

Supporting Information:

## **Experimental Section.**

### **General Methods and Materials.**

$^1\text{H}$  NMR spectra were recorded on a Bruker Avance (600 MHz and 300 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the residual solvent resonance resulting from incomplete deuteration as the internal standard ( $\text{CDCl}_3$ :  $\delta$  7.25 ppm,  $\text{DMSO}-d_6$ :  $\delta$  2.54 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants.  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance (150 MHz or 75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ( $\text{CDCl}_3$ :  $\delta$  77.0 ppm,  $\text{DMSO}-d_6$ :  $\delta$  39.5 ppm). Data reported in parentheses refer to the fluorine-coupling partner of the preceeding signal. Please note in certain cases the solvent may conceal compound related signals during routine  $^{13}\text{C}$  NMR analysis.

Low-resolution mass spectrometry was performed on an Agilent Technologies 1100 Series LC/MS ESI-MS (positive mode). High-resolution mass spectrometry was performed on an Ionspec Ultima FTMS or an Agilent Technologies 1100 Series LC/MS-TOF; ESI-MS (positive mode). Preparative HPLC was performed on a Varian/PrepStar Model SD-1 using 220 and 254 nm. Flash chromatography was conducted using silica gel 230-400 mesh (60 Å), Merck.

Unless otherwise stated, all reagents were used as obtained from Aldrich, Alfa-Aesar, Fluka, Lancaster, or Strem Chemicals. All solvents were of ACS grade or higher.

Radiolabelling using [ $^{18}\text{F}$ ]fluoride (PETNet, Woburn, MA) was conducted in 5 mL Wheaton™ vials using a custom robotic synthesis platform. Whole animal imaging was conducted using a Focus 220 microPET camera (CTI Molecular Imaging, Inc. Knoxville, TN). Biodistribution samples were measured in an autogamma well counter (Wallac Wizard 1480). . All animal study protocols were approved by the Institutional Animal Care and Use Committee.

### **General Procedure for preparation of substituted *tert*-butyl 2-(3-phenylureido)ethylcarbamates (28-34, and 51)**

A solution of isocyanate (0.1 mol) dissolved in THF (1.4 – 6.0 M) was added drop-wise over 15 min to a cooled (0 °C) solution of *tert*-butyl 2-aminoethylcarbamate (0.1 mol) dissolved in THF (1.4 – 6.0 M). The reaction mixture stirred at 0 °C, warming slowly to ambient temperature over 2.5 to 16 h. The reaction mixture was then concentrated to dryness and the crude material used without further purification in the subsequent step. Yields reported are based on crude material obtained.

***tert*-Butyl 2-(3-(4-methoxyphenyl)ureido)ethylcarbamate (28)**

92% Yield; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 8.27 (s, 1H), 7.29 – 7.24 (m, 2H), 6.83 – 6.77 (m, 2H), 6.02 (d, *J* = 9.7 Hz, 1H), 3.69 (s, 3H), 3.10 (q, *J* = 6.2 Hz, 2H), 2.99 (q, *J* = 6.1 Hz, 2H), 1.38 (s, 9H). The spectral data were consistent with that previously reported by Schaefer et al.<sup>1</sup>

***tert*-Butyl 2-(3-(2-fluorophenyl)ureido)ethylcarbamate (29)**

47% Yield; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.31 (s, 1H), 8.11 (t, *J* = 8.2 Hz, 1H), 7.22 – 7.11 (m, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.96 – 6.85 (m, 2H), 6.66 (t, *J* = 4.6 Hz, 1H), 3.13 (q, *J* = 6.0 Hz, 2H), 3.00 (q, *J* = 6.0 Hz, 2H), 1.38 (s, 9H); <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sub>6</sub>): δ -130.55 (s); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 155.7, 154.9, 153.2 (150.1), 128.3 (128.2), 124.3 (124.2), 121.5 (121.3), 120.0 (120.1), 114.8 (114.6), 77.6, 40.3, 38.8, 28.2; HRMS: calcd for C<sub>14</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>3</sub> (M+Na): 320.1380; found: 320.1380.

***tert*-Butyl 2-(3-(4-fluorophenyl)ureido)ethylcarbamate (30)**

53% Yield; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 8.53 (s, 1H), 7.40 – 7.36 (m, 2H), 7.04 (t, *J* = 8.9 Hz, 2H), 6.82 (s, 1H), 6.11 (s, 1H), 3.11 (q, *J* = 6.2 Hz, 2H), 3.00 (q, *J* = 6.1 Hz, 2H), 1.37 (s, 9H); <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>): δ 157.6, 156.0 (156.6), 155.2, 136.8, 119.2 (119.2), 115.0 (114.8), 77.5, 40.4, 28.1; HRMS calcd for C<sub>14</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>3</sub> (M+Na): 320.1380; found: 320.1376.

***tert*-Butyl 2-(3-(4-(benzyloxy)phenyl)ureido)ethylcarbamate (31)**

93% Yield; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 8.28 (s, 1H), 7.43 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.29 – 7.25 (m, 2H), 6.90 – 6.86 (m, 2H), 6.80

(brs, 1H), 6.03 (t,  $J = 5.1$  Hz, 1H), 5.03 (s, 2H), 3.10 (q,  $J = 6.2$  Hz, 2H), 2.99 (q,  $J = 6.1$  Hz, 2H), 1.38 (s, 9H);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  155.7, 155.4, 152.9, 152.4, 137.3, 133.8, 128.3, 127.6, 127.5, 119.3, 114.9, 77.6, 69.4, 28.2; HRMS- calcd for  $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}_4$  ( $\text{M} + \text{Na}$ ):, 408.1893; found: 408.1893. The spectral data were consistent with that previously reported by Schaefer et al.<sup>1</sup>

***tert*-Butyl 2-(3-(4-nitrophenyl)ureido)ethylcarbamate (32)**

87% Yield;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  9.33 (s, 1H), 8.16 – 8.10 (m, 2H), 7.66 – 7.58 (m, 2H), 6.85 (t,  $J = 5.1$  Hz, 1H), 6.43 (t,  $J = 5.0$  Hz, 1H), 3.20 – 3.11 (m, 2H), 3.03 (q,  $J = 5.9$  Hz, 2H), 1.37 (s, 9H);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $dd_6$ ):  $\delta$  155.7, 154.4, 147.1, 140.3, 126.3, 125.1, 116.8, 77.6, 28.2; HRMS calcd for  $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_5$  ( $\text{M} + \text{Na}$ ): 347.1325; found: 347.1327.

***tert*-Butyl 2-(3-(4-ethoxyphenyl)ureido)ethylcarbamate (33)**

71% Yield;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  8.28 (s, 1H), 7.25 (d,  $J = 8.9$  Hz, 2H), 6.88 – 6.74 (m, 3H), 6.03 (t,  $J = 5.7$  Hz, 1H), 3.94 (q,  $J = 6.9$  Hz, 2H), 3.10 (q,  $J = 6.0$  Hz, 2H), 3.03 – 2.94 (m, 2H), 1.37 (s, 9H), 1.29 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (150 MHz, DMSO- $d_6$ ):  $\delta$  155.6, 155.4, 153.1, 133.5, 119.4, 114.4, 77.5, 66.9, 40.5, 39.0, 28.1, 14.6; HRMS calcd for  $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}_4$  ( $\text{M} + \text{H}$ ): 324.1917; found: 324.1923. The spectral data were consistent with that previously reported by Schaefer et al.<sup>1</sup>

**Ethyl 4-(3-(2-(*tert*-butoxycarbonylamino)ethyl)ureido)benzoate (34)**

>98% Yield;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ ):  $\delta$  8.95 (s, 1H), 7.81 (m, 2H), 7.5 (m, 2H), 6.82 (m, 1H), 6.29 (m, 1H), 4.25 (q,  $J = 7.2$  Hz, 2H), 3.1 (ABq,  $J_{\text{AB}} = 6.0$  Hz, 2H), 3.0 (ABq,  $J_{\text{AB}} = 6.0$  Hz, 2H), 1.37 (s, 9H), 1.29 (m, 3H); HRMS calcd for  $\text{C}_{17}\text{H}_{25}\text{N}_3\text{O}_5$  ( $\text{M} + \text{Na}$ ): 374.1686; found: 374.1687. The spectral data were consistent with that previously reported by Schaefer et al.<sup>1</sup>

***tert*-Butyl 2-(3-(4-hydroxyphenyl)ureido)ethylcarbamate (35)**

To a solution of **31** (1.0 g, 2.59 mmol) dissolved in MeOH (51.9 mL) was added Pd/C (100 mg, 94.0  $\mu\text{mol}$ ; 3.6 mol %). The reaction mixture was then placed on the Parr shaker, sparged with  $\text{H}_2$  then pressurized to 50 psi and maintained overnight. The resulting suspension

was filtered through a pad of Celite, and the filter cake washed with MeOH (2 x 30 mL). The filtrate was concentrated to obtain **35** as a white foam (0.70 g, 91% yield), which was taken to the next step without purification. <sup>1</sup>H NMR (150 MHz, DMSO-*d*<sub>6</sub>): δ 8.90 (s, 1H), 8.13 (s, 1H), 7.15 – 7.10 (m, 2H), 6.79 (t, *J* = 4.7 Hz, 1H), 6.64 – 6.59 (m, 2H), 5.98 (t, *J* = 5.4 Hz, 1H), 3.09 (q, *J* = 6.2 Hz, 2H), 2.98 (q, *J* = 6.1 Hz, 2H), 1.38 (s, 9H); <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>): δ 155.6, 155.6, 151.9, 132.0, 119.9, 115.0, 77.5, 40.6, 39.0, 28.2; HRMS calcd for C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub> (M+H)<sup>+</sup>; 296.1604; found: 296.1602.

***tert*-Butyl 2-(3-(4-(2-fluoroethoxy)phenyl)ureido)ethylcarbamate (36).**

**35** (0.400 g, 1.35 mmol) was dissolved in THF (13.5 mL) successively treated with 2-fluoroethanol (99 μL, 1.69 mmol), PPh<sub>3</sub> (666 mg, 2.54 mmol), and DIAD (417 μL, 2.12 mmol) then stirred overnight at ambient temperature. An additional 0.5 equiv of DIAD (133 μL) was then added and the reaction mixture maintained 5 h at ambient temperature. All volatiles were removed in vacuo and the residue purified by silica gel chromatography (2:1 EtOAc/ hexanes to 4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to provide **36** as a white solid (92 mg, 20% yield). <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 8.35 (s, 1H), 7.31 – 7.25 (m, 2H), 6.87 – 6.77 (m, 3H), 6.09 (s, 1H), 4.76 – 4.72 (m, 1H), 4.68 – 4.64 (m, 1H), 4.20 – 4.16 (m, 1H), 4.14 – 4.11 (m, 1H), 3.10 (q, *J* = 6.2 Hz, 2H), 2.99 (q, *J* = 6.1 Hz, 2H), 1.38 (s, 9H) <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sub>6</sub>): δ -222.29 (m); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 155.7, 155.4, 152.7, 134.0, 119.3, 114.6, 83.3 (81.1), 77.6, 67.4 (67.1), 40.5, 39.0, 28.2; HRMS calcd for C<sub>16</sub>H<sub>24</sub>FN<sub>3</sub>O<sub>4</sub> (M+Na)<sup>+</sup>, 364.1643; found: 364.1645.

***tert*-Butyl 2-(3-(4-(3-fluoropropoxy)ureido)ethylcarbamate (37).**

To a stirred solution of 3-fluoropropanol (1.00 g, 12.8 mmol) and Et<sub>3</sub>N (4.00 mL, 25.6 mmol) in THF (14 mL) was added a solution of TsCl (14.1 mmol; 7.00 mL of a 2.12 M solution in THF) at ambient temperature, and resulting mixture stirred overnight. The resulting suspension was then filtered, concentrated, re-dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and finally washed with saturated aqueous NaHCO<sub>3</sub> (15 mL) and H<sub>2</sub>O (15 mL). The organic layer was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to obtain a yellow oil. Subsequent purification by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>: hexanes 1:1) afforded 3-fluoropropyl 4-methylbenzenesulfonate (1.2 g, 40 % yield) as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.78 (m, 2H), 7.34 (m, 2H), 4.51 (m, 1H), 4.34 (m, 1H), 4.16 (m, 2H), 2.44 (s, 3H), 2.03 (m, 2H); <sup>19</sup>F NMR (CDCl<sub>3</sub>): δ -

223.41 (m). The spectral data were consistent with that previously reported by Millington, J. E. et al.<sup>2</sup>

**35** (670 mg, 2.27 mmol) and NaOH powder (127 mg, 3.18 mmol) were dissolved in DMSO (23 mL), stirred 30 min, then warmed to 75 °C and treated with 3-fluoropropyl 4-methylbenzenesulfonate (527 mg, 2.27 mmol). The reaction mixture was maintained at 75 °C for 30 min, then cooled to ambient temperature, diluted with water (25 mL) and filtered to afford crude **37** as a solid (580 mg). <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 8.30 (s, 1H), 7.29 – 7.25 (m, 2H), 6.85 – 6.79 (m, 3H), 6.04 (t, *J* = 5.4 Hz, 1H), 4.63 (t, *J* = 5.9 Hz, 1H), 4.55 (t, *J* = 5.9 Hz, 1H), 3.99 (t, *J* = 6.3 Hz, 2H), 3.11 (q, *J* = 6.2 Hz, 2H), 2.99 (q, *J* = 6.1 Hz, 2H), 2.07 (m 2H), 1.38 (s, 9H); <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sub>6</sub>): δ -222.29 (m); <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>): δ 155.6, 155.4, 153.0, 133.7, 119.4, 114.5, 81.3 (80.2), 77.5, 63.6 (63.6), 40.5, 39.0, 29.8 (29.7), 28.1; HRMS calcd for C<sub>17</sub>H<sub>26</sub>FN<sub>3</sub>O<sub>4</sub> (M+H), 378.1799; found: 378.1802.

#### Synthesis of *tert*-Butyl 2-(3-(3-(benzyloxy)phenyl)ureido)ethylcarbamate (**38**).

To a cooled (0 °C) solution of 4-nitrophenyl chloroformate (2.02 g, 10.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) was treated with a solution of 3-(benzyloxy)aniline (1.99 g, 10.0 mmol) and pyridine (0.900 mL, 11.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (13 mL). After complete addition, the reaction warmed slowly to ambient temperature as the ice bath melted overnight. The reaction mixture was then concentrated to a brown oil and purified using silica gel chromatography (EtOAc:hexanes 3:1) to obtain 4-nitrophenyl 3-(benzyloxy)phenylcarbamate as a white solid, which was used without further purification in the subsequent step.

A solution of *N*-Boc-ethylenediamine (1.80 g, 11.2 mmol) dissolved in THF (10 mL) was added dropwise to a solution of 4-nitrophenyl 3-(benzyloxy)phenylcarbamate in THF (22 mL) and the resulting mixture stirred overnight at ambient temperature. **38** formed as a white solid that was isolated through filtration (1.66 g, 43% yield). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.50 (s, 1H), 7.48 – 7.27 (m, 5H), 7.22 (t, *J* = 2.2 Hz, 1H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.90 – 6.80 (m, 2H), 6.55 (ddd, *J* = 0.9, 2.5, 8.2 Hz, 1H), 6.14 (t, *J* = 5.3 Hz, 1H), 5.04 (s, 2H), 3.17 – 3.07 (m, 2H), 3.05 – 2.96 (m, 2H), 1.38 (s, 9H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN:D<sub>2</sub>O 2:1 v/v): δ 158.7, 155.7, 155.2, 141.7, 137.2, 129.3, 128.4, 127.7, 127.5, 110.3, 107.2, 104.4, 77.6, 58.9, 28.2, 25.1.

#### Synthesis of *tert*-Butyl 2-(3-(3-hydroxyphenyl)ureido)ethylcarbamate (**39**).

To a solution of **38** (1.6 g, 4.2 mmol) in EtOH (75 mL) was added Pd/C (160 mg 0.15 mmol; 3.6 mol %). The resulting suspension was then placed on the Parr shaker, sparged with H<sub>2</sub> then pressurized to 50 psi and maintained overnight. The resulting suspension was filtered through a pad of Celite, and the filter cake washed with MeOH (2 x 30 mL). The filtrate was concentrated to obtain **39** as a colorless oil (1.18 g). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 6.88 (m, 2H), 6.63 (dd, *J* = 1.2, 8.0 Hz, 1H), 6.30 (dd, *J* = 2.2, 7.9 Hz, 1H), 3.15 (t, *J* = 5.8 Hz, 2H), 3.06 (t, *J* = 5.5 Hz, 2H), 1.28 (s, 9H); HRMS calcd for C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub> (M+H), 296.1604, found: 296.1607.

**Synthesis of *tert*-Butyl 2-(3-(3-(2-fluoroethoxy)phenyl)ureido)ethylcarbamate (40).**

K<sub>2</sub>CO<sub>3</sub> (189 mg, 1.37 mmol) and 2-fluoroethyl tosylate (199 mg, 0.910 mmol) were added to a solution of **39** (284 mg, 1.05 mmol) dissolved in dry DMF (2 mL), the resulting suspension warmed to 50 °C and maintained 12 h. After cooling to ambient temperature, the reaction mixture was diluted with H<sub>2</sub>O (4 mL) and the aqueous layer washed with EtOAc (3 x 20 mL). The combined EtOAc layers were further washed with brine (50 mL), then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to a brown oil. The crude material was purified using silica gel chromatography (10% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to afford **40** (0.10 g, 48% yield).

**Synthesis of *tert*-Butyl 2-(3-(4-(1-fluoropropan-2-ylamino)phenyl)ureido)ethylcarbamate (42).**

To a solution of **32** (1.00 g, 3.08 mmol) dissolved in MeOH (31 mL) was added Pd/C (0.100 g 47.0 μmol; 1.5 mol %). The resulting suspension was then placed on the Parr shaker, sparged with H<sub>2</sub> then pressurized to 50 psi and maintained 2.5 h. The resulting suspension was filtered through a pad of Celite, and the filter cake washed with MeOH (2 x 30 mL). The filtrate was concentrated to obtain *tert*-butyl 2-(3-(4-aminophenyl)ureido)ethylcarbamate (**41**) as a pink solid, which was used without further purification in the subsequent step. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.94 (s, 1H), 6.98 (m, 2H), 6.82 (m, 1H), 6.45 (m, 2H), 5.92 (m, 1H), 4.67 (s, 2H), 3.07 (m, 2H), 2.96 (m, 2H), 1.38 (s, 9H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 155.8, 155.6, 143.4, 129.5, 120.4, 114.1, 77.6, 40.7, 28.2; HRMS calcd for C<sub>14</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub> (M+H), 317.1584; found: 317.1587.

To a slurry of **41** (0.400 g, 1.36 mmol) dissolved in THF (14 mL) was added fluoroacetone (147  $\mu$ L, 2.04 mmol). The resulting solution was cooled to 0 °C using an ice bath, then treated with NaBH(OAc)<sub>3</sub> (864 mg, 4.08 mol) in one portion. After 20 min, the ice bath was removed and the reaction maintained at ambient temperature for 3 d. The solution pH was then adjusted to 9 using saturated aqueous NaHCO<sub>3</sub> and the resulting mixture diluted with H<sub>2</sub>O (25 mL) and Et<sub>2</sub>O (25 mL). The two phases were separated and the aqueous layer further washed with Et<sub>2</sub>O (2 x 25 mL). The combined Et<sub>2</sub>O layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to obtain **42** as a brown solid, which was used without further purification in the subsequent step. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  7.99 (s, 1H), 7.07 (m, 2H), 6.79 (m, 1H), 6.53 (m, 2H), 5.93 (m, 1H), 5.11 (br s, 1H), 4.34 (m, 1H), 4.21 (m, 1H), 3.65 (m, 1H), 3.10 (m, 2H), 2.97 (m, 2H), 1.38 (s, 9H), 1.13 (m, 3H); <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  -223.93 (m); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  155.7, 155.6, 142.7, 129.8, 120.4, 112.8, 86.6 (84.4), 77.6, 47.9 (47.6), 40.6, 28.2, 16.6 (16.6); HRMS calcd for C<sub>17</sub>H<sub>27</sub>FN<sub>4</sub>O<sub>3</sub> (M+H), 355.2140; found: 355.2141.

#### Synthesis of Ethyl 4-(3-(2-(benzylamino)ethyl)ureido)-2-fluorobenzoate (**50**).

Concentrated HCl (4 drops) was added to a solution of 2-fluoro-4-nitrobenzoic acid (0.50 g, 2.7 mmol) dissolved in EtOH (13 mL) and the resulting solution heated to reflux. After 16 h the reaction mixture was cooled to ambient temperature, concentrated then re-dissolved in ethanol (20 mL) and treated with Pd/C (2.5 mg 2.3  $\mu$ mol; 0.9 mol %). The resulting suspension was then sparged with 1 atm H<sub>2</sub>, and stirred 1.5 h at ambient temperature. Upon complete reduction, the suspension was sparged with N<sub>2</sub>, the catalyst removed by filtration through Celite and the filtrate concentrated in vacuo to yield ethyl 2-fluoro-4-amino benzoate (**26**, 0.48 g, 97% yield). The spectral data were consistent with that previously reported by Teng et al.<sup>3</sup>

**26** (0.10 g, 0.55 mmol) and pyridine (43 mg, 0.55 mmol) were successively added to a solution of 4-nitrophenyl chloroformate (120 mg, 0.60 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL). After 0.5 h all volatiles were removed and the residue re-dissolved in DMF (3 mL). Benzyl 2-aminoethyl carbamate (130 mg, 0.67 mmol) and *i*-Pr<sub>2</sub>NEt (0.7 g, 0.55 mmol) were added and the reaction mixture stirred an additional 0.5 h. The reaction mixture was then concentrated and the residue immediately re-dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The organic layer was successively washed with 0.1 N HCl (3 x 5 mL), 0.5 N NaOH (3 x 5 mL), water (10 mL) and brine then dried over

Mg<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to obtain **50** (175 mg, 78.8% yield) as a white solid that was used without further purification in the subsequent step. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.81 (m, 1H), 7.35 (m, 5H), 7.10 (m, 2H), 5.50 (m, 1H), 5.20 (m, 1H), 5.10 (s, 2H), 4.35 (m, 2H), 3.30 (m, 4H), 1.30 (m, 3H).

**Synthesis of *tert*-Butyl 2-(3-(6-(2-fluoroethoxy)pyridine-3-yl)ureido)ethylcarbamate (**52**).**

1-Fluoroethanol (1.0 g, 15.6 mmol) was added dropwise to a stirring suspension of NaOH (0.75 g, 18.8 mmol) in THF (5 mL). The reaction mixture was maintained for 1 h before dropwise addition of 2-chloro-5-nitropyridine (2.45 g, 15.5 mmol) dissolved in THF (10 mL). Upon completion of the addition, the reaction was warmed to 60 °C and maintained overnight. The reaction mixture was then cooled to ambient temperature and treated with water (5 mL). The organic layer was separated then diluted with EtOAc (50 mL), washed with 5% K<sub>2</sub>CO<sub>3</sub> (50 mL) and concentrated to obtain a yellow solid. Silica gel chromatography of the crude material (pentane: EtOAc 20:1) afforded 2-(2-fluoroethoxy)-5-nitropyridine (**61**) as a white solid (0.83 g, 94 % based on recovered starting material). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.07 (d, *J* = 2.8 Hz, 1H), 8.40 (dd, *J* = 2.8, 9.1 Hz, 1H), 6.92 (dd, *J* = 0.4, 9.1 Hz, 1H), 4.86 (dd, *J* = 3.0, 4.9 Hz, 1H), 4.76 (dd, *J* = 3.2, 4.5 Hz, 1H), 4.73 – 4.64 (m, 2H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 166.1, 144.4, 139.7, 134.8, 111.4, 82.7 (80.5), 66.6 (66.4); HRMS calcd for C<sub>7</sub>H<sub>7</sub>FN<sub>2</sub>O<sub>3</sub> (M+H), 187.0513; found: 187.0514.

To a slurry of **61** (0.91 g, 4.89 mmol) in EtOH (10 mL) was added Pd/C (0.052 g, 24.0 μmol; 0.5 mol %) in one portion at ambient temperature. The reaction mixture was sparged with 1 atm H<sub>2</sub>, maintained 6 h then filtered over Celite to remove the catalyst. The filtrate was concentrated to obtain crude 6-(2-fluoroethoxy)pyridine-3-amine (**62**) as a yellow oil (0.7 g, 92% yield). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.49-7.48 (m, 1H), 7.03-7.01 (m, 1H), 6.68-6.65 (m, 1H), 4.77 (brs, 2H), 4.72-4.71 (m, 1H), 4.66-4.63 (m, 1H), 4.37-4.35 (m, 1H), 4.31-4.30 (m, 1H); <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sub>6</sub>): δ -222.4 (m); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 155.2, 140.2, 131.3, 128.8, 110.7, 83.8 (81.7), 66.6 (64.9); HRMS calcd for C<sub>7</sub>H<sub>9</sub>FN<sub>2</sub>O (M+H), 157.0771; found: 157.0771.

To a suspension of 4-nitrophenyl chloroformate (583 mg, 2.89 mmol) and pyridine (436 mg, 5.5 mmol) in 1:1 THF: CH<sub>2</sub>Cl<sub>2</sub> (6 mL) was added crude **62** and the resulting mixture stirred overnight at ambient. *i*-Pr<sub>2</sub>NEt (356 mg, 2.75 mmol) and *N*-Boc-ethylenediamine (441 mg, 2.75



mmol) were then added and the resultant mixture maintained at ambient temperature 2 h. All volatiles were removed and the crude product purified by silica gel chromatography (hexanes:EtOAc 1:1) to afford **52** as a yellow solid (277 mg, 29% yield). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.46 (s, 1H), 8.12 (dd, *J* = 0.7, 2.8 Hz, 1H), 7.77 (dd, *J* = 2.8, 8.9 Hz, 1H), 6.89 – 6.71 (m, 2H), 6.18 (t, *J* = 5.7 Hz, 1H), 4.82 – 4.76 (m, 1H), 4.66 – 4.60 (m, 1H), 4.51 – 4.45 (m, 1H), 4.41 – 4.34 (m, 1H), 3.17 – 3.07 (m, 2H), 3.00 (q, *J* = 6.2 Hz, 2H), 1.37 (s, 9H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 157.6, 155.7, 155.4, 136.0, 131.6, 130.7, 110.1, 83.2 (81.0), 77.6, 66.5 (64.7), 40.3, 38.7, 28.2; HRMS calcd for C<sub>15</sub>H<sub>23</sub>FN<sub>4</sub>O<sub>4</sub> (M+H), 343.1776; found: 343.177.

### Synthesis of *tert*-Butyl 2-(3-(6-fluoropyridine-3-yl)ureido)ethylcarbamate (**53**).

A solution of 2-fluoro-5-aminopyridine (598 mg, 5.33 mmol) dissolved in THF (20 mL) and *i*-Pr<sub>2</sub>NEt (0.694 g, 5.37 mmol) was added to a solution of triphosgene (530 mg, 1.79 mmol) dissolved in THF (5 mL). *N*-Boc-ethylenediamine (850 mg, 5.31 mmol) was added and the reaction mixture stirred at ambient temperature overnight. The reaction mixture was then treated with water (5 mL) and washed with EtOAc (40 mL). The EtOAc layer was further washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to an oil. Silica gel chromatography of the crude material (hexanes: EtOAc 1:1) afforded **53** (379 mg, 24% yield). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.77 (s, 1H), 8.18 (ddd, *J* = 0.5, 1.7, 2.8 Hz, 1H), 7.99 (ddd, *J* = 2.9, 7.4, 8.9 Hz, 1H), 7.04 (dd, *J* = 3.2, 8.7 Hz, 1H), 6.82 (t, *J* = 5.6 Hz, 1H), 6.30 (t, *J* = 6.0 Hz, 1H), 3.20 – 2.96 (m, 4H), 1.37 (s, 9H); <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sub>6</sub>): δ -77.53 (brs); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 159.1 (156.0), 155.7, 155.2, 136.0 (135.8), 135.5 (135.4), 131.2 (131.1), 109.1 (108.6), 77.6, 40.3, 28.2; HRMS calcd for C<sub>13</sub>H<sub>19</sub>FN<sub>4</sub>O<sub>3</sub> (M+Na), 321.1333; found: 321.1334.

### Synthesis of *tert*-Butyl (2-(3-(6-bromopyridin-2-yl)ureido)ethyl)carbamate (**55**).

5-Amino-2-bromopyridine (1.73 g, 10 mmol) dissolved in THF (130 mL) was added to a solution of pyridine (9.49 g, 120 mmol, 0.97 mL) and 4-nitrophenyl chloroformate (2.12 g, 15 mmol) dissolved in THF (25 mL). Upon completion of the addition, the reaction mixture was heated to 65 °C, maintained 4 h, then treated with additional 4-nitrophenyl chloroformate (0.212 g, 1.05 mmol). After 1 h, *N*-Boc-ethylenediamine (2.00 g, 12.5 mmol) and *i*-Pr<sub>2</sub>NEt (1.61 g, 12.5 mmol, 2.17 mL) were added and the mixture stirred 30 min. The solution was then

concentrated to obtain a dark red-brown oil. The material was dissolved in EtOAc (300 mL) then washed with 10% AcOH (2 x 100 mL), H<sub>2</sub>O (100 mL), 5% K<sub>2</sub>CO<sub>3</sub> solution (2 x 100 mL), H<sub>2</sub>O (2 x 100 mL) and finally brine. The organic layer was then dried over Mg<sub>2</sub>SO<sub>4</sub> and concentrated to give a dark red solid. The crude solid was then triturated with boiling toluene (200 mL) and slowly cooled to 0 °C. Filtration yielded **55** as a pale purple solid (2.95 g, 82% yield). Mp 168-169 °C. <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 8.83 (s, 1H), 8.37 (d, *J* = 3.0 Hz, 1H), 7.83 (dd, *J* = 8.4, 3.0 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 6.83 (t, *J* = 6.0 Hz, 1H), 6.34 (t, *J* = 6.0 Hz, 1H), 3.12 (m, 2H), 3.0 (m, 2H), 1.37 (s, 9H). <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>): δ 155.6, 154.8, 139.5, 137.1, 131.4, 127.9, 127.4, 77.5, 40.1, 39.1, 28.1. HRMS calcd for C<sub>13</sub>H<sub>19</sub>BrN<sub>4</sub>O<sub>3</sub> (M+H) 359.0713; found: 359.0712.

### Synthesis of *tert*-butyl (2-(3-(5-bromopyrazin-2-yl)ureido)ethyl)carbamate (**56**).

To a solution of 4-nitrophenyl chloroformate (0.318 g, 1.58 mmol) dissolved in DMF (7 mL) was added 5-bromopyrazin-2-amine (0.25 g, 1.44 mmol) and pyridine (0.114 g, 1.44 mmol, 0.117 mL). The reaction mixture stirred for 30 min after which it was concentrated under vacuum and redissolved in DMF (3 mL). *N*-Boc-ethylenediamine (0.253 g, 1.58 mmol) and *i*Pr<sub>2</sub>NEt (0.186 g, 1.44 mmol) were added and the reaction mixture stirred 30 min. The mixture was concentrated to afford a crude oil, which was re-dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) then washed with 0.1N HCl (3 x 5 mL), 0.5N NaOH (3 x 5 mL), H<sub>2</sub>O (10 mL), brine (10 mL), dried over Mg<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford an oil. The crude material was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>: methanol 9:1) to obtain **56** (0.38 g, 73% yield over 2 steps) as an off-white solid. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN: DMSO-*d*<sub>6</sub> 3:1 v/v): δ 9.35 (s, 1H), 8.82 (s, 1H), 8.25 (s, 1H), 7.17 (m, 1H), 6.25 (br m, 1H), 3.23 (m, 2H), 3.09 (m, 2H), 1.37 (s, 9H). <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN: DMSO-*d*<sub>6</sub> 3:1 v/v): δ 157.0, 155.5, 150.4, 144.5, 136.1, 130.6, 118.4, 79.0, 28.7.

### Synthesis of *tert*-Butyl 2-(3-thiazol-2-ylureido)ethylcarbamate (**57**).

To a cooled (0 °C) solution of 4-nitrophenyl chloroformate (2.00 g, 9.99 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added a solution 2-aminothiazole (1.00 g, 9.99 mmol) and pyridine (848 µL, 10.49 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (7 mL) drop-wise. After the addition, the ice bath was removed and the reaction mixture stirred at ambient temperature overnight. A white precipitate formed during the reaction, which was removed by filtration then washed with 5%

Na<sub>2</sub>CO<sub>3</sub> (3 x 20 mL) and H<sub>2</sub>O (3 x 20 mL) to obtain 4-nitrophenyl thiazol-2-ylcarbamate as a white solid (1.57 g) that was used without further purification in the subsequent step.

To a solution of *N*-Boc-ethylenediamine (302 mg, 1.89 mmol) and Et<sub>3</sub>N (525 µL, 3.77 mmol) dissolved in DMF (7.5 mL) was added 4-nitrophenyl thiazol-2-ylcarbamate (500 mg, 1.89 mmol). The reaction mixture was warmed to 40 °C, maintained 3 h then concentrated to dryness. The crude material was triturated with CH<sub>2</sub>Cl<sub>2</sub> (10 mL), filtered and washed with 1.0N NaOH (3 x 10 mL) H<sub>2</sub>O (3 x 10 mL) and CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and dried to obtain **57** as a white solid (299 mg, 55% yield). This material was used without further purification in the subsequent step. <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 10.39 (s, 1H), 7.29 (d, *J* = 3.6 Hz, 1H), 7.00 (d, *J* = 3.6 Hz, 1H), 6.84 (s, 1H), 6.56 (s, 1H), 3.17 (q, *J* = 6.1 Hz, 2H), 3.02 (q, *J* = 6.1 Hz, 2H), 1.37 (s, 9H); <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>): δ 162.2, 160.0, 155.7, 153.9, 137.2, 111.7, 77.6, 54.8, 40.1, 39.1, 28.2; HRMS calcd for C<sub>11</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>S (M+H), 287.1172; found: 287.1170.

#### **Synthesis of *tert*-Butyl 2-(3-(2-(2-fluoroethyl)-2*H*-tetrazol-5-yl)ureido)ethylcarbamate (**63**).**

To a suspension of 4-nitrophenyl chloroformate (1.42 g, 7.05 mmol) and pyridine (0.51 mL, 8.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added a solution of 2*H*-tetrazol-5-amine (0.5 g, 5.88 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The reaction mixture was stirred at ambient temperature for 1 h then treated with a solution of Et<sub>3</sub>N (4.10 mL, 29.4 mmol) and *N*-Boc-ethylenediamine (1.04 g, 6.49 mmol) in DMF (2 mL). Upon completion of addition, the reaction mixture was stirred 0.25 h at ambient temperature then all volatiles removed, the crude material redissolved in 1N NaOH (20 mL) and washed with EtOAc (3 x 25 mL). The aqueous layer was then acidified with 1N HCl and washed with EtOAc (3 x 25 mL). All organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to yield *tert*-butyl 2-(3-2*H*-tetrazol-5-ylureido-ethylcarbamate (**58**) as a pale pink solid (1.59 g, 94% yield). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 10.43 (brs, 1H), 6.87 (brs, 1H), 6.63 (brs, 1H), 6.50 (brs, 1H), 3.18 (dd, *J* = 6.2, 12.4 Hz, 2H), 3.04 (dd, *J* = 6.0, 12.1 Hz, 2H), 1.37 (s, 9H).

To a solution of **58** (432 mg, 1.59 mmol) dissolved in DMF (5 mL) was added fluoroethyl tosylate (347 mg, 1.59 mmol) and K<sub>2</sub>CO<sub>3</sub> (529 mg, 1.59 mmol). The reaction mixture was heated to 50 °C, maintained overnight, then filtered to remove excess K<sub>2</sub>CO<sub>3</sub>. The filtrate was concentrated then purified by HPLC using a Phenomenex Luna C-18(2) column (10 µm, 41.4 x 250 mm, gradient method of 7-37% B over 30 min, where B = 100% MeCN and A = 5

mM NH<sub>4</sub>OAc) with a flow rate of 20 mL/min to afford **63** as a yellow oil (210 mg, 11% yield over 2 steps). <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN:D<sub>2</sub>O 2:1 v/v): δ 4.95 – 4.91 (m, 1H), 4.86 (t, *J* = 4.6 Hz, 2H), 4.83 – 4.79 (m, 1H), 3.28 (t, *J* = 6.0 Hz, 2H), 3.15 (t, *J* = 6.0 Hz, 2H), 1.32 (s, 9H); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>CN:D<sub>2</sub>O 2:1 v/v): δ -223.9 (m); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN:D<sub>2</sub>O 2:1 v/v): δ 162.1, 158.1, 155.6, 82.9 (80.6), 80.4, 55.0 (54.7), 40.9, 40.8, 26.6.

### Synthesis of *tert*-Butyl 2-(3-(1-benzylpiperidin-4-yl)ureido)ethylcarbamate (**59**).

To a suspension of 4-nitrophenyl chloroformate (1.11 g, 5.51 mmol) in THF (3 mL) was added a solution of 4-aminobenzyl piperidine (1.0 g, 5.26 mmol) dissolved in THF (5 mL) and pyridine (0.78 g, 9.86 mmol). After 30 min at ambient temperature *i*-Pr<sub>2</sub>NEt (0.92 mL, 5.3 mmol) and *N*-Boc-ethylenediamine (840 mg, 5.24 mmol) were added. After 2 h, the reaction mixture was concentrated to yield a crude oil. HPLC purification using a Phenomenex Luna C-18(2) column (10 μm, 41.4 x 250 mm, gradient method of 7-29% B over 30 min, where B = 90% MeCN in H<sub>2</sub>O using 0.1% formic acid as a modifier and A = 100% H<sub>2</sub>O with 0.1% formic acid as a modifier) with a flow rate of 20 mL/min to afford **59** as a pale yellow solid (767 mg, 39% yield). <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 7.34 – 7.27 (m, 4H), 7.27 – 7.23 (m, 1H), 6.74 (t, *J* = 5.2 Hz, 1H), 5.85 (d, *J* = 7.5 Hz, 1H), 5.77 (t, *J* = 5.5 Hz, 1H), 3.48 (s, 2H), 3.36 (dd, *J* = 11.0, 17.4 Hz, 1H), 3.00 (q, *J* = 6.3 Hz, 2H), 2.91 (dd, *J* = 5.9, 11.9 Hz, 2H), 2.71 (d, *J* = 10.1 Hz, 2H), 2.07 (t, *J* = 11.0 Hz, 2H), 1.72 (dd, *J* = 3.8, 12.6 Hz, 2H), 1.42 – 1.25 (m, 11H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 163.6, 157.9, 156.1, 136.4, 129.9, 128.8, 128.0, 78.0, 61.6, 51.7, 46.0, 41.3, 31.8, 28.7; HRMS calcd for C<sub>20</sub>H<sub>32</sub>N<sub>4</sub>O<sub>3</sub> (M+H), 377.2547; found: 377.2548.

### Synthesis of *tert*-Butyl 2-(3-(1-(2-fluoroethyl)piperidin-4-yl)ureido)ethylcarbamate (**65**).

**59** (350 mg, 0.93 mmol) was dissolved in EtOH (3 mL) and Pd/C (99 mg, 46 μmol; 5 mol %) was added at ambient temperature. The reaction mixture was sparged with 1 atm H<sub>2</sub>, maintained overnight then filtered over Celite to remove the catalyst. The filtrate was concentrated to afford crude *tert*-butyl 2-(3-(1-piperidin-4-yl)ureido)ethylcarbamate (**64**) as a white solid (240 mg). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 6.76 (t, *J* = 4.9 Hz, 1H), 5.84 (d, *J* = 7.8 Hz, 1H), 5.75 (t, *J* = 5.1 Hz, 1H), 3.42 – 3.32 (m, 1H), 3.00 (dd, *J* = 6.3, 12.4 Hz, 2H), 2.91 (dd, *J* = 6.1, 12.1 Hz, 2H), 2.86 (d, *J* = 12.4 Hz, 2H), 2.48 – 2.42 (m, 2H), 1.67 (dd, *J* = 3.3, 12.5 Hz,

2H), 1.37 (s, 9H), 1.13 (qd,  $J = 3.8, 11.5$  Hz, 2H); HRMS calcd for  $C_{13}H_{26}N_4O_3$  (M+H), 287.2077; found: 287.2077.

Fluoroethyl tosylate (305 mg, 1.40 mmol) and  $K_2CO_3$  (97 mg, 0.7 mmol) were added to a solution of **64** (200 mg, 69.8 mmol) dissolved in DMF (7 mL). Upon completion of the addition, the reaction mixture was warmed to 80 °C and maintained 2 h. The resulting suspension was cooled, filtered and the filtrate concentrated to yield an oil. HPLC purification of the crude material using a Phenomenex Luna C-18(2) column (10  $\mu$ m, 41.4 x 250 mm, gradient method of 0-25% B over 25 min, where B = 100% MeCN and A = 5 mM  $NH_4OAc$ ) with a flow rate of 20 mL/min afforded **65** as a colorless solid (222 mg, 96% yield).  $^1H$  NMR (600 MHz,  $CDCl_3:DMSO-d_6$  6:1 v/v):  $\delta$  6.75 (t,  $J = 5.2$  Hz, 1H), 5.84 (d,  $J = 7.8$  Hz, 1H), 5.76 (t,  $J = 6.0$  Hz, 1H), 4.55 – 4.52 (m, 1H), 4.47 – 4.44 (m, 1H), 3.00 (dd,  $J = 6.2, 12.4$  Hz, 2H), 2.92 (dd,  $J = 6.2, 12.1$  Hz, 2H), 2.75 (d,  $J = 12.1$ , 2H), 2.59 (t,  $J = 5.0$ , 1H), 2.55 (t,  $J = 5.0$ , 1H), 2.07 (t,  $J = 9.6$ , 2H), 1.71 (dd,  $J = 4.0, 12.5$  Hz, 2H), 1.37 (s, 9H), 1.29 (ddd,  $J = 3.7, 11.5, 14.4$  Hz, 2H);  $^{19}F$  NMR (282 MHz,  $DMSO-d_6$ ):  $\delta$  -217.0 (m);  $^{13}C$  NMR (150 MHz,  $DMSO-d_6$ ):  $\delta$  172.0, 157.4, 155.6, 82.4 (81.4), 77.5, 57.6 (57.5), 52.2, 46.1, 40.8, 32.4, 28.2, 21.1; HRMS calcd for  $C_{15}H_{29}FN_4O_3$  (M+H), 333.2296; found: 333.2294.

### Synthesis of *tert*-Butyl 2-(3-(morpholine-4-carboxamido)ethylcarbamate (**60**)).

A solution of morpholine-4-carbonyl chloride (14.9 g, 0.10 mol) dissolved in  $CH_2Cl_2$  (72 mL) was added drop-wise over 15 min to a cooled (0 °C) solution of *N*-Boc-ethylenediamine (16.02 g, 0.1 mol) dissolved in  $CH_2Cl_2$  (72 mL). The reaction stirred at 0 °C, warming to ambient temperature slowly over 16 h. The reaction mixture was then concentrated to dryness to obtain **60** used without further purification in the subsequent step.  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$  3.65 (m, 4H), 3.33 (m, 6H), 3.27 (m, 2H), 1.21 (s, 9H); HRMS calcd for  $C_{12}H_{23}FN_3O_4$  (M+H), 274.1761; found: 274.1760.

### Synthesis of 1-(4-iodopyridinyl)-3-(2-(*tert*-butoxycarbonylamino)ethyl) urea (**54**).<sup>4, 5</sup>

A 500 mL round bottom flask was charged with NaI (47.2 g, 316 mmol) and 2-chloro-5-nitropyridine (5.0 g, 32 mmol). Glacial acetic acid (200 mL) was then added and the solution was heated at reflux for 2.5 h. The dark solution was then cooled to ambient temperature and poured over crushed ice (300 g). Once the ice melted, the solution was filtered and the resulting

solid washed with cold water. Re-crystallization of the solid from 2-propanol (70 mL) afforded 2-iodo-5-nitropyridine (**66**) as a brown solid. Mp 161-163.5 °C; (lit 162.5-164.5 °C). A solution of **66** (1.85 g, 11.7 mmol) in anhydrous EtOH (40 mL) was treated with SnCl<sub>2</sub>·2H<sub>2</sub>O (13.2 g, 58.5 mmol) then heated to reflux. The clear solution was maintained for 1 h then concentrated to a dark yellow solid. The solid was extracted with EtOAc (3 x 100 mL) then washed with 2N NaOH (50 mL) and H<sub>2</sub>O (50 mL). The organic layer was removed and the precipitate so formed was re-dissolved in 2N NaOH (100 mL) and re-extracted with EtOAc (2 x 100 mL). The organic layers were combined and dried over Mg<sub>2</sub>SO<sub>4</sub>. Upon filtration and concentration, a brown solid was obtained (0.24 g). This solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and treated with pyridine (0.086 g, 1.3 mmol) and 4-nitrophenyl chloroformate (0.232 g, 1.15 mmol); a dark grey precipitate formed almost immediately. The mixture was stirred for 1 h then diluted with DMF (10 mL) followed by *i*-Pr<sub>2</sub>NEt (0.297 g, 2.3 mmol) and *N*-Boc-ethylenediamine (0.25 g, 1.56 mmol). The reaction mixture was stirred for another 2.5 h then concentrated under reduced pressure to afford a dark oil. The crude product was purified by preparative HPLC (method: 20-50 %B over 30 min at 20 mL/min; column: Phenomenex C18, 21.2 x 250 mm; mobile phases: A = 0.1% TFA in water and B = 0.1% TFA in 90% MeCN) to yield **54** (0.44 g, 9% yield). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN: D<sub>2</sub>O 2:1 v/v): δ 8.44 (d, *J* = 3 Hz, 1H), 7.74 (d, *J* = 9 Hz, 1H), 7.62 (dd, *J* = 3.0, 9.0 Hz, 1H), 3.15 (m, 4H), 1.33 (s, 9H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN: D<sub>2</sub>O 2:1 v/v): δ 158.3, 157.0, 140.5, 138.6, 136.6, 130.9, 104.8, 80.6, 41.0, 40.6, 28.6; HRMS calcd for C<sub>13</sub>H<sub>19</sub>IN<sub>4</sub>O<sub>3</sub> (M+H), 407.0574; found: 407.0573.

### Synthesis of *tert*-Butyl-2-(2-aminoethyl)-6-fluoronicotinamide (**67**).

To a solution 2-fluoropyridyl carboxylic acid (1.94 g, 13.75 mmol) and HBTU (5.68 g, 15.0 mmol) dissolved in DMF (5 mL) was added *i*-Pr<sub>2</sub>NEt (3.23 g, 25.00 mmol) dropwise. *N*-Boc-ethylenediamine (2.00 g, 12.5 mmol) was added and the resulting mixture stirred at ambient temperature 5 h. The reaction was diluted with EtOAc (30 mL), washed with 0.1M NaOH (3x 100 mL), and brine (30 mL), then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford **67** as a crude yellow solid that was used without further purification in the subsequent step (2.97 mg, 84% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.71 (d, *J* = 2.6, 1H), 8.29 (ddd, *J* = 2.6, 7.6, 8.5, 1H), 7.65 (s, 1H), 6.99 (ddd, *J* = 0.6, 2.9, 8.5, 1H), 5.04 (s, 1H), 3.61 – 3.53 (m, 2H), 3.44 (s, 2H), 1.44 (s, 9H); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ -73.6 (s); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ

166.8, 164.8, 163.6, 158.4, 147.5 (147.3), 140.9 (140.8), 128.4 (128.3), 109.9 (109.4), 80.7, 43.2, 39.9, 28.5; HRMS calcd for C<sub>13</sub>H<sub>18</sub>FN<sub>3</sub>O<sub>3</sub> (M+H), 306.1224; found: 306.1225.

#### Synthesis of *tert*-Butyl 4-(6-fluoropyridin-3-ylamino)-4-oxobutylcarbamate (**68**).

To a solution 4-(*tert*-butoxycarbonylamino)butanoic acid (783 mg, 3.85 mmol) and HBTU (1.59 g, 4.19 mmol) dissolved in DMF (2 mL) was added *i*-Pr<sub>2</sub>NEt (1.22 mL, 7.00 mmol) and 6-fluoropyridine-3-amine (413 mg, 3.85 mmol) dropwise. Upon completion of the addition, the reaction mixture was stirred at ambient temperature for 3 h then diluted with EtOAc (30 mL) and washed with 10% citric acid (30 mL), 0.1M NaOH, brine (30 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford a brown oil. Silica gel purification of the crude material (EtOAc: hexanes 1:1) afforded **68** as a white solid (950 mg, 83% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.56 (s, 1H), 8.33 (s, 1H), 8.26 (ddd, *J* = 2.8, 7.1, 9.0 Hz, 1H), 6.87 (dd, *J* = 3.3, 8.9 Hz, 1H), 4.93 (t, *J* = 5.8 Hz, 1H), 3.23 (dd, *J* = 6.4, 12.4 Hz, 2H), 2.42 – 2.35 (m, 2H), 1.91 – 1.79 (m, 2H), 1.44 (s, 9H); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ -73.6 (s); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 171.7, 161.1 (158.0), 157.7 138.4 (138.2), 133.4 (133.3), 132.7 (132.6), 109.4 (108.9), 80.2, 39.1, 34.2, 28.3, 27.4; HRMS calcd for C<sub>14</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>3</sub> (M+Na), 320.1380; found: 320.1382.

#### Synthesis of *tert*-Butyl 4-(2-(4-fluorophenyl)acetamido)ethylcarbamate (**69**).

To a solution of *N*-Boc-ethylenediamine (584 mg, 3.65 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added 4-fluoro-phenylacetyl chloride (500 μL, 3.65 mmol) and *i*-Pr<sub>2</sub>NEt (1.3 mL, 7.30 mmol). The resulting mixture was stirred at ambient temperature for 1 h then poured into a separatory funnel and diluted with EtOAc (20 mL). The organic layer was washed with 5% Na<sub>2</sub>CO<sub>3</sub> (2 x 20 mL), H<sub>2</sub>O (2 x 20 mL), and brine (1 x 20 mL), then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to obtain **69** as a light yellow solid (998 mg, 92% yield). The solid was used without further purification in the subsequent step. <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 8.02 (s, 1H), 7.27 (dd, *J* = 5.7, 8.5 Hz, 2H), 7.12 – 7.07 (m, 2H), 6.77 (t, *J* = 5.2 Hz, 1H), 3.38 (s, 2H), 3.06 (dd, *J* = 6.3, 12.5 Hz, 2H), 2.97 (dd, *J* = 6.2, 12.4 Hz, 2H), 1.37 (s, 9H); <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sub>6</sub>): δ -117.19 (m); <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>): δ 170.1, 161.7 (160.1), 155.6, 132.5 (132.4), 130.8 (130.7), 114.8 (114.7), 77.6, 41.3, 38.8, 28.2.

### Synthesis of Benzyl-2-(2-fluorophenylsulfonylamido)ethyl carbamate (**70**).

*i*-Pr<sub>2</sub>NEt (0.498 g, 3.85 mmol, 0.67 mL) was added to a solution of *N*-Boc-ethylenediamine (0.355 g, 1.54 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The resulting mixture was stirred for 5 min then treated with 2-fluorobenzenesulfonyl chloride (0.33 g, 1.72 mmol, 0.228 mL), maintained 2 h then successively diluted with DCM (7 mL) and H<sub>2</sub>O (5 mL). The layers separated and the organic layer was washed with water (5 mL), brine then dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to obtain a viscous oil. Purification by silica gel chromatography (gradient of 100% DCM to 2% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) afforded **70** (0.4 g, 67% yield). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 7.84 (br t, *J* = 7.2 Hz, 1H), 7.55 (m, 1H), 7.33 (m, 5H), 7.25 (t, *J* = 7.2 Hz, 2H), 7.16 (dd, *J* = 10.2 Hz, 1H), 5.25 (m, 1H), 5.0 (s, 2H), 3.3 (m, 2H), 3.1 (m, 2H); <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ -110.8 (s); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 157.9 (*J* = 247.5 Hz), 156, 137, 135.1 (*J* = 8.25 Hz), 129.5, 128.2, 127.7 (*J* = 4.5 Hz), 124.8 (*J* = 3.75 Hz), 117.3, 117.0, 65.3, 41.9; HRMS calcd for C<sub>16</sub>H<sub>17</sub>FN<sub>2</sub>O<sub>4</sub>S (M+H), 353.0965; found: 353.0966.

### General deprotection methods for substituted *tert*-Butyl 2-(3-phenylureido)ethylcarbamates.

#### Method I:

The Boc-protected amine (0.1 mol) was dissolved in a solution of HCl (1.0-4.0 M in dioxane, 0.1 M) and stirred 0.5 to 16 h at ambient temperature.

#### Method II:

The Boc-protected amine (0.1 mol) was dissolved in a solution of TFA and CH<sub>2</sub>Cl<sub>2</sub> (1:1 – 1:4, 0.1 M) and stirred 20 min to 1 h at ambient temperature.

### General methods for epoxide opening of epoxides with substituted amines.

#### Method A:

The amine (0.1 mol) dissolved in MeCN (0.1 – 0.4 M) was treated with *i*-Pr<sub>2</sub>NEt (0.2 – 0.4 mol) and placed in a reaction vessel, which was fitted with a reflux condenser and placed in pre-heated oil bath (74 – 85 °C). Upon complete dissolution, Et<sub>2</sub>BOMe (0.13 – 1.1 mol), Yb(OTf)<sub>3</sub> (0.02 – 0.08 mol) and the epoxide (0.1 – 0.17 mol) were successively added. The reaction mixture was stirred for 30 min to 44 h then concentrated to dryness. Purification by



preparative HPLC using a Phenomenex Luna column (C18, 21.2 x 250 mm) with TFA as the modifier (A = 0.1% TFA in water; B = 0.1% TFA in 90% MeCN, 10% H<sub>2</sub>O) at 20 mL/min afforded the desired product as a TFA salt.

#### Method B:

To a round bottom flask was added the substituted amine (0.1 mmol), *i*-PrOH (0.16-0.26 M), and *i*-Pr<sub>2</sub>NEt (0.15-0.4 mmol) and the mixture heated to 75 °C until a homogeneous solution was obtained. The epoxide (0.08-0.1 mmol) was added and the reaction mixture continued to stir at 75 °C for 2-36 h. All volatiles were then removed and the crude mixture purified by preparative HPLC using a Phenomenex Luna (C18 21.2 x 250 mm) with TFA as the modifier (A = 0.1% TFA in H<sub>2</sub>O and B = 0.1% TFA in 90% MeCN) afforded the desired product as a TFA salt.

#### **Synthesis of (S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(4-methoxyphenyl)urea (2).**

Deprotection: Method I; Filtered and washed the precipitate with dioxane; 51% yield.

Epoxide Opening: Method A; Purified by preparative HPLC (20-80% B over 30 min); 15% yield. <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 8.70 (s, 1H), 8.67 (s, 2H), 7.74 (dd, *J* = 1.6, 7.7 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.33 – 7.29 (m, 2H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.84 – 6.79 (m, 2H), 6.56 (t, *J* = 5.6 Hz, 1H), 4.24 (td, *J* = 4.8, 8.4 Hz, 1H), 4.20 – 4.12 (m, 2H), 3.69 (s, 3H), 3.40 (d, *J* = 4.5 Hz, 2H), 3.24 (dd, *J* = 4.5, 7.9 Hz, 1H), 3.10 (d, *J* = 4.1 Hz, 3H); <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>): δ 159.8, 156.1, 154.1, 135.0, 133.7, 133.3, 121.4, 119.7, 116.3, 113.8, 113.2, 100.8, 70.5, 64.6, 55.1, 49.3, 48.0, 36.0; HRMS- calcd for C<sub>20</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub> (M+H), 385.1870; found: 385.1873. The spectral data were consistent with that previously reported by Schaefer et al.<sup>1</sup>

#### **Synthesis of (S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(2-fluorophenyl)urea (3).**

Deprotection: Method I; Filtered and washed the precipitate with dioxane; 55% yield; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.49 (d, *J* = 2.5 Hz, 1H), 8.08 (td, *J* = 1.8, 8.3 Hz, 1H), 7.87 (s, 2H), 7.18 (ddd, *J* = 1.5, 8.1, 11.8 Hz, 1H), 7.09 (td, *J* = 1.4, 7.9 Hz, 1H), 6.94 (m, 2H), 3.38 – 3.27 (m, 2H), 2.89 (t, *J* = 6.2 Hz, 2H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ 155.4, 153.4 (150.2), 128.0

(127.8), 124.3 (124.3), 122.0 (121.9), 120.6 (120.6), 115.0 (114.7), 37.1; HRMS calcd for  $C_9H_{12}FN_3O$  (M+Na), 220.0856; found: 220.0857.

Epoxide Opening: Method A; Purified by preparative HPLC (20-80% B over 30 min); 33% yield;  $^1H$  NMR (600 MHz,  $CD_3CN:D_2O$  2:1 v/v):  $\delta$  7.74 (td,  $J = 1.8, 8.1$  Hz, 1H), 7.62 – 7.58 (m, 2H), 7.13 – 7.00 (m, 5H), 4.31 (td,  $J = 4.7, 8.5$  Hz, 1H), 4.18 – 4.12 (m, 2H), 3.54 – 3.45 (m, 2H), 3.33 – 3.17 (m, 4H);  $^{19}F$  NMR (282 MHz,  $CD_3CN:D_2O$  2:1 v/v):  $\delta$  -129.66 (brs);  $^{13}C$  NMR (75 MHz,  $CD_3CN:D_2O$  2:1 v/v):  $\delta$  161.1, 158.4, 156.1 (152.8), 136.4, 134.8, 127.8 (127.6), 125.5 (125.4), 125.2 (125.1), 123.7 (123.5), 122.7, 118.0, 116.3 (116.1), 114.0, 101.9, 71.5, 65.9, 50.8, 49.9, 37.4; HRMS calcd for  $C_{19}H_{21}FN_4O$  (M+Na), 395.1489; found: 395.1494.

#### **Synthesis of (S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(4-fluorophenyl)urea (4).**

Deprotection: Method I; Filtered and washed the precipitate with dioxane; 95% yield;  $^1H$  NMR (600 MHz,  $DMSO-d_6$ ):  $\delta$  9.12 (s, 1H), 8.00 (s, 2H), 7.42 – 7.35 (m, 2H), 7.06 – 6.98 (m, 2H), 6.65 (brs, 1H), 3.30 (t,  $J = 6.2$  Hz, 2H), 2.84 (dt,  $J = 6.0, 12.0$  Hz, 2H);  $^{19}F$  NMR (282 MHz,  $DMSO-d_6$ ):  $\delta$  -122.33 (m);  $^{13}C$  NMR (75 MHz,  $DMSO-d_6$ ):  $\delta$  158.5 (155.4), 155.8, 136.7 (136.6), 119.5 (119.4), 115.2 (114.9), 39.3, 37.2; HRMS calcd for  $C_9H_{12}FN_3O$  (M+H), 198.1037; found: 198.1039.

Epoxide Opening: Method A; Purified by preparative HPLC (20-80% B over 30 min); 10% yield.  $^1H$  NMR (600 MHz,  $DMSO-d_6$ ):  $\delta$  8.94 (s, 1H), 8.64 (s, 2H), 7.74 (dd,  $J = 1.6, 7.7$  Hz, 1H), 7.69 – 7.66 (m, 1H), 7.43 – 7.39 (m, 2H), 7.27 (d,  $J = 8.5$  Hz, 1H), 7.12 (t,  $J = 7.5$  Hz, 1H), 7.08 – 7.03 (m, 2H), 6.62 (t,  $J = 5.7$  Hz, 1H), 4.23 (td,  $J = 4.7, 8.4$  Hz, 1H), 4.19 – 4.13 (m, 2H), 3.44 – 3.39 (m, 2H), 3.27 – 3.21 (m, 1H), 3.13 – 3.07 (m, 3H);  $^{19}F$  NMR (282 MHz,  $DMSO-d_6$ ):  $\delta$  -122.44 (m);  $^{13}C$  NMR (75 MHz,  $DMSO-d_6$ ):  $\delta$  159.8, 158.5 (155.4), 155.9, 136.5, 136.1, 133.7, 121.4, 119.6 (119.5), 116.3, 115.2 (114.9), 113.2, 100.7, 70.5, 64.6, 49.3, 47.8, 35.9; HRMS calcd for  $C_{19}H_{21}FN_4O_3$  (M+H), 395.1489; found: 395.1492.

#### **Synthesis of (S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(4-(2-fluoroethoxy) phenyl)urea (5).**

Deprotection: Method II; Concentrated then washed with toluene and lyophilized; 100% yield;  $^1H$  NMR (300 MHz,  $DMSO-d_6$ ):  $\delta$  8.66 (s, 1H), 7.79 (s, 2H), 7.37 – 7.28 (m, 2H), 6.90 – 6.82

(m, 2H), 6.46 (t,  $J = 5.5$  Hz, 1H), 4.82 – 4.75 (m, 1H), 4.66 – 4.59 (m, 1H), 4.25 – 4.18 (m, 1H), 4.14 – 4.07 (m, 1H), 3.30 (dd,  $J = 5.0, 10.7$  Hz, 2H), 2.96 – 2.81 (m, 2H);  $^{19}\text{F}$  NMR (282 MHz, DMSO- $d_6$ ):  $\delta$  -222.06 (m);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  155.9, 152.9, 133.8, 119.6, 114.6, 83.3 (81.1), 67.3 (67.0), 37.2; HRMS calcd for  $\text{C}_{11}\text{H}_{16}\text{FN}_3\text{O}_2$  (M+H), 242.1299; found: 242.1296.

Epoxide Opening: Method A; Purified by preparative HPLC (20-80%B over 30 min); 11% yield;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ ):  $\delta$  8.64 – 8.50 (m, 3H), 7.75 (dd,  $J = 1.6, 7.7$  Hz, 1H), 7.70 – 7.66 (m, 1H), 7.29 (dd,  $J = 8.8, 16.6$  Hz, 2H), 7.13 (t,  $J = 7.6$  Hz, 1H), 6.88 – 6.82 (m, 2H), 6.30 (t,  $J = 5.8$  Hz, 1H), 5.94 (d,  $J = 5.0$  Hz, 1H), 4.77 – 4.72 (m, 1H), 4.69 – 4.64 (m, 1H), 4.22 (td,  $J = 4.8, 8.8$  Hz, 1H), 4.19 – 4.10 (m, 4H), 3.45 – 3.28 (m, 2H), 3.27 – 3.20 (m, 1H), 3.14 – 3.04 (m, 3H);  $^{19}\text{F}$  NMR (282 MHz, DMSO- $d_6$ ):  $\delta$  -222.25 (m);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  158.9, 154.5, 151.5, 133.8, 132.7, 132.4, 119.9, 118.2, 115.2, 113.4, 111.9, 99.4, 82.1 (79.9), 70.0, 66.1 (65.9), 65.5, 49.8, 47.6, 36.8; HRMS calcd for  $\text{C}_{21}\text{H}_{25}\text{FN}_4\text{O}_4$  (M+H), 417.1932; found: 417.1935.

**Synthesis of (S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(4-(3-fluoropropoxy) phenyl)urea (6).**

Deprotection: Method I; Concentrated en vacuo and passed through an ion exchange column (BioRad AG1-X2, 200-400 mesh, hydroxide form), then lyophilized; 84% yield;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ ):  $\delta$  7.88 (s, 3H), 7.33 – 7.30 (m, 2H), 6.85 – 6.81 (m, 2H), 6.66 (t,  $J = 5.5$  Hz, 1H), 4.63 (t,  $J = 5.9$  Hz, 1H), 4.55 (t,  $J = 5.9$  Hz, 1H), 3.99 (t,  $J = 6.3$  Hz, 2H), 3.31 (q,  $J = 5.9$  Hz, 2H), 2.89 (d,  $J = 5.5$  Hz, 2H), 2.06 (dp,  $J = 6.1$  Hz, 2H);  $^{13}\text{C}$  NMR (150 MHz, DMSO- $d_6$ ):  $\delta$  156.0, 153.2, 133.6, 119.6, 114.6, 81.3 (80.3), 63.7 (63.6), 37.2, 29.9 (29.7); HRMS calcd for  $\text{C}_{12}\text{H}_{18}\text{FN}_3\text{O}_2$  (M+H), 256.1455; found: 256.1456.

Epoxide Opening: Method A; Purified by preparative HPLC (20-80% B over 30 min); 37% yield;  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ ):  $\delta$  8.83 (s, 1H), 8.74 (s, 2H), 7.73 (dd,  $J = 1.5, 7.7$  Hz, 1H), 7.68 – 7.64 (m, 1H), 7.34 – 7.30 (m, 2H), 7.27 (d,  $J = 8.6$  Hz, 1H), 7.11 (t,  $J = 7.6$  Hz, 1H), 6.85 – 6.81 (m, 2H), 6.74 (t,  $J = 5.5$  Hz, 1H), 4.63 (t,  $J = 5.9$  Hz, 1H), 4.55 (t,  $J = 5.9$  Hz, 1H), 4.25 (td,  $J = 4.7, 8.4$  Hz, 1H), 4.20 – 4.13 (m, 2H), 3.99 (t,  $J = 6.3$  Hz, 2H), 3.41 (d,  $J = 5.7$  Hz, 2H), 3.25 (d,  $J = 9.5$  Hz, 1H), 3.10 (m, 3H), 2.12 – 2.02 (m, 2H);  $^{19}\text{F}$  NMR (282 MHz, DMSO- $d_6$ ):  $\delta$  -220.26 (m);  $^{13}\text{C}$  NMR (150 MHz, DMSO- $d_6$ ):  $\delta$  159.8, 156.2, 153.2, 135.0, 133.6, 133.5,

121.4, 119.7, 115.9, 114.6, 113.2, 100.8, 81.3, 80.3, 70.6, 65.0, 63.7 (63.6), 49.4, 48.0, 36.0, 29.9 (29.7); HRMS calcd for C<sub>22</sub>H<sub>27</sub>FN<sub>4</sub>O<sub>4</sub> (M+H), 431.2089; found: 431.2090.

**Synthesis of (S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(3-(2-fluoroethoxy) phenyl)urea (7).**

Deprotection: Method I; Filtered and washed the precipitate with dioxane; 98% yield; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN:D<sub>2</sub>O 1:1 v/v): δ 7.59 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 8.2 Hz, 1H), 7.03 (t, *J* = 2.2 Hz, 1H), 6.89 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.61 (dd, *J* = 2.4, 8.2 Hz, 1H), 4.76 – 4.73 (m, 1H), 4.68 – 4.65 (m, 1H), 4.17 (m, 2H), 3.37 (t, *J* = 5.9 Hz, 2H), 3.00 (t, *J* = 5.9 Hz, 2H); <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>CN:D<sub>2</sub>O 1:1 v/v): δ -223.07 (m).

Epoxide Opening: Method A; Purified by preparative HPLC (15-45% B over 30 min); 27% yield; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN:D<sub>2</sub>O 1:1 v/v): δ 7.63 – 7.55 (m, 2H), 7.18 – 6.97 (m, 4H), 6.84 (ddd, *J* = 0.9, 2.0, 8.1 Hz, 1H), 6.58 (ddd, *J* = 0.8, 2.5, 8.3 Hz, 1H), 4.80 – 4.74 (m, 1H), 4.64 – 4.57 (m, 1H), 4.29 (dq, *J* = 4.4, 8.0 Hz, 1H), 4.22 – 4.11 (m, 3H), 3.46 (dd, *J* = 3.2, 8.3 Hz, 2H), 3.28-3.16 (m, 5H); <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sub>6</sub>): δ - 222.11 (m); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN:D<sub>2</sub>O 1:1 v/v): δ 160.0, 158.7, 157.5, 140.3, 135.4, 133.7, 129.9, 121.7, 118.5, 112.9, 112.3, 108.9, 105.9, 100.8, 83.6 (81.4), 70.4, 67.4 (67.2), 64.8, 49.8, 48.9, 36.3; HRMS calcd for C<sub>21</sub>H<sub>25</sub>FN<sub>4</sub>O<sub>4</sub> (M+H), 417.1932; found: 417.1933.

**Synthesis of (S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(4-(1-fluoropropan-2-ylamino)phenyl)urea (8).**

Deprotection: Method II; Reaction mixture was concentrated to yield a red oil, which was used without further purification in the subsequent step; 67% yield. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 8.99 (s, 1H), 7.81 (s, 2H), 7.44 (d, *J* = 8.9 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.67 (s, 1H), 4.58 (d, *J* = 3.8 Hz, 1H), 4.42 (d, *J* = 4.1 Hz, 1H), 3.84 (ddd, *J* = 5.0, 10.7, 14.2 Hz, 1H), 3.31 (t, *J* = 6.1 Hz, 2H), 2.90 (dd, *J* = 5.6, 11.5 Hz, 2H), 1.20 (dd, *J* = 0.9, 6.8 Hz, 3H); <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sub>6</sub>): -227.4 (s); HRMS calcd for C<sub>12</sub>H<sub>19</sub>FN<sub>4</sub>O (M+H), 255.1615; found: 255.1613.

Epoxide Opening: Method A; Purified by preparative HPLC (15-45% B over 30 min); 6% yield. <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 8.82 (s, 1H), 8.70 (s, 2H), 7.74 (dd, *J* = 1.7, 7.7 Hz, 1H), 7.69 – 7.65 (m, 1H), 7.29 (dd, *J* = 8.5, 17.5 Hz, 3H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.89 (s, 2H), 6.67 (s, 1H), 4.50 – 4.44 (m, 1H), 4.42 – 4.35 (m, 1H), 4.23 (td, *J* = 4.9, 8.4 Hz, 1H), 4.20 – 4.12 (m,

2H), 3.82 – 3.72 (m, 1H), 3.40 (d,  $J = 4.9$  Hz, 2H), 3.34 – 3.20 (m, 1H), 3.10 (d,  $J = 5.7$  Hz, 3H), 1.17 (d,  $J = 6.3$  Hz, 3H);  $^{19}\text{F}$  NMR (282 MHz, DMSO- $d_6$ ):  $\delta$  -222.56 (m);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  159.8, 156.1, 135.1, 133.7, 121.4, 119.9, 118.2, 116.3, 114.3, 113.2, 100.8, 85.3 (83.0), 64.6, 51.7, 49.4, 47.9, 36.0, 14.8; HRMS calcd for  $\text{C}_{22}\text{H}_{28}\text{FN}_5\text{O}_3$  (M+H), 430.2248; found: 430.2246.

#### **Synthesis of (S)-3-Fluoro-2-cyanophenyl glycidyl ether (44).**

2-fluoro-6-hydroxybenzonitrile (1.00 g, 7.29 mmol), (*R*)-epichlorohydrin (4.05 g, 43.8 mmol) and piperidine (0.093 g, 1.09 mmol) were charged into a 15 mL round bottom flask then heated at 80 °C and maintained 2 h. The reaction mixture was then cooled to ambient temperature, treated with 2N NaOH (25 mL) then stirred an additional 45 min. The solution was poured into a separatory funnel and diluted with  $\text{CH}_2\text{Cl}_2$  (30 mL) and  $\text{H}_2\text{O}$  (15 mL). The layers separated and the aqueous layer washed with  $\text{CH}_2\text{Cl}_2$  (15 mL). The combined organic layers were further washed with brine then dried over  $\text{MgSO}_4$  and concentrated to an oil (1.33 g) that was used without further purification in the subsequent step.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.50 (m, 1H), 6.81 (m, 2H), 4.42 (m, 1H), 4.11 (m, 1H), 3.40 (m, 1H), 2.94 (m, 1H), 2.83 (m, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  165.9, 162.5, 161.3, 135.3, 111.4, 108.5, 92.3, 70.1, 49.8, 44.6, ; HRMS calcd for  $\text{C}_{10}\text{H}_8\text{FNO}_2$  (M+Na), 216.0431; found: 216.0431.

#### **Synthesis of (S)-4-(3-(2-(3-(2--Cyano-3-fluorophenoxy)-2-hydroxypropylamino)ethyl)ureido)benzoic acid (9).**

Deprotection: Method I; Collected by filtration as a solid precipitate and washed with ether (10 mL); 97% yield.  $^1\text{H}$  NMR (600 MHz,  $\text{D}_2\text{O}$ ):  $\delta$  8.0 (m, 2H), 7.50 (m, 2H), 4.48 (q,  $J = 7.2$  Hz, 2H), 3.60 (m, 2H), 3.30 (m, 2H), 1.49 (m, 3H); HRMS calcd for  $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_3$  (M+H), 252.1342; found: 252.1345.

Epoxide Opening: Method B; A solution of 1N NaOH (1.55 mL) was added and the reaction mixture was heated at 75 °C for 2 h. The mixture was then cooled to ambient temperature and concentrated. The resulting material was purified by preparative HPLC (10-40 % B over 30 min); 18% yield.  $^1\text{H}$  NMR (600 MHz,  $\text{D}_2\text{O}:\text{CD}_3\text{CN}$  3:1 v/v):  $\delta$  7.70 (m, 2H), 7.56 (m, 1H), 7.30 (m, 2H), 6.89 (m, 1H), 6.81 (t,  $J = 8.4, 9.0$  Hz, 1H), 4.32 (m, 1H), 4.20 (d,  $J = 4.2$  Hz, 2H), 3.50 (m, 2H), 3.35 (m, 2H), 3.23 (m, 2H); LRMS 417.4 (M+H).

### Synthesis of (S)-4-Fluoro-2-(oxiran-2-ylmethoxy)benzonitrile (**45**).

To a slurry of NaH (51.0 mg, 2.13 mmol) in DMF (2 mL) was added a solution of 4-fluoro-2-hydroxybenzonitrile (200 mg, 1.46 mmol) dissolved in DMF (3 mL) dropwise. Upon complete addition, the reaction mixture was stirred 5 min then treated with a solution of (2S)-(+)-glycidyl tosylate in DMF (3 mL). Upon complete addition, the reaction mixture was stirred 2 h then quenched with the addition of sat. NH<sub>4</sub>Cl (10 mL). The aqueous layer was separated then washed with EtOAc (3 x 50 mL). The combined EtOAc layers were washed with 10% NaOH (50 mL) and brine (50 mL) then dried over MgSO<sub>4</sub> filtered and concentrated to a yellow oil. Silica gel chromatography using 2% MeOH in CH<sub>2</sub>Cl<sub>2</sub> afforded **45** (0.4 g, 97% yield). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.55 (dd, *J* = 6.2, 8.4 Hz, 1H), 6.77 – 6.72 (m, 2H), 4.38 (dd, *J* = 2.7, 11.4 Hz, 1H), 4.06 (dd, *J* = 5.5, 11.4 Hz, 1H), 3.39 (ddd, *J* = 2.7, 5.4, 6.8 Hz, 1H), 2.95 – 2.92 (m, 1H), 2.83 (dd, *J* = 2.6, 4.8 Hz, 1H); <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sub>6</sub>): δ -100.30 (m); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 167.0, (165.3), 162.0 (161.9), 135.4 (135.3), 115.5, 109.1 (108.9), 101.6 (101.4), 98.6, 69.9, 49.6, 44.4; HRMS calcd for C<sub>10</sub>H<sub>8</sub>FNO<sub>4</sub> (M+H), 194.0611; found: 194.0609.

### Synthesis of (S)-4-(3-(2-(3-(2-Cyano-5-fluorophenoxy)-2-hydroxypropylamino)ethyl)ureido)benzoic acid (**10**).

Method C. To a solution of **45** (60 mg, 0.31 mmol) dissolved in *i*-PrOH (1 mL) was added *i*-Pr<sub>2</sub>NEt (80.3 mg, 0.62 mmol), MeCN (2 mL), LiBr (1.35 mg, 0.015 mmol) and **34** (89 mg, 0.31 mmol). The reaction mixture was heated to 60 °C for 3 h then cooled to ambient temperature, treated with 1N NaOH (5 mL) then stirred overnight. The reaction mixture was acidified with 1N HCl to pH = 5 and the crude material purified by preparative HPLC (method: 2-32% B over 30 min at 20 mL/min; column: Phenomenex C18, 21.2 x 250 mm; mobile phases: A = 15 mM NH<sub>4</sub>OAc in water and B = H<sub>2</sub>O). <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN: D<sub>2</sub>O 1:4 v/v): δ 7.71 – 7.66 (m, 2H), 7.55 (dd, *J* = 6.2, 8.7 Hz, 1H), 7.22 – 7.18 (m, 2H), 6.89 (dd, *J* = 2.2, 10.7 Hz, 1H), 6.76 (td, *J* = 2.2, 8.4 Hz, 1H), 4.33 (dq, *J* = 4.3, 8.5 Hz, 1H), 4.16 (d, *J* = 4.4 Hz, 2H), 3.56 – 3.43 (m, 2H), 3.37 – 3.29 (m, 2H), 3.28 – 3.15 (m, 2H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN: D<sub>2</sub>O 1:4 v/v): δ 180.8, 174.9, 168.6 (166.9), 163.0 (162.9), 158.8, 142.4, 136.8 (136.7), 131.4, 131.3, 119.5, 117.8, 110.5 (110.4), 102.6 (102.4), 98.0, 72.1, 65.8, 50.9, 49.6, 37.3, 23.8; <sup>19</sup>F NMR (282 MHz,

CD<sub>3</sub>CN: D<sub>2</sub>O 1:4 v/v):  $\delta$  -99.6 (m); HRMS calcd for C<sub>20</sub>H<sub>21</sub>FN<sub>4</sub>O<sub>5</sub> (M+H), 417.1568; found: 417.1569.

**Synthesis of (S)-4-(3-(2-(3-(2-Cyano-3-fluorophenoxy)-2-hydroxypropylamino)ethyl)ureido)benzoic acid (11).**

**50** (170 mg, 0.42 mmol) was charged to a 25 mL round bottom flask and dissolved in methanol (15 mL). Pd/C (85 mg, 80  $\mu$ mol; 19 mol %) was added and the resulting suspension sparged with 1 atm H<sub>2</sub> at ambient temperature. After 1 h, catalyst was removed by filtration through Celite, the filter cake washed with MeOH (10 mL) and the filtrate concentrated to obtain crude **71** (116 mg) that was redissolved in *i*-PrOH (4.2 mL). Yb(OTf)<sub>3</sub> (52 mg, 8.4  $\mu$ mol), Et<sub>2</sub>BOMe (126 mg, 1.26 mmol) and (S)-2-(oxiran-2-ylmethoxy)benzonitrile (**43**) (73 mg, 0.42 mmol) were added to the reaction flask, which was fitted with a reflux condenser and immersed in an oil bath at 80 °C. After 1.5 h, 3N LiOH (1.4 mL) was then added to the reaction and the mixture maintained at 80 °C for an additional 1 h. Purification of the crude material using preparative HPLC (method: 15-35 % B over 30 min at 20 mL/min; column: Phenomenex C18 21.2 x 250 mm; mobile phases: A = 0.1% TFA in water and B = 0.1% TFA in 90% MeCN) afforded **11** (60 mg, 30% yield) as a white powder. <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN: D<sub>2</sub>O 2:1 v/v):  $\delta$  7.7 (t, *J* = 8.4 Hz, 1H), 7.6 (m, 2H), 7.35 (dd, *J* = 1.8, 13.8 Hz, 1H), 7.11 (d, *J* = 9 Hz, 1H), 7.0 (m, 2H), 4.29 (m, 1H), 4.15 (m, 2H), 3.40 (m, 2H), 3.28 (m, 2H), 3.22 (m, 2H); <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN: D<sub>2</sub>O 2:1 v/v):  $\delta$  167.0, 164.6, 162.9, 161.0, 157.7, 146.7, 136.3, 134.0, 122.7, 117.9, 114.6, 113.9, 112.3, 106.7, 101.9, 71.5, 65.8, 50.8, 49.7, 37.2; HRMS calcd for C<sub>20</sub>H<sub>21</sub>FN<sub>4</sub>O<sub>5</sub> (M+H), 417.1568; found: 417.1567.

**(S)-1-(2-(3-(2-Cyano-3-fluorophenoxy)-2-hydroxypropylamino)ethyl)-3-(4-ethoxyphenyl)urea (12).**

Deprotection: Method I; Filtered and washed the precipitate with dioxane; 82% yield; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.70, (s, 1H), 7.92 (bs, 3H), 7.28 (m, 2H), 6.80 (m, 2H), 6.46 (bs, 1H), 3.94 (m, 2H), 3.31 (m, 2H), 2.87 (m, 2H), 1.29 (m, 3H); <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  155.9, 153.2, 133.3, 119.5, 114.3, 119.5, 37.1, 14.6; HRMS calcd for C<sub>11</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub> (M+H), 224.1393; found: 224.1391.

Epoxide Opening: Method A; Purified by preparative HPLC (20-80% B over 30 min); 31% yield;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ :  $\text{D}_2\text{O}$  2:1 v/v):  $\delta$  7.61 (m, 1H), 7.16 (m, 2H), 6.94 (d,  $J$  = 8.4 Hz, 1H), 6.89 (m, 1H), 6.79 (m, 2H), 4.30 (m, 1H), 4.16 (d,  $J$  = 4.8 Hz, 2H), 3.97 (q,  $J$  = 7.2 Hz, 2H), 3.45 (m, 2H), 3.22 (m, 4H), 1.30 (t,  $J$  = 6.6 Hz, 3H);  $^{19}\text{F}$  NMR ( $\text{CD}_3\text{CN}$ :  $\text{D}_2\text{O}$  2:1 v/v):  $\delta$  -108.00 (m);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ :  $\text{D}_2\text{O}$  2:1 v/v):  $\delta$  165.6 (163.9), 162.2, 159.2, 155.9, 137.6 (137.5), 132.8, 123.2, 119.3, 115.9, 113.2, 109.9 (109.9), 109.6 (109.5), 91.9 (91.9), 72.0, 65.8, 64.9, 50.7, 50.2, 37.5, 15.2; HRMS calcd for  $\text{C}_{23}\text{H}_{25}\text{FN}_4\text{O}_5$  (M+H), 439.1752; found: 439.1756.

**(S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(6-(2-fluoroethoxy) pyridin-3-yl)urea (13).**

Deprotection: Method II; Concentrated and neutralized with 5% aqueous  $\text{K}_2\text{CO}_3$  to pH = 7.

Purified by preparative HPLC using  $\text{NH}_4\text{OAc}$  as the mobile phase (2-22% B over 30 min: %A = 5  $\mu\text{M}$   $\text{NH}_4\text{OAc}$ ; %B = 90% MeCN in 10% 5 $\mu\text{M}$   $\text{NH}_4\text{OAc}$ ); 58% yield.

Epoxide Opening: Method A; Purified by preparative HPLC (10-40% B over 30 min); 23% yield;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.86 (s, 1H), 8.63 (s, 2H), 8.16 (dd,  $J$  = 0.7, 2.8 Hz, 1H), 7.76 (ddd,  $J$  = 2.2, 8.3, 9.2 Hz, 3H), 7.67 (ddd,  $J$  = 1.7, 7.5, 8.8 Hz, 1H), 7.27 (d,  $J$  = 8.2 Hz, 1H), 7.12 (td,  $J$  = 0.9, 7.6 Hz, 1H), 6.78 (dd,  $J$  = 0.6, 8.8 Hz, 1H), 6.64 (t,  $J$  = 5.6 Hz, 1H), 4.83 – 4.76 (m, 1H), 4.67 – 4.60 (m, 1H), 4.51 – 4.45 (m, 1H), 4.41 – 4.34 (m, 1H), 4.28 – 4.10 (m, 3H), 3.41 (dd,  $J$  = 5.5, 10.9 Hz, 2H), 3.24 (d,  $J$  = 11.1 Hz, 1H), 3.18 – 3.02 (m, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  159.8, 157.9, 156.1, 136.4, 135.1, 133.7, 131.4, 131.0, 121.4, 116.3, 113.2, 110.1, 100.8, 83.2 (81.0), 70.5, 64.8 (64.6), 64.5, 49.4, 47.8, 36.0; HRMS calcd for  $\text{C}_{20}\text{H}_{24}\text{FN}_5\text{O}_4$  (M+H), 418.1885; found: 418.1887.

**(S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(6-fluoropyridin-3-yl) urea (14)**

Deprotection: Method I; Filtered and washed the precipitate with dioxane; 100% yield;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ :  $\text{D}_2\text{O}$  2:1 v/v):  $\delta$  7.74 (m, 1H), 7.68 (m, 1H), 7.27 (m, 1H), 6.89 (m, 2H), 6.52 (bs, 1H), 5.03 (s, 2H), 3.30 (m, 2H), 2.87 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ :  $\text{D}_2\text{O}$  2:1 v/v):  $\delta$  160.4 (158.8), 157.9, 138.5 (138.4), 135.0, 134.5 (134.4), 110.4 (110.1), 40.8, 38.1;  $^{19}\text{F}$



NMR (282 MHz, CD<sub>3</sub>CN: D<sub>2</sub>O 2:1 v/v):  $\delta$  -77.95 (s); HRMS calcd for C<sub>8</sub>H<sub>11</sub>FN<sub>4</sub>O (M+H), 199.0989; found: 199.0989.

Epoxide Opening: Method A; Purified by preparative HPLC (20-80% B over 30 min); 18% yield; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN: D<sub>2</sub>O 1:3 v/v):  $\delta$  9.00 (bs, 1H), 8.61 (bs, 2H), 8.46 (s, 1H), 7.74 (m, 1H), 7.68 (m, 1H), 7.27 (m, 1H), 7.15 (m, 3H), 6.64 (m, 2H), 6.37 (t, 1H), 5.95 (bs, 1H), 4.22 (m, 1H), 4.17 (m, 2H), 3.39 (m, 2H), 3.23 (m, 1H), 3.08 (m, 3H); <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN: D<sub>2</sub>O 1:3 v/v):  $\delta$  172.1, 161.4, 159.8, 159.3, 139.4 (139.3), 137.1, 135.9 (139.8), 135.2, 135.1 (135.12), 123.4, 118.9, 114.3, 111.4 (111.1), 101.9, 72.1, 66.5, 51.4 (50.2), 37.8; HRMS calcd for C<sub>18</sub>H<sub>20</sub>FN<sub>5</sub>O<sub>3</sub> (M+H), 374.1623; found: 374.1628.

**Synthesis of (S)-1-(2-Cyanophenoxy)-2-hydroxy-3-(2-(1-(4-iodopyridinyl) ureido-3-yl) ethyl) amino propane (15).**

Deprotection: Method I; Filtered and washed precipitate with dioxane; 90% yield.

Epoxide Opening: Method A; Purified by preparative HPLC (method: 15-45 %B over 30 min) to yield 37 mg (52%). The TFA salt was then dissolved in MeCN:H<sub>2</sub>O (0.5 mL, 1:1 v/v) and passed through BioRad AG1-X8, OH form resin column previously equilibrated with MeCN:H<sub>2</sub>O (1:1 v/v) to give 20 mg (70% recovery) of the free base. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN):  $\delta$  8.27 (d, *J* = 3 Hz, 1H), 7.55 (m, 4H), 7.0 (m, 3H), 4.0 (m, 3H), 3.2 (m, 2H), 2.68 (m, 4H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN):  $\delta$  160.8, 156.6, 141.5, 137.5, 135.6, 135.1, 134.0, 128.8, 121.6, 117.3, 113.2, 106.7, 101.0, 71.7, 68.3, 51.3, 48.8, 39.4; HRMS calcd for C<sub>18</sub>H<sub>20</sub>IN<sub>5</sub>O<sub>3</sub> (M+H), 482.0683; found: 482.0681.

**Synthesis of (S)-1-(6-Bromopyridin-3-yl)-3-(2-(3-(2-cyanophenoxy)-2-hydroxypropylamino)ethyl)urea (16).**

Deprotection: Method I; Concentrated then passed through an ion exchange column (BioRad AG1-X2, 200-400 mesh, hydroxide form) and lyophilized to form a white solid, which was immediately used without further purification in the subsequent step; 74% yield.

Epoxide Opening: Method A; Purified by preparative HPLC (method: 15-45 % B over 30 min). Product fractions were combined, lyophilized and converted to the free base using BioRad AG1-X8, OH form resin as described above; 22% yield. <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN: D<sub>2</sub>O 2:1 v/v):  $\delta$  8.24 (d, *J* = 3.2 Hz, 1H), 7.68 (dd, *J* = 3.2, 8.4 Hz, 1H), 7.55 (m, 2H), 7.38 (d, *J* = 9.1 Hz, 1H),

7.07 (d,  $J = 9.2$  Hz, 1H), 7.0 (dt,  $J = 0.6, 7.2$  Hz, 1H), 4.05 (m, 3H), 3.24 (m, 2H), 2.72 (m, 4H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ :  $\text{D}_2\text{O}$  2:1 v/v):  $\delta$  161.4, 157.4, 141.2, 137.5, 136.3, 134.7, 130.6, 129.0, 122.3, 118.1, 113.9, 101.6, 72.3, 68.9, 51.8, 49.4, 39.0; HRMS calcd for  $\text{C}_{18}\text{H}_{20}\text{BrN}_5\text{O}_3$  (M+H), 434.0822; found: 434.0816.

**Synthesis of (S)-1-(5-Bromopyradin-2-yl)-3-(-3-(2-cyanophenoxy)-2-hydroxypropylamino)ethyl urea (17).**

Deprotection: Method II; Reaction mixture was concentrated after 20 min and azeotropically dried with toluene (2 x 4 mL); 99% yield.

Epoxide Opening: Method A; Purified by preparative HPLC (method: 10-40 % B over 25 min); 37% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{CN}$ ):  $\delta$  8.75 (s, 1H), 8.61 (s, 1H), 8.28 (s, 1H), 7.61 (m, 2H), 7.1 (m, 2H), 4.19-4.3 (brm, 5H), 3.6 (br s, 2H), 3.29 (br s, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{CN}$ ):  $\delta$  158.2, 150.0, 144.8, 136.5, 132.0, 122.9, 114.2, 103.0, 72.1, 66.2, 51.5, 38.2 HRMS calcd for  $\text{C}_{17}\text{H}_{19}\text{BrN}_6\text{O}_3$  (M+H), 435.0774; found: 435.0777.

**(S) -1-(2-(3-(2-Cyano-3-fluorophenoxy)-2-hydroxypropylamino)ethyl)-3-(thiazol-2-yl)urea (18).**

Deprotection: Method I: Filtered and washed the precipitate with dioxane; 100% yield.  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.96 (s, 3H), 7.35 (d,  $J = 3.7$  Hz, 1H), 7.09 (t,  $J = 5.1$  Hz, 1H), 7.06 (d,  $J = 3.7$  Hz, 1H), 3.39 (q,  $J = 6.0$  Hz, 2H), 2.91 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  160.6, 154.0, 134.7, 112.3, 37.2; HRMS calcd for  $\text{C}_6\text{H}_{10}\text{N}_4\text{OS}$  (M+H), 187.0648; found: 187.0648.

Epoxide Opening: Method A; DMF was added to aid in dissolution (1.9 M). Purified by preparative HPLC (20-80% B over 30 min); 17% yield;  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.71 – 8.60 (m, 2H), 7.73 (dd,  $J = 8.5, 15.6$  Hz, 1H), 7.32 (d,  $J = 3.6$  Hz, 1H), 7.14 (d,  $J = 8.7$  Hz, 1H), 7.09 (t,  $J = 8.8$  Hz, 1H), 7.03 (d,  $J = 3.6$  Hz, 1H), 6.95 (t,  $J = 5.3$  Hz, 1H), 4.25-4.20 (m, 3H), 3.51 – 3.42 (m, 2H), 3.26 – 3.18 (m, 1H), 3.15 – 3.04 (m, 3H);  $^{19}\text{F}$  NMR (282 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  -107.48 (m);  $^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  163.9 (162.2), 161.0 (160.9), 160.1, 154.4, 137.0, 136.4 (136.3), 111.9, 111.5, 109.3, 108.4 (108.2), 90.5 (90.4), 71.2, 64.5, 49.2, 47.2, 36.0; HRMS calcd for  $\text{C}_{16}\text{H}_{18}\text{FN}_5\text{O}_3\text{S}$  (M+H), 380.1187; found: 380.1190.

**(S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(2-(2-fluoroethyl)-2H-tetrazol-5-yl)urea (19).**

Deprotection: Method II: Concentrated and passed through an ion exchange column (BioRad AG1-X8, hydroxide form); 33% yield; HRMS calcd for C<sub>6</sub>H<sub>12</sub>FN<sub>7</sub>O (M+H), 218.1160; found: 218.1158.

Epoxide Opening: Method A; Purified by preparative HPLC (2-32% B over 30 min; A= 0.1% NH<sub>4</sub>OAc in water; B= 0.1% NH<sub>4</sub>OAc in 90% MeCN, 10% H<sub>2</sub>O); 16% yield; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN: D<sub>2</sub>O 1:1 v/v): δ 7.61 (m, 2H), 7.10 (m, 1H), 7.07 (m, 1H), 4.89 (m, 2H), 4.83 (m, 2H), 4.29 (m, 1H), 4.14 (m, 2H), 3.57 (m, 2H), 3.27 (m, 4H); <sup>19</sup>F NMR (CD<sub>3</sub>CN: D<sub>2</sub>O 1:1 v/v): δ -223.03 (m); <sup>13</sup>C NMR (150 MHz, CD<sub>3</sub>CN: D<sub>2</sub>O 1:1 v/v): δ 161.6, 161.1, 156.6, 136.5, 134.8, 122.8, 118.1, 114.0, 101.8, 82.4 (81.3), 71.5, 65.9, 55.0 (54.9), 50.9, 49.3, 37.6; HRMS calcd for C<sub>16</sub>H<sub>21</sub>FN<sub>8</sub>O<sub>3</sub> (M+H), 393.1793; found: 393.1796.

**(S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(1-(2-fluoroethyl) piperidin-4-yl)urea (20)**

Deprotection: Method II: Concentrated and used directly in the subsequent step; >98% yield.

Epoxide Opening: Method A; Purified by preparative HPLC (2-32% B over 30 min); 38% yield; <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN: D<sub>2</sub>O 1:1 v/v): δ 7.66 – 7.60 (m, 2H), 7.15 – 7.06 (m, 2H), 4.81 – 4.76 (m, 1H), 4.73 – 4.68 (m, 1H), 4.28 (dd, *J* = 4.9, 8.6 Hz, 1H), 3.61 (t, *J* = 11.8 Hz, 1H), 3.55 (d, *J* = 12.4 Hz, 2H), 3.48 – 3.34 (m, 5H), 3.32 – 3.09 (m, 5H), 3.03 (t, *J* = 12.5 Hz, 2H), 2.05 (d, *J* = 13.2 Hz, 2H), 1.95 (m, 1H), 1.70 – 1.56 (m, 2H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN: D<sub>2</sub>O 1:1 v/v): δ 161.1, 160.5, 136.5, 134.8, 122.8, 118.1, 114.0, 101.8, 80.2 (78.0), 71.4, 65.9, 57.6 (57.5), 53.3, 50.7, 49.9, 45.7, 37.4, 30.3; HRMS calcd for C<sub>20</sub>H<sub>30</sub>FN<sub>5</sub>O<sub>3</sub> (M+H), 408.2405; found: 408.2408.

**Synthesis of (S)-N-(2-(3-(2-Cyano-3-fluorophenoxy)-2-hydroxypropylamino)ethyl)morpholine-4-carboxamide (21).**

Deprotection: Method II; Concentrated and used directly in the subsequent step; 100% yield.

Epoxide Opening: Method B; Purified by preparative HPLC (method: 0-100% B over 12 min at 20 mL/min; 35 % yield. <sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>CN:D<sub>2</sub>O 2:3 v/v): δ 7.6 (ddd, *J* = 6.6, 8.4, 8.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.9 (t, *J* = 9.1 Hz, 1H), 4.45 (m, 1H), 4.16 (m, 2H), 3.58 (dd, *J*

= 4.8 Hz, 4H), 3.42 (m, 2H), 3.25 (dd,  $J = 4.8$  Hz, 4H), 3.2 (m, 4H);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CD}_3\text{CN}$ ):  $\delta$  -107.4 (s);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{CN}:\text{D}_2\text{O}$  2:3 v/v):  $\delta$  164.6 ( $J = 254.2$  Hz), 162.3, 162.3, 160.5, 137.6, 118.4, 116.4, 113.4, 109.7, 91.6 ( $J = 18$  Hz), 71.8, 67.1, 65.7, 50.1, 44.6, 37.8; HRMS calcd for  $\text{C}_{17}\text{H}_{23}\text{FN}_4\text{O}_4$  (M+H), 367.1776; found: 367.1776.

**(S)-4-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)-N-(6-fluoropyridin-3-yl) butanamide (22).**

Deprotection: Method II: Concentrated and used directly in the subsequent step; 100% yield;  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.49 – 8.45 (m, 1H), 8.18 (ddd,  $J = 2.8, 7.4, 8.7$  Hz, 4H), 7.11 (dd,  $J = 3.1, 8.9$  Hz, 1H), 2.89 – 2.75 (m, 2H), 2.49 (t,  $J = 7.3$  Hz, 2H), 1.94-1.84 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  170.7, 159.3 (157.7), 137.7 (137.6), 134.2 (134.2), 132.7 (132.6), 109.4 (109.2), 32.6, 30.4, 22.8; HRMS calcd for  $\text{C}_9\text{H}_{12}\text{FN}_3\text{O}$  (M+H), 198.1037; found: 198.1037.

Epoxide Opening: Method A; Purified by preparative HPLC using TFA as the modifier (10-40% B over 30 min); 30% yield;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ ):  $\delta$  9.01 (s, 1H), 8.35 (s, 1H), 8.12 – 8.07 (m, 1H), 7.65 – 7.60 (m, 2H), 7.15 (d,  $J = 9.2$  Hz, 1H), 7.09 (t,  $J = 7.9$  Hz, 1H), 6.97 (dd,  $J = 3.2, 8.8$  Hz, 1H), 4.38 (td,  $J = 5.0, 8.6$  Hz, 1H), 4.21 (dd,  $J = 4.9, 10.1$  Hz, 1H), 4.16 (dd,  $J = 5.1, 10.0$  Hz, 1H), 3.32 (dd,  $J = 2.6, 12.5$  Hz, 1H), 3.27 – 3.12 (m, 4H), 2.61 (t,  $J = 6.7$  Hz, 2H), 2.32 – 2.25 (m, 1H), 2.08 (dd,  $J = 6.6, 13.3$  Hz, 2H);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CD}_3\text{CN}$ ):  $\delta$  -76.01 (s);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ ):  $\delta$  159.8, 158.4 (156.9), 155.7, 136.3 (136.2), 135.3, 135.0, 133.7, 131.5 (131.4), 121.4, 116.2, 113.2, 109.1 (108.4), 100.8, 70.5, 64.6, 49.3, 47.6, 41.8, 36.0; HRMS calcd for  $\text{C}_{19}\text{H}_{21}\text{FN}_4\text{O}_3$  (M+H), 373.16705; found: 373.1671.

**(S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-2-(4-fluorophenyl) acetamide (23).**

Deprotection: Method I: Filtered and washed the precipitate with dioxane; 100% yield;  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.49 (t,  $J = 5.3$  Hz, 1H), 8.14 (s, 2H), 7.33 – 7.28 (m, 2H), 7.14 – 7.08 (m, 2H), 3.45 (s, 2H), 3.30 (q,  $J = 6.2$  Hz, 2H), 2.85 (h,  $J = 5.9$  Hz, 2H);  $^{19}\text{F}$  NMR (282 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  -117.05 (m);  $^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  170.6, 161.8 (160.2), 132.3 (132.2), 131.0 (130.9), 114.9 (114.7), 41.2, 38.4, 36.5; HRMS calcd for  $\text{C}_{10}\text{H}_{13}\text{FN}_2\text{O}$  (M+H), 197.1084; found: 197.1084.

Epoxide Opening: Method A; Purified by preparative HPLC (20-80% B over 30 min); 22% yield;  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}:\text{D}_2\text{O}$  2:1 v/v):  $\delta$  7.63 (td,  $J$  = 6.9, 8.6 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.26 – 7.21 (m, 3H), 6.95 – 6.89 (m, 2H), 4.27 (td,  $J$  = 4.7, 8.2 Hz, 1H), 4.13 (d,  $J$  = 4.8 Hz, 2H), 3.52 (s, 2H), 3.45 (t,  $J$  = 5.8 Hz, 2H), 3.24 (dd,  $J$  = 3.3, 12.9 Hz, 1H), 3.21 – 3.13 (m, 3H);  $^{19}\text{F}$  NMR (282 MHz,  $\text{CD}_3\text{CN}:\text{D}_2\text{O}$  2:1 v/v):  $\delta$  -107.98 (m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{CN}:\text{D}_2\text{O}$  2:1 v/v):  $\delta$  175.4, 164.5 (161.3), 161.1, 136.4, 134.8, 132.3 (132.1), 132.0, 122.7, 118.0, 116.4 (116.1), 114.0, 101.9, 71.4, 65.9, 50.8, 48.9, 42.3, 37.1; HRMS calcd for  $\text{C}_{20}\text{H}_{22}\text{FN}_3\text{O}_3$  (M+H), 372.1718; found: 372.1716.

**(S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(4-hydroxyphenyl)urea (47).**

**46** (280 mg, 0.49 mmol) dissolved in MeOH (24 mL) treated with Degussa type Pd/C (56 mg, 26  $\mu\text{mol}$ ; 5.4 mol %) and the headspace sparged with 1 atm  $\text{H}_2$ . After 12 h, the catalyst was removed by filtration through Celite then washed with MeOH (2 x 20 mL) and concentrated to dryness. Purification by preparative HPLC (10-30% B over 20 min; B = 0.1% TFA in 90% MeCN; A = 0.1% TFA in  $\text{H}_2\text{O}$ ) afforded **47** as a white powder (45 mg, 19% yield).  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.99 (s, 1H), 8.62 (brs, 2H), 8.46 (s, 1H), 7.74 (dd,  $J$  = 1.6, 7.8 Hz, 1H), 7.68 (ddd,  $J$  = 1.7, 7.5, 8.6 Hz, 1H), 7.27 (d,  $J$  = 8.3 Hz, 1H), 7.17 – 7.14 (m, 2H), 7.12 (td,  $J$  = 0.9, 7.6 Hz, 1H), 6.66 – 6.62 (m, 2H), 6.37 (t,  $J$  = 5.6 Hz, 1H), 5.95 (s, 1H), 4.22 (dt,  $J$  = 4.6, 8.4 Hz, 1H), 4.16 (qd,  $J$  = 5.0, 10.3 Hz, 2H), 3.38 (dd,  $J$  = 2.4, 5.8 Hz, 2H), 3.23 (ddd,  $J$  = 4.4, 8.6, 16.2 Hz, 1H), 3.14 – 3.04 (m, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  159.8, 156.3, 152.2, 135.0, 133.6, 131.5, 121.4, 120.3, 116.2, 115.0, 113.2, 100.8, 70.5, 64.6, 49.3, 48.1, 36.0. The spectral data were consistent with that previously reported by Schaefer et al.<sup>1</sup>

**(S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(3-benzyloxyphenyl) urea (48).**

Deprotection: Method II: Concentrated used directly in the subsequent step; 100% yield;  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.78 (s, 1H), 7.74 (bs, 3H), 7.40 (m, 5H), 7.23 (m, 1H), 7.12 (m, 1H), 6.91 (m, 1H), 6.58 (m, 1H), 6.43 (m, 1H), 5.04 (s, 2H), 3.31 (m, 2H), 2.89 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  159.2, 156.2, 142.1, 137.6, 129.8, 128.8, 128.2, 128.0, 110.9, 107.8, 105.0, 69.5, 66.8, 37.6; HRMS calcd for  $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_2$  (M+H), 286.1550; found: 286.1551.

Epoxide Opening: Method A; Purified by preparative HPLC (20-80% B over 30 min); 10% yield;  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.61 (br s, 1H), 7.75-7.65 (m, 2H), 7.44-7.10 (m, 7H), 7.15-7.10 (m, 2H), 6.91 (m, 1 H), 6.58 (m, 1 H), 6.50 (m, 1H), 5.12 (s, 2H), 4.20 (m, 4H), 3.41 (m, 2H), 3.25 (br s, 1H), 3.15 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  159.8, 158.7, 155.7, 141.4, 137.1, 135.0, 133.7, 129.3, 128.3, 127.7, 127.5, 121.4, 116.3, 113.2, 110.5, 107.5, 104.7, 100.7, 70.5, 69.0, 64.5, 49.3, 47.8, 35.9; HRMS calcd for  $\text{C}_{26}\text{H}_{28}\text{N}_4\text{O}_4$  (M+H), 461.2183; found: 461.2185.

**(S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(4-hydroxyphenyl)urea (49).**

**48** (100 mg, 0.174 mmol) dissolved in MeOH (9 mL) treated with Degussa type Pd/C (20 mg, 9.4  $\mu\text{mol}$ ; 5.4 mol %) and the headspace sparged with 1 atm  $\text{H}_2$ . After 12 h, the catalyst was removed by filtration through Celite then washed with MeOH (2 x 20 mL) and concentrated to dryness. Purification by preparative HPLC (10-30% B over 20 min; B = 0.1% TFA in 90% MeCN; A = 0.1% TFA in  $\text{H}_2\text{O}$ ) afforded **49** as a white powder (20 mg, 24% yield).  $^1\text{H}$  NMR (600 MHz,  $\text{CD}_3\text{CN}$ :  $\text{D}_2\text{O}$  1:1 v/v):  $\delta$  8.35 (s, 1H), 7.59 (m, 2H), 7.07 (m, 3H), 6.84 (m, 1H), 6.73 (m, 1H), 6.46 (m, 1H), 4.28 (m, 1H), 4.14 (m, 2H), 3.44 (m, 2H), 3.22 (m, 4H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CD}_3\text{CN}$ :  $\text{D}_2\text{O}$  1:1 v/v):  $\delta$  161.1, 158.6, 157.7, 141.1, 136.5, 134.8, 131.0, 122.8, 119.7, 118.2, 114.0, 112.3, 111.1, 107.7, 101.7, 71.5, 66.1, 50.9, 49.8, 37.5; HRMS calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_4$ , 371.1714; found: 371.1713.

**Synthesis of (S)-N-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-6-fluoronicotinamide (24).**

Deprotection: Method II; Solvent was evaporated then re-dissolved in 20% MeCN/ $\text{H}_2\text{O}$  (40 mL) and lyophilized.; 100% yield;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.11 (t,  $J$  = 5.4 Hz, 1H), 8.83 – 8.77 (m, 1H), 8.50 (ddd,  $J$  = 2.5, 7.9, 8.6 Hz, 1H), 8.19 (s, 2H), 7.31 (ddd,  $J$  = 0.6, 2.7, 8.6 Hz, 1H), 3.55 (q,  $J$  = 5.8 Hz, 2H), 3.01 (dd,  $J$  = 5.8, 11.0 Hz, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  165.8 (162.6), 164.1, 147.7 (147.5), 141.6 (141.5), 128.4 (128.3), 109.5 (108.9), 38.4, 37.0; HRMS calcd for  $\text{C}_8\text{H}_{10}\text{FN}_3\text{O}$  (M+H), 184.0880; found: 184.0882.

Epoxide Opening: Method A; Purified by preparative HPLC (20-80% B over 30 min); 38% yield;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.93 (t,  $J$  = 5.3 Hz, 1H), 8.79 (s, 2H), 8.72 (d,  $J$  = 3.1

Hz, 1H), 8.40 (td,  $J = 2.7, 8.3$  Hz, 1H), 7.74 (dd,  $J = 1.6, 7.6$  Hz, 1H), 7.71 – 7.63 (m, 1H), 7.36 – 7.25 (m, 2H), 7.12 (t,  $J = 7.5$  Hz, 1H), 4.26 (td,  $J = 5.0, 9.1$  Hz, 1H), 4.20 – 4.14 (m, 2H), 3.63 (dd,  $J = 6.2, 11.6$  Hz, 2H), 3.35 – 3.06 (m, 4H);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  165.8 (162.6), 164.33 (164.32), 159.8, 147.6 (147.3); 141.5 (141.3), 135.0, 133.6, 128.3 (128.2), 121.3, 116.3, 113.2, 109.6 (109.1), 100.7, 70.5, 64.6, 49.3, 46.6, 35.7; HRMS calcd for  $\text{C}_{18}\text{H}_{19}\text{FN}_4\text{O}_3$  (M+H), 359.1514; found: 359.1516.

**Synthesis of (S)-N-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-2-fluorobenzenesulfonamide (25).**

A 10 mL round bottom flask was successively charged with benzyl-2-aminoethyl carbamate (0.355 g, 1.54 mmol),  $\text{CH}_2\text{Cl}_2$  (5 mL) and  $i\text{-Pr}_2\text{Net}$  (0.498 g, 3.85 mmol, 0.67 mL) at ambient temperature. 2-Fluorobenzenesulfonyl chloride (0.33 g, 1.72 mmol, 0.228 mL) was then added to the resulting suspension; the reaction mixture became homogeneous. The reaction mixture was stirred for 2 h, diluted with  $\text{CH}_2\text{Cl}_2$  (7 mL), poured into a separatory funnel, washed with  $\text{H}_2\text{O}$  (5 mL) and brine then dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo to an oil. This crude oil was purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2$ (100%) to  $\text{CH}_2\text{Cl}_2$ : MeOH (98:2)) to obtain **27** (0.4 g, 67% yield).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.84 (brt, 1H,  $J = 7.2$  Hz), 7.55 (m, 1H), 7.33 (m, 5H), 7.25 (t, 2H,  $J = 7.2$  Hz), 7.16 (dd, 1H,  $J = 10.2$  Hz), 5.25 (br t, 1H), 5.0 (s, 2H), 3.3 (m, 2H), 3.1 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  157.9 ( $J = 247.5$  Hz), 157.9, 156.0, 137.2, 135.1 ( $J = 8.25$  Hz), 129.5, 128.2, 127.7 ( $J = 4.5$  Hz), 124.8 ( $J = 3.75$  Hz), 117.3, 117.1, 65.3, 41.9;  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -110.8; HRMS calcd for  $\text{C}_{16}\text{H}_{17}\text{FN}_2\text{O}_4\text{S}$  (M+H), 353.0965; found: 353.0966.

**27** (0.2 g, 0.56 mmol) was charged into a 10 mL round bottom flask and dissolved in MeOH (2.0 mL) treated with Pd/C (45 mg, 42  $\mu\text{mol}$ ; 7.5 mol %) and the headspace sparged with 1 atm  $\text{H}_2$ . After 16 h, the catalyst was removed by filtration through Celite then concentrated to dryness to obtain 1-(2-fluorophenylsulfonylamido)-2-amino ethane (**51**), which was used without further purification in the subsequent step.

Epoxide Opening: Method A; Purified by preparative HPLC (0-90%B over 30 min); 45% yield.

$^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{CN}$ ;  $\text{D}_2\text{O}$  2:1 v/v):  $\delta$  7.82 (ddd, 1H,  $J = 1.5, 8.2, 8.2$  Hz), 7.65 (m, 3H), 7.36 (m, 2H), 7.11 (m, 2H), 4.31 (m, 1H), 4.14 (m, 2H), 3.27 (m, 6H);  $^{19}\text{F}$  NMR (282 MHz, DMSO- $d_6$ ):  $\delta$  -110.1 (s);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{CN}$ ;  $\text{D}_2\text{O}$  2:1 v/v):  $\delta$  161.1, 137.1, 136.4,

134.4, 131.1, 126.0, 122.7, 118.5, 117.9, 113.9, 101.9, 71.4, 65.8, 50.6, 48.4, 39.5,; HRMS calcd for C<sub>18</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>4</sub>S (M+H), 394.1231; found: 394.1229.

**(S)-1-(2-(3-(2-Cyanophenoxy)-2-hydroxypropylamino)ethyl)-3-(4-benzyloxyphenyl) urea (46)**

Deprotection: Method I: Filtered and washed the precipitate with dioxane; 100% yield; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 8.79 (s, 1H), 7.96 (s, 3H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.34 – 7.28 (m, 3H), 6.93 – 6.86 (m, 2H), 6.52 (s, 1H), 5.03 (s, 2H), 3.31 (t, *J* = 5.9 Hz, 2H), 2.87 (h, *J* = 5.9 Hz, 2H). The spectral data were consistent with that previously reported by Schaefer et al.<sup>42</sup>

Epoxide Opening: Method A; Purified by preparative HPLC (20-80% B over 30 min); 18% yield; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>): δ 8.60 (s, 1H), 7.74 (dd, *J* = 1.7, 7.7 Hz, 1H), 7.69 – 7.65 (m, 1H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.34 – 7.25 (m, 4H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.91 – 6.87 (m, 2H), 6.37 (t, *J* = 5.3 Hz, 1H), 5.87 (s, 1H), 5.03 (s, 2H), 4.22 – 4.12 (m, 3H), 3.42 – 3.29 (m, 3H), 3.18 (d, *J* = 10.5 Hz, 1H), 3.05 (t, *J* = 10.4 Hz, 3H). The spectral data were consistent with that previously reported by Schaefer et al.<sup>1</sup>

**General procedure for the preparation of [<sup>18</sup>F]5-7**

500 mCi [<sup>18</sup>F]NaF, prepared through the <sup>18</sup>O(p,n)<sup>18</sup>F reaction (PETNet Pharmaceutical Services, Cummings Park, Woburn, MA) was trapped on an anion exchange cartridge (ORTG Inc., Oak Ridge, TN) and placed into an elution loop contained within a remote control radiosynthesis system. The radioactivity was eluted using K<sub>2</sub>CO<sub>3</sub> (11.6 μmol; 0.8 mL of a 14.5 mM solution in H<sub>2</sub>O) and collected into a silanized 25 mL pear-shaped flask. The eluate was then concentrated to dryness by applying a gentle stream of heated He and weak vacuum, while heating the vessel to 105 °C. The evacuation flask was then cooled to 70 °C and treated with Kryptofix 222 (58.4 μmol; 0.5 mL of a 117 mM solution in MeCN).

After 5 min, the solution was transferred to a 5 mL Wheaton™ reaction vessel containing 3.0 mg of the required tosylate precursor, then heated at 90 °C and maintained 15 min. The derived [<sup>18</sup>F]fluoroethyl- and fluoropropyl tosylates (**62** and **41** respectively) were then isolated by preparative HPLC and stored in 5 mL Wheaton™ following removal of the HPLC solvents; 40% overall yield. The purified tosylates **62** and **41** were then treated with solid K<sub>2</sub>CO<sub>3</sub> (2.5 mg)



and a solution of the required phenol (**47** or **49**; 4.0 mg) dissolved in anhydrous MeCN (0.5 mL). The resulting mixture was then heated 95 °C and maintained 20 min. After cooling to ambient temperature, the reaction solution was transferred to a 25 mL pear-shaped flask and diluted with H<sub>2</sub>O (15 mL). The resulting mixture was then loaded onto a C18 Sep Pak™ cartridge, washed with H<sub>2</sub>O (5 mL) then eluted with MeCN (3 mL); the column was further dried with N<sub>2</sub> to ensure complete recovery. The eluent was purified by HPLC using a Phenomenex Luna C-18 column (10 x 250 mm, 5 μ), with a gradient from 0-100%B over 15 min at 2.5 mL/min: mobile phase A = 10% aqueous MeCN; B = 100% MeCN, each containing 0.1% TFA; , Like fractions were concentrated on the rotovap then reconstituted with a 0.9% sterile saline. The completed process typically delivered ~25 mCi of each tracer and required 90 min to complete. Specific activity was determined via direct HPLC comparison of the labeled product with the appropriate standard reference material described above.

### **Lipophilicity calculations:**

Log<sub>D</sub>(7.4) is a partition coefficient for charged species between octanol and H<sub>2</sub>O at pH=7.4. In general, the log<sub>D</sub>(pH) is defined as:  $\log D_{pH} = \log (\sum a_{iorg} / \sum a_{iwater})$  where  $a_{iorg}$  is the concentration of the  $i$ th microspecies in octanol and  $a_{iwater}$  is the concentration of the  $i$ th microspecies in water. The computed lipophilicity, clog D7.4, was calculated with ACD/LogD Suite Software (Advanced Chemistry Development Inc. Toronto, Canada) for all the compounds in this study (Table 1).

### **Tissue Biodistribution**

Tissue biodistribution studies were conducted in sodium pentobarbital (50 mg/kg, ip) anesthetized Sprague Dawley rats (300-400 g). After anesthesia, the left femoral vein was cannulated. To determine specificity of the test agent to β-AR, propranolol (2.5 mg/kg iv) or vehicle was first injected into each rat. Five min later, test compounds were administered at a dose of approximately 15 μCi in 0.3 mL 10% ethanolic saline. 15 min post injection, rats (n=2-3/group) were euthanized tissue samples of blood, heart, lung, liver, spleen, kidney, femur, muscle, and brain collected, weighed and counted using an autogamma counter (Wallac Wizard 1480, PerkinElmer Life and Analytical Sciences, Shelton, CT). Radioactivity measurements were decay corrected and the net injected dose was calculated by subtracting residual activities in

the syringe and venous catheter. The tissue biodistribution was expressed as percent of injected dose per gram of tissue (%ID/g).

### **Cardiac Imaging**

Rats were anesthetized and the left femoral vein cannulated as described above. Cardiac imaging was performed using a microPET camera (Focus220, CTI Molecular Imaging, Inc. Knoxville, TN), which provides 95 transaxial slices in 22 cm operational field of view. Once positioned, the animal was injected with approximately 1 mCi of the test compound ; image acquisition started immediately prior to injection and lasted 30 min. Images were reconstructed using a FBP logarithm with a 256 x 256 matrix at zoom 2 with no attenuation correction. Image visualization, ROI placement, and quantification were performed using the ASIPRO software package developed by the manufacturer. Each compound was imaged with one animal.

### **$\beta_1$ and $\beta_2$ receptor binding assay.**

To determine the affinity of test compounds to  $\beta_1$  and  $\beta_2$  receptors, in-vitro experiments were performed using cloned human  $\beta_1$ - and  $\beta_2$  -adrenergic receptor overexpressed cell membranes and [ $^3$ H](-)-CGP-12177. Aliquots of membrane suspensions were incubated with [ $^3$ H] (-)-CGP-12177 along with test agents at various concentrations and the binding of [ $^3$ H] (-)-CGP-12177 to the cell membrane at each concentration of test agent determined. The  $K_i$  values of the test agents were then calculated from the relative binding data using Prism software (GraphPad Software Inc).

### **In vivo metabolism assay.**

*In vivo* blood stability of  $^{18}$ F-compounds was assessed following intravenous administration in rat (~1.0 mCi/kg), through up to 30 min post injection. All blood samples were collected into acetonitrile (1:3 v/v) and analyzed as described below.

Samples collected into acetonitrile were vortexed and centrifuged at 2500 x g for 20 min to pellet precipitate plasma protein and red blood cells. The supernatant was collected and placed under a stream of nitrogen in a heating block at 37°C to evaporate the acetonitrile. Extracted samples were re-constituted in HPLC mobile phase A and analyzed on an Agilent 1100 multisolvent HPLC delivery system (Agilent Technologies, Burlington, Massachusetts). The analytical

column was a Phenomenex Luna C18 Column (5 $\mu$ , 4.6 x 150 mm) maintained at room temperature and a flow rate of 1.0 mL/min. Mobile phase A was 0.1% formic acid in water and mobile phase B was 0.1% formic acid in 100% acetonitrile. A linear gradient from 5% to 90% B over 15 min was used for the elution of  $^{18}\text{F}$ -compounds and their metabolites. A five-minute post time of 5% mobile phase B was used to equilibrate the column. Radioactive  $^{18}\text{F}$ -compound HPLC effluent was detected by a gamma flow detector (INUS, Tampa, FL).

	%RCP
[ $^{18}\text{F}$ ]7 Kit	100
[ $^{18}\text{F}$ ]7 Kit Extracted	100
2 min in vivo Rat blood	83
5 min in vivo Rat blood	59
15 min in vivo Rat blood	28
30 min in vivo Rat blood	44
30 min Rat Urine	76

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