Electronic Supplementary Information for:

Design and synthesis of a novel series of cyclohexyloxy-pyridyl derivatives as inhibitors of diacylglycerol acyl transferase 1

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Experimental Information

Chemistry. All solvents and reagents were obtained from commercially available sources and used without further purification. Reactions were carried out under nitrogen atmosphere unless otherwise stated. Reactions carried out using a microwave reactor were performed using a Biotage Initiator or Personal Chemistry [Biotage] Emrys Optimizer. Flash chromatography was carried out on prepacked silica gel columns supplied by Biotage and using Horizon/Biotage systems. Analytical HPLC/MS was conducted on a Waters Zevo QTof or Waters LCT Premiere mass spectrometer using an Acquity PDA (Waters) UV detector monitoring either at (a) 210 nm with an Acquity BEH C18 column (2.1x100 mm, 1.7 µm, 0.7 mL/min flow rate), using a gradient of 2% v/v CH_3CN in H_2O (ammonium carbonate buffer pH10) to 98% v/v CH_3CN in H_2O or (b) 230 nm with an Acquity HSS C18 column (2.1x100 mm, 1.8 µm, 0.7 mL/min flow rate), using a gradient of 2% v/v CH_3CN in H_2O (ammonium formate buffer pH3) to 98% v/v CH_3CN in H_2O. All tested compounds were determined to be > 95% pure using the analytical method (a) described above based on the peak area percentage. ^{1}H NMR spectra were generated on a Varian 300 MHz or Varian 400 MHz instrument as indicated. Chemical shifts (δ) are given in parts per million (ppm), with the residual solvent signal used as a reference. Coupling constants (*J*) are reported as Hz. NMR abbreviations are used as follows: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

***cis*-4-{4-[({5-[(3,4-Difluorophenyl)amino]-1,3,4-oxadiazol-2-yl}carbonyl)amino]-phenoxy}cyclohexanecarboxylic acid (16).** Sodium hydride (60% dispersion in oil, 4.39 g, 110 mmol) was added in portions over 1 min to a stirred solution of ethyl 4-hydroxycyclohexanecarboxylate (18 g, 105 mmol) and 1-fluoro-4-nitrobenzene (11.1 mL, 110 mmol) in DMF (200 mL) at 0°C. The reaction mixture was stirred at 0°C for 5 mins and then warmed

to room temperature and stirred for 2 h. Water (750 mL) and EtOAc (300 mL) were then added and the layers were separated. The aqueous layer was extracted with EtOAc (2x300 mL) and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave a residue. The crude residue was purified by column chromatography, using a gradient of 10-40% EtOAc in isohexane as eluent, to give ethyl *cis*-4-(4-nitrophenoxy)cyclohexanecarboxylate as a yellow oil (6.95 g, 23%). The corresponding *trans*-cyclohexyl isomer, ethyl *trans*-4-(4-nitrophenoxy)cyclohexanecarboxylate was also isolated from this reaction as a white solid (5.50 g, 18%).

Palladium (10 wt. %) on C (200 mg) was added to a solution of ethyl 4-(4-nitrophenoxy)cyclohexanecarboxylate (6.95 g, 23.7 mmol) in EtOH (200 mL) and the reaction mixture was stirred under a hydrogen atmosphere at room temperature for 16 h. The reaction mixture was filtered and concentrated *in vacuo* to leave ethyl *cis*-4-(4-aminophenoxy)cyclohexanecarboxylate as a yellow oil (6.24 g, 100%), which was used with no further purification.

Methyl chlorooxoacetate (2.41 mL, 26.1 mmol) was added dropwise over 2 mins to a stirred solution of ethyl *cis*-4-(4-aminophenoxy)cyclohexanecarboxylate (6.24 g, 23.7 mmol) and diisopropylethylamine (8.25 mL, 47.4 mmol) in DCM (200 mL) and the reaction mixture was stirred at room temperature for 16 h. Water (75 mL) was added and the layers were separated. The organic layer was washed with an aqueous solution of hydrochloric acid (1M, 75 mL) and then a saturated aqueous solution of sodium hydrogen carbonate (75 mL), dried ($MgSO_4$) and concentrated *in vacuo* to provide ethyl *cis*-4-(4-{[methoxy(oxo)acetyl]amino}phenoxy)-cyclohexanecarboxylate as a white solid (8.23 g, 100%), which was used with no further purification.

Hydrazine monohydrate (2.29 mL, 47.1 mmol) was added in one portion to a stirred solution of ethyl *cis*-4-(4-{[methoxy(oxo)acetyl]amino}phenoxy)cyclohexanecarboxylate (8.23 g, 23.6 mmol) in EtOH (200 mL) and the reaction mixture was stirred at 70°C for 1 h. After cooling to room temperature the mixture was filtered and washed with ether (200 mL) to leave ethyl *cis*-4-(4-{[hydrazino(oxo)acetyl]amino}phenoxy)cyclohexanecarboxylate as a white solid (7.80 g, 95%) that was used with no further purification.

Ethyl *cis*-4-(4-{[hydrazino(oxo)acetyl]amino}phenoxy)cyclohexanecarboxylate (700 mg, 2.0 mmol) was added in one portion to a stirred solution of 3,4-difluorophenyl isothiocyanate (411 mg, 2.40 mmol) in DMF (10 mL) and the reaction mixture was stirred at 65°C for 30 mins. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 460 mg, 2.40 mmol) was added in one portion and the reaction mixture was heated to 85°C for 3 h. The

mixture was cooled to room temperature and water (15 mL) was added and the resulting suspension was filtered to leave a cream solid. The solid was taken up in a mixture of MeOH (8 mL) and THF (4 mL) and a 2N aqueous solution of NaOH (4 mL) was added in one portion and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was acidified by the addition of 2M HCl and the resulting precipitate was filtered, washed with water (10 mL) and dried under high vacuum to leave a solid. The solid was recrystallised from refluxing glacial acetic acid to give the title compound as a white solid (428 mg, 47%). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 1.60 - 1.86 (m, 8H), 2.32 - 2.42 (m, 1H), 4.51 (s, 1H), 6.96 (d, 2H), 7.31 - 7.38 (m, 1H), 7.49 (m, 1H), 7.66 - 7.75 (m, 3H), 10.97 (s, 1H), 11.27 (s, 1H), 12.12 (s, 1H); MS (ESI) *m/z* $C_{22}H_{21}F_2N_4O_5$ $[M + H]^+$ found 459.3.

3-[4-[[5-(3,4-Difluoroanilino)-1,3,4-oxadiazole-2-carbonyl]amino]phenoxy]benzoic acid (15). Following an analogous procedure for **16**, using methyl 3-hydroxybenzoate in place of ethyl 4-hydroxycyclohexanecarboxylate provided the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.09 – 7.15 (2 H, m), 7.29 (1 H, ddd, *J* 8.2, 2.6, 1.0), 7.32 – 7.39 (1 H, m), 7.44 – 7.48 (1 H, m), 7.52 (2 H, t, *J* 8.0), 7.65 – 7.75 (2 H, m), 7.83 – 7.9 (2 H, m), 11.12 (1 H, s), 11.25 (1 H, s), 12.99 (1 H, s); HRMS (ESI) *m/z* calcd for $C_{22}H_{15}F_2N_4O_5$ $[M + H]^+$ 453.1005; found 453.1007.

***cis*-4-{4-[({5-[(4-Fluorophenyl)amino]-1,3,4-oxadiazol-2-yl}carbonyl)amino]-phenoxy}-cyclohexanecarboxylic acid (17).** Following an analogous procedure for **16**, using 4-fluoro-phenyl isothiocyanate in place of 3,4-difluorophenyl isothiocyanate provided the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 1.60 - 1.86 (m, 8H), 2.32 - 2.43, (m, 1H), 4.50 (s, 1H), 6.95 (d, 2H), 7.25 (m, 2H), 7.58 - 7.65 (m, 2H), 7.69 (d, 2H), 10.94 (s, 1H), 11.03 (s, 1H), 12.11 (s, 1H); MS (ESI) *m/z* $C_{22}H_{22}FN_4O_5$ $[M + H]^+$ found 441.4.

***cis*-4-{4-[({5-[(4-Cyanophenyl)amino]-1,3,4-oxadiazol-2-yl}carbonyl)amino]-phenoxy}-cyclohexanecarboxylic acid (18).** Following an analogous procedure for **16**, using 4-cyano-phenyl isothiocyanate in place of 3,4-difluorophenyl isothiocyanate provided the title compound as a white solid. 1H NMR (400 MHz, DMSO-*d*6) δ1.58 - 1.87 (m, 8H), 2.30 - 2.43 (m, 1H), 4.51 (s, 1H), 6.95 (m, 2H), 7.54 (d, 1H), 7.63 (m, 1H), 7.70 (d, 2H), 7.86 (d, 1H), 8.02 (s, 1H), 10.99 (s, 1H), 11.46 (s, 1H), 12.10 (s, 1H); MS (ESI) *m/z* $C_{23}H_{22}N_5O_5$ $[M + H]^+$ found 448.4.

***cis*-4-{4-[({5-[(2,4,5-Trifluorophenyl)amino]-1,3,4-oxadiazol-2-yl}carbonyl)amino]-phenoxy}cyclohexanecarboxylic acid (19).** Following an analogous procedure for **16**, using 2,4,5-trifluorophenyl isothiocyanate in place of 3,4-difluorophenyl isothiocyanate provided

the title compound as a pale yellow solid (118 mg, 56%). The compound may be further recrystallised from EtOH, melting point 251-253°C; ^{1}H NMR (400 MHz, DMSO-*d*6) δ1.60 – 1.72 (4 H, m), 1.72 – 1.87 (4 H, m), 2.3 – 2.43 (1 H, m), 4.46 – 4.54 (1 H, m), 6.93 – 6.99 (2 H, m), 7.64 – 7.75 (3 H, m), 8.1 – 8.23 (1 H, m), 10.90 (1 H, s), 11.03 (1 H, s), 12.05 (1 H, s); HRMS (ESI) *m/z* calcd for $C_{22}H_{20}F_3N_4O_5$ $[M + H]^+$ 477.1386; found 477.1380.

***trans*-4-{4-[({5-[(2,4,5-Trifluorophenyl)amino]-1,3,4-oxadiazol-2-yl}carbonyl)amino]-phenoxy}cyclohexanecarboxylic acid (20).** Following an analogous procedure for **16**, using the *trans*-isomer isolated in the first step (ethyl *trans*-4-(4-nitrophenoxy)cyclohexanecarboxylate) and 2,4,5-trifluorophenyl isothiocyanate in place of 3,4-difluorophenyl isothiocyanate provided the title compound as a white solid (93 mg, 79%). The compound may be recrystallised from a 4:6:1 mixture of EtOH:MeOH:H_2O; melting point 263-265°C. ^{1}H NMR (400 MHz, DMSO-*d*6) δ1.34-1.44 (2H, m), 1.46-1.56 (2H, m), 1.93-1.97 (2H, m), 2.05-2.09 (2H, m), 2.23-2.30 (1H, m), 4.24-4.31 (1H, m), 6.94-6.96 (2H, d), 7.67-7.69 (2H, d), 7.71 (1H, m), 8.13-8.20 (1H, m), 10.90 (1H, s), 11.03 (1H, s), 12.06 (1H, s); MS (ESI) *m/z* $C_{22}H_{18}F_3N_4O_5$ $[M - H]^-$ found 475.3.

***cis*-4-(3-Fluoro-4-{[5-(2,4,5-trifluorophenylamino)[1,3,4]oxadiazole-2-carbonyl]-amino}-phenoxy)cyclohexane-1-carboxylic acid (22).** Following an analogous procedure for **16**, using 2,4-difluoronitrobenzene in place of 1-fluoro-4-nitrobenzene and 2,4,5-trifluorophenyl isothiocyanate in place of 3,4-difluorophenyl isothiocyanate provided the title compound as a white solid (700 mg, 64%); ^{1}H NMR (400 MHz, DMSO-*d*6) δ 1.6-1.9 (8H, m), 2.35-2.44 (1H, m), 4.52-4.62 (1H, m), 6.83 (1H, dd, *J* 8.8, 2.0), 6.97 (1H, dd, *J* 12.4, 2.6), 7.39 (1H, t, *J* 8.9), 7.70 (1 H, td, *J* 10.6, 7.5), 8.16 (1 H, dt, *J* 12.3, 8.1), 10.60 (1 H, s), 11.05 (1 H, s), 12.07 (1 H, s); HRMS (ESI) *m/z* calcd for $C_{22}H_{19}F_4N_4O_5$ $[M + H]^+$ 495.1292; found 495.1302.

***trans*-4-(3-Fluoro-4-{[5-(2,4,5-trifluorophenylamino)[1,3,4]oxadiazole-2-carbonyl]-amino}phenoxy)cyclohexane-1-carboxylic acid (23).** Following an analogous procedure for **16**, using 2,4-difluoronitrobenzene in place of 1-fluoro-4-nitrobenzene, the *trans*-isomer isolated in the first step and 2,4,5-trifluorophenyl isothiocyanate in place of 3,4-difluorophenyl isothiocyanate provided the title compound as a white solid (600 mg, 56%); ^{1}H NMR (400 MHz, DMSO-*d*6) δ 1.32–1.46 (2H, m), 1.48–1.63 (2H, m), 1.88–2.0 (2H, m), 2.03–2.11 (2H, m), 2.26 (1H, ddt, *J* 11.3, 7.5, 3.7), 4.34 (1H, td, *J* 10.0, 4.9), 6.82 (1H, dd, *J* 8.8, 2.0), 6.97 (1H, dd, *J* 12.4, 2.7), 7.38 (1H, t, *J* 8.9), 7.70 (1H, td, *J* 10.7, 7.5), 8.16 (1H, dt, *J* 12.2, 8.1), 10.60 (1H, s), 11.04 (1H, s), 12.07 (1H, s); HRMS (ESI) *m/z* calcd for $C_{22}H_{19}F_4N_4O_5$ $[M + H]^+$ 495.1292; found 495.1286.

***cis*-4-[2-Fluoro-4-[[5-(2,4,5-trifluoroanilino)-1,3,4-oxadiazole-2-carbonyl]amino]phenoxy]cyclohexanecarboxylic acid (24).** Following an analogous procedure for **16**, using 3,4-difluoronitrobenzene in place of 1-fluoro-4-nitrobenzene and 2,4,5-trifluorophenyl isothiocyanate in place of 3,4-difluorophenyl isothiocyanate provided the title compound as a white solid (1.0 g, 40%); ^{1}H NMR (400 MHz, DMSO-*d*6) δ 1.58 – 1.73 (4 H, m), 1.75 – 1.89 (4 H, m), 2.28 – 2.43 (1 H, m), 4.50 (1 H, s), 7.21 (1 H, t, *J* 9.2), 7.54 (1 H, d, *J* 8.8), 7.62 – 7.77 (2 H, m), 8.08 – 8.21 (1 H, m), 11.06 (1 H, s), 11.09 (1 H, s), 12.07 (1 H, s); HRMS (ESI) *m/z* calcd for $C_{22}H_{19}F_4N_4O_5$ $[M + H]^+$ 495.1286; found 495.1284.

***cis*-4-[5-[[5-[(3,4-Difluorophenyl)amino]1,3,4-oxadiazole-2-carbonyl]amino]pyridin-2-yl]oxycyclohexane-1-carboxylic acid (21).** A solution of *cis*-4-hydroxycyclohexanecarboxylic acid (4.98 g, 34.5 mmol) in DMA (20 mL) was added to a stirred mixture of sodium hydride (2.76 g, 69.0 mmol) in DMA (80 mL) cooled to 0 ºC. The resulting suspension was stirred at room temperature for 30 mins. 5-Bromo-2-fluoropyridine (6.08g, 34.5 mmol) was added and the resulting suspension was stirred at 100 ºC for 1h. The reaction mixture was cooled to room temperature, diluted with water (50 mL) and 2M hydrochloric acid was added. The precipitate was collected by filtration, washed with water (50 mL) and dried under vacuum to afford *cis*-4-(5-bromopyridin-2-yl)oxycyclohexane-1-carboxylic acid (6.8 g), which was used without further purification.

A few drops of concentrated hydrochloric acid were added to a stirred solution of *cis*-4-(5-bromopyridin-2-yl)oxycyclohexane-1-carboxylic acid (6.8 g, 23.0 mmol) in methanol at 20 ºC. The resulting solution was stirred at 60 ºC for 3 hours. The solvent was evaporated to afford the crude product (6.4 g) that was used without further purification.

Benzophenone imine (0.40 mL, 2.4 mmol) was added to *cis*-methyl 4-(5-bromopyridin-2-yl)oxycyclohexane-1-carboxylate (0.50 g, 1.6 mmol), palladium(II)acetate (0.02 g, 0.10 mmol), cesium carbonate (0.18 mL, 2.2 mmol) and (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.060 g, 0.10 mmol) in THF (10 mL) at 20 ºC. The resulting solution was stirred at reflux for 8 h. The reaction mixture was concentrated *in vacuo* and redissolved in ethyl acetate (10 mL) and washed with water (10 mL) and saturated brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was used without further purification.

2M Hydrochloric acid (5 mL) was added to a stirred solution of methyl *cis*-4-[5-(benzhydrylideneamino)pyridin-2-yl]oxycyclohexane-1-carboxylate (0.80 g, 1.93 mmol) in THF (10 mL) at room temperature and the reaction mixture was stirred at room temperature for 2 h. The

reaction mixture was adjusted to pH 7 with 2M NaOH and then concentrated *in vacuo*. The resulting aqueous solution was extracted with ethyl acetate (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a residue. The residue was purified by flash column chromatography, eluting with 0 to 80% ethyl acetate in isohexane, to give methyl *cis*-4-(5-aminopyridin-2-yl)oxycyclohexane-1-carboxylate as a solid (0.35 g, 73%). Methyl oxalyl chloride (1.7 mL, 18.0 mmol) was added to a stirred solution of methyl *cis*-4-(5-amino-pyridin-2-yl)oxycyclohexane-1-carboxylate (3.8 g, 15 mmol), and pyridine (2.4 mL, 30.0 mmol) in DCM (50 mL) at 0 ºC. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was quenched with water (20 mL), extracted with DCM (2 × 20 mL), the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave the crude product (4.6 g), which was used without further purification.

Hydrazine hydrate (0.74 mL, 15 mmol) was added to a stirred solution of methyl *cis*-4-[5-[(methoxycarbonylformyl)amino]pyridin-2-yl]oxycyclohexane-1-carboxylate (4.6 g, 14 mmol) in ethanol (50 mL) at 70 ºC and the resulting solution was stirred at 70 °C for 30 mins. The precipitate was collected by filtration, washed with diethyl ether (100 mL) and dried under vacuum to afford methyl *cis*-4-[5-[(hydrazinecarbonylformyl)amino]pyridin-2-yl]oxycyclohexane-1-carboxylate (2.7 g), which was used without further purification.

3,4-Difluorophenylisocyanate (1.6 g, 9.5 mmol) was added to a stirred solution of methyl *cis*-4-[5-[(hydrazinecarbonylformyl)amino]pyridin-2-yl]oxycyclohexane-1-carboxylate (2.7 g, 7.9 mmol) in DMF (50 mL) at 65 ºC and the reaction mixture was stirred at 65 ºC for 30 mins. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.83 g, 9.5 mmol) was added to the mixture and the resulting solution was stirred at 85 ºC for 30 mins. The reaction mixture was cooled to room temperature and then water was added (50 mL).

The precipitate was collected by filtration, washed with water (25 mL) and dried under vacuum to afford the oxadiazole product (3.2 g), which was used without further purification.

Sodium hydroxide (2M aqueous, 13.5 mL, 27 mmol) was added to a stirred solution of methyl *cis*-4-[5-[[5-[(3,4-difluorophenyl)amino]1,3,4-oxadiazole-2-carbonyl]amino]pyridin-2-yl]-oxycyclohexane-1-carboxylate (3.2 g, 6.8 mmol) in methanol (50 mL) at room temperature. The resulting solution was stirred at room temperature for 3 h and then the reaction mixture was cooled in an ice bath and acidified with 2M hydrochloric acid. The precipitate was collected by filtration, washed with water (10 mL) and dried under vacuum to afford the crude product which was purified by crystallisation from acetic acid to give the title compound as a crystalline solid (2.2 g, 71%). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 1.63 – 1.89 (8 H, m), 2.39 (1 H, dd, *J* 8.6, 4.3), 5.09 – 5.15 (1 H, m), 6.83 (1 H, d, *J* 8.9), 7.33 – 7.39

(1 H, m), 7.43 – 7.54 (1 H, m), 7.70 (1 H, ddd, *J* 12.8, 7.1, 2.7), 8.05 (1 H, dd, *J* 9.0, 2.7), 8.51 (1 H, d, *J* 2.7), 11.09 (1 H, s), 11.23 (1 H, s), 12.04 (1 H, s). HRMS (ESI) *m/z* calcd for $C_{21}H_{20}F_2N_5O_5$ $[M + H]^+$ 460.1432; found 460.1447.

4-(5-(5-(3,4-Difluorophenylamino)-1,3,4-oxadiazole-2-carboxamido)-pyridin-2-yloxy)-benzoic acid (25). Following an analogous procedure for **16**, using methyl 4-hydroxy-benzoate in place of ethyl 4-hydroxycyclohexanecarboxylate and 2-chloro-5-nitropyridine in place of 1-fluoro-4-nitrobenzene provided the title compound as a white solid. ^{1}H NMR (300 MHz, DMSO-*d*6) δ 7.17 - 7.23 (3H, m), 7.34 - 7.38 (1H, m), 7.45 - 7.52 (1H, m), 7.67 - 7.73 (1H, m), 7.97 - 8.01 (2H, m), 8.29 - 8.32 (1H, m), 8.61 (1H, d), 11.26 (1H, s), 11.31 (1H, s), 12.50 (1H, s). MS (ESI) *m/z* $C_{21}H_{14}F_2N_5O_5$ $[M + H]^+$ found 454.3.

***cis*-4-(5-(5-(3,4-difluorophenylamino)-1,3,4-oxadiazole-2-carboxamido)-pyridin-2-yloxy)cyclohexyl)acetic acid (26).** Methyl 2-(4-hydroxyphenyl)acetate (81.3 g, 489 mmol) and Rhodium (5% on Alumina) (8.10 g, 3.95 mmol) in methanol (800 mL) were stirred under an atmosphere of hydrogen at 3 bar and 25 °C for 3 h. The reaction mixture was filtered through celite and concentrated *in vacuo* to afford the desired product (84 g, 100 %) as a mixture of *cis*- and *trans*-isomers. The mixture was purified by flash column chromatography, using a gradient of 30 to 50% ethyl acetate in isohexane, as eluent to give methyl *cis*-(4-hydroxycyclohexyl)acetate (5.6 g, 7 %) as a colourless oil.

Diisopropyl azodicarboxylate (1.34 mL, 6.78 mmol) was added to a stirred solution of 5-nitropyridin-2-ol (500 mg, 3.57 mmol) and triphenylphosphine (2.2 g, 8.21 mmol) in THF (15 mL). After 5 mins methyl *cis*-(4-hydroxycyclohexyl)acetate (620 mg, 3.57 mmol) in THF (1 mL) was added. The reaction mixture was heated at 180 °C for 45 mins in a microwave and then concentrated *in vacuo* to leave a residue. Purification by flash column chromatography, using a gradient of 20 to 50% ethyl acetate in isohexane as eluent, gave methyl *cis*-(4-(5-nitropyridin-2-yloxy)cyclohexyl)acetate as a yellow solid. The reaction was performed 6 times to give 3.4 g (54 %).

Following the remainder of the reaction sequence for **16**, using analogous procedures provided the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 1.30 – 1.43 (2 H, m), 1.51 – 1.68 (4 H, m), 1.77 – 1.93 (3 H, m), 2.17 (2 H, d, *J* 7.1), 5.13 – 5.19 (1 H, m), 6.82 (1 H, d, *J* 8.9), 7.32 – 7.39 (1 H, m), 7.44 – 7.54 (1 H, m), 7.70 (1 H, ddd, *J* 12.8, 7.1, 2.7), 8.05 (1 H, dd, *J* 9.0, 2.7), 8.50 (1 H, d, *J* 2.7), 11.08 (1 H, s), 11.24 (1 H, s), 11.96 (1 H, s). HRMS (ESI) *m/z* calcd for $C_{22}H_{22}F_2N_5O_5$ $[M + H]^+$ 474.1589; found 474.1621.

***cis*-4-(6-Fluoro-5-(5-(2,4,5-trifluorophenylamino)-1,3,4-oxadiazole-2-carboxamido)-pyridin-2-yloxy)cyclohexanecarboxylic acid (28).** A suspension of 2-chloro-6-methoxy-3-

nitropyridine (20.9 g, 110 mmol) in concentrated hydrochloric acid (37%) (170 mL, 5530 mmol) was stirred at 90 °C for 3 h. The reaction mixture was adjusted to pH 5 with 2M NaOH and the aqueous mixture was then extracted with ethyl acetate (250 mL). The organic layer was concentrated *in vacuo* to leave a yellow solid which was filtered and washed with Et_2O (200 mL). The solid was stirred in ethyl acetate (200 mL) and the green insoluble solid filtered off. Both filtrates were combined and dried ($MgSO_4$) and then concentrated *in vacuo* to give 6-chloro-5-nitropyridin-2-ol as a yellow solid (14.7 g, 76 %).

Diisopropyl azodicarboxylate (21.0 mL, 107 mmol) was added to a stirred solution of 6-chloro-5-nitropyridin-2-ol (14.9 g, 85.4 mmol) and triphenylphosphine (33.6 g, 128 mmol) in THF (200 mL). The reaction mixture was stirred at room temperature for 10 mins and then methyl *cis*-4-hydroxycyclohexanecarboxylate (13.5 g, 85.4 mmol) in THF (50 mL) was added and the resulting solution was stirred at room temperature for 48 h. The reaction mixture was filtered and the filtrate concentrated *in vacuo* to leave a viscous oil which was stirred with ether (200 mL) to produce a suspension. The solid was filtered and washed with ether (100 mL). The filtrate was concentrated *in vacuo* to leave a residue, which was purified by flash column chromatography, using a gradient of 0 to 20% EtOAc in isohexane as eluent, to give methyl *cis*-4-(6-chloro-5-nitropyridin-2-yloxy)cyclohexanecarboxylate as a yellow solid (9.5 g, 35 %).

To a solution of tetrabutylammonium cyanide (22 g, 82 mmol) in DMSO (80 mL) at 0 °C was added hexafluorobenzene (9.5 mL, 82 mmol) dropwise and the resulting red brown solution was stirred at room temperature for 2.5 h. The reaction mixture was cooled to 0 ºC and methyl *cis*-4-(6-chloro-5-nitropyridin-2-yloxy)cyclohexanecarboxylate (9.5 g, 30.1 mmol) was added. The reaction mixture was stirred at room temperature for 2 mins and then water (500 mL) was added. The mixture was extracted with EtOAc (2 x 500 mL) and the combined organic extracts were washed with brine (200 mL) and concentrated *in vacuo* to leave a residue, which was purified by flash column chromatography, using a gradient of 0 to 30% EtOAc in isohexane as eluent, to give methyl *cis*-4-(6-fluoro-5-nitropyridin-2-yloxy)-cyclohexanecarboxylate as a yellow solid (6.8 g, 76 %).

Following the remainder of the reaction sequence for **16**, using analogous procedures and using 2,4,5-trifluorophenyl isothiocyanate in place of 3,4-difluorophenyl isothiocyanate provided, after crystallisation from ethanol, the title compound as a white crystalline solid; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 1.65 – 1.92 (8 H, m), 2.39 (1 H, s), 4.96 – 5.07 (1 H, m), 6.81 (1 H, d, *J* 8.4), 7.67 – 7.76 (1 H, m), 7.87 – 7.95 (1 H, m), 8.16 (1 H, dt, *J* 12.1, 8.1), 10.77 (1

H, s), 11.06 (1 H, s), 12.09 (1 H, s). HRMS (ESI) *m/z* calcd for $C_{21}H_{18}F_4N_5O_5$ $[M + H]^+$ 496.1244; found 496.1230.

***cis*-4-(5-(5-(3,4-Difluorophenylamino)-1,3,4-oxadiazole-2-carboxamido)-6-fluoropyridin-2-yloxy)cyclohexanecarboxylic acid (27).** Following an analogous procedure for **28**, using 3,4-difluorophenyl isothiocyanate in place of 2,4,5-trifluorophenyl isothiocyanate provided the title compound as a white solid; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 1.67 - 1.84 (8H, m), 2.37 - 2.40 (1H, m), 5.00 (1H, m), 6.80 (1H, d), 7.33 - 7.36 (1H, m), 7.43 - 7.51 (1H, m), 7.66 - 7.71 (1H, m), 7.87 - 7.92 (1H, m), 10.77 (1H, s), 11.23 (1H, s), 12.09 (1H, s). MS (ESI) *m/z* $C_{21}H_{19}F_3N_5O_5$ $[M + H]^+$ found 478.2.

***cis*-4-(4-Fluoro-5-(5-(2,4,5-trifluorophenylamino)-1,3,4-oxadiazole-2-carboxamido)-pyridin-2-yloxy)cyclohexanecarboxylic acid (29).** Ammonia (74.0 mL, 3420 mmol) was condensed into THF (170 mL) at -78 °C. Potassium *tert*-butoxide (24.0 g, 213 mmol) was added and the reaction mixture warmed to -35 °C. *tert*-Butyl hydroperoxide (5.5 M in decane, 16.3 mL, 89.7 mmol) was added dropwise to 4-chloro-3-nitropyridine (13.6 g, 85.5 mmol) in THF (200 mL) at 0 ºC over 5 mins. The resulting solution was added slowly to the other flask and the mixture stirred at -35 °C for 1.5 h. A saturated aqueous solution of NH_4Cl (50 mL) was added and the reaction mixture warmed to room temperature over 16 h. The reaction mixture was concentrated *in vacuo* and the brown precipitate filtered and washed with cold water to leave a solid. The solid was dried under vacuum for 16 h to give 4-chloro-5-nitropyridin-2-ol as a yellow solid (14.7 g, 84 mmol, 98 %).

Diisopropyl azodicarboxylate (9.9 mL, 50.1 mmol) was added to a stirred solution of 4-chloro-5-nitropyridin-2-ol (7.0 g, 40.1 mmol) and triphenylphosphine (15.8 g, 60.2 mmol) in THF (180 mL). The reaction mixture was stirred at room temperature for 10 mins and then methyl *cis*-4-hydroxycyclohexanecarboxylate (6.34 g, 40.1 mmol) in THF (45 mL) was added and the resulting solution was stirred at room temperature for 48 h. The mixture was concentrated *in vacuo* to leave a residue, which was purified by flash column chromatography, using a gradient of 0 to 20% EtOAc in isohexane as eluent, to give methyl *cis*- 4-(4-chloro-5-nitropyridin-2-yloxy)cyclohexanecarboxylate as a solid (2.9 g, 23 %).

A solution of 1M tetrabutylammonium fluoride in THF (6.4 mL, 6.4 mmol) was added to a stirred solution of methyl *cis*-4-(4-chloro-5-nitropyridin-2-yloxy)cyclohexanecarboxylate (1.0 g, 3.2 mmol) in DMF (6 mL). The reaction mixture was stirred at room temperature for 10 mins and then EtOAc (100 mL) was added. The mixture was extracted with saturated brine (3 x 75 mL) and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a residue, which was purified by flash column chromatography, using a

gradient of 0 to 20% EtOAc in isohexane as eluent, to give methyl *cis*-4-(4-fluoro-5-nitropyridin-2-yloxy)cyclohexanecarboxylate (0.28 g, 30 %) as a pale yellow solid. Following the remainder of the reaction sequence for **16**, using analogous procedures and using 2,4,5-trifluorophenyl isothiocyanate in place of 3,4-difluorophenyl isothiocyanate provided, after crystallisation from ethanol, the title compound as a white crystalline solid; 1H NMR (400 MHz, DMSO-*d*6) δ 1.66 - 1.90 (8H, m), 2.36 - 2.40 (1H, m), 5.13 - 5.16 (1H, m), 6.87 (1H, d), 7.66 - 7.73 (1H, m), 8.11 - 8.17 (1H, m), 8.20 (1H, d), 10.84 (1H, s), 11.07 (1H, s), 12.09 (1H, s); MS (ESI) *m/z* $C_{21}H_{18}F_4N_5O_5$ $[M + H]^+$ found 496.3.

PK-PD Analyses. A direct response PK/PD model (Emax model) was used to fit the PK/PD data showing a clear correlation between compound levels in plasma and an effect in the oral lipid tolerance test. PK/PD parameters for the model fit are shown in Table 4. There was good agreement between the rat microsome *in vitro* IC_{50} (0.9 nM) and the *in vivo* generated free IC_{50} (0.0002 uM).

Table 4. PK/PD parameters for model fit for **26** in the rat oral lipid tolerance test.

Parameter	**Estimate**	**Units**	**Stderr%**
IC_{50}	0.0002	uM	43
E0	4.9	mM	9.2
Imax	4.1	mM	12

$$E = E0 - \frac{I_{max} \times C}{IC_{50} + C}$$

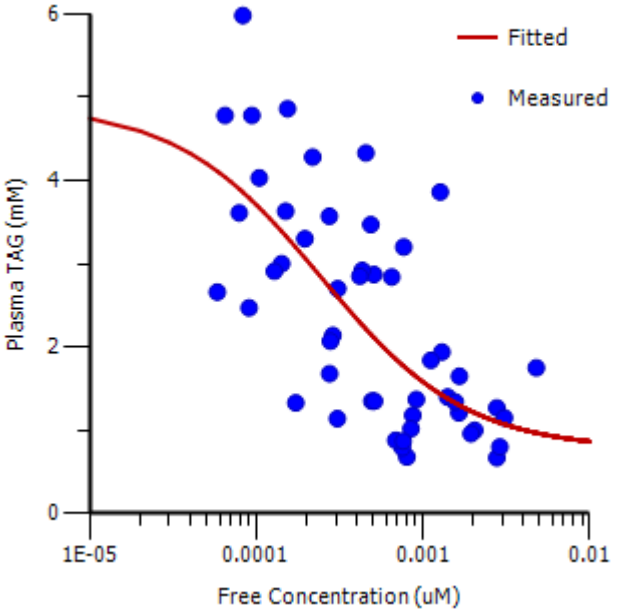

Fig. 4 PK/PD analysis showing the relationship between plasma triglycerides (TAG) and free compound levels in plasma for **26** in a rat oral lipid tolerance test. A direct response (Emax) model was used to fit the PK/PD data.