Supporting Information

$\alpha_v\beta_3$ Integrin-Targeting Arg-Gly-Asp (RGD) Peptidomimetics Containing Oligoethylene Glycol (OEG) Spacers

Vincent Rerat[a], Georges Dive[b], Alex A. Cordi[c], Gordon C. Tucker[c], Reine Bareille[d], Joëlle Amédée[d], Laurence Bordenave[d], and Jacqueline Marchand-Brynaert[a].*

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I. Large-scale synthesis of (S)-*t*-butyl 3-(4-hydroxy-3-nitrophenyl)-2-(3-trifluoromethyl-benzenesulfonylamino)-propionate (1).

Synthesis of *t*-butyl (L)-tyrosinate.

t-Butyl ester of tyrosine was prepared by transesterification with *t*-butyl acetate in the presence of an acid catalyst. Reaction of (L)-Tyr (1 equiv.) with a 1:1 mixture of *t*-BuOAc and *t*-BuOH (10-15 equiv.) and 10% H_2SO_4, at 0 °C, 20 °C or 40 °C, gave modest yields of *t*-butyl tyrosinate (between 20% to 40%). Using *t*-BuOAc as reagent and solvent, and $HClO_4$ as catalyst, we could improve the yields (about 70%), but a side-product (10-15% yield) was also formed corresponding to aromatic-OH alkylation (*t*-butyl 3-(4-*t*-butyloxy-phenyl)-2-aminopropionate).

Protocol.

In a 500 mL reactor (equipped with a dropping funnel, a mechanical stirrer and a cooling system with temperature control), (L)-tyrosine (18.1 g, 0.1 mol, 1 equiv.) was suspended in *t*-butyl acetate (335 mL, 2.5 mol, 25 equiv.) and the mixture was cooled at 14 °C. $HClO_4$ (13 mL, 0.2 mol, 2 equiv.) was added dropwise over 15 min. The mixture was stirred for 18 h at 14 °C. The organic phase was successively extracted with H_2O (3 x 50 mL), 1 N HCl (2 x 50 mL) and H_2O (1 x 50 mL). The aqueous phases were gathered, diluted with H_2O (200 mL) and brought to pH 9 by careful addition of solid potassium carbonate, in small portions (formation of a white precipitate). Extraction with EtOAc (3 x 100 mL), drying over Na_2SO_4, filtration and concentration under vacuum afforded crude ester as a white solid. This was washed with cold cyclohexane (for removing the side-product) and dried under vacuum to afford pure *t*-butyl (L)-tyrosinate (13.5 g, 0.057 mol, 57% yield) as a white solid. R*f* (SiO_2; EtOAc/acetone 9:1) = 0.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 2.75-3.01 (m, 2 H), 3.58 (m, 1 H), 6.66 (d, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 8.4 Hz, 2 H). $[\alpha]_D^{20}$ 26.4 (*c* = 0.5, MeOH); for commercial product from Fluka: $[\alpha]_D^{20}$ 26.1 (*c* = 0.5, MeOH).

Synthesis of (S)-*t*-butyl 3-(4-hydroxyphenyl)-2-(3-trifluoromethyl-benzenesulfonylamino)-propionate.

Sulfonylation of *t*-butyl tyrosinate under usual conditions,[3] i.e. with 3-trifluoromethyl-benzenesulfonyl chloride and pyridine in DCM at 20 °C, gave a mixture of the desired *N*-sulfonyl derivative (25-35%) and *O*,*N*-*bis*-sulfonyl derivative (30-40%). The two products could be separated by column-chromatography on silica gel. The chemoselectivity in favour of aliphatic NH_2 *versus* aromatic OH could be improved by using a mixture of THF and DMF as solvent. This specific solvatation effect was initially developed by Albanese et al.[1,2]

Protocol.

In a 500 mL reactor (equipped with a dropping funnel, a mechanical stirrer and a cooling system with temperature control), (L)-*t*-butyl tyrosinate (19 g, 80 mmol, 1.1 equiv.) was introduced and dissolved in DMF (30.4 mL) and THF (152 mL). After cooling at 0 °C, 3-(trifluoromethyl)benzenesulfonyl chloride (11.65 mL, 72.7 mmol, 1 equiv.) dissolved in THF (91 mL) was added dropwise over 3 h. The reaction mixture was allowed to reach room temperature and stirring was maintained for 1 h. Solid Na_2CO_3 (7.7 g, 72.7 mmol, 1 equiv.) was then added in one portion and the mixture was stirred for another 1 h. Filtration over a celite pad, and concentration under reduced pressure left a residue which was dissolved in ether/EtOAc (9:1 mixture, v/v; 200 mL). Extraction with brine (3 x 50 mL), 1 N HCl (2 x 50 mL) and H_2O (1 x 20 mL), drying over $MgSO_4$, filtration and concentration gave the title compound (32.1 g, 72 mmol, 90% yield) as a colorless oil.[4] R*f* (SiO_2; DCM/EtOAc 9:1) = 0.8. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9 H), 2.97 (m, 2 H), 4.11 (m, 1 H), 5.94 (d, *J* = 9.6 Hz, 1H, N*H*SO_2), 5.88 (s, 1 H, O*H*), 6.67 (d, *J* = 8.7 Hz, 2 H), 6.97 (d, *J* = 8.7 Hz, 2 H), 7.60 (dd, *J* = 8.1, 7.6 Hz, 1 H), 7.80 (d, *J* = 7.6 Hz, 1 H), 8.02 (d, *J* = 8.1 Hz, 1 H), 8.07 (s, 1H).

Enantionmeric purity control.

The previous protocol has been applied to racemic *t*-butyl tyrosinate and the *N*-sulfonated product was analyzed by HPLC (Gilson equipment: two pumps 306, manometric modulus 805, dynamic

mixer 811D, injector Rheodyne 7725i, detector Jasco CD2095 Plus, computer program Unipoint). An AD-H chiral column from Daicel (FR) was used (250 mm x 4.6 mm; 5 µM). Elution was made with *n*-hexane/*i*-propanol 85:15 (v/v) at a flow rate of 1 mL/min and detection was recorded at 280 nm. The enantiomers were detected at R_T = 11.1 min and R_T = 23.0 min. The compound synthesized from (L)-tyrosinate gave one major peak at R_T = 23.0 min (enantiomeric purity ≥ 97%).

Synthesis of (S)-*t*-butyl 3-(4-hydroxy-3-nitro-phenyl)-2-(3-trifluoromethyl-benzene sulfonylamino)-propionate.

Protocol.

In a 500 mL reactor (equipped with a dropping funnel, a mechanical stirrer and a cooling system with temperature control), the previous intermediate (22.82 g, 51.3 mmol, 1 equiv.) was introduced and dissolved in acetic acid (200 mL). The solution was cooled at 15 °C and 90% nitric acid (3.06 mL) dissolved in acetic acid (100 mL) was added dropwise over a period of 1 h (the temperature was not allowed to increase over 19 °C). After complete addition, the mixture was stirred for 15 min, then poured on ice (200 g). The mixture was introduced in a separation funnel and diluted with DCM (200 mL) and water (300 mL). The organic layer was recovered. The aqueous phase was extracted with DCM (2 x 100 mL). The organic phases were gathered, washed with brine (50 mL) and transferred in the reactor. Water (100 mL) was added and the residual acetic acid was neutralized by careful addition of solid Na_2CO_3 in small portions, under stirring, in order to reach pH 9. The mixture was transferred in the separation funnel; the organic layer was recovered, dried over $MgSO_4$, filtered over a short pad of celite and silicagel using DCM/EtOAc (95:5, v/v) as eluent. The filtrate was concentrated under vacuum to afford the title compound (25 g, 51 mmol, 98% yield) as a yellow solid (spontaneous crystallization). [4] R*f* (SiO_2; DCM) = 0.7. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 9 H), 3.04 (m, 2 H), 4.08 (m, 1 H), 5.38 (d, *J* = 9.3 Hz, 1 H, SO_2NH), 7.08 (d, *J* = 8.9 Hz, 1 H), 7.46 (dd, *J* = 8.9, 2.0 Hz, 1 H), 7.63 (t, *J* = 8.7 Hz, 1 H), 7.81 (d, *J* = 8.7 Hz, 1 H), 7.84 (d, *J* = 2.0 Hz, 1 H), 7.98 (d, *J* = 8.7 Hz, 1 H), 8.04 (s, 1 H), 10.47 (br s, 1 H, O*H*).

Enantiomeric purity control.

Nitration was similarly performed on the racemic precursor and the product was analyzed by HPLC as above. The enantiomers were detected at R_T = 10.4 min and R_T = 18.5 min. The compound synthesized from (L)-precursor gave only one peak at R_T = 18.5 min (enantiomeric purity ≥ 99%).

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II. Synthesis of the various Arg-mimics

This section describes the intermediates drawn in Scheme 2.

Synthesis of *N*-*t*-butoxycarbonyl-3-amino-1-propanol (10a).

A solution of 3-amino-1-propanol (3.05 mL, 40 mmol) in *t*-BuOH (40 mL) and water (50 mL) was treated successively with NaOH (1.6 g, 40 mmol) and Boc_2O (13.34 g, 48 mmol) added in small portions. The mixture was stirred for 24 h at 20 °C, then extracted with ether (2 x 25 mL). The organic phase was washed with brine (10 mL), dried ($MgSO_4$), concentrated and purified by chromatography on silica gel to give **10a** (6.3 g, 90%) as a colorless oil. R*f* (DCM/EtOAc 4:1) = 0.32. IR 3400, 2979, 2938, 2881, 1699, 1539, 1367, 1278, 1253, 1174 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 1.66 (m, 2 H), 2.3 (br m, OH, 1 H), 3.28 (m, 2 H), 3.66 (t, *J* = 5.7 Hz, 2 H), 4.8 (br s, BocNH, 1 H,). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 32.8, 37, 59.3, 79.5, 157.1. MS (ESI) *m/z* 198 $[M + Na]^+$, 142, 98. RN: 58885-58-8 ($C_8H_{17}NO_3$).

Synthesis of *N*-*t*-butoxycarbonyl-4-amino-1-butanol (10b).

The title compound was prepared as above from 4-amino-1-butanol (2.07 mL, 22.4 mmol), as a colorless oil (4.1 g, 97%). R*f* (EtOAc/ DCM 6:4) = 0.3. IR 3366, 2976, 2933, 2869, 1689, 1537, 1454, 1392, 1366, 1280, 1252, 1172 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 1.57 (m, 4 H), 1.90 (br m, OH, 1 H), 3.15 (t, *J* = 6.6 Hz, 2 H), 3.67 (t, *J* = 6.6 Hz, 2 H), 4.62 (br s, BocNH, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.74, 28.59, 29.88, 40.48, 62.35, 79.33, 156.41. MS (ESI) *m/z* 212 $[M + Na]^+$, 190 $[M + H]^+$, 134. RN: 75178-87-9 ($C_9H_{19}NO_3$).

Synthesis of *N*,*N*'-di-*t*-butoxycarbonyl-3,5-dimetylpyrazolyl-1-carboxamidine (11).

NaH (1.5 g, 60% weight in paraffin 37.3 mmol) was washed with petroleum ether (3 times) in a flask placed under Ar atmosphere, then covered with dry THF (60 mL). Under stirring, 3,5-dimethyl-1H-pyrazolyl-1-carboxamidine (HNO_3 salt, 1.5 g, 7.2 mmol) was added followed by Boc_2O (8.13 g, 37.3 mmol) dissolved in THF (5 mL) and introduced dropwise with a syringe. The mixture was refluxed for 6 h under Ar atmosphere. After cooling, EtOH (50 mL) was added

dropwise under vigorous stirring. The crude mixture was concentrated under vacuum and the residue was dissolved in DCM (30 mL). The organic phase was washed with water (2 x 10 ml), brine (1 x 10 mL), dried ($MgSO_4$) and purified by chromatography on silica gel to afford **11** (1.98 g, 81%) as a white solid. R*f* (*n*-Hex/EtOAc 5:1) = 0.47. Mp 96-98 °C. IR 2982, 2930, 1771, 1711, 1655, 1621, 1495, 1294, 1138 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9 H), 1.51 (s, 9 H), 2.22 (s, 3 H), 2.56 (s, 3 H), 5.96 (s, 1 H), (NHBoc, not visible). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 15.09, 27.94, 80.49, 82.53, 111.24, 140.37, 144, 149.52, 150.32, 157.46. MS (ESI) *m/z* 361 $[M + Na]^+$, 339 $[M + H]^+$, 239, 183, 139. RN: 153114-31-9 ($C_{16}H_{26}N_4O_4$).

Synthesis of 3-(*N*,*N*'-di-*t*-butoxycarbonylguanidino)-propan-1-ol (12a).

To a solution of 3-amino-1-propanol (0.2 mL, 2.66 mmol) in DCM (20 mL) were added successively Et_3N (0.2 mL, 2.66 mmol) and **11** (1 g, 2.96 mmol), under stirring at room temperature. After 18 h, the mixture was diluted with DCM (30 mL) and washed with 0.1 N HCl (2 x 10 mL), 0.1 N NaOH (2 x 10 mL), brine (1 x 20 mL). Drying ($MgSO_4$), concentration and chromatography on silica gel gave **12a** (0.78 g, 92%) as a white solid. R*f* (DCM/EtOAc 1:1) = 0.66. Mp 112-113 °C. IR 3329, 2979, 2930, 1724, 1650, 1415, 1333, 1160, 1136 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9 H), 1.5 (s, 9 H), 1.69 (m, 2 H), 3.45 (m, 2 H), 3.57 (m, 2 H), 4.8 (br s, OH, 1 H), 8.46 (br s, NH, 1 H), 11.45 (br s, NH, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.98, 28.12, 32.8, 36.66, 57.59, 79.41, 83.4, 153.11, 157.13, 163.7. MS (ESI) *m/z* 340 $[M + Na]^+$. RN: 405075-82-3 ($C_{14}H_{27}N_3O_5$).

Synthesis of 4-(*N*,*N*'-di-*t*-butoxycarbonylguanidino)-butan-1-ol (12b).

The title compound was prepared as above from 4-amino-1-butanol (0.1 mL, 1.08 mmol) as a white solid (0.35 g, 97%). R*f* (DCM/EtOAc 1:1) = 0.63. Mp 124-125 °C. IR 3334, 2983, 2930, 2869, 1722, 1644, 1613, 1570, 1417, 1368, 1334, 1161, 1135, 1052, 1027 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.5 (s, 18 H), 1.64 (m, 4 H), 3.45 (m, 2 H), 3.7 (t, *J* = 5.7 Hz, 2 H), 4.7 (br s, OH, 1 H), 8.39 (s, NH, 1 H), 11.48 (s, NH, 1 H). MS (ESI) *m/z* 354 $[M + Na]^+$, 276, 220. RN: 208465-10-5 ($C_{16}H_{29}N_3O_5$).

Synthesis of 3-(pyrimidin-2-yl-amino)-propan-1-ol (13a).

A mixture of 2-chloropyrimidine (0.15 g, 1.31 mmol) and 3-amino-1-propanol (0.2 mL, 2.62 mmol) in ethanol (5 mL) was refluxed for 18 h under Ar atmosphere. Concentration under vacuum and chromatography on silica gel gave **13a** (0.2 g, 99%) as white crystals. R*f* (EtOAc/*i*-PrOH 8:2) = 0.28. Mp 53-54 °C. IR 3266, 2938, 2875, 1592, 1539, 1456, 1417, 1368, 1272, 1063 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (m, 2 H), 3.57 (m, 2 H), 3.66 (t, *J* = 5.7 Hz, 2 H), 4.67 (br s, OH, 1 H), 6.18 (br s, NH, 1 H), 6.52 (t, *J* = 4.8 Hz, 1 H), 8.25 (d, *J* = 4.8 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.36, 37.77, 58.8, 110.6, 155.65, 158.17. HRMS $C_7H_{11}N_3O$ calcd for $[M + H]^+$, 154.0980; found, 154.0979.

Synthesis of 4-(pyrimidin-2-yl-amino)-butan-1-ol (13b).

The title compound was prepared as above from 2-chloropyrimidine (1 g) and 4-amino-1-butanol, as a pale yellow crystallin solid (1.36 g, 93%). R*f* (EtOAc/*i*-PrOH 8:2) = 0.36. Mp 36-37 °C. IR 3334, 2937, 2866, 1594, 1534, 1456, 1417, 1371, 1059 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (m, 4 H), 2.58 (br s, OH, 1 H), 3.45 (m, 2 H), 3.71 (m, 2 H), 5.44 (br s, NH, 1 H), 6.51 (t, *J* = 4.8 Hz, 1 H), 8.26 (d, *J* = 4.8 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.41, 29.96, 41.29, 62.49, 110.44, 158.07, 162.38. HRMS $C_8H_{13}N_3O$ calcd for $[M + H]^+$, 168.1137; found, 168.1142.

Synthesis of 3-(1-oxi-pyridin-2-yl-amino)-propan-1-ol (14a).

A mixture of 2-chloropyridine N-oxide hydrochloride (0.435 g, 2.62 mmol), $NaHCO_3$ (0.485 g, 5.76 mmol) and 3-amino-1-propanol (0.2 mL, 2.62 mmol) in *t*-amyl alcohol (5 mL) was refluxed for 12 h under Ar atmosphere. Filtration, concentration under vacuum, and chromatography on silica gel gave **14a** (0.425 g, 82%) as a pale yellow solid. R*f* (DCM/MeOH 9:1) = 0.33. Mp 97-98 °C. IR 3297, 2920, 2850, 1627, 1575, 1532, 1466, 1435, 1194, 1126, 1069, 751 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88 (m, 2 H), 2.7 (br s, OH, 1 H), 3.53 (m, 2 H), 3.77 (t, *J* = 6 Hz, 2 H), 6.53 (dd, *J* = 8.7, 7.5 Hz, 1 H), 6.64 (d, *J* = 8.7 Hz, 1 H), 6.9 (br s, NH, 1 H), 7.21 (dd, *J* = 8.7, 7.5 Hz, 1 H), 8.08 (d, *J* = 7.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.58, 38.95, 58.99, 106.44, 111.41,

129.84, 137.54, 150.52. HRMS $C_8H_{12}N_2O_2$ calcd for $[M + H]^+$, 169.0977; found, 169.0972. RN: 187339-14-6.

Synthesis of 4-(1-oxi-pyridin-2-yl-amino)-butan-1-ol (14b).

The title compound was obtained as above from 2-chloropyridine N-oxide hydrochloride (0.365 g) and 4-amino-1-butanol, as a yellow solid (0.27 g, 69%). R*f* (DCM/MeOH 9:1) = 0.39. Mp 85-86 °C. IR 3349, 2925, 2854, 1626, 1574, 1531, 1439, 1265, 1195, 1060, 738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.69 (m, 4 H), 2.63 (br s, OH, 1 H), 3.3 (m, 2 H), 3.69 (t, *J* = 6 Hz, 2 H), 6.58 (m, 2 H), 6.85 (br s, NH, 1 H), 7.19 (dd, *J* = 8.7, 7.5 Hz, 1 H), 8.09 (d, *J* = 7.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.79, 30.14, 42.13, 61.92, 106.14, 111.39, 129.48, 137.72, 150.61. HRMS $C_9H_{14}N_2O_2$ calcd for $[M + H]^+$, 183.1134; found, 183.1138. RN: 258881-10-8

Synthesis of 3-(4-methyl-pyridin-2-yl-amino)-propan-1-ol (15a).

To a solution of 2-amino-4-picoline (0.758 g, 7 mmol) in dry THF (10 mL), placed at 0 °C under Ar atmosphere, was added 1.6 N *n*-BuLi in hexane (4.37 mL, 7 mmol) dropwise with a syringe. The mixture was stirred for 10 min at 0 °C, then *t*-butyl-(3-iodopropoxy)-dimethylsilane (2.1 g, 7 mmol) in THF (5 mL) was added dropwise with a syringe. After 10 min at 0 °C, the mixture was stirred for 18 h at 20 °C. Concentration under vacuum and chromatography on silica gel gave the silylether **15a'** (1.19 g, 63%) as a pale orange oil. R*f* (EtOAc/*n*-Hex 7:3) = 0.60. IR 2927, 1600, 1462, 1255, 1097 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.9 (s, 9 H), 1.82 (m, 2 H), 2.22 (s, 3 H), 3.37 (m, 2 H), 3.75 (t, *J* = 5.7 Hz, 2 H), 4.75 (br s, NH, 1 H), 6.19 (s, 1 H), 6.38 (d, *J* = 5.4 Hz, 1 H), 7.92 (d, *J* = 5.4 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.09, 18.51, 21.45, 26.18, 32.39, 40.01, 61.57, 106.95, 114.22, 147.53, 148.48, 159.1. HRMS $C_{15}H_{28}N_2OSi$ calcd for $[M + H]^+$, 281.2049; found, 281.2044.

The *O*-protected precursor **15a'** (0.508 g, 2.07 mmol) in THF (5 mL) was treated with 1 N tetrabutylammonium fluoride in THF (4.2 mL, 4.2 mmol) for 1 h at 20 °C. Concentration and chromatography on silica gel gave **15a** as a yellow oil (0.333 g, 97%). R*f* (DCM/*i*-PrOH 9:1) = 0.4. ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (m, 2 H), 2.21 (s, 3 H), 3.3 (br m, OH, 1 H), 3.51 (m, 2 H), 3.63

(t, *J* = 5.6 Hz, 2 H), 4.55 (br s, NH, 1 H), 6.21 (s, 1 H), 6.38 (d, *J* = 5.2 Hz, 1 H), 7.87 (d, *J* = 5.2 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.38, 33.9, 38.2, 58.85, 108.79, 114.7, 147.22, 148.86, 159.61. RN: 939770-03-3 ($C_9H_{14}N_2O$).

Synthesis of 4-(4-methyl-pyridin-2-yl-amino)-butan-1-ol (15b).

The previous procedure was applied to 2-amino-4-picoline (0.504 g, 4.66 mmol) and *t*-butyl-(4-iodobutoxy)-dimethylsilane (1.2 mL, 4.6 mmol) to furnish **15b'** (silyl ether) as a pale orange oil (0.625 g, 46%). R*f* (EtOAc) = 0.7. IR 3248, 2951, 1616, 1471, 1101 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.65 (m, 4 H), 2.23 (s, 3 H), 3.26 (td, *J* = 5.7, 6.6 Hz, 2 H), 3.65 (t, *J* = 5.7 Hz, 2 H), 4.47 (br s, NH, 1 H), 6.19 (s, 1 H), 6.4 (d, *J* = 5.8 Hz, 1 H), 7.93 (d, *J* = 5.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.96, 19.2, 21.51, 26.23, 26.38, 30.55, 42.39, 63.04, 106.79, 114.39, 147.95, 148.4, 159.27. HRMS $C_{16}H_{30}N_2OSi$ calcd for $[M + H]^+$, 295.2206; found, 295.2215.

Deprotection of **15b'** (0.273 g, 0.927 mmol) with TBAF as above gave **15b** (0.163 g, 98%) as a yellow oil. R*f* (DCM/*i*-PrOH 9:1) = 0.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (m, 4 H), 2.22 (s, 3 H), 2.89 (br s, OH, 1 H), 3.28 (m, 2 H), 3.69 (t, *J* = 5.7 Hz, 2 H), 4.62 (br s, NH, 1 H), 6.19 (s, 1 H), 6.39 (d, *J* = 4.8 Hz, 1 H), 7.9 (d, *J* = 4.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.44, 26.45, 30.03, 42.04, 62.59, 107.38, 114.54, 147.58, 148.86, 159.09. MS (APCI) *m/z* 181 $[M + H]^+$, 163, 109 ($C_{10}H_{16}N_2O$).

Synthesis of 3-(6-methyl-pyridin-2-yl-amino)-propan-1-ol (16a).

The procedure described for **15a** was applied to 2-amino-6-picoline (1 g, 9.2 mmol) to furnish **16a'** (silyl ether) as a pale orange oil (1.55 g, 60%). R*f* (EtOAc/*n*-Hex 7:3) = 0.8. IR 2927, 1600, 1462, 1255, 1097 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.91 (s, 9 H), 1.81 (quint, *J* = 6.9 Hz, 2 H), 2.35 (s, 3 H), 3.32 (td, *J* = 5.7, 6.9 Hz, 2 H), 3.74 (t, *J* = 6.9 Hz, 2 H), 4.71 (br s, NH, 1 H), 6.2 (d, *J* = 7.8 Hz, 1 H), 6.42 (d, *J* = 7.8 Hz, 1 H), 7.32 (t, *J* = 7.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.02, 18.6, 24.55, 26.25, 32.57, 40.01, 61.42, 102.82, 112.11, 138.06, 156.88, 158.7. HRMS $C_{15}H_{28}N_2OSi$ calcd for $[M + H]^+$, 281.2049; found, 281.2053.

Deprotection of **16a'** was performed as for **15a'** to give the title compound in quantitative yield, as a yellowish oil. R*f* (DCM/*i*-PrOH 9:1) = 0.5. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (m, 2 H), 2.35 (s, 3 H), 3.51 (m, 2 H), 3.63 (t, *J* = 5.7 Hz, 2 H), 4.74 (br s, OH, 1 H), 5.21 (br s, NH, 1 H), 6.19 (d, *J* = 8.0 Hz, 1 H), 6.39 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 8.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.81, 33.11, 38.15, 58.52, 104.73, 111.66, 137.98, 156.08, 158.82. RN: 939769-96-7 ($C_9H_{14}N_2O$).

Synthesis of 4-(6-methyl-pyridin-2-yl-amino)-butan-1-ol (16b).

The procedure described for **15b** was applied to 2-amino-6-picoline (0.504 g, 4.66 mmol) to furnish **16b'** (silyl ether) as an orange oil (0.856 g, 62%). R*f* (EtOAc) = 0.8. IR 2952, 1599, 1462, 1097 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.64 (m, 4 H), 2.35 (s, 3 H), 3.21 (td, *J* = 6.6, 5.7 Hz, 2 H), 3.64 (t, *J* = 5.7 Hz, 2 H), 4.47 (br s, NH, 1 H), 6.17 (d, *J* = 8.1 Hz, 1 H), 6.43 (d, *J* = 8.0 Hz, 1 H), 7.33 (t, *J* = 8.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.01, 19.1, 24.58, 26.21, 26.31, 30.49, 42.56, 62.96, 102.42, 112.17, 137.98, 157.04, 158.67. HRMS $C_{16}H_{30}N_2OSi$ calcd for $[M + H]^+$, 295.2206; found, 295.2209.

Deprotection of **16b'** was performed as for **15a'** to give the title compound in 91% yield, as a yellow oil. R*f* (DCM/*i*-PrOH 9:1) = 0.5. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (m, 4 H), 2.35 (s, 3 H), 3.24 (m, 2 H), 3.68 (t + br s, *J* = 5.7 Hz, 2 H + OH), 4.77 (br s, NH, 1 H), 6.18 (d, *J* = 7.8 Hz, 1 H), 6.41 (d, *J* = 7.8 Hz, 1 H), 7.3 (t, *J* = 7.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 26.45, 30.14, 42.23, 61.98, 102.84, 112.13, 138.28, 156.74, 158.67. MS (APCI) *m/z* 181 $[M + H]^+$, 163, 109 ($C_{10}H_{16}N_2O$).

Synthesis of *t*-butyl *N*-(3-hydroxypropyl)-*N*-(4-methyl-pyridin-2-yl)-carbamate (17a).

To a mixture of **15a'** (0.5 g, 1.78 mmol) and DMAP (0.022 g, 0.178 mmol) in DCM (5 mL) was added Boc_2O (0.855 g, 3.92 mmol) in one portion. The solution was stirred for 8 h at 20 °C under Ar atmosphere. Concentration under vacuum and chromatography on silica gel gave **17a'** (silyl ether) as a yellow oil (0.57 g, 84%). R*f* (DCM/*i*-PrOH 98:2) = 0.8. IR 2930, 1708, 1580, 1460, 1390, 1367, 1161, 1099 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6 H), 0.86 (s, 9 H), 1.5 (s, 9 H), 1.83 (m, 2 H), 2.33 (s, 3 H), 3.64 (t, *J* = 6.2 Hz, 2 H), 3.98 (t, *J* = 7.2 Hz, 2 H), 6.83 (d, *J* = 4.8

Hz, 1 H), 6.39 (s, 1 H), 8.22 (d, *J* = 4.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.07, 18.5, 21.29, 26.12, 28.55, 32.48, 44.58, 61.3, 80.87, 120.93, 121.07, 147.55, 148.23, 154.53, 155.03. MS (APCI) *m/z* 381 $[M + H]^+$, 325, 281, 149 ($C_{20}H_{36}N_2O_3Si$).

The *O*-protected precursor **17a'** (0.469 g, 1.23 mmol) in THF (5 mL) was treated with 1 N TBAF solution in THF (1.9 mL, 1.9 mmol) added dropwise with a syringe. The mixture was stirred for 3 h at 20 °C, then concentrated under vacuum. The oily residue was dissolved in EtOAc (10 mL), washed with water (2 x 5 mL), brine (1 x 5 mL), dried ($MgSO_4$) and concentrated. Chromatography on silica gel furnished quantitatively **17a** (0.329 g) as a pale yellow oil. R*f* (DCM/*i*-PrOH 97:3) = 0.65. IR 3417, 2931, 1705, 1458, 1390, 1367, 1159 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9 H), 1.92 (m, 2 H), 2.35 (s, 3 H), 3.66 (t, *J* = 5.8 Hz, 2 H), 3.94 (t, *J* = 5.7 Hz, 2 H), 5.68 (br s, OH, 1 H), 6.85 (d, *J* = 4.8 Hz, 1 H), 7.5 (s, 1 H), 8.16 (d, *J* = 4.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 28.46, 31.6, 44.66, 57.98, 81.57, 120.18, 120.97, 146.67, 149.09, 154.28, 155.64. MS (APCI) *m/z* 267 $[M + H]^+$, 211, 167. RN: 939770-06-6 ($C_{14}H_{22}N_2O_3$).

Synthesis of *t*-butyl *N*-(4-hydroxybutyl)-*N*-(4-methyl-pyridin-2-yl)-carbamate (17b).

The procedure described for **17a** was applied starting from **15b'** (0.361 g, 1.23 mmol). Intermediate **17b'** (silyl ether) was obtained (0.441 g, 91%) as a colorless oil. R*f* (*n*-Hex/EtOAc 9:1) = 0.8. IR 2930, 1708, 1604, 1390, 1277, 1276, 1253, 1163, 1119 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.016 (s, 6 H), 0.86 (s, 9 H), 1.5 (s, 9 H), 1.42-1.63 (m, 4 H), 2.33 (s, 3 H), 3.59 (t, *J* = 6.3 Hz, 2 H), 3.92 (t, *J* = 6.7 Hz, 2 H), 6.83 (d, *J* = 4.8 Hz, 1 H), 6.39 (s, 1 H), 8.22 (d, *J* = 4.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.07, 18.5, 21.34, 25.61, 26.16, 28.55, 30.41, 46.98, 62.78, 80.88, 121.06, 121.11, 147.5, 148.34, 154.56, 154.9. HRMS $C_{21}H_{38}N_2O_3Si$ calcd for $[M + Na]^+$, 417.2549; found, 417.2547.

Deprotection with TBAF as above gave quantitatively **17b** (0.270 g from 0.381 g of **17b'**, 0.97 mmol) as a pale yellow oil. R*f* (DCM/*i*-PrOH 97:3) = 0.60. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.5 (s, 9 H), 1.57 (m, 2 H), 1.71 (m, 2 H), 2.32 (s, 3 H), 3.5 (br s, OH, 1 H), 3.63 (t, *J* = 6.3 Hz, 2 H), 3.91 (t, *J* = 7.3 Hz, 2 H), 6.84 (d, *J* = 4.8 Hz, 1 H), 7.46 (s, 1 H), 8.2 (d, *J* = 4.8 Hz, 1 H). ^{13}C NMR (75

MHz, $CDCl_3$) δ 21.43, 25.29, 28.54, 29.46, 46.48, 62.43, 81.27, 120.56, 121.06, 147.13, 148.85, 154.41, 154.71. HRMS $C_{15}H_{24}N_2O_3$ calcd for $[M + Na]^+$, 303.1685; found, 303.1690.

Synthesis of *t*-butyl *N*-(3-hydroxypropyl)-*N*-(6-methyl-pyridin-2-yl)-carbamate (18a).

The procedure described for **17a** was applied starting from **16a'** (0.5 g, 1.78 mmol). Intermediate **18a'** (silyl ether) was obtained (0.413 g, 61%) as a yellow oil. R*f* (DCM) = 0.5. IR 2954, 2929, 2856, 1708, 1604, 1390, 1168, 1097 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0 (s, 6 H), 0.86 (s, 9 H), 1.49 (s, 9 H), 1.84 (m, 2 H), 2.47 (s, 3 H), 3.64 (t, *J* = 6.9 Hz, 2 H), 3.98 (t, *J* = 6.6 Hz, 2 H), 6.86 (d, *J* = 6.6 Hz, 1 H), 7.29 (d, *J* = 7.5 Hz, 1 H), 7.5 (dd, *J* = 6.6, 7.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.18, 19, 24.48, 26.1, 28.53, 32.46, 44.62, 61.3, 80.77, 117.43, 119.13, 137.26, 154.2, 154.5, 156.9. MS (APCI) *m/z* 381 $[M + H]^+$, 325, 281 ($C_{20}H_{36}N_2O_3Si$).

Deprotection with TBAF as above gave **18a** (0.195 g from 0.297 g of **18a'**, 94%) as a pale yellow oil. R*f* (DCM/*i*-PrOH 97:3) = 0.60. IR 3417, 2931, 1705, 1458, 1390, 1367, 1159 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (s, 9 H), 1.92 (m, 2 H), 2.49 (s, 3 H), 3.68 (m, 2 H), 3.94 (t, *J* = 5.9 Hz, 2 H), 5.8 (br s, OH, 1 H), 6.87 (d, *J* = 6.6 Hz, 1 H), 7.42 (d, *J* = 7.5 Hz, 1 H), 7.54 (dd, *J* = 6.6, 7.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.82, 28.5, 31.49, 44.78, 57.97, 81.61, 116.82, 119.14, 137.96, 154.31, 155.15, 156.43. MS (APCI) *m/z* 267 $[M + H]^+$, 211, 167 ($C_{14}H_{22}N_2O_3$).

Synthesis of *t*-butyl N-(4-hydroxypropyl)-N-(6-methyl-pyridin-2-yl)-carbamate (18b).

The procedure described for **17a** was applied starting from **16b'** (0.585 g, 1.99 mmol). Intermediate **18b'** (silyl ether) was obtained (0.7 g, 89%) as a colorless oil. R*f* (*n*-Hex/EtOAc 1:1) = 0.7. IR 1707, 1635, 1458, 1389, 1367, 1159 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6 H), 0.86 (s, 9 H), 1.5 (s, 9 H), 1.42-1.66 (m, 4 H), 2.48 (s, 3 H), 3.59 (t, *J* = 6.3 Hz, 2 H), 3.92 (t, *J* = 6.7 Hz, 2 H), 6.85 (d, *J* = 7.8 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.5 (d, *J* = 7.8, 8.4 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.09, 18.5, 24.48, 25.03, 25.56, 28.53, 30.45, 46.98, 63.13, 80.72, 117.57, 119.13, 137.27, 154.2, 154.3, 156.88. HRMS $C_{21}H_{38}N_2O_3$ calcd for $[M + Na]^+$, 417.2549; found, 417.2551.

Deprotection with TBAF as above gave **18b** (0.420 g from 0.6 g of **18b'**, 98%) as a pale yellow oil. R*f* (EtOAc/*i*-PrOH 98:2) = 0.8. IR 3417, 2931, 1705, 1458, 1390, 1367, 1159 cm^{-1}. ^1H NMR (300

MHz, $CDCl_3$) δ 1.49 (s, 9 H), 1.61-1.73 (m, 4 H), 2.48 (s, 3 H), 2.54 (br s, OH, 1 H), 3.67 (m, 2 H), 3.92 (t, *J* = 7.2 Hz, 2 H), 6.87 (d, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 8.7 Hz, 1 H), 7.51 (dd, *J* = 7.6, 8.7 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.29, 25.15, 28.45, 29.59, 46.66, 62.23, 80.88, 117.36, 119.22, 137.32, 153.9, 154.26, 156.7. HRMS $C_{15}H_{24}N_2O_3$ calcd for $[M + Na]^+$, 303.1685; found, 303.1679.

Synthesis of 3-(1,8-naphthyridin-2-yl)-propan-1-ol (19a).

A mixture of 2-amino-3-pyridine carboxaldehyde (0.486 g, 4.1 mmol), 3-acetyl-1-propanol (0.415 mL, 4.1 mmol) and (L)-proline (0.249 g, 2.11 mmol) in EtOH (15 mL) was refluxed for 24 h. After cooling, H_2O (5 mL) and 1 N NaOH (5 mL) were added. The crude solution was extracted with DMC (3 x 10 mL). The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. Chromatography on silica gel gave **19a** (0.26 g, 33%) as a red oil. R*f* (DCM/*i*-PrOH 9:1) = 0.57. IR 3392, 2934, 2866, 1609, 1556, 1499, 1060 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15 (m, 2 H), 3.17 (t, *J* = 7.5 Hz, 2 H), 3.5 (br m, OH, 1 H), 3.76 (t, *J* = 6.1 Hz, 2 H), 7.39 (d, *J* = 8.1 Hz, 1 H), 7.41 (m, 1 H), 8.07 (d, *J* = 8.1 Hz, 1 H), 8.12 (dd, *J* = 8.1, 1.8 Hz, 1 H), 9.03 (dd, *J* = 4.4, 1.8 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.31, 35.63, 61.77, 120.85, 121.38, 122.64, 136.6, 137.08, 153.15, 155.36, 166.11. MS (APCI) *m/z* 189 $[M + H]^+$, 171. RN: 870089-46-6 ($C_{11}H_{12}N_2O$).

Synthesis of 4-(1,8-naphthyridin-2-yl)-butan-1-ol (19b).

A mixture of 2-amino-3-pyridine carboxaldehyde (1 g, 8.43 mmol), ethyl 5-oxo-hexanoate (1.35 mL, 8.43 mmol) and (L)-proline (0.48 g, 4.2 mmol) in EtOH (20 mL) was refluxed for 18 h. Concentration and chromatography gave **19b'** intermediate (ethyl ester) as a yellow solid (1.24 g, 60%). R*f* (DCM/EtOAc 8:2) = 0.27. IR 2980, 1731, 1610, 1556, 1500 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3 H), 2.24 (m, 2 H), 2.42 (t, *J* = 7.6 Hz, 2 H), 3.09 (t, *J* = 7.6 Hz, 2 H), 4.1 (q, *J* = 7.2 Hz, 2 H), 7.39 (d, *J* = 8.1 Hz, 1 H), 7.43 (dd, *J* = 8.1, 4 Hz, 1 H), 8.09 (d, *J* = 8.1 Hz, 1 H), 8.14 (dd, *J* = 8.1, 1.9 Hz, 1 H), 9.06 (dd, *J* = 4, 1.9 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.08, 24.11, 38.08, 33.61, 60.14, 120.94, 121.37, 122.45, 136.57, 136.93, 153.2, 155.82, 165.48, 173.25. MS (APCI) *m/z* 245 $[M + H]^+$, 199, 171. RN: 193818-28-9 ($C_{14}H_{16}N_2O_2$).

A solution of **19b'** (0.5 g, 2.04 mmol) in THF (2 mL) was treated with 1 N $LiAlH_4$ in THF (4.1 mL, 4.1 mmol), by dropwise addition at -78 °C under Ar atmosphere. The mixture was stirred for 1 h at -78 °C and 2 h at 20 °C. After concentration, DCM was added (10 mL) and the organic phase was washed with 1 N NaOH (5 mL) and brine (5 mL). Drying ($MgSO_4$), concentration and chromatography afforded **19b** (0.228 g, 55%) as a pale yellow oil. R*f* (DCM/*i*-PrOH 9:1) = 0.7. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.68 (m, 2 H), 1.96 (m, 2 H), 2.75 (br m, OH, 1 H), 3.06 (t, *J* = 7.5 Hz, 2 H), 3.69 (t, *J* = 6.3 Hz, 2 H), 7.33 (d, *J* = 8.3 Hz, 1 H), 7.45 (m, 1 H), 8.1 (d, *J* = 8.3 Hz, 1 H), 8.15 (dd, *J* = 7.9, 1.9 Hz, 1 H), 9.04 (dd, *J* = 4, 1.9 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.36, 32.55, 38.76, 62.44, 121.39, 121.82, 123.02, 137.13, 137.44, 153.6, 156.07, 166.85. MS (APCI) *m/z* 203 $[M + H]^+$, 185 ($C_{12}H_{14}N_2O$).

Synthesis of 4-(2-methyl-[1,3]-dioxolan-2-yl)-butan-1-ol (21).

A mixture of ethyl 5-oxo-hexanoate (10.1 mL, 63 mmol), ethylene glycol (5.23 mL, 94 mmol) and *p*-toluenesulfonic acid (0.2 g, 1.08 mmol) in benzene (80 mL) was refluxed in a flask equipped with a Dean-Stark trap, during 18 h under vigorous stirring. The solution was washed with 10% $NaHCO_3$ (20 mL) and water (20 mL). Drying ($MgSO_4$), concentration and distillation of the residue (pale green oil) under reduced pressure gave **21'** (ethyl ester intermediate) as a colorless oil (8.32 g, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.5 Hz, 3 H), 1.32 (s, 3 H), 1.67-1.74 (m, 4 H), 2.32 (t, *J* = 7.5 Hz, 2 H), 3.94 (sharp m, 4 H), 4.12 (q, *J* = 7.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.35, 19.64, 23.82, 34.35, 38.41, 60.25, 64.7, 109.77, 173.52. MS (APCI) *m/z* 203 $[M + H]^+$, 157. RN: 944-27-4 ($C_{10}H_{18}O_4$).

A solution of ester **21'** (1 g, 4.9 mmol) in ether (2.5 mL) was added dropwise during 30 min to a cooled solution (ice-bath) of 1 N $LiAlH_4$ in ether (5.4 mL, 5.4 mmol) under Ar atmosphere and vigorous stirring. The mixture was further stirred for 15 min at 0 °C and 2 h at 20 °C. After careful addition of brine (20 mL) and EtOAc (20 mL), the organic layer was recovered, washed with brine (5 mL), dried ($MgSO_4$) and concentrated under vacuum to furnish **21** (0.726 g, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3 H), 1.47-1.7 (m, 6 H), 2.0 (br m, OH, 1 H), 3.65 (t, *J* =

6.6 Hz, 2 H), 3.94 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.37, 23.89, 32.94, 38.97, 62.76, 64.77, 110.22. MS (CI/CH_4-N_2O) *m/z* 161 $[M + H]^+$, 99. RN: 5745-75-5 ($C_8H_{16}O_3$).

Synthesis of *N*-(phthalimido)-3-amino-1-propanol (22).

Potassium phthalimide (1 g, 5.4 mmol) was dissolved in DMF (10 mL) by heating at 90 °C, under stirring (Ar atmosphere). 1-Iodo-3-propanol (0.62 mL, 6.5 mmol) was added dropwise with a syringe and the mixture was stirred for 18 h at 90 °C. After addition of water (50 mL), the solution was extracted with DCM (3 x 15 mL). Drying ($MgSO_4$), concentration and chromatography gave **22** (1.47 g, 67%) as a white solid. R*f* (*n*-Hex/EtOAc 6:4) = 0.43. IR 3454, 1706, 1051 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (m, 2 H), 2.70 (br m, OH, 1 H), 3.64 (t, *J* = 5.7 Hz, 2 H), 3.86 (t, *J* = 6.6 Hz, 2 H), 7.74 (m, 2 H), 7.85 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.5, 34.5, 59.24, 123.6, 132.15, 134.3, 169.1. MS (ESI) *m/z* 228 $[M + Na]^+$, 206 $[M + H]^+$, 188. RN: 883-44-3 ($C_{11}H_{11}NO_3$).

Synthesis of 2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azohexadecan-16-oic acid (23a).

2-(2-(2-Azidoethoxy)ethoxy)ethanol.

2-(Chloroethoxy)ethoxy-ethanol (10 g, 60 mmol) in water (60 mL) was treated with NaN_3 (10 g, 600 mmol) and NaI (1.8 g, 12 mmol) at 50 °C for 48 h under vigorous stirring. Extraction with EtOAc (3 x 30 mL), washing the organic phase with brine (10 mL), drying ($MgSO_4$) and concentration under reduced pressure gave 2-(azidoethoxy)ethoxy-ethanol as a yellow oil (7.46 g, 71%). IR 3428, 2936, 2868, 2107, 1298, 1120, 1067 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.16 (br s, OH, 1 H), 3.41 (t, *J* = 5.8 Hz, 2 H), 3.62-3.77 (m, 10 H). RN: 86520-52-7 ($C_6H_{13}N_3O_3$).

2-(2-(2-Aminoethoxy)ethoxy)ethanol.

10% Pd/C (0.1 g) in EtOAc (5 mL) was placed under H_2 atmosphere (1 atm) and stirred for 2 h. The azide solution (0.985 g, 5.63 mmol in EtOAc, 1 mL) was added dropwise and the mixture was vigorously stirred under H_2 atmosphere for 18 h at 20 °C. Filtration on celite and concentration furnished crude amine (0.678 g, 81%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 2.3 (br s, OH + NH_2, 3 H), 2.9 (m, 2 H), 3.56-3.76 (m, 10 H). RN: 6338-55-2 ($C_6H_{15}NO_3$).

t-Butyl N-2-(2-(2-hydroxyethoxy)ethoxy)ethyl carbamate.

Amine precursor (0.971 g, 5.7 mmol) in EtOAc (5 mL) was treated with Boc_2O (1.489 g, 6.8 mmol) for 18 h at 20 °C under stirring. After washing with water (5 mL), brine (5 mL), drying ($MgSO_4$) and concentration, the residue was purified by chromatography on silica gel to furnish the carbamate (0.959 g, 69%) as a yellow oil. R*f* (EtOAc) = 0.4. IR 3361, 2913, 2871, 2108, 1706, 1284, 1251, 1170, 1120 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 2.38 (br s, OH, 1 H), 3.23 (m, 2 H), 3.57 (t, *J* = 4.8 Hz, 2 H), 3.6-3.7 (m, 6 H), 3.76 (t, *J* = 4.8 Hz, 2 H), 5.11 (br s, NHBoc, 1 H). RN: 139115-92-7 ($C_{11}H_{23}NO_5$).

Methyl 2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azahexadecan-16-oate.

The previous compound (0.45 g, 1.8 mmol) in dry THF (10 mL) was treated with 1 N *t*-BuOK in THF (3.6 mL, 3.6 mmol) at 0 °C, under Ar atmosphere, by dropwise addition with a syringe. After 30 min at 0 °C, methyl bromoacetate (0.2 mL, 2.17 mmol) was added with a syringe over 10 min. The mixture was stirred for 3 h at 0 °C and 15 h at 20 °C. Concentration and chromatography gave the ester (0.475 g, 82%) as a colorless oil. R*f* (EtOAc/*n*-Hex 7:3) = 0.47. IR 2929, 1755, 1712, 1519, 1450 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 3.31 (m, 2 H), 3.56 (t, *J* = 5.7 Hz, 2 H), 3.6-3.8 (m + s, 8 H + 3 H), 4.19 (s, 2 H), 5.1 (br s, NH, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 40.54, 51.98, 68.78, 70.37-71.09, 79.33, 156.21, 171.07. HRMS $C_{14}H_{27}NO_7$ calcd for $[M + Na]^+$, 344.1685; found, 344.1695.

*Title compound (**23a**).*

The ester precursor (0.69 g, 2.15 mmol) in acetonitrile (5 mL) was treated with 1 N LiOH (5 mL), by dropwise addition with a syringe over 20 min at 20 °C. The mixture was diluted with water (5 mL) and the pH adjusted to 3 by addition of 10% HCl. Extraction with EtOAc (3 x 7 mL), drying ($MgSO_4$) and concentration gave **23a** (0.532 g, 80%) as a yellow oil. IR 3362, 2930, 1712, 1531, 1122 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 3.31 (m, 2 H), 3.55 (t, *J* = 5.5 Hz, 2 H), 3.5-3.8 (m, 8 H), 4.19 (s, 2 H), 5.20 (br m, NHBoc, 1 H), 11.5 (br m, CO_2H, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 40.53, 68.5-71.05, 79.55, 156.37, 173.5. MS (ESI) *m/z* 346 $[M + K]^+$, 330 $[M + Na]^+$, 308 $[M + H]^+$, 252, 208. RN: 462100-06-7 ($C_{13}H_{25}NO_7$).

Synthesis of 2-(2-(2-(2-(2-(2-*t*-butoxycarbonylaminoethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxy)-ethoxy-acetic acid (23b).

2,2-Dimethyl-4-oxo-3,8,11-trioxa-5-azatridecane-13-yl-methane sulfonate.

2-(2-(2-*t*-Butoxycarbonyl-aminoethoxy)ethoxy-ethanol (5.26 g, 0.0211 mmol), tetramethylammonium chloride (0.296 g, 2.7 mmol) and Et_3N (6 mL, 0.0422 mmol) were dissolved in dry DCM (10 mL) and cooled at 0 °C. A solution of mesyl chloride (1.96 mL, 25.3 mmol) in DCM (10 mL) was added dropwise with a syringe over 40 min. The mixture was stirred for 1 h at 0 °C and 3 h at 20 °C. Evaporation under vacuum gave an oily residue which was dissolved in EtOAc

(40 mL), washed with 5% NH_4Cl (2 x 5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated. Chromatography on silica gel gave the mesylate (6.08 g, 88%) as a colorless oil. R*f* (ether) = 0.4. IR 2935, 1704, 1518, 1352, 1175, 1108 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 3.07 (s, 3 H), 3.3 (m, 2 H), 3.53 (t, *J* = 4.8 Hz, 2 H), 3.61-3.8 (m, 6 H), 4.38 (m, 2 H), 4.94 (br s, NH, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 37.9, 40.5, 69.1, 69.2-70.9, 156.1, (*C*Me_3 not visible). HRMS $C_{12}H_{25}NO_7$ calcd for $[M + Na]^+$, 344.1249; found, 344.1248. RN: 430430-57-2.

t-Butyl 17-hydroxyl-3,6,9,12,15-pentaoxaheptadecylcarbamate.

A mixture of triethyleneglycol (2.5 mL, 18.8 mmol) and 50% aqueous NaOH (1.14 mL) was heated at 100 °C for 1 h under vigorous stirring. Mesylate (3.08 g, 9.5 mmol) in toluene (3 mL) was added dropwise with a syringe over 30 min. The mixture was stirred at 100 °C for 18 h, then concentrated under vacuum. The residue was diluted in brine (5 mL) and extracted with EtOAc (3 x 10 mL). The organic phase was washed with water (2 x 5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated to furnish the coupling product (1.87 g, 52%) as a pale orange oil. R*f* (EtOAc/acetone 1:1) = 0.55. IR 3353, 2872, 1693, 1519, 1365, 1278, 1251, 1172, 1105 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 2.76 (br s, OH, 1 H), 3.32 (m, 2 H), 3.54 (t, *J* = 5 Hz, 2 H), 3.63-3.67 (m, 18 H), 3.73 (t, *J* = 4 Hz, 2 H), 5.16 (br s, NH, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.43, 40.36, 61.71, 70.23-70.57, 72.56, 156.04, (*C*Me_3 not visible). MS (ESI) *m/z* 404 $[M + Na]^+$. RN: 331242-61-6 ($C_{17}H_{35}NO_8$).

Ethyl 2-(2-(2-(2-(2-(2-t-butyloxycarbonylaminoethoxy)- ethoxy)- ethoxy)- ethoxy)- ethoxy)- acetate.

The previous compound (1.81 g, 4.74 mmol) in DCM (10 mL) was treated successively with ethyl diazoacetate (0.498 mL, 4.74 mmol) and BF_3.ether (0.06 mL, 0.0474 mmol) added dropwise with a syringe, at 0 °C under Ar atmosphere. The mixture was stirred for 30 min at 0 °C and 2 h at 20 °C. After concentration under vacuum, the residue was dissolved in EtOAc (10 mL), washed with water (2 x 3 mL) and brine (5 mL), dried ($MgSO_4$), concentrated and chromatographied on silica gel to afford the ester precursor (0.798 g, 36%) as an orange oil. R*f* (EtOAc/acetone 9:1) = 0.5. IR 2870, 2104, 1751, 1121 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3 H), 1.44 (s, 9 H), 3.3

(m, 2 H), 3.54 (t, *J* = 5.2 Hz, 2 H), 3.6-3.75 (m, 20 H), 4.15 (s, 2 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 5.06 (br s, NHBoc, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 28.64, 40.58, 61, 68.93, 70.45-71.1, 170.68, (CO_2CMe_3 not visible). MS (APCI) *m/z* 468 $[M + H]^+$ ($C_{21}H_{41}NO_{10}$).

*Title compound (**23b**).*

A solution of ester (0.798 g, 1.71 mmol) in CH_3CN (2 mL) was treated with 1 N aqueous LiOH (3.4 mL, 3.4 mmol) for 2 h at 20 °C. The mixture was concentrated and the pH adjusted to 3 with 1 N HCl. The aqueous phase was extracted with EtOAc (2 x 10 mL). The organic phase was washed with brine (5 mL), dried ($MgSO_4$) and concentrated to furnish **23b** (0.736 g, 97%) as a pale yellow oil. IR 3362, 2930, 1712, 1531, 1122 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 3.31 (br m, 2 H), 3.54 (t, *J* = 5 Hz, 2 H), 3.62-3.8 (m, 20 H), 4.17 (s, 2 H), 5.16 (br s, NHBoc, 1 H), 12 (br m, CO_2H, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 40.51, 69.06, 70.38-71.25, 172.44, (CO_2CMe_3 not visible). MS (ESI) *m/z* 438 $[M - H]^-$, 364, 338. RN: 391684-36-9 ($C_{19}H_{37}NO_{10}$).

Synthesis of 2-(2-(2-methoxy-ethoxy)-ethoxy)-ethoxy)-acetic acid (24).

Methyl 2,5,8,11-tetraoxatridecan-13-oate.

Triethylene glycol monomethyl ether (5 g, 30 mmol) in dry THF (5 mL) was treated, at 0 °C under Ar atmosphere, with 1 N *t*-BuOK in THF (30 mL, 30 mmol), by dropwise addition during 15 min. Methyl bromoacetate (2.76 mL, 30 mmol) was added dropwise with a syringe at 0 °C. The mixture was stirred for 18 h at 20 °C, then filtered on a celite pad. The filtrate was concentrated, and the residue purified by chromatography on silica gel to give the methyl ester (2.63 g, 46%) as a yellow oil. R*f* (EtOAc/acetone 8:2) = 0.6. IR 2878, 1755, 1454, 1111 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38 (s, 3 H), 3.55 (m, 2 H), 3.6-3.7 (m, 10 H), 3.75 (s, 3 H), 4.17 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.96, 59.23, 68.85, 70.7-71.1, 72.14, 171.07. HRMS $C_{10}H_{20}O_6$ calcd for $[M + Na]^+$, 259.1158; found, 259.1163.

*Title compound (**24**).*

1 N aqueous LiOH (20 mL, 20 mmol) was added dropwise to a solution of the previous ester (2.6 g, 11 mmol) in CH_3CN (5 mL), at 20 °C under stirring. After 20 min, the mixture was diluted with

water (5 mL) and the pH adjusted to 3 with 10% HCl. The aqueous phase was extracted with EtOAc (3 x 10 mL). The organic phase was dried and concentrated to furnish acid **24** (0.756 g, 31%) as a yellow oil. IR 3447, 2881, 1732, 1456, 1109 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (s, 3 H), 3.58 (m, 2 H), 3.6-3.7 (m, 8 H), 3.77 (m, 2 H), 4.17 (s, 2 H), 10 (br m, CO_2H, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 59.16, 69.16, 70.5-70.9, 71.7, 72.16, 173.5. HRMS $C_9H_{18}O_6$ calcd for $[M + Na]^+$, 245.1001; found, 245.1007. RN: 16024-60-5.

IV. Synthesis of compounds cited in Tables 1, 2, 3 and 4 (see Scheme 1 of the main text)

General procedure for coupling alcohols to key-intermediate 1 (Table 1).

Tyrosine scaffold **1** (0.5 g, 1.02 mmol, 1 equiv.) and alcohol (from Scheme 2, 1.12 mmol, 1.1 equiv.) were dissolved in dry THF (4 mL) under argon atmosphere, and cooled at 0 °C. Ph_3P (0.4 g, 1.53 mmol, 1.5 equiv.) and then DIAD (0.3 mL, 1.43 mmol, 1.4 equiv.) were added dropwise. The stirred mixture was allowed to reach slowly room temperature and further left for 1 to 12 h at 20 °C. Concentration under vacuum and flash chromatography on silica gel gave the coupled product **2** of Table 1.

(S)-*t*-Butyl 3-(4-(4-*t*-butoxycarbonylamino-butoxy)-3-nitro-phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propionate (2b). The title compound was obtained from **10b** (0.212 g, 1.12 mmol) as a yellow oil (0.43 g, 64%). R*f* (DCM/EtOAc 9:1) = 0.8. IR 3403, 3272, 2979, 1694, 1533, 1367, 1327, 1262, 1165, 1105 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 9 H), 1.44 (s, 9 H), 1.70 (m, 2 H), 1.87 (m, 2 H), 3.03 (m, 2 H), 3.20 (m, 2 H), 4.09 (m, 3 H), 4.64 (br s, 1 H), 5.27 (d, *J* = 8.7 Hz, 1 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 7.38 (dd, *J* = 8.7, 1.8 Hz, 1 H), 7.6 (m, 2 H), 7.81 (d, *J* = 7.5 Hz, 1 H), 7.98 (d, *J* = 8.7 Hz, 1 H), 8.05 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.4, 26.8, 27.59, 28.29, 29.03, 38.01, 38.02, 56.73, 67.85, 79.06, 83.82, 114.39, 122.89 (*C*F_3), 124.09, 126.58, 127.54, 129.36, 129.85, 130.37, 131.68, 135.61, 139.09, 140.79, 151.45, 156.08, 169.01. MS (ESI) *m/z* 684 $[M + Na]^+$ for $C_{29}H_{38}F_3N_3O_9S$.

(S)-*t*-Butyl 3-(3-nitro-4-(3-(pyrimidin-2-ylamino)propoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (2c). The title compound was obtained from **13a** (0.141 g, 0.92 mmol) as a pale yellow oil (0.122 g, 22%). R*f* (DCM/EtOAc 6:4) = 0.37. IR 2977 1730 1531 1327 1153 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 9 H), 2.14 (m, 2 H), 2.99 (m, 1 H), 3.07 (m, 1 H), 3.64 (m, 2 H), 4.11 (m, 1 H), 4.15 (t, *J* = 5.3 Hz, 2 H), 5.72 (br t, NH, 1 H), 6.07 (d, *J* = 6.5 Hz, $NHSO_2$, 1 H), 6.5 (t, *J* = 4.8 Hz, 1 H), 6.92 (d, *J* = 8.6 Hz, 1 H), 7.35 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.58 (d, *J* = 2.2 Hz, 1 H), 7.61 (t, *J* = 7.8 Hz, 1 H), 7.79 (d, *J* = 7.8 Hz, 1 H), 7.97

(d, *J* = 7.8 Hz, 1 H), 8.04 (s, 1 H), 8.26 (d, *J* = 4.8 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.55, 28.58, 38.02, 38.19, 56.74, 67.29, 83.68, 110.43, 114.38, 124.1, 126.5, 127.37, 129.26, 129.79, 130.36, 131.6, 135.59, 139.01, 140.94, 151.57, 157.94, 162.25, 169.15, (*C*F_3 not visible). MS (ESI) *m/z* 626 $[M + H]^+$, 570 $[M - t\text{Bu}]^+$. HRMS $C_{27}H_{30}F_3N_5O_7S$ calcd for $[M + H]^+$, 626.1896; found, 626.1906.

(S)-*t*-Butyl 3-(3-nitro-4-(4-(pyrimidin-2-ylamino)butoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (2d). The title compound was obtained from **13b** (0.136 g, 0.82 mmol) as a yellow gum (0.32 g, 61%). R*f* (EtOAc) = 0.7. IR 2938, 1726, 1591, 1531, 1327, 1157 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 9 H), 1.81 (m, 2 H), 1.9 (m, 2 H), 2.99 (m, 1 H), 3.07 (m, 1 H), 3.47 (m, 2 H), 4.08 (t, *J* = 5.5 Hz, 2 H), 4.13 (m, 1 H), 5.46 (br t, NH, 1 H), 6.23 (br d, SO_2NH, 1 H), 6.5 (t, *J* = 4.8 Hz, 1 H), 6.92 (d, *J* = 8.6 Hz, 1 H), 7.35 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.56 (d, *J* = 2.2 Hz, 1 H), 7.61 (t, *J* = 7.8 Hz, 1 H), 7.79 (d, *J* = 7.8 Hz, 1 H), 7.97 (d, *J* = 7.8 Hz, 1 H), 8.04 (s, 1 H), 8.26 (d, *J* = 4.8 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.55, 25.9, 26.18, 38.03, 40.71, 56.73, 69.07, 83.63, 110.28, 114.38, 124.08, 126.41, 127.18, 129.24, 129.76, 130.34, 131.55, 135.44, 139.08, 140.95, 151.54, 157.92, 162.17, 169.23, (*C*F_3 not visible). MS (ESI) *m/z* 638.17 (M – 1), 582.1, 536.1, 209.1, HRMS $C_{28}H_{32}F_3N_5O_7S$ calcd for $[M + H]^+$, 640.2053; found, 640.2065.

(S)-2-(3-(4-(3-*t*-Butoxy-3-oxo-2-(3-(trifluoromethyl)phenylsulfonamido)propyl)-2-nitrophenoxy)propylamino)pyridine 1-oxide (2e). The title compound was obtained from **14a** (0.137 g, 0.82 mmol) as a yellow powder (0.360 g, 69%). R*f* (DCM/*i*-PrOH 9:1) = 0.53. Mp = 185-186 °C. IR 2979, 1734, 1531, 1327, 1157 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 9 H), 2.18 (m, 2 H), 2.95 (m, 1 H), 3.05 (m, 1 H), 3.59 (m, 2 H), 4.06 (m, 1 H), 4.16 (t, *J* = 5.4 Hz, 2 H), 6.55 (br d, SO_2NH, 1 H), 6.54 (m, 1 H), 6.75 (dd, *J* = 8.5, 1.6 Hz, 1 H), 6.92 (d, *J* = 8.6 Hz, 1 H), 6.95 (t, *J* = 6.4 Hz, NH, 1 H), 7.2 (td, *J* = 7.9, 1.4 Hz, 1 H), 7.35 (dd, *J* = 8.5, 2.3 Hz, 1 H), 7.59 (t, *J* = 7.8 Hz, 1 H), 7.62 (d, *J* = 2.3 Hz, 1 H), 7.76 (d, *J* = 7.8 Hz, 1 H), 7.96 (d, *J* = 7.8 Hz, 1 H), 8.01 (s, 1 H), 8.12 (dd, *J* = 6.5, 1.2 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.56, 28.69, 37.82, 38.21,

56.85, 65.9, 83.34, 105.87, 111.38, 114.3, 123.05 (*C*F_3), 123.94, 126.59, 127.93, 129.01, 129.08, 129.71, 130.3, 131.45, 135.52, 137.33, 138.88, 141.23, 150.28, 151.16, 169.2. MS (APCI) *m/z* 639.2 (M – 1), 583.0, 537.1, 209.1. HRMS $C_{28}H_{31}F_3N_4O_8S$ calcd for $[M + H]^+$, 641.1893; found, 641.1891.

(S)-2-(4-(4-(3-*t*-Butoxy-3-oxo-2-(3-(trifluoromethyl)phenylsulfonamido)propyl)-2-nitrophenoxy)butylamino)pyridine-1-oxide (2f). The title compound was obtained from **14b** (0.150 g, 0.82 mmol) as a yellow powder (0.350 g, 65%). R*f* (DCM/*i*-PrOH 9:1) = 0.34. Mp = 180-181 °C. IR 2939, 1734, 1531, 1327, 1157 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 9 H), 1.95 (m, 4 H), 2.95(m, 1 H), 3.05 (m, 1 H), 3.38 (m, 2 H), 4.08 (m, 1 H), 4.12 (t, *J* = 5.5 Hz, 2 H), 6.53 (m, 1 H), 6.55 (br d, SO_2NH, 1 H), 6.64 (dd, *J* = 8.5, 1.6 Hz, 1 H), 6.85 (br t, NH, 1 H), 6.93 (d, *J* = 8.6 Hz, 1 H), 7.21 (m, 1 H), 7.36 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.6 (m, 2 H), 7.76 (d, *J* = 7.8 Hz, 1 H), 7.96 (d, *J* = 7.9 Hz, 1 H), 8.01 (s, 1 H), 8.16 (dd, *J* = 7.0, 1.4 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.56, 26.1, 27.57, 37.82, 41.61, 56.88, 68.88, 83.34, 105.74, 111.22, 114.32, 123.05 (*C*F_3), 123.93, 126.53, 127.7, 128.8, 129.07, 129.71, 130.31, 131.42, 135.5, 137.36, 139.08, 141.23, 150.16, 151.24, 169.19. MS (ESI) *m/z* 653 $[M – H]^-$, 209. HRMS $C_{29}H_{33}F_3N_4O_8S$ calcd for $[M + H]^+$, 655.2049; found, 655.2051.

(S)-*t*-Butyl 3-(4-(4-(*t*-butoxycarbonyl(6-methylpyridin-2-yl)amino)butoxy)-3-nitrophenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (2h). The title compound was obtained from **18b** (0.2 g, 0.714 mmol) as a pale yellow oil (0.350 g, 65%). R*f* (*n*Hex/EtOAc 6:4) = 0.57. IR 2978, 1701, 1533, 1327, 1161 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 9 H), 1.48 (s, 9 H), 1.83 (m, 4 H), 2.46 (s, 3 H), 2.99 (m, 1 H), 3.07 (m, 1 H), 3.97 (t, *J* = 6.4 Hz, 2H), 4.06 (m, 3 H), 5.26 (d, *J* = 6.5 Hz, SO_2NH,1 H), 6.87 (d, *J* = 7.8 Hz, 1 H), 6.93 (d, *J* = 8.6 Hz, 1 H), 7.31 (d, *J* = 8.7 Hz, 1 H), 7.35 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.51 (t, *J* = 7.8 Hz, 1 H), 7.55 (s, 1 H), 7.61 (t, *J* = 7.8 Hz, 1 H), 7.79 (d, *J* = 7.8 Hz, 1 H), 7.96 (d, *J* = 7.9 Hz, 1 H), 8.04 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.17, 25.25, 26.25, 27.55, 28.2, 37.98, 46.15, 56.68, 69.23, 80.68, 83.63, 114.38, 117.12, 118.94, 124.08,

124.7 (*C*F_3), 126.41, 127.18, 129.24, 129.76, 130.34, 131.55, 135.44, 137.11, 139.08, 140.95, 151.54, 153.7, 154.18, 156.62, 169.23. MS (APCI) *m/z* 753 $[M + H]^+$, 697, 641 for $C_{35}H_{43}F_3N_4O_9S$.

(S)-*t*-Butyl 3-(*N*(*N*,*N*'-di-*t*-butoxycarbonylguanidinyl)-4-aminobutoxy)-3-nitrophenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (2i). The title compound was obtained from **12b** (0.203 g, 0.612 mmol) as a pale yellow foam (0.486 g, 98%). R*f* (DCM/*i*-PrOH 98:2) = 0.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9 H), 1.5 (br s, 18 H), 1.81 (m, 2 H), 1.9 (m, 2 H), 2.95-3.1 (m, 2 H), 3.49 (m, 2 H), 4.11 (m, 3 H), 5.3 (br d, SO_2NH, 1 H), 6.97 (d, *J* = 8.6 Hz, 1 H), 7.38 (d, *J* = 8.6 Hz, 1 H), 7.59 (s, 1 H), 7.63 (t, *J* = 7.8 Hz, 1 H), 7.8 (d, *J* = 7.8 Hz, 1 H), 7.97 (d, *J* = 7.8 Hz, 1 H), 8.04 (s, 1 H), 8.38 (br s, NH, 1 H), 11.5 (br s, NHBoc, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 26.7, 27.9, 28.2, 28.4, 38.31, 41, 57, 67.92, 83.38, 83.6, 114.91, 124.4, 126.82, 127.82, 129.7, 130.2, 130.68, 131.71, 135.77, 139.46, 141.06, 153.4, 156.2, 156.57, 163, 169.23, (*C*F_3 not visible). MS (APCI) *m/z* 802 $[M - H]^-$ for $C_{35}H_{48}F_3N_5O_{11}S$.

(S)-*t*-Butyl 3-(4-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-3-nitrophenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (2j). The title compound was obtained from **22** (0.113 g, 0.61 mmol) as a pale yellow gum (0.217 g, 52%). R*f* (*n*Hex/EtOAc 6:4) = 0.3. IR 2979, 1712, 1533, 1327, 1159 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 9 H), 2.21 (m, 2 H), 2.99 (m, 1 H), 3.07 (m, 1 H), 3.93 (t, *J* = 6.5 Hz, 2 H), 4.06 (m, 1 H), 4.14 (t, *J* = 6 Hz, 2 H), 5.56 (d, *J* = 8.9 Hz, SO_2NH, 1 H), 6.96 (d, *J* = 8.6 Hz, 1 H), 7.37 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.58 (d, *J* = 2.2 Hz, 1 H), 7.63 (t, *J* = 7.9 Hz, 1 H), 7.69-7.74 (m, 2 H), 7.79-7.84 (m, 3 H), 7.96 (d, *J* = 7.9 Hz, 1 H), 8.04 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.83, 28.53, 35.26, 38.21, 57.07, 67.63, 83.91, 114.88, 123.43, 124.32, 126.74, 127.87, 129.65, 130.18, 130.64, 131.55, 132.22, 134.16, 135.75, 139.3, 141.1, 151.66, 168.56, 169.39, (*C*F_3 not visible). MS (APCI) *m/z* 677.8 (M + 1), 621.8. HRMS $C_{31}H_{30}F_3N_3O_9S$ calcd for $[M + Na]^+$, 700.1553; found, 700.1558.

(S)-*t*-Butyl 3-(4-(4-(2-methyl-1,3-dioxolan-2-yl)butoxy)-3-nitrophenyl) -2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (2l). The title compound was obtained from **21** (0.130 g, 0.816 mmol) as a pale yellow foam (0.450 g, 87%). R*f* (ether/*n*Hex 9:1) = 0.63. IR 2950,

1732, 1622, 1533, 1326, 1161 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9 H), 1.34 (s, 3 H), 1.6 (m, 2 H), 1.72 (m, 2 H), 1.85 (m, 2 H), 2.96 (m, 1 H), 3.07 (m, 1 H), 3.93 (m, 4 H), 4.07 (m, 3 H), 5.48 (d, *J* = 9 Hz, SO_2NH, 1 H), 6.95 (d, *J* = 8.6 Hz, 1 H), 7.37 (dd, *J* = 8.6, 2.2Hz, 1 H), 7.57 (d, *J* = 2.2 Hz, 1 H), 7.62 (t, *J* = 7.8 Hz, 1 H), 7.8 (d, *J* = 7.8 Hz, 1 H), 7.97 (d, *J* = 7.8 Hz, 1 H), 8.05 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.64, 24, 27.85, 29.21, 38.24, 38.86, 57.08, 64.88, 69.72, 83.98, 110.12, 114.7, 124.33, 126.62, 127.41, 129.65, 130.16, 130.66, 131.62, 135.66, 139.46, 141.07, 151.92, 169.4, (*C*F_3 not visible). MS (ESI) *m/z* 1262 $[M - H]^-$ x 2, 631 $[M - H]^-$. HRMS $C_{28}H_{35}F_3N_2O_9S$ calcd for $[M + Na]^+$, 655.1913; found, 655.1940.

(S)-*t*-Butyl 3-(4-(3-aminopropoxy)-3-nitrophenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (3a). To a solution of precursor **2j** (0.305 g, 0.45 mmol) in DCM (3 mL) and EtOH (12 mL) was added dropwise hydrazine (0.13 mL, 2.7 mmol) at 20 °C under Ar atmosphere. The mixture was heated 2 h at 80 °C. After addition of DCM (dissolution of the precipitate), and then hexane (until the solution becomes cloudy), the mixture was placed in the fridge (- 4 °C) for 4 h. Filtration, washing with ice-cold hexane, and concentration of the filtrate gave the title compound (0.181 g, 73%) as a yellow gum. R*f* (acetone/*i*-PrOH 9:1) = 0.3. IR 3375 (br), 2931, 1734, 1624, 1532, 1327, 1157 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 9 H), 1.98 (m, 2 H), 2.72 (br s, NH_2, 2 H), 2.97 (t, *J* = 6.6 Hz, 2 H), 3 (m, 1 H), 3.1 (m, 1 H), 4.08 (m, 1 H), 4.19 (t, *J* = 6Hz, 2 H), 5.60 (d, *J* = 9 Hz, $NHSO_2$, 1H), 7 (d, *J* = 8.6 Hz, 1 H), 7.38 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.59 (d, *J* = 2.2 Hz, 1 H), 7.63 (t, *J* = 7.8 Hz, 1 H), 7.8 (d, *J* = 7.8 Hz, 1 H), 7.98 (d, *J* = 7.8 Hz, 1 H), 8.04 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.54, 32.27, 37.93, 38.84, 56.74, 67.62, 83.64, 114.34, 124, 126.4, 127.31, 129.31, 129.82, 130.32, 131.55, 135.48, 139.05, 140.86, 151.56, 169.06, (*C*F_3 not visible). MS (APCI) *m/z* 548 $[M + H]^+$, 492. HRMS $C_{23}H_{28}F_3N_3O_7S$ calcd for $[M + H]^+$, 548.1678; found, 548.1659.

(S)-*t*-Butyl 3-(*N*(*N*,*N'*-di-*t*-butoxycarbonylguanidinyl)-3-aminopropoxy)-3-nitrophenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (3b). To a mixture of precursor **3a** (0.1 g, 0.183 mmol) and di(Boc)thiourea (0.06 g, 0.219 mmol) in DMF (0.1 mL) under Ar atmosphere, were

added successively Et_3N (0.056 mL, 0.403 mmol) and Mukaiyama salt (0.056 g, 0.219 mmol) dissolved in DMF (0.2 mL), dropwise with a syringe, under vigorous stirring. After 1 h at 20 °C, water (3 mL) was added and the solution was extracted with ether (3 x 3 mL). The organic phase was washed with brine (2 mL), dried ($MgSO_4$), concentrated under vacuum and the residue was chromatographied to furnish the title compound (0.097 g, 66%) as a pale yellow solid. R*f* (DCM/*i*-PrOH 98:2) = 0.35. Mp = 103-104 °C. IR 2987, 1722, 1622, 1533, 1327, 1157 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 9 H), 1.48 (s, 9 H), 1.5 (s, 9 H), 2.13 (m, 2 H), 3 (m, 1 H), 3.1 (m, 1 H), 3.64 (m, 2 H), 4.07 (m, 1 H), 4.15 (t, *J* = 6 Hz, 2 H), 5.36 (br d, *J* = 8 Hz, SO_2NH, 1 H), 6.97 (d, *J* = 8.6 Hz, 1 H), 7.34 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.6 (d, *J* = 2.2 Hz, 1 H), 7.63 (t, *J* = 7.8 Hz, 1 H), 7.81 (d, *J* = 7.8 Hz, 1 H), 7.98 (d, *J* = 7.8 Hz, 1 H), 8.04 (s, 1 H), 8.47 (m, NH, 1 H), 11.47 (s, NH, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 28.27, 28.52, 28.88, 37.95, 38.31, 57, 67.55, 79.48, 83.38, 84.1, 114.91, 124.4, 126.82, 127.82, 129.7, 130.2, 130.68, 131.71, 135.77, 139.46, 141.06, 151.74, 153.43, 156.57, 163.78, 169.23, (*C*F_3 not visible). MS (ESI) *m/z* 788 $[M - H]^-$, 671, 571. HRMS $C_{34}H_{46}F_3N_5O_{11}S$ calcd for $[M + H]^+$, 790.2945; found, 790.2921.

(S)-*t*-Butyl 3-(3-nitro-4-(5-oxohexyloxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (3d). A mixture of precursor **2l** (0.320 g, 0.506 mmol) and $FeCl_3$ adsorbed on SiO_2 (5%, 0.054 g) in acetone (12 mL) was stirred for 2 h at 20 °C. Concentration and chromatography gave the title compound (0.254 g, 85%) as a colorless oil. R*f* (ether/*n*-Hex 9:1) = 0.67. IR 2939, 1731, 1622, 1533, 1327, 1163 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 9 H), 1.79 (m, 4 H), 2.17 (s, 3 H), 2.56 (t, *J* = 6.5 Hz, 2 H), 2.96 (m, 1 H), 3.07 (m, 1 H), 4.08 (m, 3 H), 5.87 (d, *J* = 9 Hz, SO_2NH, 1 H), 6.97 (d, *J* = 8.6 Hz, 1 H), 7.38 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.59 (d, *J* = 2.2 Hz, 1 H), 7.63 (t, *J* = 7.8 Hz, 1 H), 7.8 (d, *J* = 7.8 Hz, 1 H), 7.97 (d, *J* = 7.8 Hz, 1 H), 8.04 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.37, 27.7, 28.34, 29.92, 38.01, 43.11, 57.15, 69.42, 83.67, 114.55, 124.15, 126.5, 127.65, 129.46, 130.08, 130.56, 131.37, 135.64, 139.23, 141.14, 151.63, 169.42, 209.09, (*C*F_3 not visible). MS (ESI) *m/z* 587 $[M - H]^-$, 209. HRMS $C_{26}H_{31}F_3N_2O_8S$ calcd for $[M + Na]^+$, 611.1651; found, 611.1640.

(S)-*t*-Butyl 3-(4-(4-(1,8-naphthyridin-2-yl)butoxy)-3-nitrophenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (3e). A solution of 2-amino-3-pyridin-carboxaldhehyde (0.074 g, 0.627 mmol), precursor **3d** (0.335 g, 0.570 mmol) and (L)-proline (0.033 g, 0.285 mmol) in EtOH (6 mL) was refluxed for 48 h under Ar atmosphere. Concentration and chromatography afforded the title compound (0.194 g, 50%) as a yellow foam. R*f* (DCM/*i*-PrOH 98:2) = 0.3. IR 2935, 1734, 1608, 1531, 1327, 1159 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 9 H), 1.92 (m, 2 H), 2.13 (m, 2 H), 2.97-3.08 (m, 2 H), 3.14 (t, *J* = 7.4 Hz, 2 H), 4.09 (m, 3 H), 5.7 (d, *J* = 8.9 Hz, SO_2NH, 1 H), 6.93 (d, *J* = 8.6 Hz, 1 H), 7.35 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.43-7.47 (m, 2 H), 7.57 (d, *J* = 2.2 Hz, 1 H), 7.61 (t, *J* = 7.8 Hz, 1 H), 7.79 (d, *J* = 7.8 Hz, 1 H), 7.97 (d, *J* = 7.8 Hz, 1 H), 8.04 (s, 1 H), 8.11 (d, *J* = 8.4 Hz, 1 H), 8.17 (dd, *J* = 8.1, 2 Hz, 1 H), 9.08 (dd, *J* = 4.3, 2 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.49, 27.83, 28.6, 38.17, 38.63, 57.16, 69.43, 83.87, 114.67, 121.29, 121.67, 122.77, 124.3, 124.7 (*C*F_3), 126.62, 127.51, 129.6, 130.12, 130.65, 131.59, 135.72, 137.01, 137.35, 139.32, 141.18, 151.85, 153.47, 156.07, 166.36, 169.41. MS (ESI) *m/z* 1346 $[M - H]^-$ x 2, 673 $[M - H]^-$. HRMS $C_{32}H_{33}F_3N_4O_7S$ calcd for $[M + Na]^+$, 697.1920; found, 697.1898.

General procedure for reduction of 2-3 (Table 2).

Method A. A solution of **2** or **3** in MeOH or EtOH (0.1 mmol/3mL) containing Pd/C (10%) as catalyst (0.01 g/0.1 mmol product **2** or **3**) was placed under H_2 atmosphere (1 atm) and stirred for 18 h at 20 °C. The mixture was filtered over a short celite pad, using MeOH (EtOH); filtrate concentration under vacuum gave quantitatively crude **4**.

Method B. A solution of **2** (0.2 mmol) in HOAc (5 mL) and 37% HCl_{aq} (0.5 mL), containing Pd/C (10%) as catalyst (0.1 g) was introduced in a Parr flask. The mixture was hydrogenated (Parr apparatus) for 2 h at 20 °C, under a pressure of 45 psi. The mixture was filtered on a celite pad, using MeOH-H_2O. Concentration under vacuum and chromatography gave crude **4**, recovered by lyophilization.

Method C. A solution of **2** (0.5 mmol) and ammonium formate (5 mmol) in EtOH (5 mL), containing Pd/C (10%) as catalyst (0.05 g), was refluxed for 12 h under Ar atmosphere and vigorous

stirring. The mixture was filtered on a celite pad, using EtOH. After concentration, the residue was dissolved in EtOAc (10 mL), washed with brine (2 x 5 mL) and dried ($MgSO_4$). Solvent evaporation gave crude compound **4**.

(S)-*t*-Butyl 3-(3-amino-4-(4-*t*-butoxycarbonylamino-butoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (4b). The title compound was obtained from **2b** (0.052 g, 0.078 mmol), according to Method A, as a white foam (0.05 g, 100%). R*f* (DCM/EtOAc 8:2) = 0.9. $[\alpha]_D^{20}$ – 12 (*c* = 1.2, $CHCl_3$). IR 3383, 2978, 1697, 1518, 1327, 1163 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 9 H), 1.43 (s, 9 H), 1.66 (m, 2 H), 1.81 (m, 2 H), 2.88 (m, 2 H), 3.18 (m, 2 H), 3.72 (br s, NH_2, 2 H), 3.95 (t, *J* = 6 Hz, 2 H), 4.06 (m, 1 H), 4.62 (br s, NH-CO_2, 1 H), 5.34 (d, *J* = 9 Hz, SO_2NH, 1 H), 6.45 (d, *J* = 8.6 Hz, 1 H), 6.55 (s, 1 H), 6.61 (d, *J* = 8.6 Hz, 1 H), 7.58 (t, *J* = 7.8 Hz, 1 H), 7.75 (d, *J* = 7.8 Hz, 1 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 8.04 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.4, 26.8, 27.56, 28.28, 38.64, 40.16, 57.01, 67.74, 79.09, 82.67, 111.21, 116.73, 120.08, 124.08, 127.37, 129.04, 129.62, 130.4, 131.35, 134.68, 141.19, 146.01, 155.91, 169.56, (*C*F_3 not visible). MS (APCI) *m/z* 1260 $[M - H]^-$ x 2, 630 $[M - H]^-$. HRMS $C_{29}H_{40}F_3N_3O_7S$ calcd for $[M + H]^+$, 632.2617; found, 632.2620. Anal. calcd (%) C, 55.15; H, 6.34; N, 6.66; S, 5.07 – Found C, 54.88; H, 6.36; N, 6.61; S, 6.16.

(S)-3-(3-Amino-4-(3-(1,4,5,6-tetrahydropyrimidin-2-ylamino) propoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoic acid (4c). The title compound was obtained from **2c** (0.115 g, 0.184 mmol), according to Method B, as a white foam (0.062 g, 62%) after chromatography. R*f* (EtOH/NH_4OH/H_2O 8:1:1) = 0.8. ^1H NMR (300 MHz, CD_3OD) δ 1.85 (m, 2 H), 2.01 (m, 2 H), 2.66 (m, 1 H), 2.93 (m, 1 H), 3.27 (m, 6 H), 3.81 (m, 1 H), 3.99 (t, *J* = 5.7 Hz, 2 H), 6.5 (dd, *J* = 8.1, 2 Hz, 1 H), 6.63 (m, 2 H), 7.63 (t, *J* = 8.1 Hz, 1 H), 7.82 (d, *J* = 8.1 Hz, 1 H), 7.92 (d, *J* = 8.5 Hz, 1 H), 8 (s, 1 H). ^{13}C NMR (75 MHz, CD_3OD) δ 22.02, 30.68, 39.81, 40.52, 40.97, 61.84, 67.02, 113.26, 119.32, 122.04, 125.66, 130.66, 131.98, 132.54, 132.6, 133, 137.87, 144.48, 147.73, 155.47, 177.88, (*C*F_3 not visible). MS (ESI) *m/z* 578 $[M + 2\ H_2O - H]^-$. HRMS $C_{23}H_{28}F_3N_5O_5S$ calcd for $[M + H]^+$, 544.1842; found, 544.1829.

(S)-3-(3-Amino-4-(4-(1,4,5,6-tetrahydropyrimidin-2-ylamino) butoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoic acid (4d). The title compound was obtained from **2d** (0.120 g, 0.156 mmol), according to Method B, as a white foam (0.083 g, 95%) after chromatography. R*f* (EtOH/NH_4OH/H_2O 8:1:1) = 0.9. ^{1}H NMR (500 MHz, CD_3OD) δ 1.91 (m, 2 H), 1.77 (m, 2 H), 1.85 (m, 2 H), 2.65 (m, 1 H), 2.92 (m, 1 H), 3.2 (t, *J* = 7.2 Hz, 2 H), 3.33 (m, 4 H), 3.82 (m, 1 H), 3.94 (t, *J* = 5.6 Hz, 2 H), 6.42 (dd, *J* = 8.7, 2.1 Hz, 1 H), 6.54 (d, *J* = 8.7 Hz, 1 H), 6.55 (d, *J* = 2.1 Hz, 1 H), 7.6 (t, *J* = 8.1 Hz, 1 H), 7.79 (d, *J* = 8.1 Hz, 1 H), 7.82 (d, *J* = 8.1 Hz, 1 H), 7.93 (s, 1 H). ^{13}C NMR (125 MHz, CD_3OD) δ 21.18, 26.82, 27.6, 39.61, 39.82, 41.8, 61.31, 68.72, 112.37, 118.04, 120.79, 124.52, 129.77, 131.16, 131.34, 131.56, 131.81, 136.88, 143.52, 146.97, 154.44, 177.9, (*C*F_3 not visible). MS (ESI) *m/z* 1112 $[M - H]^-$ x 2, 556 $[M - H]^-$. HRMS $C_{24}H_{30}F_3N_5O_5S$ calcd for $[M + H]^+$, 558.1998; found, 558.1976.

(S)-*t*-Butyl 3-(3-amino-4-(3-(pyridin-2-ylamino)propoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (4e). The title compound was obtained from **2e** (0.325 g, 0.507 mmol), according to Method C, as a yellow oil (0.240 g, 80%). R*f* (DCM/*i*-PrOH 9:1) = 0.8. $[\alpha]_D^{20}$ - 11.5 (*c* = 0.1, $CHCl_3$). IR 3364, 2923, 1734, 1516, 1327, 1155 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 2.13 (m, 2 H), 2.89 (m, 2 H), 3.5 (m, 2 H), 3.75 (br s, NH_2, 2 H), 4.07 (m, 3 H), 4.81 (br s, NH, 1 H), 5.54 (d, *J* = 9.3 Hz, SO_2NH, 1 H), 6.41 (m, 2 H), 6.46 (d, *J* = 1.9 Hz, 1 H), 6.59 (m, 1 H), 6.61 (d, *J* = 8.1 Hz, 1 H), 7.42 (m, 1 H), 7.57 (t, *J* = 7.8 Hz, 1 H), 7.76 (d, *J* = 7.8 Hz, 1 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 8.05 (s, 1 H), 8.08 (dd, *J* = 4.2, 1.2 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.88, 29.14, 38.99, 39.74, 57.43, 65.92, 82.91, 107.97, 111.53, 112.54, 116.39, 119.57, 124.36, 128.02, 129.32, 129.92, 130.71, 131.3, 136.39, 139.95, 141.58, 144, 145.68, 158, 169.6, (*C*F_3 not visible). MS (ESI) *m/z* 593 $[M - H]^-$, 537, 209. HRMS $C_{28}H_{33}F_3N_4O_5S$ calcd for $[M + H]^+$, 595.2202; found, 595.2188. Anal. calcd for M.H_2O (%) C, 54.95; H, 5.70; N, 9.15 – Found C, 55.26; H, 5.45; N, 9.11.

(S)-*t*-Butyl 3-(3-amino-4-(4-(pyridin-2-ylamino)butoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (4f). The title compound was obtained from **2f**

(0.1 g, 0.152 mmol), according to Method C, as a yellow oil (0.082 g, 88%). R*f* (DCM/*i*-PrOH 9:1) = 0.8. $[\alpha]_D^{20}$ - 8 (*c* = 1.7, $CHCl_3$). IR 3365, 2935, 1730, 1518, 1327, 1155 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 1.82 (m, 2 H), 1.9 (m, 2 H), 2.86-2.9 (m, 2 H), 3.34 (m, 2 H), 3.71 (br s, NH_2, 2 H), 3.99 (t, *J* = 6 Hz, 2 H), 4.07 (m, 1 H), 4.7 (br s, NH, 1 H), 5.3 (d, *J* = 9.4 Hz, SO_2NH, 1 H), 6.4 (m, 2 H), 6.45 (d, *J* = 2 Hz, 1 H), 6.57 (m, 1 H), 6.61 (d, *J* = 8.2 Hz, 1 H), 7.43 (m, 1 H), 7.58 (t, *J* = 7.8 Hz, 1 H), 7.77 (d, *J* = 7.8 Hz, 1 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 8.05 (s, 1 H), 8.07 (dd, *J* = 5.1, 1.2 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.08, 26.71, 27.56, 38.73, 41.75, 57.01, 67.66, 82.6, 106.75, 111.19, 112.48, 115.94, 119.19, 124.08, 127.36, 129.01, 129.57, 130.37, 131.32, 136.14, 138.1, 141.25, 145.59, 146.6, 158.09, 169.64, (*C*F_3 not visible). MS (ESI) *m/z* 607 $[M - H]^-$, 209. HRMS $C_{29}H_{35}F_3N_4O_5S$ calcd for $[M + H]^+$, 609.2359; found, 609.2339.

(S)-*t*-Butyl 3-(3-amino-4-(4-(*t*-butoxycarbonyl(6-methylpyridin-2-yl)amino)butoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (4h). The title compound was obtained from **2h** (0.350 g, 0.460 mmol), according to Method A, as a pale yellow oil (0.310 g, 93%). R*f* (ether/EtOAc 9:1) = 0.9. $[\alpha]_D^{20}$ - 11 (*c* = 1.3, $CHCl_3$). IR 2976, 1703, 1518, 1327, 1159 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 1.48 (s, 9 H), 1.79 (m, 4 H), 2.47 (s, 3 H), 2.86-2.90 (m, 2 H), 3.69 (br s, NH_2, 2 H), 3.93 (t, *J* = 6 Hz, 2 H), 3.99 (t, *J* = 7 Hz, 2 H), 4.05 (m, 1 H), 5.13 (d, *J* = 9.1 Hz, SO_2NH, 1 H), 6.39 (dd, *J* = 8.4, 2.1 Hz, 1 H), 6.43 (d, *J* = 2.1 Hz, 1 H), 6.57 (d, *J* = 8.4 Hz, 1 H), 6.87 (d, *J* = 7.9 Hz, 1 H), 7.29 (d, *J* = 7.9 Hz, 1 H), 7.51 (t, *J* = 7.9 Hz, 1 H), 7.57 (t, *J* = 8.1 Hz, 1 H), 7.76 (d, *J* = 8.1 Hz , 1 H), 7.91 (d, *J* = 8.1 Hz, 1 H), 8.04 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.18, 25.44, 26.56, 27.57, 28.22, 38.76, 46.42, 56.96, 67.86, 80.64, 82.6, 111.07, 115.78, 117.2, 118.94, 119.16, 124.1, 127.07, 129.04, 129.6, 130.37, 131.35, 136.12, 137.05, 141.13, 145.72, 153.76, 154.16, 156.64, 169.53, (*C*F_3 not visible). MS (APCI) *m/z* 721 $[M - H]^-$, 621, 209. HRMS $C_{35}H_{45}F_3N_4O_7S$ calcd for $[M + H]^+$, 723.3039; found, 723.3063.

(S)-*t*-Butyl 3-(*N*(*N*,*N*'-di-*t*-butoxycarbonylguanidinyl)-4-aminobutoxy))-3-aminophenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (4i). The title compound was obtained from **2i**

(0.5 g, 0.62 mmol), according to Method A, as a pale brown foam (0.461 g, 95%). $[\alpha]_D^{20}$ - 5 (*c* = 1, $CHCl_3$). IR 2955, 1724, 1640, 1518, 1327, 1157 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 1.5 (s, 18 H), 1.77-1.87 (m, 4 H), 2.86-2.90 (m, 2 H), 3.5 (m, 2 H), 3.73 (br s, NH_2, 2 H), 3.96 (t, *J* = 6 Hz, 2 H), 4.06 (m, 1 H), 5.41 (d, *J* = 9 Hz, SO_2NH, 1H), 6.41 (d, *J* = 8.2 Hz, 1 H), 6.46 (s, 1 H), 6.59 (d, *J* = 8.2 Hz, 1 H), 7.58 (t, *J* = 7.8 Hz, 1 H), 7.76 (d, *J* = 7.8 Hz, 1 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 8.04 (s, 1 H), 8.43 (br s, NH, 1 H), 11.4 (br s, NH, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.12, 26.7, 27.86, 28.22, 28.43, 38.83, 41, 57.43, 67.92, 82.93, 83.61, 111.48, 117.52, 120.8, 124.28, 127.77, 129.31, 129.99, 130.73, 131.35, 135.47, 141.49, 146.53, 153.4, 156.16, 163, 169.92, (*C*F_3 not visible). MS (APCI) *m/z* 772 $[M - H]^-$, 672, 655. HRMS $C_{35}H_{50}F_3N_5O_9S$ calcd for $[M + Na]^+$, 796.3179; found, 796.6159. Anal. calcd for M.H_2O (%) C, 53.10; H, 6.57 – Found C, 58.34; H, 6.58.

(S)-*t*-Butyl 3-(*N*-(*N*,*N*'-di-*t*-butoxycarbonylguanidinyl)-3-aminopropoxy)-3-aminophenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (4j). The title compound was obtained from **3b** (0.097 g, 0.122 mmol), according to Method A, as a pale brown foam (0.082 g, 88%). $[\alpha]_D^{20}$ - 8 (*c* = 0.9, $CHCl_3$). IR 2977, 1723, 1638, 1518, 1327, 1157 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 9 H), 1.45 (s, 9 H), 1.48 (s, 9 H), 2.09 (m, 2 H), 2.88 (m, 2 H), 3.63 (m, 2 H), 3.75 (br s, NH_2, 2 H), 4.01 (t, *J* = 6 Hz, 2 H), 4.06 (m, 1 H), 5.26 (d, *J* = 9 Hz, SO_2NH, 1 H), 6.40 (dd, *J* = 8.2, 2 Hz, 1 H), 6.46 (d, *J* = 2 Hz, 1 H), 6.6 (d, *J* = 8.2 Hz, 1 H), 7.58 (t, *J* = 7.8 Hz, 1 H), 7.77 (d, *J* = 7.8 Hz, 1 H), 7.91 (d, *J* = 7.8 Hz, 1 H), 8.05 (s, 1 H), 8.48 (br s, NH, 1 H), 11.53 (br s, NH, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.92, 28.3, 28.35, 29.13, 38.78, 39.08, 57.36, 66.49, 79.54, 83, 83.43, 111.45, 116.35, 119.53, 124.43, 127.88, 129.39, 129.94, 130.72, 131.6, 136.61, 141.5, 145.8, 153.55, 156.42, 163.79, 169.92, (*C*F_3 not visible). MS (ESI) *m/z* 1517 $[2M - H]^-$, 758 $[M - H]^-$, 641. HRMS $C_{34}H_{48}F_3N_5O_9S$ calcd for $[M + H]^+$, 760.3203; found, 760.3209.

(S)-*t*-Butyl 3-(3-amino-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (4l). The title compound was obtained from **3e**

(0.145 g, 0.215 mmol), according to Method A, as a pale brown foam (0.123 g, 88%). R*f* (EtOAc/acetone 8:2) = 0.2. $[\alpha]_D^{20}$ - 11 (*c* = 1, $CHCl_3$). IR 2933, 1734, 1651, 1516, 1327, 1159 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 1.8-2.01 (m, 6 H), 2.71-2.79 (m, 4 H), 2.88 (m, 2 H), 3.46 (m, 2 H), 3.69 (br s, NH_2, 2 H), 3.96 (t, *J* = 5.8 Hz, 2 H), 4.05 (m, 1 H), 5.25 (m, SO_2NH, 1 H), 6.36-6.39 (m, 2 H), 6.43 (d, *J* = 2 Hz, 1 H), 6.57 (d, *J* = 8.4 Hz, 1 H), 7.24 (d, *J* = 3.5 Hz, 1 H), 7.59 (t, *J* = 7.8 Hz, 1 H), 7.77 (d, *J* = 7.8 Hz, 1 H), 7.92 (d, *J* = 7.8 Hz, 1 H), 8.05 (s, 1 H), 8.11 (br s, NH, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.11, 25.8, 25.87, 27.93, 28.98, 34.19, 39.06, 41.34, 57.35, 67.73, 82.99, 110.27, 111.35, 115, 116.15, 119.4, 124.41, 127.5, 129.39, 129.97, 130.73, 131.35, 136.57, 139.7, 141.13, 145.97, 169.92 , (*C*F_3 and two naphthyridinyl quaternary C not visible). MS (ESI) *m/z* 647 $[M - H]^-$, 591, 209. HRMS $C_{32}H_{39}F_3N_4O_5S$ calcd for $[M + H]^+$, 649.2672; found, 649.2685.

General procedure for the coupling of spacer-arms (Table 3).

Acid **23** or **24** (see Scheme 1, 0.2 mmol) dissolved in DMF (1 mL) was treated successively with PyBOP (0.011 g, 0.2 mmol) and Et_3N (0.027 mL, 0.2 mmol) at 20 °C under Ar atmosphere. After 2 h, precursor **4** (0.18 mmol) dissolved in DMF (0.3 mL) was added dropwise with a syringe, and the mixture was stirred for 18 h at 20 °C. After dilution with brine (5 mL), the solution was extracted with ether (3 x 5 mL) and EtOAc (1 x 5 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue (brown oil) was purified by chromatography on silica gel.

(S)-*t*-Butyl 3-(3-(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)acetamido)-4-(4-(4-methylpyridin-2-yl-*t*-butoxycarbonylamino)butoxy)phenyl-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (6c). The title compound was obtained from **24** (0.1 g) and **4g** (0.1 g) as a white foam (0.078 g, 61%). R*f* (EtOAc/*n*-Hex 9:1) = 0.6. IR 2932, 1699, 1327, 1161 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 9 H), 1.49 (s, 9 H), 1.82-1.86 (m, 4 H), 2.33 (s, 3 H), 2.88 (m, 1 H), 3.01 (m, 1 H), 3.36 (s, 3 H), 3.51-3.73 (m, 12 H), 3.99 (m, 4 H), 4.05 (m, 1 H), 4.11 (s, 2 H), 5.4 (br s, SO_2NH, 1 H), 6.71 (d, *J* = 8.3 Hz, 1 H), 6.83 (dd, *J* = 8.3, 2 Hz, 1

H), 6.85 (d, *J* = 5.4 Hz, 1 H), 7.4 (s, 1 H), 7.56 (t, *J* = 7.8 Hz, 1 H), 7.74 (d, *J* = 7.8 Hz, 1 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 8.02 (s, 1 H), 8.13 (d, *J* = 2 Hz, 1 H), 8.2 (d, *J* = 5.4 Hz, 1 H), 8.9 (s, CONH, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.32, 25.54, 26.75, 27.88, 28.51, 38.96, 46.47, 57.4, 59.21, 68.36, 70.72-72.04, 72.04, 81.14, 83.22, 111.05, 120.72, 120.89, 121.15, 124.37, 125.26, 127.11, 127.69, 129.26, 129.88, 130.78, 131.2, 141.42, 146.91, 147.48, 148.38, 154.37, 154.74, 167.78, 169.93, (*C*F_3 not visible). MS (APCI) *m/z* 925 [M – H]$^-$, 825. HRMS $C_{44}H_{61}F_3N_4O_{12}S$ calcd for [M + Na]$^+$, 949.3857; found, 949.3874.

(S)-*t*-Butyl 3-(3-(2,5,8,11-tetraoxatridecanamido-4-(3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoate (6d). The title compound was obtained from **24** (0.076 g) and **4k** (0.2 g) as a white foam (0.118 g, 45%). R*f* (EtOAc/acetone 9:1) = 0.75. IR 2930, 1736, 1327, 1159 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 9 H), 1.91 (m, 2 H), 2.19 (m, 2 H), 2.67-2.76 (m, 4 H), 2.85-3.04 (m, 2 H), 3.36 (s, 3 H), 3.41 (m, 2 H), 3.5-3.8 (m, 12 H), 3.99 (t, *J* = 6.4 Hz, 2 H), 4.07 (m, 1 H), 4.13 (s, 2 H), 4.9 (br s, NH-C=N, 1 H), 5.4 (br s, SO_2NH, 1 H), 6.35 (d, *J* = 7.3 Hz, 1 H), 6.71 (d, *J* = 8.3 Hz, 1 H), 6.82 (d, *J* = 8.3 Hz, 1 H), 7.12 (d, *J* = 7.3 Hz, 1 H), 7.56 (t, *J* = 7.9 Hz, 1 H), 7.74 (d, *J* = 7.9 Hz, 1 H), 7.94 (d, *J* = 7.9 Hz, 1 H), 8.03 (s, 1 H), 8.14 (s, 1 H), 8.9 (s, CONH, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.63, 26.55, 27.9, 29.24, 33.97, 38.96, 41.78, 57.44, 59.22, 67.97, 70.7-70.89, 71.33, 72.09, 83.21, 111.14, 111.6, 113.85, 120.8, 124.38, 125.23, 127.16, 127.65, 129.23, 129.86, 130.77, 131.72, 136.48, 141.48, 147.23, 156.03, 156.84, 167.74, 170.01, (*C*F_3 not visible). MS (ESI) *m/z* 1675 [2M – H]$^-$, 837 [M – H]$^-$. HRMS $C_{40}H_{53}F_3N_4O_{10}S$ calcd for [M + H]$^+$, 839.3513; found, 839.3546.

General procedure for Boc deprotection (Table 4).

Boc-protected compound (0.1 g) dissolved in DCM (1 mL) was treated with TFA (1 mL) during 2 h at 20 °C. Concentration under vacuum quantitatively gave the peptidomimetic (for testing) as TFA salt. Compounds are stored in the fridge (- 18 °C) as TFA salt. Neutralisation could be performed by dissolution in DCM (0.1 g / 5 mL DCM), washing with phosphate buffer (pH 8, 2 x 1 mL), drying ($MgSO_4$) and concentration (yellow oils).

(S)-3-(3-Amino-4-(4-amino-butoxy)-phenyl)-2-(3-trifluoromethyl)phenylsulfonamido)-propionic acid (5b). ^{1}H NMR (300 MHz, CD_3OD) δ 1.93 (m, 4 H), 2.86 (m, 1 H), 3.04 (m, 2 H), 3.12 (m, 1 H), 4.13 (m, 3 H), 7.03 (d, *J* = 8.5 Hz, 1 H), 7.25 (dd, *J* = 8.5, 2 Hz, 1 H), 7.28 (d, *J* = 2 Hz, 1 H), 7.68 (t, *J* = 7.9 Hz, 1 H), 7.86 (d, *J* = 7.9 Hz, 1 H), 7.97 (d, *J* = 7.9 Hz, 1 H), 8.03 (s, 1 H). ^{13}C NMR (75 MHz, CD_3OD) δ 25.98, 27.92, 39.65, 41.28, 59.66, 70.05, 114.65, 121.37, 125.7, 126.81, 130.9, 131.98, 132.03, 132.4, 133.27, 133.3, 144.46, 153.01, 174.41, (*C*F_3 not visible). HRMS $C_{20}H_{24}F_3N_3O_5S$ calcd for $[M + H]^+$, 475.1389; found, 475.1453.

(S)-3-(3-Amino-4-(3-(pyridin-2-ylamino)propoxy)phenyl)-2-(3-(trifluoro methyl)phenylsulfonamido)propanoic acid (5e). ^{1}H NMR (300 MHz, CD_3OD) δ 2.27 (m, 2 H), 2.84 (m, 1 H), 3.1 (m, 1 H), 3.65 (t, *J* = 6.9 Hz, 2 H), 4.1 (m, 1 H), 4.23 (t, *J* = 5.9 Hz, 2 H), 6.88 (t, *J* = 7 Hz, 1 H), 7.03 (d, *J* = 8.5 Hz, 1 H), 7.1 (d, *J* = 7 Hz, 1 H), 7.21 (dd, *J* = 8.5, 2 Hz, 1 H), 7.25 (d, *J* = 2Hz, 1 H), 7.68 (t, *J* = 7.9 Hz, 1 H), 7.83-7.94 (m, 3 H), 7.97 (d, *J* = 7.9 Hz, 1 H), 8.03 (s, 1 H). ^{13}C NMR (75 MHz, CD_3OD) δ 29.76, 39.78, 40.74, 59.68, 67.72, 114.34, 114.53, 114.54, 122.67, 125.7, 126.22, 130.91, 132, 132.22, 132.44, 132.46, 137.38, 144.53, 145.57, 152.5, 155.46, 174.29, (*C*-*C*F_3 not visible). HRMS $C_{24}H_{25}F_3N_4O_5S$ calcd for $[M + H]^+$, 539.1576; found, 539.1564.

(S)-3-(3-Amino-4-(4-(pyridin-2-ylamino)butoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoic acid (5f). ^{1}H NMR (300 MHz, CD_3OD) δ 1.96 (m, 4 H), 2.84 (m, 1 H), 3.1 (m, 1 H), 3.45 (m, 2 H), 4.14 (m, 3 H), 6.87 (t, *J* = 6.9 Hz, 1 H), 7.06 (m, 2 H), 7.26 (m, 2 H), 7.68 (t, *J* = 7.9 Hz, 1 H), 7.83-7.93 (m, 3 H), 7.97 (d, *J* = 7.9 Hz, 1 H), 8.03 (s, 1 H). ^{13}C NMR (75 MHz, CD_3OD) δ 26.66, 28.25, 39.71, 43.77, 59.65, 70.34, 114.17, 114.67, 121.4, 125.7, 126.71, 130.09, 131.96, 132, 132.42, 132.84, 133.27, 137.24, 144.53, 145.35, 153.07, 155.35, 174.27, (*C*F_3 not visible). HRMS $C_{25}H_{27}F_3N_4O_5S$ calcd for $[M + H]^+$, 553.1733; found, 553.1723.

(S)-3-(3-Amino-4-(4-(6-methylpyridin-2-ylamino)butoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoic acid (5h). ^{1}H NMR (500 MHz, CD_3OD) δ 1.96

(m, 4 H), 2.5 (s, 3 H), 2.86 (m, 1 H), 3.11 (m, 1 H), 3.46 (t, *J* = 6.2 Hz, 2 H), 4.11 (m, 1 H), 4.17 (t, *J* = 5.8 Hz, 2 H), 6.68 (d, *J* = 7.2 Hz, 1 H), 6.89 (d, *J* = 9Hz, 1 H), 7.04 (d, *J* = 8.5 Hz, 1 H), 7.23 (m, 2 H), 7.68 (t, *J* = 7.9 Hz, 1 H), 7.81 (dd, *J* = 9, 7.2 Hz, 1 H), 7.86 (d, *J* = 7.9 Hz, 1 H), 7.96 (d, *J* = 7.9 Hz, 1 H), 8.02 (s, 1 H). ^{13}C NMR (75 MHz, CD_3OD) δ 19.84, 26.83, 28.19, 39.62, 43.96, 59.7, 70.31, 110.54, 113.74, 114.94, 121.92, 125.62, 126.47, 130.85, 131.76, 132.02, 132.4, 132.77, 133.22, 144.44, 146.17, 149.79, 152.89, 155.93, 174.41, (*C*F_3 not visible). HRMS $C_{26}H_{29}F_3N_4O_5S$ calcd for $[M + H]^+$, 567.1889; found, 567.1879.

(S)-3-(*N*-Guanidinyl)-3-aminopropoxy)-3-aminophenyl)-2-(3-(trifluoromethyl)phenylsulfonamido) propanoic acid (5i). ^{1}H NMR (300 MHz, CD_3OD) δ 2.14 (m, 2 H), 2.85 (m, 1 H), 3.1 (m, 1 H), 3.45 (t, *J* = 6.9 Hz, 2 H), 4.1 (m, 1 H), 4.19 (t, *J* = 5.8 Hz, 2 H), 7.07 (d, *J* = 8.5 Hz, 1 H), 7.26 (m, 2 H), 7.68 (t, *J* = 7.9 Hz, 1 H), 7.86 (d, *J* = 7.9 Hz, 1 H), 7.97 (d, *J* = 7.9 Hz, 1 H), 8.03 (s, 1 H). ^{13}C NMR (75 MHz, CD_3OD) δ 30.27, 39.76, 39.96, 59.67, 67.77, 114.6, 122.24, 125.71, 126.42, 130.9, 132.03, 132.21, 132.45, 132.78, 133.16, 144.53, 152.68, 159.65, 174.31, (*C*F_3 not visible). HRMS $C_{20}H_{24}F_3N_5O_5S$ calcd for $[M + H]^+$, 504.1529; found, 504.1520.

(S)-3-(*N*-Guanidinyl)-4-aminobutoxy)-3-aminophenyl)-2-(3-(trifluoromethyl)phenylsulfonamido) propanoate (5j). ^{1}H NMR (500 MHz, CD_3OD) δ 1.82-1.94 (m, 4 H), 2.85 (m, 1 H), 3.1 (m, 1 H), 3.27 (t, *J* = 6.9 Hz, 2 H), 4.1 (m, 1 H), 4.15 (t, *J* = 6Hz, 2 H), 7.07 (d, *J* = 8.5 Hz, 1 H), 7.25 (m, 2 H), 7.69 (t, *J* = 7.9 Hz, 1 H), 7.86 (d, *J* = 7.9 Hz, 1 H), 7.97 (d, *J* = 7.9 Hz, 1 H), 8.03 (s, 1 H). ^{13}C NMR (125 MHz, CD_3OD) δ 27.02, 28.11, 39.72, 43.01, 59.64, 70.34, 114.64, 121.93, 125.68, 126.58, 130.9, 131.93, 132.01, 132.43, 132.9, 133.09, 144.51, 152.99, 159.58, 174.27, (*C*F_3 not visible). HRMS $C_{21}H_{26}F_3N_5O_5S$ calcd for $[M + H]^+$, 518.1685; found, 518.1676.

(S)-3-(3-Amino-4-(3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoic acid (5k). ^{1}H NMR (300 MHz, CD_3OD) δ 1.93 (m, 2 H), 2.23 (m, 2 H), 2.81 (t, *J* = 5.7 Hz, 2 H), 2.86 (m, 1 H), 2.97 (t, *J* = 7.8 Hz, 2 H), 3.1 (m, 1

H), 3.49 (t, *J* = 5.6 Hz, 2 H), 4.1 (m, 1 H), 4.16 (t, *J* = 6 Hz, 2 H), 6.63 (d, *J* = 7.4 Hz, 1 H), 7.03 (d, *J* = 9 Hz, 1 H), 7.25 (m, 2 H), 7.57 (d, *J* = 7.4 Hz, 1 H), 7.69 (t, *J* = 7.8 Hz, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 7.98 (d, *J* = 7.8 Hz, 1 H), 8.02 (s, 1 H). ^{13}C NMR (75 MHz, CD_3OD) δ 21.3, 27.27, 30.2, 30.77, 39.77, 42.94, 59.66, 69.3, 112.48, 114.56, 121.73, 121.99, 125.7, 126.44, 130.91, 132, 132.18, 132.43, 132.96, 143.52, 144.56, 149.73, 152.73, 153.92, 174.25, (*C*-*C*F_3 not visible). HRMS $C_{27}H_{29}F_3N_4O_5S$ calcd for $[M + H]^+$, 579.1889; found, 579.1888.

(S)-3-(3-2,5,8,11-Tetraoxatridecanamido-4-(4-(4-methylpyridin-2-ylamino)butoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoic acid (8c). ^{1}H NMR (500 MHz, CD_3OD) δ 1.96 (m, 4 H), 2.37 (s, 3 H), 2.72 (m, 1 H), 3.05 (m, 1 H), 3.28 (s, 3 H), 3.43 (t, *J* = 6.8 Hz, 2 H), 3.43-3.81 (m, 12 H), 4.05-4.12 (m, 5 H), 6.73 (dd, *J* = 6.5, 1.2 Hz, 1 H), 6.8 (s, 1 H), 6.82 (d, *J* = 8.3 Hz, 1 H), 6.88 (dd, *J* = 8.3, 2 Hz, 1 H), 7.57 (t, *J* = 7.8 Hz, 1 H), 7.7 (d, *J* = 6.6 Hz, 1 H), 7.78 (d, *J* = 7.8 Hz, 1 H), 7.85 (d, *J* = 7.8 Hz, 1 H), 7.9 (s, 1 H), 7.91 (d, *J* = 2 Hz, 1 H). ^{13}C NMR (125 MHz, CD_3OD) δ 22.84, 26.9, 28.51, 40.09, 43.66, 59.86, 60.08, 69.75, 72.21-73.66, 113.29, 113.3, 116.37, 123.17, 125.4, 127.68, 128.22, 130.5, 131.2, 131.86, 132.33, 132.89, 136.37, 144.7, 149.2, 149.28, 154.8, 170.8, 174.96, (*C*F_3 not visible). HRMS $C_{35}H_{45}F_3N_4O_{10}S$ calcd for $[M + H]^+$, 771.2887; found, 771.2906.

(S)-3-(3-2,5,8,11-Tetraoxatridecanamido-4-(3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propoxy)phenyl)-2-(3-(trifluoromethyl)phenylsulfonamido)propanoic acid (8d). ^{1}H NMR (500 MHz, CD_3OD) δ 1.92 (m, 2 H), 2.23 (m, 2 H), 2.72 (m, 1 H), 2.78 (t, *J* = 6.1 Hz, 2 H), 2.94 (t, *J* = 7.4 Hz, 2 H), 3.04 (m, 1 H), 3.27 (s, 3 H), 3.4 (m, 2 H), 3.46, 3.57, 3.61, 3.65, 3.72, 3.8 (m, 12 H), 4.05 (m, 1 H), 4.11 (t, *J* = 5.7 Hz, 2 H), 4.14 (s, 2 H), 6.61 (d, *J* = 7.3 Hz, 1 H), 6.8 (d, *J* = 8.4 Hz, 1 H), 6.88 (dd, *J* = 8.3, 2 Hz, 1 H), 7.53 (d, *J* = 7.3 Hz, 1 H), 7.59 (t, *J* = 7.8 Hz, 1 H), 7.8 (d, *J* = 7.8 Hz, 1 H), 7.87-7.91 (m, 3 H). ^{13}C NMR (125 MHz, CD_3OD) δ 21.3, 27.24, 29.96, 31.5, 40.13, 43.12, 59.9, 60.1, 69, 72.2-73.66, 112.79, 113.2, 121.6, 123.4, 125.5, 127.8, 128.16, 130.62, 131.36, 131.9, 132.38, 132.95, 143.72, 144.71, 149.08, 149.67, 153.56, 170.85, 174.91, (*C*F_3 not visible). HRMS $C_{36}H_{45}F_3N_4O_{10}S$ calcd for $[M + H]^+$, 783.2887; found, 783.2863.

V. Modelisation of the cyclic peptide

Cilengitide, i.e. *cyclo*-[RGD*f*N(Me)V]-, was optimized at the RHF/6-31G(d) level. Several conformations could be located, close to the X-ray conformation observed in the complex with the extracellular fragment of $\alpha_v\beta_3$ integrin. The observed X-ray conformation remained a local minimum when reoptimized (energetic range minder than 3 kcal $mole^{-1}$).

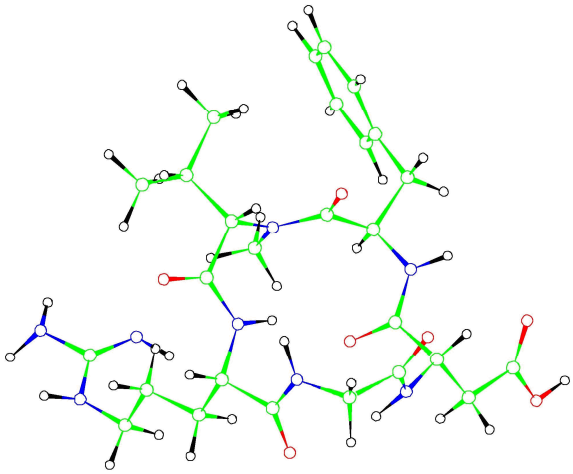

Figure S1. Optimized geometry of Cilengitide.

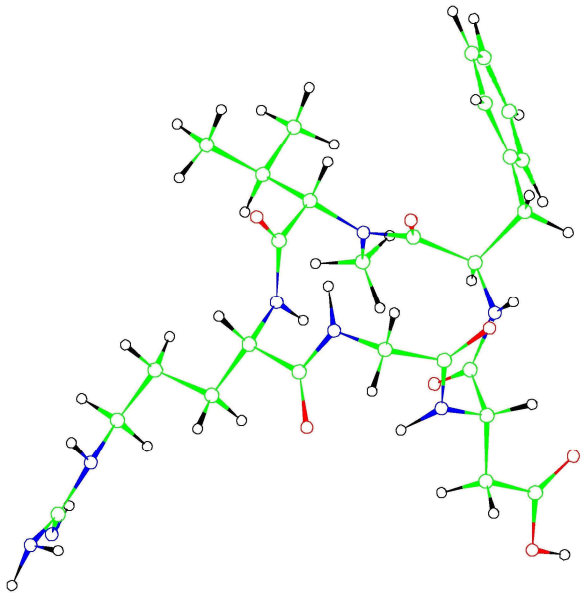

Figure S2. Re-optimized geometry of Cilengitide from the X-ray structure.