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Synthesis and binding affinities for sst receptors of cyclic peptoid SRIF-mimetics

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Supporting Information

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General Experimental Information

Equipment

Melting points were determined on a Reichert microscope apparatus and are uncorrected. Specific rotations were measured on a Jasco DIP-370 polarimeter using a 10 cm cell. IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer equipped with a Pike Technologies MIRacle^{TM} ATR or on a Perkin-Elmer 881 spectrometer and ν are expressed in cm^{-1}. NMR spectra were recorded on a 400 MHz Bruker AC 400 spectrometer. Chemical shifts are referenced to the residual solvent peak and *J* values are given in Hz. The following multiplicity abbreviations are used: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, and (br) broad. Where applicable, assignments were based on COSY, HMBC, HSQC and *J*-mod-experiments. TLC was performed on Merck TLC aluminum sheets, silicagel 60, F254. Progression of reactions was, when applicable, followed by NMR and/or TLC. Visualizing of spots was effected with UV-light and/or ninhydrin in EtOH/AcOH. Flash chromatography was performed with Merck silica gel 60, 40-63 µm. Unless otherwise stated, flash chromatography was performed in the eluent system for which the R_f values are given. HRMS were recorded on a Micromass Q-Tof Micro (3000V) apparatus. HPLC analysis was performed on a Waters 590 instrument equipped with an Acclaim® 120 column (C18, 5 µm, 120 Å, 4.6×250 mm) and a Waters 484 UV detector.

Solvents and chemicals

THF was distilled under N_2 from potassium/benzophenone and stored over 4Å molecular sieves. CH_2Cl_2 was distilled under N_2 from CaH_2 and stored over 4Å molecular sieves. MeOH was distilled under N_2 from CaH_2 and stored over 4Å molecular sieves. $CHCl_3$ was distilled before use. EtOAc, CH_2Cl_2, cyclohexane, and MeOH for column chromatography were distilled before use. DMF, Et_2O, Et_3N and $^{i}Pr_2NEt$ were dried over 4Å molecular sieves. All other solvents and chemicals obtained from commercial sources were used as received. Primary amines required are commercially available in the case of benzylamine (for *Nphe* residue) and tryptamine (for *Nhtrp* residue); (*R*)-2-(*t*-butyldimethylsilanyloxy)propylamine (for *Nhthr* residue) was obtained from (*R*)-1-aminopropan-2-ol by alcool protection with a *t*-butyldimethylsilyl group (see experimental protocols section for details); 1-*N*-Boc-1,4-diaminobutane (for *Nlys* residue) was obtained from the commercially available 1,4-diaminobutane after monoprotection by a Boc group (see experimental protocols section for details).

[125I]-somatostatin binding assays

All binding experiments were done in 96-well plates in 10 mM $MgCl_2$, 0,25% BSA, 50 mM HEPES pH 7.5, 1% protease inhibitor cocktail (Sigma, St Quentin Fallavier, France). Membrane preparation expressing the human sst-receptor subtypes (PerkinElmer, France) was adjusted so that no more than 10% of proposed radio-ligand was specifically bound. Typically, 0.05 nM [^{125}I]-somatostatin was incubated with membrane preparation and various concentrations of the peptoids for 2 hours in a final assay volume of 100µl. Non-specific binding was determined in the presence of 5µM somatostatin-28. The reaction was stopped by filtration of the 96-well simultaneously through a GF/C plate presoaked in 0.5% polyethylenimine, using a FilterMate harvester (PerkinElmer, France). The filters were washed twice with ice-cold buffer, dried and the bound radioactivity was counted, after the addition of 25 µl of MicroScint per well, by scintillation spectrometry on a TopCount beta counter (PerkinElmer, France). IC_{50} values were converted to K_i for competition experiments using the Cheng-Prusoff equation.

General Experimental Procedures

General procedure A: β-peptoid residues synthesis: Acylation step. To a solution of the secondary amine (1.0 equiv, 0.2 M) in THF at 0 °C under Ar was added Et_3N (1.4 equiv) and then acryloyl chloride (1.2 equiv). After stirring for 1 h at 0 °C the resulting mixture was filtered, washing the solids with THF. The filtrate was then concentrated and dried *in vacuo*, yielding the crude acrylamide.

General procedure B: β-peptoid residues synthesis: aza-Michael step. To a solution of the acrylamide (1.0 equiv, 0.4 M) in MeOH at rt under Ar was added the chosen primary amine (2.0 equiv). After stirring overnight at 50 °C, the mixture was concentrated under reduced pressure and the residue was dried *in vacuo*, yielding the desired crude secondary amine.

General procedure C: α-peptoid residues synthesis: Acylation step. To a solution of the secondary amine (1.0 equiv, 0.2 M) in THF at 0 °C under Ar was added Et_3N (1.2 equiv) and then bromoacetyl bromide (1.2 equiv). After stirring for 1 h at 0°C the resulting mixture filtered, washing the solids with THF. The filtrate was then concentrated and dried *in vacuo*, yielding the crude bromoacetyl amide.

General procedure D: α-peptoid residues synthesis: Substitution step. To a solution of the bromoacetyl amide (1.0 equiv, 0.2 M) in THF at 0 °C under Ar was added Et_3N (2.0 equiv) followed by the chosen primary amine (2.0 equiv). After stirring overnight at rt, the resulting mixture filtered, washing the solids with THF. The filtrate was then concentrated under reduced pressure and the residue was dried *in vacuo*, yielding the desired crude secondary amine.

General procedure E: silyl group removal and head-to-tail macrocyclization. To a solution of the silyl compound (1.0 equiv) in DMF (25 mM) at 0°C under Ar was added 1M TBAF in THF (3.1 eq). The reaction mixture was allowed to heat to rt and stirring was continued for 2.5 hours. The reaction mixture was poured into a mixture of brine and satd. aq. $NaHCO_3$ (1:1, 4 mL per mL of DMF) and the resulting mixture was extracted 16 times with EtOAc (4 mL per mL of DMF). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried in vacuo, yielding the crude deprotected intermediate. The residue was dissolved in DCM/DMF (4:1, 5 mM) at 0°C under Ar and DIPEA (2.0 eq) and HATU (1.2 eq) were added. The mixture was allowed to heat at rt and stirred for 3 days. The solvents were evaporated under reduced pressure and the residue was taken up in EtOAc (approx. 1/3 the volume used for cyclization). The organic layer was washed with satd. aq. $NaHCO_3$ (2×1/5 the volume of EtOAc), satd. aq. NH_4Cl (2×1/5 the volume of EtOAc) and brine (1/5 the volume of EtOAc), dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

General procedure F: *t*-butyl carbamate removal. The protected compound (1 equiv) was dissolved into DCM (0.05-0.1 M) at 0°C under argon atmosphere and TFA (equal volume of that of DCM) was added. After stirring 30 minutes at 0°C the mixture is concentrated under reduced pressure. The residue was dissolved and concentrated from Et_2O or DCM (three times) to afford evaporation of TFA and furnish the trifluoroacetate salt.

General procedure G: acetylation of *N*-terminal peptoid. To a solution of peptoid (1 equiv) and Et_3N (1.4 equiv) in THF or EtOAc (0.2 M) at 0°C under Ar, was added AcCl (1.2 equiv). After stirring for 1 hour at 0°C, the mixture was filtered washing the solids with EtOAc. The filtrate was then concentrated and dried *in vacuo*, yielding the crude *N*-acylated compound.

Experimental Protocols and Characterization Data for all Synthesized Compounds

(*R*)-2-(*t*-butyldimethylsilanyloxy)propylamine: To a solution of (*R*)-(–)-1-amino-2-propanol (4.11 g, 54.7 mmol, 1.0 equiv) in DCM (127 mL) at – 15°C under argon was added Et_3N (7.63 mL, 54.7 mmol, 1.0 equiv) and DMAP (67 mg, 0.55 mmol, 0.01 equiv). After 10 minutes TBDMSCl (8.41 g, 55.8 mmol, 1.02 equiv) was added and the resulting mixture was stirred for 16 hours at rt. The reaction mixture was washed with water (60 mL) and the organic layer was dried over $MgSO_4$, filtered, concentrated and dried *in vacuo* for 2 minutes at oil pump, yielding (*R*)-2-(*t*-butyldimethylsilanyloxy)propylamine (9.81 g, 51.8 mmol, 95 %) as a yellow oil. $[\alpha]_D^{22}$ = – 22.1 (*c* 0.92, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.08 (s, 6H, $Si(CH_3)_2C(CH_3)_3$), 0.90 (s, 9H, $Si(CH_3)_2C(CH_3)_3$), 1.11 (d, *J* = 6.2 Hz, 3H, $CH_3CHOTBDMS$), 1.36-1.51 (bs, 2H, NH_2), 2.58 (dd, *J* = 12.8 Hz and 6.4 Hz, 1H, $CH_AH_BNH_2$), 2.66 (dd, *J* = 12.8 Hz and 4.0 Hz, 1H, $CH_AH_BNH_2$), 3.77-3.82 (m, 1H, $CH_3CHOTBDMS$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ – 4.7 (CH_3, $Si(CH_3)_2C(CH_3)_3$), – 4.4 (CH_3, $Si(CH_3)_2C(CH_3)_3$), 18.1 (C, $Si(CH_3)_2C(CH_3)_3$), 21.1 (CH_3, $CH_3CHOTBDMS$), 25.8 ($3CH_3$, $Si(CH_3)_2C(CH_3)_3$), 49.6 (CH_2, CH_2NH_2), 69.8 (CH, $CH_3CHOTBDMS$). NMR spectra were in accordance with those reported in literature.[1]

1-*N*-Boc-1,4-diaminobutane: To a solution of 1,4-diaminobutane (8.80 g, 99.8 mmol) in $CHCl_3$ (80 mL) at 0 °C was added dropwise a solution of Boc_2O (4.36 g, 20.0 mmol) in $CHCl_3$ (24 mL). After stirring overnight (18 h) at rt, the resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc (200 mL) and the organic layer was washed with brine (2×30 mL). The combined aqueous layers were extracted with EtOAc (20 mL) and the combined organic layers were dried over Na_2SO_4, filtered, concentrated, and dried *in vacuo*, yielding 1-*N*-Boc-1,4-diaminobutane (3.73 g, 99%) as a pale yellowish oil which was used in the ensuing reaction without further purification: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.05-1.18 (2H, br s, NH_2), 1.40 (9H, s, Boc), 1.36-1.53 (4H, m, CH_2CH_2NHBoc and $CH_2CH_2NH_2$), 2.67 (2H, t, *J* = 6.7 Hz, CH_2NH_2), 3.03-3.13 (2H, m, CH_2NHBoc), 4.45-4.80 (1H, br s, NHBoc); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.4 (CH_2), 28.3 ($3CH_3$, Boc), 30.9 (CH_2), 40.3 (CH_2, CH_2NHBoc), 41.8 (CH_2, CH_2NH_2), 78.9 (C, Boc), 155.9 (C, Boc). NMR spectra were in full accordance with those reported in the literature.[2]

Acrylic acid 2-trimethylsilanyl-ethyl ester (7): To a solution of 2-trimethyl ethanol (3.55 g, 30.0 mmol) and Et_3N (6.30 mL, 45.2 mmol) in Et_2O (120 mL) at 0 °C under Ar was added dropwise acryloyl chloride (3.40 mL, 42.0 mmol) and stirring was continued for 2 h 30 min at rt. The reaction mixture was diluted with Et_2O (60 mL) and washed satd. aq. $NaHCO_3$ (2×60 mL), 1M HCl (2×60 mL) and then brine (60 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure (at rt) giving a pale yellowish oil which was further dried on oil pump for 30 secs, yielding **7** (3.98 g, 77%) as a pale yellowish oil: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.05 (9H, s, TMS), 0.99-1.06 (2H, m, CH_2CH_2TMS), 4.22-4.28 (2H, m, CH_2CH_2TMS), 5.80 (1H, dd, *J* = 10.4, 1.5 Hz, H_2C=CH), 6.10 (1H, dd, *J* = 17.3, 10.4 Hz, H_2C=CH), 6.38 (1H, dd, *J* = 17.3, 1.5 Hz, H_2C=CH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -1.5 ($3CH_3$, TMS), 17.3 (CH_2, CH_2CH_2TMS), 62.7 (CH_2, CH_2CH_2TMS), 128.8 (CH, H_2C=CH), 130.3 (CH_2, H_2C=CH), 166.4 (C, C=O). NMR spectra were in full accordance with those reported in the literature.[3]

3-Benzylamino-propionic acid 2-trimethylsilanyl-ethyl ester (8). To a mixture of **1** (2.84 mg, 16.5 mmol) and water (16.5 mL) at 0 °C was added benzylamine (4.85 mL, 44.4 mmol)

and the resulting heterogeneous mixture was stirred vigorously at rt for 2 h. The mixture was then extracted with EtOAc (3×30 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography of the residue yielded **8** (4.13 g, 90%) as a pale yellowish oil: R_f (cyclohexane/EtOAc 50:50) = 0.43; **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 3327 (NH), 3064, 3028, 2954, 2898, 2835, 1730 (C=O, ester), 1495, 1454, 1422, 1386, 1351, 1250, 1170, 1122, 1062, 937, 859, 837, 735, 698, 666; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.04 (9H, s, TMS), 0.95-1.01 (2H, m, CH_2CH_2TMS), 1.84-2.06 (1H, br s, N*H*), 2.52 (2H, t, *J* = 6.5 Hz, $HNCH_2CH_2C=O$), 2.90 (2H, t, *J* = 6.5 Hz, $HNCH_2CH_2C=O$), 3.81 (2H, s, CH_2Ph), 4.14-4.21 (2H, m, CH_2CH_2TMS), 7.22-7.36 (5H, m, Ph*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -1.5 ($3CH_3$, TMS), 17.3 (CH_2, CH_2CH_2TMS), 34.8 (CH_2, $HNCH_2CH_2C=O$), 44.5 (CH_2, $HNCH_2CH_2C=O$), 53.7 (CH_2, CH_2Ph), 62.7 (CH_2, CH_2CH_2TMS), 126.9 (CH, Ph), 128.1 (2CH, Ph), 128.4 (2CH, Ph), 140.0 (C, Ph), 172.9 (C, *C*=O); **HRMS** (TOF MS ES$^+$) calcd for $C_{15}H_{26}NO_2Si$ $[M + H]^+$ *m*/*z* 280.1727, found 280.1701.

Linear β-peptoid (9) was synthesised by application of the general procedure A starting from **8** (5.13 g, 18.4 mmol, 1.0 equiv). Flash chromatography on silica gel of the crude product using cyclohexane/EtOAc 75:25 as solvent yielded the intermediate acrylamide **9-I** (5.17 g, 15.5 mmol, 84 %) as a pale yellow oil. Application of general procedure B on **9-I** (5.17 g, 15.5 mmol, 1.0 equiv) using **(*R*)-2-(*t*-butyldimethylsilanyloxy)propylamine** as primary amine, then flash chromatography on silica gel of the crude product using DCM/MeOH 90:10 as solvent yielded **9** (7.52 g, 14.4 mmol, **93 %**) as a yellowish oil: R_f = 0.6/0.5 (DCM/MeOH 90:10). $[\alpha]_D^{21}$ = – 10.7 (*c* 0. 87, $CHCl_3$). **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 3332 (NH), 3065, 3031, 2954, 2930, 2897, 2856, 1732 (C=O, ester), 1656, 1651 1645 (C=O amides), 1496, 1472, 1468, 1453, 1423, 1387, 1372, 1314, 1251, 1175, 1059, 1005, 981, 939, 860, 837, 776, 731, 697, 666. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.00-0.90 (m, 15H, 5×SiCH_3), 0.85-0.90 (2×s, 9H, $Si(CH_3)_2C(CH_3)_3$), 0.92-0.98 (m, 2H, CH_2TMS), 1.12,1.14 (2×d, *J* = 6.0 Hz, 3H, $CH_2CH(CH_3)O$), 2.46-2.67 (m, 6H, 2×$NCH_2CH_2C=O$ and $NCH_2CH(CH_3)O$ or $NHCH_2CH_2C=O$), 2.82-3.03 (m, 2H, $NCH_2CH(CH_3)O$ or $NHCH_2CH_2C=O$), 3.51-3.67 (m, 2H, $NCH_2CH_2C=O$), 3.86-3.99 (m, 1H, $NCH_2CH(CH_3)O$), 4.08-4.17 (m, 2H, $TMSCH_2CH_2O$), 4.53-4.65 (m, 2H, NCH_2Ph), 7.11-7.37 (m, 5H, C*H*(Ar)). **^{13}C NMR** (100 MHz, $CDCl_3$): δ –4.8 (CH_3, $Si(CH_3)_2C(CH_3)_3$), –4.4, –4.3 (CH_3, $Si(CH_3)_2C(CH_3)_3$), –1.6, –1.5 ($3CH_3$, 3×SiCH_3), 17.2 (CH_2, CH_2TMS), 17.9 (C, $Si(CH_3)_2C(CH_3)_3$), 21.6 (CH_3, $CH_2CH(CH_3)O$), 25.8 ($3CH_3$, $Si(CH_3)_2C(CH_3)_3$), 30.8, 31.1 (CH_2, $NHCH_2CH_2C=O$), 32.7, 33.1 (CH_2, $NCH_2CH_2C=O$), 42.4, 43.0 (CH_2, $NCH_2CH_2C=O$), 45.1, 45.3 (CH_2, $NHCH_2CH_2C=O$), 48.1, 52.1 (CH_2, NCH_2Ph), 56.2 (CH_2, $NCH_2CH(CH_3)O$), 62.9, 63.2 (CH_2, $TMSCH_2CH_2O$), 66.0, 66.2 (CH, $CH_2CH(CH_3)O$), 126.2, 127.5, 127.7, 128.0, 128.7, 129.0 (5CH, Ph), 136.2, 136.8 (C, Ph), 171.0, 171.6, 172.0 (2C, *C*=O). **HRMS (TOF MS ES$^+$)**: calcd for $C_{27}H_{51}N_2O_4Si_2$ $[M + H]^+$ *m*/*z* 523.3382, found 523.3390.

Linear β-peptoid (10) was synthesised by application of the General procedure A starting from **9** (7.42 g, 14.2 mmol, 1.0 equiv). Flash chromatography on silica gel of the crude product using cyclohexane/EtOAc 60:40 as solvent yielded the intermediate acrylamide **10-I** (7.15 g, 12.4 mmol, 87 %) as a pale yellow oil. Reaction of the intermediate **10-I** (2.20 g, 3.81 mmol, 1.0 equiv) following general procedure B using **1-*N*-Boc-1,4-diaminobutane** as primary amine, then flash chromatography on silica gel of the crude product using DCM/MeOH 90:10 as solvent yielded **10** (2.04 g, 2.67 mmol, 70 %) as a yellowish oil. R_f = 0.30/0.16 (CH_2Cl_2/MeOH 90:10). $[\alpha]_D^{23}$ = – 7.8 (*c* 0.74, $CHCl_3$). **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 3350 (NH), 3041, 3030, 2954, 2930, 2899, 2858, 1731 (C=O ester), 1714, 1704, 1698, 1652, 1644, 1634 (CO amide and carbamate), 1520, 1506, 1496, 1471, 1463, 1455, 1435, 1417, 1391, 1366, 1251, 1174, 1141, 1116, 1092, 106, 104, 997, 939, 860, 837, 777, 732, 698, 666. **^{1}H**

NMR (400 MHz, $CDCl_3$): δ – 0.07-0.04 (m, 15H, 5×SiC*H*$_3$), 0.79-0.88 (m, 9H, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$), 0.90-0.97 (m, 2H, C*H*$_2$TMS), 1.03 (d, *J* = 6.0 Hz, 0.5H, 0.2×CH$_2$CH(C*H*$_3$)O), 1.08-1.14 (m, 2.5H, 0.8×CH$_2$CH(C*H*$_3$)O), 1.42 (s, 9H, ^{t}Bu(NHBoc)), 1.48-1.80 (m, 4H, NCH$_2$(C*H*$_2$)$_2$CH$_2$NHBoc), 2.45-3.91 (m, 18H, 3×NC*H*$_2$C*H*$_2$C=O, NC*H*$_2$CH(CH$_3$)O and NC*H*$_2$(CH$_2$)$_2$C*H*$_2$NHBoc), 3.91-4.24 (m, 3H, TMSCH$_2$C*H*$_2$O and NCH$_2$C*H*(CH$_3$)O), 4.47-4.65 (m, 2H, NC*H*$_2$Ph), 4.30-4.95 (brs, 1H, N*H*Boc), 7.10-7.40 (m, 5H, C*H*(Ar)). **^{13}C NMR** (100 MHz, $CDCl_3$): δ –4.9, –4.8 (2CH$_3$, Si(*C*H$_3$)$_2$C(CH$_3$)$_3$), –1.6 (3CH$_3$, 3×Si*C*H$_3$), 17.2 (CH$_2$, *C*H$_2$TMS), 17.8 (C, Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), 21.5 (CH$_3$, CH$_2$CH(*C*H$_3$)O), 25.7, 25.8 (3CH$_3$, Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 26.0, 26.4, 27.5, 27.6 (2CH$_2$, NCH$_2$(*C*H$_2$)$_2$CH$_2$NHBoc), 28.4 (3CH$_3$, NHBoc), 29.6, 32.0, 31.3, 31.6, 31.8, 32.8, 32.9, 33.4, 33.6 (3CH$_2$, 3×NCH$_2$*C*H$_2$C=O), 40.1, 42.5, 42.7, 42.9, 43.1, 43.2, 45.1, 45.2, 45.7, 45.9, 48.9, 49.0 (5CH$_2$, 3×N*C*H$_2$CH$_2$C=O and NCH$_2$(*C*H$_2$)$_2$*C*H$_2$NHBoc), 48.0, 48.4, 52.0, 52.2 (CH$_2$, N*C*H$_2$Ph), 53.4, 53.5, 55.4 (CH$_2$, N*C*H$_2$CH(CH$_3$)O), 62.8, 63.2 (CH$_2$, TMSCH$_2$*C*H$_2$O), 66.5, 66.8, 66.9 (CH, NCH$_2$*C*H(CH$_3$)O), 79.0 (C, ^{t}Bu(NHBoc)), 125.9, 126.3, 127.4, 127.5, 127.6, 127.7, 127.8, 128.6, 128.9, 129.0 (5CH, Ph), 136.6, 137.0, 137.2 (C, Ph), 155.9 (C, *C*=O(NHBoc)), 170.3, 170.7, 170.9, 171.0, 171.3, 171.7, 171.8, 172.0, 172.6 (3C, 3×*C*=O). **HRMS (TOF MS ES$^+$)**: calcd for $C_{39}H_{73}N_4O_7Si_2$ $[M + H]^+$ *m/z* 765.5012, found 765.5026.

Linear α,β-peptoid (11) was synthesised starting from **10** (2.54 g, 3.32 mmol, 1.0 equiv) by application of the general procedures C (the intermediate bromoacetyl amide was not purified) and D using tryptamine as primary amine. Flash chromatography on silica gel of the residue using EtOAc/MeOH 90:10 as solvent yielded **11** (1.34 g, 1.39 mmol, 42 %) as a yellowish foam. R_f = 0.25 (EtOAc/MeOH 90:10). $[\alpha]_D^{21}$ = –7.9 (*c* 0.98, $CHCl_3$). **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 3303 (NH), 3061, 3027, 2956, 2929, 2896, 2858, 1729, 1707, 1640 (C=O), 1473, 1452, 1449, 1436, 1420, 1364, 1251, 1175, 1169, 995, 836, 742. **^{1}H NMR** (400 MHz, $CDCl_3$): δ –0.15-0.19 (m, 15H, 5×SiC*H*$_3$), 0.74-0.89 (m, 9H, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$), 0.90-0.99 (m, 2H, C*H*$_2$TMS), 0.99-1.17 (m, 3H, CH$_2$CH(C*H*$_3$)O), 1.30-1.54 (m, 13H, ^{t}Bu(NHBoc) and NCH$_2$(C*H*$_2$)$_2$CH$_2$NHBoc), 2.38-4.19 (m, 27H, 3×NC*H*$_2$C*H*$_2$C=O, NHC*H*$_2$C=O, TMSCH$_2$C*H*$_2$O, NC*H*$_2$C*H*(CH$_3$)O, NC*H*$_2$(CH$_2$)$_2$C*H*$_2$NHBoc and NHC*H*$_2$C*H*$_2$Indole), 4.49-4.86 (m, 3H, NC*H*$_2$Ph and N*H*Boc), 7.00-7.41 (m, 10H, C*H*(Ar)), 7.50-7.63 (m, 1H, C=C*H*NH), 8.45-8.82 (1H, N*H*(indole)). **^{13}C NMR** (100 MHz, $CDCl_3$): δ –4.8 (2CH$_3$, Si(*C*H$_3$)$_2$C(CH$_3$)$_3$), –1.6 (3CH$_3$, 3×Si*C*H$_3$), 17.2 (CH$_2$, *C*H$_2$TMS), 17.8 (C, Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), 21.4, 21.5 (CH$_3$, CH$_2$CH(*C*H$_3$)O), 23.9, 24.0, 24.4, 24.7, 24.9, 25.1, 25.9, 27.2 (2CH$_2$, NCH$_2$(*C*H$_2$)$_2$CH$_2$NHBoc), 25.7 (3CH$_3$, Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 28.4 (3CH$_3$, NHBoc), 31.0, 31.1, 31.4, 31.7, 31.9, 32.0, 32.8, 32.9, 33.5 (3CH$_2$, 3×NCH$_2$*C*H$_2$C=O), 39.0, 40.0, 42.3, 42.4, 42.7, 42.8, 43.0, 43.2, 43.4, 45.0, 45.2, 45.3, 45.4, 45.7, 45.8, 47.2, 47.4, 48.3, 48.7, 48.8, 49.0, 49.2, 49.3, 49.5, 51.6, 51.9, 52.1, 52.2, 52.9, 53.4, 55.4, 55.5 (10CH$_2$, 3×N*C*H$_2$CH$_2$C=O, NH*C*H$_2$C=O, N*C*H$_2$Ph, N*C*H$_2$CH(CH$_3$)O, NCH$_2$(CH$_2$)$_2$*C*H$_2$NHBoc and NH*C*H$_2$*C*H$_2$Indole), 62.8, 62.9, 63.1, 63.2, 63.3 (CH$_2$, TMSCH$_2$*C*H$_2$O), 66.3, 66.5, 66.7, 66.8, 66.9 (CH, CH$_2$*C*H(CH$_3$)O), 79.2 (C, ^{t}Bu(NHBoc)), 111.3, 111.5, 118.5, 118.6, 119.2, 121.9, 122.3, 122.4, 122.6, 122.7, 122.8, 122.9, 125.3 (5CH, indole), 126.0, 126.3, 127.3, 127.4, 127.5, 127.7, 127.8, 128.6, 128.7, 128.9, 129.0, 129.1 (5CH, Ph), 112.3, 127.0, 127.1, 136.4, 136.6, 136.7, 136.9, 137.0, 137.2, 137.3 (4C, Ar), 156.078 (C, *C*=O(NHBoc)), 167.8, 168.5, 170.1, 170.2, 170.5, 170.6, 170.7, 170.8, 170.9, 171.0, 171.1, 171.3, 171.3, 171.4, 171.6, 171.7, 171.7, 172.0 (4C, 4×*C*=O). **HRMS** (TOF MS ES+): calcd for $C_{51}H_{85}N_6O_8Si_2$ $[M + H]^+$ *m/z* 965.5984, found 965.5967.

Linear β-peptoid (12) was synthesised starting from **10** (1.15 g, 1.50 mmol) by application of the general procedures A (the intermediate acrylamide was not purified) and B using tryptamine as primary amine, then flash chromatography on silica gel of the crude product using DCM/MeOH 90:10 as solvent yielded **12** (835 mg, 57%) as a pale yellowish solid: R_f

(CH_2Cl_2/MeOH 90:10) = 0.43/0.40. $[\alpha]^{21}_D$ = –5.8 (*c* 0.67, $CHCl_3$). Mp = 31-33 °C. **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 2957, 2951, 2932, 1718 (C=O, ester), 1707 (C=O, ester/boc), 1702 (C=O, ester/boc), 1697 (C=O, boc), 1693 (C=O, boc), 1638 (C=O, amide), 1509, 1473, 1458, 1452, 1417, 1390, 1365, 1315, 1251, 1173, 1140, 1113, 1089, 1044, 997, 936, 892, 857, 837, 807, 776, 766, 744; **^{1}H NMR** (400 MHz, $CDCl_3$): δ −0.11-0.02 (15H, m, TMS and TBDMS), 0.77-0.86 (9H, m, TBDMS), 0.87-0.94 (2H, m, CH_2CH_2TMS), 0.94-1.12 (3H, m, CH_3CHO), 1.28-1.52 (13H, m, $CH_2CH_2CH_2NHBoc$, $CH_2CH_2CH_2NHBoc$ and Boc), 2.39-4.15 (27H, m), 4.03-4.12 (2H, m, CH_2CH_2TMS), 4.46-4.64 (2H, m, CH_2Ph), 4.77-4.96 (1H, m N*H*Boc), 6.98-7.39 (9H, m, Ar*H*), 7.46-7.54 (1H, m, Ar*H*), 9.62-9.24 (1H, m, indole-N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ -4.8 ($2CH_3$, TBDMS), -1.5 ($3CH_3$, TMS), 17.2 (CH_2, CH_2CH_2TMS), 17.9 (C, TBDMS), 21.5, 21.5 (CH_3, CH_3CHO), 22.6, 22.6 (CH_2, CH_2-indole), 25.8 ($3CH_3$, TBDMS), 24.5, 24.5, 27.0, 27.1 ($2CH_2$, $CH_2CH_2CH_2NHBoc$ and $CH_2CH_2CH_2NHBoc$), 28.4, 28.5 ($3CH_3$, Boc), 28.7, 28.9, 31.0, 31.0, 31.3, 31.4, 31.4, 31.6, 31.8, 31.9, 32.0, 32.8, 32.9, 33.4, 33.5, 33.5, ($4CH_2$, $4\times NCH_2CH_2C{=}O$), 39.9, 40.0, 42.7, 42.7, 42.9, 43.1, 43.3, 43.4, 44.4, 44.6, 44.7, 45.3, 45.8, 46.0, 48.0, 48.1, 48.2, 48.3, 48.4, 52.0, 52.2, 52.3, 53.0, 53.3, 53.4, 55.3, 55.4, 55.5 ($9CH_2$), 62.8, 62.9, 62.9, 63.2, 63.3, 63.3 (CH_2, CH_2CH_2TMS), 66.3, 66.5, 66.5, 66.7, 66.9, 67.0 (CH, CH_3CHO), 79.1, 79.3 (C, Boc), 108.9, 109.0, 109.1, 109.4, 109.5 (C, Ar), 111.6, 111.8 (CH, Ar), 118.0, 118.2 (CH, Ar), 119.3, 119.4 (CH, Ar), 122.0, 123.4, 123.9 (2CH, Ar), 126.5, 126.5, 126.7 (C, Ar), 125.9, 126.0, 126.3, 126.3, 127.4, 127.6, 127.7, 127.8, 127.8, 128.6, 128.7, 128.9, 129.0, 129.1 (5CH, Ar), 136.4, 136.5, 136.6, 136.7, 136.8, 137.2, 137.3 (2C, Ar), 156.1, 156.2 (C, Boc), 170.1, 170.3, 170.4, 170.6, 170.7, 170.7, 170.9, 171.0, 171.1, 171.1, 171.2, 171.3, 171.5, 171.6, 171.7, 171.8, 171.9, 172.0, 172.0 (4C, $4\times C{=}O$); **HRMS** (TOF MS ES$^+$) calcd for $C_{52}H_{87}N_6O_8Si_2$ $[M + H]^+$ *m/z* 979.6118, found 979.6116; **HPLC** (Water (0.1% TFA)/MeOH 10:90, flow = 0.75): t_r = 7.38 min, purity = 92.6%.

Cyclic α,β-peptoid (13) was synthesised starting from **11** (297 mg, 0.31 mmol, 1.0 equiv) by application of the general procedure E. Flash chromatography on silica gel of the residue using EtOAc/MeOH 90:10 as solvent yielded **13** (147 mg, 0.20 mmol, 65 %) as a yellowish foam. R_f = 0.28 (EtOAc/MeOH 9:1). $[\alpha]^{21}_D$ = – 11.8 (*c* 0.99, $CHCl_3$). **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 3326 (OH and NH), 2972, 2931, 1700, 1636 (C=O), 1479, 1452, 1424, 1366, 1251, 1169. **^{1}H NMR** (400 MHz, Acetone-d_6): δ 1.01-1.22 (m, 3H, $CH_2CH(CH_3)O$), 1.24-1.67 (m, 13H, ^{t}Bu(NHBoc) and $NCH_2(CH_2)_2CH_2NHBoc$), 2.16-5.00 (m, 27H, $3\times NCH_2CH_2C{=}O$, $NCH_2C{=}O$, $NCH_2CH(CH_3)OH$, NCH_2Ph, NCH_2CH_2indole and $NCH_2(CH_2)_2CH_2NHBoc$), 5.92-6.17 (bs, 1H, N*H*Boc), 6.96-7.77 (m, 10H, C*H*(Ar)), 9.93-10.18 (m, 1H, N*H*(indole)). **^{13}C NMR** (100 MHz, Acetone-d_6): δ 22.2, 22.4, 22.7, 22.8 (CH_3, $CH_2CH(CH_3)O$), 25.5, 25.8, 25.8, 26.0, 27.2, 27.7, 29.1 ($2CH_2$, $NCH_2(CH_2)_2CH_2NHBoc$), 29.7 ($3CH_3$, NHBoc), 32.4, 32.5, 32.8, 33.1, 33.2, 33.7, 34.0, 35.1 ($3CH_2$, $3\times NCH_2CH_2C{=}O$), 41.6, 41.7, 42.8, 44.1, 44.8, 45.3, 45.9, 46.0, 46.1, 46.4, 46.9, 47.1, 47.2, 49.2, 49.8, 49.9, 50.3, 50.6, 50.7, 50.8, 52.0, 52.2, 52.6, 56.0, 56.7, 57.4, 58.7 ($10CH_2$, $3\times NCH_2CH_2C{=}O$, $NCH_2C{=}O$, NCH_2Ph, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NHBoc$ and NCH_2CH_2Indole), 66.7, 67.2, 67.5, 67.8, 68.2, 68.3 (CH, $CH_2CH(CH_3)O$), 79.3, 79.5 (C, ^{t}Bu(NHBoc)), 113.2, 113.3, 113.5, 119.9, 120.2, 120.3, 120.4, 122.9, 124.2, 124.4 (5CH, indole), 128.6, 128.7, 128.8, 128.9, 129.2, 129.5, 129.6, 129.7, 130.2, 130.4, 130.5, 130.6 (5CH, Ph), 114.3, 129.5, 138.7, 140.3, 140.5, 140.8 (4C, Ar), 157.8, 157.9, 158.0 (C, *C*=O(NHBoc)), 170.315, 172.122, 172.404, 172.824, 172.925, 173.017, 173.134, 173.575, 173.936, 174.259 (4C, $4\times C{=}O$). **HRMS** (TOF MS ES+): for $C_{40}H_{56}N_6O_7Na$ $[M + Na]^+$ *m/z* 755.4108, found 755.4092.

Cyclic β-peptoid (14) was synthesised starting from **12** (408 mg, 0.420 mmol) application of the general procedure E. Flash chromatography on silica gel of the residue using EtOAc/MeOH 90:10 until the impurities had passed followed by change to CH_2Cl_2/MeOH

90:10 yielded **14** (235 mg, 75%) as a pale brownish solid: R_f (CH_2Cl_2/MeOH 90:10) = 0.50. $[\alpha]^{22}_D$ = –0.3 (*c* 0.66, $CHCl_3$). mp = 60-62 °C. **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 1702 (C=O, Boc), 1697 (C=O, Boc), 1694 (C=O, Boc), 1629 (C=O, amide), 1517, 1475, 1453, 1424, 1418, 1391, 1366, 1272, 1251, 1232, 1168, 1135, 1099, 1081, 1026, 1011, 837, 745, 702; **^{1}H NMR** (400 MHz, acetone-d_6): δ 0.80 (0.20H, d, *J* = 6.2 Hz, C*H*$_3$CHO), 1.01-1.19 (2.80H, m, C*H*$_3$CHO), 1.35-1.65 (13H, m, C*H*$_2$CH$_2$CH$_2$NHBoc, CH$_2$C*H*$_2$CH$_2$NHBoc and Boc), 2.13-4.90 (29H, m), 6.17-6.98 (1H, m, N*H*Boc), 6.87-7.43 (9H, m, Ar*H*), 7.54-7.73 (1H, m, Ar*H*), 10.08-10.27 (1H, m, indole-N*H*); **^{13}C NMR** (100 MHz, acetone-d_6): δ 21.7, 22.1, 22.2, 22.4, 22.6, 22.7 (CH$_3$, *C*H$_3$CHO), 25.0, 25.1, 25.4, 25.6, 25.8, 26.4, 26.4, 26.6, 27.0, 28.0, 28.5, 29.0, 29.1 (3CH$_2$, *C*H$_2$CH$_2$CH$_2$NHBoc, CH$_2$*C*H$_2$CH$_2$NHBoc and *C*H$_2$-indole), 29.7 (3CH$_3$, Boc), 31.9, 32.2, 32.3, 32.9, 32.9, 33.1, 33.1, 33.3, 33.3, 33.4, 33.5, 35.6, 33.7, 33.8, 33.9, 34.3, 34.6, 35.5 (4CH$_2$, 4×NCH$_2$*C*H$_2$C=O), 41.5, 41.7, 41.8, 43.0, 43.8, 44.2, 44.2, 44.8, 45.0, 45.1, 45.3, 45.5, 45.6, 45.8, 45.9, 46.0, 46.1, 46.2, 46.5, 46.5, 46.6, 46.9, 47.0, 47.3, 47.7, 48.0, 48.1, 48.3, 48.4, 48.8, 49.2, 49.3, 49.5, 50.0, 50.1, 50.6, 51.1, 51.3, 51.7, 51.9, 52.3, 53.3, 53.4, 53.8, 54.3, 55.5, 55.9, 56.0, 56.1, 56.3, 58.1, 58.3, 58.4, 59.0, 59.5 (9CH$_2$), 66.4, 66.5, 66.9, 67.0, 67.3, 67.4, 67.5, 67.9, 68.0, 68.1 (CH, CH$_3$*C*HO), 79.3, 79.5 (C, Boc), 113.2, 113.2, 113.3, 113.3 (CH, Ar), 113.4, 113.4, 113.5, 114.2, 114.3, 114.4 (C, Ar), 120.1, 120.2, 120.4, 120.6, 120.6 (2CH, Ar), 123.0, 123.1, 123.2, 124.2, 124.4, 124.5, 124.6, 124.7, 124.8, 124.9, 124.9, 124.9, 125.0, 125.1, 125.1 (2CH, Ar), 129.3, 129.6 (C, Ar), 128.2, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9, 129.0, 129.0, 129.2, 129.7, 129.7, 130.2, 130.5 (5CH, Ar), 138.4, 138.6, 139.6, 139.7, 139.8, 139.9, 140.0, 140.2, 140.3, 140.3, 140.5, 140.5 (2C, Ar), 157.7 (C, Boc), 171.4, 171.5, 171.6, 171.8, 171.9, 172.0, 172.3, 172.5, 172.6, 172.7, 172.7, 172.8, 172.9, 172.9, 173.1, 173.2, 173.3, 173.5, 173.5, 173.6, 173.6, 174.0, 174.1, 174.2 (4C, 4×*C*=O); **HRMS** (TOF MS ES$^+$) calcd for $C_{41}H_{59}N_6O_7$ $[M + H]^+$ *m/z* 747.4259, found 769.4249; **HPLC** (Water (0.1% TFA)/MeOH 20:80, flow = 0.60): t_r = 8.47 min, purity = 98.4%.

Cyclic αβ3 peptoid TFA salt (1.TFA) was synthesised starting from **13** (62 mg, 0.09 mmol, 1.0 equiv) by application of general procedure F yielding **1.TFA** (69 mg, 0.09 mmol, quantitative) as an orange foam. A sample was purified by preparative HPLC (MeOH/H_2O+0.1%TFA) 60:40, t_r = 14.02 min, lyophilized and sent for biological tests. $[\alpha]^{23}_D$ = – 27.8 (*c* 0.95, MeOH). **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 2988, 2931, 2872, 1700, 1684, 1669, 1653, 1647, 1636 (C=O), 1623, 1616, 1559, 1539, 1506, 1457, 1374, 1363, 1203, 1182, 1137, 835, 800. **^{1}H NMR** (400 MHz, MeOD): δ 0.77-2.18 (m, 7H, CH$_2$CH(C*H*$_3$)O and NCH$_2$(C*H*$_2$)$_2$CH$_2$NH$_2$), 2.21-4.88 (m, 27H, 3×NC*H*$_2$C*H*$_2$C=O, NC*H*$_2$C=O, NC*H*$_2$C*H*(CH$_3$)OH, NC*H*$_2$Ph, NC*H*$_2$C*H*$_2$indole and NC*H*$_2$(CH$_2$)$_2$C*H*$_2$NH$_2$), 6.85-7.72 (m, 10H, C*H*(Ar)). **^{13}C NMR** (100 MHz, MeOD): δ 20.9, 21.1, 21.2, 21.4 (CH$_3$, CH$_2$CH(*C*H$_3$)O), 24.8, 25.0, 25.2, 25.3, 25.9, 26.2, 26.4, 27.2, 27.6, 30.9, 31.7, 32.0, 32.4, 32.5, 33.2, 33.6, 34.4, 34.8, 40.7, 42.4, 42.9, 43.8, 44.6, 45.3, 45.8, 45.9, 46.1, 46.6, 46.8, 50.1, 50.3, 50.6, 52.1, 52.3, 52.5, 52.9, 53.7, 55.5, 55.6, 56.4, 57.4, 58.3 (15CH$_2$, NCH$_2$(*C*H$_2$)$_2$*C*H$_2$NH$_2$, 3×NC*H*$_2$C*H*$_2$C=O, NC*H*$_2$C=O, NC*H*$_2$Ph, NC*H*$_2$CH(CH$_3$)O, and NC*H*$_2$C*H*$_2$Indole), 66.8, 67.2, 67.3 (CH, CH$_2$*C*H(CH$_3$)O), 112.5, 112.7, 119.2, 119.5, 119.6, 119.8, 120.0, 120.1, 122.5, 122.7, 123.7, 124.2, 124.3, 124.6 (5CH, indole), 127.9, 128.2, 128.4, 128.6, 128.7, 128.9, 129.0, 129.1, 129.8, 129.8, 130.1 (5CH, Ph), 113.2, 113.3, 138.3, 138.3, 138.9, 139.3 (4C, Ar), 161.5, 161.9 (C, *C*=O(TFA)), 170.1, 170.4, 170.6, 172.1, 172.7, 173.6, 173.8, 174.2, 174.3, 174.4 (4C, 4×*C*=O). **HRMS** (TOF MS ES+): for $C_{35}H_{49}N_6O_5$ $[M + H]^+$ *m/z* 633.3764, found 633.3781.

Cyclic β4 peptoid TFA salt (2.TFA) was synthesised starting from **14** (45 mg, 0.060 mmol) by application of general procedure F yielding **2.TFA** (46 mg, quantitative) as a pale rose solid: $[\alpha]^{21}_D$ = –5.2 (*c* 0.48, MeOH). Mp = 69-72 °C. **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 2981, 2973, 2967, 2950, 2938, 2923, 2867, 2844, 1685 (C=O), 1677 (C=O), 1672 (C=O), 1637 (C=O), 1624

(C=O), 1619 (C=O), 1477, 1453, 1430, 1371, 1341, 1260, 1201, 1176, 1172, 1134, 1056, 1033, 1010, 830, 798, 747, 738; **^{1}H NMR** (400 MHz, methanol-d_4): δ 0.73 (0.11H, d, J = 6.3 Hz, CH_3CHO), 1.06-1.45 (2.89H, m, CH_3CHO), 1.52-1.73 (4H, m, CH_2CH$_2$CH$_2$NH$_2$ and CH$_2$CH_2CH$_2$NH$_2$), 1.88-3.10 (12H, m, 4×NCH$_2$CH_2C=O, CH_2-indole and CH_2), 3.11-4.74-(17H, m), 6.94-7.68 (10H, m, ArH); **^{13}C NMR** (100 MHz, methanol-d_4): δ 17.2, 17.3, 17.5, 17.8, 20.7, 20.9, 21.1, 21.2, 21.3 (CH$_3$, CH$_3$CHO), 24.2, 24.4, 24.6, 24.6, 24.9, 25.1, 25.4, 25.5, 25.6, 25.8, 26.2, 26.5, 26.7, 26.8, 27.0, 27.3, 27.4 (3CH$_2$, CH$_2$CH$_2$CH$_2$NH$_2$, CH$_2$$CH_2CH_2NH_2$ and CH$_2$-indole), 31.3, 31.5, 31.6, 31.7, 32.2, 32.3, 32.4, 32.5, 32.6, 32.7, 32.8, 33.0, 33.1, 33.3, 33.6, 33.7, 34.0 (4CH$_2$, 4×NCH$_2$$CH_2$C=O), 40.4, 40.5 (CH$_2$), 42.1, 42.8, 43.2, 43.5, 43.8, 44.0, 44.2, 44.3, 44.4, 44.6, 44.7, 44.8, 45.0, 45.2, 45.3, 45.5, 45.7, 45.8, 46.0, 46.2, 46.2, 46.5, 46.6, 46.7, 46.8, 47.1, 47.5, 47.7, 47.8, 48.0, 48.0, 49.8, 50.2, 50.5, 50.7, 51.0, 51.3, 51.4, 51.7, 53.0, 53.4, 53.6, 53.9, 54.1, 54.3, 54.6, 54.9, 55.0, 55.3, 55.4, 56.7, 56.9, 57.5, 57.7, 59.0 (8CH$_2$), 66.4, 66.6, 66.7, 66.8, 66.8, 67.0, 67.1 (CH, CH$_3$$C$HO), 112.5, 112.5, 112.6, 112.7 (CH, Ar), 112.2, 112.3, 113.1, 113.2, 113.3, 113.5, 115.9, 118.8 (C, Ar), 119.0, 119.1, 119.2, 119.3, 119.4, 119.4, 119.8, 119.8, 120.0, 120.2, 120.2 (2CH, Ar), 122.4, 122.5, 122.6, 122.6, 123.7, 123.7, 124.2, 124.4, 124.5, 122.8 (2CH, Ar), 128.6 (C, Ar), 127.5, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.4, 128.5, 128.8, 128.9, 129.0, 129.1, 129.6, 129.7, 130.1 (5CH, Ar), 138.1, 138.3, 138.5, 138.6, 138.7, 139.0, 139.0 (2C, Ar), 161.3 (C, q, J = 38.5 Hz, F$_3$CC=O), 172.2, 172.2, 172.3, 172.4, 172.6, 172.7, 172.8, 172.8, 172.9, 173.0, 173.1, 173.2, 173.2, 173.5, 173.6, 173.7, 173.9, 173.9, 174.0, 174.3, 174.4, 174.5, 174.5, 174.7, 174.8 (4C, 4×C=O); **HRMS** (TOF MS ES$^+$) calcd for C$_{36}$H$_{51}$N$_6$O$_5$ [M - TFA + H]$^+$ m/z 647.3921, found 647.3936; **HPLC** (Water (0.1% TFA)/MeOH 20:80, flow = 0.60): t$_r$ = 5.26 min, purity = 96.4%.

Linear α,β-peptoid (15) was synthesised starting from **11** (707 mg, 0.73 mmol, 1.0 equiv) by application of the general procedures A (the intermediate acrylamide was not purified) and B using benzylamine as primary amine. Flash chromatography on silica gel of the residue in DCM/MeOH 90:10 as solvent yielded **15** (547 mg, 0.49 mmol, 67 %) as a white foam. R_f = 0.40 (DCM/MeOH 90:10). $[\alpha]_D^{21}$ = – 6.5 (c 0.85, CHCl$_3$). **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 3318 (NH), 2954, 2930, 2901, 2857, 1726, 1706, 1640 (C=O), 1473, 1452, 1436, 1420, 1365, 1251, 1171, 995, 859, 838, 776, 742, 698; **^{1}H NMR** (400 MHz, CDCl$_3$): δ –0.16-0.18 (m, 15H, 5×SiCH_3), 0.76-0.90 (m, 9H, Si(CH$_3$)$_2$C(CH_3)$_3$), 0.90-0.98 (m, 2H, CH_2TMS), 0.98-1.20 (m, 3H, CH$_2$CH(CH_3)O), 1.21-1.55 (m, 13H, ^{t}Bu(NHBoc) and NCH$_2$(CH_2)$_2$CH$_2$NHBoc), 2.34-4.26 (m, 33H, 4×NCH_2CH_2C=O, NCH_2C=O, TMSCH$_2$CH_2O, NCH_2CH(CH$_3$)O, NCH_2(CH$_2$)$_2$CH_2NHBoc, NCH_2CH_2Indole and NHCH_2Ph), 4.47-4.93 (m, 3H, NCH_2Ph and NHBoc), 6.96-7.65 (m, 15H, CH(Ar)), 8.52-9.43 (m, 1H, NH(indole)). **^{13}C NMR** (100 MHz, CDCl$_3$): δ –4.9 (2CH$_3$, Si(CH$_3$)$_2$C(CH$_3$)$_3$), –1.6 (3CH$_3$, 3×SiCH$_3$), 17.1 (CH$_2$, CH$_2$TMS), 17.7 (C, Si(CH$_3$)$_2$$C$(CH$_3$)$_3$), 21.3, 21.4 (CH$_3$, CH$_2$CH($CH_3$)O), 23.4, 23.8, 24.3, 24.4, 24.5, 24.8, 27.1, 27.2 (2CH$_2$, NCH$_2$ (CH$_2$)$_2$CH$_2$NHBoc), 25.6, 25.8 (3CH$_3$, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 28.3 (3CH$_3$, NHBoc), 30.3, 30.5, 30.6, 30.7, 30.8, 30.9, 31.0, 31.2, 31.3, 31.5, 31.7, 31.9, 32.7, 32.8, 33.4 (4CH$_2$, 4×NCH$_2$$CH_2$C=O), 39.9, 42.5, 42.8, 42.9, 43.0, 43.1, 43.3, 44.3, 44.5, 45.2, 45.3, 45.4, 45.5, 45.6, 45.8, 46.9, 47.3, 47.4, 47.5, 48.2, 48.8, 49.6, 49.8, 49.9, 51.8, 52.0, 52.1, 52.3, 52.5, 52.7, 53.0, 53.3, 55.2, 55.3 (12CH$_2$, 4×NCH$_2$CH$_2$C=O, NCH$_2$C=O, 2×NCH$_2$Ph, NCH$_2$CH(CH$_3$)O, NCH$_2$(CH$_2$)$_2$$CH_2$NHBoc, N$CH_2$$CH_2$Indole), 62.7, 63.0, 63.1, 63.2 (CH$_2$, TMSCH$_2$$CH_2$O), 66.2, 66.4, 66.6, 66.8 (CH, CH$_2$$C$H(CH$_3$)O), 78.8, 79.2, 79.4, 79.4 (C, ^{t}Bu(NHBoc)), 111.2, 111.4, 111.5, 118.1, 118.3, 118.5, 118.9, 119.1, 119.2, 121.6, 121.8, 122.3, 122.7 (5CH, indole), 111.6, 111.7, 112.9, 126.8, 127.2, 136.2, 136.3, 136.7, 136.5, 136.6, 137.1, 137.2 (5C, Ar), 125.8, 125.9, 126.2, 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.5, 128.7, 128.8, 128.9 (10CH, Ph), 155.9, 156.1, 156.2 (C, C=O(NHBoc)), 167.1, 167.1, 167.6, 167.8, 170.1, 170.3, 170.3, 170.4, 170.6, 170.6, 170.7,

170.9, 170.9, 171.1, 171.3, 171.3, 171.4, 171.5, 171.6, 171.7, 171.9, 171.9, 172.0, 172.1, 172.3 (5C, 5×*C*=O). **HRMS** (TOF MS ES+): calcd for $C_{61}H_{96}NaN_7O_9Si_2$ $[M + H + Na]^{2+}$ *m/z* 574.8348, found 574.8341.

Linear β-peptoid (16) was synthesised starting from **12** (735 mg, 0.75 mmol) by application of the general procedures A (the intermediate acrylamide was passed through a short column (R_f (CH_2Cl_2/MeOH 90:10) = 0.61, 726 mg, pale brownish solid) and B using benzylamine as primary amine. Flash chromatography on silica gel of the residue in DCM/MeOH 90:10 as solvent yielded **16** (608 mg, 71%) as a colorless solid. R_f (CH_2Cl_2/MeOH 90:10) = 0.49. $[\alpha]^{22}_D$ = –6.0 (*c* 0.58, $CHCl_3$). Mp = 28-30 °C. **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 2952, 2930, 1708 (C=O, ester/boc), 1637 (C=O, amide), 1495, 1472, 1453, 1435, 1424, 1364, 1309, 1251, 1173, 1141, 1113, 1092, 1042, 997, 938, 888, 859, 837, 808, 777, 742; **^{1}H NMR** (400 MHz, $CDCl_3$): δ −0.09-0.04 (15H, m, TMS and TBDMS), 0.77-0.86 (9H, m, TBDMS), 0.87-0.96 (2H, m, CH_2CH_2TMS), 0.96-1.12 (3H, m, CH_3CHO), 1.28-1.60 (13H, m, $CH_2CH_2CH_2NHBoc$, $CH_2CH_2CH_2NHBoc$ and Boc), 2.14-4.17 (33H, m), 4.05-4.13 (2H, m, CH_2CH_2TMS), 4.48-4.64 (2H, m, C(=O)CH_2Ph), 4.69-5.18 (1H, m N*H*Boc), 6.84-7.60 (15H, m, Ar*H*), 9.20-8.84 (1H, m, indole-N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ −4.9 ($2CH_3$, TBDMS), −1.6 ($3CH_3$, TMS), 17.1 (CH_2, CH_2CH_2TMS), 17.7 (C, TBDMS), 21.4, 21.5 (CH_3, CH_3CHO), 25.6 ($3CH_3$, TBDMS), 23.1, 23.1, 23.2, 24.3, 24.5, 24.6, 24.7, 26.1, 27.0, 27.2 ($3CH_2$, $CH_2CH_2CH_2NHBoc$, $CH_2CH_2CH_2NHBoc$ and CH_2-indole), 28.3 ($3CH_3$, Boc), 30.4, 30.5, 31.0, 31.1, 31.3, 31.6, 31.7, 31.9, 32.7, 32.8, 33.3, 33.3, 33.5, 34.1 ($5CH_2$, 5×NCH_2CH_2C=O), 39.9, 42.5, 42.7, 42.9, 43.0, 43.0, 43.2, 43.3, 43.4, 43.9, 44.0, 44.3, 44.7, 45.0, 45.5, 45.7, 45.8, 47.6, 47.8, 48.1, 48.2, 49.4, 51.9, 52.0, 52.1, 52.4, 52.6, 52.8, 53.1, 53.4, 55.3, 55.4 ($11CH_2$), 62.7, 62.8, 63.0, 63.1 (CH_2, CH_2CH_2TMS), 66.2, 66.4, 66.7, 66.8 (CH, CH_3CHO), 78.9 (C, Boc), 111.2, 111.4 (CH, Ar), 112.5 (C, Ar), 118.0, 118.5 (CH, Ar), 119.0, 119.3 (CH, Ar), 121.6, 121.9, 122.4, 122.4, 122.7 (2CH, Ar), 126.9 (C, Ar), 125.7, 125.9, 126.2, 127.2, 127.4, 127.6, 127.7, 127.9, 128.0, 128.0, 128.3, 128.5, 128.6, 128.8, 128.9 (10 CH, Ar), 136.1, 136.5, 136.5, 136.6, 137.2 (3C, Ar), 155.9, 156.0 (C, Boc), 169.8, 169.8, 170.3, 170.7, 170.7, 170.8, 170.9, 171.0, 171.3, 171.6, 171.6, 171.6, 171.8, 171.9, 171.9 (5C, *C*=O); **HRMS** (TOF MS ES^+) calcd for $C_{62}H_{98}N_7O_9Si_2Na$ $[M + H + Na]^{2+}$ *m/z* 581.8426, found 581.8457; **HPLC** (Water (0.1% TFA)/MeOH 10:90, flow = 0.75): t_r = 7.74 min, purity = 97.4%.

Cyclic α,β-peptoid (17): to a solution of peptoid **15** (75 mg, 0.067 mmol, 1.0 equiv) in anhydrous DMF (7 mL) under Ar atmosphere was added KF (79 mg, 1.34 mmol, 20 equiv). The resulting mixture was stirred at 75°C for 24 hours then allowed to cool at room temperature and concentrated under reduced pressure. KF salts were precipitated by addition of DCM (5mL) and filtered off. The filtrate was evaporated under reduced pressure yielding the crude unprotected intermediate (62 mg) as a slightly yellow solid. The intermediate was dissolved in DCM/DMF (4:1, 13 mL, 5 mM) at 0°C under Ar and DIPEA (23 µL, 130 µmol, 2.0 eq) and HATU (30 mg, 78 µmol, 1.2 eq) were added. The mixture was allowed to heat at rt and stirred for 3 days. The solvents were evaporated under reduced pressure and the residue was taken up in EtOAc (4 mL). The organic layer was washed with satd. aq. $NaHCO_3$ (2×3 mL), satd. aq. NH_4Cl (2×3 mL) and brine (3 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography of the residue in EtOAc/MeOH 90:10 to 80:20 yielded **17** (26 mg, 29 µmol, 43 %) as a white foam. R_f = 0.51 (DCM/MeOH 90:10). $[\alpha]^{21}_D$ = – 0.6 (*c* 0.89, $CHCl_3$). **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 3327 (NH and OH), 2971, 2931, 1700, 1635 (C=O), 1472, 1453, 1365, 1270, 1251, 1081, 1028, 842, 738, 695. **^{1}H NMR** (400 MHz, Acetone-d^6): δ 1.00-1.23 (m, 3H, $CH_2CH(CH_3)O$), 1.24-1.65 (m, 13H, ^{t}Bu(NHBoc) and $NCH_2(CH_2)_2CH_2NHBoc$), 2.28-4.85 (m, 33H, 4×NCH_2CH_2C=O, NCH_2C=O, $NCH_2CH(CH_3)OH$, 2×NCH_2Ph, NCH_2CH_2indole and $NCH_2(CH_2)_2CH_2NHBoc$), 5.95-6.21

(bs, 1H, N*H*Boc), 6.93-7.73 (m, 15H, C*H*(Ar)), 9.97-10.23 (m, 1H, N*H*(indole)). **^{13}C NMR** (100 MHz, Acetone-d^6): δ 21.8 (CH_3, $CH_2CH(CH_3)O$), 24.4, 24.6, 25.4, 26.0, 26.8, 27.2, 28.2 ($2CH_2$, NCH_2 $(CH_2)_2CH_2NHBoc$), 28.7 ($3CH_3$, NHBoc), 30.6, 31.3, 31.5, 31.8, 32.2, 32.7, 33.7 ($4CH_2$, $4\times NCH_2CH_2C=O$), 40.8, 41.7, 42.1, 43.0, 43.2, 43.6, 43.7, 44.0, 44.4, 44.6, 45.3, 45.7, 46.1, 46.6, 47.4, 48.2, 48.5, 49.0, 49.2, 49.5, 49.6, 50.5, 50.8, 51.0, 51.5, 52.4, 54.6, 55.0, 55.6, 56.5, 57.0, 59.4 ($12CH_2$, $4\times NCH_2CH_2C=O$, $NCH_2C=O$, $2\times NCH_2Ph$, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NHBoc$, NCH_2CH_2Indole), 66.1, 67.2 (CH, $CH_2CH(CH_3)O$), 78.3, 81.1 (C, ^{t}Bu(NHBoc)), 110.91, 112.12, 112.50, 119.18, 119.39, 119.52, 119.73, 122.09, 122.33, 123.16, 124.23 (5CH, indole), 127.59, 127.71, 127.86, 128.58, 128.77, 128.86, 129.02, 129.09, 129.14, 129.18, 129.25, 129.51, 129.61 (10CH, Ph), 112.7, 137.7, 138.9, 139.1, 139.4, 139.7 (5C, Ar), 155.6, 156.7 (C, *C*=O(NHBoc)), 168.6, 168.8, 169.0, 169.1, 171.0, 171.7, 171.9, 172.2, 172.7, 172.9, 173.9, 186.1 (5C, 5×*C*=O). **HRMS** (TOF MS ES+): calcd for $C_{50}H_{67}NaN_7O_8$ $[M + Na]^+$ *m/z* 916.4949, found 916.4938.

Cyclic β-peptoid (18) was synthesised starting from **16** (399 mg, 0.350 mmol) by application of the general procedure E. Flash chromatography on silica gel of the residue using EtOAc/MeOH 90:10 until the impurities had passed followed by change to CH_2Cl_2/MeOH 90:10 yielded **18** (246 mg, 77%) as a pale tan solid: R_f (CH_2Cl_2/MeOH 90:10) = 0.49. $[\alpha]^{22}_D$ = –0.9 (*c* 0.57, $CHCl_3$). Mp = 60-63 °C. **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 1707 (C=O, boc), 1701 (C=O, boc), 1697 (C=O, boc), 1691 (C=O, boc), 1686 (C=O, boc), 1637 (C=O, amide), 1630 (C=O, amide), 1626 (C=O, amide), 1615 (C=O, amide), 1522, 1507, 1476, 1467, 1458, 1452, 1425, 1367, 1343, 1270, 1255, 1245, 1204, 1189, 1170, 1028, 744, 735; **^{1}H NMR** (400 MHz, acetone-d_6): δ 0.97-1.20 (3H, m, CH_3CHO), 1.32-1.65 (13H, m, $CH_2CH_2CH_2NHBoc$, $CH_2CH_2CH_2NHBoc$ and Boc), 2.14-4.89 (35H, m), 6.16-6.95 (1H, m, N*H*Boc), 6.97-7.45 (14H, m, Ar*H*), 7.55-7.77 (1H, m, Ar*H*), 10.08-10.29 (1H, m, indole-N*H*); **^{13}C NMR** (100 MHz, acetone-d_6): δ 22.1, 22.2, 22.4, 22.5, 22.6, 22.7 (CH_3, CH_3CHO), 25.0, 25.2, 25.4, 26.1, 26.1, 26.3, 26.4, 26.7, 26.8, 26.9, 27.9, 28.0, 28.1, 28.2, 28.3, 28.9, 29.1, 29.2 ($3CH_2$, $CH_2CH_2CH_2NHBoc$, $CH_2CH_2CH_2NHBoc$ and CH_2-indole), 29.7 ($3CH_3$, Boc), 32.1, 32.3, 32.4, 32.6, 32.8, 33.0, 33.2, 33.3, 33.4, 33.6, 33.9, 34.1, 34.1, 34.4, 34.7, 34.9 ($5CH_2$, $5\times NCH_2CH_2C=O$), 41.7, 41.8, 44.1, 44.2, 44.4, 44.5, 44.7, 44.8, 45.1, 45.2, 45.5, 45.6, 45.8, 46.1, 46.2, 46.3, 46.5, 46.6, 46.7, 47.0, 47.3, 47.7, 48.1, 48.2, 48.8, 49.0, 49.1, 49.3, 49.4, 49.4, 49.6, 49.7, 49.9, 50.1, 50.4, 50.6, 50.7, 50.9, 51.0, 51.0, 51.5, 51.6, 51.7, 51.9, 52.0, 52.1, 52.8, 53.0, 53.2, 53.2, 53.4, 53.5, 54.2, 54.8, 55.0, 55.0, 55.3, 55.9, 55.9, 56.2, 56.3, 56.4, 56.6, 56.8, 57.7, 57.9, 58.0, 59.2, 59.8 ($11CH_2$), 66.7, 66.8, 67.0, 67.0, 67.2, 67.4, 67.5, 67.7, 67.7, 67.8, 67.9, 68.0, 68.1, 68.2 (CH, CH_3CHO), 79.3, 79.4 (C, Boc), 113.1, 113.2, 113.3, 113.4 (CH, Ar), 113.5, 113.6, 114.4, 114.4, 114.5, 114.6 (C, Ar), 120.1, 120.3, 120.3, 120.4, 120.5, 120.6, 120.7 (2CH, Ar), 123.0, 123.1, 123.3, 124.1, 124.2, 124.3, 124.4, 124.9, 125.0, 125.2, 125.3 (2CH, Ar), 129.3 (C, Ar), 128.3, 128.4, 128.5, 128.6, 128.8, 128.9, 129.1, 129.1, 129.5, 129.8, 130.2, 130.4, 130.5 (10CH, Ar), 138.4, 138.6, 139.4, 139.5, 139.5, 139.6, 139.9, 140.1, 140.1, 140.2, 140.2, 140.3, 140.4, 140.5 (3C, Ar), 157.7 (C, Boc), 171.6, 171.7, 171.7, 171.8, 171.9, 171.9, 172.0, 172.1, 172.2, 172.2, 172.4, 172.4, 172.5, 172.7, 172.9, 173.0, 173.1, 173.2, 173.3, 173.4, 173.5, 173.6, 173.7, 173.9, 174.0, 174.1, 174.2 (5C, *C*=O),; **HRMS** (TOF MS ES$^+$) calcd for $C_{51}H_{69}N_7O_8Na$ $[M + Na]^+$ *m/z* 930.5088, found 930.5100; **HPLC** (Water (0.1% TFA)/MeOH 20:80, flow = 0.60): t_r = 11.70 min, purity = 98.8%.

Cyclic αβ4 peptoid TFA salt (3.TFA) was synthesised starting from **17** (24 mg, 0.027 mmol, 1.0 equiv) by application of general procedure F yielding **3.TFA** (25 mg, 0.027 mmol, quantitative) as an orange foam. A sample was purified by preparative HPLC (MeOH/H_2O(0.1%TFA) 60:30, t_r = 14.95 min, lyophilized and sent for biological tests. R_f = 0.31 (CH_2Cl_2/MeOH 80:20); $[\alpha]^{23}_D$ = – 10.3 (*c* 0.98, MeOH); **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 2928, 2858, 1718, 1684, 1671, 1653, 1646, 1623, 1617 (C=O), 1473, 1457, 1436, 1420, 1374, 1363,

1203, 1185, 1135, 837, 800. **^{1}H NMR** (400 MHz, MeOD): δ 0.66-1.86 (m, 7H, $CH_2CH(CH_3)O$ and $NCH_2(CH_2)_2CH_2NH_2$), 1.96-4.82 (m, 33H, 4×NCH_2CH_2C=O, NCH_2C=O, $NCH_2CH(CH_3)OH$, 2×NCH_2Ph, NCH_2CH_2indole and $NCH_2(CH_2)_2CH_2NH_2$), 6.80-7.76 (m, 15H, C*H*(Ar)). **^{13}C NMR** (100 MHz, MeOD): δ 21.1, 21.5 (CH_3, $CH_2CH(CH_3)O$), 24.7, 24.9, 25.1, 25.3, 25.6, 25.9, 26.5, 27.0 ($2CH_2$, NCH_2 $(CH_2)_2CH_2NH_2$), 30.9, 31.1, 31.5, 31.7, 32.1, 32.3, 32.4, 32.7, 33.0, 33.2, 33.3, 33.6, 34.0, 34.1 $4CH_2$, 4×NCH_2CH_2C=O), 40.5, 42.7, 43.3, 43.8, 44.0, 44.3, 44.8, 45.1, 45.5, 45.7, 46.9, 47.0, 47.3, 47.5, 51.5, 52.9, 53.1, 55.0, 55.2, 55.7, 56.7, 57.0, 59.6 ($12CH_2$, 4×NCH_2CH_2C=O, NCH_2C=O, 2×NCH_2Ph, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NH_2$, NCH_2CH_2Indole), 66.5, 66.9, 67.2 (CH, $CH_2CH(CH_3)O$), 112.5, 112.7, 113.4, 119.2, 119.5, 119.8, 120.0, 120.2, 122.6, 122.7, 122.9, 123.7, 123.9, 124.6, 124.7 (5CH, indole), 127.6, 127.7, 127.8, 127.9, 128.0, 128.4, 128.5, 128.6, 128.9, 129.1, 129.4, 129.7, 129.8, 130.2 (10CH, Ph), 112.6, 112.9, 138.3, 138.5, 139.0, 139.2 (5C, Ar), 162.8, 163.2 (C, *C*=O(TFA)), 169.9, 170.2, 170.4, 170.9, 171.2, 172.8, 173.2, 173.4, 173.5, 173.7, 173.9, 174.1, 174.3, 174.8, 175.4 (5C, 5×*C*=O). **HRMS** (TOF MS ES+): calcd for $C_{45}H_{60}N_7O_6$ $[M + H]^+$ *m/z* 794.4605, found 794.4626.

Cyclic β5 peptoid TFA salt (4.TFA) was synthesised starting from **18** (54 mg, 0.059 mmol) by application of general procedure F yielding **4.TFA** (55 mg, quantitative) as a pale tan solid: $[\alpha]^{21}_D$ = –2.1 (*c* 0.48, MeOH); mp = 72-74 °C; **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 1685 (C=O), 1677 (C=O), 1654 (C=O), 1637 (C=O), 1625 (C=O), 1619 (C=O), 1614 (C=O), 1478, 1458, 1453, 1424, 1374, 1202, 1176, 1171, 1150, 1135, 1053, 1033, 1015, 835, 800, 746, 736, 721; **1H NMR** (400 MHz, methanol-d_4): δ 1.01-1.42 (3H, m, CH_3CHO), 1.48-1.72 (4H, m, $CH_2CH_2CH_2NH_2$ and $CH_2CH_2CH_2NH_2$), 1.94-3.08 (14H, m, 5×NCH_2CH_2C=O, CH_2-indole and CH_2), 3.08-4.75 (21H, m), 6.96-7.68 (15H, m, Ar*H*); **^{13}C NMR** (100 MHz, methanol-d_4): δ 17.5, 17.8, 20.9, 21.1, 21.2 (CH_3, CH_3CHO), 24.4, 24.4, 25.2,25.4, 25.5, 25.6, 25.8, 26.8, 26.9, 27.1 ($3CH_2$, $CH_2CH_2CH_2NH_2$, $CH_2CH_2CH_2NH_2$ and CH_2-indole), 31.3, 31.4, 31.6, 31.7, 31.9, 32.1, 32.2, 32.3, 32.5, 32.6, 32.8, 32.9, 33.1, 33.2, 33.3, 33.4, 33.5, 33.6, 33.7, 33.9 ($5CH_2$, 5×NCH_2CH_2C=O), 40.4 (CH_2), 43.7, 43.9, 44.1, 44.2, 44.3, 44.4, 44.4, 44.7, 44.7, 44.9, 45.0, 45.0, 45.2, 45.4, 45.5, 45.7, 45.8, 45.9, 46.1, 46.3, 46.5, 46.9, 49.8, 49.9, 50.0, 50.1, 50.1, 50.2, 50.4, 50.7, 51.1, 51.3, 51.5, 52.8, 52.9, 53.1, 53.2, 53.4, 53.8, 54.9, 55.0, 56.8, 57.1, 57.2, 57.7 ($10CH_2$), 66.3, 66.4, 66.5, 66.7, 66.8, 67.0, 67.1 (CH, CH_3CHO), 112.5, 112.6, 112.8, 112.9 (CH, Ar), 112.2, 112.3, 112.4, 113.2, 113.2, 113.4, 115.9, 118.7 (C, Ar), 119.2, 119.4, 119.4, 119.7, 119.8, 120.0, 120.2, 120.2 (2CH, Ar), 122.4, 122.5, 122.6, 122.6, 122.7, 122.8, 123.8, 124.3, 124.4, 124.4, 124.6, 124.7, 124.8 (2CH, Ar), 127.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.4, 128.5, 128.6, 128.8, 128.9, 129.0, 129.0, 129.1, 129.6, 129.7, 129.9, 130.1 (10CH and 1C, Ar), 138.1, 138.3, 138.3, 138.4, 138.4, 138.5, 138.6, 138.6, 138.8, 138.8, 138.9, 139.0, 139.1 (3C, Ar), 161.2 (C, q, *J* = 36.7 Hz, F_3CC=O), 172.6, 172.7, 172.8, 172.9, 173.0, 173.1, 173.1, 173.2, 173.3, 173.4, 173.5, 173.6, 173.7, 173.7, 173.9, 174.0, 174.0, 174.2, 174.3, 174.5, 174.5, 174.6, 174.7, 174.8 (5C, 5×*C*=O),; **HRMS** (TOF MS ES^+) calcd for $C_{46}H_{62}N_7O_6$ $[M - TFA + H]^+$ *m/z* 808.4762, found 808.4767; **HPLC** (Water (0.1% TFA)/MeOH 20:80, flow = 0.60): t_r = 6.10 min, purity = 97.5%.

Linear α,β-peptoid (19) was synthesised starting from **15** (151 mg, 0.13 mmol, 1.0 equiv) by application of the General procedure G using THF as solvent. Flash chromatography on silica gel of the residue using DCM/MeOH 95:5 as solvent yielded **19** (145 mg, 0.12 mmol, 92 %) as a white foam. R_f = 0.23 (DCM/MeOH 95:5); $[\alpha]^{22}_D$ = – 5.6 (*c* 1.09, $CHCl_3$); **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 3305 (NH), 2954, 2930, 2858, 1727, 1709, 1640, 1634 (C=O), 1471, 1452, 1422, 1365, 1250, 1171, 1002, 857, 838, 776, 742, 739, 731, 701, 696. **^{1}H NMR** (400 MHz, $CDCl_3$): δ – 0.18-0.17 (m, 15H, 5×$SiCH_3$), 0.73-0.86 (m, 9H, $Si(CH_3)_2C(CH_3)_3$), 0.89-0.96 (m, 2H, CH_2TMS), 0.96-1.14 (m, 3H, $CH_2CH(CH_3)O$), 1.15-1.53 (m, 13H, ^{t}Bu(NHBoc) and $NCH_2(CH_2)_2CH_2NHBoc$), 1.89-2.21 (m, 3H, NAc), 2.22-4.28 (m, 31H, 4×NCH_2CH_2C=O,

NC*H*$_2$C=O, TMSCH$_2$C*H*$_2$O, NC*H*$_2$C*H*(CH$_3$)O, NC*H*$_2$(CH$_2$)$_2$C*H*$_2$NHBoc and NC*H*$_2$C*H*$_2$Indole), 4.28-5.00 (m, 5H, 2×NC*H*$_2$Ph and N*H*Boc), 6.87-7.64 (m, 15H, C*H*(Ar)), 8.89-9.54 (m, 1H, N*H*(indole)). **^{13}C NMR** (100 MHz, $CDCl_3$): δ – 4.9 (2CH$_3$, Si(*C*H$_3$)$_2$C(CH$_3$)$_3$), –1.7 (3CH$_3$, 3×Si*C*H$_3$), 17.1 (CH$_2$, *C*H$_2$TMS), 17.7 (C, Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), 21.1, 21.2, 21.3, 21.5, 21.6 (2CH$_3$, CH$_2$CH(*C*H$_3$)O and NAc), 23.7, 24.6, 24.8, 24.9, 25.8, 27.1 (2CH$_2$, NCH$_2$(*C*H$_2$)$_2$CH$_2$NHBoc), 26.0 (3CH$_3$, Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 28.3 (3CH$_3$, NHBoc), 29.5, 30.9, 31.2, 31.3, 31.7, 32.0, 32.7, 33.4 (4CH$_2$, 4×NCH$_2$*C*H$_2$C=O), 39.9, 40.0, 42.5, 42.7, 42.9, 43.0, 43.1, 43.4, 43.5, 43.6, 43.8, 44.0, 44.4, 44.9, 45.2, 45.3, 45.5, 46.7, 46.8, 46.9, 47.2, 47.3, 47.9, 48.1, 48.3, 49.2, 49.4, 50.2, 51.8, 51.9, 52.0, 52.7, 52.9, 53.0, 53.1, 53.3, 55.2, 55.3 (12CH$_2$, 4×NC*H*$_2$CH$_2$C=O, NC*H*$_2$C=O, 2×NC*H*$_2$Ph, NC*H*$_2$CH(CH$_3$)O, NC*H*$_2$(CH$_2$)$_2$C*H*$_2$NHBoc and NC*H*$_2$C*H*$_2$Indole), 62.6, 63.0, 63.1 (CH$_2$, TMSCH$_2$C*H*$_2$O), 66.2, 66.3, 66.6, 66.7 (CH, CH$_2$C*H*(CH$_3$)O), 79.2 (C, ^{t}Bu(NHBoc)), 111.2, 111.3, 111.5, 117.9, 118.2, 118.8, 119.0, 119.1, 119.4, 121.5, 121.7, 121.9, 122.0, 122.4, 122.5, 122.6 (5CH, indole), 111.7, 111.9, 112.0, 113.2, 126.7, 127.0, 136.2, 136.3, 136.4, 136.5, 136.8, 137.1, 137.4, (5C, Ar), 125.7, 125.9, 126.0, 126.1, 127.1, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.3, 128.3, 128.4, 128.5, 128.6, 128.7, 128.9 (10CH, Ph), 155.8, 156.0, 156.3 (C, *C*=O(NHBoc)), 167.2, 167.4, 167.5, 167.6, 170.5, 170.9, 171.0, 171.2, 171.4, 171.6, 171.7, 171.9 (6C, 6×*C*=O). **HRMS** (TOF MS ES+): for $C_{63}H_{97}N_7O_{10}Si_2Na_2$ $[M + 2Na]^{2+}$ *m/z* 606.8315, found 606.8312.

Linear β-peptoid (20) was synthesised starting from **16** (57 mg, 0.05 mmol, 1.0 equiv) by application of the General procedure G using AcOEt as solvent. Flash chromatography on silica gel of the crude product using DCM/MeOH 90:10 as solvent yielded **20** (58 mg, 0.05 mmol, quant.) as a white foam. R_f = 0.61 (CH_2Cl_2/MeOH 90:10); $[\alpha]_D^{22}$ = –5.5 (*c* 1.10, $CHCl_3$); **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 837, 1172, 1250, 1364, 1421, 1452, 1634, 1638, 1711, 2929, 2952, 3599, 3625, 3705, 3727. **^{1}H NMR** (400 MHz, $CDCl_3$): δ – 0.08-0.03 (m, 15H, 5×Si*C*H$_3$), 0.79-0.86 (m, 9H, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$), 0.88-0.96 (m, 2H, C*H*$_2$TMS), 0.98-1.12 (m, 3H, CH$_2$CH(C*H*$_3$)O), 1.37-1.51 (m, 13H, ^{t}Bu(NHBoc) and NCH$_2$(C*H*$_2$)$_2$CH$_2$NHBoc), 1.91-2.10 (m, 3H, NAc), 2.19-4.01 (m, 31H, 5×NC*H*$_2$C*H*$_2$C=O, NC*H*$_2$C*H*(CH$_3$)O, NC*H*$_2$(CH$_2$)$_2$C*H*$_2$NHBoc and NC*H*$_2$C*H*$_2$Indole), 4.04-4.64 (m, 6H, 2×NC*H*$_2$Ph and C*H*$_2$CH$_2$TMS), 4.68-5.15 (m, 1H, N*H*Boc), 6.87-7.35 (m, 14H, C*H*(Ar)), 7.47-7.62 (m, 1H, C=C*H*NH), 8.80-9.04 (m, 1H, N*H*(indole)). **^{13}C NMR** (100 MHz, $CDCl_3$): δ – 4.7 (2CH$_3$, Si(*C*H$_3$)$_2$C(CH$_3$)$_3$), –1.5 (3CH$_3$, 3×Si*C*H$_3$), 17.3 (CH$_2$, *C*H$_2$TMS), 17.9 (C, Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), 21.3, 21.6, 21.7, 21.8 (2CH$_3$, CH$_2$CH(*C*H$_3$)O and NAc), 23.5, 24.5, 24.8 (CH$_2$, NCH$_2$(*C*H$_2$)$_2$CH$_2$NHBoc), 25.8 (3CH$_3$, Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 26.2, 27.2, 27.4 (CH$_2$, NCH$_2$(*C*H$_2$)$_2$CH$_2$NHBoc), 28.5 (3CH$_3$, NHBoc), 29.7, 31.2, 31.5, 32.0, 32.6, 32.9, 33.0, 33.6 (5CH$_2$, 5×NCH$_2$*C*H$_2$C=O), 40.1, 42.7, 43.1, 43.4, 44.0, 44.4, 44.9, 45.2, 45.9, 47.9, 48.1, 48.3, 48.4, 49.1, 49.4, 52.1, 52.2, 52.7, 52.8, 53.4, 53.6, 55.5 (12CH$_2$, 5×N*C*H$_2$CH$_2$C=O, 2×N*C*H$_2$Ph, N*C*H$_2$CH(CH$_3$)O, N*C*H$_2$(CH$_2$)$_2$*C*H$_2$NHBoc and N*C*H$_2$*C*H$_2$Indole), 62.9, 63.2 (CH$_2$, TMSCH$_2$*C*H$_2$O), 66.4, 66.6, 66.9 (CH, CH$_2$*C*H(CH$_3$)O), 79.3 (C, ^{t}Bu(NHBoc)), 111.3, 111.5, 111.8 (CH), 111.9, 113.1 (C, indole), 118.1, 118.5, 118.8, 119.3, 119.5, 119.8 (2CH, indole), 121.8, 122.0, 122.3, 122.9 (2CH, indole), 125.9, 126.1, 126.2, 126.4 (2CH, Ar), 127.0, 127.2 (C, indole), 127.3, 127.5, 127.6, 127.9, 128.1, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.1 (8CH, Ph), 136.4, 136.7, 136.8, 136.9, 137.0, 137.4, 137.6 (3C, Ar), 156.1, 156.2, 156.4 (C, *C*=O(NHBoc)), 170.1, 170.4, 170.9, 171.1, 171.6, 171.9, 172.1 (6C, 6×*C*=O). **HRMS** (TOF MS ES+): *m/z* calcd for $C_{64}H_{99}N_7O_{10}Si_2Na_2$ $[M + 2Na]^{2+}$ 613.8394, found 613.8412.

Linear α,β-peptoid (21): To a solution of **19** (109 mg, 93 µmol, 1 equiv) in MeOH (1 mL) was added butylamine (55 µL, 560 µmol, 6 equiv). The resulting mixture was stirred at 50°C

for 24 hours then allowed to cool at room temperature and concentrated under reduced pressure. Flash chromatography on silica gel of the residue using EtOAc/MeOH 95:5 as solvent yielded **21** (62 mg, 57 µmol, 61 %) as a white foam. R_f = 0.33 (EtOAc/MeOH 95:5); $[\alpha]_D^{21}$ = – 6.4 (*c* 0.92, $CHCl_3$); **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 3308 (NH), 2950, 2928, 2855, 1734, 1700, 1636 (C=O), 1473, 1456, 1437, 1420, 1364, 1170, 1091, 995, 890, 837, 777, 731, 697, 668. **^{1}H NMR** (400 MHz, $CDCl_3$): δ – 0.12-0.09 (m, 6H, 2×SiCH_3), 0.74-0.91 (m, 9H, $Si(CH_3)_2C(CH_3)_3$), 0.98-1.16 (m, 3H, $CH_2CH(CH_3)O$), 1.17-1.56 (m, 13H, ^{t}Bu(NHBoc) and $NCH_2(CH_2)_2CH_2NHBoc$), 1.90-2.13 (m, 3H, NAc), 2.14-4.29 (m, 32H, 4×NCH_2CH_2C=O, NCH_2C=O, CH_3OC=O, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NHBoc$ and NCH_2CH_2Indole), 4.30-4.94 (m, 5H, 2×NCH_2Ph and N*H*Boc), 6.92-7.66 (m, 15H, C*H*(Ar)), 8.54-9.36 (m, 1H, N*H*(indole)). **^{13}C NMR** (100 MHz, $CDCl_3$): δ –4.9,–3.63 ($2CH_3$, $Si(CH_3)_2C(CH_3)_3$), 14.1 (C, $Si(CH_3)_2C(CH_3)_3$), 20.7, 21.4, 21.7 ($2CH_3$, $CH_2CH(CH_3)O$ and NAc), 23.9, 24.7, 25.0, 25.9, 27.2 ($2CH_2$, $NCH_2(CH_2)_2CH_2NHBoc$), 25.7 ($3CH_3$, $Si(CH_3)_2C(CH_3)_3$), 28.4 ($3CH_3$, NHBoc), 29.6, 31.0, 31.4, 31.8, 32.4, 33.1 ($4CH_2$, 4×NCH_2CH_2C=O), 40.0, 42.6, 43.0, 43.6, 44.1, 45.3, 45.9, 47.3, 48.0, 48.3, 49.3, 49.5, 50.3, 51.9, 52.8, 53.0, 53.2, 55.4, 60.3 ($12CH_2$, 4×NCH_2CH_2C=O, NCH_2C=O, 2×NCH_2Ph, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NHBoc$ and NCH_2CH_2Indole), 51.6, 51.8 (CH_3, CH_3OC=O), 66.3, 66.5, 66.7 (CH, $CH_2CH(CH_3)O$), 79.5 (C, ^{t}Bu(NHBoc)), 111.4, 111.6, 118.1, 118.3, 119.2, 119.3, 119.6, 121.9, 122.2, 122.6 (5CH, indole), 112.0, 112.3, 126.9, 127.1, 136.4, 136.6, 136.9, 137.6 (5C, Ar), 125.8, 126.0, 126.2, 126.3, 127.4, 127.5, 127.6, 127.8, 127.9, 128.5, 128.6, 128.8, 128.8, 129.0 (10CH, Ph), 155.9, 156.1, 156.4 (C, *C*=O(NHBoc)), 167.7, 170.8, 171.4, 171.6, 171.8, 172.3 (6C, 6×*C*=O). **HRMS** (TOF MS ES+): for $C_{59}H_{87}N_7O_{10}SiNa_2$ $[M + 2Na]^{2+}$ *m/z* 563.8040, found 563.8051.

Linear β-peptoid (22): To a solution of **20** (53 mg, 44 µmol, 1 equiv) in MeOH (1 mL) was added butylamine (26 µL, 267 µmol, 6 equiv). The resulting mixture was stirred at 50°C for 24 hours then allowed to cool at room temperature and concentrated under reduced pressure. Flash chromatography on silica gel of the crude product using EtOAc/MeOH 95:5 as solvent yielded **21** (32 mg, 29 µmol, 66 %) as a white foam. R_f = 0.24 (EtOAc/MeOH 95:5); $[\alpha]_D^{22}$ = – 7.5 (*c* 0.93, $CHCl_3$); **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 2954, 2929, 1733, 1708, 1634, 1451, 1365, 1250, 1170, 993. **^{1}H NMR** (400 MHz, $CDCl_3$): δ – 0.05-0.09 (m, 6H, 2×SiCH_3), 0.81-0.91 (m, 9H, $Si(CH_3)_2C(CH_3)_3$), 1.00-1.12 (m, 3H, $CH_2CH(CH_3)O$), 1.35-1.59 (m, 13H, ^{t}Bu(NHBoc) and $NCH_2(CH_2)_2CH_2NHBoc$), 1.96-2.17 (m, 3H, NAc), 2.23-3.98 (m, 32H, 5×NCH_2CH_2C=O, CH_3OC=O, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NHBoc$ and NCH_2CH_2Indole), 4.17-5.12 (m, 5H, 2×NCH_2Ph and N*H*Boc), 6.88-7.39 (m, 14H, C*H*(Ar)), 7.49-7.64 (m, 1H, C=C*H*NH), 8.49-8.72 (m, 1H, N*H*(indole)). **^{13}C NMR** (100 MHz, $CDCl_3$): δ –4.6 ($2CH_3$, $Si(CH_3)_2C(CH_3)_3$), 18.0 (C, $Si(CH_3)_2C(CH_3)_3$), 21.3, 21.6, 21.7 ($2CH_3$, $CH_2CH(CH_3)O$ and NAc), 23.6, 24.6, 24.8, 24.9 (CH_2, $NCH_2(CH_2)_2CH_2NHBoc$), 26.2, 26.3, 27.3, 27.5 (CH_2, $NCH_2(CH_2)_2CH_2NHBoc$), 25.9 ($3CH_3$, $Si(CH_3)_2C(CH_3)_3$), 28.5 ($3CH_3$, NHBoc), 31.1, 31.2, 31.6, 32.0, 32.6, 32.7, 33.3 ($5CH_2$, 5×NCH_2CH_2C=O), 40.3, 40.4, 42.8, 43.2, 43.5, 44.0, 44.4, 45.3, 47.9, 48.2, 48.4, 49.1, 49.5, 52.0, 52.1, 52.3, 52.8, 53.5, 55.6 ($12CH_2$, 5×NCH_2CH_2C=O, 2×NCH_2Ph, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NHBoc$ and NCH_2CH_2Indole), 51.8, 51.9 (CH_3, CH_3OC=O), 66.4, 66.7, 66.9 (CH, $CH_2CH(CH_3)O$), 79.4 (C, ^{t}Bu(NHBoc)), 111.4, 111.5, 111.9 (CH, indole), 112.0, 112.1, 113.4 (C, indole), 118.2, 118.6, 118.9, 119.4, 119.6, 119.9 (2CH, indole), 122.0, 122.1, 122.5, 122.9 (2CH, indole), 126.0, 126.2, 126.3, 126.4, 126.5 (2CH, Ph), 127.1, 127.3 (C, indole), 127.4, 127.6, 127.7, 128.0, 128.2, 128.6, 128.8, 129.0, 129.2 (8CH, Ph), 136.4, 136.8, 137.4, 137.6 (3C, Ar), 156.2 (C, *C*=O(NHBoc)), 171.0, 171.2, 171.5, 171.6, 172.1, 172.5 (6C, 6×*C*=O). **HRMS** (TOF MS ES+): for $C_{60}H_{89}N_7O_{10}SiNa_2$ $[M + 2Na]^{2+}$ *m/z* 570.8118, found 570.8099.

Linear α,β-peptoid (23): To a solution of **21** (59 mg, 55 µmol, 1 equiv) in anhydrous THF (1 mL) under Ar atmosphere, was added 1M TBAF in THF (110 µL, 110 µmol, 2.0 equiv) and

the resulting mixture was stirred at rt for 3 hours. The solvent was then removed under reduced pressure and the residue was dissolved into 10 mL of EtOAc and washed with NH_4Cl satd. (2×3 mL), and $NaHCO_3$ satd. (2×3 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. Flash chromatography on silica gel of the crude product using DCM/MeOH 95:5 as solvent yielded **23** (25 mg, 26 µmol, 47 %) as a white foam. R_f = 0.24 (DCM/MeOH 95:5); $[\alpha]_D^{21}$ = – 1.6 (*c* 0.80, $CHCl_3$); **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 3308 (NH), 2967, 2927, 2860, 1733, 1704 , 1695, 1635 (C=O), 1524, 1496, 1476, 1471, 1451, 1438, 1366, 1269, 1251, 1217, 1200, 1169, 1012, 840, 759, 744. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 0.77-1.59 (m, 16H, $CH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NHBoc$ and ^{t}Bu(NHBoc)), 1.92-2.15 (m, 3H, NAc), 2.15-4.91 (m, 37H, 4×NCH_2CH_2C=O, NCH_2C=O, 2×NCH_2Ph, CH_3OC=O, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NH$Boc and NCH_2CH_2Indole), 6.96-7.65 (m, 15H, CH(Ar)), 8.33-9.46 (m, 1H, NH(indole)). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 19.8. 20.8, 21.2, 21.4, 21.6 ($2CH_3$, $CH_2CH(CH_3)O$ and NAc), 24.7, 26.0, 27.3 ($2CH_2$, $NCH_2(CH_2)_2CH_2NHBoc$), 28.4 ($3CH_3$, NHBoc), 31.3, 31.5, 32.0, 32.3, 32.5, 33.1 ($4CH_2$, 4×NCH_2CH_2C=O), 40.1, 42.5, 42.7, 43.7, 44.1, 45.9, 47.8, 48.0, 48.2, 48.4, 49.8, 53.1, 56.2, 56.9 ($12CH_2$, 4×NCH_2CH_2C=O, NCH_2C=O, 2×NCH_2Ph, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NHBoc$ and NCH_2CH_2Indole), 51.7, 52.1 (CH_3, CH_3OC=O), 65.2 (CH, $CH_2CH(CH_3)O$), 79.5 (C, ^{t}Bu(NHBoc)), 111.2, 111.4, 111.5, 111.7, 118.0, 118.4, 118.6, 119.2, 119.4, 119.7, 121.9, 122.0, 122.3, 122.6, 122.9 (5CH, indole), 126.0, 126.3, 126.4, 127.5, 127.9, 128.0, 128.6, 128.9, 129.1, 130.0 (10CH, Ph), 112.35, 126.90, 127.12, 129.0, 130.1, 133.6, 134.1, 136.3, 136.4, 136.6, 137.1 (5C, Ar), 156.2 (C, C=O(NHBoc)), 167.8, 168.7, 171.0, 171.7, 171.8, 172.1, 172.4, 173.2 (6C, 6×C=O). **HRMS** (TOF MS ES+): $C_{53}H_{73}N_7O_{10}Na$ $[M + Na]^+$ *m/z* 990.5317, found 990.5323.

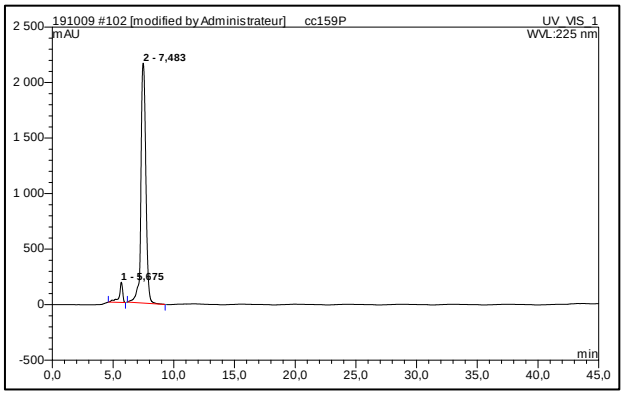
Linear β-peptoid (24): To a solution of **22** (31 mg, 28 µmol, 1 equiv) in anhydrous THF (1 mL) under Ar atmosphere, was added 1M TBAF in THF (57 µL, 57 µmol, 2.0 equiv) and the resulting mixture was stirred at rt for 3 hours. The solvent was then removed under reduced pressure and the residue was dissolved into 10 mL of EtOAc and washed with NH_4Cl satd. (2×3 mL), and $NaHCO_3$ satd. (2×3 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. Flash chromatography on silica gel of the crude product using DCM/MeOH 95:5 as solvent yielded **24** (21 mg, 21 µmol, 76 %) as a white foam. R_f = 0.24 (DCM/MeOH 95:5); $[\alpha]_D^{22}$ = – 3.29 (*c* 0.94, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 0.81-1.60 (m, 16H, $CH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NHBoc$ and ^{t}Bu(NHBoc)), 1.95-2.10 (m, 3H, NAc), 2.18-4.05 (m, 34H, 5×NCH_2CH_2C=O, CH_3OC=O, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NHBoc$ and NCH_2CH_2Indole), 4.19-5.05 (m, 5H, 2×NCH_2Ph and NHBoc), 6.91-7.37 (m, 14H, CH(Ar)), 7.50-7.63 (m, 1H, C=CHNH), 8.62-8.88 (m, 1H, NH(indole)). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 21.0, 21.1, 21.3, 21.7, 21.9 ($2CH_3$, $CH_2CH(CH_3)O$ and NAc), 23.5, 24.8, 25.0, 26.3, 27.3, 27.5 ($2CH_2$, $NCH_2(CH_2)_2CH_2NHBoc$), 28.5 ($3CH_3$, NHBoc), 29.8, 31.2, 31.6, 32.2, 32.7, 33.3 ($5CH_2$, 5×NCH_2CH_2C=O), 40.3, 42.9, 43.2, 43.5, 43.6, 44.0, 45.5, 45.7, 45.9, 48.2, 48.5, 49.0, 49.6 ($9CH_2$, 5×NCH_2CH_2C=O, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NHBoc$ and NCH_2CH_2Indole), 51.8, 51.9, 52.0 (CH_3, CH_3OC=O), 52.2, 52.4, 52.6, 52.7, 53.6, 54.9, 56.6, 57.0 ($3CH_2$, 2×NCH_2Ph and $NCH_2(CH_2)_2CH_2NHBoc$), 65.4, 65.5, 66.7 (CH, $CH_2CH(CH_3)O$), 79.4 (C, ^{t}Bu(NHBoc)), 111.5, 111.6, 111.9 (CH, indole), 111.9, 112.0, 113.3 (C, indole), 118.2, 118.5, 118.9, 119.4, 119.6, 119.9 (2CH, indole), 122.0, 122.1, 122.5, 123.0 (2CH, indole), 126.2, 126.3, 126.4, 126.5 (2CH, Ph), 127.1, 127.3 (C, indole), 127.4, 127.7, 127.8, 128.0, 128.2, 128.6, 128.7, 128.8, 128.9, 129.0, 129.2 (8CH, Ph), 136.4, 136.7, 136.9, 137.3, 137.6 (3C, Ar), 156.3 (C, C=O(NHBoc)), 171.0, 171.5, 171.7, 172.5 (6C, 6×C=O). **HRMS** (TOF MS ES+): Calcd for $C_{54}H_{75}N_7O_{10}Na_2^{2+}$ $[M + Na_2]^{2+}$ *m/z* 513.7685; found 513.7690.

Linear αβ4 peptoid TFA salt (5.TFA) was synthesised starting from **23** (9 mg, 9 µmol, 1.0 equiv) by application of General procedure F yielding **5.TFA** (9 mg, 9 µmol, quantitative) as a white foam. The residue was lyophilized and sent for biological tests. R_f = 0.29 (CH_2Cl_2/MeOH 80:20); $[\alpha]_D^{23}$ = – 6.9 (*c* 0.61, MeOH); **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 3258 (NH), 2953, 2925, 2857, 1729, 1695, 1684, 1669, 1636, 1628, 1623, 1617, 1559, 1539, 1473, 1457, 1449, 1437, 1430, 1420, 1373, 1369, 1363, 1202, 1176, 1131, 1078, 1014, 800. **^{1}H NMR** (400 MHz, methanol-d_4) δ (ppm): 0.69-1.13 (m, 3H, $CH_2CH(CH_3)O$), 1.32-1.74 (m, 4H, $NCH_2(CH_2)_2CH_2NHBoc$), 1.79-2.04 (m, 3H, NAc), 2.04-4.64 (m, 36H, 4×NCH_2CH_2C=O, NCH_2C=O, 2×NCH_2Ph, CH_3OC=O, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NH_2$ and NCH_2CH_2Indole), 6.79-7.57 (m, 15H, CH(Ar)). **^{13}C NMR** (100 MHz, methanol-d_4) δ (ppm): 21.4, 21.8, 22.0 ($2CH_3$, $CH_2CH(CH_3)O$ and NAc), 24.7, 25.4, 25.9, 26.6 ($2CH_2$, $NCH_2(CH_2)_2CH_2NH_2$), 29.9, 30.4, 30.9, 31.6, 32.2, 32.7, 32.9, 33.3, 33.9 ($4CH_2$, 4×NCH_2CH_2C=O), 40.5, 40.6, 43.4, 44.1, 44.45, 45.0, 45.2, 45.8, 48.2, 51.2, 51.5, 52.1, 52.9, 53.2, 53.5, 54.3, 54.7, 57.1 ($12CH_2$, 4×NCH_2CH_2C=O, NCH_2C=O, 2×NCH_2Ph, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NH_2$ and NCH_2CH_2Indole), 52.4, 52.5 (CH_3, CH_3OC=O), 66.5, 66.7, 67.1 (CH, $CH_2CH(CH_3)O$), 112.7, 112.9, 119.3, 119.4, 119.8, 120.2, 120.3, 122.8, 122.9, 124.6, 124.7 (5CH, indole), 127.7, 127.9, 128.5, 128.6, 128.9, 128.9, 129.7, 129.8, 130.2, 130.3 (10CH, Ph), 113.4, 112.7, 138.3, 138.4, 138.9 (5C, Ar), 162.0 (C, *C*=O(TFA)), 170.3, 170.7, 173.6, 174.0, 174.3, 174.7 (6C, 6×*C*=O). **HRMS** (TOF MS ES+): $C_{48}H_{66}N_7O_8$ $[M - TFA]^+$ *m/z* 868.4973, found 868.4937.

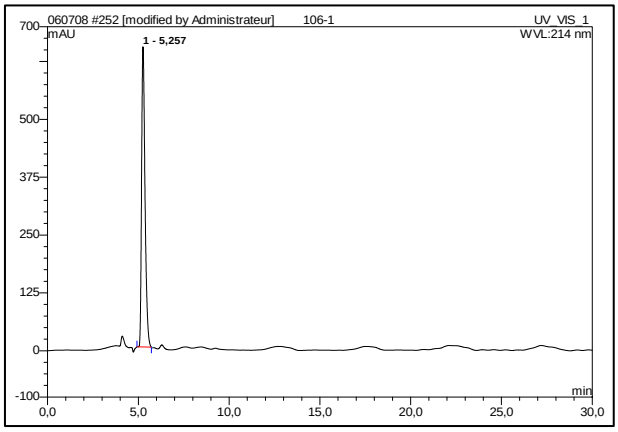
Linear β5 peptoid TFA salt (6.TFA) was synthesised starting from **24** (17 mg, 17 µmol, 1.0 equiv) by application of General procedure F yielding **6.TFA** (17 mg, 17 µmol, quant.) as a pale yellow foam. The residue was lyophilized prior to biological evaluation. R_f = 0.58 (nPrOH/H_2O 70:30); $[\alpha]_D^{22}$ = – 3.7 (*c* 0.71, MeOH); **IR** (ATR) $\bar{\nu}$ (cm^{-1}): 3291, 2954, 2926, 2859, 1731, 1689, 1624, 1617, 1472, 1447, 1419, 1374, 1363, 1200, 1178, 1132, 798. **^{1}H NMR** (400 MHz, methanol-d_4) δ (ppm): 0.76-1.16 (m, 3H, $CH_2CH(CH_3)O$), 1.32-1.69 (m, 4H, $NCH_2(CH_2)_2CH_2NHBoc$), 1.89-2.05 (m, 3H, NAc), 2.05-4.01 (m, 34H, 5×NCH_2CH_2C=O, CH_3OC=O, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NH_2$ and NCH_2CH_2Indole), 4.14-4.68 (4H, 2×NCH_2Ph), 6.93-7.39 (m, 14H, CH(Ar)), 7.52-7.61 (m, 1H, C=CHNH). **^{13}C NMR** (100 MHz, methanol-d_4) δ (ppm): 21.0, 21.2 ($2CH_3$, $CH_2CH(CH_3)O$ and NAc), 25.1, 25.4, 25.8, 26.9 ($2CH_2$, $NCH_2(CH_2)_2CH_2NH_2$), 30.8, 31.7, 32.1, 32.5, 33.1, 33.8 ($5CH_2$, 5×NCH_2CH_2C=O), 40.4, 43.9, 44.3, 44.9, 45.2, 45.6, 49.4, 50.0, 50.3, 50.6, 50.7 ($10CH_2$, 5×NCH_2CH_2C=O, $NCH_2CH(CH_3)O$, $NCH_2(CH_2)_2CH_2NH_2$ and NCH_2CH_2Indole), 52.3 (CH_3, CH_3OC=O), 52.7, 53.0, 53.3, 56.9, 59.6 ($2CH_2$, 2×NCH_2Ph), 66.4, 66.6, 66.8, 67.0 (CH, $CH_2CH(CH_3)O$), 112.4 (C, indole), 112.6, 112.8 (CH, indole), 119.1, 119.3, 119.8, 120.0, 120.2, (2CH, indole), 122.4, 122.6, 122.8, 123.7, 124.5 (2CH, indole), 126.9 (C, indole), 127.6, 127.7 (2CH, Ph), 128.5, 128.7, 128.8, 129.7, 130.1, 130.1 (8CH, Ph), 138.1, 138.8 (3C, Ar), 161.0 (C, q, *J* = 39 Hz, F_3CC=O), 172.9, 173.6, 173.8, 174.2 (6C, 6×*C*=O). **HRMS** (TOF MS ES+): Calcd for $C_{49}H_{68}N_7O_8^+$ $[M + H]^+$ *m/z* 882.5129; found 882.5114.

HPLC chromatograms of peptoid analogues 1-5

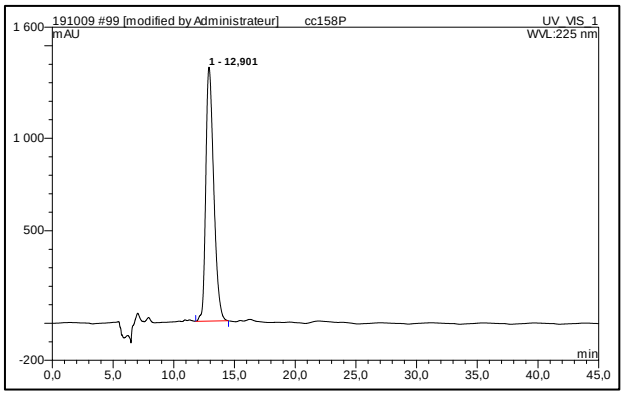
General conditions: Solvent A: water (0.1% TFA); solvent B: MeCN; solvent C: MeOH.



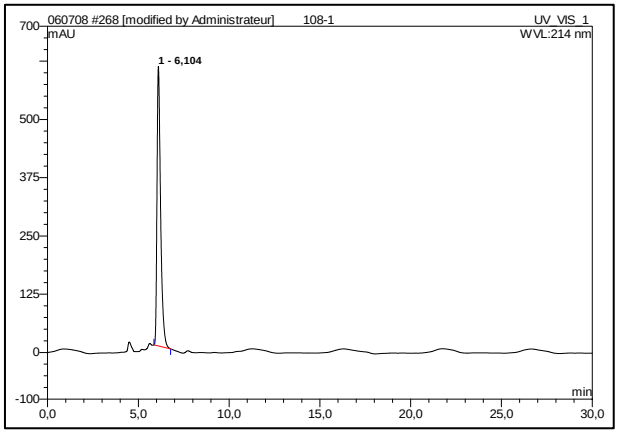
Peptoid **1·TFA** (A/C 30:70, flow = 0.50).



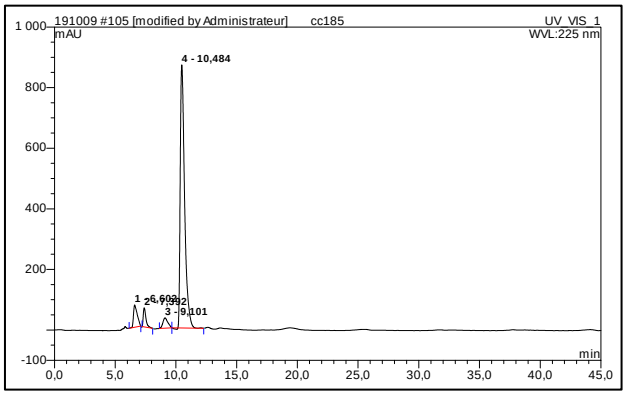
Peptoid **2·TFA** (A/C 20:80, flow = 0.60).



Peptoid **3·TFA** (A/C 30:70, flow = 0.50).



Peptoid **4·TFA** (A/C 20:80, flow = 0.60).

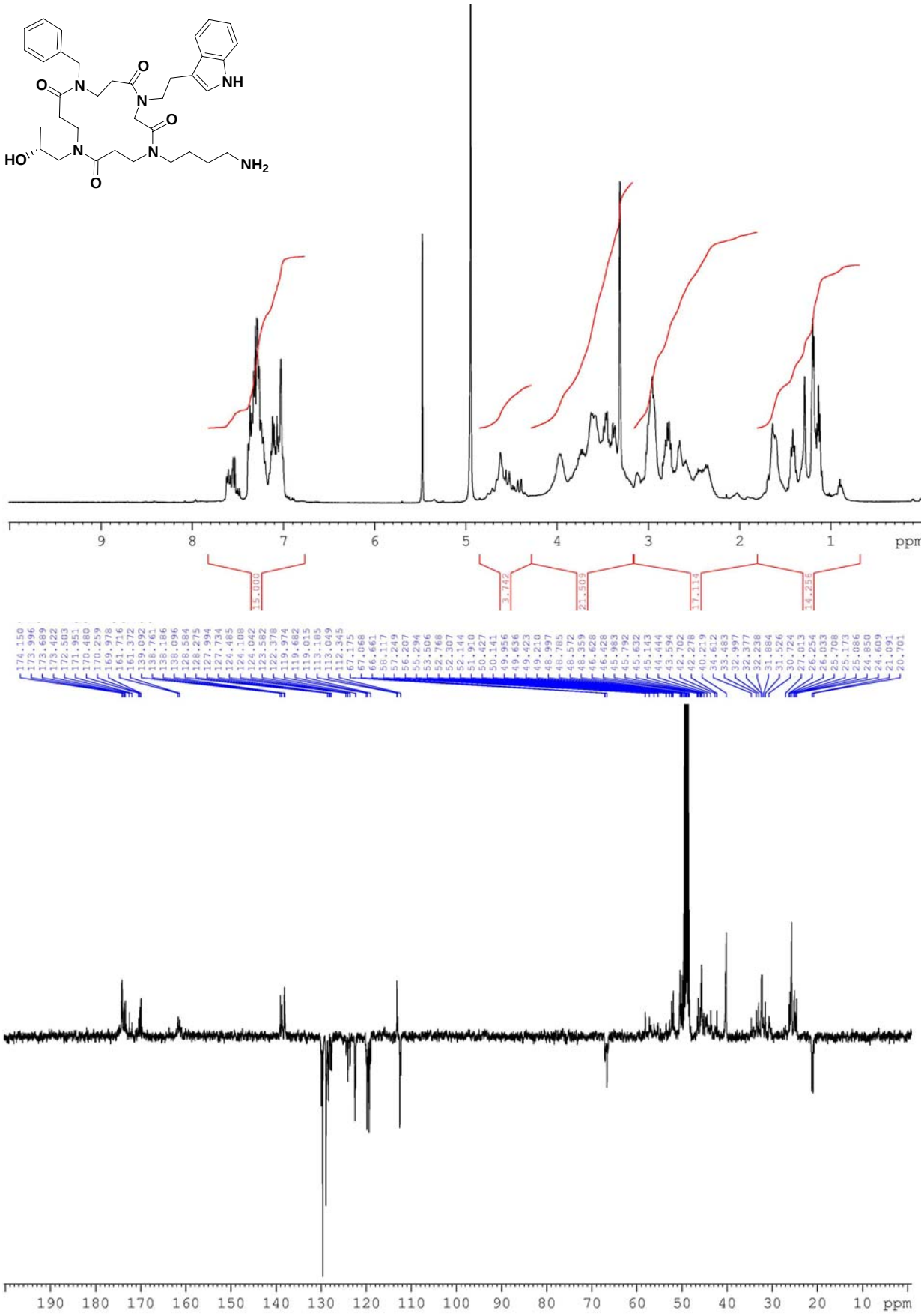


Peptoid **5·TFA** (A/C 30:70, flow = 0.50).

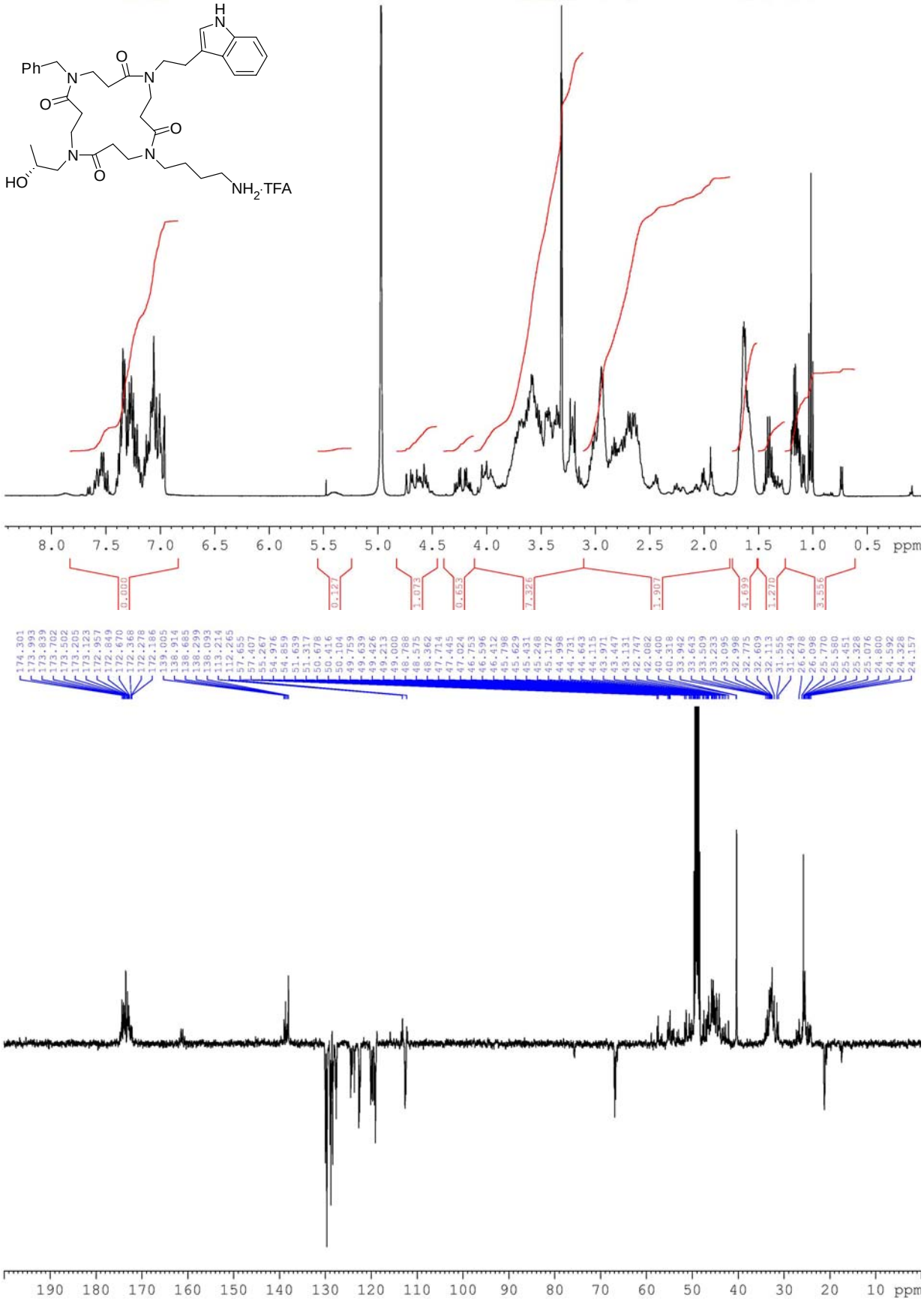
NMR spectra of somatostatin analogues

General information: The NMR spectra of peptoids are often very complex and difficult to interpret because both *cis* and *trans* conformations of the peptoid tertiary amides are populated and observable on the NMR time scale. Until 16 rotameric forms can be observed in solution for a cyclotetramer such as peptoids **1** and **2** (32 rotameric forms for a cyclopentamer such as peptoids **3** and **4**). This phenomenon in short peptoids (up to trimers) has been well described and discussed previously.[4]

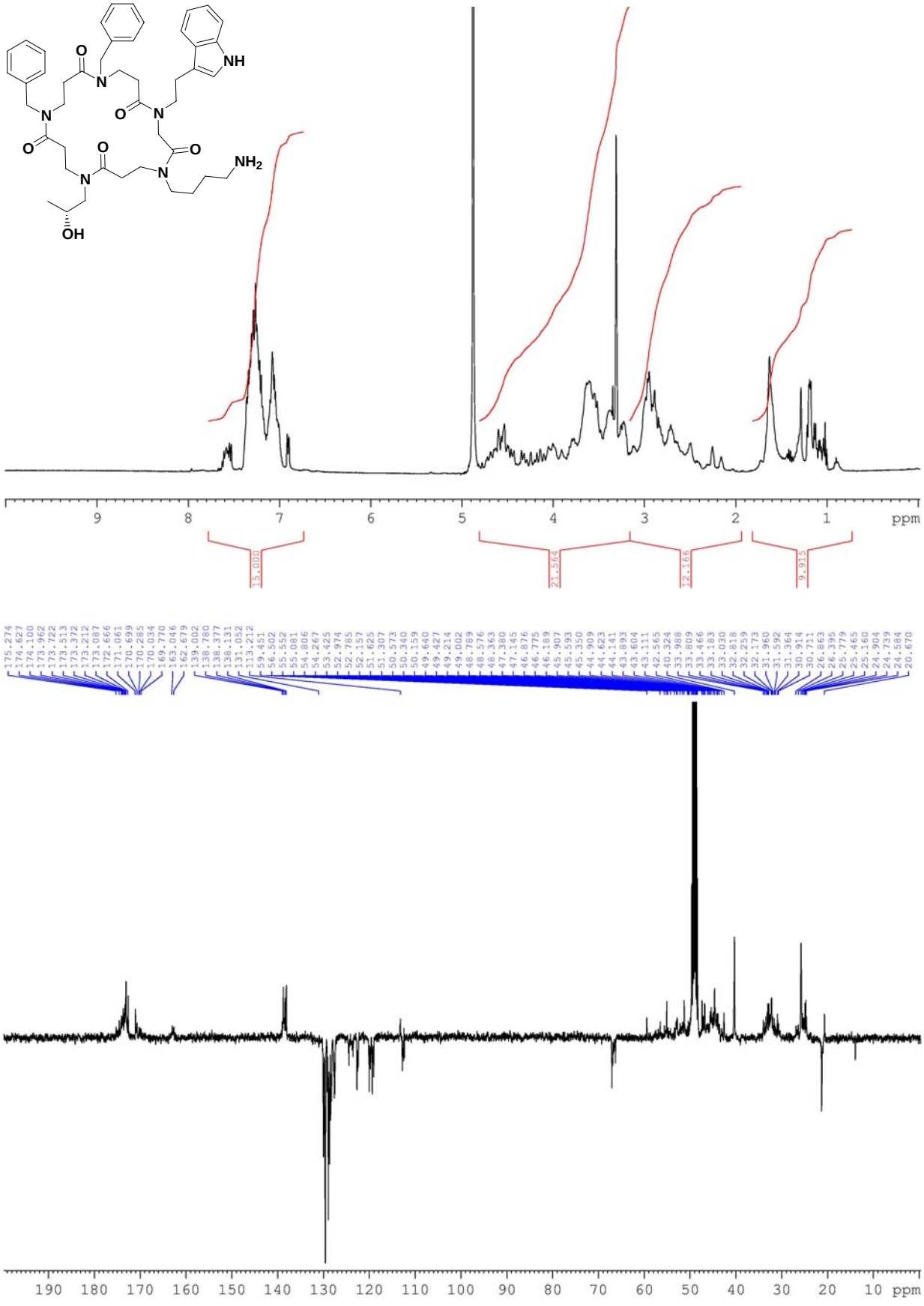
^{1}H and ^{13}C NMR spectra of cyclic peptoid 1 (methanol-d_4)



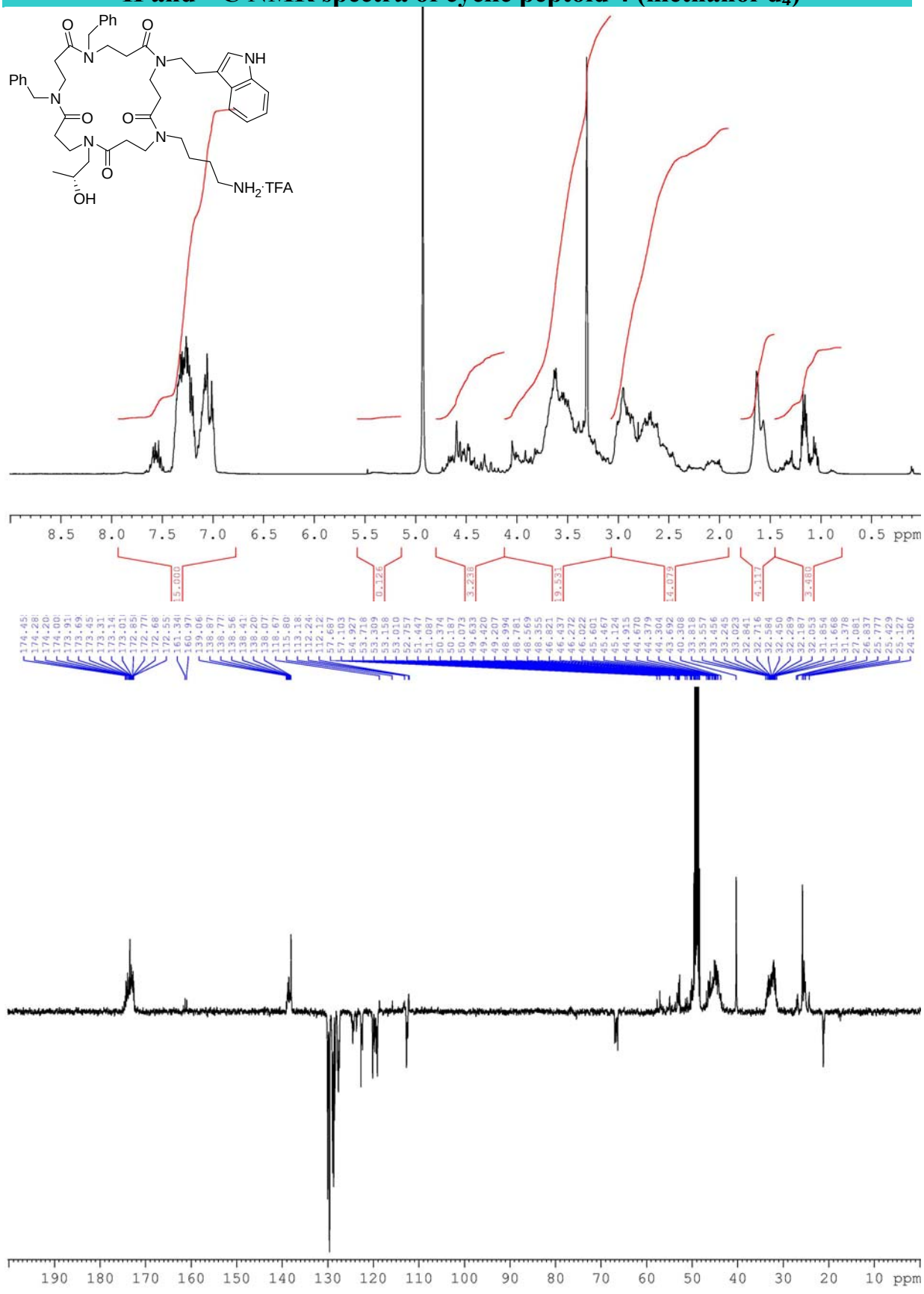
^{1}H and ^{13}C NMR spectra of cyclic peptoid 2 (methanol-d_4)



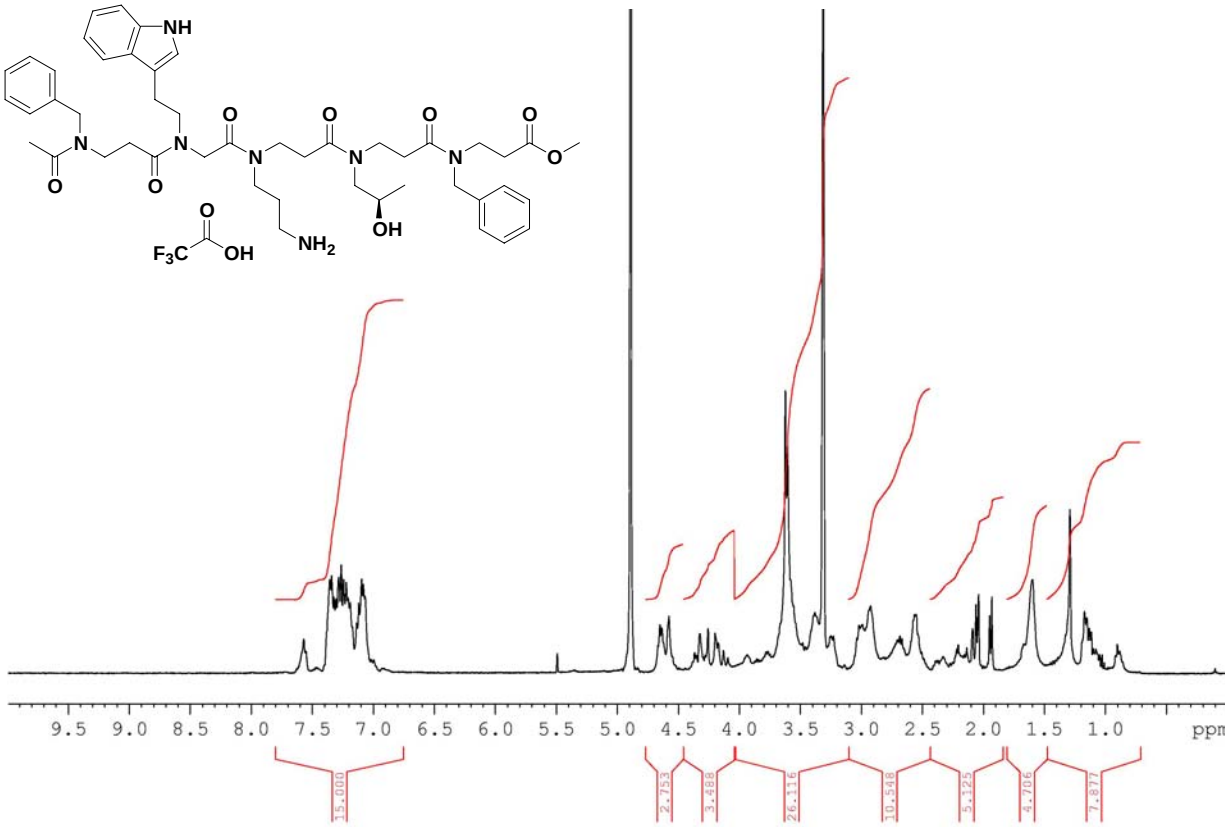
^{1}H and ^{13}C NMR spectra of cyclic peptoid 3 (methanol-d_4)

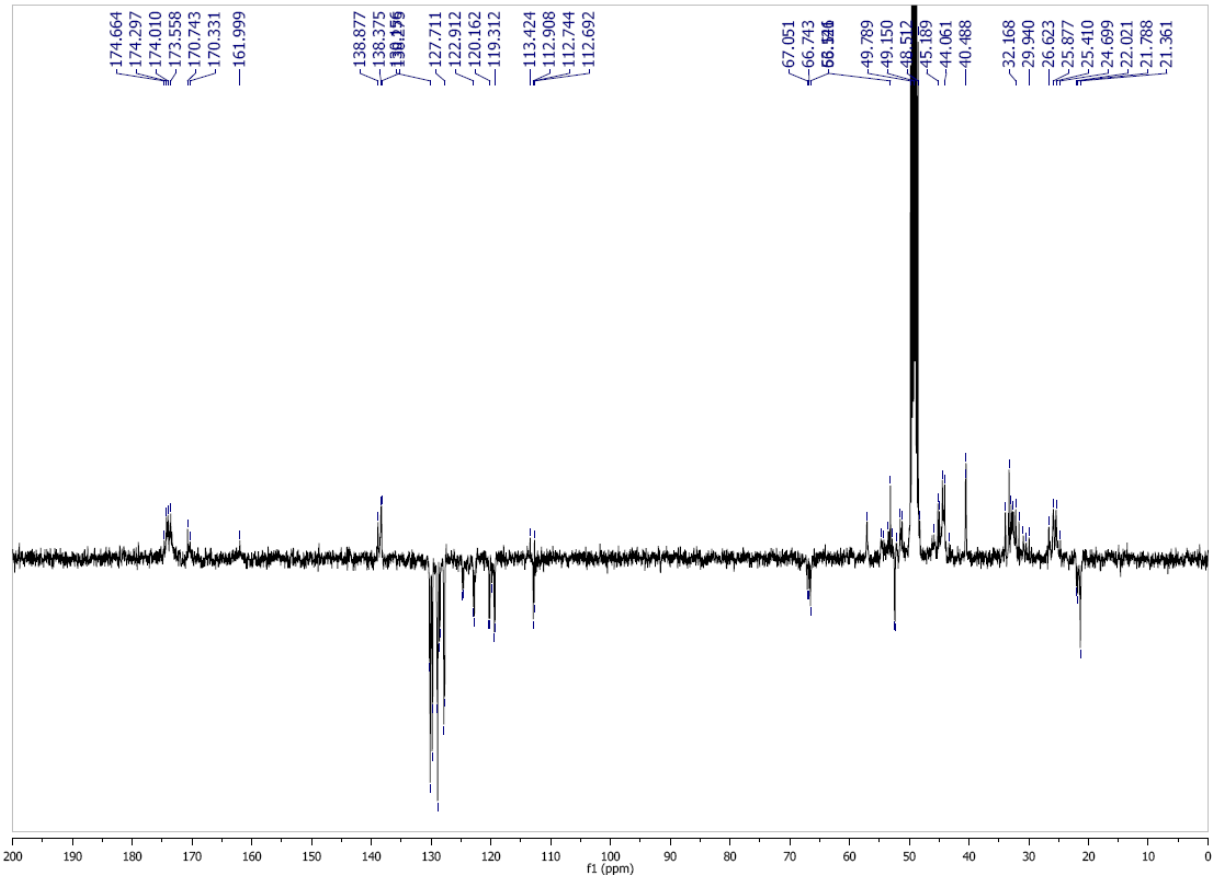


^{1}H and ^{13}C NMR spectra of cyclic peptoid 4 (methanol-d_4)

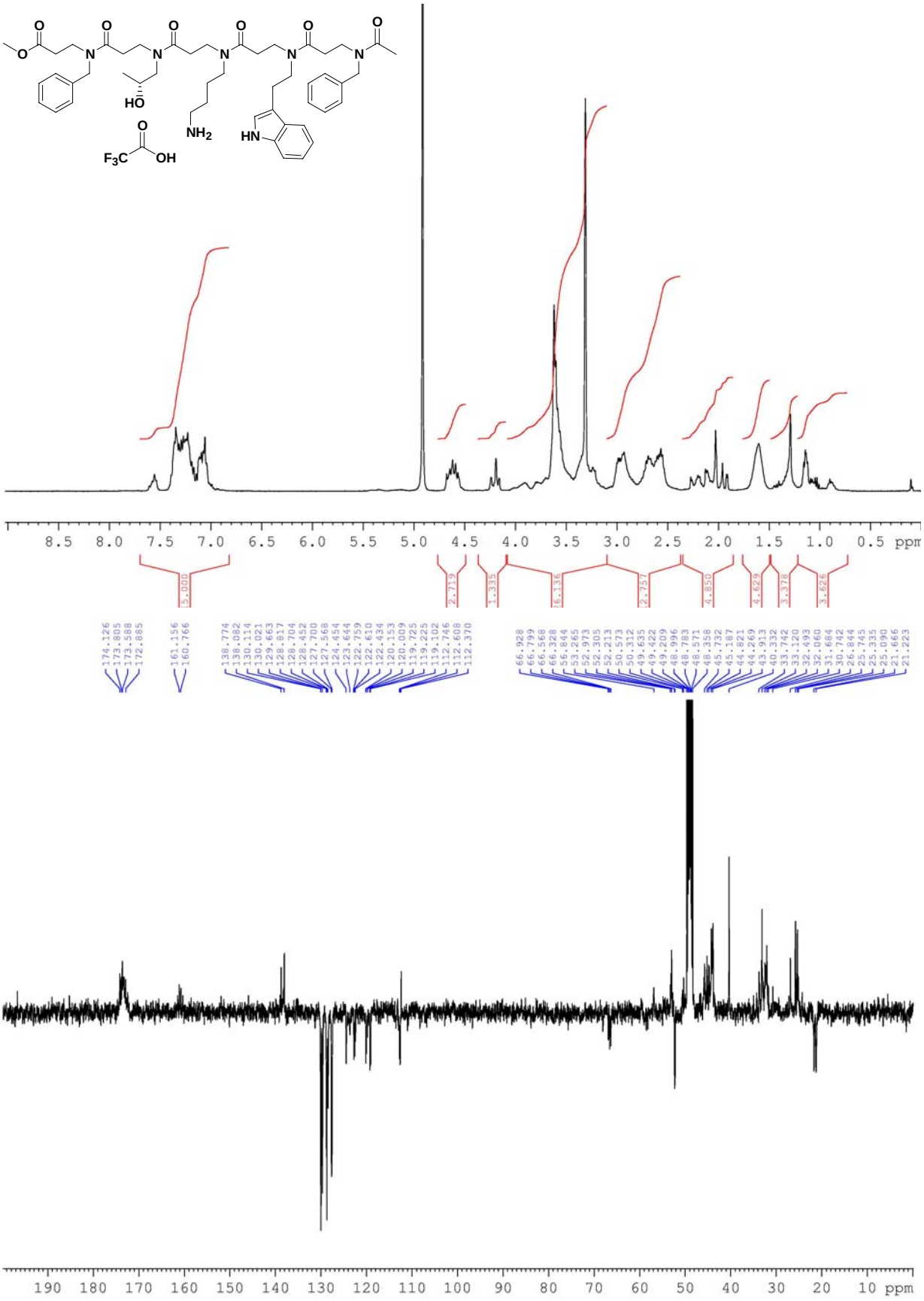


^{1}H and ^{13}C NMR spectra of cyclic peptoid 5 (methanol-d_4)

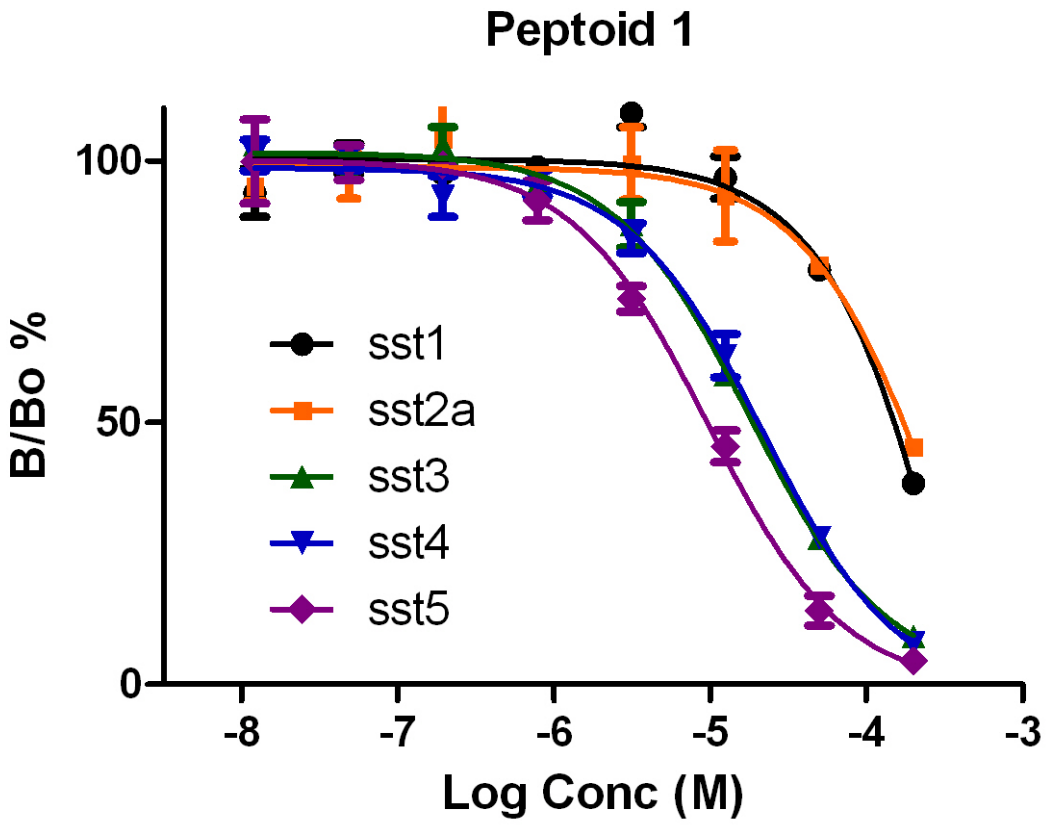


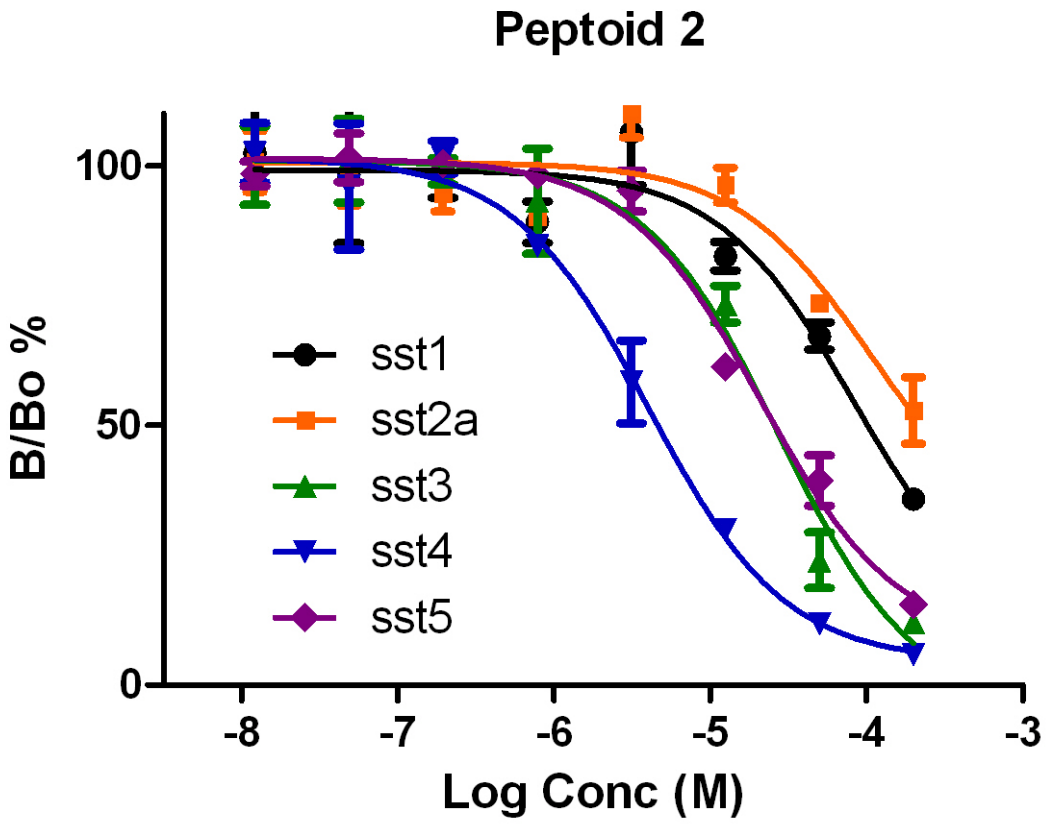


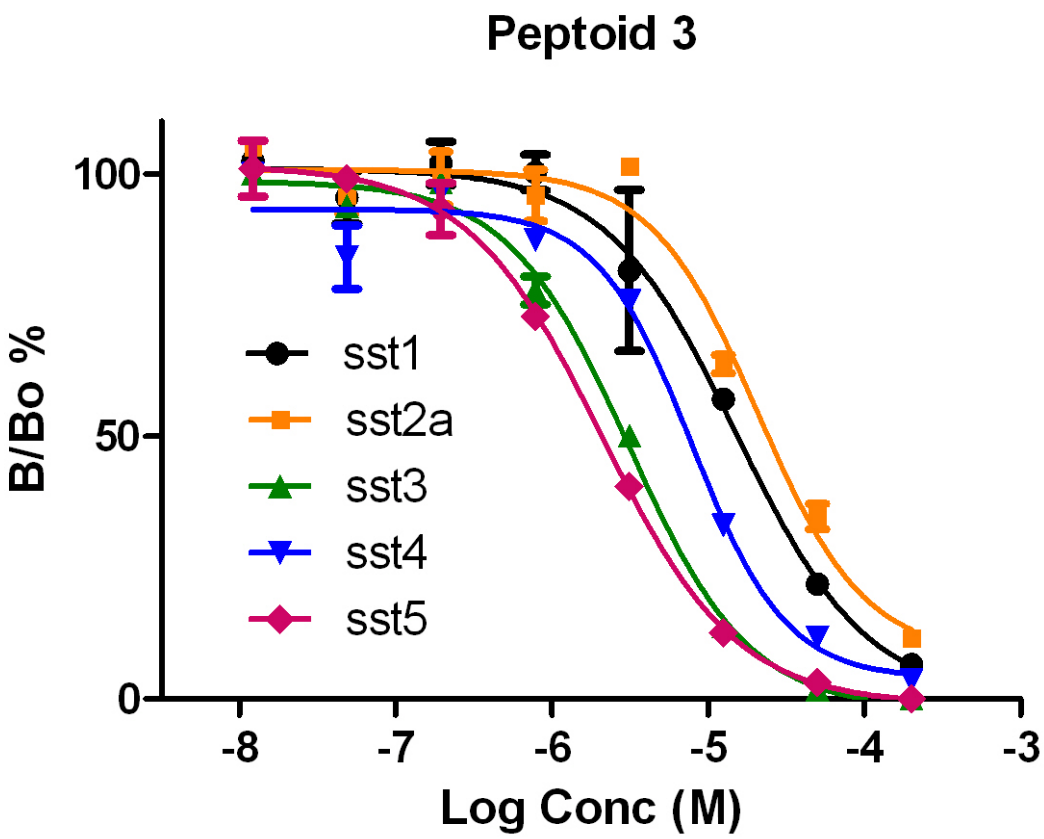
^{1}H and ^{13}C NMR spectra of cyclic peptoid 6 (methanol-d_4)

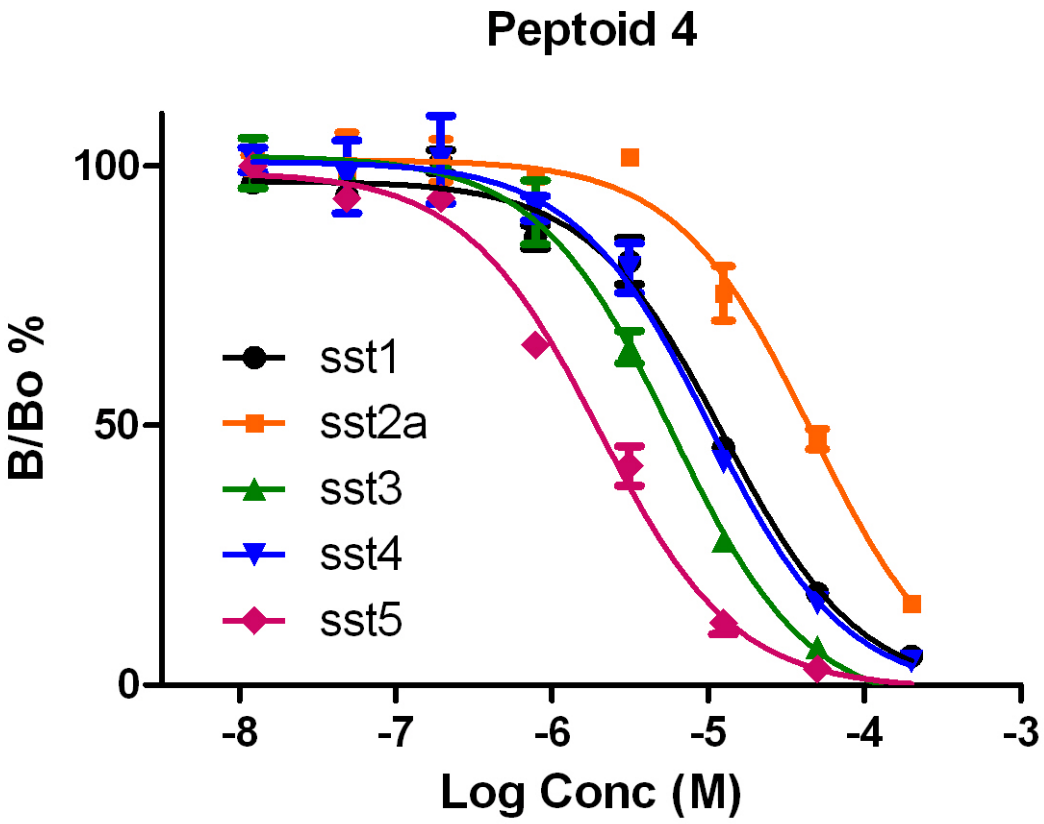


Binding curves






Peptoid 3
100
50
0
B/Bo %
sst1
sst2a
sst3
sst4
sst5
-8
-7
-6
-5
-4
-3
Log Conc (M)


Peptoid 4
100
50
0
B/Bo %
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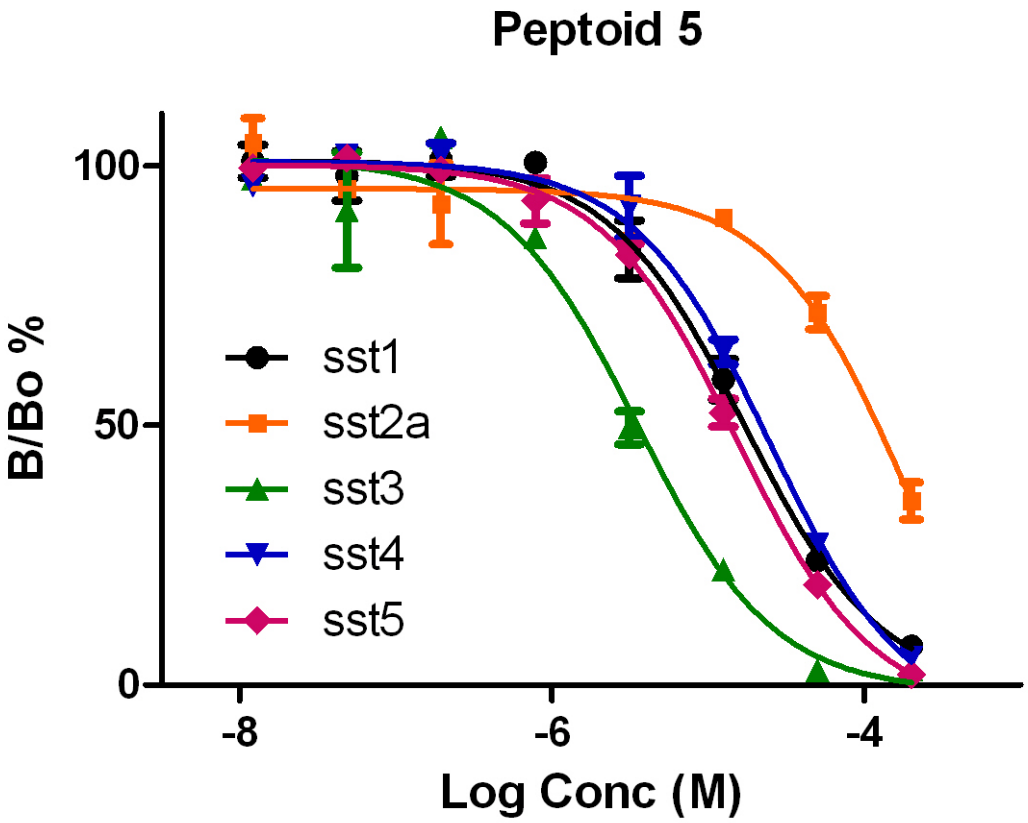
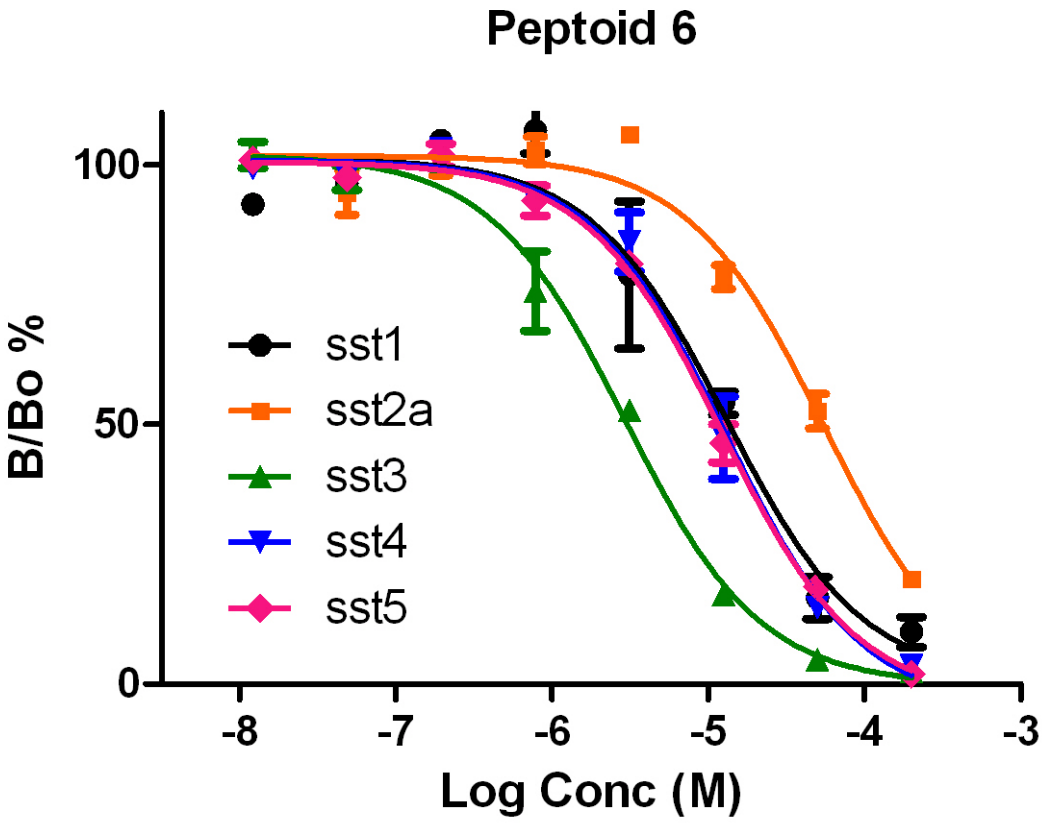
sst2a
sst3
sst4
sst5
-8
-7
-6
-5
-4
-3
Log Conc (M)





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