

Supplemental material

The Design of Substituted Imidazolidinylpiperidinylbenzoic Acids as C-C-R Chemokine Receptor 5 Antagonists: Potent Inhibitors of M-tropic (R5) HIV-1 Replication

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General Procedures

General procedure E: To a solution of *N*-Boc-2-substituted-glycinol (1 equivalent) in dry THF (3 L/mol) was added phthalimide (1.15 equivalents) and triphenylphosphine (1.2 equivalents). The mixture was cooled in an ice/water bath and DEAD (1.15 equivalents) was added slowly. The mixture was then warmed to room temperature and stirred until the reaction was complete (typically 2-3 h). The mixture was concentrated under reduced pressure and the resulting residue was suspended in ethanol (5 L/mol) and hydrazine hydrate (10 equivalents) was added. The mixture was stirred for 1-18 h then diluted with diethyl ether and filtered. The filtrate was concentrated, and then diluted with CH₂Cl₂ and the product extracted with 1 N HCl in the aqueous. The resulting acidic aqueous solution was basified with 1 N or 10 N NaOH to pH ~ 11-12 and then extracted with CH₂Cl₂. The organic layers were combined, dried (Na₂SO₄ or MgSO₄), filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel.

General procedure F: To a solution of the phthalimide protected amine in EtOH (0.05-0.2M) was added hydrazine hydrate (~ 10 equivalents). The resulting mixture was stirred at room temperature overnight or heated at 40-50°C for 2-16 h. In a standard workup, the mixture was concentrated under reduced pressure, diluted with CH₂Cl₂ and filtered. The filtrate was concentrated under reduced pressure and purified by flash column chromatography on silica gel.

General procedure G: To a 0°C solution of the diamine (1 equivalent) and pyridine or triethylamine (~ 2 equivalents) in CH₂Cl₂ (concentration ~0.05-0.1 M) was added triphosgene or thiophosgene (0.35-0.55 equivalent) and the resulting solution was stirred at 0°C for 5 min and at 0°C or at room temperature for an additional 1-2 h. In a standard workup, the reaction mixture was poured into saturated aqueous NaHCO₃. The phases were separated and the aqueous extracted with CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄ or MgSO₄), filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel.

General procedure H: To a stirred solution of an acid (1.0 equivalent) in THF (concentration ~1-2M) at 0°C was added NMM (1.0 equivalent). The solution was stirred for 5 min then IBCF (1.0 equivalent) was added. The solution was stirred for 10 min before the amine (1.2-2.0

equivalents) was added. The reaction was allowed to return to room temperature and stirred for 18 h. THF was removed under reduced pressure and EtOAc was added. The organic layer was washed with saturated aqueous NH_4Cl then with saturated aqueous NaHCO_3 . The organic layer was dried (Na_2SO_4 or MgSO_4), filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel or by recrystallization.

General procedure I: To a stirred solution of the amine (1 equivalent) in MeOH (concentration ~ 0.1 M) at room temperature were added the carbonyl compound (1-3 equivalents), glacial AcOH (0-1 equivalent), NaCNBH_3 (1.5-3.0 equivalents) and the resultant solution was heated to reflux. In a standard workup, the reaction mixture was concentrated under reduced pressure and diluted with saturated aqueous NaHCO_3 . The aqueous was extracted with CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4 or MgSO_4), filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel or by recrystallization.

General procedure J: To a stirred solution of a primary or secondary amine (1 equivalent), a carboxylic acid (1.1-2.0 equivalents), HOBt (1.1-2.0 equivalents) and DIPEA or NMM (1.5-3 equivalents) in CH_2Cl_2 or DMF (concentration ~ 0.05 -1.5M) was added EDCI (1.1-2.0 equivalents). The solution was stirred at room temperature for 1-3 d and concentrated *in vacuo*. In a standard work-up, the mixture was diluted with CH_2Cl_2 or EtOAc and washed consecutively with saturated aqueous NaHCO_3 and brine. The organic layer was dried (Na_2SO_4 or MgSO_4), filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography or by radial chromatography on silica gel.

General Procedure K: To a stirred solution of a halide (1 equivalent), a boronic acid (1.3-3.0 equivalents), sodium carbonate mono-hydrate (1.3-3.0 equivalents) in a mixture of dimethoxyethane / water 4:1 (concentration (~ 0.05 -0.2 M) was added $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.1 equivalent). The solution was stirred at 90°C for ~ 18 h and then treated with water. In a standard work-up, the mixture was extracted with CH_2Cl_2 and the organic layer was dried (Na_2SO_4 or MgSO_4), filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography or by radial chromatography on silica gel.

General procedure L: The cyanide (1.0 equivalent) was dissolved in a 4:1 to 1:1 EtOH / 10 N NaOH solution. The reaction was heated to 60-90°C for 5-18 h. The mixture was concentrated under reduced pressure and water was added. The pH of the solution was adjusted to ~ 4-5 with a 6 N HCl solution. The aqueous solution was then extracted with CH₂Cl₂ or a mixture of CH₂Cl₂/MeOH (9:1). The combined organic extracts were dried (Na₂SO₄ or MgSO₄), filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel or by recrystallization.

General procedure M (O'Brien, P., *et al.*, *J. Chem. Soc.* **1998**, *Perkin Trans.1*, 2519-2526): To a stirred solution of *t*-butyl carbamate (2.0 equivalents) in *n*-propanol (4 L/mol) in a cold-water bath (~ 15°C) was added 1 N NaOH (2.05 equivalents), and *t*-butyl hypochlorite (2.3 equivalents). The mixture was stirred for 10 min and then cooled to 0°C. Solutions of (DHQD)₂PHAL (0.02 equivalent) in *n*-propanol (4 L/mol), styrene (1 equivalent) in *n*-propanol (8 L/mol), and K₂OsO₄·2H₂O (0.015 equivalent) were added sequentially. The mixture was stirred at 0°C until the reaction was complete. The reaction was quenched by the addition of an aqueous Na₂SO₃ solution until any remaining green color was reduced to yellow/brown. The mixture was concentrated under reduced pressure. In a standard workup, the reaction mixture was partitioned between water and CH₂Cl₂. The phases were separated and the aqueous extracted with CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄ or MgSO₄), filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel.

Representative examples to make imidazolidinone intermediates (10):

(*R*)-1-Cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one (10b; R₁=Ph, R₂=*c*-Hex). Di-*t*-butyl dicarbonate (31.82 g, 146.8 mmol) was added to a cooled (0°C) solution of (*R*)-(-)-2-phenylglycinol (20.00 g, 145.8 mmol) and triethylamine (24.4 ml, 175.0 mmol) in dry THF (292 ml). The mixture was stirred for 3 h at 0°C then concentrated *in vacuo*. The residue was taken up in CH₂Cl₂ (200 ml) and washed with 1 N HCl (240 ml). The aqueous layer was extracted with CH₂Cl₂ (200 ml). The combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo* to afford (*R*)-*t*-butyl (2-hydroxy-1-phenylethyl)carbamate **8b** (R₁=Ph) (34.59 g, >99%) as a white

solid. ^1H NMR (300 MHz, CDCl_3) δ 1.43 (s, 9H), 2.29 (br s, 1H), 3.84-3.87 (m, 2H), 4.79 (br s, 1H), 7.29-7.39 (m, 5H). Following general procedure E (*R*)-*t*-butyl (2-hydroxy-1-phenylethyl)carbamate **8b** ($\text{R}_1=\text{Ph}$) (34.59 g, 145.8 mmol), phthalimide (22.5 g, 153.1 mmol), triphenylphosphine (42.1 g, 160.4 mmol) and diethylazodicarboxylate (24 mL, 153.1 mmol) in dry THF (1 L) led to intermediate which was treated accordingly to general procedure F, hydrazine hydrate (50 mL, 1.61 mol) in ethanol (1 L) at reflux to afford (*R*)-*t*-butyl (2-amino-1-phenylethyl)carbamate (27.27 g, 79%) as a white solid. ^1H NMR (300 MHz, CDCl_3) δ 1.09 (br s, 2H), 1.42 (s, 9H), 2.99-3.01 (m, 2H), 4.65 (br s, 1H), 7.28-7.34 (m, 5H). Using general procedure A followed by general procedure B, (*R*)-*t*-butyl (2-amino-1-phenylethyl)carbamate (8.00 g, 33.85 mmol), cyclohexanone (3.32 mL, 33.85 mmol) and $\text{NaBH}(\text{OAc})_3$ (8.61 g, 40.62 mmol) in CH_2Cl_2 (340 mL) afford (*R*)-*N*1-cyclohexyl-2-phenylethane-1,2-diamine **9b** ($\text{R}_1=\text{Ph}$, $\text{R}_2=c\text{Hex}$) (7.67 g, >99%) as a yellow oil. The yellow oil was carried on without further purification. Following general procedure A, the above diamine **9b** ($\text{R}_1=\text{Ph}$, $\text{R}_2=c\text{Hex}$) (7.67 g, 33.85 mmol), 1-Boc-4-piperidone (6.74 g, 33.85 mmol) and $\text{NaBH}(\text{OAc})_3$ (8.61 g, 40.62 mmol) in CH_2Cl_2 (335 mL) afforded (*R*)-*t*-butyl 4-((2-(cyclohexylamino)-1-phenylethyl)amino)piperidine-1-carboxylate (11.59 g, 85%) as a light yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 0.97-1.17 (m, 2H), 1.14-1.31 (m, 5H), 1.43 (s, 9H), 1.64-1.75 (m, 3H), 1.78-1.92 (m, 3H), 2.33-2.52 (m, 2H), 2.60-2.74 (m, 3H), 2.81 (dd, 1H, $J=10.0, 4.2$ Hz), 3.84 (dd, 1H, $J=10.0, 4.2$ Hz), 3.88-4.00 (m, 2H), 7.26-7.36 (m, 5H). Following general procedure G, (*R*)-*t*-butyl 4-((2-(cyclohexylamino)-1-phenylethyl)amino)piperidine-1-carboxylate (11.59 g, 28.85 mmol), pyridine (9.3 mL, 115.4 mmol) and triphosgene (8.56 g, 28.85 mmol) in CH_2Cl_2 afforded crude material which was treated accordingly with general procedure B to afford (*R*)-1-cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one **10b** ($\text{R}_1=\text{Ph}$, $\text{R}_2=c\text{Hex}$) as a tacky orange foamy solid (8.4 g, 89%). ^1H NMR (300 MHz, CDCl_3) δ 0.95-1.15 (m, 2H), 1.19-1.49 (m, 5H), 1.65-1.81 (m, 6H), 2.48 (dt 1H, $J=12.0, 3.1$ Hz), 2.60 (dt, 1H, $J=12.0, 3.1$ Hz), 2.85-2.92 (m, 1H), 3.03-3.10 (m, 2H), 3.63 (t, 1H, $J=8.9$ Hz), 3.68-3.82 (m, 3H), 4.58 (dd, 1H, $J=9.6, 7.0$ Hz), 8.28-7.33 (m, 5H).

(*R*)-1-(*t*-Butyl)-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one (10b; $\text{R}_1=\text{Ph}$, $\text{R}_2=t\text{-Bu}$). To a solution of (*R*)-(-)-2-phenylglycine (3.83 g, 25.3 mmol) in 1 M NaOH (35 ml) was added a solution of Boc_2O (6.14 g, 28.1 mmol) in *t*-BuOH (20 ml). The resulting suspension was stirred

at room temperature for 1 h. The volatile solvent was removed under reduced pressure and the remaining solution was adjusted to pH 3 with 4 M HCl. The resulting suspension was diluted with CHCl₃ (50 ml), the layers were separated and the aqueous solution was extracted with CHCl₃ (25 ml x 2). The combined organic solution was dried (Na₂SO₄), filtered and concentrated under reduced pressure, to give crude (*R*)-2-((*t*-butoxycarbonyl)amino)-2-phenylacetic acid **11b** as a colorless oil (6.92 g, quantitative). Using general procedure H, *t*-butylamine (2.14 g, 20.3 mmol) and (*R*)-2-((*t*-butoxycarbonyl)amino)-2-phenylacetic acid **11b** (2.55 g, 10.1 mmol) afforded (*R*)-*t*-butyl (2-(*t*-butylamino)-2-oxo-1-phenylethyl)carbamate **12b** (2.88 g, 93%). Using general procedure B, substrate **12b** (2.88 g, 9.40 mmol) afforded (*R*)-2-amino-*N*-(*t*-butyl)-2-phenylacetamide (1.94 g, 100%). To a solution of (*R*)-2-amino-*N*-(*t*-butyl)-2-phenylacetamide (1.94 g, 9.40 mmol) in dry THF was added BH₃·THF (37.0 ml of 1 M in THF, 37.6 mmol). This solution was stirred at 60°C for 18 h. The reaction mixture was then cooled to room temperature. MeOH (10 ml) was added dropwise, and then 6 N HCl (10 ml) was added. The mixture was stirred at 60°C for 1 h then the mixture was concentrated under reduced pressure. CH₂Cl₂ (100 ml), saturated aqueous NaHCO₃ (100 ml) and 10 N NaOH (4 ml) were added. The aqueous layer was extracted with CH₂Cl₂ (3 x 100 ml) and the combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. (*R*)-*N*¹-(*t*-butyl)-2-phenylethane-1,2-diamine **13b** (1.63 g, 90%) was used in the next step without further purification. Using general procedure A, diamine **13b** (1.63 g, 8.05 mmol) and 1-boc-4-piperidone (1.86 g, 9.35 mmol) afforded (*R*)-*t*-butyl 4-((2-(*t*-butylamino)-1-phenylethyl)amino)piperidine-1-carboxylate (3.19 g, 100%). Using general procedure G, the above substrate (3.19 g, 8.05 mmol), pyridine (1.32 ml, 16.32 mmol) and triphosgene (1.21 g, 4.08 mmol) in CH₂Cl₂ (50 ml) afforded (*R*)-*t*-butyl 4-(3-(*t*-butyl)-2-oxo-5-phenylimidazolidin-1-yl)piperidine-1-carboxylate (2.91 g, 89%). Using general procedure B, (*R*)-*t*-butyl 4-(3-(*t*-butyl)-2-oxo-5-phenylimidazolidin-1-yl)piperidine-1-carboxylate (2.91 g, 7.25 mmol) afforded (*R*)-1-(*t*-butyl)-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one **10b** (R₁=Ph, R₂=*t*-Bu) (1.96 g, 90%). ¹H NMR (300 MHz, CDCl₃) δ 1.02 (ddd, 1H, *J*= 24.6, 12.3, 3.9 Hz), 1.36 (s, 9H), 1.42-1.47 (m, 1H), 1.64-1.80 (m, 2H), 2.46 (td, 1H, *J*= 12.0, 2.4 Hz), 2.54-2.64 (m, 1H), 2.85-2.89 (m, 1H), 3.03-3.11 (m, 2H), 3.63-3.78 (m, 2H), 4.50 (dd, 1H, *J*= 8.4, 7.5 Hz), 7.28-7.35 (m, 5H).

Compound Syntheses and Characterizations:

6-Chloro-*N*-(3-(4-(3-cyclohexyl-2-oxo-5-(thiophen-3-yl)imidazolidin-1-yl)piperidin-1-yl)butyl)-2,4-dimethylnicotinamide (2c). To a solution of NH₄Cl (1.07 g, 20.0 mmol) and NaCN (0.980 g, 20.0 mmol) in ammonium hydroxide was added a solution of thiophene-3-carbaldehyde **7a** (R₁=3-thiophene) (1.12 g, 10.0 mmol) in methanol (5 ml). The mixture was stirred at room temperature for 4 h. 6 N HCl (10 ml) was added to the flask and the mixture was heated at refluxing temperature for 2 h. Solvents were evaporated under reduced pressure. The dried pale yellow solid was dissolved in methanol (10 ml) and 1 N NaOH (20 ml). Boc₂O (2.06 g) was added to the reaction and the mixture was stirred at room temperature for 2 h. The mixture was acidified with 1 N HCl to pH= 4-5, extracted with CHCl₃ (4 x30 ml). The combined organic extracts were dried (MgSO₄) and concentrated to give a brown oil. This was purified by column chromatography on silica gel, eluted with CH₂Cl₂/MeOH (9:1) to give *t*-butoxycarbonylamino-thiophen-3-yl-acetic acid (1.34 g, 52%). 1-cyclohexyl-3-(piperidin-4-yl)-4-(thiophen-3-yl)imidazolidin-2-one **10a** (R₁=3-thiophene, R₂= *c*-Hex) was prepared using the same chemistry as (*R*)-1-(*t*-butyl)-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one (**10b**; R₁=Ph, R₂=*t*-Bu) except that cyclohexylamine was used in lieu of *t*-butylamine. Homologation to the desired product using the sequential transformations reported to synthesize **4g** afforded analog **2i** as a yellow solid. ¹H NMR (300 MHz, CDCl₃) (mixture of diastereoisomers) δ 0.91-1.04 (m, 4H), 1.20-1.37 (m, 5H), 1.50-1.75 (m, 8H), 1.85-2.13 (m, 1H), 2.32 & 2.33 (double s, 3H), 2.51 & 2.53 (s, 3H), 2.64-2.74 (m, 2H), 2.97-3.03 (m, 1H), 3.10-3.40 (m, 1H), 3.56 (t, 2H, *J*= 6.0 Hz), 3.61-4.30 (m, 2H), 6.99-7.01 (m, 1H), 7.07-7.10 (m, 2H), 7.24-7.27 (m, 1H), 8.19-8.37 (m, 1H); ¹³C-NMR (75 MHz, CDCl₃) δ 14.44, 14.92, 20.22, 20.25, 23.53, 26.86, 26.92, 26.96, 30.29, 31.55, 31.87, 32.72, 32.93, 41.02, 44.67, 45.45, 49.03, 49.08, 52.19, 52.39, 52.63, 52.83, 53.13, 53.60, 61.16, 61.86, 122.70, 122.84, 127.06, 128.06, 134.12, 134.26, 145.90, 146.08, 149.07, 149.23, 151.40, 151.46, 156.76, 160.87, 168.23, 168.83; ES-MS *m/z* 572 (M+H)⁺. Anal Calcd. for C₃₀H₄₂N₅ClO₂S·0.6CH₂Cl₂: C, 58.98; H, 6.99; N, 11.24; Br, 37.11. Found: C, 59.12; H, 6.94; N, 11.17.

***N*-(3-(4-(3-cyclohexyl-2-oxo-5-(pyridin-3-yl)imidazolidin-1-yl)piperidin-1-yl)butyl)-4,6-dimethylpyrimidine-5-carboxamide (3m).** To a solution of NH₄Cl (1.07 g, 20.0 mmol) and NaCN (0.980 g, 20.0 mmol) in ammonium hydroxide was added a solution of nicotinaldehyde

7a ($R_1=3$ -pyridine) (1.07 g, 10.0 mmol) in methanol (5 ml). The mixture was stirred at room temperature for 4 h. 6 N HCl (10 ml) was added to the flask and the mixture was heated at refluxing temperature for 2 h. Solvents were evaporated under reduced pressure. The dried solid was dissolved in methanol (10 ml) and 1 N NaOH (20 ml). Boc_2O (2.06 g) was added to the reaction and the mixture was stirred at room temperature for 2 h. The mixture was acidified with 1 N HCl to pH= 4-5, extracted with $CHCl_3$ (4 x30 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated to give a brown oil. This was purified by column chromatography on silica gel, eluted with $CH_2Cl_2/MeOH$ (9:1) to give 2-((tert-butoxycarbonyl)amino)-2-(pyridin-3-yl)acetic acid **11a** (555 mg, 22%). N1-cyclohexyl-2-(pyridin-3-yl)ethane-1,2-diamine **13a** ($R_1=3$ -pyridine, $R_2= c$ -Hex) was prepared using the same chemistry as (*R*)-1-(*t*-butyl)-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one (**10b**; $R_1=Ph$, $R_2=t$ -Bu) except that cyclohexylamine was used in lieu of *t*-butylamine. Using general procedure A, diamine **13a** (1.77 g, 8.05 mmol) and tert-butyl (3-(4-oxopiperidin-1-yl)butyl)carbamate²⁵ (2.53 g, 9.35 mmol) afforded tert-butyl (3-(4-((2-(cyclohexylamino)-1-(pyridin-3-yl)ethyl)amino)piperidin-1-yl)butyl)carbamate which was then transformed using the general procedure G to the corresponding tert-butyl (3-(4-(3-cyclohexyl-2-oxo-5-(pyridin-3-yl)imidazolidin-1-yl)piperidin-1-yl)butyl)carbamate (4.02 g, 19%, 2 steps). Following sequential general procedures B and J with 4,6-dimethylpyrimidine-5-carboxylic acid (349 mg, 2.29 mmol) led to N-(3-(4-(3-cyclohexyl-2-oxo-5-(pyridin-3-yl)imidazolidin-1-yl)piperidin-1-yl)butyl)-4,6-dimethylpyrimidine-5-carboxamide **3m** (245 mg, 30%, 2 steps). ¹H NMR (300 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 0.62-1.07 (m, 4H), 1.08-1.43 (m, 5H), 1.45-1.83 (m, 8H), 1.87-2.76 (m, 9H), 2.50 & 2.51 (double s, 3H), 2.96 (dd, $J = 8.9, 5.6$ Hz, 1H), 3.15-3.94 (m, 5H), 4.10 (dd, $J = 9.4, 5.6$ Hz, 1H), 4.22 (dd, $J = 9.3, 5.6$ Hz, 1H), 7.10-7.40 (m, 1H), 7.57 (dd, $J = 7.9, 5.6$ Hz, 1H), 7.80-8.05 (m, 1H), 8.42-8.60 (m, 2H), 8.80-8.90 (m, 1 H); ¹³C-NMR (75 MHz, $CDCl_3$) δ 11.79, 12.18, 15.40, 20.67, 24.10, 24.15, 24.20, 27.86, 28.07, 28.80, 28.89, 29.62, 29.66, 30.53, 30.71, 38.11, 38.30, 40.14, 42.06, 42.66, 43.54, 44.22, 46.91, 46.94, 49.95, 49.99, 50.16, 50.37, 50.57, 51.57, 51.87, 52.10, 55.61, 57.90, 58.53, 122.42, 129.48, 129.59, 132.46, 132.50, 137.45, 137.60, 146.76, 146.81, 148.29, 156.13, 158.24, 161.80, 161.85, 164.80, 165.27; ES-MS m/z 534 (M+H)⁺

6-Chloro-N-(3-(4-((*R*)-3-isopropyl-2-oxo-5-phenylimidazolidin-1-yl)piperidin-1-yl)butyl)-2,4-dimethylnicotinamide (4c). (*R*)-1-isopropyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one (**10b**; $R_1=Ph$, $R_2=i$ -Pr) was prepared using the same chemistry as (*R*)-1-cyclohexyl-4-phenyl-3-

(piperidin-4-yl)imidazolidin-2-one (**10b**; R₁=Ph, R₂=cHex) except that acetone was used in lieu of cyclohexanone. Homologation to the desired product using the sequential transformations reported to synthesize **4g** afforded analog **4c** as a yellow solid. ¹H NMR (300 MHz, CDCl₃) (mixture of diastereoisomers) δ 0.77-2.20 (m, 10H), 2.26-2.80 (m, 10H), 3.10-4.00 (m, 7H), 4.01-4.25 (m, 1H), 4.35 (s, 2H), 5.97 (s, 2H), 6.57 (s, 1H), 7.16 (s, 1H), 7.18-7.33 (m, 5H), 7.95-8.13 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 13.41, 13.90, 19.21, 22.52, 29.52, 30.54, 30.81, 31.04, 31.88, 32.06, 33.16, 34.20, 39.95, 40.22, 40.57, 43.68, 44.36, 52.04, 52.45, 52.59, 55.58, 55.83, 59.94, 60.60, 106.98, 109.91, 117.16, 122.98, 123.41, 124.88, 126.54, 127.13, 127.66, 128.35, 129.15, 130.04, 133.01, 133.12, 143.20, 143.36, 147.91, 148.02, 150.56, 155.73, 160.54, 167.35, 167.84; ES-MS m/z 577 (M+H)⁺.

6-Chloro-N-(3-(4-((R)-3-cyclobutyl-2-oxo-5-phenylimidazolidin-1-yl)piperidin-1-yl)butyl)-2,4-dimethylnicotinamide (4e). (*R*)-1-cyclobutyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one (**10b**; R₁=Ph, R₂=c-Bu) was prepared using the same chemistry as (*R*)-1-cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one (**10b**; R₁=Ph, R₂=cHex) except that cyclobutanone was used in lieu of cyclohexanone. Homologation to the desired product using the sequential transformations reported to synthesize **4g** afforded analog **4e** as a white foam. ¹H NMR (300 MHz, CDCl₃) (mixture of diastereoisomers) δ 0.73-2.22 (m, 19H), 2.34 (s, 3H), 2.50 (s, 3H), 2.61-4.57 (m, 8H), 7.09 (s, 1H), 7.18-7.45 (m, 5H), 7.95-8.31 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 11.36, 11.67, 13.18, 17.24, 17.30, 20.56, 25.52, 25.57, 26.85, 28.06, 29.22, 30.00, 37.46, 41.89, 42.60, 45.79, 47.40, 49.67, 49.96, 50.34, 53.43, 53.64, 57.84, 58.49, 121.00, 124.73, 126.45, 127.20, 131.00, 141.66, 146.04, 148.48, 153.71, 157.89, 165.51, 166.09; ES-MS m/z 539 (M+2)⁺. Anal. Calcd. for C₃₀H₄₀N₅ClO₂·0.7CH₂Cl₂: C, 61.70; H, 6.98; N, 11.72. Found: C, 61.89; H, 7.02; N, 11.51.

6-Chloro-N-(3-(4-((R)-3-cyclopentyl-2-oxo-5-phenylimidazolidin-1-yl)piperidin-1-yl)butyl)-2,4-dimethylnicotinamide (4f). (*R*)-1-cyclopentyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one (**10b**; R₁=Ph, R₂=c-Pent) was prepared using the same chemistry as (*R*)-1-cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one (**10b**; R₁=Ph, R₂=cHex) except that cyclopentanone was used in lieu of cyclohexanone. Homologation to the desired product using the sequential transformations reported to synthesize **4g** afforded analog **4f** as a white foam. ¹H NMR (300 MHz, CDCl₃) (mixture of diastereoisomers) δ 0.78-0.94 (m, 4H), 1.25-1.93 (m, 15H), 2.09 (m,

1H), 2.33 (d, 3H, J = 4.2 Hz), 2.49 (m, 1H), 2.53 (d, 3H, J = 7.2 Hz), 2.64-2.71 (m, 2H), 2.96 (m, 1H), 3.13-3.36 (m, 1H), 3.51-3.60 (m, 1H), 3.65 (t, 2H, J = 9.0 Hz), 3.94-4.15 (m, 1H), 4.31 (m, 1H), 7.12 (d, 1H, J = 2.7 Hz), 7.22-7.36 (m, 5H), 8.13-8.33 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.01, 13.53, 18.83, 22.15, 24.06, 24.16, 28.46, 28.55, 28.91, 29.98, 30.52, 31.66, 39.60, 39.80, 43.24, 44.00, 48.67, 51.67, 51.83, 52.13, 53.48, 55.05, 55.31, 59.66, 60.37, 122.62, 126.16, 127.90, 128.77, 132.70, 132.83, 143.47, 143.67, 147.61, 147.75, 150.10, 155.37, 160.27, 166.89, 167.49; ES-MS m/z 552 ($\text{M}+\text{H}$) $^+$, 574 ($\text{M}+\text{Na}$) $^+$. Anal. Calcd. for $\text{C}_{31}\text{H}_{42}\text{N}_5\text{O}_2\text{Cl}\cdot 0.1\text{CH}_2\text{Cl}_2$: C, 66.63; H, 7.59; N, 12.49. Found: C, 66.85; H, 7.70; N, 12.44.

6-Chloro-2,4-dimethyl-*N*-(3-(4-((*R*)-2-oxo-5-phenyl-3-(tetrahydro-2*H*-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)butyl)nicotinamide (4g). (*R*)-4-phenyl-3-(piperidin-4-yl)-1-(tetrahydro-2*H*-pyran-4-yl)imidazolidin-2-one (**10b**; $\text{R}_1=\text{Ph}$, $\text{R}_2=4\text{-THP}$) was prepared using the same chemistry as (*R*)-1-cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one (**10b**; $\text{R}_1=\text{Ph}$, $\text{R}_2=c\text{Hex}$) except that tetrahydro-4*H*-pyran-4-one was used in lieu of cyclohexanone. ^1H NMR (300 MHz, CDCl_3) δ 1.07 (qd, 1H, J = 12.4, 4.3 Hz), 1.41-1.50 (m, 2H), 1.56-1.84 (m, 6H), 2.47 (td, 1H, J = 12.3, 2.5 Hz), 2.58 (td, 1H, J = 12.0, 3.1 Hz), 2.84-2.92 (m, 1H), 3.02-3.09 (m, 1H), 3.06 (dd, 1H, J = 8.4, 6.9 Hz), 3.43-3.52 (m, 2H), 3.64 (t, 1H, J = 8.9 Hz), 3.69 (tt, 1H, J = 11.9, 3.9 Hz), 3.94-4.10 (m, 3H), 4.60 (dd, 1H, J = 9.5, 6.7 Hz), 7.28-7.37 (m, 5H). Following general procedure I, piperidine (**10b**; $\text{R}_1=\text{Ph}$, $\text{R}_2=4\text{-THP}$) (128 mg, 0.39 mmol), 2-(3-oxobutyl)isoindoline-1,3-dione (173 mg, 0.80 mmol), NaBH_3CN (80 mg, 1.27 mmol) and glacial AcOH (6 drops) in MeOH (2.0 ml) at 55°C gave the phthalimide as a white foam (126 mg, 61%). Following general procedure F, the phthalimide (126 mg, 0.24 mmol) gave (4*R*)-3-(1-(4-aminobutan-2-yl)piperidin-4-yl)-4-phenyl-1-(tetrahydro-2*H*-pyran-4-yl)imidazolidin-2-one as a colorless oil (90.3 mg, 95%). ^1H NMR (300 MHz, CDCl_3) (mixture of diastereoisomers) δ 0.86 (d, 3H, J = 6.6 Hz), 1.00-1.92 (m, 12H), 1.99 & 2.12 (td, 1H, J = 11.6, 2.2 Hz), 2.24 & 2.37 (td, 1H, J = 11.4, 2.2 Hz), 2.49-2.79 (m, 5H), 3.05 (t, 1H, J = 7.2 Hz), 3.43-3.52 (m, 2H), 3.54-3.64 & 4.00-4.10 (m, 1H), 3.63 (t, 2H, J = 9.0 Hz), 3.94-4.03 (m, 2H), 4.59 (dd, 1H, J = 9.2, 6.6 Hz), 7.28-7.37 (m, 5H). Following general procedure J, (4*R*)-3-(1-(4-aminobutan-2-yl)piperidin-4-yl)-4-phenyl-1-(tetrahydro-2*H*-pyran-4-yl)imidazolidin-2-one (30.1 mg, 0.075 mmol), 6-chloro-2,4-dimethylnicotinic acid hydrochloride (22 mg, 0.099 mmol), EDCI (21 mg, 0.11 mmol), HOBt (17 mg, 0.13 mmol) and NMM (22 μL , 0.20 mmol) in DMF (0.50 mL) gave 6-chloro-2,4-

dimethyl-N-(3-(4-((*R*)-2-oxo-5-phenyl-3-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)butyl)nicotinamide (**4g**) as a light yellow foam (32.9 mg, 77%). ¹H NMR (300 MHz, CDCl₃) (mixture of diastereoisomer) δ 0.70-1.03 (m, 1H), 0.90 & 0.92 (d, 3H, *J*= 6.6 Hz), 1.19-1.37 (m, 2H), 1.45-1.76 (m, 7H), 1.86-2.12 (m, 1H), 2.33 & 2.34 (s, 3H), 2.35-3.00 (m, 4H), 2.52 & 2.54 (s, 3H), 3.08-3.69 (m, 6H), 3.91-4.20 (m, 5H), 7.11 & 7.12 (s, 1H), 7.20-7.37 (m, 5H), 8.11 & 8.31 (br s, 1H); ES-MS *m/z* 568 (M+H)⁺, 570 (M+H+2)⁺.

4-(((4*R*)-3-(1-(4-(6-Chloro-2,4-dimethylnicotinamido)butan-2-yl)piperidin-4-yl)-2-oxo-4-phenylimidazolidin-1-yl)methyl)benzoic acid (4p). (*R*)-methyl 4-((2-oxo-4-phenyl-3-(piperidin-4-yl)imidazolidin-1-yl)methyl)benzoate (**10b**; R₁=Ph, R₂=MeO₂C-4-PhCH₂) was prepared using the same chemistry as (*R*)-1-cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one (**10b**; R₁=Ph, R₂=*c*Hex) except that methyl 4-formylbenzoate was used in lieu of cyclohexanone. Homologation to the desired product using the sequential transformations reported to synthesize **4g** followed by hydrolysis of the methyl ester general procedure C afforded analog **4p** as a white solid. ¹H NMR (300 MHz, CD₃OD) (mixture of diastereoisomers) δ 1.26-1.25 (m, 4H), 1.95-2.20 (m, 6H), 2.28-2.80 (m, 4H), 2.29 (s, 3H), 2.30-2.50 (m, 4H), 3.00-3.10 (m, 3H), 3.20-3.75 (m, 16H, CH₃OH signal), 4.41 (d, 1H, *J*= 15.3 Hz), 4.52 (d, 1H, *J*= 15.3 Hz), 7.21-7.35 (m, 8H), 7.93 (d, 2H, *J*= 7.2 Hz); ES-MS *m/z* 618 (M+H)⁺.

(*R*)-1-Cyclohexyl-4-phenyl-3-(1-(4-(pyrimidin-5-yl)benzyl)piperidin-4-yl)imidazolidin-2-one (5b). Using general procedure K, 5-bromopyrimidine (199 mg, 1.25 mmol) and 4-formylbenzene boronic acid (469 mg, 3.13 mmol) afforded 4-pyrimidin-5-yl-benzaldehyde (162 mg, 99%). Using general procedure A, 1-cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one **10b** (R₁=Ph, R₂=*c*Hex) (40 mg, 0.12 mmol) and the above aldehyde (24 mg, 0.13 mmol) afforded **5b** as a white solid (40 mg, 68%). ¹H NMR (300 MHz, CDCl₃) δ 0.88-2.20 (m, 16H), 2.70 (d, 1H, *J*= 11.4 Hz), 2.88 (d, 1H, *J*= 10.4 Hz), 3.03 (dd, 1H, *J*= 8.7, 6.9 Hz), 3.39-3.51 (m, 2H), 3.58-3.83 (m, 3H), 4.57 (dd, 1H, *J*= 9.1, 6.6 Hz), 7.27-7.35 (m, 5H), 7.38 (d, 2H, *J*= 8.3 Hz), 7.48 (d, 2H, *J*= 8.1 Hz), 8.91 (s, 2H), 9.17 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 26.0, 29.4, 30.3, 30.8, 31.3, 48.9, 51.7, 52.5, 53.6, 53.8, 56.5, 62.7, 127.1, 128.4, 129.2, 130.4, 132.4, 133.2, 134.6, 140.2, 143.6, 155.2, 157.7, 160.6. ES-MS *m/z* 496 (M+H)⁺.

(*R*)-1-Cyclohexyl-4-phenyl-3-(1-(4-(pyridin-3-yl)benzyl)piperidin-4-yl)imidazolidin-2-one (5d). Using general procedure K, 3-bromopyridine (120 mg, 1.25 mmol) and 4-formylbenzene

boronic acid (469 mg, 3.13 mmol) afforded 4-pyridin-3-yl-benzaldehyde (142 mg, 62%). Using general procedure A, 1-cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one **10b** ($R_1=Ph$, $R_2=cHex$) (40 mg, 0.12 mmol) and the above aldehyde (22 mg, 0.12 mmol) afforded **5d** as a white solid (45 mg, 76%). 1H NMR (300 MHz, $CDCl_3$) δ 0.92-2.12 (m, 16H), 2.72 (d, 1H, $J=12.8$ Hz), 2.91 (d, 1H, $J=10.5$ Hz), 3.03 (dd, 1H, $J=8.2, 6.4$ Hz), 3.42 (d, 1H, $J=13.1$ Hz), 3.48 (d, 1H, $J=13.1$ Hz), 3.63 (t, 1H, $J=9.2$ Hz), 3.65-3.83 (m, 2H), 4.58 (dd, 1H, $J=9.2, 6.5$ Hz), 7.26-7.39 (m, 8H), 7.49 (d, 2H, $J=8.5$ Hz), 7.84 (td, 1H, $J=8.8, 1.8$ Hz), 8.57 (dd, 1H, $J=4.8, 1.6$ Hz), 8.82 (d, 1H, $J=1.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 29.4, 30.4, 30.8, 31.4, 48.9, 51.7, 52.5, 53.6, 53.7, 56.4, 62.8, 123.9, 127.1, 127.3, 128.4, 129.1, 130.1, 134.6, 136.8, 139.0, 143.6, 148.7, 160.6. ES-MS m/z 495 ($M+H$)⁺. Anal. Calcd. for $C_{32}H_{38}N_4O \cdot 0.25CH_2Cl_2$: C, 75.06; H, 7.52; N, 10.86. Found: C, 75.06; H, 7.54; N, 10.83.

(R)-4-((4-(3-Cyclohexyl-2-oxo-5-phenylimidazolidin-1-yl)piperidin-1-yl)methyl)-N-methylbenzamide (5j). Using general procedure J, 4-carboxybenzaldehyde (245 mg, 1.63 mmol) and methylamine hydrochloride (100 mg, 1.48 mmol) afforded 4-formyl-N-methylbenzamide (121 mg, 50%). Using general procedure A, 1-cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one **10b** ($R_1=Ph$, $R_2=cHex$) (40 mg, 0.12 mmol) and the above aldehyde (24 mg, 0.15 mmol) afforded **5j** as a white solid (35 mg, 62%). 1H NMR (300 MHz, $CDCl_3$) δ 0.88-2.09 (m, 16H), 2.64 (d, 1H, $J=11.5$ Hz), 2.81 (d, 1H, $J=9.6$ Hz), 2.98 (d, 3H, $J=4.8$ Hz), 3.03 (dd, 1H, $J=8.2, 6.4$ Hz), 3.41 (s, 2H), 3.55-3.68 (m, 1H), 3.62 (t, 1H, $J=9.1$ Hz), 3.75 (tt, 1H, $J=11.4, 3.5$ Hz), 4.56 (dd, 1H, $J=9.7, 7.2$ Hz), 6.33 (s, 1H), 7.27-7.35 (m, 7H), 7.66 (d, 2H, $J=8.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 27.2, 29.4, 30.1, 30.3, 30.8, 31.2, 41.7, 48.9, 51.7, 52.5, 53.5, 53.7, 56.5, 62.7, 127.1, 128.4, 129.2, 129.4, 133.7, 142.6, 143.5, 160.6, 168.5. ES-MS m/z 475 ($M+H$)⁺. Anal. Calcd. for $C_{29}H_{38}N_4O_2 \cdot 0.9CH_2Cl_2$: C, 65.17; H, 7.28; N, 10.17. Found: C, 65.39; H, 7.30; N, 10.17.

(R)-1-Cyclohexyl-3-(1'-(4,6-dimethylpyrimidine-5-carbonyl)-4'-methyl-[1,4'-bipiperidin]-4-yl)-4-phenylimidazolidin-2-one (5p). To a solution of 1-cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one **10b** ($R_1=Ph$, $R_2=cHex$) (302 mg, 0.922 mmol) and 1-Boc-4-piperidone (184 mg, 0.923 mmol) in CH_2Cl_2 (2 ml) was added titanium (IV) isopropoxide (0.27 ml, 0.92 mmol) and the mixture was stirred at room temperature for 48 h. Diethylaluminum cyanide (1.0 M in toluene, 1.1 ml, 1.1 mmol) was added and the mixture stirred for an additional 20 h.

Standard work-up afforded a pale yellow solid (510 mg). To a solution of the above nitrile in THF (5 ml) cooled to 0°C was added MgMeBr (3.0 M in ether, 1.6 ml, 4.8 mmol) dropwise. The mixture was stirred at 0°C for 1 h and at room temperature for 18 h. The reaction was quenched with saturated aqueous NH₄Cl and standard work-up followed by purification afforded (*R*)-*t*-butyl 4-(3-cyclohexyl-2-oxo-5-phenylimidazolidin-1-yl)-4'-methyl-[1,4'-bipiperidine]-1'-carboxylate (260 mg, 54% over 2 steps). Following general procedure B, the above carbamate (260 mg, 0.496 mmol) afforded (*R*)-1-cyclohexyl-3-(4'-methyl-[1,4'-bipiperidin]-4-yl)-4-phenylimidazolidin-2-one (180 mg, 85%). Following general procedure J, the above amine (60 mg, 0.14 mmol) and 4,6-dimethylpyrimidine-5-carboxylic acid (30 mg, 0.20 mmol) in CH₂Cl₂ (2 ml) afforded **5p** as a white foam (55 mg, 70%). ¹H NMR (300 MHz, CDCl₃) (mixture of rotomers) δ 0.84 (s, 3H), 0.98-2.12 (m, 19H), 2.40, 2.43, 2.44, 2.45 (s, 6H), 2.55-2.61 (m, 1H), 2.71-2.98 (m, 3H), 3.02-3.52 (m, 4H), 3.62 (td, 1H, *J* = 9.3, 1.8 Hz), 3.75 (br t, 1H, *J* = 11.1 Hz), 4.12-4.25 (m, 1H), 4.52-4.58 (m, 1H), 7.28-7.35 (m, 5H), 8.92, 8.93 (s, 1H). ES-MS *m/z* 559 (M+H)⁺.

(*R*)-3-(1'-(6-Chloro-2,4-dimethylnicotinoyl)-4'-methyl-[1,4'-bipiperidin]-4-yl)-1-cyclohexyl-4-phenylimidazolidin-2-one (5q). Following general procedure J, (*R*)-1-cyclohexyl-3-(4'-methyl-[1,4'-bipiperidin]-4-yl)-4-phenylimidazolidin-2-one (60 mg, 0.14 mmol) and 6-chloro-2,4-dimethylnicotinic acid (34 mg, 0.15 mmol) in CH₂Cl₂ (2 mL) afforded **5q** as a white foam (60 mg, 72%). ¹H NMR (300 MHz, CDCl₃) (mixture of rotomers) δ 0.83 (s, 3H), 0.94-2.11 (m, 19H), 2.18, 2.21, 2.22, 2.23 (s, 3H), 2.37, 2.41, 2.42, 2.43 (s, 3H), 2.52-2.61 (m, 1H), 2.70-2.94 (m, 3H), 3.02-3.52 (m, 1H), 3.58-3.64 (m, 1H), 3.74 (br t, 1H, *J* = 11.4 Hz), 4.08-4.22 (m, 1H), 4.50-4.57 (m, 1H), 7.00-7.02 (m, 1H), 7.28-7.33 (m, 5H). ES-MS *m/z* 592 (M+H)⁺.

(*R*)-4-(4-((4-(2-Oxo-5-phenyl-3-(tetrahydro-2*H*-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)methyl)phenoxy)benzoic acid (6a). Methyl 4-hydroxybenzoate (7.6 g, 50 mmol) was dissolved in *N,N*-dimethylacetamide (50 ml). Anhydrous K₂CO₃ (10.4 g, 75 mmol) was added, followed by *p*-fluorobenzaldehyde (6.29 g, 50.7 mmol). The mixture was heated to 150°C and stirred under N₂ for 3 h. The reaction mixture was cooled to room temperature and was poured onto ~ 300 g of crashed ice. The aqueous was carefully adjusted to pH 1-2 with 6 M HCl and diluted with 500 ml of water. The product was recovered by filtration and dried on high vacuum overnight. The crude material was purified by flash chromatography on silica (EtOAc/hexanes,

15%-33%) to give methyl 4-(4-formylphenoxy)benzoate (10.18 g, 80%) as a white powder. ¹H NMR (300 MHz, CDCl₃) δ 3.93 (s, 3H), 7.10 (d, 2H, *J*= 8.4 Hz), 7.14 (d, 2H, *J*= 8.7 Hz), 7.90 (d, 2H, *J*= 8.3 Hz), 8.08 (d, 2H, *J*= 8.4 Hz), 9.96 (s, 1H). Following general procedure A, (*R*)-1-cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one **10b** (R₁=Ph, R₂=4-THP) and the above aldehyde provided (*R*)-methyl 4-(4-((4-(2-oxo-5-phenyl-3-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)methyl)phenoxy)benzoate which was treated under general procedure C to afford **6a** as a white powder (28.8 mg, 39%). ¹H NMR (300 MHz, CDCl₃) δ 1.47-1.83 (m, 7H), 2.18 (qd, 1H, *J*= 12.7, 3.5 Hz), 2.37-2.51 (m, 2H), 3.02-3.22 (m, 3H), 3.43-3.53 (m, 2H), 3.59 (tt, 1H, *J*= 11.8, 4.0 Hz), 3.74-3.81 (m, 1H), 3.78 (s, 2H), 3.88-4.02 (m, 3H), 4.74 (dd, 1H, *J*= 9.2, 7.0 Hz), 6.96 (d, 2H, *J*= 8.3 Hz), 7.01 (d, 2H, *J*= 8.3 Hz), 7.28-7.41 (m, 7H), 7.97 (d, 2H, *J*= 8.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 28.58, 29.80, 30.80, 31.16, 49.53, 50.45, 52.26, 53.21, 53.44, 57.91, 61.60, 68.16, 68.25, 118.69, 120.43, 128.04, 129.54, 129.76, 130.11, 131.44, 132.65, 133.38, 143.35, 158.34, 161.18, 161.77, 170.93; ES-MS *m/z* 556 (M+H)⁺. Anal. Calcd. for C₃₃H₁₇N₃O₅·0.7CH₂Cl₂: C, 65.80; H, 6.29; N, 6.83. Found: C, 65.88; H, 6.40; N, 6.82.

(*R*)-4-((5-((4-(2-Oxo-5-phenyl-3-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)benzoic acid (6b). A mixture of 4-chlorophenol (12.0 g, 93.4 mmol), 2-bromo-5-methylpyridine (14.8 g, 86.0 mmol) and K₂CO₃ (20.7 g, 150 mmol) was stirred at 200°C for 5 h. Aqueous work-up followed by purification by flash chromatography on silica gel (Et₂O/hexanes, 1:6 in *v/v*) afforded 2-(4-chlorophenoxy)-5-methylpyridine as a colorless oil (14.1 g, 75%). ¹H NMR (300 MHz, CDCl₃) δ 2.28 (s, 3H), 6.83 (d, 1H, *J*= 8.1 Hz), 7.02-7.08 (m, 2H), 7.26-7.36 (m, 2H), 7.49-7.53 (m, 1H), 7.99-8.01 (m, 1H). Under N₂, to a dry flask charged with 2-(4-chlorophenoxy)-5-methylpyridine (6.75 g, 30.8 mmol), Zn(CN)₂ (2.35 g, 20.0 mmol), Zn dust (0.40 g, 6.16 mmol), dppf (0.427 g, 0.770 mmol) and Pd₂(dba)₃ (0.284 g, 0.310 mmol) was added dry *N,N*-dimethylacetamide (40 mL). The mixture was stirred at 145°C for 3 d and then cooled to room temperature. Aqueous ammonia (1 N, 50 ml) was added and the mixture was extracted with EtOAc (3 x 100 ml). The combined extract was washed with brine (100 ml) and dried over anhydrous Na₂SO₄. After filtration the solvent was removed, and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:4 in *v/v*) to afford 4-(5-methyl-pyridio-2-yloxy)-benzonitrile as a pale yellow solid (3.15 g, 49%). ¹H NMR (300

MHz, CDCl₃) δ 2.32 (s, 3H), 6.91 (d, 1H, *J*= 8.1 Hz), 7.16-7.22 (m, 2H), 7.58 (dd, 1H, *J*= 2.4, 8.1 Hz), 7.64-7.68 (m, 2H), 8.04 (d, 1H, *J*= 2.4 Hz). A mixture of 4-(5-methylpyridin-2-yloxy)benzonitrile (0.56 g, 2.69 mmol), NBS (0.958 g, 5.38 mmol) and benzoyl peroxide (0.10 g, 0.413 mmol) in CCl₄ (30 ml) was heated at reflux for 18 h. After the mixture was cooled to room temperature a solution of Na₂S₂O₃ (1g) in water (20 ml) was added and the mixture was extracted with CH₂Cl₂ (2 x 30 ml). The combined organic extract was dried over anhydrous MgSO₄. After filtration, the solvent was removed to afford a residue. The residue was dissolved in THF (10 ml), and diethyl phosphate (0.373 g, 2.70 mmol) and DIPEA (0.348 g, 2.70 mmol) was added. After the mixture was stirred at room temperature for 2 d, a saturated aqueous NaHCO₃ solution (15 ml) was added, and the mixture was extracted with EtOAc (2 x 20 ml). The combine extract was dried over Na₂SO₄. After filtration, the solvent was removed and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:4 in *v/v*) to afford 4-((5-(bromomethyl)pyridin-2-yl)oxy)benzonitrile as a pale yellow solid (0.41 g, 53%). ¹H NMR (300 MHz, CDCl₃) δ 4.47 (s, 3H), 7.01 (d, 1H, *J*= 8.4 Hz), 7.22-7.27 (m, 2H), 7.67-7.72 (m, 2H), 7.81 (dd, 1H, *J*= 2.4, 8.4 Hz), 8.18 (d, 1H, *J*= 2.4 Hz). Following general procedure D, (*R*)-1-cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one **10b** (R₁=Ph, R₂=4-THP) (0.329 g, 1.00 mmol) and 4-((5-(bromomethyl)pyridin-2-yl)oxy)benzonitrile (0.287 g, 1.00 mmol) in CH₃CN (4 mL) afforded (*R*)-4-((5-((4-(2-oxo-5-phenyl-3-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)benzonitrile as a white foam (0.290g, 54%). ¹H NMR (300 MHz, CDCl₃) δ 1.18-1.27 (m, 1H), 1.40-1.45 (m, 1H), 1.64-1.72 (m, 5H), 1.85-2.02 (m, 3H), 2.64-2.68 (m, 1H), 2.82-2.87 (m, 1H), 3.06 (dd, 1H, *J*= 8.4, 6.9 Hz), 3.34-3.45 (m, 2H), 3.45-3.52 (m, 2H), 3.60-3.68 (m, 2H), 3.97-4.07 (m, 3H), 4.59 (dd, 1H, *J*= 9.3, 6.9 Hz), 6.92 (d, 1H, *J*= 8.4 Hz), 7.17-7.22 (m, 2H), 7.28-7.38 (m, 5H), 7.64-7.69 (m, 3H), 8.02 (d, 1H, *J*= 2.4 Hz). ES-MS *m/z* 538 (M+H)⁺. Following general procedure L, 4-(5-{4-[(*R*)-2-oxo-5-phenyl-3-(tetrahydropyran-4-yl)-imidazolidin-1-yl]-piperidin-1-ylmethyl}-pyridin-2-yl-oxy)-benzonitrile (0.100 g, 0.187 mmol) was suspended in a EtOH/10 N NaOH (5 mL, 3:2 in *v/v*) to afford the corresponding acid **6b** as a pale yellow solid (0.079 g, 76%). ¹H NMR (300 MHz, CD₃OD) δ 1.61-1.87 (m, 7H), 2.33-2.40 (m, 1H), 2.90-3.05 (m, 2H), 3.13-3.18 (m, 1H), 3.38-3.58 (m, 5H), 3.75-3.82 (m, 1H), 3.87-4.00 (m, 3H), 4.24 (s, 2H), 4.70-4.86 (m, 1H), 7.12 (d, 1H, *J*= 8.4 Hz), 7.19-7.22 (m, 2H), 7.30-7.41 (m, 5H), 7.93 (dd, 1H, *J*= 8.4, 1.8 Hz), 8.05-8.10 (m, 2H), 8.20 (d, 1H, *J*= 1.8 Hz); ¹³C NMR(75 MHz, CD₃OD) δ 28.69, 29.25, 31.40, 31.92,

50.86, 51.48, 54.11, 58.81, 68.74, 68.85, 114.25, 122.58, 128.91, 130.23, 130.89, 133.28, 143.49, 145.69, 152.35, 159.50, 165.54, 169.36; ES-MS m/z 557 (M+H)⁺. Anal. Calcd. for C₃₂H₃₆N₄O₅·1.6CH₂Cl₂·2.2H₂O: C, 55.12; H, 6.00; N, 7.65. Found: C, 55.07; H, 5.94; N, 7.90.

(R)-4-((5-((4-(5-(3-Chlorophenyl)-2-oxo-3-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)benzoic acid (6c). Using general procedure M, 3-chlorostyrene (28.0 g, 200 mmol) was converted to (*R*)-*t*-butyl (1-(3-chlorophenyl)-2-hydroxyethyl)carbamate (27.9 g, 51% yield, 93.7%ee by HPLC). ¹H NMR (300 MHz, CD₃OD) δ 3.63-3.72 (m, 2H), 4.63-4.67 (m, 1H), 7.26-7.37 (m, 2H), 7.43 (s, 1H). Using general procedure E, (*R*)-*t*-butyl (1-(3-chlorophenyl)-2-hydroxyethyl)carbamate (33.81 g, 122 mmol) was converted to (*R*)-*t*-butyl (2-amino-1-(3-chlorophenyl)ethyl)carbamate (27.73 g, 82%). ¹H NMR (300 MHz, CDCl₃) δ 1.42 (s, 9H), 3.98-3.99 (m, 2H), 4.57-4.70 (m, 1H), 5.38-5.45 (m, 1H), 7.17-7.18 (m, 1H), 7.23-7.28 (m, 3H). (*R*)-4-(3-chlorophenyl)-3-(piperidin-4-yl)-1-(tetrahydro-2H-pyran-4-yl)imidazolidin-2-one **10b** (R₁=Ph-3-Cl, R₂=4-THP) (30.0 g, 88.7% over 5 steps) was prepared using the same chemistry as that (*R*)-1-cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one (**9b**; R₁=Ph, R₂=*c*-Hex) except that (*R*)-*t*-butyl (2-amino-1-(3-chlorophenyl)ethyl)carbamate (26.5 g, 97.9 mmol) was used in lieu of (*R*)-*tert*-butyl (2-amino-1-phenylethyl)carbamate and tetrahydro-4H-pyranone was used in lieu of cyclohexanone. ¹H NMR (300 MHz, CDCl₃) δ 1.05-1.19 (m, 1H), 1.46-1.53 (m, 1H), 1.60-1.89 (m, 9H), 2.53 (dt, 1H, *J*= 12.4, 2.2 Hz), 2.63 (dt, 1H, *J*= 11.8, 3.7 Hz), 2.91-2.99 (m, 1H), 3.04 (dd, 1H, *J*= 8.8, 6.6 Hz), 3.08-3.15 (m, 1H), 3.44-3.57 (m, 2H), 3.63-3.80 (m, 2H), 3.97-4.10 (m, 3H), 4.58 (dd, 1H, *J*= 9.2, 6.6 Hz), 7.19-7.23 (m, 1H), 7.28-7.33 (m, 3H). Following general procedure D, (*R*)-4-(3-chlorophenyl)-3-(piperidin-4-yl)-1-(tetrahydro-2H-pyran-4-yl)imidazolidin-2-one **10b** (R₁=Ph-3-Cl, R₂=4-THP) and 4-((5-(bromomethyl)pyridin-2-yl)oxy)benzotrile provided (*R*)-4-((5-((4-(5-(3-chlorophenyl)-2-oxo-3-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)-methyl)pyridin-2-yl)oxy)benzotrile which was treated under general procedure L to afford **6c** as a white powder foam (0.165 g, 81% over 2 steps). ¹H NMR (300 MHz, CD₃OD) δ 1.47-1.75 (m, 7H), 2.04-2.15 (m, 1H), 2.30-2.35 (m, 2H), 2.98-3.14 (m, 3H), 3.42-3.50 (m, 2H), 3.60-3.80 (m, 4H), 3.94-3.98 (m, 3H), 4.73 (dd, 1H, *J*= 9.0, 6.6 Hz), 6.95 (d, 1H, *J*= 8.4 Hz), 7.09-7.12 (m, 2H), 7.26-7.32 (m, 3H), 7.37 (br s, 1H), 7.78-7.83 (m, 1H), 7.96-8.03 (m, 2H), 8.08 (br s, 1H), ¹³C NMR (75 MHz, CD₃OD) δ 29.12, 30.78, 31.02, 31.18, 50.62, 52.78, 53.44, 53.72, 54.97, 57.15,

59.13, 68.31, 113.15, 121.30, 126.51, 127.55, 128.15, 129.69, 131.85, 132.67, 135.94, 143.65, 146.25, 150.19, 158.88, 161.85, 164.50; ES-MS m/z 591 (M+H)⁺. Anal. Calcd. For C₃₂H₃₅ClN₄O₅·0.3CH₂Cl₂·0.2H₂O: C, 62.37; H, 5.87; N, 9.01. Found: C, 62.41; H, 5.94; N, 8.78.

(R)-4-((6-methyl-5-((4-(2-oxo-3-(tetrahydro-2H-pyran-4-yl)-5-(m-tolyl)imidazolidin-1-yl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)benzoic acid (6f). Following general procedure M, 3-methylstyrene (3.00 g, 25.3 mmol) was converted to (*R*)-*t*-butyl (2-hydroxy-1-(*m*-tolyl)ethyl)carbamate (3.20 g, 12.7 mmol, 50% yield, 93%*ee*), ¹H NMR (300 MHz, CDCl₃) δ 1.43 (s, 9H), 2.35 (s, 3H), 2.36 (s, 1H), 3.83 (m, 2H), 4.74 (s, 1H), 5.20 (s, 1H), 7.11 (s, 3H), 7.23 (m, 1H). Following general procedure E, the above alcohol (2.50 g, 9.9 mmol) afforded (*R*)-*t*-butyl (2-amino-1-(*m*-tolyl)ethyl)carbamate as a brown solid (1.40 g, 57% over 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 1.42 (s, 9H), 2.35 (s, 3H), 2.99 (m, 2H), 4.60 (s, 1H), 5.22 (s, 1H), 7.0 (s, 3H), 7.22 (d, 1H, *J* = 7.5 Hz). (*R*)-3-(piperidin-4-yl)-1-(tetrahydro-2H-pyran-4-yl)-4-(*m*-tolyl)imidazolidin-2-one **10b** (R₁=Ph-3-Me, R₂=4-THP) (0.31g, 16% over 5 steps) was prepared using the same chemistry as that for the (*R*)-1-cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one **10b** (R₁=Ph, R₂=*c*Hex) except that (*R*)-*t*-butyl (2-amino-1-(*m*-tolyl)ethyl)carbamate (1.40 g, 5.6 mmol) was used in lieu of (*R*)-*t*-butyl (2-amino-1-phenylethyl)carbamate and tetrahydro-4*H*-pyranone was used in lieu of cyclohexanone. ¹H NMR (300 MHz, CDCl₃) δ 1.23 (dq, 1H, *J* = 7.5, 3.6 Hz), 1.45 (d, 1H, *J* = 12.0 Hz), 1.60-1.75 (m, 5H), 1.82 (dq, 1H, *J* = 7.5, 2.5 Hz), 2.35 (s, 3H), 2.57 (dt, 1H, *J* = 7.5, 2.5 Hz), 2.68 (dt, 1H, *J* = 7.5, 2.5 Hz), 2.95 (d, 1H, *J* = 12.3 Hz), 3.49 (m, 2H), 3.64 (t, 1H, *J* = 9.0 Hz), 3.75 (m, 1H), 4.00 (m, 3H), 4.56 (m, 1H), 7.12 (m, 3H), 7.22 (d, 1H, *J* = 6.9 Hz). Following general procedure A, (*R*)-3-(piperidin-4-yl)-1-(tetrahydro-2H-pyran-4-yl)-4-(*m*-tolyl)imidazolidin-2-one **10b** (R₁=Ph-3-Me, R₂=4-THP) and 4-((5-formyl-6-methylpyridin-2-yl)oxy)benzotrile provided (*R*)-4-((6-methyl-5-((4-(2-oxo-3-(tetrahydro-2H-pyran-4-yl)-5-(*m*-tolyl)imidazolidin-1-yl)piperidin-1-yl)-methyl)pyridin-2-yl)oxy)benzotrile which was treated under general procedure L to afford **6f** as a white solid (112 mg, 65% over 2 steps). ¹H NMR (300 MHz, CD₃OD) δ 1.50-1.80 (m, 7H), 2.14 (dq, 1H, *J* = 12.6, 3.6 Hz), 2.34 (s, 3H), 2.42 (s, 3H), 2.45 (q, 1H, *J* = 12.9 Hz), 3.03 (d, 1H, *J* = 11.4 Hz), 3.12 (t, 1H, *J* = 8.1 Hz), 3.15 (m, 1H), 3.48 (t, 2H, *J* = 11.7 Hz), 3.55 (m, 1H), 3.76 (t, 1H, *J* = 9.3 Hz), 3.78 (s, 2H), 3.92 (m, 3H), 4.66 (m, 1H), 6.80 (d, 1H, *J* = 8.4 Hz), 7.13 (d, 2H, *J* = 8.7 Hz), 7.16-7.30 (m, 4H), 7.72 (d, 1H, *J* = 8.4 Hz), 8.03 (d, 2H, *J* = 8.4 Hz); ¹³C NMR (75

MHz, CD₃OD) δ 20.58, 21.10, 27.43, 28.60, 29.82, 30.18, 48.57, 49.44, 50.96, 52.37, 52.54, 56.86, 57.01, 67.17, 67.26, 109.46, 120.07 (3C), 122.53, 124.05, 127.61, 129.07, 129.24, 131.62 (2C), 138.96, 142.27, 143.78, 157.96, 158.20, 160.75, 162.53, 169.55; ES-MS m/z 585 (M+H)⁺. Anal. Calcd. For C₃₄H₄₀N₄O·0.6CH₂Cl₂: C, 65.38; H, 6.53; N, 8.81. Found: C, 65.19; H, 6.63; N, 8.71.

(R)-4-((6-Methyl-5-((4-(2-oxo-5-phenyl-3-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)methyl)pyridin-2-yl)thio)benzoic acid (6j). Following general procedure A, (R)-1-cyclohexyl-4-phenyl-3-(piperidin-4-yl)imidazolidin-2-one **10b** (R₁=Ph, R₂=4-THP) and methyl 4-((5-formyl-6-methylpyridin-2-yl)thio)benzoate provided (R)-methyl 4-((6-methyl-5-((4-(2-oxo-5-phenyl-3-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)methyl)pyridin-2-yl)thio)benzoate which was treated under general procedure C to afford **6j** as a white foam (0.065 g, 44% over 2 steps). ¹H NMR (300 MHz, CD₃OD) δ 1.62-1.81 (m, 7H), 2.19-2.25 (m, 1H), 2.50 (s, 3H), 2.56-2.68 (m, 2H), 3.11-3.32 (m, 4H), 3.43-3.56 (m, 3H), 3.77 (t, 1H, J = 9.0 Hz), 3.89 (s, 2H), 3.90-3.99 (m, 3H), 4.88 (dd, 1H, J = 9.3, 7.2 Hz), 6.90 (d, 1H, J = 7.8 Hz), 7.31-7.38 (m, 5H), 7.54-7.60 (m, 3H), 8.02-8.05 (m, 2H); ¹³C NMR (75 MHz, CD₃OD) δ 22.25, 28.44, 29.38, 30.91, 31.31, 50.60, 51.89, 53.48, 53.74, 58.20, 68.30, 68.39, 121.35, 124.79, 128.21, 129.74, 130.28, 131.95, 134.15, 134.80, 137.67, 141.91, 143.26, 160.35, 161.37, 161.83, 170.14; ES-MS m/z 605 (M+H)⁺. Anal. Calcd. for C₃₃H₃₈N₄O₄S·0.1CH₂Cl₂·1.6H₂O: C, 63.71; H, 6.69; N, 8.98; S, 5.14. Found: C, 63.68; H, 6.77; N, 8.74; S, 5.00.

(R)-N-Methyl-4-((6-methyl-5-((4-(2-oxo-5-phenyl-3-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)benzamide (6l). Following general procedure J, (R)-4-((6-methyl-5-((4-(2-oxo-5-phenyl-3-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)methyl)pyridin-2-yl)oxy)benzoic acid **6d** afforded **6l** as white solid (69 mg, 84%). ¹H NMR (300 MHz, CDCl₃) δ 1.19 (dq, 1H, J = 12.0, 3.6 Hz), 1.42 (d, 1H, J = 12.0 Hz), 1.66 (m, 5H), 1.92 (m, 2H), 1.99 (m, 1H), 2.38 (s, 3H), 2.64 (d, 1H, J = 11.4 Hz), 2.83 (d, 1H, J = 11.4 Hz), 3.02 (d, 3H, J = 4.8 Hz), 3.07 (m, 1H), 3.31 (s, 2H), 3.46 (m, 2H), 3.65 (t, 1H, J = 9.0 Hz), 3.65 (m, 1H), 4.01 (m, 3H), 4.59 (m, 1H), 6.07 (s, 1H), 6.60 (d, 1H, J = 8.1 Hz); 7.12 (d, 2H, J = 8.4 Hz), 7.33 (s, 5H), 7.49 (d, 1H, J = 8.1 Hz), 7.74 (d, 2H, J = 8.7 Hz); ES-MS m/z 584 (M+H)⁺. Anal. Calcd. for C₃₄H₄₁N₅O₄·0.9CH₂Cl₂: C, 63.50; H, 6.53; N, 10.61; Found: C, 63.46; H, 6.69; N, 10.53.

(R)-4-((5-((4-(5-(3-chlorophenyl)-2-oxo-3-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)methyl)pyrimidin-2-yl)thio)benzoic acid (6m). To a solution of 4-mercaptobenzoic acid (182 mg, 1.18 mmol) in DMF (10 ml) at room temperature was added NaH (60%, 104 mg, 2.59 mmol) and the mixture was stirred for 30 min. 5-Bromo-2-chloropyrimidine (228 mg, 1.18 mmol) was added and the mixture heated to 130°C for 3 h. Standard work-up and purification afforded the desired acid which was treated with H₂SO₄ (0.2 ml) in MeOH (5ml) to afford methyl 4-((5-bromopyrimidin-2-yl)thio)benzoate (370 mg, 100%). To a solution of the above pyrimidine (370 mg, 1.13 mmol), bis(triphenylphosphine)palladium(II) dichloride (118 mg, 0.170 mmol), LiCl (189 mg) and triphenylphosphine (89 mg, 0.34 mmol) in degassed DMF (5 ml) was added tributylvinyltin (0.4 ml, 1.4 mmol) and the mixture was heated at 100°C for 18 h. Standard work-up and purification afforded methyl 4-((5-vinylpyrimidin-2-yl)thio)benzoate (78 mg, 25%). To a solution of the above substrate (79 mg, 0.29 mmol) and NMO (67 mg, 0.57 mmol) in CH₂Cl₂ (3 ml) was added OsO₄ (2.5 %, 0.05 ml, 0.004 mmol) and the mixture stirred at room temperature for 18 h. Standard work-up afforded the crude intermediate. To a solution of the diol in acetone (2 ml) was added a solution of NaIO₄ (91 mg, 0.58 mmol) in H₂O (1 ml) and the mixture was stirred at room temperature for 2 h. Standard work-up and purification afforded methyl 4-((5-formylpyrimidin-2-yl)thio)benzoate (40 mg, 50% over 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 3.94 (s, 3H), 7.69 (d, 2H, *J*= 8.4 Hz), 8.10 (d, 2H, *J*= 8.1 Hz), 8.87 (s, 2H), 9.99 (s, 1H). Following general procedure A, (*R*)-4-(3-chlorophenyl)-3-(piperidin-4-yl)-1-(tetrahydro-2H-pyran-4-yl)imidazolidin-2-one **10b** (R₁=Ph-3-Cl, R₂=4-THP) and the above aldehyde provided (*R*)-methyl 4-((5-((4-(5-(3-chlorophenyl)-2-oxo-3-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)-methyl)pyrimidin-2-yl)thio)benzoate which was treated under general procedure C to afford **6m** as a white solid (484 mg, 70% over 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 1.51 (br s, 2H), 1.64-1.71 (m, 3H), 1.77 (br d, 1H, *J*= 13.2 Hz), 2.30 (br s, 2H), 2.39 (br s, 1H), 3.06 (dd, 2H, *J*= 8.4, 6.3 Hz), 3.34 (br d, 1H, *J*= 9.3 Hz), 3.41-3.52 (m, 3H), 3.64-3.75 (m, 3H), 3.98-4.02 (m, 4H), 4.60 (dd, 1H, *J*= 9.0, 6.0 Hz), 7.08-7.16 (m, 3H), 7.29 (s, 1H), 7.65 (d, 2H, *J*= 8.4 Hz), 8.01 (d, 2H, *J*= 8.1 Hz), 8.48 (s, 2H); ES-MS *m/z* 608 (M+H)⁺. Anal. Calcd. for C₃₁H₃₄N₅ClO₄S·0.5CH₂Cl₂: C, 58.15; H, 5.42; N, 10.76. Found: C, 58.09; H, 5.62; N, 10.69.

(R)-4-((5-((4-(5-(3-Chlorophenyl)-2-oxo-3-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)methyl)-4-methylpyrimidin-2-yl)amino)benzoic acid (6n). Under N₂, to a

dry flask charged with ethyl 2-amino-4-methylpyrimidine-5-carboxylate (2.50 g, 3.8 mmol), 1,4-dibromobenzene (6.51 g, 27.6 mmol), *t*-BuOK (2.02 g, 18 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.176 g, 0.304 mmol) and Pd₂(dba)₃ (0.126 g, 0.138 mmol) was added anhydrous toluene (100 ml). The mixture was degassed and filled with N₂ twice, and then was stirred at 100°C for 16 h. After the mixture was cooled to room temperature, saturated aqueous NH₄Cl solution (20 ml) and brine (50 ml) were added and the mixture was extracted with EtOAc/THF (3 x 60 ml, 5:1 v/v). The combined extracts were dried over Na₂SO₄. After filtration through a silica gel plug the solvent was removed, and the residue was purified by recrystallization from EtOAc/hexanes to afford ethyl 2-((4-bromophenyl)amino)-4-methylpyrimidine-5-carboxylate as a pale yellow solid (2.80 g, 60%). Under N₂, to a solution of ethyl 2-((4-bromophenyl)amino)-4-methylpyrimidine-5-carboxylate (2.80 g, 8.33 mmol) in THF (100 ml) cooled at -78°C was added DIBAL-H (1.0 M in toluene, 21.0 ml, 21.0 mmol). After the mixture was stirred at -78°C for 30 min, the cooling bath was removed and the mixture was stirred at room temperature for 2 h. Saturated aqueous NH₄Cl (60 ml) was added and the mixture was extracted with EtOAc (3 x 50 ml). The combined extracts were dried over Na₂SO₄. After filtration the solvent was removed and the residue was purified by flash chromatography on silica gel (EtOAc) to afford (2-((4-bromophenyl)amino)-4-methylpyrimidin-5-yl)methanol as a pale yellow solid (2.0 g, 82%). (2-((4-bromophenyl)amino)-4-methylpyrimidin-5-yl)methanol (2.0 g, 6.85 mmol) was dissolved in CH₂Cl₂ (200 ml). MnO₂ (15.0 g, 174 mmol) was added, and the suspension was stirred at room temperature for 4 h. The suspension was then filtered through a Celite® cake. The filtrate was collected and concentrated to afford 2-((4-bromophenyl)amino)-4-methylpyrimidine-5-carbaldehyde as a pale yellow solid (1.49 g, 75 %). Under N₂, to a dry flask charged with 2-((4-bromophenyl)amino)-4-methylpyrimidine-5-carbaldehyde (1.52 g, 5.21 mmol), Zn(CN)₂ (0.352 g, 3.00 mmol), dppf (0.036 g, 0.065 mmol) and Pd₂(dba)₃ (0.024 g, 0.026 mmol) was added anhydrous DMF (40 ml). The mixture was stirred at 140°C for 16 h and then cooled to room temperature. DMF was removed, the residue was taken up with EtOAc and purified by flash chromatography on silica gel (EtOAc/hexanes, 1:1 v/v) to afford 4-((5-formyl-4-methylpyrimidin-2-yl)amino)benzotrile as a pale yellow solid (0.711 g, 57%). ¹H NMR (300 MHz, CDCl₃) δ 2.79 (s, 3H), 7.64 (br s, 1H), 7.64-7.68 (m, 2H), 7.85-7.88 (m, 2H), 8.79 (s, 1H), 10.09 (s, 1H). Following general procedure A, (*R*)-4-(3-chlorophenyl)-3-(piperidin-4-yl)-1-(tetrahydro-2H-pyran-4-yl)imidazolidin-2-one **10b** (R₁=Ph-3-Cl, R₂=4-THP) and the above

aldehyde provided (R)-4-(((5-((4-(5-(3-chlorophenyl)-2-oxo-3-(tetrahydro-2H-pyran-4-yl)imidazolidin-1-yl)piperidin-1-yl)methyl)-4-methylpyrimidin-2-yl)thio)benzotrile which was treated under general procedure L to afford **6n** as a brown solid (0.036 g, 22% over 2 steps). ¹H NMR (300 MHz, CD₃OD) δ 1.65-1.94 (m, 7H), 2.32-2.37 (m, 1H), 2.55 (s, 3H), 2.92-2.99 (m, 2H), 3.17 (dd, 1H, *J*= 9.0, 7.2 Hz), 3.36-3.39 (m, 1H), 3.47-3.55 (m, 3H), 3.61-3.65 (m, 1H), 3.83 (t, 1H, *J*= 9.0 Hz), 3.95-4.03 (m, 3H), 4.14 (s, 2H), 4.79 (dd, 1H, *J*= 9.0, 6.9 Hz), 7.38-7.46 (m, 4H), 7.86-7.89 (m, 2H), 7.97-8.00 (m, 2H), 8.42 (s, 1H); ¹³C NMR (75 MHz, CD₃OD) δ 22.66, 28.09, 28.74, 30.94, 31.22, 50.62, 51.36, 53.07, 53.20, 55.84, 57.65, 68.26, 68.34, 115.11, 119.39, 126.59, 128.28, 129.86, 131.87, 132.01, 136.02, 145.64, 145.89, 161.26, 161.62, 162.26, 170.39; ES-MS *m/z* 605 (M+-H)⁺. Anal. Calcd. for C₃₂H₃₇N₆O₄·0.9CH₂Cl₂·1.9H₂O: C, 55.21; H, 6.00; N, 11.74. Found: C, 55.49; H, 6.13; N, 11.35.