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for

Rational Design of Highly Active and Selective Ligands for a5 ß1 Integrin Receptor

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Experimental Section

All technical solvents were distilled prior to use. Dry solvents were purchased from Aldrich, Fluka or Merck. Reactions sensible to oxygen or water were performed in flame-dried reaction vessels under an argon atmosphere (99.996%). All chemicals used in synthesis were purchased from Aldrich, Acros, Fluka or Lancaster and used without further purification. Apart from the Mitsunobu reaction, yields are not optimized. Column chromatography was performed using silica gel purchased from Merck at 0.8 – 1.5 atm pressure. Analytical and preparative HPLC was performed on A) Amersham Pharmacia Biotech: Äkta Basic 10F; Pump system P-900; Detector UV-900; Driver software Unicorn, vers. 3.00; Column material: ODS-A C_{18} (120 Å, 5 µm, 250 mm x 4.6 mm); B) Amersham Pharmacia Biotech: Äkta Basic 100F; Pump system P-900; Detector UV-900, Driver software Unicorn vers. 3.00; Column material ODS-A C_{18} (120 Å, 10 µm, 250 mm x 20 mm), C) Beckman: System Gold, High pressure pump module 125; UV-Detector 166; Column material: ODS-A C_{18} (120 Å, 5 µm, 250 mm x 20 mm), D) Waters: System Breeze; Pump System 1525, UV-Detector 2487 Dual; Driver Software Breeze vers. 3.20; Column material ODS-A C_{18} (120 Å,

10 µm, 250 mm x 20 mm). ESI mass spectra were recorded on a Finnigan LCQ combined with an HPLC-system Hewlett Packard HP1100 (Column material: Omnicrom YMC ODS-A C_{18} (120 Å, 3 µm, 125 mm x 2 mm). NMR spectra were recorded on *Bruker* AC250, DMX500 and DMX900 using $CDCl_3$ or DMSO-d_6 as solvent and internal standard. Assignment was performed using different 2D-experiments such as TOCSY, HMQC-COSY.

Solid phase binding assay

The inhibiting activity and integrin selectivity of the integrin inhibitors were determined in a solid phase binding assay using soluble integrins and coated extracellular matrix protein. Binding of integrins was than detected by specific antibodies in an enzyme-linked immunosorbant assay. Fibronectin and vitronectin were purchased from Sigma (St. Louis, MO) and fibrinogen from Calbiochem (EMD Biosciences, Darmstadt, Germany). The integrin $\alpha5\beta1$ extracellular domain Fc-fusion protein was a generous gift from M. Humphries (University of Manchester), $\alpha v\beta3$ was purchased from Chemicon (Chemicon Europe, Germany) and $\alpha IIb\beta3$ from Kordia (Kordia Life Science, Leiden, Netherlands). The integrin antibodies were purchased from Pharmingen, BD Bioscience Europe ($\alpha v\beta3$, and $\alpha IIb\beta3$) and Sigma (anti-human-Fc-HRP antibody conjugate and anti-mouse-HRP conjugate). The detection of HRP was performed using HRP substrate solution 3.3.5.5'-tetramethylethylenediamine (TMB, Seramun, Germany) and 1 M H_2SO_4 for stopping the reaction. The developed color was measured at 450 nm with SpectraMax Plus reader (Molecular Devices). The resulting inhibition curves were analyzed using SoftMaxPro 4.0 software, the turning point describes the IC_{50} value.

$\alpha5\beta1$: Nunc-Immuno maxisorp plates (Nalge Nunc Europe Ltd) were coated overnight at 4°C with fibronectin (0.25 µg/mL) in 15 mM Na_2CO_3, 35 mM $NaHCO_3$, pH9.6. All subsequent washing and binding were performed in 25 mM Tris, pH7.6, 150 mM NaCl, 1 mM $MnCl_2$, 1 mg/mL BSA. The plates were blocked with 3 % BSA in PBS 0.1% Tween20 for 1 hour at room temperature. Soluble integrin $\alpha5\beta1$ (0.5 µg/mL) and a serial dilution of integrin inhibitor were incubated in the coated wells for 1 h at room temperature. The detection antibody (anti-human-Fc-HRP antibody conjugate) was then applied for 1 hour at room temperature and the binding visualized as described above. For the $\alpha v\beta3$ assay, plates were coated with vitronectin (1 µg/mL) and blocked as described for $\alpha5\beta1$. Soluble $\alpha v\beta3$ (1 µg/mL) was incubated with a serial

dilution of integrin inhibitor for one hour at room temperature. Primary (anti-αvβ3) and secondary antibody (anti-mouse-HRP conjugate) were applied for 1 h at room temperature and the binding visualized as described above.

For the αIIbβ3 assay, plates were coated with fibrinogen (10 µg/mL) and blocked as described for α5β1. Soluble αIIbβ3 (5 µg/mL) was incubated with a serial dilution of integrin inhibitor (25 mM Tris, pH7.6, 150 mM NaCl, 1 mM $MnCl_2$, 1 mg/mL BSA 1 mM $MgCl_2$, 1 mM $CaCl_2$) for one hour at room temperature. Primary (anti-CD41b) and secondary antibody (anti-mouse-HRP conjugate) were applied for 1 h at room temperature and the binding visualized as described above. (HRP – horse radish peroxidase)

Molecular docking

Automated docking studies were performed using the AutoDock 3.05 program package on the basis of the α5β1 homology model published before. The protein structure was set up for docking experiments as follows: Unpolar hydrogens were removed and Kollman united-atom partial charges were assigned. Solvation parameters were added to the energy-minimized protein file using the ADDSOL utility of the AutoDock program. The grid maps were calculated with AutoGrid. The grids were chosen to be large enough to include a significant part of the protein around the binding site using maps with 61×61×61 points with a grid-point spacing of 0.375 Å. The structures of the ligands were generated from the standard fragment library of the SYBYL software version 7.1 (Tripos). Geometry optimizations were achieved with the SYBYL/MAXIMIN2 minimizer by applying the BFGS (Broyden, Fletcher, Goldfarb and Shannon) algorithm with a convergence criterion of 0.001 kcal/mol and employing the TRIPOS force field. Partial atomic charges were assigned using Gasteiger and Marsili formalism as implemented in the SYBYL package. Rotable bonds were defined by the Autotors module of AutoDock .

Docking itself was performed by LGA algorithm as implemented in AutoDock applying a protocol with a maximum number of 1.5×10^6 energy evaluations, a mutation rate of 0.01, a crossover rate of 0.80 and an elitism value of 1. For the local search the pseudo-Solis and Wets algorithm was applied using a maximum of 300 interactions per local search and a search freq of 0.06. 50 independent docking runs were carried out for each ligand and results differing by less than 1.5 Å in positional root-mean-square deviation (rmsd) were clustered together and represented by the bind-

ing mode with most favorable free energy of binding. Pictures were generated using the PyMol program version 0.97.

General Procedures

GP-1: Acylation of ligand precursors with acid chlorides

The particular starting material was dissolved in a 3:1 mixture of dioxane and concentrated aqueous HCl (~0.1 M). After stirring for 1 h, the solvents were removed under reduced pressure. The deprotected amine was redissolved in dioxane/water 1:1 (~0.1 M), $NaHCO_3$ was added and the resulting solution treated with 1.1 equiv of the corresponding acid chloride. After stirring for 30 min, the solvents were removed in vacuo and the residue redissolved in methanol-water 3:1. LiOH (5 equiv) was ad-ded under stirring and the reaction monitored by analytical HPLC (usually 1 d). The resulting deprotected compound was purified using preparative reversed-phase HPLC.

GP-2: Acylation of ligand precursors with aromatic acids

The particular starting material was dissolved in a 3:1 mixture of dioxane and concentrated aqueous HCl (~0.1 M). After stirring for 1 h, the solvents were removed under reduced pressure. The deprotected amine was redissolved in DMF (~0.2 M) followed by addition of the corresponding aromatic acid (1.3 equiv), HATU (1.3 equiv) and DIEA (5 equiv). The resulting yellow solution was stirred for 24 h at ambient temperature. After evaporation of the DMF, the residue was taken up in methanol/water 3:1. LiOH (5 equiv) was added under stirring and the reaction monitored by analytical HPLC (usually 1 d). The resulting deprotected compound was purified using preparative reversed-phase HPLC.

GP-3: Acylation of ligand precursors with sulfonic acids

The particular starting material was dissolved in a 3:1 mixture of dioxane and concentrated aqueous HCl (~0.1 M). After stirring for 1h, the solvents were removed under reduced pressure. The deprotected amine was taken up in dry DCM (~0.1 M), followed by addition of the corresponding aromatic sulfonic acid chloride and DIEA (5 equiv). After stirring over night at ambient temperature and solvent evaporation, the residue was redissolved in methanol – water 3:1. LiOH (5 equiv) was added un-

der stirring and the reaction monitored by analytical HPLC (usually 1 d). The resulting deprotected compound was purified using preparative reversed-phase HPLC.

Preparation of methyl 4-(4-benzyloxyphenyl)-3-(*S*)-(tert-butyloxycarbonylamino) butanoate, 2

1. Preparation of diazomethane:

A 100 mL Erlenmeyer flask was filled with 35 mL of 40% aqueous KOH solution and 50 mL of diethyl ether and cooled in an ice-salt bath to -5 - 0 °C. 5.3 g *N*-methyl nitroso urea was added in portions keeping the temperature below 0 °C at any time. After 1.5 h, the mixture was carefully converted into a separating funnel (with a Teflon stopcock), the layer were separated and the organic layer dried for 3 h over KOH.

2. Preparation of the diazoketone

A solution of Boc-Tyr(OBn)-OH (3.71 g, 10.0 mmol, 1 equiv) in 35 mL dry THF under an argon atmosphere was cooled to -15°C. After addition of TEA (2.9 mL, 20 mmol, 2 equiv) and ethyl chloroformate (1.05 mL, 11 mmol, 1.1 equiv), the colorless suspension was stirred for 0.5 h at -5°C. Subsequently, the reaction flask was opened and the freshly prepared diazomethane solution was added carefully via a PP pipette. The yellow suspension was stirred at -15 to -5°C for 1 h. The reaction was quenched by addition of acetic acid (0.5 mL), followed by diethyl ether and saturated $NaHCO_3$ solution. The layers were separated and the organic layer washed with saturated NH_4Cl solution and brine, dried with Na_2SO_4, filtered and evaporated. The crude diazoketone was purified by column chromatography on silica gel (hexane/ethyl acetate, 8:2) to give the diazoketone as a yellow solid (3.91 g, 9.89 mmol, 99 %), which was instantly used in the next step.

3. Wolff rearrangement

The diazoketone (3.91 g, 9.89 mmol, 1 equiv) was dissolved in 150 mL abs. MeOH and cooled to -25°C. Silver benzoate (228 mg, 1 mmol, 0.1 equiv) was dissolved in triethylamine (5.5 mL, 40 mmol, 4 equiv) and added dropwise to the diazoketon. The mixture was allowed to warm to room temperature over night. After evaporation of the solvent, the residue was taken up in ethyl acetate, washed with sat. $NaHCO_3$, 5% aqueous citric acid and brine, dried over Na_2SO_4 and filtered. After evaporation, the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 2:1) to give 3.94 g (9.87 mmol, 99%) of a colorless solid. ^{1}H NMR (250 MHz,

$CDCl_3$): δ = 7.45 - 7.29 (m, 5H, Ar-*H*), 7.09 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.91 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 5.05 (s, 2H, CH_2O), 4.11 (m, 1H, *H*), 4.94 (br s, 1H, N*H*Boc), 3.68 (s, 3H, -CH_3), 2.86 (dd, *J* = 13.6 Hz, ^3J = 6.5 Hz, 1H, -C*H*), 2.75 (dd, ^2J = 13.6 Hz, ^3J = 7.6 Hz, 1H, -C*H*), 2.52 (dd, ^2J = 15.7 Hz, ^3J = 5.6 Hz, 1H, -C*H*), 2.43 (dd, ^2J = 15.7 Hz, ^3J = 5.7 Hz, 1H, -C*H*), 1.42 (s, 9H, *H*-*t*Bu). ^{13}C NMR (125 MHz, DMSO): δ = 172.0, 157.6, 155.1, 137.1, 130.3, 130.0, 128.5, 127.8, 127.3, 114.9, 79.3, 70.0, 51.5, 49.0, 39.5, 37.6, 28.3. MS (EI): *m/z* 399.1 [*M*]$^+$, 202.0 [BocNHCHCH$_2$COOCH$_3$], 146.0 [OOCNHCHCH$_2$COOCH$_3$], 102.0 [NHCHCH$_2$COOCH$_3$], 91.0 [Bn], 57.1 [*t*Bu].

Preparation of methyl 4-(4-hydroxyphenyl)-3-(*S*)-(tert-butyloxycarbonylamino) butanoate, 3

Benzyl ether **27** (3.94 g, 9.87 mmol) was hydrogenated with Pd on carbon (400 mg 5% Pd/C) in methanol at 1 atm H_2 for 10h. After filtration over Celite® and evaporation of the solvents, the product was purified by flash chromatography on silica gel (hexane/ethyl acetate 2:1) to give **28** (2.21 g, 7.14 mmol, 71%) as colorless solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.15 (br s, 1H, -O*H*), 6.97 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 6.75 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 5.16 (d, *J* = 7.6 Hz, 1H, -N*H*Boc), 4.10 (m, 1H, -C*H*), 2.81 (dd, *J* = 12.9 Hz, *J* = 5.0 Hz, 1H, -C*H*), 2.68 (dd, *J* = 13.3 Hz, *J* = 7.7 Hz, 1H, -C*H*), 2.49 (dd, *J* = 15.9 Hz, *J* = 5.5 Hz, 1H, -C*H*), 2.39 (dd, *J* = 15.8 Hz, *J* = 6.1 Hz, 1H, -C*H*), 1.40 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, DMSO): δ = 172.3, 155.5, 155.1, 130.3, 128.7, 115.4, 79.8, 51.7, 49.1, 39.6, 37.5, 28.3. MS (ESI): *m/z* 310.2 [*M*+H$^+$].

Preparation of (*S*)-1,2,3,4-tetrahydro-7-hydroxy-6,8-diiodoisoquinoline-3-carboxylic acid, 4

Ortho-diiodotyrosine (20 g, 42.6 mmol, 1 equiv) was dissolved in a mixture of conc. hydrochloric acid (200 mL) and DME (13 mL). 15 mL of a 35% aqueous solution of formalin was added and the resulting suspension was stirred at 75 °C for 30 min. After an additional 100 mL of hydrochloric acid, 8 mL of DME and 8 mL of formalin, heating and stirring was continued for additional 18 h. The mixture was cooled down with an ice bath and filtered. The residue was washed twice with cold DME and dried under reduced pressure. The yield was 10.3 g (21.4 mmol, 50%) of **47** as hydrochloride (light brown solid). ^{1}H NMR (500 MHz, DMSO): δ = 14.08 (br s, 1H, -COO*H*), 10.23 (br s, 2H, -N*H*), 9.66 (s, 1H, -O*H*), 7.71 (s, 1H, Ar-*H*5), 4.31 (dd, *J* = 11.1 Hz, *J* = 4.9 Hz, 1H, -C*H*), 4.10 (d, *J* = 16.1 Hz, 1H, -C*H*), 4.01 (d, *J* = 16.4 Hz, 1H, -C*H*), 3.21 (dd, *J* = 16.8 Hz, *J* = 4.6 Hz, 1H, -C*H*), 3.09 (dd, *J* = 16.8 Hz, *J* = 11.1 Hz, 1H, -

C*H*). ^{13}C NMR (125 MHz, DMSO): δ = 169.4, 154.3, 138.7, 132.0, 127.0, 90.8, 86.1, 52.4, 50.0, 27.0. MS (ESI): *m/z* 890.4 $^{[2M+H+]+}$, 445.9 [*M*+H$^+$]$^+$, 400.0 [*M*+H$^+$-COOH].

Preparation of methyl (*S*)-1,2,3,4-tetrahydro-7-hydroxy-6,8-diiodoisoquinoline-3-carboxylate, 5

Compound **5** (10.0 g, 22.5 mmol, 1 equiv) was dissolved in 200 mL of methanol and cooled with an ice bath. Thionyl chloride (0.11 mol, 5 equiv) was added dropwise and the resulting brown mixture stirred over night. The solution was concentrated under reduced pressure, taken up with ethyl acetate and washed with saturated $NaHCO_3$ solution, water and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated. The resulting product could be used without further purification. Yield was 7.1 g (15.3 mmol, 69%) of an orange solid. ^{1}H NMR (500 MHz, DMSO): δ = 7.55 (s, 1H, Ar-*H*), 3.83 (d, *J* = 16.8 Hz, 1H, -C*H*), 3.72 (dd, *J* = 9.3 Hz, *J* = 4.6 Hz, 1H, -C*H*), 3.68 (s, 3H, -CH_3), 3.68-3.64 (m, 1H, -C*H*), 2.89 (dd, *J* = 16.0 Hz, *J* = 4.5 Hz, 1H, -C*H*), 2.78 (dd, *J* = 15.9 Hz, *J* = 9.5 Hz, 1H, -C*H*). ^{13}C NMR (125 MHz, DMSO): δ = 172.2, 153.2, 138.6, 137.7, 129.2, 91.4, 84.2, 53.5, 53.0, 51.8, 29.3. MS (ESI): *m/z* 459.9 [*M*+H$^+$]$^+$, 400.0 [*M*+H$^+$- COOCH$_3$]$^+$.

Preparation of methyl 1-(*tert-but*yloxycarbonyl)-2-(*S*)-1,2,3,4-tetrahydro-7-hydroxy-6,8-diiodoisoquinoline-3-carboxylate, 6

Amine **5** (6.0 g, 13.07 mmol, 1 equiv) was dissolved in 100 mL of THF. Boc-anhydride (3.1 g, 14.38 mmol, 1.1 equiv) and triethylamine (2.36 mL, 16.99 mmol, 1.3 equiv) were added and the resulting red solution stirred over night at ambient temperature. The reaction mixture was concentrated under reduced pressure, taken up in ethyl acetate and washed with 5% aqueous solution of citric acid, water and brine. The organic layer was dried with Na_2SO_4, filtered and evaporated. Purification by column chromatography on silica gel (hexane/ethyl acetate 2:1) gave 6.9 g (12.3 mmol, 94%) of a yellow foam. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.49 (s, 1H, Ar-*H*5), 5.83 (br s, 1H, Ar-O*H*), 5.13 (m, 1H**, -C*H*), 4.89 (m, 1H*, -C*H*), 4.62 (d, *J* = 18.0 Hz, 1H, -C*H*), 4.24 (d, *J* = 18.0 Hz, 1H, C*H*), 3.65 (s, 3H*, -CH_3), 3.64 (s, 3H**, -CH_3), 3.12-3.09 (m, 2H, -CH_2), 1.54 (s, 9H**, H-*t*Bu), 1.48 (s, 9H*, H-*t*Bu). ^{13}C NMR (125 MHz, DMSO): δ = (171.4, 171.3), (155.1, 154.5), (152.3, 152.2), (138.6, 138.3), (137.2, 136.6), (127.6, 127.4), 113.0, (86.9, 86.4), 81.149, (79.7, 79.5), 53.3, 52.5, 51.7, 51.0, 50.2, 30.3, 29.9, 29.7, 28.3. MS (EI): *m/z* 501.9 [*M*-*t*Bu]$^+$, 457.9 [*M*-Boc]$^+$, 400.0 [*M*-Boc-COOMe]$^+$.

*represents the minor rotamer of the Boc group.

** represents the major rotamer of the Boc group.

^{13}C shifts that could be assigned to one carbon are given in parentheses.

Preparation of methyl 1-(*tert-but*yloxycarbonyl)-2-(*S*)-1,2,3,4-tetrahydro-7-hydroxy-isoquinoline-3-carboxylate, 7

Compound **6** (6.9 g, 12.3 mmol, 1 equiv) was dissolved in methanol (200 mL). 3.75 mL triethylamine (27.1 mmol, 2.2 equiv) and catalyst (5 % Pd/C, 500 mg) were added and the resulting mixture hydrogenated at 1 atm H_2 under rapid stirring for 12 h. After the TLC indicated total conversion, the catalyst was removed by filtration over Celite®, the filtrate was evaporated and the crude product subjected to flash chromatography on silica gel (hexane/ethyl acetate 1:1) to yield 3.21 g (10.4 mmol, 85 %) of a light yellow foam. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.36 (br s, 1H, -O*H*)**, 7.16 (br s, 1H, -O*H*)*, 7.00-6.92 (m, 1H, Ar-*H*), 6.70-6.60 (m, 2H, Ar-*H*), 5.08 (dd, *J* = 5.5 Hz, *J* = 3.2 Hz, 1H, -C*H*)*, 4.74 (t, *J* = 5.5 Hz, 1H, -C*H*)**, 4.63 (d, *J* = 15.9 Hz, 1H, -C*H*)**, 4.60 (d, *J* = 16.7 Hz, 1H, -C*H*)*, 4.46 (d, *J* = 16.6 Hz, 1H, -CH)*, 4.42 (d, *J* = 16.1 Hz, 1H, -C*H*)**, 3.64 (s, 3H, -C*H*$_3$), 3.57 (s, 3H, -C*H*$_3$), 3.20-3.00 (m, 2H, -C*H*$_2$), 1.51 (s, 9H, H-*t*Bu)*, 1.45 (s, 9H, H-*t*Bu)**. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 172.7**, 172.5*, 155.7*, 155.6**, 155.2, 134.5**, 133.8*, 129.4*, 128.8**, 123.1**, 122.9*, 114.4, 112.9**, 112.8*, 81.2**, 81.0*, 54.8, 53.0*, 52.3**, 44.8*, 44.3**, 30.8**, 30.5*, 28.4*, 28.3**. MS (ESI): *m/z*308.3 [*M*+H$^+$]$^+$, 208.2 [*M*+H$^+$-Boc]$^+$. MS (EI): *m/z* 307.1 [*M*]$^+$, 250.0 [*M*-*t*Bu], 206.0 [*M*-Boc]$^+$, 192.0 [*M*-Boc-CH_3]$^+$, 148.1 [*M*-Boc-$COOCH_3$], 57.1 [*t*Bu]$^+$.

*represents the minor rotamer of the Boc-group

**represents the major rotamer.of the Boc-group

Preparation of 3-(pyridine-2-ylamino)propan-1-ol, 8a

2-Bromopyridine (5.2 g, 33 mmol) and 3-aminopropan-1-ol (6.0 g, 80 mmol) were heated in to 140 °C in a sealed glass tube over night. The reaction mixture was directly subjected to flash chromatography on silica gel (DCM/MeOH 95:5) to give **8a** (4.8 g, 31.5 mmol, 95%) as a light brown oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.99 (dd, *J* = 5.1 Hz, *J* = 1.0 Hz, 1H, Ar-*H*), 7.34 (ddd, *J* = 8.6 Hz, *J* = 7.1 Hz, *J* = 1.9 Hz, 1H, Ar-*H*), 6.51 (ddd, *J* = 7.0 Hz, *J* = 5.2 Hz, *J* = 0.8 Hz, 1H, Ar-*H*), 6.37 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 4.70 (br s, 1H); 4.60 (br s, 1H); 3.63 (m, 2H, -C*H*$_2$), 3.49 (dd, *J* = 12.2

Hz, *J* = 6.2 Hz, 2H, -C*H*$_2$), 1.73 (m, 2H, -C*H*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 147.4, 136.5, 111.2, 107.8, 58.7, 37.9, 32.4. MS (ESI): *m/z* 153.0 [*M*+H$^+$].

Preparation of 3-(pyridine-2-ylamino)butan-1-ol, 8b

2-Bromopyridine (1.0 g, 6.33 mmol) and 4-aminobutan-1-ol (1.4 g, 15.82 mmol) were heated in to 140 °C in a sealed glass tube over night. The reaction mixture was directly subjected to flash chromatography on silica gel (DCM/MeOH, 95:5 + 1% TEA) to give **8b** (1.04 g, 6.26 mmol, 99%) as a light brown oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 5.2 Hz, 1H, Ar-*H*), 7.33 (ddd, *J* = 8.8 Hz, *J* = 7.2 Hz, *J* = 1.9 Hz, 1H, Ar-*H*), 6.80 (br s, 1H, -N*H*), 6.46 (ddd, *J* = 6.9 Hz, *J* = 5.2 Hz, *J* = 0.8 Hz, 1H, Ar-*H*), 6.38 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 5.27 (br s, 1H, -O*H*), 3.60 (t, *J* = 8.5 Hz, 2H, -C*H*$_2$), 3.23 (m, 2H, -C*H*$_2$), 1.61 (m, 4H, -C*H*$_2$C*H*$_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): 158.1, 146.4, 138.0, 112.4, 107.4, 62.1, 41.8, 29.7, 26.0. MS (ESI): *m/z* 167.0 [*M*+H$^+$].

Preparation of 1-(*tert*-*but*yldiphenylsilyloxy)-3-(pyridine-2-ylamino)propane, 9a

To a solution of **8a** (1.56 g, 10.3 mmol) and imidazole (1.96 g, 28.8 mmol) in 100 mL of dry DCM was added TBDPS chloride (3.5 mL, 13.4 mmol) and the colorless suspension stirred for 18 h at ambient temperature. After solvent evaporation, the crude product was directly subjected to flash chromatography on silica gel (hexane/ethyl acetate, 7:3 + 1% TEA) to give (9.05 mmol, 88%) of a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 4.1 Hz, 1H, Ar-*H*), 7.69 (m, 4H, ^{TBDPS}Ar-*H*), 7.70-7.68 (m, 7H, ^{TBDPS}Ar-*H*, Ar-*H*), 6.54 (t, *J* = 6.0 Hz, 1H, Ar-*H*), 6.33 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 3.82 (t, *J* = 5.7 Hz, 2H, -C*H*$_2$), 3.44 (q, *J* = 6.2 Hz, 2H, -C*H*$_2$), 1.87 (m, 2H, -C*H*$_2$), 1.10 (s, 9H, H-*t*Bu). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 158.7, 147.9, 137.2, 135.5, 133.5, 129.6, 127.7, 112.4, 106.8, 62.1, 39.5, 31.9, 26.9, 19.1. MS (ESI): *m/z* 391.2 [*M*+H$^+$]$^+$.

Preparation of 1-(*tert*-*but*yldiphenylsilyloxy)-4-(pyridine-2-ylamino)butane, 9b

The compound was synthesized from **8b** (660 mg, 4.0 mmol), imidazole (490 mg, 7.2 mmol) and TBDPS chloride (1.35 mL, 5.2 mmol) as described for **9a**. Column chromatography on silica gel (hexane/ethyl acetate 8:2 + 1% TEA) gave 995 mg (2.46 mmol, 66%) of a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.08 (ddd, *J* = 5.0 Hz, *J* = 0.8 Hz, 1H, Ar-*H*), 7.70 - 7.66 (m, 4H, ^{TBDPS}Ar-*H*), 7.44-7.35 (m, 6H, ^{TBDPS}Ar-*H* + Ar-*H*), 6.55 (ddd, *J* = 7.1 Hz, *J* = 5.0 Hz, *J* = 0.9 Hz, 1H, Ar-*H*), 6.34 (dt, *J* = 8.4 Hz, *J* = 0.8 Hz, 1H, Ar-*H*), 4.54 (br s, 1H, -N*H*), 3.73 (t, *J* = 6.0 Hz, 2H, -C*H*$_2$),

3.27 (q, *J* = 6.7 Hz, 2H, -CH_2), 1.70 (m, 4H, -CH_2CH_2), 1.07 (s, 9H, *H*-*t*Bu). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 158.9, 148.1, 137.3, 135.5, 134.0, 129.5, 127.6, 112.6, 106.4, 63.5, 42.1, 30.0, 26.9, 26.0, 19.2. MS (ESI): *m/z* 405.2 [*M*+H^+].

Preparation of 1-(*tert-but*yldiphenylsilyloxy)-3-(pyridine-2-yl)-3-*tert*-butyloxycarbonylaminopropane, 10a

Compound **9a** (616 mg, 1.58 mmol) was dissolved in 30 mL of dry THF. After addition of TEA (657 µL, 4.74 mmol), Boc-anhydride (379 mg, 1.73 mmol), and DMAP (20 mg, 0.16 mmol), the reaction mixture was stirred for 12 h at ambient temperature. The solvent was evaporated and the crude product subjected to flash chromatography (hexane/ethyl acetate, 8:2 + 1% TEA) to give **10a** (696 mg, 1.42 mmol, 90 %) as colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.37 (dd, *J* = 5.0 Hz, *J* = 1.6 Hz, 1H, Ar-*H*), 7.71 - 7.53 (m, 6H, ^{TBDPS}Ar-*H*, Ar-*H*), 7.46-7.33 (m, 6H, ^{TBDPS}Ar-*H*), 7.00 (ddd, *J* = 6.6 Hz, *J* = 4.9 Hz, *J* = 1.5 Hz, 1H, Ar-*H*), 4.12 (m, 2H, -CH_2), 3.72 (t, *J* = 6.3 Hz, 2H, -CH_2), 1.94 (m, 2H, -CH_2), 1.50 (s, 9H, *H*-*t*Bu), 1.05 (s, 9H, ^{TBDPS} *t*Bu). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 154.7, 154.2, 147.6, 136.8, 135.5, 133.8, 129.5, 127.5, 120.1, 119.4, 80.8, 61.9, 44.3, 32.0, 28.3, 26.8, 19.1. MS (ESI): *m/z* 513.2 [*M*+Na^+]$^+$, 391.4 [*M*+H^+-Boc]$^+$.

Preparation of 1-(*tert-but*yldiphenylsilyloxy)-4-(pyridine-2-yl)-4-*tert*-butyloxycarbonylaminobutane, 10b

The title compound was prepared from **9b** (965 mg, 2.38 mmol), TEA (990 µL, 4.74 mmol), di-*tert-but*ylcarbonate (625 mg, 2.86 mmol) and DMAP (30 mg, 0.24 mmol) as described for **10a**. Flash chromatography (hexane/ethyl acetate 8:2 + 1% TEA) gave (717 mg, 1.84 mmol, 77%) of a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.40 (m, 1H, Ar-*H*), 7.74-7.70 (m, 4H, ^{TBDPS}Ar-*H*), 7.64 - 7.36 (m, 8H, 2Ar-*H*, ^{TBDPS}Ar-*H*), 6.99 (ddd, *J* = 6.1 Hz, *J* = 4.9 Hz, *J* = 2.3 Hz, 1H, Ar-*H*), 4.03 (t, *J* = 7.2 Hz, 2H, -CH_2), 3.73 (t, *J* = 6.2 Hz, 2H, -CH_2), 1.77 (m, 2H, -CH_2), 1.65 (m, 2H, -CH_2), 1.55 (s, 9H, *H*-*t*Bu), 1.09 (s, 9H, TBDPS-*t*Bu). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 154.5, 154.1, 147.4, 136.6, 135.4, 133.8, 129.4, 127.4, 119.9, 119.2, 80.6, 63.5, 46.5, 29.9, 28.1, 26.7, 25.3, 19.0. MS (ESI): *m/z* 527.1 [*M*+Na^+]$^+$, 449.0 [*M*+H^+-*t*Bu]$^+$, 405.2 [*M*+H^+-Boc]$^+$.

Preparation of 3-(pyridine-2-yl)-3-*tert-but*yloxycarbonylaminopropan-1-ol, 11a

A solution of **10a** (666 mg, 1.36 mmol) and TBAF (473 mg, 1.50 mmol) in 20 mL THF was stirred for 12 h at ambient temperature. After evaporation of the solvents, the

crude product was subjected to flash chromatography (hexane/ethyl acetate 2:1) to give **11a** (220 mg, 0.87 mmol, 64%) as light brown oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.16 (dt, *J* = 4.9 Hz, *J* = 1.2 Hz, Ar-*H*), 7.49 (m, 2H, Ar-*H*), 6.87 (dd, *J* = 8.8 Hz, *J* = 4.5 Hz, 1H, Ar-*H*), 5.24 (t, *J* = 6.8 Hz, 1H, -O*H*), 3.83 (t, *J* = 6.0 Hz, 2H, -CH_2), 3.51 (q, *J* = 6.2 Hz, -CH_2), 1.78 (m, 2H, -CH_2), 1.38 (s, 9H, *H*-*t*Bu). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 155.0, 153.7, 146.6, 137.0, 119.3, 119.1, 81.1, 57.7, 44.0, 31.1, 27.9. MS (ESI): *m/z* 253.3 [*M*+H$^+$], 196.2 [*M*+H$^+$-^{t}Bu], 153.2 [*M*+H$^+$-Boc].

Preparation of 4-(pyridine-2-yl)-4-*tert*-*but*yloxycarbonylaminobutan-1-ol, 11b

A solution of **10b** (717 mg, 1.84 mmol) and TBAF (637 mg, 2.02 mmol) in 20 mL THF was stirred for 12 h at ambient temperature. After evaporation of the solvents, the crude product was subjected to flash chromatography (hexane/ethyl acetate 2:1) to give **11b** (292 mg, 1.16 mmol, 63%) as light brown oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.24 (m, 1H, Ar-*H*), 7.56-7.44 (m, 2H, Ar-*H*), 6.98 (m, 1H, Ar-*H*), 3.82 (t, *J* = 7.3 Hz, 2H, -CH_2), 3.52 (t, *J* = 6.2 Hz, 2H, -CH_2), 3.37 (br s, -O*H*), 1.61 (m, 2H, -CH_2), 1.46 (m, 2H, -CH_2), 1.40 (s, 9H, *H*-*t*Bu). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 154.4, 153.9, 147.2, 136.8, 119.9, 119.4, 80.8, 61.7, 46.3, 29.3, 28.0, 24.8. MS (ESI): *m/z* 167.0 [*M*+H$^+$]$^+$.

Preparation of 3-(benzyloxycarbonylamino)propan-1-ol, 12a

3-Aminopropanol (1.10 g, 14.65 mmol) and $NaHCO_3$ (1.45 g, 17.32 mmol) were dissolved in water-dioxane 1:1 (100 mL) and cooled to 0^{o}C. A solution of benzyloxy-carbonyl-*O*-succinimide (3.10 g, 13.32 mmol) in dioxane (20 mL) was added drop-wise and the reaction mixture stirred for 12 h. After partial evaporation of the dioxane, the mixture was acidified with 1 N hydrochloric acid and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried with Na_2SO_4 and filtered. After evaporation of the solvents, the crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate 1:1) t give the title compound (2.12 , 10.12 mmol, 76%) as a colorless solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.34 (m, 5H, Ar-*H*), 5.15 (br s, 1H, -N*H*), 5.10 (s, 2H, -CH_2), 3.66 (t, *J* = 5.8 Hz, 2H, -CH_2), 3.33 (dd, *J* = 12.2 Hz, *J* = 6.0 Hz, 2H, -CH_2), 2.73 (br s, 1H, -O*H*), 1.69 (m, 2H, -CH_2). ^{13}C NMR (108 MHz, $CDCl_3$): δ = 157.2, 136.4, 128.4, 128.1, 128.0, 66.7, 59.6, 37.8, 32.4. MS (EI): 209.1 [*M*]$^+$, 108.0 [BnOH]$^+$, 91 [Bn]$^+$.

Preparation of 4-(benzyloxycarbonylamino)butan-1-ol, 12b

The title compound was synthesized from 4-aminobutanol (2.94 g, 33.0 mmol), TEA (1.45 g, 17.32 mmol) and benzyloxycarbonyl-*O*-succinimide (8.22 g, 33.0 mmol) as described for **12a**. Recrystallization from hexane/ethyl acetate gave **12b** (6.45 g, 29.0 mmol, 88%) as a colorless solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.32 (m, 5H, Ar-*H*), 5.20 (br s, 1H, -N*H*), 5.06 (s, 2H, -CH_2), 3.59 (t, *J* = 5.5 Hz, 2H, -CH_2), 3.17 (m, 2H, -CH_2), 2.84 (br s, 1H, -O*H*), 1.54 (m, 4H, -CH_2CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 156.5, 136.5, 128.4, 127.9, 127.9, 66.5, 62.0, 40.7, 29.5, 26.3. MS (EI): 223.1 [*M*], 108.0 $[BnOH]^+$, 91.0 $[Bn]^+$.

Preparation of 3-(pyrimidin-2-ylamino)propan-1-ol, 13

The title compound was synthesized from 2-chloropyrimidine (4.00 g, 34 mmol) and 3-aminopropanol (8.00 g, 107 mmol) as described for **8a**. Column chromatography on silica gel (DCM/MeOH 95:5) gave **13** (4.54 g, 29.6 mmol, 85%) as light yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 4.9 Hz, 2H, Ar-*H*), 6.51 (t, *J* = 4.8 Hz, 1H, Ar-*H*), 5.68 (br s, 1H, -N*H*), 3.92 (br s, 1H, -O*H*), 3.63 (t, *J* = 5.6 Hz, 2H, -CH_2), 3.57 (q, *J* = 6.0 Hz, 2H, -CH_2), 1.75 (m, 2H, -CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): 162.8, 158.0, 110.4, 99.9, 58.6, 37.5, 33.0. MS (ESI): 154.2 $[M+H^+]^+$.

Preparation of 3-(pyridazin-2-ylamino)propan-1-ol, 14

The title compound was synthesized from 2-chloropyridazine (4.00 g, 34 mmol) and 3-aminopropanol (8.00 g, 107 mmol) as described for **8a**. Column chromatography on silica gel (DCM/MeOH 95:5) gave **14** (3.71 g, 24.3 mmol, 82%) as light yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.90 - 7.85 (m+s, 2H, Ar-*H*), 7.71 (d, *J* = 2.7 Hz, 1H, Ar-*H*), 5.29 (br s, 1H, -N*H*), 4.02 (br s, 1H, -O*H*), 3.66 (t, *J* = 5.7 Hz, 2H, -CH_2), 3.50 (dd, *J* = 11.4 Hz, *J* = 5.6 Hz, 1H, -CH_2), 1.78 (m, 2H, -CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 154.9, 141.3, 132.9, 132.0, 59.3, 38.1, 32.5. MS (ESI): 154.0 $[M+H^+]^+$, 136.0 $[M+H^+-H_2O]^+$.

Preparation of 3-(pyrimidin-6-ylamino)propan-1-ol, 15

The title compound was synthesized from 6-chloropyrimidine (0.54 g, 4.71 mmol) and 3-aminopropanol (0.98 g, 26.15 mmol) as described for **8a**. Column chromatography on silica gel (DCM/MeOH 9:1) gave **15** (0.51 g, 3.34 mmol, 71%) as light yellow solid. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.43 (s, Ar-*H*), 8.00 (dd, *J* = 5.7 Hz, *J* = 1.2 Hz, 1H, Ar-*H*), 6.30 (d, *J* = 6.1 Hz, 1H, Ar-*H*), 6.07 (s, 1H, -N*H*), 4.35 (s, 1H, -O*H*), 3.65 (m, 2H, -CH_2), 3.46 (m, 2H, -CH_2), 1.76 (m, 2H, -CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ =

162.2, 158.1, 154.3, 59.4, 38.1, 32.0, 22.8. MS (ESI): 154.0 $[M+H^+]^+$, 136.0 $[M+H^+-H_2O]^+$.

Preparation of 1-bromo-2,6-dimethyl-4-methoxybenzene, 16a

4-bromo-3,5-dimethylphenol (3.0 g, 15.0 mmol) was dissolved in 150 mL dry THF. After addition of K_2CO_3 (4.2 g, 30.0 mmol) and dimethyl sulfate (1.1 mL, 11.3 mmol), the mixture was refluxed for 8 h. After cooling to room temperature, the reaction was quenched with saturated NH_4Cl solution, the mixture extracted with ethyl acetate (2x 50 mL). The organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate 8:2) to give the title compound (2.7 g, 12.6 mmol, 84 %) as colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.68 (s, 2H, Ar-*H*), 3.79 (s, 3H, -OC*H*$_3$), 2.43 (s, 6H, 2-C*H*$_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 158.0, 138.9, 118.0, 113.7, 55.1, 23.9. GC-MS (EI): *m/z* 214.1 $[M]^+$(1Br), 199.1 $[M-CH_3]^+$(1Br), 171.1 $[M-CH_3-CO]^+$(1Br), 135.2 $[M-Br]^+$.

Preparation of 1-bromo-2,6-dimethyl-4-isopropoxybenzene, 16b

4-Bromo-3,5-dimethylphenol (1.0 g, 5.0 mmol, 1 equiv) was dissolved in 60 mL dry DMF. After addition of K_2CO_3 (4.2 g, 15.0 mmol, 3 equiv), 2-bromopropane (3.1 g, 25.0 mmol, 5 equiv) and potassium iodide (2.5 g, 15.0 mmol, 3 equiv), the mixture was heated to 120°C for 8 h. After cooling to room temperature, the DMF was removed under reduced pressure, the residue taken up in ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate 8:2) to give the title compound (0.86 g, 3.5 mmol, 70%) as colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.69 (s, 2H, Ar-*H*), 4.53 (sept, *J* = 6.1 Hz, 1H, -C*H*), 2.42 (s, 6H, 2C*H*$_3$), 1.36 (d, *J* = 6.1 Hz, 6H, 2C*H*$_3$). ^{13}C NMR (63 MHz, DMSO): δ = 156.3, 138.9, 117.9, 115.8, 69.9, 23.9, 22.0. GC-MS (EI): *m/z* 242.2 $[M]^+$(1Br), 200.1 $[M-C_3H_7]^+$(1Br), 121.2 $[M-C_3H_7-Br]^+$.

Preparation of 2,6-dimethyl-4-methoxybenzoic acid, 17a

Compound **16a** (2.7 g, 12.55 mmol) was dissolved in 20 mL of dry THF and cooled to -78 °C under an atmosphere of argon. *n*BuLi (1.6 M in hexane, 9.4 mL, 15.06 mmol) was added and the resulting mixture stirred at -78 °C for 1 h. ~5 g of crushed dry ice

were added, the ice bath was removed and the reaction mixture allowed to warm up to room temperature. The THF was removed under reduced pressure and the residue taken up in 1 N hydrochloric acid and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated. Recrystallization of pure **17a** from DCM/hexane gave 1.30 g (7.23 mmol, 58 %) of colorless crystals. ^{1}H NMR (250 MHz, DMSO): δ = 12.8 (br s, 1H, -COO*H*), 6.64 (s, 2H, Ar-*H*), 3.74 (s, 3H, -OCH_3), 2.26 (s, 6H, 2CH_3). ^{13}C NMR (62.9 MHz, DMSO): δ = 170.4, 159.1, 136.0, 127.6, 112.7, 54.9, 19.8. MS (EI): *m/z* 180.1 [*M*], 163.0 [*M*-OH$^{\cdot}$]$^+$ 135.1 [*M*-COOH]$^+$.

Preparation of 2,6-dimethyl-4-isopropoxybenzoic acid, 17b

The title compound was synthesized from **16b** (0.86 g, 3.5 mmol), *n*BuLi and CO_2 as described for **17a**. Recrystallization from DCM/hexane yielded 0.47 g (2.28 mmol, 65 %) of colorless crystals. ^{1}H NMR (250 MHz, DMSO): δ = 12.78 (br s, 1H, -COO*H*), 6.61 (s, 2H, Ar-*H*), 4.60 (sept, *J* = 6.0 Hz, 1H, -C*H*), 2.25 (s, 6H, 2CH_3), 1.24 (d, *J* = 6.0 Hz, 6H, 2CH_3). ^{13}C NMR (62.9 MHz, DMSO): δ = 170.4, 157.3, 136.1, 127.3, 114.3, 68.8, 21.7, 19.8. MS (EI): *m/z* 208.1 [*M*]$^+$, 166.0 [*M*-C_3H_7]$^+$, 148.0 [*M*-C_3H_7-H_2O].

Preparation of 2,6-diethylbenzoic acid, 18

The title compound was synthesized from 1-bromo-2,6-diethylbenzene (1.0 g, 4.69 mmol), *n*BuLi (1.6 M in hexane, 3.81 mL, 6.10 mmol) and CO_2 as described for **17a**. Recrystallization from DCM/hexane yielded 0.27 g (1.5 mmol, 32%) of colorless crystals. ^{1}H NMR (500 MHz, DMSO): δ = 7.28 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.11 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 2.58 (q, *J* = 7.5 Hz, 2H, -CH_2), 1.16 (t, ^{3}*J* = 7.5 Hz, 3H, -CH_3). ^{13}C NMR (125 MHz, DMSO): δ = 170.8, 139.3, 134.6, 128.8, 125.8, 26.1, 15.6. MS (EI): *m/z* 178.1 [*M*], 160.0 [*M*-H_2O]$^+$.

Preparation of 3-bromo-2,4,6-trimethylpyridine, 19

2,4,6-Trimethylpyridine (18.3 g, 154 mmol) was dissolved in 30 mL trifluoracetic acid cooled by a water bath. After addition of 40 mL of concentrated sulfuric acid, NBS (30.2 g, 169.4 mmol) was added in small portions. The resulting red solution was stirred at ambient temperature for 24 h. The reaction mixture was poured on ice, alkalized with sodium hydroxide and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated on a

rotary evaporator. The resulting oil was purified by fractionized distillation under vacuum (6.5 mbar, $bp_{(collidine)}$ = ~50°C, $bp_{(product)}$ = 75-77°C). Yield was 28.74 g (144 mmol, 93%) of a colorless liquid, which turned brown on standing. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.68 (s, 1H, Ar-*H*), 2.50 (s, 3H, -CH_3), 2.29 (s, 3H, -CH_3), 2.19 (s, 3H, -CH_3). ^{13}C NMR (125 MHz, DMSO): δ = 156.1, 155.2, 146.9, 122.8, 120.8, 25.3, 23.3, 22.8. MS (ESI): *m/z* 200.3 [*M*+H$^+$]$^+$(1Br).

Preparation of 2,4,6-trimethylnicotinic acid, 20

To a cooled (-78°C) solution of the **33** (2.00 g, 10 mmol, 1 equiv) in dry THF (40 mL) was added *n*BuLi (1.6 M in hexane, 6.25 mL, 10 mmol, 1 equiv) under an argon atmosphere. The resulting reaction mixture was stirred for 30 min. After addition of crushed dry ice (~10 g), the cooling bath was removed and the reaction mixture allowed to warm to room temperature. The THF was evaporated and the residue dissolved in 2N NaOH/diethyl ether. The aqueous phase was separated and acidified to pH 6. The mixture was concentrated, triturated with ethanol and filtered. The filtrate was evaporated and the product recrystallized from methanol/ethyl acetate. Yield: 1.49 g (7.4 mmol, 74%) of a tan solid (as hydrochloride salt). ^{1}H NMR (500 MHz, DMSO): δ = 7.57 (s, 1H, Ar-*H*), 6.89 (br s, 1H, N*H*$^+$), 2.67 (s, 3H, -CH_3), 2.66 (s, 3H, -CH_3), 2.42 (s, 3H, -CH_3). ^{13}C NMR (125 MHz, DMSO): δ = 166.6, 153.5, 152.1, 150.0, 130.7, 125.7, 19.9, 19.5, 18.4. MS (ESI): *m/z* 166.3.

Preparation of methyl 4-[4-(3-*N*-pyridin-2-yl-3-*N*-(*tert-but*yloxycarbonylamino)propoxy)phenyl]-3-(*S*)-(tert-butyloxycarbonylamino) butanoate, 21

Boc-tyrosine methyl ester (**1**, 1.17 g, 3.97 mmol), **11a** (1.2 g, 4.76 mmol) and tributylphosphine (1.3 mL, 5.16 mmol) was dissolved in 50 mL of dry THF and cooled by an ice bath. A solution of ADDP (1.3 g, 5.16 mmol) in 20 mL of dry THF was added dropwise over 4 h. The resulting yellow suspension was allowed to warm up to room temperature and stirred over night. After addition of silica gel, the solvents were removed and the crude product subjected to column chromatography on silica gel (hexane/ethyl acetate 7:3) to give **21** (418 mg, 790 µmol, 40%) as a colorless foam. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.31 (dt, *J* = 4.8 Hz, *J* = 1.3 Hz, 1H, Ar-*H*), 7.59 - 7.57 (m, 2H, Ar-*H*), 7.00-6.94 (m, 3H, Ar-*H*), 6.74 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 4.96 (d, *J* = 7.8 Hz, 1H, -N*H*Boc), 4.51 (m, 1H, -C*H*), 4.12 (t, *J* = 7.0 Hz, 2H, -OCH_2), 3.96 (t, *J* = 6.3 Hz, 2H, -NCH_2), 3.68 (s, 3H, -OCH_3), 2.98 (m, 2H, -CH_2), 2.10 (m, 2H, -CH_2), 1.47 (s, 9H, *H*-*t*Bu), 1.40 (s, 9H, *H*-*t*Bu). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 172.3, 158.0, 155.0,

154.4, 154.1, 147.6, 136.8, 130.1, 127.6, 119.8, 119.4, 114.3, 82.0, 81.0, 79.8, 65.5, 44.0, 37.3, 28.8, 28.2, 28.1. MS (ESI): *m/z* 552.2 $[M+Na^+]^+$, 530.1 $[M+H^+]^+$, 474.1 $[M+H^+-t\text{Bu}]^+$, 430.2 $[M+H^+\text{-Boc}]^+$, 374.3 $[M+H^+\text{-Boc-}t\text{Bu}]^+$, 330.6 $[M+H^+\text{-2Boc}]^+$.

Preparation of methyl 3-[4-(3-pyridin-2-ylamino)propoxy)phenyl]-3-(*R*)-(*tert*-butyloxycarbonylamino) propanoate, 22

The title compound was synthesized from Boc-D-tyrosine methyl ester (*ent*-**1**, 660 mg, 2.24 mmol), **8a** (440 mg, 2.46 mmol), triphenylphosphine (720 µL, 2.91 mmol) and ADDP (730 mg, 2.91 mmol) as described for **21**. Column chromatography on silica gel (DCM/ethyl acetate 7:3) gave **22** (257 mg, 582 µmol, 26%) as colorless foam. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 5.6 Hz, 1H, Ar-*H*), 7.41 (dd, *J* = 5.6 Hz, *J* = 1.8 Hz, 1H, Ar-*H*), 7.02 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.82 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.57 (m, 1H, Ar-*H*), 6.41 (d, *J* = 8.7 Hz, 1H, Ar-*H*), 4.96 (br s, 1H, -N*H*), 4.81 (br s, 1H, -N*H*), 4.54 (m, 1H, -C*H*), 4.06 (t, *J* = 5.9 Hz, 2H, -OCH_2), 3.71 (s, 3H, -OCH_3) 3.50 (m, 2H, -CH_2), 3.02 (m, 2H, -CH_2), 2.10 (m, 2H, -CH_2), 1.42 (s, 9H, *H*-*t*Bu). ^{13}C NMR (91 MHz, $CDCl_3$): δ = 172.4, 158.6, 157.9, 155.1, 147.8, 137.6, 130.3, 128.1, 114.6, 112.8, 106.8, 79.8, 65.8, 54.6, 52.2, 39.5, 37.5, 29.2, 28.3. MS (ESI): *m/z* 430.2 $[M+H^+]^+$, 374.4 $[M+H^+-t\text{Bu}]^+$, 330.5 $[M+H^+\text{-Boc}]^+$.

Preparation of methyl 4-[4-(3-pyridin-2-ylaminopropoxy)-phenyl]-3-(*S*)-(*tert*-butyloxycarbonylamino) butanoate, 23

The title compound was synthesized from Boc-β-tyrosine methyl ester (**3**, 261 mg, 825 µmol), **8a** (152 mg, 1.0 mmol), triphenylphosphine (264 µL, 1.07 mmol) and ADDP (269 mg, 1.07 mmol) as described for **21**. Column chromatography on silica gel (DCM/ethyl acetate 7:3) gave **22** (106 mg, 244 µmol, 30%) as colorless foam. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.36 (m, 1H, Ar-*H*), 7.06 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.80 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.52 (dd, *J* = 5.2 Hz, *J* = 6.9 Hz, 1H, Ar-*H*), 6.37 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 5.05 (br s, 1H, -N*H*), 4.95 (br s, 1H, -N*H*), 4.08 (m, 1H, -C*H*), 4.05 (t, *J* = 5.9 Hz, 2H, OCH_2), 3.65 (s, 3H, -OCH_3), 3.46 (m, 2H, -CH_2), 2.84 (m, 2H, -C*H'*), 2.71 (dd, *J* = 13.6 Hz, *J* = 7.7 Hz, 1H, -C*H''*), 2.44 (m, 2H, -CH_2); 2.07 (m, 2H, -CH_2); 1.39 (s, 9H, *H*-*t*Bu). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 178.0, 158.6, 157.5, 155.0, 147.8, 137.4, 130.2, 129.8, 114.4, 112.6, 106.6, 79.2, 65.7, 51.6, 48.9, 39.4, 39.3, 37.3, 29.0, 28.3. MS (ESI): *m/z* 466.2 $[M+Na]^+$, 444.2 $[M+H]^+$, 388.2 $[M+H-t\text{Bu}]^+$, 344.3 $[M+H\text{-Boc}]^+$.

Preparation of methyl 3-[4-(4-*N*-*tert*-butyloxycarbonyl-*N*-pyridin-2-ylaminopropoxy)phenyl]-2-(*S*)-(*tert*-butyloxycarbonylamino) propionate, 24

The title compound was synthesized from Boc-tyrosine methyl ester (**1**, 647 mg, 2.20 mmol), **11b** (641 mg, 2.40 mmol), triphenylphosphine (706 µL, 2.86 mmol) and ADDP (722 mg, 2.86 mmol) as described for **21**. Column chromatography on silica gel (hexane/ethyl acetate 2:1 + 1% TEA) gave **24** (624 mg, 1.18 mmol, 49%) as colorless foam. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.30 (ddd, *J* = 5.0 Hz, *J* = 1.2 Hz, *J* =1.2 Hz, 1H, Ar-*H*), 7.56-7.52 (m, 2H, Ar-*H*), 6.96 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.93 (m, 1H, Ar-*H*), 6.73 (d, 2H, *J* = 8.6 Hz, Ar-*H*), 5.02 (d, *J* = 8.1 Hz, 1H, -N*H*), 4.46 (m, 1H, -C*H*), 3.96 (t, *J* = 6.7 Hz, 2H, -OCH_2), 3.87 (t, *J* = 5.5 Hz, -NCH_2), 3.64 (s, 3H, -OCH_3), 2.99 (dd, *J* = 13.7 Hz, *J* = 5.7 Hz, 1H, -C*H'*), 2.91 (dd, *J* = 13.9 Hz, *J* = 5.8 Hz, 1H, C*H''*), 1.74 (m, 4H, -CH_2CH_2), 1.45 (s, 9H, *H*-*t*Bu), 1.36 (s, 9H, *H*-*t*Bu). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 172.1, 157.9, 154.3, 153.9, 147.4, 136.6, 130.0, 127.6, 119.8, 119.2, 114.3, 80.6, 79.5, 67.3, 54.4, 51.8, 46.2, 37.2, 28.1, 26.4, 25.3. MS (ESI): *m/z* 566.2 [*M*+Na^+]$^+$, 544.1 [*M*+H^+]$^+$, 488.1 [*M*+H^+-*t*Bu]$^+$, 444.2 [*M*+H^+-Boc]$^+$, 388.3 [*M*+H^+-Boc-*t*Bu]$^+$, 344.4 [*M*+H^+-2Boc]$^+$.

Preparation of methyl (*S*)-2-(tert-butyloxycarbonyl)-3-[4-(3-(pyrimidin-2-ylamino)propoxy)phenyl]propanoate, 25

The title compound was synthesized from Boc-tyrosine methyl ester (**1**, 1.07 g, 3.63 mmol), **13** (611 mg, 3.99 mmol), triphenylphosphine (1.17 mL, 4.72 mmol) and ADDP (1.19 g, 4.72 mmol) as described for **21**. Column chromatography on silica gel ((DCM/ethyl acetate 2:1) gave **25** (1.39 g, 3.23 mmol, 89%) as colorless solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 4.8 Hz, 2H, Ar-*H*), 7.00 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.80 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.49 (t, *J* = 4.8 Hz, 1H, Ar-*H*), 5.59 (t, *J* = 5.1 Hz, 1H, -N*H*), 5.04 (d, *J* = 8.1 Hz, 1H, -N*H*), 4.52 (m, 1H, -C*H*), 4.03 (t, *J* = 6.0 Hz, 2H, -OCH_2), 3.69 (s, 3H, -OCH_3), 3.60 (q, *J* = 6.5 Hz, 2H, -CH_2), 2.08 (m, 2H, -CH_2), 1.40 (s, 9H, *H*-*t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 162.4, 157.9, 155.1, 130.0, 128.0, 114.5, 140.4, 79.8, 65.8, 54.5, 52.1, 38.7, 37.4, 29.1, 28.3. MS (ESI): *m/z* 453.3 [*M*+Na^+]$^+$, 431.2 [*M*+H^+]$^+$, 375.4 [*M*+H^+-*t*Bu]$^+$, 331.6 [*M*+H^+-Boc]$^+$.

Preparation of methyl (*S*)-2-(tert-butyloxycarbonyl)-3-[4-(3-(pyridazin-2-ylamino)propoxy)phenyl]propanoate, 26

The title compound was synthesized from Boc-tyrosine methyl ester (**1**, 1.07 g, 3.63 mmol), **14** (611 mg, 3.99 mmol), triphenylphosphine (1.17 mL, 4.72 mmol) and

ADDP (1.19 g, 4.72 mmol) as described for **21**. Column chromatography on silica gel ((DCM/ethyl acetate 2:1) gave **26** (1.34 g, 3.21 mmol, 86%) as colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (m, 1H, Ar-*H*), 7.89 (s, 1H, Ar-*H*), 7.78 (d, *J* = 3.1 Hz, 1H, Ar-*H*), 7.03 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.82 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 4.97-4.95 (m, 2H, -N*H*, -N*H*), 4.53 (m, 1H, -C*H*), 4.07 (t, *J* = 5.7 Hz, 2H, -OCH_2), 3.71 (s, 3H, -OCH_3), 3.56 (m, 2H, -NCH_2-), 3.04 (dd, *J* = 13.8, Hz, *J* = 5.0 Hz, 1H, -C*H'*), 3.00 (dd, *J* = 13.4 Hz, *J* = 5.4 Hz, 1H, -C*H''*), 2.11 (m, 2H, -CH_2), 1.41 (s, 9H, *H*-*t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3, 157.6, 155.0, 154.6, 141.7, 132.3, 132.1, 130.2, 128.1, 114.4, 79.7, 65.7, 54.5, 52.0, 38.7, 37.3, 28.7, 28.1. MS (ESI): 453.3 [*M*+Na^+]$^+$, 431.2 [*M*+H^+]$^+$, 375.3 [*M*+H^+-*t*Bu]$^+$, 331.5 [*M*+H^+-Boc]$^+$.

Preparation of methyl (*S*)-2-(tert-butyloxycarbonyl)-3-[4-(3-(pyrimidin-4-ylamino)propoxy)phenyl]propionate, 27

The title compound was synthesized from Boc-tyrosine methyl ester (**1**, 0.69 g, 2.35 mmol), **15** (0.39 g, 2.35 mmol), triphenylphosphine (0.22 mL, 3.06 mmol) and ADDP (0.22 g, 3.06 mmol) as described for **21**. Column chromatography on silica gel (DCM/methanol 95:5) gave **27** (0.66 g, 1.55 mmol, 66%) as colorless solid. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.40 (s, 1H, Ar-*H*), 8.74 (m, 1H, Ar-*H*), 8.20 (m, 1H, Ar-*H*), 7.32 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 7.32 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.82 (br s, 1H, -N*H*), 4.18 (m, 1H, -C*H*), 4.10 (t, *J* = 6.1 Hz, -OCH_2), 3.68 (s, 3H, -OCH_3), 2.59 (m, 2H, -CH_2), 2.19 (m, 2H, -CH_2). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 162.9, 161.2, 155.2, 151.4, 140.9, 130.3, 114.5, 106.7, 106.7, 80.0, 67.1, 65.4, 52.2, 37.5, 29.7, 28.3. MS (ESI): *m/z* 431.3 [*M*+H^+]$^+$.

Preparation of methyl 3-[4-(3-benzyloxycarbonyl-aminopropoxy)phenyl]-2-(*S*)-(*tert-but*yloxycarbonylamino) propionate, 28

The title compound was synthesized from Boc-tyrosine methyl ester (**1**, 0.89 g, 3.00 mmol), **12a** (0.63 g, 3.00 mmol), triphenylphosphine (0.96 mL, 3.90 mmol) and ADDP (0.98 g, 3.90 mmol) as described for **21**. Column chromatography on silica gel (hexane/ethyl acetate 2:1) gave 28 (1.33 g, 2.73 mmol, 91%) as colorless solid. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.34 (m, 5H, Ar-*H*), 7.02 (d, 2H, *J* = 8.6 Hz, 2H, Ar-*H*), 6.78 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 5.10 (s, 2H, -OCH_2), 4.53 (m, 1H, -C*H*), 3.99 (t, *J* = 5.9 Hz, 2H, -OCH_2), 3.70 (s, 3H, -OCH_3), 3.40 (q, *J* = 8.0 Hz, 2H, -OCH_2), 3.03 (m, 2H, -CH_2), 1.99 (m, 2H, -CH_2), 1.42 (s, 9H, *H*-*t*Bu). ^{13}C NMR (108 MHz, $CDCl_3$): δ =172.4, 157.8, 156.4, 136.6, 130.3, 128.5, 128.1, 114.6, 79.9, 66.7, 65.8, 54.5, 52.1, 38.7,

37.5, 29.4, 28.3. MS (ESI): *m/z* 487.3 $[M+H^+]^+$, 481.3 $[M+H^+$-*t*Bu$]^+$, 387.2 $[M+H^+$-Boc$]^+$.

Preparation of methyl 3-[4-(3-benzyloxycarbonylaminobutoxy)phenyl]-2-(*S*)-(*tert-but*yloxycarbonylamino) propionate, 29

The title compound was synthesized from Boc-tyrosine methyl ester (**1**, 1.20 g, 4.07 mmol), **12b** (1.00 g, 4.48 mmol), triphenylphosphine (1.3 mL, 5.29 mmol) and ADDP (1.30 g, 5.29 mmol) as described for **21**. Column chromatography on silica gel (hexane/ethyl acetate 2:1) gave **29** (1.54 g, 3.17 mmol, 71%) as colorless solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.35 - 7.04 (m, 5H, Ar-*H*), 7.01 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.79 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 5.10 (s, 2H, -OCH_2), 4.98 (d, *J* = 7.7 Hz, 1H, -N*H*), 4.94 (br s, 1H, -N*H*), 4.53 (m, 1H, -C*H*), 3.93 (t, *J* = 5.8 Hz, 2H, -OCH_2), 3.70 (s, 3H, -OCH_3), 3.26 (q, *J* = 6.3 Hz, 2H, -NCH_2), 3.04 (dd, *J* = 13.7 Hz, *J* = 5.6 Hz, 1H, -C*H'*), 2.98 (dd, *J* = 13.8 Hz, *J* = 5.7 Hz, 1H, -C*H"*), 1.80 (m, 2H, -CH_2), 1.68 (m, 2H, -CH_2), 1.42 (s, 9H, *H*-*t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 157.9, 156.4, 155.0, 136.6, 130.2, 128.4, 128.0, 114.5, 79.8, 67.3, 66.6, 54.5, 52.1, 40.7, 37.4, 28.3, 26.7, 26.4. MS (ESI): *m/z* 1022.9 $[2M+Na^+]^+$, 523.2 $[M+Na^+]^+$, 467.3 $[M+Na^+$-*t*Bu$]^+$, 401.4 $[M+H^+$-Boc$]^+$.

Preparation of methyl 1-(*tert*-butyloxycarbonyl)-7-[4-benzyloxycarbonylamino-butoxy]-1,2,3,4-tetrahydroisochinolin-2-(*S*)-carboxylate, 30

The title compound was synthesized from **7** (583 mg, 1.90 mmol), **12b** (436 mg, 2.09 mmol), tributylphosphine (610 µL, 2.47 mmol) and ADDP (622 mg, 2.47 mmol) as described for **21**. Column chromatography on silica gel (hexane/ethyl acetate 2:1) gave 29 (908 mg, 1.77 mmol, 93%) as colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (m, 5H, Ar-*H*), 7.03 (d, *J* = 6.5 Hz, 1H, Ar-*H*), 6.71 (d, *J* = 7.0 Hz, 1H, Ar-*H*), 6.68 (s, 1H*, Ar-*H*), 6.62 (s, 1H**, Ar-*H*), 5.10 (s, 2H+1H*, -CH_3 + -C*H*), 4.88 (br s, 1H, -N*H*), 4.75 (t, *J* = 4.8 Hz, 1H**, C*H*), 4.69 (d, *J* = 15.0 Hz, 1H*, -NC*H'*), 4.69 (d, *J* = 14.6 Hz, 1H**, -NC*H'*), 4.48 (d, *J* = 16.6 Hz, 1H*, -NC*H"*), 4.43 (d, *J* = 16.0 Hz, 1H**, NC*H"*), 3.94 (m, 2H, -OCH_2), 3.64 (s, 3H*, -OCH_3), 3.61 (s, 3H**, -OCH_3), 3.28 (m, 2H, -NCH_2), 3.09 (m, 2H, -CH_2), 1.79 (m, 2H, -CH_2), 1.69 (m, 2H, -CH_2), 1.53 (s, 9H*, *H*-*t*Bu), 1.46 (s, 9H**, *H*-*t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$): δ = (173.0, 172.5), (158.4, 158.2), (157.0, 156.0), 155.3, 137.0, 135.6, 134.3, (129.8, 129.3), 129.0, 128.5, (124.6, 124.3), (113.9, 113.9), (112.4, 112.0), (81.1, 81.0), (67.8, 67.1), (55.0, 53.1), (52.6, 52.6), (45.2, 44.6), 41.2, (31.3, 30.8), (28.9, 28.8), 27.2, 26.9. MS (ESI):

m/z 535.2 [*M*+Na$^+$]$^+$, 479.2 [*M*+H$^+$-tBu]$^+$, 413.2 [*M*+H$^+$-Boc]. Signal doublings due to different rotamers of the Boc group.

Preparation of methyl 3-{4-[3-*N*,*N*'-(bis-*tert-but*yloxycarbonyl)-guanidyl-propoxy]phenyl}-2-(*S*)-(*tert-but*yloxycarbonylamino) propionate, 31

A solution of **28** (0.51 g, 1.05 mmol) in 50 mL of methanol and 0.1 mL of acetic acid was hydrogenated at 1 atm H_2 using 50 mg of catalyst (5% Pd on carbon). After the starting material was consumed (TLC control), the catalyst was removed by filtration over Celite®, the solvent evaporated and the residue taken up in dry methanol (20 mL) and cooled in an ice bath. To this solution was added bis-Boc-thiourea (0.41 g, 1.5 mmol), $HgCl_2$ (0.54 g, 2.00 mmol). Triethylamine (1.03 mL, 10 mmol) was added dropwise and the resulting grey slurry was stirred at ambient temperature for 8 h. The reaction mixture was filtered over Celite® and evaporated. The crude product was directly subjected to column chromatography on silica gel (hexane/ethyl acetate 2:1) to give 31 (206 mg, 0.35 mmol, 33%) as colorless solid. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 11.50 (br s, 1H, -N*H*), 8.64 (br s, 1H, -N*H*), 7.01 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.87 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 4.95 (d, *J* = 7.7 Hz, 1H, -N*H*), 4.51 (m, 1H, -C*H*), 4.02 (t, *J* = 5.8 Hz, 2H, -OCH_2), 3.69 (s, 3H, -OCH_3), 3.63 (dd, *J* = 11.8 Hz, *J* = 6.3 Hz, 2H, -NCH_2), 3.01 (m, 2H, -CH_2), 2.05 (m, 2H, -CH_2), 1.50 (s, 9H, *H*-*t*Bu), 1.49 (s, 9H, *H*-*t*Bu), 1.41 (s, 9H, -*t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4, 163.6, 157.8, 156.1, 153.1, 130.2, 128.1, 114.5, 83.0, 82.5, 79.2, 66.3, 54.5, 52.1, 39.1, 37.5, 28.6, 28.2 (2C), 28.1, 28.0. MS (ESI): *m/z* 617.26 [*M*+Na$^+$]$^+$, 595.19 [*M*+H$^+$]$^+$, 495.22 [*M*+H$^+$-Boc]$^+$, 395.42 [*M*+H$^+$-2Boc]$^+$, 339.42 [*M*+H$^+$-2Boc-*t*Bu]$^+$, 295.51 [*M*+H$^+$-3Boc]$^+$.

Preparation of methyl 3-{4-[4-*N*,*N*'-(bis-*tert-but*yloxycarbonyl)guanidyl-butoxy]-phenyl}-2-(*S*)-(*tert-but*yloxycarbonylamino) propionate, 32

The title compound was synthesized from **29** (840 mg, 1.68 mmol), bis-Boc-thiourea (696 mg, 2.52 mmol), $HgCl_2$ (910 mg, 3.36 mmol) and triethylamine (2.35 mL, 17 mmol) as described for **31**. Column chromatography on silica gel (hexane/ethyl acetate 7:3)gave **32** (253 mg, 0.42 mmol, 25%) as colorless solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.48 (br s, 1H, -N*H*), 8.34 (br s, 1H, -N*H*), 6.98 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.78 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 4.94 (d, *J* = 7.8 Hz, 1H, -N*H*), 4.49 (m, 1H, -NC*H*), 3.92 (d, *J* = 5.6 Hz, 2H, -OCH_2), 3.67 (s, 3H, -OCH_3), 3.46 (m, 2H, -NCH_2), 2.98 (m, 2H, -CH_2), 1.88 - 1.64 (m, 4H, -CH_2CH_2), 1.47, 1.46 (2s, 18H, 2*H*-*t*Bu), 1.39 (s, 9H, *H*-*t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 163.5, 157.9, 156.1, 155.0, 153.2,

130.1, 127.8, 114.4, 82.9, 79.7, 77.2, 67.1, 28.2, 28.0, 26.5, 25.7. MS (ESI): *m/z* 631.2 $[M+Na]^+$, 609.1 $[M+H]^+$, 509.2 $[M+H\text{-Boc}]^+$, 409.2 $[M+H\text{-2Boc}]^+$, 353.3 $[M+H\text{-2Boc-}t\text{Bu}]^+$, 309.3 $[M+H\text{-3Boc}]^+$.

Preparation of methyl 1-(*tert*-butyloxycarbonyl)-7-[4-(*N,N'*-(bis-*tert-but*yloxy-carbonyl)guanidinylbutoxy]-1,2,3,4-tetrahydroisochinolin-2-(*S*)-carboxylate, 33

The title compound was synthesized from **30** (658 mg, 1.74 mmol), bis-Boc-thiourea (721mg, 2.61 mmol), $HgCl_2$ (945 mg, 3.48 mmol) and triethylamine (2.50 mL, 17.4 mmol) as described for **31**. Column chromatography on silica gel (hexane/ethyl acetate 7:3) gave **33** (814 mg, 1.3 mmol, 75%) as colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.50 (s, 1H, -N*H*), 8.37 (s, 1H, -N*H*), 7.02 (d, *J* = 8.2 Hz, 1H, Ar-*H*), 6.74-6.60 (m, 2H, Ar-*H*), 5.11 (dd, *J* = 6.1 Hz, *J* = 3.4 Hz, 1H°, -C*H*), 4.74 (m, 1H**, -C*H*), 4.70 (d, *J* = 6.0 Hz, 1H*, -NC*H'*), 4.64 (d, *J* = 6.0 Hz, 1H**, -NC*H'*), 4.48 (d, *J* = 12.1 Hz, 1H**, -NC*H''*), 4.41 (d, *J* = 11.7 Hz, 1H*, -NC*H''*), 3.94 (t, *J* = 5.8 Hz, 1H, -OCH_2), 3.63 (s, 3H*, -OCH_3), 3.61 (s, 3H**, -OCH_3), 3.48 (*pseudo*q, *J* = 6.6 Hz, 2H, -CH_2), 3.22-3.01 (m, 2H, -CH_2), 1.91-1.68 (m, 4H, -CH_2CH_2), 1.51 (s, 9H**, *H-t*Bu), 1.50 (s, 9H, *H-t*Bu), 1.49 (s, 9H, *H-t*Bu), 1.45 (s, 9H*, *H-t*Bu).^{13}C NMR (125 MHz, $CDCl_3$): δ = (172.5, 172.0), 163.6, (157.9, 157.7), 156.2, (155.4, 154.8), 153.3, (135.0, 133.9), (129.4, 128.7), (124.1, 123.8), 113.4, (112.0, 111.6), 83.1, 80.5, 79.2, 67.3, (54.6, 52.7), 52.1, (44.7, 44.2), 40.5, (30.8, 30.4), (28.4, 28.2), 28.3, 28.1, 26.6, 25.8. MS (ESI): *m/z* 1240.8 $[2M+H^+]^+$, 621.5 $[M+H^+]^+$, 521.4 $[M+H^+\text{-Boc}]^+$, 421.6 $[M+H^+\text{-2Boc}]^+$.

*represents the minor rotamer of the Boc-group

**represents the major rotamer of the Boc-group

^{13}C signals with different chemical shifts in both rotamers are given in parentheses.

Preparation of 2-(*S*)-benzamido-3-(4-(3-pyridin-2-ylaminopropoxy)phenyl) propionic acid, 34a

The title compound was prepared from **21** (94 mg, 219 µmol) following **GP-1**. [benzoyl chloride (33 µL, 285 µmol), $NaHCO_3$ (92 mg, 1.1 mmol), LiOH (26 mg, 1.1 mmol)] Purification using preparative HPLC and lyophilization afforded **34a** (10 mg, 24.1 µmol, 11%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 13.32 (br s, 1H), 12.77 (br s, 1H), 8.71 (br s, 1H, -N*H*), 8.66 (d, *J* = 8.2 Hz, 1H, -N*H*), 7.89 (d, *J* = 6.1 Hz, 1H, Ar-*H*), 7.83 (t, *J* = 7.9 Hz, 1H, Ar-*H*), 7.80 (d, *J* = 7.5 Hz, 2H, Ar-*H*), 7.52

(t, *J* = 7.3 Hz, 1H, Ar-*H*), 7.45 (t, *J* = 7.6 Hz, 2H, Ar-*H*), 7.23 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.00 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.83 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.80 (t, *J* = 6.8 Hz, 1H, Ar-*H*), 4.57 (m, 1H, -C*H*), 4.01 (t, *J* = 6.0 Hz, 2H, -OCH_2), 3.45 (t, *J* = 6.2 Hz, 2H, -NCH_2), 3.12 (dd, *J* = 13.8 Hz, *J* = 4.3 Hz, 1H, -C*H'*-), 3.00 (dd, 1H, *J* = 13.7 Hz, *J* = 10.9 Hz, 1H, -C*H"*), 2.01 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 173.1, 166.2, 156.8, 152.9, 142.4, 136.5, 133.8, 131.2, 130.1, 129.9, 128.1, 127.2, 114.0, 112.7, 111.7, 64.6, 54.3, 39.4, 38.5, 35.4, 27.6. MS (ESI): *m/z* 420.4 [*M*+H]$^+$. HR-MS (ESI) ($C_{24}H_{26}N_3O_4^+$): calc.: 420.1918, found: 420.1909.

Preparation of 2-(*R*)-benzamido-3-(4-(3-pyridin-2-ylaminopropoxy)phenyl) propionic acid, *ent*-34a

The title compound was prepared from **22** (100 mg, 220 µmol) following **GP-1**. [benzoyl chloride (33 µL, 285 µmol), $NaHCO_3$ (92 mg, 1.1 mmol), LiOH (30 mg, 1.25 mmol)] Purification using preparative HPLC and lyophilization afforded *ent*-**34a** (23 mg, 54.9 µmol, 25%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 8.82 (br s, 1H, -N*H*), 8.66 (d, *J* = 8.2 Hz, 1H, -N*H*), 7.89 (d, *J* = 6.2 Hz, 1H, Ar-*H*), 7.88-783 (m, 1H, Ar-*H*), 7.80 (d, *J* = 7.3 Hz, 2H, Ar-*H*), 7.52 (t, *J* = 7.3 Hz, 1H, Ar-*H*), 7.45 (t, *J* = 7.5 Hz, 2H, Ar-*H*), 7.23 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.03 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.83 (d+m, *J* = 8.6 Hz, 2H, Ar-*H*), 4.57 (m, 1H, -C*H*), 4.02 (t, *J* = 6.0 Hz, 2H, -OCH_2), 3.46 (t, *J* = 5.9 Hz, 2H, -NCH_2), 3.12 (dd, *J* = 13.8 Hz, *J* = 4.2 Hz, 1H, C*H'*), 3.00 (dd, 1H, *J* = 13.7 Hz, *J* = 10.9 Hz, 1H, -C*H"*), 2.01 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 173.1, 166.2, 156.8, 152.6, 142.7, 135.9, 133.8, 131.2, 130.1, 130.0, 128.1, 127.2, 114.0, 113.3, 111.8, 64.5, 54.3, 38.6, 35.4, 27.5. MS (ESI): *m/z* 420.6 [*M*+H]$^+$. HR-MS (ESI) ($C_{24}H_{26}N_3O_4^+$): calc.: 420.1918, found: 420.1909.

Preparation of 2-(*S*)-(4-methylbenzamido)-3-[4-(3-pyridin-2-ylaminoprooxy)-phenyl]propionic acid, 34b

The title compound was prepared from **21** (100 mg, 233 µmol) following **GP-2** [4-methylbenzoic acid (33 mg, 280 µmol), HATU (107 mg, 280 µmol), DIEA (238 µL, 1.4 mmol), LiOH (34 mg, 1.4 mmol]. Purification using preparative HPLC and lyophilization afforded **34b** (28 mg, 65 µmol, 28%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 14.50 (br s), 8.82 (br s, 1H, -N*H*), 8.54 (d, *J* = 8.2 Hz, 1H, -N*H*), 7.85 (d, *J* = 6.1 Hz, 1H, Ar-*H*), 7.82 (m, 1H, Ar-*H*), 7.68 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 7.21 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.19 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.00 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.79 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.79 (m, 1H, Ar-*H*), 4.52 (m, 1H, -C*H*), 3.98

(t, *J* = 5.9 Hz, 2H, -OC*H*$_2$), 3.42 (m, 1H, -NC*H*$_2$), 3.07 (dd, *J* = 13.8 Hz, *J* = 4.0 Hz, 1H, C*H'*), 2.96 (m, 1H, -C*H''*), 2.30 (s, 3H, -C*H*$_3$), 1.98 (m, 2H, -C*H*$_2$). ^{13}C NMR (125 MHz, DMSO): δ = 173.2, 166.1, 156.1, 152.7, 142.7, 141.2, 135.9, 131.0, 130.2, 130.0, 128.7, 127.3, 114.0, 113.2, 111.8, 64.5, 54.3, 38.6, 35.4, 27.5, 20.8. MS (ESI): *m/z* 434.5 [*M*+H]$^+$. HR-MS (ESI) ($C_{25}H_{28}N_3O_4^+$) calcd: 434.2074, found: 434.2070.

Preparation of 2-(*S*)-(2,6-dimethylbenzamido)-3-[4-(3-pyridin-2-ylaminoprooxy)-phenyl]propionic acid, 34c

The title compound was prepared from **21** (75 mg, 175 μmol) following **GP-2** [2,6-dimethylbenzoic acid (32 mg, 210 μmol), HATU (80 mg, 210 μmol), DIEA (149 μL, 875 μmol), LiOH (21 mg, 875 mmol]. Purification using preparative HPLC and lyophilization afforded **34c** (17 mg, 30 μmol, 17%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 12.71 (br s, 1H, -COO*H*), 8.65 (br s, 1H, -N*H*), 8.57 (d, *J* = 8.3 Hz, 1H, -N*H*), 7.92 (d, *J* = 6.0 Hz, 1H, Ar-*H*), 7.85 (t, *J* = 7.7 Hz, 1H, Ar-*H*), 7.21 (d, *J* = 8.5 Hz, Ar-*H*), 7.11 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.01 (d, *J* = 8.9 Hz, 2H, Ar-*H*), 6.95 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 6.86 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.82 (t, *J* = 6.6 Hz, 1H, Ar-*H*), 4.63 (m, 1H, -C*H*), 4.05 (t, *J* = 6.0 Hz, 2H, -OC*H*$_2$), 3.47 (m, 2H, -NC*H*$_2$), 3.11 (dd, *J* = 13.9 Hz, *J* = 4.0 Hz, 1H, -C*H'*), 2.79 (dd, *J* = 13.7 Hz, *J* = 11.5 Hz, 1H, -C*H''*), 2.04 (m, 2H, -C*H*$_2$), 1.96 (s, 6H, 2C*H*$_3$). ^{13}C NMR (125 MHz, DMSO): δ = 173.0, 168.9, 156.9, 153.1, 142.2, 137.9, 136.9, 133.7, 130.0, 127.8, 126.7, 114.1, 112.9, 111.7, 64.8, 53.3, 39.4, 38.5, 35.4, 27.6, 18.4. MS (ESI): *m/z* 448.4 [*M*+H]$^+$. HR-MS ($C_{26}H_{30}N_3O_4^+$): calcd: 448.2231, found: 448.2227.

Preparation of 2-(*S*)-(3,5-dimethylbenzamido)-3-[4-(3-pyridin-2-ylaminoprooxy)-phenyl]propionic acid, 34d

The title compound was prepared from **21** (75 mg, 175 μmol) following **GP-2** [3,5-dimethylbenzoic acid (39 mg, 263 μmol), HATU (107 mg, 263 μmol), DIEA (149 μL, 875 μmol), LiOH (21 mg, 875 mmol]. Purification using preparative HPLC and lyophilization afforded **34d** (15 mg, 30 μmol, 15%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 12.47 (br s, 1H, -COO*H*), 8.74 (br s, 1H, -N*H*), 8.54 (d, *J* = 8.2 Hz, 1H, -N*H*), 7.89 (d, *J* = 6.1 Hz, 1H, Ar-*H*), 7.84 (t, *J* = 8.0 Hz, Ar-*H*), 7.42 (s, 2H, Ar-*H*), 7.22 (d, *J* = 8.6 Hz, Ar-*H*), 7.15 (s, 1H, Ar-*H*), 7.01 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.83 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (t, *J* = 6.6 Hz, Ar-*H*), 4.56 (m, 1H, -C*H*), 4.01 (t, *J* = 6.0 Hz, 2H, -OC*H*$_2$), 3.45 (m, 2H, -NC*H*$_2$), 3.10 (dd, *J* = 13.9 Hz, *J* = 4.3 Hz, 1H, -

C*H'*), 2.98 (dd, *J* = 13.8 Hz, *J* = 10.7 Hz, 1H, -C*H''*), 2.30 (s, 6H, 2CH_3), 2.02 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 173.1, 166.4, 156.8, 152.8, 142.5, 137.2, 136.3, 133.8, 132.5, 130.2, 130.0, 125.0, 114.0, 113.2, 111.8, 64.5, 54.2, 39.4, 38.5, 35.4, 27.5, 20.7. MS (ESI): *m/z* 448.4 [*M*+H]$^+$. HR-MS ($C_{26}H_{30}N_3O_4^+$): calcd: 448.2231, found: 448.2233.

Preparation of 2-(*S*)-(2, 4, 6-trimethylbenzamido)-3-[4-(3-pyridin-2-ylaminopro-oxy)phenyl]-propionic acid, 34e

The title compound was prepared from **21** (100 mg, 233 μmol) following **GP-2** [2,4,6-trimethylbenzoic acid (46 mg, 279 μmol), HATU (107 mg, 279 μmol), DIEA (238 μL, 1.17 mmol), LiOH (28 mg, 1.17 mmol]. Purification using preparative HPLC and lyo-philization afforded **34e** (32 mg, 55 μmol, 24%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 15-12 (br s, 1H, -COO*H*), 8.86 (br s, 1H, -N*H*), 8.47 (d, *J* = 7.6 Hz, 1H, -N*H*CO), 7.93 (m, 1H, Ar-*H*), 7.89 (m, 1H, Ar-*H*), 7.21 (d, *J* = 7.0 Hz, 2H, Ar-*H*), 7.06 (d, *J* = 8.1 Hz, 1H, Ar-*H*), 6.85 (d, *J* = 6.6 Hz, 3H, Ar-*H*), 6.75 (s, 2H, Ar-*H*), 4.62 (m, 1H, -C*H*), 4.05 (m, 2H, -OCH_2), 3.48 (m, 2H, -NCH_2), 3.10 (d, *J* = 13.3 Hz, 1H, -C*H'*), 2.79 (t, *J* = 12.2 Hz, 1H, -C*H''*), 2.20 (s, 3H, CH_3), 2.05 (m, 2H, -CH_2), 1.93 (s, 6H, 2CH_3). ^{13}C NMR (125 MHz, DMSO): δ = 173.1, 169.1, 156.9, 152.8, 142.7, 136.9, 136.1, 135.3, 133.7, 130.0, 127.3, 114.1, 113.1, 111.8, 64.7, 53.4, 38.6, 35.4, 27.5, 20.5, 18.4. MS (ESI): *m/z* 961.4 [2*M*+K$^+$]$^+$, 945.4 [2*M*+Na$^+$]$^+$, 923.1 [2*M*+H$^+$]$^+$, 462.4 [*M*+H$^+$]$^+$. HR-MS (ESI) ($C_{27}H_{32}N_3O_4^+$): calcd: 462.2387, found: 462.2382.

Preparation of 2-(*R*)-(2, 4, 6-trimethylbenzamido)-3-[4-(3-pyridin-2-ylaminopro-oxy)phenyl]-propionic acid, *ent*-34e

The title compound was prepared from **22** (125 mg, 291 μmol) following **GP-2** [2,4,6-trimethylbenzoic acid (57 mg, 347 μmol), HATU (132 mg, 347 μmol), DIEA (247 μL, 1.46 mmol), LiOH (35 mg, 1.46 mmol)]. Purification using preparative HPLC and lyo-philization afforded e*nt*-**34e** (32 mg, 61 μmol, 21%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 8.74 (br s, 1H, -N*H*), 8.46 (d, *J* = 8.3 Hz, 1H, N*H*CO), 7.93 (d, *J* = 6.01 Hz, 1H, Ar-*H*), 7.88 (t, *J* = 7.92 Hz, 1H, Ar-*H*), 7.21 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.04 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.85 (d + m, *J* = 8.5 Hz, 3H, Ar-*H*), 6.75 (s, 2H, Ar-*H*), 4.62 (m, 1H, -C*H*), 4.05 (t, *J* = 7.8 Hz, 2H, -OCH_2), 3.47 (m, 2H, -NCH_2), 3.10 (dd, *J* = 13.9 Hz, *J* = 3.8 Hz, 1H, -C*H'*), 2.79 (dd, *J* = 13.9 Hz, *J* = 11.7 Hz, 1H, -C*H''*), 2.20 (s, 3H, -CH_3), 2.05 (m, 2H, -CH_2), 1.93 (s, 6H, 2CH_3). ^{13}C NMR (125 MHz,

DMSO): δ = 173.1, 169.1, 156.9, 152.8, 142.7, 136.9, 136.1, 135.3, 133.7, 130.0, 127.3, 114.1, 113.2, 111.8, 64.7, 53.4, 38.6, 35.4, 27.5, 20.5, 18.4. MS (ESI): *m/z* 462.3 $[M+H^+]^+$. HR-MS (ESI) ($C_{27}H_{32}N_3O_4^+$): calcd: 462.2387, found: 462.2376.

Preparation of 2-(*S*)-phenylsulfonamido-3-[4-(3-pyridin-2-ylaminopropoxy)phenyl] propionic acid, 34f.

The title compound was prepared from **21** (60 mg, 140 μmol) following **GP-3** [phenylsulfonic acid chloride (22 μL, 168 μmol), DIEA (143 μL, 840 μmol), LiOH (20 mg, 840 mmol)]. Purification using preparative HPLC and lyophilization afforded **34f** (13 mg, 61 μmol, 16%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 12.74 (br s, 1H, -COO*H*), 8.70 (br s, 1H, -N*H*), 8.22 (d, *J* = 9.0 Hz, 1H, -N*H*SO_2), 7.92 (d, *J* = 5.6 Hz, 1H, Ar-*H*), 7.85 (ddd, *J* = 8.4 Hz, *J* = 7.2 Hz, *J* = 1.4 Hz, 1H, Ar-*H*), 7.58 (dd, *J* = 8.2 Hz, *J* = 1.0 Hz, 2H, Ar-*H*), 7.53 (tt, *J* = 7.4 Hz, *J* = 1.1 Hz, 1H, Ar-*H*), 7.43 (t, *J* = 7.7 Hz, 2H, Ar-*H*), 7.03 (d, *J* = 8.6 Hz, 3H, Ar-*H*), 6.82 (t, *J* = 6.4 Hz, Ar-*H*), 6.76 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 4.03 (t, *J* = 6.1 Hz, -OCH_2), 3.82 (dt, *J* = 9.0 Hz, *J* = 5.7 Hz, 1H, -C*H*), 3.49 (t, *J* = 6.3 Hz, 1H, -NCH_2), 2.87 (dd, *J* = 13.8 Hz, *J* = 5.6 Hz, 1H, -C*H'*), 2.63 (dd, *J* = 13.8 Hz, *J* = 9.0 Hz, 1H, -C*H''*), 2.05 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 172.1, 157.0, 153.1, 142.3, 141.0, 136.7, 131.9, 130.1, 128.6, 126.1, 114.0, 112.8, 111.8, 64.6, 57.5, 39.4, 38.5, 36.9, 27.6. MS (ESI): *m/z* 933.0 $[2M+Na^+]^+$, 911.0 $[2M+H^+]^+$, 456.4 $[M+H^+]^+$. HR-MS (ESI) ($C_{23}H_{26}N_3O_5S^+$): calcd: 456.2387, found: 456.1588.

Preparation of 2-(S)-(2,4,6-trimethylphenylsulfonamido)-3-[4-(3-pyridin-2-ylaminopropoxy)phenyl] propionic acid, 34g

The title compound was prepared from **21** (60 mg, 140 μmol) following **GP-3** [2,4,6-trimethylphenylsulfonic acid chloride (37 mg, 168 μmol), DIEA (143 μL, 840 μmol), LiOH (20 mg, 840 mmol)]. Purification using preparative HPLC and lyophilization afforded **34g** (14 mg, 23 μmol, 15%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 8.86 (br s, 1H, -N*H*), 8.00 (d, *J* = 9.5 Hz, 1H, -N*H*SO_2), 7.93 (d, *J* = 6.1 Hz, 1H, Ar-*H*), 7.88 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.06 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.96 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.85 (s, 2H, Ar-*H*), 6.85 (m, 1H, Ar-*H*), 6.65 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 4.02 (t, *J* = 6.1 Hz, 2H, -OCH_2), 3.70 (dt, *J* = 5.3 Hz, *J* = 9.4 Hz, 1H, -C*H*), 3.49 (t, *J* = 6.4 Hz, H, -NCH_2), 2.85 (dd, *J* = 13.8 Hz, *J* = 5.2 Hz, 1H, -C*H'*), 2.66 (dd, *J* = 13.8 Hz, *J* = 9.6 Hz, 1H, -C*H''*), 2.41 (s, 6H, 2CH_3), 2.21 (s, 3H, -CH_3), 2.05 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 172.4, 156.9, 152.8, 142.7, 140.8 , 138.0,

136.1 134.4, 131.2, 129.7, 128.7, 113.8, 113.0, 111.8, 64.5, 57.0, 38.6, 36.7, 27.6, 22.4, 20.2. MS (ESI): *m/z* 498.5 (M+H^+). HR-MS (ESI) ($C_{26}H_{32}N_3O_5S^+$): calcd: 498.2057, found: 498.2049.

Preparation of 2-(*S*)-(3-phenylureido)-3-[4-(3-pyridin-2-ylaminopropoxy)phenyl] propionic acid, 34h

Compound **21** (100 mg, 233 µmol, 1 equiv) was dissolved in 3 mL dioxane. After addition of 1 mL concentrated hydrochloric acid, the mixture was stirred at ambient temperature for 30 min. The solvents were evaporated *in vacuo* and the residue taken up in 3 mL of dry DCM. DIEA (210 µL, 1.76 mmol, 5 equiv) were added, followed by 44 µL (527 µmol, 1.5 equiv) of phenyl isocyanate. After 20 min, the reaction was quenched by addition of one drop of water and the solvents were evaporated under reduced pressure. The residue was dissolved in 4 mL of methanol/water (3:1). LiOH (42 mg, 1.76 mmol, 5 equiv) was added and the reaction mixture was stirred at ambient temperature for one day (HPLC monitoring). The solvents were removed and the crude product purified by preparative HPLC to give **34h** (53 mg, 97 µmol, 41 %) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 12.85 (br s, 1H, -COO*H*), 8.77 (s, 1H, -N*H*CO), 8.47 (br s, 1H, -N*H*), 7.92 (t, *J* = 5.9 Hz, 1H, Ar-*H*), 7.77 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.35 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.20 (t, *J* = 7.7 Hz, 2H, Ar-*H*), 7.13 (d, *J* = 7.7 Hz, 2H, Ar-*H*), 6.94 (d, *J* = 8.9 Hz, Ar-*H*), 6.89 (m, 1H, Ar-*H*), 6.86 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 6.76 (t, *J* = 6.5 Hz, 1H, Ar-*H*), 6.43 (d, *J* = 8.0 Hz, 1H, -N*H*CO), 4.38 (m, 1H, -C*H*), 4.04 (t, *J* = 5.9 Hz, 2H, CH_2OAr), 3.45 (m, 2H, PyNHCH_2), 3.01 (dd, ^2J = 13.9 Hz, ^3J = 4.8 Hz, 1H, Ar-C*H'*), 2.86 (dd, *J* = 13.9 Hz, *J* = 7.8 Hz, 1H, -C*H'*), 2.02 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 173.5, 157.1, 154.6, 153.8, 141.6, 140.2, 138.0, 130.2, 129.2, 128.6, 121.1, 117.4, 114.1, 112.2, 111.7, 64.7, 53.8, 39.4, 36.5, 27.7. MS (ESI): *m/z* 869.2 [2M+H^+]$^+$, 435.4 [M+H^+]$^+$. HR-MS (ESI) $(C_{24}H_{27}N_4O_4)^+$: calcd: 435.2027; found: 435.2023.

Preparation of 2-(*S*)-(*tert-but*ylamido)-3-[4-(3-pyridin-2-ylaminopropoxy)phenyl]-propionic acid 34i

The title compound was prepared from **21** (300 mg, 577 µmol) following **GP-1**. [pivalyl chloride (78 µL, 635 µmol), $NaHCO_3$ (145 mg, 1.73 mmol), LiOH (70 mg, 2.89 mmol)] Purification using preparative HPLC and lyophilization afforded **34i** (135 mg, 260 µmol, 45%) as TFA salt (colorless oil). ^{1}H NMR (500 MHz, DMSO): δ = 8.90 (br s, 1H, -N*H*), 7.92 (d, *J* = 6.08 Hz, 1H, Ar-*H*), 7.88 (t, *J* = 8.25 Hz, Ar-*H*), 7.45 (d, *J* = 8.3

Hz, 1H, -N*H*CO), 7.13 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 7.06 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.84 (m, 1H, Ar-*H*), 6.82 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 4.36 (ddd, *J* = 9.9 Hz, *J* = 8.4 Hz, *J* = 4.6 Hz, 1H, -C*H*), 4.03 (t, *J* = 6.1 Hz, 2H, -OCH_2), 3.48 (t, *J* = 6.5 Hz, 2H, -NCH_2), 3.01 (dd, *J* = 13.8 Hz, *J* = 4.5 Hz, 1H, -C*H'*), 2.90 (dd, *J* = 13.7 Hz, *J* = 10.2 Hz, 1H, -C*H''*), 2.03 (m, 2H, -CH_2), 1.01 (s, 9H, *H*-*t*Bu). ^{13}C NMR (125 MHz, DMSO): δ = 177.1, 173.2, 156.8, 152.7, 142.8, 136.0, 130.1, 113.9, 113.2, 111.8, 64.6, 53.5, 38.6, 37.8, 35.3, 27.6, 27.1. MS (ESI): *m/z* 400.5 [*M*+H$^+$]$^+$. HR-MS (ESI) ($C_{22}H_{30}N_3O_4^+$)$^+$: calcd: 400.2231; found: 400.2222.

Preparation of 2-(*S*)-(2,6-dimethyl-4-methoxybenzamido)-3-[4-(3-pyridin-2-yl-aminopropoxy)phenyl]propionic acid, 34j

The title compound was prepared from **21** (66 mg, 155 μmol) following **GP-2** [**17a** (34 mg, 186 μmol), HATU (71 mg, 186 μmol), DIEA (131 μL, 775 μmol), LiOH (19 mg, 775 μmol)]. Purification using preparative HPLC and lyophilization afforded **34j** (25 mg, 42 μmol, 27%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 12.67 (br s, 1H, -COO*H*), 8.62 (s, 1H, -N*H*), 8.43 (d, *J* = 8.3 Hz, 1H, -N*H*CO), 7.92 (d, *J* = 6.0 Hz, 1H, Ar-*H*), 7.84 (t, *J* = 7.7 Hz, 1H, Ar-*H*), 7.20 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 7.01 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.85 (d, *J* = 8.6 Hz, Ar-*H*), 6.82 (t, *J* = 6.6 Hz, 1H, Ar-*H*), 6.52 (s, 2H, Ar-*H*), 4.61 (m, 1H, -C*H*), 4.05 (t, *J* = 6.1 Hz, 2H, -OCH_2), 3.69 (s, 3H, -OCH_3), 3.47 (m, 2H, -NCH_2), 3.09 (dd, *J* = 14.0 Hz, *J* = 4.1 Hz, 1H, -C*H'*), 2.79 (dd, *J* = 13.9 Hz, *J* = 11.4 Hz, -C*H''*), 2.04 (m, 2H, -CH_2), 1.95 (s, 6H, 2CH_3). ^{13}C NMR (125 MHz, DMSO): δ = 173.1, 169.0, 158.5, 156.9, 152.7, 142.7, 136.0, 135.5, 130.9, 130.1, 130.0, 114.1, 113.3, 113.2, 111.8, 64.7, 54.9, 53.5, 39.4, 38.6, 35.4, 27.5, 18.7. MS (ESI): *m/z* 478.6 [*M*+H]$^+$, 163.2 [$COC_6H_2(CH_3)_2OCH_3$]$^{\cdot+}$. HR-MS (ESI) ($C_{27}H_{32}N_3O_5^+$): calcd: 478.2336, found: 478.2332.

Preparation of 2-(*S*)-(2,6-dimethyl-4-isopropoxybenzamido)-3-[4-(3-pyridin-2-yl-aminopropoxy)phenyl]propionic acid, 34k

The title compound was prepared from **21** (66 mg, 155 μmol) following **GP-2** [**17b** (39 mg, 186 μmol), HATU (71 mg, 186 μmol), DIEA (131 μL, 775 μmol), LiOH (19 mg, 775 μmol)]. Purification using preparative HPLC and lyophilization afforded **34k** (27 mg, 44 μmol, 28%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 2.70 (br s, 1H, -COO*H*), 8.74 (br s, 1H, -N*H*), 8.45 (d, *J* = 8.3 Hz, 1H, -N*H*CO), 7.92 (d, *J* = 5.8 Hz, 1H, Ar-*H*), 7.86 (t, *J* = 7.7 Hz, 1H, Ar-*H*), 7.20 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.03 (d, *J* = 8.9 Hz, 1H, Ar-*H*), 6.85 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 6.83 (t, *J* = 6.7 Hz, 1H,

Ar-*H*), 6.50 (s, 2H, Ar-*H*), 4.60 (m, 1H, -OC*H*), 4.55 (m, 1H, -C*H*), 4.05 (t, *J* = 5.1 Hz, 2H, -OCH_2), 3.47 (m, 2H, -NCH_2), 3.09 (dd, *J* = 13.8 Hz, *J* = 3.5 Hz, 1H, -C*H'*), 2.79 (dd, *J* = 13.4 Hz, *J* = 11.7 Hz, 1H, -C*H"*), 2.04 (m, 2H, -CH_2), 1.94 (s, 6H, 2CH_3). ^{13}C NMR (125 MHz, DMSO): δ = 173.1, 169.0, 156.9, 156.7, 152.9, 142.5, 136.6, 135.5, 130.7, 130.0, 130.0, 114.1, 113.8, 113.1, 111.8, 68.7, 64.7, 53.4, 39.4, 38.5, 27.5, 21.7, 18.7. MS (ESI): *m/z* 506.5 [*M*+H]$^+$, 191.2 [$COC_6H_2(CH_3)_2OCH(CH_3)_2]^{\cdot+}$, 149.2 [$C_6H_2(CH_3)_2OCH(CH_3)_2]^{\cdot+}$, HR-MS (ESI) ($C_{27}H_{32}N_3O_5^+$): calcd: 506.2649, found: 506.2645.

Preparation of 2-(*S*)-(2,4,6-trichlorobenzamido)-3-[4-(3-pyridin-2-yl-aminoprop-oxy)phenyl]propionic acid, 34l

The title compound was prepared from **21** (60 mg, 140 μmol) following **GP-1** [2,4,6-trichlorobenzoic acid chloride (41 mg, 168 μmol), $NaHCO_3$ (36 mg, 420 μmol), LiOH (17 mg, 700 μmol)]. Purification using preparative HPLC and lyophilization afforded **34l** (56 mg, 88 μmol, 63%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 12.81 (br s, 1H, -COO*H*), 9.08 (d, *J* = 8.2 Hz, 1H, -N*H*CO), 8.77 (br s, 1H, -N*H*), 7.92 (d, *J* = 5.8 Hz, 1H, Ar-*H*), 7.87 (t, *J* = 7.7 Hz, 1H, Ar-*H*), 7.66 (s, 2H, Ar-*H*), 7.19 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.04 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 6.84 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 6.83 (m, 1H, Ar-*H*), 4.61 (m, 1H, -C*H*), 4.04 (t, *J* = 5.7 Hz, 2H, -OCH_2), 3.47 (m, 2H, -NCH_2), 3.06 (dd, *J* = 14.0 Hz, *J* = 4.8 Hz, 1H, -C*H'*), 2.84 (dd, *J* = 13.9 Hz, *J* = 9.8 Hz, 1H, -C*H"*), 2.04 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 172.1, 162.6, 157.0, 152.8, 142.6, 136.3, 135.2, 134.1, 132.1, 130.1, 129.2, 127.6, 114.1, 113.1, 111.8, 64.7, 53.6, 38.5, 35.9, 27.5. MS (ESI): *m/z* 1042.9 [2*M*+H]$^+$ (6Cl), 522.6 [*M*+H]$^+$ (3Cl). HR-MS (ESI) ($C_{24}H_{23}Cl_3N_3O_4$)$^+$: calcd: 522.0749; found: 522.0744.

Preparation of 2-(*S*)-(2,4,6-trimethylpyridincarboxamido)-3-[4-(3-pyridin-2-yl-aminopropoxy)phenyl]propionic acid, 34m

The title compound was prepared from **21** (66 mg, 155 μmol) following **GP-2** [**20** (31 mg, 155 μmol), HATU (59 mg, 155 μmol), DIEA (131 μL, 775 μmol), LiOH (19 mg, 775 μmol)]. Purification using preparative HPLC and lyophilization afforded **34m** (18 mg, 31 μmol, 20%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 13.14 (br s, 1H, -COO*H*), 9.01 (d, *J* = 8.4 Hz, 1H, -N*H*CO), 8.92 (br s, 1H, -N*H*), 7.95 (d, *J* = 6.2 Hz, 1H, Ar-*H*), 7.88 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.42 (s, 1H, Ar-*H*), 7.20 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.06 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.87 (d, *J* = 8.5 Hz, 2H, Ar-*H*),

6.84 (t, *J* = 6.7 Hz, 1H, Ar-*H*), 4.69 (m, 1H, -C*H*), 4.05 (m, 2H, -OCH_2), 3.49 (t, *J* = 6.4 Hz, 2H, -NCH_2), 3.18 (dd, *J* = 14.0 Hz, *J* = 4.0 Hz, 1H, -C*H'*), 2.79 (dd, *J* = 13.9, 11.4 Hz, 1H, -C*H"*), 2.56 (s, 3H, -CH_3), 2.31 (s, 3H, -CH_3), 2.10 (s, 3H, -CH_3), 2.04 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ =172.5, 164.8, 157.1, 153.2, 152.9, 151.8, 149.9, 142.7, 136.3, 132.6, 130.0, 129.5, 124.6, 114.2, 113.0, 111.8, 64.8, 53.4, 39.4, 38.6, 35.4, 27.6, 19.9, 18.6, 18.0. MS (ESI): *m/z* 463.3 [*M*+H]$^+$, 232.3 [*M*+2H]$^{2+}$. HR-MS (ESI) ($C_{26}H_{31}N_4O_4^+$): calcd: 463.2340, found: 463.2330.

Preparation of 3-(*S*)-benzamido-4-(4-(3-pyridin-2-ylaminopropoxy)phenyl) butanoic acid, 35a

The title compound was prepared from **23** (50 mg, 112 μmol) following **GP-1**. [benzoyl chloride (17 μL, 145 μmol), $NaHCO_3$ (34 mg, 404 μmol), LiOH (13 mg, 560 mmol)] Purification using preparative HPLC and lyophilization afforded **35a** (11 mg, 20 μmol, 18%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 12.26 (br s, 1H, -COO*H*), 8.82 (br s, 1H, -N*H*), 8.32 (d, 1H, *J* = 8.4 Hz, 1H, -N*H*CO), 7.91 (d, *J* = 6.1 Hz, 1H, Ar-*H*), 7.85 (t, *J* = 7.9 Hz, 1H, Ar-*H*), 7.76 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.50 (t, *J* = 7.3 Hz, 1H, Ar-*H*), 7.44 (t, *J* = 7.5 Hz, 2H, Ar-*H*), 7.14 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.03 (d, *J* = 9.0 Hz, Ar-*H*), 6.83 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81 (t, *J* = 6.5 Hz, 1H, Ar-*H*), 4.44 (m, 1H, -C*H*), 4.02 (t, *J* = 6.0 Hz, 2H, -OCH_2), 3.47 (t, *J* = 6.5 Hz, 2H, -NCH_2), 2.82 (dd, *J* = 13.6 Hz, *J* = 8.0 Hz, 1H, -C*H'*), 2.76 (dd, *J* = 13.6 Hz, *J* = 5.9 Hz, 1H, -C*H"*), 2.53 (dd, *J* = 15.5 Hz, *J* = 7.7 Hz, 1H, -C*H'*), 2.44 (dd, *J* = 15.4 Hz, *J* = 6.2 Hz, 1H, -C*H")*, 2.02 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 172.3, 165.5, 156.7, 152.9, 142.6, 136.3, 134.6, 130.9, 130.8, 130.0, 128.0, 127.0, 114.1, 112.9, 111.7, 64.6, 48.3, 38.8, 38.7, 38.5, 27.6. MS (ESI): *m/z* 434.3 [*M*+H]$^+$. HR-MS (ESI) ($C_{25}H_{28}N_3O_4^+$): calcd: 434.2074, found: 434.2076.

Preparation of 3-(*S*)-(4-methylbenzamido)-4-[4-(3-pyridin-2-ylaminopropoxy)-phenyl]butanoic acid, 35b

The title compound was prepared from **23** (71 mg, 161 μmol) following **GP-2**. [4-methylbenzoic acid (44 mg, 320 μmol), HATU (122 mg, 320 μmol), DIEA (220 μL, 1.28 mmol), LiOH (20 mg, 0.8 mmol)] Purification using preparative HPLC and lyophilization afforded **35b** (12 mg, 21 μmol, 13%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 12.20 (br s, 1H, -COO*H*), 8.22 (d, *J* = 8.0 Hz, 1H, -N*H*CO), 7.90 (d, *J* = 6.2 Hz, 1H, Ar-*H*), 7.78 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.67 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.23 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.12 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.95 (d, *J* = 9.2

Hz, 1H, Ar-*H*), 6.82 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.76 (t, *J* = 6.5 Hz, 1H, Ar-*H*), 4.42 (m, 1H, -C*H*), 4.01 (t, *J* = 6.0 Hz, 2H, -OCH_2), 3.44 (m, 2H, -NCH_2), 2.80 (dd, *J* = 13.8 Hz, *J* = 7.6 Hz, 1H, -C*H'*), 2.74 (dd, *J* = 13.4 Hz, *J* = 5.7 Hz, 1H, -C*H"*), 2.50 (dd, *J* = 14.9 Hz, *J* = 7.7 Hz, -C*H'*), 2.42 (dd, *J* = 15.5 Hz, *J* = 6.3 Hz, 1H, -C*H"*), 2.33 (s, 3H, -CH_3), 2.00 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 172.4, 165.4, 156.7, 153.6, 141.8, 140.7, 137.6, 131.8, 130.7, 130.0, 128.6, 127.1, 114.1, 112.4, 111.7, 64.6, 48.2, 38.8, 38.7, 38.4, 27.7, 20.8. MS (ESI): *m/z* 448.3 [*M*+H$^+$]$^+$. HR-MS (ESI) $(C_{26}H_{30}N_3O_4)^+$: calcd: 448.2231; found: 448.2226.

Preparation of 3-(*S*)-(2, 6-dimethylbenzamido)-4-[4-(3-pyridin-2-ylaminoprop-oxy)phenyl]butanoic acid, 35c

The title compound was prepared from **23** (71 mg, 161 μmol) following **GP-2**. [2,6-dimethylbenzoic acid (48 mg, 320 μmol), HATU (122 mg, 320 μmol), DIEA (220 μL, 1.28 mmol), LiOH (20 mg, 0.8 mmol)] Purification using preparative HPLC and lyophilization afforded **35b** (10 mg, 17 μmol, 11%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 12.23 (br s, 1H, -COO*H*), 8.80 (br s, 1H, -N*H*), 8.25 (d, *J* = 8.4 Hz, 1H, -N*H*CO), 7.93 (d, *J* = 5.8 Hz, 1H, Ar-*H*), 7.87 (t, *J* = 7.7 Hz, 1H, Ar-*H*), 7.16 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.11 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.04 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 6.95 (d, *J* = 7.7 Hz, 2H, Ar-*H*), 6.87 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.83 (t, *J* = 6.7 Hz, 1H, Ar-*H*), 4.49 (m, 1H, -C*H*), 4.05 (t, *J* = 5.9 Hz, 2H, -OCH_2), 3.49 (m, 2H, -NCH_2), 2.73 (m, 2H, -CH_2), 2.47 (dd, *J* = 15.6 Hz, *J* = 9.6 Hz, 1H, -C*H'*), 2.38 (dd, *J* = 15.6 Hz, *J* = 5.9 Hz, 1H, -C*H"*), 2.05 (m, 2H, -CH_2), 2.02 (s, 6H, 2CH_3). ^{13}C NMR (125 MHz, DMSO): δ = 172.3, 168.1, 156.8, 153.0, 142.5, 138.5, 136.5, 133.5, 130.7, 130.0, 127.7, 126.8, 114.2, 112.9, 111.8, 64.7, 47.6, 38.9, 38.7, 38.5, 27.6, 18.5. MS (ESI): *m/z* 462.1 [*M*+H]$^+$. HR-MS (ESI) $(C_{27}H_{32}N_3O_4)^+$: calcd: 462.2387; found: 462.2385.

Preparation of 3-(*S*)-(3, 5-dimethylbenzamido)-4-[4-(3-pyridin-2-ylaminoprop-oxy)phenyl]butanoic acid 35d

The title compound was prepared from **23** (71 mg, 161 μmol) following **GP-2**. [3,5-dimethylbenzoic acid (48 mg, 320 μmol), HATU (122 mg, 320 μmol), DIEA (220 μL, 1.28 mmol), LiOH (20 mg, 0.8 mmol)] Purification using preparative HPLC and lyophilization afforded **35d** (15 mg, 26 μmol, 16%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ =12.27 (br s, 1H, -COO*H*), 8.87 (br s, 1H, -N*H*), 8.22 (d, *J* = 8.4 Hz, 1H, -N*H*CO), 7.91 (d, *J* = 6.1 Hz, 1H, Ar-*H*), 7.86 (t, *J* = 7.8 Hz, 1H, Ar-*H*),

7.47 (s, 2H, Ar-*H*), 7.13 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.12 (s, 1H, Ar-*H*), 7.04 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 6.84 (d, *J* = 8.7 Hz, 2H, Ar-*H*), 6.81 (t, *J* = 6.9 Hz 1H, Ar-*H*), 4.43 (m, 1H, -C*H*), 4.02 (t, *J* = 5.9 Hz, 2H, -OCH_2), 3.47 (t, *J* = 6.3 Hz, 2H, -NCH_2), 2.81 (dd, *J* = 13.6 Hz, *J* = 7.9 Hz, 1H, -C*H'*), 2.73 (dd, *J* = 13.8 Hz, *J* = 6.1 Hz, 1H, -C*H''*), 2.51 (dd, *J* = 15.5 Hz, *J* = 7.8 Hz, 1H, -C*H'*), 2.42 (dd, *J* = 15.3 Hz, *J* = 6.2 Hz, 1H, -C*H''*), 2.29 (s, 6H, 2CH_3), 2.03 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 172.4, 165.8, 156.7, 152.9, 142.7, 137.1, 136.2, 134.6, 132.1, 130.8, 130.0, 124.8, 114.1, 113.0, 111.7, 64.6, 48.2, 38.8, 38.6, 38.6, 27.6, 20.7. MS (ESI): *m/z* 462.2 [*M*+H]$^+$. HR-MS $(C_{27}H_{32}N_3O_4)^+$: calcd: 462.2387; found: 462.2382.

Preparation of 3-(*S*)-(2, 4, 6-dimethylbenzamido)-4-[4-(3-pyridin-2-ylaminoprop-oxy)phenyl]butanoic acid, 35e

The title compound was prepared from **23** (71 mg, 161 µmol) following **GP-2**. [2,4,6-trimethylbenzoic acid (50 mg, 320 µmol), HATU (122 mg, 320 µmol), DIEA (220 µL, 1.28 mmol), LiOH (20 mg, 0.8 mmol)] Purification using preparative HPLC and lyophilization afforded **35d** (21 mg, 36 µmol, 22%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 8.88 (br s, 1H, -N*H*), 8.16 (d, *J* = 8.8 Hz, 1H, -N*H*CO), 7.93 (d, *J* = 6.1 Hz, 1H, Ar-*H*), 7.87 (t, *J* = 7.9 Hz, 1H, Ar-*H*), 7.15 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.06 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 6.86 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.83 (t, *J* = 6.5 Hz, 1H, Ar-*H*), 6.76 (s, 2H, Ar-*H*), 4.47 (m, 1H, -C*H*), 4.05 (t, *J* = 5.9 Hz, -OCH_2), 3.49 (t, *J* = 6.5 Hz, 2H, -NCH_2), 2.73 (m, 2H, -CH_2), 2.46 (dd, *J* = 15.7 Hz, *J* = 7.7 Hz, 1H, -C*H'*), 2.37 (dd, *J* = 15.3 Hz, *J* = 6.2 Hz, 1H, -C*H''*), 2.19 (s, 3H, -CH_3), 2.04 (m, 2H, -CH_2), 1.97 (s, 6H, 2CH_3). ^{13}C NMR (125 MHz, DMSO): δ = 172.3, 168.3, 156.8, 152.9, 142.7, 136.8, 136.3, 135.8, 133.5, 130.7, 130.0, 127.4, 114.2, 113.0, 111.8, 64.7, 47.6, 38.9, 38.7, 38.6, 27.6, 20.5, 18.5. MS (ESI): *m/z* 476.4 [*M*+H]$^+$. HR-MS $(C_{28}H_{34}N_3O_4^+)$: calcd: 476.2544; found: 476.2532.

Preparation of 2-(*S*)-benzamido-3-[4-(4-pyridin-2-ylaminobutoxy)phenyl]propi-onic acid, 36a

The title compound was prepared from **24** (120 mg, 221 µmol) following **GP-1**. [benzoyl chloride (28 µL, 243 µmol), $NaHCO_3$ (55 mg, 663 µmol), LiOH (52 mg, 2.21 mmol)] Purification using preparative HPLC and lyophilization afforded **36a** (15 mg, 27 µmol, 12%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 8.65 (d+bs, *J* = 6.5 Hz, 2H, -N*H*CO, -N*H*), 7.89 (d, *J* = 6.2 Hz, 1H, Ar-*H*), 7.85 (t, *J* = 7.9 Hz, 1H, Ar-*H*), 7.80 (d, *J* = 7.3 Hz, 2H, Ar-*H*), 7.52 (t, *J* = 7.3 Hz, 1H, Ar-*H*), 7.45 (t, *J*

= 7.5 Hz, 2H, Ar-*H*), 7.22 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.01 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.86 (d, *J* = 8.5 Hz, 3H, Ar-*H*) 6.85 (m, 1H, Ar-*H*), 4.56 (m, 1H, -C*H*), 3.95 (t, 1H, *J* = 6.0 Hz, 2H, -OCH_2), 3.11 (dd, *J* = 13.9 Hz, *J* = 4.3 Hz, 1H, -C*H'*), 2.99 (dd, *J* = 13.9 Hz, *J* = 10.8 Hz, -C*H''*), 1.77 (m, 2H, -CH_2), 1.73 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 173.0, 166.2, 157.0, 152.7, 142.5, 137.2, 133.8, 131.2, 129.9, 128.1, 127.2, 114.0, 112.2, 111.7, 66.7, 54.3, 41.1, 35.3, 25.9, 24.5. MS (ESI): *m/z* 434.5 [*M*+H$^+$]$^+$. HR-MS (ESI) ($C_{25}H_{28}N_3O_4$)$^+$: calcd: 434.2074; found: 434.2069.

Preparation of 2-(*S*)-(2,4,6-trimethylbenzamido-3-[4-(4-pyridin-2-ylaminobutoxy)phenyl]propionic acid, 36b

The title compound was prepared from **24** (120 mg, 221 μmol) following **GP-2**. [2,4,6-trimethylbenzoic acid (73 mg, 442 μmol), HATU (210 mg, 552 μmol), DIEA (300 μL, 1.76 mmol), LiOH (52 mg, 2.21 mmol)] Purification using preparative HPLC and lyophilization afforded **36b** (24 mg, 41 μmol, 18%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): 12.68 (br s, 1H, -COO*H*), 8.74 (br s, 1H, -N*H*), 8.43 (d, *J* = 8.2 Hz, 1H, -N*H*CO), 7.89 (m, 1H, Ar-*H*), 7.83 (m, 1H, Ar-*H*), 7.16 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.00 (d, *J* = 8.9 Hz, 1H, Ar-*H*), 6.81 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 6.72 (s, 2H, Ar-*H*), 4.58 (m, 1H, -C*H*), 3.94 (m, 2H, -OCH_2), 3.33 (m, 2H, -NCH_2-), 3.06 (d, *J* = 13.9 Hz, 1H, -C*H'*), 2.75 (dd, *J* = 14.2 Hz, *J* = 11.3 Hz, 1H, -C*H''*), 2.15 (s, 3H, -CH_3), 1.89 (s, 6H, 2CH_3), 1.76 (m, 2H, -CH_2), 1.71 (m, 2H, -CH_2).^{13}C NMR (125 MHz, DMSO): δ = 173.1, 169.1, 157.1, 152.8, 142.5, 136.9, 136.2, 135.3, 133.7, 130.0, 129.8, 127.3, 114.1, 113.1, 111.7, 66.9, 53.4, 41.2, 35.4, 25.9, 24.5, 20.5, 18.4. MS (ESI): *m/z* 476.5 [*M*+H$^+$]$^+$. HR-MS (ESI) ($C_{28}H_{34}N_3O_4^+$): calcd: 476.2544, found: 476.2539.

Preparation of (*S*)-2-(2,6 dimethyl-4-isopropoxy)-3-[4-(4-(pyridin-2-ylamino)butoxy)phenyl]propanoic acid, 36c

The title compound was prepared from **24** (120 mg, 220 μmol) following **GP-2** [**17b** (48 mg, 265 μmol), HATU (100 mg, 265 μmol), DIEA (187 μL, 1.10 mmol), LiOH (26 mg, 1.10 mmol)]. Purification using preparative HPLC and lyophilization afforded **36c** (47 mg, 74 μmol, 34%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 12.70 (br s, 1H, -COO*H*), 8.74 (br s, 1H, -N*H*), 8.44 (d, *J* = 8.3 Hz, 1H, -N*HCO*), 7.92 (d, *J* = 6.1 Hz, 1H, Ar-*H*), 7.87 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.19 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.04 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.84 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 6.83 (m, 1H, Ar-*H*), 6.50 (s, 2H, Ar-*H*), 4.60 (m, 1H, -OC*H*), 4.55 (m, 1H, -C*H*), 3.98 (t, *J* = 5.9 Hz, 2H, -OCH_2), 3.37 (m, 2H, -NCH_2), 3.09 (dd, *J* = 14.0 Hz, *J* = 4.0 Hz, 1H, -C*H'*), 2.79

(dd, *J* = 13.8 Hz, *J* = 11.4 Hz, 1H, -C*H''*), 1.94 (s, 6H, -2CH_3), 1.80 (m, 2H, -CH_2), 1.74 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 173.1, 169.0, 157.1, 156.7, 152.8, 142.5, 136.3, 135.5, 130.7, 130.0, 129.8, 114.1, 113.8, 113.1, 111.7, 68.7, 66.9, 53.4, 41.2, 35.3, 25.9, 24.5, 21.7, 18.7. MS (ESI): *m/z* 520.7 [*M*+H$^+$]$^+$. HR-MS (ESI) ($C_{30}H_{38}N_3O_5^+$): calcd: 520.2806, found: 520.2792.

Preparation of 2-(*S*)-(2,4-diethylbenzamido)-3-[4-(4-pyridin-2-yl-aminobutoxy)-phenyl]propionic acid, 36d

The title compound was prepared from **24** (120 mg, 220 μmol) following **GP-2** [**18** (47 mg, 265 μmol), HATU (100 mg, 265 μmol), DIEA (187 μL, 1.10 mmol), LiOH (26 mg, 1.10 mmol)]. Purification using preparative HPLC and lyophilization afforded **36d** (34 mg, 69 μmol, 32%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 8.75 (br s, 1H, -N*H*), 8.53 (d, *J* = 8.3 Hz, 1H, -N*H*CO), 7.93 (d, *J* = 6.1 Hz, 1H, Ar-*H*), 7.89 (t, *J* = 7.9 Hz, 1H, Ar-*H*), 7.20 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.18 (t, *J* = 7.3 Hz, 1H, Ar-*H*), 7.03 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.99 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 6.85 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.82 (t, *J* = 6.7 Hz, 1H, Ar-*H*), 4.70 (m, 1H, -C*H*), 3.99 (t, *J* = 6.0 Hz, 2H, -OCH_2), 3.38 (m, 2H, -NCH_2), 3.12 (dd, *J* = 14.0 Hz, *J* = 3.9 Hz, 1H, -C*H'*), 2.79 (dd, *J* = 13.7 Hz, *J* = 11.7 Hz, 1H, -C*H''*), 2.80-1.80 (br s, 2H, -CH_2)*, 1.80 (m, 2H, -CH_2), 1.75 (m, 2H, -CH_2), 0.97 (br s, 3H, -CH_3)*. ^{13}C NMR (125 MHz, DMSO): δ = 172.3, 168.4, 156.9, 141.3, 139.6, 137.7, 137.6, 136.8, 129.5, 127.7, 124.7, 114.0, 111.7, 111.3, 66.9, 53.0, 40.8, 35.3, 25.7, 24.8, 24.5, 14.8. MS (ESI): *m/z* 979.0 [2*M*+H$^+$]$^+$, 490.3 [*M*+H$^+$]$^+$, 161.0 [$C_6H_2(C_2H_5)_2CO$]$^+$. HR-MS (ESI) ($C_{29}H_{36}N_3O_4^+$): calcd: 490.2700, found: 490.2688.

* rotation around the –CH_2-CH_3- bond is restricted and lies on NMR-timescale. Spectra at lower temperature show line-sharpening, but still no *J*-coupling.

Preparation of (*S*)-2-(2-methylnaphthalene-1-carboxamido)-3-[4-(4-(pyridin-2-ylamino)butoxy)phenyl]propanoic acid, 36e

The title compound was prepared from **24** (120 mg, 220 μmol) following **GP-2** [2-methylnaphtalene-1-carboxylic acid (49 mg, 265 μmol), HATU (100 mg, 265 μmol), DIEA (187 μL, 1.10 mmol), LiOH (26 mg, 1.10 mmol)]. Purification using preparative HPLC and lyophilization afforded **36e** (60 mg, 98 μmol, 45%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 8.83 (d, *J* = 8.3 Hz, 1H, -N*H*CO), 8.82 (br s, 1H, -N*H*), 7.93 (d, *J* = 6.9 Hz, 1H, Ar-*H*), 7.89-7.80 (m, 3H, Ar-*H*), 7.42 (t, *J* = 6.9 Hz,

1H, Ar-*H*), 7.32 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.23 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.05 (d, *J* = 8.9 Hz, 1H, Ar-*H*), 6.89 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.83 (t, *J* = 6.5 Hz, 1H, Ar-*H*), 4.82 (m, 1H, -C*H*), 4.03 (t, *J* = 5.2 Hz, 2H, -OCH_2), 3.39 (m, 2H, -NCH_2), 3.19 (dd, *J* = 11.6 Hz, *J* = 3.1 Hz, 1H, -C*H'*), 2.81 (dd, *J* = 12.6 Hz, *J* = 6.3 Hz, 1H, -C*H"*), 2.19 (br s, 3H, -CH_3), 1.84 (m, 2H, -CH_2), 1.79 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 173.0, 168.4, 157.2, 152.8, 142.5, 136.3, 134.4, 131.3, 131.0, 130.1, 129.9, 129.6, 128.2, 127.8, 127.4, 125.9, 125.0, 114.1, 113.1, 111.7, 66.9, 53.6, 41.2, 35.4, 26.0, 24.6, 18.7. MS (ESI): *m/z* 1169.3 [2*M*+H$^+$]$^+$, 512.6 [*M*+H$^+$]$^+$. HR-MS (ESI) ($C_{30}H_{32}N_3O_4^+$): calcd: 498.2387, found: 498.2374.

Preparation of 2-(benzamido)-3-[4-(3-guanidylpropoxy)phenyl] propionic acid, 37a.

The title compound was synthesized from **31** (55 mg, 150 μmol) according to **GP-1** [Benzoyl chloride (20 μL, 165 μmol), $NaHCO_3$ (63 mg, 750 μmol), LiOH (18 mg, 0.75 mmol)]. Purification using preparative HPLC and lyophilization afforded **37a** (12 mg, 31.2 μmol, 21%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 12.77 (s, 1H, COO*H*), 8.66 (d, *J* = 8.0 Hz, 1H, -N*H*CO), 7.80 (d, *J* = 7.3 Hz, 2H, Ph-*H*), 7.71 (t, *J* = 5.4 Hz, 1H, -N*H*), 7.52 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.45 (t, *J* = 7.5 Hz, 2H, Ar-*H*), 7.23 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.83 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 4.57 (m, 1H, -C*H*), 3.95 (t, *J* = 6.1 Hz, 2H, -OCH_2), 3.25 (m, 2H, -NCH_2-), 3.12 (dd, *J* = 13.8 Hz, *J* = 4.2 Hz, 1H, -C*H'*), 3.00 (dd, *J* = 13.8 Hz, *J* = 10.7 Hz, 1H, -C*H"*), 1.89 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 173.1, 166.2, 156.9, 156.8, 133.8, 131.2, 130.2, 130.0, 128.1, 127.2, 114.1, 64.5, 54.4, 37.8, 35.4, 28.1. MS (ESI): *m/z* 385.5 [*M*+H]$^+$. HR-MS (ESI) ($C_{20}H_{25}N_4O_4^+$): calcd: 385.1870, found: 385.1866.

Preparation of 2-(benzamido)-3-[4-(4-guanidylbutoxy)phenyl] propionic acid, 37b.

The title compound was synthesized from **32** (161 mg, 271 μmol) according to **GP-1** [Benzoyl chloride (50 μL, 407 μmol), $NaHCO_3$ (68 mg, 813 μmol), LiOH (110 mg, 2.7 mmol)]. Purification using preparative HPLC and lyophilization afforded **37b** (30 mg, 60.2 μmol, 22%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 12.76 (br s, 1H, COO*H*), 8.66 (d, *J* = 8.2 Hz, 1H, -N*H*CO), 7.81 (d, *J* = 7.1 Hz, 2H, Ar-*H*), 7.69 (t, *J* = 5.5 Hz, 1H, -N*H*), 7.52 (t, *J* = 7.3 Hz, 1H, Ar-*H*), 7.45 (t, *J* = 7.5 Hz. 2H, Ar-*H*), 7.22 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.82 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 4.56 (m, 1H, -C*H*), 3.92 (t, *J* = 6.3 Hz, 2H, -OCH_2), 3.14 (m, 2H, -NCH_2-), 3.12 (m, 1H, -C*H'*),

3.00 (dd, *J* = 13.8 Hz, *J* = 10.7 Hz, -C*H''*), 1.70 (m, 2H, -C*H*$_2$), 1.59 (m, 2H, -C*H*$_2$). ^{13}C NMR (125 MHz, DMSO): δ = 173.1, 166.2, 157.0, 156.7, 133.8, 131.2, 129.9, 128.1, 127.2, 114.0, 66.7, 54.4, 40.3, 39.4, 35.3, 25.7, 25.2. MS (ESI): *m/z* 399.3 [*M*+H]$^+$. HR-MS (ESI) ($C_{21}H_{27}N_4O_4$)$^+$: calcd: 399.2027; found: 399.2023.

Preparation of (*S*)-2-(2,4,6-trimethylbenzamido)-3-[4-(3-(pyrimidin-2-ylamino)-propoxy)phenyl]propanoic acid, 38a

The title compound was prepared from **25** (260 mg, 604 μmol) following **GP-2** [2,4,6-trimethylbenzoic acid (118 mg, 725 μmol), HATU (276 mg, 725 μmol), DIEA (514 μL, 3.02 mmol), LiOH (73 mg, 3.02 mmol)]. Purification using preparative HPLC and lyophilization afforded **38a** (62 mg, 108 μmol, 18%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 8.47 (d, *J* = 8.4 Hz, 1H, -N*H*CO), 8.40 (d, *J* = 4.2 Hz, 2H, Ar-*H*), 7.89 (br s, 1H, -N*H*), 7.19 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.84 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.74 (s, 2H, Ar-*H*), 6.71 (t, *J* = 4.9 Hz, 1H, Ar-*H*), 4.62 (m, 1H, -C*H*), 4.01 (t, *J* = 6.3 Hz, 2H, -OC*H*$_2$), 3.47 (t, *J* = 6.9 Hz, 2H, -NC*H*$_2$), 3.10 (dd, *J* = 14.0 Hz, *J* = 4.0 Hz, 1H, -C*H'*), 2.79 (dd, *J* = 13.8 Hz, *J* = 11.5 Hz, 1H, -C*H''*), 2.19 (s, 3H, -C*H*$_3$), 1.99 (m, 2H, -C*H*$_2$), 1.94 (s, 6H, 2C*H*$_3$). ^{13}C NMR (125 MHz, DMSO): δ = 173.1, 169.2, 159.4, 157.5, 157.1, 136.9, 135.3, 133.7, 130.0, 129.8, 127.4, 114.2, 109.7, 65.3, 53.4, 37.9, 35.4, 28.3, 20.5, 18.4. MS (ESI): *m/z* 463.3 [*M*+H]$^+$. HR-MS (ESI) ($C_{26}H_{31}N_4O_4^+$) calcd: 463.2340, found: 463.2335.

Preparation of (*S*)-2-(2,4,6-trimethylbenzamido)-3-[4-(3-(pyridazin-2-ylamino)-propoxy)phenyl]propanoic acid, 38b

The title compound was prepared from **26** (256 mg, 594 μmol) following **GP-2** [2,4,6-trimethylbenzoic acid (117 mg, 714 μmol), HATU (271 mg, 714 μmol), DIEA (506 μL, 2.98 mmol), LiOH (72 mg, 2.98 mmol)]. Purification using preparative HPLC and lyophilization afforded **38b** (59 mg, 102 μmol, 17%) as TFA salt (yellow solid). ^{1}H NMR (500 MHz, DMSO): δ = 8.46 (d, *J* = 8.3 Hz, 1H, -N*H*CO), 8.00 (s, 1H, Ar-*H*), 7.95 (d, *J* = 1.6 Hz, 1H, Ar-*H*), 7.67 (d, *J* = 2.8 Hz, 1H, Ar-*H*), 7.20 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.85 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 6.75 (s, 2H, Ar-*H*), 4.63 (m, 1H, -C*H*), 4.03 (t, *J* = 6.2 Hz, 1H, -OC*H*$_2$), 3.42 (t, *J* = 6.8 Hz, 1H, -NC*H*$_2$), 3.10 (dd, *J* = 13.9 Hz, *J* = 4.0 Hz, 1H, -C*H'*), 2.80 (dd, *J* = 13.8 Hz, *J* = 11.4 Hz, 1H, -C*H''*), 2.19 (s, 3H, -C*H*$_3$), 1.99 (m, 2H, -C*H*$_2$), 1.94 (s, 6H, 2C*H*$_3$). ^{13}C NMR (125 MHz, DMSO): δ = 173.1, 169.2, 157.1, 154.3, 140.4, 136.9, 135.3, 133.7, 133.5, 130.0, 129.8, 127.4, 114.2, 65.2, 53.4, 37.2,

35.4, 28.2, 20.5, 18.4. MS (ESI): *m/z* 463.3 $[M+H^+]^+$. HR-MS (ESI) ($C_{26}H_{31}N_4O_4^+$) calcd: 463.2340, found: 463.2336.

Preparation of (*S*)-2-(2,4,6-trimethylbenzamido)-3-[4-(3-(pyrimidin-4-ylamino)-propoxy)phenyl]propionic acid, 38c

The title compound was prepared from **27** (150 mg, 348 µmol) following **GP-2** [2,4,6-trimethylbenzoic acid (180 mg, 1.08 µmol), HATU (410 mg, 1.08 µmol), DIEA (830 µL, 4.90 mmol), LiOH (115 mg, 4.8 mmol)]. Purification using preparative HPLC and lyophilization afforded **38c** (21 mg, 36 µmol, 10%) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 12.70 (br s, 1H, -COO*H*), 9.43 (br s, 1H, -N*H*), 8.78 (s, 1H, Ar-*H*), 8.47 (d, *J* = 8.2 Hz, 1H, -N*H*CO), 7.20 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 6.84 (d, *J* = 8.2 Hz, 2H, Ar-*H*), 6.76 (m, 3H, Ar-*H*), 4.62 (m, 1H, -C*H*), 4.02 (t, *J* = 5.5 Hz, 2H, -OCH_2), 3.62 (m, 2H, -NCH_2), 3.09 (dd, *J* = 13.9 Hz, *J* = 3.5 Hz, 1H, -C*H'*), 2.79 (dd, *J* = 13.3 Hz, *J* = 11.9 Hz, 1H, -C*H''*), 2.19 (s, 3H, -CH_3), 2.01 (m, 2H, -CH_2), 1.93 (s, 6H, 2CH_3). ^{13}C NMR (125 MHz, DMSO): δ = 173.1, 169.1, 162.2, 156.9, 152.6, 142.3, 136.9, 135.3, 133.7, 130.0, 127.3, 114.1, 106.0, 64.9, 53.4, 39.4, 37.8, 35.4, 27.8, 20.5, 18.4. MS (ESI): *m/z* 463.3 $[M+H^+]^+$, 147.1 $[COC_6H_2(CH_3)_3]^+$. HR-MS (ESI) ($C_{26}H_{31}N_4O_4^+$) calcd: 463.2340, found: 463.2336.

Preparation of (*S*)-2-(2,4,6-trimethylbenzamido)-3-(4-(3-(tetrahydropyrimidin-2(1*H*)-ylideneamino)propoxy)phenyl)propanoic acid, 38d

Compound **38a** (TFA salt, 43 mg, 75 µmol) was dissolved in 4 mL of methanol. After addition of 0.1 mL of acetic acid and 10 mg Pd on carbon, the resulting mixture was hydrogenated in an autoclave at 30 bar for 1 h. The mixture was filtered, concentrated and purified by preparative HPLC to give **38d** (36 mg, 62 µmol, 83 %) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 12.68 (br s, 1H, -COO*H*), 8.48 (d, *J* = 8.8 Hz, 1H, -N*H*CO), 7.71 (br s, 2H, -N*H*), 7.21 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.85 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 6.77 (s, 2H, Ar-*H*), 4.61 (m, 1H, -C*H*), 3.97 (m, 2H, -OCH_2), 3.24 (m, 4H, -CH_2), 3.23 (m, 2H, =NCH_2), 3.09 (dd, *J* = 13.8 Hz, *J* = 3.1 Hz, 1H, -C*H'*), 2.79 (dd, *J* = 13.8 Hz, *J* = 11.5 Hz, -C*H''*), 2.20 (s, 3H, -CH_3), 1.94 (s, 6H, 2CH_3), 1.91 (m, 2H, -CH_2), 1.79 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 173.1, 169.1, 156.9, 152.6, 136.9, 135.3, 133.7, 130.0, 127.3, 114.1, 64.7, 53.4, 38.0, 37.4, 35.4, 28.1, 20.5, 19.6, 18.4. MS (ESI): *m/z* 467.6 $[M+H]^+$. HR-MS (ESI) ($C_{26}H_{35}N_4O_4^+$) calcd: 467.2653, found: 467.2649.

Preparation of (*S*)-2-(2,4,6-trimethylbenzamido)-3-(4-(3-(1,4,5,6-tetrahydropyridazin-2-ylamino)propoxy)phenyl)propanoic acid, 38e

Compound **38b** (TFA salt, 40 mg, 70 µmol) was dissolved in 4 mL of methanol. After addition of 0.1 mL of acetic acid and 10 mg Pd on carbon, the resulting mixture was hydrogenated in an autoclave at 30 bar for 1 h. The mixture was filtered, concentrated and purified by preparative HPLC to give **38e** (37 mg, 64 µmol, 91 %) as TFA salt (colorless solid). ^{1}H NMR (500 MHz, DMSO): δ = 9.92 (br s, 1H, -N*H*), 9.83 (br s, 1H, -N*H*), 9.74 (br s, 1H, -N*H*), 8.49 (d, *J* = 8.2 Hz, 1H, -N*H*CO), 7.22 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 6.86 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 6.77 (s, 2H, Ar-*H*), 4.61 (m, 1H, -C*H*), 4.09 (m, 2H), 4.01 (m, 2H, -OCH_2), 3.51 (m, 2H, -CH_2), 3.38 (m, 2H, -CH_2), 3.33 (m, 2H, -CH_2), 3.09 (dd, *J* = 13.9 Hz, *J* = 3.5 Hz, 1H, -C*H'*), 2.80 (dd, *J* = 13.4 Hz, *J* = 11.7 Hz, 1H, -C*H''*), 2.20 (s, 3H, -CH_3), 2.00 (m, 2H, -CH_2), 1.95 (s, 6H, 2CH_3). ^{13}C NMR (125 MHz, DMSO): δ =173.1, 169.1, 157.6, 156.8, 136.9, 135.3, 133.7, 130.1, 130.0, 127.4, 114.1, 64.4, 53.4, 41.2, 38.5, 38.0, 35.4, 26.8, 20.5, 18.4. MS (ESI): *m/z* 1399.4 [3*M*+H]$^+$, 933.4 [2*M*+H]$^+$, 467.6 [*M*+H]$^+$. HR-MS ($C_{26}H_{35}N_4O_4^+$) calcd: 467.2653, found: 467.2649.

Preparation of (*S*)-2-(2, 4, 6-trimethylbenzamido)-3-(4-(3-(1,4,5,6-tetrahydropyridin-2-ylamino)propoxy)phenyl)propanoic acid, 38f

Compound **34e** (TFA salt, 31 mg, 54 µmol) was dissolved in 4 mL of methanol. After addition of 0.1 mL of acetic acid and 10 mg Pd on carbon, the resulting mixture was hydrogenated in an autoclave at 30 bar for 1 h. The mixture was filtered, concentrated and purified by preparative HPLC to give **38f** (27 mg, 62 µmol, 86 %) as TFA salt (colorless solid). **^{1}H NMR** (500 MHz, DMSO): δ = 9.16 (br s, 1H, -N*H*), 9.13 (br s, 1H, -N*H*), 8.47 (d, *J* = 8.3 Hz, -N*H*CO), 7.21 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.85 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.77 (s, 2H, Ar-*H*), 4.61 (m, 1H, -C*H*), 4.01 (m, 2H, -OCH_2), 3.03 (m, 3H, -CH_2, =C*H*), 3.10 (dd, *J* = 13.9 Hz, *J* = 4.1 Hz, 1H, -C*H'*), 2.80 (dd, *J* = 13.9 Hz, *J* = 11.3 Hz, 1H, -C*H''*)), 2.54 (t, *J* = 5.8 Hz, 2H, -CH_2N), 2.20 (s, 3H, -CH_3), 1.98 (m, 2H, -CH_2), 1.95 (s, 6H, 2CH_3), 1.71 (m, 4H, -CH_2CH_2). **^{13}C NMR** (125 MHz, DMSO): δ = 173.1, 169.1, 162.7, 156.8, 136.9, 135.7, 133.7, 130.1, 130.0, 127.3, 114.1, 64.6, 53.4, 41.0, 38.1, 35.4, 26.9, 25.8, 20.5, 20.4, 18.4, 17.6. MS (ESI): *m/z* 1419.2 [3*M*+Na$^+$]$^+$, 1396.1 [3*M*+H$^+$]$^+$, 953.2 [2*M*+Na$^+$]$^+$, 931.1 [2*M*+H$^+$]$^+$, 466.3 [*M*+H$^+$]$^+$. HR-MS ($C_{27}H_{36}N_3O_4^+$) calcd: 466.2700, found: 466.2698.

Preparation of 2-(*S*)-carboxy-7-(4-guanidylbutoxy)-1,2,3,4-tetrahydroisochinolin, 39a

The title compound was synthesized from **33** (100 mg, 161 µmol) by Boc deprotection (dioxane/*conc.* hydrochloric acid 3:1) and evaporation followed by saponification of the methyl ester with LiOH (38 mg, 1.6 mmol, 10 equiv) in methanol/water 3:1. Purification via preparative HPLC afforded **39a** (56 mg, 105 µmol, 65 %) as colorless solid (TFA salt). ^{1}H NMR (500 MHz, DMSO): δ = 9.66 (br s, 1H, -N*H*), 7.86 (s, 1H, -N*H*), 7.50-7.00 (br s, 2H, -NH_2^+), 7.17 (d, *J* = 8.5 Hz, 1H, Ar-*H*),6.87-6.83 (m, 2H, Ar-*H*), 4.34 (dd, *J* = 11.3 Hz, *J* = 6.7 Hz, 1H, -C*H*), 4.29 (m, 2H, -NCH_2), 3.95 (t, *J* = 6.4 Hz, 2H, -OCH_2), 3.22 (dd, *J* = 16.8 Hz, *J* = 4.9 Hz, 2H, -C*H'*), 3.16 (dd, *J* = 12.9 Hz, *J* = 6.7 Hz, 1H, -C*H'*), 3.01 (dd, *J* = 16.7 Hz, *J* = 11.5 Hz, 1H, -C*H"*), 1.72 (m, 2H, -CH_2), 1.60 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 170.0, 157.3, 156.8, 129.8, 129.3, 122.5, 114.5, 111.6, 67.1, 53.5, 43.9, 40.3, 27.4, 25.7, 25.2. MS (ESI): *m/z* 307.2 [*M*+H$^+$]$^+$. HR-MS (ESI) ($C_{22}H_{27}N_4O_4^+$): calcd: 307.1765; found: 307.1760.

Preparation of 1-Benzoyl-2-(*S*)-carboxy-7-(4-guanidylbutoxy)-1,2,3,4-tetrahydroisochinolin, 39b

The title compound was synthesized from **33** (250 mg, 403 µmol), benzoyl chloride (46 µL, 403 µmol), $NaHCO_3$ (68 mg, 806 µmol) and LiOH (96 mg, 4.30 mmol) according to **GP-1**. Purification via preparative HPLC gave **39b** (25 mg, 48 µmol, 12%) as a colorless solid (TFA salt). ^{1}H NMR (500 MHz, DMSO): δ = 7.51-7.39 (m, 5H, Ar-*H*), 7.08 (m, 1H, Ar-*H*), 6.82 (s, 1H*, Ar-*H*), 6.72 (m, 1H, Ar-*H*), 6.61 (s, 1H**, Ar-*H*), 5.14 (t, *J* = 4.7 Hz, 1H**, -C*H*), 4.93 (d, 17.8 Hz, 1H*, -C*H*), 4.60-4.39 (m, 2H, -CH_2N), 3.93 (t, *J* = 5.9 Hz, 2H**, -OCH_2), 3.85 (t, *J* = 5.9 Hz, 2H*, -OCH_2), 3.18-3.01 (m, 4H, -NCH_2, -CH_2), 1.72-1.49 (m, 4H, -CH_2CH_2). ^{13}C NMR (125 MHz, DMSO): δ = (172.0, 171.8), (170.9, 170.8), 157.2, 156.6, 138.3, (136.0, 135.9), 133.0, (129.8, 129.6), (129.4, 129.1), (128.6, 128.5), (126.7, 126.2), (124.5, 123.6), (113.8, 113.3), (111.7, 111.1), 66.9, (56.2, 51.9), (47.5, 43.1), (40.4, 40.3), (30.0, 29.3), (25.7, 25.7), (25.2, 25.2). MS (ESI): *m/z* 411.4 [*M*+H$^+$]$^+$, 821.3 [2*M*+H$^+$]$^+$, 1231.4 [3*M*+H$^+$]$^+$. MS (ESI): *m/z* 411.2 [*M*+H$^+$]$^+$. HR-MS (ESI) ($C_{22}H_{27}N_4O_4^+$): calcd: 411.2027; found: 411.2022.

*represents the minor rotamer of the benzoyl-group

**represents the major rotamer.of the benzoyl-group

^{13}C signals with different chemical shifts in both rotamers are given in parentheses.

Preparation of 1-(2,4,6-trimethylphenylsulfonyl)-2-(*S*)-carboxy-7-(4-guanidylbutoxy)-1,2,3,4-tetrahydroisochinolin, 39c

The title compound was synthesized from **33** (295 mg, 476 µmol), 2,4,6-trimethylphenylsulfonyl chloride (208 mg, 952 µmol), DIEA (404 µL, 2.38 mmol) and LiOH (57 mg, 2.38 mmol) according to **GP-3**. Purification via preparative HPLC gave **39c** (63 mg, 105 µmol, 22%) as colorless solid (TFA salt). ^{1}H NMR (500 MHz, DMSO): δ = 7.71 (t, *J* = 5.2 Hz, 1H, -N*H*), 7.50-6.90 (br s, 2H, -N*H*), 7.07 (s, 2H, Ar-*H*), 7.05 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 6.76 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 6.73 (dd, *J* = 8.4 Hz, *J* = 2.3 Hz, 1H, Ar-*H*), 4.64 (dd, *J* = 6.1 Hz, *J* = 1.0 Hz, -C*H*), 4.50 (d, *J* = 16.3 Hz, 1H, -NC*H'*), 4.33 (d, *J* = 16.3 Hz, 1H, -NC*H''*), 3.92 (t, *J* = 6.3 Hz, 1H, -OCH_2), 3.14 (m, 2H, -NCH_2), 3.10 (d, *J* = 17.0 Hz, 1H, -C*H'*), 2.99 (dd, *J* = 16.1, *J* = 6.6 Hz, 1H, -C*H''*), 2.55 (s, 6H, 2CH_3), 2.27 (s, 3H, -CH_3), 1.79-1.65 (m, 2H, -CH_2), 1.62-1.56 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = 171.5, 157.0, 156.7, 156.7, 142.3, 139.5, 132.5, 131.8, 129.7, 122.8, 113.6, 111.1, 66.8, 52.6, 43.0, 40.3, 29.8, 25.7, 25.1, 22.2, 20.3. MS (ESI): *m/z* 489.7 $[M+H^+]^+$. HR-MS (ESI) ($C_{24}H_{33}N_4O_5S^+$): calcd: 489.2144; found: 489.2194.

Preparation of 1-acetyl-2-(*S*)-carboxy-7-(4-guanidylbutoxy)- 1,2,3,4-tetrahydroisochinolin, 39d

Compound **39a** (20 mg, 37 µmol, 1 equiv) was dissolved in 0.5 mL dioxane/water 1:1. $NaHCO_3$ (16 mg, 187 µmol, 5 equiv) and acetic acid anhydride (4 µL, 41 µmol, 1.1 equiv) were added and the mixture stirred for 0.5 h. Evaporation followed by preparative HPLC purification gave **39d** (15 mg, 32 µL, 88%) as colorless solid (TFA salt). ^{1}H NMR (500 MHz, DMSO): δ = 12.76 (br s, 1H, -COO*H*), 7.69 (m, 1H, -N*H*), 7.70-7.60 (br s, -N*H*), 7.10 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.80-6.72 (m, 2H, Ar-*H*), 5.13 (dd, *J* = 6.0 Hz, *J* = 5.1 Hz, 1H**, -C*H*), 4.91 (d, *J* = 3.3 Hz, 1H*, -C*H*), 4.70 (d, *J* = 18.9 Hz, 1H*, -NC*H'*), 4.70 (d, *J* = 15.5 Hz, 1H**, -NC*H'*), 4.58 (d, *J* = 15.9 Hz, 1H**, -NC*H''*), 4.27 (d, *J* = 17.6 Hz, 1H*, -NC*H''*), 3.94 (m, 2H, -OCH_2), 3.15 (m, 2H, NCH_2-), 3.15-3.01 (m, 1H+1H*, -C*H'*(*H''*)), 2.94 (dd, *J* = 15.6 Hz, *J* = 6.2 Hz, 1H**, -C*H''*), 2.14 (s, 3H**, -CH_3), 2.05 (s, 3H*, -CH_3), 1.71 (m, 2H, -CH_2), 1.60 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, DMSO): δ = (172.4*, 172.3**), (170.0*, 169.7**), 157.1, 156.7, (134.0**, 133.8*), 129.0, (124.2**, 124.0*), (113.3**, 113.1*), (111.7*, 111.5**), (66.9**, 66.8*), (55.0*, 50.8**), (45.6**, 42.8*), 40.3, (30.4*, 29.7**), 25.7, 25.2, (21.7**, 21.6*). MS (ESI): *m/z* 349.4 $[M+H^+]^+$. HR-MS (ESI)$(C_{17}H_{25}N_4O_4)^+$: Calc. 349.1870; found: 349.1868.

*represents the minor rotamer of the acetyl-group

**represents the major rotamer.of the acetyl-group

^{13}C signals with different chemical shifts in both rotamers are given in parentheses.

Solid Phase Synthesis of Diacylhydrazones

General Procedures

GP-4 Loading of TCP-resin

Chloro-TCP-resin (theoretical loading 1.04 mmol/g) was filled into a suitable syringe (20 mL for 1 g resin) equipped with a PP-frit and a canula. The amino acid (1.2 mmol, referring to theoretical loading) was dissolved in dry DCM (8 mL/g resin), treated with DIEA (2.5 equiv, referring to amino acid) and sucked directly into the syringe with the resin and mixed by gentle rotation for 1 h. The resin was capped by adding 0.2 mL methanol (per gram resin) and 0.2 equiv DIEA to the reaction mixture and shaken for 20 min. The loaded resin was washed with DCM (3x), NMP (3x), NMP/methanol 1:1 (1x) and pure methanol (3x). After drying under vacuum, the resin was weighted and the real loading calculated with following equation:

$$c[mol/g] = \frac{m_{total} - m_{resin}}{(MW - 36.461) \times m_{total}}$$

Equation: Calculation of resin loading. m_{total} = mass of loaded resin. m_{resin} = mass of unloaded resin. MW = molecular weight of immobilized amino acid.

In cases, where the loading was not calculated, an average loading of 0.6 mmol/g was assumed.

GP-5 Fmoc deprotection

The washed and swollen resin was treated twice with a solution of piperidine (20%) in NMP (*v/v*), 5 min and 15 min, respectively and washed 5 times with NMP.

GP-6 Alloc deprotection

The dry resin was swollen with dry DCM for 5 min. The resin was then treated with a solution of *tetrakis*-triphenylphosphinepalladium (0.25 equiv) and phenylsilane (10 equiv) in dry DCM at ambient temperature. Care had to be taken due to gas evolution and the pressure had to be released from the reaction vessel from time to time. After 1.5 h of shaking, the mixture was filtered and the resin washed twice with a 0.5%

solution of DDTC (sodium *N*,*N*-diethyldithiocarbamate) in DMF and a 0.5% solution of DIEA in DMF. The washing procedure was repeated and the resin washed five times with NMP.

GP-7 Amide bond formation

The coupling reagent of choice in case of glycine or aliphatic acids was TBTU, while the more deactivated, aromatic acids were coupled using HATU as coupling reagent. The acid (2 equiv) and coupling reagent (2 equiv) were dissolved in NMP, mixed with DIEA (5 equiv) and shaken for 4 h – over night, depending on sterical demand and electronic properties of the aromate. The reaction mixture was discarded and the resin washed 5 times with NMP.

GP-8 Formation of aza-glycines

The amino-functionalized, dry resin was swollen with dry DCM for 5 min. The freshly prepared, dry building block **40** was dissolved in dry DCM, mixed with the resin and shaken for 90 minutes. The resin was washed with DCM (5x).

GP-9 Guanidinylation

The amino-functionalized resin added to a solution of 10 equiv *N*,*N*'-bis-Boc-guanidinylpyrazole in dry chloroform (10 mL/g resin) in a closed reaction vessel. The mixture was shaken over night at 50°C. The resin was filtered and washed five times with DCM. The unconsumed guanidinylpyrazole could be recycled by concentration of the filtrate and recrystallization from hexane/ethyl acetate.

GP-10 Cleavage from TCP-resin and Boc-deprotection

The resin was swollen in DCM and then treated 3x with a mixture of DCM, TFA, water and triisopropylsilane (47.5:47.5:2.5:2.5, *v/v/v/v*) for 30 min. Combined solution was monitored by ESI-MS until full Boc-deprotection was observed. The solvents were evaporated under reduced pressure and the crude product directly subjected to HPLC-purification on reversed-phase silica gel.

Preparation of 5-(9*H*-fluoren-9-yloxy)-1,3,4-oxadiazolidin-2-one, 40

Fmoc-hydrazine hydrochloride (0.33 g, 1.28 mmol, 1 equiv) was suspended in 25 mL of DCM/saturated $NaHCO_3$ solution (1/1) in an ice-bath for five minutes under vigorous stirring. Stirring was stopped and the layers were allowed to separate for an additional 5 min. 2 mL of a 1.9 M solution of phosgene in toluene (3.80 mmol, 3.0 equiv)

were injected into the lower, organic phase and stirring was restarted for ten minutes. The organic layer was separated, the aqueous layer extracted twice with 10 mL DCM and the combined organic layers dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The crude product was thoughtfully dried under vacuum and used without further purification. Yield: 0.32 g (1.13 mmol, 89%) of a colorless solid which was directly used for the aza-gyzin formation (general procedure **GP-8**).

Preparation of 3-[*N*-(*N*'-(3-(guanidylbenzoyl)-hydrazino)carbonyl]amino-2-(*S*)-(2,4,6-trimethylbenzamido)propionic acid 42a

The title compound was synthesized from β-*N*-Alloc-α-*N*-Fmoc-diaminoproanoic acid according to following reaction sequence: a) Loading of 100 mg resin (theroretical loading 104 μmol, real loading ~62 μmol, general procedure 4); b) Fmoc deprotection (general procedure 5); c) Coupling of 2,4,6-trimethylbenzoic acid with HATU (general procedure 6), d) Alloc-deprotection (general procedure 7); e) Formation of *aza*-glycine (general procedure 8); f) Fmoc-deprotection (general procedure 5); g) Coupling of *N*-Fmoc-3-aminobenzoic acid with HATU (general procedure 6); h) Fmoc-deprotection (general procedure 5); i) Guadinylation (general procedure 8), followed by cleavage from the resin (general procedure 9). HPLC-purification yielded 4.8 mg (8.2 μmol, 14%) as colorless solid (TFA salt). ^{1}H NMR (500 MHz, DMSO): δ = 12.69 (br s, 1H, COO*H*), 10.22 (s, 1H, -N*H*NH), 9.93 (s, 1H, -N*H*), 8.40 (d, *J* = 6.8 Hz, 1H, -N*H*CO), 8.26 (s, 1H, -NHN*H*), 7.77 (d, *J* = 7.7 Hz, 1H, Ar-*H*), 7.72 (s, 1H, Ar-*H*), 7.54 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.46 (m, 3H, -N*H*),7.41 (d, *J* = 7.9 Hz, 1H, Ar-*H*), 6.83 (s, 2H, Ar-*H*), 6.53 (br s, 1H, -N*H*CO), 4.39 (m, 1H, -C*H*), 3.56 (td, *J* = 12.6 Hz, *J* = 5.2 Hz,1H, -C*H'*), 3.31 (m, 1H, -C*H"*), 2.23 (s, 3H, -CH_3), 2.21 (s, 6H, 2CH_3). ^{13}C NMR (125.1 MHz, DMSO): δ = 171.8, 169.3, 165.4, 158.2, 155.6, 137.2, 135.5, 135.1, 134.0, 133.9, 129.7, 127.5, 125.2, 123.3, 53.1, 40.2, 39.4, 20.5, 18.7. MS (ESI): *m/z* 939.2 [2*M*+H$^+$]$^+$, 470.2 [*M*+H$^+$]$^+$. HR-MS (ESI) ($C_{22}H_{28}N_7O_5^+$): calcd: 470.2146; found: 470.2137.

Preparation of 3-[*N*-(*N*'-(3-(guanidylpropylcarbonyl)-hydrazino)carbonyl]amino-2-(*S*)-(2,4,6-trimethylbenzamido)propionic acid, 42b

The title compound was synthesized from β-*N*-Alloc-α-*N*-Fmoc-diaminoproanoic acid according to following reaction sequence: a) Loading of 100 mg resin (theroretical loading 104 μmol, real loading ~62 μmol, general procedure 4); b) Fmoc deprotection

(general procedure 5); c) Coupling of 2,4,6-trimethylbenzoic acid with HATU (general procedure 6), d) Alloc-deprotection (general procedure 7); e) Formation of *aza*-glycine (general procedure 8); f) Fmoc-deprotection (general procedure 5); g) Coupling of *N*-Fmoc-4-aminobutanoic acid with TBTU (general procedure 6); h) Fmoc-deprotection (general procedure 5); i) Guadinylation (general procedure 8), followed by cleavage from the resin (general procedure 9). HPLC-purification yielded 3.8 mg (6.9 μmol, 11%) as colorless solid (TFA salt). ^{1}H NMR (500 MHz, DMSO): δ = 9.56 (s, 1H, -N*H*NH), 8.39 (d, *J* = 7.1 Hz. 1H, N*H*CO), 8.07 (br s, 1H, -NHN*H*), 7.56 (t, *J* = 5.6 Hz, 1H, -N*H*), 6.84 (s, 2H, Ar-*H*), 6.42 (br s, 1H, -N*H*CO), 4.37 (m, 1H, -C*H*), 3.54-3.49 (m, 1H, -C*H'*), 3.29 (m, 1H, -C*H''*), 3.11 (dd, *J* = 13.1 Hz, *J* = 6.7 Hz, 2H, -NCH_2), 2.23 (s, 3H, -CH_3), 2.20 (s, 6H, 2CH_3), 2.13 (t, *J* = 7.24 Hz, 2H, -CH_2), 1.70 (m, 2H, -CH_2). ^{13}C NMR (125.1 MHz, DMSO): δ = 171.8, 171.5, 169.2, 158.2, 156.6, 137.2, 135.1, 133.8, 127.5, 53.0, 30.0, 24.3, 20.5, 18.7. MS (ESI): *m/z* 436.2 [*M*+H$^+$]$^+$. HR-MS (ESI) ($C_{19}H_{30}N_7O_5^+$): calcd: 436.2303; found: 436.2294.

Preparation of 3-[*N*-(*N'*-(3-(guanidylbenzoyl)-hydrazino)carbonyl]amino-2-(*S*)-(2,6-dimethyl-4-isopropoxybenzamido)propionic acid, 43a

The title compound was synthesized from β-*N*-Alloc-α-*N*-Fmoc-diaminoproanoic acid according to following reaction sequence: a) Loading of 200 mg resin (theroretical loading 104 μmol, real loading ~67 μmol, general procedure 4); b) Fmoc deprotection (general procedure 5); c) Coupling of 2,6-dimethyl-4-isopropoxybenzoic acid with HATU (general procedure 6), d) Alloc-deprotection (general procedure 7); e) Formation of *aza*-glycine (general procedure 8); f) Fmoc-deprotection (general procedure 5); g) Coupling of *N*-Fmoc-3-aminobenzoic acid with HATU (general procedure 6); h) Fmoc-deprotection (general procedure 5); i) Guadinylation (general procedure 8), followed by cleavage from the resin (general procedure 9). HPLC-purification yielded 6.3 mg (12.2 μmol, 9%) as colorless solid (TFA salt). ^{1}H NMR (500 MHz, DMSO): δ = 10.21 (s, 1H, -COO*H*), 9.94 (s, 1H, -CN*H*NH_2), 8.33 (br s, 1H, N*H*CO), 8.27 (s, 1H, -NHN*H*), 7.76 (d, *J* = 7.7 Hz, 1H, Ar-*H*), 7.7 (s, 1H, Ar-*H*), 7.54 (s, 1H, Ar-*H*), 7.41 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.56 (s, 2H, Ar-*H*), 6.53 (br s, 1H, -N*H*CO), 4.59 (m, 1H, -C*H*), 4.38-4.34 (m, 1H, -C*H'*), 3.57-3.52 (m, 1H, -C*H''*), 2.20 (s, 6H, 2CH_3), 1.23 (d, *J* = 5.9 Hz, 6H, 2CH_3). ^{13}C NMR (226.3 MHz, DMSO): δ = 172.9, 170.1, 166.4, 159.1, 157.8, 156.6, 136.9, 136.5, 134.9, 131.5, 130.7, 128.4, 126.2, 124.3, 115.0, 69.6, 54.1, 41.3,

22.7, 19.9. MS (ESI): *m/z* 514.2 $[M+H^+]^+$. HR-MS (ESI) ($C_{24}H_{32}N_7O_6^+$): calcd: 514.2414; found: 514.2418.

Preparation of 3-[*N*-(*N*'-(3-(guanidylpropylcarbonyl)-hydrazino)carbonyl]amino-2-(*S*)-(2,6-dimethyl-4-isopropoxybenzamido)propionic acid, 43b

The title compound was synthesized from β-*N*-Alloc-α-*N*-Fmoc-diaminoproanoic acid according to following reaction sequence: a) Loading of 100 mg resin (theroretical loading 104 μmol, real loading ~62 μmol, general procedure 4); b) Fmoc deprotection (general procedure 5); c) Coupling of 2,6-dimethyl-4-isopropoxybenzoic acid with HATU (general procedure 6), d) Alloc-deprotection (general procedure 7); e) Formation of *aza*-glycine (general procedure 8); f) Fmoc-deprotection (general procedure 5); g) Coupling of *N*-Fmoc-4-aminobutanoic acid with TBTU (general procedure 6); h) Fmoc-deprotection (general procedure 5); i) Guadinylation (general procedure 8), followed by cleavage from the resin (general procedure 9). HPLC-purification yielded 3.8 mg (6.9 μmol, 11%) as colorless solid (TFA salt). The title compound was synthesized from β-*N*-Alloc-α-*N*-Fmoc-diaminoproanoic acid according to following reaction sequence: a) Loading of 200 mg resin (theroretical loading 104 μmol, real loading ~67 μmol, general procedure 4); b) Fmoc deprotection (general procedure 5); c) Coupling of 2,6-dimethyl-4-isopropoxybenzoic acid with HATU (general procedure 6), d) Alloc-deprotection (general procedure 7); e) Formation of *aza*-glycine (general procedure 8); f) Fmoc-deprotection (general procedure 5); g) Coupling of *N*-Fmoc-3-aminobenzoic acid with HATU (general procedure 6); h) Fmoc-deprotection (general procedure 5); i) Guadinylation (general procedure 8), followed by cleavage from the resin (general procedure 9). HPLC-purification yielded 6.3 mg (12.2 μmol, 9%) as colorless solid (TFA salt). ^{1}H NMR (500 MHz, DMSO): δ = 10.21 (s, 1H, -COO*H*), 9.94 (s, 1H, -CN*H*NH_2), 8.33 (br s, 1H, N*H*CO), 8.27 (s, 1H, -NHN*H*), 7.76 (d, *J* = 7.7 Hz, 1H, Ar-*H*), 7.7 (s, 1H, Ar-*H*), 7.54 (s, 1H, Ar-*H*), 7.41 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.56 (s, 2H, Ar-*H*), 6.53 (br s, 1H, -N*H*CO), 4.59 (m, 1H, -C*H*), 4.38-4.34 (m, 1H, -C*H'*), 3.57-3.52 (m, 1H, -C*H"*), 2.20 (s, 6H, 2CH_3), 1.23 (d, *J* = 5.9 Hz, 6H, 2CH_3). ^{13}C NMR (226.3 MHz, DMSO): δ = 172.9, 170.1, 166.4, 159.1, 157.8, 156.6, 136.9, 136.5, 134.9, 131.5, 130.7, 128.4, 126.2, 124.3, 115.0, 69.6, 54.1, 41.3, 22.7, 19.9. MS (ESI): *m/z* 480.3 $[M+H^+]^+$. HR-MS (ESI) ($C_{21}H_{34}N_7O_6^+$): calcd: 480.2571; found: 480.2583.

Preparation of 3-[*N*-(*N*'-(2-(guanidylethylcarbonyl)-hydrazino)carbonyl]amino-2-(*S*)-(2,6-dimethyl-4-isopropoxybenzamido)propionic acid, 43c

The title compound was synthesized from β-*N*-Alloc-α-*N*-Fmoc-diaminoproanoic acid according to following reaction sequence: a) Loading of 200 mg resin (theroretical loading 104 μmol, real loading ~67 μmol, general procedure 4); b) Fmoc deprotection (general procedure 5); c) Coupling of 2,6-dimethyl-4-isopropoxybenzoic acid with HATU (general procedure 6), d) Alloc-deprotection (general procedure 7); e) Formation of *aza*-glycine (general procedure 8); f) Fmoc-deprotection (general procedure 5); g) Coupling of *N*-Fmoc-3-aminopropanoic acid with TBTU (general procedure 7); h) Fmoc-deprotection (general procedure 5); i) Guadinylation (general procedure 8), followed by cleavage from the resin (general procedure 9). HPLC-purification yielded 5.3 mg (11.4 μmol, 9%) as colorless solid (TFA salt). ^{1}H NMR (900 MHz, DMSO): δ = 9.65 (s, 1H, -N*H*NH), 8.36 (br s, 1H, N*H*CO), 8.06 (br s, 1H, -NHN*H*), 7.40 (s, 1H, -N*H*), 6.57 (s, 2H, Ar-*H*), 6.50 (br s, 1H, -N*H*CO), 4.59 (m, 1H, -C*H*), 4.37 (m, 1H, -C*H*), 3.50-3.46 (m, 2H, -CH_2), 2.51 (m, 2H, -CH_2), 2.37 (m, 2H, -CH_2), 2.19 (s, 6H, 2CH_3), 1.23 (d, *J* = 5.7 Hz, 6H, 2CH_3). ^{13}C NMR (226.3 MHz, DMSO): δ = 136.3, 122.7, 115.0, 69.4, 56.8, 37.4, 35.3, 22.3, 19.6. MS (ESI): *m/z* 466.3 [*M*+H$^+$]$^+$. HR-MS (ESI) ($C_{20}H_{32}N_7O_6^+$): calcd: 466.2414; found: 466.3540.

Preparation of 3-[*N*-(*N*'-(3-(guanidylpropylcarbonyl)-aminomethylen)carbonyl]-amino-2-(*S*)-(2,6-dimethyl-4-isopropoxybenzamido)propionic acid, 44a

The title compound was synthesized from β-*N*-Alloc-α-*N*-Fmoc-diaminoproanoic acid according to following reaction sequence: a) Loading of 200 mg resin (theroretical loading 104 μmol, real loading ~67 μmol, general procedure 4); b) Fmoc deprotection (general procedure 5); c) Coupling of 2,6-dimethyl-4-isopropoxybenzoic acid with HATU (general procedure 6), d) Alloc-deprotection (general procedure 7); e) Coupling of Fmoc-glycine with TBTU (general procedure 6); f) Fmoc-deprotection (general procedure 5); g) Coupling of *N*-Fmoc-4-aminobutanoic acid with TBTU (general procedure 6); h) Fmoc-deprotection (general procedure 5); i) Guadinylation (general procedure 8), followed by cleavage from the resin (general procedure 9). HPLC-purification yielded 4.8 mg (9.4 μmol, 7%) as colorless solid (TFA salt). ^{1}H NMR (900 MHz, DMSO): δ = 9.84 (s, 1H, -N*H*NH), 8.78 (br s, 1H, N*H*CO), 8.05 (s, 1H, -NHN*H*), 7.76 (d, *J* = 7.7 Hz, 1H, Ar-*H*), 7.73 (s, 1H, Ar-*H*), 7.53 (m, 1H, N*H*CO), 7.50 (s, 2H, Ar-*H*), 7.38 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 6.58 (s, 2H, Ar-*H*), 4.59 (m, 1H, -C*H*), 3.88 (m,

1H, -C*H'*), 3.84 (m, 1H, -C*H''*), 3.48 (m, 2H, -CH_2), 3.42 (m, 2H, -CH_2), 2.19 (s, 6H, 2CH_3), 1.23 (d, *J* = 5.9 Hz, 6H, 2CH_3). ^{13}C NMR (226.3 MHz, DMSO): δ = 169.6, 167.8, 167.0, 166.2, 157.5, 156.1, 136.3, 136.0, 131.2, 130.1, 125.6, 123.8, 117.3, 114.5, 69.3, 52.4, 43.0, 40.6, 22.2, 19.6. HR-MS (ESI) ($C_{22}H_{35}N_6O_6^+$): calcd: 479.2618; found: 479.3580.

Preparation of 3-[*N*-(*N*'-(3-(guanidylbenzoyl)-aminomethylen)carbonyl]amino-2-(*S*)-(2,6-dimethyl-4-isopropoxybenzamido)propionic acid, 44b

The title compound was synthesized from β-*N*-Alloc-α-*N*-Fmoc-diaminoproanoic acid according to following reaction sequence: a) Loading of 200 mg resin (theroretical loading 104 μmol, real loading ~67 μmol, general procedure 4); b) Fmoc deprotection (general procedure 5); c) Coupling of 2,6-dimethyl-4-isopropoxybenzoic acid with HATU (general procedure 6), d) Alloc-deprotection (general procedure 7); e) Coupling of Fmoc-glycine with TBTU (general procedure 6); f) Fmoc-deprotection (general procedure 5); g) Coupling of *N*-Fmoc-3-aminobenzoic acid with HATU (general procedure 6); h) Fmoc-deprotection (general procedure 5); i) Guadinylation (general procedure 8), followed by cleavage from the resin (general procedure 9). HPLC-purification yielded 6.2 mg (12.9 μmol, 10%) as colorless solid (TFA salt). ^{1}H NMR (900 MHz, DMSO): δ = 8.32 (d, *J* = 7.7 Hz, 1H, N*H*CO), 8.12 (t, 1H, *J* = 5.7 Hz, 1H, N*H*CO), 7.92 (t, 1H, *J* = 5.7 Hz, 1H, N*H*CO), 7.52 (br s, 1H,-NHN*H*), 7.28 (br s, 1H, -N*H*), 6.57 (s, 2H, Ar-*H*), 4.59 (m, 1H, -C*H*), 4.50 (m, 1H, -C*H*), 3.70 (m, 1H, -C*H'*), 3.63 (m, 1H, -C*H'*), 3.51 (m, 2H, -CH_2), 3.10 (dd, *J* = 6.7 Hz, *J* = 13.2 Hz, 2H, -CH_2), 2.19 (s, 6H, 2CH_3), 2.18 (t, 2H, -CH_2), 1.69 (m, 2H, -CH_2), 1.23 (d, *J* = 6.0 Hz, 6H, 2CH_3). ^{13}C NMR (226.3 MHz, DMSO): δ = 172.5, 172.2, 169.9, 169.7, 157.4, 157.2, 136.3, 130.9, 114.6, 69.3, 52.3, 42.4, 40.8, 32.4, 25.1, 22.3, 19.6. MS (ESI): *m/z* 479.3 [*M*+H$^+$]$^+$. MS (ESI): *m/z* 513.2 [*M*+H$^+$]$^+$. HR-MS (ESI) ($C_{25}H_{33}N_6O_6^+$): calcd: 513.2462; found: 513.2469.

Preparation of 3-[*N*-(*N*'-(3-(4-methylpyridin-2-ylamino)propylcarbonyl)-hydrazino)carbonyl]amino-2-(*S*)-(2,4,6-trimethylbenzamido)propionic acid, 45

The title compound was synthesized from β-*N*-Alloc-α-*N*-Fmoc-diaminoproanoic acid according to following reaction sequence: a) Loading of 100 mg resin (theroretical loading 104 μmol, real loading ~51 μmol, general procedure 4); b) Fmoc deprotection (general procedure 5); c) Coupling of 2,4,6-trimethylbenzoic acid with HATU (general procedure 6), d) Alloc-deprotection (general procedure 7); e) Formation of *aza*-gly-

cine (general procedure 8); f) Fmoc-deprotection (general procedure 5); g) Coupling of 4-(4-methylpyridin-2-yl)aminobutanoic acid with TBTU (general procedure 6, double coupling necessary), followed by cleavage from the resin (general procedure 9). HPLC-purification yielded 3.1 mg (5.3 µmol, 11%) as colorless solid (TFA salt). ^{1}H NMR (500 MHz, DMSO): δ = 12.90 (br s, 1H, -COO*H*), 9.56 (s, 1H, -N*H*), 8.54 (br s, 1H, -N*H*), 8.38 (d, *J* = 7.0 Hz, 1H, -N*H*), 8.08 (s, 1H, -N*H*), 7.81 (d, *J* = 6.5 Hz, 1H, Ar-*H*), 6.84 (s, 1H, Ar-*H*), 6.83 (s, 2H, Ar-*H*), 6.72 (d, *J* = 6.1 Hz, 1H, Ar-*H*), 6.44 (s, 1H, -N*H*), 4.40 (dd, *J* = 12.3 Hz, *J* = 7.0 Hz, 1H, -C*H*), 3.57-3.49 (m, 1H, -CH_2), 3.35-3.23 (m, 2H, -NCH_2), 2.33 (s, 3H, -CH_3), 2.22 (s, 3H, -CH_3), 2.20 (s, 6H, 2CH_3), 1.81 (m, 2H, -CH_2). ^{13}C NMR (226 MHz, DMSO): δ = 171.9, 171.6, 169.4, 158.3, 158.1, 158.0, 152.4, 137.3, 135.1, 133.9, 127.6, 114.0, 53.1, 40.8, 40.3, 30.2, 23.9, 21.4, 20.6, 18.8. MS (ESI): *m/z* 485.2 [*M*+H$^+$]$^+$. HR-MS (ESI) ($C_{24}H_{33}N_6O_5^+$): calcd: 485.2507; found: 485.2514.