Supporting Information

Discovery of Synthetic Small molecules that Enhance the Number of Stomata: C–H Functionalization Chemistry for Plant Biology

Asraa Ziadi, Naoyuki Uchida, Hiroe Kato, Rina Hisamatsu, Ayato Sato, Shinya Hagihara, Kenichiro Itami, and Keiko U. Torii

Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University, Japan
Graduate School of Science, Nagoya University, Japan

Email: itami@chem.nagoya-u-ac.jp, ktorii@u.washington.edu

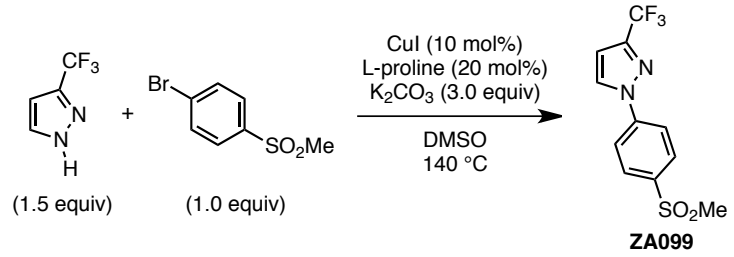
1. General – Chemical procedures

Unless otherwise noted, all materials including dry solvents were obtained from commercial suppliers and used without further purification. Unless otherwise noted, work-up and purification procedures were performed with reagent-grade solvents under air. Analytical thin-layer chromatography (TLC) was performed using

E. Merk silica gel $60F_{254}$ pre-coated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm). Flash chromatography was performed with silica gel 60N (Kanto Chemial Co., spherical, neutral, 40-100 mesh). Preparative thin-layer chromatography (PTLC) was performed using Wako-gel® B5-F silica coated plates (0.75 mm) prepared in our laboratory. Gel Permeation Chromatography (GPC) was run with $CHCl_3$ as solvent on JAI (Japan Analytical Industry, Co. Ltd.) LC-9204. Gas chromatography (GC) analysis was conducted on a Shimadzu GC-2010 instrument equipped with a HP-5 column (30 m x 0.25 mm, Hewlett-Packard). High-resolution mass spectroscopy (HRMS) was obtained using the ESI method from ThermoFischer Scientific Exactive equipped with a Dionex UltiMate 3000 Autosampler. Nuclear magnetic resonance (NMR) spectra were recorded on JEOL ECZ-400 and JEOL ECA-500 (^{1}H-NMR 400 MHz, ^{13}C-NMR 100 MHz and ^{1}H-NMR 500 MHz, ^{13}C-NMR 125 MHz, respectively) spectrometers. Chemical shifts for ^{1}H-NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm). Chemical shifts for ^{13}C-NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm) and MeOH-d_4 (δ 49.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, tt = triplet of triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration.

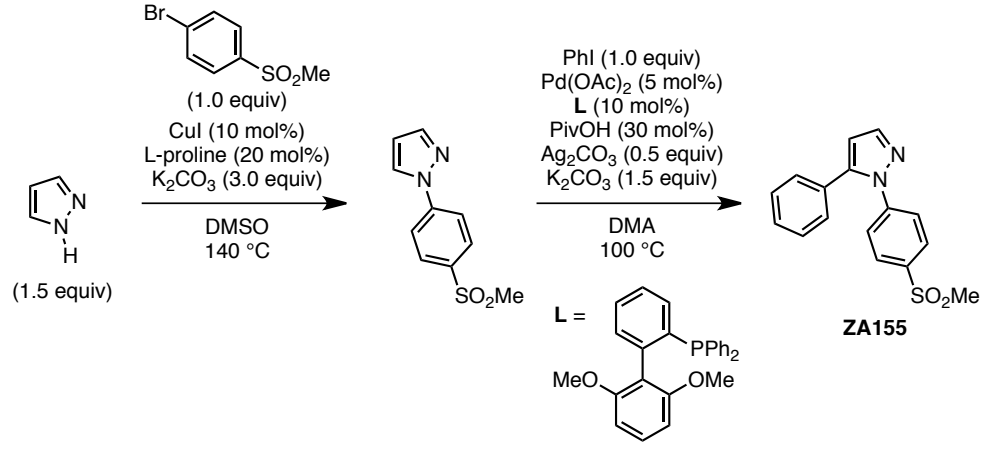
1.1. Synthesis of ZA099, ZA155 and ZA160

1.1.1. Synthesis of ZA099



Compound **ZA099** was synthesized in accordance with the reported procedure.[i] In a dry 50 mL-round bottomed flask equipped with a magnetic stirrer and a reflux condenser, 1.0 g of 3-(trifluoromethyl)-1*H*-pyrazole (7.4 mmol, 1.5 eq.), 1.2 g of 4-bromobenzene methyl sulfone (4.9 mmol, 1.0 eq.), 2.0 g of K_2CO_3 (14.7 mmol, 3.0 eq.), 113 mg of L-proline (0.9 mmol, 20 mol%) and 93 mg of CuI (0.5 mmol, 10 mol%) were mixed. After three vacuum/nitrogen cycles, dry DMSO (25 mL) was added under nitrogen flow and the reaction was let to stir at 140 °C overnight. After cooling the crude to room temperature, it was quenched with ammonia solution and then water. The precipitation was filtered off and collected; then dissolved in CH_2Cl_2 (DCM). The organic phase was washed with ammonia solution, water (x 2) and brine (x 2) then, subsequently, dried over Na_2SO_4 and concentrated in vacuo. The desired final product was obtained as a white solid in 60% yield (0.85 g, 2.9 mmol) after column chromatography (DCM/EtOAc = 5:1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16–8.04 (m, 3H), 7.96 (dt, *J* = 9.4, 2.3 Hz, 2H), 6.80 (d, *J* = 2.4 Hz, 1H), 3.10 (s, 3H). ^{19}F-NMR (376 MHz, $CDCl_3$) δ –62.38 (s).

1.1.2. Synthesis of ZA155

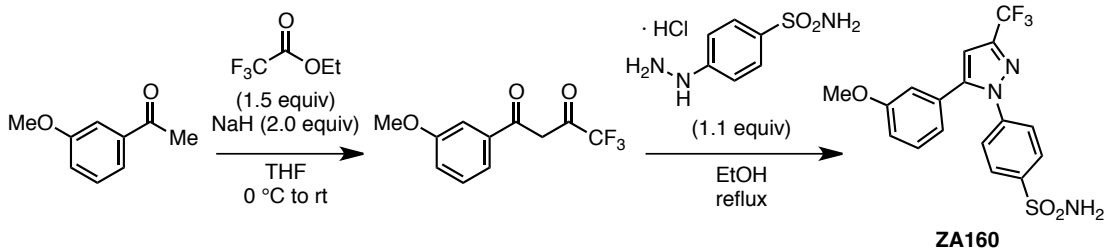


Compound **ZA155** was synthesized in a two-step fashion in accordance with the

reported procedures.[i,ii] **Step 1:** To a dry 250-mL round bottomed flask equipped with a magnetic stirrer and a reflux condenser, 2.2 g of pyrazole (32 mmol, 1.5 eq.), 5.0 g of 4-bromobenzene methyl sulfone (21 mmol, 1.0 eq.), 8.7 g of K_2CO_3 (63 mmol, 3.0 eq.), 484 mg of L-proline (4.2 mmol, 20 mol%) and 400 mg of CuI (2.1 mmol, 10 mol%) were mixed. After three vacuum/nitrogen cycles, dry DMSO (100 mL) was added under nitrogen flow and the reaction was let to stir at 140 °C overnight. After cooling the crude to room temperature, the reaction was quenched with ammonia solution and water. The precipitate was filtered off and collected; then dissolved in DCM. The organic phase was washed with ammonia solution, water (x 2) and brine (x 2) then, subsequently, dried over Na_2SO_4 and concentrated in vacuo. The desired final product (1-(4-(methylsulfonyl)phenyl)-1*H*-pyrazole) was obtained as a white solid in 26% yield (1.21 g, 5.4 mmol) after column chromatography (DCM/EtOAc = 5:1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06–7.98 (m, 3H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.79 (s, 1H), 6.55 (q, *J* = 1.3 Hz, 1H), 3.09 (d, *J* = 0.9 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.9, 142.6, 137.8, 129.3, 127.1, 119.1, 109.2, 44.8.

Step 2: To a dry screw-cap tube equipped with a magnetic stirrer, 30 mg of 1-(4-(methylsulfonyl)phenyl)-1*H*-pyrazole (0.13 mmol, 1.1 eq.), 1.5 mg of $Pd(OAc)_2$ (0.006 mmol, 5 mol%), 5 mg of **L** (0.012 mmol, 10 mol%), 18 mg of K_2CO_3 (0.18 mmol, 1.5 eq.), 17 mg of Ag_2CO_3 (0.06 mmol, 0.5 eq.) and 4 mg of PivOH (0.04 mmol, 30 mol%) were added. After 3 cycles of vacuum/nitrogen, 14 μL of iodobenzene (0.12 mmol, 1.0 eq.) and DMA (2 mL) were added. The tube was closed and stirred at 100 °C overnight. After cooling the crude to room temperature, it was filtered over a short plug of Celite® and silica and washed with EtOAc. The mixture was concentrated with the rotary evaporator and separated on PTLC. The desired final product was obtained as white solid in 66% yield (24 mg, 0.08 mmol). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.78 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.44–7.32 (m, 3H), 7.30–7.20 (m, 2H), 6.54 (s, 1H), 3.06 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 144.3, 143.5, 141.6, 138.6, 130.0, 128.9, 128.9, 128.8, 128.3, 125.0, 109.4, 44.5.

1.1.3. Synthesis of ZA160



ZA160

Compound **ZA160** was synthesized in a two-step fashion in accordance with the reported procedure.[iii] **Step 1:** To a dry 100-mL Schlenk flask equipped with a magnetic stirrer, 1.0 g of 3-methoxy acetophenone (6.7 mmol, 1.0 eq.) was added. After three cycles of vacuum/nitrogen, dry THF (50 mL) was added under N_2 and the mixture was immersed in a 0 °C ice-bath. 320 mg of NaH (13 mmol, 2.0 eq.) was added portion-wise and the mixture was let to stir for 30 min in the ice-bath. Subsequently, 1.2 mL of ethyl trifluoroacetate (10 mmol, 1.5 eq.) was added dropwise and the mixture was let to stir at room temperature overnight. The reaction was quenched by evaporation of the solvent, addition of ice-water and acidification with 2 M HCl to pH = 6. Later, the crude was extracted with EtOAc, washed with water, dried over $MgSO_4$ and finally concentrated to give a solid residue. This was washed with hexane and dried under high vacuum, which was re-dissolved in DCM, and dried under high vacuum to give a white solid in 82% yield (1.34 g, 5.4 mmol). ^{1}H-NMR and ^{19}F-NMR are in accordance with the reported data.

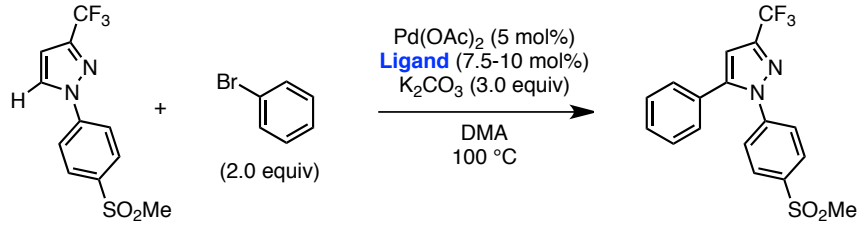
Step 2: To a 100-mL round-bottomed flask equipped with a magnetic stirrer, a reflux condenser and 4,4,4-trifluoro-1-(3-methoxyphenyl)butane-1,3-dione (100 mg, 0.4 mmol) in EtOH (50 mL), 4-hydrazinyl benzenesulfonamide hydrochloride (100 mg, 0.4 mmol) were added at room temperature. The mixture was heated to reflux overnight. The reaction mixture was concentrated in vacuo, extracted with EtOAc, washed with water, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (12% MeOH/DCM) to give **ZA160** in 72% yield (116 mg, 0.29 mmol) as a white solid. ^{1}H-NMR (400 MHz, acetone-d_6) δ 7.97 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.32 (t, J = 8.0 Hz, 1H), 7.04 (s, 1H), 7.01 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 6.94 (dd, J = 2.5, 1.6 Hz, 1H), 6.90 (ddd, J = 7.7, 1.6, 0.9 Hz, 1H), 6.75 (bs, 1H), 3.71 (s, 3H). ^{13}C-NMR (125 MHz, MeOH-d_4) δ 161.3, 146.9, 145.2, 144.8 (q, J = 38 Hz), 143.2, 131.2, 131.2, 128.3, 127.1, 122.7 (q, J = 268 Hz), 122.4, 116.2, 115.6, 107.1 (q, J = 2.5 Hz), 55.8. ^{19}F-NMR (471 MHz, acetone-d_6) δ –62.55.

2. Optimization of the Pd-catalyzed C–H arylation reaction

2.1. General procedure

To a dry 10-mL screw-capped tube were added 30 mg (0.10 mmol, 1.0 eq.) of 1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazole (**ZA099**), 3.0 eq. of base (0.31 mmol), 7.5-10 mol% of ligand (0.0075-0.01 mmol) and 5 mol% of palladium acetate (0.06 mmol). After three cycles of vacuum and nitrogen, 44 µL of bromobenzene (0.21 mmol, 2.0 eq.) and DMA (2 mL) were added under nitrogen and the tube was closed and stirred at 100 °C for 15 h. The reaction mixture was cooled to room temperature, 25 µL of tridecane (0.10 mmol, 1.0 eq.) was added as internal standard. The crude was diluted with EtOAc and directly filtered over a short plug of Celite®, then injected on GC for analysis.

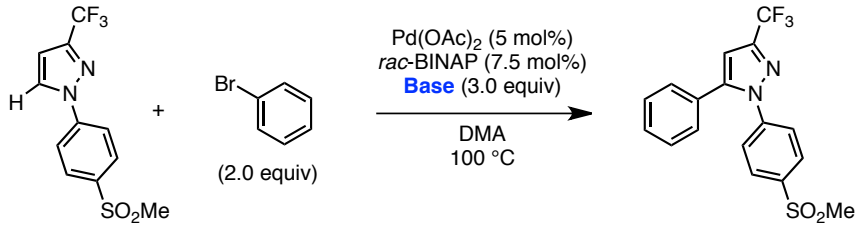
2.1.1. Ligand screening



ZA099 (1.0 equiv) **ZA138**

Entry	Ligand	GC yield of **ZA138**
1	PPh_3	65%
2	P(*p*-tolyl)$_3$	30%
3	PMe_3	26%
4	P*t*Bu$_3$	19%
5	PCy_3	70%
6	PCy_2Ph	76%
7	DPPF	47%
8	***rac*-BINAP**	**86%**
9	DPPP	50%
10	XPhos	64%
11	SPhos	70%
12	RuPhos	53%
13	BrettPhos	31%
14	IMes · HCl	17%
15	I*t*Bu · BF_4	23%
16	ICy · BF_4	0%
17	no ligand	0%

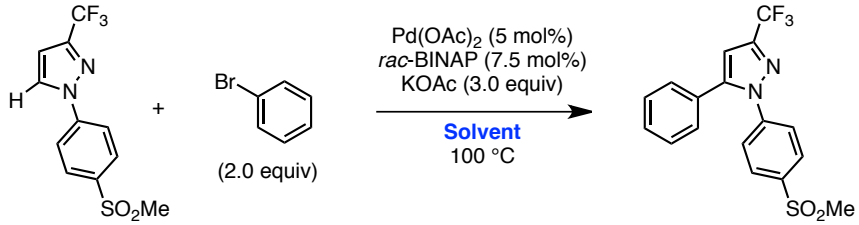
2.1.2. Base screening



ZA099 (1.0 equiv) **ZA138**

Entry	Base	GC yield of **ZA138**
1	Na_2CO_3	57%
2	K_2CO_3	70%
3	Cs_2CO_3	12%
4	Li_2CO_3	5%
5	NaOMe	27%
6	NaOAc	69%
7	**KOAc**	**90%**
8	KOH	14%
9	$NaHCO_3$	41%
10	NaH_2PO_4	8%
11	Na_2HPO_4	0%
12	K_3PO_3	9%
13	K_2HPO_4	8%
14	KH_2PO_4	1%
15	no base	1%

2.1.3. Solvent screening

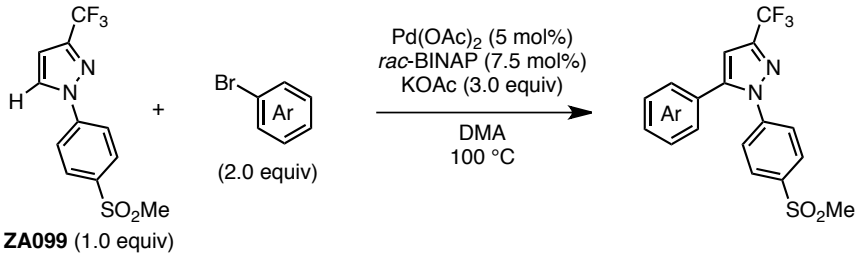


ZA099 (1.0 equiv) **ZA138**

Entry	Solvent	GC yield of **ZA138**
1	MeCN	14%
2	*t*BuOH	33%
3	ethylene glycol	7%
4	DME	61%
5	DMF	73%
6	DMSO	19%
7	1,4-dioxane	49%
8	THF	47%
9	**DMA**	**>99%**
10	cyclopentyl methyl ether	46%
11	*p*-xylene	63%
12	toluene	55%
13	cyclohexane	28%

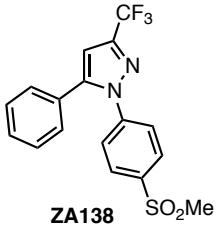
3. Scope of the Pd-catalyzed C–H arylation reaction

3.1 General procedure for the scope of the reaction



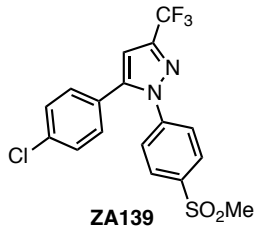
To a dry 10-mL screw-capped glass vial were added 30 mg of **ZA099** (0.103 mmol, 1 eq.), 30 mg of KOAc (0.310 mmol, 3.0 eq.), 5 mg of *rac*-BINAP (7 mol%, 0.01 mmol), 1.2 mg of $Pd(OAc)_2$ (0.005 mmol, 5 mol%) and the aryl bromide (if solid). The mixture was put under vacuum and three cycles of vacuum and nitrogen were made to ensure an inert atmosphere in the system. The aryl bromide (if liquid) and DMA (2 mL) were added under nitrogen and the reaction mixture was stirred at 100 °C for 15 h. The mixture was cooled down and filtered over Celite®, while washing with EtOAc, then concentrated under vacuum. The products were isolated with PTLC (hexane/EtOAc = 7:3) and purified further with GPC.

3.2. Description of the small molecules obtained



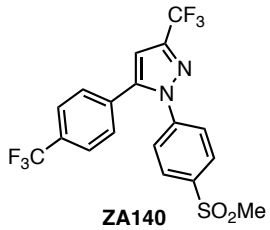
ZA138

1-(4-(Methylsulfonyl)phenyl)-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazole (ZA138). Following the general procedure, 22 μL of bromobenzene was used as the aryl bromide. The product was obtained as colorless oil in 88% yield (32 mg). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 9.2 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.45–7.32 (m, 3H), 7.24 (dd, *J* = 7.8, 1.3 Hz, 2H), 6.78 (s, 1H), 3.05 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 145.2, 144.4 (d, *J* = 38 Hz), 143.3, 139.9, 129.7, 129.1, 128.8, 128.5, 125.7, 120.9 (d, *J* = 269 Hz), 106.8 (q, *J* = 2.3 Hz), 44.5. ^{19}F-NMR (470 MHz, $CDCl_3$) δ –62.41. HRMS (ESI) *m/z* calcd for $C_{17}H_{13}O_2N_2SF_3Na$ $[M+Na]^+$: 389.0542, found 389.0543.



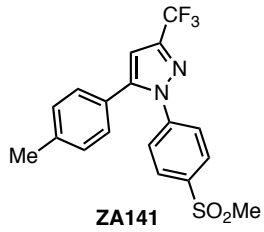
ZA139

1-(4-(Methylsulfonyl)phenyl)-5-(4-chlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole (ZA139). Following the general procedure, 40 mg of 4-chlorobromobenzene was used as the aryl bromide. The product was obtained as colorless oil in 56% yield (22 mg). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.79 (s, 1H), 3.08 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 144.5 (d, *J* = 38.7 Hz), 143.9, 143.1, 140.2, 136.0, 130.1, 129.5, 128.7, 127.0, 125.7, 120.8 (d, *J* = 269 Hz), 107.0 (q, *J* = 2.3 Hz), 44.4. ^{19}F-NMR (471 MHz, $CDCl_3$) δ –62.45. HRMS (ESI) *m/z* calcd for $C_{17}H_{12}ClO_2N_2SF_3Na$ $[M+Na]^+$: 423.0152, found 423.0145.



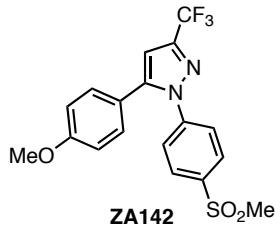
ZA140

1-(4-(Methylsulfonyl)phenyl)-3-(trifluoromethyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (ZA140). The general procedure was used with the addition of 29 μL of 4-trifluoromethyl bromobenzene. The product was obtained as oil in 74% yield (32 mg). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.99 (dt, *J* = 8.2, 2.0 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.52 (dt, *J* = 8.7, 2.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 6.86 (s, 1H), 3.08 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 144.6 (d, *J* = 38.8 Hz), 143.5, 142.9, 140.5, 132.0 (q, *J* = 1.3 Hz), 131.7 (d, *J* = 32.5 Hz), 129.2, 128.8, 126.2 (q, *J* = 2.5 Hz), 125.7, 123.5 (d, *J* = 271 Hz), 120.8 (d, *J* = 268 Hz), 107.4 (q, *J* = 1.3 Hz), 44.5. ^{19}F-NMR (376 MHz, $CDCl_3$) δ –62.83, –62.45. HRMS (ESI) *m/z* calcd for $C_{18}H_{12}O_2N_2SF_6Na$ $[M+Na]^+$: 457.0416, found 457.0420.



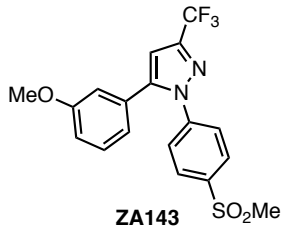
ZA141

1-(4-(Methylsulfonyl)phenyl)-5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazole (ZA141). The general procedure was used with the addition of 26 μL of 4-bromotoluene. The product was obtained as white solid in 38% yield (15 mg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.74 (s, 1H), 3.06 (s, 3H), 2.38 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ:145.3, 144.3 (d, *J* = 38 Hz), 143.5, 139.9, 139.8, 129.8, 129.0 (d, *J* = 27 Hz), 128.7, 128.5, 125.7, 121.0 (d, *J* = 269 Hz), 106.5 (q, *J* = 2.3 Hz), 44.5, 21.3. ^{19}F-NMR (376 MHz, $CDCl_3$) δ –62.42. HRMS (ESI) *m/z* calcd for $C_{18}H_{15}O_2N_2SF_3Na$ $[M+Na]^+$: 403.0699, found 403.0691.



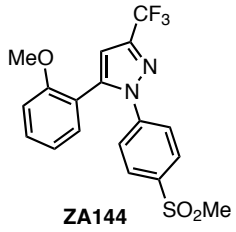
ZA142

5-(4-Methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazole (ZA142). The general procedure was used with the addition of 26 μL of 4-bromoanisole. The product was obtained as a colorless oil in 36% (14 mg). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.71 (s, 1H), 3.83 (s, 3H), 3.05 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 160.6, 145.1, 144.3 (d, *J* = 38 Hz), 143.5, 139.7, 130.2, 128.5, 125.7, 121.1 (q, *J* = 269 Hz), 120.7, 114.5, 106.3 (q, *J* = 2.5 Hz), 55.4, 44.5. ^{19}F-NMR (470 MHz, $CDCl_3$) δ –62.38. HRMS (ESI) *m/z* calcd for $C_{18}H_{15}O_3N_2SF_3Na$ $[M+Na]^+$: 457.0648, found 419.0649.



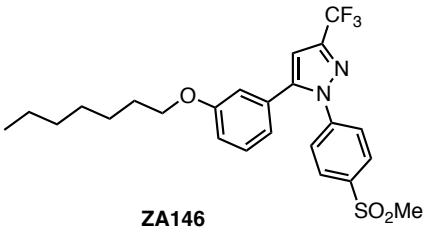
ZA143

5-(3-Methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazole (ZA143). The general procedure was used with the addition of 26 μL of 3-bromoanisole. The product was obtained as a colorless oil in 24% yield (10 mg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.31–7.25 (m, 1H), 6.95 (ddd, *J* = 8.4, 2.6, 0.8 Hz, 1H), 6.81–6.74 (m, 2H), 3.75 (s, 2H), 3.06 (s, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 159.9, 145.0, 144.3 (d, *J* = 38 Hz), 143.3, 139.9, 130.2, 129.8, 128.5, 125.6, 121.2, 120.9 (d, *J* = 269 Hz), 115.0, 114.6, 106.8 (q, *J* = 2.1 Hz), 55.3, 44.5. ^{19}F-NMR (470 MHz, $CDCl_3$) δ –62.43. HRMS (ESI) *m/z* calcd for $C_{18}H_{15}O_3N_2SF_3Na$ $[M+Na]^+$: 457.0648, found 419.0644.



ZA144

5-(2-Methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazole (ZA144). The general procedure was used with the addition of 25 μL of 2-bromoanisole. The product was obtained as a colorless oil in 41% yield (16 mg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.44 (td, *J* = 7.8, 1.6 Hz, 1H), 7.32 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.72 (s, 1H), 3.38 (s, 3H), 3.02 (s, 3H). ^{13}C-NMR (500 MHz, $CDCl_3$) δ 156.1, 144.6, 142.1, 139.3, 131.8, 131.0, 128.2, 124.1, 121.2, 117.9, 113.0, 111.5, 107.5 (q, *J* = 2.5 Hz), 54.9, 44.5. ^{19}F-NMR (376 MHz, $CDCl_3$) δ –62.26. HRMS (ESI) *m/z* calcd for $C_{18}H_{15}O_3N_2SF_3Na$ $[M+Na]^+$: 457.0648, found 419.0646.



ZA146

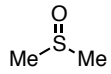
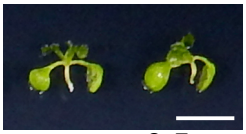
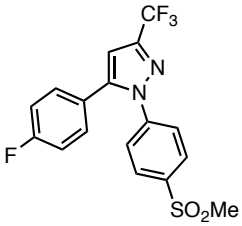
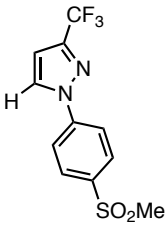
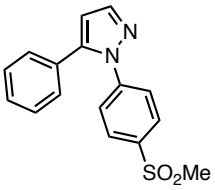
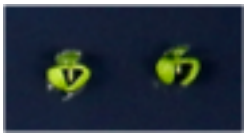
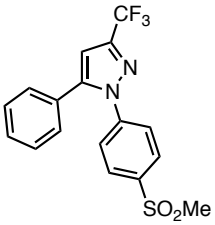
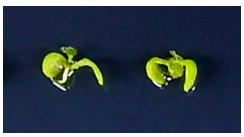
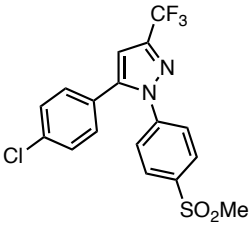
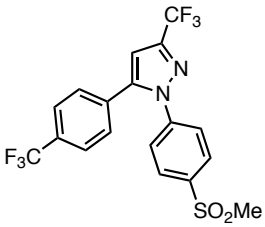
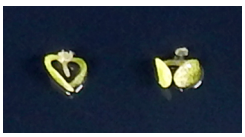
5-(3-(Heptyloxy)phenyl)-1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazole (ZA146). The general procedure was used with the addition of 56 mg of 3-heptoyl bromobenzene. The product was obtained as colorless oil in 18% yield (9 mg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.29–7.20 (m, 1H), 6.94 (ddd, *J* = 8.4, 2.5, 0.8 Hz, 1H), 6.82–6.79 (m, 1H), 6.77 (s, 1H), 6.72 (dt, *J* = 7.6, 1.2 Hz, 1H), 3.89 (t, *J* = 6.6 Hz, 2H), 3.06 (s, 3H), 1.82–1.68 (m, 2H), 1.50–1.21 (m, 8H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 159.6, 145.2, 144.4 (q, *J* = 38 Hz), 143.5, 140.0, 130.3, 129.8, 128.6, 121.1 (q, *J* = 269 Hz), 121.1, 115.7, 115.2, 106.9 (q, *J* = 2.4 Hz), 68.3, 44.6, 31.8, 29.2, 29.1, 26.0, 22.7, 14.2. ^{19}F-NMR (470 MHz, $CDCl_3$) δ –62.37. HRMS (ESI) *m/z* calcd for $C_{24}H_{27}O_3N_2SF_3Na$ $[M+Na]^+$: 503.1587, found 503.1584.

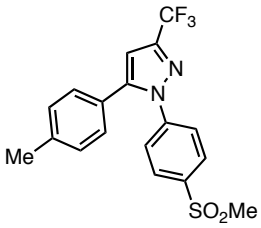
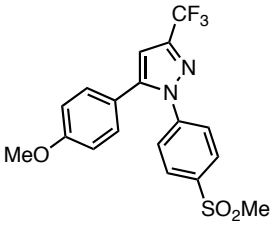
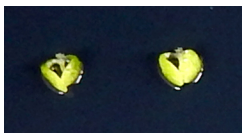
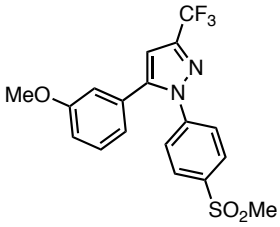
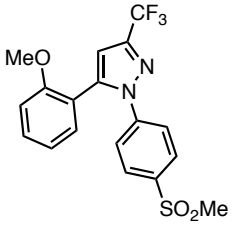
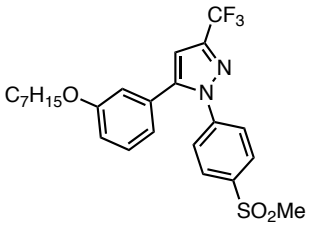
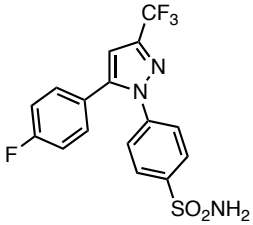
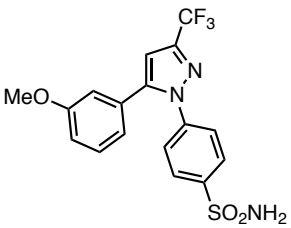
4. General – Biological testing

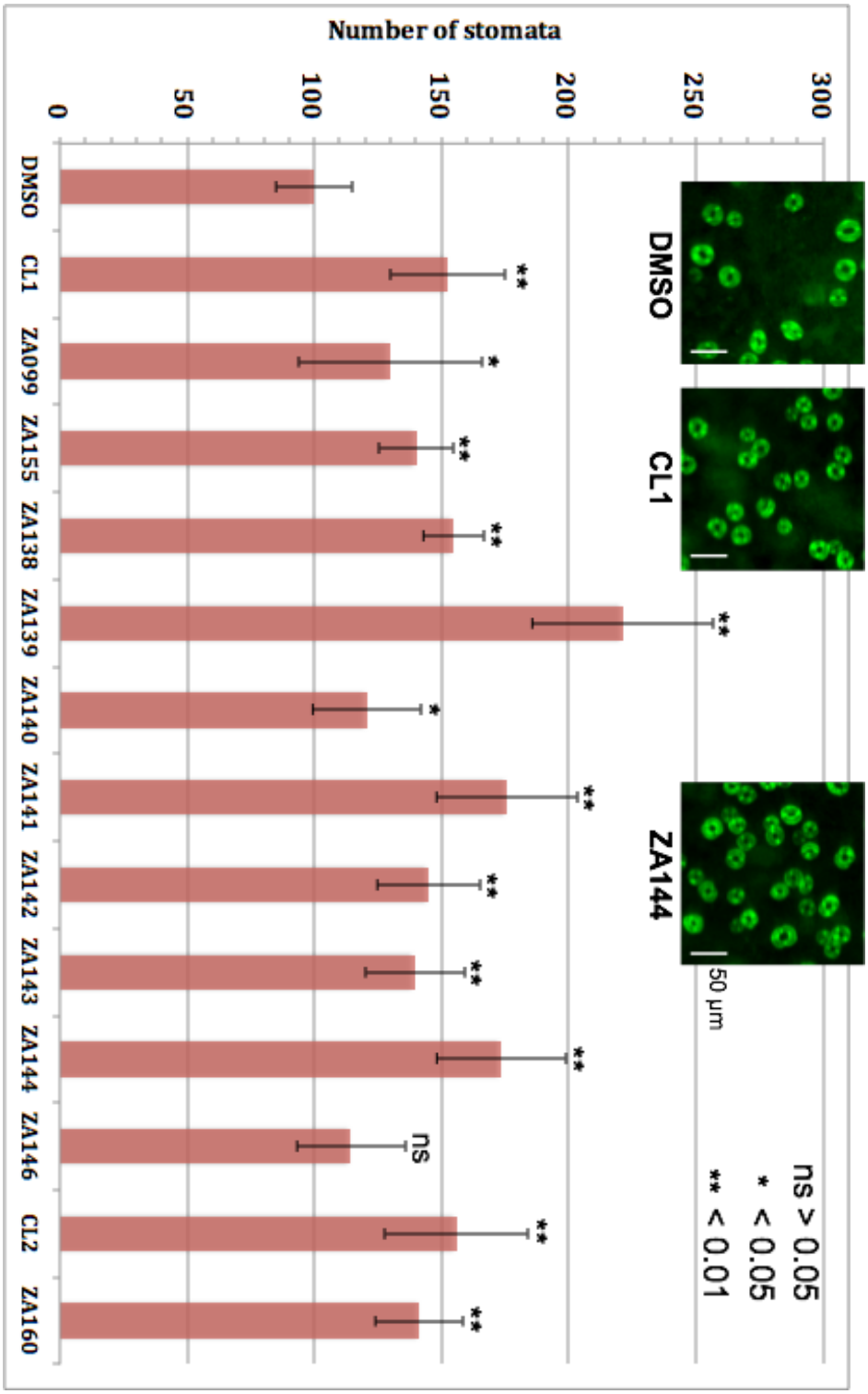
Seeds of the Arabidopsis E994 line that expresses GFP in mature stomata cells were sterilized, stored in the dark at 4 °C for a few days, transferred to wells of 96-well plates containing 95 μL of 0.5 x Murashige and Skoog (MS) liquid medium per well, and grown on a shaker set at 140 rpm under continuous white light at 22 °C. 5 μ. of each compound was added to the wells the next day. GFP signals on abaxial sides of cotyledons of 11-day-old seedlings were observed using Zeiss SteREO Discovery V20. Dry weight was measured after the seedlings were completely dried at 65 °C for 3 days.

5. Bio-images of treated 9-days old *Arabidopsis thaliana* seeds

These images are of *Arabidopsis thaliana* seeds that were treated with different compounds and then let to grow for 9 days.

Compound name	Structure	Picture
DMSO		
CL1		
ZA099		
ZA155		
ZA138		
ZA139		
ZA140		

ZA141		
ZA142		
ZA143		
ZA144		
ZA146		
CL2		
ZA160		



Stomata density (DMSO = 100%), Mean +/- s.d. (n = 10-11)

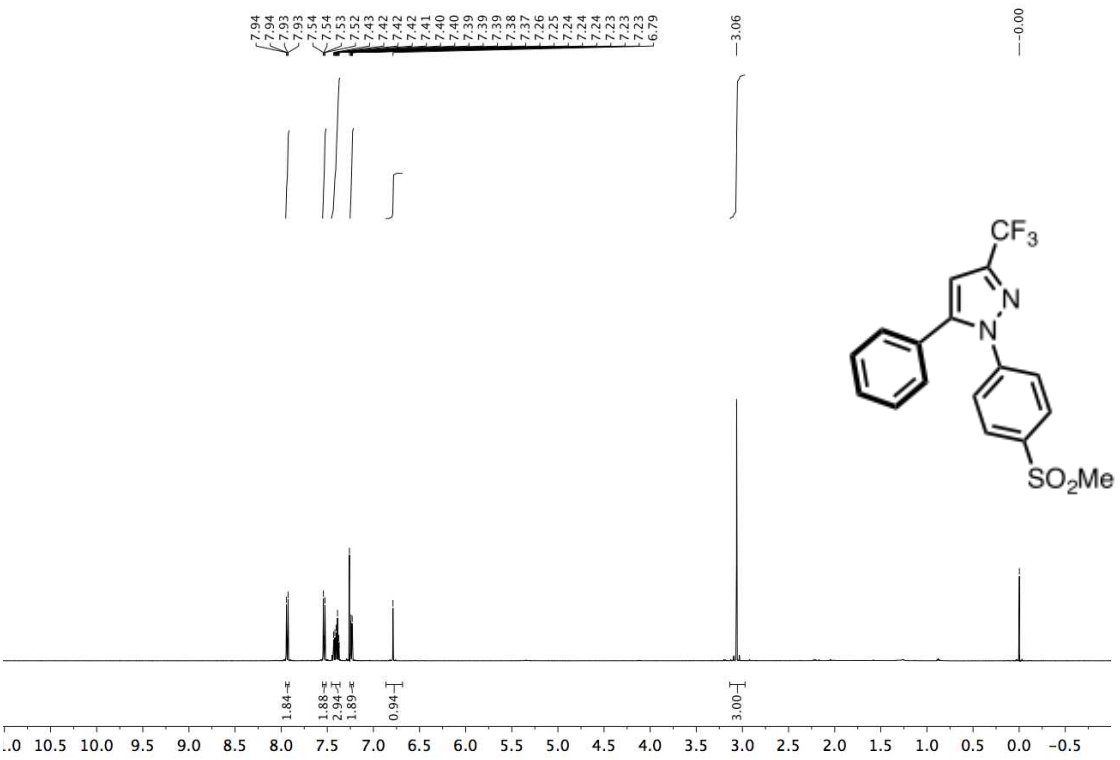
Table 1. Amount of stomata on plant leaves after treatment

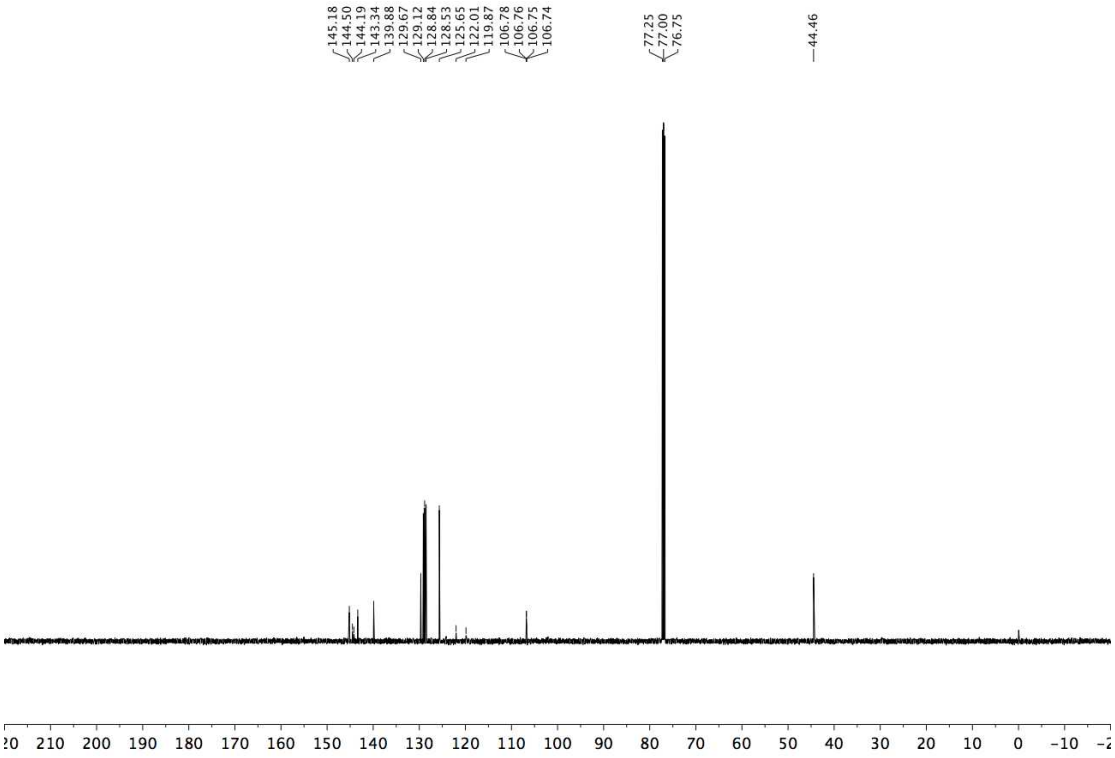
Compound	Mean	Standard deviation
DMSO	100	15.0
CL1	152.4	22.9
CL2	155.9	28.2
ZA099	129.7	36.1
ZA155	140.1	14.8
ZA138	154.8	11.9
ZA139	221.3	35.6
ZA140	120.6	21.2
ZA141	175.8	27.7
ZA142	145	20.2
ZA143	139.4	19.5
ZA144	173.4	25.2
ZA146	114.4	21.2
ZA160	141.4	17.4

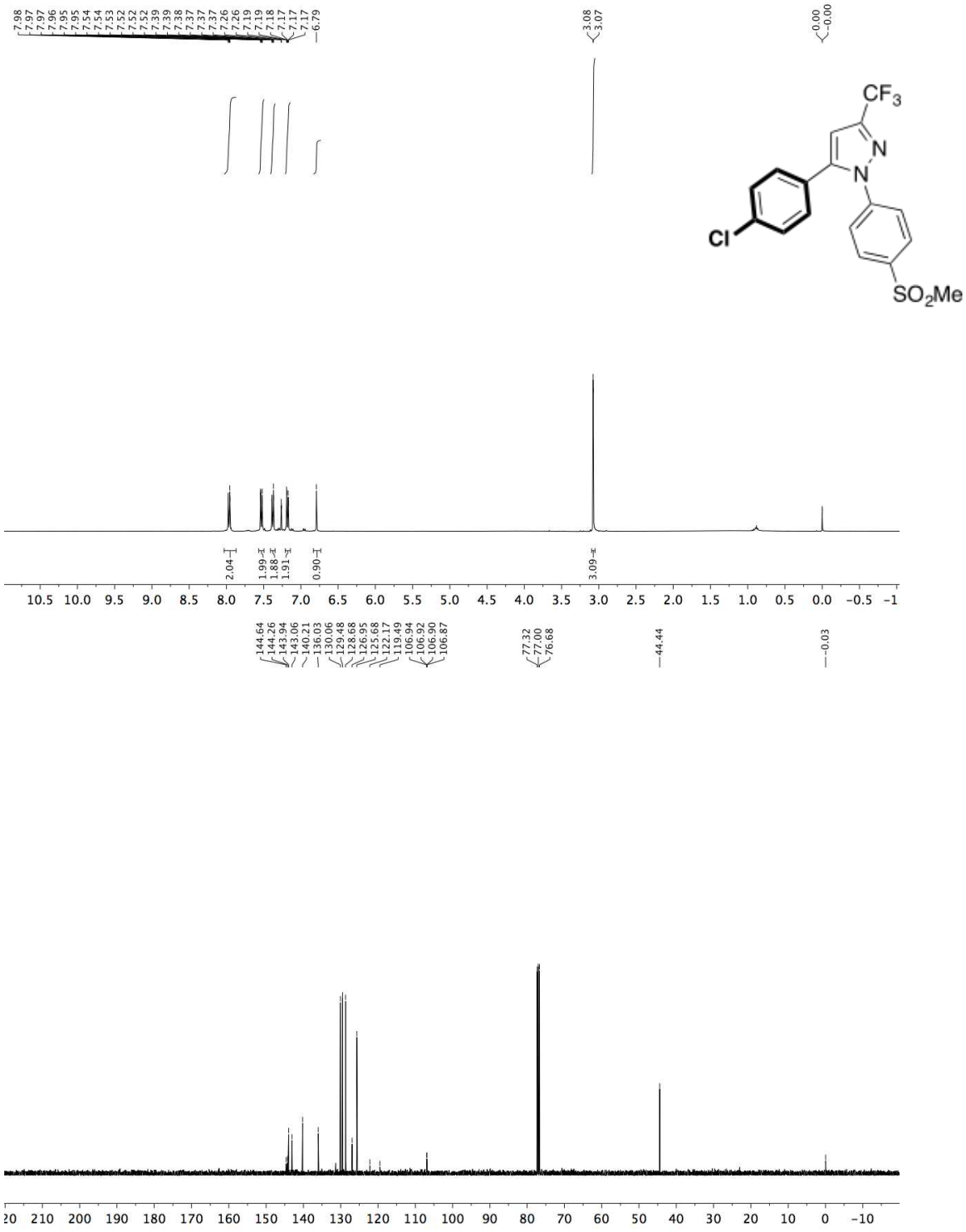
Table 2. Dry weight (mg) per 16 seedlings

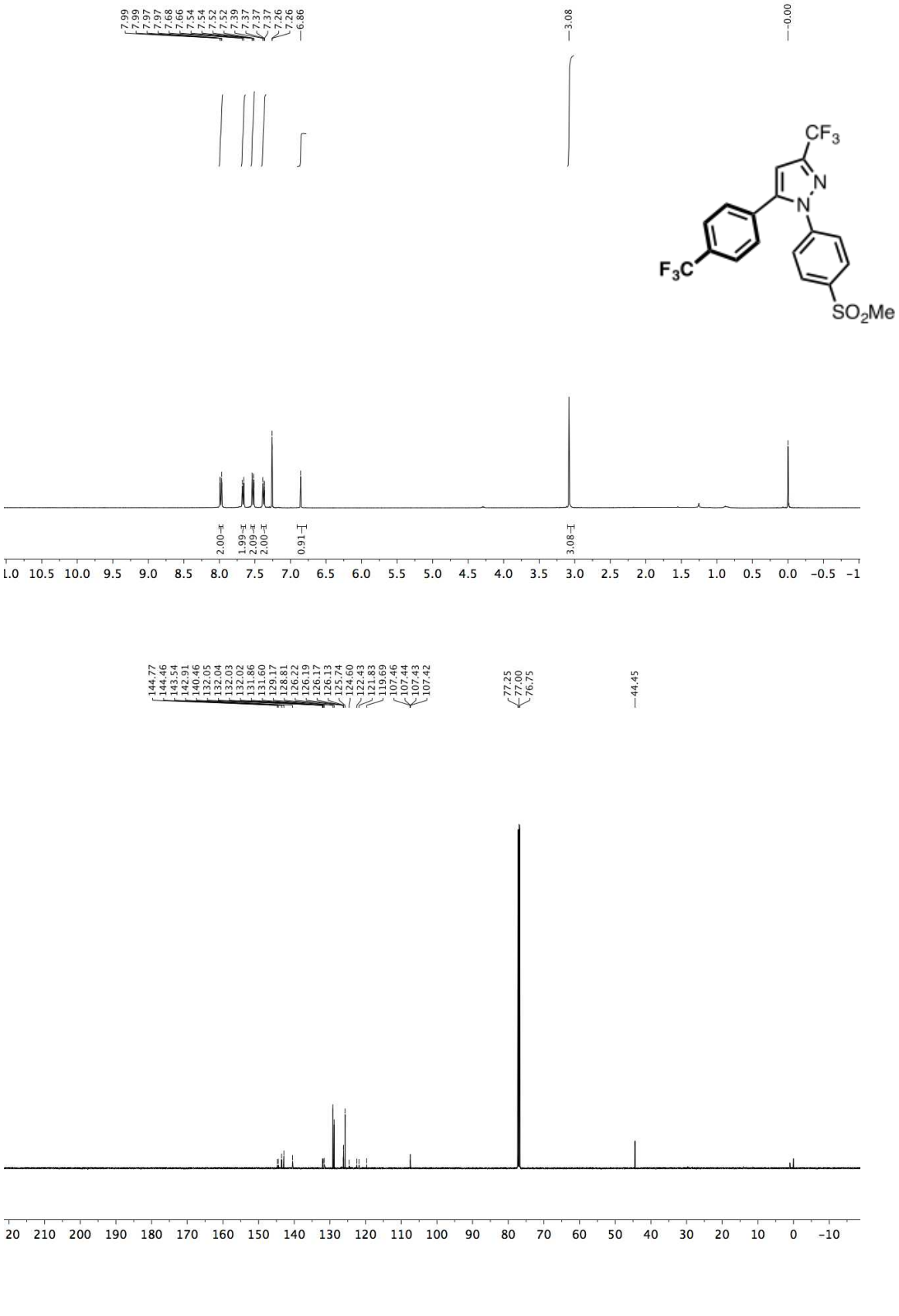
Compound	Average weight (mg)	Standard deviation
DMSO	4.09	0.26
CL1	2.82	0.19
ZA144	4.55	0.36
ZA139	1.82	0.29

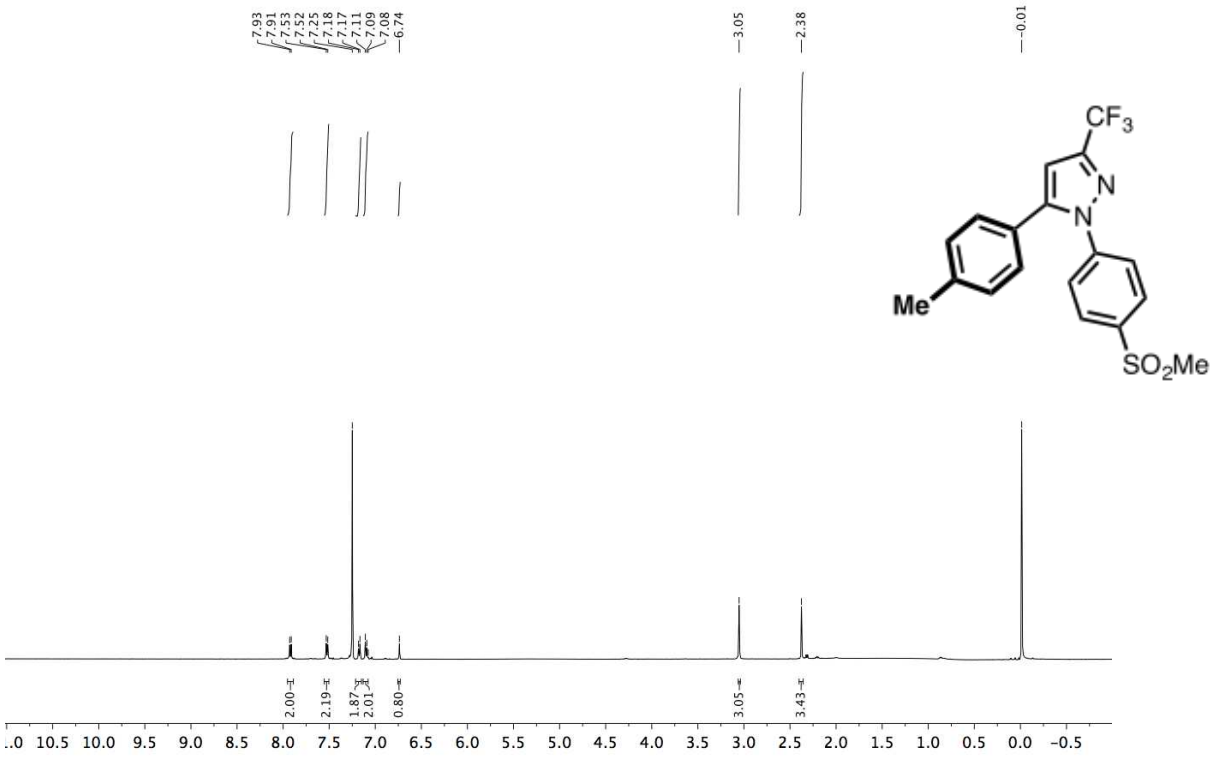
6. ^{1}H-NMR and ^{13}C-NMR spectra

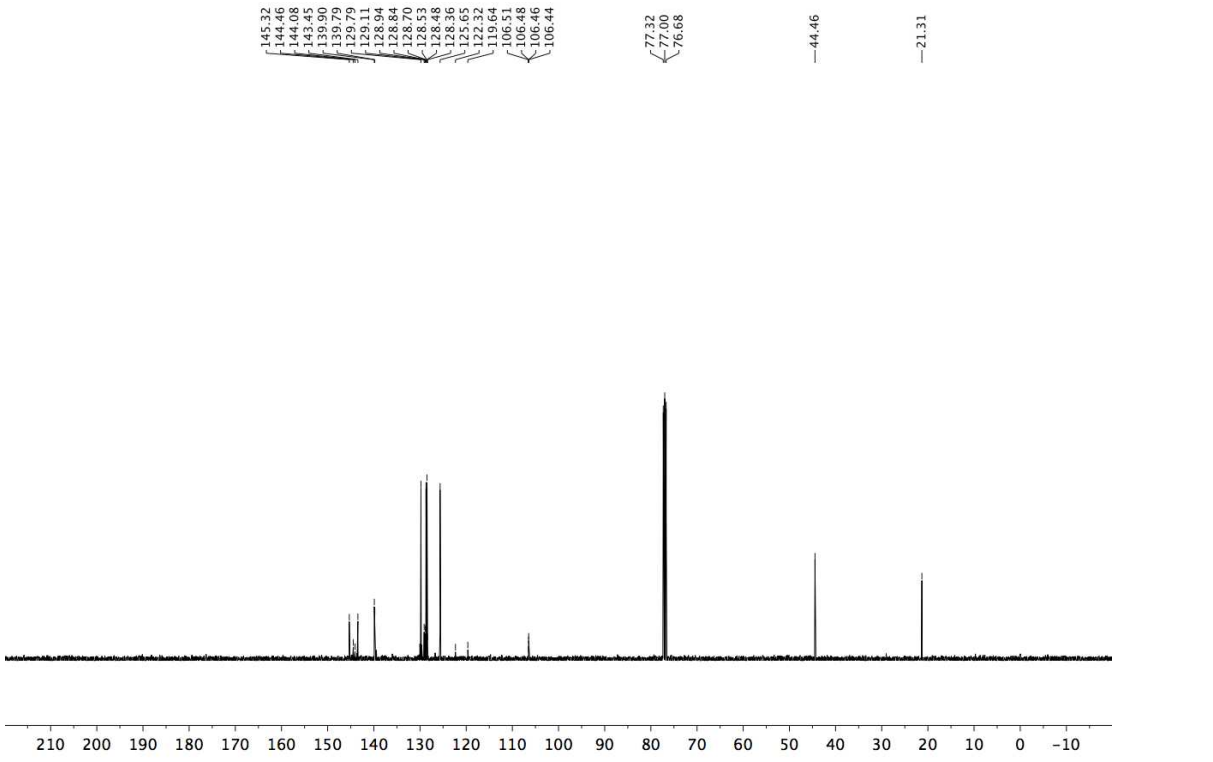


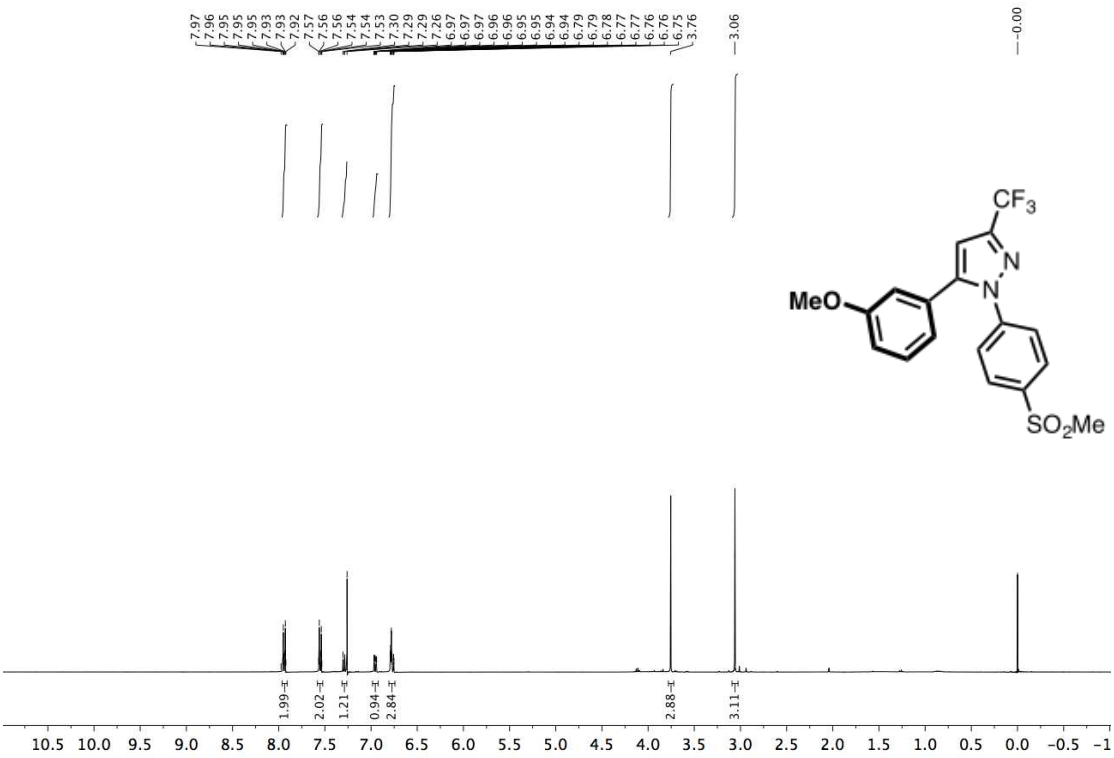


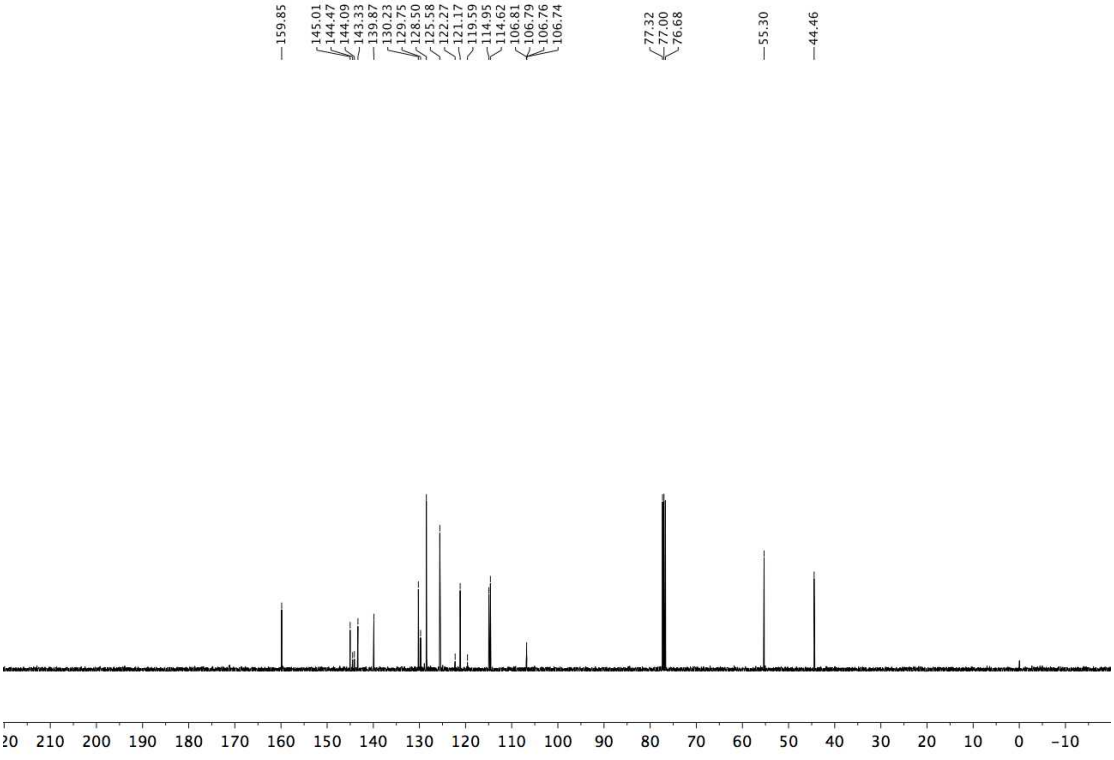

CF3
N
N
Cl
SO2Me

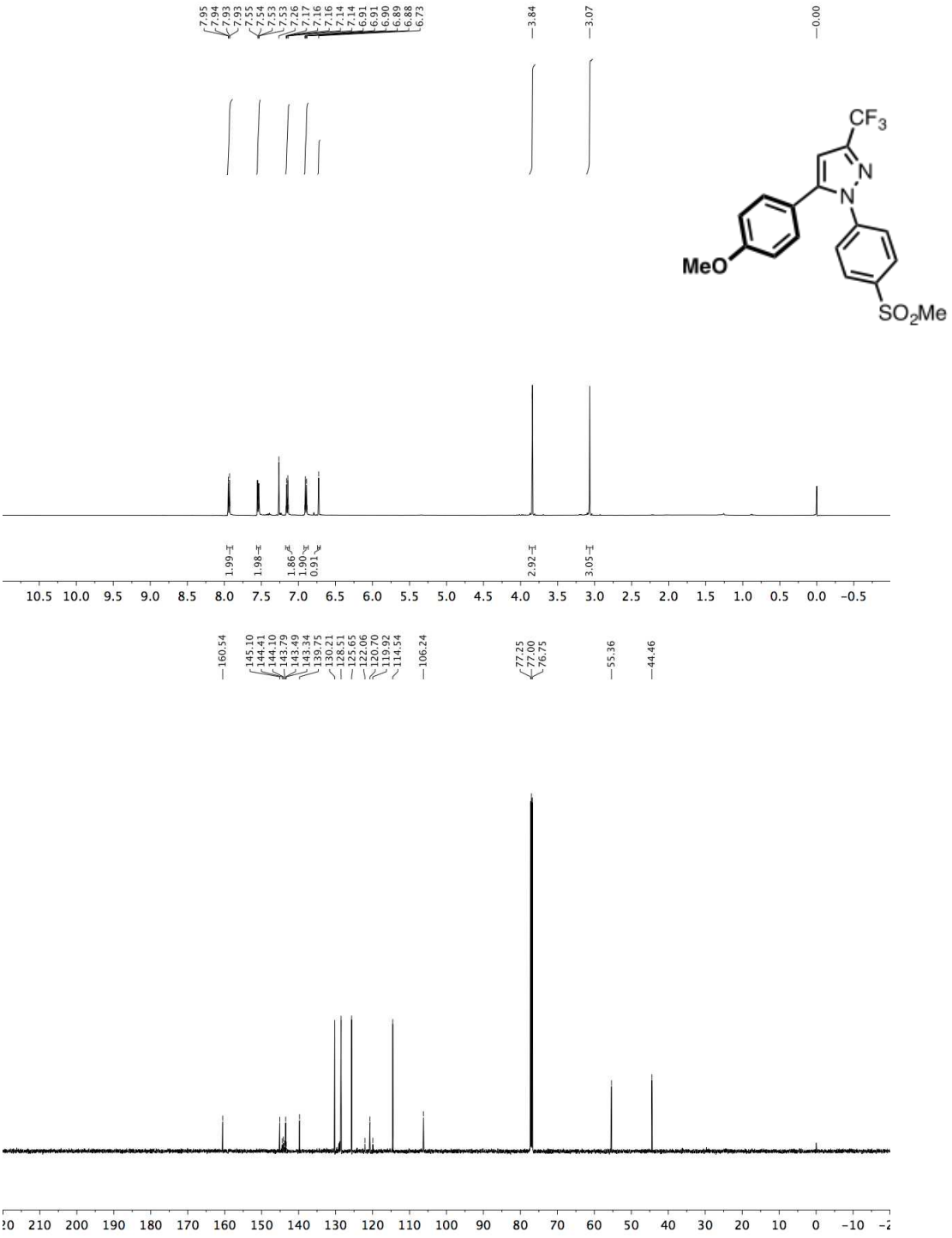

7.99
7.99
7.97
7.97
7.68
7.66
7.54
7.54
7.52
7.52
7.39
7.37
7.37
7.37
7.26
7.26
6.86
3.08
0.00
CF3
N
N
F3C
SO2Me
2.00
1.99
2.09
2.00
0.91
3.08
144.77
144.46
143.54
142.91
140.46
132.05
132.04
132.03
132.02
131.86
131.60
129.17
128.81
126.22
126.19
126.17
126.13
125.74
124.60
122.43
121.83
119.69
107.46
107.44
107.43
107.42
77.25
77.00
76.75
44.45

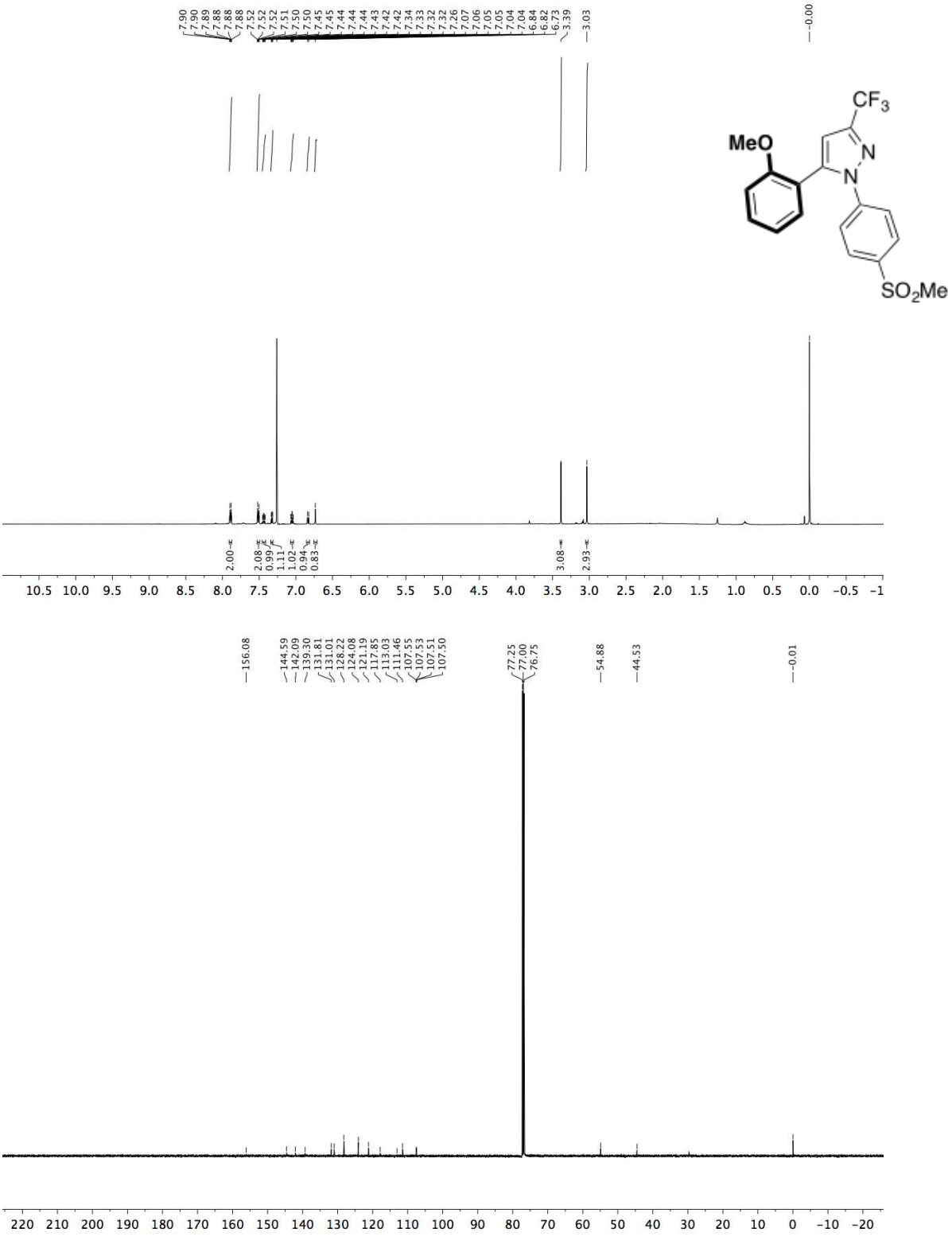

7.93
7.91
7.53
7.52
7.25
7.18
7.17
7.11
7.09
7.08
6.74
3.05
2.38
0.01
CF3
N
N
Me
SO2Me
2.00
2.19
1.87
2.01
0.80
3.05
3.43
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

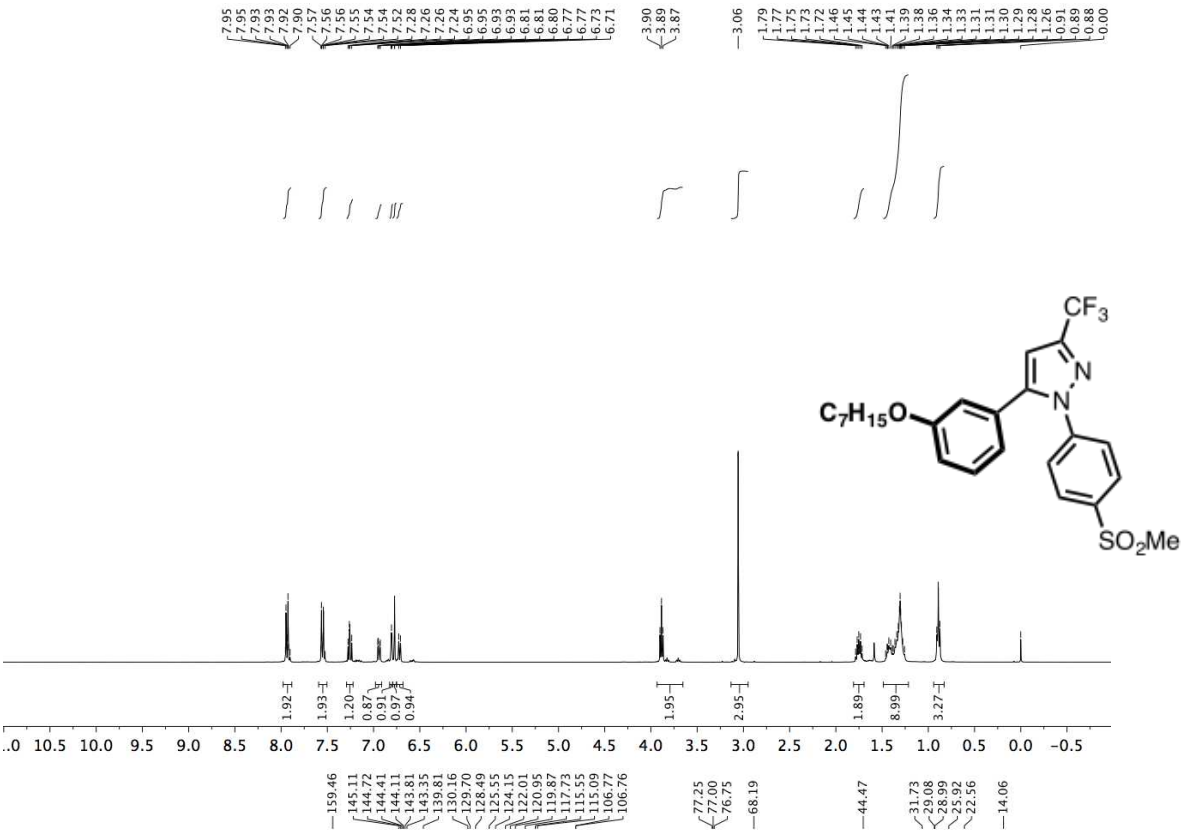

145.32
144.46
144.08
143.45
139.90
139.79
129.79
129.11
128.94
128.84
128.70
128.53
128.48
128.36
125.65
122.32
119.64
106.51
106.48
106.46
106.44
77.32
77.00
76.68
44.46
21.31
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

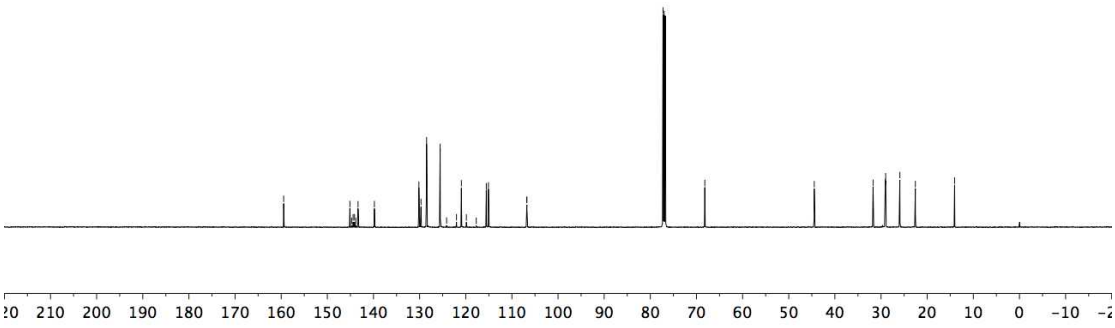

7.97
7.96
7.95
7.95
7.95
7.93
7.93
7.92
7.57
7.56
7.56
7.54
7.54
7.53
7.30
7.29
7.29
7.26
6.97
6.97
6.96
6.96
6.95
6.95
6.94
6.94
6.79
6.79
6.78
6.77
6.77
6.76
6.76
6.75
3.76
3.06
0.00
CF3
N
N
MeO
SO2Me
1.99
2.02
1.21
0.94
2.84
2.88
3.11
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1

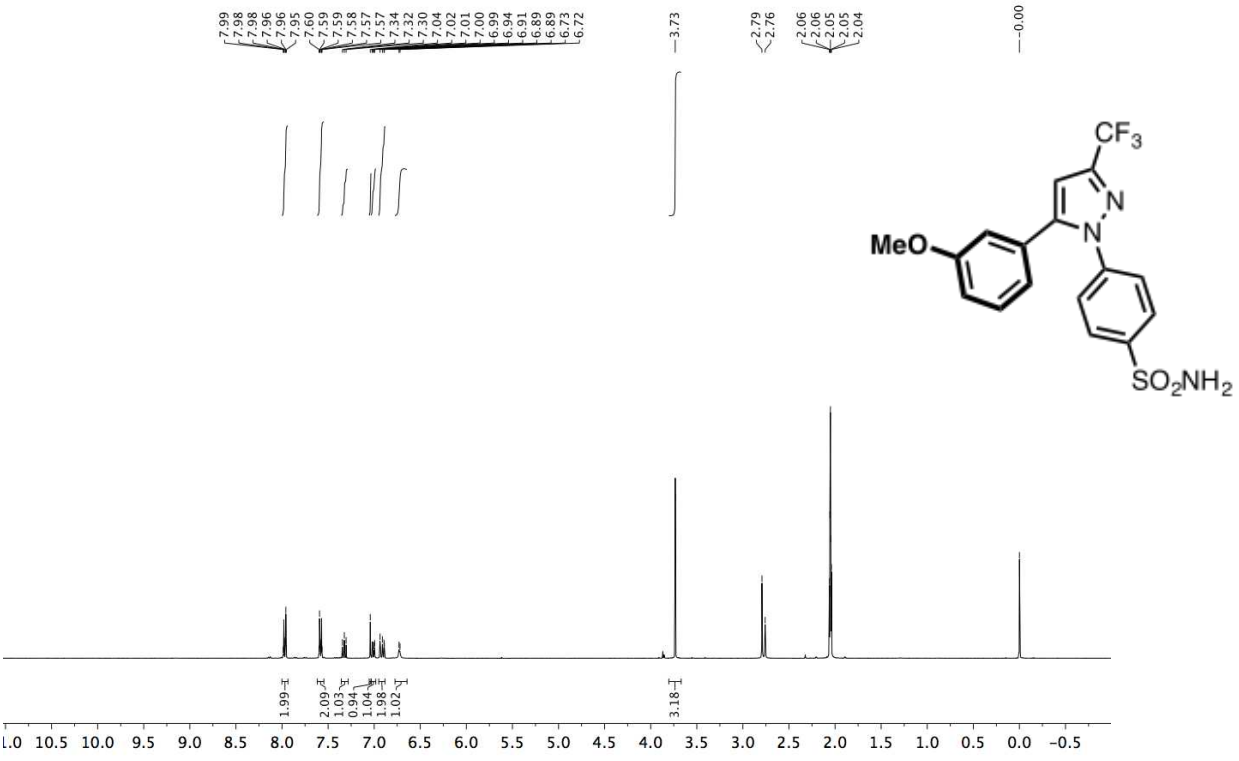

159.85
145.01
144.47
144.09
143.33
139.87
130.23
129.75
128.50
125.58
122.27
121.17
119.59
114.95
114.62
106.81
106.79
106.76
106.74
77.32
77.00
76.68
55.30
44.46
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

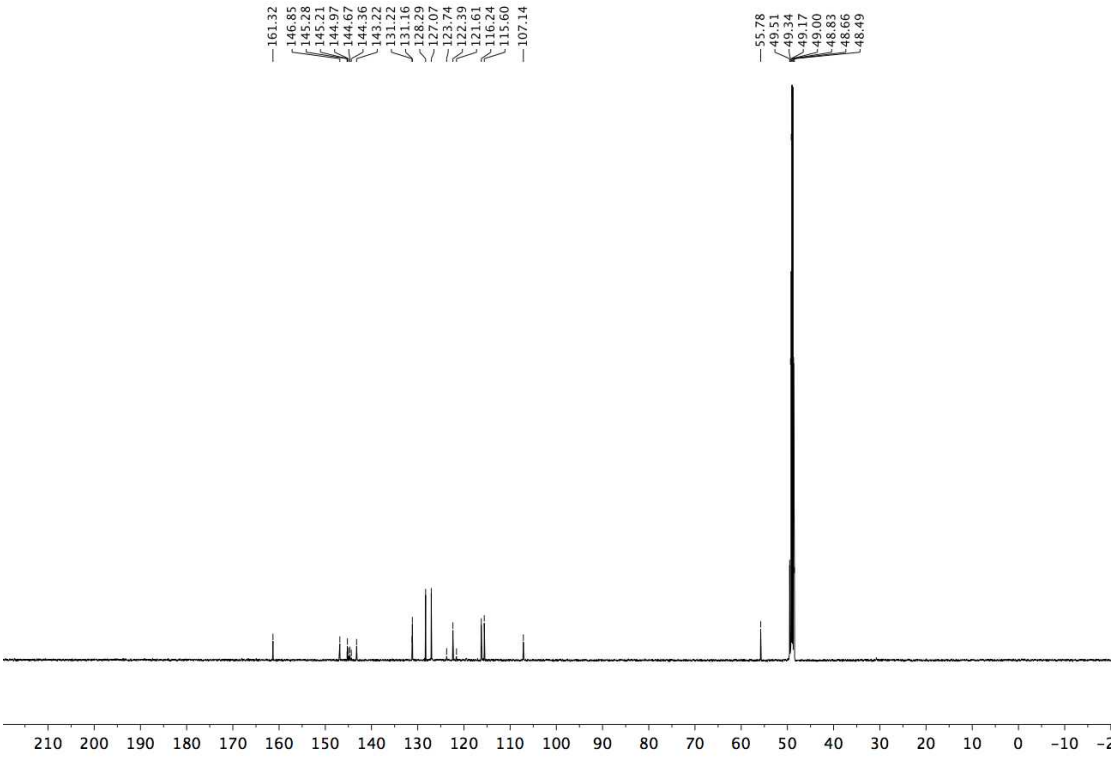

7.95
7.94
7.93
7.93
7.55
7.54
7.53
7.53
7.26
7.17
7.16
7.16
7.14
7.14
6.91
6.91
6.90
6.89
6.88
6.73
3.84
3.07
0.00
CF3
N
N
MeO
SO2Me
1.99
1.98
1.86
1.90
0.91
2.92
3.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
160.54
145.10
144.41
144.10
143.79
143.49
143.34
139.75
130.21
128.51
125.65
122.06
120.70
119.92
114.54
106.24
77.25
77.00
76.75
55.36
44.46
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


7.90
7.90
7.89
7.88
7.88
7.52
7.52
7.51
7.50
7.45
7.45
7.44
7.44
7.44
7.43
7.42
7.42
7.34
7.33
7.32
7.32
7.26
7.07
7.06
7.05
7.05
7.04
7.04
6.84
6.82
6.73
3.39
3.03
0.00
CF3
MeO
N
N
SO2Me
2.00
2.08
0.99
1.11
1.02
0.94
0.83
3.08
2.93
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
156.08
144.59
142.09
139.30
131.81
131.01
128.22
124.08
121.19
117.85
113.03
111.46
107.55
107.53
107.51
107.50
77.25
77.00
76.75
54.88
44.53
0.01
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20


CF3
N
N
C7H15O
SO2Me




7.99
7.98
7.98
7.96
7.96
7.95
7.60
7.59
7.59
7.58
7.57
7.57
7.34
7.32
7.30
7.04
7.02
7.01
7.00
6.99
6.94
6.91
6.89
6.89
6.73
6.72
3.73
2.79
2.76
2.06
2.06
2.05
2.05
2.04
0.00
CF3
N
N
MeO
SO2NH2
1.99
2.09
1.03
0.94
1.04
1.98
1.02
3.18
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


161.32
146.85
145.28
145.21
144.97
144.67
144.36
143.22
131.22
131.16
128.29
127.07
123.74
122.39
121.61
116.24
115.60
107.14
55.78
49.51
49.34
49.17
49.00
48.83
48.66
48.49
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

7. References

[i] Toreda, D.; Bünzli, A. M.; Pertegás, A.; Junquera-Hernández, J. M.; Constable, E. C.; Zampese, J. A.; Housecroft, C. E.; Ortí, E.; Bolink, H. J. *Chem. Eur. J.* **2013**, *19*, 8597–8609.

[ii] René, O.; Fagnou, K. *Adv. Synth. Catal.* **2010**, *352*, 2116–2120.

[iii] Gao, M.; Wang, M.; Miller, K. D.; Zheng, Q.-H. *Eur. J. Med. Chem.* **2011**, *46*, 4760–4767.