Supporting Information

Antimicrobial peptides incorporating halogenated marine-derived amino acid substituents

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List of non-standard abbreviations

Flash column vacuum chromatography (FCC)
Preparative reverse-phase high-performance liquid chromatography (RP-HPLC)
Diisopropylethylamine (DIPEA)
Trifluoroacetic acid (TFA)
Triisopropylethylsilane (TIPS)
Ultrahigh pressure liquid chromatography (UPLC)
Fluorenylmethyloxycarbonyl (Fmoc)
Heptanes (Hept)
4-Dimethylaminopyridine (DMAP)
Solid-phase peptide synthesis (SPPS)
Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP)
Hydroxybenzotriazole (HOBt)
Hydroxyazotriazole (HOAt)

1. Compound synthesis

General information

Commercially available reagents and solvents were purchased from Merck, Iris Biotech or Fluorochem and used as received. All manipulations with air- and moisture-sensitive compounds were carried out under positive pressure of argon in flame-dried glassware. Chromatographic separation/purification was performed either on manually packed columns with Silica gel 60 (Merck, 40 – 63 μm) for flash column vacuum chromatography (FCC) or on Reveleris® X2 Flash Chromatography Purification System (BÜCHI) with FlashPure Silica pre-packed columns. Reactions were monitored by TLC on silica gel 60 F_{254} plates (Merck). Specific rotation was measured with MCP 100 polarimeter (Anton Paar) at 25 °C. Analytical high performance liquid chromatography was performed on a Dionez UltiMate 3000 HPLC system with a Bruker amazon SL ion trap mass spectrometer with detection by UV (diode array detector, 214, 254, and 280 nm) and electrospray ionization mass spectrometry using a Penomenex Kinetex C18 column (50 × 3.0 mm, 2.6 μm particle size, 100 Å pore size) with gradients of H_2O/MeCN/0.05% HCOOH as mobile phase at a flow rate of 1.5 mL/min.Both preparative (prepHPLC) and chiral analytical HPLC was carried out on an Ultimate HPLC system (Thermo Scientific) consisting of a LPG-3200BX pump, a Rheodyne 9725i injector, a 10 mL loop and a MWD-300SD detector (detection at 214 and 220 nm). PrepHPLC was performed using Gemini-NX C18 column (21.2 × 250 mm, 5 μm, 110 Å, Phenomenex); gradient elution 10 to 100% B (MeCN-H_2O-TFA 90:10:0.1 v/v/v%) in solvent A (H_2O-TFA 100:0.1 v/v%) over 20 min with a flow rate 20 mL/min (unless noted otherwise). No unexpected or unusually high safety hazards were encountered.

Chiral HPLC analysis was carried out using Chiralpak® AD-H column (4.6 × 250 mm, 5 μm, Daicel) with a flow rate 0.9 mL/min, *i*PrOH-heptane 30:70 v/v% isocratic elution and detection at 214 nm (unless stated otherwise). Data for analytical and preparative HPLC were acquired and processed using Chromeleon software v. 6.80.

Preparative reverse-phase high-performance liquid chromatography (RP-HPLC) was performed by UV-triggered (254 nm) fraction collection with a Gilson HPLC system using a Machery-nagel NUCLEODUR C18 HTec column (21 × 125 mm, particle size 5 μm) and H_2O/MeCN/0.1%TFA as mobile phase at a flow rate of 15 mL/min. NMR-spectra were acquired using 600 MHz Bruker Avance III HD equipped with 5 mm DCH cryoprobe and 400 MHz Bruker Avance II equipped with a 5 mm BBFO probe. Chemical shifts were referenced to residual protio- and perdeuterio- solvent resonances (δ_H 7.26 and δ_C 77.16 for $CDCl_3$; δ_H 3.31 and δ_C 49.00 for CD_3OD; δ_H 2.50 and δ_C 39.52 for DMSO-d_6) as internal standards for ^{1}H NMR and ^{13}C NMR spectra, respectively. NMR spectra recorded in D_2O were referenced to TMSP-d_4 as internal standard (0.03 wt. %; δ_H 0.00 and δ_C 0.00 for $Si(CH_3)_3$).

LCMS (liquid chromatography mass spectrometry) data were obtained from Waters Acquity H-class UPLC with a Sample Manager FTN and a TUV dual wavelength detector coupled to a QDa single quadrupole analyser using electrospray ionization (ESI). UPLC separation was achieved with a C18 reversed-phase column (Acquity UPLC BEH C18, 2.1 mm × 50 mm, 1.7 μm) operated at 40 °C,

using a linear gradient of the binary solvent system of buffer A (H_2O:MeCN:formic acid, 95:5:0.1 v/v/v%) to buffer B (MeCN:formic acid, 100:0.1 v/v%) from 0 to 100% B in 3.5 min, then 1 min at 100%B, maintaining a flow rate of 0.8 mL⁄min. High resolution mass-spectra were recorded on either a QE Orbitrap or on a LTQ Velos Pro, with samples being analysed by direct infusion with electrospray ionization in positive mode. Data were collected at 140,000 resolution (at *m/z* 400) and 50 transients were co-added.

Synthesis of building blocks for SPPS

General procedures

Method A – N-Fmoc protection

Following the previously published protocol[1], sodium bicarbonate (2.2 equiv.*) and 9-fluorenylmethyloxycarbonyl succinimide (1.0 equiv.) were sequentially added to the solution/suspension of amino acid (1 mmol, 1 equiv.) in dioxane–H_2O (1:1, 5 mL/mmol) at 0 °C. The mixture was stirred for 1 h, then the ice bath was removed, and stirring was continued overnight. Dioxane was removed *in vacuo*, the aqueous phase was then acidified with 1M HCl till pH 3 and extracted with EtOAc (3×10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was further purified by chromatography on SiO_2; the corresponding product-containing fractions were concentrated to dryness and co-evaporated with toluene.

Method B – Suzuki-Miyaura cross-coupling for Fmoc-protected compounds

Based on the previously reported procedure.[2] A reaction flask charged with Fmoc-protected 4-iodophenylalanine (1 mmol, 1 equiv.), the corresponding boronic acid derivative (1.2 equiv.), $Pd(dppf)Cl_2•CH_2Cl_2$ (5 mol%), K_2CO_3 (5 equiv) and degassed *i*PrOH – H_2O mixture (2:1, 10 mL/mmol) was purged with argon and stirred at room temperature for 24 h. The reaction mixture was partitioned between 15 mL DCM and 15 mL 2M citric acid; the organic phase was separated; the aqueous layer was extracted with DCM (2×10 mL). The combined organic phases were filtered through a pad of Na_2SO_4 with Celite® on top and the filtrate was concentrated under reduced pressure and further purified by column chromatography. The corresponding product-containing fractions were concentrated to dryness and co-evaporated with toluene.

Method C – N,N,N-trimethylation of primary amine

Three chemical steps; based on previously reported procedures.[3, 4]

The corresponding primary ammonium salt (1 mmol, 1 equiv.) was distributed between carbonate buffer (0.5M, pH 9.5, 20 mL/mmol) and EtOAc (15 mL/mmol). The aqueous layer was extracted with EtOAc (3×10 mL), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The freebased amine (~1 mmol) was used directly in the next step.

Formaldehyde (37% in H_2O, 3.5 equiv.) and acetic acid (5 equiv.) were added to the solution of amine (1 mmol, 1 equiv.) obtained above in MeOH (3 mL/mmol) at 0 °C. The mixture was stirred for 10 min,

*3.2 equiv of $NaHCO_3$ was used if a starting amino acid was in the form of HCl salt. In this case, FmocOSu was added after 10 min of stirring amino acid with base at 0 °C.

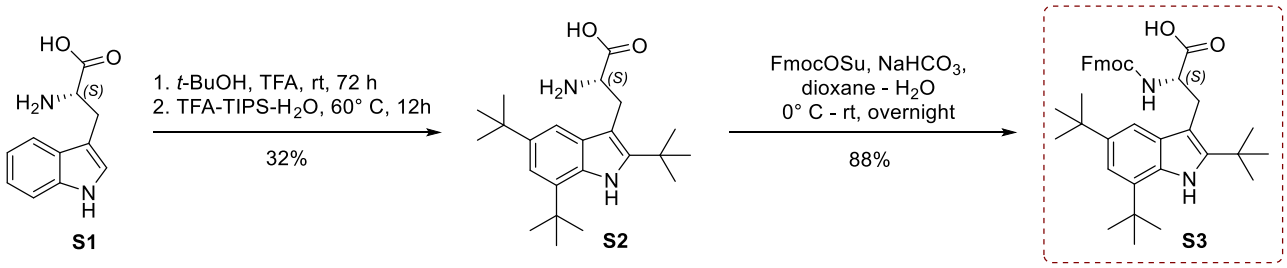
followed by $NaBH_3CN$ (3 equiv.) added portion-wise. The reaction mixture was stirred 15 min at the same temperature, then the cooling bath was removed; the reaction was stirred for additional 45 min at room temperature and diluted with carbonate buffer (0.5M, pH 9.5, 20 mL) and EtOAc (15 mL). The aqueous phase was extracted with EtOAc (2×10 mL), the organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude *N*,*N*-dimethylamine was used in the next step without further purification.

The intermediate tertiary amine (~1 mmol) from above was dissolved in MeCN – MeOH mixture (3:1, 2 mL/mmol), followed by DIPEA (0.5 equiv.) and MeI (5 equiv.). The reaction mixture was stirred overnight at room temperature and then concentrated under reduced pressure.

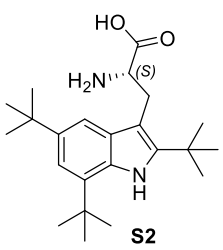
Method D – anion exchange (I^- to Cl^-)
A glass column packed with 5.0 g of Dowex 1X4-200 (Cl-form, Sigma-Aldrich) was conditioned with deionized water (50 mL), followed by MeOH (50 mL). A solution of corresponding iodide (1 mmol, 1 equiv.) in MeOH (10 mL/mmol) was applied on the column and slowly eluted (gravity-driven) with excess of the same solvent. The progress was monitored TLC. UV-active fractions were combined and evaporated in vacuo to give the desired quaternary ammonium chloride with a quantitative yield.

Method E – hydrogenolysis of benzyl ester
A round-bottom flask containing 0.05M methanol solution of the corresponding benzyl ester (1 mmol, 1 equiv) was charged with Pd/C (10% w/w, 0.02 equiv.), sealed and evacuated/backfilled with hydrogen (3 times). The reaction mixture was hydrogenated at atmospheric pressure (H_2 balloon) overnight under vigorous stirring, then filtered through a pad of Celite® and the filter cake was washed with methanol; the combined filtrates were concentrated to dryness under reduced pressure. Details of further purification are specified for each product.

Fmoc-Tbt-OH



(*S*)-2-amino-3-(2,5,7-tri-tert-butyl-1*H*-indol-3-yl)propanoic acid / H-Tbt-OH (S2)

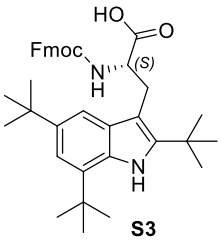


According to a modified version of the reported procedure[1], a mixture of *L*-tryptophan **S1** (3.06 g, 15.0 mmol) and *tert*-butanol (14.2 mL, 150 mmol) in 45 mL TFA was stirred at room temperature for 72 h and concentrated in vacuo (reaction progress was monitored by UPLC-MS). The dark oily residue was re-dissolved in 30 mL TFA–H_2O–TIPS mixture (95/2.5/2.5 v/v/v%) and stirred at 60 °C for 12 h. The volatiles were removed under reduced pressure; the dry

residue was recrystallized from EtOH–H_2O (1:1), providing 1.78 g (32%) of **S2** as a white crystalline solid.

^{1}H NMR (600 MHz, CD_3OD) δ 8.28 (br s, 1H), 7.48 (d, *J* = 1.7 Hz, 1H), 7.16 (d, *J* = 1.7 Hz, 1H), 3.94 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.71 (dd, *J* = 15.4, 4.9 Hz, 1H), 3.21 (dd, *J* = 15.4, 10.5 Hz, 1H), 1.54 (s, 9H), 1.49 (s, 9H), 1.39 (s, 9H); **^{13}C NMR** (151 MHz, CD_3OD) δ 174.2, 144.5, 143.5, 133.4, 131.6, 131.4, 117.5, 113.0, 105.0, 57.9, 35.7, 35.5, 34.2, 32.5 (×3), 31.4 (×3), 30.8 (×3), 28.7; **LCMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{37}N_2O_2$ 373.3, found 373.3. The analytical data are consistent with those reported in the literature.[6]

(*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(2,5,7-tri-tert-butyl-1*H*-indol-3-yl)propanoic acid / Fmoc-Tbt-OH (S3)

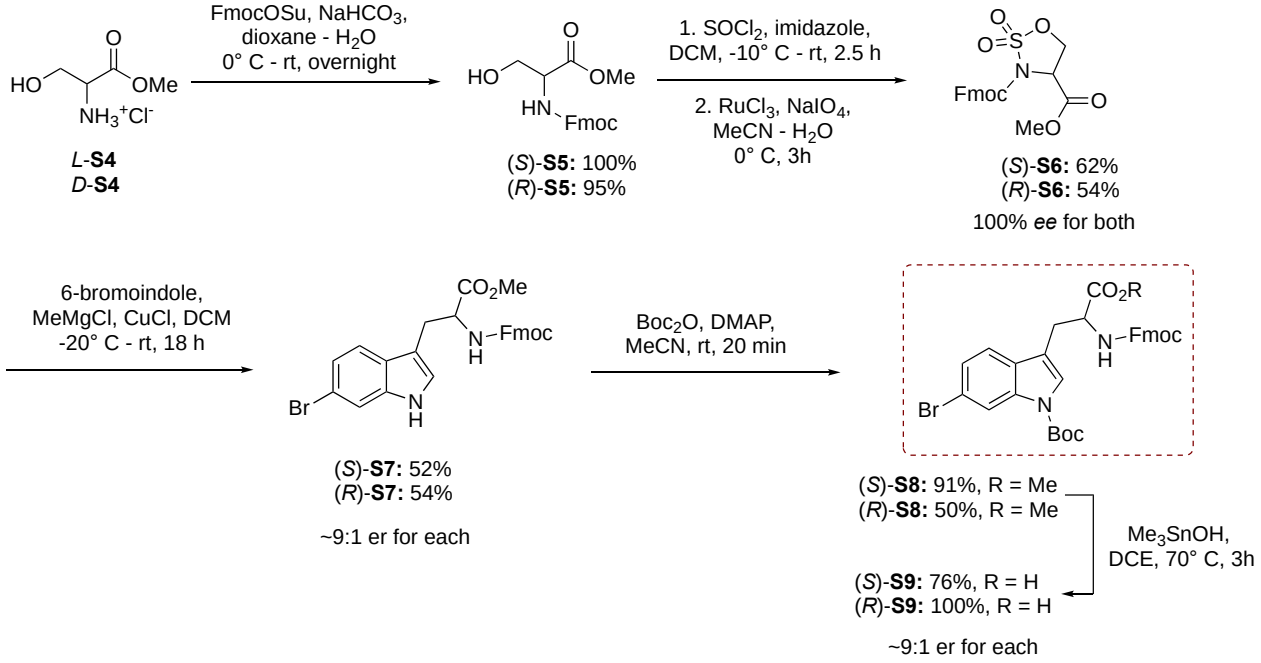


S3

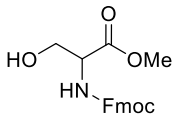
N-Fmoc protection of starting H-Tbt-OH **S2** (method A) gave, following purification by FCC (10% EtOAc–toluene + 1% AcOH), the desired compound **S3** as a white foam in 88% yield (625 mg).

[α]$_D^{25}$ -2.2° (*c* 0.5, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$, 2.7:1 rotamer ratio) δ 8.02 (br s, 1H, major rotamer), 7.92 (br s, 1H, minor rotamer), 7.74 (d, *J* = 7.6 Hz, 2H, major rotamer), 7.68 (br s, 2H, minor rotamer), 7.61 – 7.14 (m, 8H, overlapped with solvent peak), 5.39 (d, *J* = 6.8 Hz, 1H), 4.82 – 4.75 (m, 1H, minor rotamer), 4.75 – 4.62 (m, 1H, major rotamer), 4.38 – 3.74 (m, 3H), 3.70 – 3.36 (m, 2H), 1.57 – 1.34 (m, 27H, contains 1.55 (br s, 18H, 2×$(CH_3)_3$C-, major rotamers) and 1.42 (s, 9H)); **^{13}C NMR** (151 MHz, $CDCl_3$, 3:1 rotamer ratio, minor rotamer is denoted by asterisk) δ 177.5, 176.9*, 156.8*, 156.2, 144.6*, 144.0, 143.9, 143.3*, 143.0, 142.8, 142.7*, 142.5*, 141.3 (×2), 141.1* (×2), 132.2, 132.1*, 130.5*, 130.4, 130.0, 129.7*, 127.7 (×2), 127.6* (×2), 127.2, 127.1, 125.4, 125.2, 125.0*, 120.0 (×2), 119.9* (×2), 117.1, 117.0*, 112.2*, 111.8, 105.9*, 104.1, 67.8*, 67.3, 56.5*, 55.4, 47.2, 46.7*, 35.0, 34.9, 34.7*, 33.2, 33.1*, 32.2 (×3), 31.0 (×3), 30.8 (×3), 30.5* (×4), 27.8; **LCMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{38}H_{47}N_2O_4$ 595.4, found 595.4; $[M-H]^-$ calcd for $C_{38}H_{45}N_2O_4$ 593.3, found 593.3.

6-Bromotryptophans



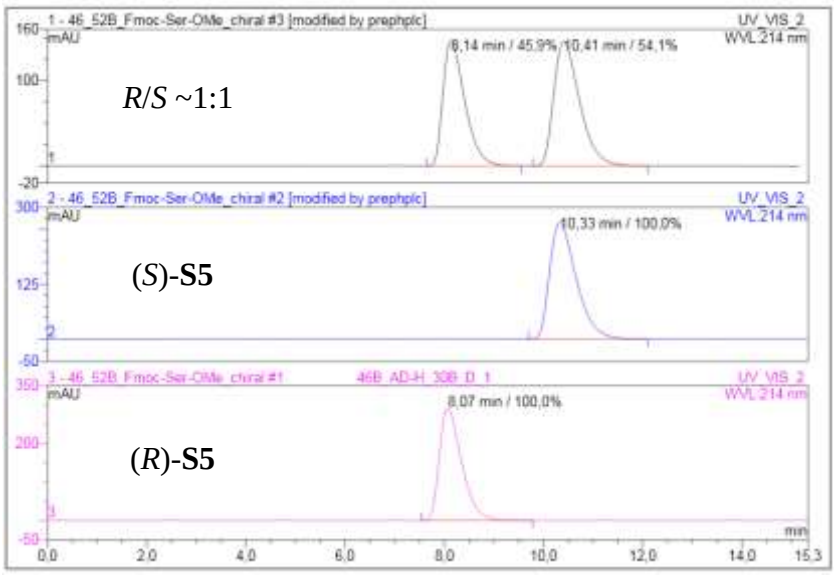
Methyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-serinate ((*S*)-S5)



(*S*)-**S5** & (*R*)-**S5**

N-Fmoc protection of *L*-serine methyl ester hydrochloride *L*-**S4** (method A) gave, following purification by FCC (50% EtOAc–Hept), the desired compound (*S*)-**S5** as a white crystalline solid in 95% yield (2.26 g).

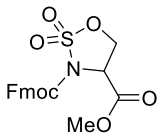
[α]$_D^{25}$ +6.4° (*c* 0.5, $CHCl_3$); **chiral HPLC** (AD-H) t_R= 10.33 min, 100% *ee*; **^{1}H NMR** (600 MHz, $CDCl_3$, 9.8:1 rotamer ratio, chemical shifts are reported for major rotamer) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 6.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 2H), 5.77 (d, *J* = 7.7 Hz, 1H), 4.61 – 4.37 (m, 3H), 4.23 (t, *J* = 6.9 Hz, 1H), 4.05 – 3.87 (m, 2H), 3.79 (s, 3H), 2.43 – 2.29 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$, >10:1 rotamer ratio, chemical shifts are reported for major rotamer) δ 171.1, 156.4, 143.9, 143.8, 141.5, 141.4, 127.9 (×2), 127.23, 127.20, 125.2 (×2), 120.15, 120.13, 67.3, 63.4, 56.1, 52.9, 47.3; **LCMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{20}NO_5$ 342.1, found 342.3.



Enantiomer (*R*)-**S5** was synthesized from *D*-**S4** according to the procedure described above for (*S*)-**S5** as a white crystalline solid in 100% yield (2.04 g). **[α]$_D^{25}$** -6.6° (*c* 0.5, $CHCl_3$); **chiral HPLC** (AD-H) t_R= 8.07 min, 100% *ee*.

The analytical data are consistent with those reported in the literature.[7, 8]

3-((9*H*-Fluoren-9-yl)methyl) 4-methyl (*S*)-1,2,3-oxathiazolidine-3,4-dicarboxylate 2,2-dioxide ((*S*)-S6)

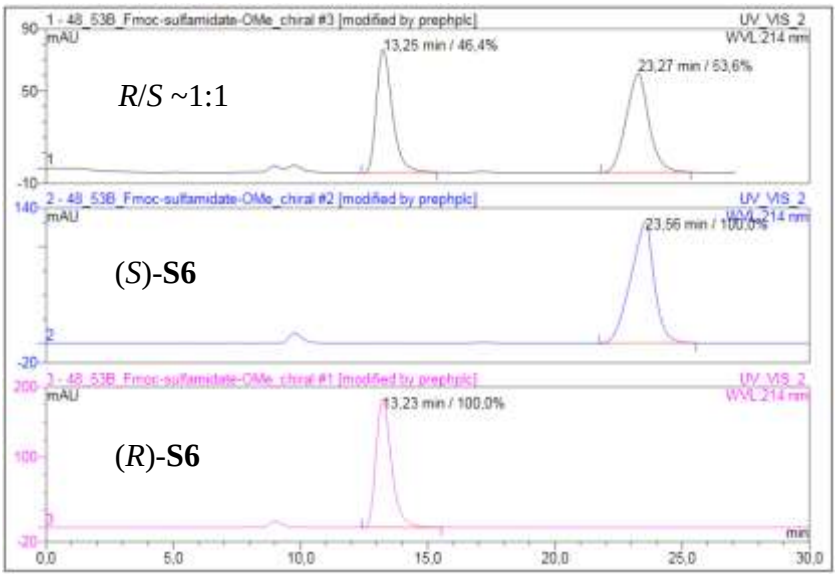


(*S*)-**S6** & (*R*)-**S6**

Based on the previously reported procedure[9], a solution of $SOCl_2$ (788 µL, 10.8 mmol) in dry DCM (9.6 mL) was added dropwise within 10 min to the argon-flushed reaction flask charged with imidazole (2.53 g, 37.2 mmol) in 24 mL DCM at 0 °C. The cooling bath was removed, and the reaction mixture was stirred for 1 h at room temperature, then cooled to -10 °C. Over 30 min, a solution of methyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-serinate (*S*)-**S5** (2.05 g, 6.00 mmol) in 24 mL of dry DCM was added dropwise. The mixture was then quickly warmed to room temperature, stirred for 2 h and quenched by the dropwise addition of water (45 mL). After 10 min of stirring, the organic phase was separated, sequentially washed with 2M citric acid, water, brine (45 mL of each) and dried over Na_2SO_4. The solvent was removed under reduced pressure, providing an intermediate cyclic sulfamidite (2.34 g) as a colourless oil, which was subjected to the next step without additional purification.

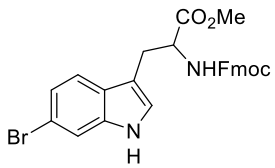
The residue from above was dissolved in acetonitrile (24 mL). The reaction flask equipped with a stirring bar was placed in an ice-water bath, and $RuCl_3 \cdot xH_2O$ (31.4 mg), $NaIO_4$ (2.05 g, 9.60 mmol) and water (24 mL) were added. The mixture was stirred for 3 h at approx. +4 °C, then Et_2O (30 mL) was added, and the layers were separated. The aqueous phase was extracted with diethyl ether (2×30 mL); the combined organic phases were washed with saturated $NaHCO_{3aq}$, water, brine (30 mL of each) and dried over Na_2SO_4. Volatiles were removed by rotary evaporation. The residue was purified by column chromatography (Reveleris®, 0→50% EtOAc–Hept gradient) to afford 1.50 g (62% over 2 steps) of the desired compound (*S*)-**S6** as a white foam.

[α]$_D^{25}$ -21.4° (*c* 0.5, $CHCl_3$); **chiral HPLC** (AD-H) t_R= 23.56 min, 100% *ee*; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.71 (br s, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.35 (tdd, *J* = 7.5, 2.6, 1.1 Hz, 2H), 5.03 – 4.69 (m, 3H), 4.62 (dd, *J* = 10.4, 7.3 Hz, 1H), 4.58 – 4.47 (m, 1H), 4.36 (t, *J* = 7.3 Hz, 1H), 3.85 (br s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.2, 149.6, 143.0 (×2), 141.5, 141.4, 128.22, 128.20, 127.5 (×2), 125.5 (×2, br), 120.21, 120.20, 70.8 (br), 68.2, 57.9, 54.0, 46.6; **LCMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{19}H_{16}NO_7S$ 402.1, found 402.4.



Enantiomer (*R*)-**S6** was synthesized from (*R*)-**S5** according to the procedure described above for (*S*)-**S6** as a white foam in 54% yield over 2 steps (865 mg). **[α]$_D^{25}$** +21.2° (*c* 0.5, $CHCl_3$); **chiral HPLC** (AD-H) t_R= 13.23 min, 100% *ee*.

Methyl (S)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-bromo-1*H*-indol-3-yl)propanoate ((*S*)-S7)

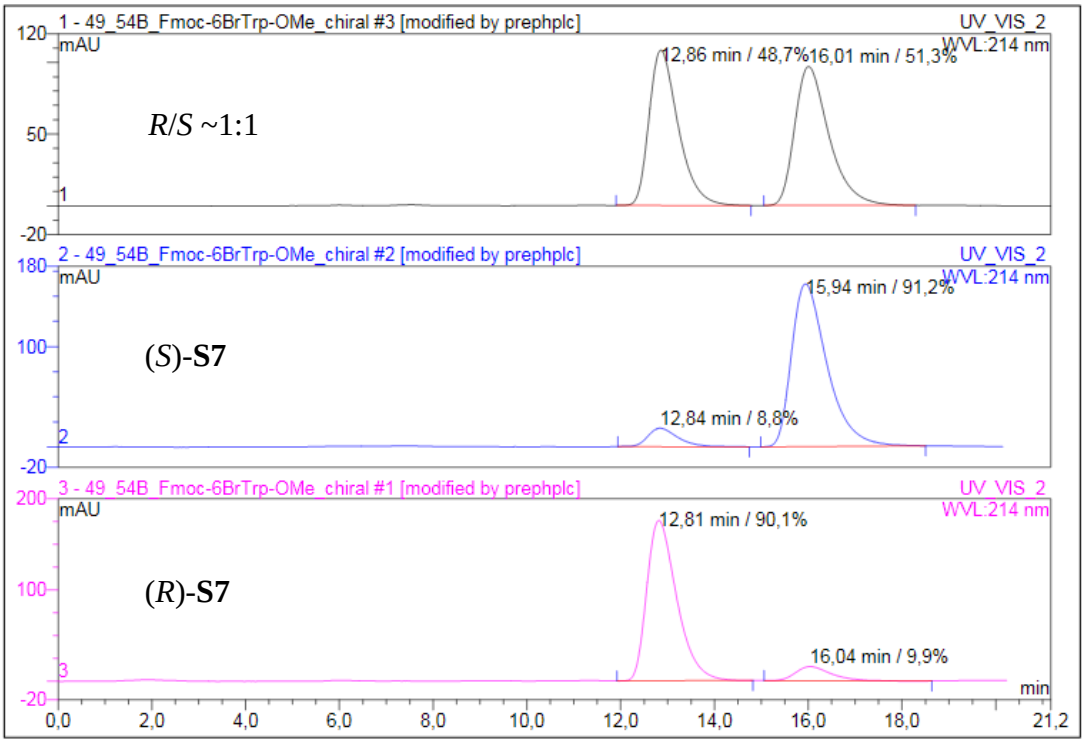


(*S*)-**S7** & (*R*)-**S7**

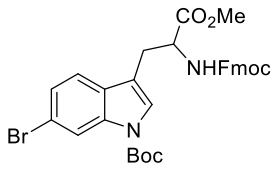
According to the reported procedure[10], a solution of MeMgCl (1.48 mL, 4.45 mmol, 3M in THF) was added dropwise over 10 min to a suspension of 6-bromoindole (1.01 g, 5.13 mmol) and fresh CuCl (440 mg, 4.45 mmol) in dry DCM (17.1 mL) at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 1 h and cooled to -20 °C. A solution of cyclic sulfamidate (*S*)-**S6** (1.38 g, 3.42 mmol) in DCM (6.9 mL) was added to the reaction mixture over 20 min dropwise at -20 °C. The reaction was allowed to warm to room temperature and stirred for 18 h, then diluted with DCM (35 mL). Citric acid (35 mL, 2M in H_2O) was added dropwise at 0 °C and stirring was continued at room temperature for 30 min. The phases were separated. The aqueous phase was extracted with DCM (2×35 mL). The combined organic phases were filtered through a pad of Na_2SO_4 with Celite® on top, and the filtrate was concentrated under reduced pressure. The solid residue was further purified by column chromatography on SiO_2 (Reveleris®, 0→40% EtOAc–Hept gradient) providing 919 mg (52%) of (*S*)-**S7** as a beige crystalline solid.

Chiral HPLC (AD-H) t_R= 15.94 min, 82% *ee*; **LCMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{27}H_{24}{}^{79}BrN_2O_4$ 519.1, found 519.2.

Enantiomer (*R*)-**S7** was synthesized from (*R*)-**S6** according to the procedure described above for (*S*)-**S7** as a beige crystalline solid in 54% yield (539 mg). C**hiral HPLC** (AD-H) t_R= 12.81 min, 80% *ee*.



***tert*-Butyl (*S*)-3-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl)-6-bromo-1*H*-indole-1-carboxylate ((*S*)-S8)**

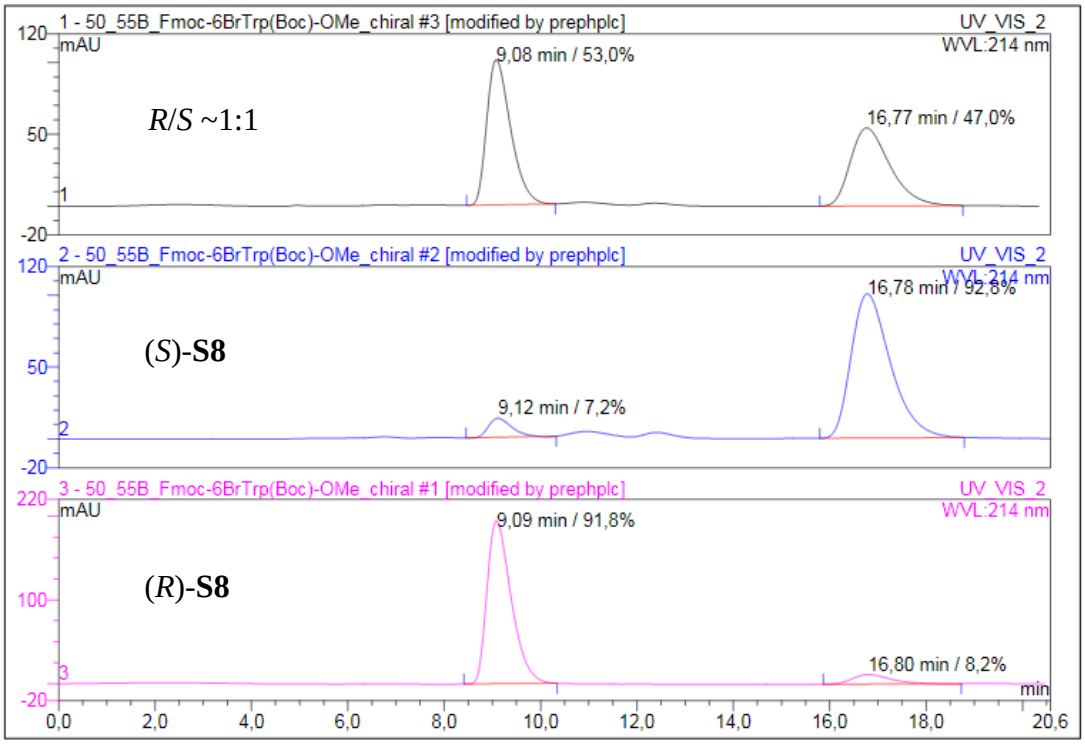


(*S*)-**S8** & (*R*)-**S8**

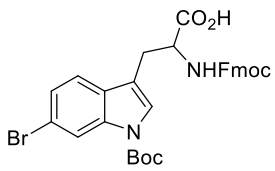
Di-*tert*-butyl dicarbonate (424 mg, 1.94 mmol) and DMAP (21.6 mg, 177 µmol) were added to a suspension of starting indole (*S*)-**S7** (917 mg, 1.77 mmol) in MeCN (17.7 mL) at room temperature. The reaction mixture was stirred for 20 min (suspension gradually turns into clear yellow solution), then concentrated, redissolved in Et_2O (70 mL) and transferred to separatory funnel. The solution was successively washed with 2M citric acid, sat. $NaHCO_{3aq}$, water and brine (35 mL of each), then dried over Na_2SO_4 and concentrated to dryness. The further purification by column chromatography on SiO_2 (Reveleris®, 0→20% EtOAc–Hept gradient) gave N_1-Boc protected indole derivative (*S*)-**S8** (541 mg, 50%) as a white foam.

Chiral HPLC (AD-H) t_R= 16.78 min, 86% *ee*; **^{1}H NMR** (600 MHz, $CDCl_3$, ~9:1 rotamer ratio, chemical shifts are reported for major rotamer) δ 8.33 (br s, 1H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.55 (dd, *J* = 12.9, 7.5 Hz, 2H), 7.43 – 7.37 (m, 3H), 7.34 – 7.28 (m, 4H), 5.39 (d, *J* = 8.1 Hz, 1H), 4.74 (dd, *J* = 9.0, 4.6 Hz, 1H), 4.45 – 4.36 (m, 2H), 4.21 (t, *J* = 7.2 Hz, 1H), 3.71 (s, 3H), 3.29 – 3.17 (m, 2H), 1.65 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$, ~10:1 rotamer ratio, chemical shifts are reported for major rotamer) δ 172.0, 155.8, 149.2, 143.9, 143.8, 141.4 (×2), 136.2 (br), 129.5 (br), 127.9 (×2), 127.24, 127.22, 126.1, 125.2 (×2), 124.7, 120.14 (×2), 120.07, 118.7, 118.5, 114.9, 84.5, 67.3, 54.2, 52.7, 47.3, 28.3 (×3), 28.0; **LCMS** (ESI) *m/z*: $[M\text{-Boc+H}]^+$ calcd for $C_{27}H_{24}{}^{79}BrN_2O_4$ 519.1, found 519.1.

Enantiomer (*R*)-**S8** was synthesized from (*R*)-**S7** according to the procedure described above for (*S*)-**S8** as white foam in 91% yield (588 mg). **Chiral HPLC** (AD-H) t_R= 9.09 min, 84% *ee*.



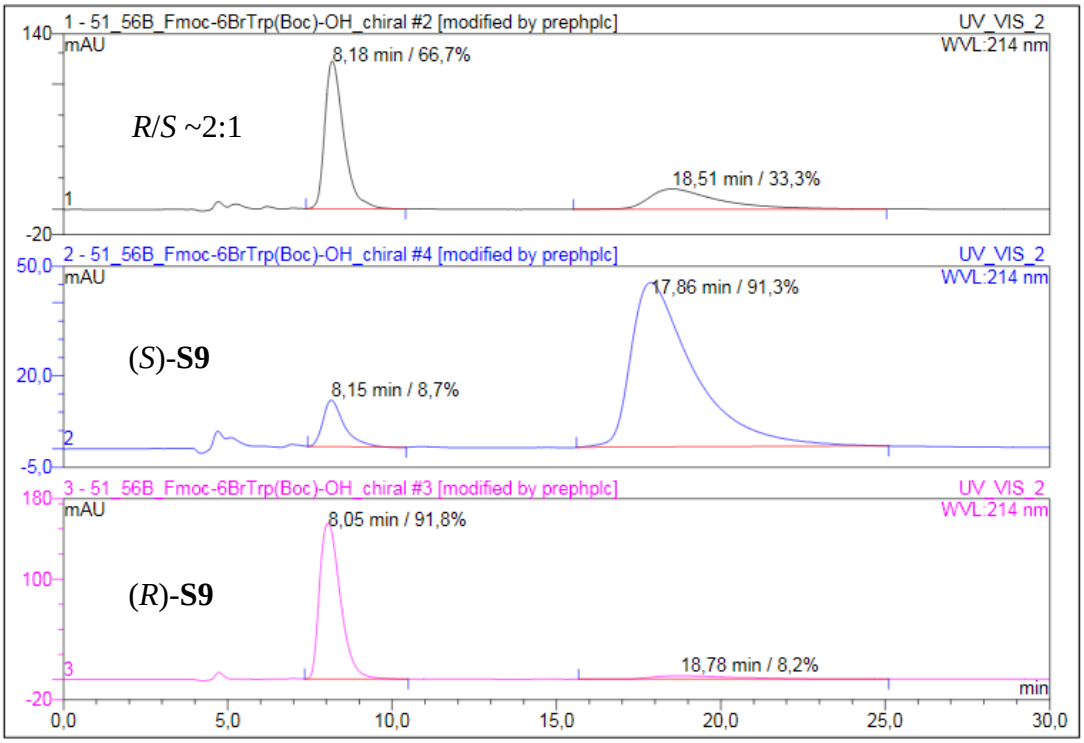
(*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-bromo-1-(tert-butoxycarbonyl)-1*H*-indol-3-yl)propanoic acid ((*S*)-S9)



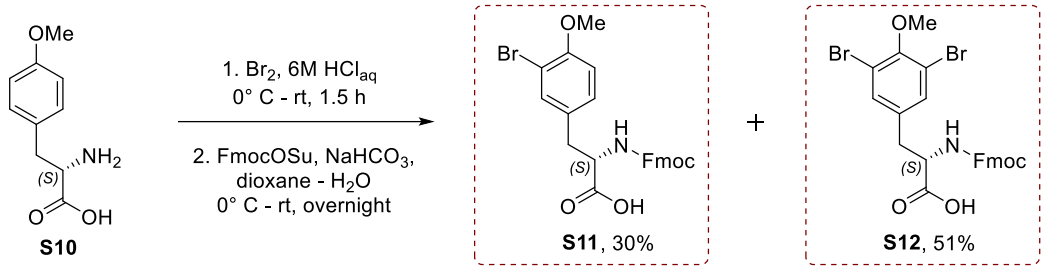
(*S*)-**S9** & (*R*)-**S9**

Following the procedure from Nicolaou et al.[11], Me_3SnOH (628 mg, 3.47 mmol) was added to a solution methyl ester (*S*)-**S8** (538 mg, 0.868 mmol) in 1,2-dichloroethane (8.7 mL). The resulting mixture was heated at 70 °C for 3 h (reaction progress was monitored by TLC), then concentrated under reduced pressure and redissolved in EtOAc (40 mL). The organic layer was washed with 2M citric acid (3×20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by FCC on SiO_2 (10%, then 15% EtOAc–toluene + 1% AcOH), providing 400 mg (76%) of the desired carboxylic acid (*S*)-**S9** as a white foam. **Chiral HPLC** (Chiralpak® OD-H column (4.6 × 250 mm, 5 µm, Daicel; *i*PrOH-Hept-TFA 30:70:0.1 v/v/v% isocratic, 0.9 mL/min) t_R= 17.86 min, 82% *e* ; **^{1}H NMR** (600 MHz, $CDCl_3$, 3.8:1 rotamer ratio) δ 8.30 (br s, 1H), 7.77 – 7.67 (m, 2H, contains 7.75 (d, *J* = 7.0 Hz, 2H, major rotamer) and 7.71 (br s, 2H, minor rotamer), 7.56 – 7.43 (m, 3H), 7.42 – 7.20 (m, 6H, overlapped with solvent peak), 6.07 (br s, 1H, minor rotamer), 5.40 (d, *J* = 8.0 Hz, 1H, major rotamer), 4.76 (dd, *J* = 6.8, 6.5 Hz, 1H, major rotamer), 4.50 – 4.33 (m, 3H, contains 4.38 (d, *J* = 7.2 Hz, 2H, major rotamer)), 4.19 (t, *J* = 7.2 Hz, 1H, major rotamer), 4.10 (br s, 1H, minor rotamer), 3.31 (dd, *J* = 15.1, 5.4 Hz, 1H, major rotamer), 3.21 (dd, *J* = 15.0, 6.3s Hz, 1H, major rotamer), 3.07 – 2.87 (m, 2H, minor rotamer), 1.63 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$, ~5:1 rotamer ratio, chemical shifts are reported for major rotamer) δ 175.6, 156.1, 149.4, 143.8, 143.7, 141.4 (×2), 136.1 (br), 129.5 (br), 127.9 (×2), 127.2 (×2), 126.1, 125.2 (×2), 124.8, 120.1 (×3), 118.8, 118.6, 114.9, 84.7, 67.5, 54.0, 47.2, 28.2 (×3), 27.7; **LCMS** (ESI) *m/z*: $[M\text{-Boc+H}]^+$ calcd for $C_{26}H_{22}{}^{79}BrN_2O_4$ 505.1, found 505.2; $[M\text{-H}]^-$ calcd for $C_{31}H_{28}{}^{79}BrN_2O_6$ 603.1, found 603.2.

Enantiomer (*R*)-**S9** was synthesized from (*R*)-**S8** according to the procedure described above for (*S*)-**S9** as colorless amorphous solid in 100% yield (247 mg). **Chiral HPLC** (Chiralpak® OD-H column (4.6 × 250 mm, 5 µm, Daicel; *i*PrOH-Hept-TFA 30:70:0.1 v/v/v% isocratic, 0.9 mL/min) t_R= 8.05 min, 84% *ee*.



Brominated *O*-methyltyrosines and *O*-methyltyramines



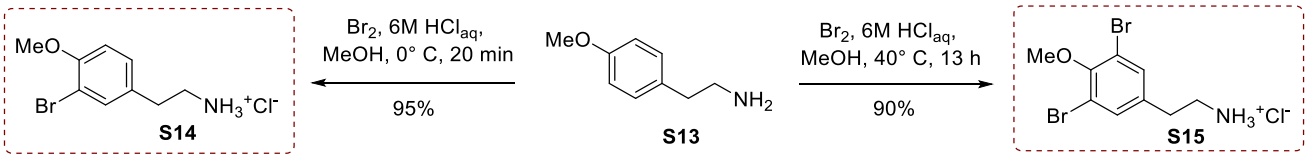
Mono- and dibrominated *N*-Fmoc-*O*-methyl-*L*-tyrosines (S11 & S12)

Bromination (step 1)[12]. *O*-Methyl-*L*-tyrosine **S10** (781 mg, 4.0 mmol) was dissolved in 6M HCl_{aq} (16 mL) and cooled to 0 °C before bromine (799 μL, 16.0 mmol) was added. The reaction was run for 30 min at 0 °C, then the cooling bath was removed, and stirring was for continued for 1 h at room temperature. The excess of Br_2 was purged away with a stream of nitrogen gas. The remaining volatiles were removed under reduced pressure. A crude mixture of bromination products was co-evaporated with toluene and used directly in the next step.

N-Fmoc protection (step 2) of mono- and dibrominated derivatives from the previous step was carried out according to method A. Purification by column chromatography (20%, then 40% EtOAc–toluene + 1% AcOH) afforded a mixture of **S11** & **S12** as a pale yellow foam (2.12 g), which was further separated by prepHPLC (50→100 solvent B gradient over 15 min) in the following order of elution:

1. (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(3-bromo-4-methoxyphenyl)propanoic acid **S11** as a white crystalline solid. Yield 30% (596 mg) over 2 steps. **$[\alpha]_D^{25}$** +26.6° (*c* 0.5, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$, 4.8:1 rotamer ratio) δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.60 – 7.47 (m, 2H), 7.43 – 7.14 (m, 5H, overlapped with solvent peak), 7.05 (d, *J* = 8.0 Hz, 1H, major rotamer), 6.90 (br s, 1H, minor rotamer), 6.80 (d, *J* = 8.3 Hz, 1H, major rotamer), 6.75 (br s, 1H, minor rotamer), 5.66 (br s, 1H, minor rotamer), 5.22 (d, *J* = 8.1 Hz, 1H, major rotamer), 4.72 – 4.41 (m, 2H), 4.41 – 4.14 (m, 2H), 3.85 (s, 3H), 3.21 – 2.97 (m, 2H, major rotamer), 2.87 – 2.66 (m, 2H, minor rotamer); **^{13}C NMR** (151 MHz, $CDCl_3$, 7:1 rotamer ratio, chemical shifts are reported for major rotamer) δ 175.1, 155.9, 155.3, 143.9, 143.8, 141.5 (×2), 134.2, 129.5, 129.2, 127.9 (×2), 127.3 (×2), 125.3, 125.2, 120.2 (×2), 112.2, 111.9, 67.4, 56.4, 54.7, 47.3, 36.7; **LCMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{25}H_{21}{}^{79}BrNO_5$ 494.1, found 494.1.

2. (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(3,5-dibromo-4-methoxyphenyl)propanoic acid **S12** as a white crystalline solid. Yield 54% (1.17 g) over 2 steps. **$[\alpha]_D^{25}$** +29.6° (*c* 0.5, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$, 3:1 rotamer ratio) δ 7.83 – 7.69 (m, 2H), 7.61 – 7.46 (m, 2H), 7.44 – 7.06 (m, 6H, overlapped with solvent peak), 6.21 (br s, 1H, minor rotamer), 5.32 (d, *J* = 8.0 Hz, 1H, major rotamer), 4.72 – 4.57 (m, 1H), 4.56 – 4.41 (m, 1H), 4.40 – 4.08 (m, 2H), 3.84 (s, 3H), 3.20 – 2.91 (m, 2H, major rotamer), 2.75 – 2.57 (m, 2H, minor rotamer); **^{13}C NMR** (151 MHz, $CDCl_3$, 5:1 rotamer ratio, minor rotamer is denoted by asterisk) δ 174.8, 174.2*, 156.5*, 155.9, 153.5, 153.4*, 143.8, 143.7, 143.5* (×2), 141.5 (×2), 134.6, 134.5*, 133.6 (×2), 128.1* (×2), 127.9 (×2), 127.4* (×2), 127.3 (×2), 125.2, 125.1, 124.8*, 124.6*, 120.2 (×2), 118.4 (×2), 118.2* (×2), 67.5, 60.8, 55.1*, 54.5, 47.3, 36.9*, 36.7, 36.4; **LCMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{25}H_{20}{}^{79}Br_2NO_5$ 572.0, found 572.2.



2-(3-Bromo-4-methoxyphenyl)ethan-1-aminium chloride (S14)

A solution of *O*-methyltyramine **S13** (294 µL, 2.0 mmol, 1 equiv) in 2 mL MeOH was slowly treated with 6M HCl_{aq} (8 mL) at 0 °C. Bromine (200 µL, 4.0 mmol, 2 equiv) was added to the resulting white suspension, and the reaction mixture was stirred 20 min at the same temperature (reaction progress was monitored by UPLC-MS). The excess of Br_2 was removed by blowing the stream of nitrogen gas through reaction vessel. The reaction mixture was concentrated in vacuo followed by co-evaporation with toluene. The crude residue was purified by prepHPLC (0→100 solvent B gradient over 15 min). Fractions containing product were concentrated in vacuo and co-evaporated with 1M HCl_{aq} (2×15 mL), affording 505 mg (95%) of monobrominated derivative **S14** in the form of hydrochloride salt as a white crystalline solid.

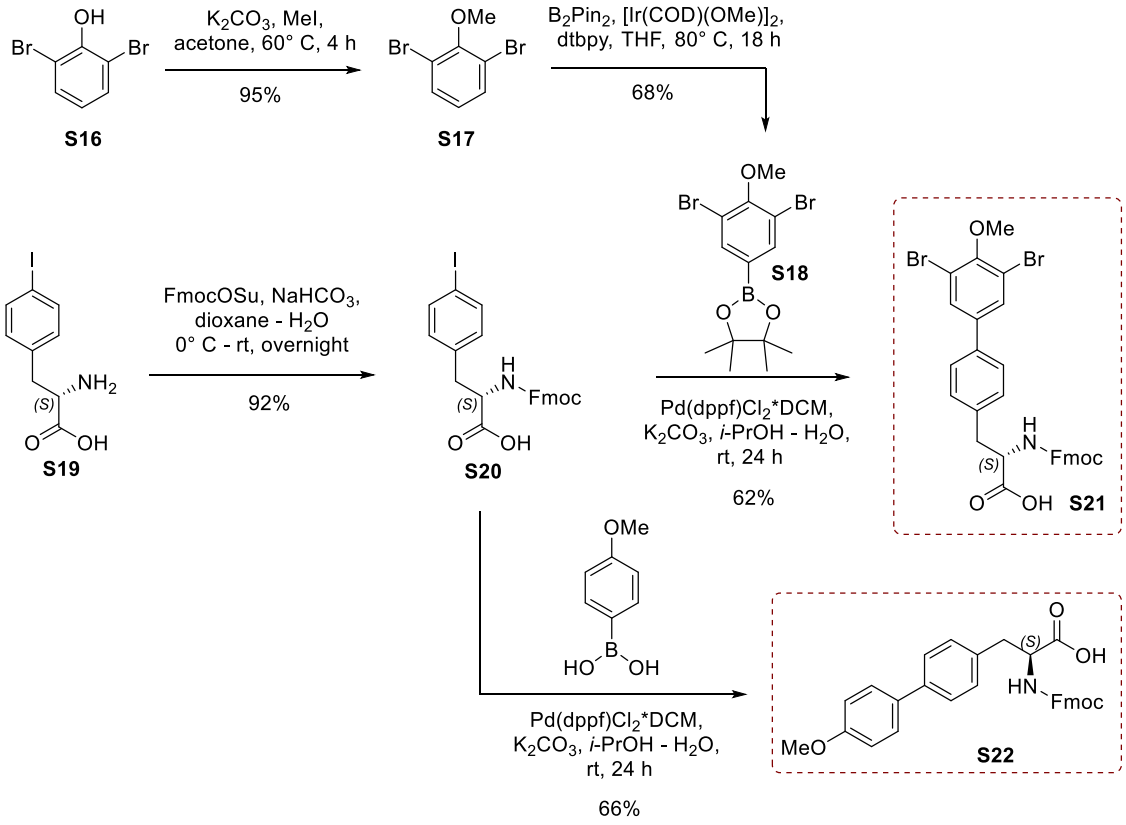
^{1}H NMR (600 MHz, CD_3OD) δ 7.49 (d, *J* = 2.1 Hz, 1H), 7.24 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 3.86 (s, 3H), 3.14 (t, *J* = 7.7 Hz, 2H), 2.90 (t, *J* = 7.8 Hz, 2H); **^{13}C NMR** (151 MHz, CD_3OD) δ 156.7, 134.5, 131.4, 130.2, 113.7, 112.8, 56.8, 41.9, 33.2; **LCMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_9H_{13}{}^{79}BrNO$ 230.1, found 230.1.

2-(3,5-Dibromo-4-methoxyphenyl)ethan-1-aminium chloride (S15)

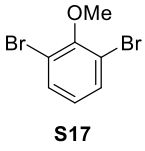
The title compound was synthesized according to the procedure described above for 3-bromo-*O*-methyltyramine hydrochloride **S14** with the following modifications: after adding Br_2 (4 equiv) at 0 °C, a cooling bath was removed, and reaction mixture was stirred for 1 h at room temperature, then heated for 13 h (overnight) at 40 °C. Purification by prepHPLC followed by co-evaporation with 1M HCl_{aq} gave **S15** as a pale beige solid (in the form of hydrochloride salt). Yield 90% (1.11 g).

^{1}H NMR (600 MHz, CD_3OD) δ 7.55 (s, 2H), 3.84 (s, 3H), 3.17 (t, *J* = 7.7 Hz, 2H), 2.92 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (151 MHz, CD_3OD) δ 154.7, 137.2, 134.4 (×2), 119.3 (×2), 61.1, 41.5, 33.1; **LCMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_9H_{12}{}^{79}Br_2NO$ 307.9, found 308.1.

3-(4-Biphenylyl)-*L*-alanine derivatives



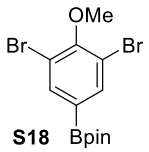
1,3-Dibromo-2-methoxybenzene (S17)



Based on the previously reported procedure[13], anhydrous K_2CO_3 (1.63 g, 11.8 mmol) was added to a stirred solution of 2,6-dibromophenol **S16** (1.98 g, 7.85 mmol) in dry acetone (52 mL), and the mixture was stirred at room temperature for 30 min. Iodomethane (0.782 mL, 12.6 mmol) was then added, and the mixture was heated at 60 °C for 3 h. After being cooled to room temperature, the mixture was filtered; the filtrate was evaporated under reduced pressure. The residue was partitioned between heptane (30 mL) and H_2O (30 mL). The aqueous layer was further extracted with heptane (2×30 mL). The combined organic phases were washed with brine (30 mL) and dried over Na_2SO_4. The volatiles were removed by rotary evaporation, providing 1.99 g (95%) of **S17** as a colorless oil. The product was used directly in the next step without additional purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 2H), 6.86 (t, *J* = 8.0 Hz, 1H), 3.90 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 154.4, 132.9 (×2), 126.5, 118.5 (×2), 60.7. The spectral data are consistent with those reported in the literature.[14]

2-(3,5-Dibromo-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S18)

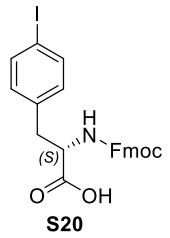


Based on the previously reported procedures[15, 16], a microwave vial charged with a mixture of 1,3-dibromo-2-methoxybenzene (1.33 g, 5.0 mmol), bis(pinacolato)diboron (0.889 g, 3.50 mmol), 4,4'-di-*tert*-butyl-2,2'-dipyridyl (26.8 mg, 100 µmol), $[Ir(COD)(OMe)]_2$ (33.1 mg, 50 µmol) in degassed anhydrous THF (7.5 mL) was purged with argon, sealed and stirred at 80 °C for 18 h. The reaction mixture was cooled to

room temperature and concentrated under reduced pressure. The residue was purified by FCC (toluene) to afford 1.33 g (68%) of **S18** as a colorless oil, crystallizing upon standing.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (s, 2H), 3.90 (s, 3H), 1.33 (s, 12H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.6, 139.1 (×2), 128.3 (br), 118.3 (×2), 84.6 (×2), 60.8, 25.0 (×4). The spectral data are consistent with those reported in the literature.[16]

(*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-iodophenyl)propanoic acid (S20)

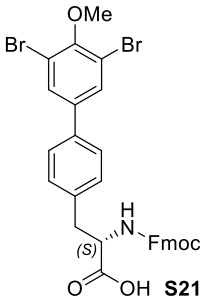


S20

N-Fmoc protection of starting 4-iodo-*L*-phenylalanine **S19** (method A) gave, following purification by FCC (0→5% MeOH–DCM gradient + 1% AcOH), the desired compound **S20** as a white crystalline solid in 92% yield (1.41 g).

[α]$_D^{25}$ +45.2° (*c* 0.5, $CHCl_3$); **^{1}H NMR** (600 MHz, DMSO-d_6, 7.9:1 rotamer ratio, chemical shifts are reported for major rotamer) δ 12.79 (br s, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.76 – 7.45 (m, 5H, contains 7.72 (d, *J* = 8.5 Hz, 1H)), 7.45 – 7.38 (m, 2H), 7.34 – 7.26 (m, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 4.25 – 4.12 (m, 4H), 3.05 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.83 (dd, *J* = 13.8, 10.6 Hz, 1H); **^{13}C NMR** (151 MHz, DMSO-d_6, 8.5:1 rotamer ratio, chemical shifts are reported for major rotamer) δ 173.1, 155.9, 143.8, 143.7, 140.69, 140.67, 137.8, 136.9 (×2), 131.6 (×2), 127.6 (×2), 127.0 (×2), 125.23, 125.18, 120.1 (×2), 92.3, 65.6, 55.2, 46.6, 35.9; **LCMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{21}INO_4$ 514.1, found 514.4; $[M-H]^-$ calcd for $C_{24}H_{19}INO_4$ 512.0, found 512.4. The analytical data are consistent with those reported in the literature.[17-19]

(*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(3',5'-dibromo-4'-methoxy-[1,1'-biphenyl]-4-yl)propanoic acid (S21)



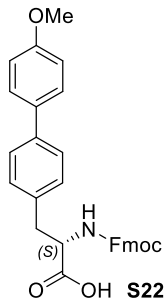
S21

Suzuki-Miyaura cross-coupling of Fmoc-protected 4-iodo-*L*-phenylalanine **S20** with pinacol boronate **S18** (method B) gave, following separation by FCC (1% MeOH–DCM + 1% AcOH) 685 mg of crude **S21** as a brown solid. The further purification by prepHPLC (70→100 solvent B gradient over 15 min) yielded in 403 mg (62%) of the title compound as a pale beige crystalline solid.

[α]$_D^{25}$ +14.4° (*c* 0.5, $CHCl_3$); **^{1}H NMR** (600 MHz, DMSO-d_6, 8.9:1 rotamer ratio, chemical shifts are reported for major rotamer) δ 12.79 (br s, 1H), 7.93 – 7.83 (m, 4H, contains 7.87 (d, *J* = 7.5 Hz, 2H)), 7.76 (d, *J* = 8.6 Hz, 1H), 7.64 (t, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 7.9 Hz, 2H), 7.43 – 7.34 (m, 4H), 7.33 – 7.25 (m, 2H), 4.27 – 4.10 (m, 4H), 3.82 (s, 3H), 3.14 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.91 (dd, *J* = 13.8, 10.8 Hz, 1H); **^{13}C NMR** (151 MHz, DMSO-d_6, 10:1 rotamer ratio, chemical shifts are reported for major rotamer) δ 173.2, 156.0, 152.6, 143.74, 143.70, 140.7, 140.6, 139.0, 138.3, 134.8, 130.5 (×2), 129.8 (×2), 127.6, 127.6, 127.0 (×2), 126.6 (×2), 125.3, 125.2, 120.1 (×2), 118.0 (×2), 65.6, 60.5, 55.3, 46.5, 36.1; **LCMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{31}H_{24}{}^{79}Br_2NO_5$ 648.0, found 648.2.

(*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4'-methoxy-[1,1'-biphenyl]-4-yl)propanoic acid (S22)

Suzuki-Miyaura cross-coupling of Fmoc-protected 4-iodo-*L*-phenylalanine **S20** with 4-methoxyphenylboronic acid (method B) gave, following separation by FCC (1% MeOH–DCM, then 1% MeOH–DCM + 1% AcOH) 442 mg of product **S22** and starting iodide mixture (5.5:1 molar ratio

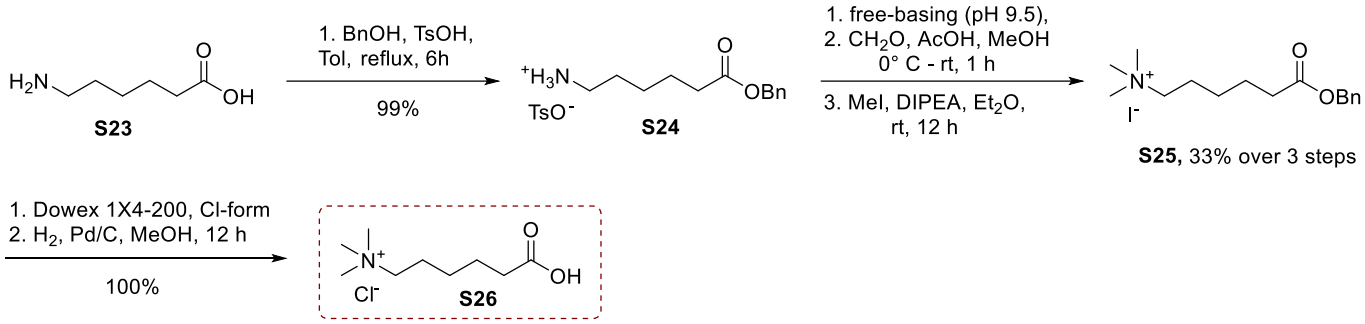


S22

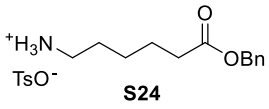
by ^{1}H NMR). The mixture was triturated with EtOAc–Hept (1:2, 15 mL, sonication) and filtered; the precipitate was washed with heptane (2×5 mL) and dried in vacuo, providing 327 mg (66%) of the title compound as a pink crystalline solid.

[α]$_D^{25}$ +26.4° (*c* 0.5, $CHCl_3$);**^{1}H NMR** (600 MHz, DMSO-d_6, ~6.5:1 rotamer ratio, chemical shifts are reported for major rotamer) δ 12.77 (br s, 1H), 7.88 (d, *J* = 7.6 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.69 – 7.63 (d, *J* = 8.7 Hz, 2H), 7.55 (m, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.34 – 7.25 (m, 4H), 7.02 – 6.97 (m, 2H), 4.25 – 4.14 (m, 4H), 3.78 (s, 3H), 3.11 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.91 (dd, *J* = 13.8, 10.6 Hz, 1H); **^{13}C NMR** (151 MHz, DMSO-d_6, 9.5:1 rotamer ratio, chemical shifts are reported for major rotamer) δ 173.3, 158.7, 156.0, 143.7 (×2), 140.7 (×2), 137.9, 136.4, 132.3, 129.6 (×2), 127.59, 127.57, 127.5 (×2), 127.0 (×2), 125.9 (×2), 125.3, 125.2, 120.1 (×2), 114.3 (×2), 65.6, 55.5, 55.1, 46.6, 36.0; **LCMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{31}H_{28}NO_5$ 494.2, found 494.3; $[M-H]^-$ calcd for $C_{31}H_{26}NO_5$ 492.2, found 492.1. The analytical data are consistent with those reported in the literature.[2]

*N*ε,*N*ε,*N*ε-Trimethylaminohexanoic acid chloride



6-(Benzyloxy)-6-oxohexan-1-aminium *p*-toluenesulfonate (S24)

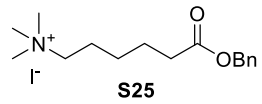


S24

Based on the previously reported procedure,[20] dry toluene (50 mL) was added to 100-mL round bottom flask charged with 6-aminohexanoic acid (2.62 g, 20.0 mmol), *p*-TsOH•H_2O (3.99 g, 21.0 mmol) and benzyl alcohol (7.25 mL, 70.0 mmol). The mixture was heated to reflux with Dean-Stark trap for 6 h while stirring, then cooled to ambient temperature and stirred overnight. The reaction mixture was diluted with Et_2O and filtered; the precipitate was collected and dried under reduced pressure, providing 7.76 g (99%) of **S24** as a white crystalline solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.68 (br s, 3H), 7.38 – 7.28 (m, 5H), 7.16 (d, *J* = 7.9 Hz, 2H), 5.08 (s, 2H), 2.78 – 2.70 (m, 2H), 2.32 (s, 3H), 2.21 (t, *J* = 7.5 Hz, 2H), 1.54 – 1.44 (m, 4H), 1.23 – 1.15 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.2, 141.3, 141.0, 136.2, 129.2 (×2), 128.7 (×2), 128.34, 128.31 (×2), 126.0 (×2), 66.3, 39.8, 34.0, 27.2, 25.9, 24.3, 21.4. **LCMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{20}NO_2$ 222.1, found 222.2. The analytical data are consistent with those reported in the literature.[20]

6-(Benzyloxy)-*N*,*N*,*N*-trimethyl-6-oxohexan-1-aminium iodide (S25)

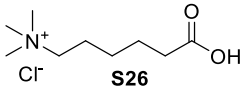


S25

N,*N*,*N*-trimethylation of **S24** was carried out according to method C. The resulting dry residue was triturated with EtOAc – Et_2O (3:1, 20 mL) under sonication to give 642 mg (33% over 3 steps) of the title product as a white crystalline solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 5H), 5.09 (s, 2H), 3.62 – 3.55 (m, 2H), 3.39 (s, 9H), 2.39 (t, *J* = 7.2 Hz, 2H), 1.81 – 1.74 (m, 2H), 1.74 – 1.68 (m, 2H), 1.47 – 1.40 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.1, 136.1, 128.7 (×2), 128.4, 128.3 (×2), 66.9, 66.4, 53.9 (×3), 33.8, 25.6, 24.3, 23.0. **LCMS** (ESI) *m/z*: $[M]^+$ calcd for $C_{16}H_{26}NO_2$ 264.2, found 264.3.

5-Carboxy-*N*,*N*,*N*-trimethylpentan-1-aminium chloride (S26)

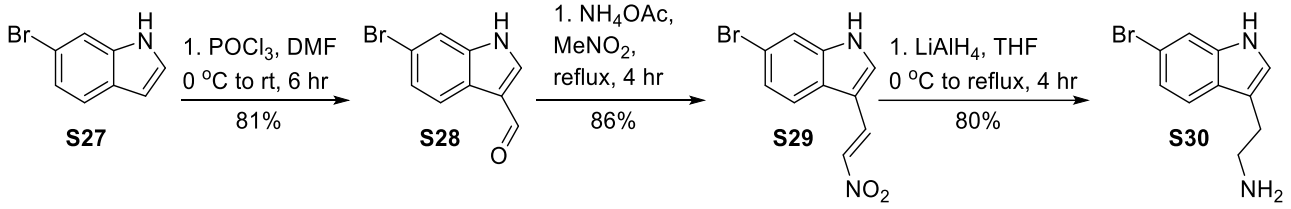


S26

The title compound was obtained from **S25** in two consecutive steps: anion exchange (method D), followed by hydrogenative debenzylation (method E) without additional purification. White crystalline solid; yield 100% (286 mg).

^{1}H NMR (600 MHz, CD_3OD) δ 3.38 – 3.33 (m, 2H), 3.14 (s, 9H), 2.32 (t, *J* = 7.3 Hz, 2H), 1.86 – 1.79 (m, 2H), 1.73 – 1.67 (m, 2H), 1.46 – 1.40 (m, 2H). **LCMS** (ESI) *m/z*: $[M]^+$ calcd for $C_9H_{20}NO_2$ 174.1, found 174.1. The spectral data are consistent with those reported in the literature.[21]

2-(6-bromo-1H-indol-3-yl)ethanamine



S27 **S28** **S29** **S30**

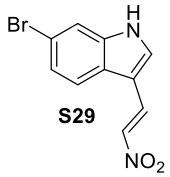
6-bromo-1H-indole-3-carbaldehyde (S28)

S28

To a solution of $POCl_3$ (4.47 g, 2.67 mL, 29.2 mmol) in dry DMF (17 mL) was slowly added a solution of 6-bromo-1H-indole **S31** (2.498 g, 12.7 mmol) in dry DMF (12 mL) at 0 °C under a nitrogen atmosphere. The mixture was warmed to room temperature and stirred until a thick yellow precipitate formed. After 6 hours, a solution of KOH (6.65 g) in distilled water (20 mL) was added. The mixture was diluted with sat. aq. $NaHCO_3$ solution, and extracted twice with ethyl acetate. The organic portions were combined and washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to afford the title compound as a brown crystalline solid (2.32 g, 81 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.77 (br s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.83-7.82 (m, 1H), 7.62 (d, *J* = 1.7 Hz, 1H), 7.43 (dd, *J* = 8.5, 1.7 Hz, 1H). **LCMS** (ESI) *m/z*: $[M+H]^+$ calcd for $C_9H_7NBrO^+$ 223.9, found 224.3. The spectral data are consistent with those reported in the literature.[22]

6-bromo-3-[(E)-2-nitrovinyl]-1H-indole (S29)

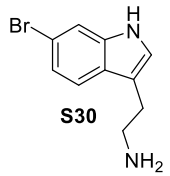


S29

To a solution of 6-bromo-1H-indole-3-carbaldehyde **S32** (0.593 g, 2.65 mmol) in nitromethane (12 mL) was added ammonium acetate (0.816 g, 10.6 mmol) at room temperature under a nitrogen atmosphere. The mixture was heated to reflux and monitored by TLC. After 4 hours, the mixture was cooled to room temperature, and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate and washed sequentially with distilled water, sat. aq. $NaHCO_3$ solution, and brine. The resulting solution was dried over sodium sulfate, and concentrated *in vacuo* to afford the title compound as an orange brown amorphous solid (0.605 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (br s, 1H), 8.25 (d, *J* = 13.5 Hz, 1H), 7.54 (d, *J* = 13.5 Hz, 1H), 7.66-7.64 (m, 3H), 7.44 (dd, *J* = 8.4, 1.8 Hz, 1H). **LCMS** (ESI) *m/z*: $[M-H]^-$ calcd for $C_{10}H_7N_2BrO_2^+$ 265.0, found 265.0. The spectral data are consistent with those reported in the literature.[22]

2-(6-bromo-1H-indol-3-yl)ethanamine (S30)

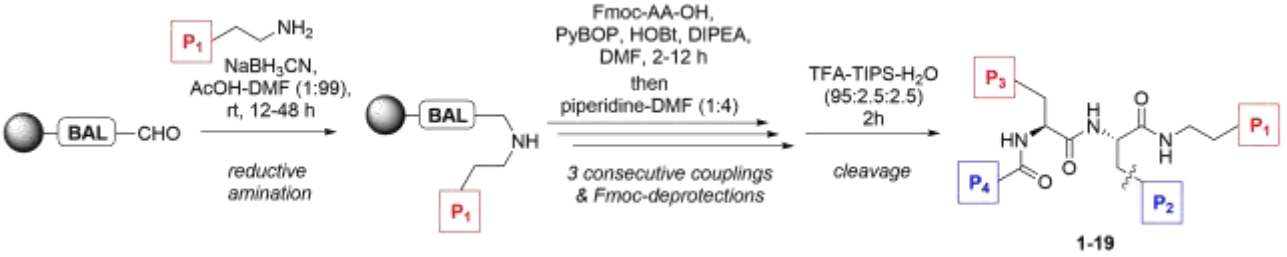


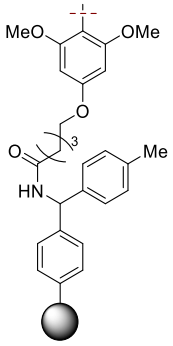
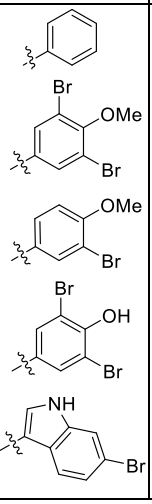
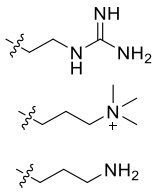
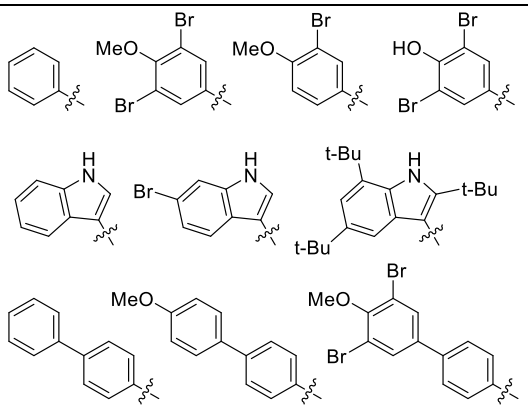
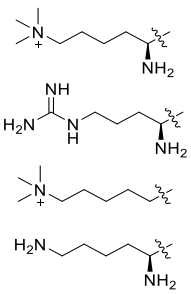
S30

To a stirred suspension of $LiAlH_4$ (0.855 g, 22.5 mmol), in dry THF (25 mL) was slowly added a solution of 6-bromo-3-[(E)-2-nitrovinyl]-1H-indole **S33** (1.003 g, 3.76 mmol) in dry THF (25 mL) at 0 °C under a nitrogen atmosphere. Once addition was complete, the mixture was heated to reflux and stirred for 4 hours. At completion, the mixture was cooled to 0 °C. Consecutively, 0.85 mL distilled water, then 0.85 mL 4 M aq. NaOH solution, then 2.55 mL distilled water were added dropwise. The mixture was stirred for 15 minutes, before being filtered. The filter cake was washed with 200 mL of diethyl ether. The resulting solution was separated, and the organic portion was washed with distilled water. The aqueous portions were combined and extracted twice with diethyl ether, before the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford the title compound as a yellow/brown semi solid (0.724 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.52 (d, *J* = 1.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.21 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.02-7.01 (m, 1H), 3.01 (t, *J* = 6.4 Hz, 2H), 2.88 (t, *J* = 6.6 Hz, 2H). **LCMS** (ESI) *m/z*: $[M-H_2N]^+$ calcd for $C_{10}H_9NBr^+$ 221.9, found 222.1. The spectral data are consistent with those reported in the literature.[22]

Peptide synthesis (general procedure)



BAL	P_1	P_2	P_3	P_4
				

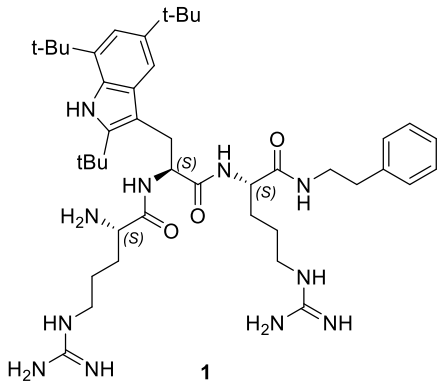
The peptides were prepared according to standard Fmoc SPPS on polystyrene resin with BAL linker [23, 24]. A sample of BAL resin** (100 mg, 0.08 mmol, 1 equiv) in 5-mL reactor for peptide synthesis was swollen in DCM for 30 min and washed with DMF (×3) before the corresponding 2-arylethylamine (free base or hydrochloride salt, 10 equiv), $NaBH_3CN$ (10 equiv) in AcOH-DMF (1.6 mL, 1:99) were added. A viscous mixture was shaken for 12-48 h and sequentially washed with ×5 DMF, ×5 MeOH, ×5 DCM, ×2 DMF. The progress of reductive amination was monitored by positive chloranil test[25] and negative anisaldehyde test[26]. The further peptide chain construction was performed by coupling with corresponding amino acids (3 equiv), PyBOP (3 equiv), HOBt (3 equiv), and DIPEA (6 equiv) in DMF (1.2 mL). For couplings using Fmoc-Lys(Me)$_3$-OH chloride, HBTU (3 equiv), HOAt (3 equiv), and DIPEA (10 equiv) in DMF (1.2 mL) were used. After coupling completion, the resins were washed with DMF (×5) and DCM (×5). Completion of the coupling was confirmed by negative chloranil test[3] (for secondary amines) or Kaiser test[27] (primary amines).

Fmoc-deprotection after each coupling was carried out by consecutive treatment with 20% piperidine in DMF (×1, 5 min), DMF wash (×3), then again 20% piperidine in DMF (×1, 15 min) and wash with DMF (×5). After the final Fmoc-deprotection the resin was washed with MeOH (×3), DCM (×5) and dried in vacuo. The final peptide was cleaved from the resin, unless noted otherwise, with TFA/H_2O/TIPS 95/2.5/2.5 v/v/v% (×2, 1 h), concentrated under reduced pressure and further purified by preparative HPLC.

** 100-200 mesh, 0.8 mmol/g, Iris Biotech GmbH

Preparative HPLC was carried out under gradient elution 10 to 100% B (MeCN-H_2O-TFA 90:10:0.1 v/v/v%) in solvent A (H_2O-TFA 100:0.1 v/v%) over 20 min. Fractions containing products were combined, concentrated under reduced pressure and freeze-dried, providing final peptides (TFA salts) as fluffy white solids. The signals of trifluoroacetate counterions are omitted in the corresponding ^{13}C NMR spectra.

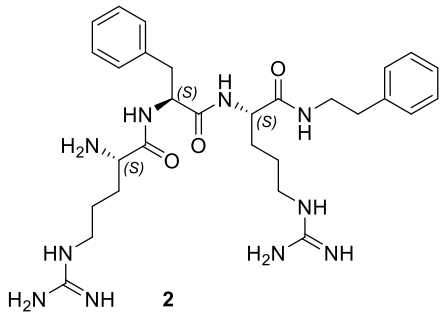
Peptide 1



1

^{1}H NMR (600 MHz, D_2O) δ 8.52 (br s, 1H, exchangeable N*H*), 7.32-7.30 (m, 3H), 7.25-7.23 (m, 2H), 7.12 (d, *J* = 7.5 Hz, 2H), 6.87 (br s, 1H, exchangeable N*H*), 4.55 (dd, *J* = 10.5, 4.9 Hz, 1H), 4.10-4.06 (m, 2H), 3.42-3.33 (m, 2H), 3.25 (t, *J* = 7.2 Hz, 2H), 3.16-3.11 (m, 1H), 3.05-2.96 (m, 3H), 2.64-2.60 (m, 1H), 2.57-2.52 (m, 1H) 2.01-1.92 (m, 2H), 1.72-1.63 (m, 2H), 1.50 (s, 9H), 1.47 (s, 9H), 1.41-1.31 (m, 11H), 1.27-1.20 (m, 2H), The spectral data are consistent with those reported in the literature.[28]

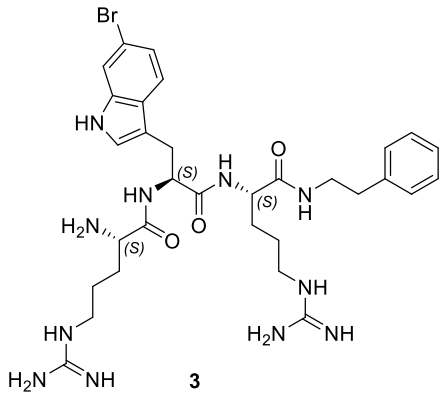
Peptide 2



2

^{1}H NMR (600 MHz, D_2O) δ 7.38-7.34 (m, 5H), 7.29-7.24 (m, 5H), 4.62 (t, *J* = 7.9 Hz, 1H), 4.05 (t, *J* = 7.2 Hz, 1H), 4.00 (t, *J* = 6.5 Hz, 1H), 3.51-3.47 (m, 1H), 3.41-3.36 (m, 1H) 3.19 (t, *J* = 7.0 Hz, 2H), 3.11-2.98 (m, 4H), 2.84-2.76 (m, 2H), 1.94-1.84 (m, 2H), 1.65-1.46 (m, 4H), 1.38-1.30 (m, 1H), 1.26-1.19 (m, 1H), **HRMS-ESI** calculated for $[C_{29}H_{45}N_{10}O_3]^+$; 581.3671, found; 581.3672.

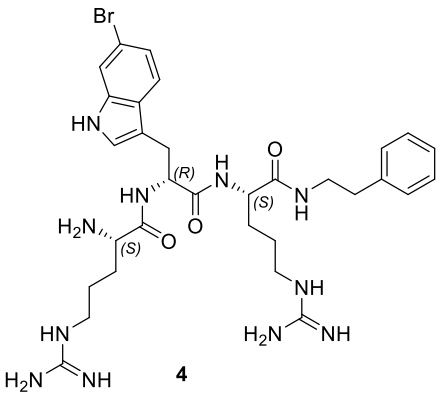
Peptide 3



3

^{1}H NMR (600 MHz, D_2O) δ 7.69 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.2-7.26 (m, 3H), 7.20 (d, *J* = 7.6 Hz, 2H), 4.58 (dd, *J* = 9.9, 6.2 Hz, 1H), 4.05 (t, *J* = 6.5 Hz, 1H), 3.91 (t, *J* = 6.9 Hz, 1H), 3.33-3.15 (m, 6H), 2.96 (t, *J* = 7.1 Hz, 2H), 2.74-2.67 (m, 2H), 1.96-1.86 (m, 2H), 1.68-1.57 (m, 2H), 1.46-1.40 (m, 1H), 1.37-1.30 (m, 1H), 1.23-1.08 (m, 2H), **HRMS-ESI** calculated for $[C_{31}H_{45}N_{11}O_3Br]^+$; 698.2885, found; 698.2885.

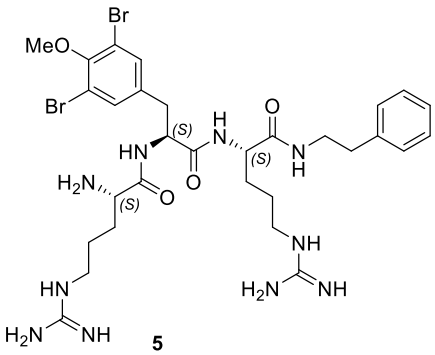
Peptide 4



4

^{1}H NMR (600 MHz, D_2O) δ 7.65-7.64 (m, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.28-7.24 (m, 5H), 4.69 (t, *J* = 8.2 Hz, 1H), 4.00 (t, *J* = 6.4 Hz, 1H), 3.84 (dd, *J* = 8.9, 5.4 Hz, 1H), 3.54-3.49 (m, 1H), 3.46-3.42 (m, 1H), 3.25 – 3.16 (m, 2H), 3.03-2.99 (m, 1H), 2.96-2.92 (m, 1H), 2.86-2.77 (m, 4H), 1.79-1.69 (m, 2H), 1.33-1.26 (m, 3H), 1.13-1.07 (m, 1H), 0.80-0.68 (m, 2H), **HRMS-ESI** calculated for $[C_{31}H_{46}N_{11}O_3Br]^{2+}$; 349.6479, found; 349.6481.

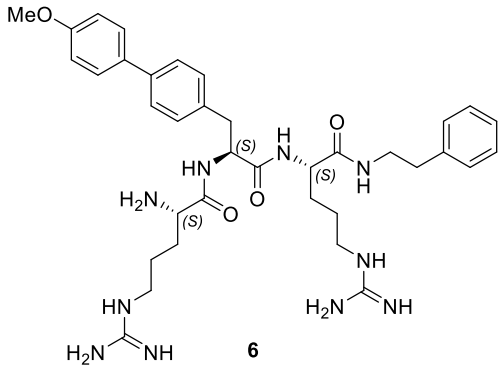
Peptide 5



5

^{1}H NMR (600 MHz, D_2O) δ 7.48 (s, 2H), 7.37-7.34 (m, 2H), 7.29-7.26 (m, 3H), 4.55 (dd, *J* = 8.7, 6.7 Hz, 1H), 4.09 (t, *J* = 7.1 Hz, 1H), 4.01 (t, *J* = 6.5 Hz, 1H), 3.90 (s, 3H), 3.62-3.57 (m, 1H), 3.42-3.38 (m, 1H), 3.20 (t, *J* = 7.0 Hz, 2H), 3.09-3.04 (m, 3H), 2.93 (dd, *J* = 13.9, 8.7 Hz, 1H) 2.87-2.83 (m, 1H), 2.81-2.77 (m, 1H), 1.93-1.84 (m, 2H), 1.66-1.58 (m, 2H), 1.58-1.46 (m, 2H), 1.38-1.30 (m, 1H), 1.27-1.20 (m, 1H), **HRMS-ESI** calculated for $[C_{30}H_{45}N_{10}O_4Br_2]^+$; 767.1987, found; 767.1985.

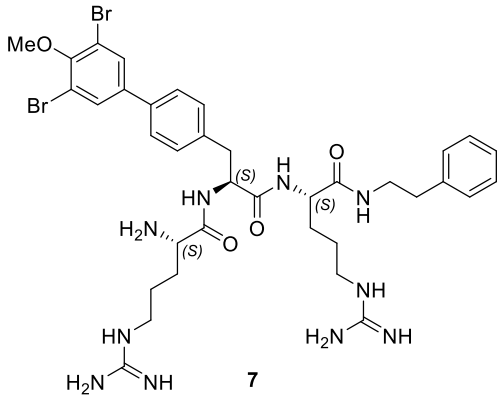
Peptide 6



6

^{1}H NMR (600 MHz, D_2O) δ 7.63-7.59 (m, 4H), 7.31-7.22 (m, 5H), 7.03-7.00 (m, 4H), 4.63 (dd, *J* = 10.0, 6.5 Hz, 1H), 4.07 (t, *J* = 6.8 Hz, 2H), 3.84 (s, 3H), 3.22-2.96 (m, 8H), 2.54 (t, *J* = 7.3 Hz, 2H), 1.97-1.87 (m, 2H), 1.68-1.55 (m, 3H), 1.52-1.46 (m, 1H), 1.39-1.32 (m, 1H), 1.30-1.23 (m, 1H), **HRMS-ESI** calculated for $[C_{36}H_{51}N_{10}O_4]^+$; 687.4090, found; 687.4086.

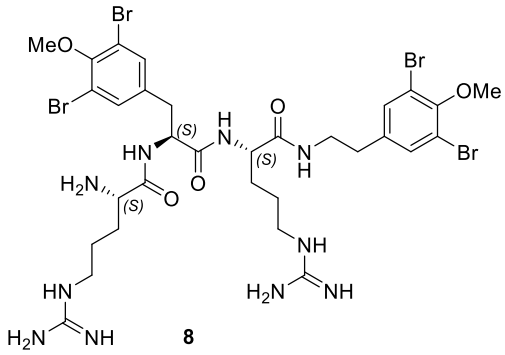
Peptide 7



7

^{1}H NMR (400 MHz, MeOD) δ 7.82 (s, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.29-7.25 (m, 2H), 7.21-7.15 (m, 3H), 4.72 (dd, 1H, *J* = 8.4, 6.4 Hz, 1H), 4.26 (dd, *J* = 7.9, 5.8 Hz, 1H), 3.98-3.92 (m, 1H), 3.89 (s, 3H), 3.43-3.28 (m, 2H), 3.25-3.15 (m, 5H), 3.06 (dd, *J* = 13.6, 8.8 Hz, 1H), 2.74 (t, *J* = 7.5 Hz, 2H), 2.01-1.92 (m, 2H), 1.78-1.49 (m, 6H), **HRMS-ESI** calculated for $[C_{36}H_{50}N_{10}O_4{}^{79}Br_2]^{2+}$; 422.1186, found; 422.1188.

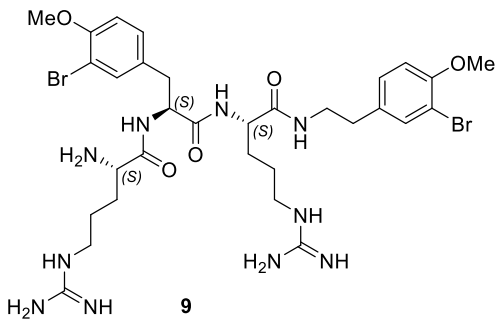
Peptide 8



8

^{1}H NMR (600 MHz, D_2O) δ 7.46 (s, 2H), 7.42 (s, 2H), 4.54 (dd, *J* = 8.6, 6.5 Hz, 1H), 4.10 (dd, *J* = 7.9, 6.4 Hz, 1H), 4.03 (t, *J* = 6.5 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.55 – 3.50 (m, 1H), 3.42-3.38 (m, 1H), 3.19 (t, *J* = 7.0 Hz, 2H), 3.09 (t, *J* = 7.0 Hz, 2H), 3.04 (dd, *J* = 13.8, 6.3 Hz, 1H), 2.91 (dd, *J* = 13.8, 8.7 Hz, 1H), 2.81-2.77 (m, 1H), 2.75-2.70 (m, 1H), 1.94-1.84 (m, 2H), 1.66-1.49 (m, 4H), 1.44-1.37 (m, 1H), 1.34-1.27 (m, 1H), **HRMS-ESI** calculated for $[C_{31}H_{45}N_{10}O_5Br_4]^+$; 953.0303, found; 953.0300.

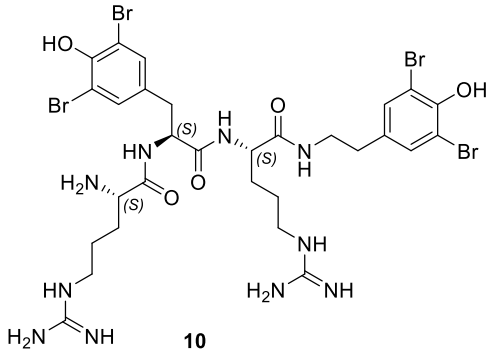
Peptide 9



9

^{1}H NMR (600 MHz, D_2O) δ 7.43 (d, *J* = 1.8 Hz, 1H), 7.42 (d, *J* = 1.8 Hz, 1H), 7.22 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.19 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 4.54 (dd, *J* = 8.8, 6.9 Hz, 1H), 4.07 (t, *J* = 7.1 Hz, 1H), 4.02 (t, *J* = 6.5 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.48-3.44 (m, 1H), 3.40-3.35 (m, 1H), 3.19 (t, *J* = 7.0 Hz, 2H), 3.05-3.00 (m, 3H), 2.85 (dd, *J* = 13.8, 8.9 Hz, 1H), 2.78-2.69 (m, 2H), 1.94-1.84 (m, 2H), 1.66-1.47 (m, 4H), 1.39-1.31 (m, 1H), 1.27-1.20 (m, 1H), **HRMS-ESI** calculated for $[C_{31}H_{47}N_{10}O_5Br_2]^+$; 797.2092, found; 797.2093.

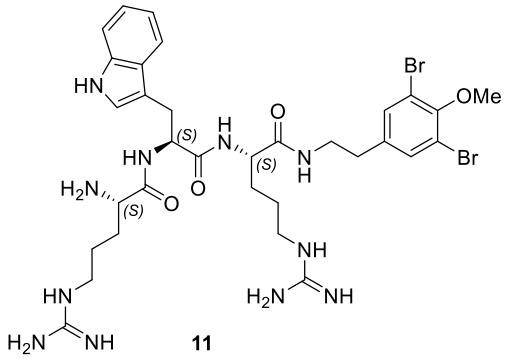
Peptide 10



10

The target peptide was cleaved from resin with TFA/TfOH/thioanisole 40/36/24 v/v/v% (×2, 1 h) cocktail. **^{1}H NMR** (600 MHz, D_2O) δ 7.39 (s, 2H), 7.36 (s, 2H), 4.52 (dd, *J* = 8.8, 6.6 Hz, 1H), 4.07 (t, *J* = 7.1 Hz, 1H), 4.03 (t, *J* = 6.6 Hz, 1H), 3.53-3.48 (m, 1H), 3.41-3.37 (m, 1H), 3.18 (t, *J* = 7.0 Hz, 2H), 3.06-3.00 (m, 3H), 2.83 (dd, *J* = 13.9, 8.8 Hz, 1H), 2.77-2.67 (m, 2H), 1.90-1.87 (m, 2H), 1.63-1.58 (m, 2H), 1.57-1.46 (m, 2H), 1.38-1.31 (m, 1H), 1.26-1.19 (m, 1H), **HRMS-ESI** calculated for $[C_{29}H_{41}N_{10}O_5Br_4]^+$; 924.9990, found; 924.9995.

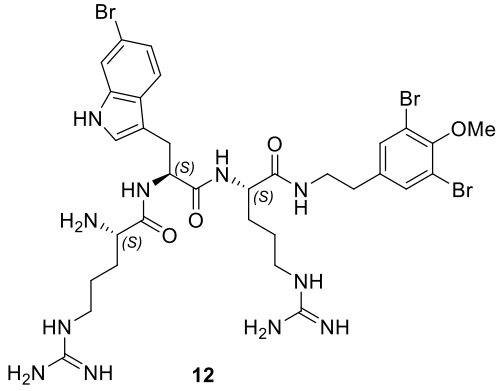
Peptide 11



11

^{1}H NMR (600 MHz, D_2O) δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.32 (s, 2H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.21 (s, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.91 (t, *J* = 6.1 Hz, 1H, exchangeable N*H*), 4.68 (dd, *J* = 9.3, 6.4 Hz, 1H), 4.06 (t, *J* = 6.5 Hz, 1H), 3.96 (dd, *J* = 8.2, 5.8 Hz, 1H), 3.80 (s, 3H), 3.29-3.15 (m, 6H), 3.01 (t, *J* = 7.0 Hz, 2H), 2.63-2.54 (m, 2H), 1.96-1.86 (m, 2H), 1.67-1.56 (m, 2H), 1.49-1.43 (m, 1H), 1.40-1.34 (m, 1H), 1.32-1.17 (m, 2H), **HRMS-ESI** calculated for $[C_{32}H_{46}N_{11}O_4Br_2]^+$; 806.2096, found; 806.2097.

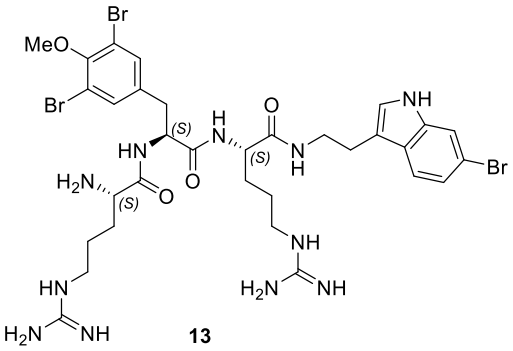
Peptide 12



12

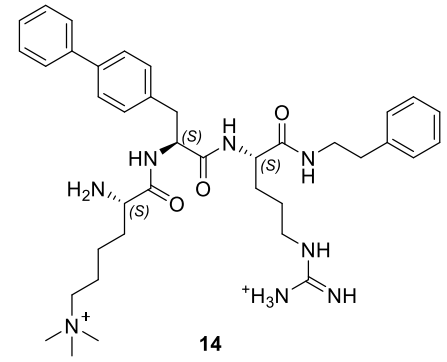
^{1}H NMR (600 MHz, D_2O) δ 7.67 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.37 (s, 2H), 7.25-7.23 (m, 2H), 4.59 (dd, *J* = 9.9, 6.0 Hz, 1H), 4.06 (t, *J* = 6.5 Hz, 1H), 3.91 (t, *J* = 7.0 Hz, 1H), 3.82 (s, 3H), 3.28-3.15 (m, 6H), 2.98 (t, *J* = 7.0 Hz, 2H), 2.62 (t, *J* = 6.5 Hz, 2H), 1.96-1.86 (m, 2H), 1.67-1.56 (m, 2H), 1.45-1.39 (m, 1H), 1.37-1.31 (m, 1H), 1.28-1.14 (m, 2H), LCMS-ESI calculated for $[C_{32}H_{46}N_{11}O_4{}^{79}Br_2{}^{81}Br]^{2+}$; 443.6, found; 443.9.

Peptide 13



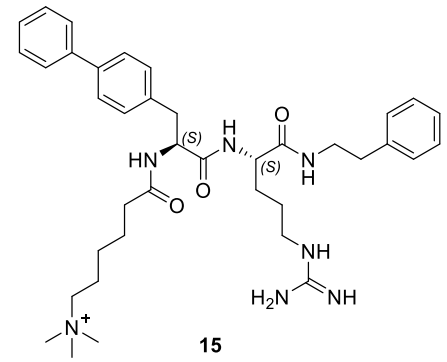
^{1}H NMR (400 MHz, MeOD) δ 7.54-7.53 (m, 2H), 7.0 (m, *J* = 7.8 Hz, 1H), 6.86-6.83 (m, 2H), 4.62 (dd, *J* = 9.7, 5.1 Hz, 1H), 4.27 (dd, *J* = 7.9, 5.5 Hz, 1H), 3.90 (app t, *J* = 5.7 Hz, 1H), 3.83 (s, 3H), 3.26-3.12 (m, 7H), 2.93-2.86 (m, 1H), 2.03-1.54 (m, 9H). LCMS-ESI calculated for $[C_{32}H_{46}N_{11}O_4{}^{79}Br_2{}^{81}Br]^{2+}$; 443.6, found; 443.5.

Peptide 14



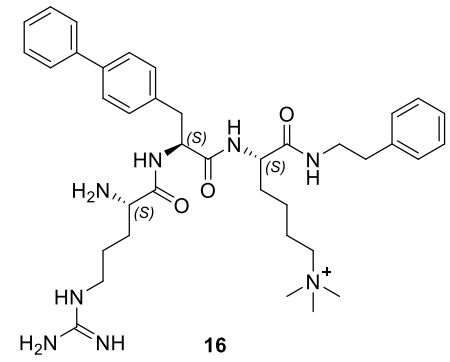
^{1}H NMR (400 MHz, MeOD) δ 7.60-7.56 (m, 4H), 7.43-7.36 (m, 4H), 7.34-7.30 (m, 1H), 7.27-7.23 (m, 2H), 7.19-7.12 (m, 3H), 4.70 (dd, *J* = 8.9, 6.1 Hz, 1H), 4.24 (dd, *J* = 8.1, 5.7 Hz), 3.90 (app t, *J* = 6.4 Hz, 1H), 3.42-3.27 (m, 4H), 3.22-3.11 (m, 12H), 3.03 (dd, *J* = 14.1, 9.0 Hz, 1H), 2.73 (app t, *J* = 7.2 Hz, 2H), 1.98 – 1.73 (m, 5H), 1.70-1.39 (m, 5H), **HRMS-ESI** calculated for $[C_{38}H_{56}N_8O_3]^{2+}$; 336.2233, found; 336.2227.

Peptide 15



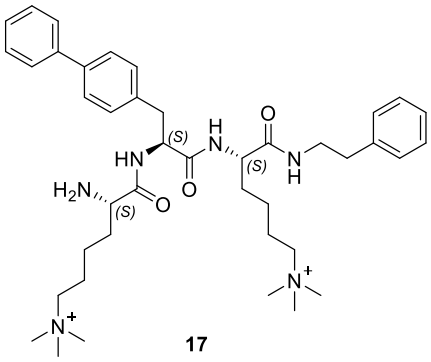
^{1}H NMR (400 MHz, MeOD) δ 8.57 (br s, 2H), 7.65-7.63 (m, 2H), 7.60-7.58 (m, 2H), 7.45-7.41 (m, 2H), 7.38-7.36 (m, 2H), 7.35-7.31 (m, 1H), 7.28-7.24 (m, 2H), 7.19-7.14 (m, 3H), 4.67 (dd, *J* = 9.8, 5.6 Hz, 1H), 4.29 (dd, *J* = 8.6, 5.2 Hz), 3.42-3.33 (m, 2H), 3.21-3.11 (m, 5H), 2.97 (s, 9H), 2.75 (t, *J* = 7.2 Hz, 2H), 2.24 (t, *J* = 7.2 Hz, 2H), 1.84-1.76 (m, 1H), 1.72-1.49 (m, 7H), 1.25-1.07 (m, 2H), **HRMS-ESI** calculated for $[C_{38}H_{54}N_7O_3]^{+}$; 656.4283, found; 656.4269.

Peptide 16



^{1}H NMR (400 MHz, MeOD) δ 7.60-7.56 (m, 4H), 7.43-7.38 (m, 4H), 7.34-7.30 (m, 1H), 7.28-7.24 (m, 2H), 7.20-7.14 (m, 3H), 4.74-4.70 (m, 1H), 4.26-4.23 (m, 1H), 3.43-3.19 (m, 7H), 3.11-2.98 (m, 11H), 2.75 (t, *J* = 6.8 Hz, 2H), 2.00-1.90 (m, 2H), 1.84-1.60 (m, 6H), 1.43-1.24 (m, 2H), **HRMS-ESI** calculated for $[C_{38}H_{56}N_8O_3]^{2+}$; 336.2233, found; 336.2231.

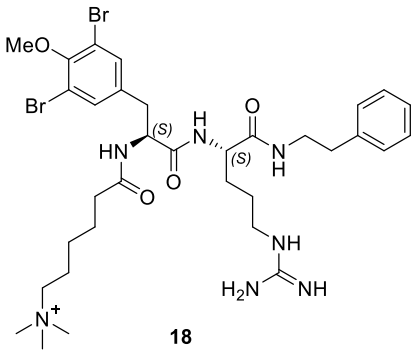
Peptide 17



17

^{1}H NMR (400 MHz, MeOD) δ 7.61-7.57 (m, 4H), 7.44-7.37 (m, 4H), 7.35-7.31 (m, 1H), 7.28-7.25 (m, 2H), 7.20-7.15 (m, 3H), 4.70 (dd, *J* = 8.8, 5.9 Hz, 1H), 4.22 (dd, *J* = 8.0, 5.8 Hz, 1H), 3.91 (app t, *J* = 5.5 Hz, 1H), 3.44-3.34 (m, 3H), 3.27-3.18 (m, 4H), 3.11 (s, 9H), 3.09 (s, 9H), 3.05-3.02 (m, 1H, 2.75 (app t, *J* = 7.4 Hz, 2H), 1.99-1.66 (m, 8H), 1.53-1.42 (m, 2H), 1.39-1.23 (m, 2H), **HRMS-ESI** calculated for $[C_{41}H_{62}N_6O_3]^{2+}$; 343.2436, found; 343.2435.

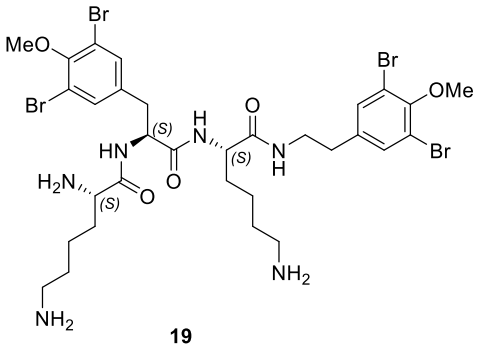
Peptide 18



18

^{1}H NMR (400 MHz, MeOD) δ 7.52 (s, 2H), 7.30-7.26 (m, 2H), 7.32-7.17 (m, 2H), 4.63 (dd, *J* = 10.2, 4.7 Hz, 1H), 4.29 (dd, *J* = 8.1, 5.8 Hz, 1H), 3.85 (s, 3H), 3.52-3.37 (m, 2H), 3.23-3.07 (m, 14H), 2.87-2.75 (m, 3H), 2.21 (t, *J* = 7.1 Hz, 1H), 1.82-1.46 (m, 8H), 1.23-1.12 (m, 1H), 1.10-1.00 (m, 1H), **HRMS-ESI** calculated for $[C_{33}H_{50}N_7O_4{}^{79}Br_2]^+$; 768.2265, found; 768.2257.

Peptide 19



19

^{1}H NMR (400 MHz, MeOD) δ 7.55 (s, 2H), 7.47 (s, 2H), 4.60 (dd, *J* = 9.3, 5.1 Hz, 1H), 4.19 (dd, *J* = 8.4, 5.8 Hz), 3.86-3.84 (m, 4H), 3.83 (s, 3H), 3.54-3.48 (m, 1H), 3.38-3.32 (m, 1H), 3.11 (dd, *J* = 14.2, 4.2 Hz, 1H), 2.97-2.86 (m, 5H), 2.82-2.70 (m, 2H), 1.90-1.83 (m, 2H), 1.75-1.60 (m, 6H), 1.53-1.46 (m, 2H), 1.42-1.25 (m, 2H), **HRMS-ESI** calculated for $[C_{31}H_{45}N_6O_5Br_4]^+$; 897.0179, found; 897.0187.

Figure S1. ^{1}H NMR spectra of S2

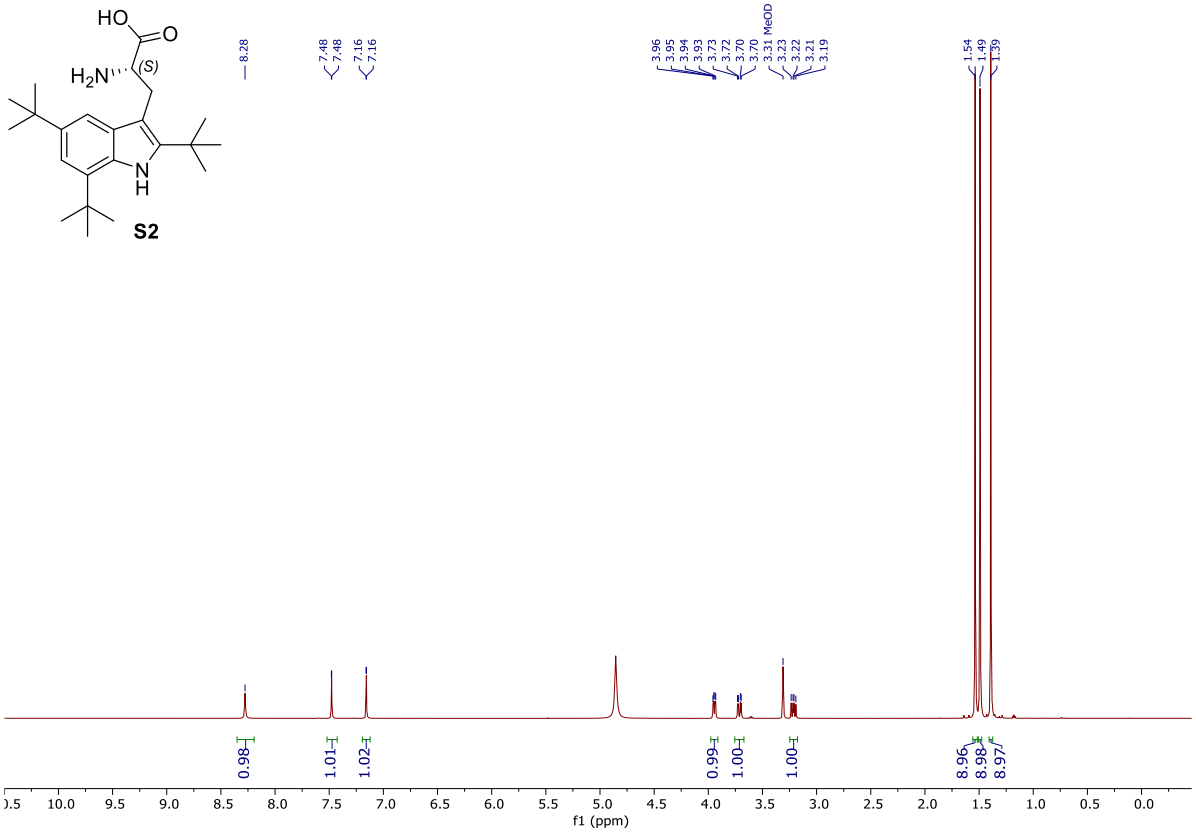


Figure S2. ^{13}C NMR spectra of S2

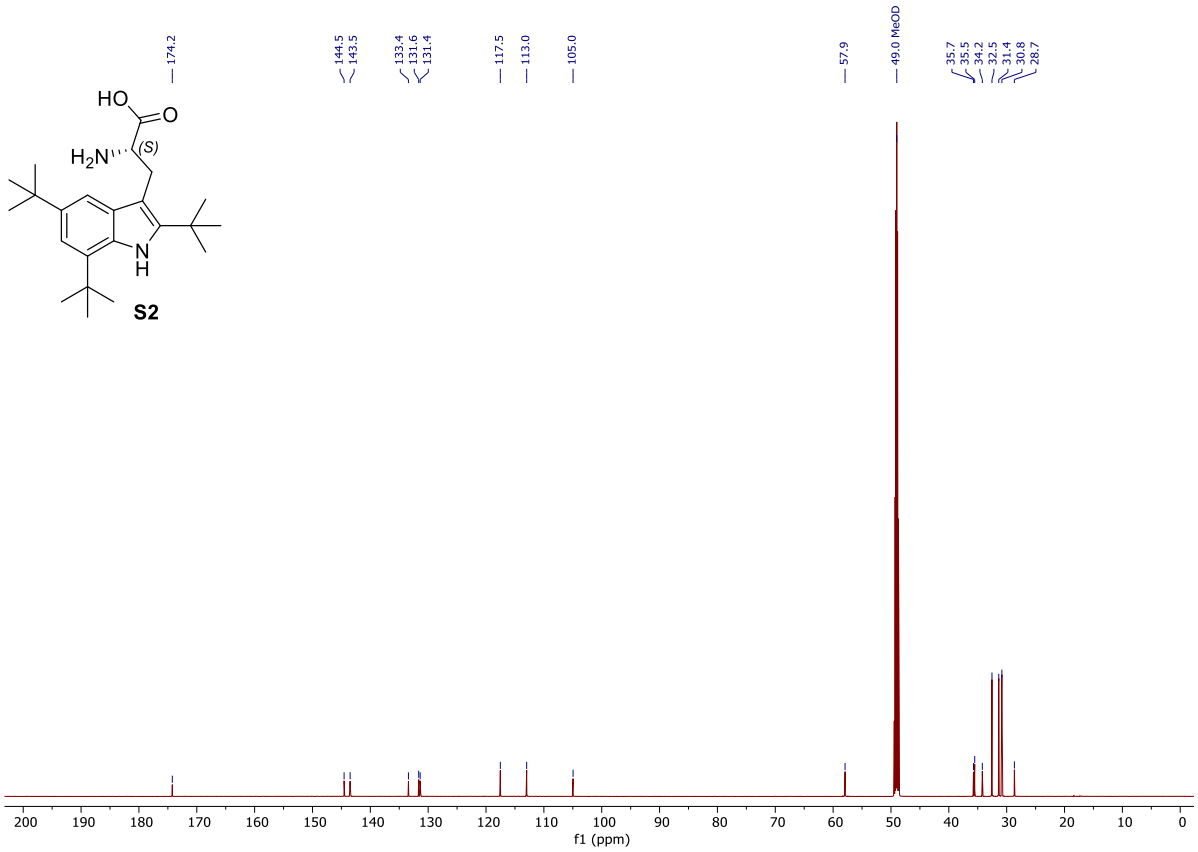


Figure S3. ^{1}H NMR spectra of S3

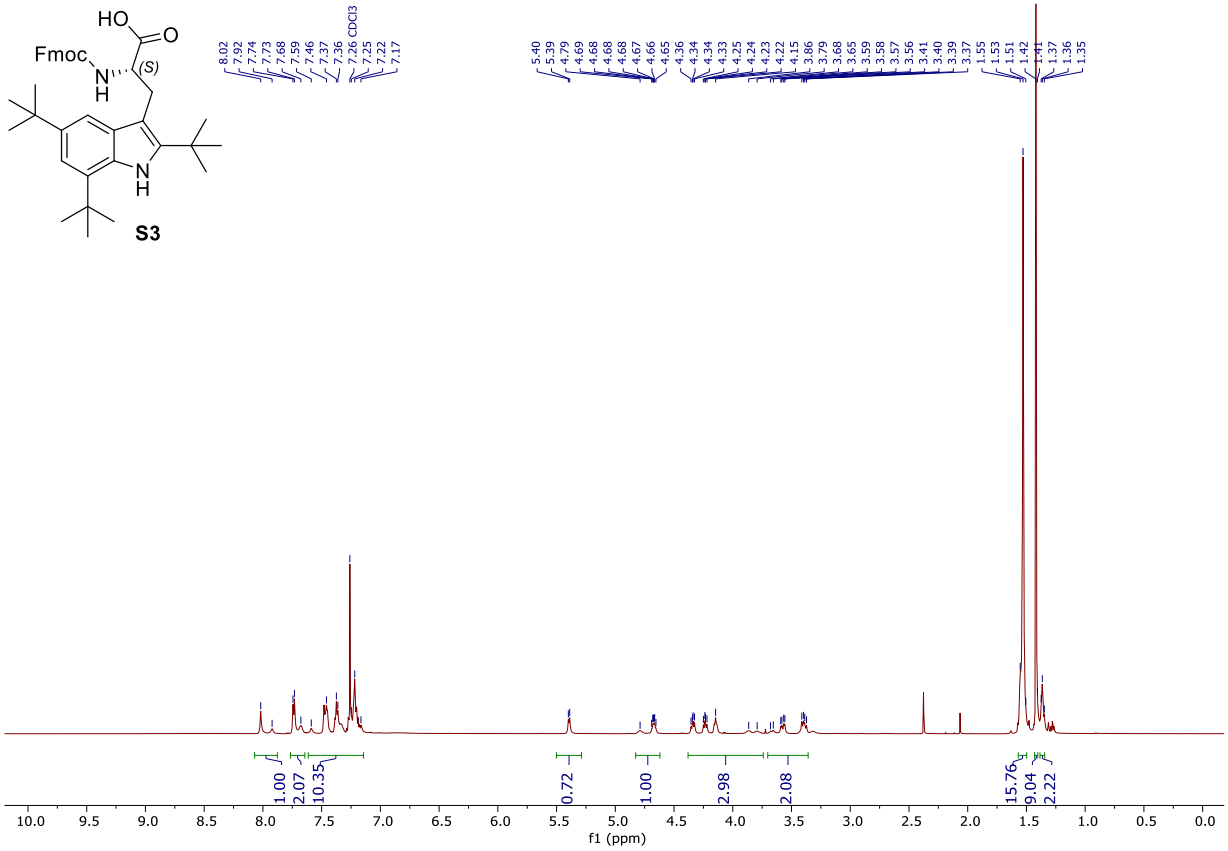


Figure S4. ^{13}C NMR spectra of S3

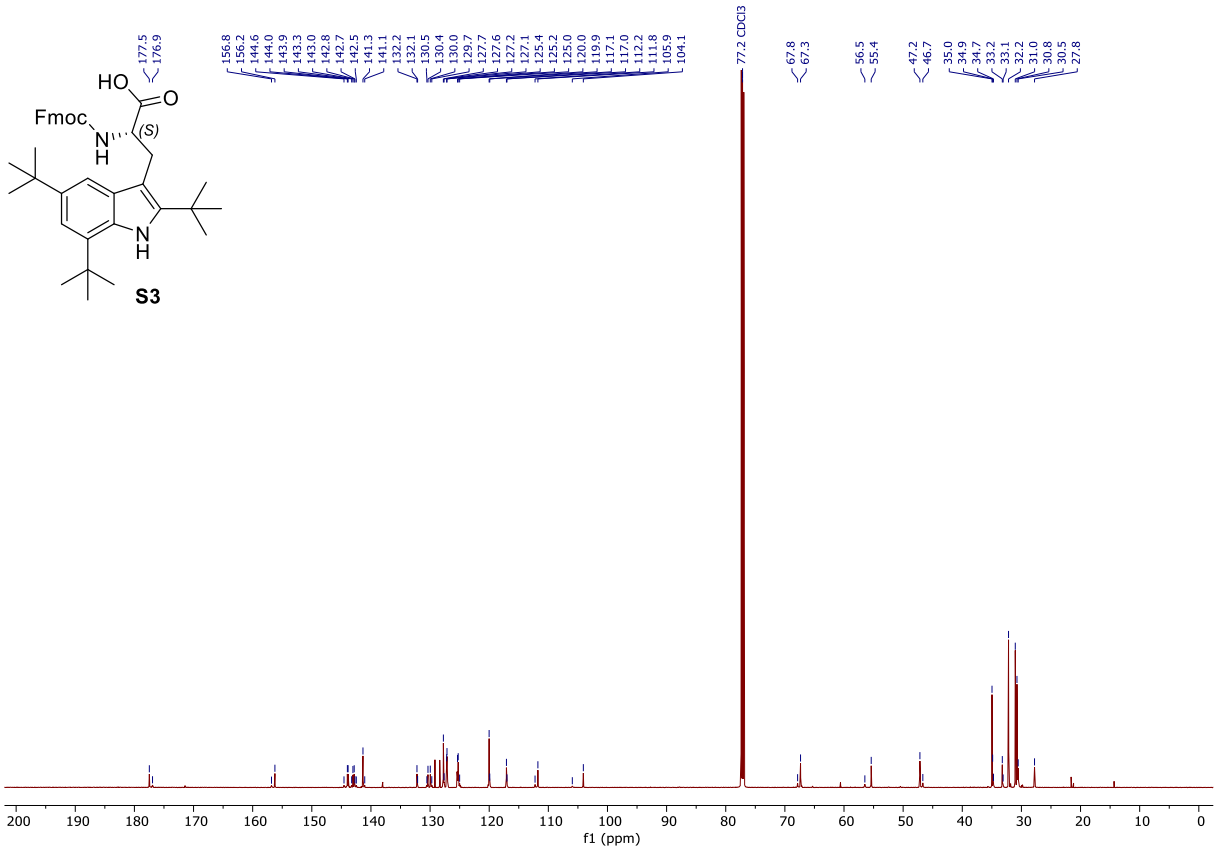


Figure S5. ^{1}H NMR spectra of (*S*)-S5

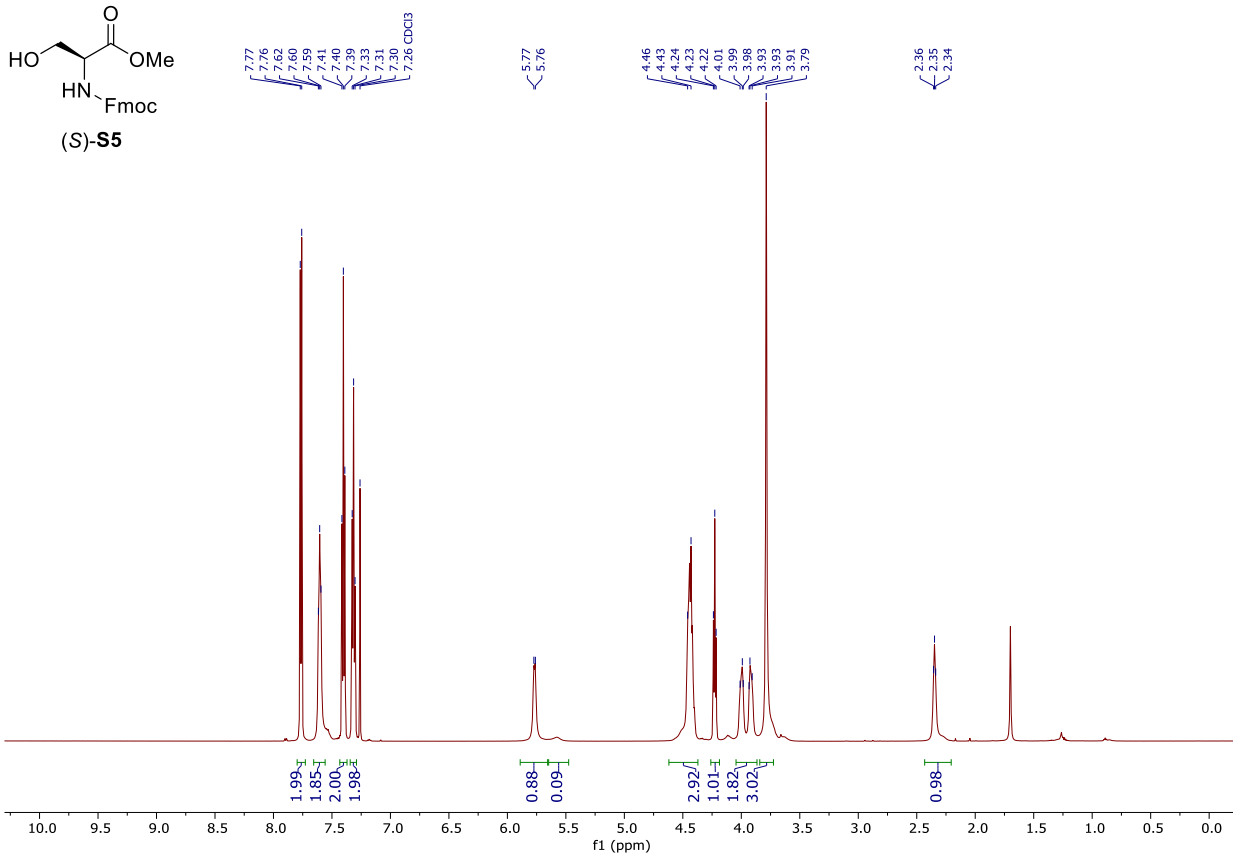


Figure S6. ^{13}C NMR spectra of (*S*)-S5

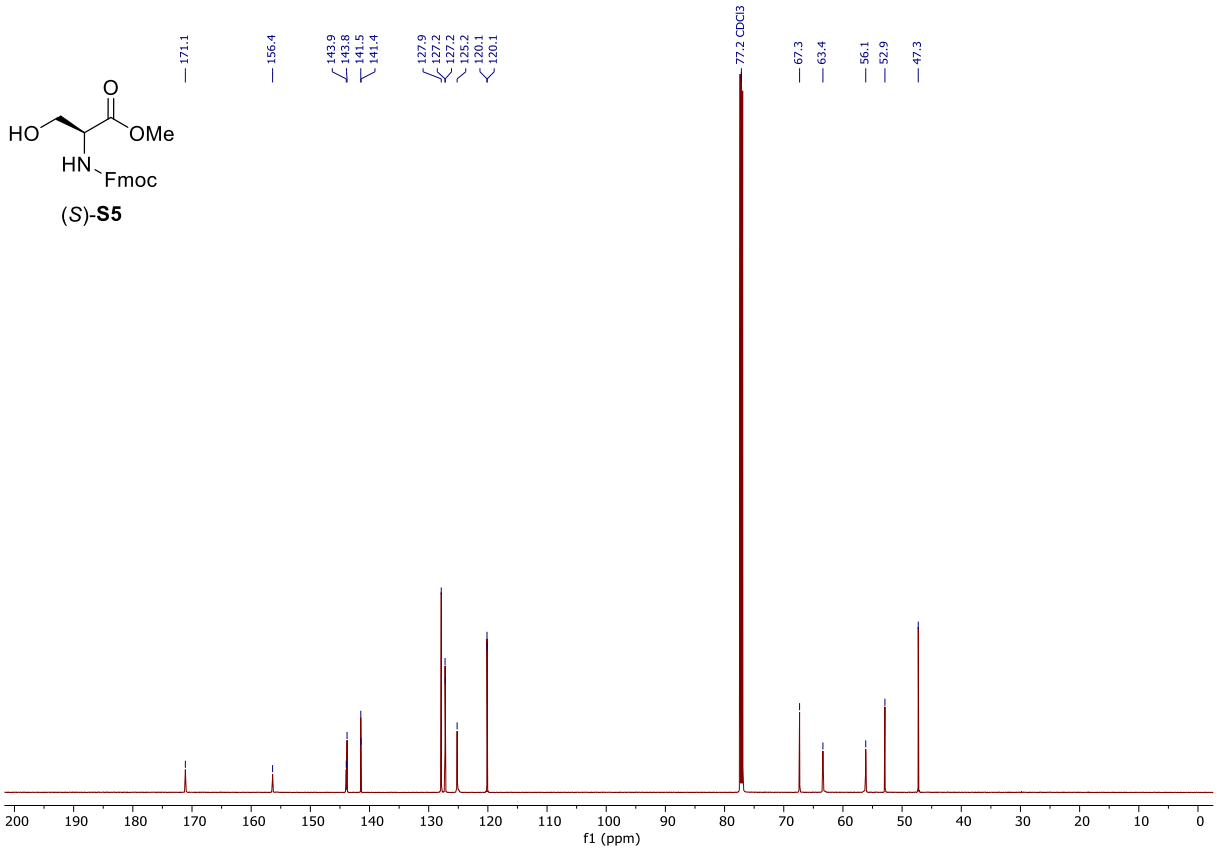


Figure S7. ^{1}H NMR spectra of (*S*)-S6

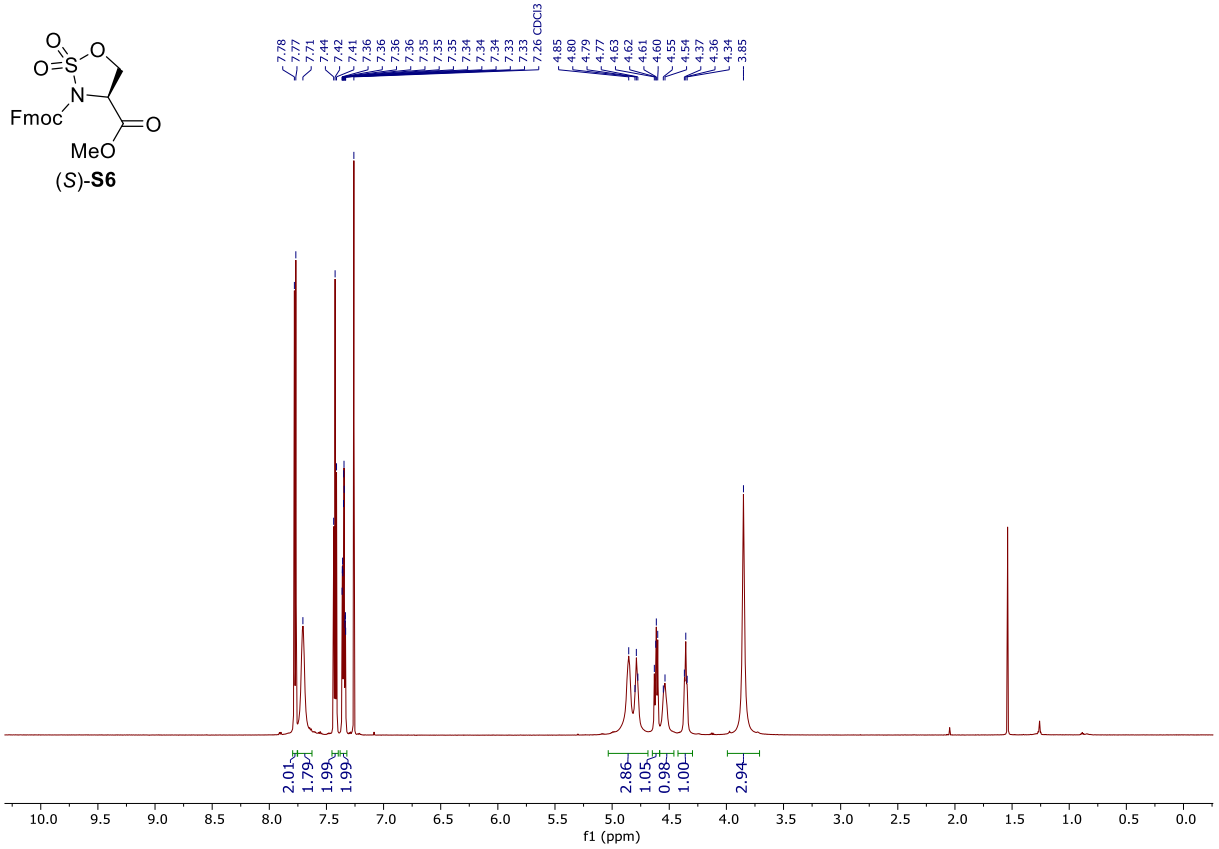


Figure S8. ^{13}C NMR spectra of (*S*)-S6

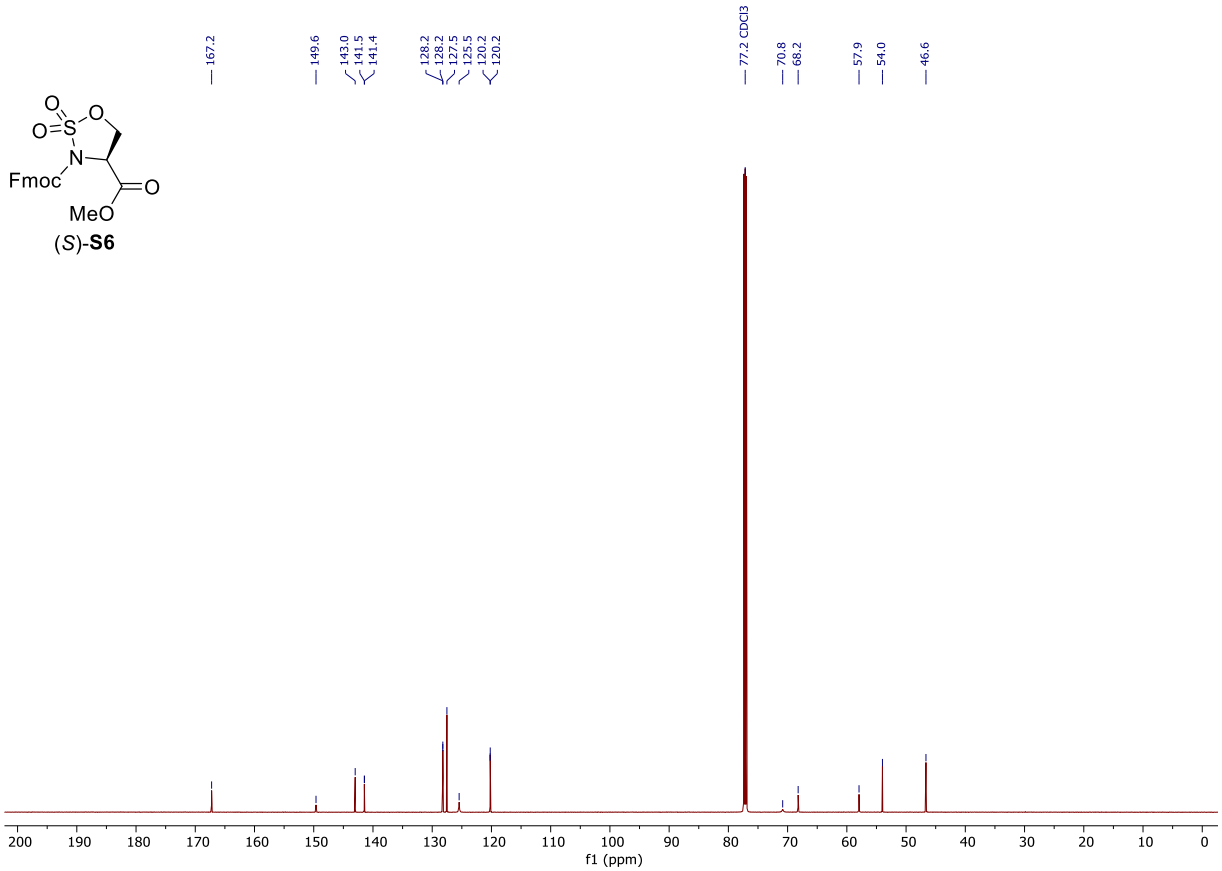


Figure S9. ^{1}H NMR spectra of (*S*)-S8

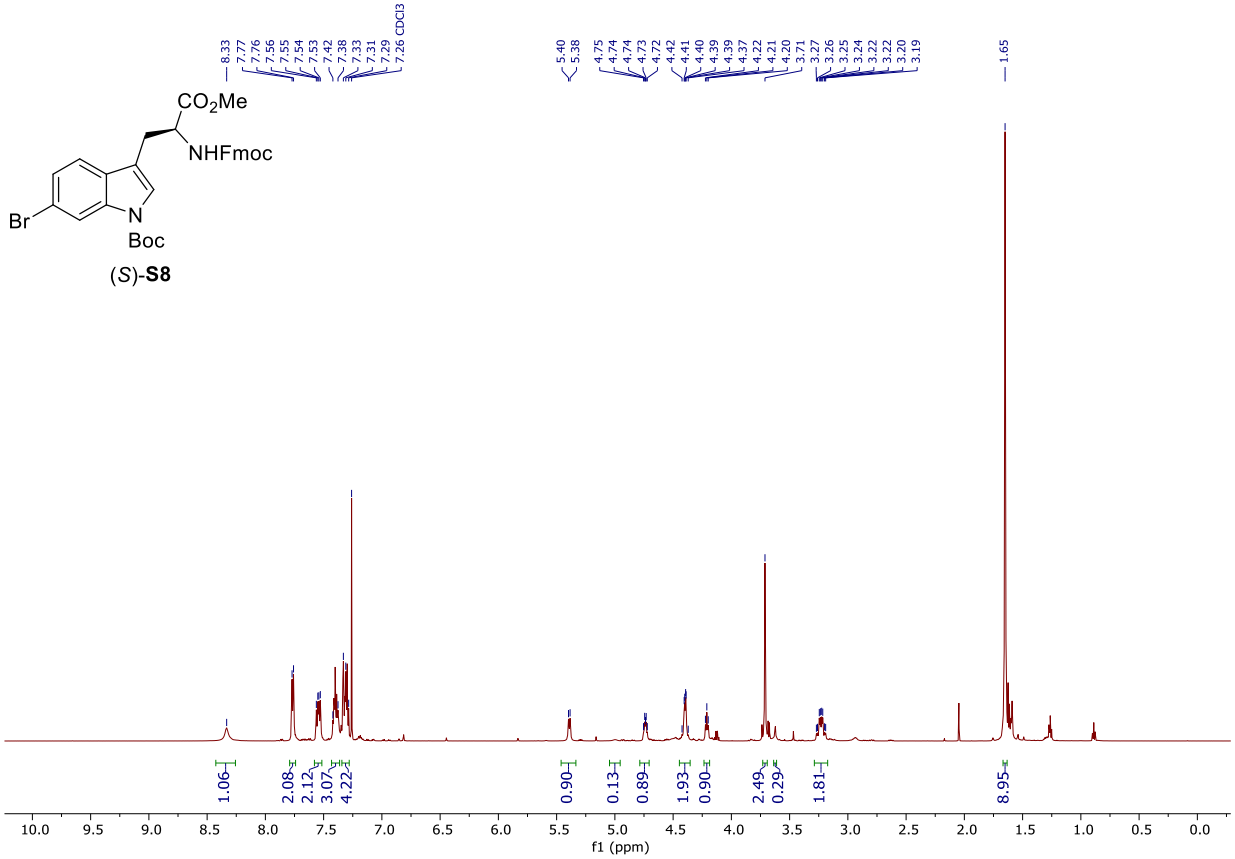


Figure S10. ^{13}C NMR spectra of (*S*)-S8

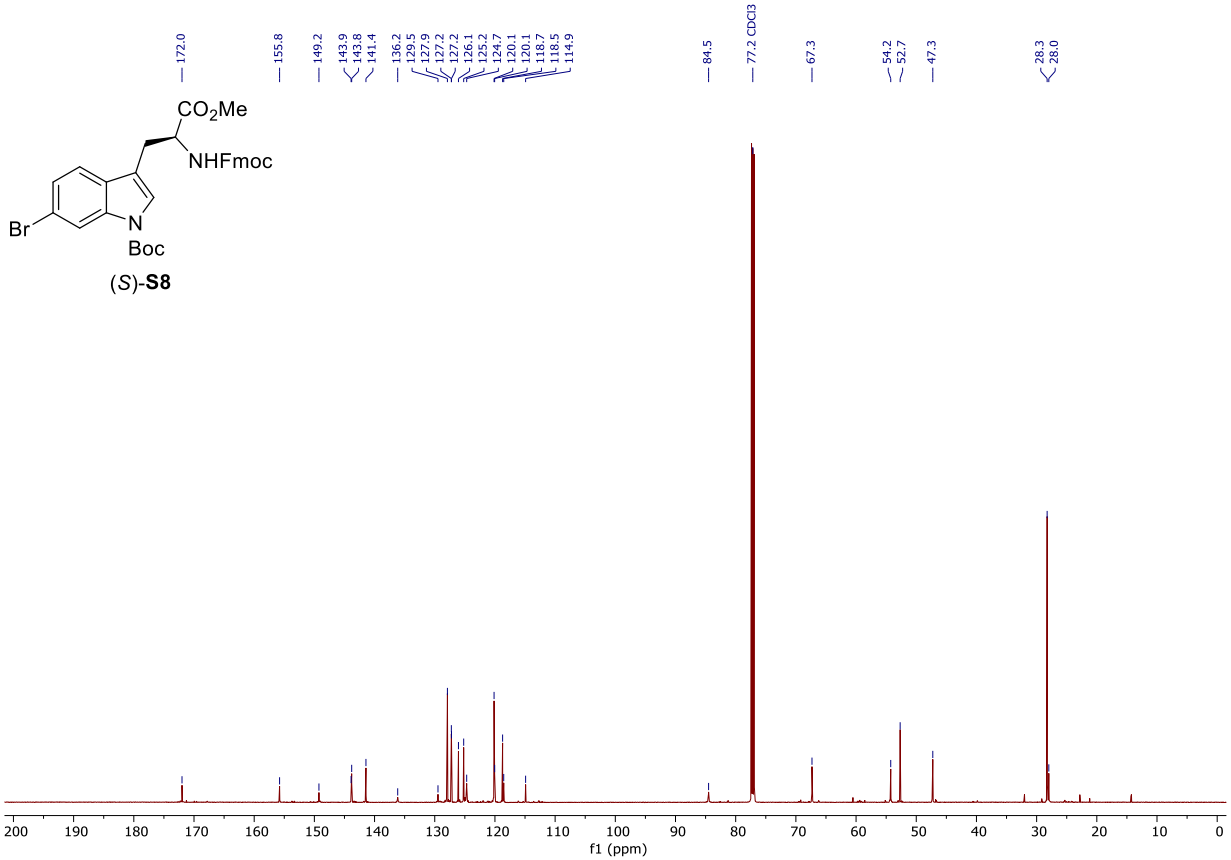


Figure S11. ^{1}H NMR spectra of (*S*)-S9

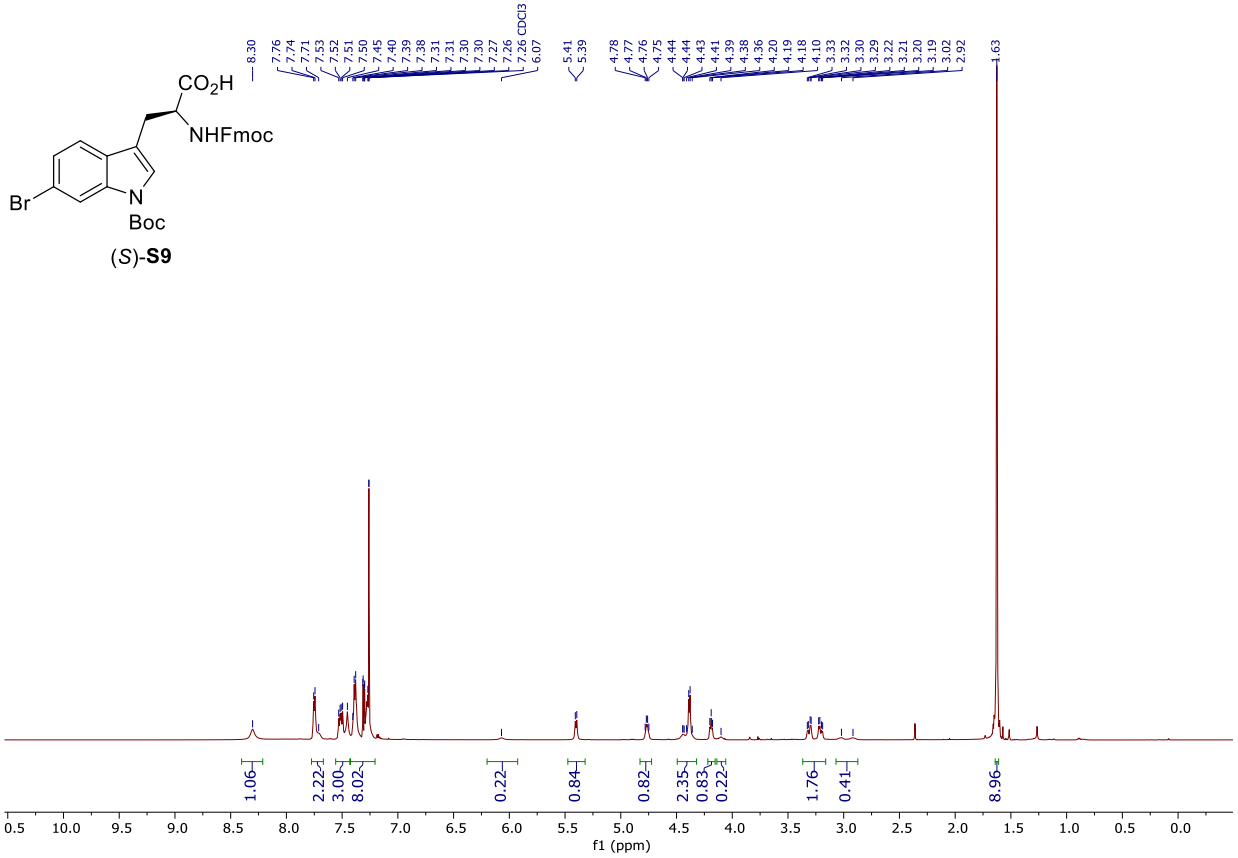


Figure S12. ^{13}C NMR spectra of (*S*)-S9

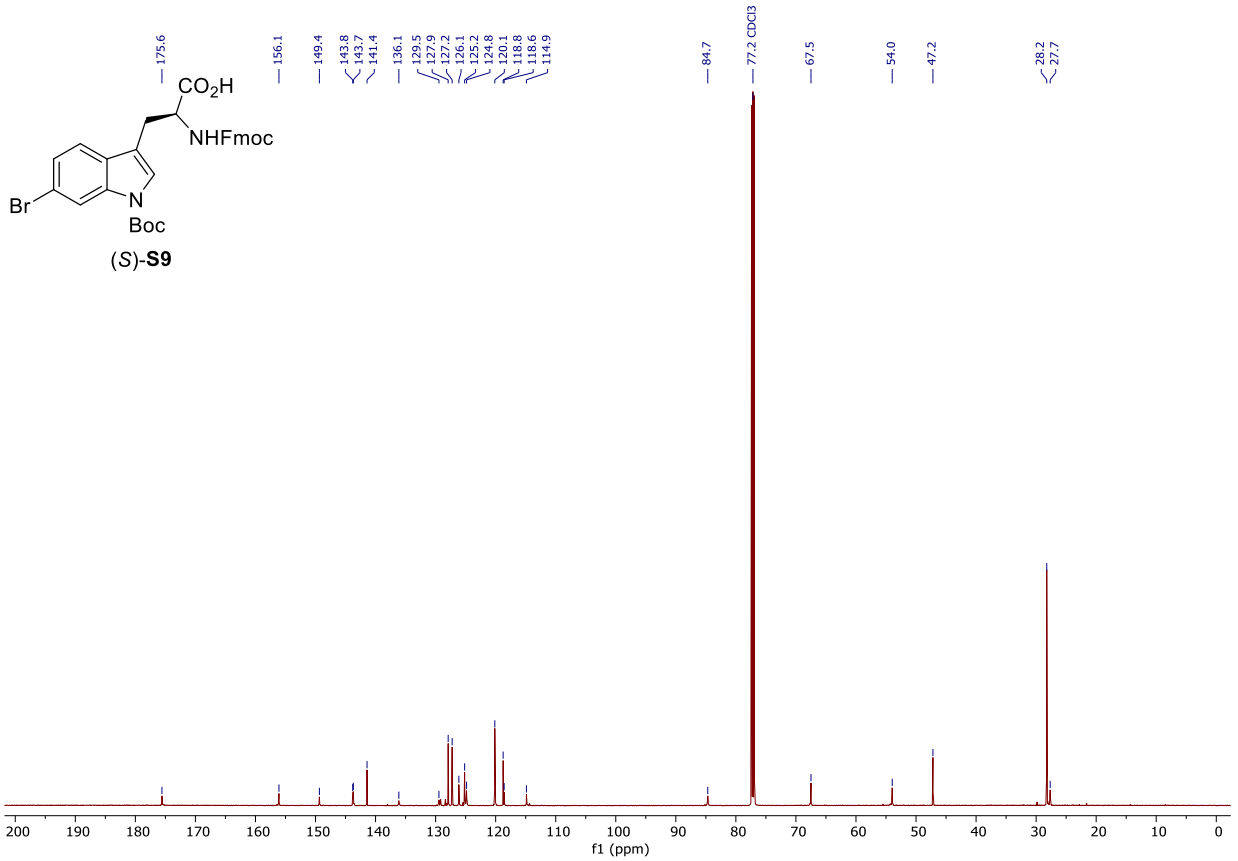


Figure S13. ^{1}H NMR spectra of S11

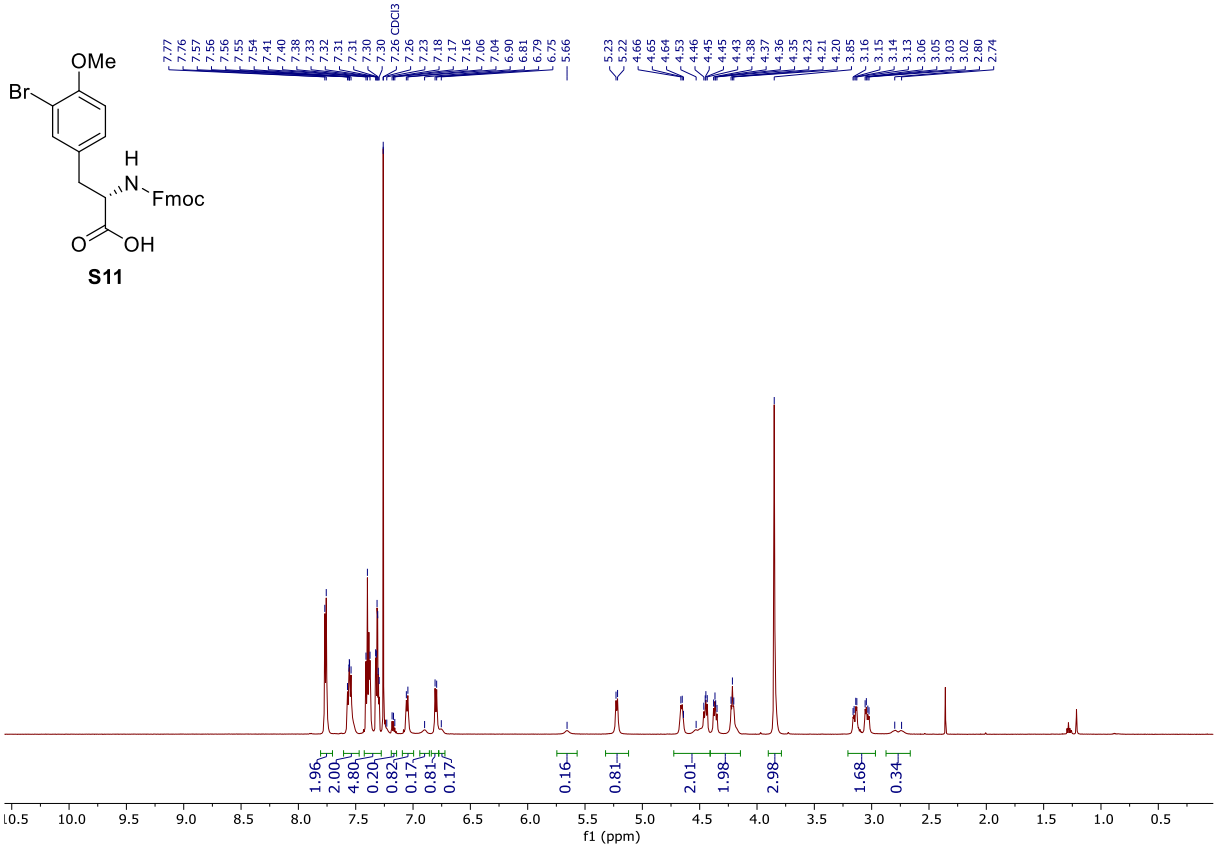


Figure S14. ^{13}C NMR spectra of S11

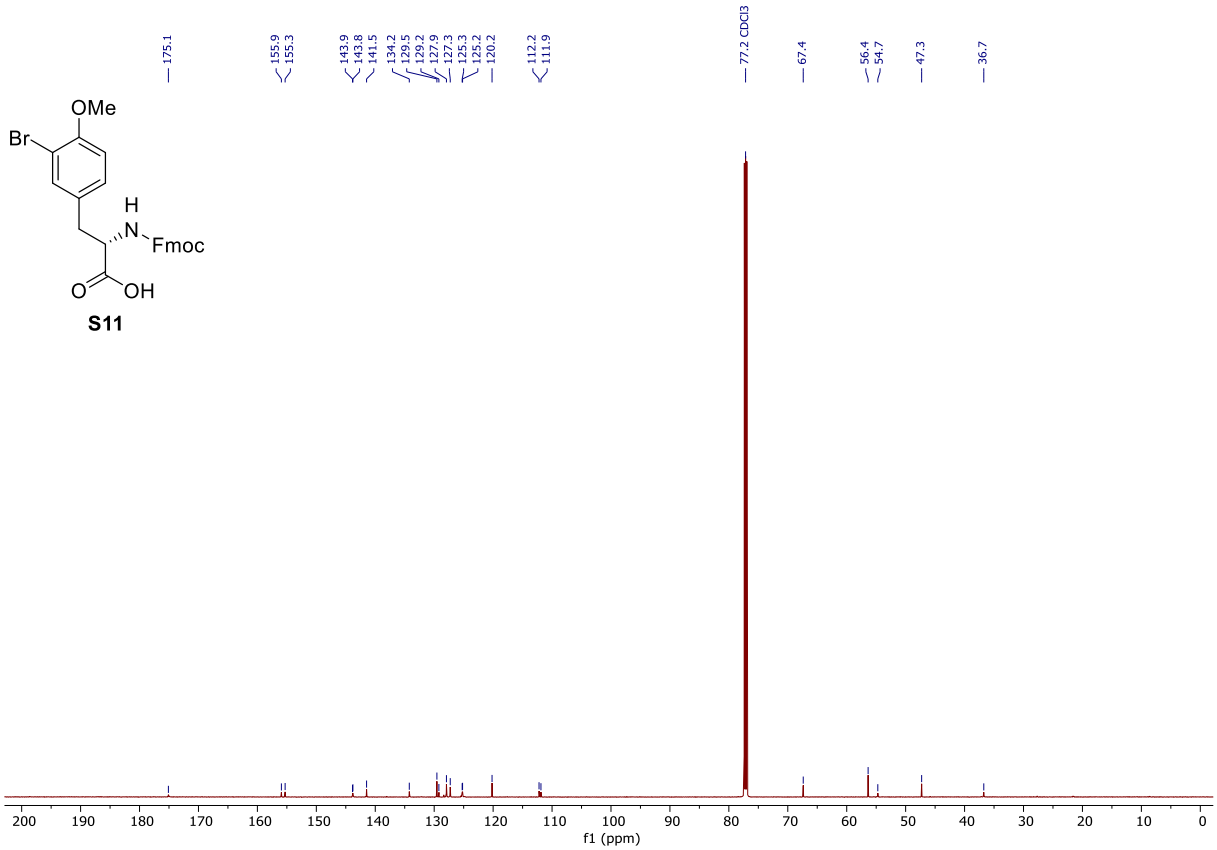


Figure S15. ^{1}H NMR spectra of S12

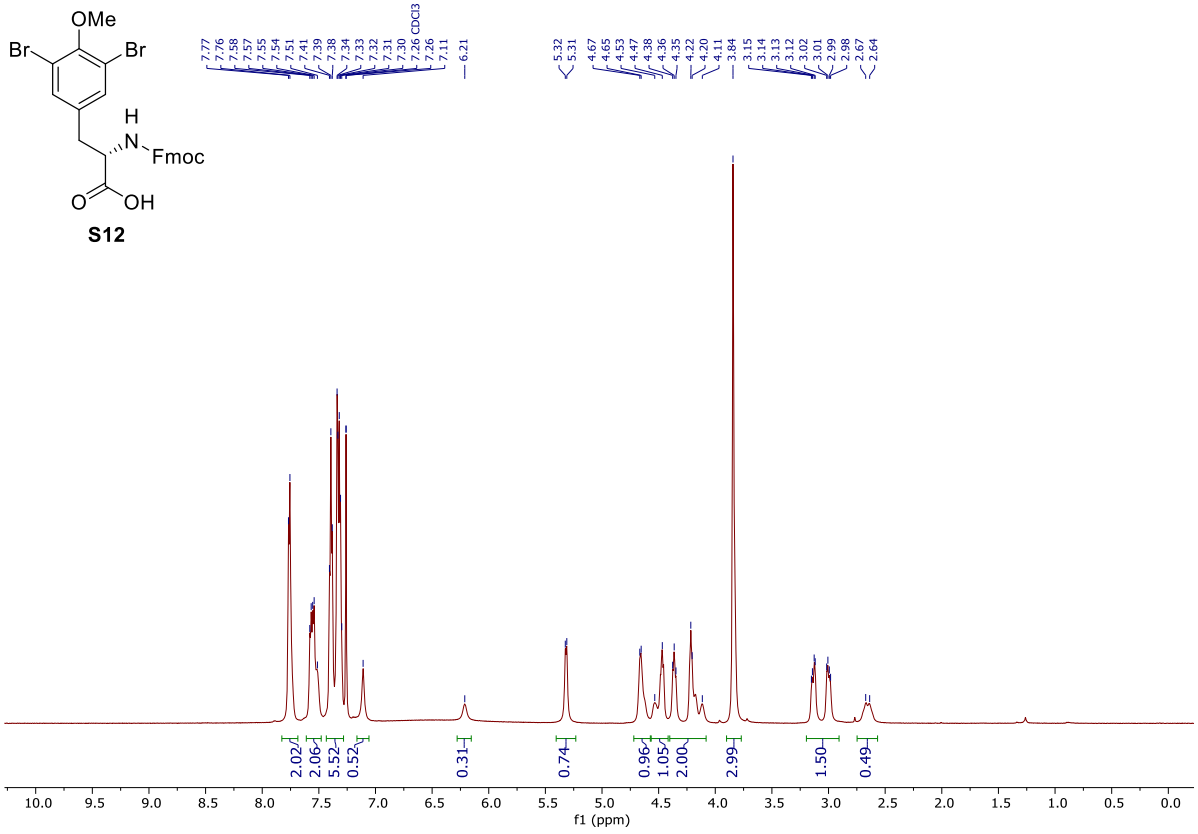


Figure S16. ^{13}C NMR spectra of S12

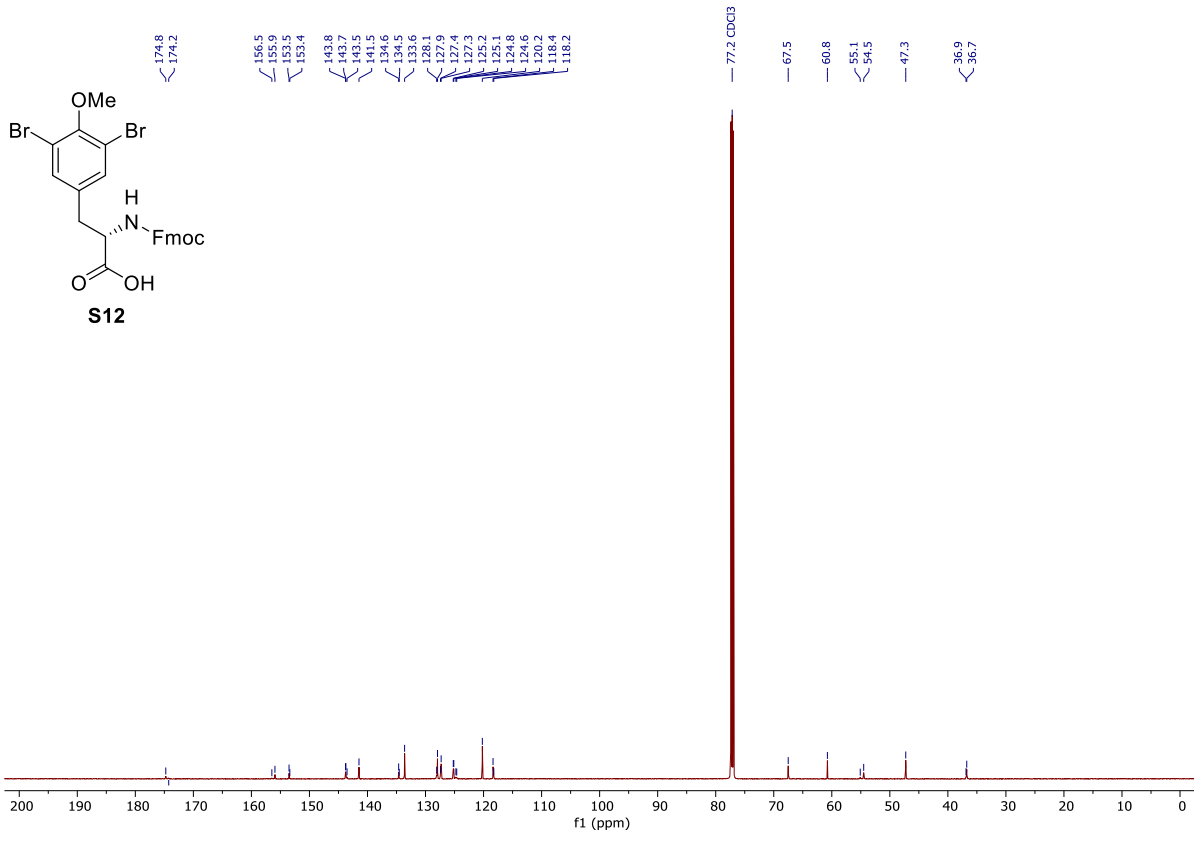


Figure S17. ^{1}H NMR spectra of S14

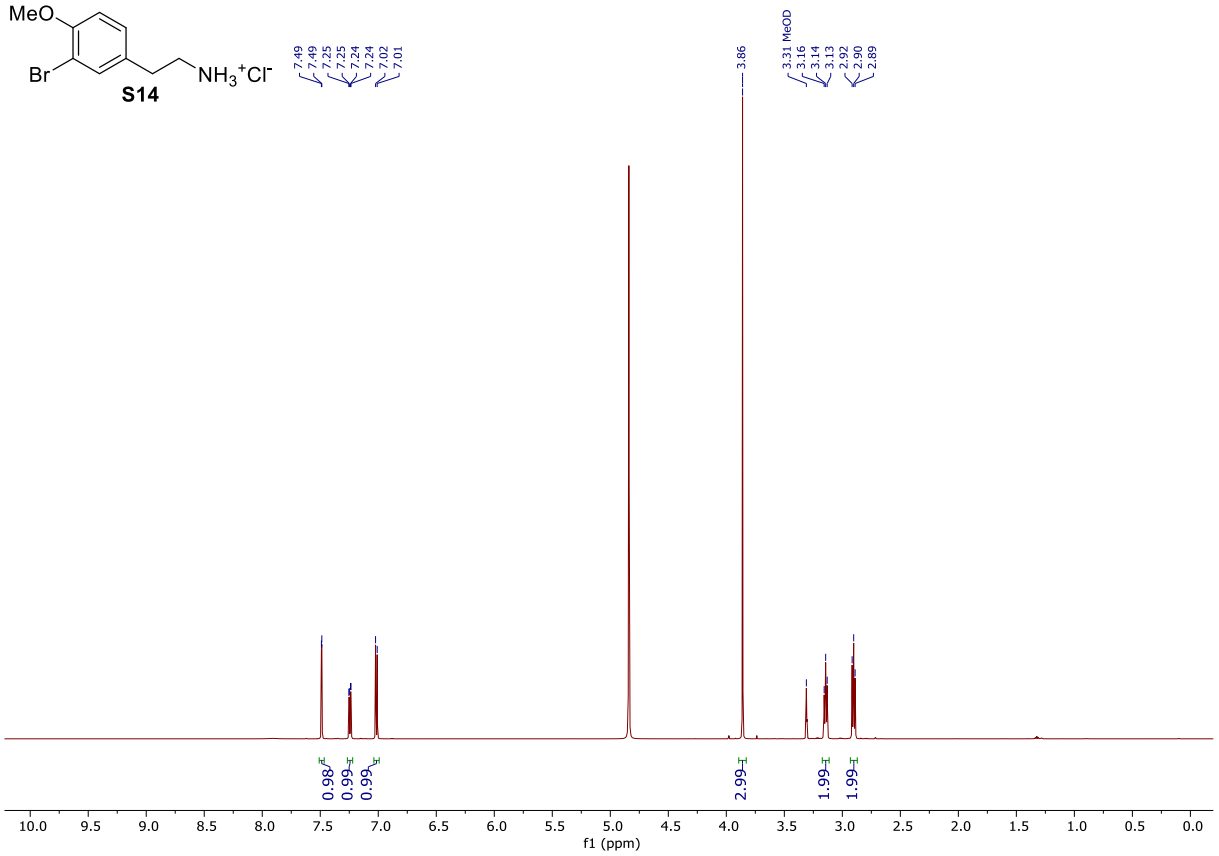


Figure S18. ^{13}C NMR spectra of S14

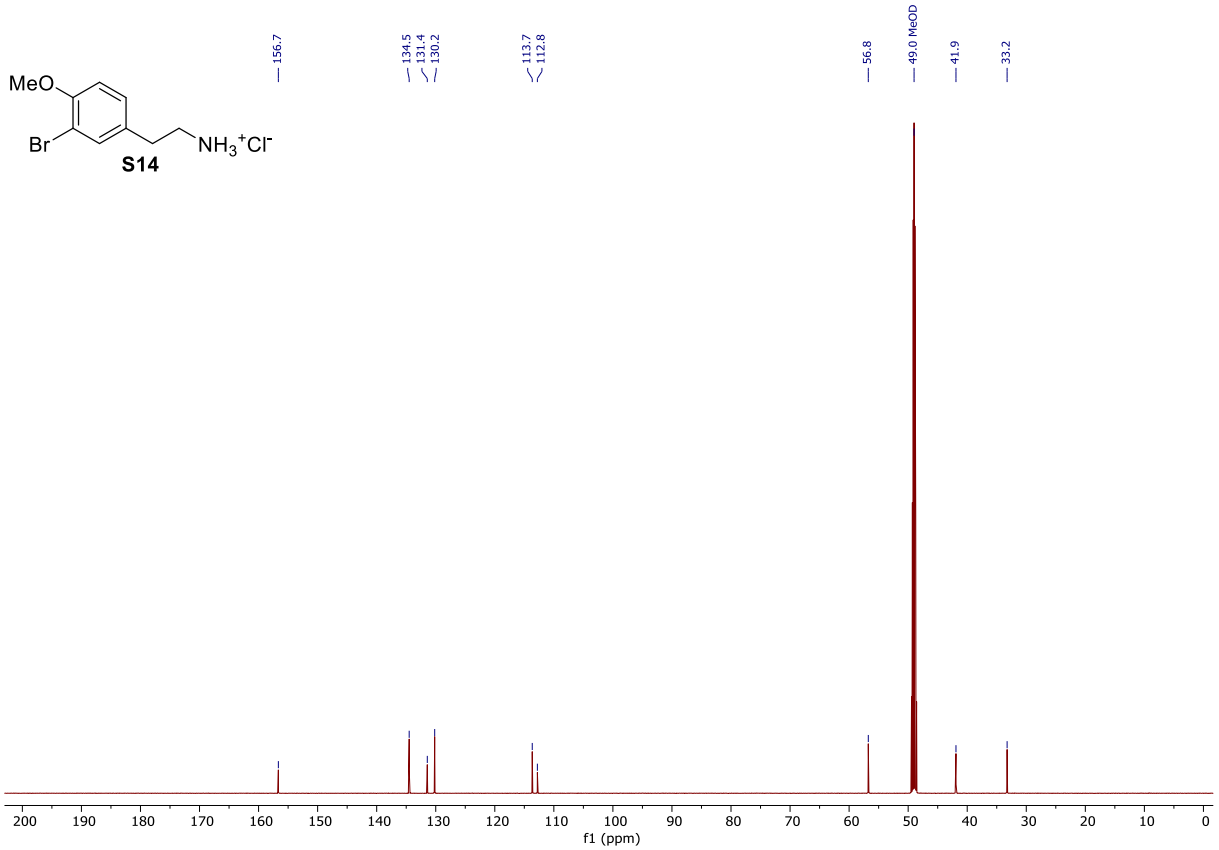


Figure S19. ^{1}H NMR spectra of S15

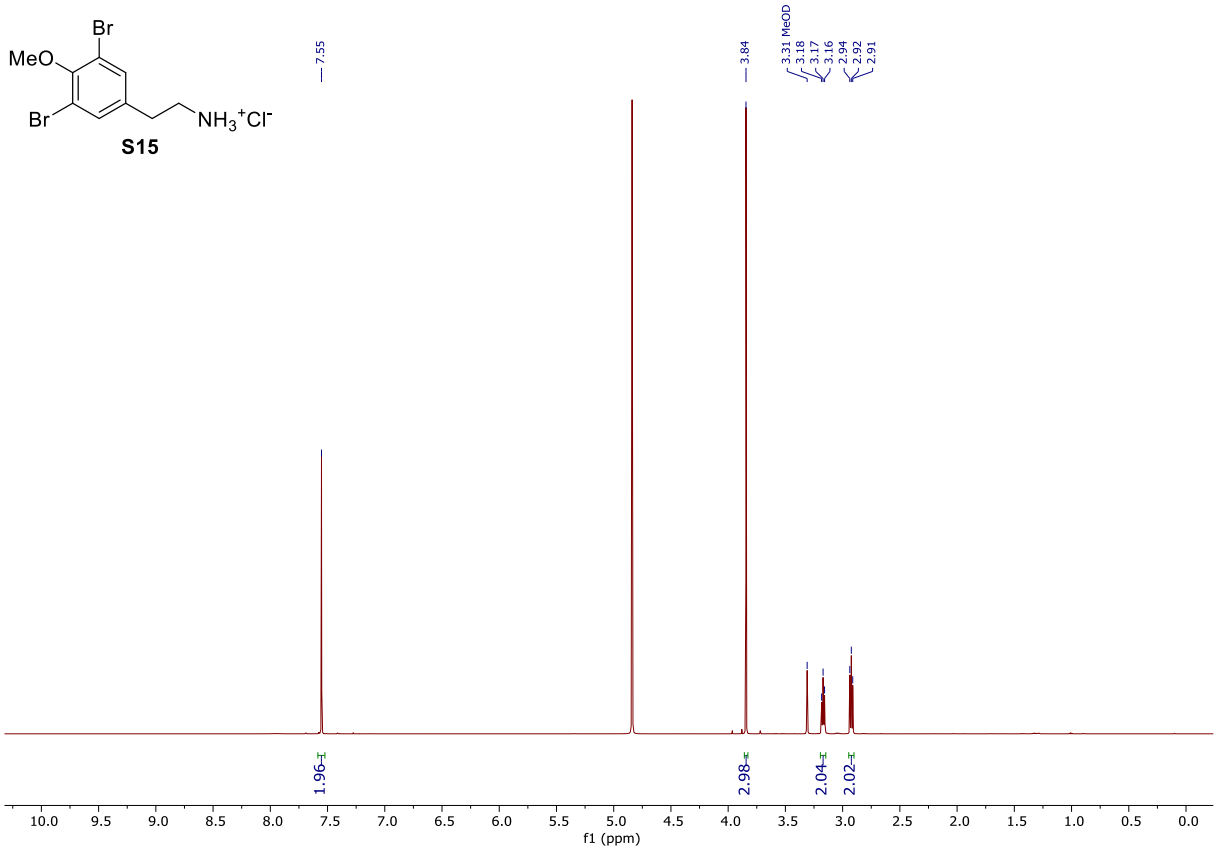


Figure S20. ^{13}C NMR spectra of S15

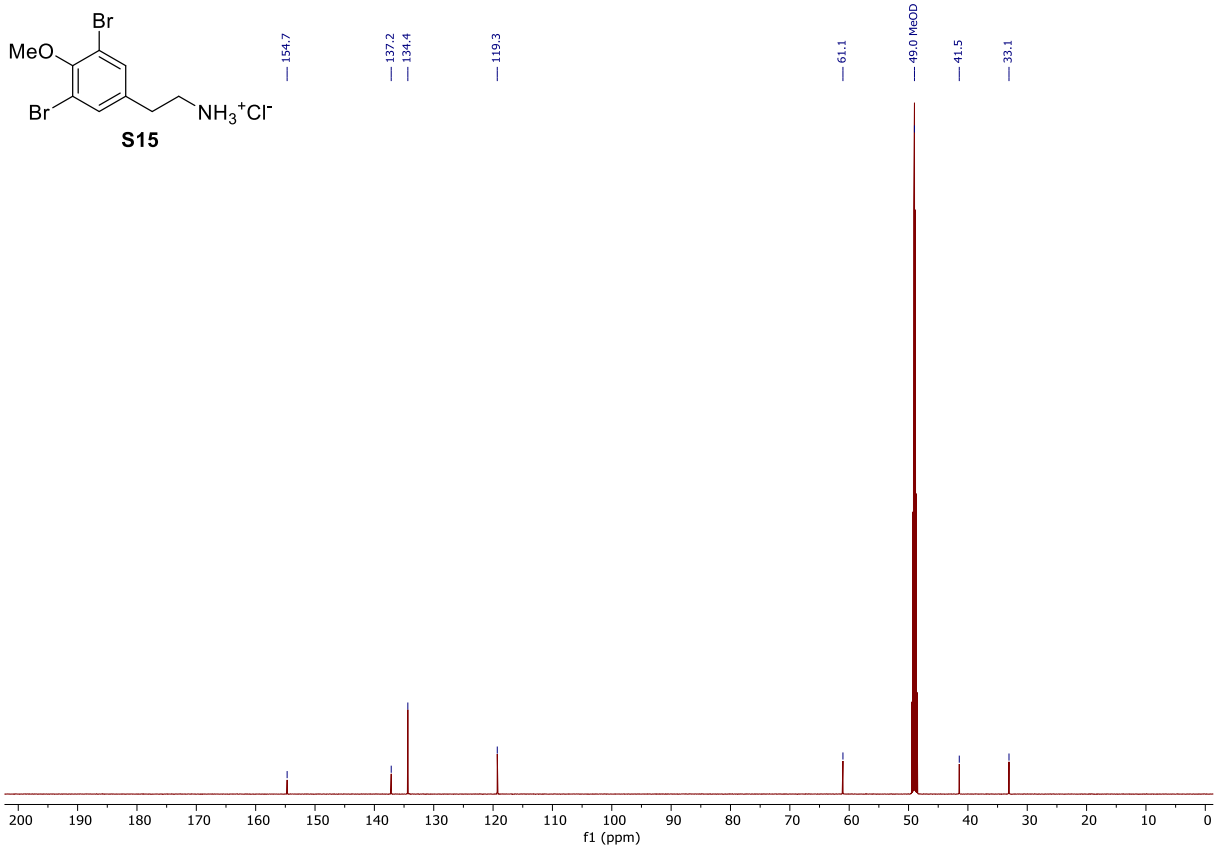


Figure S21. ^{1}H NMR spectra of S17

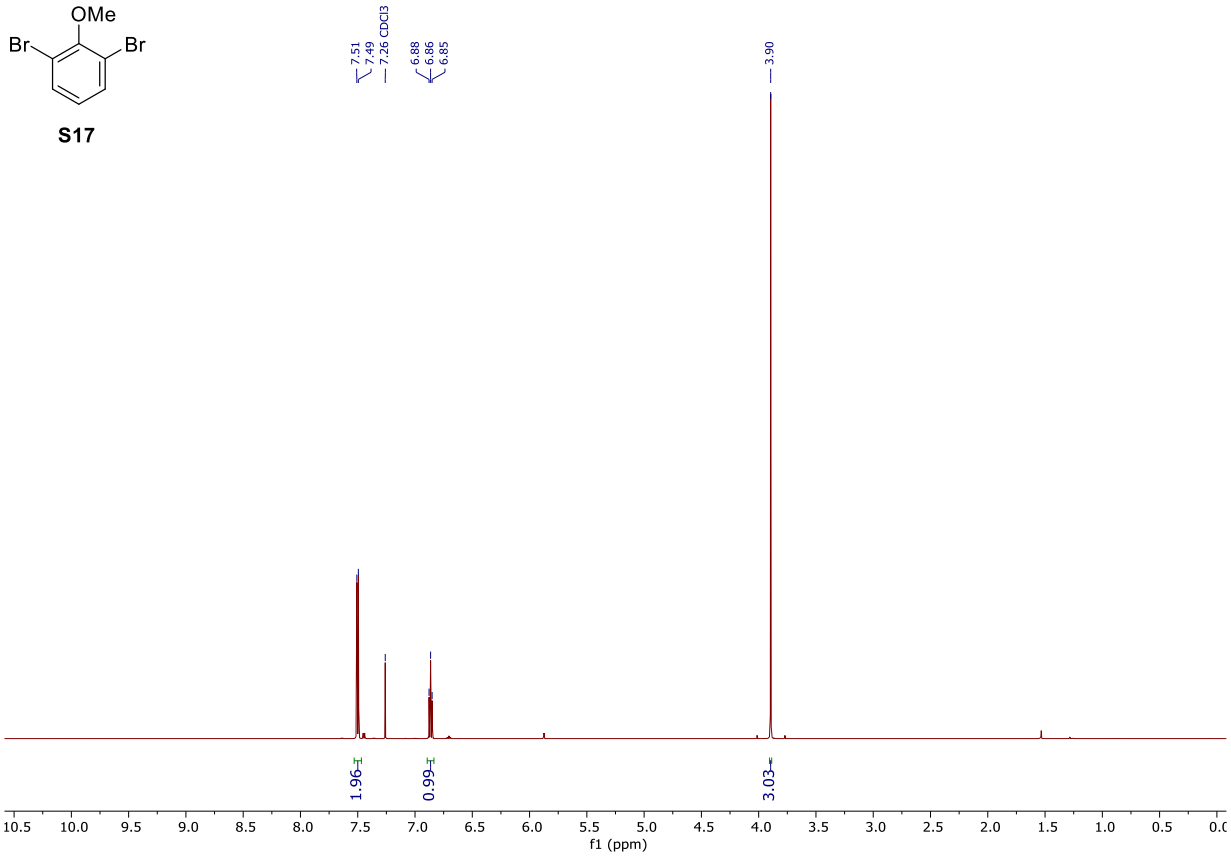


Figure S22. ^{13}C NMR spectra of S17

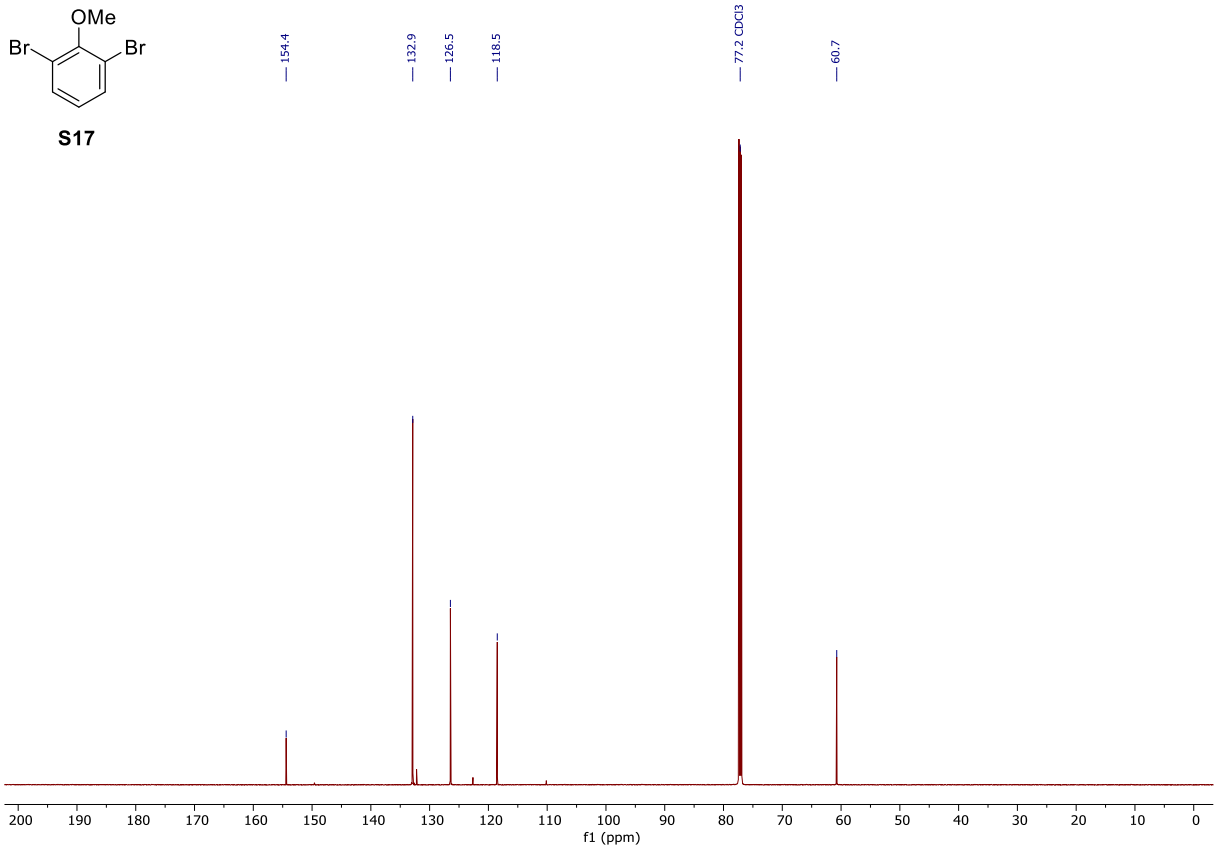


Figure S23. ^{1}H NMR spectra of S18

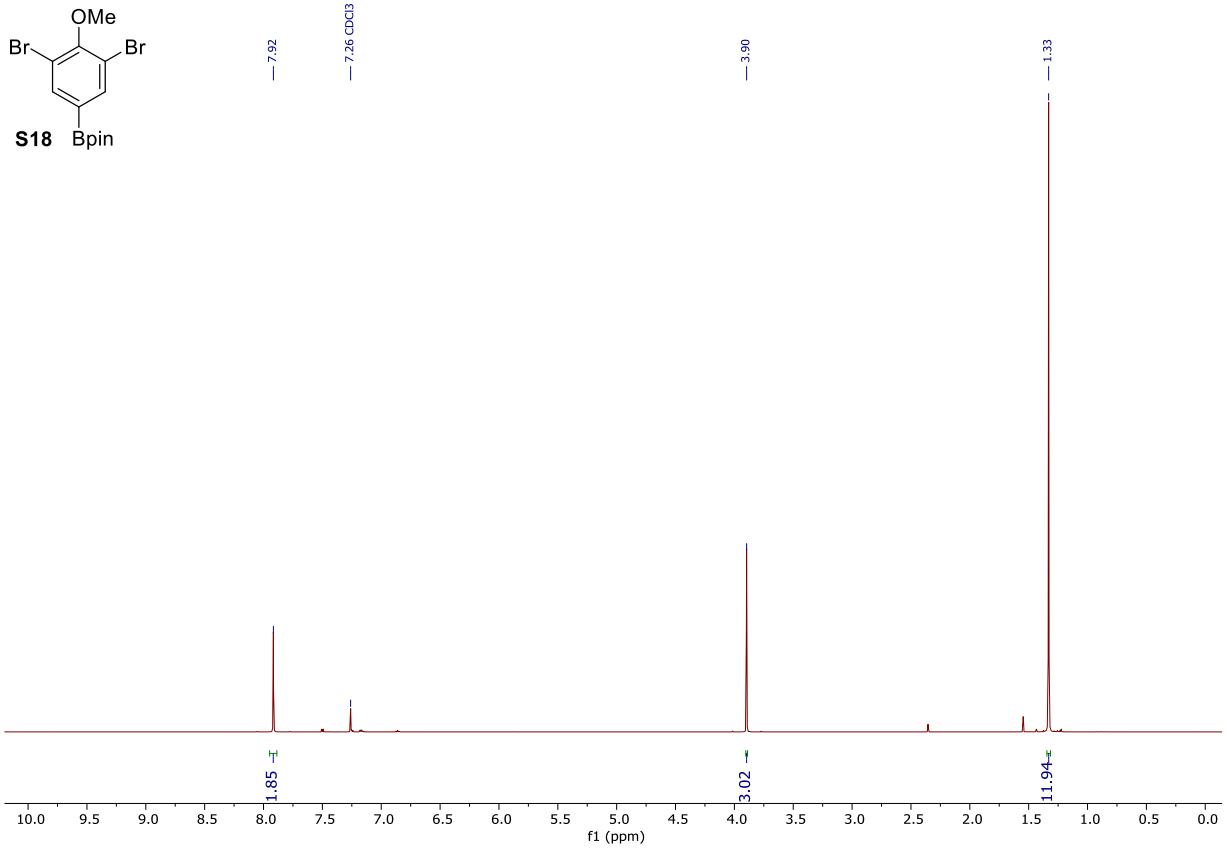


Figure S24. ^{13}C NMR spectra of S18

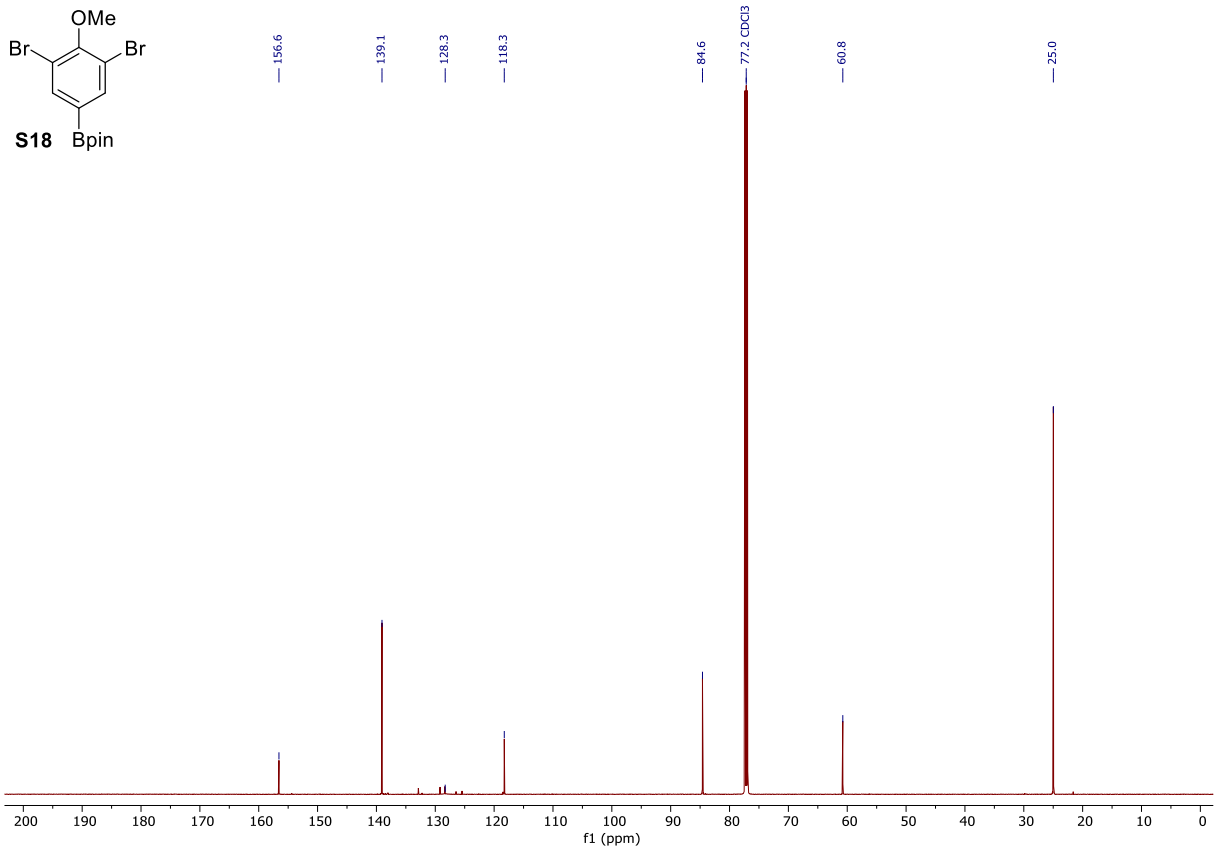


Figure S25. ^{1}H NMR spectra of S20

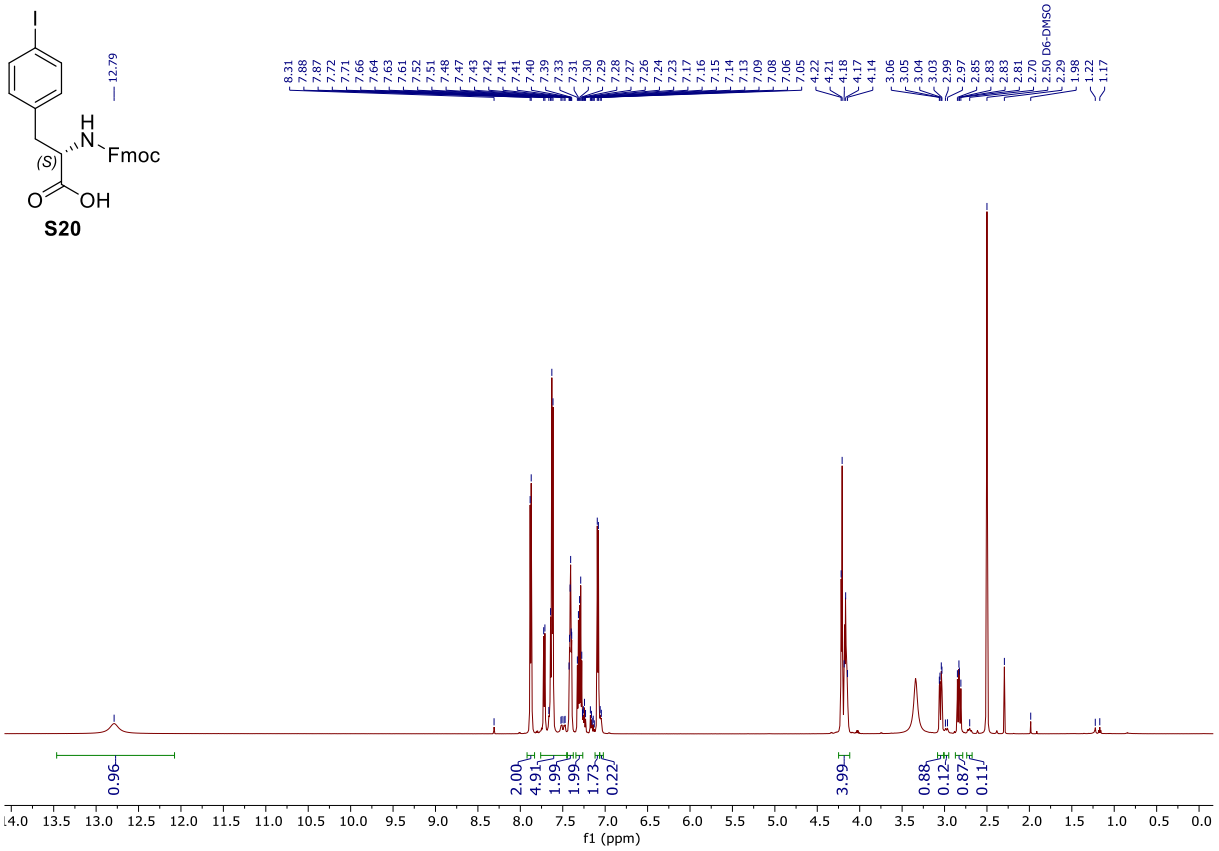


Figure S26. ^{13}C NMR spectra of S20

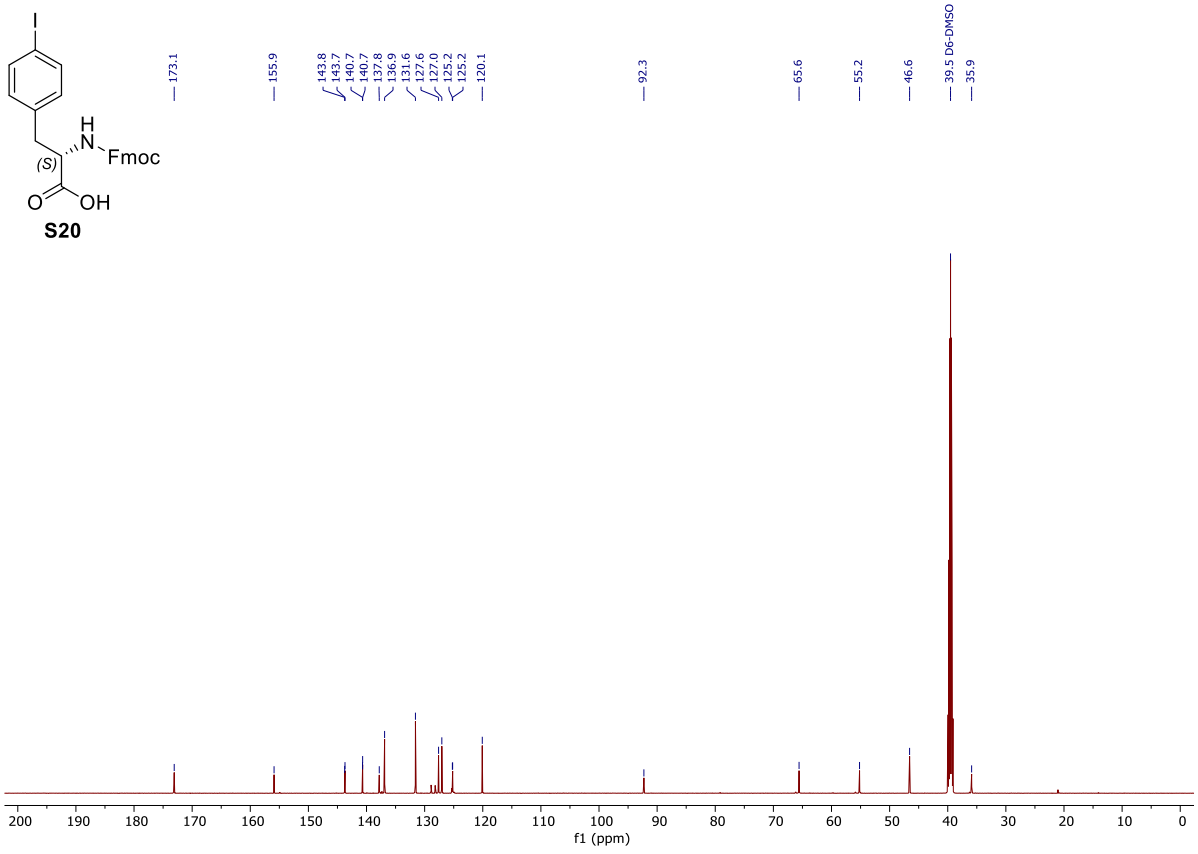


Figure S27. ^{1}H NMR spectra of S21

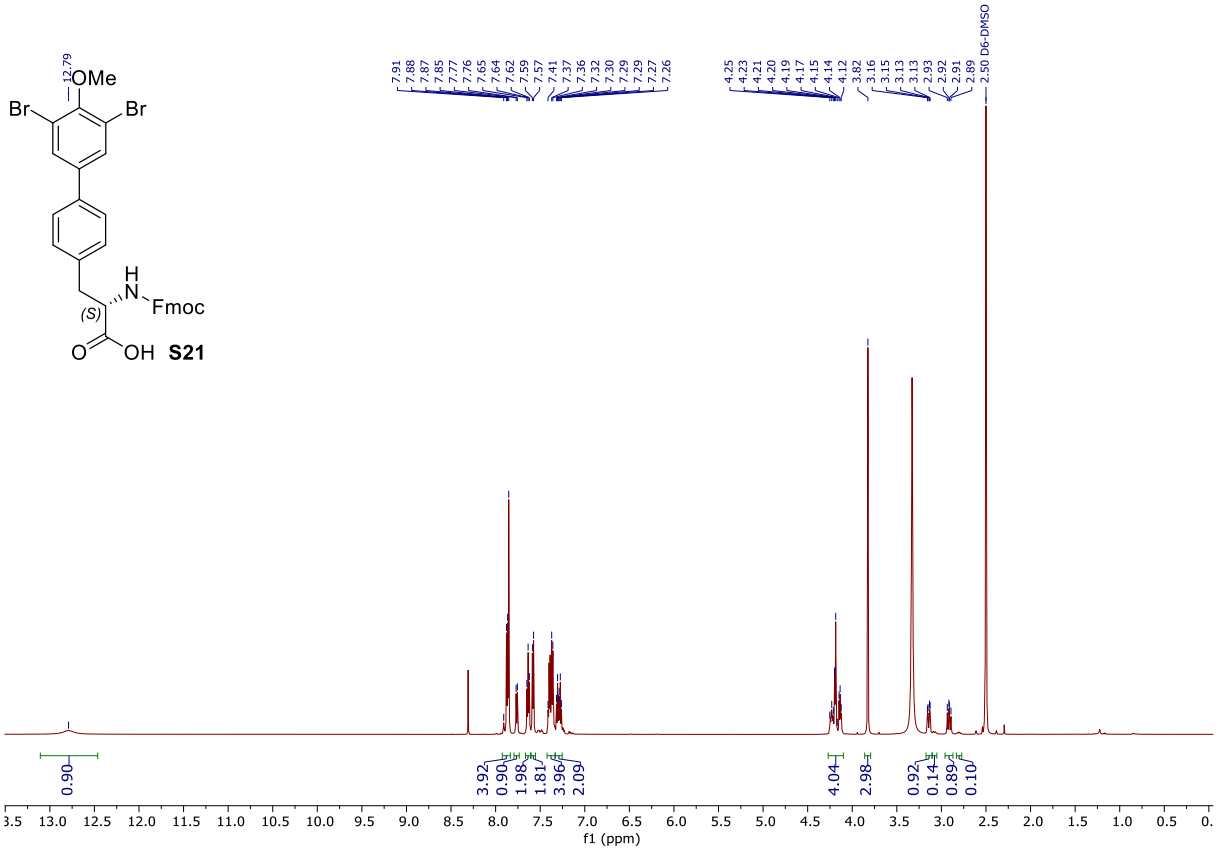


Figure S28. ^{13}C NMR spectra of S21

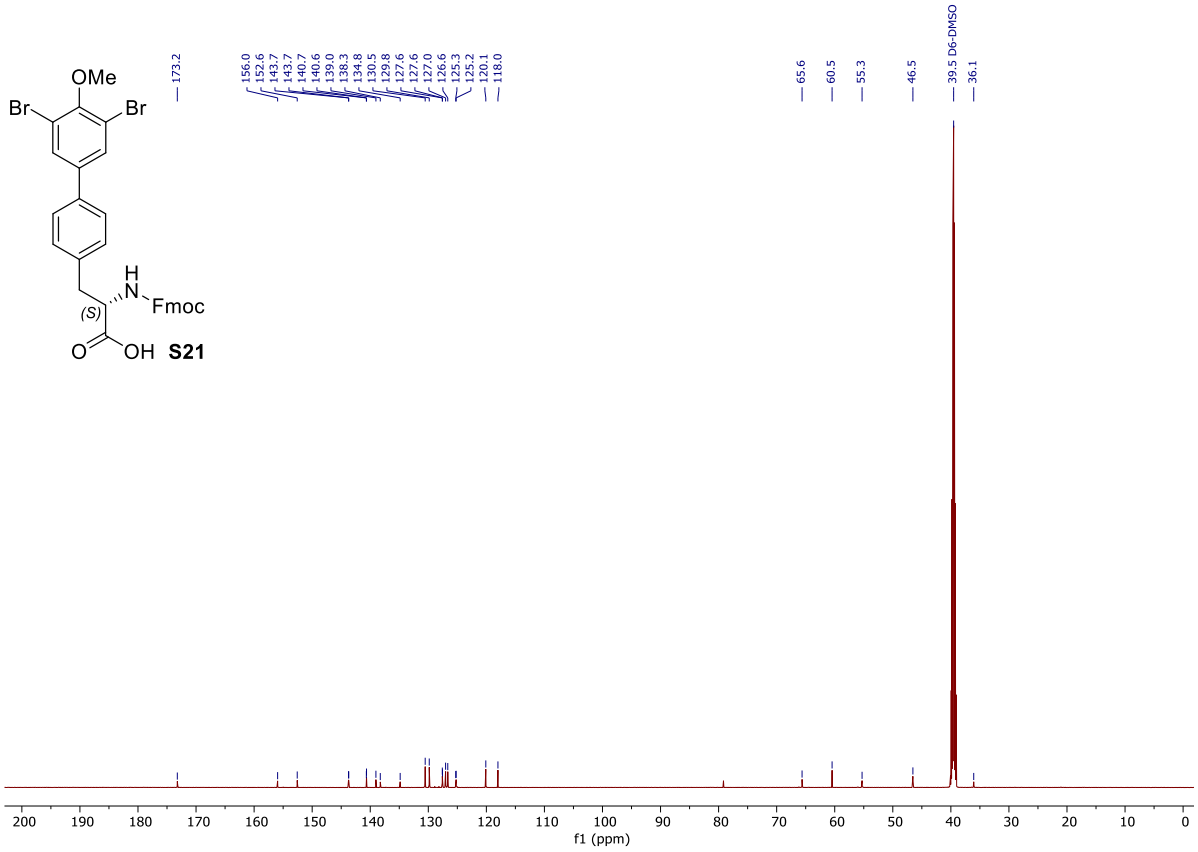


Figure S29. ^{1}H NMR spectra of S22

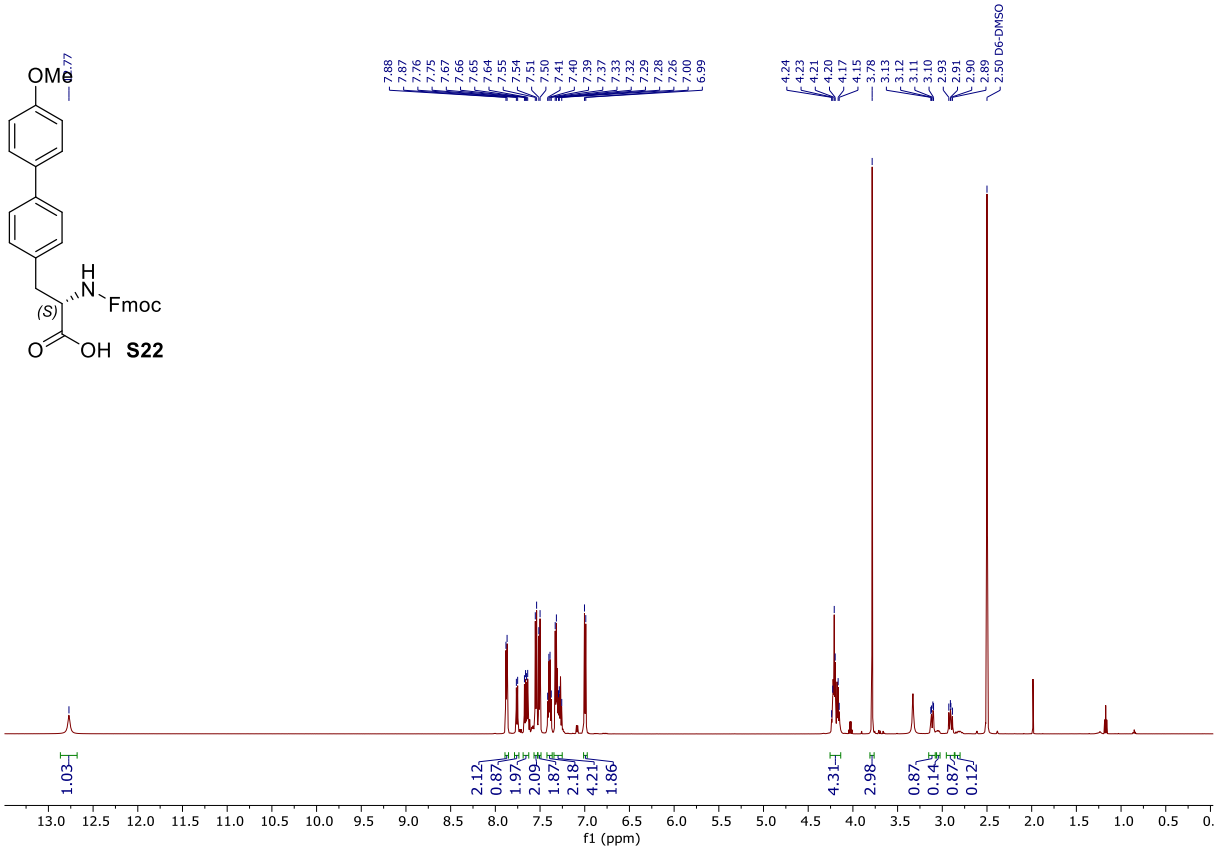


Figure S30. ^{13}C NMR spectra of S22

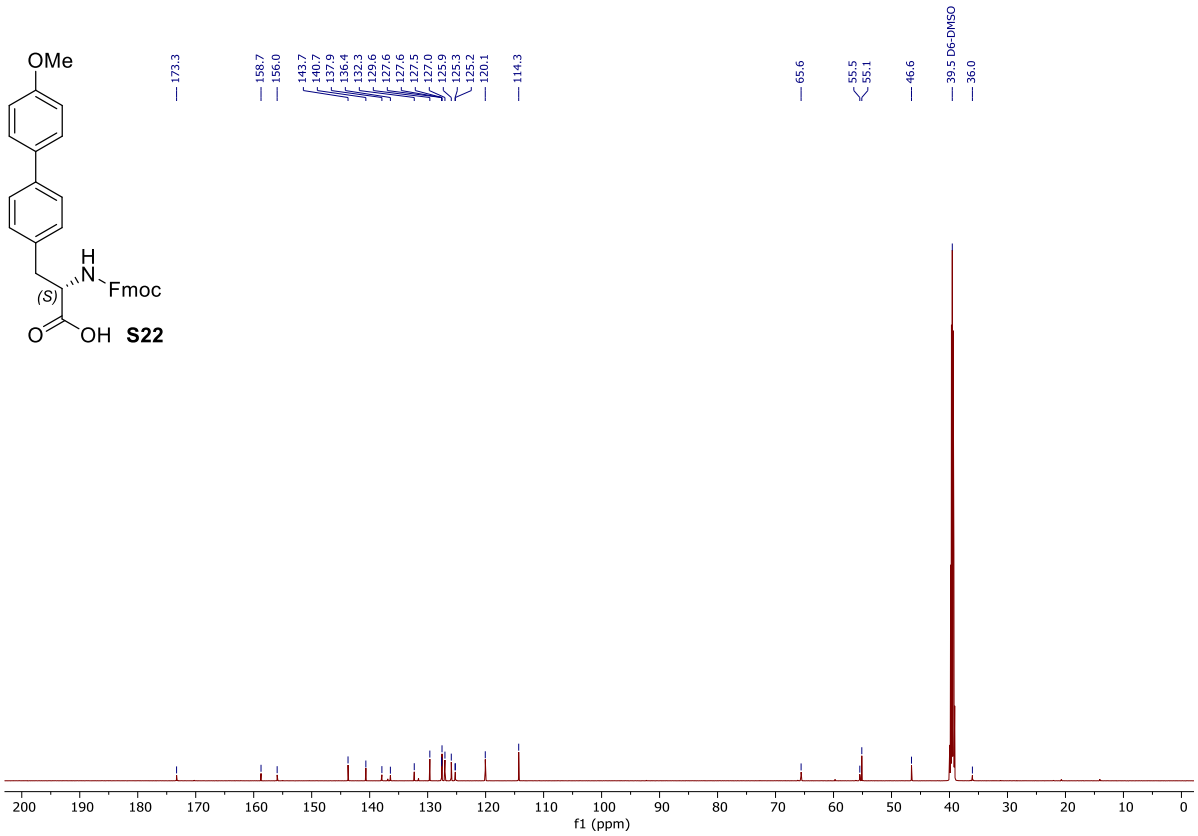


Figure S31. ^{1}H NMR spectra of S24

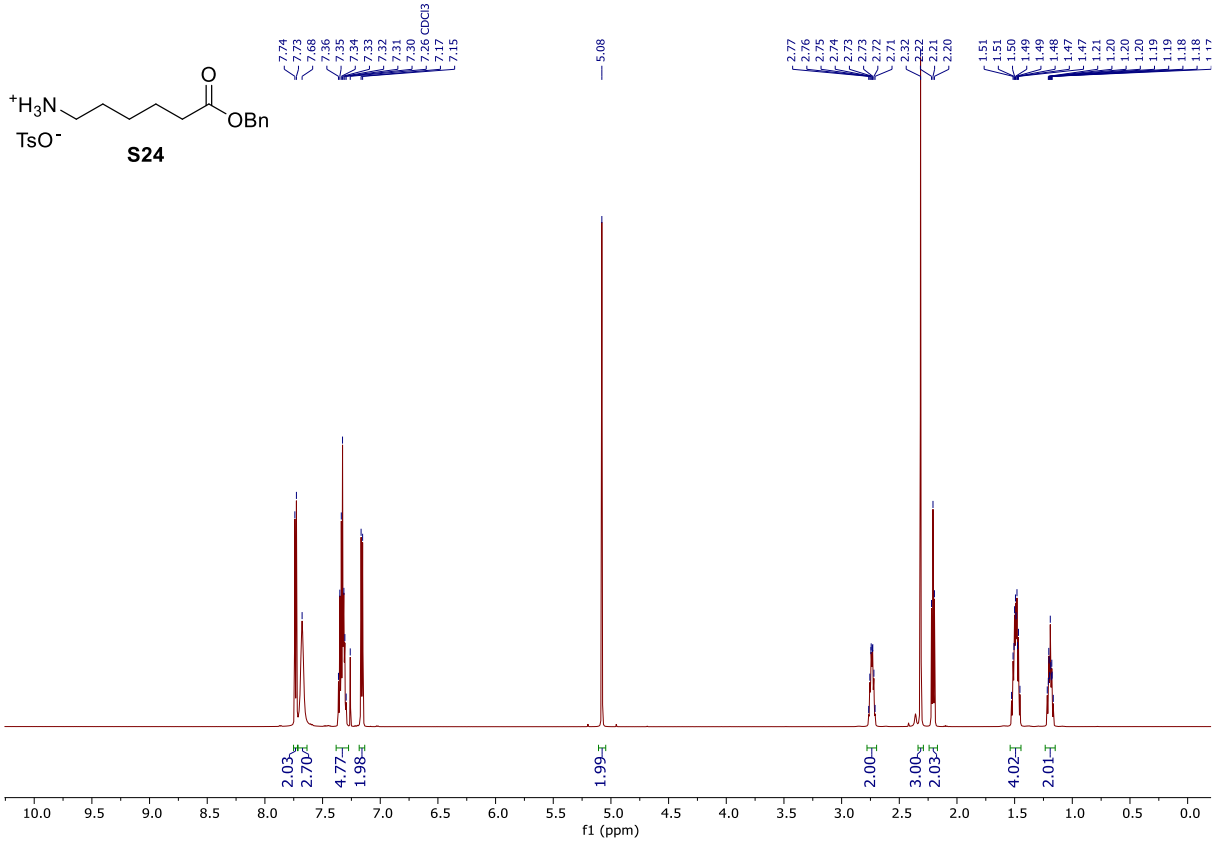


Figure S32. ^{13}C NMR spectra of S24

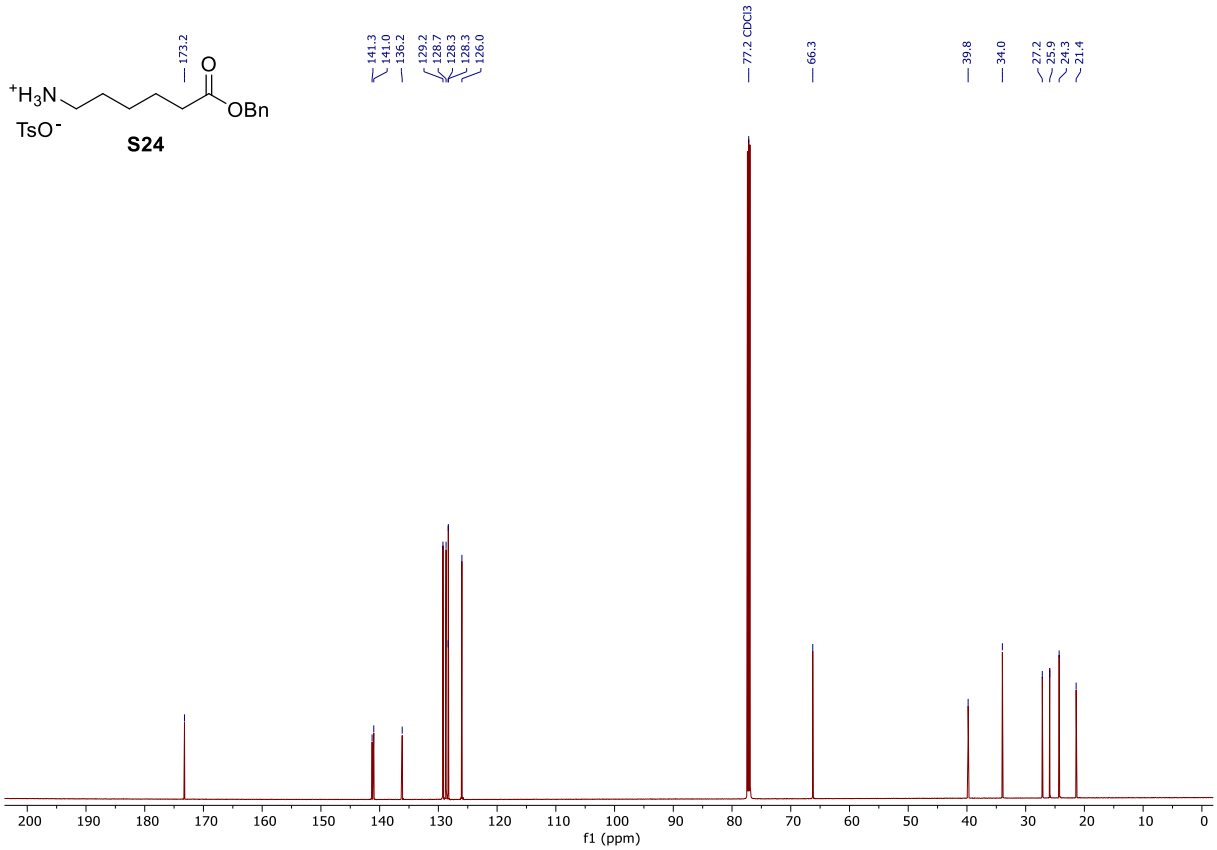


Figure S33. ^{1}H NMR spectra of S25

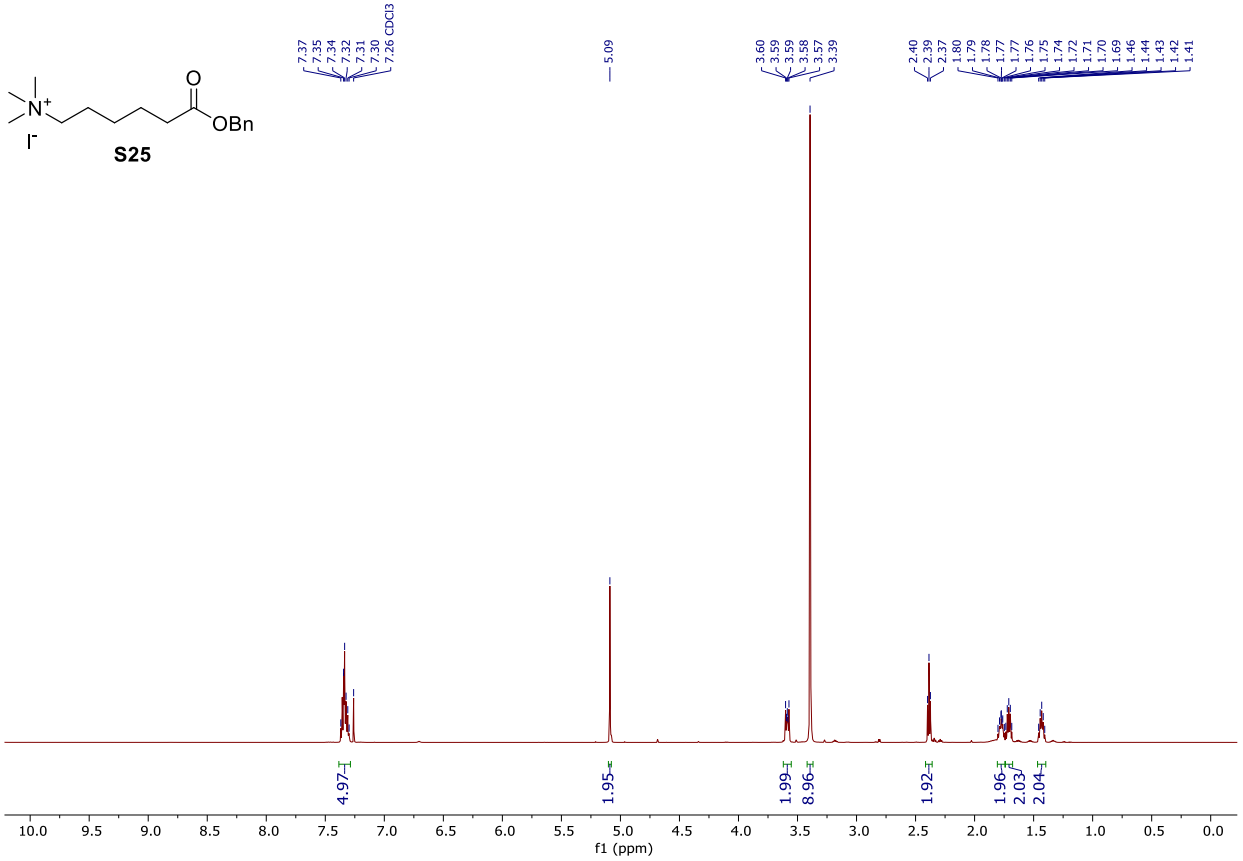


Figure S34. ^{13}C NMR spectra of S25

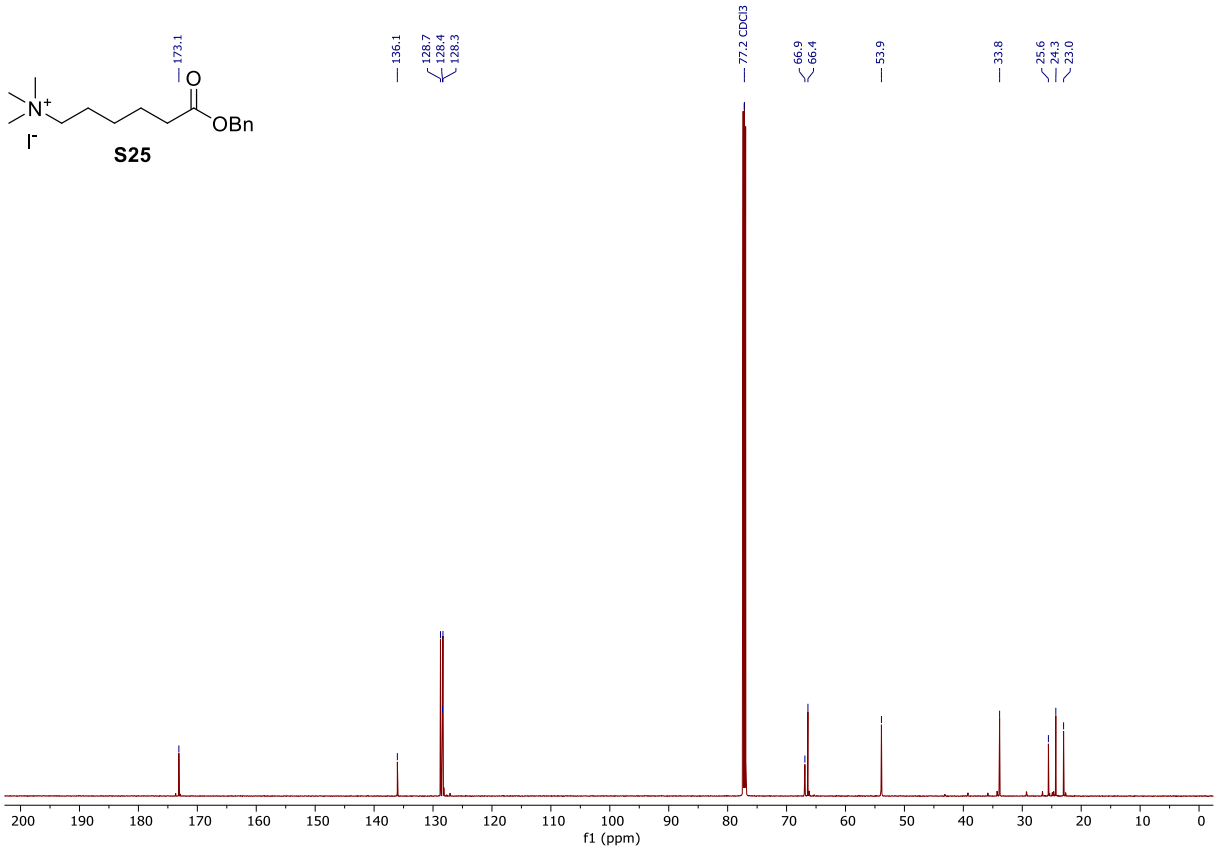


Figure S35. ^{1}H NMR spectra of S26

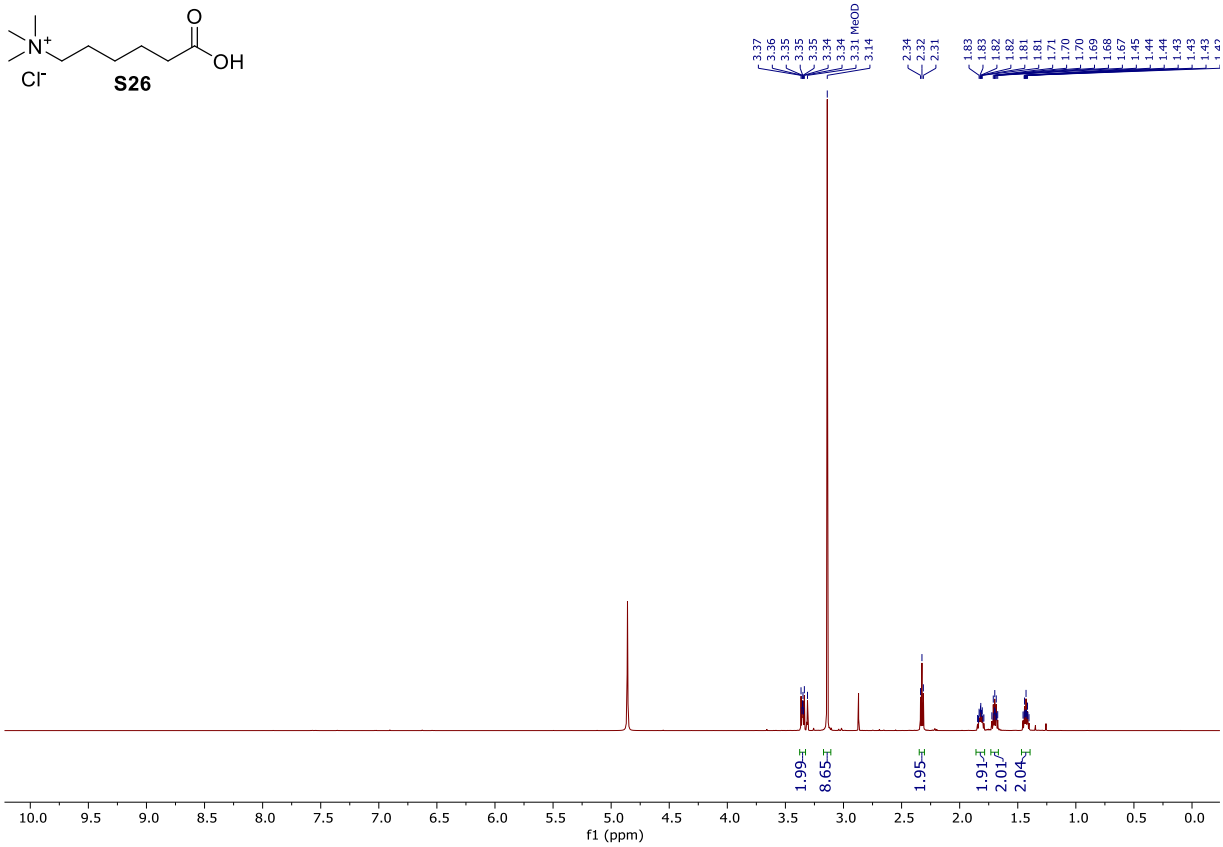


Figure S36. ^{1}H NMR spectra of S28

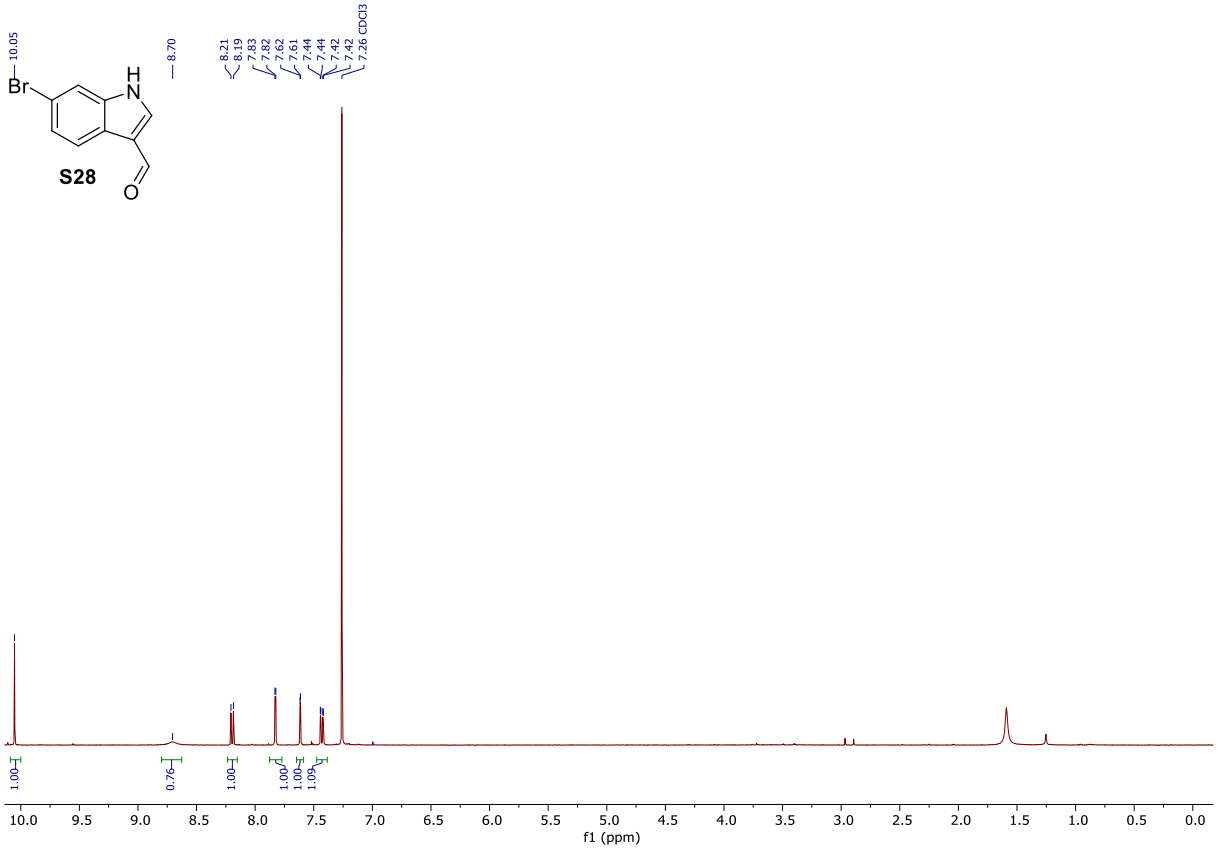


Figure S37. ^{1}H NMR spectra of S29

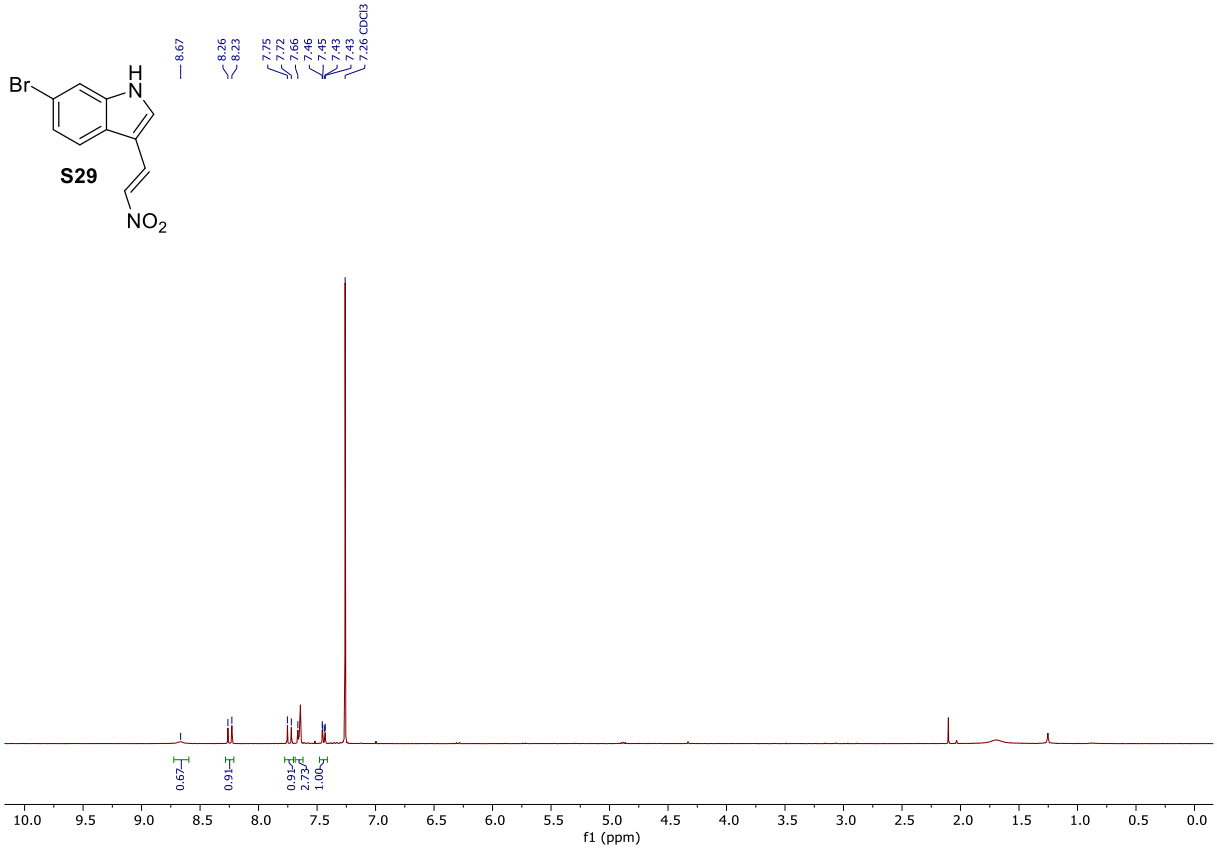


Figure S38. ^{1}H NMR spectra of S30

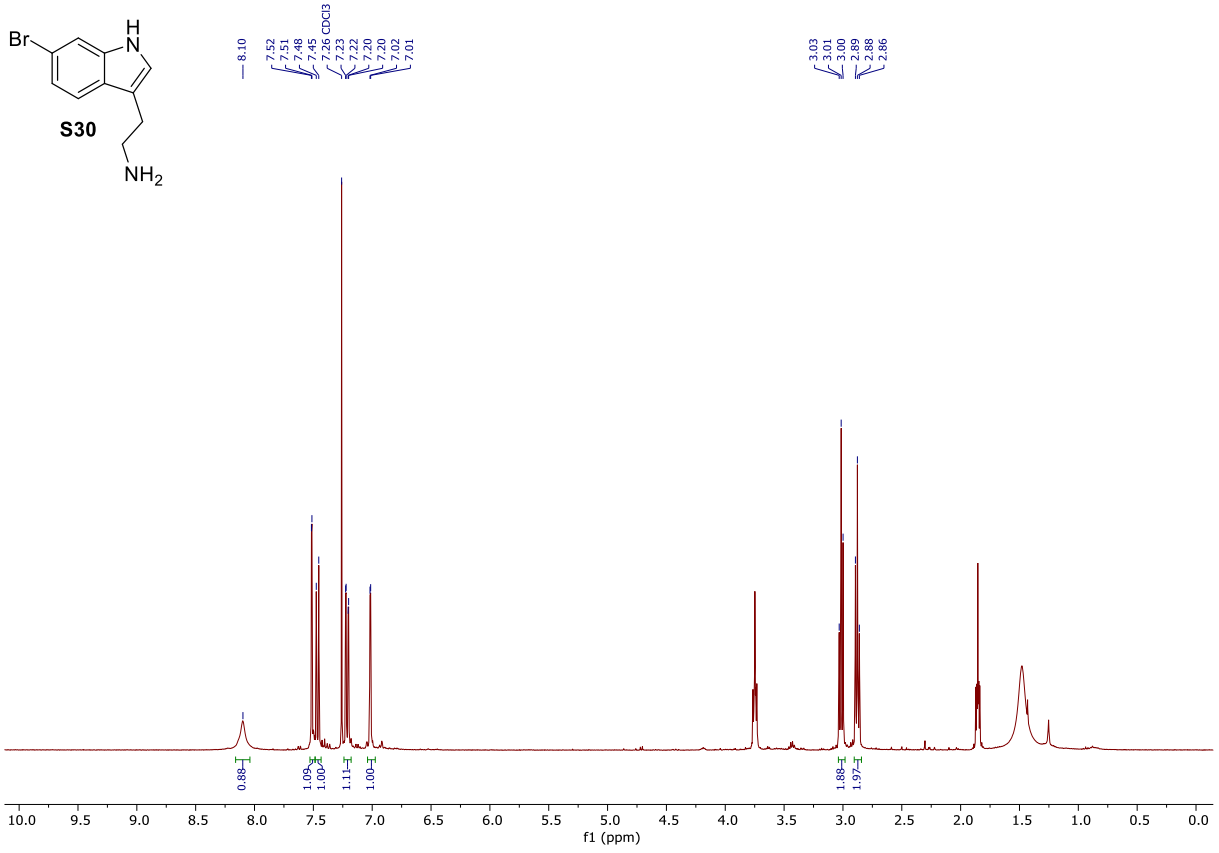


Figure S39: ^{1}H NMR spectrum of **1**

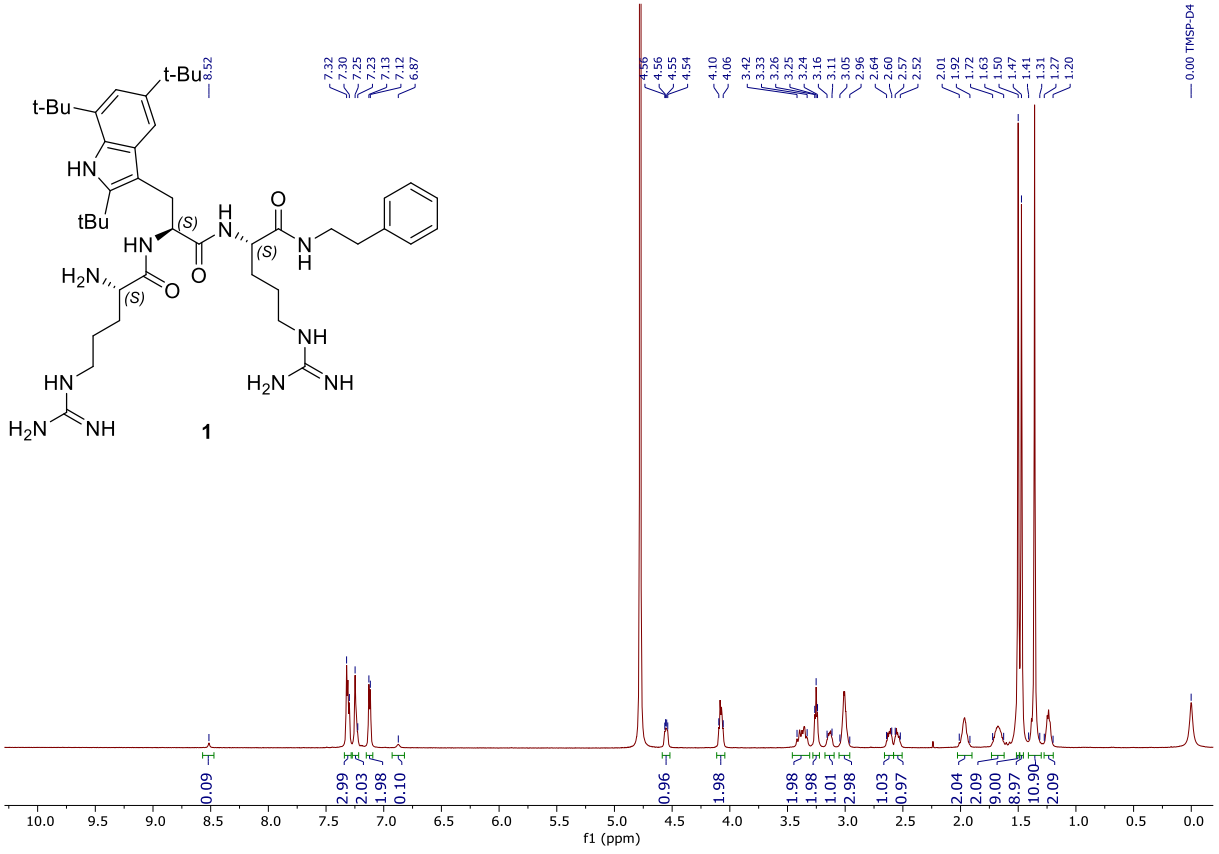
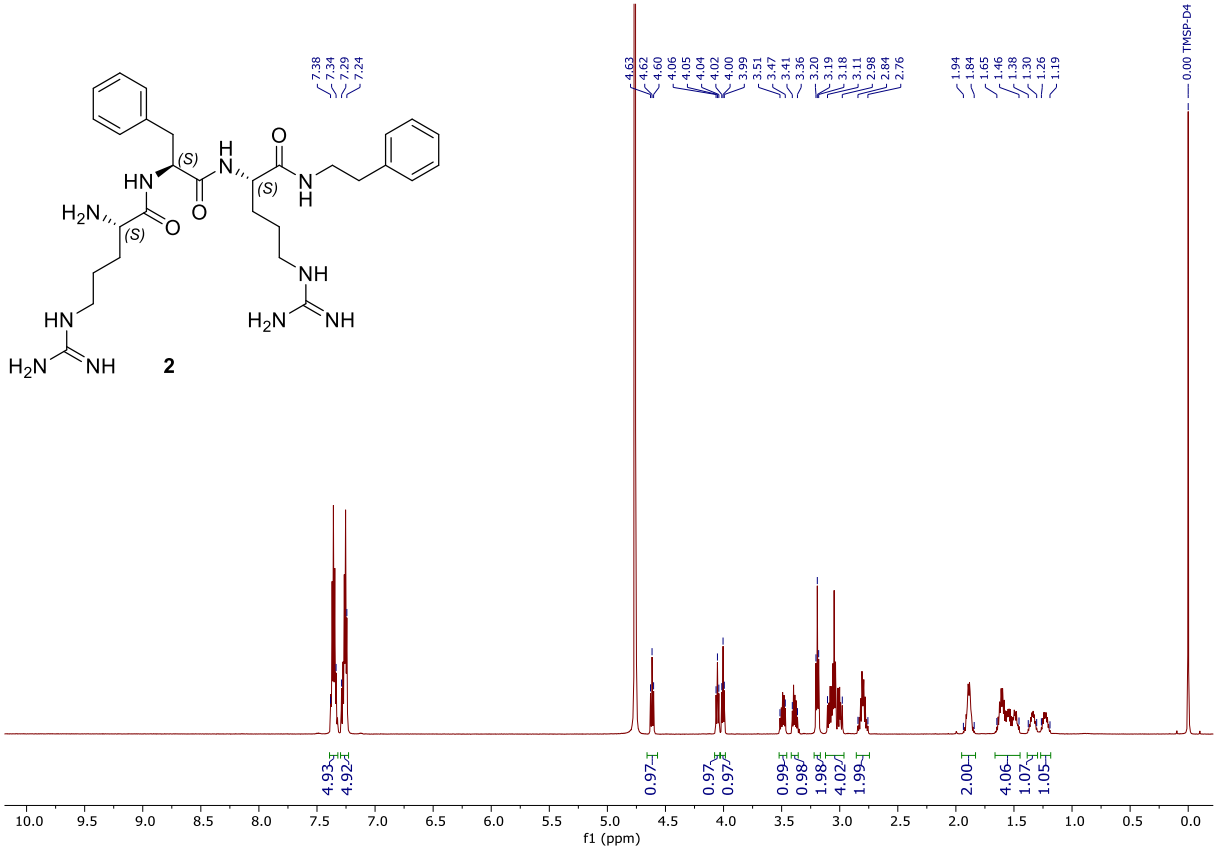


Figure S40: ^{1}H NMR spectrum of **2**



2

Figure S41: ^{1}H NMR spectrum of **3**

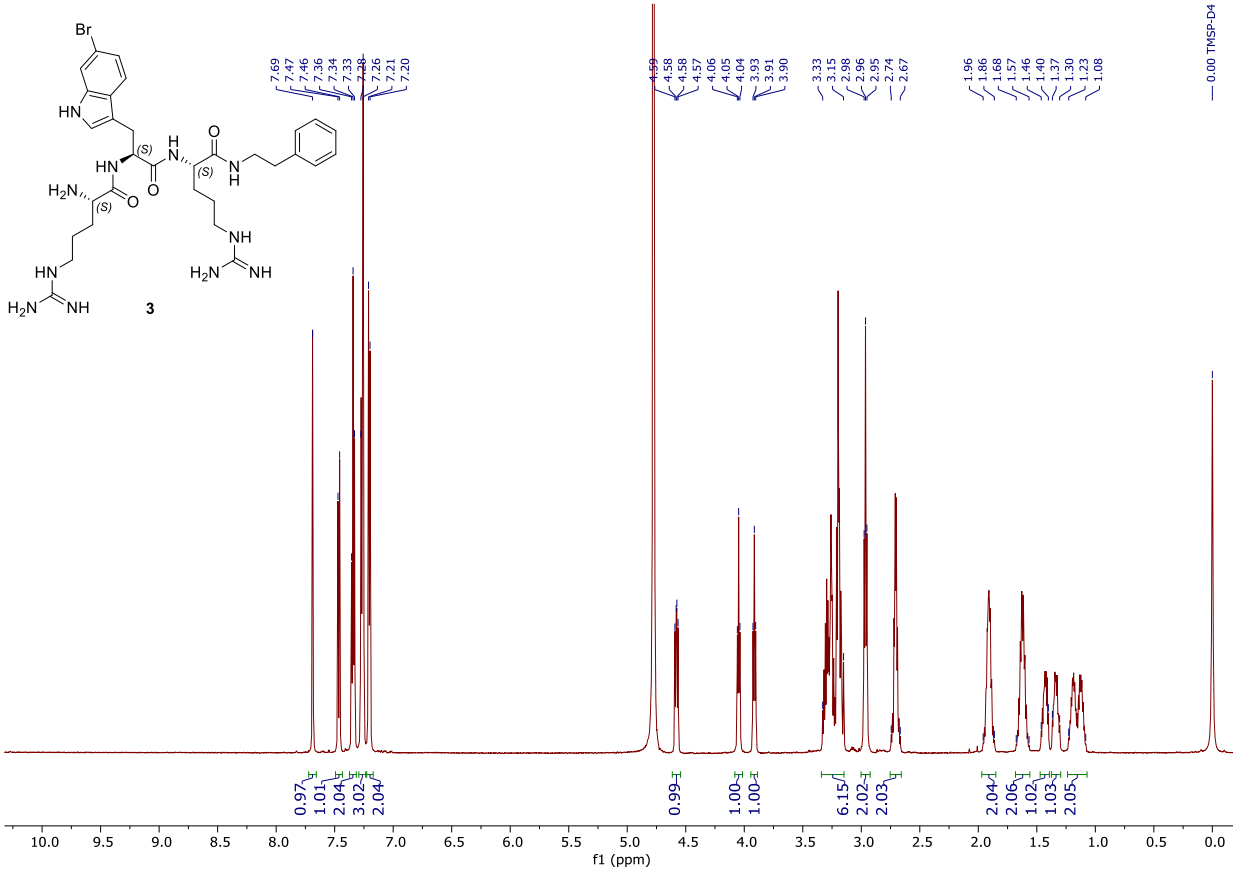


Figure S42: ^{1}H NMR spectrum of **4**

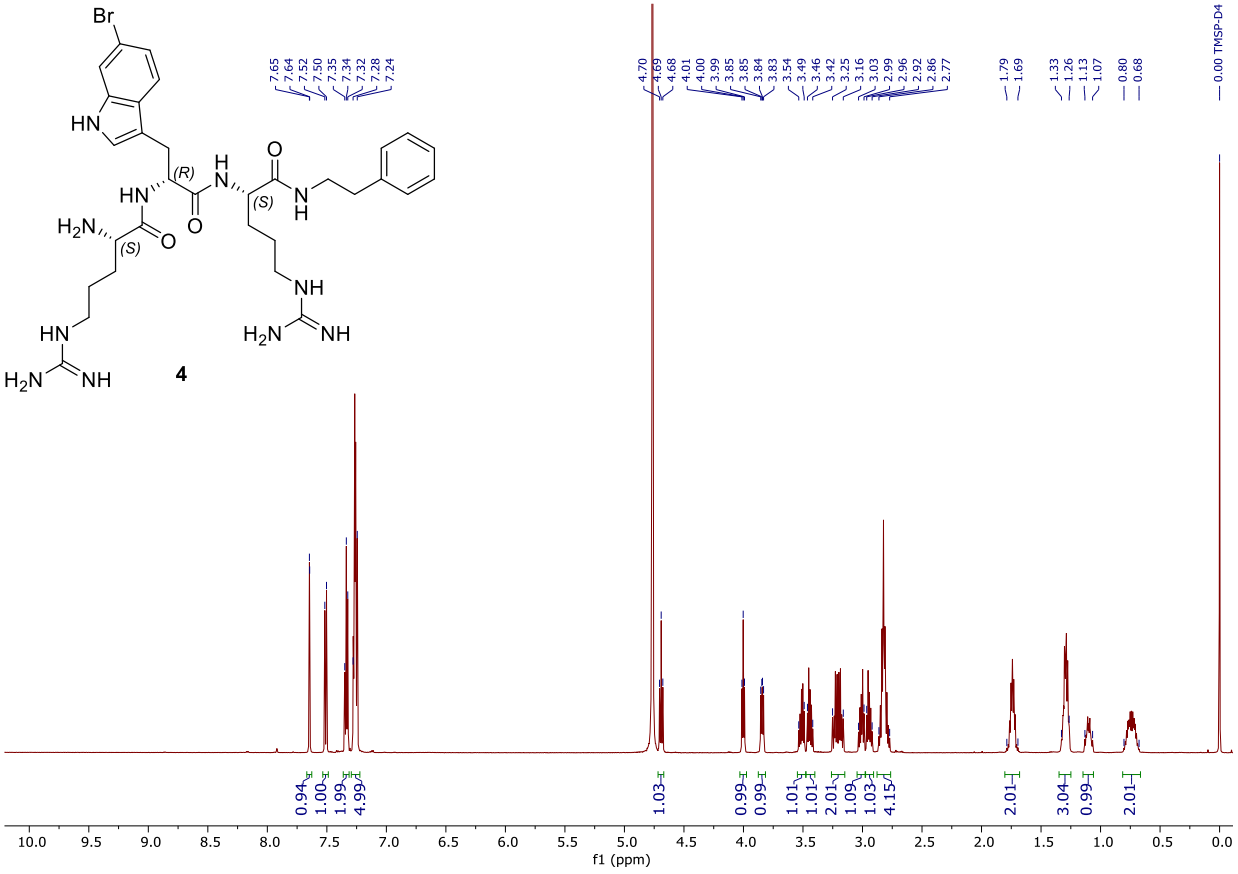


Figure S43: ^{1}H NMR spectrum of **5**

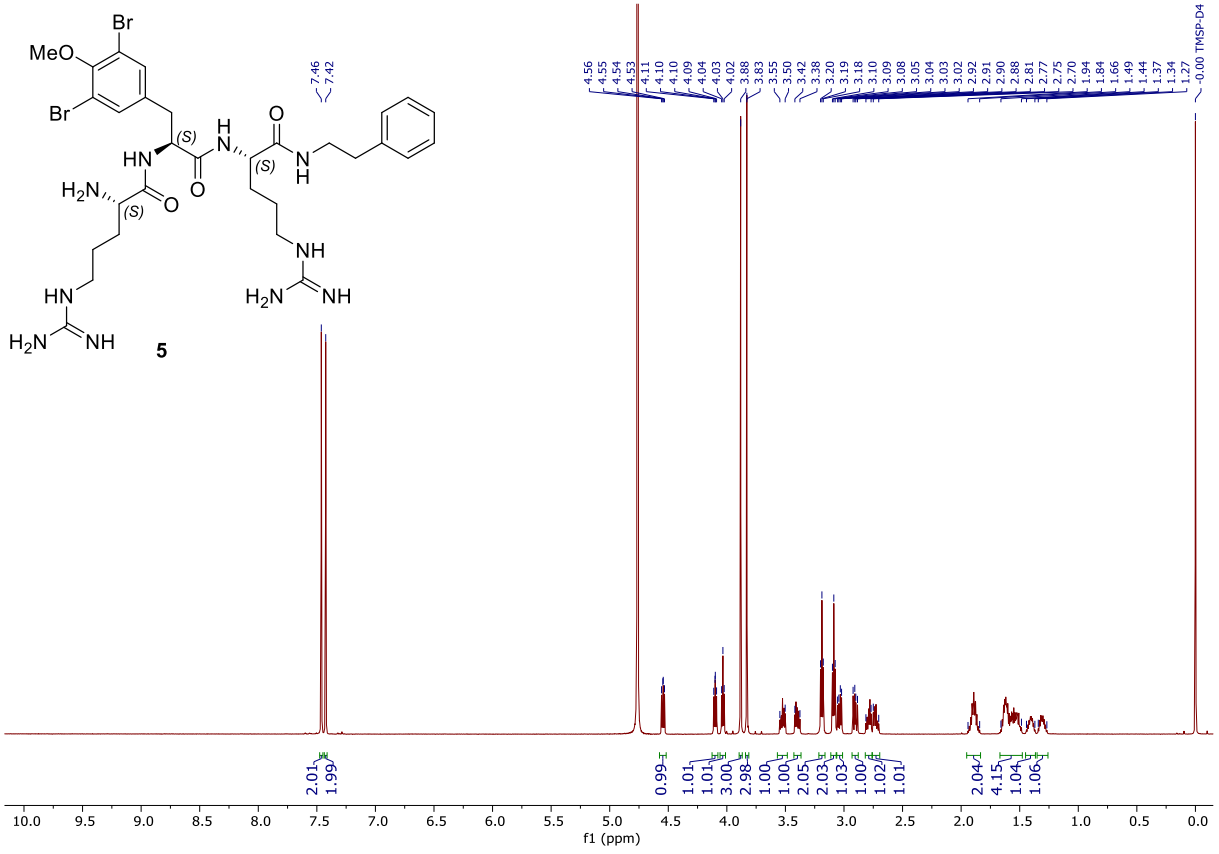


Figure S44: ^{1}H NMR spectrum of **6**

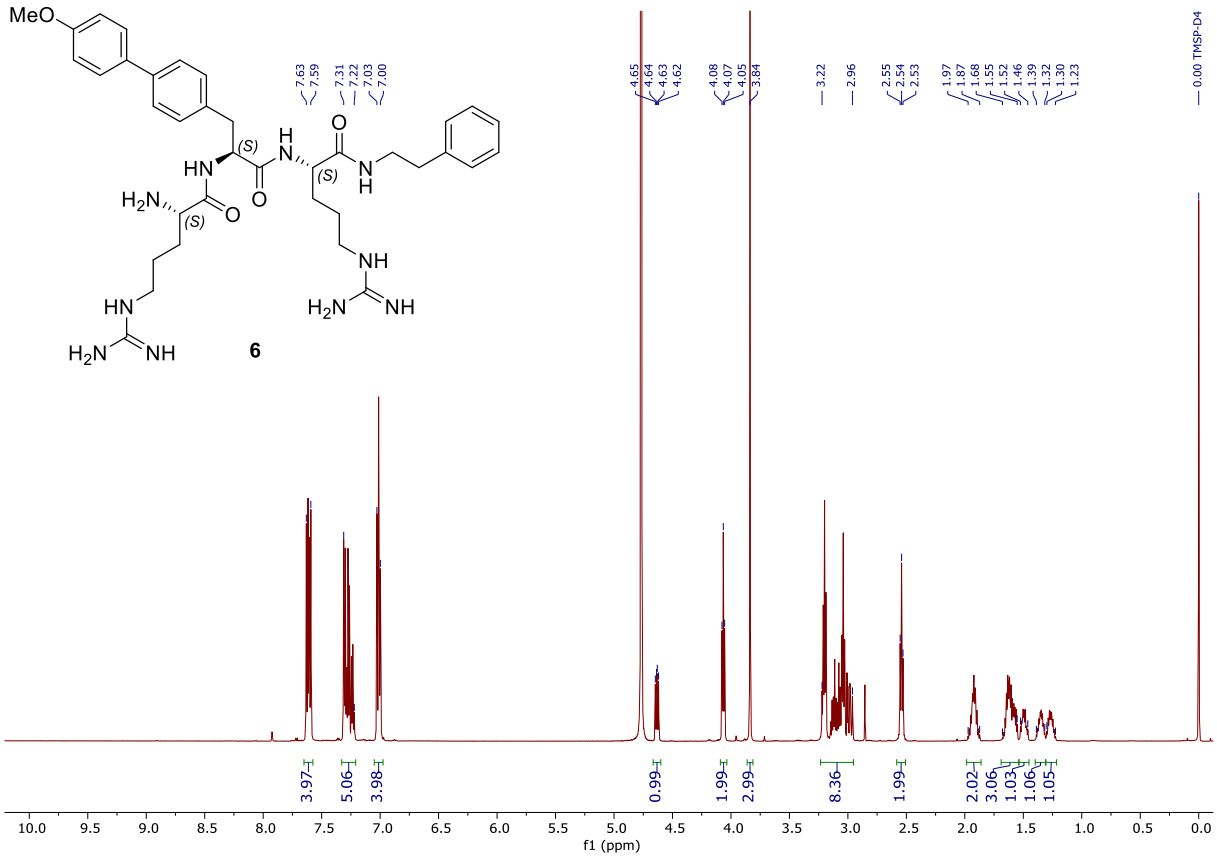


Figure S45: ^{1}H NMR spectrum of **7**

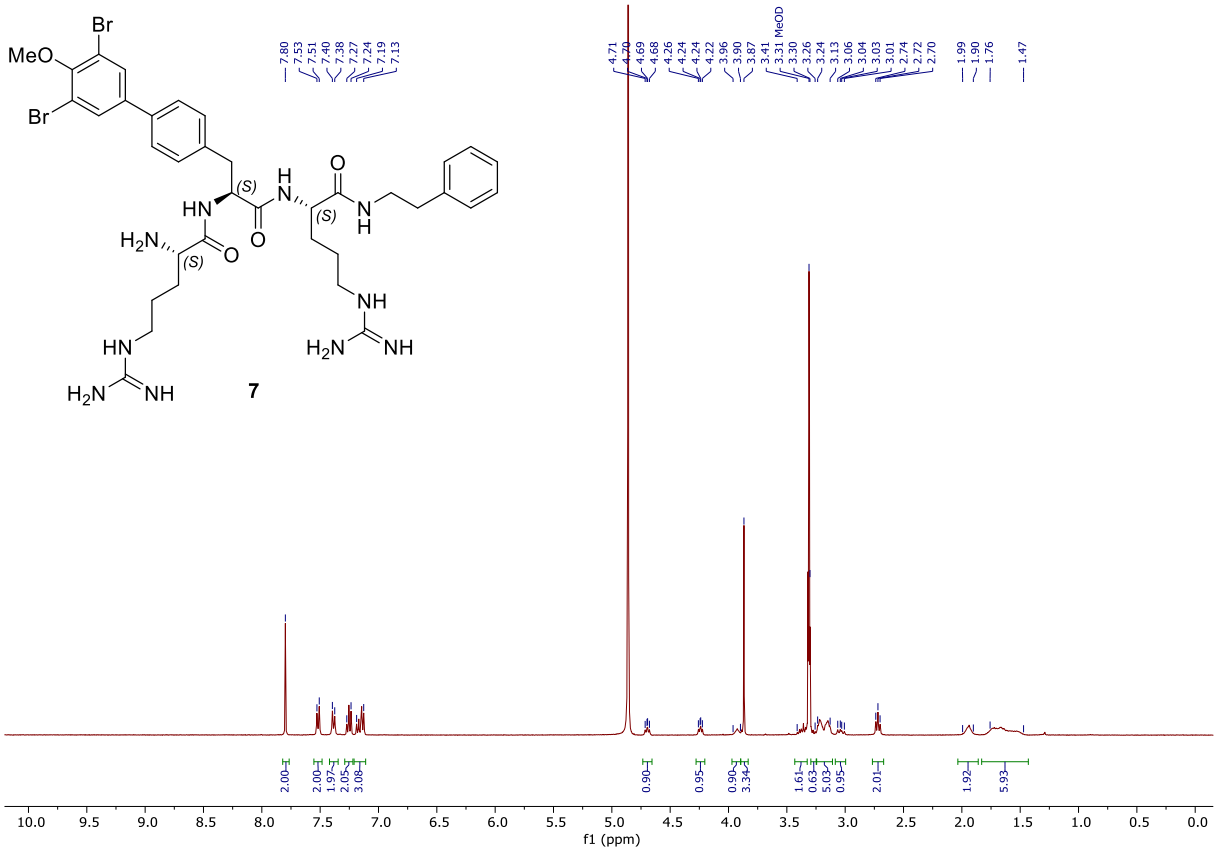


Figure S46: ^{1}H NMR spectrum of **8**

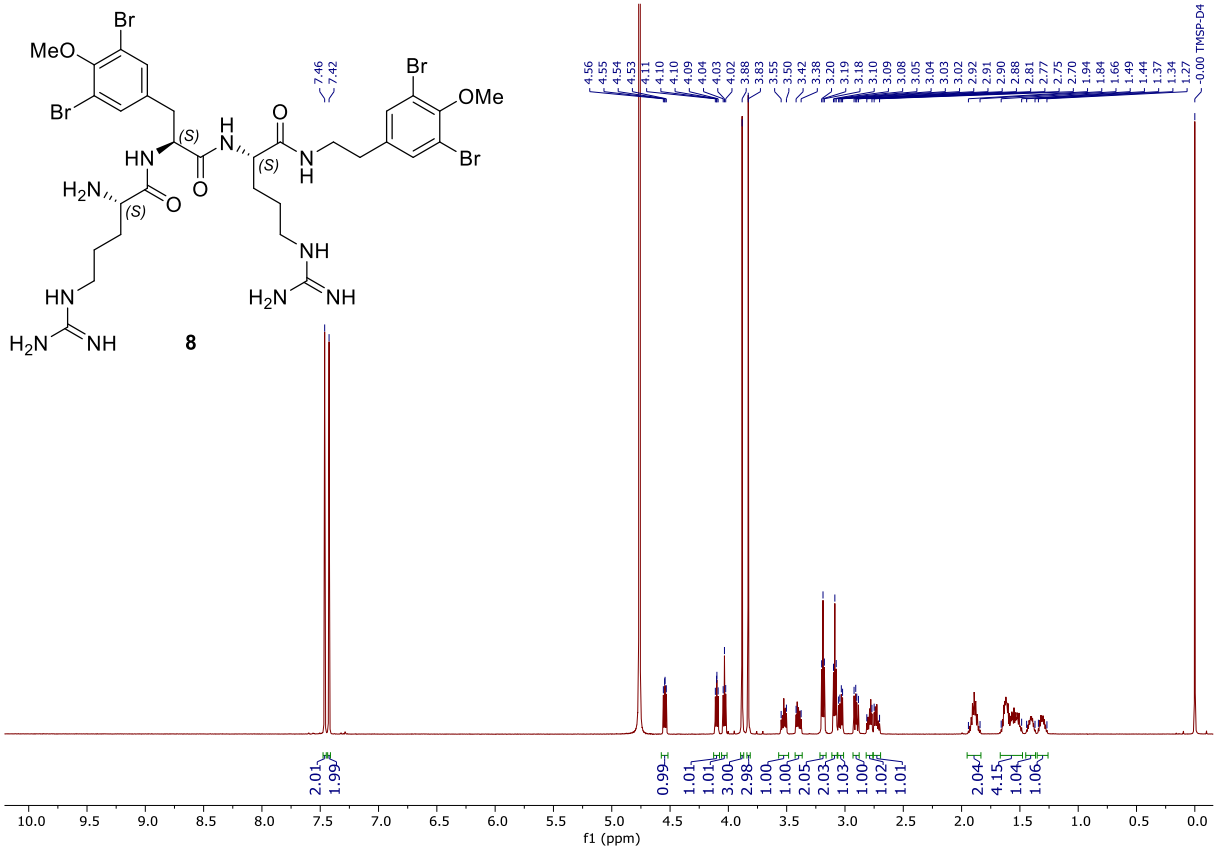


Figure S47: ^{1}H NMR spectrum of **9**

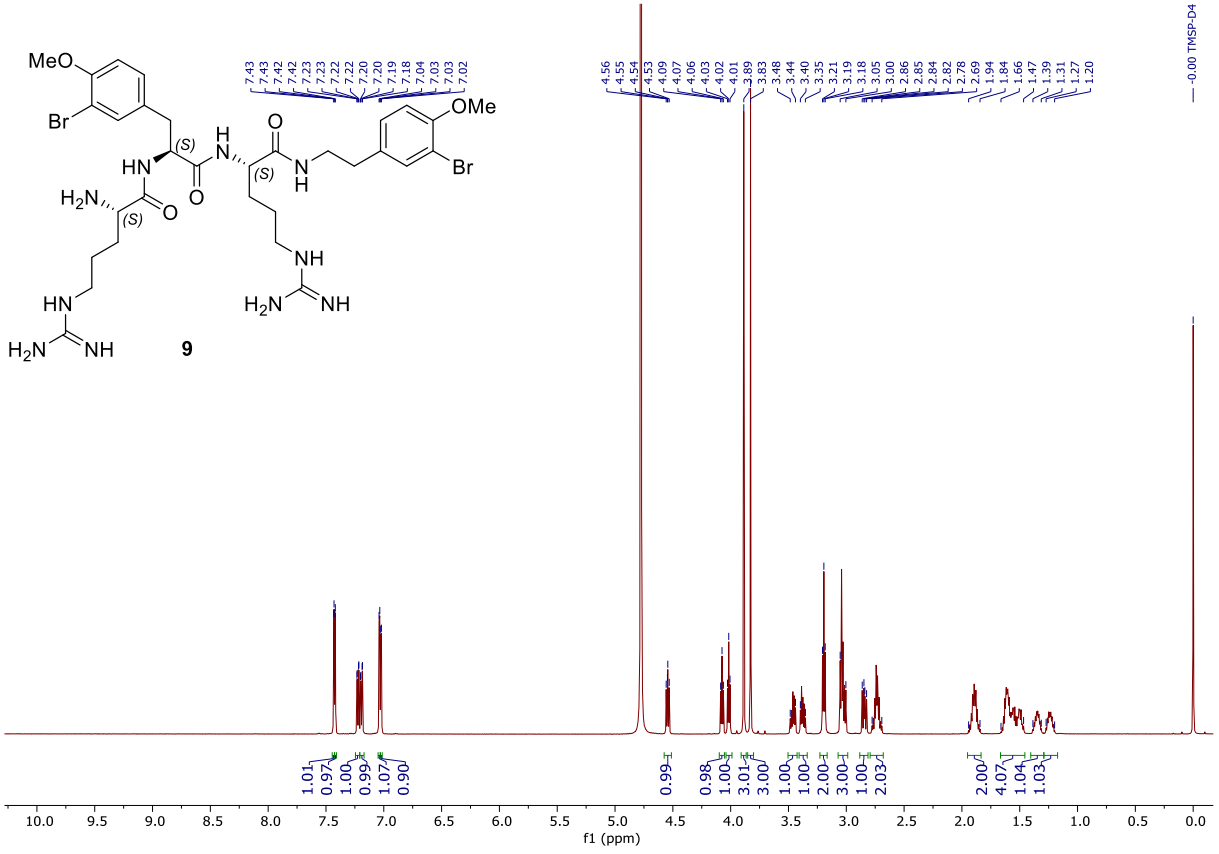


Figure S48: ^{1}H NMR spectrum of **10**

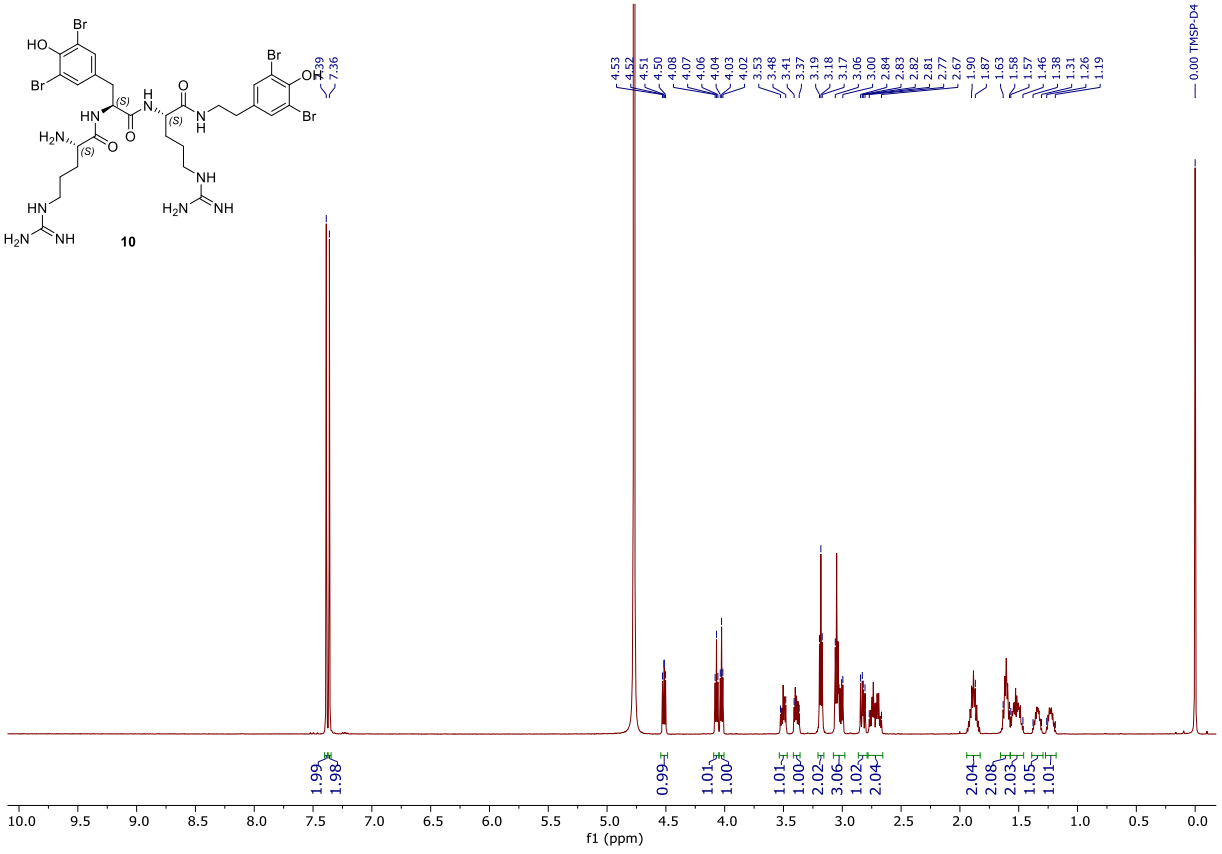


Figure S49: ^{1}H NMR spectrum of **11**

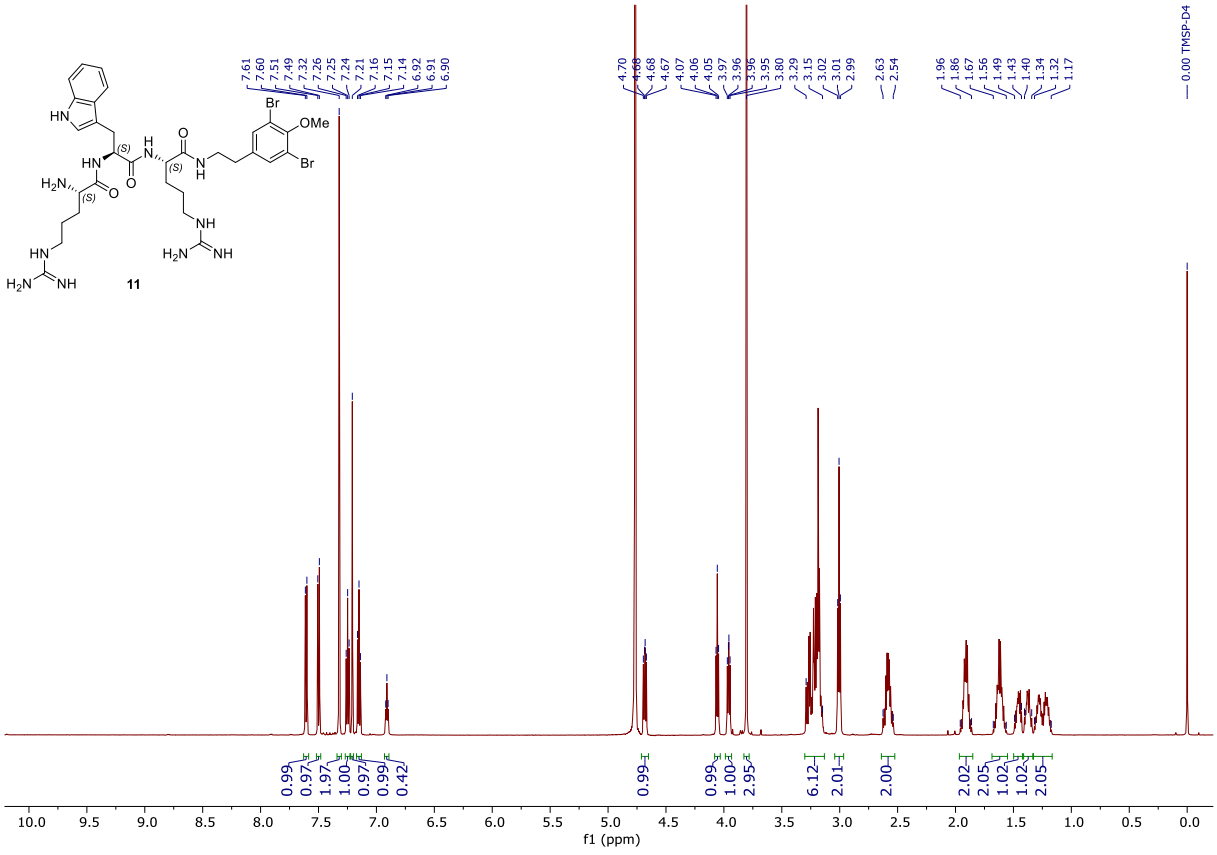


Figure S50: ^{1}H NMR spectrum of **12**

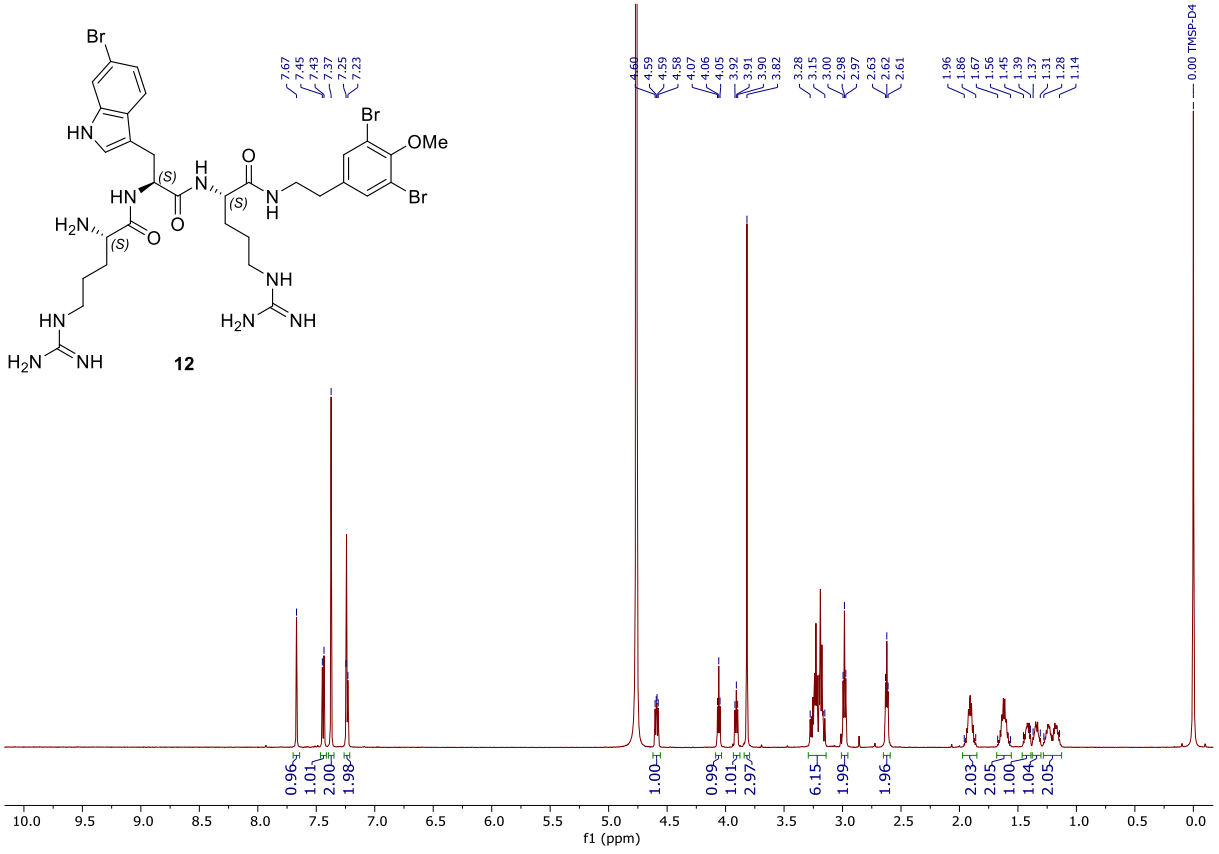


Figure S51: ^{1}H NMR spectrum of **13**

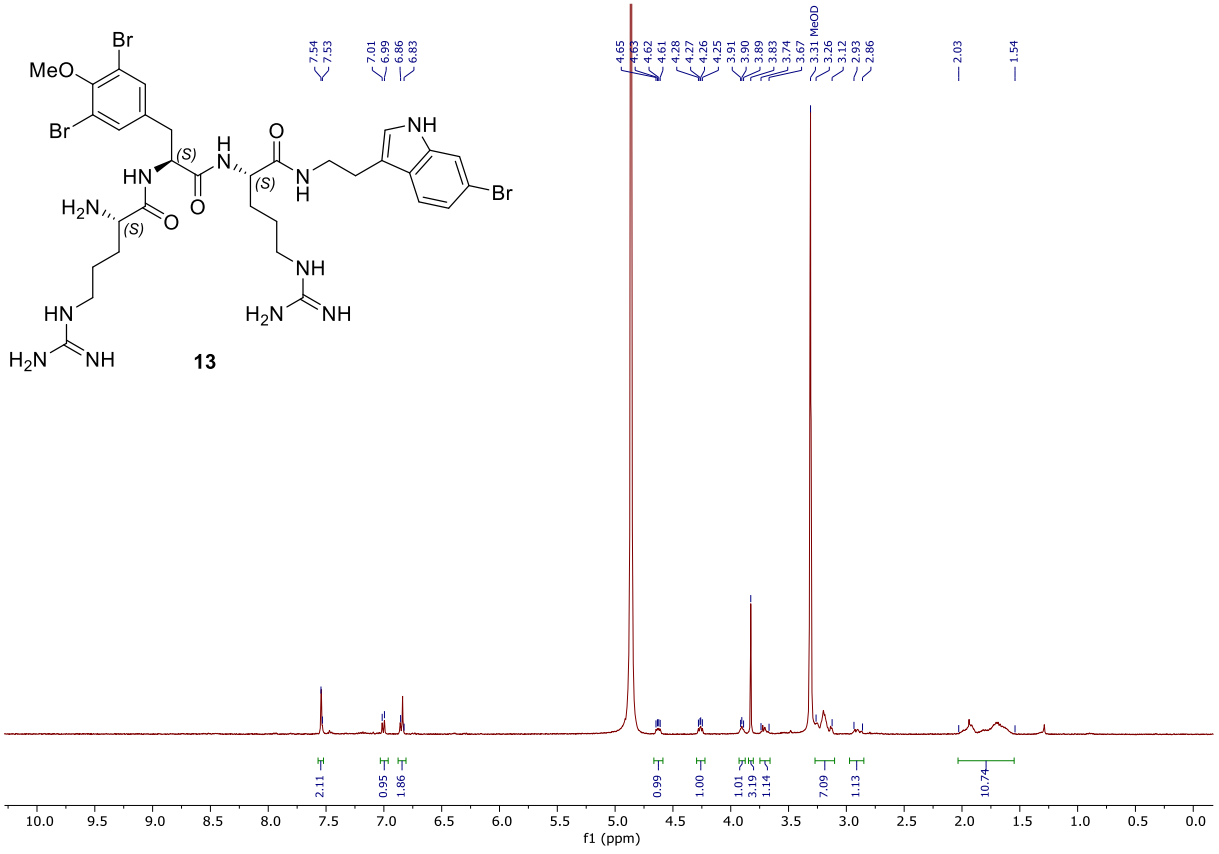


Figure S52: ^{1}H NMR spectrum of **14**

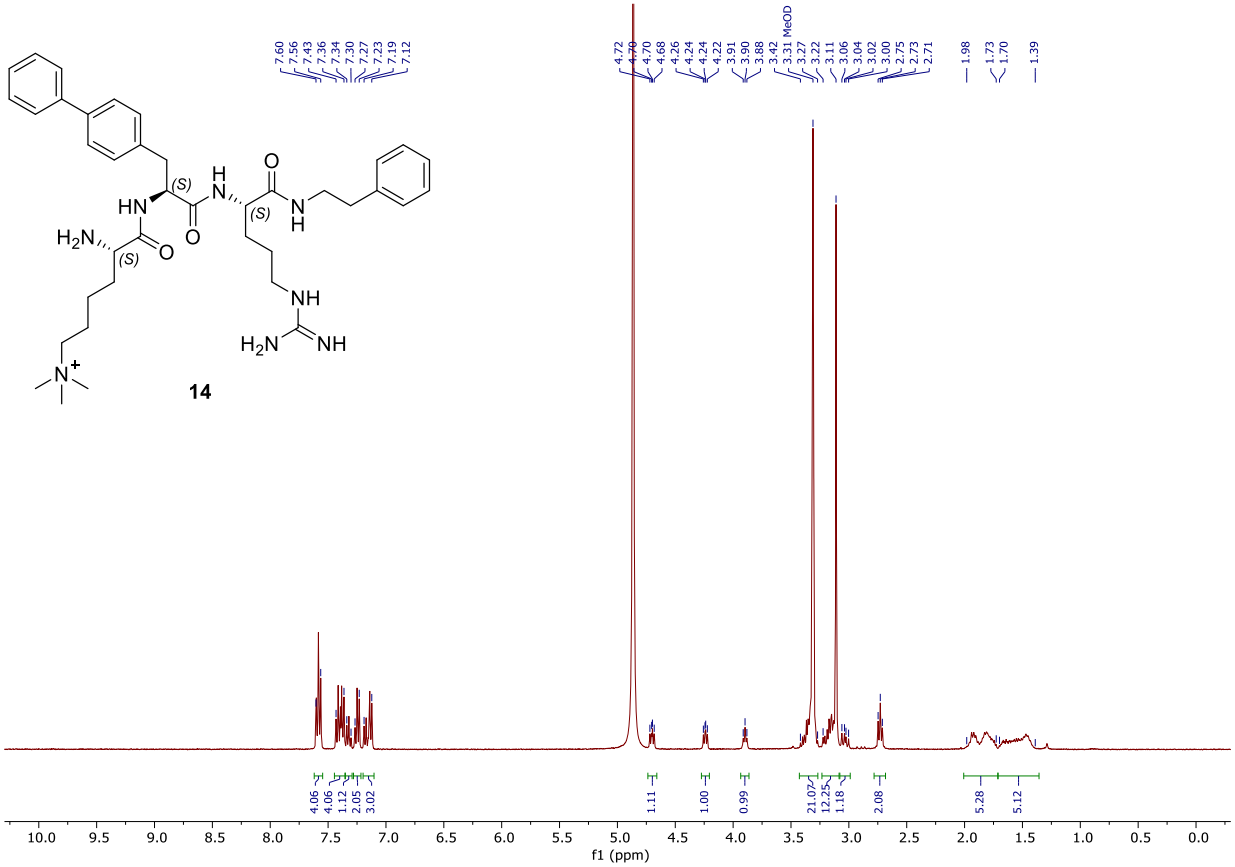
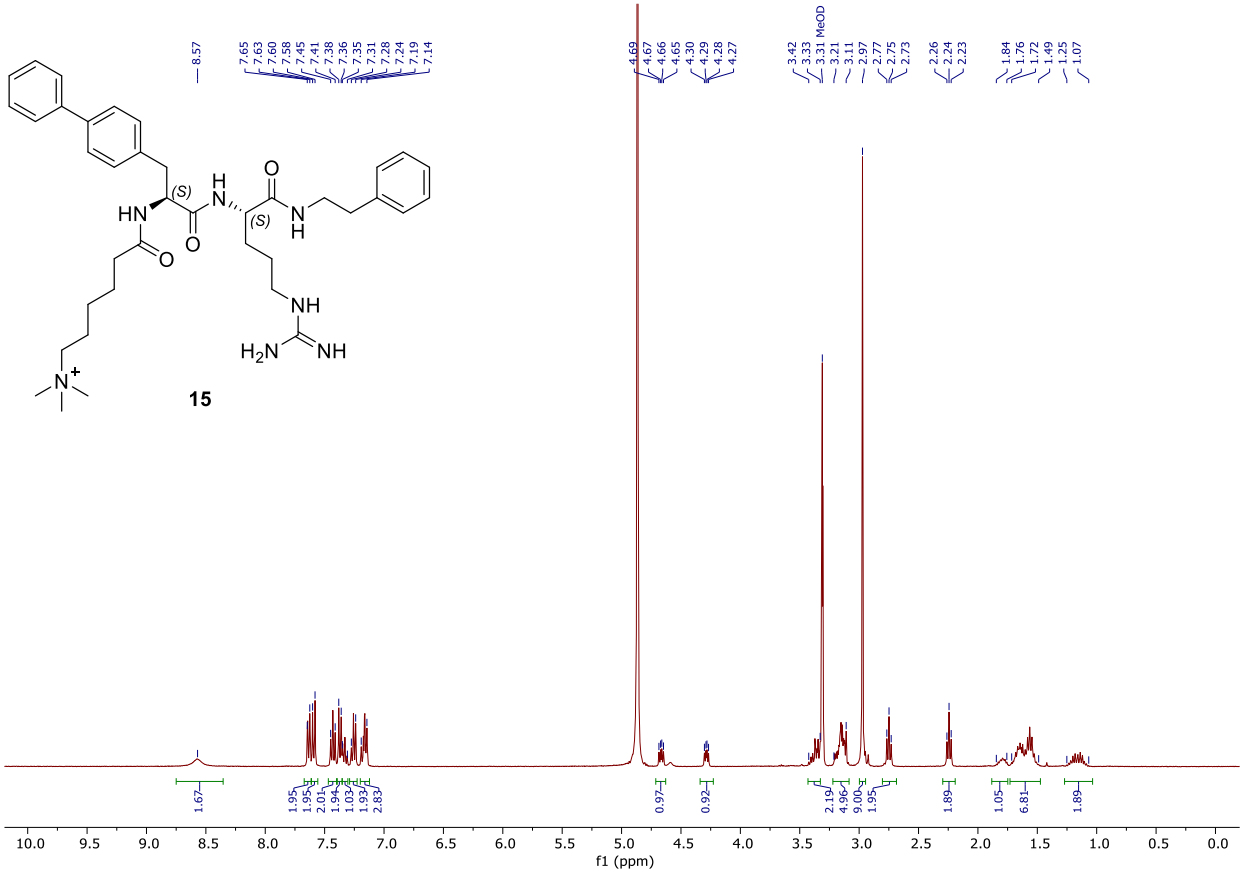
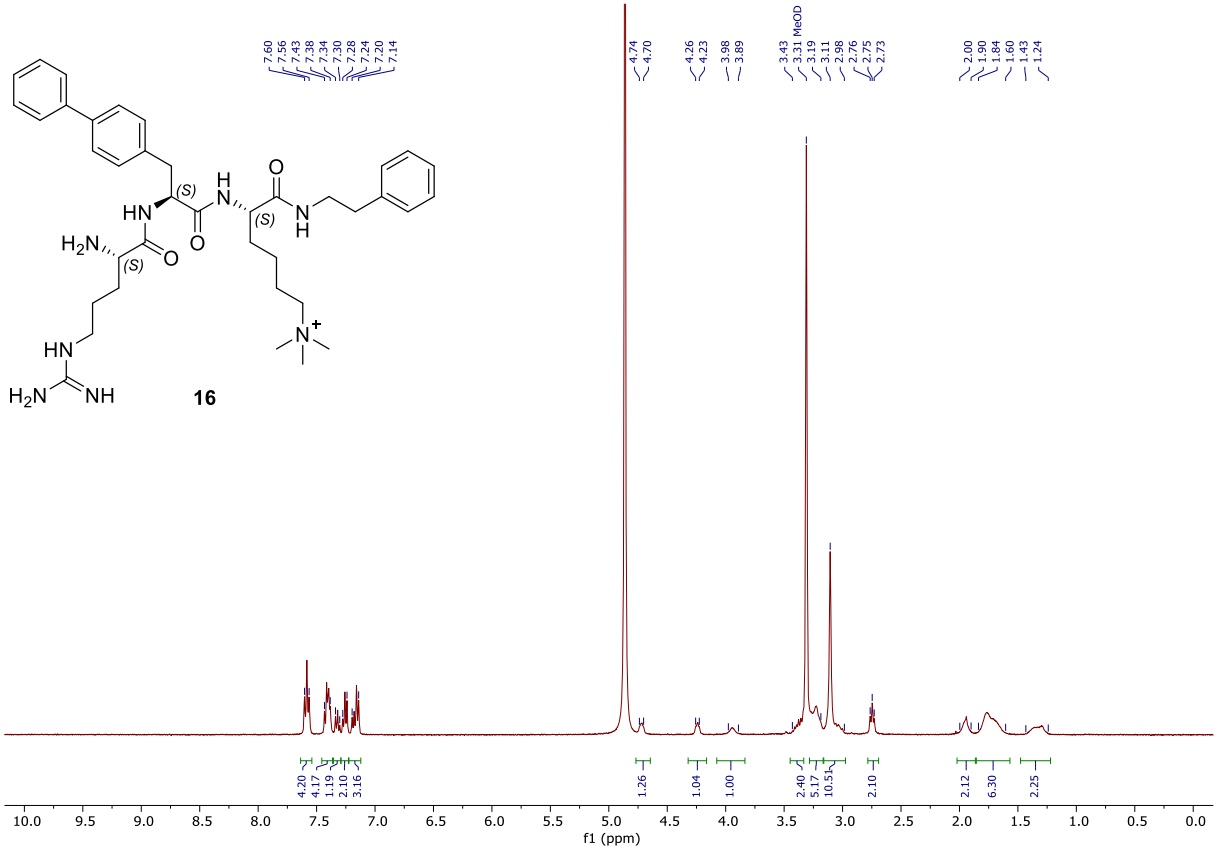


Figure S53: ^{1}H NMR spectrum of **15**



15

Figure S54: ^{1}H NMR spectrum of **16**



16

Figure S55: ^{1}H NMR spectrum of **17**

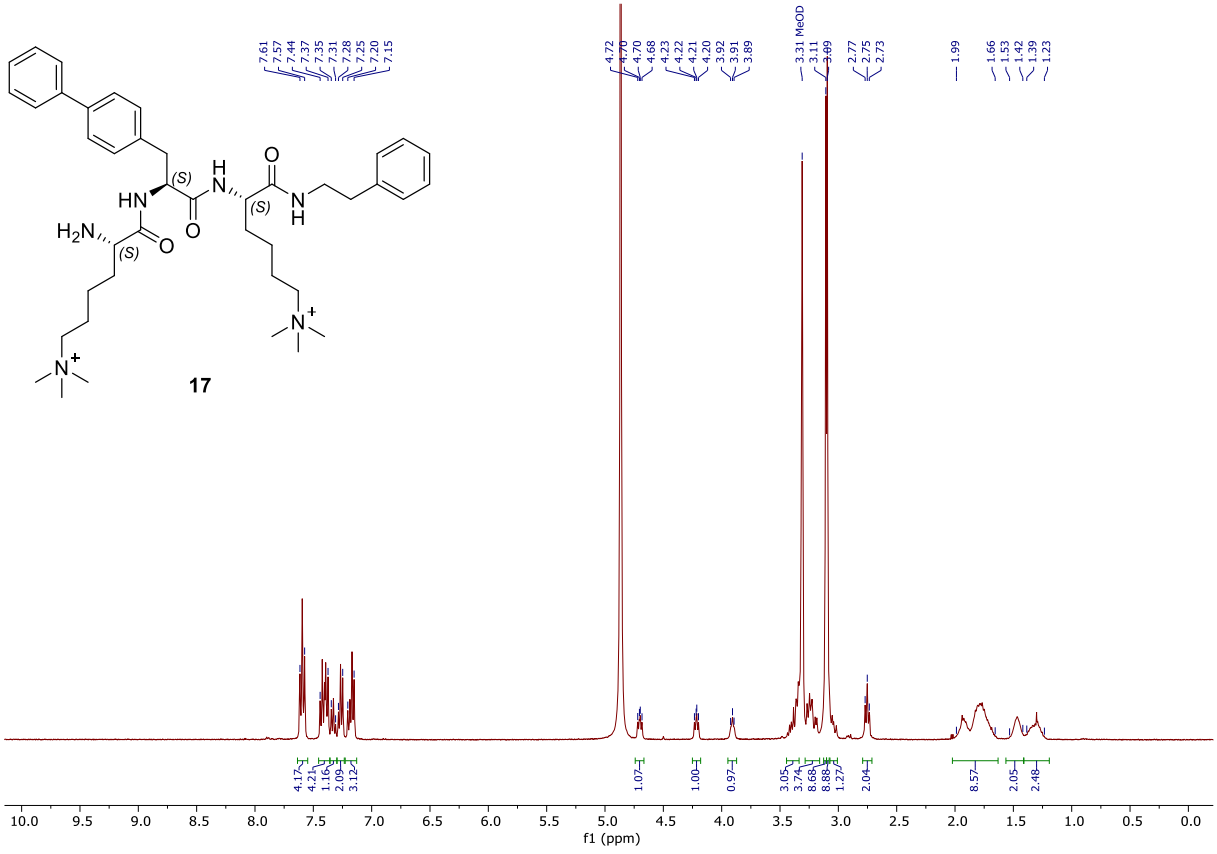


Figure S56: ^{1}H NMR spectrum of **18**

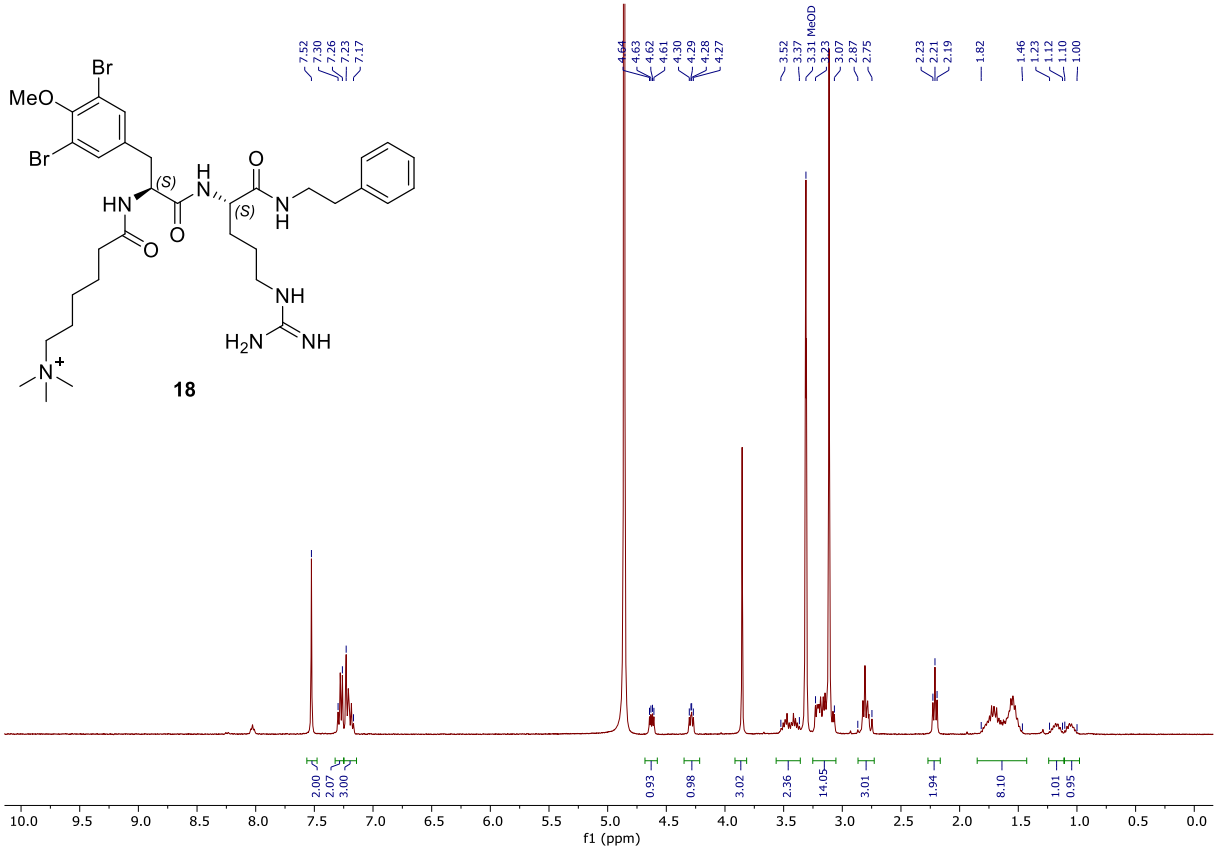


Figure S57: ^{1}H NMR spectrum of **19**

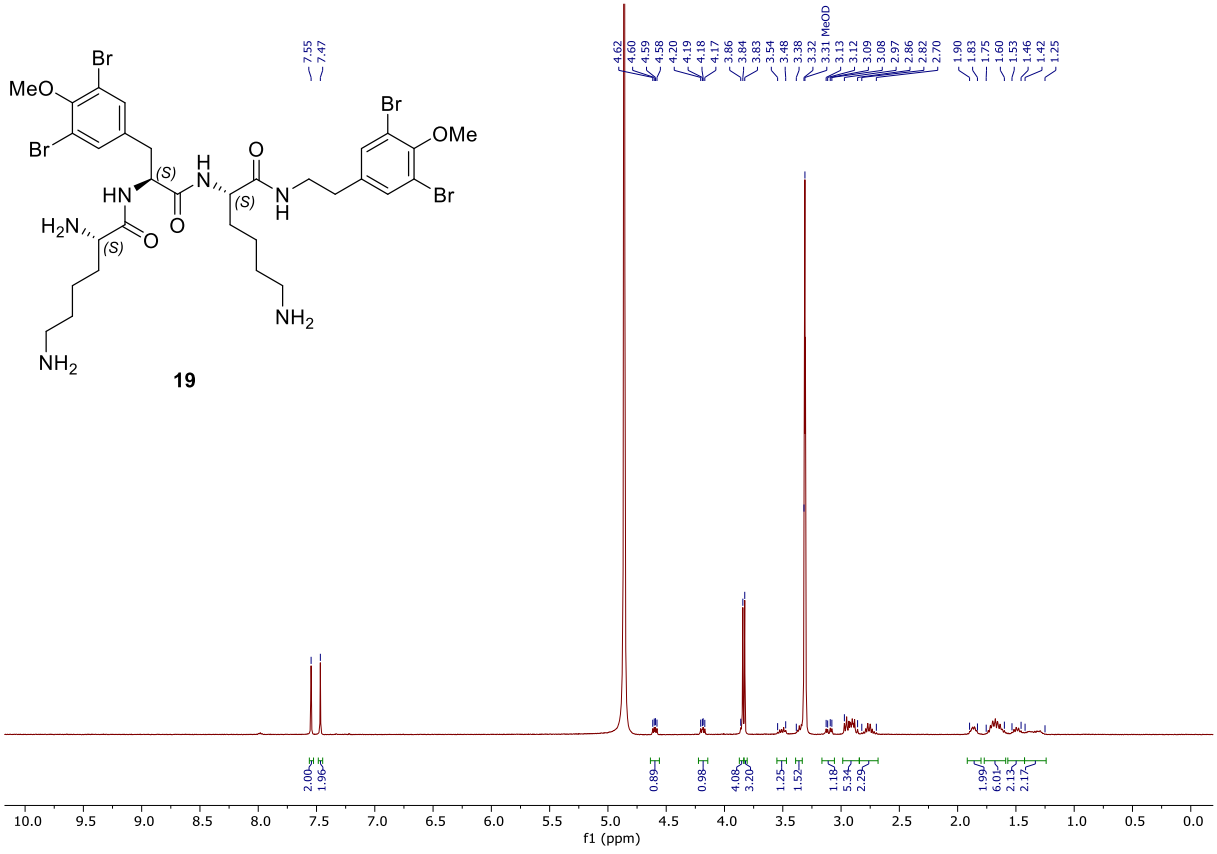


Figure S58: LCMS trace of injection solvent blank (methanol)

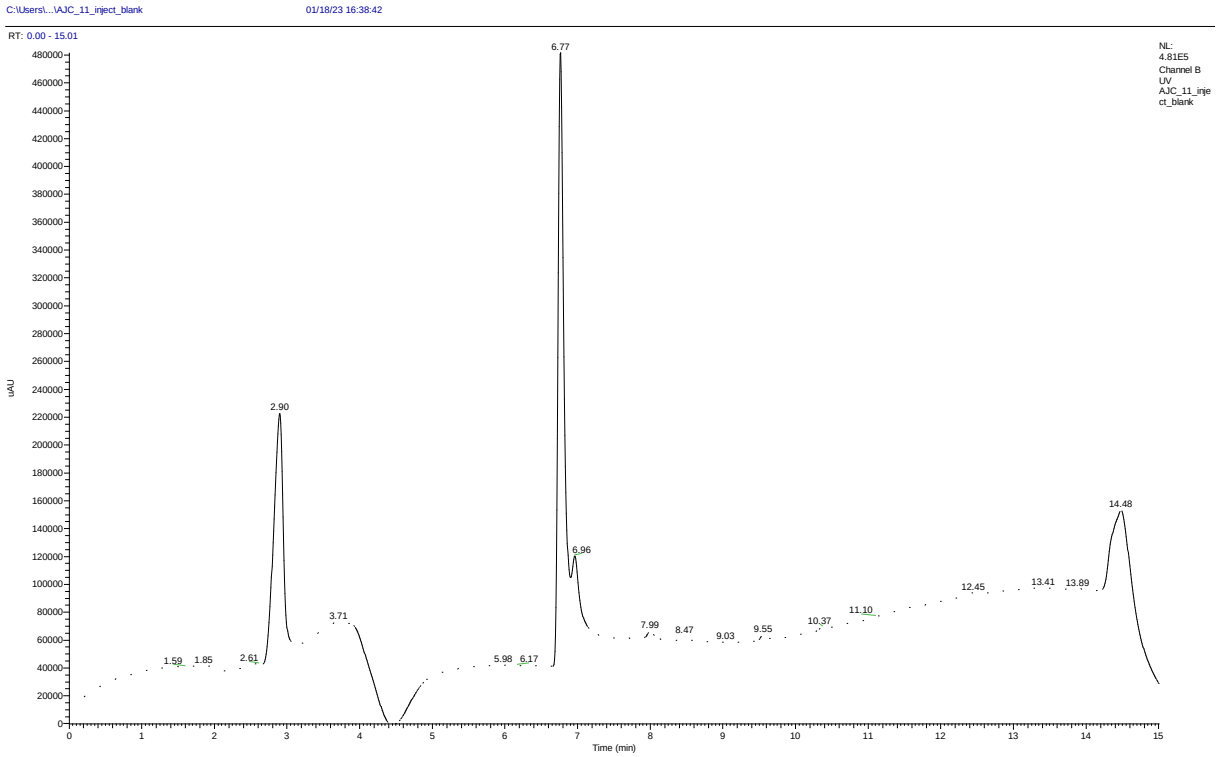
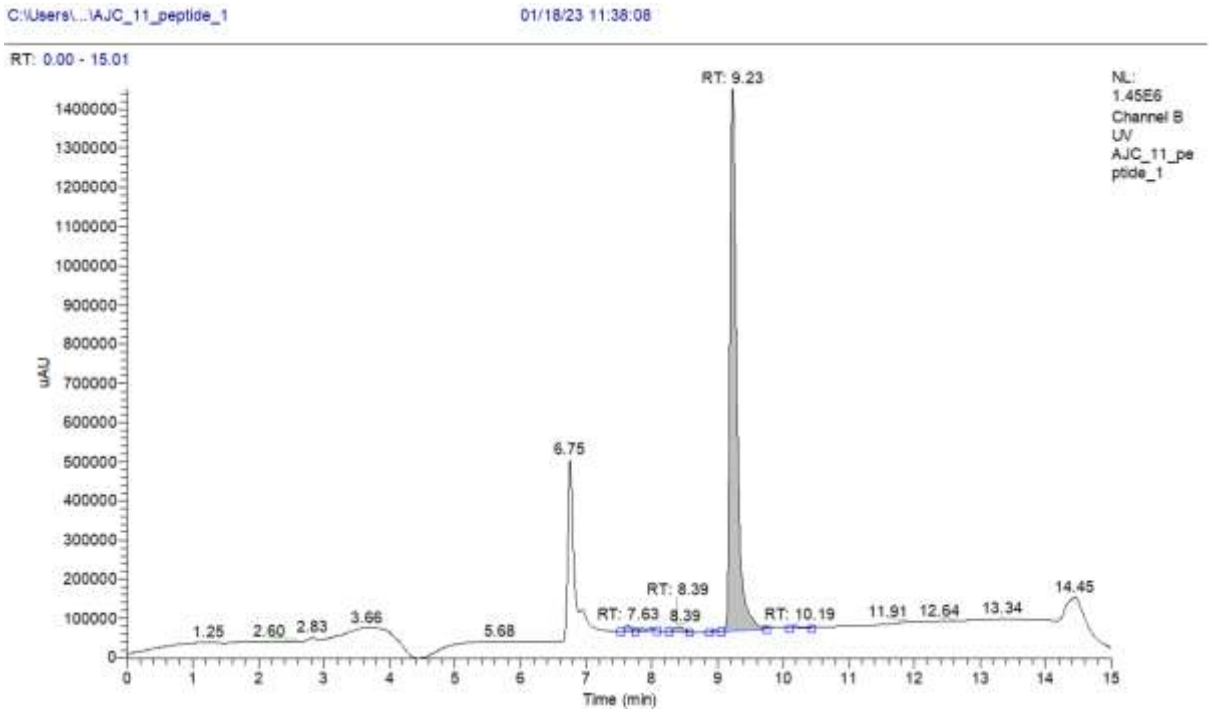


Figure S59: LCMS trace of **1**



PEAK LIST

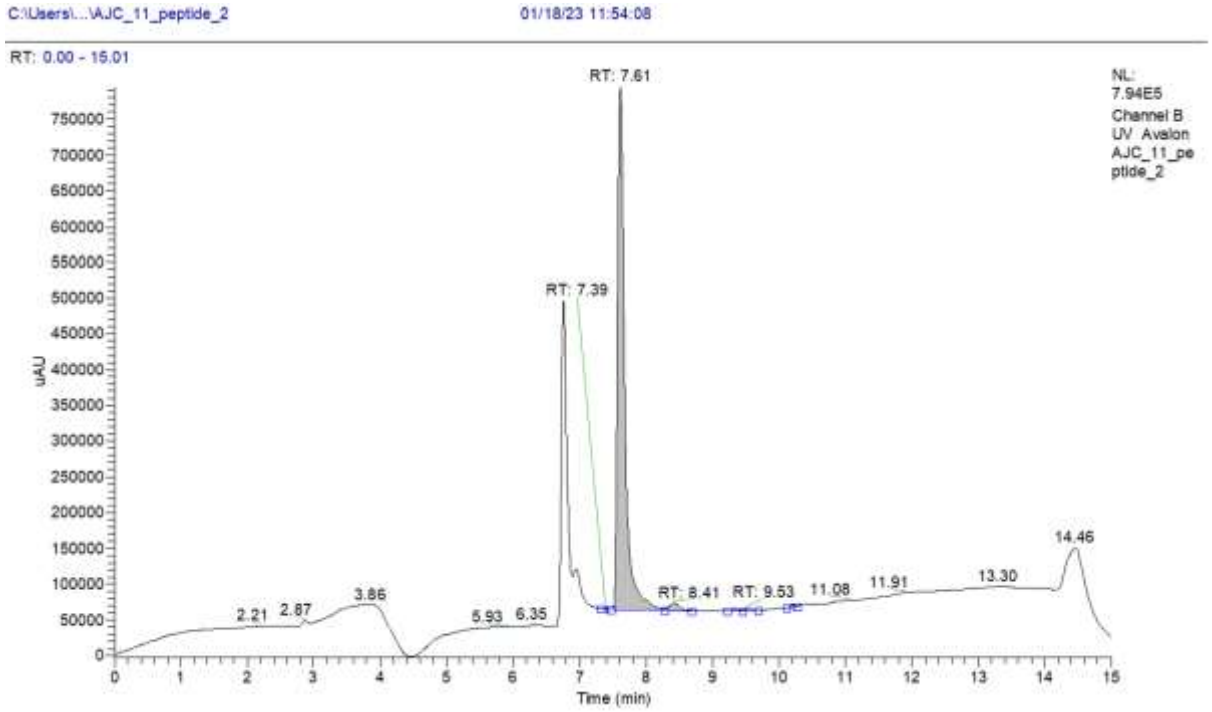
AJC_11_peptide_1.raw

RT: 0.00 - 15.01

Number of detected peaks: 6

Apex RT		Start RT	End RT		Area	%Area	Height	%Height
7.63	7.52	7.75	104287.807	0.98	16982.540	1.19		
7.85	7.75	8.07	103026.878	0.97	7267.128	0.51		
8.39	8.26	8.56	126698.413	1.19	12726.362	0.89		
8.95	8.87	9.05	23276.760	0.22	4331.483	0.30		
9.23	9.05	9.75	10205528.939	95.97	1383758.432	96.59		
10.19	10.09	10.43	71814.046	0.68	7598.682	0.53		

Figure S60: LCMS trace of **2**



PEAK LIST

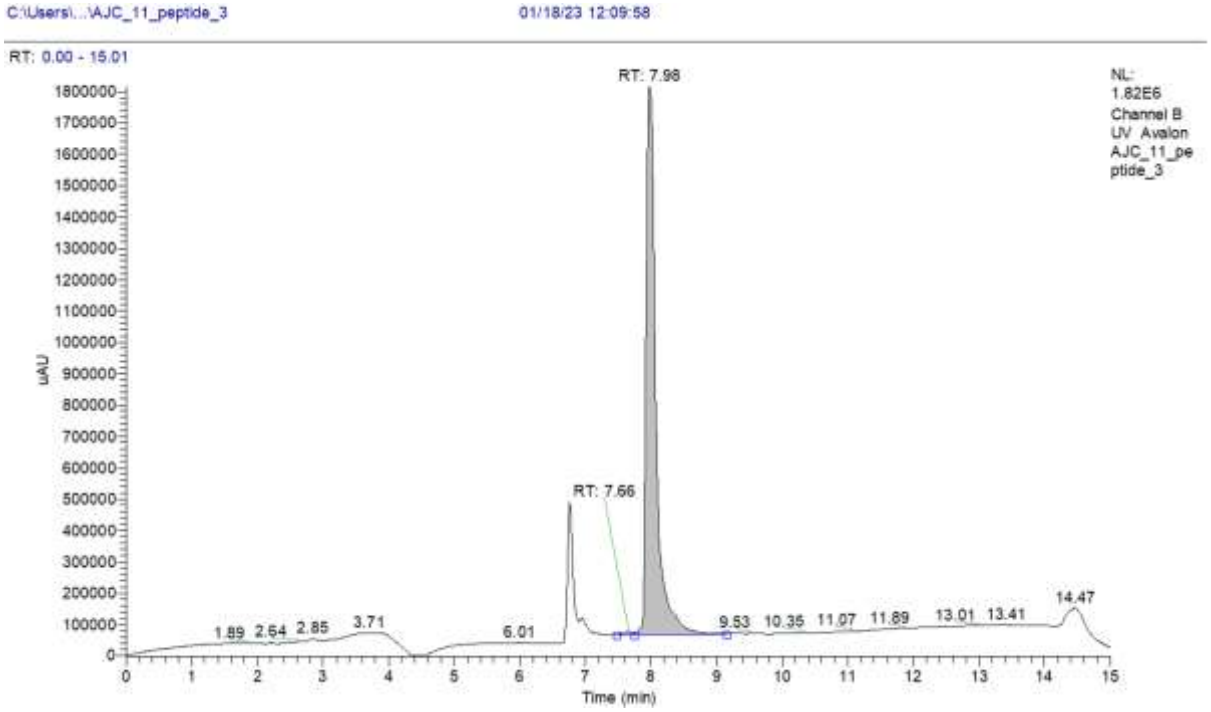
AJC_11_peptide_2.raw

RT: 0.00 - 15.01

Number of detected peaks: 6

Apex RT		Start RT	End RT		Area	%Area	Height	%Height
7.39	7.33	7.47	9566.819	0.17	2123.363	0.28		
7.61	7.48	8.28	5463406.658	96.35	729919.646	96.47		
8.41	8.28	8.69	106230.704	1.87	9691.238	1.28		
9.33	9.22	9.44	32968.906	0.58	5209.360	0.69		
9.53	9.44	9.69	36490.793	0.64	5392.796	0.71		
10.21	10.11	10.27	21749.697	0.38	4318.782	0.57		

Figure S61: LCMS trace of **3**



PEAK LIST

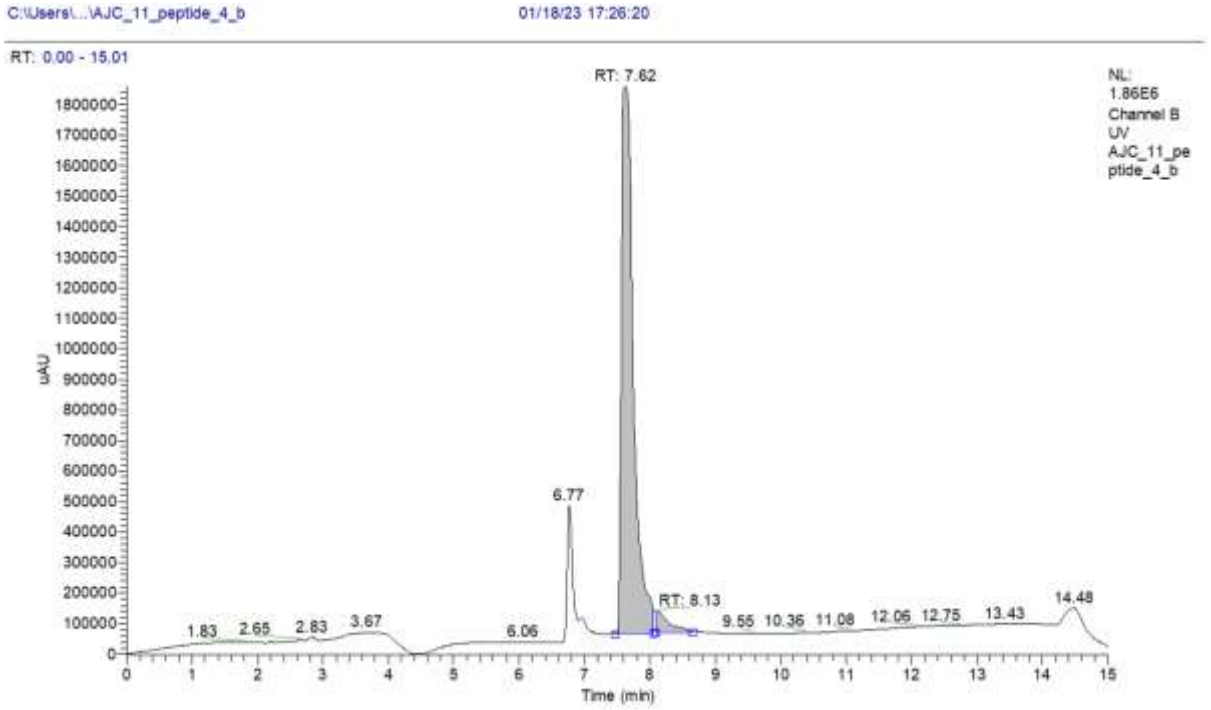
AJC_11_peptide_3.raw

RT: 0.00 - 15.01

Number of detected peaks: 2

Apex RT	Start RT	End RT	Area	%Area	Height	%Height
7.66	7.47	7.75	122442.779	0.67	13623.701	0.77
7.98	7.75	9.15	18229234.549	99.33	1750179.166	99.23

Figure S62: LCMS trace of **4**



PEAK LIST

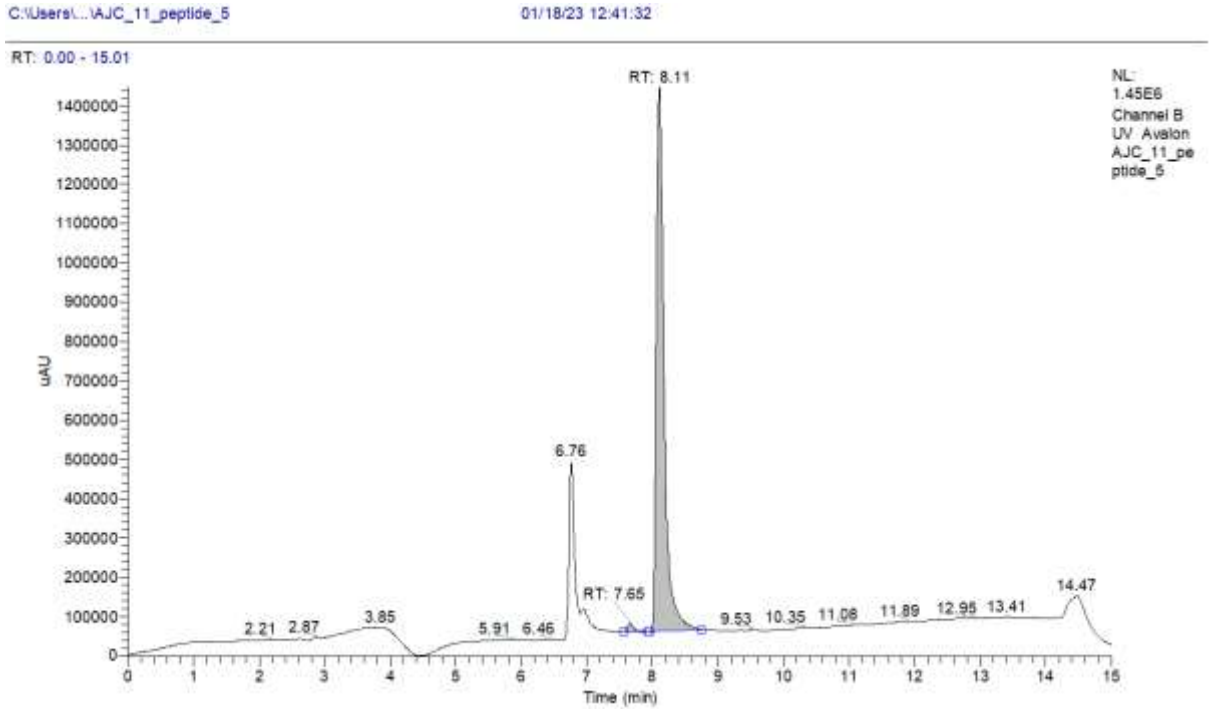
AJC_11_peptide_4_b.raw

RT: 0.00 - 15.01

Number of detected peaks: 2

Apex RT	Start RT	End RT	Area	%Area	Height	%Height
7.62	7.46	8.05	23116922.520	96.06	1790744.160	96.33
8.13	8.08	8.65	947129.134	3.94	68315.452	3.67

Figure S63: LCMS trace of **5**



PEAK LIST

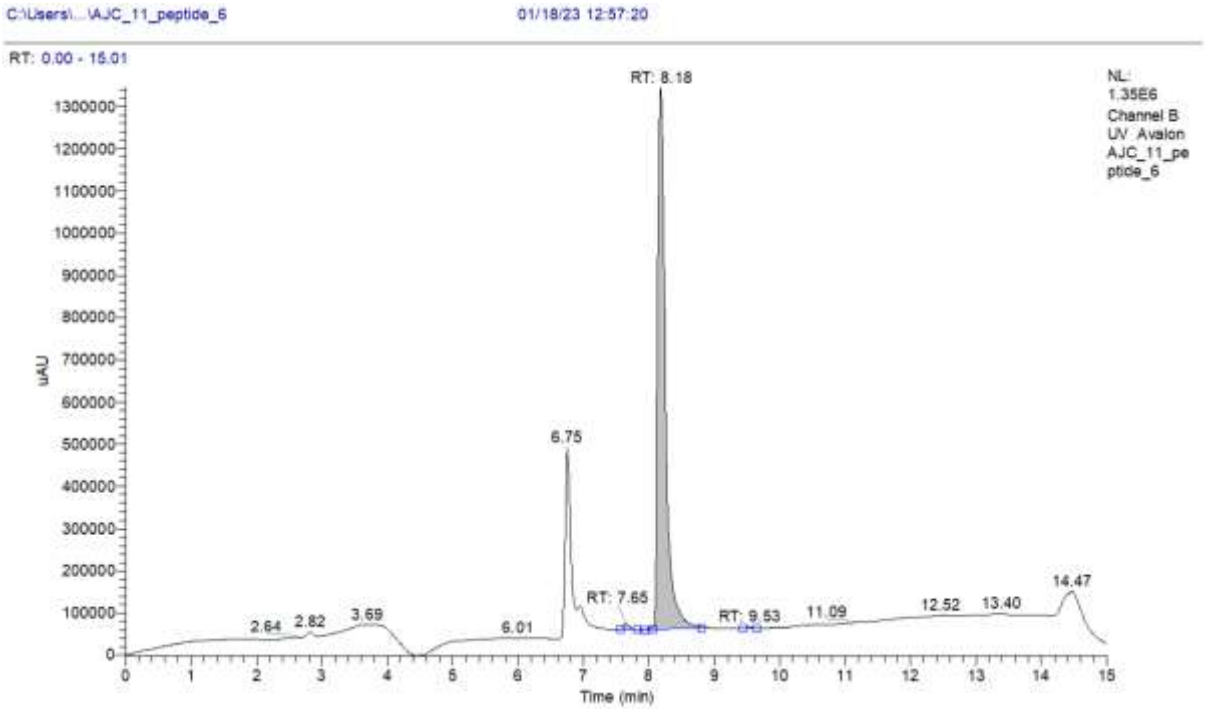
AJC_11_peptide_5.raw

RT: 0.00 - 15.01

Number of detected peaks: 2

Apex RT	Start RT	End RT	Area	%Area	Height	%Height
7.65	7.55	7.93	136320.877	1.18	21047.132	1.50
8.11	7.95	8.75	11447927.823	98.82	1383987.442	98.50

Figure S64: LCMS trace of **6**



PEAK LIST

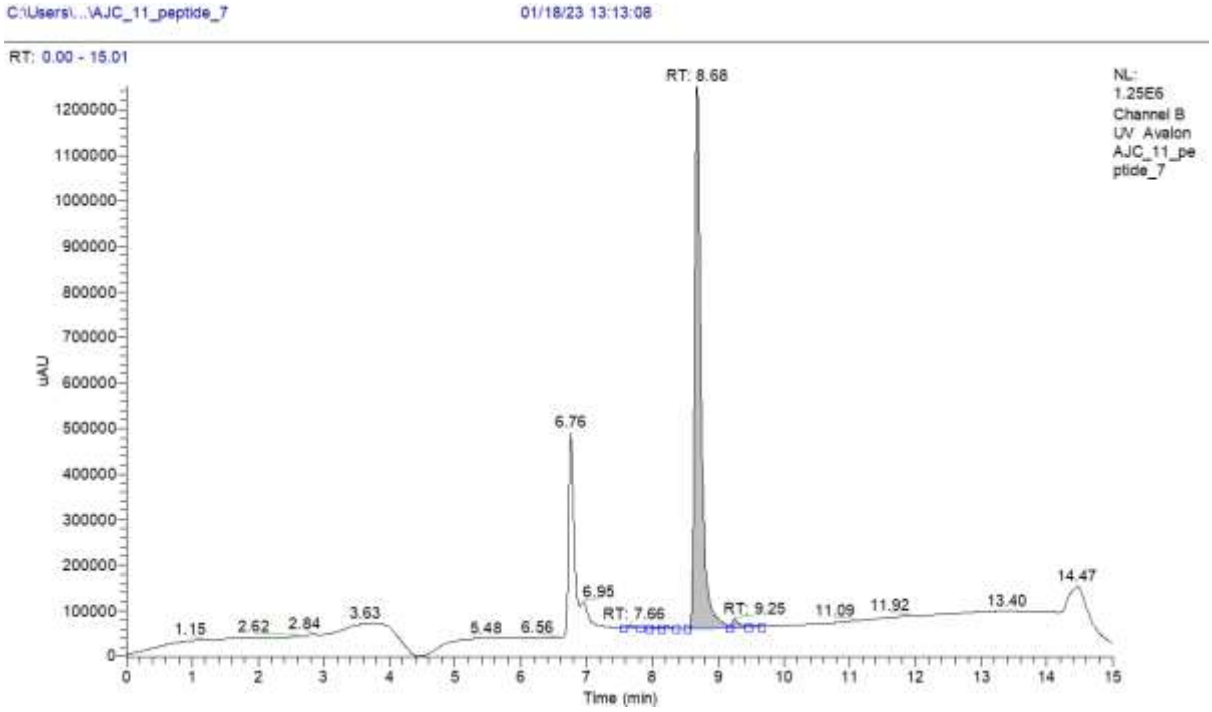
AJC_11_peptide_6.raw

RT: 0.00 - 15.01

Number of detected peaks: 4

Apex RT		Start RT	End RT		Area	%Area	Height	%Height
7.65	7.55	7.82	87418.941	0.81	14751.673	1.13		
8.02	7.93	8.06	23144.509	0.21	5384.874	0.41		
8.18	8.06	8.80	10664402.138	98.78	1283103.702	98.16		
9.53	9.44	9.64	20912.589	0.19	3890.428	0.30		

Figure S65: LCMS trace of **7**



PEAK LIST

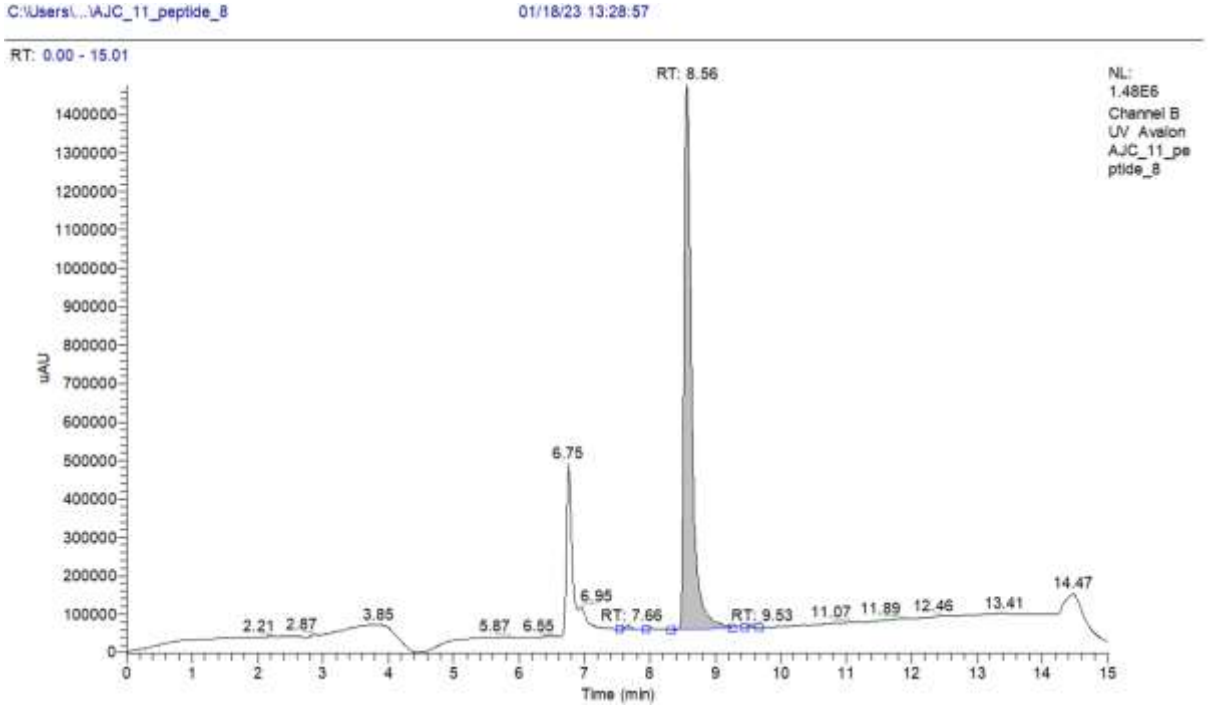
AJC_11_peptide_7.raw

RT: 0.00 - 15.01

Number of detected peaks: 6

Apex RT	Start RT	End RT	Area	%Area	Height	%Height
7.66	7.55	7.82	45412.576	0.53	7808.372	0.63
8.03	7.95	8.14	22948.975	0.27	3732.595	0.30
8.23	8.14	8.36	30892.995	0.36	5232.888	0.43
8.68	8.53	9.17	8357730.646	96.76	1189463.040	96.71
9.25	9.17	9.46	151573.079	1.75	19081.553	1.55
9.54	9.46	9.66	29431.270	0.34	4667.468	0.38

Figure S66: LCMS trace of **8**



PEAK LIST

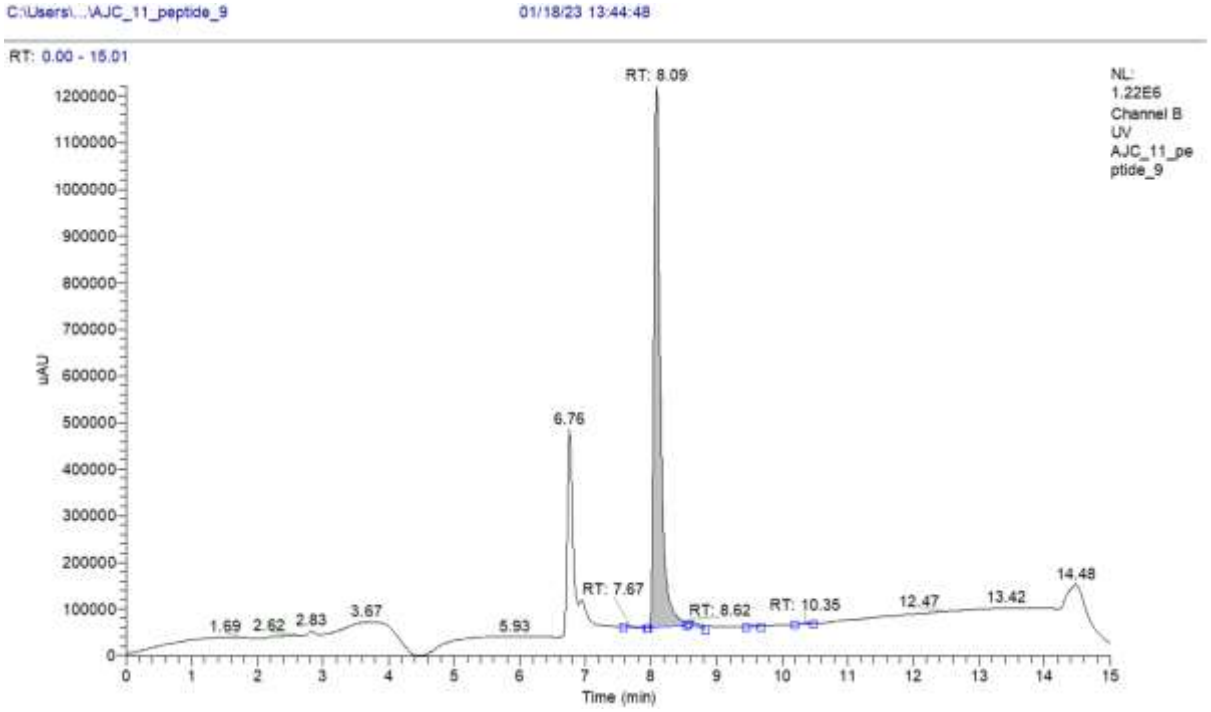
AJC_11_peptide_8.raw

RT: 0.00 - 15.01

Number of detected peaks: 3

Apex RT	Start RT	End RT	Area	%Area	Height	%Height
7.66	7.53	7.94	58425.369	0.50	7658.060	0.54
8.56	8.32	9.25	11518991.078	99.34	1415856.507	99.21
9.53	9.45	9.67	18165.986	0.16	3662.287	0.26

Figure S67: LCMS trace of **9**



PEAK LIST

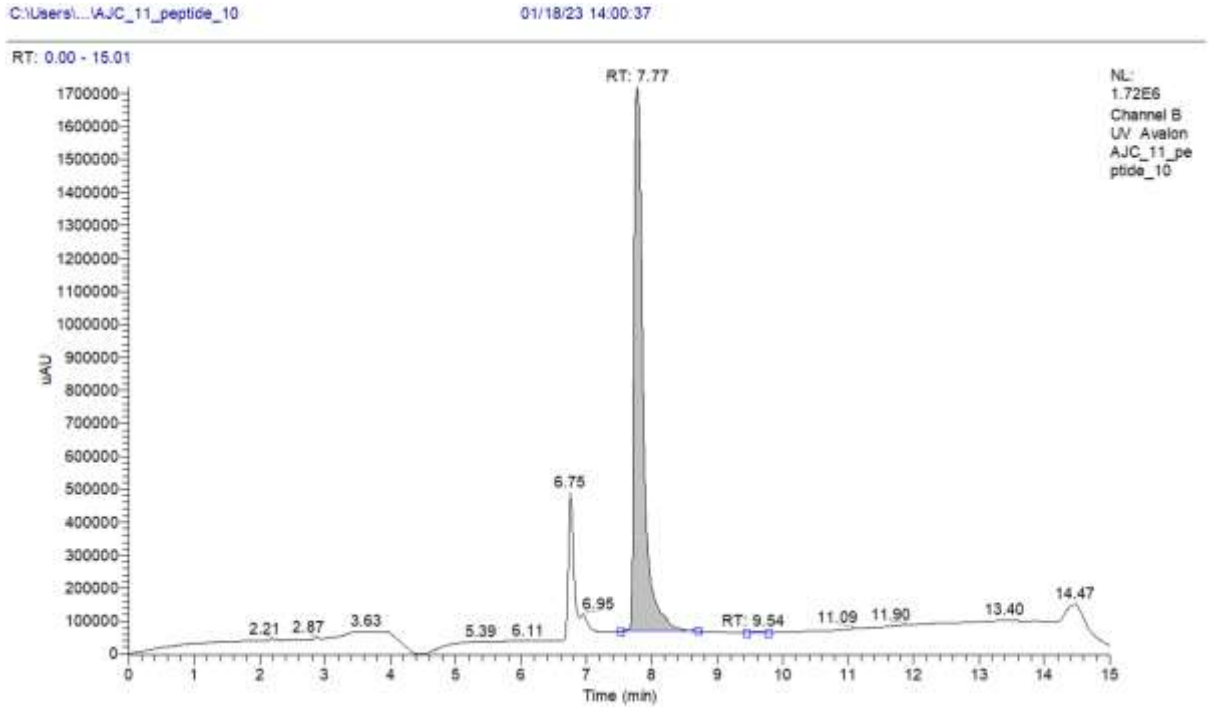
AJC_11_peptide_9.raw

RT: 0.00 - 15.01

Number of detected peaks: 5

Apex RT		Start RT	End RT		Area	%Area	Height	%Height
7.67	7.57	7.93	23212.433	0.28	3612.960	0.31		
8.09	7.95	8.53	8206124.515	97.78	1159910.982	98.22		
8.62	8.56	8.83	109554.908	1.31	9552.352	0.81		
9.54	9.45	9.67	22236.496	0.26	4036.460	0.34		
10.35	10.18	10.47	31431.146	0.37	3781.117	0.32		

Figure S68: LCMS trace of **10**



PEAK LIST

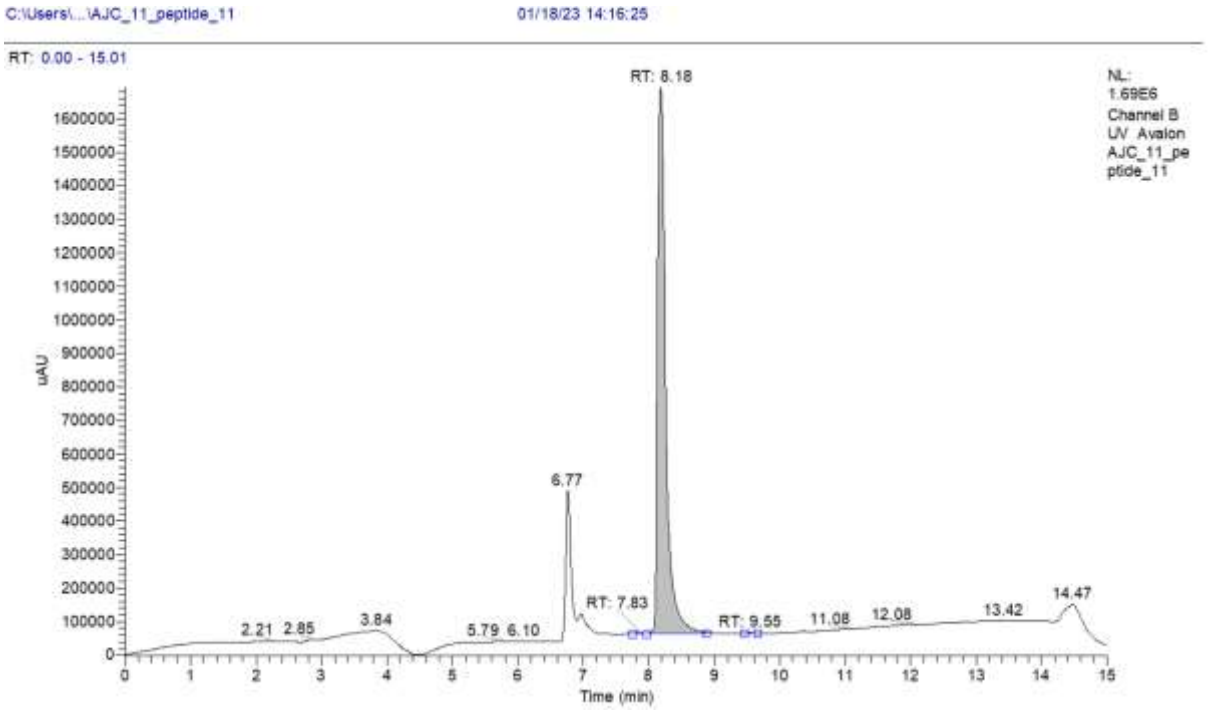
AJC_11_peptide_10.raw

RT: 0.00 - 15.01

Number of detected peaks: 2

Apex RT	Start RT	End RT	Area	%Area	Height	%Height
7.77	7.53	8.70	16276197.845	99.76	1649855.838	99.69
9.54	9.45	9.77	38641.155	0.24	5138.444	0.31

Figure S69: LCMS trace of **11**



PEAK LIST

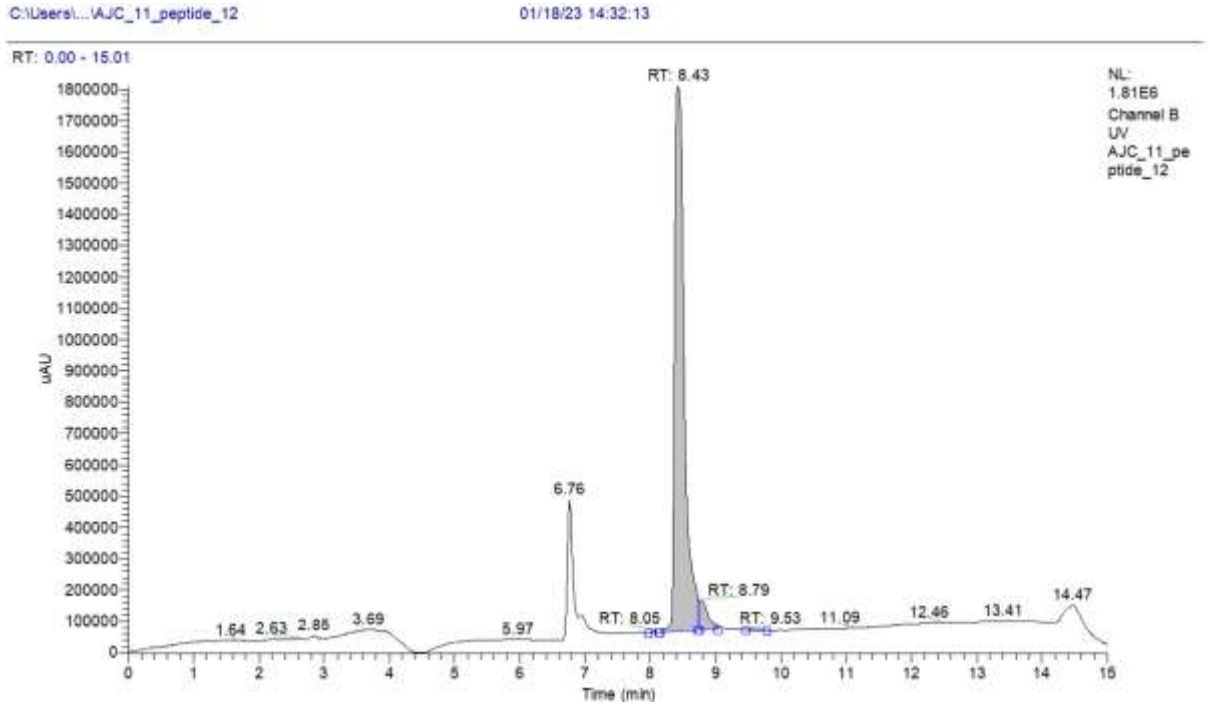
AJC_11_peptide_11.raw

RT: 0.00 - 15.01

Number of detected peaks: 3

Apex RT	Start RT	End RT	Area	%Area	Height	%Height
7.83	7.74	7.96	52148.306	0.36	9242.760	0.56
8.18	7.96	8.88	14314939.322	99.50	1630096.799	99.20
9.55	9.45	9.66	20287.914	0.14	3833.858	0.23

Figure S70: LCMS trace of **12**



PEAK LIST

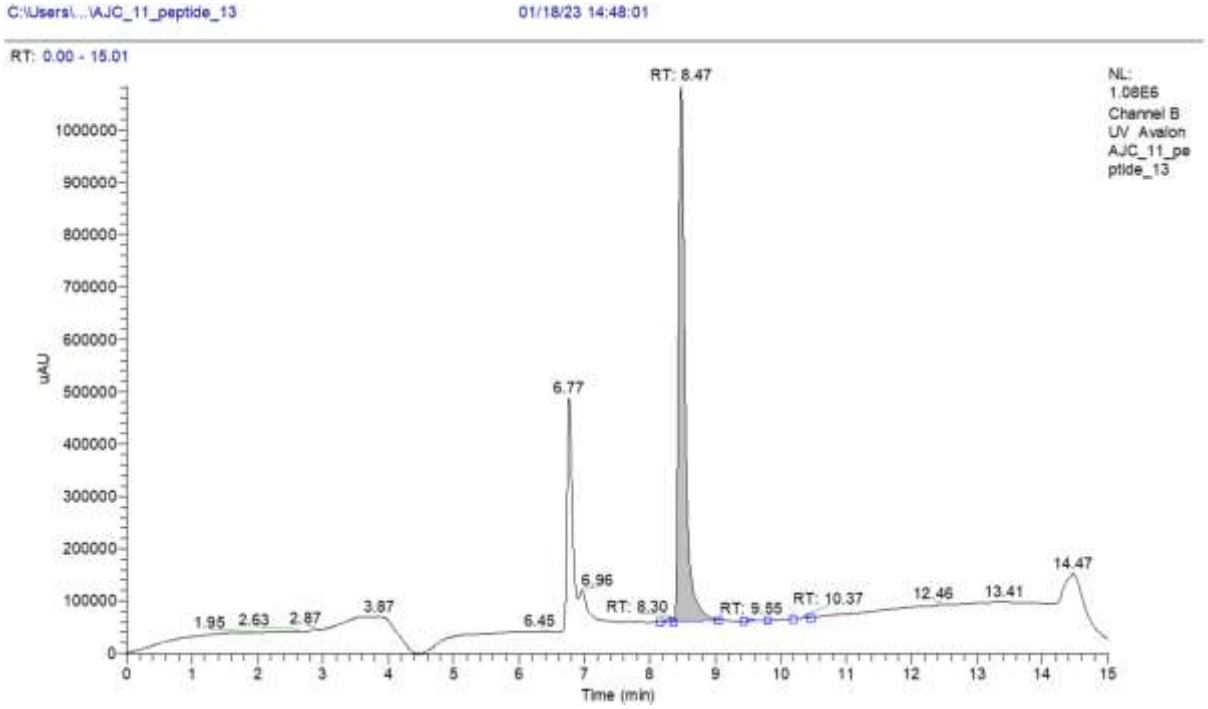
AJC_11_peptide_12.raw

RT: 0.00 - 15.01

Number of detected peaks: 3

Apex RT	Start RT	End RT	Area	%Area	Height	%Height
8.05	7.97	8.13	24084.663	0.13	5129.198	0.28
8.43	8.13	9.03	18,608,967.532	98.87	1738196.061	99.50
9.53	9.46	9.77	28560.412	0.15	4004.239	0.22

Figure S71: LCMS trace of **13**



PEAK LIST

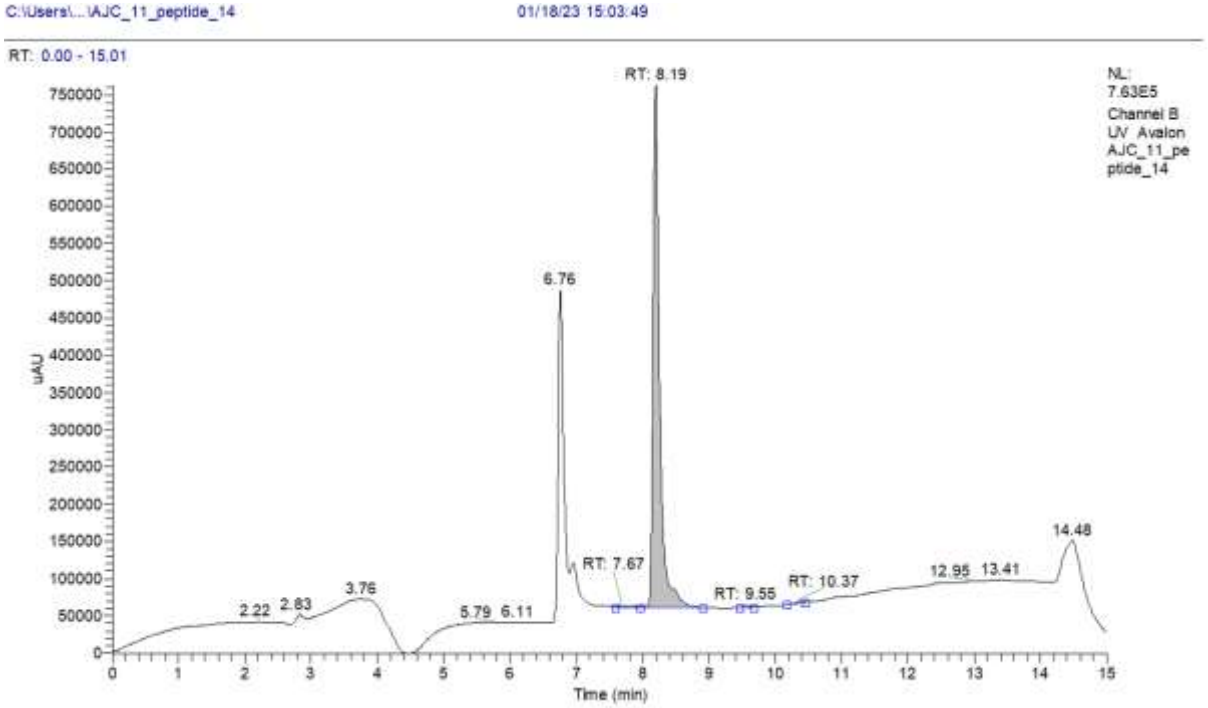
AJC_11_peptide_13.raw

RT: 0.00 - 15.01

Number of detected peaks: 4

Apex RT		Start RT	End RT		Area	%Area	Height	%Height
8.30	8.15	8.36	52714.907	0.72	9452.792	0.91		
8.47	8.36	9.04	7201724.815	98.57	1022745.205	98.37		
9.55	9.44	9.79	30700.546	0.42	4042.751	0.39		
10.37	10.19	10.45	21092.521	0.29	3490.468	0.34		

Figure S72: LCMS trace of **14**



PEAK LIST

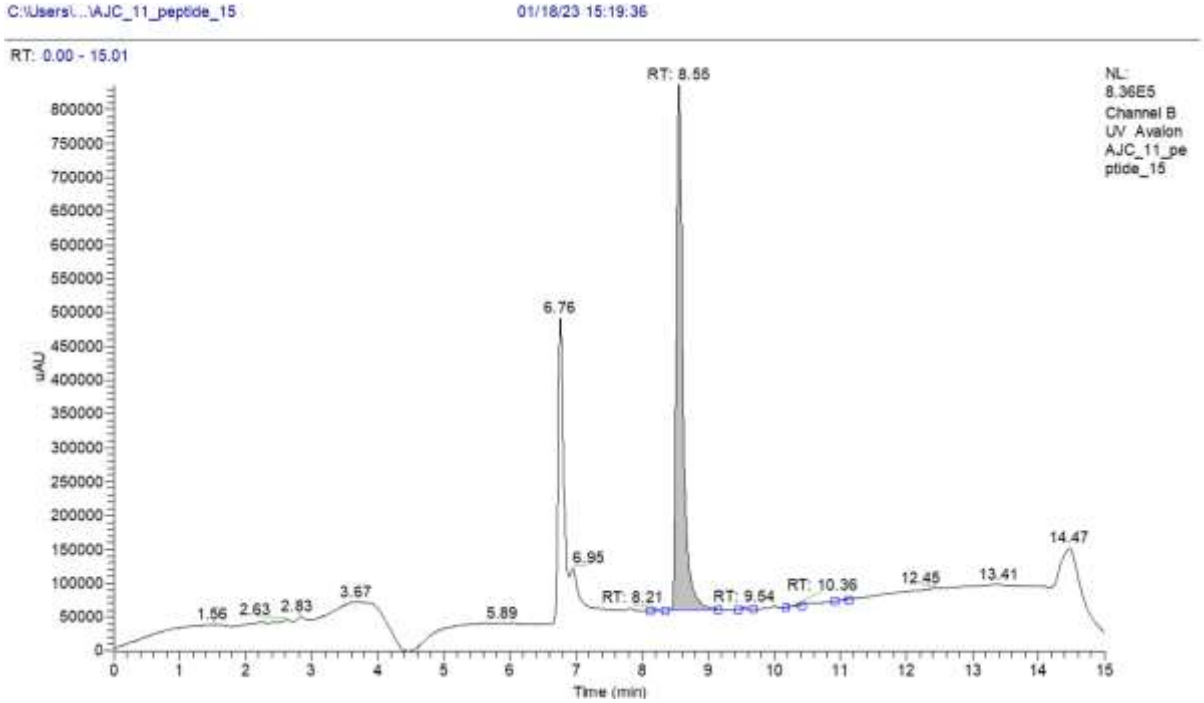
AJC_11_peptide_14.raw

RT: 0.00 - 15.01

Number of detected peaks: 4

Apex RT		Start RT	End RT		Area	%Area	Height	%Height
7.67	7.59	7.95	30535.720	0.61	2764.687	0.39		
8.19	7.95	8.91	4945810.276	98.34	701520.351	98.52		
9.55	9.45	9.68	22721.134	0.45	3949.615	0.55		
10.37	10.17	10.45	29980.196	0.60	3793.357	0.53		

Figure S73: LCMS trace of **15**



PEAK LIST

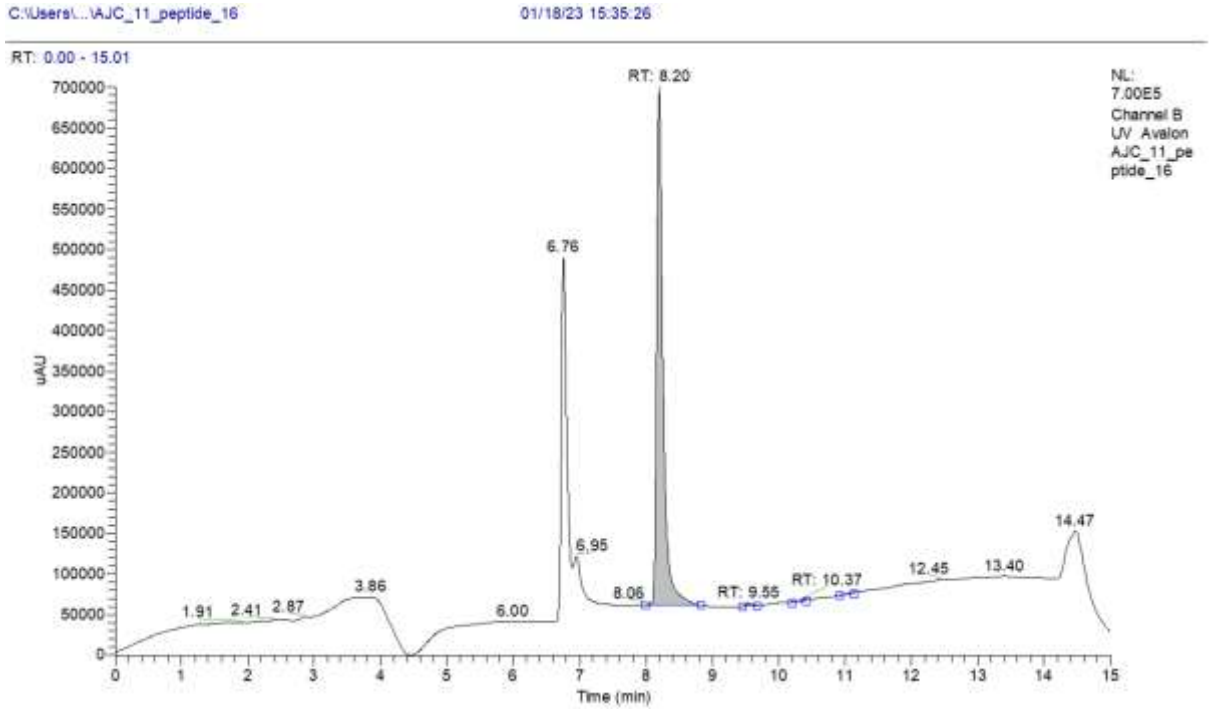
AJC_11_peptide_15.raw

RT: 0.00 - 15.01

Number of detected peaks: 5

Apex RT		Start RT	End RT		Area	%Area	Height	%Height
8.21	8.11	8.35	13555.141	0.24	2296.627	0.29		
8.55	8.35	9.15	5468344.496	98.77	776568.939	98.56		
9.54	9.44	9.68	24184.988	0.44	4059.087	0.52		
10.36	10.17	10.41	17458.320	0.32	3050.965	0.39		
11.09	10.91	11.13	12649.662	0.23	1926.985	0.24		

Figure S74: LCMS trace of **16**



PEAK LIST

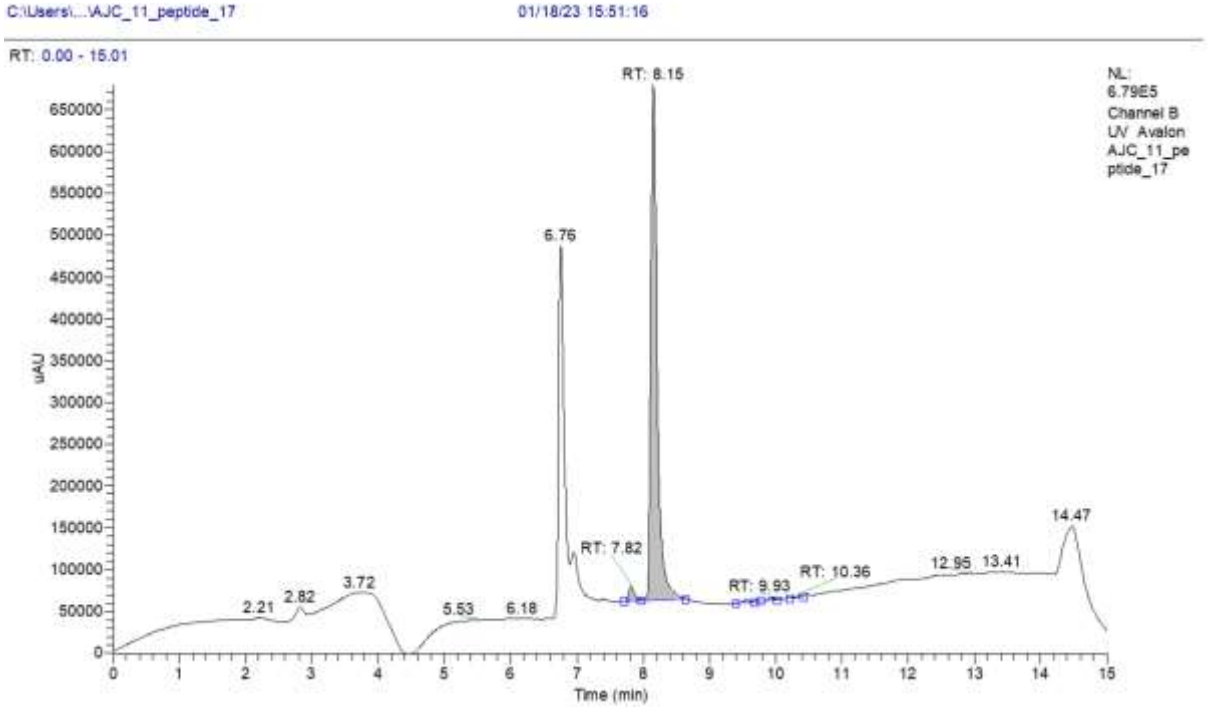
AJC_11_peptide_16.raw

RT: 0.00 - 15.01

Number of detected peaks: 4

Apex RT		Start RT	End RT		Area	%Area	Height	%Height
8.20	7.98	8.83	4358300.424	98.79	638498.693		98.63	
9.55	9.44	9.68	26870.209	0.61	4193.892		0.65	
10.37	10.20	10.41	13774.481	0.31	2657.154		0.41	
11.09	10.91	11.13	12553.221	0.28	2007.000		0.31	

Figure S75: LCMS trace of **17**



PEAK LIST

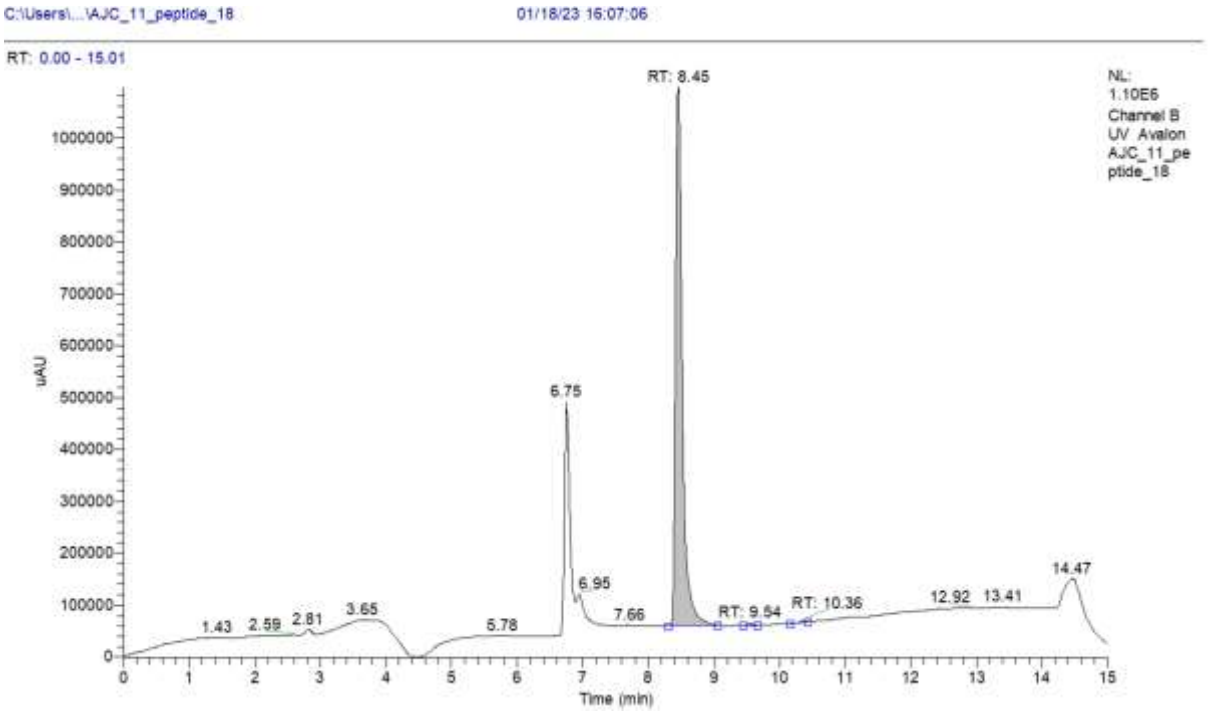
AJC_11_peptide_17.raw

RT: 0.00 - 15.01

Number of detected peaks: 5

Apex RT		Start RT	End RT		Area	%Area	Height	%Height
7.82	7.71	7.95	107354.112	2.49	17486.019	2.71		
8.15	7.95	8.64	4147274.194	96.14	616095.063	95.64		
9.55	9.39	9.68	24260.073	0.56	3752.850	0.58		
9.93	9.77	10.01	22717.036	0.53	4462.023	0.69		
10.36	10.21	10.41	12059.368	0.28	2415.805	0.38		

Figure S76: LCMS trace of **18**



PEAK LIST

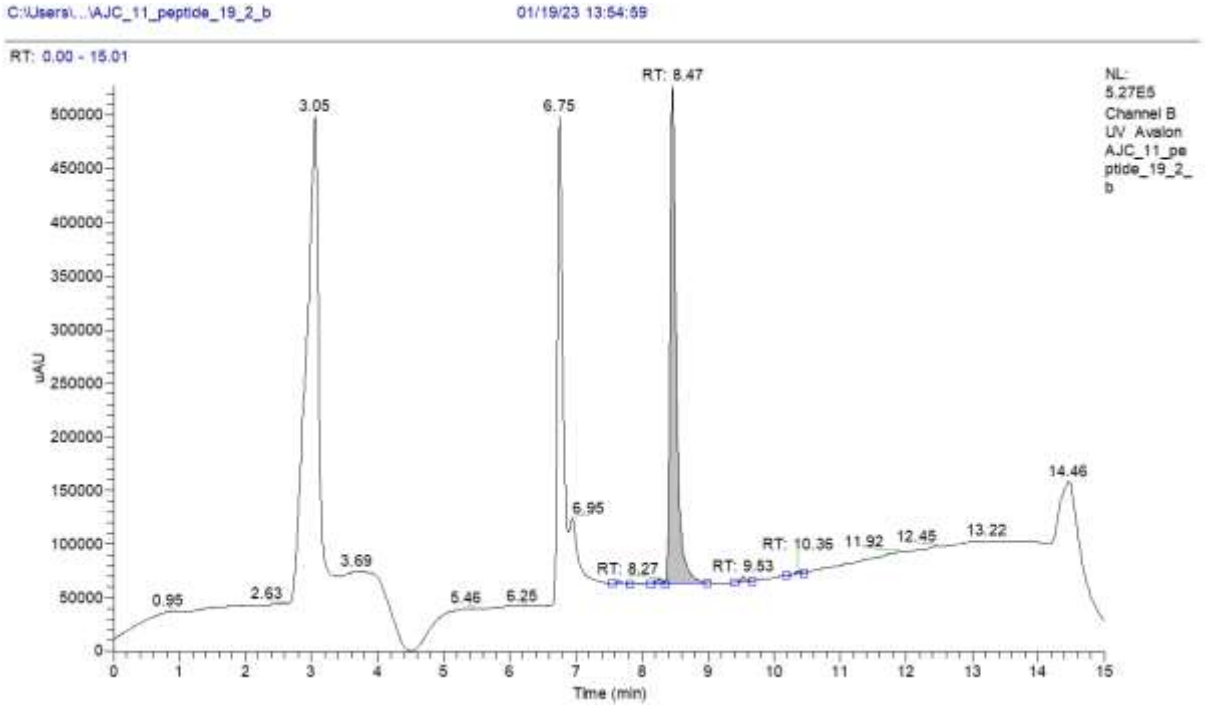
AJC_11_peptide_18.raw

RT: 0.00 - 15.01

Number of detected peaks: 3

Apex RT		Start RT	End RT		Area	%Area	Height	%Height
8.45	8.30	9.06	7370009.186	99.40	1037177.890	99.31		
9.54	9.45	9.65	21313.301	0.29	3867.396	0.37		
10.36	10.16	10.43	23027.168	0.31	3323.940	0.32		

Figure S77: LCMS trace of **19**



PEAK LIST

AJC_11_peptide_19_2_b.raw

RT: 0.00 - 15.01

Number of detected peaks: 5

Apex RT		Start RT	End RT		Area	%Area	Height	%Height
7.65	7.55	7.81	17623.395	0.56	2874.823	0.60		
8.27	8.13	8.34	32723.812	1.05	4702.172	0.98		
8.47	8.34	8.98	3031492.310	96.85	464312.182	96.81		
9.53	9.40	9.67	29712.157	0.95	4915.837	1.02		
10.36	10.19	10.45	18486.018	0.59	2826.539	0.59		

Peptide purity table

Peptide	Purity %
1	**96.6**
2	**96.5**
3	**99.2**
4	**96.3**
5	**98.5**
6	**98.2**
7	**96.7**
8	**99.2**
9	**98.2**
10	**99.7**
11	**99.2**
12	**99.5**
13	**98.4**
14	**98.5**
15	**98.6**
16	**98.6**
17	**95.6**
18	**99.3**
19	**96.8**

Microbiology

Antibacterial screening

Minimum inhibitory concentration (MIC) assays were performed in accordance with the Clinical and Laboratory Standards Institute (CLSI) recommended protocol and as previously reported. Briefly, *Escherichia. coli* (ATCC 25922) and *Staphylococcus. aureus* (ATCC 29213) were grown with shaking (200 rpm) in cation-adjusted Mueller Hinton (MH) broth at 37 °C. A two-fold dilution series of the test compounds (from 64 M to 0.125 M, final) was prepared in triplicate in polypropylene 96-well plates, using cation adjusted MH media. Diluted bacterial inoculums (50 μL) were added to the plate, to achieve a final well volume of 100 μL with a uniform bacterial CFU/ml of ~5 × 105 in each well. Untreated growth controls and non-inoculated sterility controls were included for each test compound replicate. MICs were determined as the lowest concentration at which growth did not occur after 18 h of incubation at 37 °C with shaking[29].

Minimum Inhibitory Concentration Assay Protocol for yeasts and filamentous fungi

The antifungal activity of the compounds against the yeasts *Candida albicans* (SC5314, type strain) and *Candida utilis* (SVB-Y1, clinical isolate, subcultured from Auckland City Hospital) was assessed as recently reported by broth microdilution in accordance with the CLSI recommended protocols[29]. Briefly, dilution series of the test compounds were prepared, using RPMI 1640 media (with glutamine and phenol red, without bicarbonate). Yeast inoculum was prepared from a 24 h old culture by picking and resuspending 5 colonies (~1 mm in diameter) and resuspending these in 0.85% saline. The resulting suspension was diluted to achieve a final inoculum of 0.5 × 103 to 2.5 × 103 CFU/mL upon addition to the plate. Inoculum of the filamentous fungus *Aspergillus fumigatus* (SVB-F136 clinical isolate subcultured from Auckland City Hospital) was generated from a 7-day culture by harvesting spores with 1 mL of sterile 0.85% saline and gently scraping the surface with an inoculating loop. After gentle mixing, heavy fragments were allowed to settle for 3 min prior to transferring the upper homogenous suspension to a new tube. The suspension was vortexed and diluted in RPMI 1640 media to achieve a final inoculum of 0.4 × 104 to 5 × 104 CFU/mL upon addition to the plate. The plates were incubated at 35 °C for 48 h at which time the antifungal MIC was determined as the lowest test concentration at which no turbidity was observed across all three replicates. The assay was performed independently on three occasions and the reported MIC defined as the lowest concentration in which agreement was observed for all three biological replicates.

Toxicity assessment

Hemolysis assay

Fresh red blood cells were obtained from Uppsala University Hospital and were washed three times with Tyrode buffer (130 mM NaCl, 4 mM KCl, 2.8 mM sodium acetate, 1 mM MgCl2, 10 mM HEPES, 10 mM glucose, 1 mM CaCl2, adjusted to pH 7.4 with NaOH) and resuspended. The assay was performed in microtiter plates with final assay concentrations were 100 μM compound, 1% DMSO, and 50% RBC, assayed in a 200 μL/well microtiter plate. After incubation of microtiter plates at 37 °C for 45 min with shaking (250 rpm), the RBCs were pelleted by centrifugation at 1000 × g for 10 min at room temperature and the clear plasma transferred to a new plate. The hemoglobin concentration remaining in plasma was measured spectrophotometrically at 540 nm. The percentage of hemolysis was calculated by the equation: % Hem = [Abs compound] – [Abs negative control] / [Abs Lysis control] – [Abs negative control] × 100. For the complete lysis control, 1% Triton X-100 (in Tyrode buffer) was used instead of compound, and the negative control contained only Tyrode buffer. Compounds displaying hemolysis values greater than 1% at 100 μM were regarded as hemolytic[30].

Cytotoxicity assay

HeLa cells (ATCC-CCL-2) were maintained in Dulbecco's Modified Eagle Medium (DMEM, Thermo Fisher Scientific) supplemented with 10% (v/v) fetal bovine serum (FBS, Thermo Fisher Scientific), penicillin (100 units/mL) and streptomycin (100 μg/mL, both from Sigma) at 37 °C, 5% CO2. For the cell viability assay, HeLa cells were seeded in 96-well plates (Corning®, Merck) at 20 × 103 cells/well and incubated for 24 h (37 °C, 5% CO2). Stock solutions of peptides were prepared in DMSO at 10 mM and cells were incubated with serial dilutions of peptides (1.4-87.5 μM) for 24 h under standard growth conditions. For the positive control, cells were treated with DMSO (0.6-40%, v/v, Sigma) for 24 h. The cells were washed twice with phosphate buffered saline (PBS, Thermo Fisher Scientific) and cell viability was then assessed using PrestoBlue™ reagent (Invitrogen), which was directly added to the cells (1:10 dilution in culture medium). Following recommended incubation times (manufacturer's instructions), fluorescence was measured using a Spark plate reader (Tecan, Austria) at Ex/Em 560 nm/590 nm and corrected for background fluorescence by including control wells containing only cell culture media (no cells). Two independent experiments were performed[31].

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