Supporting Information

Optimization of Pharmacokinetics through Manipulation of Physicochemical Properties in a Series of HCV Inhibitors

Scott E. Lazerwith,* [1] Gina Bahador,[3] Eda Canales,[1] Guofeng Cheng,[3] Lee Chong,[1] Michael O. Clarke,[1] Edward Doerffler,[1] Gene Eisenberg,[2] Jaclyn Hayes,[2] Bing Lu,[2] Qi Liu,[1] Mike Matles,[2] Michael Mertzman,[1] Michael Mitchell,[1] Philip Morganelli,[1] Bernard P. Murray,[2] Margaret Robinson,[3] Robert Strickley,[4] Megan Tessler,[4] Neeraj Tirunagari,[3] Jianhong Wang,[2] Yujin Wang,[2] Jennifer Zhang,[1] Xubin Zheng,[2] William J. Watkins[1]

[1]*Medicinal Chemistry,*[2] *Drug Metabolism,* [3]*Biology,* [4]*Formulation and Process Development*
Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404
E-mail: scott.lazerwith@gilead.com

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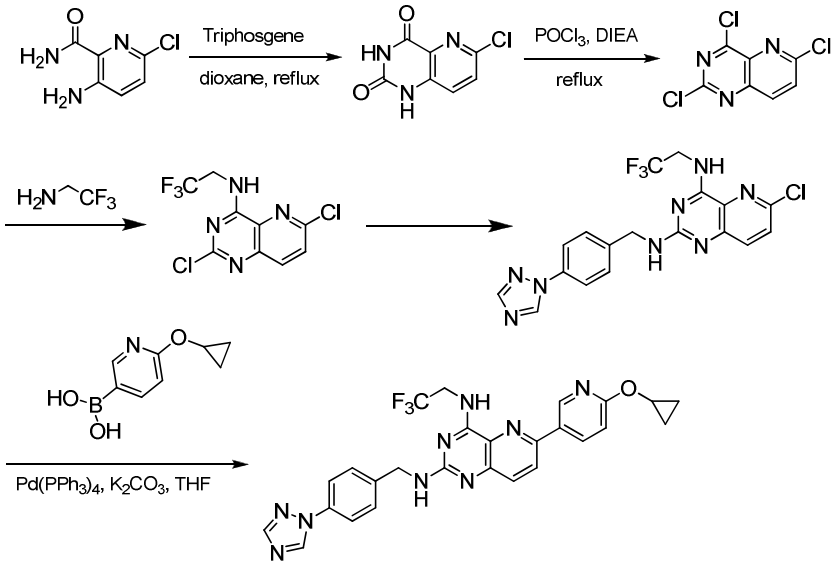
Scheme 1



To 3-amino-6-chloro-pyridine-2-carboxylic acid amide (10 g, 58.3 mmol) in 1,4-dioxane (300 mL) , was added triphosgene (6.9 g, 23.3 mmol). The reaction was heated to 100 ^{O}C for 1.5 hours. It was then cooled to RT and 3 ml of water was added to quench excess triphosgene. The solid was filtered and washed with EtOAc twice to provide 11 g of crude product which used without further purification.

A mixture of 6-chloro-1H-pyrido[3,2-d]pyrimidine-2,4-dione (11 g, 55.7 mmol), $POCl_3$ (100 ml) and DIEA (20 ml) was heated to reflux overnight. The $POCl_3$ was removed in vacuo and the residue was dissolved in dichloromethane and passed through a short silica gel plug. The combined organic fractions were concentrated to provide 8 g of the product as a beige solid.

To a solution of 2,4,6-trichloro-pyrido[3,2-d]pyrimidine (21.5 g, 91.8 mmol) in THF (275 ml) at 10 deg C, was added 1-trifluoroethylamine (7.9 mL, 101 mmol) and diisopropylethylamine (14.1 mL, 101 mmol). The heterogenous mixture was stirred at room temperature for 16 h. Water (50 mL) was added followed by acetonitrile (300 mL) resulting in a clear solution. Additional water (300 mL) was added, resulting in some precipitate. A further 50 mL water was added and the mixture was stirred 16 h. The solid was filtered and washed with water. Additional solid precipitated out of the filtrate and was also filtered and washed with water. This process was repeated twice more, and the combined solids were dried in vacuo to afford 25.0 g (91%) of the desired dichloropyridopyrimidine and was carried on without further purification.

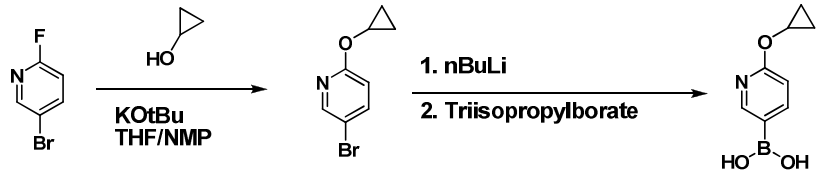
2,6-dichloro-N-(2,2,2-trifluoroethyl)pyrido[3,2-d]pyrimidin-4-amine (10.3 g, 34.7 mmol) and (4-(1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride (8.0 g, 38.0 mmol) were suspended in NMP (35 mL), treated with diisopropylethylamine (15 mL, 86 mmol) and heated to 120 ºC. After 18 h, the reaction mixture was added to a

stirred mixture of water:acetonitrile (1200 mL, 45:55) over 45 min, resulting in an off-white precipitate. This mixture was stirred vigorously for another 45 min, and filtered. The solid was washed with 1:1 water:acetonitrile and dried in vacuo to afford 12.9 g (86%) of crude product that was used without further purification.

N2-(4-(1H-1,2,4-triazol-1-yl)benzyl)-6-chloro-N4-(2,2,2-trifluoroethyl)pyrido[3,2-d]pyrimidine-2,4-diamine (0.250 g, 0.58 mmol) was combined with 6-cyclopropoxypyridin-3-ylboronic acid (0.75 mmol in 1.5 mL DME), palladium tetrakistriphenylphosphine (0.013 g, 0.012 mmol) and potassium carbonate (0.159 g, 1.15 mmol). The mixture was treated with DME (1 mL) and water (1 mL) heated to 90 °C for 30 min. Additional portions of 6-cyclopropoxypyridin-3-ylboronic acid (0.38 mmol in 0.75 mL DME), palladium tetrakistriphenylphosphine (0.003 g, 0.003 mmol), and water (0.5 mL) were added, and the reaction mixture was reheated to 90 °C for 20 min. Water (7.5 mL) and acetonitrile (7.5 mL) were added, and crude solid was isolated by filtration. The solid was dissolved in THF and concentrated onto a small amount of silica gel. Flash chromatography (1-10% MeOH:DCM) afforded 0.202 g (66% yield) of the title compound **2**, and was characterized by its NMR and mass spectrum as follows: ^{1}H NMR (d_6-DMSO): δ 0.70 – 0. 83 (m, 4H), 4.29 (m, 1H), 4.45 (m, 2H), 4.79 (m, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J*= 8.7 Hz, 2H), 7.84 (d, *J*= 8.1 Hz, 2H), 8.01 (d, *J*= 8.7 Hz, 1H), 8.23 (s, 1H), 8.47 (m, 1H), 8.70 (dd, *J*= 8.7, 2.7 Hz, 1H), 9.08 (bs, 1H), 9.27 (d, *J* = 5.1 Hz, 2H), 10.05 (bs, 1H); HRMS (ESI) *m/z* 534.1983 [(M+H)+; calcd for $C_{26}H_{23}F_3N_9O$: 534.1972].

6-cyclopropoxypyridin-3-ylboronic acid was synthesized as follows:

Scheme 2



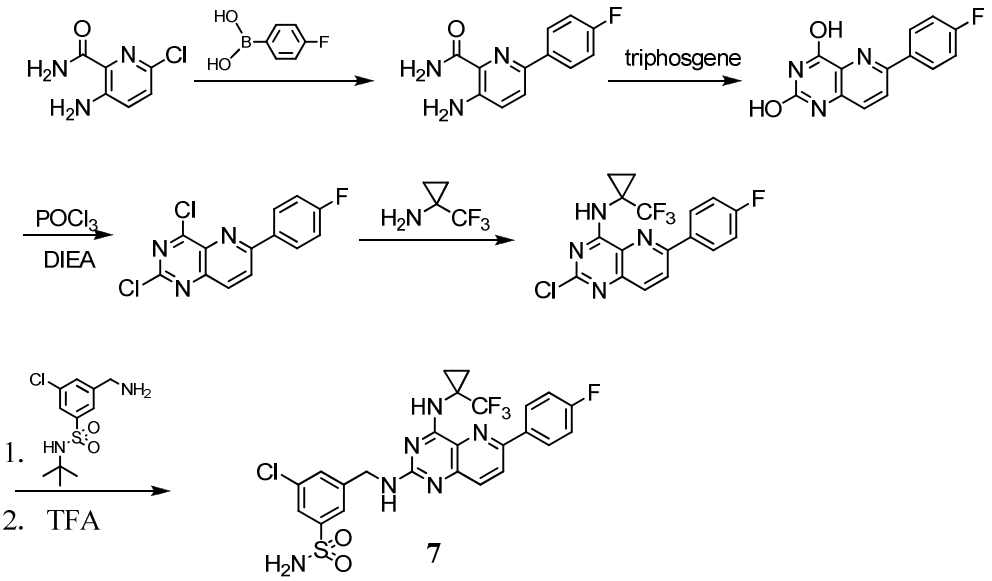
5-bromo-2-fluoropyridine (1.50 g, 8.52 mmol) and cyclopropanol (1.43 g, 12.8 mmol) were disspolved in NMP (12 mL) and treated with potassium *tert*-butoxide (12.8 mL, 1M solution in THF, 12.8 mmol). The solution became dark and cloudy, and warmed. After 30 min, the reaction mixture was partitioned between ethyl acetate:heptane (1:1, 100 mL) and water (100 mL). The organic layer was separated, washed with water and 5% aq. LiCl, dried over sodium sulfate (anhyd), filtered and concentrated. The residue was purified by flash chromatography (0-6% EtOAc:hexanes. Impure fractions were combined, concentrated and repurified by flash chromatography (0-100% DCM:hexanes). Clean fractions from both purifications were combined and concentrated to 1.12 g (61% yield) of the desired cyclopropyl ether and carried on to the next step.

To a solution of *n*BuLi (5.23 mL, 2.5 M in hexanes, 13.1 mmol) in ether (15 mL) at -78 deg C, was added dropwise a solution of 5-bromo-2-cyclopropoxypyridine (1.12 g, 5.23 mmol) in ether (4 + 2 mL) over 5 min. After stirring at – 78 deg C for 1h the yellow slurry was treated with triisopropyl borate (3.0 mL, 13 mmol) over 2 min, resulting in a gel. The reaction mixture was allowed to warm to ambient temperature during which the gel became an off-white heterogenous mixture. After 1h, the reaction mixture was treated with NaOH (30 mL, 1 M aq) and became a biphasic clear mixture. The organic layer was removed and washed with water (10 mL). The combined aqueous layers were cooled to 0 deg C, and acidified to pH ~4 with 1M HCl. The cloudy mixture was

extracted twice with EtOAc, dried over sodium sulfate (anhyd), filtered and concentrated 1.0 g (>100% yield) of a gooey solid, which was dissolved in DME (10 mL) and used without purification (assume 0.5 mmol/mL solution).

Example 7 - synthesis of 3-chloro-5-((6-(4-fluorophenyl)-4-(1-(trifluoromethyl)cyclopropylamino)pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide

Scheme 3



A mixture of 3-amino-6-chloropicolinamide (2 g), potassium carbonate (3.2 g), tetrakis(triphenylphosphine) palladium (0.674 g) and 4-fluorophenylboronic acid (1.79 g) in DMF (50 mL) and water (10 mL) was heated to 120°C for 16 hours. Solvents were removed and 1N HCl (30 ml) was added to the mixture. The resulting solid was filtered to provide 2.48 g of 3-amino-6-(4-fluorophenyl)picolinamide which was characterized by its mass spectrum as follows: MS (*m/z*) 232 $[M+H]^+$.

A solution of 3-amino-6-(4-fluorophenyl)picolinamide (2.48 g) and triphosgene in 1,4-dioxane (50 mL) was heated to 100°C for 1 hour. Cooling and filtration provided 2.2 g of 6-(4-fluorophenyl)pyrido[3,2-*d*]pyrimidine-2,4-diol which was characterized by its mass spectrum as follows: MS (*m/z*) 258 $[M+H]^+$.

A solution of 6-(4-fluorophenyl)pyrido[3,2-*d*]pyrimidine-2,4-diol (1 g), $POCl_3$ (20 ml) and DIEA (2.0 ml) was heated to reflux for 16 hours. $POCl_3$ was removed and the residue was dissolved in ethyl acetate. The organic layer was extracted with brine three times. It was dried and concentrated to provide 0.97 g of 2,4-dichloro-6-(4-fluorophenyl)pyrido[3,2-*d*]pyrimidine which was characterized by its mass spectrum as follows: MS (*m/z*) 294 $[M+H]^+$.

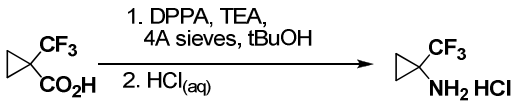
2,4-Dichloro-6-(4-fluoro-phenyl)-pyrido[3,2-d]pyrimidine (3.3 g, 11.2 mmol), 1-trifluoromethyl-cyclopropylamine hydrochloride (2.25 g, 14.1 mmol, see Scheme 2 below) and diisopropylethylamine (4.8 ml, 25.5 mmol) were suspended in N-methylpyrrolidinone (10 mL) and stirred at 80 ºC. After 3 hours, the reaction mixture was cooled to 40 ºC and stirred an additional 16 hours. Methanol (20 mL) was added and the solution was heated to 70 ºC. Water was slowly added until the mixture became cloudy. After cooling, a precipitate was collected, and washed with acetonitrile:water (1:1) followed by ether. Two additional batches of precipitate were

formed in the filtrate which were collected and washed. The combined solids were dried to 3.46 g (81%). This material was used without further purification in the next step.

A mixture of [2-Chloro-6-(4-fluoro-phenyl)-pyrido[3,2-d]pyrimidin-4-yl]-(1-trifluoromethyl-cyclopropyl)-amine (107 mg, 0.28 mmol) and 3-(aminomethyl)-N-tert-butyl-5-chlorobenzenesulfonamide (105 mg, 0.34 mmol) was dissolved in NMP (0.75 mL) and treated with diisopropylethylamine (0.145 mL, 0.56 mmol). The reaction mixture was sealed and heated by microwave to 120 ℃ for 3 h. An additional portion of diisopropylethylamine was added (0.100 mL) and the mixture was heated to 120 ℃ for 8 h. The reaction mixture was cooled and, after an unsuccessful attempt at crystallization by addition of MeOH (1 mL) and water (1 mL), partitioned between ethyl acetate (100 mL) and 5% LiCl (aq, 20 mL). The organic layer was separated and washed with 5% LiCl (aq), brine and dried over sodium sulfate (anhyd). After filtration and concentration, the residue was purified by flash chromatography (30-100% EtOAc:Hex) to afford 110 mg (63% yield) of the desired N-tert-butyl-3-chloro-5-((6-(4-fluorophenyl)-4-(1-(trifluoromethyl)cyclopropylamino)pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide.

N-tert-butyl-3-chloro-5-((6-(4-fluorophenyl)-4-(1-(trifluoromethyl)-cyclopropylamino)-pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide (0.110 g, 0.177 mmol) was dissolved in a mixture of TFA (3 mL) and water (0.15 mL) and heated to 70-80 ℃ for 15 min. Toluene (3 mL) and the solution was concentrated. An additional portion of toluene (3 mL) was added and the mixture concentrated again to afford a solid which was recrystallized from acetonitrile/water to afford 68 mg (56% yield) of the desired 3-chloro-5-((6-(4-fluorophenyl)-4-(1-(trifluoromethyl)cyclopropylamino)pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide **7** as its TFA which was characterized by its NMR and mass spectrum as follows: ^{1}H NMR (d_6-DMSO): δ 1.23 (br s, 2H), 1.35 (br s, 2H), 4.77 (br s, 2H), 7.37 (t, 2H, *J* = 8.3 Hz), 7.51 (s, 2H), 7.70 (s, 1H), 7.75 (s, 2H), 7.98 (d, 1H, *J* = 9.3 Hz), 8.50 (m, 3H), 8.9 (br s, 1H), 10.08 (br s, 1H); HRMS (ESI) *m/z* 566.0916 [(M+H)+; calcd for $C_{24}H_{19}ClF_4N_6O_2S$: 566.0915].

Scheme 4



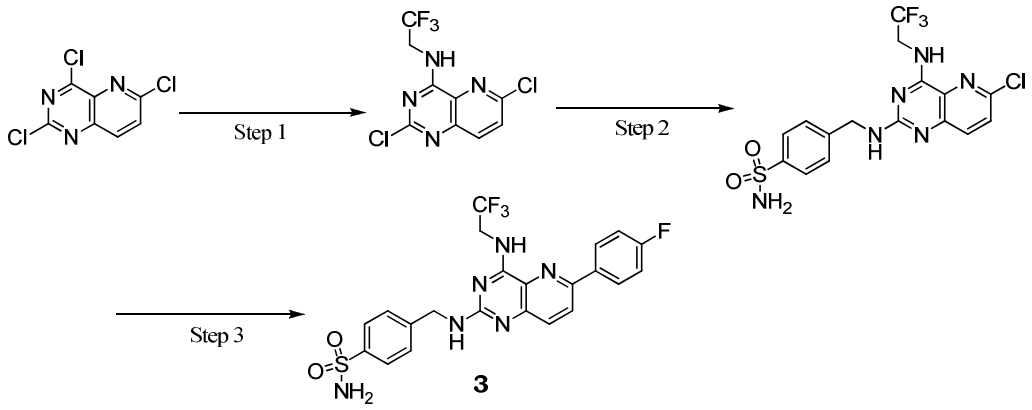
1-Trifluoromethyl-cyclopropylamine was synthesized using a variation of the procedure found in *J.Med.Chem.* 2006, **49**, 4127:

A solution of 1-(trifluoromethyl)cyclopropanecarboxylic acid (5.1 g, 33.1 mmol) and dry triethylamine (4.6 mL, 33 mmol) in dry *tert*-butanol (24 mL) was stirred at room temperature in the presence of 0.4 nm molecular sieves (3.4 g). Diphenyl phosphorazidate (7.5 mL, 34.7 mmol) was added dropwise and the mixture was heated to reflux for 22 h under nitrogen and then concentrated in vacuo. The residue was taken up in diethyl ether and sieves were removed by gravity filtration. The filtrate was washed sequentially with 5% citric acid solution, saturated aqueous $NaHCO_3$, and brine and dried. Concentration afforded 4.08 g (55%) of *tert*-butyl 1-(trifluoromethyl)cyclopropylcarbamate, which was used without further purification in the next step.

Tert-butyl 1-(trifluoromethyl)cyclopropylcarbamate (4.08 g, 18.3 mmol) was suspended in 1 N $HCl_{(aq)}$ (150 mL) and stirred at reflux for 3.5 h. The solution was concentrated in vacuo and the residue was triturated with acetone. The filtrate was collected, concentrated, and the residue triturated with diethyl ether to afford 2.67 g (91%) of 1-(trifluoromethyl)cyclopropylamine hydrochloride as a white solid.

Example 3 – synthesis of 4-((6-(4-fluorophenyl)-4-(2,2,2-trifluoroethylamino)pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide

Scheme 5



Step 1: Synthesis of 2,6-dichloro-N-(2,2,2-trifluoroethyl)pyrido[3,2-d]pyrimidin-4-amine

To a cooled (0°C) solution of 2, 4, 6-trichloropyrido [3, 2-d]pyrimidine (9 g, 38.38 mmol) and 2,2,2-trifluoroethanamine (3.62 mL, 46.05 mmol) in THF (100 mL) was added triethylamine (5.34 mL, 38.38 mmol). The reaction mixture was allowed to stir at ambient temperature for 1.5 h and the solvent was evaporated to a small volumn (~30 to 40 mL). Water (100 mL) was added, and the resulting white fluffy solid was collected by vacuum filtration, washed with water, dried under high vacuum to provide 11.5 g of the title compound.

Step 2: Synthesis of 4-((6-chloro-4-(2,2,2-trifluoroethylamino)pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide

A mixture of 2,6-dichloro-N-(2,2,2-trifluoroethyl)pyrido[3,2-d]pyrimidin-4-amine (8.48 g, 35.48 mmol), 4-(aminomethyl)benzenesulfonamide (8.77 g, 46.12 mmol) and N, N-diisopropylethylamine (6.2mL, 35.48 mmol) in N-methylpyrrolidone (70 mL) was heated at 120°C for 18 h. The reaction mixture was allowed to cool down and poured into 300 mL solution of 25% acetonitrile/water. The resulting solid was collected and washed first with a solution of 25% acetonitrile/water, and then water to afford crude product which was dissolved in 400 mL of acetone and 50 mL of 1, 2-Dimethoxyethane at 56°C. The mixture was allowed to cool over a weekend and the resulting solid was collected by vacuum filtration and dried under high vacuum to afford 7.55 g of the title compound. The filtrate was concentrated down and recrystallized from methanol to provide 2.5 g of the title compound.

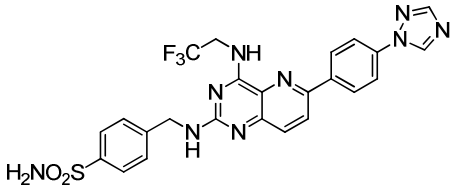
Step 3: Synthesis of 4-((6-(4-fluorophenyl)-4-(2,2,2-trifluoroethylamino)

pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide

A mixture of 4-((6-chloro-4-(2,2,2-trifluoroethylamino)pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide(22 mg, 0.05 mmol), 4-fluorophenylboronic acid (7 mg, 0.05 mmol), potassium carbonate (28 mg, 0.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (10mg) in 1,2-Dimethoxyethane (1.5 mL) and water (0.5mL) was heated to 120 ^{o}C for 4min in microwave. The reaction was diluted with ethyl acetate filtered through a Celite pad. After filtration and concentration the residue was purified by HPLC with CH_3CN (0.1% TFA)/H_2O (0.1% TFA) to afford the title compound.

1H NMR (400 MHz, d_6-DMSO) δ 10.03 (s, 1H), 9.10 (s, 1H), 8.54 – 8.38 (m, 3H), 8.07 (d, J = 8.9 Hz, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.37 (dd, J = 18.7, 9.9 Hz, 4H), 4.80 (d, J = 5.4 Hz, 2H), 4.46 – 4.35 (m, 2H); HRMS (ESI) *m/z* 506.1155 [(M+H)+; calcd for $C_{22}H_{18}F_4N_6O_2S$: 506.1148].

Example 4 – synthesis of 4-((6-(4-(1H-1,2,4-triazol-1-yl)phenyl)-4-(2,2,2-trifluoro ethylamino)pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide

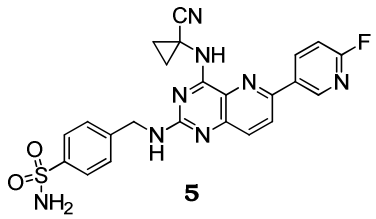


4

4 was prepared in a manner similar to **3** using 1-(4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenyl)-1H-1,2,4-triazole instead of 4-fluorophenylboronic acid in step 3.

^{1}H NMR (400 MHz, d_6-DMSO) δ 9.83 (br s, 1H), 9.38 (s, 1H), 9.16 – 9.06 (m, 1H), 8.94 (br s, 1H), 8.47 (d, J = 7.6 Hz, 1H), 8.23 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.49 – 7.23 (m, 3H), 7.26 (s, 2H), 4.78-4.63 (m, 2H), 4.38 – 4.32 (m, 2H); HRMS (ESI) *m/z* 555.1419 [(M+H)+; calcd for $C_{24}H_{20}F_3N_9O_2S$: 555.1413].

Example 5 – GS-424537 synthesis of 4-((4-(1-cyanocyclopropylamino)-6-(6-fluoropyridin-3-yl)pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide

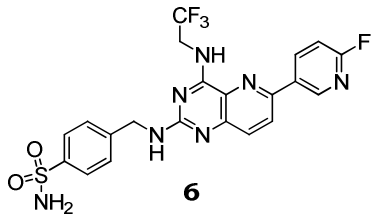


5

5 was prepared in a manner similar to **3** using 1-aminocyclopropanecarbonitrile instead of 2,2,2-trifluoroethanamine in step 1 and using 6-fluoropyridin-3-ylboronic acid instead of 4-fluorophenylboronic acid in step 3.

1H NMR (300 MHz, d_6-DMSO) δ 10.33 (s, 1H), 9.38 (m, 1H), 9.24 (s, 1H), 8.90 (d, J = 10.6 Hz, 1H), 8.51 (d, J = 9.1 Hz, 1H), 7.99 (d, J = 8.9 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.34 (m, 3H), 4.84 (d, J = 5.6 Hz, 2H), 1.61 (m, 2H), 1.39 (m, 2H); HRMS (ESI) *m/z* 490.1343 [(M+H)+; calcd for $C_{23}H_{19}FN_8O_2S$: 490.1336].

Example 6 – synthesis of 4-((6-(4-fluorophenyl)-4-(2,2,2-trifluoroethylamino)pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide

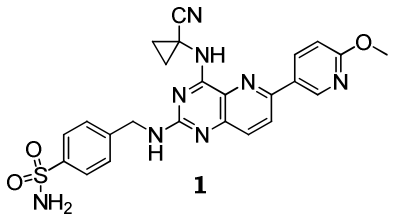


6

6 was prepared in a manner similar to **3** using 6-fluoropyridin-3-ylboronic acid instead of 4-fluorophenylboronic acid in step 3.

1H NMR (400 MHz, d_6-DMSO) δ 10.01 (br s, 1H), 9.28 (s, 1H), 9.16 – 9.06 (m, 1H), 8.94 (m, 1H), 8.53 (d, J = 8.7 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.41 – 7.25 (m, 3H), 4.79 (m, 2H), 4.46 – 4.32 (m, 2H); HRMS (ESI) *m/z* 507.1107 [(M+H)+; calcd for $C_{21}H_{17}F_4N_7O_2S$: 507.1101].

Example 1 – synthesis of 4-((4-(1-cyanocyclopropylamino)-6-(6-methoxypyridin-3-yl)pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide



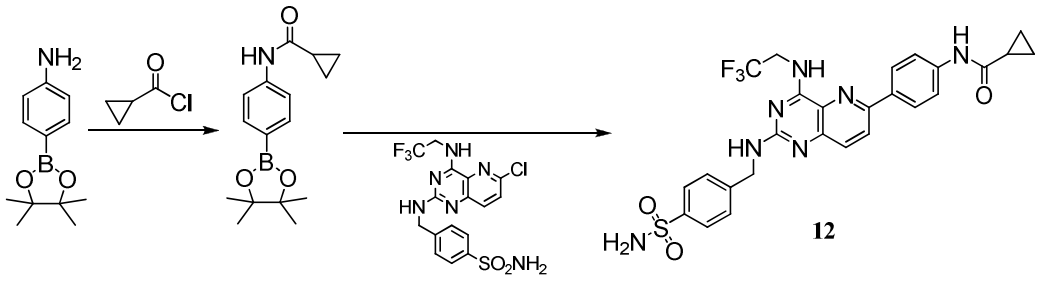
1

1 was prepared in a manner similar to **3** using 1-aminocyclopropanecarbonitrile instead of 2,2,2-trifluoroethanamine in step 1 and using 6-methoxypyridin-3-ylboronic acid instead of 4-fluorophenylboronic acid in step 3.

1H NMR (400 MHz, d_6-DMSO) δ 10.23 (s, 1H), 9.19 (s, 2H), 8.71 (dd, J = 8.8, 2.5 Hz, 1H), 8.46 (d, J = 8.9 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.79 (d, J = 8.3 Hz, 2H), 7.63 (s, 2H), 7.33 (s, 2H), 6.97 (d, J = 8.7 Hz, 1H), 4.87 (d, J = 5.4 Hz, 2H), 3.93 (s, 3H), 1.63 (m, 2H), 1.42 (m, 2H); HRMS (ESI) *m/z* 502.1551 [(M+H)+; calcd for $C_{24}H_{22}N_8O_3S$: 502.1536].

Example 12 - synthesis of N-(4-(2-(4-sulfamoylbenzylamino)-4-(2,2,2-trifluoroethylamino)pyrido[3,2-d]pyrimidin-6-yl)phenyl)cyclopropanecarboxamide

Scheme 7

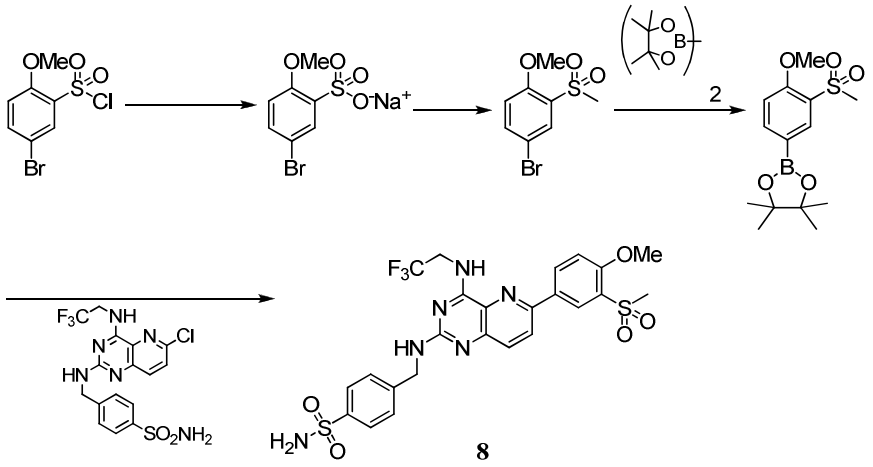


At room temperature cyclopropanecarbonyl chloride (0.772 mL, 10.5mmol) was added in a drop-wise manner to a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.19g, 10mmol), and $(i\text{Pr})_2\text{NEt}$ (3.5mL, 20mmol) in DMF (20mL). After 20min it was determined by LC/MS that some of the aniline remained. The reaction was cooled to 5°C and additional cyclopropanecarbonyl chloride (0.200 mL) was added. LC/MS showed no remaining starting aniline. The reaction was poured into a 5% $LiCl_{(aq.)}$ solution. The aqueous layer was extracted with EtOAc. The combined organics were dried over Na_2SO_4. The filtrate was concentrated to yield a solid. Attempt to dissolve solid in CH_2Cl_2 resulted in some solids that would not dissolve. These solids were isolated by filtration and determined to be N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarboxamide. The product in the filtrate was isolated by silica gel column chromatography (eleunt: EtOAc/hexanes) to provide N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarboxamide in a combined yield of 1.1g (38%).

A round bottom flask was charged with N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarboxamide (100 mg, 0.349 mmol), 4-((6-chloro-4-(2,2,2-trifluoroethylamino)pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide (104 mg, 0.233 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (9.5mg, 0.012mmol). DME (2mL) and a solution of sat. $NaHCO_{3(aq.)}$ (1mL) was added to the reaction flask. The reaction was placed in a 65°C oil bath and heated overnight. Trace chloride remains as determined by LC/MS. The reaction was suspended in MeOH and the solids were isolated by filtration. The solids were dissolved as much as possible in DMF (7mL) and the solution was filtered through a 0.45□ syringe filter. The product was purified from the filtrate by reverse phase HPLC (eluent: acetonitrile/water with 0.1% TFA) and isolated by freez-drying the pure fractions to yield 75 mg (40%) of N-(4-(2-(4-sulfamoylbenzylamino)-4-(2,2,2-trifluoroethylamino)pyrido[3,2-d]pyrimidin-6-yl)phenyl)cyclopropanecarboxamide as the bis-TFA salt. ^{1}H NMR (d_6-DMSO): δ 0.84 (brs, 4H), 1.82 (m, 1H), 4.44 (quintet, *J* = 8Hz, 2H), 4.81 (brs, 2H), 7.34 (s, 2H), 7.57 (d, *J* = 8.8Hz, 2H), 7.78 (d, *J* = 8.8Hz, 2H), 7.80 (d, *J* = 7.2Hz, 2H), 7.95 (d, *J* = 8.8Hz, 1H), 8.33 (d, *J* = 8.8Hz, 2H), 8.44 (d, *J* = 8.8Hz, 1H), 9.30 (s, 1H), 9.95 (s, 1H), 10.45 (s, 1H); HRMS (ESI) *m/z* 571.1618 [(M+H)+; calcd for $C_{26}H_{24}F_3N_7O_3S$: 571.1613].

Example 8 - synthesis of 4-((6-(4-methoxy-3-(methylsulfonyl)phenyl)-4-(2,2,2-trifluoroethylamino)pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide

Scheme 8



Na_2SO_3 (1.42g, 11.28mmol), and $NaHCO_3$ (948mg, 11.28mmol) were dissolved in H_2O (17mL), and the solution was heated in a 70°C oil bath. To this heated solution was added, in a drop-wise manner, a solution of 5-bromo-2-methoxybenzene-1-sulfonyl chloride (2g, 7mmol) in dioxane (17mL). The reaction was determined to be complete by LC/MS after 1h. The reaction was cooled to room temperature and transferred to a larger round bottom flask, using MeOH and H_2O to facilitate the transfer. The entire solution was concentrated *in vacuo* to yield a white solid that was placed under high vacuum overnight, as used as is in the next reaction.

To the flask containing sodium 5-bromo-2-methoxybenzenesulfonate was added DMF (32mL). To the resulting suspension was added MeI (873□L, 14mmol). The reaction turns bright yellow and begins to slightly clear up. After 2 reaction determined to be complete by LC/MS. The reaction was quenched by adding H_2O. The mixture was diluted with EtOAc, and then extracted with a 5% solution of $LiCl_{(aq.)}$ and brine. The organic layer was dried over a mixture Na_2SO_4 and $MgSO_4$. The filtrate was concentrated and 1.62g (87% over two steps) of 4-bromo-1-methoxy-2-(methylsulfonyl)benzene was isolated silica gel column chromatography (eluent: EtOAc/hexanes) as a white crystalline solid. MS (m/z): 267.09 $[M+H]^+$

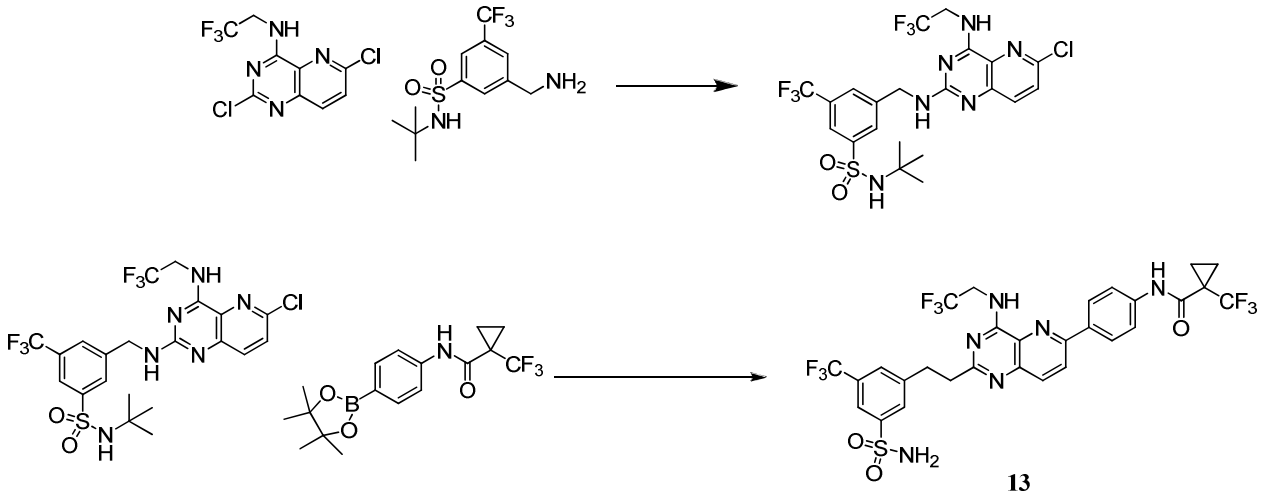
To a flask charged with bis(pinacolato)diboron (1.78g, 7.02mmol), XPhos (44mg, 0.093mmol), $Pd(dba)_3$ (43mg, 0.047mmol), and KOAc (604mg, 7.02mmol) was added dioxane (8mL). The resulting purple solution was placed in an 110°C bath. A solution of 4-bromo-1-methoxy-2-(methylsulfonyl)benzene (620mg, 2.33mmol) in dioxane (4mL) was slowly added to the first solution over 7min. After 1h the reaction was determined to be complete by LC/MS. The reaction was cooled to room temperature and precipitated solids were removed by vacuum filtration. The filtrate was then filtered through Celite 521. The filtrate was washed with H_2O, using brine to break emulsions. The organic was then washed with brine and dried over a mixture of Na_2SO_4 and $MgSO_4$. 640mg (88%) of 2-(4-methoxy-3-(methylsulfonyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was isolated by

silica gel column chromatography (eluent: EtOAc/hexanes). ^{1}H NMR (d_3-ACN): δ 1.33 (s, 12H), 3.16 (s, 3H), 3.99 (s, 3H), 7.20 (d, *J* = 8.4Hz, 1H), 7.96 (dd, *J* = 8.4, 1.6Hz, 1H), 8.15 (d, *J* = 1.6Hz, 1H)

To a flask charged with 2-(4-methoxy-3-(methylsulfonyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (157mg, 0.504mmol), 4-((6-chloro-4-(2,2,2-trifluoroethylamino)pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide (150mg, 0.336mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (14mg, 0.017mmol) was added DME (3mL) and sat. $NaHCO_{3(aq.)}$. The reaction was placed in a 65°C oil bath and stirred overnight. The reaction was incomplete so additional borate ester (85mg), catalyst (15mg), and sat. $NaHCO_{3(aq.)}$ was added to the reaction. After another hour the reaction was complete. The reaction was cooled to room temperature, diltuted with MeOH and the solids were isolated by filtration. The solids were dissolved as much as possible in DMF and the resulting solution was filtered through 0.45μ syringe filters. The product was purified from the filtrate by reverse phase HPLC (eluent: acetonitrile/water with 0.1% TFA) and isolated by freez-drying the pure fractions to yield 124mg (48%) of 4-((6-(4-methoxy-3-(methylsulfonyl)phenyl)-4-(2,2,2-trifluoroethylamino)pyrido[3,2-d]pyrimidin-2-ylamino)methyl)benzenesulfonamide as the bis-TFA salt. ^{1}H NMR (d_6-DMSO): δ 3.32 (s, 3H), 4.07 (s, 3H), 4.45 (m, 2H), 4.82 (brs, 2H), 7.34 (s, 2H), 7.48 (d, *J* = 9.2Hz, 1H), 7.57 (d, *J* = 8.8Hz, 2H), 7.79 (d, *J* = 7.6Hz, 2H), 8.00 (d, *J* = 9.2Hz, 1H), 8.44 (d, *J* = 8.8Hz, 1H), 8.49 (d, *J* = 2Hz, 1H), 8.76 (dd, *J* = 8.8, 2Hz, 1H), 9.33 (s, 1H), 10.0 (s, 1H); MS (m/z): HRMS (ESI) *m/z* 596.1123 [(M+H)+; calcd for $C_{24}H_{23}F_3N_6O_5S_2$: 596.1123].

Example 13 - synthesis of N-(4-(2-(3-sulfamoyl-5-(trifluoromethyl)phenethyl)-4-(2,2,2-trifluoroethylamino)pyrido[3,2-d]pyrimidine-6-yl)phenyl)-1-(trifluoromethyl)cyclopropanecarboxamide.

Scheme 9



13

Charge 2,6-dichloro-N-(2,2,2-trifluoroethyl)pyrido[3,2-d]pyrimidin-4-amine (894mg, 3.02mmol), 3-(aminomethyl)-N-*tert*-butyl-5-(trifluoromethyl)benzenesulfonamide (1.03g, 3.32mmol), diisopropylethylamine (1.08mL, 6.04mmol) in N-methylpyrrolidinone (15mL). The reaction was heated to 120 °C for 5 hours. It was then cooled to RT and partitioned between EtOAc and 5% $LiCl_{(aq)}$. The organics were separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and N-*tert*-butyl-3-((6-chloro-4-(2,2,2-

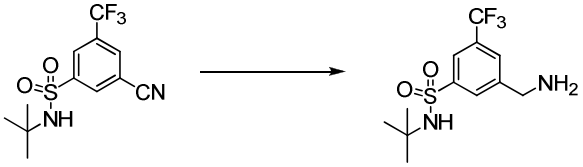
trifluoroethylamino) pyrido[3,2,d]pyrimidin-2-ylamino)methyl)-5-(trifluoromethyl) benzenesulfonamide (1.25g, 73%) was isolated by silica gel chromatography as a yellow solid.

Charge a microwave synthesizer vial with N-*tert*-butyl-3-((6-chloro-4-(2,2,2-trifluoroethylamino)pyrido[3,2,d]pyrimidin-2-ylamino)methyl)-5-(trifluoromethyl)benzenesulfonamide (143mg, 0.250mmol), N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaboran-2-yl)-1-(trifluoromethyl)cyclopropanecarboxamide (246mg, 0.692mmol), and DME (1.0mL). Stir for 5min, then add 2N K_2CO_3 (100μL) followed by palladium tetrakistriphenylphosphine (15mg, 0.012mmol). The reaction was heated to 130 °C for 30 min in the microwave. The reaction was diluted with CH_2Cl_2 (3mL). The organics were separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and N-(4-(2-(3-(N-*tert*-butylsulfamoyl)-5-(trifluoromethyl)phenethyl)-4-(2,2,2-trifluoroethylamino)pyrido[3,2-d]pyrimidin-6-yl)phenyl)-1-(trifluoromethyl)cyclopropanecarboxamide (178mg, 93%) was isolated by silica gel chromatography as a yellow solid.

N-(4-(2-(3-(N-*tert*-butylsulfamoyl)-5-(trifluoromethyl)phenethyl)-4-(2,2,2-trifluoroethylamino)pyrido[3,2-d]pyrimidin-6-yl)phenyl)-1-(trifluoromethyl)cyclopropanecarboxamide (178mg, 0.233mmol) was charged with TFA (4mL) and stirred at rt for 6h. The TFA was removed under reduced pressure and the reaction mixture was diluted with CH_3OH (3mL) and N-(4-(2-(3-(sulfamoyl-5-(trifluoromethyl)phenethyl)-4-(2,2,2-trifluoroethylamino)pyrido[3,2-d]pyrimidin-6-yl)phenyl)-1-(trifluoromethyl)cyclopropanecarboxamide **13** (75mg, 45%) was isolated by reverse phase HPLC: HRMS (ESI) *m/z* 707.1353 [(M+H)+; calcd for $C_{28}H_{22}F_9N_7O_3S$: 707.1361].

3-(aminomethyl)-N-*tert*-butyl-5-(trifluoromethyl) benzenesulfonamide was synthesized as follows:

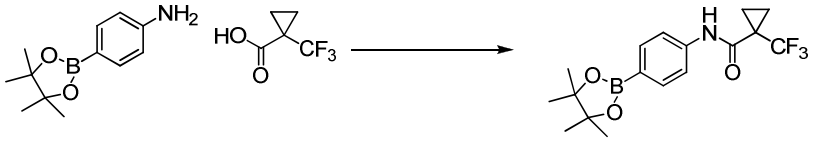
Scheme 10



N-*tert*-butyl-3-cyano-5-(trifluoromethyl)benzenesulfonamide (1.87g, 6.11mmol) was taken up in EtOH (20mL) and con HCl (2mL). the flask was purged with $Ar_{(g)}$. 10% Pd/C was added to the reaction mixture and the flask was evacuated and backfilled with $H_{2(g)}$. The reaction was stirred under $H_{2(g)}$ for 2h. The reaction was filtered through a PTFE filter and the solvents were removed under reduced pressure. The crude material was partitioned between EtOAc, and ½ sat. brine. The organics were separated and dried over Na_2SO_4 to afford 3-(aminomethyl)-N-*tert*-butyl-5-(trifluoromethyl) benzenesulfonamide (1.26g, 67%) as a beige solid.

N-(4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(trifluoromethyl)cyclopropanecarboxamide was synthesized as follows:

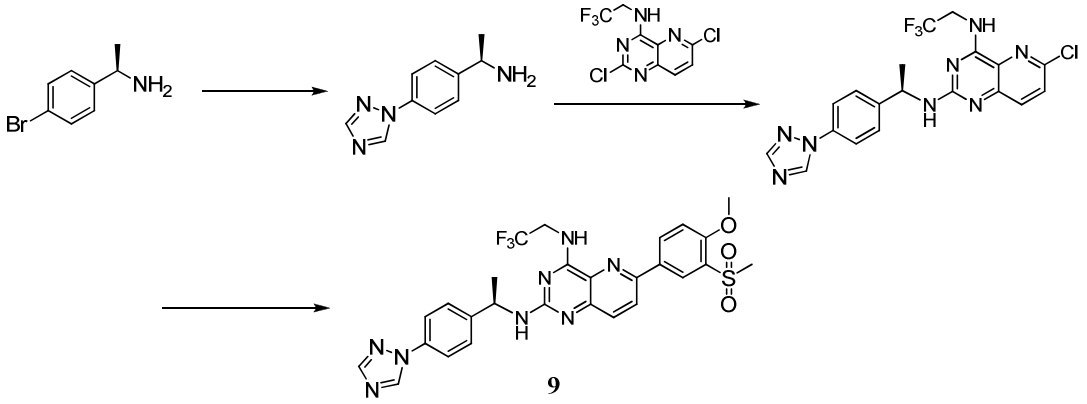
Scheme 11



Take up $(COCl)_2$ (2.83mL, 32.45mmol) was taken up in THF (5mL). Add DMF (3drops) to the reaction mixture. Take up 1-(trifluoromethyl) cyclopropanecarboxylic acid (1.0g, 6.49mmol) in THF (5mL) then add slowly to the $(COCl)_2$ solution. Stir at rt for 1h, then remove solvent under reduced pressure and coevaporate with toluene (10mL). Take up 4-(4,4,5,5-tetramethyl-1,3,2-dioxolan-2-yl)aniline (2.13g, 9.73mL) in THF (10mL) and charge to the reaction mixture. The reaction was stirred at rt for 3h. Remove solvent under reduced pressure and diluted with CH_2Cl_2 (5mL). N-(4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(trifluoromethyl)cyclopropanecarboxamide (246mg, 10%) was isolated by silica gel chromatography as an off-white solid.

Example 9 - synthesis of (R)-N2-(1-(4-(1H-1,2,4-triazol-1-yl)phenyl)ethyl)-6-(4-methoxy-3-(methylsulfonyl)phenyl)-N4-(2,2,2-trifluoroethyl)pyrido[3,2-d]pyrimidine-2,4-diamine

Scheme 12



9

(R)-1-(4-bromophenyl)ethanamine (0.500 g, 2.50 mmol), sodium iodide (0.937 g, 6.25 mmol), copper iodide (0.238 g, 1.25 mmol), N1,N2-dimethylethane-1,2-diamine (0.270 mL, 2.50 mmol) and potassium phosphate tribasic (1.06 g, 5.00 mmol) were combined, placed under nitrogen, suspended in DMF (5 mL, previously degassed by bubbling with nitrogen for 30 min), and heated to 110 deg C. After stirring for 2h, 1H-1,2,4-triazole (0.863 g, 12.5 mmol) was added and stirring was continued at 110 deg C. After stirring an addition 4h, the reaction mixture was cooled, diluted with EtOAc and filtered through celite. High vacuum concentration at 75 deg C (to remove DMF), followed by flash chromatography (0 to 15% EtOH (containing 11% aqueous ammonium hydroxide):DCM) affords 0.225 g (48% yield) of the desired (R)-1-(4-(1H-1,2,4-triazol-1-yl)phenyl)ethanamine as an orange oil.

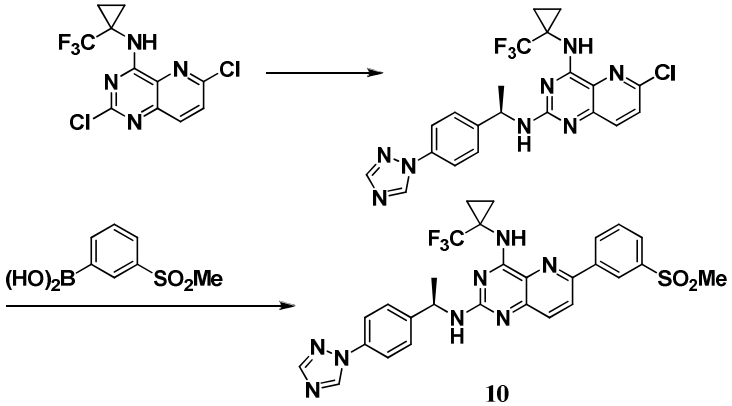
(R)-1-(4-(1H-1,2,4-triazol-1-yl)phenyl)ethanamine (0.225 g, 1.20 mmol), 2,6-dichloro-N-(2,2,2-trifluoroethyl)pyrido[3,2-d]pyrimidin-4-amine (0.356, 1.20 mmol) and diisopropylethylamine (0.416 mL, 2.4 mmol) were suspended in NMP and heated to 125 deg C. After stirring for 16 h, the reaction mixture was cooled, partitioned between ethyl acetate (50 mL) and water (20 mL) and separated. The organic layer was washed

again with water, dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (0 to 10% EtOH (containing 11% aqueous ammonium hydroxide):DCM) to afford 0.370 g (69% yield) of the desired (R)-N2-(1-(4-(1H-1,2,4-triazol-1-yl)phenyl)ethyl)-6-chloro-N4-(2,2,2-trifluoroethyl)pyrido[3,2-d]pyrimidine-2,4-diamine.

(R)-N2-(1-(4-(1H-1,2,4-triazol-1-yl)phenyl)ethyl)-6-chloro-N4-(2,2,2-trifluoroethyl)pyrido[3,2-d]pyrimidine-2,4-diamine (0.370 g, 0.82 mmol), 2-(4-methoxy-3-(methylsulfonyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.237 g, 1.03 mmol), palladium tetrakistriphenylphosphine (0.019 g, 0.016 mmol) and potassium carbonate (0.226 g, 1.64 mmol) were combined in DME (1.5 mL) and water (0.75 mL), sealed and heated to 120 deg C for 20 min. The reaction mixture was diluted with EtOAc (100 mL), washed twice with water, dried over sodium sulfate (anhyd), filtered and concentrated. The residue was purified by flash chromatography (0-9% EtOH:EtOAc) to afford 0.075 g (15% yield) of the title compound **9** and was characterized by 1H NMR and high-resolution mass-spec: ^{1}H NMR (d_6-DMSO): δ 1.60 (d, 3H, *J* = 6.9 Hz), 3.31 (3H, s), 4.05 (s, 3H), 4.2-4.6 (m, 2H), 5.42 (m, 1H), 7.47 (d, 1H, *J* = 9.0 Hz), 7.63 (br d, 2H, *J* = 8.7 Hz), 7.85 (2H, d, *J* = 8.7 Hz), 8.02 (d, 1H, *J* = 9.0 Hz), 8.22 (s, 1H), 8.45 (m, 2H), 8.76 (d, 1H, *J* = 10.5 Hz), 9.27 (s, 2H), 9.99 (br s, 1H); HRMS (ESI) *m/z* 598.1715 [(M+H)+; calcd for $C_{27}H_{25}F_3N_8O_3S$: 598.1722].

Example 10 - synthesis of (R)-N2-(1-(4-(1H-1,2,4-triazol-1-yl)phenyl)ethyl)-6-(3-(methylsulfonyl)phenyl)-N4-(1-(trifluoromethyl)cyclopropyl)pyrido[3,2-d]pyrimidine-2,4-diamine

Scheme 13

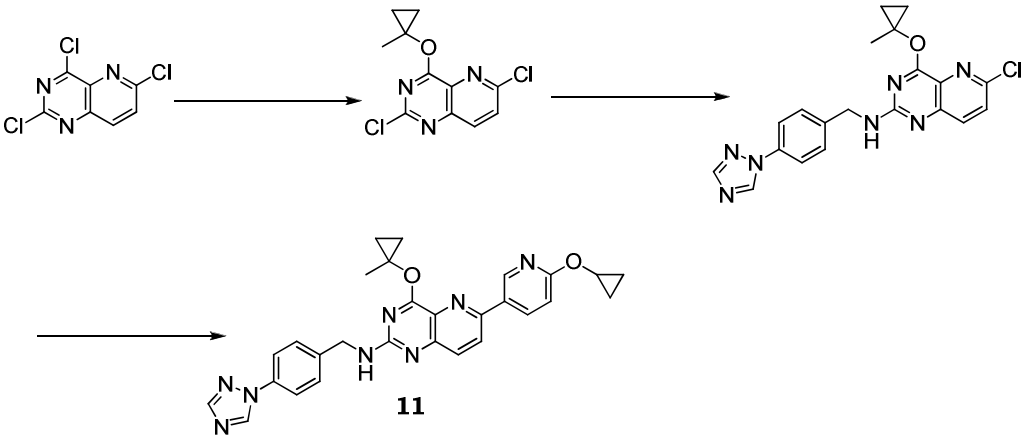


2,6-dichloro-N-(1-(trifluoromethyl)cyclopropyl)pyrido[3,2-d]pyrimidin-4-amine[1] (477 mg, 1.5 mmol) and (R)-1-(4-(1H-1,2,4-triazol-1-yl)phenyl)ethanamine (300 mg, 1.6 mmol) were suspended in NMP (1 mL), treated with diisopropylethylamine (0.30 mL, 1.7 mmol) and heated to 160 ºC. After 2.5 h, the reaction mixture was partitioned between ethyl acetate and 5% $LiCl_{(aq)}$. The organic phase was washed with 5% $LiCl_{(aq)}$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (0-30% [8:1 EtOH:NH_4OH]/DCM) to afford (R)-N2-(1-(4-(1H-1,2,4-triazol-1-yl)phenyl)ethyl)-6-chloro-N4-(1-(trifluoromethyl)cyclopropyl)pyrido[3,2-d]pyrimidine-2,4-diamine (198 mg, 0.42 mmol).

(R)-N2-(1-(4-(1H-1,2,4-triazol-1-yl)phenyl)ethyl)-6-chloro-N4-(1-(trifluoromethyl)cyclopropyl)pyrido[3,2-d]pyrimidine-2,4-diamine (97 mg, 0.20 mmol) was combined with 3-(methylsulfonyl)phenylboronic acid (62 mg, 0.31 mmol)), palladium tetrakistriphenylphosphine (30 mg, 0.026 mmol) and potassium carbonate (81 mg, 0.58 mmol). The mixture was treated with DME (1.2 mL) and water (0.6 mL) microwaved at 120 ℃ for 5 min. DMF and water were added, and a crude solid was isolated by filtration. The solid was dissolved in DMF and purified by preparative HPLC (5-95% acetonitrile:water with 0.1% TFA) to afford 87 mg (53% yield) of the title compound as its bis-TFA salt which was characterized by its NMR and mass spectrum as follows: ^{1}H NMR (d_6-DMSO): δ 1.10 – 1. 60 (m, 4H), 1.62 (d, *J* = 6.6 Hz, 3H), 3.33 (s, 3H), 5.40 (m, 1H), 7.59-7.70 (m, 2H), 7.82-7.90 (m, 3H), 8.00-8.13 (m, 2H), 8.22 (s, 1H), 8.58-8.65 (m, 2H), 8.95 (d, *J* = 7.5 Hz, 1H), 9.21 (bs, 1H), 9.28 (s, 1H), 10.15 (bs, 1H); HRMS (ESI) *m/z* 594.1776 [(M+H)+; calcd for $C_{28}H_{25}F_3N_8O_2S$: 594.1773].

Example 11 - synthesis of N-(4-(1H-1,2,4-triazol-1-yl)benzyl)-6-(6-cyclopropoxypyridin-3-yl)-4-(1-methylcyclopropoxy)pyrido[3,2-d]pyrimidin-2-amine

Scheme 14



2,4,6-trichloropyrido[3,2-d]pyrimidine (2.00 g, 8.53 mmol) and 1-methylcyclopropanol (1.23 g, 17.1 mmol) was dissolved in THF (21 mL) and cooled to 0 deg C. Sodium hydride (0.34 g, 8.53 mmol, 60% oil dispersion) was added portionwise over 8 min. After stirring for 5 min, the cloudy, pink mixture was added to a stirring mixture of water:ammonium chloride (sat aq):acetonitrile (2:1:1) dropwise over 10 minutes resulting in a fluffy white precipitate. After stirring an additional 10 min, the mixture was filtered and the solid was washed with water (50 mL) and dried by suction and then high vacuum. 1.875 g (81% yield) of the desired 2,6-dichloro-4-(1-methylcyclopropoxy)pyrido[3,2-d]pyrimidine was recovered as a white powder.

2,6-dichloro-4-(1-methylcyclopropoxy)pyrido[3,2-d]pyrimidine (1.34 g, 5.11 mmol), (4-(1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride (1.35 g, 6.39 mmol) and sodium iodide (0.384 g, 2.56 mmol) were suspended in NMP, treated with diisopropylethylamine, capped and heated to 40 deg C. After 27 h, the reaction mixture was cooled and partitioned between EtOAc (200 mL) and water (100 mL). Solids were filtered off and washed with EtOAc. The organic layer was separated and the aqueous was extracted again with EtOAc. The combined organic layers were washed with LiCl (5% aq). The 5% LiCl wash was extracted with EtOAc, and the combined organics were dried over sodium sulfate (anhyd), filtered and concentrated. Flash chromatography

(50% EtOAc:DCM to 10% MeOH:DCM) afforded 1.04 g (50% yield) of the desired N-(4-(1H-1,2,4-triazol-1-yl)benzyl)-6-chloro-4-(1-methylcyclopropoxy)pyrido[3,2-d]pyrimidin-2-amine.

Synthesis of **11** was completed in a manner similar to the final step of Example **2** using N-(4-(1H-1,2,4-triazol-1-yl)benzyl)-6-chloro-4-(1-methylcyclopropoxy)pyrido[3,2-d]pyrimidin-2-amine in place of N2-(4-(1H-1,2,4-triazol-1-yl)benzyl)-6-chloro-N4-(2,2,2-trifluoroethyl)pyrido[3,2-d]pyrimidine-2,4-diamine and characterized as follows: ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.75 (m, 6H), 1.04 (m, 2H), 1.55 (br s, 2H), 1.77 (br s, 1H), 4.28 m (m, 1H), 4.7 (m, 2H), 7.01 (d, 1H, *J* = 9.0 Hz), 7.58 (d, 2H, *J* = 8.7 Hz), 7.82 (d, 2H, *J* = 8.1 Hz), 7.95 (m, 1H), 8.21 (s, 1H), 8.22-8.40 (m, 1H), 8.43 (dd, 1H, *J* = 8.7, 2.4 Hz), 8.93 (br s, 1H), 9.26 (s, 1H); HRMS (ESI) *m/z* 506.2184 [(M+H)+; calcd for $C_{28}H_{26}N_8O_2$: 506.2179].

2. General Procedures

Replicon Antiviral assays. Replicon cells were seeded in 96-well plates at a density of 5,000 cells per well in 100 µl of DMEM culture medium without G418. Compounds were serially 3-fold diluted in 100% dimethyl sulfoxide (DMSO) and added to cells at a 1:200 dilution, achieving a final concentration of 0.5% DMSO in a total volume of 200 µl. There were totoal 11 concentrations used and the starting concentrations were 50 µM. Cell plates were incubated at 37°C for 3 days, after which culture medium was removed and cells were assayed for luciferase activity as markers for replicon levels. Luciferase expression was quantified using a commercial luciferase assay (Promega). Luciferase levels were converted into percentages relative to the levels in the untreated controls (defined as 100%), and data were fitted to the logistic dose response equation using XLFit4 software (IDBS, Emeryville, CA).

Stability in rat hepatic microsomal fraction (RLM). *In vitro* rat hepatic stability was determined in duplicate using pooled hepatic microsomal fractions from male Sprague Dawley rats. Incubation mixtures consisted of 0.5 mg/mL microsomal protein in 0.05 M potassium phosphate buffer pH 7.0 and a substrate concentration of 3 µM. After warming to 37°C reactions were initiated by the addition of NADPH regenerating system (final concentrations 1.25 mM NADP, 3.3 mM glucose-6-phosphate, 0.4 U/mL glucose-6-phosphate dehydrogenase and 3.3 mM $MgCl_2$). Aliquots were removed serially over 60 min and terminated by the addition of a quench solution (acetonitrile / methanol / water, 1:2:1 v/v/v) containing MS internal standard (IS). Substrate concentrations remaining were then determined using specific IS-controlled LC-MS/MS methods on a Micromass Quattro Premier triple quadrupole MS operating in positive ionization electrospray mode. The kinetics of loss of substrate were fit to a first order model and the rate quantified as the *in vitro* half-life.

Rat pharmacokinetics. Pharmacokinetics for each compound were determined individually in male Sprague Dawley rats (n = 3 per group). All procedures were approved by and conducted in accordance with Institutional Animal Care and Use Committee guidelines and regulations. Compounds were formulated as solutions in

aqueous cosolvent mixtures of polyetheylene glycol 400, propylene glycol and ethanol, and dosed by oral gavage or by intravenous infusion over 30 minutes. Blood samples were removed through jugular vein catheters and plasma prepared by centrifugation. Parent compounds were quantified by specific LC-MS/MS methods on SciEx API4000 or ThermoFinnigan TSQ Quantun Ultra triple quadrupole MS using standard curves extracted in parallel. Plasma clearance (CL) and mean residence time (MRT) were calculated using noncompartmental methods. Relative oral bioavailabilities was calculated from the ratio of areas under the plasma concentration time curve (AUC) extrapolated to infinite time, after oral and intravenous dosing, corrected for relative dose.

Formulations. Typical oral solutions were 1 mg/mL in co-solvent solution composed of 30-65% water, 30-60% PEG 400, with/without 5% ethanol. For example: 1 mg/mL in 50% PEG 400, 50% water, 1 equivalent HCl; 1.0 mg/mL in 5% EtOH; 30% PEG 400; 65% Water; 1 equiv. HCl.

3. Calculated Properties and Pharmacokinetic Data for all compounds

Compound #	MW	Rot Bonds	PSA	HBA	HBD	cLogP-Pallas	rat predicted hepatic extractn (%) (m'some)	Rat CL (L/h/kg)	Rat Vss (L/kg)	Rat MRT (h)	Rat F(%)	3*HBD - cLogP
1	503	8	177	10	3	2.6	29	4.5	1.6	0.4	2	6.4
2	534	10	116	9	2	4.7	9	1.2	6.1	5.3	59	1.34
3	507	8	131	7	3	4.7	9	0.3	2.3	6.9	147	4.3
4	556	9	162	9	3	3.6	9	0.5	1.2	2.6	3.6	5.43
5	491	7	168	9	3	2.8	9	0.9	0.9	0.9	4	6.2
6	508	8	144	8	3	3.8	13	0.2	1	4.9		5.2
7	567	8	131	7	3	6.0	9	0.4	4.3	11	109	3
8	597	10	183	10	3	3.2	9	1	0.8	0.8	2	5.8
9	599	10	145	10	2	4.5	10	2	5.1	2.6	47	1.48
10	595	9	136	9	2	4.7	15	2.2	5.9	3.5	88	1.33
11	507	9	113	9	1	2.9	9	1.7	3.3	1.9	100	0.08
12	572	10	160	8	4	4.3	37	0.5	0.6	1.2	1.3	7.7
13	708	12	160	8	4	6.5	9	0.4	6.4	15	25	5.5
14	527	11	116	9	2	6.6	9	1.6	3.5	2.2	11	-0.64
15	556	8	133	9	1	3.3	27	2.6	2	0.8	15	-0.28
16	438	7	128	7	2	3.8	48	3.3	2.3	0.7	65	2.2
17	605	10	120	8	2	4.4	26	1.6	4.7	3.1	11	1.64
18	571	9	136	9	2	3.9	9	0.8	1.2	1.5	23	2.08
19	554	9	123	8	2	4.3	9	2.2	2.9	1.3	22	1.7
20	580	10	142	10	1	2.7	15	1	3.2	3.3		0.3
21	594	10	142	10	1	2.8	32	1.4	3.1	2.4	66	0.24
22	464	8	128	7	2	4.2	33	3.9	3.4	0.9		1.8
23	424	6	128	7	2	3.0	9	2.6	2.2	0.9	95	3
24	434	6	128	7	2	3.2	9	0.8	2	2.5	141	2.8
25	528	8	133	9	1	2.3	9	0.7	1.4	1.9	56	0.75
26	569	9	136	9	2	4.5	39	1.9	2.6	1.4	11	1.55

27	633	10	158	8	3	5.7	9	0.2	1.7	7.8	27	3.3
28	556	9	149	10	2	3.5	27	1.5	1.2	0.9	17	2.55
29	660	11	123	8	3	6.6	9	1.5	3.3	2.3	24	2.37
30	436	7	131	7	3	2.8	22	0.4	0.6	1.7	53	6.2
31	654	11	160	8	4	5.7	26	0.6	5	7.9	5	6.3
32	600	11	171	10	3	4.2	63	2.4	4	1.7		4.84
33	574	9	162	9	3	3.8	14	1.5	4	2.6	4	5.22
34	592	10	143	10	3	2.6	10	2	5	2.5	3	6.39
35	658	11	160	8	4	5.2	9	0.5	0.8	1.7	1	6.8
36	646	11	123	8	3	6.1	50	6.3	19.4	3.2	2	2.89
37	532	8	161	9	3	2.2	13	7	2.8	0.4		6.8
38	556	9	162	9	3	3.6	9	2.1	4.2	1.9	4	5.43
39	450	7	131	7	3	3.4	9	0.9	1	1.2	106	5.6
40	585	10	158	9	3	4.5	9	5	3.1	0.6	0	4.5
41	521	9	136	9	2	3.6	13	7.1	3.4	0.5	8	2.45
42	621	11	145	10	2	4.5	35	0.7	1.3	1.3	13	1.55
43	531	8	155	8	3	4.7	12	1.7	1.8	1.1	10	4.3
44	511	9	131	7	3	4.9	23	0.5	1.7	3.4	53	4.1
45	569	9	136	9	2	4.5	9	2.6	4.8	1.8	95	1.55
46	575	9	126	8	3	4.0	22	3	4.7	1.6	14	4.98
47	521	10	103	8	2	5.4	9	4.1	1.7	0.4	0	0.6
48	633	11	183	10	3	4.3	9	0.9	1	1.1	0.1	4.7
49	555	9	136	9	2	3.9	9	1	1.5	1.5	20	2.06
50	494	10	141	8	3	3.3	34	4	2.7	0.7	40	5.7
51	522	10	116	9	2	4.5	37	5.1	4.6	0.9	9	1.49
52	561	10	183	10	3	1.9	15	3.5	1.8	0.5	1	7.1
53	517	9	131	7	3	4.8	29	1.2	2	1.7		4.2
54	596	10	157	10	2	3.7	32	0.3	0.4	1.3	32	2.3
55	645	9	174	9	3	4.4	14	0.2	0.3	2	5	4.6
56	551	8	144	8	3	4.6	18	0.5	0.6	1.3	57	4.4
57	491	9	131	7	3	4.5	14	2.2	3.8	1.7	115	4.5
58	623	11	183	10	3	3.8	11	0.7	0.6	0.8	2	5.2
59	561	8	131	7	3	6.2	9	0.2	3.6	21	28	2.8
60	665	11	183	10	3	4.3	9	0.6	0.8	1.4	12	4.7
61	601	9	131	7	3	6.4	9	0.3	2.9	9.5	25	2.6
62	551	8	131	7	3	5.3	11	0.6	3.1	4.8	98	3.7
63	524	8	131	7	3	5.2	9	0.3	3	9.1	49	3.8
64	581	9	174	9	3	3.7	9	0.6	0.5	0.8	1	5.3
65	665	11	183	10	3	4.6	14	0.2	0.5	2.1		4.4
66	541	8	131	7	3	5.6	13	0.4	4.7	11	40	3.4
67	541	8	131	7	3	5.4	9	0.6	3.3	6.3	57	3.6
68	547	8	131	7	3	5.6	9	0.4	6.2	18.2	130	3.4
69	546	8	155	8	3	5.1	12	7.9	26	3	47	3.9
70	541	8	131	7	3	5.4	11	1.6	6.6	4.2	133	3.6
71	535	8	131	7	3	5.8	13	0.2	2.9	12.6		3.2
72	599	10	145	10	2	4.5	47	1.4	2.7	2.1	46	1.48
73	524	8	131	7	3	5.0	9	0.9	13.8	16	138	4
74	510	8	160	8	4	3.0	12	4.4	5.1	1.2	2	9
75	521	9	117	7	3	4.9	71	1.7	2.2	1.3	24	4.1
76	533	10	118	9	3	5.1	18	8	10.1	1.3	10	3.94
77	574	9	131	7	3	6.0	9	0.3	5.5	17	35	3
78	535	9	131	7	3	5.7	12	0.3	8.7	32	81	3.3
79	574	9	131	7	3	5.8	14	0.5	4	8.3	90	3.2

80	507	8	144	8	3	3.5	13	1.1	1.5	1.4	29	5.5
81	492	8	132	9	3	3.8	35	2.8	3.6	1.3	9	5.24
82	485	7	135	7	3	3.4	10	6.2	4.1	0.7	52	5.6
83	573	9	160	8	4	4.7	17	4.2	3.4	0.8	3.9	7.3
84	591	9	164	8	4	3.0	39	0.9	0.5	0.6	1	9
85	598	10	209	10	4	3.2	28	2.3	2	0.9	0	8.8
86	521	8	131	7	3	5.2	14	0.5	5.5	12.3	85	3.8
87	522	8	170	9	4	3.2	17	0.9	1.9	2.1	9	8.8
88	464	7	167	9	3	2.4	13	4.4	7.1	1.6	8	6.6
89	450	8	161	9	3	3.0	36	6.1	2.6	0.4		6.04
90	497	9	109	7	3	4.2	68	10.1	19.3	1.7	0	4.8
91	667	12	207	11	5	2.9	11	4.1	1.4	0.3		12.1
92	588	10	199	10	5	2.2	14	1.6	0.8	0.5		12.8
93	528	10	143	9	4	2.9	13	2.5	0.9	0.4	5	9.11
94	444	8	132	9	3	2.9	13	9	7.2	0.8	39	6.15
95	644	13	187	10	4	4.5	95	1.4	0.1	0.1		7.5
96	617	10	193	10	5	3.4	47	1.6	0.7	0.4		11.6
97	567	9	174	9	3	3.7	11	0.9	0.8	0.9	1	5.3
98	547	9	178	9	4	2.8	9	0.4	0.3	0.8	15	9.2
99	573	9	160	8	4	4.6	15	4.3	4.4	1	0.3	7.4
100	587	9	178	9	4	2.7	40	1.4	1.1	0.8	0	9.3
101	529	8	160	8	4	3.8	65	0.8	1.4	1.6	5	8.2
102	519	9	156	9	4	3.5	26	2.9	4.7	1.7	2	8.5
103	574	9	159	10	4	2.8	24	4	7.2	1.8	0.1	9.2
104	588	9	172	9	4	2.9	10	1.7	2.1	1.2	3	9.1
105	573	9	164	8	4	2.7	40	1.6	1.1	0.7	3	9.3
106	488	7	194	10	4	1.9	14	13.7	13.1	1	0	10.1
107	503	8	177	10	3	2.7	9	2.2	1	0.5	1	6.3
108	480	7	128	7	2	4.4	17	0.9	1.3	1.5		1.6
109	431	8	81	6	2	4.3	50	7.6	7.5	1	67	1.7
110	446	8	93	7	2	4.6	39	4.1	3.7	0.9	44	1.4
111	468	8	100	7	3	5.9	10	0.2	0.3	1.1	29	3.1
112	562	11	203	10	4	0.1	16	1.5	0.5	0.3		11.9
113	507	8	131	7	3	4.8	9	0.3	2.1	6.2		4.2
114	505	8	170	9	4	2.9	15	1.1	1.9	1.8	2	9.1
115	506	8	183	10	4	2.4	13	1	1.6	1.6	1	9.6
116	412	7	131	7	3	2.4	9	1.4	4.3	3		6.6
117	615	10	164	9	4	3.6	38	3.6	4.3	1.2		8.4
118	588	9	172	9	4	2.9	13	2.3	2.3	1		9.1
119	490	7	155	8	3	3.7	16	0.7	2.5	3.7		5.3
120	588	10	181	9	5	3.3	12	0.9	0.7	0.8	2	11.7
121	546	9	181	9	5	2.9	12	1.3	1.1	0.9		12.1
122	549	10	207	10	6	1.6	19	3.6	3.4	0.9		16.4
123	511	8	198	9	4	3.1	9	1.8	1.8	1		8.9
124	479	8	149	8	3	2.8	13	1.8	0.9	0.5		6.2
125	480	7	128	7	2	4.8	11	1.5	4.5	3.2	91	1.2
126	671	11	198	10	5	3.3	9	1	0.2	0.2		11.7
127	491	8	157	9	3	2.3	15	2.3	1.2	0.6		6.7
128	434	7	104	6	2	2.9	9	11.7	6.5	0.6		3.1
129	508	8	144	8	3	3.7	18	0.5	0.9	1.8		5.3
130	563	10	134	8	3	4.7		2.4	0.3	0.1		4.3
131	514	8	155	8	3	4.2	13	0.3	1.7	6.2	18	4.8
132	655	11	198	10	5	3.1	9	4.4	0.9	0.2	0	11.9

133	432	8	93	7	2	4.1	13	6	4.2	0.7		1.9
134	509	8	93	7	2	6.0	9	0.3	2.7	9.4		0
135	501	12	108	8	2	4.3	9	3.1	6	1.9	72	1.7
136	521	8	131	7	3	5.2	11	0.2	2.1	12.7	87	3.8
137	494	8	93	7	2	5.4	14	1.7	8.3	4.9		0.6
138	619	10	172	9	5	3.6	23	1.7	7.5	4.4	0	11.4
139	601	10	172	9	5	3.3	9	2	9.6	5	0	11.7
140	645	13	173	10	4	4.3	13	1	3.8	3.9		7.7
141	586	9	200	9	4	3.4	14	3.8	4.1	1.1		8.6
142	465	7	131	7	3	4.3	11	1	4.9	5.2		4.7
143	470	8	106	6	3	5.1	9	7.7	4.6	0.6	77	3.9
144	541	8	131	7	3	5.5	9	0.7	7.3	10.7		3.5
145	466	7	128	7	2	4.3	9	0.5	4	7.6	167	1.7
146	566	9	170	9	4	3.1	16	3.6	10.6	2.9		8.9
147	548	9	170	9	4	2.8	55	1.9	4.6	2.6		9.2
148	535	8	169	9	3	2.4	74	3.9	2.5	0.7		6.6
149	460	7	157	7	2	4.2	50	1.6	9.3	7.6		1.8
150	458	7	196	9	3	2.6	49	1	0.8	0.8		6.4
151	488	7	128	7	2	5.0	9	2.2	6.9	3.8		1
152	433	7	115	6	3	4.3	22	1.3	1.4	1.1		4.7
153	515	8	197	9	3	2.4	11	2.8	2.8	1		6.6
154	538	10	204	10	5	1.5	13	2	0.9	0.4		13.5
155	591	11	207	10	6	2.0	9	3.3	3.1	0.7		16
156	597	10	184	9	4	3.5	9	1.3	0.6	0.4		8.5
157	532	9	174	8	4	3.2	11	1.3	0.9	0.8		8.8
158	479	8	172	8	3	2.7	11	1.9	1.3	0.7		6.3
159	573	10	183	9	3	3.5	16	1.6	0.8	0.5		5.5
160	519	9	158	8	3	3.5	19	0.6	0.2	0.4		5.5
161	454	7	128	7	2	3.9	22	3.5	3	0.9		2.1
162	527	8	103	7	3	4.4	17	3.4	7.5	2.2		4.6
163	487	8	101	7	3	4.3	9	2.8	17.9	6.3		4.7
164	531	11	102	8	2	5.4	39	2.2	4.1	1.8		0.6
165	453	7	102	7	1	4.2	27	6.8	83	14.4		-1.2
166	483	8	113	7	2	4.5	11	6.6	9.5	1.4		1.5
167	445	7	63	5	2	6.3	9	3.8	29	8.4		-0.3
168	474	8	172	9	3	2.3	23	3.8	4.4	1.2		6.7
169	473	8	106	6	3	5.1	39	22	16	0.7		3.9
170	454	7	128	7	2	4.2	18	0.9	3.3	4	35	1.8
171	473	8	115	7	3	4.1	57	6.3	2.6	0.4	22	4.9
172	474	8	109	7	3	4.3	65	2.1	0.9	0.5		4.7
174	475	8	115	7	3	4.6	48	6.3	5.6	1		4.4
175	470	8	105	7	2	3.9		5.2	10.3	2	20	2.1
176	489	10	92	7	2	4.3	92	3.6	4.6	1.3		1.7
177	458	8	89	6	2	5.0	59	3.8	1.5	0.4		1
178	410	6	60	5	1	5.9	53	1.1	22.3	19.6		-2.9
179	366	6	60	5	1	4.9	49	22.2	9.9	0.5		-1.9
180	434	6	69	6	1	5.2	94	5.5	7.9	1.5	1	-2.2
181	338	6	60	5	1	4.8	64	11	10.6	1		-1.8
182	392	6	60	5	1	5.7	53	1.3	5.6	4.4	21	-2.7

[1] 2,6-dichloro-N-(1-(trifluoromethyl)cyclopropyl)pyrido[3,2-d]pyrimidin-4-amine was made using a procedure similar to Example **1**, step 3, and substituting 1-trifluoromethyl-cyclopropylamine for trifluoroethanamine.