Selective perfluoroalkylation and defluorinative functionalization of Indoles

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General information

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. All manipulations were carried out in glass reaction tube equipped with a magnetic stir bar. ^1H NMR, ^{19}F-NMR and ^{13}C NMR spectra were recorded on a Bruker AM500/300 spectrometer using d^6-DMSO or $CDCl_3$ as solvent, TMS as internal standard substance. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The Mass spectrum was received via Agilent (7000C) GC-MS/Waters (Quattro Micro) and LC-MS/MS X500R QTOF (AB SCIEX)

General procedure

Synthesis of hydrofluoroalkylated/ hydroxyfluoroalkylated indoles

Indoles (39.3 mg, 0.3 mmol, 1.0 equiv.) **1a**, $Na_2S_2O_4$/additives (52-469 mg, 0.3-2.7 mmol, 1.0-9.0 equiv.), and 2 mL solvent were added to a Schlenk sealed tube, following perfluoroalkyl iodide **2** (0.3-0.9 mmol, 1.0-3.0 equiv.) was added to the mixture solution. After addition, the mixture was allowed for string 4-12h under set temperature (heated in a heating module). Then, 10ml $NaHCO_3$ (Saturated aq.) was added, and the reaction mixture was extracted by ethyl acetate 3 times. The organic layer was combined, washed with brine for once, and dried over Na_2SO_4. The solvent was removed by reduced pressure rotary evaporation and purified by column chromatography on silica gel with petroleum ether/ethyl acetate (PE/EA 20/1-5/1) to give **3**/**4**.

Optimization of reaction condition for hydrofluoroalkylated indoles 3a

S-Table 2 Solvent effect[a]

Entry	Solvent Ratio (v/v)		Yield（%）
1	CH_3CN/H_2O	4:1	51.0
2	CH_3CN/H_2O	2:1	63.8
3	CH_3CN/H_2O	1:1	73.7
4	CH_3CN/H_2O	1:2	72.8
5	CH_3CN/H_2O	1:4	55.5

[a]Reaction conditions: **1a** (39.3 mg, 0.3 mmol, 1.0 equiv.), **2a C_3F_7I** (265.5 mg, 0.9 mmol, 3.0 equiv.), $Na_2S_2O_4$ (0.9 mmol 3.0 eq), solvent (2.0 mL), 100 ℃, 4 h, ^{19}F NMR yields using $PhCF_3$ as an internal standard.

S-Table 3 Additives effect[a]

Entry	Additives	Yield (%)
1	$Na_2S_2O_4$	73.7
2	Thiourea Dioxide	27.6
3	$Na_2S_2O_5$	50.9
4	$Na_2S_2O_3$	N.D.
5	Rongalite	N.D.
6	$Na_2S_2O_4$ (1.0 eq.)	43.0
7	$Na_2S_2O_4$ (1.5 eq.)	64.1
8	$Na_2S_2O_4$ (2.0 eq.)	61.7
9	$Na_2S_2O_4$ (3.0 eq.)	73.7
10	$Na_2S_2O_4$ (4.0 eq.)	63.8
11	$Na_2S_2O_4$ (5.0 eq.)	56.5

[a]Reaction conditions: **1a** (39.3 mg, 0.3 mmol, 1.0 equiv.), **2a C_3F_7I** (265.5 mg, 0.9 mmol, 3.0 equiv.), additives, CH_3CN/H_2O(1/1) (2.0 mL), 100 ℃, 4 h, ^{19}F NMR yields using $PhCF_3$ as an internal standard.

S-Table 4 Reaction ratio[a]

Entry	**1**(eq.)	**2**(eq.)	$Na_2S_2O_4$(eq.)	Yield (%)
1	1	3.0	1.0	43.0
2	1	3.0	1.5	64.1
3	1	3.0	2.0	61.7
4	1	3.0	3.0	73.7
5	1	3.0	4.0	63.8
6	1	3.0	5.0	56.5

[a]Reaction conditions: **1a**, **2a C_3F_7I**, $Na_2S_2O_4$, CH_3CN/H_2O(1/1) solvent (2.0 mL), 100 °C, 4 h, ^{19}F NMR yields using $PhCF_3$ as an internal standard.

S-Table 5 Reaction ratio[a]

Entry	**1**(mmol)	**2**(mmol)	$Na_2S_2O_4$(mmol)	Yield (%)
1	1	1.0	3.0	36.7
2	1	2.0	3.0	62.5
3	1	3.0	3.0	75
4	1	4.0	3.0	75.5
5	1	5.0	3.0	75.6

[a]Reaction conditions: **1a**, **2a C_3F_7I**, $Na_2S_2O_4$, CH_3CN/H_2O(1/1) solvent (2.0 mL), 100 °C, 4 h, ^{19}F NMR yields using $PhCF_3$ as an internal standard.

S-Table 6 Temperature effect[a]

Entry	Temperature (°C)	Yield（%）
1	80	N.D.
2	100	73.7
3	110	73.9
4	120	70
5	130	71

[a]Reaction conditions: **1a** (39.3 mg, 0.3 mmol, 1.0 equiv.), **2a C_3F_7I** (265.5 mg, 0.9 mmol, 3.0 equiv.), $Na_2S_2O_4$ (2.7 mmol equiv.), CH_3CN/H_2O(1/1) (2.0 mL), 4 h, ^{19}F NMR yields using $PhCF_3$ as an internal standard.

S-Table 7 Reaction time[a]

Entry	Time(h)	Yield (%)
1	1	41
2	2	57
3	3	72
4	4	74
5	5	73

[a]Reaction conditions: **1a** (39.3 mg, 0.3 mmol, 1.0 equiv.), **2a C_3F_7I** (265.5 mg, 0.9 mmol, 3.0 equiv.), $Na_2S_2O_4$ (2.7 mmol, 9 equiv.), CH_3CN/H_2O(1/1) (2.0 mL), 100 ℃, ^{19}F NMR yields using $PhCF_3$ as an internal standard.

Optimization of reaction condition for hydroxyfluoroalkylated indoles 4a

S-Table 1 Solvent effect [a]

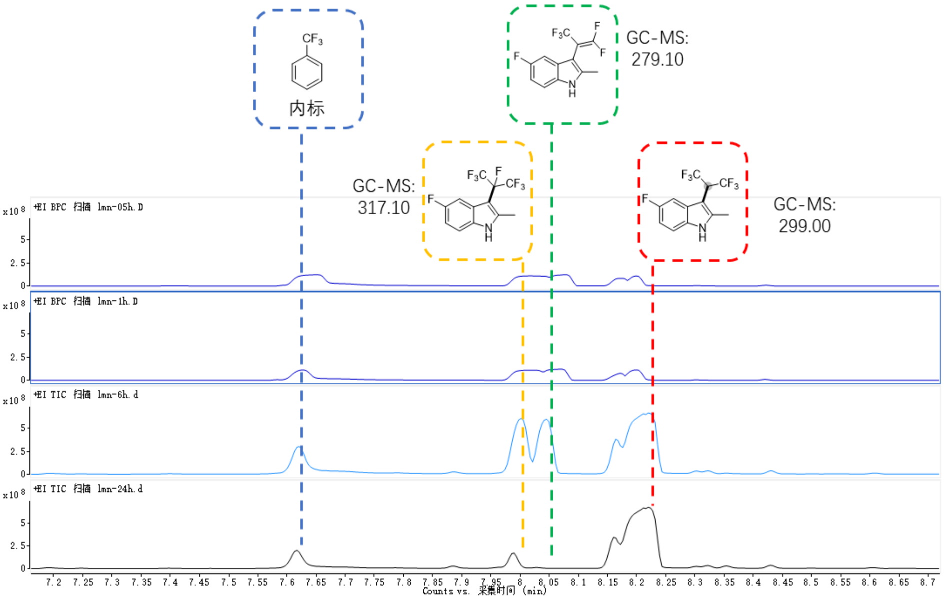
Entry	Sovent	Yield (%)
1	CH_3CN	trace
2	H_2O	trace
4	DMSO	trace
5	THF	trace
6	DMF	trace
7	DMSO/CH_3CN/H_2O 0.5:2:1	23
8	DMSO/CH_3CN/H_2O 1:2:1	31
9	DMSO/CH_3CN/H_2O 2:2:1	42
9	DMSO/CH_3CN/H_2O 4:2:1	36
10	DMSO/CH_3CN/H_2O 1:5:1	40

[a]Reaction conditions: **1a** (39.3 mg, 0.3 mmol, 1.0 equiv.), **2a C_3F_7I** (265.5 mg, 0.9 mmol, 3.0 equiv.), $Na_2S_2O_4$ (0.9 mmol 3.0 eq), solvent (2.0 mL), 100 ℃, 4 h, ^{19}F NMR yields using $PhCF_3$ as an internal standard.

In-situ GC-MS analysis

Investigating the Impact of Reaction Solvents on Selectivity: Steps

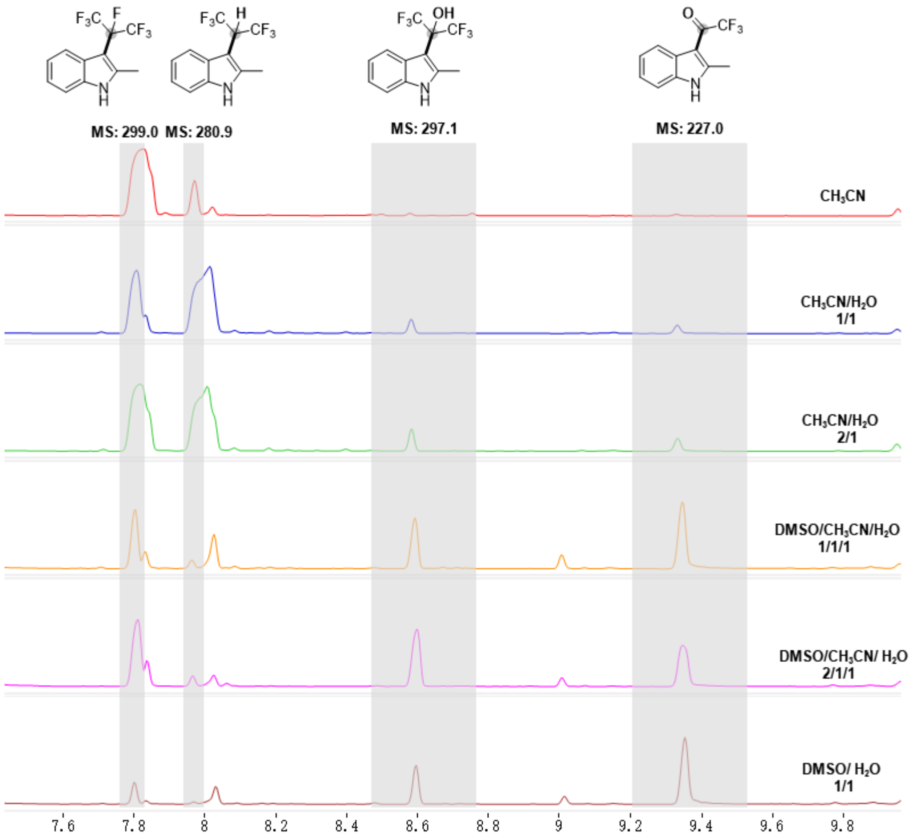
2-Methyl-1H-indole (39.3 mg, 0.3 mmol, 1.0 equiv.), $Na_2S_2O_4$ (156.6 mg, 0.9 mmol, 3.0 equiv.), and 2 mL of mixed solvent were added to a sealed Schlenk tube. Subsequently, C_3F_7I 2a (0.9 mmol, 3.0 equiv.) was added to the mixture, and the resulting mixture was stirred for 10 minutes. After the addition, the mixture was heated and stirred at 100 ℃ (in a heating module). After filtration, the reaction mixture was analyzed by GC-MS.



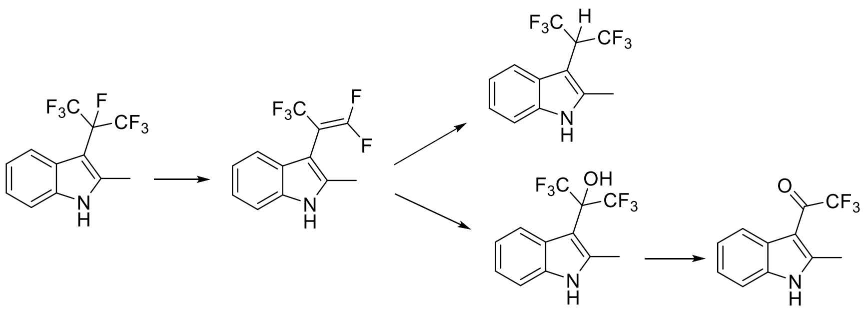
S-Figure 1a. The effect of mixed solvents on reaction selectivity analyzed via GC-MS

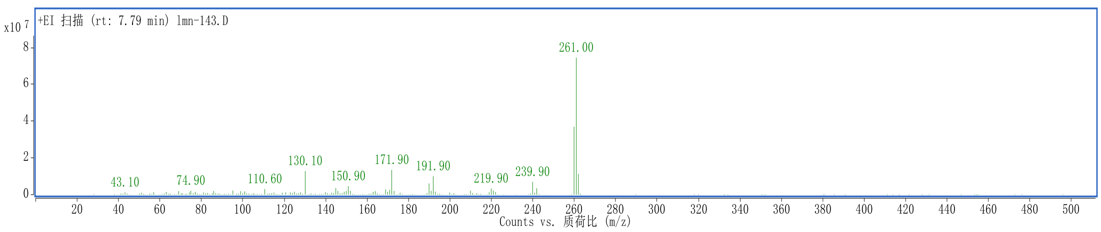
***In-Situ* GC-MS Analysis of 3g in a CH_3CN/H_2O (1:1) Mixture: Step-by-Step Procedure**

Additionally, the experiment was monitored in situ using GC-MS. 2-methyl-1H-indole (39.3 mg, 0.3 mmol, 1.0 equiv.), $Na_2S_2O_4$ (156.6 mg, 0.9 mmol, 3.0 equiv.), and 2 mL of a CH_3CN/H_2O (1/1) mixed solvent were added to a sealed Schlenk tube. Then, C_3F_7I 2a (0.9 mmol, 3.0 equiv.) was added to the mixture, which was subsequently heated and stirred at 100 ℃ (in a heating module). Samples of 200 μL of the reaction solution were taken for analysis at 0.5 hours, 1 hour, 2 hours, and 3 hours, respectively.



S-Figure 1b. ***In-situ*** **GC-MS analysis of 3g in CH_3CN/H_2O 1/1**

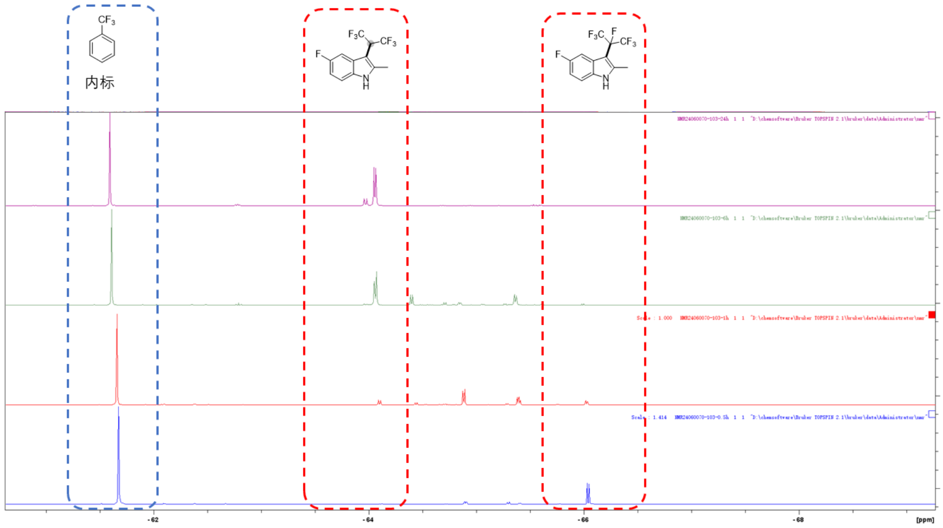




S-Figure 1c. GC-MS of control experiments

In-situ ^{19}F NMR analysis

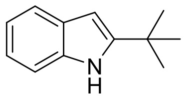
To understand the fluoroacylation reaction further, the experiment was conducted and monitored by the in-situ ^{19}F NMR. 2-methyl-1H-indole (39.3 mg, 0.3 mmol, 1.0 equiv.), $Na_2S_2O_4$ (156.6 mg, 0.9 mmol, 3.0 equiv.), and 2 mL DMSO/CH_3CN/H_2O (1/2/1) solvent were added to a Schlenk sealed tube, following C_4F_9I 2a (311.3 mg, 0.9 mmol, 3.0 equiv.) was added to the mixture solution and then the resulting mixture was a string for 10 min. After addition, the mixture was allowed for string under 100 °C (heated in a heating module). Then, 200 μL of the reaction solution was taken at 0.5 h, 1 h, 2 h, 3 h, respectively, and then deuterated solvent DMSO (400 μL) was added, and the reaction mixture was checked by ^{19}F-NMR after filtration. After 0.5 h of the start of the reaction, we found two peaks at chemical shifts of -79 and -80 ppm that should should be attributed to the perfluoroalkylation and acylation products, respectively. As from 0.5 h to 3 h, the signal at -79 ppm start-ed to fade gradually, while the signal at -80 ppm gradually increased.



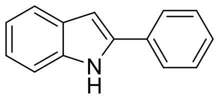
S-Figure 2. F^{19}-NMR of control experiments 3a

Unsatisfactory examples of hydrodefluorination

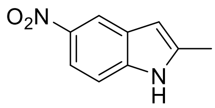
The scope of unsatisfactory substrates was summarized as following:



trace



trace



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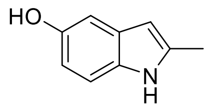
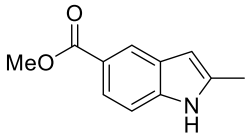
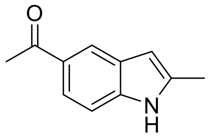


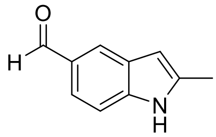
trace



trace



trace



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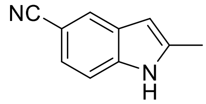
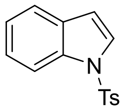


trace

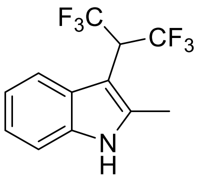


n. d.

S-Figure 3. the scope of hydrofluoroalkylation indoles with C_3F_7I

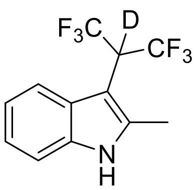
“Trace” means that the conversion of starting material is low, no products or only unidentified mixture were obtained; “n. d.” means not detected

Characterization data of Compounds



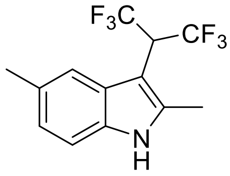
3a

3-(1,1,1,3,3,3-hexafluoropropan-2-yl)-2-methyl-1H-indole 3a, brown solid (74 % yield). **^{1}H-NMR 3a** (300 MHz, DMSO-d^6, ppm)) δ = 11.44 (s, 1H), 7.47 (d, *J* = 7.93 Hz, 1H), 7.34 (d, *J* = 7.78 Hz, 1H), 7.11-6.90 (m, 2H), 5.33 (sept, *J* = 9.58 Hz, 1H), 2.46 (s, 3H; **^{13}C-NMR** (75 MHz, DMSO-d^6, ppm) δ = 138.98 (s), 136.02 (s), 126.07 (s), 124.66 (q, *J* = 280.19 Hz, 2C), 121.29 (s), 120.04 (s), 119.24 (s), 111.52 (s), 95.91 (s), 45.78 (t, *J* = 29.78 Hz, 1C), 11.54 (s); **^{19}F-NMR** (475 MHz, DMSO-d^6, ppm) δ = -63.63 (d, *J* = 9.56 Hz, 6F); **HRMS(ESI)** m/z [M+H]$^+$:Calcd. for $C_{12}H_9F_6N$ 282.0717, found 282.0708.



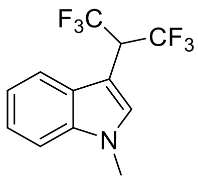
3a'

3-(1,1,1,3,3,3-hexafluoropropan-2-yl-2-d)-2-methyl-1H-indole 3a', brown solid (67 % yield). **^{1}H-NMR 3a** (500 MHz, DMSO-d^6, ppm) δ = 11.45 (s, 1H), 7.48 (d, *J* = 7.40 Hz, 1H), 7.34 (d, *J* = 7.95 Hz, 1H), 7.13-7.09 (m, 2H), 2.47 (s, 3H); **^{13}C-NMR** (125 MHz, DMSO-d^6, ppm) δ = 139.00 (s), 136.02 (s), 126.07 (s), 124.66 (q, *J* = 280.00 Hz, 2C), 121.29 (s), 120.06 (s), 119.26 (s), 111.54 (s), 95.90 (s), 45.70 (t, *J* = 29.78Hz, 1C), 11.54 (s); **^{19}F-NMR** (475 MHz, DMSO-d^6, ppm) δ = -63.73 (s, 6F); **HRMS(EI)** m/z [M]$^+$:Calcd. for $C_{12}H_8DF_6N$ 282.0702, found 282.0690.



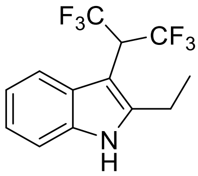
3b

3-(1,1,1,3,3,3-hexafluoropropan-2-yl)-2,5-dimethyl-1H-indole 3b, brown solid (63 % yield). **^{1}H-NMR** (300 MHz, Chlorform-d, ppm) δ = 7.89 (s,1H), 7.37 (s,1H), 7.10 (d, *J* = 8.33 Hz, 1H), 6.93 (d, *J* = 8.25 Hz, 1H), 4.15 (sept, *J* = 8.92 Hz, 1H), 2.37 (s, 3H), 2.31 (s, 3H); **^{13}C-NMR** (300 MHz, Chlorform-d, ppm) δ = 131.5, 128.8, 125.2, 121.5, 119.0, (q, *J* = 277.4 Hz), 118..8, 115.1,105.5, 92.5, 42.6(q, *J* = 30.5 Hz), 17.0, 6.9; **^{19}F-NMR** (475 MHz, DMSO-d^6, ppm) δ = -63.63 (d, *J* = 9.56 Hz, 6F); **HRMS(ESI)** m/z [M+H]$^+$Calcd. for $C_{13}H_{11}F_6N$ 296.0874, found 296.0869.



3c

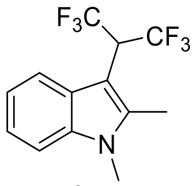
3-(1,1,1,3,3,3-hexafluoropropan-2-yl)-1-methyl-1H-indole 3c, light brown solid (25 % yield). **^{1}H-NMR** (300 MHz, DMSO-d^6, ppm) δ = 7.78 (d, *J* = 8.01 Hz, 1H）,7.58 (s,1H), 7.50 (d, *J* = 8.26 Hz, 1H), 7.19 (dt, J_1 = 31.02 Hz, J_2 = 7.45 Hz, 2H), 5.72 (sept, *J* = 9.23 Hz, 1H), 3.84 (s, 3H); **^{13}C-NMR** (300 MHz, DMSO-d^6, ppm) δ = 136.7, 130.7, 127.6, 124.2(q, *J* = 278.1 Hz), 122.4, 120.3, 119.1, 110.7, 98.6, 44.6 (sept, *J* = 29.2 Hz), 33.1; **^{19}F-NMR** (475 MHz, DMSO-d^6, ppm) δ = -65.46 (d, *J* = 8.66 Hz, 6F); **HRMS(ESI)** m/z [M +H]$^+$Calcd. for $C_{12}H_9F_6N$ = 282.0717, found 282.0715.



3d

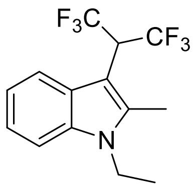
2-ethyl-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)-1H-indole 3d, brown solid (79 %

yield).; **^{1}H-NMR** (300MHz, DMSO-d^{6}, ppm) δ = 11.37 (s, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 7.71 Hz, 1H), 7.05-6.90 (m, 2H), 5.33 (sept, *J* = 9.58 Hz, 1H), 2.46 (s, 3H); **^{13}C-NMR** (75 MHz, DMSO-d^{6}, ppm) δ = 144.6, 136.2, 125.9, 124.6 (q, *J* =282.2Hz,), 121.4, 120.0, 119.6, 111.6, 95.0, 45.7 (q, *J* =29.9 Hz,),18.7,15.0; **^{19}F-NMR** (475 MHz, DMSO-d^{6}, ppm) δ = -63.52 (d, *J* = 10.19 Hz, 6F); **HRMS(ESI)** m/z [M+H]$^{+}$Calcd. for $C_{13}H_{12}F_{6}N$ = 296.0874, found[M+1] 296.0877.



3e

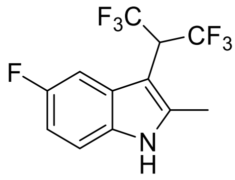
3-(1,1,1,3,3,3-hexafluoropropan-2-yl)-1,2-dimethyl-1H-indole 3e, light brown solid (76 % yield). **^{1}H-NMR** (300MHz, DMSO-d^{6}, ppm) δ =7.54-7.43 (m, 2H）,7.16-7.10 (m, 1H), 7.09-7.00 (m, 1H), 5.42 (sept, *J* = 9.6 Hz, 1H), 3.71 (s, 3H), 2.49 (s, 3H); **^{13}C-NMR** (300 MHz, DMSO-d^{6}, ppm) δ =140.4, ,137.1, 125.3, 124.6(q, *J* = 280.8 Hz), 121.4, 120.3, 119.5, 110.2, 95.9, 46.1 (sept, *J* = 29.7 Hz), 30.2, 10.3; **^{19}F-NMR** (475 MHz, DMSO-d^{6}, ppm) δ = -63.50 (d, *J* = 8.71 Hz, 6F); **HRMS(ESI)** m/z [M+H]$^{+}$Calcd. for $C_{13}H_{12}F_{6}N$ = 296.0874, found[M+1] 296.0857.



3f

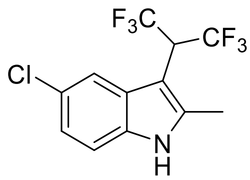
1-ethyl-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)-2-methyl-1H-indole 3f, brown solid (93 % yield). **^{1}H-NMR** (300MHz, DMSO-d^{6}, ppm）δ = 7.49 (d, *J* = 8.69 Hz, 2H), 7.10 (dt, J_1 = 26.95 Hz, J_2 = 7.85 Hz, 2H), 5.42 (sept, *J* = 9.57 Hz, 1H), 4.22 (q, *J* = 7.12 Hz, 2H), 2.51 (s, 1H); **^{13}C-NMR** (300 MHz, DMSO-d^{6}, ppm) δ = 139.5, ,136.1, 125.5, 123.7 (q, *J* = 287.8 Hz), 121.5, 120.3, 119.5, 110.1, 96.0, 46.0

(sept, J = 29.9 Hz), 38.1, 15.3, 9.9; ^{19}**F-NMR** (475 MHz, DMSO-d^6, ppm) δ = -63.45 (d, J = 10.72Hz, 6F); **HRMS(ESI)** m/z [M+H]$^+$Calcd. for $C_{14}H_{14}F_6N$ = 310.1030, found[M+1] 310.1035.



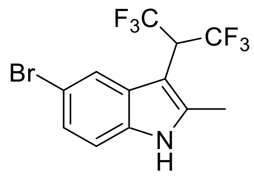
3g

5-fluoro-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)-2-methyl-1H-indole 3g, brownish-yellow solid (71 % yield). ^{1}**H-NMR** (300MHz, Chlorform-d, ppm) δ = 8.04 (s, 1H）,7.26 (d, J = 10.18 Hz, 1H), 7.19-7.10 (m, 1H), 6.86 (dt, J_1 = 2.46 Hz, J_2 = 9.07 Hz, 1H), 4.16 (sept, J = 8.94 Hz, 1H), 2.37 (s, 3H); ^{13}**C-NMR** (300 MHz, DMSO-d^6, ppm) δ = 153.7(d, J = 233.07 Hz), 133.3, 127.0, 121.7, 118.9 (q, J = 277.8 Hz), 106.3 (d, J = 9.8 Hz), 105.7 (d, J = 26.1 Hz), 100.8 (d, J = 23.3 Hz), 93.4, 42.4 (sept, J = 30.5 Hz), 7.1; ^{19}**F-NMR** (475 MHz, DMSO-d^6, ppm) δ = -69.35 (d, J = 8.56 Hz, 6F), 127.85-127.93 (m, 1F); **HRMS(ESI)** m/z [M+H]$^+$Calcd. for $C_{12}H_9F_7N$ = 300.0623, found 300.0627.



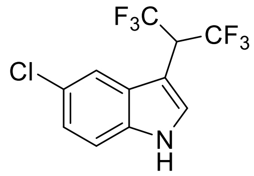
3h

5-chloro-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)-2-methyl-1H-indole 3h (41 % yield). ^{1}**H-NMR** (300MHz, DMSO-d^6, ppm) δ =11.7 (s, 1H）,7.4-7.3(m, *2H*), 7.1 (dd, J = 1.92 Hz J = 8.6 Hz, 1H), 5.41 (sept, J = 9.6 Hz, 1H), 2.48 (s, 3H); ^{13}**C-NMR** (300 MHz, DMSO-d^6, ppm) δ = 141.1, 134.6, 127.1, 124.7, 124.5 (q, J = 279.6 Hz), 121.3, 118.3, 113.1, 95.8, 45.5 (sept, J = 29.7 Hz), 11.6.; ^{19}**F-NMR** (475 MHz, DMSO-d^6, ppm) δ = -63.73 (d, J = 8.65 Hz, 6F); **HRMS(ESI)** m/z [M+H]$^+$Calcd. for $C_{12}H_9ClF_6N$ = 316.0328, found 316.0325.



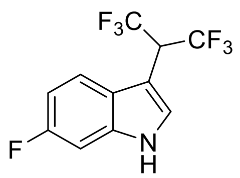
3i

5-bromo-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)-2-methyl-1H-indole 3i, dark brown solid (38 % yield). **^{1}H-NMR** (300MHz, DMSO-d^{6}) δ = 11.7 (s, 1H）,7.5(s, 1H), 7.35-7.30 (m, 1H), 7.24-7.17 (m, 1H), 5.4 (sept, *J* = 9.5 Hz, 1H), 2.47 (s, 3H); **^{13}C-NMR** (300 MHz, DMSO-d^{6}, ppm) δ = 141.0, 134.8, 127.8, 124.5(q, *J* = 279.4 Hz), 123.9, 121.2, 113.6, 112.7, 95.7, 45.5 (sept, *J* = 30.3 Hz), 11.6; **^{19}F-NMR** (475 MHz, DMSO-d^{6}, ppm) δ = -63.72 (d, *J* = 8.73 Hz, 6F); **HRMS(ESI)** m/z [M+H]$^{+}$Calcd. for $C_{12}H_{9}BrF_{6}N$ = 359.9823, found 359.9819.



3j

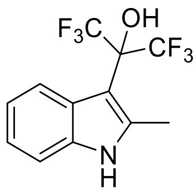
5-chloro-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)-1H-indole 3j, brown solid (20 % yield). **^{1}H-NMR** (300 MHz, DMSO-d^{6}, ppm) δ = 11.75 (s, 1H), 7.85 (d, *J* = 1.68Hz 1H), 7.62 (d, *J* = 2.36 Hz 1H), 7.48 (d, *J* = 8.65 Hz, 1H), 7.18 (dd, *J* = 1.95 Hz *J* = 8.68 Hz, 1H), 5.76 (sept, *J* = 9.1Hz, 1H); **^{13}C-NMR** (300MHz, DMSO-d^{6}, ppm) δ = 134.7, 128.5, 128.4, 125.0, 124.2(q, *J* = 279.7 Hz), 122.5, 118.2, 114.1, 99.4, 44.5 (sept, *J* = 29.4 Hz); **^{19}F-NMR** (475 MHz, DMSO-d^{6}, ppm) δ = -65.58 (d, *J* = 8.65 Hz, 6F); **HRMS(ESI)** m/z [M]$^{+}$Calcd. for $C_{11}H_{7}ClF_{6}N$ = 301.0093, found[M+1] 301.0403.



3k

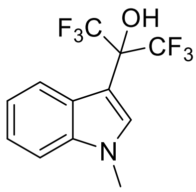
6-fluoro-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)-1H-indole 3k, brown solid (22 %

yield). **^{1}H-NMR** (300MHz, DMSO-d^{6}, ppm) δ = 11.60 (s, 1H), 7.75 (dd, J_1 = 8.87 Hz, J_2 = 5.35 Hz, 1H), 7.55 (d, J = 2.57 Hz, 1H), 7.24 (dd, J_1 = 9.87 Hz, J_2 = 2.39 Hz, 1H), 6.98 (dt, J_1 = 2.44 Hz, J_2 = 9.34 Hz, 1H), 5.72 (sept, J = 9.16 Hz, 1H); **^{13}C-NMR** (300 MHz, DMSO-d^{6}, ppm) δ = 159.5 (d, J = 234.2 Hz), ,136.1 (d, J = 12.8 Hz), 127.6, 124.2 (q, J = 282.5 Hz), 123.9, 120.1 (d, J = 10.1 Hz), 108.9 (d, J = 24.6 Hz), 99.8, 98.3 (d, J = 25.6 Hz), 44.7 (sept, J = 29.16 Hz); **^{19}F-NMR** (475 MHz, DMSO-d^{6}, ppm) δ = -65.46 (d, J = 8.67 Hz, 6F); **HRMS(ESI)** m/z $[2M+H]^{+}$Calcd. for $C_{22}H_{13}F_{14}N_{2}$= 571.0855, found[M+1] 571.0871.



4a

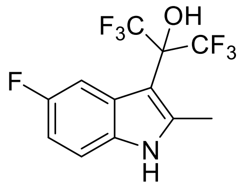
1, 1, 1, 3, 3, 3-hexafluoro-2-(2-methyl-1H-indol-3-yl)propan-2-ol, known compound, (4a[1]), light yellow liquid (51 % yield). **^{1}H-NMR** (500 MHz, DMSO-d^{6}, ppm) δ = 11.42 (s, 1H), 8.17 (s, 1H), 7.66 (d, J = 7.94 Hz, 1H), 7.33 (d, J = 7.99 Hz, 1H), 7.10-6.96 (m, 2H), 2.54 (s, 3H); **^{13}C-NMR** (125 MHz, DMSO-d^{6}, ppm) δ = 135.2, 126.8, 124.3 (q, J = 287.5 Hz), 121.5 (q, J = 126.4 Hz), 121.1, 120.3, 119.9, 111.3, 100.6; **^{19}F-NMR** (475 MHz, DMSO-d^{6}, ppm) δ = -73.8 (s, 6F). **HRMS(ESI)** m/z: Calcd. for $C_{12}H_{9}F_{6}NO$ = 297.0588, found 297.0586.



4b

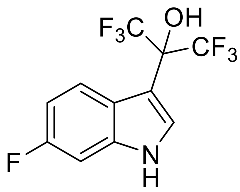
1, 1, 1, 3, 3, 3-hexafluoro-2-(1-methyl-1H-indol-3-yl)propan-2-ol, known compound, (4b[2]), light yellow liquid (40 % yield). **^{1}H-NMR** (500 MHz, DMSO-d^{6}, ppm) δ = 8.39 (s, 1H), 7.82 (d, J = 8.23 Hz, 1H), 7.62(m, 1H), 7.50-7.47(s, 1H), 7.51 (d, J = 8.23 Hz, 1H), 7.17-7.11 (m, 1H), 3.86 (s, 3H); **^{13}C-NMR** (125 MHz, DMSO-d^{6}, ppm) δ = 137.2, 130.1, 126.3, 124.0 (t, J = 289.8 Hz), 122.3, 121.7, 120.3, 110.7, 103.9, 77.4, 76.2, 33.1; **^{19}F-NMR** (475 MHz, DMSO-d^{6}, ppm) δ = -74.9 (s, 6F);

HRMS(ESI) m/z: Calcd. for $C_{12}H_9F_6NO$ = 297.0588, found 297.0587.



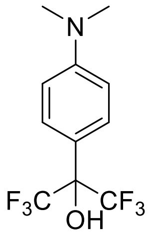
4c

1,1,1,3,3,3-hexafluoro-2-(5-fluoro-2-methyl-1H-indol-3-yl)propan-2-ol, known compound, 4c[3], light brown solid (43 % yield). **^{1}H-NMR** (300 MHz, DMSO-d^6, ppm) δ = 11.58 (s, 1H）,8.29(s, 1H), 7.37-7.25(m, 2H), 6.92 (dt, *J* = 2.45 Hz, *J* = 9.0 Hz, 1H), 2.50 (s, 3H); **^{13}C-NMR** (300 MHz, DMSO-d^6, ppm) δ = 159.3 (d, *J* = 235.5 Hz), 135.6 (d, *J* = 12.7 Hz), 126.7, 123.9 (q, *J* = 289.5 Hz), 122.6, 120.1 (d, *J* = 10.1 Hz), 108.8 (d, *J* = 24.3 Hz), 105.2, 98.2 (d, *J* = 25.5 Hz), 76.4 (t, *J* = 30.2 Hz); **^{19}F-NMR** (475 MHz, DMSO-d^6, ppm) δ = -75.89 (s, 6F); **GC-MS(EI)** m/z: Calcd. for $C_{12}H_9F_6NO$ = 315.0, found 315.0



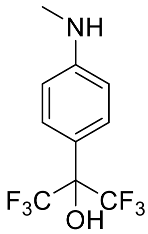
4d

1,1,1,3,3,3-hexafluoro-2-(6-fluoro-1H-indol-3-yl)propan-2-ol, known compound, 4d[3], light brown solid (35 % yield). **^{1}H-NMR** (300MHz, DMSO-d^6, ppm) δ = 11.63 (s, 1H）,8.42(s, 1H), 7.80-7.71(m, 1H), 7.54 (d, *J* = 2.51 Hz, 1H), 7.23 (dd, *J* = 2.42 Hz, *J* = 7.44 Hz, 1H), 6.95 (dt, *J* = 2.47 Hz, *J* = 9.33 Hz,1H). **^{13}C-NMR** (300 MHz, DMSO-d^6, ppm) δ = 159.3 (d, *J* = 235.5 Hz), 135.6 (d, *J* = 12.7 Hz), 126.7, 123.9(q, *J* = 289.5 Hz), 122.6, 120.1 (d, *J* = 10.1 Hz), 108.8 (d, *J* = 24.3 Hz), 105.2, 98.2 (d, *J* = 25.5 Hz), 76.4 (t, *J* = 30.2 Hz). **^{19}F-NMR** (475 MHz, DMSO-d^6, ppm) δ = -75.3 (s, 6F), -124.0 (m, 1F); **GC-MS(EI)** m/z: Calcd. for $C_{12}H_9F_6NO$ = 301.0, found 301.1



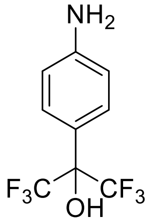
4e

2-(4-(dimethylamino)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol, known compound, 4e[4], white solid (30 % yield). **^{1}H-NMR** (300MHz, DMSO-d^{6}, ppm) δ = 8.30 (s, 1H), 7.42 (d, *J* = 8.81 Hz, 2H), 6.81-6.74 (m, 2H), 2.93(s, 6H). **^{13}C-NMR** (300 MHz, DMSO-d^{6}, ppm) δ = 150.5, 150.5, 128.0, 125.1, 122.3, 117.2, 113.7; **^{19}F-NMR** (475 MHz, DMSO-d^{6}, ppm) δ = -74.3 (s, 6F); **GC-MS(EI)** m/z: Calcd. for $C_{12}H_9F_6NO$ = 287.1, found 287.1



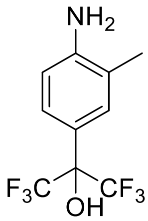
4f

1,1,1,3,3,3-hexafluoro-2-(4-(methylamino)phenyl)propan-2-ol, 4f[4], white solid (26 % yield). **^{1}H-NMR** (300 MHz, DMSO-d^{6}) δ = 8.17 (s, 1H), 7.28(d, *J* = 8.46 Hz, 2H), 6.65-6.57 (m, 2H), 5.42(s, 2H); **^{13}C-NMR** (300MHz, DMSO-d^{6}, ppm) δ =150.5, 150.5, 128.0, 125.1, 122.3, 117.2, 113.7; **^{19}F-NMR** (475 MHz, DMSO-d^{6}, ppm) δ = -74.36 (s, 6F); **GC-MS(EI)** m/z: Calcd. for $C_{12}H_9F_6NO$ = 273.0, found 273.0



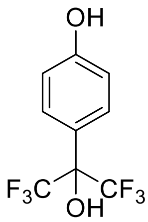
4g

2-(4-aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol, known compound, 4g[4], white solid (20 % yield). **^{1}H-NMR** (300 MHz, DMSO-d^{6}, ppm ^{6}) δ = 8.17 (s, 1H), 7.28 (d, *J* = 8.46 Hz, 2H), 6.65-6.57 (m, 2H), 5.42 (s, 2H); **^{13}C-NMR** (300 MHz, DMSO-d[6], ppm) δ = 150.5, 150.5, 128.0, 125.1, 122.3, 117.2, 113.7; **[19]F-NMR** (475 MHz, DMSO-d[6], ppm) δ = -74.36 (s, 6F); **GC-MS(EI)** m/z: Calcd. for $C_{12}H_9F_6NO$ = 259.0, found 259.0



4h

2-(4-amino-3-methylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol, known compound, 4g[4], white solid (38 % yield). **[1]H-NMR** (300 MHz, DMSO-d[6]) δ = 8.15 (s, 1H), 7.23-7.10 (m, 2H), 6.64 (d, *J* = 8.35 Hz, 1H), 5.19 (s, 2H), 2.07 (s, 3H); **[13]C-NMR** (300 MHz, DMSO-d[6], ppm) δ =148.5, 128.7, 125.5, 125.2, 122.3, 120.9, 117.5, 113.7, 18.1; **[19]F-NMR** (475 MHz, DMSO-d[6], ppm) δ = -74.28 (s, 6F); **GC-MS(EI)** m/z: Calcd. for $C_{12}H_9F_6NO$ = 273.0, found 273.0.



4h

4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenol, known compound, 4h, **[1]H-NMR** (300MHz, DMSO-d[6], ppm) δ =9.87 (s, 1H), 8.43 (s, 1H), 7.47(d, *J* = 8.61 Hz, 1H), 6.90-6.82 (m, 2H); **GC-MS(EI)** m/z: Calcd. for $C_{12}H_9F_6NO$ = 260.0, found 260.0.

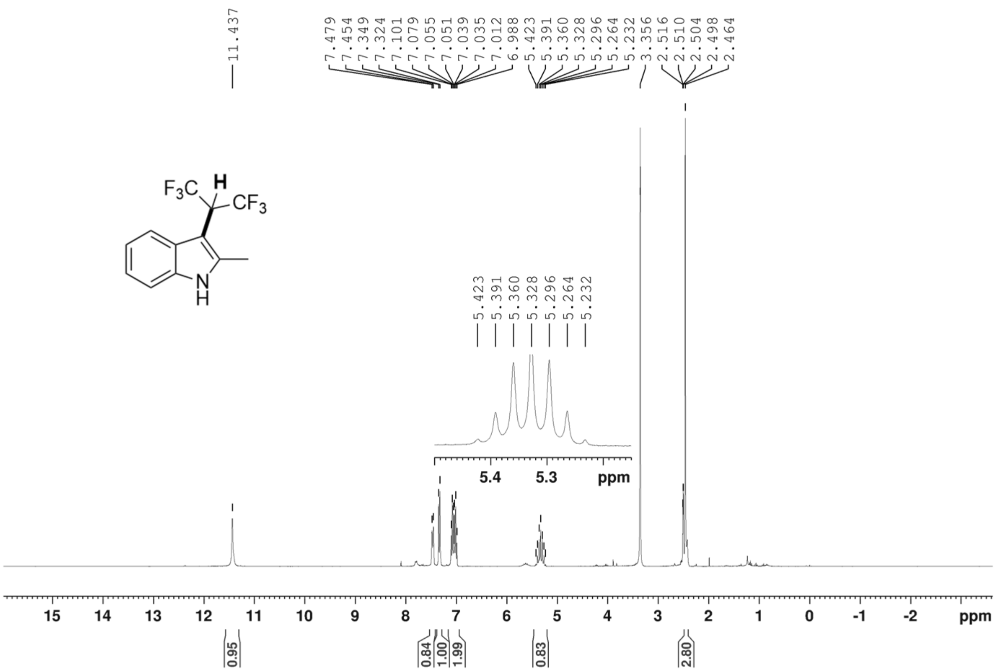
Reference

1. Wang, G.; Yu, N.; Wen, Y.; Leng, F., Direct fluoroacylation of indole with perfluoroalkyl iodides. *Org. Lett.* **2023,** *25*, 5548-5551.
2. Chen, J.; Li, M.; Zhang, J.; Sun, W.; Jiang, Y., Copper-catalyzed functionalization of aza-aromatic rings with fluoroalcohols via direct $C(sp^2)$-H/$C(sp^3)$-H coupling reactions. *Org. Lett.* **2020,** *22,*

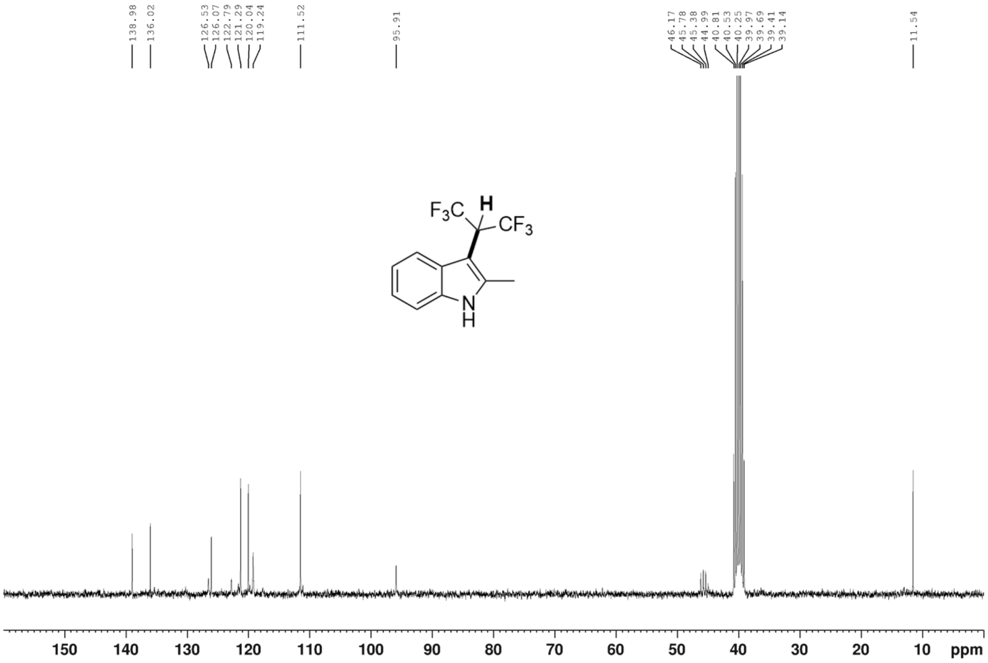
3033-3038.
3. Qin, H.; Zhang, Z.; Qiao, K.; Chen, X.; He, W.; Liu, C.; Yang, X.; Yang, Z.; Fang, Z.; Guo, K., Regioselective C3-fluoroalcoholation of indoles with heptafluoroisopropyl iodide via palladium-catalyzed C(sp2)–C(sp3) cross-coupling in the presence of O_2. *J. Org. Chem.* **2022,** *87*, 9128-9138.
4. Zhao, H.; Zhao, S.; Li, X.; Deng, Y.; Jiang, H.; Zhang, M., Cobalt-catalyzed selective functionalization of aniline derivatives with hexafluoroisopropanol. *Org. Lett.* **2019,** *21*, 218-222.

Copies of NMR spectra

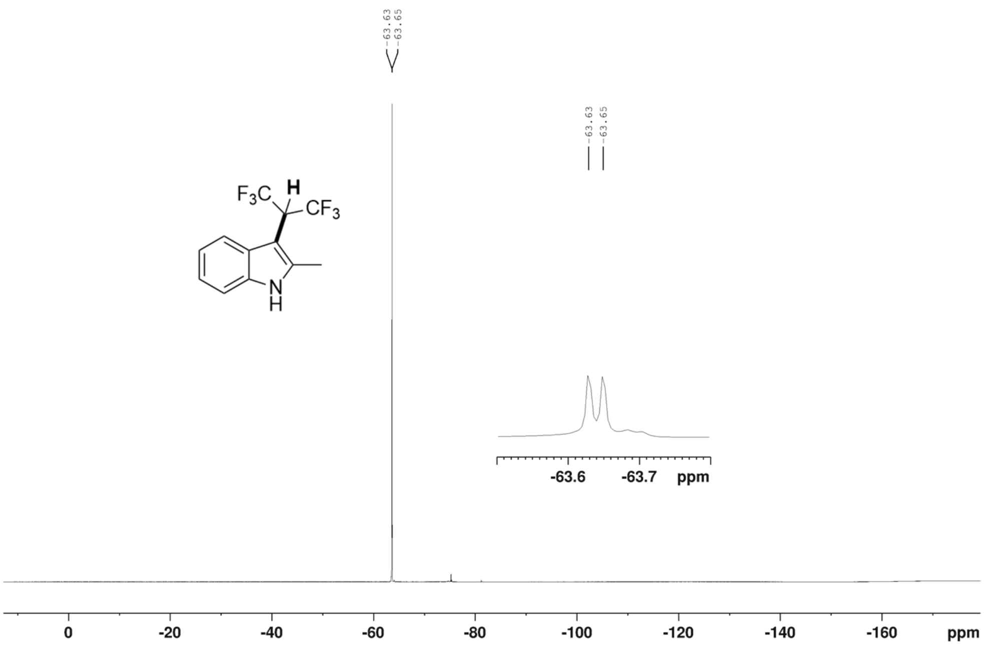
^{1}H-NMR(d_6-DMSO, 300MHz) of 3a



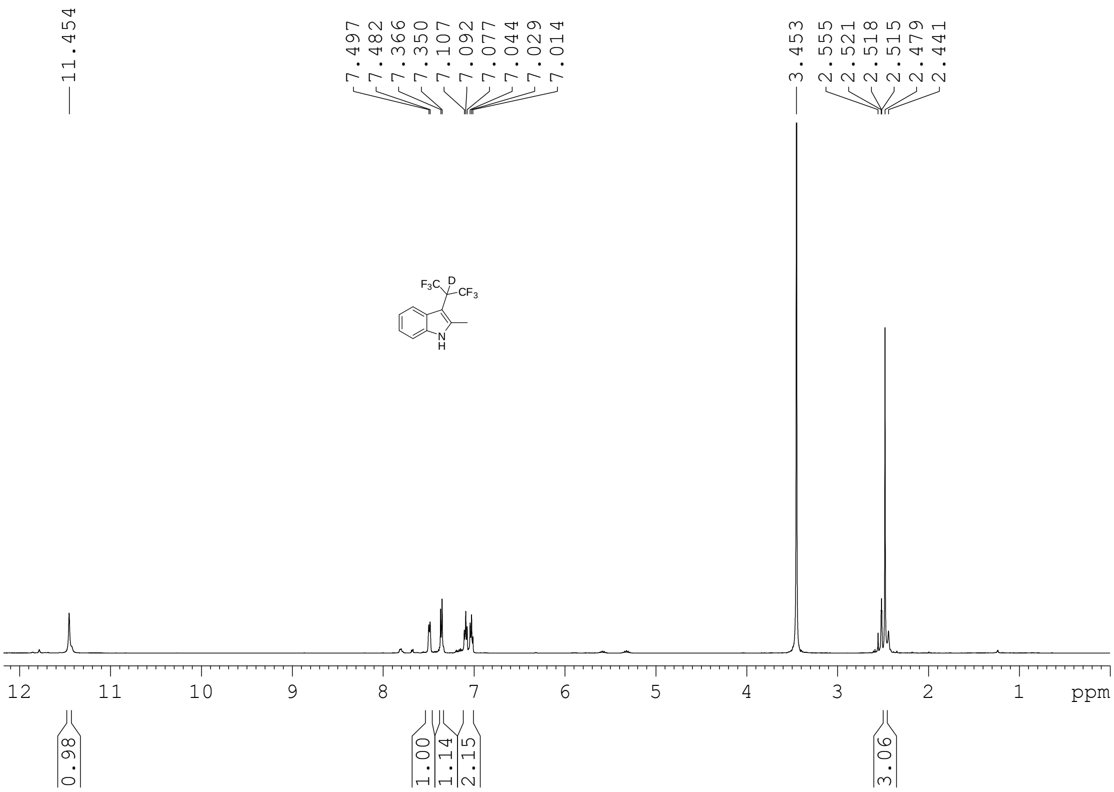
^{13}C-NMR(d_6-DMSO, 75MHz) of 3a



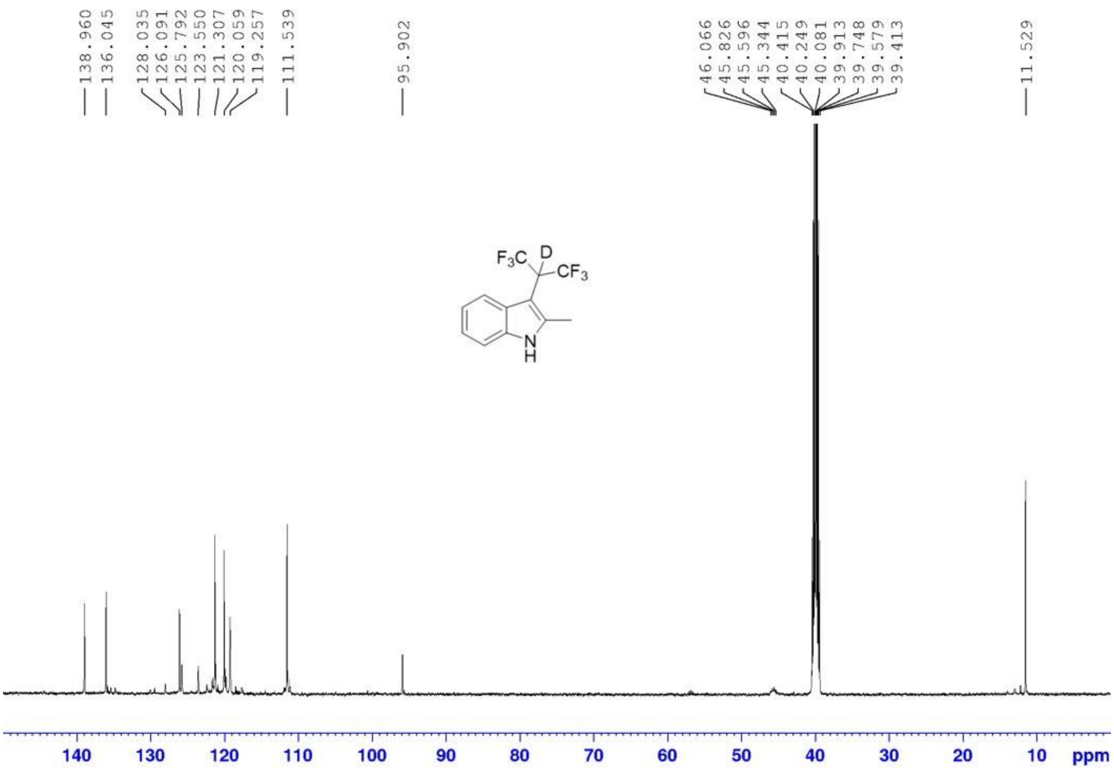
[19]F-NMR(d$_6$-DMSO, 470MHz) of 3a



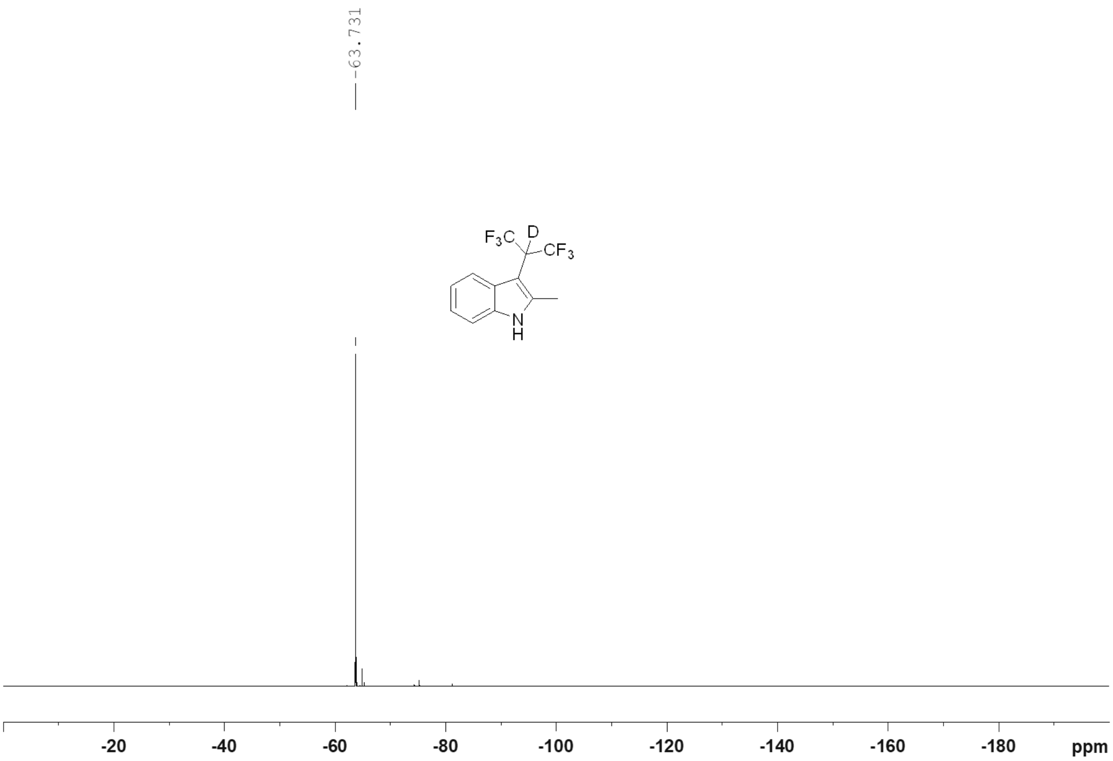
[1]H-NMR(d$_6$-DMSO, 500MHz) of 3a'



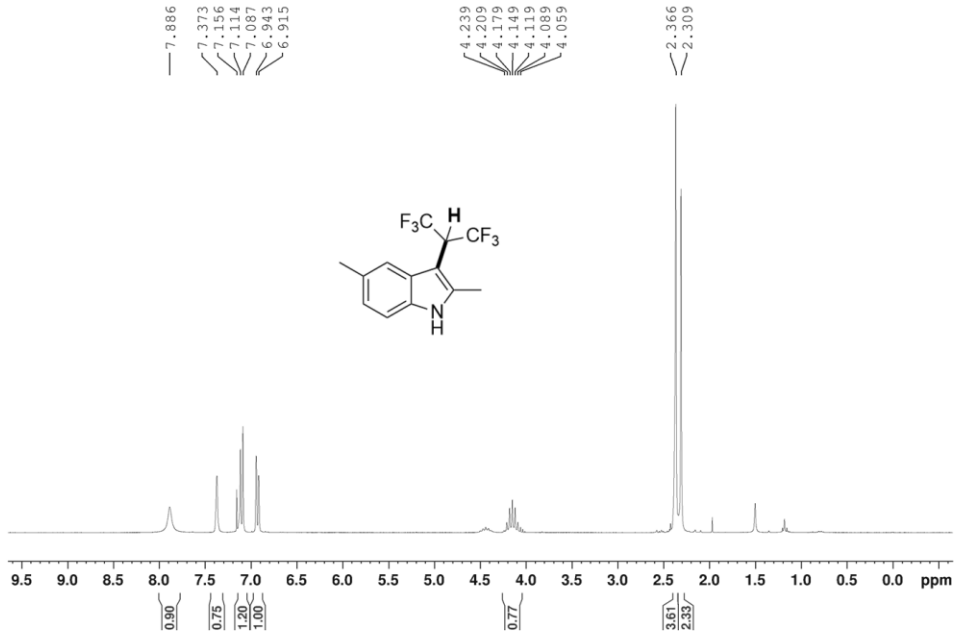
^{13}C-NMR(d_6-DMSO, 500MHz) of 3a'



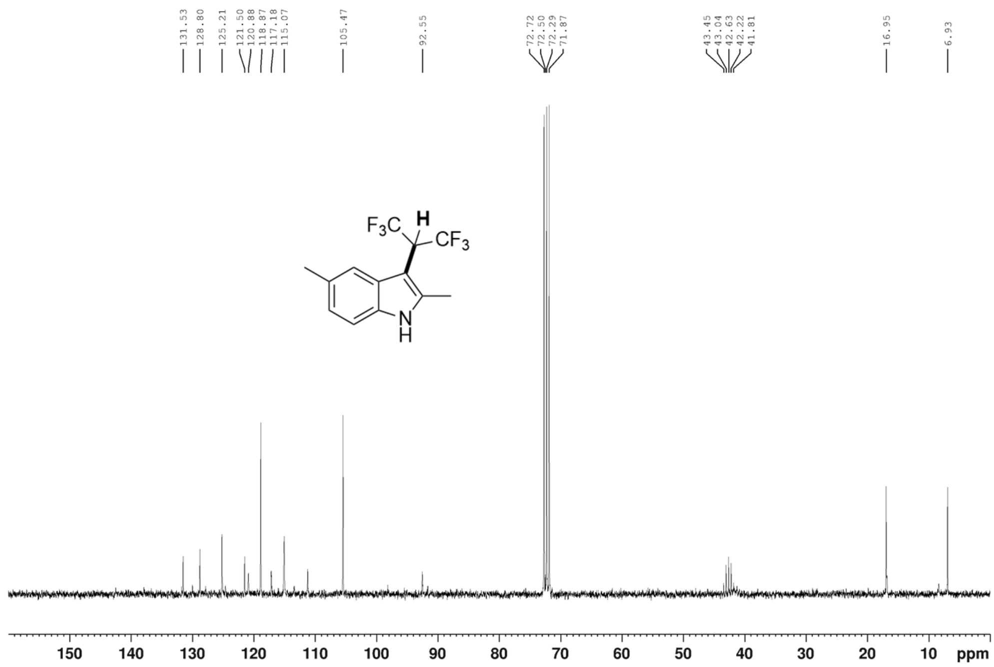
^{19}F-NMR(d_6-DMSO, 500MHz) of 3a'



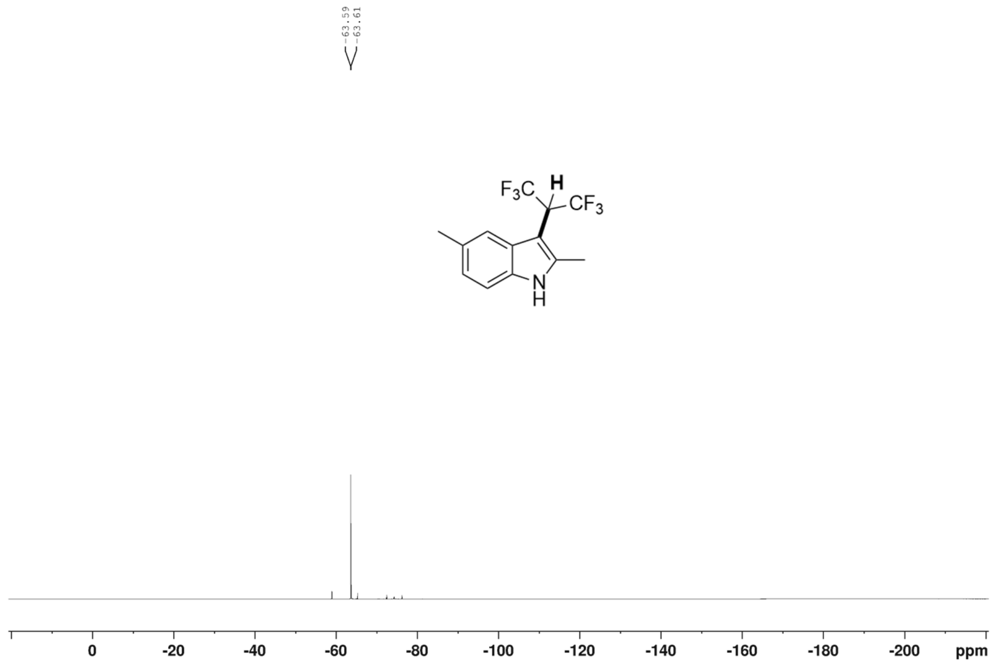
[1]H-NMR($CDCl_3$, 300MHz) of 3b



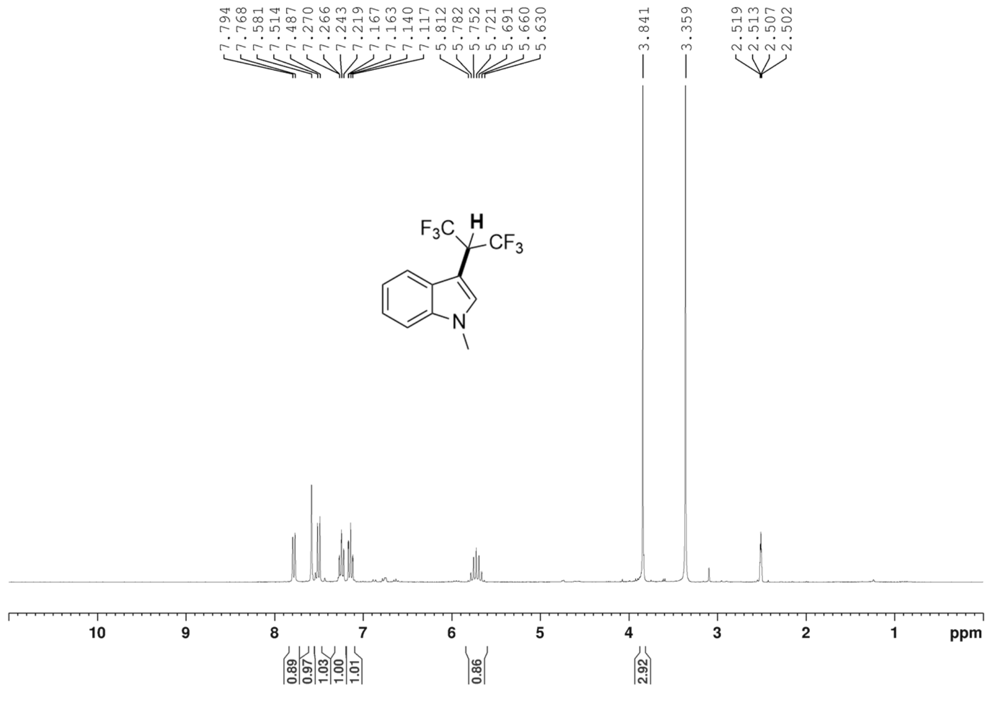
[13]C-NMR($CDCl_3$, 75MHz) of 3b



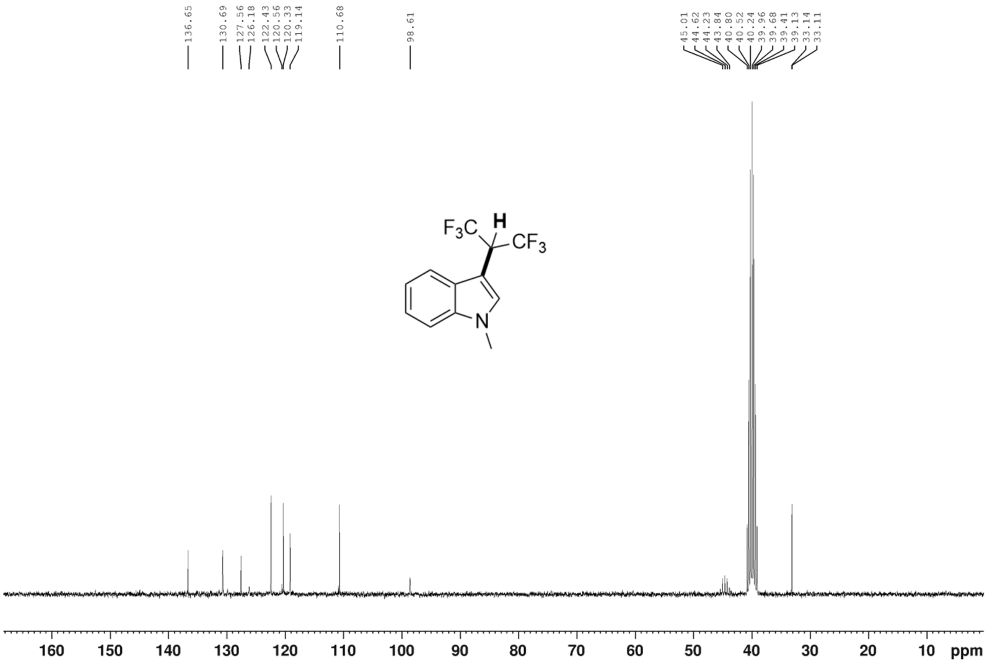
^{19}F-NMR(d$_6$-DMSO, 470MHz) of 3b



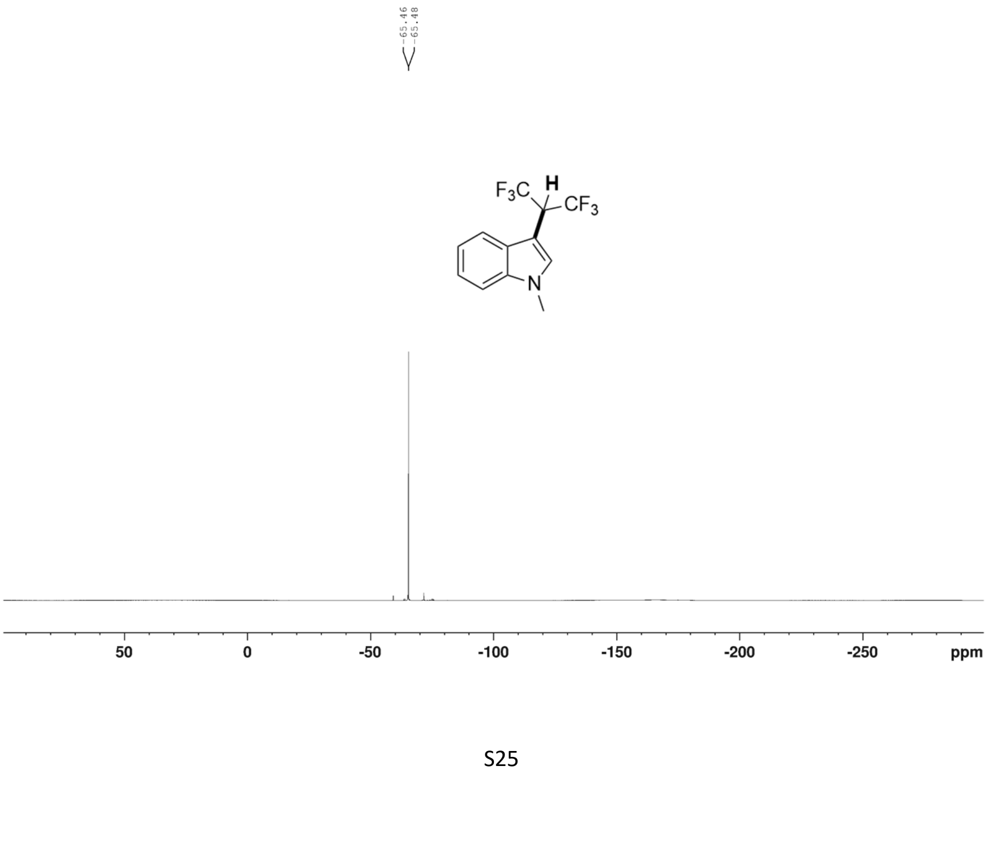
^{1}H-NMR(d$_6$-DMSO, 300MHz) of 3c



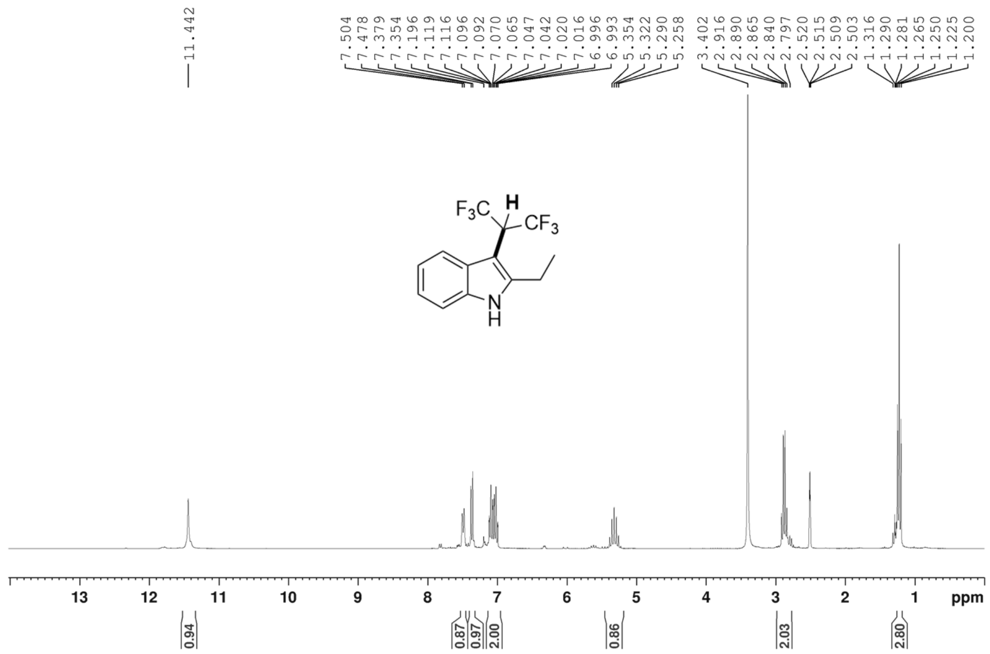
^{13}C-NMR(d_6-DMSO, 75MHz) of 3c



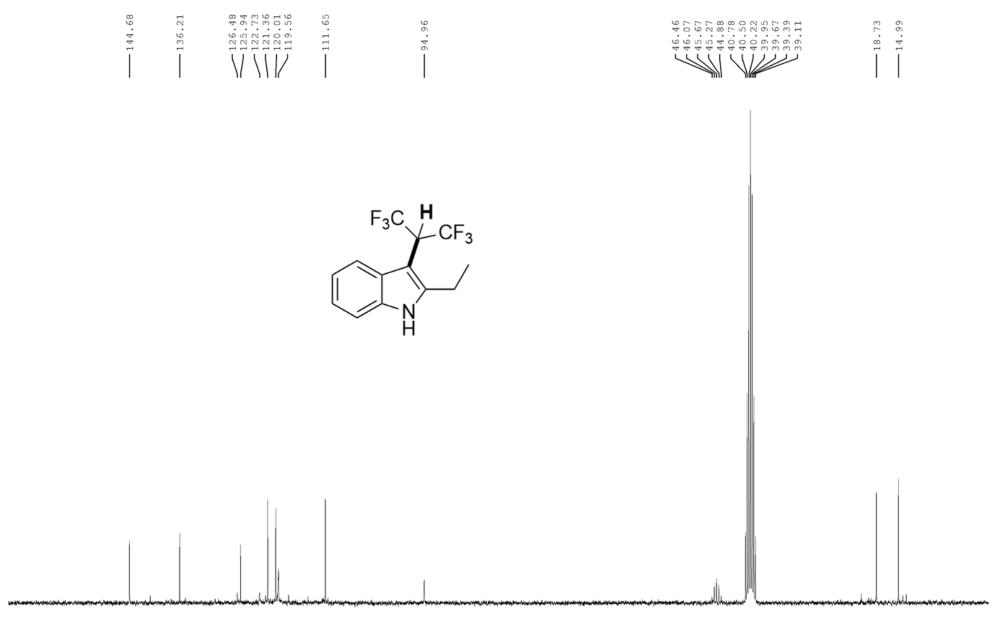
^{19}F-NMR(d_6-DMSO, 470MHz) of 3c



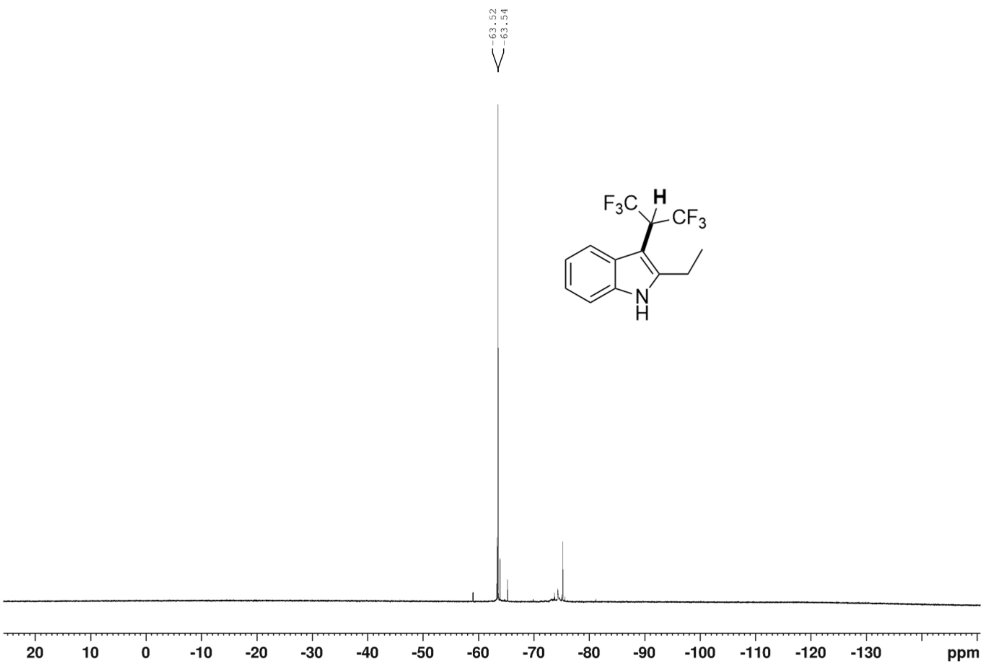
^{1}H-NMR(d_6-DMSO, 300MHz) of 3d



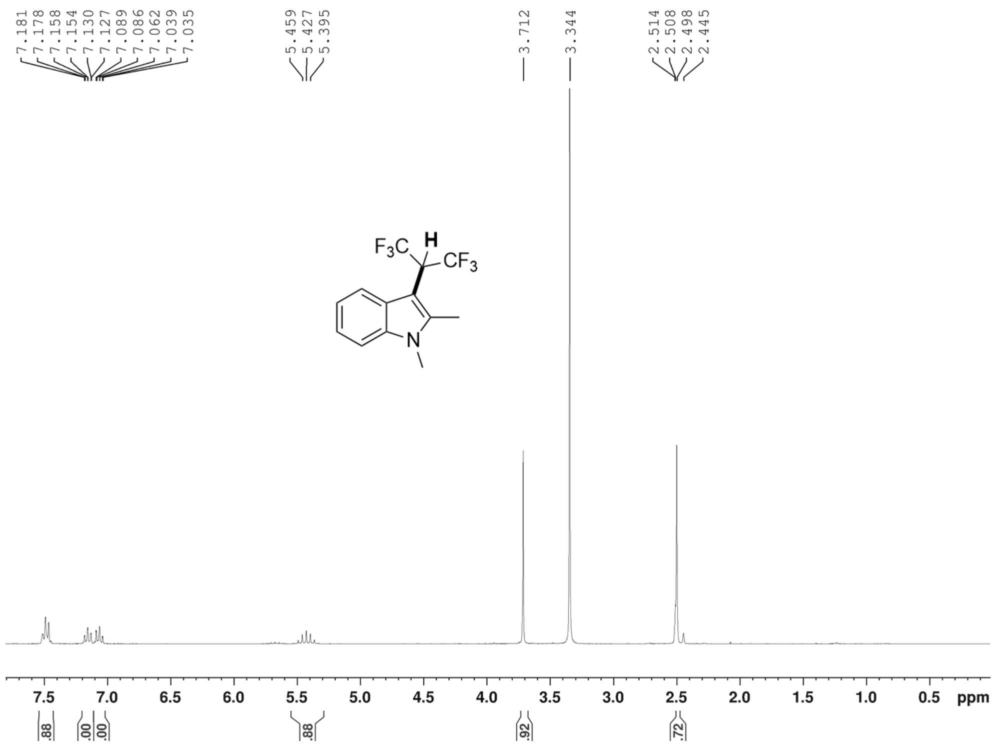
^{13}C-NMR(d_6-DMSO, 75MHz) of 3d



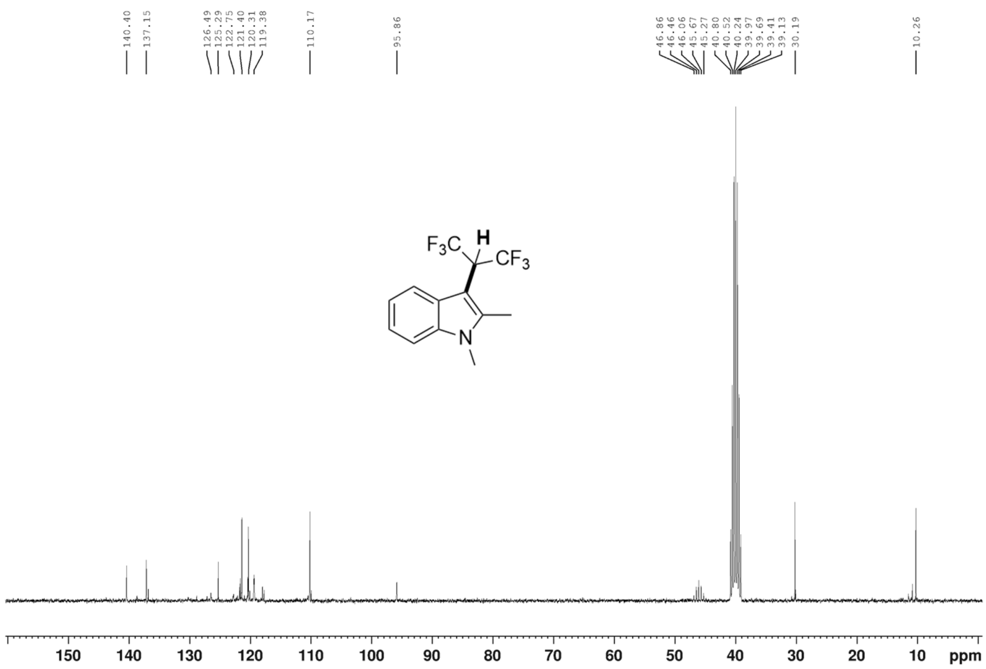
^{19}F-NMR(d$_6$-DMSO, 470MHz) of 3d



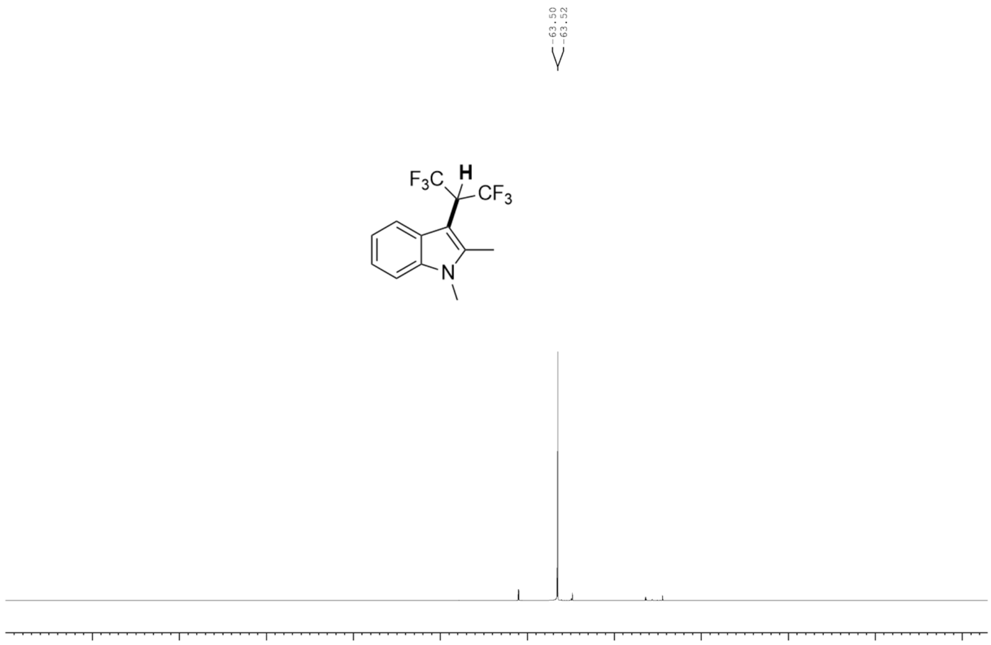
^{1}H-NMR(d$_6$-DMSO, 300MHz) of 3e



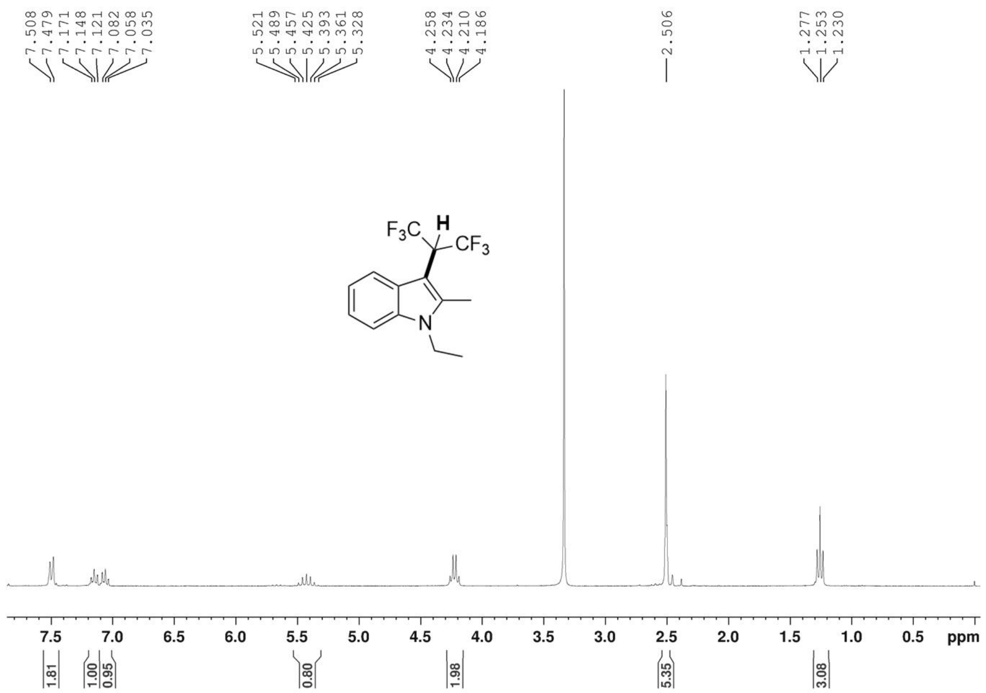
^{13}C-NMR(d$_6$-DMSO, 75MHz) of 3e



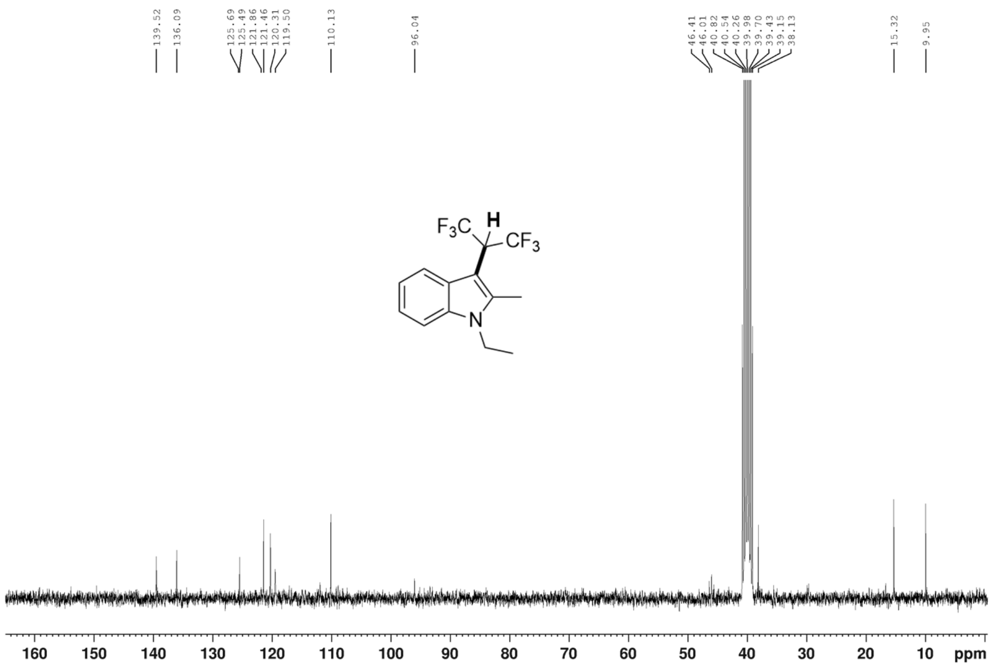
^{19}F-NMR(d$_6$-DMSO, 470MHz) of 3e



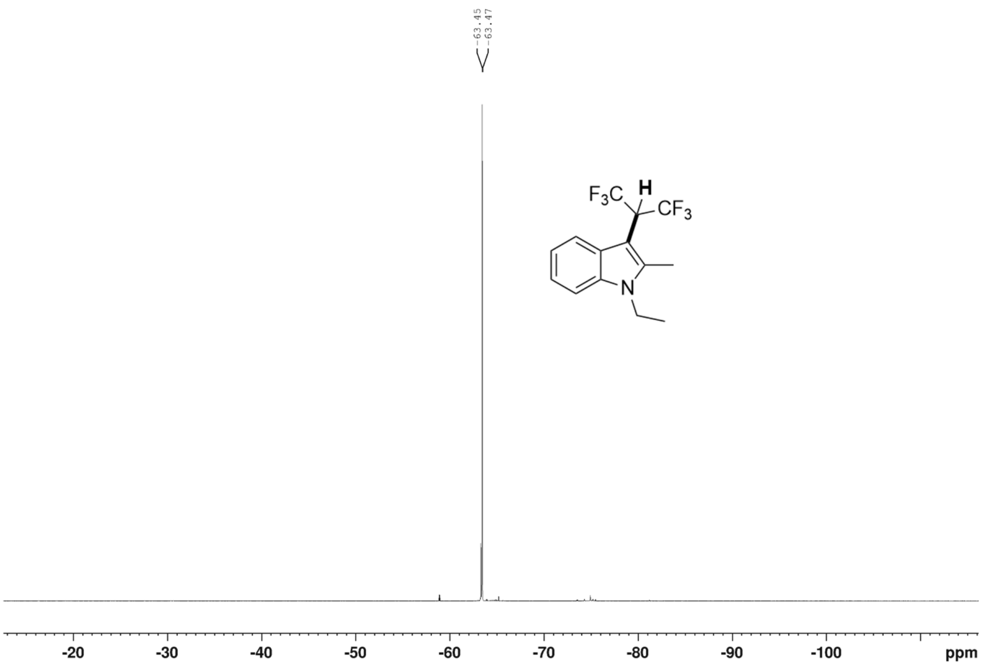
^{1}H-NMR(d_6-DMSO, 300MHz) of 3f



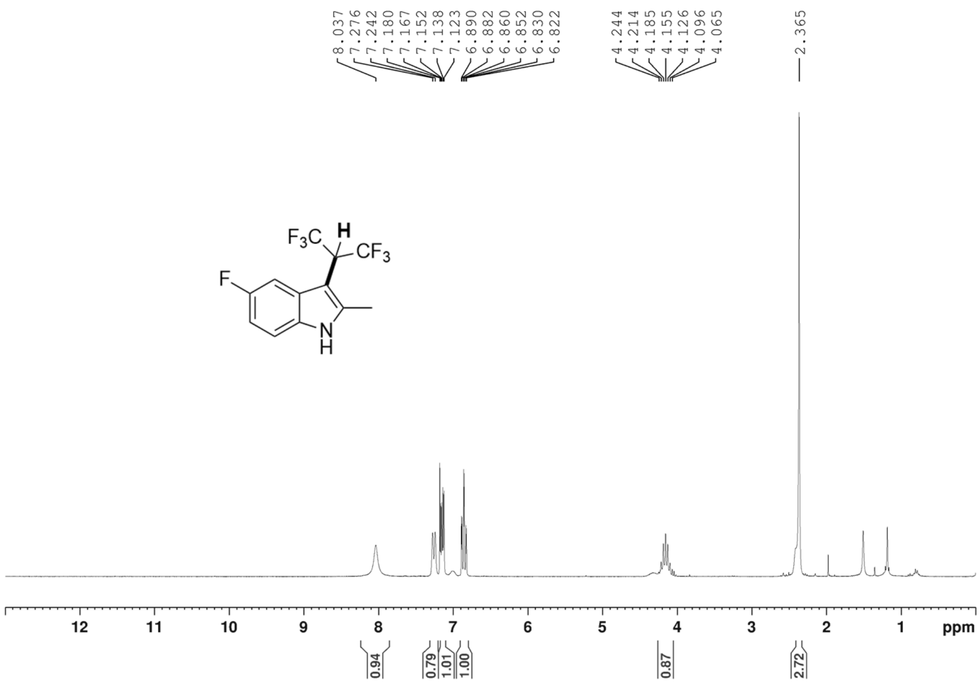
^{13}C-NMR(d_6-DMSO, 75MHz) of 3f



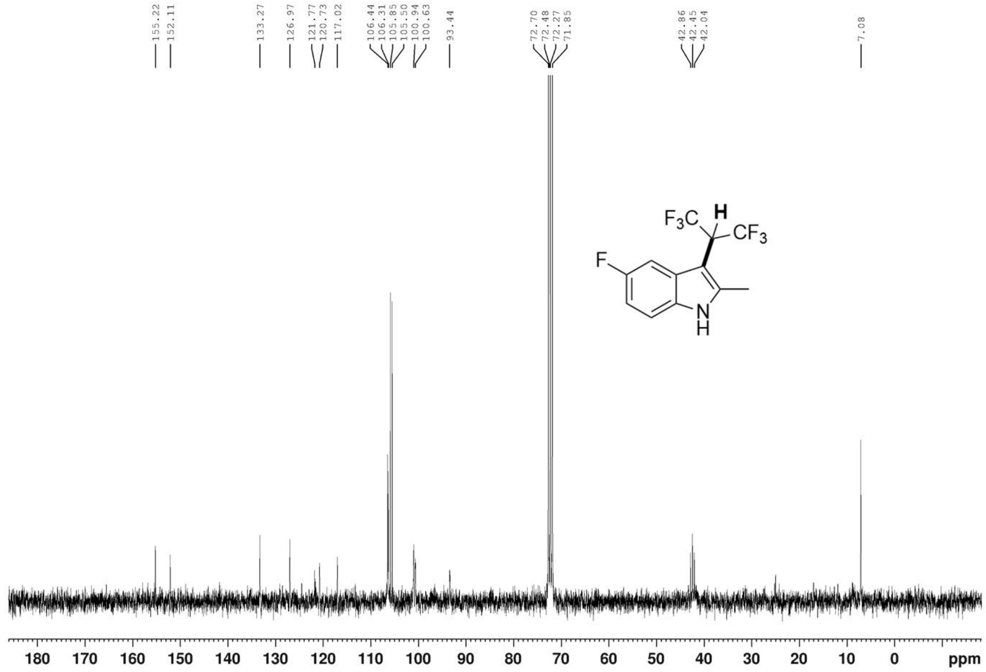
^{19}F-NMR(d$_6$-DMSO, 470MHz) of 3f



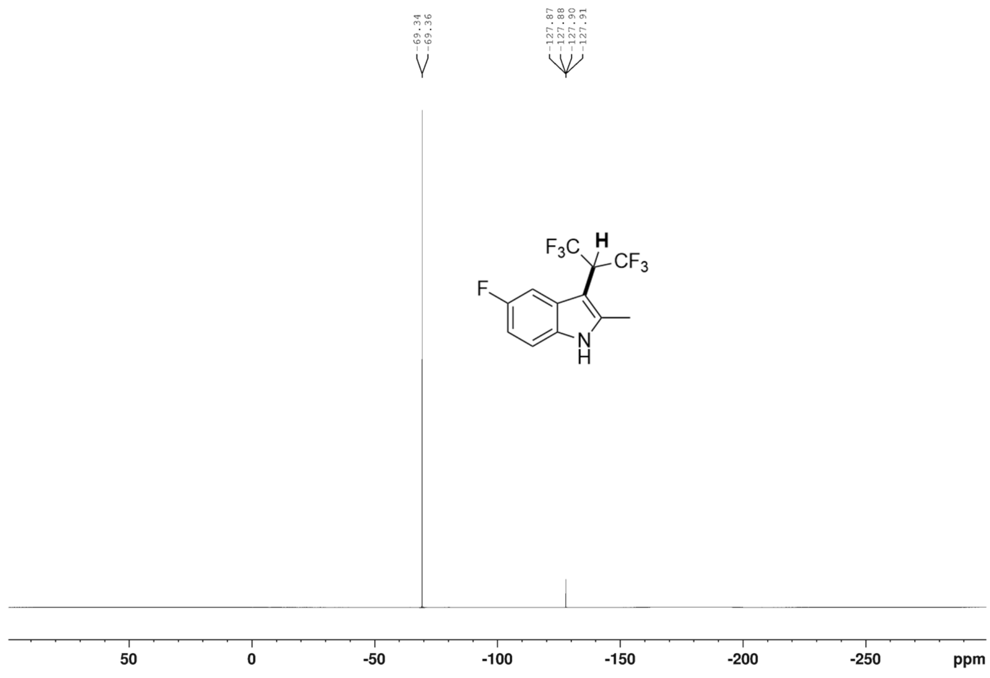
^{1}H-NMR(d$_6$-DMSO, 300MHz) of 3g



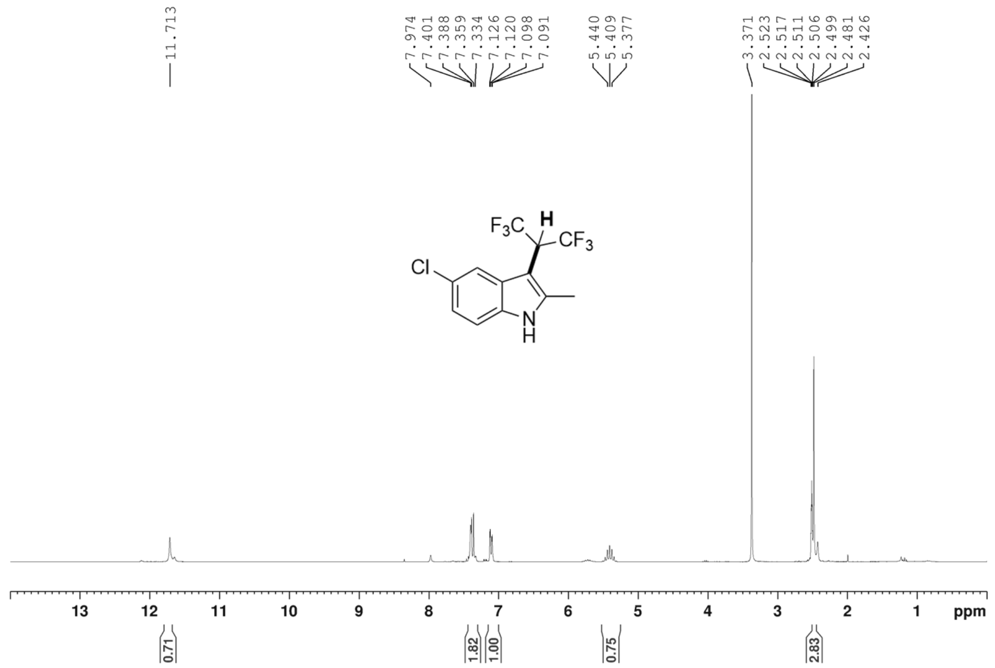
^{13}C-NMR(d$_6$-DMSO, 75MHz) of 3g



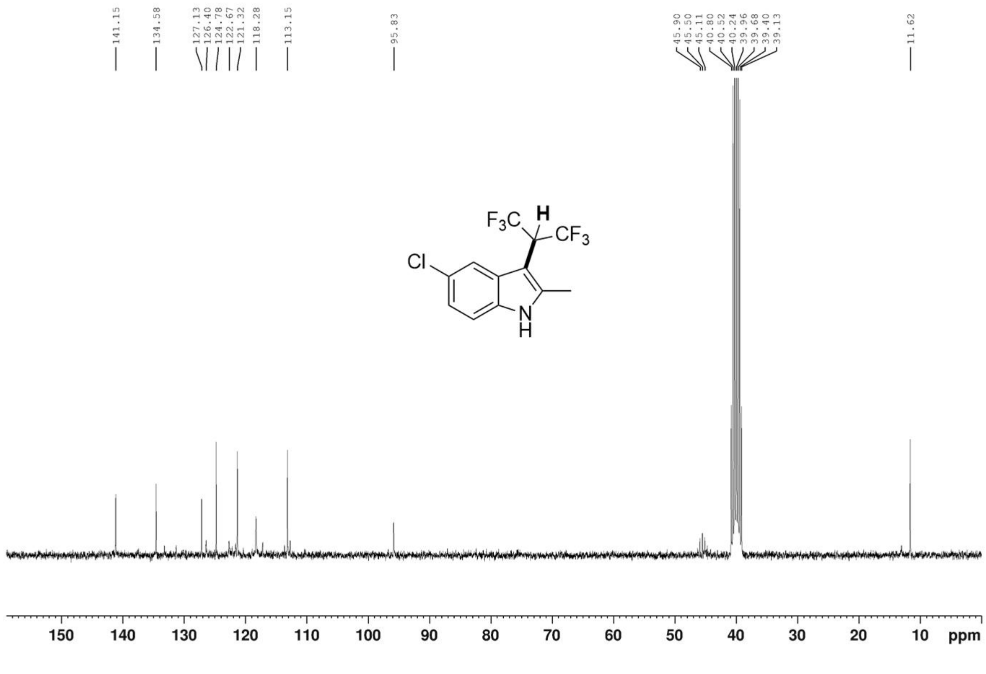
^{19}F-NMR(d$_6$-DMSO, 470MHz) of 3g



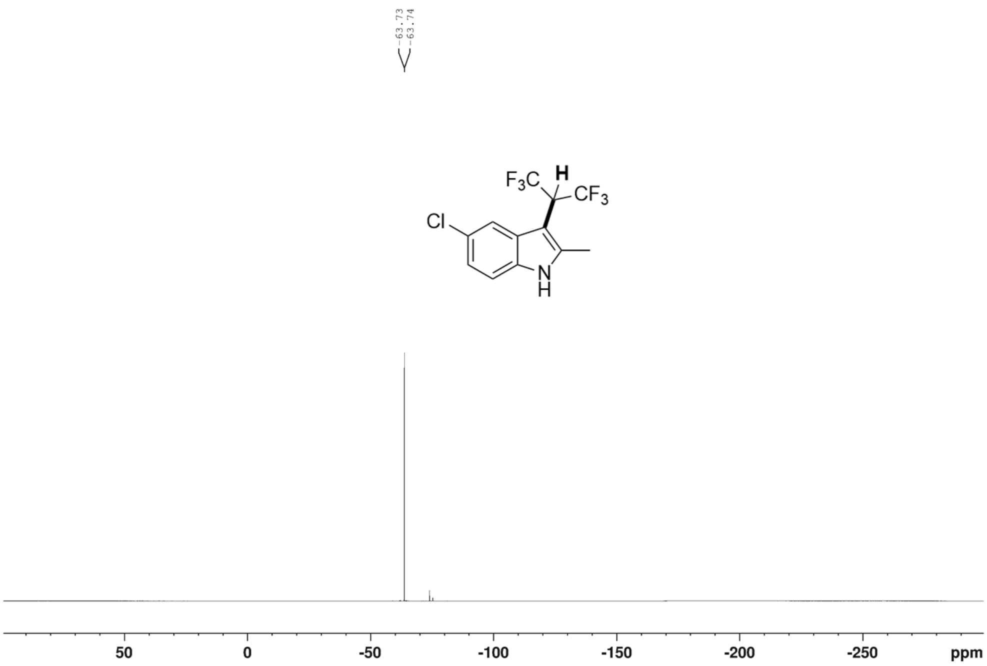
[1]H-NMR(d_6-DMSO, 300MHz) of 3h



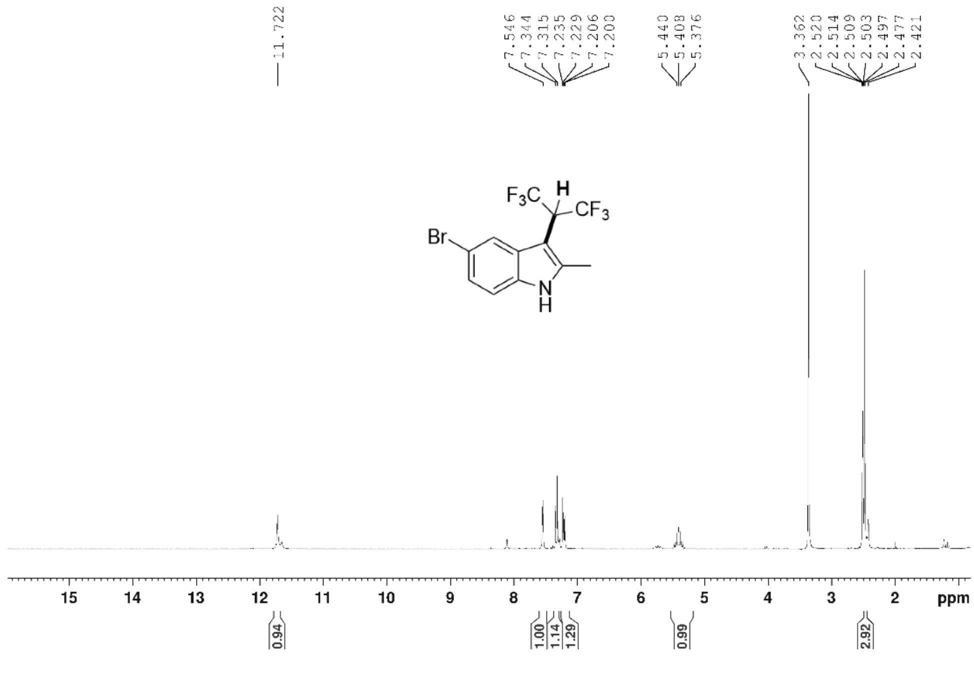
[13]C-NMR(d_6-DMSO, 75MHz) of 3h



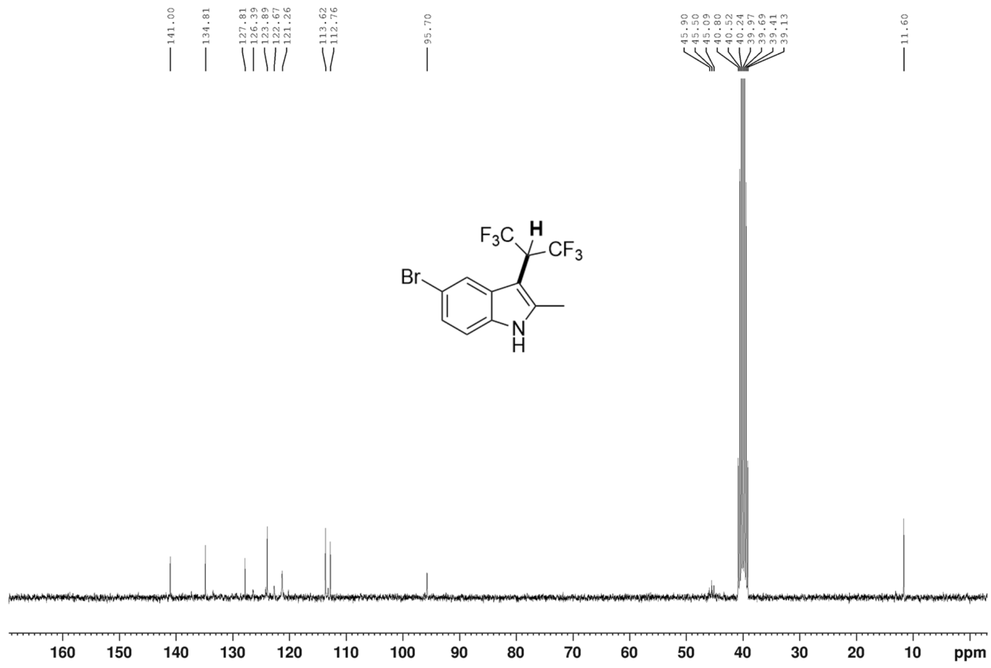
^{19}F-NMR(d$_6$-DMSO, 470MHz) of 3h



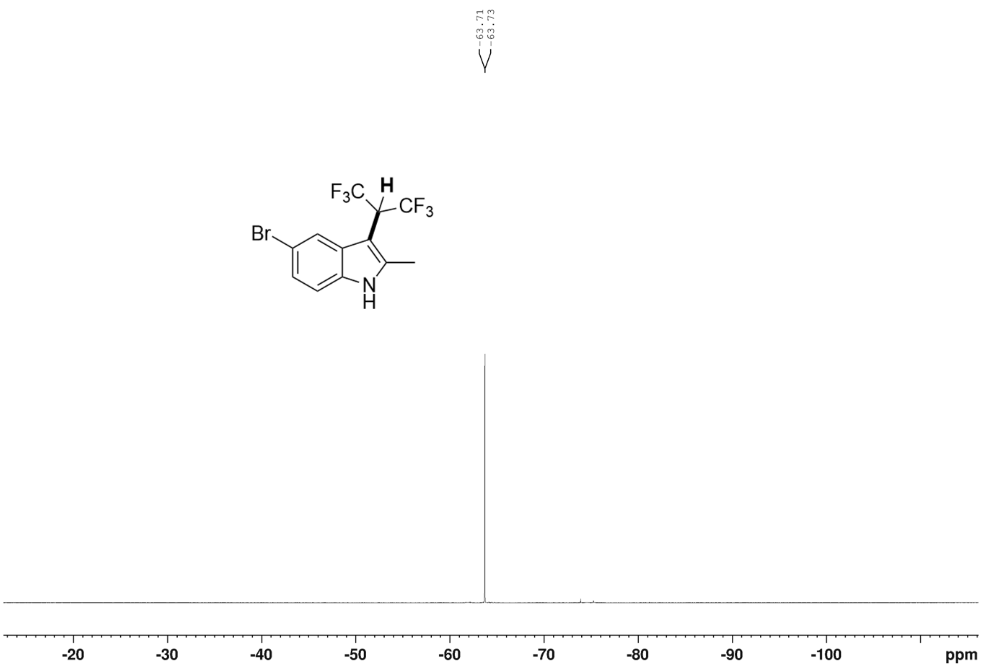
^{1}H-NMR(d$_6$-DMSO, 300MHz) of 3i



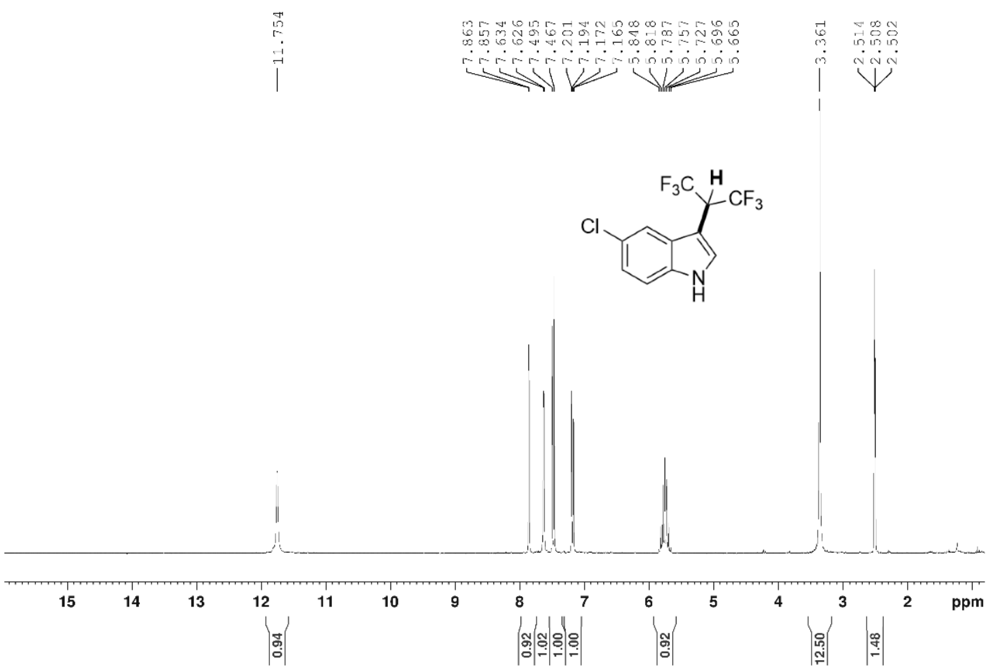
^{13}C-NMR(d_6-DMSO, 75MHz) of 3i



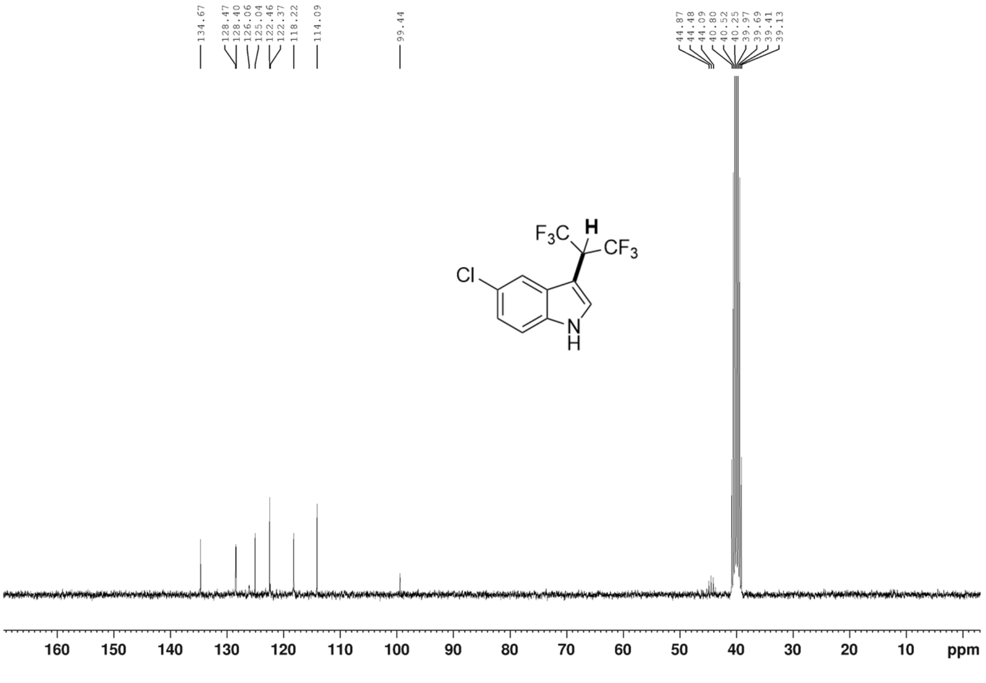
^{19}F-NMR(d_6-DMSO, 470MHz) of 3i



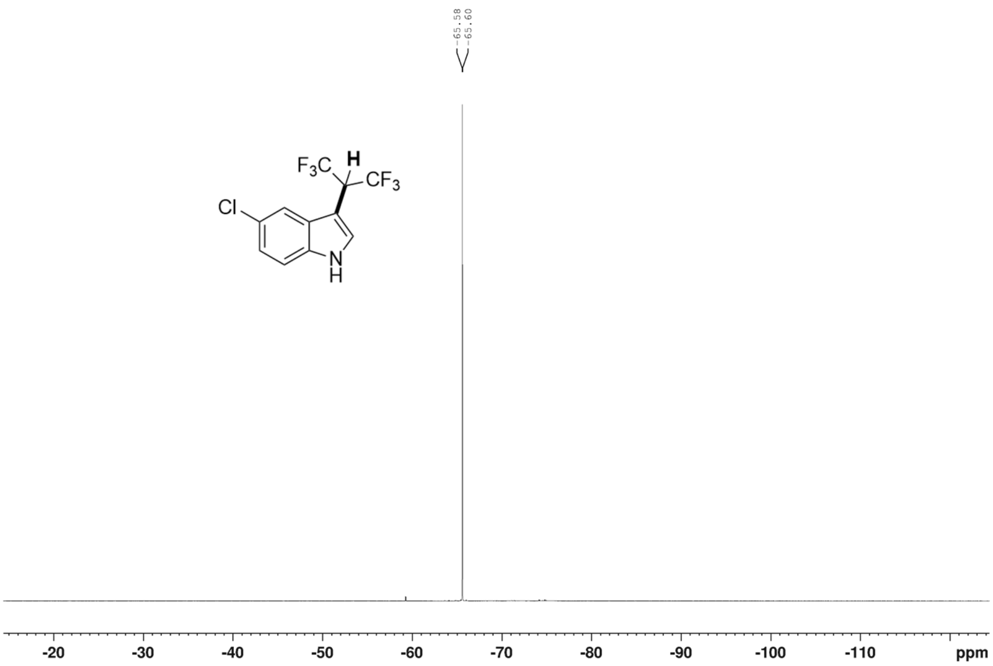
^{1}H-NMR(d_6-DMSO, 300MHz) of 3j



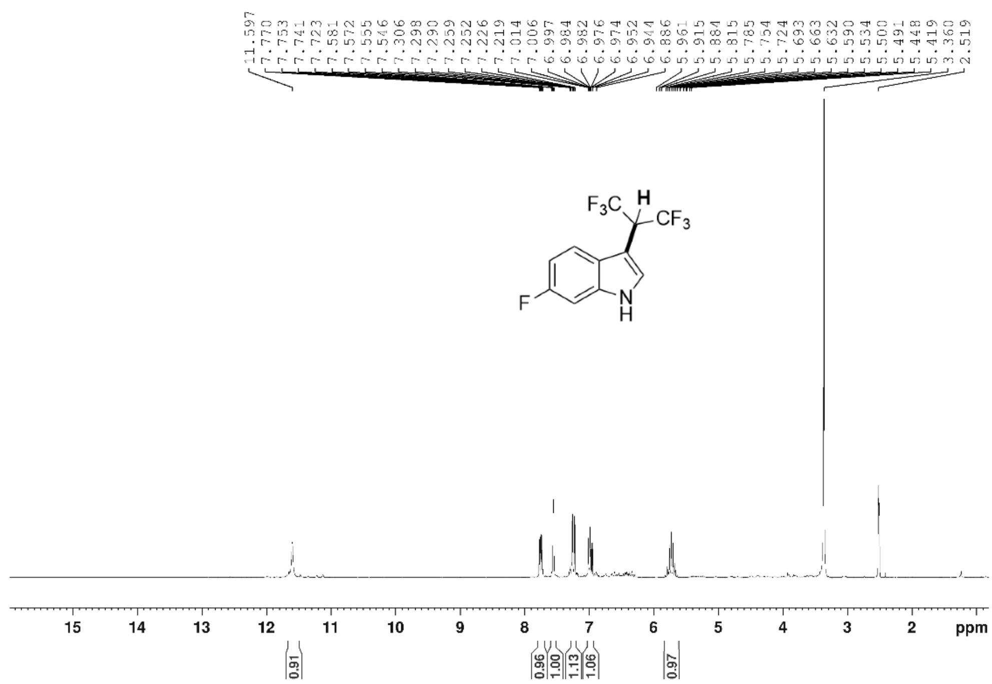
^{13}C-NMR(d_6-DMSO, 75MHz) of 3j



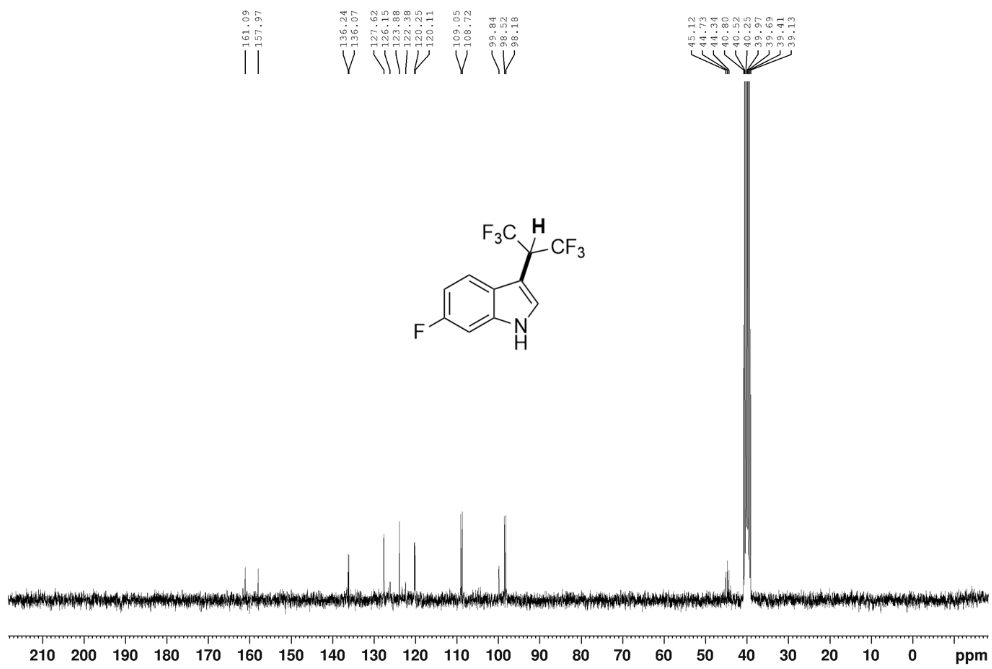
^{19}F-NMR(d$_6$-DMSO, 470MHz) of 3j



^{1}H-NMR(d$_6$-DMSO, 300MHz) of 3k



^{13}C-NMR(d$_6$-DMSO, 75MHz) of 3k



^{19}F-NMR(d$_6$-DMSO, 470MHz) of 3k