ESI

Synthesis of a Series of Amino Acid Derived Ionic Liquids and Tertiary Amines: Green chemistry metrics including microbial toxicity and preliminary biodegradation data analysis

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General experimental methods

Chemicals used were purchased from Sigma Aldrich or TCI Europe. Methanol and ethanol were distilled over magnesium turnings activated by iodine before use. DCM and ethyl acetate were pre-dried over magnesium sulphate and then distilled over CaH_2 before use. THF and diethyl ether were dried over sodium wire and benzophenone and distilled before use. DMF used was purchased from Sigma Aldrich as an anhydrous sureseal preparation. Sigma Aldrich (Riedel de Haën) 220-440 mesh, 60 Å pore size, 35-75 µm particle size, silica gel was used for flash and thin layer chromatography.

The majority of NMR analysis was performed on a Bruker AC 400 MHz spectrometer operating at 400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C-NMR. Samples were run in deuterated chloroform ($CDCl_3$), deuterated water (D_2O), deuterated methanol (MeOD), or deuterated dimethyl sulfoxide (DMSO) where appropriate. A 600 MHz Bruker spectrometer, operating at 600 MHz for ^{1}H-NMR and 150 MHz for ^{13}C-NMR was also used for analysis of some examples. All chemical shifts are reported in parts per million (ppm) are relative to the internal standard TMS and coupling constants (*J*) are measured in Hertz (Hz). Multiplicity is stated as follows: s-singlet, d-doublet, t-triplet, q-quartet, dd-doublet of doublets, dt doublet of triplets, dq-doublet of quartets, tt-triplet of triplets, tq-triplet of quartets, ddd-doublet of doublet of doublets, m-multiplet, bs-broad singlet. All IR analysis was carried out on a Perkin Elmer 100 FT-IR spectrometer with ATR. The strength of reported peaks are described as weak (w), medium (m), broad (b), strong (s) and very strong (vs). Melting points were determined using a Lennox automated melting point apparatus and the values are expressed in degrees Celsius (°C). The parameters for the melting point analysis were set at 5 °C per minute ramp and melting point was determined manually. Melting points are uncorrected. Optical rotations were measured using a Perkin Elmer 343 Polarimeter in chloroform, methanol or ethanol at 20 °C and values are expressed in degrees. High resolution mass

spectrometry (HRMS) with accurate mass measurement to four decimal places was obtained for new ILs, new tertiary amines and new alkylating regents reported. The analysis was conducted in the ABCRF Mass Spectrometry Lab, Cavanagh Building, in University College Cork. Accurate mass measurement was obtained using a Waters Micromass LCT Premier run in ESI+ mode. An external reference standard of leucine encephalin was used in order to confirm mass accuracy and a sulfadimethoxine concentration test was performed to ensure the accuracy of peaks in the ion count range of $1x10^3$ – $1x10^6$.

Typical procedure for preparation of IL via amination of L-phenylalanine derivative-

general procedure "A"

To a stirred solution of aminoacid ethyl ester α-bromoamide in diethyl ether (10 mL) was added pyridine derivative. The reaction was stirred at room temperature under an N_2 atmosphere for 24 hours. After 24 hours a waxy precipitate had formed. The supernatant was decanted and the crude product was washed with diethyl ether (3 x 25 mL) to afford the desired compound.

(*S*)-1-(2-((1-Ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)pyridin-1-ium bromide (5). The general procedure A was applied to L-phenylalanine ethyl ester α-bromoamide (**26**) (0.58 g, 1.85 mmol) and pyridine (135 µL, 1.68 mmol). The title compound (**5**) was isolated as a white solid in 98% yield (0.64 g, 1.64 mmol). Mp: 98-100°C. $[\alpha]_D^{20}$ = +2.26 (0.4 c, $CHCl_3$);-^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.36 (d, *J* = 7.6 Hz, 1H), 9.22 (d, *J* = 4.8 Hz, 2H), 8.41 (t, *J* = 8.0 Hz, 1H), 7.96 (t, *J* = 7.6 Hz, 2H), 7.37-7.25 (m, 2H), 7.24-7.14 (m, 3H), 6.04 (d, *J* = 14.4 Hz, 1H), 5.98 (d, *J* = 14.8 Hz, 1H), 4.70-4.65 (m, 1H), 4.12-4.06 (m, 2H), 3.25 (dd, *J* = 14.0, 8.2 Hz, 1H), 3.18 (dd, *J* = 14.0, 8.0 Hz 1H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.95, 163.97, 146.06, 145.31, 136.61, 129.61, 128.43, 127.63, 126.80, 62.12, 61.55, 54.95, 37.53,

14.07. IR (neat) (cm^{-1}): 3184 (w), 3042 (w), 1736 (vs), 1686 (vs), 1632 (m), 1560 (s), 1484 (s), 1368 (s), 1264 (s), 1188 (vs). ESI-MS (+ve) m/z: Found $[M–Br^–]^+$ 313.1543, $C_{18}H_{21}N_2O_3^+$ requires 313.1547.

(*S*)-1-(2-((1-Ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-3-methoxypyridin-1-ium bromide (**6**).The general procedure A was applied to L-phenylalanine ethyl ester α-bromoamide (**26**) (1.05 g, 3.33 mmol) and 3-methoxypyridine (320 µL, 3.18 mmol). The title compound (**6)** was isolated as a white hygroscopic solid in 96% yield (1.295 g, 3.06 mmol). Mp: 72-74°C. $[\alpha]_D^{20}$ = –7.2 (2.0 c, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 9.39 (d, *J* = 7.8 Hz, 1H), 9.32 (d, *J* = 1.1 Hz, 1H), 8.54 (d, *J* = 5.8 Hz, 1H), 7.87-7.85 (ddd, *J* = 9.0, 2.4, 0.8 Hz, 1H), 7.77 (dd, *J* = 8.8, 5.8 Hz, 1H), 7.35-7.33 (m, 2H), 7.23-7.12 (m, 3H), 5.94 (d, *J* = 14.1 Hz, 1H) 5.88 (d, *J* = 14.1 Hz, 1H), 4.66 (ddd, *J* = 8.9 ,8.1, 5.9 Hz, 1H), 4.10 (s, 3H), 4.09-4.03 (m, 2H), 3.24 (dd, *J* = 13.9, 5.8 Hz, 1H), 3.17 (dd, *J* = 13.8, 8.0 Hz, 1H), 1.16 (t, *J* = 7.2, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* 170.83, 163.93, 158.38, 138.15, 136.66, 132.40, 131.99, 129.56, 128.36, 127.58, 126.75, 62.23, 61.51, 58.29, 54.91, 37.40, 14.07. IR (neat) (cm^{-1}): 3187 (w), 3028 (w), 1736 (s), 1683 (vs), 1507 (vs), 1294 (vs), 1198 (b). ESI-MS (+ve) m/z: Found $[M–Br^–]^+$ 343.1649, $C_{19}H_{23}N_2O_4^+$ requires 343.1652.

(*S*)-1-(2-((1-Ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-3-(ethoxycarbonyl)pyridin-1-ium bromide (7). To a stirred solution of L-phenylalanine ethyl ester α-bromoamide (**26**) (0.51 g, 1.61 mmol) in THF (25 ml) was added ethyl nicotinate (200 µL, 1.46 mmol). The reaction was stirred under reflux conditions for 24 hours. After 24 hours the THF was removed *in vacuo* to afford a crude brown product. The crude product was purified by silica gel chromatography (gradient elution of 5:95 MeOH:DCM to 10:90 MeOH:DCM) to afford the title compound (**7**) as an orange solid in 56% yield (0.38 g, 0.819 mmol). Mp: 60-62°C. $[\alpha]_D^{20}$ = + 1.4 (2.0 c, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 9.71 (d, *J* = 6.0Hz, 1H), 9.37 (m, 2H), 8.93-8.90 (m, 1H), 8.10 (dd, *J* = 8.0, 6.4 Hz, 1H), 7.37-7.35 (m, 2H), 7.25-7.22 (m, 2H), 7.17-7.13 (m, 1H), 6.26 (d, *J* = 15.2 Hz, 1H), 6.19 (d, *J* = 15.2 Hz, 1H), 4.72-4.67 (m, 1H), 4.48 (q, *J* = 7.2 Hz, 2H), 4.11-4.05 (m, 2H), 3.25-3.14 (m, 2H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$)

δ (ppm): 171.00, 163.80, 160.96, 149.75, 146.96, 145.36, 136.74, 130.41, 129.72, 128.49, 127.73, 126.87, 63.63, 62.88, 61.59, 55.14, 37.73, 14.28, 14.14. IR (neat) (cm^{-1}): 3180 (w), 3027 (w), 1730 (vs), 1683 (vs), 1296 (vs), 1188 (b), 1110 (m), 1014 (s). ESI-MS (+ve) m/z: Found $[M–Br^–]^+$ 385.1755, $C_{20}H_{26}N_3O_3^+$ requires 385.1758.

(*S*)-4-(Dimethylamino)-1-(2-((1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)pyridin-1-ium bromide (**8**).The general procedure A was applied to L-phenylalanine ethyl ester α-bromoamide (**26**) (0.45 g, 1.42 mmol) and dimethylaminopyridine (0.16 g, 1.29 mmol). The title compound (**8**) was isolated as a white solid in 88% yield (0.50 g, 1.14 mmol). Mp: 135-137°C. $[\alpha]_D^{20}$ = –13.2 (2.0 c, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 9.26 (d, *J* = 7.2 Hz, 1H), 8.36 (d, *J* = 7.8 Hz, 2H), 7.35-7.33 (m, 2H), 7.21-7.19 (m, 2H), 7.15-7.11 (m, 1H), 6.73 (d, *J* = 7.8, 2H), 5.38 (d, *J* = 14.6, 1H), 5.31 (d, *J* = 14.6 Hz, 1H), 4.58 (dd, *J* = 14.9, 7.4 Hz, 1H), 4.06 (q, *J* = 6.8 Hz, 2H), 3.22 (s, 6H), 3.21-3.19 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 170.70, 165.33, 156.37, 143.17, 136.86, 129.62, 128.35, 126.62, 107.43, 61.33, 58.62, 55.12, 40.43, 37.30, 14.09. IR (neat) (cm^{-1}): 3165 (w), 3012 (w), 1743 (s), 1678 (vs), 1651 (vs), 1574 (m), 1404 (w), 1181 (b), 1024 (w), 818 (s). ESI-MS (+ve) m/z: Found $[M–Br^–]^+$ 356.1969, $C_{20}H_{26}N_3O_3^+$ requires 356.1969.

***(S)*-4-(2-((1-Ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-4-methylmorpholin-4-ium bromide** (**9**). The general procedure A was applied to L-phenylalanine ethyl ester α-bromoamide (**26**) (1.17 g, 3.71 mmol) and *N*-methylmorpholine (370 µL, 3.37 mmol). The title compound (**9**) was isolated as a white solid in 34% yield (0.482 g, 1.16 mmol). Mp: 162-164°C. $[\alpha]_D^{20}$ = –22.71 (0.5 c, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 9.40 (d, *J* = 8.0 Hz, 1H), 7.43-7.41 (m, 2H), 7.29-7.26 (m, 2H), 7.20-7.17 (m, 1H), 5.06 (d, *J* = 13.8 Hz, 1H), 4.79 (d, *J* = 14.1 Hz, 1H), 4.76-4.72 (m, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.08-4.03 (m, 2H), 3.91 (d, *J* = 10.2 Hz, 2H), 3.85-3.75 (m, 2H), 3.57 – 3.49 (m, 1H), 3.47 (s, 3H), 3.36-3.33 (m, 1H), 3.33 (dd, *J* = 14.0, 4.6 Hz, 1H), 3.11 (dd, *J* = 14.1, 10.8 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* 170.80,

162.78, 136.73, 129.62, 128.44, 126.82, 61.67, 61.30, 60.57, 60.50, 54.43, 51.40, 37.03, 14.12. IR (neat) (cm^{-1}): 3186 (w), 3019 (w), 1735 (s), 1674 (vs), 1534 (s), 1456 (w), 1247 (b), 1120 (m), 1029 (m), 897 (m). ESI-MS (+ve) m/z: Found $[M–Br^–]^+$ 335.1963, $C_{18}H_{27}N_2O_4^+$ requires 335.1965.

(*S*)-2-((1-Ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-*N*-(2-hydroxyethyl)-*N,N*-dimethyl-2-oxoethan-1-aminium bromide (**10**). The general procedure A was applied to L-phenylalanine ethyl ester α-bromoamide (**26**) (0.59 g, 1.89 mmol) and dimethylaminoethanol (175 μL, 1.70 mmol). The title compound (**10**) was isolated as white solid in 99% yield (0.68 g, 1.69 mmol). Mp: 97-99 °C. $[\alpha]_D^{20} = –45.24$ (0.4 c, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.01 (d, *J* = 7.6 Hz, 1H), 7.40-7.38 (m, 2H), 7.30-7.20 (m, 3H), 4.80 (d, *J* = 14 Hz, 1H), 4.74 (ddd, *J* = 10.3, 7.9, 4.8 Hz, 1H), 4.67 (t, *J* = 5.2 Hz, 1H), 4.43 (d, *J* = 14 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.12-4.08 (m, 2H), 3.65 (ddd, *J* = 13.5, 6.2, 2.5 Hz, 1H), 3.56 (ddd, *J* = 13.7, 6.8, 2.8 Hz, 1H), 3.36 (s, 3H), 3.29 (s, 3H), 3.29 (dd, *J* = 13.6 Hz, 5.1 Hz, 1H), 3.11 (dd, *J* = 14.0, 10.3 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.01, 163.08, 136.47, 129.52, 128.55, 127.01, 67.47, 63.29, 61.73, 55.86, 54.42, 53.40, 37.21, 14.11. IR (neat) (cm^{-1}): 3345 (m), 3207 (m), 3056 (w), 1741 (s), 1686 (vs), 1547 (s), 1281 (s), 1210 (s) 1177 (s), 1079 (m). ESI-MS (+ve) m/z: Found $[M–Br^–]^+$ 323.1959, $C_{17}H_{27}N_2O_4^+$ requires 323.1965.

1,3-bis(2-(((*S*)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-1*H*-imidazol-3-ium bromide (11). To a stirred solution of L-phenylalanine ethyl ester α-bromoamide (**26**) (3.26 g, 10.38 mmol) in diethyl ether (25 mL) was added TMS-imidazole (0.72 g, 5.10 mmol). The reaction was stirred at room temperature under an N_2 atmosphere for 24 hours. After 24 hours a white precipitate of TMS-imidazolium ionic liquid had formed. The diethyl ether was removed *in vacuo* and the white precipitate was rapidly dissolved in ethyl acetate (25 mL). The reaction mixture was then heated under reflux for 24 hours. After 24 hours the reaction was cooled to room temperature and the solvent removed *in vacuo*. The resulting white solid was washed with diethyl ether (3 x 50 mL). Further drying under high vacuum

afforded the title compound (**11**) as a white solid in 91% yield, (2.86 g, 4.64 mmol). Mp: 102-104°C. $[\alpha]_D^{20}$ = +8.20 (1.0 c, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 9.36 (s, 1H), 8.65 (d, *J* = 7.72 Hz, 2H), 7.30-7.17 (m, 12H), 5.28 (d, *J* = 15.6 Hz, 2H), 5.05 (d, *J* = 15.6, 2H), 4.71-4.66 (m, 2H), 4.06 (q, *J* = 7.2 Hz, 4H), 3.20 (dd, *J* = 13.8, 6.0 Hz, 2H), 3.14 (dd, *J* = 13.9, 8.6 Hz, 2H), 1.16 (t, *J* = 7.2 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 171.31, 164.50, 137.63, 129.46, 128.46, 126.91, 122.79, 61.61, 54.72, 51.51, 37.43, 14.01. IR (neat) (cm^{-1}): 3336 (w), 3092 (w), 3047 (w), 2988 (w), 2951 (w), 2899 (w), 1732 (vs), 1663 (vs), 1537 (m), 1198 (s), 747 (m), 701 (m). ESI-MS (+ve) m/z: Found $[M–Br^–]^+$ 535.2555, $C_{29}H_{35}N_4O_6^+$ requires 535.2551.

Preparation of (1*S*,2*S*)-1-({[(2*S*)-1-ethoxy-1-oxo-3-phenylpropan-2-yl]carbamoyl}methyl)-2-(ethoxy-carbonyl)-1-methylpyrrolidin-1-ium bromide (12) and **(1*R*,2*S*)-1-(2-(((*S*)-1-ethoxy-1-oxo-3-phenyl-propan-2-yl)amino)-2-oxoethyl)-2-(ethoxycarbonyl)-1-methylpyrrolidin-1-ium bromide (13).** To a stirred solution of L-phenylalanine ethyl ester α-bromoamide (**26**) (0.56 g, 1.79 mmol) in DMF (5 mL) was added *N*-methyl-L-proline-ethyl ester (**31**) (0.25 g, 1.61 mmol). The reaction was stirred under reflux conditions for 48 hours. After 48 hours the reaction mixture was allowed to cool to room temperature and the DMF was removed *in vacuo*. Analysis by TLC (1:10 MeOH:DCM) showed the presence of two spots separated by 0.05 Rf and were presumed to be diastereomers of the target compound. The crude product was purified by silica gel chromatography (gradient elution of 5:95 MeOH:DCM to 10:90 MeOH:DCM) to afford the title compound (**12**) as a pale yellow oil in 37% yield (0.28 g, 0.60 mmol). $[\alpha]_D^{20}$ = – 52.9 (2.5 c, EtOH). ^{1}H-NMR (600 MHz, $CDCl_3$): *δ* 9.05 (d, *J* = 8.2 Hz, 1H), 7.38 – 7.37 (m, 2H), 7.23-7.20 (m, 2H), 7.13 – 7.11 (m, 1H), 5.14 (t, *J* = 9.5 Hz, 1H), 5.04 (d, *J* = 13.2 Hz, 1H), 4.73 (ddd, *J* = 10.6, 8.1, 4.7 Hz, 1H), 4.61 (d, *J* = 13.2 Hz, 1H), 4.21 (qd, *J* = 7.2, 2.1 Hz, 2H), 4.14-4.09 (m, 3H), 3.26 (dd, *J* = 14.1, 4.8 Hz, 1H), 3.17-3.14 (m, 1H), 3.15 (s, 3H), 3.06 (dd, *J* = 14.1, 10.7 Hz, 1H), 2.61-2.59 (m, 1H), 2.21 – 2.10 (m, 2H), 1.98-1.90 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$): *δ* 170.34, 165.63, 163.13, 136.73, 129.86, 128.46, 126.78, 73.00, 64.26, 63.37, 62.48, 61.73, 54.58, 45.71, 37.12, 24.16, 18.94, 14.15, 14.00. IR (neat) (cm^{-1}): 3715 (w), 2981 (b), 1735 (vs), 1678 (vs),

1548 (m), 1454 (m), 1371 (m), 1202 (b), 1020 (m), 700 (s). ESI-MS (+ve) m/z: Found $[M–Br^–]^+$ 391.2230, $C_{21}H_{31}N_2O_5^+$ requires 391.2227.

The diastereomer (**13**) was also isolated as a pale yellow oil in 13% yield (0.10 g, 0.21 mmol). $[\alpha]_D^{20}$ = –46.7 (3.0 c, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 9.49 (d, *J* = 7.4 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.24 – 7.20 (m, 2H), 7.17 – 7.08 (m, 1H), 5.16 (d, *J* = 13.6 Hz, 1H), 4.58 – 4.52 (m, 1H), 4.53 – 4.45 (m, 1H), 4.33 (d, *J* = 13.5 Hz, 1H), 4.23 – 4.14 (m, 2H), 4.12 – 4.03 (m, 2H), 4.03 – 3.95 (m, 1H), 3.88 – 3.80 (m, 1H), 3.51 (s, 3H), 3.19 (dd, *J* = 13.9, 4.7 Hz, 1H), 3.11 (dd, *J* = 14.0, 10.2 Hz, 1H), 2.65 – 2.55 (m, 1H), 2.45 – 2.34 (m, 2H), 2.33 – 2.21 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.80. 166.97, 163.70, 136.78, 129.48, 128.51, 126.88, 73.60, 64.96, 63.20, 61.62, 58.75, 55.40, 51.01, 37.28, 26.11, 19.42, 14.13, 13.91. IR (neat) (cm^{-1}): 3183 (w), 2981 (b), 1737 (vs), 1682 (s), 1552 (m), 1455 (m), 1372 (w), 1211 (b), 1027 (m), 702 (m). ESI-MS (+ve) m/z: Found $[M–Br^–]^+$ 391.2227, $C_{21}H_{31}N_2O_5^+$ requires 391.2227.

Preparation of (1*S*,2*R)*-1-(2-(((*S*)-1-ythoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-2-(ethoxy-carbonyl)-1-methylpyrrolidin-1-ium bromide (14) and (1*R*,2*R)*-1-(2-(((*S*)-1-ythoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-2-(ethoxycarbonyl)-1-methylpyrrolidin-1-ium bromide (15). To a stirred solution of L-phenylalanine ethyl ester α-bromoamide (**26**) (0.95 g, 3.02 mmol) in ethyl acetate (25 mL) was added *N*-methyl-D-proline-ethyl ester (**32**) (0.48 g, 3.02 mmol). The reaction was stirred under reflux conditions for 48 hours. After 48 hours the reaction was allowed to cool to room temperature and the solvent was removed *in vacuo* to afford a crude product. Analysis by TLC (1:10 MeOH:DCM) showed the presence of two spots separated by 0.05 Rf and were presumed to be diastereomers. The crude product was purified by silica gel chromatography (gradient elution of 5:95 MeOH:DCM to 10:90 MeOH:DCM) to afford the title compound (**14**) as a pale yellow oil in 25% yield (0.36 g, 0.76 mmol). $[\alpha]_D^{20}$ = +1.92 (0.1 c, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 9.26 (d, *J* = 8.6 Hz,

1H), 7.38 – 7.36 (m, 2H), 7.24 – 7.12 (m, 3H), 4.87 – 4.78 (m, 3H), 4.42 (d, *J* = 14.2 Hz, 1H), 4.20 (qd, *J* = 7.1, 1.7 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.87 – 3.81 (m, 1H), 3.46 – 3.39 (m, 1H), 3.34 (s, 3H), 3.26 (dd, *J* = 13.8, 4.6 Hz, 1H), 3.04 (dd, *J* = 13.9, 10.9 Hz, 1H), 2.61-2.53 (m, 1H), 2.48 – 2.39 (m, 1H), 2.33 – 2.18 (m, 1H), 2.28 – 2.22 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* 170.62, 166.69, 163.14, 139.84, 129.72, 128.46, 126.91, 74.30, 64.48, 63.07, 61.66, 58.17, 54.12, 50.51, 37.39, 25.56, 19.40, 14.18, 13.94. IR (neat) (cm^{-1}): 3183 (w), 2981 (b), 1737 (vs), 1682 (vs), 1552 (m), 1455 (m), 1372 (w), 1211 (b), 1027 (m), 702 (w). ESI-MS (+ve) m/z: Found $[M–Br^–]^+$ 391.2223, $C_{21}H_{31}N_2O_5^+$ requires 391.2227.

The diastereomer (**15**) was also isolated as a pale yellow oil in 34% yield (0.49 g, 1.03 mmol). $[\alpha]_D^{20}$ = +1.86 (1.0 c, EtOH). ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 9.28 (d, *J* = 7.3 Hz, 1H), 7.43 – 7.41 (m, 2H), 7.30 – 7.27 (m, 2H), 7.22-7.21 (m, 1H), 5.32 (d, *J* = 13.1 Hz, 1H), 5.11 (t, *J* = 9.5 Hz, 1H), 4.62 (ddd, *J* = 10.4, 7.4, 4.8 Hz, 1H), 4.48-4.43 (m, 1H), 4.42 (d, *J* = 13.0 Hz, 1H), 4.27 (qd, *J* = 7.2, 1.3 Hz, 2H), 4.16 (qd, *J* = 7.2, 2.7 Hz, 2H), 3.86-3.79 (m, 1H), 3.31 – 3.28 (m, 1H), 3.26 (s, 3H), 3.13 (dd, *J* = 14.0, 10.4 Hz, 1H), 2.72-2.63 (m, 1H), 2.39 – 2.31 (m, 1H), 2.28-2.21 (m, 1H), 2.13-2.02 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* 170.57, 165.61, 163.38, 136.61, 129.62, 128.56, 126.92, 73.41, 64.84, 63.39, 62.64, 61.66, 55.23, 45.47, 36.82, 24.24, 18.97, 14.16, 14.01. IR (neat) (cm^{-1}): 3175 (w), 2981 (b), 1737 (vs), 1678 (vs), 1548 (m), 1545 (m), 1371 (w), 1202 (b), 1020 (s), 700 (w). ESI-MS (+ve) m/z: Found $[M–Br^–]^+$ 391.2215, $C_{21}H_{31}N_2O_5^+$ requires 391.2227.

Preparation of L-phenylalanine tertiary amino compounds

Ethyl (2-(1*H*-imidazol-1-yl)acetyl)-L-phenylalaninate (21). To a stirred solution of L-phenylalanine ethyl ester α-bromoamide (**26**) (1.01 g, 3.22 mmol) in diethyl ether (20 mL) was added TMS-imidazole (0.32 g, 2.29 mmol). The reaction was stirred at room temperature under an N_2 atmosphere for 24 hours. After 24 hours a white precipitate of TMS-imidazolium ionic liquid had formed. Diethyl ether was removed *in*

vacuo and the white precipitate was dissolved in 5 mL of water and stirred for 30 minutes to facilitate the removal of the TMS group. Water was removed *in vacuo* and the resulting crude product was purified by silica gel chromatography (eluent 10:90 MeOH:DCM) to afford the title compound (**21**) as a pale yellow oil in 55% yield, (0.38 g, 1.27 mmol). $[\alpha]_D^{20}$ = +19.6 (2.0 c, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 7.42 (s, 1H), 7.29 – 7.26 (m, 3H), 7.11 (s, 1H), 6.98 – 6.95 (m, 2H), 6.81 (s, 1H), 5.84 (d, *J* = 7.9 Hz, 1H), 4.82-4.77 (m, 1H), 4.61 (d, *J* = 17.2 Hz, 1H), 4.56 (d, *J* = 17.7 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.12 (dd, *J* = 13.9, 5.7 Hz, 1H), 3.00 (dd, *J* = 14.0, 6.5 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* 170.81, 166.40, 137.50, 135.31, 130.94, 129.14, 128.86, 127.47, 119.58, 61.92, 53.11, 50.00, 37.56, 14.18. IR (neat) (cm^{-1}): 3202 (w), 2982 (b), 1735 (s), 1673 (s), 1548 (m), 1509 (m), 1454 (w), 1372 (w), 1199 (b), 1107 (s), 1079 (s), 1030 (s), 744 (s), 701 (s). ESI-MS (+ve) m/z: Found $[M+H]^+$ 302.1493, $C_{16}H_{20}N_3O_3^+$ requires 302.1499.

Ethyl *N*-(2-hydroxyethyl)-*N*-methylglycyl-L-phenylalaninate (22). To a stirred solution of L-phenylalanine ethyl ester α-bromoamide (**26**) (0.51 g, 1.60 mmol) in diethyl ether (25 mL) was added 2-(methylamino)ethanol (115 μL, 1.43 mmol). The reaction was stirred at room temperature under an N_2 atmosphere for 24 hours. After 24 hours a waxy precipitate had formed. The supernatant was decanted and the waxy crude product was purified by silica gel chromatography (gradient elution of 1:99 MeOH:DCM to 5:95 MeOH:DCM) to afford the title compound (**22**) as a pale yellow oil in 34% yield, (0.148 g, 0.480 mmol). $[\alpha]_D^{20}$ = +29.1 (0.9 c, $CHCl_3$).^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.74 (d, *J* = 8.8 Hz, 1H) 7.29-7.22 (m, 3H), 7.14-7.12 (m, 2H), 4.86 (ddd, *J* = 8.7, 7.0, 6.1 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.63 – 3.49 (m, 2H), 3.15 (dd, *J* = 13.9, 5.9 Hz, 1H), 3.07 (dd, *J* = 14.0, 6.8 Hz, 1H), 3.05 (d, *J* = 16.7 Hz, 1H), 2.99 (d, *J* = 16.9 Hz, 1H), 2.56-2.46 (m, 2H), 2.35 (bs, 1H), 2.28 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 172.46, 170.78, 136.06, 129.22, 128.57, 127.15, 61.73, 61.24, 60.07, 59.61, 52.54, 43.50, 37.90, 14.09. IR (neat) (cm^{-1}): 3298 (b), 2939 (w), 1737 (s), 1656 (vs), 1517 (s), 1455 (m), 1373 (w),

1199 (b), 1129 (w), 1079 (w), 1040 (m), 746 (m), 702 (s). ESI-MS (+ve) m/z: Found $[M+H]^+$ 309.1809, $C_{16}H_{25}N_2O_4^+$ requires 309.1809

Ethyl (2-morpholinoacetyl)-L-phenylalaninate (23). To a stirred solution of L-phenylalanine ethyl ester α-bromoamide (**26)** (1.07 g, 3.42 mmol) in THF (50 mL) was added morpholine (280 µL, 3.25 mmol). The reaction was stirred under reflux conditions for 24 hours. After 24 hours the reactions was allowed to cool to room temperature and solid Na_2CO_3 (0.37 g, 3.50 mmol) was added to the reaction and stirred vigorously for 1 hour. After one hour the Na_2CO_3 was removed by gravity filtration and the solvent was removed *in vacuo*. The crude product was purified by silica gel chromatography (eluent 50:50 ethyl acetate:hexane) to afford the title compound (**23**) as a brown oil in 56% yield, (0.59 g, 1.83 mmol). $[\alpha]_D^{20}$ = +15.4 (1.0 c, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.56 (bs, 1H), 7.30-7.21 (m, 3H), 7.14-7.13 (m, 2H), 4.85 (ddd, *J* = 8.4, 6.9, 5.7 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.58 (m, 3.61-3.54, 4H), 3.19 (dd, *J* = 14.0, 5.7 Hz, 1H), 3.10 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.02-2.92 (m, 2H), 2.46 (s, 2H), 2.34 (s, 2H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.68, 136.09, 129.29, 128.74, 127.29, 66.90, 61.66, 53.61, 52.46, 37.77, 14.26. IR (neat) (cm^{-1}): 3344 (w), 2962 (w), 2856 (w), 2822 (w), 1737 (s), 1676 (s), 1507 (s), 1454 (m), 1373 (w), 1190 (b), 1114 (vs), 1032 (m), 865 (m), 747 (vs), 700 (m). ESI-MS (+ve) m/z: Found $[M+H]^+$ 321.1809, $C_{17}H_{25}N_2O_4^+$ requires 321.1809.

Ethyl (2-(((*S*)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-L-prolinate (24). To a stirred solution of L-phenylalanine ethyl ester α-bromoamide (**26**) (0.58 g, 1.85 mmol) in THF (10 mL) was added L-proline ethyl ester hydrochloride (**34**) (0.30 g, 1.68 mmol) and solid Na_2CO_3 (0.36 g, 3.36 mmol). The reaction mixture was stirred at room temperature for 24 hours. After 24 hours the Na_2CO_3 was removed by gravity filtration and the solvent was removed *in vacuo*. The crude product was purified by silica gel chromatography (eluent 50:50 ethyl acetate:hexane) to afford the title compound (**24**) as a yellow oil in 53% yield, (0.334 g, 0.887 mmol). $[\alpha]_D^{20}$ = –6.2 (2.0 c, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.4

Hz, 1H), 7.31 – 7.27 (m, 1H), 7.26 – 7.15 (m, 4H), 4.88-4.82 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 4H), 3.43-3.39 (m, 2H), 3.15-3.09 (m, 4H), 2.41 (dd, *J* = 8.0, 7.6 Hz, 1H), 2.41 (dd, *J* = 16.6, 7.9 Hz, 1H), 1.97-1.92 (m, 1H), 1.84-1.79 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* 173.79, 171.62, 170.76, 136.21, 129.35, 128.45, 126.96, 65.40, 61.28, 60.76, 57.67, 54.07, 52.68, 38.07, 29.59, 23.92, 14.29, 14.10. IR (neat) (cm^{-1}): 3340 (w), 2980 (w), 1733 (s), 1679 (s), 1509 (m), 1454 (w), 1372 (w), 1187 (b), 1027 (m), 746 (w), 701 (m). ESI-MS (+ve) m/z: Found $[M+H]^+$ 377.2067, $C_{20}H_{29}N_2O_5^+$ requires 377.2071.

Preparation of ethyl (2-bromoacetyl)-L-tyrosinate (29).

To a stirred solution of L-tyrosine ethyl ester hydrochloride (**27**), (3.65 g, 14.85 mmol), in DCM (50 mL) was added solid Na_2CO_3 (3.46 g, 32.66 mmol). The reaction mixture was stirred vigorously for one hour to neutralise the L-tyrosine hydrochloride salt. The reaction mixture was then cooled to 0 °C and bromoacetyl bromide was added dropwise (2.6 mL, 30 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 12 hours. After 12 hours the Na_2CO_3 and other salts were removed by gravity filtration. The DCM layer was washed with saturated sodium bicarbonate solution (3 x 50 mL), dried over anhydrous magnesium sulphate and gravity filtered. A small sample was purified by silica gel chromatography (eluent 50:50 ethyl acetate:hexane) to give intermediate ethyl (*S*)-2-(2-bromoacetamido)-3-(4-(2-bromoacetoxy)phenyl)propanoate **(28)** isolated. $[\alpha]_D^{20}$ = +33.1 (1.0 c, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): *δ* 7.17 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 7.8 Hz, 1H), 4.82 (dt, *J* = 7.8, 5.9 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.05 (s, 2H), 3.87 (d, *J* = 13.6 Hz, 1H), 3.83 (d, *J* = 13.6 Hz, 1H), 3.18 (dd, *J* = 13.8, 5.9 Hz, 1H), 3.13 (dd, *J* = 13.9, 5.7 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* 170.79, 165.87, 165.27, 149.72, 133.83, 130.62, 133.83, 130.62, 121.39, 62.06, 53.79, 37.30, 28.80, 25.67, 14.24. IR (neat) (cm^{-1}): 3426(m), 3303(m), 1721(s), 1672 (s), 1519 (m), 1227 (vs),

1199 (vs), 1101 (m), 822 (w). ESI-MS (+ve) m/z: Found $[M+H]^+$ 449.9550, $C_{15}H_{18}Br_2NO_5^+$ requires 449.9546.

The DCM was removed *in vacuo* and the solid crude product isolated was dissolved in ethanol (10 mL) and acidified to pH 1 using conc. HCl. The solution was stirred for 24 hours until TLC showed the complete hydrolysis of the phenolic ester and the ethyl ester remaining intact. Precipitation of the product by dropwise addition of hexane afforded the title compound (**29**) as a white solid in 54% yield (4.34 g, 13.14 mmol). Mp: 111-113° C. $[\alpha]_D^{20}$ = +20.9 (1.0 c, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.99 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.5 Hz, 2H), 5.35 (s, 1H), 4.79 (dt, *J* = 8.0, 5.8 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.87 (d, *J* = 13.7 Hz, 1H), 3.83 (d, *J* = 13.7 Hz, 1H), 3.10 (dd, *J* = 14.1, 5.7 Hz, 1H), 3.04 (dd, *J* = 14.0, 5.9 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.26, 165.51, 155.24, 130.76, 127.40, 115.78, 62.11, 54.11, 37.23, 28.95, 14.40. IR (neat) (cm^{-1}): 3300(b), 1734(s), 1646 (s), 1547 (m), 1268 (m), 1194 (vs), 1101 (s), 1019 (m), 932 (w), 851 (w). ESI-MS (+ve) m/z: Found $[M+H]^+$ 330.0334, $C_{13}H_{17}BrNO_4^+$ requires 330.0335.

Preparation of ILs via amination of L-tyrosine ethyl ester α-bromoamide (29) – general procedure "B"

To a stirred solution of (**29**) in ethyl acetate (50 mL) was added the N-heterocycle. The reaction was stirred under reflux conditions for 24 hours. After 24 hours the reaction was allowed to cool to room temperature and the solvent was removed *in vacuo* to afford a crude product. The crude product was washed with diethyl ether (3 x 50 ml) to afford the corresponding title compound.

(*S*)-3-(2-((1-Ethoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)amino)-2-oxoethyl)-1-methyl-1*H*-imidazol-3-ium bromide (16). According to the general procedure "B", using pyridine 1-methylimidazole (0.12 mL, 1.5 mmol) and L-tyrosine ethyl ester α-bromoamide (**29**) (0.50 g, 1.53 mmol), the title compound (**16**)

was isolated as a white solid in 83% yield, (0.51 g, 1.25 mmol). $[\alpha]_D^{20}$ = +9.8 (0.6 c, EtOH). ^{1}H-NMR (400 MHz, DMSO): δ 9.30 (s, 1H), 9.08 (s, 1H), 8.98 (d, *J* = 7.5 Hz, 1H), 7.69 (t, *J* = 1.8 Hz, 1H), 7.63 (t, *J* = 1.8 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 5.05 (d, *J* = 16.6 Hz, 1H), 5.00 (d, *J* = 16.8 Hz, 1H), 4.43 – 4.38 (m, 1H), 4.07 – 4.01 (m, 2H), 3.88 (s, 3H), 2.91 (dd, *J* = 13.8, 6.2 Hz, 1H), 2.83 (dd, *J* = 13.8, 8.2 Hz, 1H), 1.10 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO): δ 171.07, 165.04, 156.16, 137.71, 130.10, 126.57, 123.67, 123.00, 115.12, 60.68, 54.42, 50.29, 36.17, 35.82, 13.97.

(*S*)-1-(2-((1-Ethoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)amino)-2-oxoethyl)pyridin-1-ium bromide (17). According to the general procedure "B", using pyridine (250 µL, 3.16 mmol), and alkylating reagent (**29**) (1.07 g, 3.23 mmol), the title compound (**17**) was isolated as a white solid in 99% yield, (1.290 g, 3.152 mmol). Mp: 30-32° C. $[\alpha]_D^{20}$ = +15.4 (1.0 c, $CHCl_3$). ^{1}H-NMR (400 MHz, DMSO) : δ 9.30 (s, 1H), 9.19 (d, *J* = 7.5 Hz, 1H), 8.92 (d, *J* = 5.3 Hz, 2H), 8.66 (t, *J* = 7.8 Hz, 1H), 8.17 (d, *J* = 7.1 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 5.52 (d, *J* = 16.0 Hz, 2H), 5.48 (d, *J* = 16.1 Hz, 1H), 4.45 – 4.40 (m, 1H), 4.07 – 3.99 (m, 2H), 2.91 (dd, *J* = 13.9, 6.5 Hz, 1H), 2.86 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO): δ 171.86, 165.44, 156.19, 146.22, 146.19, 130.15, 127.54, 126.43, 115.14, 61.32, 60.72, 54.53, 36.31, 13.95. IR (neat) (cm^{-1}): 3197 (b), 3052 (b), 1732 (m), 1683 (s), 1514 (s), 1201 (bs), 1112 (m), 1021 (m), 853 (m). ESI-MS (+ve) m/z: Found $[M–Br^–]^+$ 329.1501, $C_{18}H_{21}N_2O_4^+$ requires 329.1496.

(*S*)-1-(2-((1-Ethoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)amino)-2-oxoethyl)-3-methoxypyridin-1-ium bromide (18). According to the general procedure "E", using 3-methoxy pyridine (280 µL, 2.88 mmol) and alkylating reagent (**29**) (0.97 g, 2.95 mmol), the title compound (**18**) was isolated as a white solid in 99% yield, (1.25 g, 2.85 mmol). Mp: 117-119 °C. $[\alpha]_D^{20}$ = +12.7 (1.0 c, $CHCl_3$). ^{1}H-NMR (400 MHz, MeOD) : δ 8.67 (dd, *J* = 2.7, 1.3 Hz, 1H), 8.44 (d, *J* = 6.0 Hz, 1H), 8.25 (ddd, *J* = 8.8, 2.6, 0.9 Hz, 1H), 8.03 (dd, *J* = 8.9, 5.9 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 5.48 (d, *J* = 16.3 Hz, 1H), 5.43 (d, *J*

= 15.8 Hz, 1H), 4.68 (dd, *J* = 8.7, 5.8 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.08 (s, 3H), 3.13 (dd, *J* = 14.0, 5.8 Hz, 1H), 2.95 (dd, *J* = 14.0, 8.7 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO): δ 172.66, 165.71, 159.97, 157.53, 139.52, 134.89, 132.38, 131.33, 129.21, 128.24, 116.26, 63.01, 62.57, 58.08, 56.03, 37.77, 14.36. IR (neat) (cm^{-1}): 3196 (b), 3038 (b), 1731 (m), 1682 (m), 1509 (s), 1201 (bs), 1112 (m), 1012 (m), 826 (w). ESI-MS (+ve) m/z: Found $[M–Br^–]^+$ 359.1607, $C_{19}H_{23}N_2O_5^+$ requires 359.1601.

(*S*)-1-(2-((1-Ethoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)amino)-2-oxoethyl)-3-(ethoxycarbonyl)-pyridin-1-ium bromide (19). The target compound was synthesised according to the general procedure "B", using ethyl nicotinate (0.40 mL, 2.98 mmol) and alkylating reagent (**29**) (1.00 g, 3.04 mmol) to give a crude product as a brown solid. The crude product was purified by silica gel chromatography (eluent 5:95 MeOH:DCM) to afford the title compound (**19**) as an orange solid in 71% yield, (1.016 g, 2.11 mmol). Mp: 53-55° C. $[\alpha]_D^{20}$ = +9.0 (1.0 c, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 9.34 (s, 1H), 9.21 (d, *J* = 6.1 Hz, 1H), 8.86 (d, *J* = 8.2 Hz, 1H), 8.82 (d, *J* = 8.3 Hz, 1H), 8.20 (dd, *J* = 8.1, 6.1 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 6.14 (d, *J* = 15.5 Hz, 1H), 5.89 (d, *J* = 15.4 Hz, 1H), 4.72 (td, *J* = 8.6, 4.3 Hz, 1H), 4.47 – 4.35 (m, 2H), 4.13 (q, *J* = 6.9 Hz, 2H), 3.12 (dd, *J* = 14.1, 4.3 Hz, 1H), 2.97 (dd, *J* = 14.1, 9.1 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.11, 164.01, 161.25, 155.64, 149.02, 146.89, 145.75, 130.78, 130.16, 128.45, 127.27, 115.65, 63.55, 62.73, 61.85, 54.80, 36.58, 14.27, 14.23. IR (neat) (cm^{-1}): 3191 (b), 3047 (b), 1729 (vs), 1685 (vs), 1514 (s), 1297 (s), 1191 (bs), 1111 (m), 1014 (m), 855 (m), 736 (m). ESI-MS (+ve) m/z: Found $[M–Br^–]^+$ 401.1713, $C_{21}H_{25}N_2O_6^+$ requires 401.1707.

(*S*)-2-((1-Ethoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)amino)-*N*-(2-hydroxyethyl)-*N*,*N*-dimethyl-2-oxoethanaminium bromide (20). To a stirred solution of L-tyrosine ethyl ester α-bromoamide (**27**) (1.03 g, 3.11 mmol) in diethyl ether (25 mL) was added dimethylaminoethanol (0.30 mL, 3.1 mmol). The reaction was stirred at room temperature under an N_2 atmosphere for 24 hours. After 24 hours a white

precipitate had formed. The supernatant was decanted and the white precipitate was washed with diethyl ether (3 x 50 mL) to afford the title compound (**20**) as a white solid in 79% yield, (1.004 g, 2.394 mmol). Mp: 141-143° C. $[\alpha]_D^{20} = -3.0$ (1.0 c, $CHCl_3$). ^{1}H-NMR (400 MHz, DMSO): *δ* 9.27 (s, 1H), 9.00 (d, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 2H), 6.67 (d, *J* = 8.2 Hz, 2H), 5.33 (s, 1H), 4.47 (d, *J* = 5.6 Hz, 1H), 4.21 – 4.11 (m, 2H), 4.08 (q, *J* = 6.7 Hz, 2H), 3.80 (s, 2H), 3.52 (s, 2H), 3.17 (s, 3H), 3.16 (s, 3H), 2.95 (dd, *J* = 14.3, 5.3 Hz, 1H), 2.81 (dd, *J* = 13.7, 9.0 Hz, 1H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO): *δ* 170.81, 163.39, 156.16, 130.17, 126.57, 115.11, 66.02, 62.50, 60.86, 54.97, 53.98, 52.07, 52.03, 35.78, 13.99. IR (neat) (cm^{-1}): 3357 (b), 3188 (b), 3056 (m), 1737 (vs), 1665 (vs), 1556 (m), 1514 (m), 1369 (m), 1342 (m), 1287 (s), 1218 (vs), 1179 (vs), 1103 (m), 1071 (m), 1015 (m), 804 (m), 732 (m). ES-MS (+ve) m/z: Found $[M–Br^–]^+$ 339.1920, $C_{19}H_{23}N_2O_5^+$ requires 339.1914.

(*S*)-2-((1-Carboxy-2-phenylethyl)amino)-*N*-(2-hydroxyethyl)-*N*,*N*-dimethyl-2-oxoethan-1-aminium bromide (37). To a stirred solution of IL (**10**) (0.24 g, 0.65 mmol) in a 50% (v/v) THF/H_2O solution (10 mL) was added LiOH (0.25 g, 5.96 mmol). The solution was allowed to stand in the fridge for 12 hours. After 12 hours the basic solution was acidified to pH 6 by dropwise addition of HBr. Evaporation of the solvent *in vacuo* yielded a waxy crude white product. The crude product was washed with acetonitrile (3 x 10 mL) to extract the title compound leaving the inorganic salt behind. Solvent was removed *in vacuo* to afford the title compound (**37**) as a white solid in 85% yield (0.21 g, 0.55 mmol). Mp: 59-61°C. $[\alpha]_D^{20}$ = +5.0 (0.1 c, EtOH). ^{1}H-NMR (400 MHz, DMSO): *δ* 8.37 (d, *J* = 8.5 Hz, 1H), 7.30 – 7.14 (m, 5H), 7.14 – 7.02 (m, 1H), 5.36 (s, 1H), 4.21 (td, *J* = 9.7, 3.9 Hz, 2H), 4.13 (d, *J* = 14.2 Hz, 1H), 4.06 (d, *J* = 14.2 Hz, 1H), 3.48 – 3.38 (m, 2H), 3.22 – 3.10 (m, 2H), 3.09 (s, 3H), 3.06 (s, 3H), 2.70 (dd, *J* = 13.7, 10.0 Hz, 1H). ^{13}C-NMR (100 MHz, DMSO): *δ* 174.74, 162.46, 139.32, 129.53, 128.32, 126.31, 66.12, 63.72, 56.47, 55.17, 52.30, 52.16, 38.01. IR (neat) (cm^{-1}): 3406 (s), 3236 (m), 1636 (s), 1614 (vs), 1395 (m), 1085 (m), 699 (m). ESI-MS (+ve) m/z: Found $[M\text{-}Br^-]^+$ 295.1660, $C_{15}H_{23}O_4N_2^+$ requires 295.1652

(*S*)-1-(2-(Benzyloxy)-2-oxoethyl)-3-(2-((1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-1*H*-imidazol-3-ium bromide (39). To a stirred solution of ethyl alkylating reagent (**26**) (0.67 g, 2.13 mmol) in diethyl ether (25 mL) and ethyl acetate (5 mL) was added imidazole intermediate (**38**) (0.38 g, 1.77 mmol). An off-white precipitate was observed forming after 30 minutes. The reaction was stirred at room temperature for 72 hours. After 72 hours the solvent was decanted and the resulting white crude product was washed with diethyl ether (3 x 25 mL) to afford the title compound (**39**) as an off white solid in 97% yield (0.91 g, 1.72 mmol). Mp: 57-59° C. $[\alpha]_D^{20}$ = +9.5 (1.95 c, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.58 (s, 1H), 8.95 (d, *J* = 7.7 Hz, 1H), 7.46 – 7.28 (m, 9H), 7.25 – 7.07 (m, 3H), 5.36 – 5.28 (m, 3H), 5.27 – 5.18 (m, 1H), 5.17 (s, 2H), 4.69 – 4.59 (m, 1H), 4.08 – 3.96 (m, 2H), 3.17 (d, *J* = 2.0 Hz, 1H), 3.14 (dd, *J* = 12.0, 3.9 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.47, 165.96, 164.78, 138.39, 136.76, 134.45, 129.66, 129.06, 128.93, 128.89, 128.62, 127.01, 123.41, 123.04, 68.73, 61.71, 54.98, 51.75, 50.56, 37.52, 14.18. IR (neat) (cm^{-1}): 3033 (b), 1736 (vs), 1684 (vs), 1551 (s), 1178 (vs), 1024 (s), 743 (s), 697 (vs). ESI-MS (+ve) m/z: Found $[M\text{-}Br^-]^+$ 450.2027, $C_{25}H_{28}N_3O_5^+$ requires 450.2023

(*S*)-1-(Carboxymethyl)-3-(2-((1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-1*H*-imidazol-3-ium bromide (40).To a stirred solution of IL (**39**) (0.45 g, 0.85 mmol) in DCM (25 mL) was added 10% Pd/C (0.045 g). The reaction mixture was stirred vigorously under 1 atmosphere of H_2 for 12 hours. After 12 hours the reaction mixture was degassed with a stream of N_2 and filtered over a pad of celite. The celite filter pad was washed with DCM (3 x 25 mL). The combined filtrate was collected and organic solvent was removed *in vacuo*. The resulting crude product was washed with chloroform (3 x 25 mL) to afford the title compound (**40**) as an off white solid in 87% yield (0.33 g, 0.74 mmol). Mp: 162-164° C. $[\alpha]_D^{20}$ = +4.0 (0.1 c, EtOH). ^{1}H-NMR (400 MHz, D_2O): δ 8.71 (t, *J* = 1.6 Hz, 1H), 7.45 (t, *J* = 1.9 Hz, 1H), 7.36 – 7.16 (m, 6H), 5.05 – 4.88 (m, 4H), 4.74 – 4.68 (m, 1H), 4.14 (qd, *J* = 7.2, 1.3 Hz, 2H), 3.23 (dd, *J* = 13.9, 5.7 Hz, 1H), 2.96 (dd, *J* = 13.9, 9.4 Hz, 1H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, D_2O): δ 172.61,

170.12, 166.42, 137.85, 136.20, 129.11, 128.65, 127.14, 123.48, 123.07, 62.76, 54.41, 50.54, 50.48, 36.62, 13.09. IR (neat) (cm^{-1}): 3311 (b), 3108 (m), 2981 (m), 1726 (vs), 1664 (vs), 1555 (s), 1537 (s), 1215 (s), 1195 (s), 1178 (s), 691 (s). ESI-MS (+ve) m/z: Found $[M\text{-}Br^-]^+$ 360.1559, $C_{19}H_{21}N_2O_5^+$ requires 360.1559.

(*S*)-3-Carboxy-1-(2-((1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)pyridin-1-ium bromide (41). To a stirred solution of sodium nicotinate (0.48 g, 3.3 mmol) in DMF (25 mL) was added alkylating reagent (**26**) (3.21 g, 10.22 mmol). The reaction mixture was heated under reflux conditions for 72 hours and was observed to change from colourless to yellow. After 72 hours the reaction mixture was allowed to cool to room temperature. DMF was removed *in vacuo* and the crude orange product was purified by silica gel chromatography (eluent 5:95 MeOH:DCM) to afford the title compound (**41**) as an orange solid in 37% yield (0.53 g, 1.22 mmol). $[\alpha]_D^{20}$ = -8.0 (0.1 c, EtOH). ^{1}H-NMR (400 MHz, D_2O) δ (ppm): 8.92 (s, 1H), 8.86 (dt, *J* = 8.1, 1.4 Hz, 1H), 8.61 (dt, *J* = 6.2, 1.3 Hz, 1H), 8.04 (dd, *J* = 8.0, 6.2 Hz, 1H), 7.32 – 7.16 (m, 5H), 5.42 (d, *J* = 16.0 Hz, 1H), 5.34 (d, *J* = 16.0 Hz, 1H), 4.77 – 4.72 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.24 (dd, *J* = 13.9, 5.5 Hz, 1H), 2.93 (dd, *J* = 13.8, 9.7 Hz, 1H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, D_2O+DMSO): *δ* 175.04, 169.21, 167.77, 149.14, 148.79, 138.76, 131.75, 131.23, 130.30, 129.76, 65.40, 64.15, 57.07, 37.00, 15.71. IR (neat) (cm^{-1}): 2969 (b), 2779 (s), 2437 (m), 1733 (m), 1686 (s), 1641 (s), 1372 (s), 1211 (s), 1022 (vs), 705 (s), 668 (s). ESI-MS (+ve) m/z: Found $[M\text{-}Br^-]^+$ 357.1451, $C_{19}H_{21}N_2O_5^+$ requires 357.1450.

(*S*)-1-(2-((1-Carboxy-2-phenylethyl)amino)-2-oxoethyl)-3-(ethoxycarbonyl)pyridin-1-ium bromide (42). To a stirred suspension of L-phenylalanine (0.87 g, 5.23 mmol) in deionised water (10 mL) at 0 °C was added a 1M NaOH solution (0.2 mL). The solution was stirred for 30 minutes until dissolution of the L-phenylalanine was achieved. After complete dissolution was observed, a solution of bromoacetyl bromide (0.50 mL, 5.7 mmol) in toluene (10 mL) was added to the stirred aqueous reaction mixture

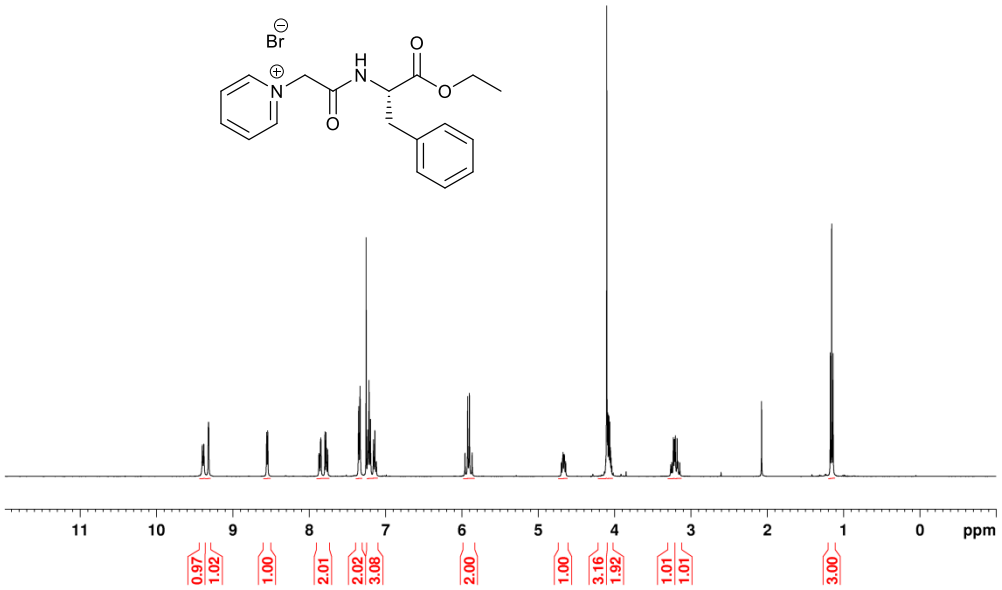
dropwise. Reaction pH was maintained at pH 9 by the concomitant addition of supplementary 1M NaOH if pH was determined to be decreasing by universal indicator paper checks every 5 minutes. After 30 minutes the reaction mixture was acidified to pH 1 and the target product was observed to precipitate as a white solid. Isolation of the target product was achieved by vacuum filtration of the reaction mixture followed by washing with ice cold deionised water (3 x 5 mL). Excess water was removed *in vacuo* to afford (2-bromoacetyl)-L-phenylalanine as a white solid in 58% yield (0.86 g, 3.01 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.26 (m, 3H), 7.21 – 7.13 (m, 2H), 6.83 (d, *J* = 7.7 Hz, 1H), 4.93 – 4.83 (m, 1H), 3.89 (d, *J* = 13.9 Hz, 1H), 3.84 (d, *J* = 13.9 Hz, 1H), 3.25 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.17 (dd, *J* = 14.0, 6.1 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.42, 165.88, 137.29, 129.10, 128.19, 126.50, 53.78, 36.47, 28.97. No ^{1}H or ^{13}C-NMR were previously reported in the literature procedure[63].

To a stirred solution of ethyl nicotinate (0.66 mL, 4.8 mmol) in DMF (25 mL) was added alkylating reagent (2-bromoacetyl)-L-phenylalanine (0.70 g, 2.41 mmol). The reaction was heated under reflux conditions for 72 hours and was observed to change from colourless to yellow. After 72 hours the reaction mixture was allowed to cool to room temperature. DMF was removed *in vacuo* and the crude orange product was purified by silica gel chromatography (eluent 5:95 MeOH:DCM) to afford the title compound (**42**) as an orange solid in 57% yield (0.60 g, 1.38 mmol). Mp: 85-87° C. $[\alpha]_D^{20}$ =+-9.0 (0.1 c, EtOH). ^{1}H-NMR (400 MHz, D_2O): δ 9.18 (s, 1H), 9.02 (d, *J* = 8.2 Hz, 1H), 8.74 (d, *J* = 6.1 Hz, 1H), 8.17 – 8.09 (m, 1H), 7.32 – 7.19 (m, 5H), 5.45 (d, *J* = 16.1 Hz, 1H), 5.35 (d, *J* = 16.0 Hz, 1H), 4.70 (dd, *J* = 9.9, 5.1 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.26 (dd, *J* = 13.9, 4.9 Hz, 1H), 2.92 (dd, *J* = 13.7, 10.0 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, D_2O): δ 177.13, 167.39, 164.99, 150.98, 149.32, 149.14, 139.14, 133.31, 131.75, 131.20, 130.66, 129.66, 66.45, 64.26, 57.20, 39.50, 15.71. IR (neat) (cm^{-1}): 3201 (b), 3029 (m), 2928 (m), 1729 (vs), 1682 (vs), 1540 (s), 1298 (vs), 1207 (vs), 1188 (vs), 741 (s), 643 (s). ESI-MS (+ve) m/z: Found $[M\text{-}Br^-]^+$ 357.1449; $C_{19}H_{21}N_2O_5^+$ requires 357.1450

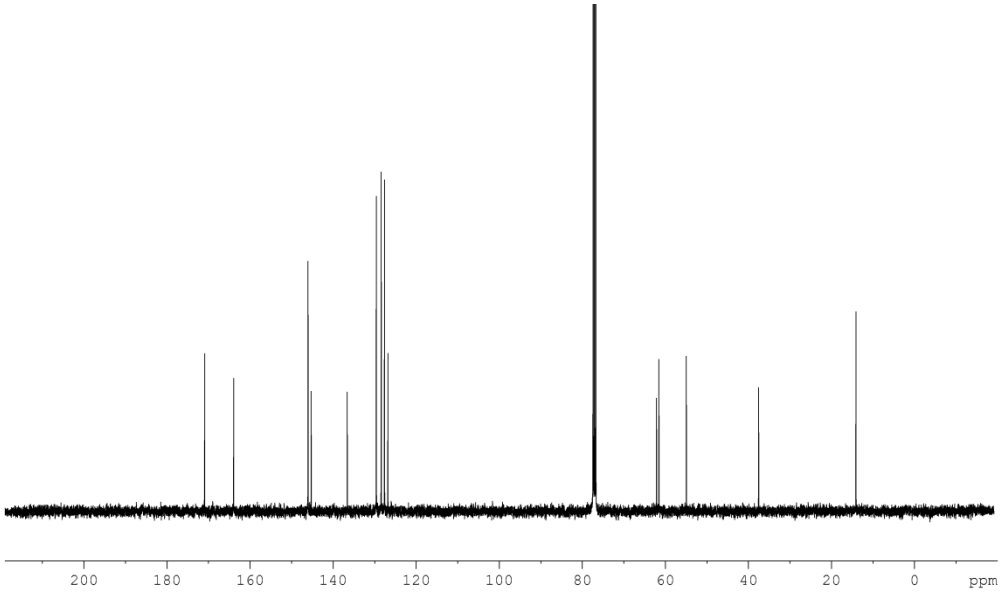
NMR spectra

(*S*)-1-(2-((1-Ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)pyridin-1-ium bromide (5).

^{1}H-NMR

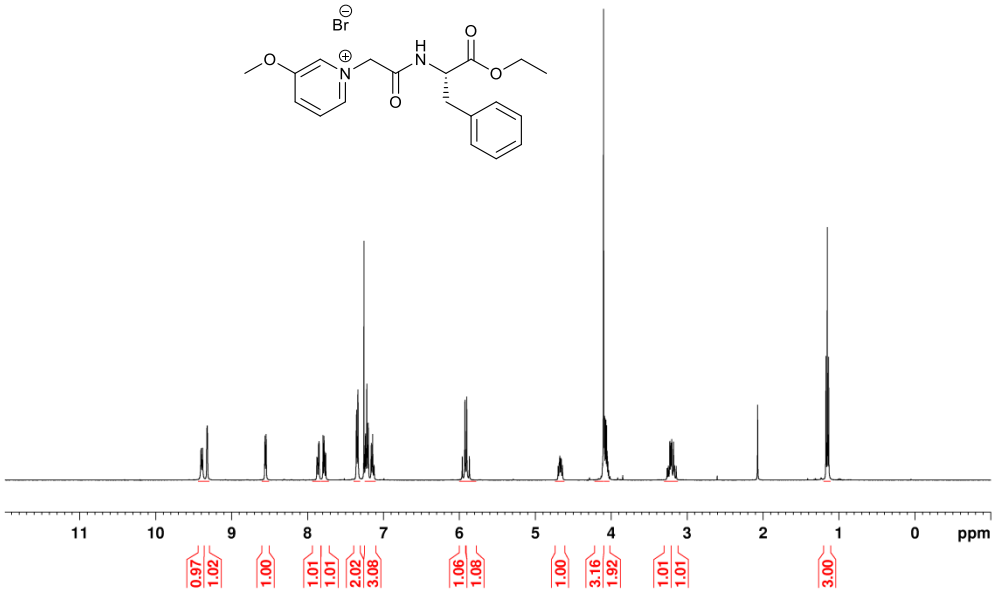


^{13}C-NMR

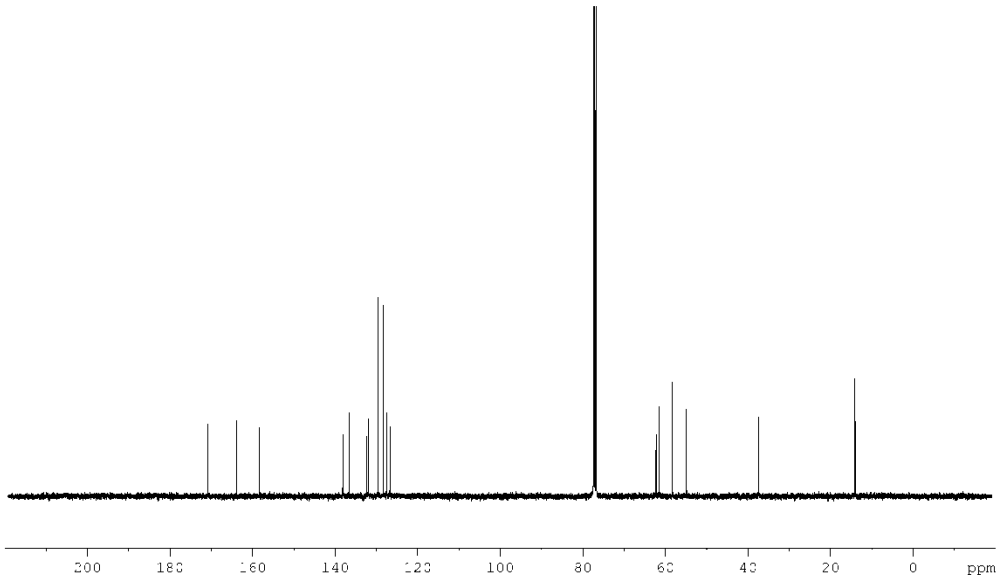


(*S*)-1-(2-((1-Ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-3-methoxypyridin-1-ium bromide (6)

^{1}H -NMR

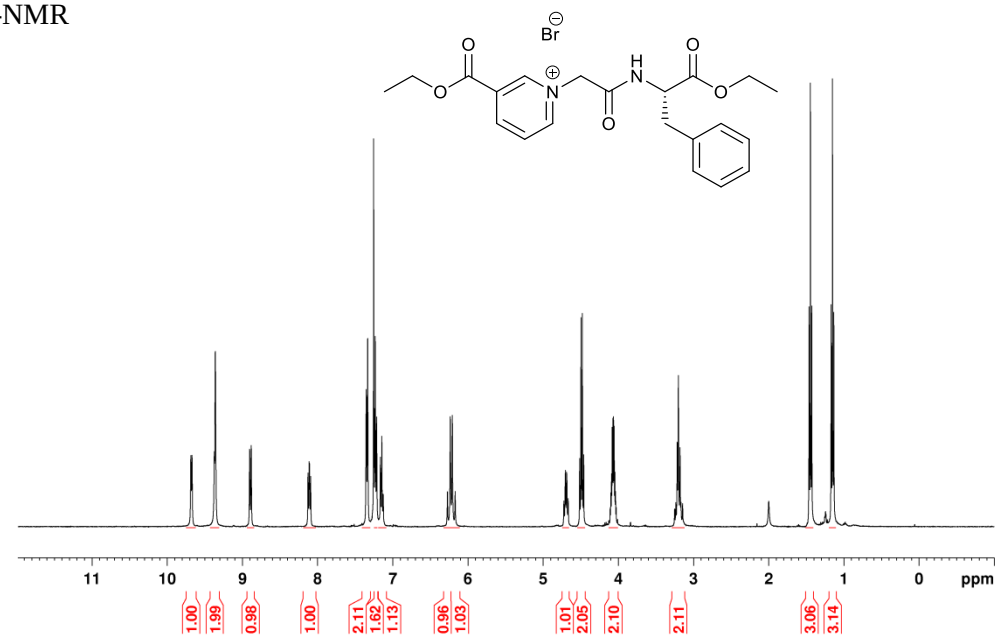


^{13}C-NMR

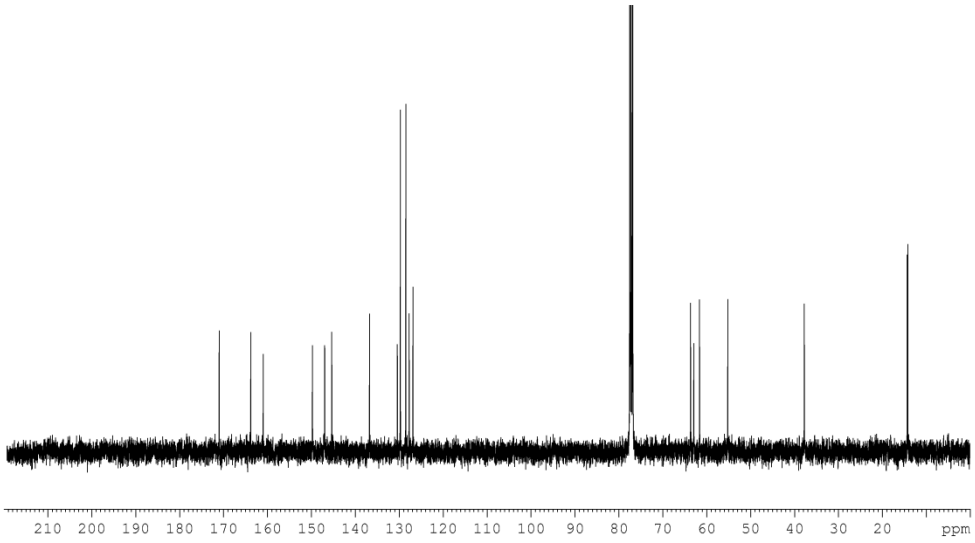


(*S*)-1-(2-((1-Ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-3-(ethoxycarbonyl)pyridin-1-ium bromide (7)

^{1}H-NMR

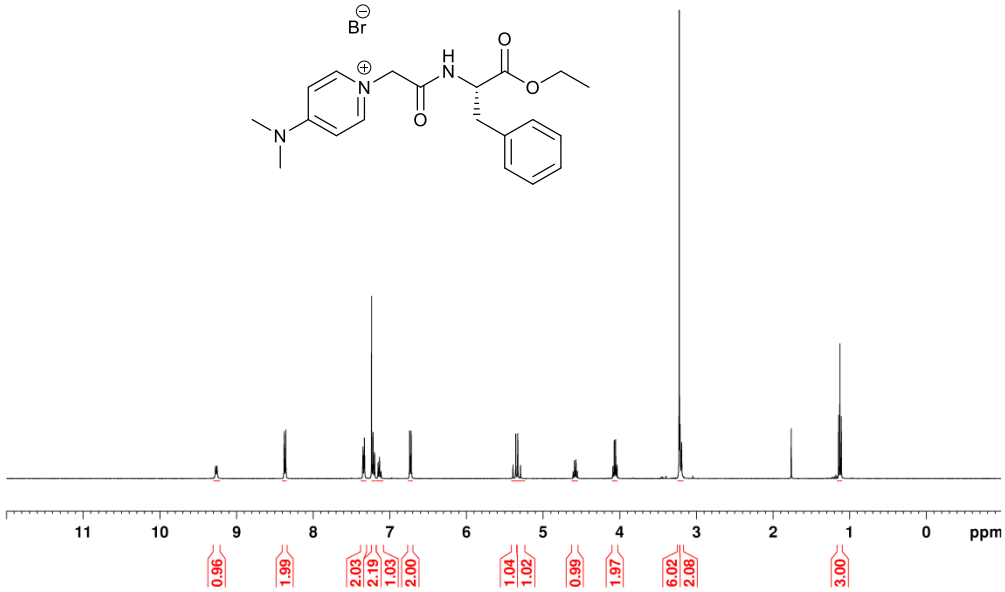


^{13}C-NMR

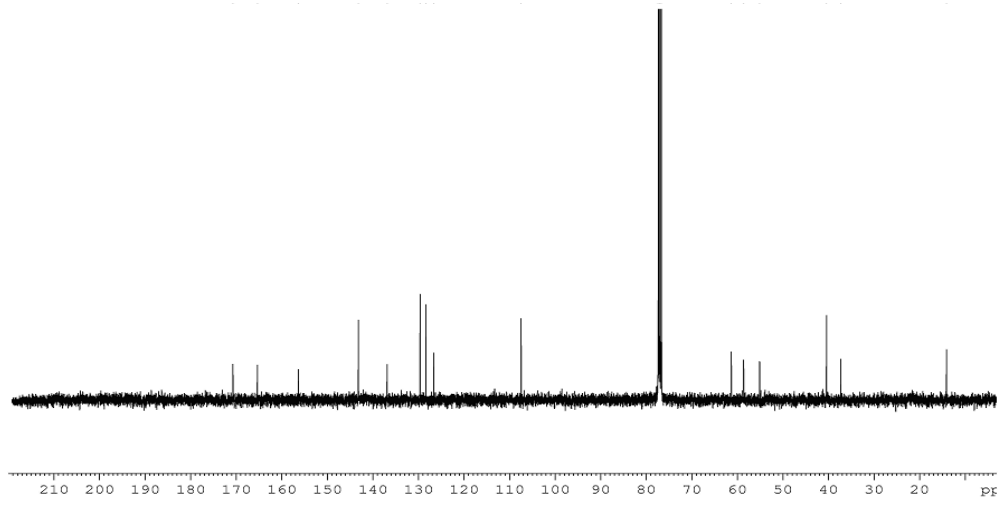


(S)-4-(Dimethylamino)-1-(2-((1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)pyridin-1-ium bromide (8).

^{1}H -NMR

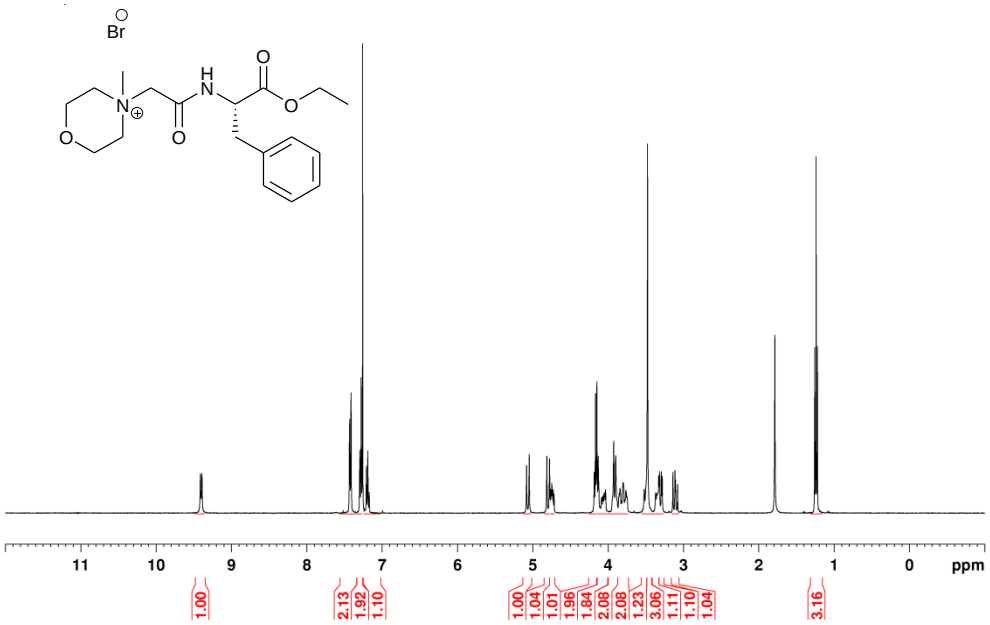


^{13}C -NMR

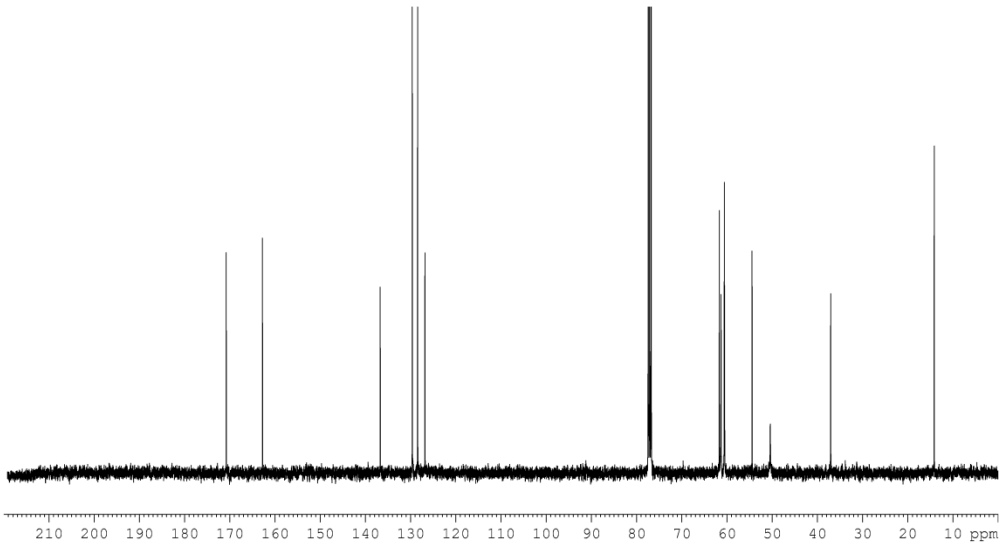


(*S*)-4-(2-((1-Ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-4-methylmorpholin-4-ium bromide (9)

^{1}H-NMR

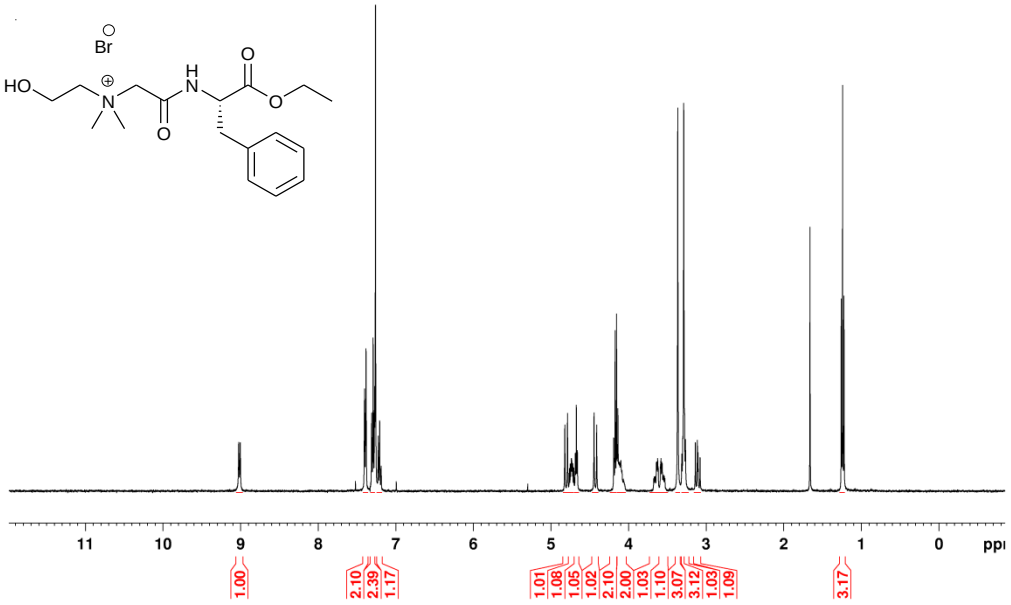


^{13}C-NMR

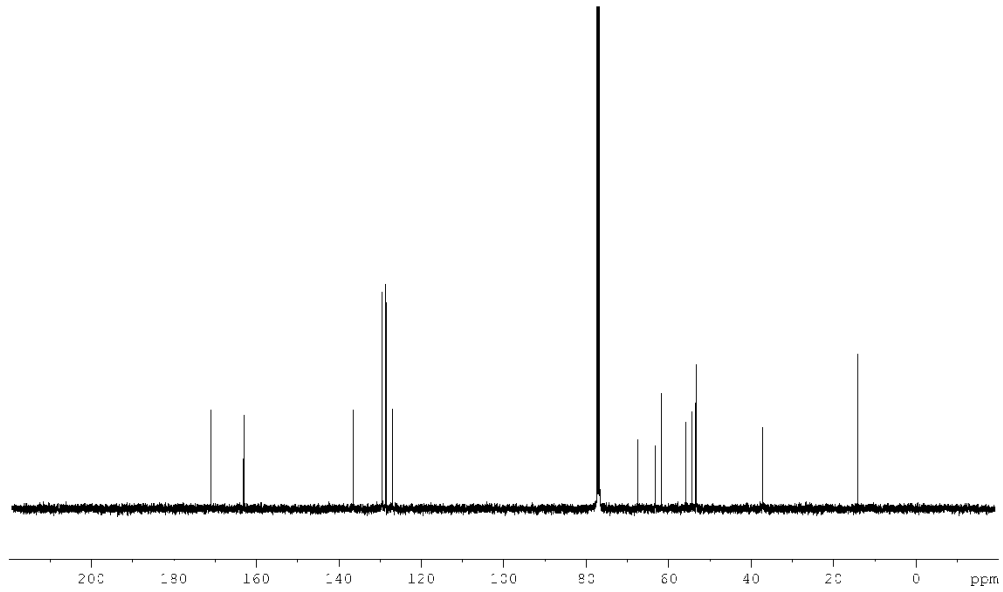


(*S*)-2-((1-Ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-*N*-(2-hydroxyethyl)-*N*,*N*-dimethyl-2-oxoethan-1-aminium bromide (10)

^{1}H-NMR

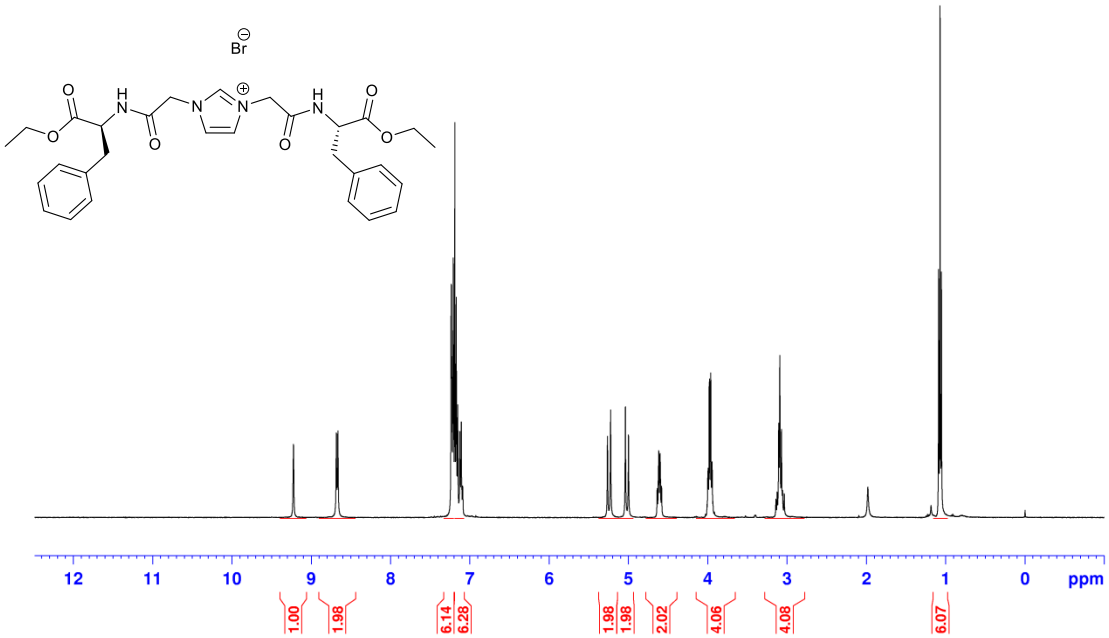


^{13}C -NMR

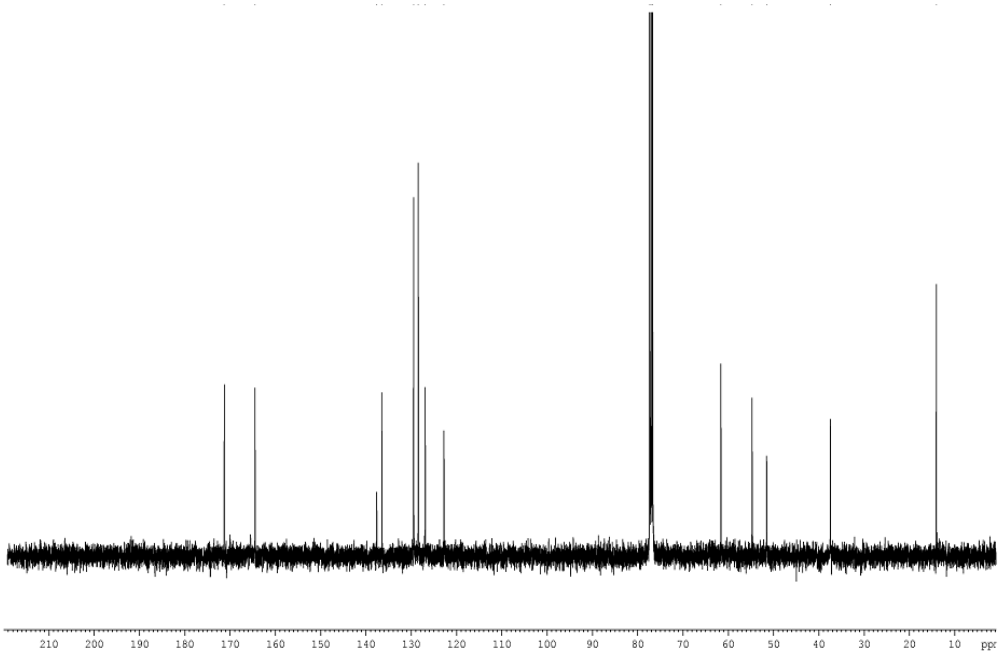


1,3-bis(2-(((*S*)-1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-1H-imidazol-3-ium bromide (11).

^{1}H-NMR

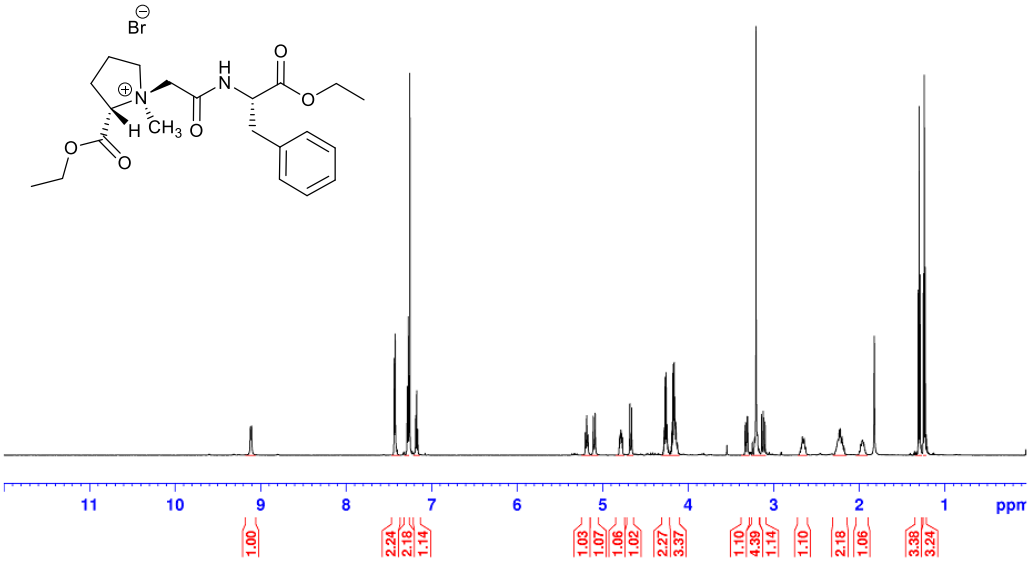


^{13}C-NMR

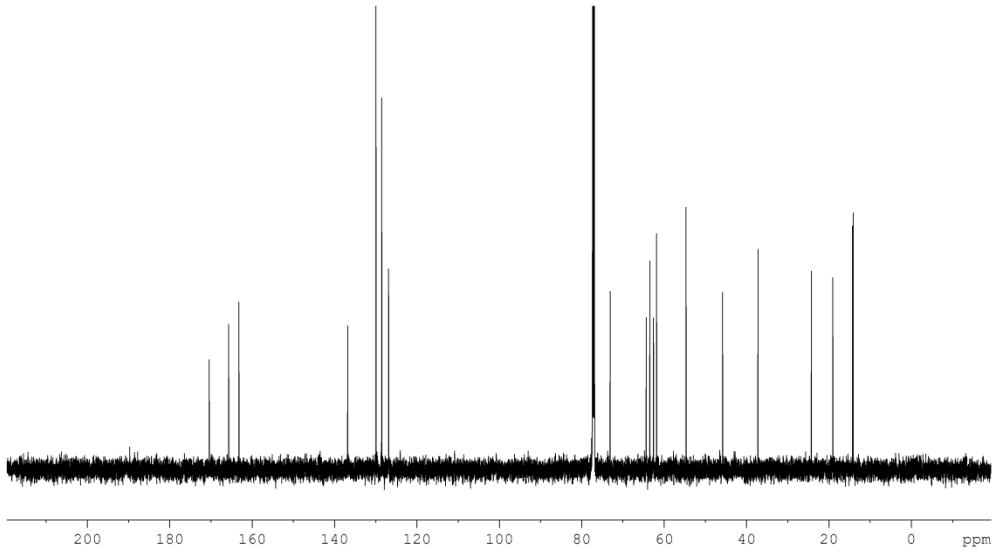


(1*S*,2*S*)-1-({[(2*S*)-1-Ethoxy-1-oxo-3-phenylpropan-2-yl]carbamoyl}methyl)-2-(ethoxycarbonyl)-1-methylpyrrolidin-1-ium bromide (12).

^{1}H-NMR

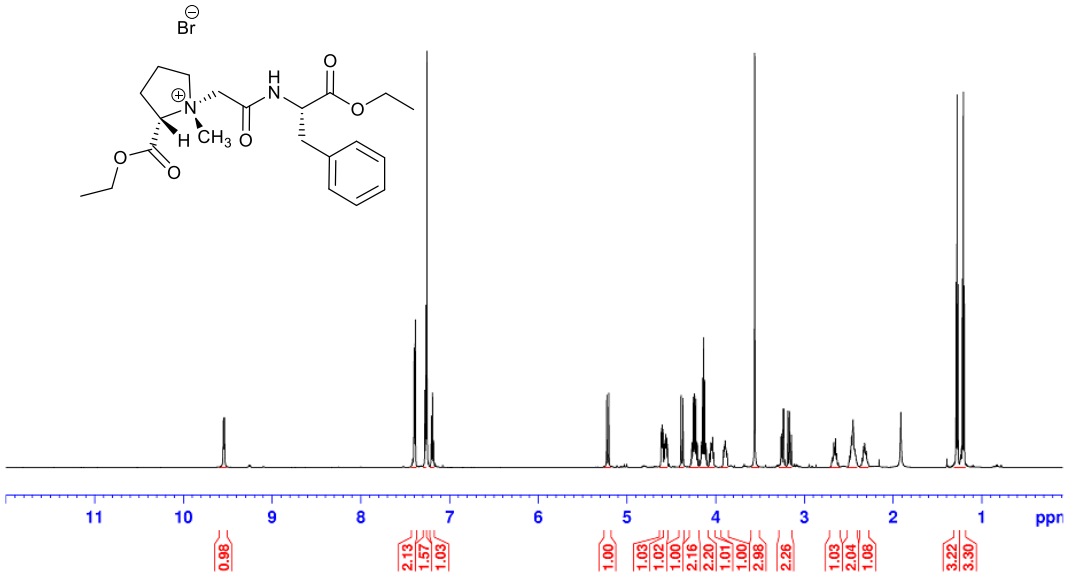


^{13}C-NMR

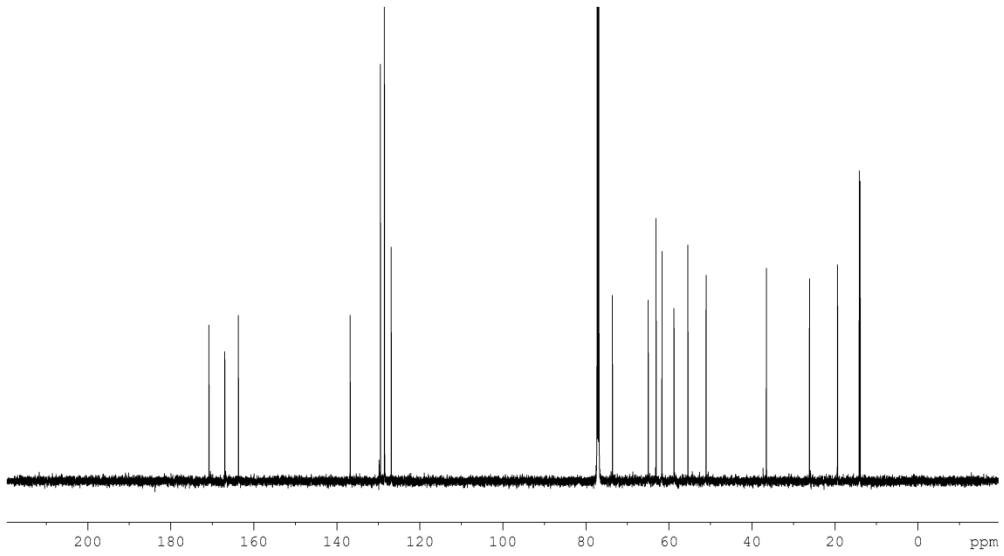


(1*R*,2*S*)-1-(2-(((*S*)-1-Ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-2-(ethoxycarbonyl)-1-methylpyrrolidin-1-ium bromide (13).

^{1}H-NMR

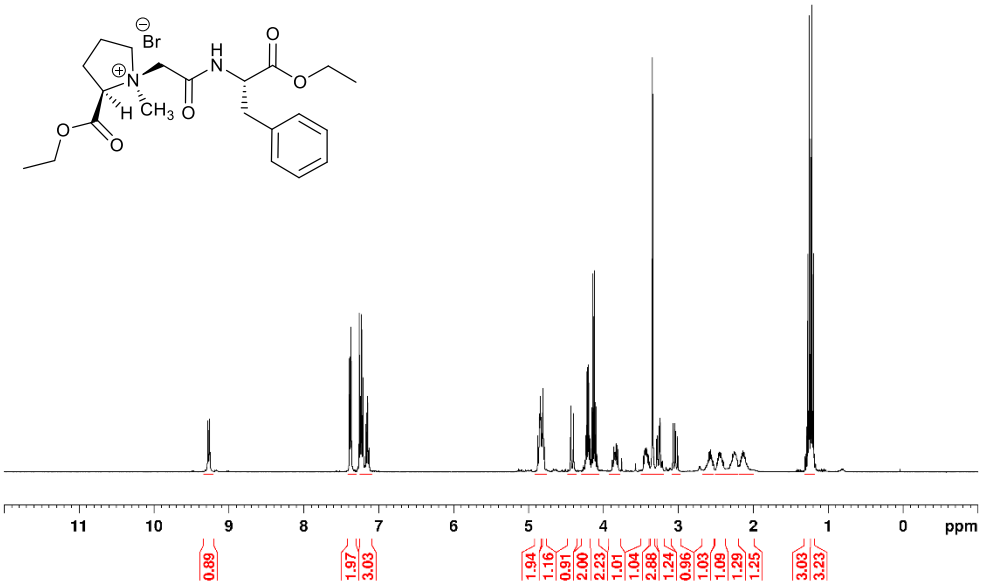


^{13}C-NMR

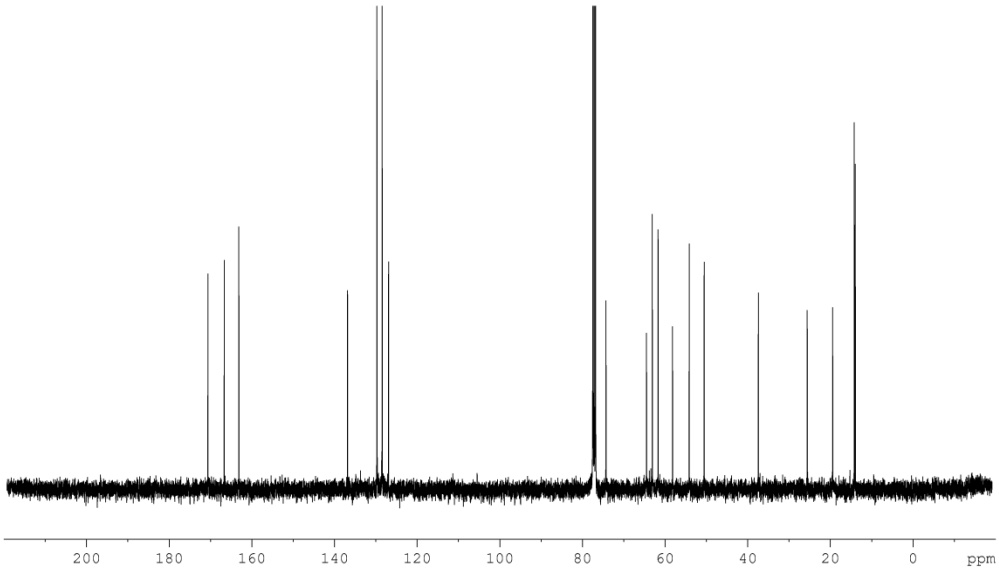


(1*S*,2*R*)-1-(2-(((*S*)-1-Ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-2-(ethoxycarbonyl)-1-methylpyrrolidin-1-ium bromide (14).

^{1}H-NMR:

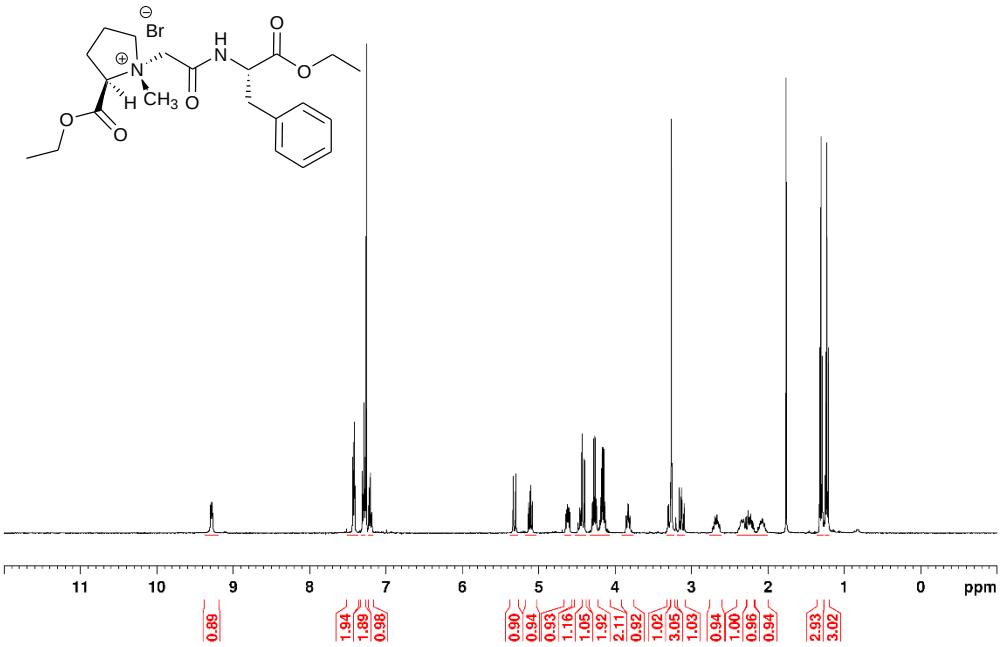


^{13}C-NMR

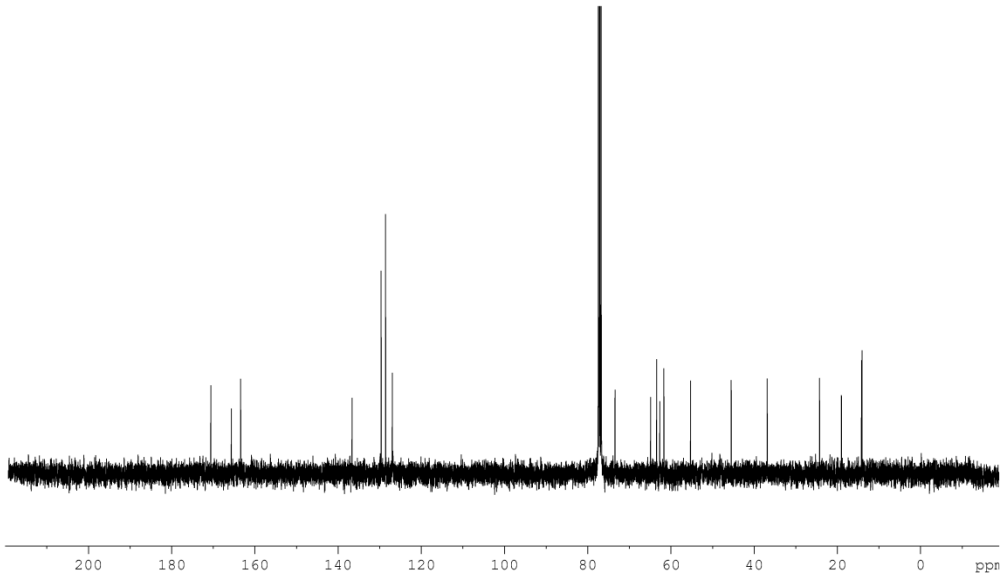


(1*R*,2*R*)-1-(2-(((*S*)-1-Ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-2-(ethoxycarbonyl)-1-methylpyrrolidin-1-ium bromide (15).

^{1}H-NMR:

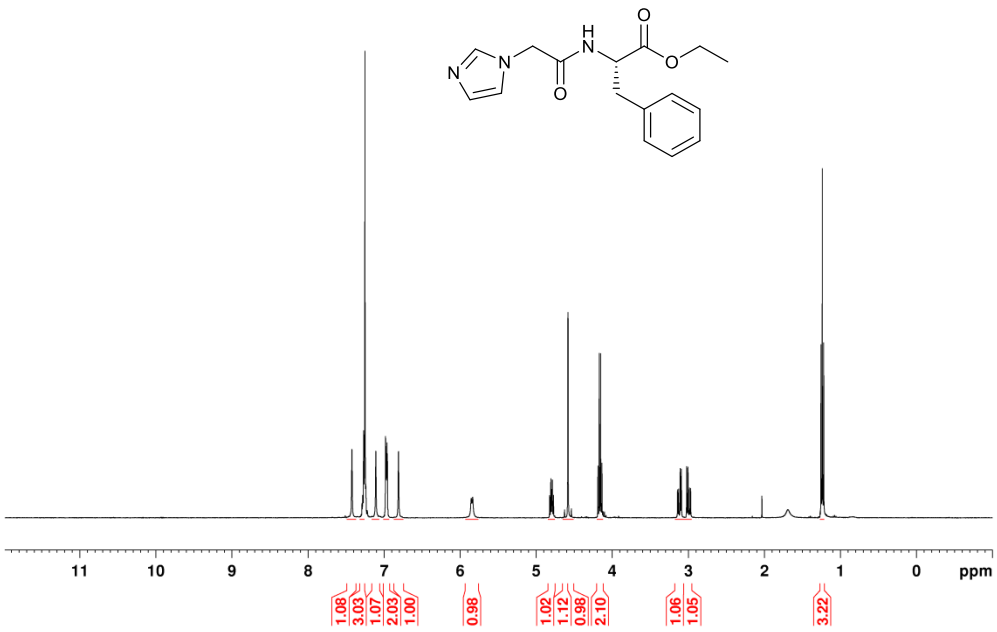


^{13}C-NMR:

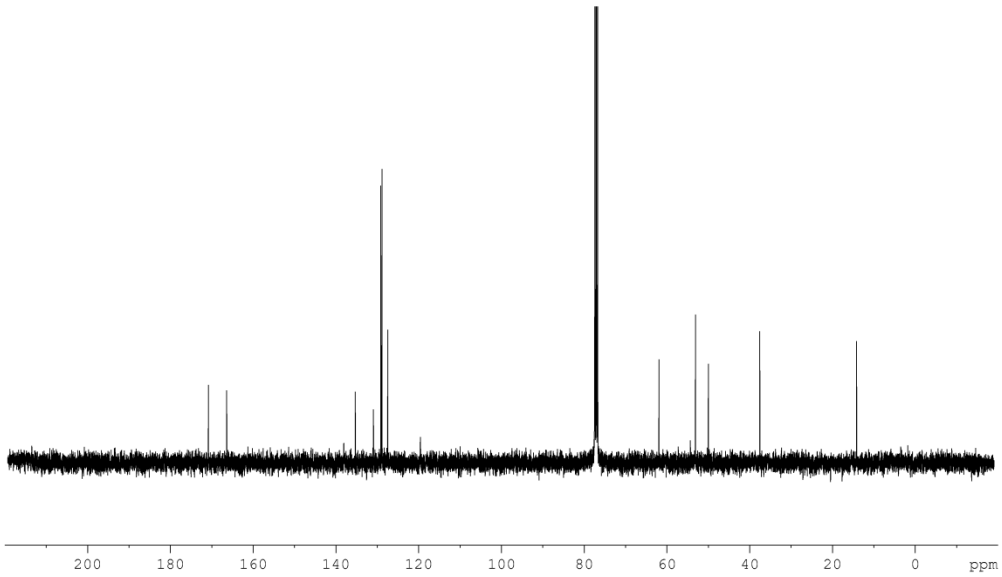


Ethyl (2-(1*H*-imidazol-1-yl)acetyl)-L-phenylalaninate (21).

^{1}H-NMR

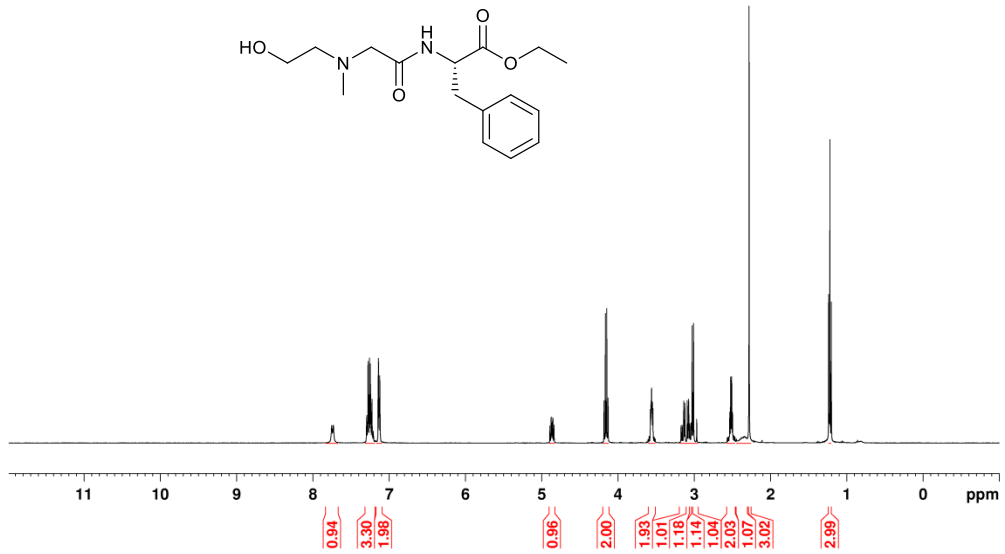


^{13}C-NMR

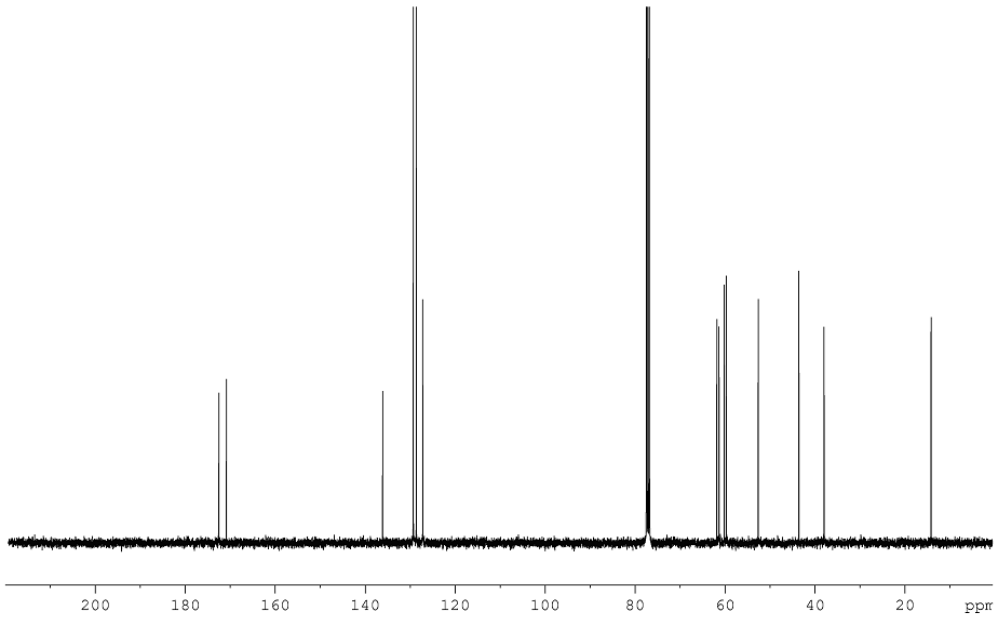


Ethyl *N*-(2-hydroxyethyl)-*N*-methylglycyl-L-phenylalaninate (22).

^{1}H-NMR

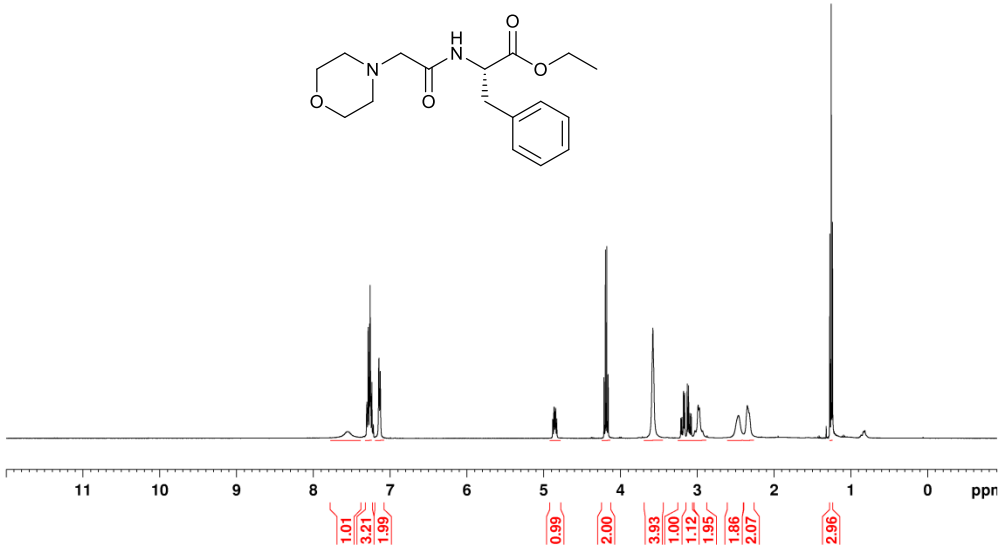


^{13}C-NMR

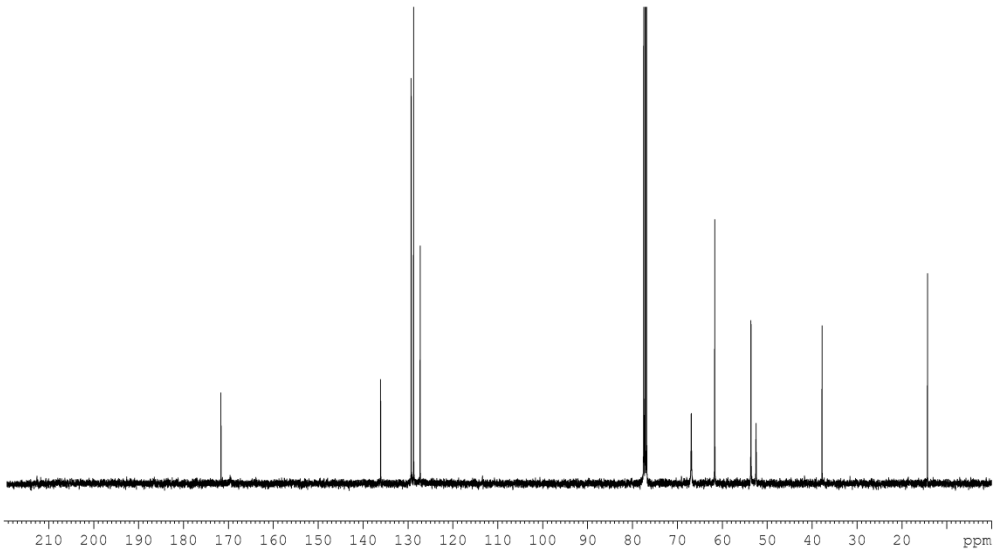


Ethyl (2-morpholinoacetyl)-L-phenylalaninate (23)

^{1}H-NMR

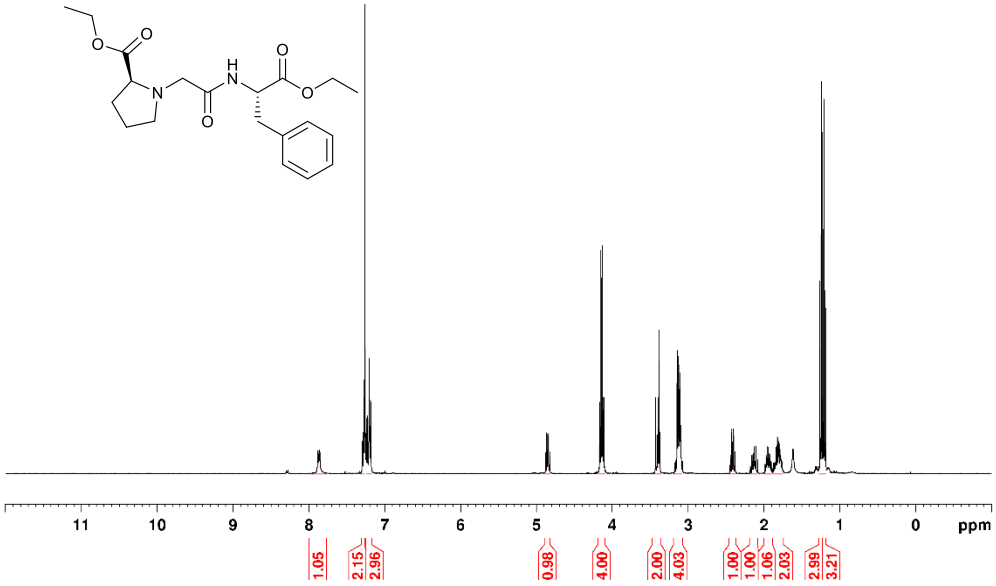


^{13}C-NMR

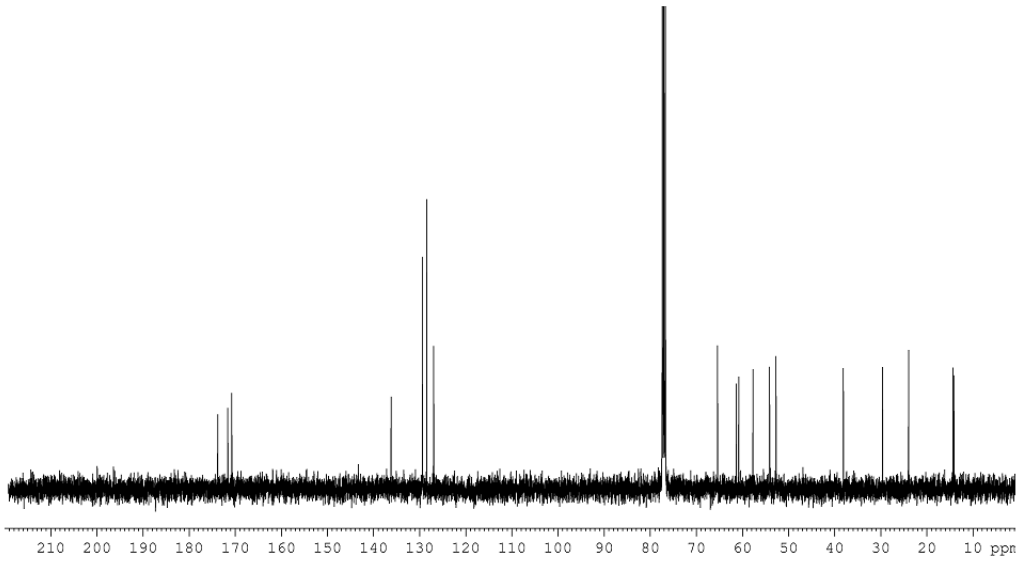


Ethyl (2-(((*S*)-1-Ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-L-prolinate (24).

^{1}H-NMR

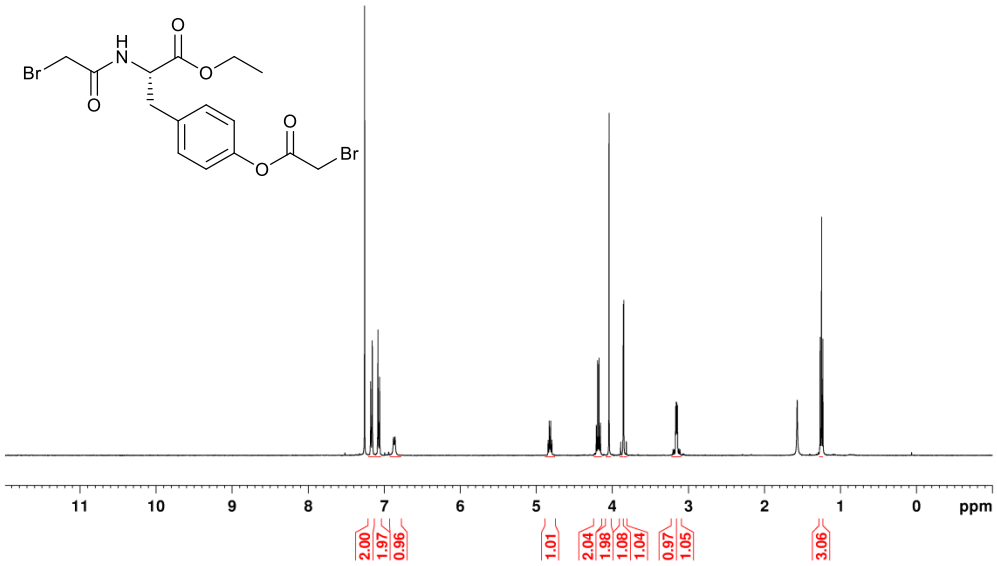


^{13}C-NMR

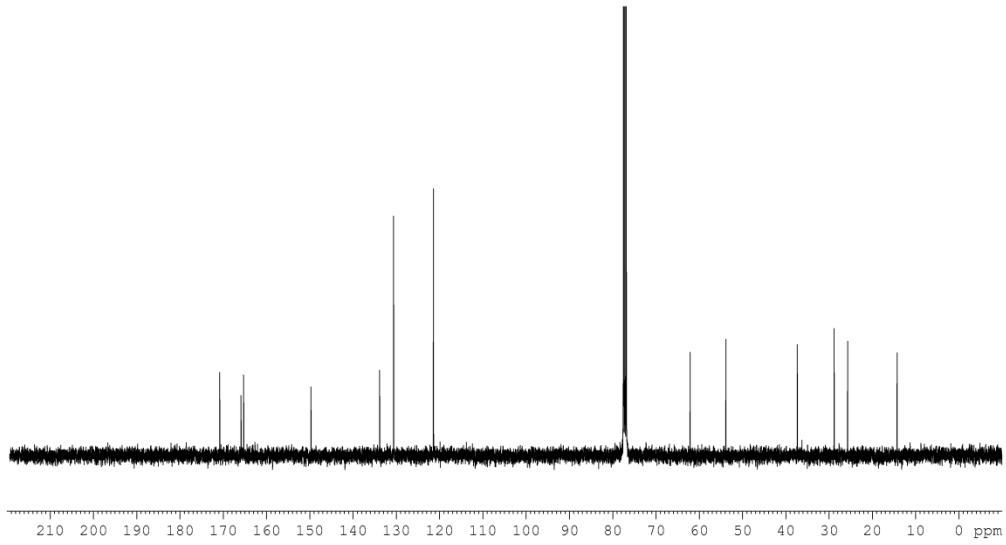


Ethyl (*S*)-2-(2-bromoacetamido)-3-(4-(2-bromoacetoxy)phenyl)propanoate (28).

^{1}H-NMR

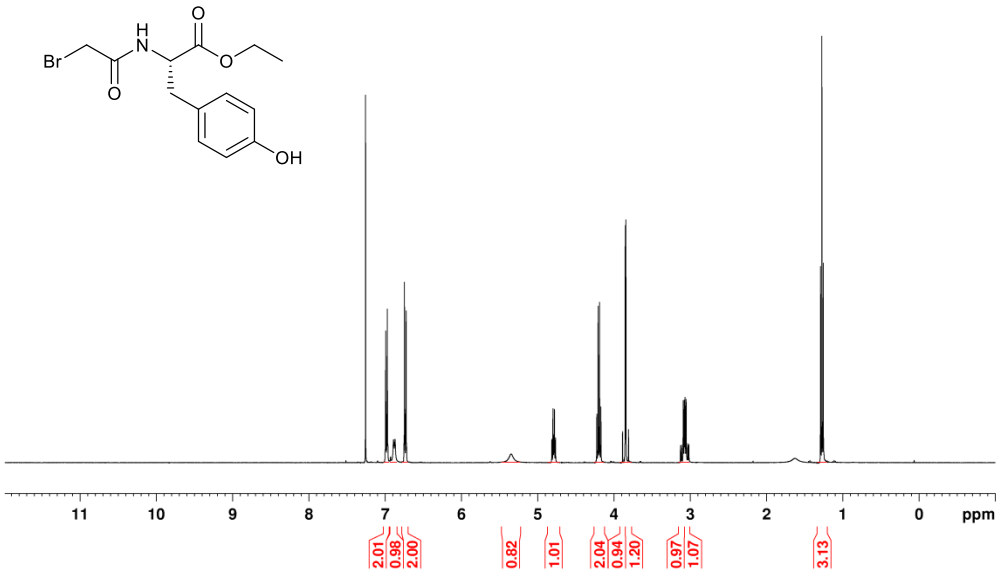


^{13}C-NMR

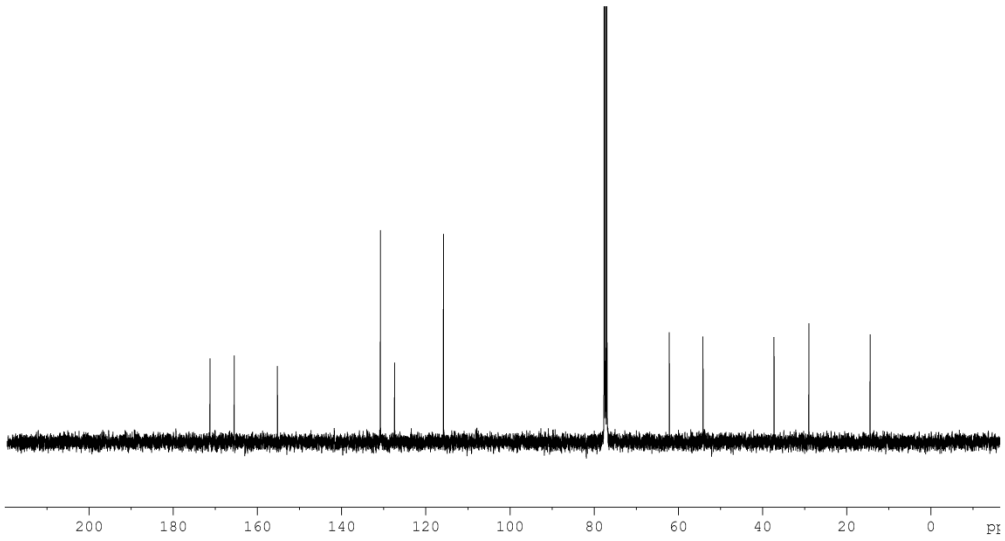


Ethyl (2-bromoacetyl)-L-tyrosinate (29)

^{1}H-NMR

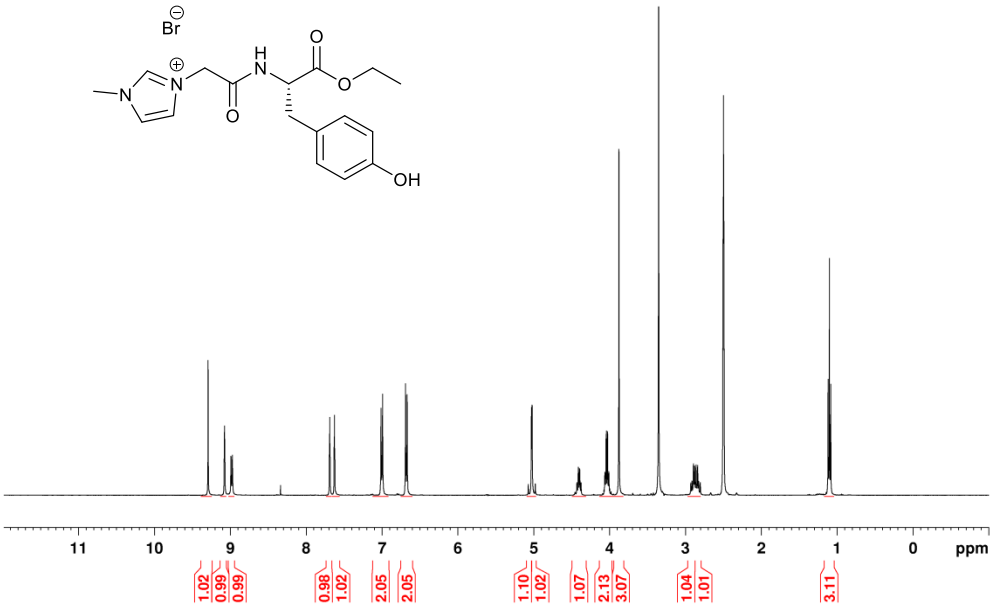


^{13}C-NMR

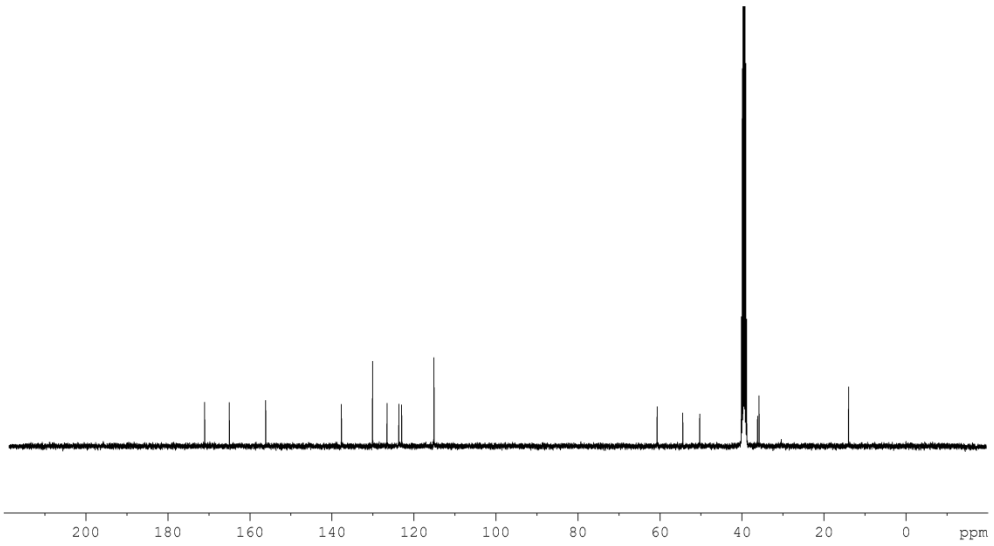


(*S*)-3-(2-((1-Ethoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)amino)-2-oxoethyl)-1-methyl-1H-imidazol-3-ium bromide (16).

^{1}H-NMR:

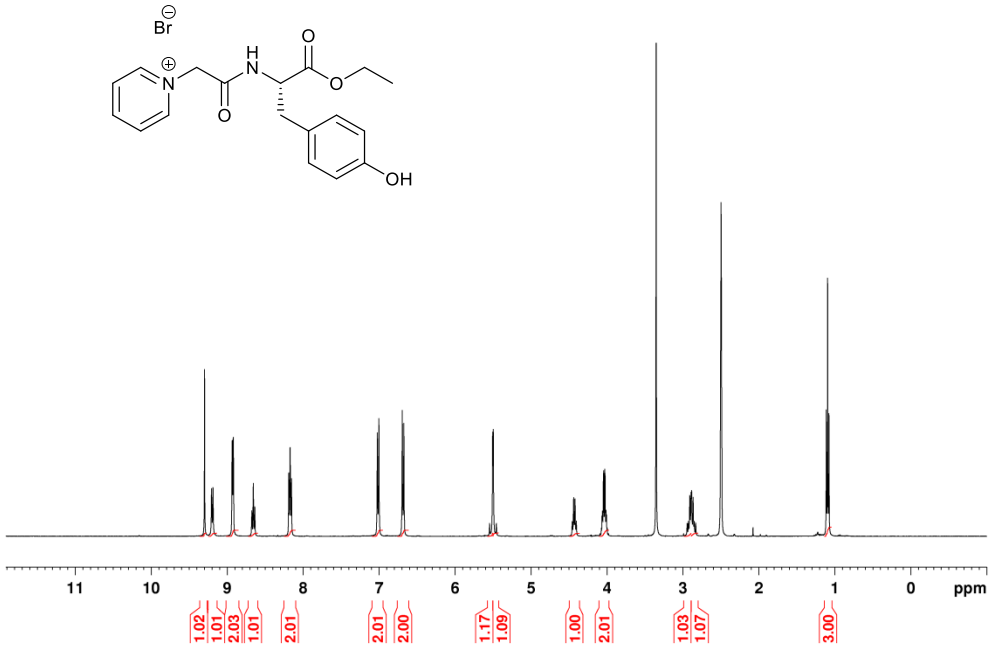


^{13}C-NMR

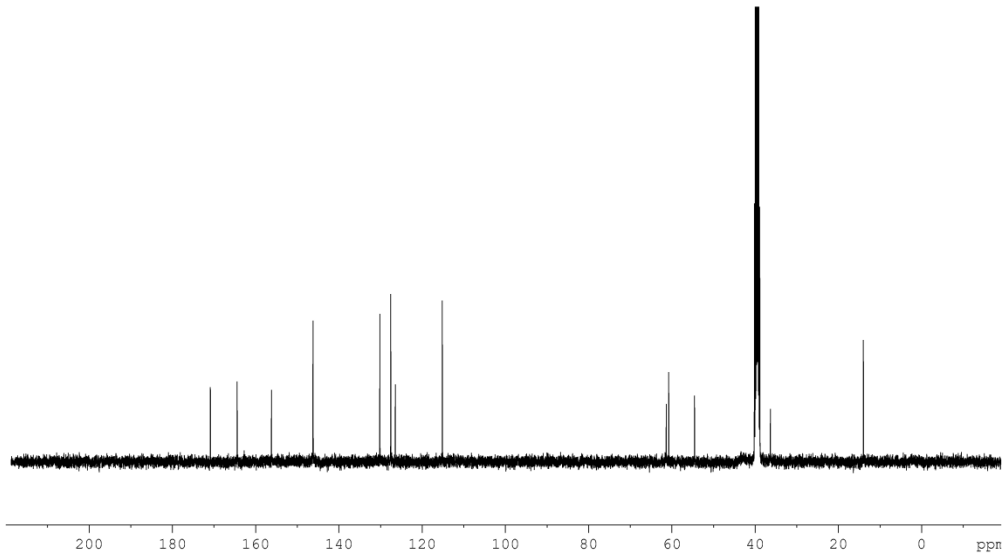


(*S*)-1-(2-((1-Ethoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)amino)-2-oxoethyl)pyridin-1-ium bromide (17).

^{1}H-NMR

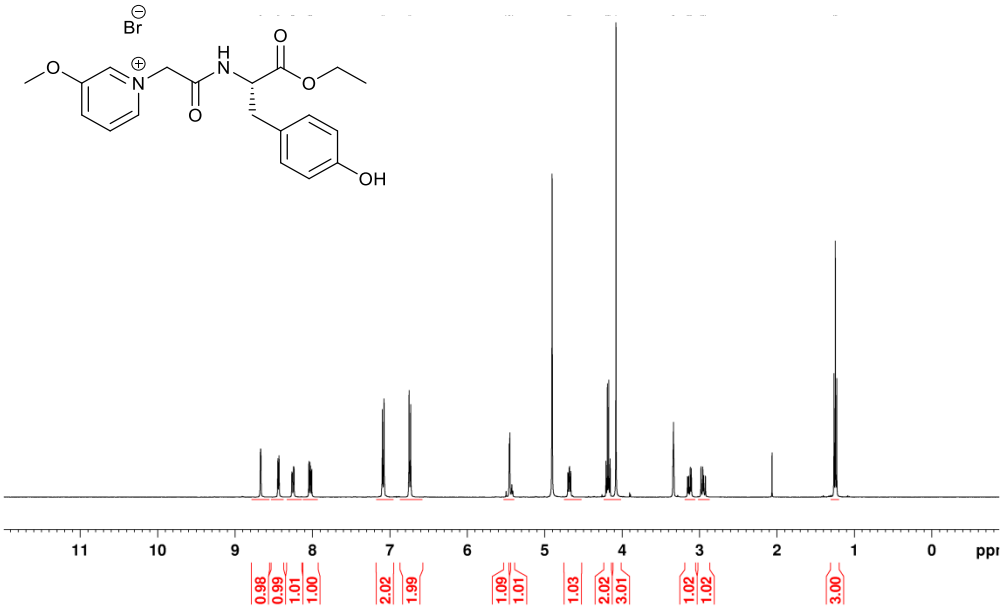


^{13}C-NMR

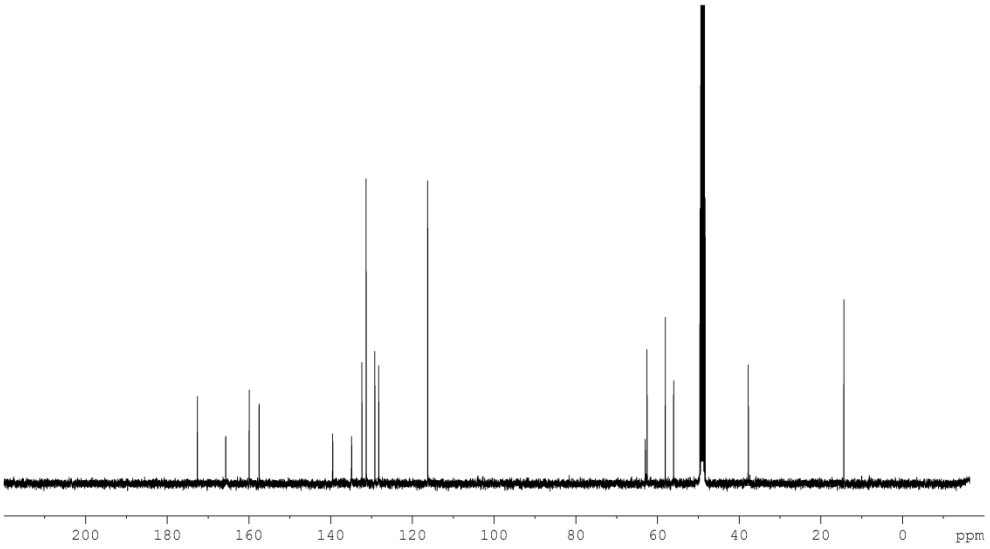


(*S*)-1-(2-((1-Ethoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)amino)-2-oxoethyl)-3-methoxypyridin-1-ium bromide (18).

^{1}H-NMR

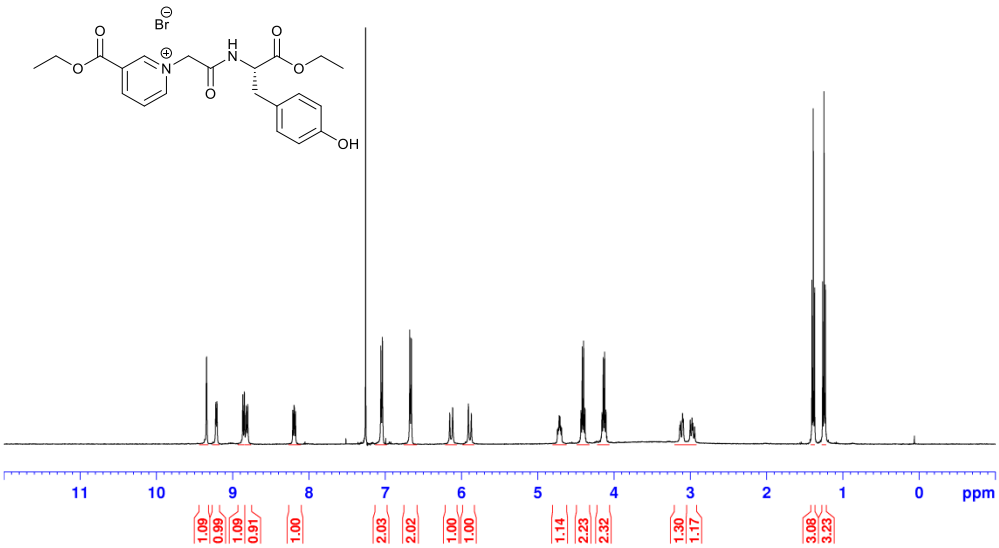


^{13}C-NMR

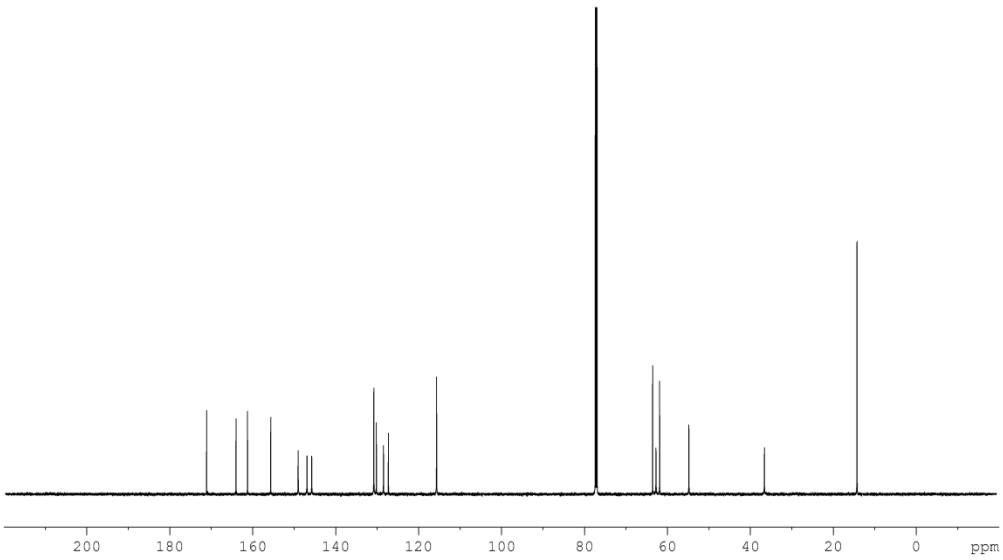


(*S*)-1-(2-((1-Ethoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)amino)-2-oxoethyl)-3-(ethoxycarbonyl)-pyridin-1-ium bromide (19).

^{1}H-NMR

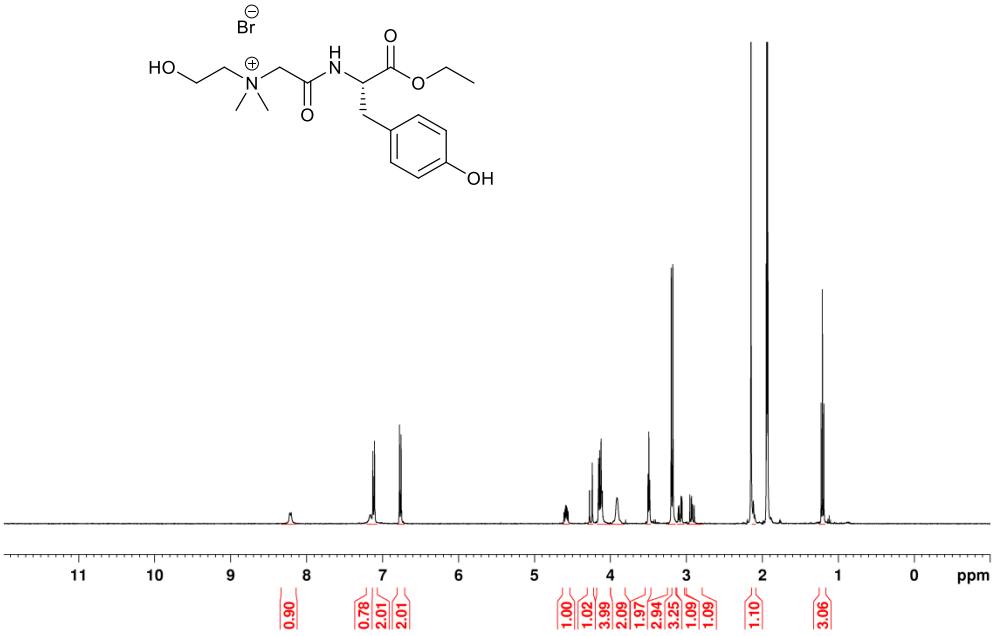


^{13}C-NMR

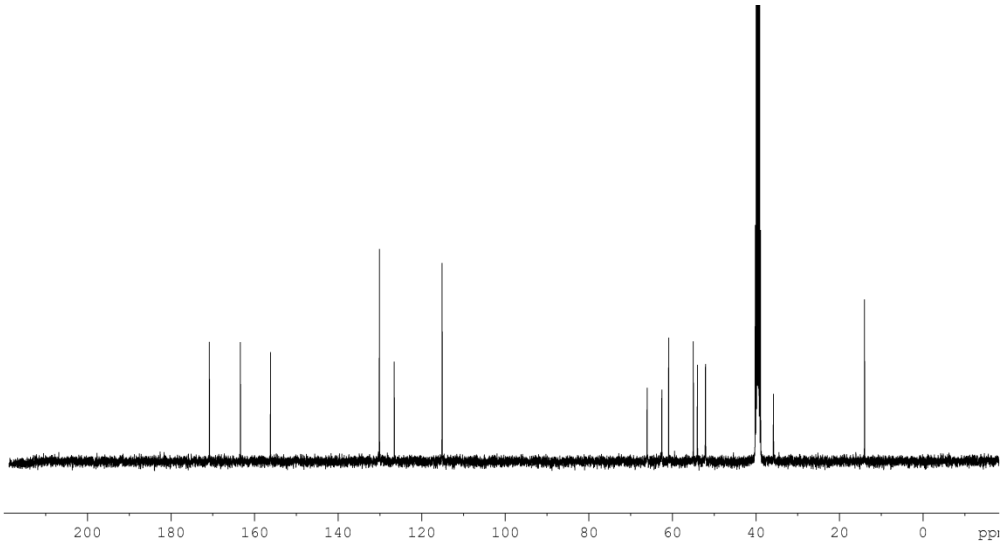


(*S*)-2-((1-ethoxy-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)amino)-*N*-(2-hydroxyethyl)-*N*,*N*-dimethyl-2-oxoethanaminium bromide (20)

^{1}H-NMR

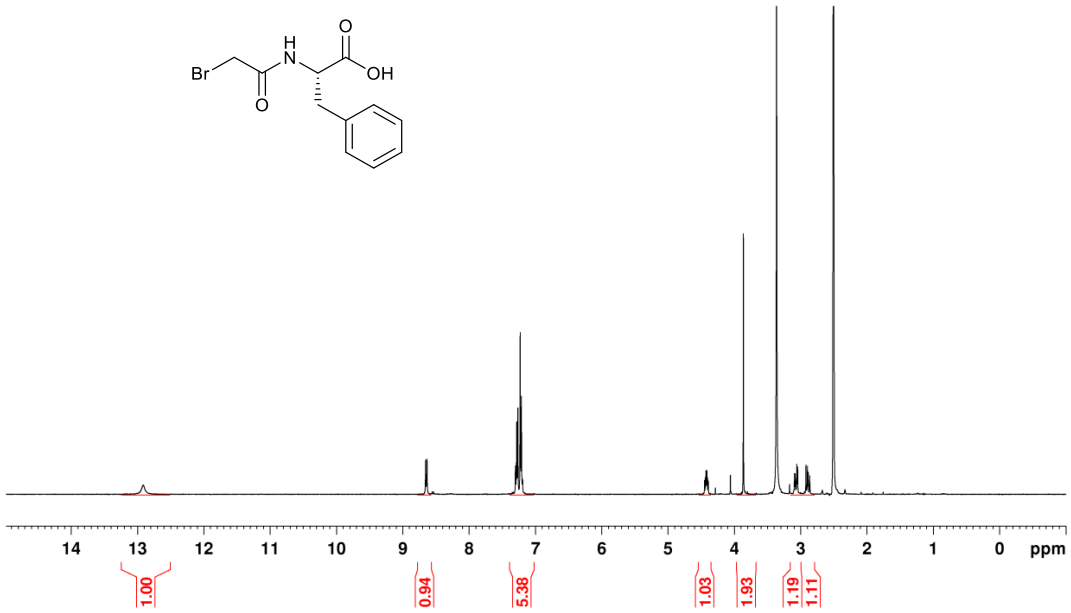


^{13}C-NMR

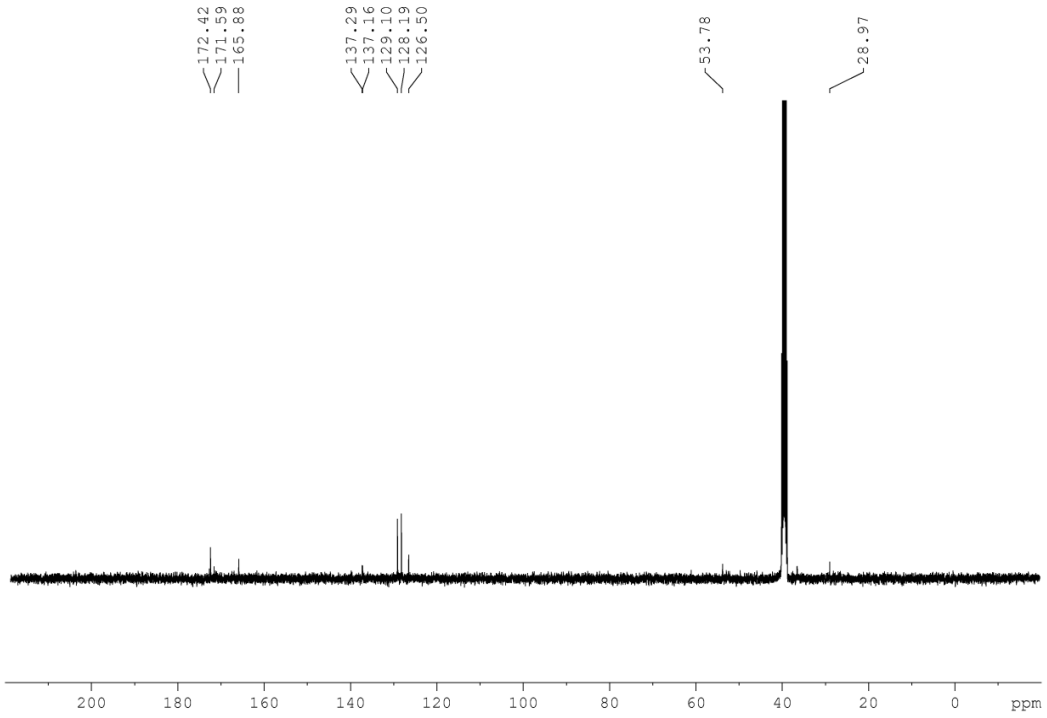


(2-Bromoacetyl)-L-phenylalanine .

^{1}H-NMR

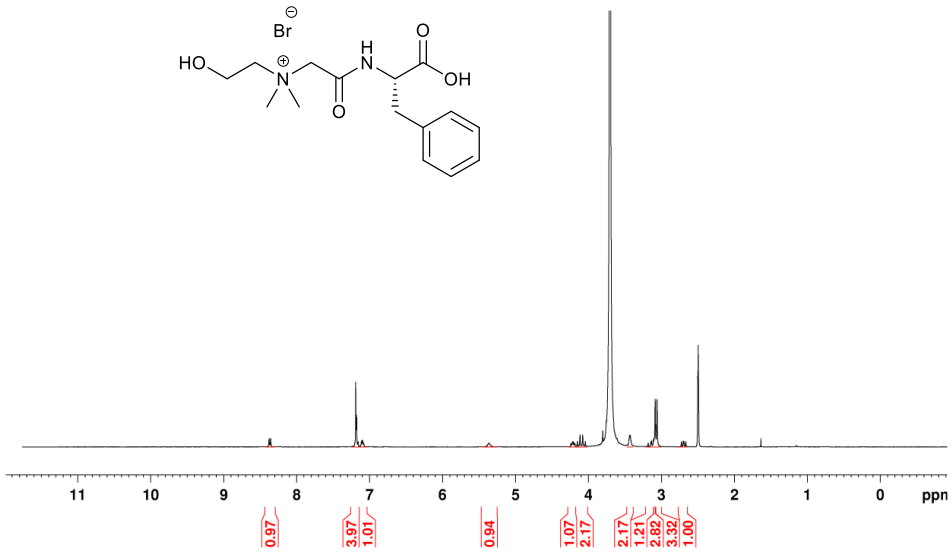


^{13}C-NMR

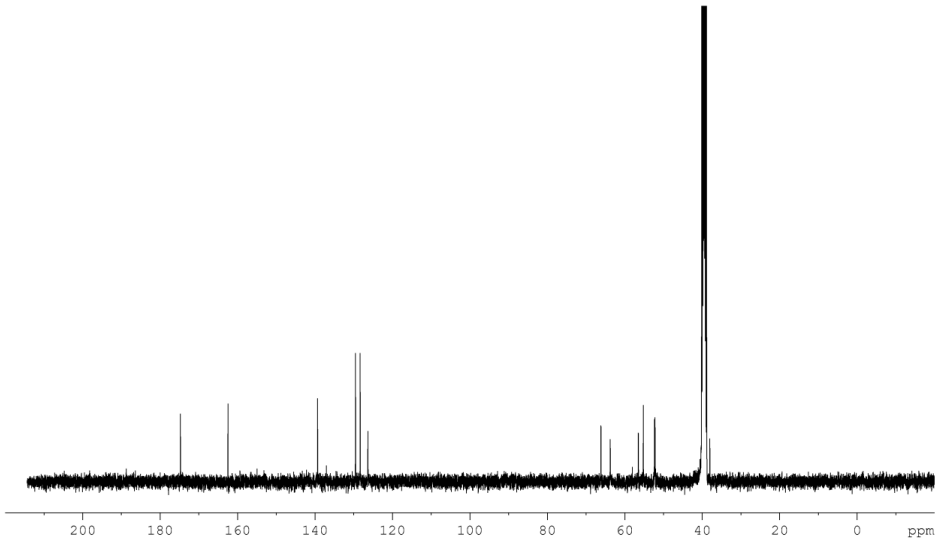


(*S*)-2-((1-carboxy-2-phenylethyl)amino)-*N*-(2-hydroxyethyl)-*N*,*N*-dimethyl-2-oxoethan-1-aminium bromide (**37**).

^{1}H-NMR

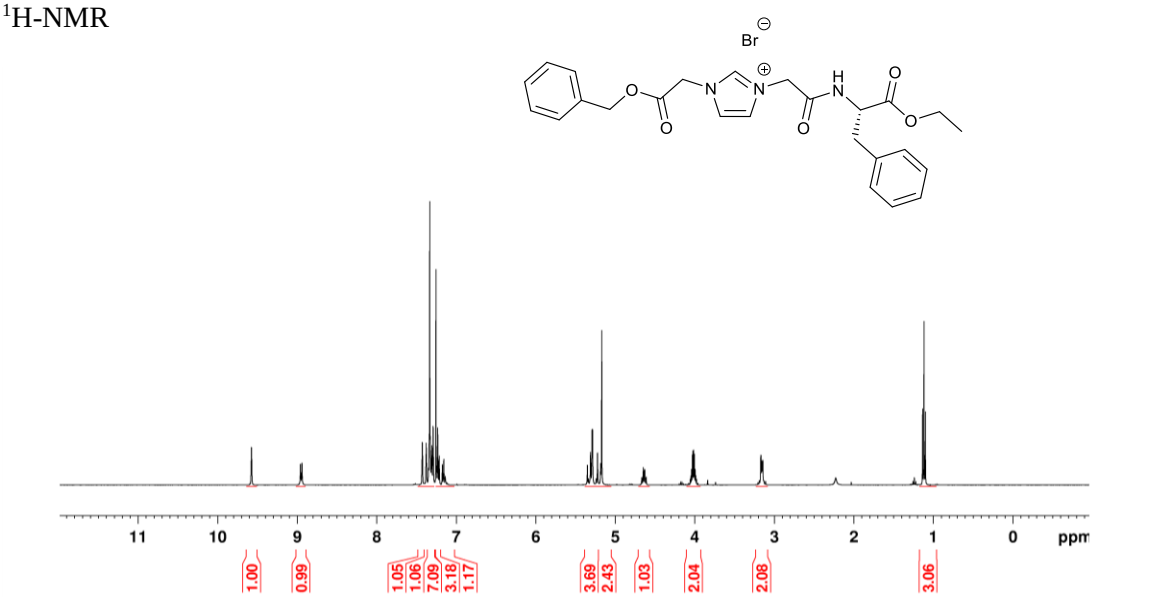


^{13}C-NMR

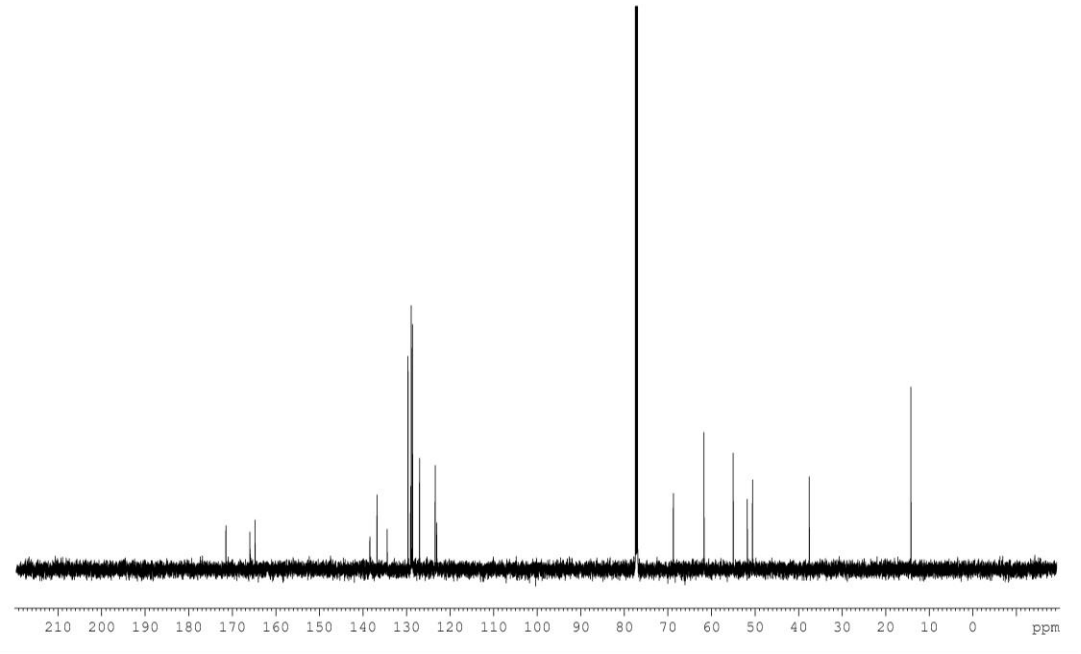


(*S*)-1-(2-(Benzyloxy)-2-oxoethyl)-3-(2-((1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-1*H*-imidazol-3-ium bromide (39).

^{1}H-NMR

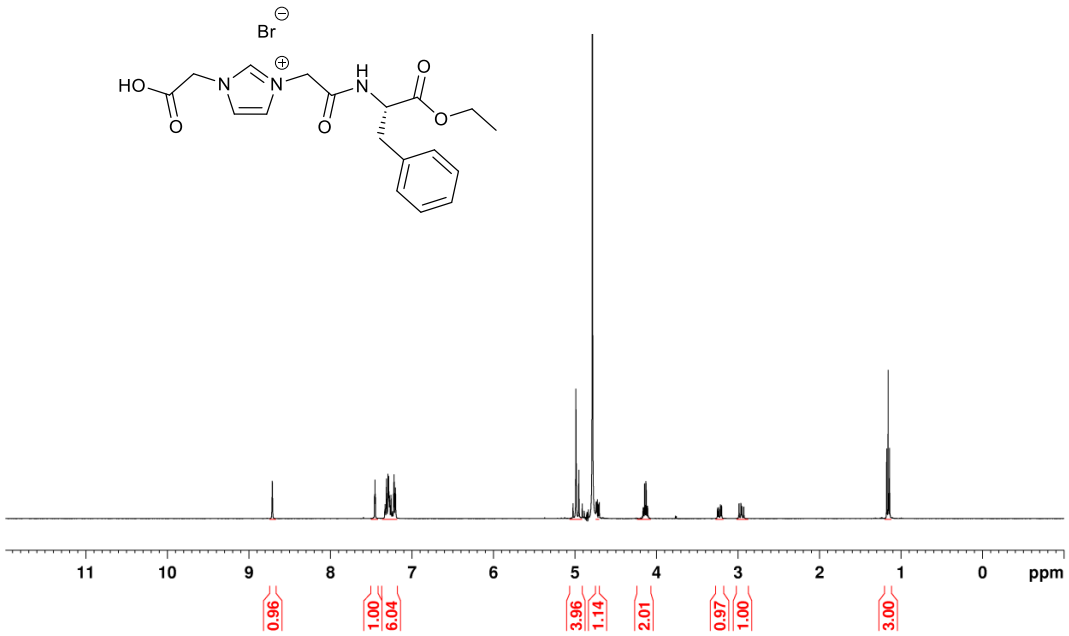


^{13}C-NMR

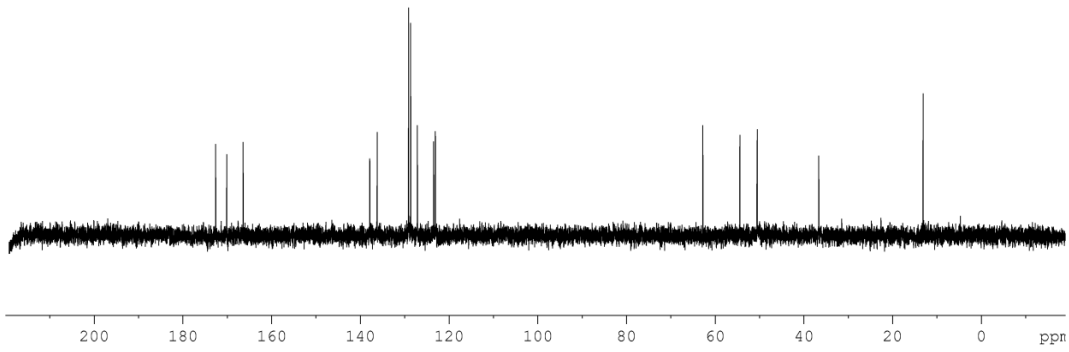


(*S*)-1-(Carboxymethyl)-3-(2-((1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-1H-imidazol-3-ium bromide (40).

^{1}H-NMR

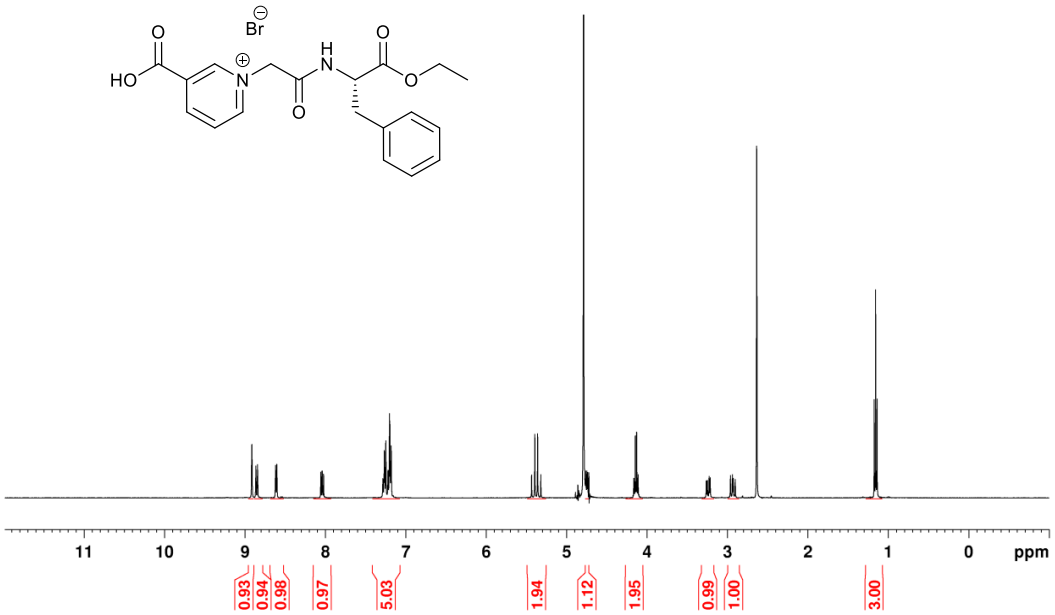


^{13}C-NMR

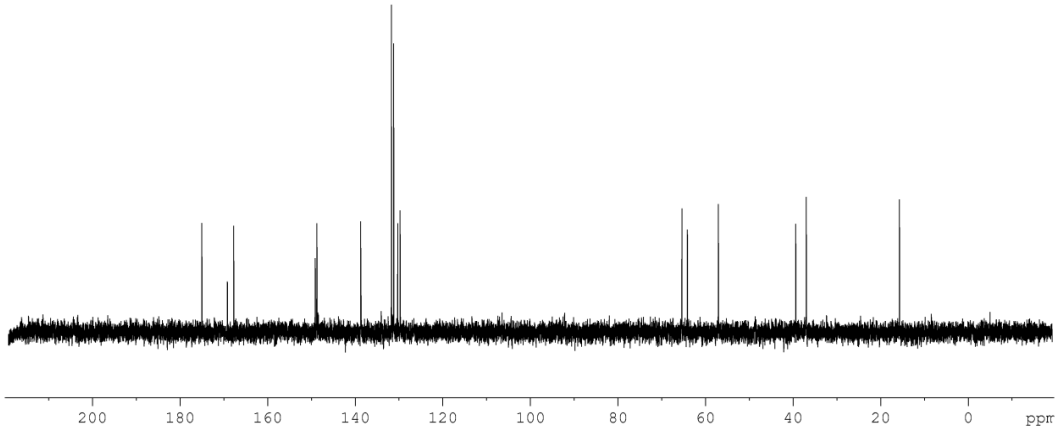


(*S*)-3-Carboxy-1-(2-((1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)pyridin-1-ium bromide (**41**).

^{1}H-NMR

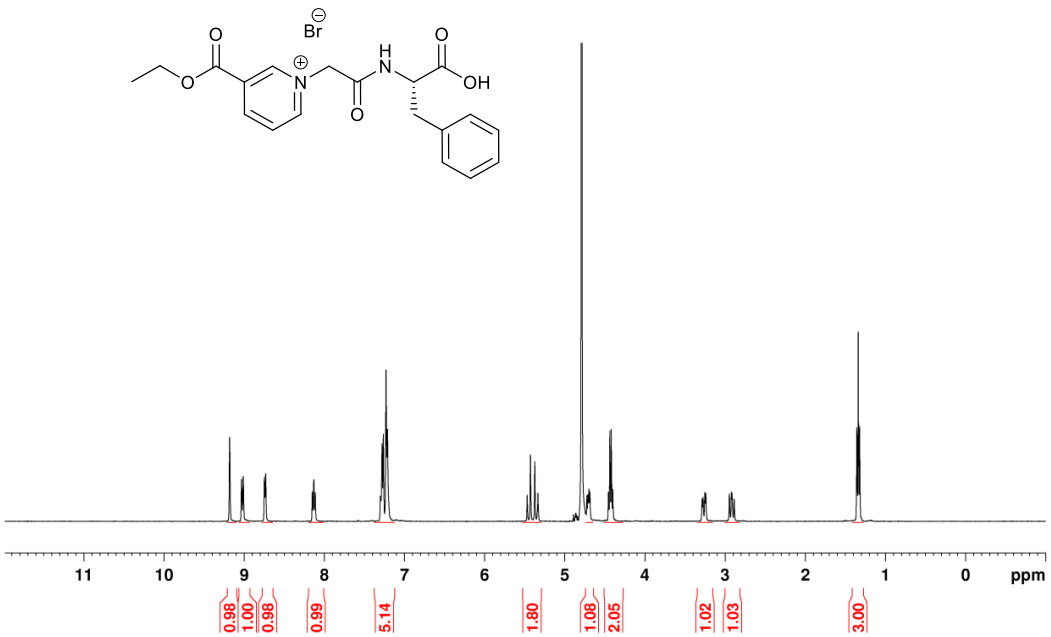


^{13}C-NMR

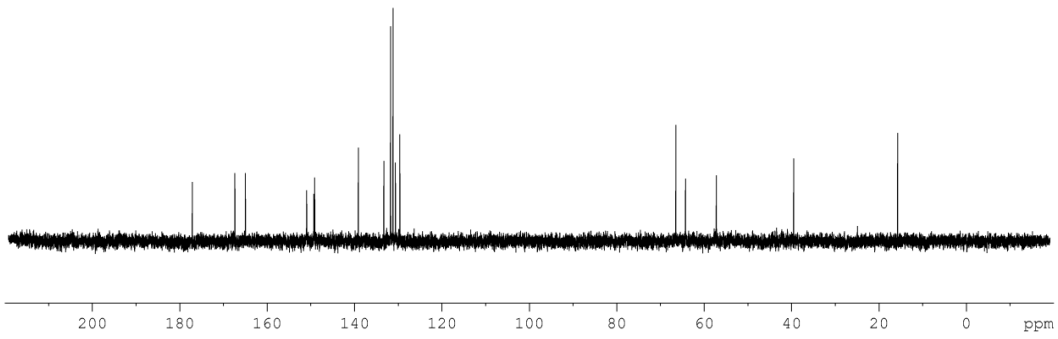


(*S*)-1-(2-((1-carboxy-2-phenylethyl)amino)-2-oxoethyl)-3-(ethoxycarbonyl)pyridin-1-ium bromide (42).

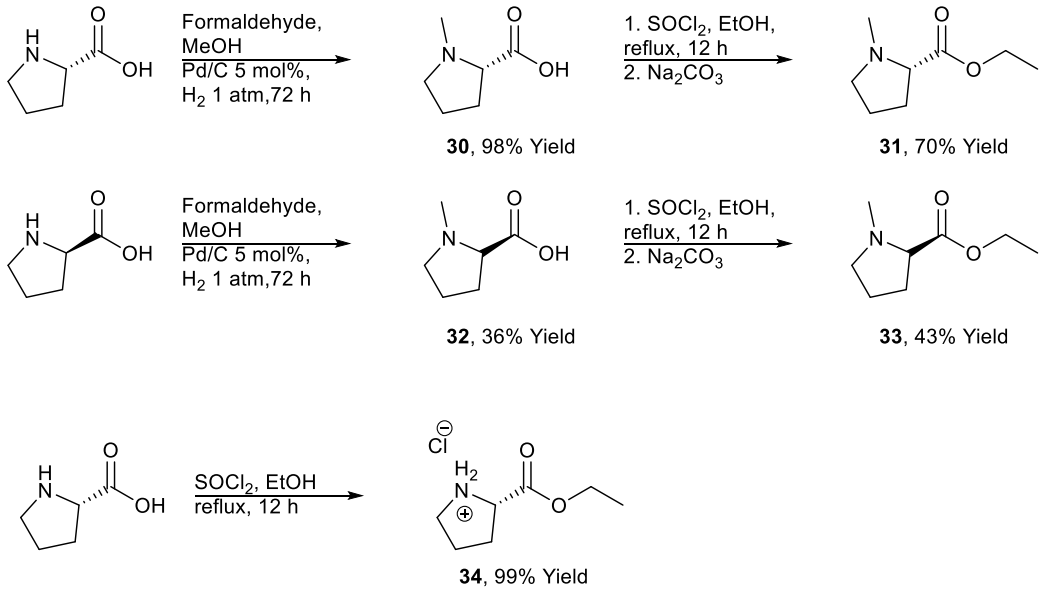
^{1}H-NMR

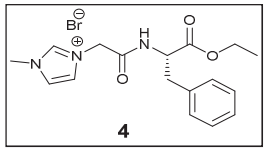


^{13}C-NMR



Scheme S1. Synthesis of proline derivatives **30**-**34**





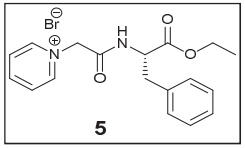
4

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
wu solvent	Diethyl ether	60-29-7	74.12	0.706		52.95	g	**75**	mL					
solvent	Diethyl ether	60-29-7	74.12	0.706		7.06	g	**10**	mL					
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175			0.606358	g			**1.93**	mmol	1.109195		
reactant	1-Methylimidazole	616-47-7	82.11			0.142871	g			**1.74**	mmol	**1**	x	
product	**4**		396.279			0.689525	g			1.74	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	4		396.279			**0.622**	g		1.570	mmol	90.20697

total reaction mass	60.76	g
total reagents / reactants / cat. mass	0.75	g
total workup reagents mass		g
total solvents (excl. water)	60.01	g
total water		g
total waste	60.14	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	97.7	97.7
solvent intensity	96.5	96.5
Sheldon E-factor	96.7	96.7
GSK Reaction Mass Efficiency	0.830	
Andraos Reaction Mass Efficiency	0.010	0.010
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.920	
material recovery parameter	0.012	0.012
yield	0.902	



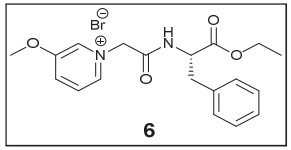
5

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
solvent	Diethyl ether	60-29-7	74.12	0.706		7.0600	g	**10**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		52.9500	g	**75**	mL					
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175			0.5341	g			**1.7**	mmol	1.011905		
reactant	Pyridine	110-86-1	79.1	0.978		0.1329	g	0.135877	mL	**1.68**	mmol	**1**	x	
product	**5**		393.281			0.6607	g			1.68	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**5**		393.281			**0.643**	g		1.63	mmol	97

total reaction mass	60.68	g
total reagents / reactants / cat. mass	0.67	g
total workup reagents mass		g
total solvents (excl. water)	60.01	g
total water		g
total waste	60.03	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	94.4	94.4
solvent intensity	93.3	93.3
Sheldon E-factor	93.4	93.4
GSK Reaction Mass Efficiency	0.964	
Andraos Reaction Mass Efficiency	0.011	0.011
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.991	
material recovery parameter	0.011	0.011
yield	0.973	



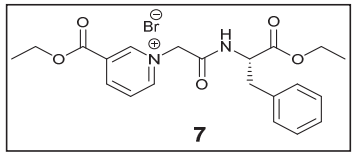
6

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
solvent	Diethyl ether	60-29-7	74.12	0.706		7.06	g	**10**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		52.95	g	**75**	mL					
reactant	3-Methoxy Pyridine	7295-76-3	109.128	1.083		0.190974	g	0.176338	mL	**1.75**	mmol	**1**	x	
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175			0.612641	g			**1.95**	mmol	1.114286		
product	**6**		423.307			0.740787	g			1.75	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**6**		423.307			**0.554**	g		1.308743	mmol	75

total reaction mass	60.81	g
total reagents / reactants / cat. mass	0.80	g
total workup reagents mass		g
total solvents (excl. water)	60.01	g
total water		g
total waste	60.26	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	109.8	109.8
solvent intensity	108.3	108.3
Sheldon E-factor	108.8	108.8
GSK Reaction Mass Efficiency	0.689	
Andraos Reaction Mass Efficiency	0.009	0.009
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.922	
material recovery parameter	0.013	0.013
yield	0.748	



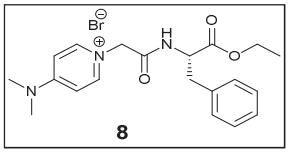
7

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
solvent	Tetrahydrofuran	109-99-9	72.11	0.889		22.225	g	**25**	mL					
wu solvent	Methanol	67-56-1	32.04	0.791		11.865	g	**15**	mL					
wu solvent	Dichloromethane	75-09-2	84.93	1.325		377.625	g	**285**	mL					
reactant	Ethyl nicotinate	614-18-6	151.163	1.107		0.221	g	0.199639	mL	**1.462**	mmol	**1**	x	
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175			0.507078	g			**1.614**	mmol	1.103967		
product	**7**		465.344			0.680333	g			1.462	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**7**		465.344			**0.381**	g		0.818749	mmol	56.00199

total reaction mass	412.44	g
total reagents / reactants / cat. mass	0.73	g
total workup reagents mass		g
total solvents (excl. water)	411.72	g
total water		g
total waste	412.06	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	1082.5	1082.5
solvent intensity	1080.6	1080.6
Sheldon E-factor	1081.5	1081.5
GSK Reaction Mass Efficiency	0.523	
Andraos Reaction Mass Efficiency	0.001	0.001
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.934	
material recovery parameter	0.002	0.002
yield	0.560	



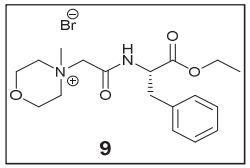
8

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
solvent	Diethyl ether	60-29-7	74.12	0.706		7.06	g	**10**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		52.95	g	**75**	mL					
reactant	DMAP		122.171			0.157601	g			**1.29**	mmol	**1**	x	
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175			0.455554	g			**1.45**	mmol	1.124031		
product	**8**		436.35			0.562892	g			1.29	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**8**		436.35			**0.498**	g		1.141286	mmol	88

total reaction mass	60.62	g
total reagents / reactants / cat. mass	0.61	g
total workup reagents mass		g
total solvents (excl. water)	60.01	g
total water		g
total waste	60.13	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	121.7	121.7
solvent intensity	120.5	120.5
Sheldon E-factor	120.7	120.7
GSK Reaction Mass Efficiency	0.812	
Andraos Reaction Mass Efficiency	0.008	0.008
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.918	
material recovery parameter	0.010	0.010
yield	0.88	



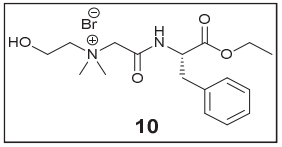
9

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
solvent	Diethyl ether	60-29-7	74.12	0.706		7.06	g	**10**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		52.95	g	**75**	mL					
reactant	N-Methylmorpholine	109-02-4	101.149	0.92		0.346941	g	0.37711	mL	**3.43**	mmol	**1**	x	
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175			1.090187	g			**3.47**	mmol	1.011662		
product	**9**		415.328			1.424575	g			3.43	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**9**		415.328			**0.482**	g		1.160529	mmol	34

total reaction mass	61.45	g
total reagents / reactants / cat. mass	1.44	g
total workup reagents mass		g
total solvents (excl. water)	60.01	g
total water		g
total waste	60.97	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	127.5	127.5
solvent intensity	124.5	124.5
Sheldon E-factor	126.5	126.5
GSK Reaction Mass Efficiency	0.335	
Andraos Reaction Mass Efficiency	0.008	0.008
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.991	
material recovery parameter	0.023	0.023
yield	0.338	



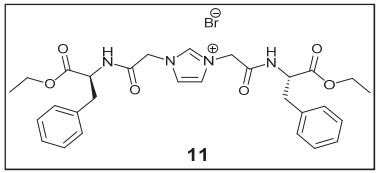
10

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
solvent	Diethyl ether	60-29-7	74.12	0.706		7.06	g	**10**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		52.95	g	**75**	mL					
reactant	Dimethyl Ethanolamine	108-01-0	89.14	0.886		0.151538	g	0.171036	mL	**1.7**	mmol	**1**	x	
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175			0.603216	g			**1.92**	mmol	1.129412		
product	**10**		403.317			0.685639	g			1.7	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**10**		403.317			**0.682**	g		1.69	mmol	99

total reaction mass	60.76	g
total reagents / reactants / cat. mass	0.75	g
total workup reagents mass		g
total solvents (excl. water)	60.01	g
total water		g
total waste	60.08	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	89.1	89.1
solvent intensity	88.0	88.0
Sheldon E-factor	88.1	88.1
GSK Reaction Mass Efficiency	0.904	
Andraos Reaction Mass Efficiency	0.011	0.011
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.908	
material recovery parameter	0.012	0.012
yield	0.995	



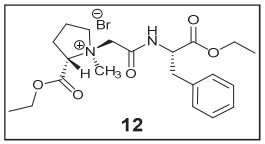
11

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
solvent	Diethyl ether	60-29-7	74.12	0.706		17.65	g	**25**	mL					
wu solvent	Diethyl ether	60-29-7	74.12	0.706		52.95	g	**75**	mL					
solvent	Ethyl acetate	141-78-6	88.11	0.902		22.55	g	**25**	mL					
reactant	TMS-Imidazole	18156-74-6	140.261	0.956		0.715331	g	0.748254	mL	**5.1**	mmol	**1**	x	
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175			3.261137	g			**10.38**	mmol	2.035294		
product	**11**		615.525			3.139178	g			5.1	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**11**		615.525			**2.857**	g		4.641566	mmol	91.0111

total reaction mass	97.13	g
total reagents / reactants / cat. mass	3.98	g
total workup reagents mass		g
total solvents (excl. water)	93.15	g
total water		g
total waste	94.27	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	34.0	34.0
solvent intensity	32.6	32.6
Sheldon E-factor	33.0	33.0
GSK Reaction Mass Efficiency	0.718	
Andraos Reaction Mass Efficiency	0.029	0.029
atom economy	0.801	
1 / stoichiom. factor (excess reagents)	0.986	
material recovery parameter	0.041	0.041
yield	0.910	



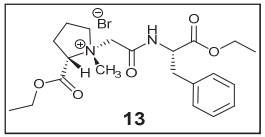
12

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
wu solvent	Dichloromethane	75-09-2	84.93	1.325		357.75 g	**270** mL				
solvent	Ethyl acetate	141-78-6	88.11	0.902		22.55 g	**25** mL				
wu solvent	Methanol	67-56-1	32.04	0.791		23.73 g	**30** mL				
reactant	N-Methyl-L-Proline Ethyl Ester		157.213			**0.25** g		1.590199 mmol	**1**	x	
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175			**0.564** g		1.795178 mmol	1.128901		
product	12		471.392			0.749607 g		1.590199 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	12		471.392			**281** mg		0.596107 mmol	37.4863

total reaction mass	404844.00	mg
total reagents / reactants / cat. mass	814.00	mg
total workup reagents mass		mg
total solvents (excl. water)	404030.00	mg
total water		mg
total waste	404563.00	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	1440.7	1440.7
solvent intensity	1437.8	1437.8
Sheldon E-factor	1439.7	1439.7
GSK Reaction Mass Efficiency	0.345	
Andraos Reaction Mass Efficiency	0.001	0.001
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.921	
material recovery parameter	0.002	0.002
yield	0.375	



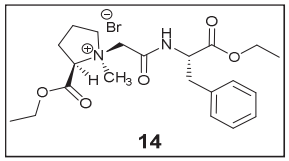
13

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
wu solvent	Dichloromethane	75-09-2	84.93	1.325		357.75 g	**270** mL				
solvent	Ethyl acetate	141-78-6	88.11	0.902		22.55 g	**25** mL				
wu solvent	Methanol	67-56-1	32.04	0.791		23.73 g	**30** mL				
reactant	N-Methyl-L-Proline Ethyl Ester		157.213			**0.25** g		1590.199 µmol	**1**	x	
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175			**0.564** g		1.795178 mmol	1.128901		
product	**13**		471.392			749.6072 mg		1590.199 µmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	**13**		471.392			**99** mg		210.0163 µmol	13.20692

total reaction mass	404844.00	mg
total reagents / reactants / cat. mass	814.00	mg
total workup reagents mass		mg
total solvents (excl. water)	404030.00	mg
total water		mg
total waste	404745.00	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	4089.3	4089.3
solvent intensity	4081.1	4081.1
Sheldon E-factor	4088.3	4088.3
GSK Reaction Mass Efficiency	0.122	
Andraos Reaction Mass Efficiency	0.000	0.000
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.921	
material recovery parameter	0.002	0.002
yield	0.132	



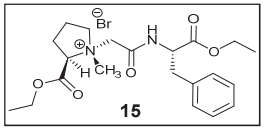
14

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
wu solvent	Dichloromethane	75-09-2	84.93	1.325		357.75	g	**270**	mL					
solvent	Ethyl acetate	141-78-6	88.11	0.902		22.55	g	**25**	mL					
wu solvent	Methanol	67-56-1	32.04	0.791		23.73	g	**30**	mL					
reactant	N-Methyl-D-Proline Ethyl Ester		157.213			**0.475**	g			3.021379	mmol	0.998151		
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175			**0.951**	g			3026.975	µmol	**1**	x	
product	**14**		471.392			1426.892	mg			3026.975	µmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**14**		471.392			**362**	mg		767.9384	µmol	25.36982

total reaction mass	405456.00	mg
total reagents / reactants / cat. mass	1426.00	mg
total workup reagents mass		mg
total solvents (excl. water)	404030.00	mg
total water		mg
total waste	405094.00	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	1120.0	1120.0
solvent intensity	1116.1	1116.1
Sheldon E-factor	1119.0	1119.0
GSK Reaction Mass Efficiency	0.254	
Andraos Reaction Mass Efficiency	0.001	0.001
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	1.001	
material recovery parameter	0.004	0.004
yield	0.254	

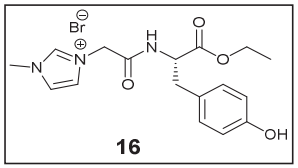


Type	Name	[CAS]	M.W.	d	wt% or conc.		mass		volume		moles		eq.	Pivot reagent	recycled
wu solvent	Dichloromethane	75-09-2	84.93	1.325			357.75	g	**270**	mL					
solvent	Ethyl acetate	141-78-6	88.11	0.902			22.55	g	**25**	mL					
wu solvent	Methanol	67-56-1	32.04	0.791			23.73	g	**30**	mL					
reactant	N-Methyl-D-Proline Ethyl Ester		157.213				**0.475**	g			3.021379	mmol	0.998151		
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175				**0.951**	g			3026.975	µmol	**1**	x	
product	**15**		471.392				1426.892	mg			3026.975	µmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**15**		471.392			**486**	mg		1030.989	µmol	34.06004

total reaction mass	405456.00	mg
total reagents / reactants / cat. mass	1426.00	mg
total workup reagents mass		mg
total solvents (excl. water)	404030.00	mg
total water		mg
total waste	404970.00	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	834.3	834.3
solvent intensity	831.3	831.3
Sheldon E-factor	833.3	833.3
GSK Reaction Mass Efficiency	0.341	
Andraos Reaction Mass Efficiency	0.001	0.001
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	1.001	
material recovery parameter	0.004	0.004
yield	0.341	



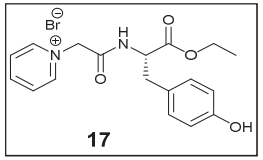
16

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
wu solvent	Diethyl ether	60-29-7	74.12	0.706		105.9	g	**150**	mL					
solvent	Ethyl acetate	141-78-6	88.11	0.902		45.1	g	**50**	mL					
reactant	L-Tyrosine ethyl ester α bromo amide		330.178			0.505172	g			**1.53**	mmol	1.026846		
reactant	1-Methylimidazole	616-47-7	82.1			0.122329	g			**1.49**	mmol	**1**	x	
product	**16**		412.284			0.614303	g			1.49	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**16**		412.284			**0.514**	g		1.246713	mmol	83.67204

total reaction mass	151.63	g
total reagents / reactants / cat. mass	0.63	g
total workup reagents mass		g
total solvents (excl. water)	151.00	g
total water		g
total waste	151.11	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	295.0	295.0
solvent intensity	293.8	293.8
Sheldon E-factor	294.0	294.0
GSK Reaction Mass Efficiency	0.819	
Andraos Reaction Mass Efficiency	0.003	0.003
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.979	
material recovery parameter	0.004	0.004
yield	0.837	



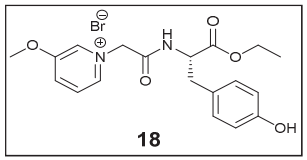
17

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
wu solvent	Diethyl ether	60-29-7	74.12	0.706		105.9	g	**150**	mL					
solvent	Ethyl acetate	141-78-6	88.11	0.902		45.1	g	**50**	mL					
reactant	Pyridine	110-86-1	79.1	0.978		0.249956	g	0.255579	mL	**3.16**	mmol	**1**	x	
reactant	L-Tyrosine ethyl ester α bromo amide		330.178			1.066475	g			**3.23**	mmol	1.022152		
product	**17**		409.28			1.293325	g			3.16	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**17**		409.28			**1.29**	g		3.151876	mmol	99.74293

total reaction mass	152.32	g
total reagents / reactants / cat. mass	1.32	g
total workup reagents mass		g
total solvents (excl. water)	151.00	g
total water		g
total waste	151.03	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	118.1	118.1
solvent intensity	117.1	117.1
Sheldon E-factor	117.1	117.1
GSK Reaction Mass Efficiency	0.980	
Andraos Reaction Mass Efficiency	0.008	0.008
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.982	
material recovery parameter	0.009	0.009
yield	0.997	



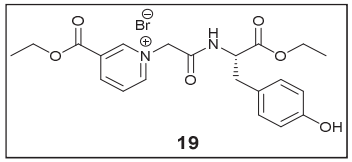
18

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
wu solvent	Diethyl ether	60-29-7	74.12	0.706		105.9	g	**150**	mL					
solvent	Ethyl acetate	141-78-6	88.11	0.902		45.1	g	**50**	mL					
reactant	L-Tyrosine ethyl ester α bromo amide		330.178			0.974025	g			**2.95**	mmol	1.024306		
reactant	3-Methoxy Pyridine	7295-76-3	109.128	1.083		0.314289	g	0.290202	mL	**2.88**	mmol	**1**	x	
product	**18**		439.306			1.265201	g			2.88	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**18**		439.306			**1.251**	g		2.847673	mmol	98.87755

total reaction mass	152.29	g
total reagents / reactants / cat. mass	1.29	g
total workup reagents mass		g
total solvents (excl. water)	151.00	g
total water		g
total waste	151.04	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	121.7	121.7
solvent intensity	120.7	120.7
Sheldon E-factor	120.7	120.7
GSK Reaction Mass Efficiency	0.971	
Andraos Reaction Mass Efficiency	0.008	0.008
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.982	
material recovery parameter	0.008	0.008
yield	0.989	



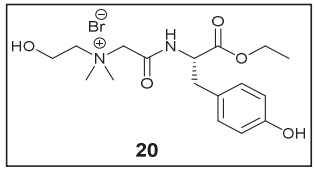
19

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
solvent	Ethyl acetate	141-78-6	88.11	0.902		45.1	g	**50**	mL					
wu solvent	Dichloromethane	75-09-2	84.93	1.325		357.75	g	**270**	mL					
wu solvent	Methanol	67-56-1	32.04	0.791		23.73	g	**30**	mL					
reactant	L-Tyrosine ethyl ester α bromo amide		330.178			1.003741	g			**3.04**	mmol	1.020134		
reactant	Ethyl nicotinate	614-18-6	151.163	1.107		0.450466	g	0.406925	mL	**2.98**	mmol	**1**	x	
product	**19**		481.343			1.434402	g			2.98	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**19**		481.343			**1.016**	g		2.110761	mmol	70.8309

total reaction mass	428.03	g
total reagents / reactants / cat. mass	1.45	g
total workup reagents mass		g
total solvents (excl. water)	426.58	g
total water		g
total waste	427.02	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	421.3	421.3
solvent intensity	419.9	419.9
Sheldon E-factor	420.3	420.3
GSK Reaction Mass Efficiency	0.699	
Andraos Reaction Mass Efficiency	0.002	0.002
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.986	
material recovery parameter	0.003	0.003
yield	0.708	



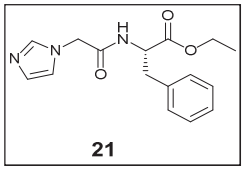
20

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
wu solvent	Diethyl ether	60-29-7	74.12	0.706		105.9	g	**150**	mL					
solvent	Ethyl acetate	141-78-6	88.11	0.902		45.1	g	**50**	mL					
reactant	Dimethyl Ethanolamine	108-01-0	89.14	0.886		0.271877	g	0.306859	mL	**3.05**	mmol	**1**	x	
reactant	L-Tyrosine ethyl ester α bromo amide		330.178			1.026854	g			**3.11**	mmol	1.019672		
product	**20**		419.316			1.278914	g			3.05	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**20**		419.316			**1.004**	g		2.394376	mmol	78.50412

total reaction mass	152.30	g
total reagents / reactants / cat. mass	1.30	g
total workup reagents mass		g
total solvents (excl. water)	151.00	g
total water		g
total waste	151.29	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	151.7	151.7
solvent intensity	150.4	150.4
Sheldon E-factor	150.7	150.7
GSK Reaction Mass Efficiency	0.773	
Andraos Reaction Mass Efficiency	0.007	0.007
atom economy	1.000	
1 / stoichiom. factor (excess reagents)	0.985	
material recovery parameter	0.009	0.009
yield	0.785	



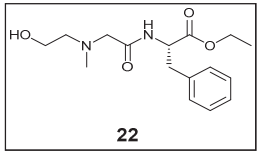
21

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
solvent	Diethyl ether	60-29-7	74.12	0.706		14.12	g	**20**	mL					
wu solvent	Dichloromethane	75-09-2	84.93	1.325		357.75	g	**270**	mL					
wu solvent	Methanol	67-56-1	32.04	0.791		23.73	g	**30**	mL					
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175			1.008502	g			**3.21**	mmol	1.401747		
wu solvent	Water		18	1		5	g	**5**	mL					
reactant	TMS-Imidazole	18156-74-6	140.261	0.956		0.321198	g	0.335981	mL	**2.29**	mmol	**1**	x	
product	**21**		301.346			0.690082	g			2.29	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		yield(%)
Output	**21**		**301.346**			**0.383**	**g**			**1.270964**	**mmol**	**55.50062**

total reaction mass	401.93	g
total reagents / reactants / cat. mass	1.33	g
total workup reagents mass		g
total solvents (excl. water)	395.60	g
total water	5.00	g
total waste	401.55	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	1036.4	1049.4
solvent intensity	1032.9	1046.0
Sheldon E-factor	1035.4	1048.4
GSK Reaction Mass Efficiency	0.288	
Andraos Reaction Mass Efficiency	0.001	0.001
atom economy	0.663	
1 / stoichiom. factor (excess reagents)	0.783	
material recovery parameter	0.003	0.003
yield	0.555	



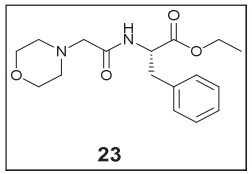
22

Type	Name	[CAS]	M.W.	d	wt% or conc.		mass		volume		moles		eq.	Pivot reagent	recycled
reactant	Methyl ethanolamine		75.11	0.935			0.107407	g	0.114874	mL	**1.43**	mmol	**1**	x	
solvent	Diethyl ether	60-29-7	74.12	0.706			17.65	g	**25**	mL					
wu solvent	Dichloromethane	75-09-2	84.93	1.325			377.625	g	**285**	mL					
wu solvent	Methanol	67-56-1	32.04	0.791			11.865	g	**15**	mL					
reagent	L-Phenylalanine ethyl ester α bromo amide		314.175				0.50268	g			**1.6**	mmol	1.118881		
product	**22**		308.378				0.440981	g			1.43	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**22**		308.378			**0.148**	g		0.47993	mmol	33.56157

total reaction mass	407.75	g
total reagents / reactants / cat. mass	0.61	g
total workup reagents mass		g
total solvents (excl. water)	407.14	g
total water		g
total waste	407.60	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	2755.1	2755.1
solvent intensity	2750.9	2750.9
Sheldon E-factor	2754.1	2754.1
GSK Reaction Mass Efficiency	0.243	
Andraos Reaction Mass Efficiency	0.0004	0.000
atom economy	0.792	
1 / stoichiom. factor (excess reagents)	0.912	
material recovery parameter	0.001	0.001
yield	0.336	



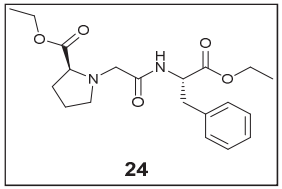
23

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
solvent	Tetrahydrofuran	109-99-9	72.11	0.889		44.45	g	**50**	mL					
wu solvent	Ethyl acetate	141-78-6	88.11	0.902		135.3	g	**150**	mL					
wu solvent	Hexane	110-54-3	86.18	0.659		98.85	g	**150**	mL					
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175			1.074479	g			**3.42**	mmol	1.052308		
wu reagent	Sodium carbonate		105.988			0.376257	g			**3.55**	mmol	1.092308		
reactant	Morpholine		87.122	0.996		0.283147	g	0.284284	mL	**3.25**	mmol	**1**	x	
product	**23**		320.389			1.041264	g			3.25	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**23**		320.389			**0.587**	g		1.832148	mmol	56.37378

total reaction mass	280.33	g
total reagents / reactants / cat. mass	1.36	g
total workup reagents mass	0.38	g
total solvents (excl. water)	278.60	g
total water		g
total waste	279.75	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	477.6	477.6
solvent intensity	474.6	474.6
Sheldon E-factor	476.6	476.6
GSK Reaction Mass Efficiency	0.432	
Andraos Reaction Mass Efficiency	0.002	0.002
atom economy	0.798	
1 / stoichiom. factor (excess reagents)	0.961	
material recovery parameter	0.005	0.005
yield	0.564	



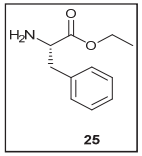
24

Type	Name	[CAS]	M.W.	d	wt% or conc.		mass		volume		moles		eq.	Pivot reagent	recycled
wu solvent	Ethyl acetate	141-78-6	88.11	0.902			135.3	g	**150**	mL					
wu solvent	Hexane	110-54-3	86.18	0.659			98.85	g	**150**	mL					
solvent	Tetrahydrofuran	109-99-9	72.11	0.889			22.225	g	**25**	mL					
reactant	L-Proline Ethyl ester HCL		179.644				0.301802	g			**1.68**	mmol	**1**	x	
reactant	L-Phenylalanine ethyl ester α bromo amide		314.175				0.581224	g			**1.85**	mmol	1.10119		
reagent	Sodium carbonate		105.988				0.370958	g			**3.5**	mmol	2.083333		
product	**24**		376.453				0.632441	g			1.68	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**24**		376.453			**0.334**	g		0.887229	mmol	52.81125

total reaction mass	257.63	g
total reagents / reactants / cat. mass	1.25	g
total workup reagents mass		g
total solvents (excl. water)	256.38	g
total water		g
total waste	257.29	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	771.3	771.3
solvent intensity	767.6	767.6
Sheldon E-factor	770.3	770.3
GSK Reaction Mass Efficiency	0.266	
Andraos Reaction Mass Efficiency	0.001	0.001
atom economy	0.533	
1 / stoichiom. factor (excess reagents)	0.946	
material recovery parameter	0.005	0.005
yield	0.528	

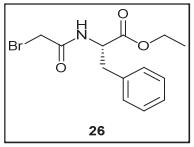


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
wu solvent	Ethyl acetate	141-78-6	88.11	0.902		225.5 g	**250** mL				
solvent	Ethanol	64-17-5	46.07	0.816		115.4232 g	**141.45** mL				
reactant	Ethanol	64-17-5	46.07	0.816		6.977894 g	8.551341 mL	151.4629 mmol	**1**		
reactant	L-Phenylalanine	63-91-2	165.189			**25.02** g		151.4629 mmol	**1**	x	
reagent	Thionyl Chloride	7719-09-7	118.971	1.373		36039.38 mg	26.24864 mL	302.9257 mmol	**2**		
wu solvent	brine (NaCl)	7647-14-5	58.44	1.202	**26** wt%	180.3 g	**150** mL				
wu reagent	Magnesium sulfate	7487-88-9	120.36			**25** g		207.7102 mmol	1.371361		
wu reagent	Sodium bicarbonate soln. in water		84.007	1	**9.6** wt%	150 g	**150** mL	171.4143 mmol	1.131725		
wu solvent	Water		18	1		50 g	**50** mL				
product	L-Phenylalanine ethyl ester		193.242			29.26899 g		151.4629 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	L-Phenylalanine ethyl ester		193.242			**28.888** g		149.4913 mmol	98.69832

total reaction mass	814.26	g
total reagents / reactants / cat. mass	68.04	g
total workup reagents mass	39.40	g
total solvents (excl. water)	340.92	g
total water	185.60	g
total waste	785.37	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	21.8	28.2
solvent intensity	11.8	18.2
Sheldon E-factor	20.8	27.2
GSK Reaction Mass Efficiency	0.425	
Andraos Reaction Mass Efficiency	0.046	0.035
atom economy	0.585	
1 / stoichiom. factor (excess reagents)	0.735	
material recovery parameter	0.108	0.084
yield	0.987	



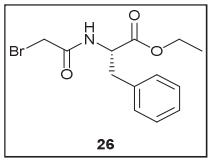
26

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
solvent	Dichloromethane	75-09-2	84.93	1.325		33.125 g	**25** mL				
reactant	L-Phenylalanine ethyl ester HCL		229.704			**2.22** g		9.664612 mmol	**1**	x	
reagent	Triethylamine	121-44-8	101.2	0.726		2.053923 g	2.829095 mL	20.29568 mmol	**2.1**		
reactant	bromoacetyl bromide	598-21-0	201.845	2.317		**2.503** g	1.080276 mL	12.4006 mmol	1.283094		
wu solvent	Water		18	1		40 g	**40** mL				
wu reagent	ammonium chloride solution in water		54.49	1	**28** wt%	30 g	**30** mL	154.1567 mmol	15.95064		
wu reagent	Sodium bicarbonate soln. in water		84.007	1	**9.6** wt%	30 g	**30** mL	34.28286 mmol	3.547257		
wu solvent	brine (NaCl) in water	7647-14-5	58.44	1.202	**26** wt%	36.06 g	**30** mL				
wu reagent	Magnesium sulfate	7487-88-9	120.36			**20** g		166.1682 mmol	17.19346		
wu solvent	Ethyl acetate	141-78-6	88.11	0.902		135.3 g	**150** mL				
wu solvent	Hexane	110-54-3	86.18	0.659		98.85 g	**150** mL				
product	**26**		314.179			3036.418 mg		9664.612 µmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	**26**		314.179			**2.078** g		6.614064 mmol	68.4359

total reaction mass	430111.92	mg
total reagents / reactants / cat. mass	6776.92	mg
total workup reagents mass	31280.00	mg
total solvents (excl. water)	267275.00	mg
total water	88720.00	mg
total waste	428033.92	mg
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	709.4	893.8
solvent intensity	555.4	739.8
Sheldon E-factor	705.1	889.5
GSK Reaction Mass Efficiency	0.307	
Andraos Reaction Mass Efficiency	0.001	0.001
atom economy	0.496	
1 / stoichiom. factor (excess reagents)	0.904	
material recovery parameter	0.005	0.004
yield	0.684	



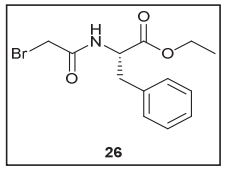
26

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
solvent	Dichloromethane	75-09-2	84.93	1.325		66.25	g	**50**	mL					
reactant	L-Phenylalanine ethyl ester HCL		229.704			**6.935**	g			30.19103	mmol	**1**	x	
reagent	Sodium carbonate		105.988			**6.36**	g			60.00679	mmol	1.98757		
reactant	bromoacetyl bromide	598-21-0	201.845	2.317		6.09371	g	**2.63**	mL	30.19005	mmol	0.999967		
wu solvent	Water		18	1		50	g	**50**	mL					
wu reagent	Sodium bicarbonate soln. in water		84.007	1		150	g	**150**	mL	1785.565	mmol	59.14225		
wu reagent	Magnesium sulfate	7487-88-9	120.36			**20**	g			166.1682	mmol	5.503892		
wu solvent	Ethyl acetate	141-78-6	88.11	0.902		135.3	g	**150**	mL					
wu solvent	Hexane	110-54-3	86.18	0.659		98.85	g	**150**	mL					
product	**26**		314.175			9.485266	g			30.19103	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**26**		314.175			**5.751**	g		18.30508	mmol	60.63088

total reaction mass	539.79	g
total reagents / reactants / cat. mass	19.39	g
total workup reagents mass	170.00	g
total solvents (excl. water)	300.40	g
total water	50.00	g
total waste	534.04	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	85.2	93.9
solvent intensity	52.2	60.9
Sheldon E-factor	84.2	92.9
GSK Reaction Mass Efficiency	0.297	
Andraos Reaction Mass Efficiency	0.012	0.011
atom economy	0.488	
1 / stoichiom. factor (excess reagents)	1.002	
material recovery parameter	0.040	0.036
yield	0.606	



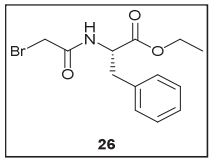
26

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	bromoacetyl bromide	598-21-0	201.845	2.317		7.80829	g	**3.37**	mL	38.68458	mmol	1.199894		
solvent	Dichloromethane	75-09-2	84.93	1.325		66.25	g	**50**	mL					
wu reagent	Sodium bicarbonate soln. in water		84.007	1	**9.6**	wt% 150	g	**150**	mL	171.4143	mmol	5.31682		
reagent	Sodium carbonate		105.988			5.12558	g			**48.36**	mmol	1.5		
reactant	L-Phenylalanine ethyl ester (**25**)		193.242			6.230122	g			**32.24**	mmol	**1**	x	
product	**26**		314.175			10.129	g			32.24	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**26**		314.175			**8.998**	g		28.64009	mmol	88.83402

total reaction mass	235.41	g
total reagents / reactants / cat. mass	19.16	g
total workup reagents mass	14.40	g
total solvents (excl. water)	66.25	g
total water	135.60	g
total waste	226.42	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	11.1	26.2
solvent intensity	7.4	22.4
Sheldon E-factor	10.1	25.2
GSK Reaction Mass Efficiency	0.470	
Andraos Reaction Mass Efficiency	0.090	0.038
atom economy	0.627	
1 / stoichiom. factor (excess reagents)	0.843	
material recovery parameter	0.192	0.081
yield	0.888	



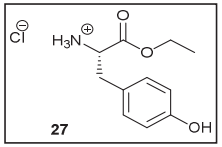
26

Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
solvent	Tetrahydrofuran	109-99-9	72.11	0.889		44.45	g	**50**	mL					
reactant	L-Phenylalanine ethyl ester (**25**)		193.242			**5.01**	g			25926.04	µmol	**1**	x	
reagent	Sodium carbonate		105.988			**3.298**	g			31.11673	mmol	1.200211		
reactant	bromoacetyl bromide	598-21-0	201.845	2.317		5.83884	g	**2.52**	mL	28.92735	mmol	1.115764		
wu solvent	Water		18	1		50	g	**50**	mL					
wu reagent	Sodium bicarbonate soln. in water		84.007	1		150	g	**150**	mL	1785.565	mmol	68.87151		
wu reagent	Magnesium sulfate	7487-88-9	120.36			**20**	g			166.1682	mmol	6.409315		
product	**26**		314.175			8.145314	g			25.92604	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**26**		314.175			**6.061**	g		19.2918	mmol	74.41088

total reaction mass	278.60	g
total reagents / reactants / cat. mass	14.15	g
total workup reagents mass	170.00	g
total solvents (excl. water)	44.45	g
total water	50.00	g
total waste	272.54	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	37.7	46.0
solvent intensity	7.3	15.6
Sheldon E-factor	36.7	45.0
GSK Reaction Mass Efficiency	0.428	
Andraos Reaction Mass Efficiency	0.027	0.022
atom economy	0.627	
1 / stoichiom. factor (excess reagents)	0.918	
material recovery parameter	0.062	0.051
yield	0.744	

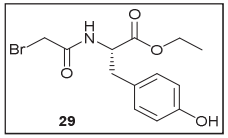


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	Ethanol	64-17-5	46.07	0.816		2.512658 g	3.079238 mL	**54.54** mmol	1		
solvent	Ethanol	64-17-5	46.07	0.816		36.72 g	**45** mL				
reactant	L-Tyrosine		181.191			9.882157 g		**54.54** mmol	**1**	x	
reagent	Thionyl Chloride	7719-09-7	118.971	1.638		6488.678 mg	3.961342 mL	54.54 mmol	**1**		
product	**27**		245.703			13.40064 g		54.54 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	**27**		245.703			**11.712** g		47.66731 mmol	87.3988

total reaction mass	55.60	g
total reagents / reactants / cat. mass	18.88	g
total workup reagents mass		g
total solvents (excl. water)	36.72	g
total water		g
total waste	43.89	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	4.7	4.7
solvent intensity	3.1	3.1
Sheldon E-factor	3.7	3.7
GSK Reaction Mass Efficiency	0.620	
Andraos Reaction Mass Efficiency	0.211	0.211
atom economy	0.710	
1 / stoichiom. factor (excess reagents)	1.000	
material recovery parameter	0.340	0.340
yield	0.874	

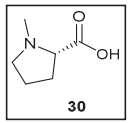


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	bromoacetyl bromide	598-21-0	201.845	2.317		5.994797 g	2.58731 mL	**29.7** mmol	1.220715		
solvent	Dichloromethane	75-09-2	84.93	1.325		66.25 g	**50** mL				
wu reagent	Sodium bicarbonate soln. in water		84.007	1		150 g	**150** mL	1785.565 mmol	73.38946		
reagent	Sodium carbonate		105.988			3.461568 g		**32.66** mmol	1.342376		
reactant	L-Tyrosine Ethyl ester HCl		245.703			5.977954 g		**24.33** mmol	**1**	x	
wu solvent	Hexane	110-54-3	86.18	0.659		3.295 g	**5** mL				
wu solvent	Ethanol	64-17-5	46.07	0.816		8.16 g	**10** mL				
wu reagent	HCl 1N in water	7647-01-0	36.46	1.015	**1** M	1.015 g	**1** mL	1 mmol	0.041102		
product	L-Tyrosine ethyl ester α bromo amide		330.178			8.033231 g		24.33 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	L-Tyrosine ethyl ester α bromo amide		330.178			**4.337** g		13.13534 mmol	53.98824

total reaction mass	244.15	g
total reagents / reactants / cat. mass	15.43	g
total workup reagents mass	150.04	g
total solvents (excl. water)	77.71	g
total water	0.98	g
total waste	239.82	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	56.1	56.3
solvent intensity	17.9	18.1
Sheldon E-factor	55.1	55.3
GSK Reaction Mass Efficiency	0.281	
Andraos Reaction Mass Efficiency	0.018	0.018
atom economy	0.596	
1 / stoichiom. factor (excess reagents)	0.873	
material recovery parameter	0.063	0.063
yield	0.540	



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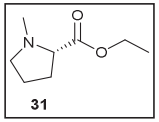
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	Formalin in water		30.026	0.815	**37** wt%	1.78533 g	2.190589 mL	**22** mmol	1.21424		
reactant	L-Proline		115.132			**2.086** g		18.11833 mmol	**1**	x	
catalyst	Pd/C		106.42			0.031926 g		**0.3** mmol	0.016558		
solvent	Methanol	67-56-1	32.04	0.791		15.82 g	**20** mL				
product	**30**		129.159			2.340146 g		18.11833 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	**30**		129.159			**2.29** g		17.73008 mmol	97.85715

total reaction mass	19.72	g
total reagents / reactants / cat. mass	2.78	g
total workup reagents mass		g
total solvents (excl. water)	15.82	g
total water	1.12	g
total waste	17.43	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	8.1	8.6
solvent intensity	6.9	7.4
Sheldon E-factor	7.1	7.6
GSK Reaction Mass Efficiency	0.824	
Andraos Reaction Mass Efficiency	0.123	0.116
atom economy	0.890	
1 / stoichiom. factor (excess reagents)	0.958	
material recovery parameter	0.148	0.139
yield	0.979	

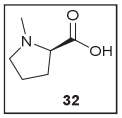


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	Ethanol	64-17-5	46.07	0.816		0.452868 g	0.554985 mL	9.83 mmol	**1**		
reagent	Thionyl Chloride	7719-09-7	118.971	1.638		1.169485 g	0.713971 mL	9.83 mmol	**1**		
solvent	Ethanol	64-17-5	46.07	0.816		15.8712 g	**19.45** mL				
reactant	**30**		129.159			1.269633 g		**9.83** mmol	**1**	x	
wu solvent	Dichloromethane	75-09-2	84.93	1.325		33.125 g	**25** mL				
wu reagent	Sodium carbonate		105.988			1.05988 g		**10** mmol	1.017294		
product	**31**		157.213			1.545404 g		9.83 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	**31**		157.213			**1.283** g		8.160903 mmol	83.02037

total reaction mass	52.95	g
total reagents / reactants / cat. mass	2.89	g
total workup reagents mass	1.06	g
total solvents (excl. water)	49.00	g
total water		g
total waste	51.67	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	41.3	41.3
solvent intensity	38.2	38.2
Sheldon E-factor	40.3	40.3
GSK Reaction Mass Efficiency	0.444	
Andraos Reaction Mass Efficiency	0.024	0.024
atom economy	0.897	
1 / stoichiom. factor (excess reagents)	0.596	
material recovery parameter	0.055	0.055
yield	0.830	



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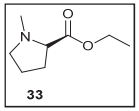
Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	Formalin in water		30.026	0.815	**37** wt%	2.386986 g	2.928817 mL	29.414 mmol	**1.1**		
reactant	L-Proline		115.132			3.07863 g		**26.74** mmol	**1**	x	
catalyst	Pd/C		106.42			0.031926 g		**0.3** mmol	0.011219		
solvent	Methanol	67-56-1	32.04	0.791		15.82 g	**20** mL				
product	**32**		129.159			3.453712 g		26.74 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	**32**		129.159			**1.235** g		9.561858 mmol	35.75863

total reaction mass	21.32	g
total reagents / reactants / cat. mass	3.99	g
total workup reagents mass		g
total solvents (excl. water)	15.82	g
total water	1.50	g
total waste	20.08	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	16.0	17.3
solvent intensity	12.8	14.0
Sheldon E-factor	15.0	16.3
GSK Reaction Mass Efficiency	0.309	
Andraos Reaction Mass Efficiency	0.062	0.058
atom economy	0.890	
1 / stoichiom. factor (excess reagents)	0.980	
material recovery parameter	0.200	0.186
yield	0.358	

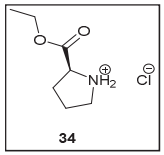


Type	Name	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	eq.	Pivot reagent	recycled
reactant	Ethanol	64-17-5	46.07	0.816		0.440429 g	0.539742 mL	9.56 mmol	**1**		
reagent	Thionyl Chloride	7719-09-7	118.971	1.638		1.137363 g	0.694361 mL	9.56 mmol	**1**		
solvent	Ethanol	64-17-5	46.07	0.816		15.88752 g	**19.47** mL				
reactant	**32**		129.159			1.23476 g		**9.56** mmol	**1**	x	
wu solvent	Dichloromethane	75-09-2	84.93	1.325		33.125 g	**25** mL				
wu reagent	Sodium carbonate		105.988			1.05988 g		**10** mmol	1.046025		
product	**33**		157.213			1.502956 g		9.56 mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass	volume	moles	yield(%)
Output	**33**		157.213			**0.649** g		4.128157 mmol	43.18156

total reaction mass	52.88	g
total reagents / reactants / cat. mass	2.81	g
total workup reagents mass	1.06	g
total solvents (excl. water)	49.01	g
total water		g
total waste	52.24	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	81.5	81.5
solvent intensity	75.5	75.5
Sheldon E-factor	80.5	80.5
GSK Reaction Mass Efficiency	0.231	
Andraos Reaction Mass Efficiency	0.012	0.012
atom economy	0.897	
1 / stoichiom. factor (excess reagents)	0.596	
material recovery parameter	0.053	0.053
yield	0.432	



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Type	Name	[CAS]	M.W.	d	wt% or conc.	mass		volume		moles		eq.	Pivot reagent	recycled
reactant	Ethanol	64-17-5	46.07	0.816		2.005149	g	2.45729	mL	43.52396	mmol	**1**		
reagent	Thionyl Chloride	7719-09-7	118.971	1.638		5.178088	g	3.161226	mL	43.52396	mmol	**1**		
solvent	Ethanol	64-17-5	46.07	0.816		38.79264	g	**47.54**	mL					
reactant	L-Proline		115.132			**5.011**	g			43.52396	mmol	**1**	x	
product	**34**		179.644			7.818817	g			43.52396	mmol	**1**		

	product	[CAS]	M.W.	d	wt% or conc.	mass		volume	moles		yield(%)
Output	**34**		179.644			**7.751**	g		43.14645	mmol	99.13264

total reaction mass	50.99	g
total reagents / reactants / cat. mass	12.19	g
total workup reagents mass		g
total solvents (excl. water)	38.79	g
total water		g
total waste	43.24	g
total raw material cost		

Metrics	excl. water	incl. water
mass intensity	6.6	6.6
solvent intensity	5.0	5.0
Sheldon E-factor	5.6	5.6
GSK Reaction Mass Efficiency	0.636	
Andraos Reaction Mass Efficiency	0.152	0.152
atom economy	0.814	
1 / stoichiom. factor (excess reagents)	0.788	
material recovery parameter	0.239	0.239
yield	0.991	