Discovery, synthesis and biological characterization of a series of N-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1H-pyrazol-5-yl)acetamide ethers as novel GIRK1/2 potassium channel activators

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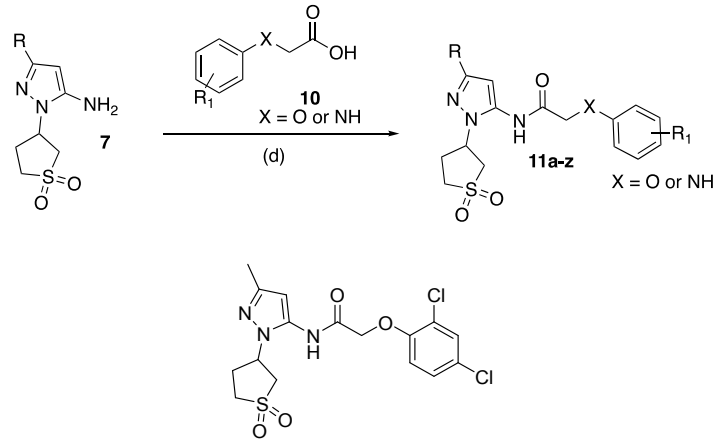
General Experimental Methods.

All ^{1}H & ^{13}C NMR spectra were recorded on Bruker AV-400 (500 MHz) instrument. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δH 3.31 or δC 49.00 (CD_3OD) or δH 2.50 or δC 39.52 ($(CD_3)_2SO$). Data are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. Low resolution mass spectra were obtained on an Agilent 1260 LCMS with electrospray ionization, with a gradient of 5-95% MeCN in 0.1% formic acid water over 4 min. Analytical thin layer chromatography was performed on LuxPlate silica gel 60 F254 plates. Visualization was accomplished with UV light, and/or the use of ninhydrin, anisaldehyde and ceric ammonium molybdate solutions followed by charring on a hot-plate. Chromatography on silica gel was performed using Silica Gel 60Å (230-400 mesh) from Sorbent Technologies. Solvents for extraction, washing and chromatography were HPLC grade. All reagents were purchased from Aldrich Chemical Co. (or similar) and were used without purification. All reagents and solvents were commercial grade and purified prior to use when necessary.

Final compounds were purified on a Gilson preparative reversed-phase HPLC system comprised of a 322 aqueous pump with solvent-selection valve, 334 organic pump, GX-271 liquid hander, two column switching valves, and a 159 UV detector. UV wavelength for fraction collection was user-defined, with absorbance at 254 nm always monitored. Column: Phenomenex Axia-packed Luna C18, 50 x 21.2 mm, 5 μm. For Acidic Method: Mobile phase: CH_3CN in H_2O (0.1% formic acid). Gradient conditions: 2.0 min equilibration, followed by user-defined gradient (starting organic percentage, ending organic percentage, duration, typically 15 mins), hold at 95% CH_3CN in H_2O (0.1% TFA) for 2 min, 20 mL/min, 23 °C.

1. General synthetic procedure

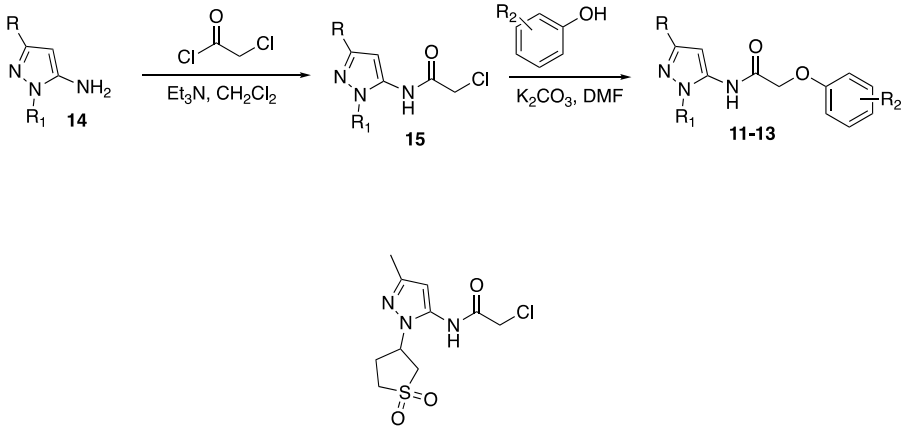
General Procedure: A



2-(2,4-dichlorophenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11a). To a stirred solution of 3-(5-amino-3-methyl-1H-pyrazol-1-yl)tetrahydrothiophene 1,1-dioxide (50 mg, 0.23 mmol), 2-(2,4-dichlorophenoxy)acetic acid (51 mg, 0.23 mmol) and Et_3N (96 µL, 0.69 mmol) in CH_2Cl_2 (1.0 mL) was dropwise added propylphosphonic anhydride solution ≥50 wt. % in ethyl acetate (0.17 mL, 0.27 mmol). The reaction was stirred at RT overnight. The product was partitioned between ethyl acetate (15 mL x 2) and water (15 mL). Organic layers were combined, washed with brine, dried over sodium sulphate, concentrated and purified by reverse phase preparative chromatography (0-100% ACN in water).

Yield = 78 mg (80%, white solid). LCMS: R_T = 2.5 min., >95% @ 215 and 254 nm, *m/z* = 418.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.18 (s, 1H), 7.62 (d, *J* = 2.5 Hz, 1H), 7.39 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.13 (d, *J* = 8.9 Hz, 1H), 6.04 (s, 1H), 5.11 (p, *J* = 8.0 Hz, 1H), 4.93 (s, 2H), 3.58 (dd, *J* = 13.4, 8.4 Hz, 1H), 3.49 (dt, *J* = 12.8, 6.3 Hz, 1H), 3.29 (dd, *J* = 13.4, 8.5 Hz, 1H), 3.18 (dt, *J* = 12.7, 8.5 Hz, 1H), 2.46 (dd, *J* = 11.2, 4.5 Hz, 2H), 2.15 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.89, 152.97, 147.87, 136.05, 129.93, 128.49, 125.62, 122.95, 115.77, 100.14, 67.84, 54.95, 52.13, 51.56, 29.53, 14.43.

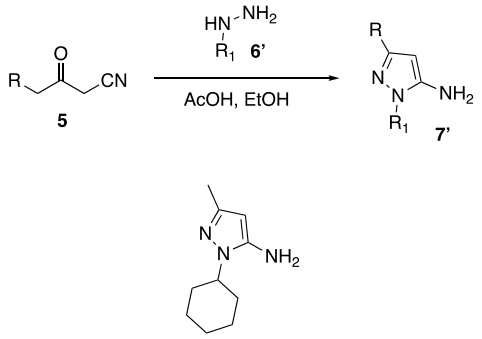
General Procedure: B



2-chloro-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (15). To a stirred solution of 3-(5-amino-3-methyl-1*H*-pyrazol-1-yl)tetrahydrothiophene 1,1-dioxide (0.50 g, 2.3 mmol) and chloroacetyl chloride (0.28 g, 2.6 mmol) in DCM (7.0 mL) under nitrogen, was added TEA (0.97 mL; 7.0 mmol). The reaction was stirred at rt for 2 hours. After checking completion on TLC. The reaction was quenched with saturated $NaHCO_3$ solution (15 mL) and product was extracted with ethyl acetate (30 mL ×2). Combined organic layer was washed with brine, dried over sodium sulfate, concentrated and used as such. Yield = 0.55 g (81%, light brown solid). LCMS: R_T = 2.407 min., >90% @ 215 and 254 nm, *m/z* = 292.0 $[M + H]^+$. ^1H NMR (499 MHz, DMSO-d_6) δ 6.05 (s, 1H), 5.19 – 5.12 (m, 1H), 4.36 (s, 2H), 3.62 – 3.58 (m, 1H), 3.48 (dd, *J* = 12.7, 6.0 Hz, 1H), 3.28 (dd, *J* = 13.4, 8.3 Hz, 1H), 3.23 – 3.15 (m, 1H), 3.08 (tt, *J* = 12.1, 6.1 Hz, 1H), 2.48 – 2.42 (m, 2H), 2.15 (s, 3H).

Respective chloroacetamide, **15**, (1.0 equiv., 0.10 mmol), phenol (1.0 equiv.) and K_2CO_3 (2.0 equiv.) in DMF (0.50 mL) are stirred at 60 ºC for 6h. After completion of reaction by TLC. Product is separated between water and ethyl acetate. Organic layer is purified using Semi-prep-HPLC (Reverse phase) to yield the final compounds.

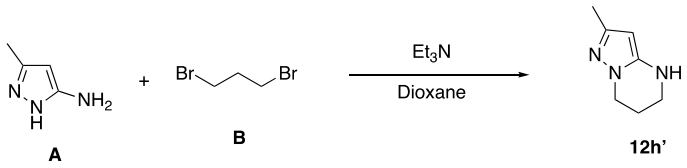
General Procedure: C



1-cyclohexyl-3-methyl-1*H*-pyrazol-5-amine. In a 250 mL RBF, 3-aminobut-2-enenitrile (2.0 g, 0.24 mole) was added to a stirred solution of cyclohexyl hydrazine hydrochloride (4.0 g, 0.030 mol) and acetic acid (0.10 mL) in ethanol (60 mL). The reaction was refluxed for 6 h. Crude was evaporated and loaded on column to elute out product at 40% ethyl acetate in hexane.

Yield = 1.7 g (40%, yellow solid). LCMS: R_T = 1.50 min., >98% @ 215 and 254 nm, *m/z* = 180.1 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 5.02 (s, 1H), 4.92 (s, 2H), 3.86 – 3.78 (m, 1H), 1.94 (s, 3H), 1.78 – 1.68 (m, 4H), 1.63 (dd, *J* = 16.3, 7.4 Hz, 3H), 1.31 (q, *J* = 12.9 Hz, 2H), 1.18 – 1.08 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 145.90, 144.64, 87.80, 53.50, 32.13, 25.21, 25.05, 14.02.

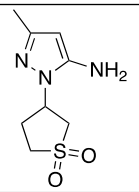
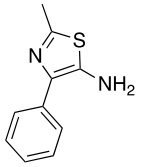
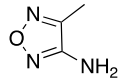
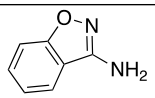
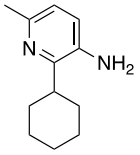
General Procedure: D



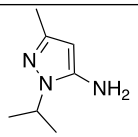
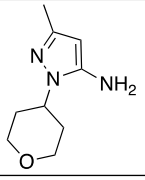
2-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine. A mixture of 3-methyl-1*H*-pyrazol-5-amine (0.67 g, 6.9 mmol), dibromo propane (0.76 mL, 7.59 mmol) and TEA (2.9 mL, 20.78 mmol) in Dioxane (5.0 mL) was stirred at 80 ºC for 12 hours. Volatiles were evaporated under vacuum and loaded on silica gel. Product was eluted out by flash chromatography at 50% Ethyl acetate in hexane. Yield = 0.48 g (50%, light brown solid). LCMS: R_T = 1.50 min., >90% @ 215 and 254 nm, *m/z* = 138.0 $[M + H]^+$. ^{1}H NMR ^{1}H

NMR (499 MHz, CD_3CN) δ 5.10 (s, 1H), 3.92 (t, J = 6.2 Hz, 2H), 3.21 – 3.17 (m, 2H), 2.05 (s, 3H), 2.04 – 2.00 (m, 2H). ^{13}C NMR (126 MHz, CD_3CN) δ 146.70, 146.33, 85.76, 44.53, 39.35, 22.28, 12.87.

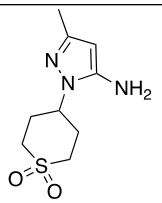
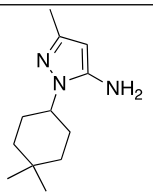
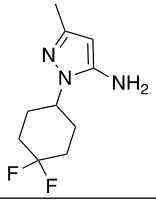
The following left-hand amine portions were commercially available:

11a’		3-(5-amino-3-methyl-1*H*-pyrazol-1-yl)tetrahydrothiophene 1,1-dioxide
12a’		2-methyl-4-phenylthiazol-5-amine
12b’		4-methyl-1,2,5-oxadiazol-3-amine
12c’		benzo[*d*]isoxazol-3-amine
12d’		2-cyclohexyl-6-methylpyridin-3-amine

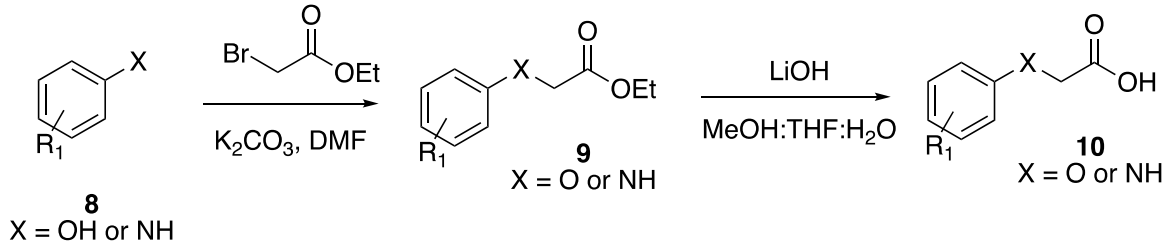
The following left-hand amine portions were previously synthesized and reported in *ACS Chem. Neurosci.* **2017**, *8*, 1873.

13a’		1-isopropyl-3-methyl-1*H*-pyrazol-5-amine
13f’		3-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-5-amine

The following left-hand amine portions were previously synthesized and reported in *Bioorg. Med. Chem. Lett.* **2019**, *29*, 791.

13b’		4-(5-amino-3-methyl-1*H*-pyrazol-1-yl)tetrahydro-2*H*-thiopyran 1,1-dioxide
13d’		1-(4,4-dimethylcyclohexyl)-3-methyl-1*H*-pyrazol-5-amine
13e’		1-(4,4-difluorocyclohexyl)-3-methyl-1*H*-pyrazol-5-amine

General Procedure: D

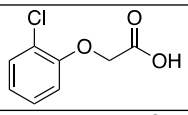
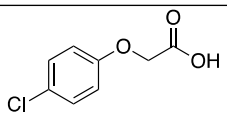
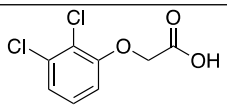
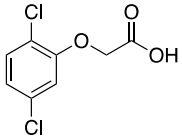
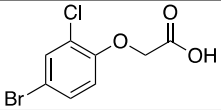
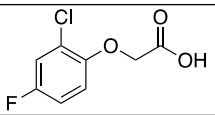
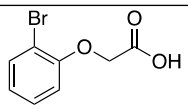
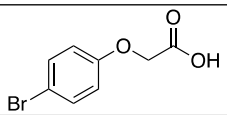
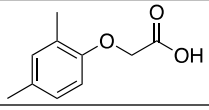
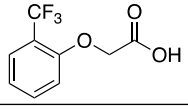
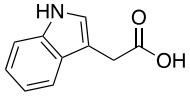
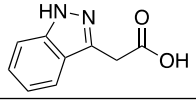


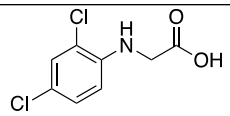
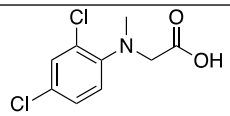
Step 1: In a vial, the substituted phenol or aniline, **8**, (3.9 mmol) and potassium carbonate (1.5 g, 11 mmol) were dissolved in DMF (3.0 mL), followed by the addition of ethyl 2-bromoacetate (0.52 mL, 4.7 mmol). The reaction was stirred at 60 ˚C overnight, then diluted with ethyl acetate and washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was used without further purification.

Step 2: In a vial, the substituted ethyl 2-phenoxyacetate or ethyl 2-phenylglycinate (3.3 mmol), **9**, and lithium hydroxide (0.12 g, 5.0 mmol) were dissolved in 12 mL of a 3:1.5:7.5 mixture of H_2O, methanol, and tetrahydrofuran, respectively. The reaction was stirred overnight at room temperature, then diluted with water and washed with ethyl acetate, the aqueous layer was acidified, and precipitated product was

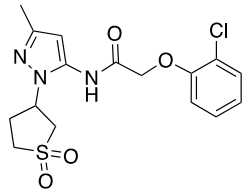
extracted again with ethyl acetate. Organic layer washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Product used as such.

Acids that were prepared via Procedure E and used without further purification utilizing Procedure A to synthesize the final compounds.

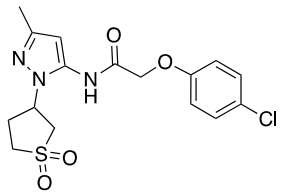
11b”		2-(2-chlorophenoxy)acetic acid
11c”		2-(4-chlorophenoxy)acetic acid
11d”		2-(2,3-dichlorophenoxy)acetic acid
11e”		2-(2,5-dichlorophenoxy)acetic acid
11f”		2-(4-bromo-2-chlorophenoxy)acetic acid
11g”		2-(2-chloro-4-fluorophenoxy)acetic acid
11j”		2-(2-bromophenoxy)acetic acid
11k”		2-(4-bromophenoxy)acetic acid
11n”		2-(2,4-dimethylphenoxy)acetic acid
11p”		2-(2-(trifluoromethyl)phenoxy)acetic acid
11u”		2-(1*H*-indol-3-yl)acetic acid[1]
11v”		2-(1*H*-indazol-3-yl)acetic acid[1]

11w”		(2,4-dichlorophenyl)glycine
11x”		*N*-(2,4-dichlorophenyl)-*N*-methylglycine
[1]Commercially available		

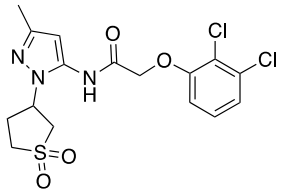
Compound Characterization



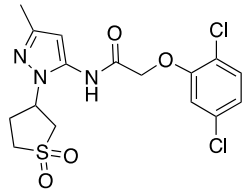
2-(2-chlorophenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11b). Prepared using general procedure A. Yield = 30 mg (78%, white solid). LCMS: R_T = 2.407 min., >98% @ 215 and 254 nm, *m/z* = 384.0 $[M + H]^+$ **.** ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.16 (s, 1H), 7.50 – 7.44 (m, 1H), 7.32 (dd, *J* = 11.5, 4.2 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.05 (s, 1H), 5.11 (p, *J* = 8.1 Hz, 1H), 4.90 (s, 2H), 3.58 (dd, *J* = 13.4, 8.4 Hz, 1H), 3.49 (dt, *J* = 12.9, 6.3 Hz, 1H), 3.32 – 3.25 (m, 1H), 3.17 (dt, *J* = 13.1, 8.5 Hz, 1H), 2.46 (dd, *J* = 15.1, 8.1 Hz, 2H), 2.15 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.61, 154.21, 148.31, 136.57, 131.07, 129.17, 123.17, 122.36, 114.97, 100.61, 68.14, 55.41, 52.59, 52.01, 29.99, 14.89.



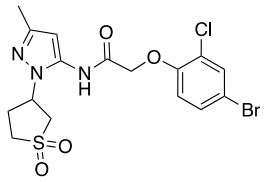
2-(4-chlorophenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11c). Prepared using general procedure A. Yield = 8.5 mg (22%, white solid). LCMS: R_T = 2.444 min., >98% @ 215 and 254 nm, *m/z* = 384.0 $[M + H]^+$ **.** ^{1}H NMR (499 MHz, 499 MHz, DMSO-d_6) δ 10.16 (s, 1H), 7.38 (d, *J* = 8.9 Hz, 2H), 7.04 (d, *J* = 8.9 Hz, 2H), 6.01 (s, 1H), 5.12 – 4.99 (m, 1H), 4.78 (s, 2H), 3.55 (dd, *J* = 13.4, 8.4 Hz, 1H), 3.48 (dt, *J* = 12.8, 6.2 Hz, 1H), 3.27 (dd, *J* = 13.6, 8.4 Hz, 1H), 3.17 (dt, *J* = 13.2, 8.6 Hz, 1H), 2.47 – 2.42 (m, 2H), 2.15 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.71, 156.98, 147.83, 136.03, 129.76, 125.49, 116.97, 100.68, 67.37, 54.97, 52.13, 51.51, 29.56, 14.44.



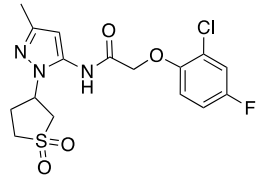
2-(2,3-dichlorophenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11d). Prepared using general procedure A. Yield = 19 mg (46%, yellow oil). LCMS: R_T = 2.553 min., >98% @ 215 and 254 nm, *m/z* = 418.0 $[M + H]^+$. ^{1}H NMR (499 MHz, 499 MHz, DMSO-d_6) δ 10.18 (s, 1H), 7.34 (t, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 6.04 (s, 1H), 5.11 (p, *J* = 8.0 Hz, 1H), 4.96 (s, 2H), 3.58 (dd, *J* = 13.4, 8.4 Hz, 1H), 3.49 (dt, *J* = 12.9, 6.3 Hz, 1H), 3.29 (dd, *J* = 13.4, 8.4 Hz, 1H), 3.18 (dt, *J* = 12.2, 8.6 Hz, 1H), 2.46 (dd, *J* = 15.3, 8.1 Hz, 2H), 2.14 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.84, 155.33, 147.85, 136.09, 132.91, 128.87, 123.13, 120.67, 112.93, 100.13, 67.95, 54.94, 52.12, 51.55, 29.52, 14.43.



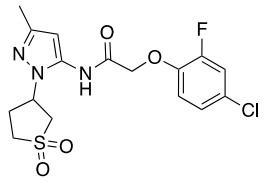
2-(2,5-dichlorophenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11e). Prepared using general procedure A. Yield = 0.30 g (80%, white solid). LCMS: R_T = 2.556 min., >98% @ 215 and 254 nm, *m/z* = 418.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.17 (s, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.24 (d, *J* = 2.1 Hz, 1H), 7.09 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.05 (s, 1H), 5.20 – 5.10 (m, 1H), 4.98 (s, 2H), 3.59 (dd, *J* = 13.5, 8.4 Hz, 1H), 3.54 – 3.45 (m, 1H), 3.29 (d, *J* = 8.4 Hz, 1H), 3.21 – 3.12 (m, 1H), 2.50 – 2.44 (m, 2H), 2.15 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.71, 154.49, 147.88, 136.06, 132.67, 131.57, 122.43, 120.83, 114.88, 100.06, 67.79, 54.94, 52.12, 51.55, 29.56, 14.43.



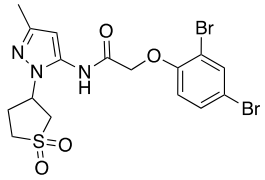
2-(4-bromo-2-chlorophenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11f). Prepared using general procedure A. Yield = 0.47 g (74%, white solid). LCMS: R_T = 2.60 min., >95% @ 215 and 254 nm, *m/z* = 461.9 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.23 (s, 1H), 7.72 (d, *J* = 2.3 Hz, 1H), 7.51 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.07 (d, *J* = 8.9 Hz, 1H), 6.04 (s, 1H), 5.16 – 5.08 (m, 1H), 4.93 (s, 2H), 3.58 (dd, *J* = 13.4, 8.4 Hz, 1H), 3.53 – 3.46 (m, 2H), 3.29 – 3.26 (m, 1H), 3.18 (dt, *J* = 13.2, 8.6 Hz, 1H), 2.46 (M, 2H), 2.14 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.84, 153.39, 147.87, 136.06, 132.56, 131.40, 123.26, 116.25, 112.96, 100.09, 67.75, 54.95, 52.14, 51.56, 29.54, 14.43.



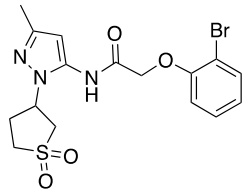
2-(2-chloro-4-fluorophenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11g). Prepared using general procedure A. Yield = 0.29 g (81%, yellow solid). LCMS: R_T = 2.460 min., >95% @ 215 and 254 nm, *m/z* = 402.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.16 (s, 1H), 7.48 (dd, *J* = 8.3, 3.0 Hz, 1H), 7.20 (td, *J* = 8.6, 3.0 Hz, 1H), 7.14 (dd, *J* = 9.2, 4.9 Hz, 1H), 6.04 (s, 1H), 5.11 (p, *J* = 8.0 Hz, 1H), 3.58 (dd, *J* = 13.4, 8.4 Hz, 1H), 3.49 (dt, *J* = 12.9, 6.3 Hz, 1H), 3.29 (dd, *J* = 13.4, 8.4 Hz, 2H), 3.18 (dt, *J* = 13.1, 8.6 Hz, 1H), 2.47 (dd, *J* = 15.4, 8.3 Hz, 3H), 2.15 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.09, 150.63, 147.85, 136.08, 117.86, 115.58, 115.15, 114.97, 100.18, 68.23, 54.95, 52.12, 51.55, 29.53, 14.43.



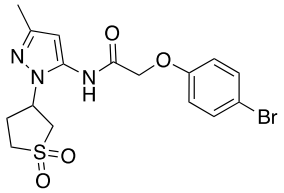
2-(4-chloro-2-fluorophenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11h). Prepared using general procedure B. Yield = 25 mg (36%, white solid). LCMS: R_T = 2.43 min., >95% @ 215 and 254 nm, *m/z* = 402.0 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.23 (dd, *J* = 10.7, 2.2 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.00 (t, *J* = 8.8 Hz, 1H), 6.03 (s, 1H), 4.93 – 4.84 (m, 1H), 4.72 (s, 2H), 3.61 (ddd, *J* = 14.2, 11.1, 7.7 Hz, 2H), 3.51 (dd, *J* = 13.4, 7.9 Hz, 1H), 3.21 – 3.12 (m, 1H), 2.78 (dq, *J* = 16.2, 8.1 Hz, 1H), 2.66 (td, *J* = 13.8, 6.9 Hz, 1H), 2.27 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.06, 153.37, 151.38, 149.36, 143.81, 143.72, 133.62, 128.35, 125.02, 124.99, 117.78, 117.61, 116.84, 101.59, 68.97, 54.66, 52.37, 50.97, 29.06, 14.10.



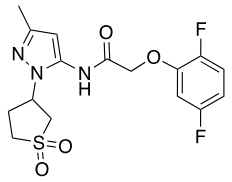
2-(2,4-dibromophenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11i). Prepared using general procedure B. Yield = 43 mg (50%, off-white solid). LCMS: R_T = 2.62 min., >95% @ 215 and 254 nm, *m/z* = 505.9 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.17 (s, 1H), 7.84 (d, *J* = 2.1 Hz, 1H), 7.55 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 1H), 6.05 (s, 1H), 5.16 – 5.08 (m, 1H), 4.92 (s, 2H), 3.58 (dd, *J* = 13.4, 8.3 Hz, 1H), 3.49 (M, 1H), 3.30 – 3.25 (m, 1H), 3.18 (dt, *J* = 13.0, 8.5 Hz, 1H), 2.14 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.77, 154.30, 147.87, 136.04, 135.27, 131.97, 116.10, 113.37, 112.66, 100.06, 67.93, 54.95, 52.13, 51.56, 29.53, 14.42



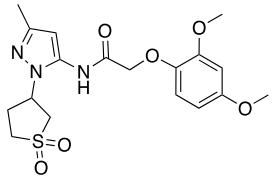
2-(2-bromophenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11j). Prepared using general procedure A. Yield = 4.7 mg (11%, white solid). LCMS: R_T = 2.452 min., >95% @ 215 and 254 nm, *m/z* = 428.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.16 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 5.17 – 5.08 (m, 1H), 4.89 (s, 1H), 3.58 (dd, *J* = 13.4, 8.4 Hz, 1H), 3.49 (dt, *J* = 12.8, 6.3 Hz, 1H), 3.27 (dd, *J* = 16.4, 7.7 Hz, 1H), 3.17 (dt, *J* = 13.6, 8.7 Hz, 1H), 2.49 – 2.44 (m, 1H), 2.14 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.58, 154.15, 147.37, 135.64, 133.15, 128.90, 122.74, 113.96, 111.01, 99.60, 67.38, 54.47, 51.65, 51.08, 29.04, 13.94



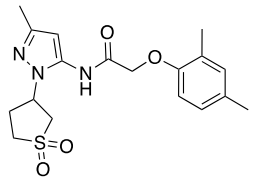
2-(4-bromophenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11k). Prepared using general procedure A. Yield = 10 mg (24%, white solid). LCMS: R_T = 2.485 min., >98% @ 215 and 254 nm, *m/z* = 428.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.15 (s, 1H), 7.50 (d, *J* = 8.9 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 2H), 6.01 (s, 1H), 5.10 – 5.01 (m, 1H), 4.77 (s, 2H), 3.55 (dd, *J* = 13.4, 8.4 Hz, 1H), 3.48 (dt, *J* = 12.8, 6.3 Hz, 1H), 3.27 (dd, *J* = 13.6, 8.5 Hz, 2H), 3.17 (dt, *J* = 13.1, 8.6 Hz, 1H), 2.47 – 2.41 (m, 3H), 2.15 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.69, 157.45, 147.81, 132.65, 117.49, 113.21, 100.65, 67.32, 54.96, 52.11, 51.51, 29.56, 14.44.



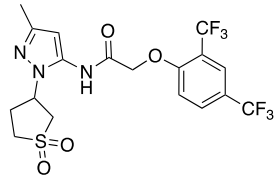
2-(2,5-difluorophenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11l). Prepared using general procedure B. Yield = 22 mg (33%, off-white solid). LCMS: R_T = 2.31 min., >95% @ 215 and 254 nm, *m/z* = 386.0 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.16 (td, *J* = 9.6, 5.1 Hz, 1H), 6.85 – 6.75 (m, 1H), 6.03 (s, 1H), 4.92 – 4.84 (m, 1H), 4.72 (s, 1H), 3.68 – 3.56 (m, 1H), 3.50 (dd, *J* = 13.4, 7.8 Hz, 1H), 3.20 – 3.12 (m, 1H), 2.77 (dq, *J* = 16.2, 8.1 Hz, 1H), 2.66 (td, *J* = 13.8, 6.8 Hz, 1H), 2.27 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.81, 149.36, 133.52, 117.27, 117.19, 117.11, 117.03, 109.67, 109.62, 109.48, 109.43, 104.25, 104.03, 101.59, 68.77, 54.69, 52.35, 50.97, 29.11, 14.12.



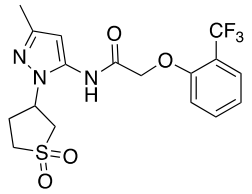
2-(2,4-dimethoxyphenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11m). Prepared using general procedure B. Yield = 26 mg (37%, yellow solid). LCMS: R_T = 2.90 min., >95% @ 215 and 254 nm, *m/z* = 410.1 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.83 (s, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 6.58 (t, *J* = 6.0 Hz, 1H), 6.48 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.00 (s, 1H), 4.90 – 4.82 (m, 1H), 4.66 (s, 2H), 3.90 (s, 3H), 3.82 (s, 3H), 3.66 – 3.56 (m, 2H), 3.48 (dd, *J* = 13.4, 7.9 Hz, 1H), 3.17 – 3.09 (m, 1H), 2.78 (td, *J* = 16.1, 8.0 Hz, 1H), 2.64 (td, *J* = 13.8, 6.9 Hz, 1H), 2.27 (s, 3H). (10-15% rotamers observed). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.88, 156.54, 150.66, 149.27, 141.15, 134.50, 117.78, 104.17, 101.01, 100.76, 71.04, 56.17, 55.73, 54.64, 52.33, 50.98, 29.03, 14.05.



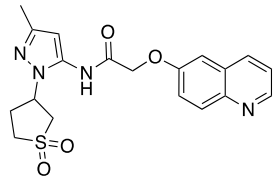
2-(2,4-dimethylphenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11n). Prepared using general procedure A. Yield = 25 mg (48%, off-white solid). LCMS: R_T = 2.49 min., >95% @ 215 and 254 nm, *m/z* = 378.1 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.00 (s, 1H), 6.98 (d, *J* = 9.7 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.02 (s, 1H), 5.06 – 4.97 (m, 1H), 4.72 (s, 2H), 3.56 – 3.49 (m, 1H), 3.46 (dd, *J* = 12.9, 6.4 Hz, 1H), 3.27 (dd, *J* = 13.4, 8.3 Hz, 1H), 3.14 (dt, *J* = 13.1, 8.6 Hz, 1H), 2.43 (dd, *J* = 16.0, 8.3 Hz, 2H), 2.22 (d, *J* = 5.1 Hz, 6H), 2.15 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 168.22, 154.23, 147.80, 136.11, 131.88, 130.21, 127.46, 126.44, 111.92, 100.66, 67.65, 54.93, 52.12, 51.49, 29.51, 20.53, 16.55, 14.43.



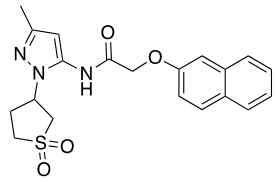
2-(2,4-bis(trifluoromethyl)phenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11o). Prepared using general procedure B. Yield = 22 mg (17%, white solid). LCMS: R_T = 2.70 min., >95% @ 215 and 254 nm, *m/z* = 486.1 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.96 (s, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 6.10 (s, 1H), 4.88 (d, *J* = 7.0 Hz, 1H), 4.85 (s, 2H), 3.70 – 3.57 (m, 3H), 3.51 (dd, *J* = 13.5, 7.8 Hz, 1H), 3.21 – 3.12 (m, 1H), 2.78 (td, *J* = 16.1, 8.0 Hz, 1H), 2.67 (td, *J* = 13.8, 6.9 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.43, 156.41, 149.47, 133.48, 131.55, 125.39, 124.86, 124.07, 121.89, 119.46, 113.30, 101.15, 67.44, 54.61, 52.33, 50.93, 29.13, 14.08.



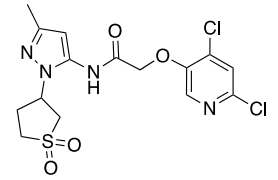
***N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1H-pyrazol-5-yl)-2-(2-(trifluoromethyl)phenoxy)acetamide (11p).** Prepared using general procedure A. Yield = 16 mg (38%, white solid). LCMS: R_T = 2.513 min., >98% @ 215 and 254 nm, *m/z* = 418.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.18 (s, 1H), 7.68 – 7.60 (m, 2H), 7.20 (d, *J* = 8.3 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.06 (s, 1H), 5.13 (p, *J* = 8.1 Hz, 1H), 4.97 (s, 2H), 3.58 (dd, *J* = 13.4, 8.4 Hz, 1H), 3.50 (dt, *J* = 12.9, 6.3 Hz, 1H), 3.31 – 3.27 (m, 1H), 3.17 (dt, *J* = 13.1, 8.5 Hz, 1H), 2.46 (dd, *J* = 11.2, 5.0 Hz, 2H), 2.14 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.73, 156.26, 147.87, 136.19, 136.03, 134.59, 127.34, 121.41, 114.23, 99.87, 67.39, 54.93, 52.09, 51.55, 29.54, 14.42.



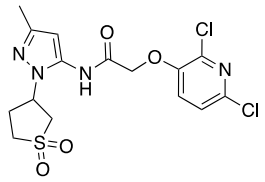
***N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)-2-(quinolin-6-yloxy)acetamide (11q).** Prepared using general procedure B. Yield = 16 mg (19%, clear oil). LCMS: R_T = 1.71 min., >95% @ 215 and 254 nm, *m/z* = 401.1 $[M + H]^+$. ^{1}H NMR (499 MHz, CD_3CN) δ 8.81 (d, *J* = 3.5 Hz, 1H), 8.79 (s, 1H), 8.32 (d, *J* = 8.2 Hz, 1H), 8.14 (d, *J* = 9.2 Hz, 1H), 7.63 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.54 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.42 (d, *J* = 2.7 Hz, 1H), 6.01 (s, 1H), 5.04 – 4.95 (m, 1H), 4.85 (s, 2H), 3.49 – 3.40 (m, 2H), 3.36 (dd, *J* = 13.7, 7.8 Hz, 1H), 3.08 – 3.00 (m, 1H), 2.56 (dd, *J* = 8.3, 5.2 Hz, 1H), 2.52 – 2.47 (m, 1H), 2.22 (s, 3H). ^{13}C NMR (126 MHz, CD_3CN) δ 167.83, 155.71, 148.45, 147.65, 136.29, 134.85, 129.89, 129.37, 122.65, 121.92, 107.17, 101.39, 67.33, 54.69, 52.18, 51.04, 29.26, 13.24.



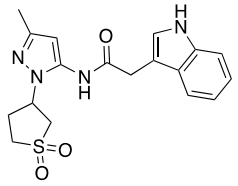
***N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)-2-(naphthalen-2-yloxy)acetamide (11r).** Prepared using general procedure B. Yield = 17 mg (21%, yellow oil). LCMS: R_T = 2.45 min., >95% @ 215 and 254 nm, *m/z* = 400.1 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.20 (s, 1H), 7.91 – 7.80 (m, 1H), 7.52 – 7.46 (m, 1H), 7.40 – 7.35 (m, 1H), 7.32 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.03 (s, 1H), 5.10 – 5.04 (m, 1H), 4.89 (s, 1H), 3.55 (dd, *J* = 13.4, 8.5 Hz, 1H), 3.48 – 3.41 (m, 1H), 3.31 – 3.25 (m, 1H), 3.10 (dt, *J* = 13.1, 8.7 Hz, 1H), 2.46 – 2.38 (m, 1H), 2.15 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.91, 155.97, 147.83, 136.06, 134.46, 129.93, 129.26, 128.03, 127.23, 127.04, 124.45, 119.07, 107.70, 100.81, 67.29, 54.96, 52.15, 51.45, 29.58, 14.44.



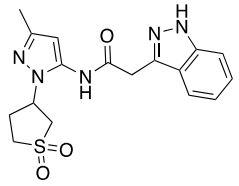
2-((4,6-dichloropyridin-3-yl)oxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11s). Prepared using general procedure B. Yield = 14 mg (33%, white solid). LCMS: R_T = 2.28 min., >95% @ 215 and 254 nm, *m/z* = 419.0 $[M + H]^+$. ^{1}H NMR (499 MHz, CD_3CN) δ 8.19 (s, 1H), 7.59 (s, 1H), 6.04 (s, 1H), 5.04 – 4.97 (m, 1H), 4.89 (s, 2H), 3.48 (ddd, *J* = 15.5, 13.7, 7.6 Hz, 2H), 3.39 (dd, *J* = 13.6, 7.9 Hz, 1H), 3.12 (dt, *J* = 13.2, 8.2 Hz, 1H), 2.61 – 2.52 (m, 2H), 2.22 (s, 3H). ^{13}C NMR (126 MHz, CD_3CN) δ 166.71, 150.00, 148.53, 143.56, 135.73, 134.65, 134.54, 125.15, 101.07, 68.56, 54.64, 52.20, 51.06, 29.20, 13.20.



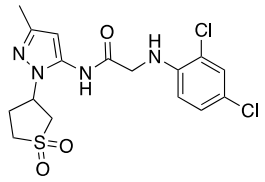
2-((2,6-dichloropyridin-3-yl)oxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11t). Prepared using general procedure B. Yield = 22 mg (15%, clear oil). LCMS: R_T = 2.30 min., >95% @ 215 and 254 nm, *m/z* = 419.0 $[M + H]^+$. ^{1}H NMR (499 MHz, CD_3CN) δ 7.50 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 6.03 (s, 1H), 4.99 (dt, *J* = 15.4, 7.8 Hz, 1H), 4.85 (d, *J* = 15.3 Hz, 2H), 3.52 – 3.43 (m, 2H), 3.38 (dd, *J* = 13.6, 7.9 Hz, 1H), 3.12 (dt, *J* = 13.2, 8.2 Hz, 1H), 2.61 – 2.52 (m, 2H), 2.21 (s, 3H). ^{13}C NMR (126 MHz, CD_3CN) δ 166.75, 149.68, 148.51, 140.70, 138.92, 134.61, 125.04, 124.04, 101.08, 68.20, 54.64, 52.20, 51.05, 29.17, 13.20.



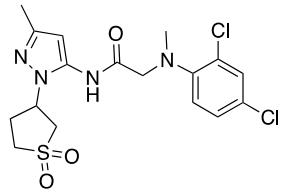
***N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)-2-(1*H*-indol-3-yl)acetamide (11u).** Prepared using general procedure A. Yield = 12 mg (23%, clear oil). LCMS: R_T = 2.47 min., >95% @ 215 and 254 nm, *m/z* = 373.1 $[M + H]^+$. ^{1}H NMR (499 MHz, CD_3CN) δ 9.44 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 2H), 7.44 (t, *J* = 11.3 Hz, 2H), 7.29 (s, 2H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 2H), 5.90 (s, 2H), 4.82 – 4.74 (m, 2H), 3.84 (s, 4H), 3.42 – 3.29 (m, 5H), 2.95 (ddd, *J* = 13.2, 9.0, 7.6 Hz, 2H), 2.50 – 2.44 (m, 2H), 2.38 (dd, *J* = 13.6, 7.0 Hz, 2H), 2.17 (s, 5H). ^{13}C NMR (126 MHz, CD_3CN) δ 171.43, 148.24, 135.99, 127.26, 124.47, 124.31, 121.82, 119.28, 118.42, 111.57, 111.52, 100.79, 100.76, 54.54, 52.07, 51.01, 32.88, 29.13, 13.20.



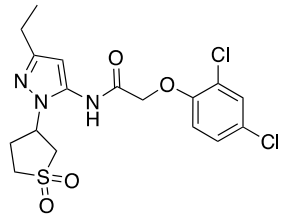
***N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)-2-(1*H*-indazol-3-yl)acetamide (11v).** Prepared using general procedure A. Yield = 21 mg (16%, clear oil). LCMS: R_T = 2.04min., >95% @ 215 and 254 nm, *m/z* = 374.1 $[M + H]^+$. ^{1}H NMR (499 MHz, CD_3CN) δ 8.64 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 5.97 (s, 1H), 5.05 – 4.97 (m, 1H), 4.10 (s, 2H), 3.43 (td, *J* = 13.6, 7.7 Hz, 2H), 3.38 – 3.30 (m, 1H), 3.05 (dt, *J* = 13.2, 8.2 Hz, 1H), 2.55 – 2.45 (m, 3H), 2.18 (s, 3H). ^{13}C NMR (126 MHz, CD_3CN) δ 169.26, 148.28, 141.24, 139.97, 135.94, 126.70, 122.16, 120.59, 119.96, 110.29, 100.60, 54.65, 52.17, 51.09, 34.63, 29.13, 13.24.



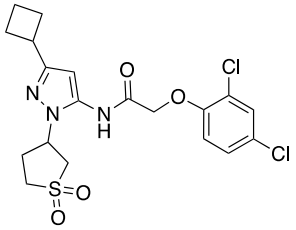
2-((2,4-dichlorophenyl)amino)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11w). Prepared using general procedure A. Yield = 13 mg (13%, clear oil). LCMS: R_T = 2.51 min., >95% @ 215 and 254 nm, *m/z* = 417.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.09 (s, 1H), 7.41 (d, *J* = 2.3 Hz, 1H), 7.22 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.62 (d, *J* = 8.8 Hz, 1H), 6.00 (s, 1H), 5.93 (t, *J* = 5.8 Hz, 1H), 5.11 – 5.03 (m, 1H), 4.06 (d, *J* = 5.8 Hz, 1H), 3.56 (dd, *J* = 13.4, 8.4 Hz, 1H), 3.49 (dt, *J* = 12.8, 6.3 Hz, 1H), 3.28 (dd, *J* = 13.4, 8.4 Hz, 1H), 3.16 (dt, *J* = 13.1, 8.5 Hz, 1H), 2.45 (dd, *J* = 14.8, 7.6 Hz, 2H), 2.14 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.42, 147.80, 143.40, 136.56, 128.74, 128.30, 120.15, 118.99, 112.86, 99.98, 54.95, 52.11, 51.53, 46.52, 29.52, 14.44.



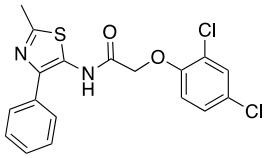
2-((2,4-dichlorophenyl)(methyl)amino)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (11x). Prepared using general procedure A. Yield = 29 mg (67%, white solid). LCMS: R_T = 2.617 min., >95% @ 215 and 254 nm, *m/z* = 431.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 9.95 (s, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.35 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 6.00 (s, 1H), 5.02 (p, *J* = 7.9 Hz, 1H), 3.56 (dd, *J* = 13.4, 8.3 Hz, 1H), 3.48 (dt, *J* = 13.0, 6.4 Hz, 1H), 3.31 – 3.24 (m, 1H), 3.17 (dt, *J* = 13.2, 8.4 Hz, 1H), 2.90 (s, 3H), 2.45 (dd, *J* = 14.9, 7.7 Hz, 2H), 2.13 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.11, 148.02, 147.73, 136.58, 130.08, 128.03, 127.43, 126.66, 123.50, 100.01, 57.80, 54.96, 52.13, 51.46, 41.45, 29.49, 14.42.



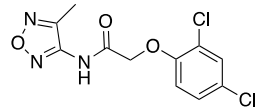
2-(2,4-dichlorophenoxy)-*N*-(1-(1,1-dioxidotetrahydrothiophen-3-yl)-3-ethyl-1*H*-pyrazol-5-yl)acetamide (11y). Prepared using general procedure A. Yield = 5.8 mg (10%, white solid). LCMS: R_T = 2.704 min., >95% @ 215 and 254 nm, *m/z* = 432.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.23 (s, 1H), 7.62 (d, *J* = 2.5 Hz, 1H), 7.39 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.13 (d, *J* = 8.9 Hz, 1H), 6.08 (s, 1H), 5.19 – 5.08 (m, 1H), 4.93 (s, 2H), 3.58 (dd, *J* = 13.4, 8.3 Hz, 1H), 3.49 (dt, *J* = 12.8, 6.3 Hz, 1H), 3.33 – 3.31 (m, 4H), 3.31 – 3.26 (m, 1H), 3.18 (dt, *J* = 13.1, 8.6 Hz, 1H), 2.50 – 2.43 (m, 3H), 1.15 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.87, 153.71, 152.98, 129.90, 128.48, 125.57, 122.93, 115.75, 98.58, 67.86, 54.96, 52.17, 51.58, 29.54, 21.94, 13.93.



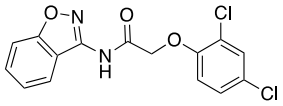
***N*-(3-cyclobutyl-1-(1,1-dioxidotetrahydrothiophen-3-yl)-1*H*-pyrazol-5-yl)-2-(2,4-dichlorophenoxy)acetamide (11z).** Prepared using general procedure A. Yield = 9.0 mg (20%, off-white solid). LCMS: R_T = 2.812 min., >95% @ 215 and 254 nm, *m/z* = 458.1 $[M + H]^+$.^{1}H NMR (499 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.47 (d, *J* = 2.3 Hz, 1H), 7.30 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.14 (s, 1H), 4.90 (d, *J* = 7.7 Hz, 1H), 4.70 (s, 2H), 3.69 – 3.53 (m, 2H), 3.48 (p, *J* = 8.1 Hz, 2H), 3.19 – 3.09 (m, 1H), 2.78 (dq, *J* = 16.0, 8.0 Hz, 1H), 2.64 (td, *J* = 13.8, 6.9 Hz, 1H), 2.31 (td, *J* = 11.3, 2.7 Hz, 2H), 2.17 (p, *J* = 9.1 Hz, 2H), 2.00 (dq, *J* = 18.0, 9.0 Hz, 1H), 1.88 (dd, *J* = 19.8, 8.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.81, 157.95, 151.40, 133.85, 130.81, 128.72, 128.67, 124.07, 115.21, 99.30, 68.55, 55.02, 52.81, 51.32, 34.73, 29.45, 29.41, 19.02.



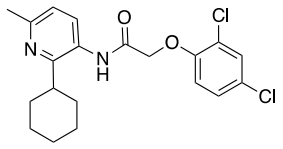
2-(2,4-dichlorophenoxy)-*N*-(2-methyl-4-phenylthiazol-5-yl)acetamide (12a). Prepared using general procedure A. Yield = 15 mg (24%, light yellow solid). LCMS: R_T = 2.98 min., >95% @ 215 and 254 nm, *m/z* = 393.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.51 (s, 1H), 7.74 (d, *J* = 7.3 Hz, 2H), 7.63 (d, *J* = 2.5 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.39 (dt, *J* = 11.2, 5.0 Hz, 2H), 7.13 (d, *J* = 8.9 Hz, 1H), 4.96 (s, 2H), 2.61 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.45, 159.36, 152.72, 141.40, 134.33, 129.90, 129.11, 128.53, 128.32, 128.12, 127.85, 125.66, 122.87, 115.59, 67.80, 19.17.



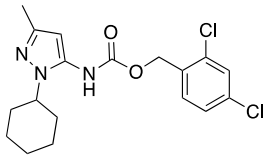
2-(2,4-dichlorophenoxy)-*N*-(4-methyl-1,2,5-oxadiazol-3-yl)acetamide (12b). Prepared using general procedure A. Yield = 29 mg (67%, white solid). LCMS: R_T = 2.60 min., >95% @ 215 and 254 nm, *m/z* = 302.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 11.02 (s, 1H), 7.62 (d, *J* = 2.5 Hz, 1H), 7.39 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.13 (d, *J* = 8.9 Hz, 1H), 5.03 (s, 2H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.25, 152.86, 150.75, 148.73, 129.93, 128.48, 125.66, 122.92, 115.71, 67.56, 8.89.



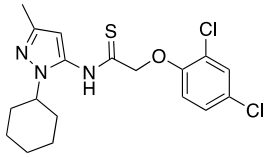
***N*-(benzo[*d*]isoxazol-3-yl)-2-(2,4-dichlorophenoxy)acetamide (12c).** Prepared using general procedure A. Yield = 29 mg (67%, off-white solid) LCMS: R_T = 2.82 min., >95% @ 215 and 254 nm, *m/z* = 336.9 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 11.41 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.73 – 7.65 (m, 2H), 7.63 (d, *J* = 2.5 Hz, 1H), 7.39 (dt, *J* = 7.1, 4.3 Hz, 2H), 7.17 (d, *J* = 8.9 Hz, 1H), 5.10 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.44, 153.45, 152.99, 131.36, 129.90, 128.50, 125.52, 123.90, 122.86, 116.33, 115.67, 110.40, 67.65.



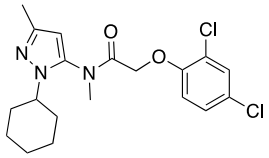
***N*-(2-cyclohexyl-6-methylpyridin-3-yl)-2-(2,4-dichlorophenoxy)acetamide (12d).** Prepared using general procedure A. Yield = 20 mg (20%, off-white solid). LCMS: R_T = 2.86 min., >95% @ 215 and 254 nm, *m/z* = 393.0 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.59 (s, 1H), 7.47 (d, *J* = 2.5 Hz, 1H), 7.27 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 5.90 (s, 1H), 4.66 (s, 2H), 2.55 (d, *J* = 12.5 Hz, 3H), 2.36 (d, *J* = 1.8 Hz, 2H), 2.15 (dd, *J* = 6.0, 2.6 Hz, 2H), 1.81 – 1.75 (m, 2H), 1.71 – 1.65 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.54, 151.55, 151.03, 130.45, 128.11, 128.04, 124.03, 115.08, 68.95, 28.11, 25.26, 22.47, 21.62.



2,4-dichlorobenzyl (1-cyclohexyl-3-methyl-1*H*-pyrazol-5-yl)carbamate (12e). Yield = 20 mg (9.0%, white solid). LCMS: R_T = 2.93 min., >95% @ 215 and 254 nm, *m/z* = 382.0 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 6.80 (s, 1H), 5.96 (s, 1H), 5.27 (s, 2H), 3.88 (m, 1H), 2.24 (s, 3H), 1.87 (m, 5H), 1.68 (m, 1H), 1.36 – 1.21 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.71, 147.16, 135.05, 133.74, 132.01, 129.50, 127.28, 64.36, 56.47, 32.67, 25.72, 25.08, 14.06.

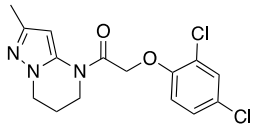


***N*-(1-cyclohexyl-3-methyl-1*H*-pyrazol-5-yl)-2-(2,4-dichlorophenoxy)ethanethioamide (12f).** Yield = 10 mg (18%, light brown oil). LCMS: R_T = 4.55 min. (8 min method), >95% @ 215 and 254 nm, *m/z* = 398.0 $[M + H]^+$. ^{1}H NMR (499 MHz, CD_3OD) δ 7.53 (d, *J* = 2.4 Hz, 1H), 7.34 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.17 (d, *J* = 8.9 Hz, 1H), 6.14 (s, 1H), 5.13 (s, 2H), 3.78 – 3.70 (m, 1H), 2.25 (s, 3H), 1.80 (d, *J* = 22.0 Hz, 6H), 1.68 (s, 1H), 1.23 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 152.22, 147.22, 129.83, 127.78, 126.90, 123.69, 115.37, 100.91, 75.56, 56.66, 32.20, 25.32, 24.91, 12.40.

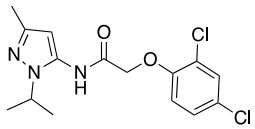


***N*-(1-cyclohexyl-3-methyl-1*H*-pyrazol-5-yl)-2-(2,4-dichlorophenoxy)-*N*-methylacetamide (12g).** Prepared using general procedure A. Yield = 9.4 mg (29%, light yellow oil). LCMS: R_T = 3.08 min., >95% @ 215 and 254 nm, *m/z* = 396.1 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.38 (d, *J* = 2.3 Hz, 1H), 7.15 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 5.94 (s, 1H), 4.61 (d, *J* = 15.1 Hz, 1H), 4.34 (d, *J* = 15.1

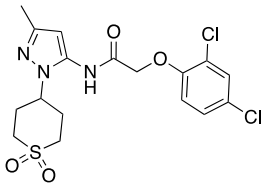
Hz, 1H), 3.87 – 3.78 (m, 1H), 3.23 (s, 3H), 2.29 (s, 3H), 2.14 – 2.04 (m, 1H), 2.00 – 1.89 (m, 3H), 1.82 (s, 2H), 1.75 (d, *J* = 11.0 Hz, 1H), 1.41 – 1.41 (m, 1H), 1.42 – 1.27 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.80, 152.71, 148.22, 137.98, 130.30, 127.50, 127.16, 124.53, 115.38, 101.69, 66.99, 56.45, 36.87, 33.72, 32.76, 25.69, 25.65, 24.93, 14.21.



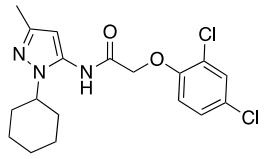
2-(2,4-dichlorophenoxy)-1-(2-methyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-4(5*H*)-yl)ethan-1-one (12h). Prepared using general procedure A. Yield =10 mg (8.0%, light brown solid). LCMS: R_T = 2.63 min., >95% @ 215 and 254 nm, *m/z* = 340.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 7.59 (d, *J* = 2.5 Hz, 1H), 7.33 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 1H), 6.34 (s, 1H), 5.24 (s, 2H), 2.14 (s, 2H), 2.09 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.41, 153.04, 129.70, 128.21, 125.12, 122.59, 115.80, 85.53, 67.07, 44.81, 39.33, 21.89, 14.03.



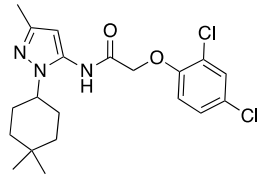
2-(2,4-dichlorophenoxy)-*N*-(1-isopropyl-3-methyl-1*H*-pyrazol-5-yl)acetamide (13a). Prepared using general procedure A. Yield = 22 mg (47%, white solid). LCMS: R_T = 2.61 min., >95% @ 215 and 254 nm, *m/z* = 342.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 9.99 (s, 1H), 7.62 (d, *J* = 2.5 Hz, 1H), 7.40 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.10 (d, *J* = 8.9 Hz, 1H), 5.96 (s, 1H), 4.91 (s, 1H), 4.44 – 4.36 (m, 1H), 2.12 (s, 1H), 1.30 (d, *J* = 6.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.55, 152.97, 146.03, 134.55, 129.90, 128.46, 125.57, 122.96, 115.68, 99.32, 67.95, 48.20, 22.78, 14.43.



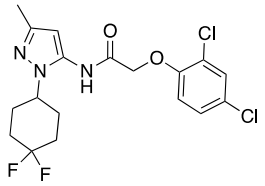
2-(2,4-dichlorophenoxy)-*N*-(1-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (13b). Prepared using general procedure A. Yield = 15 mg (32%, white solid). LCMS: R_T = 2.43 min., >95% @ 215 and 254 nm, *m/z* = 432.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.09 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.64 – 7.54 (m, 2H), 6.03 (s, 1H), 5.83 (s, 1H), 4.52 – 4.46 (m, 1H), 3.30 (d, *J* = 7.2 Hz, 2H), 2.48 – 2.37 (m, 1H), 2.14 (s, 1H), 2.12 (s, 1H), 1.31 – 1.19 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.71, 164.37, 147.07, 134.83, 131.18, 129.82, 126.83, 100.12, 55.27, 51.40, 49.60, 30.24, 22.21, 14.40.



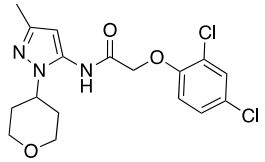
***N*-(1-cyclohexyl-3-methyl-1*H*-pyrazol-5-yl)-2-(2,4-dichlorophenoxy)acetamide (13c).** Prepared using general procedure A. Yield = 26 mg (43%, white solid). LCMS: R_T = 2.88 min., >95% @ 215 and 254 nm, *m/z* = 382.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 9.97 (s, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.40 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.11 (d, *J* = 8.9 Hz, 1H), 5.97 (s, 1H), 3.93 (dt, *J* = 9.8, 5.3 Hz, 1H), 2.11 (s, 1H), 1.82 – 1.68 (m, 3H), 1.64 (d, *J* = 12.5 Hz, 1H), 1.28 (dd, *J* = 25.0, 12.5 Hz, 1H), 1.16 (dd, *J* = 24.8, 12.1 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.47, 152.91, 145.89, 134.59, 129.93, 128.47, 125.58, 122.95, 115.59, 99.13, 68.01, 55.54, 32.88, 25.60, 25.39, 14.39.



2-(2,4-dichlorophenoxy)-*N*-(1-(4,4-dimethylcyclohexyl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (13d). Prepared using general procedure A. Yield = 29 mg (76% off-white solid). LCMS: R_T = 3.15 min., >95% @ 215 and 254 nm, *m/z* = 410.1 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 9.96 (s, 1H), 7.64 (d, *J* = 2.2 Hz, 1H), 7.39 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.12 (d, *J* = 8.9 Hz, 1H), 5.96 (s, 1H), 4.90 (s, 2H), 3.84 (t, *J* = 11.6 Hz, 1H), 2.12 (s, 3H), 1.91 (dd, *J* = 24.1, 11.5 Hz, 2H), 1.56 (d, *J* = 11.4 Hz, 2H), 1.43 (d, *J* = 12.8 Hz, 2H), 1.24 (t, *J* = 12.2 Hz, 2H), 0.95 (d, *J* = 9.8 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.56, 152.88, 145.96, 134.67, 129.96, 128.49, 125.58, 122.95, 115.52, 99.34, 68.00, 55.79, 38.31, 32.94, 29.67, 28.58, 24.30, 14.42.

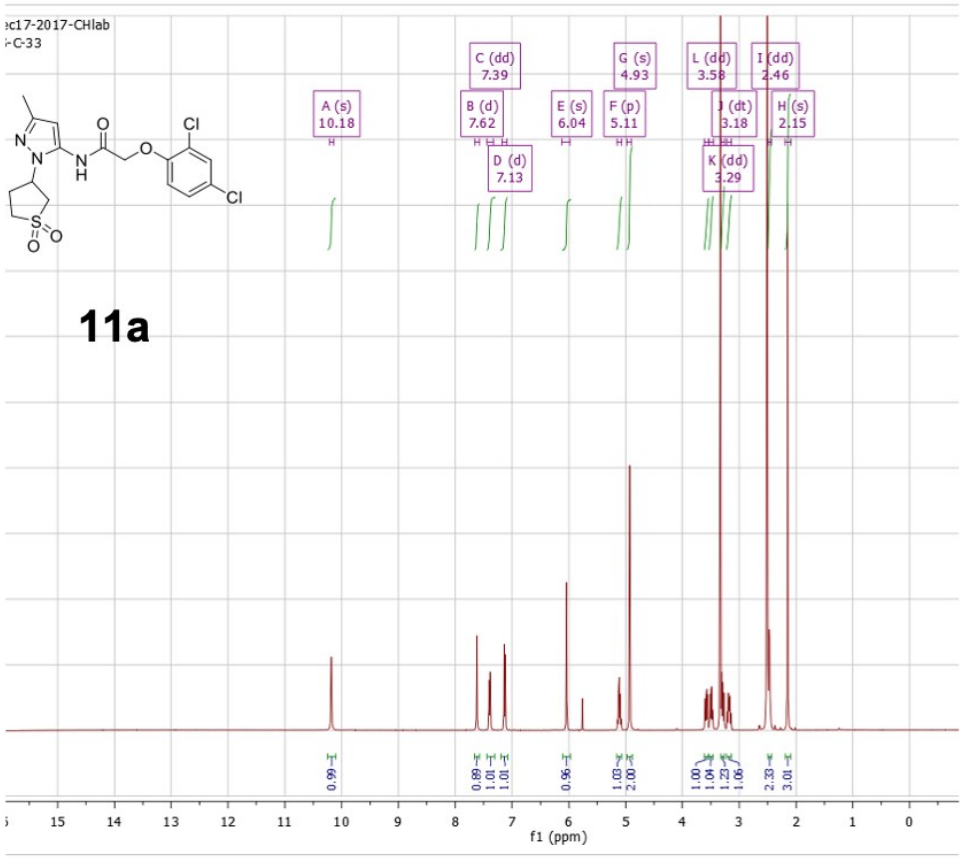


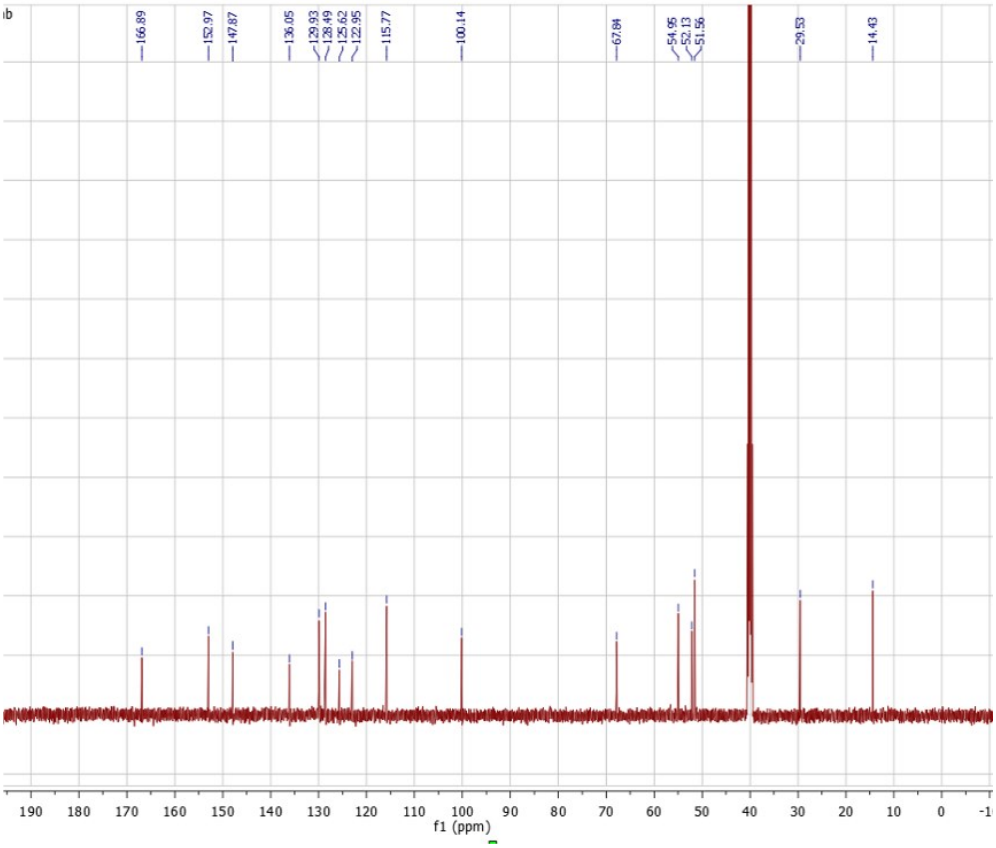
2-(2,4-dichlorophenoxy)-*N*-(1-(4,4-difluorocyclohexyl)-3-methyl-1*H*-pyrazol-5-yl)acetamide (13e). Prepared using general procedure A. Yield = 36 mg (62%, white solid). LCMS: R_T = 2.78 min., >95% @ 215 and 254 nm, *m/z* = 418.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.02 (s, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.41 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.13 (d, *J* = 8.9 Hz, 1H), 5.98 (s, 1H), 4.92 (s, 2H), 4.16 (t, *J* = 10.0 Hz, 1H), 2.13 (d, *J* = 5.3 Hz, 2H), 2.12 (s, 3H), 2.04 – 1.92 (m, 3H), 1.86 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.82, 152.95, 146.45, 135.02, 129.95, 128.48, 125.62, 122.97, 115.66, 99.77, 67.91, 52.78, 32.41, 28.66, 28.58, 14.39.

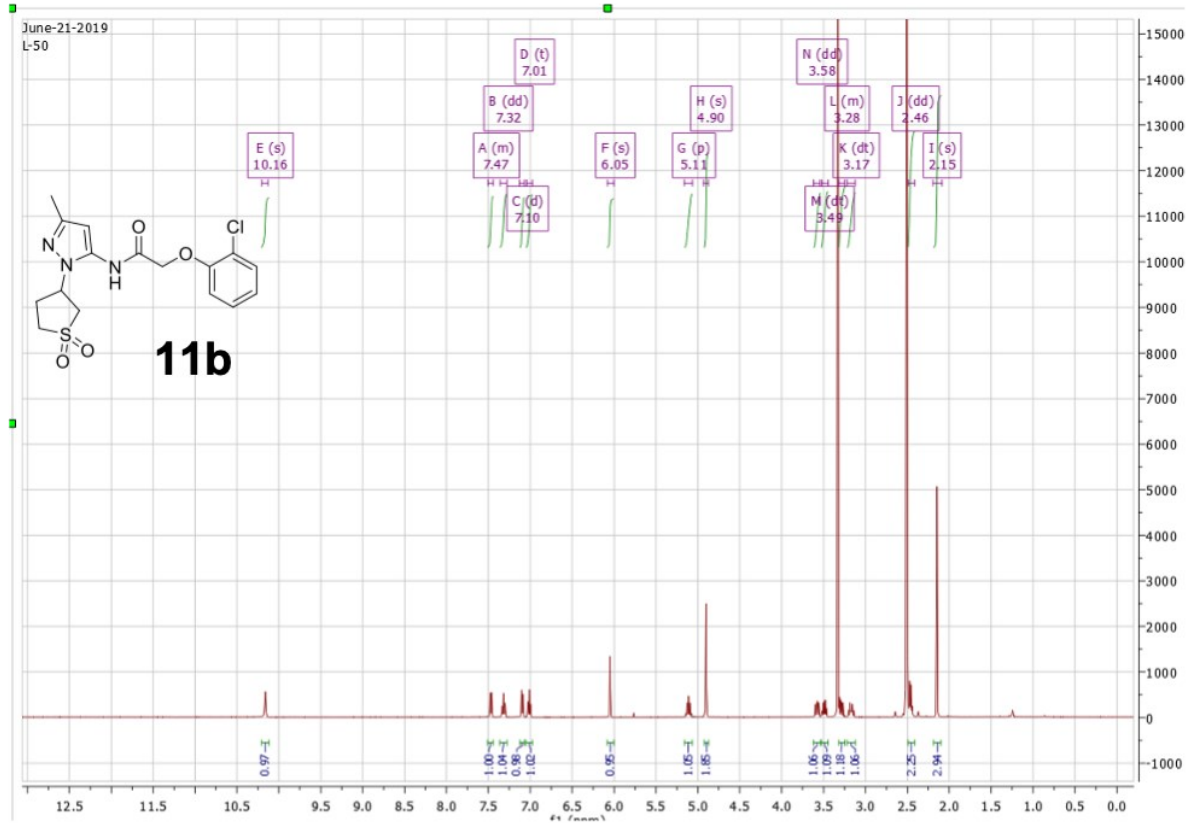


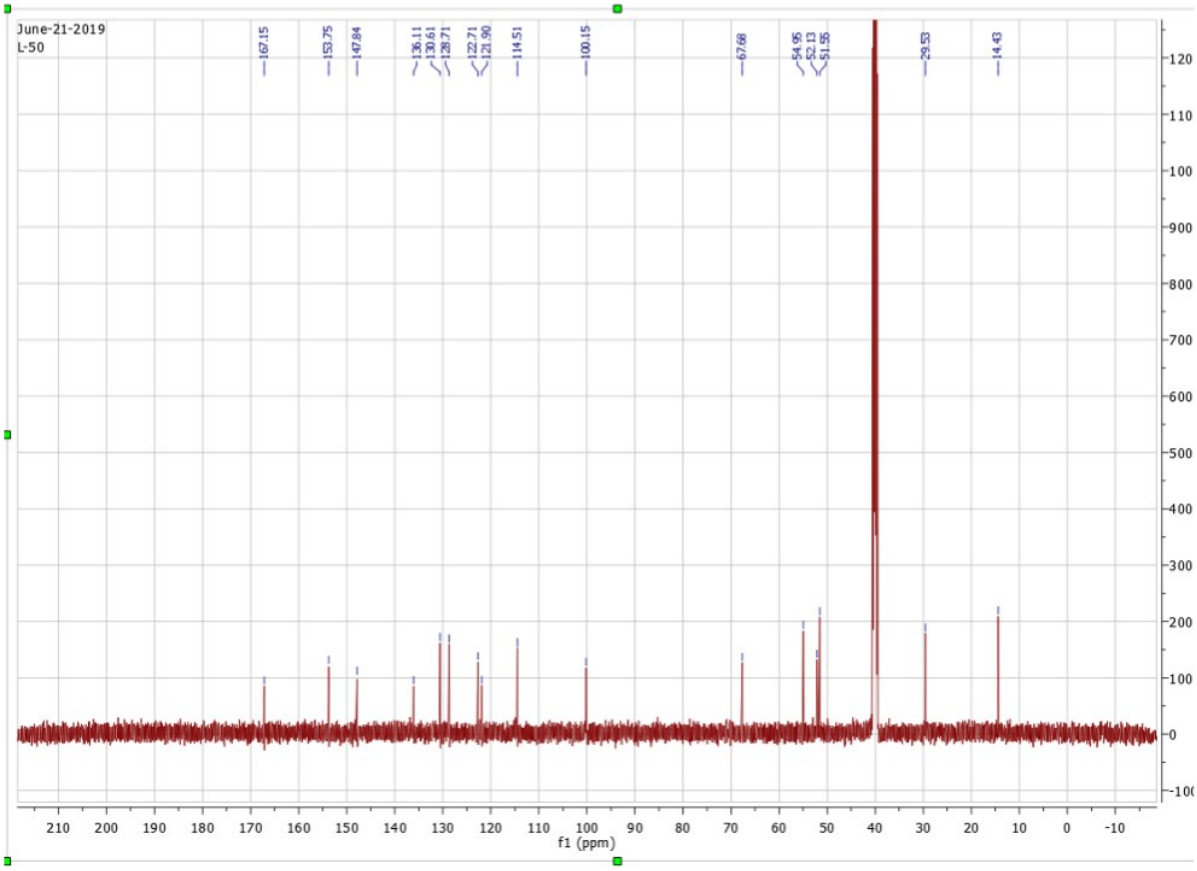
2-(2,4-dichlorophenoxy)-*N*-(3-methyl-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-5-yl)acetamide (13f). Prepared using general procedure A. Yield = 40 mg (63%, white solid). LCMS: R_T = 2.47 min.,

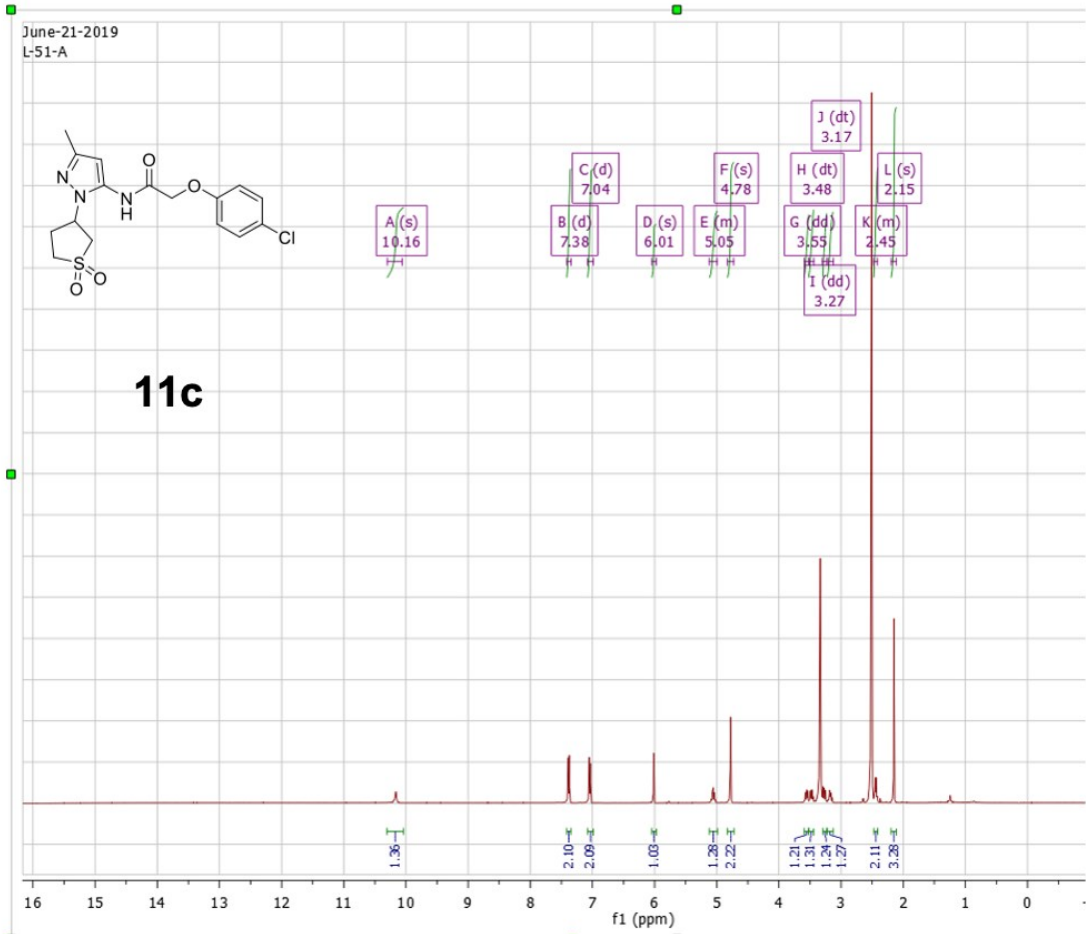
>95% @ 215 and 254 nm, *m/z* = 384.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO-d_6) δ 10.04 (s, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.41 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.12 (d, *J* = 8.9 Hz, 1H), 5.99 (s, 1H), 4.92 (s, 2H), 4.92 (s, 2H), 4.24 – 4.15 (m, 1H), 3.95 (dd, *J* = 11.3, 3.8 Hz, 2H), 3.41 – 3.34 (m, 2H), 2.12 (s, 3H), 2.01 – 1.92 (m, 2H), 1.69 (d, *J* = 10.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.63, 152.93, 146.31, 134.87, 129.96, 128.50, 125.60, 122.96, 115.61, 99.49, 67.97, 66.74, 52.83, 32.91, 14.41.


c17-2017-CHlab
C-33
A (s) 10.18
B (d) 7.62
C (dd) 7.39
D (d) 7.13
E (s) 6.04
F (p) 5.11
G (s) 4.93
J (dt) 3.18
K (dd) 3.29
L (dd) 3.58
I (dd) 2.46
H (s) 2.15
11a
f1 (ppm)


166.89
152.97
147.87
136.05
129.93
128.49
125.62
122.95
115.77
100.14
67.84
54.95
52.13
51.56
29.53
14.43
f1 (ppm)


June-21-2019
L-50
D (t)
7.01
B (dd)
7.32
A (m)
7.47
C (d)
7.10
E (s)
10.16
F (s)
6.05
H (s)
4.90
G (p)
5.11
N (dd)
3.58
L (m)
3.28
M (dt)
3.49
K (dt)
3.17
J (dd)
2.46
I (s)
2.15
11b


June-21-2019
L-50
f1 (ppm)


June-21-2019
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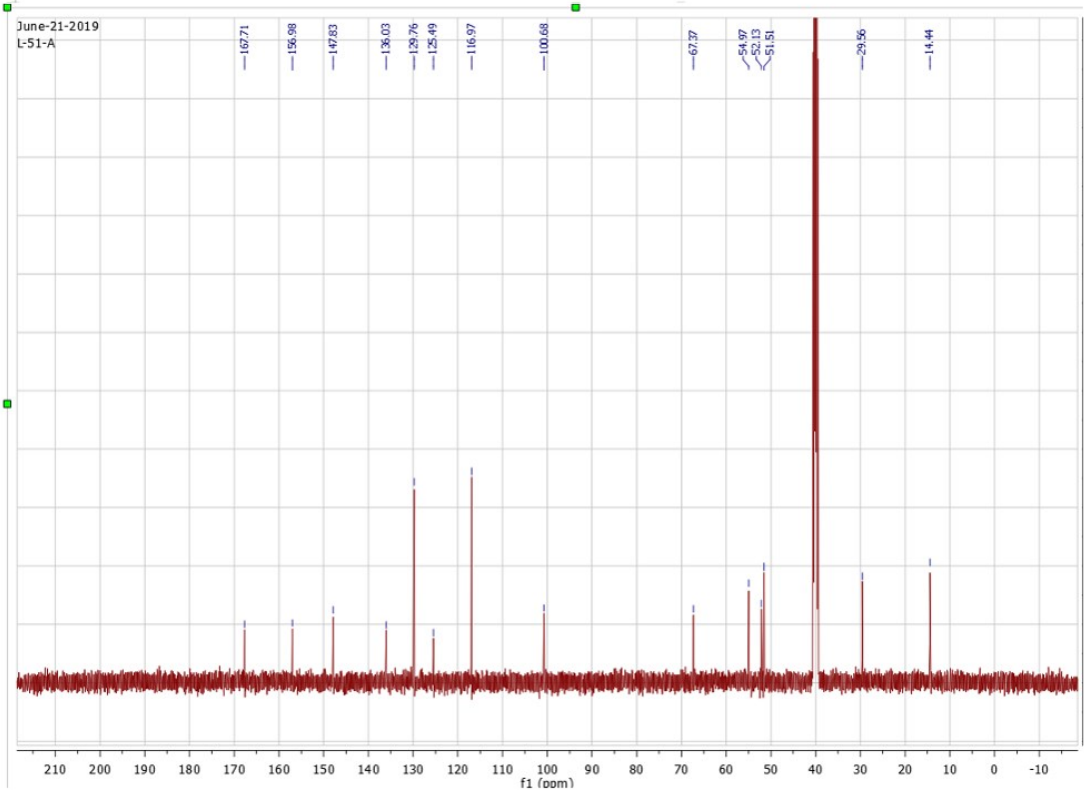
B (d) 7.38
C (d) 7.04
D (s) 6.01
E (m) 5.05
F (s) 4.78
G (dd) 3.55
H (dt) 3.48
I (dd) 3.27
J (dt) 3.17
K (m) 2.45
L (s) 2.15
11c
f1 (ppm)


June-21-2019
L-51-A
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147.83
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116.97
100.68
67.37
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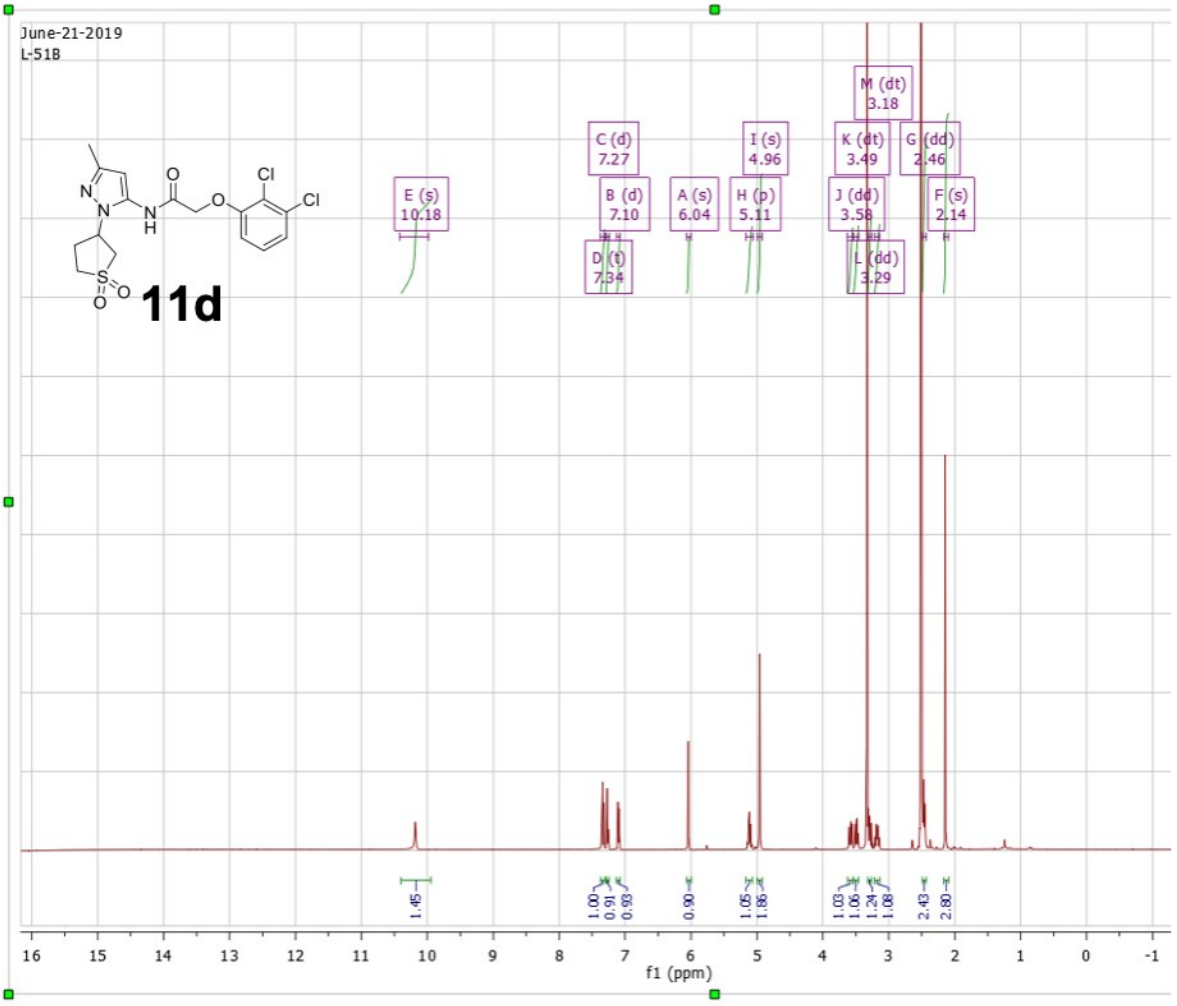
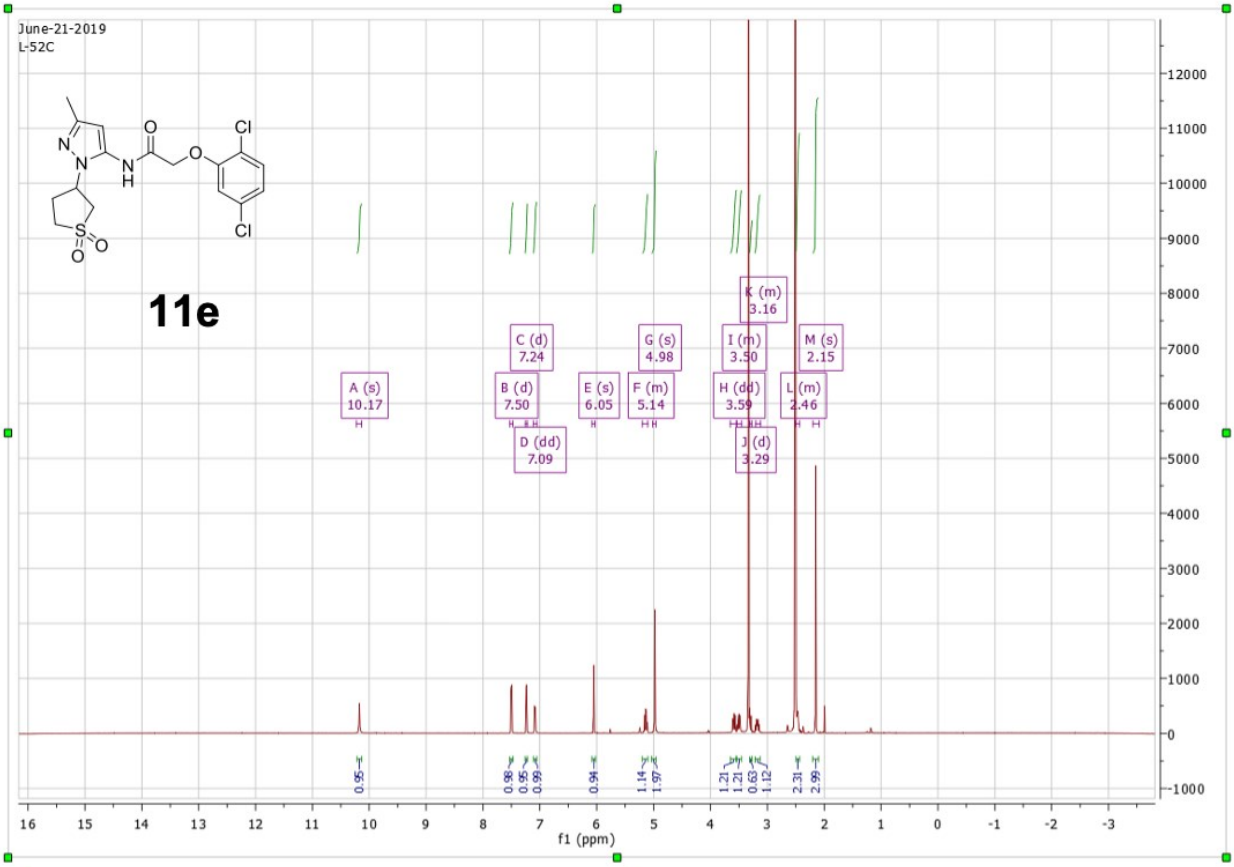
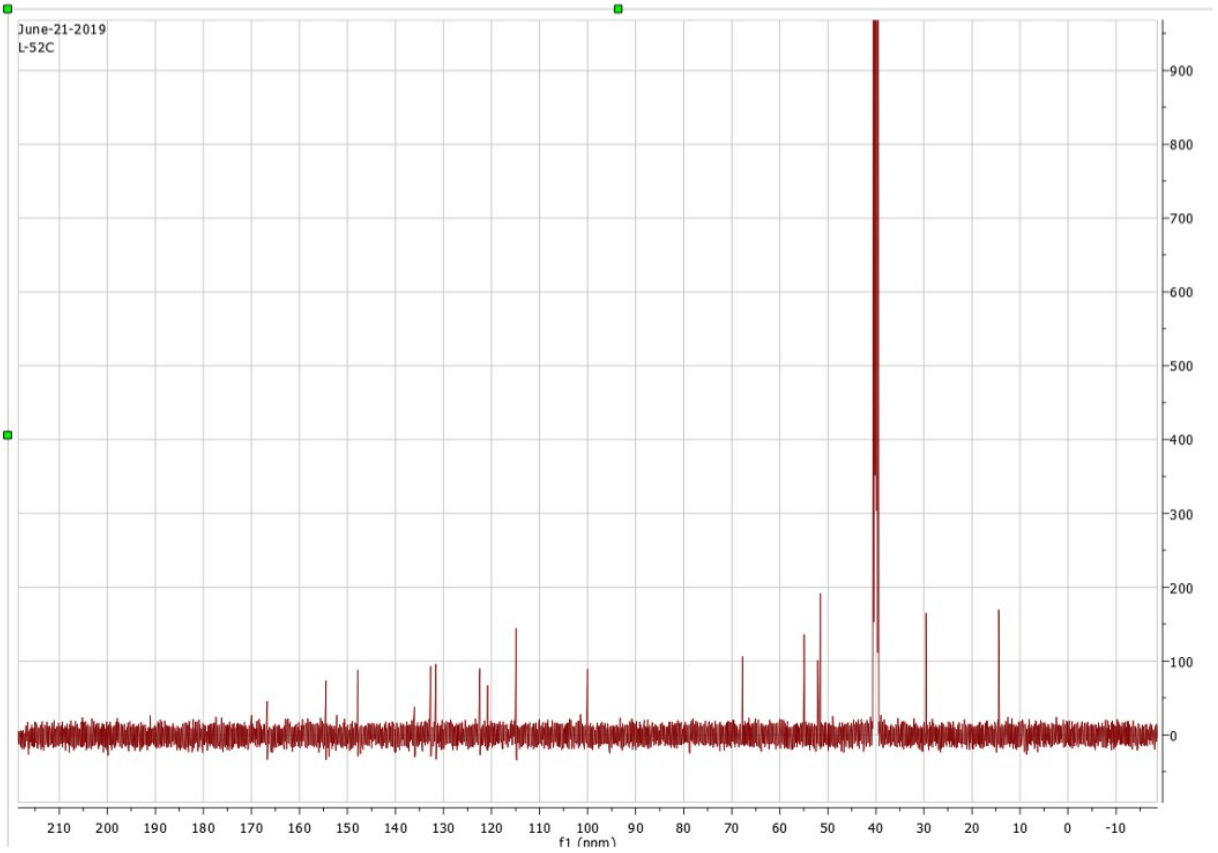
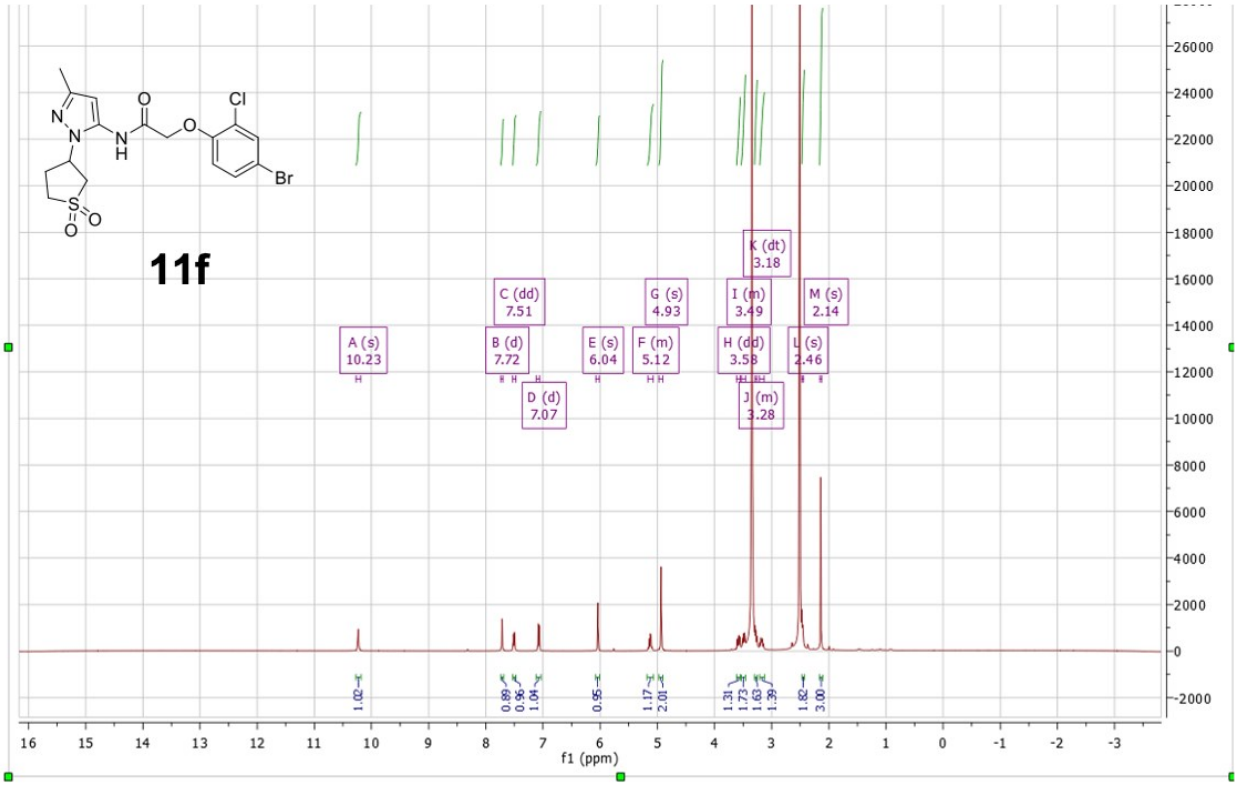
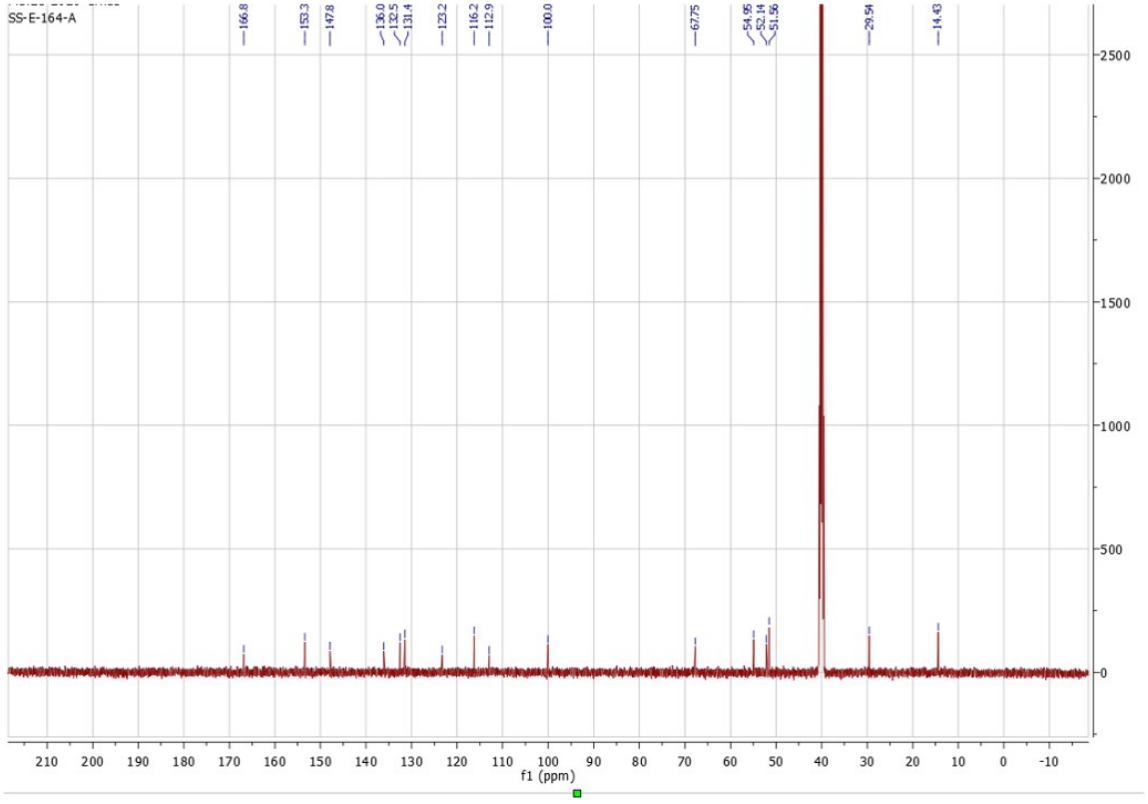
52.13
51.51
29.56
14.44
f1 (ppm)


June-21-2019
L-51B
11d
E (s) 10.18
C (d) 7.27
B (d) 7.10
D (t) 7.34
A (s) 6.04
I (s) 4.96
H (p) 5.11
M (dt) 3.18
K (dt) 3.49
J (dd) 3.58
L (dd) 3.29
G (dd) 2.46
F (s) 2.14
1.45
1.00
0.91
0.93
0.90
1.05
1.86
1.03
1.06
1.24
1.08
2.43
2.80
f1 (ppm)


June-21-2019
L-52C
11e
A (s) 10.17
B (d) 7.50
C (d) 7.24
D (dd) 7.09
E (s) 6.05
F (m) 5.14
G (s) 4.98
H (dd) 3.59
I (m) 3.50
J (d) 3.29
K (m) 3.16
L (m) 2.46
M (s) 2.15
f1 (ppm)


June-21-2019
L-52C
f1 (ppm)


11f
A (s)
10.23
B (d)
7.72
C (dd)
7.51
D (d)
7.07
E (s)
6.04
F (m)
5.12
G (s)
4.93
H (dd)
3.58
I (m)
3.49
J (m)
3.28
K (dt)
3.18
L (s)
2.46
M (s)
2.14
f1 (ppm)


SS-E-164-A
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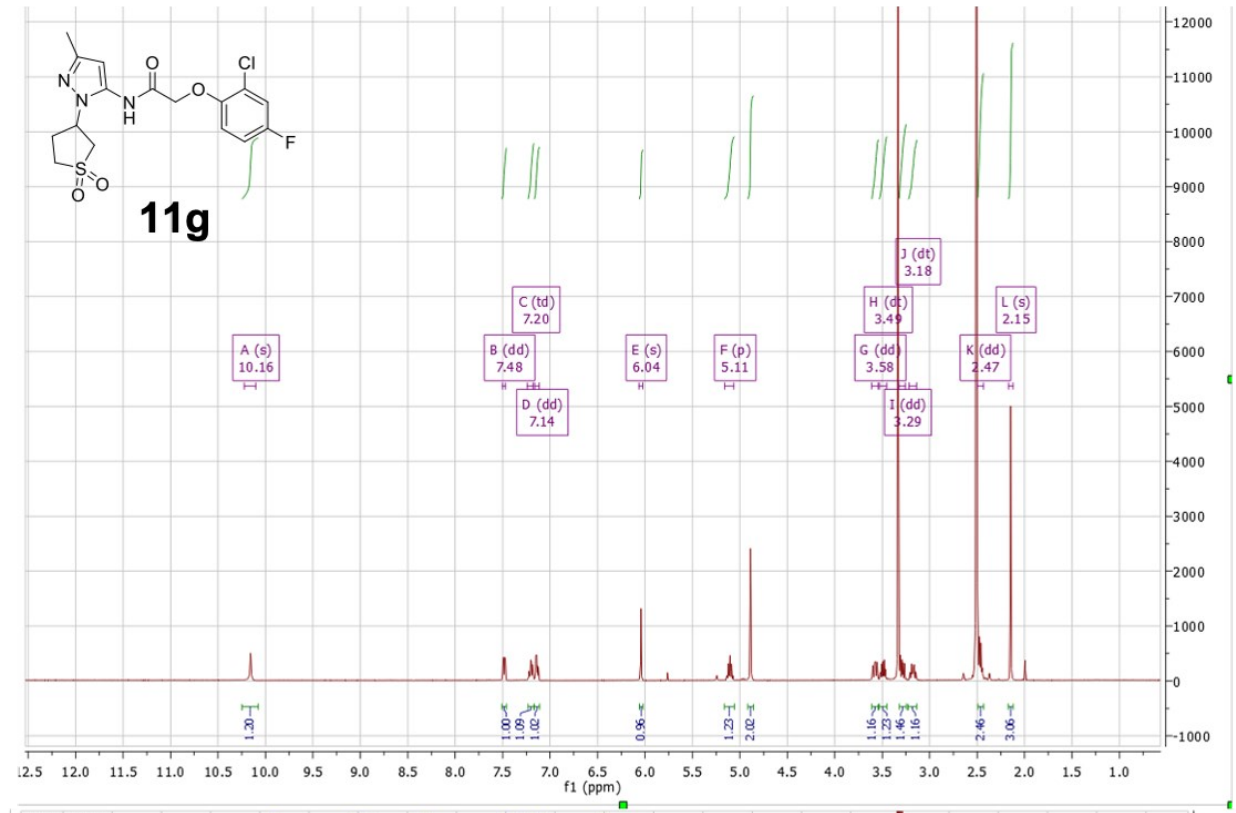
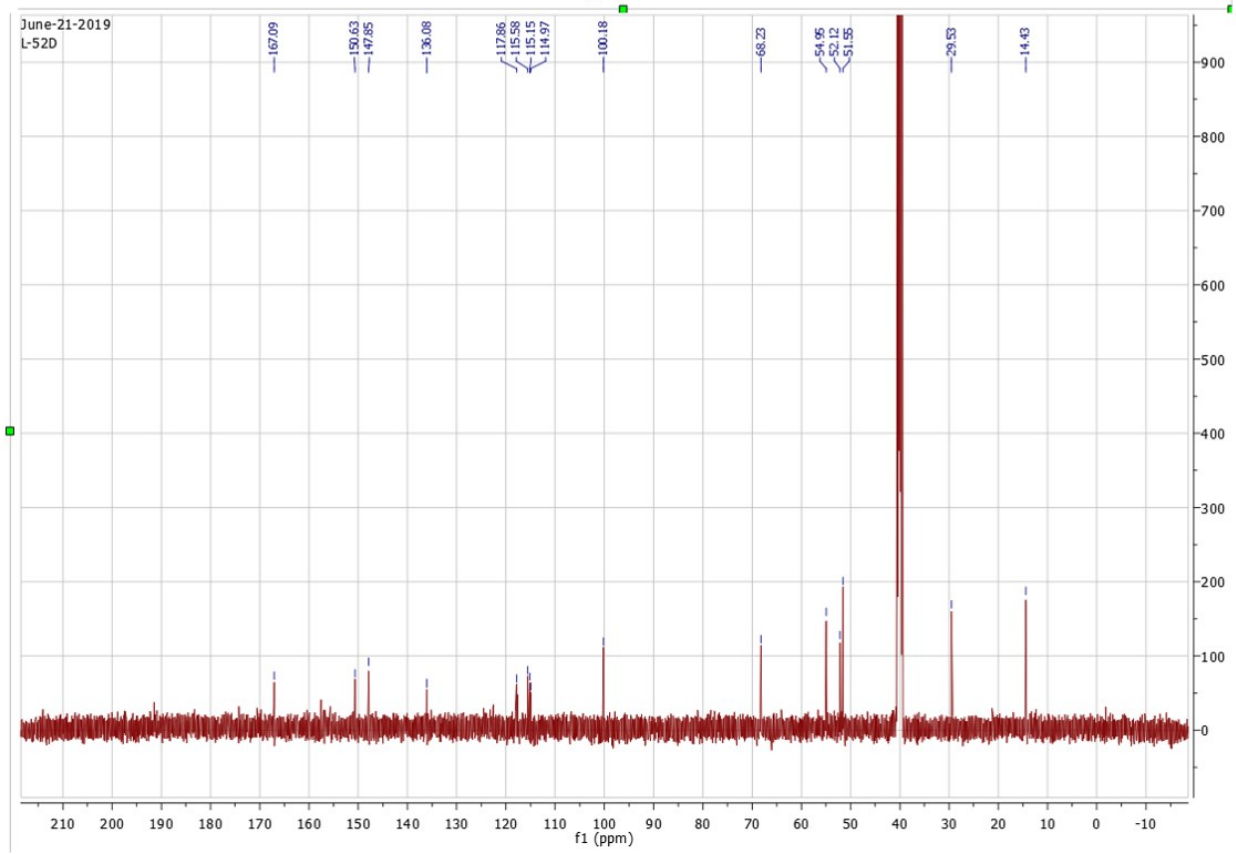
153.3
147.8
136.0
132.5
131.4
123.2
116.2
112.9
100.0
67.75
54.95
52.14
51.56
29.94
14.43
f1 (ppm)


11g
A (s) 10.16
B (dd) 7.48
C (td) 7.20
D (dd) 7.14
E (s) 6.04
F (p) 5.11
G (dd) 3.58
H (dt) 3.49
I (dd) 3.29
J (dt) 3.18
K (dd) 2.47
L (s) 2.15
f1 (ppm)


June-21-2019
L-52D
167.09
150.63
147.85
136.08
117.86
115.58
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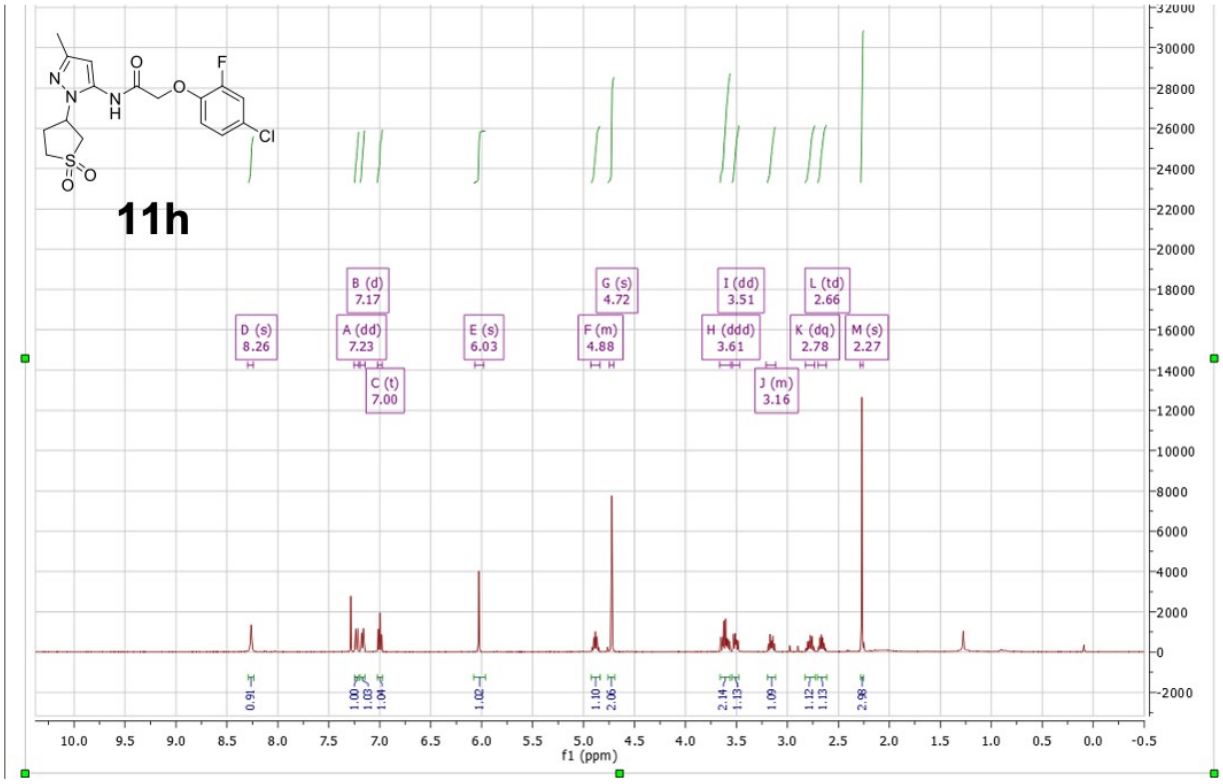
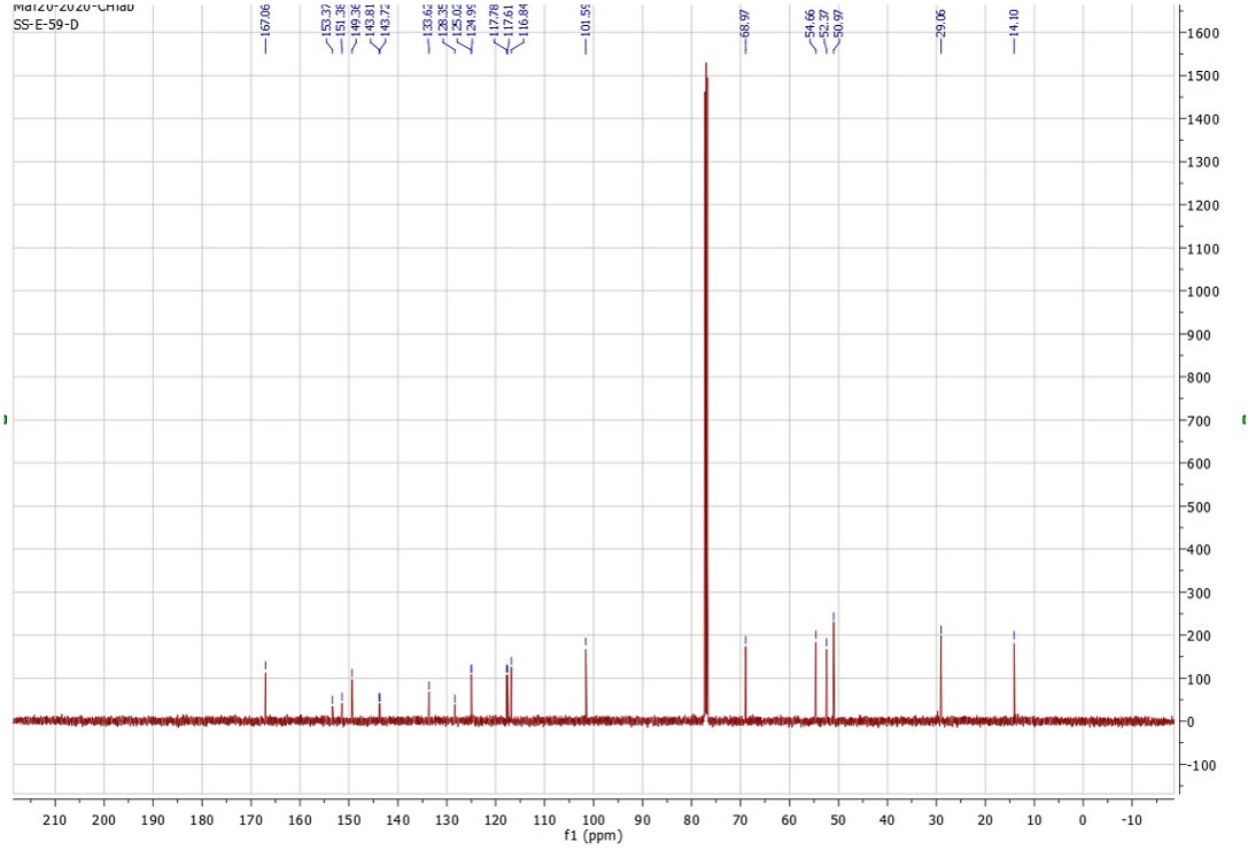
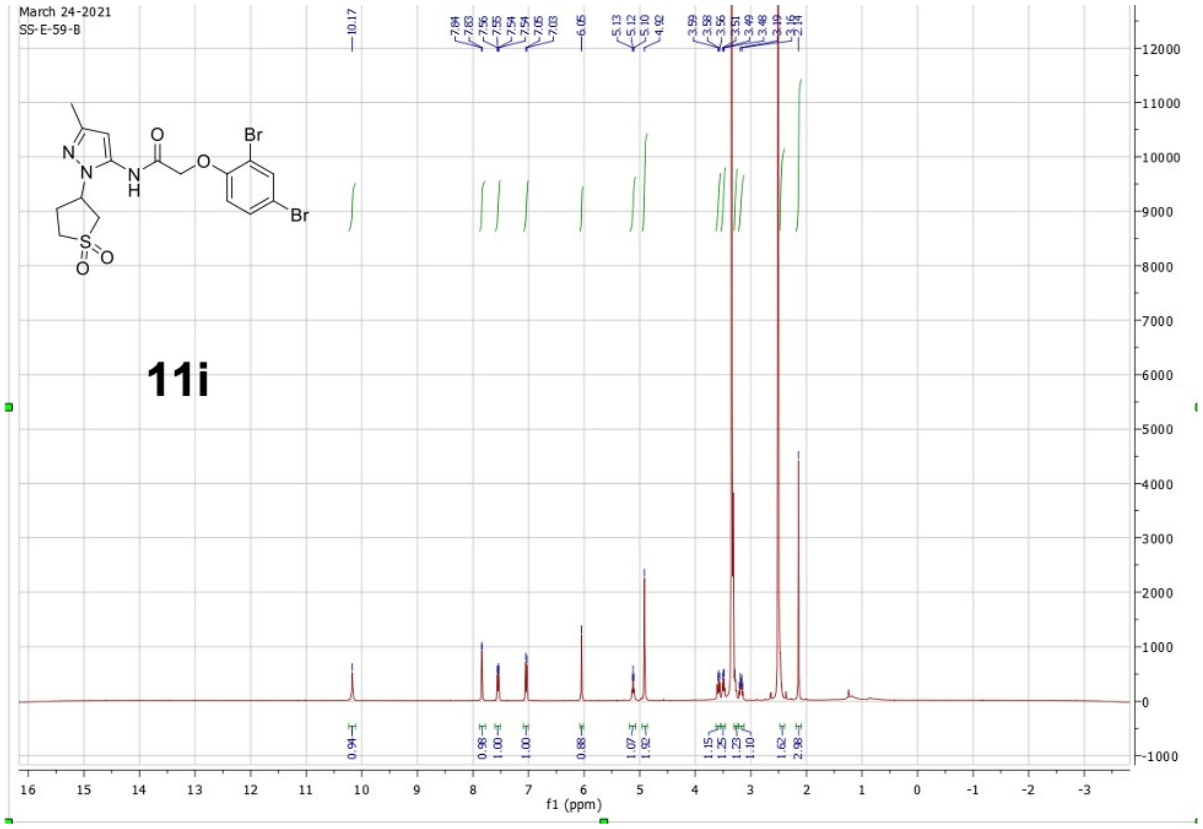
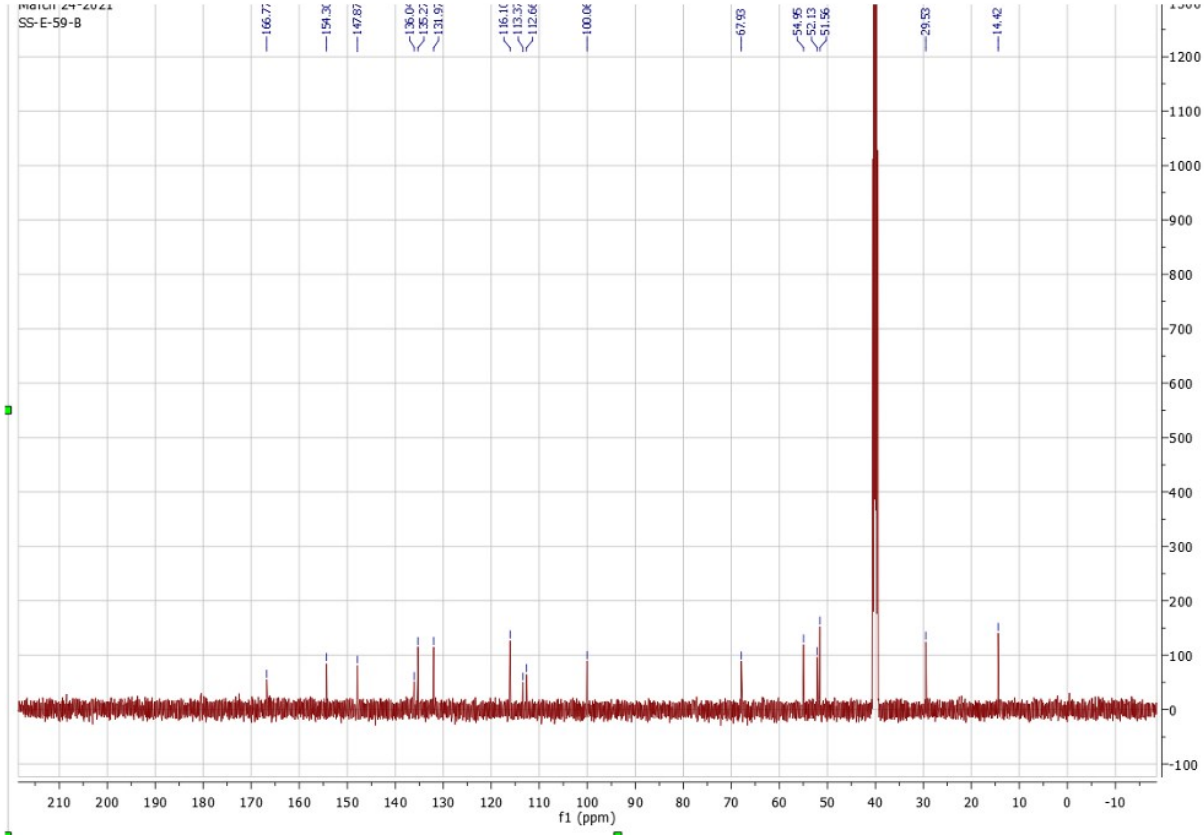
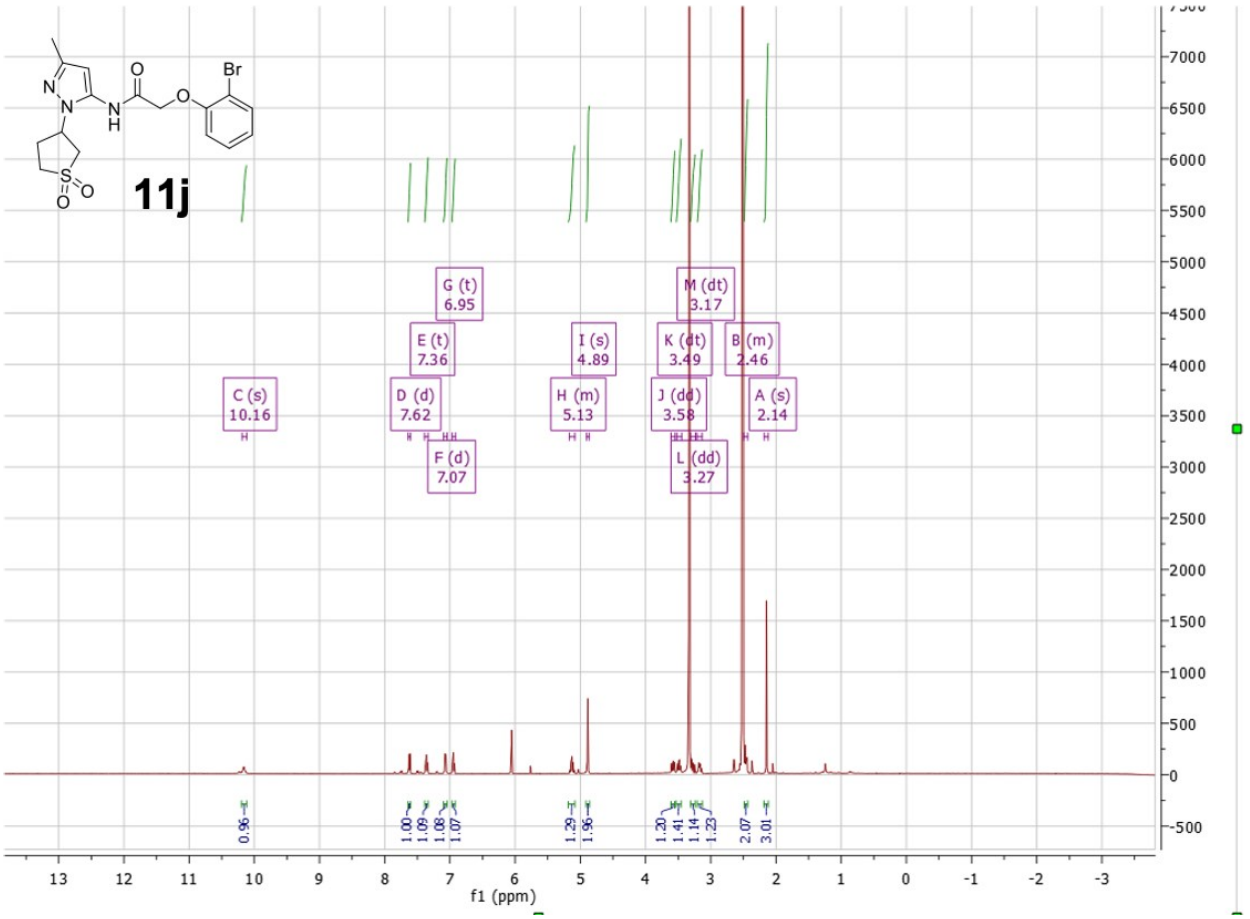
114.97
100.18
68.23
54.95
52.12
51.55
29.53
14.43
f1 (ppm)

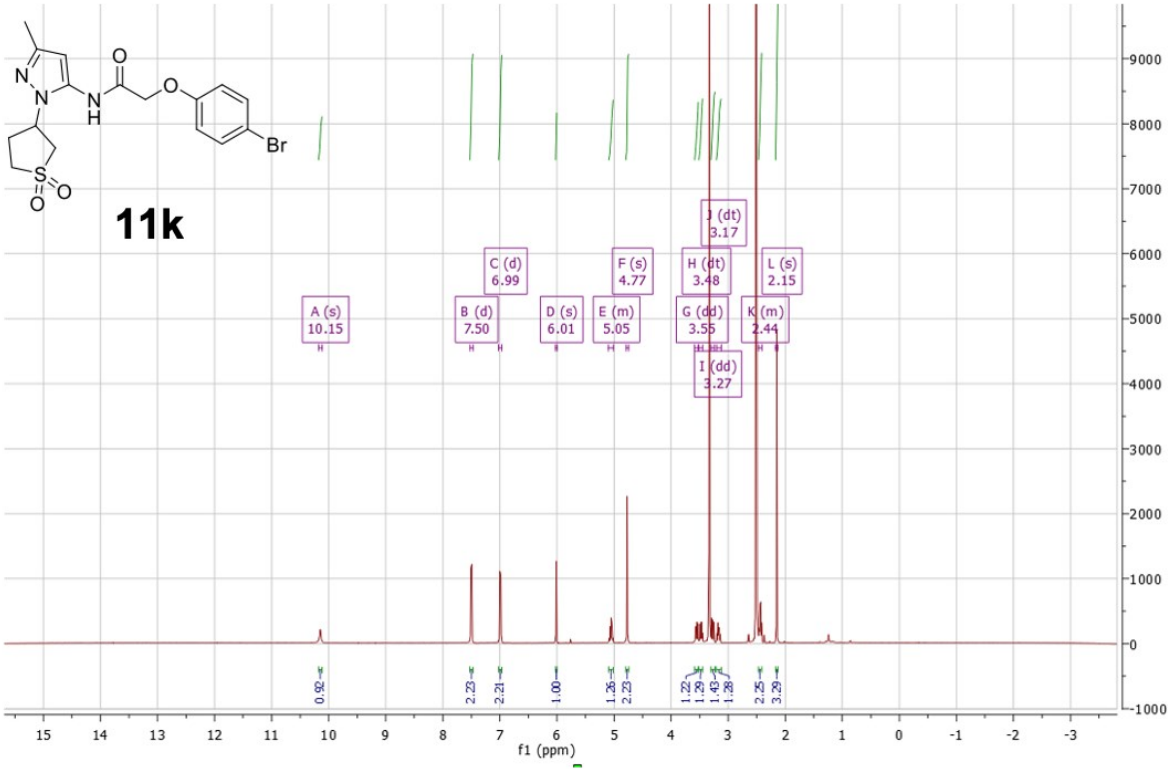

11h
B (d) 7.17
G (s) 4.72
I (dd) 3.51
L (td) 2.66
D (s) 8.26
A (dd) 7.23
E (s) 6.03
F (m) 4.88
H (ddd) 3.61
K (dq) 2.78
M (s) 2.27
C (t) 7.00
J (m) 3.16
f1 (ppm)

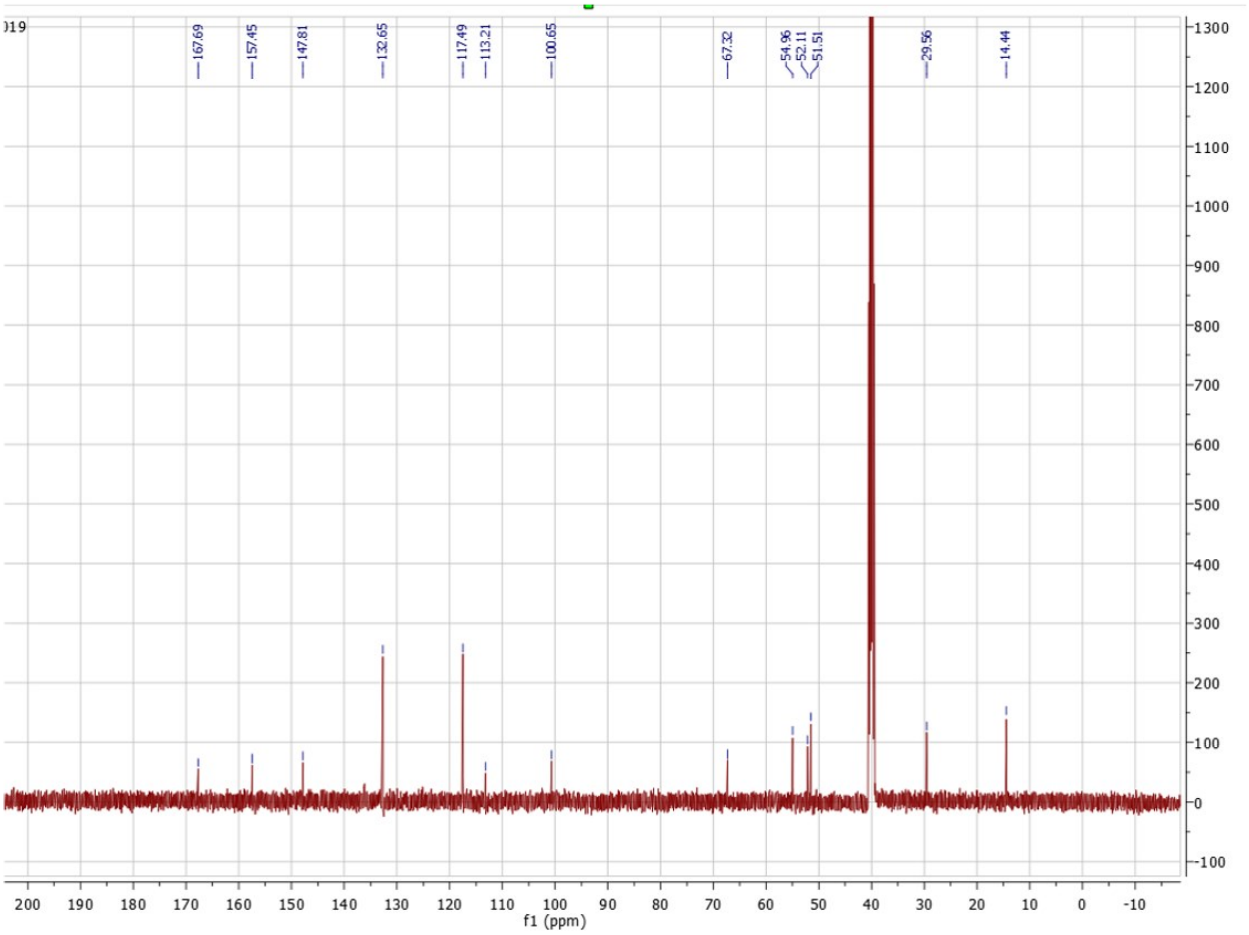

SS-E-59-D
167.06
153.37
151.38
149.38
143.81
143.72
133.62
128.38
125.02
124.96
117.78
117.61
116.84
101.55
68.97
54.66
52.37
50.97
29.06
14.10
f1 (ppm)

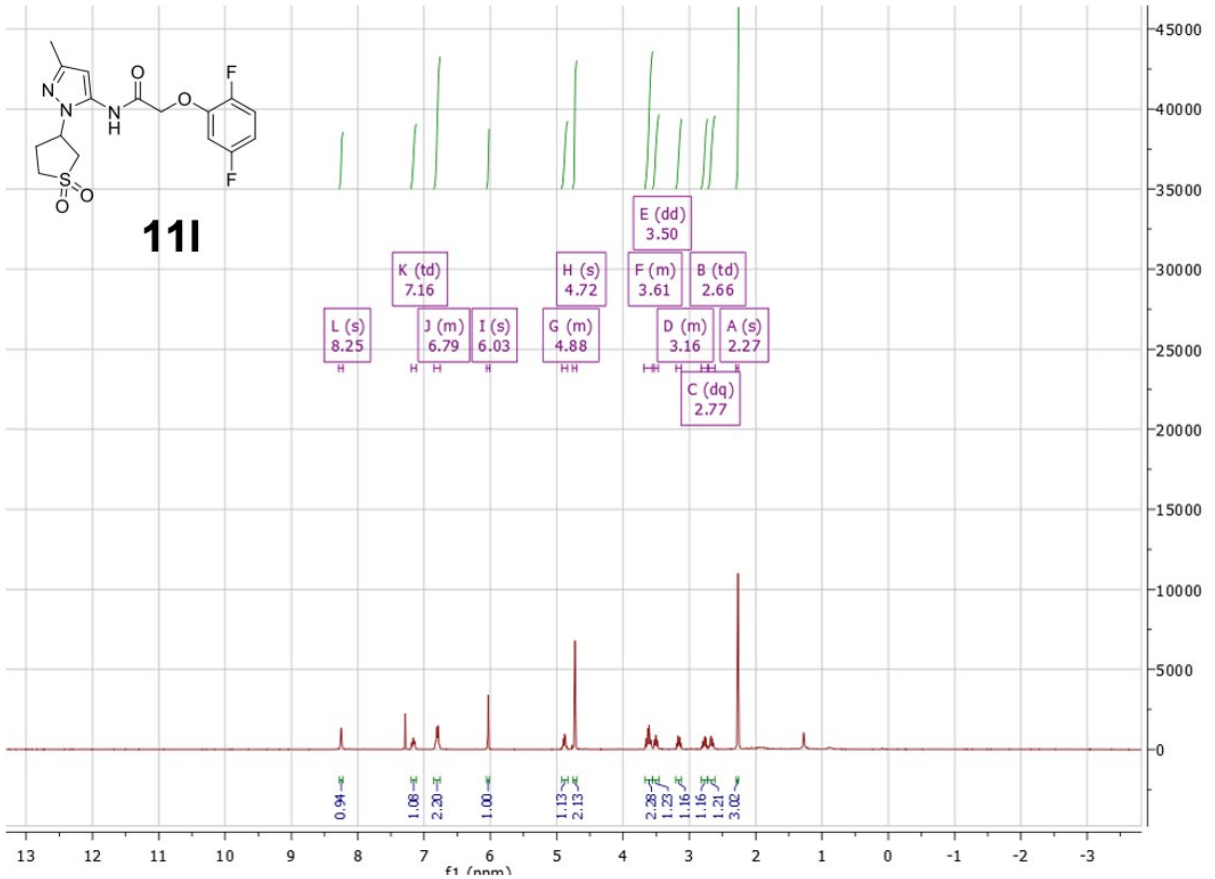

March 24-2021
SS-E-59-B
11i
f1 (ppm)

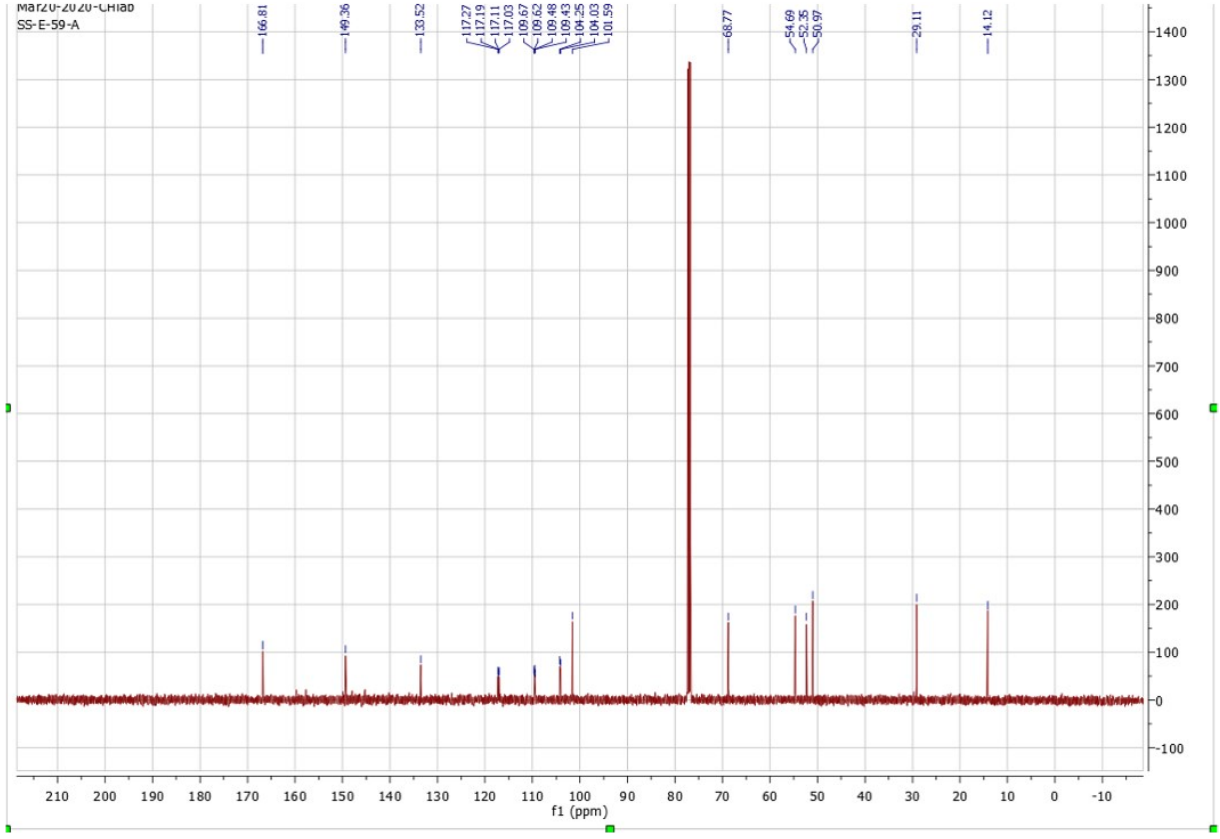

SS-E-59-B
f1 (ppm)

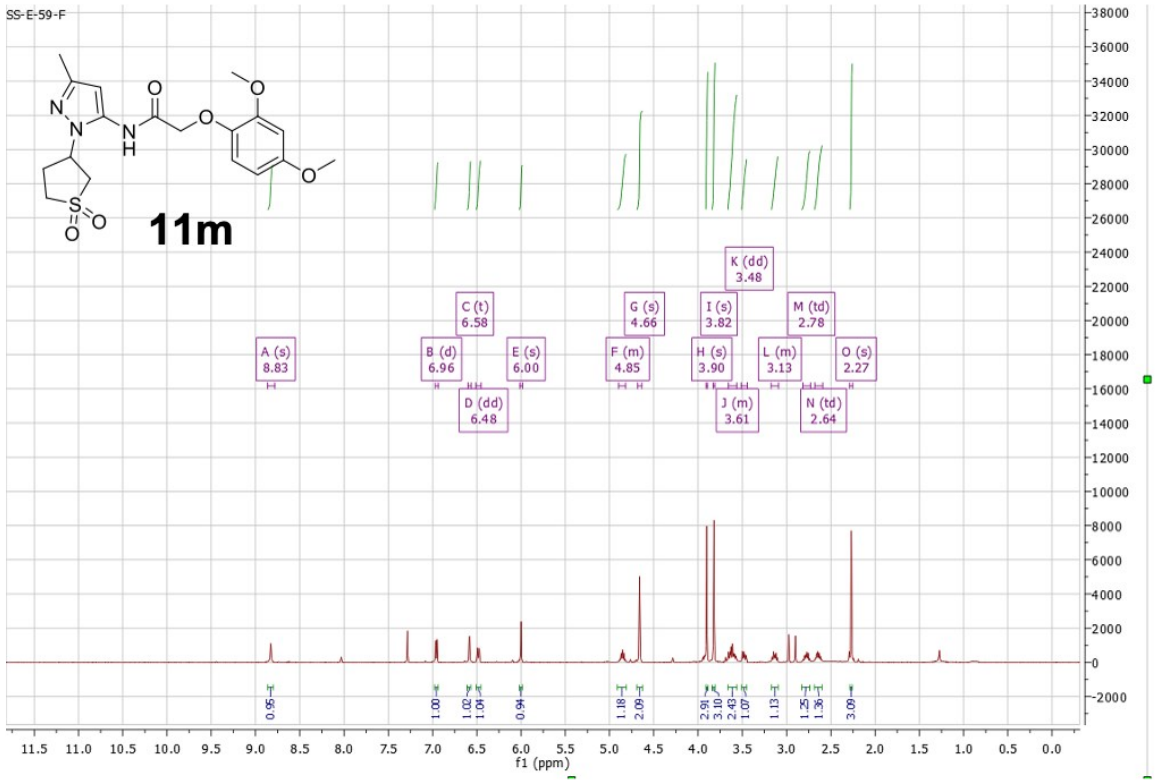

11j
G (t) 6.95
E (t) 7.36
D (d) 7.62
F (d) 7.07
C (s) 10.16
I (s) 4.89
H (m) 5.13
M (dt) 3.17
K (dt) 3.49
J (dd) 3.58
L (dd) 3.27
B (m) 2.46
A (s) 2.14
f1 (ppm)

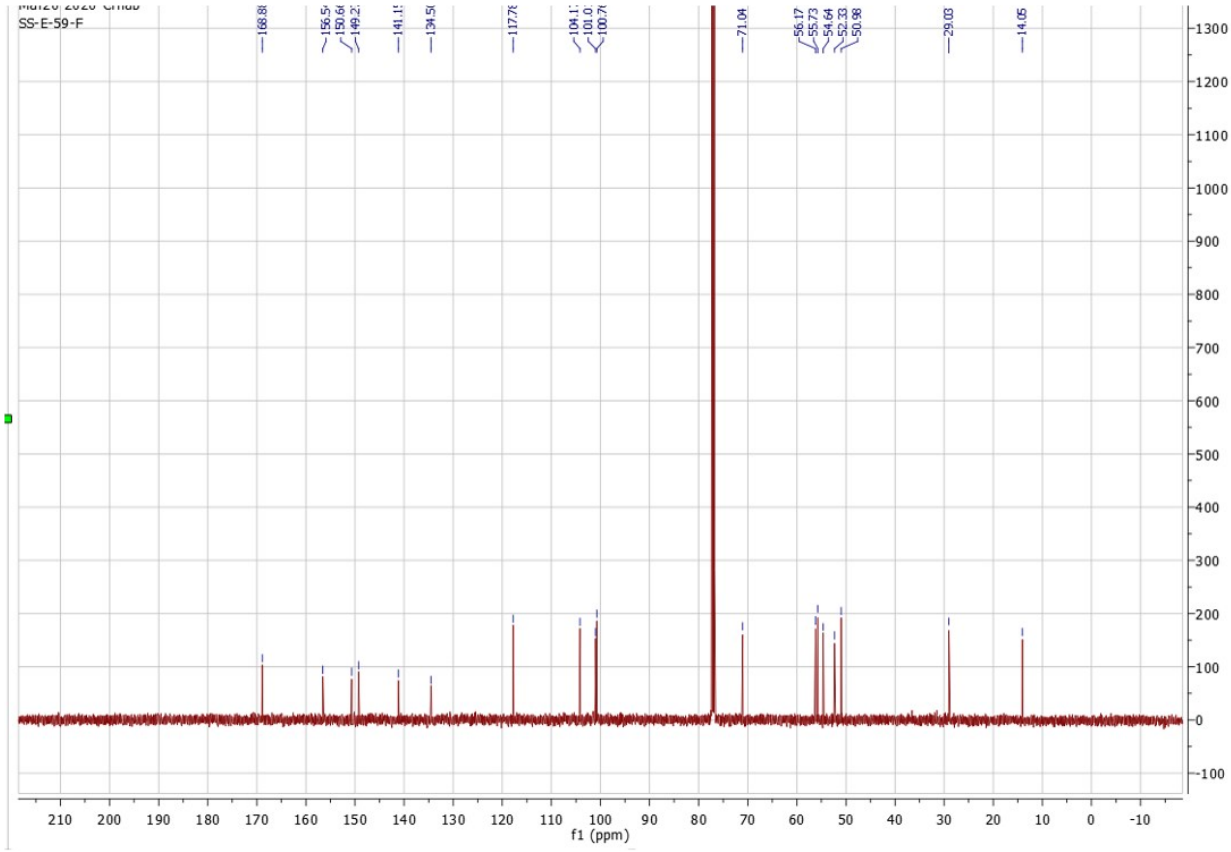

11k
A (s) 10.15
B (d) 7.50
C (d) 6.99
D (s) 6.01
E (m) 5.05
F (s) 4.77
G (dd) 3.55
H (dt) 3.48
I (dd) 3.27
J (dt) 3.17
K (m) 2.44
L (s) 2.15
f1 (ppm)

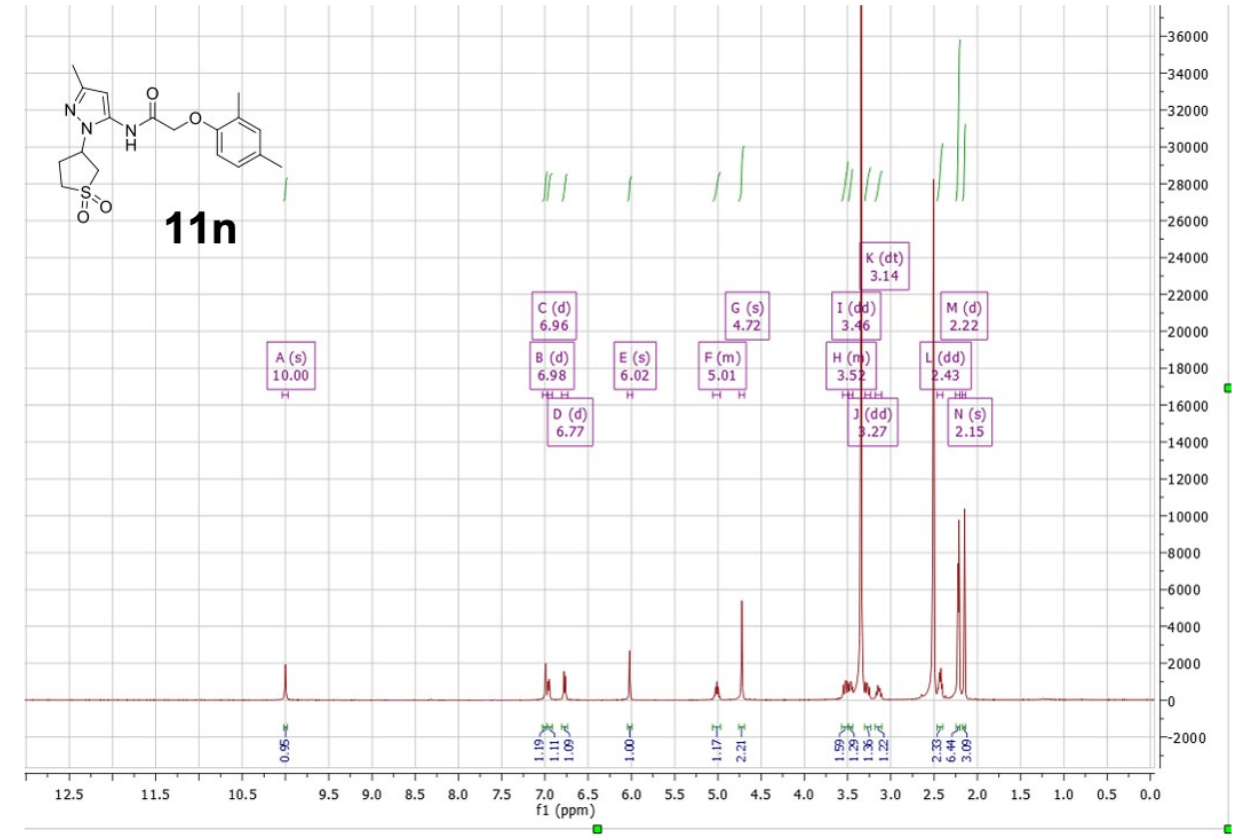

167.69
157.45
147.81
132.65
117.49
113.21
100.65
67.32
54.96
52.11
51.51
29.56
14.44
f1 (ppm)

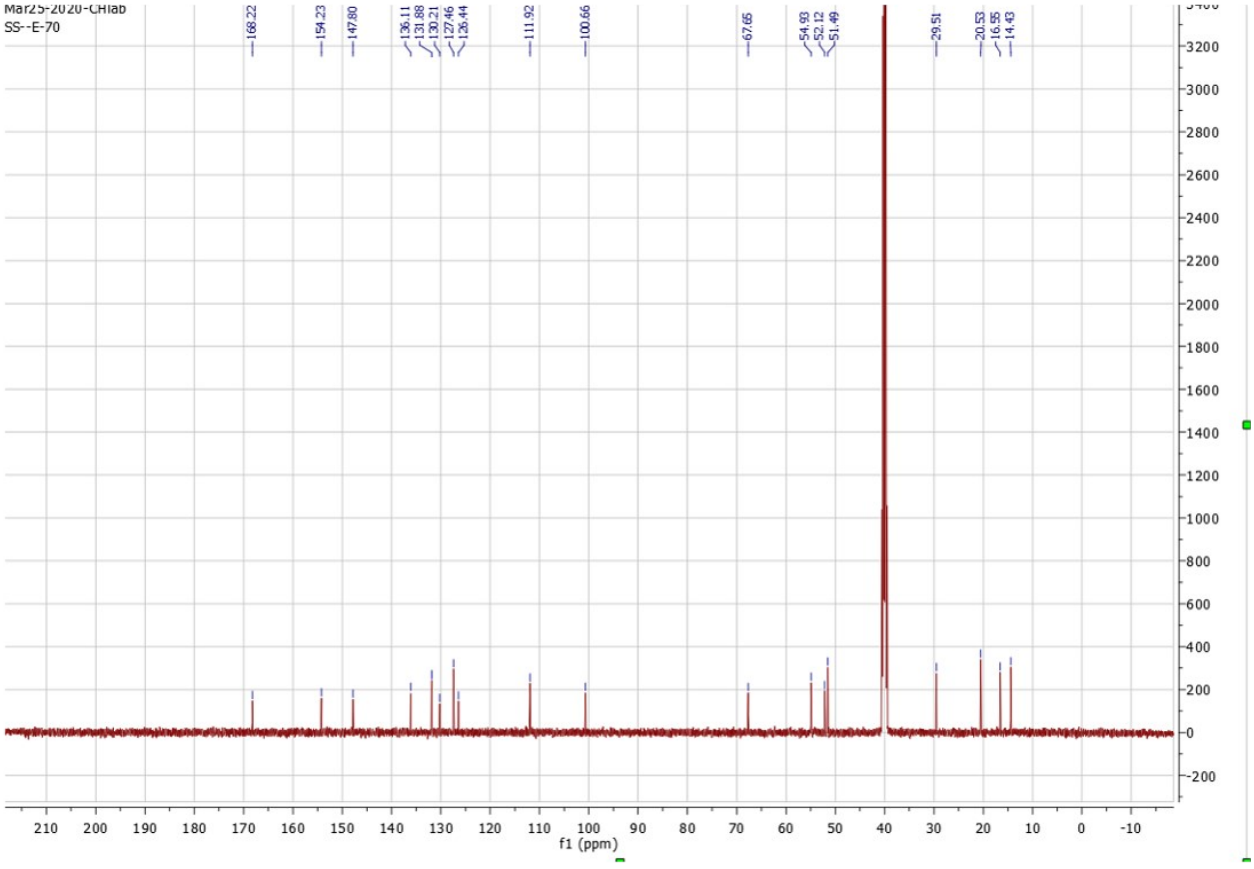

11l
L (s) 8.25
K (td) 7.16
J (m) 6.79
I (s) 6.03
H (s) 4.72
G (m) 4.88
E (dd) 3.50
F (m) 3.61
B (td) 2.66
D (m) 3.16
A (s) 2.27
C (dq) 2.77
f1 (ppm)

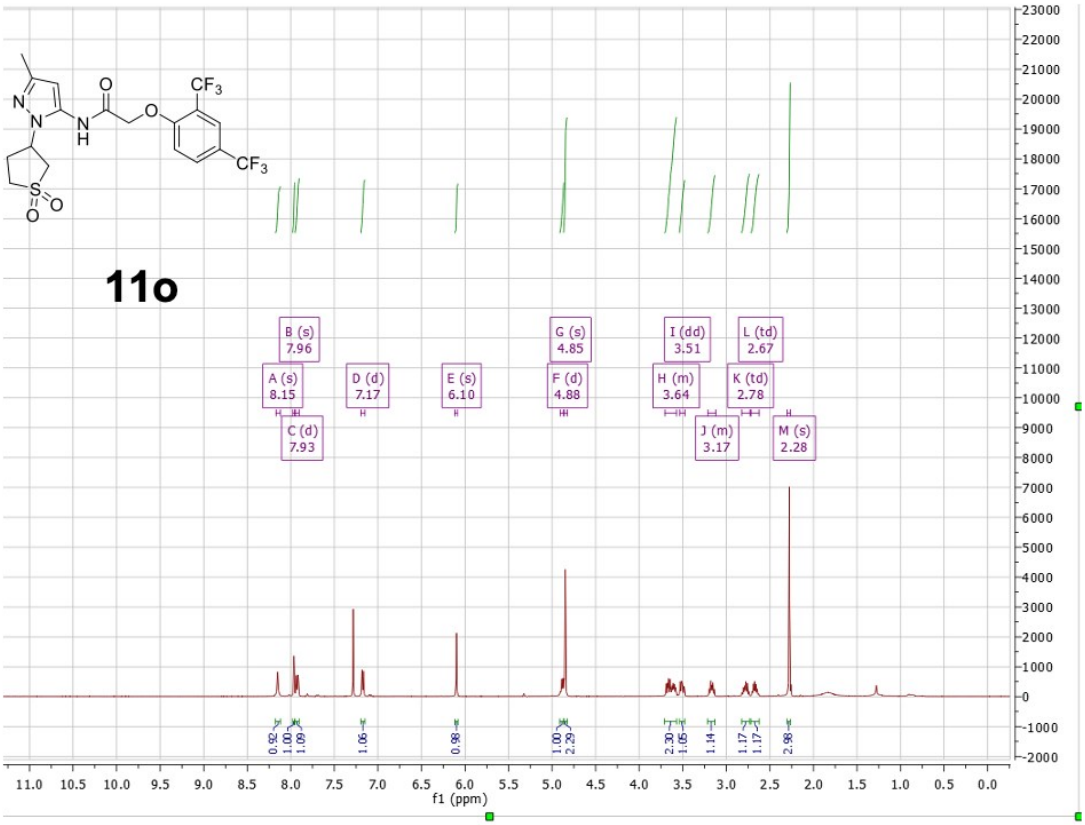

SS-E-59-A
166.81
149.36
133.52
117.27
117.19
117.11
117.03
109.67
109.62
109.48
109.43
104.25
104.03
101.59
68.77
54.69
52.35
50.97
29.11
14.12
f1 (ppm)

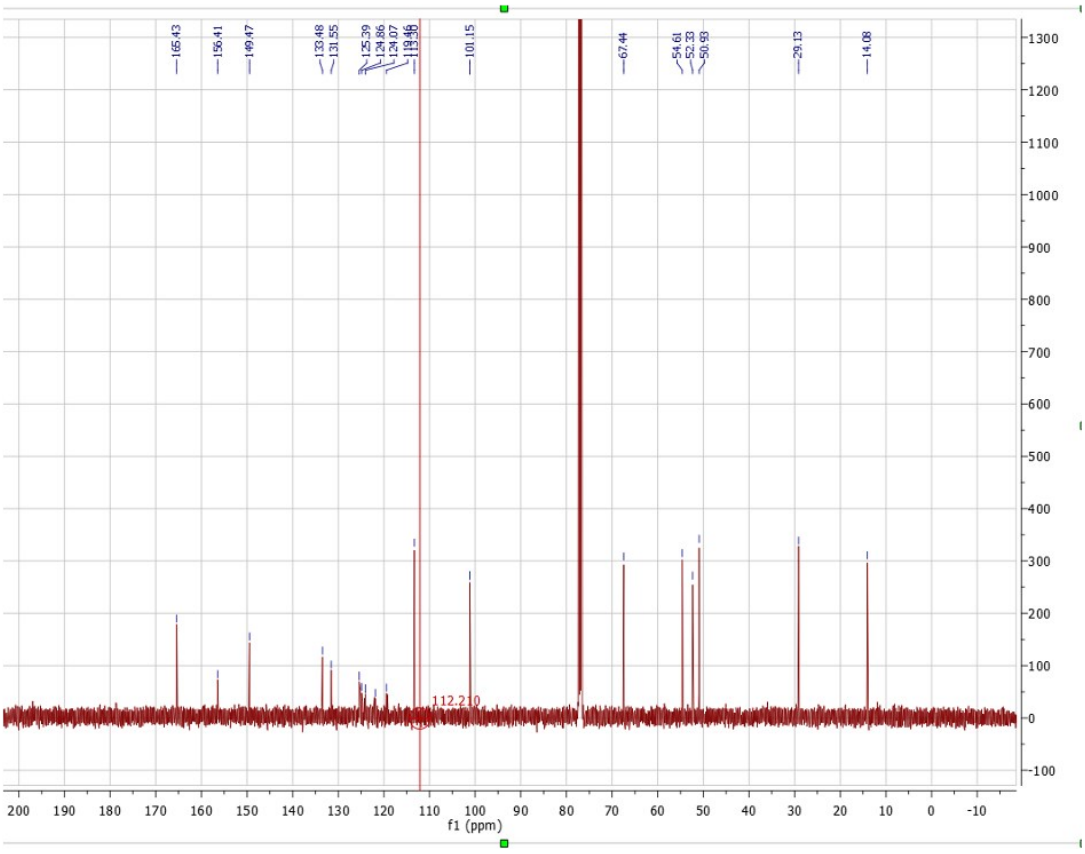

SS-E-59-F
11m
A (s) 8.83
B (d) 6.96
C (t) 6.58
D (dd) 6.48
E (s) 6.00
F (m) 4.85
G (s) 4.66
H (s) 3.90
I (s) 3.82
J (m) 3.61
K (dd) 3.48
L (m) 3.13
M (td) 2.78
N (td) 2.64
O (s) 2.27
f1 (ppm)

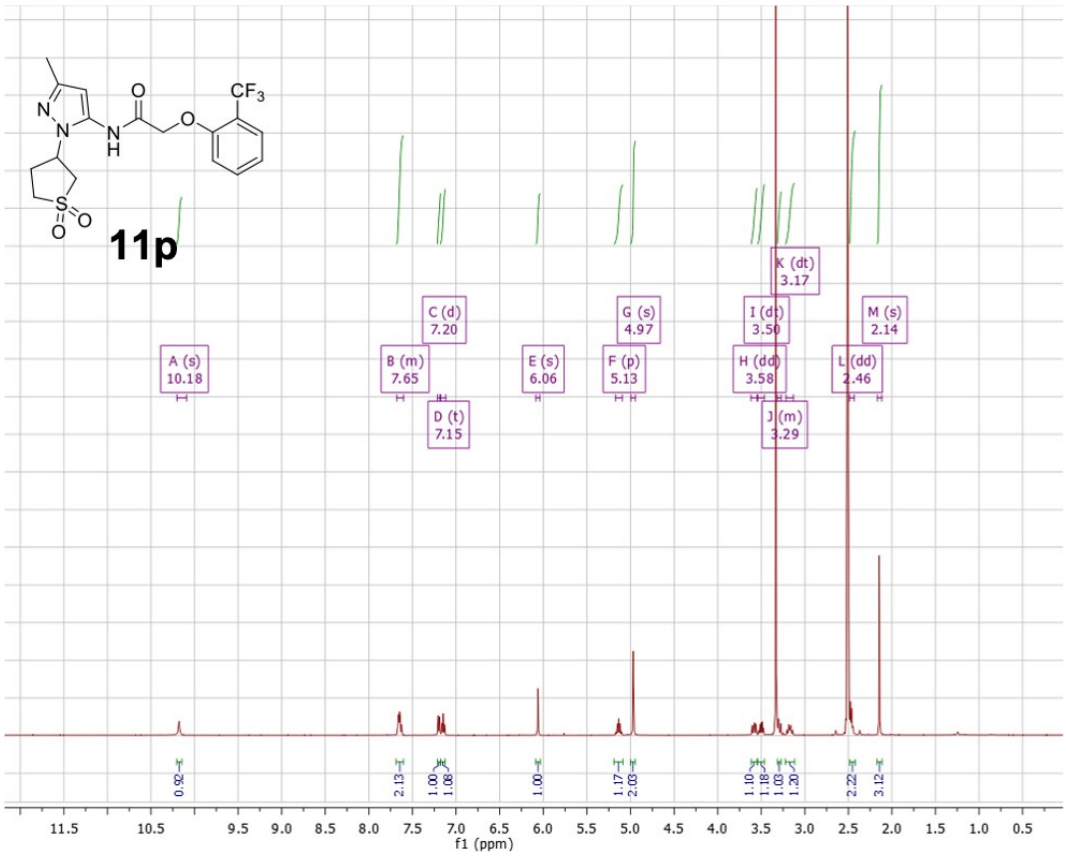

SS-E-59-F
f1 (ppm)

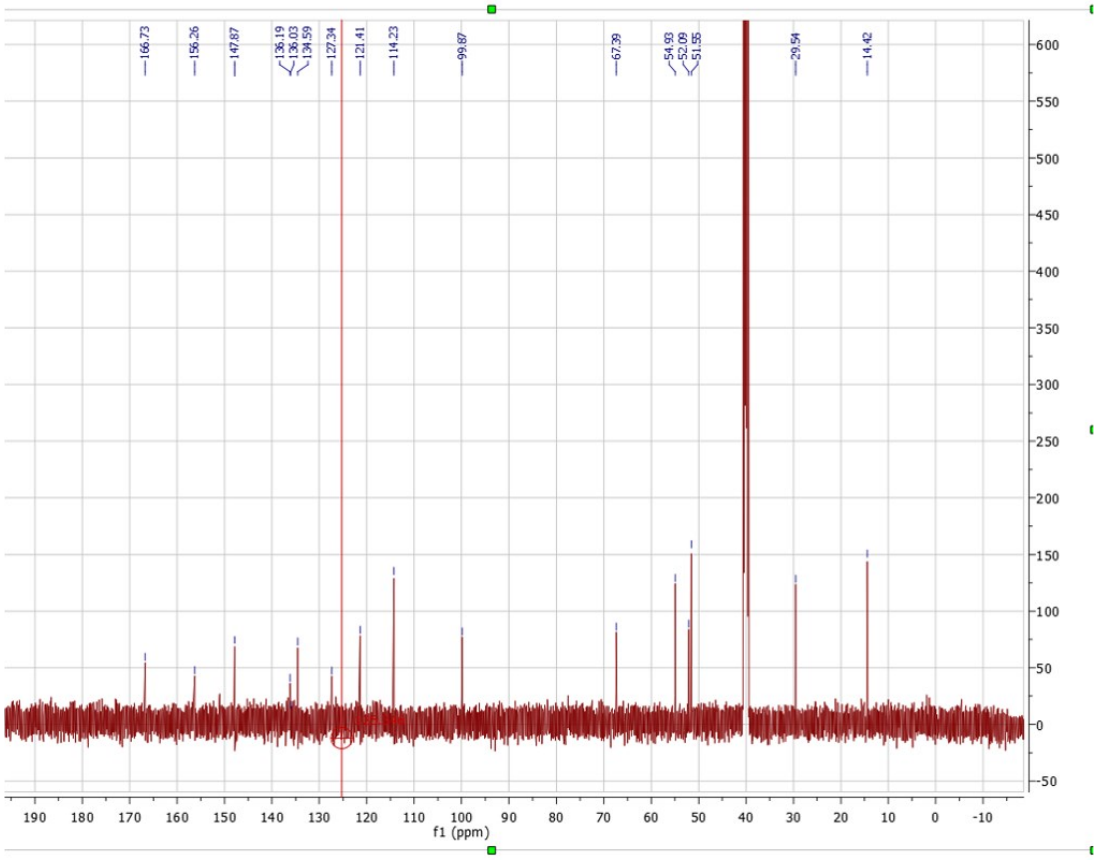

11n
A (s) 10.00
B (d) 6.98
C (d) 6.96
D (d) 6.77
E (s) 6.02
F (m) 5.01
G (s) 4.72
H (m) 3.52
I (dd) 3.46
J (dd) 3.27
K (dt) 3.14
L (dd) 2.43
M (d) 2.22
N (s) 2.15
f1 (ppm)


Mar25-2020-CHlab
SS--E-70
168.22
154.23
147.80
136.11
131.88
130.21
127.46
126.44
111.92
100.66
67.65
54.93
52.12
51.49
29.51
20.53
16.95
14.43
f1 (ppm)

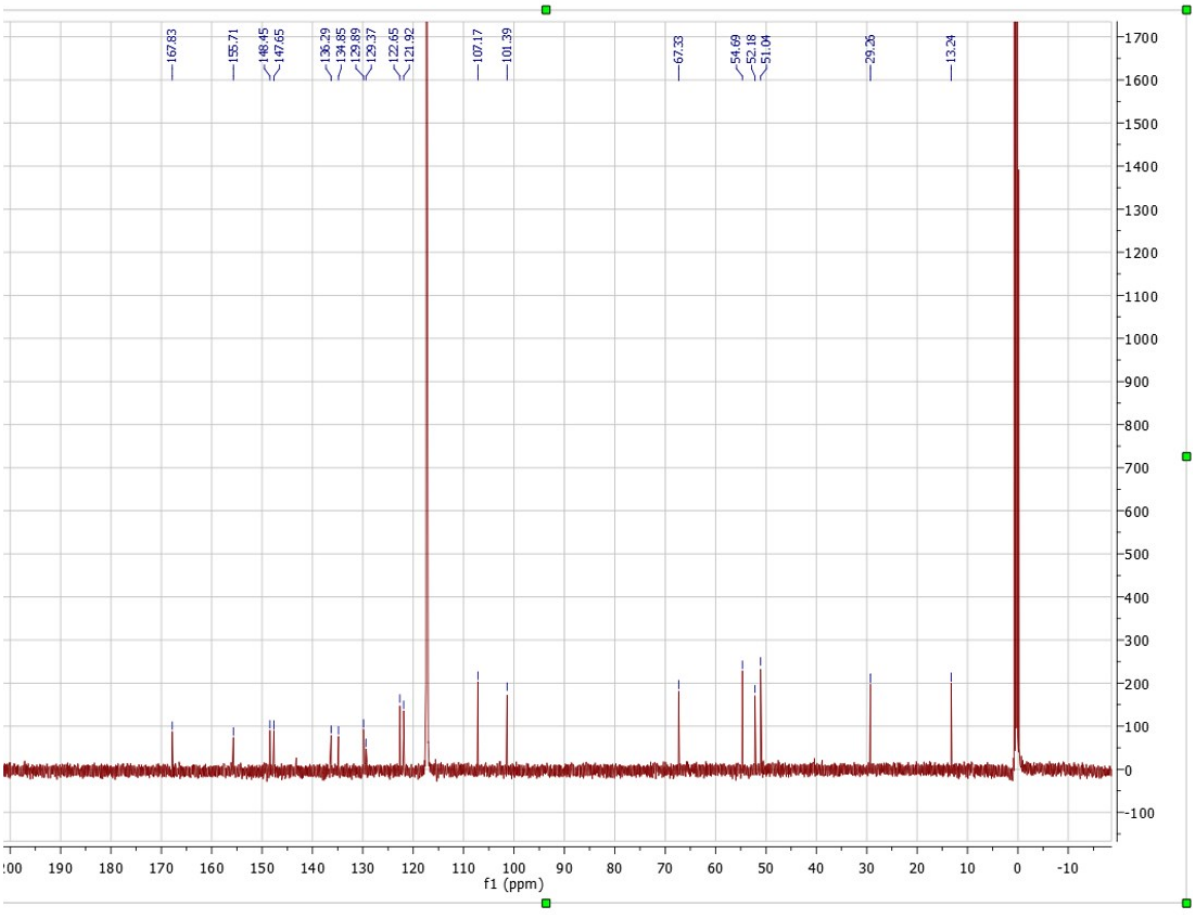

11o
B (s) 7.96
A (s) 8.15
C (d) 7.93
D (d) 7.17
E (s) 6.10
G (s) 4.85
F (d) 4.88
I (dd) 3.51
H (m) 3.64
J (m) 3.17
L (td) 2.67
K (td) 2.78
M (s) 2.28
f1 (ppm)

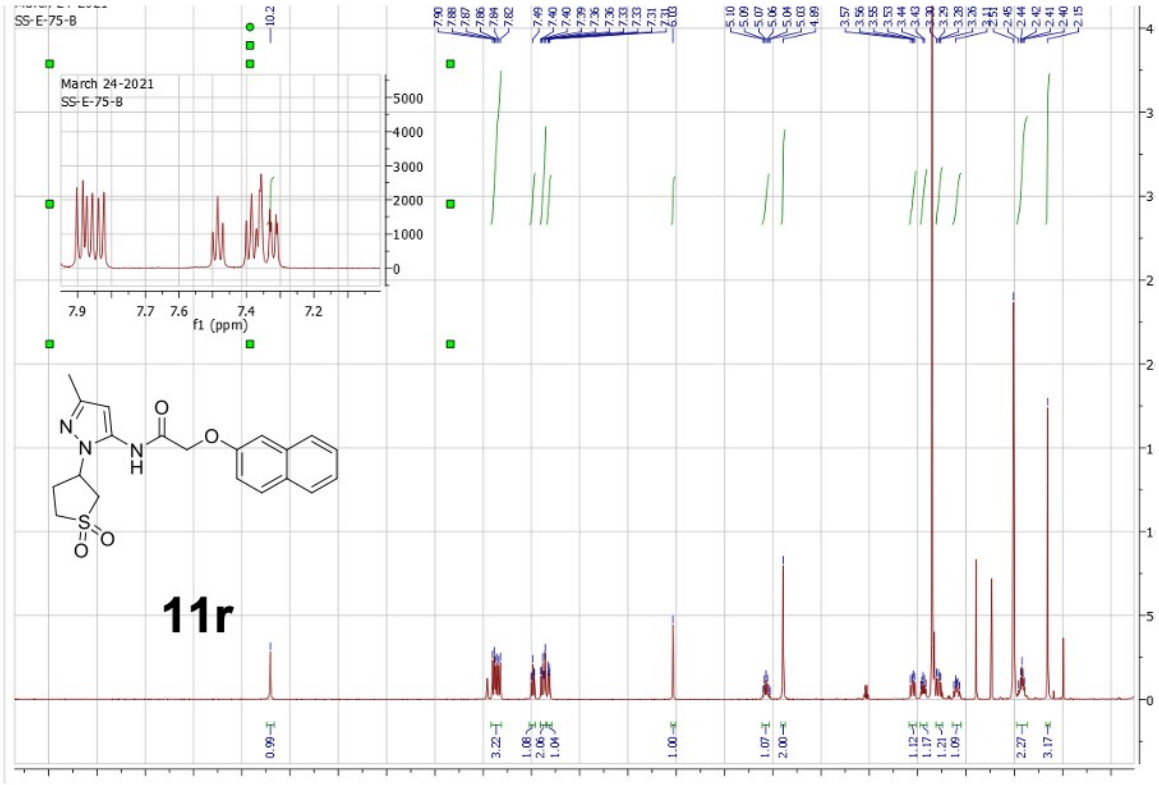

165.43
156.41
149.47
133.48
131.55
125.39
124.86
124.07
119.46
119.30
101.15
67.44
54.61
52.33
50.93
29.13
14.08
112.210
f1 (ppm)

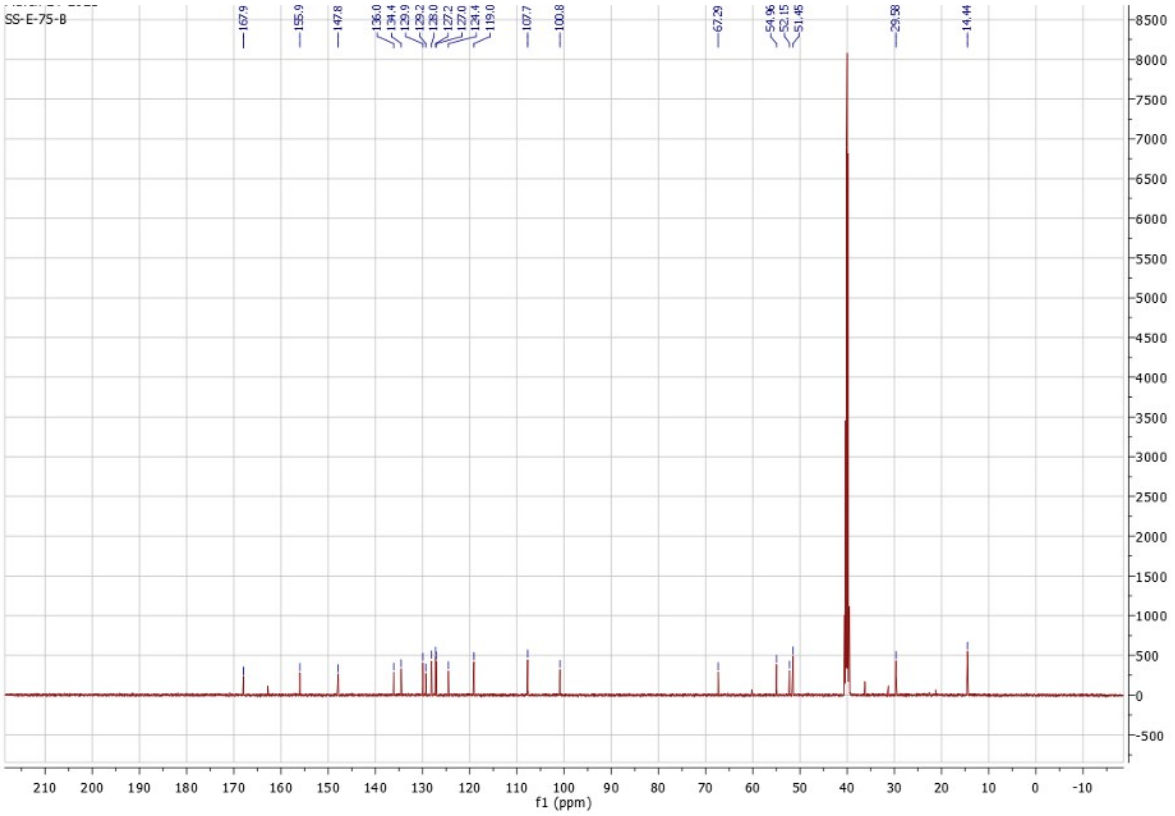

11p
A (s) 10.18
B (m) 7.65
C (d) 7.20
D (t) 7.15
E (s) 6.06
F (p) 5.13
G (s) 4.97
H (dd) 3.58
I (dt) 3.50
J (m) 3.29
K (dt) 3.17
L (dd) 2.46
M (s) 2.14
0.92
2.13
1.00
1.08
1.00
1.17
2.03
1.10
1.18
1.03
1.20
2.22
3.12
f1 (ppm)

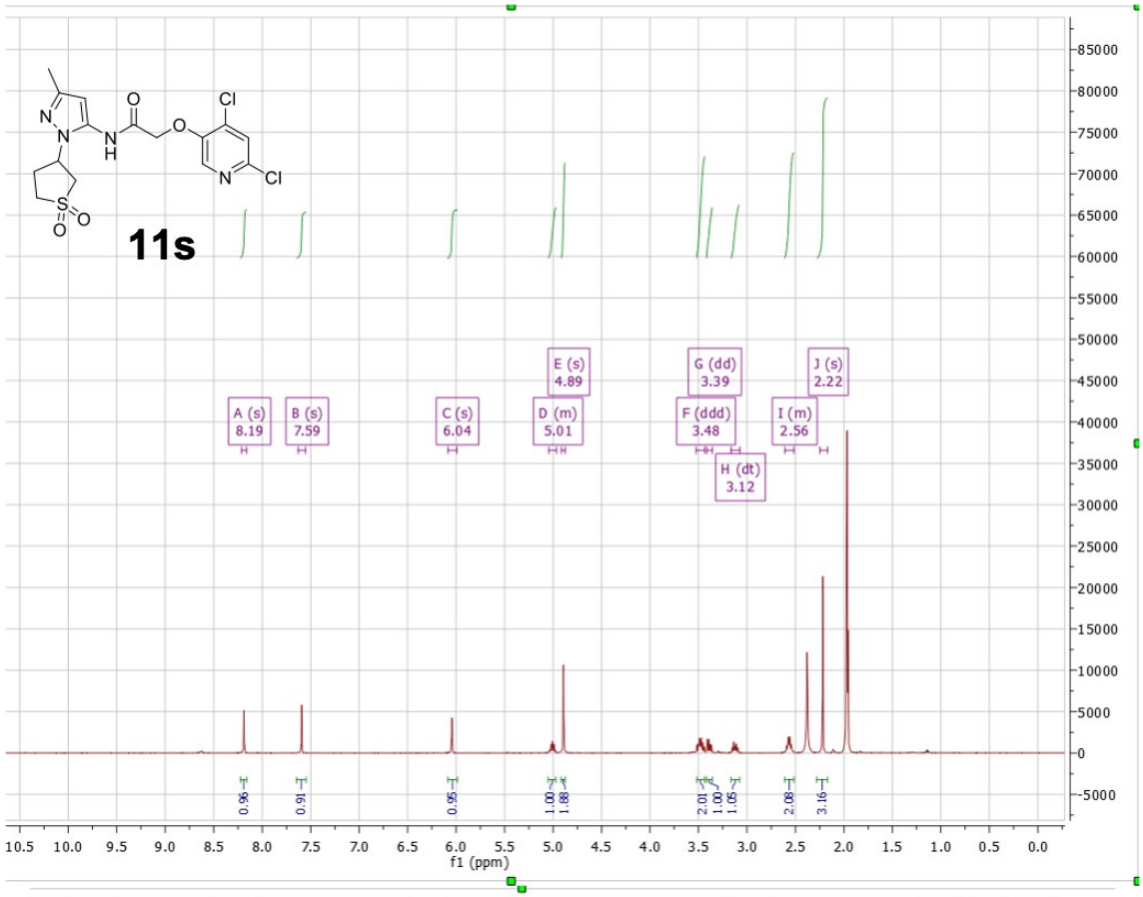

166.73
156.26
147.87
136.19
136.03
134.59
127.34
121.41
114.23
99.87
67.39
54.93
52.09
51.55
29.54
14.42
f1 (ppm)

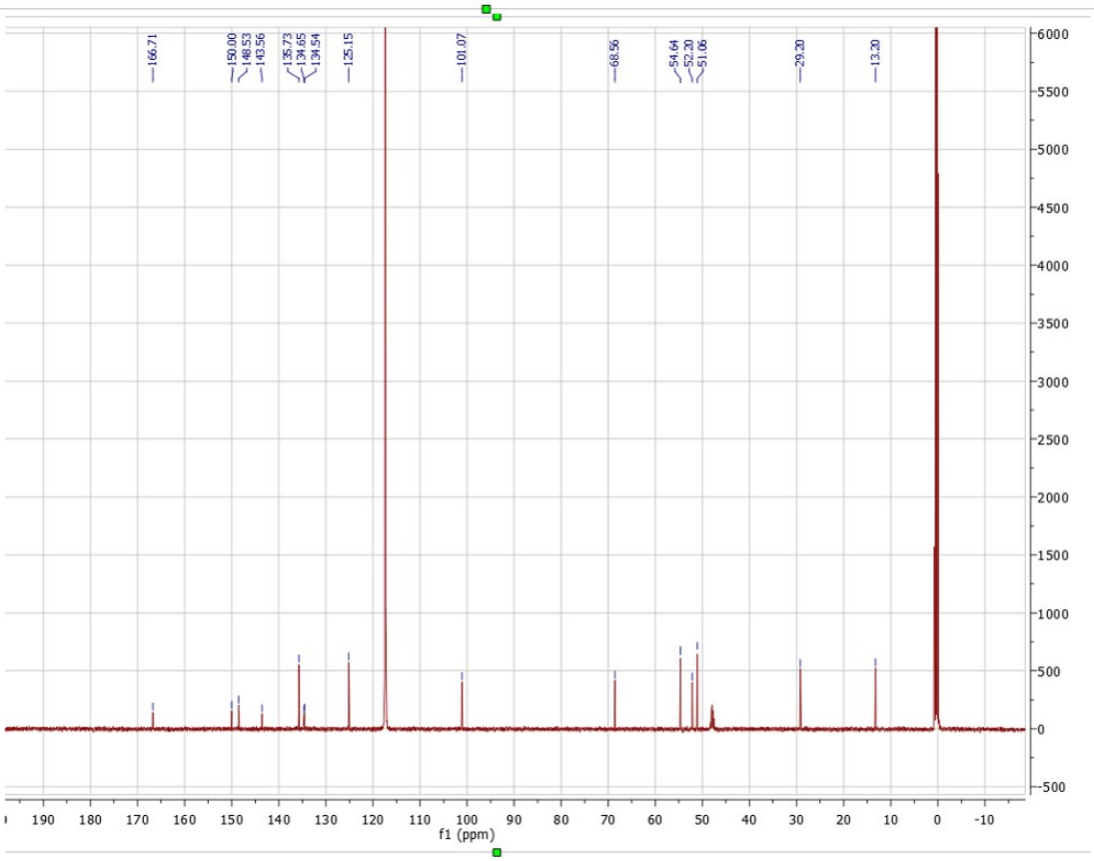

11q
B (s) 8.79
A (d) 8.81
D (d) 8.14
C (d) 8.32
F (dd) 7.54
E (dd) 7.63
G (d) 7.42
H (s) 6.01
J (s) 4.85
I (m) 4.99
L (dd) 3.36
K (m) 3.45
M (m) 3.04
O (m) 2.49
N (dd) 2.56
P (s) 2.22
f1 (ppm)

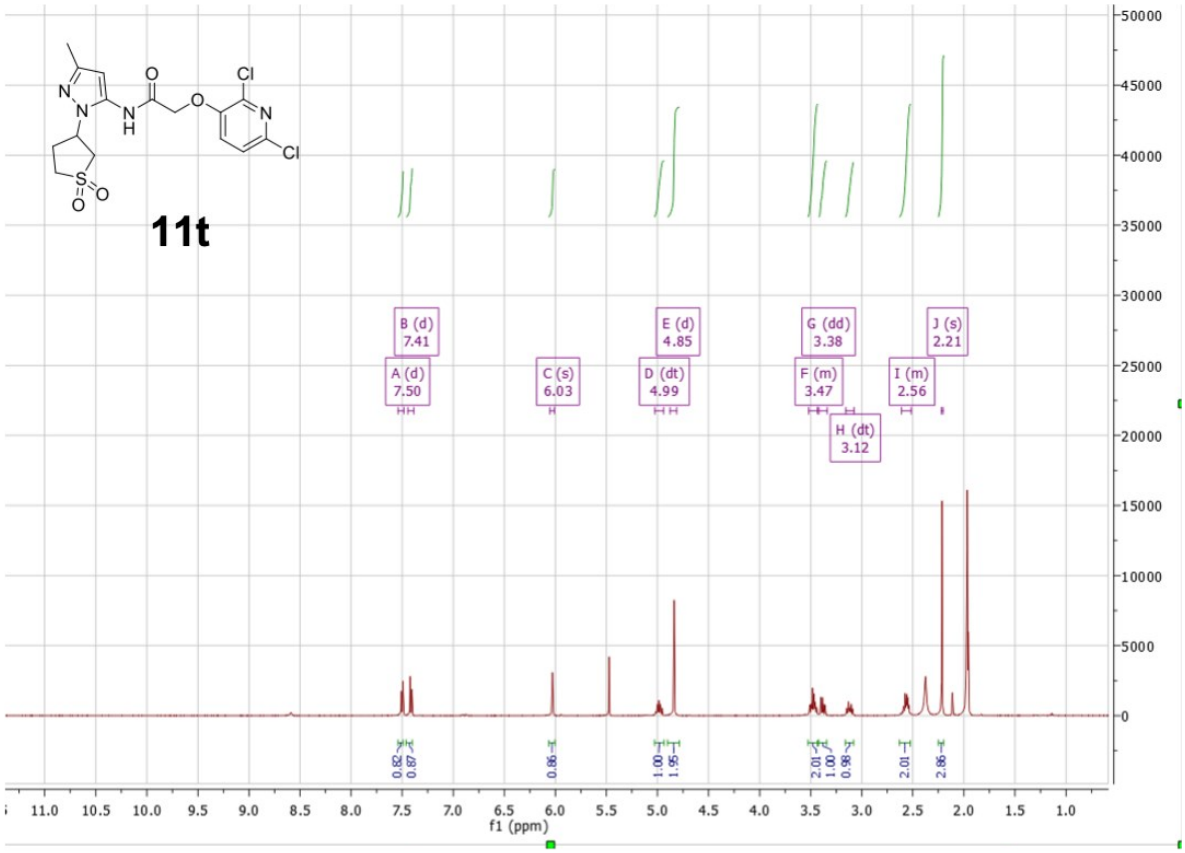

167.83
155.71
148.45
147.65
136.29
134.85
129.89
129.37
122.65
121.92
107.17
101.39
67.33
54.69
52.18
51.04
29.26
13.24
f1 (ppm)

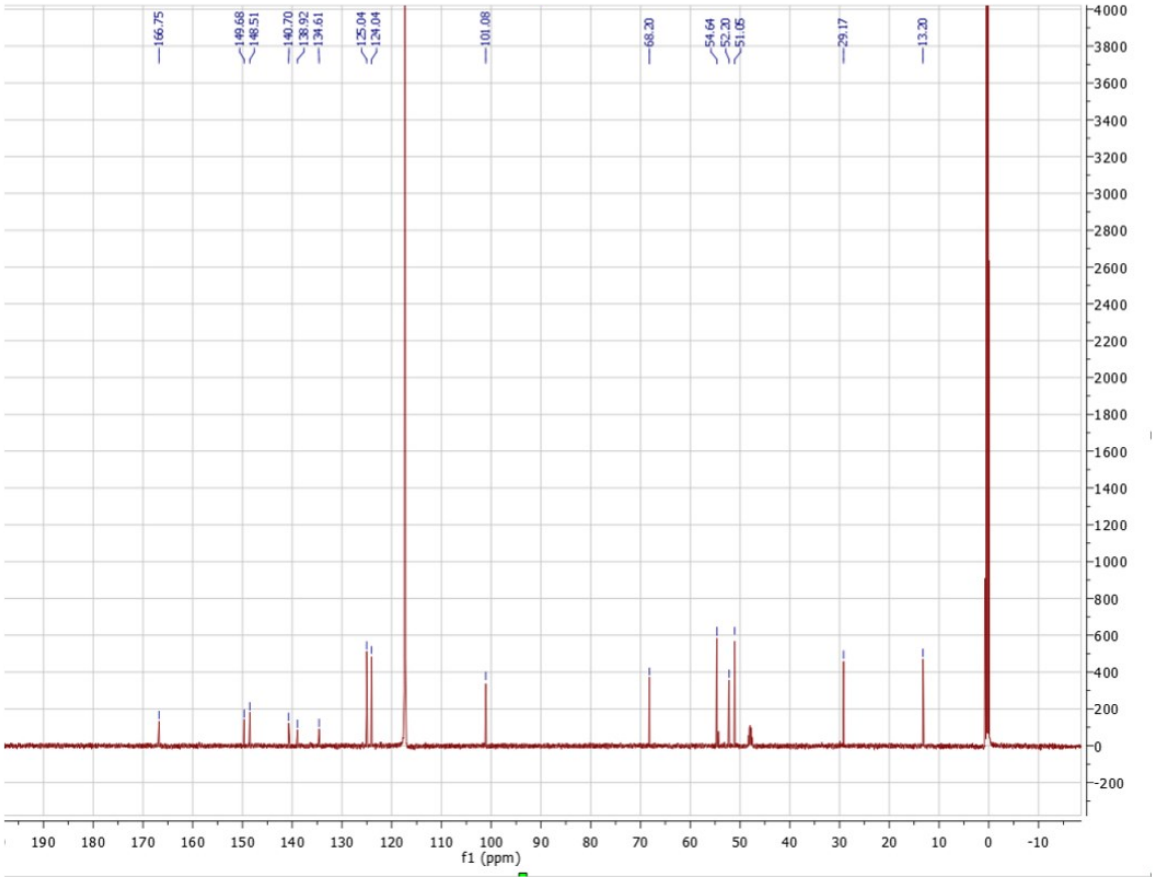

SS-E-75-B
March 24-2021
SS-E-75-B
f1 (ppm)
11r

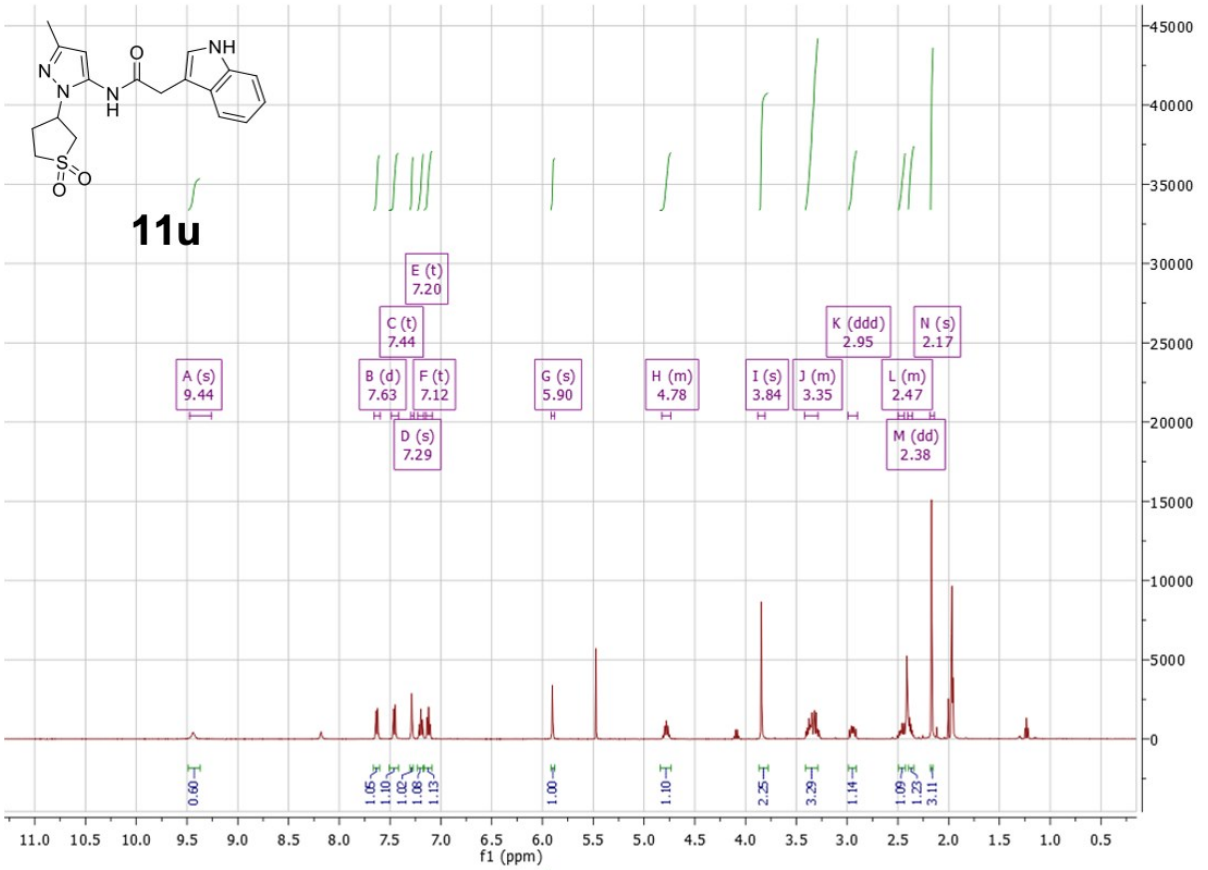

SS-E-75-B
f1 (ppm)

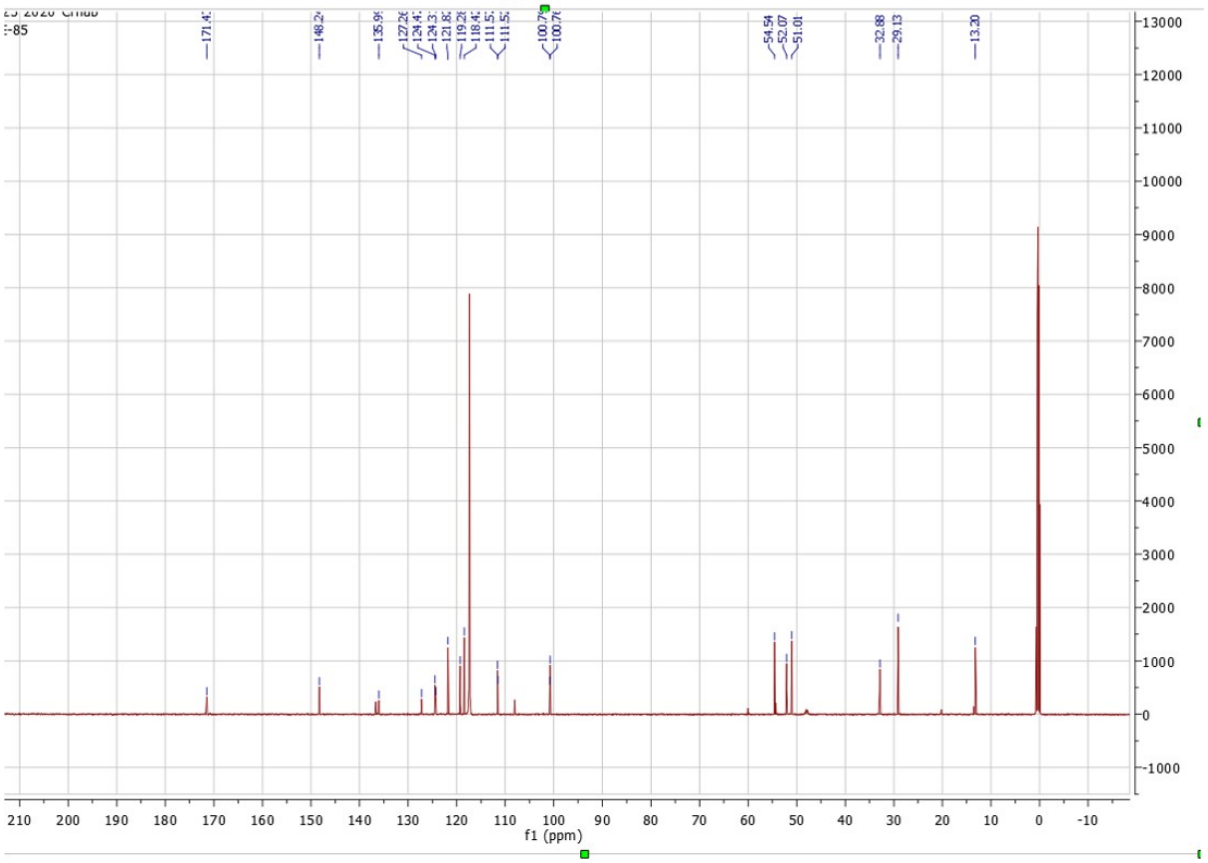

11s
A (s) 8.19
B (s) 7.59
C (s) 6.04
D (m) 5.01
E (s) 4.89
F (ddd) 3.48
G (dd) 3.39
H (dt) 3.12
I (m) 2.56
J (s) 2.22
f1 (ppm)

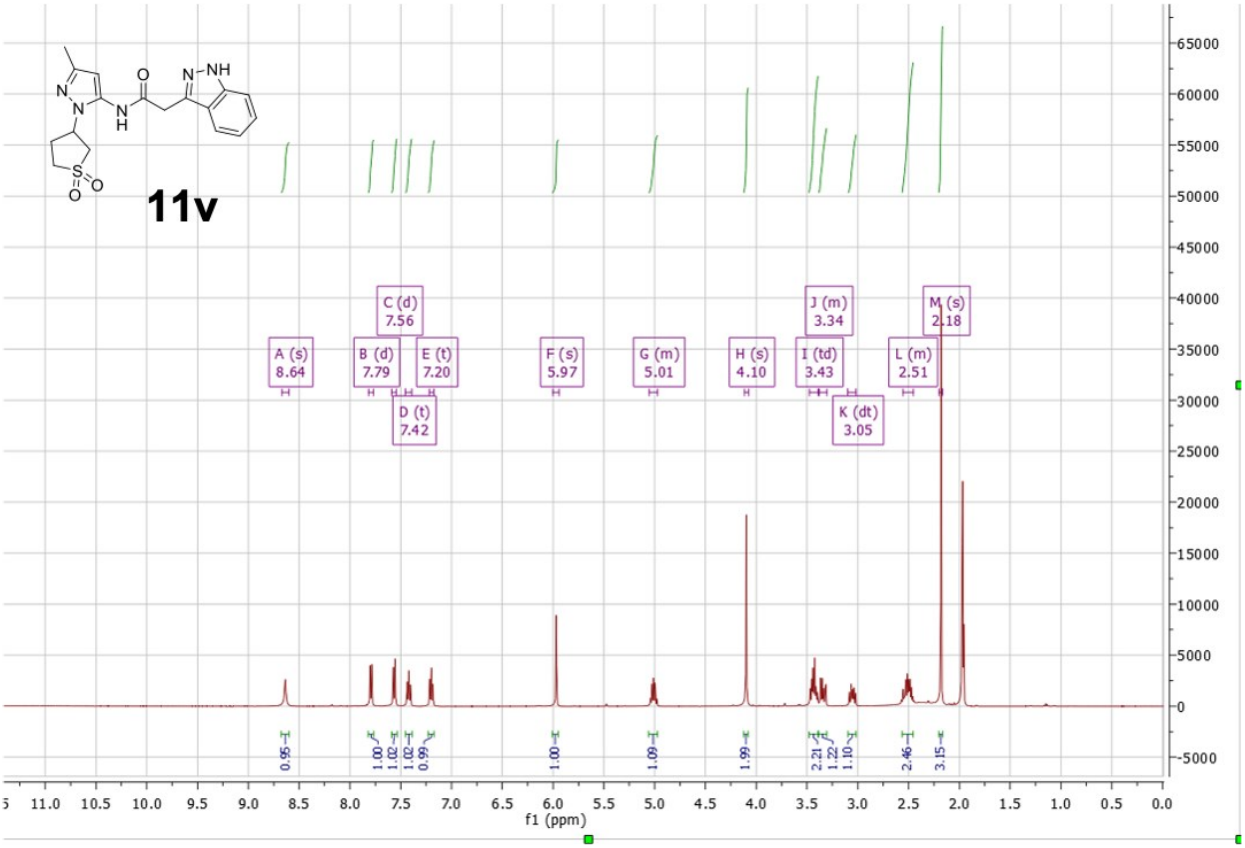

166.71
150.00
148.53
143.56
135.73
134.65
134.54
125.15
101.07
68.56
54.64
52.20
51.06
29.20
13.20
f1 (ppm)

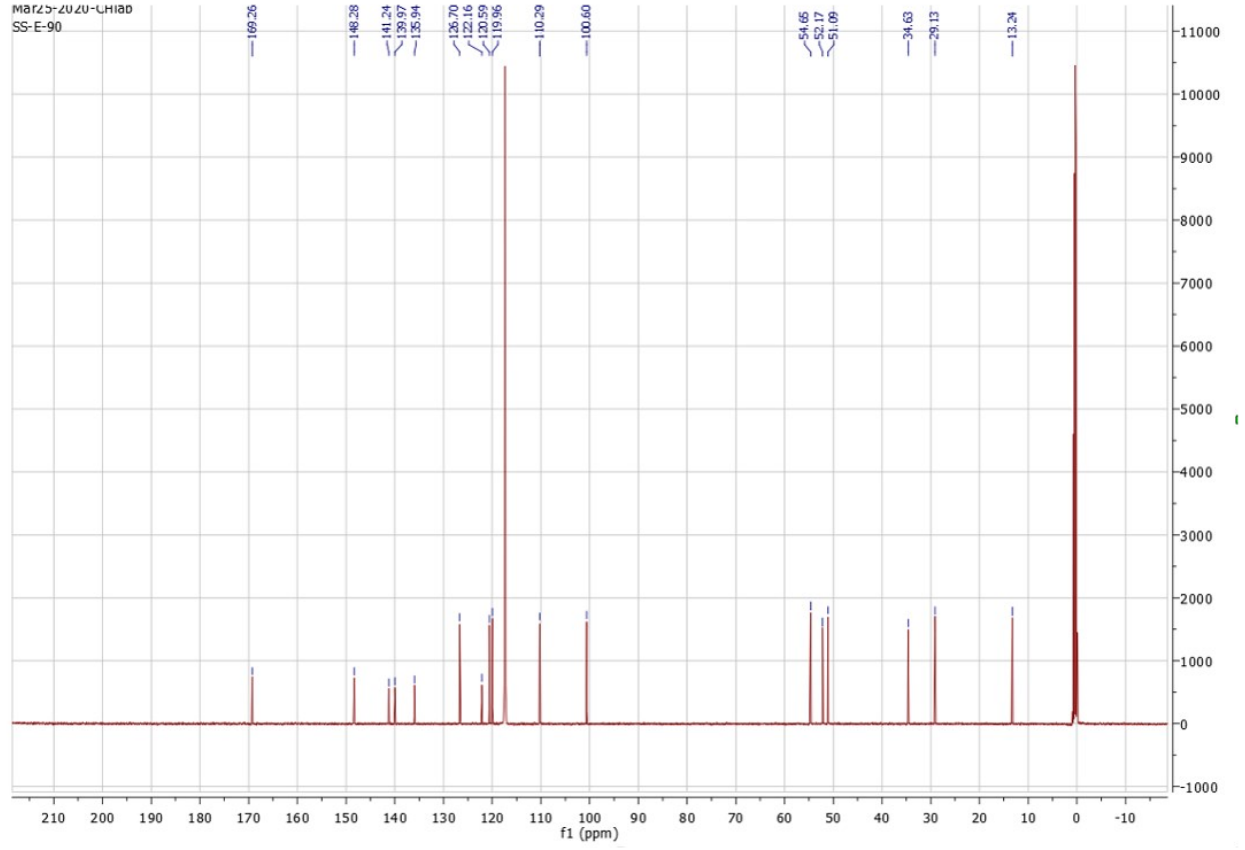

11t
B (d) 7.41
A (d) 7.50
C (s) 6.03
E (d) 4.85
D (dt) 4.99
G (dd) 3.38
F (m) 3.47
H (dt) 3.12
I (m) 2.56
J (s) 2.21
f1 (ppm)

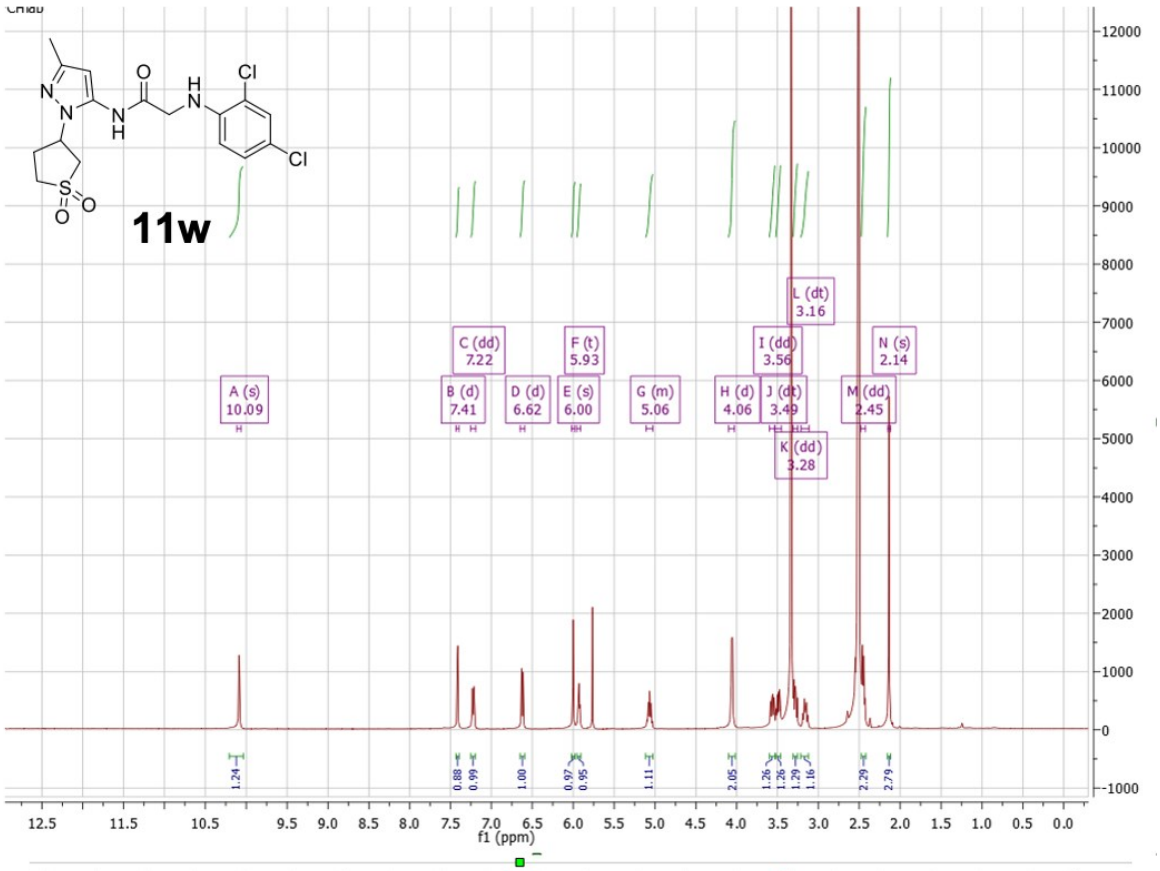

166.75
149.68
148.51
140.70
138.92
134.61
125.04
124.04
101.08
68.20
54.64
52.20
51.05
29.17
13.20
f1 (ppm)

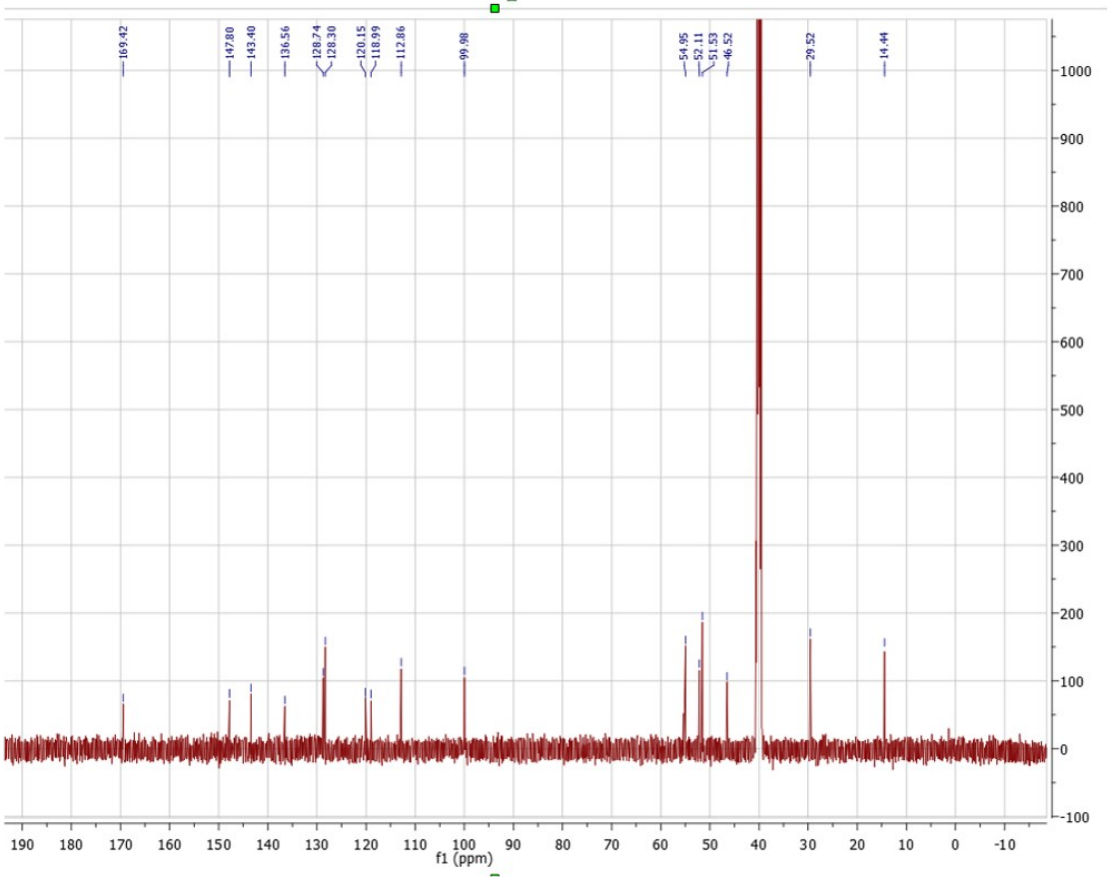

11u
A (s) 9.44
B (d) 7.63
C (t) 7.44
D (s) 7.29
E (t) 7.20
F (t) 7.12
G (s) 5.90
H (m) 4.78
I (s) 3.84
J (m) 3.35
K (ddd) 2.95
L (m) 2.47
M (dd) 2.38
N (s) 2.17
f1 (ppm)

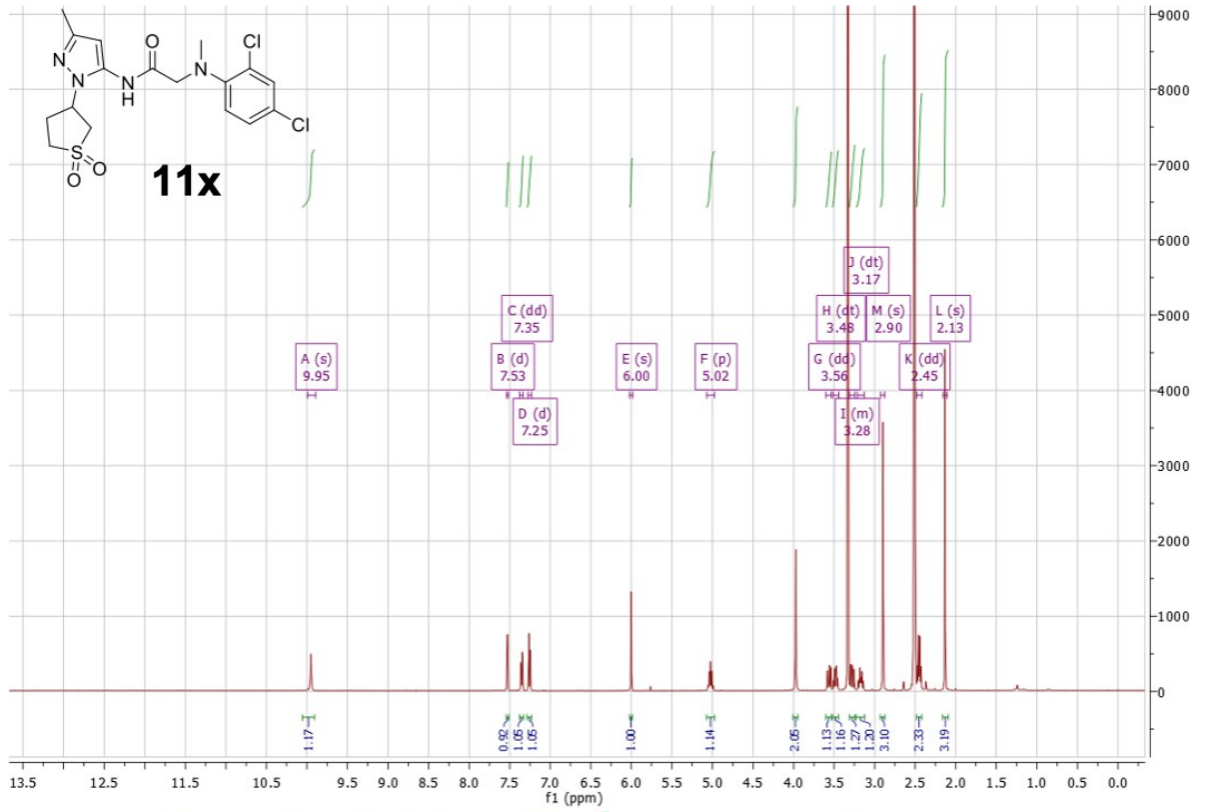

f1 (ppm)

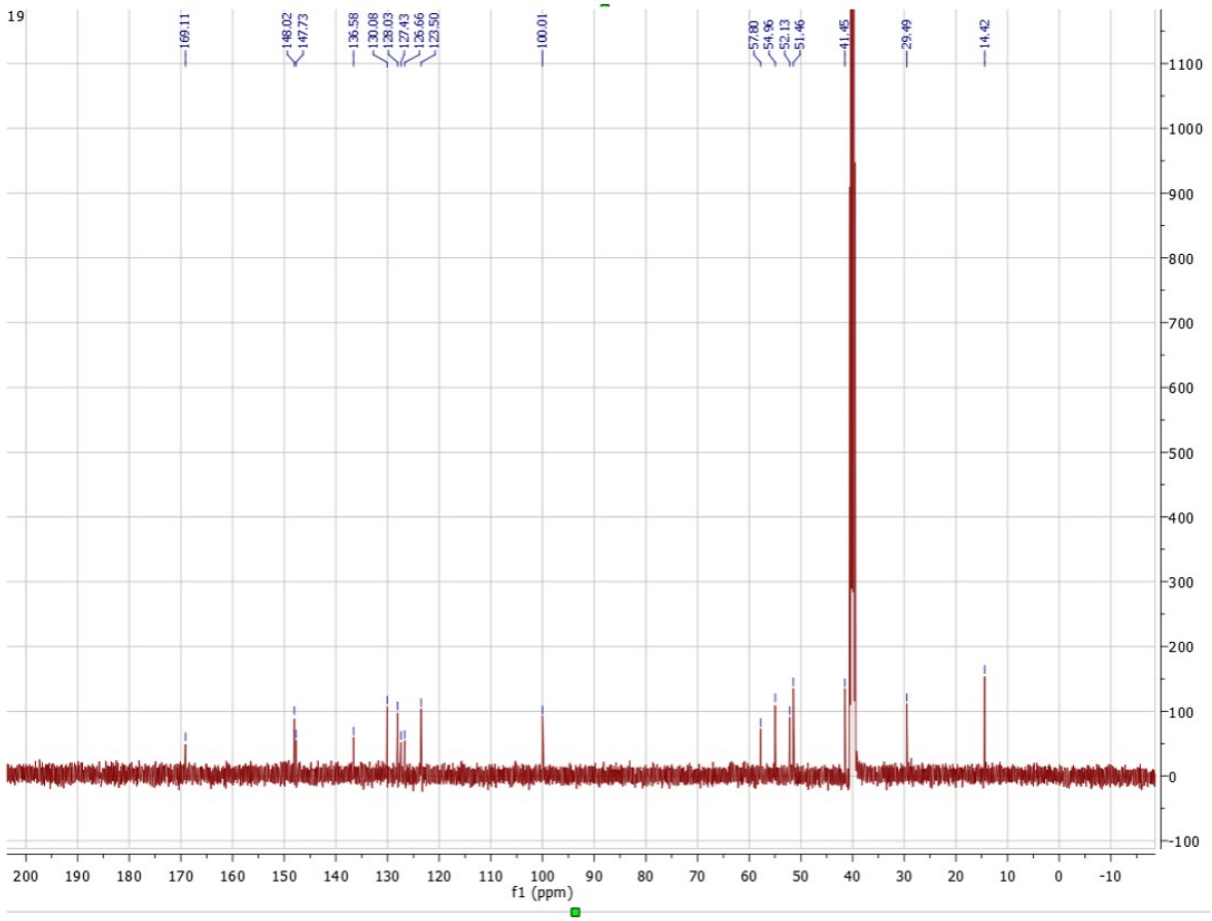

11v
A (s) 8.64
B (d) 7.79
C (d) 7.56
D (t) 7.42
E (t) 7.20
F (s) 5.97
G (m) 5.01
H (s) 4.10
I (td) 3.43
J (m) 3.34
K (dt) 3.05
L (m) 2.51
M (s) 2.18
f1 (ppm)

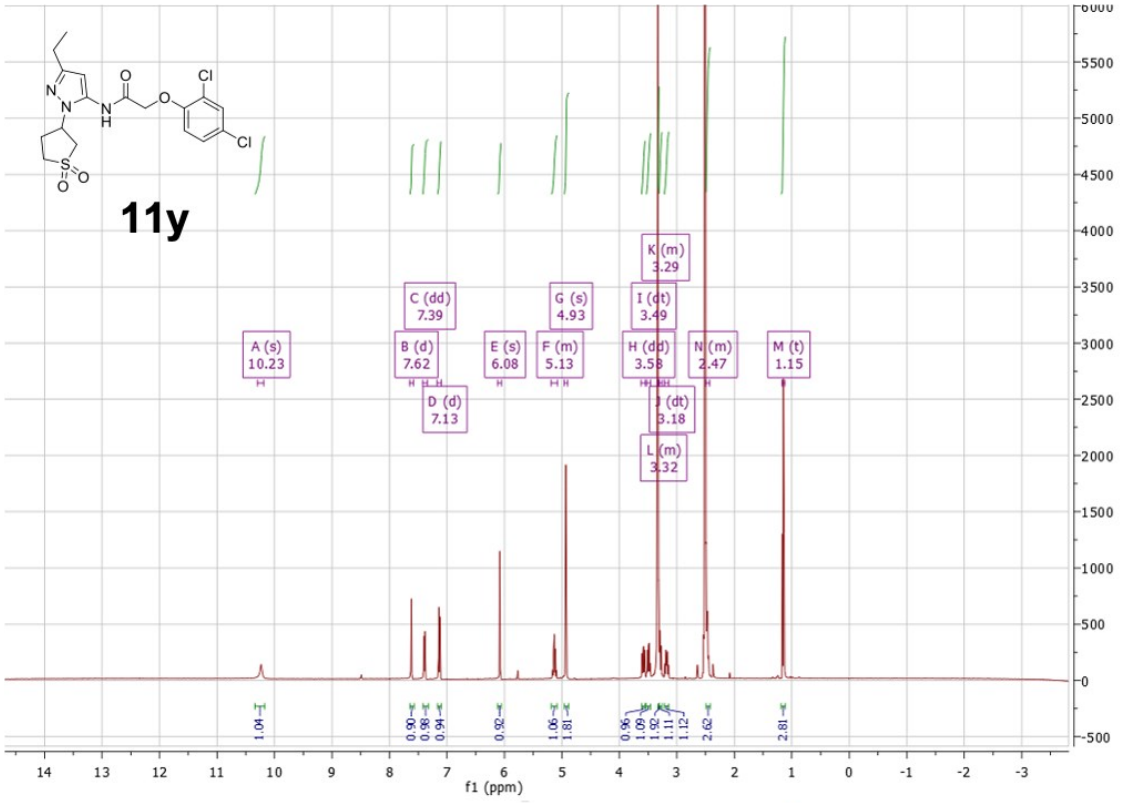

Mar25-2020-CHlab
SS-E-90
169.26
148.28
141.24
139.97
135.94
126.70
122.16
120.59
119.96
110.29
100.60
54.65
52.17
51.09
34.63
29.13
13.24
f1 (ppm)

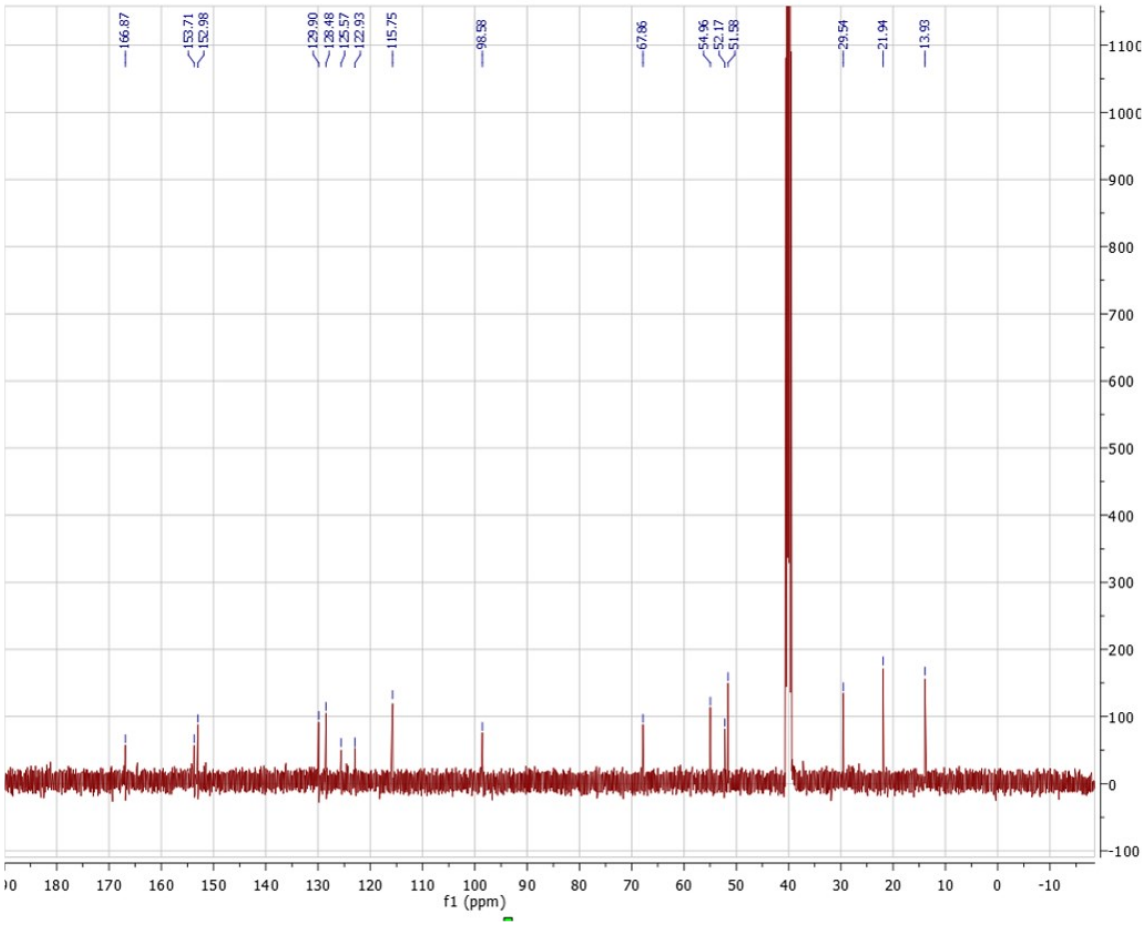

11w
A (s) 10.09
B (d) 7.41
C (dd) 7.22
D (d) 6.62
E (s) 6.00
F (t) 5.93
G (m) 5.06
H (d) 4.06
I (dd) 3.56
J (dt) 3.49
K (dd) 3.28
L (dt) 3.16
M (dd) 2.45
N (s) 2.14
f1 (ppm)

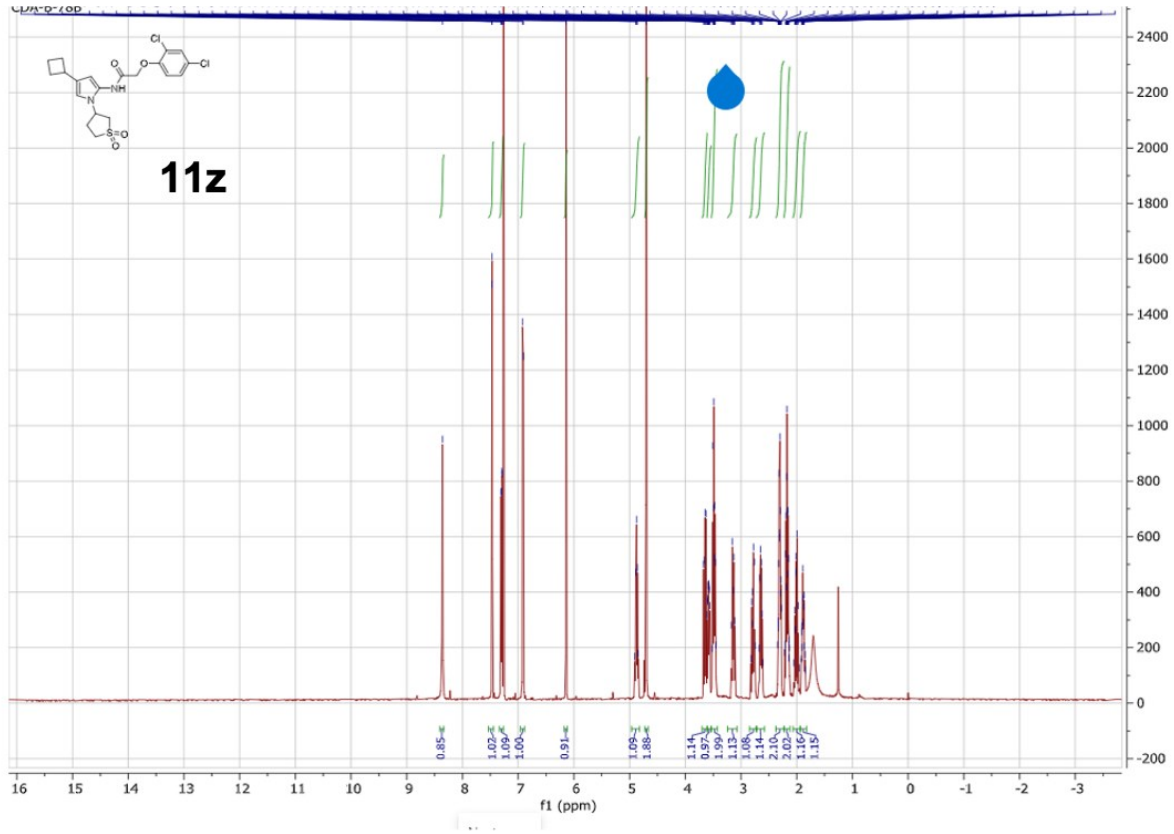

169.42
147.80
143.40
136.56
128.74
128.30
120.15
118.99
112.86
99.98
54.95
52.11
51.53
46.52
29.52
14.44
f1 (ppm)

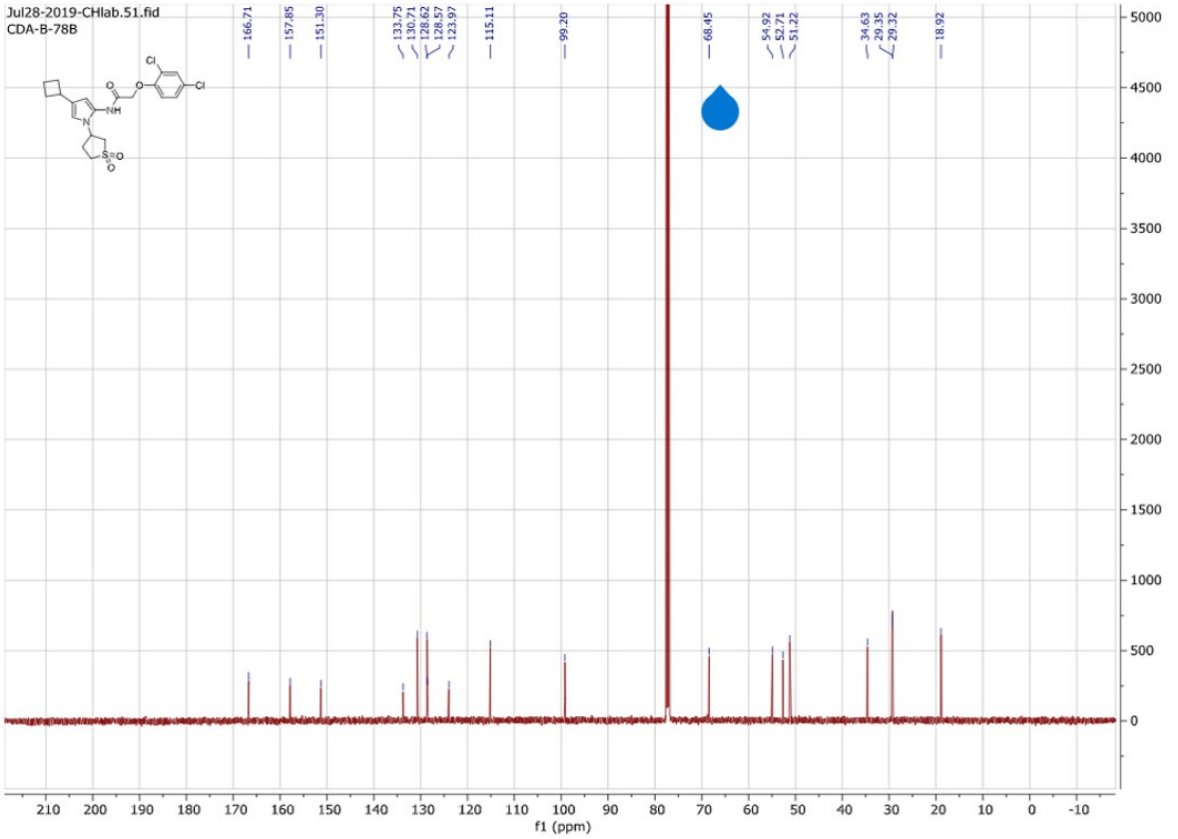

11x
A (s) 9.95
B (d) 7.53
C (dd) 7.35
D (d) 7.25
E (s) 6.00
F (p) 5.02
G (dd) 3.56
H (dt) 3.48
I (m) 3.28
J (dt) 3.17
K (dd) 2.45
M (s) 2.90
L (s) 2.13
f1 (ppm)

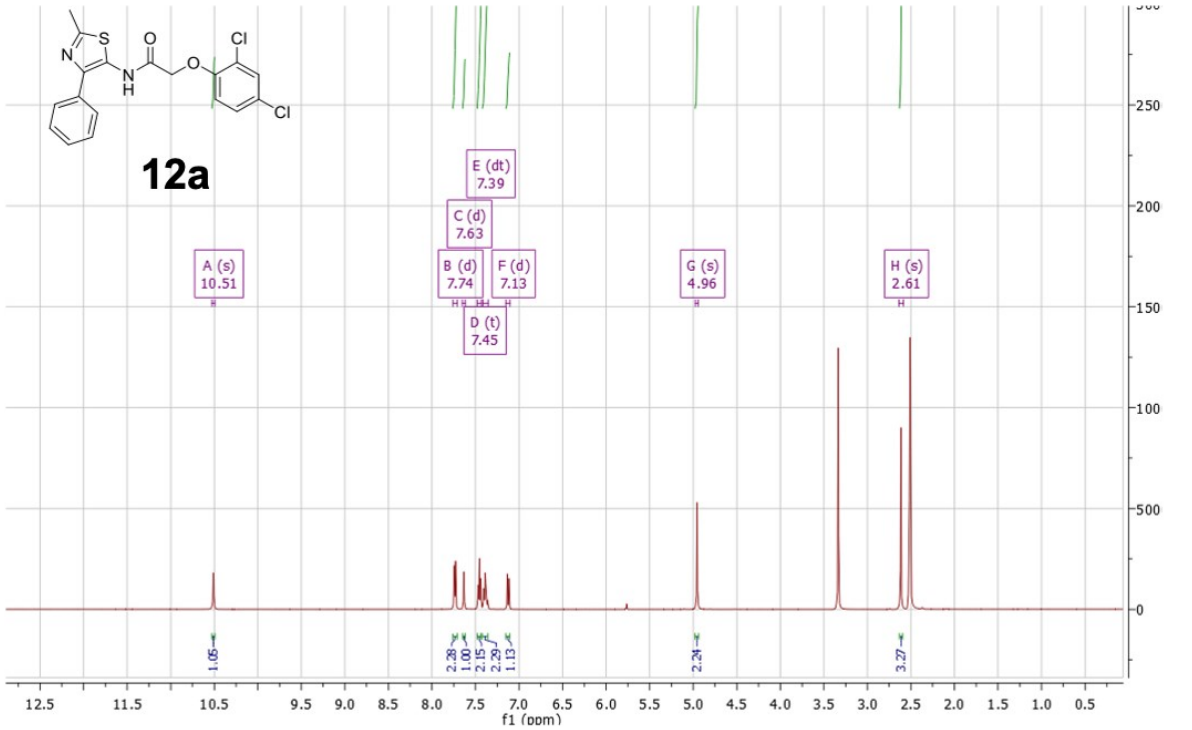

19
169.11
148.02
147.73
136.58
130.08
128.03
127.43
126.66
123.50
100.01
57.80
54.96
52.13
51.46
41.95
29.49
14.42
f1 (ppm)

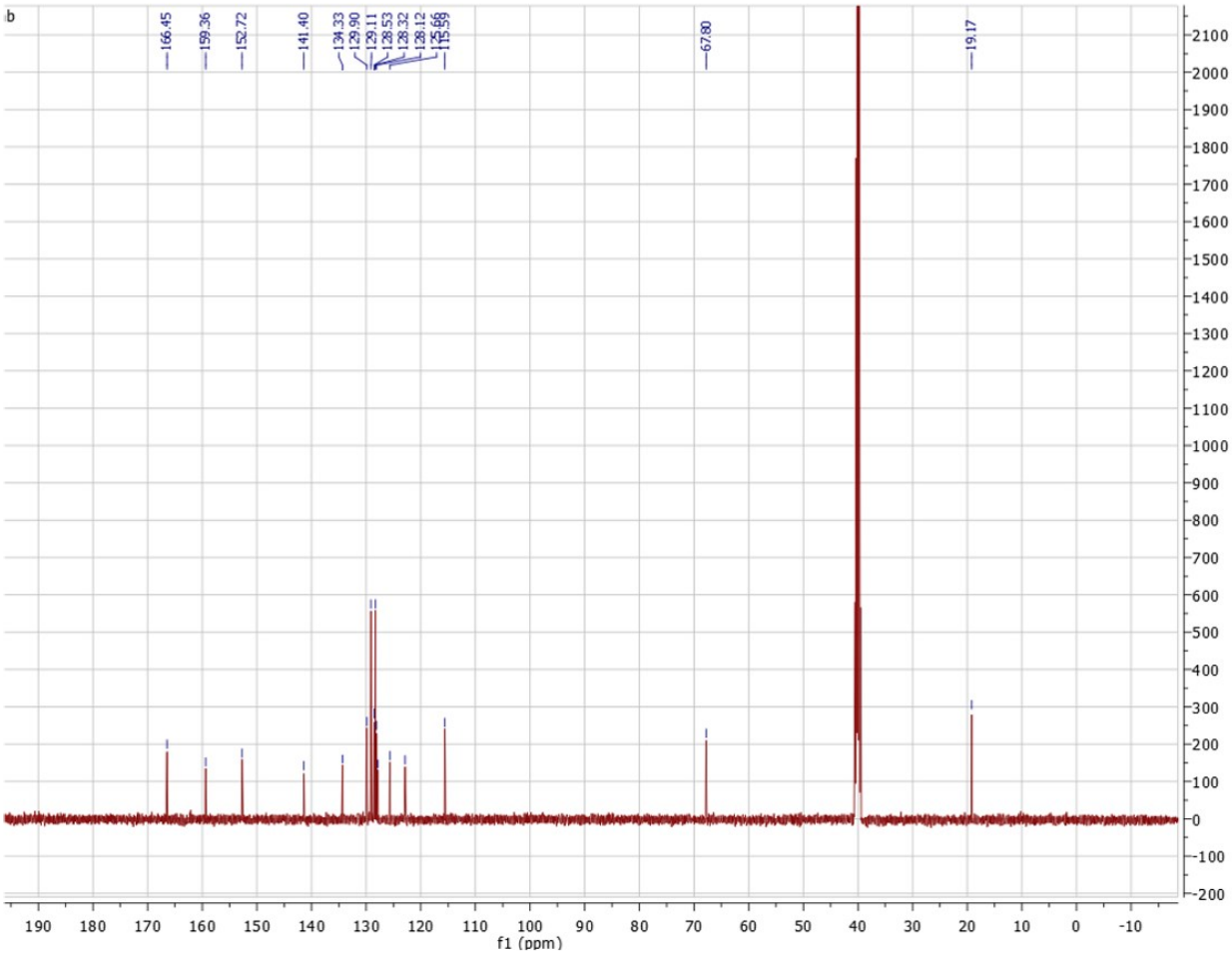

11y
A (s) 10.23
B (d) 7.62
C (dd) 7.39
D (d) 7.13
E (s) 6.08
F (m) 5.13
G (s) 4.93
H (dd) 3.58
I (dt) 3.49
J (dt) 3.18
K (m) 3.29
L (m) 3.32
N (m) 2.47
M (t) 1.15
f1 (ppm)

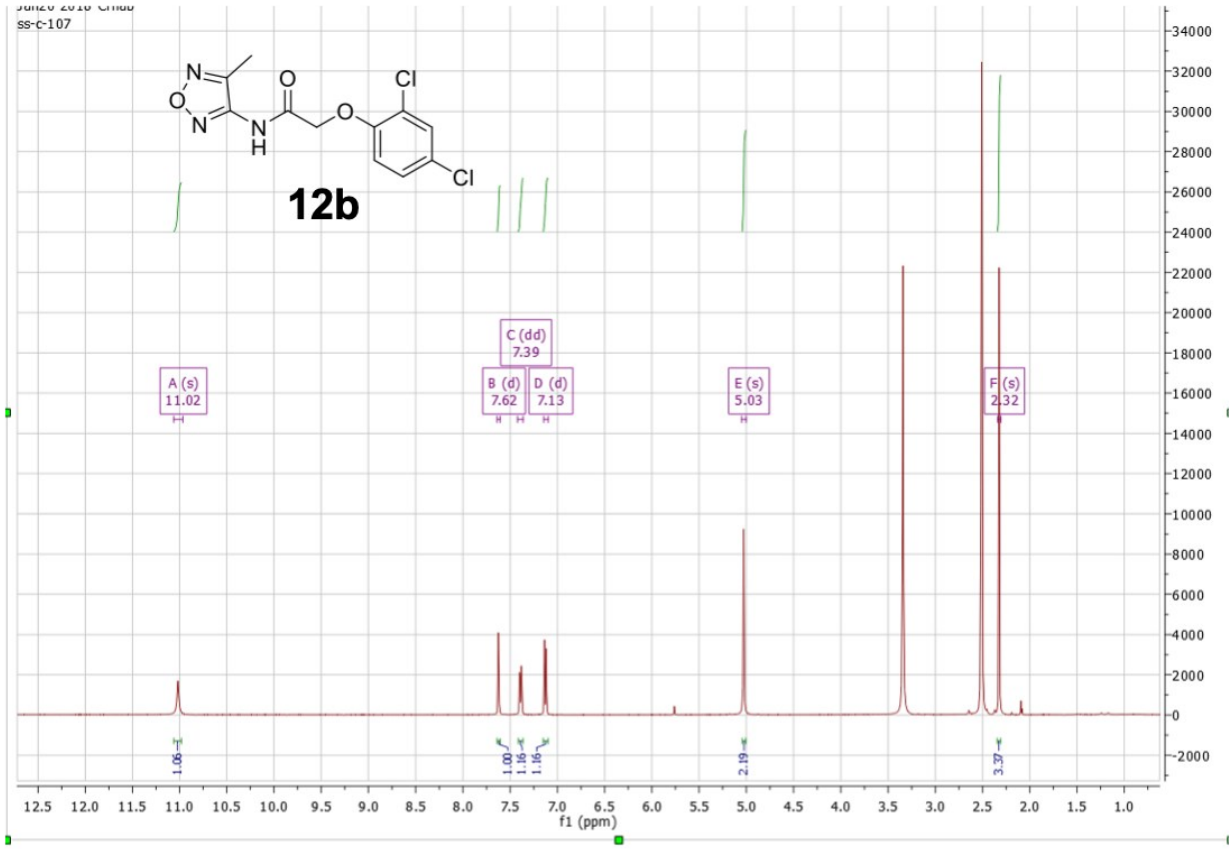

166.87
153.71
152.98
129.90
128.48
125.57
122.93
115.75
98.58
67.86
54.96
52.17
51.58
29.54
21.94
13.93
f1 (ppm)

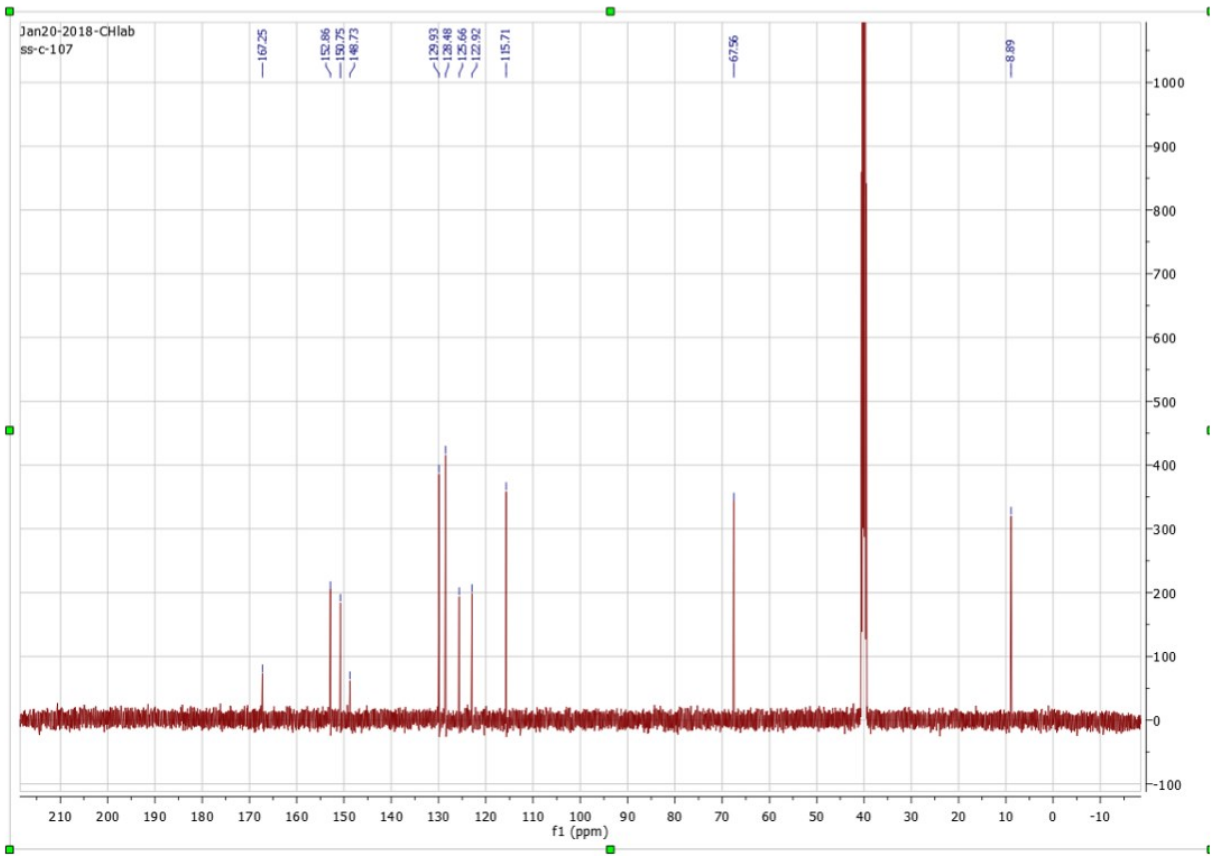

11z
f1 (ppm)

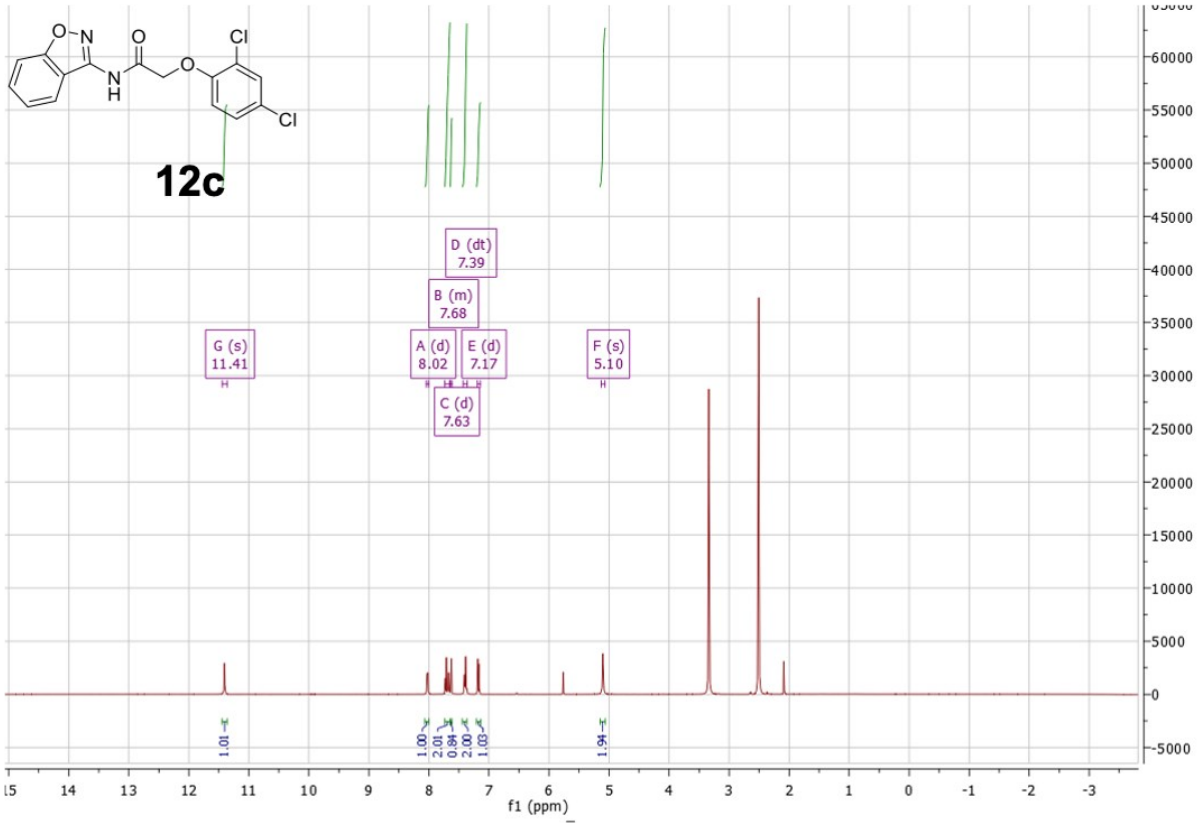

Jul28-2019-CHlab.51.fid
CDA-B-78B
166.71
157.85
151.30
133.75
130.71
128.62
128.57
123.97
115.11
99.20
68.45
54.92
52.71
51.22
34.63
29.35
29.32
18.92
f1 (ppm)

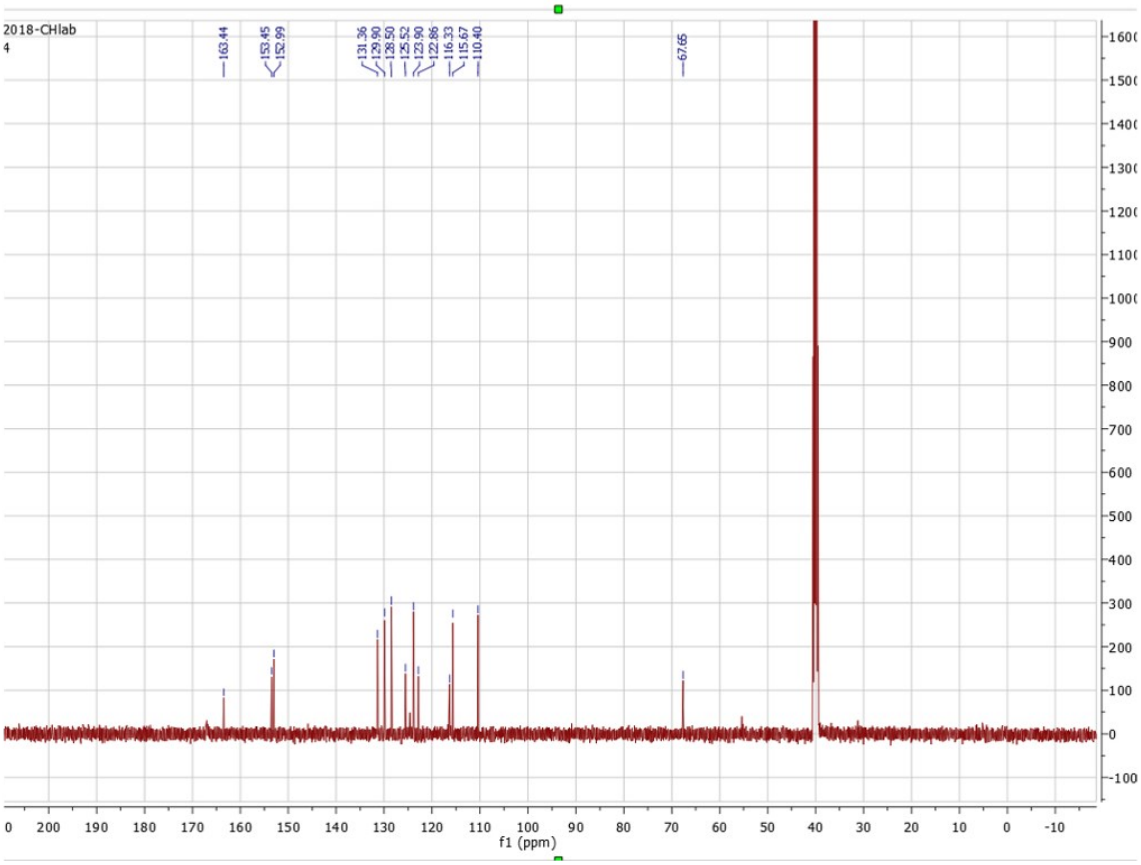

12a
A (s)
10.51
B (d)
7.74
C (d)
7.63
D (t)
7.45
E (dt)
7.39
F (d)
7.13
G (s)
4.96
H (s)
2.61
f1 (ppm)

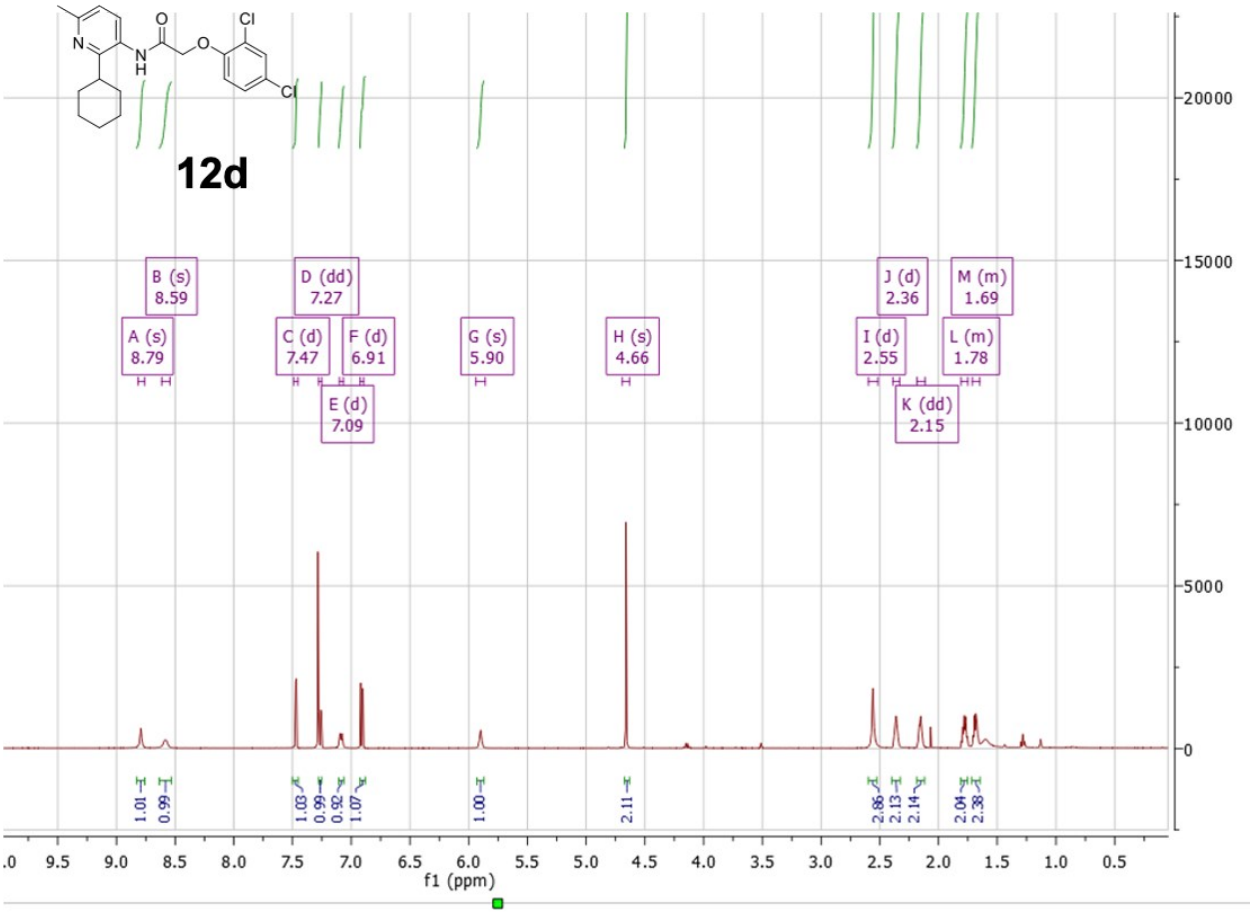

166.45
159.36
152.72
141.40
134.33
129.90
129.11
128.53
128.32
128.12
125.66
115.59
67.80
19.17
f1 (ppm)

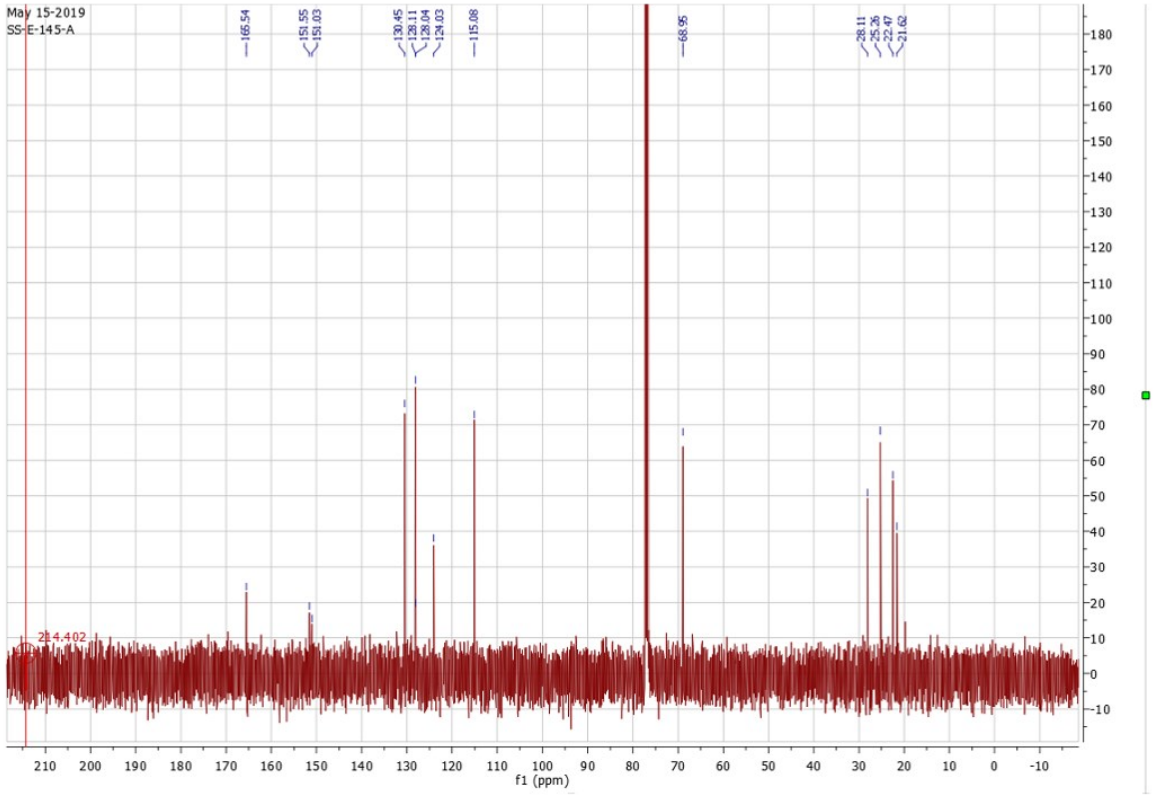

ss-c-107
12b
A (s)
11.02
C (dd)
7.39
B (d)
7.62
D (d)
7.13
E (s)
5.03
F (s)
2.32
f1 (ppm)

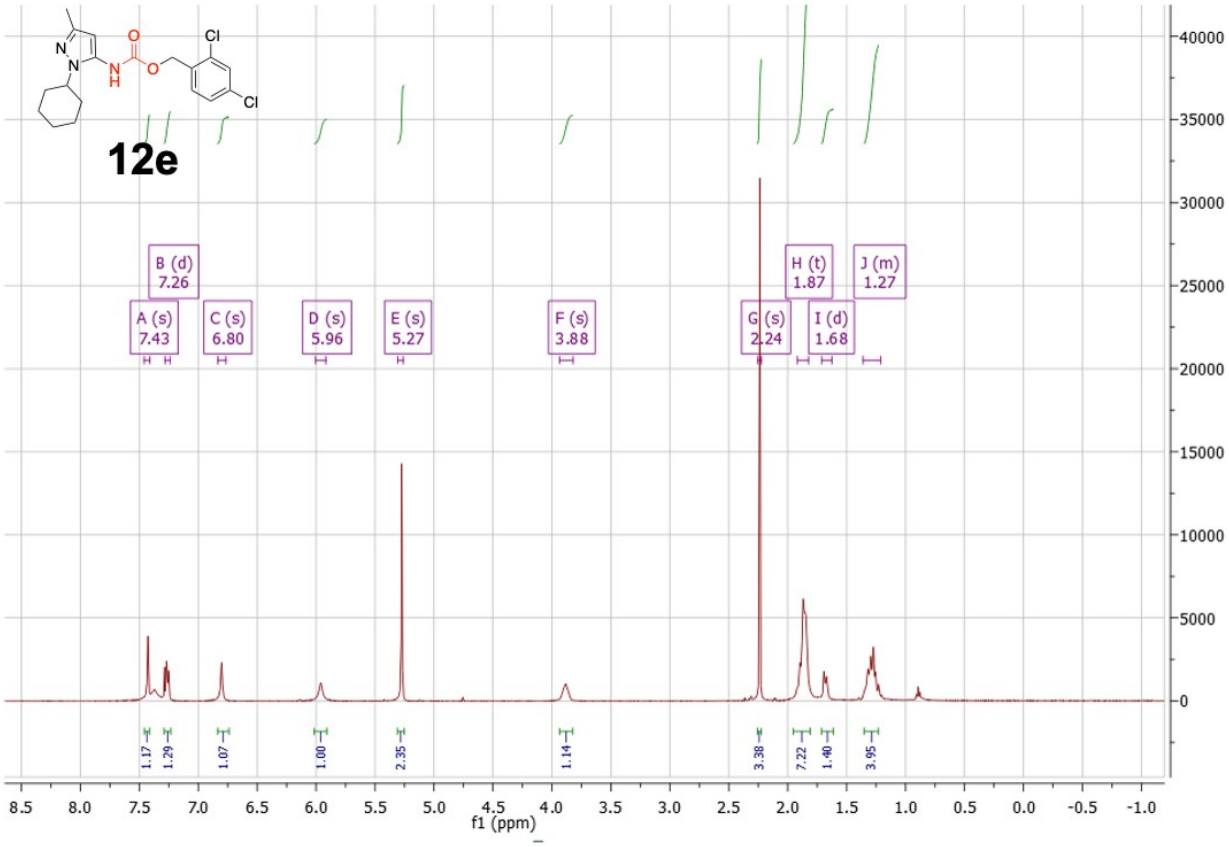

Jan20-2018-CHlab
ss-c-107
167.25
152.86
150.75
148.73
129.93
128.48
125.66
122.92
115.71
67.56
8.89
f1 (ppm)

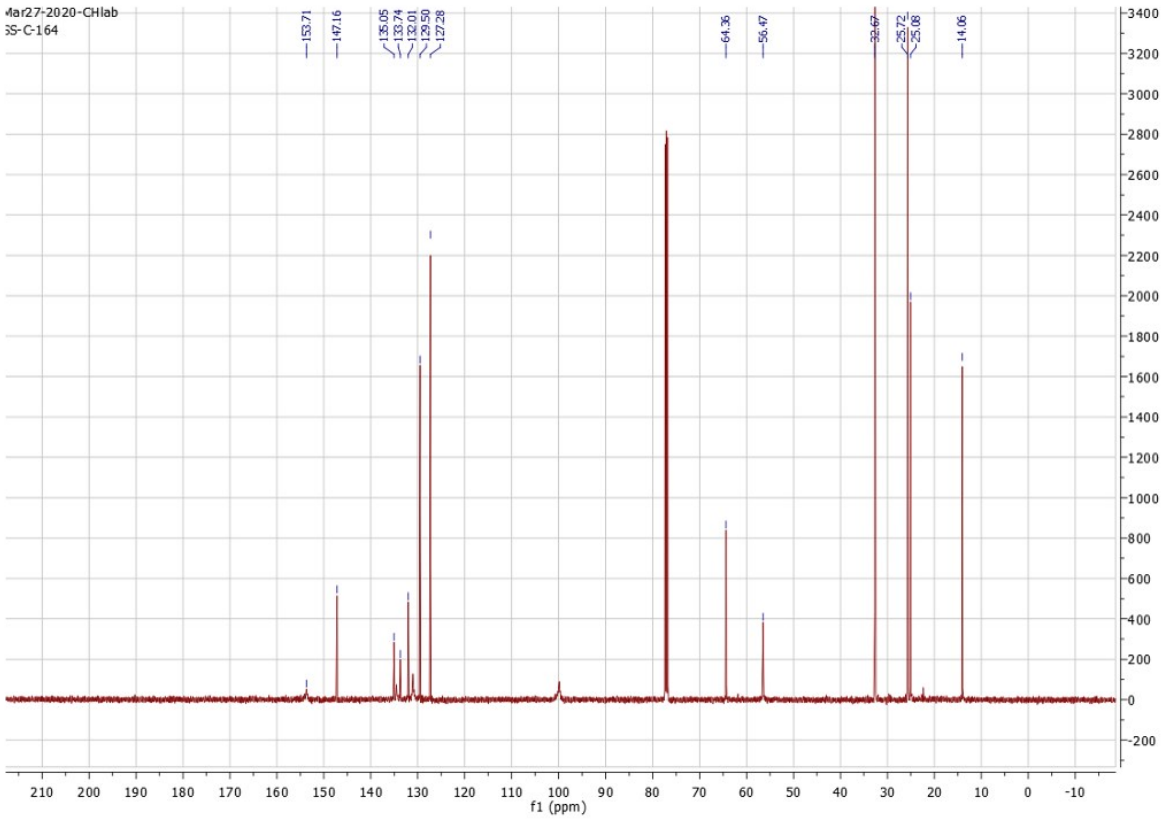

12c
D (dt)
7.39
B (m)
7.68
G (s)
11.41
A (d)
8.02
E (d)
7.17
F (s)
5.10
C (d)
7.63
1.01
1.00
2.01
0.84
2.00
1.03
1.94
f1 (ppm)

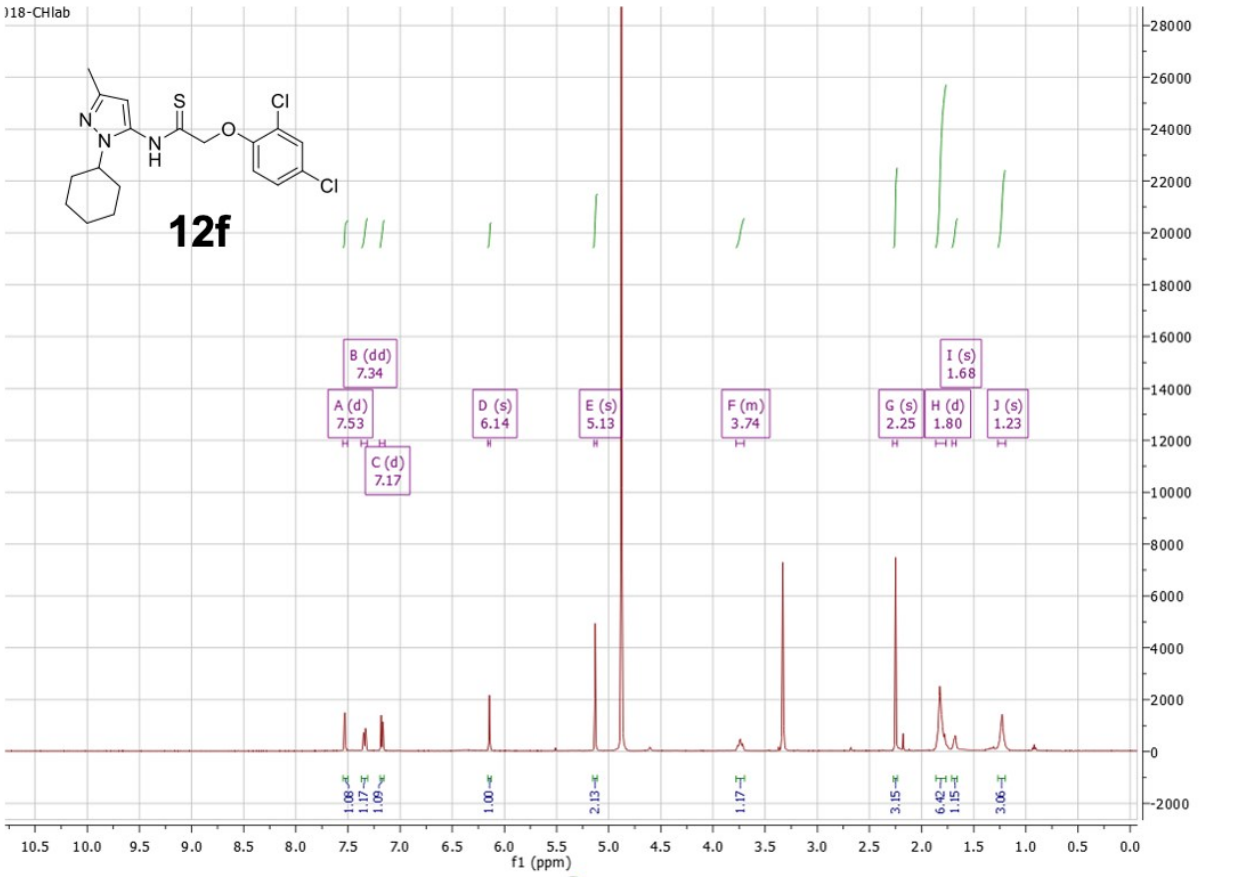

2018-CHlab
4
163.44
153.45
152.99
131.36
129.90
128.50
125.52
123.90
122.86
116.33
115.67
110.40
67.65
f1 (ppm)

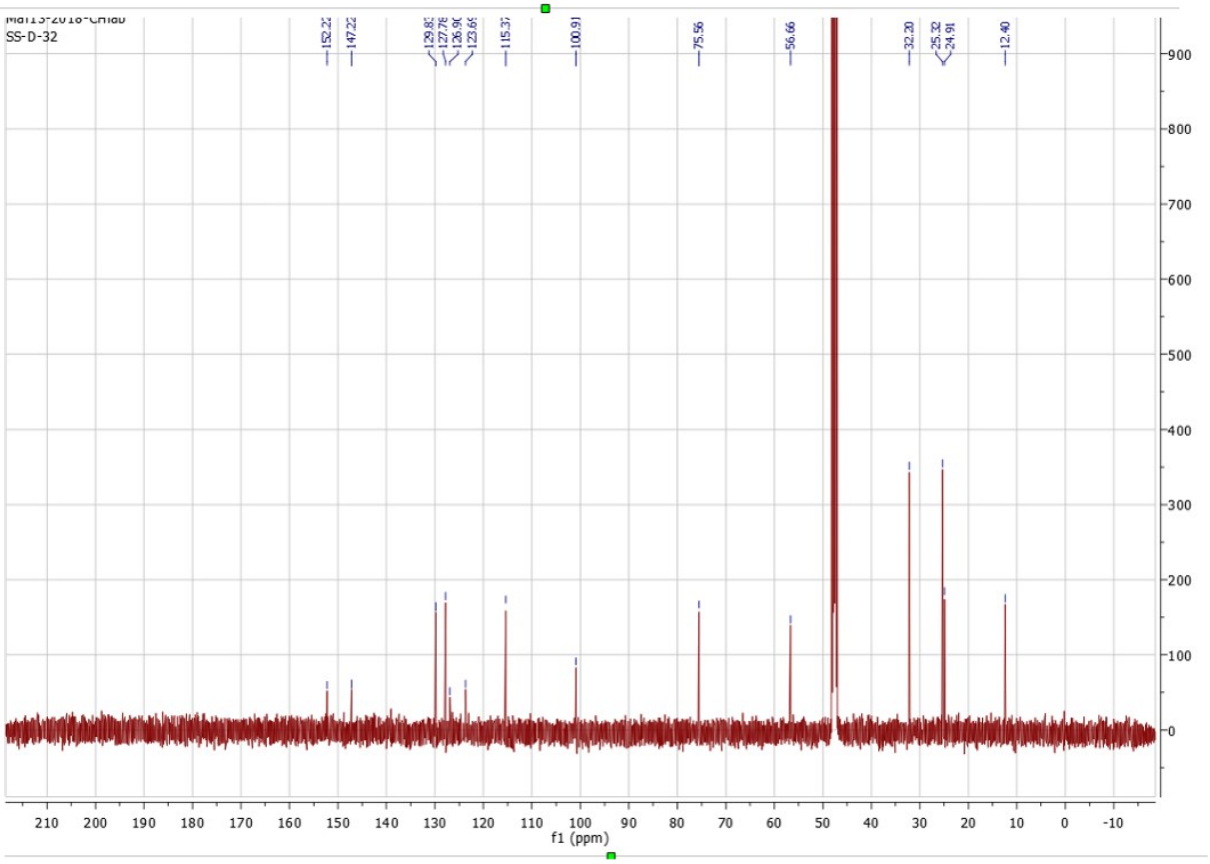

12d
B (s)
8.59
A (s)
8.79
D (dd)
7.27
C (d)
7.47
F (d)
6.91
E (d)
7.09
G (s)
5.90
H (s)
4.66
J (d)
2.36
I (d)
2.55
M (m)
1.69
L (m)
1.78
K (dd)
2.15
f1 (ppm)


May 15-2019
SS-E-145-A
165.54
151.55
151.03
130.45
128.11
128.04
124.03
115.08
68.95
28.11
25.26
22.47
21.62
214.402
f1 (ppm)

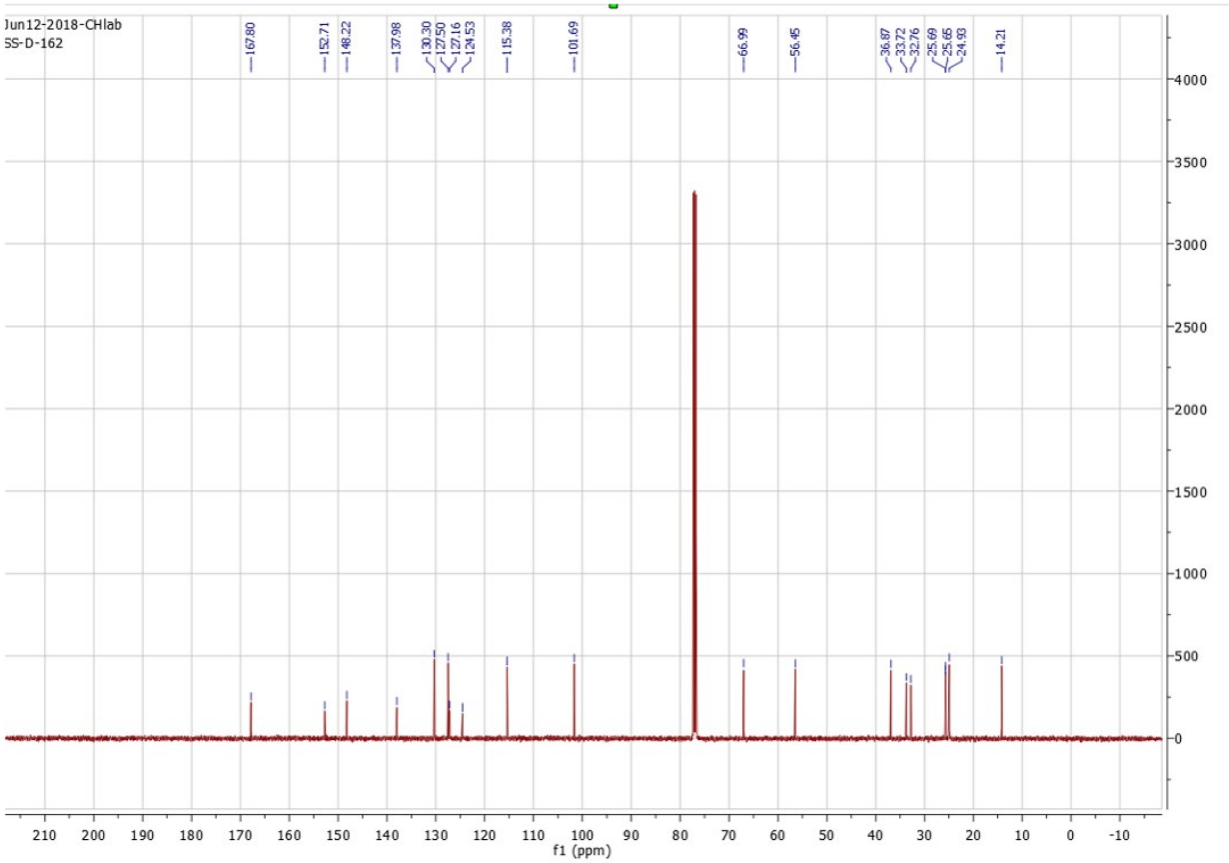

12e
B (d) 7.26
A (s) 7.43
C (s) 6.80
D (s) 5.96
E (s) 5.27
F (s) 3.88
G (s) 2.24
H (t) 1.87
I (d) 1.68
J (m) 1.27
1.17
1.29
1.07
1.00
2.35
1.14
3.38
7.22
1.40
3.95
f1 (ppm)

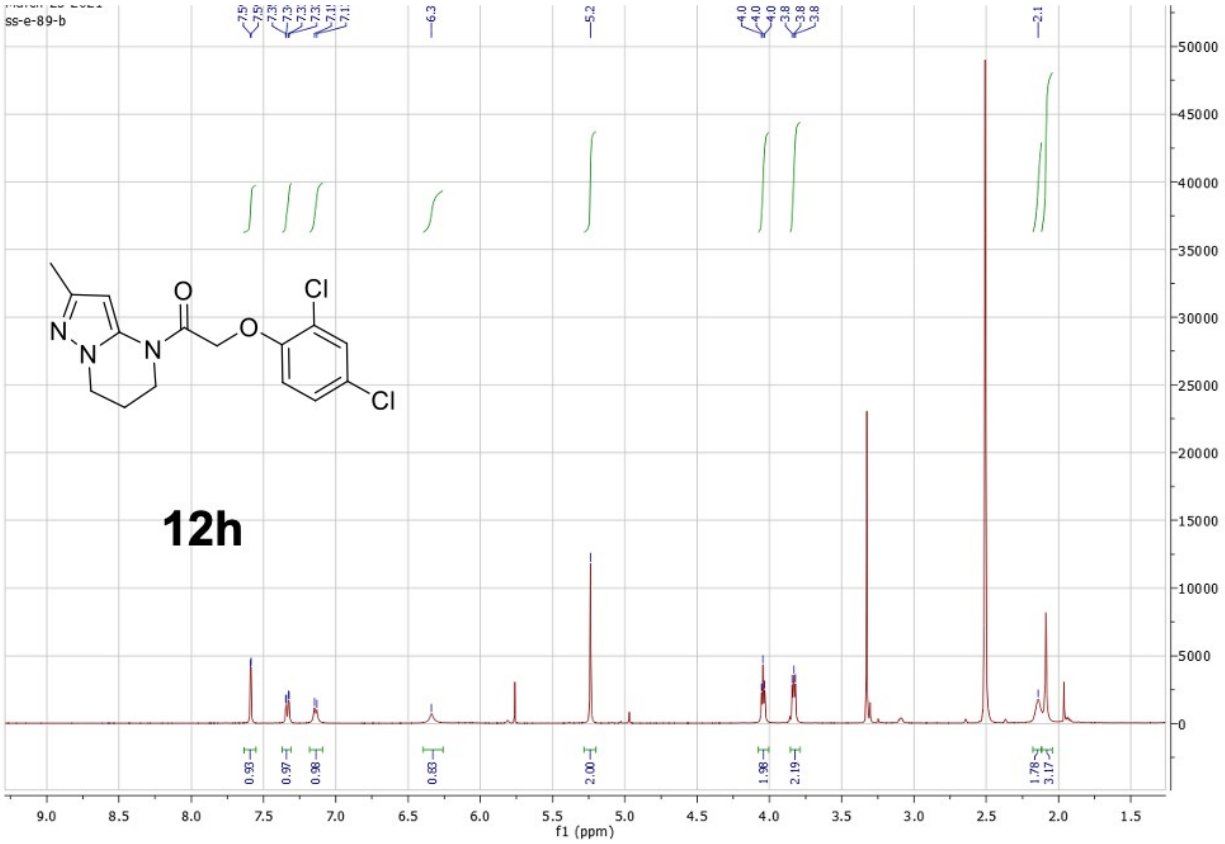

Mar27-2020-CHlab
GS-C-164
153.71
147.16
135.05
133.74
132.01
129.50
127.28
64.36
56.47
32.67
25.72
25.08
14.06
f1 (ppm)

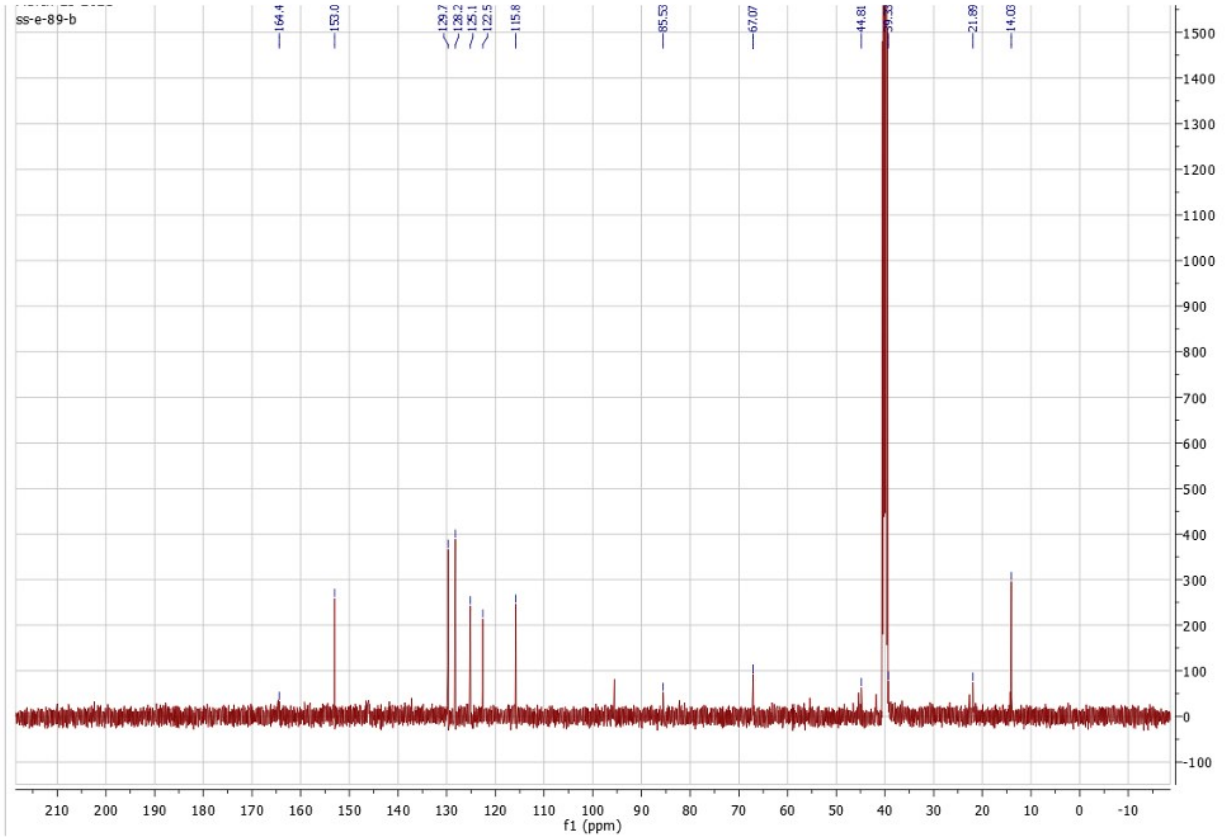

)18-CHlab
12f
B (dd) 7.34
A (d) 7.53
C (d) 7.17
D (s) 6.14
E (s) 5.13
F (m) 3.74
G (s) 2.25
H (d) 1.80
I (s) 1.68
J (s) 1.23
f1 (ppm)

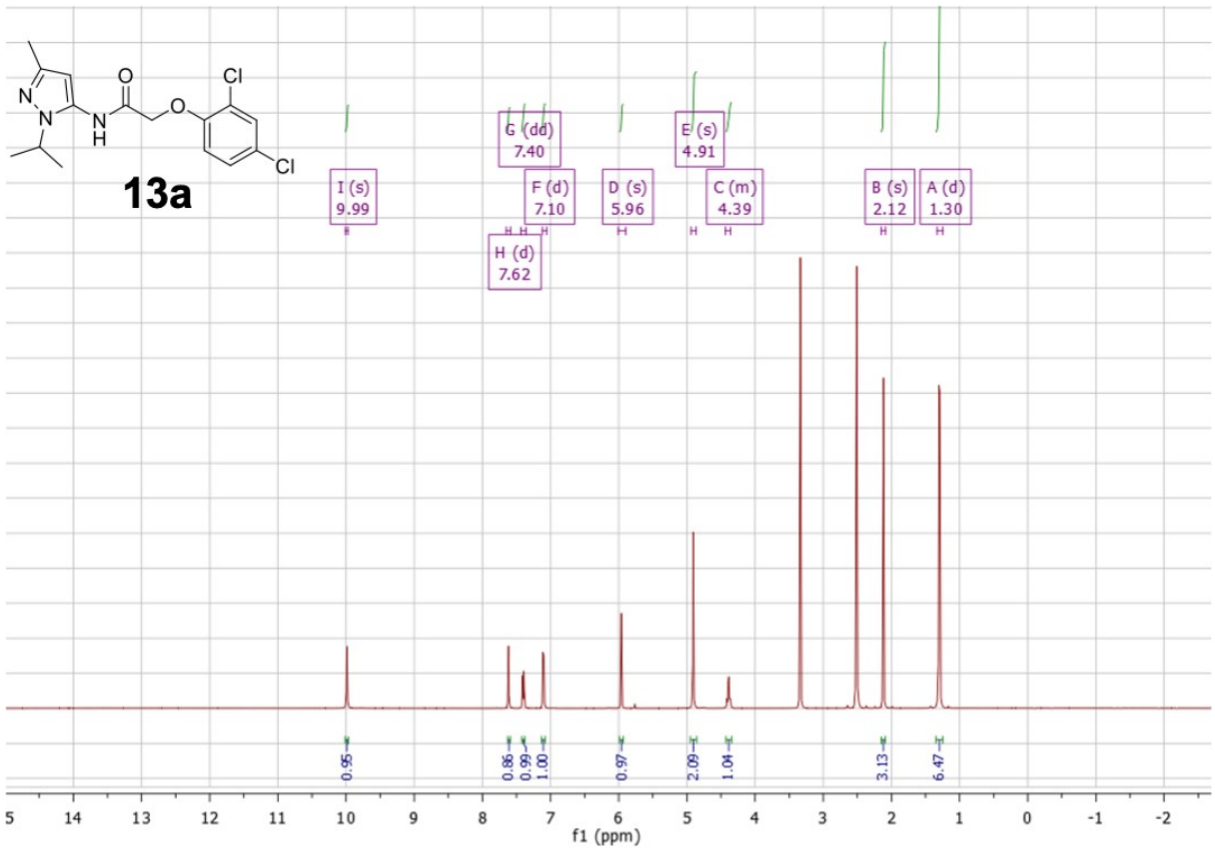

SS-D-32
152.22
147.22
129.85
127.78
126.90
123.65
115.37
100.91
75.56
56.66
32.20
25.32
24.91
12.40
f1 (ppm)

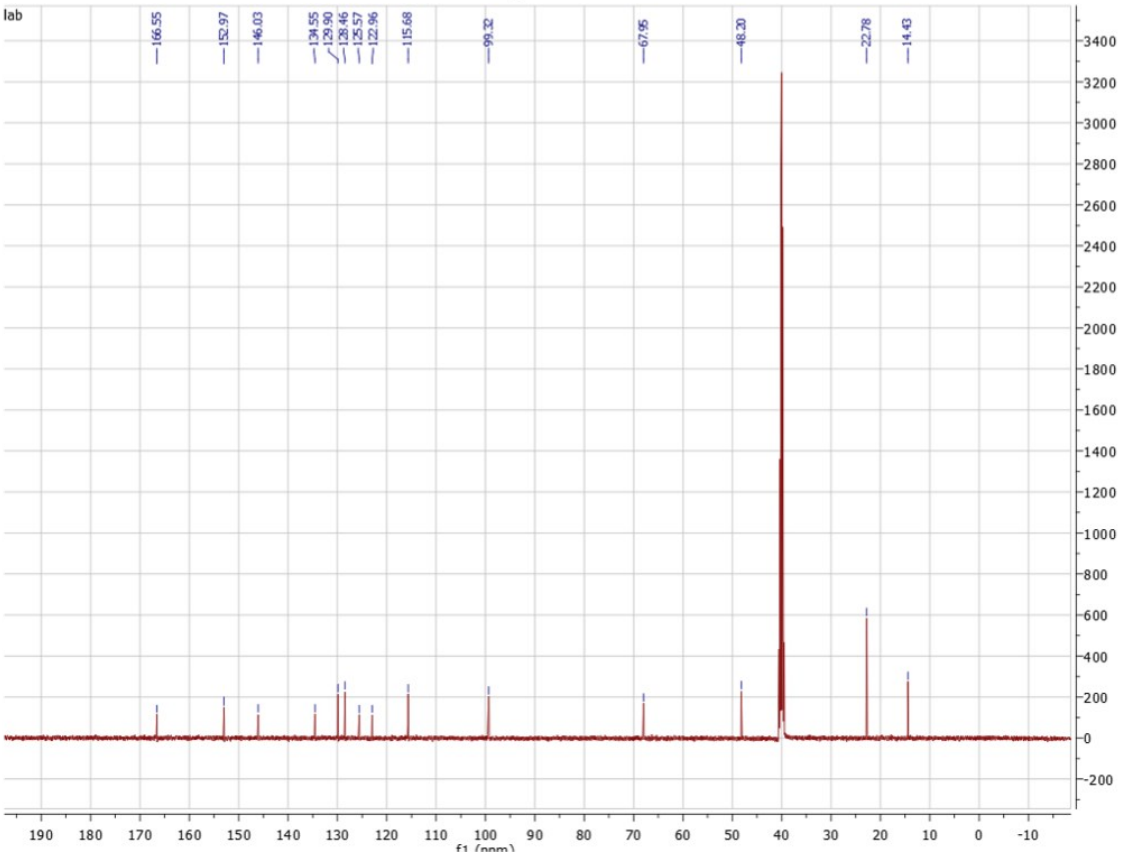

SS-D-162
12g
C (dd) 7.15
A (d) 7.38
B (d) 6.72
D (s) 5.94
F (d) 4.34
E (d) 4.61
G (m) 3.82
H (s) 3.23
M (d) 1.75
J (m) 2.08
O (m) 1.41
I (s) 2.29
L (s) 1.82
N (m) 1.35
K (m) 1.95
f1 (ppm)

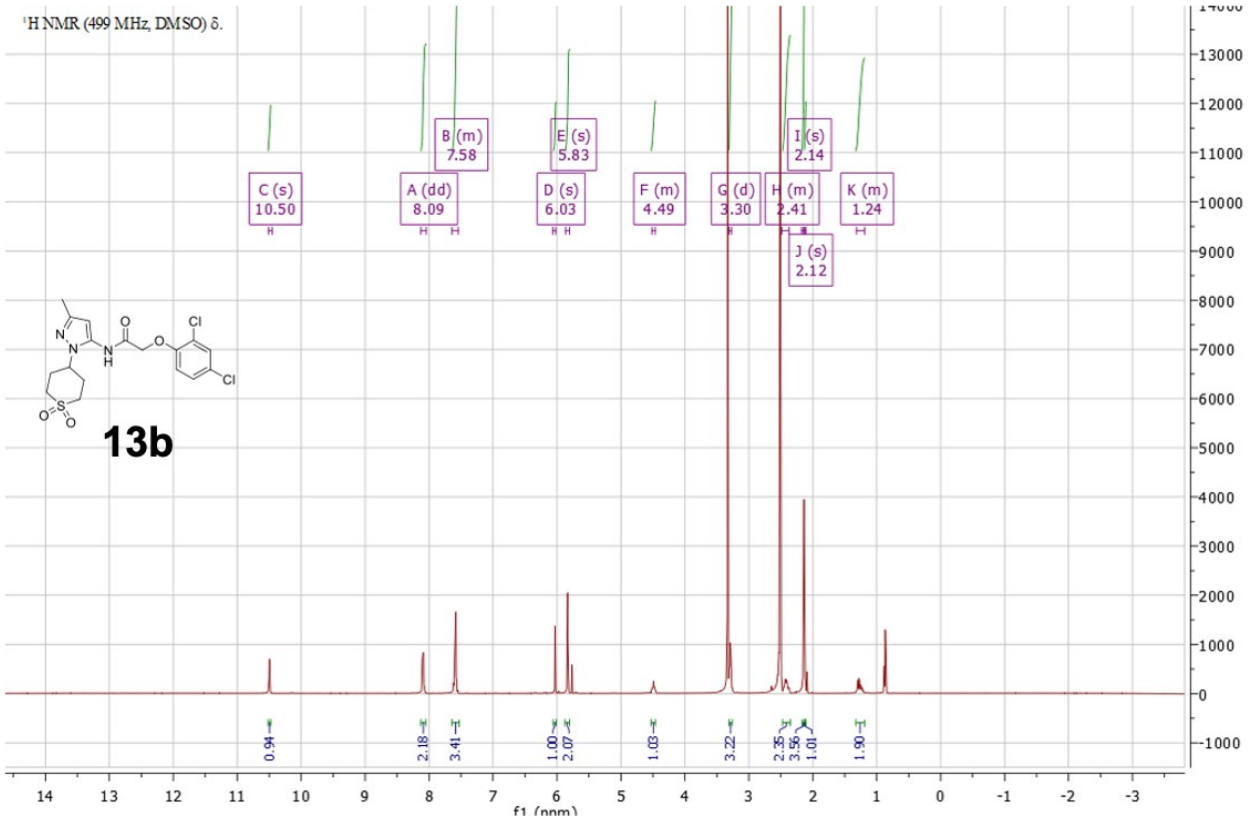

Jun12-2018-CHlab
SS-D-162
167.80
152.71
148.22
137.98
130.30
127.50
127.16
124.53
115.38
101.69
66.99
56.45
36.87
33.72
32.76
25.69
25.65
24.93
14.21
f1 (ppm)

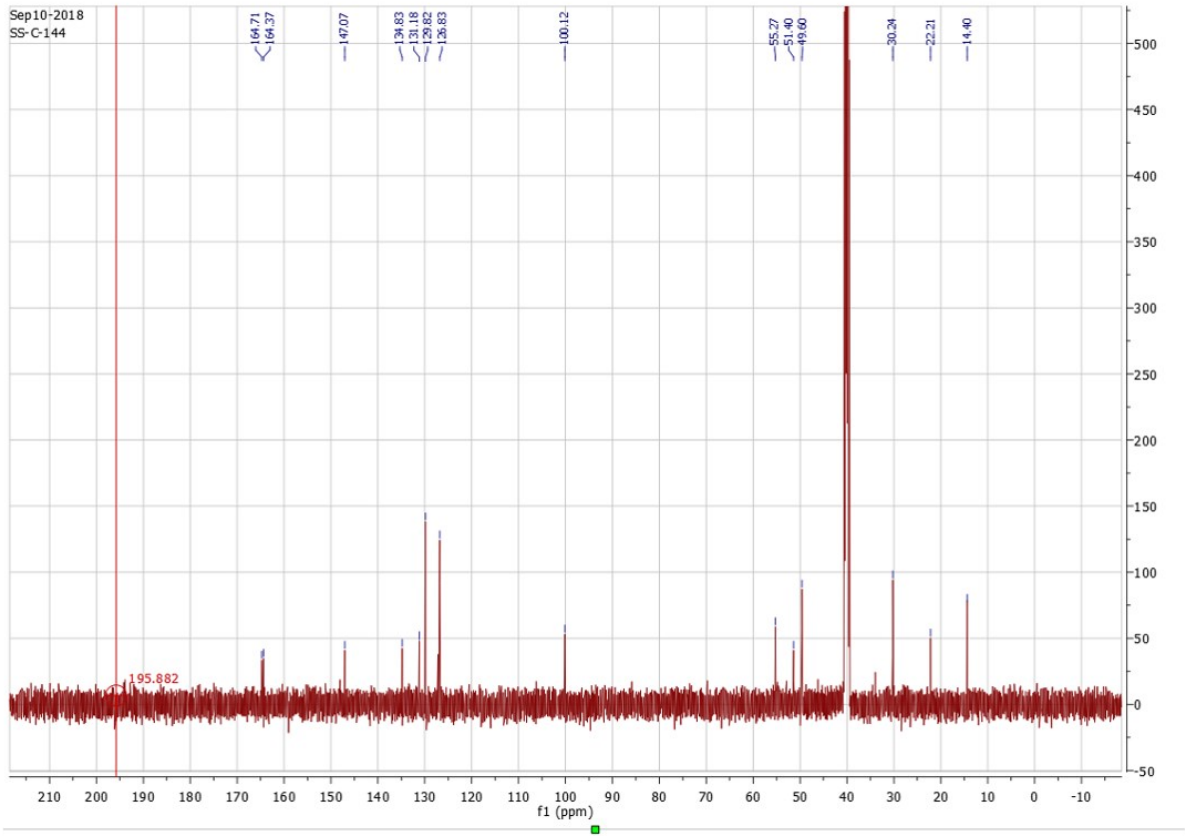

ss-e-89-b
12h
f1 (ppm)

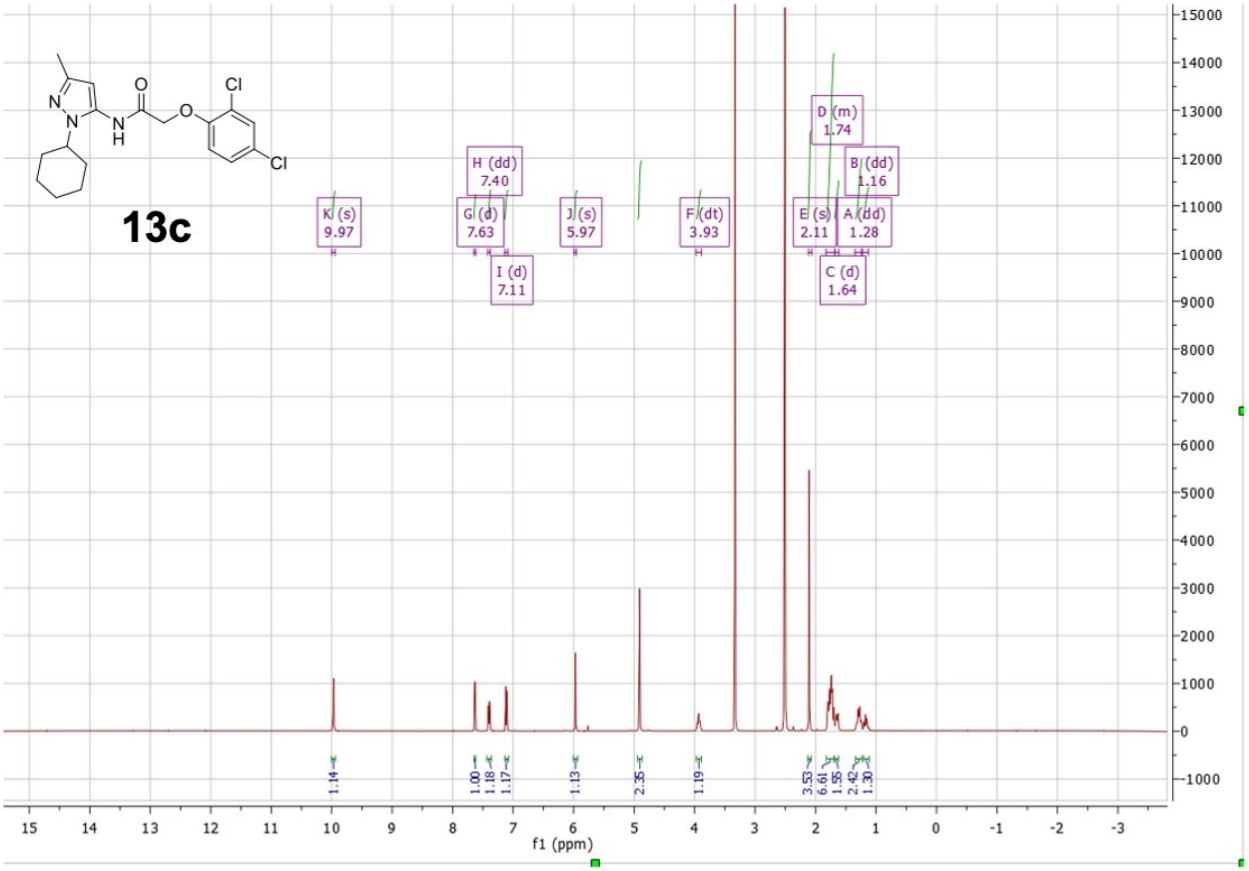

ss-e-89-b
f1 (ppm)

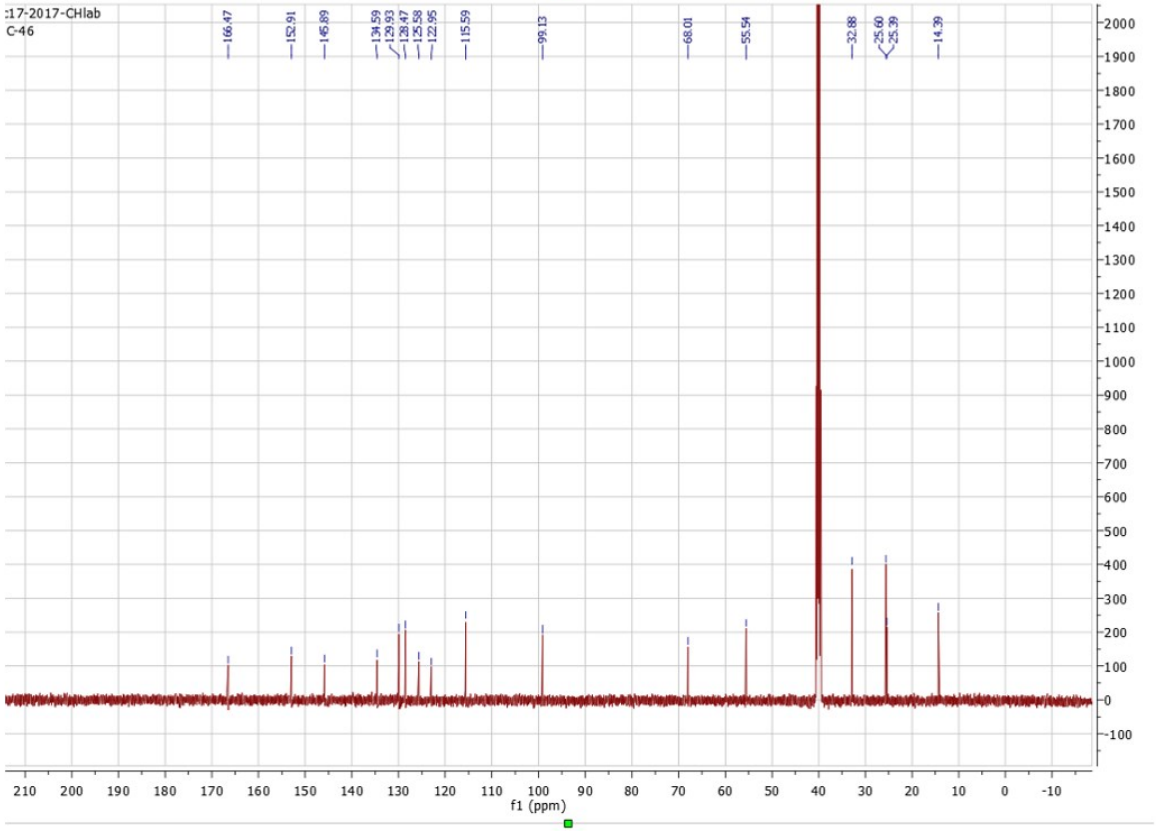

13a
I (s) 9.99
G (dd) 7.40
F (d) 7.10
H (d) 7.62
D (s) 5.96
E (s) 4.91
C (m) 4.39
B (s) 2.12
A (d) 1.30
f1 (ppm)

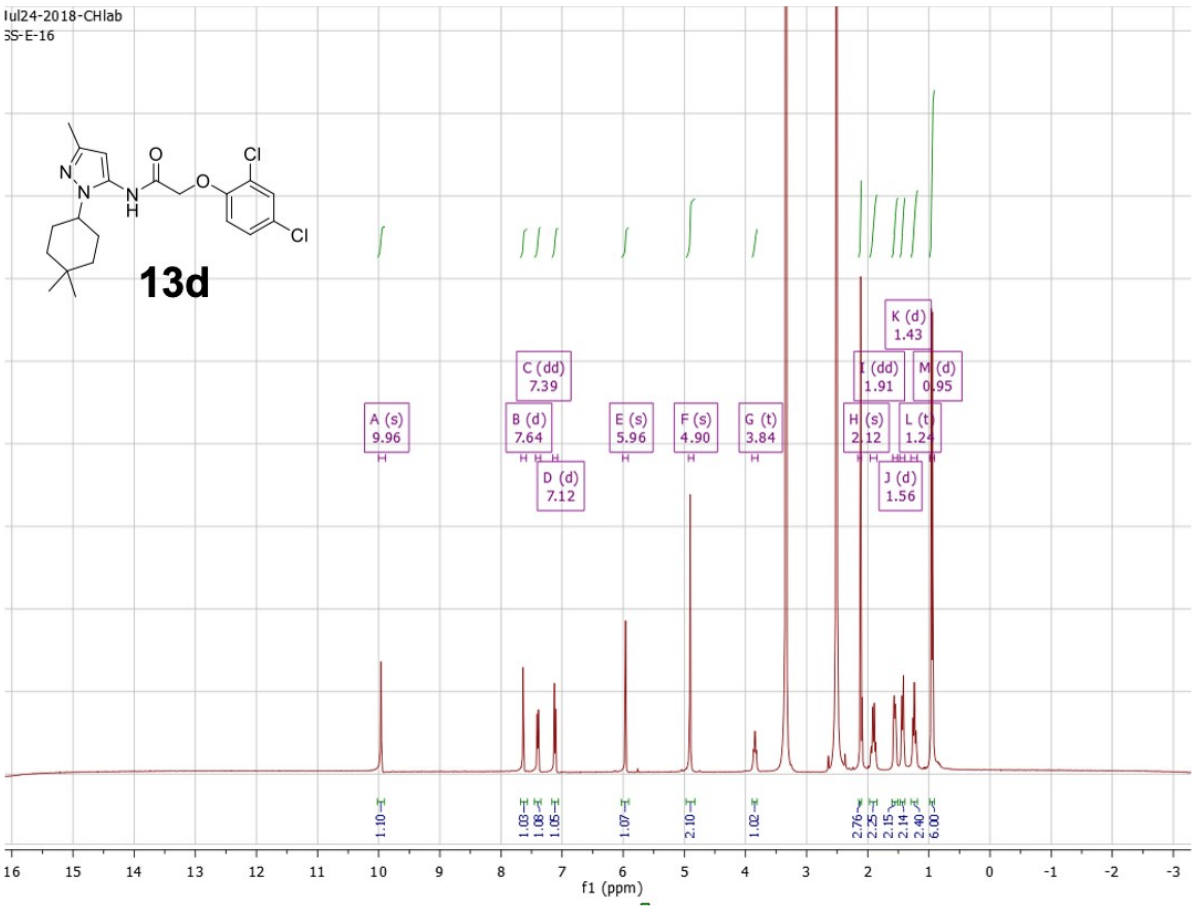

lab
166.55
152.97
146.03
134.55
129.90
128.46
125.57
122.96
115.68
99.32
67.95
48.30
22.78
14.43

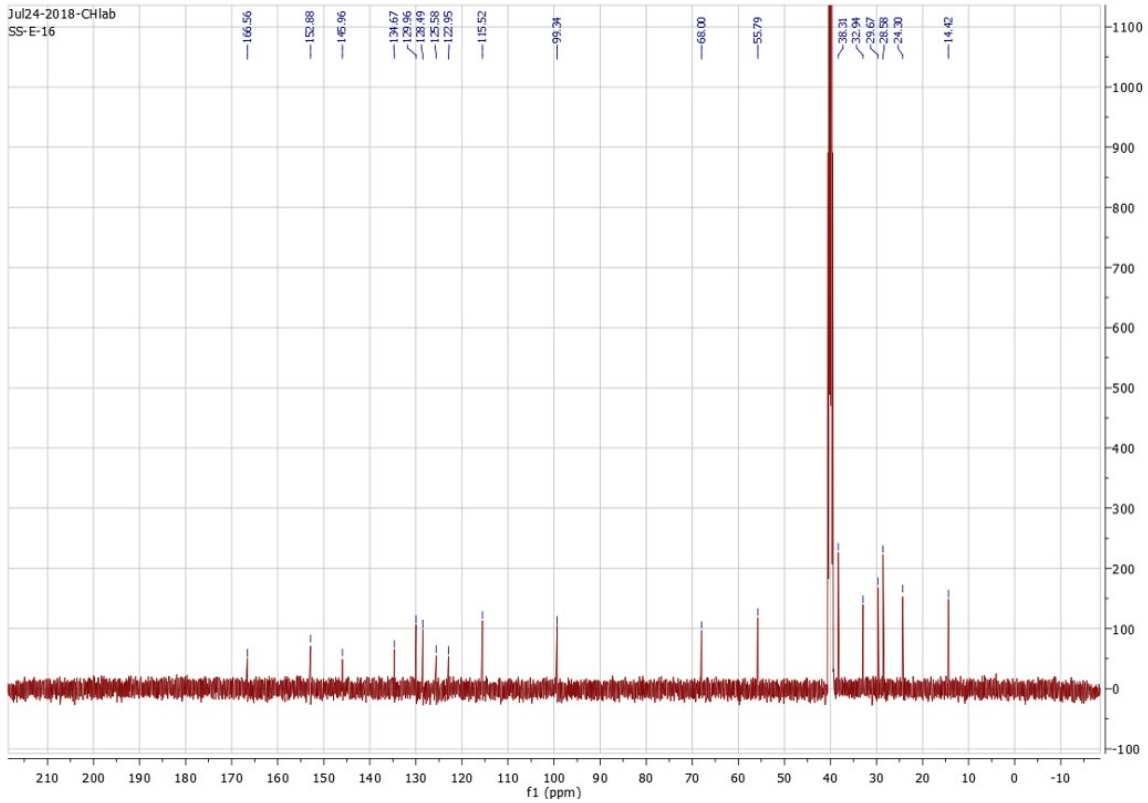

¹H NMR (499 MHz, DMSO) δ.
C (s) 10.50
A (dd) 8.09
B (m) 7.58
D (s) 6.03
E (s) 5.83
F (m) 4.49
G (d) 3.30
H (m) 2.41
I (s) 2.14
J (s) 2.12
K (m) 1.24
13b
f1 (ppm)

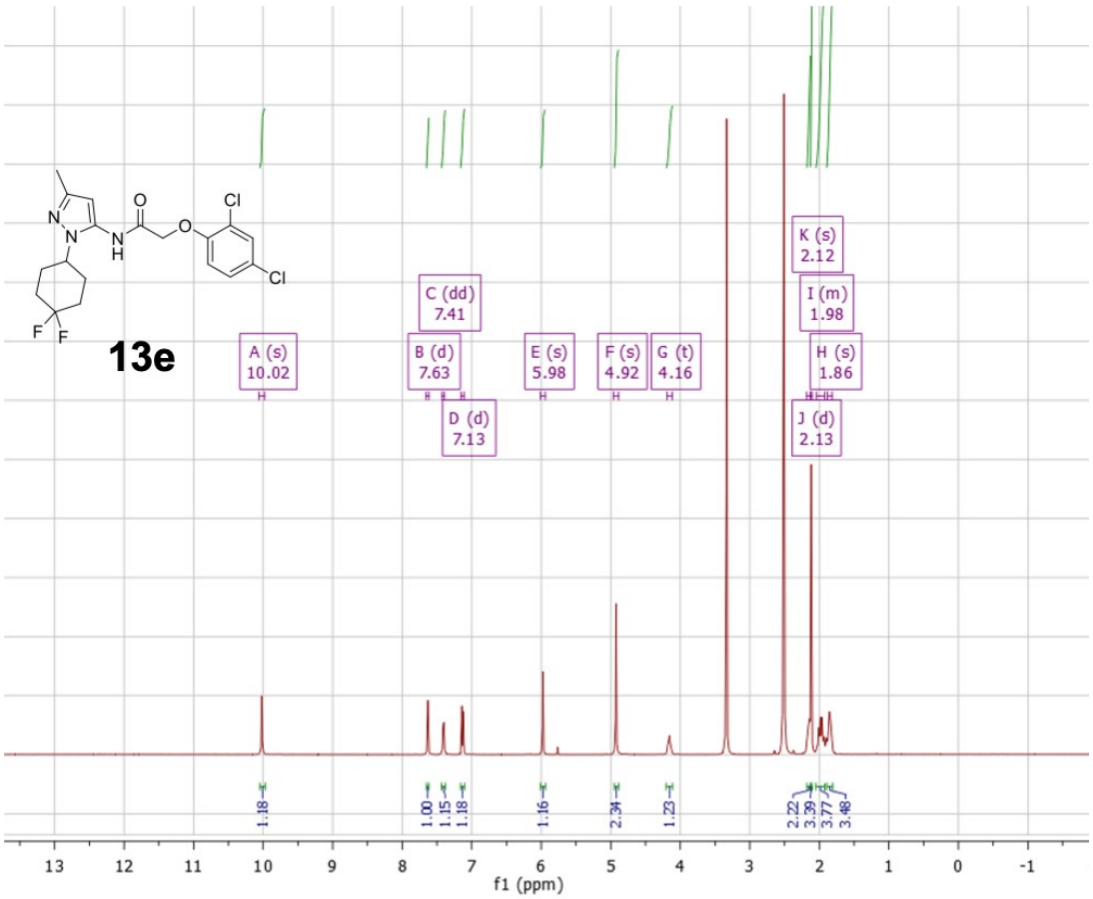

Sep10-2018
SS-C-144
164.71
164.37
147.07
134.83
131.18
129.82
126.83
100.12
55.27
51.40
49.60
30.24
22.21
14.40
195.882
f1 (ppm)

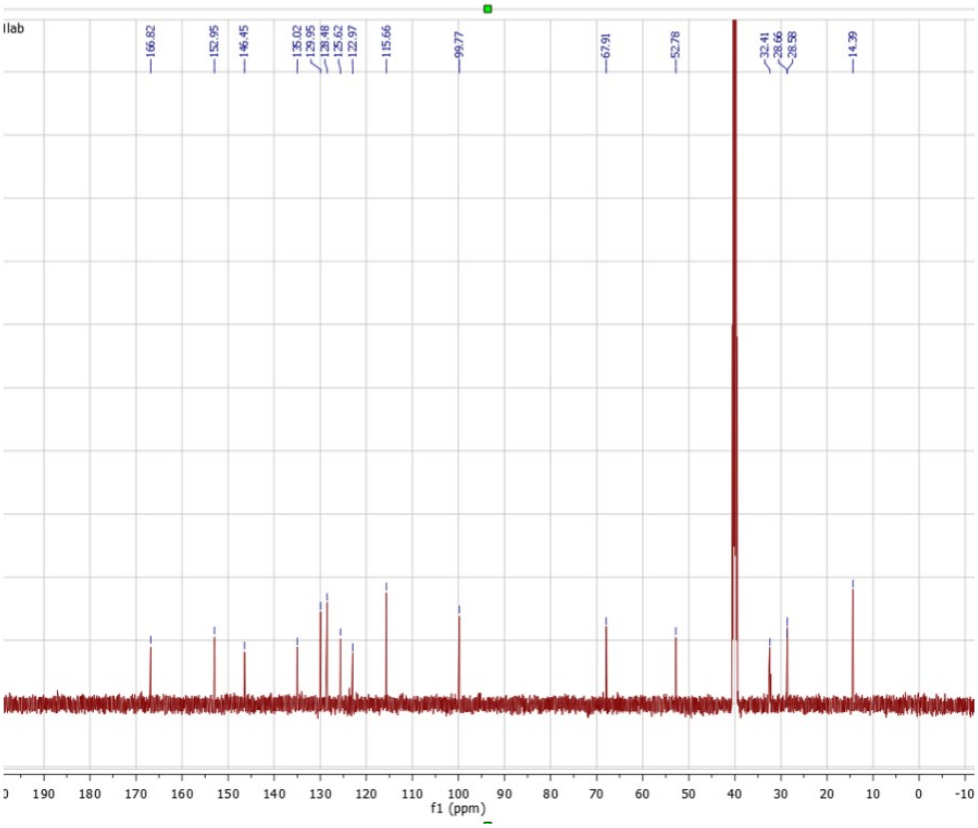

13c
K (s) 9.97
H (dd) 7.40
G (d) 7.63
I (d) 7.11
J (s) 5.97
F (dt) 3.93
D (m) 1.74
B (dd) 1.16
E (s) 2.11
A (dd) 1.28
C (d) 1.64
f1 (ppm)

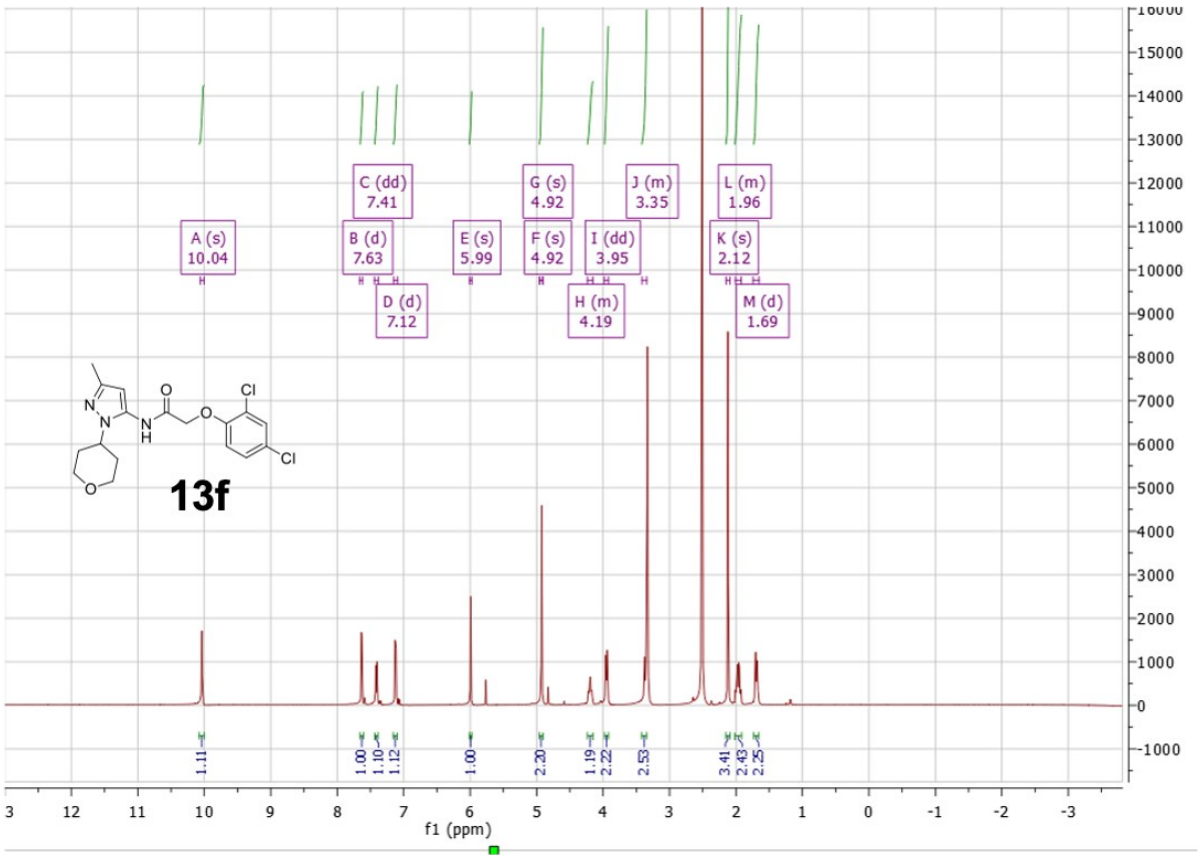

:17-2017-CHlab
C-46
166.47
152.91
145.89
134.59
129.93
128.47
125.58
122.95
115.59
99.13
68.01
55.54
32.88
25.60
25.39
14.39
f1 (ppm)

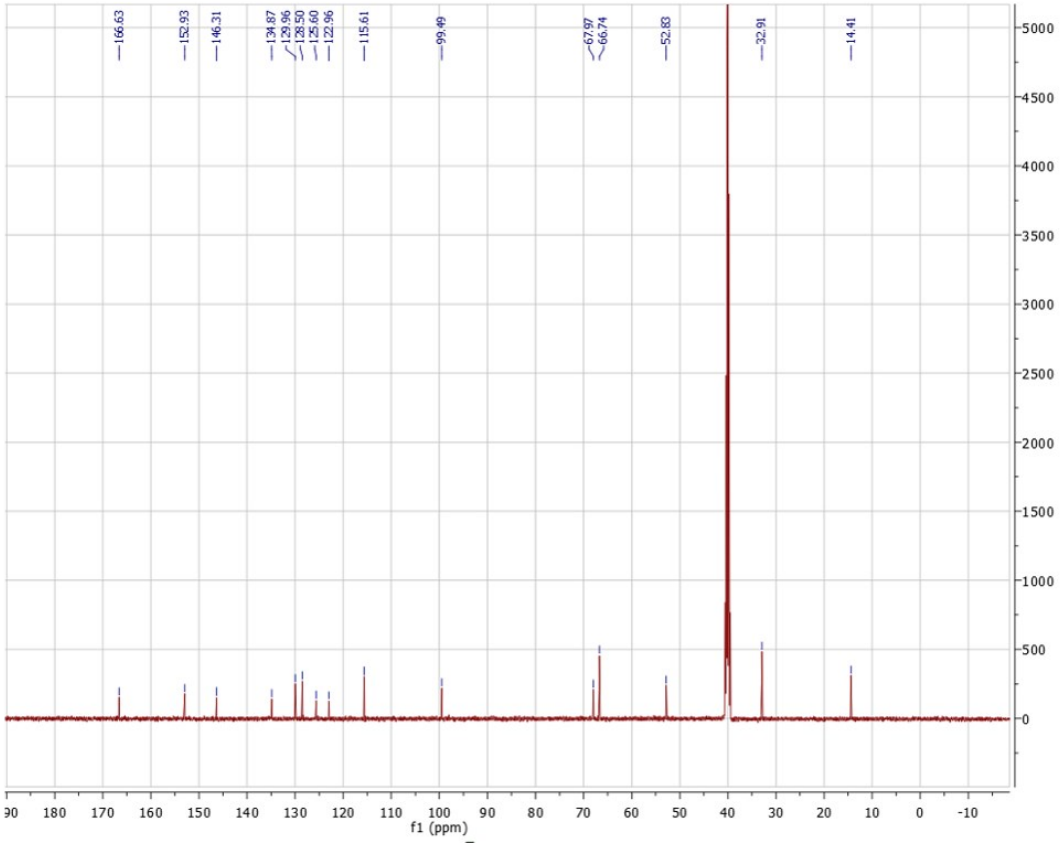

Jul24-2018-CHlab
SS-E-16
13d
A (s) 9.96
B (d) 7.64
C (dd) 7.39
D (d) 7.12
E (s) 5.96
F (s) 4.90
G (t) 3.84
H (s) 2.12
I (dd) 1.91
J (d) 1.56
K (d) 1.43
L (t) 1.24
M (d) 0.95
f1 (ppm)


Jul24-2018-CHlab
SS-E-16
166.56
152.88
145.96
134.67
129.96
128.49
125.58
122.95
115.52
99.34
68.00
55.79
38.31
32.94
29.67
28.58
24.30
14.42
f1 (ppm)


13e
A (s) 10.02
B (d) 7.63
C (dd) 7.41
D (d) 7.13
E (s) 5.98
F (s) 4.92
G (t) 4.16
H (s) 1.86
I (m) 1.98
J (d) 2.13
K (s) 2.12
f1 (ppm)


ilab
166.82
152.95
146.45
135.02
129.95
128.48
125.62
122.97
115.66
99.77
67.91
52.78
32.41
28.66
28.58
14.39
f1 (ppm)


A (s)
10.04
B (d)
7.63
C (dd)
7.41
D (d)
7.12
E (s)
5.99
F (s)
4.92
G (s)
4.92
H (m)
4.19
I (dd)
3.95
J (m)
3.35
K (s)
2.12
L (m)
1.96
M (d)
1.69
13f
f1 (ppm)


166.63
152.93
146.31
134.87
129.96
128.50
125.60
122.96
115.61
99.49
67.97
66.74
52.83
32.91
14.41
f1 (ppm)

Materials and Methods for *in vitro* Pharmacology

Thallium flux assays were preformed essentially as previously described (Ref. 9). Briefly, HEK-293 cells expressing either GIRK1 and GIRK2 or GIRK1 and GIRK4 were cultured in a-MEM (Corning, Corning, NY) containing 10% (v/v) fetal bovine serum (Thermo Fisher Scientific, Waltham, MA) plus 1x glutagro (Corning, Corning, NY) (referred to hereafter as cell culture medium) at 37 ^{o}C in a humidified 5% CO2 atmosphere. Cells at ~90% confluence were dislodged from the tissue culture vessel using TrypLE Express (Thermo Fisher Scientific, Waltham, MA) and plated at a density of 20,000 cells/well in 20 ml/well cell culture medium in 384-well, clear-bottom, black-walled, BD PureCoat Amine plates (Corning, Corning, NY) and incubated over night at 37 ^{o}C in a humidified 5% CO2 atmosphere. On the day of assay the medium was removed from the plates and replaced with 20 µl/well of a solution containing assay buffer (Hanks Buffered Saline Solution (Thermo Fisher Scientific, Waltham, MA) plus 10 mM HEPES (Thermo Fisher Scientific, Waltham, MA)-NaOH, pH 7.2), 1 µM Thallos (TEFlabs, Austin, TX), 0.5% DMSO and 0.036% Pluronic F-127 (Sigma-Aldrich, St. Louis, MO). Cell plates containing Thallos solution were incubated 1 hour at room temperature. Following incubation, the Thallos- containing solution was replaced with 20 µl/well assay buffer. The Thallos-loaded cell plates were transferred to a Panoptic kinetic imaging plate reader (WaveFront Biosciences, Franklin, TN). Images acquired at 1 Hz, 480/40 nm excitation and 538/40 nm emission were collected for 10 seconds after which time 20 µl/well of assay buffer containing test compounds at 2-fold over their final concentrations were added. Imaging continued for four minutes at which time 10 ml/well of a solution containing 125 mM $NaHCO_3$, 1.8 mM $CaSO_4$, 1 mM $MgSO_4$, 5 mM glucose, and 2 mM Tl_2SO_4, 10 mM HEPES-NaOH pH 7.2 was added and images were collected for an additional 2 minutes. To quantify test compound effects on GIRK activity, the initial slopes of the thallium-evoked changes in fluorescence were fit to a four-parameter logistic equation using the Excel (Microsoft, Redmond, WA) plugin XLfit (IDBS, Guildford, UK) to obtain potency and efficacy values. Efficacies are relative to a maximally effective concentration of our standard compound, VU551, our most potent and effective activator which shows low selectivity between GIRK1/2 and GIRK1/4 channels. Ten-point concentration series from 30 µM to 1.5 nM were generated using an Echo liquid handler (Labcyte, San Jose, CA). Final DMSO concentration, 0.24% (v/v), in the assay was constant across all compound concentrations. Unless otherwise indicated, all buffer salts were obtained from Sigma-Aldrich, St. Louis, MO.

Figure 1. Metabolite ID study in human and mouse liver microsomes

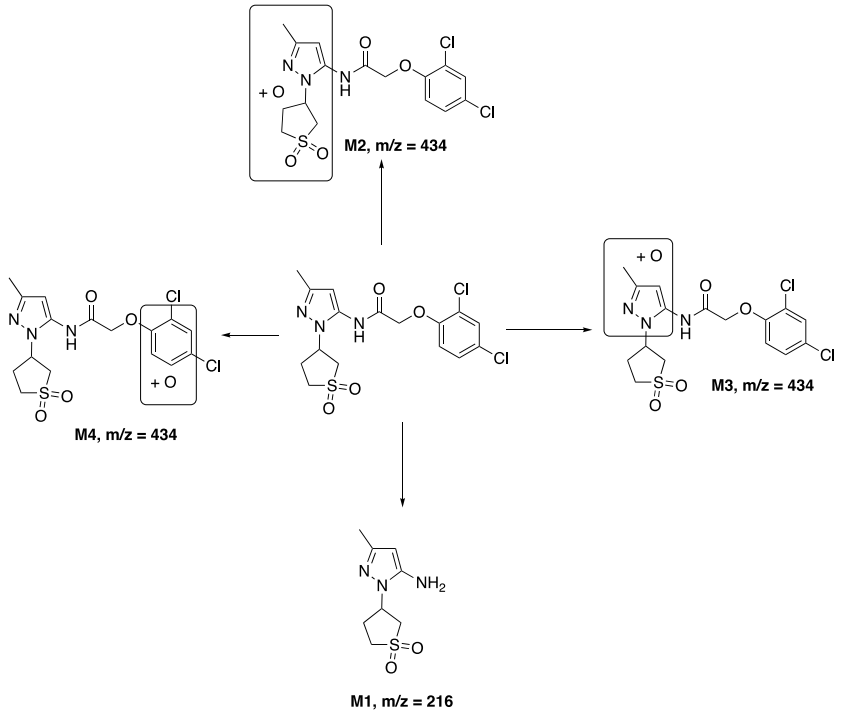


Table 1. Metabolite ID Study in mouse and human liver microsomes with NADPH at 0 and 60 min.

MLM	**0 min**	**60 min**
Parent	97.4%	0.6%
M1	2.6%	95.4%
HLM	**0 min**	**60 min**
Parent	99.9%	54.8%
M1	0.1%	18.3%

SS-C-33 is highly metabolized in mouse liver microsomes and moderately metabolized in human liver microsomes. At 60 min of incubation, the metabolite M1 (amide hydrolysis) was the largest component in MLM and the parent was the largest component in HLM. The amide hydrolysis in MLM was independent of NADPH. All other oxidative metabolites are present in <2% at 60 mins.

Table 2. Selectivity profile against closely related ion channels and the PDSP CNS panel.

Cmpd	SS-C-33, **11a**	CDA-B-78A, **11y**	SS-C-48, **13a**	SS-D-104, **13e**	SS-D-82, **13f**
GIRK1/2 (nM)	131	233	133	33	88
Receptor[1]	**EC_{50} (mM), % Efficacy**				
Kv2.1	>30	>30	>30	>30	>30
Kv2.1/6.4					
Kv2.1/9.1					
Kv2.1/8.2					
Kv7.2					
Kv2.2					
hERG		21.1, -77	40.1, -59		29.5, -21
KCNMA1/B4		>30	>30		>30
SLACK		33.5, 42.1	61.4, 12.9		
SLACK-A934T		>30	>30		
SLICK		17.8, -132			
Kir6.2		>30			
[1]Selectivity determined at Vanderbilt University					

PDSP Selectivity	
11a	
Receptor	**Mean % inhibition at 10 mM**
5-HT1A	-0.21
5-HT1B	10.12
5-HT1D	4.33
5-HT1E	17.55
5-HT2A	-1.46
5-HT2B	45.66
5-HT2C	6.81
5-HT3	-1.19
5-HT5A	-24.61
5-HT6	-6.99
5-HT7A	2
Alpha1A	4.23
Alpha1B	5.89
Alpha1D	-1.23
Alpha2A	22.98
Alpha2B	6.14
Alpha2C	-1.19
Beta1	11.56
Beta2	-8.4
Beta3	-2.45
BZP Rat Brain Site	33.66
D1	9.94
D2	-9.11
D3	-8.24
D4	-8.28
D5	-3.85
DAT	-9.46
DOR	4.44
GABAA	-10.87
H1	0.12
H2	-4.02
H3	6.45
H4	-3.56
KOR	29.85
M1	0.51
M2	8.82

M3	6.89
M4	39.14
M5	9.29
MOR	20.43
NET	44.18
PBR	-7.95
SERT	-0.61
Sigma 1	33.73
Sigma 2	17.4