TCFH-NMI: Direct Access to *N*-Acyl Imidazoliums for Challenging Amide Bond Formations.

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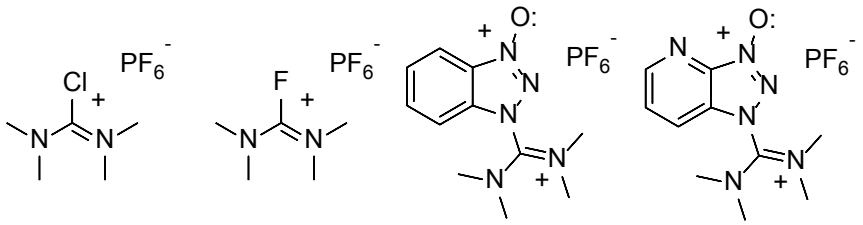
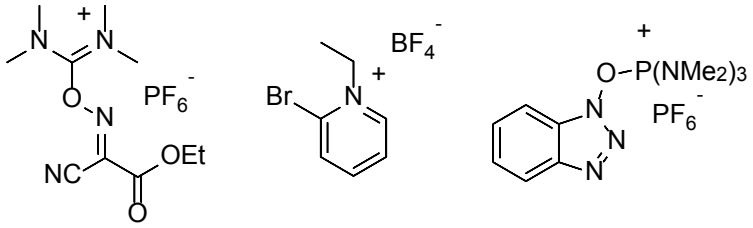
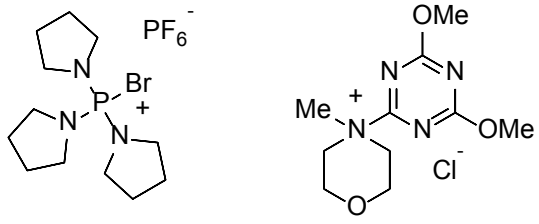
General Experimental. All reactions were performed using commercial materials as received without additional purification. ^{1}H, ^{13}C and ^{19}F Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz instrument at ambient temperature. All ^{1}H NMR spectra were measured in parts per million (ppm) relative to residual chloroform signal (δ 7.26 ppm) in deuterated solvent unless otherwise stated. Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (br = broad, app = apparent, s = singlet, d = doublet, t = triplet, q= quartet, p = pentet, m = multiplet), coupling constants in Hertz, and integration. All ^{13}C NMR spectra were reported in ppm relative to deuterochloroform (δ 77.00 ppm) with complete ^{1}H decoupling. All ^{19}F NMR spectra were obtained with ^{1}H decoupling. Structures of the coupling agent acronyms mentioned in text are shown below. Some safety concerns have been identified with BEP and caution should be exercised, see: Li. P.; Xu, J. C. *Tetrahedron* **2000**, *56*, 8119-8131.



TCFH **TFFH** **HBTU** **HATU**

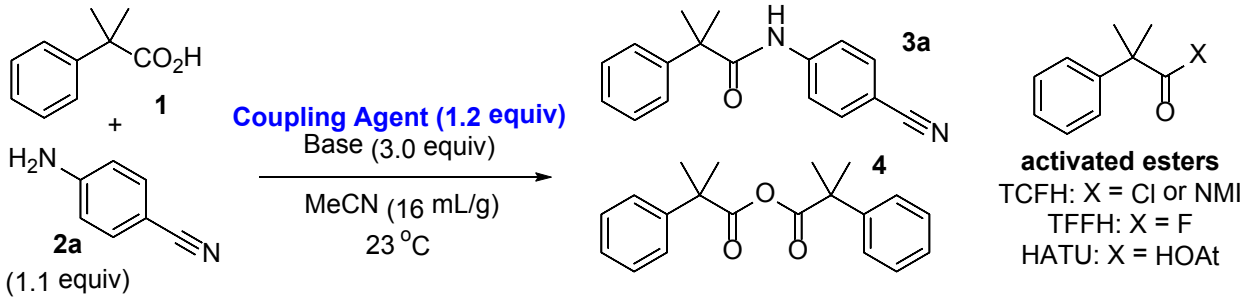


HOTU **BEP** **BOP**



PyBrOP **DMTMM**

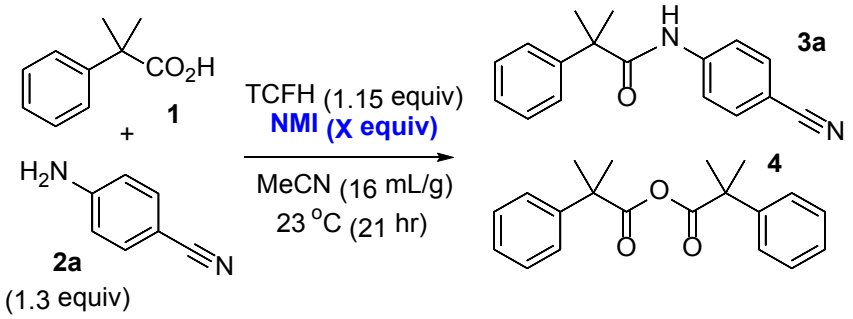
Table S1. Initial Optimization Studies with Coupling Agents. 2-Methyl-2-phenylpropanoic acid **1** (25 mg, 0.152 mmol) and 4-aminobenzonitrile **2a** (20 mg, 0.167 mmol, 1.1 equiv) were dissolved in the appropriate solvent (0.40 mL). Base (0.457 mmol, 3.0 equiv) was added, followed by the coupling agent (0.183 mmol, 1.2 equiv). The reaction was stirred at room temperature for between 19-22 hr, and reaction progress monitored by HPLC.



entry	activator	solvent	base	base equiv	acid (1) AP	amide (3a) AP	anhydride (4) AP	act ester AP
1	HATU	DMF	DIPEA	3.0	2.1	2.5	0.0	89.9
2	HATU	DMF	NMI	3.0	1.3	2.1	0.0	92.4
3	HATU	MeCN	DIPEA	3.0	1.9	0.0	0.0	82.0
4	HATU	MeCN	NMI	3.0	2.3	2.7	0.0	95.0
5	BEP	DMF	DIPEA	3.0	0.0	0.0	99.5	0.0
6	BEP	DMF	NMI	3.0	49.3	28.5	22.2	0.0
7	BEP	MeCN	DIPEA	3.0	2.5	6.0	61.5	0.0
8	BEP	MeCN	NMI	3.0	7.5	91.2	1.3	0.0
9	TFFH	DMF	DIPEA	3.0	27.5	0.0	15.5	56.9
10	TFFH	DMF	NMI	3.0	12.7	0.0	28.2	52.2
11	TFFH	MeCN	DIPEA	3.0	36.0	6.0	4.1	53.0
12	TFFH	MeCN	NMI	3.0	12.1	34.7	2.8	49.2
13	TCFH	DMF	DIPEA	3.0	3.8	7.3	88.8	0.0
14	TCFH	DMF	NMI	3.0	14.7	61.6	23.2	0.0
15	TCFH	MeCN	DIPEA	3.0	0.0	67.4	31.7	0.0
16	TCFH	MeCN	NMI	3.0	1.5	96.2	0.0	0.0
C17*	TCFH	DMF	DIPEA	3.0	11.4	0.0	88.6	0.0
C18*	TCFH	DMF	NMI	3.0	15.3	0.0	84.7	0.0
C19*	TCFH	MeCN	DIPEA	3.0	21.8	0.0	76.4	0.0
C20*	TCFH	MeCN	NMI	3.0	90.9	0.0	9.1	0.0

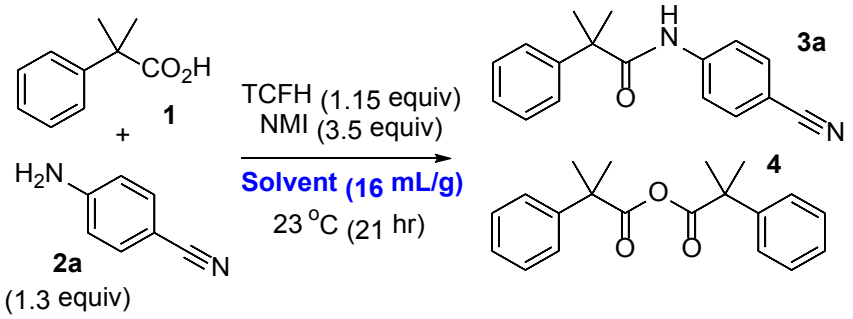
* Control reactions omitted aniline **2a**. It is likely that the acid observed in the control is derived from hydrolysis of the acyl chloride or imidazole on the HPLC.

Table S2. Optimization of NMI Equivalents with TCFH. 2-Methyl-2-phenylpropanoic acid **1** (40 mg, 0.244 mmol) and 4-aminobenzonitrile **2a** (37 mg, 0.317 mmol, 1.3 equiv) were dissolved in acetonitrile (0.60 mL). N-Methylimidazole (0.244 – 0.854 mmol, 1.0 – 3.5 equiv) was added, followed by TCFH (79 mg, 0.280 mmol, 1.15 equiv). The reaction was stirred at room temperature for 21 hr, and reaction progress monitored by HPLC.



entry	activator	solvent	base	base equiv	acid (1) AP	amide (3a) AP	anhydride (4) AP	act ester AP
1	TCFH	MeCN	NMI	1.0	2.4	86.8	9.9	0.0
2	TCFH	MeCN	NMI	1.5	0.0	90.3	9.3	0.0
3	TCFH	MeCN	NMI	2.0	0.0	89.4	9.7	0.0
4	TCFH	MeCN	NMI	2.5	2.2	96.1	0.0	0.0
5	TCFH	MeCN	NMI	3.0	1.5	96.2	0.0	0.0
6	TCFH	MeCN	NMI	3.5	0.0	98.8	0.0	0.0

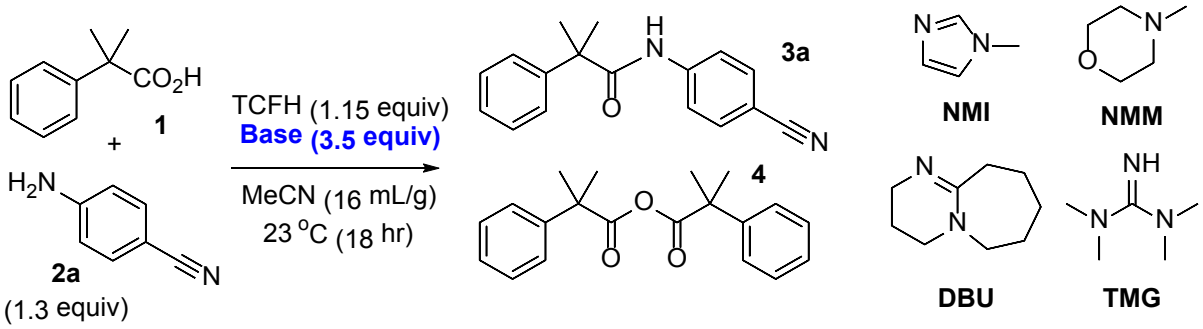
Table S3. Solvent Optimization with TCFH-NMI. 2-Methyl-2-phenylpropanoic acid **1** (25 mg, 0.152 mmol) and 4-aminobenzonitrile **2a** (23 mg, 0.197 mmol, 1.3 equiv) were dissolved in the appropriate solvent (0.40 mL). N-Methylimidazole (0.042 mL, 0.533 mmol, 3.5 equiv) was added, followed by TCFH (50 mg, 0.175 mmol, 1.15 equiv). The reaction was stirred at room temperature for 21 hr, and reaction progress monitored by HPLC.



entry	activator	solvent	base	Base Equiv	acid (1) AP	amide (3a) AP	anhydride (4) AP	act ester AP
1	TCFH	MeCN	NMI	3.5	1.5	96.2	0.0	0.0
2	TCFH	THF	NMI	3.5	2.6	86.2	10.0	0.0
3	TCFH	DMF	NMI	3.5	32.5	51.3	13.5	0.0
4	TCFH	CH_2Cl_2	NMI	3.5	0.0	98.2	0.0	0.0
5	TCFH	$PhCH_3$	NMI	3.5	2.0	97.2	0.0	0.0
6	TCFH	CpMe[a]	NMI	3.5	12.8	85.8	0.0	0.0
7	TCFH	IPAc[b]	NMI	3.5	12.1	86.2	0.0	0.0

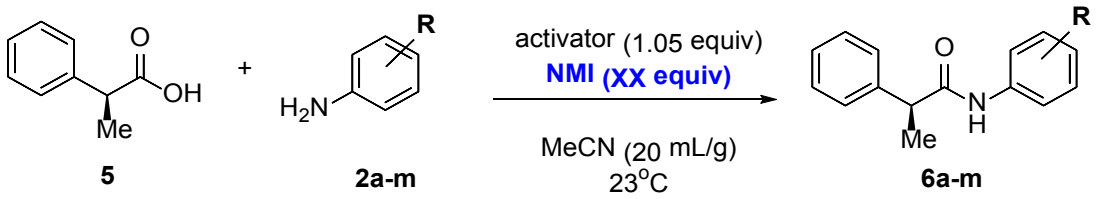
a. CpMe = cyclopentyl methyl ether. B. IPAc = isopropyl acetate.

Table S4. Base Screen with TCFH. 2-Methyl-2-phenylpropanoic acid **1** (25 mg, 0.152 mmol) and 4-aminobenzonitrile **2a** (23 mg, 0.197 mmol, 1.3 equiv) were dissolved in the acetonitrile (0.40 mL). Base (0.533 mmol, 3.5 equiv) was added, followed by TCFH (50 mg, 0.175 mmol, 1.15 equiv). The reaction was stirred at room temperature for 18 hr, and reaction progress monitored by HPLC.



entry	activator	solvent	base	base equiv	acid (1) AP	amide (3a) AP	anhydride (4) AP	act ester AP
1	TCFH	MeCN	NMI	3.5	1.5	96.2	0.0	0.0
2	TCFH	MeCN	DIPEA	3.5	0.0	67.5	32.0	0.0
3	TCFH	MeCN	NEt_3	3.5	0.0	75.0	23.8	0.0
4	TCFH	MeCN	pyridine	3.5	4.1	76.8	17.8	0.0
5	TCFH	MeCN	NMM	3.5	3.1	88.7	8.3	0.0
6	TCFH	MeCN	DBU	3.5	39.0	1.2	16.8	17.0
7	TCFH	MeCN	TMG	3.5	12.1	0.0	0.0	82.0

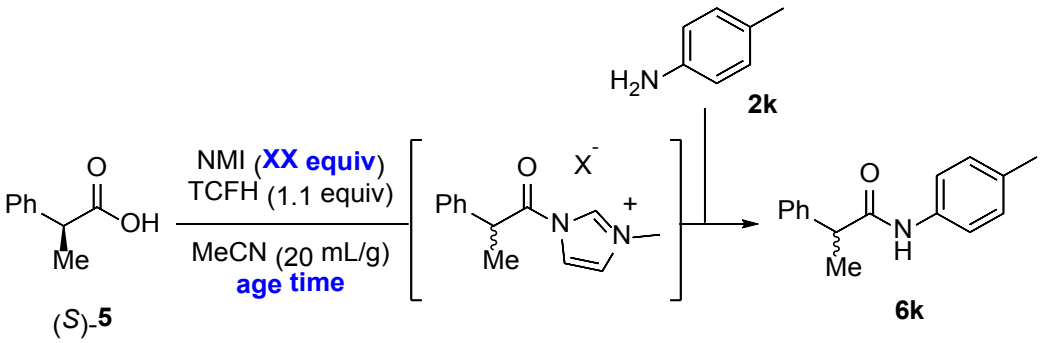
Table S5. Base Loading Effects on Coupling of (*S*)-5. 2-Methyl-2-phenylpropanoic acid **5** (0.1 mL, 0.71 mmol) and aniline (0.85 mmol, 1.2 equiv) were dissolved in 2 mL acetonitrile. NMI (2.1-3.5 equiv) was added, followed by 219 mg of TCFH (0.78 mmol, 1.1 equiv). The reaction was stirred at room temperature and reaction progress monitored by HPLC. When reactions were at >99% conversion, chiral HPLC analysis was performed on the crude reaction mixtures.



5 **2a-m** **6a-m**

R	sigma	yield	er	er
			3.5 equiv NMI	**2.1 equiv NMI**
4-Me	-0.17	88	100.0 : 0.0	100.0 : 0.0
H	0	91	99.8 : 0.2	100.0 : 0.0
4-F	0.06	82	99.8 : 0.2	100.0 : 0.0
4-Cl	0.23	70	99.5 : 0.5	99.7 : 0.3
4-CF_3	0.54	91	97.1 : 2.9	100.0 : 0.0
4-CN	0.66	93	85.6 : 14.4	99.8 : 0.2
2-Me	NA	84	93.7 : 6.3	99.8 : 0.2
2,6-diMe	NA	92	73.4 : 26.6	100.0 : 0.0

Table S6. Stability of the Acyl Imidazolium derived from (*S*)-5. The (*S*)-2-phenylpropionic acid (*S*)-**5** (0.45 mL, 3.23 mmol, 1.0 equiv) was dissolved in 10 mL MeCN for addition of *N*-methylimidazole (2.1-3.5 equiv) and the 1.0 g of TCFH (3.55 mmol, 1.1 equiv) in a single portion. Aged for a specified time before removal of a 1.0 mL aliquot which was quenched into a vial containing 42 mg 4-Me aniline **2k**. The reaction was stirred at room temperature for 30 min (>99% conversion) and the crude reaction mixture analyzed by chiral HPLC.



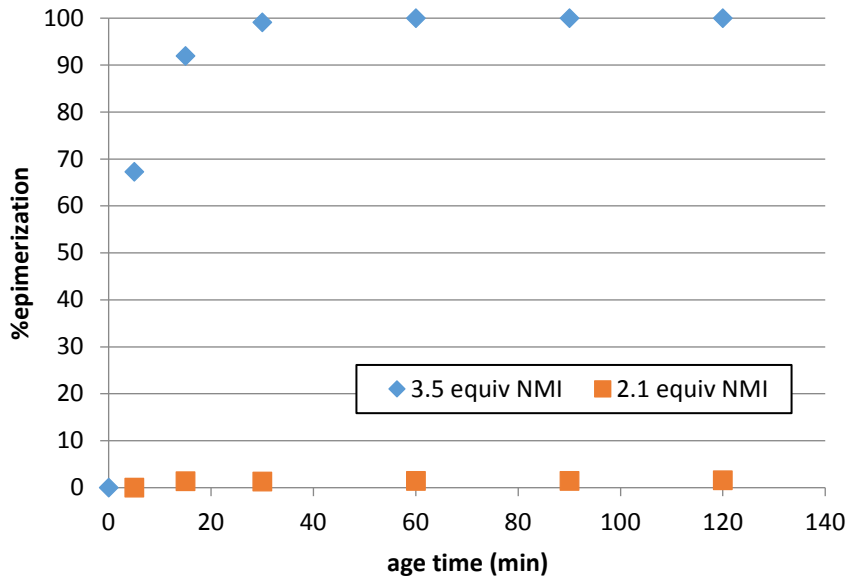
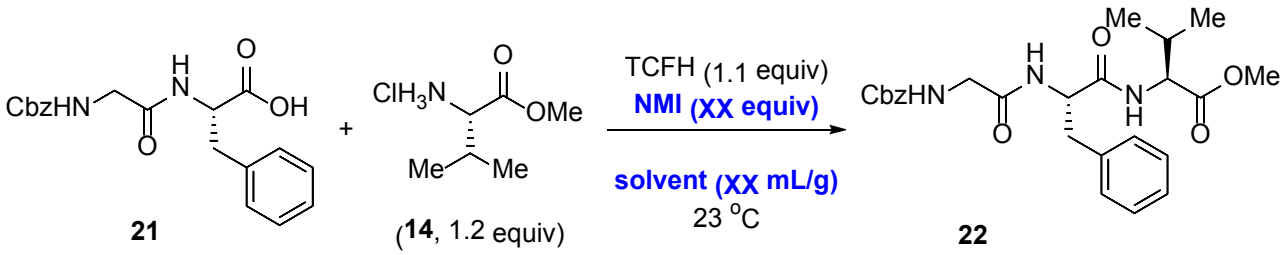
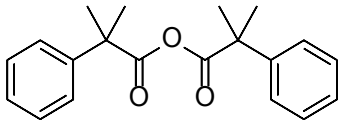


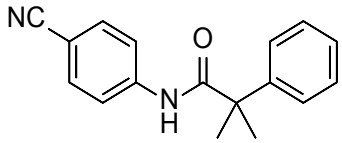
Table S7. Optimization Studies on the Coupling of 14 and 21. The (2*S*)-2-[[2-(benzyloxycarbonylamino)acetyl]amino]-3-phenyl-propanoic acid **21** (0.1 g, 0.28 mmol), 36 mg L-valine methyl ester hydrochloride **14** (0.34 mmol, 1.2 equiv) and *N*-methylimidazole (2.1-4.6 equiv) were dissolved in MeCN for addition of the TCFH (88 mg, 0.31 mmol, 1.1 equiv). The reaction was stirred at room temperature and reaction progress monitored by HPLC.



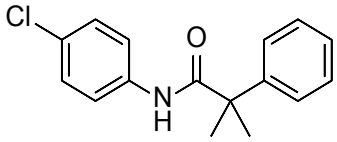
NMI equiv	pre-activation?	solvent	solvent mL/g	conv	dr		
2.1	yes	MeCN	20	39.9	73.6	:	26.4
2.6	yes	MeCN	20	59.7	70.7	:	29.3
3.1	yes	MeCN	20	81.4	59.0	:	41.0
2.1	no	MeCN	20	46.7	83.4	:	16.6
2.6	no	MeCN	20	57.8	88.5	:	11.5
3.1	no	MeCN	20	100.0	90.7	:	9.3
3.6	no	MeCN	20	99.6	87.5	:	12.5
4.1	no	MeCN	20	100.0	86.7	:	13.3
4.6	no	MeCN	20	100.0	85.3	:	14.7
3.1	no	MeCN	20	100.0	90.7	:	9.3
3.1	no	MeCN	10	100.0	89.0	:	11.0
3.1	no	MeCN	5	100.0	90.2	:	9.8
3.1	no	DMF	20	43.6	82.8	:	17.2
3.1	no	THF	20	42.8	83.2	:	16.8
3.1	no	EtOAc	20	87.7	72.0	:	28.0
3.1	no	DCM	20	100.0	92.1	:	7.9



2-Methyl-2-phenylpropanoic anhydride (4): The 2-methyl-2-phenylpropanoic acid **1** (300 mg, 1.83 mmol, 1.0 equiv) was dissolved in 5.0 mL MeCN and 1.12 mL diisopropylethylamine (6.40 mmol, 3.5 equiv) was added, followed by 0.310 g TCFH (1.10 mmol, 0.60 equiv). The reaction was stirred for 20 min before addition of 5 mL water and extraction with isopropyl acetate (2x5 mL). The combined organics were dried with $MgSO_4$ and concentrated. The resulting residue was purified by silica gel flash column chromatography with heptane/isopropyl acetate to yield 236 mg of compound **4** as a colorless oil (83% yield).[1] TLC R_f = 0.73 (7:3 heptane/isopropyl acetate, UV 254 nm). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.28–7.20 (m, 6H), 7.14–7.09 (m, 4H), 1.44 (s, 12H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 171.4, 142.6, 128.4, 126.9, 125.6, 47.6, 25.5. IR (solid state): 3061, 3017, 2979, 2936, 2880, 1806, 1716, 1700, 1507, 1447, 1214, 1108, 1023, 763, 695 cm^{-1}. HRMS = ($C_{20}H_{22}O_3$, MNH_4^+): calc'd: 328.1913, observed: 328.1914.

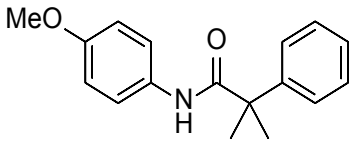


General Procedure 1. **N-(4-cyanophenyl)-2-methyl-2-phenylpropanamide (3a):** The 2-methyl-2-phenylpropanoic acid **1** (0.250 g, 1.52 mmol, 1.0 equiv), 0.234 g 4-aminobenzonitrile (**2a**) (1.98 mmol, 1.3 equiv) and 0.42 mL *N*-methylimidazole (5.33 mmol, 3.5 equiv) were combined and dissolved in 4 mL MeCN for addition of 0.517 g TCFH (1.83 mmol, 1.2 equiv) in a single portion. The reaction was stirred until complete by HPLC (21h). The reaction was then diluted with 6 mL of isopropyl acetate and 4 mL of water. The layers were separated, the aqueous layer was extracted with 4 mL of isopropyl acetate and the combined organics were washed with 4 mL of water, dried with $MgSO_4$, filtered and concentrated before purification by silica gel chromatography with heptane/isopropyl acetate to give 374 mg of **3a** as a white solid (93% yield).[2] In some cases, direct isolation of the desired amide could be achieved through addition of 4-6 mL water, filtration and washing with 5 mL of 2:1 water/MeCN before drying under nitrogen without a significant change in yield. Reported yields represent those obtained by chromatography for consistency. TLC R_f = 0.38 (7:3 heptane/isopropyl acetate, UV 254 nm). mp = 140-141 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 (app. dt, *J* = 8.8, 2.0 Hz, 2H), 7.48 (app. dt, *J* = 8.8, 2.0 Hz, 2H), 7.44-7.41 (m, 4H), 7.38-7.32 (m, 1H), 6.93 (br s, 1H), 1.67 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 175.9, 143.8, 141.9, 133.1, 129.2, 127.7, 126.4, 119.3 118.8, 107.0, 48.4, 26.9. IR (solid state): 3344, 2983, 2933, 2223, 1716, 1602, 1586, 1509, 1405, 1308, 1247, 1173, 1133, 1102, 840, 737, 698, 635, 547 cm^{-1}. HRMS = ($C_{17}H_{16}N_2O$, MH^+): calc'd: 265.1341, observed: 265.1341.

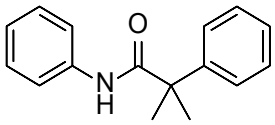


N-(4-chlorophenyl)-2-methyl-2-phenylpropanamide (3b): Following General Procedure 1, 0.250 g 2-methyl-2-phenylpropanoic acid **1** (1.52 mmol, 1.0 equiv), 0.253 g 4-chloroaniline **2b** (1.98 mmol, 1.3

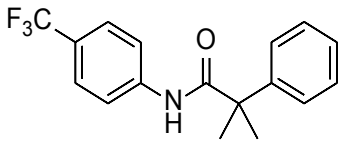
equiv), 0.42 mL *N*-methylimidazole (5.33 mmol, 3.5 equiv), 0.517 g TCFH (1.83 mmol, 1.2 equiv) in 4 mL MeCN for 20 min before purification by SiO_2 chromatography with heptane/isopropyl acetate to yield 390 mg of **3b** as a white solid (94% yield).[2] TLC R_f = 0.60 (7:3 heptane/isopropyl acetate, UV 254). mp = 132-134 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45-7.39 (m, 4H), 7.35-7.28 (m, 3H), 7.23-7.19 (m, 2H), 6.79 (br s, 1H), 1.66 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 175.6, 144.3, 136.5, 129.0, 128.8, 127.5, 126.4, 120.9, 48.1, 27.0. IR (solid state): 3280, 3253, 2973, 2959, 1655, 1593, 1519, 1490, 1393, 1305, 1233, 1144, 1089, 1012, 825, 755, 695, 555, 510 cm^{-1}. HRMS = ($C_{16}H_{16}ClNO$, MH^+): calc'd: 274.0999, observed: 274.0997.



N-(4-Methoxyphenyl)-2-methyl-2-phenylpropanamide (3c): Following General Procedure 1, 0.250 g 2-methyl-2-phenylpropanoic acid **1** (1.52 mmol, 1.0 equiv), 0.243 g 4-methoxyaniline **2c** (1.98 mmol, 1.3 equiv), 0.42 mL *N*-methylimidazole (5.33 mmol, 3.5 equiv), 0.517 g TCFH (1.83 mmol, 1.2 equiv) in 4 mL MeCN for 10 min before purification by SiO_2 chromatography with heptane/isopropyl acetate to yield 384 mg of **3c** as an off-white solid (94% yield).[2] TLC R_f = 0.43 (7:3 heptane/isopropyl acetate, UV 254 nm). mp = 136-137 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.37 (m, 4H), 7.33-7.29 (m, 1H), 7.27-7.23 (m, 2H), 6.82-6.78 (m, 2H), 6.69 (br s, 1H), 3.75 (s, 3H), 1.66 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 175.4, 156.3, 144.7, 131.1, 128.9, 127.3, 126.5, 121.5, 114.0, 55.0, 47.8, 27.1. IR (solid state): 3290, 2960, 1650, 1603, 1510, 1244, 1146, 1032, 837, 752, 697 cm^{-1}. HRMS = ($C_{17}H_{19}NO_2$, MH^+): calc'd: 270.1494, observed: 270.1492.

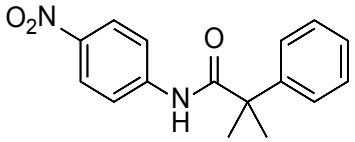


2-Methyl-N,2-diphenylpropanamide (3d): Following General Procedure 1, 0.250 g 2-methyl-2-phenylpropanoic acid **1** (1.52 mmol, 1.0 equiv), 0.183 g aniline **2d** (1.98 mmol, 1.3 equiv), 0.42 mL *N*-methylimidazole (5.33 mmol, 3.5 equiv), 0.517 g TCFH (1.83 mmol, 1.2 equiv) in 4 mL MeCN for 40 min before purification by SiO_2 chromatography with heptane/isopropyl acetate to yield 331 mg of **3d** as a white solid (91% yield).[2] TLC R_f = 0.63 (7:3 heptane/isopropyl acetate, UV 254 nm). mp = 100-101 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47-7.39 (m, 4H), 7.37-7.31 (m, 3H), 7.28-7.24 (m, 2H), 7.08-7.03 (m, 1H), 6.78 (br s, 1H), 1.67 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 175.5, 144.6, 138.0, 129.0, 128.9, 127.4, 126.5, 124.1, 119.6, 48.1, 27.0. IR (solid state): 3307, 3057, 2993, 2972, 1654, 1599, 1532, 1489, 1436, 1316, 1252, 1146, 909, 756, 696, 544 cm^{-1}. HRMS = ($C_{16}H_{17}NO$, MH^+): calc'd: 240.1388, observed: 240.1383.

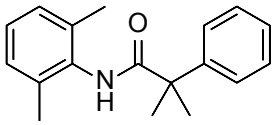


2-Methyl-2-phenyl-N-(4-(trifluoromethyl)phenyl)propanamide (3e). Following General Procedure 1, 0.250 g 2-methyl-2-phenylpropanoic acid **1** (1.52 mmol, 1.0 equiv), 0.319 g 4-trifluoromethylaniline **2e**

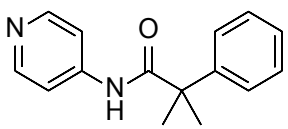
(1.98 mmol, 1.3 equiv), 0.42 mL *N*-methylimidazole (5.33 mmol, 3.5 equiv), 0.517 g TCFH (1.83 mmol, 1.2 equiv) in 4 mL MeCN for 21 h before purification by SiO_2 chromatography with heptane/isopropyl acetate to yield 436 mg of **3e** as a white solid (92% yield).[2] TLC R_f = 0.60 (7:3 heptane/isopropyl acetate, UV 254 nm). mp = 116-117 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52-7.40 (m, 8H), 7.38-7.32 (m, 1H), 6.90 (br s, 1H), 1.68 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 175.8, 144.1, 141.0, 129.1, 127.5, 126.3, 126.0 (q, $^3J_{CF}$ = 5.0 Hz), 125.8 (q, $^2J_{CF}$ = 33.0 Hz), 124.1 (q, $^1J_{CF}$ = 271.5 Hz), 119.2, 48.2, 26.8. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -62.16. IR (solid state): 3362, 3302, 2972, 2934, 1667, 1618, 1558, 1524, 1407, 1316, 1249, 1166, 1114, 1066, 844, 699, 649 cm^{-1}. HRMS = ($C_{17}H_{16}F_3NO$, MH^+): calc'd: 308.1262, observed: 308.1263.



2-Methyl-N-(4-nitrophenyl)-2-phenylpropanamide (3f): Following General Procedure 1, 0.250 g 2-methyl-2-phenylpropanoic acid **1** (1.52 mmol, 1.0 equiv), 0.273 g 4-nitroaniline **2f** (1.98 mmol, 1.3 equiv), 0.42 mL *N*-methylimidazole (5.33 mmol, 3.5 equiv), 0.517 g TCFH (1.83 mmol, 1.2 equiv) in 4 mL MeCN for 30 h before purification by SiO_2 chromatography with heptane/isopropyl acetate to yield 375 mg of **3f** as a pale yellow solid (87% yield).[2] TLC R_f = 0.50 (7:3 heptane/isopropyl acetate, UV 254). mp = 162-163 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (app dd, *J* =9.2, 2.4 Hz, 2H), 7.53 (app dd, *J* =9.2, 2.4 Hz, 2H), 7.46-7.41 (m, 4H), 7.37-7.34 (m, 1H), 7.06 (br s, 1H), 1.68 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 176.0, 143.71, 143.67, 143.4, 129.3, 127.8, 126.4, 124.9, 118.9, 48.4, 26.8. IR (solid state): 3353, 3336, 3115, 3089, 3058, 2966, 1672, 1595, 1557, 1506, 1326, 1301, 1242, 1138, 1102, 909, 854, 822, 753, 737, 697, 653, 549 cm^{-1}. HRMS = ($C_{16}H_{16}N_2O_3$, MH^+): calc'd: 285.1239, observed: 285.1243.

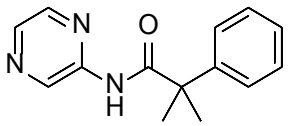


N-(2,6-Dimethylphenyl)-2-methyl-2-phenylpropanamide (3g): Following General Procedure 1, 0.250 g 2-methyl-2-phenylpropanoic acid **1** (1.52 mmol, 1.0 equiv), 0.240 g 2,6-dimethylanaline **2g** (1.98 mmol, 1.3 equiv), 0.42 mL *N*-methylimidazole (5.33 mmol, 3.5 equiv), 0.517 g TCFH (1.83 mmol, 1.2 equiv) in 4 mL MeCN for 26h before purification by SiO_2 chromatography with heptane/isopropyl acetate to yield 329 mg of **3g** as a white solid (81% yield). TLC R_f = 0.40 (7:3 heptane/isopropyl acetate, UV 254 nm). mp = 158-159°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56-7.53 (m, 2H), 7.45-7.40 (m, 2H), 7.33 (tt, *J* = 7.2, 1.6 Hz, 1H), 7.05-6.98 (m, 3H), 6.33 (br s, 1H), 2.06 (s, 6H), 1.73 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 175.4, 144.9, 135.2, 133.9, 128.8, 128.1, 127.3, 127.0, 126.5, 47.5, 26.9, 18.3. IR (solid state): 3296, 3059, 2963, 2924, 1652, 1509, 1247, 1217, 1149, 1032, 839, 764, 697 cm^{-1}. HRMS = ($C_{18}H_{21}NO$, MH^+): calc'd: 268.1701, observed: 268.1699.

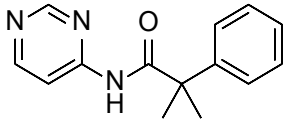


2-Methyl-2-phenyl-N-(pyridin-4-yl)propanamide (3h): Following General Procedure 1, 0.250 g 2-methyl-2-phenylpropanoic acid **1** (1.52 mmol, 1.0 equiv), 0.186 g 4-aminopyridine **2h** (1.98 mmol, 1.3 equiv), 0.42 mL *N*-methylimidazole (5.33 mmol, 3.5 equiv), 0.517 g TCFH (1.83 mmol, 1.2 equiv) in 4 mL MeCN for 5 h

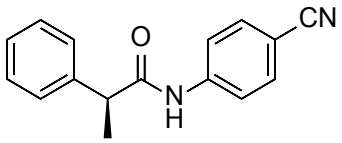
before purification by SiO_2 chromatography with heptane/isopropyl acetate to yield 337 mg of **3h** as a white solid (92% yield). TLC R_f = 0.29 (100% Isopropyl acetate, UV 254). mp = 134-135 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.41-8.40 (m, 2H), 7.43-7.40 (m, 4H), 7.36-7.31 (m, 1H), 7.31-7.29 (m, 2H), 6.94 (br s), 1.67 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 176.2, 150.6, 144.9, 143.8, 129.2, 127.7, 126.3, 113.3, 48.4, 26.8. IR (solid state): 3326, 3190, 3042, 2973, 1674, 1590, 1498, 1410, 1397, 1327, 1284, 1212, 1140, 822, 764, 698, 541 cm^{-1}. HRMS = ($C_{15}H_{16}N_2O$, MH^+): calc'd: 241.1341, observed: 241.1337.



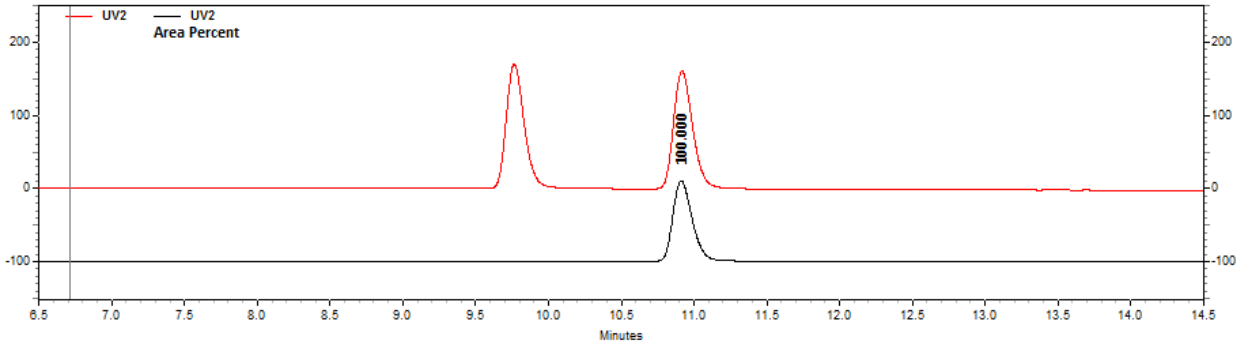
2-Methyl-2-phenyl-N-(pyrazin-2-yl)propanamide (3i): Following General Procedure 1, 0.250 g 2-methyl-2-phenylpropanoic acid **1** (1.52 mmol, 1.0 equiv), 0.188 g aminopyrazine **2i** (1.98 mmol, 1.3 equiv), 0.42 mL *N*-methylimidazole (5.33 mmol, 3.5 equiv), 0.517 g TCFH (1.83 mmol, 1.2 equiv) in 4 mL MeCN for 21 h before purification by SiO_2 chromatography with heptane/isopropyl acetate to yield 315 mg of **3i** as an off-white solid (86% yield). TLC R_f = 0.22 (7:3 heptane/isopropyl acetate UV 254). mp = 84-86 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.57 (d, *J* = 1.6 Hz, 1H), 8.29 (dd, *J* = 2.4, 0.4 Hz, 1H), 8.12 (dd, *J* = 2.4, 1.6 Hz, 1H), 7.45-7.38 (m, 5H), 7.35-7.30 (m, 1H), 1.67 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 175.8, 148.1, 143.6, 141.8, 140.1, 136.8, 129.2, 127.7, 126.3, 48.1, 26.8. IR (solid state): 3190, 3026, 2974, 2936, 1690, 1533, 1496, 1409, 1295, 1240, 1150, 1012, 699, 528 cm^{-1}. HRMS = ($C_{14}H_{15}N_3O$, MH^+): calc'd: 242.1293, observed: 242.1293.

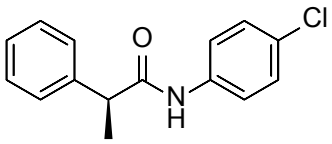


2-Methyl-2-phenyl-N-(pyrimidin-4-yl)propanamide (3j). Following General Procedure 1, 0.250 g 2-methyl-2-phenylpropanoic acid **1** (1.52 mmol, 1.0 equiv), 0.188 g 4-aminopyrimidine **2j** (1.98 mmol, 1.3 equiv), 0.42 mL *N*-methylimidazole (5.33 mmol, 3.5 equiv), 0.517 g TCFH (1.83 mmol, 1.2 equiv) in 4 mL MeCN for 28 h before purification by SiO_2 chromatography with heptane/isopropyl acetate to yield 285 mg of **3j** as a pale yellow solid (78% yield). TLC R_f = 0.17 (7:3 heptane/isopropyl acetate, UV 254 nm). mp = 110-112 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.74 (d, *J* = 1.2 Hz, 1H), 8.60 (dt, *J* = 5.6, 1.2 Hz, 1H), 8.19 (dd, *J* = 5.6, 1.2 Hz, 1H), 7.52 (br s, 1H), 7.44-7.38 (m, 4H), 7.35-7.31 (m, 1H), 1.67 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 176.7, 158.3, 158.2, 157.1, 143.2, 129.2, 127.8, 126.2, 109.9, 48.5, 26.6 ppm. IR (solid state): 3297, 3054, 2994, 2975, 2934, 1686, 1585, 1489, 1385, 1303, 1241, 1137, 989, 902, 855, 754 cm^{-1}. HRMS = ($C_{14}H_{15}N_3O$, MH^+): calc'd: 242.1293, observed: 242.1294.



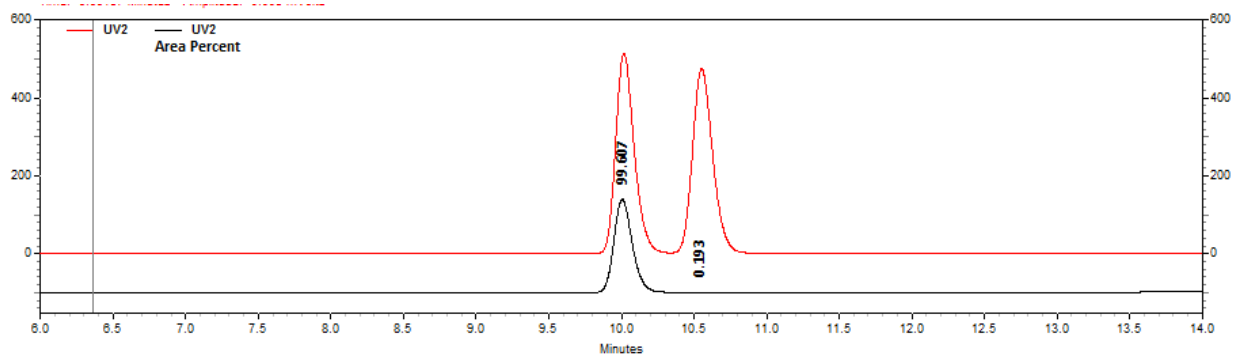
General Procedure 2. (*S*)-N-(4-cyanophenyl)-2-phenylpropanamide (6a): The (*S*)-2-phenylpropionic acid (*S*)-**5** (0.45 mL, 3.23 mmol, 1.0 equiv), 0.47 g 4-aminobenzonitrile **2a** (3.87 mmol, 1.2 equiv), 0.54 mL *N*-methylimidazole (6.78 mmol, 2.1 equiv) were combined and dissolved in 10 mL MeCN for addition of the 1.0 g of TCFH (3.55 mmol, 1.1 equiv) in a single portion. The reaction was stirred until complete by HPLC (30 min). The reaction was then diluted with 20 mL isopropyl acetate and 20 mL of water. The layers were separated, dried over Na_2SO_4, filtered and concentrated before purification by silica gel chromatography with heptane/ethyl acetate to give 749 mg of **6a** as a white solid (93% yield).[3] Direct isolation of the desired amide could be achieved through addition of 4-6 mL water, filtration and washing with 5 mL of 2:1 water/MeCN before drying under nitrogen without a significant change in yield. Reported yields represent those obtained by chromatography for consistency and to avoid enrichment through crystallization. TLC R_f = 0.29 (7:3 heptane/EtOAc, UV 254 nm). mp = 156.7°C (DSC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.6 (m, 4H), 7.4 (m, 2H), 7.35 (m, 3H), 7.3 (s, 1H), 3.7 (q, *J* = 7.3 Hz, 1H), 1.6 (d, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 172.6, 141.9, 140.3, 133.2, 129.4, 127.9, 127.7, 119.4, 118.8, 107.1, 48.3, 18.5. IR (solid state): 2226, 1700, 1591, 1515, 1502, 1452, 1407, 1307, 1251 cm^{-1}. HRMS ($C_{16}H_{14}ON_2$, MH$^+$): calc'd: 251.1179, observed: 251.1176. HPLC: RT 9.76 min (<0.1%), RT 10.92 min (>99.9%) (254 nm, heptane/EtOH gradient, (*R*,*R*)-Whelk-O1, 3 μm, 4.6x150 mm).

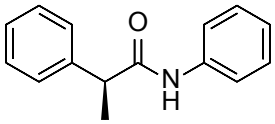




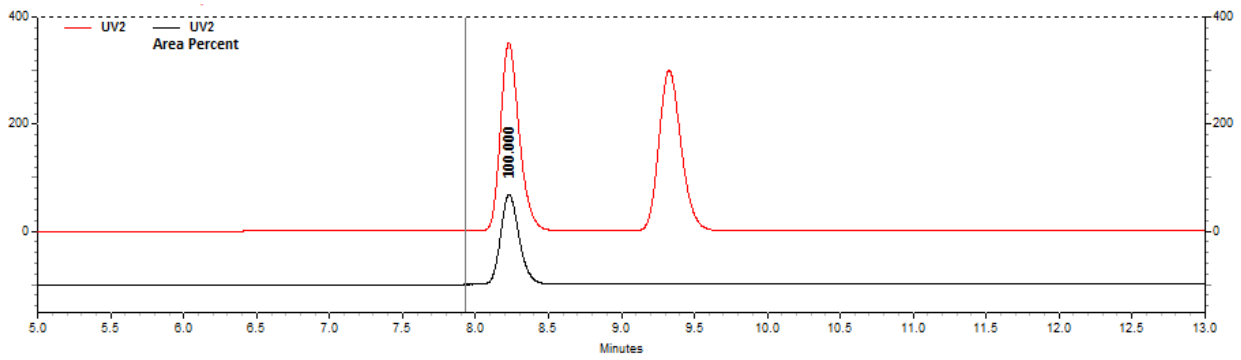
(*S*)-N-(4-chlorophenyl)-2-phenylpropanamide (6b): Following General Procedure 2, 0.45 mL (*S*)-2-phenylpropionic acid (*S*)-**5** (3.23 mmol, 1.0 equiv), 0.50 g 4-chloroaniline **2b** (3.87 mmol, 1.2 equiv), 0.54 mL *N*-methylimidazole (6.78 mmol, 2.1 equiv), 1.0 g of TCFH (3.55 mmol, 1.1 equiv) in 10 mL MeCN for 30 min before purification by SiO_2 chromatography with heptane/ethyl acetate to yield 590 mg of **6b** as a white solid (70% yield).[3] TLC R_f = 0.46 (7:3 heptane/EtOAc, UV 254 nm). mp = 125.0°C (DSC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45-7.3 (m, 7H), 7.2 (m, 2H), 7.1 (s, 1H), 3.7 (q, *J* = 7.1 Hz, 1H), 1.6 (d, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 172.3, 140.7, 136.4, 129.3, 129.2, 128.9, 127.7, 127.6, 120.9, 48.1, 18.6. IR (solid state): 1681, 1652, 1593, 1531, 1488, 1462, 1451, 1398, 1356 cm^{-1}. HRMS ($C_{15}H_{14}ClON$, MH$^+$):

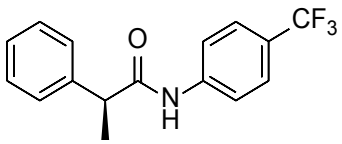
calc'd: 260.0837, observed: 260.0848. HPLC: RT 10.01 min (99.6%), RT 10.55 min (0.2%) (254 nm, TFA/MeCN/H_2O gradient, Chiralpak OB-H, 5 μm, 4.6x150 mm).





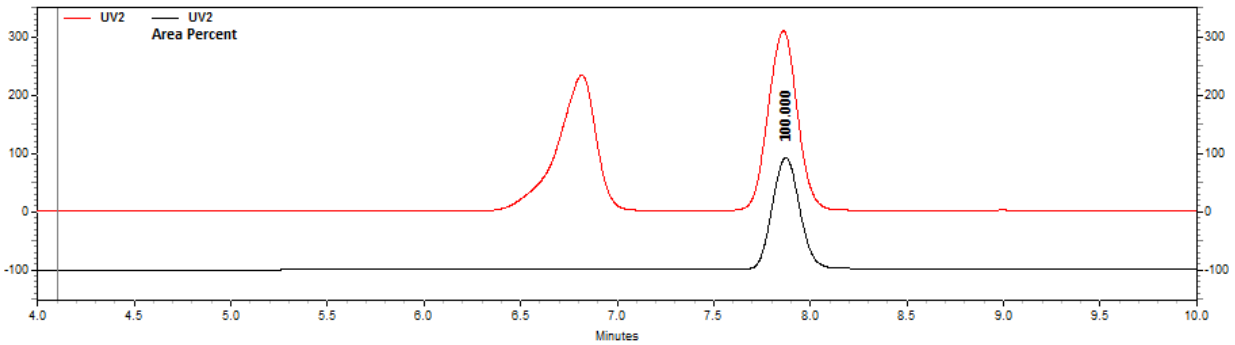
(*S*)-N,2-Diphenylpropanamide (6d): Following General Procedure 2, 0.45 mL (*S*)-2-phenylpropionic acid (*S*)-**5** (3.23 mmol, 1.0 equiv), 0.36 mL aniline **2d** (3.87 mmol, 1.2 equiv), 0.54 mL *N*-methylimidazole (6.78 mmol, 2.1 equiv), 1.0 g of TCFH (3.55 mmol, 1.1 equiv) in 10 mL MeCN for 30 min before purification by SiO_2 chromatography with heptane/ethyl acetate to yield 660 mg of **6d** as a white solid (91% yield).[4] TLC R_f = 0.48 (7:3 heptane/EtOAc, UV 254 nm). mp = 133.8 °C (DSC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.5-7.3 (m, 6H), 7.3-7.2 (m, 3H), 7.1 (t, *J* = 7.6 Hz, 1H), 7.0 (s, 1H), 3.7 (q, *J* = 7.1 Hz, 1H), 1.6 (d, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 172.2, 140.9, 137.8, 129.2, 128.9, 127.7, 127.6, 124.2, 119.6, 48.2, 18.6. IR (solid state): 1677, 1658, 1595, 1541, 1491, 1441, 1373, 1357, 1307 1296 cm^{-1}. HRMS ($C_{15}H_{15}ON$, MH^+): calc'd: 226.1226, observed: 226.1237. HPLC: RT 8.23 min (>99.9%), RT 9.32 min (<0.1%) (254 nm, TFA/MeCN/H_2O gradient, Chiralpak OB-H, 5 μm, 4.6x150 mm).

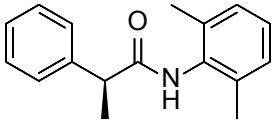




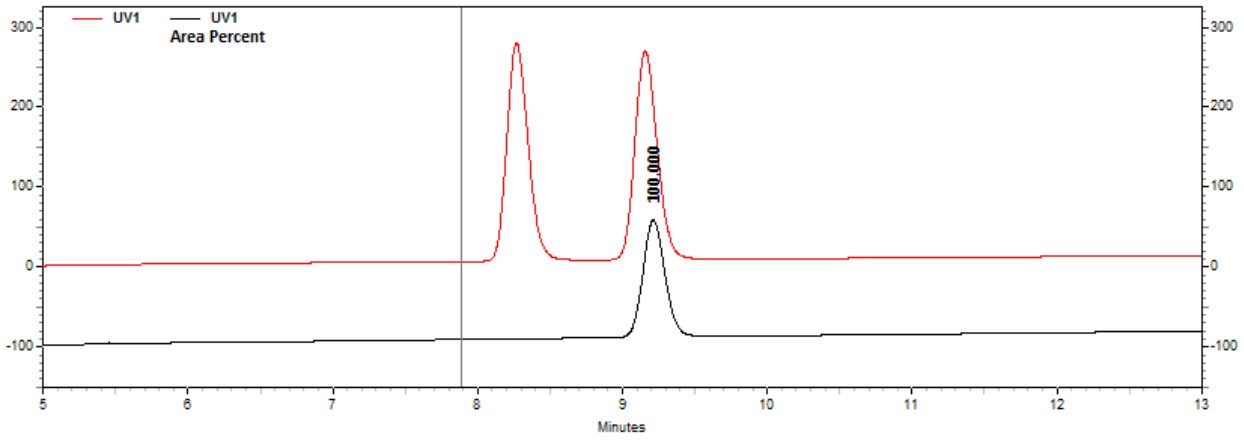
(S)-2-phenyl-N-(4-(trifluoromethyl)phenyl)propanamide (6e): Following General Procedure 2, 0.45 mL (*S*)-2-phenylpropionic acid (*S*)-**5** (3.23 mmol, 1.0 equiv), 0.51 mL 4-aminobenzotrifluoride **2e** (3.87 mmol, 1.2 equiv), 0.54 mL *N*-methylimidazole (6.78 mmol, 2.1 equiv), 1.0 g of TCFH (3.55 mmol, 1.1 equiv) in 10 mL MeCN for 30 min before purification by SiO_2 chromatography with heptane/ethyl acetate to yield 860

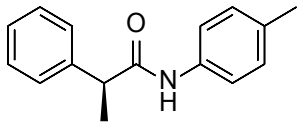
mg of **6e** as a white solid (91% yield). TLC R_f = 0.45 (7:3 heptane/EtOAc, UV 254 nm). mp = 107.1°C (DSC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.5 (m, 4H), 7.35 (m, 5H), 7.2 (s, 1H), 3.7 (q, *J* = 7.3 Hz, 1H), 1.6 (d, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 172.5, 140.8, 140.4, 129.3, 127.8, 127.7, 126.2 (q, *J* = 3.7 Hz), 125.9, 124.1 (q, *J* = 271.5 Hz), 119.2, 48.2, 18.5. ^{19}F{^{1}H} NMR ($CDCl_3$, 367 MHz): δ -62.1. IR (solid state): 1664, 1615, 1601, 1524, 1514, 1497, 1455, 1406 cm^{-1}. HRMS ($C_{16}H_{14}F_3ON$, MH$^+$): calc'd: 294.1100, observed: 294.1109. HPLC: RT 6.82 min (<0.1%), RT 7.86 min (>99.9%) (254 nm, heptane/EtOH gradient, (*R*,*R*)-Whelk-O1, 3 μm, 4.6x150 mm).



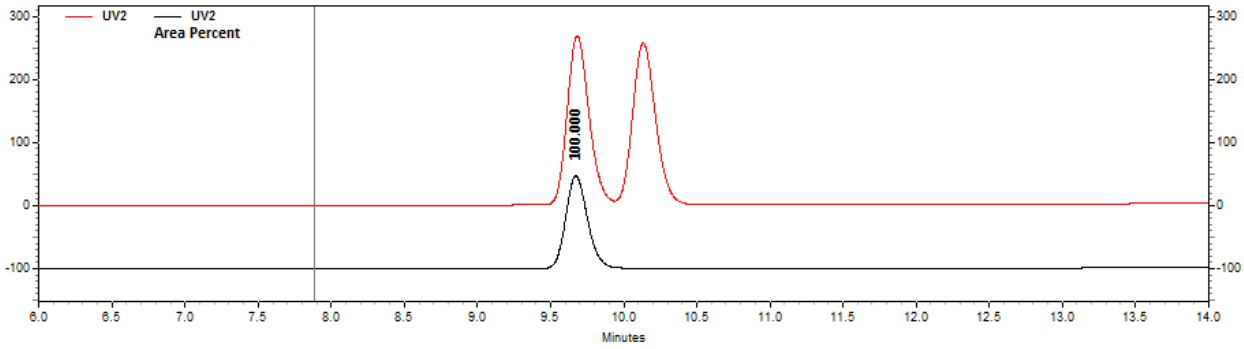


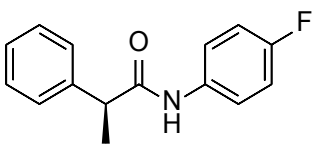
(*S*)-N-(2,6-dimethylphenyl)-2-phenylpropanamide (6g): Following General Procedure 2, 0.45 mL (*S*)-2-phenylpropionic acid (*S*)-**5** (3.23 mmol, 1.0 equiv), 0.42 g 2,6-dimethylaniline **2g** (3.87 mmol, 1.2 equiv), 0.54 mL *N*-methylimidazole (6.78 mmol, 2.1 equiv), 1.0 g of TCFH (3.55 mmol, 1.1 equiv) in 10 mL MeCN for 3 h before purification by SiO_2 chromatography with heptane/ethyl acetate to yield 762 mg of **6g** as a white solid (93% yield) which contained a mixture of two rotamers as confirmed by NOESY NMR in a 93:7 ratio. TLC R_f = 0.38 (7:3 heptane/EtOAc, UV 254 nm). mp = 155.5 °C (DSC). ^{1}H NMR (major, $CDCl_3$, 400 MHz): δ 7.4 (m, 4H), 7.3 (m, 1H), 7.1-6.95 (m, 3H), 6.55 (s, 1H), 3.8 (q, *J* = 7.1 Hz, 1H), 2.1 (s, 6H), 1.65 (d, *J* = 7.3 Hz, 3H). ^{1}H NMR (minor, $CDCl_3$, 400 MHz): δ 7.2 (m, 5H), 6.9 (m, 3H), 6.6 (s, 1H), 3.4 (q, *J* = 7.1 Hz, 1H), 2.4 (s, 3H), 1.5 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 172.4, 141.2, 135.3, 133.7, 129.1, 128.0, 127.7, 127.5, 127.1, 47.3, 18.1, 18.0. IR (solid state): 1666, 1653, 1644, 1589, 1521, 1471, 1451, 1371 cm^{-1}. HRMS ($C_{17}H_{19}ON$, MH$^+$): calc'd: 254.1539, observed: 254.1550. HPLC: RT 8.27 min (<0.1%), RT 9.16 min (>99.9%) (220 nm, TFA/MeCN/H_2O gradient, Phenomenex Lux Cellulose-3, 3 μm, 4.6x150 mm).





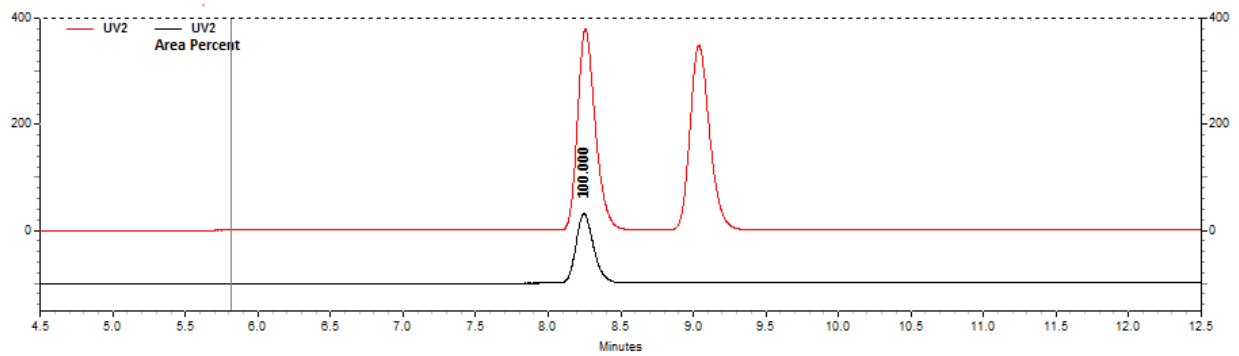
(*S*)-2-Phenyl-N-(p-tolyl)propanamide (6k): Following General Procedure 2, 0.45 mL (*S*)-2-phenylpropionic acid (*S*)-**5** (3.23 mmol, 1.0 equiv), 0.42 g p-Me aniline **2k** (3.87 mmol, 1.2 equiv), 0.54 mL *N*-methylimidazole (6.78 mmol, 2.1 equiv), 1.0 g of TCFH (3.55 mmol, 1.1 equiv) in 10 mL MeCN for 30 min before purification by SiO_2 chromatography with heptane/ethyl acetate to yield 680 mg of **6k** as a white solid (88% yield).[5] TLC R_f = 0.53 (7:3 heptane/EtOAc, UV 254 nm). mp = 122.6 °C (DSC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45-7.30 (m, 7H), 7.1 (d, *J* = 8.3 Hz, 2H), 7.0 (s, 1H), 3.7 (q, *J* = 7.1 Hz, 1H), 2.3 (s, 3H), 1.6 (d, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 172.1, 141.1, 135.3, 133.9, 129.4, 129.2, 127.7, 127.6, 119.7, 48.1, 20.8, 18.6. IR (solid state): 1652, 1602, 1535, 1511, 1494, 1403, 1372, 1354, 1332, 1307 cm^{-1}. HRMS ($C_{16}H_{17}ON$, MH^+): calc'd: 240.1383, observed: 240.1394. HPLC: RT 9.68 min (>99.9%), RT 10.13 min (<0.1%) (254 nm, TFA/MeCN/H_2O gradient, Chiralpak OB-H, 5 μm, 4.6x150 mm).

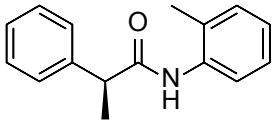




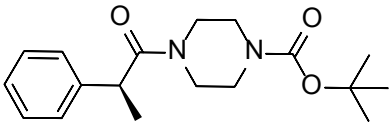
(*S*)-N-(4-fluorophenyl)-2-phenylpropanamide (6l): Following General Procedure 2, 0.45 mL (*S*)-2-phenylpropionic acid (*S*)-**5** (3.23 mmol, 1.0 equiv), 0.37 mL 4-fluoroaniline **2l** (3.87 mmol, 1.2 equiv), 0.54 mL *N*-methylimidazole (6.78 mmol, 2.1 equiv), 1.0 g of TCFH (3.55 mmol, 1.1 equiv) in 10 mL MeCN for 30

min before purification by SiO_2 chromatography with heptane/ethyl acetate to yield 641 mg of **6l** as a white solid (82% yield).[6] TLC R_f = 0.46 (7:3 heptane/EtOAc, UV 254 nm). mp = 97.9 °C (DSC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45-7.3 (m, 7H), 7.1 (s, 1H), 7.0 (m, 2H), 3.7 (q, *J* = 7.1 Hz, 1H), 1.6 (d, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 172.3, 159.3 (d, *J* = 242.9 Hz), 140.82, 133.8 (d, *J* = 2.2 Hz), 129.2, 127.7, 127.6, 121.6 (d, *J* = 8.1 Hz), 115.6 (d, *J* = 22.7 Hz), 47.9, 18.6. ^{19}F{^{1}H} NMR ($CDCl_3$, 376 MHz): δ -118.1. IR (solid state): 1662, 1649, 1614, 1547, 1505, 1563, 1451, 1405 cm^{-1}. HRMS ($C_{15}H_{14}FON$, MH^+): calc'd: 244.1132, observed: 244.1142. HPLC: RT 8.26 min (>99.9%), RT 9.04 min (<0.1%) (254 nm, TFA/MeCN/H_2O gradient, Chiralpak OB-H, 5 μm, 4.6x150 mm).



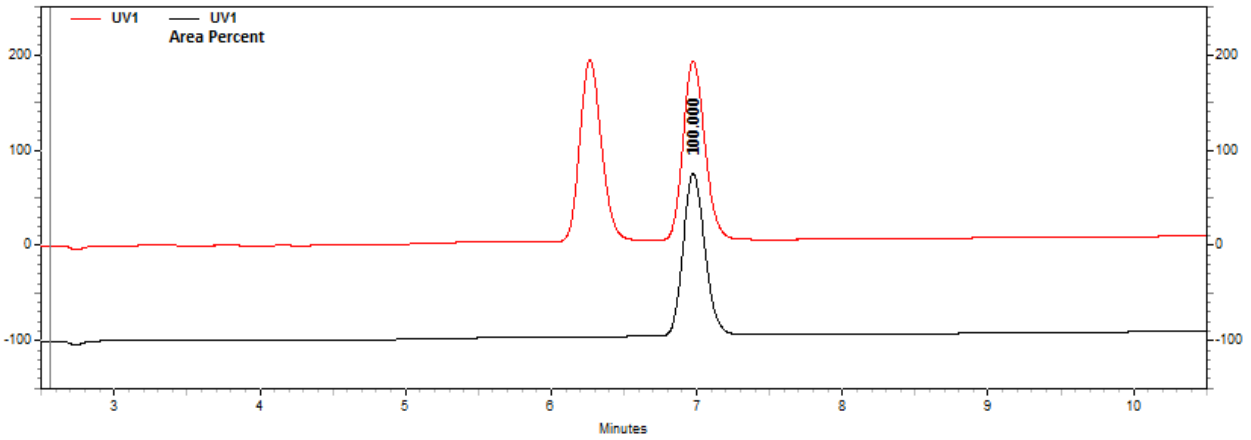


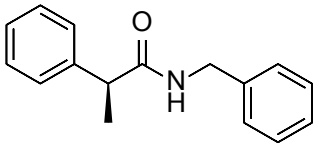
(*S*)-2-Phenyl-N-(o-tolyl)propanamide (6m): Following General Procedure 2, 0.45 mL (*S*)-2-phenylpropionic acid (*S*)-**5** (3.23 mmol, 1.0 equiv), 0.42 g o-Me aniline **2m** (3.87 mmol, 1.2 equiv), 0.54 mL *N*-methylimidazole (6.78 mmol, 2.1 equiv), 1.0 g of TCFH (3.55 mmol, 1.1 equiv) in 10 mL MeCN for 30 min before purification by SiO_2 chromatography with heptane/ethyl acetate to yield 649 mg of **6m** as a white solid (84% yield).[7] TLC R_f = 0.47 (7:3 heptane/EtOAc, UV 254 nm). mp = 85.7 °C (DSC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.9 (d, *J* = 8.1 Hz, 1H), 7.45-7.3 (m, 5H), 7.2 (m, 1H), 7.1 (m, 1H), 7.0 (m, 1H), 6.9 (s, 1H), 3.8 (q, *J* = 7.3 Hz, 1H), 1.9 (s, 3H), 1.6 (d, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 172.2, 140.9, 135.7, 130.3, 129.2, 128.0, 127.8, 127.7, 126.7, 124.7, 122.0, 48.1, 18.0, 17.1. IR (solid state): 1651, 1585, 1523, 1497, 1453, 1372, 1352, 1285 cm^{-1}. HRMS ($C_{16}H_{17}ON$, MH^+): calc'd: 240.1383, observed: 240.1394. HPLC: RT 8.83 min (<0.1%), RT 10.00 min (>99.9%) (254 nm, heptane/EtOH gradient, (*R*,*R*)-Whelk-O1, 3 μm, 4.6x150 mm).



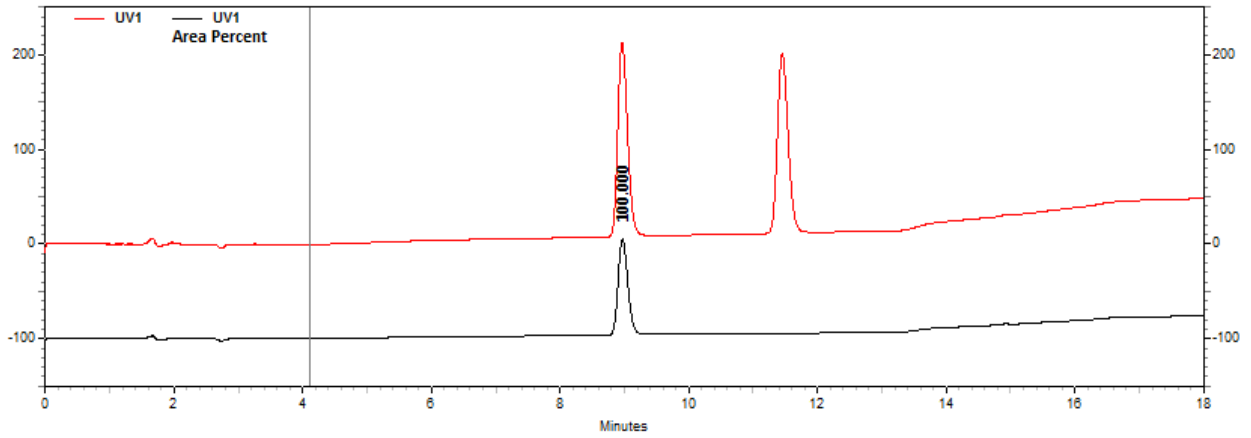
***tert*-Butyl (S)-4-(2-phenylpropanoyl)piperazine-1-carboxylate (11):** Following General Procedure 2, 0.45 mL (*S*)-2-phenylpropionic acid (*S*)-**5** (3.23 mmol, 1.0 equiv), 0.74 g *N*-Boc piperidine (3.87 mmol, 1.2 equiv), 0.54 mL *N*-methylimidazole (6.78 mmol, 2.1 equiv), 1.0 g of TCFH (3.55 mmol, 1.1 equiv) in 10 mL MeCN for 30 min before purification by SiO_2 chromatography with heptane/ethyl acetate to yield 910 mg of **11** as a white solid (89% yield).[8] TLC R_f = 0.19 (7:3 heptane/EtOAc, UV 254 nm). mp = 151.2 °C (DSC). ^{1}H NMR (CD_3CN, 400 MHz): δ 7.35 (m, 2H), 7.3 (m, 3H), 4.0 (q, *J* = 6.7 Hz, 1H), 3.6 (m, 1H), 3.4 (m, 3H), 3.3 (m, 2H), 3.2 (m, 1H), 2.8 (m, 1H), 1.45 (s, 9H), 1.35 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (CD_3CN, 100 MHz): δ 172.4, 154.9, 143.1, 129.4, 127.9, 127.7, 79.9, 45.6, 43.9, 42.9, 42.0, 28.1, 20.5. IR (solid state): 1692, 1635, 1600,

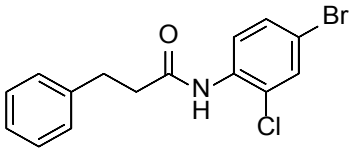
1583, 1490, 1476, 1452, 1413 cm^{-1}. HRMS ($C_{18}H_{26}N_2O_3$, MH^+): calc'd: 319.2016, observed: 319.2029. HPLC: RT 6.26 min (<0.1%), RT 7.00 min (>99.9%) (220 nm, TFA/MeCN/H_2O gradient, Phenomenex Lux Cellulose-3, 3 μm, 4.6x150 mm).



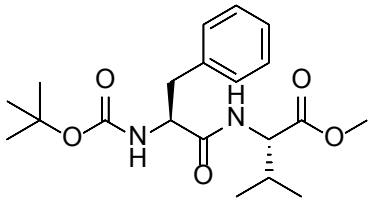


(*S*)-*N*-benzyl-2-phenylpropanamide (12): Following General Procedure 2, 0.45 mL (*S*)-2-phenylpropionic acid (*S*)-**5** (3.23 mmol, 1.0 equiv), 0.43 mL benzylamine (3.87 mmol, 1.2 equiv), 0.54 mL *N*-methylimidazole (6.78 mmol, 2.1 equiv), 1.0 g of TCFH (3.55 mmol, 1.1 equiv) in 10 mL MeCN for 30 min before purification by SiO_2 chromatography with heptane/ethyl acetate to yield 680 mg of **12** as a white solid (88% yield).[1] TLC R_f = 0.31 (7:3 heptane/EtOAc, UV 254 nm). mp = 80.1°C (DSC). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.4-7.2 (m, 8H), 7.2 (m, 2H), 5.6 (s, 1H), 4.4 (m, 2H), 3.6 (q, *J* = 7.0 Hz, 1H), 1.6 (d, *J* = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 174.0, 141.3, 138.4, 128.9, 128.6, 127.7, 127.5, 127.4, 127.3, 47.2, 43.6, 18.6. IR (solid state): 1647, 1636, 1603, 1553, 1535, 1496, 1451, 1421 cm^{-1}. HRMS ($C_{16}H_{17}NO$, MH^+): calc'd: 240.1383, observed: 240.1394. HPLC: RT 8.97 min (>99.9%), RT 11.46 min (<0.1%) (220 nm, TFA/MeCN/H_2O gradient, Phenomenex Lux Cellulose-3, 3 μm, 4.6x150 mm).

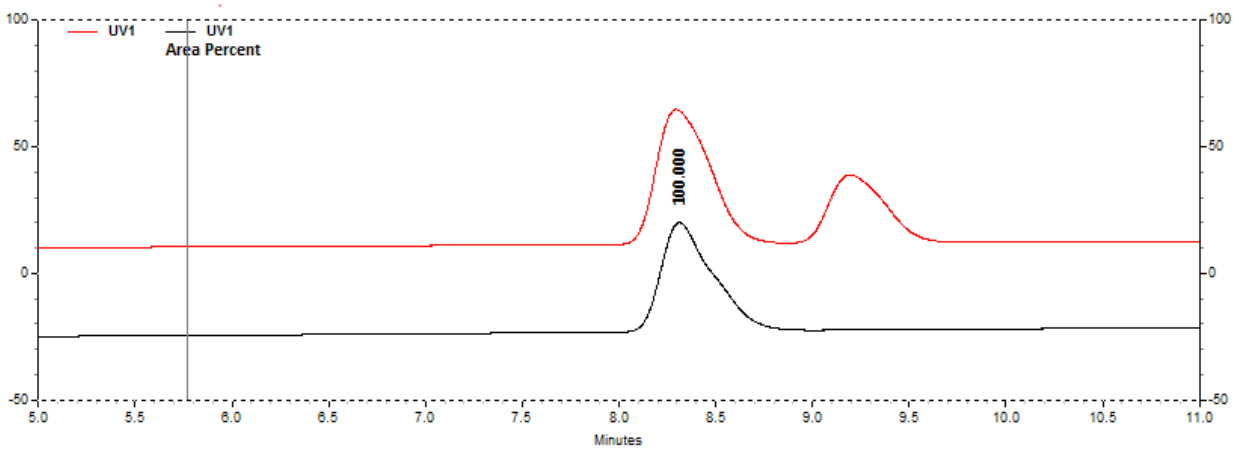


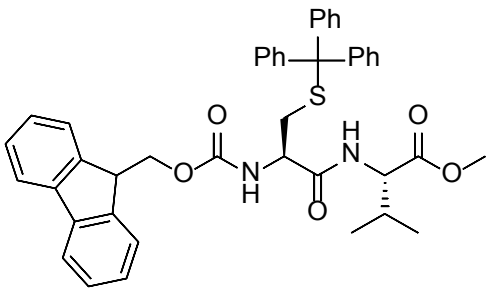


N-(4-bromo-2-chlorophenyl)-3-phenylpropanamide (13): Following General Procedure 2, 0.50 g hydrocinnamic acid (*S*)-**7** (3.30 mmol, 1.0 equiv), 0.86 g 4-bromo-2-chloroaniline (3.96 mmol, 1.2 equiv), 0.55 mL *N*-methylimidazole (6.92 mmol, 2.1 equiv), 1.03 g of TCFH (3.63 mmol, 1.1 equiv) in 10 mL MeCN for 20 h before purification by SiO_2 chromatography with heptane/ethyl acetate to yield 946 mg of **13** as a white solid (85% yield). TLC R_f = 0.6 (7:3 heptane/EtOAc, UV 254 nm). mp = 158.2 °C (DSC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.7 (bs, 1H), 7.5 (bs, 1H), 7.35 (m, 2H), 7.3-7.15 (m, 5H), 3.1 (t, *J* = 7.3 Hz, 2H), 2.8 (t, *J* = 7.3 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 170.3, 140.1, 135.5, 129.9, 128.7, 128.3, 127.4, 126.6, 124.2, 121.2, 121.1, 39.5, 31.2. IR (solid state): 1663, 1581, 1571, 1510, 1496, 1461, 1451, 1400 cm^{-1}. HRMS ($C_{15}H_{13}BrClNO$, MH$^+$): calc'd: 337.9942, observed: 337.9947.

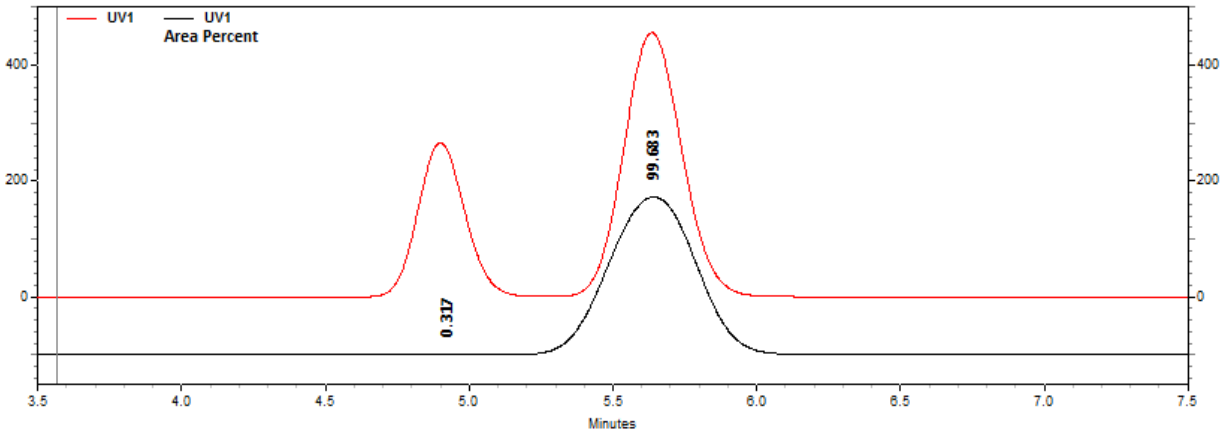


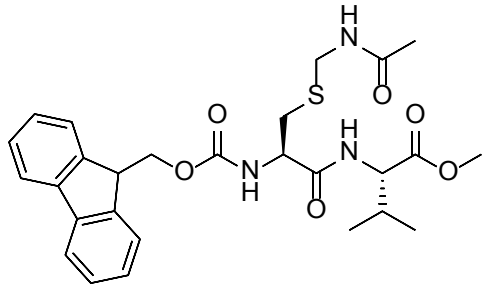
Methyl (*tert*-butoxycarbonyl)-L-phenylalanyl-L-valinate (16): Following General Procedure 1, 1.00 g (*tert*-butoxycarbonyl)-L-phenylalanine **15** (3.73 mmol, 1.0 equiv), 0.76 g L-valine methyl ester hydrochloride **14** (4.48 mmol, 1.2 equiv), 0.92 mL *N*-methylimidazole (11.6 mmol, 3.1 equiv), 1.16 g of TCFH (4.1 mmol, 1.1 equiv) in 20 mL MeCN for 30 min before purification by SiO_2 chromatography with heptane/ethyl acetate to yield 1.18 g of **16** as a white solid (84% yield).[9] TLC R_f = 0.47 (7:3 heptane/EtOAc, UV 254 nm). mp = 121.6 °C (DSC). ^{1}H NMR (MeOH-d_4, 400 MHz): δ 7.3-7.2 (m, 5H), 6.7 (bd, *J* = 7.6, 1H), 4.35 (m, 2H), 3.7 (s, 3H), 3.1 (dd, *J* = 5.5, 13.7 Hz, 1H), 2.8 (dd, *J* = 9.2, 13.7 Hz, 1H), 2.1 (m, 1H), 1.4 (s, 9H), 0.9 (***L epimer***, m, 6H), 0.8 (***D epimer***, m, 6H). ^{13}C{^{1}H} NMR (MeOH-d_4 100 MHz): δ 173.1, 171.8, 156.2, 137.2, 129.0, 128.0, 126.3, 79.2, 57.7, 55.8, 51.1, 37.6, 30.7, 27.2, 18.0, 17.0. IR (solid state): 1744, 1681, 1654, 1535, 1498, 1454, 1437, 1391 cm^{-1}. HRMS ($C_{20}H_{30}N_2O_5$, MH$^+$): calc'd: 379.2227, observed: 329.2237. HPLC: RT 8.3 min (<0.1%), RT 9.19 min (>99.9%) (220 nm, TFA/MeCN/H_2O gradient, Chiralpak IE-3, 3.0 μm, 4.6x150 mm).





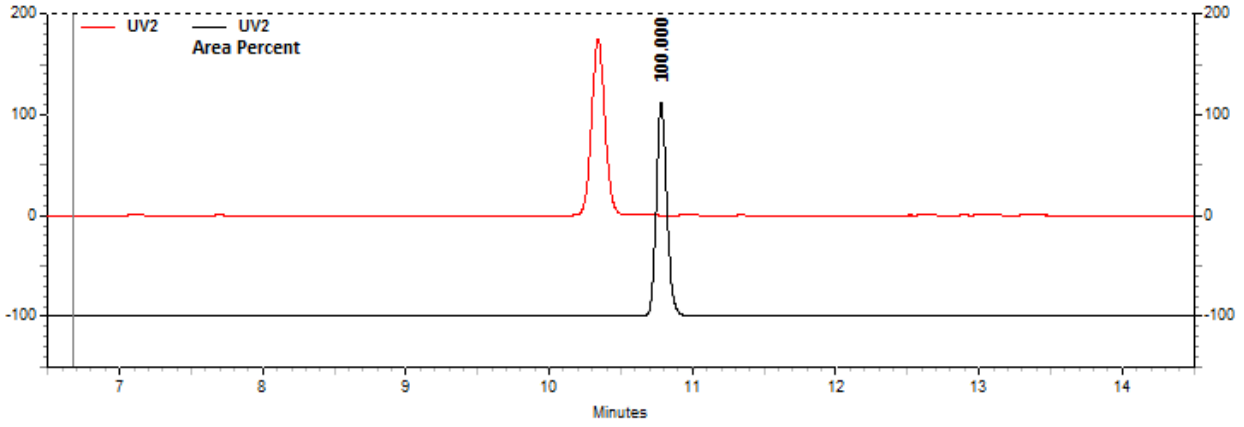
Methyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-L-cysteinyl-L-valinate (18): Following General Procedure 1, 1.00 g N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-L-cysteine **17** (1.70 mmol, 1.0 equiv), 0.35 g L-valine methyl ester hydrochloride **14** (2.04 mmol, 1.2 equiv), 0.42 mL *N*-methylimidazole (5.28 mmol, 3.1 equiv), 0.53 g of TCFH (1.87 mmol, 1.1 equiv) in 20 mL MeCN for 30 min before purification by SiO_2 chromatography with heptane/ethyl acetate to yield 1.05 g of **18** as a white solid (88% yield). TLC R_f = 0.72 (7:3 heptane/EtOAc, UV 254 nm). mp = 73.2 °C (DSC, decomposition). ^{1}H NMR (MeOH-d_4, 400 MHz): δ 7.8 (m, 2H), 7.6 (m, 2H), 7.4-7.3 (m, 8H), 7.3-7.2 (m, 11H), 4.4 (dd, *J* = 7.6, 10.7 Hz, 1H), 4.3-4.2 (m, 2H), 4.2 (t, *J* = 7.0 Hz, 1H), 4.1 (***D epimer***, t, *J* = 7.0 Hz, 1H), 4.0 (***L epimer***, t, *J* = 7.0 Hz, 1H), 3.6 (s, 3H), 2.5 (m, 2H), 2.1 (sept, *J* = 6.7 Hz, 1H), 0.9 (d, *J* = 6.7 Hz, 6H). ^{13}C{^{1}H} NMR (MeOH-d_4, 100 MHz): δ 173.2, 173.0, 158.2, 146.1, 145.4, 145.2, 142.7, 130.9, 129.2, 128.9, 128.4, 128.1, 126.4, 121.1, 68.3, 68.2, 59.3, 55.5, 52.7, 35.2, 32.1, 19.5, 18.6. IR (solid state): 1740, 1664 cm^{-1}. HRMS ($C_{43}H_{42}N_2O_5S$, M+Na): calc'd: 721.2707, observed: 721.2725. HPLC: RT 4.8 min (0.3%), RT 5.53 min (99.7%) (220 nm, EtOH isocratic, Phenomenex Lux Cellulose-2, 3.0 μm, 4.6x150 mm).

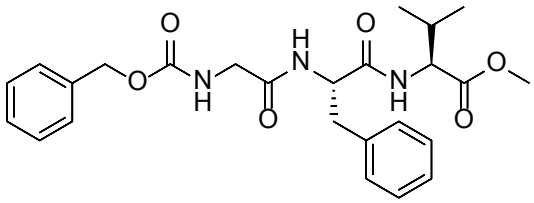




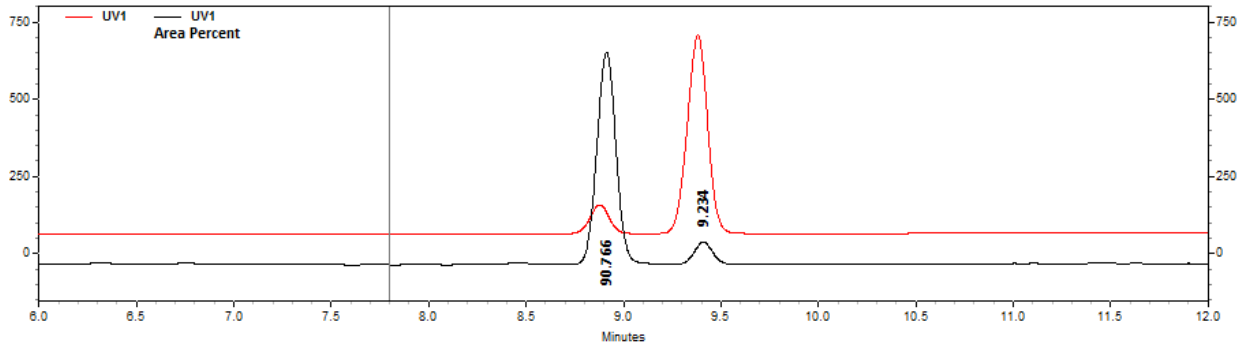
Methyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-(acetamidomethyl)-L-cysteinyl-L-valinate (20): Following General Procedure 1, 1.00 g N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-(acetamidomethyl)-L-cysteine **19** (2.41 mmol, 1.0 equiv), 0.49 g L-valine methyl ester hydrochloride **14** (2.89 mmol, 1.2 equiv),

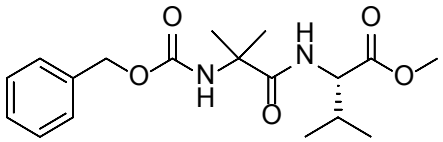
0.59 mL *N*-methylimidazole (7.46 mmol, 3.1 equiv), 0.75 g of TCFH (2.65 mmol, 1.1 equiv) in 20 mL MeCN before purification by SiO_2 chromatography with dichloromethane/MeOH to give 1.27 g of **20** as a white solid (92% yield). TLC R_f = 0.52 (9:1 DCM/MeOH, UV 254 nm). mp = 175.2 °C (DSC). ^{1}H NMR (MeOH-d_4, 400 MHz): δ 7.8 (d, *J* = 7.6 Hz, 2H), 7.7 (m, 2H), 7.4 (Ψt, *J* = 7.6 Hz, 2H), 7.3 (Ψt, *J* = 7.6 Hz, 2H), 4.6 (m, 2H), 4.4 (m, 3H), 4.2 (t, *J* = 7.0 Hz, 1H), 4.1 (d, *J* = 13.7 Hz, 1H), 3.7 (s, 3H), 3.0 (dd, *J* = 4.3, 14.0 Hz, 1H), 2.8 (***D-epimer***, dd, *J* = 8.8, 13.7 Hz, 1H), 2.7 (***L-epimer***, dd, *J* = 9.8, 13.7 Hz, 1H), 2.2 (dq, *J* = 6.7, 13.4 Hz, 1H), 2.0 (s, 2H), 1.0 (d, *J* = 7.0 Hz, 3H), 1.0 (d, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (MeOH-d_4, 100 MHz): δ 173.8, 173.7, 173.6, 158.7, 145.4, 142.7, 128.9, 128.3, 126.4, 121.1, 68.3, 59.3, 55.7, 52.9, 41.5, 34.1, 31.9, 22.9, 19.6, 18.5. IR (solid state): 1740, 1654, 1532 cm^{-1}. HRMS ($C_{27}H_{33}N_3O_6S$, MH^+): calc'd: 528.2163, observed: 528.2177. HPLC: RT 10.34 min (<0.1%), RT 10.78 min (>99.9%) (300 nm, TFA/MeCN/H_2O gradient, Ascentis Express C8, 2.7 μm, 4.6x150 mm).



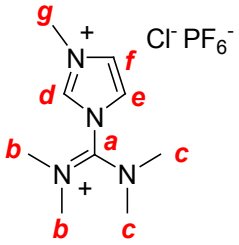


Methyl ((benzyloxy)carbonyl)glycyl-L-phenylalanyl-L-valinate (22): Following General Procedure 1, 1.00 g (2*S*)-2-[[2-(benzyloxycarbonylamino)acetyl]amino]-3-phenyl-propanoic acid **21** (2.81 mmol, 1.0 equiv), 0.36 g L-valine methyl ester hydrochloride **14** (3.37 mmol, 1.2 equiv), 0.69 mL *N*-methylimidazole (8.70 mmol, 3.1 equiv), 0.875 g of TCFH (3.09 mmol, 1.1 equiv) in 20 mL MeCN for 30 min before purification by SiO_2 chromatography with heptane/ethyl acetate to yield 1.25 g of **22** as a white solid (95% yield). Spectral data is consistent with previous literature reports.[10] TLC R_f = 0.42 (7:3 heptane/EtOAc, UV 254 nm). ^{1}H NMR (MeOH-d_4, 400 MHz): δ 7.4-7.2 (m, 10H), 5.1 (m, 2H), 4.7 (dd, *J* = 8.3, 6.1 Hz, 1H), 4.3 (***L epimer***, d, *J* = 6.1 Hz, 1H), 4.2 (***D epimer***, d, *J* = 6.1 Hz), 3.7 (m, 2H), 3.6 (s, 3H), 3.1 (dd, *J* 6.1, 14.1 Hz, 1H), 2.9 (dd, *J* = 8.2, 13.7 Hz, 1H), 2.1 (m, 1H), 0.9 (***L epimer***, Ψt, *J* = 6.4 Hz, 6H), 0.8 (***D epimer***, d, *J* = 6.7 Hz). IR (solid state): 1729, 1714, 1645 cm^{-1}. HRMS ($C_{25}H_{31}N_3O_6$, MH^+): calc'd: 470.2286, observed: 470.2298. HPLC: RT 8.91 min (90.7%), RT 9.41 min (9.3%) (215 nm, TFA/MeCN/H_2O gradient, Ascentis Express C8, 2.7 μm, 4.6x150 mm).

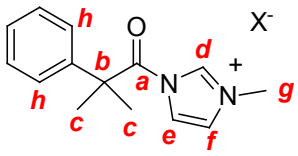




Methyl (2-(((benzyloxy)carbonyl)amino)-2-methylpropanoyl)-L-valinate (24): Following General Procedure 1, 0.50 g Z-aib-OH **23** (2.09 mmol, 1.0 equiv), 0.36 g L-valine methyl ester hydrochloride **14** (2.09 mmol, 1.0 equiv), 0.58 mL N-methylimidazole (7.31 mmol, 3.5 equiv), 0.62 g of TCFH (2.19 mmol, 1.1 equiv) in 10 mL MeCN for 30 min before purification by SiO_2 chromatography with heptane/ethyl acetate to yield 675 mg of **24** as a white solid (92% yield).[11] TLC R_f = 0.24 (7:3 heptane/EtOAc, UV 254 nm). mp = 74.7 °C (DSC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.3 (m, 5H), 6.8, (bs, 1H), 5.3 (bs, 1H), 5.1 (m, 2H), 4.5 (dd, *J* = 8.6, 4.8 Hz, 1H), 3.7 (s, 3H), 2.2 (sept, *J* = 6.8 Hz, 1H), 1.6 (s, 3H), 1.5 (s, 3H), 0.9 (d, *J* = 6.8 Hz, 3H), 0.8 (d, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 147.2, 172.4, 155.0, 136.2, 128.6, 128.2, 128.1, 66.8, 57.1, 57.0, 52.1, 31.3, 26.0, 25.1, 18.9, 17.6. IR (solid state): 1741, 1692, 1677, 1658, 1537, 1517, 1467, 1455 cm^{-1}. HRMS ($C_{18}H_{26}N_2O_5$, MH^+): calc'd: 351.1914, observed: 351.1930.



1-(dimethyl-λ^4-azaneylidene)-*N,N*-dimethyl-1-(3-methyl-1H-3λ^4-imidazol-1-yl)methanamine chloride hexafluorophosphate (*ii*): To 0.456 g TCFH (1.64 mmol, 1.0 equiv) in 5 mL CD_3CN was added 0.13 mL N-methylimidazole (1.64 mmol, 1.0 equiv). Aged 30 min then observed crude reaction mixture by NMR including ^{1}H, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC data for ^{1}H and ^{13}C NMR assignments. ^{1}H NMR (CD_3CN, 600 MHz): δ 10.9 (H-***d***, broad s, 1H), 8.1 (H-***e***, m, 1H), 7.8 (H-***f***, m, 1H), 4.0 (H-***g***, s, 3H), 3.4 (H-***b* or** H-***c***, s, 6H), 3.1 (H-***c*** or H-***b***, s, 6H). ^{13}C NMR (CD_3CN, 125 MHz): δ 152.7 (C-***a***), 142.2 (CH-***d***), 126.8 (CH-***f***), 123.5 (CH-***e***), 43.9 (CH_3-***b*** or ***c***), 43.2 (CH_3-***c*** or ***b***), 38.1 (CH_3-***g***). Key ^{1}H-^{13}C HMBC correlations: from H-***b***, H-***c***, H-***d*** and H-***e*** to C-***a***. IR (ATR, MeCN): 1691 cm^{-1}.

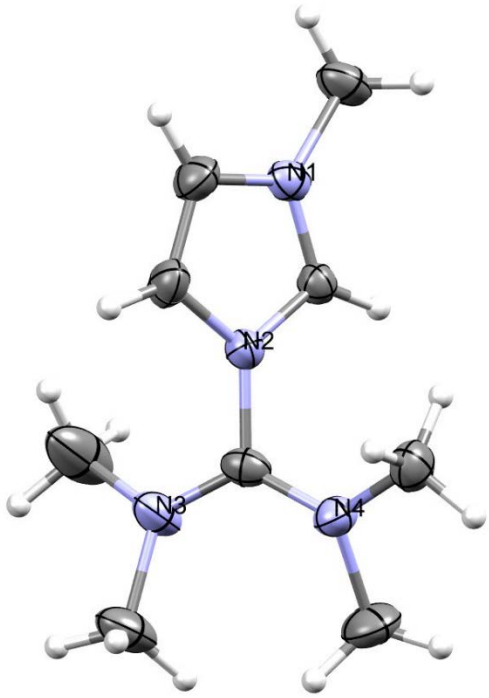


2-methyl-1-(3-methyl-1H-3λ^4-imidazol-1-yl)-2-phenylpropan-1-one anion salt (*iii*): To 0.456 g TCFH (1.64 mmol, 1.0 equiv) in 5 mL CD_3CN was added 0.26 mL N-methylimidazole (3.28 mmol, 2.0 equiv). Aged 30 min then charged 0.250 g 2-methyl-2-phenylpropanoic acid **1** (1.49 mmol, 0.9 equiv) in a single portion. Aged an additional 30 min then observed crude reaction mixture by NMR including ^{1}H, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC data for ^{1}H and ^{13}C NMR assignments. ^{1}H NMR (CD_3CN, 600 MHz): δ 9.4 (H-***d***, broad s, 1H), 7.4-7.5 (phenyl group, 5H), 7.3 (H-***f***, m, 1H), 7.2 (H-***e***, m, 1H), 3.9 (H- ***g***, s, 3H), 1.7 (H-***c***, 6H). ^{13}C NMR (CD_3CN, 125 MHz): δ 172.2 (C-***a***), 138.6 (CH-***d***), 123.8 (CH-***f***), 121.0 (CH-***e***), 50.2 (C-***b***), 36.2 (CH_3-***g***), 27.4 (CH_3-***c***). Key ^{1}H-^{13}C HMBC correlations: from H-***c***, H-***d*** and H-***e*** to C-***a***; from H-***h*** and H-***c*** to C-***b***. IR (ATR, MeCN): 1765 cm^{-1}.

Table S8. Crystal structure and X-ray refinement data of ***ii***.

Empirical formula	C22 H43 Cl F24 N10 P4	
Formula weight	1062.99	
Temperature	200(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	Pbcm	
Unit cell dimensions	a = 8.1173(2) Å	α= 90°.
	b = 19.6505(5) Å	β= 90°.
	c = 26.5415(6) Å	γ = 90°.
Volume	4233.61(18) $Å^3$	
Z	4	
Density (calculated)	1.668 Mg/m^3	
Absorption coefficient	3.538 mm^{-1}	
F(000)	2152	
Crystal size	0.320 x 0.300 x 0.200 mm^3	
Theta range for data collection	3.330 to 63.663°.	
Index ranges	-9<=h<=9, -22<=k<=22, -30<=l<=30	
Reflections collected	34706	
Independent reflections	3581 [R(int) = 0.0276]	
Completeness to theta = 63.663°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7524 and 0.5670	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3581 / 21 / 293	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2sigma(I)]	R1 = 0.0926, wR2 = 0.2666	
R indices (all data)	R1 = 0.0960, wR2 = 0.2710	
Extinction coefficient	0.00011(9)	
Largest diff. peak and hole	1.567 and -1.500 $e.Å^{-3}$	

Figure 1. Crystal structure of ***ii***. Thermal ellipsoids are drawn at 50% probability level.



[1] Shiina, I.; Nakata, K.; Sugimoto, M.; Onda, Y.; Iizumi, T.; Ono, K. *Heterocycles* **2009**, *77*, 801-810.
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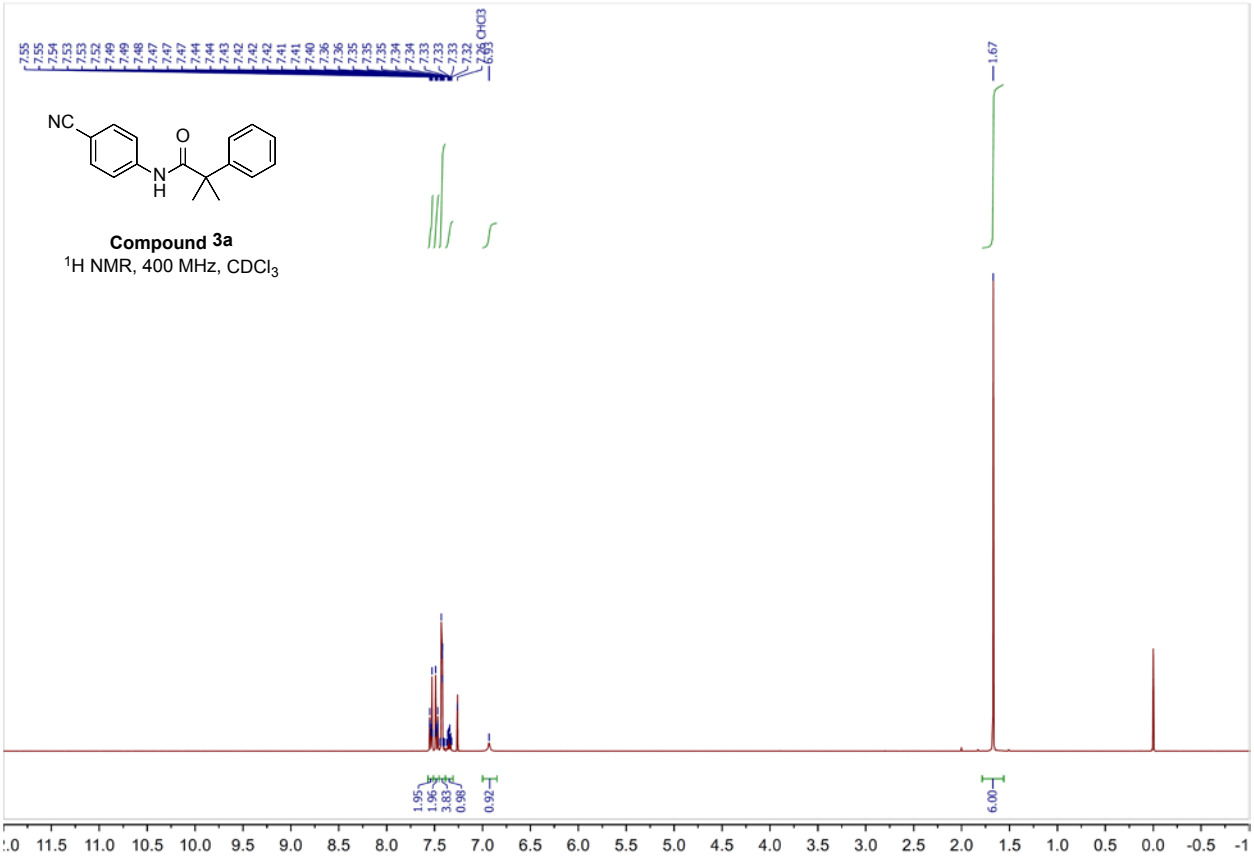
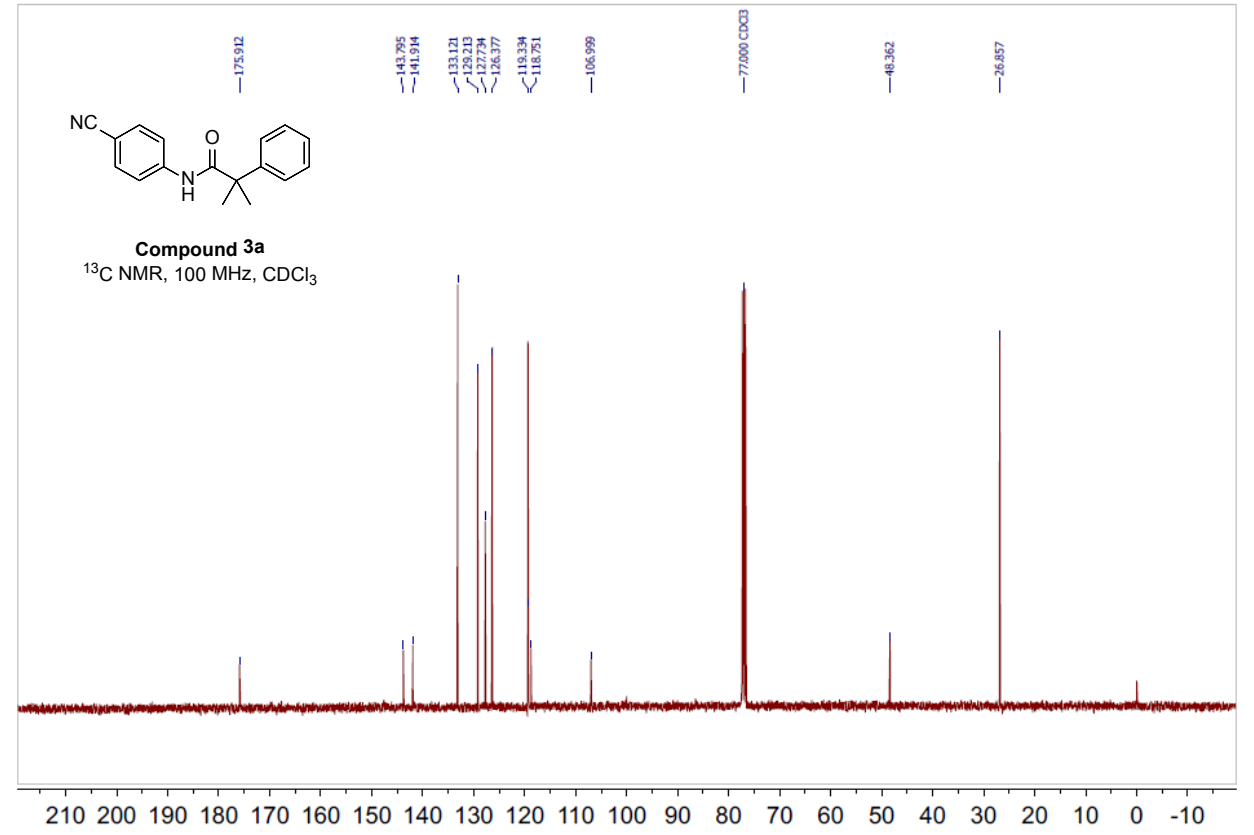


Compound 3a

^{1}H NMR, 400 MHz, $CDCl_3$



Compound 3a

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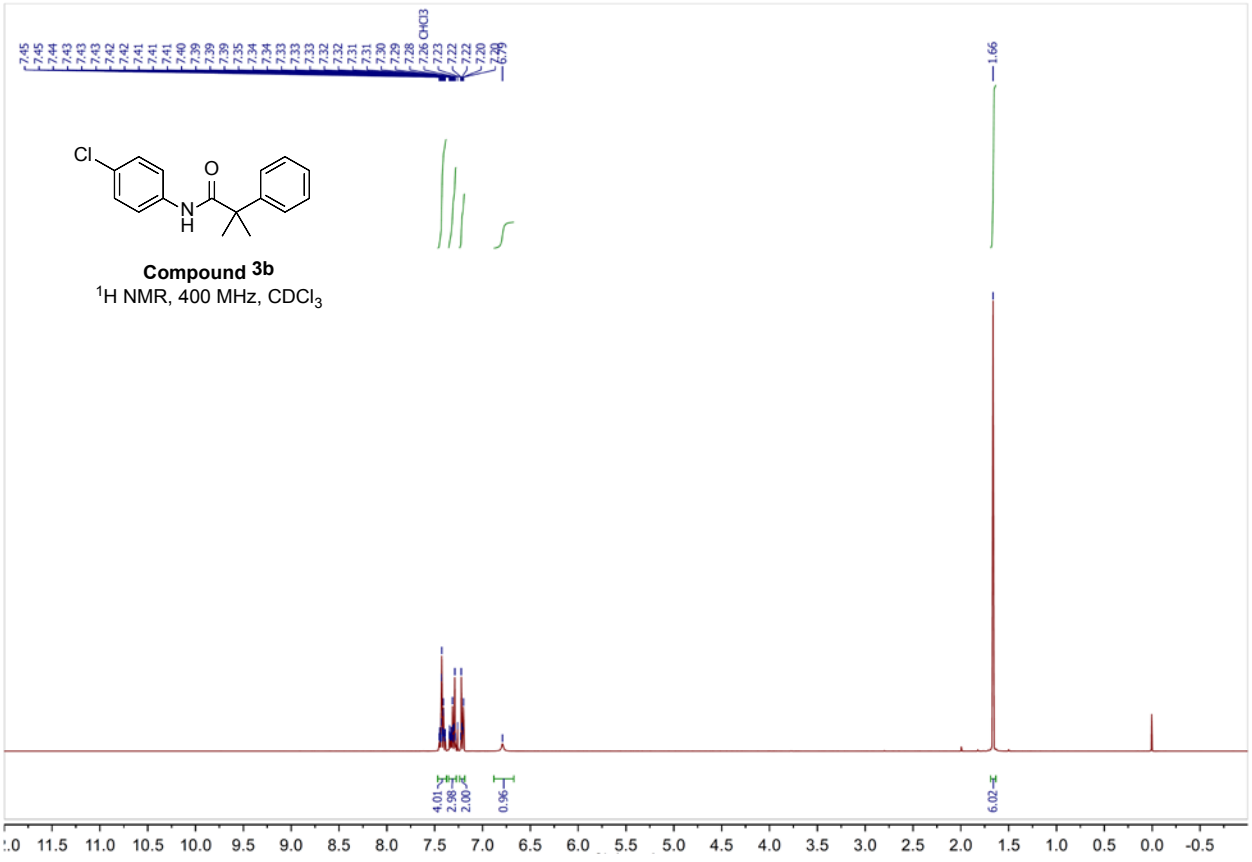

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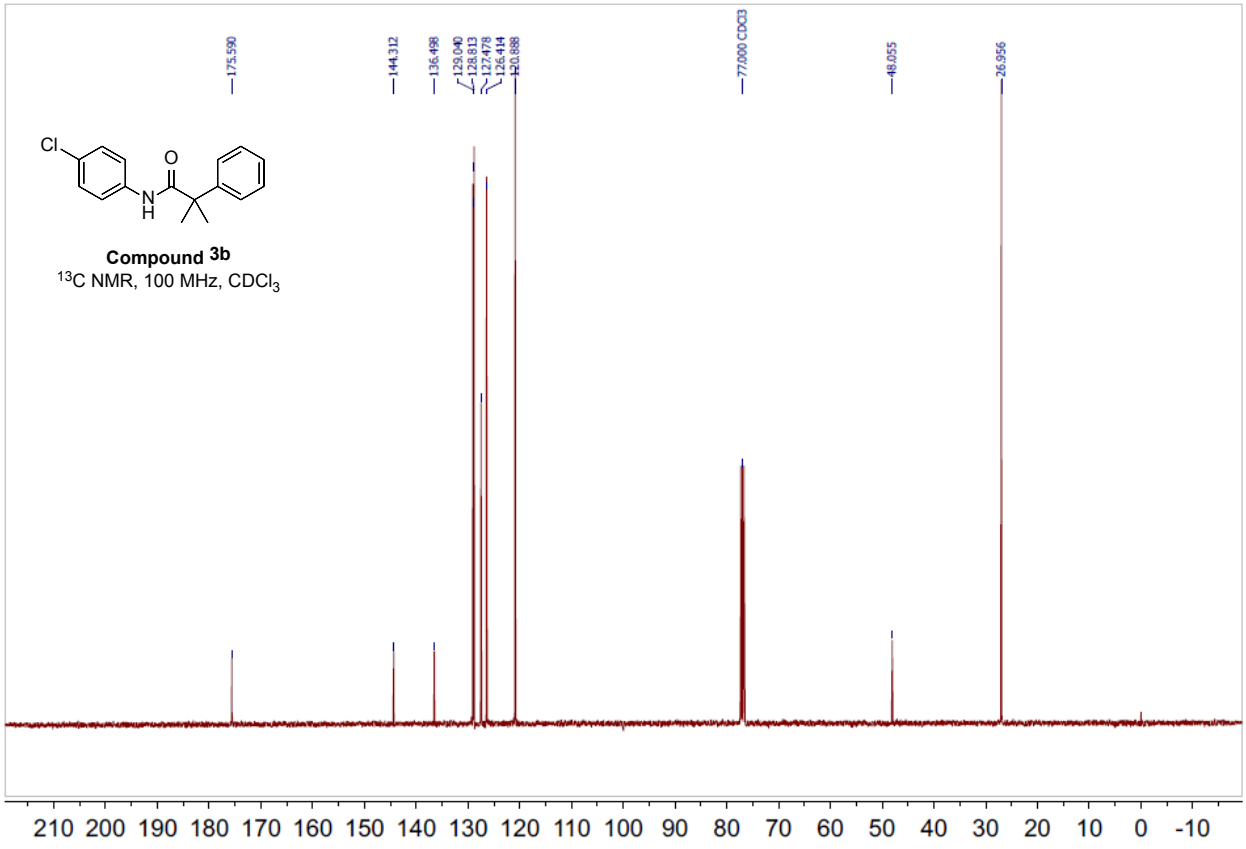

Compound 3b
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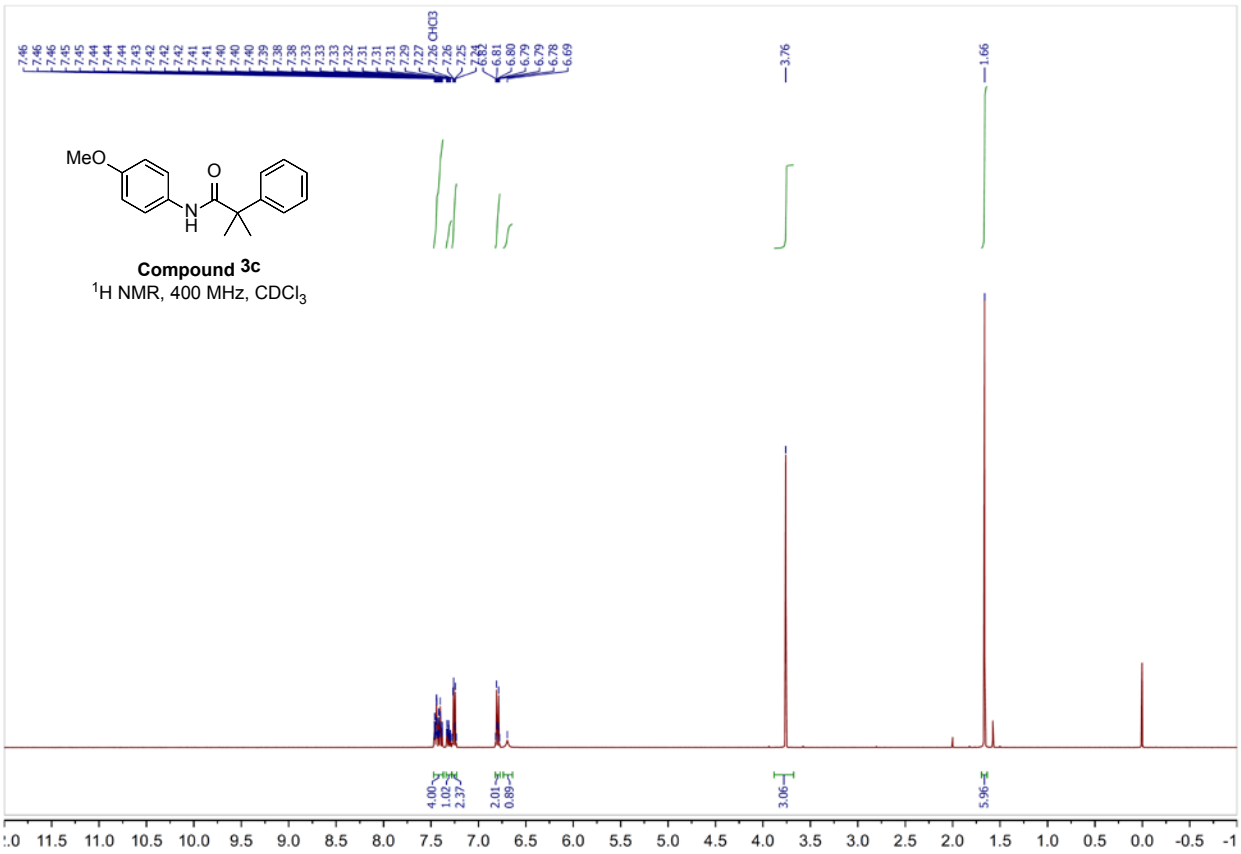

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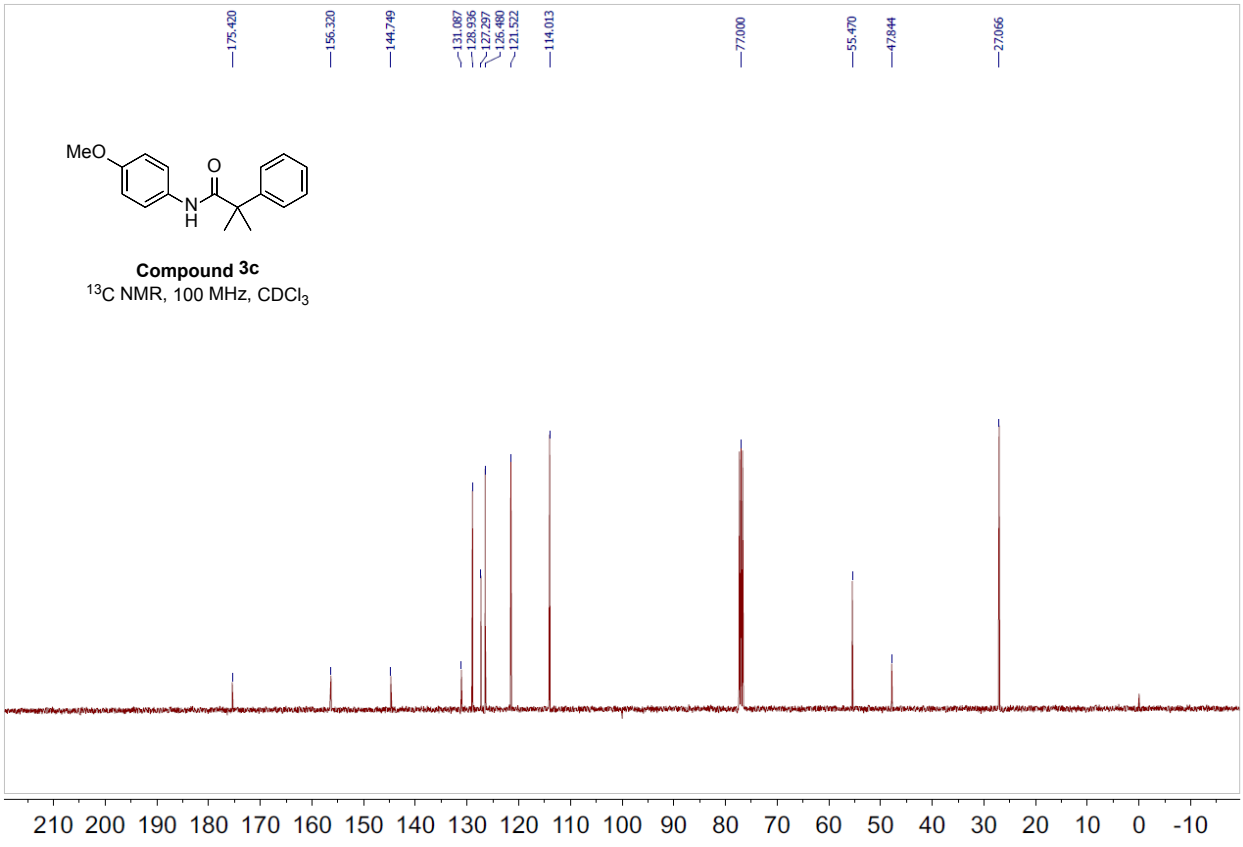

Compound 3c
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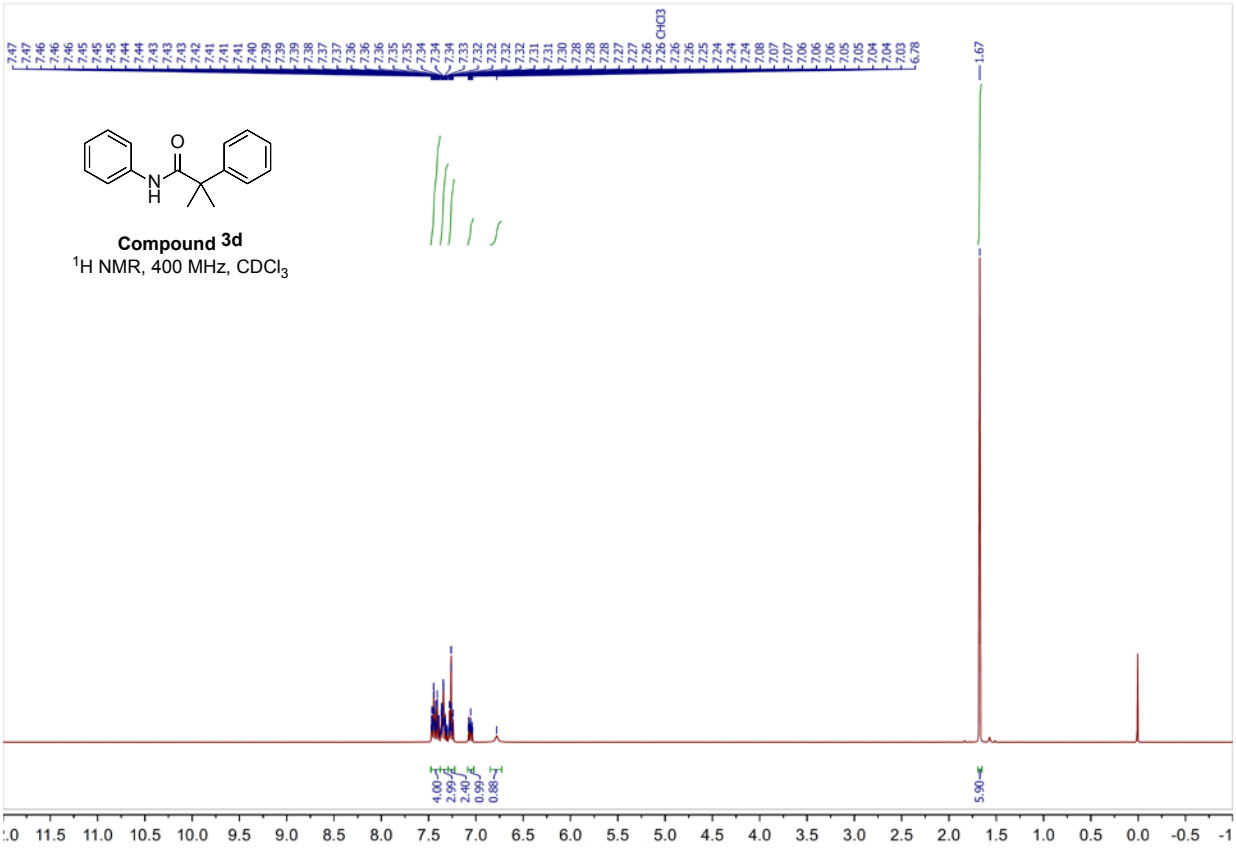

Compound 3d
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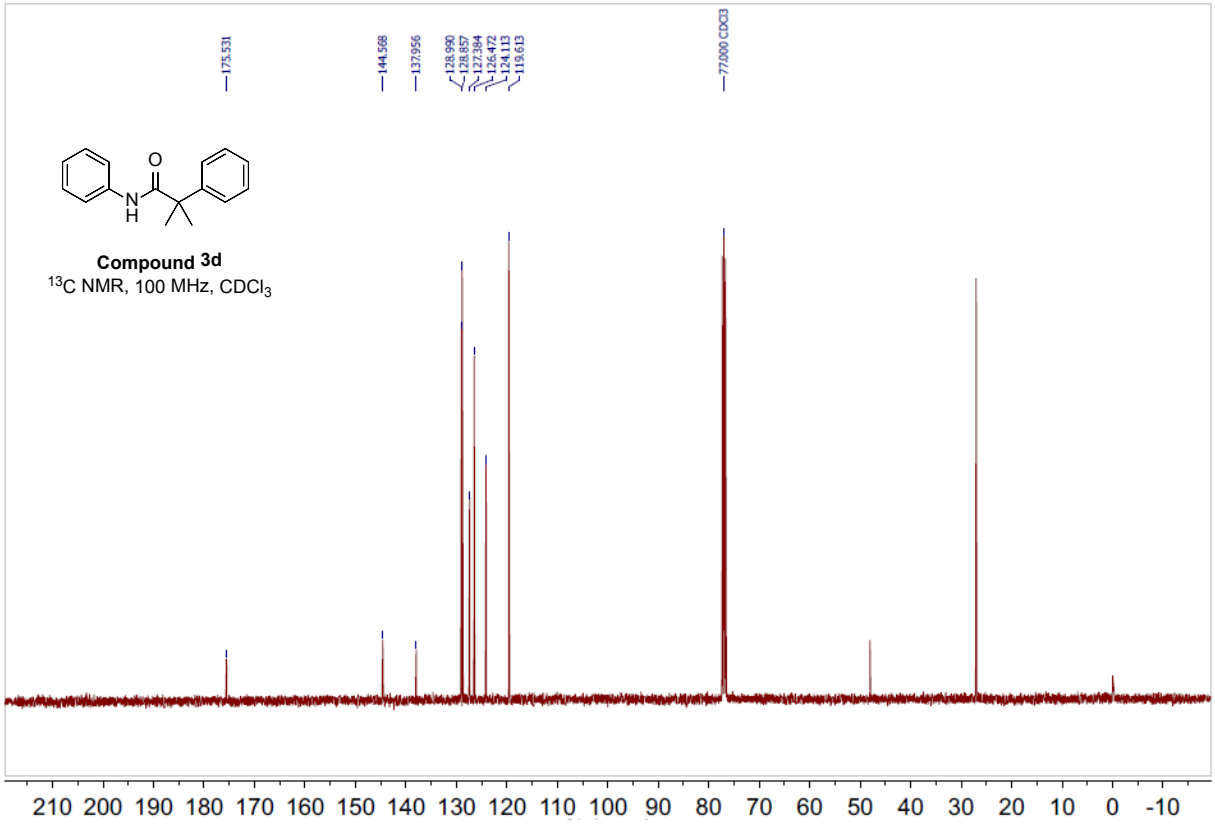

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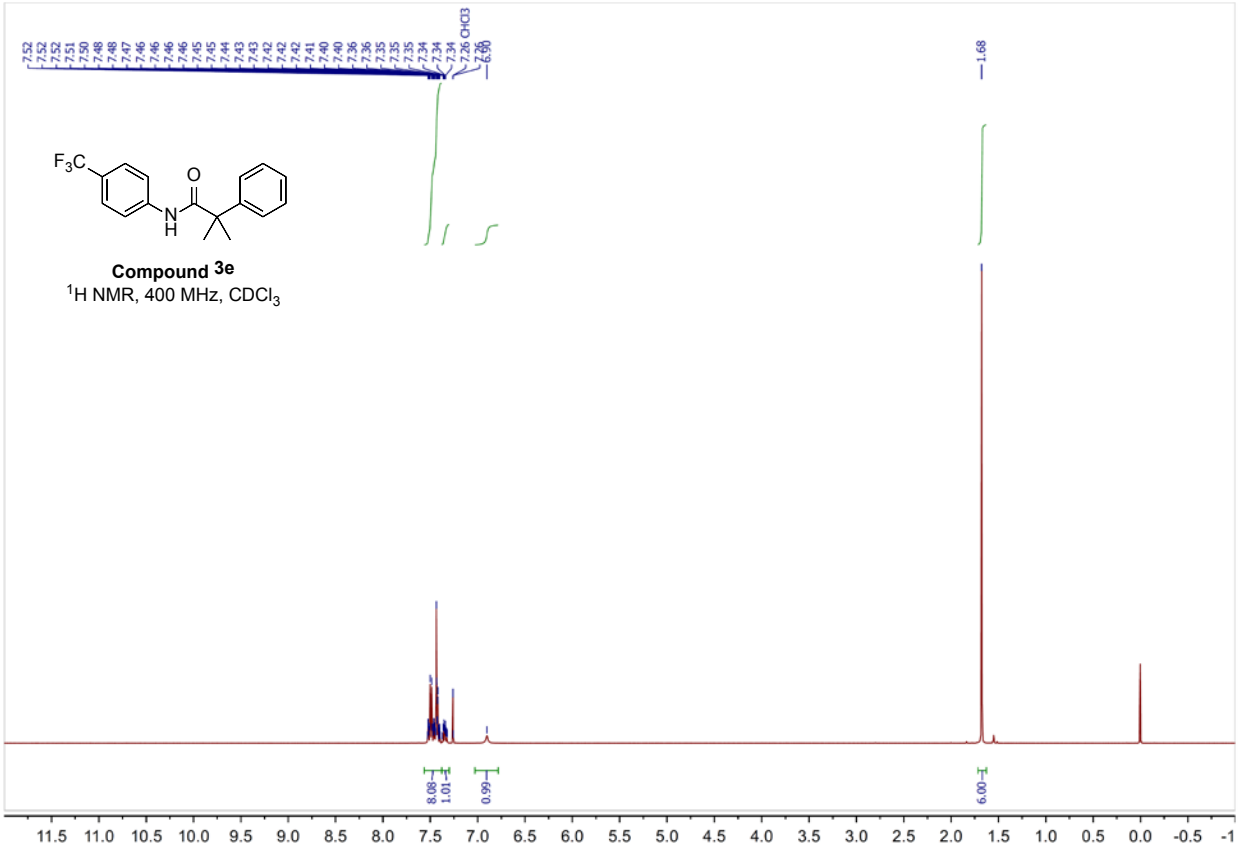

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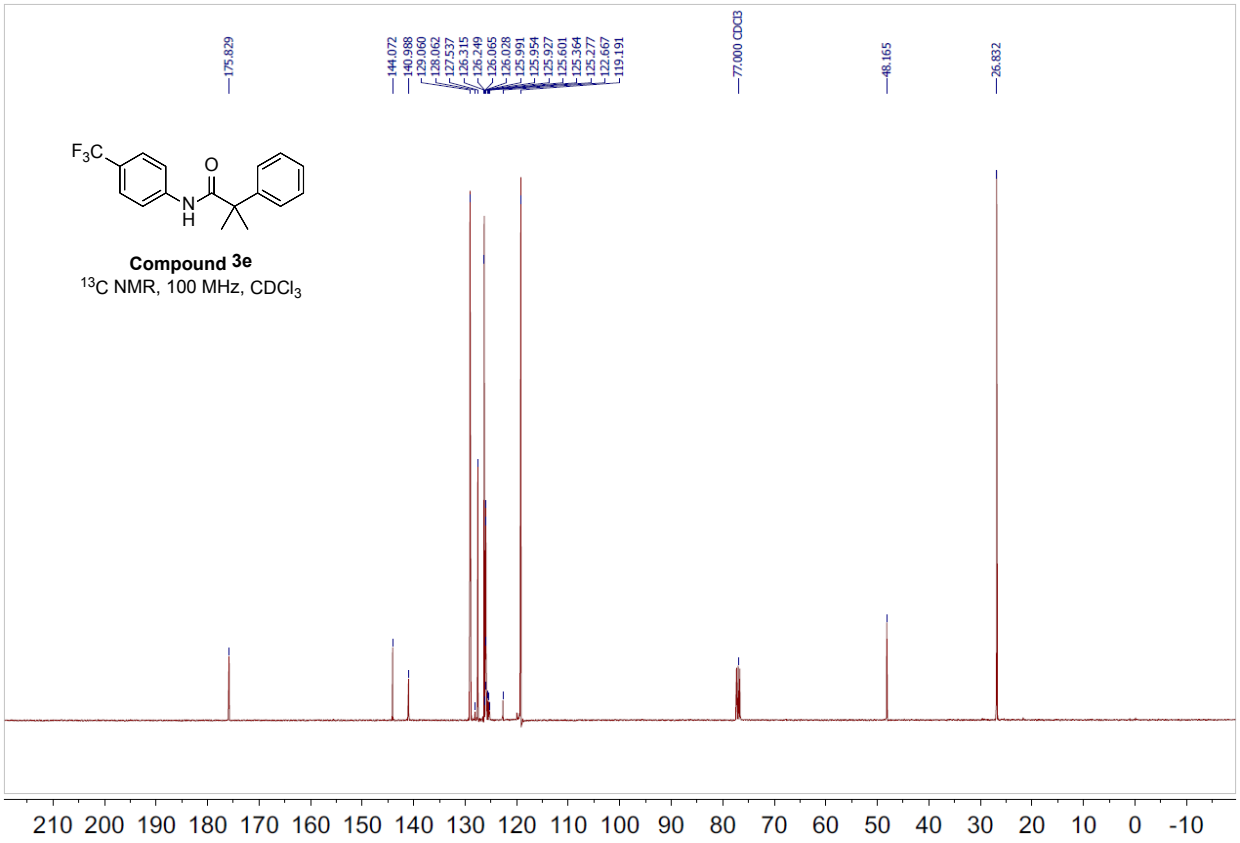

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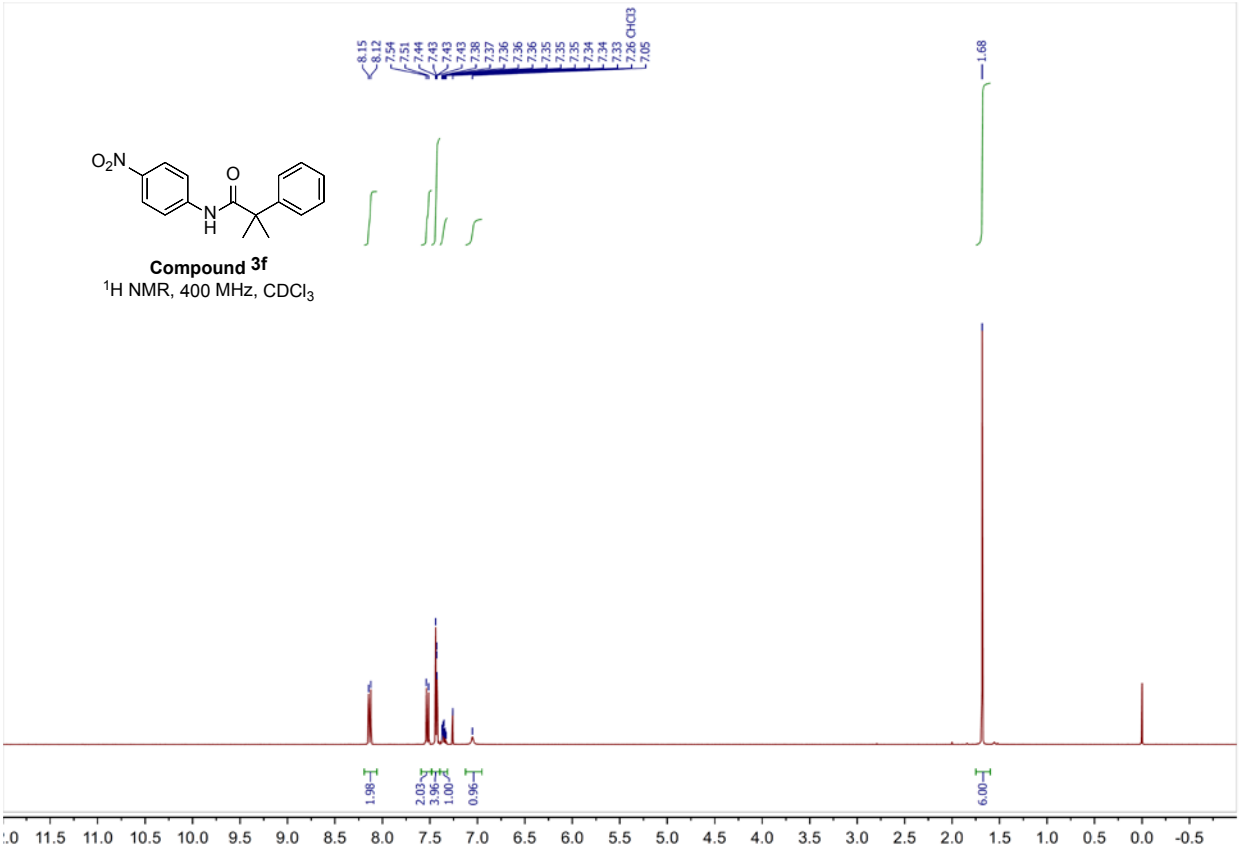

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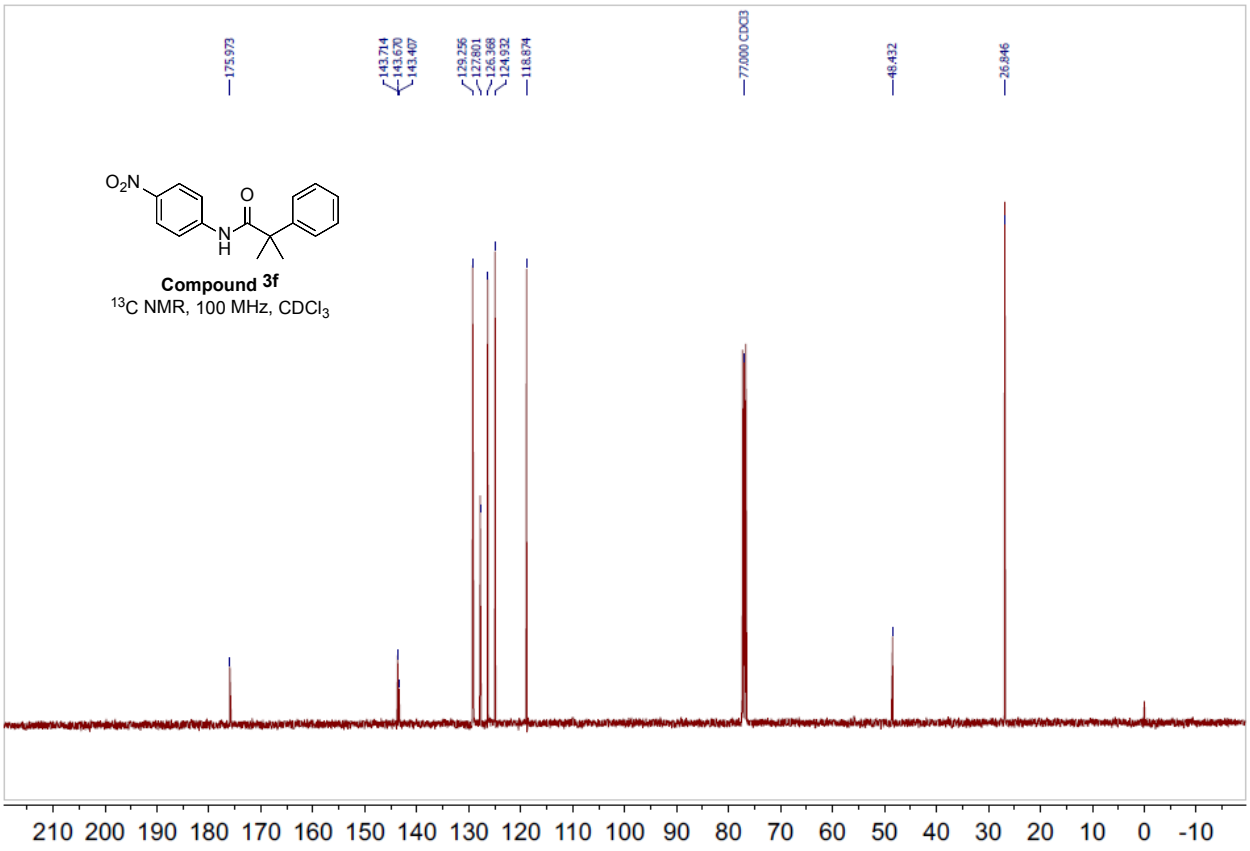

Compound 3f
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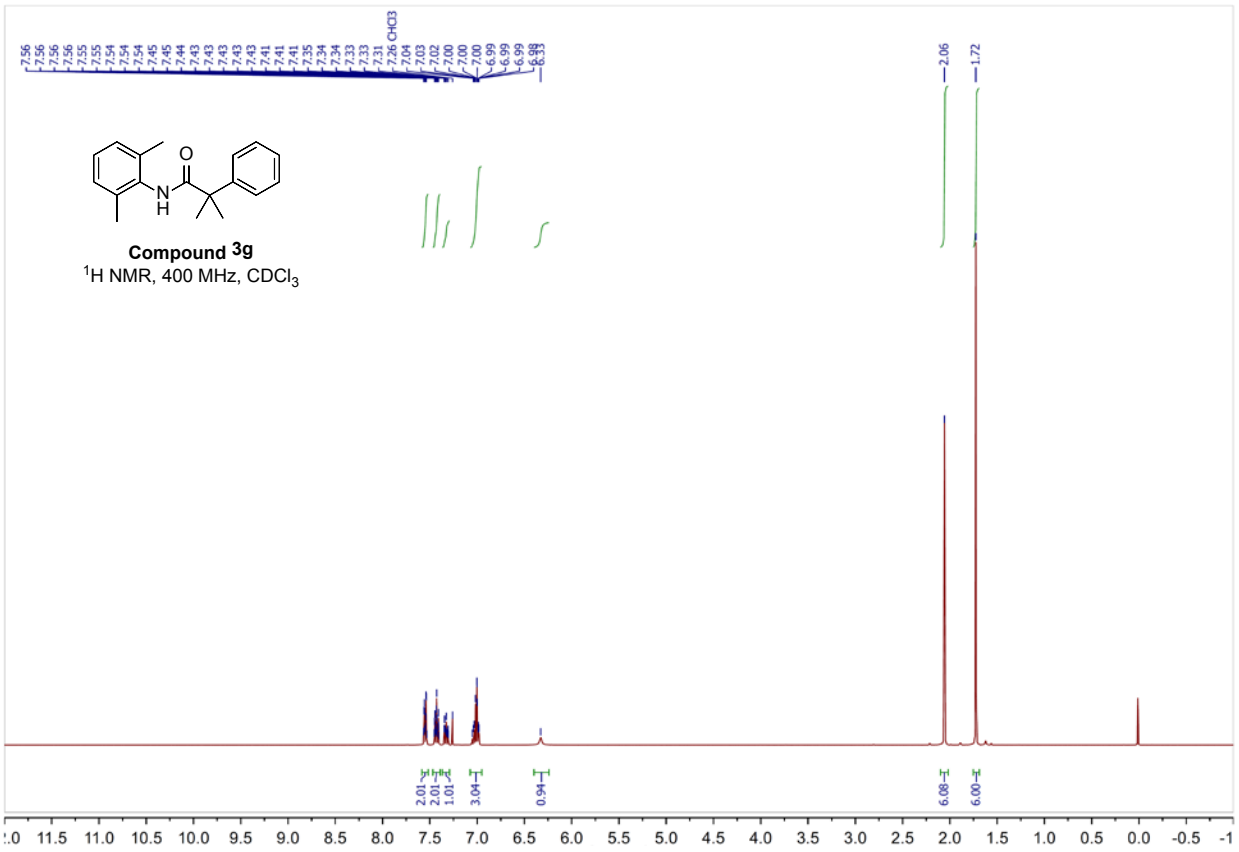
Compound 3g
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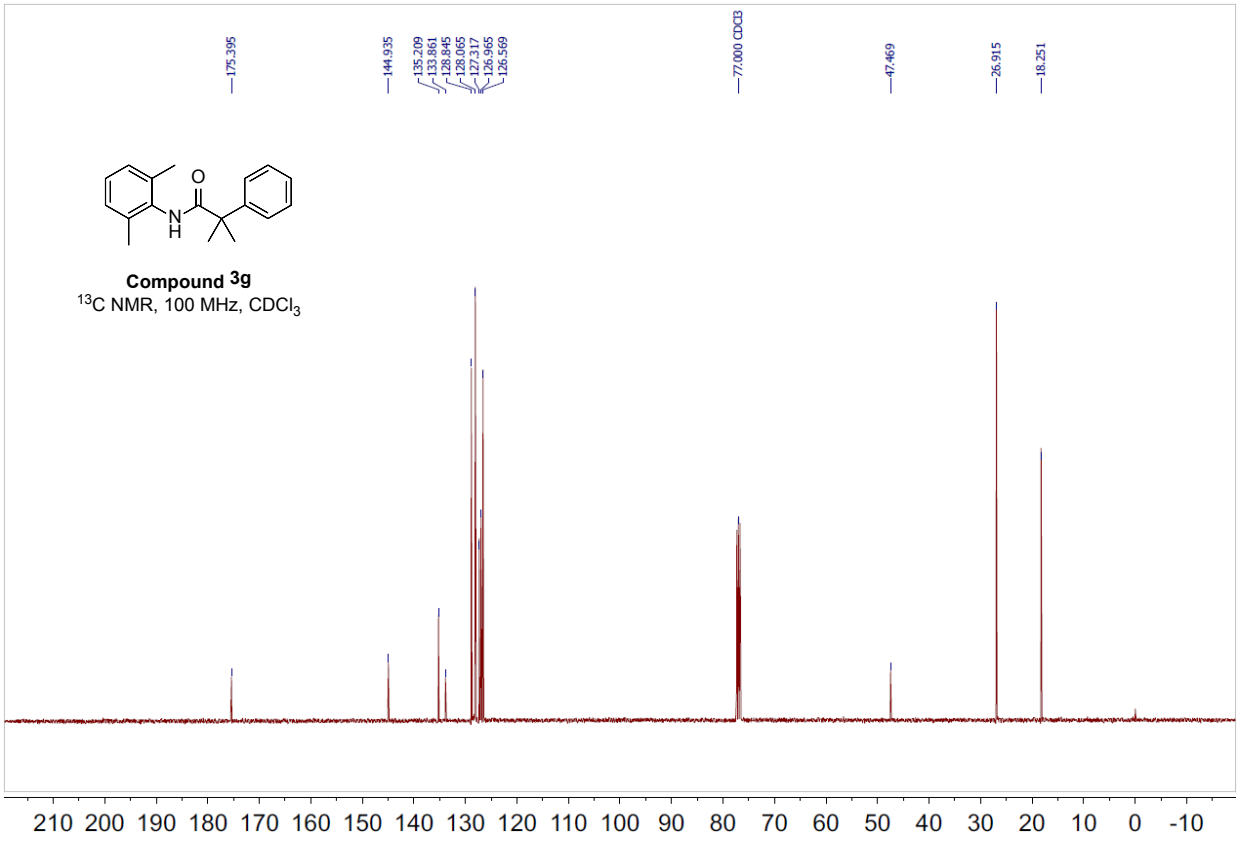
Compound 3g
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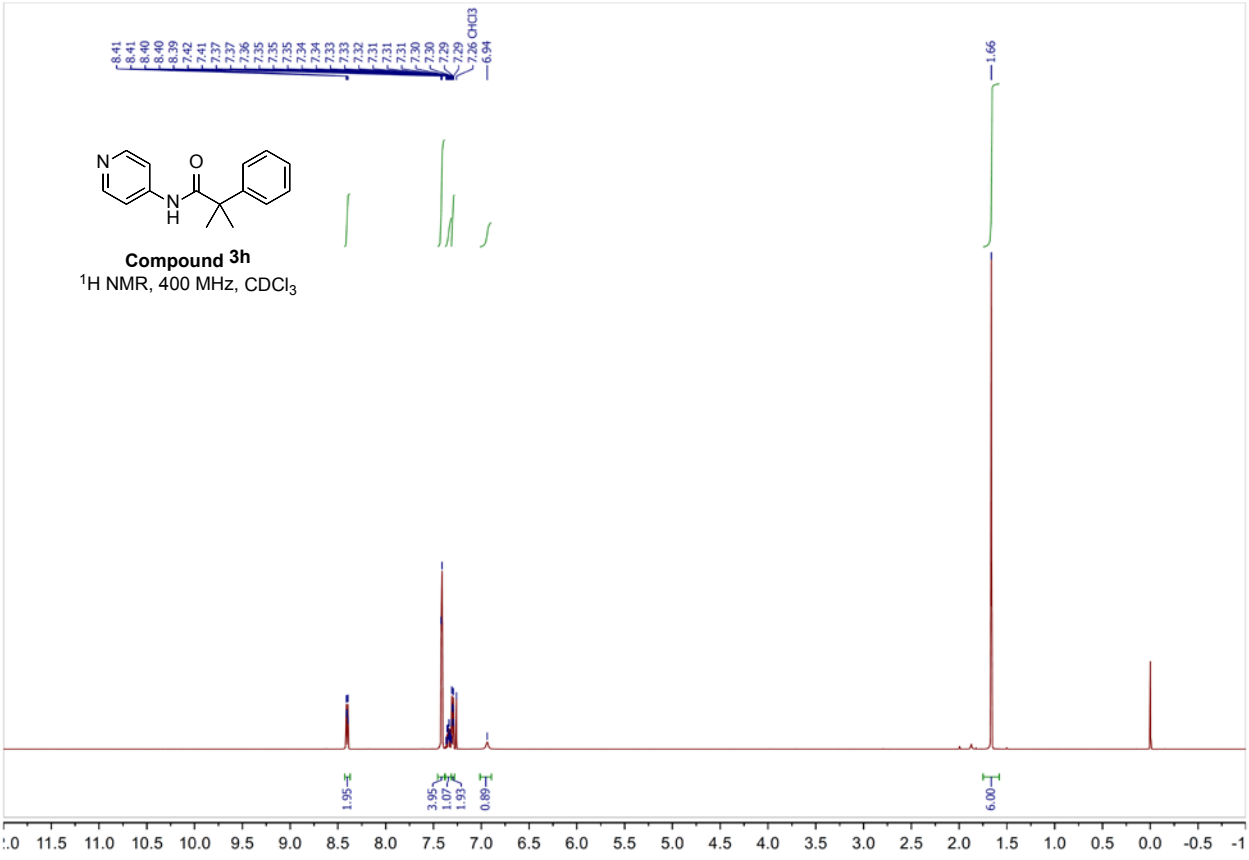

Compound 3h
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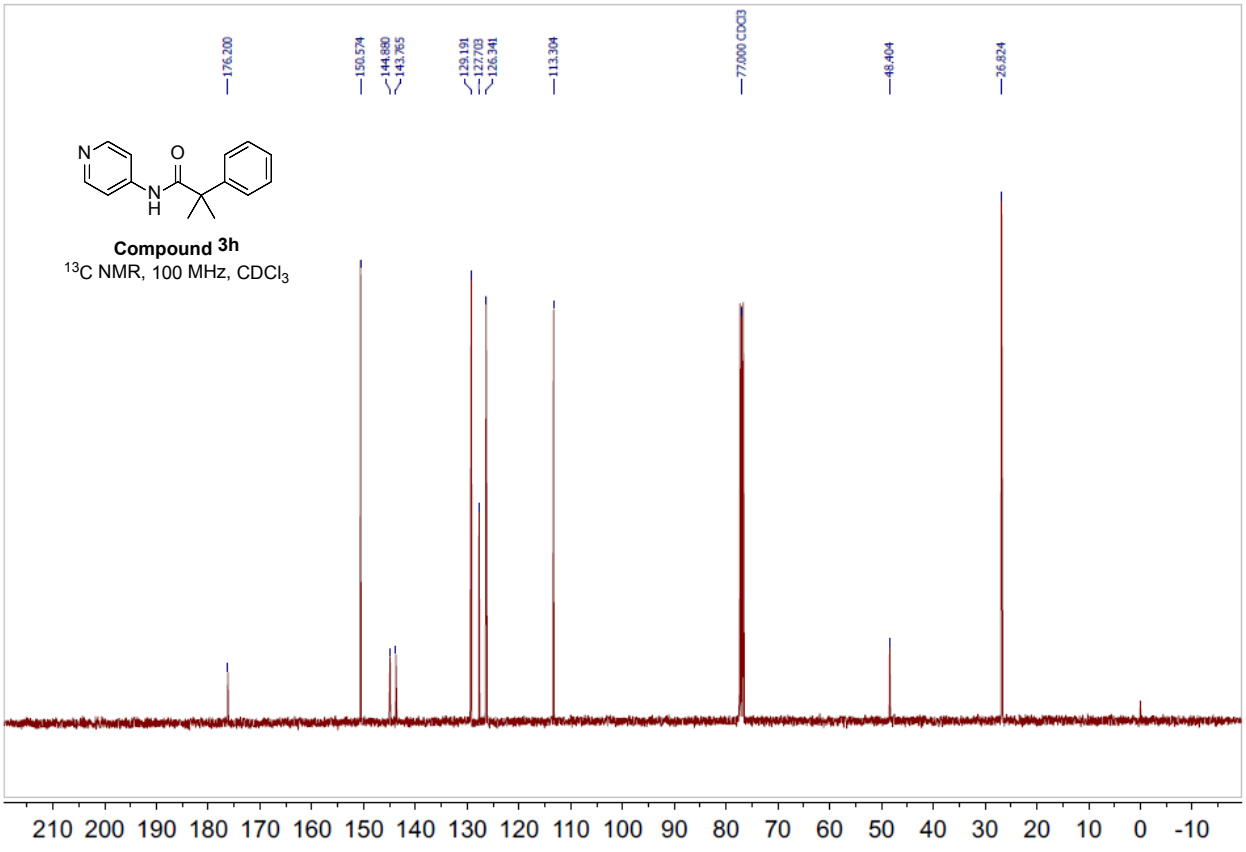

Compound 3h
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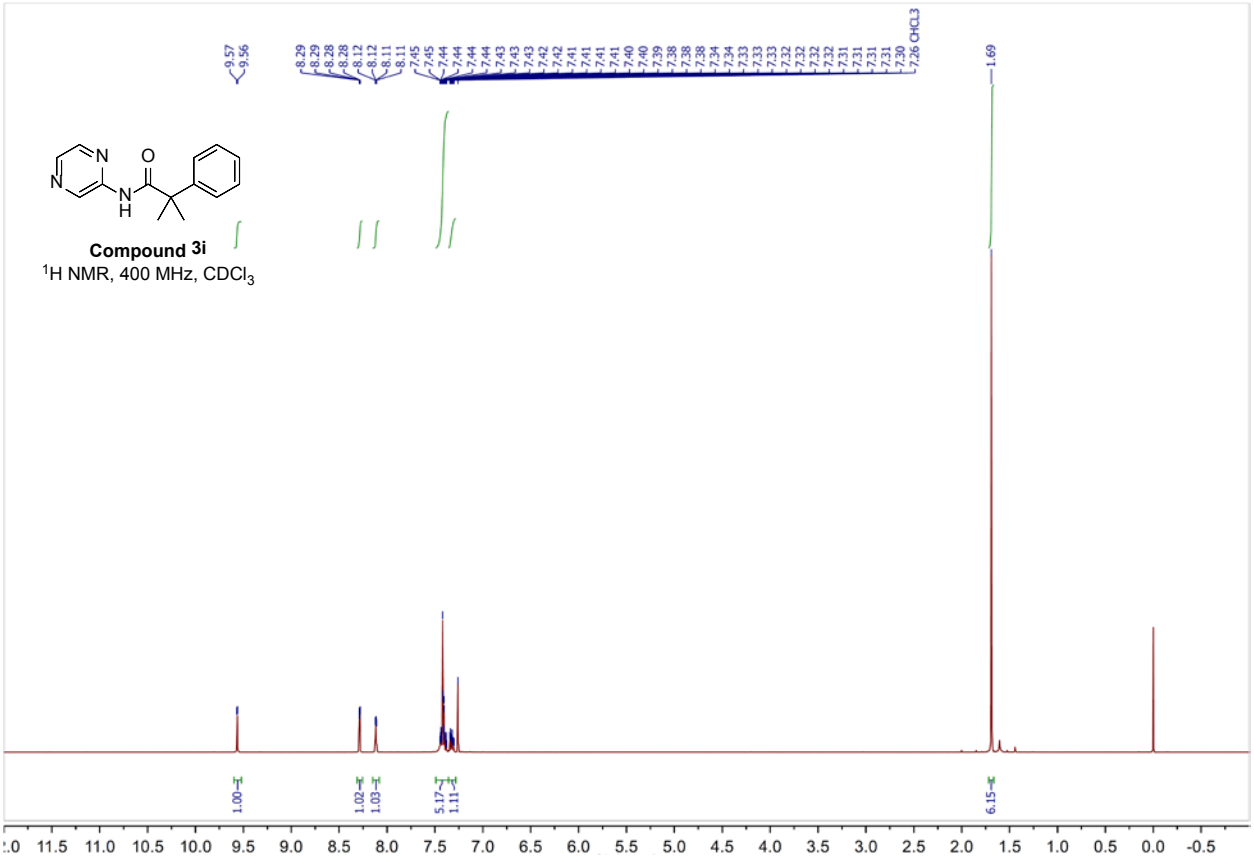

Compound 3i
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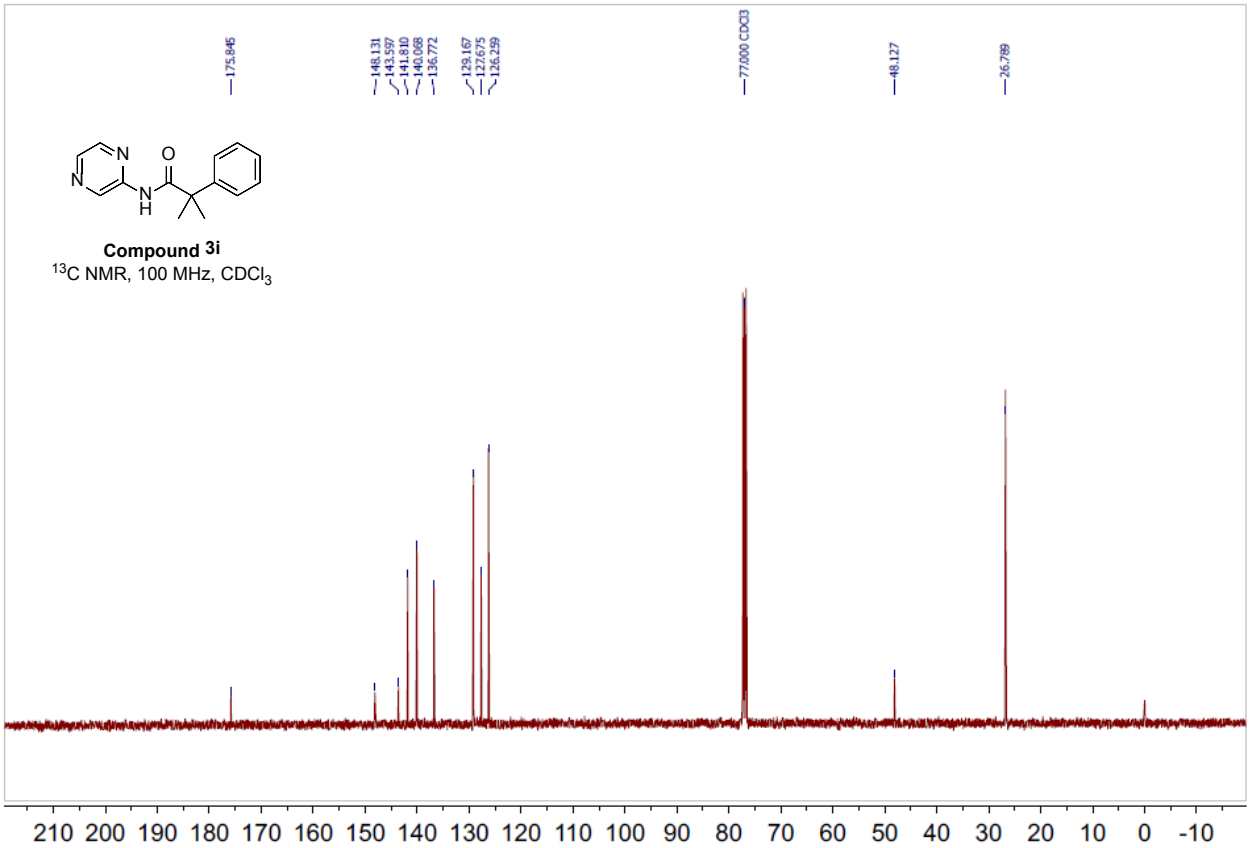

Compound 3i
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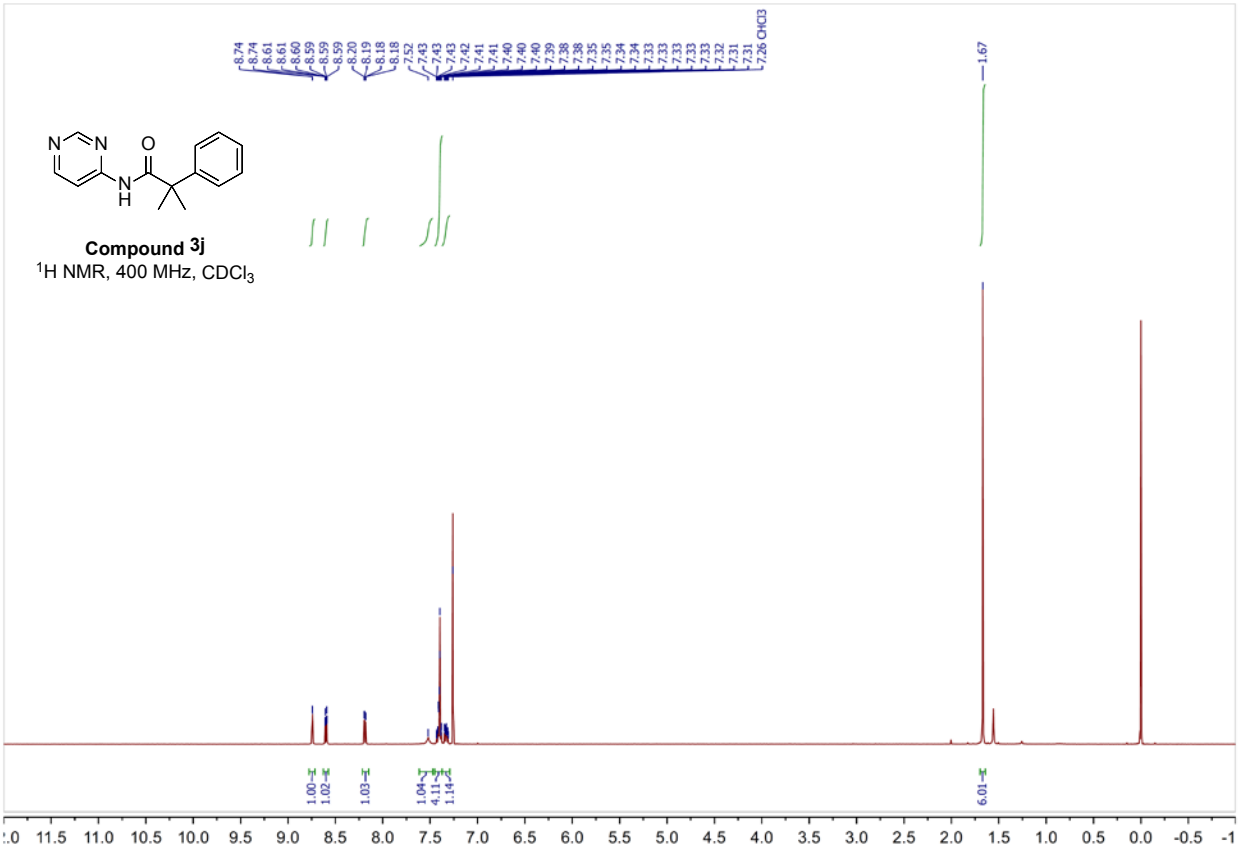
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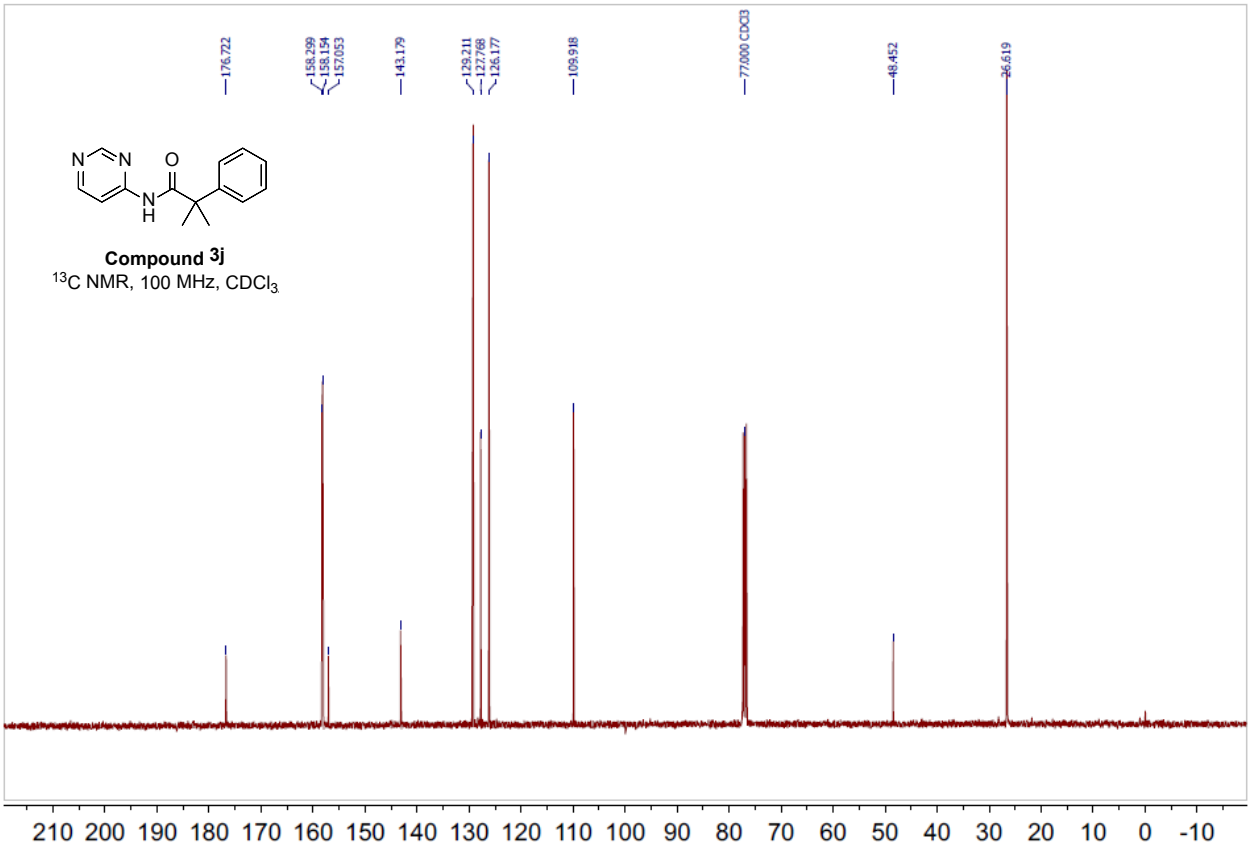
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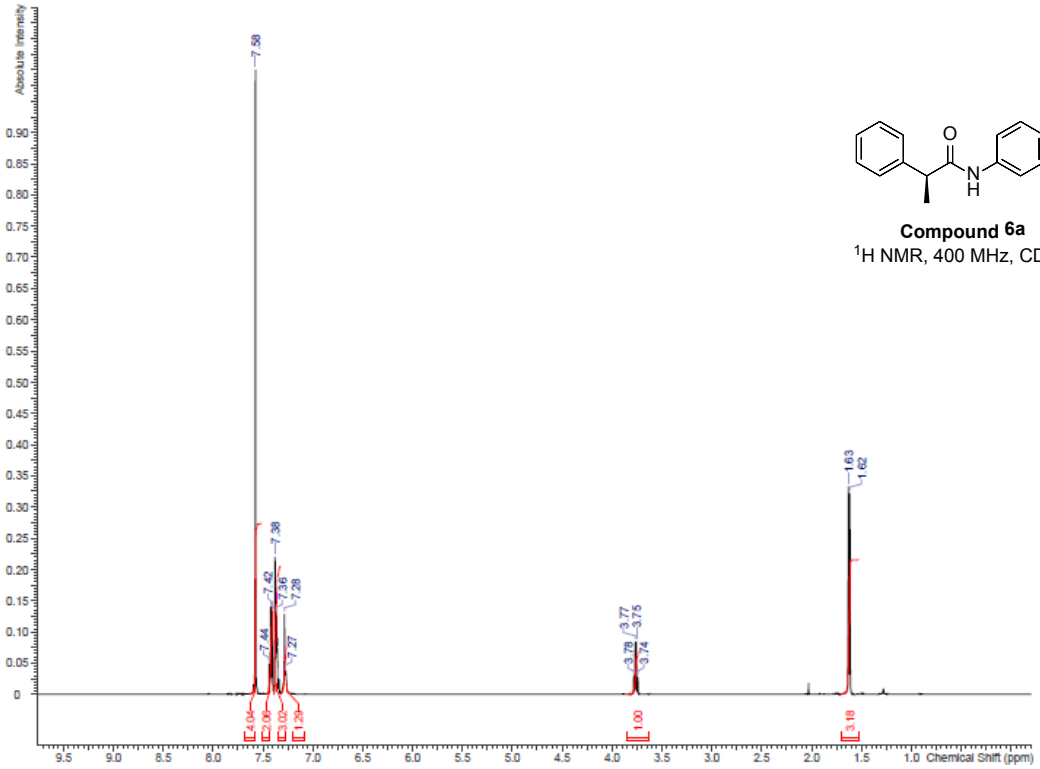

Compound 6a
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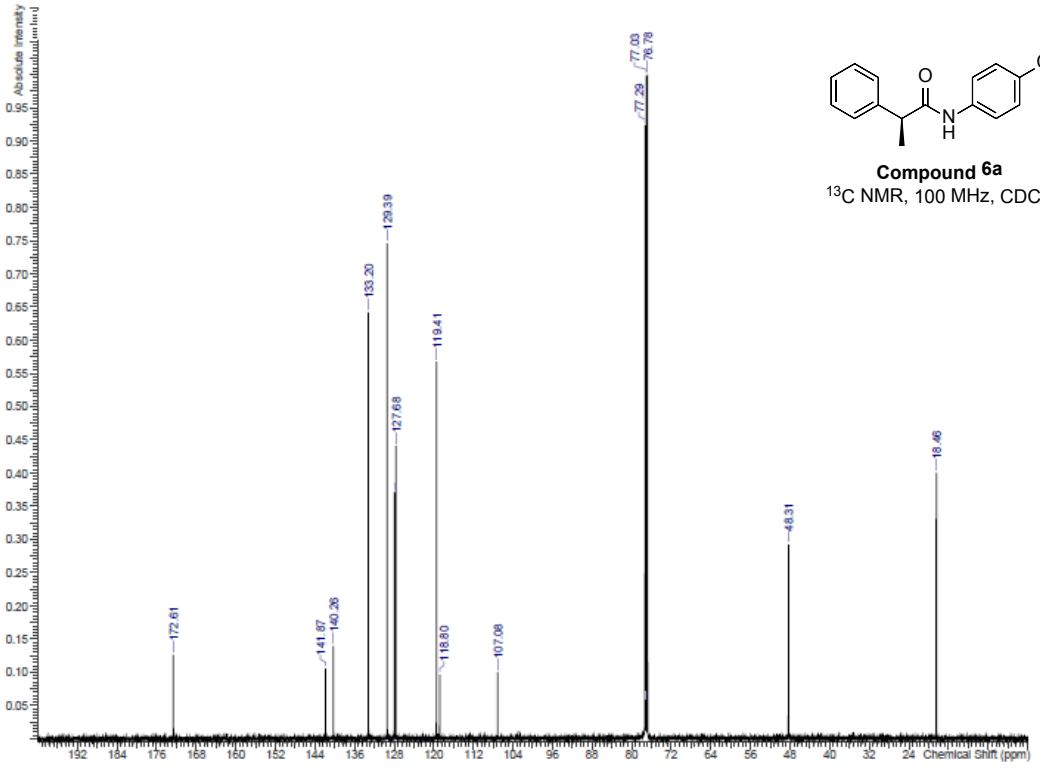

Compound 6a
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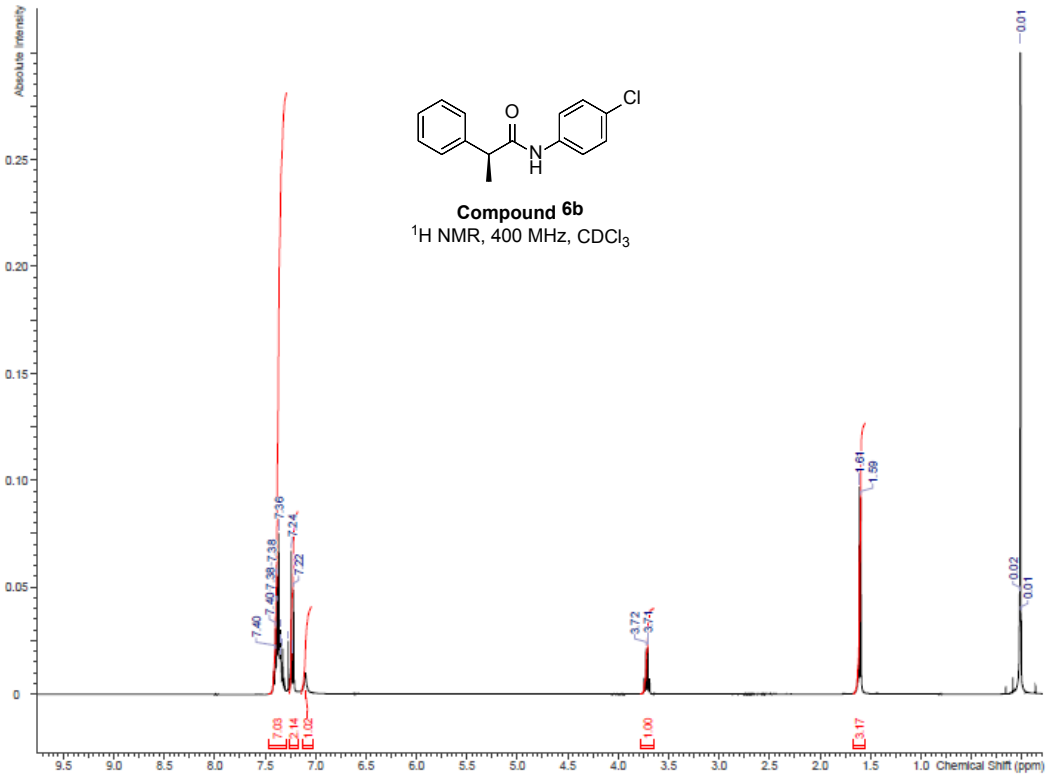

Compound 6b
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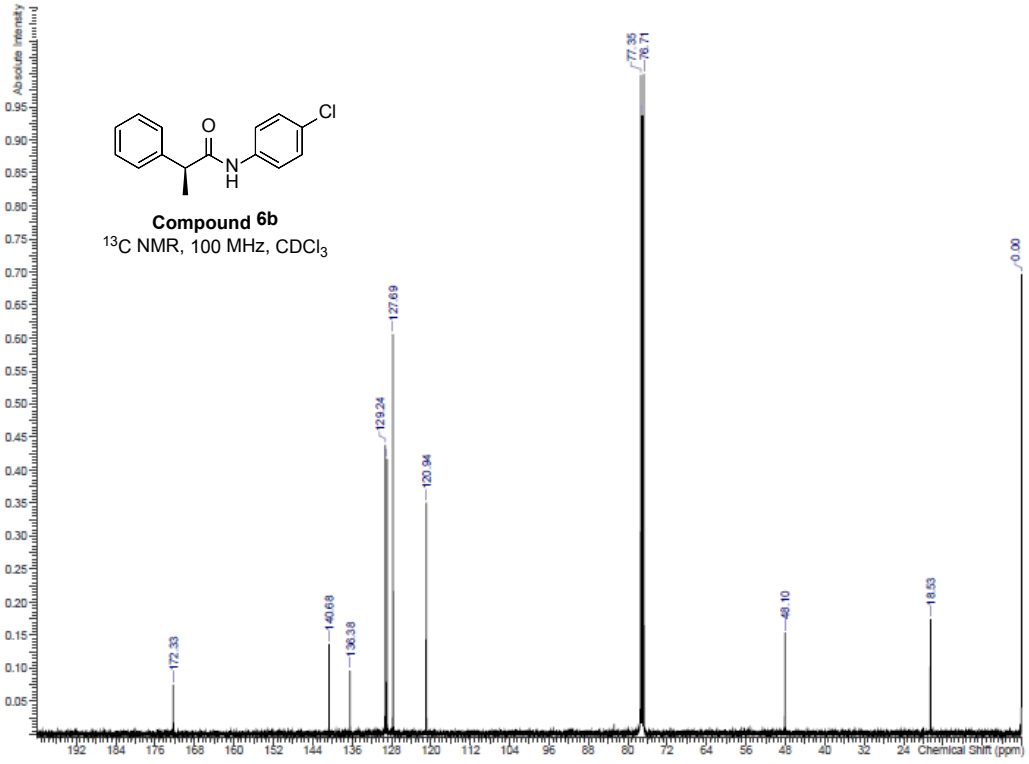
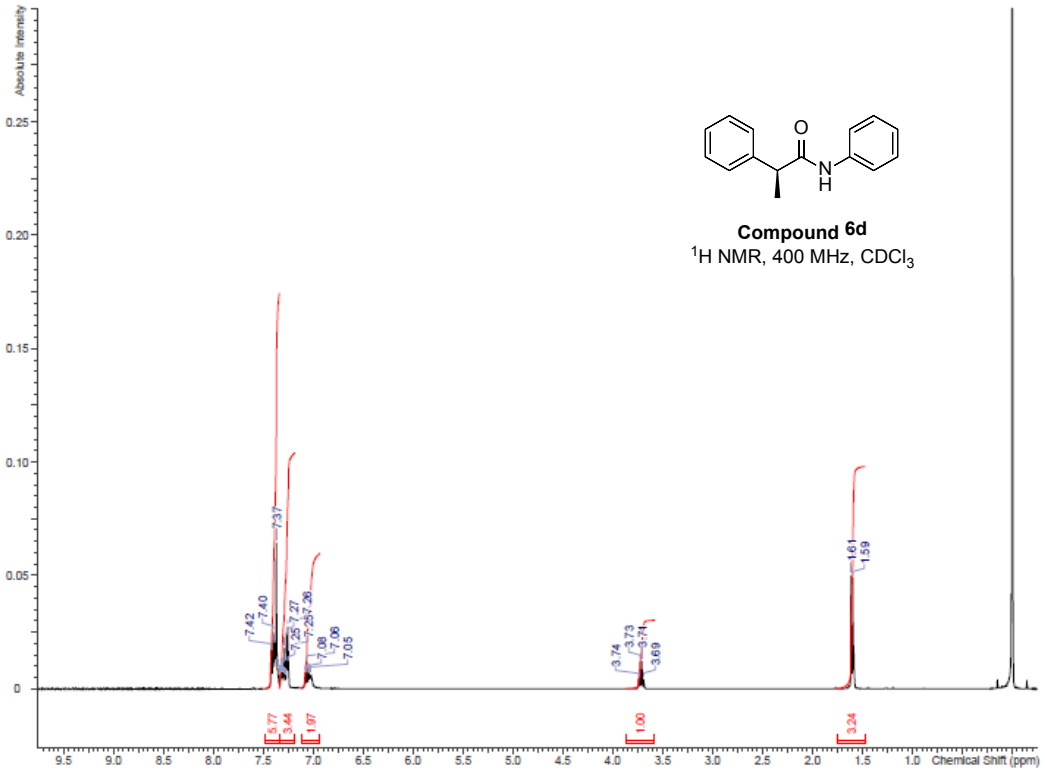
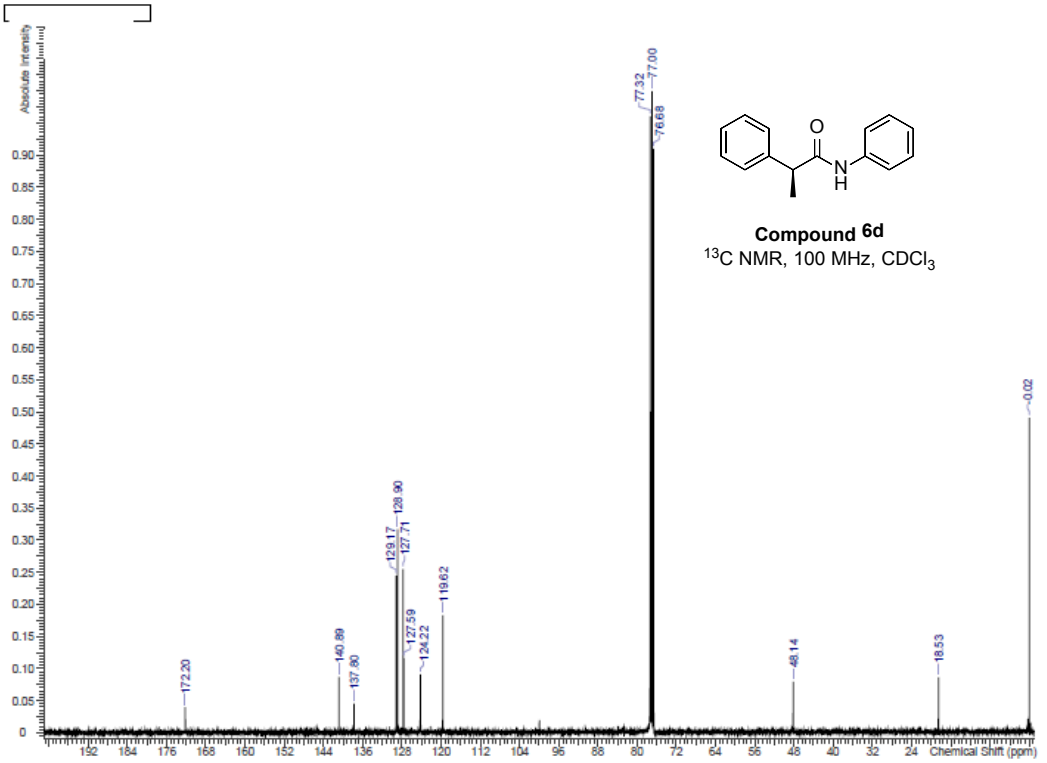


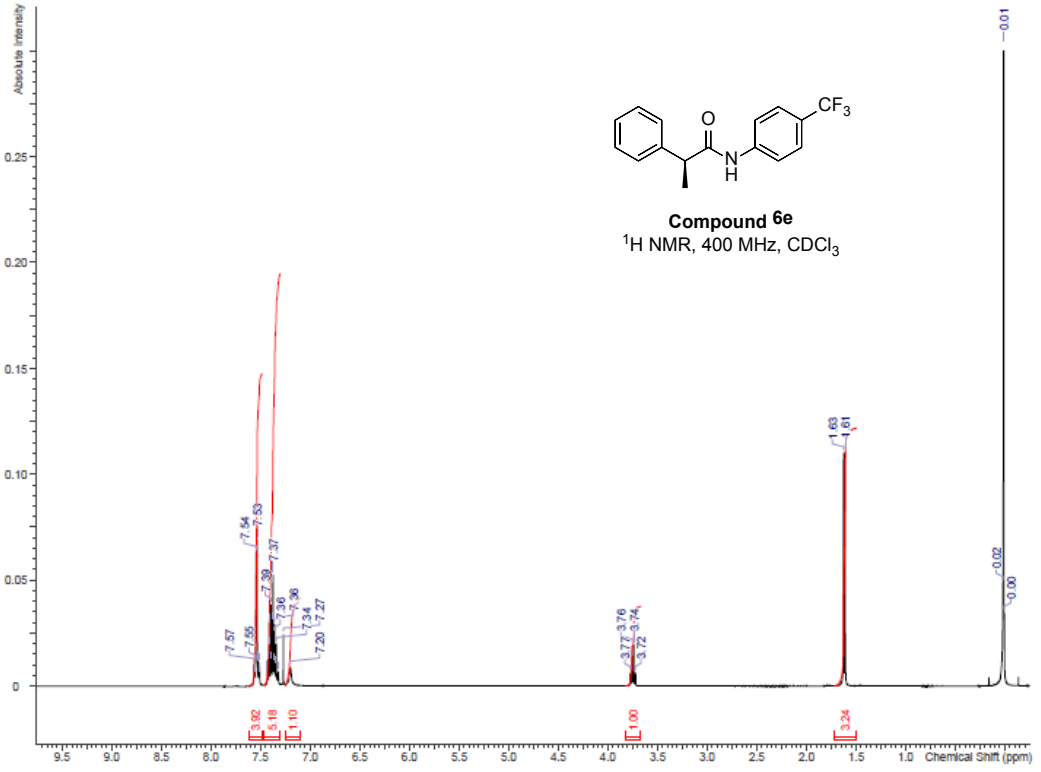
Compound 6b
^{13}C NMR, 100 MHz, $CDCl_3$

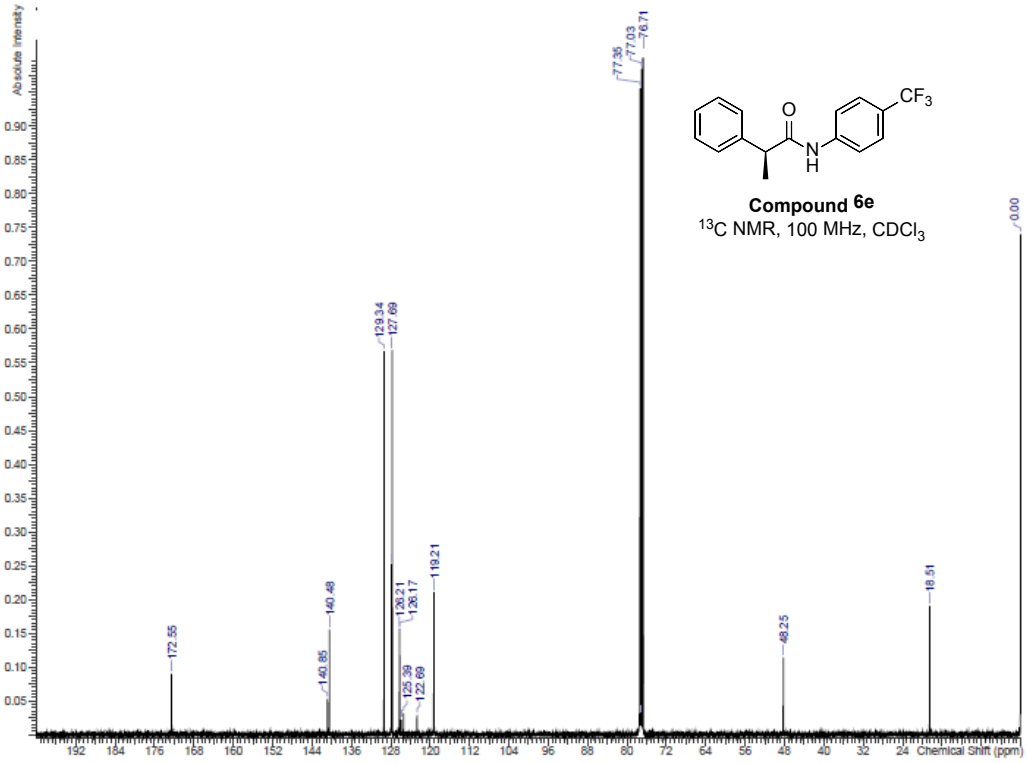


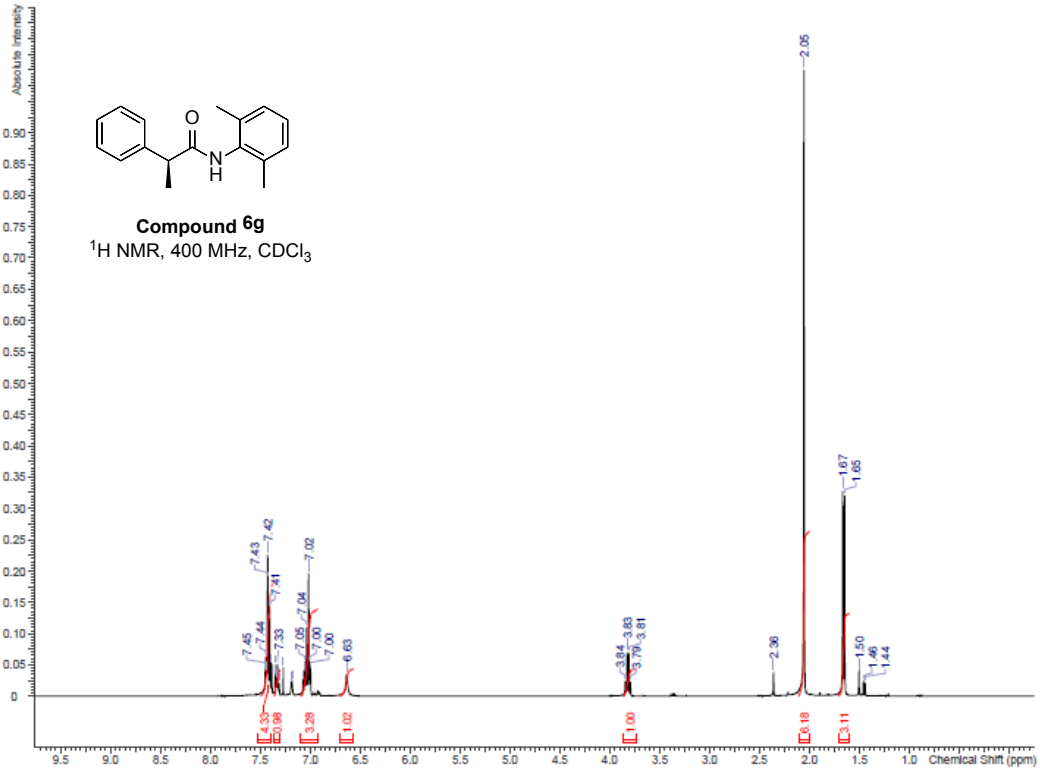
Compound 6d
^{1}H NMR, 400 MHz, $CDCl_3$



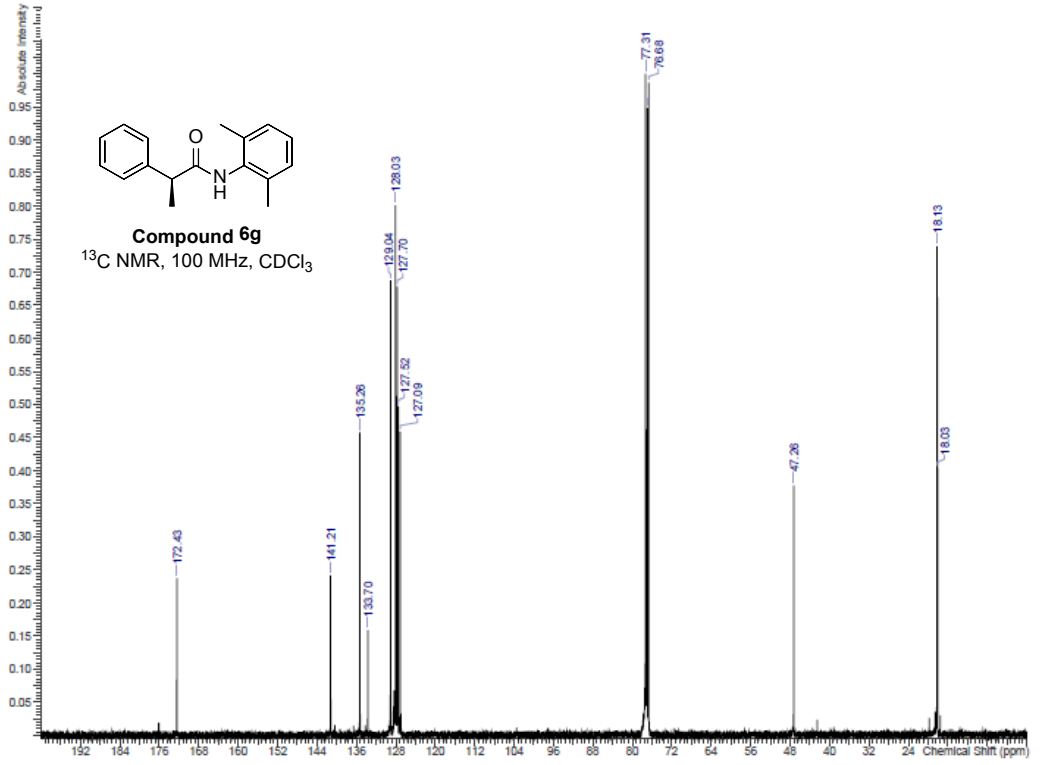
Compound 6d
^{13}C NMR, 100 MHz, $CDCl_3$


Absolute Intensity
Chemical Shift (ppm)
Compound 6e
1H NMR, 400 MHz, CDCl3

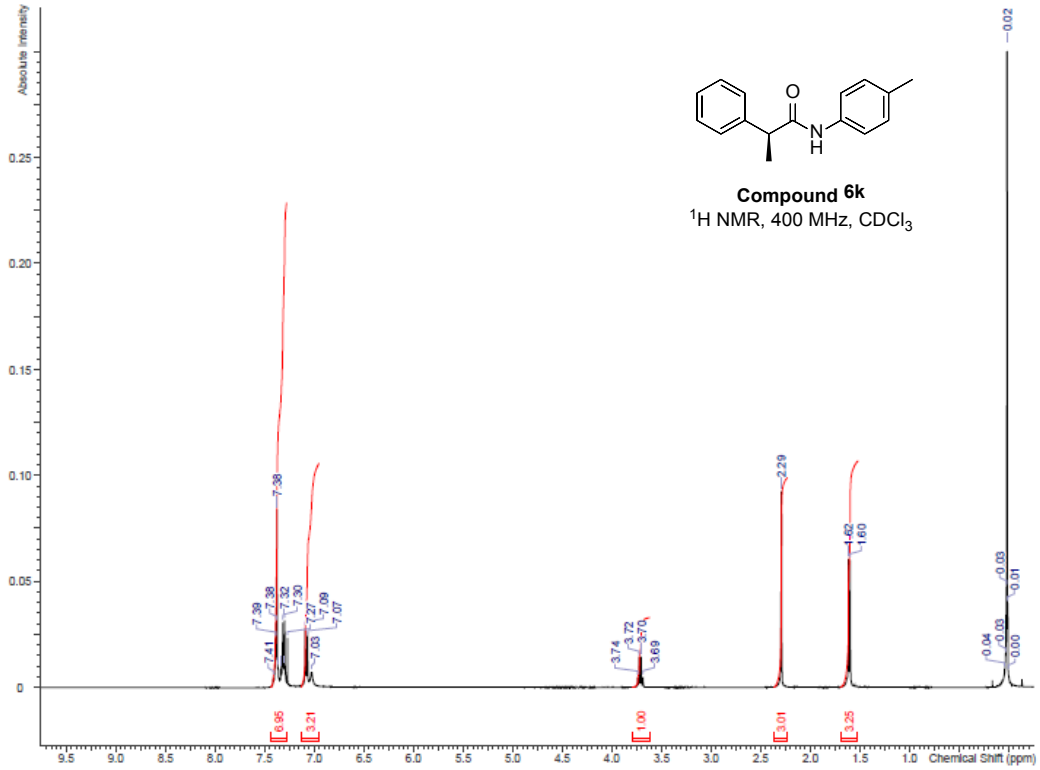

Absolute Intensity
Chemical Shift (ppm)
Compound 6e
13C NMR, 100 MHz, CDCl3



Compound 6g
^{1}H NMR, 400 MHz, $CDCl_3$

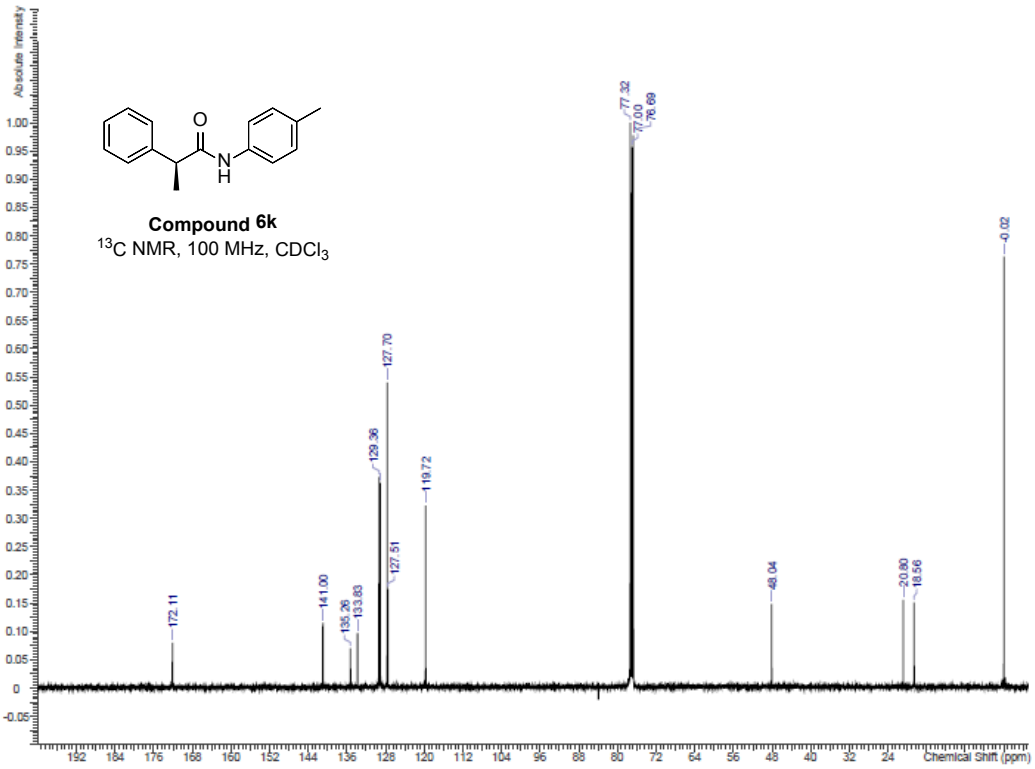


Compound 6g
^{13}C NMR, 100 MHz, $CDCl_3$



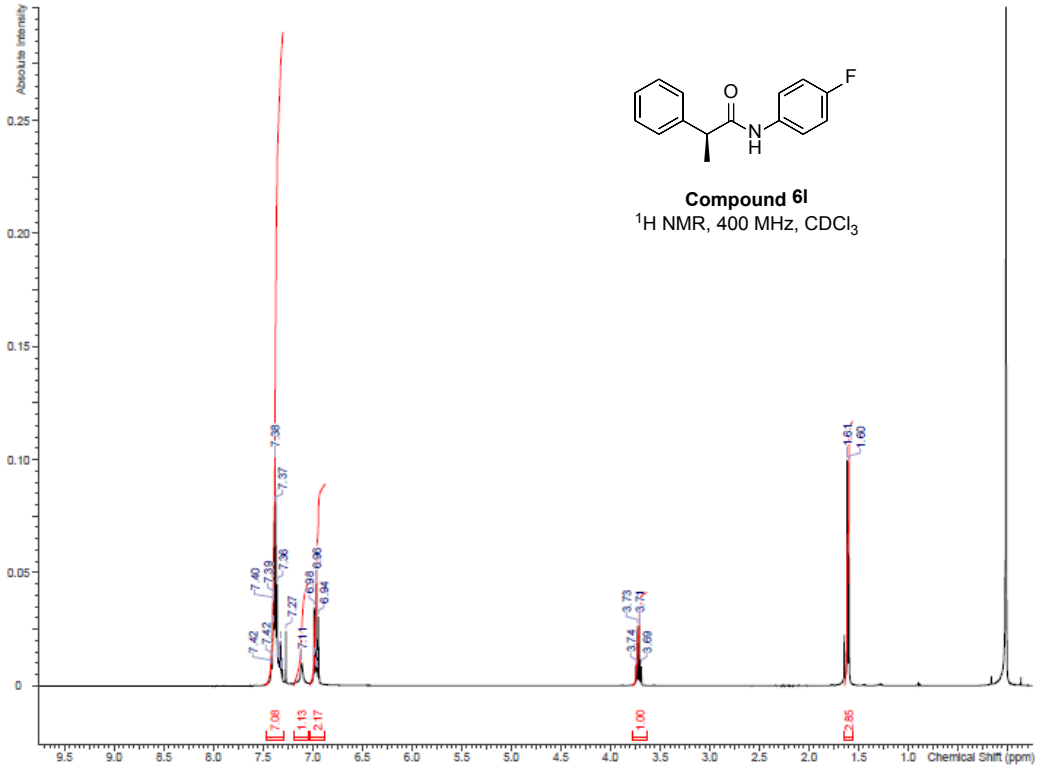
Compound 6k

^{1}H NMR, 400 MHz, $CDCl_3$



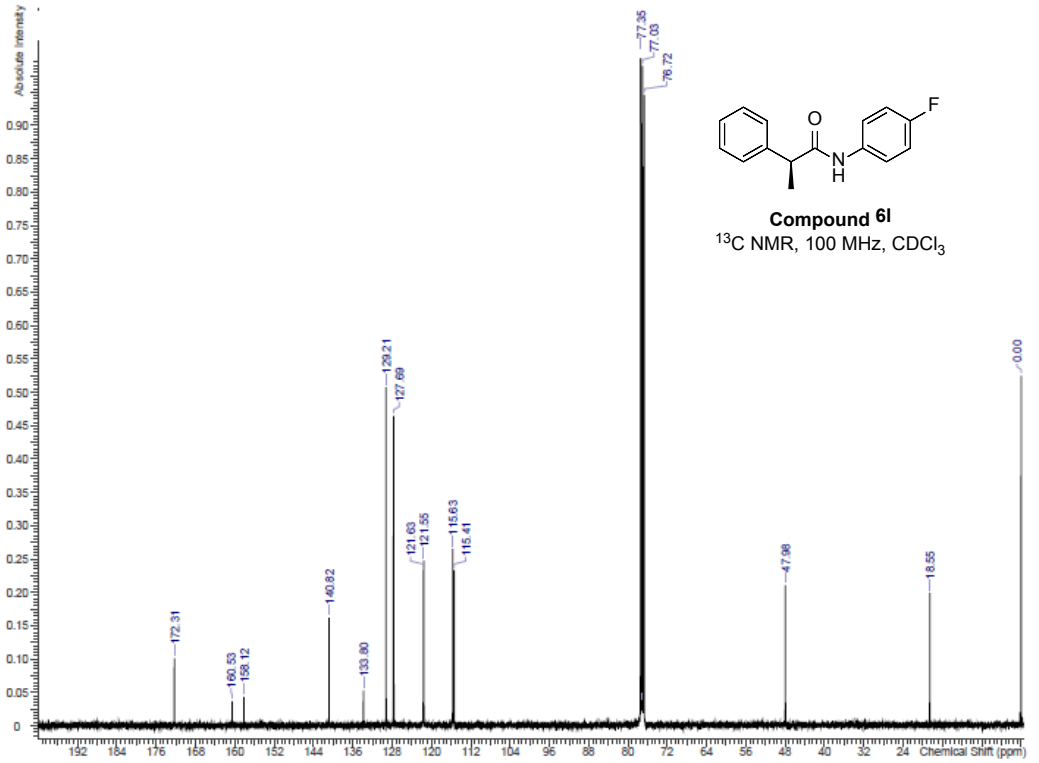
Compound 6k

^{13}C NMR, 100 MHz, $CDCl_3$



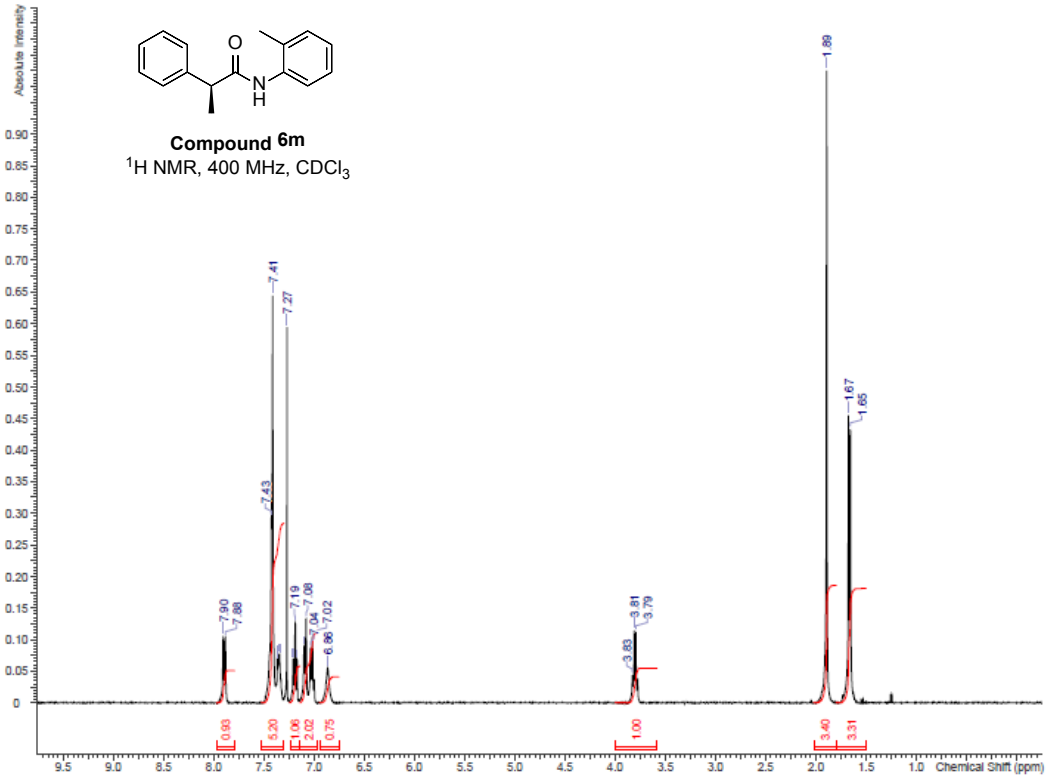
Compound 6l

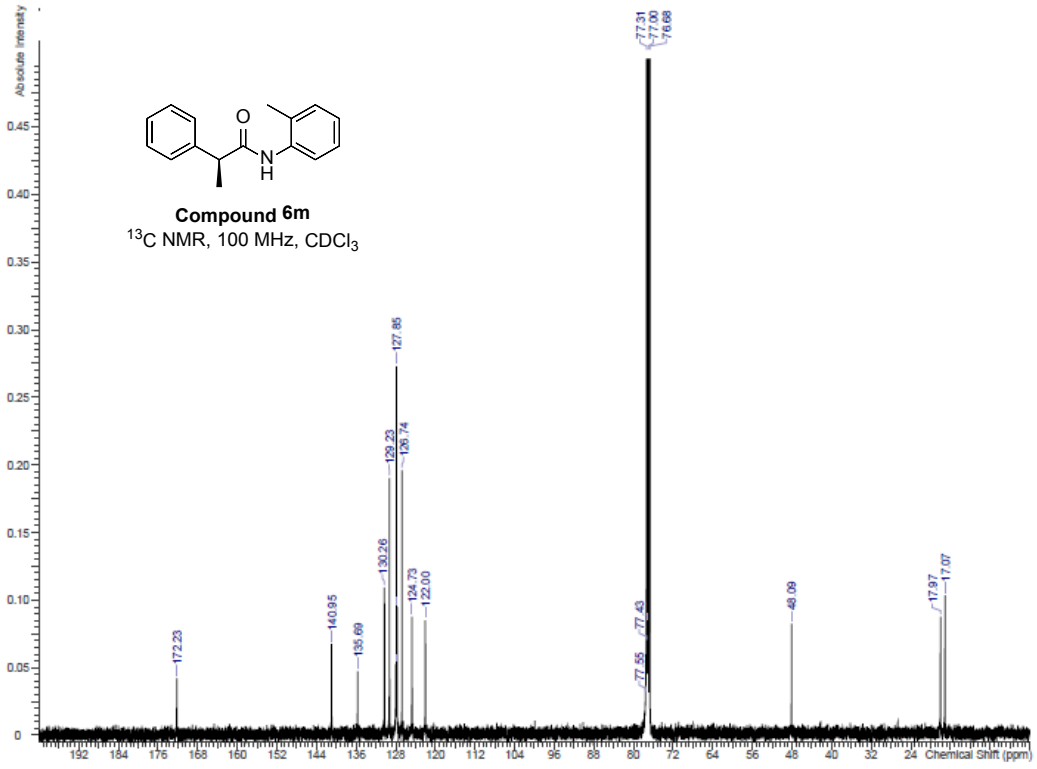
^{1}H NMR, 400 MHz, $CDCl_3$

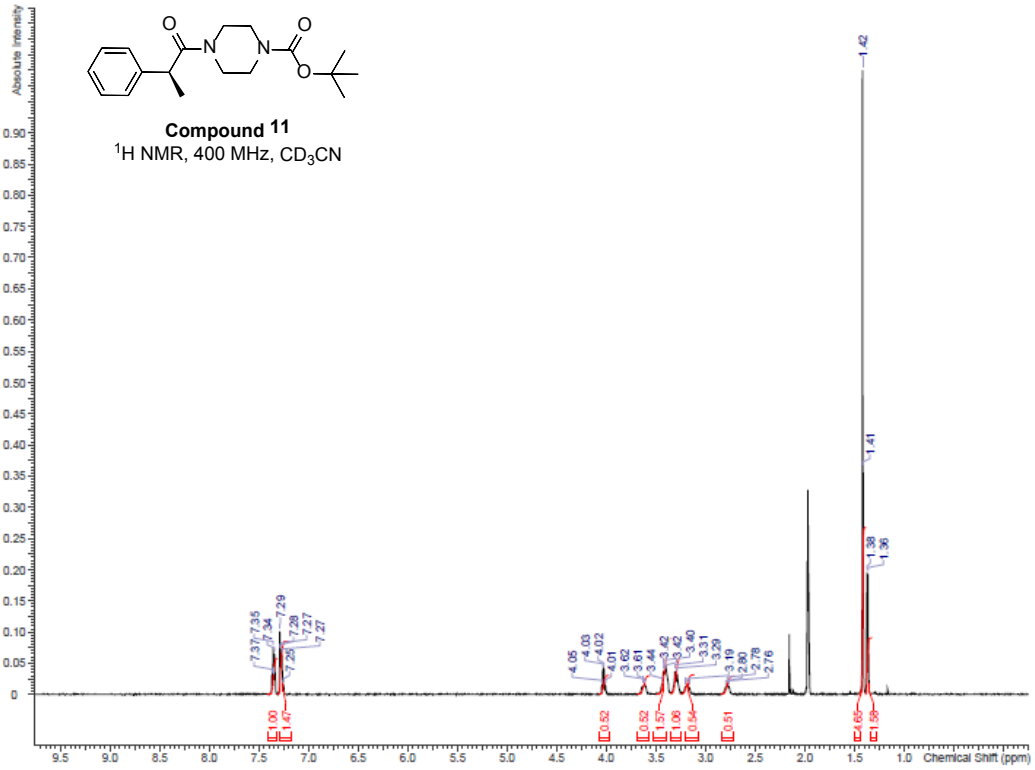


Compound 6l

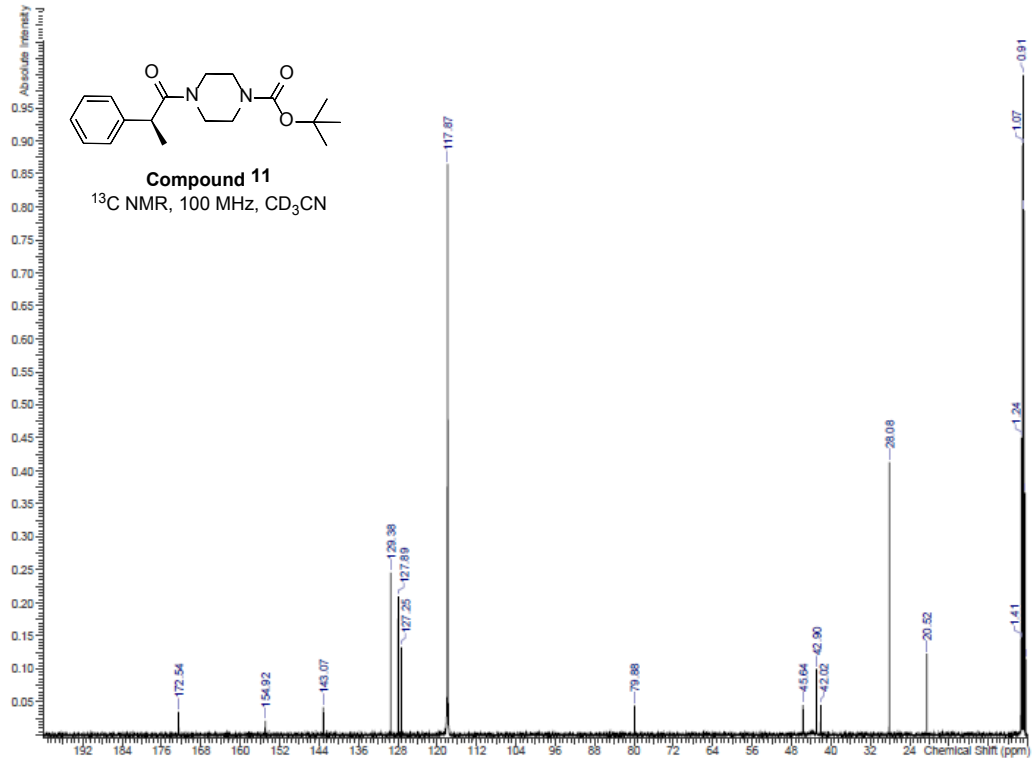
^{13}C NMR, 100 MHz, $CDCl_3$


Compound 6m
1H NMR, 400 MHz, CDCl3
Absolute Intensity
Chemical Shift (ppm)

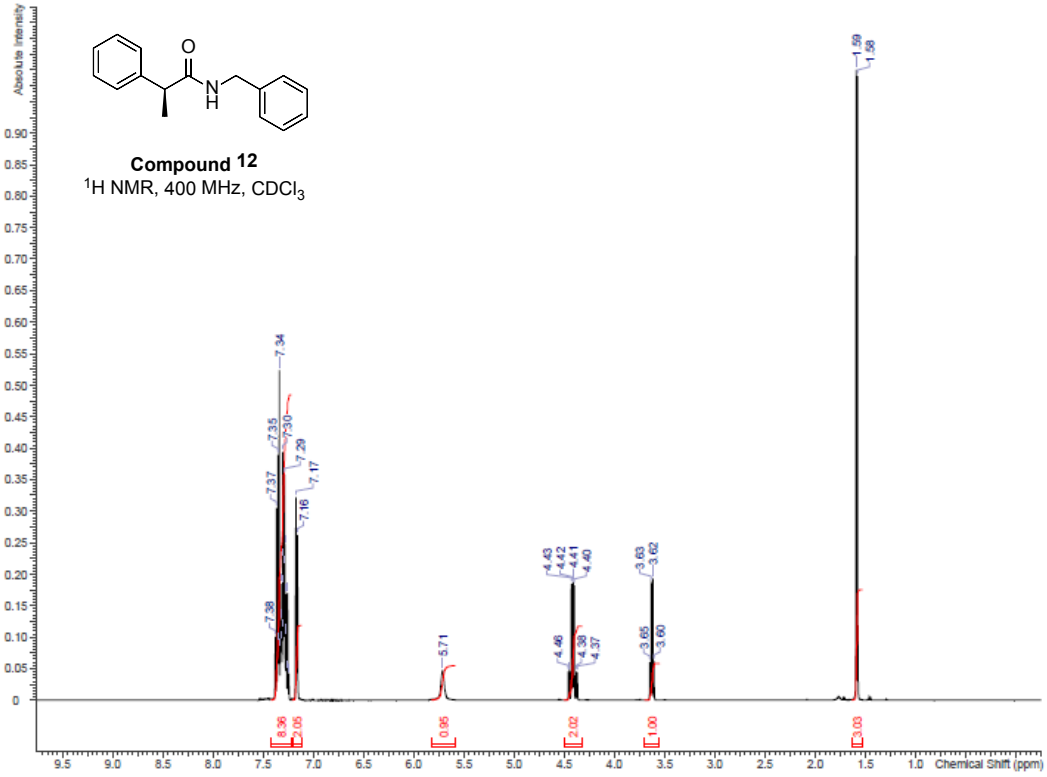

Compound 6m
13C NMR, 100 MHz, CDCl3
Absolute Intensity
Chemical Shift (ppm)



Compound 11
^{1}H NMR, 400 MHz, CD_3CN

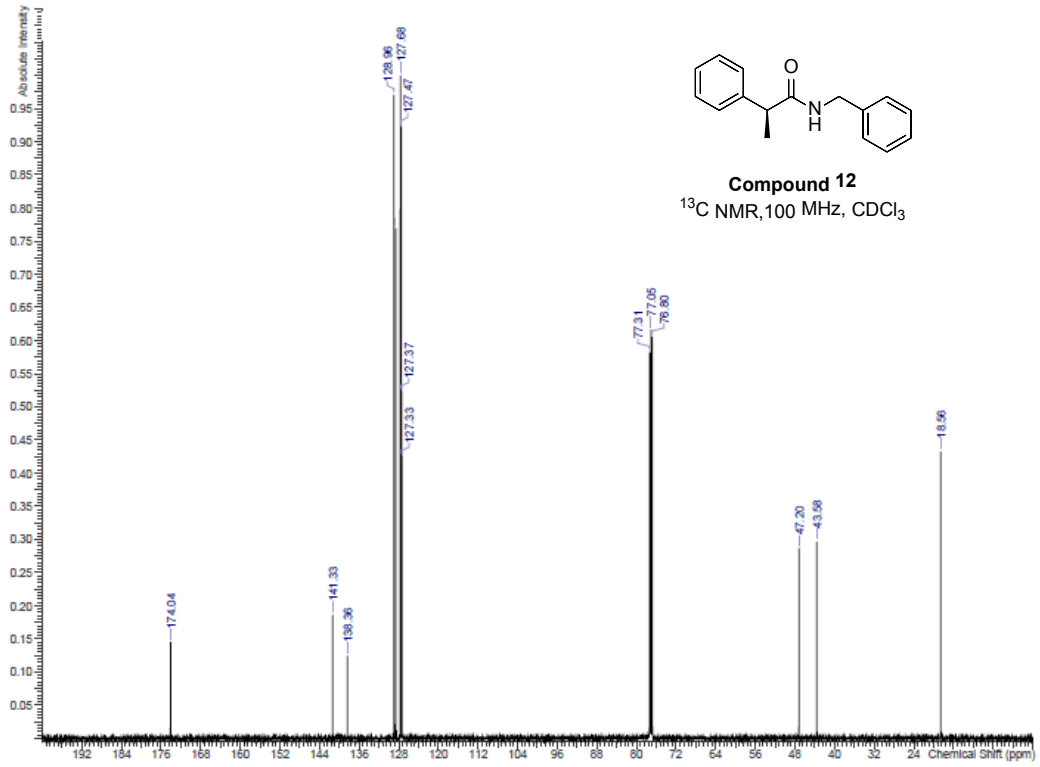


Compound 11
^{13}C NMR, 100 MHz, CD_3CN



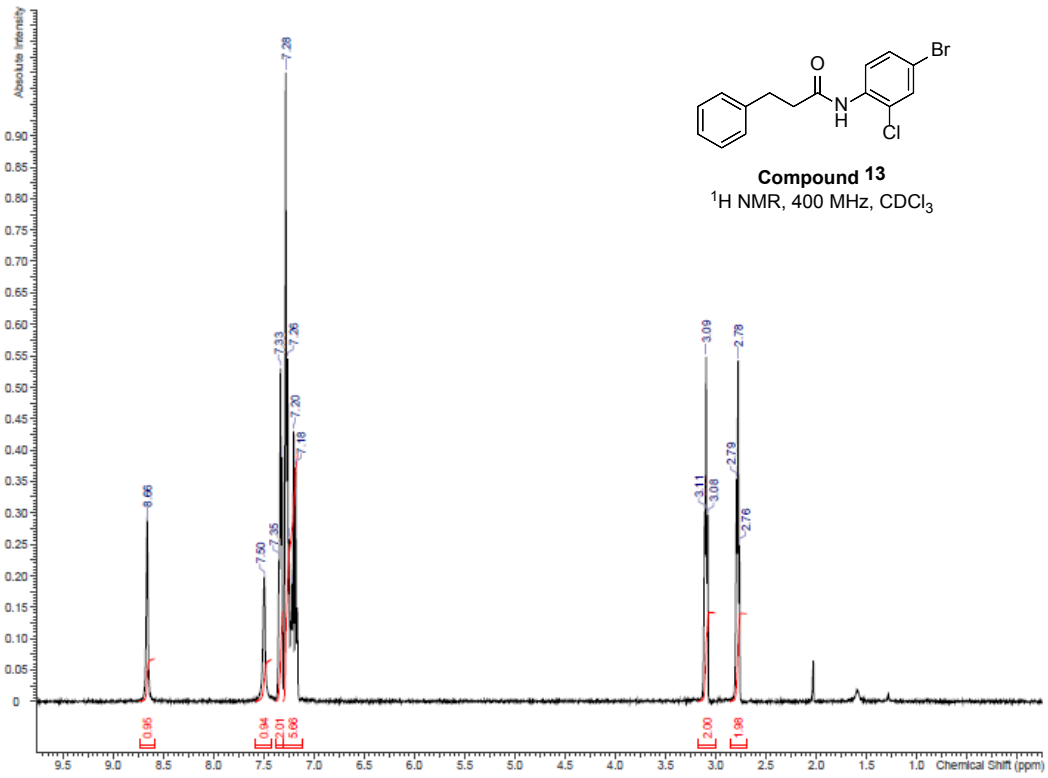
Compound 12

^{1}H NMR, 400 MHz, $CDCl_3$



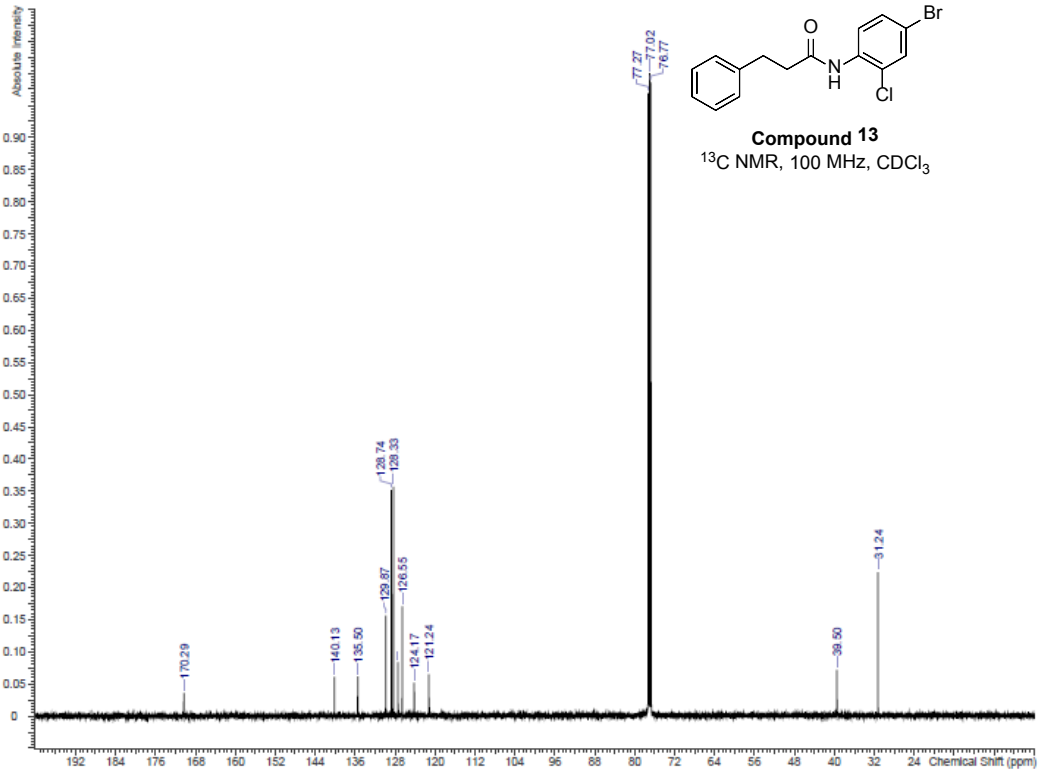
Compound 12

^{13}C NMR,100 MHz, $CDCl_3$



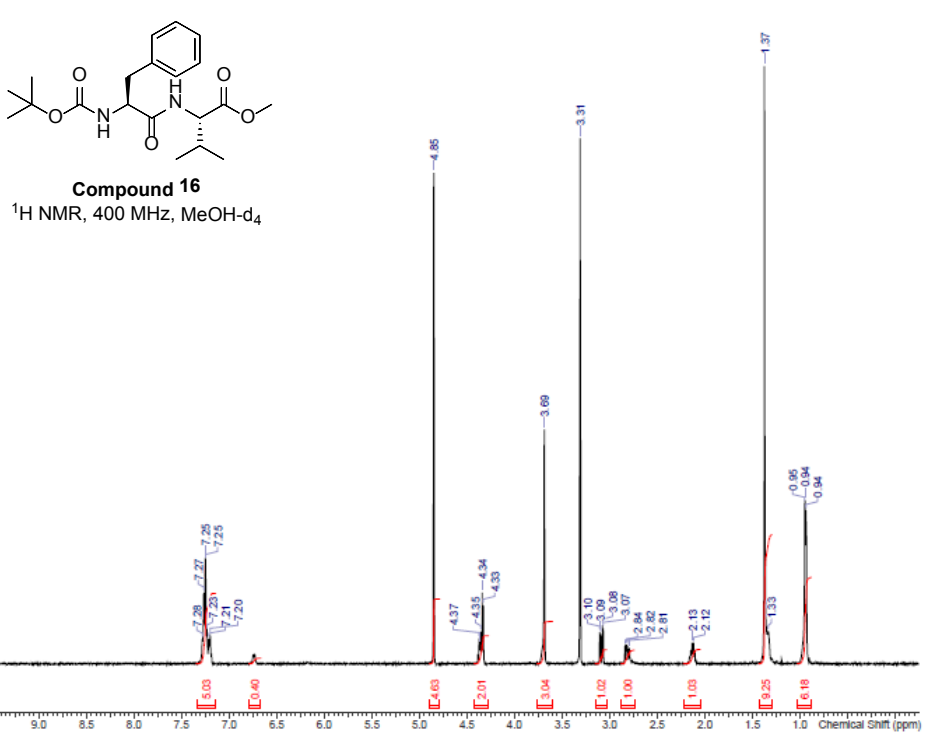
Compound 13

^{1}H NMR, 400 MHz, $CDCl_3$

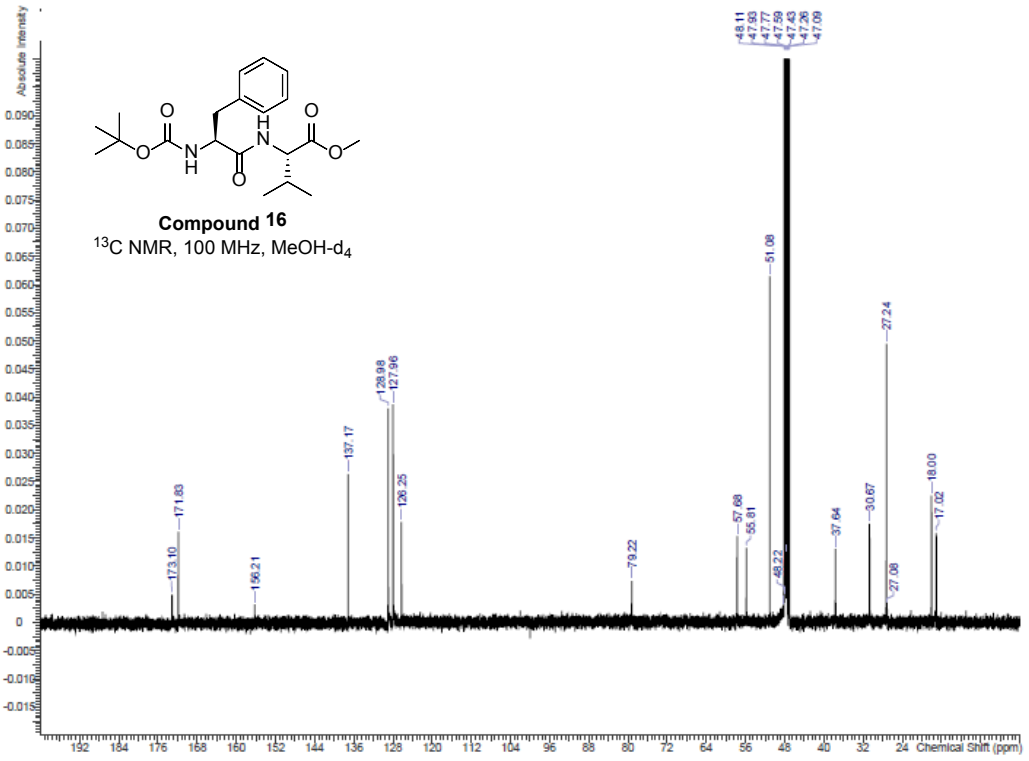


Compound 13

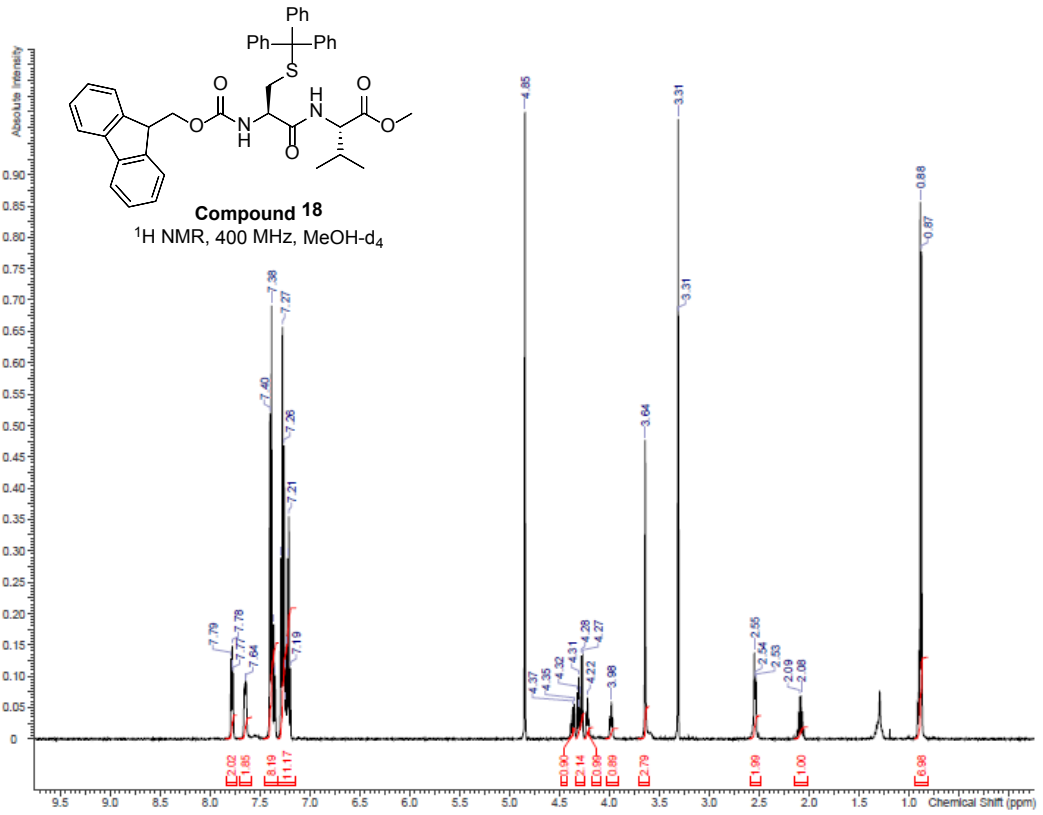
^{13}C NMR, 100 MHz, $CDCl_3$

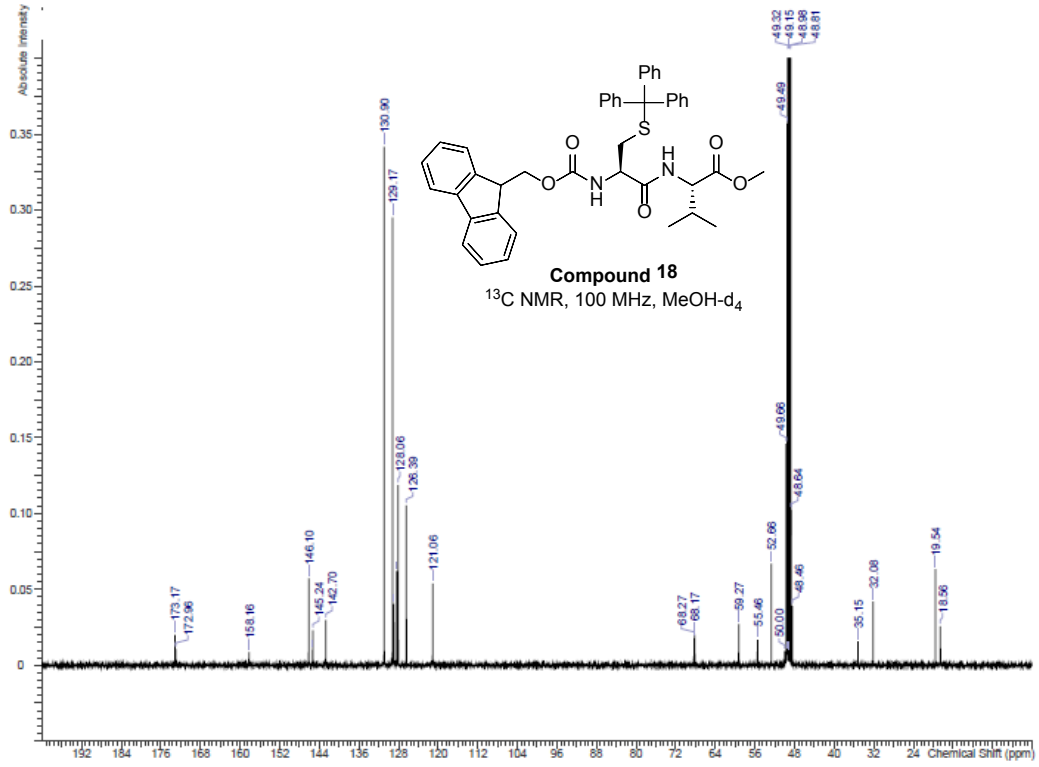


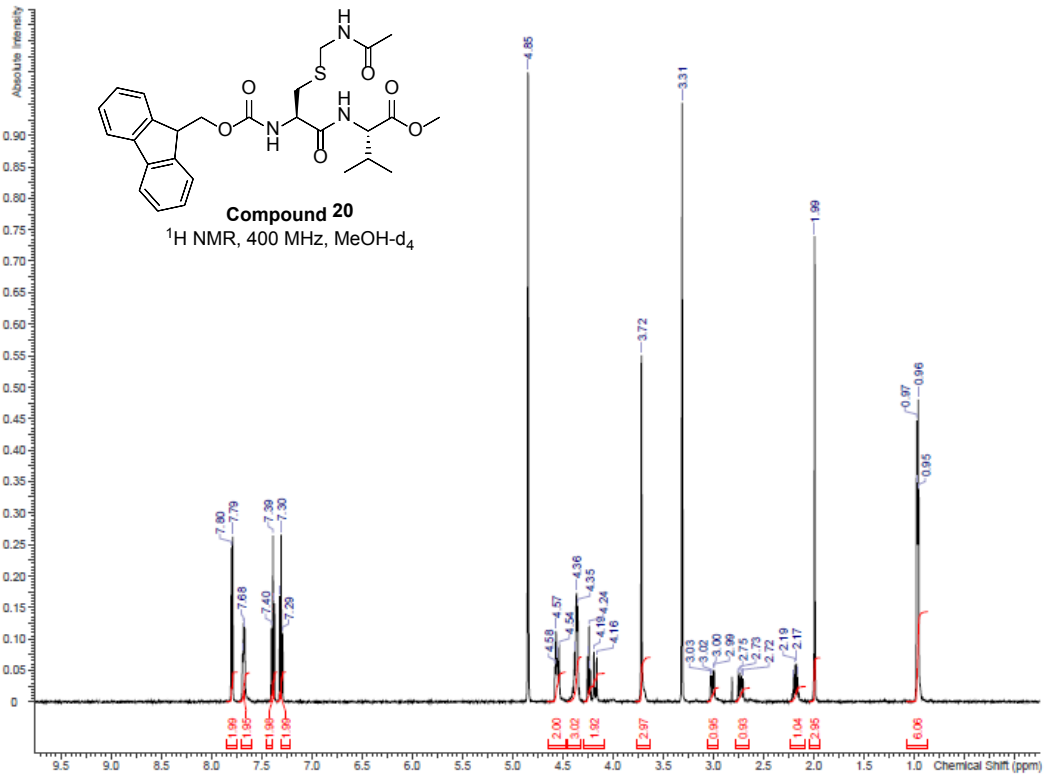
Compound 16
^{1}H NMR, 400 MHz, MeOH-d_4



Compound 16
^{13}C NMR, 100 MHz, MeOH-d_4

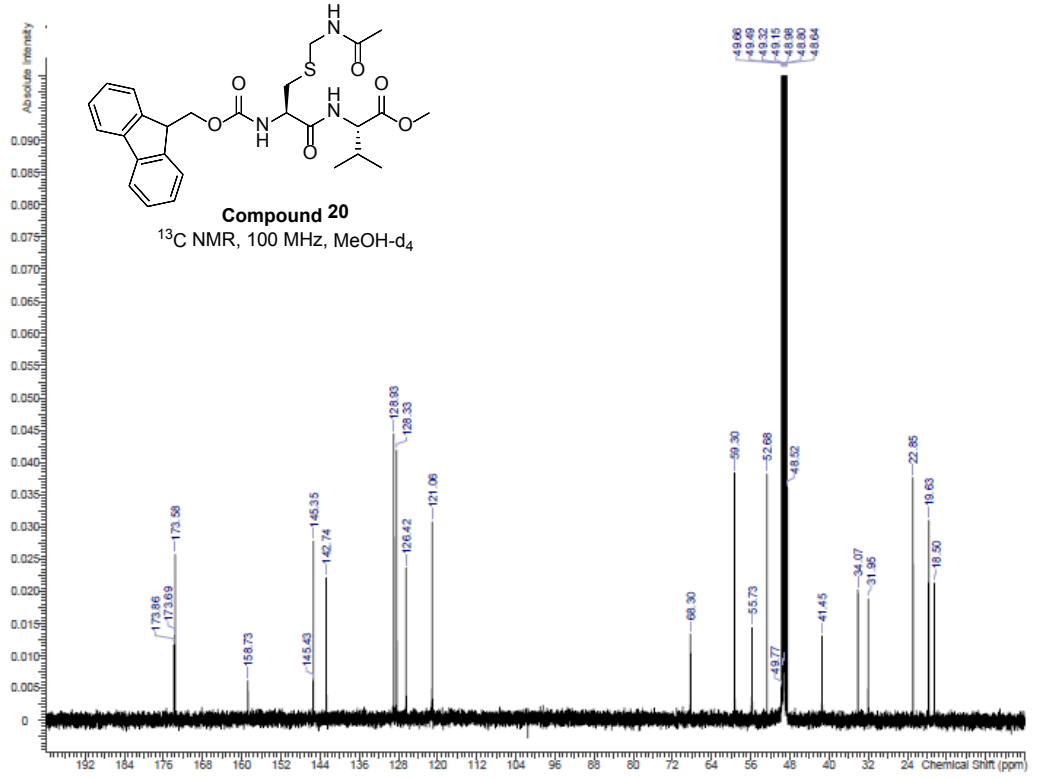

Ph
Ph
Ph
S
O
N
H
H
N
O
O
O
Compound 18
1H NMR, 400 MHz, MeOH-d4
Absolute Intensity
Chemical Shift (ppm)


Ph
Ph
Ph
S
O
N
H
H
N
O
O
O
Compound 18
13C NMR, 100 MHz, MeOH-d4
Absolute Intensity
Chemical Shift (ppm)



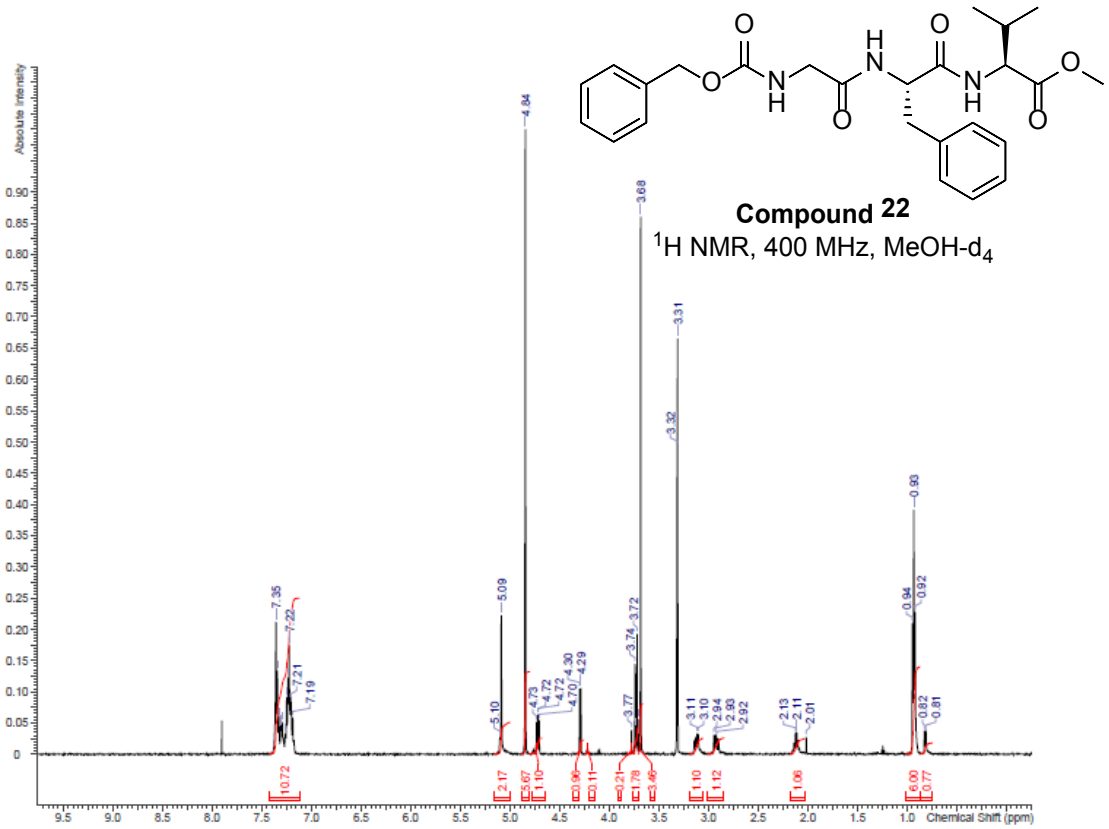
Compound 20

^{1}H NMR, 400 MHz, MeOH-d_4



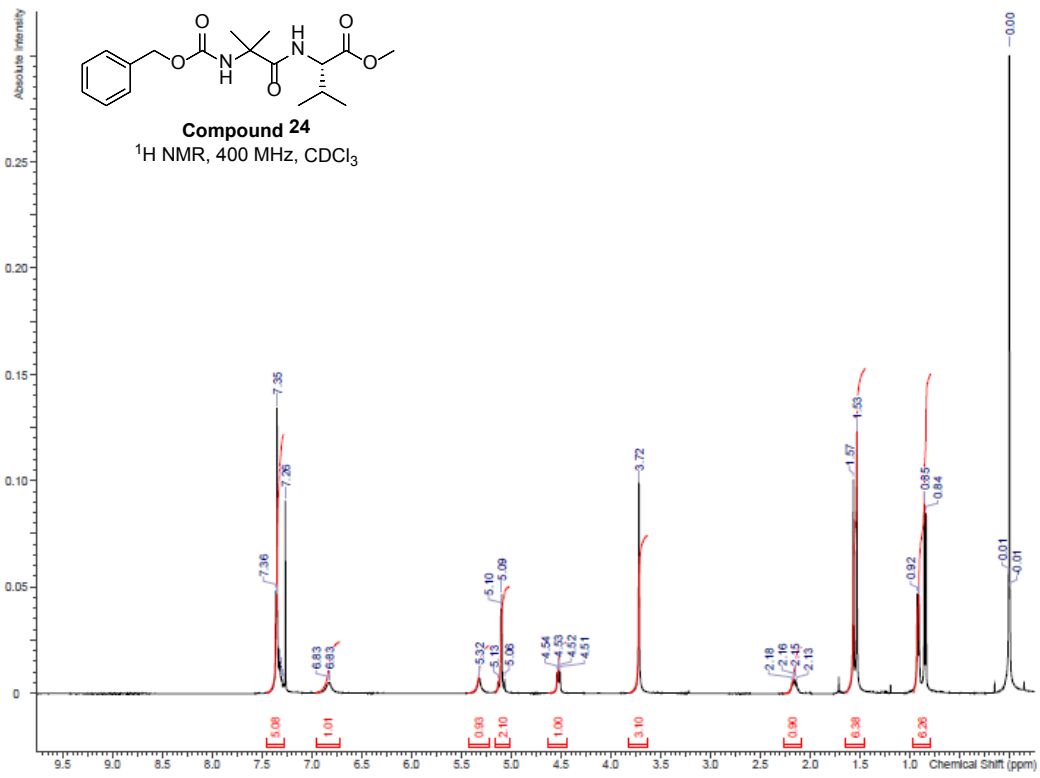
Compound 20

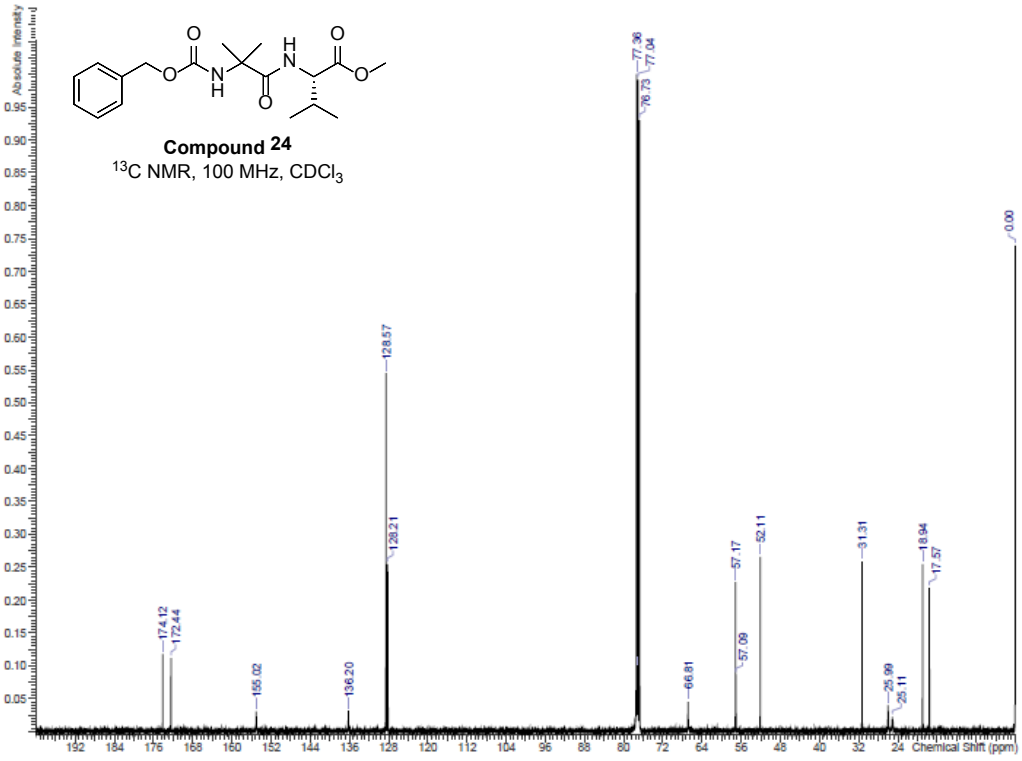
^{13}C NMR, 100 MHz, MeOH-d_4



Compound 22

^{1}H NMR, 400 MHz, MeOH-d_4


Compound 24
1H NMR, 400 MHz, CDCl3
Absolute Intensity
Chemical Shift (ppm)


Compound 24
13C NMR, 100 MHz, CDCl3
Absolute Intensity
Chemical Shift (ppm)