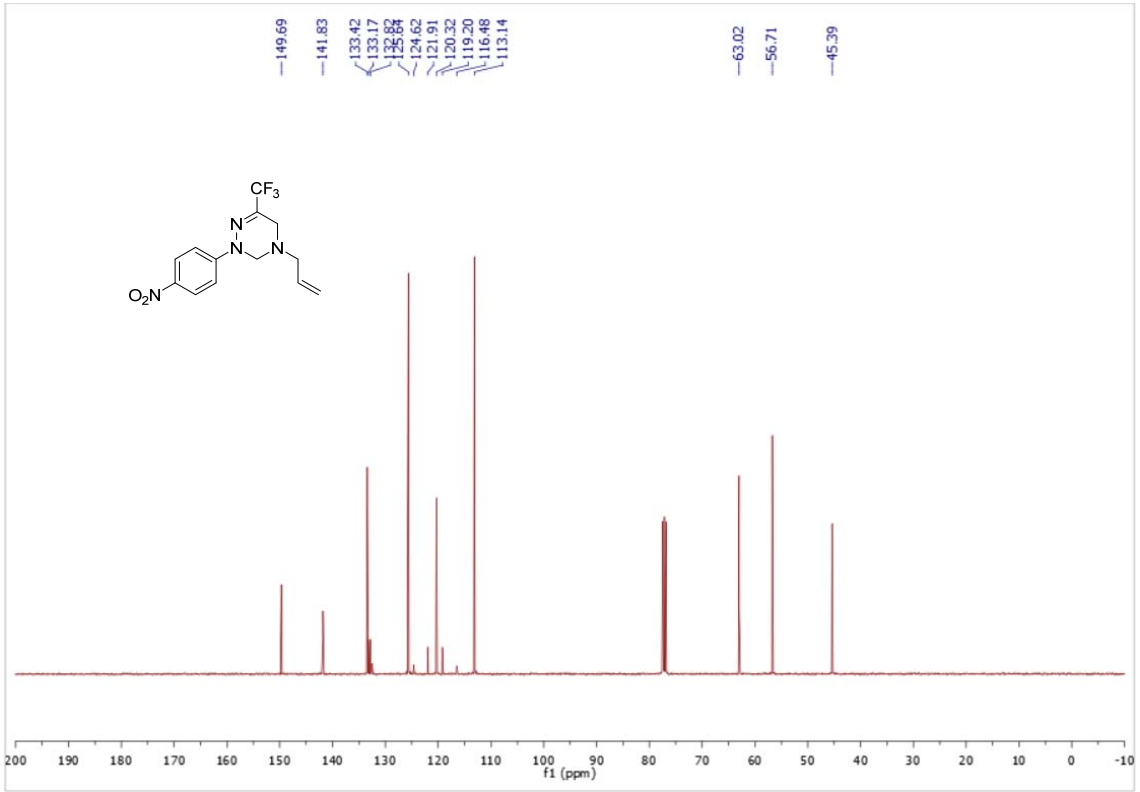
Compound 4v


12.24
8.28
8.28
8.27
8.27
8.27
8.26
8.26
7.68
7.67
7.50
7.50
7.49
7.48
7.37
7.36
7.36
7.35
7.35
7.34
6.92
6.92
6.91
4.21
2.55
1.93
1.92
1.91
CF3
H
N
N
N
N
Cl
1.00
1.08
1.14
2.12
3.63
1.11
1.05
4.32
4.32
f1 (ppm)

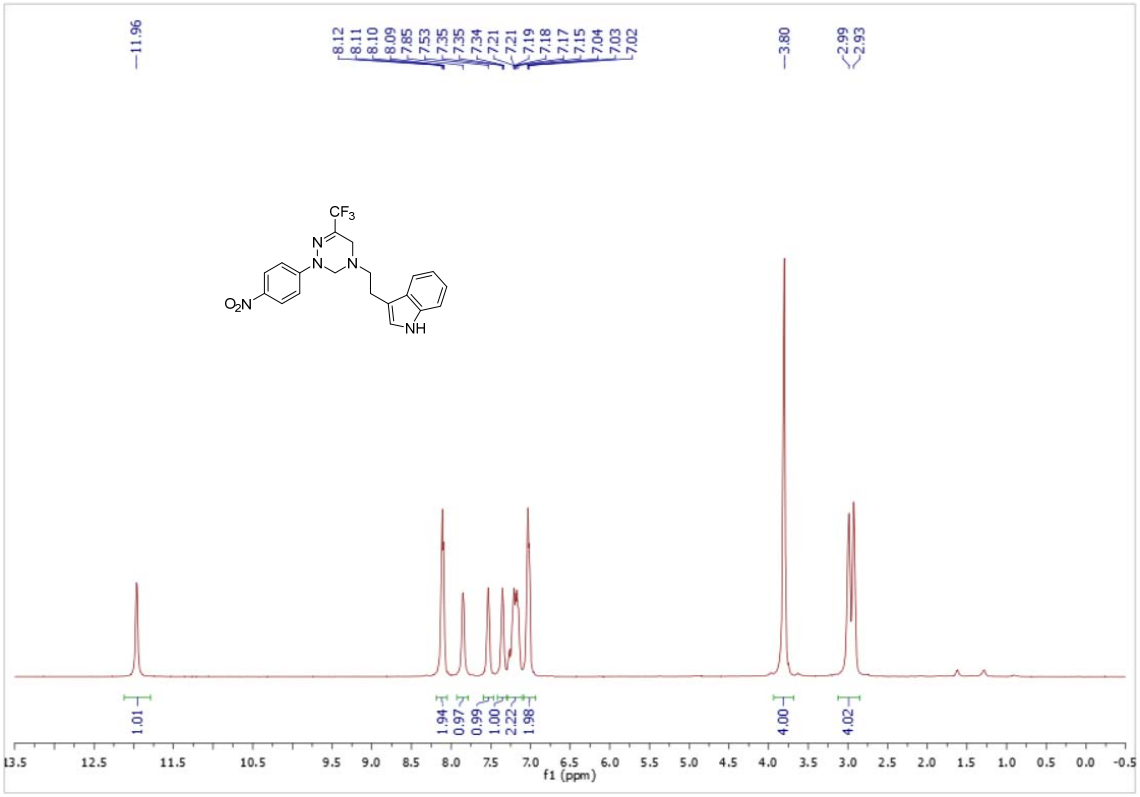

156.28
147.98
138.31
136.52
134.41
131.38
131.06
129.82
129.18
123.06
120.34
117.34
107.68
69.44
53.20
23.61
CF3
H
N
N
N
N
Cl
f1 (ppm)

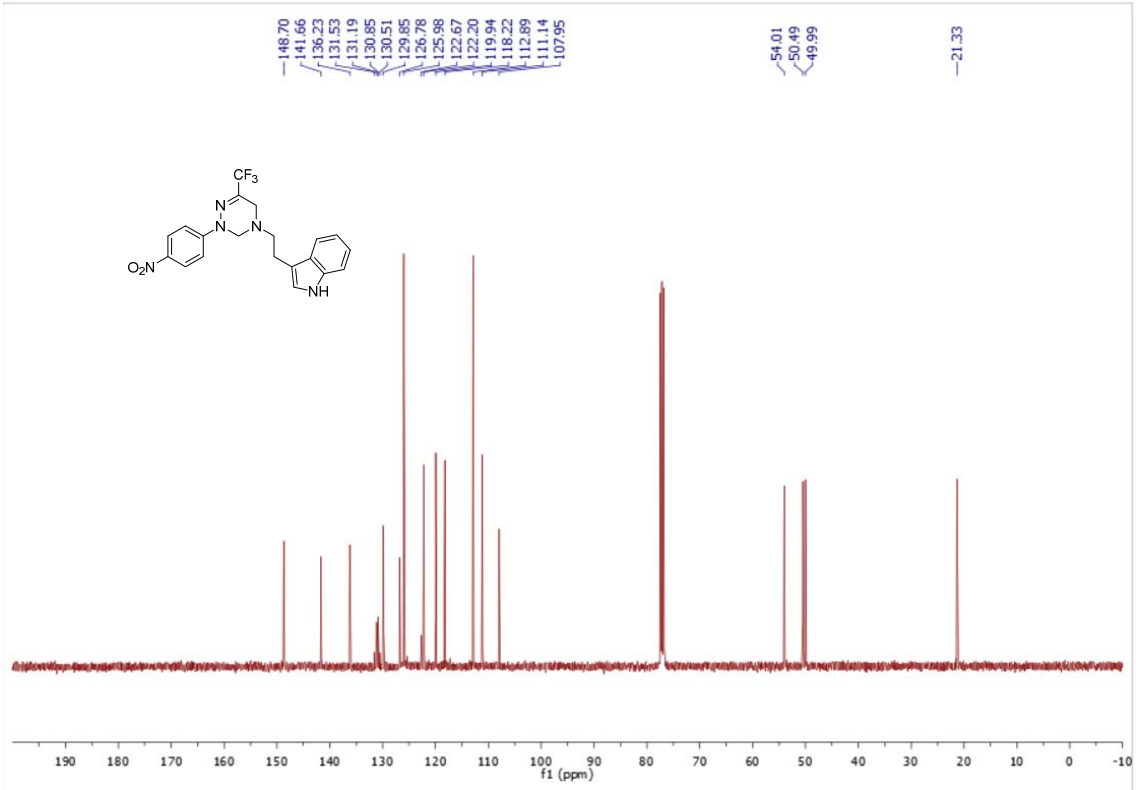
Compound 5a


8.17
8.15
7.24
7.21
5.89
5.86
5.85
5.84
5.83
5.82
5.25
5.19
5.19
4.62
3.58
3.57
3.18
3.16
CF3
N
N
N
O2N
1.93
1.98
1.00
2.05
1.99
1.99
2.02
f1 (ppm)

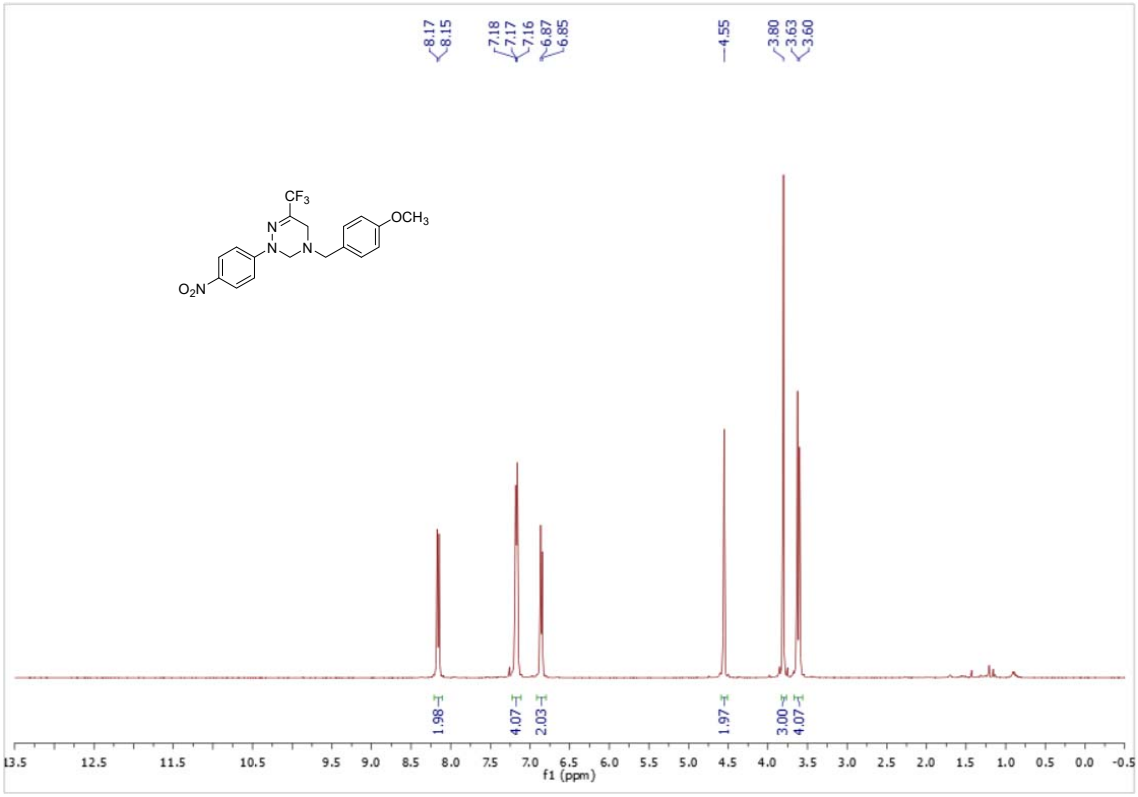

149.69
141.83
133.42
133.17
125.64
124.62
121.91
120.32
119.20
116.48
113.14
63.02
56.71
45.39
CF3
N
N
N
O2N
f1 (ppm)

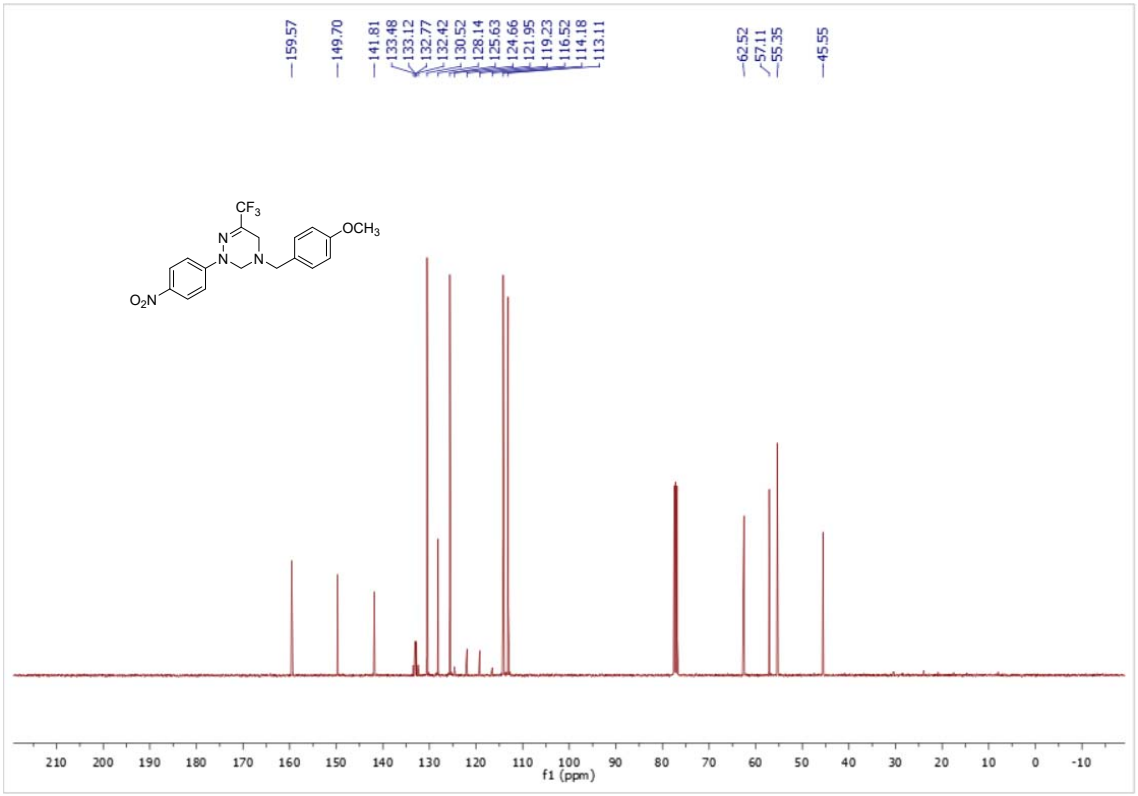
Compound 5b


11.96
8.12
8.11
8.10
8.09
7.85
7.53
7.35
7.35
7.34
7.21
7.21
7.19
7.18
7.17
7.15
7.04
7.03
7.02
3.80
2.99
2.93
CF3
N
N
N
O2N
NH
1.01
1.94
0.97
0.99
1.00
2.22
1.98
4.00
4.02
f1 (ppm)

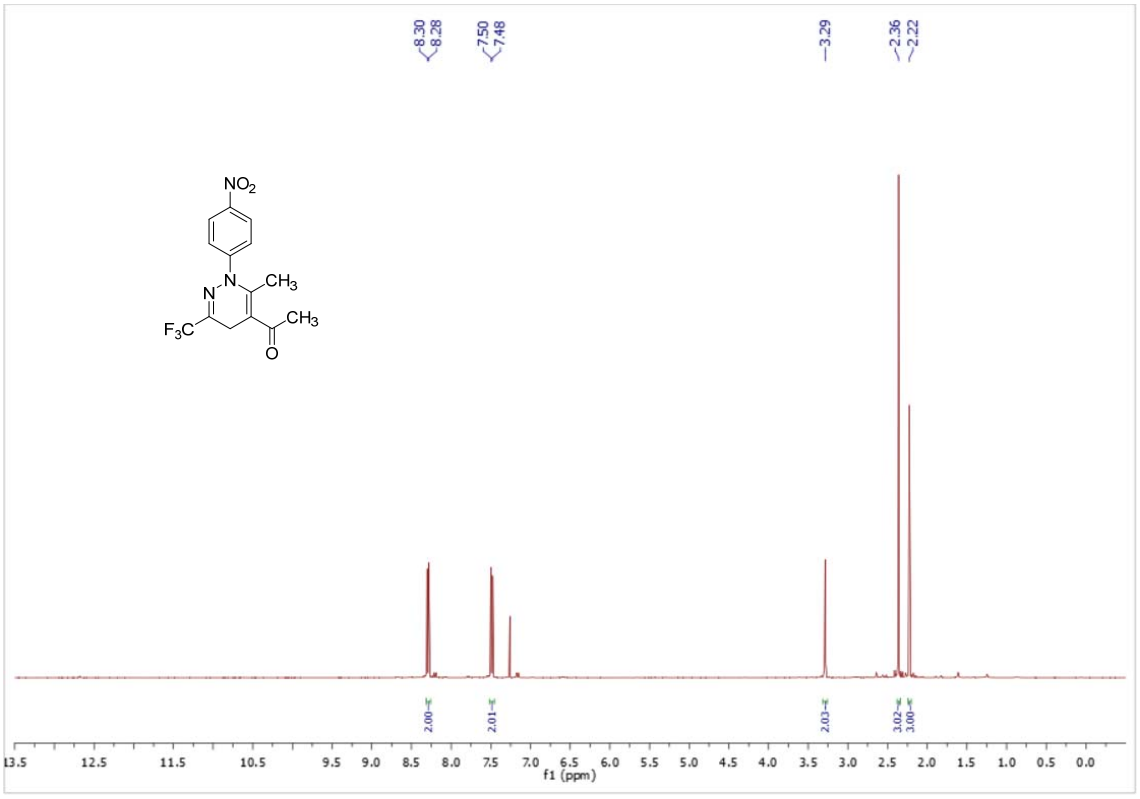

148.70
141.66
136.23
131.53
131.19
130.85
130.51
129.85
126.78
125.98
122.67
122.20
119.94
118.22
112.89
111.14
107.95
54.01
50.49
49.99
21.33
CF3
N
N
N
O2N
NH
f1 (ppm)

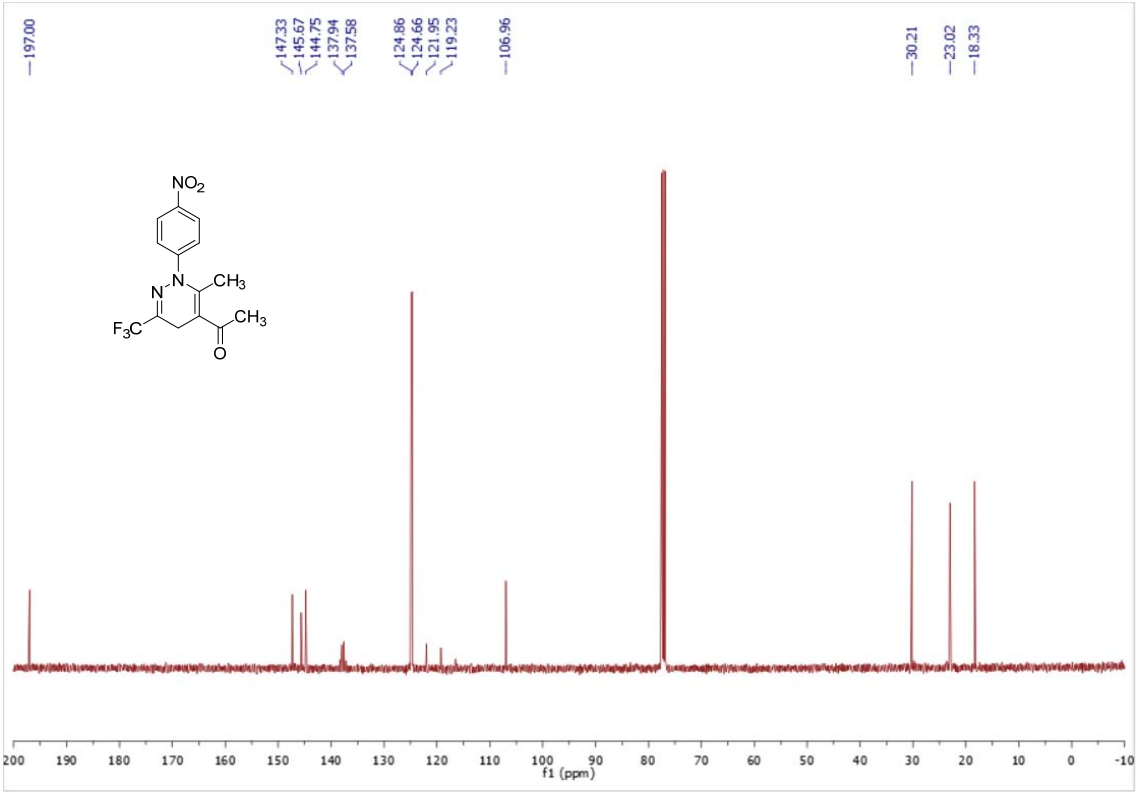
Compound 5c


8.17
8.15
7.18
7.17
7.16
6.87
6.85
4.55
3.80
3.63
3.60
CF3
OCH3
O2N
1.98
4.07
2.03
1.97
3.00
4.07
f1 (ppm)

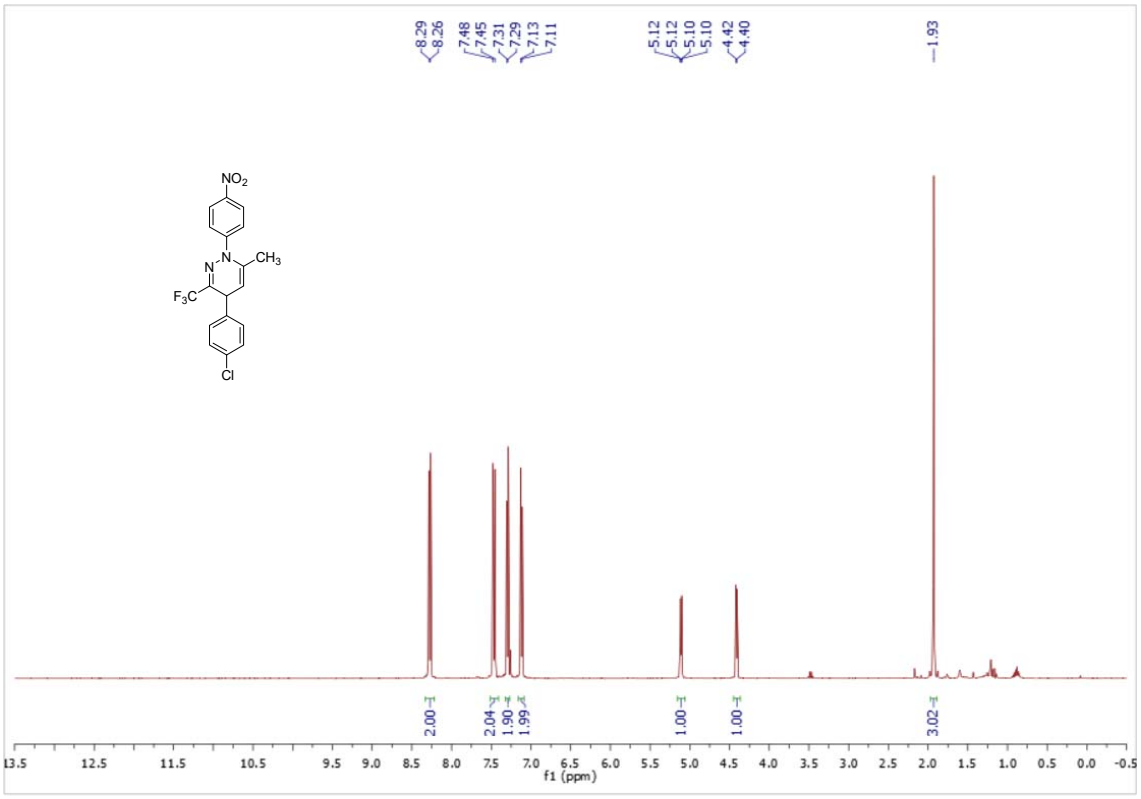

159.57
149.70
141.81
133.48
133.12
132.77
132.42
130.52
128.14
125.63
124.66
121.95
119.23
116.52
114.18
113.11
62.52
57.11
55.35
45.55
CF3
OCH3
O2N
f1 (ppm)

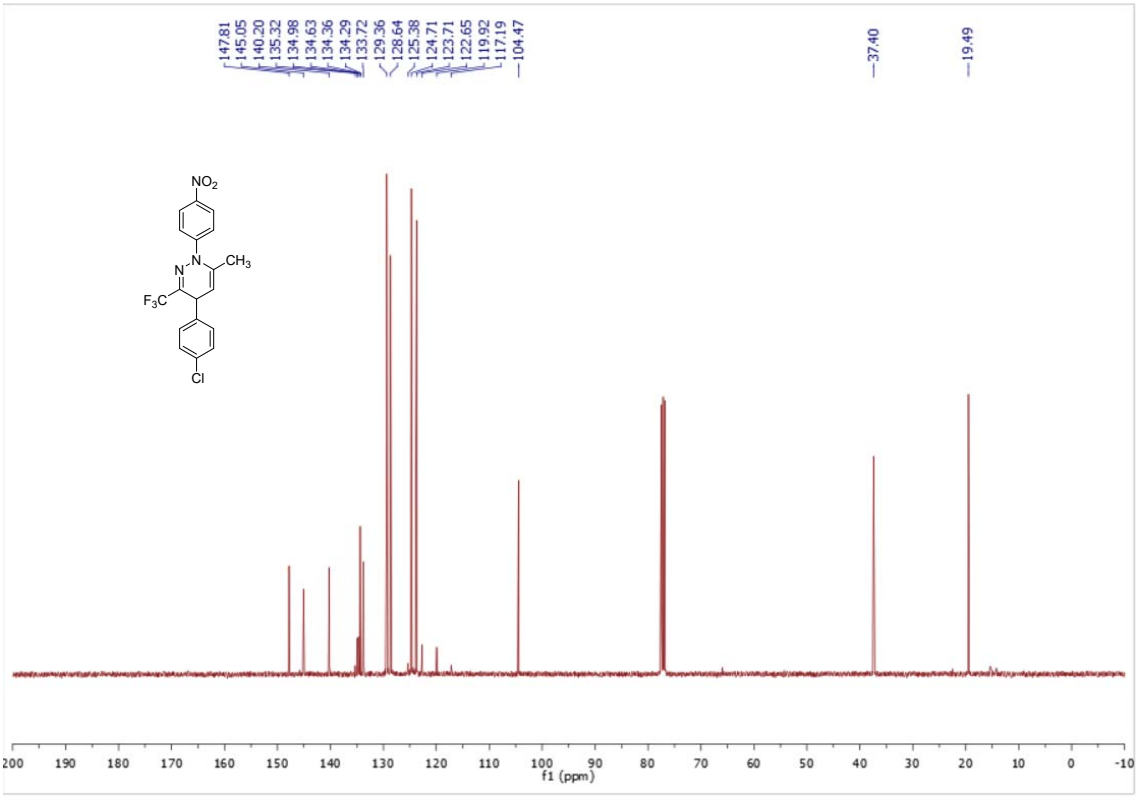
Compound 7a


8.30
8.28
7.50
7.48
3.29
2.36
2.22
NO2
CH3
N
N
F3C
CH3
O
2.00
2.01
2.03
3.02
3.00
f1 (ppm)

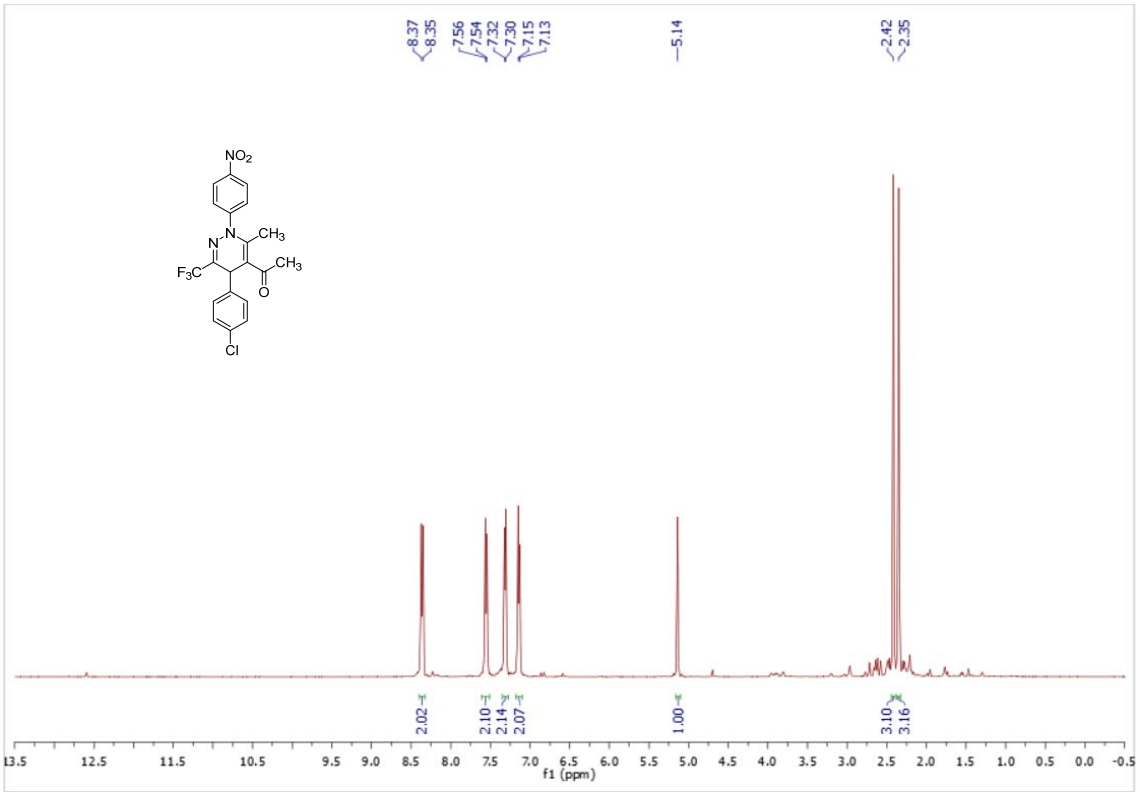

197.00
147.33
145.67
144.75
137.94
137.58
124.86
124.66
121.95
119.23
106.96
30.21
23.02
18.33
NO2
CH3
N
N
F3C
CH3
O
f1 (ppm)

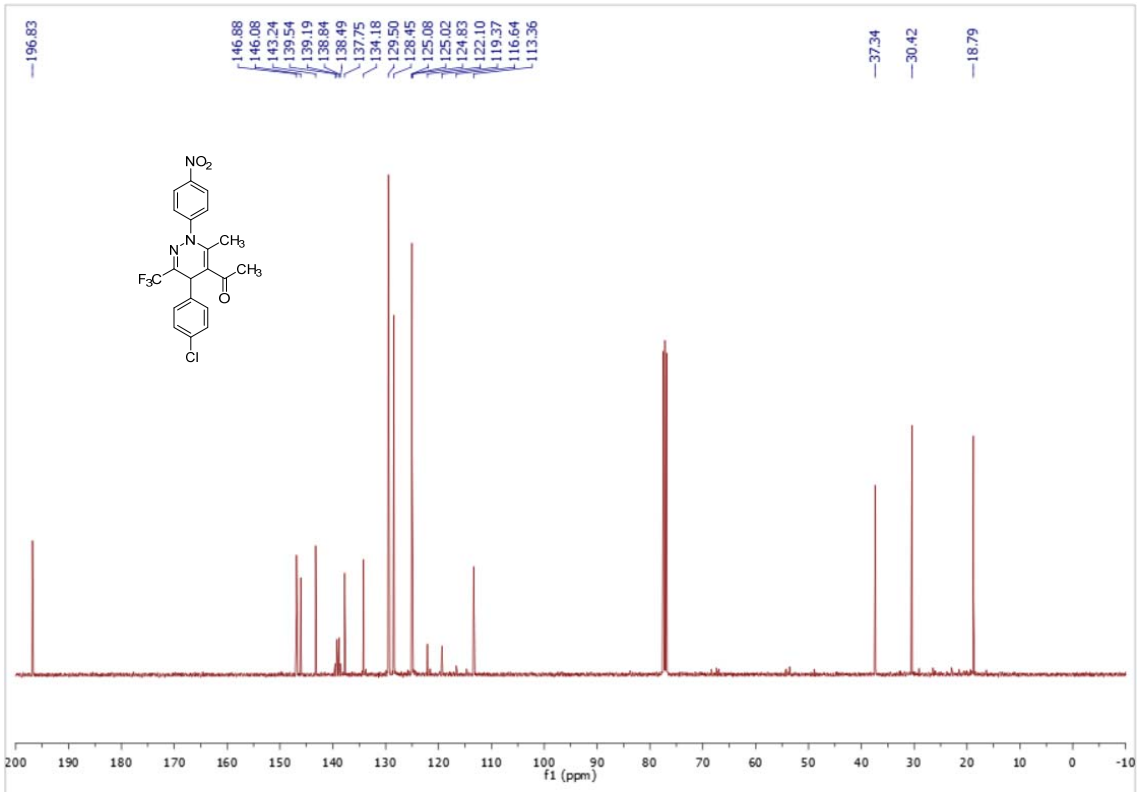
Compound 7b


8.29
8.26
7.48
7.45
7.31
7.29
7.13
7.11
5.12
5.12
5.10
5.10
4.42
4.40
1.93
NO2
CH3
N
F3C
Cl
2.00
2.04
1.90
1.99
1.00
1.00
3.02
f1 (ppm)

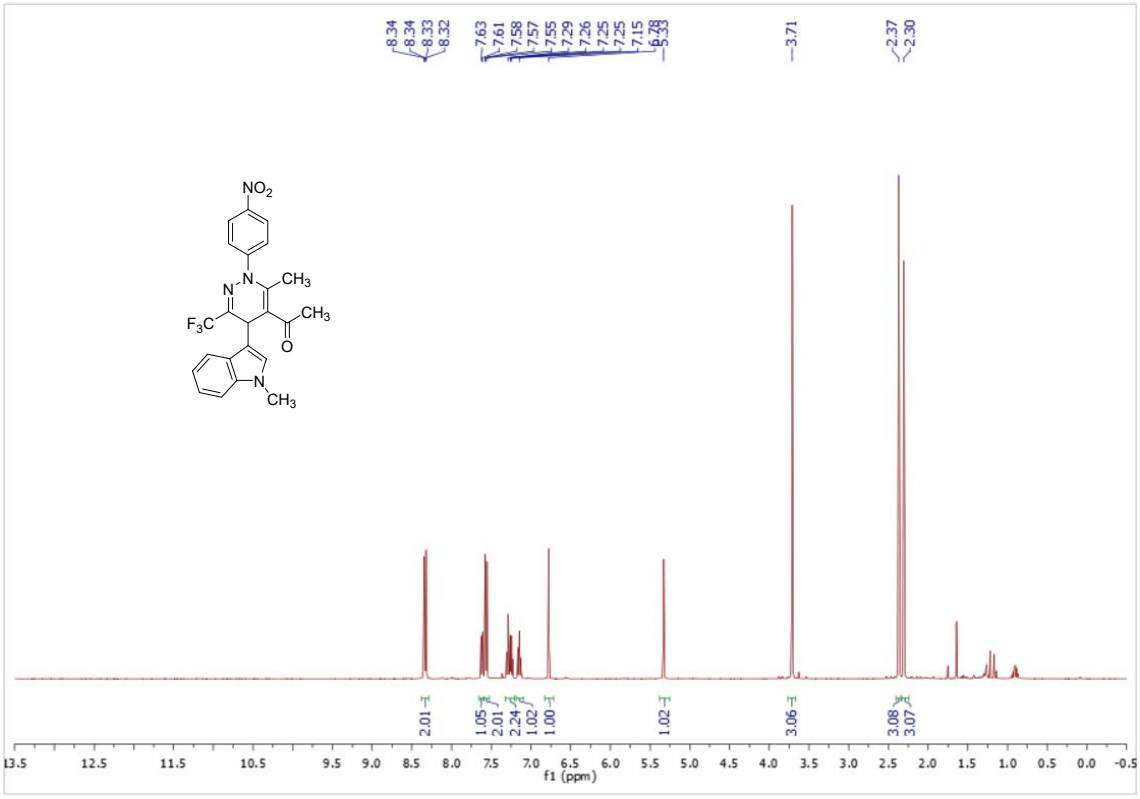

147.81
145.05
140.20
135.32
134.98
134.63
134.36
134.29
133.72
129.36
128.64
125.38
124.71
123.71
122.65
119.92
117.19
104.47
37.40
19.49
NO2
CH3
N
F3C
Cl
f1 (ppm)

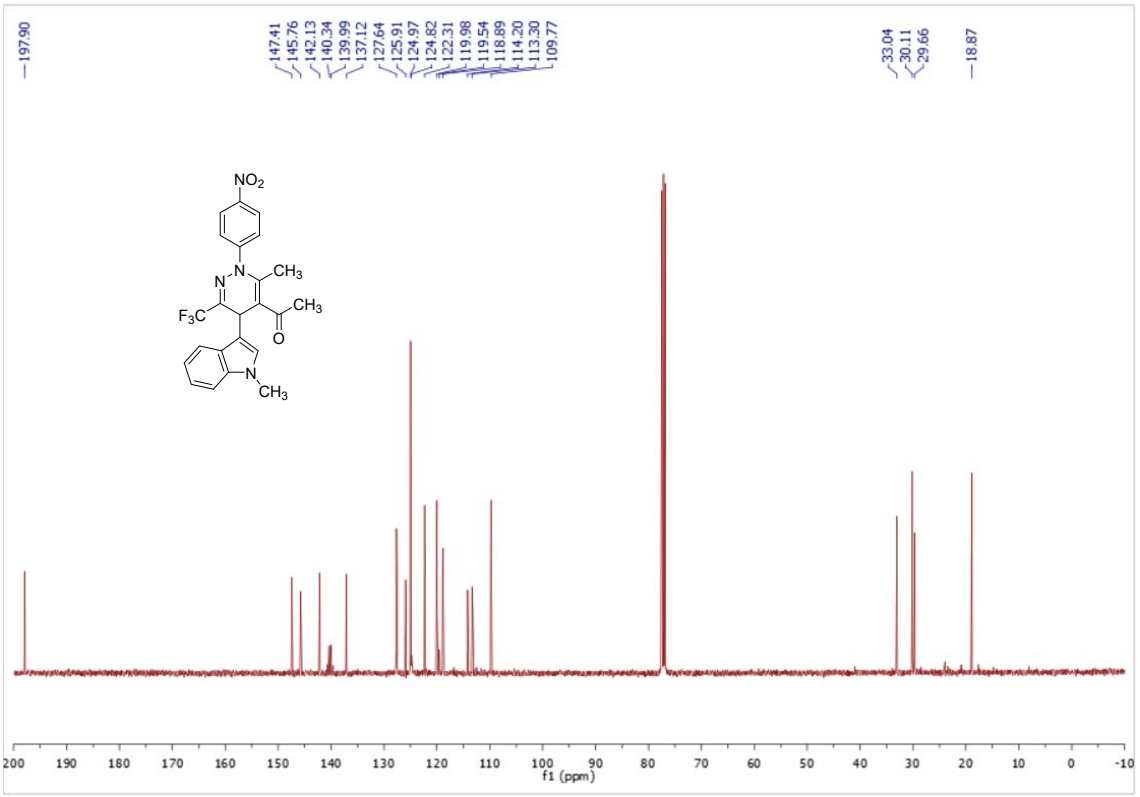
Compound 7c


8.37
8.35
7.56
7.54
7.32
7.30
7.15
7.13
5.14
2.42
2.35
NO2
CH3
N
N
F3C
CH3
O
Cl
2.02
2.10
2.14
2.07
1.00
3.10
3.16
f1 (ppm)

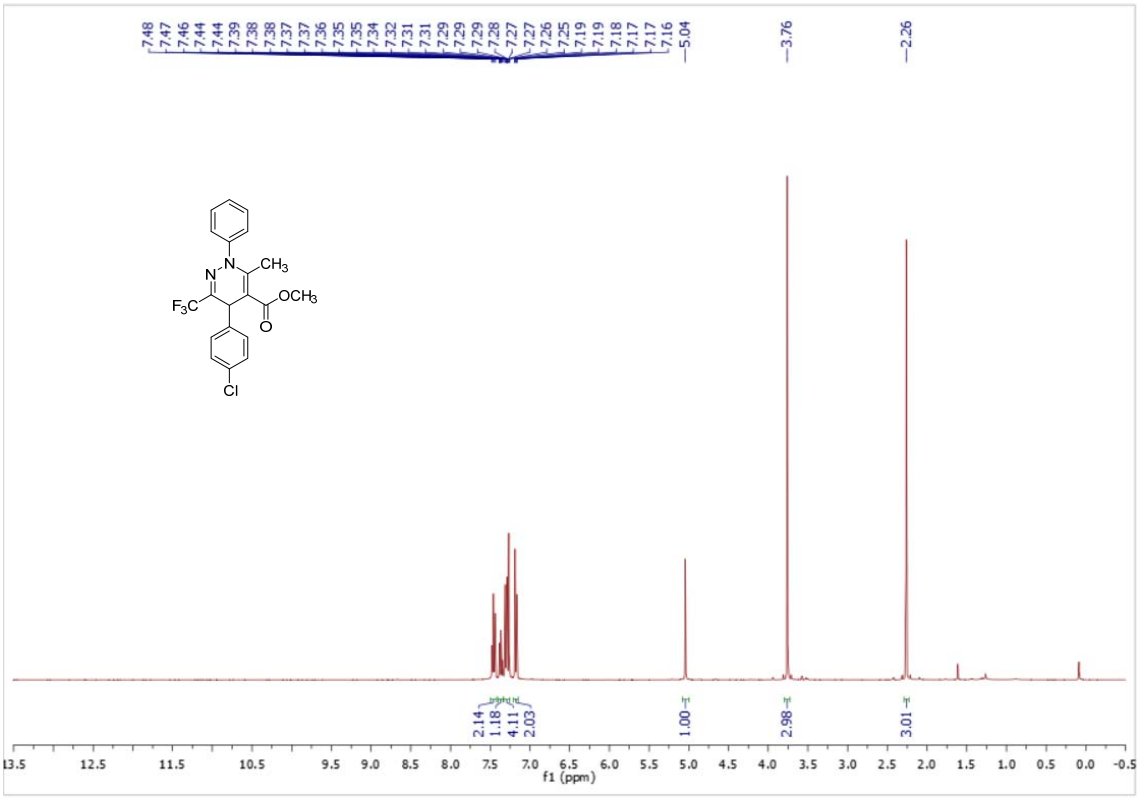

196.83
146.88
146.08
143.24
139.54
139.19
138.84
138.49
137.75
134.18
129.50
128.45
125.08
125.02
124.83
122.10
119.37
116.64
113.36
37.34
30.42
18.79
NO2
CH3
N
N
F3C
CH3
O
Cl
f1 (ppm)

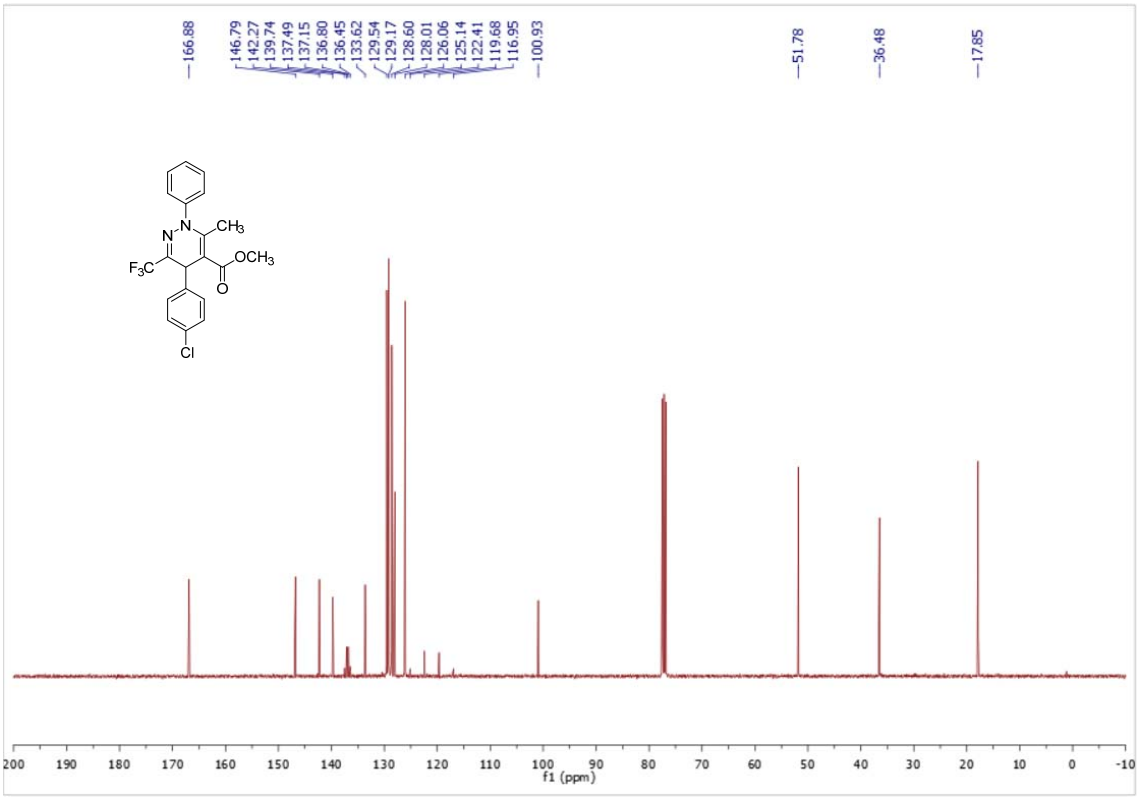
Compound 7d


8.34
8.34
8.33
8.32
7.63
7.61
7.58
7.57
7.55
7.29
7.26
7.25
7.25
7.15
6.28
5.33
3.71
2.37
2.30
NO2
CH3
N
N
F3C
CH3
O
N
CH3
2.01
1.05
2.01
2.24
1.02
1.00
1.02
3.06
3.08
3.07
f1 (ppm)

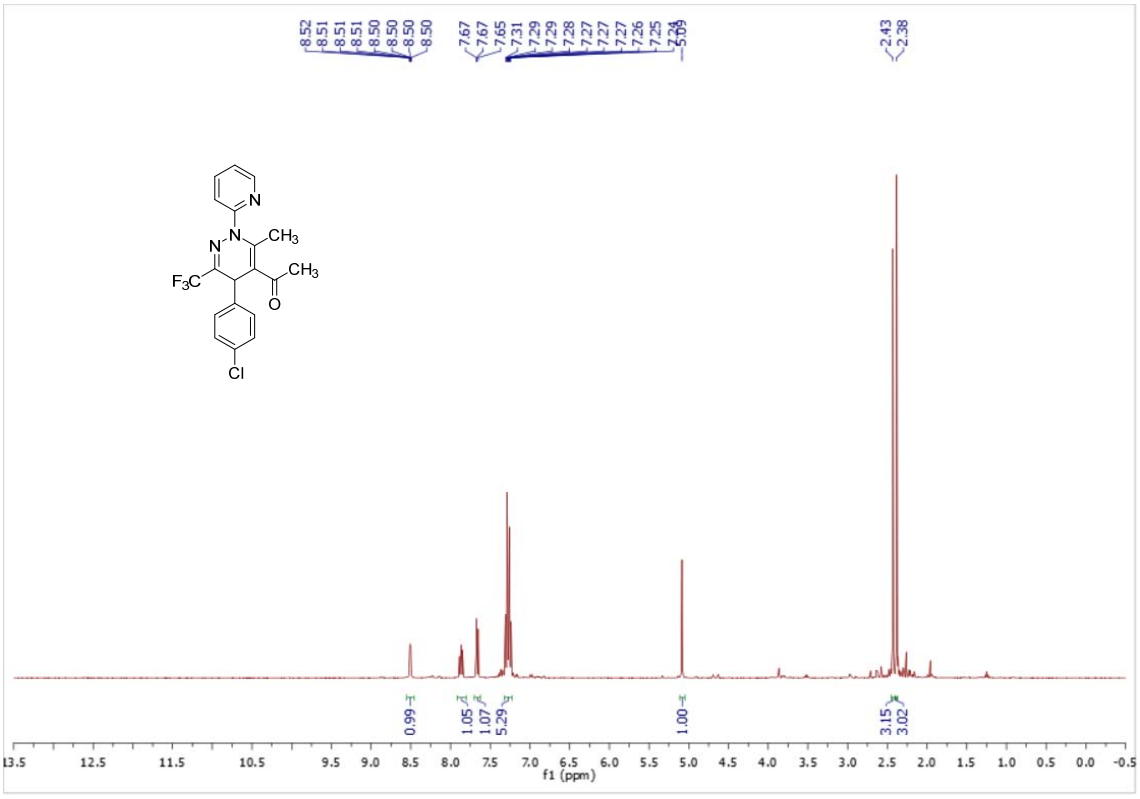

197.90
147.41
145.76
142.13
140.34
139.99
137.12
127.64
125.91
124.97
124.82
122.31
119.98
119.54
118.89
114.20
113.30
109.77
33.04
30.11
29.66
18.87
NO2
CH3
N
N
F3C
CH3
O
N
CH3
f1 (ppm)

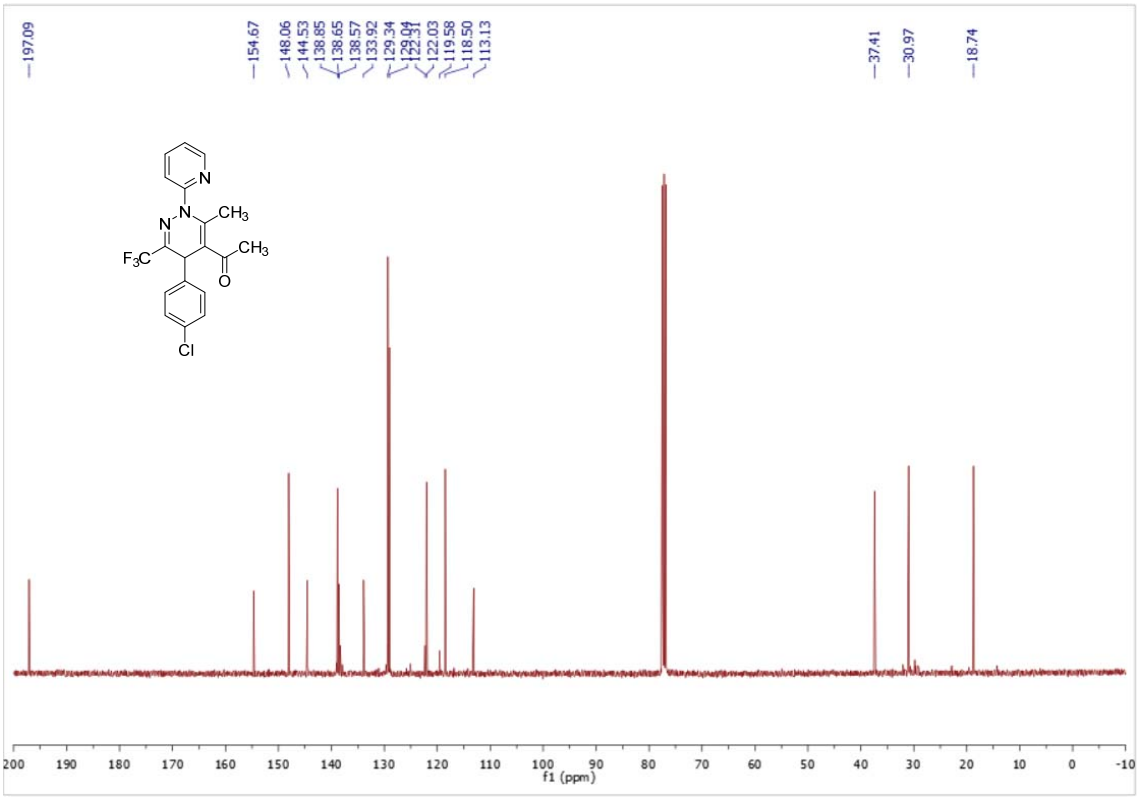
Compound 7e


7.48
7.47
7.46
7.44
7.44
7.39
7.38
7.38
7.37
7.37
7.36
7.35
7.35
7.34
7.32
7.31
7.31
7.29
7.29
7.29
7.28
7.27
7.27
7.26
7.25
7.19
7.19
7.18
7.17
7.17
7.16
5.04
3.76
2.26
CH3
N
N
F3C
OCH3
O
Cl
2.14
1.18
4.11
2.03
1.00
2.98
3.01
f1 (ppm)

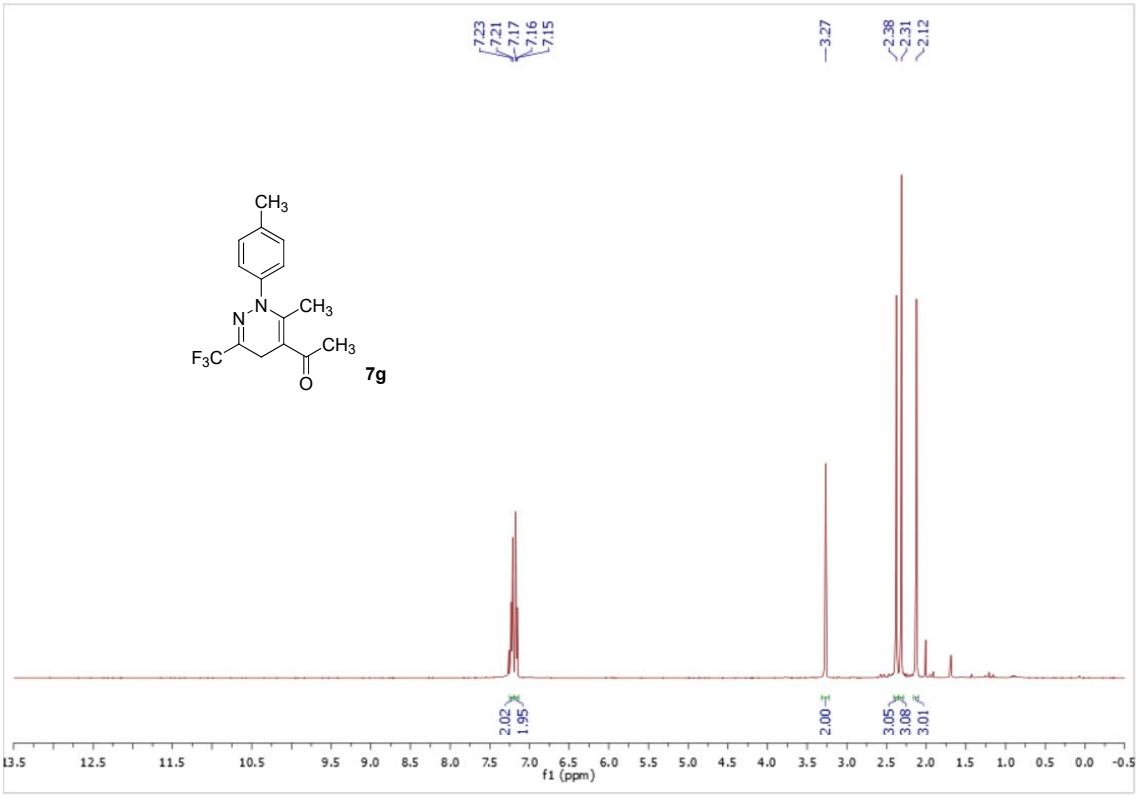

166.88
146.79
142.27
139.74
137.49
137.15
136.80
136.45
133.62
129.54
129.17
128.60
128.01
126.06
125.14
122.41
119.68
116.95
100.93
51.78
36.48
17.85
CH3
N
N
F3C
OCH3
O
Cl
f1 (ppm)

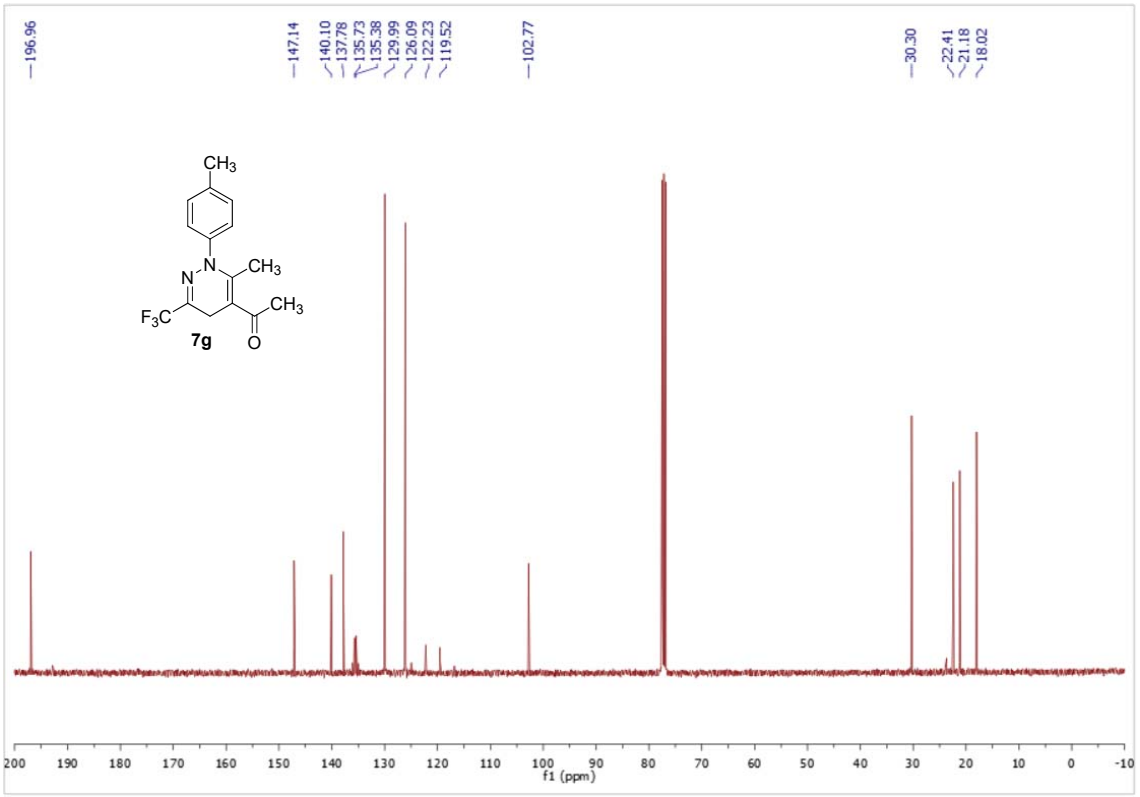
Compound **7f**


8.52
8.51
8.51
8.51
8.50
8.50
8.50
8.50
7.67
7.67
7.65
7.31
7.29
7.29
7.28
7.27
7.27
7.27
7.26
7.25
7.24
5.09
2.43
2.38
N
N
CH3
F3C
CH3
O
Cl
0.99
1.05
1.07
5.29
1.00
3.15
3.02
f1 (ppm)

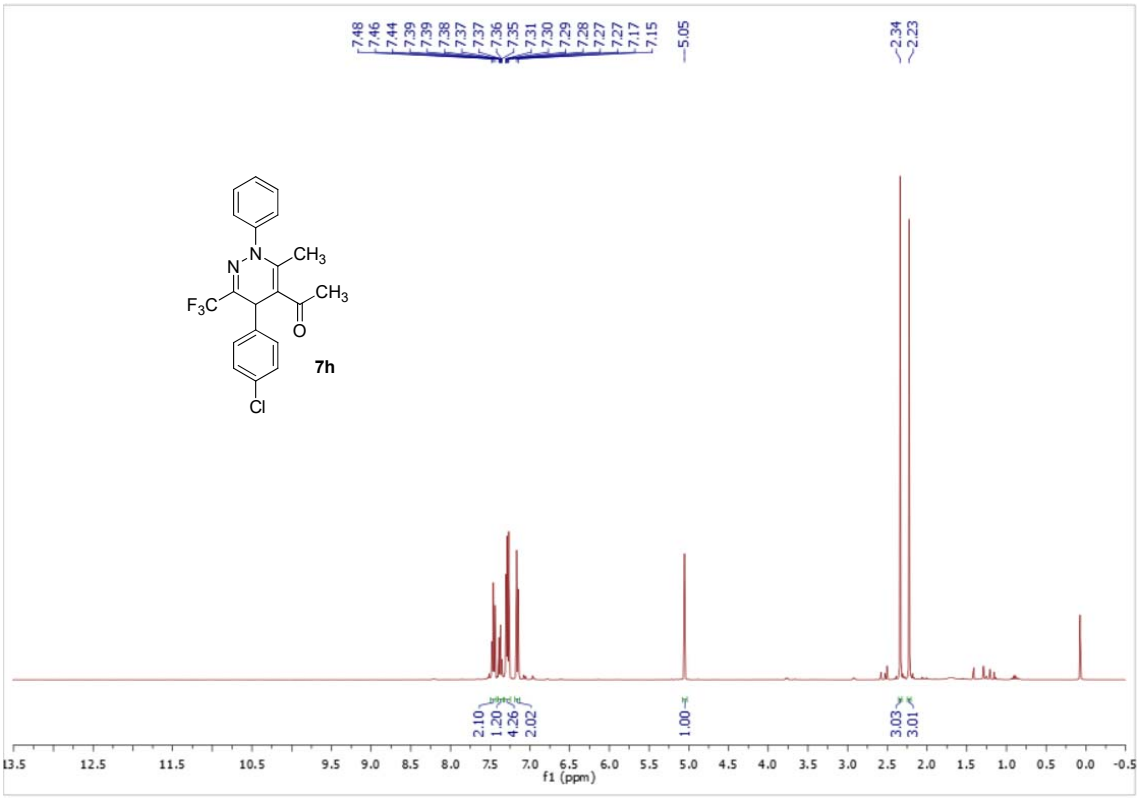

197.09
154.67
148.06
144.53
138.85
138.65
138.57
133.92
129.34
129.04
122.31
122.03
119.58
118.50
113.13
37.41
30.97
18.74
N
N
CH3
F3C
CH3
O
Cl
f1 (ppm)

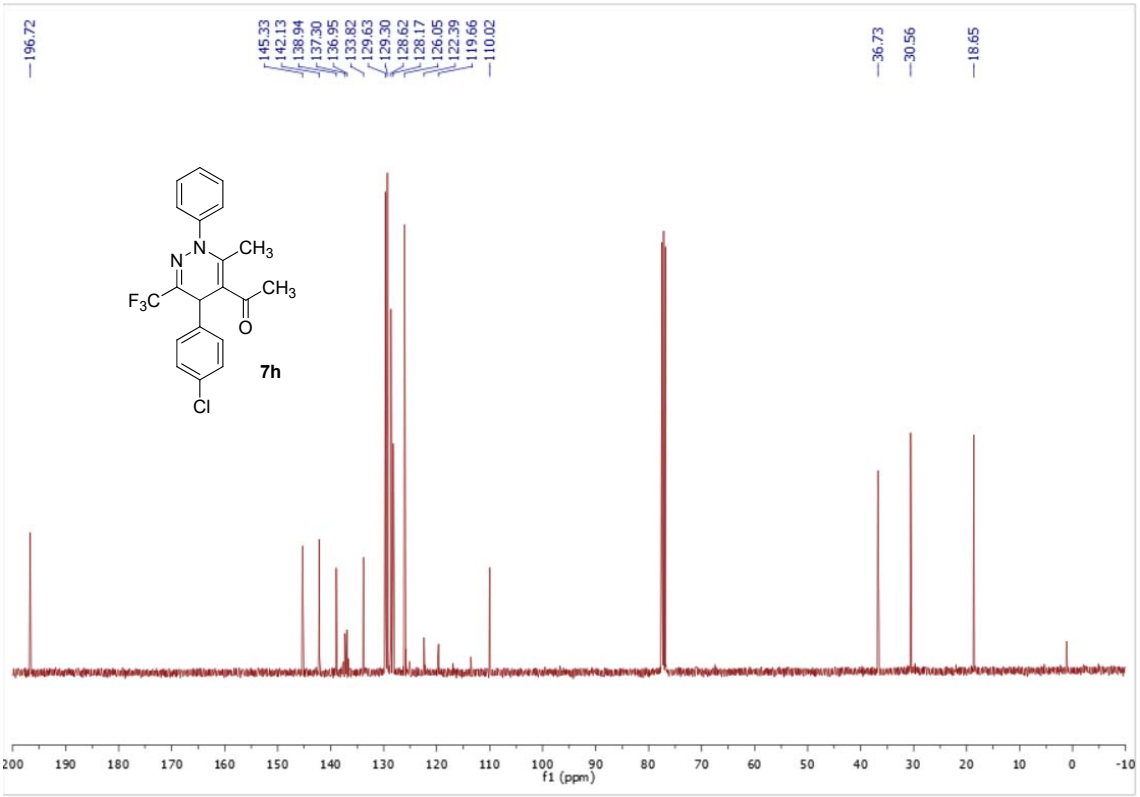
Compound **7g**


7.23
7.21
7.17
7.16
7.15
3.27
2.38
2.31
2.12
CH3
N
N
CH3
F3C
CH3
O
7g
2.02
1.95
2.00
3.05
3.08
3.01
f1 (ppm)

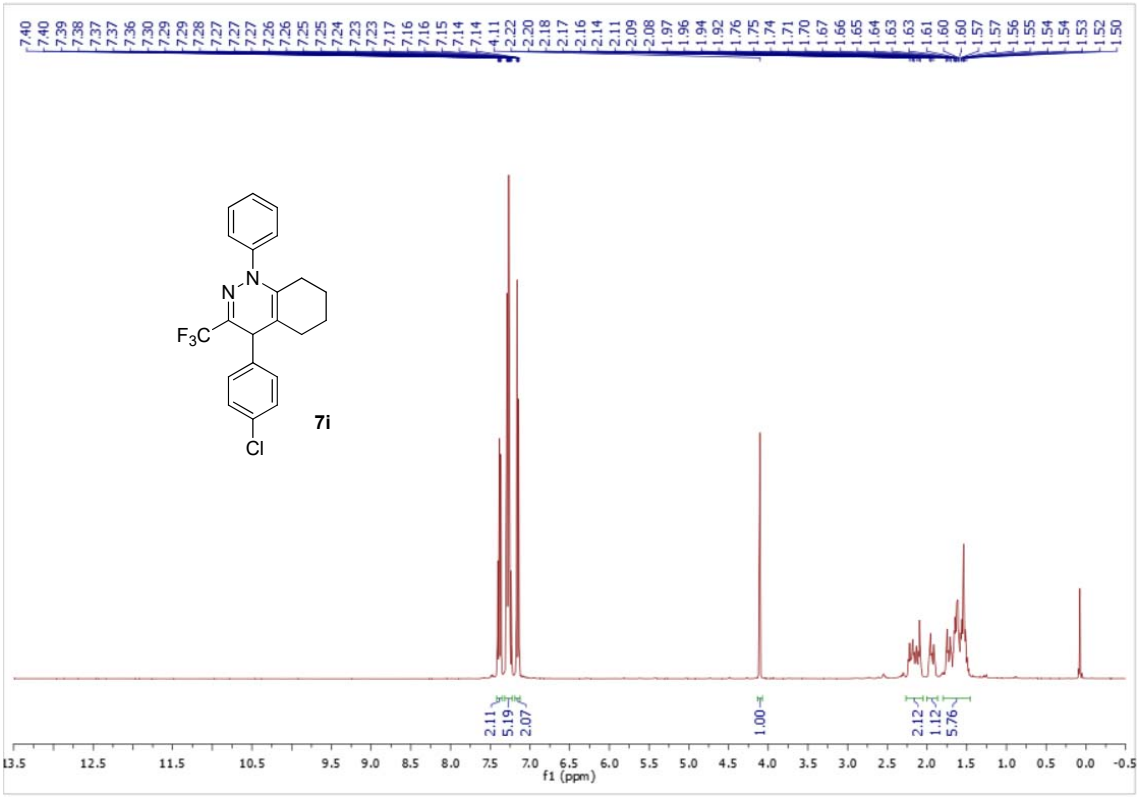

196.96
147.14
140.10
137.78
135.73
135.38
129.99
126.09
122.23
119.52
102.77
30.30
22.41
21.18
18.02
CH3
N
N
CH3
F3C
CH3
O
7g
f1 (ppm)

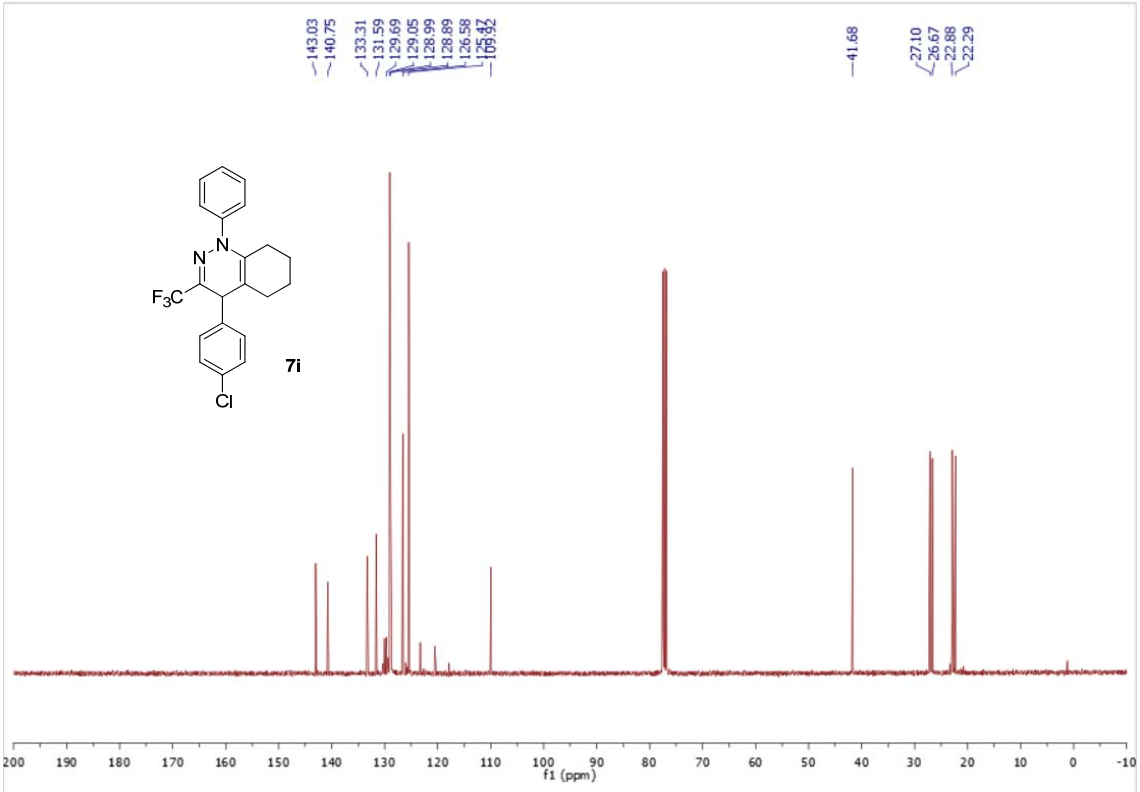
Compound **7h**


7.48
7.46
7.44
7.39
7.39
7.38
7.37
7.37
7.36
7.35
7.31
7.30
7.29
7.28
7.27
7.27
7.17
7.15
5.05
2.34
2.23
CH3
N
F3C
CH3
O
Cl
7h
2.10
1.20
4.26
2.02
1.00
3.03
3.01
f1 (ppm)

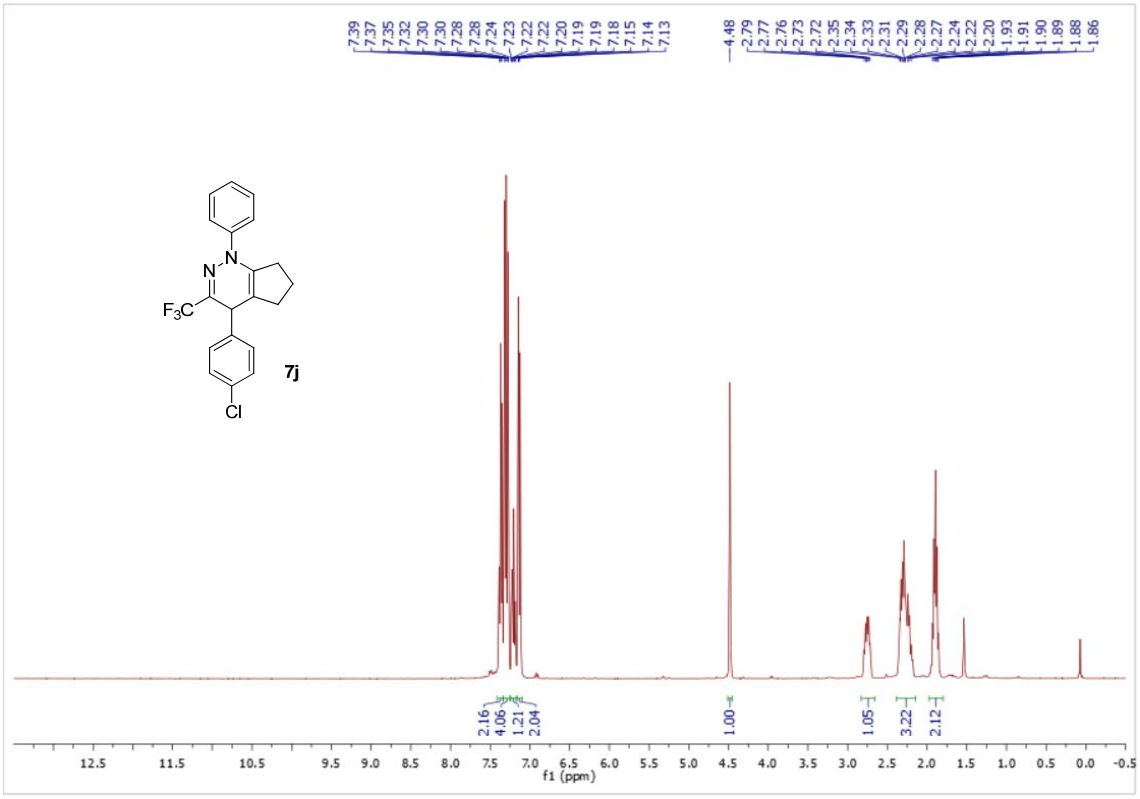

196.72
145.33
142.13
138.94
137.30
136.95
133.82
129.63
129.30
128.62
128.17
126.05
122.39
119.66
110.02
36.73
30.56
18.65
CH3
N
F3C
CH3
O
Cl
7h
f1 (ppm)

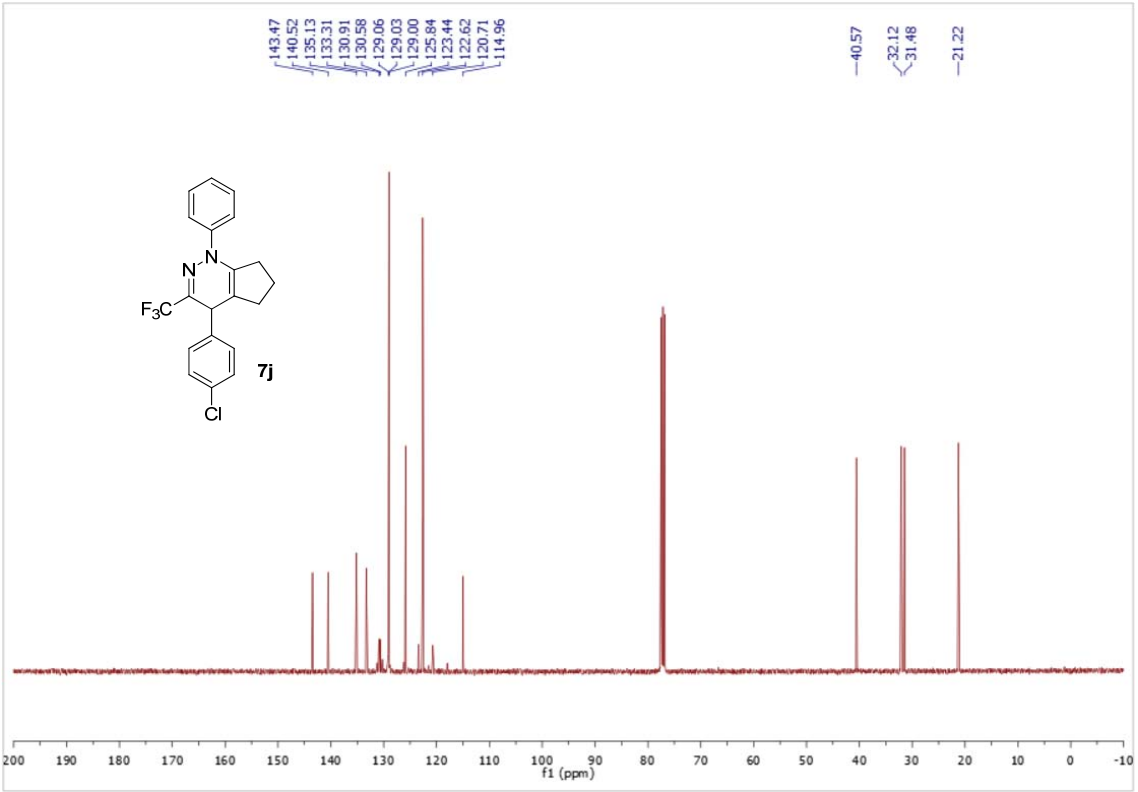
Compound **7i**





Compound **7j**


7.39
7.37
7.35
7.32
7.30
7.30
7.28
7.28
7.24
7.23
7.22
7.22
7.20
7.19
7.19
7.18
7.15
7.14
7.13
4.48
2.79
2.77
2.76
2.73
2.72
2.35
2.34
2.33
2.31
2.29
2.28
2.27
2.24
2.22
2.20
1.93
1.91
1.90
1.89
1.88
1.86
F3C
N
N
Cl
7j
2.16
4.06
1.21
2.04
1.00
1.05
3.22
2.12
f1 (ppm)


143.47
140.52
135.13
133.31
130.91
130.58
129.06
129.03
129.00
125.84
123.44
122.62
120.71
114.96
40.57
32.12
31.48
21.22
F3C
N
N
Cl
7j
f1 (ppm)