Supporting Information

Discovery and optimization of efficacious neutral 4-amino-6-biphenyl-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5-one diacylglycerol acyl transferase-1 (DGAT1) inhibitors

Contents:

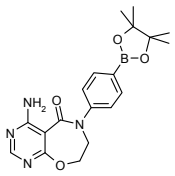
Methods S1. Procedures and characterisation for compounds 14-43 (key compounds 2, 3 and 13 are in experimental of main manuscript)

(R)-4-Amino-6-(2'-chloro-4'-(2-(3-hydroxypyrrolidin-1-yl)-2-oxoethyl)biphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **14**. Made in a similar manner to compound **3** (HATU coupling with acid **2**) to afford the title compound **14** (61 mg, 35%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 1.72 - 1.99 (2H, m), 3.16 - 3.28 (1H, m), 3.31 - 3.45 (2H, m), 3.58 - 3.71 (3H, m), 4.05 (2H, t), 4.29 (1H, d), 4.63 (2H, t), 4.90 - 5.02 (1H, m), 7.29 (1H, d), 7.37 (1H, d), 7.45 (1H, d), 7.46 - 7.51 (4H, m), 7.62 (2H, s), 8.18 (1H, s); m/z MH^+ = 494.

4-Amino-6-(2'-chloro-4'-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)biphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **15**. Made in a similar manner to compound **3** (HATU coupling with acid **2**) to afford the title compound **15** (16.5 mg, 10%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 3.49 (2H, s), 3.59 (1H, dd), 3.94 (1H, dd), 4.05 (3H, t), 4.37- 4.43 (1H, m), 4.46 (1H, dd), 4.61 - 4.65 (2H, m), 5.71 (1H, d), 7.29 (1H, dd), 7.37 (1H, d), 7.45 (1H, d), 7.45 - 7.52 (4H, m), 7.62 (2H, s), 8.18 (1H, s); m/z MH^+ = 480.

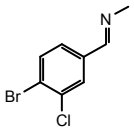
4-Amino-6-(2'-chloro-4'-(2-oxo-2-(3-oxopiperazin-1-yl)ethyl)biphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **16**. Made in a similar manner to compound **3** (HATU coupling with acid **2**) to afford the title compound **16** (92 mg, 51%) as an off white solid; ^{1}H NMR (400 MHz, DMSO) 3.22 (2H, d), 3.63 (1H, t), 3.72 (1H, t), 3.82 (2H, d), 3.96 (1H, s), 4.05 (2H, t), 4.13 (1H, s), 4.63 (2H, t), 7.26 - 7.29 (1H, m), 7.37 (1H, d), 7.43 - 7.48 (1H, m), 7.49 (4H, s), 7.62 (2H, s), 8.03 (1H, t), 8.18 (1H, s); m/z MH^+ = 507.

4-Amino-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one



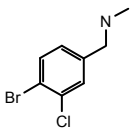
General method A: 4-Amino-6-(4-bromophenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(*6H*)-one **7** (470 mg, 1.40 mmol), potassium acetate (385 mg, 3.93 mmol) and bis(pinacolato)diboron (445 mg, 1.75 mmol) were suspended in 1,4-dioxane (12 mL) and sealed into a microwave tube. The tube was degassed under vacuum and the atmosphere replaced with nitrogen. The mixture was treated with $PdCl_2$(dppf)-CH_2Cl_2 adduct (69 mg, 0.08 mmol) and the reaction was heated at 130°C for 40 min and cooled to rt. The reaction mixture was evaporated to dryness and redissolved in DCM and washed with water. The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 100% EtOAc in isohexane followed by 0 to 20% MeOH in EtOAc, to afford the title compound (314 mg, 59%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) 1.35 (12H, s), 4.02 (2H, dd), 4.69 (2H, dd), 5.63 (1H, s), 7.26 - 7.33 (2H, m), 7.89 (2H, d), 8.14 (1H, s), 8.28 (1H, s); m/z MH^+ = 383.

N-(4-bromo-3-chlorobenzylidene)methanamine



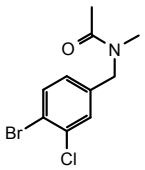
Sodium triacetoxyborohydride (4.81 g, 22.7 mmol) was added in one portion to 4-bromo-3-chlorobenzaldehyde (3.32 g, 15.1 mmol), acetic acid (0.87 mL, 15.1 mmol) and methylamine (2 M in THF) (37.8 mL, 75.6 mmol) in THF (80 mL) at rt. The resulting mixture was stirred at rt for 4 h. The reaction mixture was concentrated to half volume, quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with sat. brine, dried over Na_2SO_4, filtered and evaporated to afford the title compound (3.48 g, 99%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 3.51 (3H, d), 7.44 (1H, dd), 7.63 - 7.68 (1H, m), 7.81 (1H, d), 8.19 (1H, d).

1-(4-Bromo-3-chlorophenyl)-N-methylmethanamine



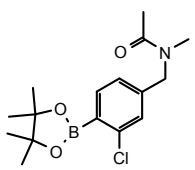
Sodium borohydride (0.57 g, 15.0 mmol) was added in one portion to *N*-(4-bromo-3-chlorobenzylidene)methanamine (3.48 g, 15.0 mmol) in MeOH (150 mL) at rt. The resulting mixture was stirred for 2 h. The reaction mixture was concentrated to half volume and the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with EtOAc (water was added to dissolve formed precipitate). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The resulting crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7 M NH_3/MeOH to afford the title compound (2.43 g, 69%) as a golden oil; ^{1}H NMR (400 MHz, $CDCl_3$) 1.37 (1H, s), 2.43 (3H, s), 3.69 (2H, s), 7.08 (1H, dd), 7.44 (1H, d), 7.53-7.56 (1H, m); m/z MH^+ = 234, 236.

N-[(4-bromo-3-chloro-phenyl)methyl]-N-methyl-acetamide



Made in a similar manner to compound **3** (HATU coupling) from acetic acid and 1-(4-bromo-3-chlorophenyl)-*N*-methylmethanamine to afford the title compound (0.190 g, 40%) as a brown gum; ^{1}H NMR (400 MHz, $CDCl_3$) 2.15 (3H, d), 2.94 (3H, d), 4.49 (2H, d), 6.97 (1H, ddd), 7.30 (1H, dd), 7.52 - 7.64 (1H, m); m/z MH^+ = 276, 278.

N-(3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-N-methylacetamide

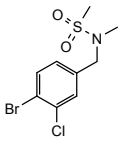


Made according to general method A from N-[(4-bromo-3-chloro-phenyl)methyl]-N-methyl-acetamide to afford the title compound (0.220 g, 99%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$)

1.25 - 1.29 (12H, m), 2.08-2.18 (3H, m), 2.93 (3H, dd), 4.47 4.58 (2H, m), 6.98 7.23 (2H, m), 7.66 (1H, dd); m/z MH^+ = 324.

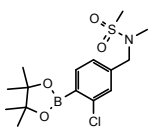
N-((4'-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)-2-chlorobiphenyl-4-yl)methyl)-N-methylacetamide **18.** Made in a similar manner to compound **13** (Suzuki coupling) from *N*-(3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-*N*-methylacetamide and compound **7** to afford the title compound (0.028 g, 11%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 2.05-2.11 (3H, m), 2.91 (3H, d), 4.05 (2H, t), 4.53 (2H, s), 4.61 4.66 (2H, m), 7.27 (1H, t), 7.38 7.50 (6H, m), 7.62 (2H, s), 8.18 (1H, s); m/z MH^+ = 452.

N-(4-Bromo-3-chlorobenzyl)-N-methylmethanesulfonamide



Pyridine (0.414 mL, 5.12 mmol) was added to 1-(4-bromo-3-chlorophenyl)-*N*-methylmethanamine (0.3 g, 1.28 mmol) and methanesulfonyl chloride (0.149 mL, 1.92 mmol) in DCM (5 mL) at rt. The reaction mixture was stirred at rt for 20 h. The reaction mixture was diluted with DCM, washed sequentially with 1 M aq. citric acid and sat. brine (20 mL) and the organic layer was filtered through a phase separation tube and concentrated. The resulting crude product was purified by flash silica chromatography, elution gradient 5 to 40% EtOAc in isohexane to afford the title compound (0.270 g, 68%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 2.78 (3H, s), 2.87 (3H, s), 4.24 (2H, s), 7.13 (1H, dd), 7.45 (1H, d), 7.59 7.62 (1H, m); m/z $(M\text{-}SO_2MeNMe)^+$ = 205.

N-(3-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-N-methylmethanesulfonamide

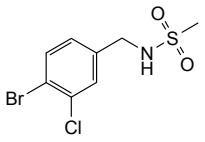


Made according to general method A from *N*-(4-Bromo-3-chlorobenzyl)-*N*-methylmethanesulfonamide to afford the title compound (0.166 g, 53%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 1.37 (12H, s), 2.75 (3H, s), 2.81 2.86 (3H, m), 4.29 (2H, d), 7.21-7.25 (1H, m), 7.35 (1H, t), 7.68 (1H, d); m/z MH^+ = 360.

N-((4'-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)-2-chlorobiphenyl-4-yl)methyl)-N-methylmethanesulfonamide **20.** Made in a similar manner to compound **13** (Suzuki coupling) from N-(3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-N-methylmethanesulfonamide and compound **7** to afford the title compound (0.046 g, 24%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 2.74 (3H, s), 3.00 (3H, s), 4.03 - 4.08 (2H, m), 4.30 (2H, s), 4.60 - 4.66 (2H, m), 7.40 (1H, dd), 7.44 - 7.54 (6H, m), 7.62 (2H, s), 8.18 (1H, s); m/z MH^+ = 488.

4-Amino-6-(2',4'-dichlorobiphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **32**. Made in a similar manner to compound **13** from 2,4-dichlorophenylboronic acid and compound **7** to afford the title compound (241 mg, 67%) as a beige solid; ^{1}H NMR (400 MHz, DMSO) 4.10-4.14 (2H, m), 4.68 4.72 (2H, m), 7.54 (1H, d), 7.57 (4H, s), 7.58 7.62 (1H, m), 7.69 (2H, s), 7.82 (1H, d), 8.25 (1H, s); m/z MH^+ = 401.

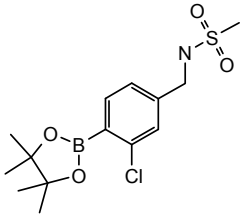
N-(4-bromo-3-chlorobenzyl)methanesulfonamide



Methanesulfonyl chloride (0.097 mL, 1.25 mmol) was added portionwise to (4-bromo-3-chlorophenyl)methanamine (250 mg, 1.13 mmol) and pyridine (0.275 mL, 3.40 mmol) in DCM (5 mL) at rt. The resulting solution was stirred overnight. The reaction mixture was concentrated and diluted with EtOAc and washed with water. The organic layer was passed through a phase separating cartridge and evaporated to afford the title compound (350 mg, 103%); ^{1}H NMR (400 MHz, $CDCl_3$)

2.93 (3H, s), 4.27 (2H, d), 4.68 (1H, s), 7.13 (1H, dd), 7.46 (1H, d), 7.59 7.63 (1H, m); m/z $[M-H]^-$ = 298.

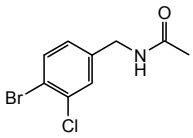
N-(3-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)methanesulfonamide



Made according to general method A from *N*-(4-bromo-3-chlorobenzyl)methanesulfonamide to afford the title compound (0.252 g, 89%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 1.37 (12H, s), 2.88 (3H, s), 4.30 (2H, d), 4.62 (1H, s), 7.22 (1H, dd), 7.34 (1H, d), 7.69 (1H, d); m/z $[M-H]^-$ = 344.

N-((4'-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)-2-chlorobiphenyl-4-yl)methyl)methanesulfonamide **21**. Made in a similar manner to compound **13** (Suzuki coupling) from N-(3-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)methanesulfonamide and compound **7** to afford the title compound (61 mg, 18%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 2.94 (3H, s), 4.01 4.09 (2H, m), 4.22 (2H, d), 4.60 4.66 (2H, m), 7.37 7.45 (2H, m), 7.48 (4H, d), 7.55 (1H, s), 7.62 (3H, s), 8.18 (1H, s); m/z MH^+ = 474.

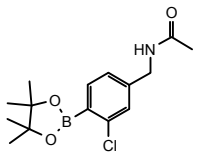
N-(4-bromo-3-chlorobenzyl)acetamide



Acetyl chloride (0.081 mL, 1.13 mmol) was added portionwise to (4-bromo-3-chlorophenyl)methanamine (250 mg, 1.13 mmol) and iPr_2NEt (0.592 mL, 3.40 mmol) in DCM (5 mL) at rt. The resulting solution was stirred overnight. The reaction mixture was concentrated and diluted with EtOAc and washed with water. The organic layer was passed through a phase separating

cartridge and evaporated to afford the title compound (300 mg, 101%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) 2.04 (3H, s), 4.37 (2H, d), 5.79 (1H, s), 7.04 (1H, dd), 7.37 (1H, d), 7.54-7.58 (1H, m); m/z MH^+ = 262, 264, 266.

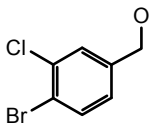
N-(3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)acetamide



Made according to general method A from N-(4-bromo-3-chlorobenzyl)acetamide to afford the title compound (0.270 g, 79%) as a colourless solid; ^{1}H NMR (400 MHz, DMSO) 1.29 (12H, d), 1.87 (3H, s), 4.24 (2H, d), 7.17 - 7.22 (1H, m), 7.26 - 7.30 (1H, m), 7.57 (1H, d), 8.35 (1H, t); m/z MH^+ = 310.

N-((4'-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)-2-chlorobiphenyl-4-yl)methyl)acetamide **19**. Made in a similar manner to compound **13** from *N*-(3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)acetamide and compound **7** to afford the title compound (0.080 g, 25%) as a colourless solid; ^{1}H NMR (400 MHz, DMSO) 1.83 (3H, s), 3.95-4.01 (2H, m), 4.22 (2H, d), 4.53 4.59 (2H, m), 7.23 (1H, dd), 7.32 (1H, d), 7.37 (1H, d), 7.41 (4H, s), 7.55 (2H, s), 8.11 (1H, s), 8.34 (1H, t); m/z MH^+ = 438.

(4-Bromo-3-chloro-phenyl)methanol

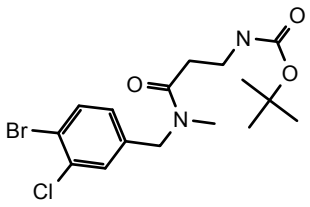


Borane-THF complex (1 M in THF, 191 mL, 191 mmol) was added dropwise to 4-bromo-3-chlorobenzoic acid (15 g, 63.7 mmol) in THF (100 mL) at 0°C over a period of 40 min. The resulting solution was stirred at rt for 18 h. The reaction was quenched with MeOH (50 mL) then 2 M aq. HCl in diethyl ether and then concentrated *in vacuo*. The residue was taken up in EtOAc and

sat. aq. $NaHCO_3$ and stirred for 1 h. The organic layer was washed with sat. brine, dried over $MgSO_4$, filtered and concentrated to afford the title compound (14.3 g, 101%) as a white solid; ^1H NMR (400 MHz, DMSO) 4.30 (2H, s), 5.16 (1H, s), 7.04 (1H, dd), 7.36 (1H, d), 7.53 (1H, dd); m/z $[M-H]^-$ = 221.

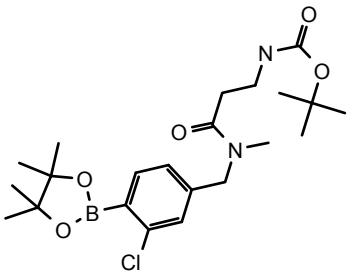
4-Amino-6-(2'-chloro-4'-(hydroxymethyl)biphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **30**. Made in a similar manner to compound **13** (Suzuki coupling) from 4-amino-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one and (4-bromo-3-chloro-phenyl)methanol to afford the title compound (61 mg, 42%) as a pale yellow solid; ^1H NMR (400 MHz, DMSO) 4.06 (2H, dd), 4.55 (2H, d), 4.58 - 4.68 (2H, m), 5.34 (1H, t), 7.32 - 7.43 (2H, m), 7.45 - 7.54 (5H, m), 7.62 (2H, s), 8.18 (1H, s); m/z MH^+ = 397.

tert-Butyl 3-((4-bromo-3-chlorobenzyl)(methyl)amino)-3-oxopropylcarbamate



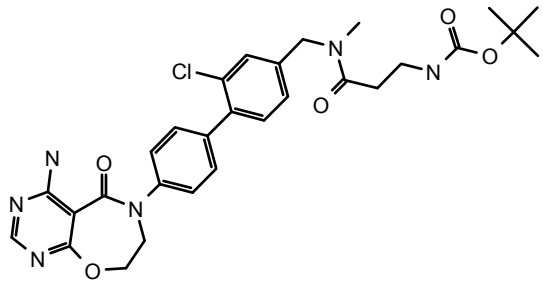
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.778 g, 2.05 mmol) was added portionwise to 1-(4-bromo-3-chlorophenyl)-N-methylmethanamine (0.4 g, 1.71 mmol), 3-(tert-butoxycarbonylamino)propanoic acid (0.323 g, 1.71 mmol) and DIPEA (1.188 ml, 6.82 mmol) in DMF (10 ml) at rt. The resulting solution was stirred for 20 h. The reaction mixture was diluted with EtOAc (50 mL), and washed sequentially with sat. aq. $NaHCO_3$, sat. brine and water. The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0-5% MeOH in DCM, to afford the title compound (0.475 g, 69%) as a brown oil; ^1H NMR (400 MHz, $CDCl_3$) 1.43 (9H, d), 2.48 - 2.61 (2H, m), 2.91 - 2.96 (3H, m), 3.42 - 3.50 (2H, m), 4.43 - 4.53 (2H, m), 5.27 (1H, s), 6.86 - 7.02 (1H, m), 7.22 - 7.32 (1H, m), 7.53 - 7.62 (1H, m); m/z $[M-Boc]^+$ = 307, 309.

tert-Butyl N-[3-[[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl-methyl-amino]-3-oxo-propyl]carbamate



Made according to general method A from tert-butyl 3-((4-bromo-3-chlorobenzyl)(methyl)amino)-3-oxopropylcarbamate to afford the title compound (0.300 g, 57%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 1.36 (12H, d), 1.43 (9H, d), 2.45 - 2.61 (2H, m), 2.86 - 2.96 (3H, m), 3.40 - 3.51 (2H, m), 4.46 - 4.57 (2H, m), 5.33 (1H, s), 6.98 - 7.10 (1H, m), 7.12 - 7.22 (1H, m), 7.66 (1H, dd); m/z MH^+ = 453.

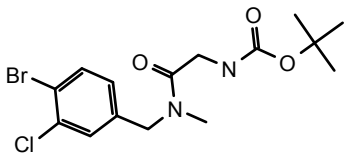
tert-Butyl N-[3-[[4-[4-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6-yl)phenyl]-3-chloro-phenyl]methyl-methyl-amino]-3-oxo-propyl]carbamate



Made in a similar manner to compound **13** (Suzuki coupling) from compound **7** and tert-butyl N-[3-[[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl-methyl-amino]-3-oxo-propyl]carbamate to afford the title compound (0.228 g, 94%) as a pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) 1.42 (9H, t), 2.53 - 2.67 (2H, m), 3.00 (3H, d), 3.49 (2H, d), 4.06 - 4.13 (2H, m), 4.58 (2H, d), 4.71 - 4.78 (2H, m), 5.34 (1H, s), 5.71 (1H, s), 7.09 - 7.21 (1H, m), 7.30 - 7.40 (4H, m), 7.53 (2H, d), 8.21 (1H, s), 8.30 (1H, s); m/z MH^+ = 581.

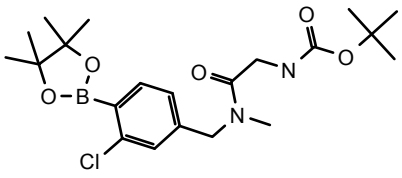
3-Amino-N-((4'-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)-2-chlorobiphenyl-4-yl)methyl)-N-methylpropanamide **25**. Trifluoroacetic acid (0.292 mL, 3.79 mmol) was added to tert-butyl-N-[3-[[4-[4-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6-yl)phenyl]-3-chloro-phenyl]methyl-methyl-amino]-3-oxo-propyl]carbamate (0.22 g, 0.38 mmol) in DCM (10 mL) at rt. The resulting solution was stirred at rt for 24 h. The reaction mixture was evaporated, and the residue was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH, evaporated to dryness and then triturated with hot EtOH to afford the title compound (0.098 g, 54%) as a white solid ; ^{1}H NMR (400 MHz, DMSO, 100°C) 1.52 (2H, s), 2.55 - 2.60 (2H, m), 2.85 (2H, t), 2.97 (3H, s), 4.00 - 4.10 (2H, m), 4.59 (2H, s), 4.62 - 4.70 (2H, m), 7.28 (1H, d), 7.33 - 7.52 (8H, m), 8.17 (1H, s); m/z MH^+ = 481.

tert-Butyl N-[2-[(4-bromo-3-chloro-phenyl)methyl-methyl-amino]-2-oxo-ethyl]carbamate



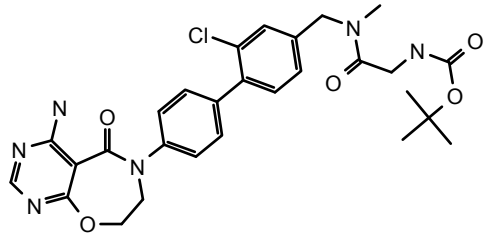
Made in a similar manner to tert-butyl 3-((4-bromo-3-chlorobenzyl)(methyl)amino)-3-oxopropylcarbamate (HATU coupling) to afford the title compound (0.640 g, 96%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) 1.43 - 1.48 (9H, m), 2.84 (3H, d), 4.01 (2H, d), 4.47 (2H, d), 5.49 (1H, s), 6.88 - 7.02 (1H, m), 7.33 (1H, d), 7.59 (1H, dd); m/z $[M\text{-}Boc]^+$ = 291, 293.

tert-butyl N-[2-[[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl-methyl-amino]-2-oxo-ethyl]carbamate



Made according to general method A from tert-butyl N-[2-[(4-bromo-3-chloro-phenyl)methyl-methyl-amino]-2-oxo-ethyl]carbamate to afford the title compound (0.580 g, 82%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 1.37 (12H, d), 1.43 - 1.48 (9H, m), 2.82 - 2.99 (3H, m), 3.98 - 4.03 (2H, m), 4.42 - 4.59 (2H, m), 5.54 (1H, d), 6.99 - 7.11 (1H, m), 7.17 (1H, d), 7.67 (1H, dd); m/z MH^+ = 439.

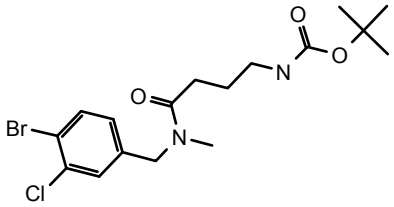
tert-butyl N-[2-[[4-[4-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6-yl)phenyl]-3-chloro-phenyl]methyl-methyl-amino]-2-oxo-ethyl]carbamate



Made in a similar manner to compound **13** (Suzuki coupling) to afford the title compound (0.373 g, 82%) as a pale yellow foam; ^{1}H NMR (400 MHz, $CDCl_3$) 1.46 (9H, d), 3.00 (3H, d), 4.01 - 4.07 (2H, m), 4.07 - 4.12 (2H, m), 4.56 (2H, d), 4.70 - 4.77 (2H, m), 5.56 (1H, s), 5.66 (1H, s), 7.10 - 7.23 (1H, m), 7.29 - 7.40 (4H, m), 7.51 - 7.57 (2H, m), 8.20 (1H, s), 8.31 (1H, s); m/z MH^+ = 567.

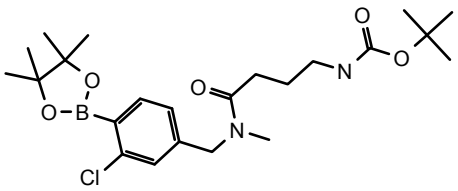
2-Amino-N-((4'-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)-2-chlorobiphenyl-4-yl)methyl)-N-methylacetamide **24**. Made in a similar manner to **25** (TFA deprotection) to afford the title compound (0.185 g, 61%) as a white solid; ^{1}H NMR (400 MHz, DMSO, 100°C) 1.61 (2H, s), 2.94 (3H, s), 3.44 (2H, s), 4.03 - 4.07 (2H, m), 4.58 (2H, s), 4.63 - 4.67 (2H, m), 7.28 (1H, d), 7.36 - 7.54 (8H, m), 8.17 (1H, s); m/z MH^+ = 467.

tert-Butyl 4-((4-bromo-3-chlorobenzyl)(methyl)amino)-4-oxobutylcarbamate



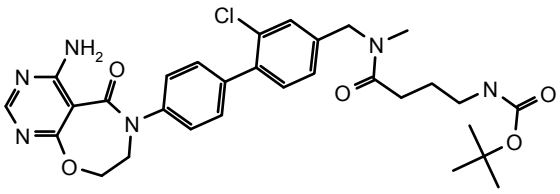
Made in a similar manner to tert-butyl 3-((4-bromo-3-chlorobenzyl)(methyl)amino)-3-oxopropylcarbamate (HATU coupling) to afford the title compound (0.330 g, 46%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) 1.43 (9H, s), 1.78 - 1.94 (2H, m), 2.33 - 2.47 (2H, m), 2.94 (3H, s), 3.09 - 3.24 (2H, m), 4.49 (2H, s), 4.84 (1H, s), 7.01 (1H, dd), 7.33 (1H, d), 7.55 (1H, dd); m/z MH^+ = 419, 421.

tert-butyl N-[4-[[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl-methyl-amino]-4-oxo-butyl]carbamate



Made according to general method A from tert-butyl 4-((4-bromo-3-chlorobenzyl)(methyl)amino)-4-oxobutylcarbamate to afford the title compound (0.230 g, 63%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 1.22 - 1.37 (12H, m), 1.43 (9H, d), 1.79 - 1.93 (2H, m), 2.32 - 2.47 (2H, m), 2.87 - 2.97 (3H, m), 3.19 (2H, dt), 4.41 - 4.59 (2H, m), 4.81 (1H, s), 6.98 - 7.16 (1H, m), 7.19 - 7.26 (1H, m), 7.54 - 7.71 (1H, m); m/z MH^+ = 467.

tert-Butyl N-[4-[[4-[4-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6-yl)phenyl]-3-chloro-phenyl]methyl-methyl-amino]-4-oxo-butyl]carbamate

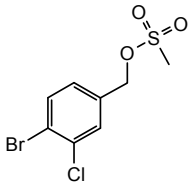


Prepared in a similar manner to compound **13** (Suzuki coupling) from compound **7** and tert-butyl N-[4-[[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl-methyl-amino]-4-oxo-butyl]carbamate to afford the title compound (0.060 g, 26%) as a pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) 1.41 - 1.46 (9H, m), 1.86 - 1.92 (2H, m), 2.44 (2H, dt), 3.00 (3H, s), 3.21 (2H, dt),

4.06 - 4.11 (2H, m), 4.54 - 4.62 (2H, m), 4.71 - 4.76 (2H, m), 5.71 (1H, s), 7.10 - 7.22 (1H, m), 7.29 - 7.39 (4H, m), 7.50 - 7.56 (3H, m), 8.17 (1H, s), 8.30 (1H, s); m/z MH^+ = 595.

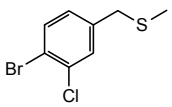
4-Amino-N-((4'-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)-2-chlorobiphenyl-4-yl)methyl)-N-methylbutanamide **26**. Made in a similar manner to compound **25** (TFA deprotection) from tert-butyl N-[4-[[4-[4-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6-yl)phenyl]-3-chloro-phenyl]methyl-methyl-amino]-4-oxo-butyl]carbamate to afford the title compound (0.151 g, 67%) as a white solid; ^{1}H NMR (400 MHz, DMSO, 100°C) 1.44 - 1.57 (2H, m), 1.63 - 1.72 (2H, m), 2.43 (2H, t), 2.62 (2H, t), 2.92 (3H, s), 4.00 - 4.08 (2H, m), 4.58 (2H, s), 4.62 - 4.67 (2H, m), 7.27 (1H, d), 7.36 - 7.55 (8H, m), 8.17 (1H, s); m/z MH^+ = 495.

4-Bromo-3-chlorobenzyl methanesulfonate



Methanesulfonyl chloride (1.660 mL, 21.36 mmol) was added dropwise to (4-bromo-3-chlorophenyl)methanol (4.3 g, 19.41 mmol) and triethylamine (3.38 mL, 24.27 mmol) in DCM (50 mL) cooled to 0°C. The resulting solution was stirred at 0°C for 1 h. The reaction mixture was then washed with water and sat. aq. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the title compound (5.36 g, 92%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 2.93 (3H, s), 5.09 (2H, s), 7.07 - 7.14 (1H, m), 7.44 (1H, t), 7.55 - 7.65 (1H, m).

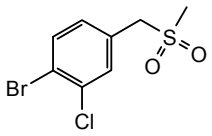
(4-Bromo-3-chlorobenzyl)(methyl)sulfane



Sodium methanethiolate (6.68 mL, 22.03 mmol) was added to a stirred solution of 4-bromo-3-chlorobenzyl methanesulfonate (3.3 g, 11.02 mmol) in THF (50 mL) at rt, then was stirred for 30

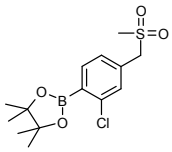
min. The reaction mixture was diluted with EtOAc (100 mL) and water (50 mL). The organic layer was separated, washed with sat. aq. $NaHCO_3$ then dried over $MgSO_4$, filtered and evaporated to afford the title compound (2.65 g, 96%) as a colourless oil which solidified on standing; ^{1}H NMR (400 MHz, $CDCl_3$) 1.92 (3H, s), 3.52 (2H, s), 7.00 (1H, dd), 7.34 (1H, d), 7.44 - 7.50 (1H, m).

1-Bromo-2-chloro-4-(methylsulfonylmethyl)benzene



3-Chloroperoxybenzoic acid (2.59 g, 11.54 mmol) was added to a stirred solution of (4-bromo-3-chlorobenzyl)(methyl)sulfane (1.32 g, 5.25 mmol) in DCM (30 mL) at 0°C. The solution was allowed to warm to rt and stirred for 30 mins. The reaction was quenched with aq. sodium thiosulphate. The organic layer was separated and washed with sat. aq. $NaHCO_3$ and concentrated *in vacuo* to give crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% EtOAC/heptane to afford the title compound (0.140 g, 9%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) 2.83 (3H, s), 4.19 (2H, s), 7.20 (1H, dd), 7.52 (1H, d), 7.68 (1H, d).

2-(2-Chloro-4-(methylsulfonylmethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

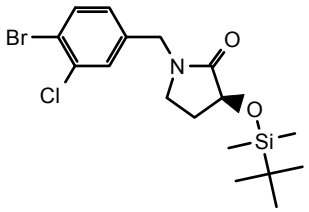


Made according to general method A from 1-bromo-2-chloro-4-(methylsulfonylmethyl)benzene to afford the title compound (80 mg, 49%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 1.37 (12H, s), 2.74 (3H, s), 4.20 (2H, s), 7.28 - 7.32 (1H, m), 7.39 - 7.43 (1H, m), 7.73 (1H, d).

4-Amino-6-(2'-chloro-4'-(methylsulfonylmethyl)biphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **17**. Made in a similar manner to compound **13** (Suzuki coupling) from compound **7** and 2-(2-chloro-4-(methylsulfonylmethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-

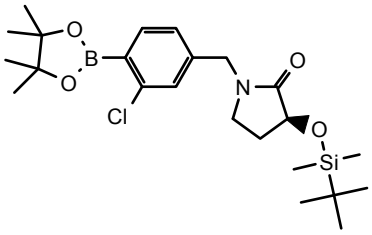
dioxaborolane to afford the title compound (6.3 mg, 8%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 2.98 (3H, s), 3.97 4.06 (2H, m), 4.58 (2H, s), 4.62 4.68 (2H, m), 7.42 7.56 (6H, m), 7.62 (3H, s), 8.18 (1H, s); m/z MH^+ = 459.

(S)-1-(4-bromo-3-chlorobenzyl)-3-(tert-butyldimethylsilyloxy)pyrrolidin-2-one



Sodium hydride (0.176 g, 4.41 mmol) was added to (S)-3-(tert-butyldimethylsilyloxy)pyrrolidin-2-one (Zheng et al, Org. Lett. 7 (2005) *553-556*) (0.863 g, 4.01 mmol) in DMF (10 mL) at 0°C. The resulting solution was stirred at rt for 30 mins and cooled to 0°C. 4-bromo-3-chlorobenzyl methanesulfonate (1.2 g, 4.01 mmol) was added and the reaction stirred at rt for 2 h. The residue was poured onto ice/water, then extracted twice with ethyl acetate. The combined organic layers were washed with sat. brine, dried over Na_2SO_4, filtered and evaporated. The resulting crude product was purified by flash silica chromatography, elution gradient 10 to 30% EtOAc in isohexane, to afford the title compound (0.810 g, 48%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 0.16 (3H, s), 0.19 (3H, s), 0.93 (9H, s), 1.92 (1H, dd), 2.29 (1H, dd), 3.07 - 3.15 (1H, m), 3.23 - 3.30 (1H, m), 4.36 (3H, dt), 7.01 (1H, dd), 7.33 (1H, d), 7.56 (1H, d); m/z MH^+ = 418, 420.

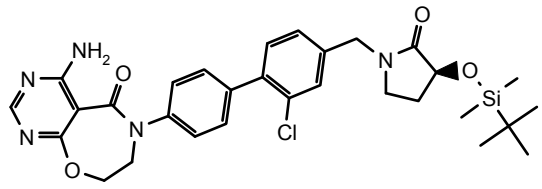
(S)-3-(tert-butyldimethylsilyloxy)-1-(3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)pyrrolidin-2-one



Made according to general method A from (S)-1-(4-bromo-3-chlorobenzyl)-3-(tert-butyldimethylsilyloxy)pyrrolidin-2-one to afford the title compound (0.130 g, 15%) as a yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$) -0.03 (3H, s), -0.01 - 0.04 (3H, m), 0.72 - 0.75 (9H, m), 1.17 (12H, s), 1.62 - 1.75 (1H, m), 2.02 - 2.15 (1H, m), 2.89 (1H, ddt), 3.02 (1H, ddd), 4.16 (1H, dd), 4.21 (2H, dd), 6.92 (1H, dt), 7.02 (1H, t), 7.45 (1H, d); m/z MH^+ = 466.

(S)-4-amino-6-(4'-((3-(tert-butyldimethylsilyloxy)-2-oxopyrrolidin-1-yl)methyl)-2'-chlorobiphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one

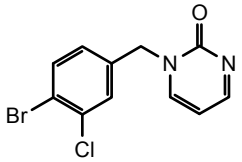


Made in a similar manner to compound **13** (Suzuki coupling) from compound **7** and (S)-3-(tert-butyldimethylsilyloxy)-1-(3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)pyrrolidin-2-one to afford the title compound (0.070 g, 40%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) -0.04 - -0.01 (3H, m), -0.01 - 0.04 (3H, m), 0.71 - 0.76 (9H, m), 1.70 - 1.79 (1H, m), 2.13 (1H, dtd), 2.99 (1H, dt), 3.07 - 3.20 (1H, m), 3.85 - 3.95 (2H, m), 4.13 - 4.21 (1H, m), 4.22 - 4.34 (2H, m), 4.52 (2H, ddd), 5.51 (1H, s), 6.90 - 7.21 (5H, m), 7.24 - 7.41 (2H, m), 7.93 (1H, d), 8.08 - 8.15 (1H, m); m/z MH^+ = 594.

(S)-4-Amino-6-(2'-chloro-4'-((3-hydroxy-2-oxopyrrolidin-1-yl)methyl)biphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **23**. 4 M HCl in 1,4-dioxane (5 mL) was added to (S)-4-amino-6-(4'-((3-(tert-butyldimethylsilyloxy)-2-oxopyrrolidin-1-yl)methyl)-2'-chlorobiphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (70 mg, 0.09 mmol) and stirred at rt for 1 h. The reaction mixture was evaporated to dryness and re-dissolved in DCM (150 mL), and washed sequentially with sat. aq. $NaHCO_3$ and sat. brine. The organic layer was isolated and evaporated. The resulting crude product was purified by flash silica chromatography, elution gradient 1 to 10% DCM in MeOH, to afford the title compound (33 mg, 78%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 2.29 (2H, d), 3.10 - 3.20 (2H, m), 3.99 - 4.08 (2H, m), 4.17 (1H, t), 4.40 (2H, q), 4.55 - 4.65 (2H, m),

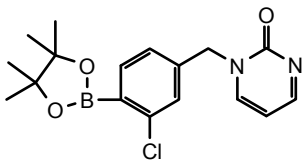
5.49 - 5.63 (1H, m), 7.26 (1H, d), 7.40 (2H, d), 7.47 (4H, s), 7.61 (2H, s), 8.16 (1H, s); m/z MH^+ = 480.

1-(4-Bromo-3-chlorobenzyl)pyrimidin-2(1H)-one



4-Bromo-3-chlorobenzyl methanesulfonate (1.2 g, 4.01 mmol) was added to pyrimidin-2-ol hydrochloride (0.637 g, 4.81 mmol) and potassium carbonate (1.384 g, 10.01 mmol) in DMF (20 mL). The resulting suspension was stirred at 80°C for 1 h. The reaction mixture was diluted with EtOAc (30 mL), and washed sequentially with water and sat. brine and evaporated. The resulting crude product was purified by flash silica chromatography, elution gradient 1 to 10% MeOH in DCM, to afford the title compound (0.690 g, 58%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 5.01 (2H, s), 6.47 (1H, dd), 7.23 (1H, dd), 7.62 (1H, d), 7.75 (1H, d), 8.36 (1H, dd), 8.57 (1H, dd); m/z MH^+ = 299, 301.

1-(3-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)pyrimidin-2(1H)-one



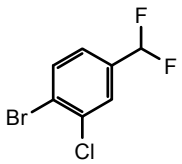
Made according to general method A from 1-(4-bromo-3-chlorobenzyl)pyrimidin-2(1H)-one to afford the title compound (0.337 g, 43%) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) 1.36 (12H, s), 5.07 (2H, s), 6.24 - 6.30 (1H, m), 7.21 (1H, dd), 7.28 - 7.35 (1H, m), 7.57 (1H, dd), 7.69 (1H, d), 8.53 - 8.63 (1H, m); m/z MH^+ = 347.

4-Amino-6-(2'-chloro-4'-((2-oxopyrimidin-1(2H)-yl)methyl)biphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **22**. Made in a similar manner to compound **13** (Suzuki coupling) from compound **7** and 1-(3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)pyrimidin-

2(1H)-one to afford the title compound (0.053 g, 12%) as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) 4.06 - 4.10 (2H, m), 4.70 - 4.77 (2H, m), 5.11 (2H, s), 5.53 - 5.79 (1H, m), 6.34 (1H, dd), 7.30 - 7.38 (4H, m), 7.47 (1H, t), 7.49 - 7.54 (2H, m), 7.69 (1H, dd), 8.03 - 8.24 (1H, m), 8.30 (1H, s), 8.63 (1H, dd); m/z MH^+ = 475.

4'-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)-2-chlorobiphenyl-4-carbonitrile **28**. Made in a similar manner to compound **13** (Suzuki coupling) from 4-amino-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one and 4-bromo-3-chlorobenzonitrile to afford the title compound (0.072 g, 37%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) 4.07 - 4.11 (2H, m), 4.72 - 4.76 (2H, m), 5.69 (1H, s), 7.39 - 7.42 (2H, m), 7.47 (1H, d), 7.51 - 7.56 (2H, m), 7.63 (1H, dd), 7.80 (1H, d), 8.15 (1H, s), 8.31 (1H, s); m/z MH^+ = 392.

1-Bromo-2-chloro-4-(difluoromethyl)benzene



Ethanol (0.053 mL, 0.91 mmol) was added to 4-bromo-3-chlorobenzaldehyde (1 g, 4.56 mmol) and Deoxo-Fluor(R) (50% in THF) (3.36 mL, 7.75 mmol) in DCM (20 mL) at rt. The resulting solution was stirred at rt for 20 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$, extracted with DCM, and the organic layer was dried over Na_2SO_4, filtered and evaporated. The resulting crude product was purified by flash alumina chromatography, elution gradient 1 to 5% EtOAc in isohexane, to afford the title compound (0.750 g, 68%) as a colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) 6.59 (1H, td), 7.23 - 7.29 (1H, m), 7.60 (1H, s), 7.72 (1H, d).

4-Amino-6-(2'-chloro-4'-(difluoromethyl)biphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **31**. Made in a similar manner to compound **13** (Suzuki coupling) from 4-amino-6-(4-

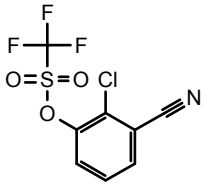
(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one and 1-bromo-2-chloro-4-(difluoromethyl)benzene to afford the title compound (146 mg, 45%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 4.03 - 4.11 (2H, m), 4.58 - 4.68 (2H, m), 7.10 (1H, t), 7.49 - 7.67 (8H, m), 7.79 (1H, s), 8.18 (1H, s); m/z MH^+ = 417.

4-Amino-6-(2'-chlorobiphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **27**. Made in a similar manner to compound **13** (Suzuki coupling) from compound **7** and 2-chlorophenylboronic acid to afford the title compound (117 mg, 40%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 3.99 - 4.10 (2H, m), 4.59 - 4.67 (2H, m), 7.37 - 7.46 (3H, m), 7.46 - 7.53 (4H, m), 7.58 (1H, dt), 7.62 (2H, s), 8.18 (1H, s); m/z MH^+ = 367.

4-Amino-6-(2',3'-dichlorobiphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **33**. Made in a similar manner to compound **13** (Suzuki coupling) from compound **7** and 2,3-dichlorophenylboronic acid to afford the title compound (88 mg, 25%) as a beige solid; ^{1}H NMR (400 MHz, DMSO) 4.03 - 4.08 (2H, m), 4.61 - 4.65 (2H, m), 7.38 - 7.42 (1H, m), 7.46 (1H, t), 7.50 (4H, s), 7.62 (2H, s), 7.66 - 7.70 (1H, m), 8.18 (1H, s); m/z MH^+ = 401.

4-Amino-6-(2',5'-dichlorobiphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **35**. Made in a similar manner to compound **13** (Suzuki coupling) from compound **7** and 2,5-dichlorophenylboronic acid to afford the title compound (268 mg, 75%) as a beige solid; ^{1}H NMR (400 MHz, DMSO) 4.03 - 4.07 (2H, m), 4.61 - 4.65 (2H, m), 7.47 - 7.54 (6H, m), 7.60 - 7.64 (3H, m), 8.18 (1H, s); m/z MH^+ = 401.

2-Chloro-3-cyanophenyl trifluoromethanesulfonate



Potassium carbonate (1.350 g, 9.77 mmol) was added to 2-chloro-3-hydroxybenzonitrile (0.5 g, 3.26 mmol) and 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (1.163 g, 3.26 mmol) in THF (40 mL) at rt. The resulting suspension was stirred at rt for 50 h. The reaction mixture was evaporated to dryness and redissolved in EtOAc, then washed sequentially with water and sat. brine. The organic layer was dried over Na_2SO_4, filtered and evaporated, and the resulting crude product was purified by flash silica chromatography, elution gradient 5 to 20% EtOAc in isohexane, to afford the title compound (0.696 g, 75%) as a colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) 7.47 - 7.53 (1H, m), 7.62 (1H, dd), 7.73 (1H, dd); m/z $[M-H]^-$ = 284.

4'-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)-2-chlorobiphenyl-3-carbonitrile **34**. Made in a similar manner to compound **13** (Suzuki coupling) from 4-amino-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one and 2-chloro-3-cyanophenyl trifluoromethanesulfonate to afford the title compound (0.067 g, 27%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 4.03 - 4.08 (2H, m), 4.60 - 4.66 (2H, m), 7.53 (4H, s), 7.59 - 7.67 (3H, m), 7.79 (1H, dd), 8.01 (1H, dd), 8.18 (1H, s); m/z MH^+ = 392.

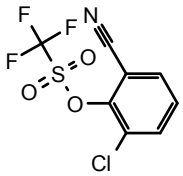
4-Amino-6-(biphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **36**. Made in a similar manner to compound **13** (Suzuki coupling) from compound **7** and benzeneboronic acid to afford the title compound (0.122 g, 49%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) 4.05 - 4.10 (2H, m), 4.68 - 4.78 (2H, m), 5.62 (1H, s), 7.34 - 7.40 (3H, m), 7.43 - 7.48 (2H, m), 7.54 - 7.61 (2H, m), 7.62 - 7.70 (2H, m), 8.10 - 8.27 (1H, m), 8.30 (1H, s); m/z MH^+ = 333.

4-Amino-6-(2'-methylbiphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **37**. Made in a similar manner to compound **13** (Suzuki coupling) from compound **7** and o-tolylboronic acid to afford the title compound (0.119 g, 46%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) 2.31 (3H, s), 4.08 (2H, dd), 4.72 - 4.76 (2H, m), 5.63 (1H, s), 7.21 - 7.30 (4H, m), 7.32 - 7.35 (2H, m), 7.39 - 7.45 (2H, m), 8.10 - 8.27 (1H, m), 8.30 (1H, s); m/z MH^+ = 347.

4-Amino-6-(2'-chloro-6'-methylbiphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **40**. Made in a similar manner to compound **13** (Suzuki coupling) from 4-amino-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one and 2-bromo-1-chloro-3-methylbenzene (111 mg, 45%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 2.07 (3H, s), 3.99 - 4.12 (2H, m), 4.64 (2H, dd), 7.21 - 7.33 (4H, m), 7.35 - 7.44 (1H, m), 7.44 - 7.53 (2H, m), 7.63 (2H, s), 8.18 (1H, s); m/z MH^+ = 381.

4-Amino-6-(4-(3-chloropyridin-2-yl)phenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **42**. Made in a similar manner to compound **13** (Suzuki coupling) from 4-amino-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one and 2-bromo-3-chloropyridine to afford the title compound (0.087 g, 29%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 4.02 - 4.10 (2H, m), 4.61 - 4.69 (2H, m), 7.45 (1H, dd), 7.49 - 7.54 (2H, m), 7.62 (2H, d), 7.72 - 7.80 (2H, m), 8.06 (1H, dd), 8.18 (1H, s), 8.64 (1H, s); m/z MH^+ = 368.

2-Chloro-6-cyanophenyl trifluoromethanesulfonate

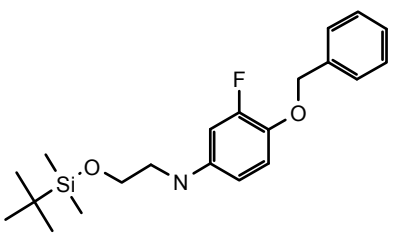


Trifluoromethanesulfonic anhydride (2.157 mL, 12.82 mmol) was added dropwise to 3-chloro-2-hydroxybenzamide (1 g, 5.83 mmol) and triethylamine (2.68 mL, 19.23 mmol) in DCM (50 mL) at 0°C over a period of 10 mins. The resulting solution was stirred at rt for 90 mins. The reaction mixture was diluted with DCM, and washed sequentially with water and sat. brine. The organic layer was dried over Na_2SO_4, filtered and evaporated. The resulting crude product was purified by flash silica chromatography, elution gradient 5 to 30% EtOAc in isohexane, to afford the title compound (1.10 g, 66%) as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) 7.47 (1H, t), 7.69 (1H, dd), 7.80 (1H, dd); m/z $[M-H]^-$ = 284.

4'-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)-6-chlorobiphenyl-2-carbonitrile **43**. Made in a similar manner to compound **13** (Suzuki coupling) from 4-amino-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one and 2-chloro-6-cyanophenyl trifluoromethanesulfonate to afford the title compound (0.092 g, 36%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 4.03 - 4.13 (2H, m), 4.62 - 4.69 (2H, m), 7.46 - 7.52 (2H, m), 7.55 - 7.66 (5H, m), 7.96 (2H, ddd), 8.18 (1H, s); m/z MH^+ = 392.

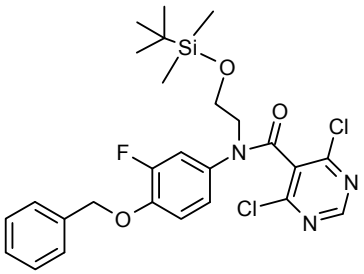
4-Amino-6-(2',6'-difluorobiphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **38**. 4-amino-6-(4-bromophenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (100 mg, 0.30 mmol), potassium (2,6-difluorophenyl)trifluoroborate (92 mg, 0.42 mmol), $PdCl_2$(dppf)-DCM adduct (12.18 mg, 0.01 mmol) and potassium phosphate (0.030 mL, 0.36 mmol) were suspended in DME (3 mL), water (0.75 mL) and MeOH (1.50 mL) and sealed into a microwave tube. The mixture was degassed under nitrogen and the atmosphere repaced with nitrogen. The reaction was heated at 110°C for 3 h and cooled to RT. The reaction mixture was evaporated to dryness and redissolved in methyl THF (50 mL), and washed sequentially with water and sat. brine. The organic layer was dried over Na_2SO_4, filtered and evaporated. The resulting crude product was purified by flash silica chromatography, elution gradient 1 to 10% MeOH in DCM, to afford the title compound (59 mg, 54%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) 3.97 - 4.14 (2H, m), 4.64 - 4.80 (2H, m), 5.51 - 5.73 (1H, m), 7.00 (2H, dd), 7.27 - 7.35 (1H, m), 7.36 - 7.41 (2H, m), 7.58 (2H, d), 8.08 - 8.24 (1H, m), 8.30 (1H, d); m/z MH^+ = 369.

4-(Benzyloxy)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-3-fluoroaniline



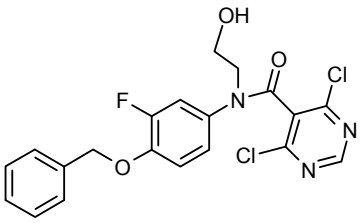
Palladium acetate (0.399 g, 1.78 mmol) and dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (0.848 g, 1.78 mmol) were added in one portion to a degassed solution of 1-(benzyloxy)-4-bromo-2-fluorobenzene (5.00 g, 17.79 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (Palomo et al, Org. Lett. 9 (2007) *101-104*) (4.16 g, 17.8 mmol) and cesium carbonate (8.69 g, 26.68 mmol) in toluene (100 mL) in a microwave vial, and the reaction was heated at 120°C for 10 h and cooled to rt. The reaction mixture was taken up in EtOAc and washed sequentially with water and sat. brine. The organic layer was filtered and dried over Na_2SO_4, and evaporated. The resulting crude product was purified by flash silica chromatography, elution gradient 0 to 30% EtOAc in isohexane, to afford the title compound (3.62 g, 54%) as a yellow oil; ^{1}H NMR (400 MHz, DMSO) -0.00 (6H, s), 0.80 - 0.86 (9H, m), 3.06 (2H, q), 3.61 - 3.70 (2H, m), 4.96 (2H, s), 5.36 (1H, t), 6.23 - 6.32 (1H, m), 6.44 (1H, dd), 6.90 (1H, tt), 7.25 - 7.44 (5H, m); m/z MH^+ = 376.

N-(4-(benzyloxy)-3-fluorophenyl)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-4,6-dichloropyrimidine-5-carboxamide



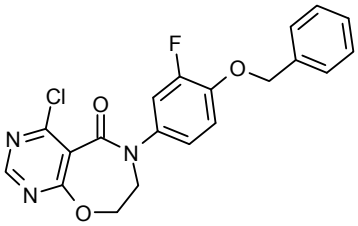
Made in a similar manner to compound **11** from 4-(benzyloxy)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-3-fluoroaniline to afford the crude title compound (4.91 g, 123% if pure) as an orange oil that was used without further purification; ^{1}H NMR (400 MHz, DMSO) -0.00 (6H, s), 0.82 (9H, d), 3.71 - 3.78 (2H, m), 3.91 (2H, t), 5.09 (2H, s), 7.06 - 7.23 (2H, m), 7.29 - 7.41 (6H, m), 8.83 (1H, s); m/z MH^+ = 550.

N-(4-(benzyloxy)-3-fluorophenyl)-4,6-dichloro-N-(2-hydroxyethyl)pyrimidine-5-carboxamide



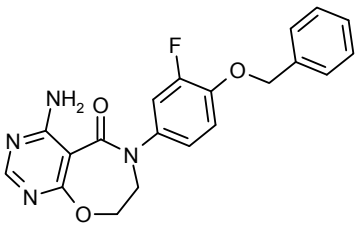
Made in a similar manner to N-(4-bromophenyl)-4,6-dichloro-N-(2-hydroxyethyl)pyrimidine-5-carboxamide from N-(4-(benzyloxy)-3-fluorophenyl)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-4,6-dichloropyrimidine-5-carboxamide to afford the title compound (3.31 g, 85%) as an orange gum; ^{1}H NMR (400 MHz, DMSO) 3.58 - 3.66 (2H, m), 3.85 - 3.94 (2H, m), 4.89 (1H, s), 5.14 (2H, d), 7.20 - 7.29 (3H, m), 7.34 - 7.53 (5H, m), 8.88 (1H, s); m/z MH^{+} = 436.

6-(4-(Benzyloxy)-3-fluorophenyl)-4-chloro-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one



Made in a similar manner to compound **12** from N-(4-(benzyloxy)-3-fluorophenyl)-4,6-dichloro-N-(2-hydroxyethyl)pyrimidine-5-carboxamide to afford the title compound (1.71 g, 62%) as a tan solid; ^{1}H NMR (400 MHz, DMSO) 4.06 - 4.23 (2H, m), 4.63 - 4.81 (2H, m), 5.23 (2H, s), 7.18 - 7.23 (1H, m), 7.27 - 7.50 (7H, m), 8.81 (1H, s); m/z MH^{+} = 400.

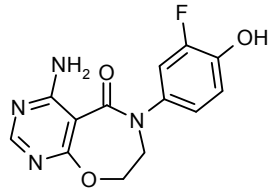
4-Amino-6-(4-(benzyloxy)-3-fluorophenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one



Made in a similar manner to compound **7** from 6-(4-(benzyloxy)-3-fluorophenyl)-4-chloro-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one to afford the title compound (1.05 g, 106%) as a

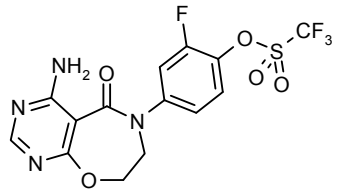
cream solid; ^{1}H NMR (400 MHz, DMSO) 3.82 - 4.02 (2H, m), 4.50 - 4.67 (2H, m), 5.21 (2H, s), 7.13 (1H, ddd), 7.27 (1H, t), 7.32 - 7.49 (6H, m), 7.60 (2H, s), 8.15 (1H, s); m/z MH^+ = 381.

4-Amino-6-(3-fluoro-4-hydroxyphenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one



4-Amino-6-(4-(benzyloxy)-3-fluorophenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (1 g, 2.63 mmol) was dissolved in methanol (100 mL) followed by addition of dihydroxypalladium (0.369 g, 0.53 mmol). The reaction mixture was put under H_2 atmosphere and stirred at rt for 2 h. The catalyst was filtered off and rinsed with MeOH. The solid still contained product so was heated in methanol (25 mL) for 30 mins. The catalyst was filtered off and the filtrates were combined and the solvent was removed under reduced pressure to afford the title compound (0.520 g, 68%) as a cream solid; ^{1}H NMR (400 MHz, DMSO) 3.84 - 4.01 (2H, m), 4.51 - 4.65 (2H, m), 6.89 - 7.07 (2H, m), 7.18 - 7.32 (1H, m), 7.61 (2H, s), 8.17 (1H, s), 9.96 (1H, s); m/z MH^+ = 291.

4-(4-Amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)-2-fluorophenyl trifluoromethanesulfonate

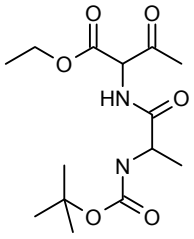


4-Amino-6-(3-fluoro-4-hydroxyphenyl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one (300 mg, 1.03 mmol), 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (739 mg, 2.07 mmol) and potassium carbonate (429 mg, 3.10 mmol) were suspended in THF (10 mL) and sealed into a microwave tube. The reaction was heated at 120°C for 60 mins and cooled to rt. The suspension was poured directly onto a SCX colum and the crude reaction mixture was purified by ion exchange chromatography, using an SCX column. The colunm was first washed with methanol

(50 mL) and the desired product was eluted from the column using 0.35 M NH_3/MeOH to afford the title compound (323 mg, 74%) as a tan solid; ^{1}H NMR (400 MHz, DMSO) 3.94 - 4.11 (2H, m), 4.52 - 4.69 (2H, m), 7.36 - 7.50 (1H, m), 7.64 (2H, s), 7.70 - 7.85 (2H, m), 8.16 (1H, s); m/z MH^+ = 423.

4-Amino-6-(2'-chloro-2-fluorobiphenyl-4-yl)-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-5(6H)-one **39**. Prepared in a similar manner to compound **13** (Suzuki coupling) from 4-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)-2-fluorophenyl trifluoromethanesulfonate and 2-chlorophenylboronic acid to afford the title compound (61 mg, 48%) as a tan solid ; ^{1}H NMR (400 MHz, DMSO) 4.01 - 4.10 (2H, m), 4.58 - 4.70 (2H, m), 7.34 - 7.38 (1H, m), 7.40 - 7.53 (5H, m), 7.58 - 7.62 (1H, m), 7.64 (2H, s), 8.18 (1H, s); m/z MH^+ = 385.

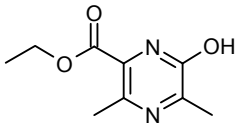
Ethyl 2-(2-(tert-butoxycarbonylamino)propanamido)-3-oxobutanoate



A solution of 4-methylmorpholine (900 g, 8933 mmol) in THF (15 mL) was added to 2-(tert-butoxycarbonylamino)propanoic acid (1690 g, 8933 mmol). The mixture was cooled to -25°C and isobutyl chloroformate (1.164 L, 8933 mmol) was added. After 20 mins additional 4-methylmorpholine (900 g, 8933 mmol) was added followed by ethyl 2-amino-3-oxobutanoate tosylate salt (See J-P Genet et al, *Eur. J. Org. Chem,* 2004,, 3017-3026.) (2700 g, 8507.78 mmol) in THF (2.5 L). The mixture was stirred at -25°C for 30 mins and left to warm to rt overnight. The reaction was quenched with water (15 L), extracted with EtOAc (3 x 5 L) and the combined extracts washed with 50% sat. brine (5 L). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product as a dark orange oil. The crude product was purified by flash silica chromatography, elution gradient 50 to 80% EtOAc in isohexane, to afford the title compound (1850

g, 69%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 1.27 - 1.33 (3H, t), 1.38 (3H, d), 1.43(9H, s), 2.38 (3H, s), 4.17 - 4.34 (3H, m), 4.95 (1H, bs), 5.24 (1H, d), 7.20 (1H, bs).

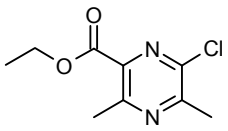
Ethyl 6-hydroxy-3,5-dimethylpyrazine-2-carboxylate



2 M Hydrochloric acid in 1,4-dioxane (1177 ml, 4710 mmol) was added to ethyl 2-(-2-(tert-butoxycarbonylamino)propanamido)-3-oxobutanoate (745 g, 2355 mmol) and stirred at rt for 15 mins then warmed to 40°C for a further 40 mins. Pyridine (6500 ml) was slowly added and then the reaction mixture was heated at 80°C for 2 h in the presence of air. The reaction was then allowed to cool to rt and evaporated to dryness to afford a viscous oil. This was suspended in DCM (2.5 L) and washed with water (1.5 L). The organic layer was dried over $MgSO_4$, filtered and concentrated, and the resulting residue was triturated with 1:1 EtOAc/ iso-hexane to afford ethyl 6-hydroxy-3,5-dimethyl-1,4-dihydropyrazine-2-carboxylate (127 g, 27%) as a cream solid. The mother liqours were purified by flash silica chromatography, elution gradient 20 to 80% EtOAc in isohexane, and then triturated with a small volume of 1:1 EtOAc/iso-hexane to afford additional ethyl 6-hydroxy-3,5-dimethylpyrazine-2-carboxylate (9.00 g, 2%).

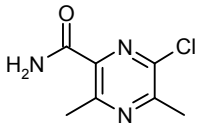
Manganese oxide (150 g, 1725 mmol) was added to a suspension of ethyl 6-hydroxy-3,5-dimethyl-1,4-dihydropyrazine-2-carboxylate (121 g, 610 mmol) in DCM (1.8 L) at rt. The reaction was stirred for 10 mins then warmed to 35°C for 1 h. The reaction was incomplete so an additional 115g of manganese oxide was added and the reaction mixture was stirred for 1 h at 35°C then allowed to cool to rt. The reaction was filtered through a short plug of silica and washed through with 2 L of 1:1 EtOAc/iso-hexane and finally 2 x 2 L of EtOAc. The combined organic layers were evaporated, and the resulting residue was slurried in 300 mL of 1:1 EtOAc/iso-hexane, filtered and washed with iso-hexane to afford the title compound (87 g, 73%) as an orange solid; ^{1}H NMR (400 MHz, DMSO) 1.31 (3H, t), 2.35 (3H, s), 2.50 (3H, s), 4.31 (2H, q), 11.93 (1H, s); m/z MH^+ = 197.

Ethyl 6-chloro-3,5-dimethylpyrazine-2-carboxylate



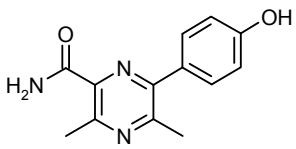
A suspension of ethyl 6-hydroxy-3,5-dimethylpyrazine-2-carboxylate (268 g, 1366 mmol) in phosphorus oxychloride (1273 ml, 13660 mmol) was heated at 90°C for 1 h then cooled to rt. The reaction mixture was cautiously added to water (6 L) with vigorous stirring. The mixture was extracted with DCM (5 x 2.5 L), the organic layer was dried over $MgSO_4$, filtered and evaporated. The resulting crude product was purified by flash silica chromatography, elution gradient 0 to 25% EtOAc in isohexane, to afford the title compound (227g, 77%) as a yellow oil which solidified on standing; ^{1}H NMR (400 MHz, $CDCl_3$) 1.43 (3H, t), 2.68 (3H, s), 2.77 (3H, s), 4.46 (2H, q); m/z MH^+ = 215.

6-Chloro-3,5-dimethylpyrazine-2-carboxamide



Ethyl 6-chloro-3,5-dimethylpyrazine-2-carboxylate (227 g, 1058 mmol) was stirred in ammonia (7 N in MeOH) (1957 mL, 89634 mmol) at rt overnight.The mixture was evaporated to dryness and the residue was triturated with ether, filtered and dried at 40°C under vacuum to afford the title compound (181 g, 92%) as a light brown solid; ^{1}H NMR (400 MHz, DMSO) 2.59 (3H, s), 2.67 (3H, s), 7.70 (1H, s), 7.99 (1H, s); m/z MH^+ = 186.

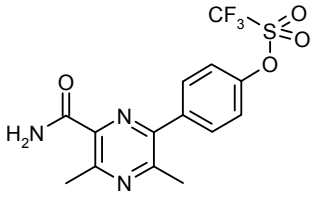
6-(4-Hydroxyphenyl)-3,5-dimethylpyrazine-2-carboxamide



A solution of 6-chloro-3,5-dimethylpyrazine-2-carboxamide (16 g, 86.2 mmol), 4-hydroxyphenylboronic acid (11.89 g, 86.2 mmol) and tripotassium phosphate (27.4 g, 129.3 mmol)

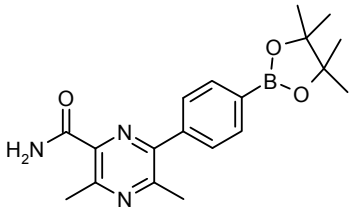
in DME (200 ml), ethanol (100 ml) and water (60 ml) was degassed before addition of (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (DCM adduct) (3.55 g, 4.31 mmol). The reaction mixture was heated at 80°C for 16 h. The reaction mixture was allowed to cool to rt and then evaporated. The residue was partitioned between water (300 mL), 2 M aq. HCl (180 mL) and EtOAc (600 mL) and filtered. The filtrate was separated, the organic layer was washed with sat. brine (300 mL) then combined with the filtered solid and evaporated. The resulting crude product was suspended in MeOH (400 mL) and DCM (400 mL), heated at reflux and the hot solvent was filtered. The filtrate was evaporated under vacuum to afford the title compound (22.30 g, 106%) as an orange solid; ^{1}H NMR (400 MHz, DMSO) 2.58 (3H, s), 2.71 (3H, s), 6.87 (2H, d), 7.56 - 7.60 (3H, m), 7.95 (1H, s), 9.73 (1H, s); m/z MH^+ = 244.

4-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl trifluoromethanesulfonate



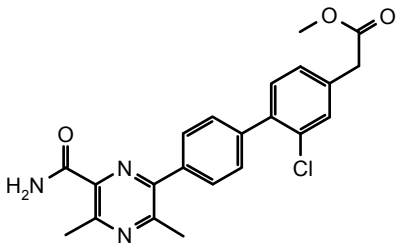
6-(4-Hydroxyphenyl)-3,5-dimethylpyrazine-2-carboxamide (2 g, 8.22 mmol), 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (2.94 g, 8.22 mmol) and potassium carbonate (3.41 g, 24.66 mmol) were suspended in THF (17 mL) and sealed into a microwave tube. The reaction was heated at 120°C for 6 mins and cooled to rt. The suspension was filtered, the solid was washed with EtOAc (100 mL) and the filtrate was evaporated. The resulting crude product was purified by flash silica chromatography, elution gradient 20 to 70% EtOAc in isohexane, to afford the title compound (2.260 g, 73%) as a cream solid; ^{1}H NMR (400 MHz, $CDCl_3$) 2.66 (3H, s), 3.00 (3H, s), 5.53 (1H, s), 7.42 (2H, d), 7.67 - 7.71 (3H, m); m/z MH^+ = 376.

3,5-Dimethyl-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrazine-2-carboxamide



A solution of 4-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)phenyl trifluoromethanesulfonate (11.7 g, 31.17 mmol), bis(pinacolato)diboron (8.71 g, 34.29 mmol) , potassium acetate (9.18 g, 93.52 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (1.048 g, 1.87 mmol) in 1,4-dioxane (140 mL) was degassed. The mixture was treated with (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (DCM adduct) (1.539 g, 1.87 mmol) and further degassed, refilling with nitrogen. The suspension was heated at 80°C overnight. The reaction mixture was allowed to cool and diluted with EtOAc (400 mL) and water (200 mL) and filtered through a pad of celite (3" diameter x 1") washing through with EtOAc. The organic layer was isolated and washed with sat. brine and evaporated. The reuslting crude product was purified by flash silica chromatography, elution gradient 20 to 80% EtOAc in isohexane, to afford the title compound (10.80 g, 98%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 1.32 (12H, s), 2.57 (3H, s), 2.74 (3H, s), 7.62 (1H, s), 7.74 (2H, d), 7.79 (2H, d), 7.97 (1H, s); m/z MH^{+} = 354.

Methyl 2-(4'-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)-2-chlorobiphenyl-4-yl)acetate



Tripotassium phosphate (141 mg, 0.67 mmol) and methyl 2-(3-chloro-4-(trifluoromethylsulfonyloxy)phenyl)acetate (185 mg, 0.55 mmol) were added to a degassed solution of 3,5-dimethyl-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrazine-2-carboxamide (196 mg, 0.55 mmol) in DME (6 mL), ethanol (1.5 mL) and water (1.5 mL). The mixture was treated with (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (DCM adduct) (36.5 mg, 0.04 mmol). The resulting mixture was stirred at 80°C for 4 h. The reaction mixture was allowed to cool

to rt, evaporated and partitioned between EtOAc and sat. brine (50 mL) and filtered through celite. The organic layer was dried over $MgSO_4$, filtered and evaporated. The resulting crude product was purified by flash silica chromatography, elution gradient 20 to 80% EtOAc in isohexane, to afford the title compound (110 mg, 48%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 2.65 (3H, s), 2.76 (3H, s), 3.65 (3H, s), 3.79 (2H, s), 7.35 (1H, d), 7.44 (1H, d), 7.53 (1H, s), 7.57 (2H, d), 7.61 (1H, s), 7.85 (2H, d), 8.03 (1H, s); m/z MH^+ = 410.

2-(4'-(6-Carbamoyl-3,5-dimethylpyrazin-2-yl)-2-chlorobiphenyl-4-yl)acetic acid **1**. Powdered potassium hydroxide (45.2 mg, 0.81 mmol) was added in one portion to methyl 2-(4'-(6-carbamoyl-3,5-dimethylpyrazin-2-yl)-2-chlorobiphenyl-4-yl)acetate (110 mg, 0.27 mmol) in tert-butanol (10 mL) at 45°C. The resulting solution was stirred at 45°C for 15 mins. 2 N aq. HCl (2 mL) was added and the mixture was evaporated to remove the organic solvent. The suspension was filtered, and the solid was washed with water (5 mL) and dried under vacuum to afford the title compound (82 mg, 77%) as a white solid; ^{1}H NMR (400 MHz, DMSO) 2.65 (3H, s), 2.76 (3H, s), 3.68 (2H, s), 7.34 (1H, d), 7.43 (1H, d), 7.51 (1H, s), 7.57 (2H, d), 7.61 (1H, s), 7.85 (2H, d), 8.04 (1H, s), 12.45 (1H, s); m/z MH^+ = 396.

Methods S2. Procedures for determining enzyme compound activity

The DGAT1 assay was performed using human DGAT1 expressed in insect cell membranes, sf9 cells were infected with recombinant baculovirus containing human DGAT1 coding sequences and harvested after 48 hours (Proc. Nat. Acad. Sci. 1998, 95, 13018). Cells were lysed by sonication and the membranes isolated by centrifugation (1h, 28000 rpm, 4 °C, 41% sucrose gradient). The membrane fraction at the interphase was collected, washed and stored in liquid nitrogen.

The DGAT1 assay was based on a modification of that described in the literature (Methods in Enzymology, 1992, 209, 98). Compounds at 3 nM to 10 µM were incubated with 4 µg/mL of membrane protein (final conc.), 5 mM $MgCl_2$ and 100 µM 1,2-dioleoyl-sn-glycerol in acetone (10% final assay conc. of acetone) in a 200 µL total volume in a 96 well plate. The reaction was started by

the addition of 14C oleoyl co-enzyme A (30 µL final conc.) and incubated for 30 minutes at rt. The reaction was stopped by the addition of propan-2-ol / heptane (7:1, 200 µL). The mixture was partitioned between heptane (300 µL) and carbonate buffer (pH 9.5, 100 µL). The DGAT1 activity was quantified by counting aliquots from the heptane fraction containing the radioactive trioleoylglycerol product by liquid scintillography.

Methods S3. ADMET references

Protocols for generation of relevant ADMET data are described in:

D. Buttar, N. Colclough, S. Gerhardt et al. Bioorg. Med. Chem. 2010, 18, 7486.

G. Camenisch, J. Alsenz, H. van de Waterbeemd and G. Folkers, Eur. J. Pharm. Sci., 1998, 6, 313.

M. H. Bridgland-Taylor, A. C. Hargreaves, A. Easter et al. J. Pharmacological and Toxicological Methods, 2006, 54, 189.

Methods S4. PK/PD parameters for model fitting for compound 13 in the rat adipose TAG synthesis test

Table S1. PK/PD parameters for model fit for compound 13 in the rat adipose TAG synthesis assay

Parameter	Estimate	Units	Stderr%
IC_{50}	0.0071	uM	14
Gamma	1.7	--	15
E_0	4.1	--	4.5
I_{max}	3.9	--	5.0

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

Table S2. PK/PD parameters for model fit for compound 13 in the rat OLTT

Parameter	Estimate	Units	Stderr%
IC_{50}	0.0127	uM	57
Gamma	0.6	--	43
E_0	2.4	mM	6.8

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

I_{max}	1.7	mM	17