Pd(0)/PR_3-Catalyzed Intermolecular Arylation of sp^3 C–H Bonds

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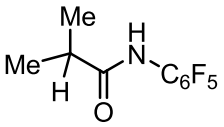
General Information: Solvents were obtained from Sigma-Aldrich, Alfa-Aesar and Acros and used directly without further purification. Carboxylic acids or carboxylic acid chlorides were obtained from the commercial sources and converted to corresponding amides by literature procedure.[1,2]

Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with UV light and Vogel's permanganate. NMR spectra were recorded on a Varian Inova-400 instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, b = broad. High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight). IR spectra were recorded on a Perkin Elmer Spectrum BX FTIR spectrometer.

Substrate Structures



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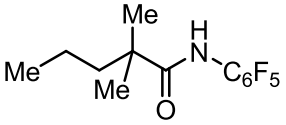

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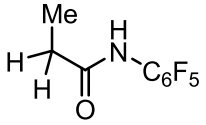

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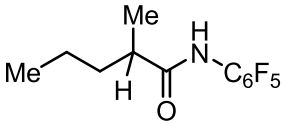

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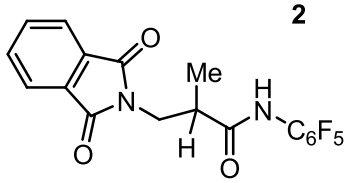

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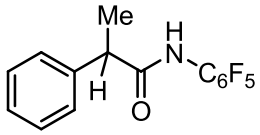

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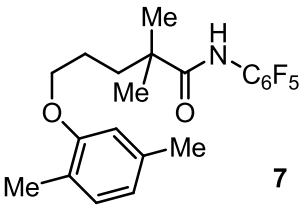

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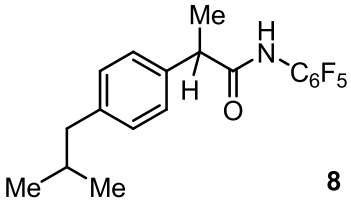

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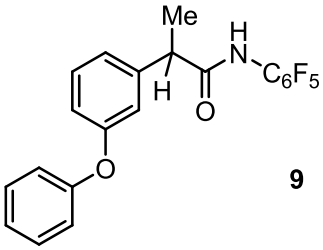

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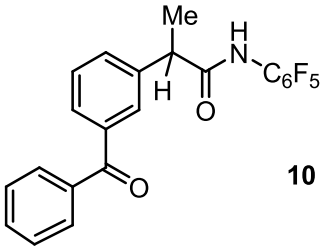

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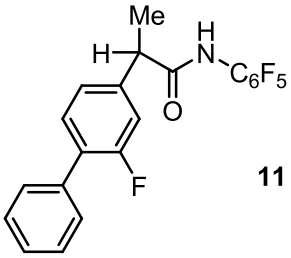

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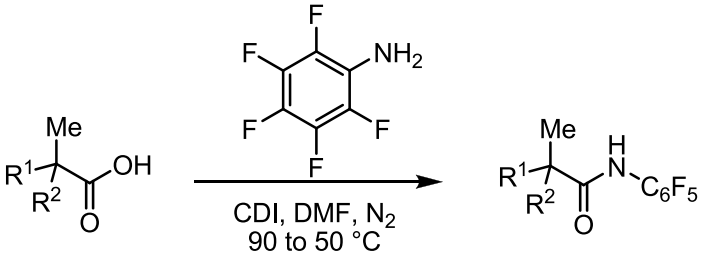
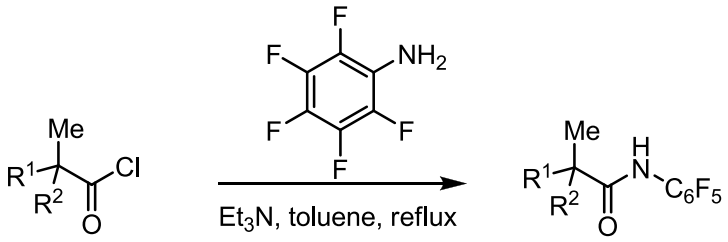
Experimental Section

A. Substrate Preparation

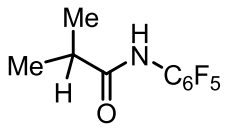


Preparation of Substrates 1, 3–6, 8–11:[1] A solution of acid (20 mmol) and CDI (22 mmol) in DMF (20 mL) was stirred at 90 °C for 1 h under a moisture-free atmosphere, then the reaction mixture was allowed to cool to room temperature. 2,3,4,5,6-pentafluoroaniline (22 mmol) was added and the reaction mixture was stirred at 50 °C for 10 h. After cooling to room temperature, CH_2Cl_2 (100 mL) was added, and the resulting

solution was washed successively with 50 mL of 1% aqueous Na_2CO_3, water, 1% HCl and again with water. The solvent was evaporated *in vacuo*, and resulting formed precipitate was filtered off, washed with ether, and dried. The products were recrystallized from toluene (100 °C to 0 °C).



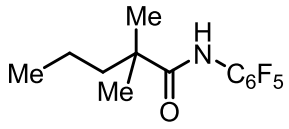
Preparation of Substrates 2 and 7:[2] An acid chloride (20 mmol), prepared from the corresponding carboxylic acid and oxalyl chloride, was added to a vigorously stirring solution of 2,3,4,5,6-pentafluoroaniline (22 mmol) and triethylamine (22 mmol) in toluene (50 mL). The reaction mixture was stirred for 6 h under reflux, and then stirred at room temperature for 4 h. The white precipitate was filtered off and washed with water, and recrystallized from toluene (100 °C to 0 °C) to give the product.



1

2-methyl-N-(perfluorophenyl)propanamide (1)

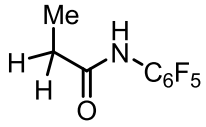
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (bs, 1H), 2.68–2.61 (m, 1H), 1.30 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.57, 35.54, 19.41.



2

2,2-dimethyl-N-(perfluorophenyl)pentanamide (2)

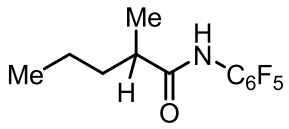
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (bs, 1H), 1.61–1.57 (m, 2H), 1.40–1.30 (m, 2H), 1.30 (s, 6H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.78, 43.62, 43.06, 25.28, 17.95, 14.40;



3

N-(perfluorophenyl)propanamide (3)

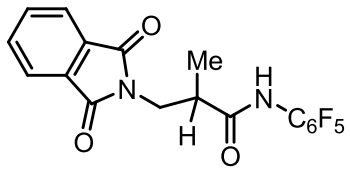
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (bs, 1H), 2.48 (q, *J* = 7.6 Hz, 2H), 1.69 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.79, 29.16, 9.34;



4

2-methyl-N-(perfluorophenyl)pentanamide (4)

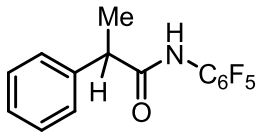
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (bs, 1H), 2.50–2.43 (m, 1H), 1.77–1.70 (m, 1H), 1.55–1.50 (m, 1H), 1.37–1.34 (m, 2H), 1.27 (d, *J* = 6.8 Hz, 3H), 0.914 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.39, 33.99, 29.41, 22.61, 17.73, 13.86;



5

2-methyl-3-(1,3-dioxoisoindolin-2-yl)-N-(perfluorophenyl)propanamide (5)

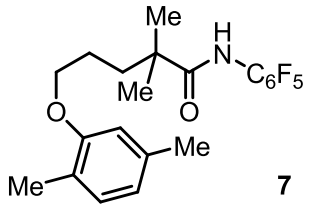
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.86 (m, 2H), 7.76–7.74 (m, 2H), 6.74 (bs, 1H), 4.10–4.04 (m, 1H), 3.83–3.80 (m, 1H), 3.21–3.16 (m, 1H), 3.16 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.96, 168.37, 134.31, 131.74, 123.53, 41.08, 40.09, 15.72.



6

N-(perfluorophenyl)-2-phenylpropanamide (6)

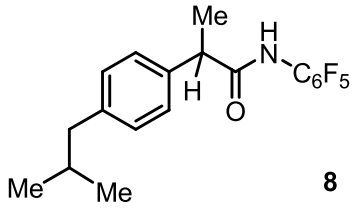
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H) 6.52 (bs, 1H), 3.83 (q, *J* = 7.2 Hz, 1H), 1.61 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.83, 140.19, 129.26, 127.84, 127.64, 47.00, 18.41;



7

2,2-dimethyl-6-(2,5-dimethylphenyl)-N-(perfluorophenyl)hexanamide (7)

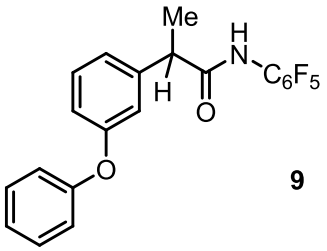
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 7.6 Hz, 1H), 6.91 (bs, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.62 (s, 1H), 3.97 (t, *J* = 5.2 Hz, 2H), 2.30 (s, 3H), 2.15 (s, 3H), 1.87–1.85 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.15, 156.73, 136.59, 130.31, 123.40, 120.87, 112.08, 67.65, 42.91, 37.58, 25.55, 25.01, 21.33, 15.70.



8

2-(4-isobutylphenyl)-N-(perfluorophenyl)propanamide (8)

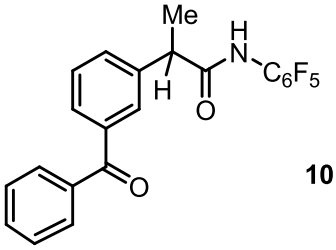
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.52 (bs, 1H), 3.80 (q, *J* = 7.2 Hz, 1H), 2.48 (d, *J* = 7.2 Hz, 2H), 1.92–1.82 (m, 1H), 1.60 (d, *J* = 7.2 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.08, 141.46, 137.35, 129.99, 127.38, 46.67, 44.98, 30.15, 22.30, 18.32.



9

N-(perfluorophenyl)-2-(3-phenoxyphenyl)propanamide (9)

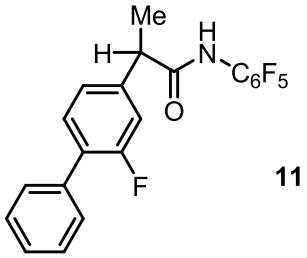
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (m, 3H), 7.14–6.95 (m, 6H), 6.55 (bs, 1H), 3.90 (q, *J* = 7.2 Hz, 1H), 1.59 (d, , *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.25, 158.22, 156.55, 142.10, 130.63, 129.88, 123.76, 122.17, 119.18, 117.85, 117.84, 46.93, 18.29;



10

2-(3-benzoylphenyl)-N-(perfluorophenyl)propanamide (10a)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.46 (m, 9H), 6.76 (bs, 1H), 3.91 (q, *J* = 6.8 Hz, 1H), 1.63 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.75, 172.22, 144.32, 141.79, 140.93, 138.91, 138.21, 137.15, 136.40, 129.96, 129.13, 129.08, 128.38, 128.30, 46.76, 18.67;



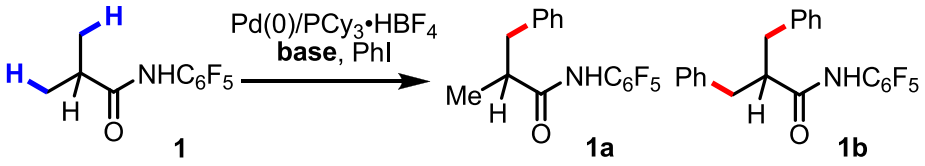
11

2-(2-fluorobiphenyl-4-yl)-N-(perfluorophenyl)propanamide (11)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.37 (m, 6H), 7.23–7.17 (m, 2H), 6.63, (bs, 1H), 3.86 (q, *J* = 6.8 Hz, 1H), 1.65 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.10, 161.17, 158.69, 141.36, 131.50, 131.46, 128.90, 128.87, 128.51, 127.90, 123.61, 123.58, 115.54, 115.30, 46.47, 18.51.

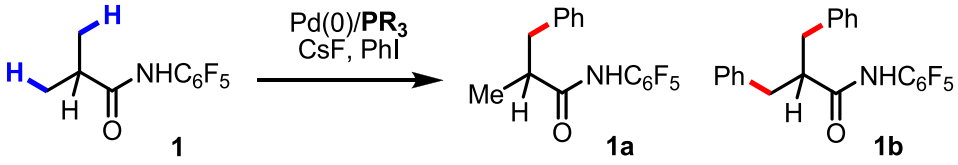
B. Palladium(0)-catalyzed arylation of sp^3 C–H bonds (1a–11a)

Optimization of reaction conditions [a]

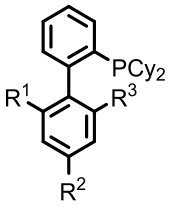


entry	base	^{1}H NMR yield (%) 1a	1b
1	NaOAc	0	0
2	K_2CO_3	2	0
3	KO^{t}Bu	0	0
4	K_2HPO_4	4	0
5	NaOH	0	0
6	Cs_2CO_3	15	2
7	CsOAc	8	0
8	CsF	42	20

[a] Conditions: 0.2 mmol of substrate, 10 mol% $Pd(OAc)_2$, 20 mol% ligand, 3.0 equiv of base, 3.0 equiv of aryl iodide, 100 mg 3Å MS, 1 mL toluene, 100 °C, N_2, 24 h.



entry	PR_3	^{1}H NMR yield (%) 1a	1b	entry	PR_3	^{1}H NMR yield (%) 1a	1b
1	PPh_3	3	0	10	$PAd_2{}^nBu•HBF_4$	0	0
2	$P(p\text{-Tol})_3$	2	0	11	$PCy_2(o\text{-Tol})•HBF_4$	0	0
3	$P^iPr_3•HBF_4$	36	18	12	Cy-JohnPhos•HBF_4	34	54
4	$PCy_3•HBF_4$	42	20	13	MePhos•HBF_4	38	53
5	$P^tBu_3•HBF_4$	0	0	14	DavePhos•HBF_4	48	18
6	$P^tBu_2Me•HBF_4$	0	0	15	SPhos•HBF_4	11	0
7	$PCy_2{}^tBu•HBF_4$	8	0	16	RuPhos•HBF_4	5	0
8	$PPhEt_2•HBF_4$	10	0	17	XPhos•HBF_4	0	0
9	$PPhHex_2•HBF_4$	7	0				



Cy-JohnPhos: $R^1=R^2=R^3=H$

MePhos: $R^1=R^2=H$, $R^3=Me$

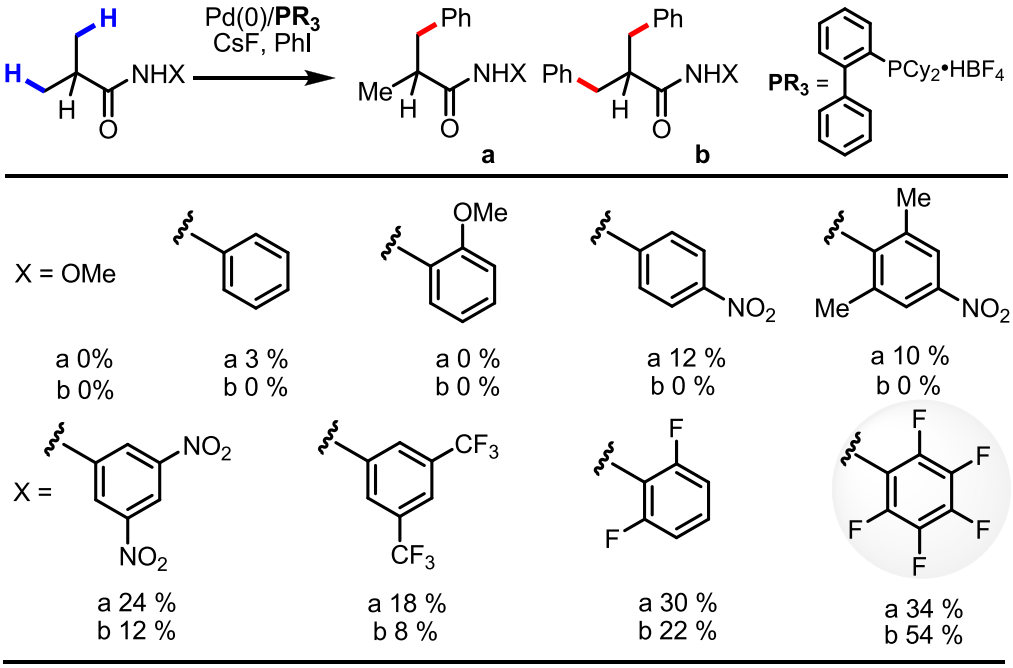
DavePhos: $R^1=R^2=H$, $R^3=NMe_2$

SPhos: $R^1=R^3=OMe$, $R^2=H$

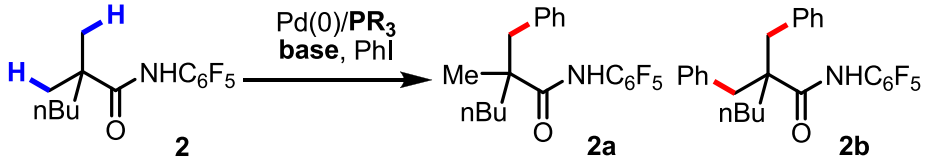
RuPhos: $R^1=R^3=O^iPr$, $R^2=H$

XPhos: $R^1=R^2=R^3={}^i$Pr

[a] Conditions: 0.2 mmol of substrate, 10 mol% $Pd(OAc)_2$, 20 mol% ligand, 3.0 equiv of CsF, 3.0 equiv of aryl iodide, 100 mg 3Å MS, 1 mL toluene, 100 °C, N_2, 24 h.



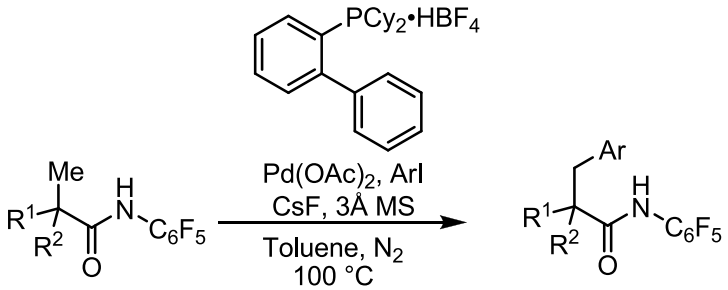
[a] Conditions: 0.2 mmol of substrate, 10 mol% $Pd(OAc)_2$, 20 mol% Ligand, 3.0 equiv of CsF, 3.0 equiv of aryl iodide, 100 mg 3Å MS, 1 mL toluene, 100 °C, N_2, 24 h.



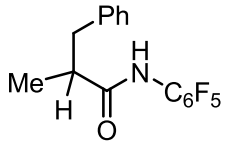
entry	PR_3	base	^{1}H NMR yield (%) 2a	2b
1	PPh_3	Cs_2CO_3	22	12
2	PCy_3•HBF_4	Cs_2CO_3	41	7
3	Cy-JohnPhos•HBF4	Cs_2CO_3	72	8

[a] Conditions: 0.2 mmol of substrate, 10 mol% $Pd(OAc)_2$, 20 mol% Ligand, 3.0 equiv of Cs_2CO_3, 3.0 equiv of aryl iodide, 100 mg 3Å MS, 1 mL toluene, 100 °C, N_2, 24 h.

General Reaction Scheme



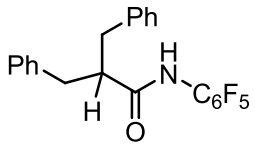
General Procedure: Substrate (0.2 mmol), $Pd(OAc)_2$ (10 mol%), Cyclohexyl JohnPhos (10 mol%), CsF (3.0 equiv), and flame-dried molecular sieves (100 mg) were weighed in air and placed in a Schlenk tube (25 mL) with a magnetic stir bar. Aryl iodide (2–3 equiv) and toluene (1 mL) were added, and the reaction vessel was immediately evacuated and backfilled with nitrogen (×3). The reaction mixture was heated to 100 °C for 24 hours under vigorous stirring. Upon completion, the reaction was cooled to room temperature and filtered through a pad of celite. The solvents were removed under reduced pressure and the resulting mixture was purified by a silica gel-packed flash chromatography column typically using hexane/ether mixtures as the eluent.



1a

2-methyl-N-(perfluorophenyl)-3-phenylpropanamide (1a)

Substrate **1** was arylated following the general procedure. After purification by column chromatography, **1a** was obtained as a colorless solid (19.8 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.10 (m, 5H), 6.72 (bs, 1H), 3.10–2.97 (m, 1H), 2.83–2.71 (m, 2H), 1.31 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.70, 139.29, 129.18, 128.95, 126.99, 44.07, 40.68, 18.14; IR (neat) ν 3256, 2927, 1682, 1498 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{16}H_{12}F_5NO$ (MH^+): 330.0912; found: 330.0907.

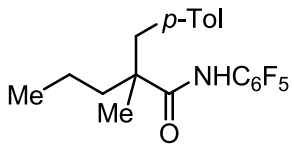


1b

2-benzyl-N-(perfluorophenyl)-3-phenylpropanamide (1b)

Substrate **1** was arylated following the general procedure. After purification by column chromatography, **1a** was obtained as a colorless solid (43.0 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.20 (m, 8H), 6.12 (bs, 1H), 3.12–3.05 (m, 2H), 2.95–2.79 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.17, 139.16, 129.18, 129.03, 127.06, 53.38, 39.54; IR (neat)

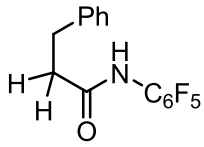
ν 3231, 2919, 1674, 1526, 1450 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{22}H_{16}F_5NO$ (MH^+): 406.1225; found: 406.1235.



2a

2-methyl-2-(4-methylbenzyl)-N-(perfluorophenyl)pentanamide (2a)

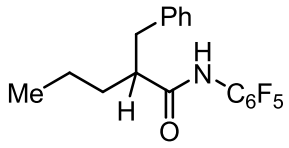
Substrate **2** was arylated following the general procedure. After purification by column chromatography, **2a** was obtained as a colorless solid (45.9 mg, 78%). Di-arylated product was observed by ^1H NMR (ca. 10%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.09–7.02 (m, 4H), 6.72 (bs, 1H), 3.13 (d, *J* = 13.2 Hz, 2H), 2.66 (d, *J* = 13.2 Hz, 2H), 2.31 (s, 3H) 1.90–1.76 (m, 1H), 1.49–1.21 (m, 6H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.56, 136.45, 134.08, 130.30, 129.07, 104.99, 48.39, 46.00, 43.01, 25.63, 20.79, 17.98, 14.74; IR (neat) ν 3275, 2962, 1671, 1522, 1490 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{20}H_{20}F_5NO$ (MH^+): 385.1465; found: 385.1470.



3a

N-(perfluorophenyl)-3-phenylpropanamide (3a)

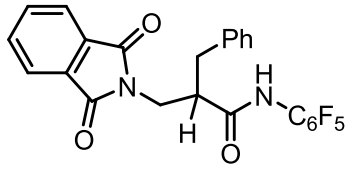
Substrate **3** was arylated following the general procedure. After purification by column chromatography, **3a** was obtained as a colorless solid (36.7 mg, 58%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.20 (m, 4H), 6.89 (bs, 1H), 3.05 (t, *J* = 7.6 Hz, 2H), 2.75 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.10, 143.30, 129.03, 128.62, 126.90, 38.26, 31.64; IR (neat) ν 3264, 2921, 1680, 1530, 1495 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{15}H_{10}F_5NO$ (MH^+): 316.0755; found: 316.0755.



4a

2-benzyl-N-(perfluorophenyl)pentanamide (4a)

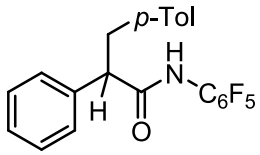
Substrate **4** was arylated following the general procedure. After purification by column chromatography, **4a** was obtained as a colorless solid (59.4 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.15 (m, 4H), 6.49 (bs, 1H), 2.95–2.82 (m, 1H), 2.82–2.80 (m, 1H), 2.61–2.54 (m, 1H), 2.04–1.99 (m, 1H), 1.88–1.68 (m, 1H), 1.53–1.32 (m, 4H), 0.93 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.59, 139.50, 129.14, 128.98, 126.94, 105.13, 44.18, 39.73, 36.19, 33.13, 22.99, 14.25; IR (neat) ν 3274, 2901, 1650, 1520 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{19}H_{18}F_5NO$ (MH^+): 371.1309; found: 371.1310.



5a

2-benzyl-3-(1,3-dioxoisoindolin-2-yl)-N-(perfluorophenyl)propanamide (5a)

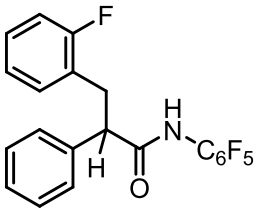
Substrate **5** was arylated following the general procedure. After purification by column chromatography, **5a** was obtained as a colorless solid (60.7 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.73 (m, 4H), 7.30–7.16 (m, 4H), 6.74 (bs, 1H), 4.18–4.13 (m, 1H), 3.92–3.86 (m, 1H), 3.51–3.39 (m, 1H), 3.15–3.09 (m, 1H), 2.96–2.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.19, 168.62, 138.08, 134.61, 134.60, 129.11, 127.24, 123.82, 48.14, 40.61, 37.15; IR (neat) ν 3268, 2918, 2850, 1716, 1522, 1495 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{24}H_{15}F_5N_2O$ (MH^+): 475.1076; found: 475.1075.



6a

N-(perfluorophenyl)-2-phenyl-3-p-tolylpropanamide (6a)

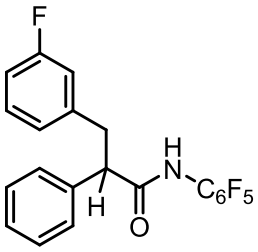
Substrate **6** was arylated following the general procedure. After purification by column chromatography, **6a** was obtained as a colorless solid (68.2 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.28 (m, 5H), 7.12–7.02 (m, 4H), 6.59 (s, 1H), 3.86 (t, *J* = 8.0 Hz, 1H), 3.60–3.53 (m, 1H), 3.05–2.99 (m, 1H), 2.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.80, 138.81, 136.31, 136.10, 131.34, 129.43, 129.19, 128.50, 128.22, 55.81, 39.46, 21.37; IR (neat) ν 3247, 3027, 2923, 1677, 1651, 1523, 1458 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{21}H_{13}F_6NO$ (MH^+): 410.0974; found: 410.0985.



6b

3-(2-fluorophenyl)-N-(perfluorophenyl)-2-phenylpropanamide (6b)

Substrate **6** was arylated following the general procedure. After purification by column chromatography, **6b** was obtained as a colorless solid (56.0 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–6.94 (m, 9H), 6.70 (s, 1H), 4.00 (t, *J* = 8.0 Hz, 1H), 3.63–3.53 (m, 1H), 3.16–3.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.54, 162.78, 160.35, 138.51, 129.41, 128.65, 128.29, 125.88, 124.31, 115.58, 115.36, 53.58, 33.63; IR (neat) ν 3250, 2923, 1677, 1523, 1498 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{21}H_{13}F_6NO$ (MH^+): 410.0974; found: 410.0966.

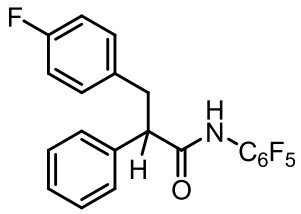


6c

3-(3-fluorophenyl)-N-(perfluorophenyl)-2-phenylpropanamide (6c)

Substrate **6** was arylated following the general procedure. After purification by column chromatography, **6c** was obtained as a colorless solid (59.0 mg, 72%). ^{1}H NMR (400 MHz,

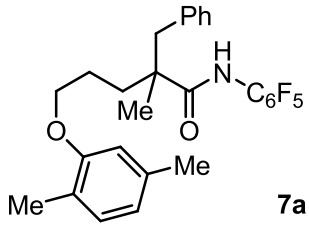
$CDCl_3$) δ 7.43–7.28 (m, 5H), 7.12–7.02 (m, 4H), 6.59 (s, 1H), 3.86 (t, *J* = 8.0 Hz, 1H), 3.60–3.53 (m, 1H), 3.05–2.99 (m, 1H), 2.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.50, 164.31, 161.87, 141.75, 141.68, 138.32, 129.55, 128.42, 125.05, 116.30, 116.09, 113.85, 113.64, 55.32, 39.52; IR (neat) ν 3250, 2923, 1677, 1523, 1498 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{21}H_{13}F_6NO$ (MH^+): 410.0974; found: 410.0966.



6d

3-(4-fluorophenyl)-N-(perfluorophenyl)-2-phenylpropanamide (6d)

Substrate **6** was arylated following the general procedure. After purification by column chromatography, **6d** was obtained as a colorless solid (54.1 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5H), 7.08–7.05 (m, 2H), 6.95–6.75 (m, 2H), 6.59 (bs, 1H), 3.87 (t, *J* = 8.0 Hz, 1H), 3.60–3.55 (m, 1H), 3.08–2.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.61, 163.19, 160.76, 138.42, 134.84, 130.89, 128.50, 128.40, 115.62, 115.41, 55.76, 39.03; IR (neat) ν 3250, 2923, 1677, 1523, 1498 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{21}H_{13}F_6NO$ (MH^+): 410.0974; found: 410.0970.

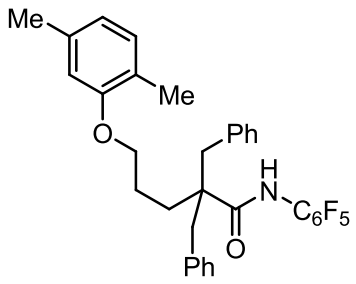


7a

2-benzyl-6-(2,5-dimethylphenyl)-2-methyl-N-(perfluorophenyl)hexanamide (7a)

Substrate **7** was arylated following the general procedure. After purification by column chromatography, **7a** was obtained as a colorless solid (59.0 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.30–7.24 (m, 5H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.77 (s, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 3.99 (t, *J* = 6.0 Hz, 3H), 3.16 (d, *J* = 13.2 Hz, 2H), 2.80 (d, *J* = 13.2 Hz, 2H), 2.80 (s, 3H), 2.10 (s, 3H) 1.98–1.40 (m, 6H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.36, 157.02, 137.08, 136.95, 130.68, 130.58, 127.15, 123.78, 121.27, 112.50, 92.57,

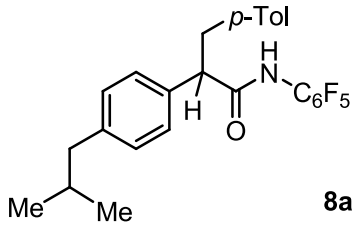
67.98, 48.25, 46.67, 36.62, 25.07, 21.47, 16.06; IR (neat) ν 3296, 2924, 2869, 1675, 1523, 1490 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{27}H_{26}F_5NO_2$ (MH^+): 492.1956; found: 492.1959.



7b

2,2-dibenzyl-6-(2,5-dimethylphenyl)-N-(perfluorophenyl)hexanamide (7b)

Substrate **7** was arylated following the general procedure. After purification by column chromatography, **7b** was obtained as a colorless solid (25.0 mg, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.21 (m, 10H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.76–6.59 (m, 3H), 4.00 (t, *J* = 5.6 Hz, 2H), 3.27 (d, *J* = 13.6 Hz, 2H), 2.94 (d, *J* = 13.6 Hz, 2H), 2.28 (s, 3H), 2.20–2.08 (m, 2H), 1.96 (s, 3H), 1.87–1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.63, 156.76, 137.00, 136.96, 130.64, 130.64, 128.74, 127.21, 123.68, 121.48, 112.43, 105.12, 67.79, 42.92, 30.05, 28.48, 21.68, 16.07; IR (neat) ν 3299, 2924, 2856, 1676, 1523, 1453 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{33}H_{30}F_5NO_2$ (MH^+): 568.2269; found: 568.2269.

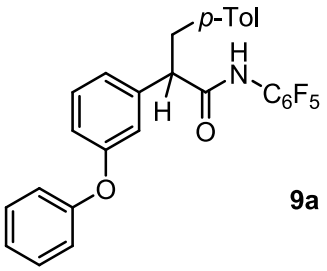


8a

2-(4-isobutylphenyl)-N-(perfluorophenyl)-3-p-tolylpropanamide (8a)

Substrate **8** was arylated following the general procedure. After purification by column chromatography, **8a** was obtained as a colorless solid (73.9 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–6.96 (m, 8H), 6.66 (s, 1H), 3.83 (t, *J* = 7.6 Hz, 1H), 3.54–3.50 (m, 1H), 3.01–2.98 (m, 1H), 2.47 (d, *J* = 7.2 Hz, 2H), 2.28 (s, 3H), 1.92–1.79 (m, 1H), 0.88 (d, *J* = 2.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.06, 141.75, 136.28, 136.21, 136.05, 130.12, 129.36, 129.21, 128.19, 55.43, 45.35, 39.42, 30.51, 22.36, 21.36; IR (neat) ν 3270,

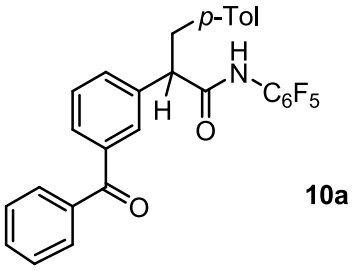
2957, 2926, 1683, 1523, 1487, 1450 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{26}H_{24}F_5NO$ (MH^+): 462.1851; found: 462.1850.



9a

N-(perfluorophenyl)-2-(3-phenoxyphenyl)-3-p-tolylpropanamide (9a)

Substrate **9** was arylated following the general procedure. After purification by column chromatography, **9a** was obtained as a colorless solid (67.7 mg, 68%). Due to difficulty of the separation between substrate and product, 32% of product was isolated as a mixture (ratio determined by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.38 (m, 6H), 7.12–6.96 (m, 7H), 6.69 (s, 1H), 4.84–4.52 (m, 1H), 3.90–3.71 (m, 1H), 3.38–3.24 (m, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.19, 156.54, 136.42, 136.10, 130.11, 129.83, 129.51, 129.09, 128.04, 127.83, 123.46, 119.23, 119.07, 112.27, 111.84, 37.60, 30.06, 21.35; IR (neat) ν 3269, 2920, 1683, 1523 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{28}H_{20}F_5NO_2$ (MH^+): 498.1414; found: 498.1414.

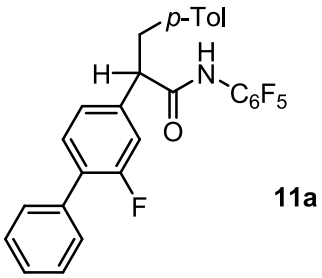


10a

2-(3-benzoylphenyl)-N-(perfluorophenyl)-3-p-tolylpropanamide (10a)

Substrate **10** was arylated following the general procedure. After purification by column chromatography, **10a** was obtained as a colorless solid (71.4 mg, 70%). Due to difficulty of the separation between substrate and product, 14% of product was isolated as a mixture (ratio determined by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.41 (m, 9H), 7.10 (s, 1H), 7.06–6.97 (m, 4H), 3.96 (t, J = 8.0 Hz, 1H), 3.56–3.51 (m, 1H), 3.07–3.01 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.93, 171.40, 138.26, 136.46, 135.65,

134.60, 132.11, 132.05, 130.41, 130.37, 129.89, 129.53, 129.44, 129.22, 128.86, 128.67, 55.47, 39.70, 21.39; IR (neat) ν 3271, 3059, 2922, 1658, 1522 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{29}H_{20}F_5NO_2$ (MH^+): 510.1487; found: 510.1495.



11a

2-(2-fluorobiphenyl-4-yl)-N-(perfluorophenyl)-3-p-tolylpropanamide (11a)

Substrate **11** was arylated following the general procedure. After purification by column chromatography, **11a** was obtained as a colorless solid (72.0 mg, 72%). Due to difficulty of the separation between substrate and product, 18% of product was isolated as a mixture (ratio determined by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.35 (m, 6H), 7.03–6.71 (m, 6H), 6.71, (s, 1H), 3.89 (t, *J* = 7.2 Hz, 1H), 3.56–3.52 (m, 1H), 3.09–3.03 (m, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.22, 161.38, 158.90, 140.11, 136.62, 135.63, 135.50, 131.53, 129.60, 129.28, 128.92, 128.84, 128.21, 124.32, 116.38, 55.28, 39.67, 21.38; IR (neat) ν 3256, 2923, 1678, 1523 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{28}H_{19}F_6NO$ (MH^+): 500.1444; found: 500.1440.

C. Amide Hydrolysis.

Acid-catalyzed hydrolysis:[3] MeI (0.24 mmol) and Na_2CO_3 (0.4 mmol) were added to a solution of **8** (0.2 mmol) in dichloromethane (1 mL), heated to 100 °C and stirred for 5 h. The reaction mixture was diluted with dichlomethane (10 mL), washed with 20 mL of saturated Na_2CO_3, 1 N HCl, and brine, and dried over Na_2SO_4. The crude product was concentrated under vacuum and dissolved in 3 N HCl/THF (1:1 mixture, 2 mL) and the solution was stirred at 50 °C for 24 h. The reaction mixture was extracted with ethyl ether, and the organic layer was washed with 1% Na_2CO_3 and brine, dried over Na_2SO_4, and concentrated under vacuum to give the carboxylic acid (33.4, 82%). The ^{1}H NMR spectrum was in agreement with those obtained using commercial ibuprofen.

Base-catalyzed hydrolysis:[4] KOH (2.0 mmol) was added to a solution of **8** (0.2 mmol) in ethylene glycol (1 mL). The mixture was heated to 80 °C and stirred for 8 h. After being cooled to room temperature, diethyl ether was added. The whole mixture was washed three times with a 3 N HCl, then once with brine. The organic phase was dried over Na_2SO_4 and concentrated under vacuum to give the carboxylic acid (36.3 mg, 88%). The ^{1}H NMR spectrum was in agreement with that obtained using commercial ibuprofen.

References:

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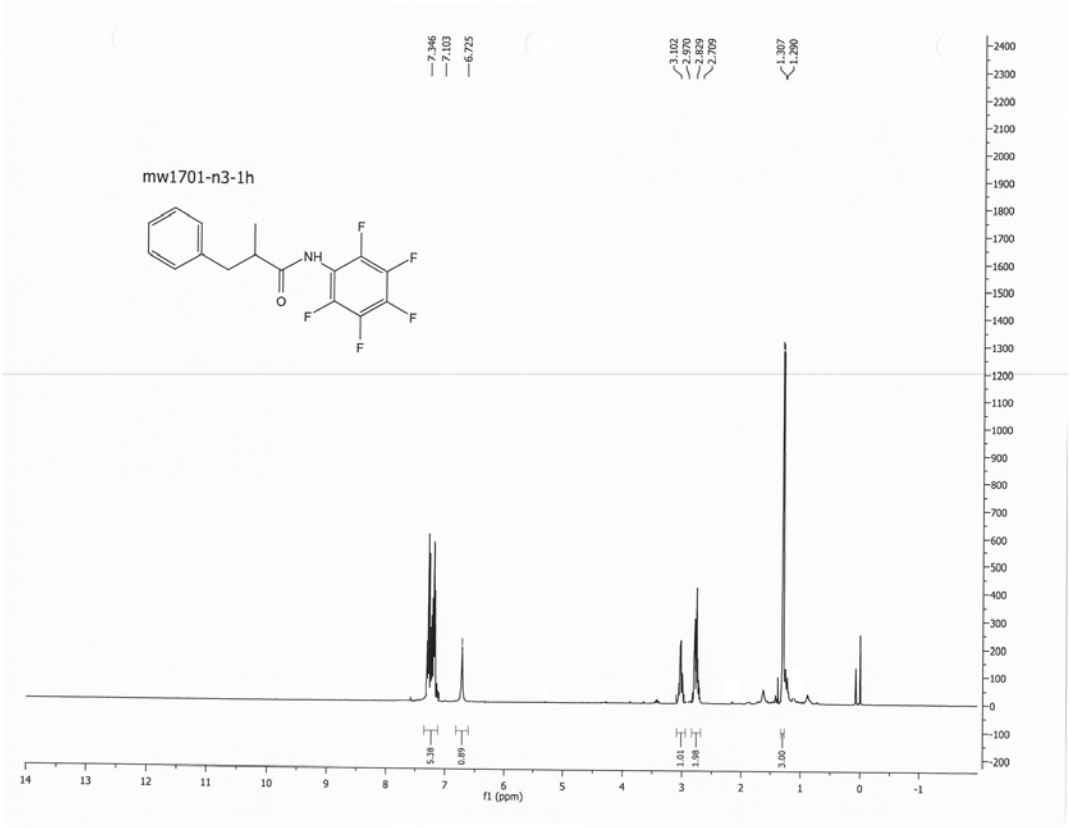
4. Ooi, T.; Fukumoto, K.; Maruoka, K. *Angew. Chem. Int. Ed.* **2006**, *118*, 3923.

1a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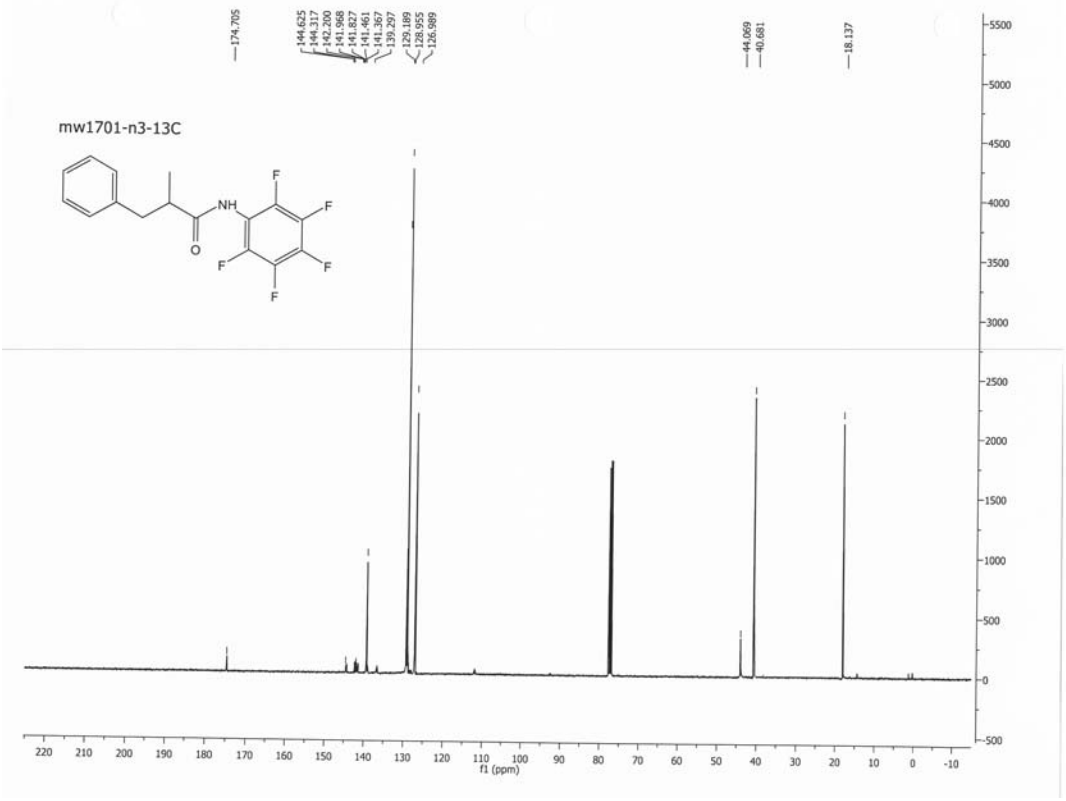
3.00
f1 (ppm)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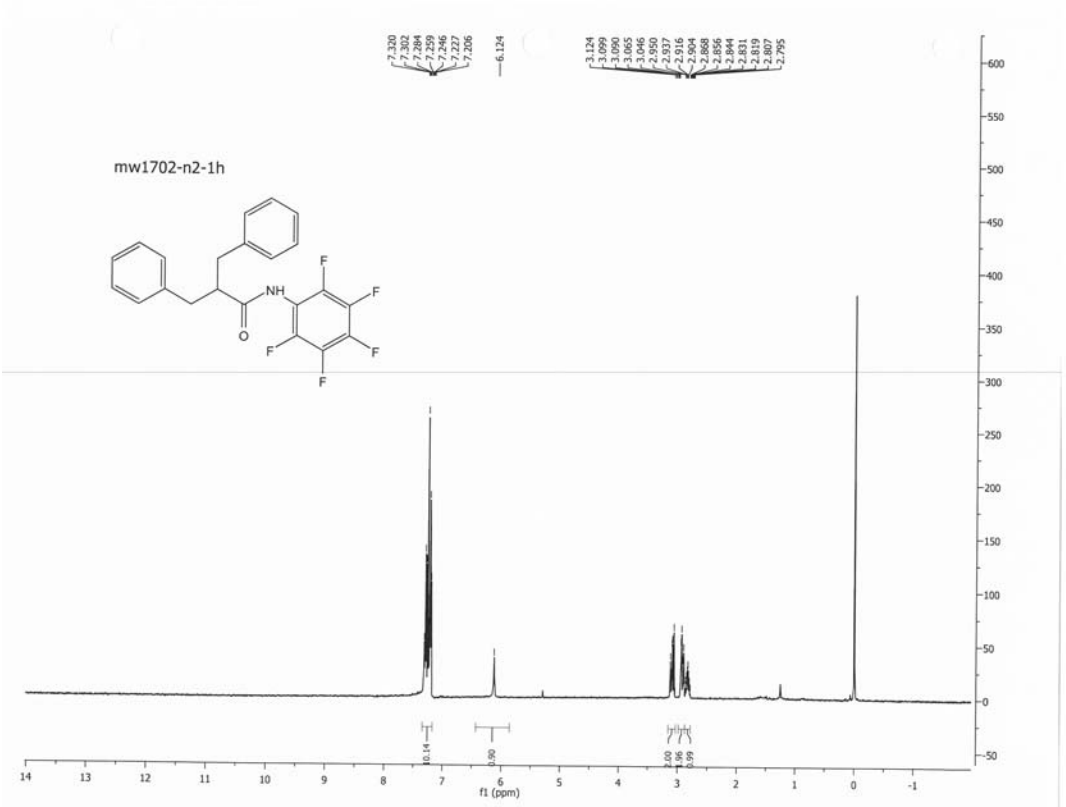
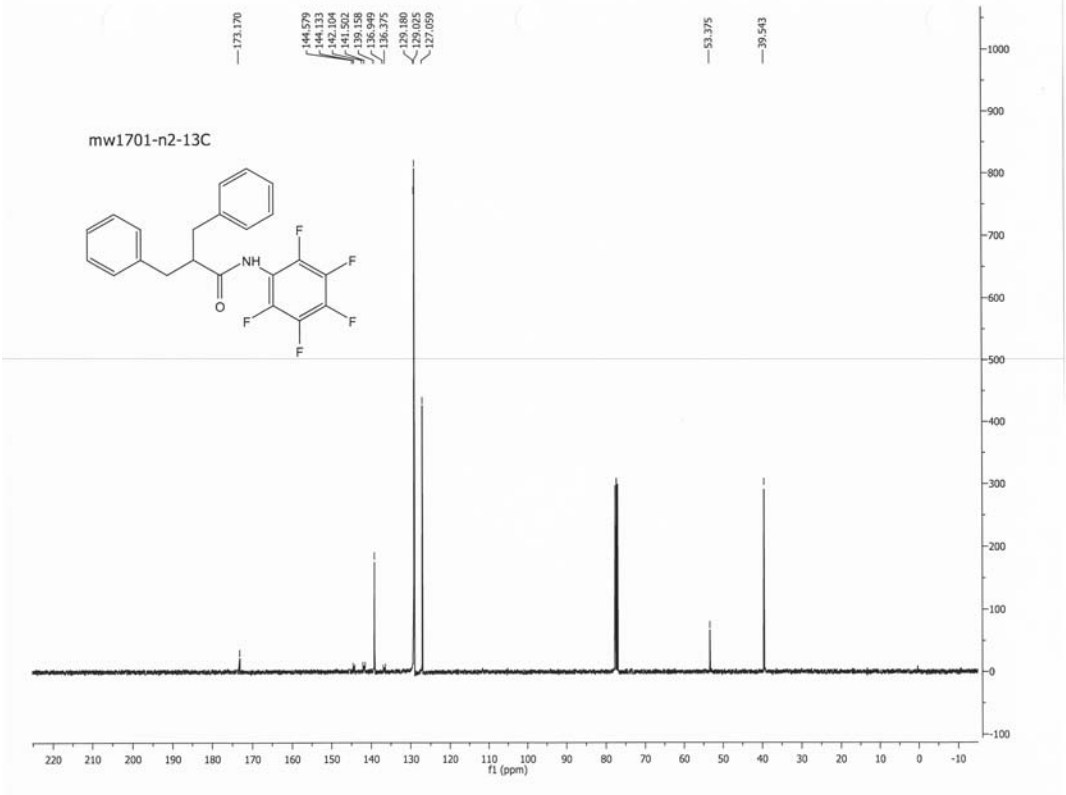
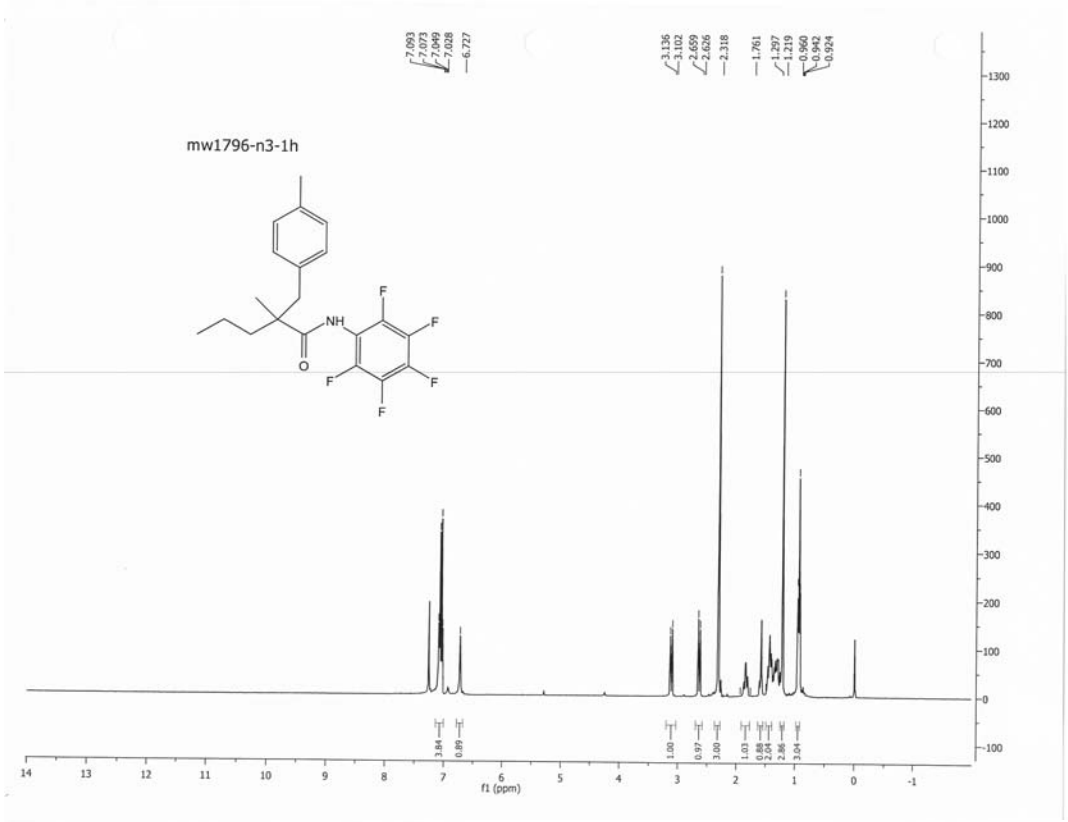
144.625
144.317
142.200
141.968
141.827
141.461
141.367
139.297
129.189
128.955
126.989
44.069
40.681
18.137
f1 (ppm)

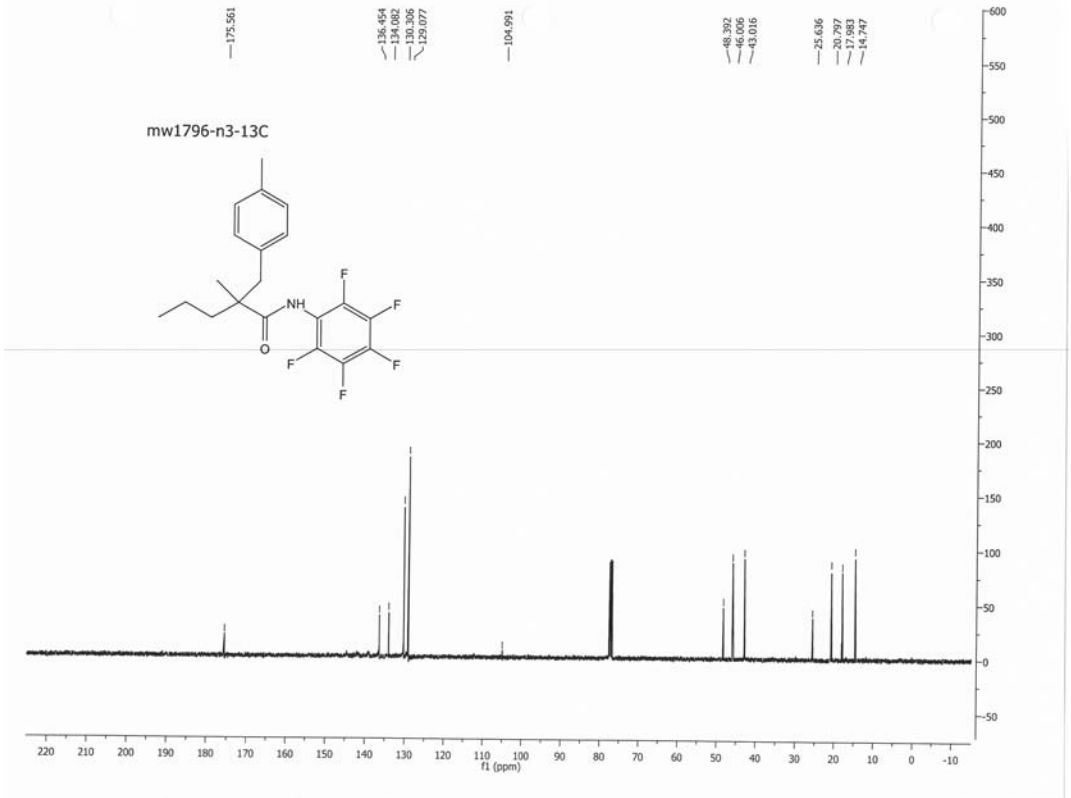
2a



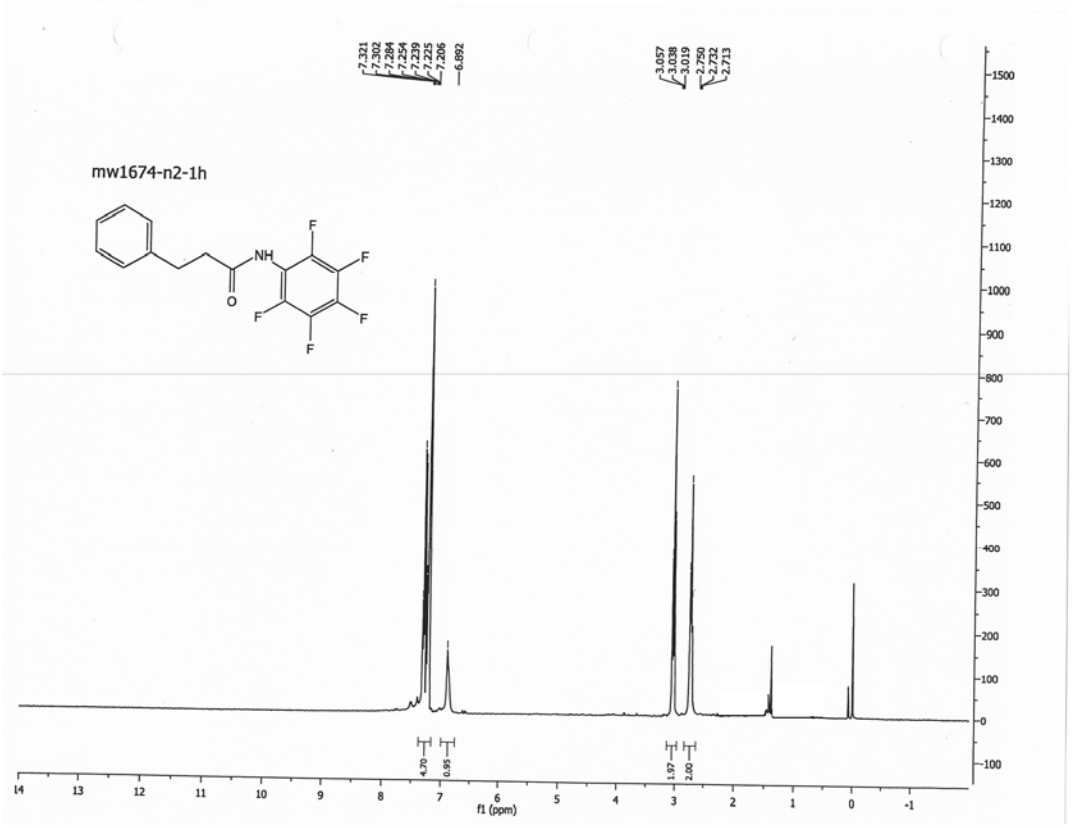


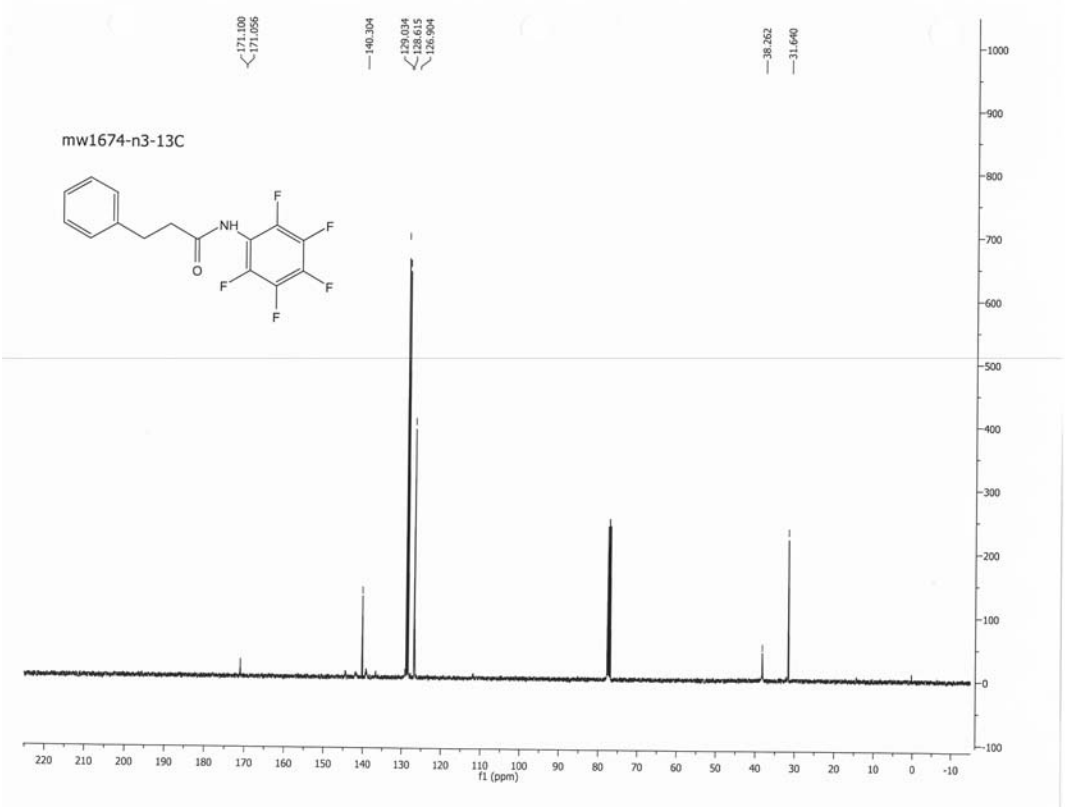
2a


mw1796-n3-1h
7.093
7.073
7.049
7.028
6.727
3.136
3.102
2.659
2.626
2.318
1.761
1.297
1.219
0.960
0.942
0.924
NH
O
F
f1 (ppm)

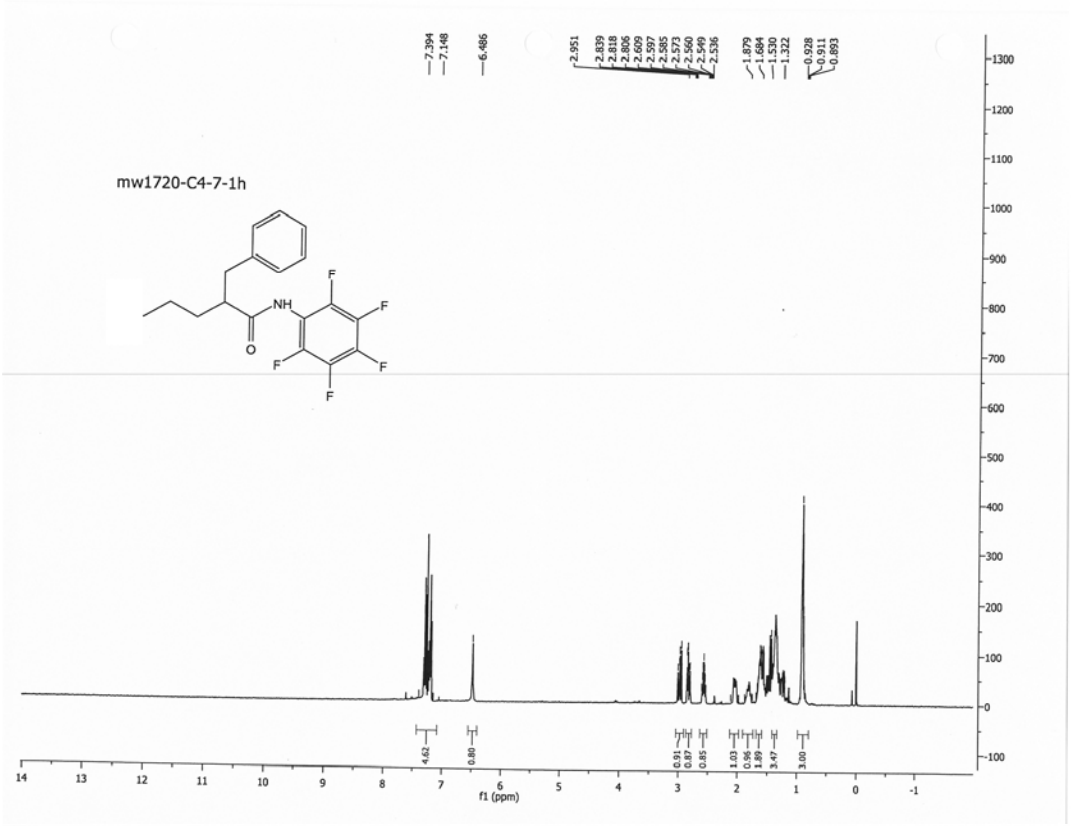

mw1796-n3-13C
175.561
136.454
134.082
130.306
129.077
104.991
48.302
46.006
43.016
25.636
20.797
17.983
14.747
NH
O
F
f1 (ppm)

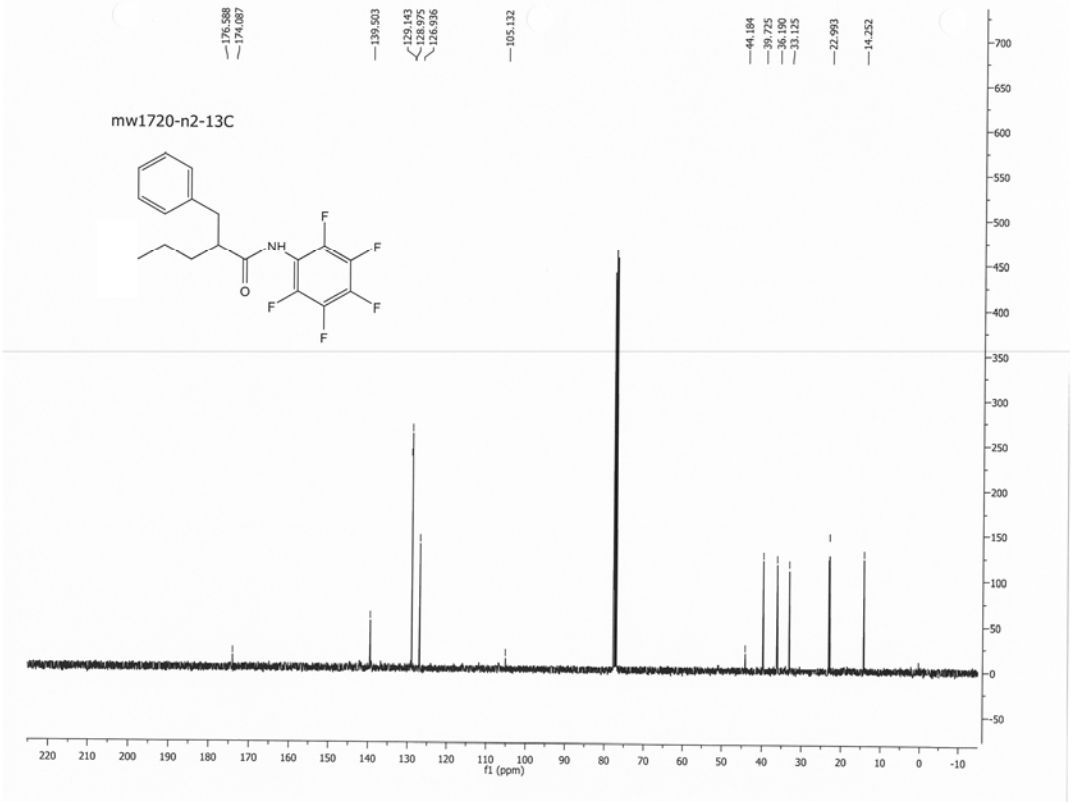
3a


7.321
7.302
7.284
7.254
7.239
7.225
7.206
6.892
3.057
3.038
3.019
2.750
2.732
2.713
mw1674-n2-1h
NH
O
F
F
F
F
F
4.70
0.95
1.97
2.00
f1 (ppm)

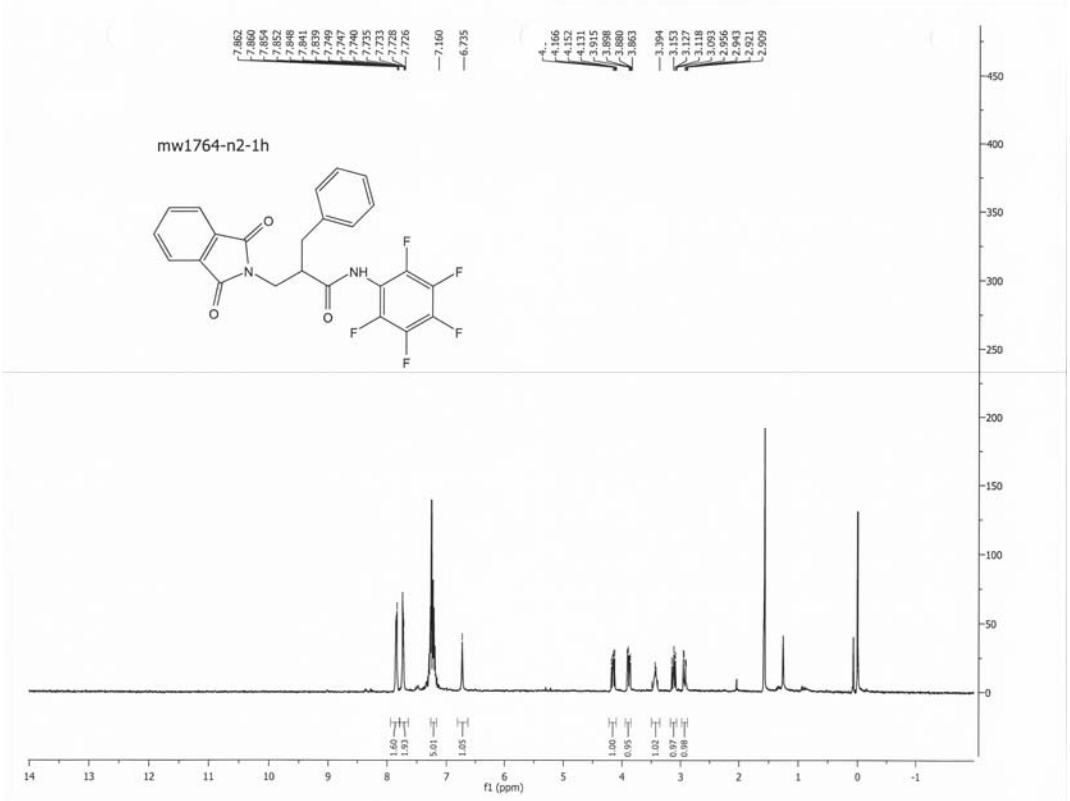

171.100
171.056
140.304
129.034
128.615
126.904
38.262
31.640
mw1674-n3-13C
NH
O
F
F
F
F
F
f1 (ppm)

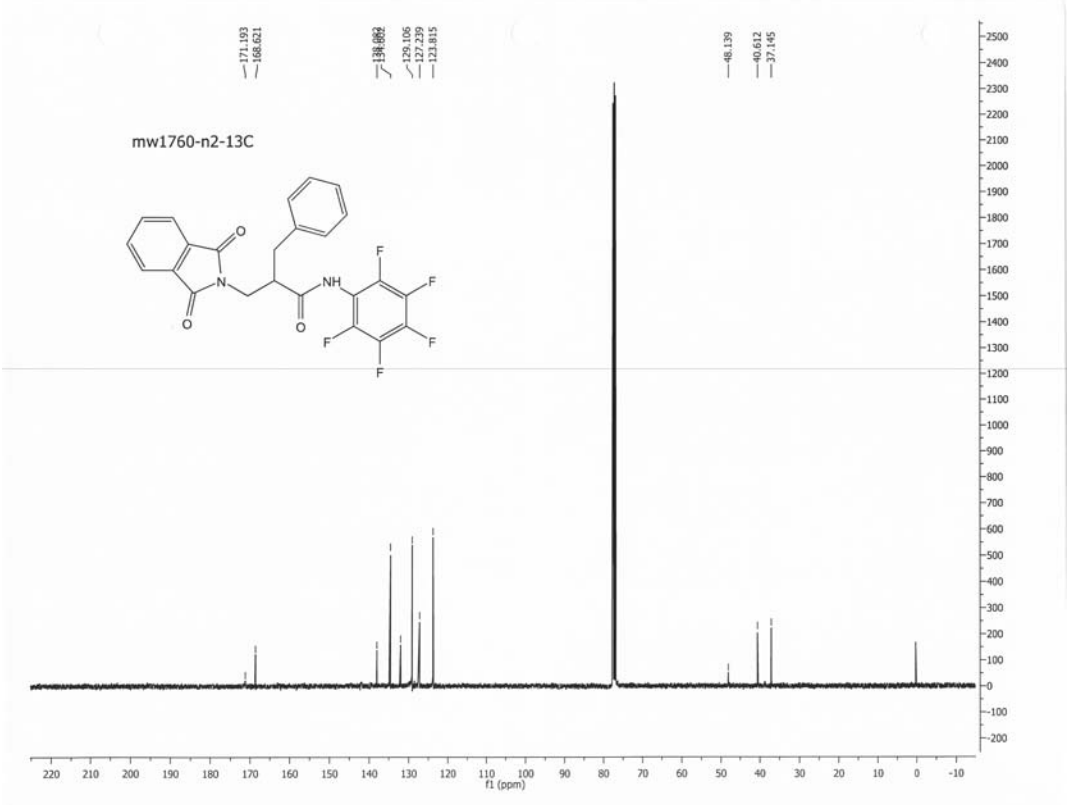
4a


mw1720-C4-7-1h
7.394
7.148
6.486
2.951
2.839
2.818
2.805
2.609
2.597
2.585
2.573
2.560
2.549
2.536
1.879
1.684
1.530
1.322
0.928
0.911
0.893
NH
O
F
F
F
F
F
4.62
0.80
0.91
0.87
0.85
1.03
0.96
1.89
3.47
3.00
f1 (ppm)

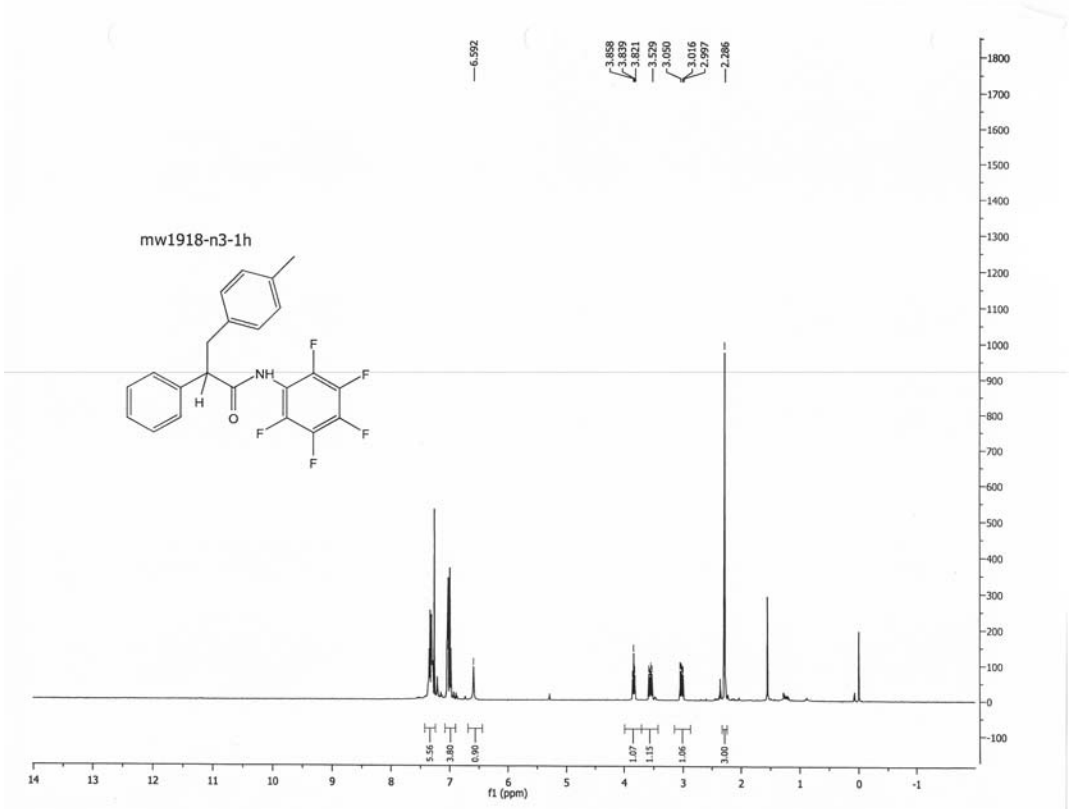

mw1720-n2-13C
176.588
174.087
139.503
129.143
128.975
126.936
105.132
44.184
39.725
36.190
33.125
22.993
14.252
NH
O
F
F
F
F
F
f1 (ppm)

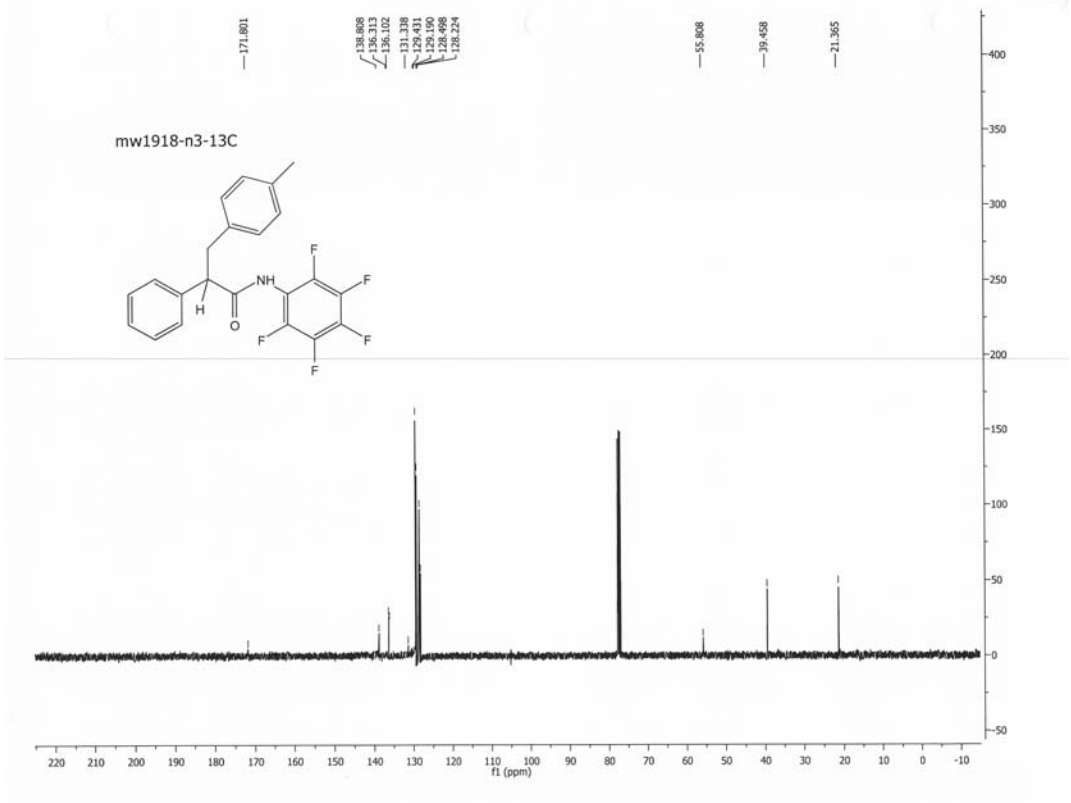
5a



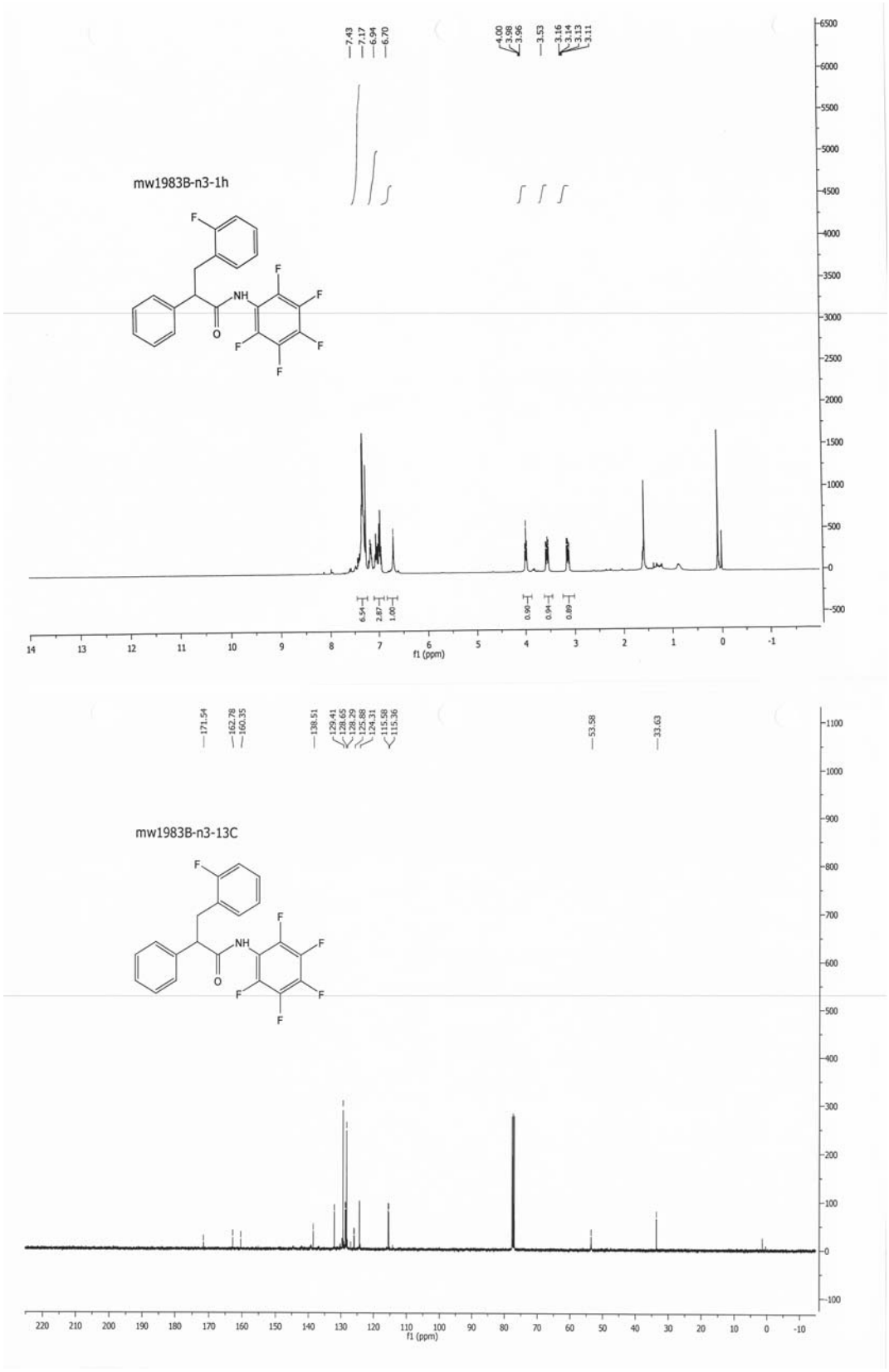


6a

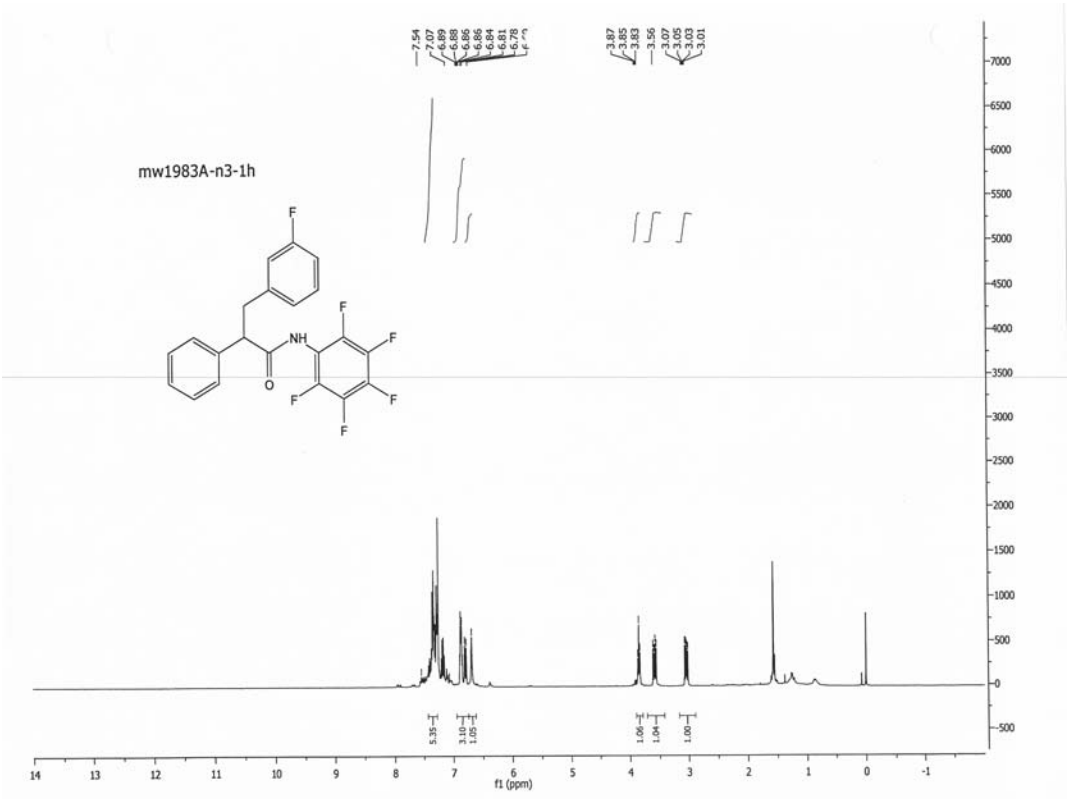

mw1918-n3-1h
6.592
3.858
3.839
3.821
3.529
3.050
3.016
2.997
2.286
5.56
3.80
0.90
1.07
1.15
1.06
3.00
f1 (ppm)

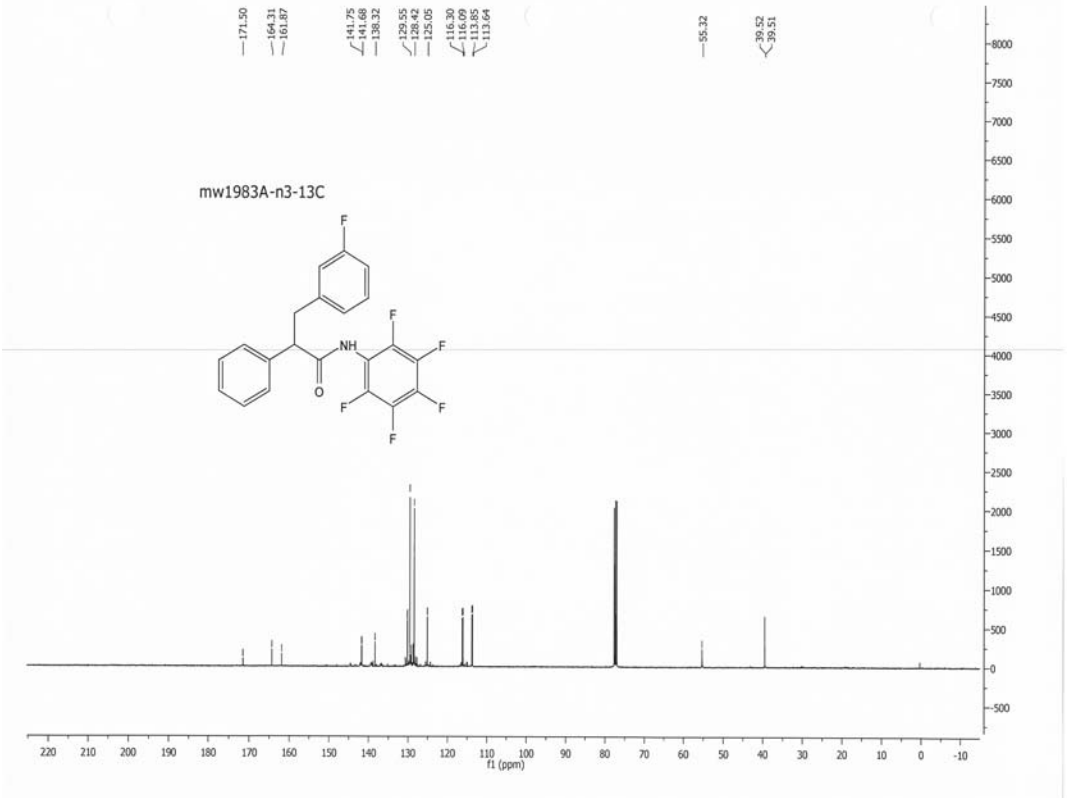

mw1918-n3-13C
171.801
138.808
136.313
136.102
131.338
129.431
129.190
128.498
128.224
55.808
39.458
21.365
f1 (ppm)

6b

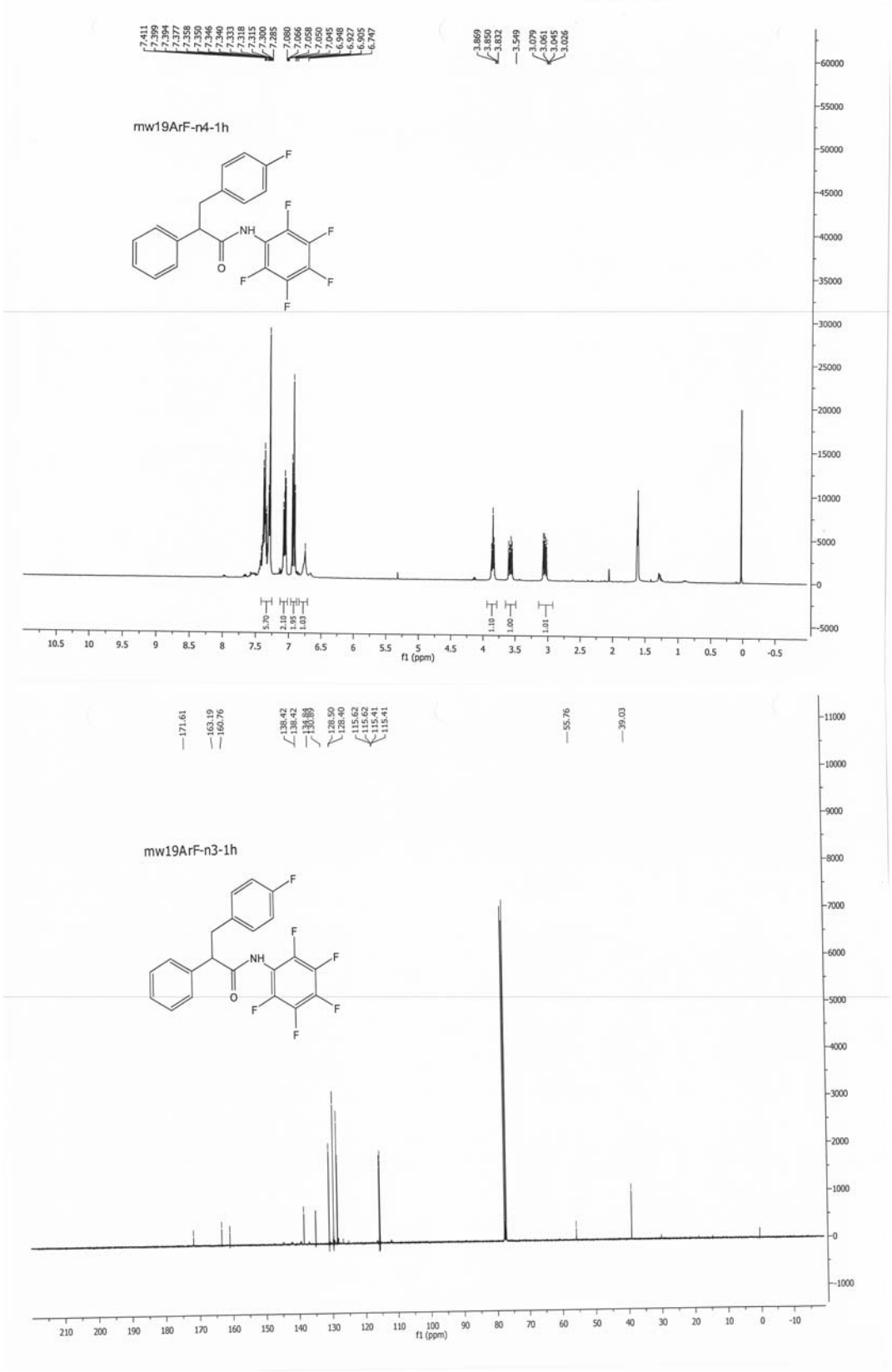

mw1983B-n3-1h
7.43
7.17
6.94
6.70
4.00
3.98
3.96
3.53
3.16
3.14
3.13
3.11
6.54
2.87
1.00
0.90
0.94
0.89
f1 (ppm)
mw1983B-n3-13C
171.54
162.78
160.35
138.51
129.41
128.65
128.29
125.88
124.31
115.58
115.36
53.58
33.63
f1 (ppm)

6c

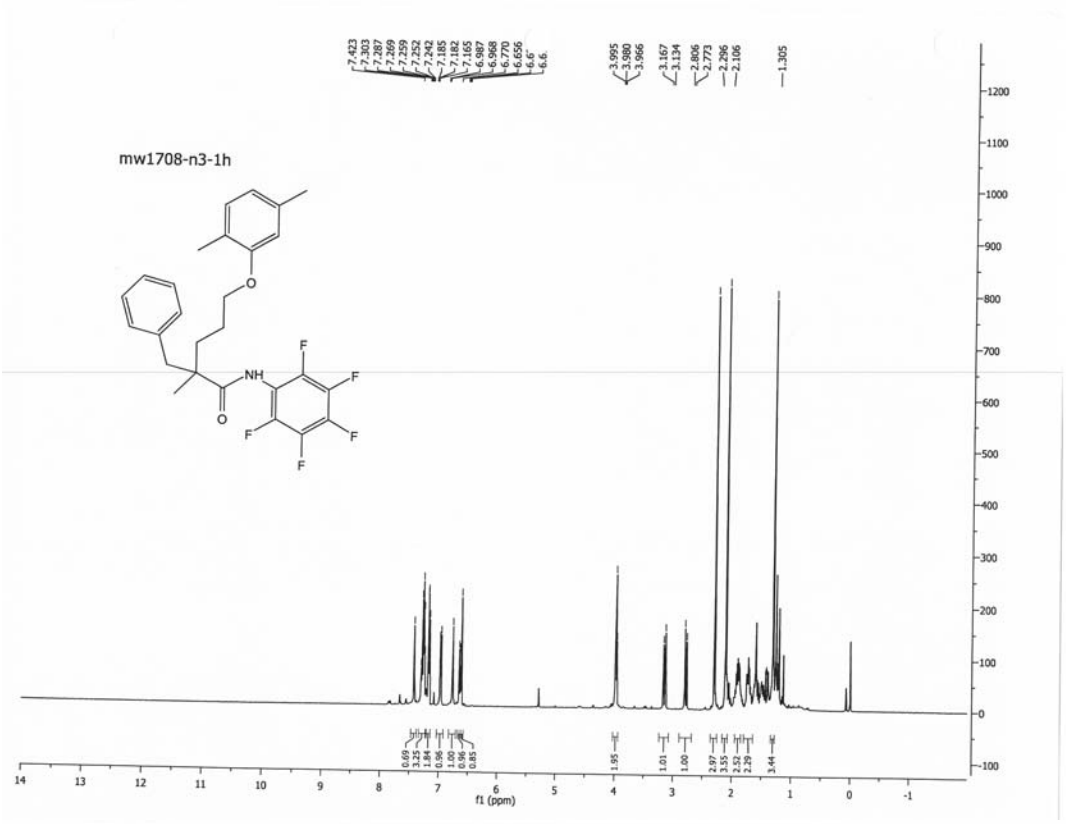

mw1983A-n3-1h
7.54
7.07
6.89
6.88
6.86
6.86
6.84
6.81
6.78
3.87
3.85
3.83
3.56
3.07
3.05
3.03
3.01
5.35
3.10
1.05
1.06
1.04
1.00
f1 (ppm)

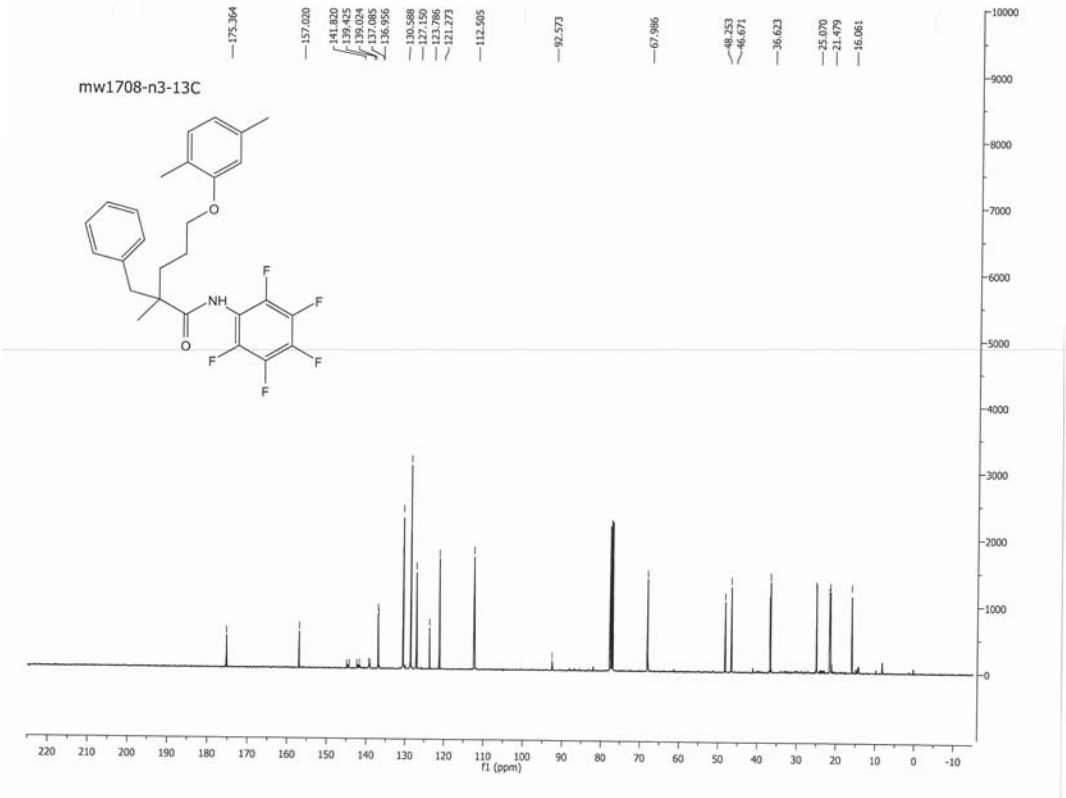

mw1983A-n3-13C
171.50
164.31
161.87
141.75
141.68
138.32
129.55
129.42
125.05
116.30
116.09
113.85
113.64
55.32
39.52
39.51
f1 (ppm)

6d

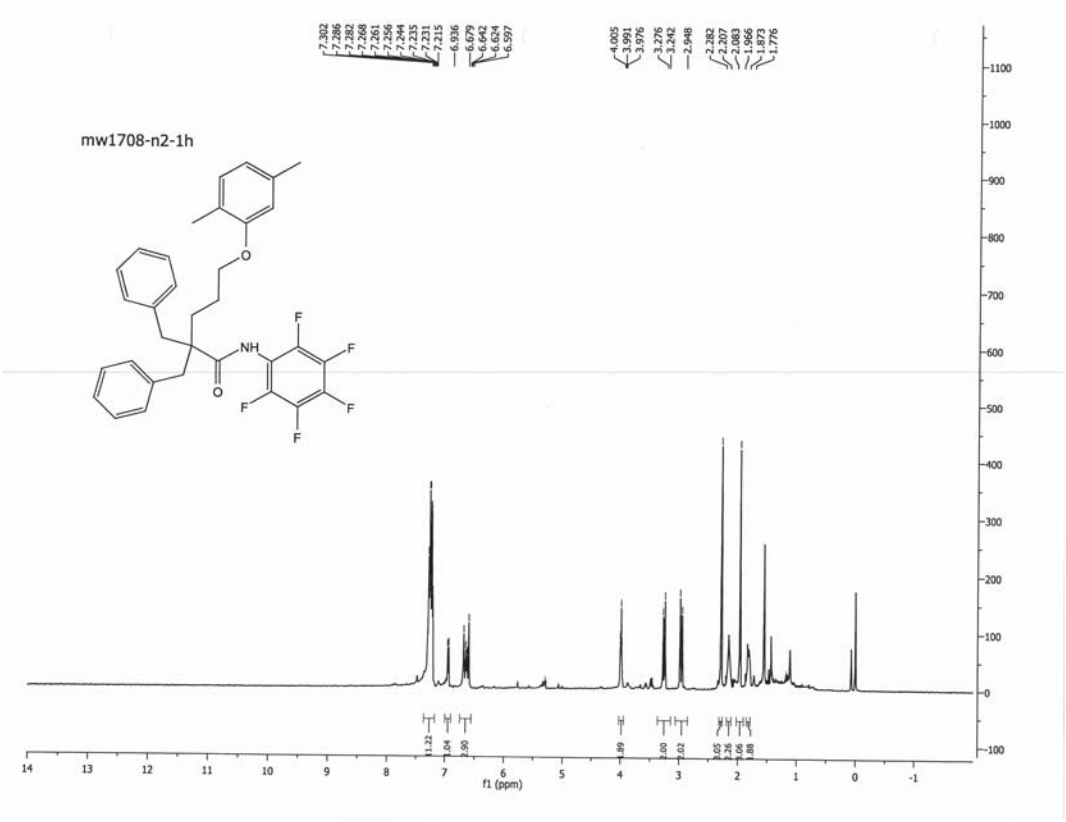


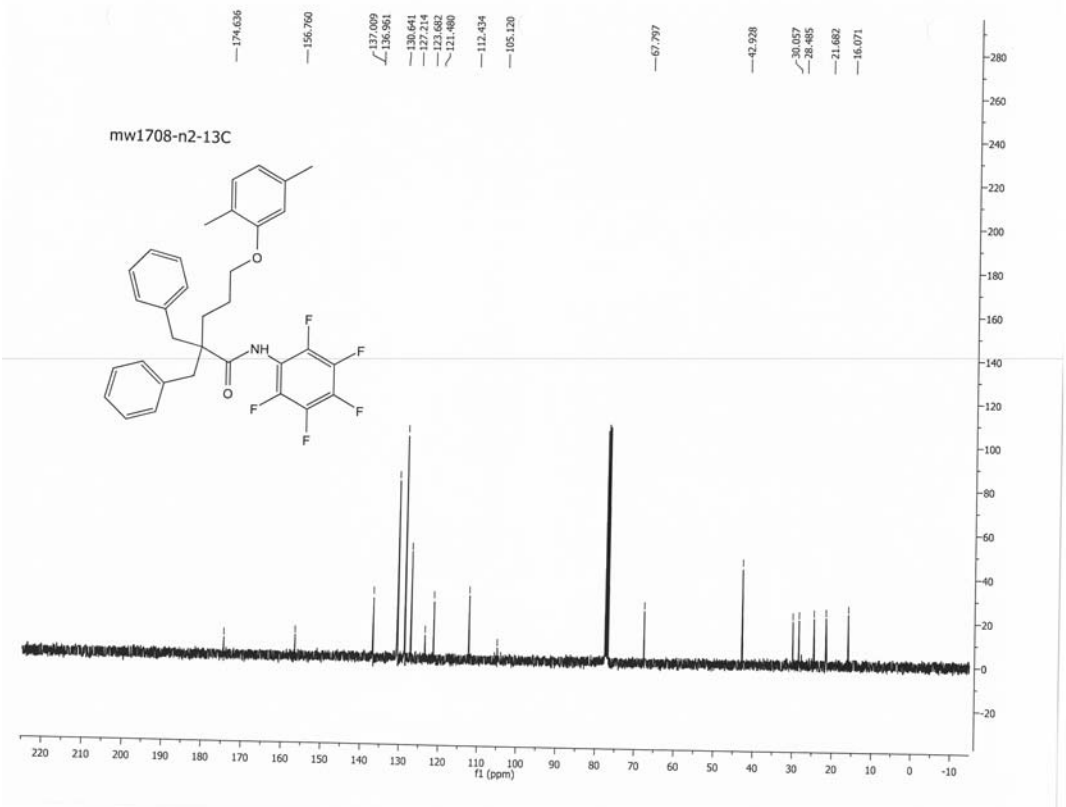
7a



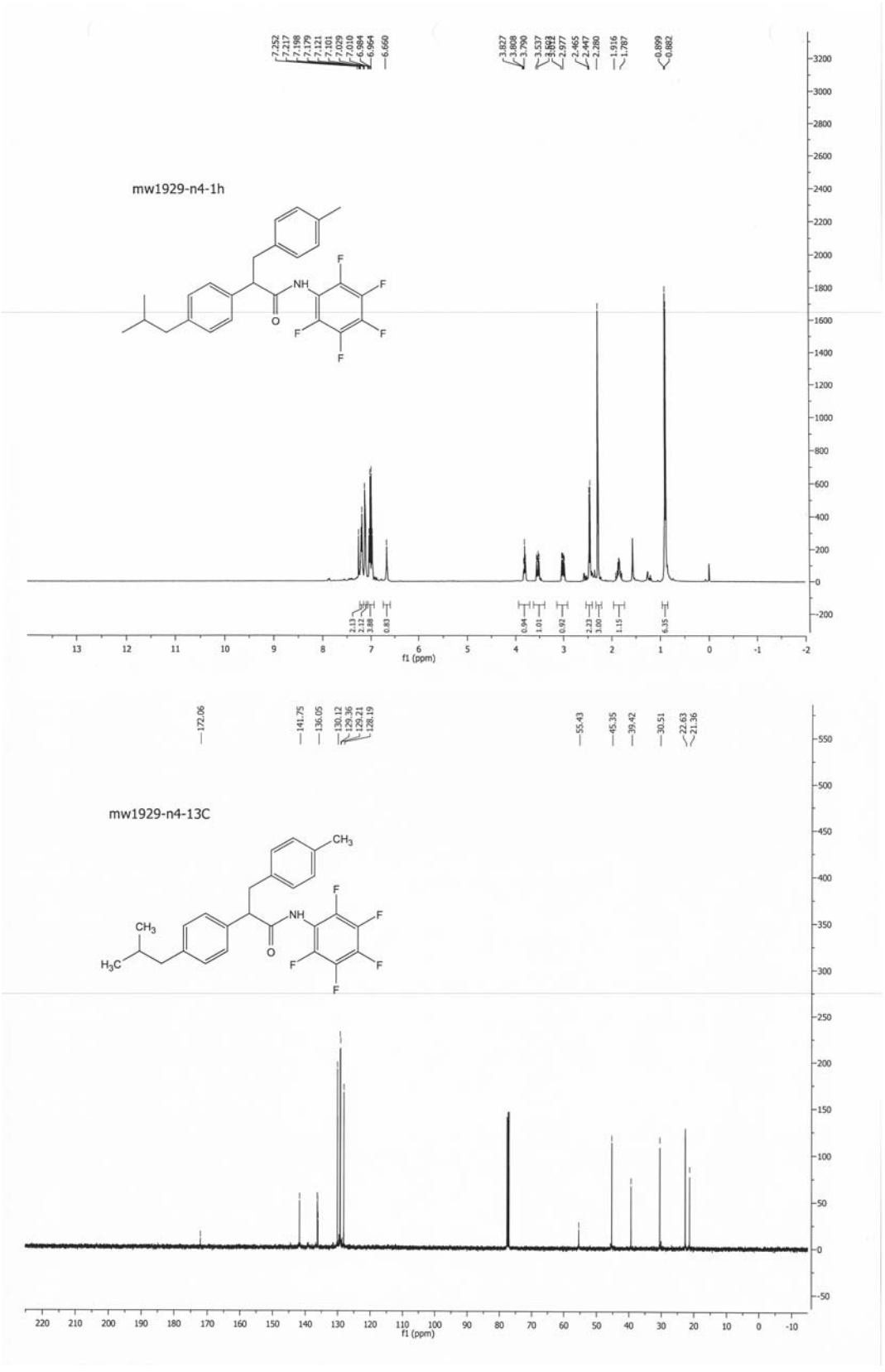


7b

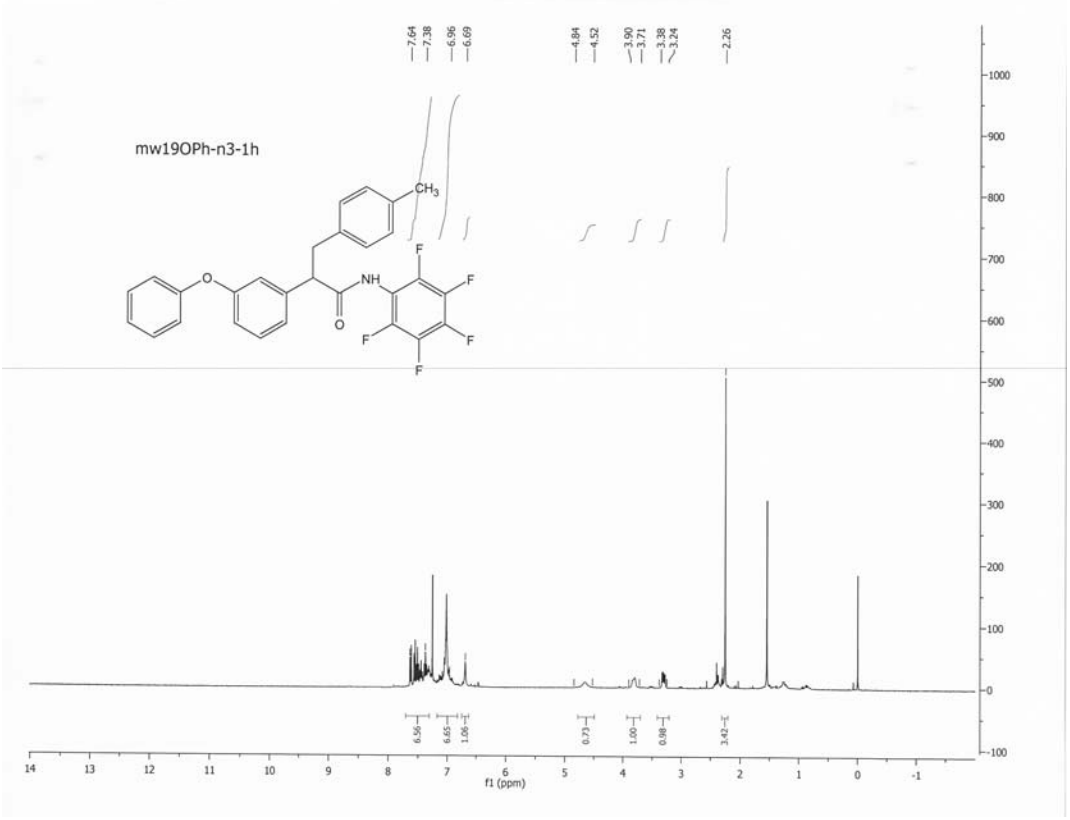

mw1708-n2-1h
7.302
7.286
7.282
7.268
7.261
7.256
7.244
7.235
7.231
7.215
6.936
6.679
6.642
6.624
6.597
4.005
3.991
3.976
3.276
3.242
2.948
2.282
2.207
2.083
1.966
1.873
1.776
f1 (ppm)

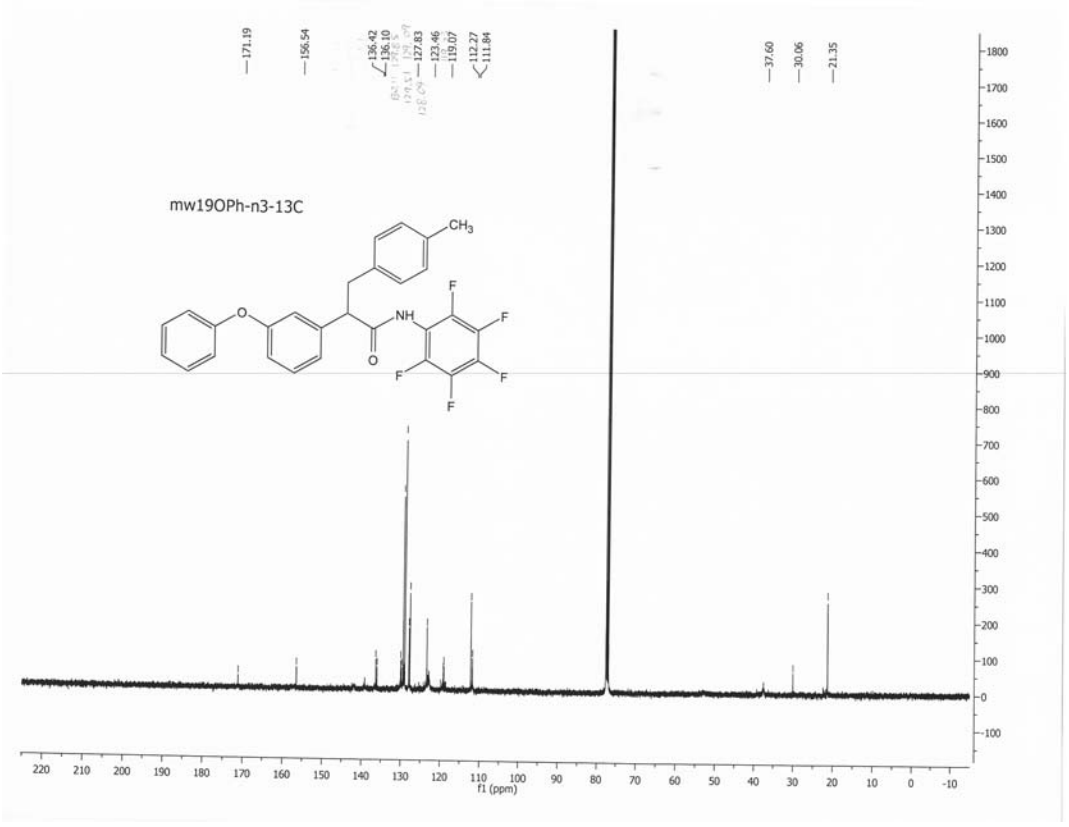

mw1708-n2-13C
174.636
156.760
137.009
136.961
130.641
127.214
123.682
121.480
112.434
105.120
67.797
42.928
30.057
28.485
21.682
16.071
f1 (ppm)

8a

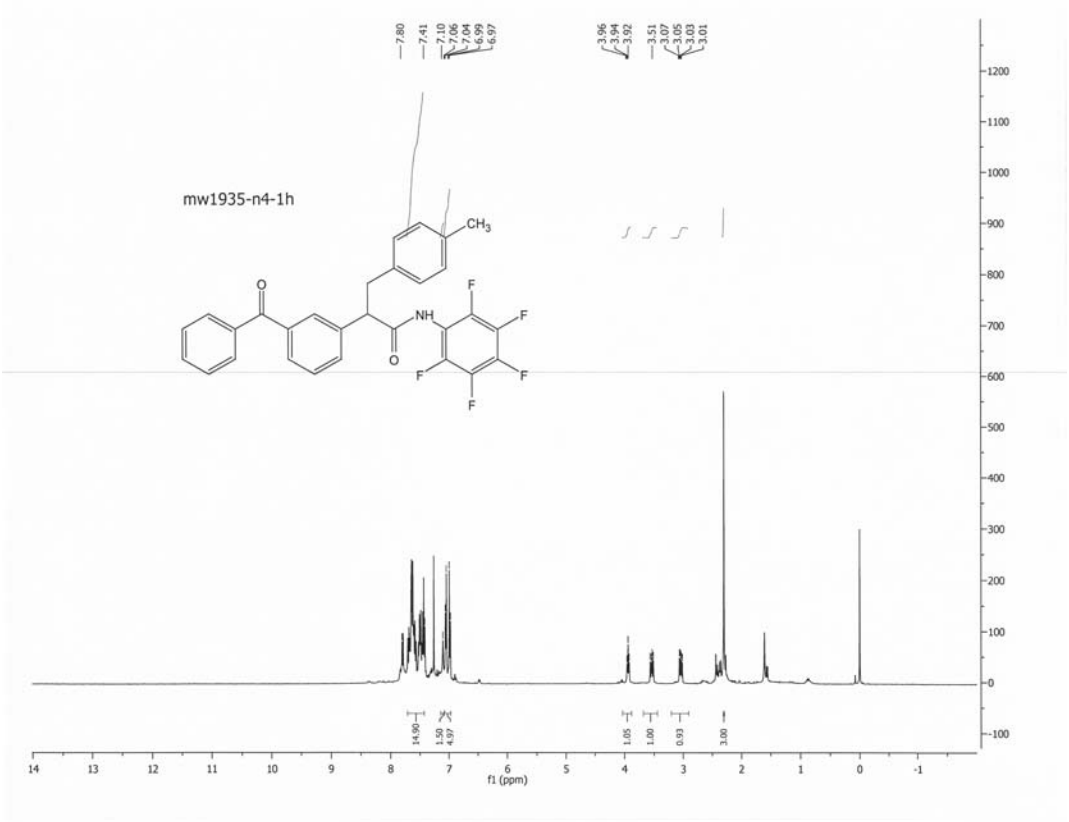


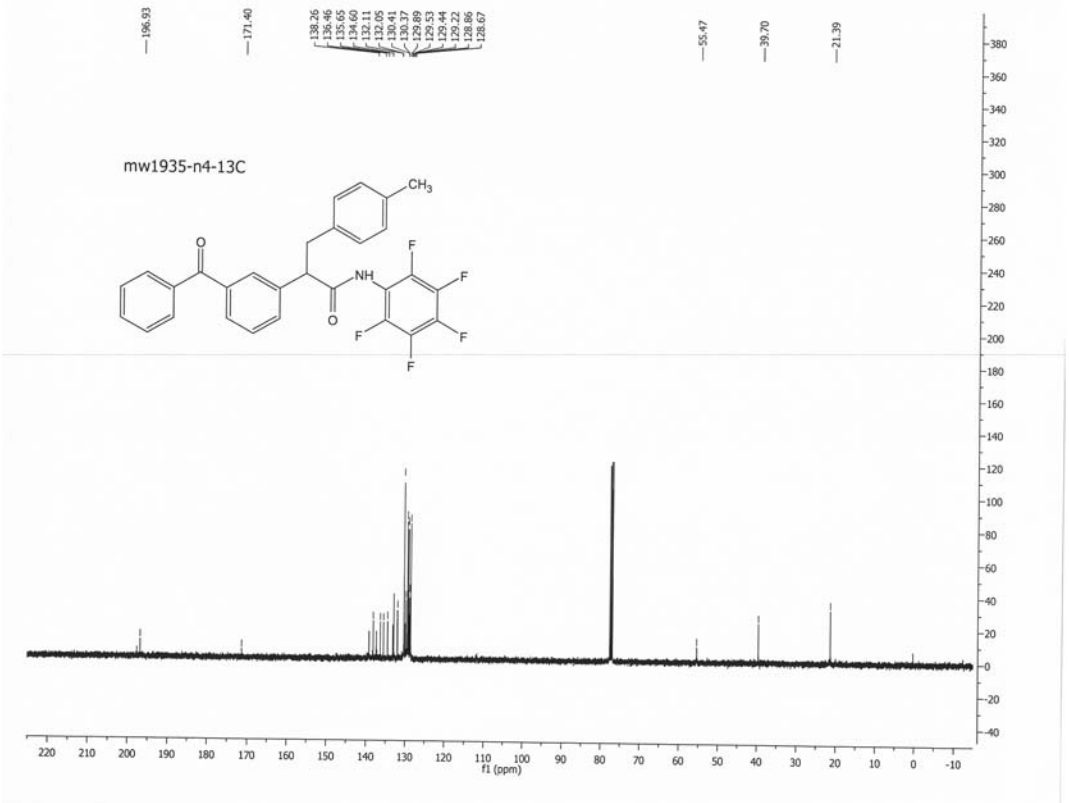
9a


mw19OPh-n3-1h
7.64
7.38
6.96
6.69
4.84
4.52
3.90
3.71
3.38
3.24
2.26
6.56
6.65
1.06
0.73
1.00
0.98
3.42
f1 (ppm)

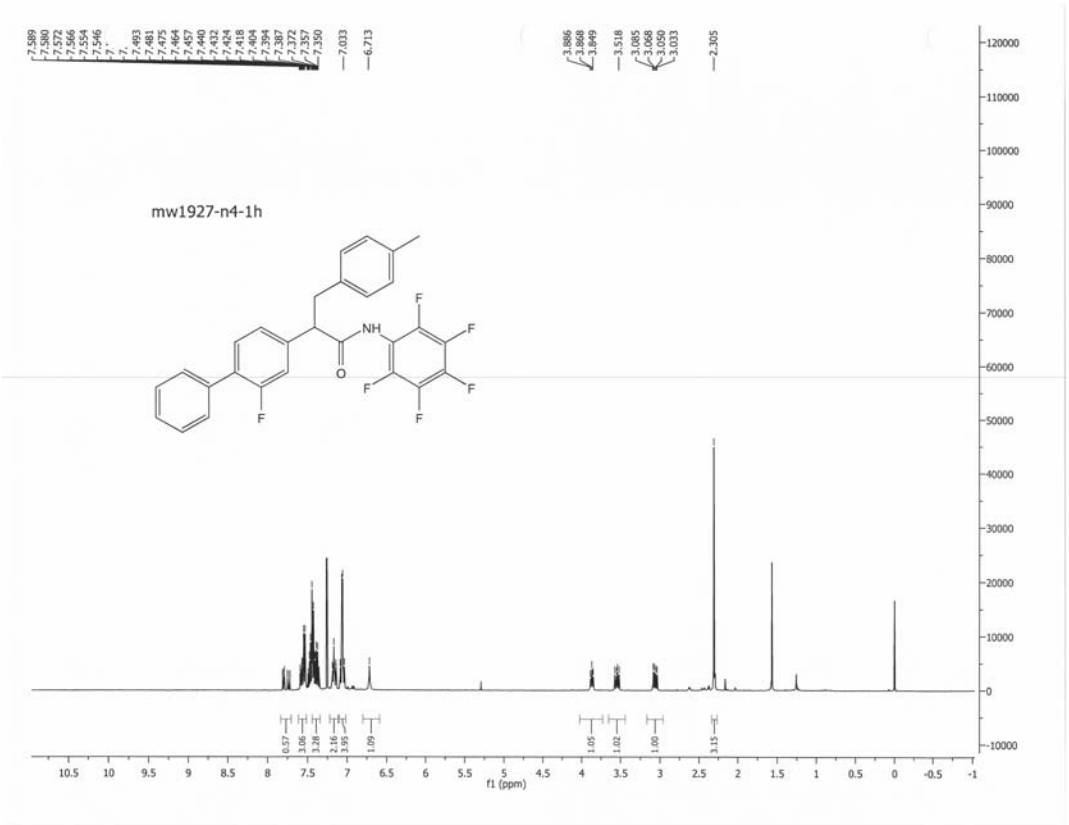

mw19OPh-n3-13C
171.19
156.54
136.42
136.10
127.83
123.46
119.07
112.27
111.84
37.60
30.06
21.35
f1 (ppm)

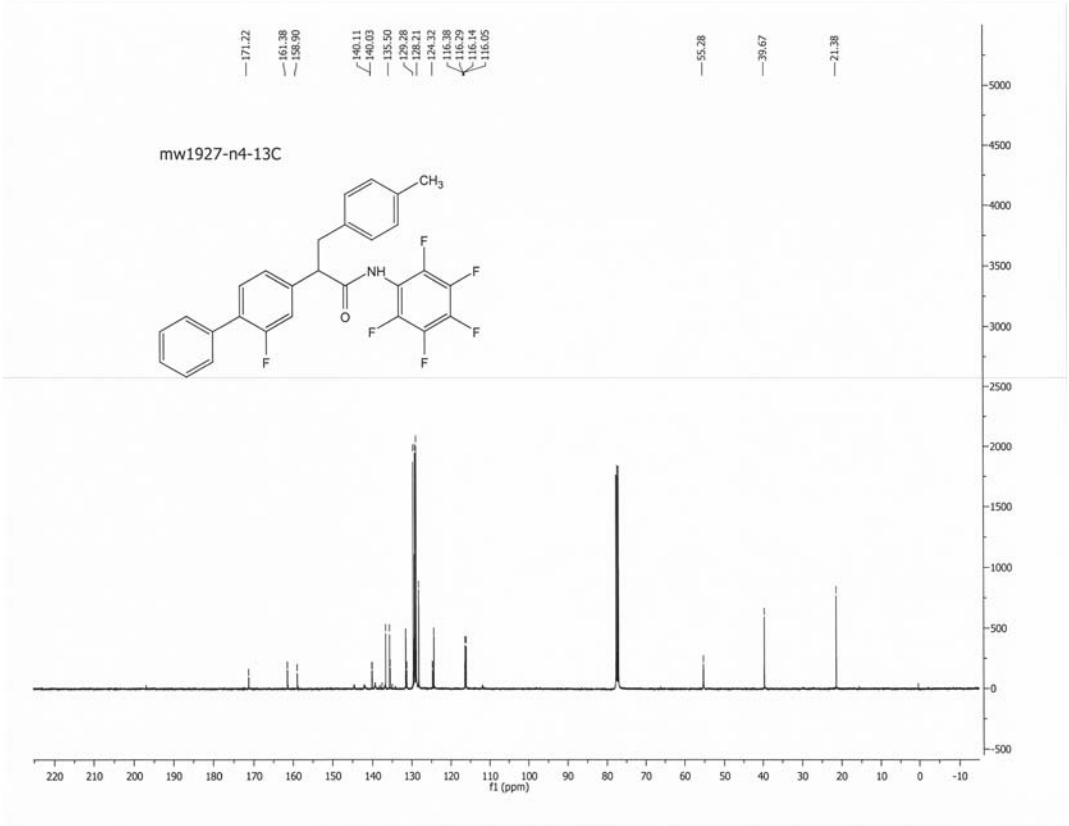
10a


mw1935-n4-1h
7.80
7.41
7.10
7.06
7.04
6.99
6.97
3.96
3.94
3.92
3.51
3.07
3.05
3.03
3.01
CH3
O
NH
F
14.90
1.59
4.97
1.05
1.00
0.93
3.00
f1 (ppm)


mw1935-n4-13C
196.93
171.40
138.26
136.46
135.65
134.60
132.11
132.05
130.41
130.37
129.89
129.53
129.44
129.22
128.86
128.67
55.47
39.70
21.39
CH3
O
NH
F
f1 (ppm)

11a


mw1927-n4-1h
NH
O
F
7.589
7.580
7.572
7.566
7.554
7.546
7.493
7.481
7.475
7.464
7.457
7.440
7.432
7.424
7.418
7.404
7.394
7.387
7.372
7.357
7.350
7.033
6.713
3.886
3.868
3.849
3.518
3.085
3.068
3.050
3.033
2.305
0.57
3.06
3.28
2.16
3.95
1.09
1.05
1.02
1.00
3.15
f1 (ppm)


mw1927-n4-13C
CH3
NH
O
F
171.22
161.38
158.90
140.11
140.03
135.50
129.28
128.21
124.32
116.38
116.29
116.14
116.05
55.28
39.67
21.38
f1 (ppm)