Supporting Information

Application of a Double aza-Michael Reaction in a *"Click, Click, Cy-Click"* Strategy: From Bench to Flow

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Procedure for Sulfonamides 2.

To a RB flask containing racemic TBS-protected serine methyl ester (1.1 equiv) was added CH_2Cl_2 (0.25 M) and Et_3N (3 equiv). This mixture was allowed to stir for several minutes until soluble, cooled to 0 ºC, and 2-2-chloroethanesulfonyl chloride (1 equiv) was added drop-wise over several minutes. The solution was slowly warmed to rt, and stirred overnight. The reaction mixture was quenched with 10% HCl and extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, and dried (Na_2SO_4). The solution was filtered, and concentrated under reduced pressure to afford crude vinyl sulfonamide **2** as a clear, viscous oil. The crude product was submitted to the following reaction without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.57 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.25 (d, *J* = 16.5 Hz, 1H), 5.91 (d, *J* = 9.9 Hz, 1H), 5.21 (d, *J* = 8.7 Hz, 1H), 4.09 – 4.04 (m, 2H), 3.88 (dd, *J* = 10.9, 4.0 Hz, 1H), 3.77 (s, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.5, 136.5, 126.3, 64.8, 57.6, 52.6, 25.6, -5.5, -5.7.

FTIR (thin film) cm^{-1}: 3290, 2955, 2930, 2858, 1749, 1342, 1256, 1138, 1113, 837.

HRMS: calculated for $C_{12}H_{26}NO_5SSi$ $(M+H)^+$ 324.1301; found 324.1288 (TOF MS ES+).

General Procedure for Tertiary Sulfonamides 3.

To the crude sulfonamide **2** (1 equiv) was added CH_3CN (0.1M) and K_2CO_3 (1.2 equiv) followed by the dropwise addition of benzyl bromide (1.2 equiv). This mixture was allowed to stir at 60 ºC for 12−14 hrs. The reaction was cooled to rt, filtered through a pad of celite/silica and concentrated under reduced pressure to afford crude tertiary sulfonamide **3** as a dark orange oil. The crude product was purified by flash column chromatography on silica gel (eluent: hexane-EtOAc, 5:1).

Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(*N*-(4-methylbenzyl)vinylsulfonamido)propanoate (**3a**):

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 6.53 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.21 (d, *J* = 16.6 Hz, 1H), 5.89 (d, *J* = 9.9 Hz, 1H), 4.54 (dd, *J* = 7.0, 4.6 Hz, 1H), 4.49 (d, *J* = 16.1 Hz, 1H), 4.45 (d, *J* = 16.1 Hz, 1H), 4.01 (dd, *J* = 10.8, 7.0 Hz, 1H), 3.96 (dd, *J* = 10.8, 4.6 Hz, 1H), 3.66 (s, 3H), 2.33 (s, 3H), 0.84 (s, 9H), -0.01 (s, 3H), -0.06 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.0, 137.1, 135.6, 134.0, 128.9, 128.0, 126.4, 62.3, 61.4, 52.1, 49.9, 25.7, 21.1, 18.1, -5.7, -5.8.

FTIR (thin film) cm^{-1}: 2953, 2930, 2856, 1747, 1342, 1258, 1150, 1119, 837, 777.

HRMS: calculated for $C_{20}H_{37}N_2O_5SSi$ $(M+NH_4)^+$ 445.2192; found 445.2184 (TOF MS ES+).

Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(*N*-(4-methoxybenzyl)vinylsulfonamido)propanoate (**3b**):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.7 Hz, 2H), 6.89 – 6.82 (m, 2H), 6.51 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.20 (d, *J* = 16.6 Hz, 1H), 5.88 (d, *J* = 9.9 Hz, 1H), 4.54 (dd, *J* = 7.0, 4.8 Hz, 1H), 4.46 (d, *J* = 15.9 Hz, 1H), 4.42 (d, *J* = 15.9 Hz, 1H), 4.00 (dd, *J* = 10.9, 7.1 Hz, 1H), 3.97 (dd, *J* = 10.9, 4.8 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 0.85 (s, 9H), 0.01 (s, 3H), -0.03 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.0, 159.1, 135.7, 129.5, 129.0, 126.3, 113.6, 62.2, 61.3, 55.3, 52.1, 49.6, 25.7, 18.1, -5.7, -5.8.

FTIR (thin film) cm^{-1}: 2953, 2932, 2856, 1747, 1512, 1342, 1250, 1151, 837, 777.

HRMS: calculated for $C_{20}H_{33}NO_6SSiK$ $(M+K)^+$ 482.1435; found 482.1429 (TOF MS ES+).

Methyl 2-(*N*-benzylvinylsulfonamido)-3-((*tert*-butyldimethylsilyl)oxy)propanoate (**3c**):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.25 (m, 1H), 6.54 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.22 (d, *J* = 16.6 Hz, 1H), 5.91 (d, *J* = 9.9 Hz, 1H), 4.59 (dd, *J* = 6.9, 4.2 Hz, 1H), 4.54 (d, *J* = 16.5 Hz, 1H), 4.51 (d, *J* = 16.4 Hz, 1H), 4.03 (dd, *J* = 10.8, 6.9 Hz, 1H), 3.96 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.67 (s, 3H), 0.83 (s, 9H), -0.03 (s, 3H), -0.09 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.0, 137.3, 135.4, 128.2, 127.8, 127.4, 126.6, 62.4, 61.5, 52.1, 50.1, 25.7, 18.1, -5.8, -5.9.

FTIR (thin film) cm^{-1}: 2953, 2930, 2856, 1745, 1342, 1254, 1150, 1119, 837, 777.

HRMS: calculated for $C_{19}H_{35}N_2O_5SSi$ $(M+NH_4)^+$ 431.2036; found 431.2051 (TOF MS ES+).

Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(*N*-(4-chlorobenzyl)vinylsulfonamido)propanoate (**3d**):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.5 Hz, 2H), 7.31 – 7.27 (m, 2H), 6.51 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.21 (d, *J* = 16.5 Hz, 1H), 5.93 (d, *J* = 9.9 Hz, 1H), 4.61 (dd, *J* = 6.6, 3.7 Hz, 1H), 4.52 (d, *J* = 16.9 Hz, 1H), 4.49 (d, *J* = 16.9 Hz, 1H), 4.05 (dd, *J* = 10.9, 6.7 Hz, 1H), 3.95 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.69 (s, 3H), 0.82 (s, 9H), -0.02 (s, 3H), -0.09 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 169.9, 136.2, 135.1, 133.1, 129.1, 128.3, 126.9, 62.6, 61.6, 52.2, 49.5, 25.7, 18.1, -5.8, -5.9.

FTIR (thin film) cm^{-1}: 2953, 2930, 2856, 1745, 1493, 1342, 1254, 1151, 837, 770.

HRMS: calculated for $C_{19}H_{34}ClN_2O_5SSi$ $(M+NH_4)^+$ 465.1646; found 465.1630 (TOF MS ES+).

Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(*N*-(4-fluorobenzyl)vinylsulfonamido)propanoate (**3e**):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.01 (t, *J* = 8.7 Hz, 2H), 6.51 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.21 (d, *J* = 16.5 Hz, 1H), 5.91 (d, *J* = 9.9 Hz, 1H), 4.60 (dd, *J* = 6.8, 4.0 Hz, 1H), 4.51 (d, *J* = 16.5 Hz, 1H), 4.48 (d, *J* = 16.4 Hz, 1H), 4.03 (dd, *J* = 10.9, 6.8 Hz, 1H), 3.95 (dd, *J* = 10.9, 4.0 Hz, 1H), 3.68 (s, 3H), 0.83 (s, 9H), -0.01 (s, 3H), -0.08 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.0, 162.2 (d, $^1J_{CF}$ = 245.5 Hz), 135.3, 133.2 (d, $^4J_{CF}$ = 3.1 Hz), 129.5 (d, $^3J_{CF}$ = 8.1 Hz), 126.7, 115.0 (d, $^2J_{CF}$ = 21.5 Hz), 62.4, 61.5, 52.2, 49.4, 25.7, 18.1, -5.8, -5.9.

FTIR (thin film) cm^{-1}: 2953, 2930, 2856, 1747, 1510, 1342, 1256, 1151, 837, 775.

HRMS: calculated for $C_{19}H_{31}FNO_5SSi$ $(M+H)^+$ 432.1676; found 432.1667 (TOF MS ES+).

Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(*N*-(4-(trifluoromethyl)benzyl)vinylsulfonamido)propanoate (**3f**):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 6.54 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.23 (d, *J* = 16.5 Hz, 1H), 5.96 (d, *J* = 9.9 Hz, 1H), 4.67 (dd, *J* = 6.1, 3.2 Hz, 1H), 4.62 (s, 2H), 4.09 (dd, *J* = 10.9, 6.1 Hz, 1H), 3.94 (dd, *J* = 10.9, 3.2 Hz, 1H), 3.72 (s, 3H), 0.77 (s, 9H), -0.07 (s, 3H), -0.17 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 169.9, 142.3, 134.7, 129.5 (q, $^2J_{CF}$ = 32.5 Hz), 127.5, 127.3, 126.3 (q, $^1J_{CF}$ = 271.9 Hz), 125.1 (q, $^3J_{CF}$ = 3.7 Hz), 62.9, 61.8, 52.3, 49.8, 25.6, 18.0, -6.0, -6.0.

FTIR (thin film) cm^{-1}: 2955, 2932, 2855, 2858, 1747, 1344, 1327, 1151, 1124, 1067, 837, 773.

HRMS: calculated for $C_{20}H_{30}F_3NO_5SSiNa$ $(M+Na)^+$ 504.1464; found 504.1460 (TOF MS ES+).

Methyl 2-(*N*-(4-methylbenzyl)vinylsulfonamido)acrylate (**4**):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 6.73 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.31 (d, *J* = 16.6 Hz, 1H), 6.27 (s, 1H), 6.02 (d, J = 9.9 Hz, *1*H), 5.68 (s, 1H), 4.50 (s, 2H), 3.79 (s, 3H), 2.33 (s, 3H).

Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(*N*-(prop-2-yn-1-yl)vinylsulfonamido)propanoate (**6**):

To the crude sulfonamide **2** (1 equiv) was added DMF (0.1M), K_2CO_3 (2 equiv) and NaI (2 equiv) followed by the addition of propargyl bromide (1.5 equiv). This was allowed to stir at 60 ºC for 14 hrs. The reaction was cooled to rt and filtered through a pad of celite/silica and concentrated to afford crude tertiary sulfonamide **3** as a dark orange oil. The crude product was purified by flash column chromatography on silica gel (eluent: hexane-EtOAc, 5:1) to provide the product as pale yellow oil (79%).

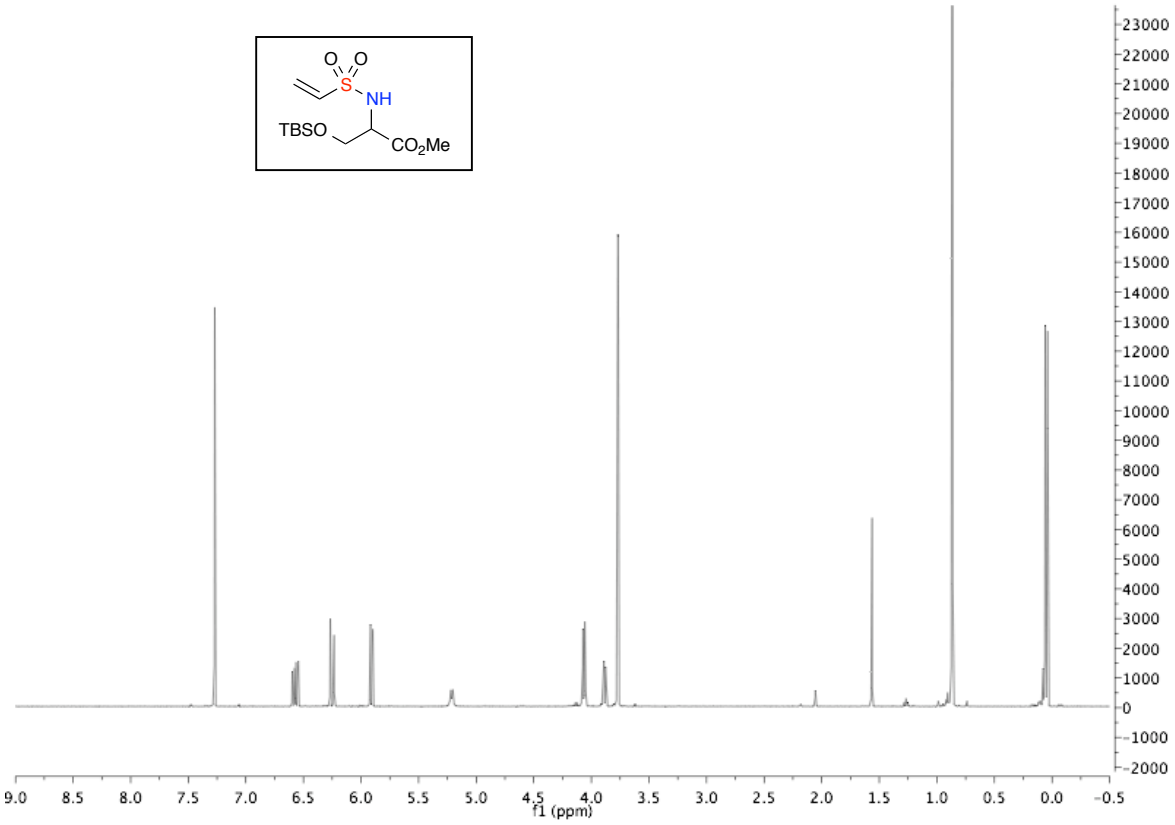
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.28 (d, *J* = 16.5 Hz, 1H), 5.95 (d, *J* = 9.9 Hz, 1H), 4.59 (m, 1H), 4.27 (dd, *J* = 18.5, 2.4 Hz, 1H), 4.22 (dd, *J* = 18.5, 2.4 Hz, 1H), 4.18 (dd, *J* = 9.1, 3.6 Hz, 1H), 4.15 (dd, J = 9.1, 2.4 Hz, 1H), 3.75 (s, 3H), 2.26 (t, *J* = 2.4 Hz, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).

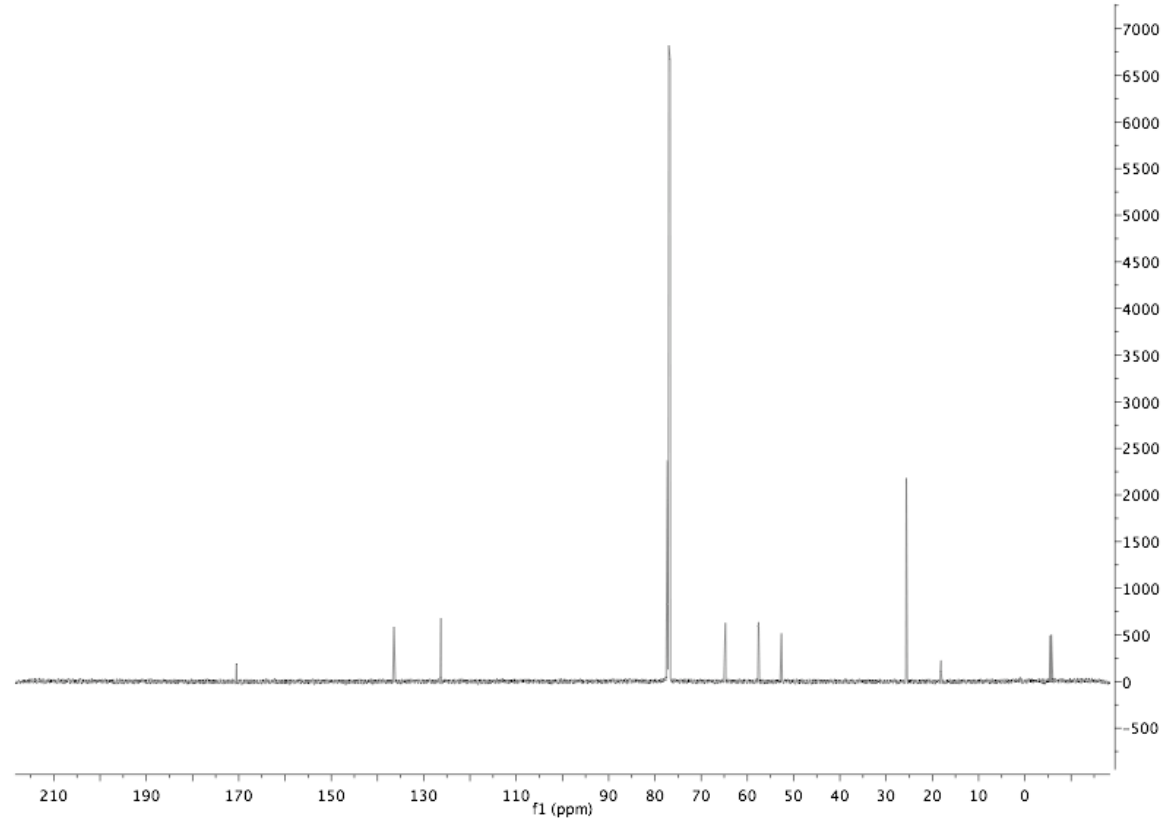
^{13}C NMR (126 MHz, $CDCl_3$): δ 169.7, 135.6, 126.8, 80.0, 71.8, 62.8, 60.9, 52.3, 35.4, 25.7, 18.1, -5.7, -5.9.

FTIR (thin film) cm^{-1}: 3275, 2959, 1745, 1339, 1146, 972, 737, 565.

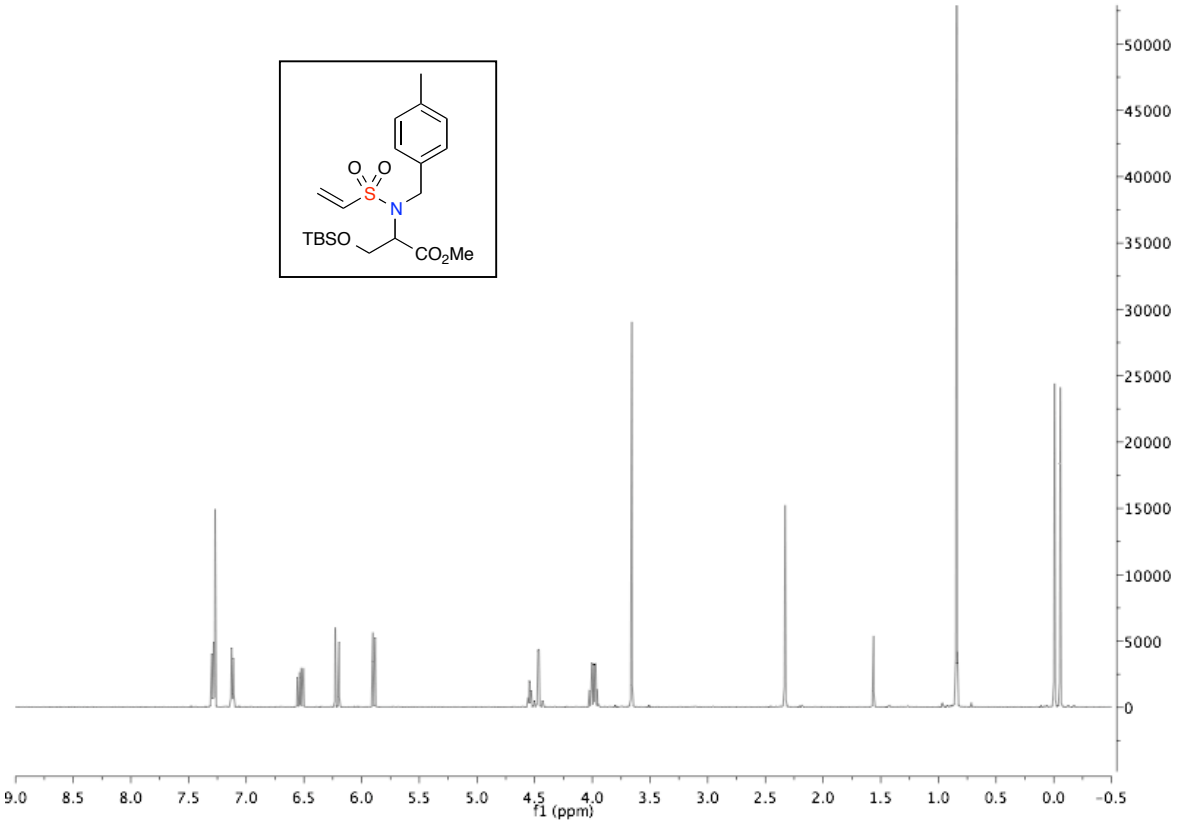
HRMS: calculated for $C_{15}H_{27}NO_5SSiNa$ $(M+Na)^+$ 384.1277; found 384.1256 (TOF MS ES+).

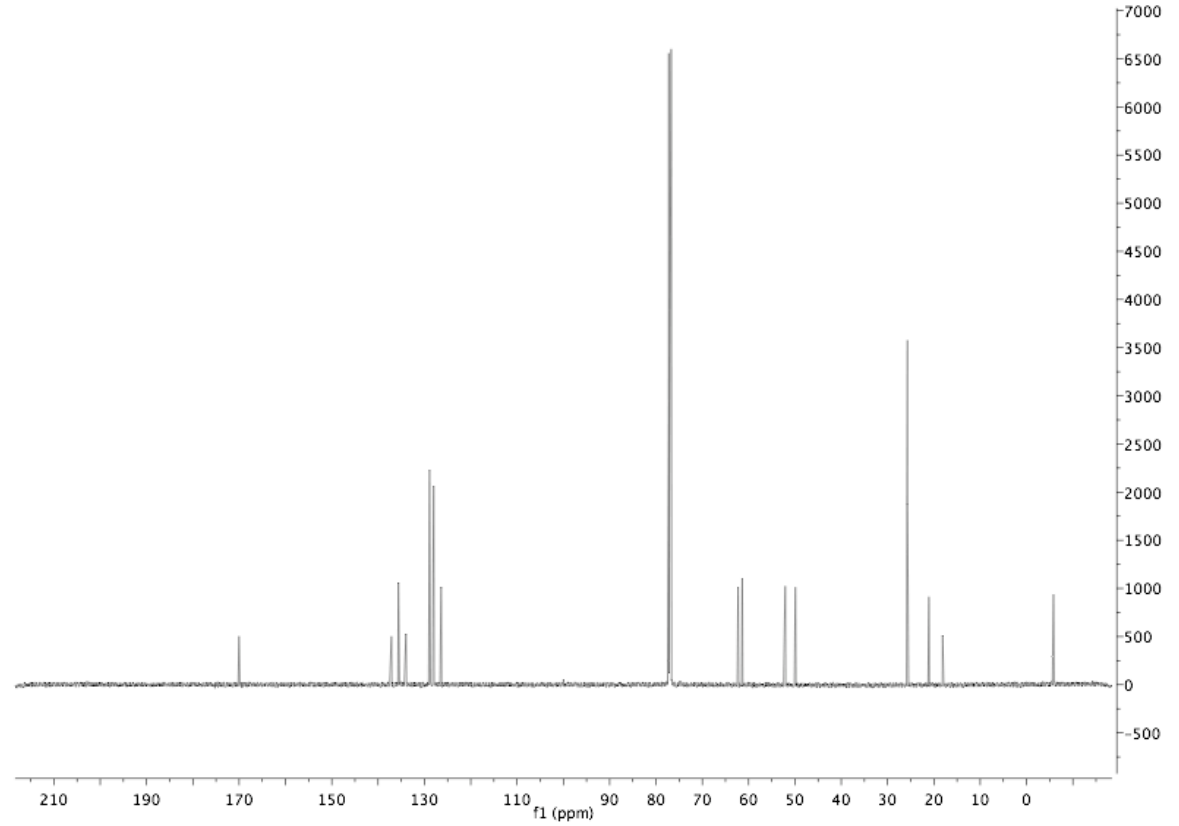
Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(vinylsulfonamido)propanoate (**2**)



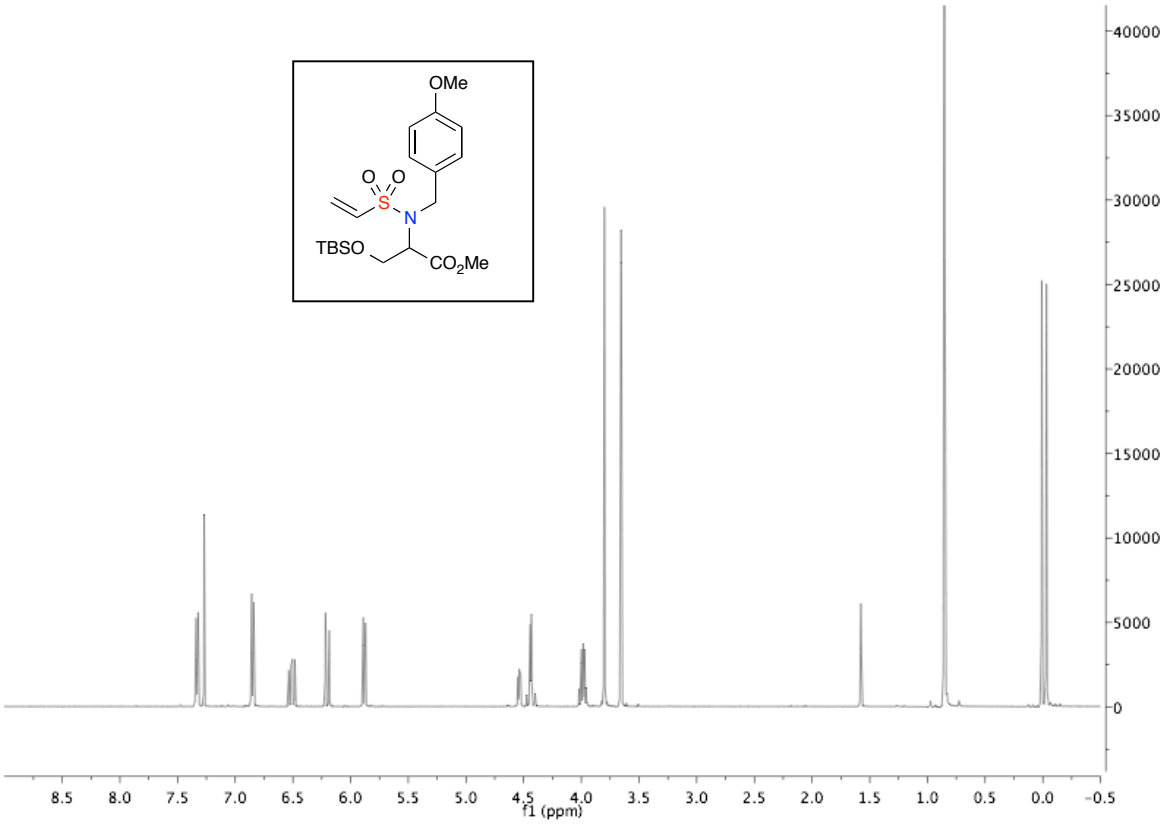


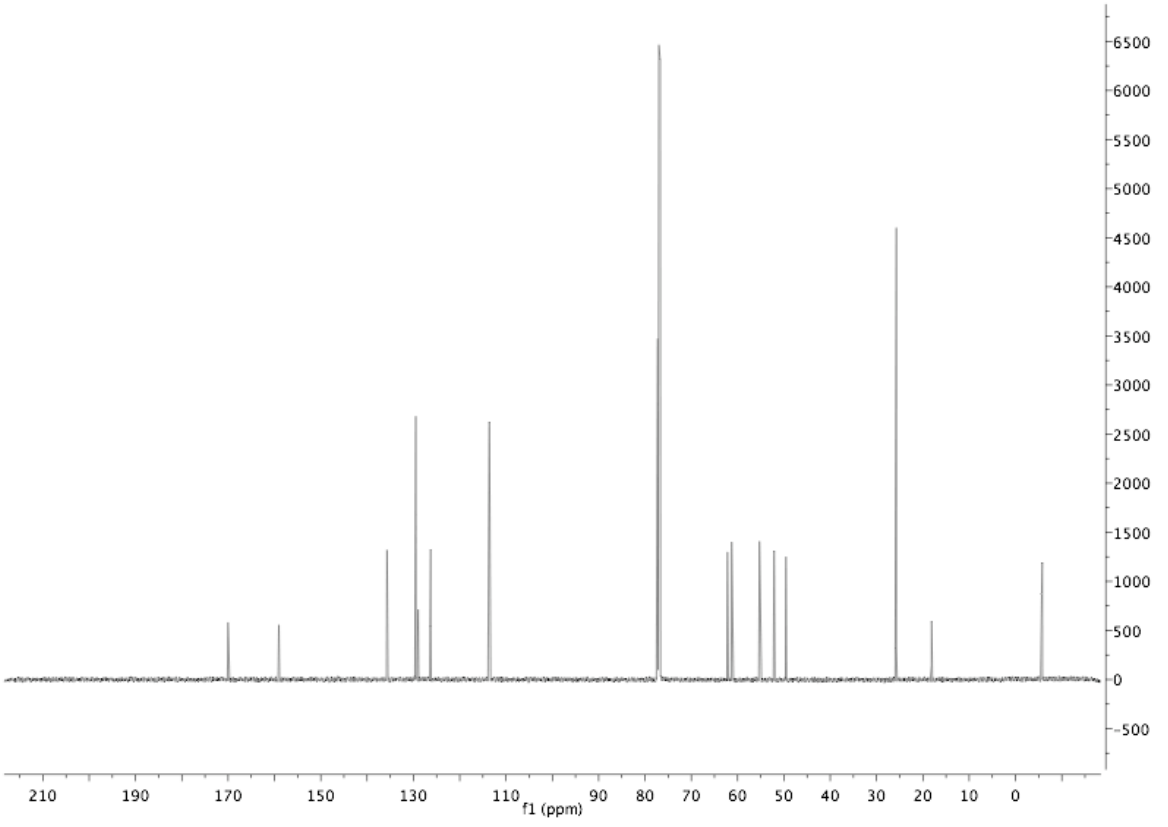
Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(*N*-(4-methylbenzyl)vinylsulfonamido)propanoate (**3a**)



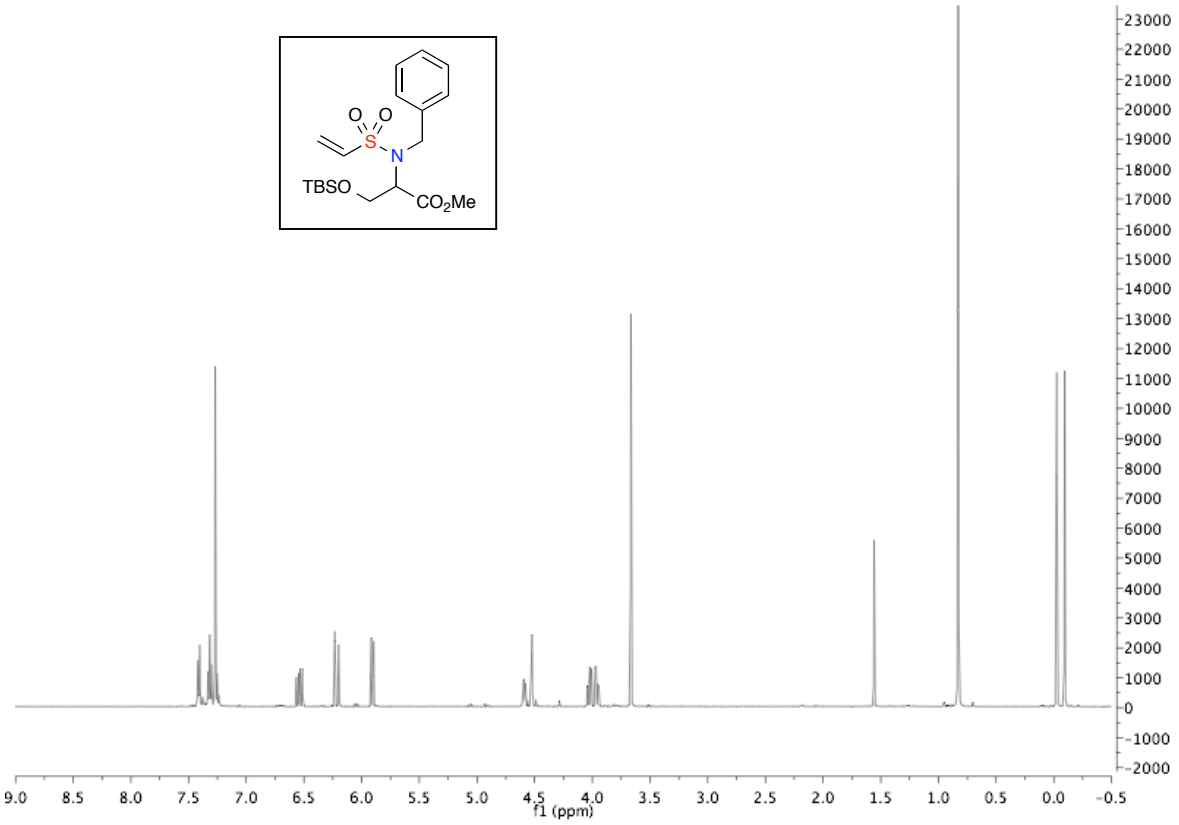


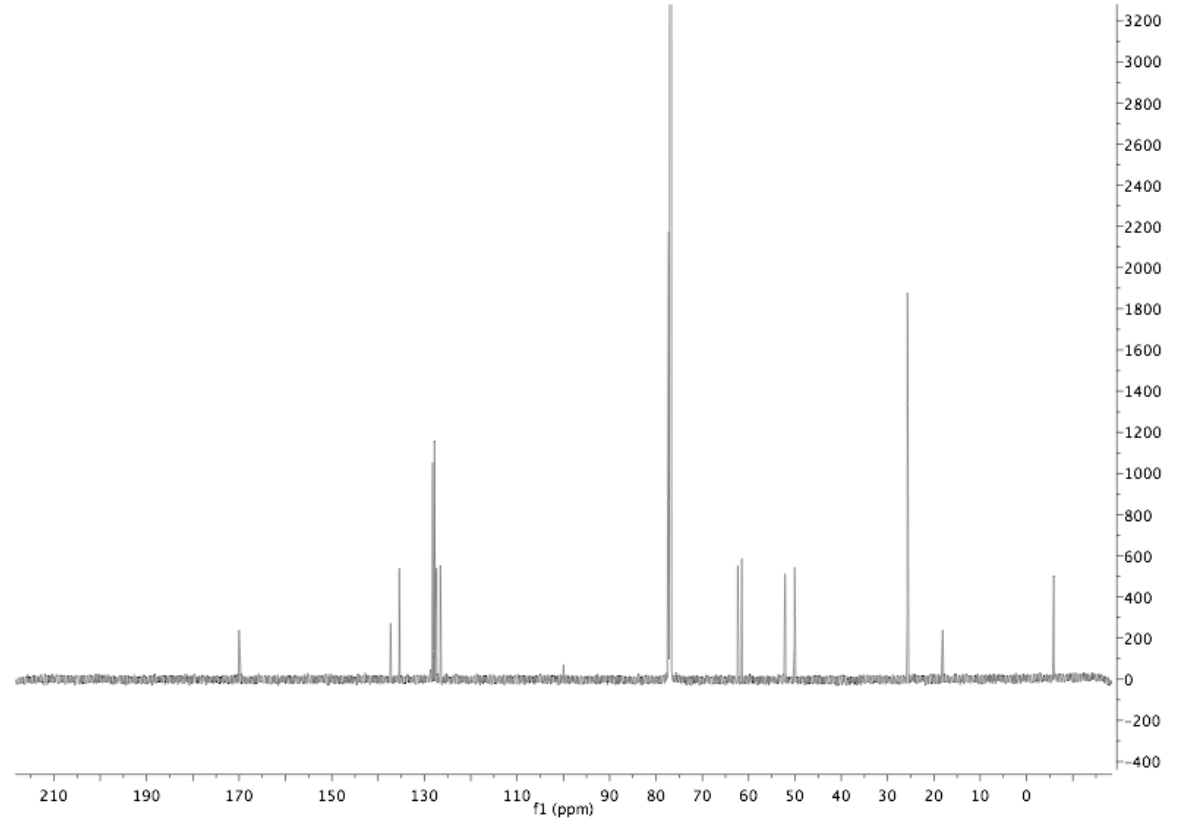
Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(*N*-(4-methoxybenzyl)vinylsulfonamido)propanoate (**3b**)



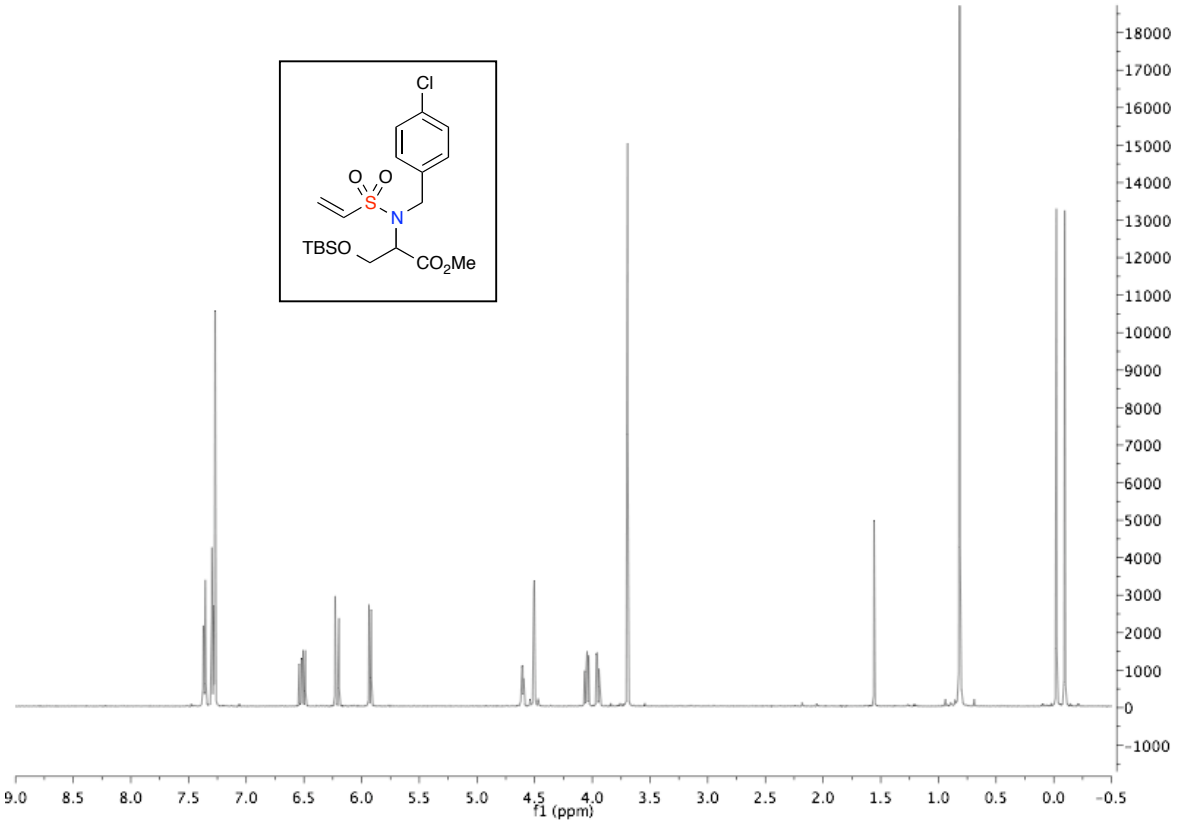


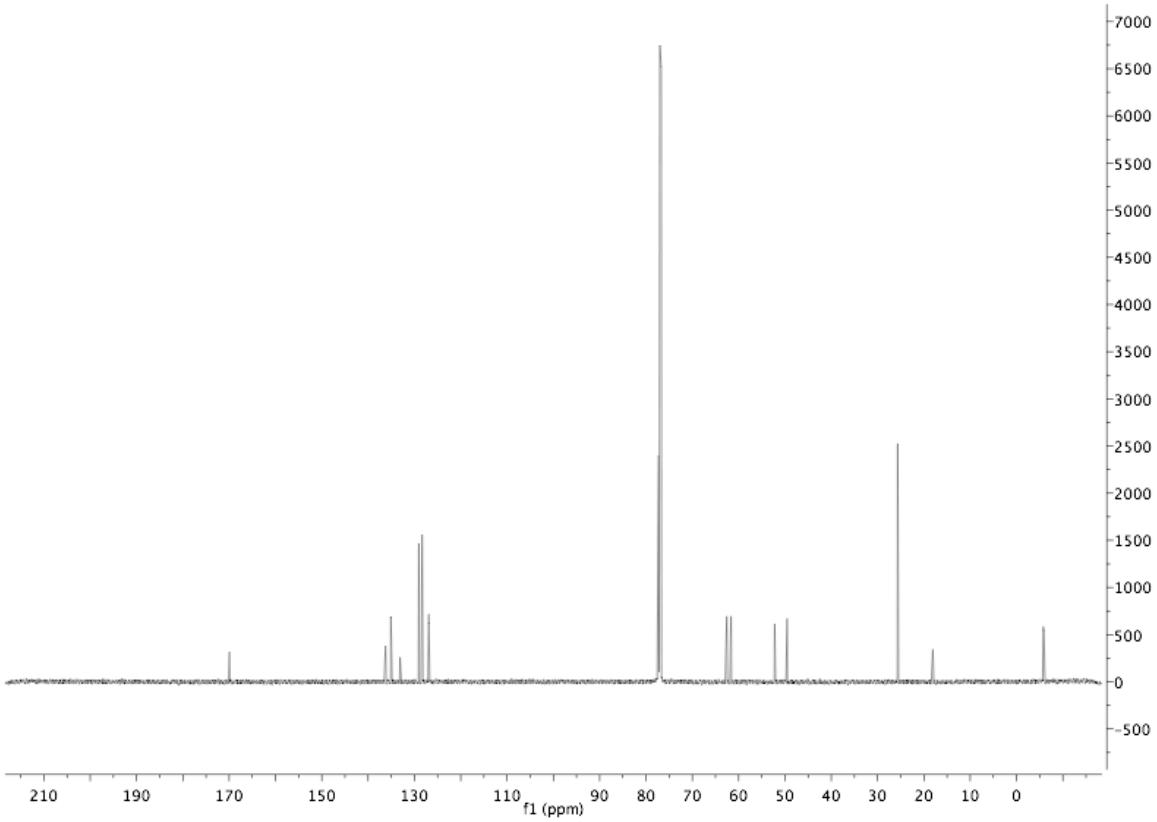
Methyl 2-(*N*-benzylvinylsulfonamido)-3-((*tert*-butyl-dimethylsilyl)oxy)propanoate (**3c**)



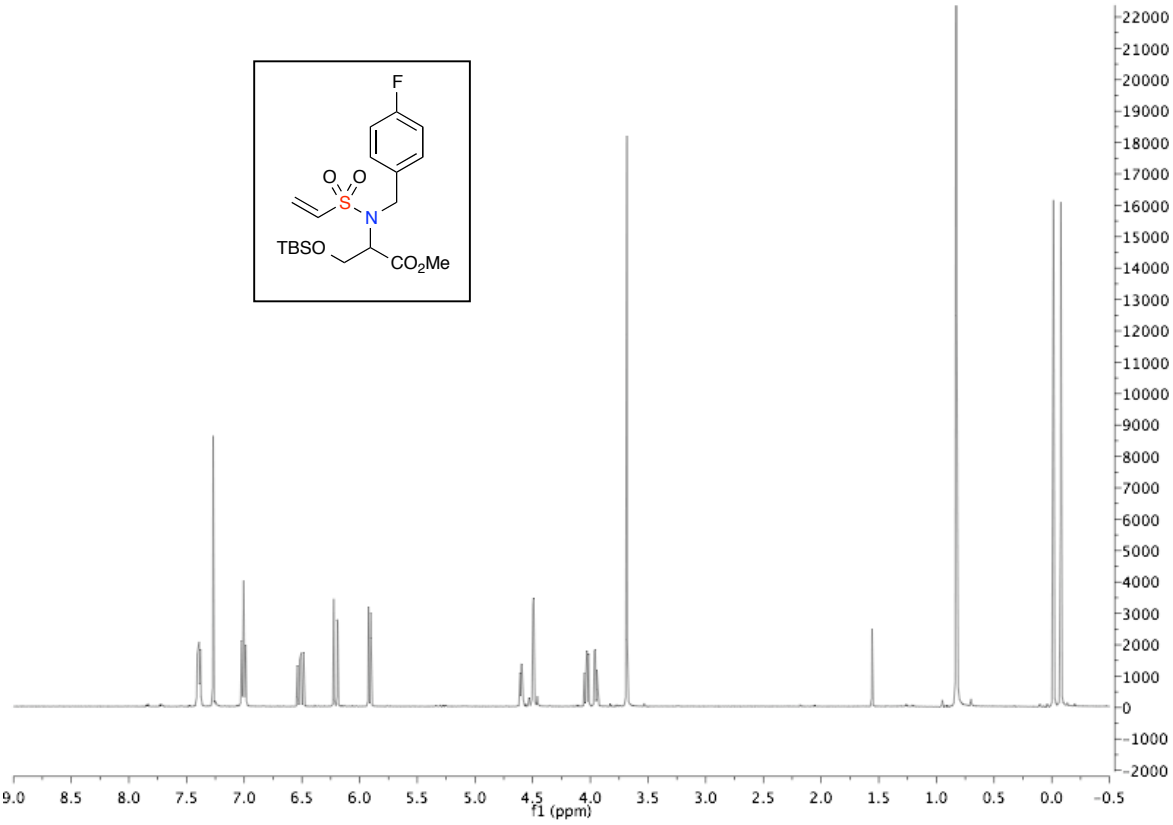


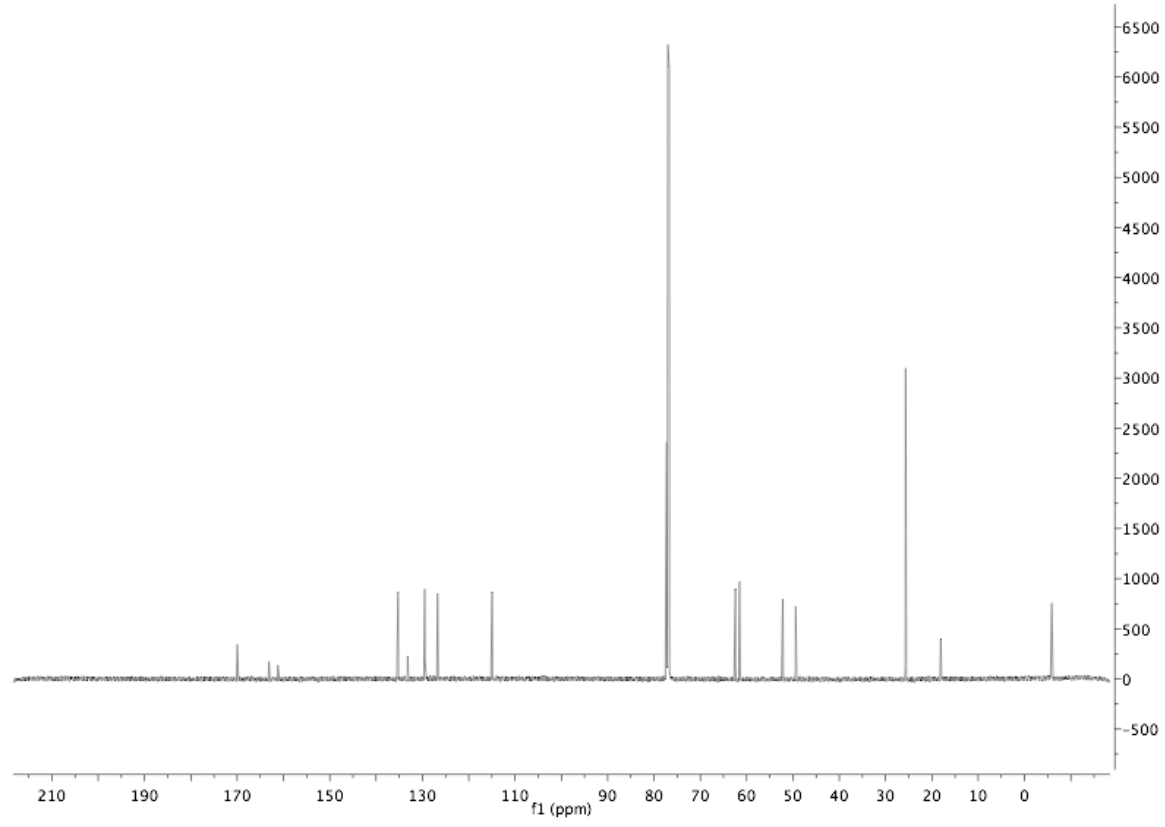
Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(*N*-(4-chlorobenzyl)vinylsulfonamido)propanoate (**3d**)



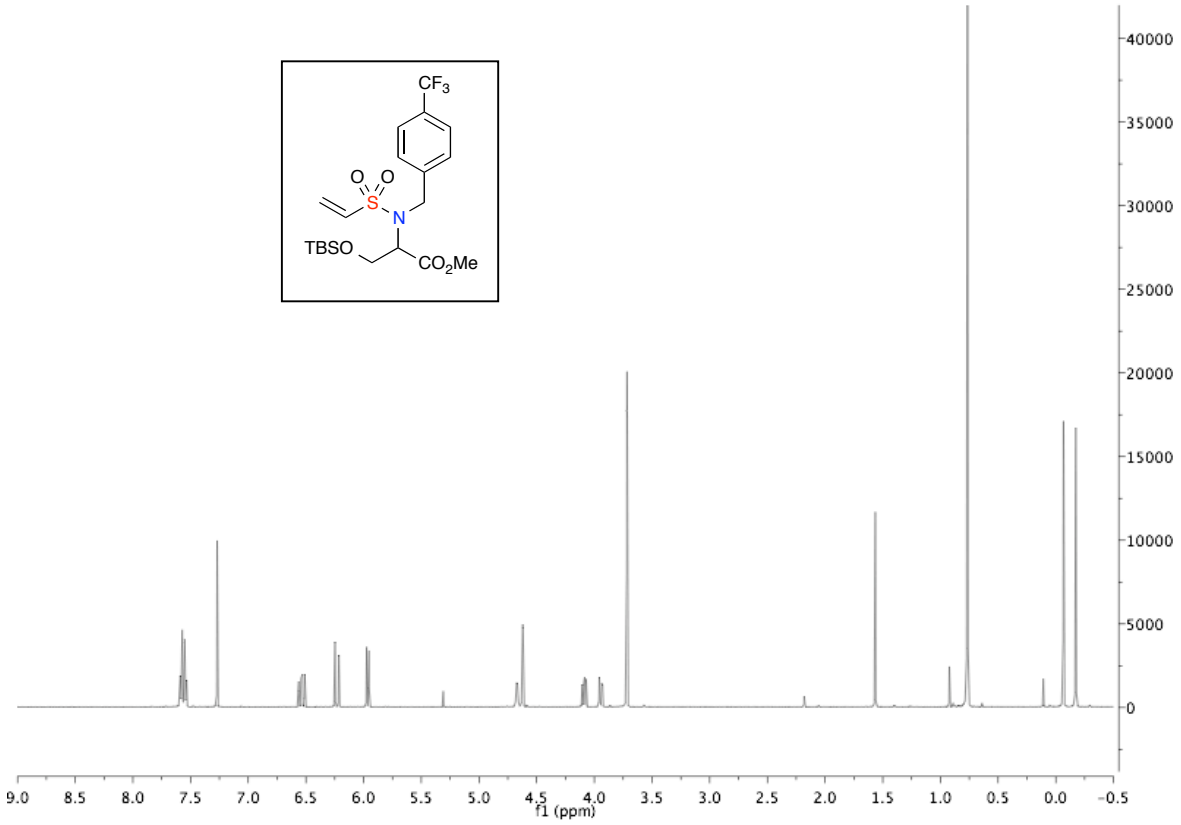


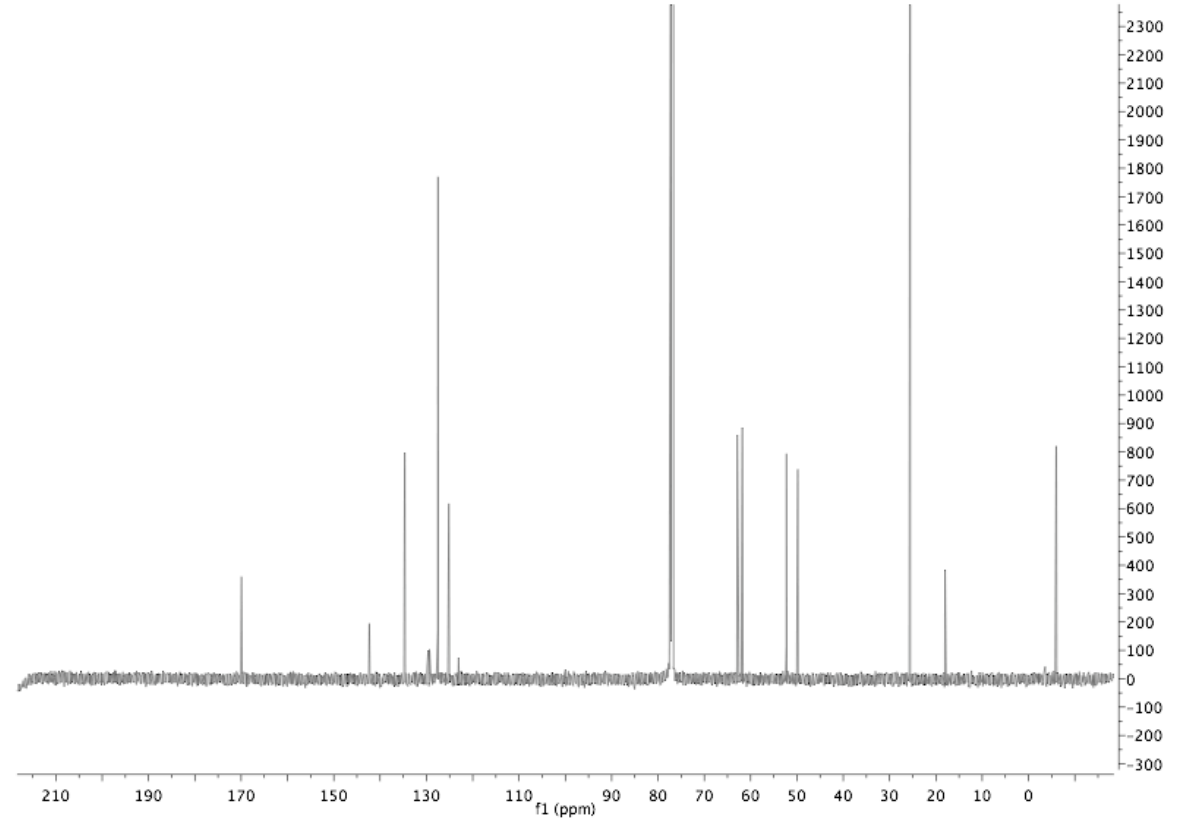
Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(*N*-(4-fluorobenzyl)vinylsulfonamido)propanoate (**3e**)



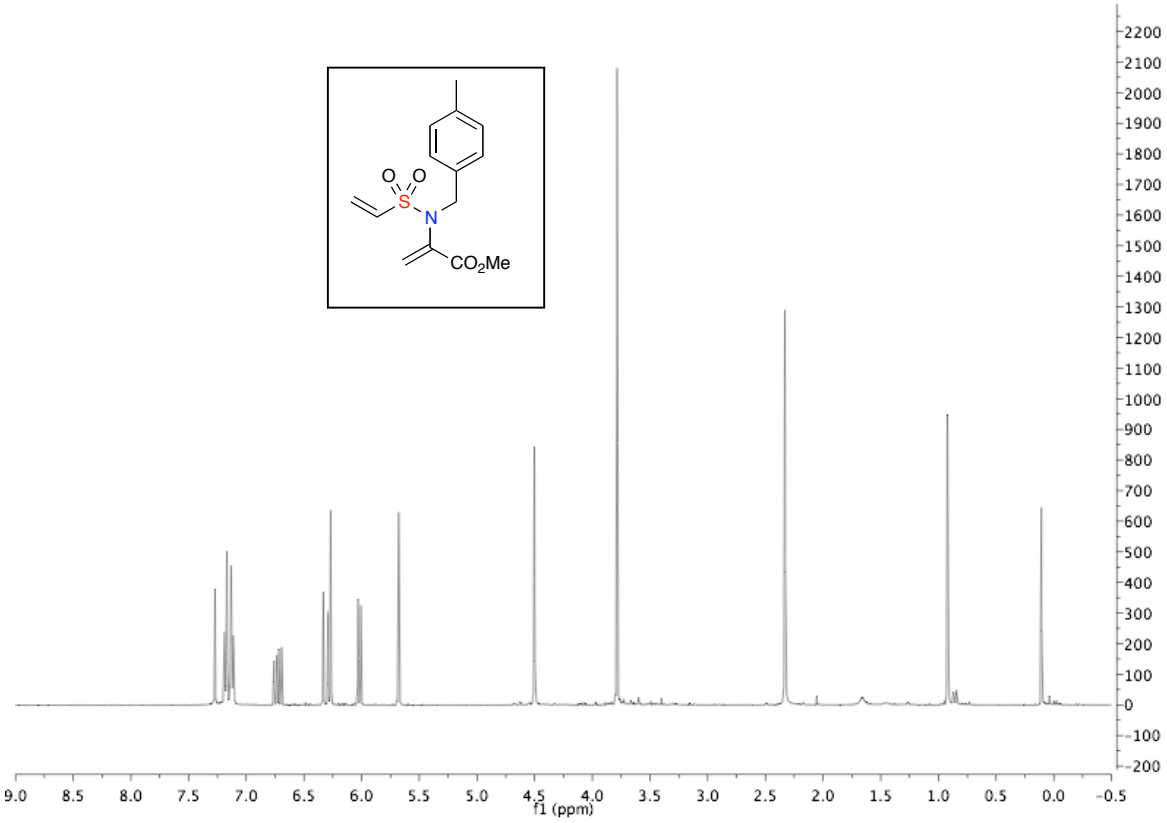


Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(*N*-(4-(trifluoromethyl)benzyl)vinylsulfonamido)propanoate (**3f**)

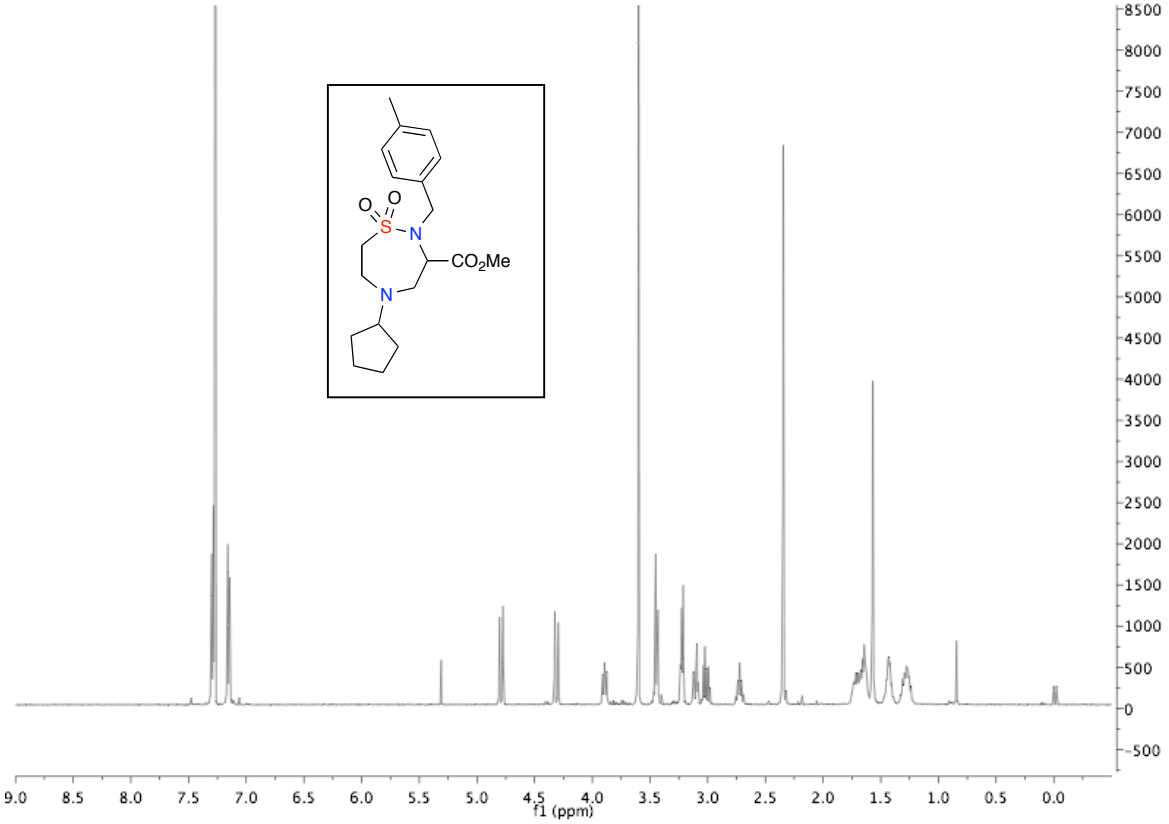


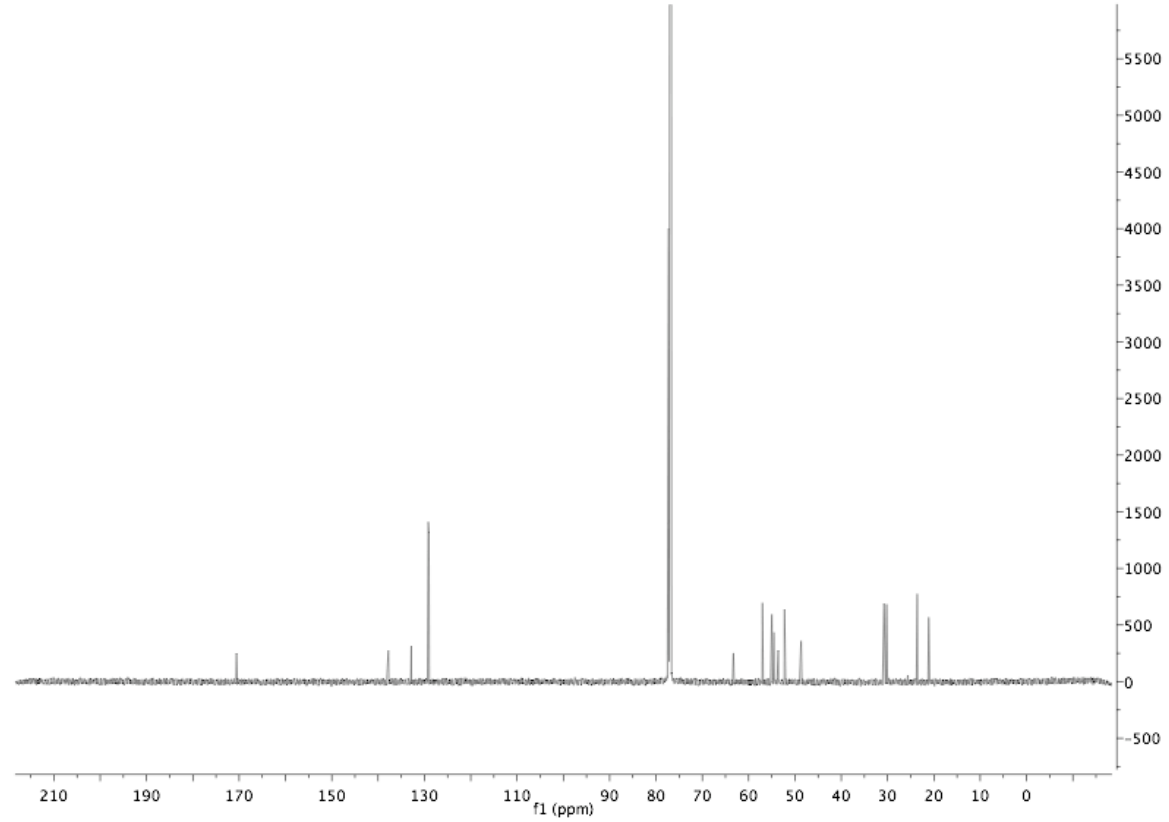


Methyl 2-(*N*-(4-methylbenzyl)vinylsulfonamido)acrylate (**4**):

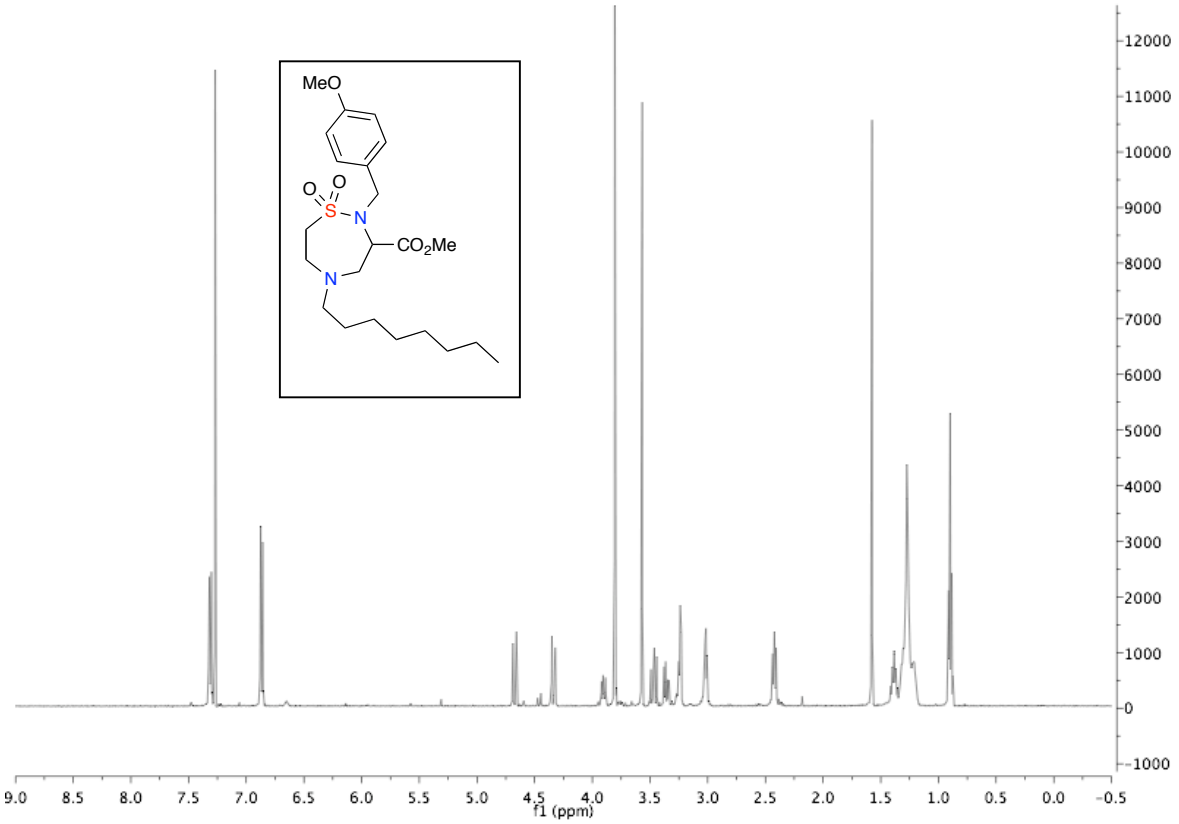


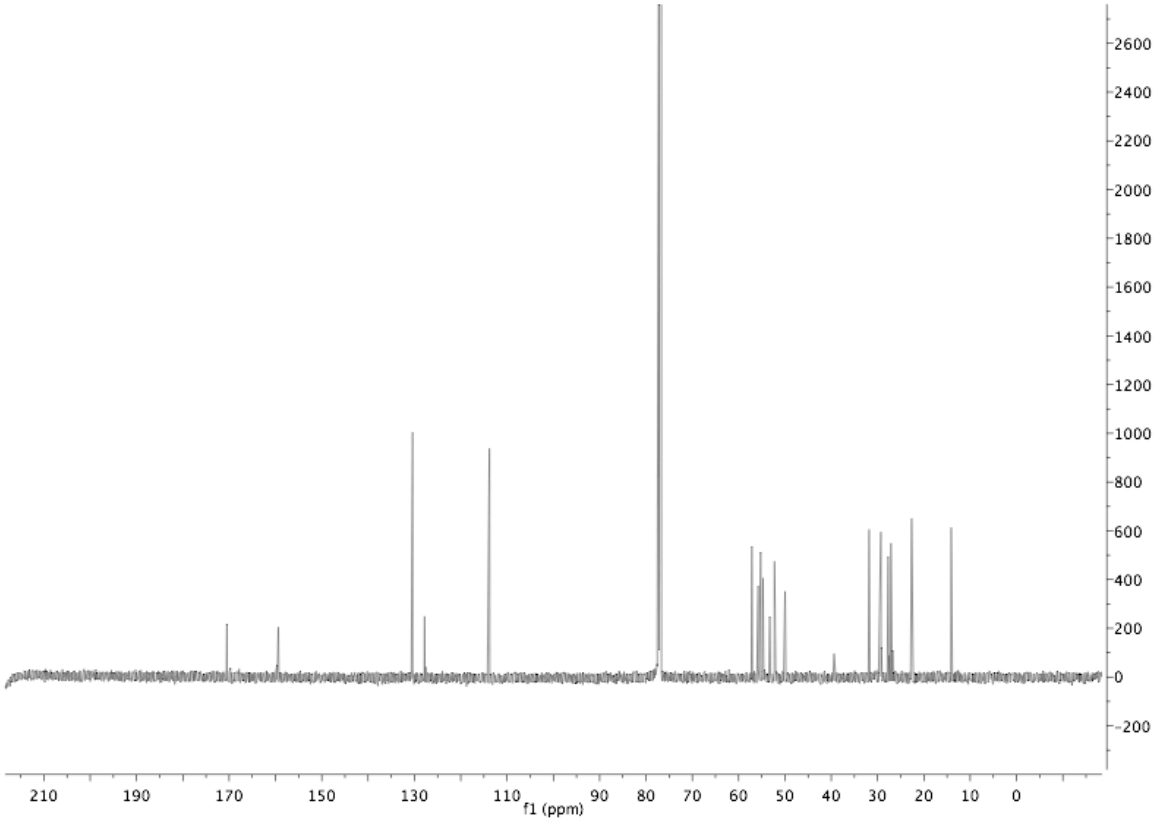
Methyl 5-cyclopentyl-2-(4-methylbenzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**5a**)



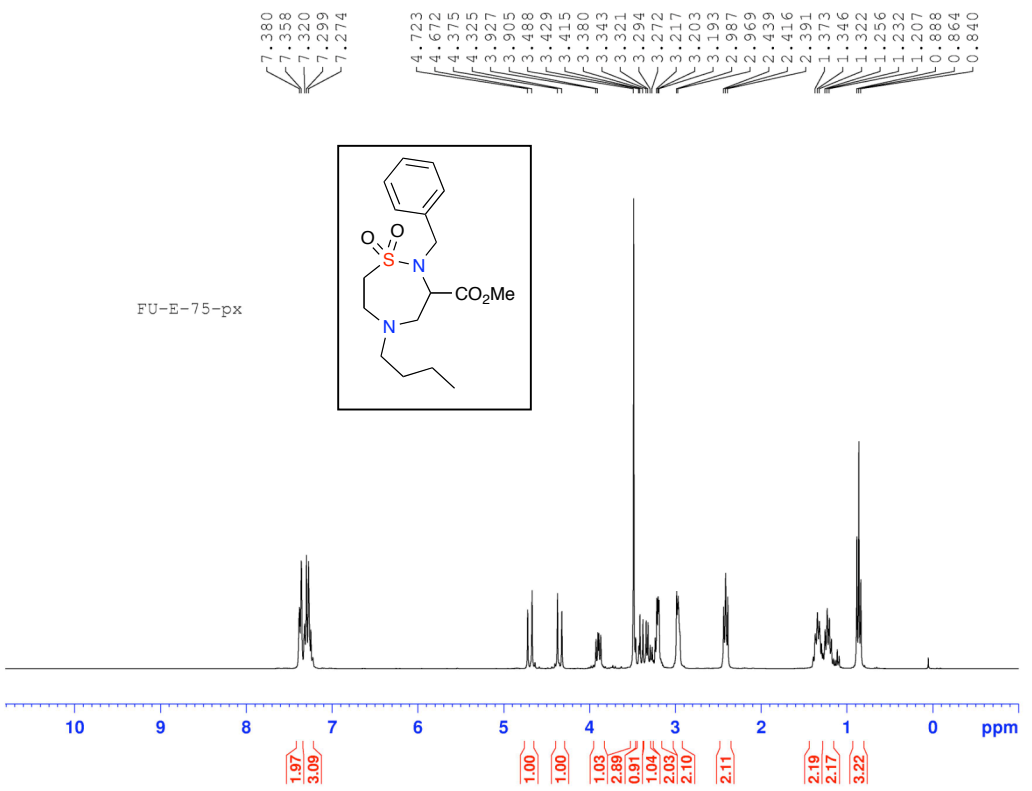


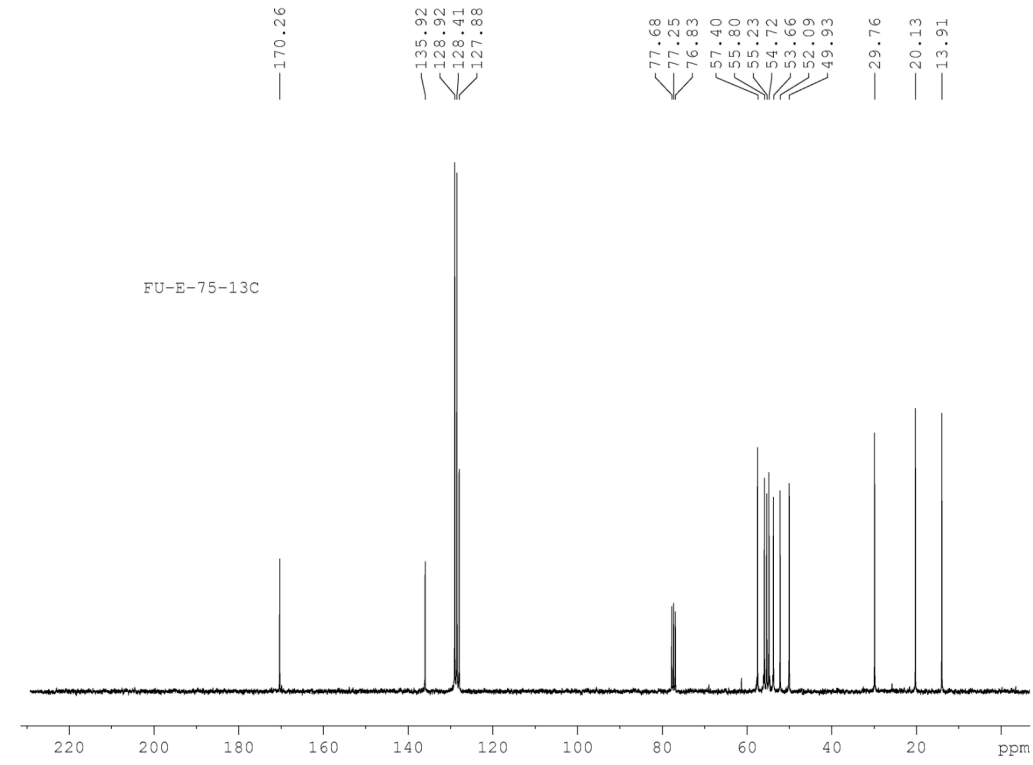
Methyl 2-(4-methoxybenzyl)-5-octyl-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**5b**)



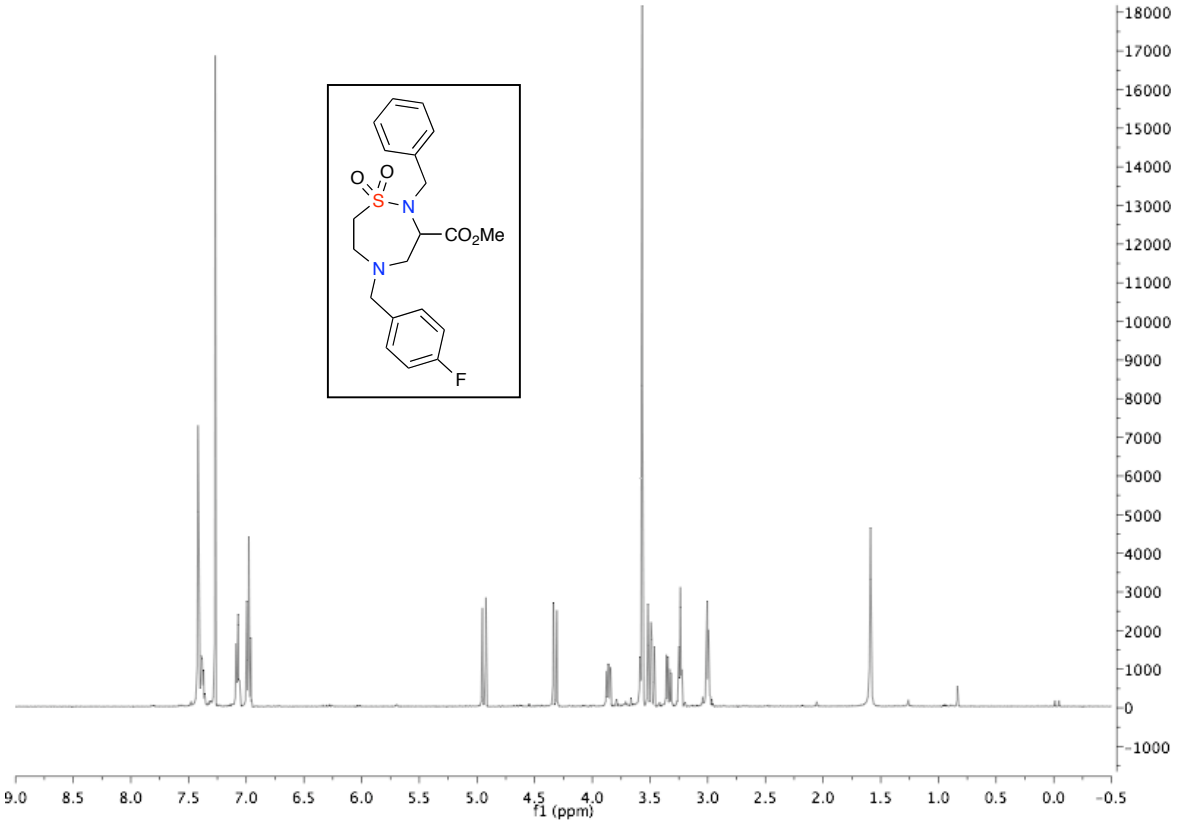


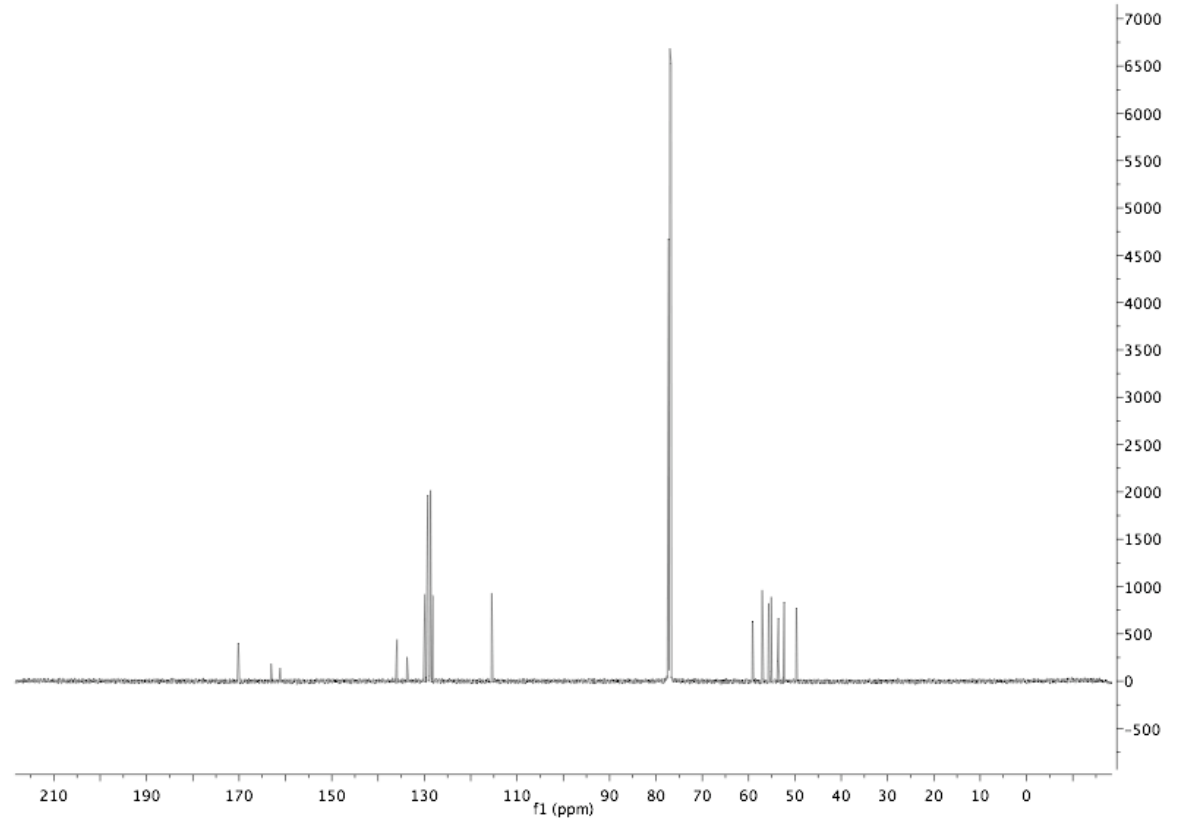
Methyl 2-benzyl-5-butyl-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**5c**)



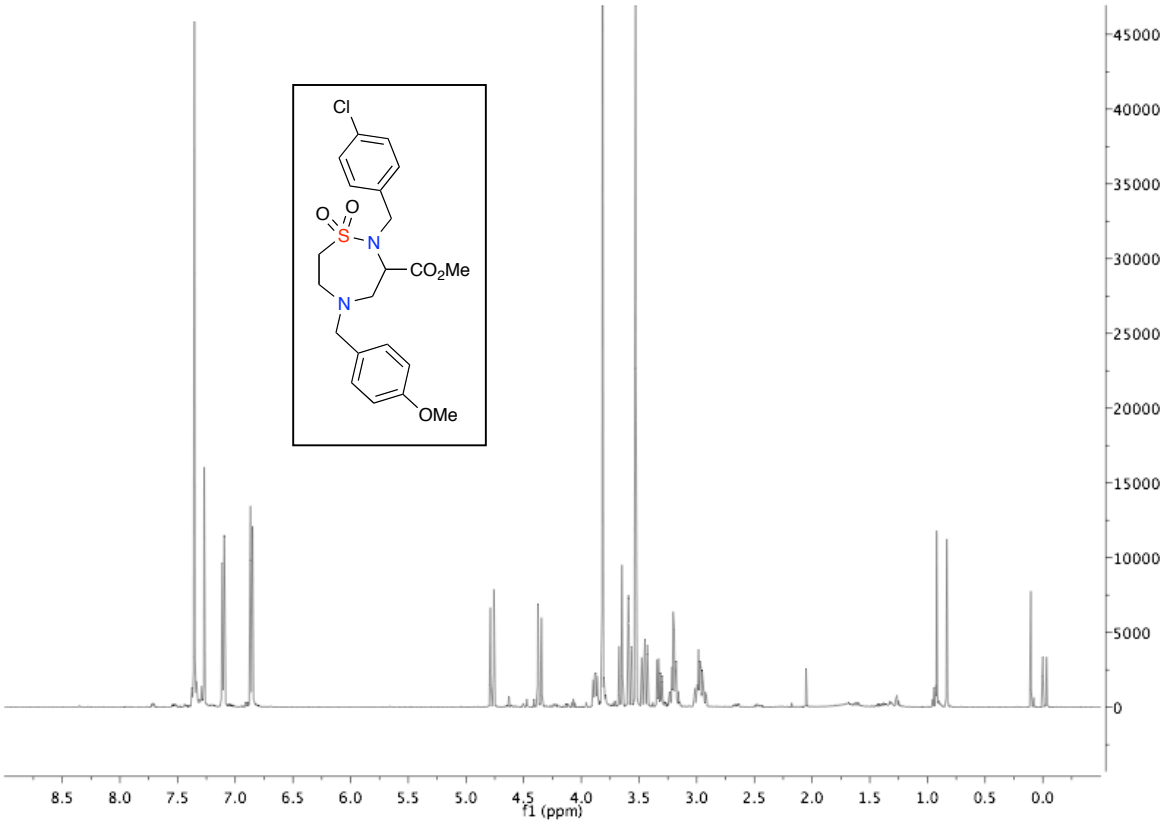


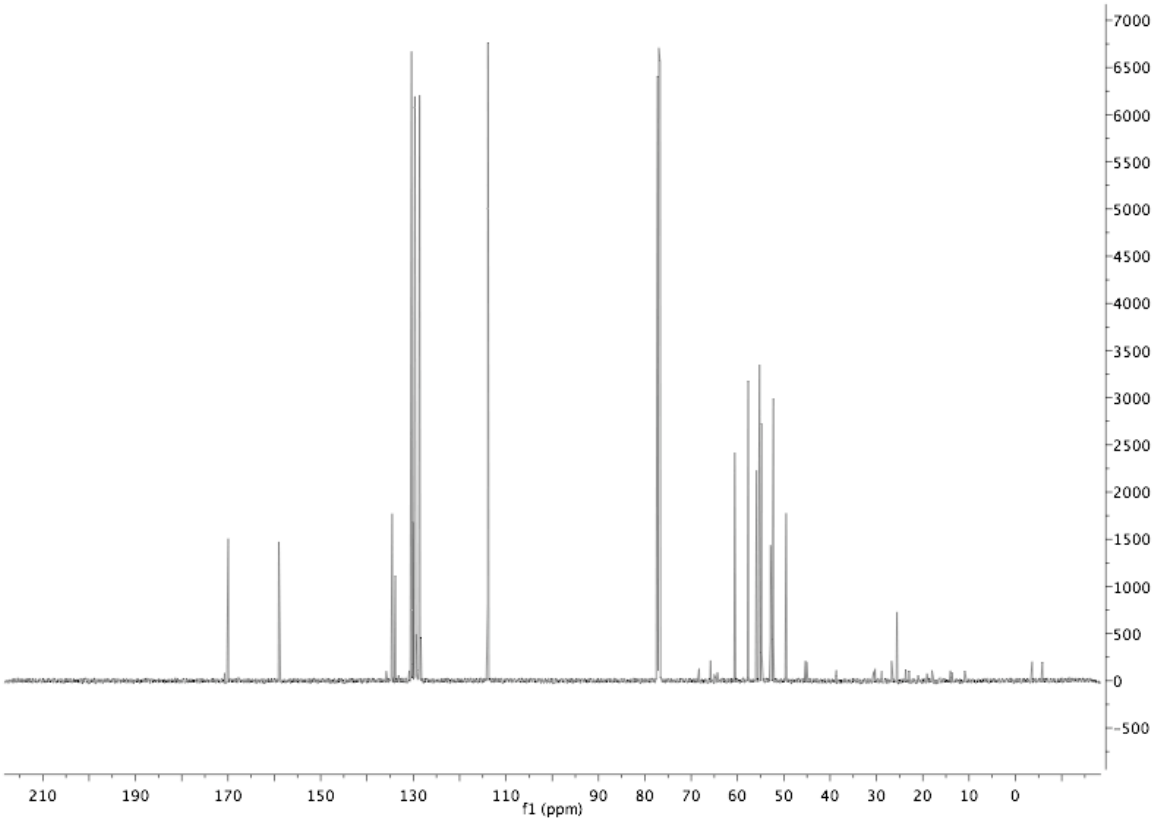
Methyl 2-benzyl-5-(4-fluorobenzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**5d**)



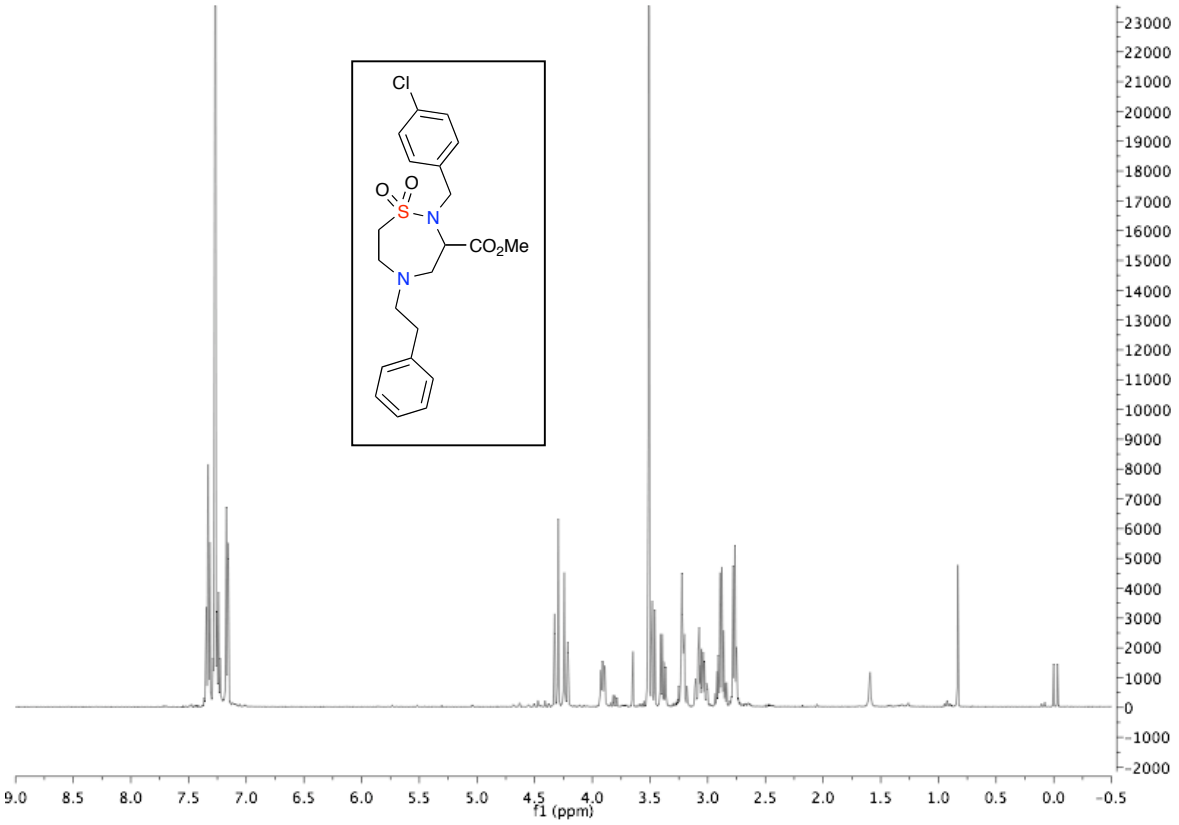


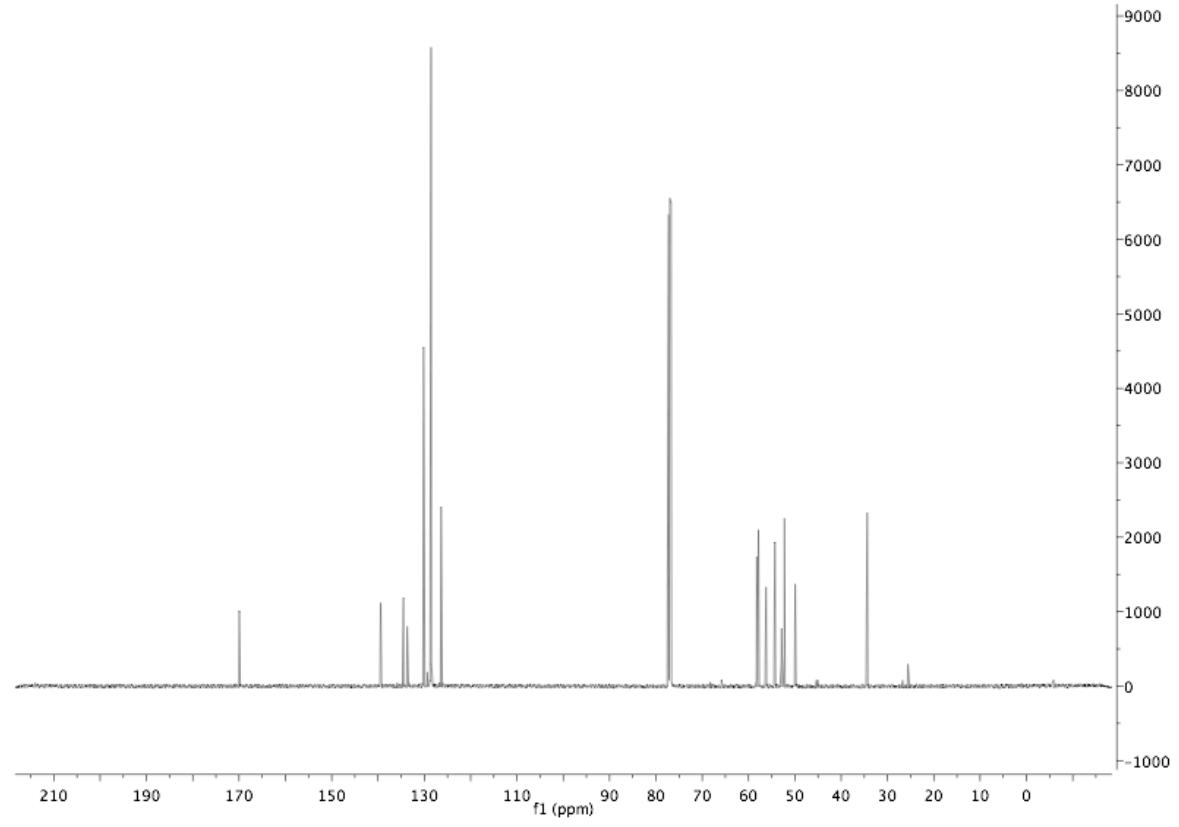
Methyl 2-(4-chlorobenzyl)-5-(4-methoxybenzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**5e**)



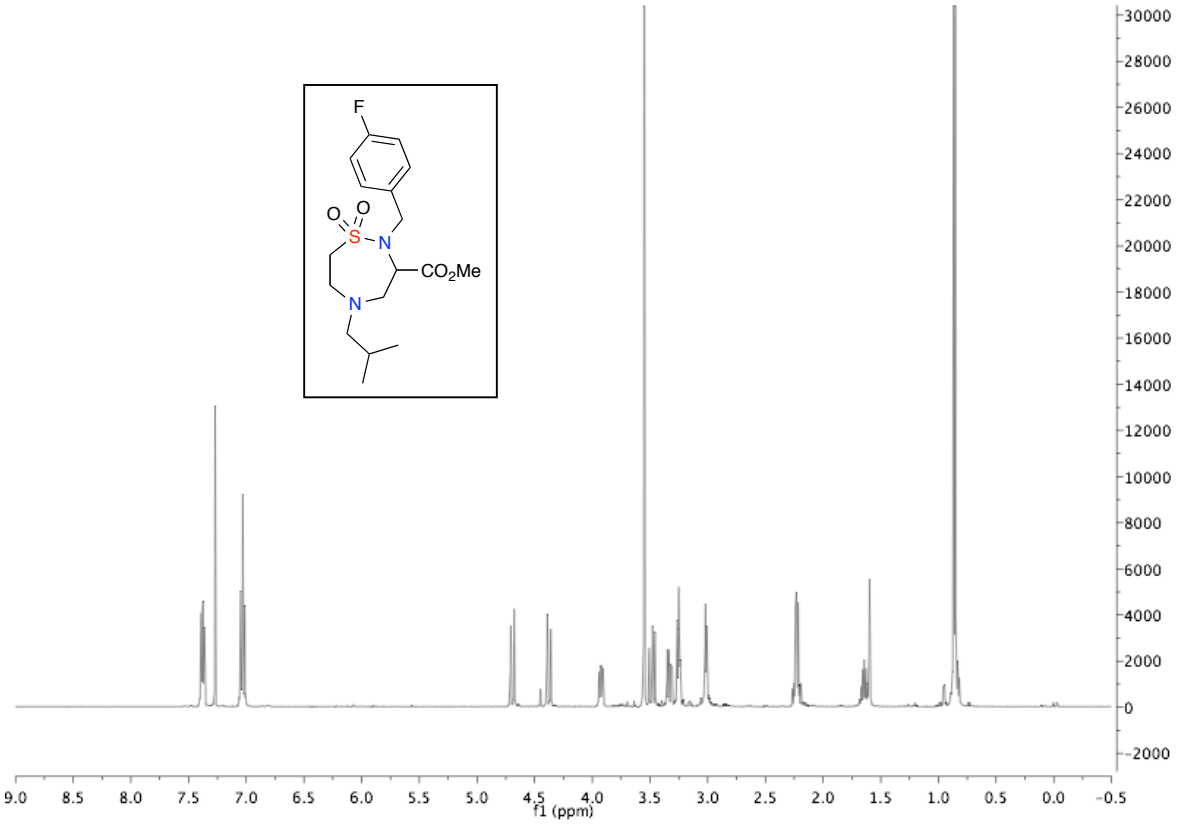


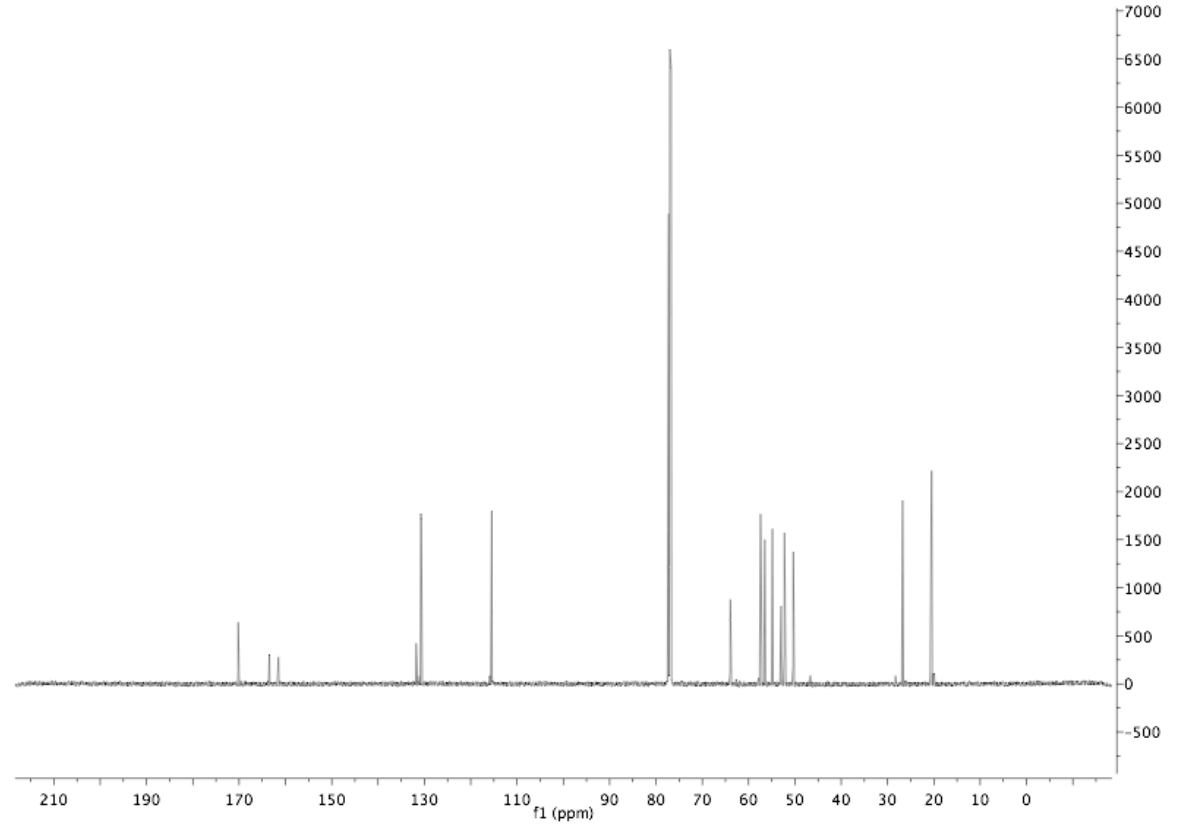
Methyl 2-(4-chlorobenzyl)-5-phenethyl-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**5f**)



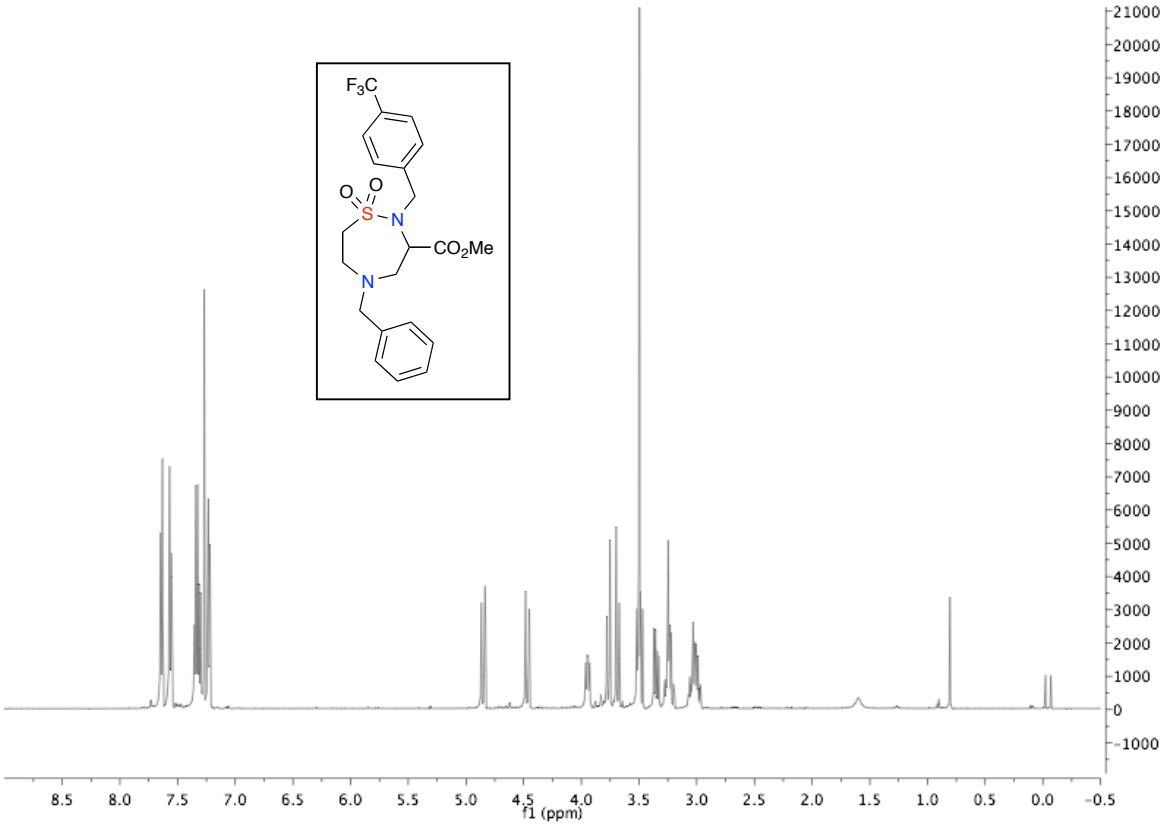


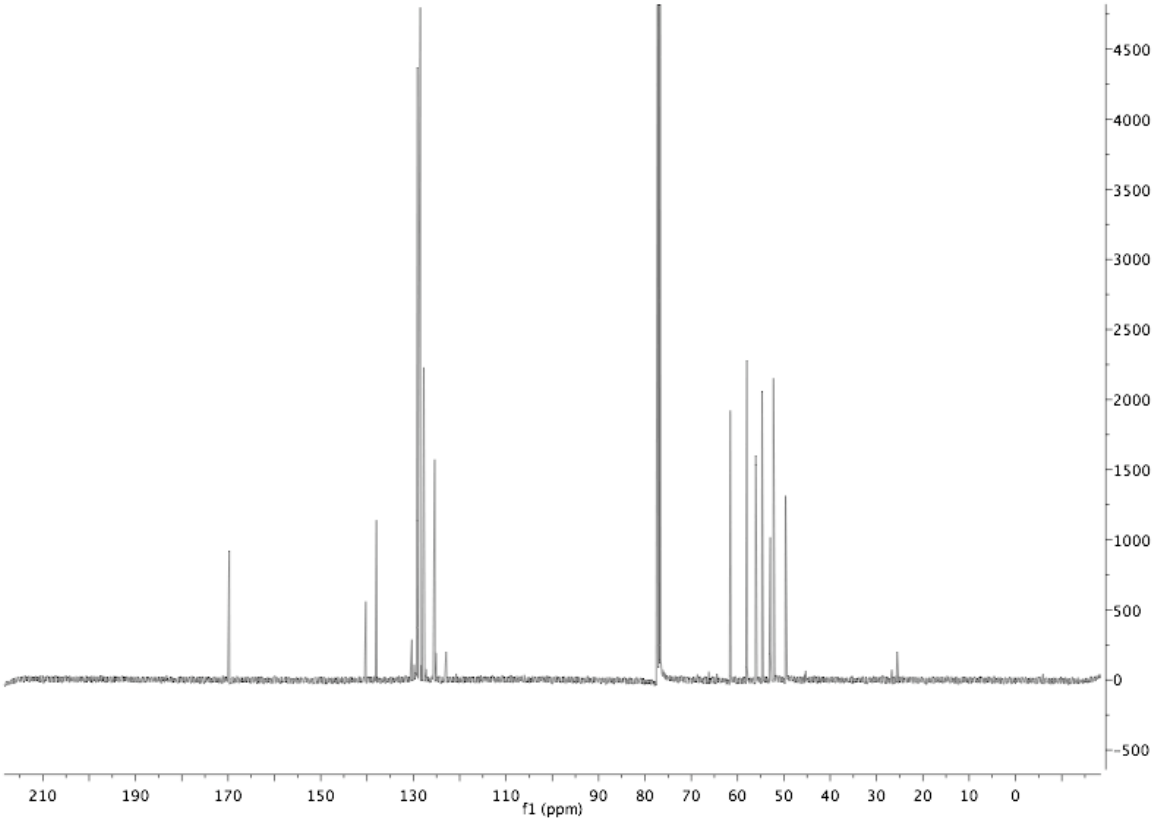
Methyl 2-(4-fluorobenzyl)-5-isobutyl-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**5g**)



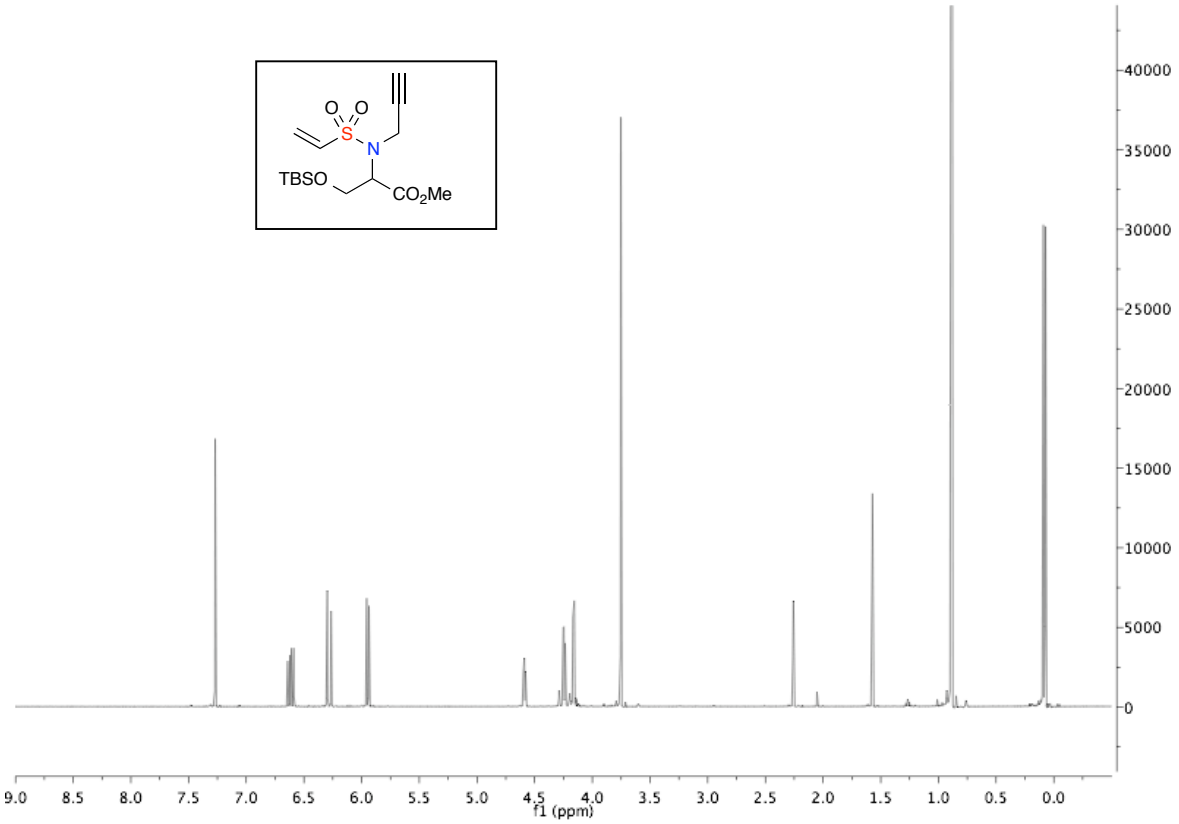


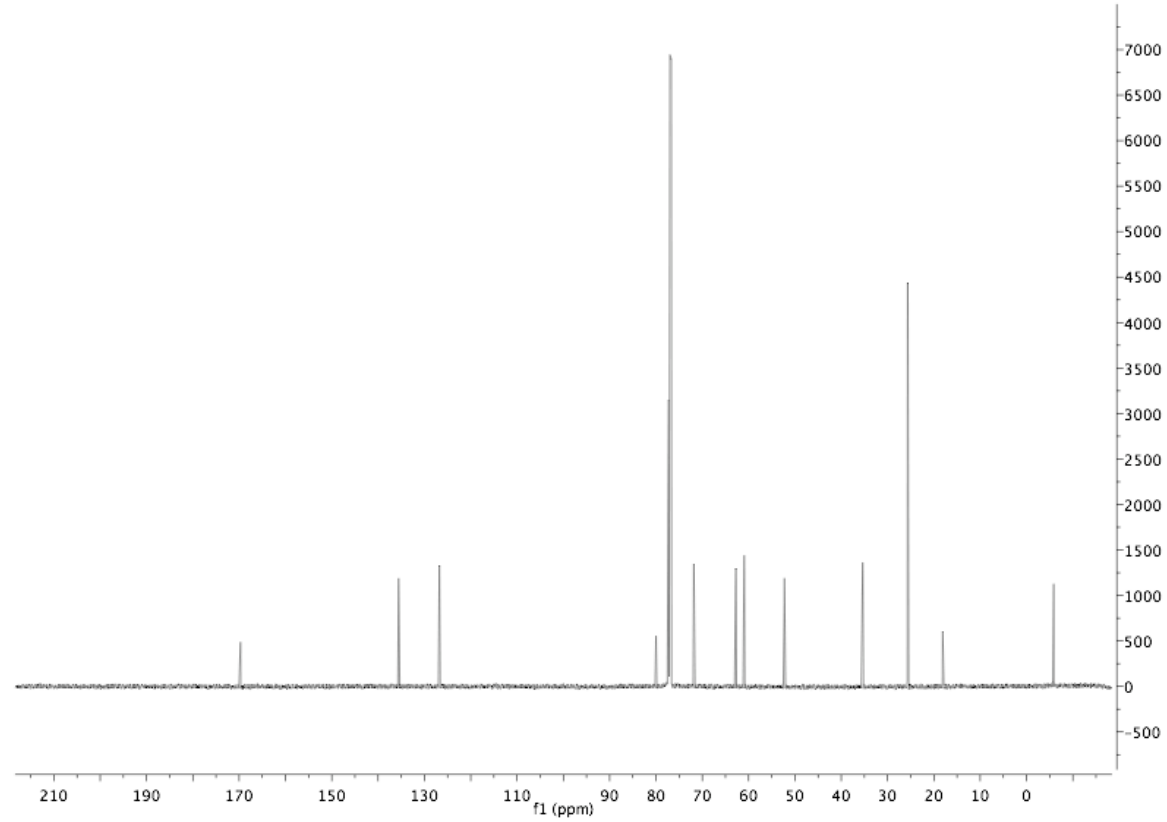
Methyl 5-benzyl-2-(4-(trifluoromethyl)benzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**5h**)



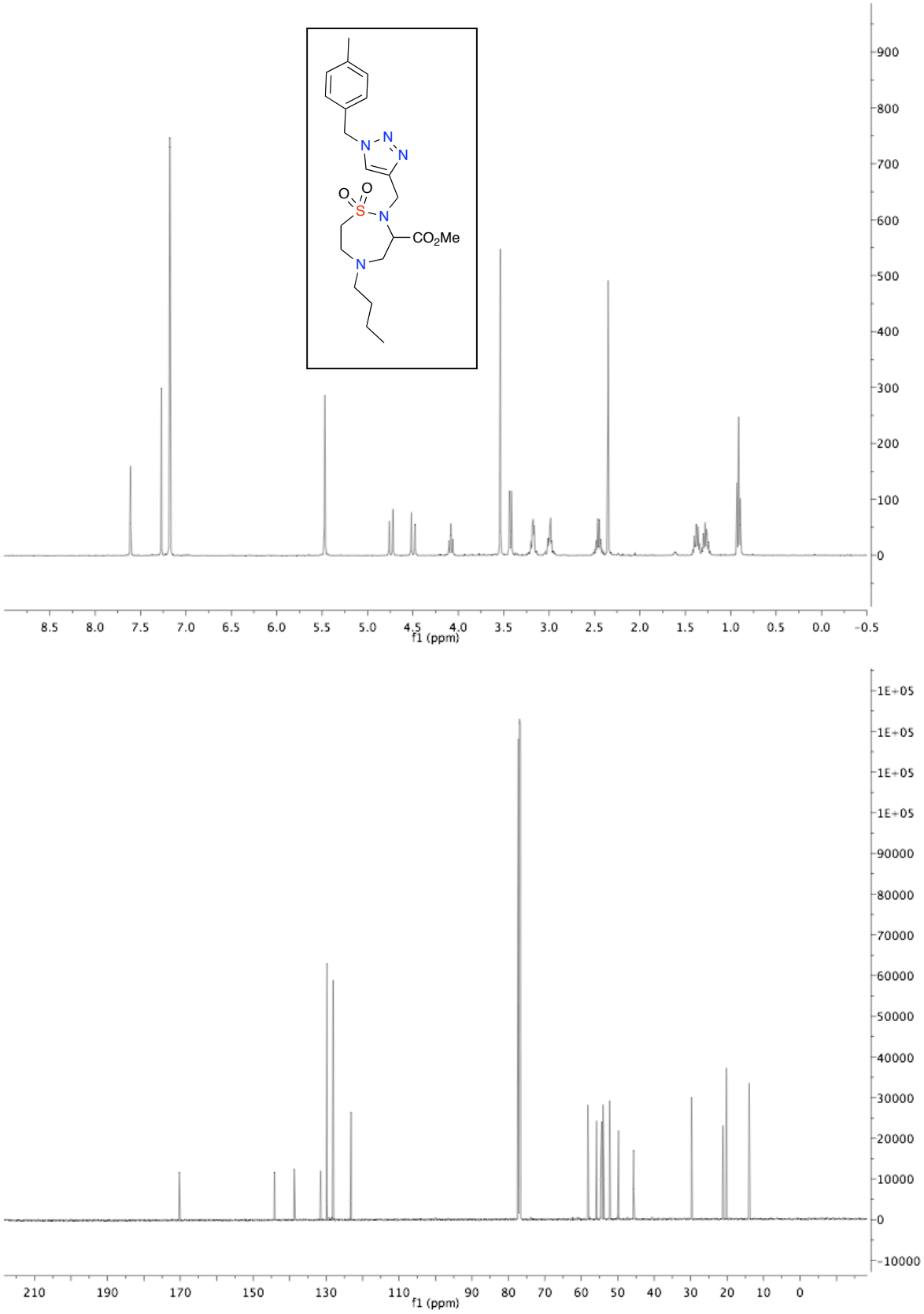


Methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-(*N*-(prop-2-yn-1-yl)vinylsulfonamido)propanoate (**6**)

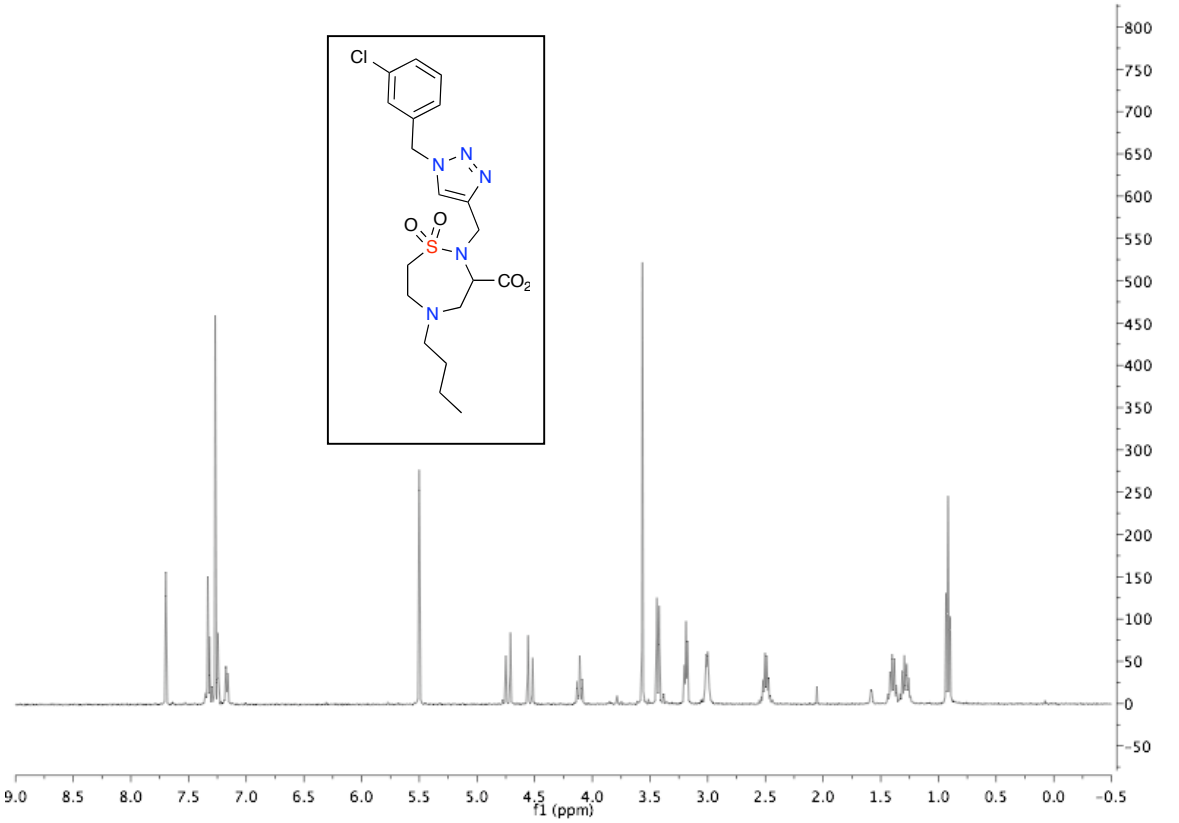


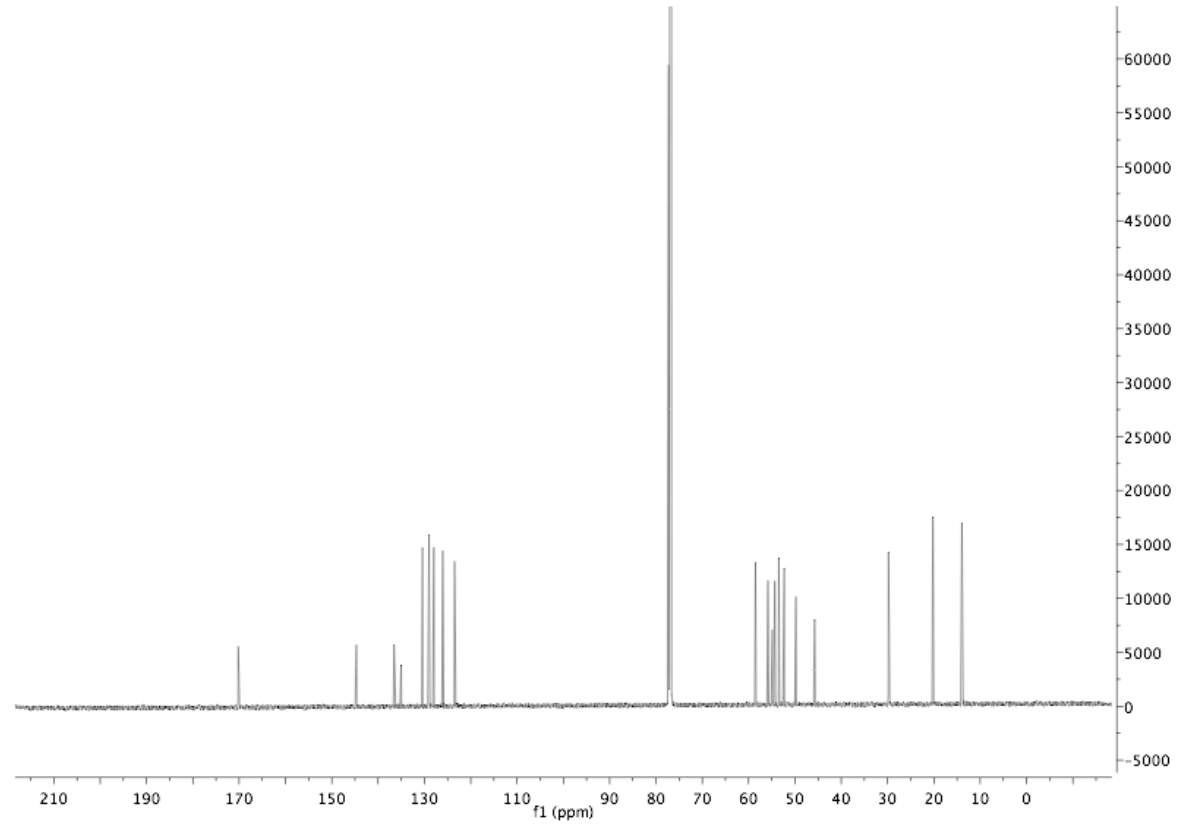


Methyl 5-butyl-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**7a**)

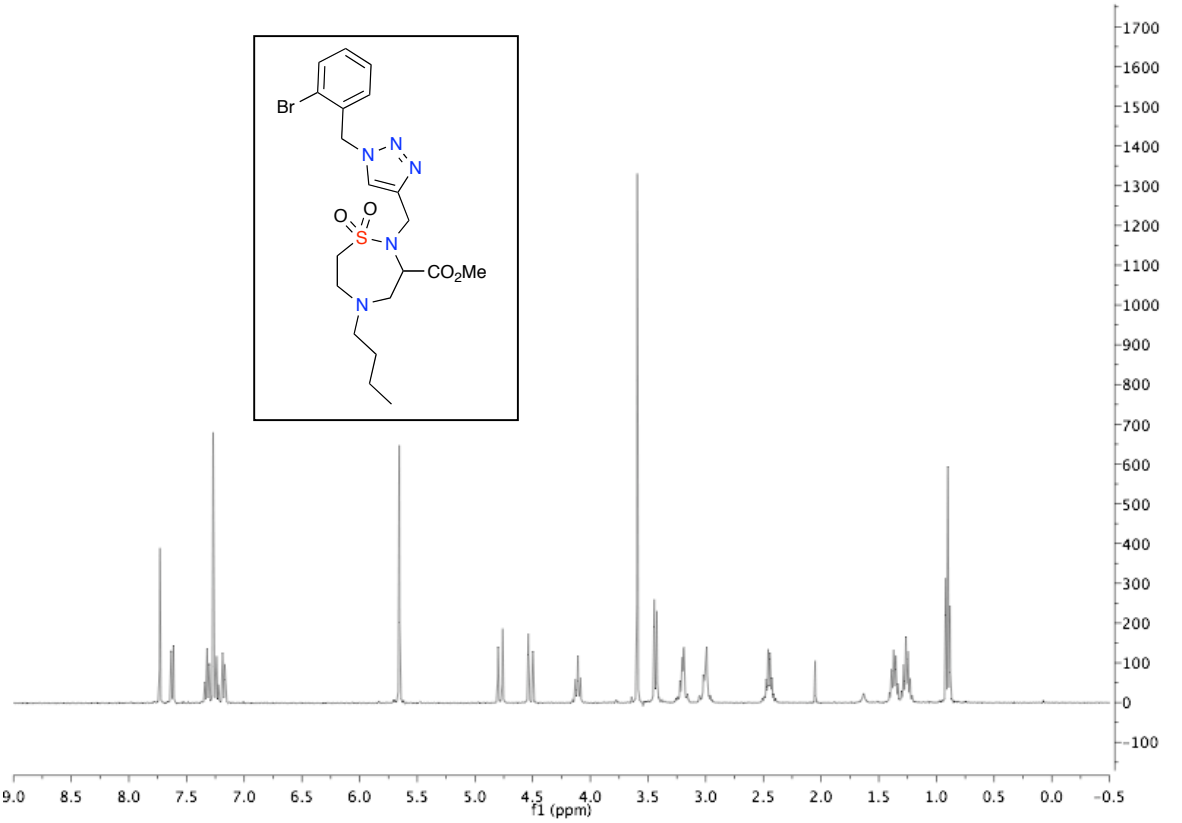


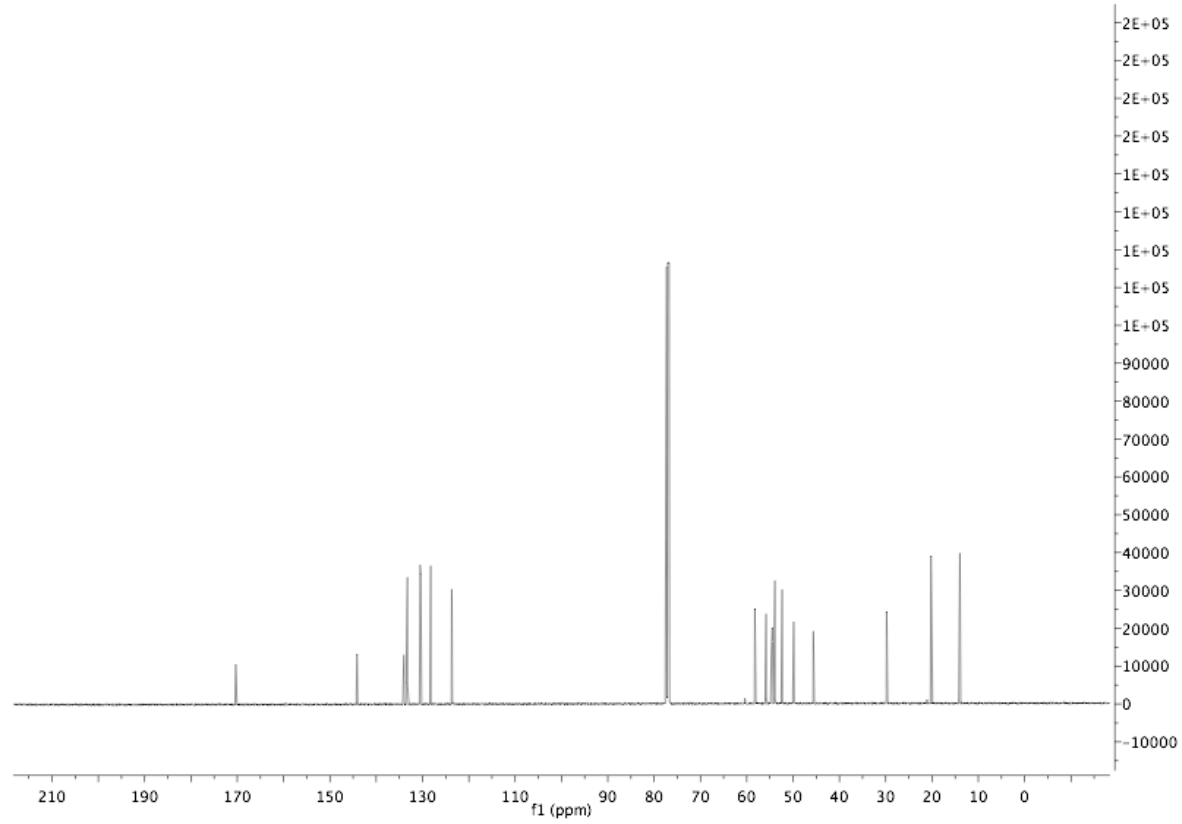
Methyl 5-butyl-2-((1-(3-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**7b**)



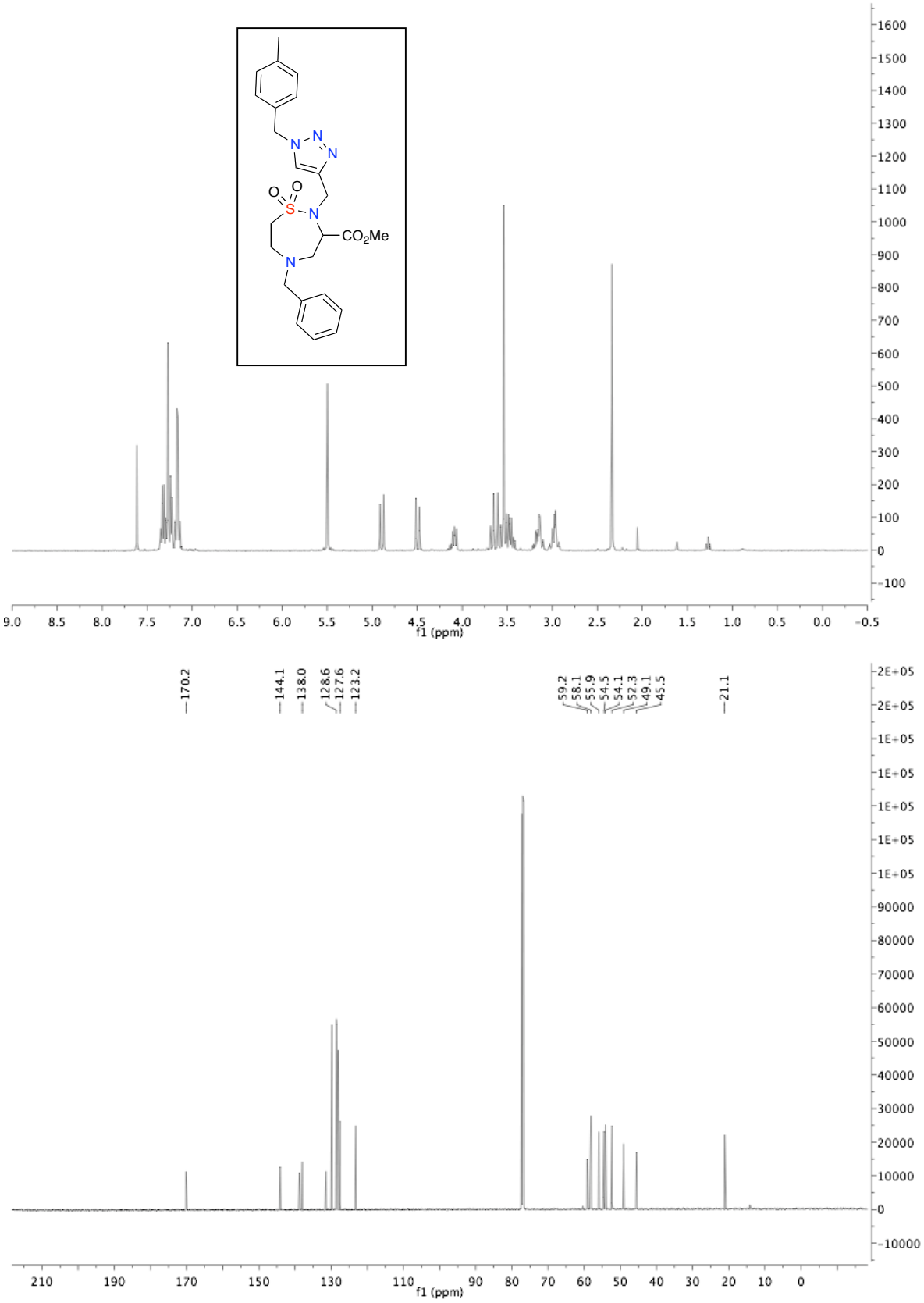


Methyl 2-((1-(2-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5-butyl-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**7c**)

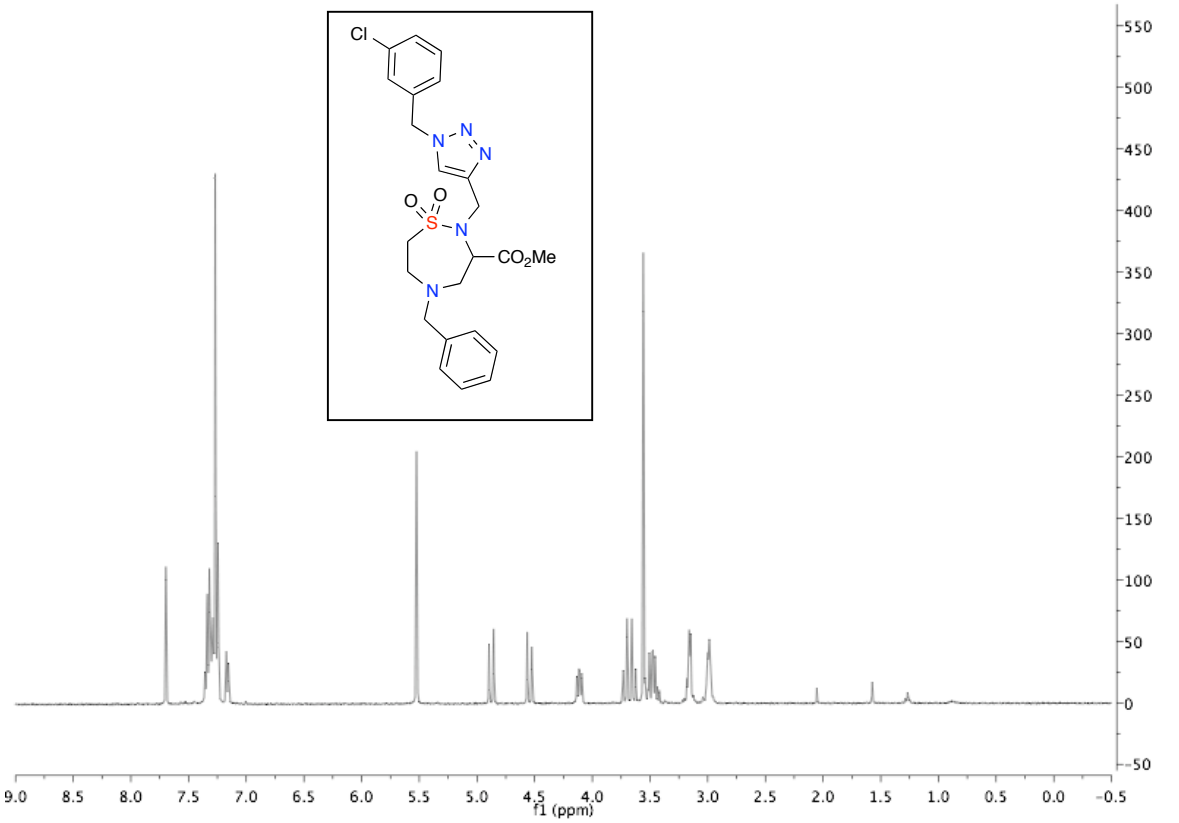


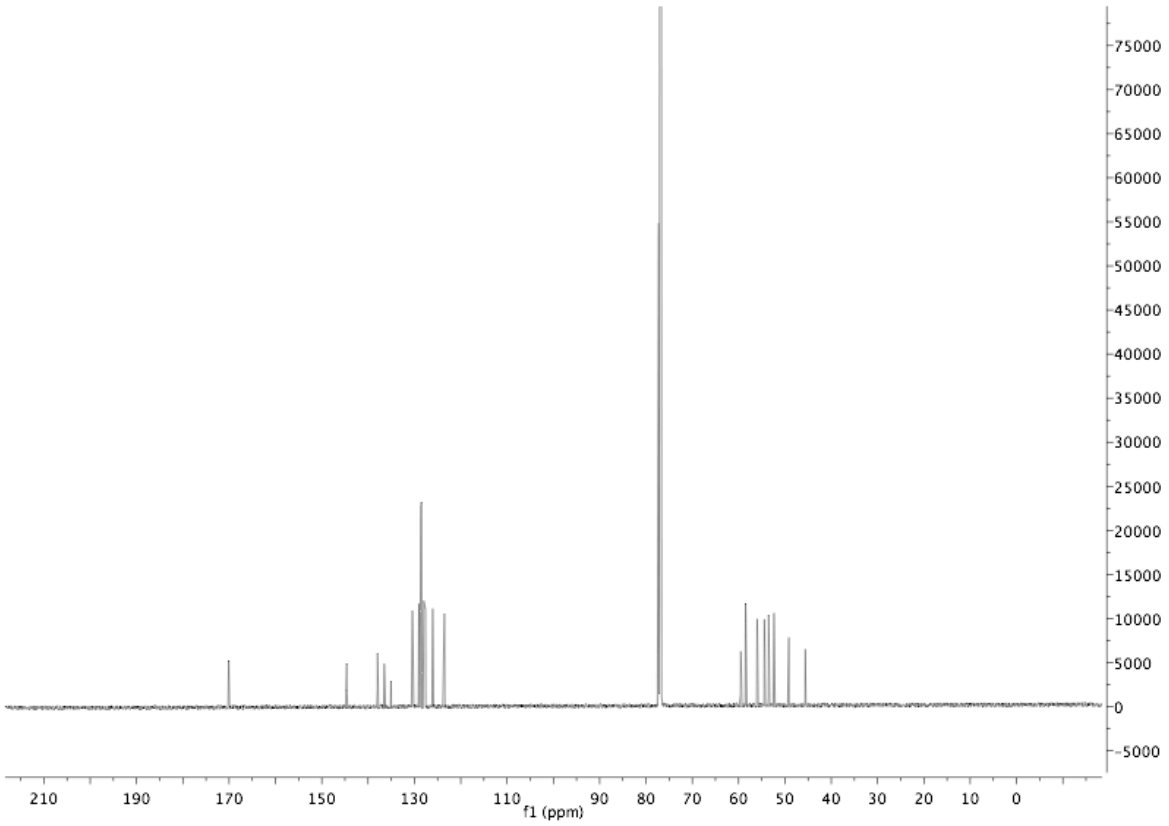


Methyl 5-benzyl-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**7d**)

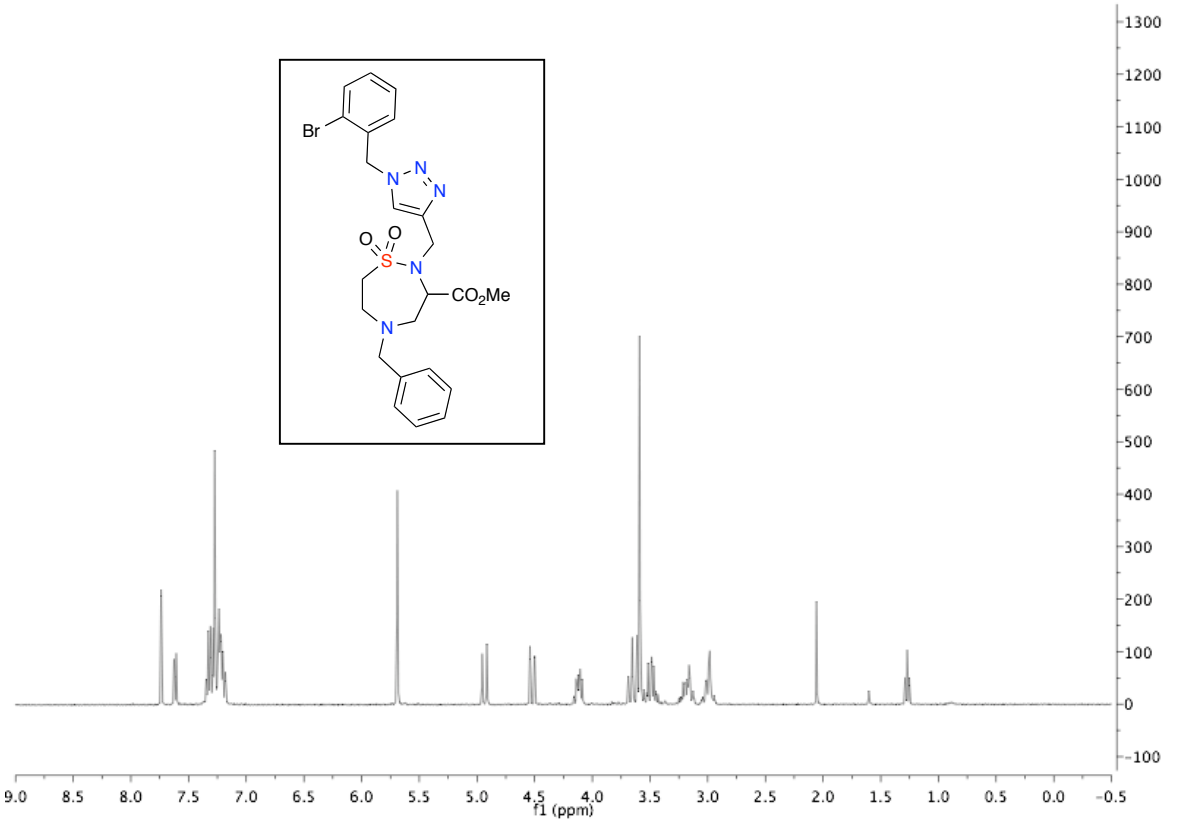


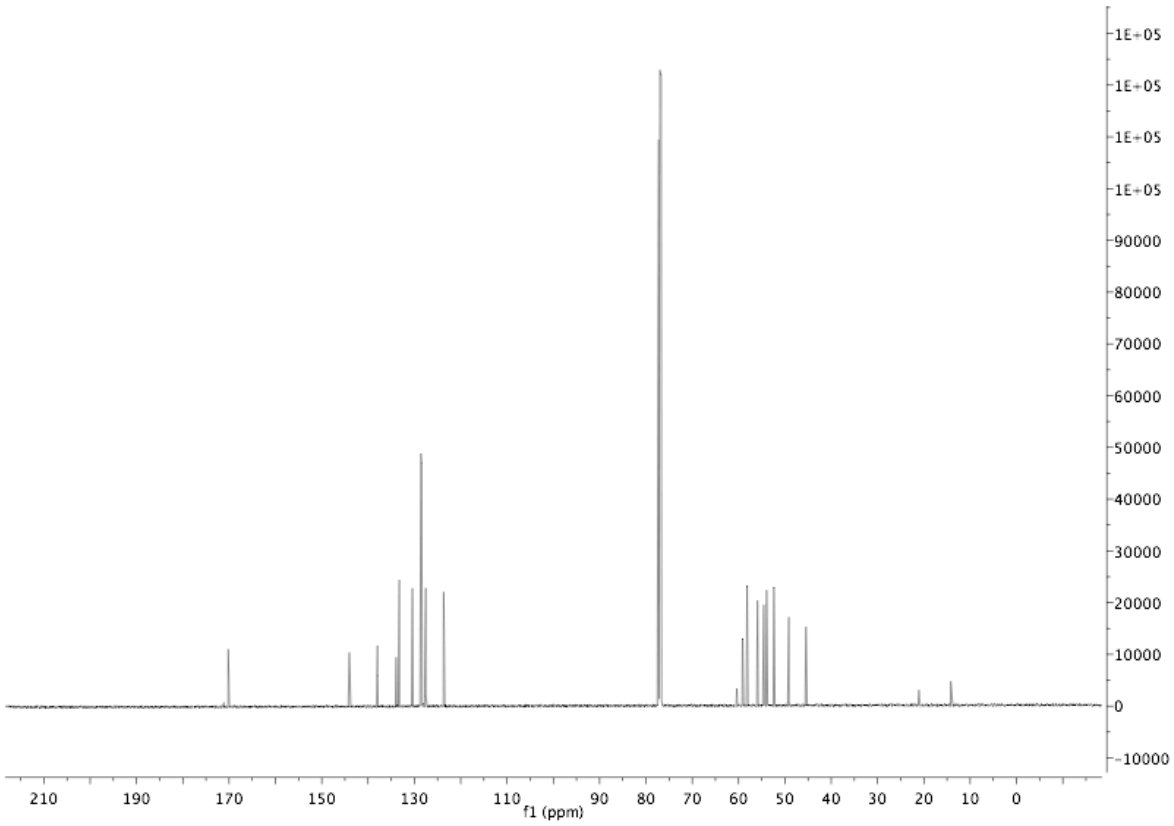
Methyl 5-benzyl-2-((1-(3-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**7e**)



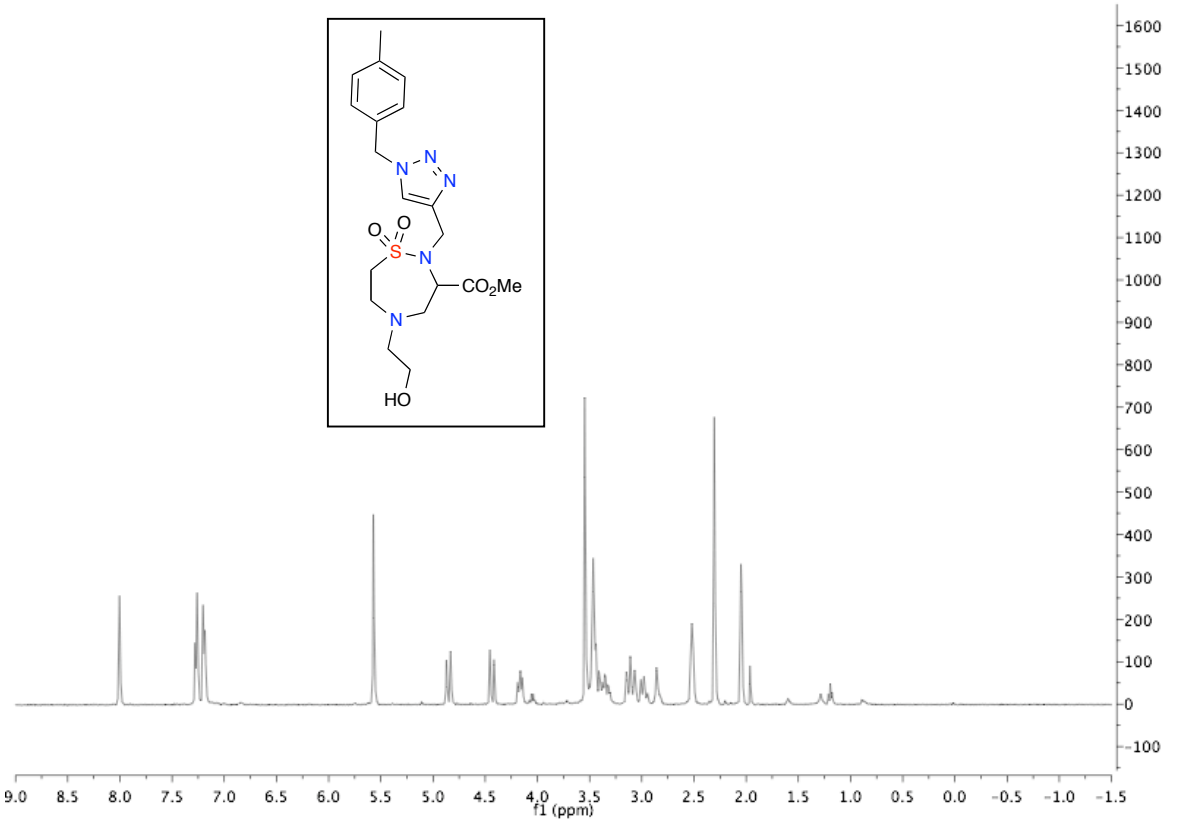


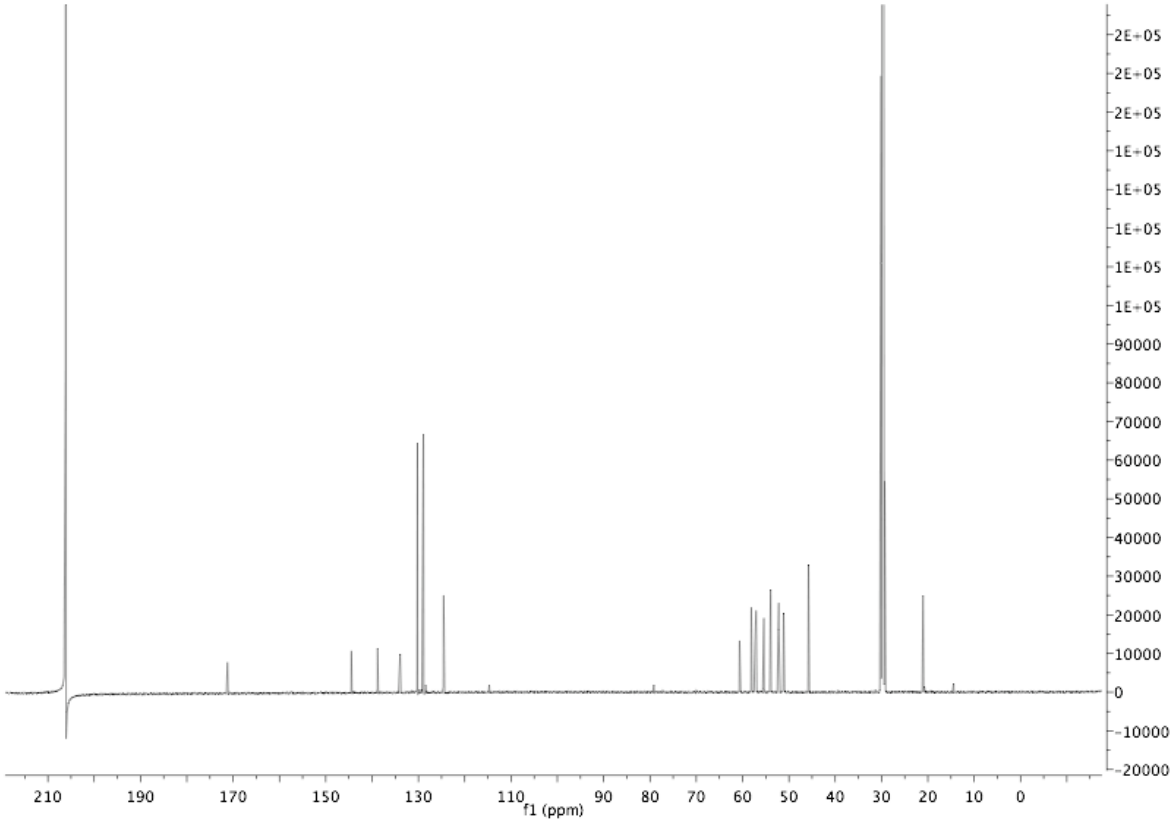
Methyl 5-benzyl-2-((1-(2-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**7f**)



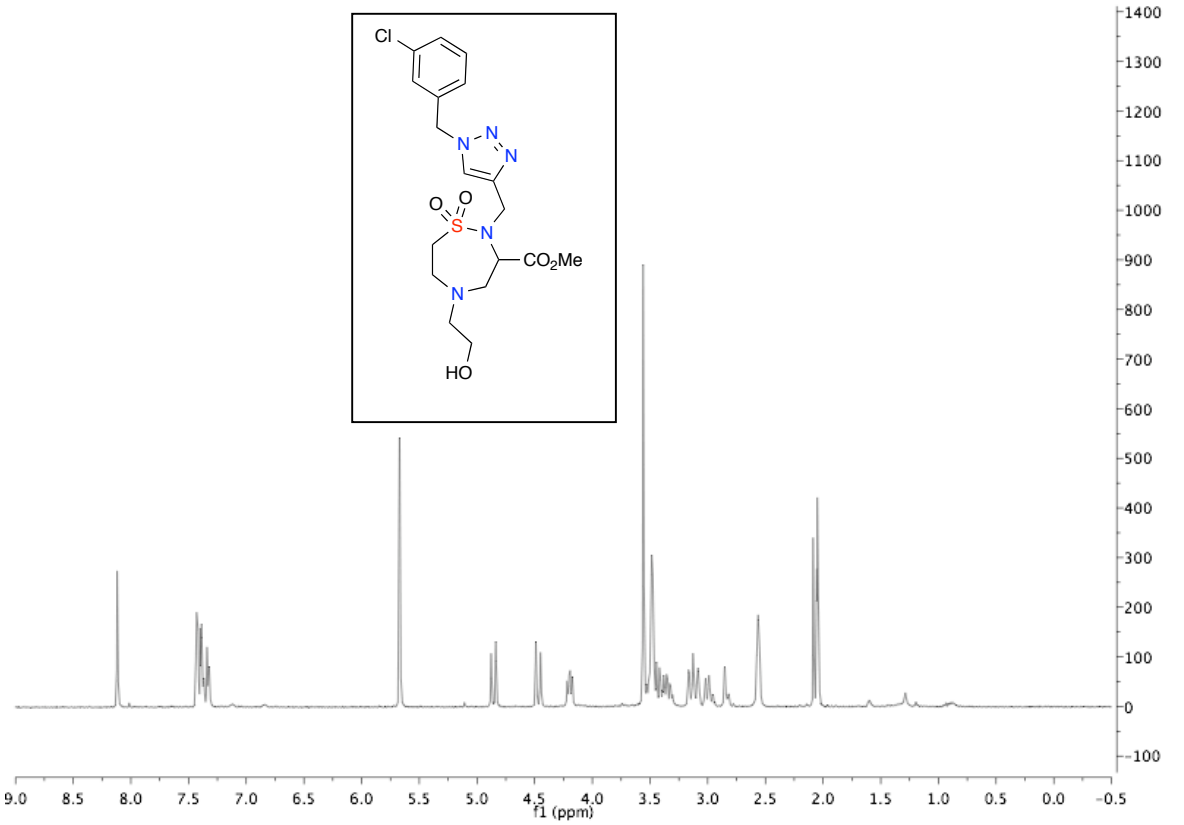


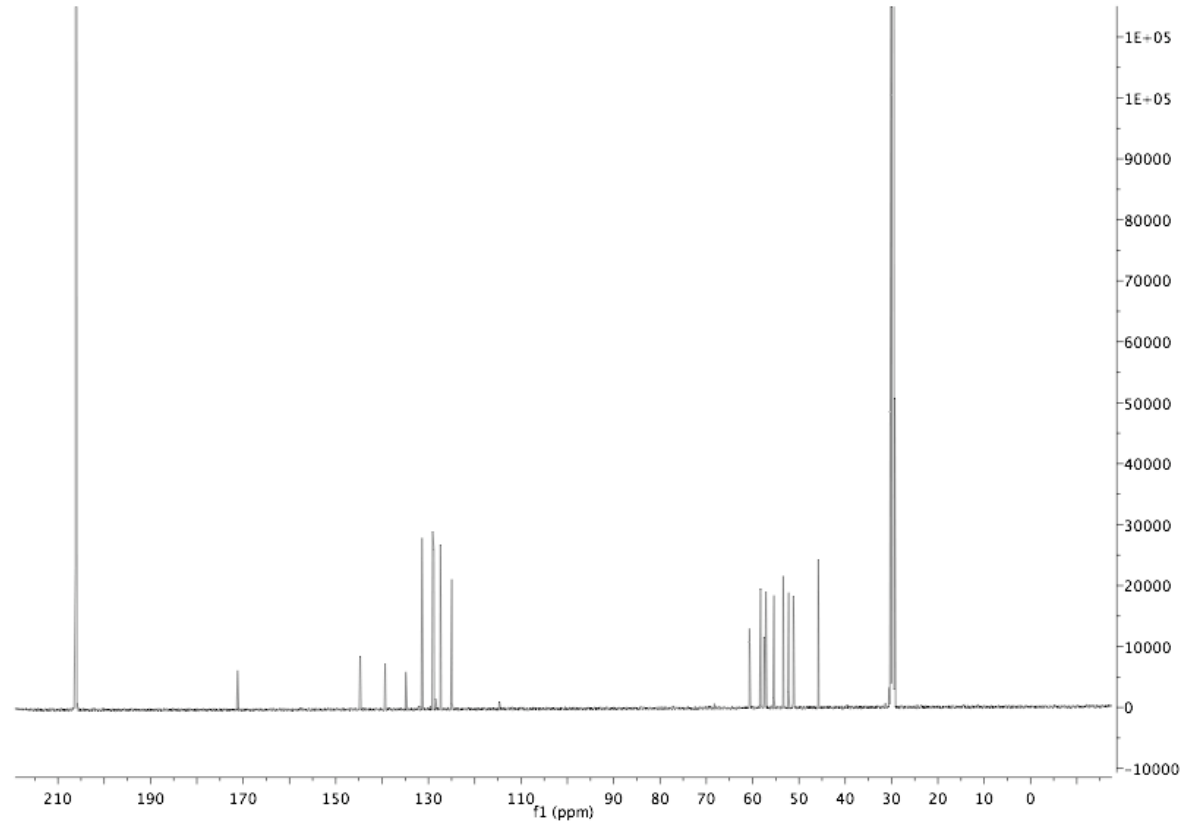
Methyl 5-(2-hydroxyethyl)-2-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**7g**)





Methyl 2-((1-(3-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5-(2-hydroxyethyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**7h**)





Methyl 2-((1-(2-bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-5-(2-hydroxyethyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (**7i**)