SUPPORTING INFORMATION

Repurposing human PDE4 inhibitors for neglected tropical diseases: Design, synthesis and evaluation of cilomilast analogues as *Trypanosoma brucei* PDEB1 inhibitors.

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Analytical Chemistry

Preparative HPLC. Preparative HPLC purification was performed using a FractionLynx system (Waters, Inc) consisting of a Waters 2525 binary pump, Waters 2767 sample manager, Waters 2489 UV/Visible detector, Waters 2x515 pumps, Waters pump control, Waters column fluidics organizer, MicroMass ZQ mass detector using electrospray ionization. Compound detection and mass-directed collection utilized UV: λ=254 nm and ESI+ mode. The Columns utilized were Waters SymmetryC8 30x50mm, 5µm or Waters Xbridge OBD RP18 30x50mm, 5µm, running A:B =H_2O/acetonitrile gradients (0.1% v/v formic acid). Compounds were analyzed using HPLC-MS, Waters e2795 Alliance HPLC separation module, Waters 2489 UV/visible detector, Waters LCT premiertime-of-flight mass spectrometer (electrospray ionization). Columns used were Waters SunFire C18 4.6x50mm, 3.5 µm or Waters SunFire C8 4.6x50mm, 3.5 µm; running A:B = H_2O/acetonitrile gradients (0.1% v/v formic acid). The purest fractions obtained were pooled and evaporated to provide the desired products in the yields stated below; impure factions were not repurified.

Typical Preparative HPLC method (start gradient may vary based on compound).

Time (m)	Flow rate	A%	B%
0	40 ml/m	95%	5%
7.50	40 ml/m	0%	100%
7.90	40 ml/m	0%	100%
7.91	40 ml/m	95%	5%
8.00	40 ml/m	95%	5%

Compound analysis. Compounds were analyzed using HPLC-MS, Waters e2795 Alliance HPLC separation module, Waters 2489 UV/visible detector, and Waters LCT premier time of flight mass spectrometer using electrospray ionization. Columns used were Waters SunFire C18 4.6x50mm, 3.5µm or Waters SunFire C8 4.6x50mm, 3.5µm; running A:B = H_2O/acetonitrile gradients (0.1% v/v formic acid).

Typical analytical HPLC method (start gradient may vary based on compound).

Time (m)	Flow rate	A%	B%
0	2 ml/m	95%	5%
3.75	2 ml/m	0%	100%
3.85	2 ml/m	0%	100%
3.95	2 ml/m	95%	5%
4.00	2 ml/m	95%	5%

Chemical Synthesis

All starting materials were obtained commercially from Aldrich, Inc, or Fisher Scientific and were used without further purification. Reaction solvents were purified by passage through alumina columns on a purification system manufactured by Innovative Technology (Newburyport, MA). NMR spectra were obtained on Varian NMR systems, operating at 400 MHz or 500 MHz for ^{1}H acquisitions.

General procedure for the ester hydrolysis (Procedure A). A solution of lithium hydroxide (0.144 mmol) in water (0.5 mL) was added to a solution of the appropriate ester (0.072 mmol) in THF (0.5 mL). The mixture was homogenized with methanol (0.5 mL) and stirred at room temperature for 2 hours. The solvent was evaporated to dryness and the residue was dissolved in water. The pH was adjusted to be acidic with 1N HCl, and the desired product was extracted with EtOAc. The combined organic phases were washed with brine, dried with anhydrous Na_2SO_4 and the solvent removed *in vacuo*. The crude was solubilized in 1 mL DMSO and filtered through 17 mm cellulose syringe filter (0.45 µm). The crude product was purified via preparative HPLC to give the desired product.

General procedure for compounds 10a, 10b and 10c (Procedure B). A mixture of methyl *cis*-4-cyano-4-(3-hydroxy-4-methoxyphenyl)cyclohexanecarboxylate **9** (0.086 mmol), appropriate (bromomethyl)pyridinium bromide (0.130 mmol) and K_2CO_3 (0.259 mmol) in DMF (2 mL) was heated to 60 °C for 4 hours. After the reaction was complete, the solvent was removed *in vacuo* and the crude was dissolved in DCM and washed with brine (1x10 mL). The solvent was dried over anhydrous Na_2SO_4, and was concentrated *in vacuo*. The alkylated ester intermediate was dissolved in THF (0.5 mL) and water (0.5 mL) containing lithium hydroxide (0.117 mmol) and homogenized with MeOH (0.5 mL) and stirred at room temperature for 1 hour. The mixture was dried under vacuum, solubilized in 1 mL DMSO and filtered through 17 mm cellulose syringe

filter (0.45 µm). The crude product was purified via preparative HPLC to provide the desired product.

General procedure for compounds 12b, 12e, 12f, 12g and 12h (Procedure C). A mixture of methyl *cis*-4-(3-(4-bromobutoxy)-4-methoxyphenyl)-4-cyanocyclohexanecarboxylate **11b** (0.059mmol), an appropriate phenol (0.088mmol) and K_2CO_3 (0.118mmol) in DMF (2 mL) was heated to 60 °C for 4 hours. After the reaction was complete, the solvent was evaporated on the Genevac and the crude residue was dissolved in DCM (2 mL), and washed with brine (1x1 mL). The organic layer was filtered through pre-packed Na_2SO_4 column. The filtrate was evaporated. The intermediate ester was then dissolved in THF (0.5 mL) and water (0.5 mL) containing lithium hydroxide (0.117 mmol), homogenized with MeOH (0.5 mL) and stirred at room temperature for 1 hour. The solvent was evaporated, and the residue was solubilized in 1 mL DMSO and filtered through 17 mm cellulose syringe filter (0.45 µm). The crude product was purified via preparative HPLC to give the desired product.

General procedure for compounds 12c, and 12d (Procedure D). A mixture of methyl *cis*-4-cyano-4-(3-hydroxy-4-methoxyphenyl)cyclohexanecarboxylate **9** (0.069 mmol), 1,3-dibromopropane or 1,5-dibromopentane (0.076 mmol) and K_2CO_3 (0.138 mmol) in DMF (1 mL) was heated to 70 °C for 4 hours in a sealed vial. After the reaction was complete, phenol (0.076 mmol) was added and the reaction was stirred for another 4 hours. The solvent was evaporated and the crude material was dissolved in DCM (2 mL) and washed with brine (1x1 mL). The organic layer was filtered through pre-packed Na_2SO_4 column and the filtrate was evaporated. The intermediate ester was dissolved in THF (0.5 mL) and water (0.5 mL) containing lithium hydroxide (0.117 mmol), homogenized with MeOH (0.5 mL) and stirred at room temperature for 1 hours. The solvents were removed, and the residue was solubilized in 1 mL DMSO and filtered through 17 mm cellulose syringe filter (0.45 µm). The crude product was purified via preparative HPLC to give the desired product.

General procedure for benzyl cyanide preparation (Procedure E). To a solution of the appropriate benzaldehyde (29.7 mmol) in MeCN (30 mL) was added LiBr (56.6mmol) followed by the dropwise addition of TMSCl (44.8mmol). After 15 min, the reaction mixture was cooled to 0 °C, 1,1,3,3-tetramethyldisiloxane (49.4 mmol) was added dropwise, and the resulting mixture was allowed to warm to room temperature. After 3 hours of stirring, the mixture was separated into two layers. The lower layer was removed, was diluted with EtOAc, and was filtered through Celite. The filtrate was concentrated under reduced pressure, dissolved in EtOAc and refiltered. The solvent was removed *in vacuo* to provide the crude benzyl bromide intermediate, which was carried forward without further purification. To a solution of this benzyl bromide in DMF (20 mL) under N_2 atmosphere was added NaCN (67.2mmol) and the resulting mixture was stirred at room temperature overnight, then was filtered through filter paper, the filtrate was evaporated to dryness, the residue was dissolved in EtOAc and washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the residue was purified by flash chromatography.

***cis*-4-Cyano-4-[3-(benzyloxy)-4-methoxyphenyl]-cyclohexane-1-carboxylic Acid (7) (NEU-685)** (Yield: 12%) **(Procedure A**, synthesized from **5b**). ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.45 (d, J = 7.30 Hz, 2H), 7.35 - 7.40 (m, 2H), 7.29 - 7.34 (m, 1H), 7.00 - 7.03 (m, 2H), 6.89 (d, J = 8.80 Hz, 1H), 5.16 (s, 2H), 3.89 (s, 3H), 2.38 (tt, J = 3.40, 12.20 Hz, 1H), 2.20 (br. d, J = 10.70 Hz, 4H), 1.96 - 2.07 (m, 2H), 1.72 (td, J = 4.40, 14.20 Hz, 2H). LCMS found 366.2, $[M + H]^+$.

trans-4-Cyano-4-[3-(benzyloxy)-4-methoxyphenyl]-cyclohexane-1-carboxylic Acid (8b) (NEU-686) (Yield: 13%) **(Procedure A,** from **6b**). ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.42 - 7.46 (m, 2H), 7.34 - 7.38 (m, 2H), 7.27 - 7.32 (m, 1H), 6.97 - 7.01 (m, 2H), 6.86 (d, J = 8.30 Hz, 1H), 5.15 (s, 2H), 3.88 (s, 3H), 2.82 - 2.87 (m, 1H), 2.23 (dd, J = 2.20, 14.40 Hz, 2H), 1.91 - 2.11 (m, 6H). LCMS found 366.2, $[M + H]^+$.

methyl *cis*-4-cyano-4-(3-hydroxy-4-methoxyphenyl)cyclohexanecarboxylate (9) (Yield: 94%). A solution of methyl *cis*-4-(3-(benzyloxy)-4-methoxyphenyl)-4-cyanocyclohexanecarboxylate **5b** (350 mg, 0.922 mmol) in MeOH (5 mL) was charged with 5% Pd/C (39.3 mg, 0.369 mmol) and vigorously shaken under H_2 atmosphere at room temperature. After reaction was complete, the catalyst was removed by filtration and the filtrate was concentrated. The crude residue was purified by flash chromatography running a gradient from 0 to 40% EtOAc in hexane. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 6.94 (d, J = 2.40 Hz, 1H), 6.91 (dd, J = 2.40, 8.30 Hz, 1H), 6.78 (d, J = 8.30 Hz, 1H), 3.81 (s, 3H), 3.64 (s, 3H), 2.28 (tt, J = 3.90, 12.70 Hz, 1H), 2.05 - 2.16 (m, 4H), 1.91 (dq, J = 2.70, 12.50 Hz, 2H), 1.69 (dt, J = 3.40, 13.20 Hz, 2H). LCMS found 289.6, $[M + H]^+$.

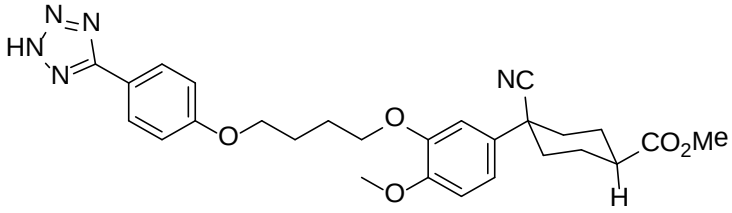
***cis*-4-cyano-4-(4-methoxy-3-(pyridin-2-ylmethoxy)phenyl)cyclohexanecarboxylic acid, formic acid salt (10a) (NEU-732)** (Yield: 15%) **(Procedure B)**. ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 8.56 (dd, J = 1.00, 4.90 Hz, 1H), 8.30 (s, 1H), 7.84 (dt, J = 1.95, 7.80 Hz, 1H), 7.54 (d, J = 7.80 Hz, 1H), 7.34 (dd, J = 4.90, 7.80 Hz, 1H), 7.19 (d, J = 2.40 Hz, 1H), 7.04 - 7.07 (m, 1H), 6.99 - 7.03 (m, 1H), 5.17 (s, 2H), 3.78 (s, 3H), 2.35 (tt, J = 3.40, 12.20 Hz, 1H), 1.99 - 2.10 (m, 4H), 1.88 (dt, J = 2.90, 13.60 Hz, 2H), 1.61 - 1.71 (m, 2H). LCMS found 367.0, $[M + H]^+$.

***cis*-4-cyano-4-(4-methoxy-3-(pyridin-3-ylmethoxy)phenyl) cyclohexanecarboxylic acid**, **formic acid salt (10b) (NEU-728)** (Yield: 54%) **(Procedure B)**. ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 8.66 (d, J = 1.95 Hz, 1H), 8.54 (dd, J = 1.95, 4.60 Hz, 1H), 8.40 (s, 1H), 7.86 (td, J = 1.95, 7.80 Hz, 1H), 7.42 (dd, J = 4.60, 7.80 Hz, 1H), 7.20 (d, J = 1.95 Hz, 1H), 7.07 (dd, J = 1.95, 8.30 Hz, 1H), 7.00 (d, J = 8.30 Hz, 1H), 5.14 (s, 2H), 3.75 (s, 3H), 2.31 (tt, J = 3.40, 12.20 Hz, 1H), 2.07 - 2.12 (m, 2H), 2.00 - 2.05 (m, 2H), 1.88 (dt, J = 2.90, 13.50 Hz, 2H), 1.62 - 1.72 (m, 2H). LCMS found 367.0, $[M + H]^+$.

***cis*-4-cyano-4-(4-methoxy-3-(pyridin-4-ylmethoxy)phenyl) cyclohexanecarboxylic acid, formic acid salt (10c) (NEU-729)** (Yield: 20%) **(Procedure B)**. ^{1}H NMR (500 MHz, DMSO-d6)

δ ppm 8.56 - 8.58 (m, 2H), 8.29 (s, 1H), 7.44 (br. d, J = 5.90 Hz, 2H), 7.16 (d, J = 1.95 Hz, 1H), 7.07 (dd, J = 2.40, 8.30 Hz, 1H), 7.02 (d, J = 8.30 Hz, 1H), 5.18 (s, 2H), 3.78 (s, 3H), 2.34 (tt, J = 3.40, 12.20 Hz, 1H), 2.07 - 2.11 (m, 2H), 2.02 (dd, J = 3.30, 13.60 Hz, 2H), 1.87 (dt, J = 2.90, 13.60 Hz, 2H), 1.66 (dq, J = 2.90, 12.20 Hz, 2H). LCMS found 367.0, $[M + H]^+$.

Methyl *cis*-4-(3-(4-bromobutoxy)-4-methoxyphenyl)-4-cyanocyclohexanecarboxylate (11b) (Yield: 70%). A mixture of methyl *cis*-4-cyano-4-(3-hydroxy-4-methoxyphenyl)cyclohexanecarboxylate **9** (100 mg, 0.346 mmol), 1,4-dibromobutane (0.132 mL, 1.106 mmol) and K_2CO_3 (86 mg, 0.622 mmol) in DMF (3.5 mL) was heated to 60 °C for 4 hours. The crude was filtered through Celite and the solvent was evaporated to dryness. The residue was then dissolved in EtOAc (50 mL) and the solution washed with a saturated solution of $NaHCO_3$ (2x30 mL) and brine (1x20 mL). The solvent was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the residue was purified by flash chromatography, eluting with 0-50% EtOAc in Hexane. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 6.97 - 7.00 (m, 2H), 6.84 - 6.87 (m, 1H), 4.06 (t, J = 6.10 Hz, 2H), 3.85 (s, 3H), 3.70 (s, 3H), 3.50 (t, J = 6.10 Hz, 2H), 2.36 (tt, J = 3.90, 12.70 Hz, 1H), 2.24 (dd, J = 1.50, 12.70 Hz, 2H), 2.17 (dd, J = 3.40, 14.40 Hz, 2H), 2.02 - 2.11 (m, 2H), 1.94 - 2.02 (m, 4H), 1.77 (dt, J = 3.40, 13.40 Hz, 2H). LCMS found 424.0, $[M + H]^+$.



Methyl cis-4-(3-(4-(4-(2H-tetrazol-5-yl)phenoxy)butoxy)-4-methoxyphenyl)-4-cyanocyclohexane-1-carboxylate (**Ester precursor to 12a**) (Yield: 52%). A mixture of methyl cis-methyl 4-(3-(4-bromobutoxy)-4-methoxyphenyl)-4-cyanocyclohexanecarboxylate **(11b)** (25

mg, 0.059 mmol), 4-(2H-tetrazol-5-yl)phenol (11.46 mg, 0.071 mmol) and potassium carbonate (9.77 mg, 0.071 mmol) in DMF (2 mL) was heated to 60 °C for 4 hours. After reaction was complete, solvent was evaporated under vacuum, the crude was dissolved in DCM (2 mL) and washed with brine (1x1 mL). The solvent was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the residue was purified by flash chromatography, eluting with 0-80% EtOAc in Hexane. 1H NMR (500 MHz, DMSO-d6) δ ppm 9.98 (br. s., 1H), 7.84 - 7.87 (m, 2H), 6.99 - 7.05 (m, 2H), 6.94 - 6.97 (m, 1H), 6.87 - 6.91 (m, 2H), 4.77 (t, J = 7.10 Hz, 2H), 4.01 (t, J = 6.40 Hz, 2H), 3.73 (s, 3H), 3.62 (s, 3H), 2.06 - 2.14 (m, 4H), 2.02 (dd, J = 3.40, 14.10 Hz, 2H), 1.89 (dt, J = 3.40, 13.40 Hz, 2H), 1.63 - 1.78 (m, 4H). LCMS found 506.1, $[M + H]^+$.

***cis*-4-(3-(4-(4-(2H-tetrazol-5-yl)phenoxy)butoxy)-4-methoxyphenyl)-4-cyanocyclohexanecarboxylic acid (12a) (NEU-750)** (Yield: 38%) **(Procedure A)**. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.95 - 8.00 (m, 2H), 7.00 (dd, J = 2.20, 8.30 Hz, 1H), 6.93 - 6.97 (m, 3H), 6.85 (d, J = 8.30 Hz, 1H), 4.73 (t, J = 6.60 Hz, 2H), 4.07 (t, J = 6.60 Hz, 2H), 3.84 (s, 3H), 2.38 (tt, J = 3.40, 12.20 Hz, 1H), 2.28 (quin, J = 6.80 Hz, 2H), 2.15 - 2.24 (m, 4H), 1.99 (dq, J = 3.40, 14.20 Hz, 2H), 1.91 (quin, J = 6.80 Hz, 2H), 1.76 (dt, J = 3.40, 14.20 Hz, 2H). LCMS found 492.0, $[M + H]^+$.

***cis*-4-cyano-4-(4-methoxy-3-(4-phenoxybutoxy)phenyl)cyclohexanecarboxylic acid (12b) (NEU-730)** (Yield: 16%) (**Procedure C**). ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 7.24 - 7.28 (m, 2H), 7.06 (d, J = 1.95 Hz, 1H), 7.02 (dd, J = 1.95, 8.30 Hz, 1H), 6.95 - 6.99 (m, 2H), 6.88 - 6.93 (m, 2H), 4.00 - 4.06 (m, 4H), 3.74 (s, 3H), 2.36 (tt, J = 3.40, 12.20 Hz, 1H), 2.10 (d, J = 13.40 Hz, 2H), 2.02 (dd, J = 2.90, 14.20 Hz, 2H), 1.84 - 1.93 (m, 6H), 1.68 (dq, J = 2.90, 13.40 Hz, 2H). LCMS found 424.2, $[M + H]^+$.

***cis*-4-cyano-4-(4-methoxy-3-(3-phenoxypropoxy)phenyl) cyclohexanecarboxylic acid (12c) (NEU-798)** (Yield: 5%) **(Procedure D)**. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.26 - 7.30 (m, 2H), 7.00 - 7.03 (m, 2H), 6.91 - 6.96 (m, 3H), 6.86 (d, J = 8.30 Hz, 1H), 4.26 (t, J = 6.10

Hz, 2H), 4.18 (t, J = 6.10 Hz, 2H), 3.85 (s, 3H), 2.29 - 2.40 (m, 3H), 2.16 - 2.26 (m, 4H), 2.01 (dq, J = 3.40, 14.20 Hz, 2H), 1.76 (dt, J = 3.42, 13.70 Hz, 2H). LCMS found 410.4, $[M + H]^+$.

***cis*-4-cyano-4-(4-methoxy-3-(5-phenoxypentyloxy)phenyl) cyclohexanecarboxylic acid (12d) (NEU-799)** (Yield: 14%) **(Procedure D)**. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.25 - 7.29 (m, 2H), 6.97 - 7.00 (m, 2H), 6.93 (t, J = 7.30 Hz, 1H), 6.85 - 6.91 (m, 3H), 4.06 (t, J = 6.60 Hz, 2H), 3.99 (t, J = 6.60 Hz, 2H), 3.86 (s, 3H), 2.38 (tt, J = 3.40, 12.20 Hz, 1H), 2.18 - 2.30 (m, 4H), 2.04 (dq, J = 2.90, 14.20 Hz, 2H), 1.90 - 1.97 (m, 2H), 1.84 - 1.90 (m, 2H), 1.79 (dt, J = 3.40, 13.40 Hz, 2H), 1.63 - 1.71 (m, 2H). LCMS found 438.4, $[M + H]^+$.

***cis*-4-cyano-4-(3-(4-(4-cyanophenoxy)butoxy)-4-methoxyphenyl)cyclohexanecarboxylic acid (12e) (NEU-731)** (Yield: 19%) **(Procedure C)**. ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 7.73 - 7.76 (m, 2H), 7.07 - 7.11 (m, 2H), 7.05 (d, J = 1.95 Hz, 1H), 7.02 (dd, J = 1.95, 8.30 Hz, 1H), 6.96 (d, J = 8.30 Hz, 1H), 4.14 (t, J = 5.90 Hz, 2H), 4.04 (t, J = 5.90 Hz, 2H), 3.73 (s, 3H), 2.35 (tt, J = 3.40, 12.20 Hz, 1H), 2.09 (d, J = 13.40 Hz, 2H), 2.02 (dd, J = 2.90, 14.20 Hz, 2H), 1.82 - 1.93 (m, 6H), 1.67 (dq, J = 2.90, 13.40 Hz, 2H). LCMS found 449.0, $[M + H]^+$.

***cis*-4-cyano-4-(4-methoxy-3-(4-(4-methoxyphenoxy)butoxy)phenyl)cyclohexanecarboxylic acid (12f) (NEU-796)** (Yield: 5%) **(Procedure C)**. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 6.98 - 7.01 (m, 2H), 6.85 - 6.88 (m, 2H), 6.82 - 6.84 (m, 3H), 4.12 (t, J = 6.35 Hz, 2H), 4.00 (t, J = 6.30 Hz, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 2.39 (tt, J = 3.40, 12.70 Hz, 1H), 2.17 - 2.29 (m, 4H), 1.93 - 2.08 (m, 6H), 1.79 (dt, J = 3.40, 13.40 Hz, 2H). LCMS found 453.4, $[M + H]^+$.

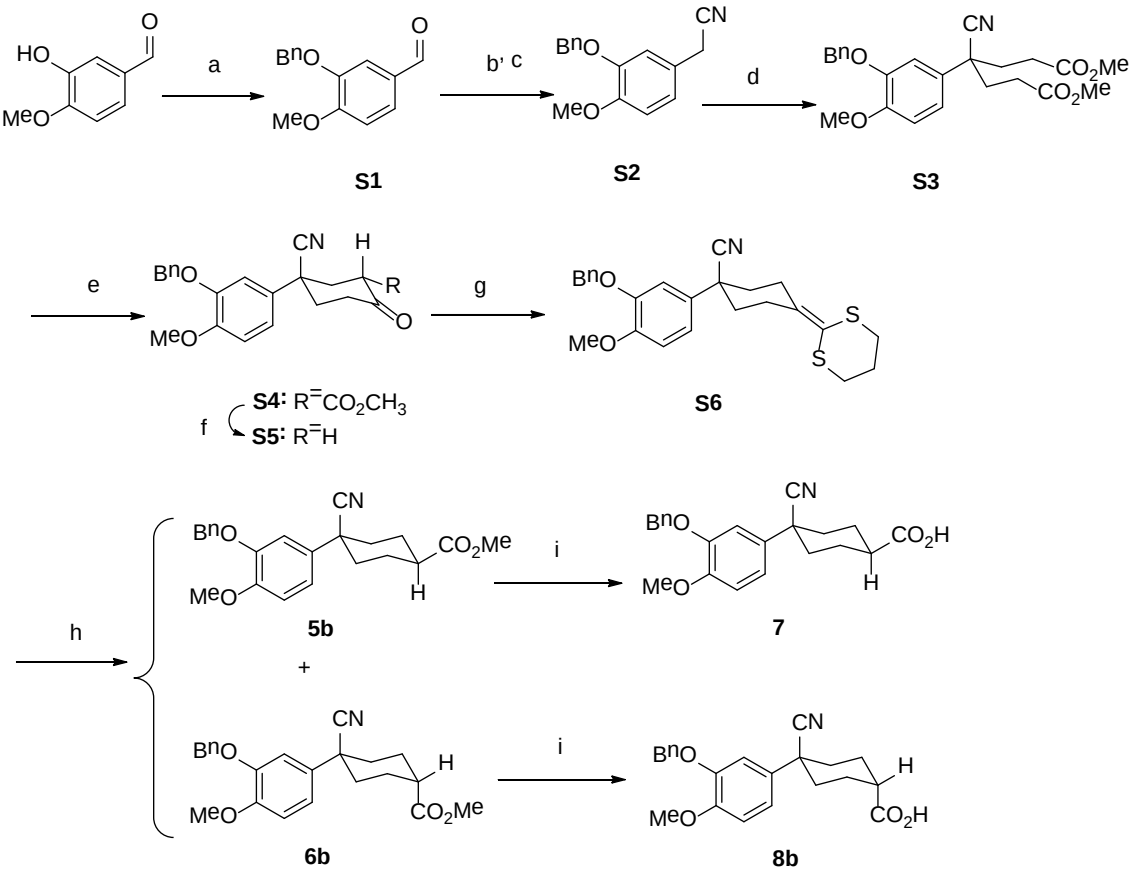
***cis*-4-cyano-4-(4-methoxy-3-(4-(p-tolyloxy)butoxy)phenyl)cyclohexanecarboxylic acid (12g) (NEU-797)** (Yield: 5%) **(Procedure C)**. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.07 (d, J = 8.30 Hz, 2H), 6.99 - 7.01 (m, 2H), 6.85 - 6.88 (m, 1H), 6.78 - 6.81 (m, 2H), 4.12 (t, J = 6.30 Hz, 2H), 4.02 (t, J = 6.30 Hz, 2H), 3.84 - 3.87 (m, 3H), 2.38 (tt, J = 3.40, 12.20 Hz, 1H), 2.28 (s, 3H), 2.18 - 2.27 (m, 4H), 1.94 - 2.08 (m, 6H), 1.79 (dt, J = 3.40, 13.40 Hz, 2H). LCMS found 438.4, $[M + H]^+$.

***Cis*-4-cyano-4-(3-(4-(4-fluorophenoxy)butoxy)-4-methoxyphenyl)cyclohexanecarboxylic acid (12h) (NEU-916)** (Yield: 5%) **(Procedure C)**. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 6.93 - 7.02 (m, 4H), 6.81 - 6.89 (m, 3H), 4.12 (t, J = 6.10 Hz, 2H), 4.02 (t, J = 6.10 Hz, 2H), 3.86 (s, 3H), 2.41 (tt, J = 3.90, 12.20 Hz, 1H), 2.19 - 2.30 (m, 4H), 1.94 - 2.09 (m, 6H), 1.81 (dt, J = 3.40, 13.40 Hz, 2H). LCMS found 441.4, $[M + H]^+$.

Methyl4-cyano-4-(4-methoxy-3-(4-phenoxybutoxy)phenyl)cyclohexanecarboxylate (**13**) (NEU-1050) (Yield: 30%). A mixture of methyl *cis*-4-(3-(4-bromobutoxy)-4-methoxyphenyl)-4-cyanocyclohexanecarboxylate **11b** (0.17mmol), phenol, (0.25mmol) and K_2CO_3 (0.50 mmol) in DMF (2 mL) was heated to 60 °C for 4 hours. After the reaction was complete, the reaction was partitioned between EtOAc and water. The water layer was extracted 3x EtOAc. The combined organic layers were washed 2x 0.1 M NaOH, 2x H_2O, 1x brine, dried over Na_2SO_4, filtered and evaporated. The resulting residue was subjected to silica gel chromatography (20-50% EtOAc/Hexanes). ^{1}H NMR (500 MHz, chloroform-*d*) δ ppm: 6.98-7.02 (m, 2H), 6.94 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 7.8 Hz, 2H), 6.87 (d, J = 9.3 Hz, 1H), 4.13 (t, J = 6.1 Hz, 2H), 4.07 (t, J = 6.1 Hz, 2H), 3.86 (s, 3H), 3.73 (s, 3H), 2.36 (tt, J = 12.3, 3.5 Hz, 1H), 2.26 (d, J = 13.7 Hz, 2H), 2.18 (dd, J = 14.4, 3.7 Hz, 2H), 1.96-2.10 (m, 6H), 1.78 (td, J = 13.6, 3.7 Hz, 2H). LCMS found 438.2 $[M + H]^+$.

The preparation of benzyl-substituted analogs **5b, 6b, 7, 8b** was analogous to that of the corresponding cyclopentyl ether analogs above.

Scheme S1. Synthesis of benzyl-substituted analogs **5b, 6b, 7,** and **8b.**



Reagents and conditions: (a) Benzyl bromide, K_2CO_3, DMF, 60 °C, overnight; (b) TMSCl, 1,1,3,3-tetramethyldisiloxane, LiBr, CH_3CN, rt, overnight; (c) NaCN, MeCN, rt, overnight; (d) Methyl acrylate, MeCN, MW, reflux, 5 h; (e) NaH, DME, reflux, 1 h; (f) NaCl, DMF, H_2O, 150 °C, overnight; (g) nBuLi, 2-(Trimethylsilyl)-1,3-dithiane, THF, -78 °C; (h) $HgCl_2$, $HClO_4$, MeOH, reflux, 2 h; (i) LiOH, H_2O, MeOH, THF, rt, 2 h.

3-(benzyloxy)-4-methoxybenzaldehyde (**S1**) (Yield: 95%). In a DMF (40 mL) suspension of 3-hydroxy-4-methoxybenzaldehyde (5 g, 32.9 mmol) and potassium carbonate (9.08 g, 65.7 mmol), benzyl bromide (4.58 ml, 42.7 mmol) was added and the reaction was stirred for 12 hours at 60 °C.The solvent was evaporated to dryness and the residue was dissolved in DCM (100 mL), filtered through Celite and washed with NaOH 10 N solution (3x30 mL) and brine (1x30 mL). The organic phase was dried with anhydrous Na_2SO_4, concentrated and the crude product was purified via silica gel chromatography, eluting with 0-50% EtOAc in Hexane. ^{1}H NMR (500 MHz, CHLOROFORM-d) δ 9.82 (s, 1H), 7.44 - 7.49 (m, 4H), 7.36 - 7.41 (m, 2H), 7.30 - 7.35 (m, 1H), 7.00 (d, J = 7.81 Hz, 1H), 5.20 (s, 2H), 3.97 (s, 3H). LCMS found 243.0, $[M + H]^+$.

2-(3-(benzyloxy)-4-methoxyphenyl)acetonitrile (S2) (Yield: 98%) **(Procedure E)**. The crude product was purified via silica gel chromatography, eluting with 0-25% EtOAc in Hexane.^{1}H NMR (500 MHz, chloroform-d) δppm 7.45 (br. d, J = 7.30 Hz, 2H), 7.36 - 7.40 (m, 2H), 7.29 - 7.34 (m, 1H), 6.83 - 6.88 (m, 3H), 5.15 (s, 2H), 3.89 (s, 3H), 3.64 (s, 2H). LCMS found 254.1, $[M + H]^+$.

dimethyl 4-(3-(benzyloxy)-4-methoxyphenyl)-4-cyanoheptanedioate (S3) (Yield: 56%). To a solution of 2-(3-(benzyloxy)-4-methoxyphenyl)acetonitrile **(S2)** (7.4 g, 29.2 mmol) in MeCN (200 ml) under an N_2 atmosphere was added Triton B (1.32 ml, 2.92 mmol) 40% solution in MeOH, and the mixture was refluxed. Methyl acrylate (26.5 ml, 292 mmol) was then added carefully, and the reaction mixture was maintained at reflux for 5 hours and then was cooled to room temperature. The mixture was concentrated under reduced pressure, dissolved in DCM and washed with a saturated solution of $NaHCO_3$ (3x30 mL) and brine (1x30 mL). The organic phase was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the residue purified via silica gel chromatography, eluting with 0-25% EtOAc in Hexane. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.42 (d, J = 7.60 Hz, 2H), 7.32 - 7.37 (m, 2H), 7.27 - 7.30 (m, 1H), 6.94 (dd, J = 2.40,

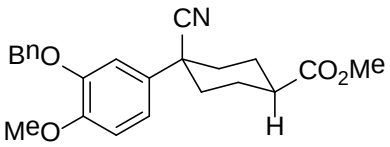
8.30 Hz, 1H), 6.87 (d, J = 8.30 Hz, 1H), 6.80 (d, J = 2.40 Hz, 1H), 5.18 (s, 2H), 3.89 (s, 3H), 3.62 (s, 6H), 2.35 - 2.43 (m, 2H), 2.23 - 2.31 (m, 2H), 2.08 - 2.16 (m, 2H), 1.95 - 2.03 (m, 2H). LCMS found 426.2, $[M + H]^+$.

methyl 5-(3-(benzyloxy)-4-methoxyphenyl)-5-cyano-2-oxocyclohexanecarboxylate (S4) (Yield: 88%). To a solution of dimethyl 4-(3-(benzyloxy)-4-methoxyphenyl)-4-cyanoheptanedioate **(S3)** (6.91 g, 16.24 mmol) in DME (30 mL) under an N_2 atmosphere was slowly added sodium hydride (1.94 g, 48.7 mmol) 60% suspension in mineral oil in DME (20 mL). The mixture was heated to reflux for 1 hour. Water (15 mL) was added and the organic phase was evaporated. HCl 1N (10 mL) was added to the mixture and washed with EtOAc (3x40 mL). The organic layer was separated and washed with brine (1x20 mL). The solvent was dried over anhydrous Na_2SO_4 and , concentrated *in vacuo*. The crude product was purified via silica gel chromatography, eluting with 0-30% EtOAc in Hexane. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 12.22 (s, 1H), 7.44 (d, J = 7.30 Hz, 2H), 7.37 (t, J = 7.30 Hz, 2H), 7.29 - 7.33 (m, 1H), 7.00 - 7.04 (m, 2H), 6.89 (d, J = 8.30 Hz, 1H), 5.17 (s, 2H), 3.90 (s, 3H), 3.77 (s, 3H), 2.92 (d, J = 16.10 Hz, 1H), 2.76 (s, 1H), 2.57 (dd, J = 1.20, 16.10 Hz, 1H), 2.39 - 2.47 (m, 1H), 2.17 - 2.23 (m, 1H), 2.03 - 2.12 (m, 1H). LCMS found 394.1, $[M + H]^+$.

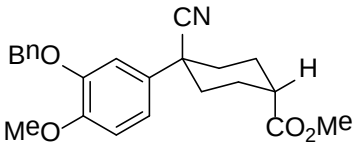
1-(3-(benzyloxy)-4-methoxyphenyl)-4-oxocyclohexanecarbonitrile (S5) (Yield: 73%). To a solution ofmethyl 5-(3-(benzyloxy)-4-methoxyphenyl)-5-cyano-2-oxocyclohexanecarboxylate **(S4)** (4.7 g, 11.95 mmol) in DMF (100 ml) under an N_2 atmosphere was added water (5.55 ml, 308 mmol) and sodium chloride (4.44 g, 76 mmol). The mixture was heated at 145 °C overnight. The crude was filtered through Celite and the solvent evaporated to dryness. The residue was then dissolved in EtOAc (50 mL) and the solution washed with a saturated solution of $NaHCO_3$ (2x30 mL) and brine (1x20 mL).The solvent was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the residue was purified via silica gel chromatography, eluting with 0-30% EtOAc in Hexane. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.44 (d, J = 7.30 Hz, 2H), 7.37 (t, J = 7.30 Hz,

2H), 7.29 - 7.34 (m, 1H), 7.04 (dd, J = 2.40, 8.30 Hz, 1H), 7.01 (d, J = 2.40 Hz, 1H), 6.91 (d, J = 8.30 Hz, 1H), 5.17 (s, 2H), 3.90 (s, 3H), 2.86 (dt, J = 5.90, 14.60 Hz, 2H), 2.49 - 2.55 (m, 2H), 2.36 - 2.43 (m, 2H), 2.16 (dt, J = 4.10, 13.80 Hz, 2H). LCMS found 336.1, $[M + H]^+$.

1-(3-(benzyloxy)-4-methoxyphenyl)-4-(1,3-dithian-2-ylidene)cyclohexanecarbonitrile (S6) (Yield: 88%). To a solution of (1,3-dithian-2-yl)trimethylsilane (1.19 ml, 6.31mmol) in dry THF (10 mL) at 0 °C under a N_2 atmosphere was added butyllithium (2.48 ml, 6.22mmol) 2.5 M in hexanes. After 10 min, the mixture was cooled to -78 °C and a solution of 1-(3-(benzyloxy)-4-methoxyphenyl)-4-oxocyclohexanecarbonitrile **(S5)** (1 g, 2.98mmol) in THF (5 mL) was added. After 30 minutes a cold saturated solution of NaCl was slowly added and the mixture was allowed to warm to room temperature and was diluted with water. The crude was concentrated under vacuum and extracted with DCM (3x30 mL). The organic solution was washed with a saturated solution of $NaHCO_3$ (2x30 mL) and brine (1x20 mL). The solvent was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the residue was purified via silica gel chromatography, eluting with 0-30% EtOAc in Hexane. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.46 (d, J = 7.30 Hz, 2H), 7.35 - 7.40 (m, 2H), 7.29 - 7.34 (m, 1H), 6.99 - 7.03 (m, 2H), 6.87 (d, J = 8.80 Hz, 1H), 5.15 (s, 2H), 3.88 (s, 3H), 3.27 (br. d, J = 15.10 Hz, 2H), 2.91 (t, J = 6.30 Hz, 4H), 2.36 (dt, J = 3.90, 14.20 Hz, 2H), 2.12 - 2.19 (m, 4H), 1.73 (dt, J = 3.70, 13.30 Hz, 2H). LCMS found 438.1, $[M + H]^+$.



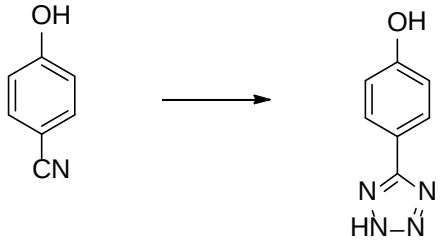
5b



6b

Methyl cis-4-cyano-4-[3-(benzyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylate (5b) (NEU-682) (Yield:76%), and **Methyl trans-4-cyano-4-[3-(benzyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylate (6b) (NEU-684)** (Yield: 12%).To a solution of 1-(3-(benzyloxy)-4-methoxyphenyl)-4-(1,3-dithian-2-ylidene)cyclohexanecarbonitrile **(S6)** (1.05 g,

2.39 mmol) in MeOH (25 ml) under N_2 atmosphere wad added perchloric acid (0.82 ml, 9.60 mmol) and mercury(II) chloride (3.32 g, 12.24 mmol) and the mixture was refluxed for 3 hours and then was allowed to warm to room temperature. The mixture was diluted with DCM (100 mL) than filtered two times on Celite and washed with a saturated solution of $NaHCO_3$ (2x30 mL). The organic was separated and the water phase was washed with DCM (2x30 mL). The collected organic phase were then washed Na_2SO_3 (2x30 mL). The solvent was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the residue was purified by chromatography.The cis isomer **5b** was isolated by silica gel chromatography, eluting with 0-30% EtOAc in Hexane. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.45 (d, J = 7.32 Hz, 2H), 7.35 - 7.40 (m, 2H), 7.29 - 7.34 (m, 1H), 6.99 - 7.03 (m, 2H), 6.88 (d, J = 8.30 Hz, 1H), 5.16 (s, 2H), 3.89 (s, 3H), 3.71 (s, 3H), 2.33 (tt, J = 3.40, 12.20 Hz, 1H), 2.12 - 2.21 (m, 4H), 1.93 - 2.04 (m, 2H), 1.65 - 1.73 (m, 2H). LCMS found 380.2, $[M + H]^+$. The trans isomer **6b** was also isolated. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 7.45 (d, J = 7.30 Hz, 2H), 7.37 (t, J = 7.30 Hz, 2H), 7.28 - 7.33 (m, 1H), 6.98 - 7.02 (m, 2H), 6.87 (d, J = 8.80 Hz, 1H), 5.16 (s, 2H), 3.88 (s, 3H), 3.71 (s, 3H), 2.75 - 2.80 (m, 1H), 2.19 (br. d, J = 13.90 Hz, 2H), 1.91 - 2.08 (m, 6H). LCMS found 380.2, $[M + H]^+$.



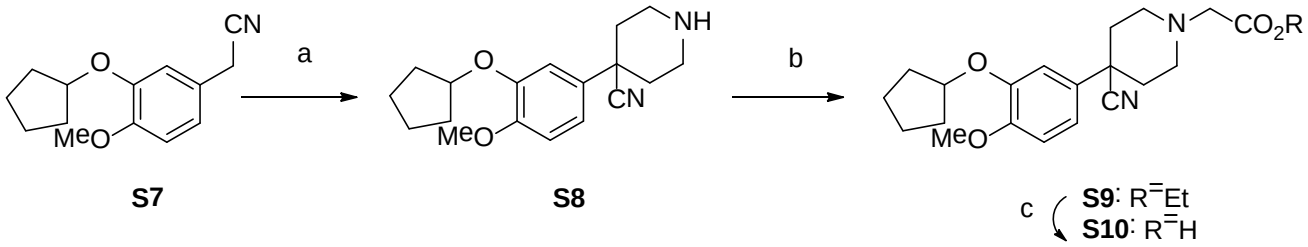
S7

4-(2H-tetrazol-5-yl)phenol (S7) (Yield: 86%).[1] A mixture of 4-hydroxybenzonitrile (650 mg, 5.46 mmol), sodium azide (356 mg, 54.8 mmol) and ammonium chloride (2.95 g, 55.2 mmol) in DMF (30 mL) was heated for 10 hours at 120 °C. The reaction mixture was cooled to room temperature and concentrated, the residue was dissolved in EtOAc (75 mL) and washed with

1N HCl (2x30 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by trituration with hexane/EtOAc 90/10 to give the desired product.^{1}H NMR (500 MHz, DMSO-d6) δ ppm 10.16 (br. s., 1H), 7.85 (td, J = 2.90, 9.90 Hz, 2H), 6.94 (td, J = 2.90, 9.90 Hz, 2H). LCMS found 163.0, $[M + H]^+$.

Preparation of piperidine analogs **S7, S8, S9, S10.** The benzyl cyanide **S7** was cyclized with bis-(2-chloroethyl)amine to give piperidine **S8**. This was alkylated with ethyl 2-bromoacetate to get the ester **S9**, which was hydrolyzed with lithium hydroxide to give the carboxylic acid **S10**.

Scheme S2. Preparation of piperidine analogues



S7 **S8**

Reagents and conditions: (a) bis(2-chloroethyl)amine, NaH, DMF, 60°C, 2 h; (b) ethyl bromoacetate, K_2CO_3, DMF, 80°C, 3 h; (c) LiOH, H_2O, MeOH, THF, rt, 2 h.

2-(3-(cyclopentyloxy)-4-methoxyphenyl)acetonitrile (S7) (Yield: 86%) **(Procedure E**). The crude product was purified via silica gel chromatography, eluting with 0-25% EtOAc in Hexane. ^{1}H NMR (500 MHz, CHLOROFORM-d) δ 6.82 - 6.88 (m, 3H), 4.77 - 4.83 (m, 1H), 3.86 (s, 3H), 3.70 (s, 2H), 1.80 - 2.02 (m, 6H), 1.58 - 1.70 (m, 2H). LCMS found 232.11, [M + H]+.

4-(3-(cyclopentyloxy)-4-methoxyphenyl)piperidine-4-carbonitrile, formic acid salt (S8) (NEU-648) (Yield: 35%). 2-(3-(cyclopentyloxy)-4-methoxyphenyl)acetonitrile **S7** (1 g, 4.32 mmol) and sodium hydride (692 mg, 17.29 mmol) were dissolved in anhydrous DMF (10 mL). The mixture was cooled in an ice/water bath, then, bis(2-chloroethyl)amine (921 mg, 6.49 mmol) in DMF (10 mL) was added to the stirring solution. After the addition was complete, the apparatus was transferred to an oil bath and the mixture was heated to 60 °C and stirred under N_2 atmosphere. After 2 hours, water was added to the reaction dropwise. The solvent was evaporated and the crude was dissolved in DCM, washed with 5%. K_2CO_3 solution (2x30 mL), brine (1x20 mL).The organic phase was dried over anhydrous Na_2SO_4, was concentrated *in vacuo* and the crude product was purified by trituration with hexane/EtOAc 90/10 to give the desired product. A portion (20 mg) of this product was purified again by prep HPLC and the pure product was used for biological assay and for analytical purposes. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 8.36 (s, 1H), 8.12 (s, 1H), 7.03 - 7.07 (m, 1H), 6.96 - 6.99 (m, 1H), 6.88 - 6.92 (m, 1H), 4.80 - 4.86 (m, 1H), 4.65 (td, J = 2.30, 13.90 Hz, 1H), 3.88 (s, 3H), 3.81 (td, J = 2.30, 13.90 Hz, 1H), 3.56 - 3.66 (m, 1H), 3.37 (dt, J = 2.40, 13.20 Hz, 1H), 3.12 (dt, J = 2.90, 13.40 Hz, 1H), 2.58 (dt, J = 2.90, 14.20 Hz, 1H), 2.16 - 2.28 (m, 2H), 1.81 - 2.05 (m, 6H), 1.61 - 1.70 (m, 2H). LCMS found 301.1, $[M + H]^+$.

ethyl 2-(4-cyano-4-(3-(cyclopentyloxy)-4-methoxyphenyl)piperidin-1-yl)acetate (S9) (NEU-650) (Yield: 65%). K_2CO_3 (276 mg, 1.997 mmol) and ethyl 2-bromoacetate (0.166 mL, 1.498 mmol) were added to a solution of 4-(3-(cyclopentyloxy)-4-methoxyphenyl)piperidine-4-carbonitrile **S8** (300 mg, 0.999 mmol) in DMF (5 mL) and stirred at 70 °C for 3 hours. The mixture was filtered over Celite and the solvent was removed under vacuum. The crude was dissolved in DCM (30 mL), washed with a saturated solution of $NaHCO_3$ (2x20 mL) and brine (1x10 mL). The organic phase was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the residue was purified by flash chromatography, eluting with 0-40% EtOAc in Hexane. ^{1}H

NMR (500 MHz, chloroform-d) δ ppm 7.05 (dd, J = 1.95, 8.30 Hz, 1H), 7.02 (d, J = 1.95 Hz, 1H), 6.88 (d, J = 8.30 Hz, 1H), 4.77 - 4.85 (m, 1H), 4.25 (q, J = 7.30 Hz, 2H), 3.87 (s, 3H), 3.33 (s, 2H), 3.11 (br. d, J = 12.20 Hz, 2H), 2.70 (dt, J = 1.95, 12.20 Hz, 2H), 2.23 (dt, J = 3.90, 12.90 Hz, 2H), 2.07 - 2.15 (m, 2H), 1.81 - 2.04 (m, 6H), 1.60 - 1.69 (m, 2H), 1.32 (t, J = 7.30 Hz, 3H). LCMS found 387.1, $[M + H]^+$.

2-(4-cyano-4-(3-(cyclopentyloxy)-4-methoxyphenyl)piperidin-1-yl)acetic acid (S10) (NEU-652) (Yield: 14%) **(Procedure A)**. The crude product was purified via preparative HPLC. ^{1}H NMR (500 MHz, chloroform-d) δ ppm 8.15 (s, 1H), 7.04 - 7.10 (m, 2H), 6.86 - 6.93 (m, 1H), 4.80 - 4.88 (m, 1H), 3.90 (d, J = 12.20 Hz, 2H), 3.87 (s, 3H), 3.67 (s, 2H), 3.15 (t, J = 12.20 Hz, 2H), 2.74 (dt, J = 2.90, 14.60 Hz, 2H), 2.24 (d, J = 13.60 Hz, 2H), 1.95 - 2.04 (m, 2H), 1.80 - 1.94 (m, 4H), 1.59 - 1.70 (m, 2H). LCMS found 359.1, $[M + H]^+$.

Biological Assays.

Human PDE4B biochemical assay. This assay was performed at Takeda Pharmaceuticals as previously reported.[2]

TbrPDEB1 Biochemical assay. Biochemical assays were performed as previously described.[3] In short, recombinant TbrPDEB1 (1 ng/mL) was assayed in 10 mM Tris pH 7.4, bovine serum albumin (0.2 mg/mL), 10 mM $MgCl_2$, 25µM cAMP (Enzo Lifesciences) and an excess of 5` endonucleotidase (>1000U) at 37°C. Excess amount of 5` endonucleotidase was determined by titration (Enzo Lifesciences). Reactions were terminated by the addition of BioMol green (Enzo Lifesciences) which was also used to detect changes in the level of phosphate. This was measured by absorbance at 620 nm using a Tecan Sunrise plate reader. All screens were carried at a final concentration of 2% (v/v) DMSO and all IC_{50} experiments were carried out at 10% (v/v) DMSO. Inhibitors were preincubated with the assay mixture for 5 min prior to the addition of substrate.. Inhibition was determined by the change in the initial velocity relative to a vehicle only control for both compound screening and for the determination of IC_{50} values. Initial velocity was determined by linear regression and IC_{50} values were calculated by non-linear regression for normalized inhibition values. Data were analyzed using GraphPad Prism 5.0.

***T. brucei* cell growth assay**. (Performed at the New York University School of Medicine, Department of Microbiology Anti-Infectives Screening Core). The assay is performed in 96 well white sterile plates. Each compound was tested in duplicate, and the controls (medium alone, parasites alone, parasites + 100 µM suramin) were tested in triplicate. To each well of a white 96-well plate was added 100 µL of HMI-9 medium (Iscove's modification of DMEM (IMDM; Cell Gro) supplemented with 10% FBS, 10%, Serum plus (SAFC), 0.05 mM bathocuproinesulfonate, 1.5 mM L-cysteine, 1 mM hypoxanthine, 0.2 mM β-mercaptoethanol, 0.16 mM thymidine 1 mM pyruvate (stock: 100 mM)). Compounds dissolved in DMSO were serially diluted into buffer the wells. Parasites were added to each well (5x105 cells/well), and after 22-24 hours, 20 µL of

Alamar blue per well was added, and the plate was incubated at 37 °C for 4 hours before obtaining a fluorescence readout (λ: 530 nm excitation; 590nm).

NIH 3T3 Cell Toxicity Assay. (Performed at the New York University School of Medicine, Department of Microbiology Anti-Infectives Screening Core Compounds were tested in duplicate using methods previously reported.[4]

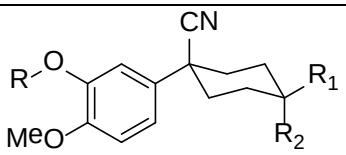
Molecular modeling.

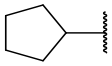
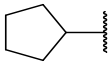
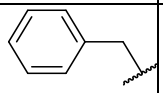
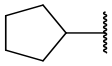
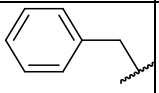
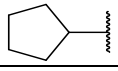
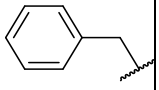
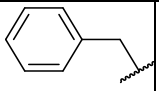
Docking was performed using POSIT v 1.0.2 (OpenEye Scientific Software: Santa Fe, NM). The coordinates of the apo crystal structure of TbrPDEB1 were downloaded from the Protein Data Bank (PDB): PDB code: 4I15.[5] The protein was prepared for docking and mild ligand−protein clashes were allowed in order to account for the average coordinate error expected in PDB structures. The "combine-receptors" option was used in order to include the binding modes observed in the two human PDE4 crystal structure in complex with **1** (PDB codes: 1XLX and 1XOM) during docking in TbrPDEB1.[6] Mild clashes were also used in pose prediction. All the other options in POSIT were kept as default. The docked poses were energy minimized using SZYBKI (v 1.7.0 OpenEye Scientific Software, Santa Fe, NM) allowing partial relaxation of the protein residues in the direct proximity to the ligand.

Tables.

The data tables included in the manuscript are recapitulated here in order to include the compound NEU registry number, which is utilized in the publically available data set at www.collaborativedrug.com.

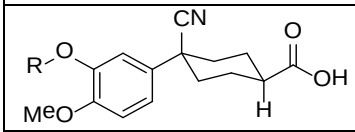
Table S1. Cilomilast analogs tested against TbrPDEB1

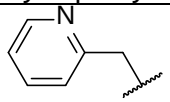
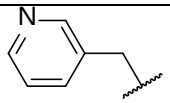
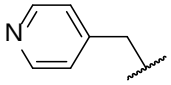
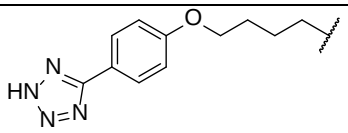
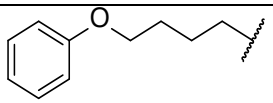
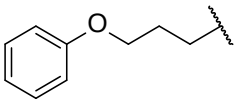
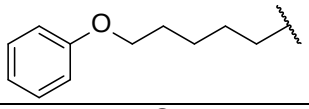
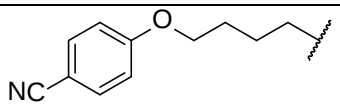
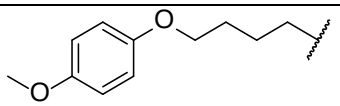
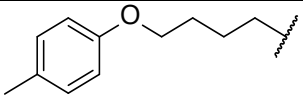
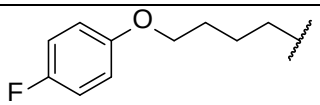


NEU Number	Cmpd	R	R_1	R_2	TbrPDEB 1 (%)[a]	TbrPDEB1 IC_{50}[b] (μM)
NEU-491	**1**		COOH	H		16±6.65
NEU-680	**5a**		$COOCH_3$	H	31±8	
NEU-683	**5b**		$COOCH_3$	H	40±14	
NEU-681	**8a**		H	COOH	9.3±9.3	
NEU-686	**8b**		H	COOH	20±4.3	
NEU-682	**6a**		H	$COOCH_3$	26±3.6	
NEU-684	**6b**		H	$COOCH_3$	28±8.9	
NEU-685	**7**		COOH	H	77±6.4	12±1.18

[a]Inhibitor concentration 10.0 μM, tested in at least two independent replicate experiments all error was within 15%. [b]Tested in at least two independent replicate experiments.

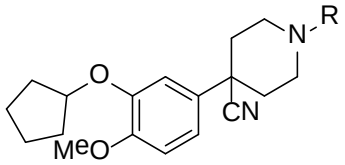
Table S2. Cilomilast analogs tested against TbrPDEB1 varying catechol substituents.



NEU Number	Cmpd	R	TbrPDEB1 (%)[a]	TbrPDEB1 IC_{50}[c](μM)
NEU-491	**1**	Cyclopentyl		16.4 ± 6.7
NEU-732	**10a**		33±12	
NEU-728	**10b**		nd[b]	
NEU-729	**10c**		11±4.4	
NEU-750	**12a**		69±1.4	7.9 ± 4.63
NEU-730	**12b**		96±0.66[c]	0.95 ±0.14
NEU-798	**12c**		66±2.2	11.0 ± 0.13
NEU-799	**12d**		54±8	9.8 ± 1.27
NEU-731	**12e**		87±12	3.6 ±0.3
NEU-796	**12f**		79±3.4	3.5 ± 0.41
NEU-797	**12g**		74±1.7	4.9 ± 2.81
NEU-916	**12h**		79±0.42[c]	9.2 ± 5.1

[a]Inhibitor concentration 10.0 μM, tested in at least two independent replicate experiments, all error was within 15%; [b]nd=no data due to insufficient solubility in the assay conditions. [c]Tested in at least two independent replicate experiments.

Table S3. Piperidine analogs tested against TbrPDEB1



NEU Number	Compd	R	TbrPDEB1 (% inh)[a]
NEU-648	**S8**	H	19±9.6
NEU-650	**S9**	CH_2CO_2Et	6±7.6
NEU-652	**S10**	CH_2CO_2H	11±11[b]

[a] Inhibitor concentration 10.0 µM, tested in at least two independent replicate experiments; [b] n=1.

Molecular Modeling Figures.

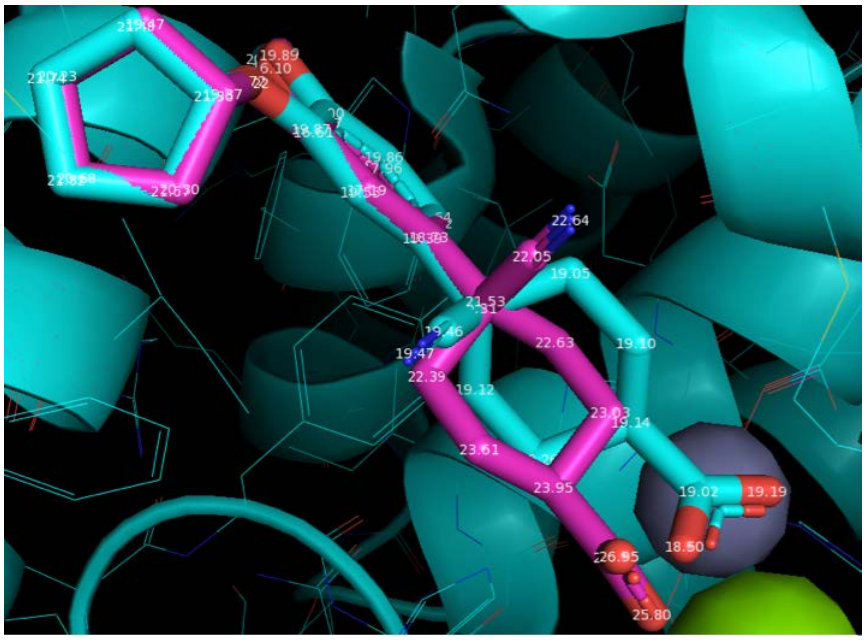


Figure S1. The two alternative binding conformations of compound **1** seen in the crystal structure in complex human PDE4D (PDB code: 1XOM).[6] Conformations A and B have magenta and cyan carbon atoms respectively. The B-factor values reported in the crystal structure are also shown. Mg and Zn are shown as green and grey spheres. The image was generated using PyMol (version 1.5.0.4, Schrodinger).

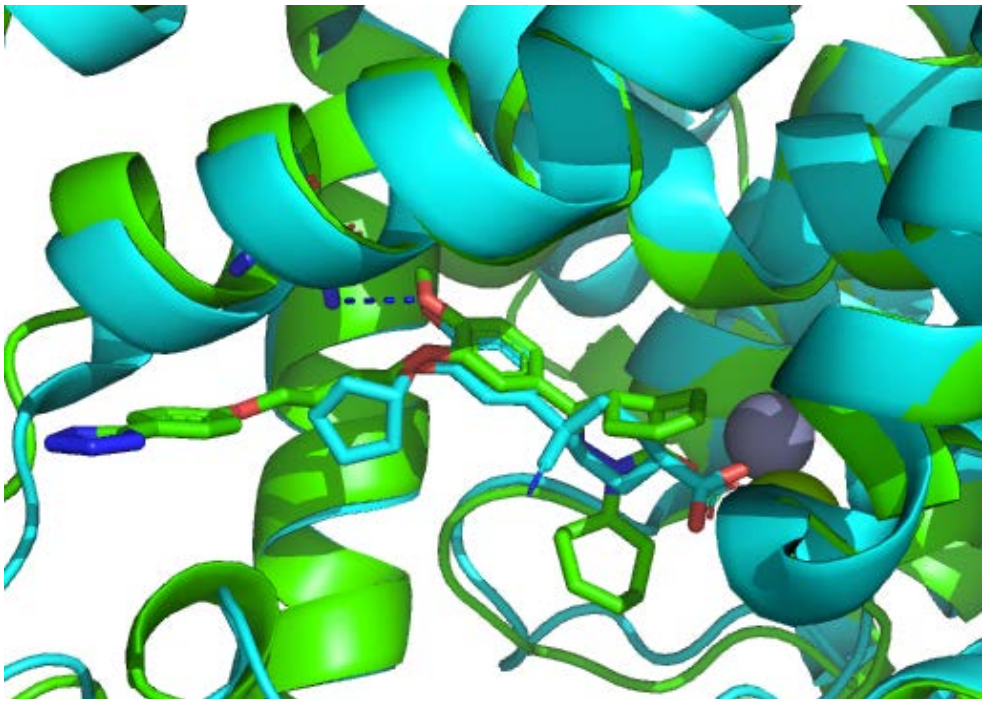


Figure S2. Overlay of the docked conformation of compound **3** in TbrPDEB1 (green carbon atoms) with the crystal structure of compound **1** in complex with the crystal structure of human PDE4D (1XOM, cyan carbon atoms; conformation B described in Figure S1). The hydrogen bond between the methoxy group and the side chain of Gln 874 is shown in blue dashed line. Magnesium and Zinc are shown as green and grey spheres. The image was generated using PyMol (version 1.5.0.4, Schrodinger).

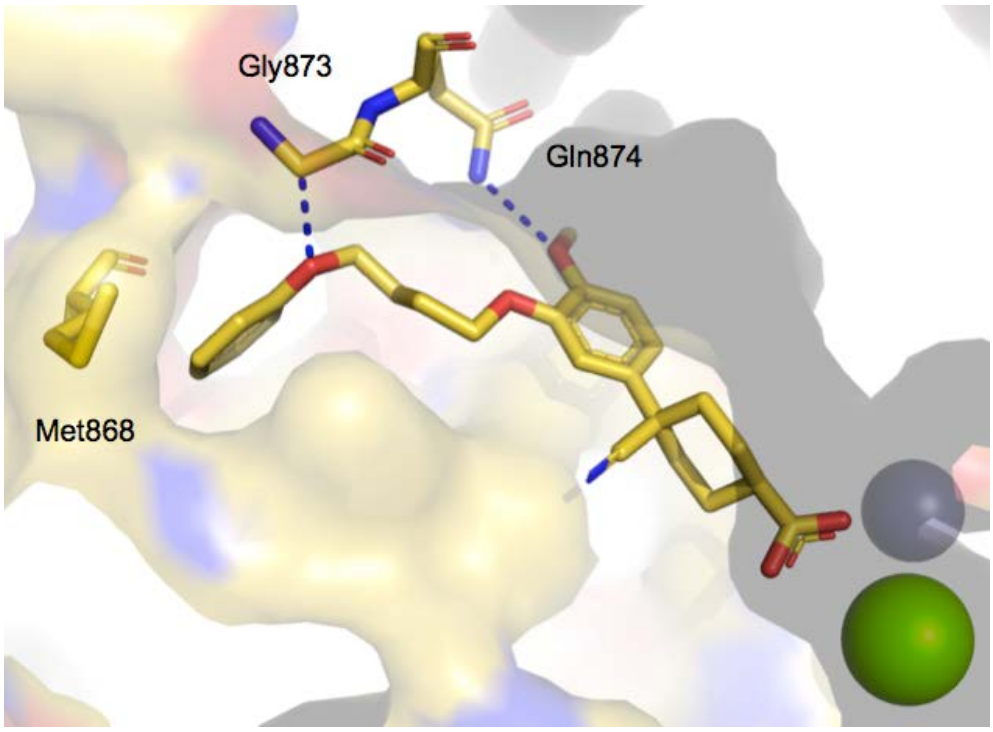


Figure S3. Docking of compound **12b** in TbrPDEB1 (both having yellow carbon atoms). A weak hydrogen bond between the oxygen atom of compound **12b** with the methylene group of Gly873 is also seen. Magnesium and Zinc are shown as green and grey spheres. The image was generated using PyMol (version 1.5.0.4, Schrodinger).

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