A Multicomponent Approach to the Synthesis of *N*-sulfonyl $\beta^{2,3}$-Amino Esters

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SUPPORTING INFORMATION

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General

All reactions were carried out under argon atmosphere. Reagents and solvents were obtained from commercial suppliers and used without further purification. All reactions were monitored by gas chromatography (GC) using a 5 m BP1 column. Melting points (mp) were determined on a capillary melting apparatus and are uncorrected. Infrared spectra were recorded on a FT-IR spectrometer in ATR mode. NMR spectra were recorded in $CDCl_3$ at 400 MHz (^1H), 100 MHz (^{13}C) and 376 MHz (^{19}F). Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent signal. Coupling constant values (J) are given in Hertz (Hz) and refer to apparent multiplicities, indicated as follows: s (singlet); d (doublet); t (triplet); q (quadruplet); m (multiplet); dd (doublet of doublets), td (triplet of doublets). Flash chromatography was performed on silica gel (40 μm-centered particles). HRMS experiments were realized by an outside facility. Yields given below for β-amino esters **4** refer to mixtures of diastereoisomers. As far as possible, the NMR spectra of separated diastereoisomers are appended below, for more clarity. Unless otherwise stated, melting points are given for separated diastereoisomers. To the best of our knowledge, all β-amino esters **4** are new compounds.

Typical procedure for the synthesis of imines 1

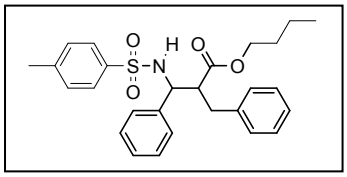
Imines **1** were synthesized in 78-91% yield according to a procedure derived from that of Lu and Kwon (*Org. Synth*. **2009**, *86*, 212). In a typical procedure, methanesulfonamide (4.75 g, 50 mmol), benzaldehyde (7 mL, 70 mmol) and aluminum chloride (1.33 g, 10 mmol) were heated at reflux in toluene for 12 h using a Dean-Stark apparatus. Toluene was removed by evaporation then ethyl acetate (100 mL) was added to the remaining solid. The mixture was filtered and the solvent removed by evaporation. The solid was washed with a diethyl ether/pentane: 15/25 (2 × 40 mL) to afford the imine as off-white needles (8.40 g, 91%).

General procedure for the synthesis of β-amino esters 4a-t

A dried 50 mL round bottom flask surrounded by a reflux condenser was flushed with argon and charged with acetonitrile (10 mL). Dodecane (0.1 mL, internal standard), zinc dust (1.5 g, 23 mmol), organic bromide **3** (12 mmol), acrylate **2** (22.5 mmol), imine **1** (5 mmol), and cobalt bromide (300 mg, 1.35 mmol) were added under vigorous stirring (~500 rpm). Trifluoroacetic acid (0.1 mL, 1.3 mmol) was added to the mixture, which was stirred for 30 minutes at room temperature. The reaction mixture was poured into a sat. NH_4Cl solution (75 mL), extracted with ethyl acetate (2 × 50 mL). The organic fractions were dried over Na_2SO_4 and concentrated over silica gel. The crude reaction product was purified by flash column chromatography over silica gel using a petroleum ether 40-60°C / ethyl acetate mixture (4:1 to 0:1) as an eluent to afford the three-component coupling product **4** (in most cases, both diastereoisomers a and b were separated).

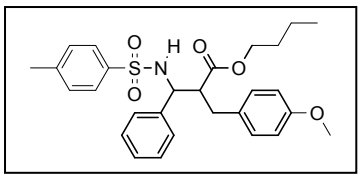
Characterization data

Butyl 2-benzyl-3-(4-methylphenylsulfonamido)-3-phenylpropanoate 4a



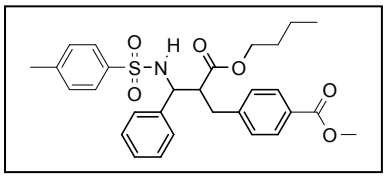
Prepared following the general procedure, using bromobenzene (1.25 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and *N*-benzylidene-4-methylbenzenesulfonamide (1.3 g, 5 mmol). Compound **4a** was obtained as a mixture of diastereoisomers; white solid (mp = 83-85°C); yield: 1.89 g (81%); **^{1}H NMR** ($CDCl_3$): δ 7.42 (dd, *J* = 14.5, 8.2 Hz, 2Ha+2Hb), 7.24 – 6.82 (m, 12Ha+12Hb), 6.21 (d, *J* = 9.3 Hz, 1Ha), 5.70 (d, *J* = 8.8 Hz, 1Hb), 4.56 (dd, *J* = 9.2, 4.5 Hz, 1Ha), 4.43 (t, *J* = 8.3 Hz, 1Hb), 3.71 (t, *J* = 6.5 Hz, 2Ha), 3.55 (td, *J* = 6.6, 2.3 Hz, 2Hb), 3.07 – 2.65 (m, 3Ha+3Hb), 2.25 (s, 3Hb), 2.22 (s, 3Ha), 1.23 – 1.12 (m, 2Ha), 1.12 – 1.03 (m, 2Hb), 0.97 – 0.80 (m, 2Ha+2Hb), 0.70 – 0.59 (m, 3Ha+3Hb); **^{13}C NMR** ($CDCl_3$): δ 173.85, 172.36, 143.13, 142.78, 138.90, 138.44, 138.09, 138.05, 137.96, 137.27, 129.33, 129.14, 128.90, 128.81, 128.52, 128.41, 128.32, 128.28, 127.74, 127.37, 127.15, 127.02, 126.90, 126.70, 126.43, 126.32, 64.67, 64.46, 59.41, 58.45, 54.16, 54.11, 36.49, 35.17, 30.20, 30.15, 21.44, 21.40, 18.76, 18.74, 13.53; **IR** (Neat): υ = 3279, 2956, 2932, 1718, 1709, 1329, 1159, 700, 664 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{27}H_{32}NO_4S$ $(M+H)^+$: 466.2047; found: 466.2047.

Butyl 2-(4-methoxybenzyl)-3-(4-methylphenylsulfonamido)-3-phenylpropanoate 4b



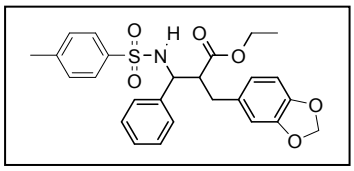
Prepared following the general procedure, using 4-bromoanisole (1.5 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and *N*-benzylidene-4-methylbenzenesulfonamide (1.3 g, 5 mmol). Compound **4b** was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 141-142°C); yield: 1.51 g (61%); **^{1}H NMR** ($CDCl_3$): δ 7.40 (d, *J* = 8.3 Hz, 2H), 7.08 – 6.90 (m, 7H), 6.85 (dd, *J* = 7.5, 1.9 Hz, 2H), 6.79 – 6.67 (m, 2H), 6.18 (d, *J* = 9.2 Hz, 1H), 4.55 (dd, *J* = 9.2, 4.2 Hz, 1H), 3.75 – 3.69 (m, 5H), 2.92 – 2.69 (m, 3H), 2.23 (s, 3H), 1.25 – 1.14 (m, 2H), 0.98 – 0.84 (m, 2H), 0.67 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** ($CDCl_3$): δ 173.99, 158.38, 142.75, 138.99, 138.09, 129.95, 129.91, 129.11, 128.27, 127.30, 126.88, 126.26, 113.91, 64.63, 58.14, 55.22, 54.29, 35.62, 30.23, 21.39, 18.75, 13.52; **IR** (Neat): υ = 3282, 2959, 2934, 1713, 1246, 1180, 1161, 1029, 817, 706, 665 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{28}H_{34}NO_5S$ $(M+H)^+$: 496.2152; found: 496.2151.

Methyl 4-(3-butoxy-2-((4-methylphenylsulfonamido)(phenyl)methyl)-3-oxopropyl)benzoate 4c



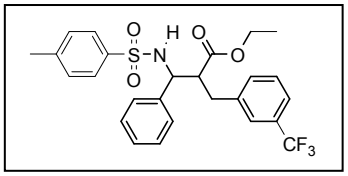
Prepared following the general procedure, using methyl 4-bromobenzoate (2.6 g, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and *N*-benzylidene-4-methylbenzenesulfonamide (1.3 g, 5 mmol). Compound **4c** was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 129-132°C); yield: 1.49 g (57%); **^{1}H NMR** ($CDCl_3$): δ 7.92 – 7.83 (m, 2H), 7.43 – 7.35 (m, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 7.07 – 6.91 (m, 5H), 6.85 (dd, *J* = 7.6, 1.9 Hz, 2H), 6.14 (d, *J* = 9.4 Hz, 1H), 4.56 (dd, *J* = 9.3, 4.6 Hz, 1H), 3.83 (s, 3H), 3.71 (t, *J* = 6.5 Hz, 2H), 3.09 – 2.78 (m, 3H), 2.23 (s, 3H), 1.24 – 1.11 (m, 2H), 0.96 – 0.79 (m, 2H), 0.65 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** ($CDCl_3$): δ 173.48, 166.94, 143.40, 142.88, 138.58, 137.92, 129.87, 129.15, 129.01, 128.70, 128.37, 127.48, 126.88, 126.26, 64.80, 58.40, 53.67, 52.08, 36.42, 30.18, 21.39, 18.72, 13.47; **IR** (Neat): υ = 3278, 2956, 2931, 1719, 1279, 1161, 704, 668 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{29}H_{34}NO_6S$ $(M+H)^+$: 524.2101; found: 524.2100.

Ethyl 2-(benzo[d][1,3]dioxol-5-ylmethyl)-3-(4-methylphenylsulfonamido)-3-phenylpropanoate 4d



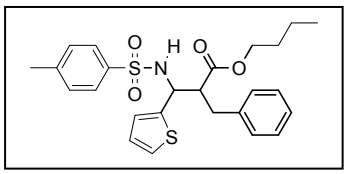
Prepared following the general procedure, using 1-bromo-3,4-(methylenedioxy)benzene (1.45 mL, 12 mmol), ethyl acrylate (2.5 mL, 22.5 mmol), and *N*-benzylidene-4-methylbenzenesulfonamide (1.3 g, 5 mmol). Compound **4d** was obtained as a mixture of diastereoisomers; off-white solid (mp = 122-124°C); yield: 1.59 g (66%); **^{1}H NMR** ($CDCl_3$): δ 7.53 (d, *J* = 8.3 Hz, 2Hb), 7.48 (d, *J* = 8.3 Hz, 2Ha), 7.20 – 6.90 (m, 7Ha+7Hb), 6.77 – 6.47 (m, 3Ha+3Hb), 6.24 (d, *J* = 9.3 Hz, 1Ha), 5.93 (s, 2Ha), 5.91 (s, 2Hb), 5.66 (d, *J* = 8.9 Hz, 1Hb), 4.62 (dd, *J* = 9.3, 4.7 Hz, 1Ha), 4.53 – 4.45 (m, 1Hb), 3.96 – 3.85 (m, 2Ha), 3.76 (q, *J* = 7.1 Hz, 2Hb), 3.02 – 2.69 (m, 3Ha+3Hb), 2.35 (s, 3Hb), 2.31 (s, 3Ha), 0.98 (t, *J* = 7.1 Hz, 3Ha), 0.87 (t, *J* = 7.1 Hz, 3Hb); **^{13}C NMR** ($CDCl_3$): δ 173.66, 172.12, 147.66, 147.57, 146.30, 146.10, 143.21, 142.80, 138.85, 138.00, 137.22, 132.12, 131.63, 129.36, 129.13, 128.31, 128.30, 127.80, 127.38, 127.14, 126.98, 126.89, 126.33, 122.04, 121.83, 109.22, 109.20, 108.26, 108.19, 100.91, 100.84, 60.85, 60.65, 59.23, 58.22, 54.31, 36.08, 34.67, 21.44, 21.39, 13.89, 13.76; **IR** (Neat): υ = 3263, 3208, 2903, 1733, 1708, 1505, 1250, 1159, 1039, 813, 665 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{26}H_{28}NO_6S$ $(M+H)^+$: 482.1632; found: 482.1629.

Ethyl 3-(4-methylphenylsulfonamido)-3-phenyl-2-(3-(trifluoromethyl)benzyl)propanoate 4e



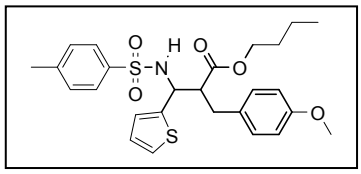
Prepared following the general procedure, using 3-bromobenzotrifluoride (1.65 mL, 12 mmol), ethyl acrylate (2.5 mL, 22.5 mmol), and *N*-benzylidene-4-methylbenzenesulfonamide (1.3 g, 5 mmol). Compound **4e** was obtained as a mixture of diastereoisomers; white solid (mp = 126-128°C); yield: 1.34 g (66%); **^{1}H NMR** ($CDCl_3$): δ 7.46 – 7.20 (m, 6Ha+6Hb), 7.15 – 6.78 (m, 7Ha+7Hb), 6.11 (d, *J* = 9.3 Hz, 1Ha), 5.48 (d, *J* = 8.9 Hz, 1Hb), 4.57 (dd, *J* = 9.4, 4.9 Hz, 1Ha), 4.50 – 4.38 (m, 1Hb), 3.86 – 3.73 (m, 2Ha), 3.63 (q, *J* = 7.1 Hz, 2Hb), 3.19 – 2.76 (m, 3Ha+3Hb), 2.27 (s, 3Hb), 2.23 (s, 3Ha), 0.83 (t, *J* = 7.1 Hz, 3Ha), 0.72 (t, *J* = 7.1 Hz, 3Hb); **^{13}C NMR** ($CDCl_3$): δ 173.27, 171.81, 143.35, 142.93, 139.50, 138.95, 138.46, 137.84, 137.80, 137.11, 132.56, 132.32, 130.98, 130.66, 129.38, 129.17, 128.99, 128.87, 128.82, 128.42, 127.96, 127.57, 127.14, 126.88, 126.31, 125.59, 125.55, 125.51, 125.47, 123.66, 123.62, 122.70, 60.98, 60.74, 59.49, 58.56, 57.54, 54.01, 53.71, 36.18, 35.03, 33.59, 29.06, 26.92, 21.43, 21.39, 13.83, 13.72, 13.59 (C-F coupling constants are not indicated; most intense peaks are reported); **^{19}F NMR** ($CDCl_3$): δ -62.63, -62.64; **IR** (Neat): υ = 3209, 2990, 1711, 1327, 1157, 1116, 702 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{26}H_{27}F_3NO_4S$ $(M+H)^+$: 506.1607; found: 506.1608.

Butyl 2-benzyl-3-(4-methylphenylsulfonamido)-3-(thiophen-2-yl)propanoate 4f



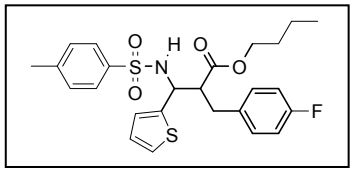
Prepared following the general procedure, using bromobenzene (1.25 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and 4-methyl-*N*-(thiophen-2-ylmethylene)benzenesulfonamide (1.32 g, 5 mmol). Compound **4f** was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 147-149°C); yield: 1.30 g (55%); **^{1}H NMR** ($CDCl_3$): δ 7.49 (d, *J* = 8.3 Hz, 2H), 7.28 – 7.00 (m, 7H), 6.96 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.64 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.57 (d, *J* = 3.4 Hz, 1H), 6.10 (d, *J* = 9.3 Hz, 1H), 4.86 (dd, *J* = 9.3, 4.3 Hz, 1H), 3.79 (t, *J* = 6.6 Hz, 2H), 3.06 – 2.76 (m, 3H), 2.27 (s, 3H), 1.32 – 1.19 (m, 2H), 1.08 – 0.92 (m, 2H), 0.71 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$): δ 173.83, 143.06, 142.92, 138.12, 137.79, 129.23, 128.93, 128.56, 126.89, 126.77, 126.45, 125.36, 124.88, 64.88, 54.49, 54.16, 36.36, 30.24, 21.47, 18.81, 13.56; **IR** (Neat): υ = 3252, 2956, 2930, 1712, 1452, 1327, 1160, 700, 669 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{25}H_{30}NO_4S_2$ $(M+H)^+$: 472.1611; found: 472.1605.

Butyl 2-(4-methoxybenzyl)-3-(4-methylphenylsulfonamido)-3-(thiophen-2-yl)propanoate 4g



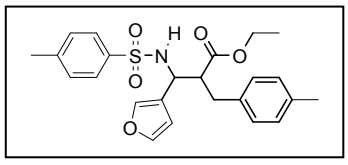
Prepared following the general procedure, using 4-bromoanisole (1.5 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and 4-methyl-*N*-(thiophen-2-ylmethylene)benzenesulfonamide (1.32 g, 5 mmol). Compound **4g** was obtained as a mixture of diastereoisomers that could be partially separated; off-white solid (mp = 93-96°C); yield: 1.41 g (56%); **^{1}H NMR** ($CDCl_3$): δ 7.45 (d, *J* = 8.2 Hz, 2H), 7.13 – 6.83 (m, 5H), 6.82 – 6.50 (m, 4H), 5.63 (d, *J* = 9.2 Hz, 1H), 4.72 (dd, *J* = 9.0, 6.8 Hz, 1H), 3.85 – 3.60 (m, 5H), 3.04 – 2.68 (m, 3H), 2.29 (s, 3H), 1.37 – 1.20 (m, 2H), 1.16 – 0.96 (m, 2H), 0.73 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$): δ 172.42, 158.28, 143.20, 141.08, 137.39, 129.86, 129.41, 127.06, 126.46, 126.37, 126.35, 125.38, 113.91, 64.89, 55.24, 54.38, 53.99, 34.12, 30.30, 21.50, 18.95, 13.61; **IR** (Neat): υ = 3235, 2954, 1729, 1512, 1249, 1157, 1034, 719, 668 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{26}H_{32}NO_5S_2$ $(M+H)^+$: 502.1716; found: 502.1712.

Butyl 2-(4-fluorobenzyl)-3-(4-methylphenylsulfonamido)-3-(thiophen-2-yl)propanoate 4h



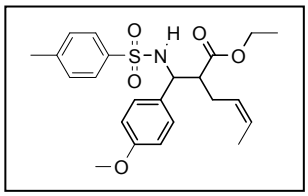
Prepared following the general procedure, using 1-bromo-4-fluorobenzene (1.3 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and 4-methyl-*N*-(thiophen-2-ylmethylene)benzenesulfonamide (1.32 g, 5 mmol). Compound **4h** was obtained as a mixture of diastereoisomers that could be partially separated; off-white solid (mp = 98-101°C); yield: 1.52 g (62%); **^{1}H NMR** ($CDCl_3$): δ 7.48 (d, *J* = 8.3 Hz, 2H), 7.16 – 6.83 (m, 7H), 6.68 – 6.50 (m, 2H), 6.08 (d, *J* = 9.4 Hz, 1H), 4.84 (dd, *J* = 9.4, 4.1 Hz, 1H), 3.80 (t, *J* = 6.6 Hz, 2H), 3.03 – 2.76 (m, 3H), 2.27 (s, 3H), 1.34 – 1.21 (m, 2H), 1.07 – 0.93 (m, 2H), 0.72 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$): δ 172.62, 160.77 (d, $^{1}J_{C\text{-}F}$ = 243.3 Hz), 141.94, 141.76, 137.00, 132.44 (d, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 129.45 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz), 128.20, 125.84, 125.43, 124.37, 123.91, 114.35 (d, $^{2}J_{C\text{-}F}$ = 21.2 Hz), 63.91, 53.33, 53.27, 34.46, 29.23, 20.43, 17.79, 12.50; **^{19}F NMR** ($CDCl_3$): δ -116.37; **IR** (Neat): υ = 3257, 2960, 1709, 1509, 1327, 1221, 1157, 706, 664 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{25}H_{29}FNO_4S_2$ $(M+H)^+$: 490.1517; found: 490.1515.

Ethyl 3-(furan-3-yl)-2-(4-methylbenzyl)-3-(4-methylphenylsulfonamido)propanoate 4i



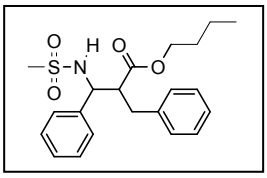
Prepared following the general procedure, using 4-bromotoluene (2.05 g, 12 mmol), ethyl acrylate (2.5 mL, 22.5 mmol), and *N*-(furan-3-ylmethylene)-4-methylbenzenesulfonamide (1.25 g, 5 mmol). Compound **4i** was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 121-123°C); yield: 1.15 g (52%); **^{1}H NMR** ($CDCl_3$): δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.15 – 7.07 (m, 3H), 7.02 – 6.93 (m, 3H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.05 – 5.96 (m, 1H), 5.58 (d, *J* = 9.3 Hz, 1H), 4.40 (dd, *J* = 9.3, 5.8 Hz, 1H), 3.86 (q, *J* = 7.2 Hz, 2H), 2.97 – 2.64 (m, 3H), 2.32 (s, 3H), 2.24 (s, 3H), 0.96 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$): δ 172.61, 143.32, 143.18, 140.29, 137.51, 136.03, 135.06, 129.45, 129.17, 128.68, 127.10, 122.71, 108.84, 60.87, 52.55, 50.78, 34.38, 21.51, 21.04, 13.87; **IR** (Neat): υ = 3304, 2929, 1721, 1331, 1156, 1038, 812, 664 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{24}H_{28}NO_5S$ $(M+H)^+$: 442.1683; found: 442.1682.

(*Z*)-Ethyl 2-((4-methoxyphenyl)(4-methylphenylsulfonamido)methyl)hex-4-enoate 4j



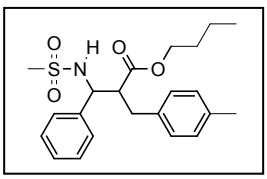
Prepared following the general procedure, using *cis*-1-bromo-1-propene (1.0 mL, 12 mmol), ethyl acrylate (2.5 mL, 22.5 mmol), and *N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide (1.45 g, 5 mmol). Compound **4j** was obtained as a mixture of diastereoisomers that could be partially separated; pale yellow solid (mp = 80-83°C); yield: 1.08 g (50%); **^{1}H NMR** ($CDCl_3$): δ 7.39 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 8.1 Hz, 2H), 6.86 – 6.78 (m, 2H), 6.59 – 6.51 (m, 2H), 6.01 (d, *J* = 9.1 Hz, 1H), 5.51 – 5.38 (m, 1H), 5.26 – 5.15 (m, 1H), 4.49 (dd, *J* = 9.0, 6.2 Hz, 1H), 3.99 – 3.88 (m, 2H), 3.65 (s, 3H), 2.65 – 2.52 (m, 1H), 2.38 – 2.28 (m, 1H), 2.24 (s, 3H), 2.11 – 1.99 (m, 1H), 1.50 – 1.43 (m, 3H), 1.04 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$): δ 174.02, 158.85, 142.60, 138.14, 131.07, 129.08, 127.66, 127.09, 126.91, 125.63, 113.65, 60.87, 58.23, 55.23, 52.15, 27.73, 21.37, 14.07, 12.84; **IR** (Neat): υ = 3246, 2962, 1728, 1515, 1156, 1031, 668 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{23}H_{30}NO_5S$ $(M+H)^+$: 432.1839; found: 432.1839.

Butyl 2-benzyl-3-(methylsulfonamido)-3-phenylpropanoate 4k



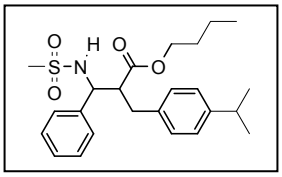
Prepared following the general procedure, using bromobenzene (1.25 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and *N*-benzylidenemethanesulfonamide (0.92 g, 5 mmol). Compound **4k** was obtained as a mixture of diastereoisomers; off-white solid (mp = 105-108°C); yield: 1.37 g (70%); **^{1}H NMR** ($CDCl_3$): δ 7.38 – 6.97 (m, 10Ha+10Hb), 6.17 (d, *J* = 9.3 Hz, 1Ha), 5.58 (d, *J* = 9.1 Hz, 1Hb), 4.74 – 4.51 (m, 1Ha+1Hb), 3.81 (t, *J* = 6.1 Hz, 2Ha), 3.66 (t, *J* = 6.6 Hz, 2Hb), 3.16 – 2.80 (m, 3Ha+3Hb), 2.54 (s, 3Hb), 2.50 (s, 3Ha), 1.33 – 1.19 (m, 2Ha), 1.19 – 1.04 (m, 2Hb), 1.03 – 0.88 (m, 2Ha+2Hb), 0.75 – 0.60 (m, 3Ha+3Hb); **^{13}C NMR** ($CDCl_3$): δ 173.97, 172.24, 139.61, 138.68, 138.28, 137.81, 129.02, 128.94, 128.91, 128.82, 128.56, 128.53, 128.49, 128.25, 127.22, 126.79, 126.56, 126.46, 64.80, 64.59, 59.54, 58.42, 54.30, 54.00, 42.08, 41.78, 36.73, 35.44, 30.25, 30.21, 18.80, 18.77, 13.55; **IR** (Neat): υ = 3296, 3264, 2957, 1726, 1706, 1319, 1156, 752, 701 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{21}H_{28}NO_4S$ $(M+H)^+$: 390.1733; found: 390.1734.

Butyl 2-(4-methylbenzyl)-3-(methylsulfonamido)-3-phenylpropanoate 4l



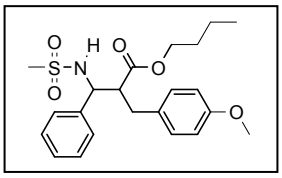
Prepared following the general procedure, using 4-bromotoluene (2.05 g, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and *N*-benzylidenemethanesulfonamide (0.92 g, 5 mmol). Compound **4l** was obtained as a mixture of diastereoisomers; white solid (mp = 99-102°C); yield: 1.33 g (66%); **^{1}H NMR** ($CDCl_3$): δ 7.33 – 7.14 (m, 5Ha+5Hb), 7.06 – 6.89 (m, 4Ha+4Hb), 6.21 (d, *J* = 9.4 Hz, 1Ha), 5.76 (d, *J* = 9.2 Hz, 1Hb), 4.67 – 4.57 (m, 1Ha+1Hb), 3.89 – 3.75 (m, 1Ha), 3.64 (t, *J* = 6.6 Hz, 1Hb), 3.09 – 2.73 (m, 3Ha+3Hb), 2.52 (s, 3Hb), 2.48 (s, 3Ha), 2.22 (s, 3Hb), 2.20 (s, 3Ha), 1.31 – 1.21 (m, 2Ha), 1.20 – 1.08 (m, 2Hb), 1.03 – 0.82 (m, 2Ha+2Hb), 0.74 – 0.60 (m, 3Ha+3Hb); **^{13}C NMR** ($CDCl_3$): δ 174.00, 172.31, 139.67, 138.85, 136.26, 135.97, 135.19, 134.69, 129.23, 129.15, 129.01, 128.89, 128.77, 128.69, 128.44, 128.22, 127.27, 126.52, 64.78, 64.50, 59.59, 58.48, 54.46, 54.17, 42.03, 41.75, 36.25, 35.11, 30.31, 30.24, 21.05, 21.02, 18.82, 18.80, 13.57; **IR** (Neat): υ = 3298, 3267, 2957, 1727, 1705, 1320, 1154, 765, 701 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{22}H_{30}NO_4S$ $(M+H)^+$: 404.1890; found: 404.1890.

Butyl 2-(4-isopropylbenzyl)-3-(methylsulfonamido)-3-phenylpropanoate 4m



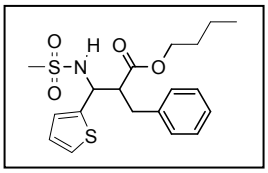
Prepared following the general procedure, using 1-bromo-4-isopropylbenzene (1.85 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and *N*-benzylidenemethanesulfonamide (0.92 g, 5 mmol). Compound **4m** was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 121-124°C); yield: 1.41 g (65%); **^{1}H NMR** ($CDCl_3$): δ 7.36 – 7.13 (m, 5H), 7.12 – 6.98 (m, 4H), 6.14 (d, *J* = 9.2 Hz, 1H), 4.63 (dd, *J* = 9.3, 4.8 Hz, 1H), 3.87 – 3.71 (m, 2H), 3.03 – 2.73 (m, 4H), 2.55 (s, 3H), 1.27 – 1.18 (m, 2H), 1.16 (s, *J* = 6.9 Hz, 6H), 1.01 – 0.89 (m, 2H), 0.69 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** ($CDCl_3$): δ 174.12, 147.32, 139.75, 135.07, 128.96, 128.81, 128.18, 126.58, 126.42, 64.72, 58.32, 53.92, 42.11, 36.37, 33.71, 30.22, 24.01, 23.99, 18.75, 13.54; **IR** (Neat): υ = 3279, 2959, 1716, 1324, 1152, 768, 709 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{24}H_{34}NO_4S$ $(M+H)^+$: 432.2203; found: 432.2218.

Butyl 2-(4-methoxybenzyl)-3-(methylsulfonamido)-3-phenylpropanoate 4n



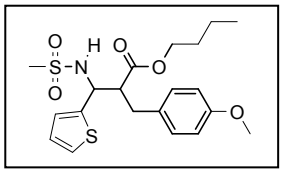
Prepared following the general procedure, using 4-bromoanisole (1.5 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and *N*-benzylidenemethanesulfonamide (0.92 g, 5 mmol). Compound **4n** was obtained as a mixture of diastereoisomers that could be partially separated; off-white solid (mp = 97-100°C); yield: 1.35 g (64%); **^{1}H NMR** ($CDCl_3$): δ 7.35 – 7.11 (m, 5H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.6 Hz, 2H), 6.14 (d, *J* = 9.2 Hz, 1H), 4.59 (dd, *J* = 9.2, 4.3 Hz, 1H), 3.80 (t, *J* = 6.5 Hz, 2H), 3.70 (s, 3H), 3.04 – 2.76 (m, 3H), 2.53 (s, 3H), 1.31 – 1.17 (m, 2H), 1.06 – 0.91 (m, 2H), 0.70 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** ($CDCl_3$): δ 174.10, 158.44, 139.74, 129.98, 129.76, 128.97, 128.18, 126.38, 113.94, 64.75, 58.05, 55.21, 54.12, 42.13, 35.87, 30.28, 18.78, 13.54; **IR** (Neat): υ = 3272, 2958, 1727, 1513, 1315, 1244, 1154, 752, 706 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{22}H_{30}NO_5S$ $(M+H)^+$: 420.1839; found: 420.1837.

Butyl 2-benzyl-3-(methylsulfonamido)-3-(thiophen-2-yl)propanoate 4o



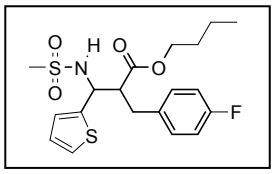
Prepared following the general procedure, using bromobenzene (1.25 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and *N*-(thiophen-2-ylmethylene)methanesulfonamide (0.95 g, 5 mmol). Compound **4o** was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 131-134°C); yield: 1.25 g (63%); **^{1}H NMR** ($CDCl_3$): δ 7.31 – 7.05 (m, 6H), 6.89 (dt, *J* = 4.9, 3.2 Hz, 2H), 6.06 (d, *J* = 9.3 Hz, 1H), 4.90 (dd, *J* = 9.3, 4.3 Hz, 1H), 3.88 (t, *J* = 6.6 Hz, 2H), 3.10 – 2.85 (m, 3H), 2.63 (s, 3H), 1.39 – 1.22 (m, 2H), 1.04 (dd, *J* = 15.1, 7.4 Hz, 2H), 0.83 – 0.66 (m, 3H); **^{13}C NMR** ($CDCl_3$): δ 174.01, 143.54, 137.60, 128.97, 128.60, 127.05, 126.87, 125.81, 125.50, 65.04, 54.35, 54.02, 41.99, 36.63, 30.28, 18.84, 13.58; **IR** (Neat): υ = 3249, 2955, 1712, 1322, 1149, 770, 700 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{19}H_{25}NNaO_4S_2$ $(M+Na)^+$: 418.1117; found: 418.1115.

Butyl 2-(4-methoxybenzyl)-3-(methylsulfonamido)-3-(thiophen-2-yl)propanoate 4p



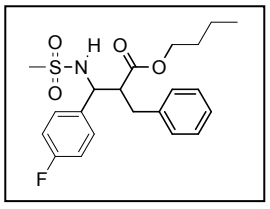
Prepared following the general procedure, using 4-bromoanisole (1.5 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and *N*-(thiophen-2-ylmethylene)methanesulfonamide (0.95 g, 5 mmol). Compound **4p** was obtained as a mixture of diastereoisomers that could be partially separated; pale yellow solid (mp = 119-121°C); yield: 1.11 g (52%); **^{1}H NMR** ($CDCl_3$): δ = 7.23 – 7.13 (m, 1H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.95 – 6.83 (m, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 6.07 (d, *J* = 9.3 Hz, 1H), 4.87 (dd, *J* = 9.3, 4.1 Hz, 1H), 3.90 (t, *J* = 6.6 Hz, 2H), 3.71 (s, 3H), 3.05 – 2.82 (m, 3H), 2.62 (s, 3H), 1.42 – 1.27 (m, 2H), 1.13 – 0.99 (m, 2H), 0.75 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$): δ 174.11, 158.50, 143.61, 130.00, 129.55, 127.02, 125.79, 125.47, 113.98, 65.02, 55.22, 54.25, 54.15, 41.97, 35.72, 30.33, 18.87, 13.58; **IR** (Neat): υ = 3251, 2954, 1711, 1513, 1320, 1247, 1151, 1038, 769, 707 cm^{-1}; **HRMS** (ESI$^+$) m/z calcd. for $C_{20}H_{27}NNaO_5S_2$ $(M+Na)^+$: 448.1223; found: 448.1221.

Butyl 2-(4-fluorobenzyl)-3-(methylsulfonamido)-3-(thiophen-2-yl)propanoate 4q



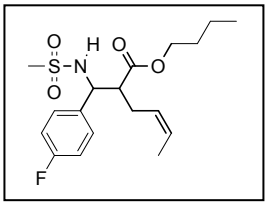
Prepared following the general procedure, using 1-bromo-4-fluorobenzene (1.3 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and *N*-(thiophen-2-ylmethylene)methanesulfonamide (0.95 g, 5 mmol). Compound **4q** was obtained as a mixture of diastereoisomers that could be partially separated; pale yellow solid (mp = 78-80°C); yield: 1.24 g (60%); **^{1}H NMR** ($CDCl_3$): δ 7.36 – 7.23 (m, 1H), 7.20 – 7.06 (m, 2H), 7.07 – 6.88 (m, 4H), 5.64 (d, *J* = 9.4 Hz, 1H), 4.98 (dd, *J* = 9.4, 7.2 Hz, 1H), 3.93 (t, *J* = 6.6 Hz, 2H), 3.29 – 3.14 (m, 1H), 3.11 – 2.88 (m, 2H), 2.67 (s, 3H), 1.48 – 1.33 (m, 2H), 1.21 – 1.08 (m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$): δ 172.18, 161.70 (d, $^{1}J_{C\text{-}F}$ = 243.1 Hz), 141.50, 133.66 (d, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 130.37 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz), 126.96, 126.94, 126.08, 115.35 (d, $^{2}J_{C\text{-}F}$ = 21.1 Hz), 65.04, 54.76, 54.20, 41.62, 34.49, 30.30, 18.91, 13.57; **^{19}F NMR** ($CDCl_3$): δ -116.19; **IR** (Neat): υ = 3269, 2961, 1725, 1510, 1322, 1221, 1152, 731, 704 cm^{-1}; **HRMS** (ESI$^+$) m/z calcd. for $C_{19}H_{24}FNNaO_4S_2$ $(M+Na)^+$: 436.1023; found: 436.1021.

Butyl 2-benzyl-3-(4-fluorophenyl)-3-(methylsulfonamido)propanoate 4r



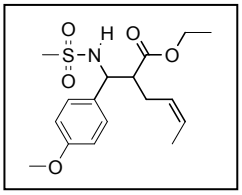
Prepared following the general procedure, using bromobenzene (1.25 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and *N*-(4-fluorobenzylidene)methanesulfonamide (1.0 g, 5 mmol). Compound **4r** was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 135-137°C); yield: 1.12 g (55%); **^{1}H NMR** ($CDCl_3$): δ 7.31 – 6.88 (m, 9H), 5.83 (d, *J* = 8.8 Hz, 1H), 4.64 (t, *J* = 8.2 Hz, 1H), 3.65 (t, *J* = 6.6 Hz, 2H), 3.11 – 2.97 (m, 2H), 2.95 – 2.87 (m, 1H), 2.53 (s, 3H), 1.22 – 1.10 (m, 2H), 1.00 – 0.89 (m, 2H), 0.68 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** ($CDCl_3$): δ 172.21, 161.49 (d, $^{1}J_{C\text{-}F}$ = 246.3 Hz), 138.06, 134.82 (d, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 129.08 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz), 128.78, 128.51, 126.63, 115.86 (d, $^{2}J_{C\text{-}F}$ = 21.4 Hz), 64.62, 58.90, 54.40, 41.85, 35.61, 30.21, 18.78, 13.50; **^{19}F NMR** ($CDCl_3$): δ -116.15; **IR** (Neat): υ = 3252, 2959, 1712, 1511, 1328, 1217, 1159, 707, 668 cm^{-1}; **HRMS** (ESI$^+$) m/z calcd. for $C_{21}H_{26}FNNaO_4S$ $(M+Na)^+$: 430.1464; found: 430.1461.

(*Z*)-Butyl 2-((4-fluorophenyl)(methylsulfonamido)methyl)hex-4-enoate 4s



Prepared following the general procedure, using *cis*-1-bromo-1-propene (1.0 mL, 12 mmol), butyl acrylate (3.2 mL, 22.5 mmol), and *N*-(4-fluorobenzylidene)methanesulfonamide (1.0 g, 5 mmol). Compound **4s** was obtained as a mixture of diastereoisomers that could be partially separated; white solid (mp = 58-60°C); yield: 1.04 g (56%); **^{1}H NMR** ($CDCl_3$): δ 7.32 – 7.13 (m, 2H), 6.97 (t, *J* = 8.6 Hz, 2H), 5.75 (d, *J* = 9.0 Hz, 1H), 5.59 – 5.41 (m, 1H), 5.36 – 5.16 (m, 1H), 4.61 (t, *J* = 8.7 Hz, 1H), 3.82 (t, *J* = 6.5 Hz, 2H), 2.87 – 2.69 (m, 1H), 2.51 (s, 3H), 2.48 – 2.30 (m, 2H), 1.50 (d, *J* = 6.6 Hz, 3H), 1.40 – 1.26 (m, 2H), 1.18 – 1.05 (m, 2H), 0.77 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$): δ 172.44, 162.49 (d, $^{1}J_{C\text{-}F}$ = 246.1 Hz), 134.82 (d, $^{4}J_{C\text{-}F}$ = 3.3 Hz), 129.08 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz), 127.13, 125.83, 115.79 (d, $^{2}J_{C\text{-}F}$ = 21.5 Hz), 64.75, 58.42, 52.23, 41.83, 30.38, 26.80, 18.95, 13.56, 12.93; **^{19}F NMR** ($CDCl_3$): δ -113.15; **IR** (Neat): υ = 3277, 2961, 1722, 1510, 1318, 1226, 1151, 731 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{18}H_{27}FNO_4S$ $(M+H)^+$: 372.1639; found: 372.1638.

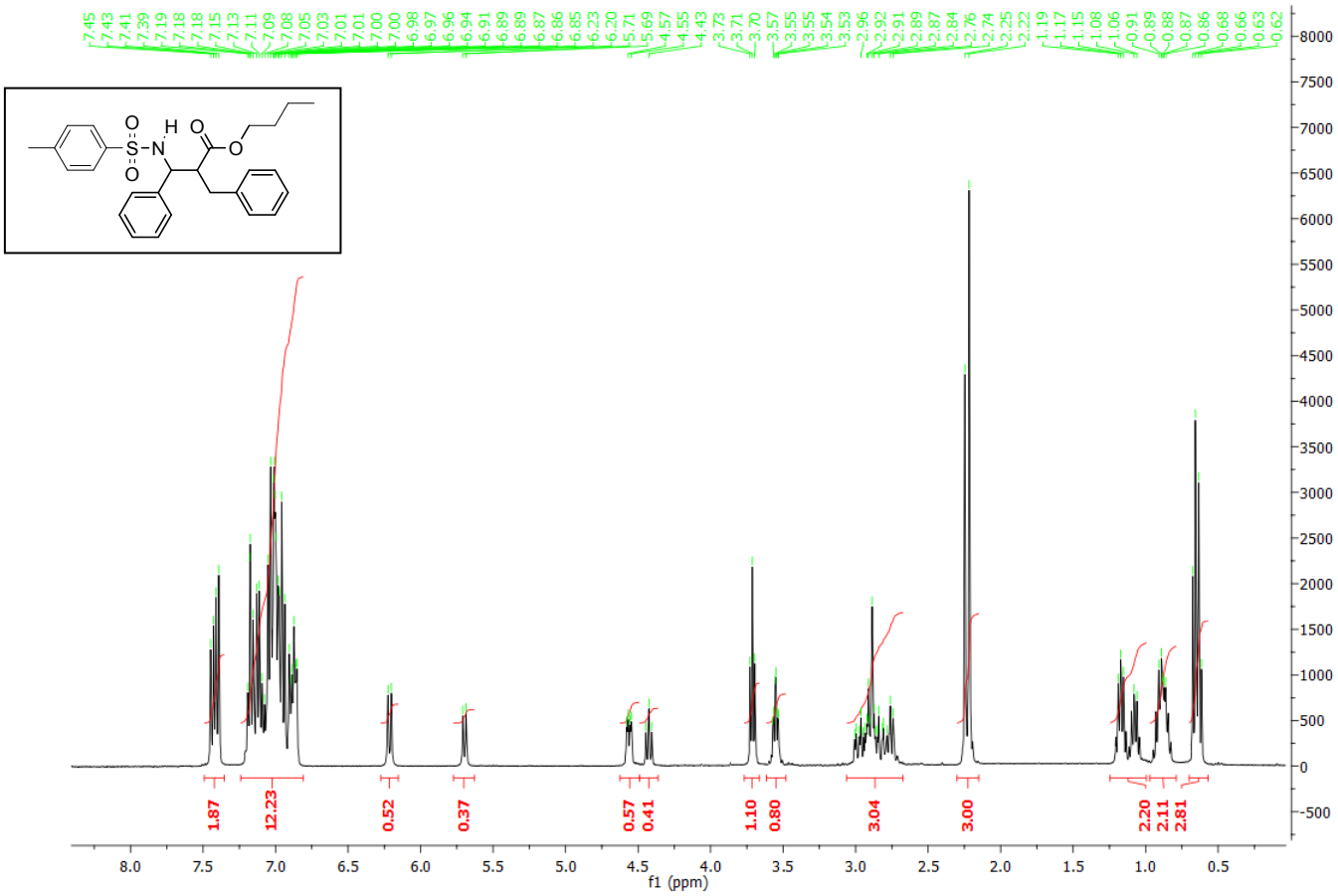
(*Z*)-Ethyl 2-((4-methoxyphenyl)(methylsulfonamido)methyl)hex-4-enoate 4t

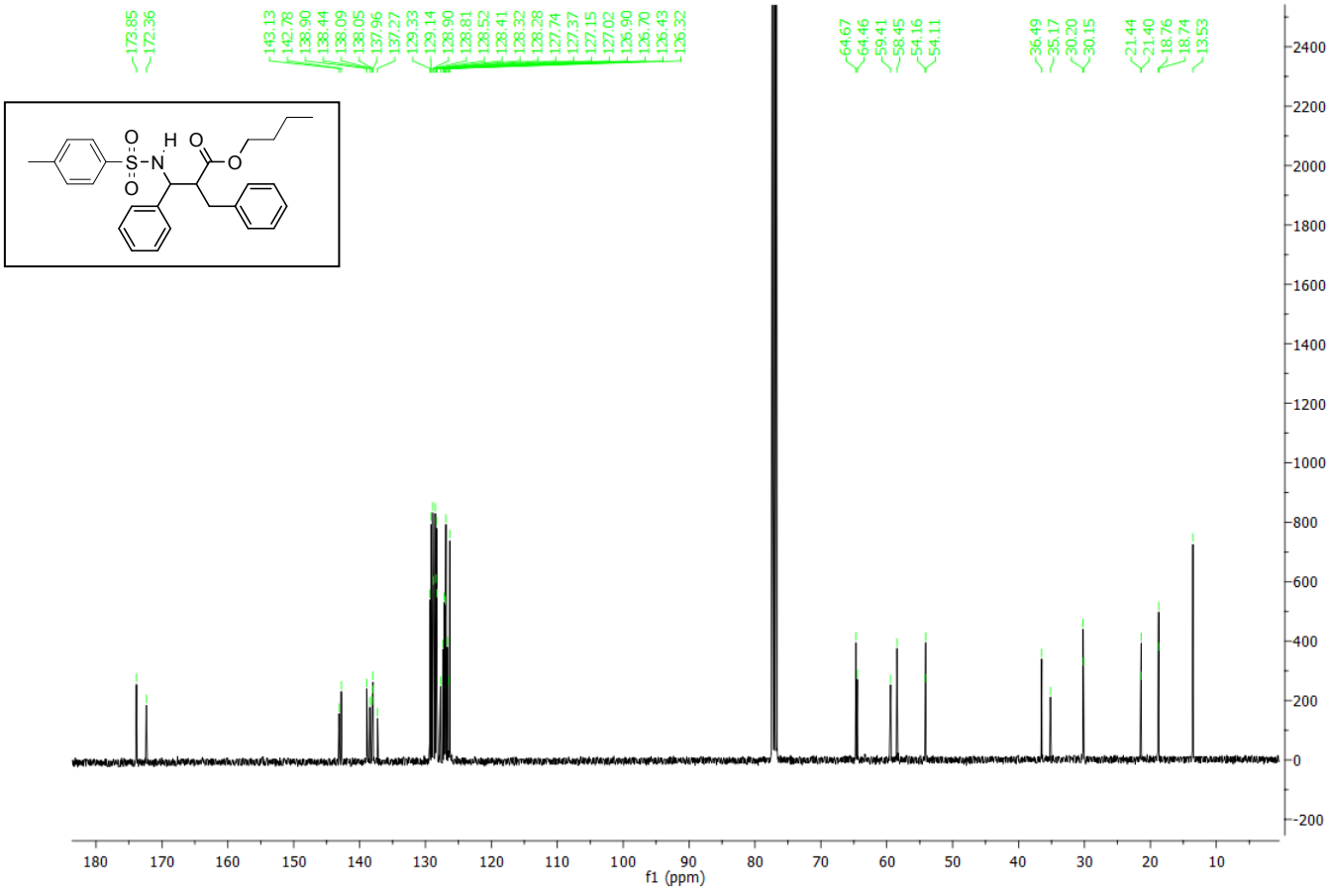


Prepared following the general procedure, using *cis*-1-bromo-1-propene (1.0 mL, 12 mmol), ethyl acrylate (2.5 mL, 22.5 mmol), and *N*-(4-methoxybenzylidene)methanesulfonamide (1.05 g, 5 mmol). Compound **4t** was obtained as a mixture of diastereoisomers; Thick pale yellow oil; yield: 0.96 g (54%); **^{1}H NMR** ($CDCl_3$): δ 7.14 (d, *J* = 8.7 Hz, 2Ha+2Hb), 6.80 (d, *J* = 8.6 Hz, 2Ha+2Hb), 5.92 (d, *J* = 9.2 Hz, 1Ha), 5.58 – 5.39 (m, 1Ha+2Hb), 5.36 – 5.17 (m, 1Ha+1Hb), 4.63 – 4.49 (m, 1Ha+1Hb), 4.13 – 3.96 (m, 2Ha), 3.90 (q, *J* = 7.1 Hz, 2Hb), 3.73 (s, 3Ha), 3.72 (s, 3Hb), 2.82 – 2.72 (m, 1Hb), 2.69 – 2.59 (m, 1Ha), 2.50 (s, 3Ha), 2.48 (s, 3Hb), 2.45 – 2.36 (m, 2Hb+Ha), 2.24 – 2.08 (m, 1Ha), 1.59 – 1.41 (m, 3Ha+3Hb), 1.12 (t, *J* = 7.1 Hz, 3Ha), 1.01 (t, *J* = 7.1 Hz, 3Hb); **^{13}C NMR** ($CDCl_3$): δ 174.09, 172.39, 159.48, 159.38, 131.61, 130.72, 128.50, 127.87, 127.26, 126.93, 126.12, 125.48, 114.31, 114.14, 61.02, 60.75, 58.62, 58.22, 55.28, 55.26, 52.26, 52.14, 41.95, 41.79, 27.82, 26.80, 14.13, 14.00, 12.94, 12.87; **IR** (Neat): υ = 3273, 2980, 1729, 1514, 1317, 1248, 1150, 1031, 834, 756 cm^{-1}; **HRMS** (ESI^+) m/z calcd. for $C_{17}H_{25}NNaO_5S$ $(M+Na)^+$: 378.1346; found: 378.1345.

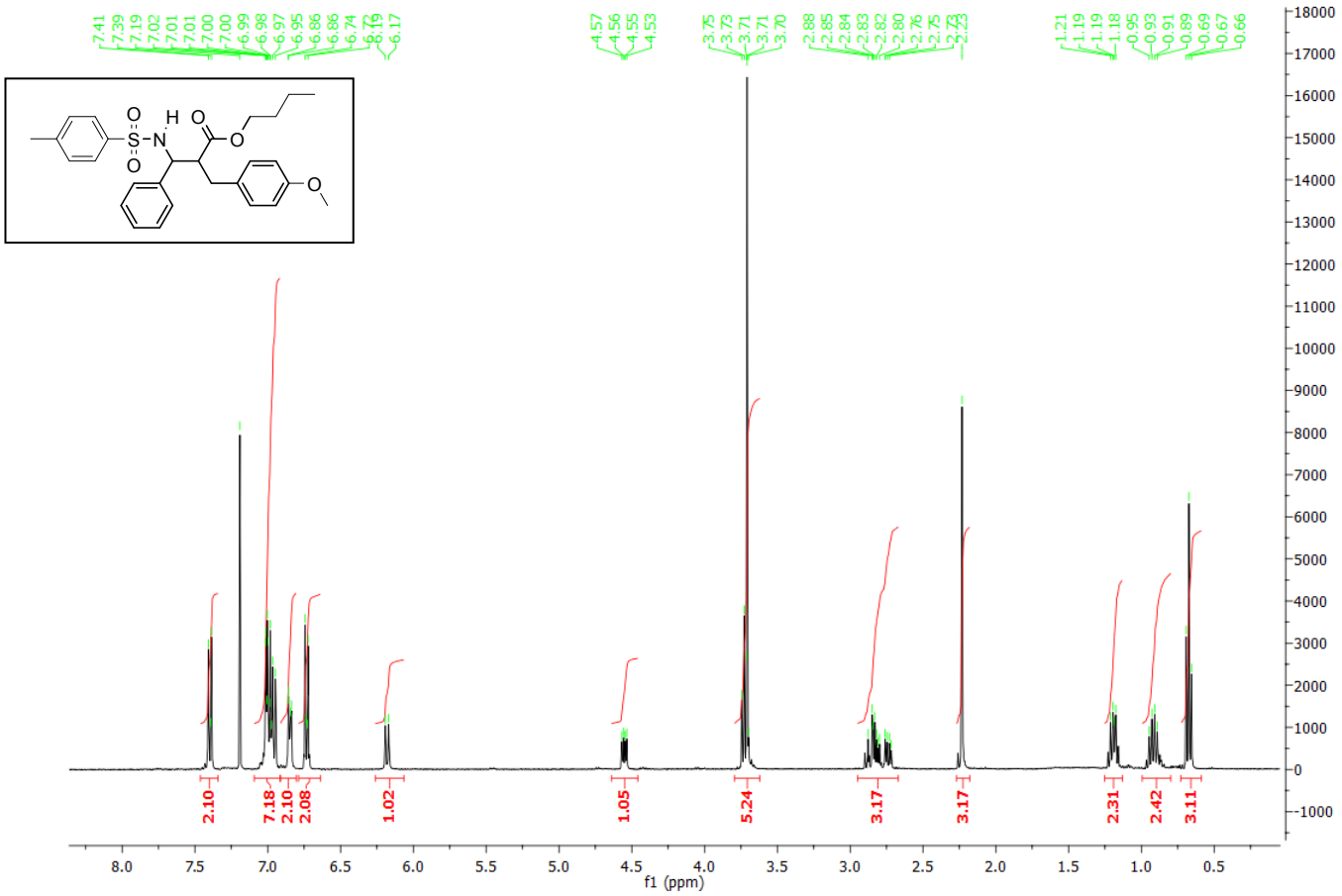
NMR Spectra

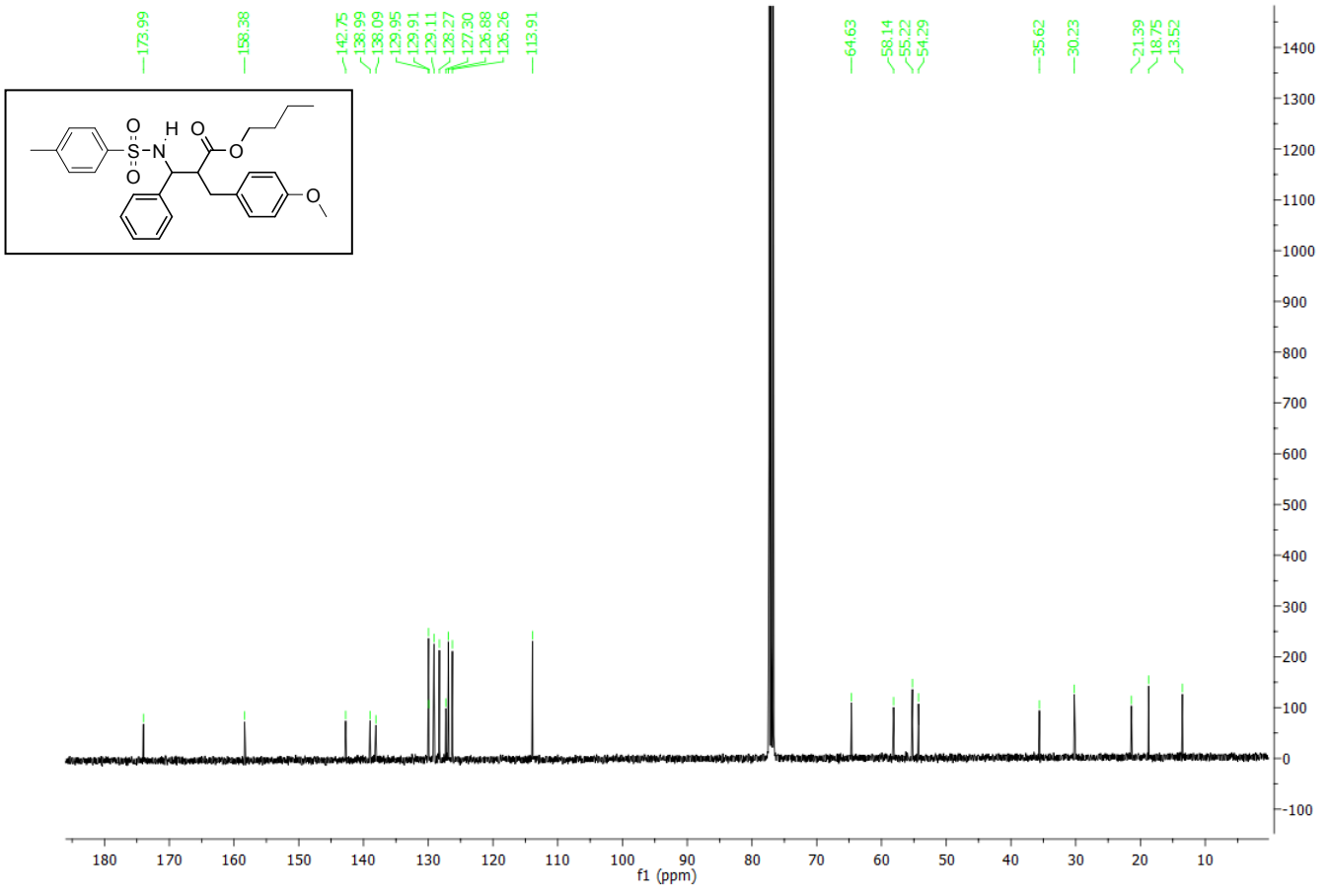
Butyl 2-benzyl-3-(4-methylphenylsulfonamido)-3-phenylpropanoate 4a



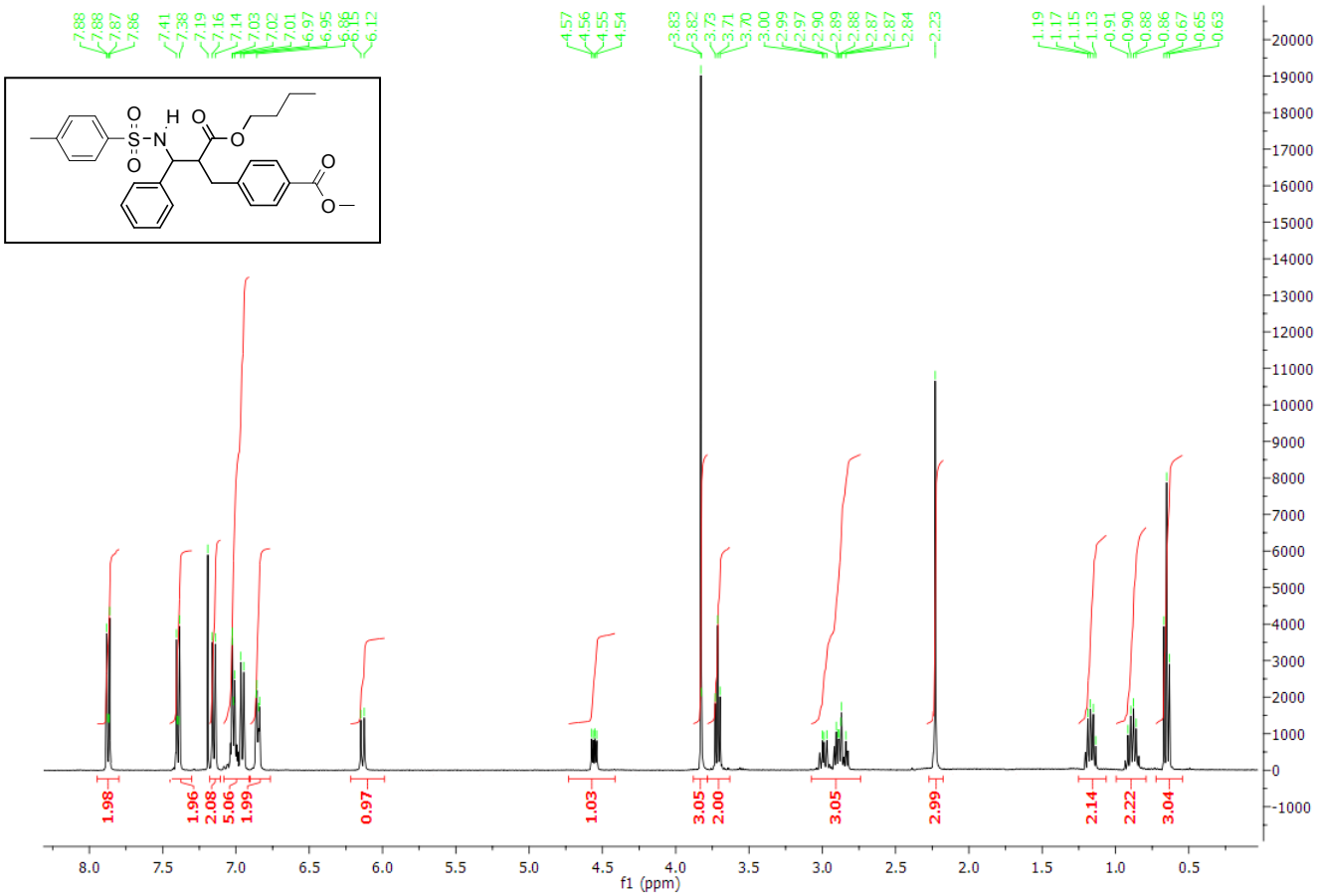


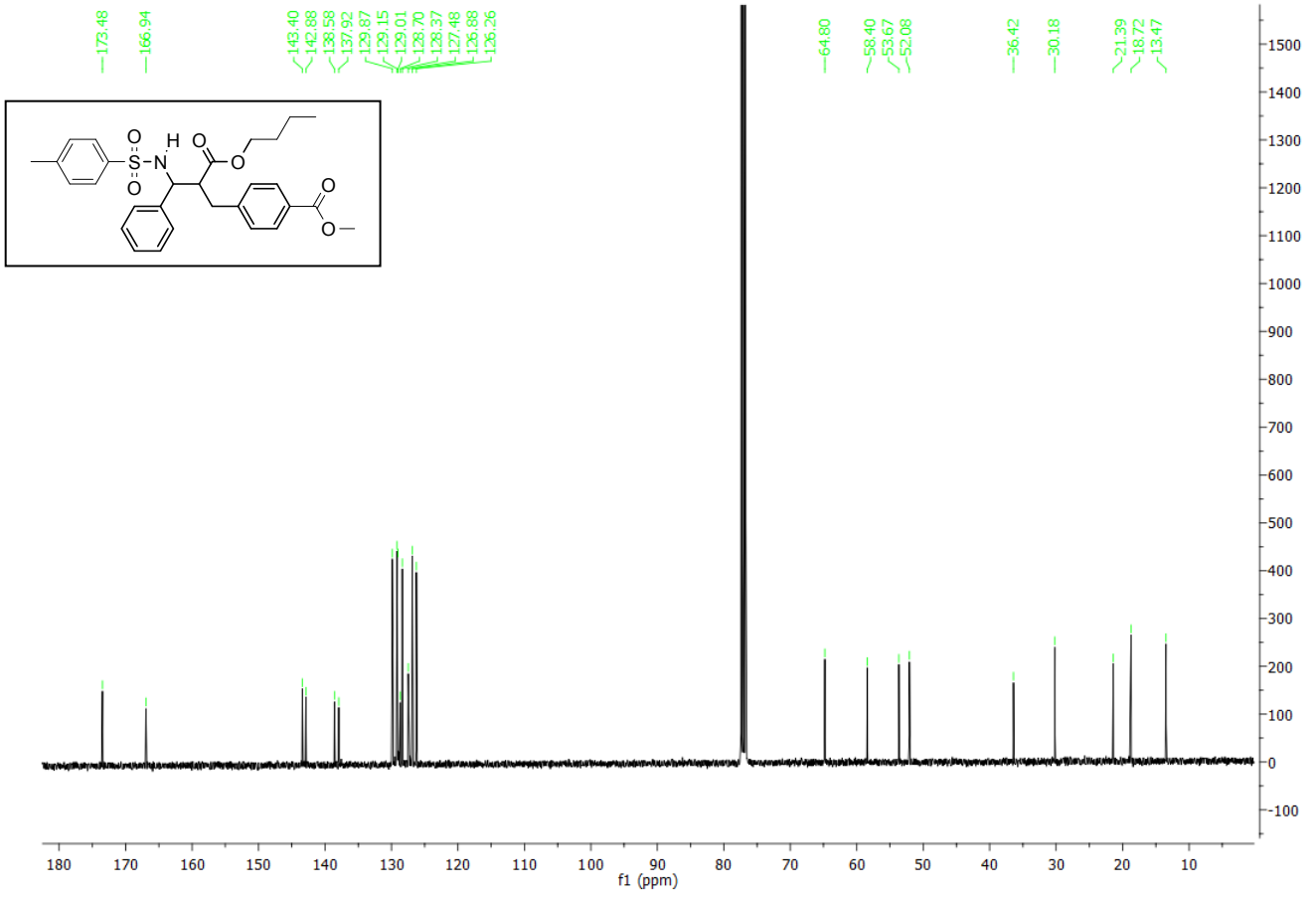
Butyl 2-(4-methoxybenzyl)-3-(4-methylphenylsulfonamido)-3-phenylpropanoate 4b



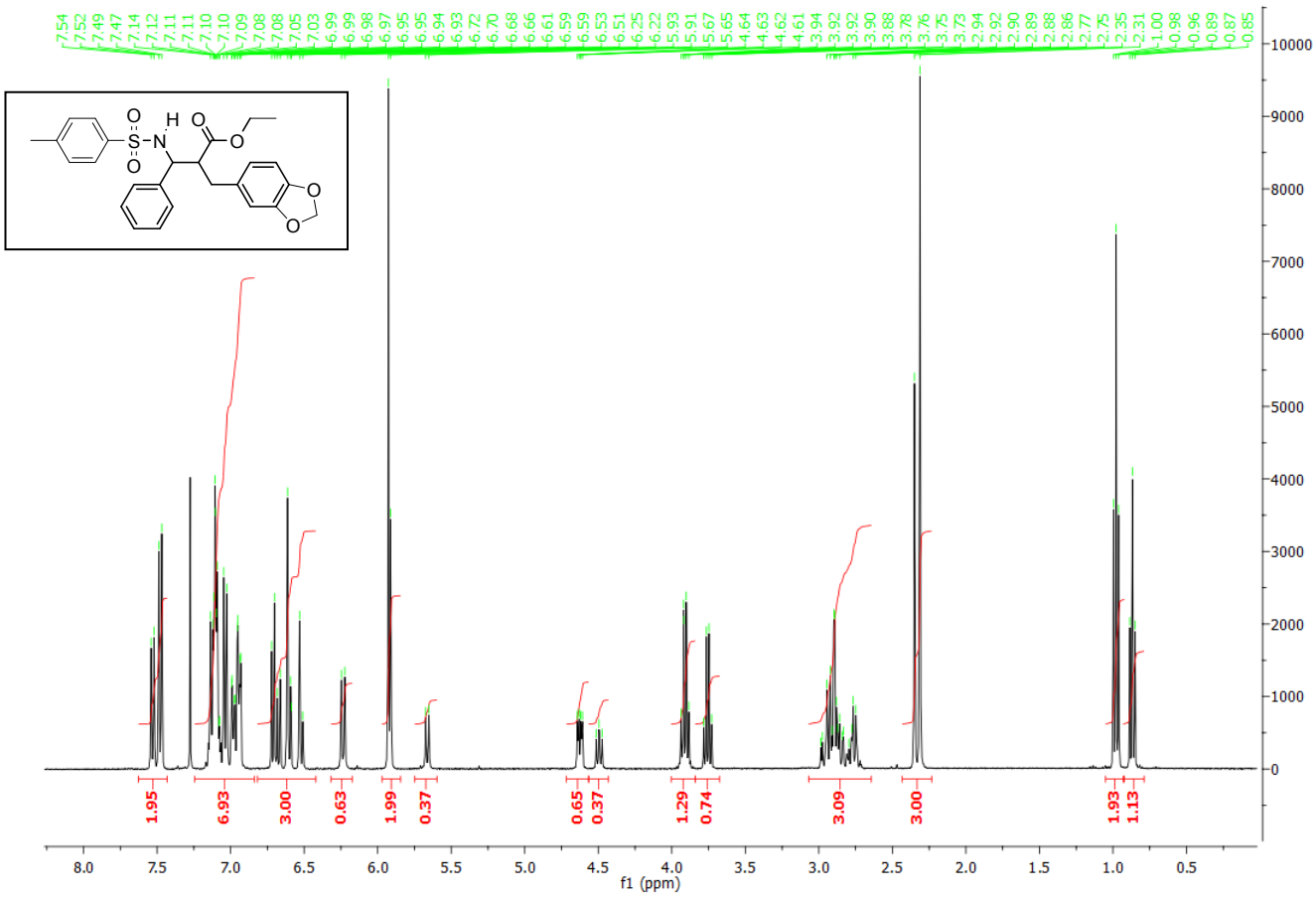


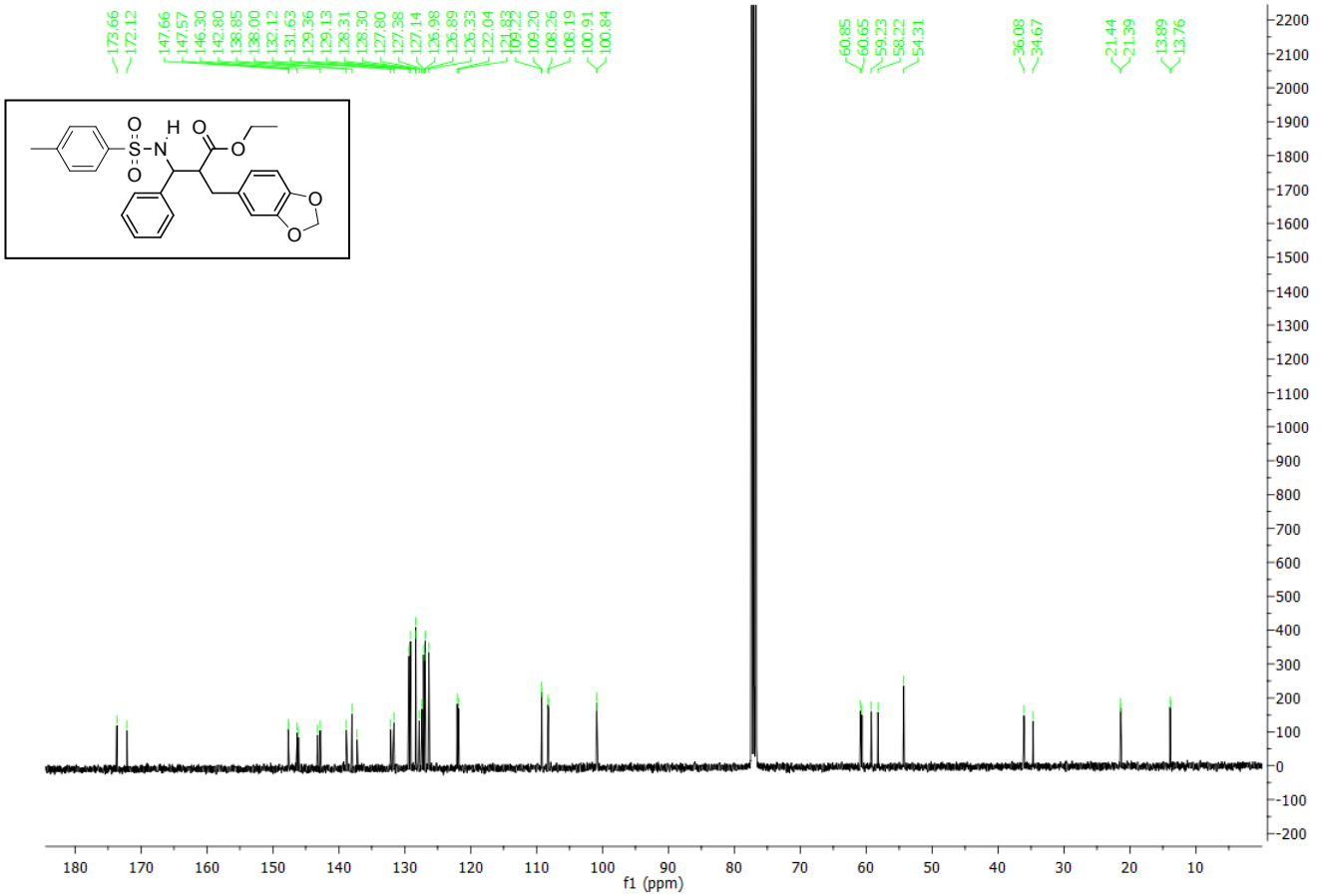
Methyl 4-(3-butoxy-2-((4-methylphenylsulfonamido)(phenyl)methyl)-3-oxopropyl)benzoate 4c



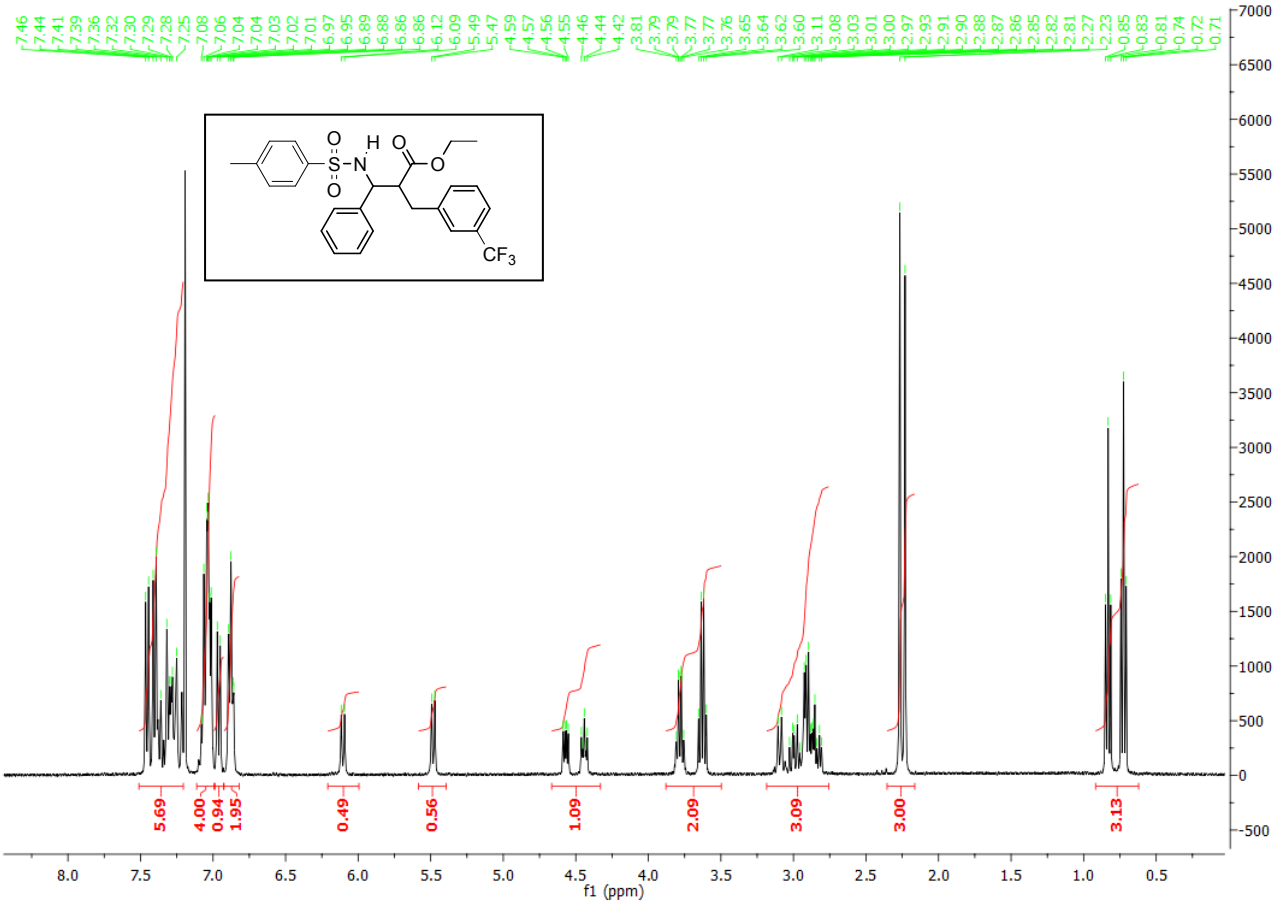


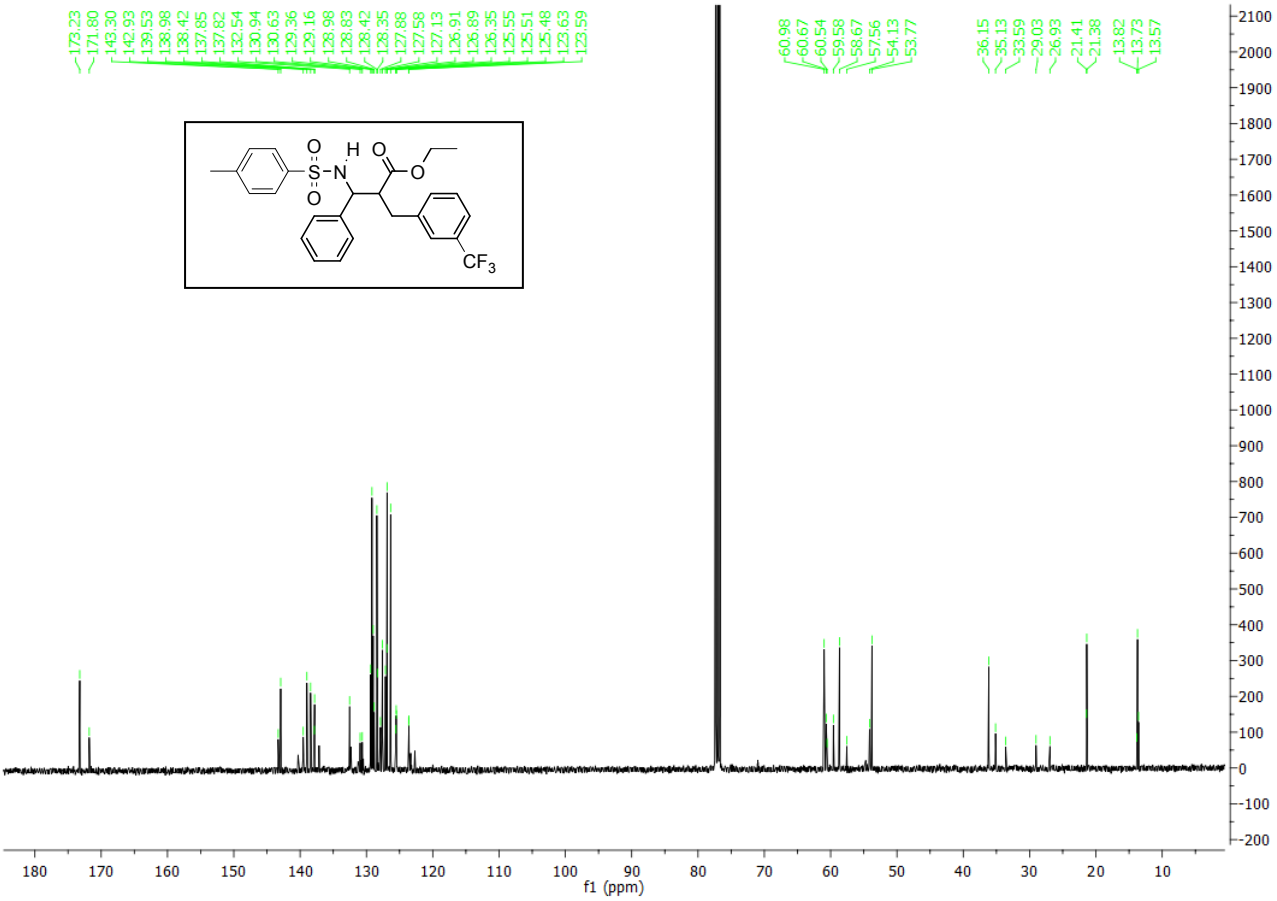
Ethyl 2-(benzo[d][1,3]dioxol-5-ylmethyl)-3-(4-methylphenylsulfonamido)-3-phenylpropanoate 4d

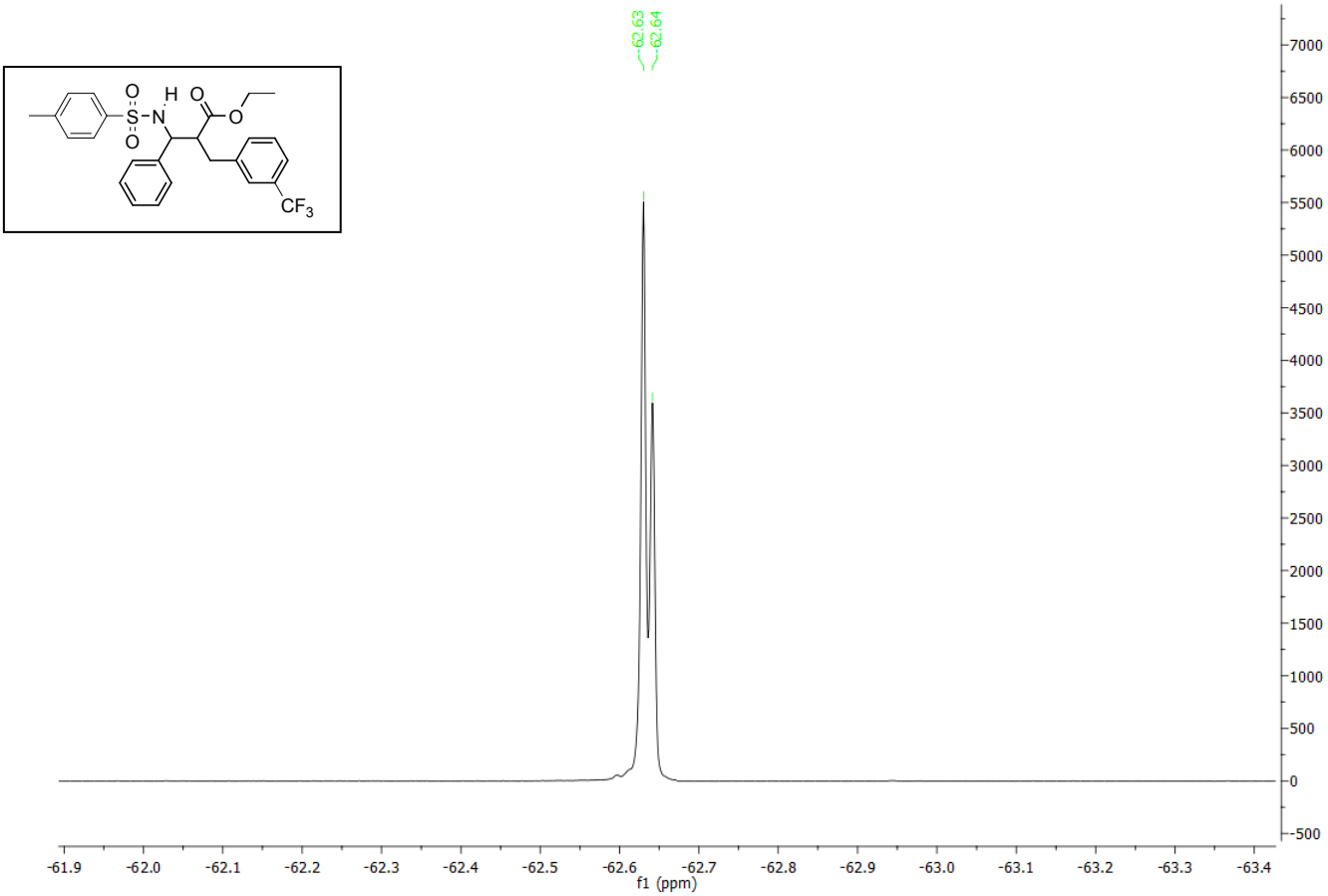




Ethyl 3-(4-methylphenylsulfonamido)-3-phenyl-2-(3-(trifluoromethyl)benzyl)propanoate 4e



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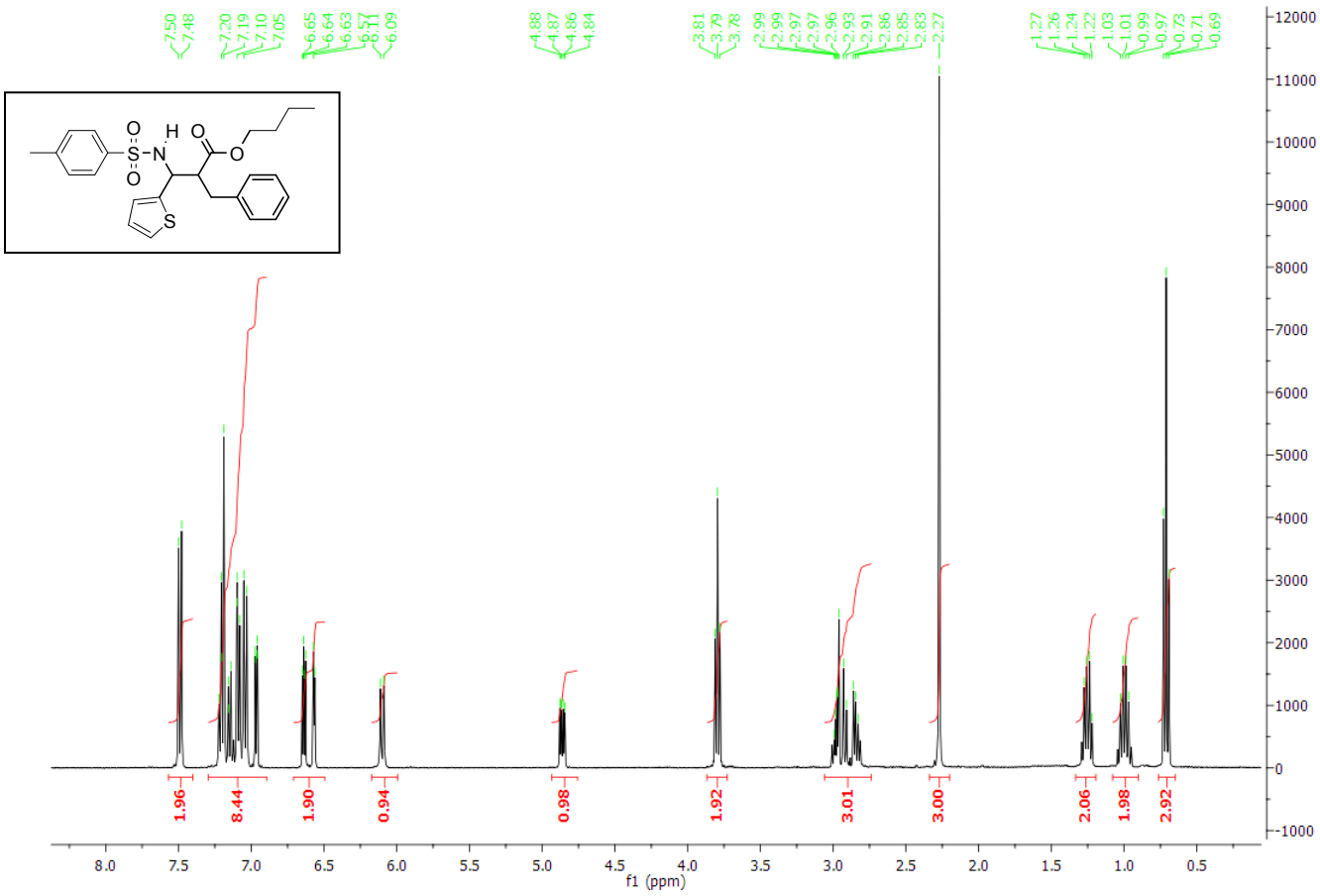
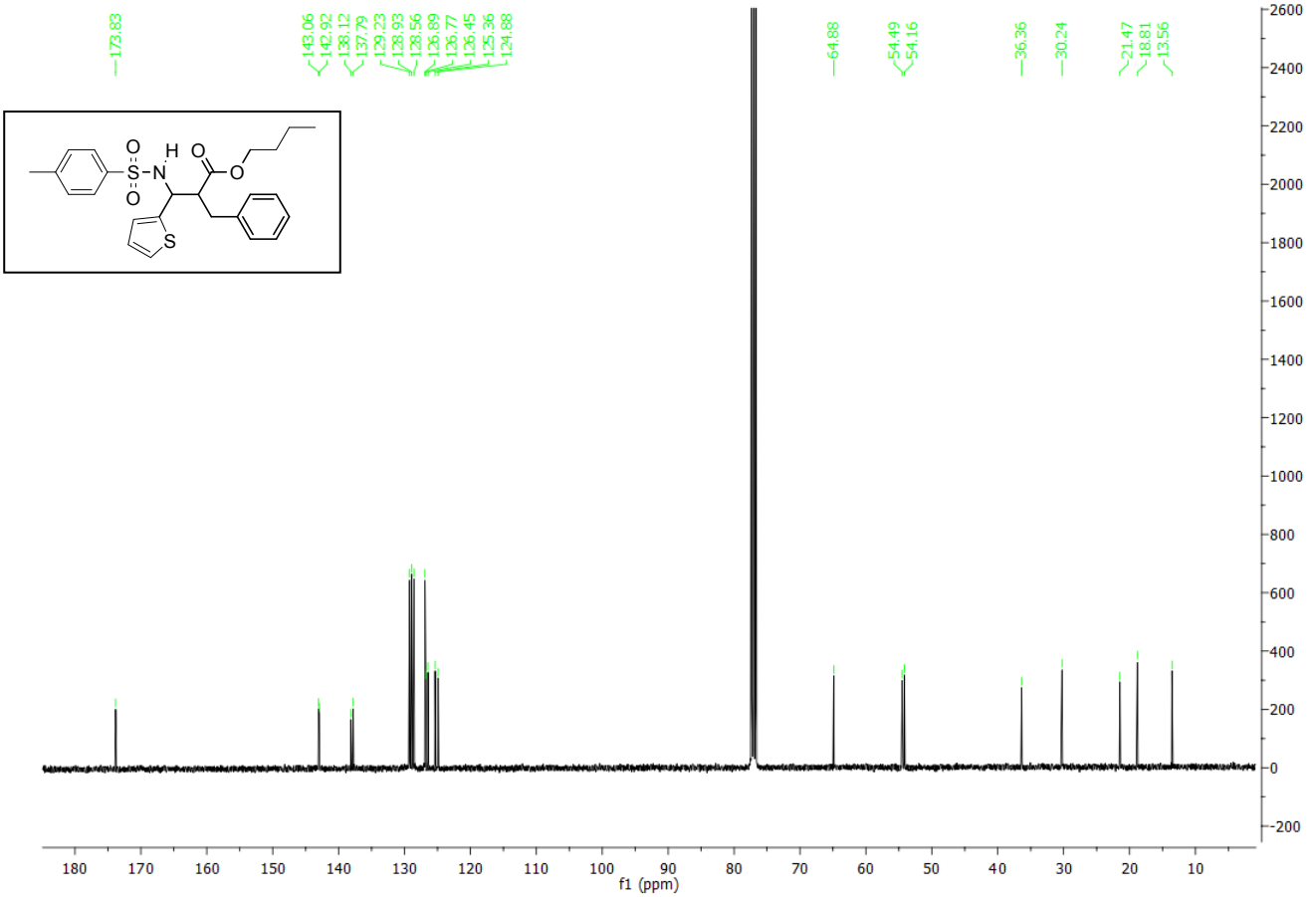
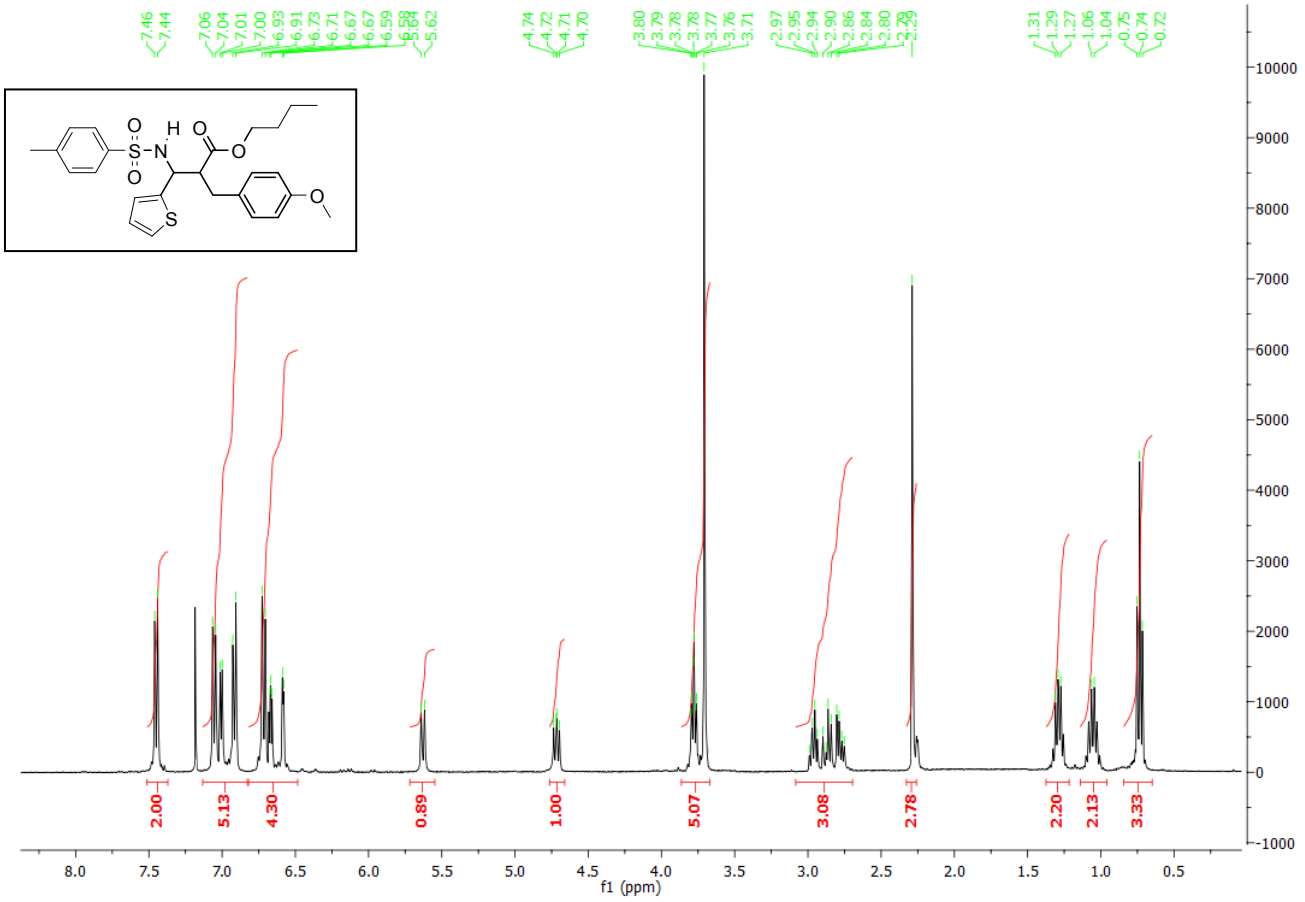
62.64
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-61.9
-62.0
-62.1
-62.2
-62.3
-62.4
-62.5
-62.6
-62.7
-62.8
-62.9
-63.0
-63.1
-63.2
-63.3
-63.4
f1 (ppm)

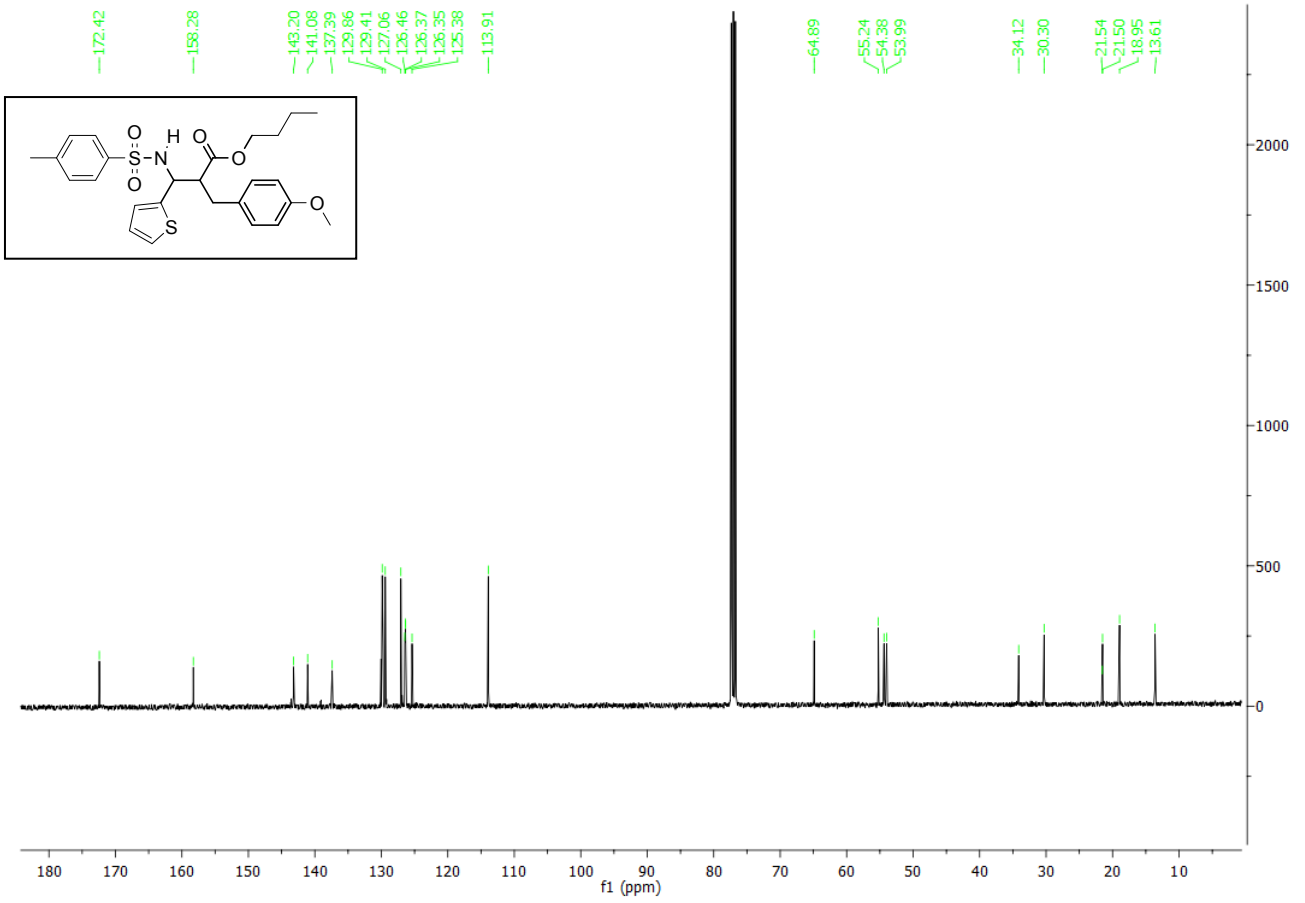
Butyl 2-benzyl-3-(4-methylphenylsulfonamido)-3-(thiophen-2-yl)propanoate 4f



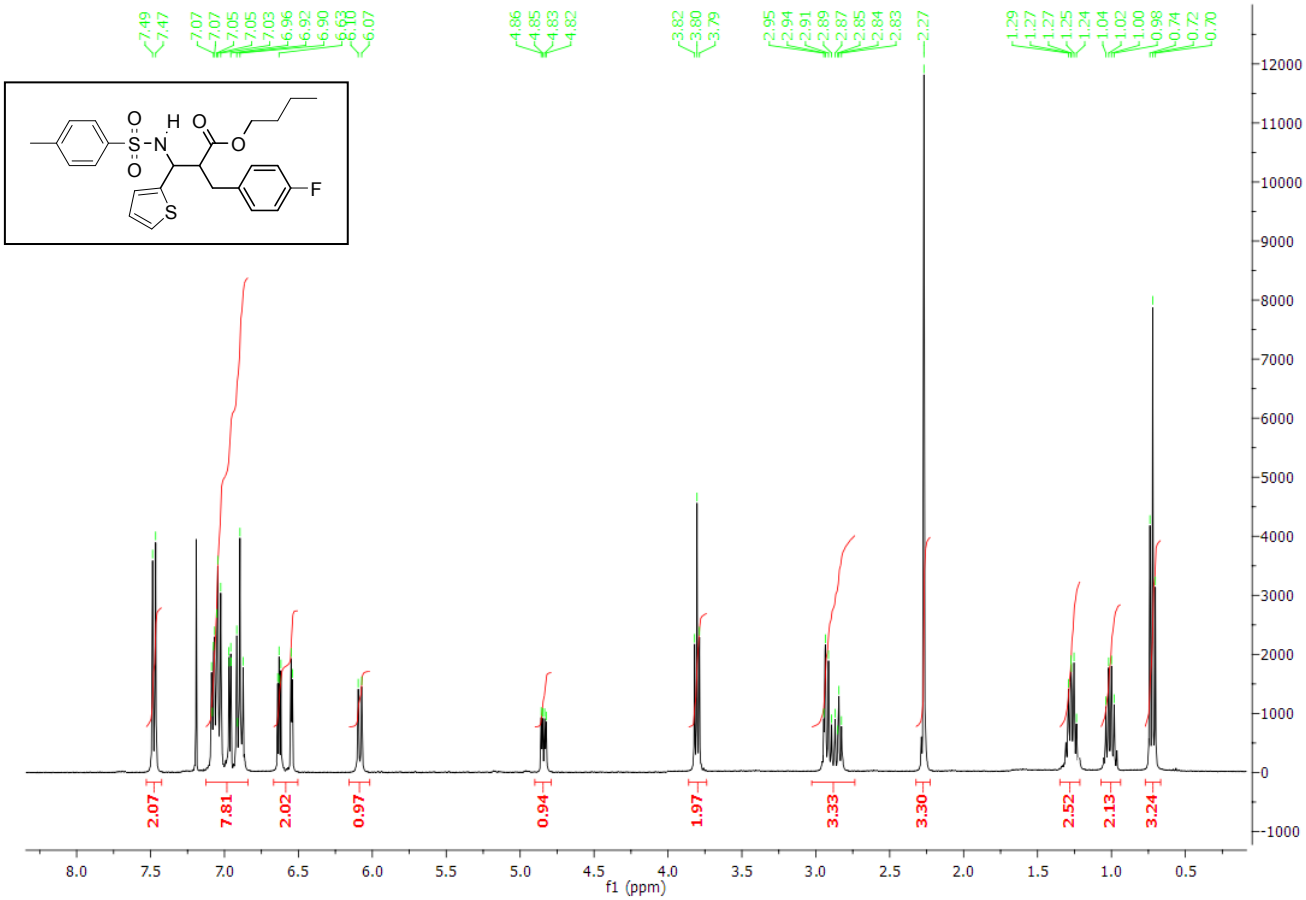


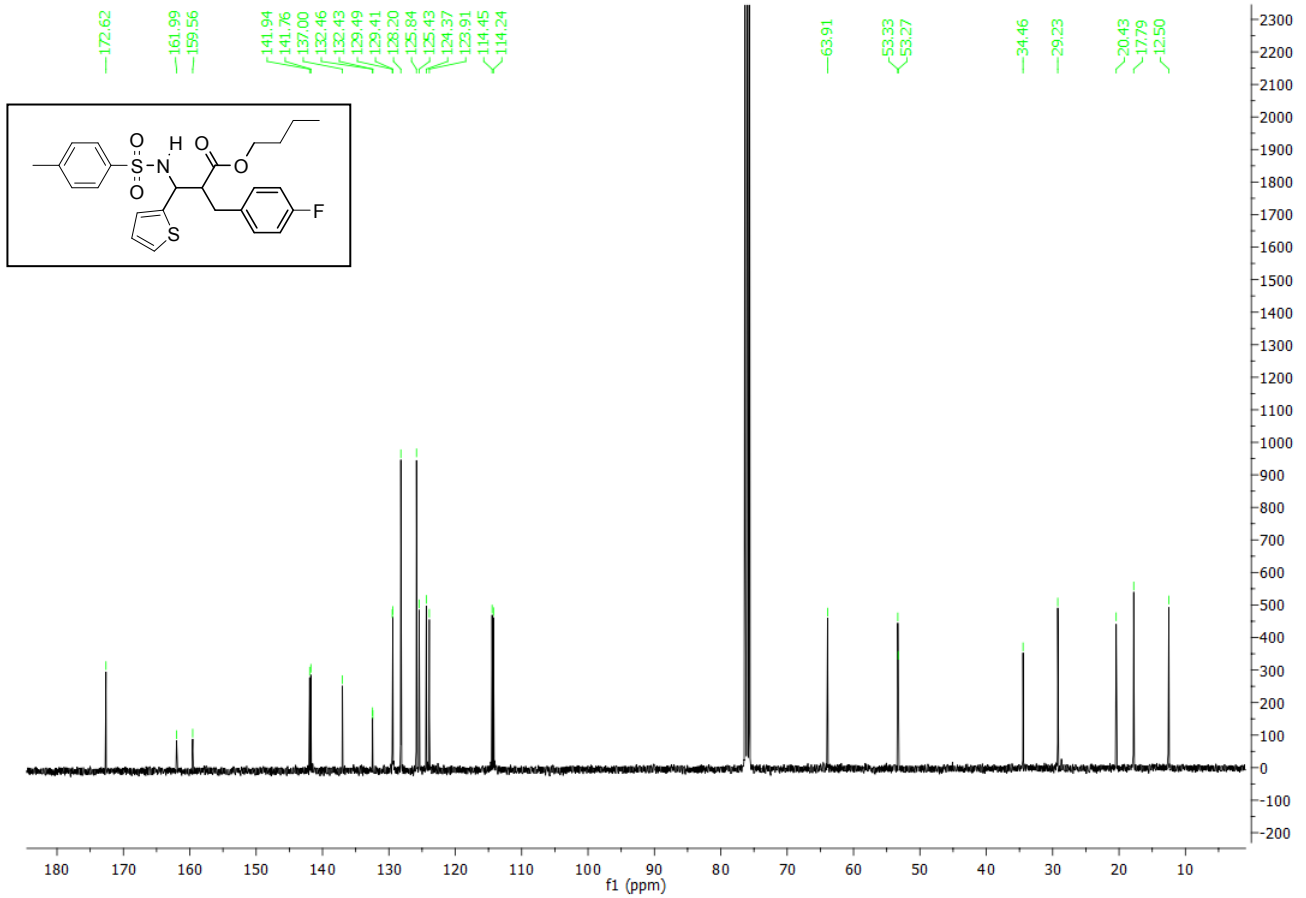
Butyl 2-(4-methoxybenzyl)-3-(4-methylphenylsulfonamido)-3-(thiophen-2-yl)propanoate 4g

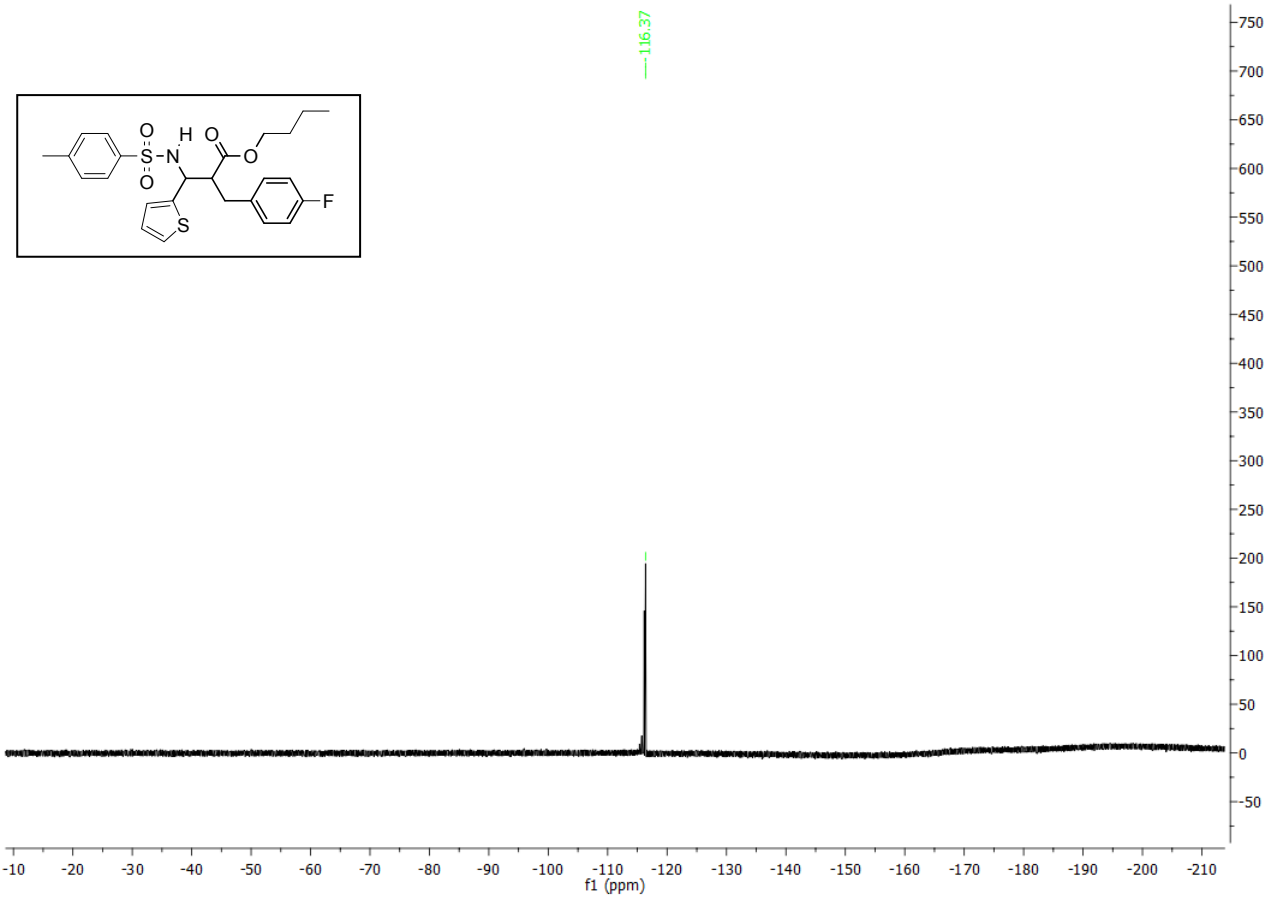




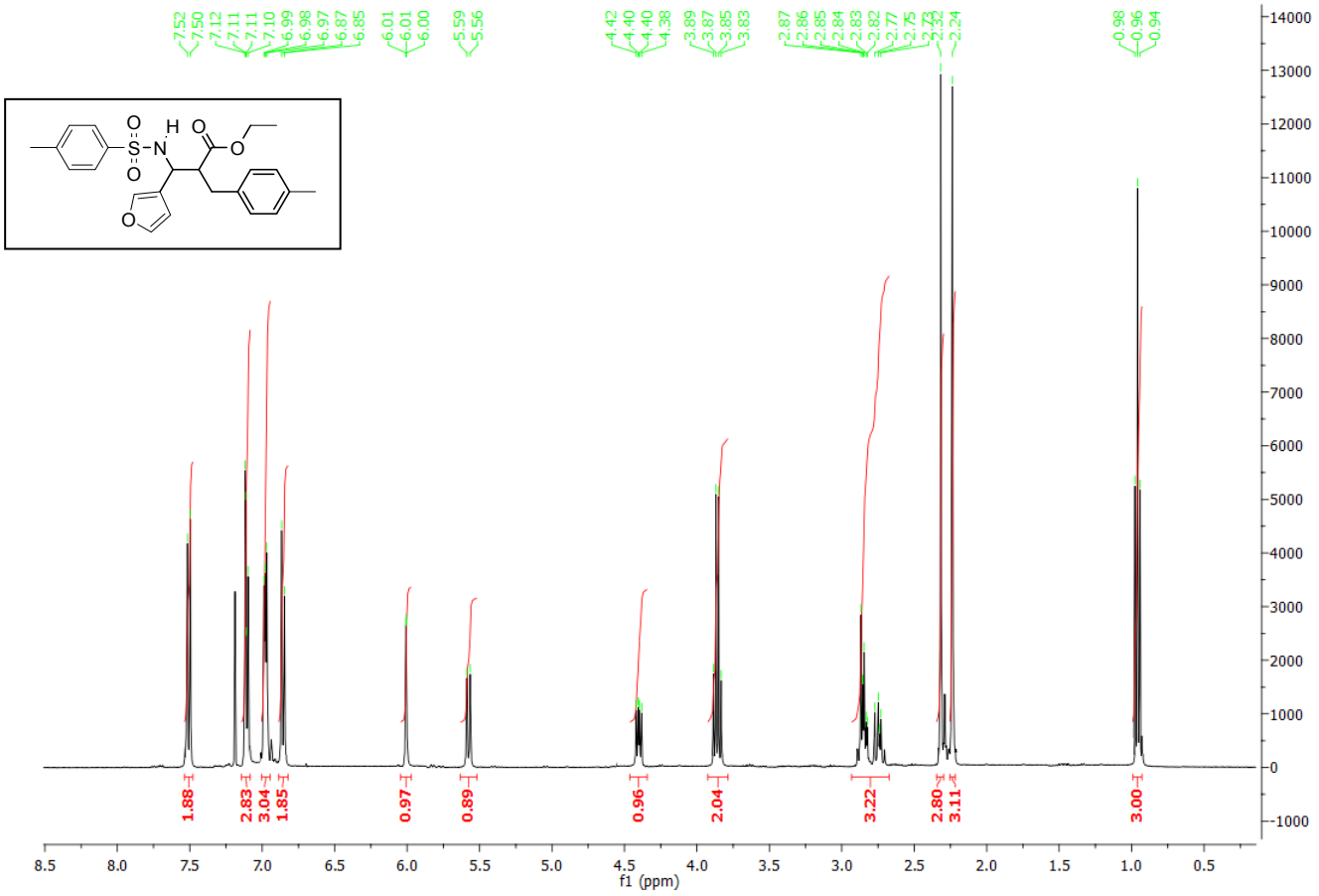
Butyl 2-(4-fluorobenzyl)-3-(4-methylphenylsulfonamido)-3-(thiophen-2-yl)propanoate 4h

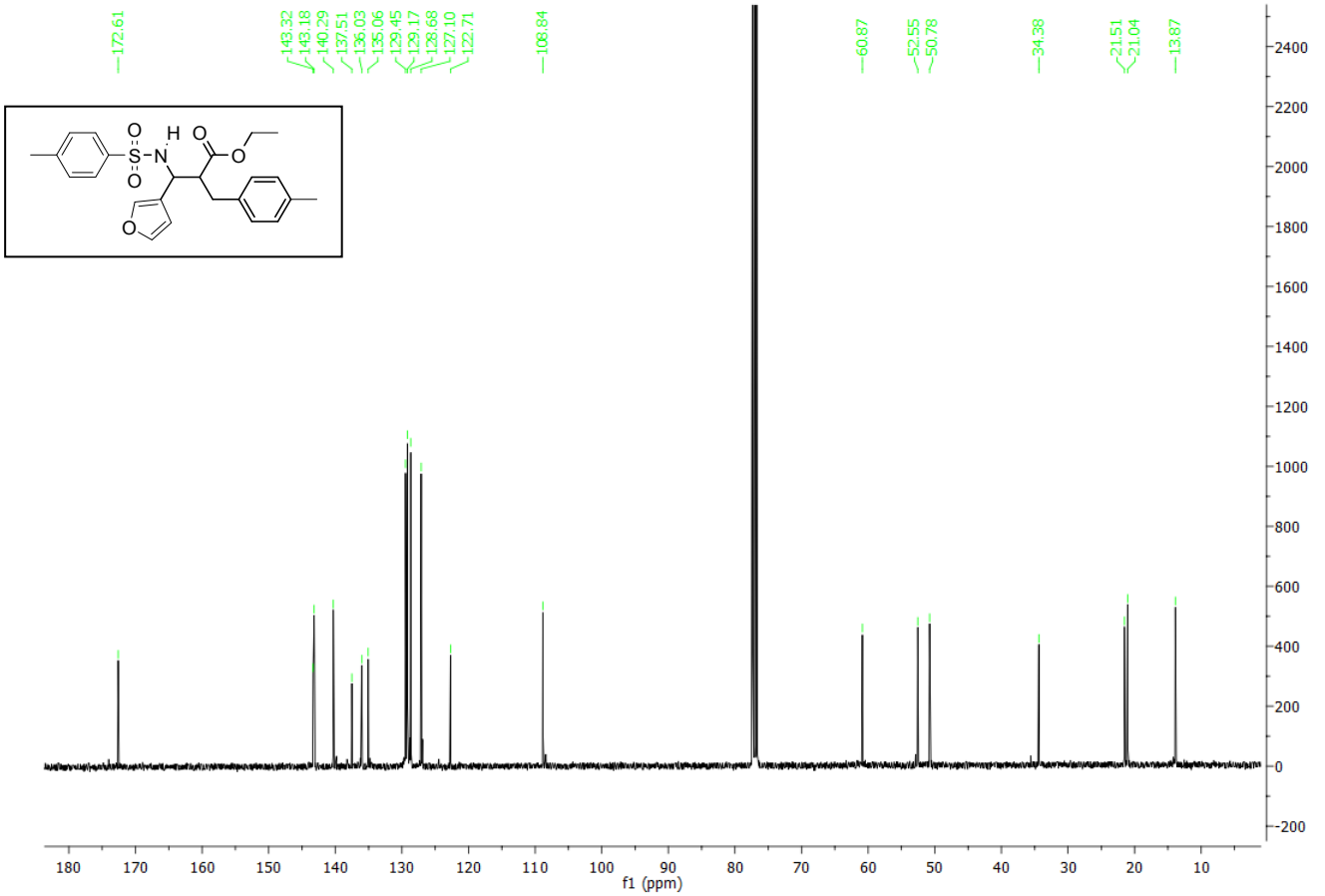




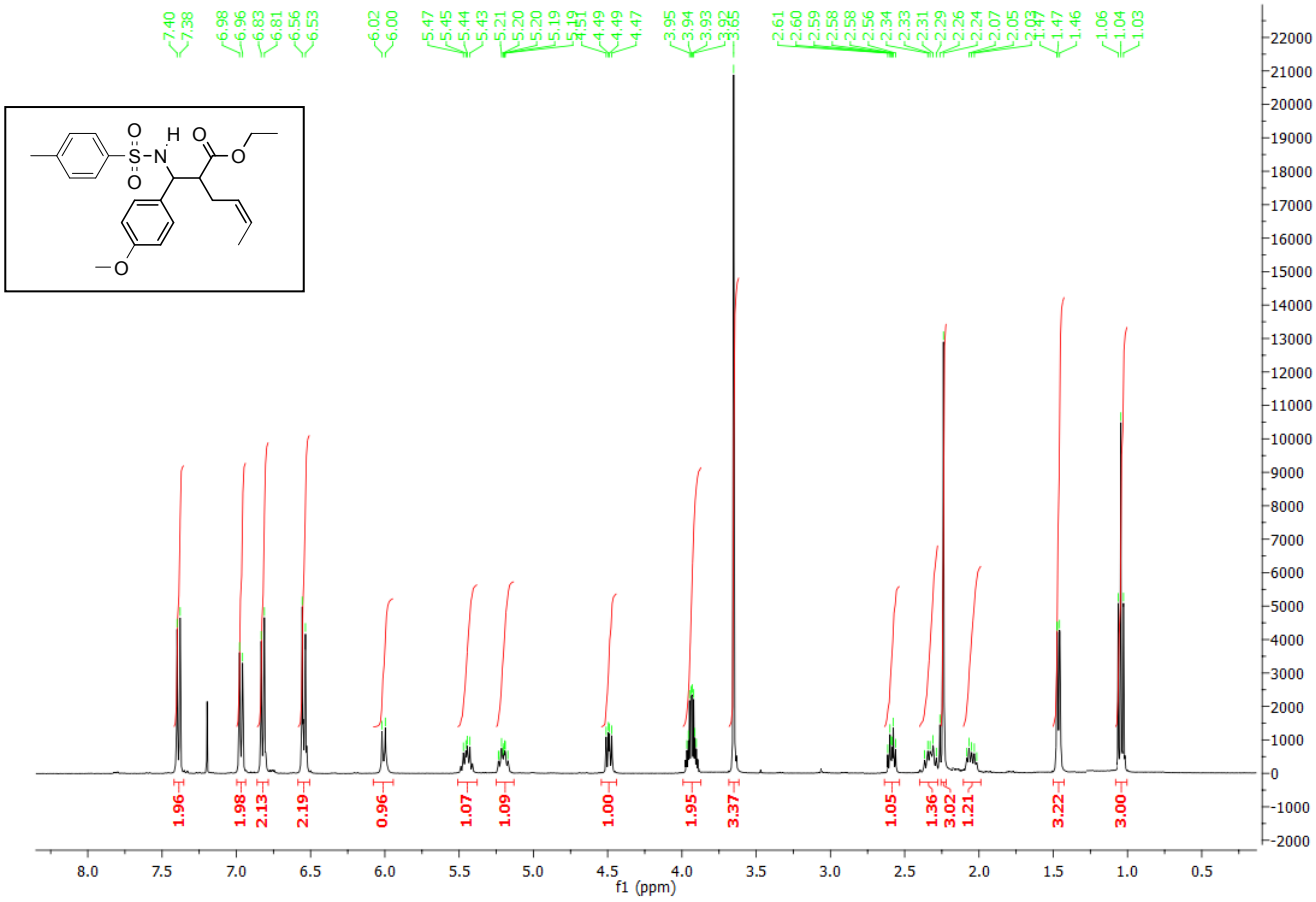

-116.37
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)
O
H
O
S
N
O
O
F
S

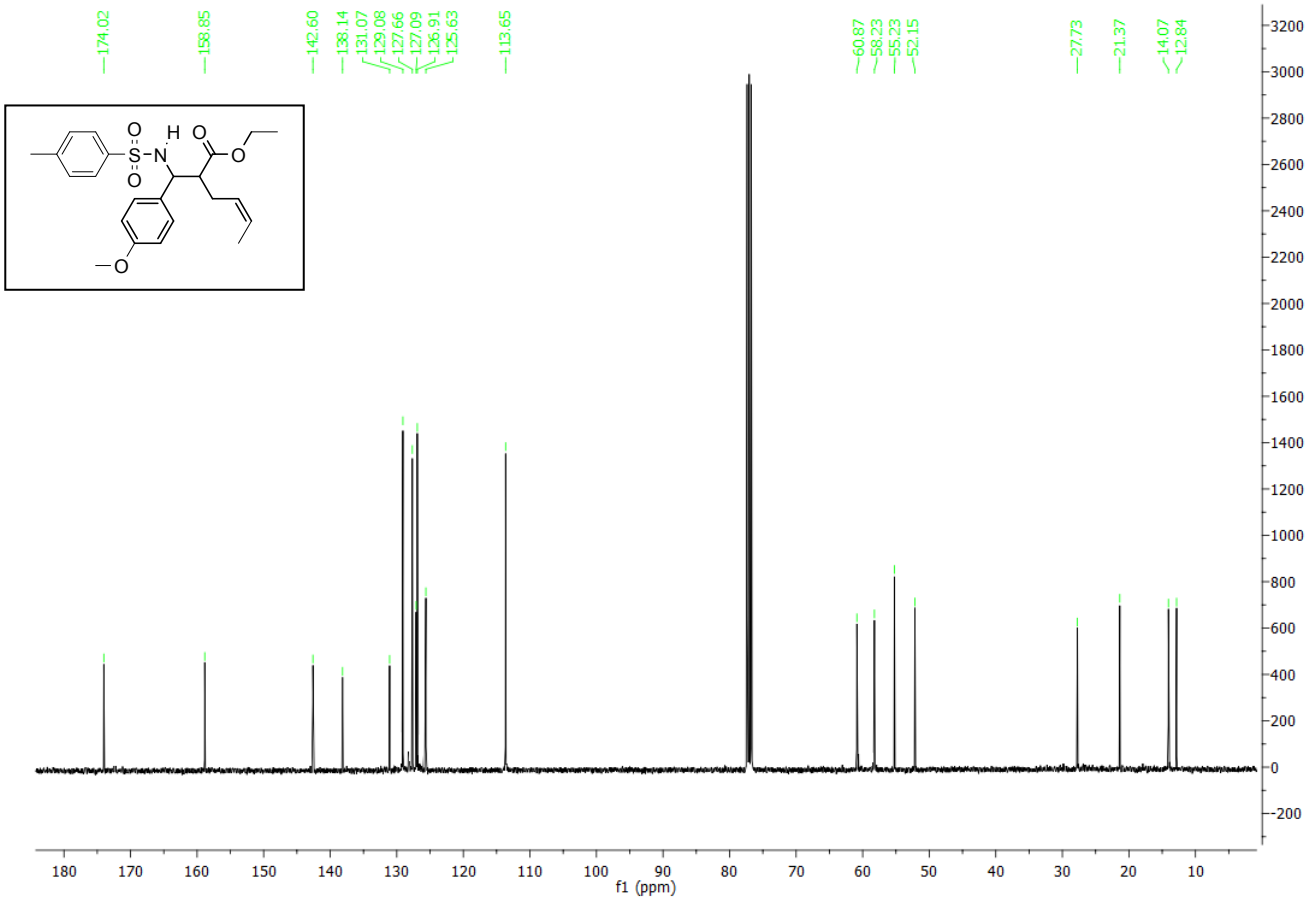
Ethyl 3-(furan-3-yl)-2-(4-methylbenzyl)-3-(4-methylphenylsulfonamido)propanoate 4i



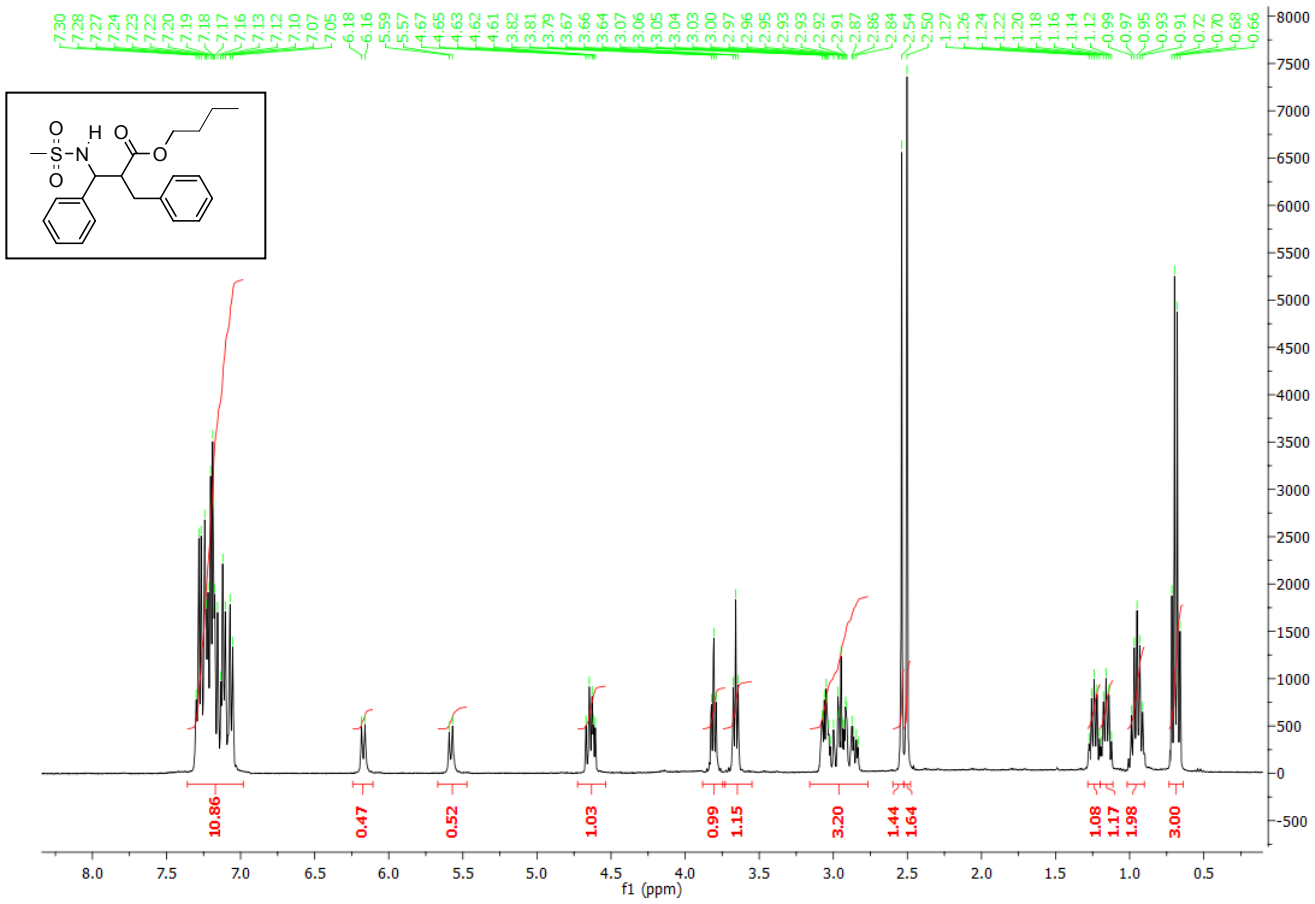


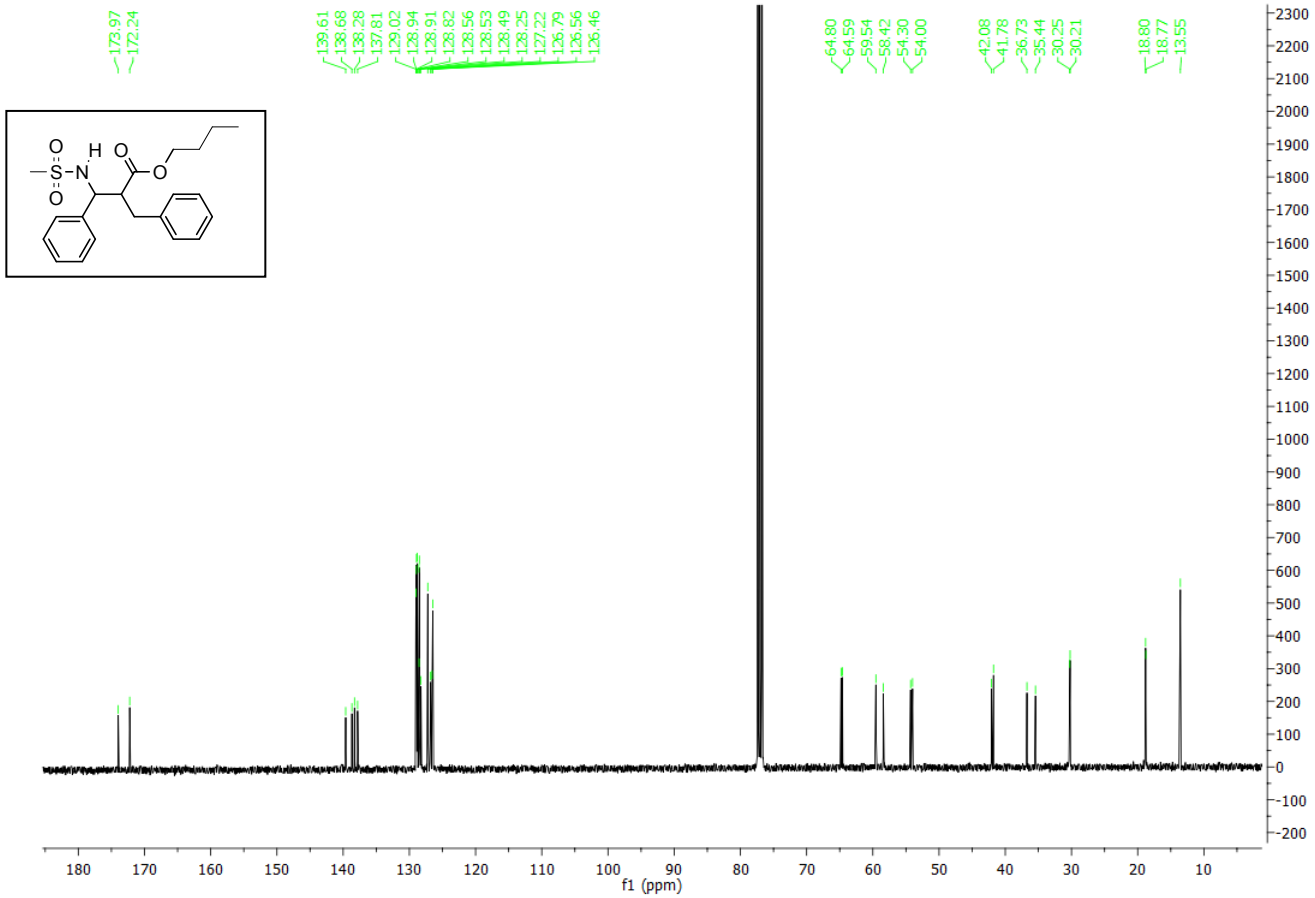
(Z)-Ethyl 2-((4-methoxyphenyl)(4-methylphenylsulfonamido)methyl)hex-4-enoate 4j



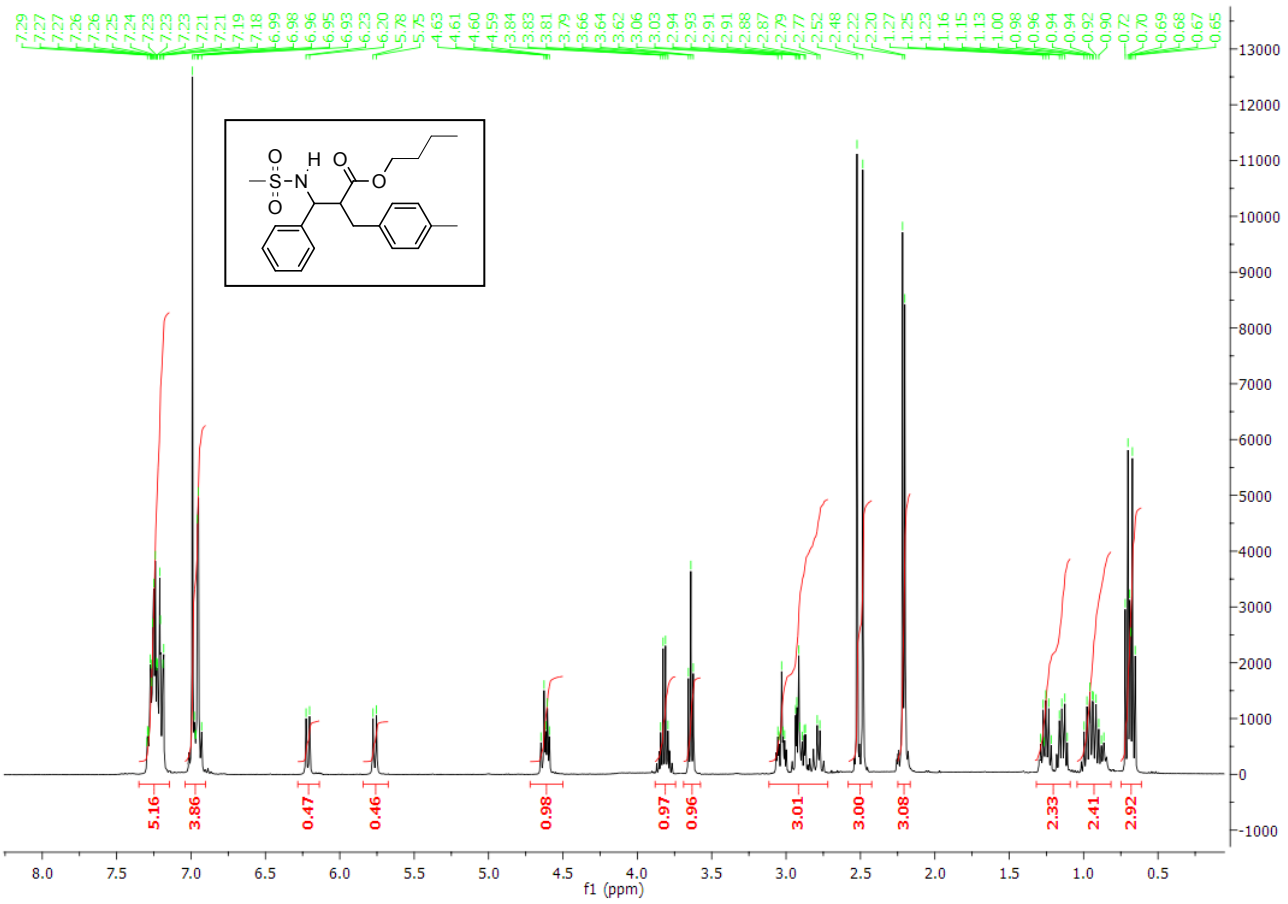


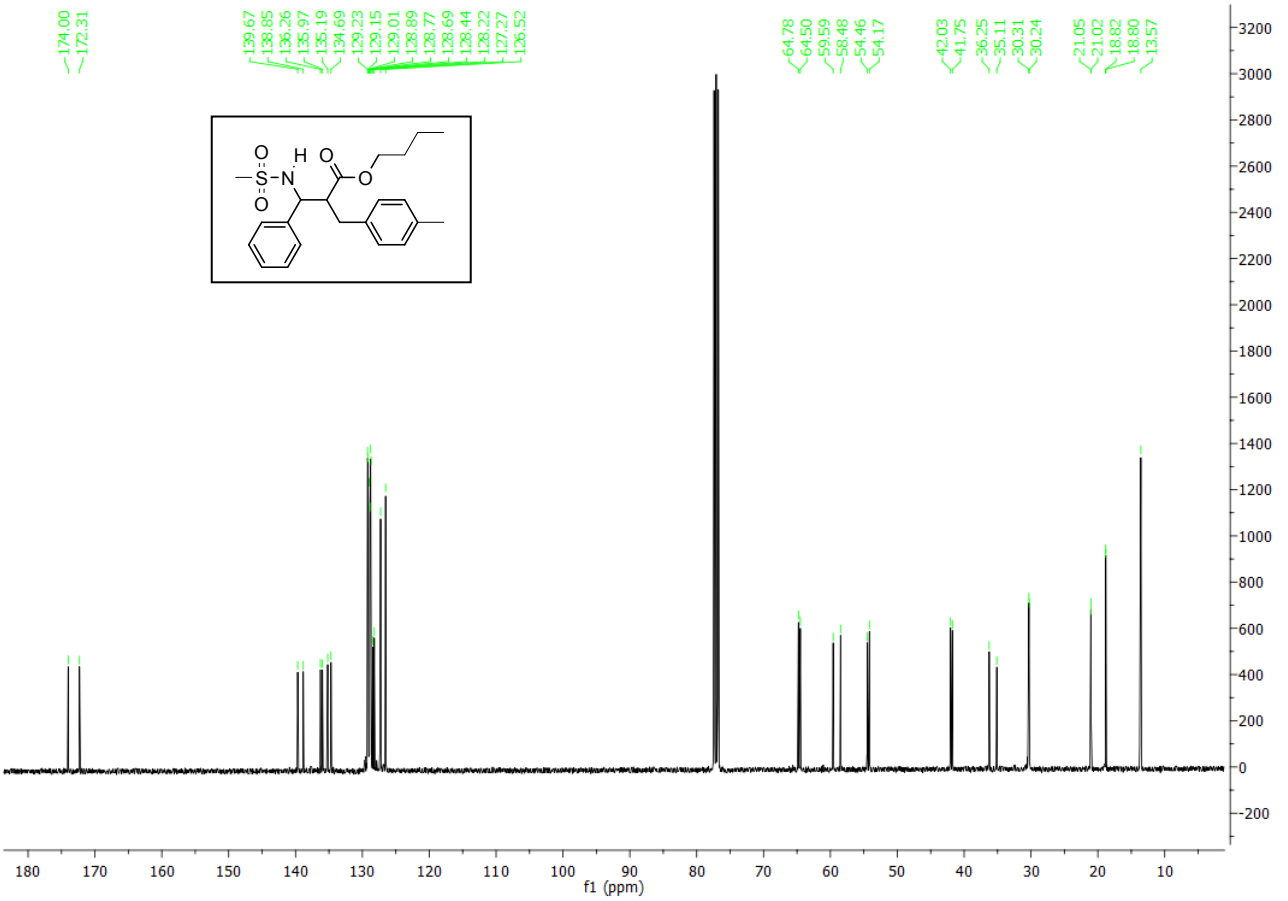
Butyl 2-benzyl-3-(methylsulfonamido)-3-phenylpropanoate 4k



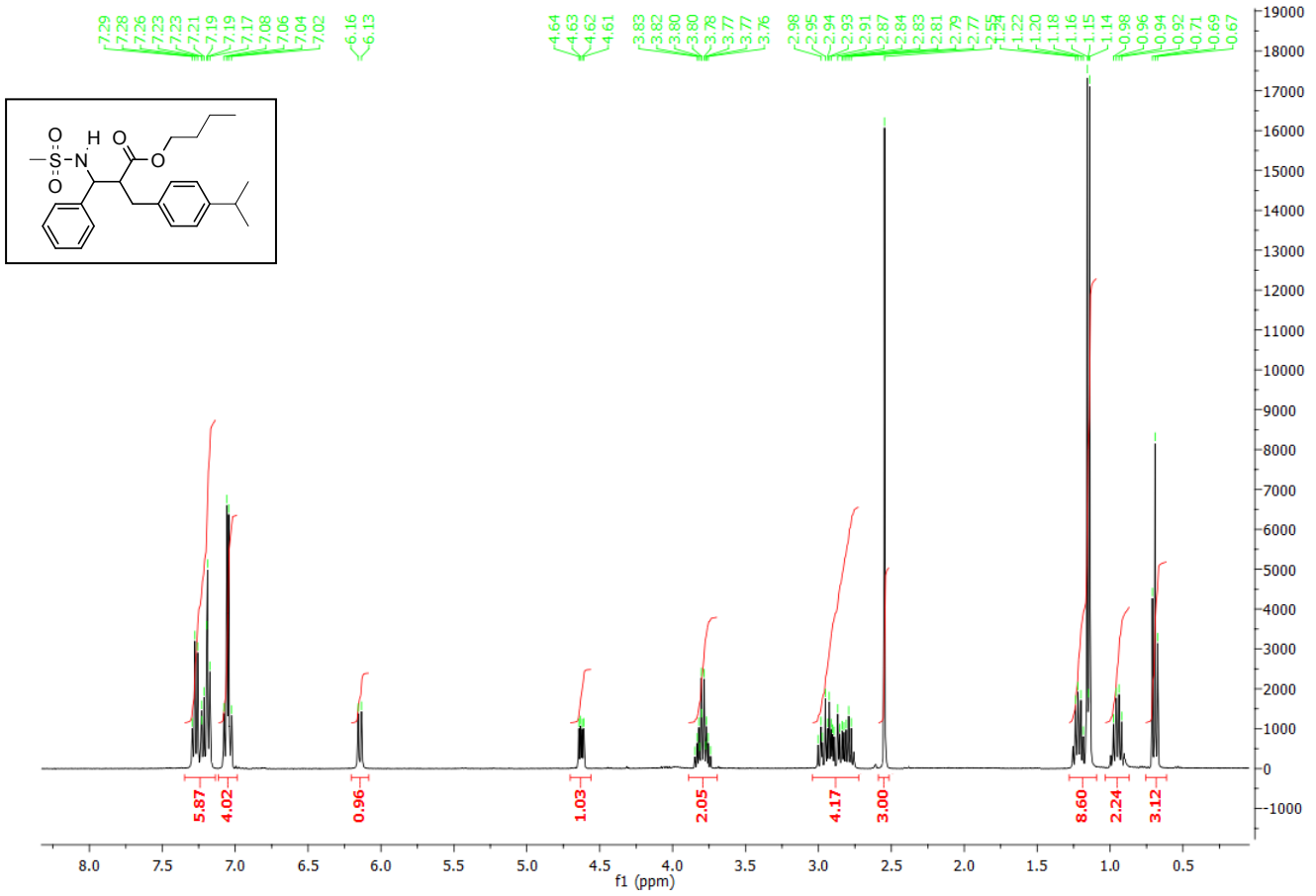


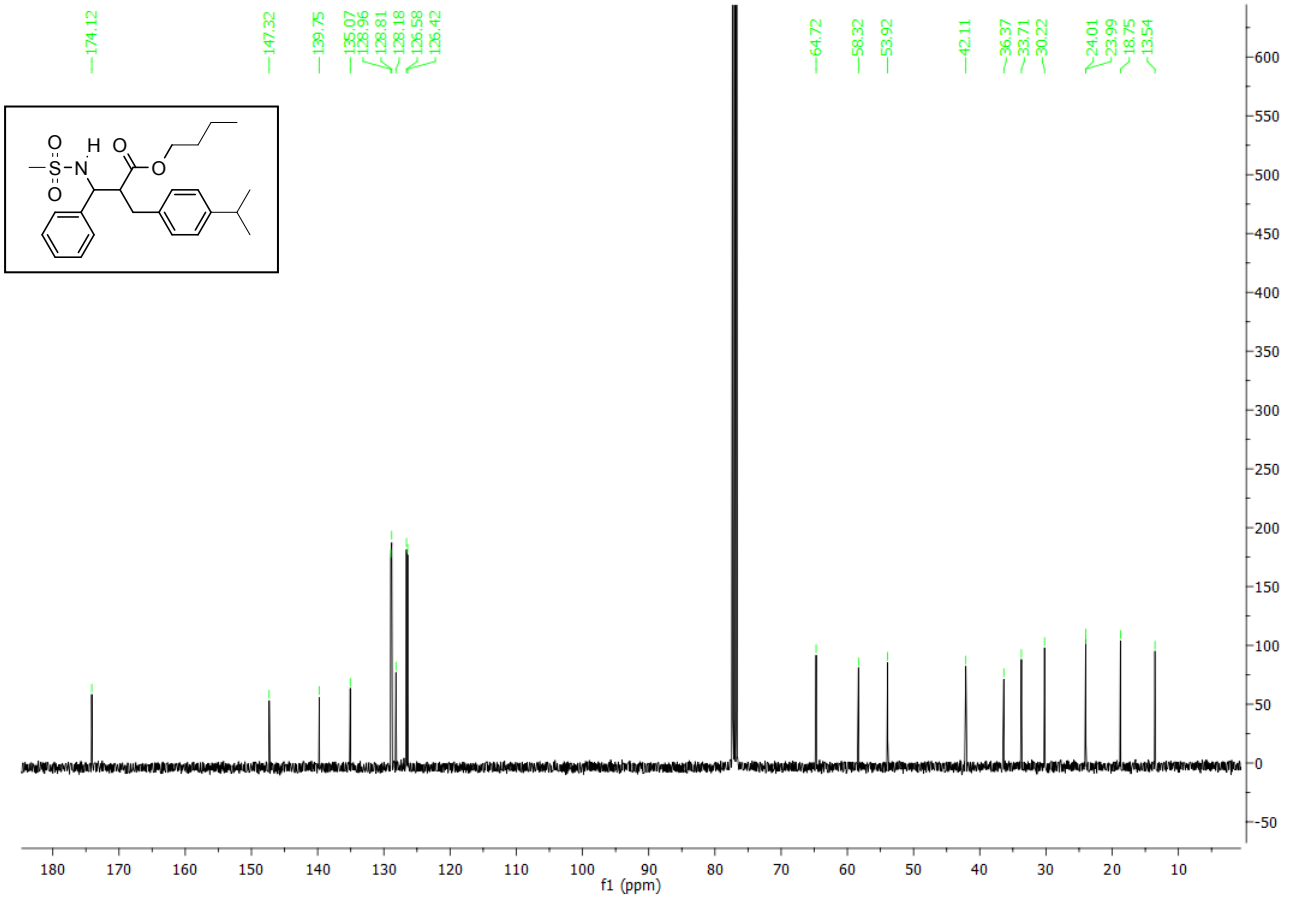
Butyl 2-(4-methylbenzyl)-3-(methylsulfonamido)-3-phenylpropanoate 4l



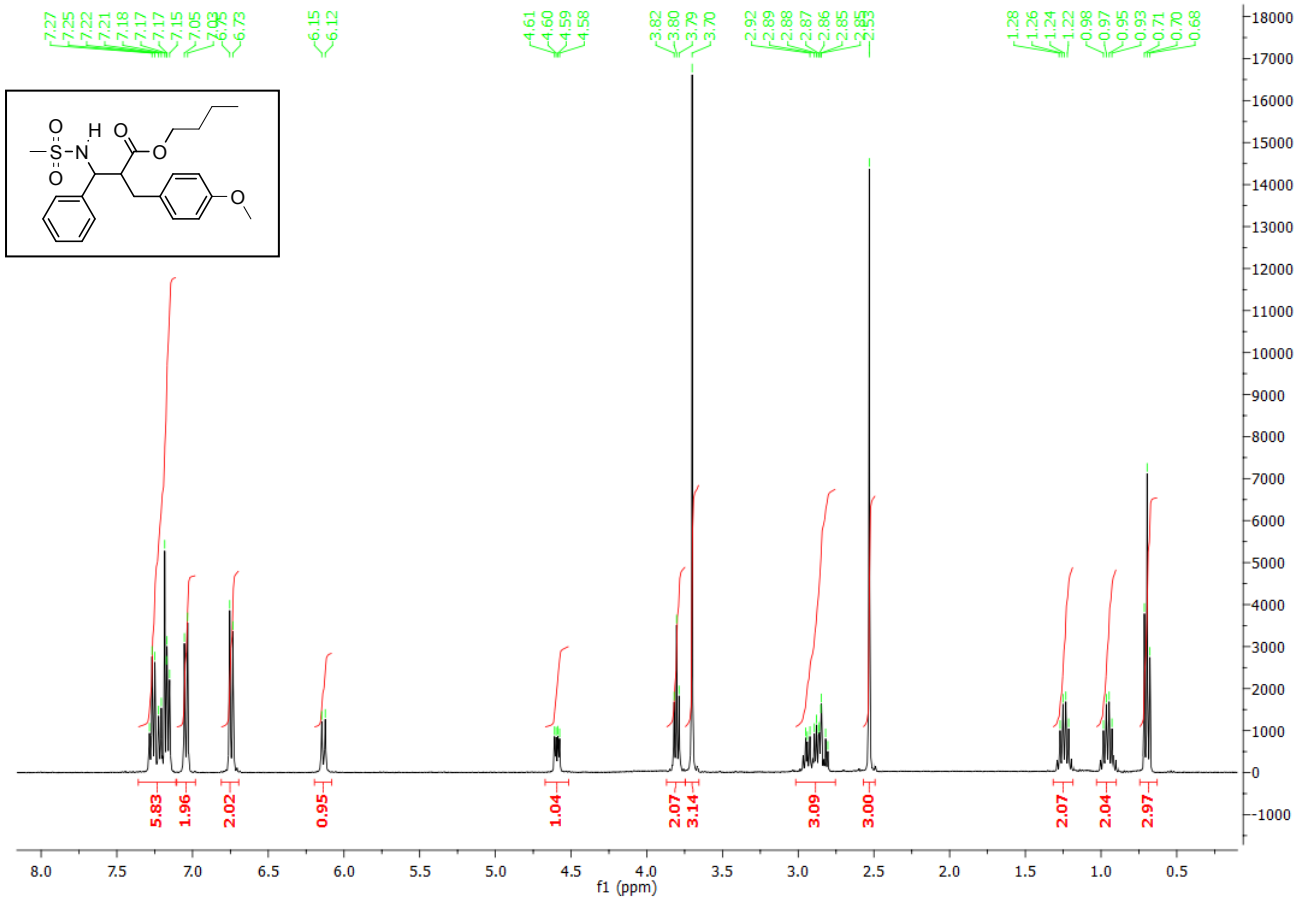


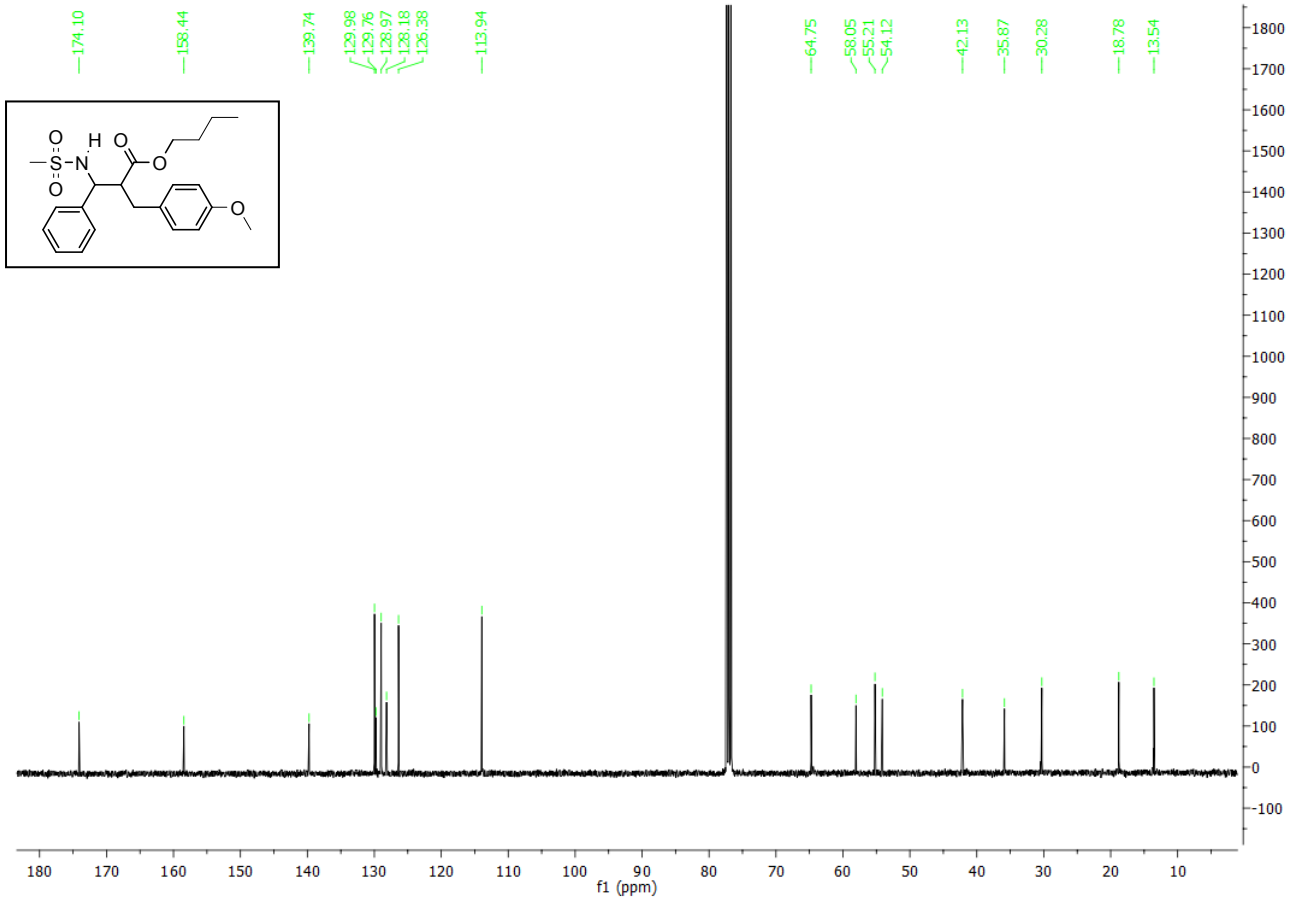
Butyl 2-(4-isopropylbenzyl)-3-(methylsulfonamido)-3-phenylpropanoate 4m



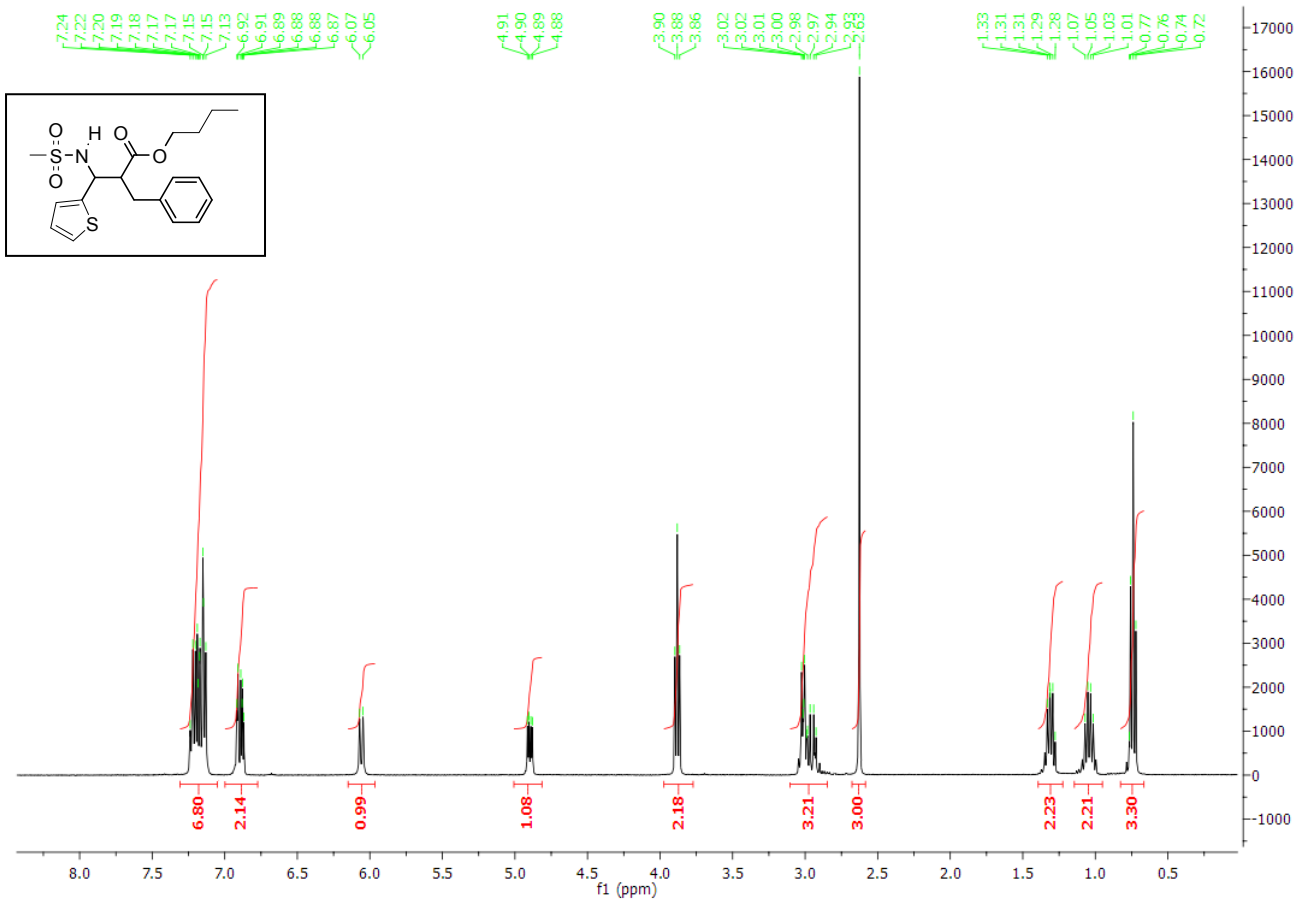


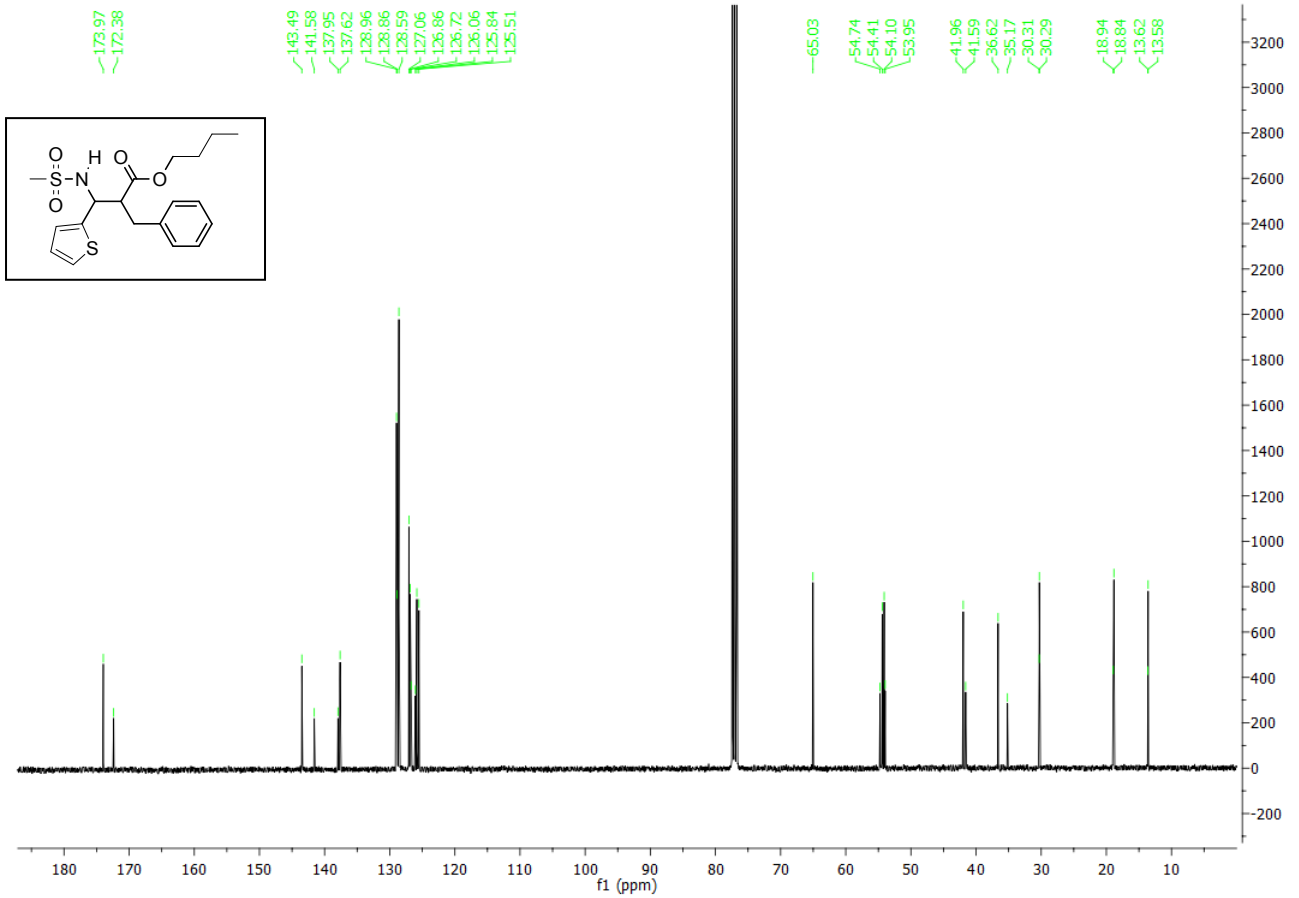
Butyl 2-(4-methoxybenzyl)-3-(methylsulfonamido)-3-phenylpropanoate 4n



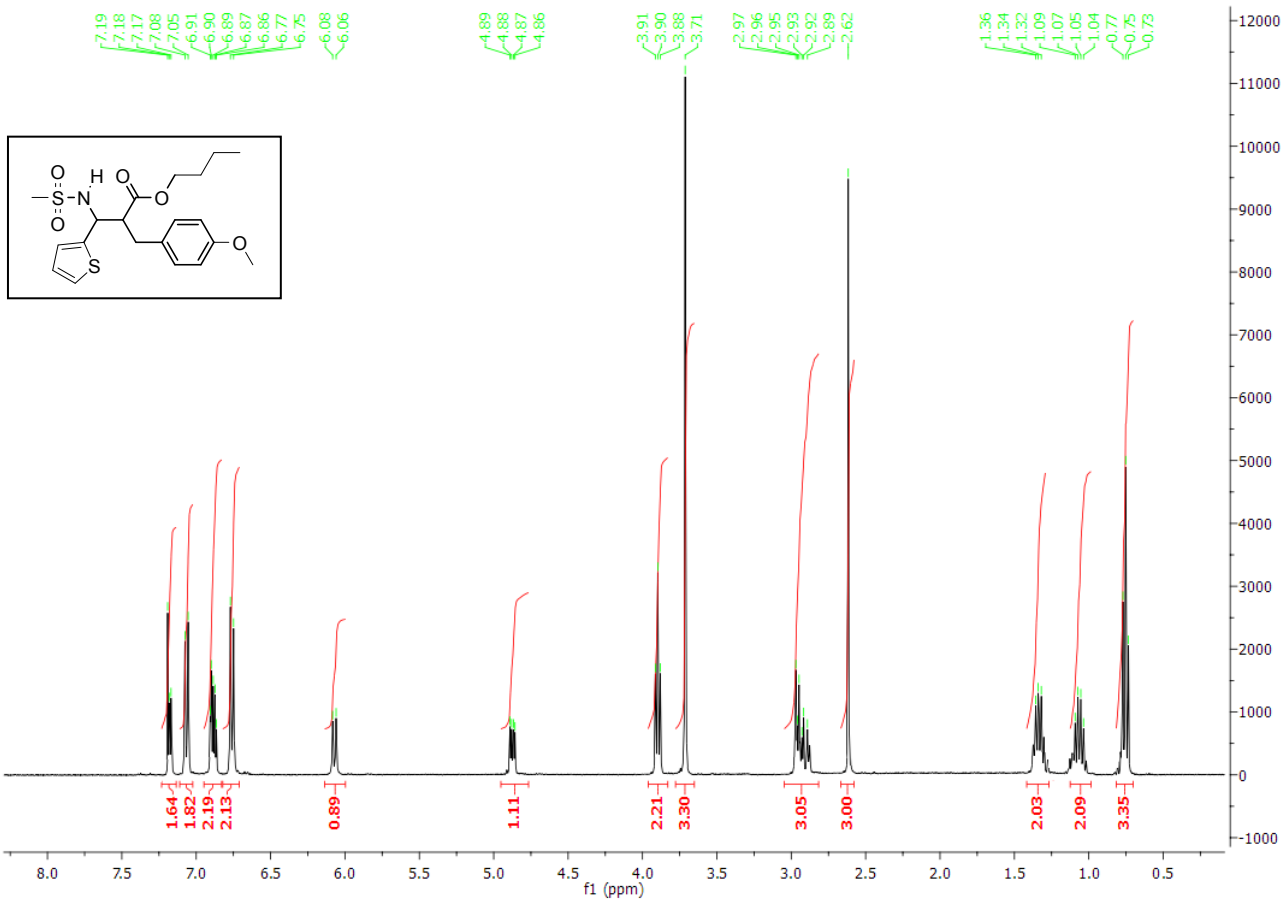


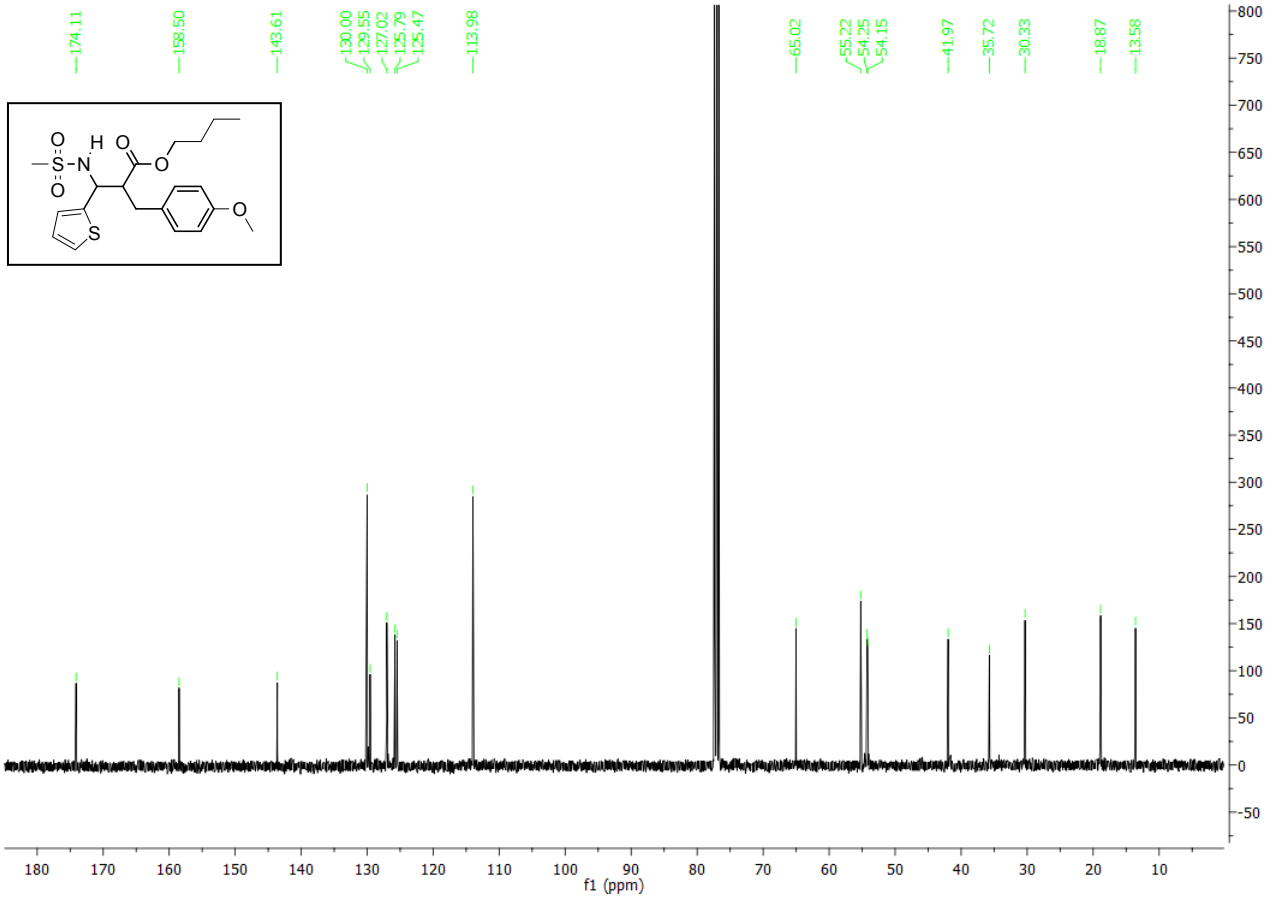
Butyl 2-benzyl-3-(methylsulfonamido)-3-(thiophen-2-yl)propanoate 4o



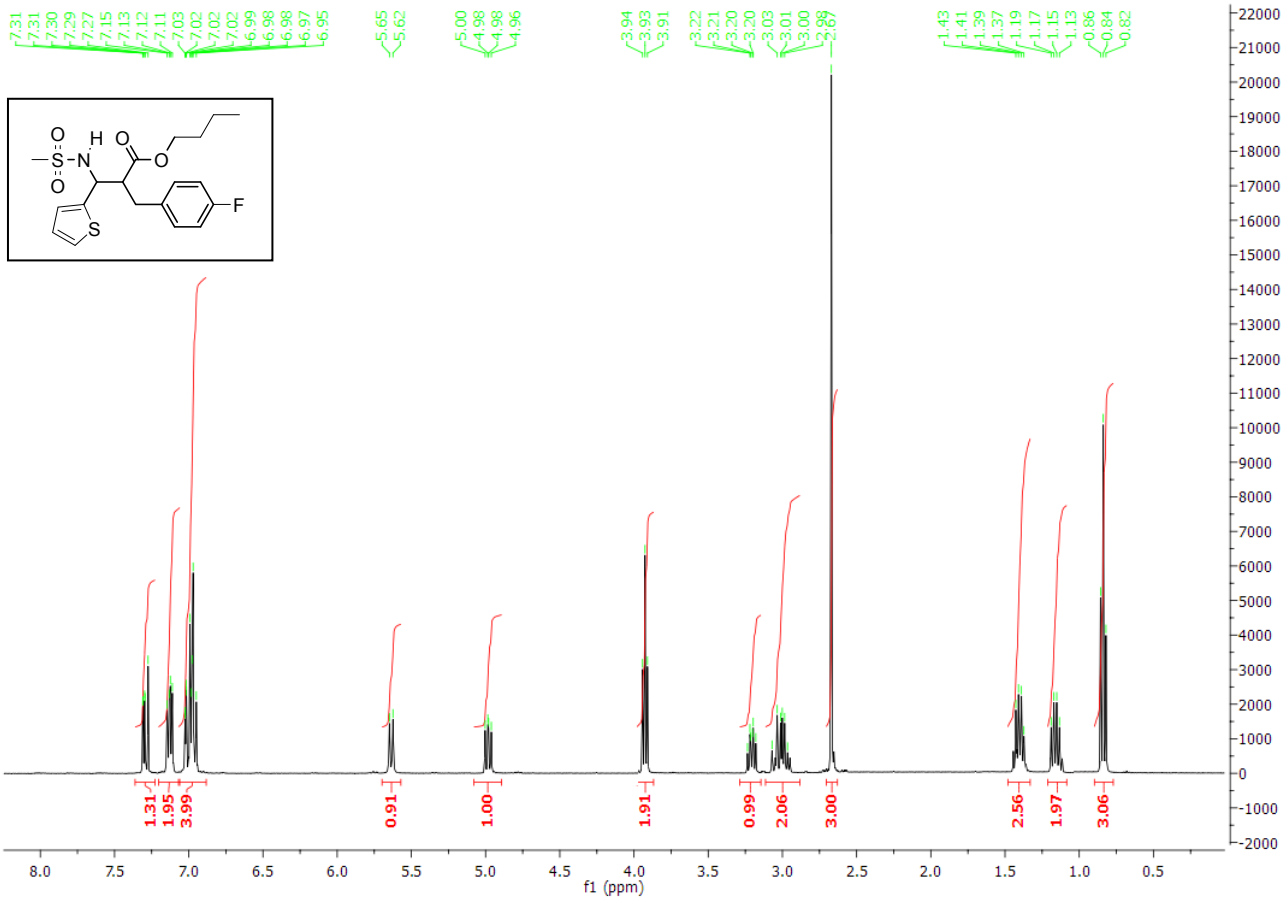


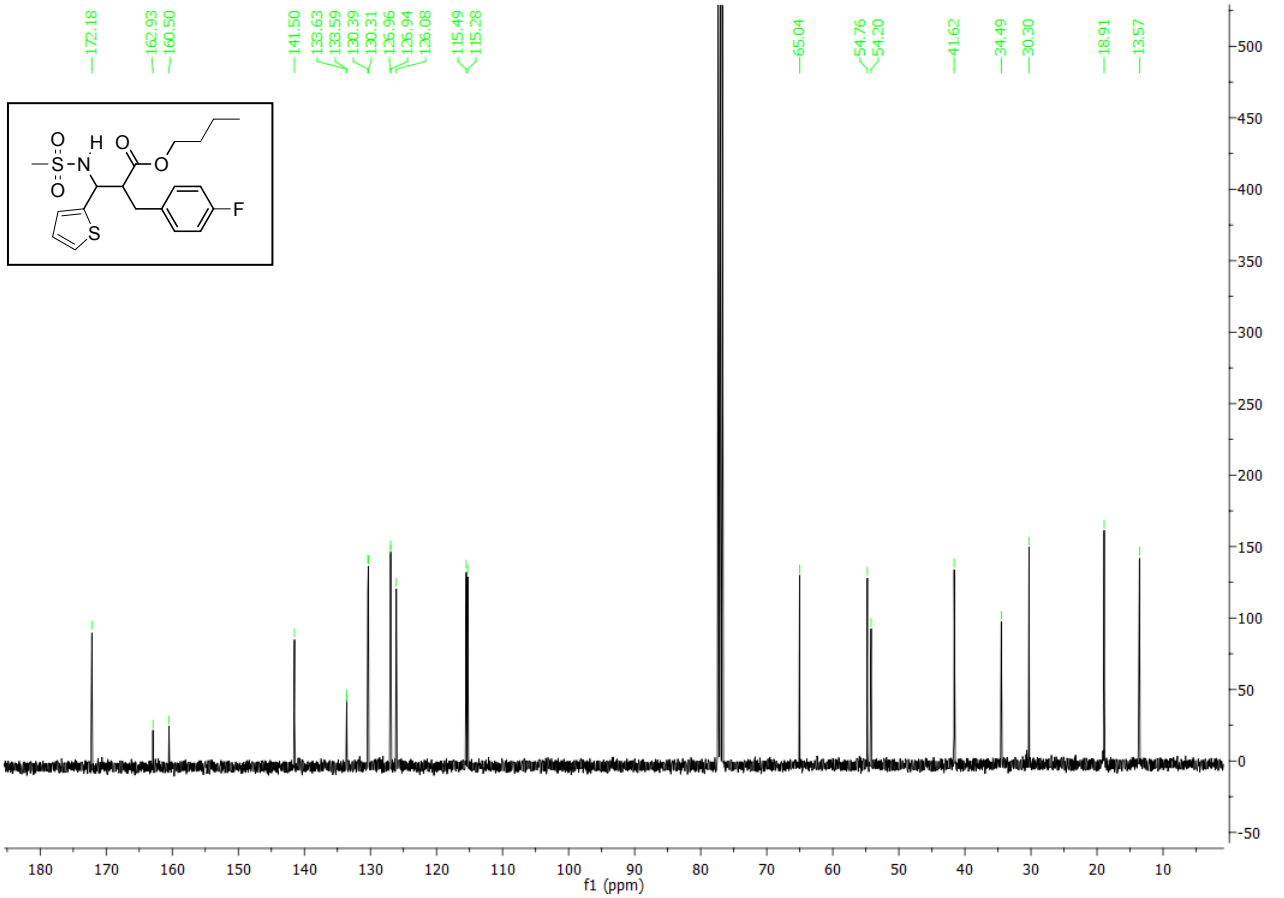
Butyl 2-(4-methoxybenzyl)-3-(methylsulfonamido)-3-(thiophen-2-yl)propanoate 4p

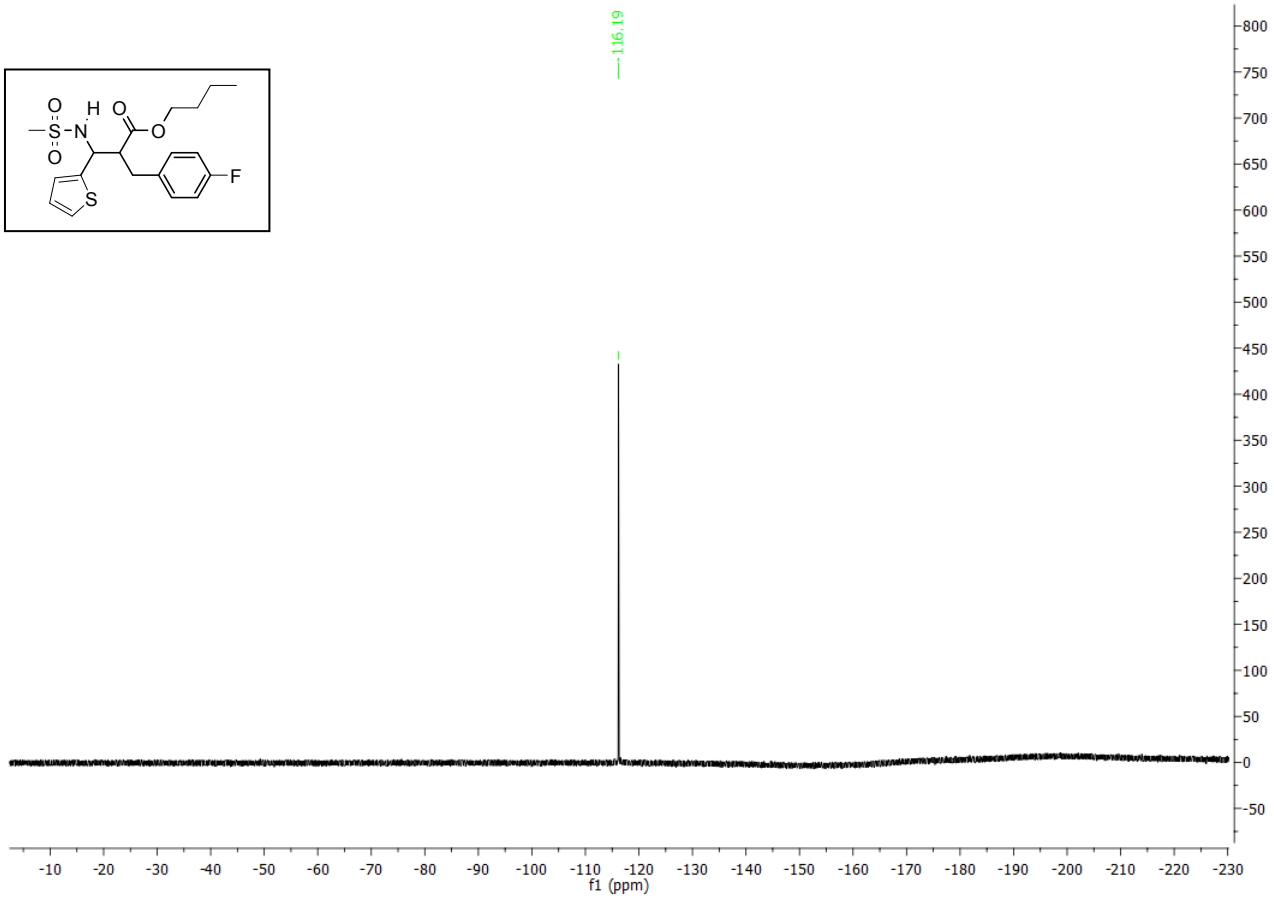




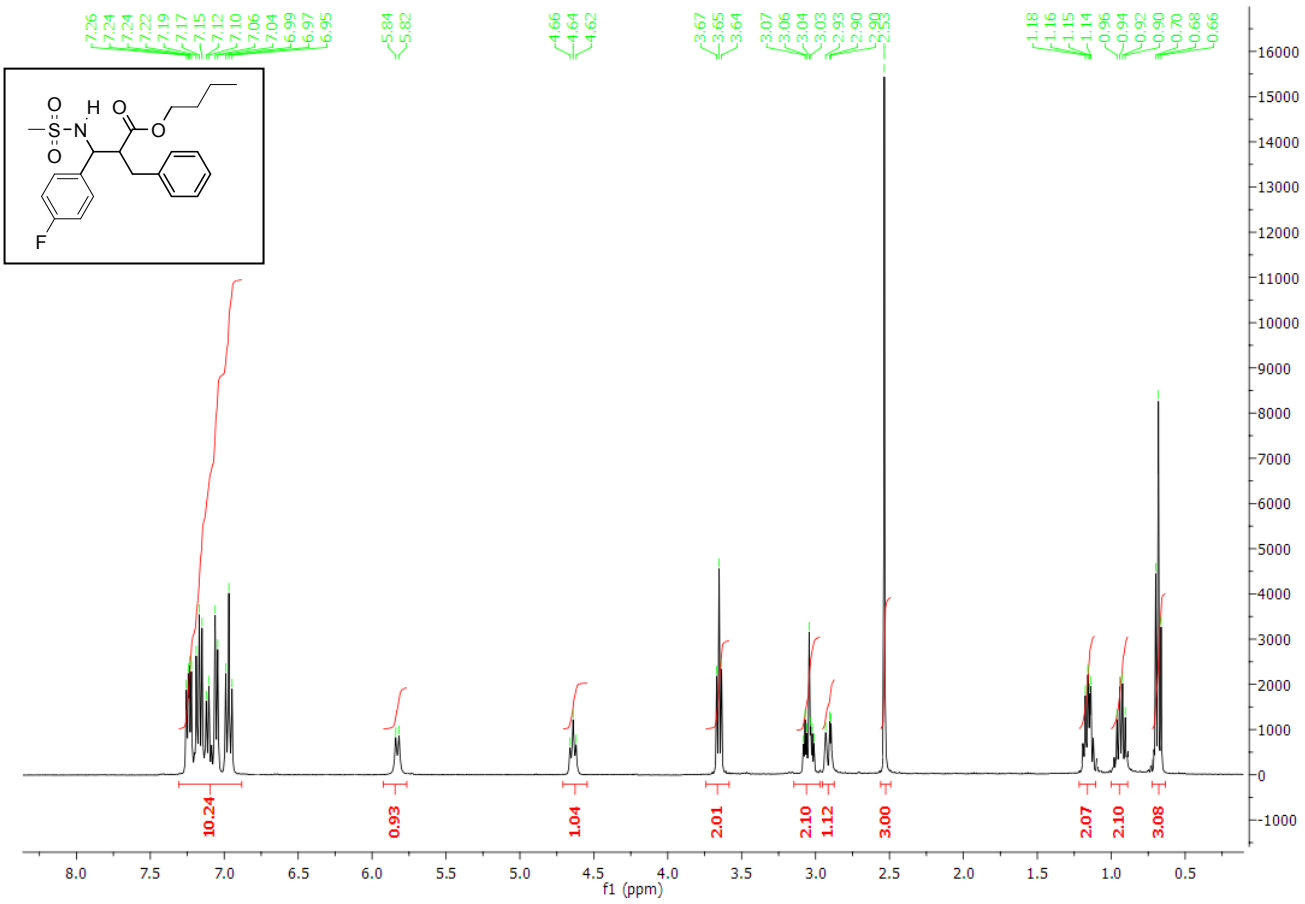
Butyl 2-(4-fluorobenzyl)-3-(methylsulfonamido)-3-(thiophen-2-yl)propanoate 4q

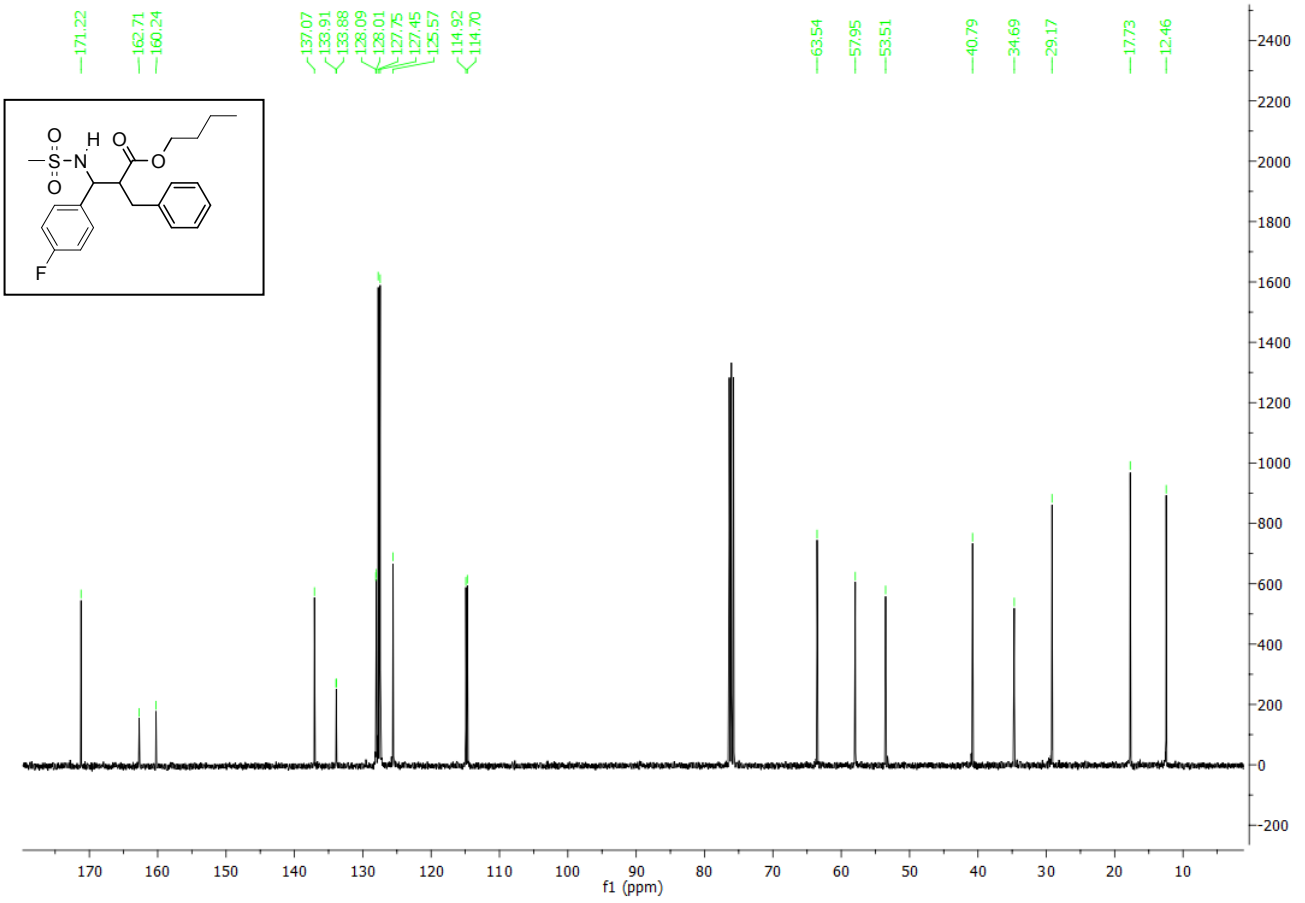


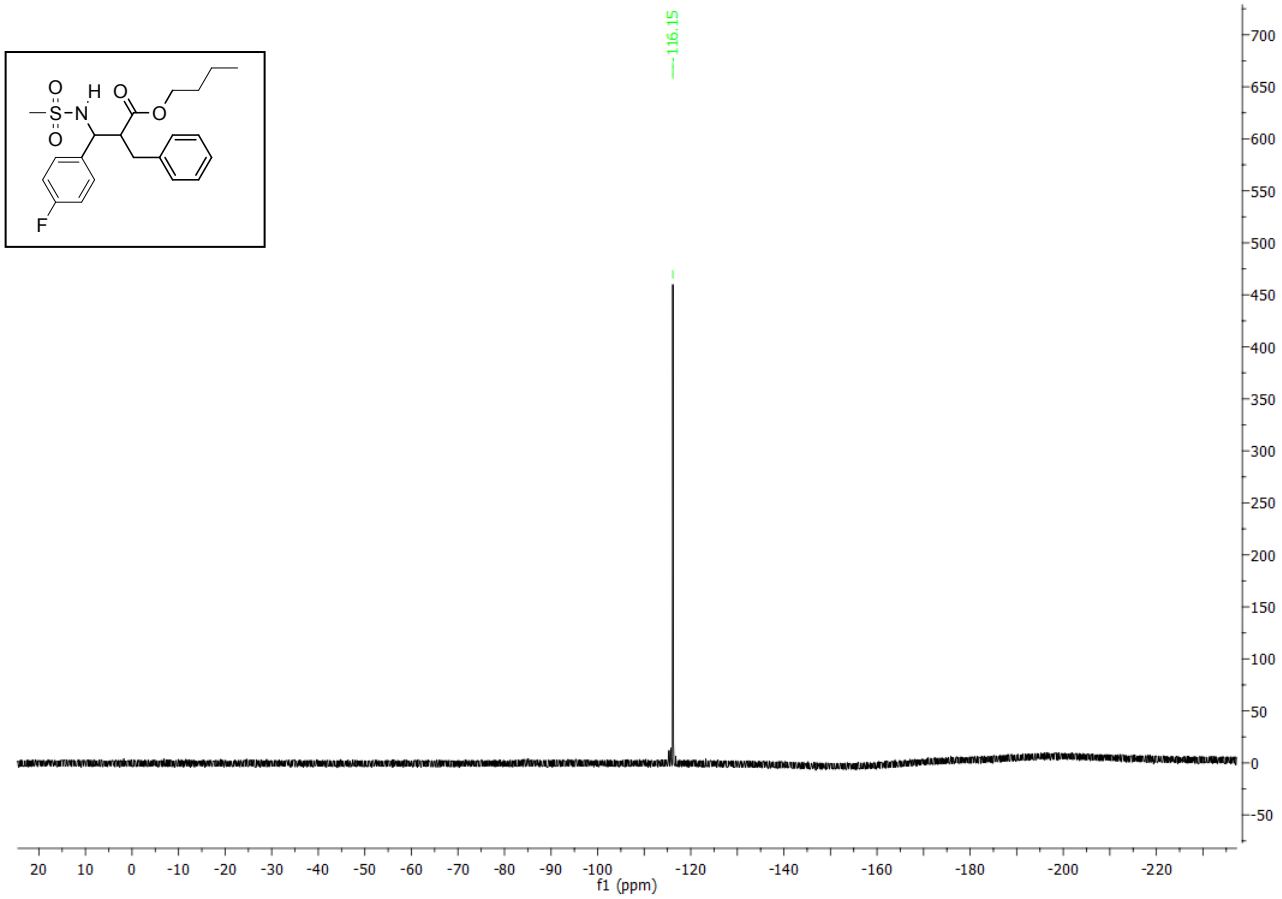



-116.19
f1 (ppm)

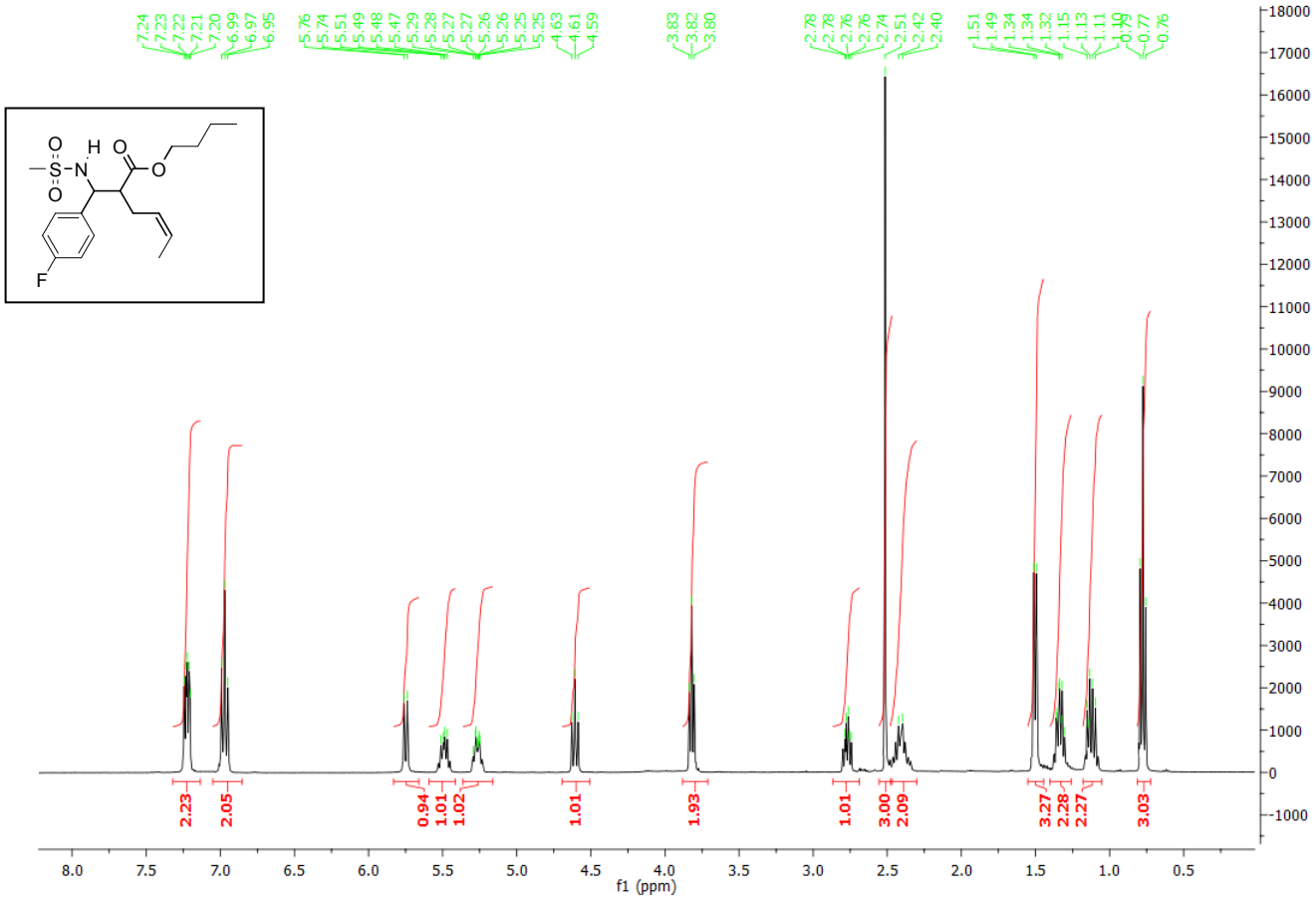
Butyl 2-benzyl-3-(4-fluorophenyl)-3-(methylsulfonamido)propanoate 4r

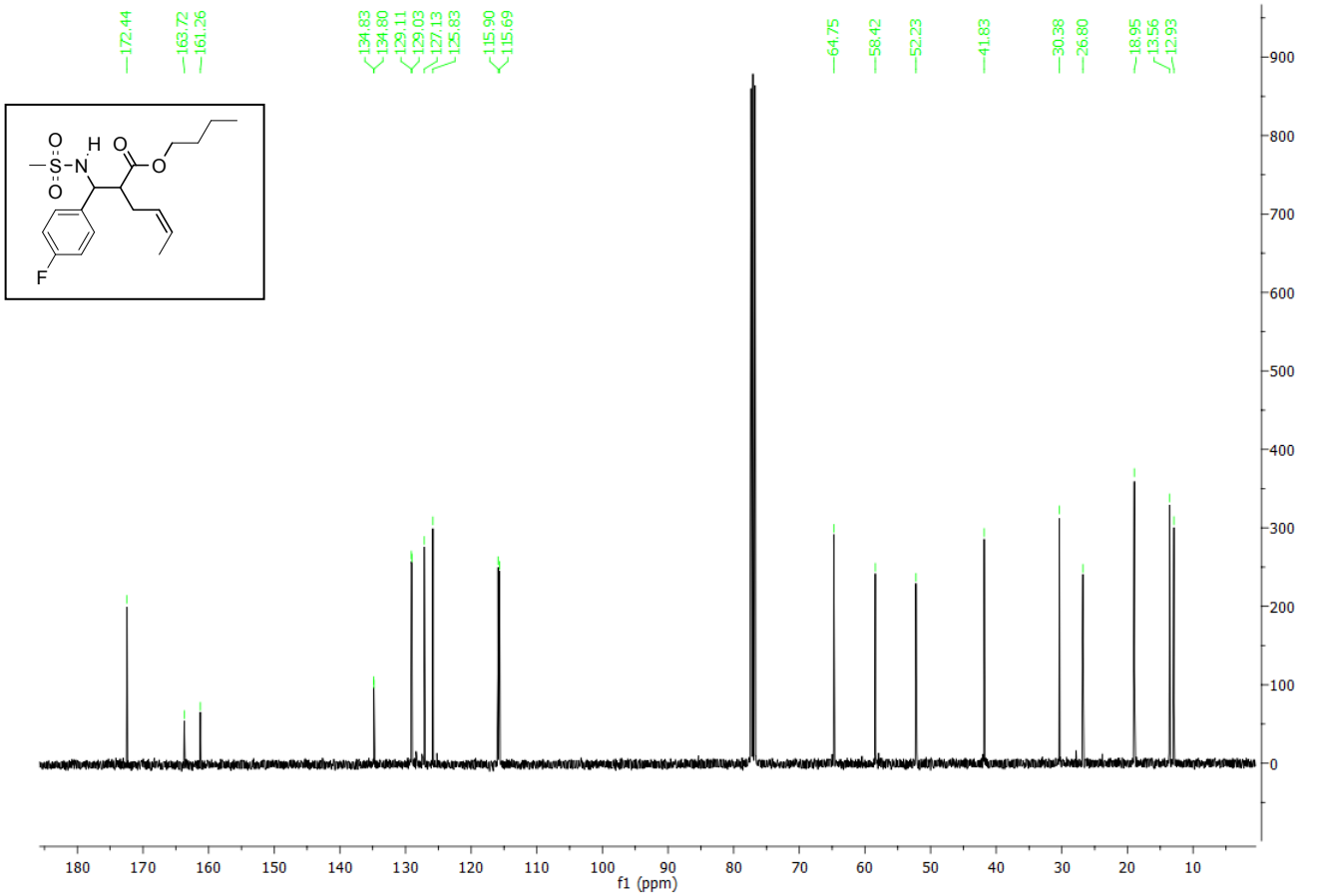


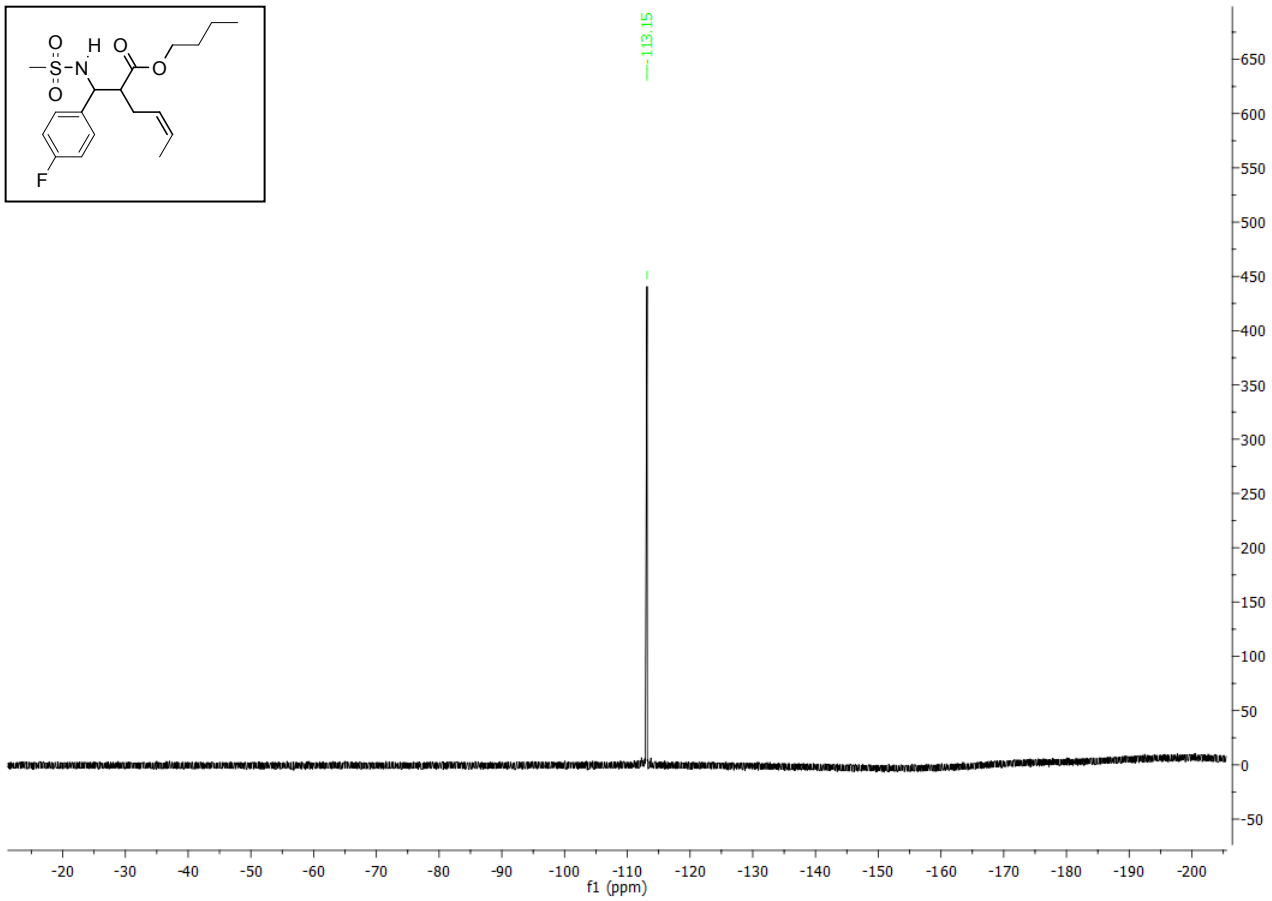



-116.15
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
-220
f1 (ppm)
O
H
O
S
N
O
O
F

(Z)-Butyl 2-((4-fluorophenyl)(methylsulfonamido)methyl)hex-4-enoate 4s






-113.15
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)
O
H
O
S
N
O
O
F

(Z)-Ethyl 2-((4-methoxyphenyl)(methylsulfonamido)methyl)hex-4-enoate 4t