Ligand-Enabled Methylene C(sp^3)–H Bond Activation with A Pd(II) Catalyst

Masayuki Wasa, Kelvin S. L. Chan, Xing-Guo Zhang, Jian He, Masanori Miura, Jin-Quan Yu*

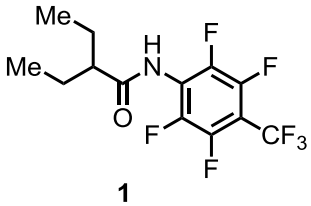
Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Table of Contents

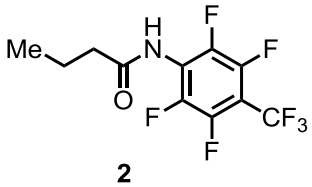
General Information: Solvents were obtained from Sigma-Aldrich, Alfa-Aesar and Acros and used directly without further purification. $Pd(TFA)_2$ was obtained from Strem. Carboxylic acids or carboxylic acid chlorides, and 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline were obtained from the commercial sources and used to prepare corresponding amides.

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, Bruker-500 and Bruker-600 instruments 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).

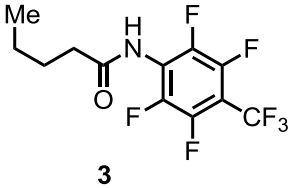
Substrate Structures



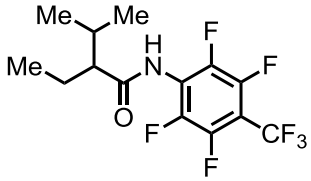
1



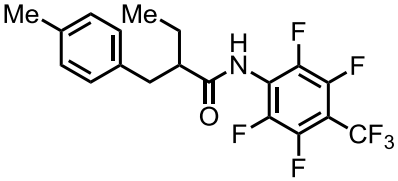
2



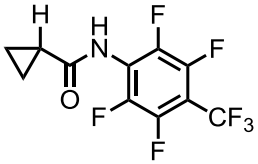
3



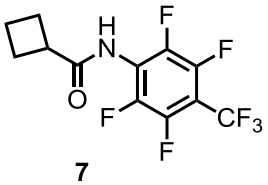
4



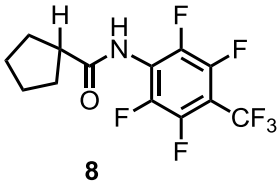
5



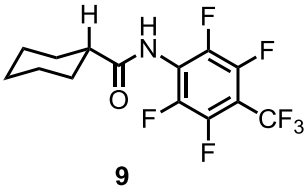
6



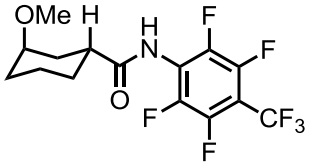
7



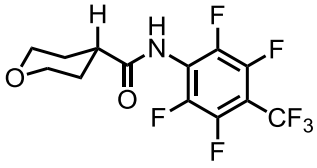
8



9



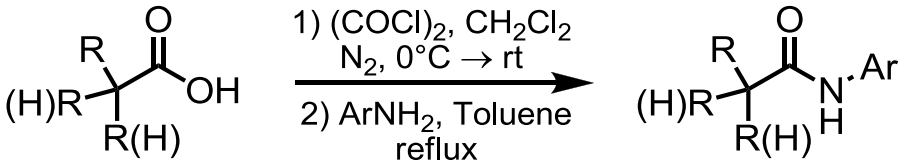
10



11

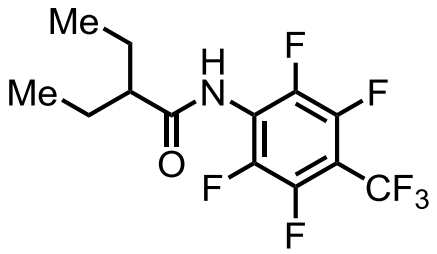
Experimental Section

A. Substrate Preparation



General Procedure for the Preparation of Amides: An acid chloride (10 mmol), prepared from the corresponding carboxylic acid and oxalyl chloride, was added to a vigorously stirred solution of 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline (11 mmol) in toluene (10 mL). The reaction mixture was stirred for 12 h under reflux, and then stirred at

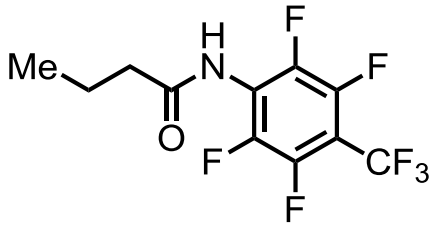
room temperature for 4 h. The product mixture was concentrated under vacuum and was recrystallized from ethyl acetate/hexane (100 ^{o}C to 0 ^{o}C) to give the amide.



1

2-Ethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butanamide (1)

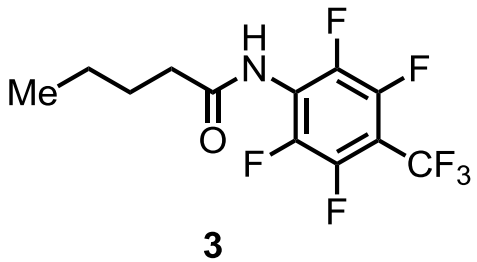
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1H), 2.28-2.21(m, 1H), 1.79-1.57 (m, 4H), 0.99 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 51.7, 26.1, 12.2.



2

***N*-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)butyramide (2)**

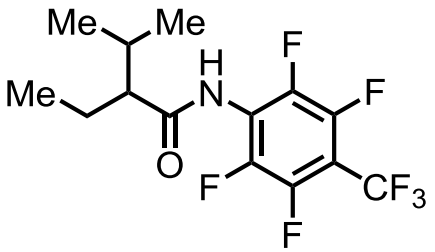
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (s, 1H), 2.46 (t, *J* = 6.0 Hz, 2H), 1.80 (q, *J* = 6.0 Hz, 2H), 1.00 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.0, 39.0, 19.7, 14.3.



3

***N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pentanamide (3)**

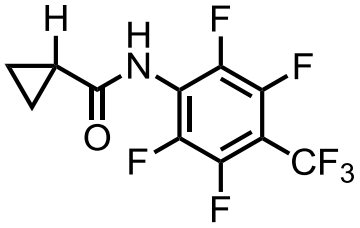
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (s, 1H), 2.47 (t, *J* = 6.0 Hz, 2H), 1.73-1.71 (m, 2H), 1.43-1.39 (m, 2H), 0.95 (t, *J* = 12.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 36.9, 28.2, 23.0, 14.5.



4

2-Ethyl-3-methyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butanamide (4)

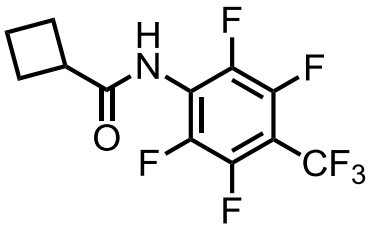
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.04 (s, 1H), 2.03-2.00 (m, 1H), 1.93-1.90 (m, 1H), 1.70-1.65 (m, 2H), 1.01 (t, *J* = 6.0 Hz, 3H), 0.97 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 57.8, 31.7, 23.1, 21.4, 12.9.



6

***N*-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)cyclopropanecarboxamide (6)**

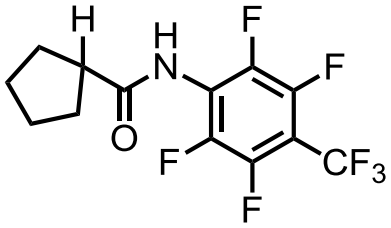
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (bs, 1H), 1.68-1.62 (m, 1H), 2.20-1.12 (m, 2H), 0.98-0.91 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 15.7, 10.1.



7

***N*-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)cyclobutanecarboxamide (7)**

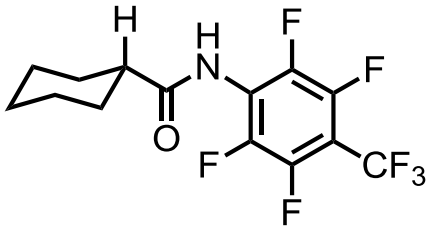
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.96 (bs, 1H), 3.32-3.26 (m, 1H), 2.44-2.27 (m, 4H), 2.06-1.97 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.5, 40.5, 26.2, 19.0.



8

***N*-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)cyclopentanecarboxamide (8)**

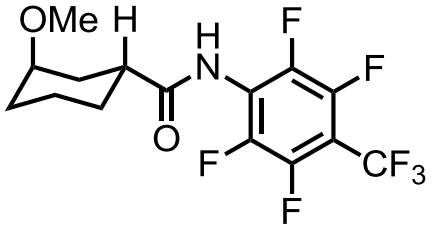
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.98 (bs, 1H), 2.87-2.82 (m, 1H), 2.00-1.90 (m, 4H), 1.79-1.66 (m, 2H), 1.65-1.58 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.8, 46.5, 32.3, 26.8.



9

***N*-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)cyclohexanecarboxamide (9)**

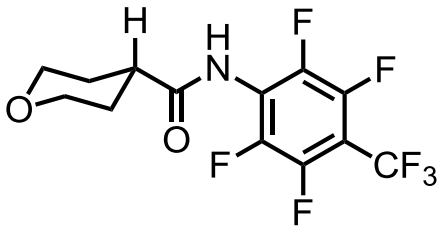
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (bs, 1H), 2.42-2.37 (m, 1H), 2.00-1.98 (m, 2H), 1.86 (m, 2H), 1.72-1.70 (m, 1H), 1.59-1.53 (m, 2H), 1.37-1.26 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.5, 46.2, 30.4, 26.4, 26.3.



10

3-Methoxy-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)cyclohexanecarboxamide (10)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (bs, 1H), 3.65-3.61 (m, 1H), 3.34 (s, 3H), 2.81-2.76 (m, 1H), 2.11-2.09 (m, 1H), 1.94-1.92 (m, 2H), 1.75-1.70 (m, 1H), 1.67-1.59 (m, 3H), 0.89 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.5, 75.3, 56.7, 40.7, 34.0, 29.7, 28.9, 20.3.



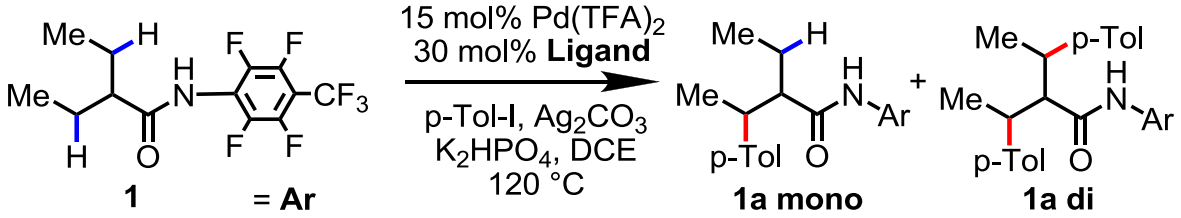
11

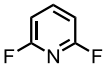
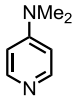
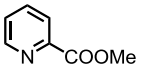
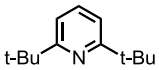
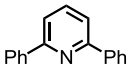
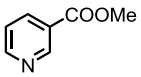
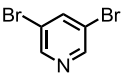
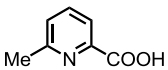
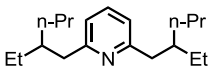
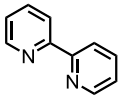
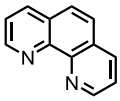
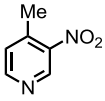
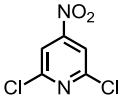
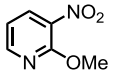
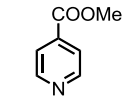
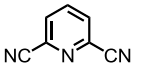
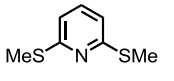
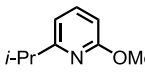
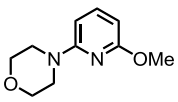
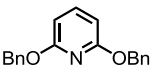
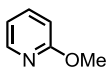
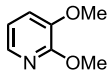
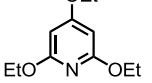
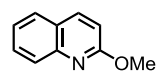
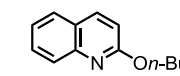
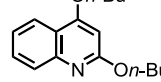
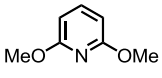
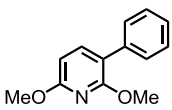
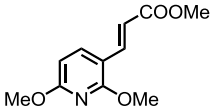
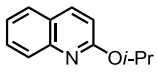
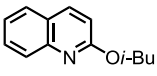
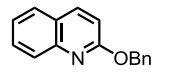
***N*-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)tetrahydro-2H-pyran-4-carboxamide (11)**

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (bs, 1H), 4.07-4.05 (m, 2H), 3.48-3.46 (m, 2H), 2.68-2.65 (m, 1H), 1.97-1.88 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.8, 67.8, 43.0, 29.8.

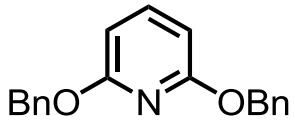
B. Ligand-Enabled Arylation of Methylene C(sp^3)–H Bond

Ligand Screening[a,b]



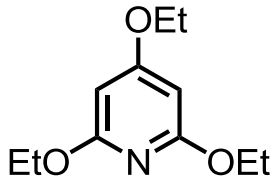
no ligand					
2% mono	SM recovered	7% mono	trace mono	2% mono	4% mono
					
SM recovered	trace mono	trace mono	trace mono	SM recovered	11% mono
					
SM recovered	SM recovered	SM recovered	trace mono	9% mono	trace mono
					
SM recovered	SM recovered	12% mono	28% mono 4% di	18% mono 1% di	53% mono 9% di
					
3% mono	2% mono	54% mono 42% di	62% mono 12% di	60% mono 26% di	41% mono 59% di
					
60% mono 16% di	45% mono 7% di	20% mono trace di	53% mono 47% di	25% mono 75% di	70% mono 11% di

[a] Conditions: 0.2 mmol of substrate, 15 mol% $Pd(TFA)_2$, 30 mol% ligand, 4.0 equiv of p-Tol–I, 3.0 equiv of Ag_2CO_3, 1.2 equiv of K_2HPO_4, 0.5 mL of DCE, 120 °C, 24 h. [b] The yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard, and GC/MS spectroscopic analysis for mono:di ratio.



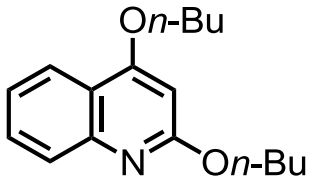
2,6-Bis(benzyloxy)pyridine

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (t, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 4H), 7.36 (t, *J* = 7.5 Hz, 4H), 7.31 (t, *J* = 7.2 Hz, 2H), 6.37 (d, *J* = 7.8 Hz, 2H), 5.34 (s, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.41, 141.26, 137.71, 128.59, 127.95, 127.90, 102.11, 67.77.



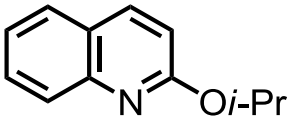
2,4,6-Triethoxypyridine

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82 (s, 2H), 4.27 (q, *J* = 7.1 Hz, 4H), 4.00 (q, *J* = 7.0 Hz, 2H), 1.39 to 1.35 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.43, 164.00, 87.92, 63.70, 61.91, 14.82, 14.64.



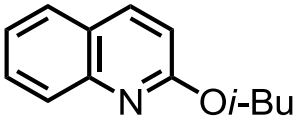
2,4-Dibutoxyquinoline

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 6.20 (s, 1H), 4.45 (t, *J* = 6.6 Hz, 2H), 4.13 (t, *J* = 6.4 Hz, 2H), 1.93 to 1.87 (2H), 1.83 to 1.77 (2H), 1.62 to 1.48 (4H), 1.03 to 0.98 (6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.90, 163.30, 147.30, 129.89, 126.95, 123.13, 122.00, 119.49, 91.44, 68.26, 65.76, 31.39, 31.06, 19.53, 19.50, 14.10, 13.98.



2-Isopropoxyquinoline

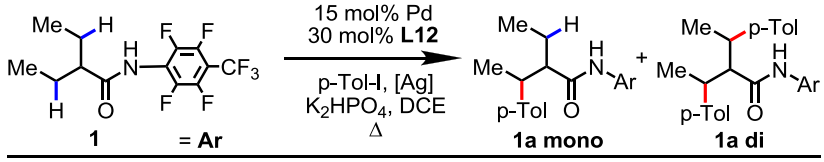
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.60 (ddd, *J* = 8.3, 7.1, 1.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 5.58 (hept, *J* = 6.2 Hz, 1H), 1.41 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.78, 146.86, 138.64, 129.43, 127.49, 127.35, 125.03, 123.83, 113.93, 68.05, 22.20.



2-Isobutoxyquinoline

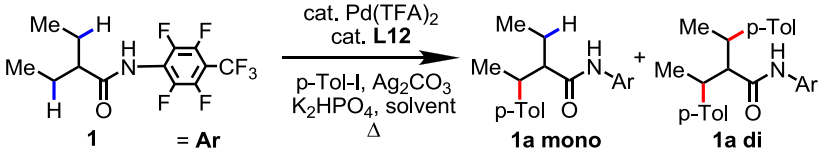
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 4.25 (d, *J* = 6.7 Hz, 2H), 2.20 to 2.09 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.61, 146.80, 138.68, 129.51, 127.52, 127.52, 127.32, 125.16, 123.94, 113.47, 72.32, 2 8.19, 19.55.

Optimization of reaction conditions[a,b]



Pd catalyst	[Ag]	temperature (°C)	conv (%)	
			1a mono	**1a di**
none	Ag_2CO_3	120	0	0
$Pd(OAc)_2$	Ag_2CO_3	120	51	21
$Pd(OAc)_2$	AgOAc (4 equiv)	120	39	15
$PdCl_2$	Ag_2CO_3	120	3	0
$Pd(TFA)_2$	Ag_2CO_3	120	25	75
$Pd(TFA)_2$	Ag_2CO_3	100	59	28
$Pd(TFA)_2$	none	120	12	2

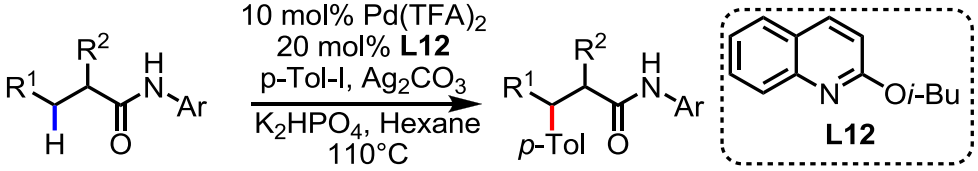
[a] Conditions: 0.2 mmol of substrate, 15 mol% Pd catalyst, 30 mol% L12, 4.0 equiv of p-Tol–I, 3.0 equiv of Ag salt, 1.2 equiv of K_2HPO_4, 1.0 mL of DCE, 24 h. [b] The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as an internal standard, and GC/MS spectroscopic analysis for mono:di ratio.



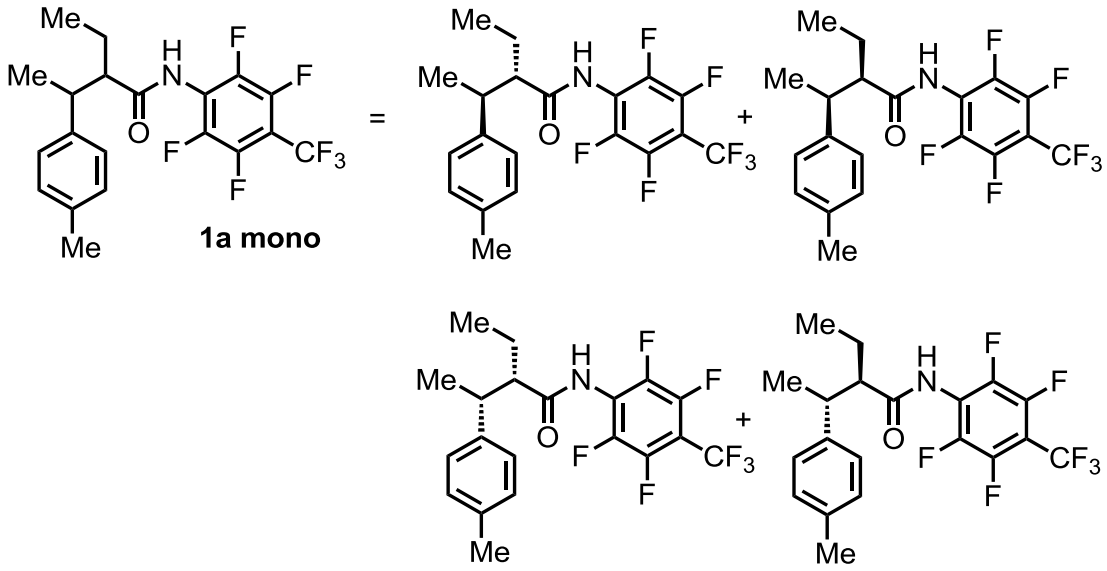
$Pd(TFA)_2$ loading (mol%)	solvent	temperature (°C)	conv (%)	
			1a mono	**1a di**
15	DCE	120	25	75
15	DCE + 0.1mL DMF	120	7	0
15	DCE + 0.1mL NMP	120	4	0
15	DCE + 0.1mL DMSO	120	2	0
15	THF	120	22	5
15	Toluene	120	38	8
15	1,4-dioxane	120	11	2
15	*t*-BuOH	120	44	12
15	*n*-hexane	120	22	78
15	*n*-hexane	110	25	75
15	*n*-hexane	80	75	11
10	*n*-hexane	120	20	80
10	*n*-hexane (3.0 equiv of p-Tol-I)	120	51	49
10	*n*-hexane (3.0 equiv of p-Tol-I, 2.0 equiv of Ag_2CO_3)	120	60	40
10	*n*-hexane (3.0 equiv of p-Tol-I, 2.0 equiv of Ag_2CO_3)	110	73	27

[a] Conditions: Unless mentioned otherwise, 0.2 mmol of substrate, $Pd(TFA)_2$, L12, 4.0 equiv of p-Tol–I, 3.0 equiv of Ag salt, 1.2 equiv of K_2HPO_4, 1.0 mL of DCE, 24 h. [b] The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as an internal standard, and GC/MS spectroscopic analysis for mono:di ratio.

General Reaction Scheme

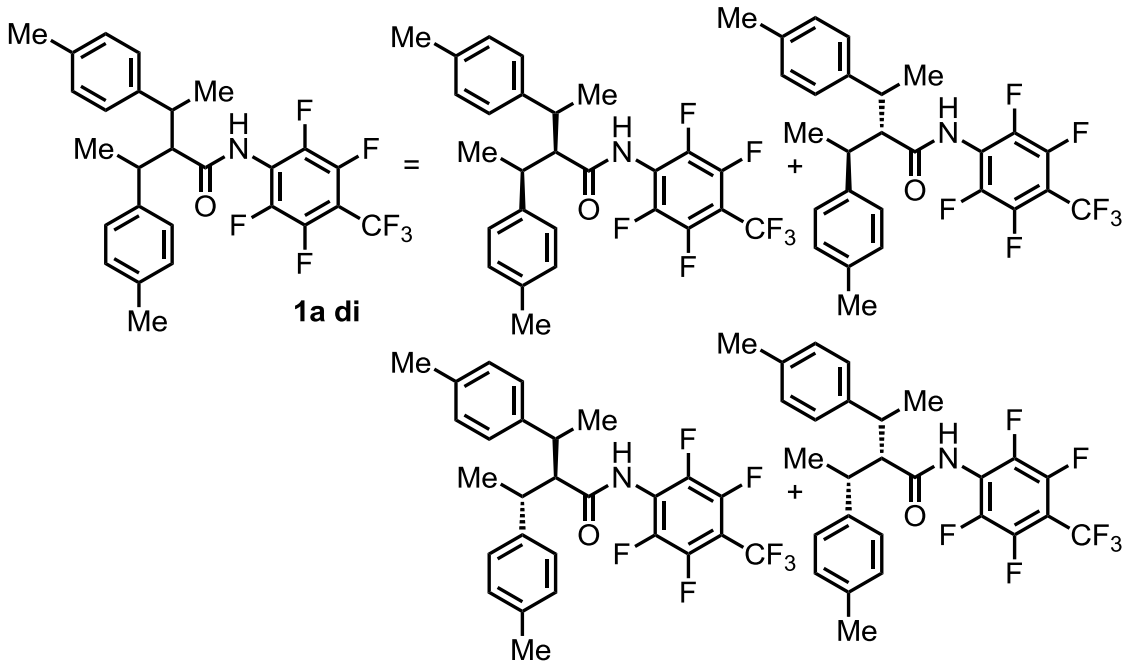


General Procedure: Substrate (0.2 mmol), $Pd(TFA)_2$ (0.02 mmol), Ag_2CO_3 (0.4 mmol), aryl–I (0.6 mmol), and K_2HPO_4 (0.24 mmol) were weighed in air and placed in a sealed tube (10 mL) with a magnetic stir bar. **L12** (0.04 mmol) and hexane (1 mL) were added, and the reaction mixture was heated to 110 °C under air for 24 hours under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature. The solvents were removed under reduced pressure and the resulting mixture was purified by a silica gel-packed flash chromatography column typically using hexane/ethyl acetate mixtures as the eluent. In the ^{13}C analysis, peaks that correspond to those of the poly-fluoroarylamide auxiliary appeared as nearly invisible, complex sets of multiplets; they are omitted in the following spectroscopic analysis.



2-Ethyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-3-p-tolylbutanamide (1a mono)

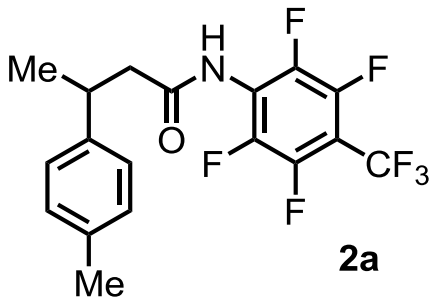
Substrate **1** was arylated following the general procedure to give a mixture of **1a** mono and **1a** di, both of them as a mixture of inseparable diastereomers by flash chromatography. By crude ^{1}H NMR and GC/MS spectroscopic analyses, the *d.r.* of **1a** mono was determined to be 4:1. After purification by column chromatography, **1a** was obtained as white solid (59.0 mg, 70%) as a mixture of the diastereomers in 4:1 ratio. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.08 (m), 6.63 (s), 6.43 (s), 3.16-3.14 (m), 3.04-2.93 (m), 2.48-2.39 (m), 2.34 (s), 2.31 (s), 1.90-1.69 (m), 1.49 (d, *J* = 8.0 Hz), 1.36 (d, *J* = 8.0 Hz), 1.00 (t, *J* = 8.0 Hz), 0.89 (t, *J* = 8.0 Hz); HRMS (ESI-TOF) Calcd for C20H18F7NO (MH^+): 422.1349; found: 422.1344.



***N*-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)-3-p-tolyl-2-(1-p-tolylethyl)butanamide (1a di)**

Substrate **1** was arylated following the general procedure to give a mixture of **1a** mono and **1a** di as described above. The *d.r.* of **1a** di was determined to be 1:1 by GC/MS. After purification by column chromatography, **1a** di was obtained as white solid (23.6 mg, 23%) as a 1:1 mixture of diastereomers. Further purification by PTLC, one of the diastereomers could be separated from the other to give the following spectra. The isomeric ratio

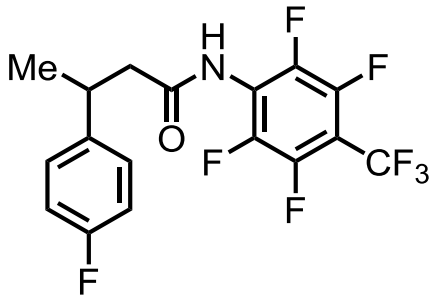
(major/minor) was determined to be 1:1 by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.04 (m, 8H), 6.01 (s, 1H), 3.32-3.20 (m, 2H), 2.74 (t, *J* = 4.0 Hz, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 1.47 (d, *J* = 4.0 Hz, 3H), 1.42 (d, *J* = 4.0 Hz, 3H); HRMS (ESI-TOF) Calcd for C27H24F7NO (MH^+): 512.1819; found: 512.1821.



2a

***N*-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)-3-p-tolylbutanamide (2a)**

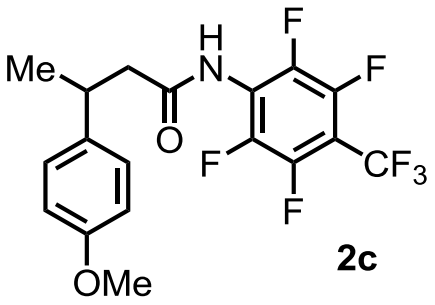
Substrate **2** was arylated following the general procedure. After purification by column chromatography, **2a** was obtained as white solid (60.7 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 4H), 6.75 (s, 1H), 3.35-3.29 (m, 1H), 2.73 (q, *J* = 4.0 Hz, 2H), 2.33 (s, 3H), 1.38 (d, *J* = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 142.0, 137.0, 130.0, 126.9, 45.8, 37.0, 22.2, 21.4; HRMS (ESI-TOF) Calcd for C18H14F7NO (MH^+): 394.1036; found: 394.1040.



3-(4-Fluorophenyl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butanamide (2b)

Substrate **2** was arylated following the general procedure. After purification by column chromatography, **2b** was obtained as white solid (56 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$)

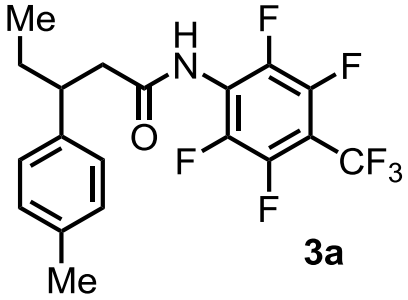
δ 7.24-7.21 (m, 2H), 7.03-7.00 (m, 2H), 6.86 (bs, 1H), 3.41-3.34 (m, 1H), 2.70 (d, *J* = 4.0 Hz, 2H), 1.39 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 163.0, 161.1, 140.8, 140.8, 128.5, 128.5, 116.1, 116.1, 115.9, 45.8, 36.7, 22.1; HRMS (ESI-TOF) Calcd for C17H11F8NO (MH^+): 398.0786; found: 398.0785.



2c

3-(4-Methoxyphenyl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butanamide (2c)

Substrate **2** was arylated following the general procedure. After purification by column chromatography, **2c** was obtained as white solid (55 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 12.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.85 (s, 1H), 3.79 (s, 3H), 3.36-3.29 (m, 1H), 2.71 (d, *J* = 8.0 Hz, 2H), 1.38 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 158.8, 137.1, 128.0, 114.6, 55.6, 46.0, 36.7, 22.3; HRMS (ESI-TOF) Calcd for C18H14F7NO2 (MH^+): 410.0985; found: 410.0982.

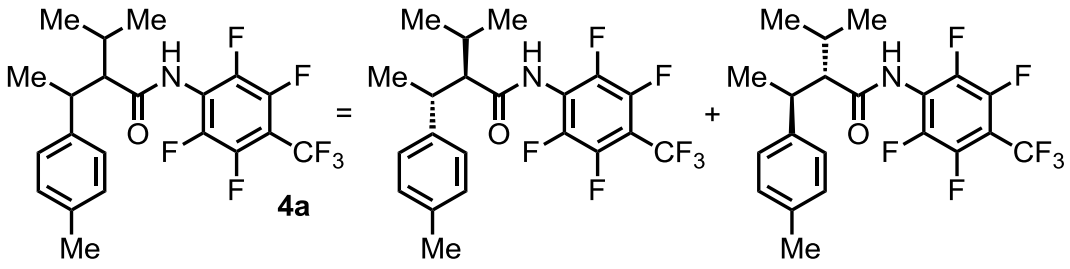


3a

***N*-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)-3-p-tolylpentanamide (3a)**

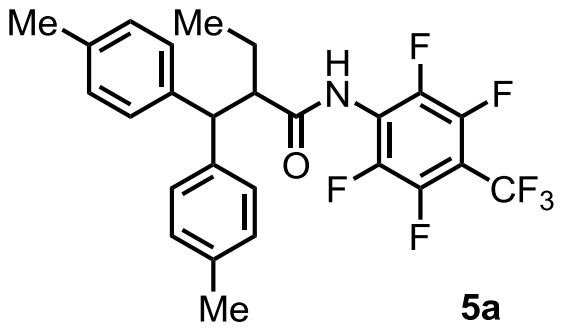
Substrate **3** was arylated following the general procedure. After purification by column chromatography, **3a** was obtained as yellow solid (44.9 mg, 55%). 7% of *α,β*-unsaturated

product formed via β-hydride elimination was also isolated. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.10 (m, 4H), 6.70 (s, 1H), 3.01-2.98 (m, 1H), 2.82-2.77 (m, 1H), 2.71-2.66 (m, 1H), 2.33 (s, 3H) 1.82-1.64 (m, 2H), 0.83 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 140.2, 137.0, 129.9, 127.6, 44.6, 30.1, 30.0, 21.4, 12.3; HRMS (ESI-TOF) Calcd for C19H16F7NO (MH^+): 408.1193; found: 408.1203.



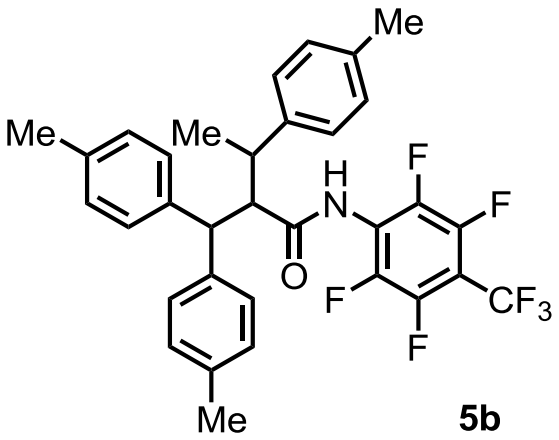
2-Isopropyl-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-3-p-tolylbutanamide (4a)

Substrate **4** was arylated following the general procedure. After purification by column chromatography, **4a** was obtained as yellow solid (71.5 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.06 (m, 4H), 6.48 (s, 1H), 3.21-3.13 (m, 1H), 2.46-2.42 (m, 1H), 2.30 (s, 3H), 1.34 (d, *J* = 4.0 Hz, 3H), 1.14 (q, *J* = 4.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 141.9, 136.7, 129.6, 127.5, 61.4, 39.6, 28.3, 22.2, 21.3, 19.6, 16.7; HRMS (ESI-TOF) Calcd for C21H20F7NO (MH^+): 436.1506; found: 436.1508.



2-(Di-p-tolylmethyl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)butanamide (5a)

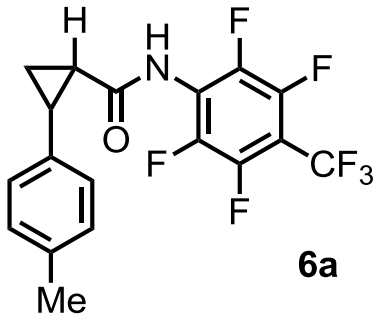
Substrate **5** was arylated following the general procedure to give a mixture of **5a** and **5b**. The crude 1H NMR and GC/MS spectroscopic analyses showed that **5a** and **5b** are obtained as a single diastereomer. After purification by column chromatography, **5a** was obtained as white solid (70.7 mg, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21-7.18 (m, 4H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.95 (s, 1H), 4.11 (d, *J* = 12.0 Hz, 1H), 3.17 (m, 1H), 2.30 (s, 3H), 2.25 (s, 3H), 1.73-1.58 (m, 2H), 0.98 (t, *J* = 4.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 139.7, 139.7, 138.9, 136.9, 136.8, 136.6, 130.1, 129.8, 129.2, 128.8, 128.1, 127.8, 59.0, 52.2, 39.7, 21.4, 21.4, 21.2, 20.9; HRMS (ESI-TOF) Calcd for C26H22F7NO (MH^+): 498.1662; found: 498.1669.



5b

2-(Dip-tolylmethyl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-3-p-tolylbutanamide (5b)

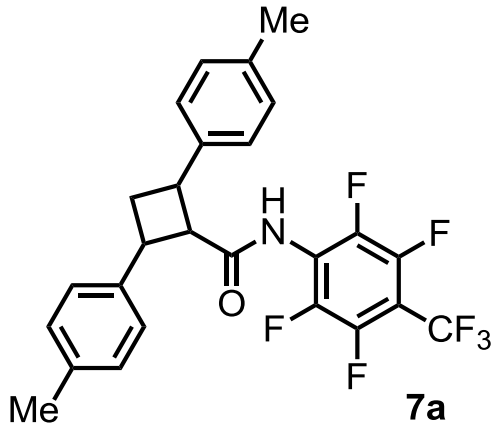
Substrate **5** was arylated following the general procedure. After purification by column chromatography, **5b** was obtained as white solid (23.5 mg, 20%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24-6.98 (m, 12H), 6.46 (s, 1H), 4.05 (d, *J* = 8.0 Hz, 1H), 3.65 (d, *J* = 4.0 Hz, 1H), 3.24-3.22 (m, 1H), 2.32 (s, 6H), 2.21 (s, 3H), 1.40 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 139.7, 139.7, 138.9, 136.9, 136.8, 136.6, 130.1, 130.0, 129.2, 128.8, 128.1, 127.8, 59.0, 52.2, 39.7, 21.4, 21.4, 21.2, 20.9; HRMS (ESI-TOF) Calcd for C33H28F7NO (MH^+): 588.2132; found: 588.2131.



6a

***N*-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)-2-p-tolylcyclopropanecarboxamide (6a)**

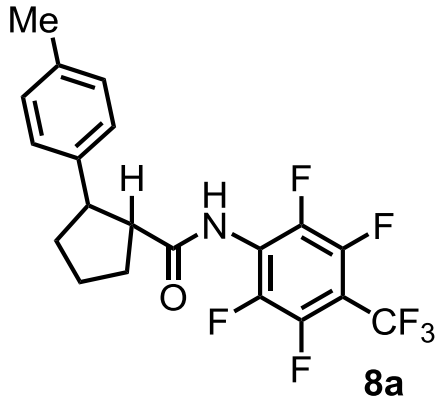
Substrate **6** was arylated following the general procedure. After purification by column chromatography, **6a** was obtained as yellow solid (67.4 mg, 86%). The crude 1H NMR and GC/MS spectroscopic analyses showed that **6a** was obtained as a single diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.88 (s, 1H), 2.71 (q, *J* = 8.0 Hz, 2H), 2.31 (s. 3H), 2.19-2.14 (m, 1H), 1.86-1.82 (m, 2H), 1.50-1.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 137.2, 132.5, 129.5, 129.2, 26.4, 23.9, 21.5, 11.9; HRMS (ESI-TOF) Calcd for C18H12F7NO (MH^+): 392.088; found: 392.0884.



7a

***N*-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)-2,4-dip-tolylcyclobutanecarboxamide (7a)**

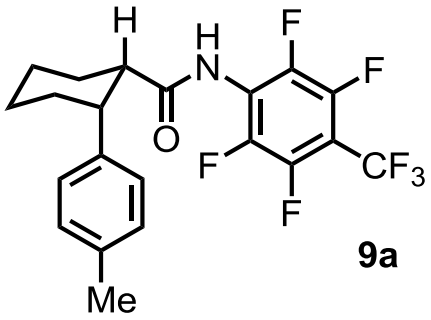
Substrate **7** was arylated following the general procedure to give a mixture of mono and di-arylated products in 1:8 ratio. The mono-arylated product was isolated as a mixture with the starting material **7**. The crude ^{1}H NMR and GC/MS spectroscopic analyses showed that **7a** was obtained as a single diastereomer. After purification by column chromatography, **7a** was obtained as yellow solid (81.4 mg, 80%). ^{1}H NMR (400 MHz, acetone) δ 9.28 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 4.32-4.27 (m, 1H), 4.04-3.97 (m, 2H), 3.35 (q, *J* = 8.0 Hz, 1H), 3.65-2.58 (m, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, acetone) δ 169.3, 138.9, 135.8, 129.3, 127.6, 52.9, 39.3, 30.6, 21.1; HRMS (ESI-TOF) Calcd for C26H20F7NO (MH^+): 496.1506; found: 496.1510.



8a

***N*-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)-2-p-tolylcyclopentanecarboxamide (8a)**

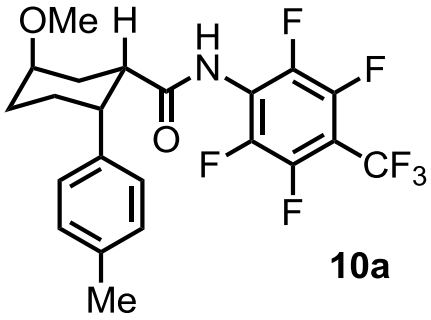
Substrate **8** was arylated following the general procedure. After purification by column chromatography, **8a** was obtained as yellow solid (52.1 mg, 62 %). The mono-arylated product was isolated as a mixture with the starting material **8**. The crude ^{1}H NMR and GC/MS spectroscopic analyses showed that **8a** was obtained as a single diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.44 (s, 1H), 3.46-3.19 (m, 1H), 3.18-3.14 (m, 1H), 2.30 (s, 3H), 2.16-1.59 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 137.5, 137.1, 129.7, 127.9, 52.0, 49.9, 30.9, 29.3, 24.5, 21.3; HRMS (ESI-TOF) Calcd for C20H16F7NO (MH^+): 420.1193; found: 420.1194.



9a

***N*-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)-2-p-tolylcyclohexanecarboxamide (9a)**

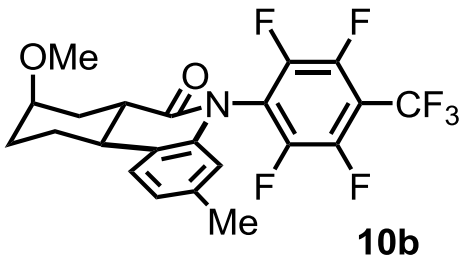
Substrate **9** was arylated following the general procedure to give 9a as a mixture of *cis*- and *trans*-arylated products in 4:1 ratio based on ^{1}H NMR and GC/MS spectroscopic analyses. After purification by column chromatography, **9a** was obtained as yellow solid (79.1 mg, 94 %) as a mixture of *cis*- and *trans*-arylated products. Further purification by PTLC permitted isolation of an isomer with the following spectra. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.33 (s, 1H), 3.03-2.98 (m, 2H), 2.32 (s, 3H), 2.22-1.39 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 140.9, 136.9, 129.9, 127.5, 48.3, 45.1, 29.8, 26.7, 26.4, 21.7, 21.3; HRMS (ESI-TOF) Calcd for C21H18F7NO (MH^+): 434.1349; found: 434.1343.



10a

5-Methoxy-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-2-(p-tolyl)cyclohexanecarboxamide (10a)

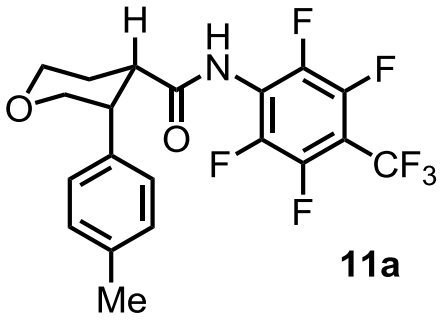
Substrate **10** was arylated following the general procedure to give a mixture of **10a** and **10b**. NOE studies have shown that **10a** is the *cis*-arylated product. After purification by column chromatography, **10a** was obtained as yellow solid (66.8 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.09 (m, 4H), 6.64 (s, 1H), 3.69-3.68 (m, 1H), 3.39 (s, 3H), 2.94-2.80 (m, 2H), 2.30 (s, 3H), 2.16-1.55 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 141.0, 137.0, 129.8, 127.3, 74.2, 56.3, 47.4, 46.5, 33.9, 28.5, 27.8, 21.3; HRMS (ESI-TOF) Calcd for C22H20F7NO2 (MH^+): 464.138; found: 464.1372.



10b

8-Methoxy-3-methyl-5-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-6a,7,8,9,10,10a-hexahydrophenanthridin-6(5H)-one (10b)

Substrate **10** was arylated following the general procedure. After purification by column chromatography, **10b** was obtained as yellow oil (11.1 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.42 (s, 1H), 3.81-3.76 (m, 3H), 3.45 (s, 3H), 3.07-3.05 (m, 1H), 2.98-2.91 (m, 1H), 2.79-2.73 (m, 1H), 2.38 (s, 3H), 2.11-2.04 (m, 2H); HRMS (ESI-TOF) Calcd for C22H18F7NO2 (MH^+): 462.1298; found: 462.1370.

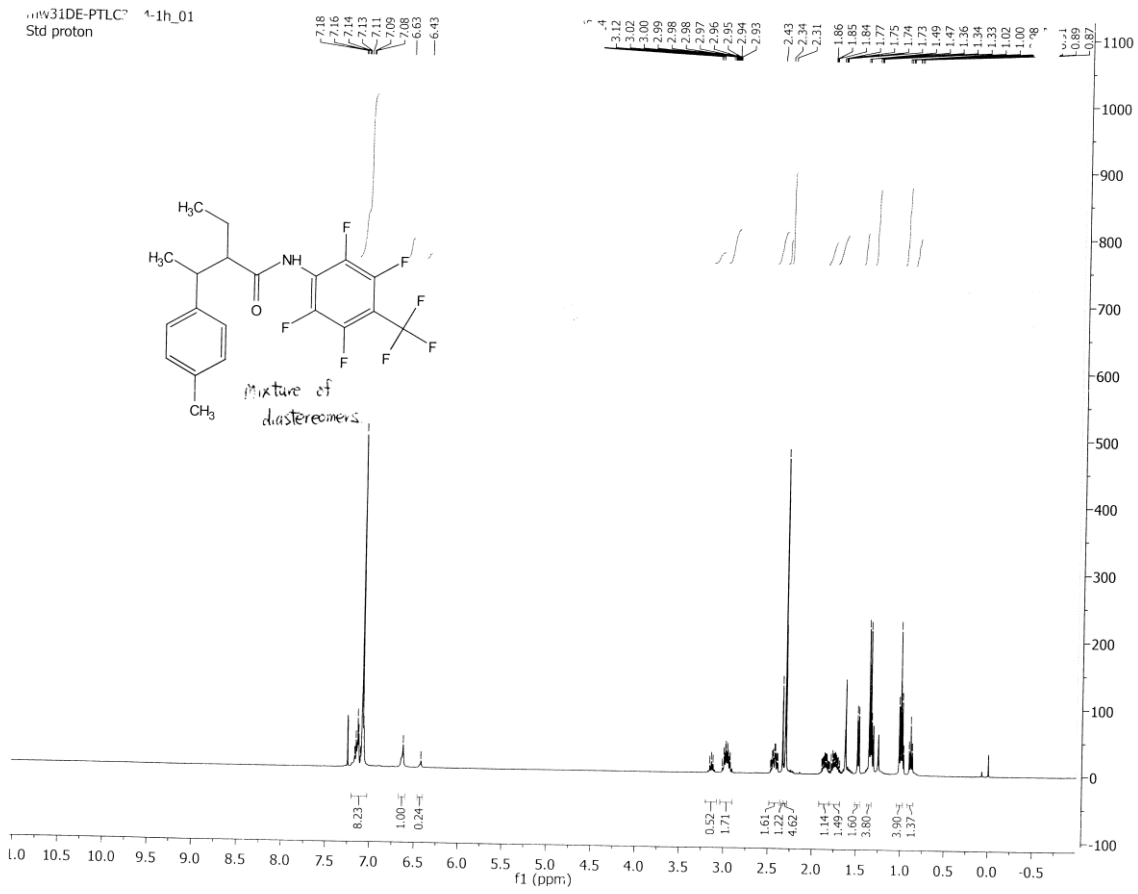


11a

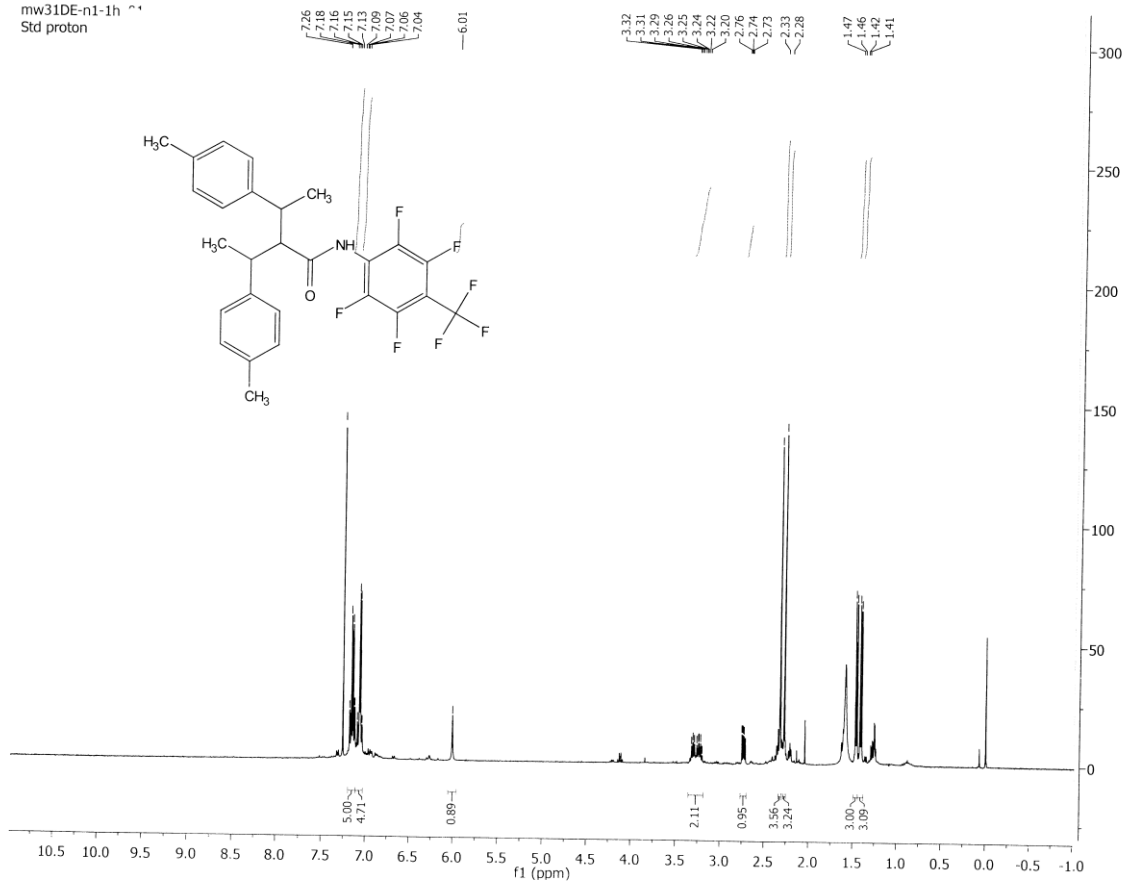
***N*-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)-3-p-tolyltetrahydro-2H-pyran-4-carboxamide (11a)**

Substrate **11** was arylated following the general procedure to give **11a** as a mixture of *cis*- and *trans*-arylated products in 6:1 ratio. After purification by column chromatography, **11a** was obtained as yellow solid (47.9 mg, 55%) as a mixture of *cis*- and *trans*-arylated products. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.22 (m), 7.14-7.11 (m), 6.82 (s), 6.76 (s), 4.33-4.14 (m), 4.02-3.90 (m), 3.77-3.75 (m), 3.59-3.44 (m), 3.12-3.06 (m), 2.90-2.83 (m), 2.32 (s), 2.16-1.96 (m); HRMS (ESI-TOF) Calcd for C20H16F7NO2 (MH^+): 436.1142; found: 436.1148.

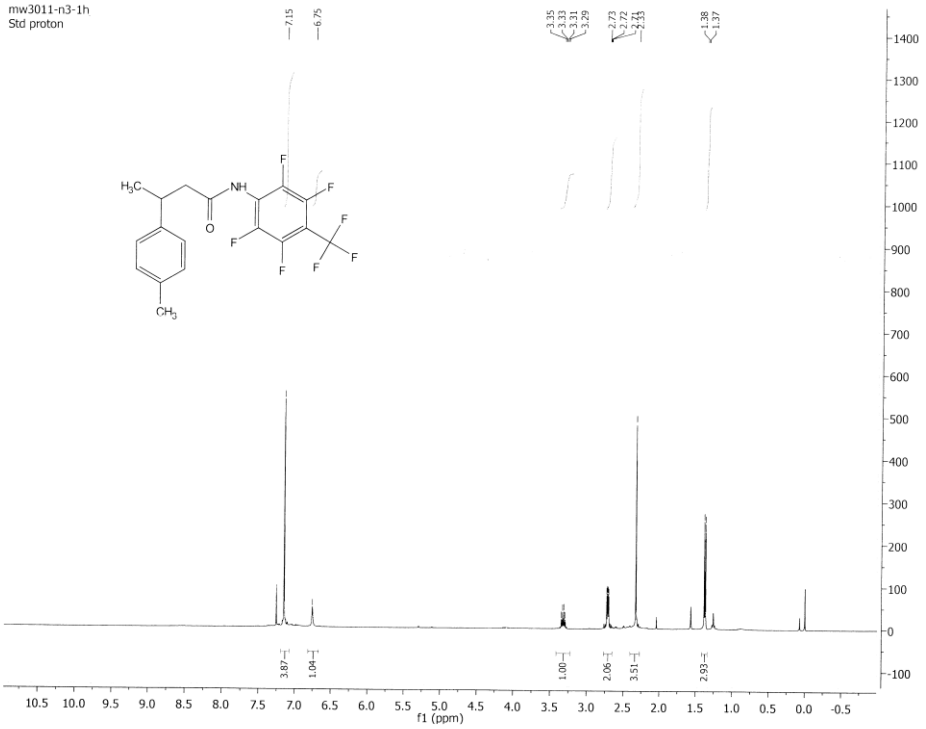
1a

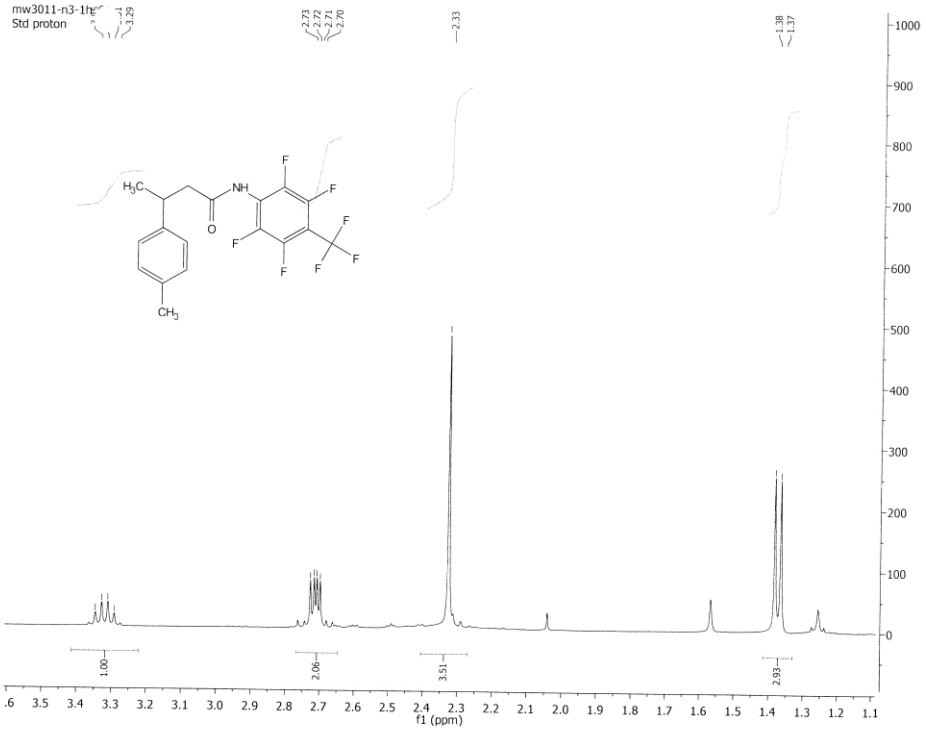


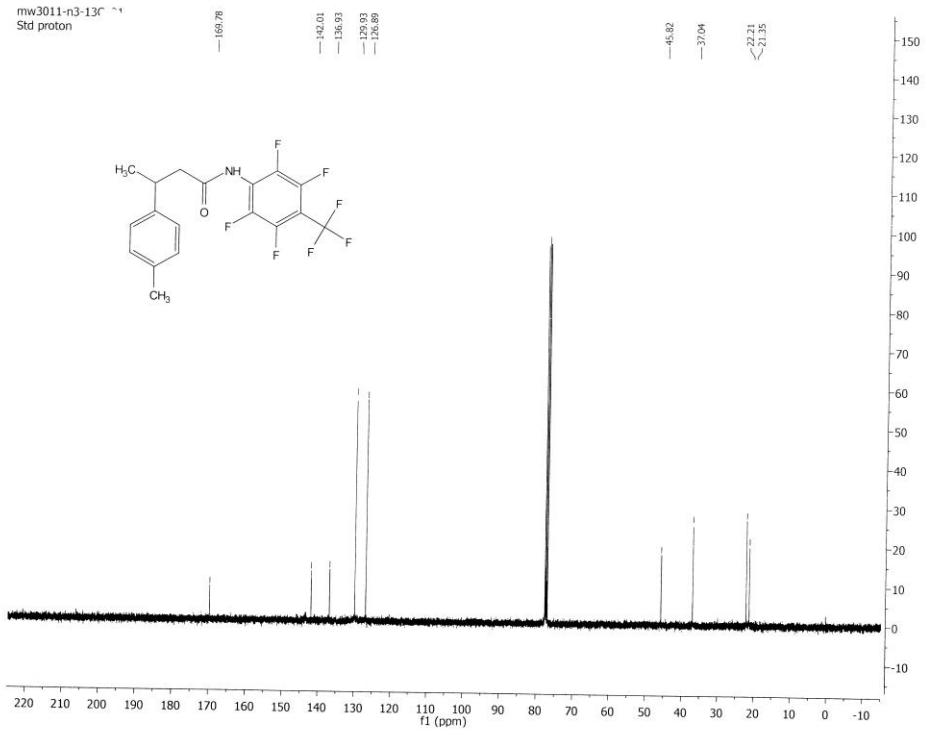
1b


mw31DE-n1-1h
Std proton
7.26
7.18
7.16
7.15
7.13
7.09
7.07
7.06
7.04
6.01
3.32
3.31
3.29
3.26
3.25
3.24
3.22
3.20
2.76
2.74
2.73
2.33
2.28
1.47
1.46
1.42
1.41
H3C
CH3
H3C
NH
O
F
F
F
F
F
F
F
CH3
5.00
4.71
0.89
2.11
0.95
3.56
3.24
3.00
3.09
f1 (ppm)

2a

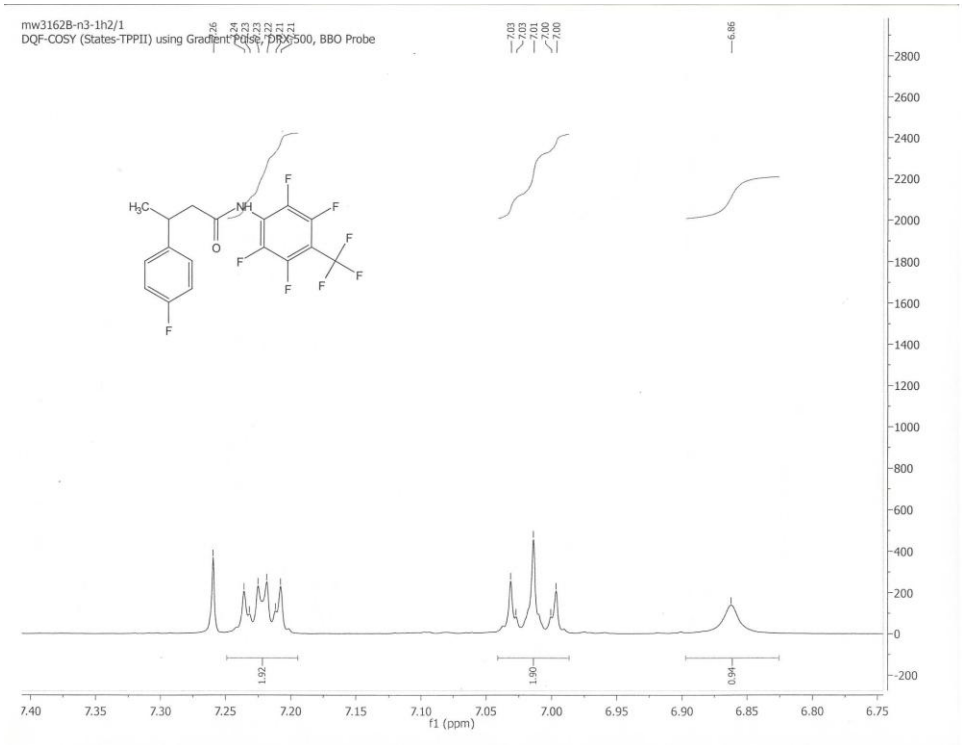

mw3011-n3-1h
Std proton
7.15
6.75
3.35
3.33
3.31
3.29
2.73
2.72
2.71
2.70
1.38
1.37
f1 (ppm)

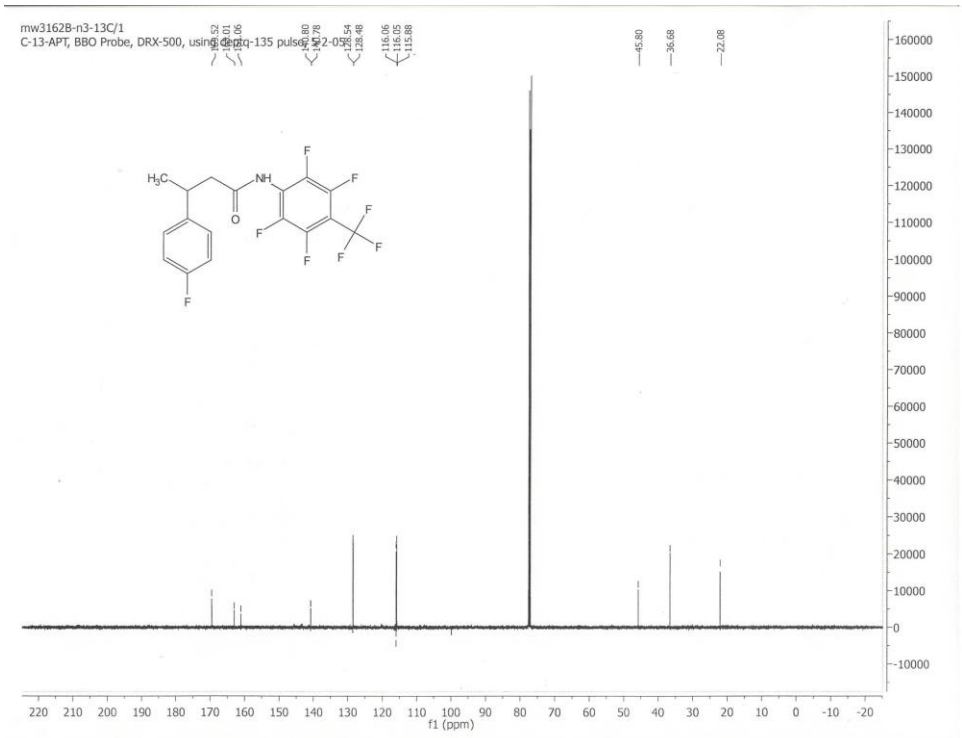

mw3011-n3-1h
Std proton
2.73
2.72
2.71
2.70
2.33
1.38
1.37
f1 (ppm)

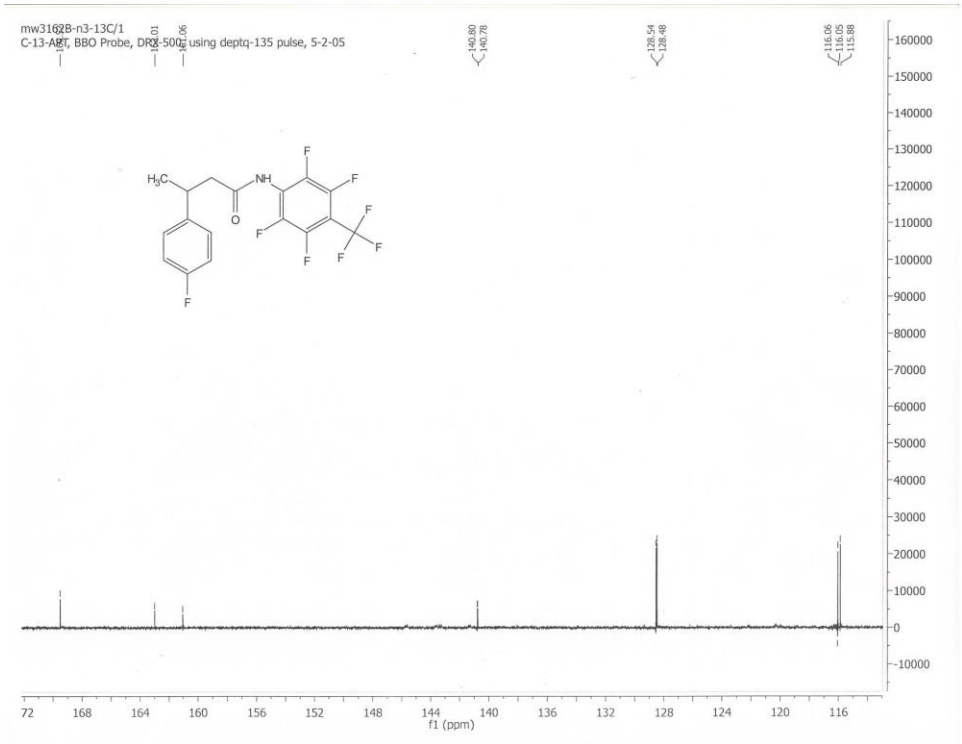

mw3011-n3-13C
Std proton
169.78
142.01
136.93
129.93
126.89
45.82
37.04
22.21
21.35
f1 (ppm)

2b

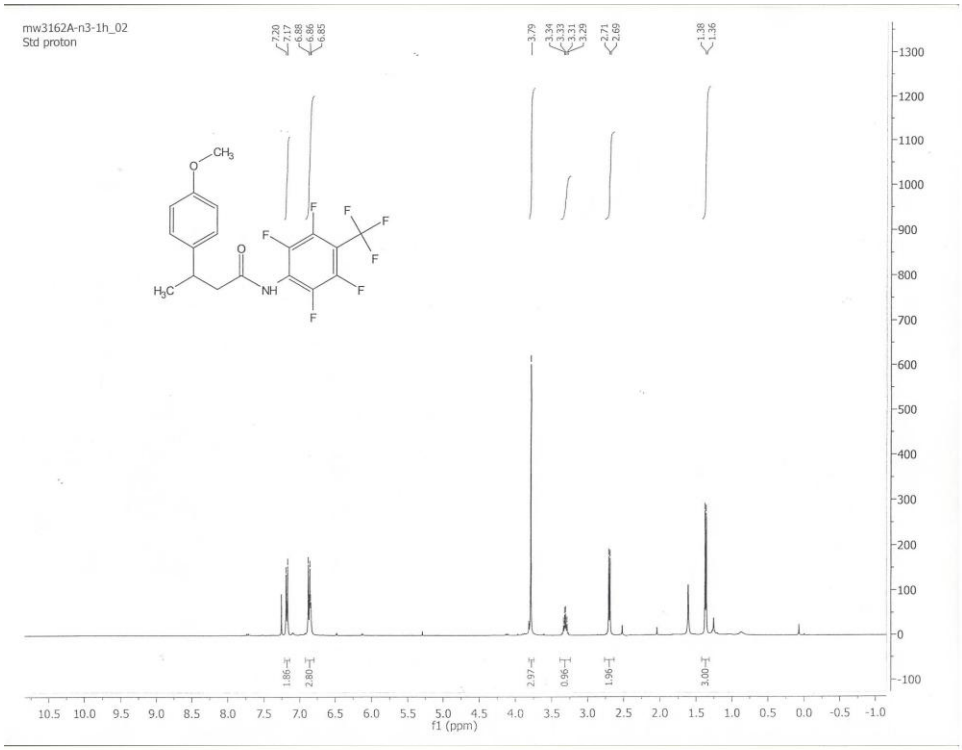

mw3162B-n3-1h2/1
DQF-COSY (States-TPPI) using Gradient Pulse, DRX-500, BBO Probe
f1 (ppm)

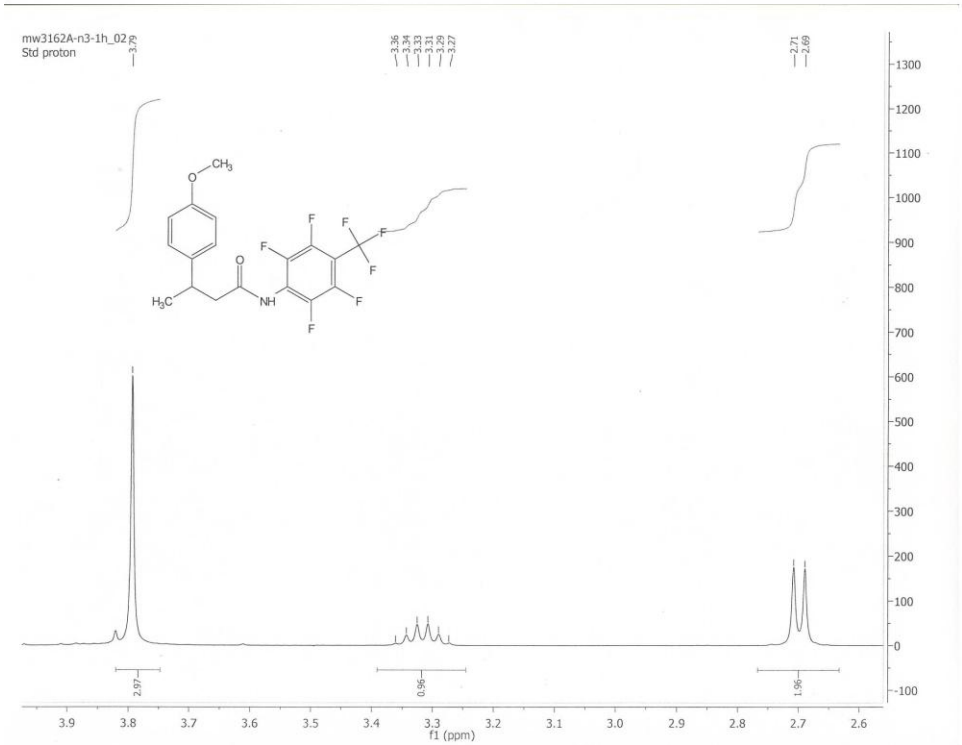

mw3162B-n3-1h2/1
DQF-COSY (States-TPPI) using Gradient Pulse, DRX-500, BBO Probe
f1 (ppm)


mw3162B-n3-13C/1
C-13-APT, BBO Probe, DRX-500, using deptq-135 pulse, 5-2-05
f1 (ppm)


mw3162B-n3-13C/1
C-13-APT, BBO Probe, DRX-500, using deptq-135 pulse, 5-2-05
f1 (ppm)

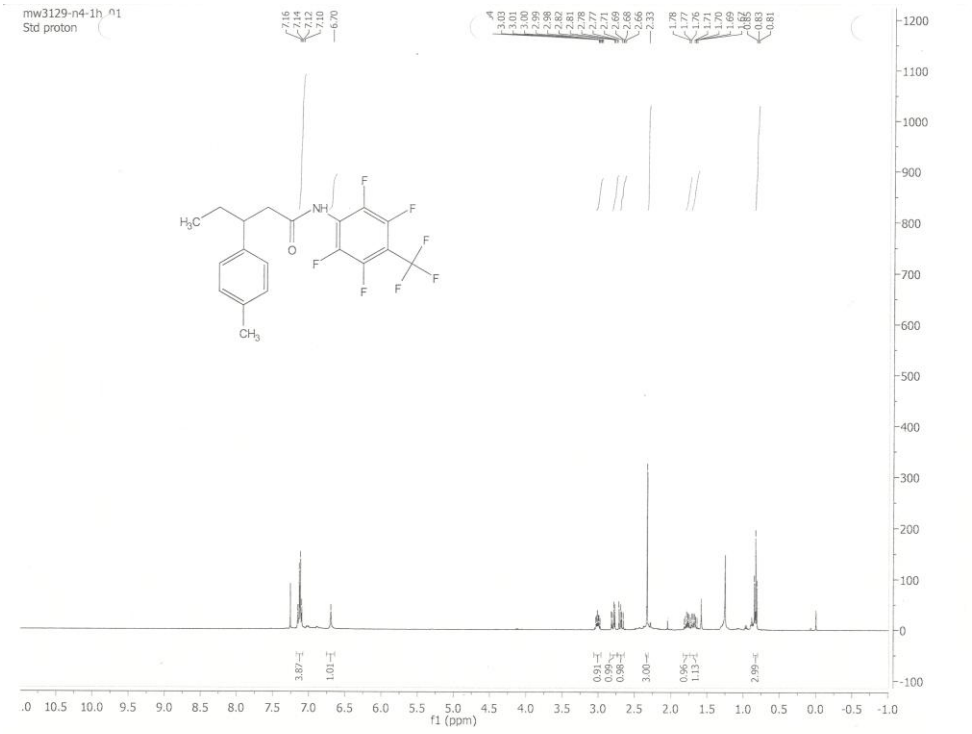
2c

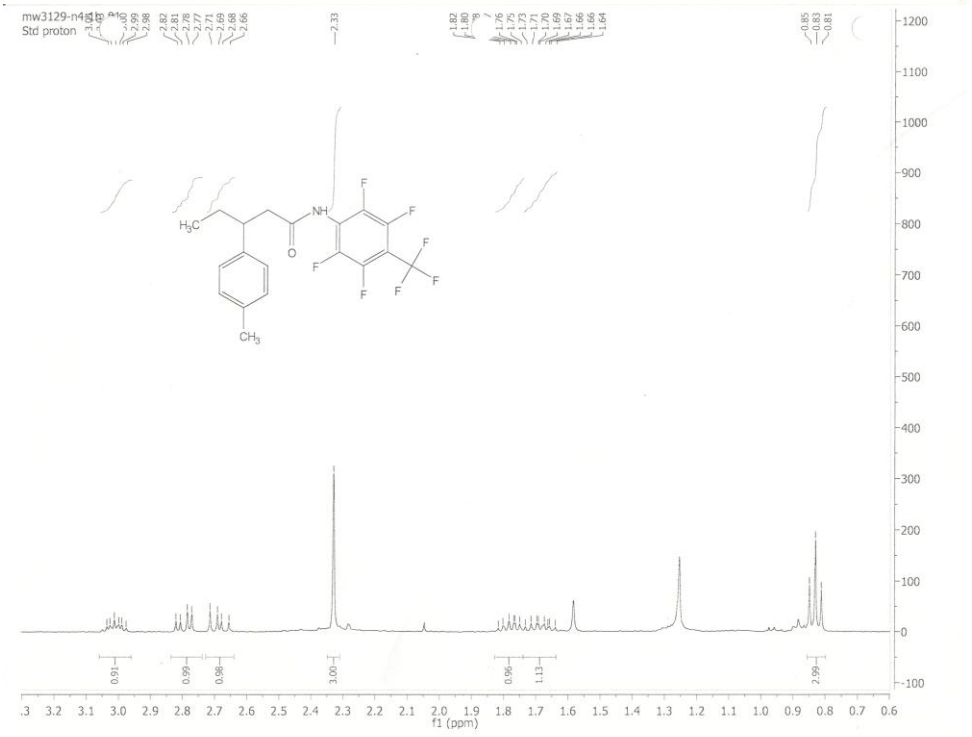

mw3162A-n3-1h_02
Std proton
7.20
7.17
6.88
6.86
6.85
3.79
3.34
3.33
3.31
3.29
2.71
2.69
1.38
1.36
O
CH3
F
F
F
F
F
F
O
H3C
NH
1.86
2.80
2.97
0.96
1.96
3.00
f1 (ppm)

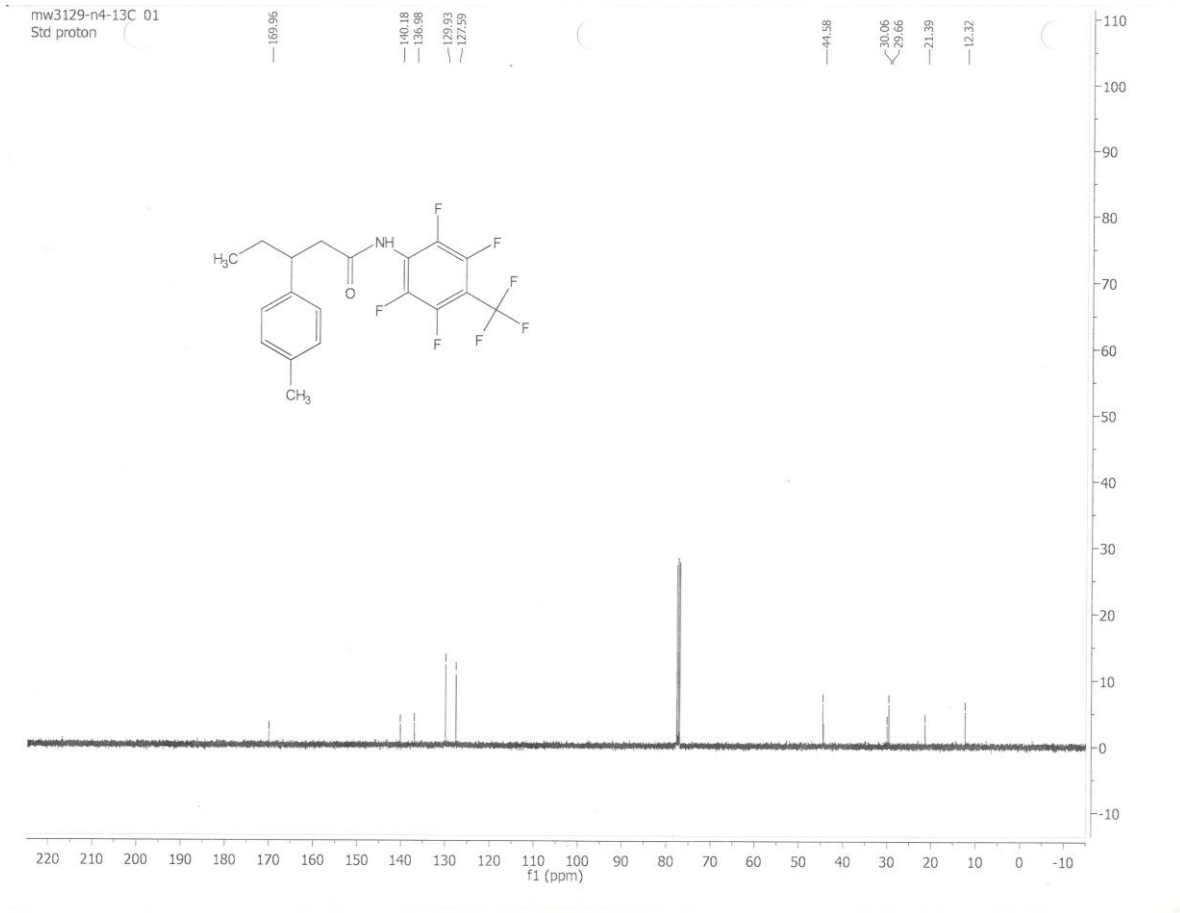

mw3162A-n3-1h_02
Std proton
3.79
3.36
3.34
3.33
3.31
3.29
3.27
2.71
2.69
O
CH3
F
F
F
F
F
F
O
H3C
NH
2.97
0.96
1.96
f1 (ppm)


mw3162A-n3-1h_03
Std proton
169.86
158.82
137.06
127.99
114.61
55.64
45.97
36.66
22.26
O
CH3
H3C
NH
F
f1 (ppm)

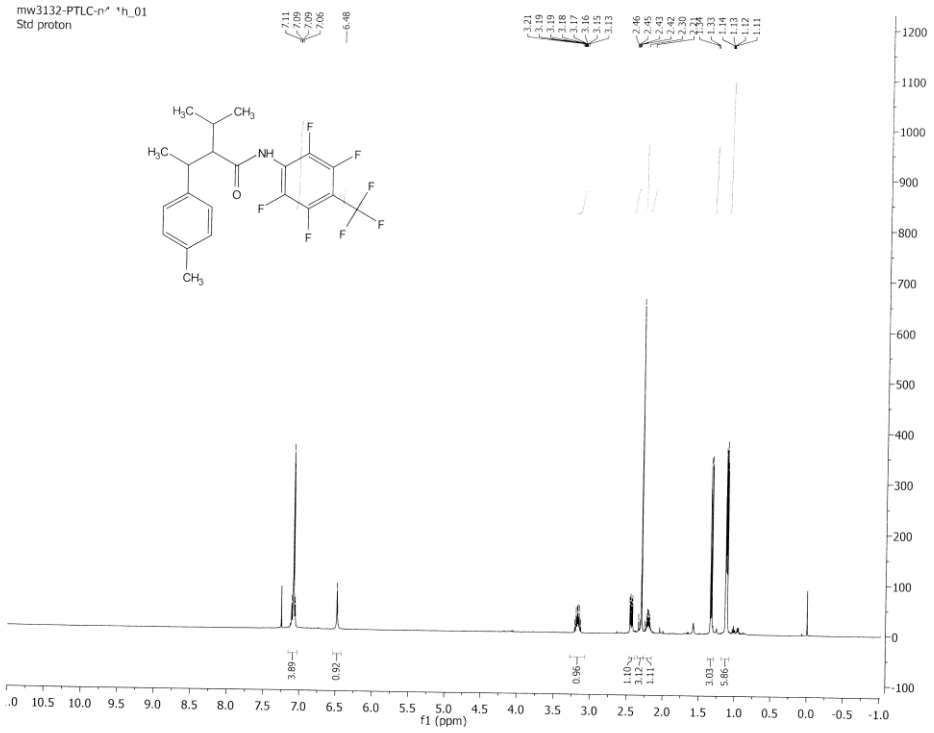
3a

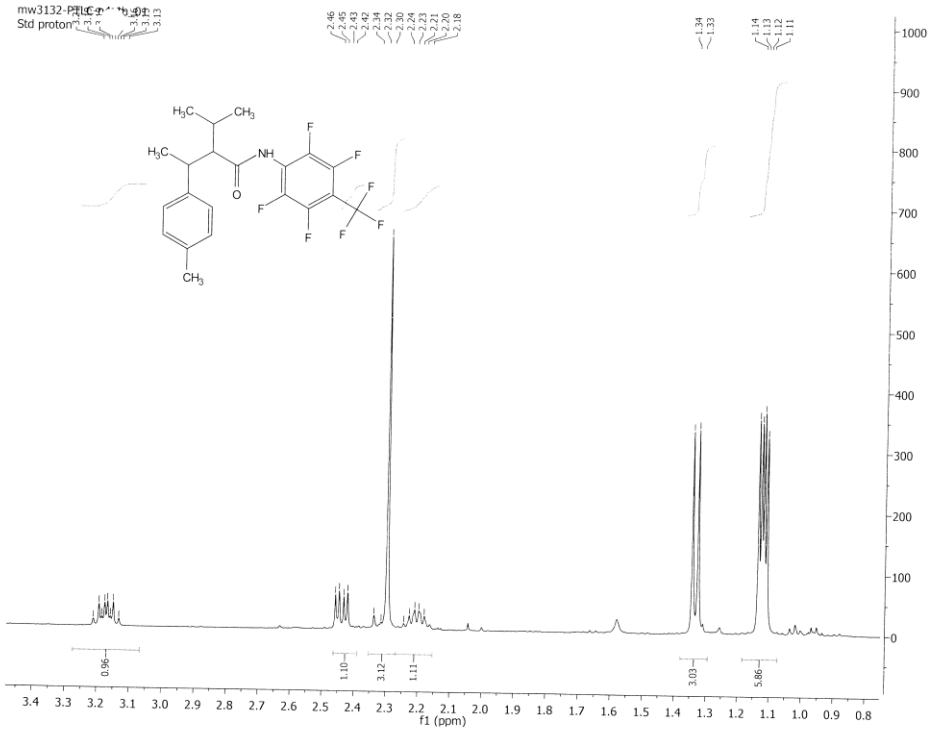


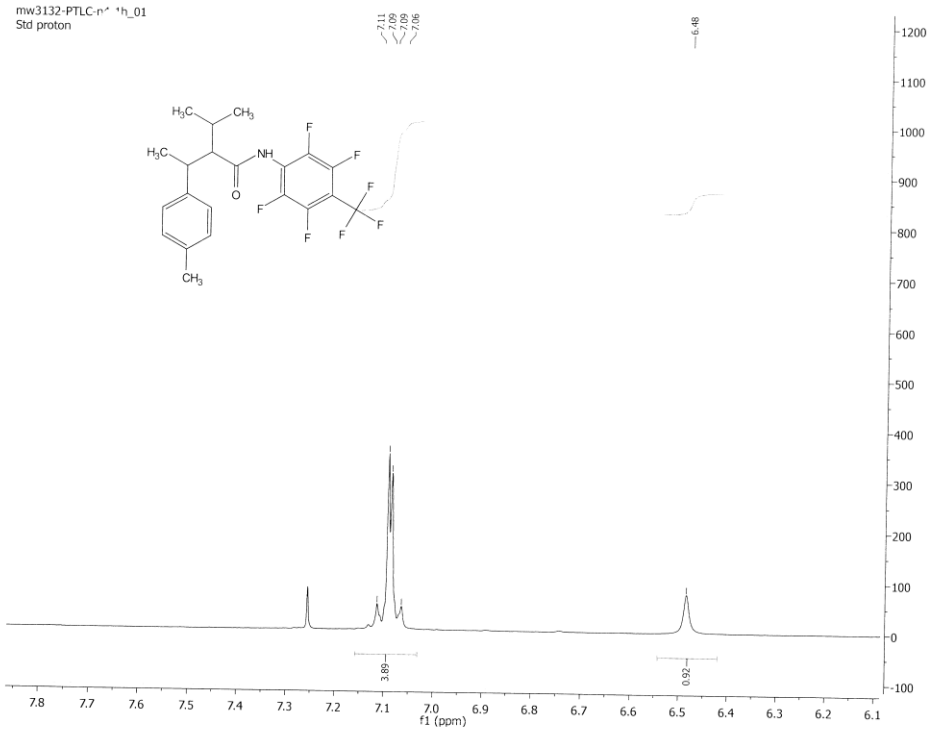


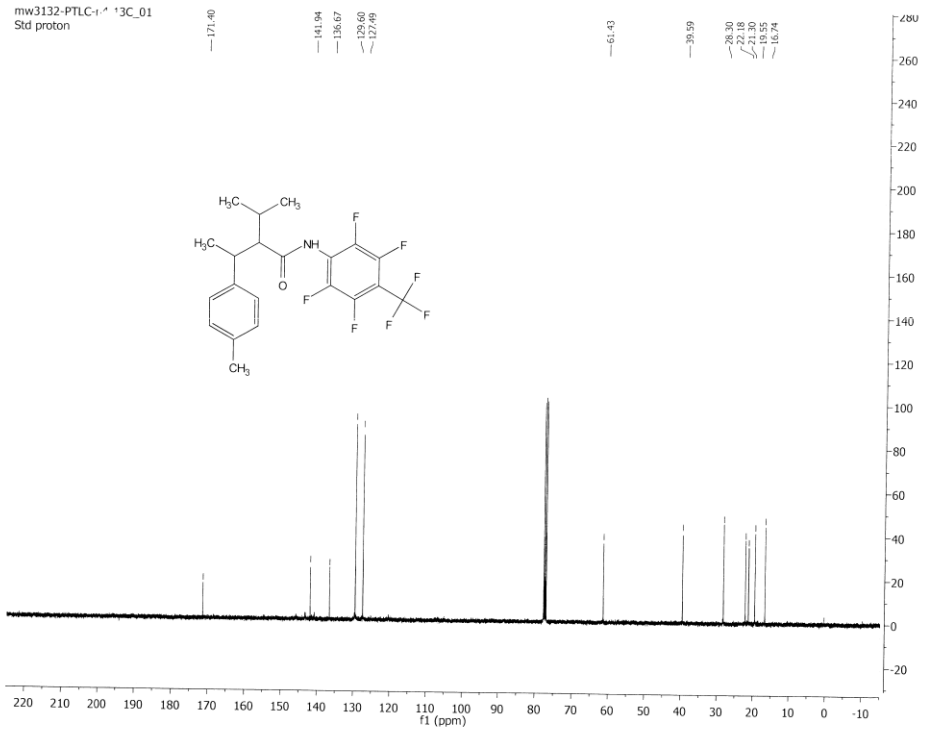

mw3129-n4-13C 01
Std proton
169.96
140.18
136.98
129.93
127.59
44.58
30.06
29.66
21.39
12.32
NH
O
F
F
F
F
F
F
F
H3C
CH3
f1 (ppm)

4a

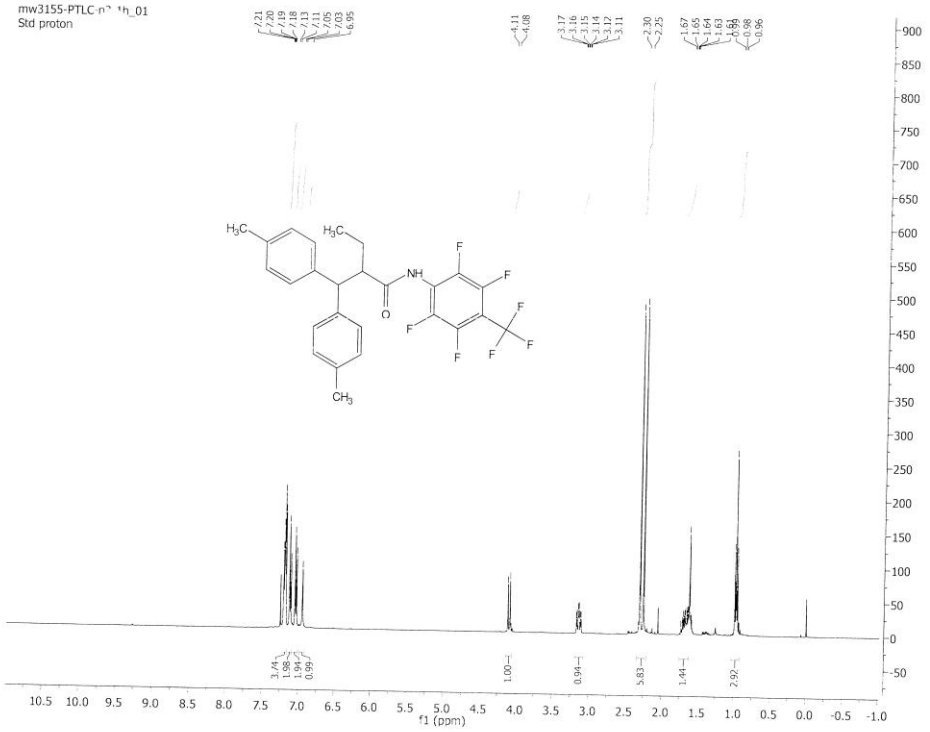


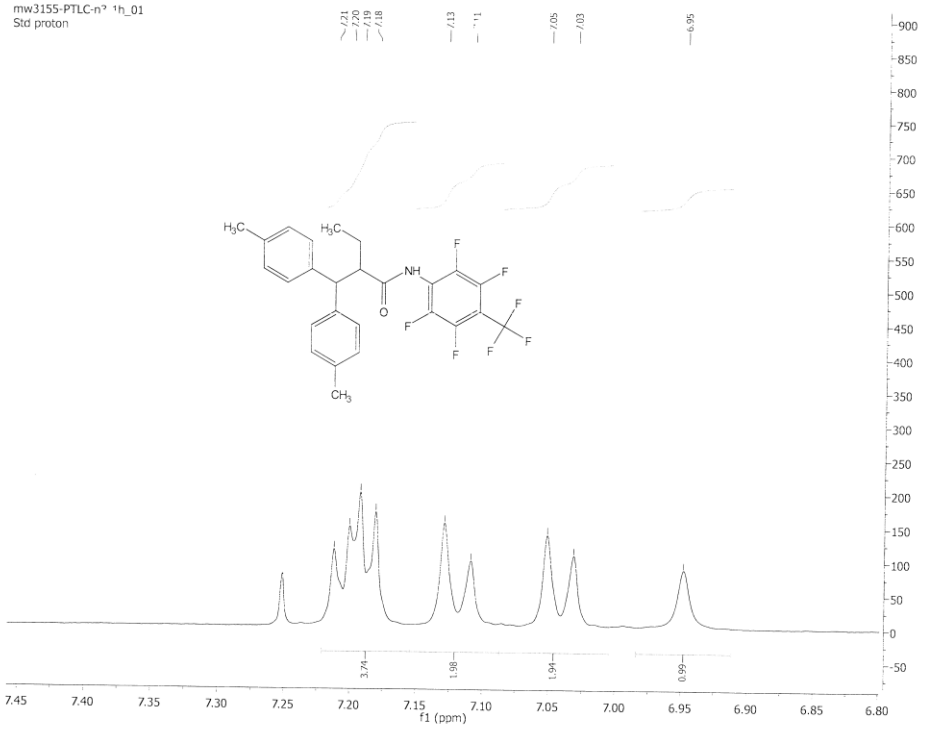


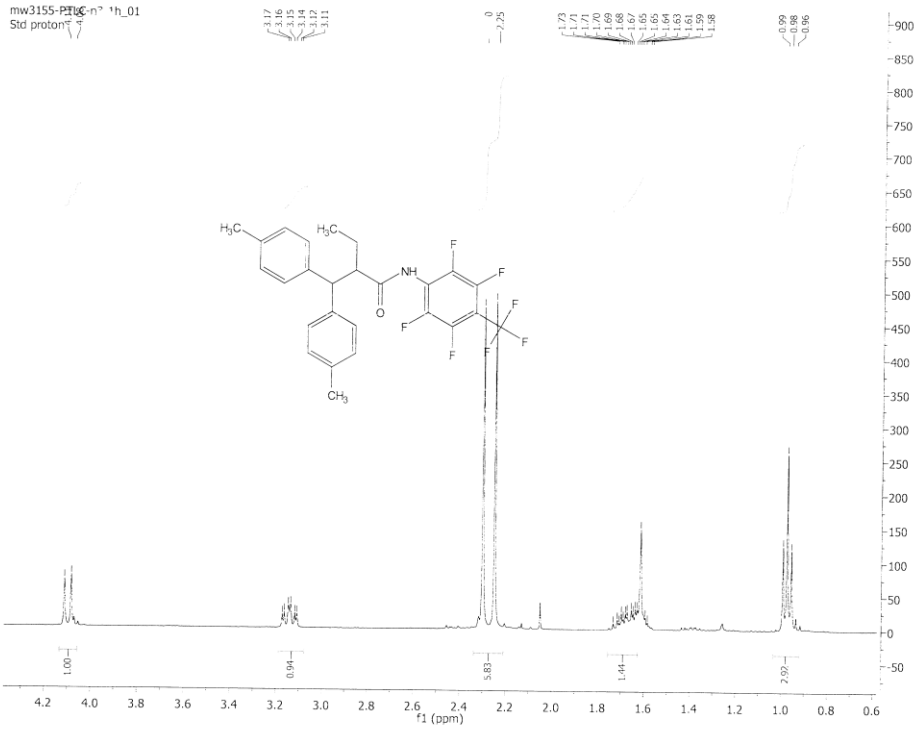

mw3132-PTLC-n^ 1h_01
Std proton
7.11
7.09
7.09
7.06
6.48
3.89
0.92
f1 (ppm)

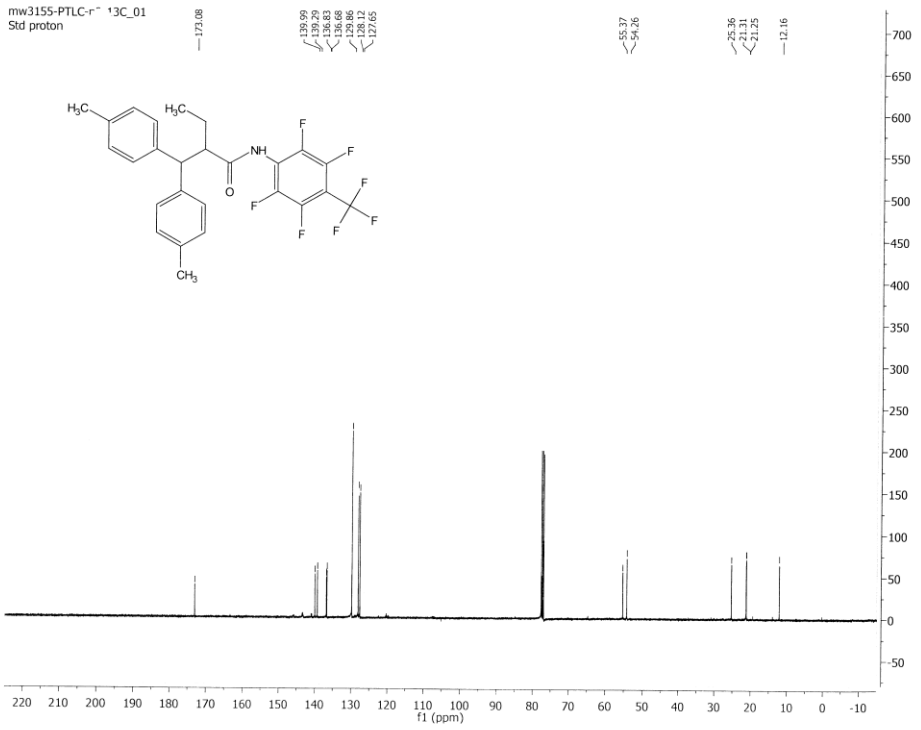

mw3132-PTLC-n^ 13C_01
Std proton
171.40
141.94
136.67
129.60
127.49
61.43
39.59
28.30
22.18
21.30
19.55
16.74
f1 (ppm)

5a

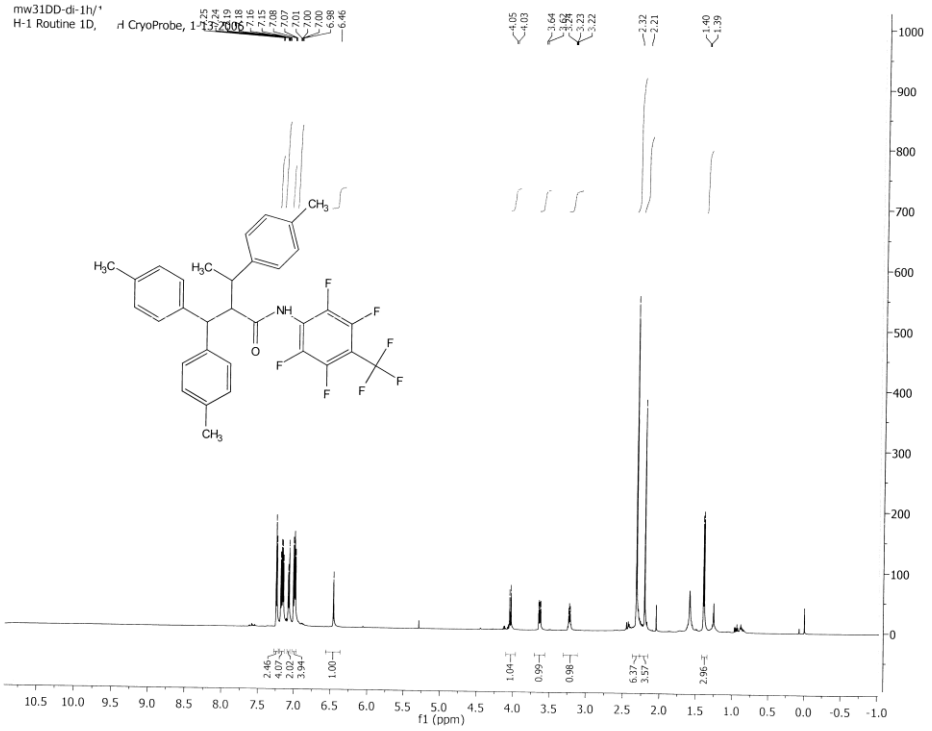

mw3155-PTLC-n? 1h_01
Std proton
f1 (ppm)

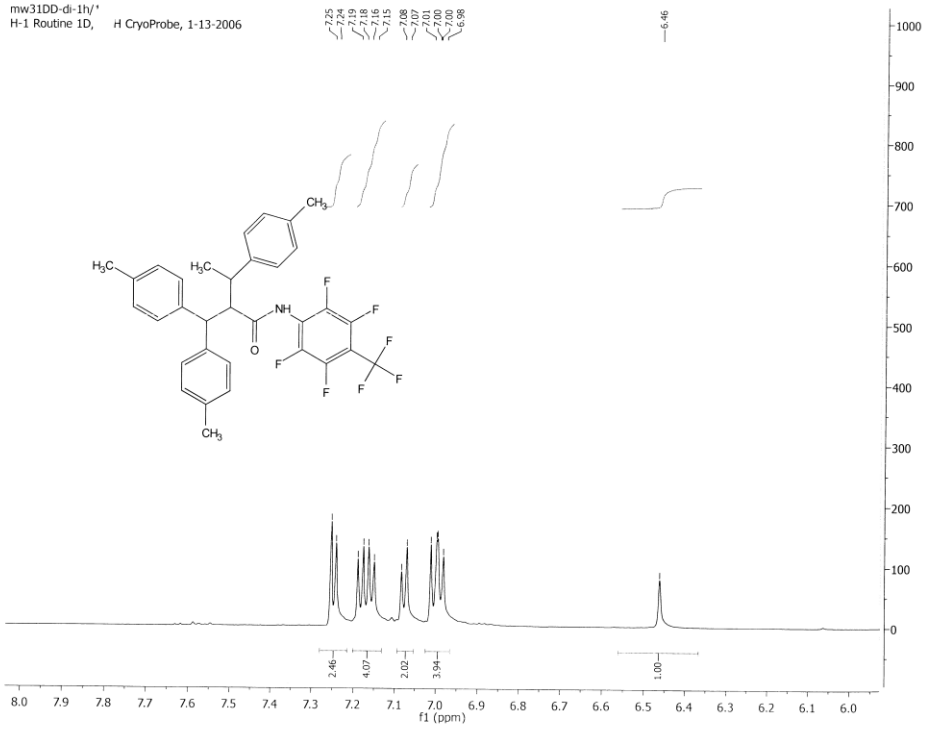

mw3155-PTLC-n? 1h_01
Std proton
f1 (ppm)

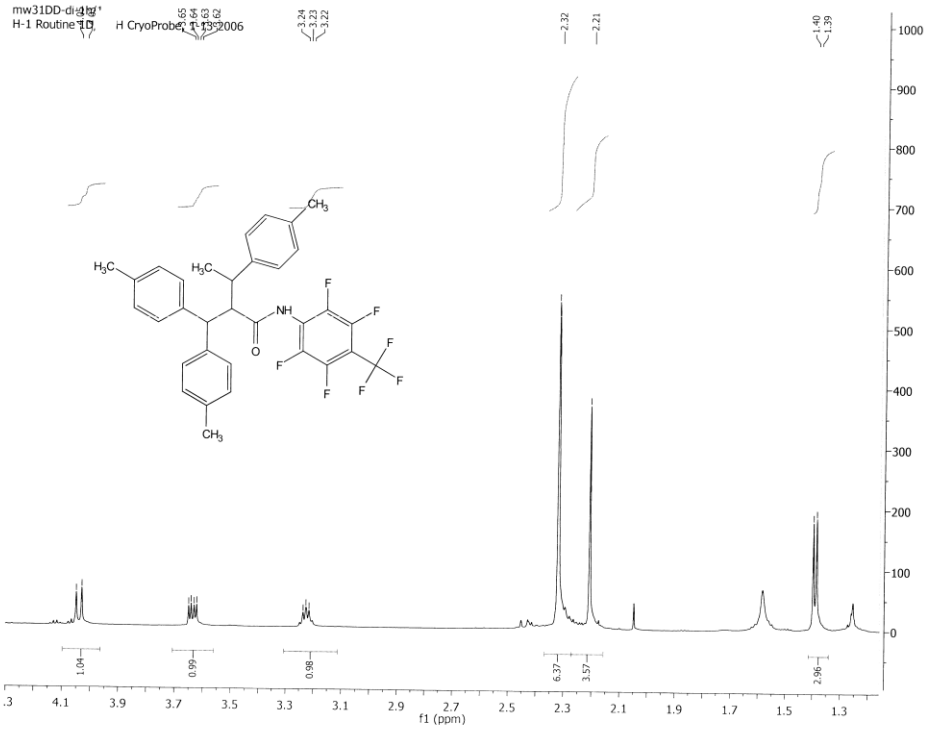

Std proton
3.17
3.16
3.15
3.14
3.12
3.11
2.25
1.73
1.71
1.71
1.70
1.69
1.68
1.67
1.66
1.65
1.64
1.63
1.61
1.59
1.58
0.99
0.98
0.96
1.00
0.94
5.83
1.44
2.93
f1 (ppm)

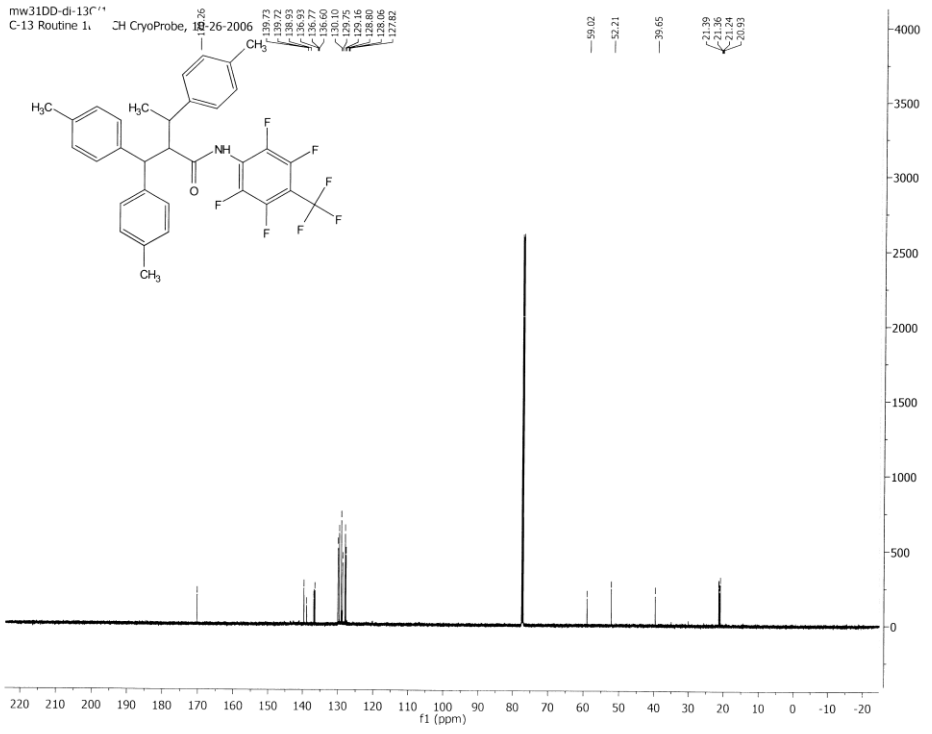

Std proton
173.08
139.99
139.29
136.83
136.68
130.86
128.12
127.65
55.37
54.26
25.36
21.31
21.25
12.16
f1 (ppm)

5b

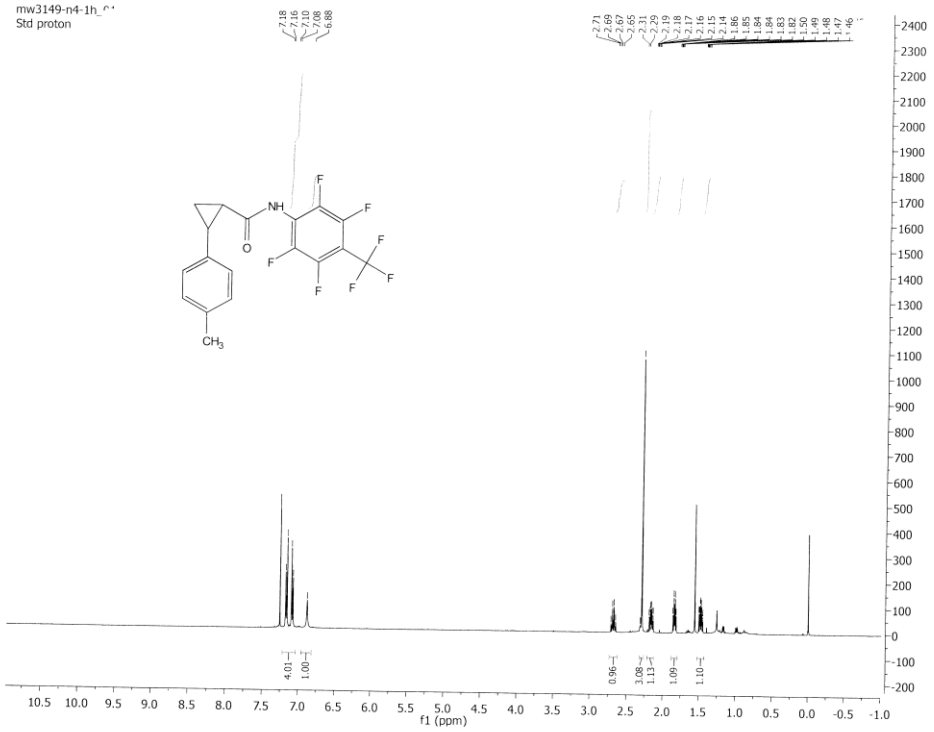

mw31DD-di-1h/*
H-1 Routine 1D, H CryoProbe, 1-13-2006
7.25
7.24
7.19
7.18
7.16
7.15
7.08
7.07
7.01
7.00
7.00
6.98
6.46
4.05
4.03
3.64
3.63
3.24
3.23
3.22
2.32
2.21
1.40
1.39
CH3
H3C
H3C
NH
O
F
F
F
F
F
F
F
F
CH3
2.46
4.07
2.02
3.94
1.00
1.04
0.99
0.98
6.37
3.57
2.96
f1 (ppm)

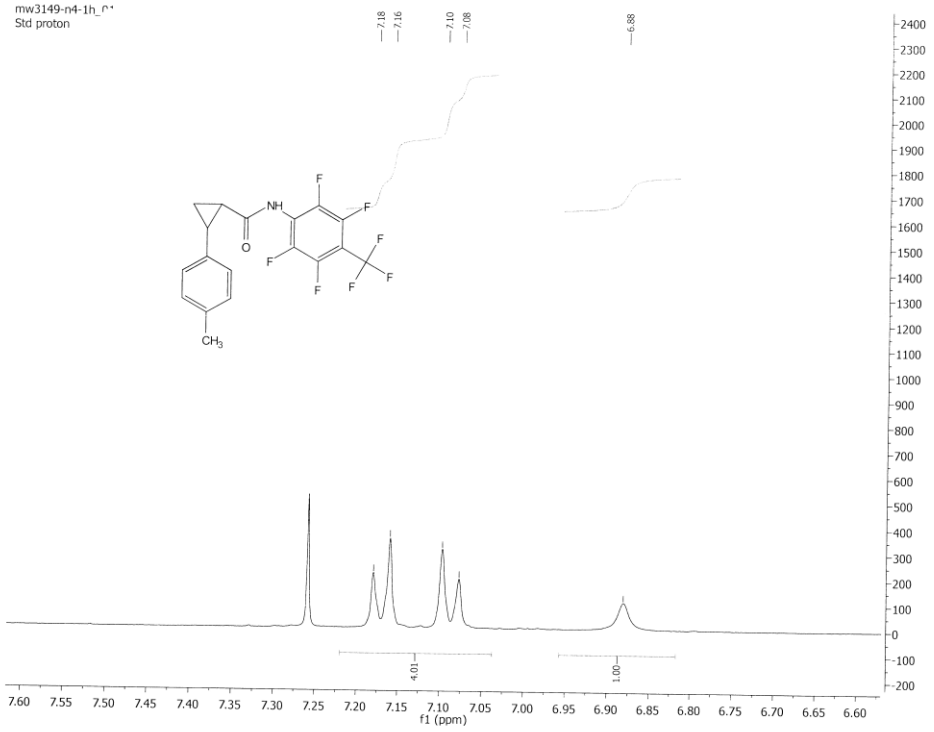

mw31DD-di-1h/*
H-1 Routine 1D, H CryoProbe, 1-13-2006
7.25
7.24
7.19
7.18
7.16
7.15
7.08
7.07
7.01
7.00
7.00
6.98
6.46
CH3
H3C
H3C
NH
O
F
F
F
F
F
F
F
F
CH3
2.46
4.07
2.02
3.94
1.00
f1 (ppm)

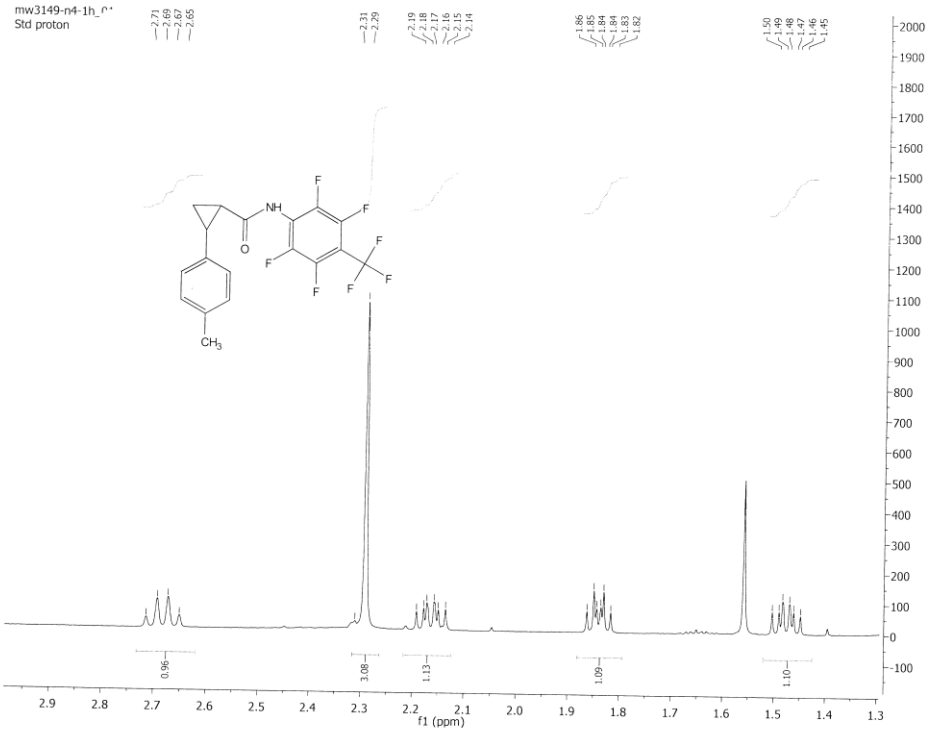

3.65
3.64
3.63
3.62
3.24
3.23
3.22
2.32
2.21
1.40
1.39
1.04
0.99
0.98
6.37
3.57
2.96
f1 (ppm)

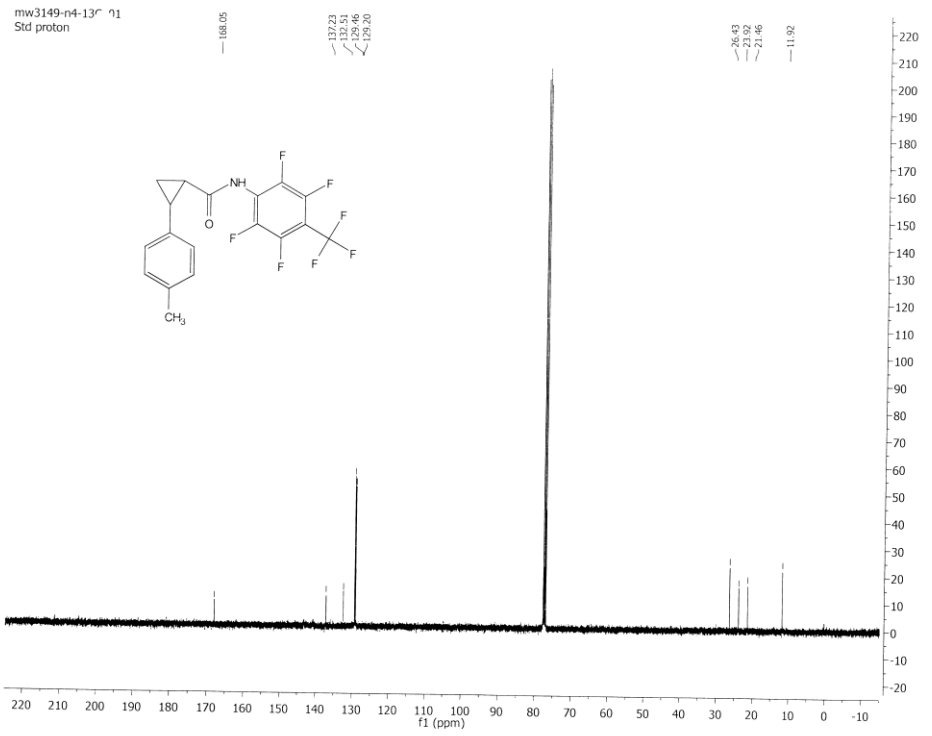

59.02
52.21
39.65
21.39
21.36
21.24
20.93
f1 (ppm)

6a

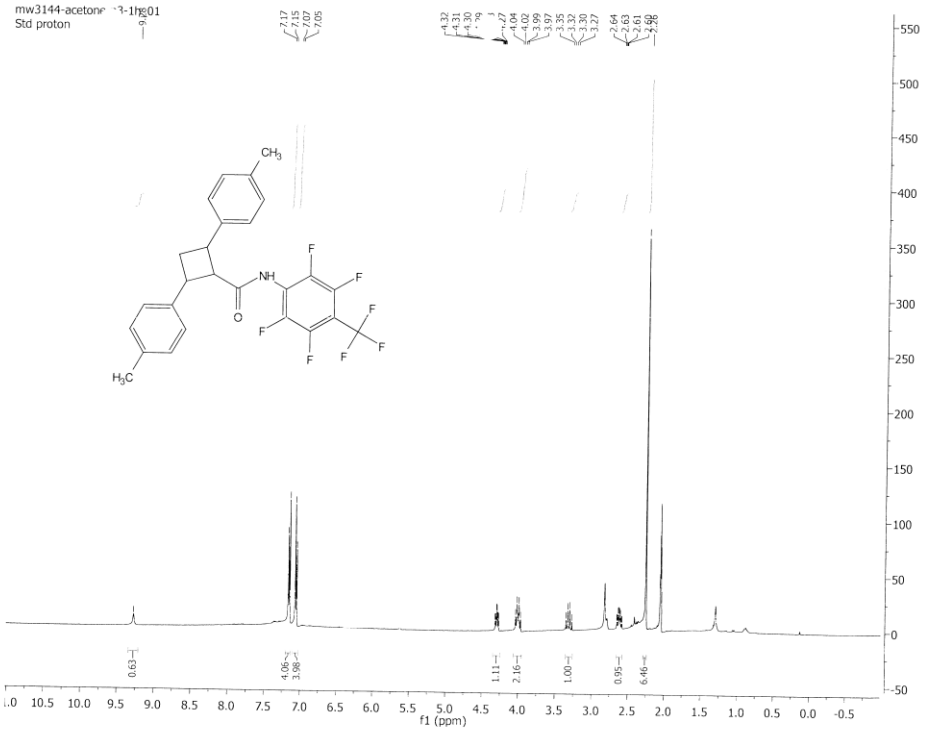

Std proton
7.18
7.16
7.10
7.08
6.88
2.71
2.69
2.67
2.65
2.31
2.29
2.19
2.18
2.17
2.16
2.15
2.14
1.86
1.85
1.84
1.83
1.82
1.50
1.49
1.48
1.47
1.46
NH
O
F
F
F
F
F
F
F
F
CH3
4.01
1.00
0.96
3.08
1.13
1.09
1.10
f1 (ppm)

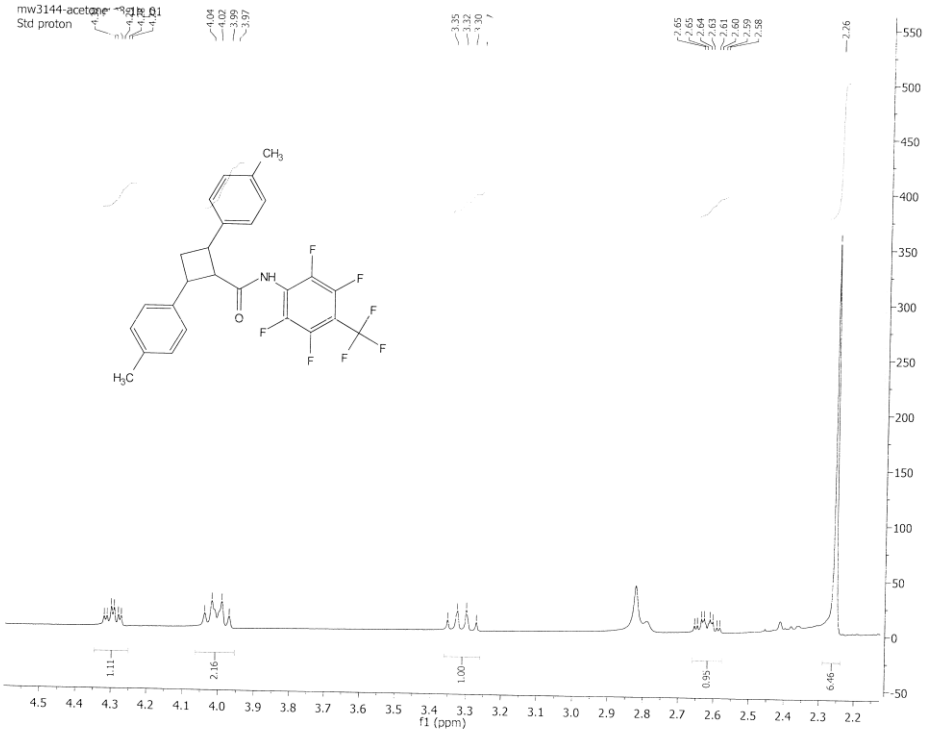

Std proton
7.18
7.16
7.10
7.08
6.88
NH
O
F
F
F
F
F
F
F
F
CH3
4.01
1.00
f1 (ppm)

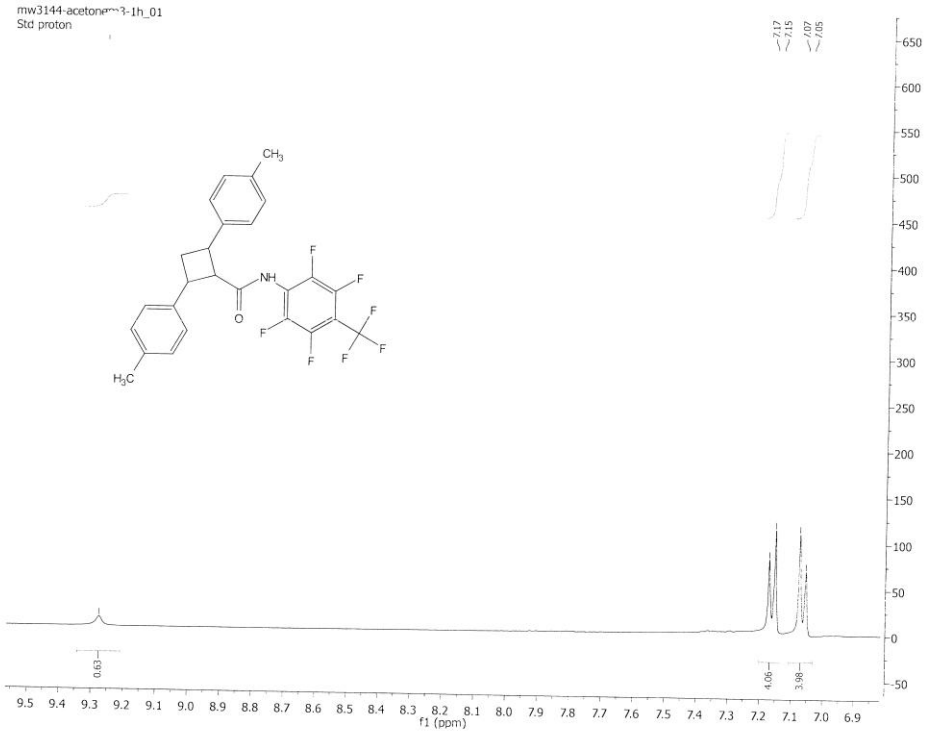

Std proton
2.71
2.69
2.67
2.65
2.31
2.29
2.19
2.18
2.17
2.16
2.15
2.14
1.86
1.85
1.84
1.84
1.83
1.82
1.50
1.49
1.48
1.47
1.46
1.45
NH
O
F
CH3
0.96
3.08
1.13
1.09
1.10
f1 (ppm)

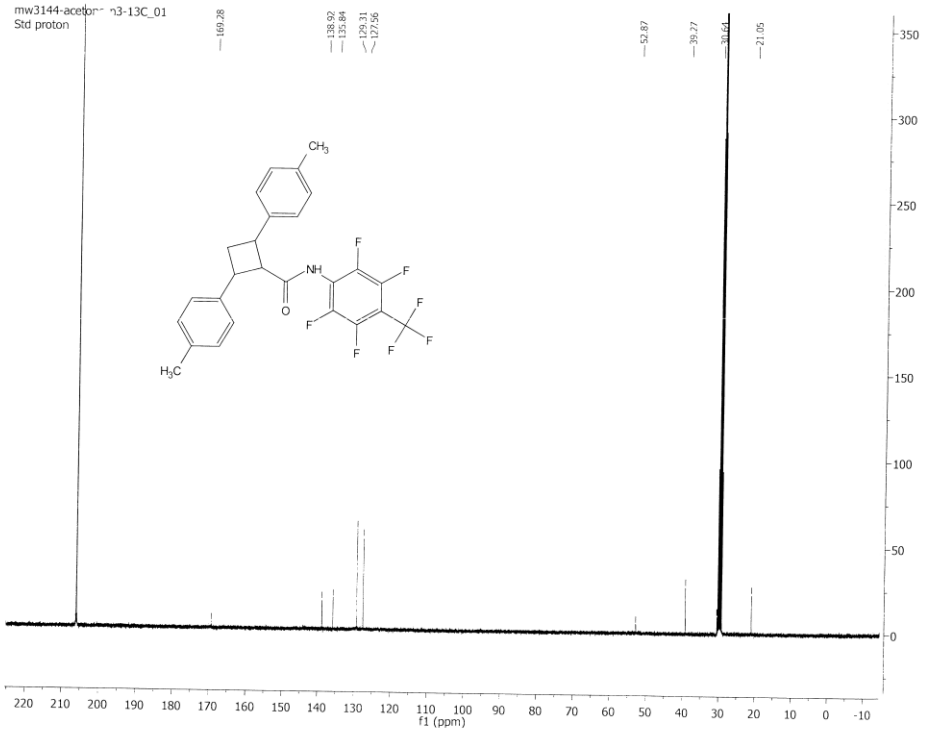

Std proton
168.05
137.23
132.51
129.46
129.20
26.43
23.92
21.46
11.92
NH
O
F
CH3
f1 (ppm)

7a

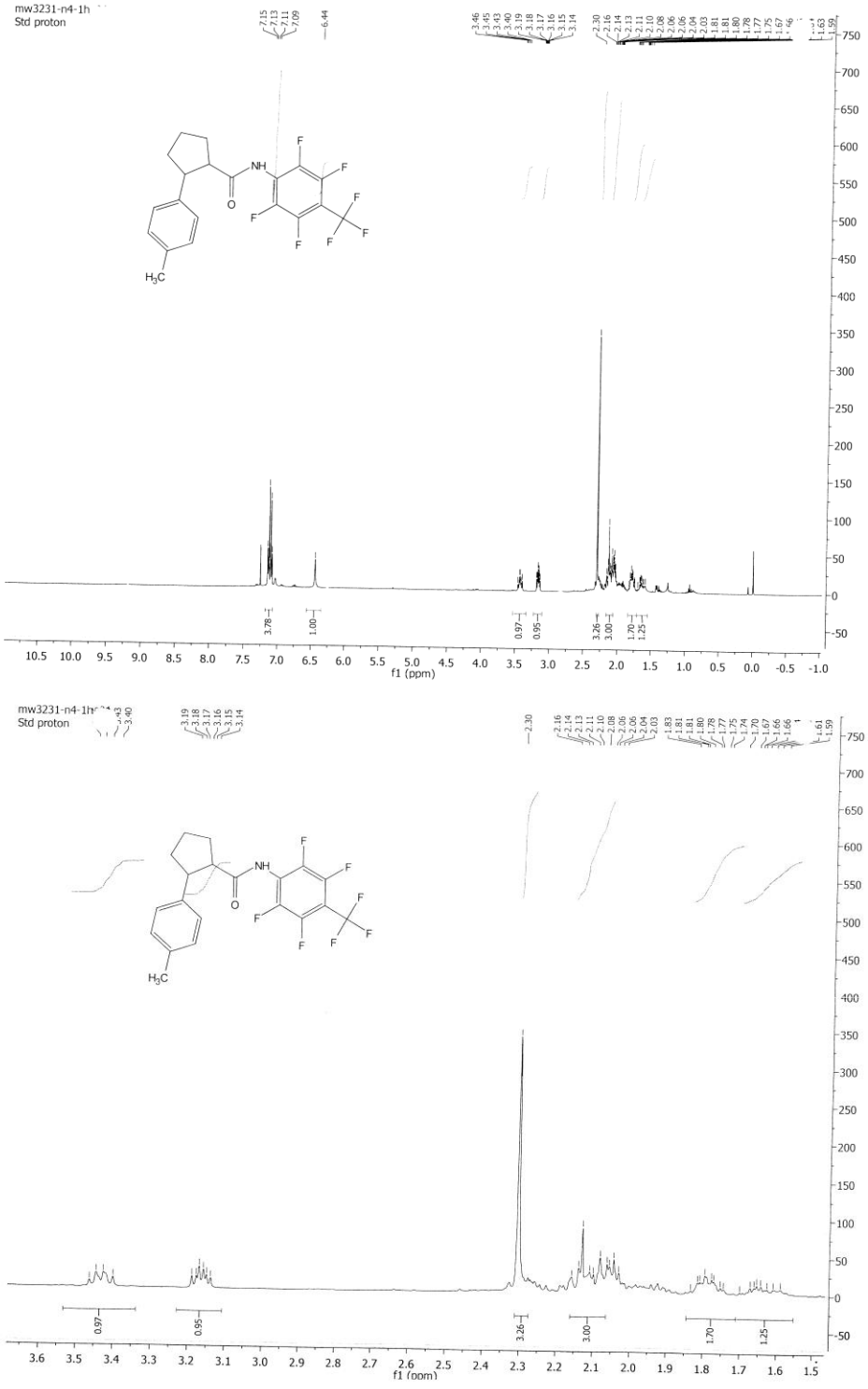


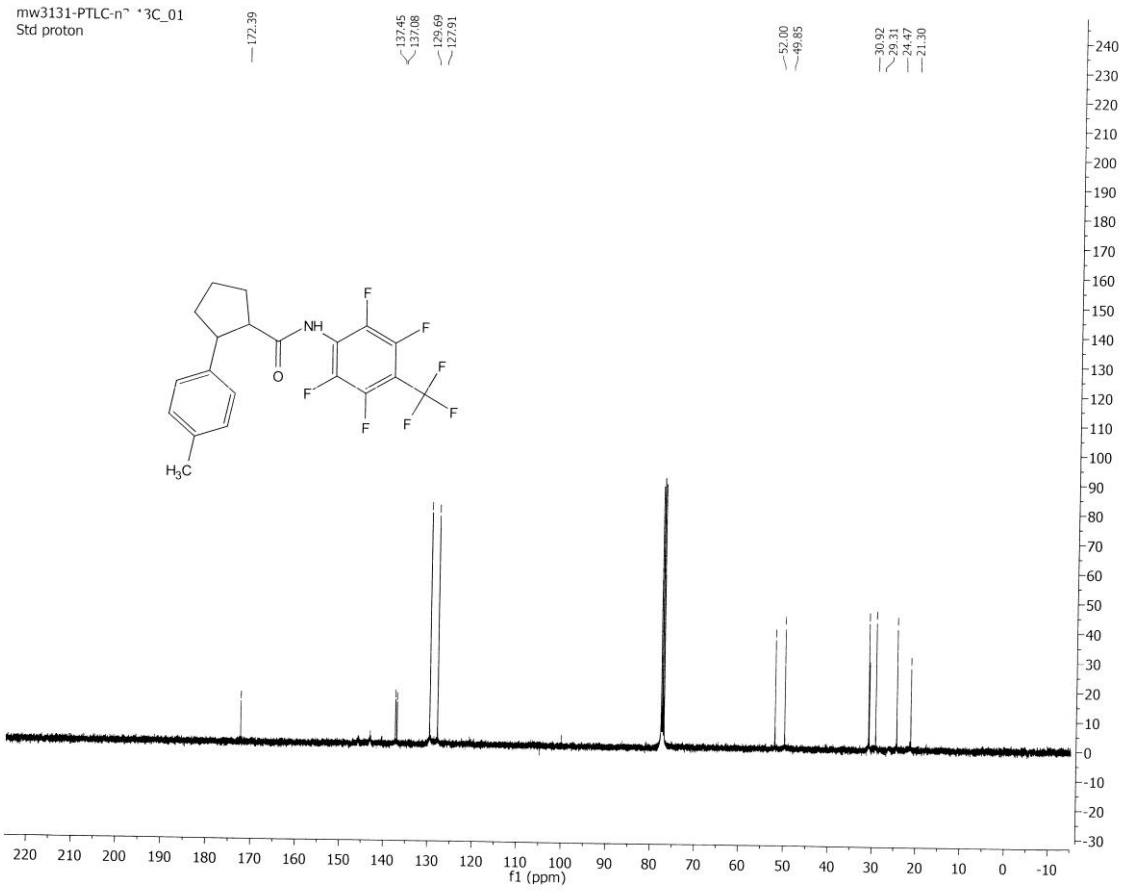



mw3144-acetone-n3-1h_01
Std proton
7.17
7.15
7.07
7.05
CH3
NH
O
F
H3C
0.63
4.06
3.98
f1 (ppm)

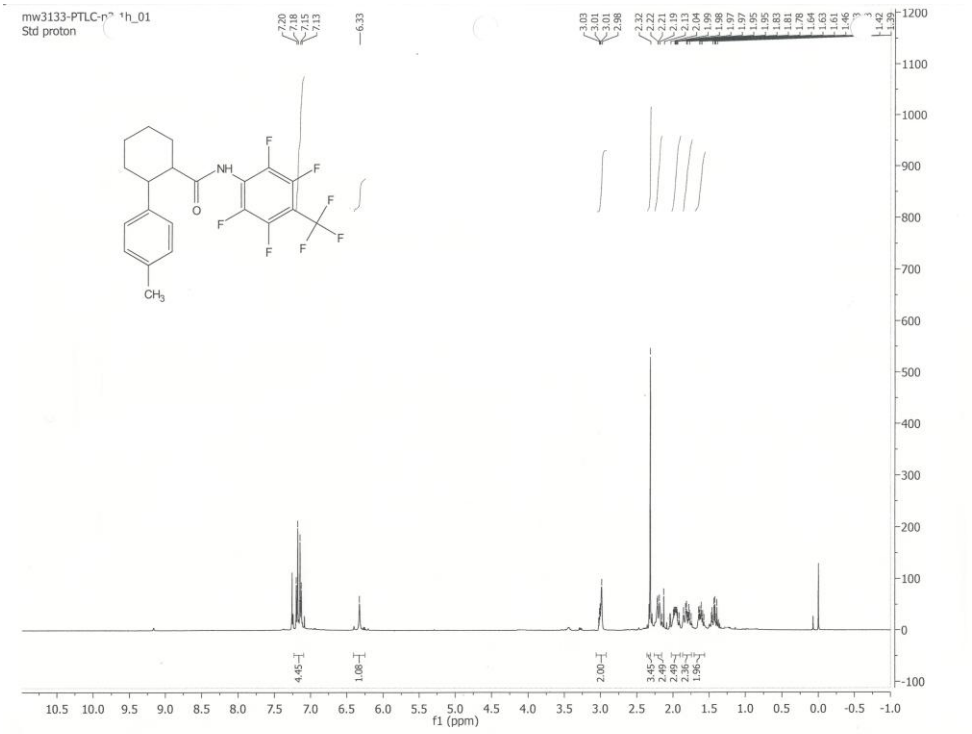

mw3144-acetone-n3-13C_01
Std proton
169.28
138.92
135.84
129.31
127.56
52.87
39.27
30.64
21.05
CH3
NH
O
F
H3C
f1 (ppm)

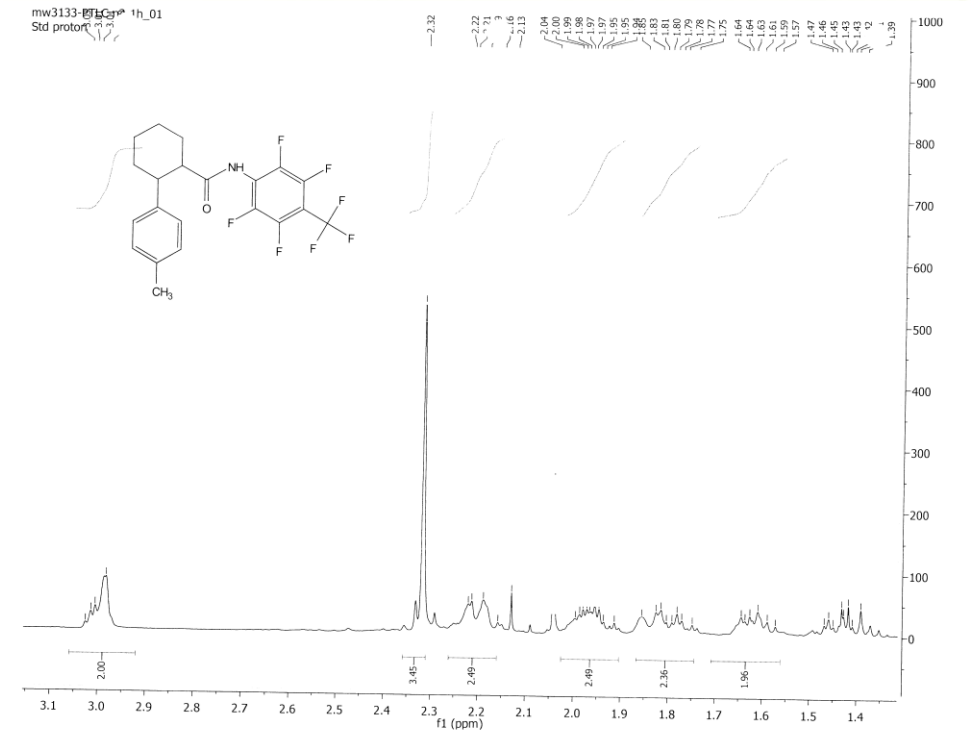
8a

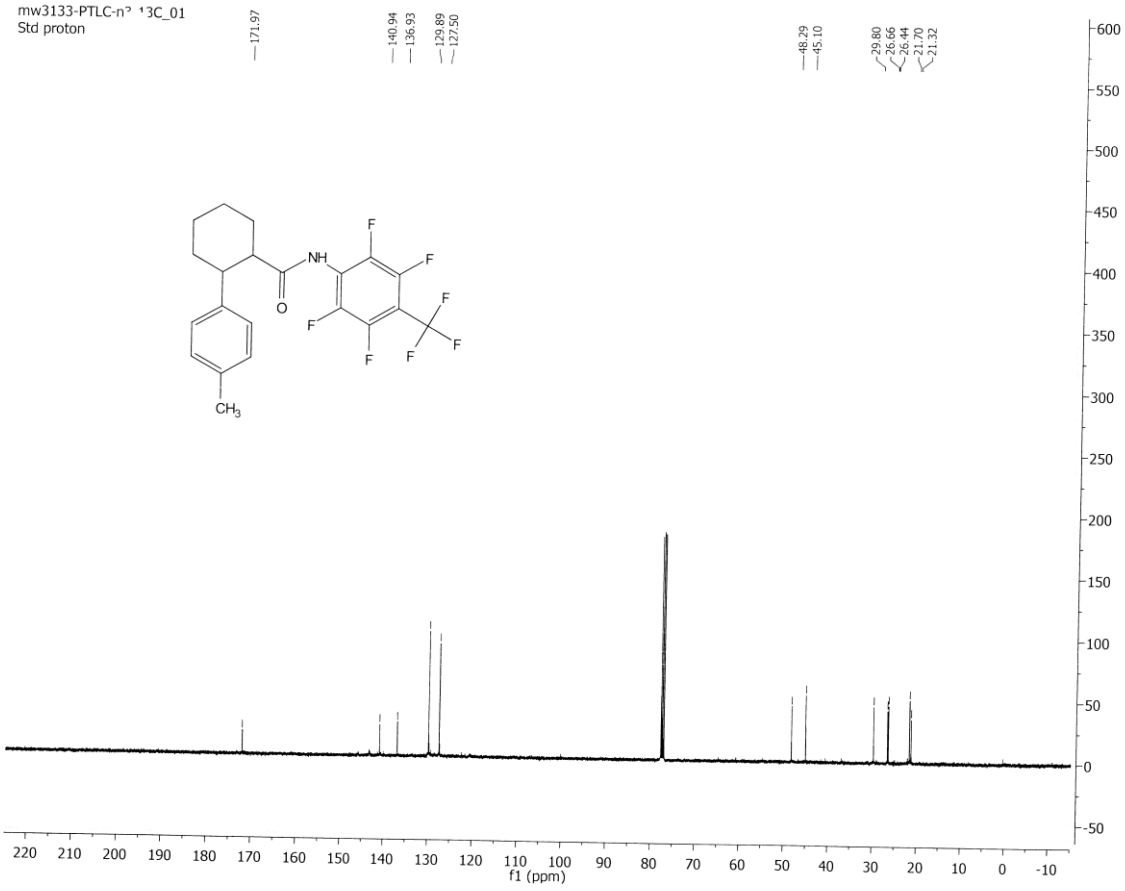



mw3131-PTLC-n^ ^3C_01
Std proton
172.39
137.45
137.08
129.69
127.91
52.00
49.85
30.92
29.31
24.47
21.30
NH
O
F
F
F
F
F
F
F
H3C
f1 (ppm)

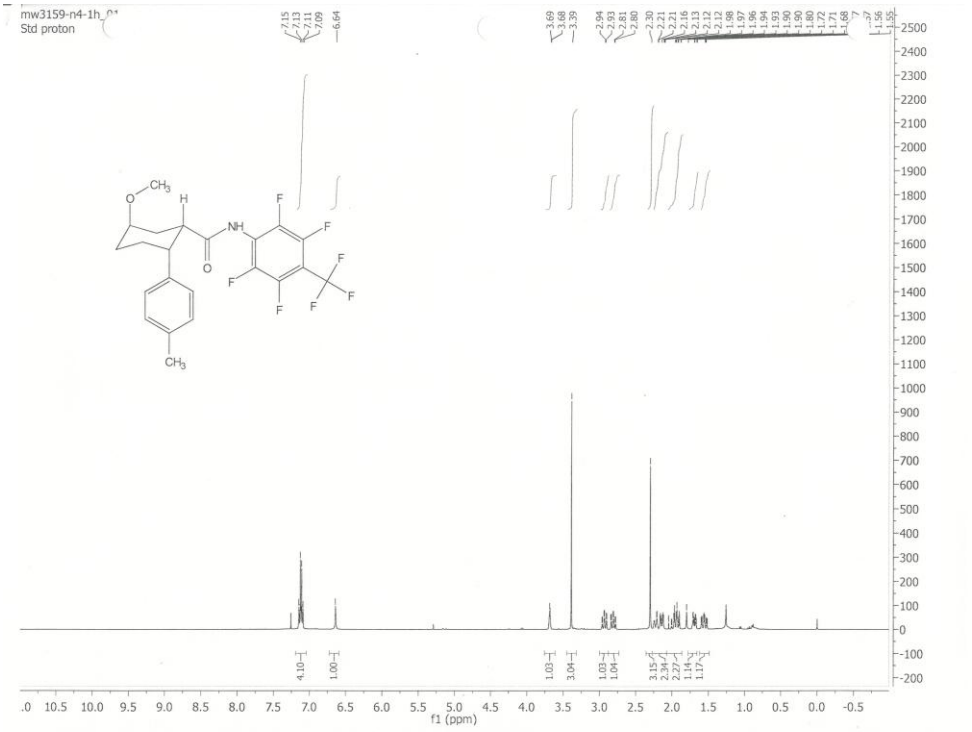
9a

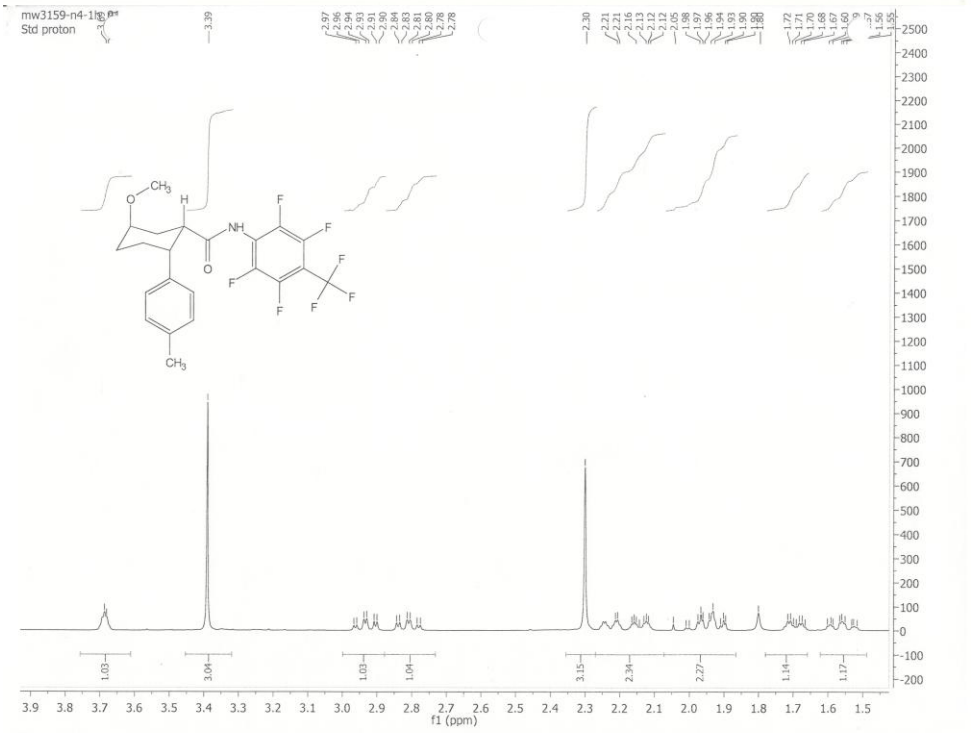


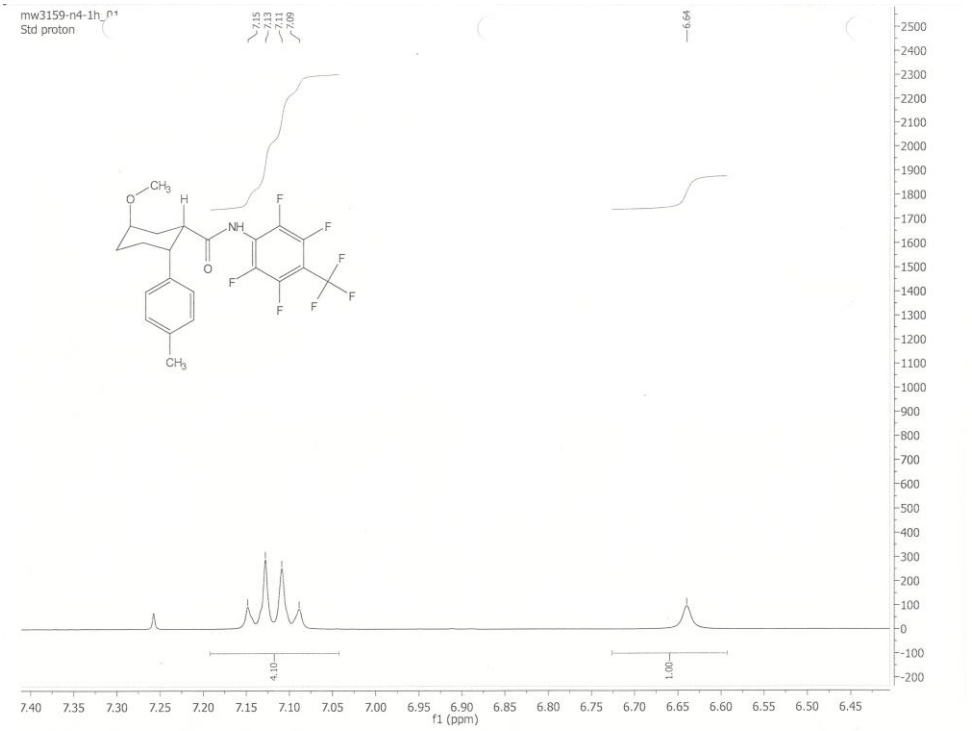


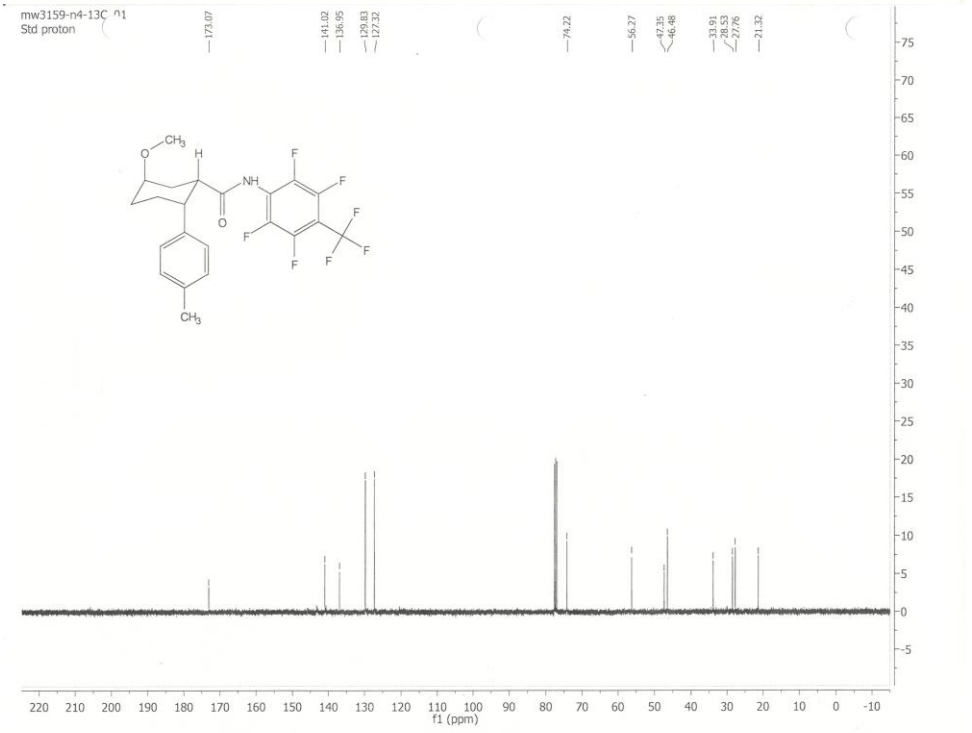

mw3133-PTLC-n° 13C_01
Std proton
171.97
140.94
136.93
129.89
127.50
48.29
45.10
29.80
26.66
26.44
21.70
21.32
NH
O
F
CH3
f1 (ppm)

10a

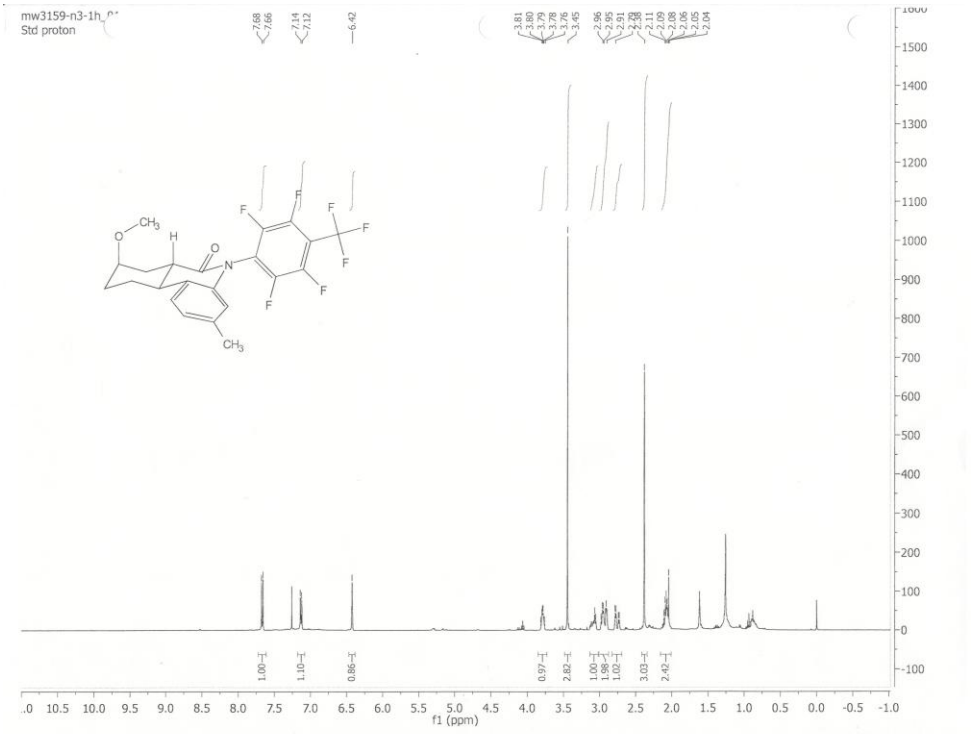


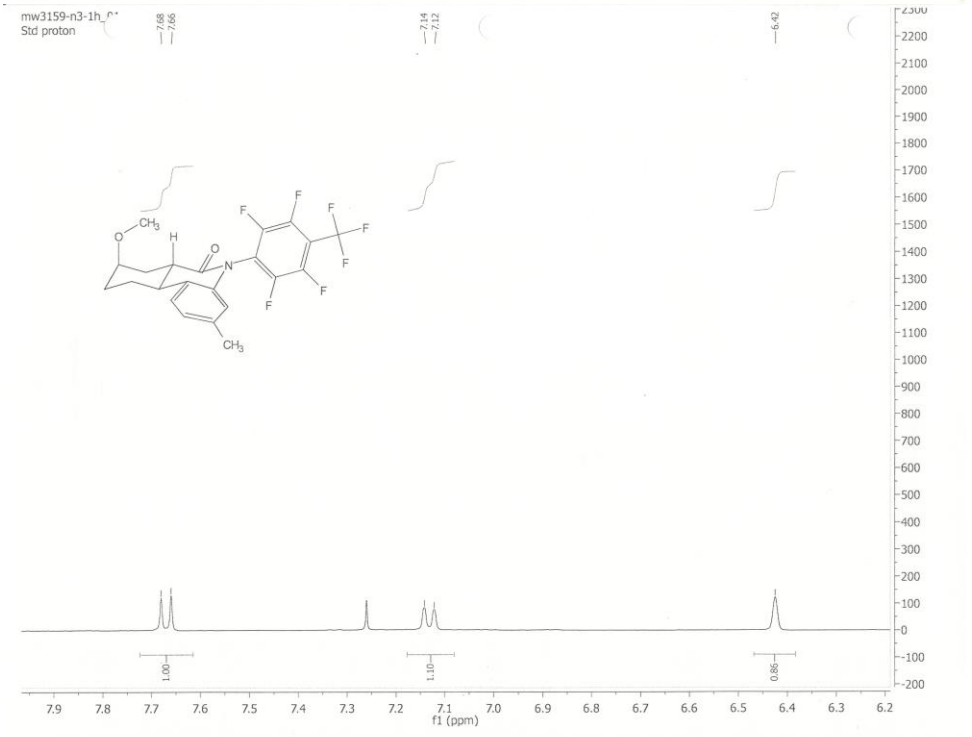


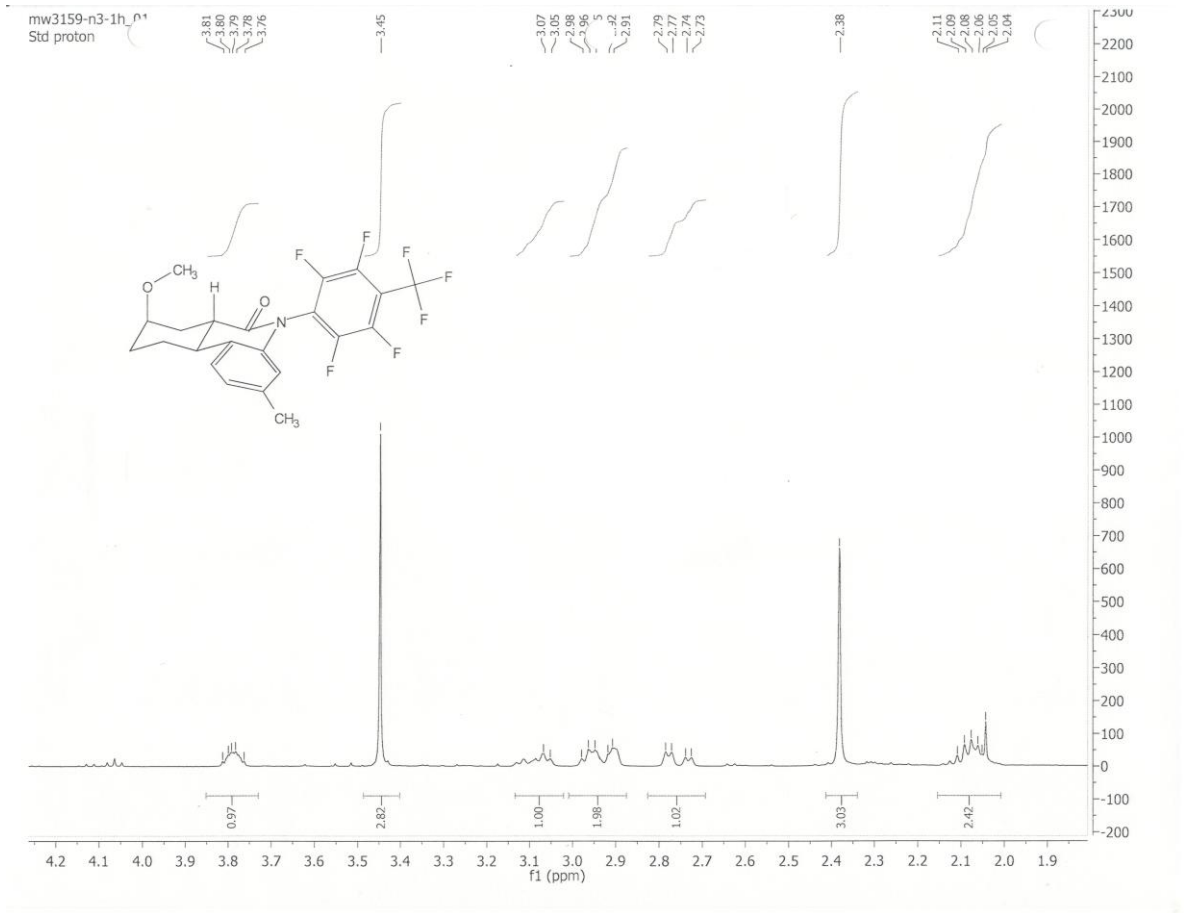

Std proton
7.15
7.13
7.11
7.09
6.64
4.10
1.00
f1 (ppm)


Std proton
173.07
141.02
136.95
129.83
127.32
74.22
56.27
47.35
46.48
33.91
28.53
27.76
21.32
f1 (ppm)

10b


mw3159-n3-1h_01
Std proton
7.68
7.66
7.14
7.12
6.42
3.81
3.80
3.79
3.78
3.76
3.45
2.96
2.95
2.91
2.88
2.11
2.09
2.08
2.06
2.05
2.04
1.00
1.10
0.86
0.97
2.82
1.00
1.98
1.02
3.03
2.42
f1 (ppm)


mw3159-n3-1h_01
Std proton
7.68
7.66
7.14
7.12
6.42
1.00
1.10
0.86
f1 (ppm)


mw3159-n3-1h_01
Std proton
3.81
3.80
3.79
3.78
3.76
3.45
3.07
3.05
2.98
2.96
2.91
2.79
2.77
2.74
2.73
2.38
2.11
2.09
2.08
2.06
2.05
2.04
O
CH3
H
O
N
F
F
F
F
F
F
F
CH3
0.97
2.82
1.00
1.98
1.02
3.03
2.42
f1 (ppm)

11a