A One-Pot, 3-Component, Domino Heck-aza-Michael Approach to Libraries of Functionalized 1,1-Dioxido-1,2-benzisothiazoline-3-acetic acids

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Experimental Section

General procedures: All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gas tight syringes, cannula, and septa. Stirring was achieved with oven-dried, magnetic stir bars. CH_3CN was purified by passage through the Solv-Tek purification system employing activated Al_2O_3 (Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520). Et_3N was purified by passage over basic alumina and stored over KOH. Flash column chromatography was performed with SiO_2 from Sorbent Technology (30930M-25, Silica Gel 60A, 40-63 um). Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 NMR spectrometer operating at 400 MHz and 100 MHz respectively; or a Bruker Avance operating at 500 MHz and 125 MHz respectively. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained in one of two manners: (i) on a VG Instrument ZAB double-focusing mass spectrometer and (ii) on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI (MeOH). All library syntheses using block technology were performed using a 24-position Mettler-Toledo Bohdan MiniBlock XT under an argon atmosphere in oven-dried Autochem 17 x 100 mm round bottom tubes. Parallel evaporations were performed using a GeneVac EZ-2 plus evaporator. Automated preparative reverse-phase HPLC purification was performed using a Waters 2767 Mass-Directed Fractionation system (2767 sample manager, 2525 Binary Pump, 515 Make-up pump) with a Waters ZQ quadrapole spectrometer and detected by UV (270 nm, Waters Xterra MS C-18 column, 19x150 mm, elution with the appropriate gradient of CH_3CN in pH 9.8 buffered aqueous ammonium formate at 18 mL min^{-1} flow rate). Purity was determined by reverse-phase HPLC with peak area (UV) at 214 nm using a Waters Alliance 2795 system (Waters Xterra MS C-18 column, 4.6x150 mm, elution with a linear gradient of 5% CH_3CN in pH 9.8 buffered aqueous ammonium formate to 100% CH_3CN at 1.0 mL/min flow rate).

2-(2-(4-Methoxybenzyl)-3-isothiazolin-1-yl)acetic acid 1,1'-dioxide (11): Prepared using general procedure **A**. FTIR (neat) 1738, 1610, 1514, 1288, 1172 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.80 (m, 1H), 7.61 – 7.51 (m, 2H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 5.8 Hz, 2H), 6.87 – 6.80 (m, 2H), 4.80 – 4.74 (m, 1H), 4.58 (d, *J* = 15.3 Hz, 1H), 4.42 (d, *J* = 15.3 Hz, 1H), 3.77 (s, 3H), 2.92 (dd, *J* = 16.5, 5.0 Hz, 1H), 2.72 (dd, *J* = 16.5, 7.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 159.4, 137.2, 134.6, 130.0, 129.5, 126.8, 124.2, 121.3, 114.1, 56.4, 55.2, 46.0, 38.7; HRMS calculated for $C_{17}H_{18}NO_5S$ $(M+H)^+$ 348.0906; found 348.0915 (TOF MS EI+).

3-(2-Oxopropyl)-2-phenylthiazolin-1-one 1,1'-dioxide (14): Prepared using general procedure **A**. FTIR (neat) 1714, 1496, 1301, 1170 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.3 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.50 – 7.44 (m, 5H), 7.31 (dt, *J* = 12.0, 4.2 Hz, 1H), 5.72 (dd, *J* = 8.7, 3.4 Hz, 1H), 3.10 (dd, *J* = 18.2, 3.4 Hz, 1H), 2.94 (dd, *J* = 18.2, 8.7 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.0, 137.0, 134.4, 133.2, 129.9, 129.6, 126.9, 124.5, 124.4, 121.4, 56.8, 47.4, 30.7; HRMS calculated for $C_{16}H_{16}NO_3S$ $(M+H)^+$ 302.0851; found 302.0865 (TOF MS EI+).

Methyl 2-(2-benzyl-6-fluoro-3-isothiazolin-1-yl)acetate 1,1'-dioxide (21): Prepared using general procedure **A**. FTIR (neat) 1735, 1436, 1296, 1170 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.5, 4.7 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.38 – 7.30 (m, 4H), 7.08 (d, *J* = 8.3 Hz, 1H), 4.83 – 4.74 (m, 1H), 4.59 (d, *J* = 15.6 Hz, 1H), 4.49 (d, *J* = 15.6 Hz, 1H), .3.62 (s, 3H), 2.87 (dd, *J* = 16.5, 5.0 Hz 1H), 2.69 (dd, *J* = 16.5, 7.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 166.2, 164.3, 140.4, 134.9, 130.8, 128.8, 127.7, 128.4, 128.2, 123.7, 117.5, 111.7, 56.5, 52.1, 46.7, 38.5; HRMS calculated for $C_{17}H_{17}FNO_4S$ $(M+H)^+$ 350.0862; found 350.0870 (TOF MS EI+).

Ethyl 2-(2-cyclopentyl-6-fluoro-3-isothiazolin-1-yl)acetate 1,1'-dioxide (24): Prepared using general procedure **A**. FTIR (neat) 1730, 1595, 1475, 1299, 1171 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.5, 4.8 Hz, 1H), 7.21 (td, *J* = 8.5, 2.2 Hz, 1H), 7.14 (dd, *J* = 8.4, 2.2 Hz 1H), 4.94 (dd, *J* = 9.0, 3.7 Hz 1H), 4.23 – 4.12 (m, 2H), 3.91 – 3.79 (m, 1H), 3.07 (dd, *J* = 16.5, 3.8 Hz, 1H), 2.75 (dd, *J* =

16.5, 9.1 Hz, 1H), 2.06 (ddd, *J* = 11.1, 7.2, 3.1 Hz, 2H), 1.94 – 1.71 (m, 4H), 1.67 – 1.55 (m, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 166.1, 141.2, 131.7, 123.4, 117.4, 117.2, 111.8, 111.60, 61.2, 57.3, 56.3, 39.6, 30.8, 29.1, 23.3, 22.6, 14.0; HRMS calculated for $C_{16}H_{22}FNO_4S$ $(M+H)^+$ 342.1175; found 342.1182 (TOF MS EI+).

Ethyl 2-(6-fluoro-2-(4-methoxybenzyl)-3-isothiazolin-1-yl)acetate 1,1'-dioxide (28): Prepared using general procedure **A**. FTIR (neat) 1730, 1514, 1298, 1171 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.6, 4.8 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.23 (dt, *J* = 8.5, 2.2 Hz, 1H), 7.08 (dd, *J* = 8.4, 2.2 Hz 1H), 6.91 – 6.84 (m, 2H), 4.75 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.57 (d, *J* = 15.3 Hz, 1H), 4.39 (d, *J* = 15.3 Hz, 1H), 4.16 – 4.01 (m, 2H), 3.80 (s, 3H), 2.87 (dd, *J* = 16.4, 4.8 Hz, 1H), 2.68 (dd, *J* = 16.4, 7.3 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 166.2, 164.1, 159.4, 140.5, 130.9, 129.9, 126.6, 123.6, 117.4, 114.1, 111.7, 61.2, 56.1, 55.2, 46.0, 38.6, 13.9; HRMS calculated for $C_{19}H_{21}FNO_5S$ $(M+H)^+$ 394.1124; found 394.1134 (TOF MS EI+).

Ethyl 2-(6-fluoro-2-octyl-3-isothiazolin-1-yl)acetate 1,1'-dioxide (30): Prepared using general procedure **A**. FTIR (neat) 1733, 1593, 1299, 1172 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.5, 4.5 Hz 1H), 7.24 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 4.93 – 4.82 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.30 (t, *J* = 7.6 Hz, 2H), 2.98 (dd, *J* = 16.5, 5.0 Hz, 1H), 2.75 (dd, *J* = 16.5, 7.3 Hz, 1H), 1.72 (d, *J* = 7.0 Hz, 2H), 1.28 (m, 13H), 0.87 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 166.4, 162.4, 140.6, 131.0, 117.5, 117.3, 111.7, 61.4, 57.1, 43.6, 38.9, 31.7, 29.1, 28.0, 26.8, 22.6, 14.0; HRMS calculated for $C_{19}H_{29}FNO_4S$ $(M+H)^+$ 386.1801; found 386.1811 (TOF MS EI+).

2-(2-Cyclopentyl-6-fluoro-3-isothiazolin-1-yl)acetic acid 1,1'-dioxide (31): Prepared using general procedure **A**. FTIR (neat) 1731, 1593, 1294, 1170 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.5, 4.8 Hz, 1H), 7.23 (td, *J* = 8.5, 2.2 Hz, 1H), 7.18 (dd, *J* = 8.3, 2.2 Hz, 1H), 4.94 (dd, *J* = 9.0, 3.5 Hz, 1H), 3.93 – 3.80 (m, 1H), 3.16 (dd, *J* = 16.8, 3.6 Hz 1H), 2.83 (dd, *J* = 16.8, 9.0 Hz, 1H), 2.15 – 2.01 (m, 2H), 1.91 – 1.74 (m, 5H), 1.63 (dd, *J* = 6.7, 4.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 166.2,

164.2, 141.0, 131.7, 123.6, 117.6, 117.4, 111.8, 111.6, 57.5, 56.0, 39.3, 30.8, 29.1, 23.3, 22.7; HRMS calculated for $C_{14}H_{17}FNO_4S$ $(M+H)^+$ 314.0862; found 314.0872 (TOF MS EI+).

2-(6-Fluoro-2-(4-methoxybenzyl)-3-isothiazolin-1-yl)acetic acid 1,1'-dioxide (34): Prepared using general procedure **A**. FTIR (neat) 1718, 1612, 1514, 1292, 1174 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.5, 4.6 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.21 (m, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 2H), 4.76 – 4.70 (m, 1H), 4.57 (d, *J* = 15.3 Hz, 1H), 4.40 (d, *J* = 15.2 Hz, 1H), 3.78 (s, 3H), 3.54 (s, 1H), 2.93 (dd, *J* = 16.7, 4.6 Hz, 1H), 2.72 (dd, *J* = 16.7, 7.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.46 , 165.2, 159.52, 140.3, 130.8, 130.0, 126.4, 123.8, 117.6, 117.4, 114.2, 111.8, 111.6, 55.9, 55.2, 46.2, 38.3; HRMS calculated for $C_{17}H_{17}FNO_5S$ $(M+H)^+$ 366.0811; found 366.0819 (TOF MS EI+).

Ethyl 2-(2-isopropyl-3-oxo-5-(trifluoromethyl) isothiazolin-1-yl)ethanoate 1,1'-dioxide (44): Prepared using general procedure **A**. FTIR (neat) 1731, 1328, 1161 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 5.08 (dd, *J* = 8.1, 4.4 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.06 (dt, *J* = 13.6, 6.8 Hz, 1H), 3.05 (dd, *J* = 16.6, 4.4 Hz, 1H), 2.83 (dd, *J* = 16.6, 8.1 Hz, 1H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.35 (d, *J* = 6.8 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 137.7, 127.6, 123.2, 116.6 (d, $J_{C\text{-}F}$ = 3.9 Hz), 59.3, 52.5, 46.9, 38.9, 19.6, 17.5, 12.0; HRMS calculated for $C_{15}H_{19}F_3NO_4S$ $(M+H)^+$ 366.0987; found 366.0987 (TOF MS EI+).

Ethyl 2-(2-(4-methoxyphenyl)-5-(trifluoromethyl)isothiazolin-1-yl)ethanoate 1,1'-dioxide (47): Prepared using general procedure **A**. FTIR (neat) 1733, 1602, 1326, 1166 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 8.2 Hz, 1H), 7.09 – 7.05 (m, 1H), 7.03 (t, *J* = 2.2 Hz, 1H), 6.93 – 6.89 (m, 1H), 5.59 (dd, *J* = 8.1, 4.0 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 3.01 (dd, *J* = 16.6, 4.1 Hz, 1H), 2.81 (d, *J* = 8.2, 4.1 H, 1H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 158.7, 133.6, 132.6, 128.4 (d, $J_{C\text{-}F}$ = 2.6 Hz), 128.0, 123.3, 117.2, 111.5, 109.4, 59.4, 56.2, 53.4, 36.3, 11.9; HRMS calculated for $C_{19}H_{18}F_3NO_5SNa$ $(M+Na)^+$

452.0756; found 452.0757 (TOF MS EI+).

2-(2-Cyclohexyl-3-oxo-6-(trifluoromethyl)isothiazolin-1-yl)acetic acid 1,1'-dioxide (53): Prepared using general procedure **A**. FTIR (neat) 2935, 1712, 1610, 1512, 1299 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.85 – 7.74 (m, 2H), 5.11 (dd, *J* = 8.1, 4.1 Hz, 1H), 3.64 (tt, *J* = 12.0, 3.5 Hz, 1H), 3.14 (dd, *J* = 16.9, 4.2 Hz, 1H), 2.92 (dd, *J* = 16.9, 8.2 Hz, 1H), 2.04 (d, J = 12.3 Hz, 1H), 1.93 (d, *J* = 12.1 Hz, 1H), 1.85 (t, *J* = 14.6 Hz, 2H), 1.72 – 1.56 (m, 4H), 1.41 – 1.28 (m, 2H), 1.16 (ddd, *J* = 16.7, 13.1, 9.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 139.7, 139.2, 134.74 (q, J_{C-F} = 33.1 Hz), 126.8, 121.8, 56.9, 54.2, 40.5, 32.0, 29.9, 25.9, 25.7, 25.2; HRMS calculated for $C_{16}H_{22}F_3N_2O_4S$ $(M+NH_4)^+$ 395.1252; found 395.1270 (TOF MS EI+).

Ethyl 2-(3-oxo-2-(3-(trifluoromethyl)benzyl)isothiazolin-1-yl)acetate 1,1'-dioxide (61): Prepared using general procedure **B**. FTIR (neat) 1731, 1328, 1298, 1172 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.1 Hz, 1H), 7.68 (d, *J* = 1.3 Hz, 2H), 7.62 (dq, *J* = 7.5, 1.3 Hz, 1H), 7.58 (dd, *J* = 11.9, 4.4 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.41 – 7.37 (m, 1H), 4.87 (t, *J* = 5.9 Hz, 1H), 4.68 – 4.59 (s, 2H), 4.10 – 3.96 (m, 2H), 2.85 (dd, *J* = 16.5, 6.1 Hz, 1H), 2.75 (dd, *J* = 16.5, 5.8 Hz, 1H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 137.0, 136.9, 134.4, 133.1, 131.7, 129.6, 129.3, 124.9 (q, J_{C-F} = 3.8), 124.1, 121.4, 61.2, 57.7, 46.7, 39.5, 13.8; HRMS calculated for $C_{19}H_{19}F_3NO_4S$ $(M+H)^+$ 414.0987; found 414.1001 (TOF MS EI+).

Methyl 2-(2-(4-(dimethylamino)phenyl)-6-fluoro-3-isothiazolin-1-yl)acetate 1,1'-dioxide (63): Prepared using general procedure **B**. FTIR (neat) 1737, 1608, 1519, 1299, 1172 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.6, 4.8 Hz, 1H), 7.35 – 7.31 (m, 2H), 7.31 – 7.27 (m, 1H), 7.21 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.77 – 6.72 (m, 2H), 5.29 (dd, *J* = 7.9, 4.5 Hz, 1H), 3.61 (s, 3H), 2.99 (s, 6H), 2.94 (dd, *J* = 16.5, 4.5 Hz, 1H), 2.75 (dd, *J* =16.5, 8.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 166.2, 164.1, 150.7, 139.8, 130.1, 124.0, 120.4, 117.6, 117.4, 112.8, 111.7, 111.5, 59.2, 40.4, 38.3; HRMS calculated for $C_{18}H_{20}FN_2O_4S$ $(M+H)^+$ 379.1128; found 379.1143 (TOF MS EI+).

Methyl 2-(6-fluoro-2-(2-methoxybenzyl)-3-isothiazolin-1-yl)acetate 1,1'-dioxide (66): Prepared using general procedure **B**. FTIR (neat) 1733, 1519, 1292, 1244 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.6, 4.8 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.33 – 7.27 (m, 1H), 7.23 (td, *J* = 8.5, 2.2 Hz, 1H), 7.11 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.96 (t, *J* = 7.1 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 4.83 (dd, *J* = 8.6, 3.7 Hz, 1H), 4.63 (d, *J* = 15.6 Hz, 1H), 4.50 (d, *J* = 15.6 Hz, 1H), 3.85 (s, 3H), 3.66 (s, 3H), 3.09 (dd, *J* = 16.6, 3.8 Hz, 1H), 2.70 (dd, *J* = 16.6, 8.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 166.1, 164.1, 157.4, 140.8, 130.8, 129.5, 123.6, 123.5, 123.1, 121.0, 117.4, 117.2, 111.9, 111.7, 110.3, 56.7, 55.3, 52.0, 40.5, 38.1; HRMS calculated for $C_{18}H_{19}FNO_5S$ $(M+H)^+$ 380.0968; found 380.0980 (TOF MS EI+).

Ethyl 2-(6-fluoro-3-oxo-2-(3,4,5-trimethoxybenzyl)isothiazolin-1-yl)acetate 1,1'-dioxide (68): Prepared using general procedure **B**. FTIR (neat) 1731, 1593, 1463, 1298, 1126 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.6, 4.7 Hz, 1H), 7.25 (dt, *J* = 8.5, 2.5 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 6.65 (s, 2H), 4.81 (t, *J* = 5.8 Hz, 1H), 4.48 (q, *J* = 15.6 Hz, 2H), 4.13 – 3.99 (m, 2H), 3.82 (s, 9H), 2.87 (dd, *J* = 16.5, 5.0 Hz 1H), 2.70 (dd, *J* = 16.5, 6.9 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 166.2, 164.2, 153.4, 140.5, 137.5, 130.7, 123.6, 117.5, 117.4, 111.7, 111.5, 105.3, 61.2, 60.8, 56.8, 56.1, 47.3, 38.9, 13.9; HRMS calculated for $C_{21}H_{25}FNO_7S$ $(M+H)^+$ 454.1336; found 454.1353 (TOF MS EI+).

2-(4-(Dimethylamino)phenyl)-3-(2-oxopropyl)-5-(trifluoromethyl)isothiazolin-1-one 1,1'-dioxide (71): Prepared using general procedure **B**. FTIR (neat) 1714, 1606, 1519, 1309, 1168 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.75 (s, 1H), 7.35 – 7.28 (m, 2H), 6.79 – 6.69 (m, 2H), 5.47 (dd, *J* = 8.5, 3.7 Hz, 1H), 3.13 (dd, *J* = 18.3, 3.7 Hz, 1H), 3.00 (s, 6H), 2.91 (dd, *J* = 18.3, 8.5 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.7, 150.7, 138.6, 138.1, 129.7, 122.3, 122.1 (d, J_{C-F} = 3.9), 120.2, 112.9, 58.6, 47.1, 40.4, 30.5; HRMS calculated for $C_{19}H_{20}F_3N_2O_3S$ $(M+H)^+$ 413.1146; found 413.1144 (TOF MS EI+).

(*E*)-Ethyl 3-(1-(2-ethoxy-2-oxoethyl)-2-octyl-3-oxoisoindolin-5-yl)acrylate 1,1'-dioxide (89):

Prepared using general procedure **C**. FTIR (neat) 2927, 2854, 1714, 1641, 1299, 1157 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.73 – 7.65 (m, 2H), 7.45 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 4.96 – 4.89 (m, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.24 – 4.13 (m, 2H), 3.32 (t, *J* = 7.6 Hz, 2H), 2.98 (dd, *J* = 16.4, 5.3 Hz, 1H), 2.77 (dd, *J* = 16.4, 7.0 Hz, 1H), 1.73 (dd, *J* = 13.9, 6.8 Hz, 2H), 1.41 – 1.18 (m, 16H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 166.2, 141.7, 138.8, 136.3, 136.0, 132.3, 124.8, 121.1, 120.1, 61.3, 60.9, 57.4, 43.6, 39.0, 31.7, 27.8, 28.1, 26.8, 22.6, 14.2, 14.0; HRMS calculated for $C_{24}H_{36}NO_6S$ $(M+H)^+$ 466.2263; found 466.2279 (TOF MS EI+).

(*E*)-3-(1-(Carboxymethyl)-2-octyl-3-isothiazolin-5-yl)acrylic acid 1,1' dioxide (90): Prepared using general procedure **C**. FTIR (neat) 2852, 1689, 1288, 1159 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ 8.03 (s, 1H), 7.94 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.75 (d, *J* = 16.0 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 4.97 (t, *J* = 5.9 Hz, 1H), 3.36 (dd, *J* = 14.4, 8.2 Hz, 2H), 2.98 (dd, *J* = 16.4, 5.8 Hz, 1H), 2.85 (dd, *J* = 16.4, 6.0 Hz, 1H), 1.74 (d, *J* = 5.7 Hz, 2H), 1.44 – 1.24 (m, 12H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 172.1, 168.2, 142.1, 139.4, 136.4, 135.7, 132.2, 125.0, 120.9, 119.8, 58.1, 43.5, 38.4, 31.5, 28.9, 27.9, 26.5, 22.3, 13.0; HRMS calculated for $C_{20}H_{28}NO_6S$ $(M+H)^+$ 410.1637; found 410.1669 (TOF MS EI+).

(*E*)-2-Octyl-6-(3-oxobut-1-enyl)-3-(2-oxopropyl)isothiazolin-1-one 1,1' dioxide (91): Prepared using general procedure **C**. FTIR (neat) 2925, 2854, 1716, 1672, 1294, 1157 cm^{-1}; 1H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 1.2 Hz, 1H), 7.70 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.51 (d, *J* = 16.2 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 6.78 (d, *J* = 16.2 Hz, 1H), 5.04 (dd, *J* = 7.2, 5.2 Hz, 1H), 3.34 – 3.19 (m, 2H), 3.16 (dd, *J* = 18.1, 5.2 Hz, 1H), 2.88 (dd, *J* = 18.1, 7.3 Hz, 1H), 2.40 (s, 3H), 2.23 (s, 3H), 1.75 – 1.59 (m, 2H), 1.41 – 1.17 (m, 10H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.7, 197.5, 140.1, 136.2, 132.4, 129.0, 125.2, 120.3, 56.3, 47.9, 44.1, 31.7, 30.8, 29.1, 28.1, 28.0, 26.8, 22.6, 14.0; HRMS calculated for $C_{22}H_{32}NO_4S$ $(M+H)^+$ 406.2052; found 406.2072 (TOF MS EI+).

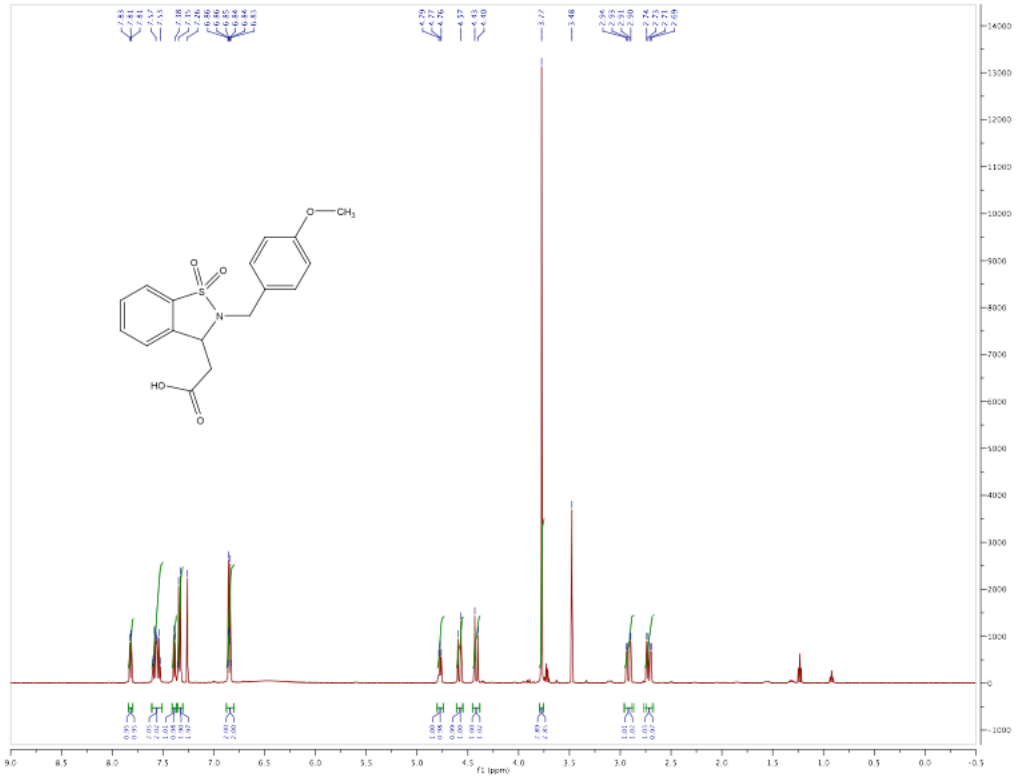
(*E*)-Methyl 3-(1-(2-methoxy-2-oxoethyl)-2-(2-methoxyphenyl)-3-oxoisoindolin-5-yl)acrylate 1,1' dioxide (92): Prepared using general procedure **C**. FTIR (neat) 1720, 1600, 1490, 1305, 1207 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 1.2 Hz, 1H), 7.77 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.73 (d, *J* = 16.0 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.37 (t, *J* = 8.2 Hz, 1H), 7.06 (ddd, *J* = 8.0, 2.1, 0.8 Hz 1H), 7.03 (t, *J* = 2.2 Hz, 1H), 6.88 (ddd, *J* = 8.4, 2.5, 0.8 Hz, 1H), 6.55 (d, *J* = 16.0 Hz, 1H), 5.57 (dd, *J* = 8.2, 4.1 Hz, 1H), 3.84 (d, *J* = 1.8 Hz, 6H), 3.64 (s, 3H), 3.00 (dd, *J* = 16.4, 4.2 Hz, 1H), 2.78 (dd, *J* = 16.4, 8.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 166.6, 160.7, 141.8, 137.5, 136.5, 135.5, 135.0, 132.7, 130.6, 124.9, 120.9, 120.4, 117.3, 113.2, 111.0, 58.1, 55.4, 52.1, 52.0, 38.3; HRMS calculated for $C_{21}H_{22}NO_7S$ $(M+H)^+$ 432.1117; found 432.1127 (TOF MS EI+).

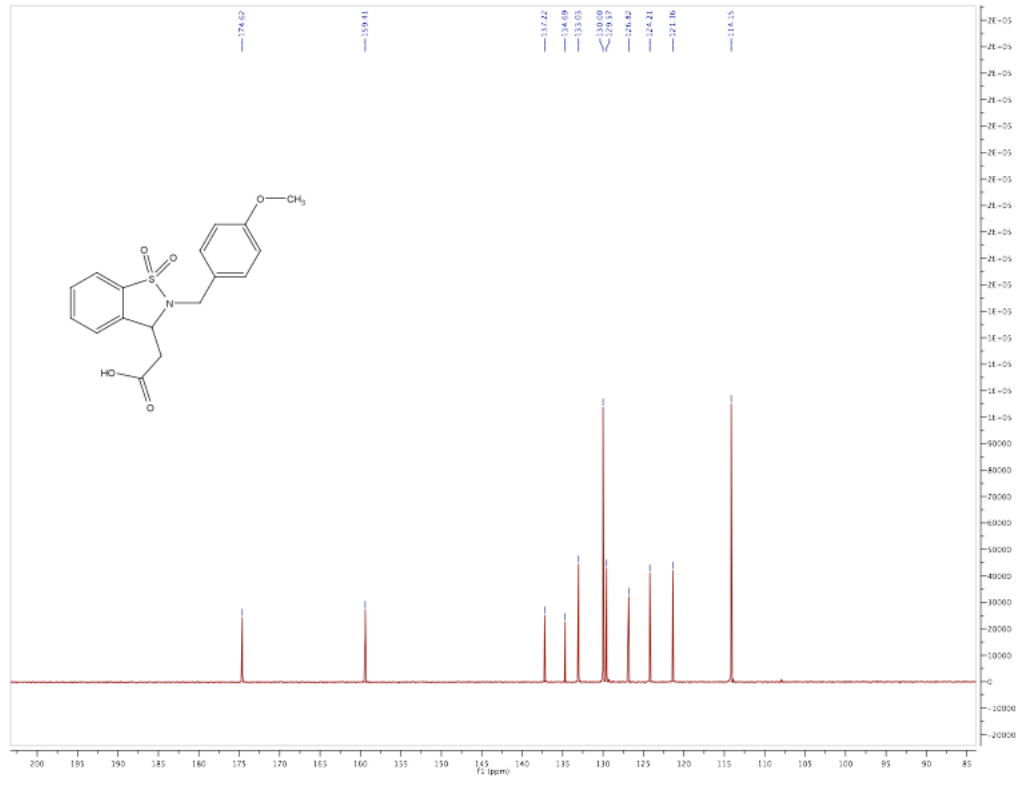
Compound No.	Calc. Mass	Mass Found	Compound No.	Calc. Mass	Mass Found
1	284.0957	284.0963	**26**	350.0862	350.0887
2	348.0906	348.0915	**27**	380.0968	380.0990
3	362.1062	362.1080	**28**	394.1124	394.1134
4	332.0957	332.0978	**29**	364.1019	364.1033
5	362.1062	362.1088	**30**	386.1723	386.1811
6	376.1219	376.1225	**31**	314.0862	314.0872
7	296.0957	296.0976	**32**	328.1019	328.1036
8	310.1113	310.1138	**33**[2]	339.0815	339.0833
9	304.0644	304.0666	**34**	366.0811	366.0819
10	334.0749	334.0761	**35**	336.0706	336.0716
11	348.0906	348.0915	**36**	358.1488	358.1513
12	294.1164	294.1181	**37**[2]	369.1069	369.1104
13	308.1320	308.1335	**38**[2]	383.1257	383.1259
14	302.0851	302.0865	**39**	378.0987	378.1011
15	332.0957	332.0974	**40**	392.1143	392.1152
16	302.0862	302.0876	**41**[2]	447.1202	447.1183
17[2]	333.1284	333.1293	**42**	400.0830	400.0863
18	336.0706	336.0741	**43**[2]	439.1887	439.1884
19	380.0968	380.0977	**44**[2]	383.1252	383.1260
20	350.0862	350.0870	**45**[3]	805.2028	805.2031
21	371.1567	371.1574	**46**[2]	423.1565	423.1585
22[2]	333.1284	333.1116	**47**[2]	447.1202	447.1220
23[2]	347.1441	347.1458	**48**[2]	461.1358	461.1370
24	342.1175	342.1182	**49**	414.0987	414.1272
25	356.1332	356.1349	**50**	435.1691	435.2048

Compound No.	Calc. Mass	Mass Found	Compound No.	Calc. Mass	Mass Found
51[2]	369.1096	369.1113	74	414.0987	414.1002
52[2]	381.1096	381.1100	75	478.2239	478.2253
53[2]	395.1252	395.1270	76[2]	481.2348	481.2343
54[2]	433.1045	433.1039	77	479.2555	479.2568
55[2]	403.0939	403.0960	78	397.1034	397.1047
56[2]	425.1722	425.1746	79	451.1503	451.1512
57	361.1222	361.1239	80	435.1554	435.1565
58	399.1742	399.1750	81	384.0717	384.0725
59	348.0906	348.0919	82	446.2177	446.2186
60	394.2416	394.2435	83	447.2493	447.2474
61	414.0987	414.1001	84	446.1273	446.1269
62	436.1430	436.1427	85	474.1586	474.1598
63	379.1128	379.1143	86	418.0960	418.0975
64	363.1179	363.1185	87	414.1375	414.1364
65	419.1441	419.1463	88	432.1117	432.1118
66	380.0968	380.0980	89	460.1430	460.1442
67	366.0811	366.0820	90	404.0804	404.0812
68	454.1336	454.1353	91	400.1219	400.1228
69	429.1096	429.1103	92	438.1950	438.1964
70	415.0939	415.0945	93	466.2263	466.2279
71	413.1147	413.1158	94	410.1637	410.1669
72	469.1409	469.1455	95	406.2052	406.2072
73	430.0936	430.0950			

[1] $(M + H)^+$ peak reported unless otherwise stated, [2] $(M + NH_4)^+$ peak reported, [3] $(2M + Na)^+$ peak reported

11.





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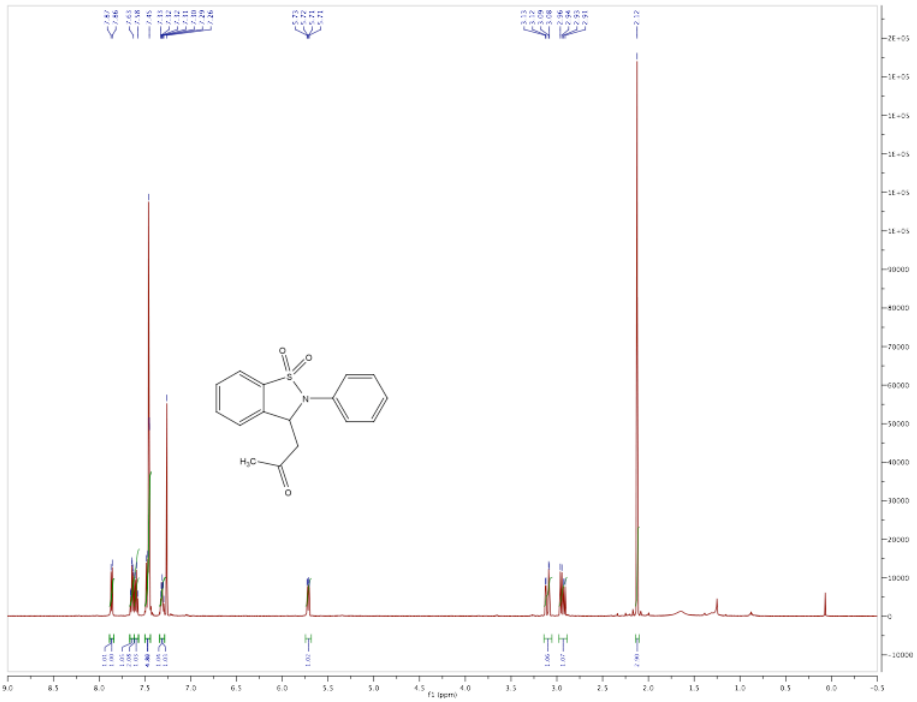

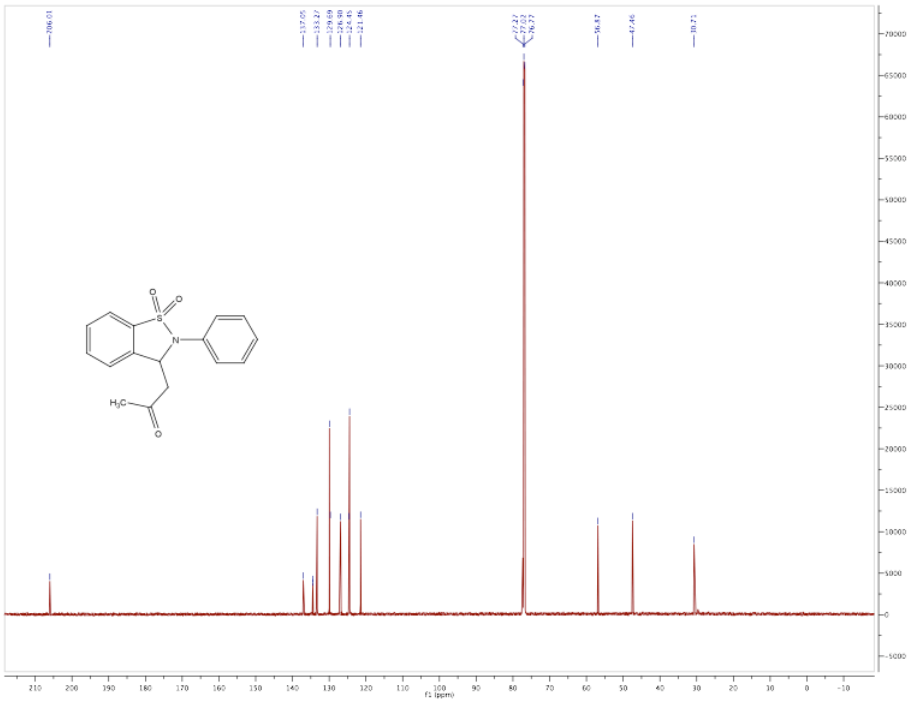

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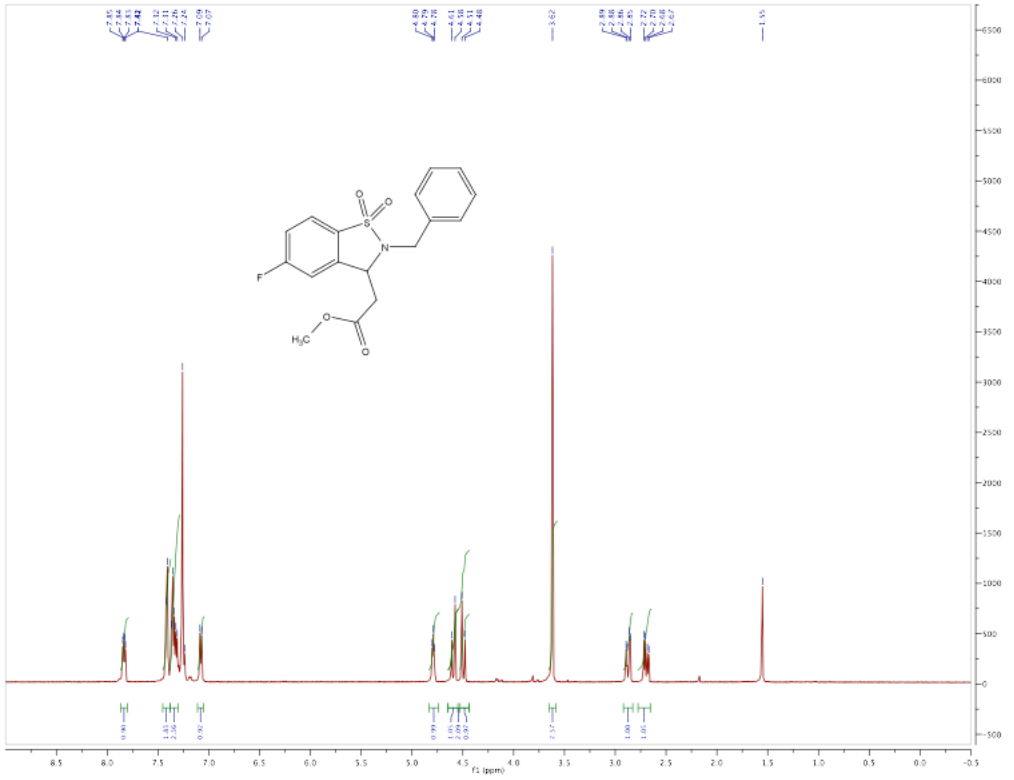

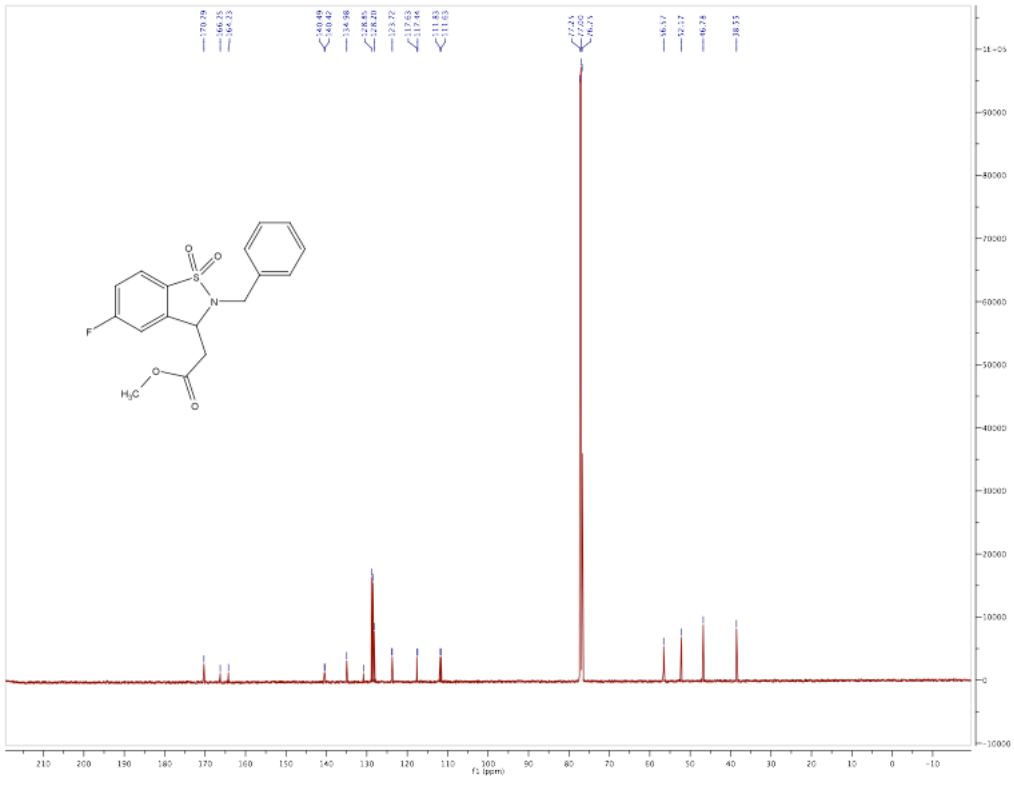

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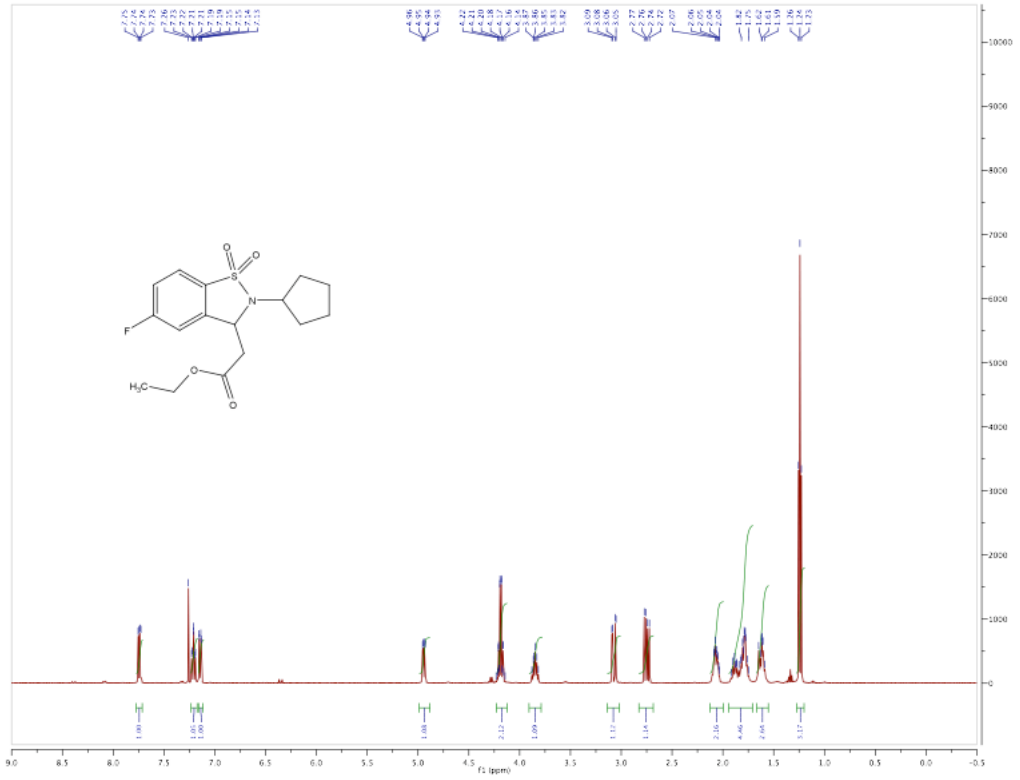

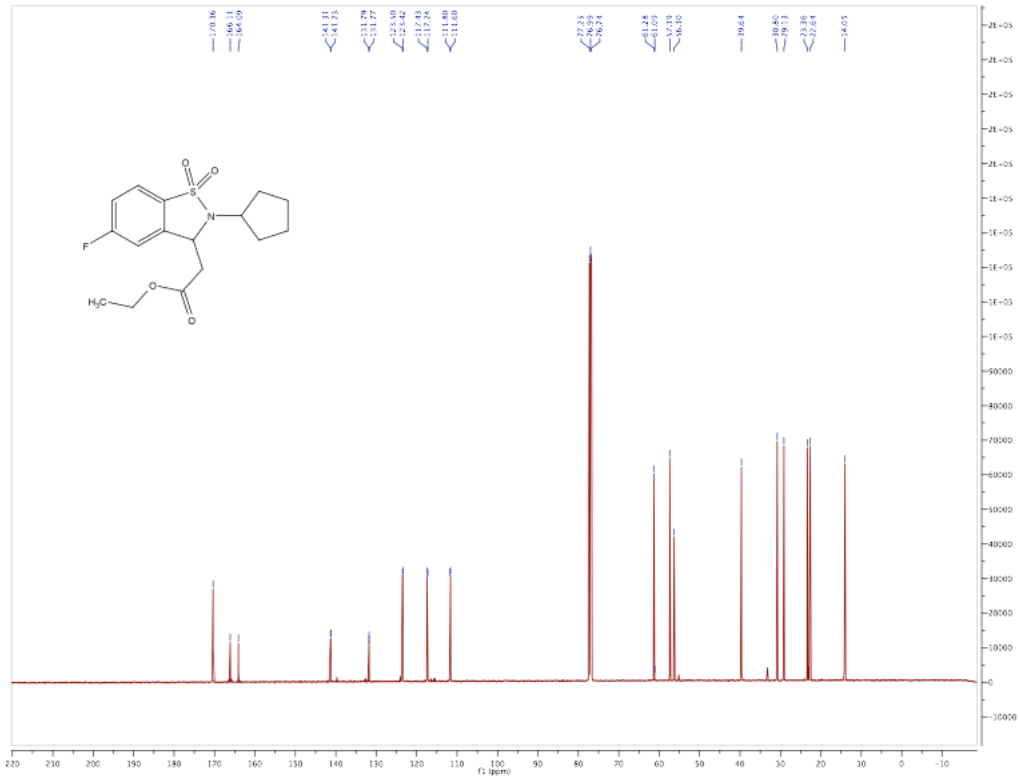

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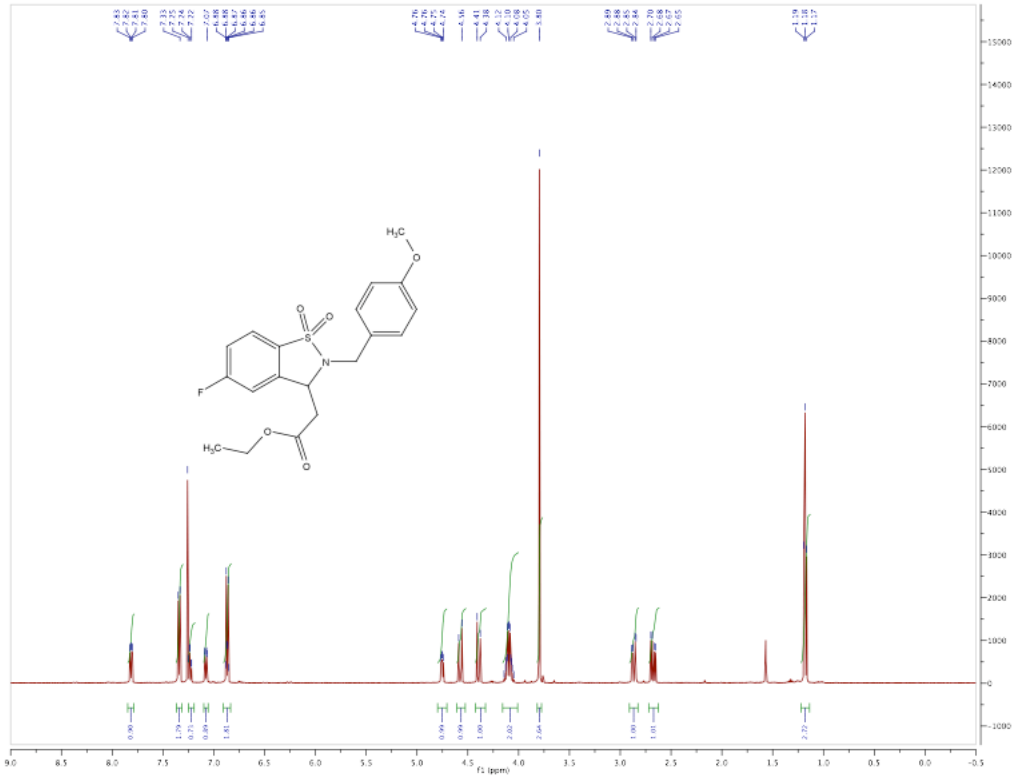

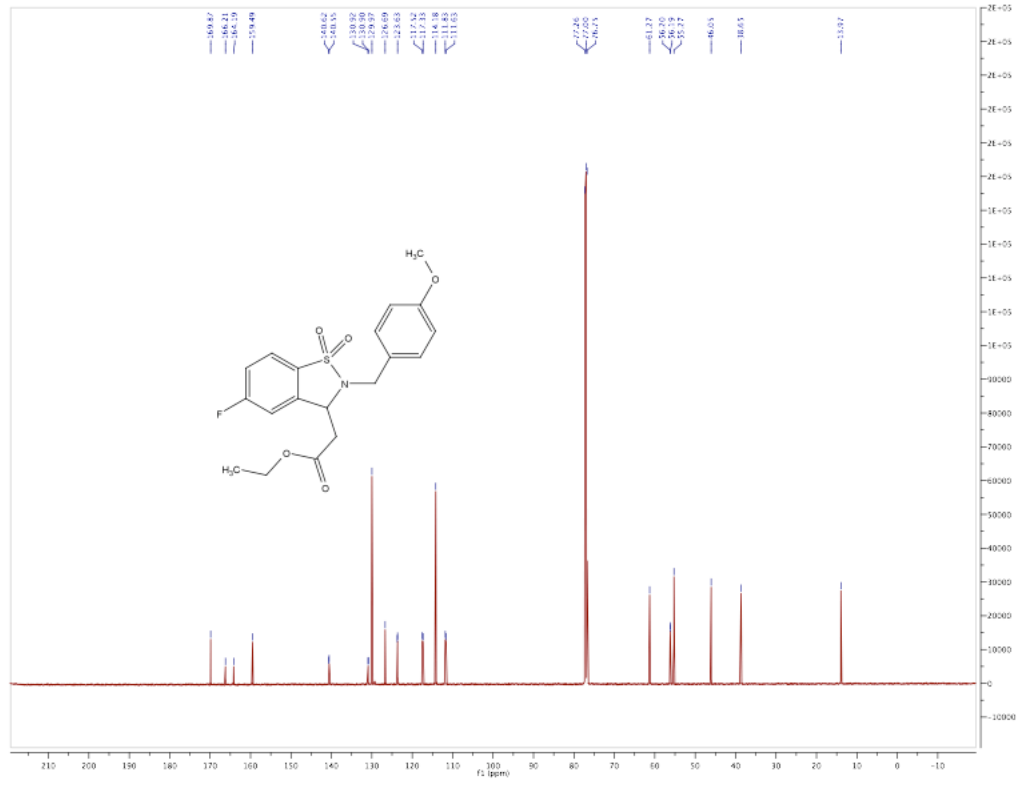

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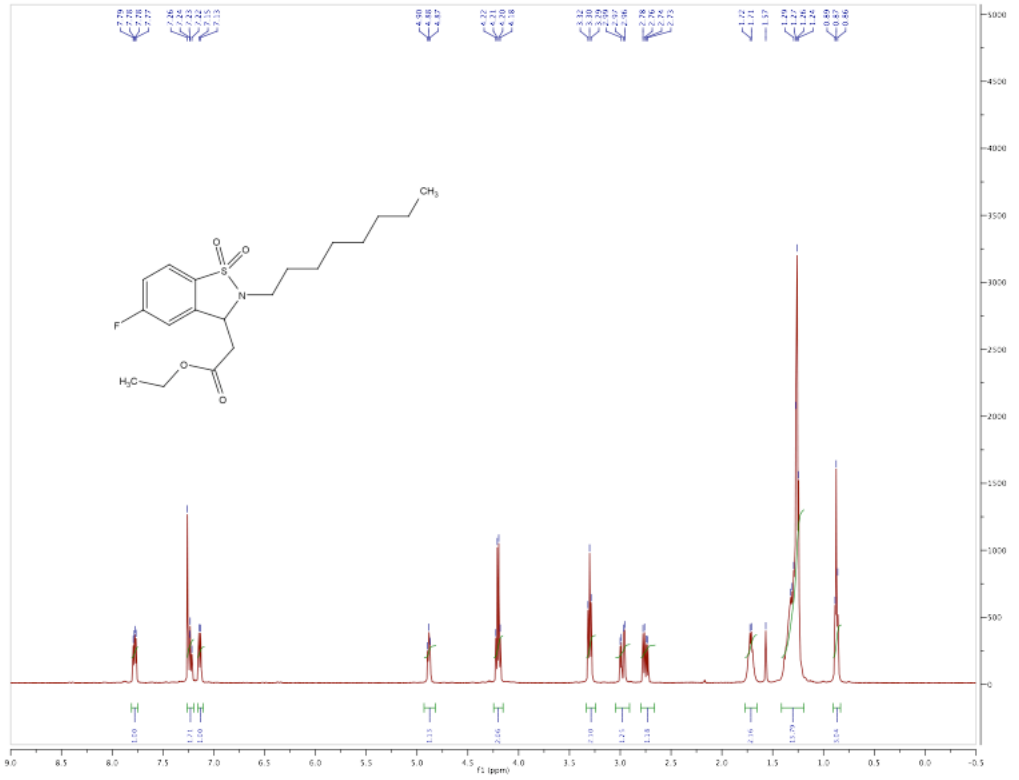

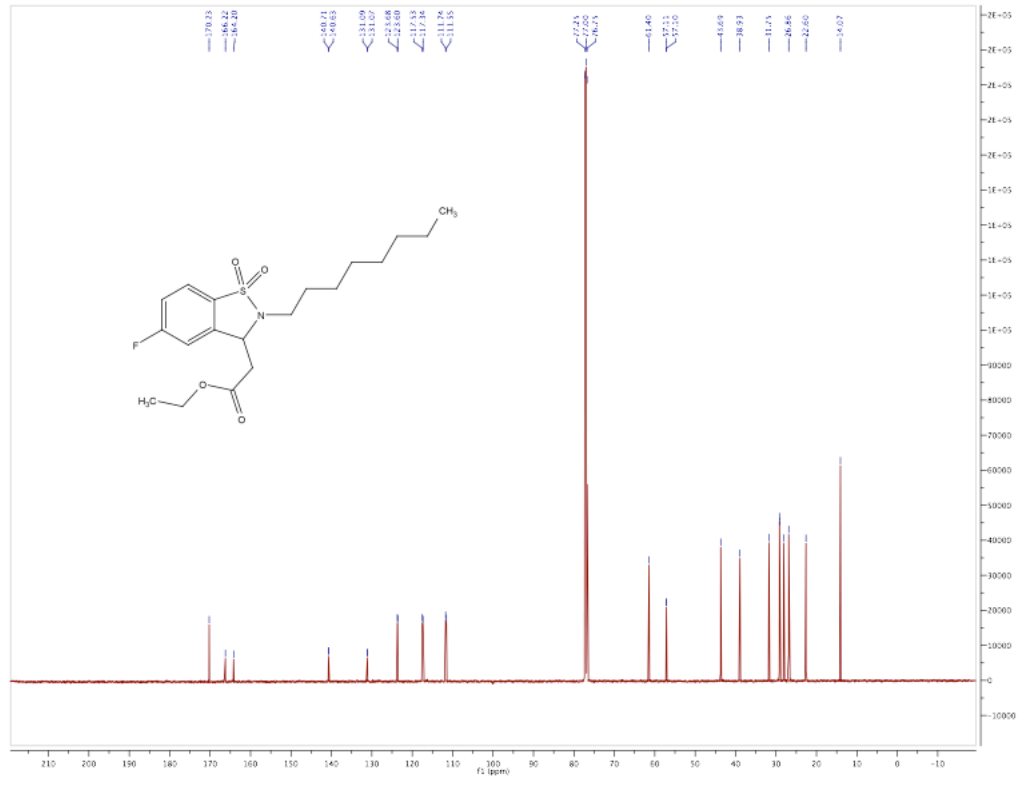

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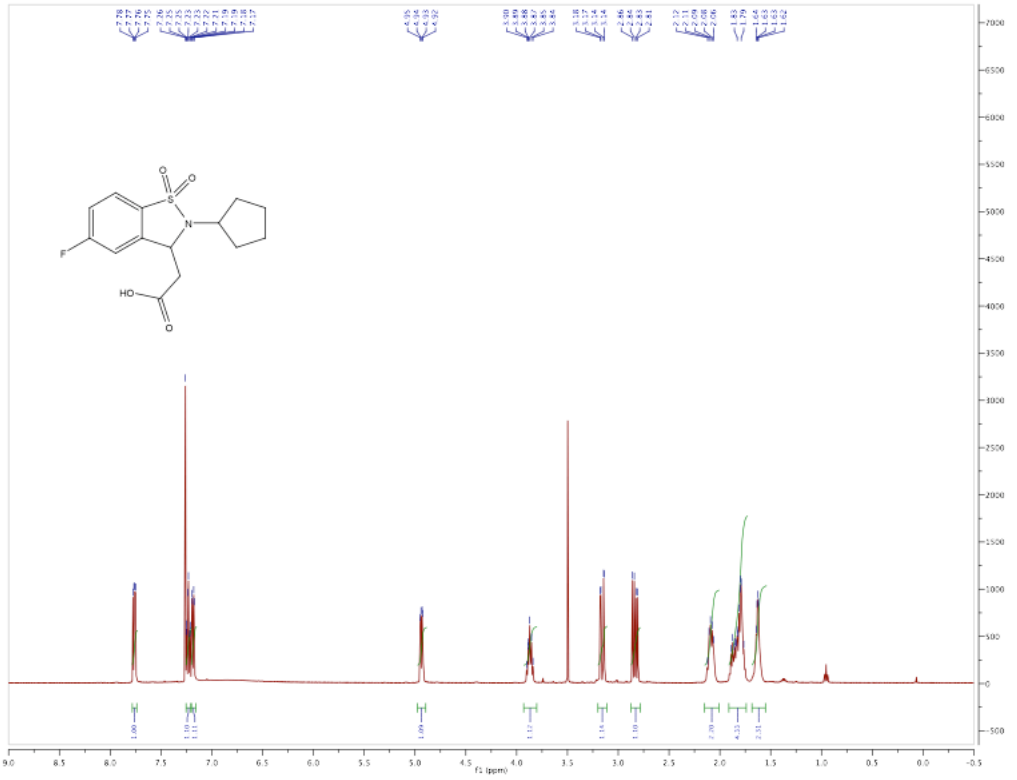

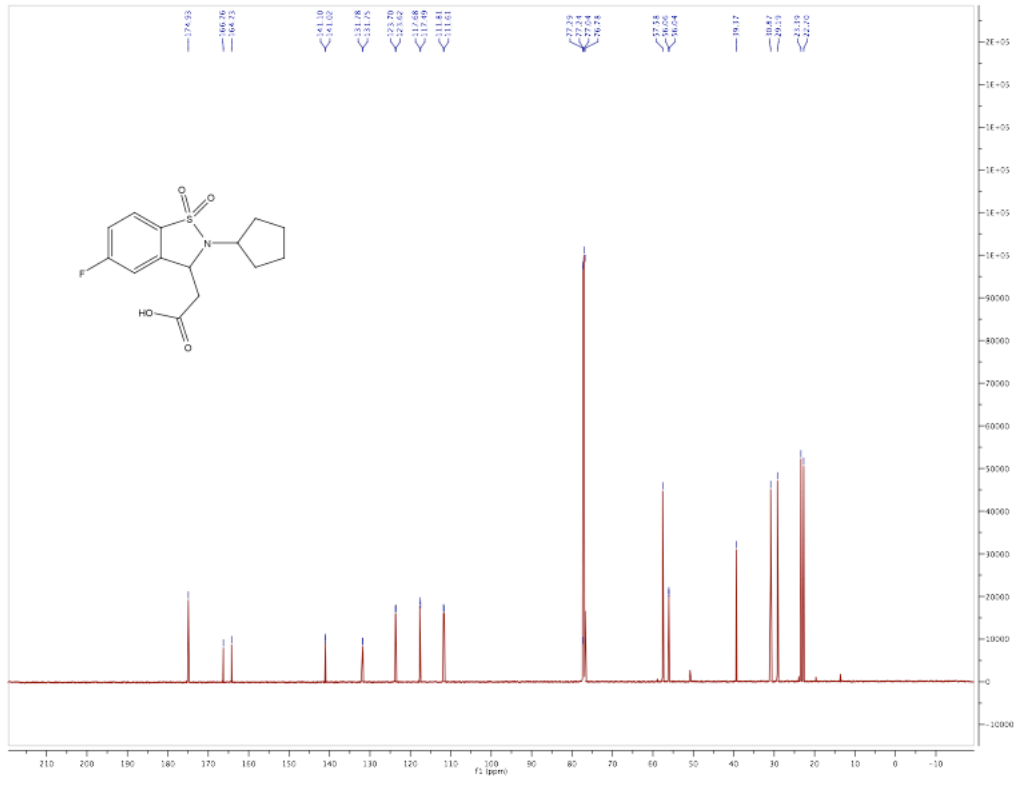

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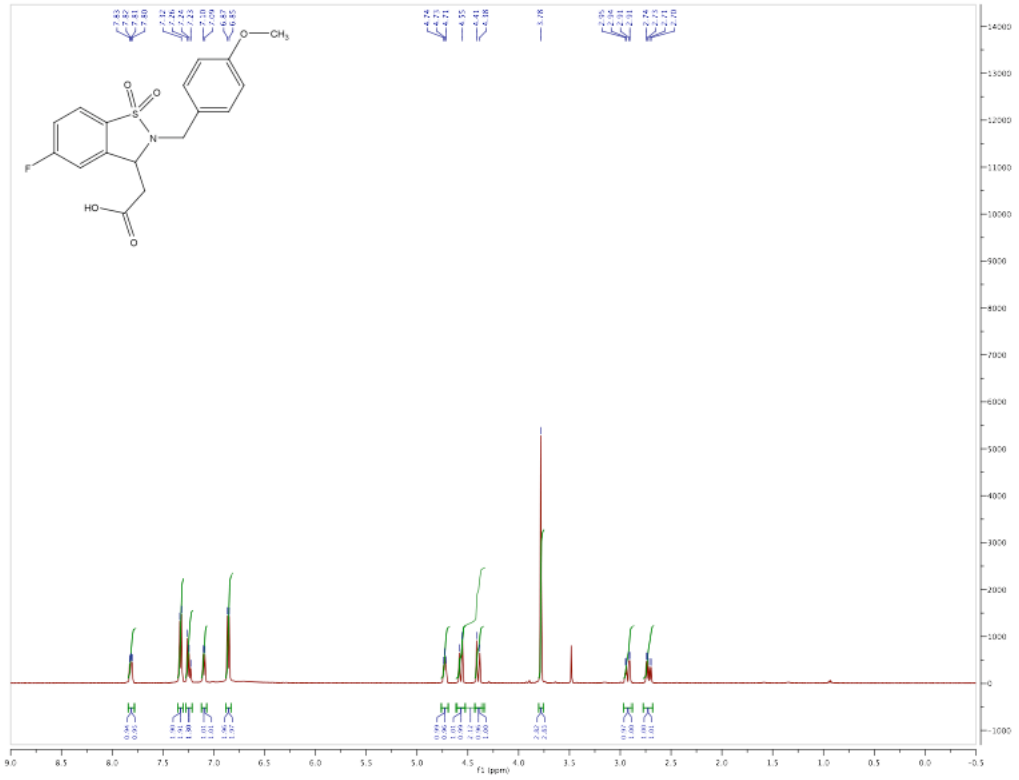

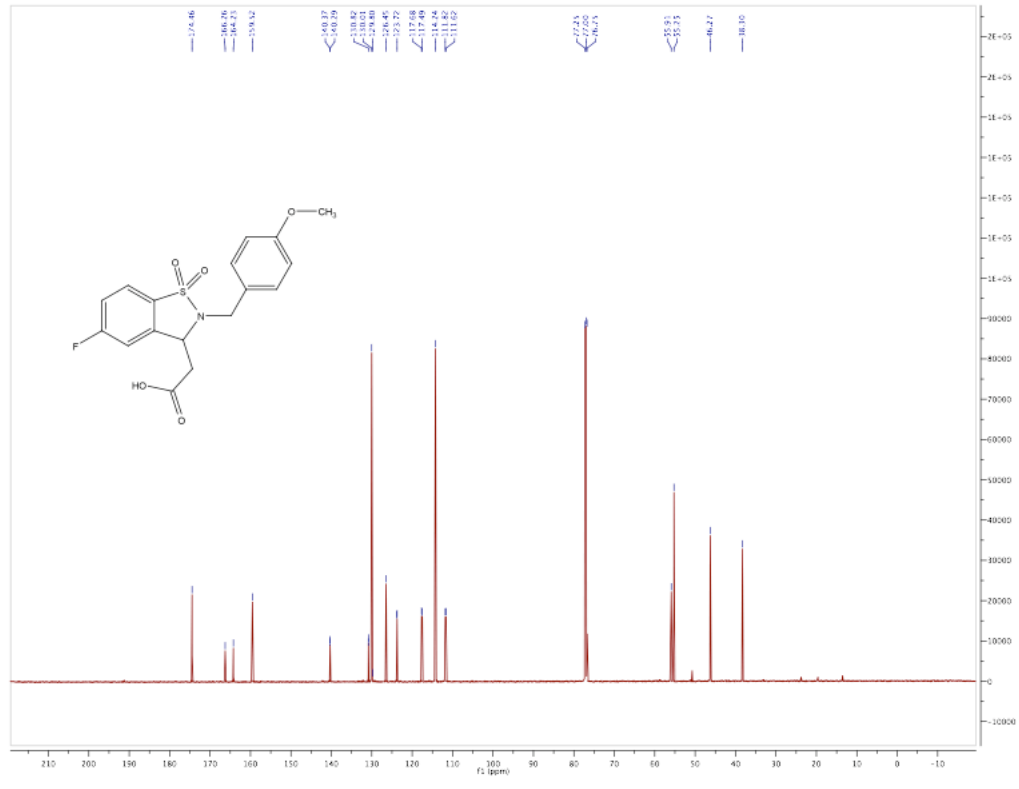

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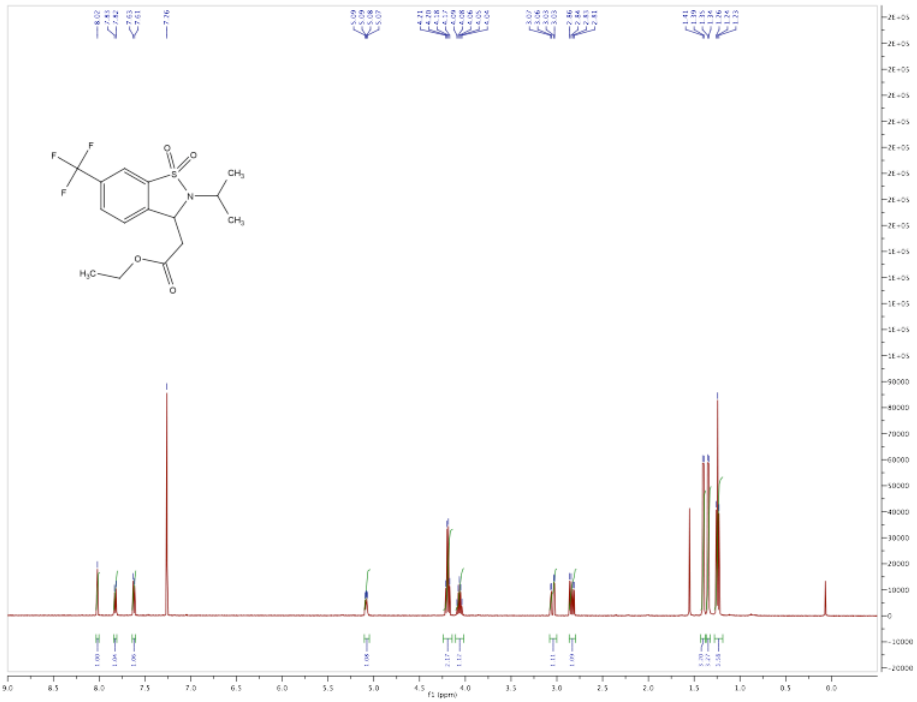

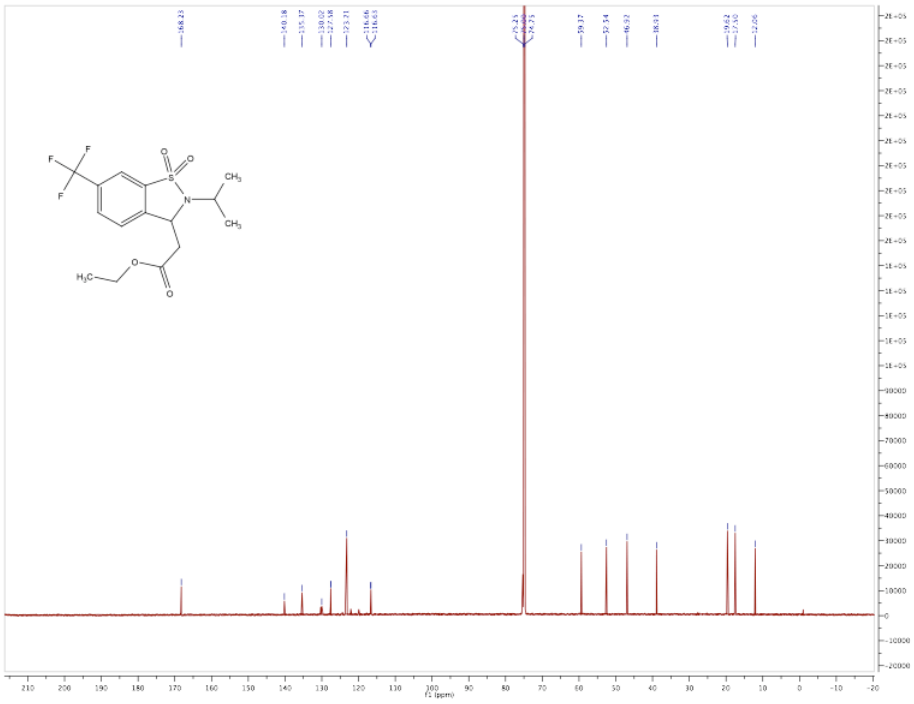

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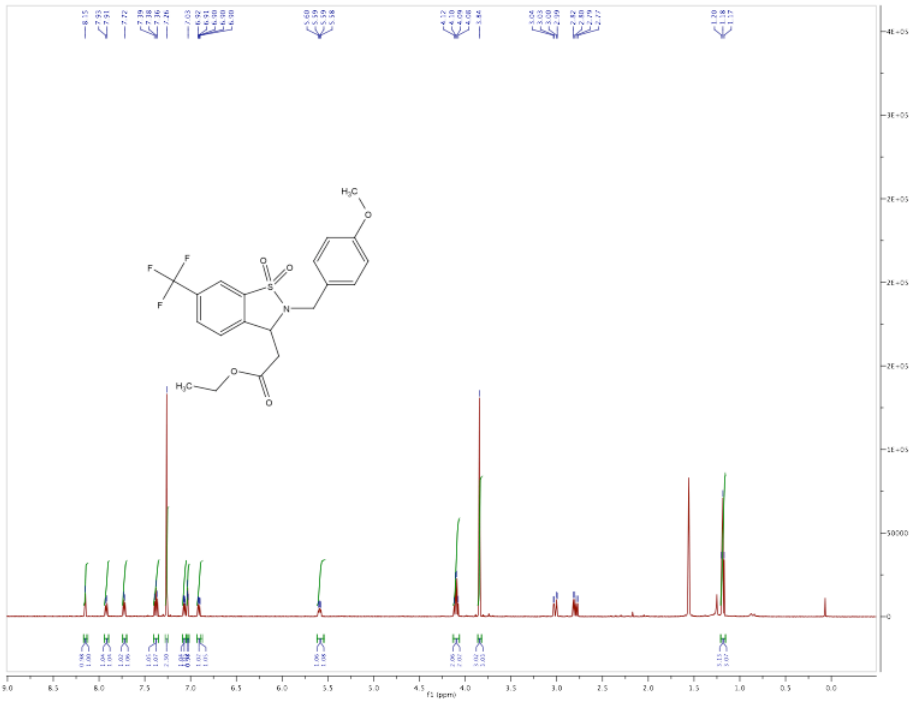

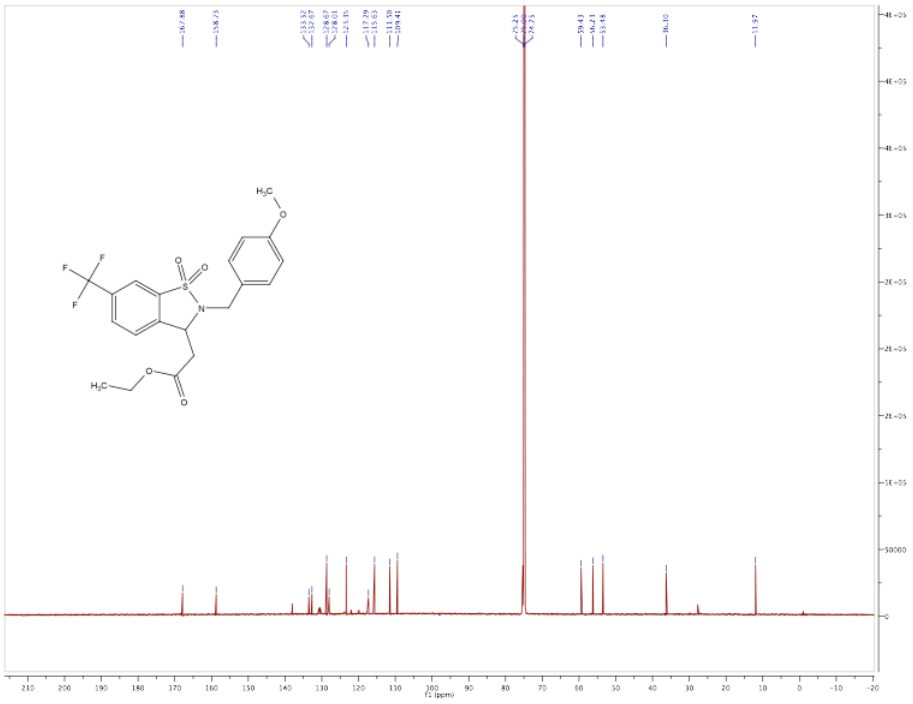

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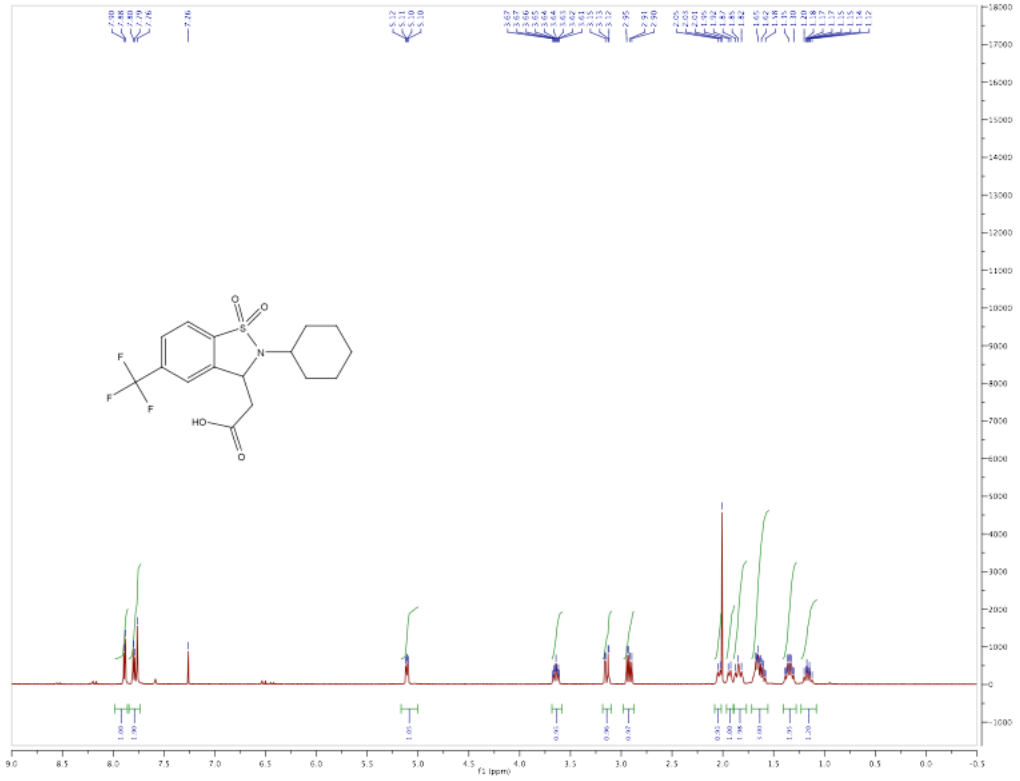

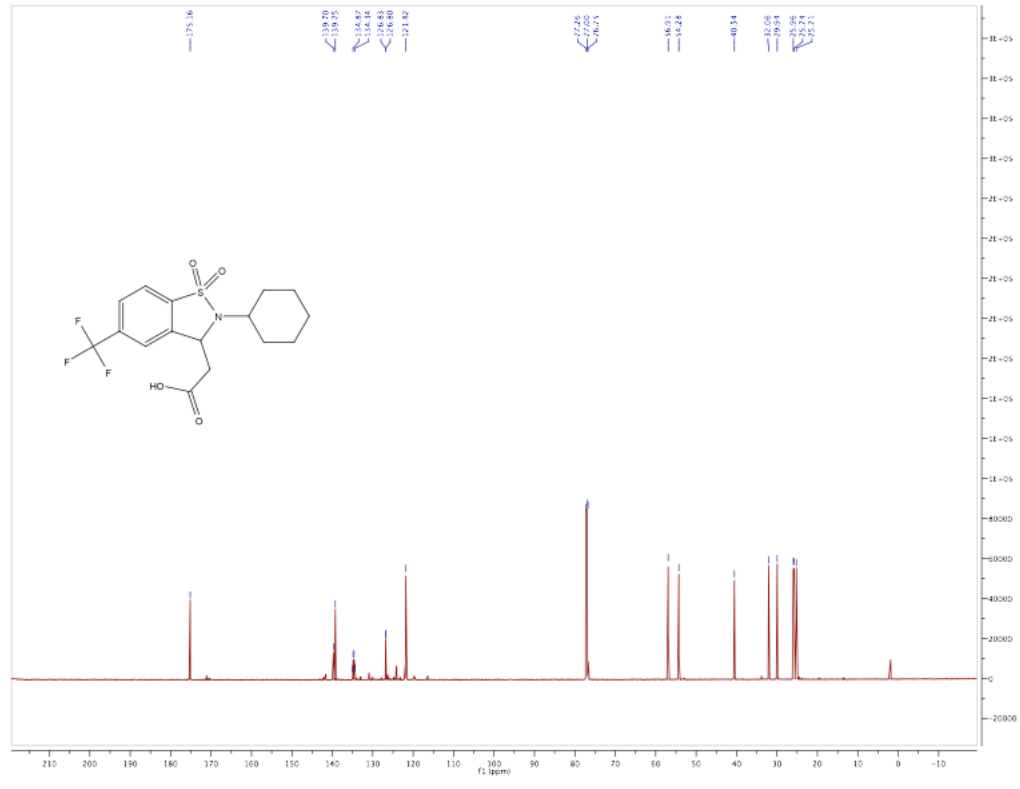

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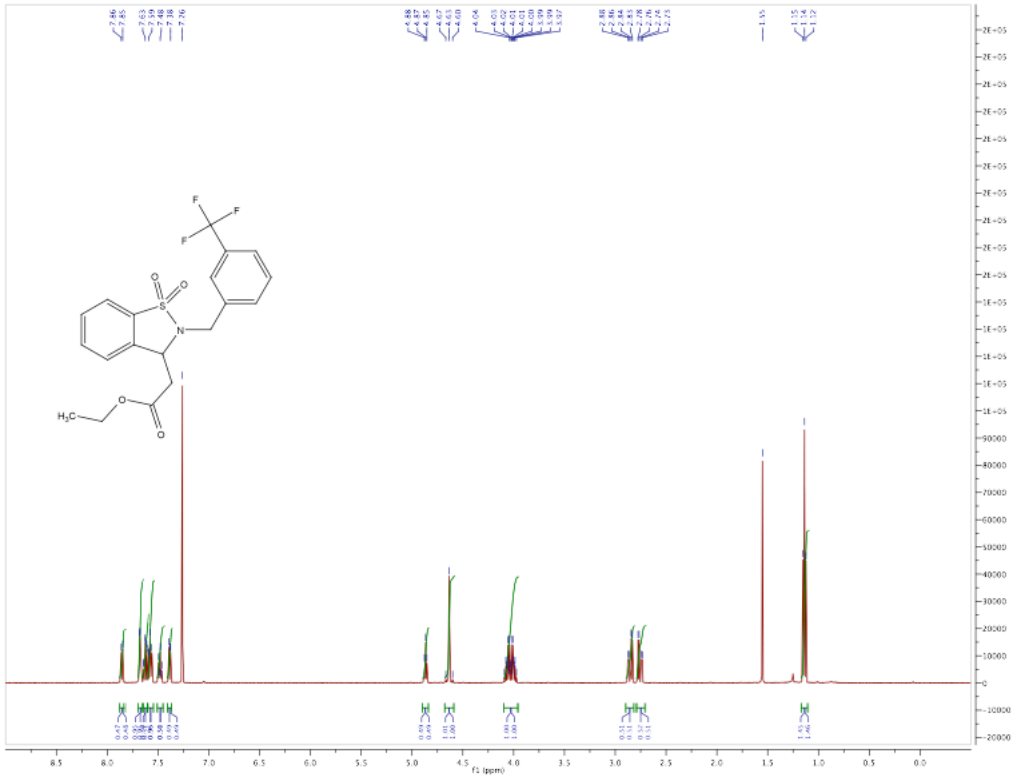

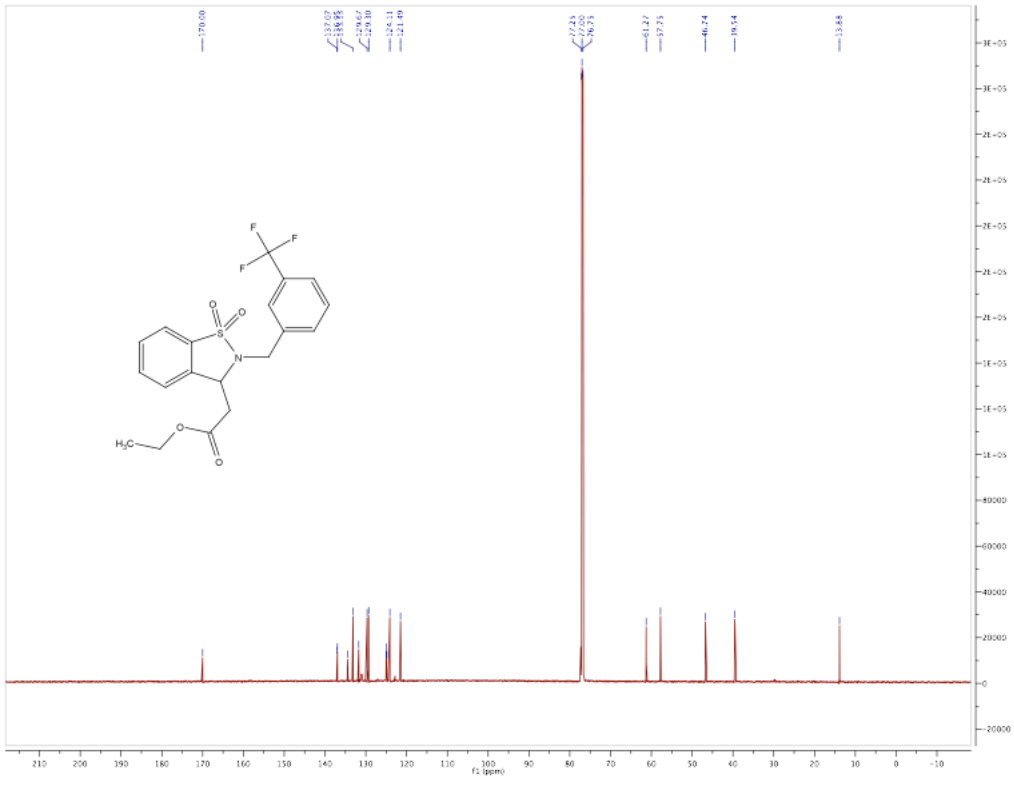

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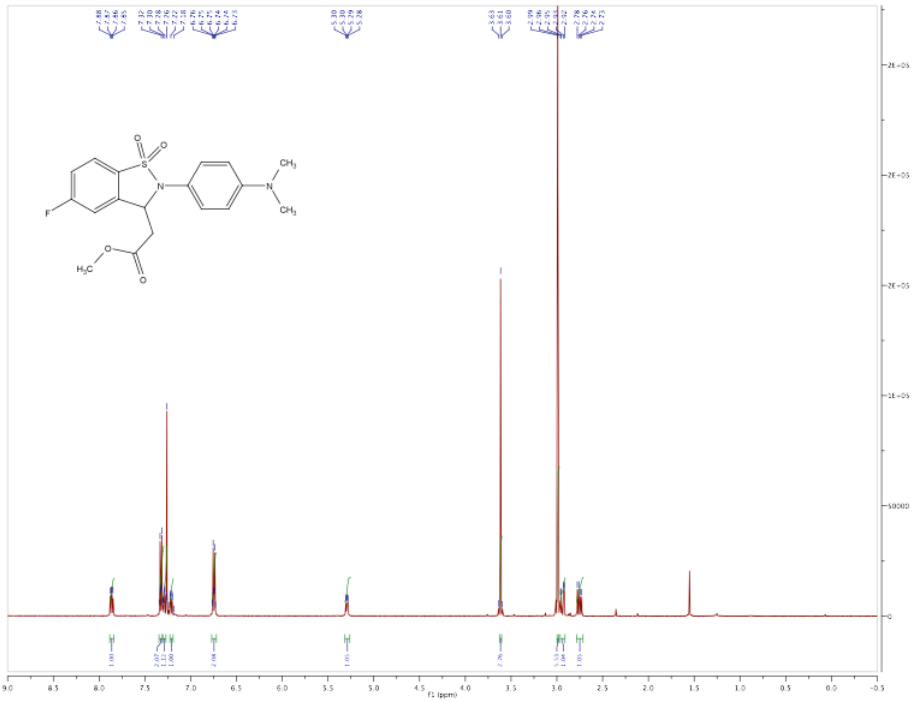

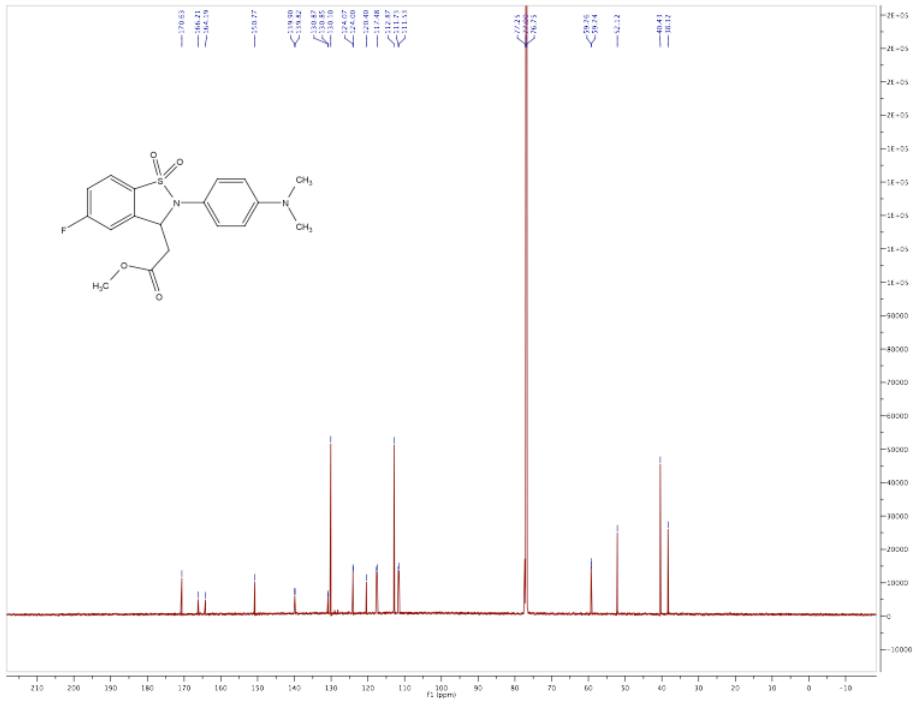

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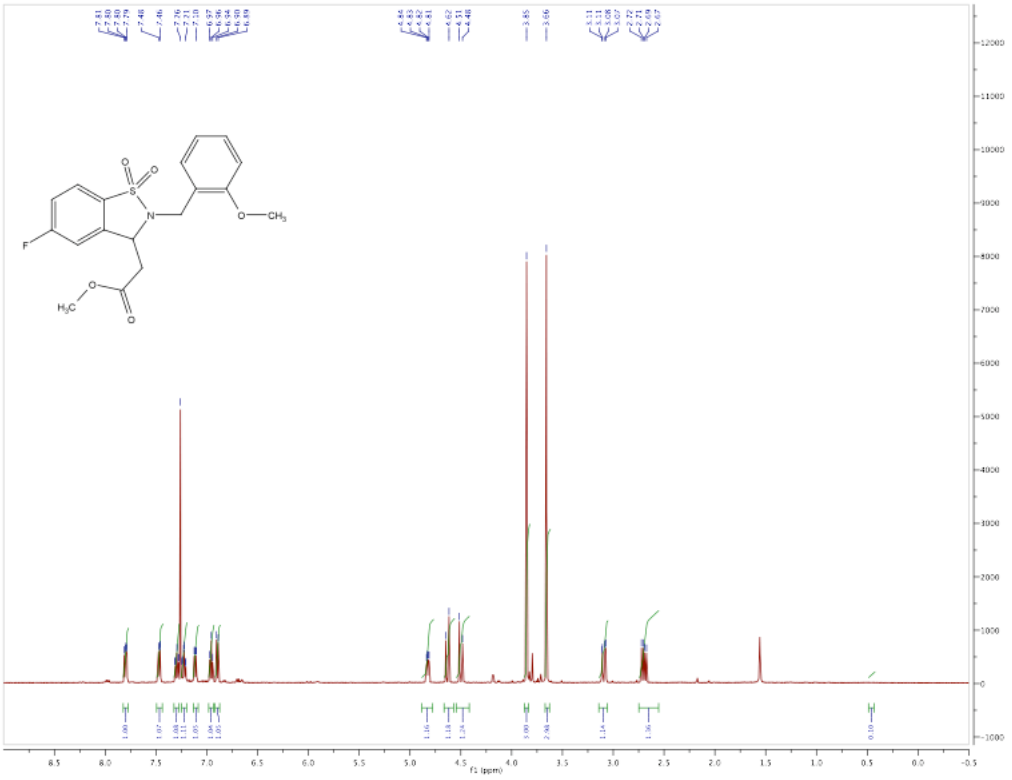

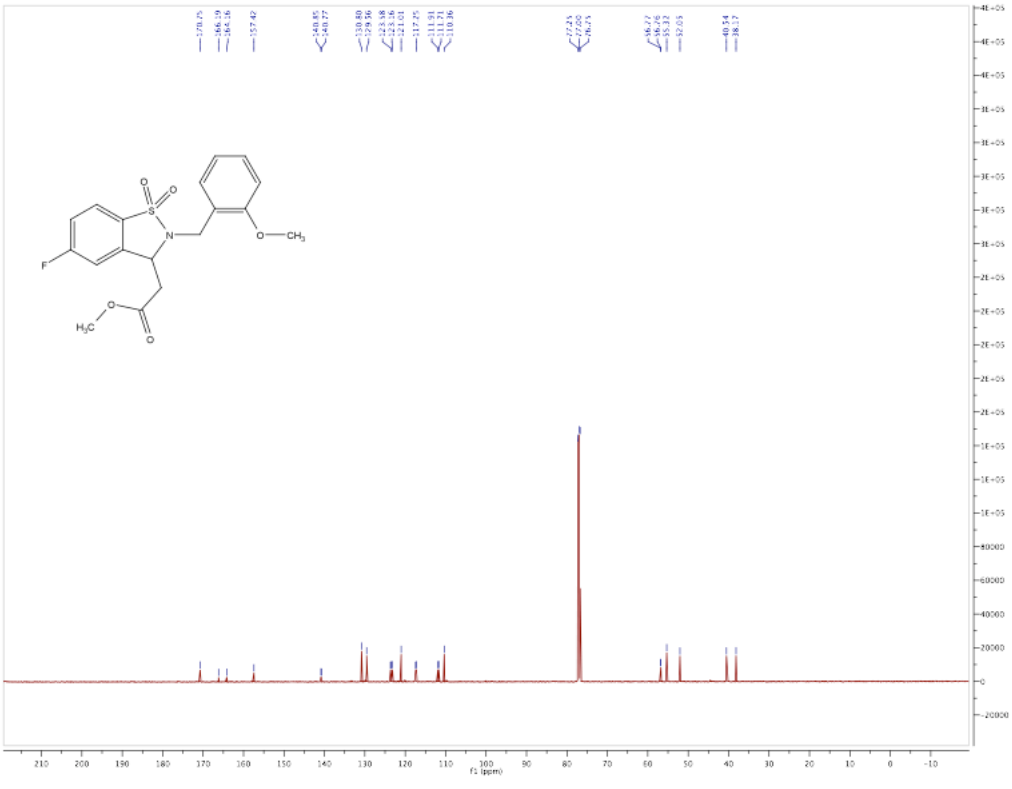

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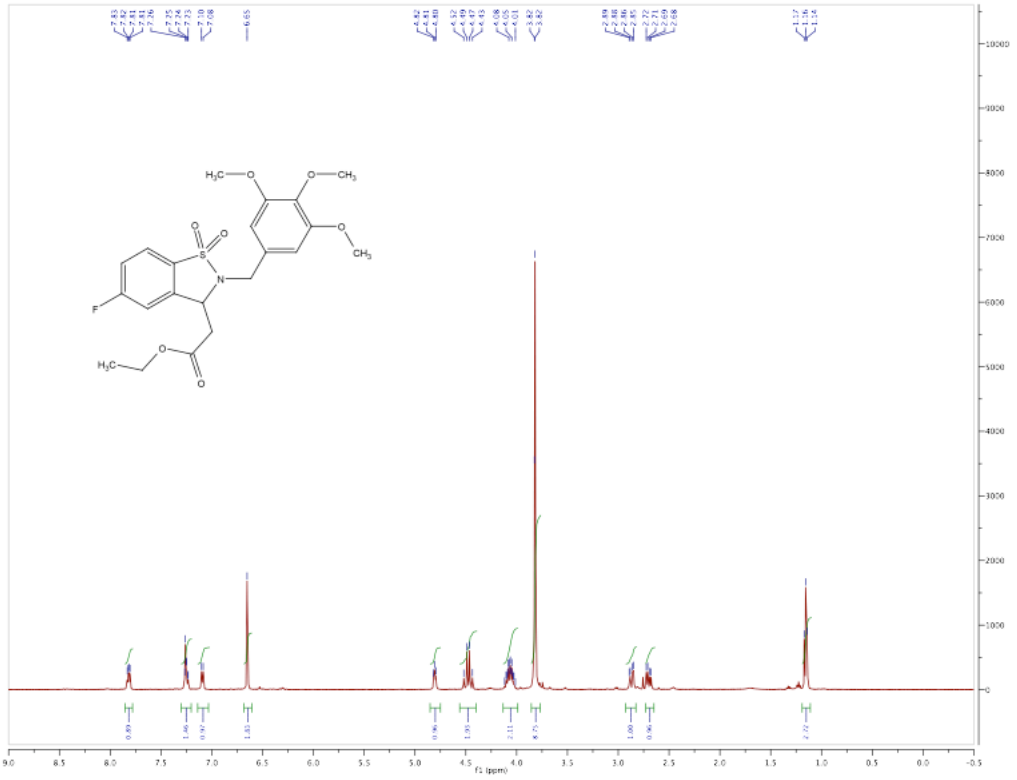

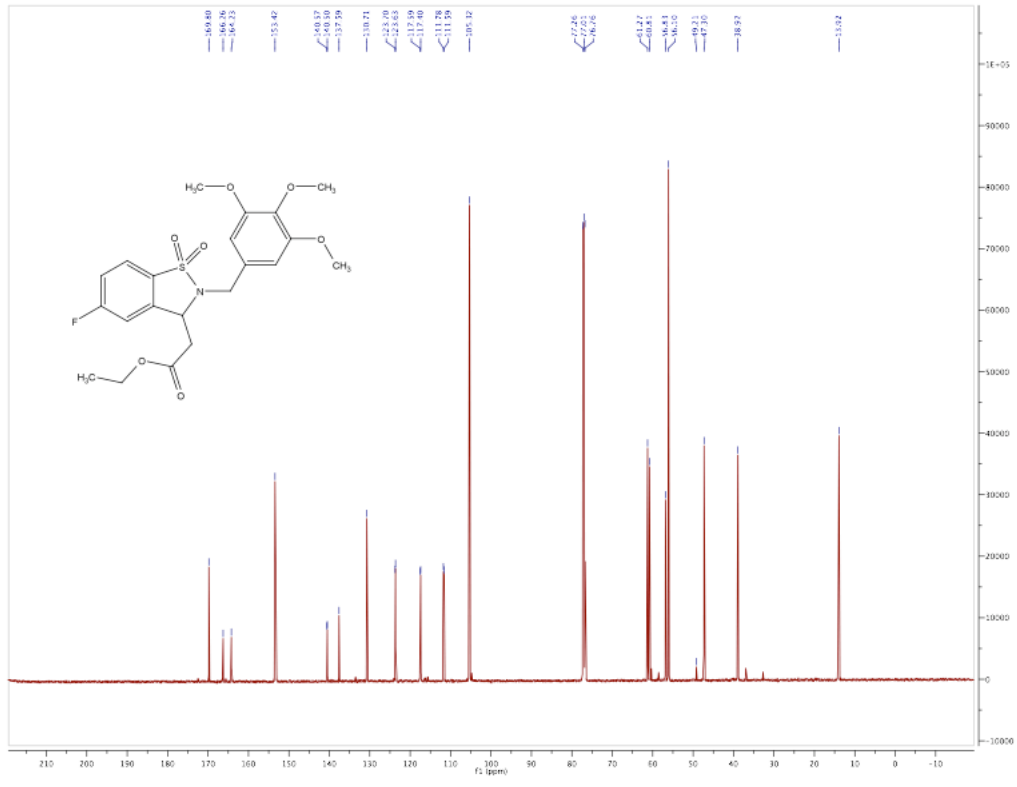

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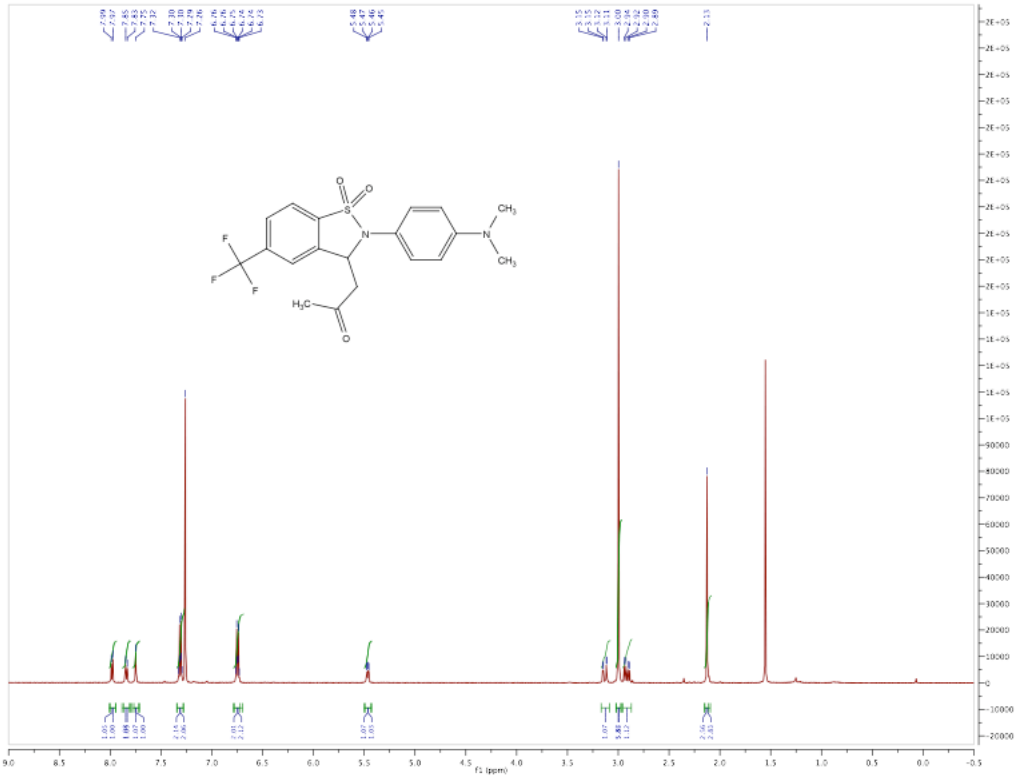

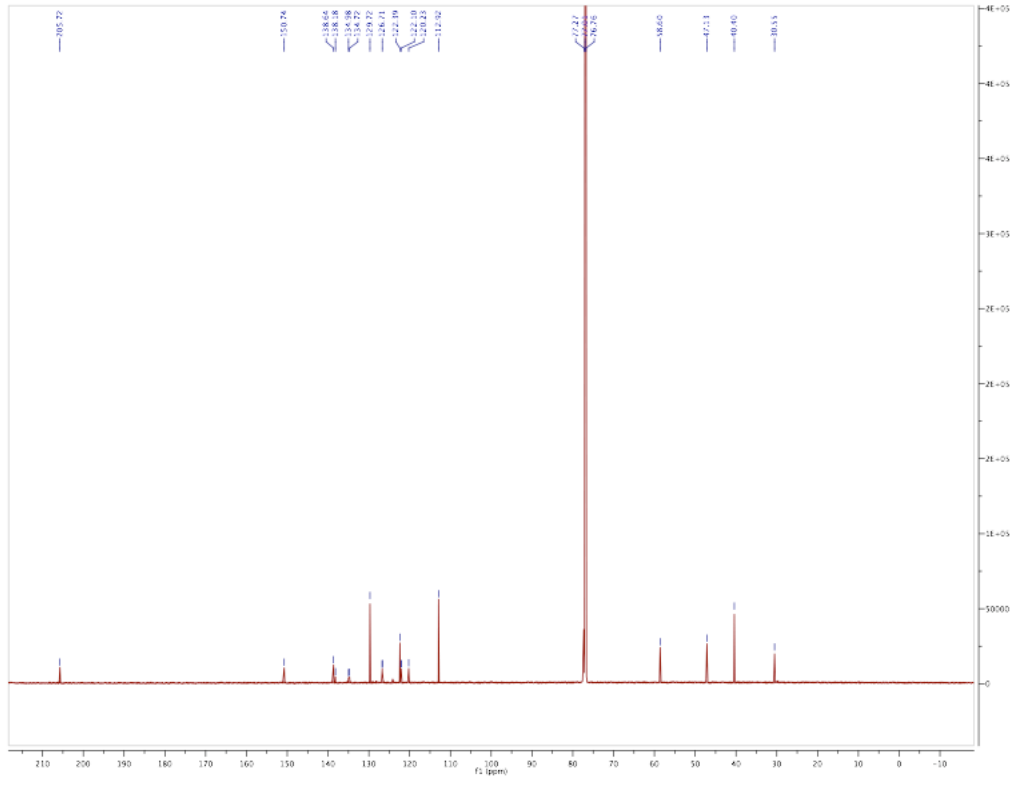

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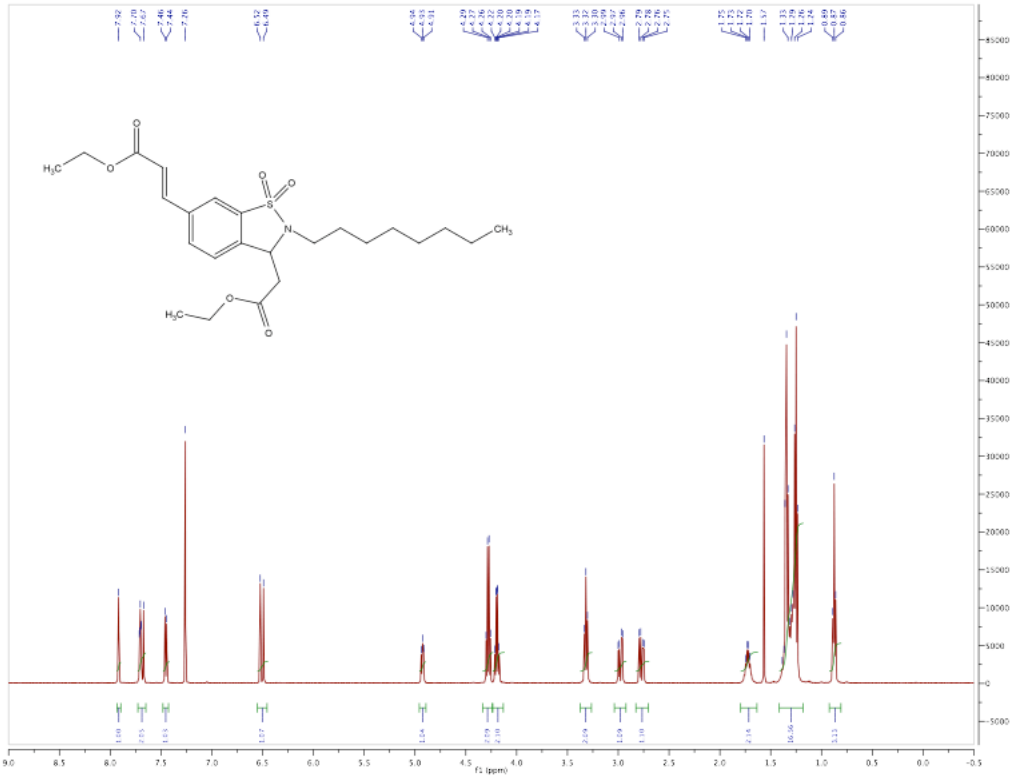

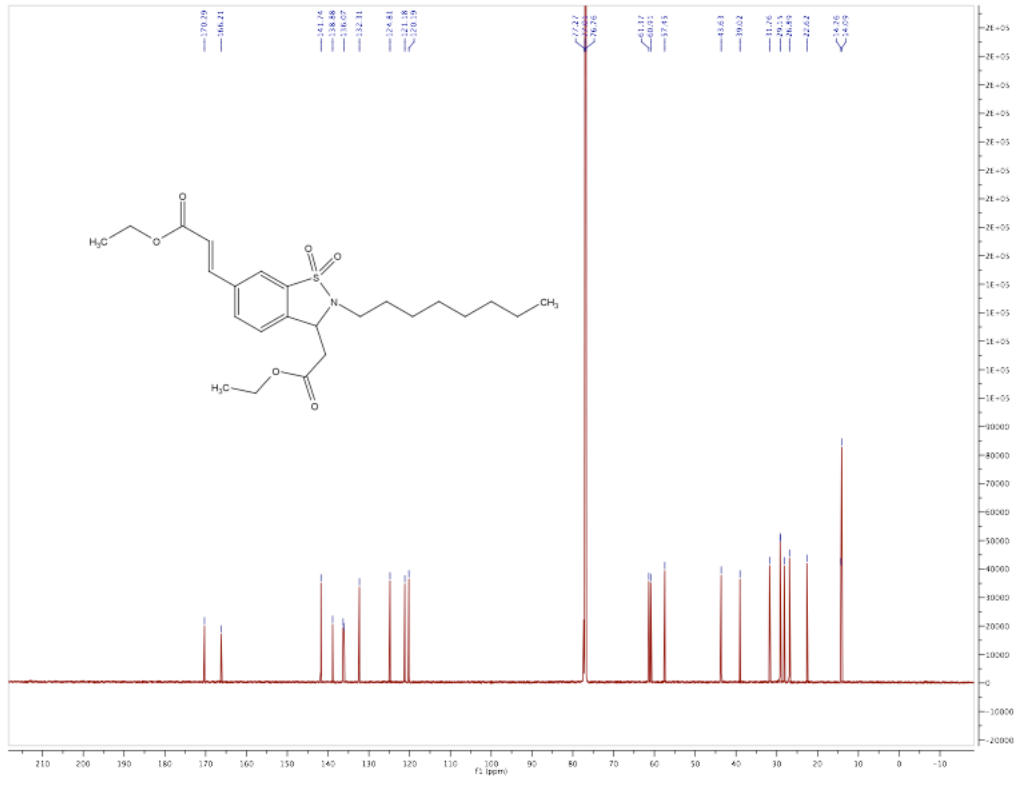

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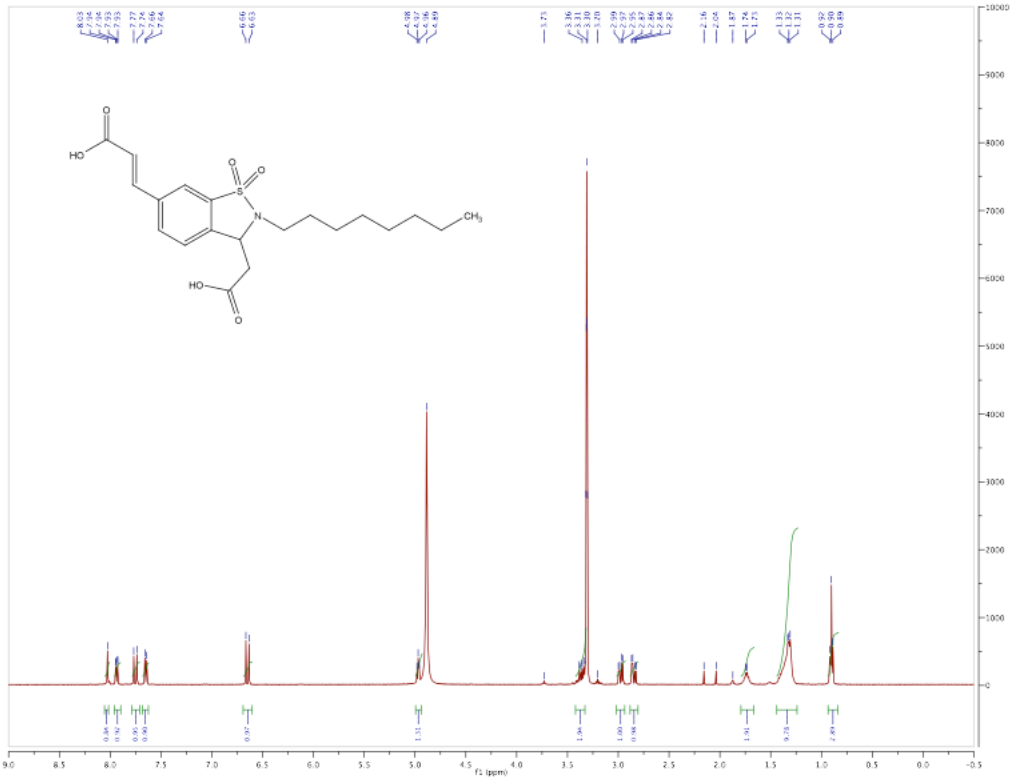
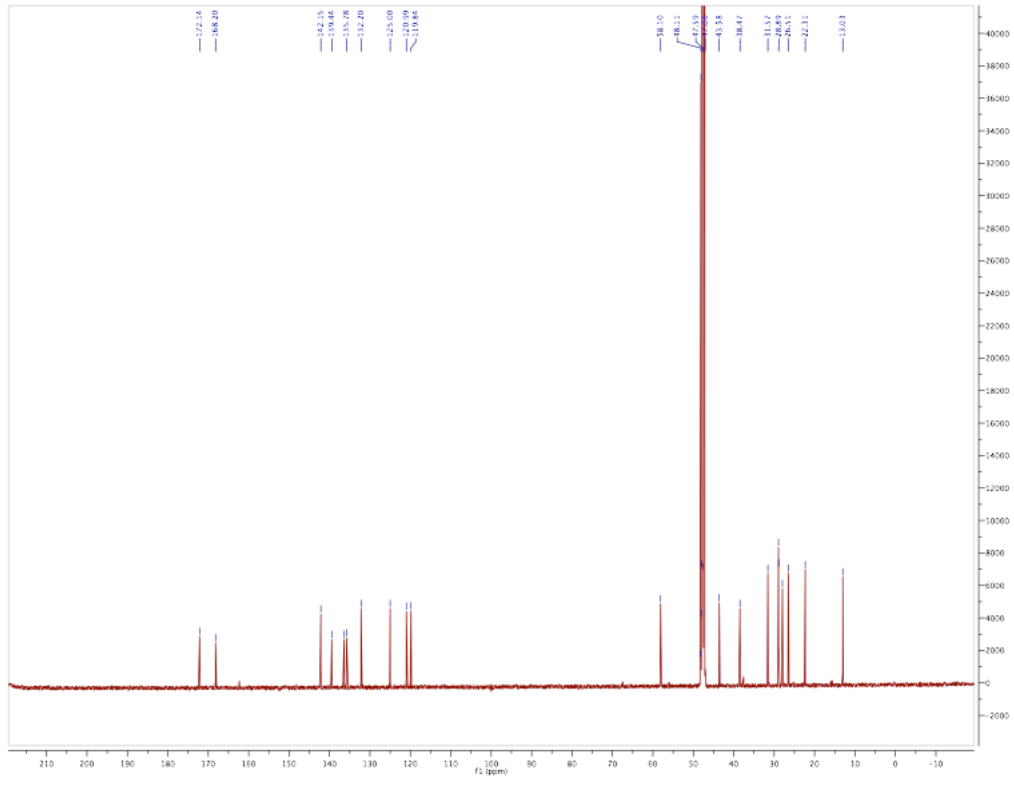
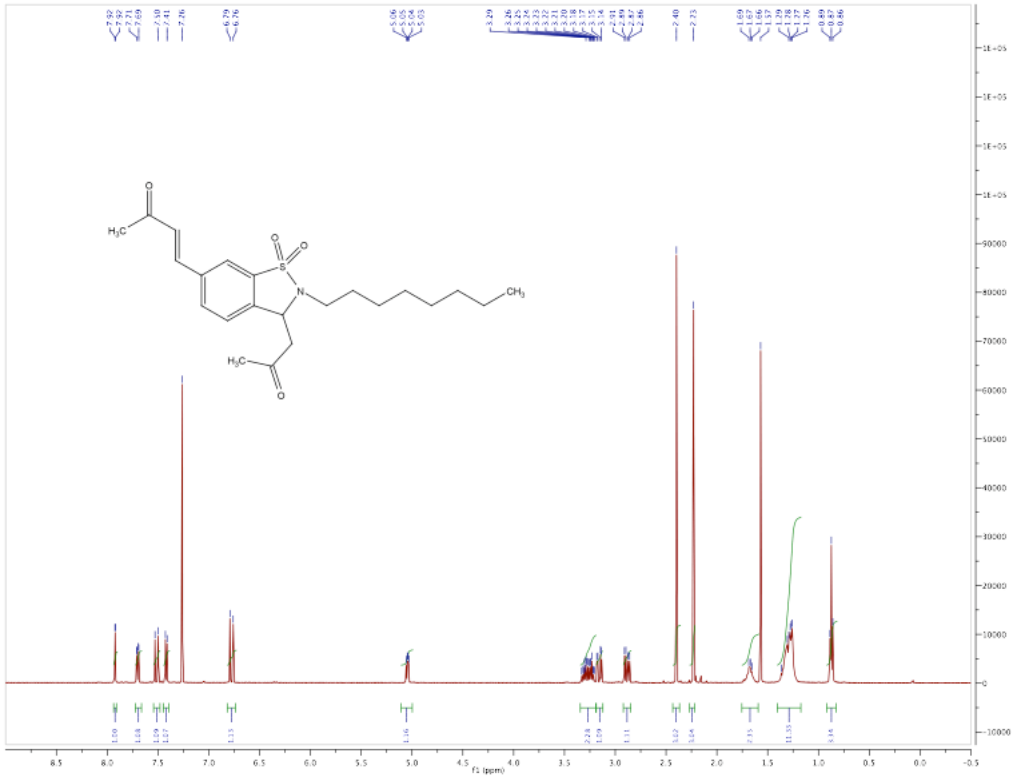
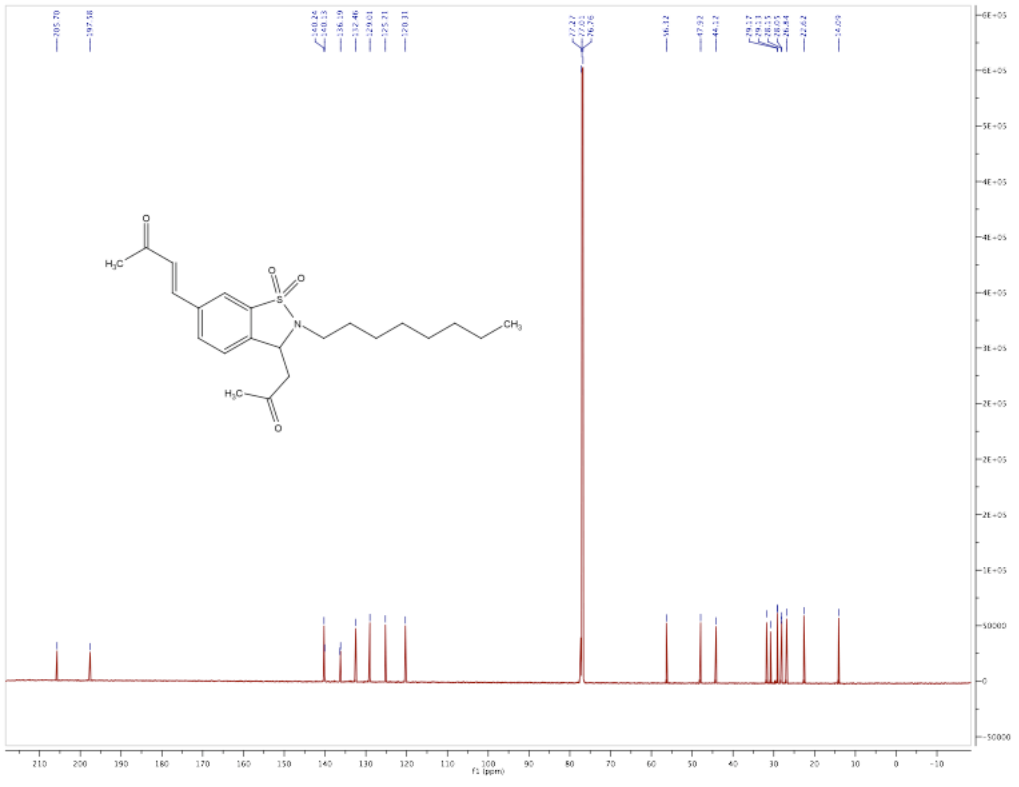


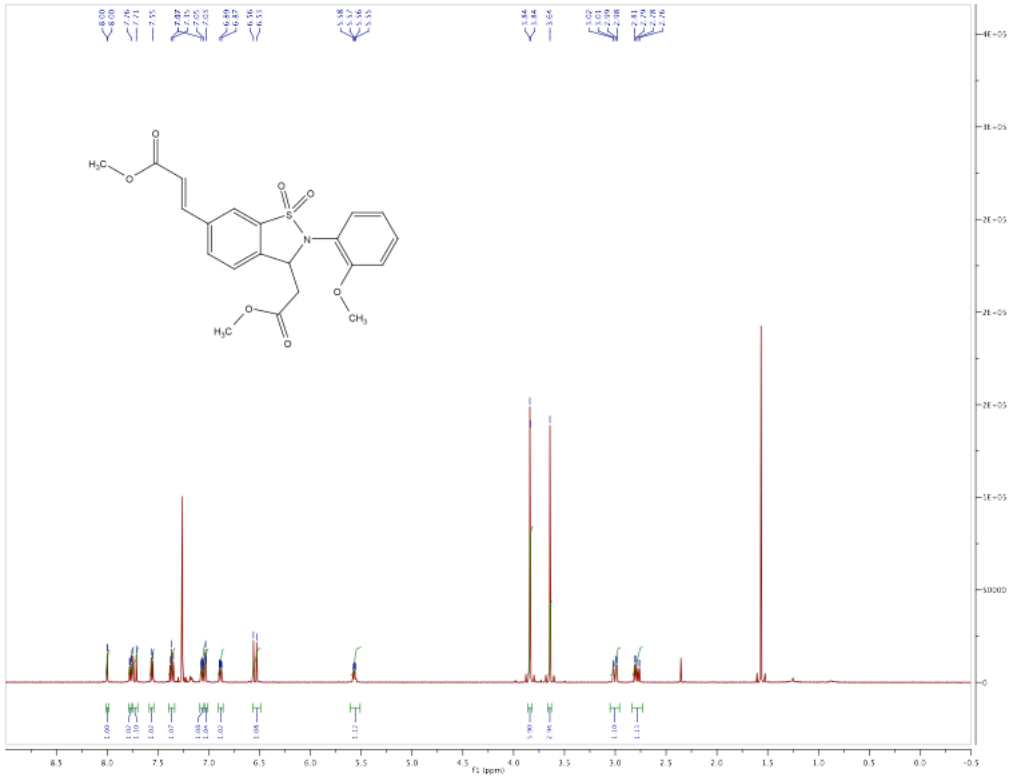


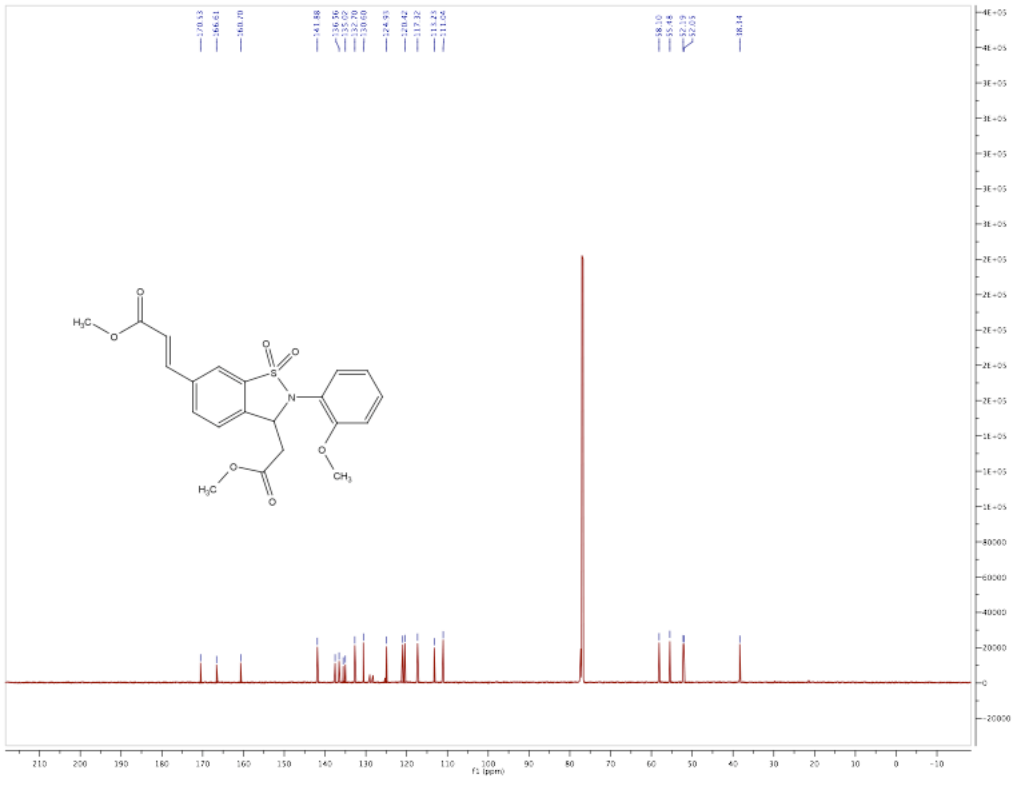
91.





92.

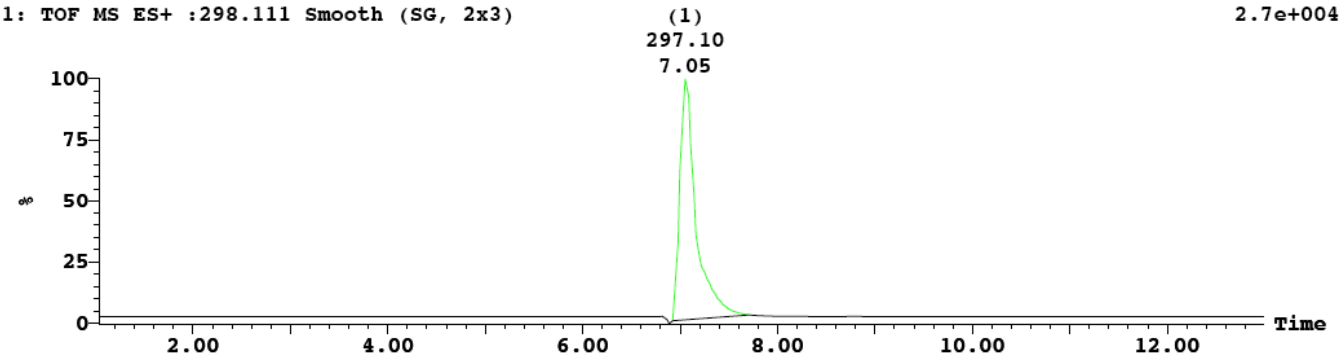




Compound 6

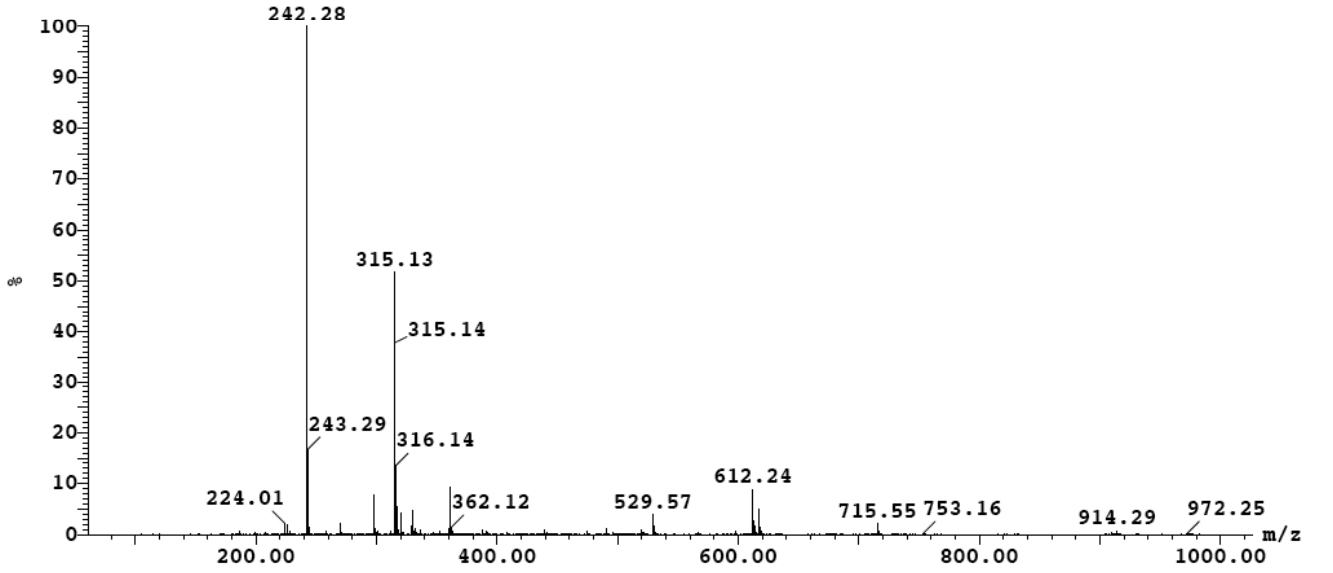
Sample Report (continued):

Sample 25 Vial 3:24 ID KY-1-151-1 File AR041307L24 Date 13-Apr-2007 Time 22:03:19 Description Crude



Peak ID	Time
1	7.05

Combine (233:242-176:179)

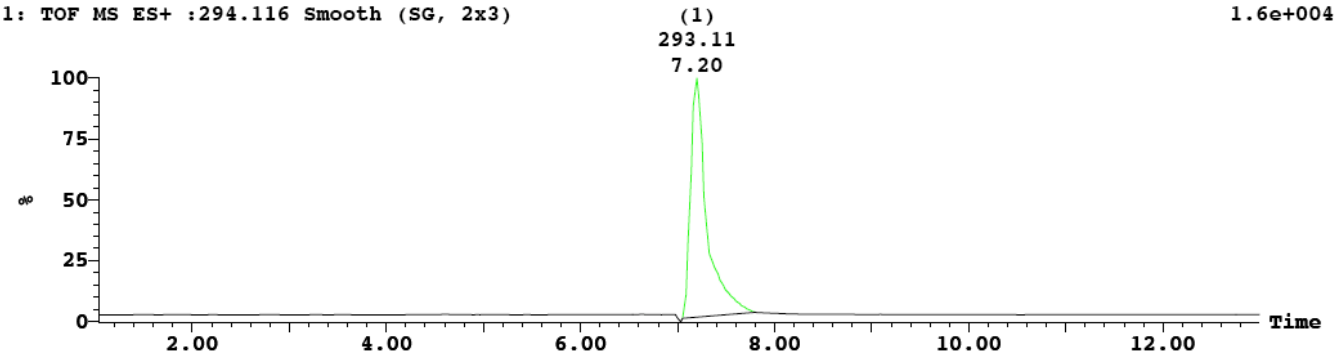


Mass
298.1132
298.1132

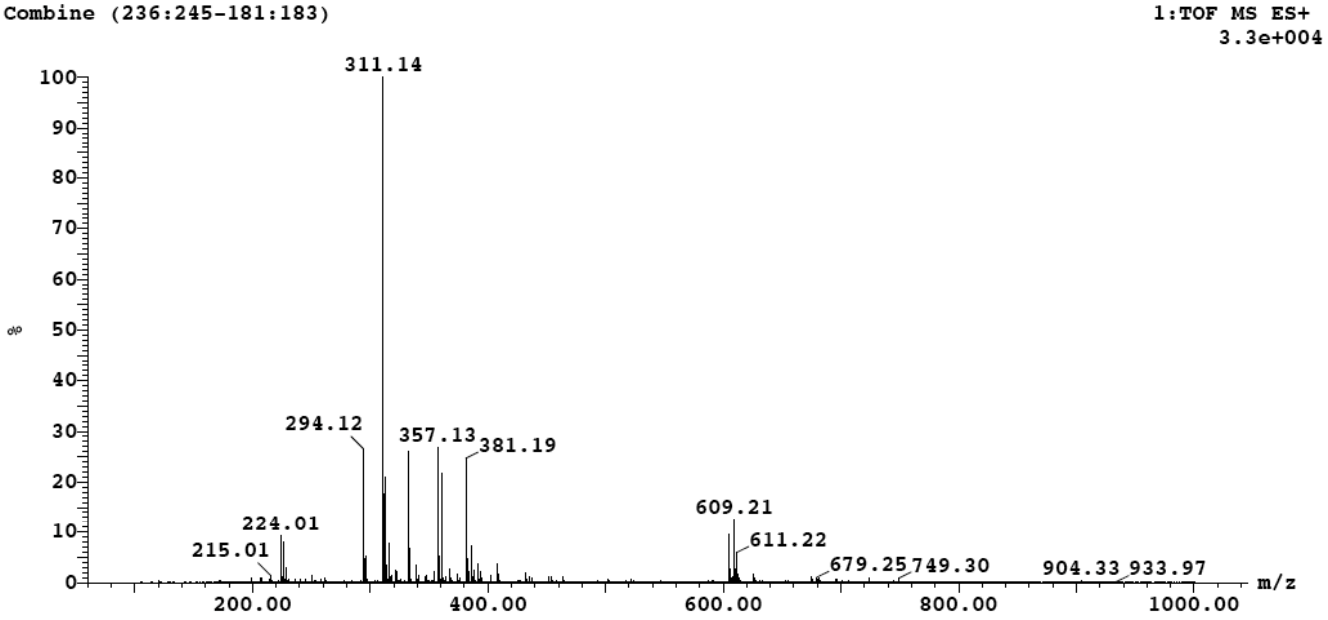
Compound 12

Sample Report (continued):

Sample 5 Vial 3:4 ID KV-1-25-4 File AR041307L04 Date 13-Apr-2007 Time 16:36:14 Description Crude



Peak ID	Time
1	7.20

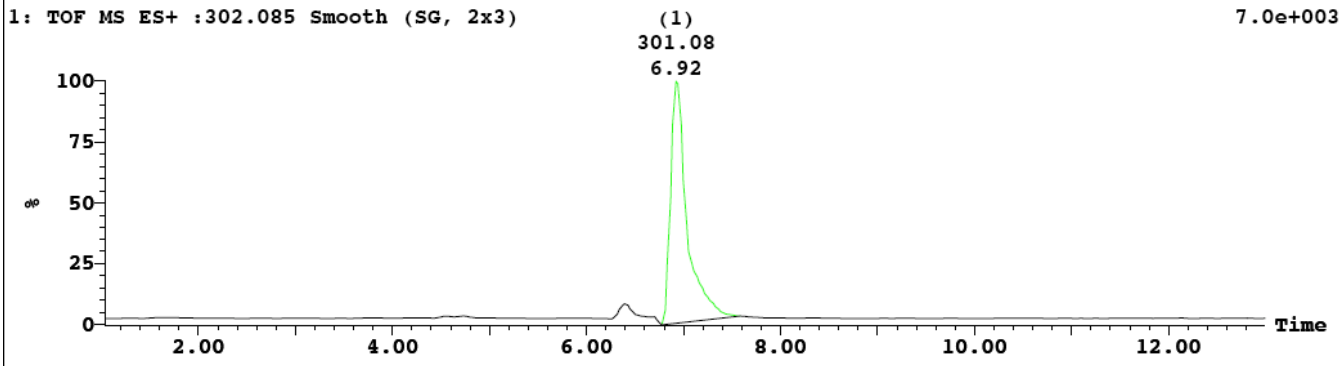


Mass
294.1181
294.1181
294.1181

Compound 14

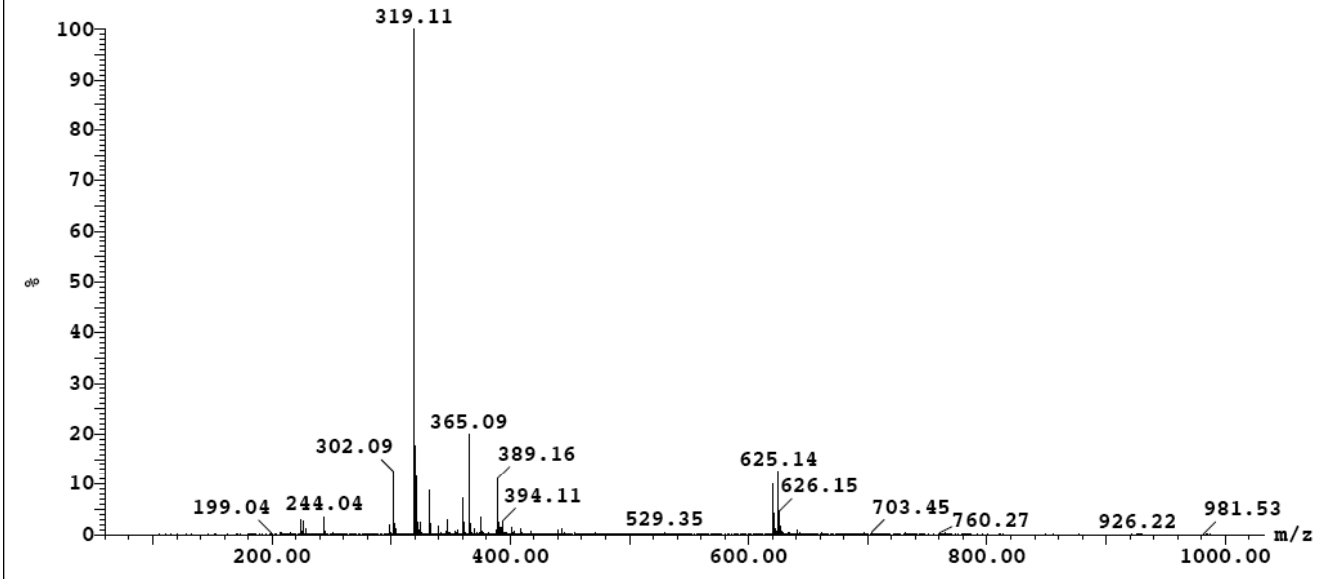
Sample Report (continued):

Sample 6 Vial 3:5 ID KV-1-25-6 File AR041307L05 Date 13-Apr-2007 Time 16:52:33 Description Crude



Peak ID	Time
1	6.92

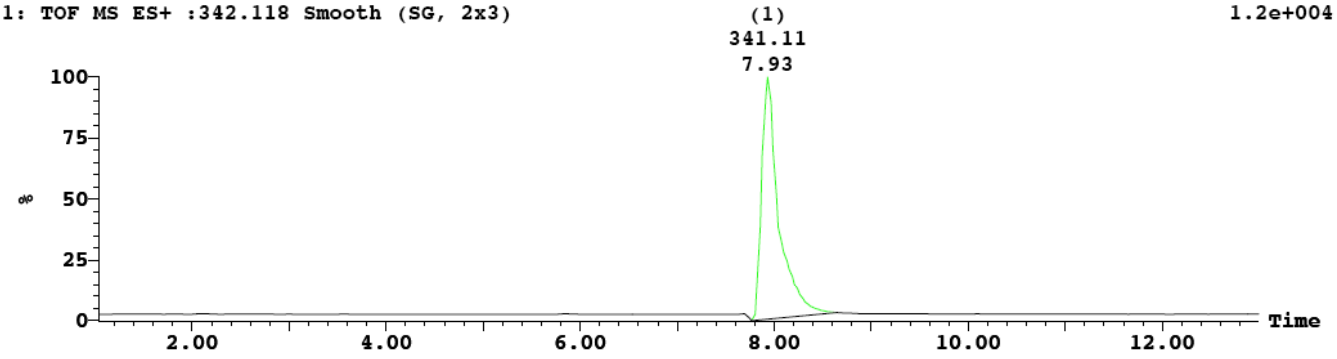
Combine (220:229-171:173)



Mass
302.0865
302.0865
302.0865
302.0865
302.0865

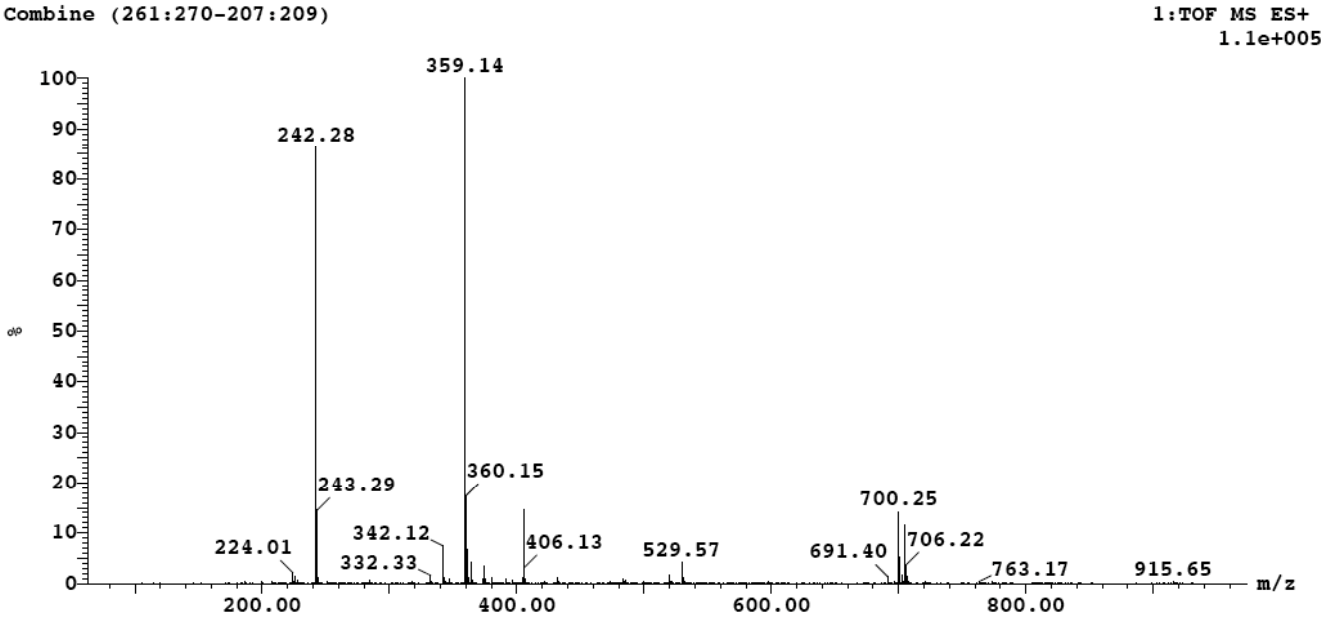
Compound 24

Sample 23 Vial 3:22 ID KY-1-148-4 File AR041307L22 Date 13-Apr-2007 Time 21:30:41 Description Crude



Peak ID	Time
1	7.93

Combine (261:270-207:209)

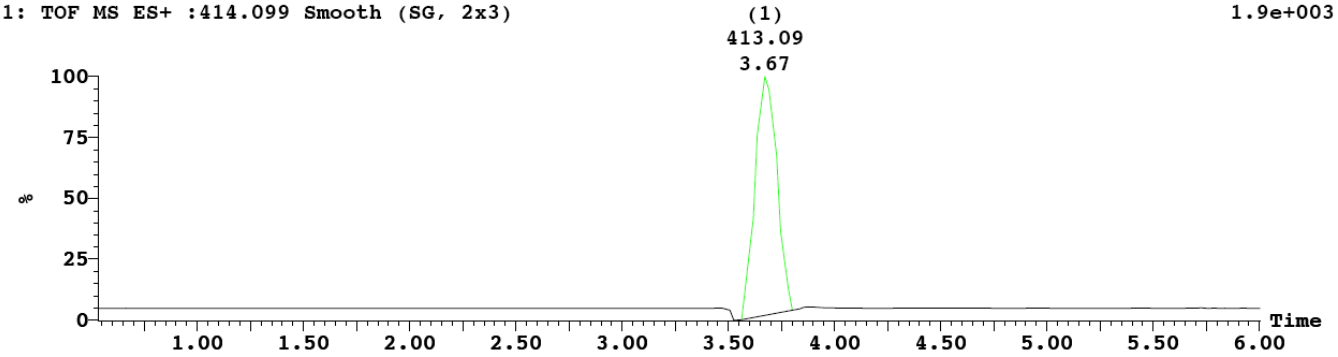


Mass
342.1182
342.1182

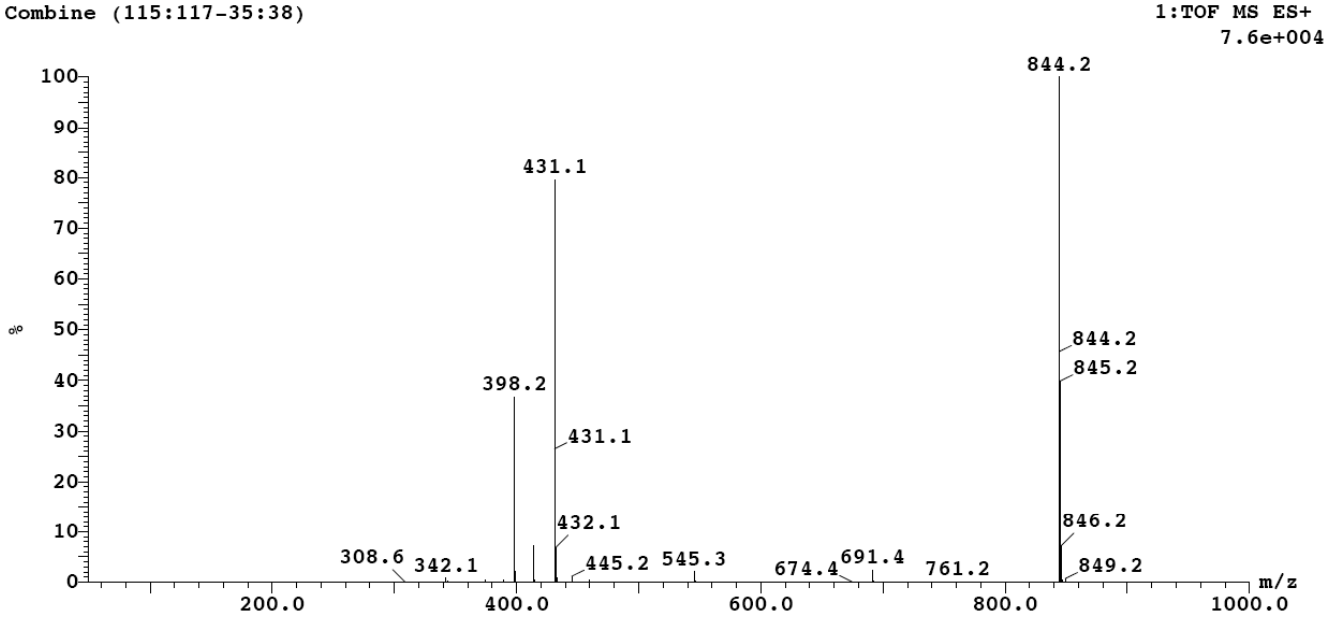
Compound 61

Sample Report (continued):

Sample 60 Vial 4:4 ID PSL4-1-367-14 File AR080107L04 Date 02-Aug-2007 Time 06:42:48 Description MDF002836



Peak ID	Time
1	3.67

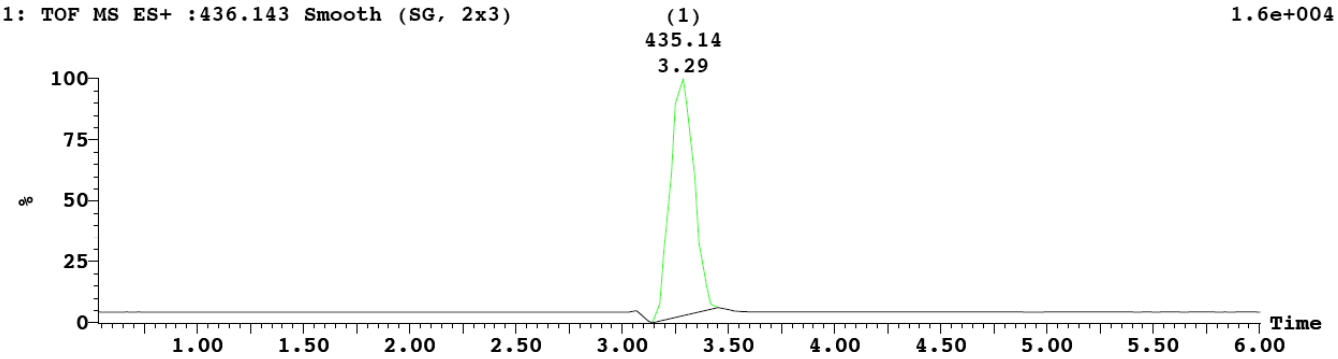


Mass
414.1001
414.1001
414.1001
414.1001
414.1001
414.1001
414.1001
414.1001
414.1001

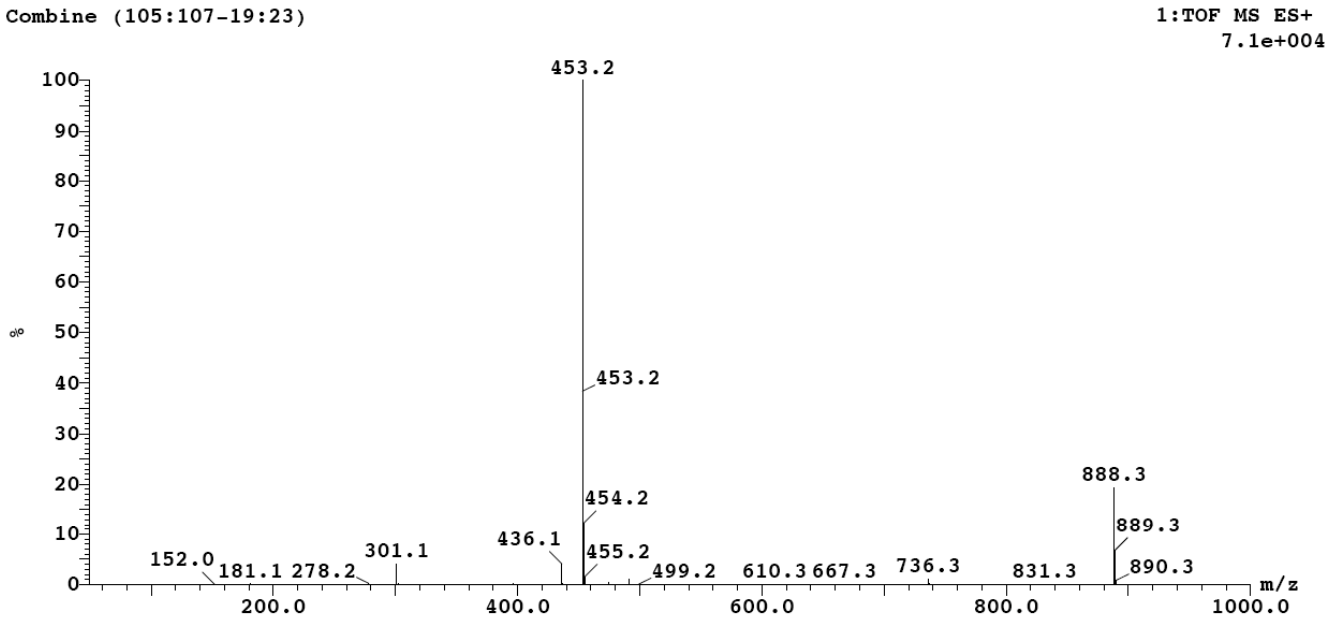
Compound 62

Sample Report:

Sample 57 Vial 4:1 ID PSL4-1-367-2 File AR080107L01 Date 02-Aug-2007 Time 06:14:48 Description MDF002830



Peak ID	Time
1	3.29

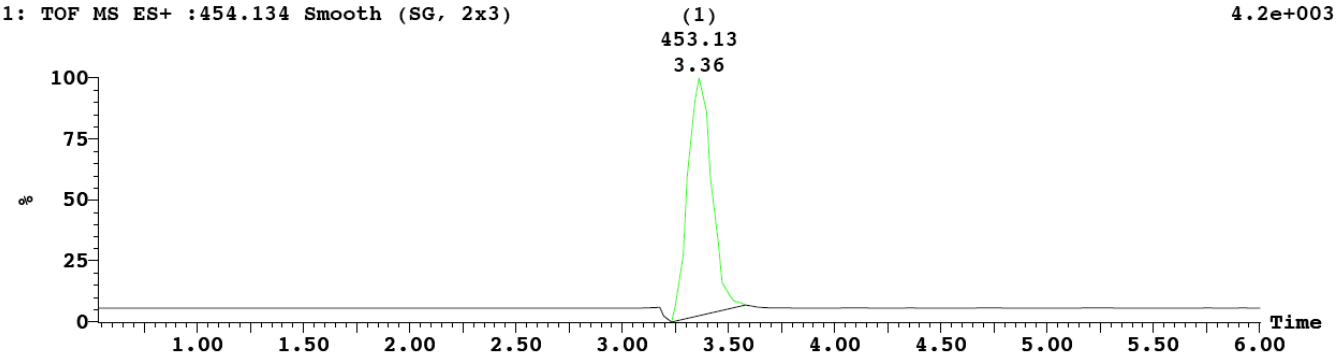


Mass
436.1427
436.1427
436.1427
436.1427
436.1427
436.1427
436.1427
436.1427
436.1427

Compound 68

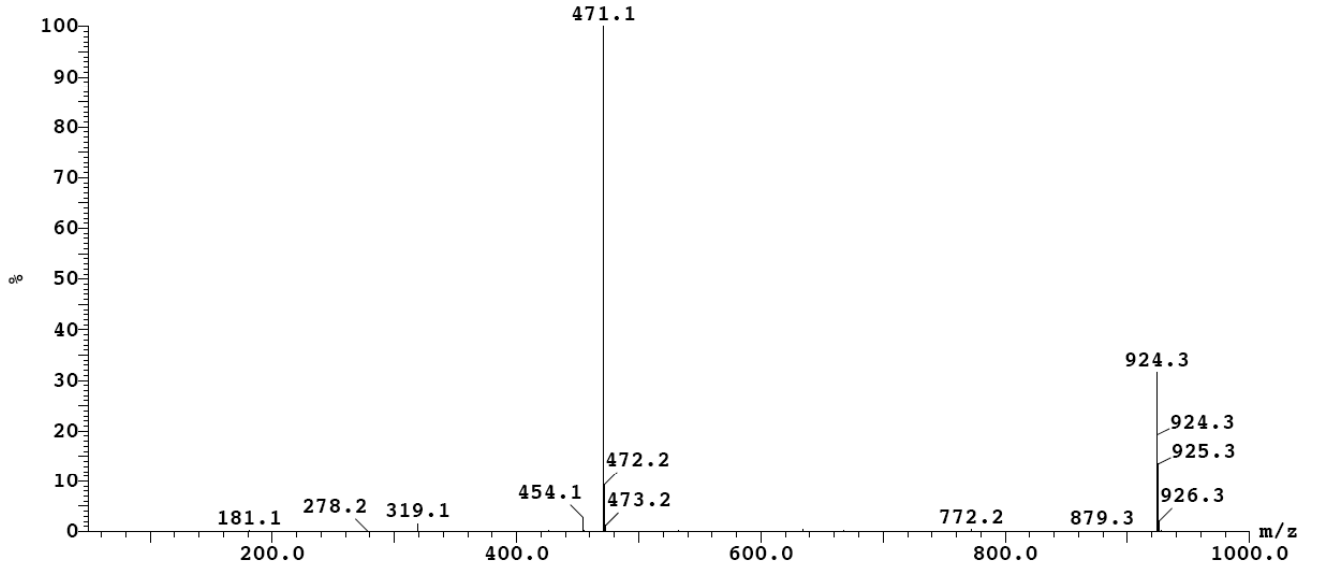
Sample Report (continued):

Sample 61 Vial 4:5 ID PSL4-1-369-2 File AR080107L05 Date 02-Aug-2007 Time 06:52:23 Description MDF002839



Peak ID	Time
1	3.36

Combine (106:108-23:26)

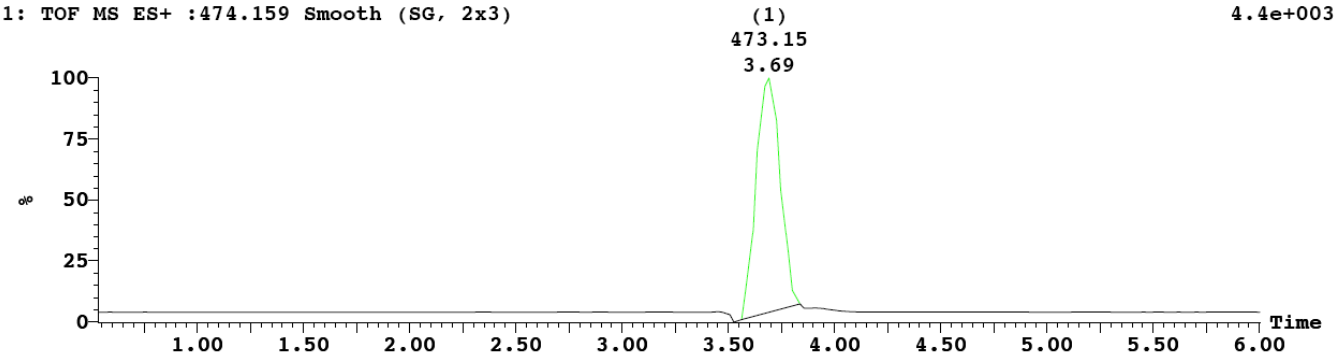


Mass
454.1353
454.1353
454.1353
454.1353
454.1353
454.1353
454.1353
454.1353
454.1353

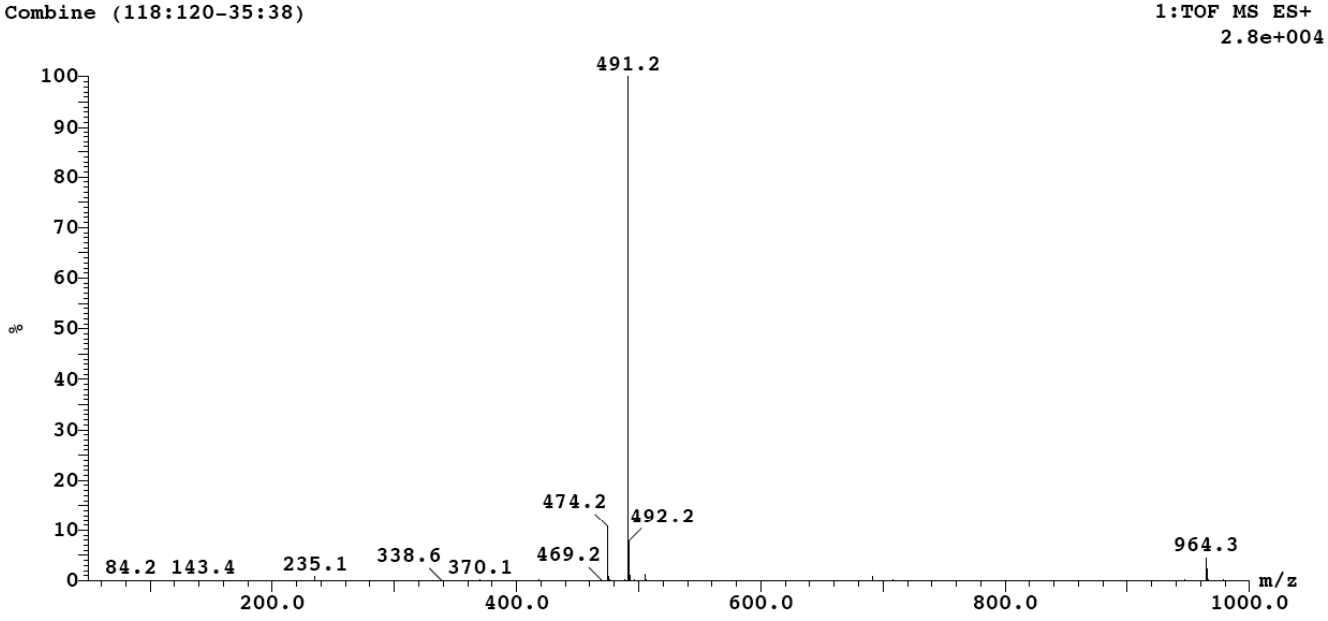
Compound 85

Sample Report (continued):

Sample 65 Vial 4:9 ID PSL4-1-373-2 File AR080107L09 Date 02-Aug-2007 Time 07:31:56 Description MDF002848



Peak ID	Time
1	3.69

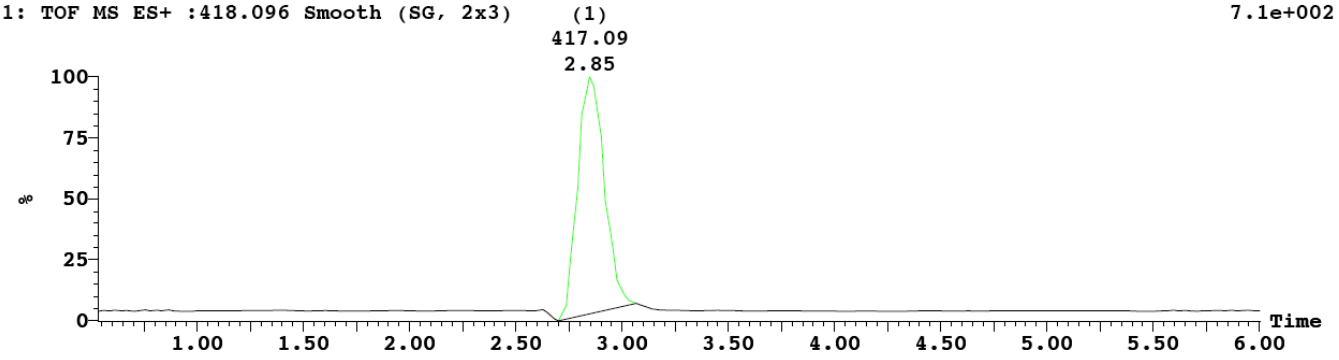


Mass
474.1598
474.1598
474.1598
474.1598
474.1598
474.1598
474.1598
474.1598
474.1598

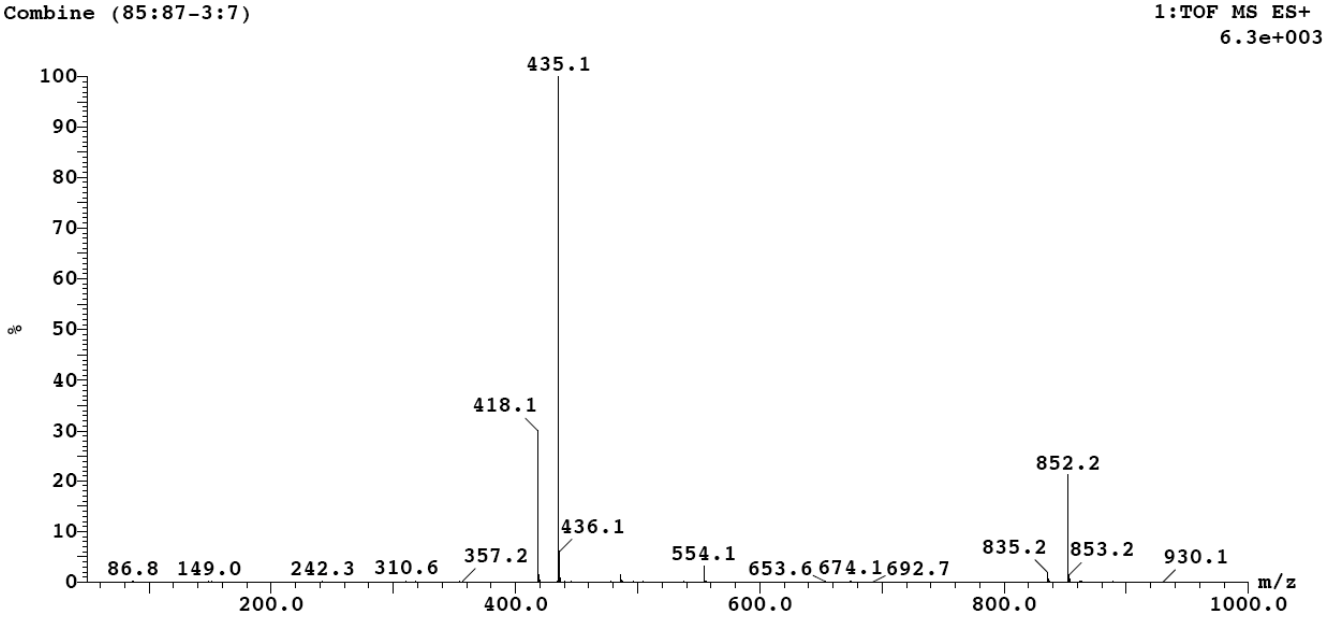
Compound 86

Sample Report (continued):

Sample 66 Vial 4:10 ID PSL4-1-373-3 File AR080107L10 Date 02-Aug-2007 Time 09:25:03 Description MDF002882



Peak ID	Time
1	2.85

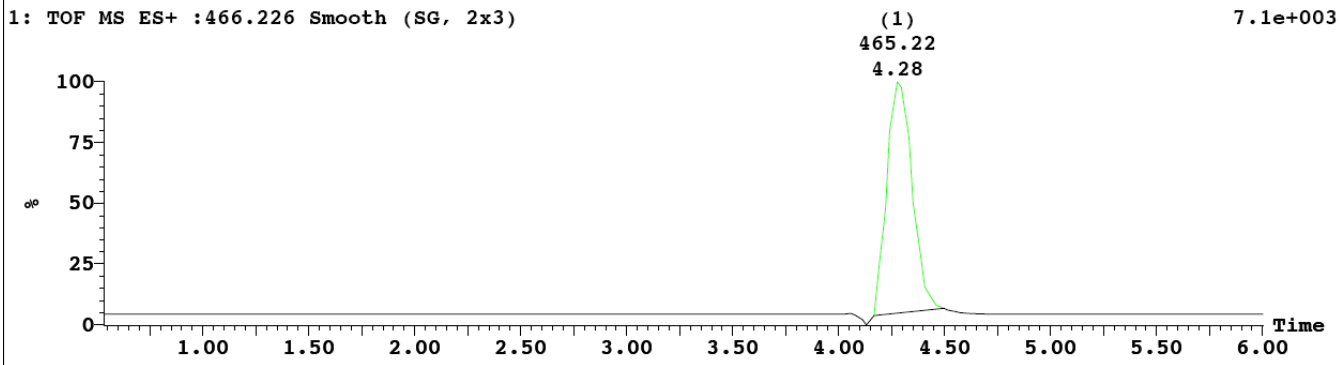


Mass
418.0975
418.0975
418.0975
418.0975
418.0975
418.0975
418.0975

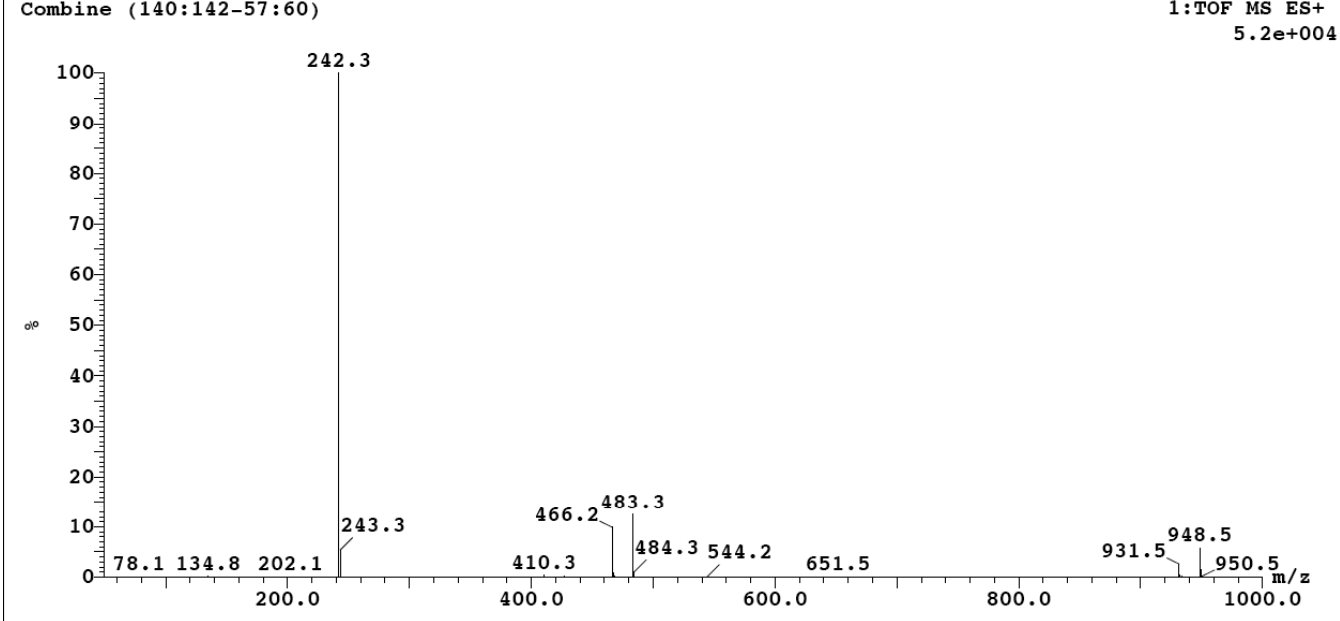
Compound 89

Sample Report (continued):

Sample 73 Vial 4:17 ID PSL4-1-375-2 File AR080107L17 Date 02-Aug-2007 Time 08:29:10 Description MDF002869



Peak ID	Time
1	4.28

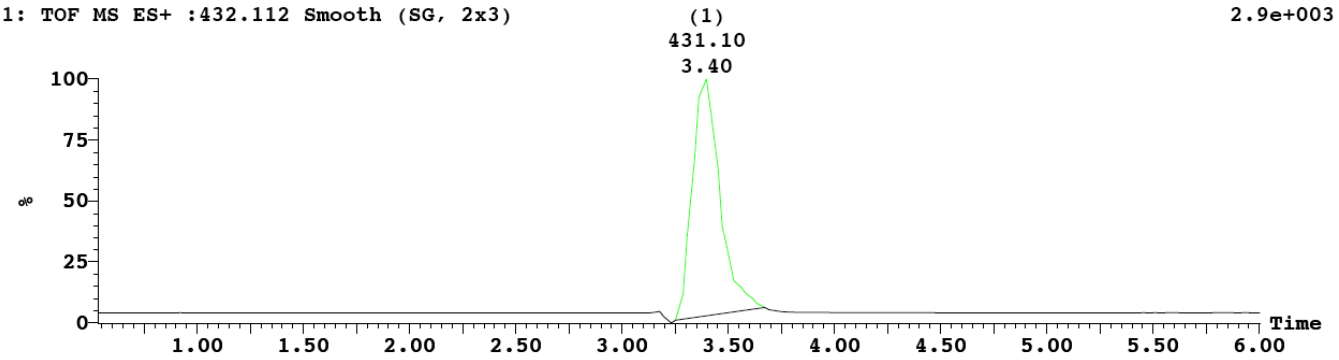


Mass
466.2279
466.2279
466.2279
466.2279
466.2279
466.2279
466.2279
466.2279
466.2279

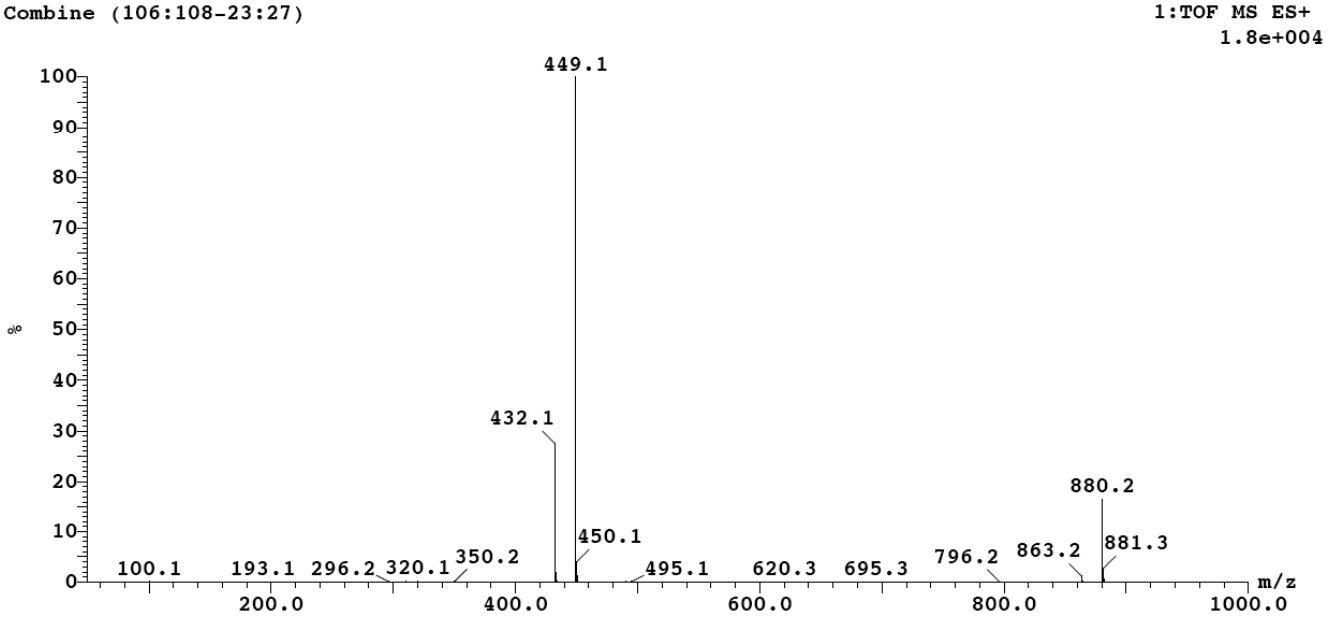
Compound 92

Sample Report (continued):

Sample 68 Vial 4:12 ID PSL4-1-374-1 File AR080107L12 Date 02-Aug-2007 Time 07:50:24 Description MDF002856



Peak ID	Time
1	3.40

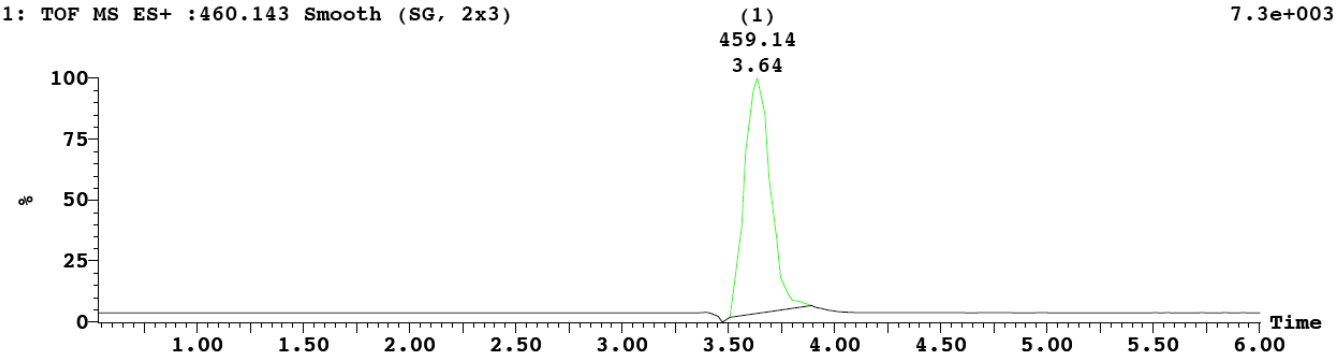


Mass
432.1118
432.1118
432.1118
432.1118
432.1118
432.1118
432.1118
432.1118
432.1118

Compound 93

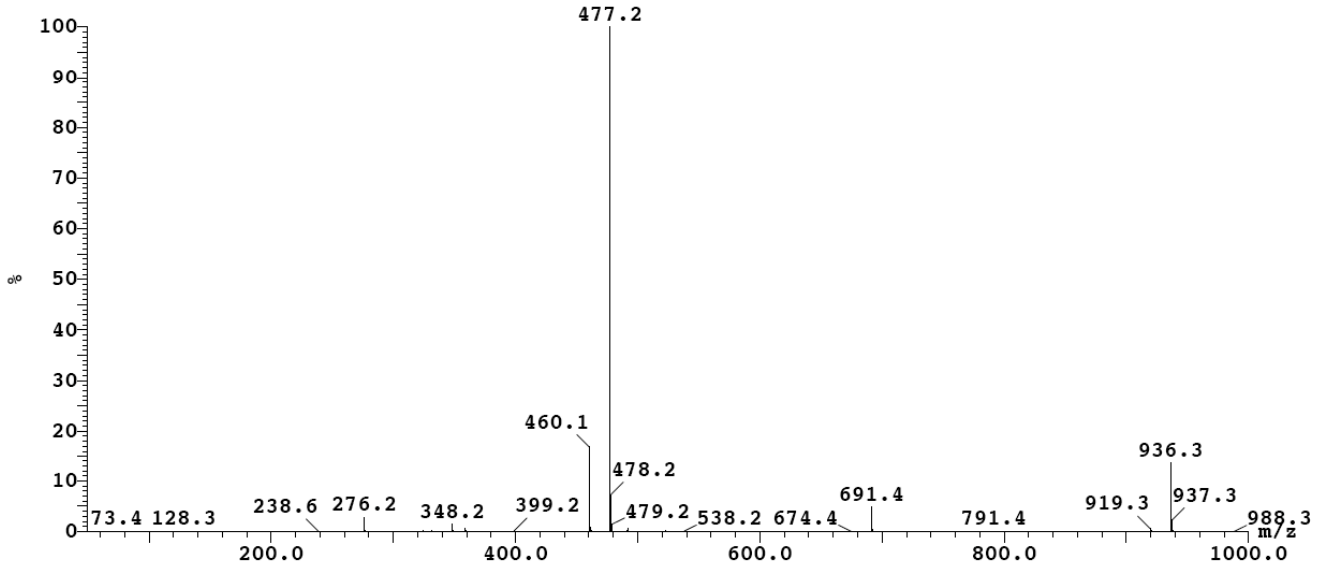
Sample Report (continued):

Sample 69 Vial 4:13 ID PSL4-1-374-2 File AR080107L13 Date 02-Aug-2007 Time 07:59:48 Description MDF002860



Peak ID	Time
1	3.64

Combine (117:119-33:36)



Mass
460.1442
460.1442
460.1442
460.1442
460.1442
460.1442
460.1442
460.1442
460.1442

Calculated Lipinski and ADME property table of all library members

Compound	ClogP	Mol.Wt [g/mol]	No. of Hydrogen Bond Acceptors	No. of Hydrogen Bong Donors	No. of Rotatable Bonds	Lipinski Violations	Diversity	Blood Brain Barrier Permeation	Aqueous Solubility [log(mol/L)]	CACO2 [10^{-6}cm/s]	Solubility [log(mol/L)]	Permeability [10^{-6}cm/s]	Protien Binding	Volume Distribution [-logL/kg]	HERG Blockers	Solubility in DMSO	Metabolic Stability
1	41.00	2.32	4	0	4	1	0.67	0.74	-3.69	0.97	0.28	0.90	72.31	-0.28	0.64	1.19	0.27
2	41.00	2.79	6	0	5	1	3.42	0.61	-4.46	1.08	-0.11	1.00	90.14	-0.58	0.47	0.93	-0.29
3	42.00	3.04	5	0	6	2	3.42	0.01	-4.39	0.76	-0.15	0.81	86.17	-0.56	0.28	1.09	-0.10
4	41.00	3.37	5	0	5	1	3.42	0.50	-4.38	0.98	-0.06	0.96	89.68	-0.54	0.70	1.25	-0.10
5	41.00	3.39	6	0	6	2	3.42	0.42	-4.15	0.76	-0.07	0.89	90.76	-0.70	0.79	0.83	-0.12
6	42.00	3.57	5	0	7	2	3.42	0.24	-4.73	0.86	-0.30	0.86	87.91	-0.60	0.18	0.72	-0.30
7	41.00	2.40	4	0	4	1	3.42	0.49	-3.57	0.48	0.40	0.47	71.16	-0.03	0.79	1.80	0.35
8	41.00	2.96	4	0	4	1	3.42	0.42	-3.54	0.42	0.34	0.48	66.08	-0.07	0.74	1.89	0.41
9	41.00	2.38	5	0	4	1	3.42	0.31	-3.63	0.69	0.22	0.73	80.56	-0.24	0.87	1.87	0.40
10	41.00	2.40	6	0	5	1	3.42	0.05	-4.04	0.51	0.09	0.52	83.37	-0.18	0.85	1.79	0.42
11	42.00	2.58	5	0	6	2	3.42	-0.32	-3.99	0.40	0.05	0.46	80.61	-0.40	0.31	1.71	0.26
12	41.00	2.56	3	0	3	1	3.42	0.51	-4.02	0.96	0.22	0.86	74.46	-0.41	0.61	1.23	-0.03
13	41.00	3.12	3	0	3	1	3.42	0.66	-4.15	0.95	0.14	0.87	79.50	-0.55	0.65	0.84	-0.22
14	41.00	2.54	4	0	3	1	3.42	0.66	-3.93	1.07	0.05	1.02	85.80	-0.39	0.66	1.24	0.16
15	41.00	2.49	5	0	4	1	3.42	0.39	-4.53	0.89	0.02	0.79	82.38	-0.37	0.18	1.30	-0.30
16	41.00	2.46	4	0	4	1	0.67	0.51	-3.80	0.69	0.38	0.74	72.78	-0.31	0.82	1.24	0.19
17	41.00	2.86	4	0	4	1	3.42	0.47	-3.88	0.67	0.33	0.74	75.30	-0.31	0.85	1.33	0.11
18	41.00	2.98	5	0	4	1	3.42	0.23	-4.36	0.70	0.10	0.80	86.53	-0.45	0.71	1.44	0.03
19	42.00	3.19	5	0	6	2	3.42	-0.31	-4.60	0.49	-0.08	0.69	91.10	-0.56	0.53	1.23	0.01
20	42.00	3.27	4	0	5	1	3.42	0.11	-4.38	0.58	0.07	0.78	90.55	-0.44	0.58	1.31	-0.08
21	41.00	5.33	4	0	10	2	3.42	-0.14	-5.28	0.56	-0.13	0.76	93.24	-0.41	0.44	1.34	-0.56
22	41.00	2.99	4	0	5	1	3.42	0.44	-4.02	0.72	0.29	0.74	74.19	-0.30	0.78	1.18	0.03
23	41.00	3.39	4	0	5	1	3.42	0.41	-3.96	0.66	0.24	0.78	76.24	-0.37	0.93	1.33	-0.03
24	41.00	3.53	4	0	5	1	3.42	0.33	-4.50	0.70	0.04	0.81	77.97	-0.45	0.86	1.31	-0.18
25	41.00	4.09	4	0	5	1	3.42	0.35	-4.54	0.60	0.06	0.71	79.23	-0.32	0.50	1.28	-0.17
26	41.00	3.51	5	0	5	1	3.42	0.23	-4.58	0.71	0.00	0.85	88.36	-0.52	0.68	1.38	-0.07
27	41.00	3.54	6	0	6	2	3.42	-0.07	-4.83	0.51	-0.11	0.60	89.90	-0.38	0.61	1.34	0.04
28	42.00	3.72	5	0	7	2	3.42	-0.38	-4.70	0.50	-0.19	0.70	89.18	-0.61	0.48	1.17	-0.13
29	42.00	3.80	4	0	6	2	3.42	0.04	-4.48	0.59	-0.04	0.78	87.91	-0.49	0.51	1.23	-0.23
30	41.00	5.85	4	0	11	2	3.42	-0.16	-5.50	0.57	-0.23	0.77	94.51	-0.46	0.36	1.27	-0.69
31	41.00	2.54	4	0	4	1	3.42	0.26	-3.71	0.09	0.46	0.20	73.70	0.00	0.97	1.90	0.43
32	41.00	3.10	4	0	4	1	3.42	0.20	-3.70	0.07	0.40	0.26	67.76	0.00	0.97	2.04	0.48
33	41.00	2.52	5	0	4	1	3.42	-0.02	-3.92	0.33	0.29	0.53	84.13	-0.29	0.97	1.94	0.40
34	42.00	2.72	5	0	6	2	3.42	-0.63	-4.22	0.07	0.12	0.30	84.80	-0.39	0.50	1.83	0.39
35	42.00	2.80	4	0	5	1	3.42	-0.30	-3.90	0.16	0.28	0.33	84.79	-0.30	0.56	1.90	0.38
36	41.00	4.86	4	0	10	2	3.42	-0.57	-4.87	0.15	0.03	0.36	86.23	-0.23	0.37	2.04	-0.14
37	41.00	3.20	4	0	5	1	3.42	0.37	-4.44	0.29	0.34	0.50	81.41	-0.40	0.75	1.06	-0.01
38	41.00	3.60	4	0	5	1	3.42	0.38	-4.72	0.34	0.21	0.52	83.61	-0.37	0.60	1.12	-0.08
39	41.00	3.74	4	0	5	1	3.42	-0.12	-4.48	0.26	0.19	0.38	81.52	-0.08	0.30	1.97	0.05
40	41.00	4.30	4	0	5	1	3.42	-0.20	-5.06	0.34	0.13	0.48	89.94	-0.41	0.28	1.64	-0.23
41	42.00	3.93	5	0	7	2	3.42	-0.43	-5.01	0.17	-0.18	0.60	98.34	-0.68	0.55	1.26	0.02
42	42.00	4.01	4	0	6	2	3.42	-0.06	-4.65	0.24	0.00	0.68	96.56	-0.54	0.66	1.47	-0.01

43	41.00	6.07	4	0	11	2	3.42	-0.34	-5.69	0.20	-0.18	0.62	102.75	-0.50	0.49	1.59	-0.56
44	41.00	2.99	4	0	5	1	3.42	0.44	-4.02	0.72	0.29	0.74	74.19	-0.30	0.78	1.18	0.03
45	41.00	4.27	4	0	6	2	3.42	0.07	-4.88	0.41	0.09	0.54	85.32	-0.40	0.49	1.29	-0.23
46	41.00	4.83	4	0	6	2	3.42	-0.16	-5.30	0.37	0.04	0.49	89.49	-0.40	0.23	1.53	-0.37
47	41.00	4.28	6	0	7	2	3.42	0.14	-5.06	0.27	-0.18	0.58	97.90	-0.44	0.52	1.09	0.01
48	42.00	4.46	5	0	8	2	3.42	-0.47	-5.13	0.20	-0.29	0.61	96.55	-0.72	0.49	1.18	-0.13
49	42.00	4.54	4	0	7	2	3.42	-0.11	-4.76	0.26	-0.11	0.69	94.38	-0.59	0.60	1.39	-0.16
50	41.00	6.59	4	0	12	2	3.42	-0.37	-5.86	0.21	-0.28	0.61	102.56	-0.55	0.41	1.46	-0.72
51	41.00	3.14	4	0	5	1	3.42	0.03	-4.28	-0.17	0.44	0.00	72.08	-0.12	0.82	1.65	0.15
52	41.00	3.28	4	0	5	1	3.42	-0.03	-4.12	-0.10	0.30	0.10	74.41	-0.15	0.74	1.91	0.31
53	41.00	3.84	4	0	5	1	3.42	-0.11	-4.54	-0.08	0.31	-0.01	75.38	0.01	0.44	1.99	0.32
54	42.00	3.46	5	0	7	2	3.42	-0.77	-4.64	-0.21	0.02	0.19	92.32	-0.51	0.56	1.79	0.43
55	42.00	3.54	4	0	6	2	3.42	-0.48	-4.18	-0.15	0.21	0.25	91.82	-0.42	0.70	2.05	0.48
56	41.00	5.60	4	0	11	2	3.42	-0.89	-5.18	-0.19	0.00	0.20	96.58	-0.40	0.51	2.23	-0.11
57	41.00	3.01	6	1	5	1	3.42	0.69	-4.26	0.74	-0.07	0.86	82.85	-0.38	0.51	0.96	-0.23
58	41.00	3.82	3	1	6	2	3.42	-0.49	-6.10	0.27	-0.53	0.48	115.67	-0.56	0.16	1.33	-0.48
59	42.00	2.84	7	0	9	2	3.42	-0.90	-4.83	-0.33	-0.08	0.13	93.74	-0.60	0.78	1.68	0.20
60	51.00	7.83	4	0	15	2	3.42	-0.34	-6.30	0.76	-0.70	1.02	101.91	-0.68	-0.30	1.28	-0.97
61	42.00	4.54	4	0	7	2	3.42	0.05	-5.40	0.29	-0.16	0.45	100.78	-0.40	0.22	1.22	-0.55
62	42.00	2.95	7	0	9	2	3.42	-0.11	-4.94	0.61	-0.36	0.76	92.27	-0.86	0.56	0.65	-0.54
63	41.00	3.15	6	1	5	1	3.42	0.48	-4.49	0.38	0.02	0.66	82.92	-0.38	0.62	0.89	-0.27
64	41.00	2.85	5	1	4	1	3.42	0.20	-4.63	0.61	-0.06	0.67	84.73	-0.37	0.66	1.21	-0.06
65	41.00	0.64	4	1	6	2	3.42	-0.31	-5.09	0.07	-0.24	0.26	91.44	-0.13	0.33	1.87	0.08
66	42.00	4.15	4	0	6	2	3.42	-0.44	-5.21	-0.11	0.08	0.24	96.55	-0.43	0.53	1.51	-0.33
67	42.00	3.69	4	0	6	2	3.42	-0.70	-4.91	-0.45	0.26	-0.14	89.68	-0.28	0.35	2.03	0.16
68	42.00	3.10	7	0	9	2	3.42	-0.41	-5.06	0.38	-0.30	0.65	94.48	-0.86	0.88	0.71	-0.38
69	41.00	3.89	6	1	6	2	3.42	0.21	-4.95	0.27	-0.08	0.58	86.97	-0.43	0.64	1.31	-0.11
70	41.00	3.43	6	1	6	2	3.42	-0.36	-4.88	-0.01	-0.03	0.31	85.43	-0.47	0.95	1.81	0.25
71	41.00	3.59	5	1	5	1	3.42	0.03	-4.54	0.29	-0.09	0.49	85.15	-0.36	0.63	1.33	0.13
72	41.00	1.38	4	1	7	2	3.42	-0.76	-5.57	-0.17	-0.35	0.19	101.84	-0.24	0.31	2.55	0.11
73	42.00	3.93	5	0	7	2	3.42	-0.40	-5.26	0.12	-0.20	0.59	100.99	-0.59	0.67	1.63	-0.08
74	42.00	3.63	4	0	6	2	3.42	-0.10	-4.80	0.26	-0.09	0.66	96.28	-0.55	0.73	1.26	0.05
75	51.00	8.18	4	0	15	2	3.42	-0.62	-6.81	0.16	-0.57	0.66	118.58	-0.59	0.06	1.79	-0.96
76	51.00	7.72	4	0	15	2	3.42	-1.14	-6.16	-0.21	-0.40	0.33	109.95	-0.43	0.04	2.55	-0.62
77	51.00	7.88	3	0	14	2	3.42	-0.55	-6.44	0.19	-0.51	0.67	114.13	-0.53	0.17	1.69	-0.96
78	41.00	3.29	6	1	5	1	3.42	0.25	-4.70	0.12	0.03	0.54	84.52	-0.37	0.93	0.97	-0.18
79	41.00	3.52	4	1	6	2	3.42	-0.33	-5.60	0.09	-0.32	0.53	104.95	-0.41	0.48	1.46	-0.39
80	41.00	0.79	4	1	6	2	3.42	-0.67	-5.19	-0.34	-0.15	0.14	93.84	-0.22	0.76	2.01	-0.02
81	42.00	2.87	5	0	6	2	3.42	-0.76	-4.21	-0.22	0.17	0.17	83.89	-0.25	0.85	2.30	0.49
82	51.00	7.58	4	0	14	2	3.42	-0.82	-6.36	0.17	-0.42	0.61	111.46	-0.35	0.20	1.85	-0.81
83	51.00	7.28	3	0	13	2	3.42	-0.60	-6.07	0.23	-0.39	0.66	108.16	-0.29	0.32	1.66	-0.85
84	42.00	3.37	7	0	9	2	3.42	-0.49	-5.41	0.41	-0.40	0.54	101.31	-0.53	0.17	1.28	-0.66
85	42.00	4.42	7	0	11	2	3.42	-0.54	-5.80	0.49	-0.61	0.60	102.59	-0.55	-0.01	1.09	-0.89
86	42.00	2.68	7	0	9	2	0.75	-1.46	-4.36	-0.47	-0.05	-0.27	82.12	-0.41	0.49	2.28	0.10
87	42.00	2.75	5	0	7	2	3.42	-0.32	-5.76	0.69	-0.44	0.52	100.21	-0.24	0.11	1.05	-0.57
88	41.00	5.51	6	0	13	2	3.42	-0.47	-5.71	0.34	-0.47	0.68	97.38	-0.48	0.05	1.69	-0.84
89	41.00	6.56	6	0	15	2	3.42	-0.30	-6.51	0.48	-0.72	0.75	100.03	-0.58	-0.10	1.05	-1.19
90	41.00	4.82	6	0	13	2	0.75	-0.96	-5.37	-0.37	-0.24	-0.07	87.38	-0.26	0.40	2.20	-0.20
91	41.00	4.88	4	0	11	2	3.42	-0.44	-5.63	0.50	-0.50	0.71	95.34	-0.27	0.13	1.72	-0.73
92	41.00	3.12	8	0	8	2	3.42	0.05	-5.43	0.82	-0.47	0.79	99.53	-0.57	0.02	0.89	-0.55
93	41.00	4.18	8	0	10	2	3.42	0.01	-6.06	0.93	-0.65	0.91	106.99	-0.64	-0.09	0.91	-0.83
94	41.00	2.43	8	0	8	2	0.75	-1.03	-4.11	-0.09	0.01	0.05	78.30	-0.19	0.54	2.56	0.12
95	41.00	2.50	6	0	6	2	3.42	-0.49	-5.06	0.65	-0.24	0.67	84.80	-0.42	0.74	1.15	-0.57

Sketched electronic versions of the library compounds were imported into the Tripos Molecular Spreadsheet[1] where in standard Lipinski Rule of 5 parameters (molecular weight, ClogP, number of H-acceptors, and number of H-donors)[2] plus the number of rotatable bonds were computed. Lipinski violations were specified according to molecular weight > 500, ClogP > 5.0, number of acceptors > 10, number of donors > 5, and number of rotatable bonds > 5. The structures were then exported into SDF format and coverted into three-dimensional protonated structures via Concord.[3] Absorption, distribution, metabolism and excretion (ADME) profiles of these compounds was then generated via Volsurf.[4] Descriptors were generated using three probes (water, hydrophobic and carbonyl oxygen) with a grid space distribution of 1.0 Å. Predictions were then projected onto internal ADME models at the 5-component level. Finally diversity analysis was carried out using DiverseSolutions[5] using standard H-aware 2D BCUT descriptors. The library was then projected onto a chemical space defined by the following descriptors: gastchrg_burden_000.100_K_H, haccept_burden_001.000_K_H, hdonor_burden_000.600_K_H, tabpolar_burden_000.400_K_H, tabpolar_burden_000.500_K_L and populated (for comparison) by a recent version of the PubChem library (ca. 11/2006; ~7,000,000 unique chemical structures). Diversity scores (*div(A)*) for our library were then generated for each of our compounds (*A*) according to the expression:

$$div(A) = \frac{pop[Cell(A)]}{\sum_{i \in Occ} pop(i) / N_{occ}}$$

where N_{occ} is the number of cells occupied by PubChem compounds in an evenly distributed 20×20×20×20×20 grid decomposition of the chemistry space, and *pop(i)* is the population of cell *i*.

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[1] SYBYL 8.0, The Tripos Associates, St. Louis MO, 2008.

[2] Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev.* **1997, *23,*** 3-25.

[3] Concord 8.0, The Tripos Associates, St. Louis MO, 2008.

[4] Cruciani, G., Meniconi, M., Carosati, E., Zamora, I., Mannhold, R. VOLSURF: A Tool for Drug ADME-Properties Prediction. In: *Methods and Principles in Medicinal Chemistry*. Eds. van de Waterbeemd, H., Lennernäs, H., Artursson, P. (Wiley-VCH Verlag GmbH & Co., Weinheim, 2003).

[5] Pearlman, R.S.; Smith, K.M. Metric Validation and the Receptor-Relevant Subspace Concept. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 28-35.