

Supporting Information

Optimization of Pyrrolamide Topoisomerase II Inhibitors Towards Identification of an Antibacterial Clinical Candidate, AZD5099

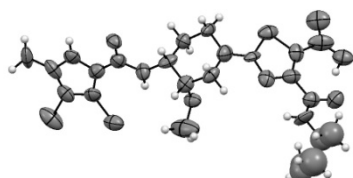
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Crystal structure of AZD5099. Colorless plate crystals of AZD5099 (anhydrous form) were obtained by evaporation of the isopropyl alcohol solution. The diffraction data were collected at 180K on the Nonius KappaCCD diffractometer. The crystal structure was solved and refined with the SHELXTL package. All the hydrogen atoms attached to the C atoms and N atoms were calculated. Absolute configuration was established by using anomalous dispersion method, and the Flack parameter is found to be 0.1(3). Below is the ORTEP representation. The diffraction data was deposited into the Cambridge Crystallographic Data Centre (CCDC 993908).

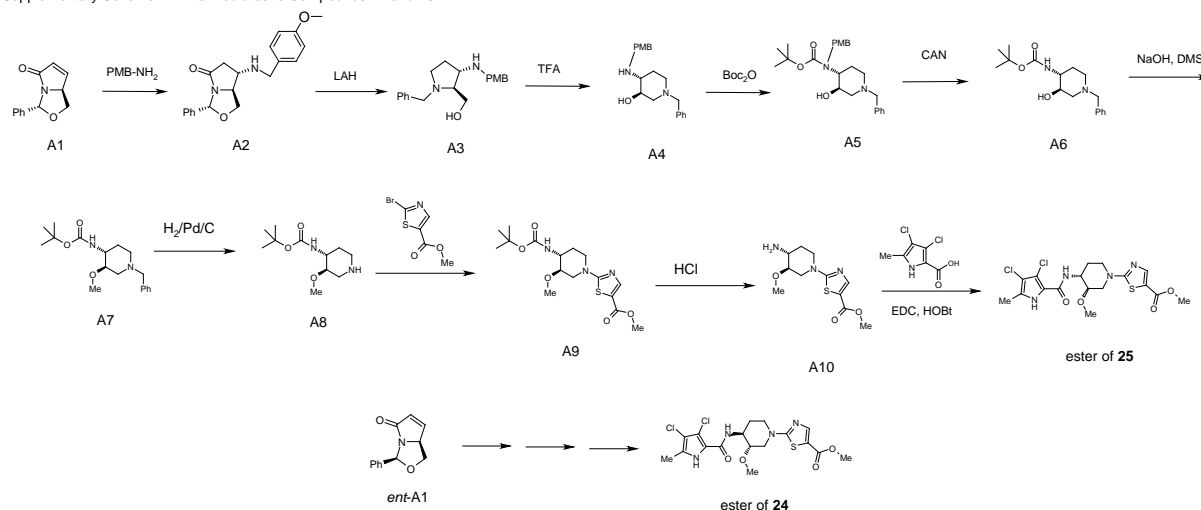


Synthetic Chemistry Experimental Procedures:

***tert*-Butyl 4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]piperidine-1-carboxylate** A solution of 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (3.0 g, 0.016 mol),¹ *tert*-butyl 4-aminopiperidine-1-carboxylate (3.1 g, 0.016 mol), and Et₃N (2.2 ml, 0.032 mol) were combined in DMF (20 ml) and stirred under N₂ for 5 minutes. HATU (6.47 g, 0.017 mol) was added in one portion, and the reaction was stirred at rt for 5 h. The reaction mixture was diluted with EtOAc and water. The organic phase was separated and washed with 1 N HCl, and the combined aq portions were extracted with EtOAc. The combined organic portions were washed sequentially with saturated NaHCO₃ and saturated NaCl, dried (MgSO₄), and concentrated to give a brown solid. Most of the crude material was isolated by trituration with EtOAc/hexanes to give an off-white solid. The remaining material was chromatographed on silica gel (gradient elution with 25-50% EtOAc in hexanes) to give a light brown solid that was trituated with EtOAc. The combined trituated solids afforded a total of 1.98 g of the title compound. MS (ESI) *m/z* (M-H)⁺: 374.33, 376.34 for C₁₆H₂₃Cl₂N₃O₃. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.16 (s, 9H); 1.20 (m, 2H); 1.53 (m, 2H); 1.93 (s, 3H); 2.65 (m, 2H); 3.65 (m, 3H); 6.97 (d, 1H); 11.72 (s, 1H).

3,4-Dichloro-5-methyl-*N*-(4-piperidyl)-1*H*-pyrrole-2-carboxamide hydrochloride salt (Intermediate to **1**) A solution of the preceding compound (1.98 g, 5.26 mmol) and 4 M HCl in dioxane (20 ml) was stirred at rt for 1.5 h. The reaction mixture was concentrated to give the title compound as a pink solid (1.61 g, 98% yield). MS (ESI) *m/z* (M-H)⁺: 274.08, 276.08 for C₁₁H₁₅Cl₂N₃O. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.71 (m, 2H); 1.95 (m, 2H); 2.18 (s, 3H); 2.99 (m, 2H); 3.27 (m, 2H); 3.99 (m, 1H); 7.64 (d, 1H); 8.67 (brs, 1H); 12.16 (s, 1H).

3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl chloride A solution of 10.4 g (54 mmol) of 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid¹ in 100 ml SOCl₂ was heated at reflux for 30 min. Solvent was removed to afford product. ¹H NMR (300 MHz, CDCl₃) δ 2.3 (s, 1H), 8.8 (s, 1H).



(3*R*,7*S*,7*aS*)-7-[(4-Methoxyphenyl)methylamino]-3-phenyl-3,6,7,7*a*-tetrahydro-1*H*-pyrrolo[1,2-*c*]oxazol-5-one (*ent*-A2) A solution of 1.79 g (8.89 mmol) of (3*R*,7*aS*)-3-phenyl-3,7*a*-dihydro-1*H*-pyrrolo[1,2-*c*]oxazol-5-one (*ent*-A1)² and 2.09 ml (16 mmol) of *p*-methoxybenzylamine in 100 ml of 7:3 Et₂O-H₂O was stirred at rt for 1 h. The mixture was diluted with ether, washed with water and dried (Na₂SO₄). After removal of solvent, the residue was purified by chromatography on silica gel (10:1 CH₂Cl₂-MeOH) to afford 2.64 g (84%) of an oil. ¹H NMR (300 MHz, CDCl₃) δ 2.6-2.9 (m, 2H) 3.43 (ddd, *J*=9.56, 8.05, 5.56 Hz, 1H) 3.61 (dd, *J*=8.29, 7.16 Hz, 1H) 3.71 (d, *J*=3.0 Hz, 2H) 3.80 (s, 3H) 3.86-3.96 (m, 1H) 4.1-4.2 (m, 1H) 6.33 (s, 1H) 6.87 (d, *J*=8.67 Hz, 2H) 7.22 (d, *J*=8.67 Hz, 2H) 7.29-7.46 (m, 6H).

[(2*S*,3*S*)-1-Benzyl-3-[(4-methoxyphenyl)methylamino]pyrrolidin-2-yl]methanol (*ent*-A3) A solution of 1 N LiAlH₄ in THF (35 ml, 35 mmol) was added to a solution of 2.64 g (7.49 mmol) of *ent*-A2 dissolved in 25 ml dry THF, the mixture was heated at reflux overnight. After cooling to 0 °C, the mixture was quenched with sat. aq. Na₂SO₄ and dilute with Et₂O. The organic layer was separated, dried (MgSO₄) and concentrated to give 2.26 g (92%) of the title compound. ¹H NMR (300 MHz, CDCl₃) δ 1.5 - 1.6 (m, 1H) 1.8 - 2.0 (m, 2H) 2.48 (m, 2H) 2.9 - 3.0 (m, 1H) 3.2 - 3.3 (m, 1H) 3.37 (d, *J*=13.00 Hz, 1H) 3.63 - 3.71 (m, 2H) 3.71 - 3.75 (m, 1H) 3.80 (s, 3H) 3.95 (d, *J*=13.00 Hz, 1H) 6.87 (d, *J*=9 Hz 2H) 7.29 (m, 8 H).

(3*R*,4*R*)-1-Benzyl-4-[(4-methoxyphenyl)methylamino]piperidin-3-ol (*ent*-A4) A mixture of 2.26 g (6.92 mmol) of *ent*-A3 and 2.65 ml of TFAA in 40 ml THF was stirred at rt for 3 h. Et₃N (7.5 ml) was added and the mixture was heated at reflux for 7 h. After adding 20 ml 2 N NaOH and stirring 2 h, the mixture was partitioned between CH₂Cl₂ and water. The organic layer was separated, dried (Na₂SO₄) and concentrated. The residue was chromatographed on silica gel (9:1 CH₂Cl₂-MeOH) to afford 1.73 g (65%) of the title compound as a solid. ¹H NMR (300 MHz, CDCl₃) δ 1.3 - 1.45 (m, 1H) 1.9 - 2.1 (m, 2H) 2.3 - 2.4 (m, 2H) 2.83 (d, *J*=11.7 Hz, 1H) 3.06 (dd, *J*=10.6, 2.9 Hz, 1H) 3.4 - 3.5 (m, 1H) 3.5 - 2.6 (m, 2H) 3.64 (d, *J*=12.8 Hz, 1H) 3.79 (s, 3H) 3.89 (d, *J*=12.8 Hz, 1H) 6.85 (d, *J*=9 Hz 2H) 7.29 (m, 8 H).

***tert*-Butyl *N*-[(3*R*,4*R*)-1-benzyl-3-hydroxy-4-piperidyl]-*N*-[(4-methoxyphenyl)methyl]carbamate (*ent*-A5)** A solution of 2.72 g (8.48 mmol) of *ent*-A4, Boc₂O (2.04 g, 9.33 mmol) and NaHCO₃ (784 mg, 9.33 mmol) in 100 ml MeOH was stirred at rt for 4 h. Solvent was removed and the residue was purified by chromatography on silica gel (1:1 EtOAc-hexanes) to afford 3.58 g (90%) of the title compound as an oil. ¹H NMR (300 MHz, CDCl₃) δ 1.43 (s, 9 H) 1.8 - 2.1 (m, 2H) 2.7 - 2.9 (m, 1H) 3.0 - 3.2 (m, 1H) 3.49 (s, 2H) 3.6 - 3.7 (m, 1H) 3.79 (s, 3H) 3.8 - 4.0 (m, 1H) 4.36 (s, 2H) 6.85 (d, *J*=8.67 Hz, 2H) 7.1 - 7.4 (m, 8 H).

***tert*-Butyl *N*-[(3*R*,4*R*)-1-benzyl-3-methoxy-4-piperidyl]carbamate (*ent*-A6)** CAN 7.04 g (12.85 mmol) was added a solution of *ent*-A5 (2.74 g, 6.42 mmol) dissolved in 40 ml 3:1 CH₃CN/H₂O, and of. After 2 h

stirring, the mixture was partitioned between CH₂Cl₂ and sat. aq. NaHCO₃. The organic layer was separated, dried (Na₂SO₃) and concentrated. The residue was purified by chromatography on silica gel (1:1 EtOAc-hexanes) to afford 1.14 g of product. ¹H NMR (300 MHz, CDCl₃) δ 1.45 (s, 9 H) 1.84 - 2.14 (m, 4 H) 2.67 - 2.83 (m, 1H) 2.95 - 3.09 (m, 1H) 3.28 - 3.40 (m, 1H) 3.41 - 3.50 (m, 1H) 3.52 (s, 3H) 3.4 - 3.5 (m, 1H) 4.49 - 4.66 (m, 1H) 7.20 - 7.36 (m, 5 H, overlaps w/ CHCl₃ peak).

***tert*-Butyl *N*-[(3*R*,4*R*)-1-benzyl-3-methoxy-4-piperidyl]carbamate (*ent*-A7)** Dimethyl sulfate (0.16 ml, 1.69 mmol) was added to a mixture of 437 mg (1.43 mmol) of the *ent*-A6, 10 mg benzyltrimethylammonium chloride and 50% aq. NaOH (6 ml) in 10 ml toluene. After stirring for 4 h, the mixture was poured into ice-water and extracted with EtOAc. The organic phase was separated, dried (Na₂SO₄) and concentrated to afford 458 mg of the title compound used in the subsequent step without further purification. ¹H NMR (300 MHz, CDCl₃) δ 1.44 (s, 9 H) 1.88 - 2.22 (m, 3H) 2.64 - 2.78 (m, 1H) 3.00 - 3.17 (m, 2H) 3.36 (s, 3H) 3.4 (m, 1H) 3.46 - 3.59 (m, 2H) 4.42 - 4.59 (m, 1H) 7.23-7.32 (m, 5H).

***tert*-Butyl *N*-[(3*R*,4*R*)-3-methoxy-4-piperidyl]carbamate (*ent*-A8)** A solution of *ent*-A7 (458 mg, 1.42 mmol), ammonium formate (269 mg, 5.72 mmol), and 10% Pd/C (200 mg) in MeOH (10 ml) was heated to 50 °C for 1 h. The reaction mixture was cooled to rt, filtered through diatomaceous earth and concentrated under reduced pressure to give the title compound (325 mg, 100%). ¹H NMR (300 MHz, CDCl₃) δ 1.45 (s, 9H), 2.43 (m, 1H), 2.50-2.57 (m, 1H), 2.59-2.66 (m, 1H), 2.89 (m, 1H), 3.01 (m, 1H), 3.24 (m, 1H), 3.41 (s, 3H), 3.67 (m, 1H), 4.71 (m, 1H).

Methyl 2-[(3*R*,4*R*)-4-(*tert*-butoxycarbonylamino)-3-methoxy-1-piperidyl]thiazole-5-carboxylate (*ent*-A9) A solution of the *ent*-A8 (76 mg, 0.33 mmol), methyl 2-bromothiazole-5-carboxylate (73 mg, 0.33 mmol) and Et₃N (0.14 ml, 1 mmol) in 4 ml DMF was heated at 120 °C for 30 min in a microwave reactor. The mixture was diluted with EtOAc, washed with 10% aq. HCl and brine. Drying (Na₂SO₄) and removal of solvent was followed by chromatography on silica gel (1:1 EtOAc-hexanes) to give the title compound as a solid (81 mg, 66%). MS (ESI) *m/z* (M+Na)⁺: 394 for C₁₆H₂₅N₃O₅S; ¹H NMR (300 MHz, CDCl₃) δ 1.46 (s, 9H), 1.66 (m, 1H), 1.89 (m, 1H), 2.29 (m, 1H), 3.13-3.20 (m, 3H), 3.47 (s, 3H), 3.75 (m, 1H), 3.83 (s, 3H), 4.20 (m, 1H), 4.60 (brs, 1H), 7.85 (s, 1H).

Methyl 2-[(3*R*,4*R*)-4-amino-3-methoxypiperidin-1-yl]-1,3-thiazole-5-carboxylate hydrochloride salt (*ent*-A10) 4 N HCl in dioxane (0.26 ml) was added to *ent*-A9 (81 mg, 0.22 mmol) in 1 ml dioxane, and the mixture was stirred at rt for 90 min. Solids that precipitated were collected by filtration and dried in vacuo to afford 73 mg (100%) of the title compound, which was used without further purification in the next step. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.63 (m, 1H), 2.08 (d, 1H), 2.97-3.01 (m, 1H), 3.21-3.24 (m, 2H), 3.25 (m, 2H), 3.40 (s, 3H), 3.73 (s, 3H), 3.88 (d, 1H), 4.34 (m, 1H), 7.87 (s, 1H), 8.28 (br. s, 3H).

Methyl 2-[(3*R*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylate (ester of **24** from main text) A solution of 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid¹ (52 mg, 0.27 mmol), *ent*-A10 (75 mg, 0.27 mol), HOBt (29 mg, 0.27 mmol) and NMM (110 μl) in anhydrous CH₂Cl₂ was stirred at ambient temperature for 60 min. EDC (75 mg, 27 mmol) was added and the mixture was stirred at ambient temperature overnight. The mixture was diluted with CH₂Cl₂ and washed with 10% aq. HCl, aq NaHCO₃ and brine. Drying (Na₂SO₄) and removal of solvent gave a residue that was purified by chromatography on silica gel (1.5: 1 EtOAc-hexanes) to afford the title compound as a white solid (73 mg, 83%). MS (ESI) *m/z* (M+H)⁺: 447 for C₁₇H₂₀Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.71 (m, 1H), 1.93 (m, 1H), 2.18 (s, 3H), 3.24-3.28 (m, 2H), 3.31 (s, 3H), 3.75 (s, 3H), 3.79 (m, 1H), 4.02-4.11 (m, 2H), 7.35 (d, 1H), 7.88 (s, 1H), 12.00 (s, 1H).

(3*S*,7*R*,7*aR*)-7-[(4-Methoxyphenyl)methylamino]-3-phenyl-3,6,7,7*a*-tetrahydro-1*H*-pyrrolo[1,2-*c*]oxazol-5-one (A2**)** Made as described for *ent*-A2 from 1.38 g (6.86 mmol) of (3*S*,7*aR*)-3-phenyl-3,7*a*-dihydro-1*H*-pyrrolo[1,2-*c*]oxazol-5-one (**A1**)² and 1.61 ml (12.3 mmol) of *p*-methoxybenzylamine to afford 2.12 g (88%) of product as an oil. ¹H NMR (300 MHz, CDCl₃) δ 2.6 - 2.9 (m, 2H) 3.43 (ddd, *J*=9.56, 8.05, 5.56 Hz, 1H) 3.61 (dd, *J*=8.29, 7.16 Hz, 1H) 3.71 (d, *J*=3.0 1Hz, 2H) 3.80 (s, 3H) 3.86 - 3.96 (m, 1H) 4.1 - 4.2 (m, 1H) 6.33 (s, 1H) 6.87 (d, *J*=8.67 Hz, 2H) 7.22 (d, *J*=8.67 Hz, 2H) 7.29 - 7.46 (m, 6 H).

[(2*R*,3*R*)-1-Benzyl-3-[(4-methoxyphenyl)methylamino]pyrrolidin-2-yl]methanol (A3**)** Made as described for *ent*-A3 from 2.12 g (6.26 mmol) of **A2** and 1 N LiAlH₄ in THF (28 ml, 28 mmol) was to

give 1.68 g (82%) of the title compound. ¹H NMR (300 MHz, CDCl₃) δ 1.5 - 1.6 (m, 1H) 1.8 - 2.0 (m, 2H) 2.48 (m, 2H) 2.9 - 3.0 (m, 1H) 3.2 - 3.3 (m, 1H) 3.37 (d, *J*=13.00 Hz, 1H) 3.63 - 3.71 (m, 2H) 3.71 - 3.75 (m, 1H) 3.80 (s, 3H) 3.95 (d, *J*=13.00 Hz, 1H) 6.87 (d, *J*= 9 Hz 2H) 7.29 (m, 8 H).

(3*S*,4*S*)-1-Benzyl-4-[(4-methoxyphenyl)methylamino]piperidin-3-ol (A4) Made as described for *ent*-**A4** from 1.68 g (5.15 mmol) of **A3** and 2.7 ml (19.3 mmol) of TFAA and 5.75 ml (39.9 mmol) Et₃N to afford 898 mg (53%) of the title compound as a solid. ¹H NMR (300 MHz, CDCl₃) δ 1.3 - 1.45 (m, 1H) 1.9 - 2.1 (m, 2H) 2.3 - 2.4 (m, 1H) 2.83 (d, *J*=11.7 Hz, 1H) 3.06 (dd, *J*=10.6, 2.9 Hz, 1H) 3.4 - 3.5 (m, 1H) 3.5 - 2.6 (m, 2H) 3.64 (d, *J*=12.8 Hz, 1H) 3.79 (s, 3H) 3.89 (d, *J*=12.8 Hz, 1H) 6.85 (d, *J*= 9 Hz 2H) 7.29 (m, 8 H).

***tert*-Butyl *N*-[(3*S*,4*S*)-1-benzyl-3-hydroxy-4-piperidyl]-*N*-[(4-methoxyphenyl)methyl]carbamate (A5)** Made as described for *ent*-**A5** from 162 mg (0.50 mmol) of **A4**, Boc₂O (119 mg, 0.55 mmol) and NaHCO₃ (46 mg, 0.55 mmol) to afford 167 g (79%) of product as an oil. ¹H NMR (300 MHz, CDCl₃) δ 1.43 (s, 9 H) 1.8 - 2.1 (m, 2H) 2.7 - 2.9 (m, 1H) 3.0 - 3.2 (m, 1H) 3.49 (s, 2H) 3.6 - 3.7 (m, 1H) 3.79 (s, 3H) 3.8 - 4.0 (m, 1H) 4.36 (s, 2H) 6.85 (d, *J*=8.67 Hz, 2H) 7.1 - 7.4 (m, 8 H).

***tert*-Butyl *N*-[(3*S*,4*S*)-1-benzyl-3-methoxy-4-piperidyl]carbamate (A7)** The title compound (810 mg, 58%) was made as described for *ent*-**A7** using 1.93 g (4.52 mmol) of **A6** and 4.96 g (9.05 mmol) of CAN. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.50 (s, 9 H) 1.82 (s, 2H) 1.94 - 2.07 (m, 1H) 2.76 - 2.87 (m, 1H) 2.89 - 3.00 (m, 1H) 3.06 - 3.24 (m, 1H) 3.42 (s, 1H) 3.45 (s, 5 H) 3.47 - 3.54 (m, 1H) 3.56 - 3.65 (m, 1H) 4.74 (d, *J*=5.65 Hz, 1H) 6.66 - 6.81 (m, 1H) 7.41 (d, *J*=5.65 Hz, 5 H).

***tert*-Butyl *N*-[(3*S*,4*S*)-1-benzyl-3-methoxy-4-piperidyl]carbamate (A8)** Made as described for *ent*-**A8** from 351 mg (1.15 mmol) of **A7** and 0.13 ml (1.38 mmol) of dimethylsulfate to afford 368 mg (100%) of product. ¹H NMR (300 MHz, CDCl₃) δ ppm 1.44 (s, 9 H) 1.88 - 2.22 (m, 3H) 2.64 - 2.78 (m, 1H) 3.00 - 3.17 (m, 2H) 3.36 (s, 3H) 3.4 (m, 1H) 3.46 - 3.59 (m, 2H) 4.42 - 4.59 (m, 1H) 7.23-7.32 (m, 5H).

***tert*-Butyl *N*-[(3*S*,4*S*)-3-methoxy-4-piperidyl]carbamate (A8)** Made as described for *ent*-**A8** from 368 mg (1.15 mmol) **A7**, ammonium formate (216 mg, 4.59 mmol), and 10% Pd/C (200 mg) to afford 265 mg (100%) of product. ¹H NMR (300 MHz, CDCl₃) δ 1.45 (s, 9H), 2.43 (m, 1H), 2.50-2.57 (m, 1H), 2.59-2.66 (m, 1H), 2.89 (m, 1H), 3.01 (m, 1H), 3.24 (m, 1H), 3.41 (s, 3H), 3.67 (m, 1H), 4.71 (m, 1H).

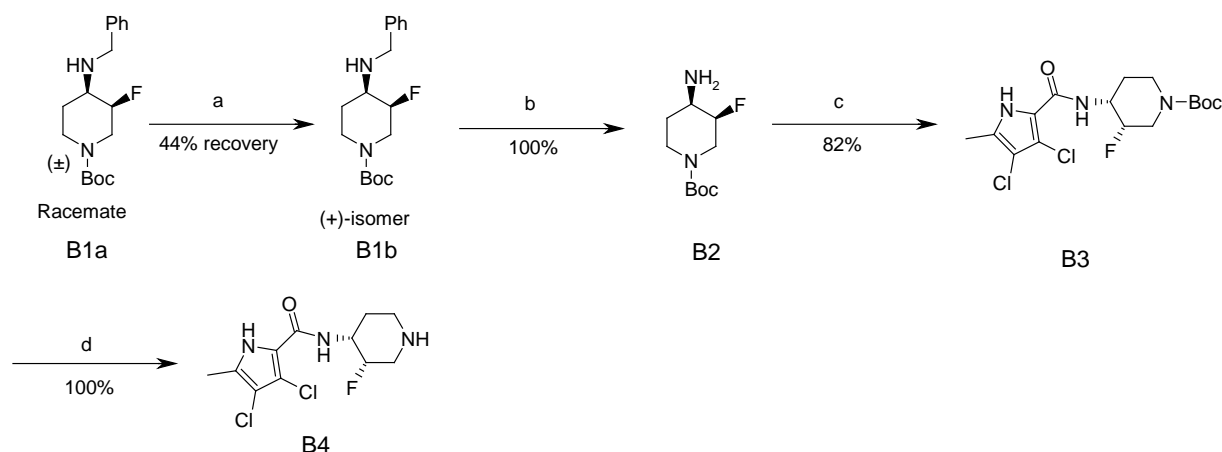
Methyl 2-[(3*R*,4*R*)-4-(*tert*-butoxycarbonylamino)-3-methoxy-1-piperidyl]thiazole-5-carboxylate (A9)

Made as described for *ent*-**A9** from 65 mg (0.28 mmol) **A8**, 73 mg (0.28 mmol) methyl 2-bromothiazole-5-carboxylate and 34 μl (0.28 mmol) Et₃N to afford 100 mg (96%) of product. MS (ESI) *m/z* (*M*+Na)⁺: 394 for C₁₆H₂₅N₃O₅S; ¹H NMR (300 MHz, CDCl₃) δ 1.46 (s, 9H), 1.66 (m, 1H), 1.89 (m, 1H), 2.29 (m, 1H), 3.13-3.20 (m, 3H), 3.47 (s, 3H), 3.75 (m, 1H), 3.83 (s, 3H), 4.20 (m, 1H), 4.60 (br. s, 1H), 7.85 (s, 1H).

Methyl 2-[(3*S*,4*S*)-4-amino-3-methoxypiperidin-1-yl]-1,3-thiazole-5-carboxylate hydrochloride salt (A10) 4 N HCl in dioxane (0.26 ml) was added to **A9** (98 mg) in 1 ml dioxane, and the mixture was stirred at rt for 90 min. Solids that precipitated were collected by filtration and dried in vacuo to afford 72 mg of the title compound, which was used without further purification in the next step. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.63 (m, 1H), 2.08 (d, 1H), 2.97-3.01 (m, 1H), 3.21-3.24 (m, 2H), 3.25 (m, 2H), 3.40 (s, 3H), 3.73 (s, 3H), 3.88 (d, 1H), 4.34 (m, 1H), 7.87 (s, 1H), 8.28 (brs, 3H).

Methyl 2-[(3*S*,4*S*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylate (ester of **25 from main text)** Made as described for the ester of **5** with 72 mg (0.21 mmol) of **A10**, 41 mg (0.21 mmol) of the 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid, 28 mg (0.21 mmol) of HOBt, 72 mg (.376 mmol) of EDC and 0.10 ml (0.941 mmol) of NNM to afford 45 mg of the title compound as a white solid. MS (ESI) *m/z* (*M*+H)⁺: 447 for C₁₇H₂₀Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.71 (m, 1H), 1.93 (m, 1H), 2.18 (s, 3H), 3.24-3.28 (m, 2H), 3.31 (s, 3H), 3.75 (s, 3H), 3.79 (m, 1H), 4.02-4.11 (m, 2H), 7.35 (d, 1H), 7.88 (s, 1H), 12.00 (s, 1H).

Supplementary Scheme B. Intermediates to Compound 2



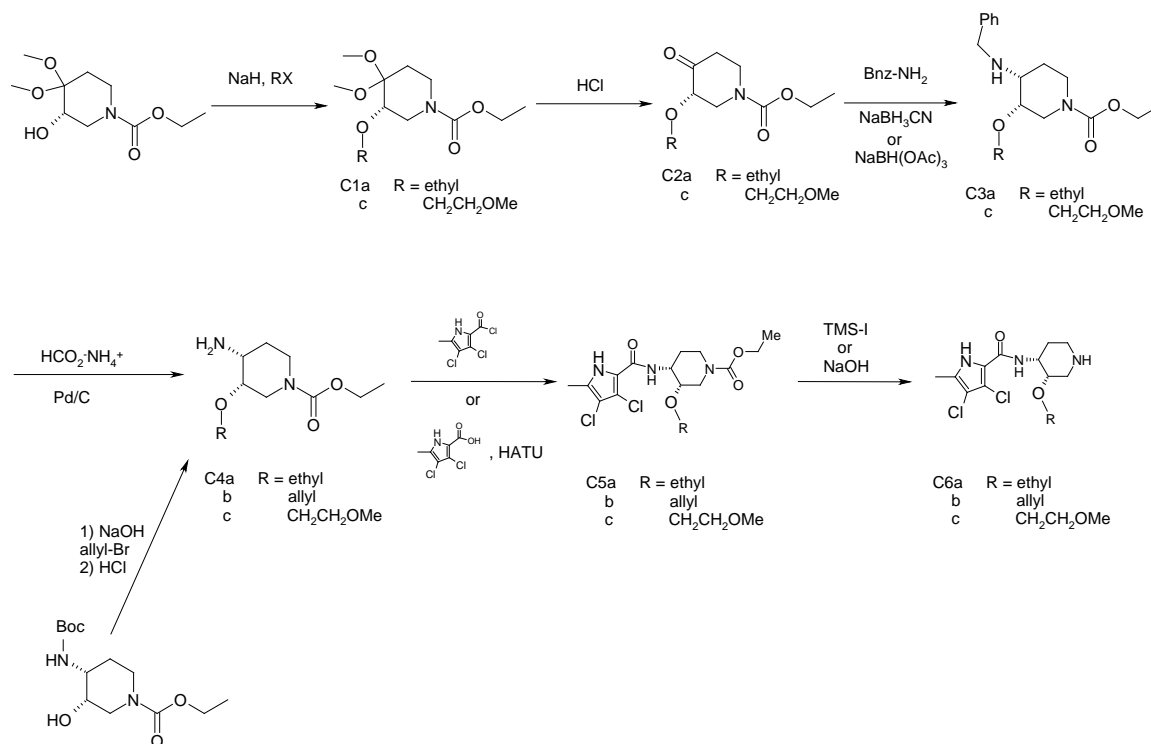
Scheme 2. Reagents and conditions: (a) Chiral chromatography - Chiralpak AD column (b) $\text{HCO}_2\text{-NH}_4^+$; Pd/C (c) HATU, NMM, EDC (d) HCl, dioxane

***tert*-Butyl (3*S*,4*R*)-4-(benzylamino)-3-fluoropiperidine-1-carboxylate and *tert*-butyl-(3*R*,4*S*)-4-(benzylamino)-3-fluoropiperidine-1-carboxylate (B1b)** *tert*-Butyl (3*S*,4*R*)-*rel*-4-(benzylamino)-3-fluoropiperidine-1-carboxylate³ (2.2 g) was separated into the enantiomers by chromatography over a Chiralpak AD column (eluent: hexanes/MeOH/EtOH; 95/2.5/2.5; 0.1% diethylamine). The fractions corresponding to the first chromatographic peak ((+)-isomer) were collected to afford the first title compound as a white solid (942 mg). The fractions corresponding to the second chromatographic peak ((-) isomer) were collected to yield the second compound (B1b) as a white solid (980 mg). ¹H NMR (300 MHz, CDCl₃) δ 1.40 (s, 9H), 1.88 (m, 2H), 3.01 (m, 2H), 3.55 (m, 2H), 3.77 (m, 1H), 4.66 (d, 1H).

***tert*-Butyl (3*R*,4*S*)-4-amino-3-fluoropiperidine-1-carboxylate (B2)** A mixture of 988 mg (3.2 mmol) the preceding compound B1b, 808 mg (12.8 mmol) ammonium formate and 200 mg 10% Pd on carbon in MeOH was heated at reflux for 30 min. The mixture was filtered through Celite®, and solvent was removed from the filtrate to afford 697 mg (100%) of the title compound as a solid. ¹H NMR (300 MHz, CDCl₃) δ 1.40 (s, 9H), 1.88 (m, 2H), 3.01 (m, 2H), 3.55 (m, 2H), 3.77 (m, 1H), 4.66 (d, 1H).

***tert*-Butyl (3*R*,4*S*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonylamino]-3-fluoropiperidine-1-carboxylate (B3)** A solution of 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid¹ (592 mg, 3.05 mmol), the preceding compound B2 (666 mg, 3.05 mol), HOBt (412 mg, 3.05 mmol) and NMM (1.17 ml, 10.7 mmol) were combined in CH₂Cl₂ (15 ml) and stirred under N₂ for 15 min. EDC (1.05 g, 5.49 mmol) was added in one portion, and the reaction was stirred at rt overnight. The reaction mixture was diluted with CH₂Cl₂ and water. The organic phase was separated and washed with 10% HCl, aq. NaHCO₃ and brine. Drying (Na₂SO₄), and gave material that was chromatographed on silica gel (1.25:1 EtOAc-hexanes) to give 939 mg (82%) of the title compound as a solid MS (ESI) m/z (M-H)⁻: 374, 376 for C₁₆H₂₃Cl₂N₃O₃. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.16 (s, 9H); 1.20 (m, 2H); 1.53 (m, 2H); 1.93 (s, 3H); 2.65 (m, 2H); 3.65 (m, 3H); 6.97 (d, 1H); 11.72 (s, 1H). MS (ES) (M + Na): 416, 418 for C₁₆H₂₂Cl₂FN₃O₃.

3,4-Dichloro-*N*-[(3*R*,4*S*)-3-fluoropiperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide hydrochloride (B4) A solution of 4 N HCl in dioxane (2.85 ml, 11.4 mmol) was added to a solution of the preceding compound B3 (1.5 g, 3.8 mmol) in 15 ml dioxane. After stirring overnight, precipitated solids were collected by filtration and dried in vacuo to afford 1.25 g (100%) of the title compound. MS (ESI) m/z (M+H)⁺: 294, 296 for C₁₁H₁₄Cl₂FN₃O; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.85-2.05 (m, 2H) 2.2 (s, 3H) 3.0-3.2 (m, 1H) 3.25 – 3.3 (m, 1H) 3.4-3.5 (m, 1H) 3.57 (s, 3H) 3.5-3.6 (m, 2H) 4.14-4.49 (m, 1H) 5.04 (d, *J* = 48 Hz, 1H) 7.58 (d, *J* = 6 Hz, 1H) 8.75 (br. s, 1H) 9.4 (br. s, 1H) 12.3 (s, 1H).



Ethyl 3-ethoxy-4,4-dimethoxy-piperidine-1-carboxylate (C1a) NaH (668 mg, 27.9 mmol, 60% dispersion) was added portionwise to a solution of 5.0 g (21.4 mmol) ethyl 3-hydroxy-4,4-dimethoxy-piperidine-1-carboxylate⁴ in 100 ml THF cooled 0 °C under an atmosphere of N₂. After 15 min stirring, 1.9 ml (23.6 mmol) ethyliodide was added, and the resulting solution was warmed to rt and stirred overnight. The reaction was incomplete by TLC, and 300 mg NaH and 90 μl ethyliodide were added sequentially. After 2H, the mixture was quenched with water and extracted with EtOAc. The EtOAc was washed with sat. aq. NaHCO₃ and water before being dried (MgSO₄) and concentrated. The residue was added chromatographed on silica gel (1:1 EtOAc-hexanes) to give the title compound as an oil (3.55 g, 69%). MS (ESI) m/z (M+H)⁺: 247 for C₁₁H₂₁NO₅. ¹H NMR (300 MHz, CDCl₃) δ 1.24 (t, 3H), 1.72-1.83 (m, 2H), 2.82 (m, 2H), 2.98 (t, 1H), 3.20 (s, 3H), 3.21 (s, 3H), 3.41 (s, 3H), 4.10 (q, 2H), 4.20-4.37 (m, 2H).

Ethyl 3-ethoxy-4-oxo-piperidine-1-carboxylate (C2a) A solution of 3.55 g (13.5 mmol) of the preceding compound C1a and 10 ml 10% H₂SO₄ in 60 ml THF was heated at reflux for 1.5 h. THF solvent was removed and the aq mixture was neutralized by addition of sat. aq. NaHCO₃ before being extracted with EtOAc. The EtOAc was washed with water and brine, dried (MgSO₄) and concentrated to give 2.55 g (87%) of the title compound. MS (ESI) m/z (M+H)⁺: 238 for C₁₀H₁₇NO₄-Na adduct; ¹H NMR (300 MHz, CDCl₃) δ 1.09 (t, 3H); 1.20 (t, 3H); 2.31 (m, 1H); 3.12 (br s, 1H); 3.45 (m, 1H); 3.59 (m, 1H); 3.94 (m, 2H); 4.03-4.11 (m, 4H).

Ethyl (3*S*,4*R*)-*rel*-4-(benzylamino)-3-ethoxy-piperidine-1-carboxylate (C3a) NaBH₃CN (2.8 g, 13.2 mmol) was added to a solution of 1.89 g (8.79 mmol) of the preceding compound C2a and benzylamine (1.05 ml, 9.66 mmol) in 20 ml CH₂Cl₂, and the mixture was stirred at rt for 3H. The mixture was quenched with sat. aq. NaHCO₃ and extracted with CH₂Cl₂. The CH₂Cl₂ was dried (MgSO₄) and concentrated, and the residue was chromatographed on silica gel (2:1 EtOAc-hexanes) to give 2.24 g (83%) of the title compound as an oil. MS (ESI) m/z (M+H)⁺: 307 for C₁₇H₂₆N₂O₃; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.15-7.45 (m, 5H), 3.9-4.1 (q, 2H), 3.6-3.8 (m, 3H), 3.5-3.6 (m, 1H), 3.45-3.5 (m, 1H), 2.9-3.0 (m, 2H), 2.6-2.7 (m, 1H), 1.50 (m, 2H), 1.16 (t, J=7.06 Hz, 3H), 1.09 (t, J=6.88 Hz, 3H).

Ethyl (3*S*,4*R*)-*rel*-4-amino-3-ethoxy-piperidine-1-carboxylate (C4a) A mixture of preceding compound (**C3a**) (2.24 g, 7.3 mmol), ammonium formate (1.84 g, 29 mmol) and 10% Pd/C (610 mg) in MeOH (40 ml) was heated at reflux for 2H. The reaction mixture was cooled to rt, filtered through diatomaceous earth and concentrated under reduced pressure to give the title compound (1.24 g, 100%) used subsequently without further purification. MS (ESI) m/z ($M+H$)⁺: 217 for C₁₀H₂₀N₂O₃; ¹H NMR (300 MHz, DMSO-*d*₆) δ 4.00 (q, $J=7.16$ Hz, 2H), 3.65-3.93 (m, 2H), 3.50-3.3 (m, 1H), 3.35-3.4 (m, 2H), 2.9-3.0 (m, 1H), 2.8-2.9 (m, 3H), 1.3-1.5 (m, 2H), 1.16 (t, $J=7.06$ Hz, 3H), 1.10 (t, $J=6.88$ Hz, 3H), 0.94 (d, $J=6.03$ Hz, 1H).

Ethyl (3*R*,4*S*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-ethoxy-piperidine-1-carboxylate (C5a) A solution 884 mg (4.16 mmol) 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl chloride (**E4**) was added to a solution of 0.9 g (4.16 mmol) of the preceding compound **C4a** in 12 ml pyridine, the resulting mixture was stirred at rt overnight. Solvent was removed, and the residue was partitioned between water and CH₂Cl₂. The organic phase was separated, washed with water and brine, dried (MgSO₄) and concentrated. The residue was chromatographed on silica gel (25-100% gradient EtOAc in hexanes) to afford 360 mg (22%) of the title compound as a solid. MS (ESI) m/z ($M+H$)⁺: 392, 944 for C₁₆H₂₃Cl₂N₃O₄; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.15 (s, 1H), 7.11 (d, $J=8.10$ Hz, 1H), 4.1-4.3 (m, 2H), 4.0-4.1 (m, 2H), 3.95-4.05 (m, 1H), 3.6-3.8 (m, 1H), 3.5 (m, 1H), 2.7-3.1 (m, 2H), 2.18 (s, 3H), 1.5-1.7 (m, 2H), 1.18 (t, $J=7.06$ Hz, 3H), 1.05-1.15 (m, 3H).

N-[(3*S*,4*R*)-*rel*-3-Ethoxy-4-piperidyl]-3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamide (C6a) A solution of (324 mg, 0.83 mmol) of the previous compound **C5a** and 0.35 ml (2.5 mmol) trimethylsilyl iodide in 10 ml CH₃CN was heated at reflux for 1.5 h. The reaction mixture was quenched with sat. aq. NaHCO₃ and diluted with EtOAc. The organic layer was separated, washed with aq. NaHSO₃ and dried (MgSO₄). Removal of solvent afforded the title compound (238 mg, 89%) as a solid that was used in subsequently without further purification. MS (ESI) m/z ($M+H$)⁺: 320, 322 for C₁₃H₁₉Cl₂N₃O₂; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.0 (br. s, 1H), 7.09 (d, $J=8.29$ Hz, 1H), 4.0 (m, 1H), 3.5-3.75 (m, 1H), 3.16 (m, 1H), 3.05 (m, 1H), 2.83 (m, 1H), 2.5-2.6 (m, 1H), 1.5-1.6 (m, 2H), 1.13 (t, $J=6.97$ Hz, 3H).

Ethyl (3*S*,4*R*)-*rel*-4-(*tert*-butoxycarbonylamino)-3-allyloxy-piperidine-1-carboxylate A mixture of a 50% aq solution of sodium hydroxide (3 ml), allyl bromide (693 mg, 5.70 mmol), cis(±)ethyl 4-[(*tert*-butoxycarbonyl)amino]-3-hydroxypiperidine-1-carboxylate⁵ (750 mg, 2.6 mmol), benzyltriethylammonium chloride (4 mg) and toluene (8 ml) was stirred overnight at rt. The reaction mixture was diluted with EtOAc (150 ml) and water (35 ml). The organic phase was separated, and the aq phase was back extracted with EtOAc (2 times). The combined organic phases were washed with brine, dried (Na₂CO₃) and concentrated. The residue was chromatographed on silica gel (hexane/EtOAc, 3:2) to give 734 mg of the title compound. MS (ESI) m/z ($M+H$)⁺: 329 for C₁₆H₂₈N₂O₅; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.28 (t, 3H), 1.47 (s, 9H), 1.68 (m, 2H), 2.88 (m, 2H), 3.50 (m, 1H), 3.68 (m, 1H), 3.90 (m, 1H), 4.00-4.45 (m, 3H), 4.10 (q, 2H), 4.92 (br. s, 1H), 5.20 (m, 2H), 5.86 (m, 1H).

Ethyl (3*S*,4*R*)-*rel*-4-amino-3-allyloxy-piperidine-1-carboxylate (C4b) 4*N* HCl/dioxane (20 ml) was added to the preceding compound (572 mg, 1.74 mmol). The mixture was stirred at rt for 90 min. The solvent was removed to give the title compound as an oily foam which was used without further purification (449 mg). MS (ESI) m/z ($M+H$)⁺: 229 for C₁₁H₂₀N₂O₃; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.18 (br. s, 3H), 5.78-6.03 (m, 1H), 5.30 (dd, $J=1.70, 17.33$ Hz, 1H), 5.15 (d, $J=9.80$ Hz, 1H), 3.86-4.33 (m, 7H), 3.70 (m, 1H), 2.74-3.03 (m, 2H), 1.66 (m, 2H), 1.17 (t, $J=7.16$ Hz, 3H).

Ethyl (3*R*,4*S*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-allyloxy-piperidine-1-carboxylate (C5b) A solution of 1.06 g (2.78 mmol) of HATU, 1.05 ml (7.5 mmol) Et₃N and 492 mg (2.53 mmol) of 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid¹ in 8 ml DMF was stirred at rt for 15 min before addition of 670 mg (2.53 mmol) of the previous compound **C4b** and stirring overnight. The mixture was diluted with EtOAc and washed with aq Na₂CO₃ and brine. Drying (MgSO₄) and removal of solvent gave an oil that was purified by chromatography (3% MeOH in CH₂Cl₂) to afford 480 mg (42%) of the title compound. MS (ESI) m/z ($M+H$)⁺: 402, 404 for C₁₇H₂₃Cl₂N₃O₄; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.15 (s, 1H), 7.12 (d, $J=8.48$ Hz, 1H), 5.70-6.09 (m, 1H), 5.27 (dd, $J=1.70, 17.14$ Hz, 1H), 5.14 (d,

$J=10.17$ Hz, 1H), 4.15 (m, 3H), 3.84-4.07 (m, 4H), 3.55 (m, 1H), 2.78-3.06 (m, 2H), 2.17 (s, 3H), 1.53-1.72 (m, 2H), 1.17 (t, $J=7.06$ Hz, 3H).

***N*-(3*S*,4*R*)-*rel*-3-Allyloxy-4-piperidyl]-3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamide (C6a)** A solution of the previous compound, C5b, (480 mg, 1.2 mmol) and 0.51 ml (3.3 mmol) trimethylsilyl iodide in 15 ml CH₃CN was heated at 80 °C for 2H. The reaction mixture was treated with aq NaHSO₃, diluted with EtOAc and extracted 5X with 1 N HCl. The combined aq layers were basified with aq. Na₂CO₃ and extracted 3X with EtOAc. The combined EtOAc extracts were washed with brine, dried (MgSO₄) and concentrated to afford the title compound (310 mg, 89%) as solid that was used in subsequently without further purification. MS (ESI) m/z ($M+H$)⁺: 290, 292 for C₁₂H₁₇Cl₂N₃O.

ethyl 4,4-dimethoxy-3-(2-methoxyethoxy)piperidine-1-carboxylate (C1c) NaH (835 mg, 33 mmol, 60% dispersion) was added portionwise to a solution of 5.14 g (22 mmol) ethyl 3-hydroxy-4,4-dimethoxy-piperidine-1-carboxylate⁴ in 30 ml DMF cooled 0 °C under an atmosphere of N₂. After 1.5 h of stirring, 0.68 ml (23.6 mmol) of 2-bromoethyl methyl ether was added, and the resulting mixture was stirred at rt overnight. The mixture was treated with water and extracted with EtOAc. The EtOAc was washed with brine, dried (MgSO₄) and concentrated to afford 6.4 g of an oil that was used in the subsequent step without purification. ¹H NMR (300 MHz, DMSO-*d*₆) δ 4.12 (m, 1H), 3.9-4.0 (m, 2H), 3.82 (m, 2H), 3.55-3.71 (m, 2H), 3.42 (m, 1H), 3.2 (s, 3H), 3.1(2s, 6H), 1.6-1.76 (m, 2H), 1.17 (t, $J=6.97$ Hz, 3H).

Ethyl 3-(2-methoxyethoxy)-4-oxo-piperidine-1-carboxylate (C2c) A solution of 6.4 g (22 mmol) of the preceding compound C1c and 10 ml 10% H₂SO₄ in 60 ml THF was heated at reflux for 1.5 h. THF solvent was removed and the aq mixture was neutralized by addition of sat. aq. NaHCO₃ before being extracted with EtOAc. The EtOAc was washed with water and brine, dried (MgSO₄) and concentrated to give 5.4 g (92%) of the title compound. MS (ESI) m/z ($M+Na$)⁺: 268 for C₁₁H₁₉NO₅-Na adduct; ¹H NMR (300 MHz, DMSO-*d*₆) δ 4.05-4.15 (m, 2H), 3.98 (m, 1H), 3.7-3.8 (m, 1H), 3.5-3.6 (m, 1H), 3.4 (m, 2H), 3.24 (s, 3H), 2.2-2.4 (m, 1H), 1.21 (t, $J=7.06$ Hz, 3H).

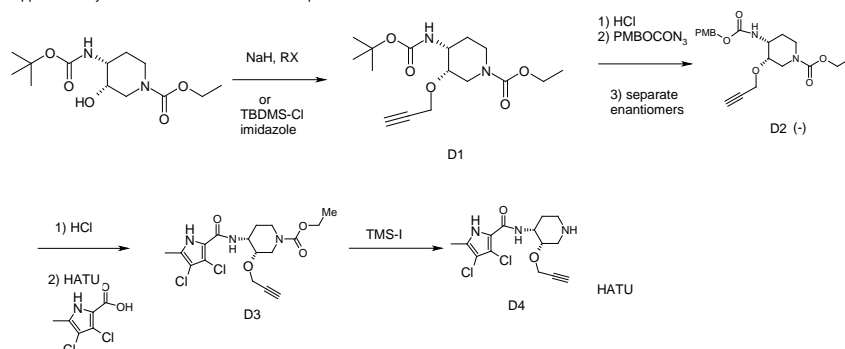
Ethyl (3*S*,4*R*)-*rel*-4-(benzylamino)-3-(2-methoxyethoxy)piperidine-1-carboxylate (C3c) NaBH(OAc)₃ (7.0 g, 330 mmol) was added to a solution of 5.42 g (22 mmol) of the preceding compound C2c and benzylamine (2.65 ml, 24 mmol) in 60 ml CH₂Cl₂ and the mixture was stirred at rt for 2.5 h. The mixture was quenched with sat. aq. NaHCO₃ and extracted with CH₂Cl₂. The CH₂Cl₂ was dried (MgSO₄) and concentrated, and the residue was chromatographed on silica gel (2:1 EtOAc-hexanes) to give 5.1 g (67%) of the title compound as an oil. MS (ESI) m/z ($M+H$)⁺: 337 for C₁₈H₂₈N₂O₄; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.1-7.4 (m, 5H), 4.0-4.1 (m, 2H), 3.6-3.8 (m, 3H), 3.5 (m, 1H), 3.44 (m, 2H), 3.23 (s, 3H), 2.85-3.0 (m, 2H), 2.7 (m, 1H), 1.50 (m, 2H), 1.09-1.22 (t, 3H).

Ethyl (3*S*,4*R*)-4-amino-3-(2-methoxyethoxy)piperidine-1-carboxylate (C4c) A mixture of the preceding compound C3c (5.1 g, 22 mmol), ammonium formate (4.5 g, 71 mmol) and 10% Pd/C (1.4 g) in MeOH (50 ml) was heated at reflux for 2H. The reaction mixture was cooled to rt, filtered through diatomaceous earth and concentrated under reduced pressure to give the title compound (1.24 g, 100%) used subsequently without further purification. MS (ESI) m/z ($M+H$)⁺: 247 for C₁₁H₂₂N₂O₄; ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.78 (q, $J=6.97$ Hz, 2H), 3.3-3.5 (m, 1H), 3.2-3.3 (m, 2H), 3.1 (m, 3H), 2.95 (s, 3H), 2.7-2.9 (m, 2H), 1.2 (m, 2H), 0.94 (t, $J=6.97$ Hz, 3H).

Ethyl (3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-(2-methoxyethoxy)piperidine-1-carboxylate (C5c) A mixture of HATU (4.79 g, 12.6 mmol), DIEA (2.1 ml, 12.6 mmol) and 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid¹ (2.44 g, 12.6 mmol) in 25 ml anhydrous DMF was stirred at ambient for 15 min. The preceding compound (3.1 g, 12.6 mmol) was added and the mixture was stirred at ambient temperature for 18 h. The mixture was diluted with EtOAc and washed with water and brine. Drying (MgSO₄) and removal of solvent gave an oil that was purified by chromatography (5% MeOH in CH₂Cl₂) to afford a solid that was triturated with acetone to afford the title compound (2.05 g, 39%). MS (ESI) m/z ($M+H$)⁺: 422, 424 for C₁₇H₂₅Cl₂N₃O₅; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.2 (s, 1H), 7.21 (d, $J=7.35$ Hz, 1H), 4.2-4.4 (m, 1H), 4.1-4.29 (m, 1H), 4.09 (q, $J=7.10$ Hz, 2H), 3.95-4.05 (m, 1H), 3.7-3.8 (m, 1H), 3.55-3.65 (m, 2H), 3.45-3.55 (m, 2H), 3.27 (s, 3H), 2.8-3.1 (m, 2H), 2.24 (s, 3H), 1.5-1.75 (m, 2H), 1.24 (t, $J=7.06$ Hz, 3H).

3,4-Dichloro-*N*-[(3*S*,4*R*)-3-(2-methoxyethoxy)-4-piperidyl]-5-methyl-1*H*-pyrrole-2-carboxamide (C6c) A mixture of 1.24 g (2.85 mmol) of the preceding compound **C5c** and 65 ml of 1 N NaOH in 50 ml water were heated at reflux for 3 d. The mixture was diluted with EtOAc and washed with water. The EtOAc layer was dried (MgSO₄) and concentrated to afford 0.99 g (80%) of the title compound used subsequently without further purification. MS (ESI) *m/z* (*M*+*H*)⁺: 350, 352 for C₁₄H₂₁Cl₂N₃O₃; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.19 (d, *J*=8.10 Hz, 1H), 4.09-4.28 (m, 1H), 3.7-3.8 (m, 1H), 3.5-3.6 (m, 1H), 3.53 (m, 2H), 3.44-3.49 (m, 1H), 3.35-3.43 (m, 1H), 3.28 (s, 3H), 3.1-3.2 (m, 1H), 2.85-2.93 (m, 1H), 2.63 (m, 1H), 2.24 (s, 3H), 1.52-1.71 (m, 2H).

Supplementary Scheme D - Intermediates to Compound **30**



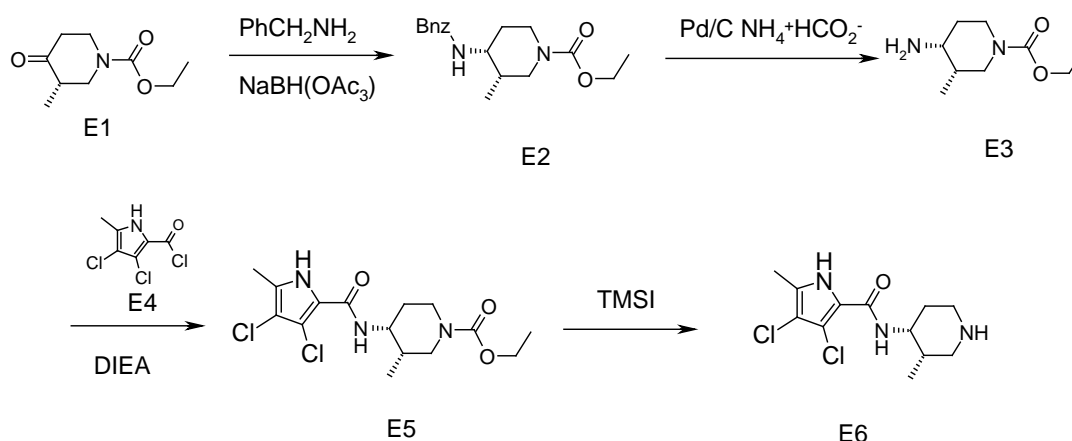
Ethyl (3*S*,4*R*)-*rel*-4-(tert-butoxycarbonylamino)-3-prop-2-ynoxy-piperidine-1-carboxylate (D1) A mixture of 3.2 g (11 mmol) of ethyl (3*R*,4*S*)-4-(tert-butoxycarbonylamino)-3-hydroxy-piperidine-1-carboxylate, ⁵ 1.85 ml (16.6 mmol) propargyl bromide, 8 ml 50% aq. NaOH and 5 mg benzyltrimethylammonium chloride in 50 ml toluene was stirred at rt overnight. The mixture was diluted with EtOAc and washed with water and brine. Drying (MgSO₄) and removal of solvent gave an oil that was chromatographed on silica gel (5-60% EtOAc in hexanes gradient) to afford 3.1 g (86%) of the title compound. MS (ESI) *m/z* (*M*+*H*)⁺: 327; ¹H NMR (300 MHz, CDCl₃) δ 1.26 (t, 3H); 1.45 (s, 9H); 1.67 (m, 2H); 2.43 (t, 1H); 2.79 (m, 2H); 3.74 (m, 2H); 4.00-4.45 (m, 6H); 5.00 (s, 1H).

Ethyl (3*S*,4*R*)-4-[(4-methoxyphenyl)methoxycarbonylamino]-3-prop-2-ynoxy-piperidine-1-carboxylate (D2) A solution of 3.1 g (9.5 mmol) of the previous compound **D1** and 4 ml of 4 N HCl in dioxane in 4 ml dioxane was stirred at rt for 4 h. Solvent was removed to afford 2.14 g (100%) of amine intermediated as the hydrochloride salt. A mixture of 2.04 g (7.73 mmol) of the amine HCl salt, 1.76 g of 4-methoxybenzyloxycarbonyl azide 1.76 g (8.5 mmol) and 1.43 g (17 mmol) NaHCO₃ in 50 ml dioxane and 20 ml water was stirred for 2H. The mixture was diluted with EtOAc and washed with water. The organic layer was dried (MgSO₄) and concentrated, and the residue was chromatographed by chiral (Chiralpak AD column) HPLC to separate the 2 enantiomers. The second eluting peak (+)- isomer correlated with the desired stereochemistry (1.2 g, 40%). MS (ESI) *m/z* (*M*+*H*)⁺: 391 for C₂₀H₂₆N₂O₆; ¹H NMR (300 MHz, CDCl₃) δ 7.31 (d, *J*=8.67 Hz, 2H), 6.89 (d, *J*=8.67 Hz, 2H), 5.20 (br. s., 1H), 5.03 (s, 2H), 4.05-4.35 (m, 6H), 3.81 (s, 3H), 3.70-3.8 (m, 2H), 2.80 (m, 2H), 2.35 (m, 1H), 1.70 (m, 2H), 1.25 (t, *J*=7.06 Hz, 3H).

Ethyl (3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-prop-2-ynoxy-piperidine-1-carboxylate (D3) A solution of 1.18 g (3.02 mmol) of the previous compound (**D2**) in 5 ml of 4 N HCl in dioxane was stirred at rt for 4 h. Solvent was removed and the residue was dissolved in 5 ml DMF. Added sequentially were 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (586 mg, 3 mmol), Et₃N (6 mmol) and HATU (1.14 g, 3 mol), and the mixture was stirred at rt overnight. The mixture was diluted with water and solids precipitated. The solids were collected by filtration and chromatographed on silica gel (20-60% EtOAc in hexanes gradient) to afford 480 mg of the title compound. MS (ESI) *m/z* (*M*+*H*)⁺: 402, 404 for C₁₇H₂₁Cl₂N₃O₄; ¹H NMR (300 MHz, CDCl₃) δ 9.53 (s, 1H), 4.3-4.6 (m, 2H), 4.0-4.3 (m, 6H), 3.8-3.9 (m, 1H), 2.9 (m, 2H), 2.40 (t, *J*=2.35 Hz, 1H), 2.27 (s, 3H), 1.7-1.9 (m, 2H), 1.27 (t, *J*=7.16 Hz, 3H).

3,4-Dichloro-5-methyl-N-[(3*S*,4*R*)-3-prop-2-yloxy-4-piperidyl]-1*H*-pyrrole-2-carboxamide (D4) A solution of (450 mg, 1.1 mmol) the previous compound **D3** and 0.24 ml (1.7 mmol) trimethylsilyl iodide in 5 ml CH₃CN was heated at reflux for 3H. The reaction mixture was diluted with EtOAc-THF (3:1) and washed with aq. NaHSO₃, aq. NaHCO₃ and brine. Drying (Na₂SO₄) of the organic layer and removal of solvent gave 330 mg (91%) of the title compound subsequently without further purification. MS (ESI) *m/z* (M+H)⁺: 330, 332 for C₁₄H₁₇Cl₂N₃O₂.

Supplementary Scheme E - Intermediates to Compound **32**



Ethyl (3*S*,4*R*)-rel-4-(benzylamino)-3-methyl-piperidine-1-carboxylate (E2) A solution of 0.71 g (3.8 mmol) ethyl 3-methyl-4-oxopiperidine-1-carboxylate ⁶ **E1**, 0.46 ml (4.3 mmol) benzylamine and 1.2 g (5.7 mmol) NaBH(OAc)₃ in 30 ml CH₂Cl₂ was stirred at rt for 3H. The mixture was treated with aq. 1 N HCl and partitioned between EtOAc and aq. Na₂CO₃. The EtOAc was separated, washed with brine, dried (MgSO₄) and concentrated. The residue was purified by reverse phase HPLC (10-50% gradient of CH₃CN in H₂O with 0.1% TFA) to afford 2 components. The major component was consistent with the title compound. MS (ESI) *m/z* (M+H)⁺: 277 for C₁₆H₂₄N₂O₂; ¹H NMR (300 MHz, CDCl₃) δ 0.9 (d, 3H), 1.2 (t, 3H), 1.6 (m, 2H), 2.0 (m, 1H), 2.8 (m, 1H), 2.9-3.2 (m, 2H), 3.7 (m, 1H), 3.8 (s, 2H), 4.1 (m, 2H), 7.2-7.4 (m, 5H).

Ethyl (3*S*,4*R*)-rel-4-amino-3-methyl-piperidine-1-carboxylate (E3) A solution of **E2** (480 mg, 1.8 mmol), ammonium formate (465 mg, 7.4 mmol), and 10% Pd/C (200 mg) in MeOH (20 ml) was heated at reflux for 1H. The reaction mixture was cooled to rt, filtered through diatomaceous earth and concentrated under reduced pressure to give the title compound (130 mg, 39%). ¹H NMR (300 MHz, CDCl₃) δ 0.9 (d, 3H), 1.2 (t, 3H), 1.5 (m, 2H), 1.6 (m, 1H), 2.2 (s, broad, 2H), 3.0 (m, 1H), 3.2 (m, 2H), 3.4 (m, 1H), 4.0-4.2 (m, 2H).

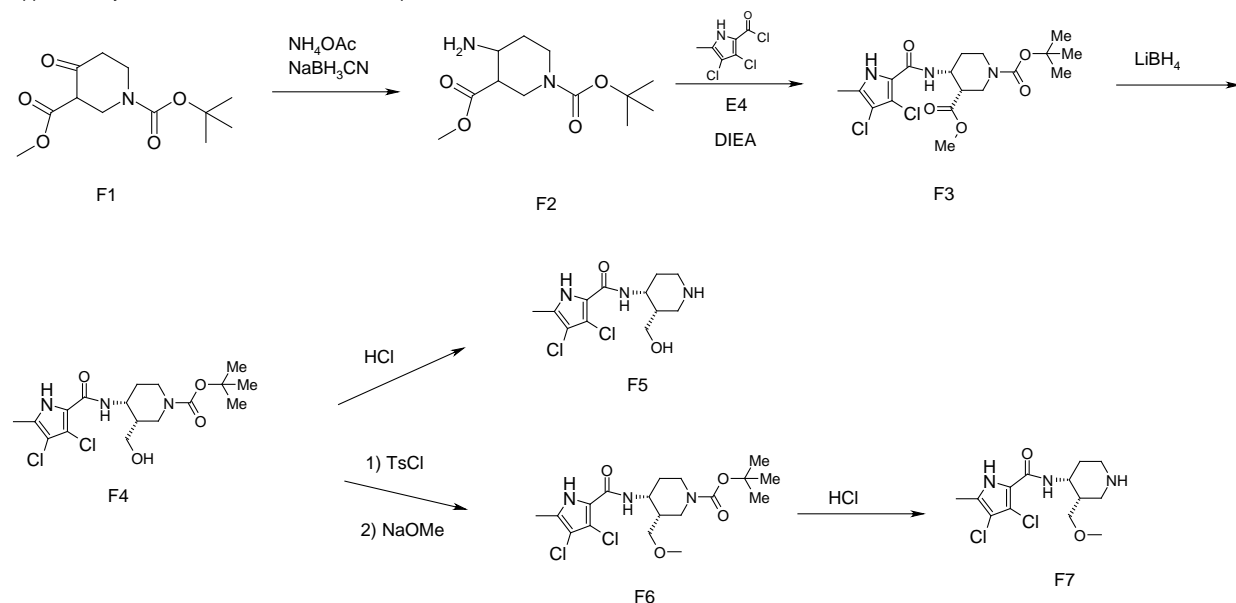
3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl chloride (E4) A solution of 10.4 g (54 mmol) of 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid¹ in 100 ml SOCl₂ was heated at reflux for 30 min. Solvent was removed to afford product. ¹H NMR (300 MHz, CDCl₃) δ 2.3 (s, 1H), 8.8 (s, 1H).

Ethyl (3*S*,4*R*)-rel-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxyl)amino]-3-methyl-piperidine-1-carboxylate (E5) A solution of 167 mg (0.9 mmol) of **E3**, 235 μl (1.25 mmol) diisopropylethylamine and 280 mg (1.35) of 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxyl chloride, **E4**, was stirred at rt for 1H. The mixture was diluted with EtOAc and washed with aq. Na₂CO₃ and brine. Drying (MgSO₄) and removal of solvent gave an oil that was purified by chromatography (100% CH₂Cl₂ followed by gradient elution to 100% EtOAc) to afford 145 mg of the title compound. MS (ESI) *m/z* (M+H)⁺: 362 for C₁₅H₂₁Cl₂N₃O₃; ¹H NMR (300 Mhz, DMSO-*d*₆) δ 0.8 (d, 3H), 1.2 (t, 3H), 1.65 (m, 2H), 1.9 (m, 1H), 2.2 (s, 3H), 3.5 (m, 1H), 4.0 (m, 2H), 4.1 (m, 1H), 7.1 (d, 1H), 12.0 (s, 1H).

3,4-Dichloro-5-methyl-N-[(3*S*,4*R*)-rel-3-methyl-4-piperidyl]-1*H*-pyrrole-2-carboxamide (E6) A solution of **E5** (143 mg, 0.40 mmol) and 0.22 ml (1.5 mmol) trimethylsilyl iodide in 3 ml CH₃CN was

heated at 80 °C in a microwave reactor for 45 min. The reaction mixture was treated with aq NaHSO₃, diluted with EtOAc and extracted 5X with 1 N HCl. The combined aq layers were basified with aq. Na₂CO₃ and extracted 3X with EtOAc. The combined EtOAc extracts were washed with brine, dried (MgSO₄) and concentrated to afford the title compound (63 mg, 54%) as an oil that was used in subsequently without further purification MS (ESI) m/z (M+H)⁺: 290, 292 for C₁₂H₁₇Cl₂N₃O.

Supplementary Scheme F - Intermediates to Compounds **33** and **34**



O1-tert-Butyl O3-methyl 4-aminopiperidine-1,3-dicarboxylate (F2) NaCNBH₃ (8.1 g, 0.13 mmol) was added in three equal portions at 1 h intervals to a solution of 33 g (0.13 mol) 1-tert-butyl-3-methyl-4-hydroxy-5,6-dihydropyridine-1,3-(2H)-dicarboxylate, **F1**, and NH₄OAc (100 g) in dry MeOH (250 ml). The reaction mixture was stirred at rt overnight. Additional NH₄OAc (2.5 equiv.) and NaCNBH₃ (0.25 equiv.) were added and the mixture was stirred 3 h. The reaction was cooled to -10 °C and acidified to pH 2 with concentrated HCl. Solvent was removed, and the solid residue was dissolved in water, and extracted with Et₂O. The pH of the aq phase was adjusted to 8-9 with solid KOH and the solution saturated with NaCl before being extracted repeatedly with EtOAc. The organic layer was dried (K₂CO₃) and concentrate to afford the title compound (25 g, 74%) as a 1:1 mixture of diastereomers. GC/MS (ES) m/z M⁺: 258 for C₁₂H₂₂N₂O₄; ¹H NMR (300 MHz, CDCl₃) δ 4.2 and 4.1 (2m, 1H), 3.71 and 3.72 (2s, 3H), 3.32-3.58 (m, 1.5H), 3.05 (dt, J=4.14, 10.74 Hz, 0.5H), 2.58-2.87 (m, 1.5H), 2.24 (dt, J=4.33, 10.74 Hz, 0.5H), 1.71-1.93 (m, 1.5H), 1.46 and 1.45 (2d, 9H), 1.20-1.38 (m, 0.5 H).

O1-tert-Butyl O3-methyl (3S,4R)-rel-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]piperidine-1,3-dicarboxylate (F3) A mixture of HATU (25 g, 65.7 mmol), DIEA (31 ml, 186 mmol) and 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylic acid (11.6 g, 60 mmol) in 100 ml anhydrous DMF was stirred at ambient for 15 min. **F2** (15.4 g, 258 mmol) was added and the mixture was stirred at ambient temperature for 18 h. The mixture was concentrated to give a solid that was re-crystallized from EtOAc to afford the title compound (10 g, 35%). MS (ESI) m/z (M+H)⁺: 434, 436 for C₁₈H₂₅Cl₂N₃O₅; ¹H NMR (300 MHz, CDCl₃) δ 1.45 (s, 9H), 2.16 (m, 1H), 2.27 (s, 3H), 2.55 (dt, 1H), 2.93 (m, 1H), 3.09 (m, 2H), 3.66 (s, 3H), 4.08 (m, 1H), 4.29 (m, 2H), 6.68 (d, 1H), 9.66 (s, 1H).

tert-Butyl (3S,4R)-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-(hydroxymethyl)piperidine-1-carboxylate (F4) MeOH (600 µl) was added to a solution of **F3** (4.26 g, 9.79 mmol) and LiBH₄ (321 mg, 15.3 mmol) in dry THF (20 ml). The mixture was heated at reflux for 1 h before cooling to rt, diluting with EtOAc and washing with 0.5% HCl. The organic layer was dried over Na₂SO₄ and concentrated, and the residue was purified by silica gel chromatography (60% EtOAc/40%

hexanes) to afford title compound (3.11 g, 78%). MS (ESI) m/z ($M+H$)⁺: 406 for C₁₇H₂₅Cl₂N₃O₄; ¹H NMR (300 MHz, CDCl₃) δ 1.47 (s, 9H), 1.56 (m, 1H), 1.96 (m, 1H), 2.27 (s, 3H), 2.84 (m, 1H), 2.9 (m, 1H), 3.49 (m, 1H), 3.71 (m, 1H), 4.16 (m, 5H), 6.58 (d, 1H), 10.1 (brs, 1H).

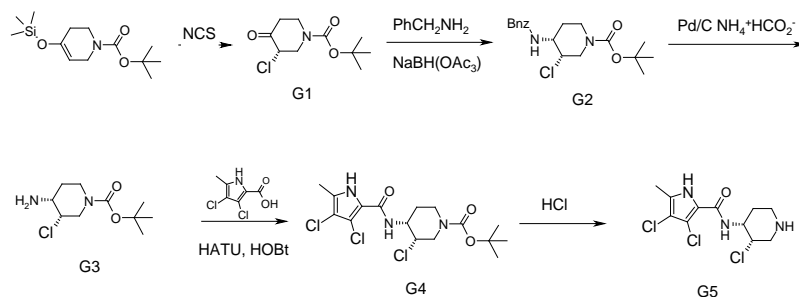
***tert*-Butyl (3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-(*p*-tolylsulfonyloxymethyl)piperidine-1-carboxylate** *p*-TsCl (822 mg, 4.32 mmol) was added in a single portion to a solution of 1.46 g (3.6 mmol) **F4** in dry pyridine (20 ml) cooled at 0 °C. The reaction was allowed to slowly warm to rt and stir overnight. The mixture was diluted with EtOAc and washed with water, dried (Na₂SO₄) and concentrated. The residue was chromatographed on silica gel (3: 2Hexanes-EtOAc) to give title compound (1.58 g, 65%) as a solid. MS (ESI) m/z ($M+H$)⁺: 560 for C₂₄H₃₁Cl₂N₃O₆S; ¹H NMR (300 MHz, CDCl₃) δ 1.46 (br. s, 11H), 1.89 (m, 1H), 1.98 (m, 1H), 2.31 (s, 3H), 2.35 (s, 3H), 2.8 (m, 2H), 3.96-4.23 (m, 4H), 6.4 (d, 1H), 7.19 (d, 2H), 7.68 (d, 2H), 10.3 (br. s, 1H).

***tert*-Butyl (3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-(methoxymethyl)piperidine-1-carboxylate (**F6**)** A solution of the preceding compound (325 mg, 0.58 mmol) and 5 ml of a 30 wt% NaOMe in MeOH and an additional 5 ml of dry MeOH was stirred at rt for 2 d. The reaction mixture was concentrated to a solid residue, re-dissolved in EtOAc and washed with saturated NH₄Cl (2x10 ml). The organic layer was dried (Na₂SO₄) and concentrated. The residual material was purified by silica gel chromatography (1:1 EtOAc / hexanes) to give the title compound (192 mg, 79%). MS (ESI) m/z ($M+H$)⁺: 420 for C₁₉H₂₇Cl₂N₃O₄; ¹H NMR (300 MHz, CDCl₃) δ 10.1 (s, 1H), 6.83 (br. s., 1H), 3.9-4.25 (m, 3H), 3.3-3.5 (m, 2H), 3.28 (s, 3H), 2.87-2.9 (m, 1H), 2.7-2.75 (m, 1H), 2.29 (s, 3H), 2.1-2.2 (m, 1H), 1.7-1.9 (m, 2H), 1.47 (s, 9H)

***tert*-Butyl (3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-(methoxymethyl)piperidine-1-carboxylate hydrochloride salt (**F7**)** A solution of **F6** (192 mg, 0.45 mmol) in 4 N HCl in dioxane (10 ml) and 10 ml of MeOH was stirred at rt for 3H. Solvent was removed and the residue was dissolved in MeOH. Solvent was again removed and the solid residue was dried in vacuo to afford 160 mg (100%) of the title compound, which was used without purification in the subsequent reaction. MS (ESI) m/z ($M+H$)⁺: 320 for C₁₃H₁₉Cl₂N₃O₂.

***tert*-Butyl (3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-(hydroxymethyl)piperidine-1-carboxylate hydrochloride salt (**F5**)** Prepared as described for **F7** from 3.11 g (7.66 mmol) of **F4** and 40 ml 4 M HCl in dioxane to afford 2.61 g (98%) of the title compound. MS (ESI) m/z ($M+H$)⁺: 306, 308 for C₁₂H₁₇Cl₂N₃O₂; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.7 (br. s., 1H), 8.95 (br. s., 2H), 8.01 (d, *J*=7.7 Hz, 1H), 4.65 (br. s., 1H), 4.3-4.4 (m, 1H), 3.45-3.6 (m, 1H), 3.2-3.4 (m, 3H), 3.1-3.2 (m, 2H), 2.20 (s, 3H), 1.8-2.00 (m, 2H).

Supplementary Scheme G - Intermediates to Compound 35



***tert*-Butyl 3-chloro-4-oxo-piperidine-1-carboxylate (**G1**)** A solution of 3.6 g (13.3 mmol) *tert*-butyl 4-trimethylsilyloxy-3,6-dihydro-2*H*-pyridine-1-carboxylate in 10 ml THF was added to a mixture of 2.22 g (16.6 mmol) *N*-chlorosuccinimide and 200 mg NaOAc in 60 ml 1:1 THF-water. After stirring overnight at rt, the mixture was poured into water and extracted with hexanes. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated. The residue was chromatographed on silica gel (5: 1Hexanes-

EtOAc) to afford 1.15 g (37%) of the title compound as an oil. ^1H NMR (300 MHz, DMSO- d_6) δ 4.7-4.8 (m, 1H), 4.1-4.3 (m, 1H), 3.75-4.0 (m, 1H), 3.35-3.6 (m, 2H), 2.55 (m, 2H), 1.44 (s, 9H).

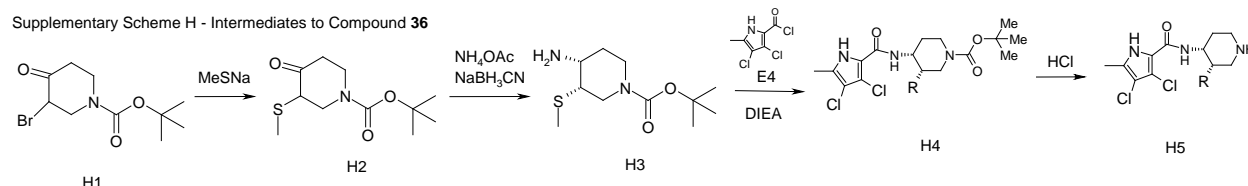
***tert*-Butyl-(3*R*,4*S*)-4-(benzylamino)-3-chloropiperidine-1-carboxylate (G2)** NaBH(OAc) $_3$ (1.56 h, 7.37 mmol) was added to a solution of 1.15 g (4.92 mmol) of the previous compound **G1** and 0.60 ml (5.41 mmol) benzylamine in 20 ml DCE, and the reaction mixture was stirred at rt for 2H. Sat. aq. K $_2$ CO $_3$ was added and the mixture was extracted with EtOAc, which was washed with brine. The organic layer was dried (Na $_2$ SO $_4$) and concentrated. The residue was chromatographed on silica gel (1: 1Hexanes-EtOAc) to afford 1.22 g (76%) of the title compound as a single diastereomer. ^1H NMR (300 MHz, DMSO- d_6) δ 1.39 (s, 9H), 1.54 (m, 2H), 1.93 (m, 1H), 2.80 (m, 2H), 3.20 (m, 1H), 3.75 (q, 2H), 4.06 (m, 1H), 4.57 (s, 1H), 7.22-7.36 (m, 5H).

***tert*-Butyl (3*S*,4*R*)-*rel*-4-amino-3-chloro-piperidine-1-carboxylate (G3)** A mixture of 1.22 g (4.3 mmol) of the previous compound **G2**, 1.06 g (16.8 mmol) ammonium formate and 250 mg 10% Pd on carbon in 10 ml MeOH was degassed by bubbling through nitrogen and heated at reflux for 20 min. The mixture was filtered through diatomaceous earth, and the filtrate was concentrated to afford 836 mg (83%) of the title compound. ^1H NMR (300 MHz, DMSO- d_6) δ 1.39 (s, 9H), 1.45 (m, 1H), 1.58 (m, 2H), 2.95 (m, 1H), 3.31 (m, 1H), 3.82 (m, 1H), 4.03 (m, 1H), 4.26 (m, 1H).

***tert*-Butyl (3*S*,4*R*)-3-chloro-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]piperidine-1-carboxylate (G4)** A solution of 830 mg (3.54 mmol) of the previous compound **G3**, 686 mg (3.54 mmol) of 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid, 1.36 ml (12.4 mmol) NMM and 478 mg (3.54 mmol) HOBt in 15 ml CH $_2$ Cl $_2$ was stirred at rt for 1H before adding 1.22 g (6.37 mmol) EDC. The reaction mixture was stirred overnight and partitioned between CH $_2$ Cl $_2$ and water. The CH $_2$ Cl $_2$ was separated and washed with 10% aq. HCl, sat. aq. NaHCO $_3$, and brine. The CH $_2$ Cl $_2$ was dried (Na $_2$ SO $_4$) and concentrated to give a solid that was triturated with 1: 1Hexanes-EtOAc to afford the title compound (779 mg, 54%) as a white solid. MS (ESI) m/z (M+H) $^+$: 411, 413 for C $_{16}$ H $_{22}$ Cl $_3$ N $_3$ O $_3$; ^1H NMR (300 MHz, DMSO- d_6) δ 12.1 (s, 1H), 7.05 (d, J =7.9 Hz, 1H), 4.58 (m, 1H), 4.3-4.4 (m, 1H), 4.15 (m, 1H), 4.0 (m, 1H), 3.35-3.5 (m, 1H), 2.8-3.0 (m, 1H), 2.19 (s, 3H), 1.6-1.8 (m, 2H), 1.40 (s, 9H).

3,4-Dichloro-*N*-[(3*S*,4*R*)-*rel*-3-chloro-4-piperidyl]-5-methyl-1*H*-pyrrole-2-carboxamide hydrochloride salt (G5) A solution of 779 mg (1.9 mmol) of the previous compound **G4** and 1.4 ml (5.7 mmol) 4 N HCl in 4 ml dioxane was stirred at rt for 3H. Et $_2$ O was added and the solids that precipitated were collected by filtration and dried in vacuo to afford 644 mg (98%) of the title compound used subsequently without further purification. MS (ESI) m/z (M+H) $^+$: 310, 312 for C $_{11}$ H $_{14}$ Cl $_3$ N $_3$ O.

Supplementary Scheme H - Intermediates to Compound 36



***tert*-Butyl 3-methylsulfamyl-4-oxo-piperidine-1-carboxylate (H2)** Sodium thiomethoxide (805 mg, 11.5 mmol) was added to a solution of *tert*-butyl 3-bromo-4-oxo-piperidine-1-carboxylate **H1** (3.20 g, 11.5 mmol) in THF (15 ml) at 0 °C. The resultant mixture was allowed to slowly warm to rt and stir overnight. The mixture was quenched with water (15 ml) and diluted with EtOAc. The organic phase was separated and washed with brine. The combined aq phases were back extracted with EtOAc. The combined organic layers were dried (MgSO $_4$) and concentrated, and the residue was purified by silica gel chromatography (hexanes/ethyl acetate, 7:1) to provide the title compound (2.4 g, 85%). MS (ESI) m/z (M) $^-$: 190.2 (M- tBu) for C $_{11}$ H $_{19}$ NO $_3$ S; ^1H NMR (300 MHz, CDCl $_3$) δ : 1.43 (s, 9H); 2.02 (s, 3H); 2.23 (dt, 1H); 2.95 (m, 1H); 3.20-3.40 (m, 2H); 3.65 (m, 1H); 3.90-4.20 (m, 2H).

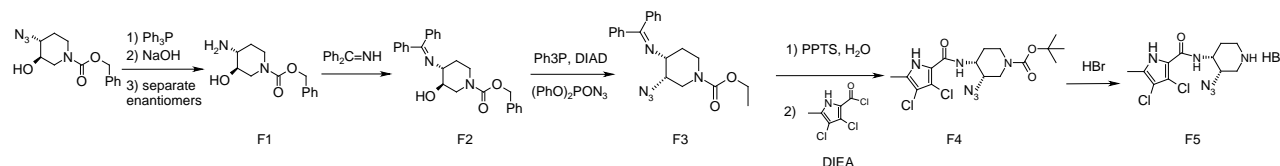
***tert*-Butyl (3*S*,4*R*)-*rel*-4-amino-3-methylsulfamyl-piperidine-1-carboxylate (H3)** Sodium cyanoborohydride (344 mg, 5.48 mmol) was added to a solution of the preceding compound **H2** (1.07 g, 4.40 mmol), NH $_4$ OAc (3.24 g, 42 mmol) and MeOH (15 ml). The resultant mixture was stirred for 4 h.

The reaction was quenched by addition of 1 N HCl (3 ml). Aq NaHCO₃ (saturated, 50 ml) was added slowly to the reaction mixture followed by extraction with EtOAc 3 times. The combined organic phases were dried (Na₂SO₄) and concentrated to afford the crude amine used in subsequent reactions without further purification. MS (ESI) m/z (M+H)⁺: 247.3 (M+H) for C₁₁H₂₂N₂O₂S.

tert-Butyl (3S,4R)-rel-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methylsulfanyl-piperidine-1-carboxylate (H4) A solution of 1.2 g (4.5 mmol) of the preceding compound **H3**, 600 μl (4.5 mmol) Et₃N and 478 mg (2.25 mmol) of 3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl chloride **E4** in 6 ml CH₂Cl₂ was stirred at rt for 2H. The mixture was diluted with CH₂Cl₂ and washed with water and brine. Drying (Na₂SO₄) and removal of solvent gave an solid that was purified by chromatography (10-40% EtOAc in hexanes gradient) to afford 200 mg (21%) of product. MS (ESI) m/z (M+H)⁺: 420.1 (M+H) for C₁₇H₂₅Cl₂N₃O₃S; ¹H NMR (300 MHz, CDCl₃) δ 1.40 (s, 9H); 1.45-1.70 (m, 2H); 2.10 (s, 3H); 2.18 (s, 3H); 2.80-3.20 (m, 2H); 3.31 (m, 1H); 3.90 (m, 2H); 4.30 (m, 1H); 7.15 (d, 1H); 12.13 (s, 1H).

(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methylsulfanyl-piperidine-1-carboxylate hydrochloride salt (H5) A mixture of 210 mg (0.5 mmol) of the preceding compound **H4** was dissolved in 4 ml 4 M HCl in dioxane, and the mixture was stirred at rt for 45 min. Solvent was removed to afford 161 mg (100%) of the title compound that was subsequently used without further purification. MS (ESI) m/z (M+H)⁺: 336, 338 for C₁₃H₁₉Cl₂N₃OS.

Supplementary Scheme F - Intermediates for Compound 38



Benzyl (3R,4R)-4-amino-3-hydroxy-piperidine-1-carboxylate (F1) and benzyl (3S,4S)-4-amino-3-hydroxy-piperidine-1-carboxylate *trans*(±)Benzyl-4-azido-3-hydroxypiperidine-1-carboxylate⁷ and Ph₃P (24 grams; 91.5 mmol) were dissolved in 100 ml anhydrous THF. The reaction solution was stirred at rt for 2H. The THF was removed, and the residue was dissolved in 100 ml MeOH and 0.5 N NaOH (100 ml). The suspension was stirred at rt overnight. The MeOH was removed, and the aq residue was diluted with water and extracted with chloroform. The organic layer was dried (Na₂SO₄) and concentrated. The residue was purified by silica gel chromatography to afford 15.5 g (75%) of material. LC/MS (ES⁺)[(M+H)⁺]: 251 for C₁₃H₁₈N₂O₃. The enantiomers were separated by chiral column chromatography (Column: AD 250 x 4.6mm, 10 microns. Eluent: 50% hexanes, 50% 1:1 ethanol-methanol, 0.1% diethyl amine. Flow: 1 ml/min) Separation gave 6.5 grams of benzyl (3R,4R)-4-amino-3-hydroxypiperidine-1-carboxylate **F1** and 6.8 grams of benzyl (3S,4S)-4-amino-3-hydroxypiperidine-1-carboxylate. MS (ESI) m/z (M+H)⁺: 251 for C₁₃H₁₈N₂O₃; ¹H NMR (300 MHz, MeOD-*d*₄) δ 1.35 (m, 1H), 1.82 (m, 1H), 2.64 (m, 2H), 2.83 (m, 1H), 3.11 (m, 1H), 4.00 (m, 2H), 5.12 (s, 2H), 7.34 (m, 5 H).

Benzyl (3R,4R)-4-(benzhydrylideneamino)-3-hydroxy-piperidine-1-carboxylate (F2) A solution of the preceding compound **F1** (6.5 grams; 25.9 mmol) and benzophenone imine (5.1 grams; 27.3 mmol) were in 50 ml anhydrous toluene was heated at reflux for 1 2H. Solvent was removed, and the residue was purified by flash column chromatography (10% - 40% EtOAc / hex with 0.1% DIEA) to afford 10 g (93%) of the title compound. MS (ESI) m/z (M+H)⁺: 415 for C₂₆H₂₆N₂O₃; ¹H NMR (300 MHz, CDCl₃) δ 1.54 (m, 1H), 1.73 (m, 1H), 2.26 (m, 1H), 2.85 (m, 2H), 3.35 (m, 1H), 3.86 (m, 1H), 4.03 (m, 1H), 4.24 (m, 1H), 5.12 (s, 2H), 7.18 – 7.68 (m, 15 H).

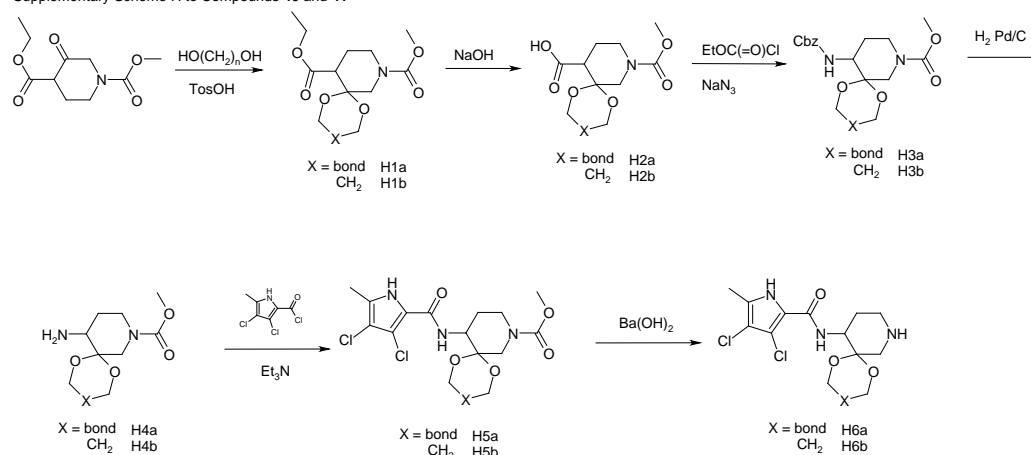
Benzyl (3S,4R)-3-azido-4-(benzhydrylideneamino)piperidine-1-carboxylate (F3) A THF solution containing diisopropyl diazodicarboxylate (2.7 grams; 13.5 mmol) was added dropwise to a solution of Ph₃P (3.5 grams; 13.5 mmol) in anhydrous 25 ml THF at 0 °C. After stirring for 30 min at 0 °C, the preceding compound **F2** (2.8 grams; 6.7 mmol) was added in a single portion. After stirring for an additional 2H, diphenylphosphoryl azide (3.7 grams; 13.5 mmol) was added dropwise. The resultant slurry was warmed to rt and stirred for 1 2Hours. Solvent was removed, and the residue was purified by flash column chromatography to afford 1.28 g (50%) of the title compound. MS (ESI) m/z (M+H)⁺: 440

for $C_{26}H_{25}N_5O_2$; 1H NMR (300 MHz, $CDCl_3$) δ 1.52 (m, 1H), 1.91 (m, 1H), 3.34 (m, 1H), 3.54 (m, 2H), 3.85 (m, 2H), 4.06 (m, 1H), 5.17 (s, 2H), 7.25 – 7.72 (m, 15 H).

Benzyl (3S,4R)-3-azido-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]piperidine-1-carboxylate (F4) A solution of the preceding compound **F3** (1.28 grams; 2.9 mmol) and *p*-TsOH (804 mg; 3.2 mmol) in THF and water was stirred at rt for 12 h. Solvent was removed the residue was dried by heating in CH_3CN with azeotropic removal of water. CH_3CN was removed, and the residue was then added to a solution of 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylic acid (622 mg; 3.2 mmol), HATU (1.44 g; 3.8 mmol; 1.3) and DIEA (1.1 grams; 8.7 mmol) in 10 ml DMF. The resultant solution was stirred for 30 min before being diluted with EtOAc and washed twice with water and then with brine. The EtOAc was dried (Na_2SO_4) concentrated to an oil that was purified by flash column chromatography (20%-50% EtOAc/Hex) to afford 914 mg (70%) of the title compound. MS (ESI) m/z ($M+H$)⁺: 451, 453 for $C_{19}H_{20}Cl_2N_6O_3$; 1H NMR (300 MHz, $CDCl_3$) δ 1.64 (m, 2H), 2.23 (s, 3H), 2.95 (m, 1H), 3.23 (m, 1H), 4.00 (m, 4 H), 5.14 (s, 2H), 7.18 (d, 1H), 7.31 (m, 5 H), 12.12 (s, 1H).

N-[(3S,4R)-3-Azido-4-piperidyl]-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxamide HBr salt (F5) A solution of the preceding compound **F4** (914 mg; 2.3 mmol) was dissolved in 2 ml HBr in HOAc. The reaction was stirred at rt for 2 h. Solvent was removed by rotary evaporation, and the residue was taken up 5 times in MeOH and re-concentrated. The residue was used in the subsequent step without further purification. MS (ESI) m/z ($M+H$)⁺: 317, 319 for $C_{11}H_{14}Cl_2N_6O$.

Supplementary Scheme H to Compounds **40** and **41**



11-Ethyl 8-methyl 1,5-dioxa-8-azaspiro[5.5]undecane-8,11-dicarboxylate (H1b) A solution of 4.0 g (17 mmol) of 4-ethyl-1-methyl 1,4-piperidinedicarboxylate,^{7,8} 50 ml 1,3-propanediol and 300 mg *p*-TsOH in 100 ml benzene was heated at reflux with azeotropic removal of water for 3 d. The solution was diluted with toluene and washed with aq Na_2CO_3 (2X). Drying ($MgSO_4$) and removal of solvent was followed by chromatography on silica gel (0-50% EtOAc gradient in CH_2Cl_2) to afford 3.33 g (68%) of the title compound as an oil. 1H NMR (300 MHz, $DMSO-d_6$) δ 1.18 (t, 3H), 1.50 (m, 1H), 1.68 (m, 3H), 2.9-3.0 (m, 1H), 3.4-3.5 (m, 2H), 3.6 (m, 4 H), 3.8-3.95 (m, 5 H), 4.0 (m, 2H).

10-Ethyl 7-methyl 1,4-dioxa-7-azaspiro[4.5]decane-7,10-dicarboxylate (H1a) Prepared as described above for **H1b** from 4-ethyl 1-methyl 3-oxopiperidine-1,4-dicarboxylate (4.0 g, 17 mmol), ethylene glycol (50 ml) and *p*-TsOH (0.35 g) to afford 3.8 g (83%) of the title compound. 1H NMR (300 MHz, $DMSO-d_6$) δ 1.25 - 1.32 (m, 3H), 1.63 (s, 1H), 1.92 - 2.07 (m, 2H), 2.80 (dd, 1H), 3.16 - 3.31 (m, 2H), 3.71 (s, 3H), 3.82 (dt, 2H), 3.94 - 4.08 (m, 3H), 4.19 (q, 2H).

8-(Methoxycarbonyl)-1,5-dioxa-8-azaspiro[5.5]undecane-11-carboxylic acid (H2b) A mixture of **H1a** (2.23 g, 7.8 mmol) and barium hydroxide (1.31 g, 15.6 mmol) in 15 ml MeOH and 10 ml water was stirred at rt for 3 d. The reaction mixture was acidified with 1 N HCl and then saturated with NaCl. The aq layer was extracted with EtOAc (3X), which was dried ($MgSO_4$) and concentrated to afford the title

compound as a colorless oil (1.8 g, 89%). ¹H NMR (300 MHz, CDCl₃) δ 1.52 (m, 1H), 1.69 (m, 3H), 2.8-2.9 (m, 1H), 3.44 (m, 3H), 3.6 (s, 3H), 3.69 (m, 1H), 3.8-4.0 (m, 5H).

7-(Methoxycarbonyl)-1,4-dioxo-7-azaspiro[4.5]decane-10-carboxylic acid (H2a) Prepared as described above for **H2b** from **H1a** (2.1 g, 10.6 mmol) and Ba(OH)₂ (3.6g, 21.2mmol) to afford 2.4 (93%) of the title compound. NMR: 1.71 - 1.81 (m, 2H), 2.72 (t, 1H), 3.11 (s, 2H), 3.33 (s, 1H), 3.58 (s, 3H), 3.64 (d, 2H), 3.81 - 3.96 (m, 3H), 12.24 (s, 1H).

Methyl 11-[(benzyloxy)carbonyl]amino-1,5-dioxo-8-azaspiro[5.5]undecane-8-carboxylate (H3b) Ethyl chloroformate (1.09 ml, 11.4 mmol) and Et₃N (1.76 ml, 12.5 mmol) were added to a mixture of **H2b** (2.7 g, 10.4 mmol) in dry acetone (50 ml) at 0 °C. After stirring at 0 °C for 1H, a solution of sodium azide (1.7 g, 26 mmol) in water (20 ml) was added, and the reaction mixture was stirred for 1.5 hours at 0 °C and then 3H at rt. Acetone was removed, and the residue was extracted with toluene (3X), which was, in turn, dried with MgSO₄ and concentrated by heating to reflux with a Dean Stark trap. Once the volume was reduced to ~100 ml, benzyl alcohol (1.62 ml, 15.6 mmol) was added, and the reaction was heated at reflux overnight. After cooling to rt, solvent was removed and the residue was diluted with CH₂Cl₂, which was washed with 1 N HCl (3X), dried (MgSO₄) and concentrated to afford a yellow oil. Purification by silica gel chromatography (gradient elution 0-30% EtOAc in CH₂Cl₂) afforded the title compound as a white solid (1.14 g, 30%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.48 (m, 2H), 1.63 (m, 3H), 3.10 (m, 3H), 3.59 (3, 3H), 3.79 (m, 6H), 3.91 (m, 1H), 5.03 (s, 2H), 7.36 (m, 5H).

Methyl 10-[(benzyloxy)carbonyl]amino-1,4-dioxo-7-azaspiro[4.5]decane-7-carboxylate (H3a) Prepared as described above for **H3b** from 1.75 g (7.1 mmol) of **H2a**, ethyl chloroformate (0.74 ml, 7.8mmol), Et₃N (1.2 ml, 8.5mmol), NaN₃ (1.2 g, 18 mmol) and benzyl alcohol (1.1 ml, 10.6 mmol) to afford product as a white solid (1.08 g, 43%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.91 (s, 1H), 2.72 (s, 2H), 2.86 (s, 1H), 3.69 (s, 3H), 3.93 - 4.08 (m, 4H), 4.13 (s, 1H), 4.89 (s, 1H), 5.11 (s, 2H), 7.30 - 7.39 (m, 5 H).

Methyl 11-amino-1,5-dioxo-8-azaspiro[5.5]undecane-8-carboxylate (H4b) A mixture of **H3b** (1.14 g, 3.1 mmol), 10% palladium on carbon (0.30 g) in 100 ml ethanol was evacuated and backfilled with N₂ several times before being hydrogenated under a H₂ balloon atmosphere overnight. The reaction mixture was filtered through diatomaceous earth rinsing through with ethanol, and solvent was evaporated to obtain the title compound as a an oil (720 mg, 100%) that was used in the subsequent reaction without further purification. ¹H NMR (300 MHz, CDCl₃) δ 1.33-1.58 (m, 2H), 1.53–1.75 (m, 1H), 3.09-3.22 (m, 8H), 3.64 (s, 3H), 3.67-4.00 (m, 2H).

Methyl 10-amino-1,4-dioxo-7-azaspiro[4.5]decane-7-carboxylate (H4a) Prepared as described above for **H4b** from (1.08 g, 3.0 mmol) of **H3a** and 10% activated palladium on carbon (0.30g) to afford product as a white solid (0.64 g, 100%). ¹H NMR (300 MHz, CDCl₃) δ 1.27 - 1.42 (m, 1H), 1.68 (ddd, 1H), 1.77 (s, 1H), 2.77 (dd, 2H), 2.99 (s, 1H), 3.54 - 3.59 (m, 3H), 3.69 (s, 2H), 3.71 (d, 1H), 3.81 (d, 1H), 3.84 - 4.00 (m, 4 H).

Methyl 11-[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino-1,5-dioxo-8-azaspiro[5.5]undecane-8-carboxylate (H5b) A solution of 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylic acid (0.60 g, 3.1 mmol), **H4b** (710 mg, 3.1 mmol), HOBt (420 mg, 3.1 mmol) and NMM (1.34 ml, 10.9 mmol) in CH₂Cl₂ (100 ml) was stirred at rt for 1H, after which EDC (1.07 g, 5.6 mmol) was added. After stirring at rt overnight, the mixture was washed with water (3X), 1 N HCl, sat. aq. NaHSO₃ and brine. The CH₂Cl₂ was dried (MgSO₄) and concentrated to give a solid that was triturated with Et₂O to afford the title compound (960 mg, 76%) as a solid. MS (ESI) *m/z* (M-H)⁻: 392 for C₁₅H₂₁Cl₂N₃O₅; ¹H NMR (300 MHz, CDCl₃) δ 1.76 (m, 2H), 2.24 (s, 3H), 3.15 (s, 3H), 3.28 (s, 3H), 3.31 (m, 2H), 3.52 (m, 2H), 3.55 (m, 1H), 3.63 (s, 3H), 4.28 (m, 1H), 7.15 (d, 1H), 12.28 (s, 1H).

Methyl 10-[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino-1,4-dioxo-7-azaspiro[4.5]decane-7-carboxylate (H5a) Prepared as described above for **H5b** from 0.50 g (2.3 mmol) **H4a**, 3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylic acid, ¹⁸OBt (0.31 g, 2.3 mmol), NMM (0.99 ml, 8.1 mmol) and EDC (0.79 g, 4.1 mmol) to afford product as a white solid (0.59 g, 66%). MS (ESI) *m/z* (M+H)⁺: 392 for C₁₅H₁₉Cl₂N₃O₅; ¹H NMR (300 MHz, CDCl₃) δ 1.53 (dd, *J*=12.43, 4.14 Hz, 1H), 1.79 - 1.91 (m, 1H), 2.15 - 2.20 (m, 3H), 2.85 (s, 1H), 2.95 (s, 1H), 3.57 - 3.61 (m, 3H), 3.73 - 3.82 (m, 1H),

3.84 - 3.98 (m, 3H), 3.99 - 4.08 (m, 1H), 4.16 (s, 1H), 4.22 - 4.33 (m, 1H), 6.91 (d, $J=8.85$ Hz, 1H), 12.16 (s, 1H).

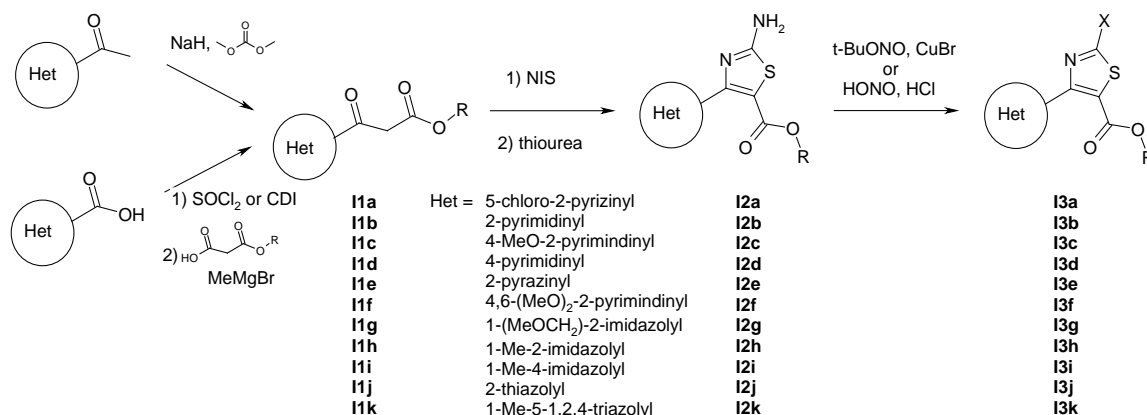
3,4-Dichloro-*N*-1,5-dioxo-8-azaspiro[5.5]undec-11-yl-5-methyl-1*H*-pyrrole-2-carboxamide (H6b)

Ba(OH)₂ (0.81 g, 4.7 mmol) was added to a solution of **H5b** (960 mg, 2.4 mmol) in 10 ml EtOH and 0.5 ml water. After heating in a microwave reactor at 130 °C for 2H and cooling to rt, the reaction mixture was diluted with methanol, and insoluble material was filtered, rinsing through with additional MeOH. The filtrate was concentrated, and the residue was partitioned between EtOAc and water. The EtOAc was dried (MgSO₄) and concentrated to afford the title compound as a solid (0.34 g, 41%). MS (ESI) m/z (M-H)⁻: 348, 350 for C₁₄H₁₉Cl₂N₃O₃; MS (ES) MH⁺: 348 for C₁₄H₁₉Cl₂N₃O₃; ¹H NMR (300 MHz, CDCl₃) δ 1.38 - 1.53 (m, 2H), 1.70-1.85 (m, 2H), 2.14-2.20 (m, 3H), 2.23 (d, 1H), 2.82 (d, 1H), 3.27-3.42 (m, 2H), 3.69 (s, 1H), 3.84-3.98 (m, 3H), 7.20 (d, 1H).

3,4-Dichloro-*N*-1,4-dioxo-7-azaspiro[4.5]dec-10-yl-5-methyl-1*H*-pyrrole-2-carboxamide (H6a)

Prepared as described above for **H6b** from 0.55 g (1.4 mmol) of **H5a** and 0.48g (2.8 mmol) Ba(OH)₂ to afford 0.40 g (87%) of product. MS (ESI) m/z (M+H)⁺: 334 for C₁₃H₁₇Cl₂N₃O₃; ¹H NMR (300 MHz, CDCl₃) δ 1.48 (td, 1H), 1.81 (dd, 1H), 2.18 (s, 3H), 2.39 (d, 1H), 2.83 (d, 2H), 3.34 (s, 1H), 3.71-3.78 (m, 1H), 3.86-3.97 (m, 2H), 4.08-4.17 (m, 2H), 6.91 (d, 1H), 12.15 (s, 1H).

Supplementary Scheme I to Compounds **73-76**, **78-82** and **86-89**



Ethyl 3-(5-chloropyrazin-2-yl)-3-oxopropanoate (11a) 5-Chloropyrazine-2-carboxylic acid (21 g, 0.13 mol) in SOCl₂ (100 ml) was heated at reflux for 2H. Excess SO₂Cl was distilled off under reduced pressure, and the residue was dissolved in 100 ml dry THF. In another flask, methyl magnesium bromide (88 ml of 3 M solution in Et₂O, 0.265 mol) was added to a solution of ethyl hydrogen malonate (15.8 g, 0.132 mol) in 500 ml THF and cooled to 0 °C. The reaction mixture was stirred for 30 min before Et₃N (39.9 g, 0.396 M) was added. To this reaction mixture, the above prepared acid chloride mixture was added and stirring was continued for 2H at rt. THF was removed from the reaction mixture, and 500 ml water was added. The mixture was extracted with EtOAc (2X). The combined organic layers were dried (Na₂SO₄) and concentrated, and the residue was chromatographed on silica gel (10% EtOAc/pet ether) to afford 16.0 g (53%) of the title compound as a white solid. MS (APCI) m/z (M-H)⁻: Mass 227. ¹H NMR (400 MHz, CDCl₃) δ 1.26 (t, 3H), 1.28 (t, 3H), 4.18 (s, 2H), 4.20 (q, 2H), 4.30 (q, 2H), 6.28 (s, 1H), 8.57 (s, 1H), 8.61 (s, 1H), 8.89 (s, 1H), 9.04 (s, 1H), 12.35 (s, 1H).

Ethyl 2-amino-4-(5-chloro-2-pyrazinyl)-5-thiazolecarboxylate (12a) A mixture of the preceding compound (2.0 g, 8.8 mmol), Amberlyst resin (2.0 g) and *N*-iodosuccinamide (2.1 g, 9.64 mmol) in 30 ml EtOAc was stirred for 1H at rt. The resin was filtered off, and solvent was removed. The residue and thiourea (0.99 g, 13.15 mmol) in MeOH (25 ml) were heated at reflux for 2H. The MeOH was removed and the residue was partitioned between sat. aq. NaHSO₃ and EtOAc. The EtOAc was separated and the aq layer was extracted with EtOAc. The organic layers were combined, dried (Na₂SO₄) and concentrated, and the residue was chromatographed on silica gel (10-50% EtOAc gradient in pet ether) to afford to

afford 500 mg (20%) of the title compound as an off-white solid. MS (APCI) m/z (M+H)⁺: m/z 285.0; ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.08 (t, 3H), 4.12 (q, 2H), 8.02 (s, 2H), 8.72 (s, 1H), 8.84 (s, 1H).

Ethyl 2-bromo-4-(5-chloropyrazin-2-yl)thiazole-5-carboxylate (I3a) A mixture of *tert*-butyl nitrite (87 mg, 0.85 mmol) and CuBr₂ (238 mg, 1.06 mmol) in 30 ml CH₃CN (30 ml) was stirred at 0 °C for 30 min before the addition of the preceding compound (200 mg, 0.70 mmol). The reaction mixture was stirred for 2H at rt and solvent was removed. Water was added and the mixture was extracted with Et₂O (2X). The organic layers were combined and dried (Na₂SO₄) and concentrated, and the residue was chromatographed on silica gel (0-10% EtOAc gradient in pet ether) to afford 50 mg (20%) of the title compound as an off white solid. MS (APCI) m/z (M+H)⁺: 349.9; ¹H NMR (400 MHz, CDCl₃) δ 1.34 (t, 3H), 4.38 (q, 2H), 8.68 (s, 1H), 8.84 (s, 1H).

Ethyl β -oxo-2-pyrimidininepropanoate (I1b) Carbonyl diimidazole (1.55 g, 9.57 mmol) was added to a suspension of pyrimidine-2-carboxylic acid (0.99 g, 7.98 mmol) in 20 ml anhydrous THF, which was heated at reflux for 2Hours. The mixture was cooled to rt. In a separate flask, mono-ethyl malonate (0.94 ml, 7.98 mmol) was suspended in 20 ml anhydrous THF and cooled to 0 °C. Methyl magnesium bromide (5.32 ml, 16 mmol, 3.0 M in Et₂O) was added dropwise. After stirring at 0 °C for 20 min, the previously prepared imidazolidine solution was added slowly. The reaction was then heated at reflux overnight. After cooling to rt, the reaction mixture was diluted with water and acidified with concentrated HCl to pH 5. The solution was extracted with EtOAc (3X), dried (MgSO₄) and concentrated to afford a yellow oil (1.19 g, 77%) that was used without further purification. NMR indicated a 2:1 mixture of keto:enol tautomers. MS (ESI) m/z (M+H)⁺: 195 for C₉H₁₀N₂O₃; ¹H NMR (300 MHz, CDCl₃) δ 1.13 and 1.22 (2t, 3H), 4.05 and 4.22 (2q, 2H), 4.18 (s, 4/3H), 6.31 (s, 1/3H), 7.62 and 7.75 (2t, 1H), 8.95 and 9.05 (2d, 2H), 11.79 (s, 1/3H).

Ethyl 2-amino-4-(2-pyrimidinyl)-5-thiazolecarboxylate (I2b) *N*-iodosuccinamide (1.38 g, 6.1 mmol) and Amberlyst-15 resin (1.2 g) were added to a suspension of the preceding compound (1.19 g, 6.1 mmol) in EtOAc. After stirring at rt for 30 min, the reaction mixture was filtered to remove the Amberlyst-15 resin. The filtrate was concentrated to an orange oil which was then suspended in diethyl ether. The resulting precipitate was filtered and washed with ether. The filtrate was concentrated to an orange oil that was dissolved in 20 ml EtOH. Thiourea (0.62 g, 8.1 mmol) was added, and the mixture was heated at reflux for 1Hour. After cooling to rt, solvent was removed, and the residue was suspended in water and basified with sat. aq. Na₂CO₃. The resulting precipitate was filtered off and the filtrate was extracted with EtOAc (3X). The organic extracts were dried (MgSO₄) and concentrated to afford an orange oil (0.55 g, 36%) that was used in the next step without further purification. MS (ESI) m/z (M+H)⁺: 251 for C₁₀H₁₀N₄O₂S; ¹H NMR (300 MHz, CDCl₃) δ 0.97 (t, 3H), 3.95 (q, 2H), 7.55 (t, 1H), 7.94 (s, 1H), 8.85 (d, 1H), 9.05 (d, 1H).

Ethyl 2-chloro-4-(2-pyrimidinyl)-5-thiazolecarboxylate (I3b) A solution of 455 mg (6.6 mmol) of NaNO₂ in 15 ml water was added dropwise to a mixture of the preceding intermediate (0.55 g, 2.2 mmol) in glacial acetic acid (20 ml) and conc. HCl (30 ml) was cooled to 0 °C. After stirring for 10 min at 0 °C, the reaction was slowly warmed to rt and stirred for 1H. A solution of urea (0.25 g) in water (10 ml) was added dropwise. After stirring at rt for 30 min, solvent was removed under reduced pressure. The residue was partitioned with sat. aq. NaHCO₃ and EtOAc. The layers were separated and the aq layers was extracted 3 times with EtOAc. The combined organic layers were dried (MgSO₄) and concentrating to afford an orange oil (0.20 g) which was used in the next step without further purification. MS (ESI) m/z (M+H)⁺: 270 for C₁₀H₈ClN₃O₂S.

1-(4-Methoxy-2-pyrimidinyl)-ethanone *i*-PrMgCl (2 M in ether, 3.42 ml, 6.84 mmol) was added to a solution of 2-Iodo-4-methoxypyrimidine (1.62 g, 6.84 mmol) in dry THF (20 ml) cooled to -10 °C. After stirring at 0 °C for 1H, *N*-methoxy-*N*-methylacetamide (776 mg, 7.52 mmol) was added, and the mixture was slowly warmed up to rt overnight. Water (10 ml) was added, and the mixture was extracted with CH₂Cl₂. The organic layer was dried (MgSO₄) and concentrated, and the residue was purified by chromatography on silica gel (Hex/EtOAc, gradient) to give the desired product as a yellowish solid (470 mg, 45%). MS (ESI) m/z (M+H)⁺: 153 for C₇H₈N₂O₂; ¹H NMR (300 MHz, CDCl₃) δ 2.77 (s, 3H), 4.10 (s, 3H), 6.89 (d, 1H), 8.62 (d, 2H).

Ethyl 4-methoxy- β -oxo-2-pyrimidinepropanoate (I1c) NaH (291 mg, 12.2 mmol, 60% dispersion) was added to a solution of 1-(4-methoxy-2-pyrimidinyl)-ethanone (462 mg, 3.04 mmol) in 20 ml dimethyl carbonate cooled to 0 °C. Sodium hydride and the mixture was stirred at 0 °C for 10 min, after which the temperature was raised to 100 °C and refluxed for 1Hr. The mixture was cooled down to RT and poured slowly into the ice cold 1 N HCl solution (20 ml). After 5 min stirring, the pH was brought to ~7 with aq NaOH, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel (gradient elution from 0-70% EtOA in CH₂Cl₂) gave the desired product as an oil (250 mg, 39%) that was carried over to the next step without further purification. MS (ESI) m/z (M+H)⁺: 211 for C₉H₁₀N₂O₄S.

Ethyl 2-amino-4-(4-methoxy-2-pyrimidinyl)-5-thiazolecarboxylate (I2c) Prepared as described for **I2b** from 250 mg (1.19 mmol) of the preceding compound, 289 mg (1.19 mmol) NIS, 230 mg Amberlyst-15 resin and 136 mg (1.78 mmol) thiourea to afford 97 mg (26%) of product. MS (ESI) m/z (M+H)⁺: 311 for C₁₂H₁₄N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.02 (t, 3H), 3.86 (s, 6H), 4.03 (q, 2H), 6.27 (s, 1H), 7.94 (s, 2H).

Ethyl 2-chloro-4-(4-methoxy-2-pyrimidinyl)-5-thiazolecarboxylate (I3c) Prepared as described for **I3b** from the 100 mg (0.38 mmol) of the preceding compound and 78 mg (1.13 mmol) NaNO₂ to give 78 mg (62%) of product as an oil. MS (ESI) m/z (M+H)⁺: 330 for C₁₂H₁₂ClN₃O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.14 (t, 3H), 3.89 (s, 6H), 4.21 (q, 2H), 6.37 (s, 1H).

Ethyl β -oxo-4-pyrimidinepropanoate (I1d) Prepared as described for **I1b** from 960 mg (7.7 mmol) of pyrimidine-4-carboxylic acid, 1.5 g (9.3 mmol) CDI, 0.91 ml mono-ethyl malonate and 5.1 ml (15.3 mmol) 3 N methyl magnesium bromide in Et₂O to afford 840 mg (46%) of product. MS (ESI) m/z (M+H)⁺: 195 for C₉H₁₀N₂O₃; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.14 (t, 3H, 2/3) 1.28 (t, 3H, 1/3) 4.17 (q, 2H, 2/3) 4.19 (s, 2H), 4.25 (q, 2H, 1/3) 6.34 (s, 1H, 1/3) 7.91 (d, 1H 1/3) 7.95 (d, 1H, 2/3) 9.04 (d, 1H, 1/3) 9.15 (d, 1H, 2/3) 9.30 (s, 1H, 1/3) 9.43 (s, 1H, 2/3) 12.03 (s, 1H, 2/3).

Ethyl 2-amino-4-(4-pyrimidinyl)-5-thiazolecarboxylate (I2d) Prepared as described for **12b** from 0.84 g (4.3 mmol) of the preceding compound, 0.97 g (4.3 mmol) NIS, 0.84 g Amberlyst-15 resin and 0.45 g (5.95 mmol) thiourea to afford 0.57 g (53%) of product. MS (ESI) m/z (M+H)⁺: 251 for C₁₀H₁₀N₄O₂S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.08 (t, 3H), 4.05 (q, 2H), 7.68 (d, 1H), 7.98 (s, 2H), 8.86 (d, 1H), 9.21 (s, 1H).

Ethyl 2-chloro-4-(4-pyrimidinyl)-5-thiazolecarboxylate (I3d) Prepared as described for **I3b** from the 570 mg (2.3 mmol) of the preceding compound and 470 mg (6.8) NaNO₂ to afford 630 mg (100%) of product. MS (ESI) m/z (M+H)⁺: 271 for C₁₀H₈ClN₃O₂S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.19 (t, 3H), 4.24 (q, 2H), 7.92 (d, 2H), 8.98 (d, 2H), 9.29 (s, 1H).

Ethyl β -oxo-2-pyrazinepropanoate (I1e) Prepared as described for **I1b** from 5.0 mg (40.3 mmol) pyrazine-2-carboxylic acid, 7.8 g (48.3 mmol) CDI, 4.76 ml (40.3) mono-ethyl malonate and 26.9 ml (80.6 mmol) 3 N methyl magnesium bromide in Et₂O to afford 6.44 g (82%) of product MS (ESI) m/z (M+H)⁺: 195 for C₉H₁₀N₂O₃; (300 MHz, DMSO-*d*₆) δ 1.15 (t, 3H), 4.11 (q, 2H), 4.18 (s, 2H), 8.82 (s, 1H), 8.94 (s, 1H), 9.17 (s, 1H).

Ethyl 2-amino-4-(2-pyrazinyl)-5-thiazolecarboxylate (I2e) Prepared as described for **I2b** from 6.44 g (33.2 mmol) of the preceding compound, 7.47 mg (33.2 mmol) NIS, 6.4 mg Amberlyst-15 resin and 3.78 g (49.7 mmol) thiourea to afford 3.3 g (40%) of product. MS (ESI) m/z (M+H)⁺: 251 for C₁₀H₁₀N₄O₂S; (300 MHz, DMSO-*d*₆) δ 1.07 (t, 3H), 4.045 (q, 2H), 7.99 (s, 2H), 8.65 (d, 1H), 8.65 (d, 1H), 8.81 (s, 1H).

Ethyl 2-chloro-4-(2-pyrazinyl)-5-thiazolecarboxylate (I3e) Prepared as described for **I3b** from 3.30 g (13.2 mmol) of the preceding compound and 2.72 g (39.6 mmol) NaNO₂ to afford 2.66 g (75%) of product. MS (ESI) m/z (M+H)⁺: 270 for C₁₀H₈ClN₃O₂S; (300 MHz, DMSO-*d*₆) δ 1.16 (t, 3H), 4.22 (q, 2H), 8.76 (m, 2H), 9.039 (s, 1H).

Ethyl 4,6-dimethoxy- β -oxo-2-pyrimidinepropanoate (I1f) Prepared as described for **I1c** from 1.0 g (5.4 mmol) of 4,6-dimethoxypyrimidine-2-carboxylic acid, 1.05 g (6.5 mmol) CDI, 0.64 ml (5.4 mmol) mono-ethyl malonate and 3.6 ml (10.8 mmol) 3 N methyl magnesium bromide in Et₂O to afford 0.41 g (30%) of product. MS (ESI) m/z (M+H)⁺: 255 for C₁₁H₁₄N₂O₅.

Ethyl 2-amino-4-(4,6-dimethoxy-2-pyrimidinyl)-5-thiazolecarboxylate (I2f) Prepared as described for **I2b** from 0.41 g (1.6 mmol) of the preceding compound, 0.37 g (1.6 mmol) NIS and 0.19 g (2.5 mmol) thiourea to afford 0.15 g (30%) of product. MS (ESI) m/z (M+H)⁺: 311 for C₁₂H₁₄N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.02 (t, 3H), 3.86 (s, 6H), 4.03 (q, 2H), 6.27 (s, 1H), 7.94 (s, 2H).

Ethyl 2-chloro-4-(4,6-dimethoxy-2-pyrimidinyl)-5-thiazolecarboxylate (I3f) Prepared as described for **I3b** from the 150 mg (0.48 mmol) of the preceding compound and 100 mg (1.4 mmol) NaNO₂ to afford 96 mg (61%) of product. MS (ESI) m/z (M+H)⁺: 330 for C₁₂H₁₂ClN₃O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.14 (t, 3H), 3.89 (s, 6H), 4.21 (q, 2H), 6.37 (s, 1H).

1-[1-(Methoxymethyl)-1H-imidazol-2-yl]ethanone A solution of 55 ml (88 mmol) of 1.6 M *n*-butyllithium in hexanes was added slowly to a solution of 9.07 g (81 mmol) 1-(methoxymethyl)-1H-imidazole⁹ in 100 ml THF cooled in a dry ice-acetone bath. After stirring 1 Hour, 9.4 ml (88 mmol) of *N*-methoxy-*N*-methylacetamide was added quickly, and the solution stirred for 40 min before being quenched with aq NH₄Cl. After warming to rt, the mixture was diluted with water and extracted 3 times with EtOAc, which was washed with brine, dried (MgSO₄) and concentrated to give 9.52 gm (70%) of an oil that was used in subsequent steps without further purification. MS (ESI) m/z (M+H)⁺: 155 for C₇H₁₀CN₂O₂; ¹H NMR (300 MHz, DMSO-*d*₆) δ 2.72 (s, 3H), 3.35 (s, 3H), 5.75 (s, 2H), 7.21 (s, 1H), 7.32 (s, 1H).

Methyl 3-[1-(2-methoxymethyl)-1H-imidazol-2-yl]-3-oxopropanoate (I1g) Prepared as described for **I1c** from 9.5 g (57 mmol) of the preceding compound, 7.8 g (195 mmol) NaH (60% dispersion) and 200 ml dimethylcarbonate to afford 12.4 g (100%) of product. MS (ESI) m/z (M+H)⁺: 213 for C₉H₁₂N₂O₄; ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.41 (s, 3H), 3.75 (s, 3H), 4.22 (s, 2H), 5.75 (s, 2H), 7.22 (s, 1H), 7.31 (s, 1H).

Methyl 2-amino-4-[1-(methoxymethyl)-1H-imidazol-2-yl]-5-thiazolecarboxylate (I2g) Prepared as described for **I2b** from 12.4 g (58 mmol) of the preceding compound, 14.4 g (64 mmol) NIS, 10 g Amberlyst-15 resin and 6.6 g (87 mmol) thiourea to afford 10 g (64%) of product. MS (ESI) m/z (M+H)⁺: 269 for C₁₀H₁₂N₄O₃S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.23 (s, 3H), 3.71 (s, 3H), 5.51 (s, 2H), 7.87 (s, 1H), 8.02 (s, 1H), 8.44 (s, 2H).

Methyl 2-chloro-4-[1-(methoxymethyl)-1H-imidazol-2-yl]-5-thiazolecarboxylate (I3g) Prepared as described for **I3a** from 10 g (37.3 mmol) of the preceding compound and 7.4 ml (55.8 mmol) *t*-butylnitrite and 7.5 g (55.8 mmol) CuCl₂ to afford 5.3 g (49%) of product. MS (ESI) m/z (M+H)⁺: 288, 290 for C₁₀H₁₀ClN₃O₃S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.22 (s, 3H), 3.78 (s, 3H), 5.35 (s, 2H), 7.32 (s, 2H).

Ethyl 3-(1-methylimidazol-2-yl)-3-oxo-propanoate (I1h) Prepared as described for **I1c** from 9.8 g (75 mmol) 1-(1-methyl-1H-imidazol-2-yl)ethanone¹⁰ and 9.0 g (225 mmol) NaH (60% dispersion) and 50 ml diethylcarbonate to afford 7.52 g (51%) product after chromatography on silica gel (0-60% gradient of EtOAc in hexanes). MS (ESI) m/z (M+H)⁺: 197 for C₉H₁₂N₂O₃; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.27 (t, 3H), 4.10 (s, 2H), 4.25 (m, 5H), 7.15 (s, 1H), 7.55 (s, 1H).

Ethyl 2-amino-4-(1-methylimidazol-2-yl)thiazole-5-carboxylate (I2h) *N*-Iodosuccinimide (8.6 g, 41 mmol) was added to a mixture of 7.52 g (38 mmol) of the preceding compound and 7.5 g Amberlyst-15 resin in 400 ml EtOAc followed by stirring for 1 Hour at rt. The resin was filtered off and rinsed with EtOAc. Solvent was removed from the filtrate and the residue was taken up in diethyl ether. Insoluble material was filtered off and rinsed with additional ether. Solvent was removed from the filtrate and the residue was dissolved in 200 ml MeOH before added 4.7 g (62 mmol) thiourea. The mixture was heated at reflux for 1H. Solvent was removed and the residue was taken up in aq Na₂CO₃. Insoluble material was collected by filtration and rinsed well with water. The solids were dried *in vacuo* affording 4.51 g (47%) of the title compound. MS (ESI) m/z (M+H)⁺: 253 for C₉H₁₀N₄O₂S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.48 (s, 3H), 3.57 (s, 3H), 6.90 (s, 1H), 7.12 (s, 1H), 7.98 (s, 2H).

Ethyl 2-chloro-4-(1-methylimidazol-2-yl)thiazole-5-carboxylate (I3h) Prepared as described for **I3a** from the 4.51 g (18 mmol) of the preceding compound, 3.6 ml (27 mmol) *tert*-butylnitrite and 3.63 g (27 mmol) CuCl₂ to afford 5.3 g (49%) of product. 3.6 g (73%). MS (ESI) m/z (M+H)⁺: 272 for

$C_{10}H_{10}ClN_3O_2S$; 1H NMR (300 MHz, DMSO- d_6) δ 1.17 (t, 3H), 3.60 (s, 3H), 4.21 (q, 2H), 7.0 (s, 1H), 7.3 (s, 1H).

Ethyl 3-(1-methylimidazol-4-yl)-3-oxo-propanoate (I1i) Prepared as described for **I1b** from 3.0 g (23.8 mmol) of 1-methyl-1*H*-imidazole-4-carboxylic acid, 4.6 g (28.4 mmol) CDI, 2.8 ml (23.8 mmol) monoethyl malonate and 16 ml (48 mmol) 3N methyl magnesium bromide in Et₂O to afford 2.3 g (49%) of product. 1H NMR (300 MHz, DMSO- d_6) δ 1.25 (t, 3H), 3.72 (s, 3H), 4.01 (s, 2H), 4.18 (q, 2H), 7.43 (s, 1H), 7.57 (s, 1H).

Ethyl 2-amino-4-(1-methylimidazol-4-yl)thiazole-5-carboxylate (I2i) Prepared as described for **I2b** from 2.28 g (11.6 mmol) of the preceding compound, 2.6 g (11.6 mmol) NIS, 2.3 g Amberlyst-15 resin and 1.1 g (14.5 mmol) thiourea to afford 810 mg (28%) of product. MS (ESI) m/z (M+H)⁺: 253 for $C_{10}H_{12}N_4O_2S$; 1H NMR (300 MHz, CDCl₃) δ 1.15 (t, 3H), 3.62 (s, 3H), 4.15 (q, 2H), 7.65 (s, 1H), 7.95 (s, 1H).

Ethyl 2-chloro-4-(1-methylimidazol-4-yl)thiazole-5-carboxylate (I3i) Prepared as described for **I3b** from the 780 mg (3.1 mmol) of the preceding compound and 618 mg NaNO₂ to afford 610 mg (72%) of the title compound. MS (ESI) m/z (M+H)⁺: 272 for $C_{10}H_{10}ClN_3O_2S$; 1H NMR (300 MHz, CDCl₃) δ 1.42 (t, 3H), 3.81 (s, 3H), 4.35 (q, 2H), 7.50 (s, 1H), 8.21 (s, 1H).

Methyl 3-oxo-2-thiazolepropanoate (I1j) Prepared as described for **I1c** from 5.78 g (45.5 mmol) 1-(2-thiazolyl)-1-ethanone, 7.3 g (182 mmol) NaH (60% dispersion) in 80 ml dimethylcarbonate to afford 4.41 g (49%). MS (ESI) m/z (M+H)⁺: 186 for $C_7H_7NO_3S$; 1H NMR (300 MHz, CDCl₃) δ 3.65 (s, 3H), 4.22 (s, 2H), 8.18 (d, 1H), 8.29 (d, 1H).

Methyl 2'-chloro-(2,4'-bithiazole)-5'-carboxylate (I2j) Prepared as described for **I2b** from 4.41 g (24 mmol) of the preceding compound, 5.36 g (24 mmol) NIS, 4.4 g Amberlyst-15 resin and 2.49 g (32.7 mmol) thiourea to afford 4.6 g (88%) of product. MS (ESI) m/z (M+H)⁺: 242 for $C_8H_7N_3O_2S_2$; 1H NMR (300 MHz, CDCl₃) δ 3.67 (s, 3H), 7.86 (d, 1H), 7.91 (d, 1H), 7.92 (s, 2H).

Methyl 2'-chloro-(2,4'-bithiazole)-5'-carboxylate (I3j) Prepared as described for **(I3b)** from 4.6 g (19 mmol) of the preceding compound and 3.94 g (57 mmol) NaNO₂ to afford 4.66 g (94%). MS (ESI) m/z (M+H)⁺: 261 for $C_8H_5ClN_2O_2S_2$; 1H NMR (300 MHz, CDCl₃) δ 3.84 (s, 3H), 8.02 (m, 2H).

Methyl 3-(1-methyl-1*H*-1,2,4-triazol-5-yl)-3-oxopropanoate (I1k) NaH (7.84 g, 196 mmol of a 60% dispersion in oil) was added portionwise to a solution of 6.18 g (34.5 mmol) of 1-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethanone¹¹ in 100 ml dimethylcarbonate. The mixture was heated to 90 °C for 2H forming a thick slurry. After cooling to rt, the mixture was slowly transferred to 1 N HCl over ice. The pH of the mixture was brought to about 7 with NaHCO₃ and the solution was saturated with NaCl before being extracted 4 times with EtOAc. The EtOAc was dried (MgSO₄) and concentrated to give an oil that was chromatographed on silica gel (100% CH₂Cl₂ followed by gradient elution to 50% EtOAc in CH₂Cl₂) to afford 5.3 g (83%) of the title compound an oil. 1H NMR (300 MHz, DMSO- d_6) δ 3.77 (s, 3H), 4.10 (s, 2H), 4.22 (s, 3H), 7.88 (s, 1H).

Methyl 2-amino-4-(1-methyl-1*H*-1,2,4-triazol-5-yl)-5-thiazolecarboxylate (I2k) *N*-iodosuccinimide (6.6 g, 29 mmol) was added to a mixture of 5.33 g (29 mmol) methyl 3-(1-methyl-1*H*-1,2,4-triazol-5-yl)-3-oxopropanoate (**I1k**) and 5 g Amberlyst-15 resin in 50 ml EtOAc followed by stirring for 1 Hour at rt. The resin was filtered off and rinsed with EtOAc. Solvent was removed from the filtrate and the residue was taken up in ethyl ether. Insoluble material was filtered off and rinsed with additional ether. Solvent was removed from the filtrate and the residue was dissolved in 60 ml MeOH before adding 3.44 g (45 mmol) thiourea. The mixture was heated at reflux for 1H. Solids precipitated on cooling. The solids were collected, washed with MeOH and dried *in vacuo* to give 2.1 g of the title compound. Solvent was removed from the filtrate and the residue was taken up in water. Insoluble material was collected by filtration and rinsed well with water. The solids were dried *in vacuo* affording 2.1 g of additional product. Total yield: 4.2 g, 60%. MS (ESI) m/z (M+H)⁺: 240 for $C_8H_9N_5O_2S$; 1H NMR (300 MHz, DMSO- d_6) δ 3.62 (s, 3H), 3.67 (s, 3H), 7.03 (s, 1H), 8.13 (s, 2H).

Methyl 2-chloro-4-(1-methyl-1*H*-1,2,4-triazol-5-yl)-5-thiazolecarboxylate (I3k) A solution of 3.9 g (56.5 mmol) NaNO₂ in 50 ml water was added dropwise to a solution of 4.64 g (19.6 mmol) of methyl 2-amino-4-(1-methyl-1*H*-1,2,4-triazol-5-yl)-1,3-thiazole-5-carboxylate (**I3k**) in 50 ml AcOH and 50 ml

conc. HCl cooled in an ice water bath. After stirring 1H, 1.7 g urea dissolved in water was added dropwise. After stirring 1H, solvent was removed and the residue was portioned between EtOAc and aq NaHCO₃. The EtOAc was separated and washed with brine. Drying (MgSO₄) and removal of solvent gave 4.3 g of product as a solid. MS (ESI) m/z (M+H)⁺: 259 for C₈H₇ClNO₂S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.86 (s, 3H), 3.93 (s, 3H), 8.03 (s, 1H).

Ethyl 2-chloro-4-(2-pyridinyl)-5-thiazolecarboxylate (IIj) Pyridine was added to a solution of ethyl 2-oxo-4-(pyridin-2-yl)-2,3-dihydro-1,3-thiazole-5-carboxylate (0.42 g, 1.7 mmol) in neat phosphorus oxychloride (5 ml), and the reaction mixture was heated to reflux for 3H. Solvent was removed, and the residue was diluted with water and extracted 3X with EtOAc. The EtOAc was dried (MgSO₄) and concentrated to afford 0.35 g (77%) of the title compound as an oil that was used in the next step without further purification. MS (ESI) m/z (M+H)⁺: 269 for C₁₁H₉ClN₂O₂S; ¹H NMR (300 MHz, CDCl₃) δ 1.16 (t, 3H), 4.21 (q, 2H), 7.52 (dd, 1H), 7.82 (d, 1H), 7.96 (t, 1H), 8.65 (d, 1H)

Methyl 2-chloro-4,4-dimethoxy-3-oxo-pentanoate SO₂Cl₂ (25 ml, 0.31 mol) was added slowly to a solution of 57.7 g (0.30 mol) of methyl 4,4-dimethoxy-3-oxopentanoate in 400 ml CH₂Cl₂ cooled in an ice water bath. The solution was warmed to rt and stirred for 2H. Solvent was removed to afford 67.4 g of the title compound as an oil that was used in the subsequent step without further purification. ¹H NMR (300 MHz, CDCl₃) δ 1.5 (s, 3H), 3.25 (2s, 6H), 4.8 (s, 3H), 5.3 (s, 1H).

Methyl 4-acetyl-2-amino-5-thiazolecarboxylate A solution of 67.4 g (0.30 mol) of the preceding compound and 39 g (0.51 mol) thiourea in 500 ml MeOH was heated at reflux overnight. Solvent was removed and the residue was dissolved in 1:1 acetone-5 N HCl, and the mixture was stirred rt for 2H. Insoluble material was filtered off. Acetone was removed from the filtrate, and the aq mixture was neutralized aq Na₂CO₃. Precipitated solids were filtered, washed with water and dried *in vacuo* to afford 25.6 g (43%) of the title compound MS (ESI) m/z (M+H)⁺: 188, 190 for C₇H₈N₂O₃S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 2.4 (s, 3H), 3.7 (s, 3H), 8.0 (s, 2H).

Methyl 4-acetyl-2-chloro-thiazole-5-carboxylate *t*-Butylnitrite (90%, 24 ml, 0.186 mol) was added to a mixture of 27.7 g (0.126 mol) of the preceding compound and 26.5 g (0.187 mmol) CuCl₂ in 400 ml CH₃CN at 0 °C, and the mixture was stirred at rt overnight. The mixture was quenched with aq. NaHSO₃, diluted with water and extracted with EtOAc. The EtOAc was washed with brine, dried (MgSO₄) and concentrated. The residue was triturated with Et₂O, which was filtered through a plug of silica gel rinsing through with CH₂Cl₂. Removal of solvent gave 19.5 g (56%) of the title compound as a solid. MS (ESI) m/z (M+H)⁺: 188, 190 for C₇H₆ClNO₃S; ¹H NMR (300 MHz, CDCl₃) δ 2.6 (s, 3H), 3.9 (s, 3H).

Methyl -2-chloro-4-(2-chloroacetyl)-5-thiazolecarboxylate A solution of 2.0 g (9.1 mmol) of the preceding compound and 6.3 g (18.2 mmol) trimethylbenzylammonium dichloriodide in 50 ml 1,2-dichloroethane and 20 ml MeOH was heated at reflux for 3H. Solvent was removed, and the residue was taken up in EtOAc and washed with aq NaHSO₃, water and brine. Drying (MgSO₄) and removal of solvent gave 2.0 g (100%) of an oil that was used without further purification in the next step MS (ESI) m/z (M+H)⁺: 222 for C₇H₅Cl₂NO₃S; ¹H NMR (300 MHz, CDCl₃) δ 3.91 (s, 3H), 4.72 (s, 2H).

Methyl 2'-amino-2-chloro-(4,4'-bithiazole)-5-carboxylate A solution of 770 mg (3.6 mmol) of the preceding compound and 270 mg (3.6 mmol) thiourea in 2 ml MeOH was heated at reflux for 90 min. Solvent was removed, and the residue was taken up in water and treated with aq Na₂CO₃ precipitating solids that were collected, washed with water and dried *in vacuo* to give 670 mg (67%) of product. MS (ESI) m/z (M+H)⁺: 276, 278 for C₈H₆ClN₃O₂S₂; ¹H NMR (300 MHz, CDCl₃) δ 7.79 (s, 1H), 5.11 (br. s., 2H), 3.88 (s, 4H).

Methyl 2-chloro-4-[(2*E*)-3-(dimethylamino)-1-oxo-2-propen-1-yl]-5-thiazolecarboxylate A solution of 1 g (4.55 mmol) methyl 4-acetyl-2-chloro-5-thiazolecarboxylate and 0.61 ml (4.6 mmol) dimethylformamide dimethylacetal in 4 ml toluene was heated at 100 °C for 3H in a microwave reactor. Solvent was removed and the residue was diluted with water, which was then saturated with NaCl. The solution was extracted 3 times with EtOAc, which was dried (MgSO₄) and concentrated. The residue was chromatographed on silica gel (100% DCM followed by gradient elution to 50% EtOAc in DCM) to give 480 mg (38%) of product as a viscous oil. ¹H NMR (300 MHz, CDCl₃) δ 2.88 (s, 3H), 3.11 (s, 3H), 3.87 (s, 3H), 5.61 (d, 1H), 7.82 (s, 1H).

Methyl 2-chloro-4-(1*H*-pyrazol-3-yl)-5-thiazolecarboxylate A solution of 700 mg (2.6 mmol) of the preceding compound and 193 mg (2.8 mmol) hydrazine hydrochloride in 4 ml AcOH was heated at 120 °C for 1 h. Solvent was removed and the residue was partitioned between aq NaHCO₃ and EtOAc. The EtOAc was separated, washed with brine, dried (MgSO₄) and concentrated. The residue was chromatographed on silica gel (100% CH₂Cl₂ followed by gradient elution to 100% EtOAc) to give 200 mg (32%) of product as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 4.00 (s, 3H), 7.12 (s, 1H), 7.73 (s, 1H), 13.04 (s, 1H).

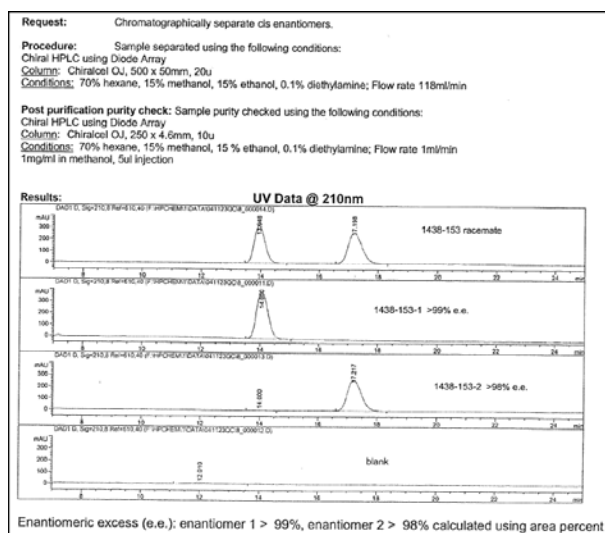
Ethyl 2-chloro-4-(chlorocarbonyl)-5-thiazolecarboxylate Oxalyl dichloride (1.13 g, 8.91 mmol) and 2 drops DMF were sequentially added to a solution of 5-ethyl 2-chloro-4,5-thiazolecarboxylate (2 g, 8.49 mmol) dissolved in dry CH₂Cl₂ (15 ml) cooled to 0 °C, and the reaction mixture was stirred at rt until the bubbling stopped. Solvent was removed and the residue was dried in vacuo overnight to afford the title compound as a solid (2.15 g, 100%). ¹H NMR (300 MHz, CDCl₃) δ 1.35 (t, 3H), 4.37 (q, 2H).

Ethyl 2-chloro-4-(3-methyl-1,2,4-oxadiazol-5-yl)-5-thiazolecarboxylate *N*-hydroxyacetimidamide (91 mg, 1.18 mmol) was added to a solution of the preceding compound (300 mg, 1.18 mmol) and 2,6-lutidine (0.206 ml, 1.77 mmol) in 5 ml of dry CH₂Cl₂ cooled to 0 °C, and the reaction mixture was stirred at 0 °C for 5 min. DMF (2 ml) was added to assist the solvation, and the reaction mixture was gradually warmed up to rt overnight. CH₂Cl₂ was removed and the remaining solution was heated at 55 °C for 4 days. The reaction mixture was diluted with EtOAc (20 ml), washed with water (3X) and brine. Drying (MgSO₄) and removal of solvent gave a residue that was chromatographed on silica gel (Hex/EtOAc) to afford 140 mg (43%) of product. MS (ESI) *m/z* (M+H)⁺: 274 for C₉H₈ClN₃O₃S; ¹H NMR (300 MHz, CDCl₃) δ 1.36 (t, 3H), 2.55 (s, 3H), 4.40 (q, 2H).

Ethyl 2-chloro-4-chlorocarbonyl-thiazole-5-carboxylate A mixture of 25.2 g (mmol) of the preceding compound in 70 ml SOCl₂ was heated at reflux for 20 min. Solvent was removed, and the residue was dissolved in CH₂Cl₂. Removal of solvent *in vacuo* gave a viscous oil that slowly solidified (25.55 g, 100%). ¹H NMR (300 MHz, CDCl₃) δ 1.26 (s, 3H).

Ethyl 2-chloro-4-(methylcarbamoyl)thiazole-5-carboxylate 2,6-Lutidine (12.9 ml, 0.11 mmol) and 2 *N*-methylamine in THF (55 ml, 0.11 mmol) were slowly added sequentially to a solution of the previous compound (25.66 g, 0.11 mmol) in 200 ml CH₂Cl₂. After stirring for 3 h, solvent was removed and the residue was partitioned between EtOAc and water. The EtOAc was separated and washed with sat. aq. NaHCO₃, 2 times with 1 N HCl and once with brine. The combined aq layers were twice more extracted with EtOAc, and each EtOAc extract was washed with sat. aq. NaHCO₃, 1 N HCl and brine. The combined EtOAc layers were dried (MgSO₄) and concentrated to give a solid that was re-crystallized from *n*-butylchloride to afford 17.5 g (64%) of the title compound. MS (ESI) *m/z* (M+H)⁺: 248, 250 for C₈H₉ClN₂O₃S; ¹H NMR (300 MHz, CDCl₃) δ 2.75 (d, 3H), 3.8 (s, 3H), 8.6 (m, 1H).

Ethyl (3*R*,4*S*)-*rel*-4-(benzylamino)-3-methoxypiperidine-1-carboxylate and ethyl (3*S*,4*R*)-*rel*-4-(benzylamino)-3-methoxypiperidine-1-carboxylate Ethyl (3*S*,4*R*)-*rel*-4-(benzylamino)-3-methoxypiperidine-1-carboxylate (6.2 g) was separated into its enantiomers by chromatography over a Chiralcel OJ column (eluant: hexanes/MeOH/EtOH;70/15/15;0.1% diethylamine). The first chromatographic peak ((-)-isomer) was consistent with the second title compound as a white solid (2.62 g) and the second chromatographic peak ((+)-isomer) was consistent with the second title compound as a white solid (2.71 g). MS (ESI) *m/z* (M+Na)⁺: 360 for C₁₇H₂₄N₂O₅; ¹H NMR (300 MHz, CDCl₃) δ 1.21 (t, 3H), 1.52-1.67 (m, 2H), 3.08 (m, 2H), 3.28 (s, 3H), 3.41 (s, 2H), 3.74-3.92 (m, 2H), 3.96 (m, 2H), 4.14 (m, 1H), 5.10 (s, 2H), 7.24 (d, 1H), 7.44 (m, 5H).



Ethyl (3*S*,4*R*)-4-amino-3-methoxypiperidine-1-carboxylate hydrochloride salt A mixture of ethyl (3*S*,4*R*)-4-(benzylamino)-3-methoxypiperidine-1-carboxylate (36.45 g, 125 mmol), 31.5 g (500 mol) ammonium formate and 4 g 10% Pd on carbon in 250 ml MeOH was heated at reflux overnight under N₂. The mixture was filtered through a bed of diatomaceous earth, and the filtrate was concentrated. Water (50 ml) was added to the residue, and the mixture extracted with a solution of ~3% methanol in chloroform (4 X 300 ml). Organic layers were combined, dried (MgSO₄) and concentrated to afford 24.18 g (96%) of the title compound as an off-white solid. MS (ESI) *m/z* (M+H)⁺: 202 for C₉H₁₈N₂O₃.

3,4-Dichloro-N-(3*R*,4*S*)-[3-methoxypiperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide (Scheme 1: chiral *ent*-6a, R1 = OMe) A mixture of 970 mg (2.55 mmol) of ethyl (3*R*,4*S*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-piperidine-1-carboxylate, 100 mL of 3N NaOH and 30 mL MeOH was heated at reflux overnight. The reaction mixture was cooled to ambient temperature and extracted with EtOAc. The EtOAc was separated, washed with water and dried (Na₂SO₄). Removal of solvent *in vacuo* gave 540 mg (69%) of the title compound, which was used in subsequent reactions without further purification. MS (ESI) *m/z* (M+H)⁺: 306; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.73 (m, 2H), 2.31 (s, 3H), 2.64 (m, 1H), 2.98 (m, 1H), 3.22 (m, 1H), 3.34 (m, 1H), 3.34 (s, 3H), 3.42 (m, 2H), 4.25 (m, 1H), 7.31 (d, 1H).

Methyl 2-[4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-1-piperidyl]thiazole-5-carboxylate (methyl ester of 1) A solution of 0.30 g (0.96 mol) 3,4-dichloro-5-methyl-N-piperidin-4-yl-1*H*-pyrrole-2-carboxamide hydrochloride, methyl 2-bromo-1,3-thiazole-5-carboxylate (0.213 g, 0.961 mmol) and Et₃N in NMP (3 mL) was heated at 150 °C for 20 minutes in a microwave reactor. The mixture was partitioned between water and EtOAc. The organic layer was washed with water and combined organic phase was dried over magnesium sulfate and concentrated to give the title compound (432 mg, 74%). MS (ESI) *m/z* (M+H)⁺: 417, 419 for C₁₆H₁₈Cl₂N₄O₃S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.70 (m, 2H); 1.97 (m, 2H); 2.24 (s, 3H); 3.39 (m, 2H); 3.81 (s, 3H); 4.03 (m, 2H); 4.13 (m, 1H); 7.34 (d, 1H); 7.93 (s, 1H); 12.03 (s, 1H).

Following the above procedure, the following 23 compounds were synthesized from the listed intermediates.

Methyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-fluoro-1-piperidyl]thiazole-5-carboxylate (methyl ester of 2) From 200 mg (0.61 mmol) of 3,4-dichloro-*N*-[(3*R*,4*S*)-3-fluoropiperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide hydrochloride, 134 mg (0.60 mmol) methyl 2-bromothiazole-5-carboxylate and 0.25 mL (1.8 mmol) Et₃N to afford 260 mg (100%) of product. MS (ESI) *m/z* *m/z* 435, 437 [M + H]⁺ for C₁₆H₁₇Cl₂FN₄O₃S; ¹H NMR (300 MHz, DMSO-*d*₆) δ

1.77-1.79 (m, 2H), 2.12 (s, 3H), 3.25-3.27 (m, 2H), 3.49-3.62 (dd, 1H), 3.68 (s, 3H), 3.95 (m, 1H), 4.00-4.24 (m, 1H), 4.82-4.99 (m, 1H), 7.21 (d, 1H), 7.79 (s, 1H), 12.05 (brs, 1H).

Methyl 2-[(3*R*,4*S*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylate (methyl ester of **26**) From 265 mg (0.865 mmol) of 3,4-dichloro-*N*-[(3*S*,4*R*)-[3-methoxypiperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide (chiral *ent*-**6a**), and 192 mg (0.865 mmol) of methyl 2-bromothiazole-5-carboxylate and 0.30 mL (1.73 mmol) of DIEA to afford 302 mg (78%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 447 for C₁₇H₂₀Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.87 (m, 2H), 2.05 (m, 2H), 2.27 (s, 3H), 3.01 (m, 2H), 3.25 (s, 3H), 3.65 (m, 1H), 3.83 (s, 3H), 4.12 (m, 1H), 4.46 (m, 2H), 7.40 (d, 1H), 8.00 (s, 1H), 12.38 (s, 1H).

Methyl 2-[(3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-ethoxy-1-piperidyl]thiazole-5-carboxylate (methyl ester of **28**) From 238 mg (0.74 mmol) of *N*-[(3*S*,4*R*)-*rel*-3-ethoxy-4-piperidyl]-3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamide, 182 mg (0.82 mmol) of methyl 2-bromothiazole-5-carboxylate and 0.78 mL (4.6 mmol) of DIEA to afford 102 mg (30%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 461, 463 for C₁₈H₂₂Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.04 (t, 3H); 1.75 (m, 2H); 2.17 (s, 3H); 3.35-3.45 (m, 3H); 3.63 (m, 2H); 3.73 (s, 3H); 3.96 (m, 1H); 4.25 (m, 2H); 7.11 (d, 1H); 7.82 (s, 1H); 12.12 (s, 1H).

Methyl 2-[(3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-allyloxy-1-piperidyl]thiazole-5-carboxylate (methyl ester of **29**) From 400 mg (1.2 mmol) of *N*-[(3*S*,4*R*)-*rel*-3-allyloxy-4-piperidyl]-3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamide, 242 mg (1.2 mmol) of methyl 2-bromothiazole-5-carboxylate and 0.23 mL (1.3 mmol) of DIEA to afford 490 mg (86%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 473, 475 for C₁₉H₂₂Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.94 (m, 2H), 2.23 (s, 3H), 3.56 (m, 2H), 3.58 (m, 2H), 3.84 (s, 3H), 4.07 (m, 2H), 4.21 (m, 1H), 4.46 (m, 2H), 5.37 (m, 2H), 5.95 (m, 1H), 7.29 (d, 1H), 7.96 (s, 1H), 12.32 (s, 1H).

Methyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-prop-2-ynoxy-1-piperidyl]thiazole-5-carboxylate (methyl ester of **30**) From 330 mg (1.0 mmol) of 3,4-dichloro-5-methyl-*N*-[(3*S*,4*R*)-3-prop-2-ynoxy-4-piperidyl]-1*H*-pyrrole-2-carboxamide, 222 mg (1.0 mmol) of methyl 2-bromothiazole-5-carboxylate and 170 μL (1.0 mmol) of DIEA to afford 371 mg (79%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 471 for C₁₉H₂₀Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.76 (m, 2H); 2.18 (s, 3H); 3.36 (m, 2H); 3.44 (t, 1H); 3.74 (s, 3H); 3.87 (s, 1H); 3.98 (m, 1H); 4.22-4.36 (m, 4H); 7.15 (d, 1H); 7.83 (s, 1H); 12.15 (s, 1H).

Methyl 2-[(3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-(2-methoxyethoxy)-1-piperidyl]thiazole-5-carboxylate (ester of **31**) From 80 mg (0.23 mmol) of 3,4-dichloro-*N*-[(3*S*,4*R*)-3-(2-methoxyethoxy)-4-piperidyl]-5-methyl-1*H*-pyrrole-2-carboxamide, 51 mg (0.23 mmol) of methyl 2-bromothiazole-5-carboxylate and 44 μL (0.25 mmol) of DIEA to afford 69 mg (61%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 491 for C₁₉H₂₄Cl₂N₄O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.72-1.80 (m, 2H), 2.17 (s, 3H), 3.13 (s, 3H), 3.25-3.42 (m, 4H), 3.52-3.60 (m, 1H), 3.65-3.75 (m, 2H), 3.73 (s, 3H); 3.85-4.05 (m, 1H); 4.20-4.35 (m, 2H), 7.14 (d, 1H), 7.82 (s, 1H), 12.14 (brs, 1H).

Methyl 2-[(3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methyl-1-piperidyl]thiazole-5-carboxylate (ester of **32**) From 63 mg (0.22 mmol) of 3,4-dichloro-5-methyl-*N*-[(3*S*,4*R*)-*rel*-3-methyl-4-piperidyl]-1*H*-pyrrole-2-carboxamide, 50 mg (0.22 mmol) of methyl 2-bromothiazole-5-carboxylate and 100 μL (0.57 mmol) of DIEA to afford 69 mg (61%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 431, 433 for C₁₇H₂₀Cl₂N₄O₃S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.9 (d, 3H), 1.8 (m, 2H), 2.2 (m, 4H), 3.2 (m, 3H), 3.4-3.7 (m, 3H), 3.7 (s, 3H), 4.1 (m, 1H), 4.25 (m, 1H), 7.1 (d, 1H), 7.9 (s, 1H), 12.0 (s, 1H).

Methyl 2-[(3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-(methoxymethyl)-1-piperidyl]thiazole-5-carboxylate (methyl ester of **33**) From 162 mg (0.45 mmol) of *tert*-butyl (3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-(methoxymethyl)piperidine-1-carboxylate hydrochloride salt, 111 mg (0.5 mmol) of methyl 2-bromothiazole-5-carboxylate and 225 μL (1.36 mmol) of DIEA to afford 130 mg (61%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 461 for C₁₈H₂₂Cl₂N₄O₄S; ¹H NMR (300 MHz, CDCl₃) δ 9.86 (s, 1H), 7.89 (s, 1H), 6.78 (d, *J*=7.9 Hz, 1H), 4.00-4.29 (m, 3H), 3.85

(s, 3H), 3.45-3.56 (m, 1H), 3.35-3.45 (m, 1H), 3.25-3.3 (m, 1H), 3.17-3.25 (m, 1H), 3.08 (dd, $J=11.21$, 13.28 Hz, 1H), 2.31 (s, 3H), 2.2-2.3 (m, 1H), 1.9-2.1 (m, 1H), 1.6-1.8 (m, 1H).

Methyl 2-[(3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-(hydroxymethyl)-1-piperidyl]thiazole-5-carboxylate (methyl ester of **34**) From 150 mg (0.44 mmol) of *tert*-butyl (3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-(hydroxymethyl)piperidine-1-carboxylate hydrochloride salt, 97 mg (0.44 mmol) of methyl 2-bromothiazole-5-carboxylate, and 76 μ L (0.44 mmol) DIEA to afford 149 mg (76%) of product. MS (ESI) m/z ($M+H$)⁺: 447, 449 for C₁₇H₂₀Cl₂N₄O₄S; ¹H NMR (300 MHz, CDCl₃) δ 10.1 (br. s., 1H), 7.86 (s, 1H), 7.15 (d, $J=7.9$ Hz, 1H), 4.6-4.7 (m, 1H), 4.0-4.35 (m, 2H), 3.85-4.0 (m, 1H), 3.84 (s, 3H), 3.70 (m, 1H), 3.35-3.6 (m, 3H), 3.28 (m, 1H), 2.29 (s, 3H), 1.9-2.2 (m, 2H).

Methyl 2-[(3*S*,4*R*)-*rel*-3-chloro-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-1-piperidyl]thiazole-5-carboxylate (methyl ester of **35**) From 150 mg (0.439 mmol) of 3,4-dichloro-*N*-[(3*S*,4*R*)-*rel*-3-chloro-4-piperidyl]-5-methyl-1*H*-pyrrole-2-carboxamide hydrochloride salt, 97 mg (0.43 mmol) of methyl 2-bromothiazole-5-carboxylate, and 270 μ L (1.54 mmol) DIEA to afford 80 mg (41%) of product. MS (ESI) m/z ($M+H$)⁺: 451, 453 for C₁₆H₁₇Cl₃N₄O₃S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.17 (t, 3H), 1.84 (m, 1H), 1.93 (m, 1H), 2.20 (s, 3H), 3.45 (m, 1H), 3.75 (s, 3H), 3.82 (d, 1H), 4.02 (m, 1H), 4.26 (m, 1H), 4.50 (m, 1H), 4.76 (s, 1H), 7.15 (d, 1H), 7.85 (s, 1H), 12.12 (s, 1H).

Methyl 2-[(3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-(methylthio)-1-piperidyl]thiazole-5-carboxylate (methyl ester of **36**) From 161 mg (0.50 mmol) of (3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methylsulfanyl-piperidine-1-carboxylate hydrochloride salt, 110 mg (0.5 mmol) of methyl 2-bromothiazole-5-carboxylate, and 250 μ L (1.5 mmol) DIEA to afford 160 mg (69%) of product. MS (ESI) m/z ($M+H$)⁺: 463, 465 for C₁₇H₂₀Cl₂N₄O₃S₂; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.90 (m, 2H); 2.14 (s, 3H); 2.28 (s, 3H); 3.28-3.45 (m, 2H); 3.74 (s, 3H); 3.77 (m, 1H); 3.95 (m, 2H); 4.44 (m, 1H); 7.25 (d, 1H); 7.85 (s, 1H); 12.14 (s, 1H).

Methyl 2-[(3*S*,4*R*)-*rel*-3-azido-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-1-piperidyl]thiazole-5-carboxylate (methyl ester of **38**) From 724 mg (22 mmol) of *N*-[(3*S*,4*R*)-3-azido-4-piperidyl]-3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamide HBr salt, 536 mg (2.4 mmol) methyl 2-bromothiazole-5-carboxylate, and 1.9 mL (11.5 mmol) DIEA to afford 96 mg (67%) of product. MS (ESI) m/z ($M+H$)⁺: 458, 460 for C₁₆H₁₇Cl₂N₇O₃S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.8 (m, 2H), 2.19 (s, 3H), 3.35 (m, 1H), 3.6 (d, 1H), 3.75 (s, 3H), 3.95 (d, 1H), 4.24 (m, 3H), 7.23 (d, 1H), 7.86 (s, 1H), 12.2 (s, 1H).

Methyl 2-[6-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-1,4-dioxo-9-azaspiro[4.5]decan-9-yl]thiazole-5-carboxylate (methyl ester of **40**) From 100 mg (0.30 mmol) of 3,4-dichloro-*N*-1,4-dioxo-7-azaspiro[4.5]dec-10-yl-5-methyl-1*H*-pyrrole-2-carboxamide, 66 mg (0.30 mmol) methyl 2-bromothiazole-5-carboxylate, and 100 μ L (0.60 mmol) DIEA to afford 96 mg (67%) of product. MS (ESI) m/z $M+H$ ⁺: 475, 477 for C₁₈H₂₀Cl₂N₄O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.69 (d, 1H), 1.93 (s, 1H), 2.18 (s, 3H), 3.30 - 3.42 (m, 4H), 3.75 (s, 3H), 3.77 - 3.86 (m, 1H), 3.90 - 4.02 (m, 2H), 4.02 - 4.09 (m, 1H), 4.09 - 4.21 (m, 2H), 4.35 - 4.48 (m, 1H), 6.95 (d, 1H), 7.83 (s, 1H), 12.17 (s, 1H).

Methyl 2-[11-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-1,5-dioxo-8-azaspiro[5.5]undecan-8-yl]thiazole-5-carboxylate (methyl ester of **41**) From 80 mg (0.23 mmol) of 3,4-dichloro-*N*-1,5-dioxo-8-azaspiro[5.5]undec-11-yl-5-methyl-1*H*-pyrrole-2-carboxamide, 51 mg (0.23 mmol) methyl 2-bromothiazole-5-carboxylate, and 80 μ L (0.46 mmol) DIEA to afford 80 mg (76%) of product. MS (ESI) m/z ($M+H$)⁺: 489 for C₁₉H₂₂Cl₂N₄O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.50 (d, 1H), 1.67 (s, 1H), 1.89 (s, 2H), 2.19 (s, 3H), 3.17 (d, 1H), 3.31 (s, 3H), 3.49 (s, 1H), 3.75 (s, 3H), 3.84 (s, 2H), 4.07 (s, 2H), 4.15 (d, 2H), 5.11 (s, 1H), 7.17 (d, 1H), 7.86 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-methyl-thiazole-5-carboxylate (ethyl ester of **47**) From 2.5 g (8.16 mmol) of chiral **6a**, 1.68 g (8.16 mmol) of ethyl 2-chloro-4-methylthiazole-5-carboxylate, and 3.14 mL (18 mmol) DIEA to afford 152 mg (91%) of the title compound. MS (ESI) m/z ($M+H$)⁺: 475, 477 for C₁₉H₂₄Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.22 (t, 3H); 1.72 (m, 2H); 2.17 (s, 3H); 2.42 (s, 3H); 3.31 (m, 5H); 3.52 (m, 1H); 3.90 (m, 1H); 4.16 (q, 2H); 4.26 (m, 2H); 7.14 (d, 1H); 12.14 (br s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-1,3-benzothiazole-7-carboxylate (ethyl ester of **48**) From 100 mg (0.35 mmol) of chiral **6a**, 80 mg (0.35 mmol) of ethyl 2-chlorobenzo[*d*]thiazole-7-carboxylate¹², and 0.18 mL (1.05 mmol) DIEA to afford 152 mg (91%) of the title compound. MS (ESI) *m/z* (*M*+*H*)⁺: 511, 513 for C₂₂H₂₄Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.36 (t, 3H), 1.79 (m, 2H), 2.18 (s, 3H), 3.32-3.59 (m, 4H), 4.21 (m, 1H), 4.37 (m, 1H), 4.37 (q, 2H), 7.19 (d, 1H), 7.41 (t, 1H), 7.66 (m, 2H), 12.17 (s, 1H).

Methyl 4-acetyl-2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-5-thiazolecarboxylate (methyl ester of **50**) From 6.64 g (19.4 mmol) of chiral **6a**, 4.26 g (19.4 mmol) of methyl 4-acetyl-2-chloro-thiazole-5-carboxylate and 8.4 mL (48 mmol) DIEA to afford 8.22 g (87%) of the title compound MS (ESI) *m/z* (*M*+*H*)⁺: 489, 491 for C₁₉H₂₄Cl₂N₄O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.75 (m, 2H), 2.2 (s, 3H), 2.45 (s, 3H), 3.2-3.4 (m), 3.9 (m, 1H), 4.3 (m, 2H), 7.15 (d, 1H), 12.15 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(hydroxymethyl)thiazole-5-carboxylate (ethyl ester of **54**) From 119 mg (0.39) of racemic **6a**, 86 mg (0.39 mmol) of ethyl 2-chloro-4-(hydroxymethyl)-thiazole-5-carboxylate and 0.10 mL Et₃N to afford 130 mg of the title compound as a white solid. MS (ESI) *m/z* (*M*+*H*)⁺: 491, 493 for C₁₉H₂₄Cl₂N₄O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.2 (t, 3H), 1.7 (m, 2H), 2.2 (s, 3H), 3.4 (s, 3H), 3.55 (m, 1H), 4.0 (m, 1H), 4.1-4.4 (m, 4H), 4.6 (s, 2H), 7.1 (d, 1H), 12.1 (s, 1H).

Methyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(methoxymethyl)thiazole-5-carboxylate (methyl ester of **55**) From 2.20 g (7.10) of chiral **6a**, 1.52 g (6.84 mmol) of ethyl 2-chloro-4-(methoxymethyl)thiazole-5-carboxylate and 2.63 mL (15.1 mmol) of DIEA to afford 2.36 g (70%) of the title compound. MS (ESI) *m/z* (*M*+*H*)⁺: 491, 493 for C₁₉H₂₄Cl₂N₄O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.66-1.81 (m, 2H), 2.14-2.22 (m, 3H), 3.29 (s, 3H), 3.33 (s, 2H), 3.36 (s, 3H), 3.55 (s, 1H), 3.73 (s, 3H), 3.97 (s, 1H), 4.20 - 4.35 (m, 2H), 4.57 (d, *J*=1.3 Hz, 2H), 7.15 (d, *J*=8.29 Hz, 1H), 12.15 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-4-carboxylate (ethyl ester of **57**) From 110 mg (0.32 mmol) of chiral **6a** and 76 mg (0.32 mmol) ethyl 2-bromo-1,3-thiazole-4-carboxylate to afford 116 mg (77%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 461, 463 for C₁₈H₂₂Cl₂N₄O₄S; ¹H NMR (300 MHz, CDCl₃) δ 10.28 (s, 1H), 7.36 (s, 1H), 7.22 (d, *J*=8.48 Hz, 1H), 7.20 (s, 1H), 4.41 (d, *J*=13.56 Hz, 1H), 4.18-4.32 (m, 3H), 3.91 (d, *J*=13.19 Hz, 1H), 3.40 (s, 3H), 3.46 (m, 1H), 3.06-3.23 (m, 2H), 2.21 (s, 3H), 1.86-1.96 (m, 1H), 1.77-1.85 (m, 1H), 1.30 (t, *J*=7.06 Hz, 3H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-5-methyl-thiazole-4-carboxylate (ethyl ester of **58**) From 750 mg (2.45) of chiral **6a**, 613 mg (2.45 mmol) of ethyl 2-chloro-5-methylthiazole-4-carboxylate and 1.3 mL (325 mg, 7.35 mmol) DIEA to afford 325 mg (28%) of the title compound. MS (ESI) *m/z* (*M*+*H*)⁺: 475, 477 for C₁₉H₂₄Cl₂N₄O₄S.

Methyl 2-[(3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-(methylsulfonyl)-1-piperidyl]thiazole-5-carboxylate (methyl ester of **37**) A solution of 100 mg (0.215 mmol) of the methyl ester of **36** and 90 mg (0.43 mmol) *m*-CPBA in 4 mL CH₂Cl₂ and 4 mL THF was stirred at rt for 4 h. The mixture was concentrated, and the residue was chromatographed on silica gel (50-90% EtOAc in hexanes gradient) to afford the title compound (60 mg, 56%) as a solid. MS (ESI) *m/z* (*M*+*H*)⁺: 495 for C₁₇H₂₀Cl₂N₄O₅S₂; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.88 (m, 2H); 2.18 (s, 3H); 3.07 (s, 3H); 3.45 (t, 1H); 3.61 (t, 1H); 3.60-3.85 (m, 2H); 3.77 (s, 3H); 4.48 (m, 1H); 4.68 (m, 1H); 7.52 (d, 1H); 7.93 (s, 1H); 12.07 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-formyl-thiazole-5-carboxylate Dess-Martin periodinane (0.61 g, 1.4 mmol) was added to a solution of the ethyl ester of **54** (0.63 g, 1.3 mmol) in CH₂Cl₂. After 1H stirring at rt, the reaction mixture was washed twice with water and with brine. Drying (MgSO₄) and removal of solvent was followed by chromatography on silica gel (100% CH₂Cl₂ with gradient elution to 1:1 EtOAc in CH₂Cl₂) to afford the title compound as a solid (0.56 g, 88%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.29 (t, 3H) 1.75 (s, 2H) 2.18

(s, 3H) 3.38 (s, 4H) 3.44 (s, 1H) 3.57 (s, 1H) 4.03 (d, 1H) 4.22 - 4.35 (m, 4H) 7.15 (d, 1H) 10.31 (s, 1H) 12.16 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(morpholinomethyl)thiazole-5-carboxylate (ethyl ester of **56**) To a solution of the preceding compound (0.15 g, 0.31 mmol) in CH₂Cl₂ (20 mL) was added sodium triacetoxyborohydride (0.1 g, 0.47 mmol) and morpholine (0.03 mL, 0.34 mmol). The reaction was stirred at rt for 3H before being quenched with 1N HCl and partitioned between EtOAc and sat. aq. NaHCO₃. The organic layer was separated and washed with brine. Drying (MgSO₄) and removal of solvent was followed by chromatography on silica gel (gradient elution 70-100% EtOAc/CH₂Cl₂) to afford product (0.091 g, 52%) as a solid. MS (ESI) *m/z* M+H⁺: 560 for C₂₃H₃₁Cl₂N₅O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.24 (t, 3H) 1.75 (s, 2H) 2.18 (s, 3H) 3.32 (s, 2H) 3.36 (s, 3H) 3.52 (s, 2H) 3.54 (d, 4H) 3.65 - 3.75 (m, 2H) 3.76 - 3.86 (m, 2H) 3.93 (s, 1H) 4.18 (q, 2H) 4.27 (s, 1H) 7.16 (d, 1H) 12.16 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(difluoromethyl)thiazole-5-carboxylate (ethyl ester of **49**) Diethylaminosulfurtrifluoride (0.03 mL, 0.22 mmol) was added to a solution of ethyl 2-[(3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-formyl-thiazole-5-carboxylate (0.10 g, 0.2 mmol) in CH₂Cl₂, and the reaction mixture was heated at reflux overnight. Upon cooling to rt, the solution was washed with water (3X) and brine, dried (MgSO₄) and concentrated to afford a yellow solid which, upon trituration with Et₂O, yielded a clean white solid (51 mg, 50%). MS (ESI) *m/z* M+H: 511, 513 for C₁₉H₂₂Cl₂F₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.26 (t, 3H) 1.75 (s, 2H) 2.18 (s, 3H) 3.37 (s, 3H) 3.43 (s, 1H) 3.56 (s, 1H) 3.96 (s, 1H) 4.25 (s, 1H) 4.36 (s, 2H) 7.16 (s, 1H) 7.31 (s, 1H) 12.17 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-*rel*-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(dimethylcarbamoyl)thiazole-5-carboxylate (ethyl ester of **52**) A solution of 0.062 g (0.12 mmol) of 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-5-ethoxycarbonyl-thiazole-4-carboxylic acid (**18**), dimethylamine (0.06 mL, 2M solution in THF), HATU (0.05 g, 0.13 mmol) and Et₃N (0.018 mL, 0.13 mmol) was stirred at rt for 30 min. The crude reaction mixture was slowly poured into water and the resulting white precipitate was filtered, washed with water and dried under vacuum to yield pure product (0.028 g). MS (ESI) *m/z* (M+H)⁺: 532 for C₂₁H₂₇Cl₂N₅O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.20 (t, 3H) 1.76 (s, 2H) 2.18 (s, 3H) 2.78 (s, 3H) 2.93 (s, 3H) 3.29 (d, 1H) 3.36 (s, 3H) 3.39 - 3.43 (m, 1H) 3.55 (s, 1H) 3.91 (s, 1H) 4.15 (q, 2H) 4.29 (s, 2H) 7.15 (d, 1H) 12.14 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-[(1-methyl-1-phenyl-ethyl)carbamoyl]thiazole-5-carboxylate (intermediate to ethyl ester of **61**) From 250 mg (0.50 mmol) of **18**, 190 mg (0.50 mmol) of HATU, 77 μL (0.55 mmol) of TEA and 190 mg (0.5 mmol) of cumylamine to afford 270 mg (88%) of product. MS (ESI) *m/z* (M+H)⁺: 622, 624 for C₂₈H₃₃Cl₂N₅O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.23 (t, 3H) 1.59 (s, 3H) 1.62 (s, 3H) 1.77 (s, 2H) 2.19 (s, 3H) 3.31 (s, 1H) 3.36 (s, 1H) 3.40 (s, 3H) 3.57 (s, 1H) 3.96 (s, 1H) 4.21 (q, 2H) 4.32 (s, 2H) 7.12 - 7.22 (m, 2H) 7.29 (t, 2H) 7.46 (d, 2H) 8.62 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(2-methoxyethylcarbamoyl)thiazole-5-carboxylate (ethyl ester of **62**) From 35 g (69 mmol) of **18**, 26.2 g (69 mmol) of HATU, 10.7 mL (76 mmol) of TEA and 26.2 mg (69 mmol) of 2-methoxyethylamine to afford 38.0 g (97%) of product. MS (ESI) *m/z* (M+H)⁺: 562 for C₂₂H₂₉Cl₂N₅O₆S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.15 - 1.25 (m, 3H) 1.74 (s, 2H) 2.18 (s, 3H) 3.26 (s, 3H) 3.30 (s, 1H) 3.36 (s, 3H) 3.41 (d, 3H) 3.55 (s, 1H) 4.00 (s, 1H) 4.10 - 4.19 (m, 2H) 4.26 (s, 2H) 7.15 (d, 1H) 8.44 - 8.56 (m, 1H) 12.16 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino]-3-methoxypiperidin-1-yl]-4-[(2*S*)-2-methoxypropyl]carbamoyl]-1,3-thiazole-5-carboxylate (ethyl ester of **64**) From 200 mg (0.395 mmol) of **18**, 50 mg (125 mmol) of (2*S*)-2-methoxypropan-1-amine, 150 mg (0.395 mmol) HATU and 0.12 mL (0.83 mmol) Et₃N to afford 182 mg (63%) of product. MS (ESI) *m/z* (M+H)⁺: 576, 578 for C₂₃H₃₁Cl₂N₅O₆S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.09 (d, 3H) 1.22 (t, 3H) 1.75 (s, 2H) 2.18 (s, 3H)

3.17 (s, 2H) 3.26 (s, 3H) 3.37 (s, 3H) 3.55 (s, 1H) 4.01 (d, 1H) 4.17 (d, 2H) 4.27 (s, 2H) 7.16 (s, 1H) 8.32 (d, 1H) 12.16 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-[[2-methoxy-1,1-bis(methoxymethyl)ethyl]carbamoyl]thiazole-5-carboxylate (ethyl ester of **66**)

From 1.5 g (3.0 mmol) of **18**, 1.14 g (3.0 mmol) of HATU, 0.46 mL (3.3 mmol) TEA and 0.60 g (3.0 mmol) of 1,3-dioxolan-2-ylmethanamine²¹ to afford 1.61 mg (75%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 651, 652 for C₂₆H₃₇Cl₂N₅O₈S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.2 (s, 1H), 7.84 (s, 1H), 7.16 (d, *J*=8.10 Hz, 1H), 4.08-4.33 (m, 4H), 3.93 (br. s., 1H), 3.63 (s, 5H), 3.55 (br. s., 1H), 3.38-3.42 (m, 1H), 3.29-3.36 (m, 4H), 3.25 (s, 6H), 2.19 (s, 3H), 1.75 (d, *J*=4.5 Hz, 2H), 1.24 (t, *J*=7.06 Hz, 3H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(1,3-dioxolan-2-ylmethylcarbamoyl)thiazole-5-carboxylate (ethyl ester of **67**)

From 150 mg (0.30 mmol) of **18**, 110 mg (0.30 mmol) of HATU, 46 μL (0.33 mmol) of Et₃N and 0.28 mL (0.30 mmol) of 1,3-dioxolan-2-ylmethanamine to afford 122 mg (69%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 590 for C₂₃H₂₉Cl₂N₅O₇S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.22 (d, 3H) 1.75 (s, 2H) 2.18 (s, 3H) 3.36 (s, 4H) 3.55 (s, 1H) 3.80 (s, 2H) 3.91 (s, 2H) 4.00 (s, 1H) 4.16 (s, 3H) 4.28 (s, 2H) 4.94 (s, 1H) 7.14 (s, 1H) 8.59 (s, 1H) 12.16 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-[(2,2-dimethyl-1,3-dioxan-5-yl)carbamoyl]thiazole-5-carboxylate (ethyl ester of **68**)

From 39 mg (0.30 mmol) of **18**, 110 mg (0.30 mmol) of HATU, 46 μL (0.30 mmol) TEA, and 79 mg (0.30 mmol) of 2,2-dimethyl-1,3-dioxan-5-ylamine to²⁰ afford 118 mg (43%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 618 for C₂₅H₃₃Cl₂N₅O₇S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.22 (t, 3H) 1.34 (s, 3H) 1.35 - 1.39 (m, 3H) 1.76 (s, 2H) 2.19 (s, 3H) 3.34 (s, 4H) 3.37 (s, 3H) 3.56 (s, 1H) 3.60 - 3.71 (m, 2H) 3.90 (d, 2H) 4.18 (q, 2H) 4.25 (s, 1H) 7.15 (d, 1H) 8.53 (d, 1H) 12.17 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-[(2-methyl-1,3-dioxolan-2-yl)methylcarbamoyl]thiazole-5-carboxylate (ethyl ester of **69**)

From 140 mg (0.30 mmol) of **18**, 110 mg of HATU, 46 μL of TEA, and 35 mg (0.30 mmol) of 2,2-dimethyl-1,3-dioxan-5-ylamine to afford 132 mg (73%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 604 for C₂₄H₃₁Cl₂N₅O₇S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.15 - 1.24 (m, 3H) 1.30 (s, 3H) 1.74 (s, 2H) 2.19 (s, 3H) 3.28 (d, 2H) 3.37 (s, 3H) 3.56 (s, 1H) 3.90 (d, 2H) 4.16 (q, 1H) 4.27 (s, 2H) 7.15 (d, 1H) 8.45 (s, 1H) 12.17 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-[2-(2-oxopyrrolidin-1-yl)ethylcarbamoyl]thiazole-5-carboxylate (ethyl ester of **70**)

From 150 mg (0.30 mmol) of **18**, 110 mg (0.30 mmol) of HATU, 46 μL (0.33 mmol) of TEA and 38 mg (0.30 mmol) of 1-(2-aminoethyl)pyrrolidin-2-one to afford 107 mg (58%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 616, 618 for C₂₅H₃₂Cl₂N₆O₆S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.2 (s, 1H), 8.5 (br. s, 1H), 7.15 (d, *J*=8.29 Hz, 1H), 4.22-4.35 (m, 2H), 4.16 (q, *J*=6.78 Hz, 2H), 3.96 (m, 1H), 3.55-3.6 (m, 1H), 3.32-3.46 (m, 10H), 2.19 (s, 3H), 1.8-2.0 (m, 2H), 1.7-1.8 (m, 2H), 1.21 (t, *J*=7.16 Hz, 3H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(2-morpholinoethylcarbamoyl)thiazole-5-carboxylate (ethyl ester of **71**)

From 100 mg (0.20 mmol) of **18**, 76 mg (0.20 mmol) of HATU, 31 μL (0.22 mmol) of TEA and 26 mg (0.20 mmol) of 2-morpholinoethanamine to afford 74 mg (60%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 617, 619 for C₂₅H₃₄Cl₂N₆O₆S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.22 (d, 3H) 1.75 (s, 2H) 2.18 (s, 3H) 3.34 (m, 5H) 3.36 (s, 3H) 3.55 (s, 1H) 3.80 (s, 2H) 3.91 (s, 2H) 4.02 (s, 1H) 4.16 (s, 2H) 4.27 (s, 2H) 4.94 (s, 1H) 7.14 (s, 1H) 8.59 (s, 1H) 12.16 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(morpholinocarbamoyl)thiazole-5-carboxylate (ethyl ester of **72**)

From 150 mg (0.30 mmol) of **18**, 110 mg (0.30 mmol) of HATU, 46 μL (0.33 mmol) of TEA and 31 mg (0.30 mmol) of 1-amino-morpholine to afford 118 mg (67%) of product. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.2 (br. s., 1H), 9.44 (s, 1H), 7.15 (d, *J*=8.29 Hz, 1H), 4.0-4.4 (m, 3H), 3.8-4.05 (m, 1H), 3.6-3.7 (m, 2H), 3.55 (m, 1H), 3.3-3.45 (m, 6H), 2.75-2.85 (m, 2H), 2.6-2.75 (m, 1H), 2.19 (s, 3H), 1.77-1.8 (m, 1H), 1.1-1.32 (t, *J*=6 Hz, 3H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-pyrimidin-4-yl-thiazole-5-carboxylic acid (ethyl ester of **76**) From 80 mg (0.23 mmol) of chiral **6a**, and 57 mg (0.21 mmol) of ethyl 2-chloro-4-(4-pyrimidinyl)-5-thiazolecarboxylate and 56 mg NaHCO₃ to afford 86 mg (69%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 539 for C₂₂H₂₄Cl₂N₆O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.02 (t, 3H), 1.70 (m, 2H), 2.12 (s, 3H), 3.25 (m, 2H), 3.31 (s, 3H), 3.50 (s, 1H), 4.00 (q, 2H), 4.22 (m, 3H), 7.09 (d, 1H), 7.66 (d, 1H), 8.83 (d, 1H), 9.17 (s, 1H), 12.10 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(4,6-dimethoxypyrimidin-2-yl)thiazole-5-carboxylate (ethyl ester of **78**) From 98 mg (0.29) of chiral **6a**, 94 mg of ethyl 2-amino-4-(4,6-dimethoxy-2-pyrimidinyl)-5-thiazolecarboxylate and 74 mg NaHCO₃ (85 mmol) to afford 131 mg (75%) of the product. MS (ESI) *m/z* (*M*+*H*)⁺: 599 for C₂₄H₂₈Cl₂N₆O₆S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.96 (t, 3H), 1.70 (m, 2H), 2.12 (s, 3H), 3.27 (s, 6H), 3.79 (m, 6H), 3.95 (q, 2H), 4.22 (m, 2H), 6.23 (s, 1H), 7.09 (d, 1H), 12.10 (s, 1H).

Methyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-[1-(methoxymethyl)imidazol-2-yl]thiazole-5-carboxylate (methyl ester of **79**) From 962 mg (3.2 mmol) of chiral **6a**, 1.1 g (3.2 mmol) methyl 2-chloro-4-[1-(methoxymethyl)-1*H*-imidazol-2-yl]-5-thiazolecarboxylate and 675 mg (8 mmol) NaHCO₃ to afford 1.45 g (81%) of the title compound. MS (ESI) *m/z* (*M*+*H*)⁺: 557, 559 for C₂₂H₂₆Cl₂N₆O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.81 (m, 2H), 2.23 (s, 3H), 3.14 (s, 3H), 3.43 (m, 4H), 3.58 (m, 1H), 3.65 (s, 3H), 4.02 (m, 1H), 4.34 (m, 2H), 5.26 (s, 2H), 7.15 (d, 1H), 7.39 (s, 2H), 12.22 (s, 1H).

Methyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(4-methoxypyrimidin-2-yl)thiazole-5-carboxylic acid (methyl ester of **80**) From 80 mg (0.26 mmol) of chiral **6a**, 75 mg (0.26 mmol) of methyl 2-chloro-4-(4-methoxypyrimidin-2-yl)thiazole-5-carboxylate and 73 μL 0.052 mmol Et₃N to afford 115 mg (79%) of the title compound. MS (ESI) *m/z* (*M*+*H*)⁺: 555, 557 for C₂₂H₂₄Cl₂N₆O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.75 (m, 2H), 2.19 (s, 3H), 3.39 (s, 3H), 3.3-3.4(m), 3.59 (s, 3H) 3.89 (s, 3H), 4.03 (m, 1H), 4.2-4.35 (m, 3H), 6.98 (d, 1H), 7.18 (d, 1H), 8.58 (d, 1H), 12.17 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(1-methylimidazol-4-yl)thiazole-5-carboxylate (ethyl ester of **81**) From 200 mg (0.65 mmol) of chiral **6a**, 142 mg (0.52 mmol) of ethyl 2-chloro-4-(1-methylimidazol-2-yl)thiazole-5-carboxylate and 0.34 mL (2.0 mmol) DIEA to afford 281 mg (79%) of product. MS (ESI) *m/z* (*M*+*H*)⁺: 541, 543 for C₂₂H₂₆Cl₂N₆O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.22 (t, 3H), 1.75 (m, 2H), 2.23 (s, 3H), 3.34 (m, 4H), 3.48 (m, 1H), 3.71 (s, 3H), 4.03 (m, 1H), 4.13 (m, 2H), 4.17-4.34 (m, 2H), 7.15 (s, 1H), 7.61 (s, 1H), 8.04 (s, 1H), 12.20 (s, 1H).

Methyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(1*H*-pyrazole-5-yl)thiazole-5-carboxylate (methyl ester of **83**) From 102 mg (0.30 mmol) of chiral **6a**, 88 mg (0.32 mmol) of methyl 2-chloro-4-(1*H*-pyrazol-3-yl)-5-thiazolecarboxylate and 63 mg (0.75 mmol) NaHCO₃ to afford 102 mg (66%) of the title compound. MS (ESI) *m/z* (*M*+*H*)⁺: 513 for C₂₀H₂₂Cl₂N₆O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.82 (m, 2H), 2.24 (s, 3H), 3.34 (m, 4H), 3.57 (m, 1H), 3.81 (s, 3H), 4.13 (m, 1H), 4.25 (m, 2H), 7.24 (d, 1H), 7.25 (s, 1H), 7.58 (s, 1H), 12.21 (s, 1H), 13.34 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(3-methyl-1,2,4-oxadiazol-5-yl)thiazole-5-carboxylate (ethyl ester of **85**) From 89 mg (0.29 mmol) of chiral **6a**, 80 mg (0.29 mmol) of ethyl 2-chloro-4-(3-methyl-1,2,4-oxadiazol-5-yl)-5-thiazolecarboxylate and 41 μL (0.29 mmol) Et₃N to afford 155 mg (98%) of the title compound. MS (ESI) *m/z* (*M*+*H*)⁺: 543, 545 for C₂₁H₂₄Cl₂N₆O₅S; ¹H NMR (300 MHz, CDCl₃) δ 1.28 (t, 3H), 2.03 (m, 2H), 2.30 (s, 3H), 2.53 (s, 3H), 3.22 (d, 1H), 3.30 (m, 1H), 3.48 (s, 3H), 3.52 (m, 1H), 4.02 (m, 1H), 4.26 (q, 2H), 4.32 (m, 1H), 4.56 (m, 1H), 7.23 (d, 1H), 9.27 (br, 1H).

Ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-pyridin-2-yl-thiazole-5-carboxylate (ethyl ester of **88**) From 120 mg (0.34 mmol) of chiral **6a**, 91 mg (0.34 mmol) of ethyl 2-chloro-4-(2-pyridinyl)-5-thiazolecarboxylate and 95 μL Et₃N to afford 80 mg (44%) of the title compound. MS (ESI) *m/z* (*M*+*H*)⁺: 538 for C₂₃H₂₅Cl₂N₅O₄S; ¹H NMR (300 MHz,

DMSO-*d*₆) δ 1.06 (t, 3H), 1.76 (m, 2H), 2.19 (s, 3H), 3.29 (m, 2H), 3.39 (s, 4H), 3.56 (m, 1H), 4.03 (q, 2H), 4.26 (m, 2H), 7.16 (d, 1H), 7.40 (dd, 1H), 7.55 (d, 1H), 8.58 (d, 1H), 12.17 (s, 1H).

Methyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-thiazol-2-yl-thiazole-5-carboxylate (methyl ester of **89**) From 80 mg (0.23 mmol) of chiral **6a**, 55 mg (0.21 mmol) of methyl 2'-chloro-(2,4'-bithiazole)-5'-carboxylate and 56 mg (0.69 mmol) NaHCO₃ to afford 86 mg (71%) of product. MS (ESI) *m/z* (M+H)⁺: 530 for C₂₀H₂₁Cl₂N₅O₄S₂; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.76 (m, 2H), 2.17 (s, 3H), 3.32 (m, 3H), 3.38 (s, 3H), 3.57 (s, 1H), 3.69 (s, 3H), 4.28 (m, 2H), 7.15 (d, 1H), 7.90 (s, 1H), 7.94 (s, 1H), 12.15 (s, 1H).

Methyl 4-(2-aminothiazol-4-yl)-2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylate (methyl ester of **90**) From 100 mg (0.29 mmol) of chiral **6a**, 76 mg (0.27 mmol) of methyl 2'-amino-2-chloro-(4,4'-bithiazole)-5-carboxylate and 61 mg (0.73 mmol) of NaHCO₃ to afford 122 mg (77%) of the title compound. MS (ESI) *m/z* (M+H)⁺: 545, 547 for C₂₀H₂₂Cl₂N₆O₄S₂; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.75 (m, 2H), 2.23 (s, 3H), 3.41 (m, 4H), 3.57 (m, 1H), 3.68 (s, 3H), 4.02 (m, 1H), 4.25 (m, 2H), 7.02 (m, 2H), 7.15 (m, 2H), 12.24 (s, 1H).

Ethyl 4-(5-chloropyrazin-2-yl)-2-((3*R*,4*S*)-4-(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamido)-3-methoxypiperidin-1-yl)thiazole-5-carboxylate From 3.55 g (11.6) of chiral **6a** and 4 g (11.5 mmol) of ethyl 2-bromo-4-(5-chloropyrazin-2-yl)thiazole-5-carboxylate and 6.0 mL (34.4 mmol) DIEA to afford 5.29 g (80%) of the title compound. MS (ESI) *m/z* (M+H)⁺: 543 for C₂₂H₂₃Cl₃N₆O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.1 (t, 3H), 1.77 (m, 2H), 2.19 (s, 3H), 3.3-3.4 (m, 2H), 3.38 (s, 3H), 3.55 (m, 1H), 4.0 (m, 1H), 4.1 (q, 2H), 4.4 (m, 3H), 4.44 (t, 2H), 7.14 (d, 1H), 8.752 (s, 1H) 8.86 (s, 1H), 12.13 (s, 1H).

Ethyl 2-((3*S*,4*R*)-4-(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamido)-3-methoxypiperidin-1-yl)-4-(5-(2-(dimethylamino)ethoxy)pyrazin-2-yl)thiazole-5-carboxylate (ethyl ester of **86**) 2-(Dimethylamino)ethanol (0.94 mL, 9.3 mmol) was added to a suspension of 1.1 g (27.6 mmol) of NaH in 17 mL THF at 0 °C. After stirring for 5 min, a solution of the preceding compound (5.29 g, 9.22 mmol) in 20 mL THF was added and the mixture was warmed to rt with stirring over 1 h. The reaction mixture was quenched with aq. NH₄Cl (4 mL) and partitioned between water and Et₂O. The aq layer was extracted twice more with Et₂O. 1 N HCl was added to the aq layer to bring the pH to about 4. The aq layer was extracted with 5% methanol/CH₂Cl₂ (3X), and the organics were concentrated to afford 5.8 g (100%) of the title compound. MS (ESI) *m/z* (M+H)⁺: 626, 628 for C₂₆H₃₃Cl₂N₇O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.1 (t, 3H), 1.77 (m, 2H), 2.19 (s, 3H), 2.23 (s, 6H), 2.68 (t, 2H), 3.3 (m, overlaps with water peak), 3.38 (s, 3H), 3.55 (m, 1H), 3.95 (m, 1H), 4.1 (q, 2H), 4.4 (m, 3H), 4.44 (t, 2H), 7.16 (d, 1H), 8.32 (s, 1H) 8.42 (s, 1H), 12.13 (s, 1H).

Ethyl 2-[(3*S*,4*R*)-4-(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxy-1-piperidinyl]-4-[5-[[2-(4-methyl-1-piperazinyl)ethyl]amino]2-pyrazin-2-yl)-5-thiazolecarboxylic acid (ethyl ester of **87**) A solution of 4.0 g (6.97) of ethyl 4-(5-chloropyrazin-2-yl)-2-((3*R*,4*S*)-4-(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamido)-3-methoxypiperidin-1-yl)thiazole-5-carboxylate, 4.0 g (28 mmol) of 2-(4-methylpiperazin-1-yl)ethanamine and 1.34 mL (7.67 mmol) DIEA in 12 mL NMP was heated at 120 °C for 90 min in a microwave reactor. The mixture was poured into water, and precipitated solids were collected by filtration. The solids were purified by chromatography on silica gel (1:1 MeOH, CH₂Cl₂ with 0.5% aq. NH₄OH) to afford 3.35 g (71%) of the title compound as a MS (ESI) *m/z* (M+H)⁺: 680, 682; ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.21 (t, 3H), 1.28 (m, 3H), 1.81 (m, 2H), 2.22 (s, 3H), , 3.04 (m, 4H), 3.21-3.56 (m, 14H), 3.98 (m, 1H), 4.12 (q, 2H), 4.34 (m, 2H), 7.18 (d, 1H), 7.25 (d, 1H), 7.96 (s, 1H), 8.22 (s, 1H), 12.18 (s, 1H).

Ethyl 4-carbamoyl-2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylate (ethyl ester of **61**) A solution of ethyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-[(1-methyl-1-phenyl-ethyl)carbamoyl]thiazole-5-carboxylate (270 mg, 0.43 mmol) 5 mL TFA was heated at 45 °C overnight. The reaction mixture was concentrated, and the residue was triturated with Et₂O and dried *in vacuo* to afford product as a solid (150 mg, 71%). MS (ESI) *m/z* (M+H)⁺: 504 for C₁₉H₂₃Cl₂N₅O₅S; ¹H NMR (300

MHz, DMSO-*d*₆) δ 1.22 (t, 3H) 1.74 (d, 2H) 2.18 (s, 3H) 3.31 (s, 1H) 3.37 (s, 3H) 3.38 - 3.43 (m, 1H) 3.55 (s, 1H) 3.95 (s, 1H) 4.17 (q, 2H) 4.27 (s, 2H) 7.15 (d, 1H) 7.53 (s, 1H) 7.82 (s, 1H) 12.17 (s, 1H).

Methyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(1*H*-imidazol-2-yl)thiazole-5-carboxylate (methyl ester of **84**) A solution of methyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-[1-(methoxymethyl)imidazol-2-yl]thiazole-5-carboxylate (methyl ester of **79**; 173 mg 0.31 mmol) in 3 mL 8:1 acetic acid-water was heated at 120 °C for 2Hours in a microwave reactor. Solvent was removed and the residue was partitioned between NaHCO₃ (aq) and EtOAc. The EtOAc was separated and washed with brine. Drying (MgSO₄) and removal of solvent gave a solid that was chromatographed on silica gel (100% EtOAc followed by gradient elution to 20% MeOH in EtOAc). Product (78 mg, 49%) was isolated as a solid. MS (ESI) *m/z* (M+H)⁺: 513 for C₂₂H₂₆Cl₂N₆O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.83 (m, 2H), 2.24 (s, 3H), 3.34 (s, 3H), 3.45 (m, 4H), 3.59 (m, 1H), 3.82 (s, 3H), 4.02 (m, 1H), 4.33 (m, 2H), 7.15 (m, 3H), 7.41 (s, 2H), 12.20 (s, 1H), 12.77 (s, 1H).

Methyl 2-[11-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3,3-dimethyl-1,5-dioxaspiro[5.5]undecan-8-yl]thiazole-5-carboxylate (methyl ester of **44**). A mixture of 150 mg (0.31) of methyl 2-[4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3,3-dimethoxy-1-piperidyl]thiazole-5-carboxylate (methyl ester of **39**), 300 mg of 2,2-dimethylpropane-1,3-diol and 10 mg *p*-TsOH in 10 mL toluene was heated at reflux overnight. The reaction mixture was diluted with EtOAc, which was washed with saturated aq Na₂CO₃ (2X), dried (MgSO₄) and concentrated. The residue was chromatographed on silica gel (gradient elution 25-100% EtOAc in CH₂Cl₂) to afford the title compound (155 mg, 97%) as a white solid. MS (ESI) *m/z* (M+H)⁺: 517 for C₂₁H₂₆Cl₂N₄O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.75 (s, 6H), 1.03 - 1.09 (m, 2H), 1.71 (s, 1H), 1.85 (s, 1H), 2.18 (s, 3H), 3.47 (s, 2H), 3.75 (s, 3H), 3.77 - 3.86 (m, 2H), 4.33 (t, 2H), 5.06 (s, 1H), 7.86 (s, 1H), 12.17 (s, 1H).

The following 2 compounds were prepared by the procedure described for the preceding compound from the methyl ester of **39** and the indicated diol.

Methyl 2-[11-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-5,12-dioxaspiro[2.2.5.6.2.3]tridecan-8-yl]thiazole-5-carboxylate (ester of **45**) From 150 mg (0.31 mmol) of the methyl ester of **39**, 0.30 mL of cyclopropane-1,1-diylmethanol and 10 mg *p*-TsOH to afford 145 mg (90%) of product. MS (ESI) *m/z* (M+H)⁺: 515 for C₂₁H₂₄Cl₂N₄O₅S.

Methyl 2-[11-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methylene-1,5-dioxaspiro[5.5]undecan-8-yl]thiazole-5-carboxylate (methyl ester of **46**). From 150 mg (0.31 mmol) of the methyl ester of **39**, 300 μL of 2-methylenepropane-1,3-diol and 10 mg *p*-TsOH to afford 31 mg (20%) of product. MS (ESI) *m/z* (M+H)⁺: 501, 503 for C₂₀H₂₂Cl₂N₄O₅S.

Methyl 4-bromo-2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylate A mixture of chiral **6a** (0.50 g, 1.46 mmol), methyl 4-bromo-2-chlorothiazole-5-carboxylate (374 mg, 1.46 mmol) and DIEA (0.51 mL, 2.92 mmol) in 6 mL DMF was heated at 100 °C for 1H in a microwave reactor. The reaction mixture was cooled to rt and then slowly poured into ice water. After stirring at rt for several minutes, the resulting precipitate was partitioned between EtOAc and water. The EtOAc was separated and washed with water and brine before being dried (MgSO₄) and concentrated to afford 442 mg (58%) of the title compound. MS (ESI) *m/z*: 526, 528 (M+H)⁺ for C₁₇H₁₉BrCl₂N₄O₄S. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.1 (s, 1H), 7.14 (d, *J*=8.28 Hz, 1H), 4.26 (m, 2H), 3.85-4.0 (m, 1H), 3.73 (s, 3H), 3.5-3.6 (m, 1H), 3.47-3.5 (m, 1H), 3.31 (m, 1H), 2.18 (s, 3H), 1.6-1.8 (m, 2H).

Methyl 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-pyrimidin-5-yl-thiazole-5-carboxylic acid (methyl ester of **77**) A mixture of 125 mg (0.24 mmol) of the preceding compound, 44 mg (0.36 mmol) pyrimidine-5-boronic acid, 76 mg (0.71 mmol) Na₂CO₃ in 5 mL DMF was purged with N₂ for 15 min. Pd(Ph₃P)₄ (27 mg, 0.02 mmol) was added with N₂ purging for 15 min before heating at 80 °C overnight. The mixture was poured into water and solids that formed were filtered and dissolved in EtOAc. The EtOAc solution was washed with water and brine. Drying (MgSO₄) and removal of solvent gave a solid that was purified by chromatography on silica gel

(100% EtOAc with gradient elution to 10% MeOH in EtOAc) to afford the title compound as a white solid (44 mg, 34%). MS (ESI) m/z : 525, 527 for $C_{21}H_{22}Cl_2N_6O_4S$; 1H NMR (400 MHz, DMSO- d_6) δ 12.15 (s, 1H), 9.21 (s, 1H), 9.08 (s, 2H), 7.16 (d, $J=8.28$ Hz, 1H), 4.35-4.5 (m, 1H), 4.25-4.35 (m, 1H), 3.9-4.1 (m, 1H), 3.69 (s, 3H), 3.6 (m, 1H), 3.45 (br. s., 1H), 3.40 (s, 3H), 3.3-3.5 (m, 2H), 2.19 (s, 3H), 1.75-1.85 (m, 2H).

2-[4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-1-piperidyl]thiazole-5-carboxylic acid (1) A solution of the corresponding ester of **1** (250 mg, 0.60 mmol) and 2N lithium hydroxide solution in water (3 mL, 6.00 mmol) in THF (3 mL) was heated at reflux for 1H. The mixture was cooled to rt and acidified with 10% HCl solution. The mixture was extracted with EtOAc and organic layer was washed with water twice, dried (Na_2SO_4) and concentrated. The residue purified by reverse phase HPLC (CH_3CN /water with 0.1% TFA) to afford the title compound (28 mg). UPLC-MS RT = 0.91 min, (ESI) m/z : 403 (MH^+) for $C_{15}H_{16}Cl_2N_4O_3S$; 1H NMR (300 MHz, DMSO- d_6) δ 12.58 (br. s., 1H), 11.92 (s, 1H), 7.71 (s, 1H), 7.23 (d, $J=7.9$ Hz, 1H), 4.00 (d, $J=7.5$ Hz, 1H), 3.87 (d, $J=13.6$ Hz, 2H), 3.17-3.25 (m, 2H), 2.11 (s, 3H), 1.85 (d, $J=10.0$ Hz, 2H), 1.47-1.67 (m, 2H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 173.5, 162.6, 158.1, 147.6, 127.2, 119.3, 116.9, 110.0, 107.9, 47.0, 45.6, 30.3, 10.6; HRMS [$M+H$] $^+$ 403.0386 (theoretical 403.0393).

2-[(3S,4R)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-fluoro-1-piperidyl]thiazole-5-carboxylate (2) From 124 mg (0.285 mmol) of the corresponding methyl ester of **2** and 2 mL 2N NaOH to afford 108 mg (90%) of product. UPLC-MS RT = 0.93 min, (ESI) m/z ($M+H$) $^+$: 421, 423 for $C_{15}H_{15}Cl_2FN_4O_3S$; 1H NMR (300 MHz, DMSO- d_6) δ 12.61 (br. s., 1H), 12.04 (s, 1H), 7.68 (s, 1H), 7.21 (d, $J=8.1$ Hz, 1H), 4.96 (d of m, $J=48$ Hz, 1H), 4.16-4.43 (m, 2H), 3.94 (d, $J=12.8$ Hz, 1H), 3.49 (dd, $J=42, 13.5$ Hz, 1H), 3.28-3.34 (m, 1H), 2.11 (s, 3H), 1.72-1.84 (m, 2H); ^{19}F NMR (DMSO- d_6 , 282 MHz) δ -201.2; ^{13}C NMR (75 MHz, DMSO- d_6) δ 171.3, 165.4, 158.3, 140.8, 128.2, 127.4, 118.6, 111.9, 108.1, 87.2 (d, $J_{CF} = 177.3$ Hz), 49.0 (d, $J_{CF} = 20.3$ Hz), 47.7 (d, $J_{CF} = 18.7$ Hz), 47.0, 25.1, 10.7; HRMS [$M+H$] $^+$ 421.0304 (theoretical 421.0299).

2-[(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylic acid (22) From 223 mg (0.5 mmol) of the corresponding methyl ester of **22** and 25 mL of 2N LiOH to afford 130 mg (60%) of the title compound. UPLC-MS RT = 0.94 min, (ESI) m/z ($M+H$) $^+$: 433, 435 for $C_{16}H_{18}Cl_2N_4O_4S$; 1H NMR (300 MHz, DMSO- d_6) δ 12.59 (br. s., 1H), 12.15 (s, 1H), 7.74 (s, 1H), 7.16 (d, $J=8.3$ Hz, 1H), 4.30 (t, $J=13.7$ Hz, 2H), 3.93 (d, $J=13.2$ Hz, 1H), 3.55 (br. s., 1H), 3.38-3.42 (m, 1H), 3.36 (s, 3H), 2.19 (s, 3H), 1.67-1.82 (m, 2H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 173.9, 162.6, 157.6, 147.6, 127.9, 118.6, 116.5, 109.7, 108.1, 75.4, 57.0, 47.9, 47.8, 46.7, 26.1, 10.6; HRMS [$M+H$] $^+$ 433.0485 (theoretical 433.0499).

2-[(3S,4S)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylic acid (24) From 52 mg (0.12 mmol) of methyl 2-[(3S,4S)-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylate and 1 mL of 2N NaOH to afford 45 mg (89%) of the title compound. UPLC-MS RT = 0.90 min, (ESI) m/z ($M+H$) $^+$: 433, 435 for $C_{16}H_{18}Cl_2N_4O_4S$; 1H NMR (300 MHz, DMSO- d_6) δ 12.70 (br. s., 1H), 12.01 (s, 1H), 7.78 (s, 1H), 7.36 (d, $J=7.9$ Hz, 1H), 3.98-4.27 (m, 2H), 3.77 (m, 1H), 3.39-3.49 (m, 2H), 3.36 (s, 3H), 3.16-3.27 (m, 2H), 2.18 (s, 3H), 1.96 (m, 1H), 1.69 (m, 1H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 173.4, 162.6, 158.4, 147.6, 127.3, 119.3, 117.1, 110.0, 107.9, 76.3, 57.1, 49.7, 49.1, 46.4, 28.2, 10.6; HRMS [$M+H$] $^+$ 433.0498 (theoretical 433.0499).

2-[(3R,4R)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylic acid (25) From 55 mg (0.12 mmol) of methyl 2-[(3R,4R)-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylate and 1.5 mL of 2N NaOH to afford 39 mg (73%) of the title compound. UPLC-MS RT = 0.90 min, (ESI) m/z ($M+H$) $^+$: 433, 435 for $C_{16}H_{18}Cl_2N_4O_4S$; 1H NMR (300 MHz, DMSO- d_6) δ 12.58 (br. s., 1H), 12.04 (br. s., 1H), 7.69 (s, 1H), 7.37 (d, $J=7.9$ Hz, 1H), 3.93-4.14 (m, 2H), 3.71 (m, 1H), 3.35 (m, 2H), 3.29 (s, 3H), 3.12-3.19 (m, 1H), 2.11 (s, 3H), 1.89 (m, 1H), 1.61 (m, 1H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 173.89, 162.6, 157.5, 147.5, 127.8, 118.6, 116.3, 109.6, 108.1, 75.4, 57.0, 47.8, 47.7, 46.7, 26.1, 10.6; HRMS [$M+H$] $^+$ 433.0498 (theoretical 433.0499).

2-[(3R,4S)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylic acid (26) From 280 mg (0.62 mmol) of the corresponding methyl ester of **26** and 20 mL of 2N LiOH to afford 195 mg (73%) of the title compound. UPLC-MS RT = 0.94 min, (ESI) m/z (M+H)⁺: 433, 435 for C₁₆H₁₈Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.59 (br. s., 1H), 12.15 (s, 1H), 7.74 (s, 1H), 7.16 (d, *J*=8.5 Hz, 1H), 4.15-4.45 (m, 2H), 3.94 (m, 1H), 3.56 (m, 1H), 3.38 (s, 1H), 3.36 (s, 3H), 2.19 (s, 3H), 1.75 (m, 2H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 174.0, 162.6, 157.6, 147.6, 127.9, 118.6, 116.4, 109.7, 108.1, 75.4, 57.0, 47.9, 47.8, 46.7, 26.1, 10.6 HRMS [M+H]⁺ 433.0502 (theoretical 433.0499).

2-[(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-ethoxy-1-piperidyl]thiazole-5-carboxylic acid (28) From 52 mg (0.12 mmol) of methyl ester of **28** and 1 mL of 2N NaOH to afford 45 mg (89%) of the title compound. UPLC-MS RT = 1.00 min, (ESI) m/z (M+H)⁺: 447, 449 for C₁₇H₂₀Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.57 (br. s., 1H), 12.18 (s, 1H), 7.74 (s, 1H), 7.14 (d, *J*=8.3 Hz, 1H), 4.26 (m, 2H), 3.88-4.11 (m, 1H), 3.59-3.78 (m, 2H), 3.35-3.52 (m, 2H), 2.19 (s, 3H), 1.76 (m, 2H), 0.99-1.11 (t, d, *J*=6.0 Hz, 3H); HRMS [M+H]⁺ 447.0634 (theoretical 447.0655).

2-[(3S,4R)-rel-3-Allyloxy-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-1-piperidyl]thiazole-5-carboxylic acid (29) From 100 mg (0.21 mmol) of the corresponding methyl ester of **29** and 30 mL of 2N LiOH to afford 72 mg (74%) of the title compound. MS (ESI) m/z (M+H)⁺: 459, 461 for C₁₈H₂₀Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.09 (s, 1H), 7.67 (s, 1H), 7.07 (d, *J*=8.3 Hz, 1H), 5.59-5.94 (m, 1H), 5.16 (d of m, *J*=17.24 Hz, 1H), 5.01-5.08 (m, d of m, *J*=9 Hz, 1H), 4.17-4.29 (m, 2H), 4.05-4.14 (m, 1H), 3.84-3.96 (m, 2H), 3.64 (m, 1H), 3.19-3.37 (m, 2H), 2.12 (s, 3H), 1.66-1.78 (m, 2H); HRMS [M+H]⁺ 501.0750 (theoretical 501.0761).

2-[(3S,4R)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-prop-2-ynoxy-1-piperidyl]thiazole-5-carboxylic acid (30) From 95 mg (0.20 mmol) of the corresponding methyl ester of **30** and 1 mL of 2N LiOH to afford 31 mg (34%) of the title compound. UPLC-MS RT = 0.96 min, (ESI) m/z (M+H)⁺: 457, 459 for C₁₈H₁₈Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.63 (s, 1H), 12.15 (s, 1H), 7.73 (s, 1H), 7.16 (d, *J*=8.3 Hz, 1H), 4.18-4.39 (m, 4H), 3.96 (m, 1H), 3.87 (m, 1H), 3.44 (t, *J*=2.35 Hz, 1H), 3.40 (m, 1H), 2.19 (s, 3H), 1.68-1.86 (m, 2H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 174.0, 162.7, 157.7, 147.6, 128.0, 118.6, 116.5, 109.7, 108.0, 79.9, 77.6, 72.8, 56.3, 48.4, 47.7, 46.7, 26.1, 10.6; HRMS [M+H]⁺ 457.0499 (theoretical 457.0499).

2-[(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-(2-methoxyethoxy)-1-piperidyl]thiazole-5-carboxylic acid (31) From 69 mg (0.14 mmol) of the corresponding methyl ester of **31** and 1.5 mL of 2N LiOH to afford 37 mg (57%) of the title compound. UPLC-MS RT = 0.93 min, (ESI) m/z (M+H)⁺: 459, 461 for C₁₈H₂₀Cl₂N₄O₄S; MS (ESI) m/z (M+H)⁺: 477 for C₁₈H₂₂Cl₂N₄O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.08 (s, 1H), 7.66 (s, 1H), 7.09 (d, *J*=8.3 Hz, 1H), 4.15-4.28 (m, 2H), 3.59-3.69 (m, 2H), 3.45-3.56 (m, 1H), 3.25-3.37 (m, 4H), 3.08 (s, 3H), 2.11 (s, 3H), 1.65-1.76 (m, 2H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 174.0, 162.7, 157.7, 147.6, 128.0, 118.6, 116.4, 109.5, 108.0, 107.6, 74.0, 71.3, 68.1, 58.0, 48.8, 47.8, 46.7, 26.0, 10.6; HRMS [M+H]⁺ 477.0774 (theoretical 477.0761).

2-[(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methyl-1-piperidyl]thiazole-5-carboxylic acid (32) From 52 mg (0.12 mmol) of the corresponding methyl ester of **32** and 0.12 mL of 2N NaOH to afford 37 mg (74%) of the title compound. MS (ESI) m/z (M+H)⁺: 417, 419 for C₁₆H₁₉Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.63 (br. s., 1H), 12.04 (br. s., 1H), 7.76 (s, 1H), 7.21 (d, *J*=8.1 Hz, 1H), 4.25 (br. s., 1H), 3.39-3.80 (m, 4H), 2.19 (s, 3H), 1.80 (br. s., 2H), 0.91 (d, *J*=6.8 Hz, 3H); HRMS [M+H]⁺ 417.0555 (theoretical 417.0549).

2-[(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-(methoxymethyl)-1-piperidyl]thiazole-5-carboxylic acid (33) From 129 mg (0.28 mmol) of the corresponding methyl ester of **33** and 2 mL of 2N NaOH to afford 56 mg (45%) of the title compound. UPLC-MS RT = 0.93 min, (ESI) m/z (M+H)⁺: 447, 449 for C₁₇H₂₀Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.1 (br. s., 1H), 7.57 (s, 1H), 7.47 (d, *J*=8.3 Hz, 1H), 4.03 (d, *J*=10.74 Hz, 1H), 3.80-3.96 (m, 2H), 3.37 (dd, *J*=3.6, 9.6 Hz, 1H), 3.22 (s, 1H), 3.20 (s, 1H), 3.15 (s, 3H), 2.90-3.03 (m, 1H), 2.11 (s, 3H), 1.93-2.06 (m, 1H), 1.84 (s, 1H), 1.80 (m, 1H), 1.47-1.68 (m, 1H); HRMS [M+H]⁺ 447.0659 (theoretical 447.0655).

2-[(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-(hydroxymethyl)-1-piperidyl]thiazole-5-carboxylic acid (34) From 249 mg (0.28 mmol) of the corresponding methyl ester of **34** and 40 mL of 2N NaOH to afford 13.7 mg (11%) of the title compound. UPLC-MS RT = 0.82 min, (ESI) m/z (M+H)⁺: 434, 445 for C₁₆H₁₈Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.03 (s, 1H), 7.76 (s, 1H), 7.55 (d, *J* = 9.0 Hz, 1H), 4.32 (m, 1H), 3.0-4.0 (m, overlaps with water peak), 2.18 (s, 3H), 1.84 (m, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 173.0, 164.1, 158.3, 148.4, 130.1, 126.4, 115.5, 115.2, 109.4, 63.0, 46.9, 46.3, 43.7, 28.4, 10.8, 10.6; HRMS [M+H]⁺ 433.0495 (theoretical 433.0499).

2-[(3S,4R)-rel-3-Chloro-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-1-piperidyl]thiazole-5-carboxylic acid (35) From 80 mg (0.18 mmol) of the corresponding methyl ester of **35** and 1 mL of 2N NaOH to afford 51 mg (65%) of the title compound. UPLC-MS RT = 0.99 min, (ESI) m/z (M+H)⁺: 437, 439 for C₁₅H₁₅Cl₃N₄O₃S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.7 (br. s., 1H), 12.15 (s, 1H), 7.75 (s, 1H), 7.18 (d, *J* = 7.7 Hz, 1H), 4.75 (m, 1H), 4.50 (m, 1H), 4.27 (d, *J* = 13.6 Hz, 1H), 4.04 (d, *J* = 13.2 Hz, 1H), 3.78-3.87 (m, 1H), 3.35-3.45 (m, 1H), 2.20 (s, 3H), 1.8-2.0 (m, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 173.9, 162.6, 157.8, 147.4, 127.9, 118.3, 117.0, 110.9, 108.3, 60.2, 52.8, 48.5, 46.5, 25.3, 10.6; HRMS [M+H]⁺ 436.9988 (theoretical 437.0003).

2-[(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-(methylthio)-1-piperidyl]thiazole-5-carboxylic acid (36) From 160 mg (0.35 mmol) of the corresponding methyl ester of **36** and 2.0 mL of 2N LiOH to afford 85 mg (54%) of the title compound. UPLC-MS RT = 1.00 min, (ESI) m/z (M+H)⁺: 449, 451 for C₁₆H₁₈Cl₂N₄O₃S₂; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.66 (br. s., 1H), 12.13 (s, 1H), 7.75 (s, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 4.33-4.58 (m, 1H), 4.02 (dd, *J* = 4.71, 13.8 Hz, 1H), 3.83-3.95 (m, 1H), 3.68-3.77 (m, 1H), 3.36-3.44 (m, 1H), 3.24-3.31 (m, 1H), 2.19 (s, 3H), 2.14 (s, 3H), 1.64-1.90 (m, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 174.0, 162.6, 157.8, 147.5, 128.0, 118.6, 116.8, 110.1, 108.2, 50.9, 48.0, 47.8, 46.1, 27.6, 15.0, 10.6; HRMS [M+H]⁺ 449.0288 (theoretical 449.0270).

2-[(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-(methylsulfonyl)-1-piperidyl]thiazole-5-carboxylic acid (37) From 58 mg (0.11 mmol) of the corresponding methyl ester of **37** and 1.5 mL of 2N LiOH to afford 29 mg (55%) of the title compound. UPLC-MS RT = 0.86 min, (ESI) m/z (M+H)⁺: 481, 483 for C₁₆H₁₈Cl₂N₄O₅S₂; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.26 (br. s., 1H), 7.45 (s, 1H), 4.53-4.82 (m, 1H), 4.35 (d, *J* = 10.2 Hz, 1H), 3.62-3.81 (m, 2H), 3.47-3.60 (m, 1H), 3.06 (s, 3H), 2.54 (s, 1H), 2.17 (s, 3H), 1.95 (m, 1H), 1.67-1.84 (m, 1H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 172.5, 170.3, 163.2, 158.1, 139.6, 127.9, 118.7, 110.2, 108.1, 60.6, 47.3, 45.7, 45.1, 40.3, 30.0, 10.7; HRMS [M+H]⁺ 481.0167 (theoretical 481.0168).

2-[(3S,4R)-rel-3-Azido-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-1-piperidyl]thiazole-5-carboxylic acid (38) From 55 mg (0.12 mmol) of the corresponding methyl ester of **38** and 0.25 mL of 1 N LiOH to afford 30 mg (68%) of the title compound. UPLC-MS RT = 1.00 min, (ESI) m/z (M+H)⁺: 444.2, 446.2 for C₁₅H₁₅Cl₂N₇O₃S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.70 (br. s., 1H), 12.10 (s, 1H), 7.77 (s, 1H), 7.24 (d, *J* = 7.2 Hz, 1H), 4.18-4.42 (m, 3H), 3.96 (m, 1H), 3.59 (m, 1H), 2.20 (s, 3H), 1.8 (m, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 173.8, 162.6, 158.0, 147.5, 127.8, 118.5, 117.1, 110.6, 108.2, 59.1, 49.8, 47.8, 46.7, 25.6, 10.7; HRMS [M+H]⁺ 444.0392 (theoretical 444.0407).

2-[11-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-1,5-dioxo-8-azaspiro[5.5]undecan-8-yl]thiazole-5-carboxylic acid (41) From 70 mg (0.14 mmol) of the corresponding methyl ester of **41** and 0.21 mL of 2N LiOH to afford 40 mg (60%) of the title compound. UPLC-MS RT = 0.92 min, (ESI) m/z (M+H)⁺: 475, 477 for C₁₈H₂₀Cl₂N₄O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.68 (br. s., 1H), 12.16 (s, 1H), 7.77 (s, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 4.37 (m., 1H), 3.89 (d, *J* = 14.5 Hz, 1H), 3.69 (d, *J* = 14.5 Hz, 1H), 3.49-3.62 (m, 2H), 3.37 (m, 2H), 3.21 (s, 3H), 3.18 (s, 3H), 2.19 (s, 3H), 1.77-1.99 (m, 2H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 173.0, 162.6, 158.0, 147.6, 128.0, 118.7, 116.7, 109.3, 108.0, 94.9, 60.6, 59.9, 52.4, 47.2, 47.1, 27.7, 24.6, 10.6; HRMS [M+H]⁺ 475.0597 (theoretical 475.0604).

2-[11-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3,3-dimethyl-1,5-dioxo-8-azaspiro[5.5]undecan-8-yl]thiazole-5-carboxylic acid (44) From 135 mg (0.26 mmol) of the corresponding methyl ester of **44** and 0.39 mL of 2N LiOH to afford 84 mg (64%) of the title compound. UPLC-MS RT = 1.08 min, (ESI) m/z (M+H)⁺: 503 for C₂₀H₂₄Cl₂N₄O₅S; ¹H NMR (300 MHz, DMSO-*d*₆)

δ ^1H NMR (300 MHz, DMSO- d_6) δ 12.67 (br. s., 1H), 12.17 (s, 1H), 7.76 (s, 1H), 7.12 (d, $J=8.8$ Hz, 1H), 5.09 (d, $J=14.3$ Hz, 1H), 4.19-4.51 (m, 1H), 3.67-4.01 (m, 3H), 3.38-3.56 (m, 3H), 3.11 (d, $J=14.1$ Hz, 1H), 2.18 (s, 3H), 1.86 (m, 1H), 1.70 (m, 1H), 1.06 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 173.0, 162.6, 157.8, 147.5, 128.1, 118.5, 116.8, 109.2, 108.0, 95.0, 70.7, 69.5, 51.5, 47.3, 46.6, 29.3, 28.1, 22.6, 21.7, 10.6; HRMS $[\text{M}+\text{H}]^+$ 503.0906 (theoretical 503.0917).

2-[11-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methylene-1,5-dioxo-8-azaspiro[5.5]undecan-8-yl]thiazole-5-carboxylic acid (46) From 30 mg (0.060 mmol) of the corresponding methyl ester of **46** and 90 μL of 2N LiOH to afford 21 mg (72%) of the title compound. MS (ESI) m/z ($\text{M}+\text{H}$) $^+$: 487, 489 for $\text{C}_{20}\text{H}_{22}\text{Cl}_2\text{N}_4\text{O}_5\text{S}$; UPLC-MS RT = 1.02 min, (ESI) m/z ($\text{M}+\text{H}$) $^+$: 487 for $\text{C}_{19}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O}_5\text{S}$; ^1H NMR (300 MHz, DMSO- d_6) δ 12.68 (br. s., 1H), 12.17 (s, 1H), 7.77 (s, 1H), 7.15 (d, $J=8.1$ Hz, 1H), 4.96 (m, 3H), 4.60 (t, $J=14.3$ Hz, 2H), 4.27 (m, 3H), 3.75 (m, 1H), 3.43-3.66 (m, 1H), 2.18 (s, 3H), 1.90 (m, 1H), 1.59-1.77 (m, 1H); HRMS $[\text{M}+\text{H}]^+$ 487.0620 (theoretical 487.0604).

2-[(3S,4R)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-methyl-thiazole-5-carboxylic acid (47) From 2 g (4.21 mmol) of the corresponding ethyl ester of **47** and 17 mL of 2N LiOH to afford 300 mg (15%) of the title compound. UPLC-MS RT = 0.97 min, (ESI) m/z ($\text{M}+\text{H}$) $^+$: 447, 449 for $\text{C}_{17}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O}_4\text{S}$; ^1H NMR (300 MHz, DMSO- d_6) δ 12.41 (br. s., 1H), 12.16 (s, 1H), 7.16 (d, $J=8.3$ Hz, 1H), 4.25 (m, 2H), 3.93 (m, 1H), 3.53 (br. s., 1H), 3.36 (s, 3H), 3.20-3.33 (m, 2H), 2.41 (s, 3H), 2.19 (s, 3H), 1.67-1.80 (m, 2H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 170.4, 163.3, 158.7, 157.6, 127.8, 118.6, 109.8, 109.5, 108.1, 75.3, 57.0, 47.8, 47.5, 46.2, 26.1, 17.2, 10.6; HRMS $[\text{M}+\text{H}]^+$ 447.0643 (theoretical 447.0655).

2-[(3S,4R)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-1,3-benzothiazole-7-carboxylate (48) From 214 mg (0.43 mmol) of the corresponding ethyl ester of **48** and 8.6 mL of 2N LiOH to afford 94 mg (45%) of the title compound. UPLC-MS RT = 1.05 min, (ESI) m/z ($\text{M}+\text{H}$) $^+$: 483, 485 for $\text{C}_{20}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O}_4\text{S}$; ^1H NMR (300 MHz, DMSO- d_6) δ 14.0 (br. s., 1H), 12.17 (s, 1H), 7.66 (m, 2H), 7.36-7.44 (m, 1H), 7.18 (d, $J=8.1$ Hz, 1H), 4.22-4.46 (m, 3H), 4.12 (m, 1H), 3.56-3.59 (m, 2H), 3.46 (m, 1H), 3.41 (m, 1H), 3.39 (s, 3H), 2.18 (s, 3H), 1.79 (m, 2H); HRMS $[\text{M}+\text{H}]^+$ 483.0648 (theoretical 483.0655).

2-[(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(difluoromethyl)thiazole-5-carboxylic acid (49) From 51 mg (0.10 mmol) of the corresponding ethyl ester of **49** and 0.15 mL 2N LiOH to afford 41 mg (85%) of the title compound. UPLC-MS RT = 1.06 min, (ESI) m/z $\text{M}+\text{H}$: 483, 485 for $\text{C}_{17}\text{H}_{18}\text{Cl}_2\text{F}_2\text{N}_4\text{O}_4\text{S}$; ^1H NMR (300 MHz, DMSO- d_6) δ 13.50 (s, 1H), 12.16 (s, 1H), 7.34 (t, $J=54.6$ Hz, 1H), 7.16 (d, $J=8.1$ Hz, 1H), 4.27 (m, 2H), 3.93 (m, 1H), 3.56 (m, 1H), 3.39-3.43 (m, 1H), 3.36 (s, 3H), 2.18 (s, 3H), 1.75 (m, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -115.84; ^{13}C NMR (126 MHz, DMSO- d_6) δ 171.7 (t, $J_{\text{CF}}=17.3$ Hz), 171.3, 161.8, 157.6, 149.6 (t, $J_{\text{CF}}=2$ Hz), 127.9, 118.6, 117.1, 110.0, 108.1 (t, $J_{\text{CF}}=244$ Hz), 75.4, 52.4, 48.1, 47.3, 46.7 26.0, 10.6; HRMS $[\text{M}+\text{H}]^+$ 483.0466 (theoretical 483.0466).

4-Acetyl-2-[(3S,4R)-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-thiazole-5-carboxylic acid (50) From 8.22 g (16.8 mmol) of the corresponding methyl ester of **50** and 30 mL 1N NaOH to afford 7.1 g (89%) of the title compound. UPLC-MS RT = 1.16 min, (ESI) m/z ($\text{M}+\text{H}$) $^+$: 475, 477 for $\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O}_5\text{S}$; ^1H NMR (300 MHz, DMSO- d_6) δ 13.2 (s, 1H), 12.16 (s, 1H), 7.16 (d, $J=8.3$ Hz, 1H), 4.2-4.4 (m, 2H), 3.7-4.0 (m, 1H), 3.56 (m, 1H), 3.30-3.40 (m, overlaps with water peak), 2.48 (s, 3H), 2.19 (s, 3H), 1.65-1.85 (m, 2H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 198.9, 171.3, 161.4, 157.6, 155.6, 127.9, 118.6, 114.5, 109.8, 108.1, 75.4, 57.0, 48.0, 47.7, 46.8, 29.7, 26.0, 10.6; HRMS $[\text{M}+\text{H}]^+$ 475.0624 (theoretical 475.0604). ee >98% by chiral SFC analysis (see below).

2-[(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(dimethylcarbamoyl)thiazole-5-carboxylic acid (52) From 26 mg (0.049 mmol) of the corresponding methyl ester of **52** and 55 μL 1 N LiOH to afford 20 mg (81%) of the title compound. UPLC-MS RT = 0.90 min, (ESI) m/z ($\text{M}+\text{H}$) $^+$: 504 for $\text{C}_{19}\text{H}_{23}\text{Cl}_2\text{N}_5\text{O}_5\text{S}$; ^1H NMR (300 MHz, DMSO- d_6) δ 12.75 (br. s., 1H), 12.14 (s, 1H), 7.15 (d, $J=8.1$ Hz, 1H), 4.26 (m, 2H), 3.55 (s, 1H), 3.38-3.42 (m, 1H), 3.36 (s, 3H),

3.33-3.34 (m, 1H), 3.29 (m, 1H), 2.92 (s, 3H), 2.78 (s, 3H), 2.18 (s, 3H), 1.76 (m, 2H); HRMS [M+H]⁺ 504.0865 (theoretical 504.0870).

2-[(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(morpholine-4-carbonyl)thiazole-5-carboxylic acid (53) From 50 mg (0.09 mmol) of the corresponding ethyl ester of **53** and 0.13 mL (0.26 mmol) 2N LiOH to afford 36 mg (73%) of the title compound. UPLC-MS RT = 0.89 min, (ESI) m/z (M+H)⁺: 546, 548 for C₂₁H₂₅Cl₂N₅O₆S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.75 (s, 2H) 2.18 (s, 3H) 3.12 - 3.22 (m, 2H) 3.35 (s, 3H) 3.53 (d, 6H) 3.60 (d, 2H) 3.85 (s, 2H) 4.27 (s, 2H) 7.14 (d, 1H) 12.13 (s, 1H) 12.81 (s, 1H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 172.3, 163.3, 161.7, 157.6, 152.7, 127.9, 118.6, 111.4, 109.7, 108.1, 75.4, 65.9, 65.6, 57.0, 47.8, 46.3, 41.4, 26.0, 10.6; HRMS [M+H]⁺ 546.0966 (theoretical 546.0975).

2-[(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(hydroxymethyl)thiazole-5-carboxylate (54) From 110 mg (0.22 mmol) of the corresponding ethyl ester of **54** and 0.20 mL (0.3 mmol) 2N LiOH to afford 53 mg (52%) of the title compound. UPLC-MS RT = 0.86 min, (ESI) m/z (M+H)⁺: 463 for C₁₇H₂₀Cl₂N₄O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.75 (br. s., 1H), 12.07 (s, 1H), 7.08 (d, *J*=8.3Hz, 1H), 4.21 (m, 2H), 3.79 (m, 1H), 3.39-3.60 (m, 6H), 3.30-3.33 (m, 1H), 3.29 (s, 3H), 3.06-3.14 (m, 2H), 2.12 (s, 3H), 1.68 (m, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 170.9, 163.0, 157.6, 127.9, 118.7, 110.4, 109.7, 108.1, 75.4, 60.1, 57.9, 57.0, 53.9, 47.9, 46.3, 26.1, 10.6; HRMS [M+H]⁺ 463.0594 (theoretical 463.0604).

2-[(3S,4R)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(methoxymethyl)thiazole-5-carboxylic acid (55) From 2.5 g (5.1 mmol) of the corresponding methyl ester of **55** and 18 mL of 2N LiOH to afford 1.25 g (94%) of the title compound. UPLC-MS RT = 0.96 min, (ESI) m/z (M+H)⁺: 477, 479 for C₁₈H₂₂Cl₂N₄O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.7 (br. s., 1H), 12.17 (s, 1H), 7.17 (d, *J*=8.3Hz, 1H), 4.56 (d, *J*=1.3Hz, 2H), 4.17-4.36 (m, 2H), 3.92 (m, 1H), 3.55 (m, 1H), 3.30-3.43 (m, 7H), 2.19 (s, 3H), 1.75 (m, 2H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 170.8, 170.1, 162.7, 157.7, 157.6, 127.8, 118.6, 112.5, 110.1, 108.1, 104.8, 75.3, 66.9, 57.8, 57.2, 47.7, 26.1, 10.6; HRMS [M+H]⁺ 477.0769 (theoretical 477.0761).

2-[(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(morpholinomethyl)thiazole-5-carboxylic acid (56) From 70 mg (0.13 mmol) of the corresponding ester of **56** and 0.19 mL of 2N LiOH to afford 20 mg (29%) of the title compound. UPLC-MS RT = 0.78 min, (ESI) m/z (M+H)⁺: 532, 534 for C₂₁H₂₉Cl₂N₅O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.12 (s, 1H), 7.10 (d, *J*=8.1Hz, 1H), 4.08-4.36 (m, 2H), 3.84 (m, 4H), 3.58 (m, 4H), 3.46 (m, 1H), 3.29 (s, 3H), 2.68 (m, 4H), 2.12 (s, 3H), 1.62-1.71 (m, 2H); HRMS [M+H]⁺ 532.1177 (theoretical 532.1183).

2-[(3S,4R)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-5-methyl-thiazole-4-carboxylic acid (58) From 325 mg of the corresponding ethyl ester of **58** and 6.9 mL of 2N LiOH to afford 275 mg (90%) of the title compound. UPLC-MS RT = 1.03 min, (ESI) m/z (M+H)⁺: 447, 449 for C₁₇H₂₀Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.58 (br. s., 1H), 12.16 (s, 1H), 7.59 (s, 1H), 7.16 (d, *J*=7.9 Hz, 1H), 4.19 (m, 3H), 3.88 (m, 1H), 3.54 (s, 1H), 3.36 (s, 3H), 3.24-3.29 (m, 2H), 2.19 (s, 3H), 1.76 (m, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.4, 163.4, 157.6, 137.9, 131.6, 127.9, 118.7, 109.6, 108.1, 75.3, 56.9, 47.8, 46.2, 26.0, 12.3, 10.6; HRMS [M+H]⁺ 447.0661 (theoretical 447.0655).

2-[(3S,4R)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-pyrimidin-4-yl-thiazole-5-carboxylic acid (76) From 37 mg (0.069 mmol) of the corresponding ethyl ester of **76** and 0.10 mL of 2N LiOH to afford 17 mg (48%) of product. UPLC-MS RT = 1.07 min, (ESI) m/z (M+H)⁺: 511 for C₂₀H₂₀Cl₂N₆O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.16 (s, 1H), 9.42 (s, 1H), 9.14 (d, *J*=5.1Hz, 1H), 8.28 (d, *J*=5.3Hz, 1H), 7.17 (d, *J*=8.3Hz, 1H), 4.41 (m, 1H), 4.29 (m, 1H), 3.9-4.1 (m, 1H), 3.59 (m, 1H), 3.44 (m, 1H), 3.39 (s, 3H), 2.18 (s, 3H), 1.8 (m, 2H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 169.7, 161.0, 160.9, 157.6, 156.5, 156.0, 146.5, 127.9, 122.8, 120.2, 118.6, 109.7, 108.1, 75.5, 57.1, 47.7, 46.6, 26.1, 10.6; HRMS [M+H]⁺ 511.0722 (theoretical 511.0717); [α]_D²⁶ = -13.5 (c = 0.14, DMSO).

2-[(3S,4R)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-pyrimidin-5-yl-thiazole-5-carboxylic acid (77) From 41 mg (0.08 mmol) of the methyl ester of **77** and 125 μL NaOH to afford 14 mg (35%) of product. UPLC-MS RT = 0.97 min, (ESI) m/z (M+H)⁺: 511, 513

for $C_{20}H_{20}Cl_2N_6O_4S$; 1H NMR (400 MHz, DMSO- d_6) δ 12.98 (s, 1H), 12.2 (s, 1H), 9.2 (s, 2H), 9.1 (s, 1H), 7.18 (d, $J=8.3$ Hz, 1H), 4.2-4.4 (m, 2H), 3.9-4.0 (m, 1H), 3.55-3.6 (m, 1H), 3.40 (s, 3H), 3.3-3.4 (m, 1H), 3.25-3.3 (m, 1H), 2.19 (s, 3H), 1.7-1.8 (m, 2H); ^{13}C NMR (126 MHz, DMSO- d_6) δ 157.6, 157.3, 156.9, 151.5, 139.2, 129.0, 127.8, 124.9, 118.6, 109.9, 108.1, 75.4, 57.0, 47.8, 47.5, 46.4, 26.2, 10.6, -11.9; HRMS $[M+H]^+$ 511.0701 (theoretical 511.0717).

2-[(3*S*,4*R*)-4-[(3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(4,6-dimethoxypyrimidin-2-yl)thiazole-5-carboxylic acid (78) From 110 mg (0.18 mmol) of corresponding ethyl ester of **78** and 0.27 mL of 2N LiOH to afford 80 mg (78%) of the title compound. UPLC-MS RT = 1.14 min, (ESI) m/z ($M+H$) $^+$: 571 for $C_{22}H_{24}Cl_2N_6O_6S$; 1H NMR (300 MHz, DMSO- d_6) δ 13.87 (br. s., 1H), 12.16 (s, 1H), 7.2 (d, $J=8.3$ Hz, 1H), 6.36 (s, 1H), 4.29 (m, 2H), 3.90 (s, 6H), 3.56 (br. s., 1H), 3.40 (s, 3H), 2.18 (s, 3H), 1.76 (m, 2H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 168.9, 163.2, 160.4, 157.6, 143.1, 127.9, 124.1, 118.6, 109.7, 108.1, 75.5, 70.7, 70.6, 58.2, 58.2, 57.1, 49.3, 47.7, 26.1, 10.6; HRMS $[M+H]^+$ 571.0925 (theoretical 571.0928).

2-[(3*S*,4*R*)-4-[(3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-[1-(methoxymethyl)imidazol-2-yl]thiazole-5-carboxylic acid (79) From 82 mg (0.15 mmol) of the corresponding methyl ester of **79** and 0.30 mL of 2N LiOH to afford 38 mg (47%) of the title compound. UPLC-MS RT = 0.97 min, (ESI) m/z ($M+H$) $^+$: 543 for $C_{21}H_{24}Cl_2N_6O_5S$; 1H NMR (300 MHz, DMSO- d_6) δ 12.17 (s, 1H), 7.70 (s, 1H), 7.41 (s, 1H), 7.17 (d, $J=8.1$ Hz, 1H), 5.98 (s, 2H), 4.30 (m, 2H), 3.99 (m, 1H), 3.59 (s, 1H), 3.39 (br. s., overlaps with H_2O peak), 3.28 (s, 3H), 2.19 (s, 3H), 1.79 (m, 2H); HRMS $[M+H]^+$ 543.0972 (theoretical 543.0979).

2-[(3*S*,4*R*)-4-[(3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(4-methoxypyrimidin-2-yl)thiazole-5-carboxylic acid (80) From 100 mg (0.18 mmol) of the corresponding methyl ester of **80** and 7.2 mg (0.18 mmol) LiOH to afford 86 mg (88%) of the title compound. UPLC-MS RT = 1.05 min, (ESI) m/z ($M+H$) $^+$: 541, 543 for $C_{21}H_{22}Cl_2N_6O_5S$; 1H NMR (300 MHz, DMSO- d_6) δ 1H NMR (300 MHz, DMSO- d_6) δ 12.17 (s, 1H), 8.69 (d, $J=6.0$ Hz, 1H), 7.18 (d, $J=8.5$ Hz, 1H), 7.08 (d, $J=6.0$ Hz, 1H), 4.43 (m, 1H), 4.29 (m, 1H), 3.99 (s, 3H), 3.84-3.97 (m, 1H), 3.57 (br. s., 1H), 3.42 (s, 3H), 2.19 (s, 3H), 1.78 (m, 2H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 169.7, 169.6, 161.5, 159.5, 157.6, 155.3, 149.7, 127.9, 120.9, 118.7, 109.7, 108.1, 107.6, 75.5, 57.0, 54.2, 47.8, 47.5, 46.7, 26.2, 10.6; HRMS $[M+H]^+$ 541.0831 (theoretical 541.0822).

2-[(3*S*,4*R*)-4-[(3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(1-methylimidazol-2-yl)thiazole-5-carboxylic acid (81) 281 mg of the corresponding ester of **81** and 5 mL of 2N LiOH to afford 127 mg (38%) of product. UPLC-MS RT = 0.91 min, (ESI) m/z ($M+H$) $^+$: 513 for $C_{20}H_{22}Cl_2N_6O_4S$; 1H NMR (300 MHz, DMSO- d_6) δ 12.22 (s, 1H), 7.53 (s, 1H), 7.34 (s, 1H), 7.24 (d, $J=8.1$ Hz, 1H), 4.31 (m, 2H), 4.03 (m, 1H), 4.12 (s, 3H), 3.63 (m, 1H), 3.42 (s, 3H), 2.22 (s, 3H), 1.82 (m, 2H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 169.9, 161.6, 157.6, 139.7, 139.6, 127.9, 125.2, 123.6, 120.3, 118.6, 109.7, 108.1, 75.4, 57.0, 47.7, 46.4, 37.2, 26.1, 10.6; HRMS $[M+H]^+$ 513.0879 (theoretical 513.0873).

2-[(3*S*,4*R*)-4-[(3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(1-methylimidazol-4-yl)thiazole-5-carboxylic acid (82) From 281 mg of the corresponding ester of **82** and 5 mL of 2N LiOH to afford 127 mg (38%) of product. UPLC-MS RT = 0.90 min, (ESI) m/z ($M+H$) $^+$: 513 for $C_{20}H_{22}Cl_2N_6O_4S$; 1H NMR (300 MHz, DMSO- d_6) δ 12.15 (s, 1H), 8.16 (s, 1H), 7.77 (s, 1H), 7.17 (d, $J=8.3$ Hz, 1H), 4.38 (m, 1H), 4.27 (m, 1H), 3.95 (m, 1H), 3.78 (s, 3H), 3.56 (br. s., 1H), 3.39 (s, 3H), 2.18 (s, 3H), 1.76 (m, 2H); ^{13}C NMR (126 MHz, DMSO- d_6) δ 170.5, 162.1, 157.6, 145.3, 137.0, 134.6, 127.9, 121.9, 118.6, 114.1, 109.7, 108.1, 75.4, 57.0, 47.8, 47.3, 46.3, 33.9, 26.1, 10.6; HRMS $[M+H]^+$ 513.0894 (theoretical 513.0873).

2-[(3*S*,4*R*)-4-[(3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(1*H*-pyrazole-5-yl)thiazole-5-carboxylic acid (83) From 70 mg (0.14 mmol) of the corresponding methyl ester of **83** and 0.21 mL 2N LiOH to afford 43 mg (62%) of the title compound. UPLC-MS RT = 1.03 min, (ESI) m/z ($M+H$) $^+$: 499 for $C_{19}H_{20}Cl_2N_6O_4S$; 1H NMR (300 MHz, DMSO- d_6) δ 13.75 (br. s., 1H), 12.17 (s, 1H), 7.91 (br. s., 1H), 7.70 (d, $J=3.4$ Hz, 1H), 7.18 (d, $J=8.3$ Hz, 1H), 6.91 (br. s., 1H), 4.48 (m,

1H), 4.28 (m, 1H), 4.14 (m, 1H), 3.88-4.09 (m, 1H), 3.57 (s, 1H), 3.39 (s, 3H), 2.19 (s, 3H), 1.78 (m, 2H); HRMS [M+H]⁺ 499.0717 (theoretical 499.0718).

2-[(3S,4R)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(1H-imidazol-2-yl)thiazole-5-carboxylic acid (84) From 70 mg (0.14 mmol) of the corresponding methyl ester of **84** and 0.28 mL of 2N LiOH to afford 51 mg (73%) of the title compound. UPLC-MS RT = 0.90 min, (ESI) m/z (M+H)⁺: 499 for C₁₉H₂₀Cl₂N₆O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.11-7.26 (m, 2H), 4.22-4.43 (m, 1H), 3.99 (m, 1H), 3.55 (m, 1H), 3.39 (s, 3H), 3.31 (m, 2H), 2.19 (s, 3H), 1.77 (m, 2H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 169.8, 162.5, 157.6, 142.1, 139.9, 127.9, 122.3, 118.7, 109.8, 108.1, 75.4, 57.0, 47.8, 47.6, 46.2, 41.4, 26.1, 11.2, 10.6; HRMS [M+H]⁺ 499.0718 (theoretical 499.0717).

2-[(3S,4R)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(3-methyl-1,2,4-oxadiazol-5-yl)thiazole-5-carboxylic acid (85) From 135 mg (0.25 mmol) of the corresponding ethyl ester of **85** and 3 mL of 2N NaOH to afford 119 mg (93%) of the title compound. UPLC-MS RT = 1.13 min, (ESI) m/z (M+H)⁺: 515, 516 for C₁₉H₂₀Cl₂N₆O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.35 (br. s., 1H), 12.16 (s, 1H), 7.17 (d, *J*=8.1 Hz, 1H), 4.27 (m, 2H), 3.97 (m, 1H), 3.57 (br. s., 1H), 3.40-3.48 (m, 1H), 3.37 (s, 3H), 2.44 (s, 3H), 2.19 (s, 3H), 1.77 (m, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 171.3, 170.4, 167.0, 160.8, 157.6, 140.0, 127.9, 118.8, 118.6, 109.7, 108.1, 75.4, 57.1, 48.3, 47.7, 46.7, 26.0, 11.2, 10.6; HRMS [M+H]⁺ 515.0643 (theoretical 515.0666).

2-[(3S,4R)-4-(3,4-Dichloro-5-methyl-1H-pyrrole-2-carboxamido)-3-methoxypiperidin-1-yl]-4-(5-(2-(dimethylamino)ethoxy)pyrazin-2-yl)thiazole-5-carboxylic acid (86) From 5.8 g (9.26 mmol) of the corresponding ethyl ester of **86** and 4.63 mL of 2N LiOH to afford 3.6 g (65%) of the title compound. UPLC-MS RT = 0.82 min; (ESI) m/z (M+H)⁺: 598, 600 for C₂₄H₂₉Cl₂N₇O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 14.87 (br. s., 1H), 12.14 (s, 1H), 8.95 (d, *J*=1.3 Hz, 1H), 8.44 (d, *J*=1.3 Hz, 1H), 7.17 (d, *J*=8.3 Hz, 1H), 4.49 (t, *J*=5.8 Hz, 2H), 4.42 (m, 1H), 4.18-4.35 (m, 1H), 3.98 (m, 1H), 3.58 (br. s., 1H), 3.40 (s, 3H), 2.72 (t, *J*=5.8 Hz, 2H), 2.25 (s, 6H), 2.19 (s, 3H), 1.79 (m, 2H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 169.8, 161.7, 159.4, 157.6, 148.3, 142.8, 139.1, 131.9, 127.9, 118.6, 117.3, 109.7, 108.1, 75.4, 64.3, 57.1, 57.0, 47.8, 45.1, 26.2, 10.6; HRMS [M+H]⁺ 598.1402 (theoretical 598.1401).

2-[(3S,4R)-4-(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxy-1-piperidiny]-4-[5-[[2-(4-methyl-1-piperazinyl)ethyl]amino]2-pyrazin-2-yl]-5-thiazolecarboxylic acid (87) From 2.45 g (3.6 mmol) of the corresponding ethyl ester of **87** and 144 mg NaOH in 2 mL water to afford 1.89 g (80%) of the title compound. UPLC-MS RT = 0.79 min, (ESI) m/z (M+H)⁺: 652, 654; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.17 (s, 1H), 8.95 (s, 1H), 8.02 (s, 1H), 7.95 (br. s, 1H), 7.18 (d, *J*=8.3 Hz, 1H), 3.49 (m, 2H), 3.40 (m, 5H), 3.15-3.36 (m, 6H), 3.57 (m, 1H), 3.89 (m, 1H), 4.29 (m, 1H), 4.49 (m, 1H), 2.89 (m, 5H), 2.52-2.79 (m, 8H), 2.19 (s, 3H), 1.78 (m, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 169.7, 161.7, 157.6, 154.6, 149.2, 147.8, 144.7, 132.3, 127.9, 118.7, 115.2, 109.8, 108.1, 75.4, 57.0, 56.8, 55.6, 53.0, 50.3, 47.8, 46.6, 43.2, 37.7, 26.2, 10.6; HRMS [M+H]⁺ 652.1957 (theoretical 652.1983).

2-[(3S,4R)-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-thiazol-2-yl-thiazole-5-carboxylic acid (89) From 66 mg (0.12 mmol) of the corresponding methyl ester of **89** and 0.19 mL of 2N LiOH to afford 53 mg (86%) of the title compound. UPLC-MS RT = 1.18 min, (ESI) m/z (M+H)⁺: 516 for C₁₉H₁₉Cl₂N₅O₄S₂; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.22 (br. s., 1H), 7.88 (s, 1H), 7.81 (b, 1H), 7.20 (d, *J*=8.3 Hz, 1H), 4.26 (m, 2H), 3.87 (m, 1H), 3.55 (m, 1H), 3.39 (s, 3H), 3.28 (m, 1H), 2.18 (s, 3H), 1.76 (m, 2H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 168.1, 163.8, 162.2, 157.7, 142.1, 140.3, 127.8, 122.4, 118.6, 109.9, 108.1, 75.4, 56.9, 47.8, 47.2, 46.3, 26.1, 10.6; HRMS [M+H]⁺ 516.0312 (theoretical 516.0328).

4-(2-Aminothiazol-4-yl)-2-[(3S,4R)-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylic acid (90) From 86 mg (0.16 mmol) of the corresponding methyl ester of **90** and 0.40 mL of 2N LiOH to afford 70 mg (84%) of the title compound. UPLC-MS RT = 0.89 min, (ESI) m/z (M+H)⁺: 531, 533 for C₁₉H₂₀Cl₂N₆O₄S₂; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.09 (s, 1H), 8.01 (s, 2H), 7.20 (s, 1H), 7.10 (d, *J*=7.7 Hz, 1H), 4.1-4.5 (m, 2H), 3.8-4.0 (m, 1H), 3.32 (m, 1H), 3.32 (s, 3H), 2.12 (s, 3H), 1.6-1.8 (m, 2H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 169.5, 161.8, 157.6,

144.7, 141.7, 127.9, 118.6, 115.7, 109.7, 109.3, 108.1, 75.4, 64.8, 57.0, 47.8, 46.3, 26.1, 10.6; HRMS $[M+H]^+$ 531.0428 (theoretical 531.0437).

2-[(3S,4R)-rel-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-hydroxy-1-piperidyl]thiazole-5-carboxylic acid (27) BBr₃ in CH₂Cl₂ (10 mL of 0.1M solution) was added to a mixture of 100 mg (0.23 mmol) 2-[(3S,4R)-rel-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylic acid (**22**) in 5 mL CH₂Cl₂ at 0 °C, and the mixture was warmed to rt with stirring overnight. After cooling to -50 °C, the mixture was quenched with water, warmed to rt and extracted with EtOAc. The organic phase was washed with water, dried (MgSO₄) and concentrated to afford the title compound as a solid (47 mg, 48%). MS (ESI) m/z ($M+H$)⁺: 419 for C₁₅H₁₆Cl₂N₄O₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.50 (br. s, 1H), 12.07 (s, 1H), 7.67 (s, 1H), 7.07 (d, *J*=7.9 Hz, 1H), 3.00-4.20 (m, 6H), 2.12 (s, 3H), 1.69 (m, 2H); HRMS $[M+H]^+$ 419.0332 (theoretical 419.0342).

2-[(3S,4R)-4-(3,4-Dichloro-5-methyl-1H-pyrrole-2-carboxamido)-3-methoxypiperidin-1-yl]-5-(methylcarbamoyl)thiazole-4-carboxylic acid (60) A mixture of 5 mL 40% aq. methylamine and 253 mg (0.50 mmol) of **18** was stirred in a stopped vessel overnight. The mixture was cooled in an ice water bath and acidified to pH 4 with conc. aq. HCl. The precipitated solids were collected by filtration, washed with water and dried *in vacuo*. The material was purified by reverse phase HPLC (CH₃CN in water gradient with 0.1% TFA) to afford 110 mg (45%) of the title compound as a white solid. MS (ESI) m/z ($M+H$)⁺: 490, 492 for C₁₈H₂₁Cl₂N₅O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.1 (br. s, 1H), 9.7 (s, 1H), 7.1 (s, 1H), 7.07 (d, *J*=7.9 Hz, 1H), 4.2-4.3 (m, 2H), 3.9-4.0 (m, 1H), 3.5-3.7 (m, 2H), 3.0-3.3 (m, 3H), 2.2 (s, 3H), 1.7-1.9 (m, 2H); HRMS $[M+H]^+$ 490.0727 (theoretical 490.0713).

2-[(3S,4R)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-4-carboxylic acid (57) Ba(OH)₂ (56 mg, 0.33 mmol) dissolved in 0.5 mL water was added to a suspension of corresponding ethyl ester of **57** (50 mg, 0.11 mmol) in MeOH (2 mL). After stirring for 3H, the reaction was acidified with 1N HCl and concentrated to remove MeOH. The residue was extracted with EtOAc (3X), which was dried (MgSO₄) and concentrated to afford the title compound as a white solid (0.022 g, 46%). UPLC-MS RT = 0.94 min, (ESI) m/z ($M+H$)⁺: 433, 435 for C₁₆H₁₈Cl₂N₄O₄S; ¹H NMR (DMSO-*d*₆) δ 1.75 (m 2H) 2.19 (s, 3H) 3.17 (d, 1H) 3.27 (s, 1H) 3.36 (s, 3H) 3.54 (s, 1H) 3.85 (s, 1H) 4.21 (d, 2H) 7.16 (d, 1H) 7.58 (s, 1H) 12.16 (s, 1H) 12.57 (s, 1H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 170.1, 162.3, 157.6, 143.7, 127.9, 118.6, 116.8, 109.7, 108.1, 75.3, 56.9, 48.1, 47.8, 46.4, 26.0, 10.6; HRMS $[M+H]^+$ 433.0489 (theoretical 433.0499).

The following 11 compounds were made as described for **57**.

2-[4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3,3-dimethoxy-1-piperidyl]thiazole-5-carboxylic acid (39) From 74 mg (0.15 mmol) of the corresponding methyl ester of **39** and 80 mg (0.47 mmol) Ba(OH)₂ to afford the 35 mg (50%) of product. UPLC-MS RT = 1.00 min, (ESI) m/z $M+H$ ⁺: 463, 465 for C₁₇H₂₀Cl₂N₄O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.62 (br. s., 1H), 12.17 (s, 1H), 7.73 (s, 1H), 6.96 (d, *J*=8.8 Hz, 1H), 4.42 (m, 1H), 3.91-4.22 (m, 4H), 3.75-3.87 (m, 1H), 3.22-3.51 (m, 5H), 2.18 (s, 3H), 1.86-2.05 (m, 2H), 1.61-1.82 (m, 1H), 1.08-1.41 (m, 2H); HRMS $[M+H]^+$ 463.0612 (theoretical 463.0604).

2-[6-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-1,4-dioxo-9-azaspiro[4.5]decan-9-yl]thiazole-5-carboxylic acid (40) From 74 mg (0.15 mmol) of the corresponding methyl ester of **40** and 80 mg (0.47 mmol) Ba(OH)₂ to afford 35 mg (50%) of product. UPLC-MS RT = 0.91 min, (ESI) m/z $M+H$ ⁺: 461 for C₁₇H₁₈Cl₂N₄O₅S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.72 (s, 1H), 1.91 (s, 1H), 2.18 (s, 3H), 3.31-3.43 (m, 4H), 3.80 (d, 1H), 4.00 (d, 2H), 4.06-4.16 (m, 1H), 4.33-4.48 (m, 1H), 6.96 (d, 1H), 7.73 (s, 1H), 12.17 (s, 1H), 12.62 (s, 1H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 173.6, 162.6, 158.0, 147.5, 128.0, 118.5, 116.9, 109.7, 108.1, 105.4, 65.9, 64.9, 52.7, 50.0, 46.3, 29.3, 10.6; HRMS $[M+H]^+$ 461.0448 (theoretical 461.0448).

4-Carbamoyl-2-[(3S,4R)-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylic acid (61) From 150 mg (0.30 mmol) of the ethyl ester of **61** and 100 mg (0.60 mmol) Ba(OH)₂ to afford 123 mg (86%) of product. UPLC-MS RT = 1.01 min, (ESI) m/z ($M+H$)⁺:

476 for $C_{17}H_{19}Cl_2N_5O_5S$; 1H NMR (300 MHz, DMSO- d_6) 13.8 (br. s., 1H), 12.16 (s, 1H), 8.92 (br. s., 1H), 7.83 (br. s., 1H), 7.16 (d, $J=8.3$ Hz, 1H), 4.26 (m, 2H), 3.92 (m, 1H), 3.54 (m, 1H), 3.37 (s, 3H), 2.18 (s, 3H), 1.75 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 168.7, 165.8, 160.6, 157.6, 143.4, 127.9, 124.8, 118.6, 109.7, 108.1, 75.4, 57.1, 47.7, 46.6, 26.1, 10.6; HRMS $[M+H]^+$ 476.0567 (theoretical 476.0557); ee >98% by chiral SFC analysis (pp S46).

2-[(3*S*,4*R*)-4-[(3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(2-methoxyethylcarbamoyl)thiazole-5-carboxylic acid (62) From the corresponding ethyl ester of **62** (38 g, 68 mmol) and 34.7 g (203 mmol) Ba(OH) $_2$ to afford the title compound as a white solid (24.6 g, 66%). UPLC-MS RT = 1.13 min, (ESI) m/z (M+H) $^+$: 534 for $C_{20}H_{25}Cl_2N_5O_6S$; 1H NMR (300 MHz, DMSO- d_6) δ 16.36 (s, 1H), 12.16 (s, 1H), 9.37 (s, 1H), 7.17 (d, $J=8.5$ Hz, 1H), 3.79-4.68 (m, 3H), 3.57 (m, 1H), 3.50 (s, 3H) 2.45-3.0 (m, 1H) 3.42 (m, 1H), 3.38 (m), 2.19 (s, 3H), 1.77 (m, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 166.6, 163.8, 161.7, 157.7, 143.0, 132.8, 127.8, 118.7, 109.8, 108.1, 75.3, 70.8, 57.9, 56.9, 47.8, 47.6, 45.6, 38.6, 26.1, 10.6; HRMS $[M+H]^+$ 534.0953 (theoretical 534.0975); $[\alpha]^{26}_D = -13.0$ (c = 0.13, DMSO); ee >98% by chiral SFC analysis (pp S46).

2-[(3*S*,4*R*)-4-[(3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-[[2-methoxy-1,1-bis(methoxymethyl)ethyl]carbamoyl]thiazole-5-carboxylic acid (66) From the corresponding ethyl ester of **66** (1.61 mg, 2.5 mmol) and 1.27 g (7.4 mmol) Ba(OH) $_2$ to afford 1.08 g (40%) of product. UPLC-MS RT = 1.31 min, (ESI) m/z (M+H) $^+$: 623, 625 for $C_{24}H_{33}Cl_2N_5O_8S$; 1H NMR (300 MHz, DMSO- d_6) δ 15.8 (s, 1H), 12.2 (s, 1H), 8.38 (s, 1H), 7.16 (d, $J=8.58$ Hz, 1H), 4.28 (m, 1H), 3.58-3.70 (br. s., 6H), 3.54-3.59 (m, 2H), 3.35-3.45 (m, 3H), 3.29 (s, 9H), 2.19 (s, 3H), 1.73-1.83 (m, 2H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 168.6, 162.8, 160.2, 157.6, 143.2, 127.9, 124.0, 118.6, 109.8, 108.1, 75.5, 70.3, 60.4, 58.9, 56.9, 47.6, 26.1, 10.6; HRMS $[M+H]^+$ 622.1519 (theoretical 622.1500).

2-[(3*S*,4*R*)-4-[(3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(1,3-dioxolan-2-ylmethylcarbamoyl)thiazole-5-carboxylic acid (67) From the corresponding ethyl ester of **67** (122 mg, 0.21 mmol) and 110 mg (0.62 mmol) Ba(OH) $_2$ to afford 71 mg (60%) of product. UPLC-MS RT = 1.11 min, (ESI) m/z (M+H) $^+$: 562 for $C_{21}H_{25}Cl_2N_5O_7S$; 1H NMR (300 MHz, DMSO- d_6) δ 16.19 (s, 1H), 12.16 (s, 1H), 9.39 (t, $J=6.2$ Hz, 1H), 7.17 (d, $J=8.3$ Hz, 1H), 5.05 (t, $J=4.2$ Hz, 1H), 4.28 (m, 2H), 3.89-3.98 (m, 2H), 3.77-3.89 (m, 2H), 3.58 (m, 1H), 3.44-3.52 (m, 2H), 3.39 (s, 3H), 2.19 (s, 3H), 1.7-1.8 (m, 2H); HRMS $[M+H]^+$ 562.0947 (theoretical 562.0925).

2-[(3*S*,4*R*)-4-[(3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-[(2-methyl-1,3-dioxolan-2-yl)methylcarbamoyl]thiazole-5-carboxylic acid (69) From the corresponding ethyl ester of **69** (107 mg, 0.177 mmol) and 91 mg (0.53 mmol) Ba(OH) $_2$ to afford 57 mg (56%) of product. UPLC-MS RT = 1.17 min, (ESI) m/z (M+H) $^+$: 576.3, 578.3 for $C_{22}H_{27}Cl_2N_5O_7S$; 1H NMR (300 MHz, DMSO- d_6) δ 1H NMR (300 MHz, DMSO- d_6) δ 13.24 (t, $J=5.6$ Hz, 1H), 12.16 (br. s., 1H), 7.17 (d, $J=7.9$ Hz, 1H), 4.04-4.37 (m, 2H), 3.72-4.00 (m, 5H), 3.50 (s, 1H), 3.36 (s, 3H), 3.06-3.29 (m, 3H), 2.18 (s, 3H), 1.72 (m, 2H), 1.26 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 168.9, 163.4, 160.4, 157.6, 143.2, 127.9, 124.0, 118.6, 109.7, 108.1, 107.8, 75.5, 64.6, 64.5, 57.1, 47.7, 44.9, 26.1, 22.6, 10.6; HRMS $[M+H]^+$ 576.1058 (theoretical 576.1081).

2-[(3*S*,4*R*)-4-[(3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-[2-(2-oxopyrrolidin-1-yl)ethylcarbamoyl]thiazole-5-carboxylic acid (70) From the corresponding ethyl ester of **70** (87 mg, 0.14 mmol) and 73 mg (0.42 mmol) Ba(OH) $_2$ to afford 38 mg (46%) of product. UPLC-MS RT = 1.03 min, (ESI) m/z (M+H) $^+$: 587, 289 for $C_{23}H_{28}Cl_2N_6O_6S$; 1H NMR (300 MHz, DMSO- d_6) δ 16.3 (s, 1H), 12.16 (s, 1H), 9.45 (br. s, 1H), 7.17 (d, $J=8.1$ Hz, 1H), 3.83-4.55 (m, 4H), 3.57 (m, 4H), 3.40 (m, 4H), 3.39-3.48 (m), 2.19 (s, 3H) 2.1-2.2 (m, 2H), 1.8-2.0 (m, 2H), 1.7-1.8 (m, 2H); ^{13}C NMR (126 MHz, DMSO- d_6) δ 174.5, 168.8, 163.5, 160.5, 157.6, 151.1, 143.1, 127.9, 123.9, 120.7, 118.6, 109.7, 108.1, 75.4, 57.1, 47.7, 46.8, 41.0, 37.8, 30.3, 26.1, 17.7, 10.6; HRMS $[M+H]^+$ 587.1251 (theoretical 587.1241).

2-[(3*S*,4*R*)-4-[(3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(2-morpholinoethylcarbamoyl)thiazole-5-carboxylic acid (71) From the corresponding ethyl ester of **71** (63 mg, 0.10 mmol) and 52 mg (0.31 mmol) Ba(OH) $_2$ to afford 35 mg (59%) of product. MS (ESI) m/z (M+H) $^+$: 589 for $C_{23}H_{30}Cl_2N_6O_6S$; 1H NMR (300 MHz, DMSO- d_6) 15.96 (br. s., 1H), 12.20 (s, 1H), 10.44

(br. s., 1H), 9.59 (br. s., 1H), 7.18 (d, $J=8.3$ Hz, 1H), 4.28 (m, 1H), 3.96 (m, 1H), 3.72 (m, 2H), 3.57 (m, 1H), 3.39 (s, 3H), 3.36 (m, 8H), 3.15 (m, 2H), 2.19 (s, 3H), 1.76 (m, 2H); HRMS $[M+H]^+$ 589.1371 (theoretical 589.1397).

2-[(3S,4R)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(morpholinocarbamoyl)thiazole-5-carboxylic acid (72) From corresponding ethyl ester of **72** (92 mg, 0.16 mmol) and (80 mg, 0.46 mmol) $Ba(OH)_2$ to afford 63 mg (66%) of product. UPLC RT = 1.04 min, (ESI) m/z $(M+H)^+$: 561.3, 563.3 for $C_{21}H_{26}Cl_2N_6O_6S$; 1H NMR (300 MHz, DMSO- d_6) δ 15.7 (br. s, 1H), 12.16 (s, 1H), 10.11 (s, 1H), 7.16 (d, $J=8.3$ Hz, 1H), 3.96-4.55 (m, 4H), 3.68 (br. s., 4H), 3.57 (m, 4H), 3.30-3.45 (m), 2.91 (m, 4H), 2.19 (s, 3H), 1.76 (m, 2H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 169.3, 161.3, 160.6, 157.6, 143.8, 127.9, 123.2, 118.6, 109.7, 108.1, 75.5, 65.8, 57.1, 53.8, 48.1, 47.7, 46.4, 26.1, 10.6; HRMS $[M+H]^+$ 561.1066 (theoretical 561.1084).

2-[(3S,4R)-4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-pyridin-2-yl-thiazole-5-carboxylic acid (88) From 78 mg (0.15 mmol) of the ester of **88** and 74 mg (0.43 mmol) $Ba(OH)_2$ to afford 41 mg (54 %) of product. UPLC-MS RT = 1.05 min, (ESI) m/z $(M+H)^+$: 510 for $C_{21}H_{21}Cl_2N_5O_4S$; 1H NMR (300 MHz, DMSO- d_6) δ 12.17 (br. s., 1H), 8.76 (d, $J=3.8$ Hz, 1H), 8.45 (d, $J=7.7$ Hz, 1H), 8.25 (t, $J=7.4$ Hz, 1H), 7.57-7.85 (m, 1H), 7.18 (d, $J=7.9$ Hz, 1H), 4.46 (m, 1H), 4.30 (m, 1H), 4.03 (m, 1H), 3.59 (br. s., 1H), 3.40 (s, 3H), 2.19 (s, 3H), 1.80 (m, 2H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 169.3, 161.8, 157.6, 149.6, 146.6, 145.4, 141.2, 127.9, 125.2, 124.4, 121.7, 118.7, 109.7, 108.1, 75.5, 57.0, 47.8, 46.5, 26.1, 10.6; HRMS $[M+H]^+$ 510.0755 (theoretical 510.0764).

5-Carbamoyl-2-[(3S,4R)-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-4-carboxylic acid (59) A mixture of 400 mg (79 mmol) of **18** and 5 mL of conc. aq. NH_4OH g was heated at 60 °C for 1 2H in sealed pressure vessel. After cooling to rt, the mixture was dilute with water and acidified with conc. aq. HCl. Solids that precipitated were collected by filtration, washed with water and dried *in vacuo* to give 225 mg (60%) of the title compound. UPLC-MS RT = 0.86 min, (ESI) m/z $(M+H)^+$: MS (ESI) m/z $(M+H)^+$: 476, 478 for $C_{17}H_{19}Cl_2N_5O_5S$; 1H NMR (300 MHz, DMSO- d_6) δ 13.9 (br. s., 1H), 12.16 (s, 1H), 8.92 (br. s., 1H), 7.83 (br. s., 1H), 7.16 (d, $J=8.3$ Hz, 1H), 4.26 (m, 2H), 3.92 (m, 1H), 3.54 (s, 1H), 3.37 (s, 3H), 2.18 (s, 3H), 1.75 (m, 2H); ^{13}C NMR (126 MHz, DMSO- d_6) δ 168.2, 164.3, 161.6, 157.6, 141.5, 128.6, 127.9, 118.6, 109.7, 108.1, 75.4, 57.0, 47.8, 47.7, 46.3, 26.0, 10.6; HRMS $[M+H]^+$ 476.0546 (theoretical 476.0556).

Methyl 2-[(3S,4R)-rel-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]thiazole-5-carboxylate (methyl ester of 22) A solution of 380 mg (1.24 mmol) of racemic **6a**, methyl 2-bromo-1,3-thiazole-5-carboxylate (276 mg, 1.55 mmol) and DIEA (216 μ L, 1.24 mmol) was heated at 120 °C for 7 h. The mixture was diluted with EtOAc, washed with citrate buffer, water and brine. Drying (Na_2SO_4) and removal of solvent afforded the title compound as a solid (337 mg, 61%). MS (ESI) m/z $(M+H)^+$: 447 for $C_{17}H_{20}Cl_2N_4O_4S$; 1H NMR (300 MHz, DMSO- d_6) δ 1.65 (m, 2H), 2.09 (s, 3H), 3.07 (m, 3H), 3.48 (m, 1H), 3.63 (s, 3H), 3.86 (m, 1H), 4.15 (m, 2H), 6.91 (d, 1H), 7.45 (s, 1H), 11.19 (s, 1H).

Sodium 2-[(3S,4R)-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(2-methoxyethylcarbamoyl)thiazole-5-carboxylate (62 Na^+ salt) Sodium hydroxide (0.056 mL, 0.056 mmol, 1N) was added to a suspension of **62** (0.03 g, 0.056 mmol) in MeOH (5 mL). After stirring five min, the reaction became homogeneous. The reaction mixture was concentrated and the resulting white solid was dried overnight (0.030 g). MS (ESI) m/z $(M+H)^+$: 534 for $C_{20}H_{24}Cl_2N_5O_6SNa$; 1H NMR (300 MHz, DMSO- d_6) δ 13.23 (br. s., 1H), 12.27 (s, 1H), 7.21 (d, $J=8.1$ Hz, 1H), 4.2 (m, 1H), 4.11. (d, $J=14.5$ Hz, 1H), 3.86 (m, 1H), 3.50 (br. s., 1H), 3.30-3.44 (m, 8H), 3.25 (s, 3H), 3.05-3.20 (m, 2H), 2.18 (s, 3H), 1.55-1.91 (m, 2H).

Sodium 2-[(3S,4R)-4-[(3,4-dichloro-5-methyl-1H-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-[(1S)-2-methoxy-1-methyl-ethyl]carbamoyl]thiazole-5-carboxylate (63 Na^+ salt) Carried out as described above for **62** Na^+ salt. MS (ESI) m/z $(M+H)^+$: 548 for $C_{21}H_{26}Cl_2N_5O_6SNa$; 1H NMR (300 MHz, DMSO- d_6) δ 13.23 (br. s., 1H), 12.27 (s, 1H), 7.21 (d, $J=8.1$ Hz, 1H), 4.2 (m, 1H), 4.11. (d, $J=14.5$ Hz, 1H), 3.86 (m, 1H), 3.50 (br. s., 1H), 3.30-3.44 (m, 8H), 3.25 (s, 3H), 3.05-3.20 (m, 2H), 2.18 (s, 3H), 1.55-1.91 (m, 2H).

Sodium 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-[[2-methoxy-1-(methoxymethyl)ethyl]carbamoyl]thiazole-5-carboxylate (65 Na⁺ salt)

Carried out as described above for 62 Na⁺ salt. MS (ESI) *m/z* (M+H)⁺: 578 for C₂₂H₂₈Cl₂N₅O₇SNa; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.33 (d, *J*=7.2 Hz, 1H), 12.19 (s, 1H), 7.18 (d, *J*=8.3 Hz, 1H), 4.20 (m, 1H), 4.01-4.15 (m, 2H), 3.86 (m, 1H), 3.50 (br. s., 1H), 3.30-3.40 (m, overlaps with water peak), 3.24 (s, 6H), 3.05-3.21 (m, 2H), 2.18 (s, 3H), 1.71 (d, *J*=4.7 Hz, 2H).

Sodium 2-[(3*S*,4*R*)-4-[(3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl)amino]-3-methoxy-1-piperidyl]-4-(methylcarbamoyl)thiazole-5-carboxylate (51 Na⁺ salt)

Carried out as described above for 62 Na⁺ salt. MS (ESI) *m/z* (M+H)⁺: 578 for C₂₂H₂₈Cl₂N₅O₇SNa; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.05 (s, 1H), 12.18 (s, 1H), 7.18 (d, *J*=8.1 Hz, 1H), 3.99-4.29 (m, 2H), 3.85 (m, 1H), 3.50 (m, 1H), 3.36 (m, 3H), 3.06-3.25 (m, 3H), 2.68 (d, *J*=3.2 Hz, 3H), 2.18 (s, 3H), 1.72 (m, 2H).

Ethyl 2-amino-4-(hydroxymethyl)-thiazole-5-carboxylate (15) A solution of 5.0 g (37 mmol) of 3-chlorofuran-2,4(3*H*,5*H*)-dione and 3.3 g (43 mmol) of thiourea in 50 mL EtOH was heated at reflux for 4 h. Solvent was removed, and the residue was dissolved in water with 1N HCl added. The aq solution was basified with aq Na₂CO₃. Thick solids that formed were filtered, rinsed with water and dried *in vacuo*. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.2 (t, 3H), 4.2 (q, 2H), 4.6 (s, 2H), 4.9 (s, broad, 1H), 7.8 (s, 2H).

Ethyl 2-amino-4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]thiazole-5-carboxylate *t*-Butyldimethylsilyl chloride (1.6 g, 10.6 mmol) was added to a solution of 2.0 g (9.8 mmol) ethyl 2-amino-4-(hydroxymethyl)-thiazole-5-carboxylate and 1.3 g (19.4 mmol) imidazole in 20 mL DMF. After stirring for 2H, solvent was removed and the residue was taken up in water. Insoluble solids were collected, ground up, washed with water and dried *in vacuo* to afford 2.95 g of the title compound as a white solid. MS (ESI) *m/z* (MH⁺): 317 for C₁₃H₂₄N₂O₃SSi; ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.03 (s, 6H), 0.86 (s, 9H), 1.2 (t, 3H), 4.1 (q, 2H), 4.8 (s, 2H), 7.8 (s, 2H).

Ethyl 4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]thiazole-2-chloro-5-carboxylate (16) *t*-Butylnitrite (1.8 mL, 14 mmol) was added slowly to a mixture of 2.9 g (9.2 mmol) of the preceding compound and 1.95 g (14 mmol) CuCl₂ in CH₃CN. After stirring at rt for 2H, solvent was removed, and the residue was taken up in EtOAc, which was washed 2 times with 1N HCl and once with brine. Drying (MgSO₄) and removal of solvent gave 2.95 g (95%) of the title compound as an oil. MS (ESI) *m/z* (MH⁺): 336, 338 for C₁₃H₂₂ClNO₃SSi; NMR (300 MHz, CDCl₃): 0.1 (s, 6H), 0.9 (s, 9H), 1.35 (t, 3H), 4.3 (q, 2H), 5.0 (s, 2H).

Ethyl 2-chloro-4-(hydroxymethyl)thiazole-5-carboxylate A solution of 17.7 g (53 mmol) of the preceding intermediate and 53 mL (53 mmol) of 1N HCl in dioxane was stirred at rt for 1H. The mixture was diluted with water and extracted 3 times with EtOAc, which was dried (MgSO₄) and concentrated to give 11.3 g of an orange oil. Purification by silica gel chromatography (CH₂Cl₂) afforded 10.9 g of the title compound as a solid. NMR (300 MHz, CDCl₃): 1.2 (t, 3H), 3.1 (s, broad, 1H), 4.2 (q, 2H), 4.8 (s, 2H).

5-Ethyl 2-chloro-4,5-thiazolecarboxylate (17) A solution of CrO₃ (42.1 g, 421 mmol) in 20% conc. sulfuric acid in water (100 mL) was added slowly to a solution of the preceding intermediate (46.7 g, 210 mmol) in 100 mL acetone at 0 °C. After stirring at rt for 2Hrs, isopropanol (10 mL) was added, and the reaction mixture was diluted with water and concentrated to remove the acetone. The mixture was extracted with EtOAc, which was washed with brine and dried (MgSO₄). Removal of solvent gave an oil that was taken up in hexanes and stirred overnight to afford 31 g (63%) of the title compound as a solid. MS (ESI) *m/z* (M+H)⁺: 236, 238 for C₇H₆ClNO₄S; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.26 (t, 3H) 4.31 (q, 2H) 13.99 - 14.15 (m, 1H).

4-[[*tert*-Butyl(dimethyl)silyl]oxymethyl]-2-chloro-N-(1-methyl-1-phenyl-ethyl)thiazole-5-carboxamide A solution of 2N CH₃Al in hexanes (1.25 mL, 2.5 mmol) was added slowly to a solution of 337 mg (2.5 mmol) of cumylamine in 3 mL ClCH₂CH₂Cl at 0 °C. After stirring for 15 min and warming to rt, a solution of 700 mg (2.1 mmol) of ethyl 4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]thiazole-2-chloro-5-carboxylate in 3 mL ClCH₂CH₂Cl was added. The solution was heated at 80 °C for 1H before being poured into dilute aq HCl. The mixture was extracted 3 times with EtOAc, which was washed with brine, dried (MgSO₄) and concentrated. The residue was purified by silica gel chromatography (100% CH₂Cl₂ followed by gradient elution to 30% EtOAc in CH₂Cl₂) to give 320 mg of the title compound as an oil. ¹H

NMR (300 MHz, DMSO- d_6) δ 0.04 (s, 6H), 0.8 (s, 9H), 1.6 (s, 6H), 4.9 (s, 2H), 7.2 (7, 1H), 7.3 (t, 2H), 7.4 (d, 2H), 8.6 (s, 1H).

2-Chloro-5-[(1-methyl-1-phenyl-ethyl)carbamoyl]thiazole-4-carboxylic acid A solution of 158 mg (1.6 mmol) CrO_3 in 1 mL of 4:1 water/ H_2SO_4 was added to a solution of 158 mg (1.6 mmol) of the preceding compound in 3 mL acetone cooled in an ice water bath. The mixture was stirred with warming at rt over 90 min. A few drops of isopropanol were added, and the mixture was diluted with water and extracted 2 times with EtOAc. The EtOAc extracts were washed with brine, dried (MgSO_4) and concentrated to give 222 mg of the title compound as a white solid used in the subsequent reaction without further purification. MS (ESI) m/z (M-H^-): 323 for $\text{C}_{14}\text{H}_{13}\text{ClN}_2\text{O}_2\text{S}$; ^1H NMR (300 MHz, DMSO- d_6) δ 1.69 (s, 6H) 7.2-7.5 (m, 5H) 10.3 (s, 1H).

Ethyl 2-chloro-5-[(1-methyl-1-phenyl-ethyl)carbamoyl]thiazole-4-carboxylate A mixture of 222 mg (0.68 mmol) of the preceding intermediate and 0.30 mL triethylorthoacetate in 20 mL toluene was heated at reflux for 2 h. Solvent was removed, and the residue taken up in 1N HCl and stirred for 20 min before being partitioned between EtOAc and water. The EtOAc was separated, washed with water and brine, dried (MgSO_4) and concentrated. Chromatography on silica gel (100% hexanes with gradient elution to 100% CH_2Cl_2) gave 210 mg (87%) of the title compound as an oil. MS (ESI) m/z (MH^+): 353 for $\text{C}_{16}\text{H}_{17}\text{ClN}_2\text{O}_2\text{S}$.

Ethyl 5-carbamoyl-2-chloro-thiazole-4-carboxylate A solution of 210 mg (0.60 mmol) of the preceding compound in 5 mL TFA was stirred at rt overnight. Solvent was removed and the residue was dissolved in 5 mL MeOH. Solvent was again removed and the residue was triturated with ether to give 57 mg of the title compound as a white solid. MS (ESI) m/z (MH^+): 235, 237 for $\text{C}_7\text{H}_7\text{ClN}_2\text{O}_3\text{S}$; ^1H NMR (300 MHz, DMSO- d_6) δ 1.3 (t, 3H), 4.3 (q, 2H), 8.2 (s, 1H), 8.8 (s, 1H).

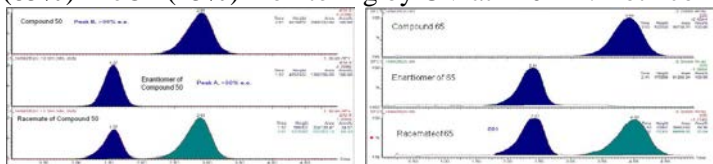
Ethyl 2-chloro-4-(methoxymethyl)thiazole-5-carboxylate A mixture of *t*-Butylnitrite (5.4 mL, 45 mmol), CuCl_2 (3.56 g, 36 mmol) of 6.0 g (30 mmol) of ethyl 2-amino-4-(methoxymethyl)thiazole-5-carboxylate in 100 mL CH_3CN was stirred at rt for 2 h. Insoluble material was filtered off, and the filtrate was poured into 100 mL of 76N HCl. The mixture was extracted with EtOAc, which was dried (MgSO_4) and concentrated. The residue was chromatographed on silica gel (gradient elution with 1:1 Hexanes- CH_2Cl_2 to 100% CH_2Cl_2 to 1:1 EtOAc- CH_2Cl_2) to afford 2.2 g (95%) of the title compound as an oil. MS (ESI) m/z (MH^+): 236, 238; $\text{C}_8\text{H}_{10}\text{ClNO}_3\text{S}$; ^1H NMR (300 MHz, DMSO- d_6) δ 4.71 (s, 2H), 3.84 (s, 3H), 3.3 (s, 3H).

Chiral Purity Analyses

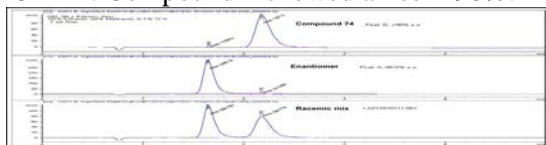
Analytical separation of AZD5099 and its enantiomer was carried out by Supercritical Fluid Chromatography on a Chiralpak A1 (4.5 x 1000 mm, 5 micron) column at 35 °C and 120 bar with CO₂(65%)-MeOH(35%) monitoring by UV at 220 nm. AZD5099 showed an ee > 98%.



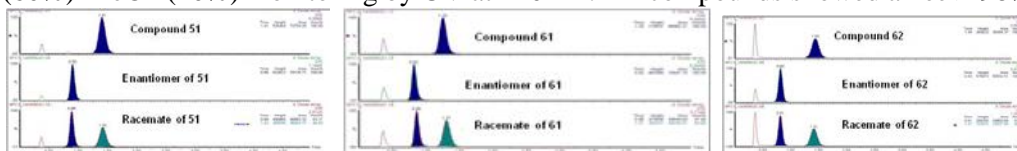
Analytical separation of **50** and **65** and their enantiomers was carried out by Supercritical Fluid Chromatography on a Chiralcel OJ (4.6 x 100 mm, 5 micron) column at 40 °C and 100 bar with CO₂ (85%)-MeOH(15%) monitoring by UV at 220 nm. Both compounds showed an ee > 98%.



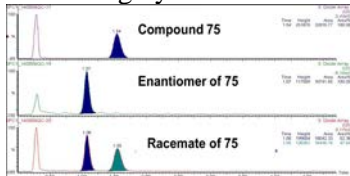
Analytical separation of compound **74** and its enantiomer was carried out by HPLC on a Chiralcel OD column (4.6 x 50 mm, 3 micron) column at rt with 1:1 MeOH-EtOH with 0.1% TFA monitoring by UV at 254 nm. Compound **4** showed an ee > 98%.



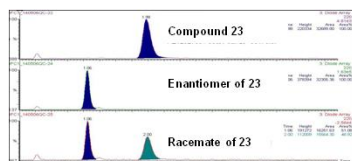
Analytical separation of **51**, **61** and **62** and their enantiomers were carried out by Supercritical Fluid Chromatography on a Chiralpak AS (4.6 x 100 mm, 5 micron) column at 40 °C and 100 bar with CO₂ (60%)-MeOH(40%) monitoring by UV at 220 nm. All compounds showed an ee > 98%.



Analytical separation of **75** and its enantiomers were carried out by Supercritical Fluid Chromatography on a Chiralpak AS (4.6 x 100 mm, 5 micron) column at 40 °C and 100 bar with CO₂ (70%)-MeOH(30%) monitoring by UV at 220 nm. Compound **75** showed an ee > 98%.



Analytical separation of **23** and its enantiomers were carried out by Supercritical Fluid Chromatography on a Chiralpak AD (4.6 x 100 mm, 5 micron) column at 40 °C and 100 bar with CO₂ (60%)-MeOH(40%) monitoring by UV at 220 nm. Compound **23** showed an ee > 98%.



Biological Experimental Procedures

Compounds for oral and iv dosing in mice, rats and dogs were formulated in 25% PEG/water and 4:4:2 dimethylacetamide-PEG400–water, respectively. Compounds for iv and ip dosing in rats were formulated in 70% PEG:30% saline (13% HP cyclodextrin). Wistar Han rats were used for pharmacokinetic studies and were obtained from Charles River Laboratories (Raleigh, NC). CD-1 mice were obtained from Charles River Laboratories (Kingston, NY) for efficacy studies. All animals were housed and acclimated in the animal facility on site before each study. All experimental procedures were conducted in accordance with protocols approved by the Institutional Animal Care and Use Committee.

Inhibition of ATPase activity of topoisomerase enzymes. Assays for the ATPase activity of the various topoisomerase isozymes were performed as described previously^{12,13} The ATPase activities of *E. coli* topoisomerase IV were measured from reconstituted tetramers of *E. coli* GyrA/GyrB and ParC/ParE, respectively. The ATPase activity of *S. aureus* DNA gyrase was measured from the reconstituted hybrid tetramer of the GyrB subunit from *S. aureus* with the GyrA subunit from *E. coli*. Inhibition of ATPase activity was monitored by reduced production of inorganic phosphate, a product of the topoisomerase-catalyzed ATP hydrolysis reaction. Inorganic phosphate was quantified using the ammonium molybdate/malachite green-based detection system, measuring absorbance at 650 (A_{650}) nm, assays were performed in microtiter plates containing of range concentrations of compounds dissolved in DMSO. For determination of the IC_{50} values reported, raw A_{650} nm was converted to percent inhibition calculated from the means of 32 wells each per assay plate of 0% inhibition (DMSO control) and 100% inhibition (2 μ M novobiocin control) wells. Curve fitting to determine IC_{50} values was performed using the equation $\%I = 100 / \{1 + (IC_{50} / [I])^n\}$.

LogD determination. The partition coefficient (logD) was measured by shake flask method, using 10 mM phosphate buffer at pH 7.4 and n-octanol. The samples were allowed to reach equilibrium by shaking for 1H at 1200 rpm, and sample analysis was done by LC/UV, with MS for mass confirmation.

pK_a Determination. pK_a values were determined at Sirius Analytical Instruments Ltd (Forest Row Business Park, Station Road, Forest Row, East Sussex, TN18 5DW) via potentiometric titrations via a Gold Standard pH metric assay on a Sirius T3 automated system in triplicate. The accuracy of the measurement was approximately 0.02 log units.¹⁴

Plasma protein binding determination. Human plasma protein binding was determined from a 10 μ M compound solution in a Dianorm plasma well incubating at 37°C for 16 hours. Free fractions were calculated from ratios of drug concentration in buffer and plasma wells determined by LC-MS/MS.

Pharmacokinetic studies. Pharmacokinetic properties of selected compounds were studied in male Wistar rats, male TR⁻ Wistar rats,¹⁵ male mice and male dogs. Plasma pharmacokinetics were determined from 0 to 24 hr following 15 min iv infusions at 10 mg/kg. Dosing formulations were prepared in 0.3 M meglumine in saline (pH 9). Serial 200 μ l samples of whole blood taken from the jugular vein of each animal at time intervals. Concentration of compound in plasma was determined by LC-MS/MS and pharmacokinetic parameters were estimated using a non-compartmental model in WinNonLin (Pharsight). Mean results were determined for each experiments with 3 mice, 3 rats or 2 dogs.

Minimum Inhibitory Concentration (MIC) MIC values were determined by the broth microdilution method in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines as described previously.¹⁶

In vivo efficacy CD-1 mice were rendered neutropenic by injecting cyclophosphamide intraperitoneally four days (150 mg/kg of body weight) and one day (100 mg/kg) before experimental infection. Mice were infected with a mid-log culture of *S. aureus* ARC516 to achieve a target inoculum of 5×10^5 CFU. Groups of five animals each received an intraperitoneal injection of test compound at doses of 3 to 100 mg/kg/day on a q24h or q6h regimen starting two hours after infection. A group of ten mice were sacrificed at two hours after infection and two further control groups of five mice received linezolid at 160 mg/kg q24 or vehicle alone. Efficacy was determined 24 h after the start of treatment. Thighs were removed, weighed, homogenized and aliquots plated onto tryptic soy agar plates and incubated at 37°C overnight for CFU/g thigh determination.

DNA biosynthesis inhibition. Incorporation of radiolabelled precursors (^3H -thymidine, ^3H -uridine, ^{14}C -leucine, ^{14}C -valine, ^{14}C -acetic acid and ^{14}C -N-acetyl glucosamine) of biological macromolecules was measured in *S. aureus* (MSSA) following previously described methods.¹⁷

Resistance frequency and isolation of resistant mutants. Resistance studies were performed following methods previously described.^{17, 18} Suspensions of bacterial cultures of methicillin-susceptible *S. aureus* (MSSA) were transferred onto Mueller-Hinton agar (BD, Franklin Lakes, NJ) plates containing compound at multiples of the MIC (0.04 µg/ml) as well as plates without compound. The frequencies of resistance were calculated from the ratio of the number of colonies on the compound-containing plates divided by the number of colonies on compound-free plates following incubation for 7 days. Values from three separate plates were averaged to yield the reported frequency of spontaneous resistance. To ensure resistance stability, the recovered colonies were passaged twice on compound-free agar plates. Resistant strains that showed a significant shift in MIC as compared to the parental strain were further characterized by PCR amplification and sequencing of *gyrA*, *gyrB*, *parC* and *parE* genes to identify mutations conferring resistance. ATPase assays

Activation/Inhibition of ATPase activity of human MRP2 and rat Mrp2 transporters Concentration ranges of test compounds (in 1 µl DMSO diluted to 50 µl final volume to afford final concentrations 0.14, 0.41, 1.2, 3.7, 11, 33, 100 and 300 µM) and glutathione (2 mM) were added to Sf9 membrane vesicles¹⁹ with and without Na_3VO_4 at $37 \pm 1^\circ\text{C}$ pre-incubating for 10 min. Concurrently, 10 mM MgATP was pre-incubated separately before adding 10 µl to the reaction mixture. The reactions were stopped by the addition of 0.1 ml of 5% SDS solution and the amount of inorganic phosphate (P_i) determined immediately by colorimetric complex formation with potassium-antimonyl-tartrate in acidic ammonium molybdate.¹⁹ For inhibition assays, an activator (sulfasalazine for human MRP2 and probenecid for rat Mrp2) is added to the assay mixture. To calculate the absolute value of specific activities the P_i liberated/mg membraneprotein/min was obtained by subtracting the P_i liberated in the presence of Na_3VO_4 from the P_i liberated in its absence. The vanadate sensitive baseline ATPase activity and the maximal vanadate sensitive ATPase activity are taken as 0% and 100% ATPase activity of the transporter, respectively, and activity values determined in the presence of test compounds were represented as percent activity on this relative scale.

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