Supporting Information

The synthesis, *in vitro* and *in vivo* characterisation of highly β_1-selective β-adrenoceptor partial agonists

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Experimental Section

General Chemistry Methods: Chemicals and solvents were purchased from standard suppliers and used without further purification. Merck Kieselgel 60, 230-400 mesh, for flash column chromatography (FCC) was supplied by Merck KgaA (Darmstadt, Germany) and deuterated solvents were purchased from Goss International Limited (England) and Sigma-Aldrich Company Ltd (England).

Unless otherwise stated, reactions were carried out at ambient temperature. Reactions were monitored by thin layer chromatography on commercially available precoated aluminium-backed plates (Merck Kieselgel 60 F_{254}). Visualisation was by examination under UV light (254 and 366 nm). General staining carried out with $KMnO_4$ or phosphomolybdic acid. A solution of Ninhydrin (in ethanol) was used to visualize primary and secondary amines. All organic extracts collected after aqueous work-up procedures were dried over anhydrous $MgSO_4$ or Na_2SO_4 before gravity filtering and evaporation to dryness. Organic solvents were evaporated *in vacuo* at ≤ 40°C (water bath temperature). Purification using preparative layer chromatography (PLC) was carried out using Fluka silica gel 60 PF_{254} containing gypsum (200 mm x 200 mm x 1 mm). Flash chromatography was performed using Merck Kieselgel 60 (0.040-0.063 mm).

Melting points (Mp) were recorded on a Reichert 7905 apparatus or Perkin Elmer Pyris 1 differential scanning calorimeter and were uncorrected. Fourier transform – infrared (FT-IR) spectra were recorded as thin films or KBr discs in the range of 4000 – 500 cm^{-1} using an Avatar 360 Nicolet FT-IR spectrophotometer.

High resolution mass spectra (HRMS) – time of flight, electrospray (TOF ES +/-) were recorded on a Waters 2795 separation module/micromass LCT platform.

^1H NMR spectra were recorded on a Bruker-AV 400 at 400.13 MHz. ^{13}C NMR spectra were recorded at 101.62 MHz. Chemical shifts (δ) are recorded in parts per million (ppm) with reference to the chemical shift of the deuterated solvent/an internal tetramethylsilane (TMS) standard. Coupling constants (*J*) and carbon-fluorine coupling constants (J_{CF}) are recorded in Hz and the significant multiplicities described by singlet (s), doublet (d), triplet (t), quadruplet (q), broad (br), multiplet (m), doublet of doublets (dd), doublet of triplets (dt). Spectra were assigned using appropriate COSY, distortionless enhanced polarisation transfer (DEPT), HSQC and HMBC sequences. Unless otherwise stated all spectra were recorded in $CDCl_3$.

Analytical reverse-phase high performance liquid chromatography (RP-HPLC) was performed on a Waters Millenium 995 LC using system 1a/1b and either system 2 or system 3 to confirm purity, or a Shimadzu UFLCXR system coupled to an Applied Biosystems API2000 using system 4 and 5. All retention times (R_t) are quoted in minutes.

System 1: Phenomenex Onyx Monolithic reverse phase C_{18} column (100 x 4.6 mm), a flow rate of 5.00 mL/min (system 1a) or 3.00 mL/min (system 1b) and UV detection at 287 nm. Linear gradient 5% - 95% solvent B over 10 minutes. Solvent A: 0.1% formic acid (FA) in water; solvent B: 0.1% FA in MeCN.

System 2: Vydac reverse phase C_8 column (150 x 4.6 mm), a flow rate of 1.00 mL/min and UV detection at 287 nm. Linear gradient 5% - 95% solvent B over 24 minutes. Solvent A: 0.06% TFA in water; solvent B: 0.06% TFA in MeCN.

System 3: Waters symmetry reverse phase C_{18} column (75 x 4.6 mm), a flow rate of 1.00 mL/min and UV detection at 287 nm. Linear gradient 5% - 95% solvent B over 20 minutes. Solvent A: 0.1% FA in water; solvent B: 0.1% FA in MeOH.

System 4: Gemini-NX 3u-110A, 50x2mm column thermostated at 40°C, a flow rate of 0.5 mL/min and UV detection at 220 and 254nm. Pre-equilibration run for one minute at 10% solvent B, then 10% - 98% solvent B over 2 minutes, then 98% solvent B for 2 minutes, then 98% - 10% solvent B in 0.5 minutes then 10% for one minute. Solvent A: 0.1% FA in water; solvent B: 0.1% FA in MeCN.

System 5: Luna 3u (PFP2) 110A, 50x2 mm. column thermostated at 40°C, a flow rate of 0.5 mL/min and UV detection at 220 and 254nm. Pre-equilibration run for one minute at 10% solvent B,

then 10% - 98% solvent B over 2 minutes, then 98% solvent B for 2 minutes, then 98% - 10% solvent B in 0.5 minutes then 10% for one minute. Solvent A: 0.1% FA in water; solvent B: 0.1% FA in MeCN.

Preparative HPLC was performed using a Phenomenex Onyx Monolithic reverse phase C_{18} column (100 x 10 mm), a flow rate of 14.10 mL/min and UV detection at 287 nm. Samples were run in 5% - 95% solvent B over 10 minutes. Solvent A: 0.1% FA in water; solvent B: 0.1% FA in MeCN.

General procedure for *O*-benzyl deprotection. 1-(2-(Alkyloxy)ethoxy)-4-(benzyloxy) benzene analogues were dissolved in EtOH (10 – 20 mL per mmol) before hydrogenating over 10% Pd/C (100 mg/g of starting material) at rt and atmospheric pressure overnight. After filtration through a bed of celite, with washings of EtOH, the collected filtrate was concentrated under reduced pressure. The desired phenol was isolated with no further purification necessary.

General procedure for aminolysis of oxiranes (19 and 29a-c) (M1). 2-((4-(2-(Alkyloxy)ethoxy)phenoxy)methyl)oxirane (30–80 mg) and substituted 1-(2-aminoethyl)-3-(aryl)urea (1 eq) were suspended in propan-2-ol (3 mL). In the case where 1-(2-aminoethyl)-3-(aryl)ureas were hydrochloride salts, NaOH (1.1 eq as 10 M aq. solution) was also added. The mixture was heated under reflux overnight, after which all solvent was removed under reduced pressure. The crude residue was purified via PLC (eluent 37% aq NH_3/MeOH/DCM 2:10:88). Analogues with substitution *ortho* to the urea group were purified using a weaker eluent (NH_3/MeOH/DCM 2:5:93). The final aryloxypropanolamines were freeze-dried. Where further purification was necessary by preparative HPLC, the final compounds were isolated as the hydroformate salt.

3-Formyl-4-hydroxyphenyl pivalate (3). 2,5-Dihydroxybenzaldehyde (**2**) (5.237 g, 37.92 mmol) was dissolved in dry DMF (40 mL) at 0 °C, under a nitrogen atmosphere. TEA (4.200 g, 5.813 mL, 41.71 mmol, 1.1 molar equivalents (eq)) followed by dropwise addition of pivaloyl chloride (4.801, 4.599 mL, 39.81 mmol, 1.05 eq). The mixture was then stirred at room temperature for 4 hours. After quenching with MeOH, all solvent was removed *in vacuo*. The resulting slurry was dispersed in water (100 mL) and extracted with ethyl acetate (EtOAc) (3 x 50 mL). The combined organic layers were washed with brine (50 mL) before concentration. Purification via FCC (eluent EtOAc/hexanes 20:80) afforded 6.100 g (72%) of viscous yellow oil. FT-IR 3411 (br, O-H, stretch (str)), 2976 (alkyl C-H. str), 2937, 2874 (aldehyde C-H, str), 1754 (ester C=O, str), 1690 (aldehyde C=O, str), 1608, 1586, 1494 (aryl, str), 1398 ($C(CH_3)_3$, str), 1293, 1188 (ester C-O, str), 1109 (C-OH, str); ^{1}H NMR δ 9.98 (s, 1H, CHO), 7.18 (d, J = 2.8 Hz, 1H, aryl 2-H), 7.00 (dd, J = 8.9/2.8 Hz, 1H, aryl 6-H), 6.94 (d, J = 8.9 Hz, 1H, aryl 5-H), 6.60 (br s, 1H, OH), 1.40 (s, 9H, $(CH_3)_3$); ^{13}C NMR δ 188.71 (CHO), 178.10 (ester C=O), 154.52 (aryl 4-C), 145.54 (aryl 1-C), 128.53 (aryl 3-C), 124.25 (aryl 6-C), 122.89 (aryl 2-C), 115.51 (aryl 5-C), 39.35 ($C(CH_3)$), 27.10 ($(CH_3)_3$); *m/z* HRMS (TOF ES$^-$) $C_{12}H_{13}O_4$ [M-H]$^-$ calcd 221.0819; found 221.0818.

4-(4-Methoxybenzyloxy)-3-formylphenyl pivalate (4). NaH 60% suspension in mineral oil (495 mg, equivalent to 297 mg of NaH, 12.37 mmol, 1.1 eq) was suspended in dry DMF (10 mL) at 0 °C, under a nitrogen atmosphere. To this was added 3-formyl-4-hydroxyphenyl pivalate **(2)** (2.500 g, 11.25 mmol) in dry DMF (5 mL) and *p*-methoxybenzyl bromide (2.488 g / 1.783 mL, 12.37 mmol, 1.1 eq) in dry DMF (5 mL). After overnight stirring at room temperature and removal of DMF *in vacuo*, the resulting slurry was dispersed in water (30 mL) and extracted with diethyl ether (Et_2O) (4 x 25 mL). The combined organic fractions were washed with aqueous 2 M NaOH (20 mL) and brine (20 mL). After concentration the crude material was purified by FCC (eluent EtOAc/petroleum ether 40-60 (PE) 5:95 for 2 column volumes, 10:90 for 6 column volumes then 30:70) to give 1.267 g (33%) of white crystalline solid. Mp = 69 – 71 °C; FT-IR 2972 (alkyl C-H, str), 2941, 2867 (aldehyde C-H, str), 1749 (ester C=O, str), 1684 (aldehyde C=O, str), 1612, 1587, 1517 (aryl, str), 1394 ($C(CH_3)_3$, str), 1268, 1255 (ester C-O, str), 1127, 1093 (C-O-C, str), 869 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR δ 10.46 (s, 1H, CHO), 7.51 (d, J = 3.2 Hz, 1H, aryl 2-H), 7.34 (d, J = 9.0 Hz, 2H, PMB C-H *meta* to methoxy group), 7.23 (dd, J = 8.6/2.9 Hz, 1H, aryl 6-H), 7.06 (d, J = 9.0 Hz, 1H, aryl 5-H), 6.92 (d, J = 8.6 Hz, 2H, PMB C-H *ortho* to methoxy group), 5.10 (s, 2H, PMB

CH_2), 3.81 (s, 3H, PMB CH_3), 1.34 (s, 9H, $(CH_3)_3$); ^{13}C NMR δ 188.94 (CHO), 177.17 (ester C=O), 159.80 (PMB *C*OCH_3), 158.74 (aryl 4-C), 144.81 (aryl 1-C), 129.23 (PMB C-H *meta* to methoxy group), 129.01 (PMB quaternary (4°) C *para* to methoxy group), 127.87 (aryl 6-C), 125.69 (aryl 3-C), 120.79 (aryl 2-C), 114.26 (aryl 5-C), 114.21 (PMB C-H *ortho* to methoxy group), 70.97 (PMB CH_2), 53.34 (PMB CH_3), 39.09 (*C*$(CH_3)_3$), 27.15 ($(CH_3)_3$); *m/z* HRMS (TOF ES$^+$) $C_{20}H_{23}O_5$ $[MH]^+$ calcd 365.1359; found 365.1341.

4-(4-Methoxybenzyloxy)-3-cyanophenyl pivalate (5). 4-(4-Methoxybenzyloxy)-3-formylphenyl pivalate (**4**) (1.250 g, 3.65 mmol) was dissolved in THF (5 mL) and aqueous 37% NH_3 solution (20 mL) with stirring. To this was added iodine (1.019 g, 4.02 mmol, 1.1 eq) and the mixture stirred for 2 hours at room temperature. After quenching with excess aqueous 10% sodium thiosulphate solution, the entire mixture was extracted with DCM (4 x 25 mL) and concentrated to afford 1.210 g (98%) of brown crystalline solid requiring no further purification. Mp = 95 – 97 °C; FT-IR 2970, 2936, 2877 (alkyl C-H, str), 2231 (CN, str), 1749 (ester C=O, str), 1612, 1586, 1516 (aryl, str), 1392 ($C(CH_3)_3$, str), 1273, 1256 (ester C-O, str), 1119, 1098 (C-O-C, str), 825 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR δ 7.36 (d, *J* = 8.5 Hz, 2H, PMB C-H *meta* to methoxy group), 7.28 (d, *J* = 3.1 Hz, 1H, aryl 2-H), 7.19 (dd, *J* = 9.2/2.6 Hz, 1H, aryl 6-H), 6.98 (d, *J* = 9.2 Hz, 1H, aryl 5-H), 6.91 (d, *J* = 8.8 Hz, 2H, PMB C-H *ortho* to methoxy group), 5.13 (s, 2H, PMB CH_2), 3.81 (s, 3H, PMB CH_3), 1.34 (s, 9H, $(CH_3)_3$); ^{13}C NMR δ 177.04 (ester C=O), 159.81 (PMB *C*OCH_3), 158.15 (aryl 4-C), 144.25 (aryl 1-C), 128.97 (PMB C-H *meta* to methoxy group), 127.73 (aryl 6-C), 127.58 (PMB 4° C *para* to methoxy group), 126.59 (aryl 2-C), 115.65 (CN), 114.31 (PMB C-H *ortho* to methoxy group), 113.98 (aryl 5-C), 103.09 (aryl 3-C), 71.21 (PMB CH_2), 55.46 (PMB CH_3), 39.22 (*C*$(CH_3)_3$), 27.18 ($(CH_3)_3$); *m/z* HRMS (TOF ES$^+$) $C_{20}H_{21}NNaO_4$ $[MNa]^+$ calcd 362.1363; found 362.1388.

2-(4-Methoxybenzyloxy)-5-hydroxybenzonitrile (6). 4-(4-Methoxybenzyloxy)-3-cyanophenyl pivalate (**5**) (1.200 g, 3.54 mmol) and sodium *tert*-butoxide (850 mg, 8.84 mmol, 2.5 eq) were dissolved in MeOH (30 mL) and stirred for 2 hours. After removal of MeOH *in vacuo*, the crude product was dispersed in water (40 mL) and washed with DCM (1 x 30 mL). This formed an inseparable emulsion and was passed through a celite filter (suction) to effect layer separation. The aqueous layer was then acidified to pH 4 with careful addition of conc HCl, before extraction with DCM (4 25 mL). Concentration of the combined organic extracts gave 311 mg (34%) of an orange solid, requiring no further purification. Mp = 165 – 167 °C; FT-IR 3299 (br, O-H, str), 3055 (aryl C-H, str), 2930, 2835 (alkyl C-H, str), 2243 (CN, str), 1614, 1587, 1499 (aryl, str), 822 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR δ 7.36 (d, *J* = 8.5 Hz, 2H, PMB C-H *meta* to methoxy group), 7.03 (d, *J* = 2.9 Hz, 1H, aryl 6-H), 6.98 (dd, *J* = 8.6/2.9 Hz, 1H, aryl 4-H), 6.91 (d, *J* = 8.6 Hz, 2H, PMB C-H *ortho* to methoxy group), 6.88 (d, *J* = 9.2 Hz, 1H, aryl 3-H), 5.21 (br, s, OH), 5.07 (s, 2H, PMB CH_2), 3.81 (s, 3H, PMB CH_3). ^{13}C NMR δ 159.71 (PMB *C*OCH_3), 154.97 (aryl 2-C), 149.59 (aryl 5-C), 129.03 (PMB C-H *meta* to methoxy group), 128.10 (PMB 4° C *para* to methoxy group), 121.79 (aryl 4-C), 119.78 (aryl 6-C), 116.31 (CN), 115.18 (aryl 3-C), 114.23 (PMB C-H *ortho* to methoxy group), 103.09 (aryl 1-C), 71.47 (PMB CH_2), 55.45 (PMB CH_3). *m/z* HRMS (TOF ES$^-$) $C_{15}H_{12}NO_3$ $[M-H]^-$ calcd 254.0823; found 254.0839.

5-(2-(Allyloxy)ethoxy)-2-(4-methoxybenzyloxy)benzonitrile (7). 2-Allyloxyethanol (174 mg, 182 µL, 1.70 mmol, 1.5 eq), triphenylphosphine (449 mg, 1.70 mmol, 1.5 eq), and 2-(4-methoxybenzyloxy)-5-hydroxybenzonitrile (**6**) (290 mg, 1.14 mmol) were dissolved in DCM (10 mL). DIAD (346 mg, 337 µL, 1.70 mmol, 1.5 eq) was added dropwise to the reaction mixture and allowed to stir overnight. The reaction mixture was then transferred to a separating funnel and washed with aqueous 2 M NaOH (1 x 10 mL), and brine (1 x 10 mL). After concentration of the organic layer, purification was achieved via FCC (eluent EtOAc/PE 10:90 for 3 column volumes then 30:70) to give the desired product as clear colourless oil in quantitative yield. FT-IR 3019 (alkene C-H, str), 2936 (alkyl C-H, str), 2231 (CN, str), 1499 (aryl, str), 1107 (C-O-C, str), 930 (alkene C-H, deformation); ^{1}H NMR δ 7.35 (d, *J* = 8.7 Hz, 2H, PMB C-H *meta* to methoxy group), 7.08 (s, 1H, aryl 6-H), 7.07 (dd, *J* = 8.6/3.1 Hz, 1H, aryl 4-H), 6.92 (d, *J* = 9.4 Hz, 1H, aryl 3-H), 6.90 (d, *J* = 8.6 Hz, 2H, PMB C-H *ortho* to methoxy group), 5.82 – 5.98 (m, 1H, H_C), 5.30 (ddt, *J* = 17.3/1.5/1.5 Hz, 1H, H_A), 5.21 (ddt,

J = 10.1/1.5/1.5 Hz, 1H, H_B), 5.08 (s, 2H, PMB CH_2), 4.05 – 4.09 (m, 4H, CH_2=CHCH_2, CH_2OAr), 3.81 (s, 3H, PMB CH_3), 3.76 (t, J = 4.8 Hz, 2H, CH_2CH_2OAr). ^{13}C NMR δ 159.70 (PMB $COCH_3$), 155.06 (aryl 2-C), 152.78 (aryl 5-C), 134.51 (C-H_C), 129.00 (PMB C-H *meta* to methoxy group), 128.09 (PMB 4° C *para* to methoxy group), 121.69 (aryl 4-C), 118.68 (aryl 6-C), 117.64 (CH_2=CH), 116.45 (CN), 115.01 (aryl 3-C), 114.21 (PMB C-H *ortho* to methoxy group), 103.97 (aryl 1-C), 72.53 (CH_2=CHCH_2), 71.39 (PMB CH_2), 68.55, 68.46 (OCH_2CH_2O), 55.42 (PMB CH_3). *m/z* HRMS (TOF ES$^+$) $C_{20}H_{22}NO_4$ $[MH]^+$ calcd 340.1543; found 340.1508.

5-(2-(Cyclopropylmethoxy)ethoxy)-2-hydroxybenzonitrile (8). 5-(2-(Allyloxy)ethoxy)-2-(4-methoxy benzyloxy)benzonitrile (**7**) (408 mg, 1.20 mmol) was dissolved in dry toluene (5 mL) under a nitrogen atmosphere and cooled to 0 °C with stirring. Diethyl zinc (2.40 mL as 1 M/hexanes, 2.40 mmol, 2 eq) was added, followed by dropwise addition of diiodomethane (644 mg / 194 µL, 2.40 mmol, 2 eq). After stirring for 15 minutes, the vessel was allowed to reach room temperature, and then stirred overnight. The reaction was quenched with aqueous saturated ammonium chloride solution (20 mL), before extraction with DCM (3 x 20 mL). After removal of solvent *in vacuo*, the residue was purified by FCC (eluent MeOH/DCM 1:199). The title compound was found to be the second band eluted from the flash column as 71 mg (25%) of clear, colourless oil. FT-IR 3280 (broad, O-H, str), 3083 (^{c}Pr C-H, str), 3006 (aryl C-H, str), 2934, 2876 (alkyl C-H, str), 2228 (CN, str), 1510 (aryl, str), 1370 (O-H, bend), 1093 (C-O-C, str); ^{1}H NMR δ 7.66 (br s, 1H, OH), 6.94 (dd, J = 9.3/3.1 Hz, 1H, aryl 4-H), 6.87 (d, J = 3.0 Hz, 1H, aryl 6-H), 6.86 (d, J = 9.1 Hz, 1H, aryl 3-H), 4.04 (t, J = 4.6 Hz, 2H, CH_2OAr), 3.81 (t, J = 4.8 Hz, 2H, CH_2CH_2OAr), 3.40 (d, J = 6.9 Hz, 2H, ^{c}PrCH_2O), 1.02 – 1.14 (m, 1H, ^{c}Pr CH), 0.46 – 0.59 (m, 2H, ^{c}Pr CH_2), 0.15 – 0.27 (^{c}Pr CH_2); ^{13}C NMR δ 153.75 (aryl 2-C), 151.96 (aryl 5-C), 122.76 (aryl 4-C), 117.89 (aryl 6-C), 116.75 (aryl 3-C), 116.63 (CN), 99.45 (aryl 1-C), 76.52 (^{c}PrCH_2O), 68.87, 68.19 (OCH_2CH_2O), 10.44 (^{c}Pr CH), 3.26 (^{c}Pr CH_2); *m/z* HRMS (TOF ES$^-$) $C_{13}H_{14}NO_3$ $[M-H]^-$ calcd 232.0979; found 232.0981.

5-(2-(Cyclopropylmethoxy)ethoxy)-2-(4-methoxybenzyloxy)benzonitrile (9). The title compound was the first of two bands to be eluted from the flash column in the synthesis of 5-(2-(cyclopropylmethoxy)ethoxy)-2-hydroxybenzonitrile (**8**), as 121 mg (29%) of dark yellow oil. FT-IR 3050 (cyclopropyl (^{c}Pr) C-H, str), 2935, 2872 (alkyl C-H, str), 2228 (CN), 1614, 1586, 1500 (aryl, str), 1109 (C-O-C, str), 824 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR δ 7.33 (d, J = 8.7 Hz, 2H, PMB C-H *meta* to methoxy group), 7.06 (s, 1H, aryl 6-H), 7.05 (dd, J = 7.4/3.2 Hz, 1H, aryl 4-H), 6.90 (d, J = 9.4 Hz, 1H, aryl 3-H), 6.87 (d, J = 8.6 Hz, 2H, PMB C-H *ortho* to methoxy group), 5.04 (s, 2H, PMB CH_2), 4.04 (t, J = 4.6 Hz, 2H, CH_2OAr), 3.77 (s, 3H, PMB CH_3), 3.76 (t, J = 4.8 Hz, 2H, CH_2CH_2OAr), 3.34 (d, J = 6.9 Hz, 2H, ^{c}PrCH_2O), 1.00 – 1.12 (m, 1H, ^{c}Pr CH), 0.47 – 0.58 (m, 2H, ^{c}Pr CH_2), 0.15 – 0.26 (^{c}Pr CH_2); ^{13}C NMR δ 159.52 (PMB $COCH_3$), 154.84 (aryl 2-C), 152.64 (aryl 5-C), 128.87 (PMB C-H *meta* to methoxy group), 127.95 (PMB 4° C *para* to methoxy group), 121.52 (aryl 4-C), 118.52 (aryl 6-C), 116.37 (CN), 114.80 (aryl 3-C), 114.03 (PMB C-H *ortho* to methoxy group), 102.67 (aryl 1-C), 76.24 (^{c}PrCH_2O), 71.16 (PMB CH_2), 68.69, 68.40 (OCH_2CH_2O), 55.27 (PMB CH_3), 10.51 (^{c}Pr CH), 3.07 (^{c}Pr CH_2); *m/z* HRMS (TOF ES$^+$) $C_{21}H_{24}NO_4$ $[MH]^+$ calcd 354.1700; found 354.1698.

2-((Oxiran-2-yl)methoxy)-5-(2-(cyclopropylmethoxy)ethoxy)benzonitrile (10). 5-(2-(cyclopropylmethoxy)ethoxy)-2-hydroxybenzonitrile (**7**) (70 mg, 0.30 mmol) and TEA (33 mg, 46 µL, 0.33 mmol, 1.1 eq) were dissolved in *rac*-epichlorohydrin (5 mL) and heated under reflux at 80 °C for 2 hours. Excess *rac*-epichlorohydrin was removed *in vacuo* before dissolving the crude residue in EtOAc (30 mL). After washing with aqueous 1 M HCl (10 mL), aqueous 1 M NaOH (10 mL) and brine (10 mL), the organic layer was concentrated to afford the desired epoxide in quantitative yield as clear colourless oil. FT-IR 2962, 2919 (alkyl C-H, str), 2227 (CN, str), 1501 (aryl, str), 1261, 800 (epoxide C-O, str), 1096 (C-O-C, str); ^{1}H NMR δ 7.09 (dd, J = 9.0/3.1 Hz, 1H, aryl 4-H), 7.06 (d, J = 2.8 Hz, 1H, aryl 6-H), 6.92 (d, J = 9.0 Hz, 1H, aryl 3-H), 4.30 (dd, J = 11.3/2.8 Hz, 1H, $ArOCH_2$) 4.06 (t, J = 4.6 Hz, 2H, CH_2OAr), 4.01 (dd, J = 11.3/5.4 Hz, 1H, $ArOCH_2$), 3.77 (t, J = 4.6 Hz, 2H, CH_2CH_2OAr), 3.34 (d, J = 7.2 Hz, 2H, ^{c}PrCH_2O), 3.31 – 3.38 (m, 1H, epoxide CH), 2.89 (dd, J = 4.7/4.7 Hz, 1H, epoxide CH_2), 2.79 (dd, J = 4.9/2.7 Hz, 1H, epoxide CH_2), 1.00 – 1.13 (m, 1H, ^{c}Pr

CH), 0.46 – 0.59 (m, 2H, ^{c}Pr CH_2), 0.15 – 0.27 (^{c}Pr CH_2); ^{13}C NMR δ 154.70 (aryl 2-C), 153.00 (aryl 5-C), 121.67 (aryl 4-C), 118.65 (aryl 6-C), 116.16 (CN), 114.52 (aryl 3-C), 102.55 (aryl 1-C), 76.29 (^{c}Pr*C*H_2O), 70.16 (ArOCH_2), 68.72, 68.52 (OCH_2CH_2O), 50.03 (epoxide CH), 45.54 (epoxide CH_2), 10.53 (^{c}Pr CH), 3.08 (^{c}Pr CH_2); *m/z* HRMS (TOF ES$^+$) $C_{16}H_{20}NO_4$ $[MH]^+$ calcd 290.1387; found 290.1411.

1-(2-(3-(2-Cyano-4-(2-(cyclopropylmethoxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(4-hydroxyphenyl)urea (1). Prepared via method **M1**. Purification was carried out by FCC (eluent 1N NH_3 in MeOH/DCM gradient 1:99 to 20:80); Yield 15%, hygrocopic semi-solid; ^{1}H NMR (DMSO-d_6) δ 8.98 (s, 1H, phenol OH), 8.52 (s, 1H, ArN*H*(C=O)NH), 7.34 (d, *J* = 3.0 Hz, 1H, cyanophenoxy ring 3H), 7.26 (dd, *J* = 9.2/3.0 Hz, 1H, cyanophenoxy ring 5H), 7.20 (d, *J* = 9.3 Hz, 1H, cyanophenoxy ring 6H), 7.15 (d, *J* = 8.9 Hz, 2H, phenylurea ring 2H/6H), 6.63 (d, *J* = 8.8 Hz, 2H, phenylurea ring 3H/5H), 6.39 (br t, *J* = 5.6 Hz, 1H, ArNH(C=O)N*H*), 5.77 (br s, 1H, CH(OH)), 4.12 – 4.22 (m, 1H, C*H*(OH)), 4.04 – 4.12 (m, 4H, ^{c}PrCH$_2$OCH$_2$C*H*$_2$, ArOC*H*$_2$CH(OH)), 3.69 (dd, *J* = 5.3/3.8 Hz, 2H, ^{c}PrCH$_2$OC*H*$_2$), 3.30 – 3.42 (m, 2H, NHCH$_2$C*H*$_2$NH(C=O)NH), 3.28 (d, *J* = 6.8 Hz, 2H, ^{c}PrCH$_2$), 3.08 – 3.16 (m, 1H, CH(OH)C*H*$_2$NH), 2.93 – 3.07 (m, 3H, CH(OH)C*H*$_2$NHC*H*$_2$), 0.93 – 1.05 (m, 1H, ^{c}Pr CH), 0.39 – 0.52 (^{c}Pr CH_2), 0.11 – 0.22 (^{c}Pr CH_2); ^{13}C NMR (DMSO-d_6) δ 156.12 (C=O), 154.39 (phenylurea ring 4C), 152.33, 152.14 (cyanophenoxy ring 1C/4C), 132.04, 131.72 (phenylurea ring 1C), 122.03 (), 120.09 (phenylurea ring 2C/6C), 119.85 (cyanophenoxy ring 5C), 118.14 (cyanophenoxy ring 3C), 116.17 (CN), 115.05 (phenylurea ring 3C/5C), 114.78 (cyanophenoxy ring 6C), 100.97 (cyanophenoxy ring 2C), 74.72 (^{c}Pr*C*H_2O), 71.26 (ArO*C*H_2CH(OH)), 68.13 (O*C*H_2*C*H_2O), 65.27 (*C*H(OH)), 49.90, 48.24 (CH(OH)*C*H_2NH, NH*C*H_2CH_2), 36.58 (NHCH$_2$*C*H$_2$NH(C=O)NH), 10.44 (^{c}Pr CH), 2.84 (^{c}Pr CH_2); *m/z* HRMS (TOF ES$^+$) $C_{25}H_{33}N_4O_6$ $[MH]^+$ calcd 485.2395; found 485.2408; RP-HPLC R_t 2.04 (System 4), 2.21 (System 5).

1-((4-(2-(Allyloxy)ethoxy)phenoxy)methyl)benzene (15). 2-Allyloxyethanol (2.043g, 2.139 mL, 20.00 mmol), 4-(benzyloxy)phenol (**14**) (4.806 g, 24.00 mmol, 1.2 eq) and triphenylphosphine (6.295 g, 24.00 mmol, 1.2 eq) were dissolved in DCM (60 mL). A solution of DIAD (4.853 g, 4.725 mL, 24.00 mmol, 1.2 eq) in DCM (20 mL) was added dropwise and the mixture allowed to stir at rt overnight. The mixture was concentrated under reduced pressure, and the residue dissolved in Et_2O (100 mL) before washing with aq. 2M NaOH solution (2 x 40 mL), water (2 x 40 mL) and brine (30 mL). The organic phase was then concentrated to give the crude product. The desired product was obtained as 4.021 g (71%) of white crystalline solid, after purification by FCC (eluent Et_2O/PE 25:75). Mp = 35 – 38 °C; FT-IR 3064 (alkene C-H, str), 2928, 2863 (alkyl C-H, str), 1510 (aryl, str), 1115 (C-O-C, str), 919 (alkene C-H, deformation), 826 (aryl C-H, bend, *para*-disubstituted ring), 735, 694 (aryl C-H, bend, phenyl ring); ^{1}H NMR δ 7.31 – 7.51 (m, 5H, aromatic benzyl C-H), 6.95, 6.91 (d, *J* = 9.1/1.9 Hz, 2 x 2H, *para*-disubstituted aryl ring), 5.93 – 6.06 (m, 1H, H_C), 5.37 (d, *J* = 17.2 Hz, 1H, H_A), 5.26 (d, *J* = 10.2 Hz, 1H, H_B), 5.04 (s, 2H, benzyl CH_2), 4.07 – 4.17 (m, 4H, CH_2OAr, CH_2=CHC*H*$_2$), 3.81 (t, *J* = 4.3 Hz, 2H, allyl-OC*H*$_2$); ^{13}C NMR δ 153.19, 153.13 (aryl-dioxy 4° C), 137.31 (benzyl 4° C), 134.66 (CH_2=*CH*), 128.52 (aromatic benzyl 3-C and 5-C), 127.84 (aromatic benzyl 4-C), 127.45 (aromatic 2-C and 6-C), 117.19 (*CH*$_2$=CH), 115.77, 115.62 (aryl-dioxy C-H), 72.30 (CH_2=CH*CH*$_2$), 70.59 (benzyl CH_2), 68.63, 68.06 (OCH_2CH_2O); *m/z* HRMS (TOF ES$^+$) $C_{18}H_{21}O_3$ $[MH]^+$ calcd 285.1485; found 285.1490.

1-(2-(Cyclopropylmethoxy)ethoxy)-4-(benzyloxy)benzene (16). 1-((4-(2-(Allyloxy)ethoxy)phenoxy)methyl)benzene (**15**) (2.000 g, 7.03 mmol) was dissolved in anhydrous toluene (20 mL) and cooled to 0°C. To this stirred solution was added diethylzinc 1M in hexanes (14.07 mL, 14.07 mmol, 2eq) in one portion, followed by dropwise addition of diiodomethane (3.768 g, 1.133 mL, 14.07 mmol, 2eq). Stirring was continued at 0°C for a further 15 minutes, before allowing the mixture to warm to rt and stir overnight. After this time, TLC analysis (EtOAc/PE 1:9, plate run twice) indicated starting material was still present, so further diethylzinc 1M in hexanes (7.03 mL, 7.03 mmol, 1 eq) and diiodomethane (1.884 g, 0.567 mL, 7.03 mmol, 1eq) were added. Stirring was continued at rt for a further 48 hours, before final addition of diethylzinc 1M in hexanes (3.52 mL, 3.52 mmol, 0.5 eq) and

diiodomethane (0.942 g, 0.284 mL, 3.52 mmol, 0.5 eq). After stirring for a further overnight period at rt, the reaction was quenched by addition of saturated aq. NH_4Cl solution (100 mL). The quenched mixture was extracted with DCM (3 x 50 mL) and the combined organic phases washed saturated aq. $NaHCO_3$ (30 mL) and water (30 mL). After removal of solvent *in vacuo*, the residue was passed through a silica plug (eluent EtOAc/PE 15:85) to remove inorganic impurities. Concentration of these washings gave 2.044 g (97%) of yellow crystalline solid. Mp = 30.5 – 32.5 °C; FT-IR 2920, 2862 (alkyl C-H, str), 1509 (aryl, str), 1137, 1114 (C-O-C, str), 827 (aryl C-H, bend, *para*-disubstituted ring), 732, 693 (aryl C-H, bend, phenyl ring); ^{1}H NMR δ 7.33 – 7.45 (m, 5H, aromatic benzyl CH), 6.95, 6.91 (d, *J* = 9.2 Hz, 2 x 2H, *para*-disubstituted aryl ring), 5.01 (s, 2H, PhCH_2O), 4.10 (t, *J* = 5.0 Hz, 2H, CH_2OArOBn), 3.82 (t, *J* = 5.0 Hz, 2H, CH_2CH$_2$OArOBn) 3.42 (d, *J* = 6.8 Hz, 2H, ^{c}PrCH$_2$O) 1.10 – 1.20 (m, 1H, CH), 0.54 – 0.66 (m, 2H, ^{c}Pr CH$_2$), 0.23 – 0.34 (m, 2H, ^{c}Pr CH$_2$); ^{13}C NMR δ 153.30, 153.19 (4° aryl C), 137.39 (4° benzyl C), 128.67, 128.47, 128.00 (benzyl CH), 115.85, 115.73 (aryl CH), 76.36 (^{c}Pr*C*H$_2$O), 70.76 (benzyl CH$_2$), 69.09 (*C*H$_2$CH$_2$OArOBn), 68.20 (CH$_2$*C*H$_2$OAr), 10.69 (^{c}Pr CH), 3.18 (^{c}Pr *C*H$_2$); *m/z* HRMS (TOF ES$^+$) $C_{19}H_{23}O_3$ [MH]$^+$ calcd 299.1642; found 299.1636.

4-(2-(Cyclopropylmethoxy)ethoxy)phenol (17). 1-(2-(Cyclopropylmethoxy)ethoxy)-4-(benzyloxy)benzene (**16**) (3.24 g, 10.87 mmol) was hydrogenated according to the general procedure for *O*-benzyl deprotection to give 2.45g of clear colourless oil (quantitative). FT-IR 3367 (br, O-H, str), 2873 (alkyl C-H, str), 1510 (aryl, str), 1448 (C-H, def), 1101 (C-O-C, str), 826 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR δ 6.72 – 6.77 (m, 4H, aryl-H), 5.70 – 5.50 (br s, 1H, OH), 4.06 (t, *J* = 5.0 Hz, 2H CH$_2$OAr), 3.81 (t, *J* = 5.0 Hz, 2H, CH_2CH$_2$OAr), 3.40 (d, *J* = 6.8 Hz, 2H, ^{c}PrCH$_2$O), 1.07 – 1.11 (m, 1H, ^{c}Pr CH), 0.48 – 0.60 (m, 2H, ^{c}Pr CH$_2$), 0.17 – 0.28 (m, 2H, ^{c}Pr CH$_2$); ^{13}C NMR δ 152.69, 149.90 (4° aryl C), 116.07, 115.76 (aryl CH), 76.38 (^{c}Pr*C*H$_2$O), 69.02 (*C*H$_2$CH$_2$OAr), 68.05 (CH$_2$OAr), 10.50 (^{c}Pr CH), 3.14 (^{c}Pr *C*H$_2$); *m/z* HRMS (TOF ES$^-$) $C_{12}H_{15}O_3$ [M-H]$^-$ calcd 207.1027; found 207.1026.

2-((4-(2-(Cyclopropylmethoxy)ethoxy)phenoxy)methyl)oxirane (18). 4-(2-(Cyclopropylmethoxy)ethoxy) phenol (**17**) (450 mg, 2.16 mmol) was dissolved in aq. 2M NaOH solution (1.5 mL) and stirred for 10 minutes. *rac*-Epichlorohydrin (507 µL, 6.481 mmol, 3 eq) was added and the mixture stirred at 60 °C for 24 hours. The cooled mixture was extracted with DCM (3 x 25 mL) and the organic layers combined. After concentration of the combined organic layers under reduced pressure, the product was purified by FCC (eluent EtOAc/hexanes 30:70) to give 356 mg (62%) of clear colourless oil. FT-IR 3080 (epoxide C-H, str), 2926, 2872 (alkyl C-H, str), 1508 (aryl, str), 1230 (epoxide C-C, str), 1113 (C-O-C, str), 826 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR δ 6.83 (s, 4H, aryl CH), 4.15 (dd, *J* = 11.0/3.2 Hz, 1H, ArOCH_2CH), 4.06 (t, 4.9 Hz, 2H, CH_2OAr), 3.88 (dd, *J* = 11.0/5.7 Hz, 1H, ArOCH_2CH), 3.78 (t, *J* = 5.0 Hz, 2H, CH_2CH$_2$OAr), 3.36 (d, *J* = 6.8 Hz, 2H, ^{c}PrCH_2O), 3.29 – 3.33 (m, 1H, epoxide CH), 2.87 (dd, *J* = 4.8/4.3 Hz, 1H, epoxide CH$_2$), 2.72 (dd, *J* = 4.9/2.7 Hz, 1H, epoxide CH$_2$), 1.05 – 1.10 (m, 1H, ^{c}Pr CH), 0.51 – 0.55 (m, 2H, ^{c}Pr CH$_2$), 0.19 – 0.22 (m, 2H, ^{c}Pr CH$_2$); ^{13}C NMR δ 153.48, 152.86 (4° aryl C), 115.68 (aryl CH), 76.32 (^{c}Pr*C*H$_2$O), 69.53 (ArO*C*H$_2$CH), 69.05 (*C*H$_2$CH$_2$OAr), 68.14 (CH$_2$OAr), 50.35 (epoxide CH), 44.80 (epoxide *C*H$_2$), 10.66 (^{c}Pr CH), 3.16 (^{c}Pr *C*H$_2$); *m/z* HRMS (TOF ES$^+$) $C_{15}H_{21}O_4$ [MH]$^+$ calcd 265.1434; found 265.1407.

1-(2-(3-(4-(2-(Cyclopropylmethoxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(4-hydroxyphenyl)urea hydroformate (19). 2-((4-(2-(Cyclopropylmethoxy)ethoxy)phenoxy)methyl)-oxirane (**18**) was opened with 1-(2-aminoethyl)-3-(4-hydroxyphenyl)urea (**13**) as described in the general procedure for aminolysis of oxiranes. Yield: 21%, semi-solid; FT-IR 3307 (br, O-H, str), 2929, 2870 (alkyl C-H, str), 1634 (urea C=O, str), 1509, 1570 (aryl, str), 1111 (C-O-C, str), 830 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR (MeOD-d$_4$) δ 7.09 – 7.16 (m, 2H, aryl C-H *ortho* to urea), 6.90 (d, *J* = 9.0 Hz, 2H, aryl-dioxy ring), 6.86 (d, *J* = 9.4 Hz, 2H, aryl-dioxy ring), 6.70 (d, *J* = 9.3 Hz, 2H, aryl C-H *ortho* to phenol), 4.18 – 4.27 (m, 1H, C*H*(OH)), 4.05 (t, *J* = 4.6 Hz, 2H, CH_2OArO), 4.00 (dd, *J* = 9.8/4.9, 1H, ArOCH_2CH(OH)), 3.95 (dd, *J* = 9.8/5.3, 1H, ArOCH_2CH(OH)), 3.79 (t, *J* = 4.7 Hz, 2H, OCH_2CH$_2$OArO), 3.51 (t, *J* = 5.3 Hz, 2H, CH$_2$CH_2NH), 3.37 (d, *J* = 6.9 Hz, 2H, ^{c}PrCH_2O), 3.28 – 3.35, 3.15 – 3.24 (m, 4H, CH(OH)CH_2NH, NHCH_2CH$_2$),

1.01 – 1.13 (m, 1H, ^{c}Pr CH), 0.50 – 0.57 (m, 2H, ^{c}Pr CH_2), 0.19 – 0.26 (m, 2H, ^{c}Pr CH_2); ^{13}C NMR (MeOD-d_4) δ 159.81, 154.90, 154.20, 132.28, 131.90 (aryl 4° C), 123.71 (aryl C-H *ortho* to urea), 116.65, 116.64 (*C*H aryl-dioxy ring), 116.38 (aryl C-H *ortho* to phenol), 77.11 (^{c}Pr*C*H_2O), 71.78 (ArO*C*H_2), 70.18 (*C*$H_2$$CH_2$OAr), 69.17 (*C*$H_2$OAr), 66.81 (*C*H(OH)), 51.54, 50.69 (CH(OH)*C*H_2NH, NH*C*$H_2$$CH_2$), 38.02 (NH$CH_2$*C*$H_2$), 11.36 (^{c}Pr CH), 3.47 (^{c}Pr CH_2); *m/z* HRMS (TOF ES$^+$) $C_{24}H_{34}N_3O_6$ $[MH]^+$ calcd 460.2442; found 460.2429; RP-HPLC R_t 2.88 (System 1a), 9.84 (System 2).

2-(Cyclopentyloxy)ethanol (21). Zirconium chloride (10.021 g, 43 mmol, 1.1 eq) was dissolved in anhydrous THF (100 mL) under a nitrogen atmosphere. To this was added sodium borohydride (6.507 g, 172 mmol, 4.4 eq) in portions at rt with stirring, resulting in hydrogen gas evolution and formation of a cream suspension. A solution of cyclopentanone ethylene ketal (**20**) (5.000 g, 4.85 mL, 39 mmol) in anhydrous THF (50 mL) was added slowly whilst maintaining the vessel temperature between 0 – 5 °C. After stirring at rt for 4 hours, the mixture was quenched with cautious addition of aqueous 2M HCl over an ice bath. All organic volatiles were removed under reduced pressure, and the remaining aqueous slurry extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (1 x 30 mL) before concentration to a crude oil. This was purified by FCC (eluent EtOAc/hexanes 1:1) to give 4.114 g (81%) of clear colourless oil. FT-IR 2943, 2865 (alkyl C-H, str), 1109 (C-O-C, str); ^{1}H NMR δ 3.84 – 3.89 (m, 1H, CH), 3.60 – 3.63 (m, C*H*$_2$OH), 3.41 (t, *J* = 4.9 Hz, 2H, ^{c}PeOCH_2), 2.84 (t, *J* = 5.6 Hz, 1H, OH), 1.51 – 1.72 (m, 6H, cyclopentyl (^{c}Pe) CH_2), 1.38 – 1.50 (m, 2H, ^{c}Pe CH_2); ^{13}C NMR δ 81.80 (CH), 69.94 (^{c}PeO*C*H_2), 61.80 (*C*H_2OH), 32.17 (2-C and 5-C ^{c}Pe ring), 23.46 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^-$) $C_8H_{15}O_4$ $[M+HCO_2]^-$ calcd 175.0976; found 175.0995.

2-(4-Fluorophenethyloxy)acetic acid (23). NaH 60% suspension in mineral oil (2.400 g, equivalent to 1.440 g of NaH, 60 mmol, 2 eq) was weighed into a flame-dried flask and suspended in anhydrous DMF (60 mL) with stirring, under a nitrogen atmosphere. To this was added 4-fluorophenethyl alcohol (**22**) (4.205 g, 3.751 mL, 30 mL) and the temperature was raised to 60 °C with stirring for 15 minutes. Chloroacetic acid (2.835 g, 30 mmol, 1 eq) was added to the flask and the mixture allowed to stir at 60 °C for a further 2.5 hours. After cooling and removal of solvent, the residue was suspended in Et_2O (30 mL) and extracted with water (2 x 30 mL). The combined aqueous layers were acidified with aq. 2M HCl (to around pH 3) before extraction with EtOAc (3 x 30 mL). After concentration under reduced pressure, the crude solid was recrystallised from cyclohexane to yield 3.00 g (50%) of pink crystals. Mp = 84 – 86 °C (lit. 82 – 85 °C)[1]; FT-IR 2964, 2893 (alkyl C-H, str), 2772, 2677, 2571 (O-H, str, carboxylic acid), 1733 (carboxylic acid), 1510 (aryl, str), 1137 (C-F, str), 1103 (C-O-C, str), 840 (aryl C-H, bend, *para*-disubstituted ring), 770 (C-F, weak); ^{1}H NMR δ 8.5 – 10.4 (br s, 1H, CO_2H), 7.19 (dd, *J* = 8.6/5.7 Hz, 2H, aryl 3-H and 5-H), 6.99 (dd, *J* = 8.6/8.6 Hz, 2H, aryl 2-H and 6-H), 4.12 (s, 2H, C*H*$_2$$CO_2H$), 3.76 (t, *J* = 6.8 Hz, 2H, CH_2O), 2.92 (t, *J* = 6.8 Hz, 2H, ArCH_2); *m/z* HRMS (TOF ES$^-$) $C_{10}H_{10}FO_3$ $[M-H]^-$ calcd 197.0619; found 197.0629.

2-(4-Fluorophenethyloxy)ethanol (24). Lithium aluminium hydride (472 mg, 12.45 mmol, 1 eq) was suspended in anhydrous THF (15 mL) with stirring, whilst cooling in an ice bath. 2-(4-Fluorophenethyloxy)acetic acid (**23**) (2.467 g, 12.45 mmol) in anhydrous THF (15 mL) was slowly dripped in the suspension over 10 minutes and the resulting mixture stirred overnight at rt under a nitrogen atmosphere. After quenching carefully with water, the suspension was filtered (gravity) and the filtrate concentrated to an oily residue. Purification was achieved by FCC (eluent EtOAc/hexanes 6:4), giving 1.52 g (67%) of clear, colourless oil. FT-IR 3417 (br, O-H, str), 2922, 2870 (alkyl C-H, str), 1510 (aryl, str), 1117 (C-O-C, str), 830 (aryl C-H, *para*-disubstituted ring).^{1}H NMR δ 7.15 (dd, *J* = 8.6/5.5 Hz, 2H, aryl 3-H and 5-H), 6.95 (dd, *J* = 8.8/8.8 Hz, 2H, aryl 2-H and 6-H), 3.65 – 3.72 (m, 2H, CH_2OH), 3.65 (t, *J* = 7.0 Hz, 2H, ArCH_2C*H*$_2$), 3.53 (t, *J* = 4.8 Hz, 2H, OC*H*$_2$$CH_2OH$), 2.85 (t, *J* = 7.0 Hz, 2H, ArCH_2), 2.38 (br s, 1H, OH); *m/z* HRMS (TOF ES$^-$) $C_{11}H_{14}FO_4$ $[M+HCO_2]^-$ calcd 229.0882; found 229.0883.

1-(2-(4-Fluorophenethyloxy)ethyloxy)-4-(benzyloxy)benzene (26b). 2-(4-Fluorophenethyloxy)-ethanol (**24**) (1.417g, 7.78 mmol), triphenylphosphine (2.448g, 9.33 mmol, 1.2 eq), and 4-

(benzyloxy)phenol (**14**) (1.558g, 7.78 mmol, 1 eq) were dissolved in anhydrous DCM (30 mL) under a nitrogen atmosphere. Di-*tert*-butyl azodicarboxylate (2.149g, 9.33 mmol, 1.2 eq) in anhydrous DCM (10 mL) was added dropwise to the reaction mixture before stirring for 4 hours at rt. After removal of approximately half of the solvent from the reaction mixture under reduced pressure, the resulting slurry was diluted with hexanes (30 mL) and washed with aq. 2M HCl (2 x 30 mL), aq. 2M NaOH (2 x 30 mL), water (2 x 30 mL) and brine (1 x 30 mL). The organic layer was concentrated and purified by FCC (eluent EtOAc/hexanes 15:85) to give 999 mg (35%) of white crystalline solid. Mp = 59 - 61°C; FT-IR 2864, 2929 (alkyl C-H, str), 1509 (aryl, str), 1119 (C-O-C, str). 827 (aryl C-H, bend, *para*-disubstituted ring), 739, 698 (aryl C-H, bend, phenyl ring); ^{1}H NMR δ 7.30 – 7.45 (m, 5H, aromatic benzyl CH), 7.19 (dd, J = 8.6/5.5 Hz, 2H, 3-H and 5-H of fluorophenyl ring), 6.97 (dd, J = 8.8/8.8 Hz, 2H, 2-H and 6-H of fluorophenyl ring), 6.91, 6.85 (d, J = 9.2 Hz, 2 x 2H, *para*-disubstituted aryl-dioxy ring), 5.02 (s, 2H, PhCH_2O), 4.06 (t, J = 4.7 Hz, 2H, CH_2OArOBn), 3.78 (t, J = 4.7 Hz, 2H, CH_2CH$_2$OArOBn), 3.72 (t, J = 7.1 Hz, 2H, FC$_6$H$_4$CH$_2$CH_2O), (t, J = 7.1 Hz, 2H, FC$_6$H$_4$CH_2); ^{13}C NMR δ 161.64 (J_{CF} = 244.1 Hz, CF), 153.26 (2 x 4° C, aryl-dioxy ring), 137.38 (4° benzyl C), 134.69 (J_{CF} = 3.0 Hz, 4-C fluorophenyl ring), 130.44 (J_{CF} = 7.7 Hz, 3-C and 5-C fluorophenyl ring), 128.68, 128.02, 127.61 (benzyl CH), 115.77, 115.90 (CH aryl-dioxy ring), 115.22 (J_{CF} = 20.8 Hz, 2-C and 6-C fluorophenyl ring), 72.48 (FC$_6$H$_4$CH$_2$*C*H$_2$O), 70.78 (benzyl CH$_2$), 69.63 (*C*H$_2$CH$_2$OArOBn), 68.19 (*C*H$_2$OArOBn), 35.55 (FC$_6$H$_4$*C*H$_2$); *m/z* HRMS (TOF ES$^+$) C$_{23}$H$_{24}$FO$_3$ [MH]$^+$ calcd 367.1704; found 367.1698.

1-((4-(2-Ethoxyethoxy)phenoxy)methyl)benzene (26c). 2-Ethoxyethanol (**25**) (0.901 g, 10.00 mmol), triphenylphosphine (3.147 g, 12.00 mmol, 1.2 eq), and 4-(benzyloxy)phenol (**14**) (2.403 g, 12.00 mmol, 1.2 eq) were dissolved in anhydrous DCM (40 mL) under a nitrogen atmosphere. Diethyl azodicarboxylate (2.090 g, 1.890 mL, 12.00 mmol, 1.2 eq) in anhydrous DCM (10 mL) was added dropwise to the reaction mixture before stirring for 48 hours at rt. After removal of approximately half of the solvent from the reaction mixture under reduced pressure, the resulting slurry was diluted with hexanes (150 mL) and washed with aq. 2M NaOH (2 x 70 mL), water (2 x 70 mL) and brine (1 x 70 mL). The organic layer was concentrated and purified by FCC (eluent EtOAc/hexanes 20:80) to give 2.324 g (85%) of white crystalline solid. Mp = 32.5 - 34.5 °C (lit: 35 – 37 °C);[2] FT-IR 2975, 2925, 2864 (alkyl C-H, str), 1509 (aryl, str), 1126 (C-O-C, str), 826 (aryl C-H, bend, *para*-disubstituted ring), 732, 693 (aryl C-H, bend, phenyl ring); ^{1}H NMR δ 7.25 – 7.32 (m, 5H, aromatic benzyl CH), 6.90, 6.86 (d, J = 9.2 Hz, 2 x 2H, *para*-disubstituted aryl ring), 5.01 (s, 2H, PhCH_2O), 4.07 (t, J = 4.9 Hz, 2H, CH_2OArOBn), 3.77 (t, J = 4.9 Hz, 2H, CH_2CH$_2$OArOBn), 3.60 (q, J = 7.0 Hz, 2H, CH$_3$CH_2O), 1.24 (t, J = 7.0 Hz, 3H CH_3); ^{13}C NMR δ 153.32, 153.21 (4° aryl C), 137.40 (4° benzyl C), 128.67, 128.01, 127.62 (benzyl CH), 115.86, 115.75 (aryl CH), 70.77 (benzyl CH$_2$), 69.20, 68.21, 66.96 (CH$_2$O), 15.31 (CH$_3$); *m/z* HRMS (TOF ES$^+$) C$_{17}$H$_{21}$O$_3$ [MH]$^+$ calcd 273.1485; found 273.1506.

4-(2-(4-Fluorophenethyloxy)ethyloxy)phenol (27b). 1-(2-(4-Fluorophenethyloxy)ethyloxy)-4-(benzyloxy)benzene (**26b**) was hydrogenated according to the general procedure for *O*-benzyl deprotection to give the title compound in quantitative yield as clear colourless oil. FT-IR 3366 (br, O-H, str), 2925, 2871 (alkyl C-H, str), 1510 (aryl, str), 1222 (C-F), 1121 (C-O-C, str), 828 (aryl C-H, bend, *para*-disubstituted ring), 738 (C-F); ^{1}H NMR δ 7.18 (dd, J = 8.6/5.5 Hz, 2H, 3-H and 5-H of fluorophenyl ring), 6.96 (dd, J = 8.8/8.8 Hz, 2H, 2-H and 6-H of fluorophenyl ring), 6.74, 6.76 (d, J = 9.2 Hz, 2 x 2H, *para*-disubstituted phenol), 6.00 (br s, 1H, OH), 4.05 (t, J = 4.7 Hz, 2H, CH_2OAr), 3.80 (t, J = 4.9 Hz, 2H, CH_2CH$_2$OAr), 3.75 (t, J = 7.2 Hz, 2H, FC$_6$H$_4$CH$_2$CH_2O), 2.90 (t, J = 7.1 Hz, 2H, FC$_6$H$_4$CH_2); ^{13}C NMR δ 161.59 (J_{CF} = 245.0 Hz, CF), 152.64, 150.08 (4° C, aryl-dioxy ring), 134.43 (J_{CF} = 3.1 Hz, 4-C fluorophenyl ring), 130.40 (J_{CF} = 8.0 Hz, 3-C and 5-C fluorophenyl ring), 116.19, 115.92 (CH phenolic ring), 115.19 (J_{CF} = 21.1 Hz, 2-C and 6-C fluorophenyl ring), 72.48 (FC$_6$H$_4$CH$_2$*C*H$_2$O), 69.58 (*C*H$_2$CH$_2$OAr), 68.13 (*C*H$_2$OAr), 35.34 (FC$_6$H$_4$*C*H$_2$); *m/z* HRMS (TOF ES$^-$) C$_{16}$H$_{16}$FO$_3$ [M-H]$^-$ calcd 275.1089; found 275.1090.

4-(2-Ethoxyethoxy)phenol (27c). 1-((4-(2-Ethoxyethoxy)phenoxy)methyl) benzene (**26c**) (904 mg, 3.32 mmol) was hydrogenated according to the general procedure for *O*-benzyl deprotection to give a

viscous amber oil. The crude oil was dissolved in DCM (20 mL) and washed with aq. 2M NaOH (3 x 20 mL). The combined aqueous extracts were acidified with conc. HCl (until the pH was below 7) to effect an emulsion, before extracting with DCM (3 x 30 mL). The combined organic layers were washed with water (1 x 30 mL) and brine (1 x 30 mL). On concentration 413 mg (68%) of clear, colourless oil was obtained. FT-IR 3365 (br, O-H, str), 2976, 2873 (alkyl C-H, str), 1602, 1511 (aryl, str), 1105 (C-O-C, str), 826 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR δ 6.81, 6.74 (d, J = 9.0 Hz, 2H, aryl-H), 4.57 (br s, 1H OH); 4.06 (t, J = 4.9 Hz, 2H, CH_2OAr), 3.77 (t, J = 4.9 Hz, 2H, CH_2CH$_2$OAr), 3.60 (q, J = 7.0 Hz, 2H, CH$_3$CH_2O), 1.24 (t, J = 7.0 Hz, 3H CH_3);[3] ^{13}C NMR δ 152.54, 150.05 (4° aryl C), 116.12, 115.80 (aryl CH), 69.11, 68.03, 66.99 (CH$_2$O), 15.06 (CH$_3$); *m/z* HRMS (TOF ES$^-$) $C_{10}H_{13}O_3$ [M-H]$^-$ calcd 181.0870; found 181.0890.

2-((4-(2-(4-Fluorophenethyloxy)ethyloxy)phenoxy)methyl)oxirane (28b). NaH 60% suspension in mineral oil (13 mg, equivalent to 7.8 mg of NaH, 0.33 mmol, 1.1 eq) was suspended in anhydrous DMF (2 mL) with stirring, under a nitrogen atmosphere. To this was added 4-(2-(4-fluorophenethyloxy)ethyloxy)phenol (**27b**) (82 mg, 0.30 mmol) in anhydrous DMF (4 mL) and stirred until no further hydrogen gas evolution was visible. *rac*-Epichlorohydrin (800 µL, 10.22 mmol, 34 eq) was added and the reaction stirred overnight at rt. The reaction mixture was diluted with water (30 mL) before extraction with Et$_2$O (3 x 30 mL). The combined organic extracts were concentrated before purification over a silica plug (initial wash with hexanes, followed by EtOH/DCM 5:95) to give 70 mg (71%) of clear yellow oil. FT-IR 3051 (epoxide C-H, str, weak), 2871, 2923 (alkyl C-H, str), 1508 (aryl, str), 1229 (C-F), 1124 (C-O-C, str), 827 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR δ 7.19 (dd, J = 8.6/5.6 Hz, 2H, 3-H and 5-H of fluorophenyl ring), 6.96 (dd, J = 8.8/8.8 Hz, 2H, 2-H and 6-H of fluorophenyl ring), 6.85 (s, 4H, aryl-dioxy ring), 4.17 (dd, J = 11.1/3.2 Hz, 1H, ArOCH_2CH), 4.06 (t, J = 4.7 Hz, 2H, CH_2OAr), 3.90 (dd, J = 11.0/5.7 Hz, 1H, ArOCH_2CH), 3.78 (t, J = 4.9 Hz, 2H, CH_2CH$_2$OAr), 3.72 (t, J = 7.1 Hz, 2H, FC$_6$H$_4$CH$_2$CH_2O), 3.32 – 3.35 (m, 1H, epoxide CH), 2.89 (t, J = 7.1 Hz, 2H, FC$_6$H$_4$CH_2), 2.87 – 2.91 (m, 1H, epoxide CH$_2$), 2.74 (dd, J = 4.9/2.7 Hz, 1H, epoxide CH$_2$); ^{13}C NMR δ 162.58 (J_{CF} = 243.7 Hz, CF), 153.43, 152.92 (4° C, aryl-dioxy ring), 134.66 (J_{CF} = 3.4 Hz, 4-C fluorophenyl ring), 130.40 (J_{CF} = 7.9 Hz, 3-C and 5-C fluorophenyl ring), 115.71 (CH aryl-dioxy ring), 115.39 (J_{CF} = 21.1 Hz, 2-C and 6-C fluorophenyl ring), 72.40 (FC$_6$H$_4$CH$_2$*C*H$_2$O), 69.54, 69.56 (*C*H$_2$CH$_2$OAr, ArO*C*H$_2$CH), 68.11 (*C*H$_2$OAr), 50.34 (epoxide CH), 44.77 (epoxide CH$_2$), 35.49 (FC$_6$H$_4$*C*H$_2$); *m/z* HRMS (TOF ES$^+$) $C_{19}H_{22}FO_4$ [MH]$^+$ calcd 355.1316; found 355.1315.

2-((4-(2-Ethoxyethoxy)phenoxy)methyl)oxirane (28c). 4-(2-Ethoxyethoxy)phenol (**27c**) (413 mg, 2.27 mmol) was dissolved in aqueous 2M NaOH solution (4.0 mL) and stirred for 10 minutes. *rac*-Epichlorohydrin (533 µL, 6.81 mmol, 3 eq) was added and the mixture stirred at 60 °C for 24 hours. The cooled mixture was extracted with DCM (3 x 20 mL) and the organic layers combined. After concentration under reduced pressure, the crude product was purified by FCC (eluent Et$_2$O) to give 417 mg (84%) of clear colourless oil. FT-IR 2975, 2927, 2872 (alkyl C-H, str), 1508 (aryl, str), 1231 (epoxide C-C, str), 1122 (C-O-C, str), 826 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR δ 6.83 – 6.88 (m, 4H, *para*-disubstituted aryl ring), 4.17 (dd, J = 11.2/3.2 Hz, 1H, ArOCH_2CH), 4.07 (t, J = 4.9 Hz, 2H, CH_2OAr), 3.91 (dd, J = 10.08/5.6 Hz, 1H, ArOCH_2CH), 3.77 (t, J = 4.9 Hz, 2H, CH_2CH$_2$OAr), 3.60 (q, J = 7.0 Hz, 2H, CH$_3$CH_2O), 3.34 (m, 1H, epoxide CH), 2.89 (dd, J = 5.0/4.0 Hz, 1H, epoxide CH$_2$), 2.74 (dd, J = 5.0/2.6 Hz, 1H, epoxide CH$_2$), 1.25 (t, J = 7.0 Hz, 3H, CH$_3$); ^{13}C NMR δ 153.41, 152.79 (4° aryl C), 115.63, 115.60 (aryl CH), 69.45 (ArO*C*H$_2$CH), 69.05 (C$_2$H$_5$O*C*H$_2$), 68.06 (*C*H$_2$OAr), 66.84 (CH$_3$*C*H$_2$O), 50.27 (epoxide *C*H), 44.74 (epoxide *C*H$_2$), 15.18 (CH$_3$); *m/z* HRMS (TOF ES$^+$) $C_{13}H_{19}O_4$ [MH]$^+$ calcd 239.1278; found 239.1262.

1-(2-(3-(4-(2-(4-Fluorophenethyloxy)ethyloxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(4-hydroxyphenyl)urea (29b). 2-((4-(2-(4-Fluorophenethyloxy)ethyloxy)phenoxy)methyl)oxirane (**28b**) was opened with 1-(2-aminoethyl)-3-(4-hydroxyphenyl)urea (**13**) as described in the general procedure for aminolysis of oxiranes. Yield: 25%, white amorphous solid, Mp = 113 – 115 °C; FT-IR 3308 (br, O-H, str), 2926, 2868 (alkyl C-H, str), 1636 (urea C=O, str), 1510, 1572 (aryl, str), 1229 (C-F), 1120 (C-O-C, str), 831 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR (DMSO-d$_6$) δ 8.92 (br

s, 1H, phenol), 8.22 (s, 1H, NH(C=O)N*H*Ar), 7.28 (dd, *J* = 8.3/5.8 Hz, 2H, 3-H and 5-H of fluorophenyl ring), 7.14 (d, *J* = 8.8 Hz, 2H, aryl C-H *ortho* to urea), 7.08 (dd, *J* = 8.9/8.9 Hz, 2H, 2-H and 6-H of fluorophenyl ring), 6.82, 6.85 (d, *J* = 9.3 Hz, 2 x 2H, aryl-dioxy ring), 6.62 (d, *J* = 8.8 Hz, 2H, aryl C-H *ortho* to phenol), 6.03 (t, *J* = 5.2 Hz, 1H, N*H*(C=O)NHAr), 5.01 (br s, 1H, NH), 3.99 (t, *J* = 4.3 Hz, 2H, CH_2OAr), 3.78 – 3.93 (m, 3H, C*H*(OH), ArOCH_2), 3.69 (t, *J* = 4.3 Hz, 2H, CH_2CH$_2$OAr), 3.64 (t, *J* = 6.9 Hz, 2H, FC$_6$H$_4$CH$_2$CH_2O), 3.11 – 3.19 (m, 2H, NHCH$_2$CH_2), 2.81 (t, *J* = 6.8 Hz, 2H, FC$_6$H$_4$CH_2), 2.58 – 2.76 (m, 4H, CH(OH)CH_2NH, NHCH_2CH$_2$); ^{13}C NMR (DMSO-d$_6$) δ 160.80 (J_{CF} = 241.3 Hz, CF), 155.70 (C=O), 152.76, 152.47, 151.88, 132.12, (aryl 4° C), 135.18 (J_{CF} = 3.2 Hz, 4-C fluorophenyl ring), 130.59 (J_{CF} = 7.8 Hz, 3-C and 5-C fluorophenyl ring), 119.28 (aryl C-H *ortho* to urea), 115.33, 115.36 (*C*H aryl-dioxy ring), 115.06 (aryl C-H *ortho* to phenol), 114.84 (J_{CF} = 21.0 Hz, 2-C and 6-C fluorophenyl ring), 71.21 (FC$_6$H$_4$CH$_2$*C*H$_2$O, ArO*C*H$_2$), 68.71 (*C*H$_2$CH$_2$OAr), 67.99 (CH(OH)), 67.49 (*C*H$_2$OAr), 51.13 (CH(OH)*C*H$_2$NH), 49.35 (NH*C*H$_2$CH$_2$), 39.05 (NHCH$_2$*C*H$_2$), 34.56 (FC$_6$H$_4$*C*H$_2$); *m/z* HRMS (TOF ES$^+$) C$_{28}$H$_{35}$FN$_3$O$_6$ [MH]$^+$ calcd 528.2510; found 528.2514; RP-HPLC R$_t$ 3.47 (System 1b), 11.50 (System 3).

1-(2-(3-(4-(2-Ethoxyethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(4-hydroxyphenyl)urea (29c). 2-((4-(2-Ethoxyethoxy)phenoxy)methyl)oxirane (**28c**) was opened with 1-(2-aminoethyl)-3-(4-hydroxyphenyl)urea (**13**) as described in the general procedure for aminolysis of oxiranes. Yield: 21%, white amorphous solid; mp = 96 - 98°C; FT-IR 3336 (br, O-H, str), 2926, 2866 (alkyl C-H, str), 1636 (urea C=O, str), 1513, 1574 (aryl, str), 1123 (C-O-C, str), 819, 835 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR (MeOD-d$_4$) δ 7.12 (d, *J* = 8.9 Hz, 2H, aryl C-H *ortho* to urea), 6.87 (d, *J* = 9.0 Hz, 2H, aryl-dioxy ring), 6.84 (d, *J* = 9.0 Hz, 2H, aryl-dioxy ring), 6.70 (d, *J* = 8.9 Hz, 2H, aryl C-H *ortho* to phenol), 4.01 – 4.08 (m, 1H, C*H*(OH)), 4.03 (t, *J* = 4.6 Hz, 2H, CH_2OArO), 3.87 – 3.95 (m, 2H, ArOCH_2CH(OH)), 3.75 (t, *J* = 4.7 Hz, 2H, OCH_2CH$_2$OArO), 3.59 (q, *J* = 7.0 Hz, 2H, CH$_3$CH_2), 3.34 (t, *J* = 6.1 Hz, 2H, CH$_2$CH_2NH), 2.74 – 2.90 (m, 4H, CH(OH)CH_2NH, NHCH_2CH$_2$), 1.21 (t, *J* = 7.0 Hz, 3H, CH$_3$); ^{13}C NMR (MeOD-d$_4$) δ 159.22, 154.63, 154.60, 132.32 (aryl 4° C), 123.56 (aryl C-H *ortho* to urea), 116.59, 116.55 (*C*H aryl-dioxy ring), 116.34 (aryl C-H *ortho* to phenol), 72.38 (ArO*C*H$_2$), 70.29 (*C*H$_2$CH$_2$OAr), 69.65 (*C*H(OH)), 69.14 (*C*H$_2$OAr), 67.72 (CH$_3$*C*H$_2$), 52.94 (CH(OH)*C*H$_2$NH), 50.55 (NH*C*H$_2$CH$_2$), 40.26 (NHCH$_2$*C*H$_2$), 14.40 (CH$_3$); *m/z* HRMS (TOF ES$^+$) C$_{22}$H$_{32}$N$_3$O$_6$ [MH]$^+$ calcd 434.2286; found 434.2291; (TOF ES$^-$) C$_{22}$H$_{30}$N$_3$O$_6$ [M-H]$^-$ calcd 432.2140; found 432.2134; RP-HPLC R$_t$ 2.29 (System 1b), 8.72 (System 2).

1-(2-Aminoethyl)-3-(*o*-tolyl)urea (32b). 1,2-Ethanediamine (**11**) (11.3 g, 12.5 mL, 188 mmol, 50 eq) was diluted with anhydrous DCM (15 mL) under a nitrogen atmosphere and cooled to 0 °C. To this, a solution of *o*-tolyl isocyanate (500 mg, 466 µL, 3.76 mmol) in anhydrous DCM (7.5 mL) was added dropwise. After 30 minutes of stirring at rt, all solvent was removed and the crude slurry purified by FCC (eluent 37% aq NH$_3$/MeOH/DCM 2:30:68) to give 466 mg (64%) of beige solid. Mp = 179 – 181 °C; FT-IR 3325 (br, 1° amine N-H, str), 2926, 2864 (alkyl C-H, str), 1634 (urea C=O, str), 1587 (aryl, str), 753 (aryl C-H, bend, *ortho*-disubstituted ring); ^{1}H NMR (DMSO-d$_6$) δ 7.81 (d, *J* = 8.1 Hz, 1H, aryl 6-H), 7.70 (br s, 1H, NH(C=O)N*H*Ar), 7.05 – 7.11 (m, 2H, aromatic C-H), 6.85 (dd, *J* = 8.1/8.1 Hz, 1H, aromatic C-H), 6.64 (t, *J* = 5.4 Hz, 1H, N*H*(C=O)NHAr), 3.07 (dt, *J* = 6.0/6.0 Hz, 2H, CH_2NH), 2.61 (t, *J* = 6.2 Hz, 2H, CH_2NH$_2$), 2.17 (s, 3H, CH$_3$); ^{13}C NMR (DMSO-d$_6$) δ 155.52 (C=O), 138.35, 126.56 (4° C), 130.02, 126.02, 121.68, 120.35 (Aryl C-H), 42.43 (*C*H$_2$NH), 41.81 (*C*H$_2$NH$_2$), 17.95 (*C*H$_3$); *m/z* HRMS (TOF ES$^+$) C$_{10}$H$_{16}$N$_3$O [MH]$^+$ calcd 194.1288; found 194.1308.

***tert*-Butyl 2-aminoethylcarbamate (31).** 1,2-Ethanediamine (**11**) (50 mL, 927 mmol, 8.75 eq) was diluted in DCM (200 mL) with vigorous stirring. Di-*tert*-butyl dicarbonate (23.2 g, 106 mmol) was dissolved in DCM (1.3 L) and then added dropwise to the solution of 1,2-ethanediamine over 24 hours. After removal of all volatiles, the remaining residue was partitioned between water (250 mL) and DCM (250 mL). The aqueous layer was washed again with DCM (250 mL) before combining the organic solvents and concentrating. The residue was dissolved in aq. 0.5M KHSO$_4$ (250 mL) and washed with DCM (2 x 100 mL). The aqueous layer was then basified with aq. 2M NaOH before final extraction with DCM (4 x 100 mL). The combined organic extracts were dried and concentrated

to give 12.98g (87%) of viscous translucent oil. FT-IR 3354 (1° amine N-H, str), 2977, 2933 (alkyl C-H, str), 1694 (carbamate C=O, str), 1524 (carbamate – amide N-H bend), 1392, 1366 ($C(CH_3)_3$, str), 1252, 1174 (C-O, str); ^{1}H NMR δ 5.16 (br s, 1H, CONH), 3.06 – 3.10 (m, 2H, C*H*$_2$NH), 2.71 (t, *J* = 6 Hz, C*H*$_2$NH$_2$), 1.36 (s, 9H, C(C*H*$_3$)$_3$), 1.24 (br s, 2H, N*H*$_2$); ^{13}C NMR δ 156.26 (C=O), 79.25 (*C*(CH$_3$)$_3$), 42.85, 41.70 (CH_2), 28.42 (C(*C*H$_3$)$_3$); *m/z* HRMS (TOF ES$^+$) $C_7H_{17}N_2O_2$ $[MH]^+$ calcd 161.1285; found 161.1300.

General procedure for synthesis of phenyl substituted *tert*-butyl 2-(3-phenylureido)ethyl carbamates (32a and 32c-r). *tert*-Butyl 2-aminoethylcarbamate (**31**) (1 eq) was dissolved in anhydrous DCM (10 mL) and cooled to 0 °C with stirring under a nitrogen atmosphere. To this was added dropwise, a solution of the desired substituted phenylisocyanate (500 mg) in anhydrous DCM (5 mL). The mixture was stirred overnight at rt, before addition of hexanes until precipitation occurred. The solid mass was collected by filtration (vacuum) and washed with hexanes before drying *in vacuo*.

***tert*-Butyl 2-(3-phenylureido)ethylcarbamate (32a).** Yield: 46%, white amorphous solid; mp = 153 – 155 °C; FT-IR 3323 (br, carbamate N-H, str), 2980, 2936 (alkyl C-H, str), 1682 (carbamate C=O, str), 1646 (urea C=O, str), 1547 (aryl, str), 755, 694 (aryl C-H bend phenyl ring); ^{1}H NMR (DMSO-d$_6$) δ 8.53 (s, 1H, NH(C=O)N*H*Ph), 7.37 (d, *J* = 7.7 Hz, 2H, 2-H and 6-H phenyl ring), 7.20 (dd, *J* = 7.5/7.5 Hz, 2H, 3-H and 5-H phenyl ring), 6.86 – 6.89 (m, 2H, 4-H phenyl ring, N*H*(C=O)NHPh), 6.16 (t, *J* = 5.5 Hz, 1H, O(C=O)N*H*), 3.11 (dt, *J* = 6.1/6.1 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.99 (dt, *J* = 5.8/5.8 Hz, 2H, C*H*$_2$NH(C=O)O), 1.38 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (DMSO-d$_6$) δ 155.73, 155.29 (C=O), 140.54 (4° C), 128.63 (phenyl 3-C and 5-C), 120.98 (phenyl 4-C), 117.63 (phenyl 2-C and 6-C), 77.64 (Boc 4° C), 40.46, 39.01 (CH_2), 28.26 (CH_3); *m/z* HRMS (TOF ES$^+$) $C_{14}H_{22}N_3O_3$ $[MH]^+$ calcd 280.1656; found 280.1668.

***tert*-Butyl 2-(3-*m*-tolylureido)ethylcarbamate (32c).** Yield: 59%, white amorphous solid; mp = 135 – 137 °C; FT-IR 3354 (br, carbamate N-H, str), 2978, 2940 (alkyl C-H, str), 1687 (carbamate C=O, str), 1658 (urea C=O, str), 1530 (aryl, str), 786 (aryl C-H bend *meta*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d$_6$) δ 8.43 (s, 1H, NH(C=O)N*H*Ar), 7.21 (s, 1H, aryl 2-H), 7.15 (d, *J* = 8.4 Hz, 1H, aryl 6-H), 7.08 (dd, *J* = 7.6/7.6 Hz, 1H, aryl 5-H), 6.86 (t, *J* = 5.2 Hz, 1H, N*H*(C=O)NHAr), 6.69 (d, *J* = 7.3 Hz, 1H, aryl 4-H), 6.12 (t, *J* = 5.5 Hz, 1H, O(C=O)N*H*), 3.11 (dt, *J* = 6.4/6.4 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.99 (dt, *J* = 5.8/5.8 Hz, 2H, C*H*$_2$NH(C=O)O), 2.23 (s, 3H, CH_3), 1.37 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (DMSO-d$_6$) δ 155.71, 155.26 (C=O), 140.43, 137.69 (4° C), 128.46 (aryl 5-C), 121.74 (aryl 4-C), 118.18 (aryl 2-C), 114.84 (aryl 6-C), 77.63 (Boc 4° C), 40.46, 39.02 (CH_2), 28.25 (Boc CH_3), 21.25 (CH_3); *m/z* HRMS (TOF ES$^+$) $C_{15}H_{24}N_3O_3$ $[MH]^+$ calcd 294.1812; found 294.1838.

***tert*-Butyl 2-(3-*p*-tolylureido)ethylcarbamate (32d).** Yield: 86%, white amorphous solid; mp = 145 – 147 °C; FT-IR 3345 (br, carbamate N-H, str), 2982, 2928 (alkyl C-H, str), 1680 (carbamate C=O, str), 1655 (urea C=O, str), 1520 (aryl, str), 823 (aryl C-H bend *para*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d$_6$) δ 8.39 (s, 1H, NH(C=O)N*H*Ar), 7.25 (d, *J* = 8.4 Hz, 2H, aryl 2-H and 6-H) 7.01 (d, *J* = 8.3 Hz, 2H, aryl 3-H and 5-H), 6.85 (t, *J* = 5.1 Hz, 1H, N*H*(C=O)NHAr), 6.09 (t, *J* = 5.5 Hz, 1H, O(C=O)N*H*), 3.10 (dt, *J* = 6.0/6.0 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.98 (dt, *J* = 5.8/5.8 Hz, 2H, C*H*$_2$NH(C=O)O), 2.20 (s, 3H, CH_3), 1.37 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (DMSO-d$_6$) δ 155.72, 155.35 (C=O), 137.96, 129.68 (4° C), 117.76, 129.03 (aryl CH), 77.63 (Boc 4° C), 40.50, 39.00 (CH_2), 28.26 (Boc CH_3), 20.31 (CH_3); *m/z* HRMS (TOF ES$^+$) $C_{15}H_{24}N_3O_3$ $[MH]^+$ calcd 294.1812; found 294.1839.

***tert*-Butyl 2-(3-(2-methoxyphenyl)ureido)ethylcarbamate (32e).** Yield: 76%, white amorphous solid; mp = 155 – 157 °C; FT-IR 3328 (br, carbamate N-H, str), 2978, 2927 (alkyl C-H, str), 1689 (carbamate C=O, str), 1650 (urea C=O, str), 1540 (aryl, str), 751 (aryl C-H bend *ortho*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d$_6$) δ 8.06 (dd, *J* = 7.5/2.0 Hz,1H, aryl 6-H), 7.91 (s, 1H, NH(C=O)N*H*Ar), 6.90 – 6.96 (m, 2H, aromatic C-H, N*H*(C=O)NHAr), 6.80 – 6.88 (m, 3H, aromatic C-H, O(C=O)N*H*), 3.82 (s, 3H, OC*H*$_3$), 3.10 (dt, *J* = 6.4/6.4 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.98 (dt, *J* =

5.9/5.9 Hz, 2H, C*H*$_2$NH(C=O)O), 1.37 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (DMSO-d$_6$) δ 155.66, 155.24 (C=O), 147.27, 129.46 (4° C), 120.93, 120.45, 110.54 (aromatic C-H), 117.94 (aryl 6-C), 77.63 (Boc 4° C), 55.64 (CH$_3$), 40.48, 38.70 (CH$_2$), 28.26 (Boc CH$_3$); *m/z* HRMS (TOF ES$^+$) $C_{15}H_{24}N_3O_4$ [MH]$^+$ calcd 310.1761; found 310.1763.

***tert*-Butyl 2-(3-(3-methoxyphenyl)ureido)ethylcarbamate (32f).** Yield: 93%, white amorphous solid; mp = 159 – 161 °C; FT-IR 3326 (br, carbamate N-H, str), 2978, 2926 (alkyl C-H, str), 2837 (O-CH$_3$, str, weak), 1678 (carbamate C=O, str), 1647 (urea C=O, str), 1513 (aryl, str), 787 (aryl C-H bend *meta*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d$_6$) δ 8.53 (s, 1H, NH(C=O)N*H*Ar), 7.13 (dd, *J* = 2.2/2.2 Hz, 1H, aryl 2-H), 7.10 (dd, *J* = 8.1/8.1 Hz, 1H, aryl 5-H), 6.83 – 6.87 (m, 2H, aryl 6-H, N*H*(C=O)NHAr), 6.46 (dd, *J* = 8.1/2.0 Hz, 1H, aryl 4-H), 6.14 (t, *J* = 5.6 Hz, 1H, O(C=O)N*H*), 3.70 (s, 3H, OC*H*$_3$), 3.11 (dt, *J* = 6.4/6.4 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.99 (dt, *J* = 5.8/5.8 Hz, 2H, C*H*$_2$NH(C=O)O), 1.37 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (DMSO-d$_6$) δ 159.63, 141.76 (4° C), 155.72, 155.19 (C=O), 129.35 (aryl 5-C), 110.00 (aryl 6-C), 106.42 (aryl 4-C), 103.41 (aryl 2-C), 77.65 (Boc 4° C), 54.83 (CH$_3$), 40.42, 38.99 (CH$_2$), 28.26 (Boc CH$_3$); *m/z* HRMS (TOF ES$^+$) $C_{15}H_{24}N_3O_4$ [MH]$^+$ calcd 310.1761; found 310.1744.

***tert*-Butyl 2-(3-(4-methoxyphenyl)ureido)ethylcarbamate (32g).** Yield: 72%, white amorphous solid; mp = 102 – 104 °C; FT-IR 3350 (br, carbamate N-H, str), 2971, 2939 (alkyl C-H, str), 2836 (O-CH$_3$, str, weak), 1684 (carbamate C=O, str), 1643 (urea C=O, str), 1511 (aryl, str), 829 (aryl C-H bend *para*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d$_6$) δ 8.31 (s, 1H, NH(C=O)N*H*Ar), 7.27 (d, *J* = 9.0 Hz, 2H, aryl 2-H and 6-H), 6.85 (t, *J* = 4.6 Hz, 1H, N*H*(C=O)NHAr), 6.80 (d, *J* = 9.0 Hz, 2H, aryl 3-H and 5-H), 6.04 (t, *J* = 5.6 Hz, 1H, O(C=O)N*H*) 3.68 (s, 3H, OC*H*$_3$), 3.10 (dt, *J* = 6.4/6.4 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.98 (dt, *J* = 5.8/5.8 Hz, 2H, C*H*$_2$NH(C=O)O), 1.37 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (DMSO-d$_6$) δ 155.72, 155.51 (C=O), 153.90, 133.65 (4° C), 119.42 (aryl 2-C and 6-C), 113.85 (aryl 3-C and 5-C), 77.63 (Boc 4° C), 55.12 (CH$_3$), 40.54, 38.81 (CH$_2$), 28.26 (Boc CH$_3$); *m/z* HRMS (TOF ES$^+$) $C_{15}H_{24}N_3O_4$ [MH]$^+$ calcd 310.1761; found 310.1769.

***tert*-Butyl 2-(3-(2-fluorophenyl)ureido)ethylcarbamate (32h).** Yield: 83%, white amorphous solid; mp = 181 – 183 °C; FT-IR 3368, 3331 (carbamate/urea N-H, str), 2981, 2935 (alkyl C-H, str), 1673 (carbamate C=O, str), 1661 (urea C=O, str), 1551 (aryl, str), 1256 (C-F, str), 752 (aryl C-H bend *ortho*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d$_6$) δ 8.32 (s, 1H, NH(C=O)N*H*Ar), 8.11 (dd, *J* = 7.2 Hz, 1H, aryl 5-H), 7.16 (ddd, *J* = 11.8/8.2/1.4 Hz, 1H, aryl 3-H), 7.06 (dd, *J* = 7.9/7.9 Hz, 1H, aryl 4-H), 6.85 – 6.93 (m, 2H, N*H*(C=O)NHAr, aryl 6-H), 6.66 (t, *J* = 5.5 Hz, 1H, O(C=O)N*H*), 3.12 (dt, *J* = 6.3/6.3 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.99 (dt, *J* = 5.8/5.8 Hz, 2H, C*H*$_2$NH(C=O)O), 1.37 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (DMSO-d$_6$) δ 155.71, 154.96 (C=O), 151.59 (J_{CF} = 240.6 Hz, CF), 128.33 (J_{CF} = 10.3 Hz, aryl 1-C), 124.35 (J_{CF} = 3.3 Hz, aryl 4-C), 121.48 (J_{CF} = 7.3 Hz, aryl 6-C), 120.16 (aryl 5-C), 114.77 (J_{CF} = 19.0 Hz, aryl 3-C), 77.65 (Boc 4° C), 40.35, 38.77 (CH$_2$), 28.25 (Boc CH$_3$); *m/z* HRMS (TOF ES$^+$) $C_{14}H_{21}FN_3O_3$ [MH]$^+$ calcd 298.1561; found 298.1550.

***tert*-Butyl 2-(3-(3-fluorophenyl)ureido)ethylcarbamate (32i).** Yield: 53%, white amorphous solid; mp = 114 – 116 °C; FT-IR 3353 (carbamate N-H, str), 2982, 2944 (alkyl C-H, str), 1679 (carbamate C=O, str), 1654 (urea C=O, str), 1515 (aryl, str), 1277 (C-F, str), 773 (aryl C-H bend *meta*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d$_6$) δ 8.78 (s, 1H, NH(C=O)N*H*Ar), 7.45 (ddd, *J* = 12.3/2.2/2.2 Hz, 1H, aryl 2-H), 7.22 (ddd, *J* = 8.2/8.2/8.2 Hz, 1H, aryl 5-H), 7.01 (dd, *J* = 8.2/1.1 Hz, 1H, aryl 6-H), 6.86 (t, *J* = 5.3 Hz, 1H, N*H*(C=O)NHAr), 6.68 (dd, *J* = 8.7/2.5 Hz, 1H, aryl 4-H), 6.22 (t, *J* = 5.5 Hz, 1H, O(C=O)N*H*), 3.12 (dt, *J* = 6.4/6.44 Hz, 2H, C*H*$_2$NH(C=O)NH), 3.00 (dt, *J* = 5.8/5.8 Hz, 2H, C*H*$_2$NH(C=O)O), 1.37 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (DMSO-d$_6$) δ 162.43 (J_{CF} = 240.0 Hz, CF), 155.73, 155.05 (C=O), 142.46 (J_{CF} = 11.5 Hz, aryl 1-C), 130.10 (J_{CF} = 9.8 Hz, aryl 5-C), 113.27 (aryl 6-C), 107.23 (J_{CF} = 21.3 Hz, aryl 4-C), 104.24 (J_{CF} = 26.5 Hz, aryl 2-C), 77.65 (Boc 4° C), 40.31, 39.04 (CH$_2$), 28.25 (Boc CH$_3$); *m/z* HRMS (TOF ES$^+$) $C_{14}H_{21}FN_3O_3$ [MH]$^+$ calcd 298.1561; found 298.1569.

***tert*-Butyl 2-(3-(4-fluorophenyl)ureido)ethylcarbamate (32j).** Yield: 85%, white amorphous solid; mp = 152 – 154 °C; FT-IR 3340 (carbamate N-H, str), 2979, 2940 (alkyl C-H, str), 1686 (carbamate C=O, str), 1639 (urea C=O, str), 1509 (aryl, str), 1286 (C-F, str), 834 (aryl C-H bend *para*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ 8.56 (s, 1H, NH(C=O)N*H*Ar), 7.38 (dd, *J* = 7.0/5.0 Hz, 2H, aryl 2-H and 6-H), 7.04 (dd, *J* = 8.9/8.9 Hz, 2H, aryl 3-H and 5-H), 6.86 (t, *J* = 5.3 Hz, 1H, N*H*(C=O)NHAr), 6.13 (t, *J* = 5.5 Hz, 1H, O(C=O)N*H*), 3.11 (dt, *J* = 6.4/6.44 Hz, 2H, CH_2NH(C=O)NH), 2.99 (dt, *J* = 5.8/5.8 Hz, 2H, CH_2NH(C=O)O), 1.37 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (DMSO-d_6) δ 156.86 (J_{CF} = 237.0 Hz, CF), 155.73, 155.33 (C=O), 136.91 (aryl 1-C), 119.22 (J_{CF} = 7.5 Hz, aryl 2-C and 6-C), 115.08 (J_{CF} = 22.0 Hz, aryl 3-C and 5-C), 77.64 (Boc 4° C), 40.43, 38.86 (CH_2), 28.26 (Boc CH_3); *m/z* HRMS (TOF ES$^+$) $C_{14}H_{21}FN_3O_3$ [MH]$^+$ calcd 298.1561; found 298.1550.

***tert*-Butyl 2-(3-(2-chlorophenyl)ureido)ethylcarbamate (32k).** Yield: 52%, white amorphous solid; mp = 167 – 169 °C; FT-IR 3332 (carbamate N-H, str), 2972, 2933 (alkyl C-H, str), 1673 (carbamate C=O, str), 1665 (urea C=O, str), 1528 (aryl, str), 751 (aryl C-H bend *ortho*-disubstituted aromatic ring), 656 (C-Cl, bend); ^{1}H NMR (DMSO-d_6) δ 8.14 (d, *J* = 8.2 Hz, 1H, aryl 6-H), 8.03 (s, 1H, NH(C=O)N*H*Ar), 7.38 (dd, *J* = 8.0/1.4 Hz, 1H, aryl 3-H), 7.23 (ddd, *J* = 7.8/7.8/1.4 Hz, 1H, aryl C-H), 7.07 (t, *J* = 5.3 Hz, 1H, N*H*(C=O)NHAr), 6.94 (dd, *J* = 7.8/1.5 Hz, 1H, aryl C-H), 6.87 (t, *J* = 5.2 Hz, 1H, O(C=O)N*H*), 3.13 (dt, *J* = 6.3/6.3 Hz, 2H, CH_2NH(C=O)NH), 3.00 (dt, *J* = 5.8/5.8 Hz, 2H, CH_2NH(C=O)O), 1.38 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (DMSO-d_6) δ 155.68, 154.85 (C=O), 136.73, 121.10 (4° C), 129.05 (aryl 3-C), 127.42, 122.38 (aryl C-H), 120.73 (aryl 6-C), 77.64 (Boc 4° C), 40.28, 38.96 (CH_2), 28.24 (Boc CH_3); *m/z* HRMS (TOF ES$^+$) $C_{14}H_{21}ClN_3O_3$ [MH]$^+$ calcd 314.1266; found 314.1274.

***tert*-Butyl 2-(3-(3-chlorophenyl)ureido)ethylcarbamate (32l).** Yield: 60%, white amorphous solid; mp = 117 – 119 °C; FT-IR 3341 (carbamate N-H, str), 2979, 2942 (alkyl C-H, str), 1685 (carbamate C=O, str), 1642 (urea C=O, str), 1528 (aryl, str), 780 (aryl C-H bend *meta*-disubstituted aromatic ring), 639 (C-Cl, bend); ^{1}H NMR (DMSO-d_6) δ 8.76 (s, 1H, NH(C=O)N*H*Ar), 7.66 (s, 1H, aryl 2-H), 7.21 (dd, *J* = 7.9/7.9 Hz, 1H, aryl 5-H), 7.17 (d, *J* = 8.2 Hz, 1H, aryl C-H), 6.92 (d, *J* = 7.7 Hz, 1H, aryl C-H), 6.87 (t, *J* = 5.1 Hz, 1H, N*H*(C=O)NHAr), 6.23 (t, *J* = 5.3 Hz, 1H, O(C=O)N*H*), 3.11 (dt, *J* = 6.1/6.1 Hz, 2H, CH_2NH(C=O)NH), 3.00 (dt, *J* = 5.8/5.8 Hz, 2H, CH_2NH(C=O)O), 1.37 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (DMSO-d_6) δ 155.73, 155.01 (C=O), 142.09, 133.07 (4° C), 130.22 (aryl 5-C), 120.57 (aryl C-H), 116.96 (aryl 2-C), 115.97 (aryl C-H), 77.65 (Boc 4° C), 40.28, 38.92 (CH_2), 28.25 (Boc CH_3); *m/z* HRMS (TOF ES$^+$) $C_{14}H_{21}ClN_3O_3$ [MH]$^+$ calcd 314.1266; found 314.1276.

***tert*-Butyl 2-(3-(4-chlorophenyl)ureido)ethylcarbamate (32m).** Yield: 82%, white amorphous solid; mp = 165 – 167 °C; FT-IR 3339 (carbamate N-H, str), 2979, 2941 (alkyl C-H, str), 1685 (carbamate C=O, str), 1641 (urea C=O, str), 1528 (aryl, str), 829 (aryl C-H bend *para*-disubstituted aromatic ring), 644 (C-Cl, bend); ^{1}H NMR (DMSO-d_6) δ 8.70 (s, 1H, NH(C=O)N*H*Ar), 7.41 (d, *J* = 8.9 Hz, 2H, aryl C-H), 7.25 (d, *J* = 8.9 Hz, 2H, aryl C-H), 6.86 (t, *J* = 5.3 Hz, 1H, N*H*(C=O)NHAr), 6.20 (t, *J* = 5.5 Hz, 1H, O(C=O)N*H*), 3.11 (dt, *J* = 6.4/6.4 Hz, 2H, CH_2NH(C=O)NH), 2.99 (dt, *J* = 5.8/5.8 Hz, 2H, CH_2NH(C=O)O), 1.37 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (DMSO-d_6) δ 155.73, 155.12 (C=O), 139.56, 124.42 (4° C), 128.45, 119.09 (aryl C-H), 77.65 (Boc 4° C), 40.35, 38.78 (CH_2), 28.25 (Boc CH_3); *m/z* HRMS (TOF ES$^+$) $C_{14}H_{21}ClN_3O_3$ [MH]$^+$ calcd 314.1266; found 314.1261.

***tert*-Butyl 2-(3-(2-bromophenyl)ureido)ethylcarbamate (32n).** Yield: 90%, white amorphous solid; mp = 136 – 138 °C; FT-IR 3345, 3312 (carbamate/urea N-H, str), 2976, 2926 (alkyl C-H, str), 1686 (carbamate C=O, str), 1657 (urea C=O, str), 1539 (aryl, str), 745 (aryl C-H bend *ortho*-disubstituted aromatic ring), 663 (C-Br, bend); ^{1}H NMR (DMSO-d_6) δ 8.06 (d, *J* = 8.2 Hz, 1H, aryl 6-H), 7.85 (s, 1H, NH(C=O)N*H*Ar), 7.54 (dd, *J* = 8.0/1.4 Hz, 1H, aryl 3-H), 7.27 (ddd, *J* = 7.8/7.8/1.4 Hz, 1H, aryl C-H), 7.14 (t, *J* = 5.4 Hz, 1H, N*H*(C=O)NHAr), 6.85 – 6.90 (m, 2H, aryl C-H, O(C=O)N*H*), 3.12 (dt, *J* = 6.4/6.4 Hz, 2H, CH_2NH(C=O)NH), 3.01 (dt, *J* = 5.8/5.8 Hz, 2H, CH_2NH(C=O)O), 1.38 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (DMSO-d_6) δ 155.67, 154.87 (C=O), 137.83, 112.15 (4° C), 132.33 (aryl 3-C), 127.91, 123.13 (aryl C-H), 121.53 (aryl 6-C), 77.63 (Boc 4° C),

40.29, 39.00 (CH_2), 28.24 (Boc CH_3). *m/z* HRMS (TOF ES^+) $C_{14}H_{21}BrN_3O_3$ $[MH]^+$ calcd 358.0761; found 358.0760.

***tert*-Butyl 2-(3-(3-bromophenyl)ureido)ethylcarbamate (32o).** Yield: 85%, white amorphous solid; mp = 122 - 124°C; FT-IR 3338 (carbamate N-H, str), 2979, 2940 (alkyl C-H, str), 1685 (carbamate C=O, str), 1645 (urea C=O, str), 1539 (aryl, str), 778 (aryl C-H bend *meta*-disubstituted aromatic ring), 682 (C-Br, bend); ^{1}H NMR (DMSO-d_6) δ 8.76 (s, 1H, NH(C=O)N*H*Ar), 7.81 (dd, *J* = 1.8/1.8 Hz, 1H, aryl 2-H), 7.21 (ddd, *J* = 8.5/1.4/1.4 Hz, 1H, aryl C-H), 7.16 (dd, *J* = 7.8/7.8 Hz, 1H, aryl 5-H), 7.05 (ddd, *J* = 7.7/1.2/1.2 Hz, 1H, aryl C-H), 6.86 (t, *J* = 5.3 Hz, 1H, N*H*(C=O)NHAr), 6.24 (t, *J* = 5.5 Hz, 1H, O(C=O)N*H*), 3.11 (dt, *J* = 6.3/6.3 Hz, 2H, C*H*$_2$NH(C=O)NH), 3.00 (dt, *J* = 5.8/5.8 Hz, 2H, C*H*$_2$NH(C=O)O), 1.37 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (DMSO-d_6) δ 155.73, 155.00 (C=O), 142.25, 121.66 (4° C), 130.55 (aryl 5-C), 123.47 (aryl C-H), 119.83 (aryl 2-C), 116.36 (aryl C-H), 77.65 (Boc 4° C), 40.28, 38.89 (CH_2), 28.25 (Boc CH_3); *m/z* HRMS (TOF ES^+) $C_{14}H_{21}BrN_3O_3$ $[MH]^+$ calcd 358.0761; found 358.0750.

***tert*-Butyl 2-(3-(4-bromophenyl)ureido)ethylcarbamate (32p).** Yield: 86%, white amorphous solid; mp = 192 – 194 °C; FT-IR 3337 (carbamate N-H, str), 2978, 2938 (alkyl C-H, str), 1686 (carbamate C=O, str), 1643 (urea C=O, str), 1528 (aryl, str), 826 (aryl C-H bend *para*-disubstituted aromatic ring), 641 (C-Br, bend); ^{1}H NMR (DMSO-d_6) δ 8.70 (s, 1H, NH(C=O)N*H*Ar), 7.37 (s, 4H, aryl C-H), 6.86 (t, *J* = 5.3 Hz, 1H, N*H*(C=O)NHAr), 6.20 (t, *J* = 5.5 Hz, 1H, O(C=O)N*H*), 3.11 (dt, *J* = 6.3/6.3 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.99 (dt, *J* = 5.8/5.8 Hz, 2H, C*H*$_2$NH(C=O)O), 1.37 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (DMSO-d_6) δ 155.71, 155.06 (C=O), 139.96, 112.23 (4° C), 131.32, 119.51 (aryl C-H), 77.63 (Boc 4° C), 40.33, 38.85 (CH_2), 28.24 (Boc CH_3); *m/z* HRMS (TOF ES^+) $C_{14}H_{21}BrN_3O_3$ $[MH]^+$ calcd 358.0761; found 358.0767.

***tert*-Butyl 2-(3-(2-(trifluoromethyl)phenyl)ureido)ethylcarbamate (32q).** Yield: 95%, white amorphous solid; mp = 149 – 151 °C; FT-IR 3331 (carbamate N-H, str), 2979, 2931 (alkyl C-H, str), 1688 (carbamate C=O, str), 1654 (urea C=O, str), 1541 (aryl, str), 1322 (C-F, str), 766 (aryl C-H bend *ortho*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ 7.96 (d, *J* = 8.2 Hz, 1H, aryl C-H), 7.80 (s, 1H, NH(C=O)N*H*Ar), 7.60 (d, *J* = 7.9 Hz, 1H, aryl C-H), 7.56 (dd, *J* = 8.1/8.1 Hz, 1H, aryl C-H), 7.17 (dd, *J* = 7.4/7.4 Hz, 1H, aryl C-H), 7.03 – 7.10 (m, 1H, N*H*(C=O)NHAr), 6.82 – 6.90 (m, 1H, O(C=O)N*H*), 3.08 – 3.18 (m, 2H, C*H*$_2$NH(C=O)NH), 2.95 - 3.06 (m, 2H, C*H*$_2$NH(C=O)O), 1.38 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (DMSO-d_6) δ 155.70, 155.07 (C=O), 137.36 (4° C), 132.74, 124.64, 122.59 (aryl C-H), 125.77 (J_{CF} = 5.3 Hz, aryl C-H), 124.10 (J_{CF} = 273.0 Hz, CF_3), 77.65 (Boc 4° C), 40.27, 38.90 (CH_2), 28.24 (Boc CH_3); *m/z* HRMS (TOF ES^+) $C_{15}H_{21}F_3N_3O_3$ $[MH]^+$ calcd 348.1530; found 348.1529.

***tert*-Butyl 2-(3-(3-(trifluoromethyl)phenyl)ureido)ethylcarbamate (31r).** Yield: 90%, white amorphous solid; mp = 102 – 103 °C; FT-IR 3338 (carbamate N-H, str), 2980, 2937 (alkyl C-H, str), 1686 (carbamate C=O, str), 1654 (urea C=O, str), 1569 (aryl, str), 1339 (C-F, str), 795 (aryl C-H bend *meta*-disubstituted aromatic ring), 700 (C-F, bend); ^{1}H NMR (DMSO-d_6) δ 8.93 (s, 1H, NH(C=O)N*H*Ar), 7.97 (s, 1H, aryl 2-H), 7.49 (d, *J* = 8.3 Hz, 1H, aryl 6-H), 7.43 (dd, *J* = 7.6/7.6 Hz, 1H, aryl 5-H), 7.21 (d, *J* = 7.4 Hz, 1H, aryl 4-H), 6.87 (t, *J* = 5.1 Hz, 1H, N*H*(C=O)NHAr), 6.28 (t, *J* = 5.2 Hz, 1H, O(C=O)N*H*), 3.13 (dt, *J* = 6.3/6.3 Hz, 2H, C*H*$_2$NH(C=O)NH), 3.01 (dt, *J* = 5.8/5.8 Hz, 2H, C*H*$_2$NH(C=O)O), 1.37 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (DMSO-d_6) δ 155.75, 155.12 (C=O), 141.40, (4° C), 129.73 (aryl 5-C), 129.41 (J_{CF} = 30.9 Hz, aryl 3-C), 124.31 (J_{CF} = 272.3 Hz, CF_3), 121.11 (aryl 6-C), 117.19 (J_{CF} = 4.2 Hz, aryl 4-C), 113.52 (J_{CF} = 4.1 Hz, aryl 2-C), 77.66 (Boc 4° C), 40.27, 38.94 (CH_2), 28.25 (Boc CH_3); *m/z* HRMS (TOF ES^+) $C_{15}H_{21}F_3N_3O_3$ $[MH]^+$ calcd 348.1530; found 348.1540.

***tert*-Butyl 2-(3-(4-(trifluoromethyl)phenyl)ureido)ethylcarbamate (32s).** Yield: 63%, white amorphous solid; mp = 194 – 196 °C; FT-IR 3391, 3336 (urea/carbamate N-H, str), 2981, 2935 (alkyl C-H, str), 1699 (carbamate C=O, str), 1666 (urea C=O, str), 1553 (aryl, str), 1329 (C-F, str), 838 (aryl C-H bend *para*-disubstituted aromatic ring), 657 (C-F, bend); ^{1}H NMR (DMSO-d_6) δ 8.99 (s, 1H,

NH(C=O)N*H*Ar), 7.59 (d, *J* = 9.1 Hz, 2H, aryl C-H), 7.55 (d, *J* = 9.1 Hz, 2H, aryl C-H), 6.88 (t, *J* = 5.3 Hz, 1H, N*H*(C=O)NHAr), 6.31 (t, *J* = 5.5 Hz, 1H, O(C=O)N*H*), 3.13 (dt, *J* = 6.3/6.3 Hz, 2H, C*H*$_2$NH(C=O)NH), 3.01 (dt, *J* = 5.8/5.8 Hz, 2H, C*H*$_2$NH(C=O)O), 1.37 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (DMSO-d$_6$) δ 155.74, 154.91 (C=O), 144.26, 121.07 (4° C), 125.96 (J_{CF} = 3.7 Hz, aryl 3-C and 5-C), 122.04 (J_{CF} = 226.7 Hz, CF$_3$), 117.19 (aryl 2-C and 6-C), 77.66 (Boc 4° C), 40.24, 38.89 (CH$_2$), 28.24 (Boc CH$_3$); *m/z* HRMS (TOF ES$^+$) $C_{15}H_{21}F_3N_3O_3$ [MH]$^+$ calcd 348.1530; found 348.1516.

General procedure for synthesis of phenyl substituted 1-(2-aminoethyl)-3-(phenyl)urea hydrochlorides (33a and 33c-r). The desired phenyl substituted Boc-protected phenylurea (compounds **32a** and **32c-r**) was dissolved in MeOH (6 mL) with the aid of sonication and heat if necessary. This was then added to vigorously stirred concentrated aqueous HCl (5 mL) and stirred for 3 hours. All solvents were removed under reduced pressure, and the resulting hydrochloride salts of the desired compounds were freeze-dried.

1-(2-Aminoethyl)-3-phenylurea hydrochloride (33a). Yield: 92%, white amorphous solid; mp = 186 – 188 °C; FT-IR 3329, 3234 (urea N-H, str), 2958 (NH$_3^+$, str), 2761, 2681 (alkyl C-H, str), 1660 (urea C=O, str), 1597, 1499 (NH$_3^+$, bend), 1563 (aryl, str), 764, 693 (aryl C-H bend phenyl ring); ^{1}H NMR (DMSO-d$_6$) δ 8.93 (s, 1H, NH(C=O)N*H*Ph), 7.89 (br s, 3H, NH$_3^+$), 7.41 (d, *J* = 7.6 Hz, 2H, 2-H and 6-H phenyl ring), 7.22 (dd, *J* = 7.5/7.5 Hz, 2H, 3-H and 5-H phenyl ring), 6.90 (dd, *J* = 7.3/7.3 Hz, 1H, 4-H phenyl ring), 6.34 (t, *J* = 5.7 Hz, N*H*(C=O)NHPh), 3.30 – 3.34 (m, 2H, C*H*$_2$NH(C=O)NH), 2.83 – 2.93 (m, 2H, C*H*$_2$NH$_3^+$); ^{13}C NMR (DMSO-d$_6$) δ 155.76 (C=O), 140.33 (4° C), 128.64 (phenyl 3-C and 5-C), 121.23 (phenyl 4-C), 117.80 (phenyl 2-C and 6-C), 39.12, 37.17 (*C*H$_2$); *m/z* HRMS (TOF ES$^+$) $C_9H_{14}N_3O$ [MH]$^+$ calcd 180.1131; found 180.1140.

1-(2-Aminoethyl)-3-(3-methylphenyl)urea hydrochloride (33c). Yield: 100%, white amorphous solid; mp = 185 – 187 °C; FT-IR 3323 (urea N-H, str), 3009 (NH$_3^+$, str), 2753 (alkyl C-H, str), 1677 (urea C=O, str), 1612, 1489 (NH$_3^+$, bend), 1567 (aryl, str), 775 (aryl C-H bend *meta*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d$_6$) δ 9.01 (s, 1H, NH(C=O)N*H*Ar), 8.02 (br s, 3H, NH$_3^+$), 7.18 – 7.25 (m, 2H, aryl 2-H, aryl C-H), 7.09 (dd, *J* = 7.7/7.7 Hz, 1H, aryl 5-H), 6.67 – 6.75 (m, 2H, aryl C-H, N*H*(C=O)NHAr), 3.31 (dt, *J* = 6.2/6.2 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.87 (t, *J* = 6.2 Hz, C*H*$_2$NH$_3^+$), 2.23 (s, 3H, CH$_3$); ^{13}C NMR (DMSO-d$_6$) δ 155.82 (C=O), 140.33, 137.67 (4° C), 128.46 (aryl 5-C), 121.90, 118.25, 114.94 (aryl C-H), 39.04 (*C*H$_2$NH$_3^+$), 37.14 (*C*H$_2$NH(C=O)NH), 21.26 (CH$_3$); *m/z* HRMS (TOF ES$^+$) $C_{10}H_{16}N_3O$ [MH]$^+$ calcd 194.1288; found 194.1289.

1-(2-Aminoethyl)-3-(4-methylphenyl)urea hydrochloride (33d). Yield: 96%, white amorphous solid; mp = 214 – 216 °C (lit. 213 °C);[4] FT-IR 3312 (urea N-H, str), 3005 (NH$_3^+$, str), 1670 (urea C=O, str), 1603, 1512 (NH$_3^+$, bend), 1558 (aryl, str), 810 (aryl C-H bend *para*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d$_6$) δ 8.95 (s, 1H, NH(C=O)N*H*Ar), 8.01 (br s, 3H, NH$_3^+$), 7.29 (d, *J* = 8.4 Hz, 2H, aryl 2-H and 6-H), 7.02 (d, *J* = 8.4 Hz, 2H, aryl 3-H and 5-H), 6.63 (t, *J* = 5.8 Hz, 1H, N*H*(C=O)NHAr), 3.31 (dt, *J* = 6.2/6.2 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.86 (t, *J* = 6.2 Hz, 2H, C*H*$_2$NH$_3^+$), 2.20 (s, 3H, CH$_3$); ^{13}C NMR (DMSO-d$_6$) δ 155.85 (C=O), 137.82, 129.84 (4° C), 129.01 (aryl 3-C and 5-C), 117.84 (aryl 2-C and 6-C), 39.07 (*C*H$_2$NH$_3^+$), 37.13 (*C*H$_2$NH(C=O)NH), 20.32 (CH$_3$); *m/z* HRMS (TOF ES$^+$) $C_{10}H_{16}N_3O$ [MH]$^+$ calcd 194.1288; found 194.1283.

1-(2-Aminoethyl)-3-(2-methoxyphenyl)urea hydrochloride (33e). Yield: 85%, white amorphous solid; mp = 156 - 158°C; FT-IR 3373, 3282 (urea N-H, str), 2998 (NH$_3^+$, str), 1647 (urea C=O, str), 1576, 1499 (NH$_3^+$, bend), 1533 (aryl, str), 755 (aryl C-H bend *ortho*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d$_6$) δ 8.05 (dd, *J* = 7.8/1.8 Hz, 1H, aryl 6-H), 8.03 (s, 1H, NH(C=O)N*H*Ar), 8.00 (br s, 3H, NH$_3^+$), 7.19 – 7.26 (m, 1H, N*H*(C=O)NHAr), 6.96 (dd, *J* = 7.9/1.6 Hz, 1H, aryl 3-H), 6.88 (ddd, *J* = 7.4/7.4/1.8 Hz, 1H, aryl C-H), 6.84 (ddd, *J* = 7.8/7.8/1.7 Hz, 1H, aryl C-H), 3.82 (s, 3H, CH$_3$), 3.31 (dt, *J* = 6.1/6.1 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.87 (tq, *J* = 5.8/5.8 Hz, C*H*$_2$NH$_3^+$); ^{13}C NMR (DMSO-d$_6$) δ 156.06 (C=O), 147.90, 129.61 (4° C), 121.75, 120.89 (aryl C-H), 118.62 (aryl 6-H), 111.10 (aryl 3-H), 56.13 (CH$_3$), 39.63 (*C*H$_2$NH$_3^+$), 37.50 (*C*H$_2$NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_{10}H_{16}N_3O_2$ [MH]$^+$ calcd 210.1237; found 210.1234.

1-(2-Aminoethyl)-3-(3-methoxyphenyl)urea hydrochloride (33f). Yield: 99%, white amorphous solid; mp = 183 – 188 °C; FT-IR 3389, 3301 (urea N-H, str), 2883 (NH_3^+, str), 1658 (urea C=O, str), 1576, 1497 (NH_3^+, bend), 1522 (aryl, str), 785 (aryl C-H bend *meta*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ 9.03 (s, 1H, NH(C=O)N*H*Ar), 7.95 (br s, 3H, NH_3^+), 7.16 (dd, *J* = 2.2/2.2 Hz, 1H, aryl 2-H), 7.11 (dd, *J* = 8.1/8.1 Hz, 1H, aryl 5-H), 6.89 (dd, *J* = 8.1/1.7 Hz, 1H, aryl 6-H), 6.61(t, *J* = 5.7 Hz, 1H, N*H*(C=O)NHAr), 6.48 (dd, *J* = 8.1/2.4 Hz, 1H, aryl 4-H), 3.69 (s, 3H, CH_3), 3.32 (dt, *J* = 6.2/6.2 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.87 (tq, *J* = 5.9/5.9 Hz, C*H*$_2$$NH_3^+$); ^{13}C NMR (DMSO-$d_6$) δ 159.60, 141.60 (4° C), 155.69 (C=O), 129.36 (aryl 5-C), 110.15 (aryl 6-C), 106.53 (aryl 4-C), 103.60 (aryl 2-C), 54.86 (CH_3), 39.06 (*C*$H_2NH_3^+$), 37.13 (*C*H_2NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_{10}H_{16}N_3O_2$ $[MH]^+$ calcd 210.1237; found 210.1216.

1-(2-Aminoethyl)-3-(4-methoxyphenyl)urea hydrochloride (33g). Yield: 88%, white amorphous solid; mp = 180 – 182 °C; FT-IR 3335 (urea N-H, str), 3007 (NH_3^+, str), 1629 (urea C=O, str), 1508 (NH_3^+, bend), 1570 (aryl, str), 827 (aryl C-H bend *para*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ 8.75 (s, 1H, NH(C=O)N*H*Ar), 7.93 (br s, 3H, NH_3^+), 7.30 (d, *J* = 9.1 Hz, 2H, aryl 2-H and 6-H), 6.81 (d, *J* = 9.1 Hz, 2H, aryl 3-H and 5-H), 6.47 (t, *J* = 5.8 Hz, 1H, N*H*(C=O)NHAr), 3.69 (s, 3H, CH_3), 3.33 (dt, *J* = 6.1/6.1 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.86 (tq, *J* = 5.8/5.8 Hz, C*H*$_2$$NH_3^+$); ^{13}C NMR (DMSO-$d_6$) δ 156.44, 154.49, 133.88 (4° C), 120.05 (aryl 2-C and 6-C), 114.30 (aryl 3-C and 5-C), 55.59 (CH_3), 39.90 (*C*$H_2NH_3^+$), 37.67 (*C*H_2NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_{10}H_{16}N_3O_2$ $[MH]^+$ calcd 210.1237; found 210.1237.

1-(2-Aminoethyl)-3-(2-fluorophenyl)urea hydrochloride (33h). Yield: 97%, white amorphous solid; mp = 208 – 210 °C; FT-IR 3320 (urea N-H, str), 3011 (NH_3^+, str), 2755 (alkyl C-H, str), 1678 (urea C=O, str), 1605, 1490 (NH_3^+, bend), 1561 (aryl, str), 1258 (C-F, str), 745 (aryl C-H bend *ortho*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ 8.57 (d, *J* = 2.1 Hz, 1H, NH(C=O)N*H*Ar), 8.05 - 8.10 (m, 4H, aryl C-H, NH_3^+), 7.11 – 7.21 (m, 2H, aryl 3-H, N*H*(C=O)NHAr), 7.08 (dd, *J* = 7.8/7.8 Hz, 1H, aryl C-H), 6.90 – 6.96 (m, 1H, aryl C-H), 3.34 (dt, *J* = 6.0/6.0 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.88 (t, *J* = 6.2 Hz, 2H, C*H*$_2$$NH_3^+$); ^{13}C NMR (DMSO-$d_6$) δ 155.44 (C=O), 151.85 (J_{CF} = 241.2 Hz, C-F), 128.65 (J_{CF} = 10.3 Hz, aryl 1-C), 124.34 (J_{CF} = 3.6 Hz, aryl C-H), 121.93 (J_{CF} = 7.4 Hz, aryl C-H), 120.64 (aryl C-H), 114.90 (J_{CF} = 19.1 Hz, aryl 3-C), 38.82 (*C*$H_2NH_3^+$), 37.11 (*C*H_2NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_9H_{13}FN_3O$ $[MH]^+$ calcd 198.1037; found 198.1034.

1-(2-Aminoethyl)-3-(3-fluorophenyl)urea hydrochloride (33i). Yield: 91%, white amorphous solid; mp = 184 – 186 °C; FT-IR 3310 (urea N-H, str), 3005 (NH_3^+, str), 2686 (alkyl C-H, str), 1678 (urea C=O, str), 1610, 1494 (NH_3^+, bend), 1558 (aryl, str), 1271 (C-F, str), 785 (aryl C-H bend *meta*-disubstituted aromatic ring), 682 (C-F, bend); ^{1}H NMR (DMSO-d_6) δ 9.42 (s, 1H, NH(C=O)N*H*Ar), 8.00 (br s, 3H, NH_3^+), 7.46 (ddd, *J* = 12.3/2.2/2.2 Hz, 1H, aryl 2-H), 7.23 (ddd, *J* = 8.2/8.2/7.0 Hz, 1H, aryl 5-H), 7.06 (dd, *J* = 8.2/1.8 Hz, 1H, aryl 6-H), 6.76 (t, *J* = 5.8 Hz, 1H, N*H*(C=O)NHAr), 6.69 (ddd, *J* = 8.7/8.7/2.5 Hz, 1H, aryl 4-H), 3.33 (dt, *J* = 6.2/6.2 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.87 (tq, *J* = 5.4/5.4 Hz, 2H, C*H*$_2$$NH_3^+$); ^{13}C NMR (DMSO-$d_6$) δ 162.40 ($J_{CF}$ = 240.1 Hz, C-F), 155.58 (C=O), 142.37 (J_{CF} = 11.6 Hz, aryl 1-C), 130.13 (J_{CF} = 9.7 Hz, aryl 5-C), 113.38 (J_{CF} = 2.2 Hz, aryl 6-C), 107.39 (J_{CF} = 21.2 Hz, aryl 4-C), 104.31 (J_{CF} = 26.5 Hz, aryl 2-C), 39.19 (*C*$H_2NH_3^+$), 37.09 (*C*H_2NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_9H_{13}FN_3O$ $[MH]^+$ calcd 198.1037; found 198.1027.

1-(2-Aminoethyl)-3-(4-fluorophenyl)urea hydrochloride (33j). Yield: 100%, white amorphous solid; mp = 203 – 205 °C; FT-IR 3336 (urea N-H, str), 3012 (NH_3^+, str), 1647 (urea C=O, str), 1615, 1509 (NH_3^+, bend), 1565 (aryl, str), 1225 (C-F, str), 827 (aryl C-H bend *para*-disubstituted aromatic ring), 756 (C-F, bend); ^{1}H NMR (DMSO-d_6) δ 9.17 (s, 1H, NH(C=O)N*H*Ar), 8.02 (br s, 3H, NH_3^+), 7.42 (dd, *J* = 9.2/5.0 Hz, 2H, aryl 2-H and 6-H), 7.05 (dd, *J* = 8.9/8.9 Hz, 2H, aryl 3-H and 5-H), 6.62 – 6.73 (m, 1H, N*H*(C=O)NHAr), 3.27 – 3.38 (m, 2H, C*H*$_2$NH(C=O)NH), 2.86 (tq, *J* = 5.7/5.7 Hz, 2H, C*H*$_2$$NH_3^+$); ^{13}C NMR (DMSO-$d_6$) δ 156.93 ($J_{CF}$ = 237.2 Hz, C-F), 155.83 (C=O), 136.81 (J_{CF} = 2.3 Hz, 1-C), 119.31 (J_{CF} = 7.5 Hz, aryl 2-C and 6-C), 115.09 (J_{CF} = 22.0 Hz, aryl 3-C and 5-C), 39.07 (*C*$H_2NH_3^+$), 37.15 (*C*H_2NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_9H_{13}FN_3O$ $[MH]^+$ calcd 198.1037; found 198.1021.

1-(2-Aminoethyl)-3-(2-chlorophenyl)urea hydrochloride (33k). Yield: 80%, white amorphous solid; mp = 205 – 207 °C; FT-IR 3327 (urea N-H, str), 2978 (NH_3^+, str), 2748 (alkyl C-H, str), 1675 (urea C=O, str), 1589, 1528 (NH_3^+, bend), 1567 (aryl, str), 748 (aryl C-H bend *ortho*-disubstituted aromatic ring), 627 (C-Cl, bend); ^{1}H NMR (DMSO-d_6) δ 8.44 (br s, 1H, NH(C=O)N*H*Ar), 8.12 (dd, *J* = 8.3/1.5 Hz, 1H, aryl C-H), 8.07 (br s, 3H, NH_3^+), 7.52 (t, *J* = 5.6 Hz, 1H, N*H*(C=O)NHAr), 7.40 (dd, *J* = 8.0/1.5 Hz, 1H, aryl C-H), 7.24 (dd, *J* = 7.8/1.4 Hz, 1H, aryl C-H), 6.96 (dd, *J* = 7.8/1.5 Hz, 1H, aryl C-H), 3.31 – 3.39 (m, 2H, C*H*$_2$NH(C=O)NH), 2.89 (br s, 2H, C*H*$_2$$NH_3^+$); ^{13}C NMR (DMSO-$d_6$) δ 155.78 (C=O), 136.97, 121.98 (4° C), 129.58, 127.87, 123.19, 121.51 (aryl C-H), 38.93 (*C*$H_2NH_3^+$), 37.54 (*C*H_2NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_9H_{13}ClN_3O$ $[MH]^+$ calcd 214.0742; found 214.0724.

1-(2-Aminoethyl)-3-(3-chlorophenyl)urea hydrochloride (33l). Yield: 92%, white amorphous solid; mp = 193 – 195 °C; FT-IR 3319 (urea N-H, str), 3009 (NH_3^+, str), 1681 (urea C=O, str), 1598, 1506 (NH_3^+, bend), 1558 (aryl, str), 774 (aryl C-H bend *meta*-disubstituted aromatic ring), 680 (C-Cl, bend); ^{1}H NMR (DMSO-d_6) δ 9.25 (s, 1H, NH(C=O)N*H*Ar), 7.86 (br s, 3H, NH_3^+), 7.66 – 7.70 (m, 1H, aryl 2-H), 7.20 – 7.27 (m, 2H, aryl C-H), 6.94 (ddd, *J* = 6.7/2.2/2.2 Hz, 1H, aryl C-H), 6.62 (t, *J* = 5.8 Hz, 1H, N*H*(C=O)NHAr), 3.32 (dt, *J* = 6.2/6.2 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.88 (tq, *J* = 5.8/5.8 Hz, 2H, C*H*$_2$$NH_3^+$); ^{13}C NMR (DMSO-$d_6$) δ 155.53 (C=O), 141.95, 133.06 (4° C), 130.27, 120.79, 116.10 (aryl C-H), 117.11 (aryl 2-C), 39.70 (*C*$H_2NH_3^+$), 37.16 (*C*H_2NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_9H_{13}ClN_3O$ $[MH]^+$ calcd 214.0742; found 214.0737.

1-(2-Aminoethyl)-3-(4-chlorophenyl)urea hydrochloride (33m). Yield: 94%, white amorphous solid. Mp = 223 – 225 °C; FT-IR 3380, 3307 (urea N-H, str), 2879 (NH_3^+, str), 1647 (urea C=O, str), 1593, 1491 (NH_3^+, bend), 1518 (aryl, str), 836 (aryl C-H bend *para*-disubstituted aromatic ring), 647 (C-Cl, bend); ^{1}H NMR (DMSO-d_6) δ 9.25 (s, 1H, NH(C=O)N*H*Ar), 7.95 (br s, 3H, NH_3^+), 7.45, 7.27 (d, *J* = 8.9 Hz, 2 x 2H, aryl C-H), 6.67 (t, *J* = 5.8 Hz, 1H, N*H*(C=O)NHAr), 3.32 (dt, *J* = 6.2/6.2 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.87 (tq, *J* = 5.7/5.7 Hz, 2H, C*H*$_2$$NH_3^+$); ^{13}C NMR (DMSO-$d_6$) δ 155.61 (C=O), 139.43, 124.59 (4° C), 128.47, 119.19 (aryl C-H), 39.24 (*C*$H_2NH_3^+$), 37.13 (*C*H_2NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_9H_{13}ClN_3O$ $[MH]^+$ calcd 214.0742; found 214.0732.

1-(2-Aminoethyl)-3-(2-bromophenyl)urea hydrochloride (33n). Yield: 89%, white amorphous solid; mp = 195 – 197 °C; FT-IR 3329 (urea N-H, str), 3014 (NH_3^+, str), 2743 (alkyl C-H, str), 1676 (urea C=O, str), 1582, 1527 (NH_3^+, bend), 1558 (aryl, str), 749 (aryl C-H bend *ortho*-disubstituted aromatic ring), 668 (C-Br, bend); ^{1}H NMR (DMSO-d_6) 8.09 (br s, 3H, NH_3^+), 7.99 – 8.06 (m, 2H, NH(C=O)N*H*Ar, aryl C-H), 7.54 – 7.60 (m, 2H, N*H*(C=O)NHAr, aryl C-H), 7.28 (dd, *J* = 7.8/1.4 Hz, 1H, aryl C-H), 6.91 (dd, *J* = 8.0/1.6 Hz, 1H, aryl C-H), 3.29 – 3.38 (m, 2H, C*H*$_2$NH(C=O)NH), 2.89 (tq, *J* = 5.6/5.6 Hz, 2H, C*H*$_2$$NH_3^+$); ^{13}C NMR (DMSO-$d_6$) δ 155.34 (C=O), 137.63, 112.60 (4° C), 132.41, 127.94, 123.50, 121.87 (aryl C-H), 38.79 (*C*$H_2NH_3^+$), 37.12 (*C*H_2NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_9H_{13}BrN_3O$ $[MH]^+$ calcd 258.0237; found 258.0211.

1-(2-Aminoethyl)-3-(3-bromophenyl)urea hydrochloride (33o). Yield: 98%, white amorphous solid; mp = 196 – 198 °C; FT-IR 3324 (urea N-H, str), 3009 (NH_3^+, str), 1680 (urea C=O, str), 1589, 1495 (NH_3^+, bend), 1556 (aryl, str), 772 (aryl C-H bend *meta*-disubstituted aromatic ring), 680 (C-Br, bend); ^{1}H NMR (DMSO-d_6) δ 9.41 (s, 1H, NH(C=O)N*H*Ar), 7.98 (br s, 3H, NH_3^+), 7.82 (dd, *J* = 1.9/1.9 Hz, 1H, aryl 2-H), 7.28 (ddd, *J* = 8.2/1.9/0.9 Hz, 1H, aryl C-H), 7.17 (dd, *J* = 8.0/8.0 Hz, 1H, aryl 5-H), 7.06 (ddd, *J* = 7.9/1.9/1.0 Hz, 1H, aryl C-H), 6.76 (t, *J* = 5.8 Hz, 1H, N*H*(C=O)NHAr), 3.32 (dt, *J* = 6.3/6.3 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.87 (t, *J* = 5.8 Hz, 2H, C*H*$_2$$NH_3^+$); ^{13}C NMR (DMSO-$d_6$) δ 155.52 (C=O), 142.14, 121.59 (4° C), 130.27 (aryl 5-C), 123.58, 116.39 (aryl C-H), 119.85 (aryl 2-C), 39.19 (*C*$H_2NH_3^+$), 37.10 (*C*H_2NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_9H_{13}BrN_3O$ $[MH]^+$ calcd 258.0237; found 258.0213.

1-(2-Aminoethyl)-3-(4-bromophenyl)urea hydrochloride (33p). Yield: 99%, white amorphous solid; mp = 229 – 231 °C (lit. 234 °C)[4]; FT-IR 3292 (urea N-H, str), 3010 (NH_3^+, str), 1675 (urea

C=O, str), 1590, 1487 (NH_3^+, bend), 1553 (aryl, str), 820 (aryl C-H bend *para*-disubstituted aromatic ring), 621 (C-Br, bend); ^{1}H NMR (DMSO-d_6) δ 9.30 (s, 1H, NH(C=O)N*H*Ar), 7.98 (br s, 3H, NH_3^+), 7.37 - 7.43 (m, 4H, aryl C-H), 6.71 (t, *J* = 5.8 Hz, 1H, N*H*(C=O)NHAr), 3.32 (dt, *J* = 6.3/6.3 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.87 (t, *J* = 5.6 Hz, 2H, C*H*$_2$$NH_3^+$); ^{13}C NMR (DMSO-$d_6$) δ 155.59 (C=O), 139.88, 112.42 (4° C), 131.35, 119.61 (aryl C-H), 39.21 (*C*$H_2NH_3^+$), 37.12 (*C*H$_2$NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_9H_{13}BrN_3O$ $[MH]^+$ calcd 258.0237; found 258.0211.

1-(2-Aminoethyl)-3-(2-trifluoromethylphenyl)urea hydrochloride (33q). Yield: 97%, white amorphous solid; mp = 153 – 155 °C; FT-IR 3317 (urea N-H, str), 2998 (NH_3^+, str), 1636 (urea C=O, str), 1573 (aryl, str), 1322 (C-F, str), 763 (aryl C-H bend *ortho*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) 8.09 (br s, 3H, NH_3^+), 8.01 (s, 1H, NH(C=O)N*H*Ar), 7.94 (d, *J* = 8.3 Hz, 1H, aryl 6-H), 7.62 (d, *J* = 7.9 Hz, 1H, aryl 3-H), 7.58 (dd, *J* = 8.1/8.1 Hz, 1H, aryl C-H), 7.46 (t, *J* = 5.5 Hz, 1H, N*H*(C=O)NHAr), 7.21 (dd, *J* = 7.6/7.6 Hz, 1H, aryl C-H), 3.32 – 3.39 (m, 2H, C*H*$_2$NH(C=O)NH), 2.89 (t, *J* = 6.3 Hz, 2H, C*H*$_2$$NH_3^+$); ^{13}C NMR (DMSO-$d_6$) δ 155.63 (C=O), 137.09 (aryl 1-C), 132.78, 123.07 (aryl C-H), 125.85 (J_{CF} = 5.3 Hz, aryl 3-C), 125.16 (aryl 6-C), 124.03 (J_{CF} = 273.0 Hz, aryl CF_3), 119.32 (J_{CF} = 29.0 Hz, aryl 2-C), 38.81 (*C*$H_2NH_3^+$), 37.22 (*C*H$_2$NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_{10}H_{13}F_3N_3O$ $[MH]^+$ calcd 248.1005; found 248.0988.

1-(2-Aminoethyl)-3-(3-trifluoromethylphenyl)urea hydrochloride (33r). Yield: 94%, white amorphous solid; mp = 175 – 177 °C; FT-IR 3302 (urea N-H, str), 3000 (NH_3^+, str), 1682 (urea C=O, str), 1604 (NH_3^+, bend), 1575 (aryl, str), 1342 (C-F, str), 799 (aryl C-H bend *meta*-disubstituted aromatic ring), 700 (C-F, bend); ^{1}H NMR (DMSO-d_6) 9.59 (s, 1H, NH(C=O)N*H*Ar), 7.92 – 8.04 (m, 4H, aryl 2-H, NH_3^+), 7.55 (d, *J* = 8.5 Hz, 1H, aryl 6-H), 7.45 (dd, *J* = 7.8/7.8 Hz, 1H, aryl 5-H), 7.22 (d, *J* = 7.6 Hz, 1H, aryl 4-H), 6.80 (t, *J* = 5.7 Hz, 1H, N*H*(C=O)NHAr), 3.30 – 3.40 (m, 2H, C*H*$_2$NH(C=O)NH), 2.89 (t, *J* = 6.1 Hz, 2H, C*H*$_2$$NH_3^+$); ^{13}C NMR (DMSO-$d_6$) δ 156.10 (C=O), 141.77 (aryl 1-C), 130.19 (aryl 5-C), 129.83 (J_{CF} = 31.3 Hz, aryl 3-C), 124.75 (J_{CF} = 272.4, aryl 3-C), 121.61 (aryl 6-C), 117.76 (J_{CF} = 3.9 Hz, aryl 4-C), 114.03 (J_{CF} = 4.0 Hz, aryl 2-C), 39.22 (*C*$H_2NH_3^+$), 37.59 (*C*H$_2$NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_{10}H_{13}F_3N_3O$ $[MH]^+$ calcd 248.1005; found 248.1019.

1-(2-Aminoethyl)-3-(4-trifluoromethylphenyl)urea hydrochloride (33s). Yield: 96%, white amorphous solid; mp = 203 – 206 °C; FT-IR 3311 (urea N-H, str), 3007 (NH_3^+, str), 1681 (urea C=O, str), 1607 (NH_3^+, bend), 1573 (aryl, str), 1330 (C-F, str), 839 (aryl C-H bend *para*-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ 9.66 (s, 1H, NH(C=O)N*H*Ar), 8.02 (br s, 3H, NH_3^+), 7.62 (d, *J* = 8.7 Hz, 2H, aryl 2-H and 6-H), 7.57 (d, *J* = 8.9 Hz, 2H, aryl 3-H and 5-H), 6.87 (t, *J* = 5.8 Hz, 1H, N*H*(C=O)NHAr), 3.35 (dt, *J* = 6.1/6.1 Hz, 2H, C*H*$_2$NH(C=O)NH), 2.89 (t, *J* = 6.2 Hz, 2H, C*H*$_2$$NH_3^+$); ^{13}C NMR (DMSO-$d_6$) δ 155.46 (C=O), 144.19 (aryl 1-C), 125.96 (J_{CF} = 3.7 Hz, aryl 3-C and 5-C), 124.67 (J_{CF} = 270.7 Hz, CF_3), 121.03 (J_{CF} = 32.0 Hz, aryl 4-C), 117.26 (aryl 2-C and 6-C), 38.84 (*C*$H_2NH_3^+$), 37.11 (*C*H$_2$NH(C=O)NH); *m/z* HRMS (TOF ES$^+$) $C_{10}H_{13}F_3N_3O$ $[MH]^+$ calcd 248.1005; found 248.1026.

3-Phthalimidopropanoic acid (35). Phthalic anhydride (14.8 g, 0.1 mol) and β-alanine (**34**) (8.9 g, 0.1 mol, 1 eq) were heated at 150 °C with stirring under a condenser for 2 hours. After cooling to rt, the crude solid was dispersed in water (150 mL) and collected by filtration (suction) before drying to give 20.7 g (94%) of white crystalline solid, requiring no further purification. Mp = 151 - 153 °C; FT-IR 3210 (br, O-H, str), 1770 (phth C=O, str), 1701 (br, C=O, str), 1610 (aryl, str), 1377 (O-H, bend), 729 (aryl C-H, bend, *ortho*-disubstituted ring); ^{1}H NMR (DMSO-d_6) δ 12.39 (s, 1H, COOH), 7.81-7.89 (m, 4H, aryl C-H), 3.79 (t, *J* = 7.3 Hz, 2H, phth-NC*H*$_2$), 2.60 (t, *J* = 7.4 Hz, 2H, C*H*$_2$COOH); ^{13}C NMR (DMSO-d_6) δ 172.14 (acid C=O), 167.63 (phth C=O), 134.42, 131.65, 123.05 (phth CH, 4 °C), 33.60 (phth-N*C*H$_2$) 32.37 (*C*H$_2$COOH); *m/z* HRMS (TOF ES$^+$) $C_{11}H_{10}NO_4$ $[MH]^+$ calcd 220.0604; found 220.0615.

1-(2-Hydroxyphenyl)-3-(2-phthalimidoethyl)urea (36a). A solution of 3-phthalimidopropanoic acid (**35**) (2.000 g, 9.12 mmol), diphenylphosphoryl azide (1.966 mL, 9.12 mmol, 1 eq) and TEA (2.543 ml, 2 eq, 18.25 mmol) in anhydrous toluene (60 mL) was stirred at rt, under a nitrogen

atmosphere. After disappearance of starting materials by TLC (approximately 1 hour), the mixture was refluxed to promote conversion to the isocyanate. After evolution of nitrogen gas had ceased, the reaction mixture was split into half (by volume). 2-aminophenol (747 mg, 1.5 eq, 6.84 mmol) was added to one half of the isocyanate solution and stirred under reflux for 16 hours. On cooling to rt a yellow precipitate formed, which was collected by filtration (suction) and washed with EtOAc. On drying, 867 mg (75%) of pale yellow solid was obtained requiring no further purification. Mp = 219 – 220 °C; FT-IR 3368 (O-H, str), 3342 (urea N-H, str), 1770, 1709 (phth C=O, str), 1674 (urea C=O, str), 1575 (aryl, str), 740, 712 (aryl C-H, bend, *ortho*-disubstituted ring); ^{1}H NMR (DMSO-d_6) δ 9.76 (s, 1H, OH), 7.81 - 7.90 (m, 4H, phth CH), 7.77 (dd, *J* = 7.8/1.5 Hz, 1H, hydroxyphenyl 6-H), 7.76 (s, 1H, NH(C=O)N*H*Ar), 6.95 (t, *J* = 6.2, 1H, N*H*(C=O)NHAr), 6.62 – 6.78 (m, 3H, hydroxyphenyl 3-H, 4-H, 5-H), 3.66 (t, *J* = 5.3Hz, 2H, phth-NCH_2), 3.35 (dt, *J* = 6.0/5.8 Hz, 2H, CH_2-NH); ^{13}C NMR (DMSO-d_6) δ 167.98 (phth C=O), 155.49 (urea C=O), 145.34 (hydroxyphenyl 2-C), 134.33 (phth C-H), 131.77 (phth 4° C), 128.34 (hydroxyphenyl 1-C), 123.02, (phth C-H), 121.24, 119.05, 114.58 (hydroxyphenyl 3-C, 4-C, 5-C), 118.45 (hydroxyphenyl 6-C) , 38.24 (phth-NCH_2) , 37.27 (CH_2-NH); *m/z* HRMS (TOF ES$^+$) $C_{17}H_{16}N_3O_4$ $[MH]^+$ calcd 326.1135; found 326.1165.

1-(3-Hydroxyphenyl)-3-(2-phthalimidoethyl)urea (36b). Isocyanate solution was prepared as described for 1-(2-hydroxyphenyl)-3-(2-phthalimidoethyl) urea (**36a**). To the remaining half portion was added 3-aminophenol (747 mg, 1.5 eq, 6.84 mmol) and stirred under reflux for 16 hours. After cooling and removal of solvent, the crude residue was dispersed in EtOAc (50 mL) and washed with aqueous 2M HCl (2 x 30 mL). Concentration of the organic layer gave 1.134 g (76%) of pale yellow solid. Mp = 225 – 228 °C; FT-IR 3393 (O-H, str), 3343 (urea N-H, str), 1769, (phth C=O, str), 1694 (urea C=O, str), 1563 (aryl, str), 727 (aryl C-H, bend, *ortho*-disubstituted ring); ^{1}H NMR (DMSO-d_6) δ 9.15 (br s, 1H, OH), 8.31 (s, 1H, NH(C=O)N*H*Ar), 7.81 – 7.88 (m, 4H, phth CH), 6.91 – 6.95 (m, 2H, aryl 2-H, 5-H), 6.63 (dd, *J* = 8.0/1.0 1H, aryl 6-H), 6.26 (dd, *J* = 7.6/1.7 Hz, 1H, aryl 4-H), 6.20 (t, *J* = 5.8 Hz, 1H, N*H*(C=O)NHAr), 3.68 (t, *J* = 5.7 Hz, 2H, phth-NCH_2), 3.34 (dt, *J* = 5.7/5.7 Hz, 2H, CH_2-NH); ^{13}C NMR (DMSO-d_6) δ 167.97 (phth C=O)**,** 157.58 (hydroxyphenyl 3-C)**,** 155.14 (urea C=O)**,** 141.44 (hydroxyphenyl 1-C), 134.27 (phth C-H), 131.76 (phth 4° C), 129.11 (hydroxyphenyl 5-C), 122.96 (phth C-H), 108.58 (hydroxyphenyl 6-C), 108.21 (hydroxyphenyl 4-C), 104.91 (hydroxyphenyl 3-C), 38.13 (phth-NCH_2), 37.51 (CH_2-NH); *m/z* HRMS (TOF ES$^+$) $C_{17}H_{16}N_3O_4$ $[MH]^+$ calcd 326.1135; found 326.1169.

1-(2-Aminoethyl)-3-(2-hydroxyphenyl)urea hydrochloride (33t). A solution of 1-(2-hydroxyphenyl)-3-(2-phthalimidoethyl)urea (**36a**) (700mg, 2.13 mmol) and hydrazine monohydrate (232 µl, 4.5 mmol, 2.1 eq) in EtOH (20 mL) was stirred under reflux for 2 hours. After cooling to rt, solvent was removed *in vacuo*. The crude residue was dispersed in EtOAc (30 mL) and washed with aq. 2M HCl (2 x 30 mL). The combined aqueous layers were concentrated under reduced pressure to give 296 mg (60%) of yellow solid requiring no further purification. Mp = 160 – 165 °C; FT-IR 3346 (O-H, str), 3267 (urea N-H, str), 3137, 3023 (br, NH_3^+, str), 1645 (urea C=O, str), 1568 (aryl, str), 751 (aryl C-H, bend, *ortho*-disubstituted ring); ^{1}H NMR (DMSO-d_6) δ 9.92 (br s, 1H, OH), 8.11 (s,1H, NH(C=O)N*H*Ar), 7.82 (dd, *J* = 7.9/1.7 Hz, 1H, aryl 6-H), 7.27 (t, *J* = 5.6 Hz, 1H, N*H*(C=O)N*H*Ar), 6.84 (dd, *J* = 7.7/1.5 Hz, 1H, aryl 3-H), 6.74 (ddd *J* = 7.4/7.4/1.7 Hz, 1H, aryl 4-H or 5-H), 6.67 (ddd, *J* = 7.8/7.8/1.5 Hz, 1H, aryl 4-H or 5-H), 3.31 (dt, *J* = 6.2/5.9 Hz, 2H, CH_2NH), 2.86 (t, *J* = 6.3 Hz, 2H, C$H_2NH_3^+$); ^{13}C NMR (DMSO-d_6) δ 156.05 (C=O), 145.86 (aryl 2-C), 128.12 (aryl 1-C), 121.64 (aryl 4-C), 118.96 (aryl 6-C), 118.87 (aryl 5-C), 114.92 (aryl 3-C), 39.15 ($CH_2NH_3^+$), 37.14 (CH_2NH); *m/z* HRMS (TOF ES$^+$) $C_9H_{14}N_3O_2$ $[MH]^+$ calcd 196.1081; found 196.1071.

1-(2-Aminoethyl)-3-(3-hydroxyphenyl)urea hydrochloride (33u). Phthalimide deprotection of 1-(3-hydroxyphenyl)-3-(2-phthalimidoethyl) urea (**36b**) (700 mg, 2.13 mmol) was carried out as described for 1-(2-hydroxyphenyl)-3-(2-phthalimidoethyl)urea (**36a**) to give 252 mg (51%) of yellow solid requiring no further purification. Mp = 106 – 109 °C; FT-IR 3406 (br, O-H, str), 3104 (br, NH_3^+, str), 2899, 2595 (alkyl C-H, str), 1682 (urea C=O, str), 1557 (aryl, str), 763 (aryl C-H, bend, *meta*-disubstituted ring); ^{1}H NMR (DMSO-d_6) δ 8.94 (s, 1H, NH(C=O)N*H*Ar), 8.05 (br s, 3H, NH_3^+), 6.96 – 6.98, (m, 2H, aryl 2H, 5-H), 6.78 (m, 1H, aryl 6-H), 6.30 (dd, *J* = 8.0/2.3/0.7 Hz, 1H aryl 4-H),

3.31 (t, J = 6.4 Hz, 2H, CH_2 NH_3^+), 2.83 (dt, J = 6.0/6.0 Hz, 1H, CH_2NH); ^{13}C NMR (DMSO-d_6) δ 157.71 (aryl 3-C), 155.78 (C=O), 141.47 (aryl 1-C), 129.18 (aryl 5-C), 108.54 (aryl 6-C), 108.41 (aryl 4-C), 104.89 (aryl 2-C), 39.18 ($CH_2NH_3^+$), 37.14 (CH_2NH); *m/z* HRMS (TOF ES$^+$) $C_9H_{14}N_3O_2$ $[MH]^+$ calcd 196.1081; found 196.1065.

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-phenylurea (37a). Prepared via method **M1**; Yield: 22%, white amorphous solid; mp = 109 – 115 °C; FT-IR 3310 (br, O-H, str), 2930, 2868 (alkyl C-H, str), 1634 (urea C=O, str), 1509, 1567 (aryl, str), 1110 (C-O-C, str), 764, 693 (aryl C-H, bend, *phenyl* ring); ^{1}H NMR (DMSO-d_6) δ 8.61 (s, 1H, NH(C=O)NHAr), 7.38 (dd, J = 8.7/1.1 Hz, 2H, 2-H and 6-H phenyl ring), 7.20 (dd, J = 7.4/7.4 Hz, 2H, 3-H and 5-H phenyl ring), 6.81 – 6.89 (m, 5H, 4-H phenyl ring, aryl-dioxy ring), 6.22 (t, J = 5.4 Hz, 1H, NH(C=O)NHAr), 5.07 (br s, 1H, NH) 3.79 – 3.97 (m, 6H, CH_2OAr, ^{c}Pe CH, CH(OH), ArOCH_2), 3.61 (t, J = 4.8 Hz, 2H, ^{c}PeOCH_2), 3.19 (dt, J = 5.8/5.8 Hz, 2H, NHCH$_2$CH_2), 2.75 (dd, J = 12.0/4.0 Hz, 1H, CH(OH)CH_2NH), 2.68 (t, J = 6.0 Hz, 2H, NHCH_2CH$_2$), 2.63 (dd, J = 12.2/6.8 Hz, 1H, CH(OH)CH_2NH), 1.52 – 1.74 (m, 6H, ^{c}Pe CH_2), 1.40 – 1.52 (m, 2H, ^{c}Pe CH_2); ^{13}C NMR (DMSO-d_6) δ 155.37 (C=O), 152.70, 152.53, 140.59 (aryl 4° C), 128.64 (phenyl 3-C and 5-C), 120.2943 (phenyl 4-C), 117.57 (phenyl 2-C and 6-C), 115.34 (*C*H aryl-dioxy ring), 80.85 (^{c}Pe *C*H), 71.14 (ArO*C*H$_2$), 67.79 (*C*H(OH)), 67.71 (*C*H$_2$OAr), 66.73 (^{c}PeO*C*H$_2$), 51.98 (CH(OH)*C*H$_2$NH), 49.14 (NH*C*H$_2$CH$_2$), 38.78 (NHCH$_2$*C*H$_2$), 31.80 (2-C and 5-C ^{c}Pe ring), 23.14 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{25}H_{36}N_3O_5$ $[MH]^+$ calcd 458.2649; found 458.2611; RP-HPLC R_t 3.62 (System 1b), 12.67 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(2-methyl-phenyl)lurea (37b). Prepared via method **M1**; Yield: 31%, white amorphous solid; mp = 114 – 115 °C; FT-IR 3329 (br, O-H, str), 2928, 2871 (alkyl C-H, str), 1636 (urea C=O, str), 1509, 1567 (aryl, str), 1109 (C-O-C, str), 827 (aryl C-H, bend, *para*-disubstituted ring), 764 (aryl C-H, bend, *ortho* -disubstituted ring); ^{1}H NMR (DMSO-d_6) δ 7.80 (d, J = 7.6 Hz, 1H, aryl 6-H), 7.70 (s, 1H, NH(C=O)NHAr), 7.05 – 7.11 (m, 2H, C-H tolyl ring), 6.80 – 6.87 (m, 5H, C-H aryl-dioxy ring, C-H tolyl ring), 6.60 (t, J = 5.4 Hz, 1H, NH(C=O)NHAr), 4.95 (br s, 1H, NH), 3.77 – 4.01 (m, 6H, CH_2OAr, ^{c}Pe CH, CH(OH), ArOCH_2), 3.61 (t, J = 4.9 Hz, 2H, ^{c}PeOCH_2), 3.17 (dt, J = 5.9/5.9 Hz, 2H,), 2.70 (dd, J = 11.8/4.2 Hz, 1H, CH(OH)CH_2NH), 2.64 (t, J = 6.0 Hz, 3H, NHCH_2CH$_2$), 2.59 (dd, J = 11.7/6.3 Hz, CH(OH)CH_2NH), 2.17 (s, 3H, CH_3), 1.52 – 1.76 (m, 6H, ^{c}Pe CH_2), 1.40 – 1.52 (m, 2H, ^{c}Pe CH_2); ^{13}C NMR (DMSO-d_6) δ 155.48 (C=O), 152.75, 152.49, 138.31 (aryl 4° C), 130.03, 126.02, 121.72 (aryl C-H), 120.42 (aryl 6-C), 115.32 (*C*H aryl-dioxy ring), 80.85 (^{c}Pe *C*H), 71.25 (ArO*C*H$_2$), 68.17 (*C*H(OH)), 67.70 (*C*H$_2$OAr), 66.73 (^{c}PeO*C*H$_2$), 52.34 (CH(OH)*C*H$_2$NH), 49.39 (NH*C*H$_2$CH$_2$), 39.10 (NHCH$_2$*C*H$_2$), 31.80 (2-C and 5-C ^{c}Pe ring), 23.14 (3-C and 4-C ^{c}Pe ring), 17.97 (CH_3); *m/z* HRMS (TOF ES$^+$) $C_{26}H_{38}N_3O_5$ $[MH]^+$ calcd 472.2806; found 472.2764; RP-HPLC R_t 4.07 (System 1b), 7.60 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(3-methyl-phenyl)urea (37c). Prepared via method **M1**; Yield: 9%, white amorphous solid; mp = 112 – 114 °C; FT-IR 3408 (urea N-H, str), 3316 (br, O-H, str), 2930, 2870 (alkyl C-H, str), 1633 (urea C=O, str), 1509, 1569 (aryl, str), 1111 (C-O-C, str), 819 (aryl C-H, bend, *para*-disubstituted ring), 760 (aryl C-H, bend, *meta*-disubstituted ring); ^{1}H NMR (DMSO-d_6) δ 8.51 (s, 1H, NH(C=O)NHAr), 7.21 (s, 1H, aryl 2-H), 7.10 (d, J = 8.4 Hz, 1H, aryl 6-H), 7.08 (dd, J = 7.6/7.6 Hz, 1H, aryl 5-H), 6.85, 6.83 (d, J = 9.2 Hz, 2 x 2H, C-H aryl-dioxy ring), 6.46 (d, J = 7.4 Hz, 1H aryl 4-H), 6.20 (t, J = 5.4 Hz, 1H, NH(C=O)NHAr), 5.09 (br s, 1H, NH), 3.78 – 4.00 (m, 6H, CH_2OAr, ^{c}Pe CH, CH(OH), ArOCH_2), 3.61 (t, J = 4.9 Hz, 2H, ^{c}PeOCH_2), 3.19 (dt, J = 5.9/5.9 Hz, 2H, NHCH$_2$CH_2), 2.77 (dd, J = 11.8/3.6 Hz, 1H, CH(OH)CH_2NH), 2.61 – 2.73 (m, 3H, CH(OH)CH_2NH, NHCH_2CH$_2$), 2.23 (s, 3H, CH_3), 1.52 – 1.75 (m, 6H, ^{c}Pe CH_2), 1.41 – 1.52 (m, 2H, ^{c}Pe CH_2); ^{13}C NMR (DMSO-d_6) δ 155.38 (C=O), 152.66, 152.53, 140.47, 121.72 (aryl 4° C), 137.70 (aryl 4-C), 128.48 (aryl 5-C), 118.12 (aryl 2-C), 115.32 (*C*H aryl-dioxy ring), 114.80 (aryl 6-C), 80.84 (^{c}Pe *C*H), 71.08 (ArO*C*H$_2$), 69.77 (*C*H(OH)), 67.69 (*C*H$_2$OAr), 66.72 (^{c}PeO*C*H$_2$), 51.82 (CH(OH)*C*H$_2$NH), 49.05 (NH*C*H$_2$CH$_2$), 38.56 (NHCH$_2$*C*H$_2$), 31.79 (2-C and 5-C ^{c}Pe ring), 23.13 (3-C and 4-C ^{c}Pe ring),21.26 (CH_3); *m/z* HRMS

(TOF ES$^+$) $C_{26}H_{38}N_3O_5$ $[MH]^+$ calcd 472.2806; found 472.2825; RP-HPLC R_t 4.25 (System 1b), 8.28 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(4-methylphenyl)urea (37d). Prepared via method **M1**; Yield: 19%, white amorphous solid; mp = 142 – 144 °C; FT-IR 3319 (br, O-H, str), 2926, 2868 (alkyl C-H, str), 1634 (urea C=O, str), 1509, 1566 (aryl, str), 1110 (C-O-C, str), 821 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR (DMSO-d_6) δ 8.46 (s, 1H, NH(C=O)N*H*Ar), 7.26 (d, *J* = 8.4 Hz, 2H, aryl 2-H and 6-H), 7.01 (d, *J* = 8.3 Hz, 2H, aryl 3-H and 5-H), 6.82, 6.85 (d, *J* = 9.2 Hz, 2 x 2H, C-H aryl-dioxy ring), 6.14 (t, *J* = 5.5 Hz, 1H, N*H*(C=O)NHAr), 5.04 (br s, 1H, NH), 3.79 – 3.97 (m, 6H, CH_2OAr, ^{c}Pe C*H*, C*H*(OH), ArOCH_2), 3.61 (t, *J* = 4.9 Hz, 2H, ^{c}PeOCH_2), 3.18 (dt, *J* = 5.8/5.8 Hz, 2H, NHCH$_2$CH_2), 2.74 (dd, *J* = 11.9/3.6 Hz, 1H, CH(OH)CH_2NH), 2.59 – 2.70 (m, 3H, CH(OH)CH_2NH, NHCH_2CH$_2$), 2.21 (s, 3H, CH$_3$), 1.52 – 1.76 (m, 6H, ^{c}Pe CH_2), 1.41 – 1.52 (m, 2H, ^{c}Pe CH_2); ^{13}C NMR (DMSO-d_6) δ 155.42 (C=O), 152.78, 152.51, 138.02, 129.61 (aryl 4° C), 129.02 (2-C and 6-C tolyl ring), 117.67 (3-C and 5-C tolyl ring), 115.31 (*C*H aryl-dioxy ring), 80.84 (^{c}Pe *C*H), 71.12 (ArO*C*H$_2$), 67.81(*C*H(OH)), 67.68 (*C*H$_2$OAr), 66.71 (^{c}PeO*C*H$_2$), 51.98 (CH(OH)*C*H$_2$NH), 49.16 (NH*C*H$_2$CH$_2$), 38.48 (NHCH$_2$*C*H$_2$), 31.79 (2-C and 5-C ^{c}Pe ring), 23.13 (3-C and 4-C ^{c}Pe ring), 20.30 (CH$_3$); *m/z* HRMS (TOF ES$^+$) $C_{26}H_{38}N_3O_5$ $[MH]^+$ calcd 472.2806; found 472.2834; RP-HPLC R_t 4.18 (System 1b), 13.52 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(2-methoxyphenyl)urea (37e). Prepared via method **M1**; Yield: 27%, white amorphous solid; mp = 78 – 83 °C; FT-IR 3332 (br, O-H, str), 2929, 2864 (alkyl C-H, str), 1651 (urea C=O, str), 1508, 1549 (aryl, str), 1109 (C-O-C, str), 823 (aryl C-H, bend, *para*-disubstituted ring), 748 (aryl C-H, bend, *ortho* -disubstituted ring); ^{1}H NMR (DMSO-d_6) δ 8.07 (dd, *J* = 7.6/2.0 Hz, 1H, aryl 6-H), 7.97 (s, 1H, NH(C=O)N*H*Ar), 6.92 – 6.99 (m, 2H, C-H methoxyphenyl ring, N*H*(C=O)NHAr), 6.79 – 6.89 (m, 6H, C-H aryl-dioxy ring, C-H methoxyphenyl ring), 5.07 (br s, 1H, NH), 3.76 – 4.00 (m, 6H, CH_2OAr, ^{c}Pe C*H*, C*H*(OH), ArOCH_2), 3.82 (s, 3H, CH$_3$), 3.61 (t, *J* = 4.8 Hz, 2H, ^{c}PeOCH_2), 3.18 (dt, *J* = 5.9/5.9 Hz, 2H, NHCH$_2$CH_2), 2.74 (dd, *J* = 11.9/3.9 Hz, 1H, CH(OH)CH_2NH), 2.59 – 2.70 (m, 3H, CH(OH)CH_2NH, NHCH_2CH$_2$), 1.52 – 1.75 (m, 6H, ^{c}Pe CH_2), 1.40 – 1.51 (m, 2H, ^{c}Pe CH_2); ^{13}C NMR (DMSO-d_6) δ 155.32 (C=O), 152.70, 152.52, 147.30, 129.51 (aryl 4° C), 120.90, 120.45, 110.54 (aryl C-H), 117.98 (aryl 6-C), 115.32 (*C*H aryl-dioxy ring), 80.85 (^{c}Pe *C*H), 71.14 (ArO*C*H$_2$), 67.80 (*C*H(OH)), 67.69 (*C*H$_2$OAr), 66.73 (^{c}PeO*C*H$_2$), 55.63 (CH$_3$), 52.03 (CH(OH)*C*H$_2$NH), 49.23 (NH*C*H$_2$CH$_2$), 38.93 (NHCH$_2$*C*H$_2$), 31.80 (2-C and 5-C ^{c}Pe ring), 23.14 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{26}H_{38}N_3O_6$ $[MH]^+$ calcd 488.2755; found 488.2777; RP-HPLC R_t 3.77 (System 1b), 12.87 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(3-methoxyphenyl)urea (37f). Prepared via method **M1**; Yield: 16%, white amorphous solid; mp = 103 – 110 °C; FT-IR 3316 (br, O-H, str), 2928, 2869 (alkyl C-H, str), 1630 (urea C=O, str), 1509, 1570 (aryl, str), 1110 (C-O-C, str), 824 (aryl C-H, bend, *para*-disubstituted ring), 765 (aryl C-H, bend, *meta*-disubstituted ring); ^{1}H NMR (DMSO-d_6) δ 8.63 (s, 1H, NH(C=O)N*H*Ar), 7.14 (dd, *J* = 2.2/2.2 Hz, 1H, aryl 2-H), 7.10 (dd, *J* = 8.1/8.1 Hz, 1H, aryl 5-H), 6.79 – 6.89 (m, 5H, C-H aryl-dioxy ring, aryl 6-H), 6.46 (ddd, *J* = 8.2/2.4/0.6 Hz, 1H aryl 4-H), 6.22 (t, *J* = 5.4 Hz, 1H, N*H*(C=O)NHAr), 5.05 (br s, 1H, NH), 3.79 – 3.97 (m, 6H, CH_2OAr, ^{c}Pe C*H*, C*H*(OH), ArOCH_2), 3.69 (s, 3H, CH$_3$), 3.61 (t, *J* = 4.8 Hz, 2H, ^{c}PeOCH_2), 3.18 (dt, *J* = 5.9/5.9 Hz, 2H, NHCH$_2$CH_2), 2.73 (dd, *J* = 11.9/3.9 Hz, 1H, CH(OH)CH_2NH), 2.50 – 2.70 (m, 3H, CH(OH)CH_2NH, NHCH_2CH$_2$), 1.52 – 1.74 (m, 6H, ^{c}Pe CH_2), 1.41 – 1.52 (m, 2H, ^{c}Pe CH_2); ^{13}C NMR (DMSO-d_6) δ 155.28 (C=O), 159.64, 152.71, 152.52, 141.84 (aryl 4° C), 129.36 (aryl 5-C), 115.34 (*C*H aryl-dioxy ring), 109.94 (aryl 6-C), 106.33 (aryl 4-C), 103.35 (aryl 2-C), 80.85 (^{c}Pe *C*H), 71.16 (ArO*C*H$_2$), 67.87 (*C*H(OH)), 67.70 (*C*H$_2$OAr), 66.73 (^{c}PeO*C*H$_2$), 54.82 (CH$_3$), 52.02 (CH(OH)*C*H$_2$NH), 49.13 (NH*C*H$_2$CH$_2$), 38.77 (NHCH$_2$*C*H$_2$), 31.80 (2-C and 5-C ^{c}Pe ring), 23.14 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{26}H_{38}N_3O_6$ $[MH]^+$ calcd 488.2755; found 488.2786; RP-HPLC R_t 3.40 (System 1b), 12.42 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(4-methoxyphenyl)urea (37g). Prepared via method **M1**; Yield: 7%, white amorphous solid; mp = 121 – 125 °C; FT-IR 3327 (br, O-H, str), 2927, 2867 (alkyl C-H, str), 1635 (urea C=O, str), 1509, 1565 (aryl, str), 1110 (C-O-C, str), 828 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR (DMSO-d_6) δ 8.37 (s, 1H, NH(C=O)N*H*Ar), 7.10 (d, *J* = 9.0 Hz, 2H, aryl 2-H and 6-H), 6.82 – 6.87 (m, 4H, C-H aryl-dioxy ring), 6.80 (d, *J* = 9.0 Hz, 2H, aryl 3-H and 5-H), 6.07 (t, *J* = 5.5 Hz, 1H, N*H*(C=O)NHAr), 5.00 (br s, 1H, NH), 3.75 – 4.00 (m, 6H, C*H*$_2$OAr, ^{c}Pe C*H*, C*H*(OH), ArOC*H*$_2$), 3.68 (s, 3H, CH$_3$), 3.61 (t, *J* = 4.7 Hz, 2H, ^{c}PeOC*H*$_2$), 3.15 (dt, *J* = 5.8/5.8 Hz, 2H, NHCH$_2$C*H*$_2$), 2.55 – 2.76 (m, 4H, CH(OH)C*H*$_2$NH, NHC*H*$_2$CH$_2$), 1.52 – 1.74 (m, 6H, ^{c}Pe C*H*$_2$), 1.41 – 1.52 (m, 2H, ^{c}Pe C*H*$_2$); ^{13}C NMR (DMSO-d_6) δ 155.55 (C=O), 153.82, 152.73, 152.49, 133.75 (aryl 4° C), 119.28 (2-C and 6-C methoxyphenyl ring), 115.32 (*C*H aryl-dioxy ring), 113.86 (3-C and 5-C methoxyphenyl ring), 80.85 (^{c}Pe *C*H), 71.20 (ArO*C*H$_2$), 68.03 (*C*H(OH)), 67.69 (*C*H$_2$OAr), 66.73 (^{c}PeO*C*H$_2$), 55.12 (CH$_3$), 52.17 (CH(OH)*C*H$_2$NH), 49.33 (NH*C*H$_2$CH$_2$), 38.27 (NHCH$_2$*C*H$_2$), 31.80 (2-C and 5-C ^{c}Pe ring), 23.14 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{26}H_{38}N_3O_6$ [MH]$^+$ calcd 488.2755; found 488.2717; RP-HPLC R_t 3.37 (System 1b), 12.02 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(2-fluorophenyl)urea (37h). Prepared via method **M1**; Yield: 11%, white amorphous solid; mp = 115 – 117 °C; FT-IR 3322 (br, O-H, str), 2929, 2871 (alkyl C-H, str), 1640 (urea C=O, str), 1509, 1568 (aryl, str), 1241 (C-F, str), 1110 (C-O-C, str), 827 (aryl C-H, bend, *para*-disubstituted ring), 764 (aryl C-H, bend, *ortho* -disubstituted ring), 744 (C-F, bend); ^{1}H NMR (DMSO-d_6) δ 8.38 (s, 1H, NH(C=O)N*H*Ar), 8.12 (dd, *J* = 8.3/1.5 Hz, 1H, aryl 6-H), 7.16 (ddd, *J* = 11.8/8.2/1.4 Hz, 1H, aryl 3-H), 7.06 (dd, *J* = 8.2/8.2 Hz, 1H, aryl 5-H), 6.87 – 6.94 (m, 1H, aryl 4-H), 6.85, 6.82 (d, *J* = 9.3 Hz, 2 x 2H, C-H aryl-dioxy ring), 6.70 (t, *J* = 5.4 Hz, 1H, N*H*(C=O)NHAr) 4.99 (br s, 1H, NH), 3.77 – 4.01 (m, 6H, C*H*$_2$OAr, ^{c}Pe C*H*, C*H*(OH), ArOC*H*$_2$), 3.61 (t, *J* = 4.8 Hz, 2H, ^{c}PeOC*H*$_2$), 3.18 (dt, *J* = 6.0/6.0 Hz, 2H, NHCH$_2$C*H*$_2$), 2.71 (dd, *J* = 11.8/3.9 Hz, 1H, CH(OH)C*H*$_2$NH), 2.56 – 2.67 (m, 3H, CH(OH)C*H*$_2$NH, NHC*H*$_2$CH$_2$), 1.51 – 1.75 (m, 6H, ^{c}Pe C*H*$_2$), 1.41 – 1.51 (m, 2H, ^{c}Pe C*H*$_2$); ^{13}C NMR (DMSO-d_6) δ 155.16 (C=O), 152.75, 152.50, 136.85 (aryl 4° C), 125.40 (aryl 6-C), 124.35 (aryl 5-C), 121.43 (aryl 4-C), 114.67 (aryl 3-C), 115.31 (*C*H aryl-dioxy ring), 80.84 (^{c}Pe *C*H), 71.22 (ArO*C*H$_2$), 68.06 (*C*H(OH)), 67.69 (*C*H$_2$OAr), 66.72 (^{c}PeO*C*H$_2$), 51.18 (CH(OH)*C*H$_2$NH), 48.89 (NH*C*H$_2$CH$_2$), 38.99 (NHCH$_2$*C*H$_2$), 31.79 (2-C and 5-C ^{c}Pe ring), 23.13 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{25}H_{35}FN_3O_5$ [MH]$^+$ calcd 476.2555; found 476.2596; RP-HPLC R_t 4.05 (System 1b), 12.35 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(3-fluorophenyl)urea (37i). Prepared via method **M1**; Yield: 27%, white amorphous solid; mp = 108 – 110 °C; FT-IR 3317 (br, O-H, str), 2926, 2869 (alkyl C-H, str), 1636 (urea C=O, str), 1509, 1569 (aryl, str), 1118 (C-O-C, str), 1238 (C-F, str), 827 (aryl C-H, bend, *para*-disubstituted ring), 765 (C-F, bend); ^{1}H NMR (DMSO-d_6) δ 8.86 (s, 1H, NH(C=O)N*H*Ar), 7.45 (ddd, *J* = 12.3/2.2/2.2 Hz, 1H, aryl 2-H), 7.22 (ddt, *J* = 8.2/8.2.2/8.2 Hz, 1H, aryl 5-H), 7.00 (ddd, *J* = 8.2/1.2 Hz, 1H, aryl 6-H), 6.79 – 6.89 (m, 4H, C-H aryl-dioxy ring), 6.68 (ddd, *J* = 8.2/8.2/2.1 Hz, 1H, aryl 4-H), 6.28 (t, *J* = 5.4 Hz, 1H, N*H*(C=O)NHAr), 5.04 (br s, 1H, NH), 3.77 – 4.01 (m, 6H, C*H*$_2$OAr, ^{c}Pe C*H*, C*H*(OH), ArOC*H*$_2$), 3.61 (t, *J* = 4.8 Hz, 2H, ^{c}PeOC*H*$_2$), 3.18 (dt, *J* = 5.8/5.8 Hz, 2H, NHCH$_2$C*H*$_2$), 2.57 – 2.79 (m, 4H, CH(OH)C*H*$_2$NH, NHC*H*$_2$CH$_2$), 1.52 – 1.75 (m, 6H, ^{c}Pe C*H*$_2$), 1.40 – 1.52 (m, 2H, ^{c}Pe C*H*$_2$); ^{13}C NMR (DMSO-d_6) δ 162.44 (J_{CF} = 240.8 Hz, C-F), 155.11 (C=O), 152.72, 152.51 (aryl 4° C), 142.53 (J_{CF} = 11.8 Hz, aryl 1-C), 130.11 (J_{CF} = 10.9 Hz, aryl 5-C), 115.33 (*C*H aryl-dioxy ring), 113.22 (J_{CF} = 2.7 Hz, aryl 6-C), 107.16 (J_{CF} = 20.5 Hz, aryl 4-C), 104.16 (J_{CF} = 26.2 Hz, aryl 2-C), 80.85 (^{c}Pe *C*H), 71.17 (ArO*C*H$_2$), 67.93 (*C*H(OH)), 67.70 (*C*H$_2$OAr), 66.73 (^{c}PeO*C*H$_2$), 52.05 (CH(OH)*C*H$_2$NH), 49.06 (NH*C*H$_2$CH$_2$), 38.66 (NHCH$_2$*C*H$_2$), 31.80 (2-C and 5-C ^{c}Pe ring), 23.14 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{25}H_{35}FN_3O_5$ [MH]$^+$ calcd 476.2555; found 476.2514; RP-HPLC R_t 4.02 (System 1b), 13.32 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(4-fluorophenyl)urea (37j). Prepared via method **M1**; Yield: 19%, white amorphous solid; mp = 130 – 133 °C; FT-IR 3318 (br, O-H, str), 2927, 2868 (alkyl C-H, str), 1630 (urea C=O, str), 1509, 1572 (aryl, str),

1111 (C-O-C, str), 1232 (C-F, str), 827 (aryl C-H, bend, *para*-disubstituted ring), 764 (C-F, bend); ^{1}H NMR (DMSO-d_6) δ 8.69 (s, 1H, NH(C=O)N*H*Ar), 7.39 (dd, *J* = 9.1/5.0 Hz, 2H, 2-H and 6-H fluorophenyl ring), 7.04 (dd, *J* = 8.9/8.9 Hz, 2H, 3-H and 5-H fluorophenyl ring), 6.80 – 6.88 (m, 4H, aryl-dioxy ring), 6.23 (t, *J* = 5.4 Hz, 1H, N*H*(C=O)NHAr), 5.13 (br s, 1H, NH), 3.78 – 4.00 (m, 6H, CH_2OAr, ^{c}Pe C*H*, C*H*(OH), ArOCH_2), 3.61 (t, *J* = 4.8 Hz, 2H, ^{c}PeOCH_2), 3.15 – 3.24 (m, 2H, NHCH$_2$CH_2), 2.78 (dd, *J* = 11.9/3.7 Hz, 1H, CH(OH)CH_2NH), 2.61 – 2.74 (m, 3H, CH(OH)CH_2NH, NHCH_2CH$_2$), 1.52 – 1.75 (m, 6H, ^{c}Pe CH_2), 1.40 – 1.52 (m, 2H, ^{c}Pe CH_2); ^{13}C NMR (DMSO-d_6) δ 155.45 (C=O), 152.66, 152.55 (aryl 4° C), 136.94 (J_{CF} = 1.8 Hz, 1-C), 119.15 (J_{CF} = 8.0 Hz, 2-C and 6-C fluorophenyl ring), 115.33 (*C*H aryl-dioxy ring), 115.08 (J_{CF} = 21.6 Hz, 3-C and 5-C fluorophenyl ring), 80.85 (^{c}Pe *C*H), 71.07 (ArO*C*H$_2$), 67.70 (*C*H$_2$OAr), 67.49 (*C*H(OH)), 66.73 (^{c}PeO*C*H$_2$), 51.80 (CH(OH)*C*H$_2$NH), 49.02 (NH*C*H$_2$CH$_2$), 38.43 (NHCH$_2$*C*H$_2$), 31.80 (2-C and 5-C ^{c}Pe ring), 23.14 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{25}H_{35}FN_3O_5$ $[MH]^+$ calcd 476.2555; found 476.2529; RP-HPLC R_t 4.12 (System 1b), 13.20 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(2-chlorophenyl)urea (37k). Prepared via method **M1**; Yield: 9%, white amorphous solid; mp = 99 - 103°C; FT-IR 3317 (br, O-H, str), 2929, 2868 (alkyl C-H, str), 1638 (urea C=O, str), 1508, 1559 (aryl, str), 1112 (C-O-C, str), 820 (aryl C-H, bend, *para*-disubstituted ring), 750 (aryl C-H, bend, *ortho* - disubstituted ring), 730 (C-Cl, bend); ^{1}H NMR (DMSO-d_6) δ 8.14 (dd, *J* = 8.3/1.3 Hz, 1H, aryl 6-H), 8.09 (s, 1H, NH(C=O)N*H*Ar), 7.38 (dd, *J* = 8.0/1.4 Hz, 1H, aryl 3-H), 7.22 (ddd, *J* = 7.8/7.8/1.4 Hz, 1H, aryl 5-H), 7.07 (t, *J* = 5.2 Hz, 1H, N*H*(C=O)NHAr), 6.93 (ddd, *J* = 7.8/7.8/1.5 Hz, 1H, aryl 4-H), 6.79 – 6.86 (m, 4H, C-H aryl-dioxy ring), 4.98 (br s, 1H, NH), 3.73 – 4.01 (m, 6H, CH_2OAr, ^{c}Pe C*H*, C*H*(OH), ArOCH_2), 3.61 (t, *J* = 4.8 Hz, 2H, ^{c}PeOCH_2), 3.18 (dt, *J* = 5.8/5.8 Hz, 2H, NHCH$_2$CH_2), 2.57 – 2.72 (m, 4H, CH(OH)CH_2NH, NHCH_2CH$_2$), 1.51 – 1.74 (m, 6H, ^{c}Pe CH_2), 1.41 – 1.51 (m, 2H, ^{c}Pe CH_2); ^{13}C NMR (DMSO-d_6) δ 154.89 (C=O), 152.76, 152.50, 136.83 (aryl 4° C), 129.07 (aryl 3-C), 127.42 (aryl 5-C), 122.34 (aryl 4-C), 120.81 (aryl 6-C), 115.33 (*C*H aryl-dioxy ring), 80.86 (^{c}Pe *C*H), 71.24 (ArO*C*H$_2$), 68.15 (*C*H(OH)), 67.71 (*C*H$_2$OAr), 66.73 (^{c}PeO*C*H$_2$), 52.30 (CH(OH)*C*H$_2$NH), 49.22 (NH*C*H$_2$CH$_2$), 39.19 (NHCH$_2$*C*H$_2$), 31.81 (2-C and 5-C ^{c}Pe ring), 23.15 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{25}H_{35}ClN_3O_5$ $[MH]^+$ calcd 492.2260; found 492.2254; RP-HPLC R_t 3.50 (System 1b), 13.09 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(3-chlorophenyl)urea (37l). Prepared via method **M1**; Yield: 17%, white amorphous solid; mp = 102 – 109 °C; FT-IR 3316 (br, O-H, str), 2930, 2869 (alkyl C-H, str), 1639 (urea C=O, str), 1509, 1570 (aryl, str), 1119 (C-O-C, str), 819 (aryl C-H, bend, *para*-disubstituted ring), 765 (C-Cl, bend); ^{1}H NMR (DMSO-d_6) δ 8.85 (s, 1H, NH(C=O)N*H*Ar), 7.67 (dd, *J* = 2.0/2.0 Hz, 1H, aryl 2-H), 7.22 (dd, *J* = 8.1/8.1 Hz, 1H, aryl 5-H), 7.16 (ddd, *J* = 8.2/1.8/1.2 Hz, 1H, aryl 6-H), 6.92 (ddd, *J* = 7.7/2.1/1.2 Hz, 1H, aryl 4-H), 6.85 (d, *J* = 9.3 Hz, 2H, C-H aryl-dioxy ring), 6.82 (d, *J* = 9.3 Hz, 2H, C-H aryl-dioxy ring), 6.29 (t, *J* = 5.4 Hz, 1H, N*H*(C=O)NHAr), 5.03 (br s, 1H, NH), 3.77 – 4.00 (m, 6H, CH_2OAr, ^{c}Pe C*H*, C*H*(OH), ArOCH_2), 3.61 (t, *J* = 4.8 Hz, 2H, ^{c}PeOCH_2), 3.18 (dt, *J* = 5.9/5.9 Hz, 2H, NHCH$_2$CH_2), 2.57 – 2.77 (m, 4H, CH(OH)CH_2NH, NHCH_2CH$_2$), 1.51 – 1.74 (m, 6H, ^{c}Pe CH_2), 1.40 – 1.51 (m, 2H, ^{c}Pe CH_2); ^{13}C NMR (DMSO-d_6) δ 155.08 (C=O), 152.71, 152.51, 146.03, 133.10 (aryl 4° C), 130.24 (aryl 5-C), 120.51 (aryl 4-C), 116.87 (aryl 2-C), 115.90 (aryl 6-C), 115.32 (*C*H aryl-dioxy ring), 80.85 (^{c}Pe *C*H), 71.17 (ArO*C*H$_2$), 67.92 (*C*H(OH)), 67.70 (*C*H$_2$OAr), 66.72 (^{c}PeO*C*H$_2$), 52.05 (CH(OH)*C*H$_2$NH), 49.04 (NH*C*H$_2$CH$_2$), 38.90 (NHCH$_2$*C*H$_2$), 31.80 (2-C and 5-C ^{c}Pe ring), 23.14 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{25}H_{35}ClN_3O_5$ $[MH]^+$ calcd 492.2260; found 492.2250; RP-HPLC R_t 3.88 (System 1b), 13.87 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(4-chlorophenyl)urea (37m). Prepared via method **M1**; Yield: 18%, white amorphous solid; mp = 133 – 140 °C; FT-IR 3321 (br, O-H, str), 2926, 2867 (alkyl C-H, str), 1633 (urea C=O, str), 1510, 1565 (aryl, str), 1110 (C-O-C, str), 827 (aryl C-H, bend, *para*-disubstituted ring), 764 (C-Cl, bend); ^{1}H NMR (DMSO-d_6) δ 8.76 (s, 1H, NH(C=O)N*H*Ar), 7.41, 7.25 (d, *J* = 8.9 Hz, 2 x 2H, C-H of chlorophenyl ring), 6.81 – 6.86 (m, 4H, C-H aryl-dioxy ring), 7.23 (t, *J* = 5.4 Hz, 1H, N*H*(C=O)NHAr), 5.00 (br s,

1H, NH), 3.76 – 3.99 (m, 6H, CH_2OAr, ^{c}Pe CH, CH(OH), ArOCH_2), 3.61 (t, J = 4.8 Hz, 2H, ^{c}PeOCH_2), 3.17 (dt, J = 5.8/5.8 Hz, 2H, NHCH$_2$CH_2), 2.57 – 2.72 (m, 4H, CH(OH)CH_2NH, NHCH_2CH$_2$), 1.52 – 1.74 (m, 6H, ^{c}Pe CH_2), 1.40 – 1.51 (m, 2H, ^{c}Pe CH_2); ^{13}C NMR (DMSO-d$_6$) δ 155.15 (C=O), 152.72, 152.50, 139.62, 124.32 (aryl 4° C), 128.45, 118.99 (CH chlorophenyl ring), 115.31 (*C*H aryl-dioxy ring), 80.84 (^{c}Pe *C*H), 71.19 (ArO*C*H$_2$), 68.01 (*C*H(OH)), 67.69 (*C*H$_2$OAr), 66.72 (^{c}PeO*C*H$_2$), 52.12 (CH(OH)*C*H$_2$NH), 49.14 (NH*C*H$_2$CH$_2$), 38.95 (NHCH$_2$*C*H$_2$), 31.79 (2-C and 5-C ^{c}Pe ring), 23.13 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{25}H_{35}ClN_3O_5$ [MH]$^+$ calcd 492.2260; found 492.2284; RP-HPLC R_t 3.80 (System 1b), 13.73 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(2-bromophenyl)urea hydroformate (37n). Prepared via method **M1**; Yield: 9%, off-white semi-solid; FT-IR 3360 (br, O-H, str), 2950, 2870 (alkyl C-H, str), 1678 (urea C=O, str), 1508, 1581 (aryl, str), 1130 (C-O-C, str), 826 (aryl C-H, bend, *para*-disubstituted ring), 753 (aryl C-H, bend, *ortho* -disubstituted ring), 722 (C-Br, bend); ^{1}H NMR (DMSO-d$_6$) δ 8.04 (dd, J = 8.3/1.5 Hz, 1H, aryl 6-H), 7.98 (s, 1H, NH(C=O)N*H*Ar), 7.56 (dd, J = 8.0/1.4 Hz, 1H, aryl 3-H), 7.22 – 7.32 (m, 2H, aryl 5-H, N*H*(C=O)NHAr), 6.79 – 6.94 (m, 5H, aryl 4-H, aryl-dioxy ring), 3.76 – 4.15 (m, 6H, CH_2OAr, ^{c}Pe CH, CH(OH), ArOCH_2), 3.61 (t, J = 4.8 Hz, 2H, ^{c}PeOCH_2), 3.18 – 3.56 (m, 10H, H$_2$O, NHCH$_2$CH_2), 2.55 – 3.13 (m, 4H, CH(OH)CH_2NH, NHCH_2CH$_2$), 1.52 – 1.75 (m, 6H, ^{c}Pe CH_2), 1.40 – 1.52 (m, 2H, ^{c}Pe CH_2); ^{13}C NMR (DMSO-d$_6$) δ 155.30 (C=O), 152.70, 152.42, 137.62 112.54 (aryl 4° C), 132.62 (aryl 3-C), 127.95 (aryl 5-C), 123.49 (aryl 4-C), 121.89 (aryl 6-C), 115.39, 115.35 (*C*H aryl-dioxy ring), 80.85 (^{c}Pe *C*H), 70.63 (ArO*C*H$_2$), 67.71 (*C*H$_2$OAr), 66.71 (^{c}PeO*C*H$_2$), 65.09 (*C*H(OH)), 50.58 (CH(OH)*C*H$_2$NH), 48.21 (NH*C*H$_2$CH$_2$), 37.21 (NHCH$_2$*C*H$_2$), 31.79 (2-C and 5-C ^{c}Pe ring), 23.13 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{25}H_{35}BrN_3O_5$ [MH]$^+$ calcd 536.1755; found 536.1800; RP-HPLC R_t 4.09 (System 1b), 13.34 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(3-bromophenyl)urea (37o). Prepared via method **M1**; Yield: 12%, white amorphous solid; mp = 120 – 122 °C; FT-IR 3323 (br, O-H, str), 2926, 2868 (alkyl C-H, str), 1630 (urea C=O, str), 1509, 1565 (aryl, str), 1111 (C-O-C, str), 825 (aryl C-H, bend, *para*-disubstituted ring), 683 (C-Br, bend); ^{1}H NMR (DMSO-d$_6$) δ 8.83 (s, 1H, NH(C=O)N*H*Ar), 7.81 (dd, J = 1.9/1.9 Hz, 1H, aryl 2-H), 7.21 (ddd, J = 8.2/1.7/1.7 Hz, 1H, aryl 6-H), 7.16 (dd, J = 7.7/7.7 Hz, 1H, aryl 5-H), 7.05 (ddd, J = 7.7/1.2/1.2 Hz, 1H, aryl 4-H), 6.85 (d, J = 9.3 Hz, 2H, C-H aryl-dioxy ring), 6.82 (d, J = 9.3 Hz, 2H, C-H aryl-dioxy ring), 6.29 (t, J = 5.3 Hz, 1H, N*H*(C=O)NHAr), 5.02 (br s, 1H, NH), 3.76 – 4.00 (m, 6H, CH_2OAr, ^{c}Pe CH, CH(OH), ArOCH_2), 3.61 (t, J = 4.8 Hz, 2H, ^{c}PeOCH_2), 3.13 – 3.21 (m, 2H, NHCH$_2$CH_2), 2.71 (dd, J = 11.7/3.7 Hz, 1H, CH(OH)CH_2NH), 2.67 (dd, J = 6.1/6.1 Hz, 2H, NHCH_2CH$_2$), 2.60 (dd, J 11.9/6.7 Hz, 1H, CH(OH)CH_2NH), 1.52 – 1.75 (m, 6H, ^{c}Pe CH_2), 1.40 – 1.52 (m, 2H, ^{c}Pe CH_2); ^{13}C NMR (DMSO-d$_6$) δ 155.05 (C=O), 152.72, 152.49, 142.33, 121.69 (aryl 4° C), 130.57 (aryl 5-C), 123.41 (aryl 4-C), 121.69 (aryl 2-C), 116.29 (aryl 6-C), 115.33 (*C*H aryl-dioxy ring), 80.85 (^{c}Pe *C*H), 71.89 (ArO*C*H$_2$), 67.97 (*C*H(OH)), 67.70 (*C*H$_2$OAr), 66.73 (^{c}PeO*C*H$_2$), 52.08 (CH(OH)*C*H$_2$NH), 49.06 (NH*C*H$_2$CH$_2$), 38.70 (NHCH$_2$*C*H$_2$), 31.81 (2-C and 5-C ^{c}Pe ring), 23.14 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{25}H_{35}BrN_3O_5$ [MH]$^+$ calcd 536.1755; found 536.1735; RP-HPLC R_t 4.47 (System 1b), 14.42 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(4-bromophenyl)urea (37p). Prepared via method **M1**; Yield: 23%, white amorphous solid; mp = 148 – 150 °C; FT-IR 3326 (br, O-H, str), 2926, 2869 (alkyl C-H, str), 1633 (urea C=O, str), 1509, 1560 (aryl, str), 1110 (C-O-C, str), 822 (aryl C-H, bend, *para*-disubstituted ring); ^{1}H NMR (DMSO-d$_6$) δ 8.77 (s, 1H, NH(C=O)N*H*Ar), 7.37 (s, 4H, C-H of bromophenyl ring), 6.84 (d, J = 9.3 Hz, 2H, C-H aryl-dioxy ring), 6.82 (d, J = 9.2 Hz, 2H, C-H aryl-dioxy ring), 6.25 (t, J = 5.4 Hz, 1H, N*H*(C=O)NHAr), 5.03 (br s, 1H, NH), 3.78 – 3.97 (m, 6H, CH_2OAr, ^{c}Pe CH, CH(OH), ArOCH_2), 3.61 (t, J = 4.8 Hz, 2H, ^{c}PeOCH_2), 3.17 (dt, J = 5.8/5.8 Hz, 2H, NHCH$_2$CH_2), 2.71 (dd, J = 11.8/3.9 Hz, 1H, CH(OH)CH_2NH), 2.57 – 2.68 (m, 3H, CH(OH)CH_2NH, NHCH_2CH$_2$), 1.51 – 1.74 (m, 6H, ^{c}Pe CH_2), 1.40 – 1.51 (m, 2H, ^{c}Pe CH_2); ^{13}C NMR (DMSO-d$_6$) δ 155.12 (C=O), 152.69, 152.49, 140.04, 112.14 (aryl 4° C), 131.34, 119.43 (CH bromophenyl ring), 115.30 (*C*H aryl-dioxy ring), 80.84 (^{c}Pe *C*H),

71.15 (ArO*C*H$_2$), 67.92 (*C*H(OH)), 67.68 (*C*H$_2$OAr), 66.72 (^{c}PeO*C*H$_2$), 52.05 (CH(OH)*C*H$_2$NH), 49.08 (NH*C*H$_2$CH$_2$), 38.85 (NHCH$_2$*C*H$_2$), 31.79 (2-C and 5-C ^{c}Pe ring), 23.13 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{25}H_{35}BrN_3O_5$ [MH]$^+$ calcd 536.1755; found 536.1773; RP-HPLC R_t 4.47 (System 1b), 14.45 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(2-(trifluoromethyl)phenyl)urea (37q). Prepared via method **M1**; Yield: 12%, white amorphous solid; mp = 128 – 130 °C; FT-IR 3330 (br, O-H, str), 2923, 2866 (alkyl C-H, str), 1645 (urea C=O, str), 1510, 1571 (aryl, str), 1121 (C-O-C, str), 1323 (C-F, str), 820 (aryl C-H, bend, *para*-disubstituted ring), 768 (aryl C-H, bend, *ortho*-disubstituted ring); ^{1}H NMR (DMSO-d$_6$) δ 7.95 (d, *J* = 8.4 Hz, 1H, aryl 6-H), 7.86 (s, 1H, NH(C=O)N*H*Ar), 7.60 (d, *J* = 7.9 Hz, 1H, aryl 3-H), 7.55 (dd, *J* = 7.9/7.9 Hz, 1H, aryl 5-H), 7.17 (dd, *J* = 7.6/7.6 Hz, 1H, aryl 4-H), 7.08 (t, *J* = 5.2 Hz, 1H, N*H*(C=O)NHAr), 6.84 (s, 4H, aryl-dioxy ring), 5.04 (br s, 1H, NH), 3.77 – 4.02 (m, 6H, C*H*$_2$OAr, ^{c}Pe C*H*, C*H*(OH), ArOC*H*$_2$), 3.61 (t, *J* = 4.9 Hz, 2H, ^{c}PeOC*H*$_2$), 3.21 (dt, *J* = 5.8/5.8 Hz, 2H, NHCH$_2$C*H*$_2$), 2.62 – 2.77 (m, 4H, CH(OH)C*H*$_2$NH, NHC*H*$_2$CH$_2$), 1.52 – 1.75 (m, 6H, ^{c}Pe C*H*$_2$), 1.42 – 1.52 (m, 2H, ^{c}Pe C*H*$_2$); ^{13}C NMR (DMSO-d$_6$) δ 155.12 (C=O), 152.69, 152.52, 137.36 (aryl 4° C), 132.72 (aryl 5-C), 126.82 (*J*$_{CF}$ = 274.6 Hz, CF_3), 125.79 (aryl 3-C), 124.77 (aryl 6-C), 122.59 (aryl 4-C), 115.32 (*C*H aryl-dioxy ring), 80.84 (^{c}Pe *C*H), 71.13 (ArO*C*H$_2$), 67.80 (*C*H(OH)), 67.69 (*C*H$_2$OAr), 66.71 (^{c}PeO*C*H$_2$), 52.03 (CH(OH)*C*H$_2$NH), 49.03 (NH*C*H$_2$CH$_2$), 39.02 (NHCH$_2$*C*H$_2$), 31.78 (2-C and 5-C ^{c}Pe ring), 23.13 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{26}H_{35}F_3N_3O_5$ [MH]$^+$ calcd 526.2523; found 526.2538; RP-HPLC R_t 4.27 (System 1b), 13.55 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(3-(trifluoromethyl)phenyl)urea (37r). Prepared via method **M1**; Yield: 7%, white amorphous solid; mp = 96 – 98 °C; FT-IR 3331 (br, O-H, str), 2927, 2869 (alkyl C-H, str), 1633 (urea C=O, str), 1509, 1566 (aryl, str), 1125 (C-O-C, str), 1344 (C-F, str), 821 (aryl C-H, bend, *para*-disubstituted ring), 764 (aryl C-H, bend, *meta*-disubstituted ring), 702 (C-F, bend); ^{1}H NMR (DMSO-d$_6$) δ 9.03 (s, 1H, NH(C=O)N*H*Ar), 7.97 (s, 1H, aryl 2-H), 7.50 (d, *J* = 8.5 Hz, 1H, aryl 6-H), 7.44 (dd, *J* = 7.7/7.7 Hz, 1H, aryl 5-H), 7.21 (d, *J* = 7.5, 1H, aryl 4-H), 6.85 (d, *J* = 9.2 Hz, 2H, C-H aryl-dioxy ring), 6.82 (d, *J* = 9.3 Hz, 2H, C-H aryl-dioxy ring), 6.36 (t, *J* = 5.3 Hz, 1H, N*H*(C=O)NHAr), 5.13 (br s, 1H, NH), 3.81 – 3.97 (m, 6H, C*H*$_2$OAr, ^{c}Pe C*H*, C*H*(OH), ArOC*H*$_2$), 3.61 (t, *J* = 4.9 Hz, 2H, ^{c}PeOC*H*$_2$), 3.22 (dt, *J* = 5.7/5.7 Hz, 2H, NHCH$_2$C*H*$_2$), 2.63 – 2.83 (m, 4H, CH(OH)C*H*$_2$NH, NHC*H*$_2$CH$_2$), 1.51 – 1.74 (m, 6H, ^{c}Pe C*H*$_2$), 1.41 – 1.51 (m, 2H, ^{c}Pe C*H*$_2$); ^{13}C NMR (DMSO-d$_6$) δ 155.22 (C=O), 152.65, 152.55, 141.43, (aryl 4° C), 129.74 (aryl 5-C), 124.31 (*J*$_{CF}$ = 270.6 Hz, CF_3), 121.06 (aryl 6-C), 117.12 (aryl 4-C), 115.32 (*C*H aryl-dioxy ring), 113.44 (aryl 2-C), 80.85 (^{c}Pe *C*H), 71.05 (ArO*C*H$_2$), 67.70 (*C*H$_2$OAr), 67.51 (*C*H(OH)), 66.72 (^{c}PeO*C*H$_2$), 51.74 (CH(OH)*C*H$_2$NH), 48.83 (NH*C*H$_2$CH$_2$), 38.60 (NHCH$_2$*C*H$_2$), 31.80 (2-C and 5-C ^{c}Pe ring), 23.14 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{26}H_{35}F_3N_3O_5$ [MH]$^+$ calcd 526.2523; found 526.2474; RP-HPLC R_t 4.64 (System 1b), 14.77 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(4-(trifluoromethyl)phenyl)urea (37s). Prepared via method **M1**; Yield: 26%, white amorphous solid; mp = 134 – 136 °C; FT-IR 3293 (br, O-H, str), 2932, 2871 (alkyl C-H, str), 1694 (urea C=O, str), 1509, 1568 (aryl, str), 1122 (C-O-C, str), 1328 (C-F, str), 821, 841 (aryl C-H, bend, *para*-disubstituted ring), 703 (C-F, bend); ^{1}H NMR (DMSO-d$_6$) δ 9.08 (s, 1H, NH(C=O)N*H*Ar), 7.59 (d, *J* = 9.0 Hz, 2H, 2-H and 6-H of trifluoromethylphenyl ring), 7.55 (d, *J* = 9.1 Hz, 2H, 3-H and 5-H of trifluoromethylphenyl ring), 6.85 (d, *J* = 9.2 Hz, 2H, C-H aryl-dioxy ring), 6.82 (d, *J* = 9.3 Hz, 2H, C-H aryl-dioxy ring), 6.38 (t, *J* = 5.4 Hz, 1H, N*H*(C=O)NHAr), 5.03 (br s, 1H, NH), 3.77 – 4.01 (m, 6H, C*H*$_2$OAr, ^{c}Pe C*H*, C*H*(OH), ArOC*H*$_2$), 3.61 (t, *J* = 4.9 Hz, 2H, ^{c}PeOC*H*$_2$), 3.21 (dt, *J* = 5.8/5.8 Hz, 2H, NHCH$_2$C*H*$_2$), 2.74 (dd, *J* = 11.8/3.8 Hz, 1H, CH(OH)C*H*$_2$NH), 2.69 (t, *J* = 5.9 Hz, 2H, NHC*H*$_2$CH$_2$), 2.63 (dd, *J* = 12.0/6.6 Hz, 1H, CH(OH)C*H*$_2$NH), 1.52 – 1.75 (m, 6H, ^{c}Pe C*H*$_2$), 1.38 – 1.52 (m, 2H, ^{c}Pe C*H*$_2$); ^{13}C NMR (DMSO-d$_6$) δ 154.97 (C=O), 152.69, 152.51, 144.32, (aryl 4° C), 125.93 (*J*$_{CF}$ = 3.4 Hz, 3-C and 5-C of trifluoromethylphenyl ring), 124.68 (*J*$_{CF}$ = 269.6 Hz, CF_3), 120.82 (*J*$_{CF}$ = 34.7 Hz, 4-C of trifluoromethylphenyl ring), 117.11 (2-C and 6-C of trifluoromethylphenyl ring), 115.31 (*C*H aryl-dioxy ring), 80.84 (^{c}Pe *C*H), 71.13 (ArO*C*H$_2$), 67.83 (*C*H(OH)), 67.68 (*C*H$_2$OAr), 66.71 (^{c}PeO*C*H$_2$),

51.96 (CH(OH)*C*H_2NH), 48.94 (NH*C*H_2CH$_2$), 38.64 (NHCH$_2$*C*H$_2$), 31.78 (2-C and 5-C ^{c}Pe ring), 23.12 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{26}H_{35}F_3N_3O_5$ [MH]$^+$ calcd 526.2523; found 526.2480; RP-HPLC R_t 4.67 (System 1b), 14.90 (System 3).

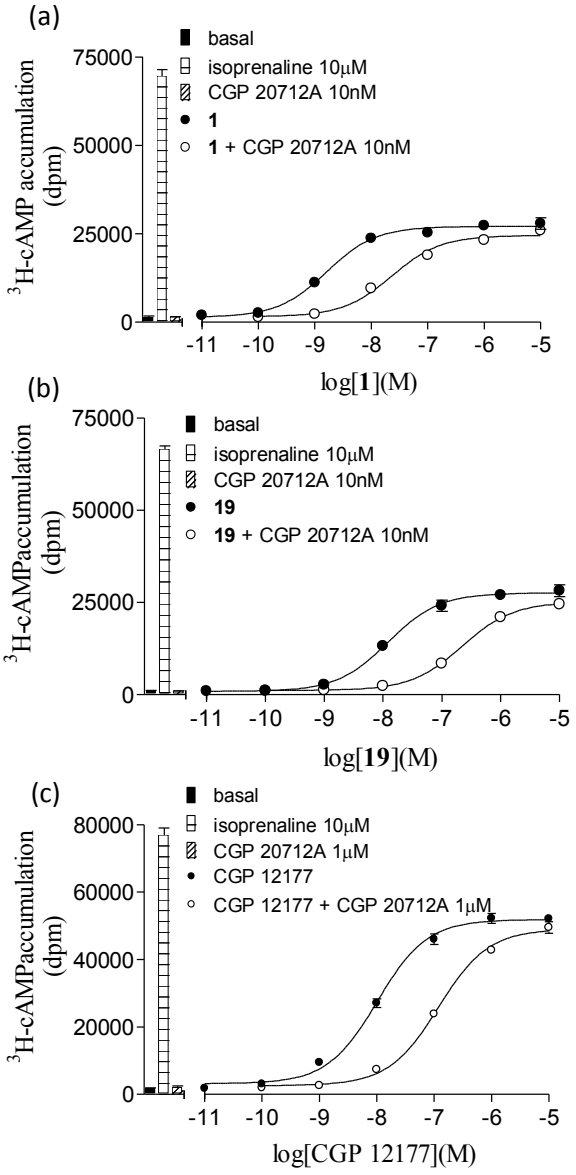
1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(2-hydroxyphenyl)urea (37t). To 2-((4-(2-(cyclopentyloxy)ethoxy)phenoxy)methyl)oxirane **(27a)** (51 mg, 0.18 mmol) was added TEA (75 µl, 0.53 mmol, 3 eq), 1-(2-aminoethyl)-3-(2-hydroxyphenyl)urea hydrochloride **(36a)** (83 mg, 0.36 mmol, 2 eq) and propan-2-ol (5 mL). The mixture was heated under reflux for 16 hours. After removal of all volatiles under reduced pressure, the crude residue was purified by PLC (eluent 37% aq NH_3/MeOH/DCM 2:5:93) to give 18 mg (21%) of beige semi-solid. FT-IR 3319 (br, O-H, str), 2920, 2900 (alkyl, C-H, str), 1653 (urea C=O, str), 1558, 1506 (aryl, str), 1109 (C-O-C, str), 823 (aryl, C-H, bend, *para*-disubstituted ring), 750 (aryl, C-H, bend, *ortho*-disubstituted ring); ^{1}H NMR (DMSO-d$_6$) δ 8.01 (s, 1H, NH(C=O)N*H*Ar), 7.83 (dd, *J* = 7.8/1.6 Hz, 1H, aryl 6-H), 6.91 (t, *J* = 5.4 Hz, 1H, N*H*(C=O)NHAr), 6.85 (d, *J* = 9.7 Hz, 2H, aryl-dioxy ring), 6.82 (d, *J* = 9.30 Hz, 2H, aryl-dioxy ring), 6.78 (dd, *J* = 7.8/1.7 Hz, 1H, aryl 3-H), 6.73, (ddd, *J* = 7.7/7.3/1.2 Hz, 1H, aryl 4-H), 6.68, (ddd, *J* = 7.8/7.3/1.7 Hz, 1H, aryl 5-H), 6.09 (br s, 1H, phenol), 3.80 – 4.00 (m, 6H C*H*$_2$OAr, ^{c}Pe C*H*, C*H*(OH), ArOC*H*$_2$), 3.61 (t, *J* = 4.8 Hz, 2H, ^{c}PeOC*H*$_2$), 3.19 (dt, *J* = 5.8/5.8 Hz, 2H, NHCH$_2$C*H*$_2$), 2.75 (dd, *J* = 12.1/3.9 Hz, 1H, CH(OH)C*H*$_2$NH), 2.61 – 2.69 (m, 3H, NHC*H*$_2$CH$_2$, CH(OH)C*H*$_2$NH), 1.40-1.72 (m, 8H, ^{c}Pe C*H*$_2$); ^{13}C NMR (DMSO-d$_6$) δ 155.81 (C=O), 152.70, 152.52, 145.63, 128.43 (aryl 4° C), 121.34 (aryl 4-C), 119.04 (aryl 5-C), 118.76 (aryl 6-C), 115.34 (CH aryl-dioxy ring), 114.82 (aryl 3-C), 80.84 (^{c}Pe CH), 71.14 (ArOCH$_2$), 67.75 (CH(OH)), 67.72 (CH$_2$OAr), 66.72 (^{c}PeOCH$_2$), 51.95 (CH(OH)*C*H$_2$NH), 49.18 (NH*C*H$_2$CH$_2$), 40.11(NHCH$_2$*C*H$_2$), 31.79 (2-C and 5-C ^{c}Pe ring), 23.12 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{25}H_{36}N_3O_6$ [MH]$^+$ calcd 474.2599; found 474.2600; RP-HPLC R_t 4.10 (System 1b), 11.84 (System 3).

1-(2-(3-(4-(2-(Cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(3-hydroxyphenyl)urea (37u). Oxirane aminolysis of 2-((4-(2-(cyclopentyloxy)ethoxy)phenoxy) methyl)oxirane **(27a)** with 1-(2-aminoethyl)-3-(3-hydroxyphenyl)urea hydrochloride **(36b)**, was carried out as described in the procedure for 1-(2-(3-(4-(2-(cyclopentyloxy)ethoxy)phenoxy)-2-hydroxypropylamino)ethyl)-3-(2-hydroxyphenyl)urea **(37t)**. Purification was achieved via PLC (eluent 37% aq NH_3/MeOH/DCM 2:10:88) to give 21 mg (25%) of beige semi-solid. FT-IR 3350 (br, O-H, str), 2932, 2868 (alkyl, C-H, str), 1675 (urea C=O, str), 1559, 1507 (aryl, str), 1108 (C-O-C, str), 826 (aryl, C-H, bend, *para*-disubstituted ring), 765 (aryl, C-H, bend, *meta*-disubstituted ring); ^{1}H NMR (DMSO-d$_6$) δ 9.18 (br s, 1H, phenol), 8.47 (s, 1H, NH(C=O)N*H*Ar), 6.98 (s, 1H, aryl 2-H), 6.96 (dd, *J* = 8.1 Hz, 1H, aryl 5-H), 6.77 – 6.90 (m, 4H, aryl-dioxy ring), 6.71 (d, *J* = 7.8 Hz, 1H, aryl 6-H) , 6.28 (dd, *J* = 7.8/1.8 Hz, 1H, aryl 4-H), 6.16 (t, *J* = 5.2 Hz, 1H, N*H*(C=O)NHAr), 3.75 - 4.02 (m, 6H, C*H*$_2$OAr, ^{c}PeC*H*, C*H*(OH), ArOC*H*$_2$), 3.61 (t, *J* = 4.8 Hz, 2H, ^{c}PeOCH$_2$), 3.15 (dt, *J* = 5.7/5.7 Hz, 2H, NHCH$_2$C*H*$_2$), 2.70 (dd, *J* = 12.0/3.7 Hz, 1H, CH(OH)C*H*$_2$NH), 2.54 – 2.67 (m, 3H, CH(OH)C*H*$_2$NH, NHC*H*$_2$CH$_2$),1.38 – 1.74 (m, 8H, ^{c}Pe C*H*$_2$); ^{13}C NMR (DMSO-d$_6$) δ 155.24 (C=O), 157.65, 152.73, 152.51, 141.66, (aryl 4° C), 129.20 (aryl 5-C), 115.34 (CH aryl-dioxy ring), 108.38 (aryl 6-C), 108.10 (aryl 4-C), 104.68 (aryl 2-C), 80.84 (^{c}Pe CH), 71.22 (ArOCH$_2$), 68.01 (CH(OH)), 67.72 (CH$_2$OAr), 66.72 (^{c}PeOCH$_2$), 52.14 (CH(OH)*C*H$_2$NH), 49.23 (NH*C*H$_2$CH$_2$), 38.99 (NHCH$_2$*C*H$_2$), 31.79 (2-C and 5-C ^{c}Pe ring), 23.12 (3-C and 4-C ^{c}Pe ring); *m/z* HRMS (TOF ES$^+$) $C_{25}H_{36}N_3O_6$ [MH]$^+$ calcd 474.2599; found 474.2642; RP-HPLC R_t 3.90 (System 1b), 11.02 (System 3).

Supporting Table 1. Assessment of β_1-agonist conformation activated by the partial agonists.

	Log K_D CGP 20712A	n
Xamoterol	-9.51 ± 0.05	4
ICI 89406	-9.25 ± 0.05	4
Cimaterol	-9.48 ± 0.06	12
1	-9.28 ± 0.10	4
19	-9.51 ± 0.11	4
29a	-9.35 ± 0.09	3
29b	-9.35 ± 0.14	3
29c	-9.59 ± 0.07	4
37a	-9.41 ± 0.09	4
37l	-9.09 ± 0.03	4
CGP 12177	-7.22 ± 0.03	5

Log K_D values for CGP 20712A obtained from ^{3}H-cAMP accumulation assays following inhibition of the partial agonist responses in CHO β_1-cells. Values represent mean ± s.e.m. of n separate experiments.



Supporting Figure 1. ^{3}H-cAMP accumulation in response to (a) **1**, (b) **19** and (c) CGP 12177 in CHO β_1 cells. Bars represent basal ^{3}H-cAMP accumulation and that in response to 10 μM isoprenaline, 10 nM CGP 20712A or 1 μM CGP 20712A alone. Data points are mean ± s.e.mean of triplicate determinations. These single experiments are representative of (a) 4, (b) 4 and (c) 5 separate experiments.

Supplementary References

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