Potent DGAT1 Inhibitors in the Benzimidazole Class with a Pyridyl-oxy-cyclohexanecarboxylic Acid Moiety

Supporting Information

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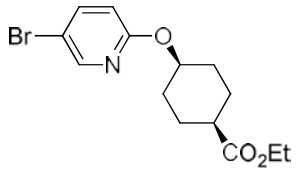
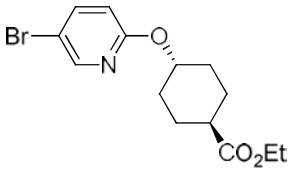
General

Normal phase column chromatography was carried out in the indicated solvent system (in the percentage of volume) using pre-packed silica gel cartridges for use on the Isco CombiFlash® or Biotage SP1®. Analytical thin layer chromatography (TLC) visualization was performed using 254 nm wavelength ultraviolet light. The LC/MS analyses were performed using a MICROMASS ZMD mass spectrometer coupled to an AGILENT 1100 Series HPLC utilizing a YMC ODS-A 4.6 x 50 mm column eluting at 4.5 mL/min with a solvent gradient of 10 to 95% B over 2.5 min, followed by 0.5 min at 95% B: solvent A = 0.06% TFA in water; solvent B =0.05% TFA in acetonitrile. The compounds had >95% purify according to LS/MS analyses. Nuclear Magnetic Resonance spectra were recorded on Varian spectrometers. Spectra were taken in the indicated solvent at ambient temperature, and the chemical shifts are reported in parts per million (ppm (δ)) relative to the lock of the solvent used. Resonance patterns are recorded with the following notations: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). High resolution mass spectra (HRMS) were acquired by use of a Bruker Daltonics 7T Fourier transform ion cyclotron resonance (FTICR) mass spectrometer. Samples were dissolved in acetonitrile:water:acetic acid (50:50:0.1%v/v), and ionized by use of electrospray ionization (ESI) yielding [M+H]+. External calibration was accomplished with oligomers of polypropylene glycol (PPG, average molecular weight 1000 Da. LogD of the compound was deterimined by reverse HPLC by comparing the retention time with the standard samples. The compound to be measured was injected into an Xterra MS C18 column with the mobile phase being buffer at pH 7.0. The retention time of the compound being measured was translated to a logD using a curve calibrated against a set of 11 drugs for which a literature logD value was known.

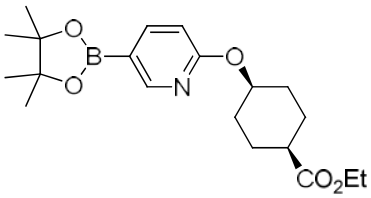
Ethyl cis-4-[(5-bromopyridin-2-yl)oxy]cyclohexanecarboxylate and ethyl trans-4-[(5-bromopyridin-2-yl)oxy]cyclohexanecarboxylate





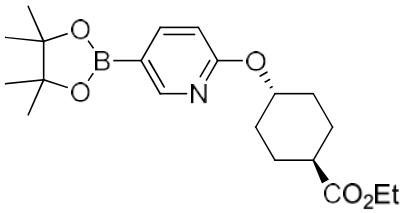
To a stirred solution of 5-bromo-2-hydroxypyridine (10 g, 230 mmol) in THF (300 mL) was added ethyl 4-hydroxycyclohexanecarboxylate (Aldrich, mixture of cis and trans isomers, 11.58 mL, 12.4 g, 71.8 mmol) at RT. Triphenylphosphine (18.84 g, 71.8 mmol) was added followed by dropwise addition of diisopropyl azadicarboxylate (14.14 ml, 71.8 mmol) at RT. The reaction mixture was stirred under N_2 at 55ºC for 40 h. The rxn was concentrated in vacuo to give an oil, which was treated with EtOAc (100 mL) followed by hexanes (100 mL). The mixture was stirred at RT overnight. The solid was filtered off, rinsed with EtOAc/hex 1:1 and discarded. The filtrate was concentrated to give a colorless oil, which was purified by preparative SFC on ChiralPak AS-20um column (300×50mmI.D.) eluted with 20% EtOH in supercritical CO_2 to give ethyl 4-[(5-bromopyridin-2-yl)oxy]cyclohexanecarboxylate as a cis/trans mixture. The mixture was separated by preparative SFC on ChiralPak AD-H (250×50mmI.D.) eluted with 20% EtOH in supercritical CO_2 to give the separated isomers: fasting eluting peak (1.91g, 10%) was ethyl cis-4-[(5-bromopyridin-2-yl)oxy]cyclohexanecarboxylate; slow eluting peak (4.85 g, 25.7%) was ethyl cis-4-[(5-bromopyridin-2-yl)oxy]cyclohexanecarboxylate.
Ethyl cis-4-[(5-bromopyridin-2-yl)oxy]cyclohexanecarboxylate: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, 1H), 7.61 (dd, 1H), 6.63 (d, 1H), 5.16 (m, 1H), 4.14 (q, 2H), 2.41 (m, 1H), 1.95 (m, 4H), 1.76 (m, 2H), 1.66 (m, 2H), 1.26 (t, 3H).
Ethyl trans-4-[(5-bromopyridin-2-yl)oxy]cyclohexanecarboxylate: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, 1H), 7.61 (dd, 1H), 6.59 (d, 1H), 4.94 (m, 1H), 4.13 (q, 2H), 2.32 (m, 1H), 2.19 (m, 2H), 2.06 (m, 2H), 1.63 (m, 2H), 1.45 (m, 2H), 1.26 (t, 3H).

Ethyl cis-4-{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]oxy} cyclohexanecarboxylate



A mixture of ethyl cis-4-[(5-bromopyridin-2-yl)oxy]cyclohexanecarboxylate (1.5 g, 4.57 mmol), bis(pinacolato)diboron (1.277 g, 5.03 mmol), potassium acetate (1.346 g, 13.71 mmol) and $PdCl_2$(dppf) (0.167 g, 0.229 mmol) in dioxane (25 mL) was purged with N_2 then heated at 80ºC overnight under N_2. The reaction was cooled to RT and concentrated in vacuo. The resiude was treated with DCM (~ 20 mL) followed by silica gel. The resulted mixture was concentrated in vacuo to dry powder, which was then loaded on a silica gel column. The column was eluted with a gradient ot 5% EtOAc in hexanes to 100% EtOAc in hexanes to afford ethyl cis-4-{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]oxy} cyclo-hexanecarboxylate(1.27 g, 74%). LCMS m/z=294.2 (boronic acid+H)$^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, 1H), 7.89 (dd, 1H), 6.68 (d, 1H), 5.29 (m, 1H), 4.14 (q, 2H), 2.40 (m, 1H), 1.98 (m, 2H), 1.93 (m, 2H), 1.76 (m, 2H), 1.67 (m, 2H), 1.32 (s, 12H), 1.25 (t, 3H).

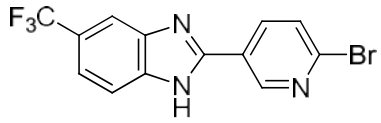
Ethyl trans-4-{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]oxy} cyclohexanecarboxylate



A mixture of ethyl trans-4-[(5-bromopyridin-2-yl)oxy]cyclohexanecarboxylate (2.0 g, 6.09 mmol), bis(pinacolato)diboron (1.702 g, 6.70 mmol), potassium acetate (1.794 g, 18.28 mmol) and $PdCl_2$(dppf) (0.223 g, 0.305 mmol) in dioxane (30 mL) was purged with N_2 then heated at 80ºC overnight under N_2. The reaction was cooled to RT and concentrated in vacuo. The resiude was treated with DCM (~ 20 mL) followed by silica

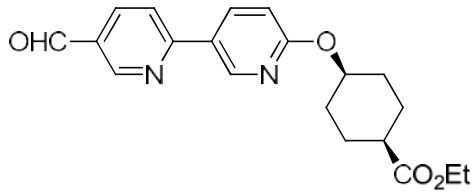
gel. The mixture was concentrated in vacuo to dry powder, which was then loaded on a silica gel column. The column was eluted with a gradient of 0% EtOAc in hexanes to 40% EtOAc in hexanes to afford ethyl trans-4-{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]oxy}cyclo-hexanecarboxylate (2.0 g, 87%). LCMS m/z =294.3 (boronic acid+H)$^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.89 (d, 1H), 6.63 (d, 1H), 5.06 (m, 1H), 4.12 (q, 2H), 2.32 (m, 1H), 2.20 (m, 2H), 2.05 (m, 2H), 1.65 (m, 2H), 1.46 (m, 2H), 1.33 (s, 12H), 1.25 (t, 3H).

2-(6-Bromopyridin-3-yl)-5-(trifluoromethyl)-1H-benzimidazole



4-(Trifluoromethyl)benzene-1,2-diamine (10 g, 56.8 mmol) and 6-bromo-nicotinaldedhyde (10.56 g, 56.8 mmol) were dissolved in DMF (172 ml) and then water (17.20 mL) was added. Potassium peroxymonosulfate (Oxone®) (22.69 g, 36.9 mmol) was added in portions over 15 min. The mixture was stirred overnight at RT under nitrogen. The reaction mixture was slowly poured into $NaHCO_3$ (sat. aq., ~1000 mL) under stirring. The resulting amorphous brown precipitate was collected by filtration, washed with water and hexane and dried with air passing through to afford 2-(6-bromopyridin-3-yl)-5-(trifluoromethyl)-1H-benzimidazole as a brown solid (14.0 g, 72%). LCMS m/z=344.0 (M+H)$^+$. ^{1}H NMR (500 MHz, CD_3OD) δ 9.06 (s, 1H), 8.35 (d, 1H), 7.93 (s, 1H), 7.80 (d, 1H), 7.76 (d, 1H), 7.56 (d, 1H).

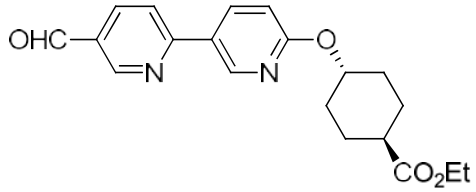
Ethyl cis-4-[(5-formyl-2,3'-bipyridin-6'-yl)oxy]cyclohexanecarboxylate



A mixture of ethyl cis-4-{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]oxy} cyclohexanecarboxylate (1.1 g, 2.93 mmol), 6-bromonicotinaldehyde (0.545 g, 2.93 mmol), soldium carbonate (0.621 g, 5.86 mmol) and $PdCl_2$(dppf) (0.107 g, 0.147

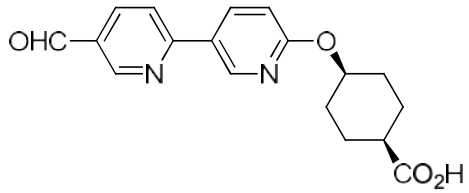
mmol) in DMF (3 mL) and water (1.5 mL) was purged with N_2 then heated at 80ºC overnight under N_2. The reaction was cooled to RT. Water (~ 20 mL) was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The resiude was purified by silica gel chromatography (eluted with a gradient of EtOAc in hex from 5 to 50%) to afford Ethyl cis-4-[(5-formyl-2,3'-bipyridin-6'-yl)oxy]cyclohexanecarboxylate (0.83 g, 80%). LCMS m/z=355.2 $(M+H)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.10 (s, 1H), 9.08 (s, 1H), 8.82 (d, 1H), 8.31 (dd, 1H), 8.19 (dd, 1H), 7.81 (d, 1H), 6.84 (d, 1H), 5.32 (s, 1H), 4.14 (q, 2H), 2.43 (m, 1H), 2.04 (m, 2H), 1.97 (m, 2H), 1.79 (m, 2H), 1.71 (m, 2H), 1.26 (t, 3H).

Ethyl trans-4-[(5-formyl-2,3'-bipyridin-6'-yl)oxy]cyclohexanecarboxylate



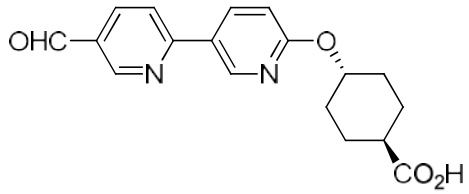
A mixture of ethyl trans-4-{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]oxy} cyclohexanecarboxylate (1.0 g, 2.66 mmol), 6-bromonicotinaldehyde (0.496 g, 2.66 mmol), soldium carbonate (0.565 g, 5.33 mmol) and $PdCl_2$(dppf) (0.097 g, 0.133 mmol) in DMF (5.2 mL) and water (2.6 mL) was purged with N_2 then heated at 80ºC overnight under N_2. The reaction was cooled to RT. Water (~ 20 mL) was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The resiude was purified by silica gel chromatography (eluted with a gradient of EtOAc in hex from 0 to 80%) to afford Ethyl trans-4-[(5-formyl-2,3'-bipyridin-6'-yl)oxy]cyclohexanecarboxylate (0.64 g, 68%). LCMS m/z=355.2 $(M+H)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.12 (s, 1H), 9.08 (s, 1H), 8.83 (s, 1H), 8.32 (d, 1H), 8.21 (d, 1H), 7.83 (d, 1H), 6.80 (d, 1H), 5.10 (m, 1H), 4.15 (q, 2H), 2.35 (m, 1H), 2.25 (m, 2H), 2.09 (m, 2H), 1.67 (m, 2H), 1.51 (m, 2H), 1.26 (t, 3H).

cis-4-[(5-formyl-2,3'-bipyridin-6'-yl)oxy]cyclohexanecarboxylic acid



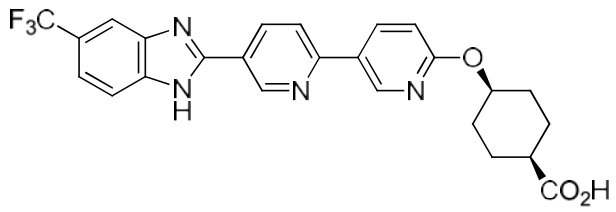
A mixture of ethyl cis-4-[(5-formyl-2,3'-bipyridin-6'-yl)oxy]cyclohexanecarboxylate (1.42 g, 4.01 mmol) and K_2CO_3 (1.11 g, 8.01 mmol) in MeOH (28 mL) and water (7 mL) was heated at 80ºC for 1.5 h under N_2. The reaction was cooled to RT and pH was ajusted to 7 by 1 N HCl (aq.). The mixture was extracted with DCM. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford cis-4-[(5-formyl-2,3'-bipyridin-6'-yl)oxy]cyclohexanecarboxylic acid (1.2 g, 92%). LCMS m/z=327.2 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 10.12 (s, 1H), 9.10 (s, 1H), 8.84 (d, 1H), 8.32 (d, 1H), 8.21 (d, 1H), 7.83 (d, 1H), 6.86 (d, 1H), 5.34 (m, 1H), 2.52 (m, 1H), 2.17 (s, 1H), 2.15-1.95 (m, 3H), 1.95-1.60 (m, 4H).

trans-4-[(5-formyl-2,3'-bipyridin-6'-yl)oxy]cyclohexanecarboxylic acid



A mixture of ethyl trans-4-[(5-formyl-2,3'-bipyridin-6'-yl)oxy]cyclohexanecarboxylate (1.25 g, 3.53 mmol) and K_2CO_3 (0.98 g, 7.05 mmol) in MeOH (25 mL) and water (6.25 mL) was heated at 80ºC for 1.5 h under N_2. The reaction was cooled to RT and pH was ajusted to 7 by 1 N HCl (aq.). The mixture was extracted with DCM. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford trans-4-[(5-formyl-2,3'-bipyridin-6'-yl)oxy]cyclohexanecarboxylic acid (0.90 g, 78%). LCMS m/z=327.2 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 10.12 (s, 1H), 9.10 (s, 1H), 8.84 (s, 1H), 8.32 (d, 1H), 8.22 (d, 1H), 7.83 (d, 1H), 6.82 (d, 1H), 5.12 (m, 1H), 2.43 (m, 1H), 2.26 (m, 2H), 2.12 (m, 2H), 1.79 (m, 2H), 1.75-1.51 (m, 2H).

cis-4-({5-[5-(trifluoromethyl)-1H-benzimidazol-2-yl]-2,3'-bipyridin-6'-yl}oxy)cyclo-hexanecarboxylic acid



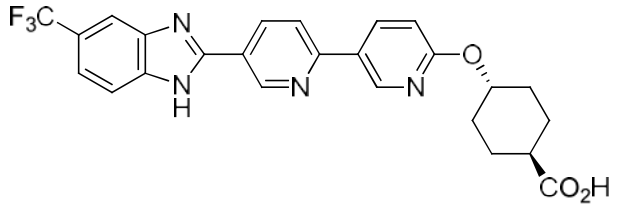
Step 1

A mixture of 4-(trifluoromethyl)benzene-1,2-diamine (100 mg, 0.568 mmol) and ethyl cis-4-[(5-formyl-2,3'-bipyridin-6'-yl)oxy]cyclohexanecarboxylate (201 mg, 0.568 mmol) in DMF (1720 µl) and water (172 µl) at RT was treated with potassium peroxymonosulfate (227 mg, 0.369 mmol). The reaction mixture stir at RT over night. The mixture was poured into $NaHCO_3$ (sat. aq.) and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The resiude was purified by silica gel chromatography (eluted with a gradient of EtOAc in hexanes from 10 to 100%) to afford ethyl cis-4-({5-[5-(trifluoromethyl)-1H-benzimidazol-2-yl]-2,3'-bipyridin-6'-yl}oxy)cyclohexanecarboxylate (0.14 g, 48%). LCMS m/z=511.3 $(M+H)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.86 (s, 1H), 8.54 (dd, 1H), 8.40 (dd, 1H), 8.05 (d, 1H), 7.95 (s, 1H), 7.78 (d, 1H), 7.57 (d, 1H), 6.92 (d, 1H), 5.28 (m, 1H), 4.14 (q, 2H), 2.41-2.58 (m, 1H), 1.85-2.10 (m, 4H), 1.70-1.84 (m, 4H), 1.26 (t, 3H).

Step 2

A mixture of ethyl cis-4-({5-[5-(trifluoromethyl)-1H-benzimidazol-2-yl]-2,3'-bipyridin-6'-yl}oxy)cyclohexanecarboxylate (70 mg, 0.141 mmol) in THF/H2O (4:1, 7.5 ml) was added LiOH (17.75 mg, 0.423 mmol) The resulting mixture was stirred at 40ºC overnight. The reaction was concentrated in vacuo. Water was added and the mixture was neutralized with TFA. The mixture was concentrated and diluted with DMSO/MeCN/H_2O (2:1:1, 8 ml) and purified by reverse phase HPLC (eluted with a gradient of 30-80% MeCN in H_2O) to afford cis-4-({5-[5-(trifluoromethyl)-1H-benzimidazol-2-yl]-2,3'-bipyridin-6'-yl}oxy)cyclo-hexanecarboxylic acid as a TFA salt (130 mg, 79%). LCMS m/z=483.2 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.50 (s, 1H), 9.04 (s, 1H), 8.66 (d, 1H), 8.55 (d, 1H), 8.28 (d, 1H), 8.09 (s, 1H), 7.92 (d, 1H), 7.66 (d, 1H), 7.03 (d, 1H), 5.34 (m, 1H), 2.58 (m, 1H), 2.49 (m, 1H), 1.65-2.05 (m, 7H).

trans-4-({5-[5-(trifluoromethyl)-1H-benzimidazol-2-yl]-2,3'-bipyridin-6'-yl}oxy) cyclohexanecarboxylic acid



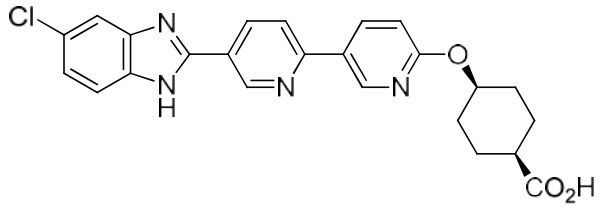
Step 1

A mixture of 2-(6-bromopyridin-3-yl)-5-(trifluoromethyl)-1H-benzimidazole (638 mg, 1.865 mmol), ethyl trans-4-{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]oxy} cyclohexanecarboxylate (700 mg, 1.865 mmol), Na_2CO_3 (395 mg, 3.73 mmol) and [1,1'-bis(diphenylphospino)ferrocence]dichloropalladium (II) (68.2 mg, 0.093 mmol) was suspended in DMF (6 ml) and water (3 ml). The mixture was degassed and heated at 80°C under N_2 overnight. The reaction was cooled to RT. Water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The resiude was purified by silica gel chromatography (eluted with a gradient of EtOAc in hexanes from 10 to 100%) to afford ethyl trans-4-({5-[5-(trifluoromethyl)-1H-benzimidazol-2-yl]-2,3'-bipyridin-6'-yl}oxy)-cyclohexanecarboxylate (688 mg, 72%). LCMS m/z=511.1 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.96 (s, 1H), 8.58 (d, 1H), 8.46 (d, 1H), 8.19 (d, 1H), 8.00 (d, 1H), 7.82 (d, 1H), 7.55 (d, 1H), 6.90 (d, 1H), 5.04 (m, 1H), 4.07 (q, 2H), 2.38 (m, 1H), 2.14 (m, 2H), 1.99 (m, 2H), 1.52 (m, 4H), 1.20 (t, 3H).

Step 2

According to Step 2 described for cis-4-({5-[5-(trifluoromethyl)-1H-benzimidazol-2-yl]-2,3'-bipyridin-6'-yl}oxy)cyclo-hexanecarboxylic acid, ethyl trans-4-({5-[5-(trifluoro-methyl)-1H-benzimidazol-2-yl]-2,3'-bipyridin-6'-yl}oxy)-cyclohexanecarboxylate (100 mg, 0.196 mmol) was converted to trans-4-({5-[5-(trifluoromethyl)-1H-benzimidazol-2-yl]-2,3'-bipyridin-6'-yl}oxy) cyclohexanecarboxylic acid as TFA salt (68 mg, 58%). LCMS m/z=483.1 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 9.43 (s, 1H), 8.97 (s, 1H), 8.59 (d, 1H), 8.46 (d, 1H), 8.20 (d, 1H), 8.00 (s, 1H), 7.83 (d, 1H), 7.58 (d, 1H), 6.90 (d, 1H), 5.03 (m, 1H), 2.29 (m, 2H), 2.13 (m, 2H), 1.98 (m, 2H), 1.50 (m, 4H).

cis-4-{[5-(5-chloro-1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclohexane-carboxylic acid



Step 1

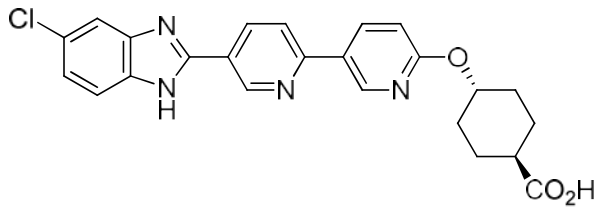
A mixture of 4-chlorobenzene-1,2-diamine (131 mg, 0.917 mmol) and ethyl cis-4-[(5-formyl-2,3'-bipyridin-6'-yl)oxy]cyclohexanecarboxylate (325 mg, 0.917 mmol) in DMF (2.8 mL) and water (0.28 mL) at RT was treated with potassium peroxymonosulfate (366 mg, 0.596 mmol). The reaction mixture stir at RT over night. The mixture was poured into $NaHCO_3$ (sat. aq.) and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The resiude was purified by silica gel chromatography (eluted with a gradient of EtOAc in hexanes from 10 to 100%) to afford ethyl cis-4-{[5-(5-chloro-1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclohexanecarboxylate (0.22 g, 50%). LCMS m/z=477.2 $(M+H)^+$. ^{1}H NMR (500 MHz, CD_3OD) δ 9.30 (s, 1H), 8.85 (s, 1H), 8.50 (dd, 1H), 8.38 (dd, 1H), 8.03 (d, 1H), 7.64 (s, 1H), 7.60 (d, 1H), 7.28 (d, 1H), 6.92 (d, 1H), 5.26 (d, 1H), 4.13 (q, 2H), 2.50 (m, 1H), 1.82-2.1 (m, 4H), 1.67-1.80 (m, 4H), 1.26 (t, 3H).

Step 2

A mixture of cis-4-{[5-(5-chloro-1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclohexanecarboxylate (220 mg, 0.461 mmol) in THF/H_2O (4:1, 4.5 ml) was added LiOH (110 mg, 4.61 mmol) The resulting mixture was stirred at 40ºC overnight. The reaction was concentrated in vacuo. Water was added and the mixture was neutralized with TFA. The mixture was concentrated and diluted with DMSO/MeCN/H_2O (2:1:1, 15 ml) and purified by reverse phase HPLC (eluted with a gradient of 30-80% MeCN in H_2O) to afford cis-4-{[5-(5-chloro-1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclohexane-carboxylic acid as a TFA salt (135 mg, 52%). LCMS m/z=449.2 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.47 (s, 1H), 9.04 (s, 1H),

8.62 (d, 1H), 8.54 (d, 1H), 8.25 (d, 1H), 7.79 (s, 1H), 7.74 (d, 1H), 7.36 (d, 1H), 7.02 (d, 1H), 5.34 (m, 1H), 2.45 (m, 1H), 1.80-2.20 (m, 8 H).

trans-4-{[5-(5-chloro-1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclohexane-carboxylic acid



Step 1

A mixture of 4-chlorobenzene-1,2-diamine (497 mg, 1.40 mmol) and ethyl trans-4-[(5-formyl-2,3'-bipyridin-6'-yl)oxy]cyclohexanecarboxylate (325 mg, 0.917 mmol) in DMF (6 mL) and water (0.6 mL) at RT was treated with potassium peroxymonosulfate (560 mg, 0.912 mmol). The reaction mixture stir at RT over night. The mixture was poured into $NaHCO_3$ (sat. aq.) and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The resiude was purified by silica gel chromatography (eluted with a gradient of EtOAc in hexanes from 10 to 100%) to afford ethyl trans-4-{[5-(5-chloro-1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclo-hexanecarboxylate (0.47 g, 70%). LCMS m/z=477.1 $(M+H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.96 (s, 1H), 8.64 (d, 1H), 8.45 (d, 1H), 8.22 (d, 1H), 7.78 (s, 1H), 7.74 (d, 1H), 7.39 (d, 1H), 6.91 (d, 1H), 5.03 (m, 1H), 4.06 (q, 2H), 2.37 (m, 1H), 2.13 (m, 2H), 1.98 (m, 2H), 1.51 (m, 4H), 1.18 (t, 3H).

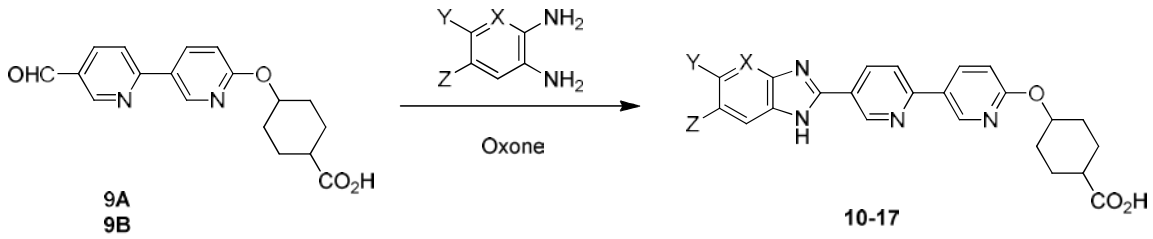
Step 2

A mixture of trans-4-{[5-(5-chloro-1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclohexanecarboxylate (70 mg, 0.147 mmol) in MeOH/THF/H_2O (2:2:1, 2.5 ml) was added LiOH (17.6 mg, 0.734 mmol) The resulting mixture was stirred at 40ºC overnight. The mixture was cooled to RT and neutralized with 1 N HCl (aq.). The mixture was concentrated and diluted with DMSO/MeCN/H_2O (2:1:1, 15 ml) and purified by reverse phase HPLC (eluted with a gradient of 30-80% MeCN in H_2O) to afford trans-4-{[5-(5-chloro-1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclo-

hexanecarboxylic acid as a TFA salt (42 mg, 51%). LCMS m/z=449.3 $(M+H)^+$. ^1H NMR (500 MHz, DMSO-d_6) δ

δ 9.40 (s, 1H), 8.99 (s, 1H), 8.56 (d, 1H), 8.46 (d, 1H), 8.18 (d, 1H), 7.72 (s, 1H), 7.66 (d, 1H), 7.28 (s, 1H), 6.92 (d, 1H), 5.04 (m, 1H), 2.30 (m, 1H), 2.15 (m, 2H), 2.00 (m, 2H), 1.50 (m, 4H).

Library synthesis of compound 10 to 17.



9A
9B

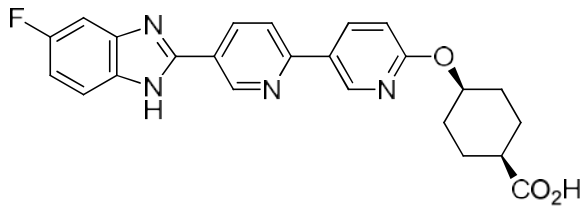
10-17

To a mixture of diamine (0.245 mmol, 1 eq) and Oxone® (0.147mmol, 0.6 eq) was added intermediate 9A or 9B (80 mg, 0.245 mmol) in 3% HOAc/DMF (3 mL). The reaction mixture was stirred at 100°C for 16 hr. LC-MS showed that the reaction was completed. The solution was neutralized with K_2CO_3. The resulting mixture was filtered and purified by preparative reverse phase HPLC (10% acetonitrile: water with 0.1% ammonium hydroxide/formic acid/TFA to 95% acetonitrile: water with 0.1% ammonium hydroxide/formic acid/TFA) to give compounds 10 to 17 as a solid.

cpd#	cis/trans	X	Y	Z	LCMS m/z $(M+H)^+$
10A	cis	CH	H	H	415.38
10B	trans	CH	H	H	415.40
11A	cis	CH	F	H	433.36
11B	trans	CH	F	H	433.42
12A	cis	CH	F	F	451.35
12B	trans	CH	F	F	451.30
13A	cis	CH	-CN	H	440.35
13B	trans	CH	-CN	H	440.34
14A	cis	CH	$-OCF_3$	H	499.37
15A	cis	CH	$-SO_2Me$	H	493.35

15B	trans	CH	-SO_2Me	H	493.34
16A	cis	N	Me	H	430.39
16B	trans	N	Me	H	430.38
17A	cis	N	-OMe	H	446.39
17B	trans	N	-OMe	H	446.37

cis-4-{[5-(5-fluoro-1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclohexane-carboxylic acid



Step 1

1,2-Diamino-4-fluorobenzene (5 g, 39.6 mmol) and 6-bromonicotinaldehyde (7.37 g, 39.6 mmol) were dissolved in DMF (100 ml) adn then water (10 ml) was added. Oxone® (15.84 g, 25.8 mmol) was then added in portions over 60 min. The resulting mixture was stirred overnight under N_2. The reaction was treated with ice and water (100 mL) then $NaHCO_3$ (sat. aq. ~400 mL). The mixture was stirred at RT for 3h. The solid was collected by filtration. The mother liquor discarded. The solid was washed with water and triturated with (Hex/EtOAc=1:1, 20 mL) and dried. This resulted in 2-(6-bromopyridin-3-yl)-5-fluoro-1H-benzo[d]imidazole as a brownish solid (10.5 g, 91%). LCMS m/z=294.1 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.36 (d, 1H), 7.82 (d, 1H), 7.60 (m, 1H), 7.40 (d, 1H), 7.08 (t, 1H).

Step 2

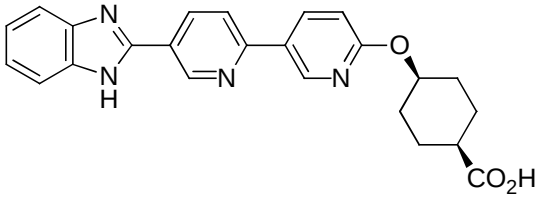
A mixture of 2-(6-bromopyridin-3-yl)-5-fluoro-1H-benzimidazole (389 mg, 1.332 mmol), ethyl cis-4-{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]oxy} cyclo-hexanecarboxylate (500 mg, 1.332 mmol), sodium carbonate (282 mg, 2.66 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (48.7 mg, 0.067 mmol) in DMF (8 mL) / H_2O (4 mL) in a round bottle was degassed and then heated at 80°C under N_2 over night. The reaction was cooled to RT. The mixture was diluted with water and

extracted with EtOAc (3x). The combined organic layers were dried (Na_2SO_4) and concentrated to give the crude product, which was purified by silica gel chromatography (eluted with a gradient of EtOAc/Hexane 0-100%) to afford ethyl cis-4-{[5-(5-fluoro-1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclohexanecarboxylate (270 mg, 44%). LCMS m/z=461.3 $(M+H)^+$. ^1H NMR (500 MHz, CD_3OD) δ 9.21 (s, 1H), 8.76 (s, 1H), 8.41 (d, 1H), 8.29 (d, 1H), 7.93 (d, 1H), 7.56 (m, 1H), 7.29 (d, 1H), 7.03 (dd, 1H), 6.87 (d, 1H), 5.21 (s, 1H), 4.14 (q, 2H), 2.45 (m, 1), 1.75-2.05 (m, 8H) , 1.26 (t, 3H).

Step 3

A mixture of ethyl cis-4-{[5-(5-fluoro-1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclohexanecarboxylate (150 mg, 0.326 mmol) in THF/H_2O (4:1, 3 ml) was added LiOH (46.8 mg, 1.95 mmol) The resulting mixture was stirred at 40ºC overnight. The reaction was concentrated in vacuo. Water was added and the mixture was neutralized with TFA. The mixture was concentrated and diluted with DMSO/MeCN/H_2O (2:1:1, 15 ml) and purified by reverse phase HPLC (eluted with a gradient of 20-80% MeCN in H_2O) to afford cis-4-{[5-(5-fluoro-1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclohexane-carboxylic acid as a TFA salt (100 mg, 56%). LCMS m/z=433.3 $(M+H)^+$. Accurate Mass $C_{24}H_{22}N_4O_3$ [M+H] measured 433.1677, calculated 433.1670. ^1H NMR (500 MHz, DMSO-d_6) δ 9.47 (s, 1H), 9.03 (s, 1H), 8.62 (d, 1H), 8.54 (d, 1H), 8.26 (d, 1H), 7.74 (d, 1H), 7.55 (d, 1H), 7.21 (dd, 1H), 7.03 (d,1H), 5.34 (s, 1H), 2.61 (m, 1H), 1.60-2.00 (m, 8H).

cis-4-{[5-(1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclohexanecarboxylic acid



Step 1

A mixture of benzene-1,2-diamine (824 mg, 7.62 mmol) and ethyl cis-4-[(5-formyl-2,3'-bipyridin-6'-yl)oxy]cyclohexanecarboxylate (2.7 g, 7.62 mmol) in DMF (23 mL) and

water (2.3 mL) at RT was treated with potassium peroxymonosulfate (3.04 g, 4.95 mmol) in portions. The reaction mixture stir at RT over night. The mixture was poured into $NaHCO_3$ (sat. aq.) and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The resiude was purified by silica gel chromatography (eluted with a gradient of EtOAc in hexanes from 10 to 100%) to afford ethyl cis-4-{[5-(1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclohexane-carboxylate (1.63 g, 48%). LCMS m/z=443.3 $(M+H)^+$. ^1H NMR (500 MHz, CD_3OD) δ 9.31 (s, 1H), 8.73 (d, 1H), 8.45 (dd, 1H), 8.20 (dd, 1H), 7.96 (d, 1H), 7.55 (d, 2H), 7.25 (d, 2H), 6.78 (dd, 1H), 5.28 (s, 1H), 4.15 (q, 2H), 2.42 (m, 1H), 2.00-1.85 (m, 4H), 1.78-1.70 (m, 4H), 1.26 (t, 3H).

Step 2

Ethyl cis-4-{[5-(1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclohexane-carboxylate (1.0 g, 2.2.6 mmol) was dissolved in EtOH/THF (1:3, 20 mL) and added LiOH (190 mg, 4.52 mmol) and water (2 mL). The mixture was heated at 60ºC for 3 h and then cooled to RT and aged vernight. The mixture was concentrated to remove the volatiles. The remainder was made acidc by the dropwise addition of HCl (aq. 1 M). Precipitate formed. The mixture was filtered and the solid dried under vacuum/N_2 sweep to give the cis-4-{[5-(1H-benzimidazol-2-yl)-2,3'-bipyridin-6'-yl]oxy}cyclohexanecarboxylic acid (0.90 g, 96%) as a solid. LCMS m/z=415.3 $(M+H)^+$. Accurate Mass $C_{24}H_{22}N_4O_3$ [M+H] measured 415.1765, calculated 415.1770. ^1H NMR (500 MHz, DMSO-d_6) δ 9.50 (s, 1H), 9.05 (s, 1H), 8.67 (dd, 1H), 8.55 (dd, 1H), 8.29 (d, 1H), 7.79 (dd, 2H), 7.41 (dd, 2H), 7.04 (d, 1H), 5.34 (s, 1H), 2.51 (m, 1H), 1.65-2.00 (m, 8H).