N-Sulfenylation of β-Lactams: Radical Reaction of *N*-Bromo-azetidinones by TEMPO Catalysis

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Supporting Information

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Detailed experimental procedures and characterization.

General methods

Commercial reagents and solvents were used further purification. Merck silica gel (240-400 mesh, 60 Å) was used for flash chromatography purifications. ^{1}H and ^{13}C NMR spectra were recorded with a Varian INOVA 400MHz instrument with a 5 mm probe. All chemical shifts were quoted relative to deuterated solvent signals (δ in ppm and J in Hz). Polarimetric analyses were conducted at 20°C on an Unipol L1000 "Schmidt−Haensch" polarimeter at 589.30 nm. ATR-FTIR spectra of pure compounds were recorded with a Bruker Alpha instrument and with an Agilent Technologies CARY 630 FTIR, in transmittance mode with a 4 cm^{-1} resolution in the 4000-400 cm^{-1} range. Melting points were found with a Buchi B-540 melting point Instrument. UPLC-MS analyses were performed with an Agilent Technologies 1260 Infinity II instrument, coupled with an Agilent Technologies Infinity Lab LC/MSD XT single-quadrupole mass spectrometer in full scan mode from m/z = 50 to 2600, in positive ion mode. The UPLC is equipped with a Phenomenex Gemini® 3 µm C18 (100x3 mm) column; the following method was used: mobile phase= H_2O/ACN (gradient from 30% to 80% of ACN in 8 minutes, then isocratic for 15 minutes), flow= 0.4 mL/min, temperature=40°C. GC-MS analyses, in EI ionization at 70 eV, were acquired on a Agilent Technologies 6950 Network GC System coupled with an Agilent 5975 Inert XL Mass Selective Detector, from 70°C to 230 °C in 20 minutes. High Resolution Mass Spectrometry analyses (HR-MS) were conducted on a Waters Acquity UPLC coupled with a Waters Xevo G2-XS QTof mass detector. ESR spectra were collected using a Bruker ELEXYS spectrometer equipped with an NMR gaussmeter for field calibration.
Compounds **1c**, **1d**, and **1e** were synthetized accordingly to already published procedures. [1,2]
Compounds **1f** was synthetized starting from **1a** in the presence of $Zn(OAc)_2$ and excess ethanol in toluene at 80°C. Compound **1g** was obtained from **1a**, in the presence of $NaHCO_3$ and phenol in a 3:2 acetone/water mixture, according to Ref. [3], whilst **1h** was obtained by reduction of **1b** with $NaBH_4$ at 0°C in ethanol [4].

Synthesis of 1-bromo-4-oxazetidin-2-yl acetate (2a)

Following GP1, starting from the commercially available 4-acetoxy azetidin-2-one **1a** (310 mg, 2.4 mmol, 1 eq) in DCM (6 mL), by using 1 equivalent of NBS (430 mg, 2.4, 1 eq) and a second addition of NBS (110 mg, 0.6 mmol, 0.25 eq) after 4 hours, **2a** was obtained, after flash chromatography on silica gel (Cy:EtOAc = 70:30), in 96% yield (478 mg, pale yellow oil which under high vacuum or by seed crystallization turns into a white solid). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (dd, 1H, J = 4.1,

1.5 Hz), 3.44 (dd, 1H, J = 13.8, 4.2 Hz), 3.19 (dd, 1H, J = 13.8, 1.5 Hz), 2.1 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 170.0, 165.2, 80.0, 46.2, 20.9. GC-MS: Rt = 11.150 min, 148 $[M\text{-}CH_3COO]^+$ 90%, 121 $[M\text{-}CH_2CHOOCCH_3]^+$ 22%, 106 $[148\text{-}CH_2CO]^+$ 65%, 86 $[M\text{-}121]^+$ 100%. ATR-FTIR (cm^{-1}) 3024, 2961, 2929, 1752, 1726, 1374, 1348, 1321, 1216, 1198, 1172, 1037, 1017, 987, 888, 831, 505. Mp 64-65 °C.

Synthesis of (2*R*,3*R*)-1-bromo-3-((*R*)-1-((tert-butyldimethylsilyl)oxy)ethyl)-4-oxoazetidin-2-yl acetate (2b)

Following GP1, starting from the commercially available **1b** (172 mg, 0.6 mmol, 1 eq) in the presence of 2 equivalents of NBS (214 mg, 1.2 mmol) in anhydrous DCM (6 mL), compound **2b** was obtained in 3 hours as a pale yellow oil in 96% yield (210 mg), after flash chromatography on silica gel (Cy:EtOAc = 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.20 (d, 1H, J = 1.3 Hz), 4.24 (qd, 1H, J = 6.3, 2.7 Hz), 3.35 (dd, 1H, J = 2.8, 1.3 Hz), 2.16 (s, 3H), 1.25 (d, 3H, J = 6.3 Hz), 0.88 (s, 9H), 0.07 (d, 6H, J = 5.2 Hz). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 169.9, 166.9, 82.3, 66.4, 64.2, 25.8, 22.3, 21.0, -4.2, -5.0. GC-MS: Rt = 18.608 min, 297 = $[M]^{+\cdot}$ 1%, 192 = $[M\text{-}C_7H_7O]^+$ 9%, 148 = $[192\text{-}CH_2O]^+$ 7%, 106 = $[148\text{-}CH_2CO]^+$ 41%, 91 = $[C_7H_7]^+$ 100%. ATR-FTIR (cm^{-1}) 2955, 2930, 2886, 2857, 1792, 1762, 1376, 1218, 1173, 1063, 1036, 827, 809, 777. Polarimetry: $[\alpha]_D^{20}$ = -14 (*c* 1.6, CH_3OH).

Synthesis of benzyl 2-(1-bromo-4-oxazetidin-2-yl)acetate (2c)

Following GP1, starting from **1c** (110 mg, 0.5 mmol, 1 eq) in the presence of 2 equivalents of NBS (178 mg, 1 mmol) in anhydrous DCM (5 mL), compound **2b** was obtained in 5 hours as a pale yellow oil in 97% yield (144 mg), after flash chromatography on silica gel (Cy:EtOAc = 75:25). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (t, 5H, J = 2.5 Hz), 5.19 (d, 1H, J_{AB}= 12.2 Hz), 5.15 (d, 1H, J_{AB}= 12.2 Hz), 4.12 (dtd, 1H, J = 7.9, 5.3, 2.6 Hz), 3.36 (dd, 1H, J = 13.5, 5.3 Hz), 3.02 (dd, 1H, J = 13.5, 2.6 Hz), 2.90 (dd, 1H, J = 16.3, 5.3 Hz), 2.62 (dd, 1H, J = 16.3, 8.0 Hz). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 169.4, 167.0, 135.3, 128.8, 128.8, 128.6, 67.3, 55.0, 44.9, 37.9. GC-MS Rt = 18.608 min, 297 = $[M]^{+\cdot}$ 1%, 192 = $[M\text{-}C_7H_7O]^+$ 9%, 148 = $[192\text{-}CH_2O]^+$ 7%, 106 = $[148\text{-}CH_2CO]^+$ 41%, 91 = $[C_7H_7]^+$ 100%. ATR-FTIR (cm^{-1}) 3089, 3065, 3033, 2955, 1764, 1727, 1389, 1259, 1168, 1093, 1015, 738, 697.

Synthesis of 1-bromo-4-(phenylsulfonyl)azetidin-2-one (2d)

Following GP1, starting from **1d** (106 mg, 0.5 mmol) in the presence of 2 equivalents of NBS (178 mg, 1 mmol) in anhydrous DCM (5 mL), compound **2d** was obtained in 4 hours as a waxy white solid in 58% yield (84 mg) after flash chromatography on silica gel (Cy:EtOAc = 85:15). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (ddd, 2H, J = 8.5, 1.3, 0.6 Hz), 7.82 – 7.73 (m, 1H), 7.66 (ddd, 2H, J = 8.6, 7.1,

0.6 Hz), 4.74 (dd, 1H, J = 5.3, 2.7 Hz), 3.49 (dd, 1H, J = 14.2, 2.7 Hz), 3.43 (dd, 1H, J = 14.2, 5.3 Hz). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.7, 135.4, 129.9, 129.9, 129.5, 72.1, 42.2. ATR-FTIR (cm^{-1}) 1770, 1447, 1308, 1144, 1064, 745, 683, 562, 513, 408.

Synthesis of (3*S*,4*R*)-1-bromo-3-((*R*)-1-((tert-butyldimethylsilyl)oxy)ethyl)-4(phenylsulfonyl)azetidin2one (2e)

Following GP1, starting from **1e** (50 mg, 0.135 mmol, 1 eq) in the presence of 2 equivalents of NBS (48 mg, 0.27 mmol) in anhydrous DCM (1.3 mL), compound **2e** was obtained in 3 hours as a waxy colourless solid in 86% yield (70 mg), after flash chromatography on silica gel (Cy:EtOAc = 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (dd, 2H, J = 8.4, 1.2 Hz), 7.79 – 7.71 (m, 1H), 7.68 – 7.60 (m, 2H), 4.81 (d, 1H, J = 2.3 Hz), 4.30 (qd, 1H, J = 6.3, 1.8 Hz), 3.67 (t, 1H, J = 2.0 Hz), 1.20 (d, 3H, J = 6.4 Hz), 0.84 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 167.2, 135.2, 129.8, 129.8, 74.3, 63.9, 63.5, 25.8, 22.4, 17.9, -4.2, -5.0. ATR-FTIR (cm^{-1}) 2955, 2930, 2885, 2857, 1787, 1447, 1325, 1254, 1140, 1057, 957, 838, 826, 778, 583. Polarimetry: $[\alpha]_D^{20}$= -79 (*c* 0.47, CH_3OH).

Synthesis of 1-bromo-4-ethoxyazetidin-2-one (2f)

Following GP1, starting from **1f** (100 mg, 0.87 mmol, 1 eq) in the presence of 2 equivalents of NBS (309 mg, 1.74 mmol) in anhydrous DCM (8.7 mL), compound **2f** was obtained in 1 hour as a yellow oil in 15% yield (24 mg), after flash chromatography on silica gel (Cy:EtOAc = 65:35). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.09 (dd, 1H, J = 4.2, 1.8 Hz), 3.86 (dq, 1H, J = 9.3, 7.0 Hz), 3.66 (dq, 1H, J = 9.3, 7.0 Hz), 3.18 (dd, 1H, J = 13.6, 4.1 Hz), 3.10 (dd, 1H, J = 13.6, 1.8 Hz), 1.24 (t, 3H, J = 7.1 Hz). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 166.5, 87.4, 64.6, 45.3, 29.6, 28.7, 15.2. ATR-FTIR (cm^{-1}) 3151, 3077, 2792, 1770, 1683, 1362, 1292, 1176, 1100, 1064, 1003, 816, 635.

Synthesis of 1-bromo-4-phenoxyazetidin-2-one (2g)

Following GP1, starting from **1g** (51 mg, 0.31 mmol, 1 eq) in the presence of 1.1 equivalents of NBS (61 mg, 0.34 mmol) in anhydrous DCM (0.75 mL), compound **2g** was obtained in 1 hour as a yellow oil in 81% yield (75 mg), after flash chromatography on silica gel (Cy:EtOAc = 75:25). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.30 (m, 2H), 7.16 – 7.08 (m, 1H), 7.08 – 7.01 (m, 2H), 5.68 (dd, 1H, J = 4.0, 1.6 Hz), 3.45 (dd, 1H, J = 13.3, 3.7 Hz), 3.32 (dd, 1H, J = 13.5, 1.6 Hz). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.6, 155.7, 129.9, 123.8, 117.5, 85.9, 46.6. ATR-FTIR (cm^{-1}) 2939, 2253, 1772, 1590, 1485, 1362, 1286, 1223, 1195, 1128, 1051, 1005, 960, 859, 823, 751, 690.

Synthesis of (*S*)-1-bromo-3-((*R*)-1-((tert-butyldimethylsilyl)oxy)ethyl)azetidin-2-one (2h)

Following GP1, starting from **1h** (100 mg, 0.44 mmol, 1 eq) in the presence of 1 equivalents of NBS (78 mg, 0.44 mmol) in anhydrous DCM (1.1 mL), compound **2h** was obtained in 2 hours as a white solid in 89% yield (120 mg), after flash chromatography on silica gel (Cy:EtOAc = 75:25). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (qd, 1H, J = 6.2, 3.1 Hz), 3.62 – 3.56 (m, 1H), 3.49 (td, 1H, J = 4.9, 1.1 Hz), 3.44 (td, 1H, J = 4.7, 2.1 Hz), 1.15 (d, 3H, J = 6.3 Hz), 0.86 (s, 9H), 0.05 (s, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 169.5, 64.8, 61.1, 49.2, 25.8, 22.6, 17.9, -4.2, -5.0. ATR-FTIR (cm^{-1}) 2954, 2928, 2894, 2857, 1772, 1750, 1716, 1465, 1407, 1375, 1251, 1196, 1068, 1005, 956, 837, 805, 777. Polarimetry: $[\alpha]_D^{20}$ = - 40 (*c* 0.14, CH_2Cl_2).

Synthesis of 1-iodo-4-oxazetidin-2-yl acetate (**3a**)

Following GP1, starting from **1a** (120 mg, 0.9 mmol, 1 eq) in the presence of NIS (405 mg, 1.8 mmol, 2 eq) in anhydrous DCM (3 mL), **3a** was obtained, after 4 hours and flash chromatography on silica gel (Cy:EtOAc = 70:30), as a brown solid in 71% yield (163 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04 (dd, 1H, *J* = 4.0, 1.4 Hz), 3.44 (dd, 1H, *J* = 14.0, 4.0 Hz), 3.32 (dd, 1H, *J* = 13.9, 1.5 Hz), 2.16 (d, 3H, *J* = 0.9 Hz). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 170.2, 169.0, 79.2, 46.1, 20.9. GC-MS: R_t = 9.531 min, 253 = $[M\text{-}H_2]^{+\cdot}$ (29%), 196 = $[M\text{-}CH_3COO]^{+}$ (27%), 195 = $[M\text{-}CH_3COOH]^{+\cdot}$ (47%), 128 = $[M\text{-}I]^{+\cdot}$ (100%), 127 = $I^{+\cdot}$ (47%). ATR-FTIR (cm^{-1}) 3012, 2981, 1747, 1720, 1216, 1199, 1182, 1038, 1017, 891, 498.

Synthesis of 1-chloro-4-oxazetidin-2-yl acetate (4a)

Following GP1, starting from **1a** (155 mg, 1.2 mmol, 1 eq) in the presence of NCS (643 mg, 4.8 mmol, 4 eq) in anhydrous DCM (4 mL), **4a** was obtained in 7 hours as a colourless liquid in 42% yield (82 mg), after flash chromatography on silica gel (Cy:EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.17 (dd, 1H, J = 4.2, 1.4 Hz), 3.50 – 3.36 (m, 1H), 3.16 – 3.07 (m, 1H), 2.18 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 170.0 164.0, 80.3, 45.4, 20.8. GC-MS: Rt = 9.657 min, 163 = $[M]^{+\cdot}$ (4%), 121 = $[M\text{-}CH_2CO]^{+}\cdot$ (6%), 113 = $[M\text{-}CH_3Cl]$ (4%), 104 = $[M\text{-}CH_3COO]^{+}$ (100%), 76 = $[104\text{-}CO]^{+}$ (66%). ATR-FTIR (cm^{-1}) 3028, 2963, 2922, 2852, 1793, 1751, 1375, 1358, 1197, 1154, 1040, 1020, 890.

Synthesis of 4-oxo-1-(phenylthio)azetidin-2-yl acetate (5)

Following GP2, **2a** (41.5 mg, 0.2 mmol) was reacted with diphenyl disulfide (44 mg, 0.2 mmol) for 5 hours, yielding compound **5** as a colourless oil in 82% yield (39 mg) after flash chromatography on

silica gel (Cy:EtOAc = 70:30). Spectroscopic data is consistent with those found in literature [1]. See below for ^{1}H NMR and HPLC-MS analyses.

Synthesis of 1-(methylthio)-4-oxoazetidin-2-yl acetate (6)

Following GP2, **2a** (41.5 mg, 0.2 mmol) was reacted with dimethyl disulfide (18 µL, 0.2 mmol) for 5 hours. Compound **6** was obtained as a colourless oil in 75% yield (26 mg) after flash chromatography on silica gel (Cy:EtOAc = 70:30). Spectroscopic data is consistent with those found in literature [1]. See below for ^{1}H NMR and HPLC-MS analyses.

Synthesis of 1-(isopropylthio)-4-oxoazetidin-2-yl acetate (7)

Following GP2, **2a** (41.5 mg, 0.2 mmol) was reacted with Diisopropyl disulfide (31 µL, 0.2 mmol), overnight. Compound **7** was obtained as a colourless oil in 64% yield (26 mg) after flash chromatography on silica gel (Cy:EtOAc = 70:30). Spectroscopic data is consistent with those found in literature [5]. See below for ^{1}H NMR and HPLC-MS analyses.

Synthesis of 1-(propylthio)-4-oxoazetidin-2-yl acetate (8)

Following GP2, **2a** (41.5 mg, 0.2 mmol) was reacted with dipropyl disulfide (31 µL, 0.2 mmol), overnight. Compound **8** was obtained as a colourless oil in 74% yield (30 mg) after flash chromatography on silica gel (Cy:EtOAc = 70: 30). Spectroscopic data is consistent with those found in literature [5]. See below for ^{1}H NMR and HPLC-MS analyses.

Synthesis of 1-(benzylthio)-4-oxoazetidin-2-yl acetate (9)

Following GP2, compound **2a** (41.5 mg, 0.2 mmol) was reacted with dibenzyl disulfide (49 mg, 0.2 mmol, 1 eq), for 5 hours. Compound **9** was isolated after flash cromatography on silica gel (Cy:EtOAc = 70:30), in 72% yield (36 mg), as a colourless oil. Spectroscopic data is consistent with data found in literature [5]. See below for ^{1}H NMR and HPLC-MS analyses.

Synthesis of 1-(benzo[d]thiazol-2-ylthio)-4-oxoazetidin-2-yl acetate (10)

Following GP2, compound **2a** (41.5 mg, 0.2 mmol) was reacted with 2,2'-Dibenzothiazolyl Disulfide (66 mg, 0.2 mmol) in 1 mL of DCM, overnight. Compound **10** was isolated after flash chromatography on silica gel (Cy:EtOAc =70:30), in 70% yield (41 mg), as a white solid. Spectroscopic data is consistent with data found in literature [5]. See below for ^{1}H NMR and HPLC-MS analyses.

Synthesis of 1-((4-methoxyphenyl)thio)-4-oxoazetidin-2-yl acetate (11)

Following GP2, compound **2a** (41.5 mg, 0.2 mmol) was reacted with bis(4-methoxyphenyl) disulfide (55.6 mg, 0.2 mmol), for 5 hours. Compound **11** was isolated after flash cromatography on silica gel (Cy:EtOAc = 70:30), in 82% yield (44 mg), as a colourless oil. Spectroscopic data is consistent with data found in literature [5]. See below for ^{1}H NMR and HPLC-MS analyses.

Synthesis of 1-((4-nitrophenyl)thio)-4-oxoazetidin-2-yl acetate (12)

Following GP2, compound **2a** (41.5 mg, 0.2 mmol) was reacted with bis(4-nitrophenyl) disulfide (61.7 mg, 0.2 mmol) in 1 mL of DCM, overnight. Compound **12** was isolated after flash cromatography on silica gel (Cy:EtOAc = 70:30), in 55% yield (29 mg), as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 – 8.11 (m, 2H), 7.47 – 7.34 (m, 2H), 6.27 (dd, 1H, J = 4.4, 1.8 Hz), 3.58 (dd, 1H, J = 15.7, 4.4 Hz), 3.26 (dd, 1H, J = 15.7, 1.8 Hz), 2.03 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.9, 167.7, 146.9, 146.1, 125.0, 124.5, 79.3, 46.7, 20.8. HPLC-MS (ESI^+) Rt = 6.478 min, 305.1 = $[M+Na]^+$, 321.0 = $[M+K]^+$, 346.0 = $[M+ACN+Na]^+$. ATR-FTIR (cm^{-1}) 3110, 3100, 3020, 2959, 2921, 2852, 1788, 1747, 1504, 1341, 122-2, 1208, 1046, 1031, 837, 793. Mp: 89.8-90.8 °C.

Synthesis of 4-oxo-1-(pyridin-2-ylthio)azetidin-2-yl acetate (13)

Following GP2, compound **2a** (42 mg, 0.2 mmol) was reacted with 2,2-dipyridyldisulfide (44 mg, 0.2 mmol) for 5 hours. Compound **13** was obtained as a colourless oil in 78% yield (37 mg), after flash chromatography on silica gel (Cy:EtOAc: 75:25). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (ddd, 1H, J = 4.9, 1.9, 1.0 Hz), 7.62 – 7.51 (m, 1H), 7.15 (dt, 1H, J = 8.1, 1.0 Hz), 7.06 (ddd, 1H, J = 7.5, 4.9, 1.0 Hz), 6.33 (dd, 1H, J = 4.4, 1.7 Hz), 3.65 (dd, 1H, J = 15.5, 4.4 Hz), 3.20 (dd, 1H, J = 15.5, 1.8 Hz), 2.08 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.2, 168.4, 158.3, 149.9, 137.0, 121.12, 118.4, 79.6, 46.8, 20.9. HPLC-MS (ESI^+): Rt =3.978 min, 239.2= $[M+H]^+$, 261.0= $[M+Na]^+$, 498.9=$[2M+Na]^+$. ATR-FTIR (cm^{-1}) 1784, 1750, 1575, 1450, 1418, 1374, 1280, 1198, 1152, 1128, 1042, 1023, 898, 826, 759, 725. HRMS (ESI^+/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_{11}N_2O_3S$ 239.0490; Found 239.0479.

Synthesis of benzyl 2-(4-oxo-1-(phenylthio)azetidin-2-yl)acetate (14)

Following GP2, compound **2c** (60 mg, 0.2 mmol) was reacted with diphenyl disulfide (44 mg, 0.2 mmol), overnight. Compound **14** was obtained as a colourless oil in 92% yield (60 mg), after flash chromatography on silica gel (Cy:EtOAc: 75:25). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.22 (m, 10H), 5.09 (d, 1H, J_{AB}= 12.3 Hz), 5.07 (d, 1H, J_{AB}= 12.3 Hz), 4.12 (dtd, 1H, J = 8.2, 5.3, 2.8 Hz),

3.32 (dd, 1H, J = 15.2, 5.5 Hz), 2.98 – 2.88 (m, 2H), 2.55 (dd, 1H, J = 16.2, 8.4 Hz). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 16.9, 136.8, 135.4, 129.4, 128.8, 128.6, 128.5, 128.4, 128.3, 67.0, 52.5, 44.7, 37.9. HPLC-MS (ESI^+): Rt = 8.831 min, 328.0 = $[M+H]^+$, 350.0 = $[M+Na]^+$, 677.0 = $[2M+Na]^+$. ATR-FTIR (cm^{-1}) 3061, 3033, 2954, 2922, 2852, 1764, 1730, 1581, 1262, 1161, 1091, 1020, 738, 690. HRMS (ESI^+/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{18}NO_3S$ 328.1007; Found 328.0993.

Synthesis of benzyl 2-(4-oxo-1-(propylthio)azetidin-2-yl)acetate (15)

Following GP2, compound **2c** (60 mg, 0.2 mmol) was reacted with dipropyl disulfide (31 μL, 0.2 mmol), overnight. Compound **15** was obtained as a colourless oil in 88% yield (52 mg), after flash chromatography on silica gel (Cy:EtOAc: 75:25). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.29 (m, 5H), 5.18 (d, 1H, J_{AB}= 12.3 Hz), 5.14 (d, 1H, J_{AB}= 12.3 Hz), 4.04 (dtd, 1H, J = 8.1, 5.4, 2.8 Hz), 3.25 (dd, 1H, J = 15.1, 5.4 Hz), 2.95 (dd, 1H, J = 16.0, 5.3 Hz), 2.83 (dd, 1H, J = 15.1, 2.8 Hz), 2.74 – 2.64 (m, 1H), 2.67 – 2.52 (m, 2H), 1.62 (h, 2H, J = 7.3 Hz), 1.00 (t, 3H, J = 7.3 Hz). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 170.4, 170.1, 135.4, 128.8, 128.6, 128.5, 67.0, 52.3, 44.4, 41.0, 38.1, 22.2, 13.2. HPLC-MS (ESI^+): Rt = 8.231 min 294.1=$[M+H]^+$, 316.0= $[M+Na]^+$, 609.0=$[2M+Na]^+$. ATR-FTIR (cm^{-1}) 2931, 2933, 2873,1760, 1729, 1497, 1455,1398, 1314, 1261, 1163, 1091, 1020, 738, 607, 579. HRMS (ESI^+/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{20}NO_3S$ 294.1164; Found 294.1151.

Synthesis of benzyl 2-(4-oxo-1-(benzylthio)azetidin-2-yl)acetate (16)

Following GP2, compound **2c** (60 mg, 0.2 mmol) was reacted with dibenzyl disulfide (49 mg, 0.2 mmol), overnight. Compound **16** was obtained as a colourless oil in 65% yield (44 mg), after flash chromatography on silica gel (Cy:EtOAc: 75:25). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.05 (m, 10 H), 5.09 (d, 1H, J_{AB}= 12.3 Hz), 5.05 (d, 1H, J_{AB}= 12.3 Hz), 4.04 (d, 1H, J = 12.6 Hz), 3.89 (d, 1H, J = 12.6 Hz), 3.49 (dtd, 1H, J = 8.2, 5.3, 2.8 Hz), 3.09 (dd, 1H, J = 15.1, 5.4 Hz), 2.80 – 2.58 (m, 2H), 2.30 (dd, 1H, J = 16.0, 8.3 Hz). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 169.9, 135.8, 135.5, 129.5, 128.9, 128.7, 128.6, 128.4, 127.9, 66.8, 52.3, 44.3, 42.9, 37.6, 27.0. HPLC-MS (ESI^+): Rt = 8.855 min, 342.0= $[M+H]^+$, 364.0=$[M+Na]^+$, 380.0= $[M+K]^+$, 705.0=$[2M+Na]^+$. ATR-FTIR (cm^{-1}) 3030, 2953, 2854, 1759, 1728, 1495, 1454, 1388, 1313, 1262, 1162, 1092, 1020, 739, 696, 506. HRMS (ESI^+/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{20}NO_3S$ 342.1164; Found 342.1154.

Synthesis of (2*R*,3*R*)-3-((*R*)-1-((tert-butyldimethylsilyl)oxy)ethyl)-4-oxo-1-(phenylthio)azetidin-2-yl acetate (17)

Following GP2, compound **2b** (73 mg, 0.2 mmol) was reacted with diphenyl disulfide (44 mg, 0.2 mmol), overnight. Compound **17** was isolated as a colourless oil in 76% yield (60 mg), after flash

chromatography on silica gel (Cy:EtOAc = 90:10.) Spectroscopic data is consistent with data found in literature [1]. See below for ^{1}H NMR and HPLC-MS analyses.

Synthesis of (2*R*,3*R*)-3-((*R*)-1-((tert-butyldimethylsilyl)oxy)ethyl)-4-oxo-1-(propylthio)azetidin-2-yl acetate (18) Following GP2, compound **2b** (73 mg, 0.2 mmol) was reacted with dipropyl disulfide (31 μL, 0.2 mmol), overnight. Compound **18** was obtained as a colourless oil in 40% yield (29 mg), after flash chromatography on silica gel (Cy:EtOAc= 90:10). Spectroscopic data is consistent with data found in literature [1]. See below for ^{1}H NMR and HPLC-MS analyses.

Synthesis of (2*R*,3*R*)-1-(benzylthio)-3-((*R*)-1-((tert-butyldimethylsilyl)oxy)ethyl)-4-oxoazetidin-2-yl acetate (19) Following GP2, compound **2b** (73 mg, 0.2 mmol) was reacted with dibenzyl disulfide (49 mg, 0.2 mmol), overnight. Compound **19** was obtained as a colourless oil in 70% yield (57 mg), after flash chromatography on silica gel (Cy:EtOAc = 90:10). Spectroscopic data is consistent with data found in literature [1]. See below for ^{1}H NMR and HPLC-MS analyses.

Synthesis of (*S*)-3-((*R*)-1-((tert-butyldimethylsilyl)oxy)ethyl)-1-(phenylthio)azetidin-2-one (20) Following GP2, compound **2h** (62 mg, 0.2 mmol) was reacted with diphenyl disulfide (44 mg, 0.2 mmol), overnight. Compound **20** was obtained as a colourless oil in 86% yield (58 mg), after flash chromatography on silica gel (Cy:EtOAc = 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, 4H, J = 4.3 Hz), 7.22 – 7.14 (m, 1H), 4.20 (qd, 1H, J = 6.2, 4.1 Hz), 3.54 (dd, 1H, J = 5.3, 3.1 Hz), 3.43 (t, 1H, J = 5.5 Hz), 3.32 (ddd, 1H, J = 5.7, 4.2, 3.1 Hz), 1.13 (d, 3H, J = 6.2 Hz), 0.79 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.8, 137.1, 129.3, 127.6, 127.1, 65.2, 59.9, 46.3, 25.8, 22.7, 18.0, -4.4, -4.8. HPLC-MS (ESI^+): Rt=10.650 min, 337.2=$[M+H]^+$, 360.2=$[M+Na]^+$, 697.2= $[2M+Na]^+$. ATR-FTIR (cm^{-1}) 3064, 2956, 2930, 2892, 2957, 1767, 1582, 1472, 1441, 1374, 1308, 1290, 1252, 1165, 1139, 1109, 1083, 1060, 1005, 958, 837, 807, 777, 736, 688. Polarimetry: $[\alpha]_D^{20}$= -45 (*c* 0.36, CH_2Cl_2). HRMS (ESI^+/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{28}NO_2SSi$ 338.1610; Found 338.1599.

Synthesis of 4-phenoxy-1-(phenylthio)azetidin-2-one (21)

Following GP2, compound **2g** (27mg, 0.11 mmol) was reacted with diphenyl disulfide (24 mg, 0.11 mmol), overnight. Compound **21** was obtained as a yellow oil in 40% yield (12 mg), after flash chromatography on silica gel (Cy:EtOAc = 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.21 (m, 7H), 7.05 (t, 1H, J = 7.4 Hz), 6.97 (d, 2H, J = 8.0 Hz), 5.73 (q, 1H, J = 2.0 Hz), 3.48 (dt, 1H, J = 15.0, 2.5 Hz), 3.25 (d, 1H, J = 15.1 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.6, 156.4, 136.7, 129.8,

129.3, 128.4, 128.3, 123.1, 116.7, 84.4, 47.2. HPLC-MS (ESI^+): Rt=6.973min, 272.2=$[M+H]^+$, 294.0=$[M+Na]^+$, $[2M+Na]^+$, 335.0=$[M+ACN+Na]^+$, 565.0=$[2M+Na]^+$. ATR-FTIR (cm^{-1}) 3058, 2954, 2371, 1774, 1588, 1489, 1457, 1441, 1362, 1282, 1221, 1155, 1154, 1131, 1077, 1055, 1014, 978, 865, 738, 686. HRMS (ESI^+/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{14}NO_2S$ 272.0745; Found 272.0734.

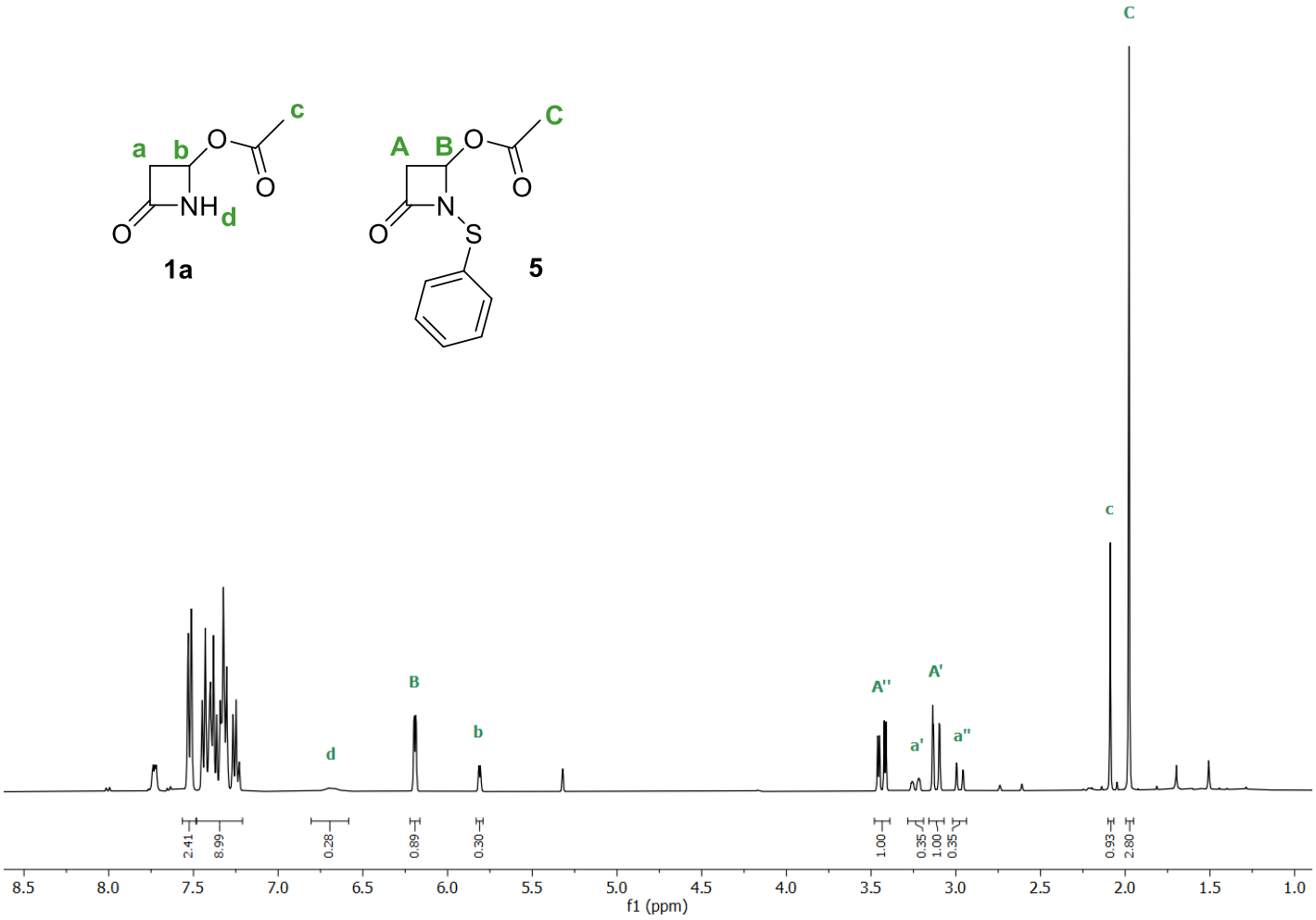


Figure S1: ^{1}H NMR ($CDCl_3$, 400 MHz) analysis of the crude mixture of N-sulfenylation of **2a** after work up by evaporation, showing the presence of the byproduct **1a** and the product **5.**

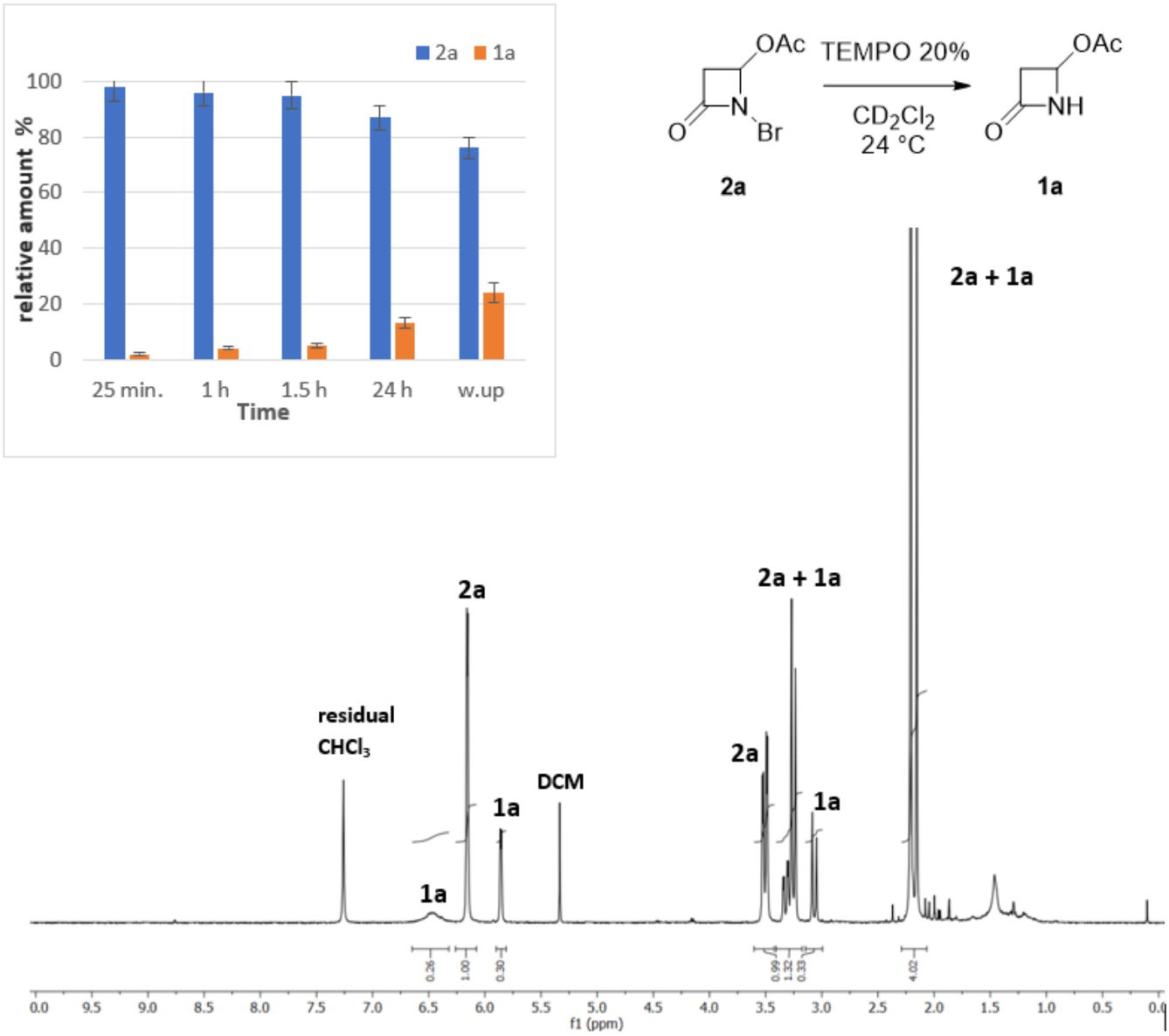


Figure S2. Time course study of ^{1}H NMR of **2a** and TEMPO in DCM-d2. The ^{1}H NMR spectra in $CDCl_3$ refers to the crude mixture after the work-up.

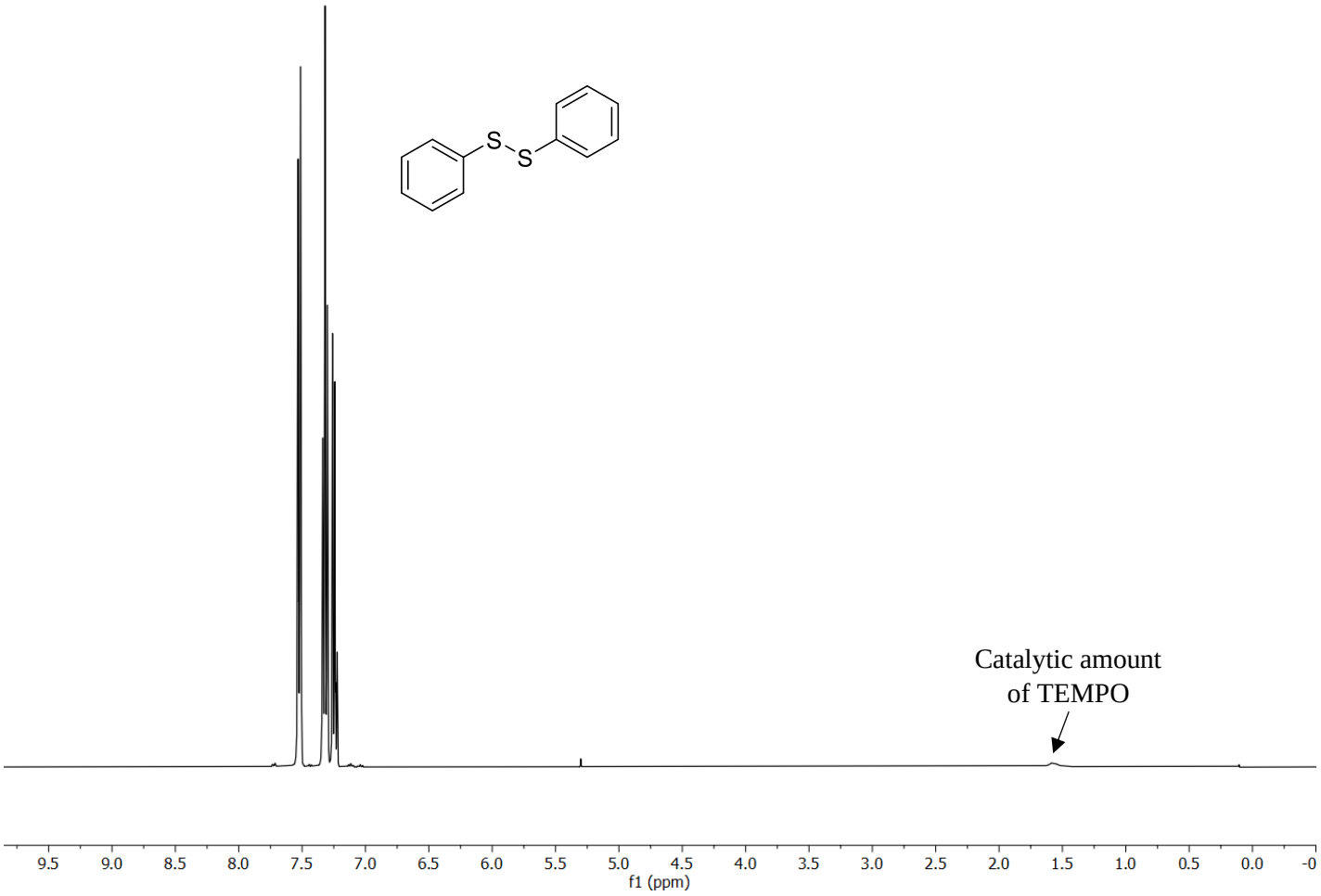


Figure S3. ^{1}H NMR ($CDCl_3$, 400 MHz) of diphenyl disulfide in the presence of TEMPO (20% mol), showing the stability of the disulfide after 24 hours.

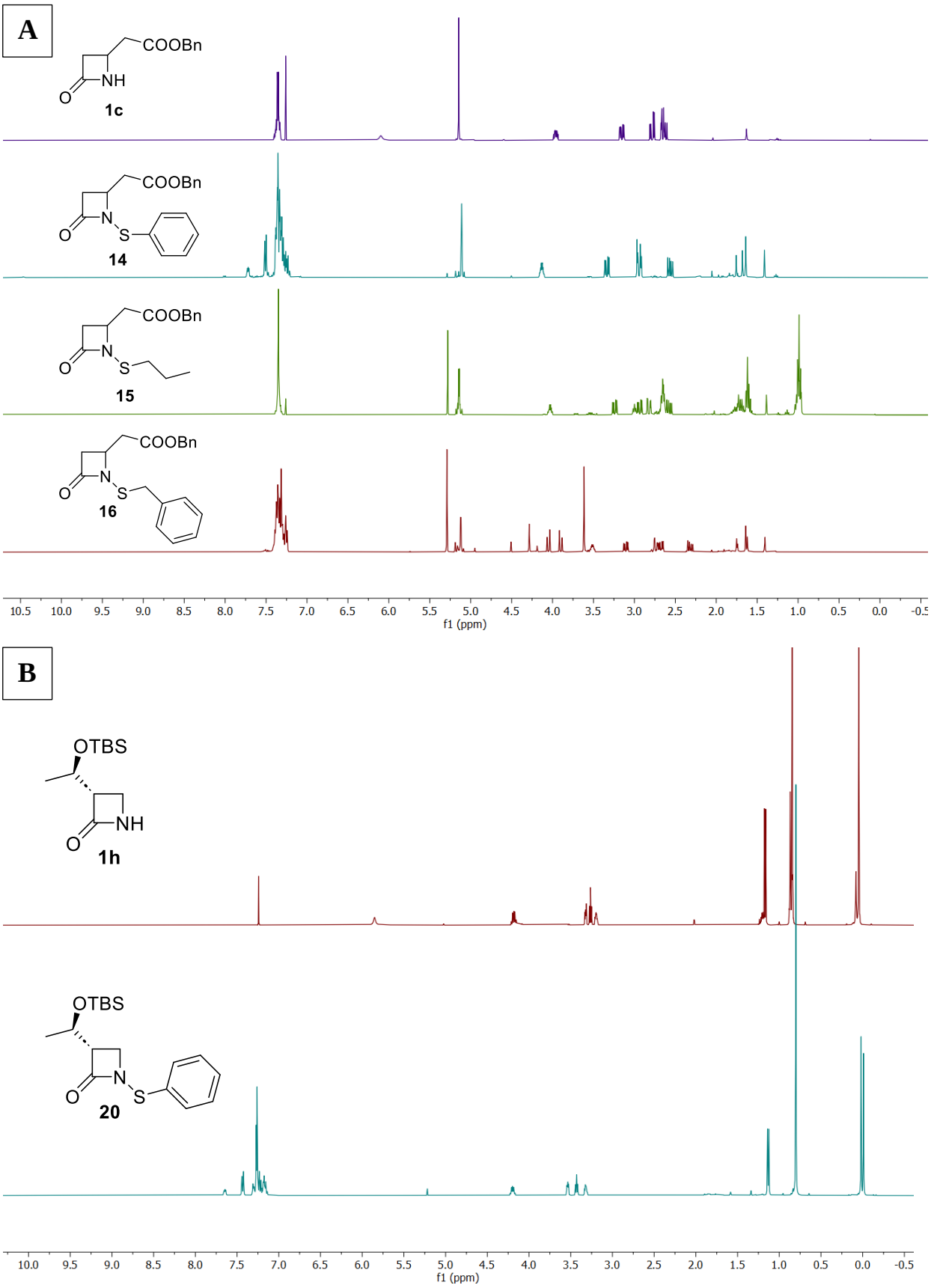
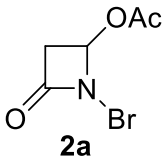


Figure S4. A) Comparison of ^{1}H NMR spectra of **1c** (purple) and the crude mixtures of N-sulfenylation of **2c** to obtain compounds **14** (blue), **15** (green) and **16** (red), showing the absence of **1c** as by-product. B) Comparison of ^{1}H NMR spectra of **1h** (red) and crude mixture of N-sulfenylation related to compound **20** (blue).

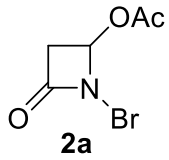
Copies of ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra

^{1}H NMR ($CDCl_3$, 400 MHz)



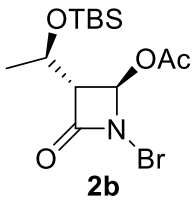
2a

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz)



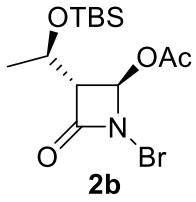
2a

^{1}H NMR ($CDCl_3$, 400 MHz)



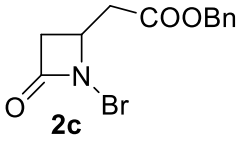
2b

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



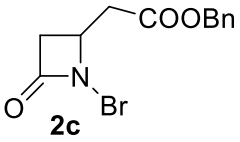
2b

^{1}H NMR ($CDCl_3$, 400 MHz)

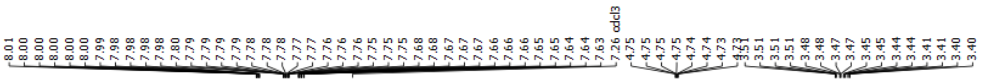


2c

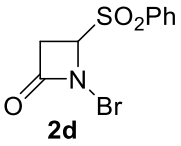
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



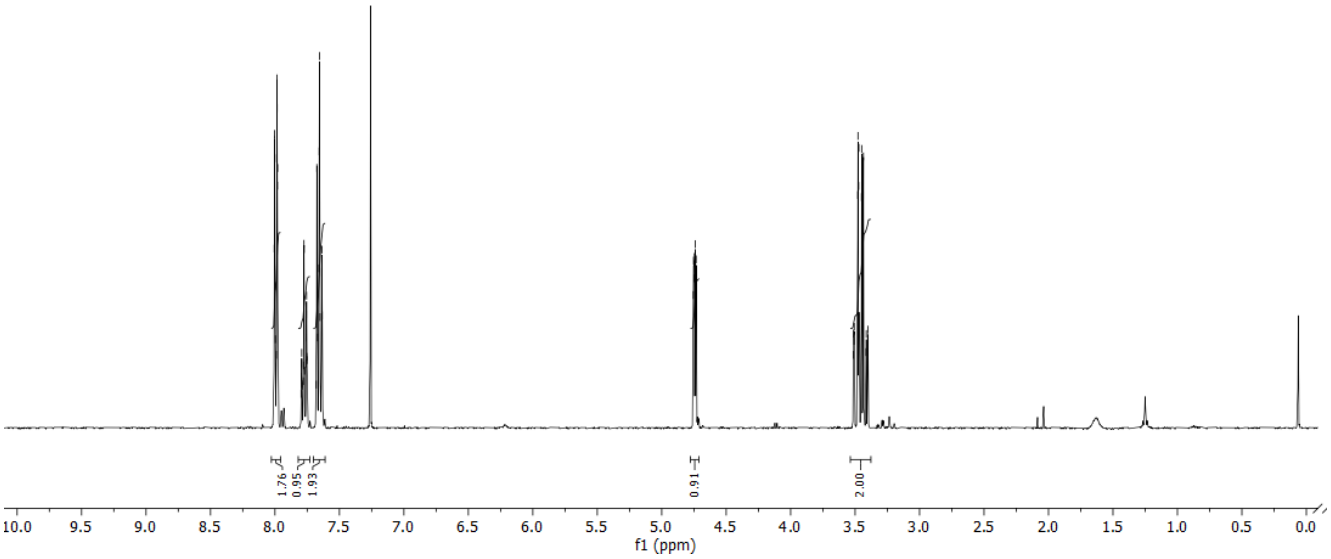
2c



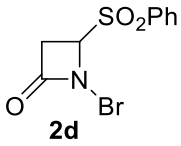
^{1}H NMR ($CDCl_3$, 400 MHz)



2d

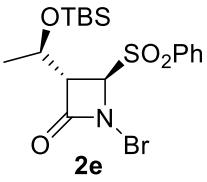


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



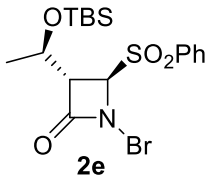
2d

^{1}H NMR ($CDCl_3$, 400 MHz)



2e

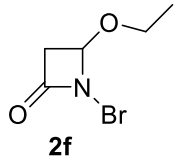
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



2e

^{1}H NMR analysis of crude mixture

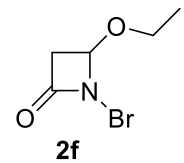
($CDCl_3$, 400 MHz)



2f

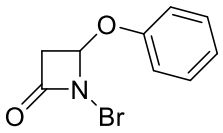
^{13}C{^{1}H}NMR analysis of crude mixture

($CDCl_3$, 100 MHz)



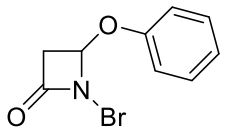
2f

^{1}H NMR ($CDCl_3$, 400 MHz)



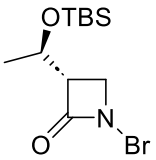
2g

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



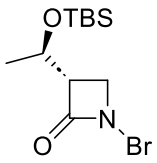
2g

^{1}H NMR ($CDCl_3$, 400 MHz)



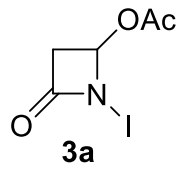
2h

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



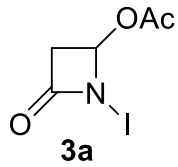
2h

^{1}H NMR ($CDCl_3$, 400 MHz)



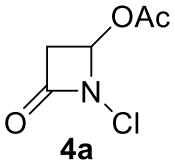
3a

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



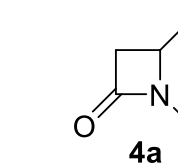
3a

^{1}H NMR ($CDCl_3$, 400 MHz)



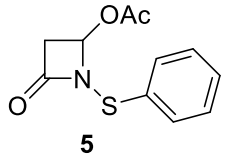
4a

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



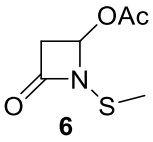
4a

^{1}H NMR ($CDCl_3$, 400 MHz)



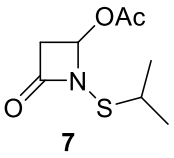
5

^{1}H NMR ($CDCl_3$, 400 MHz)



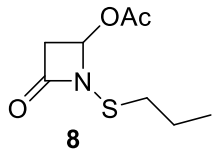
6

^{1}H NMR ($CDCl_3$, 400 MHz)



7

^{1}H NMR ($CDCl_3$, 400 MHz)



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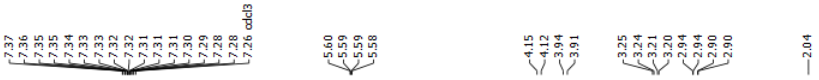
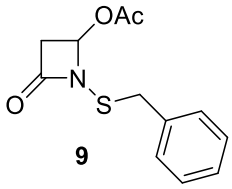


^{1}H NMR ($CDCl_3$, 400 MHz)



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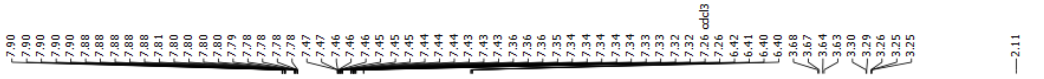
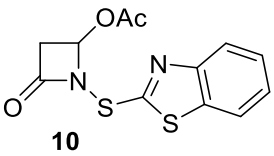
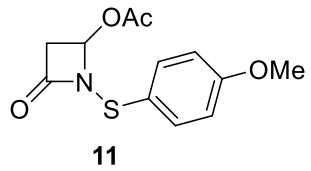


^{1}H NMR ($CDCl_3$, 400 MHz)



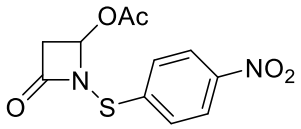
10

^{1}H NMR ($CDCl_3$, 400 MHz)



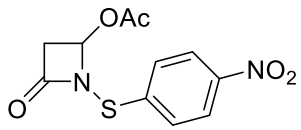
11

^{1}H NMR ($CDCl_3$, 400 MHz)



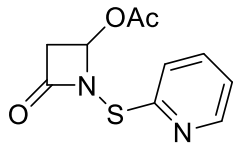
12

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



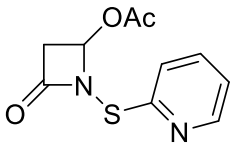
12

^{1}H NMR ($CDCl_3$, 400 MHz)



13

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



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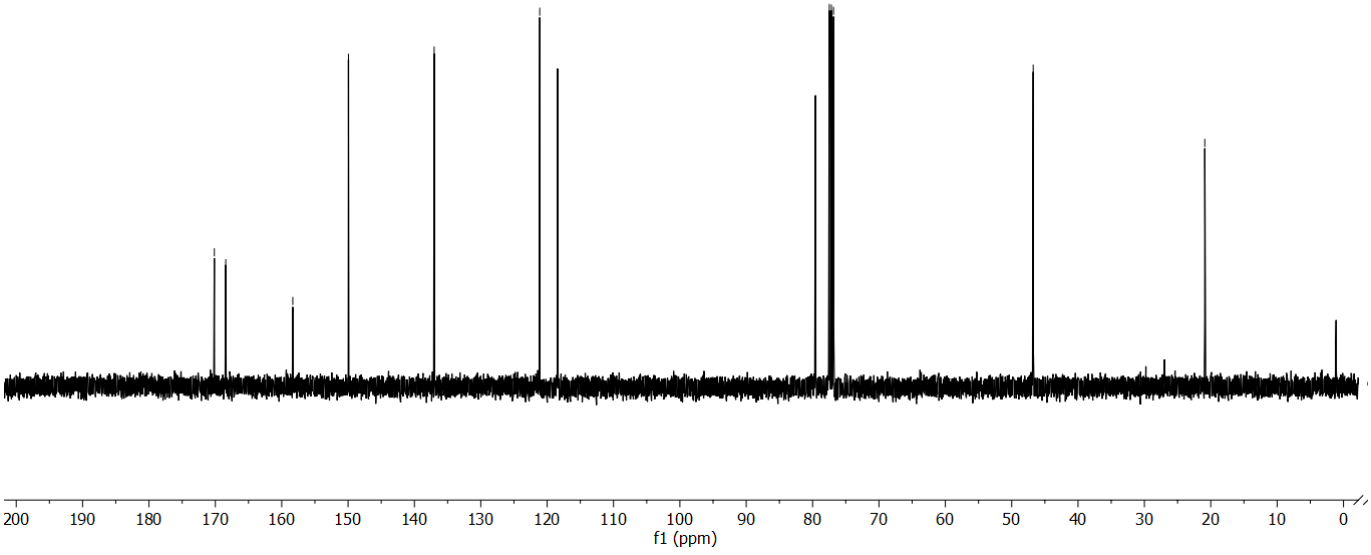
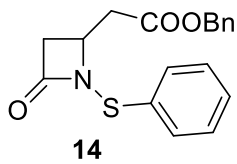
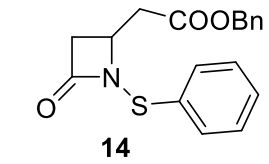


^{1}H NMR ($CDCl_3$, 400 MHz)



14

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



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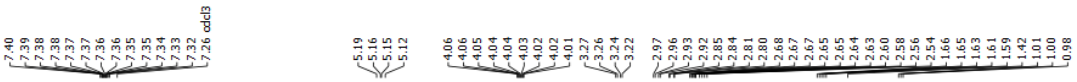
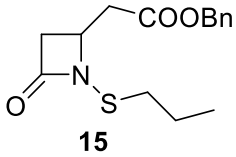


^{1}H NMR ($CDCl_3$, 400 MHz)



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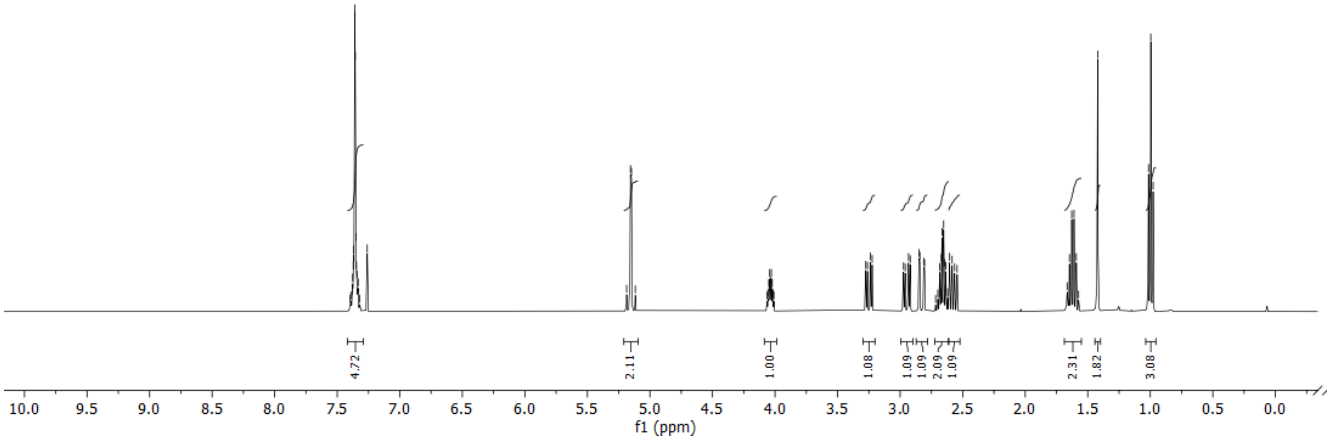
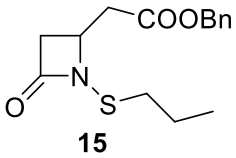


$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz)



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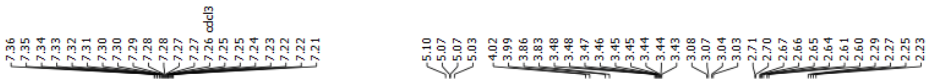
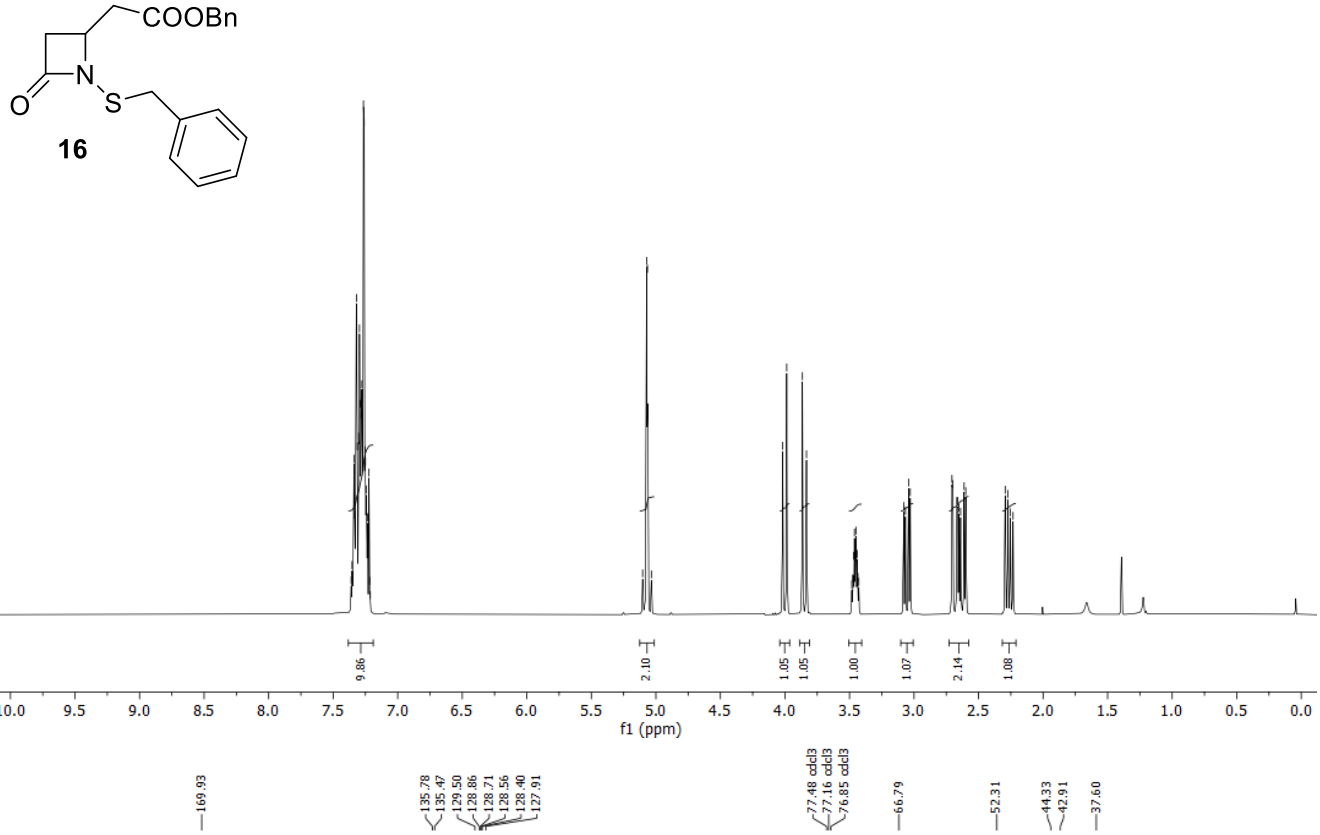
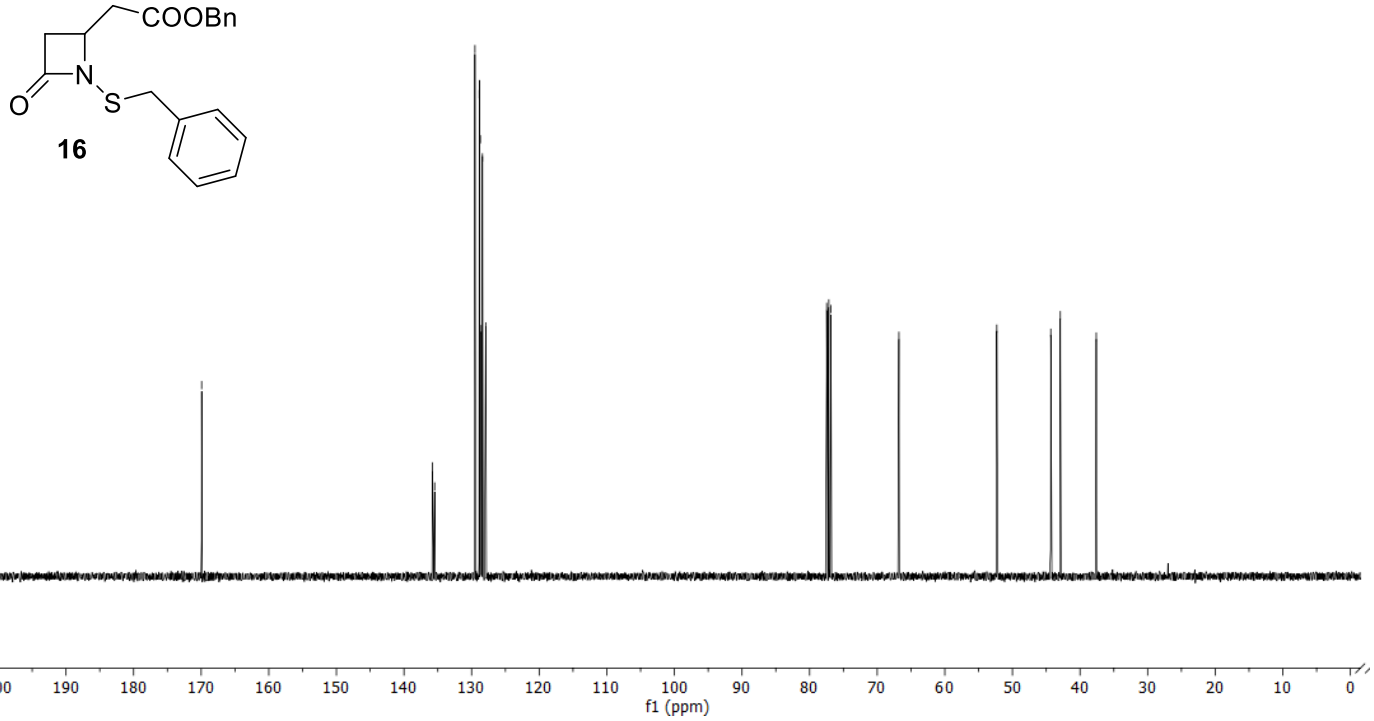


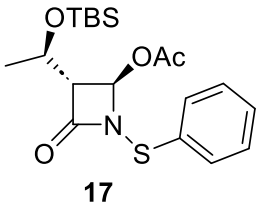
^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)

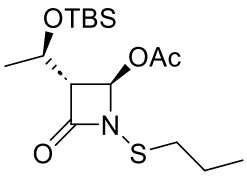


^{1}H NMR ($CDCl_3$, 400 MHz)



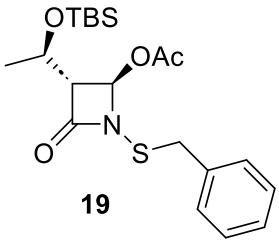
17

^{1}H NMR ($CDCl_3$, 400 MHz)



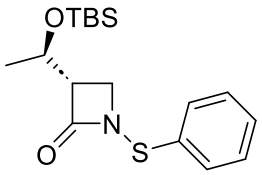
18

^{1}H NMR ($CDCl_3$, 400 MHz)



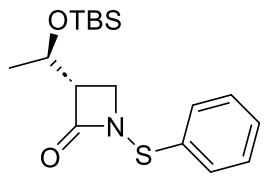
19

^{1}H NMR ($CDCl_3$, 400 MHz)



20

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



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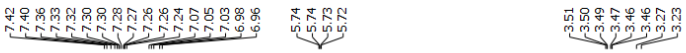
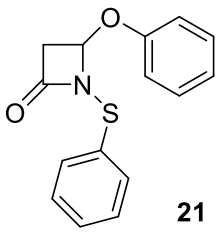


^{1}H NMR ($CDCl_3$, 400 MHz)



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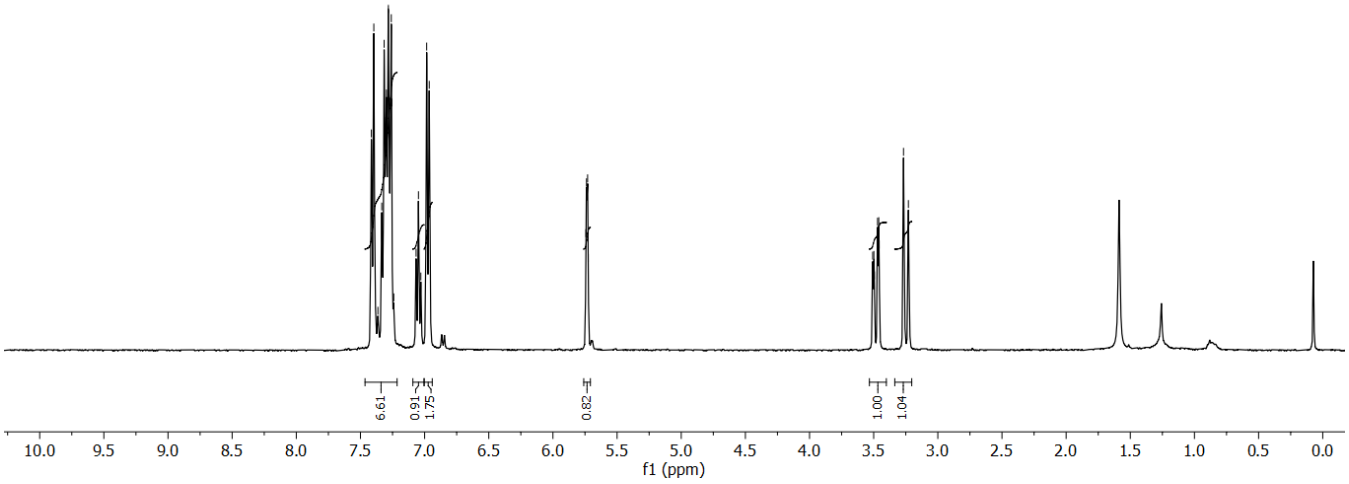
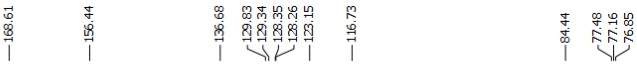
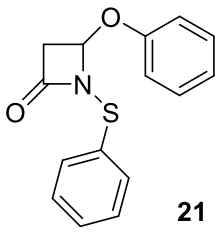


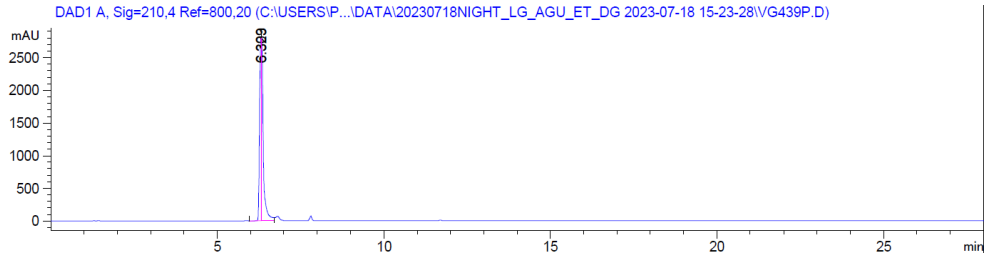


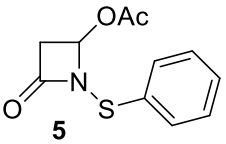
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)



21

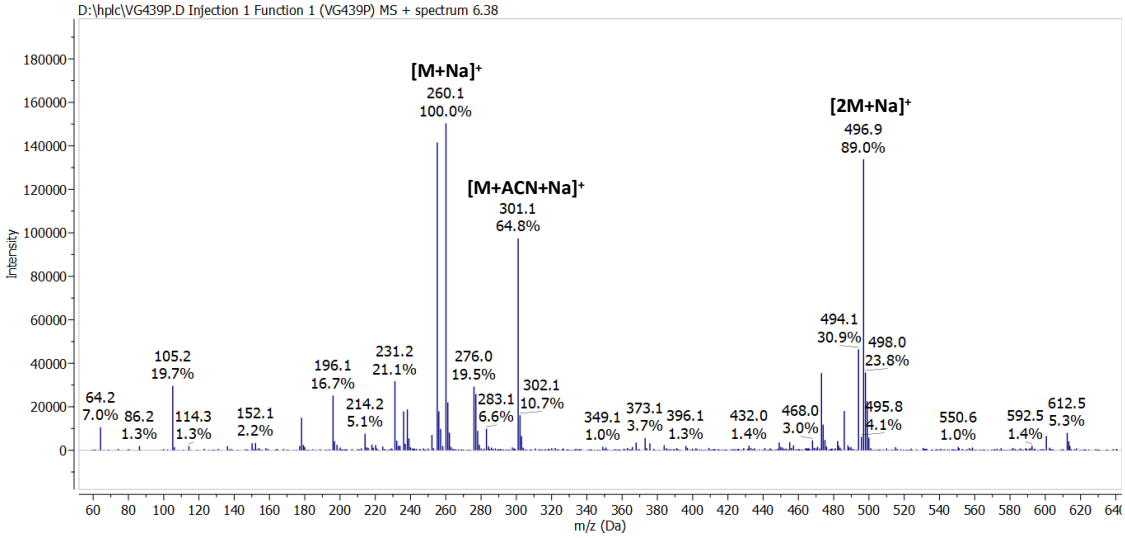
HPLC-MS spectra of N-thio β-lactams (Compounds 5-21)

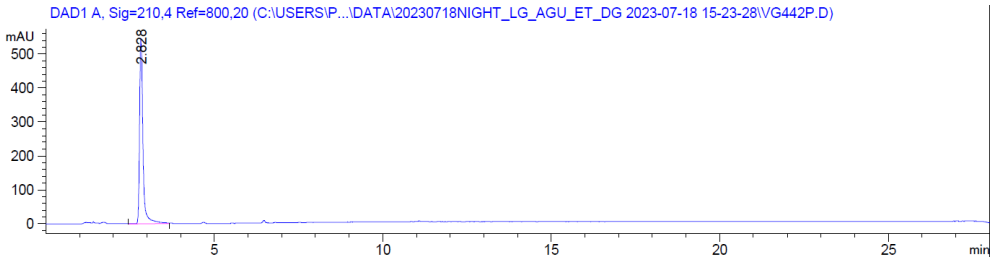


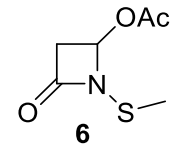


5

MW: 237,27 g/mol

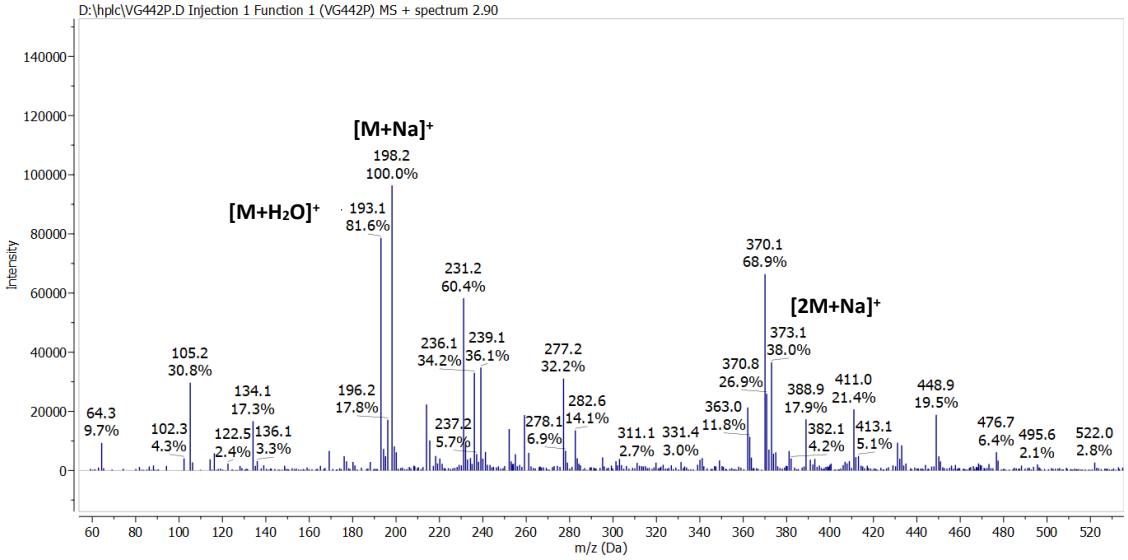


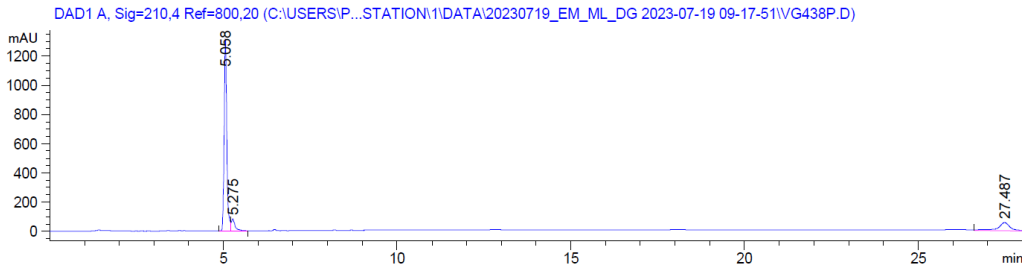


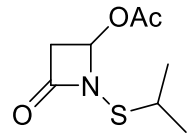


6

MW: 175,20 g/mol

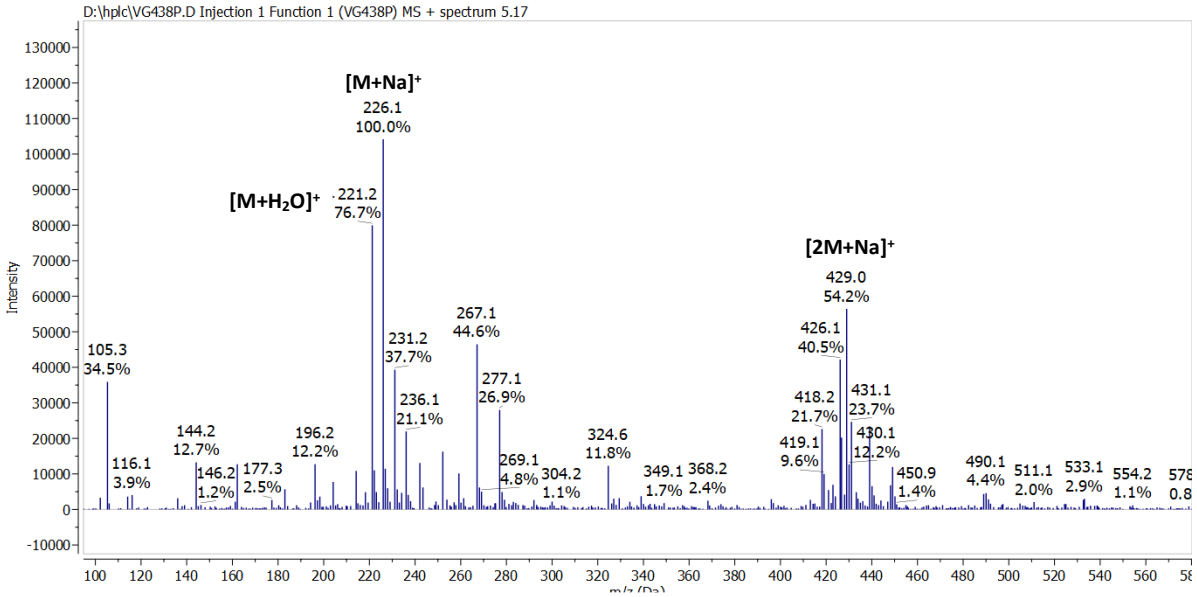


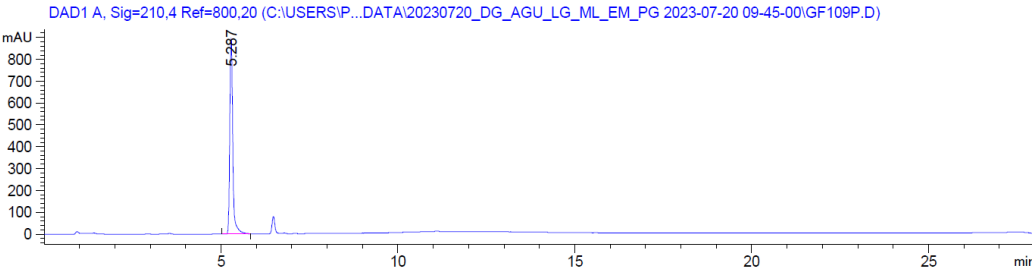


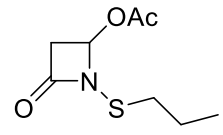


7

MW: 203,26 g/mol

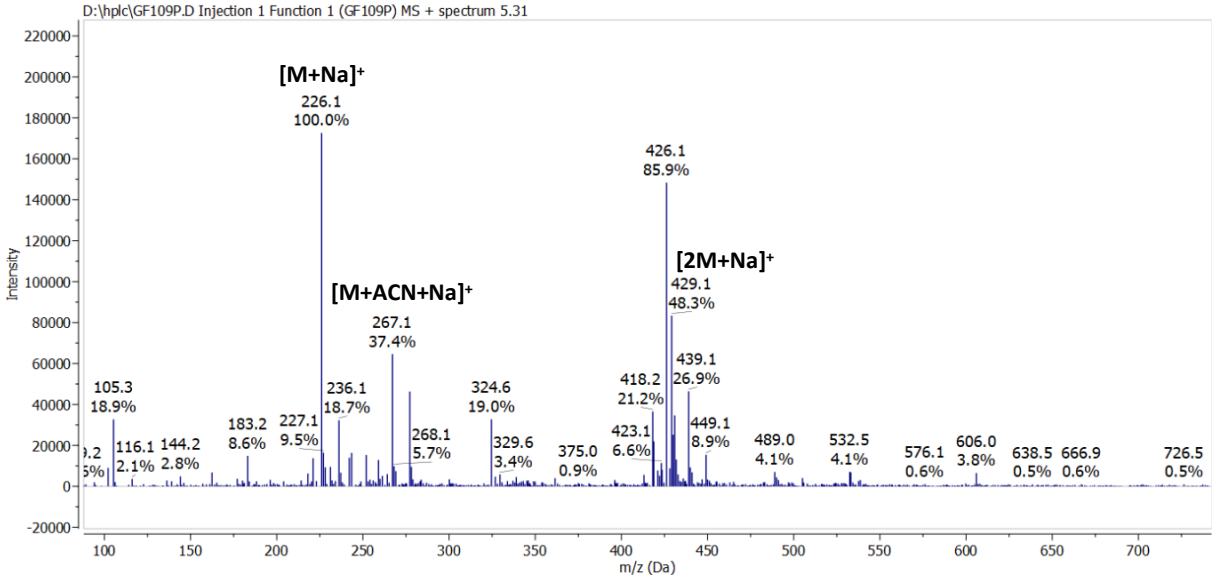


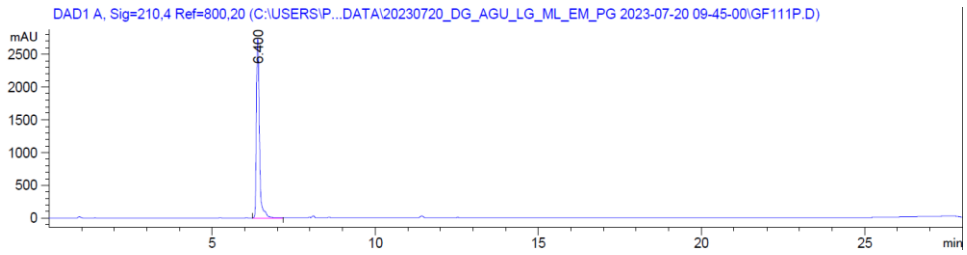


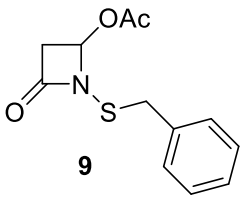


13

MW: 203,26 g/mol

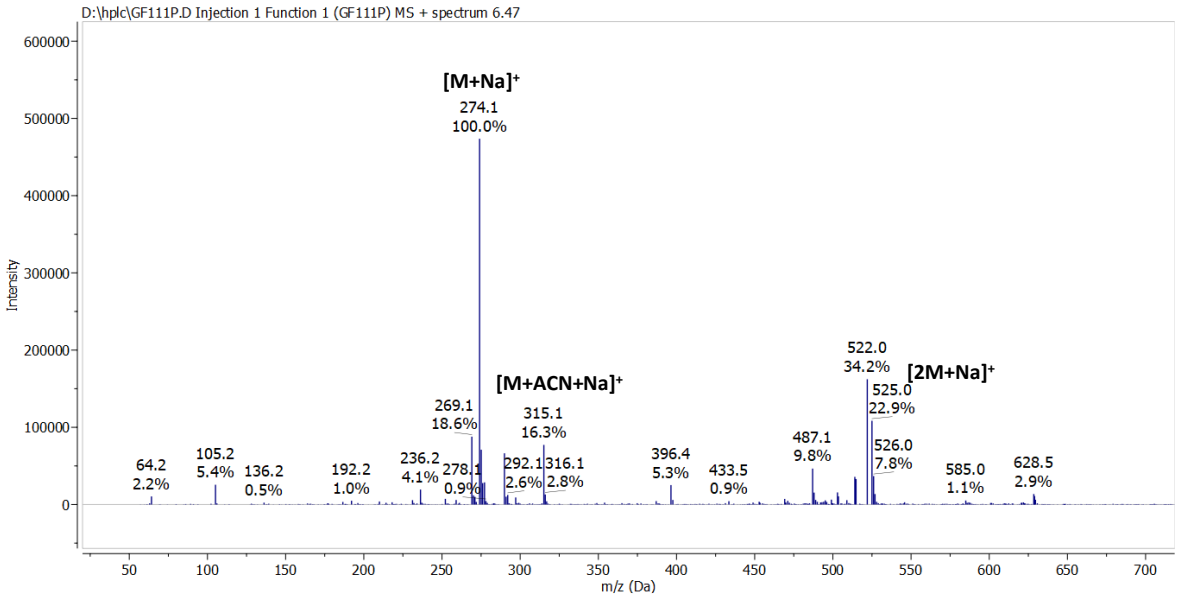




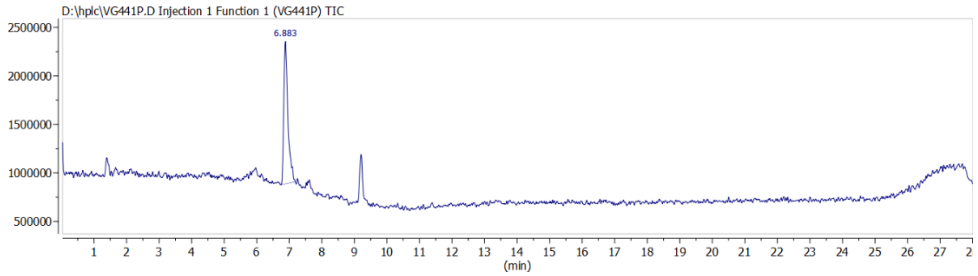


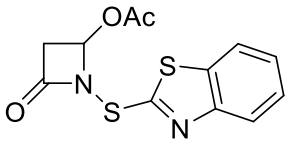
9

MW: 251,30 g/mol



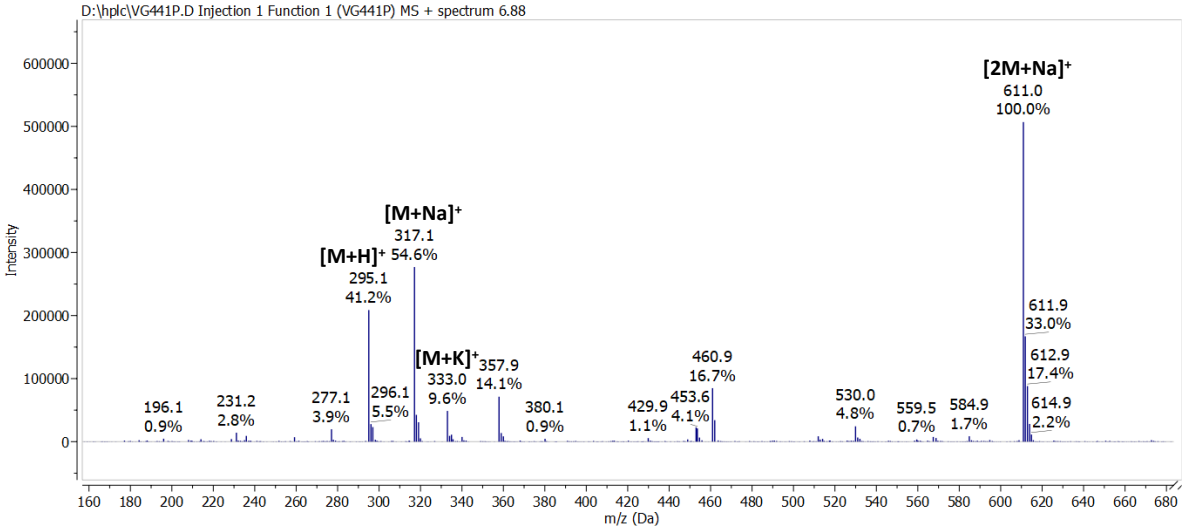
10

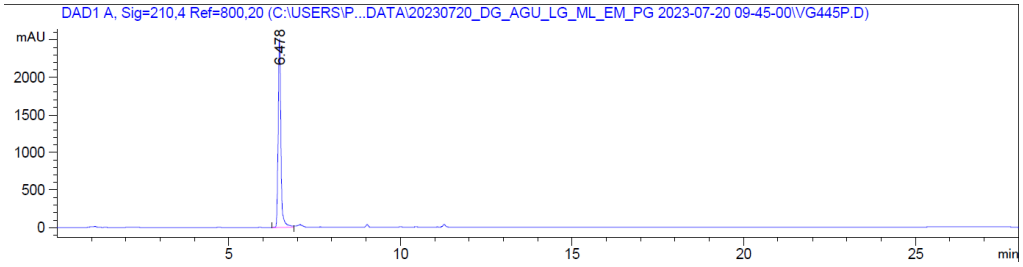


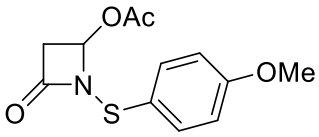


10

MW: 294,34 g/mol

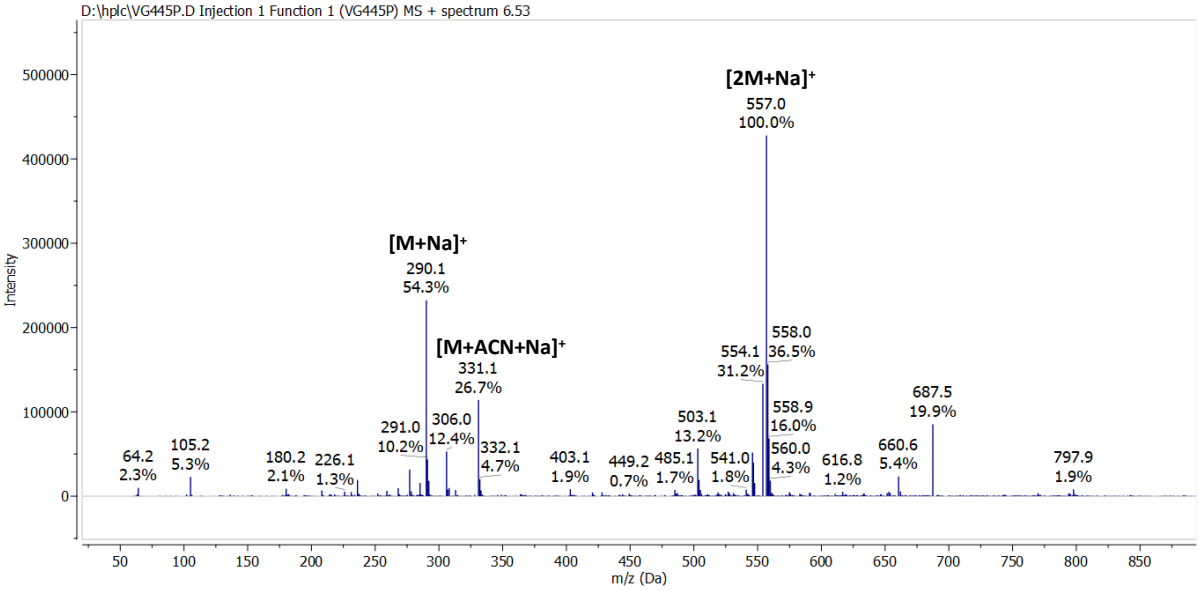


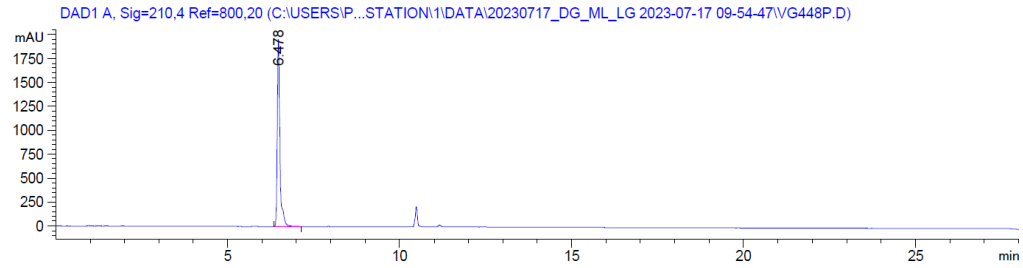


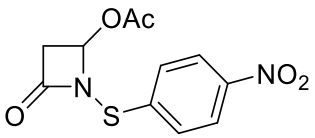


11

MW: 267,30 g/mol

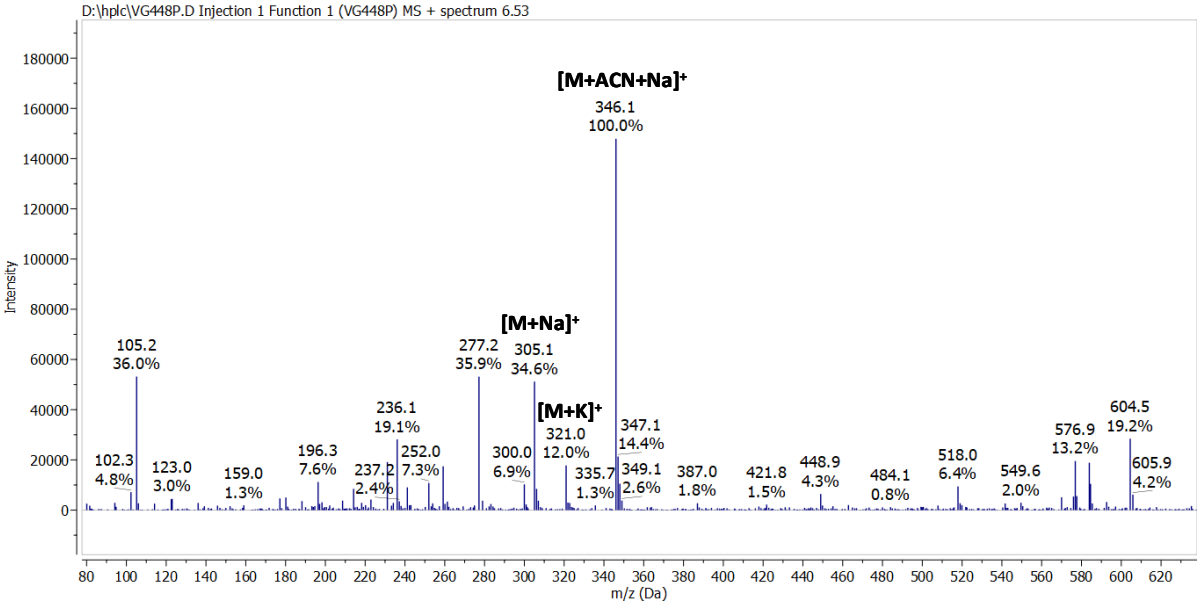


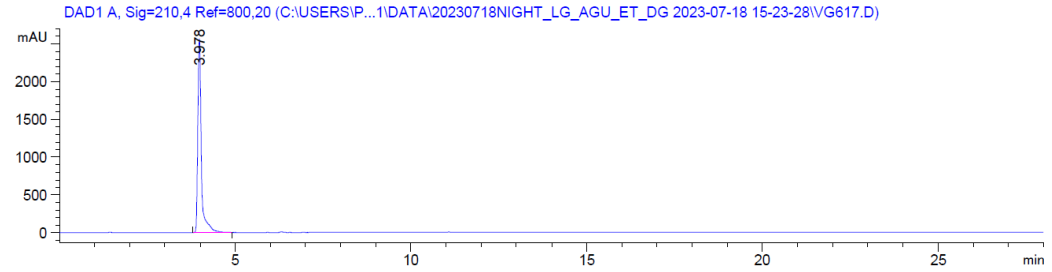


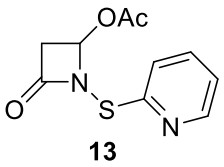


12

MW: 282,27 g/mol

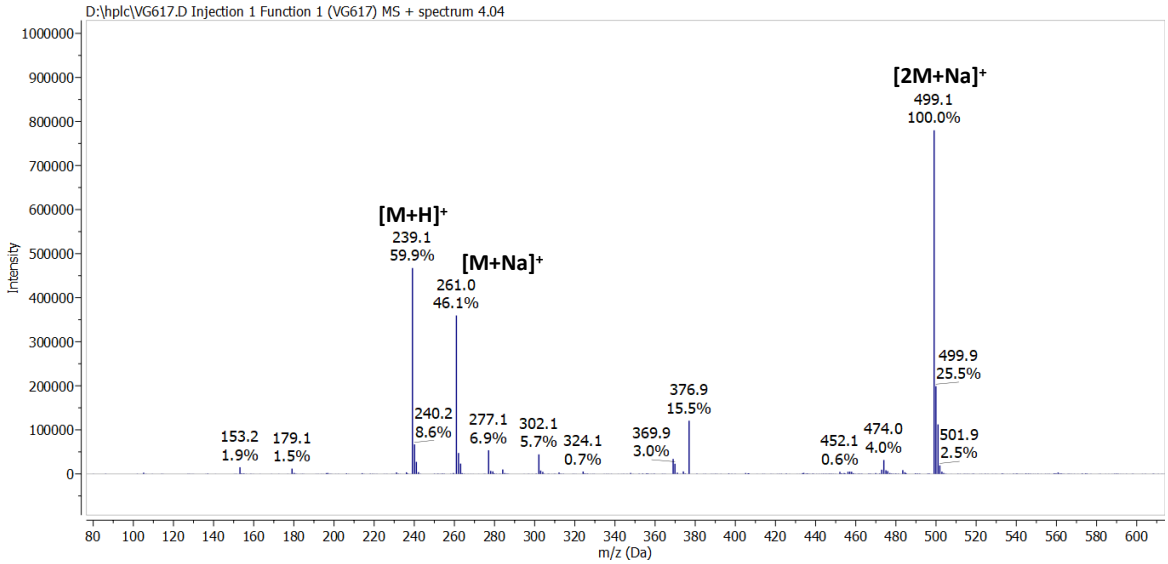


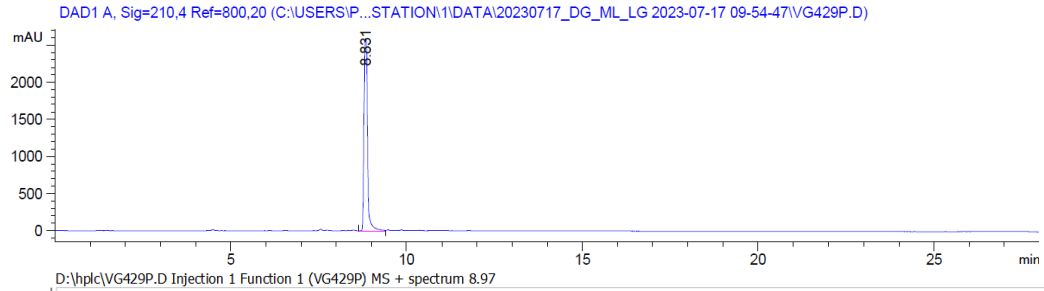


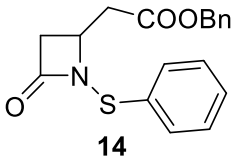


13

MW: 238,26 g/mol

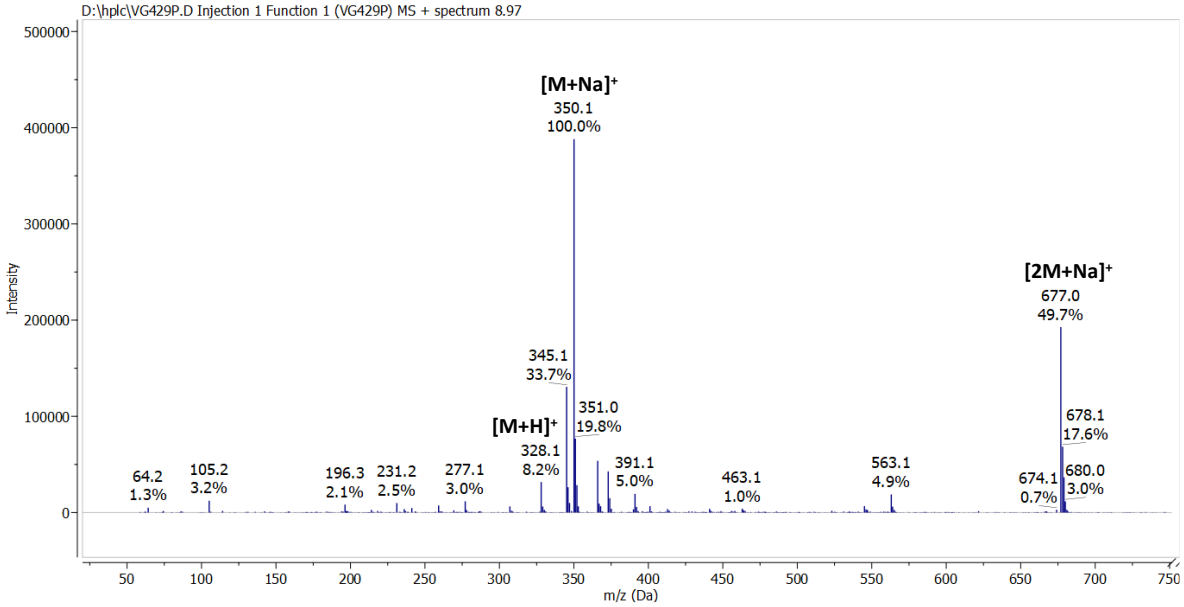


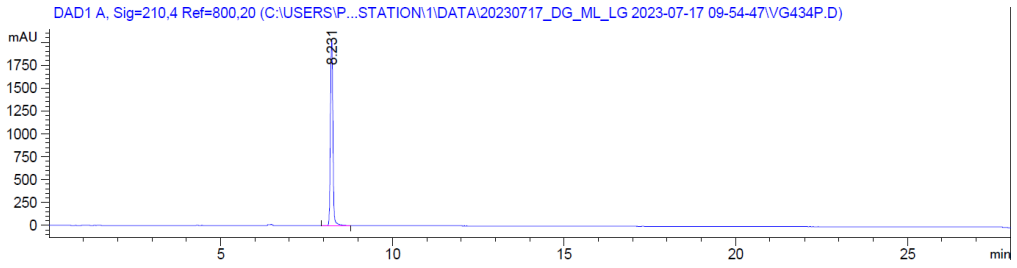


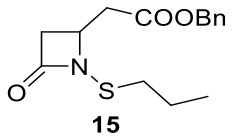


14

MW: 327,40 g/mol

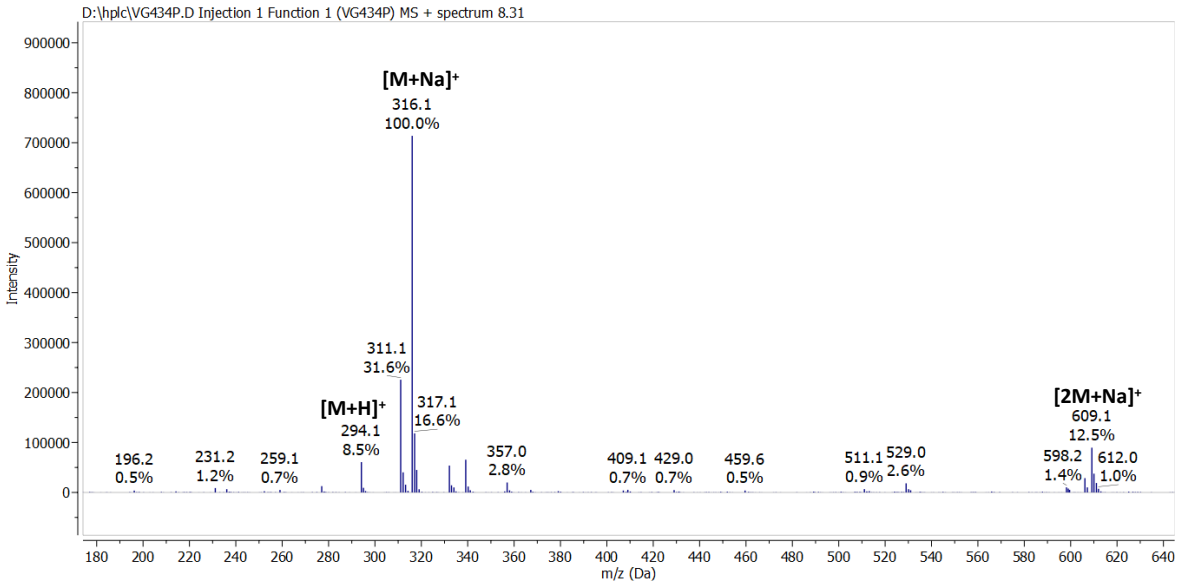


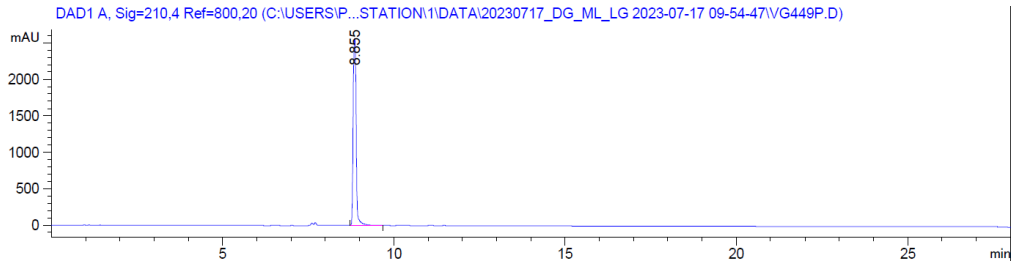


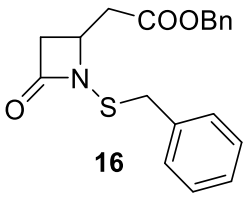


15

MW: 293,38 g/mol

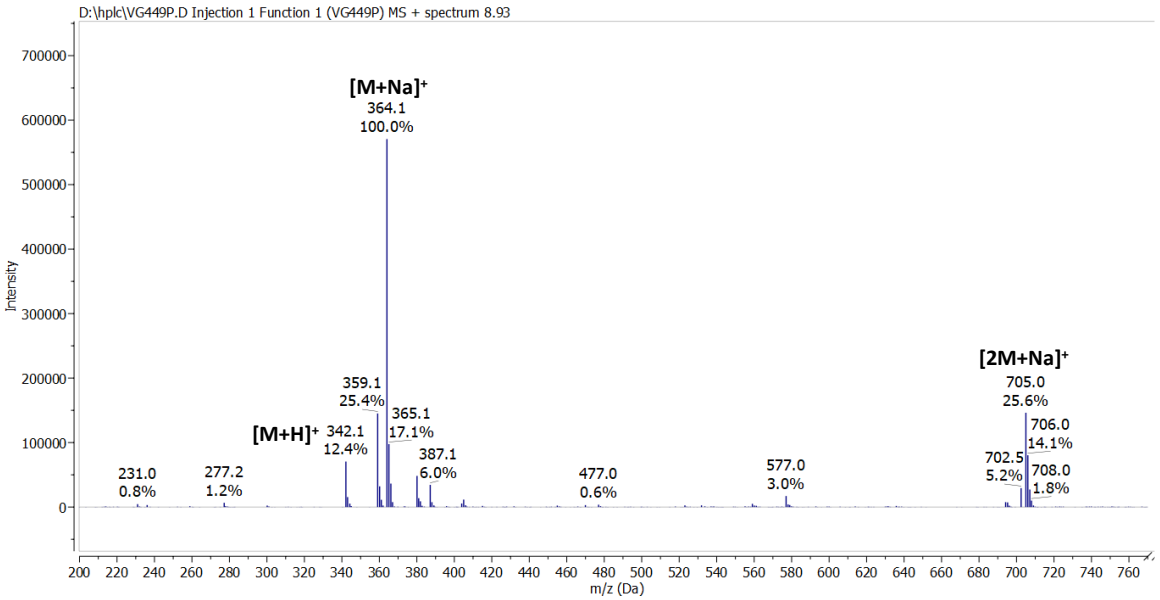


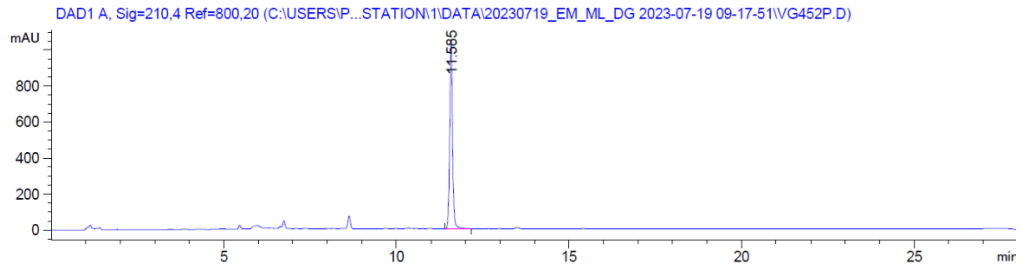


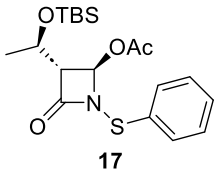


16

MW: 341,43 g/mol

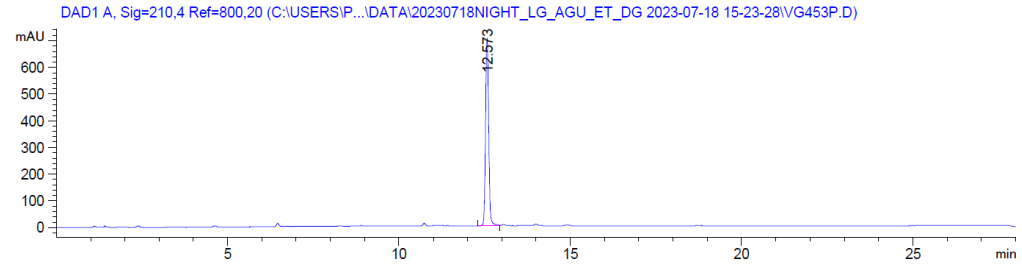


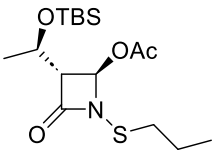




17

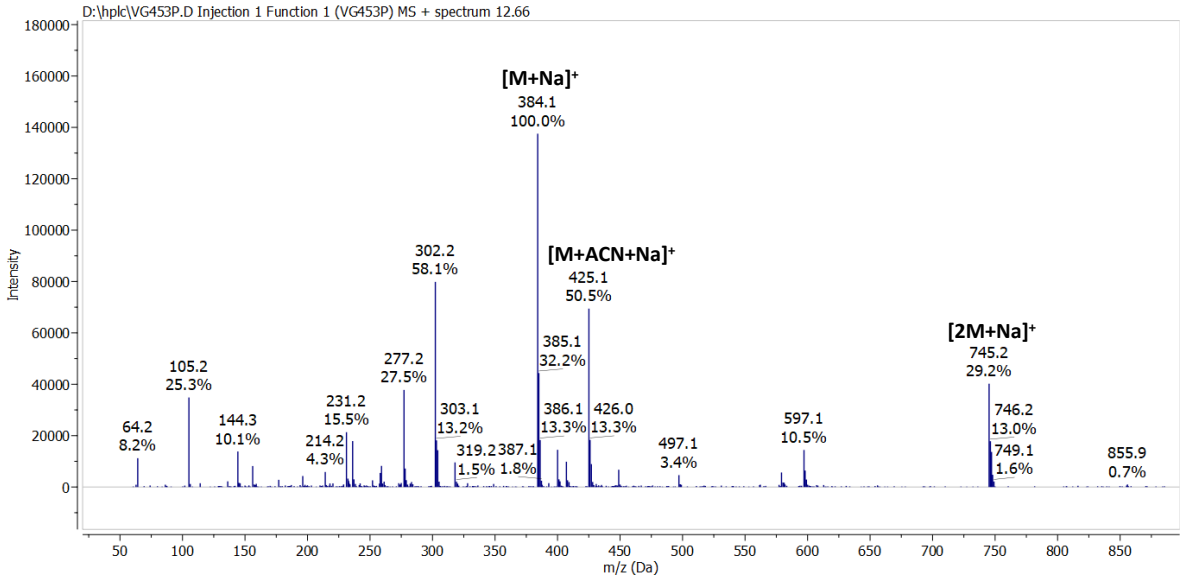
MW: 395,59 g/mol

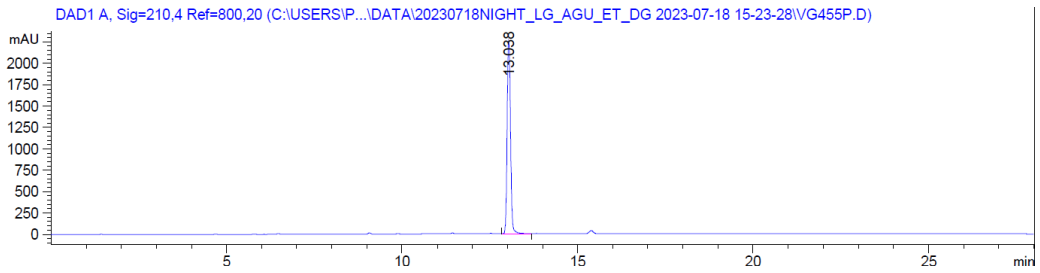


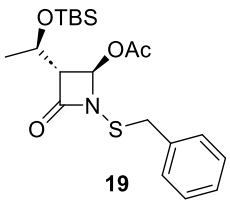


18

MW: 361,57 g/mol

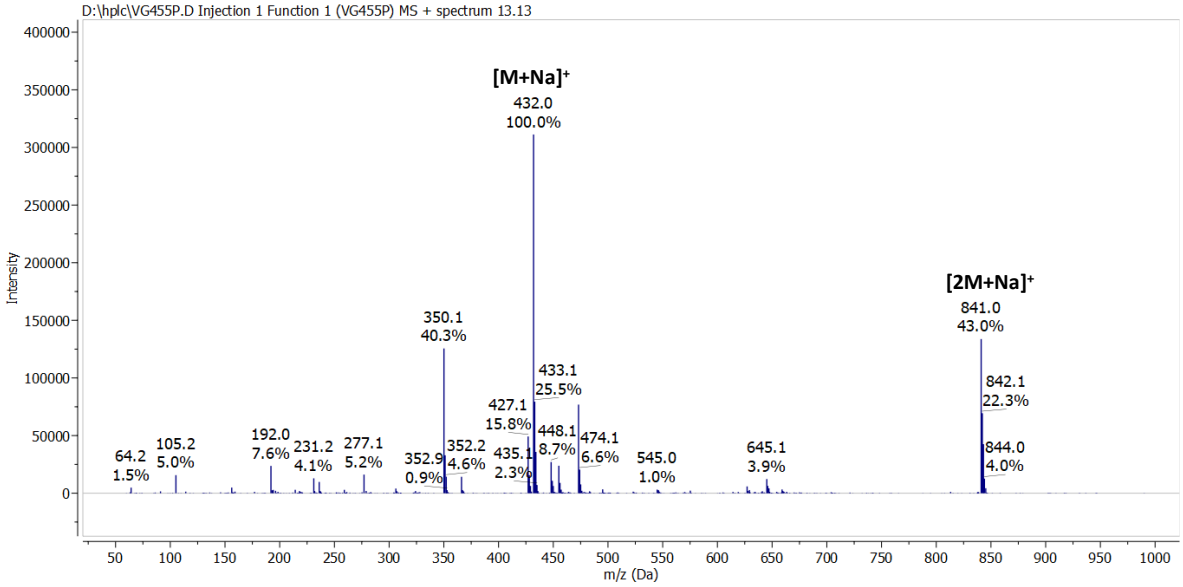


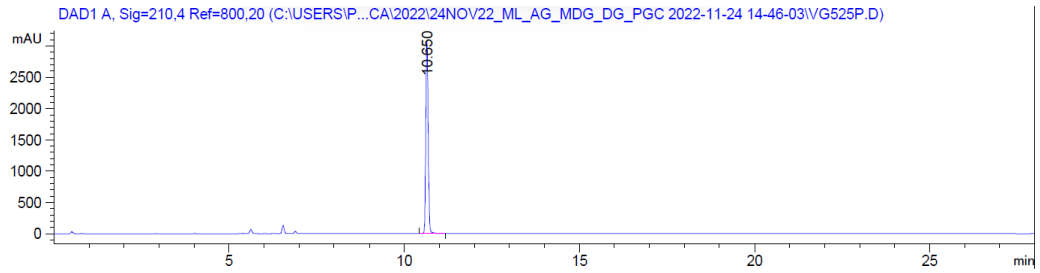


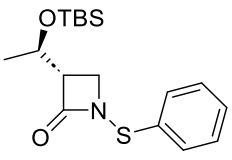


19

MW: 409,62 g/mol

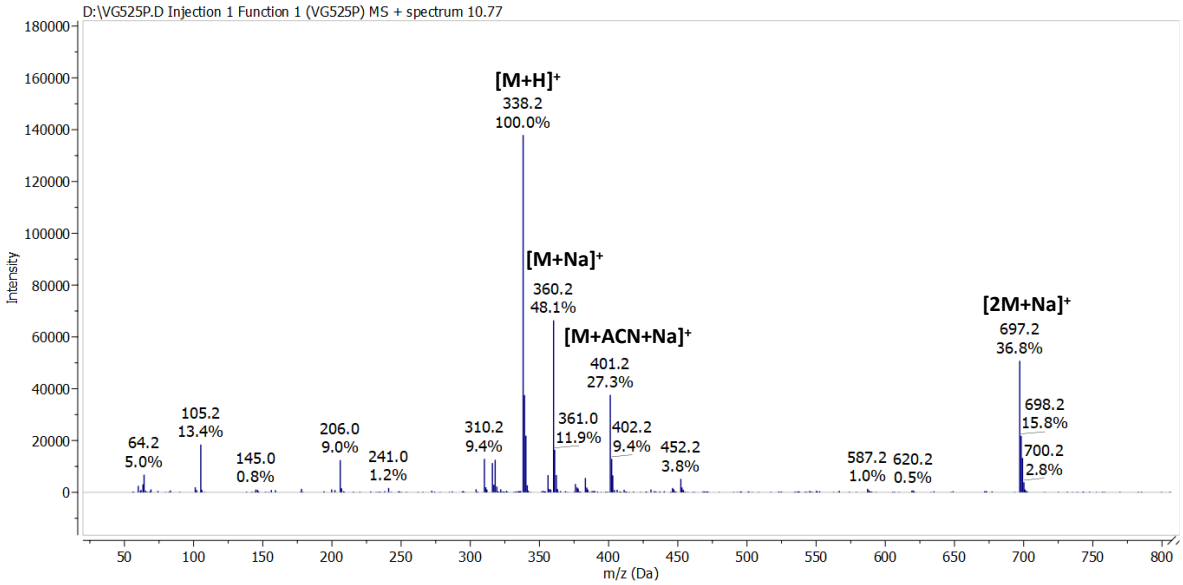


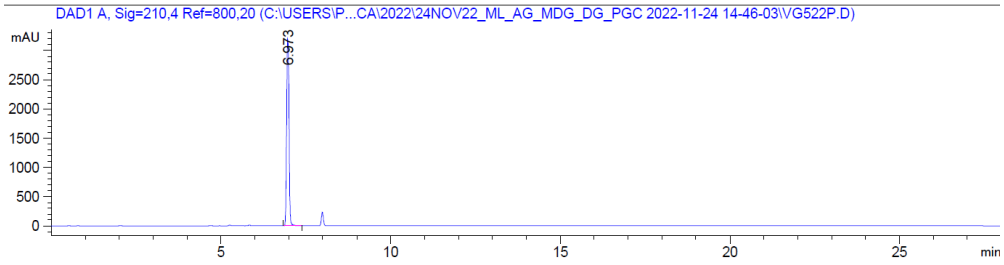


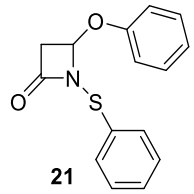


20

MW: 337,55 g/mol

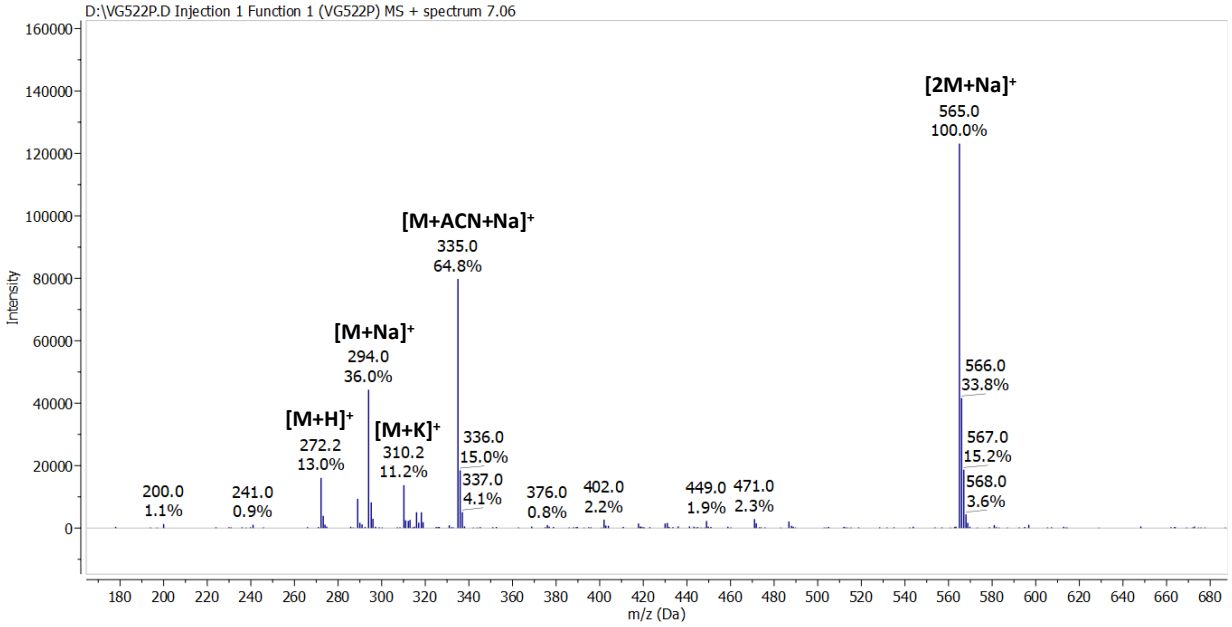






21

MW: 271,33 g/mol



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