Supporting Information

Discovery of a Series of 3-Cinnoline Carboxamides as Orally Bioavailable, Highly Potent and Selective ATM Inhibitors

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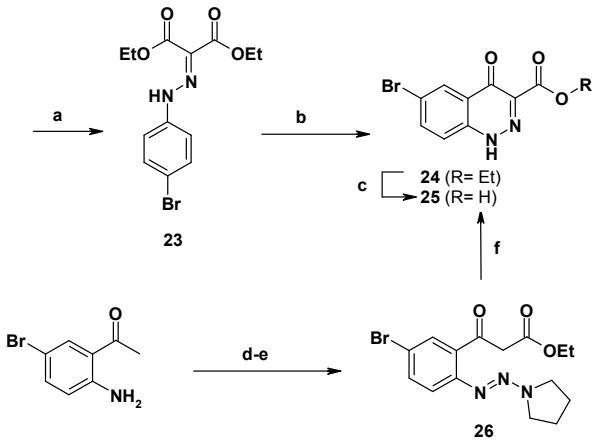
Synthesis

The synthesis of compounds **8-22** shared a common intermediate **25**, previously described.[15]

We developed two routes to intermediate **25** (Scheme 1). The first route, essentially following the methodology developed by Barber,[15] was based on the cyclisation of hydrazone **23** in the presence of titanium tetrachloride. However, purification of the resulting carboxylic acid was complex in our hands because of the presence of titanium salts and other residues. Therefore, a re-esterification / saponification sequence was introduced to obtain **25** on scale with good purity. Alternatively, following the methodology developed by Aston[16] and co-workers, cyclisation of **26**, obtained from commercially available 1-(2-amino-5-bromophenyl)ethanone followed by saponification gave **25** in excellent yield.

Scheme 1[a]

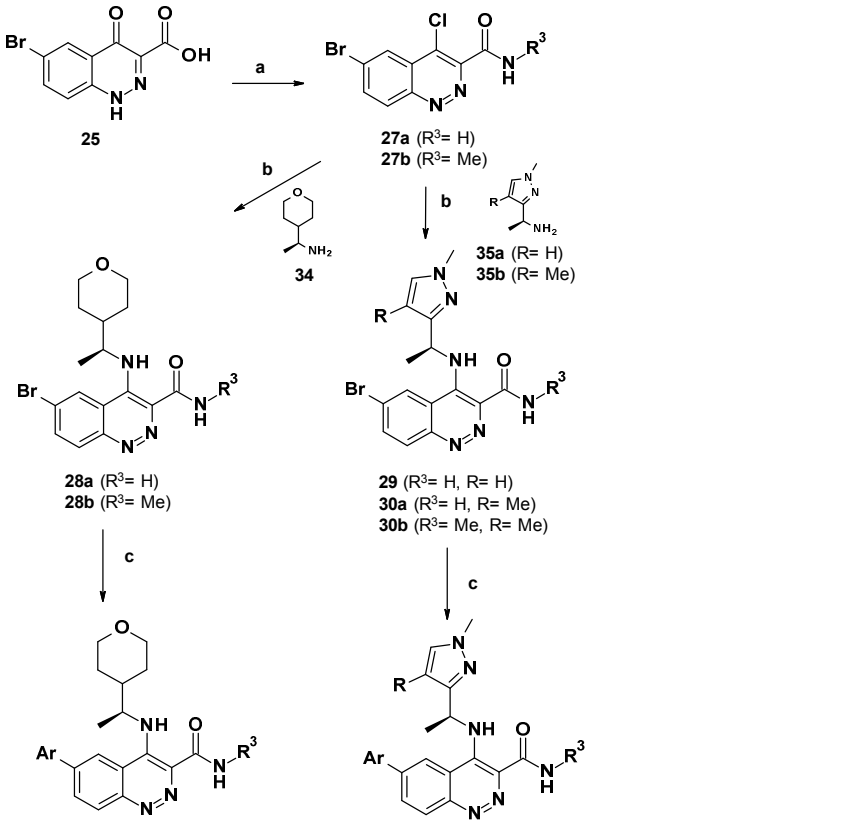


[a] **Reagents:** (a) 4-Br-PhNHNH$_2$.HCl, EtO$_2$CC(O)CO$_2$Et, 50% aq. EtOH, rt, 18 h, 92%; (b) NaOH, aq. EtOH, 78 °C, 50 min; SOCl$_2$, 40 °C, 44 h; TiCl$_4$, nitrobenzene, 120°C then 95 °C, 18 h; EtOH, conc. H$_2$SO$_4$, 90 °C, 5 h, 26% (over 3 steps); (c) NaOH, aq. MeOH - THF, 60 °C, 3 h, 96%; (d) 2M aq HCl, aq. NaNO$_2$ dropwise, 0 °C, 15 min; aq. NaOH, pyrrolidine, 0 °C, 15 min; 89%; (e) EtOC(O)OEt, NaH, THF, rt to 75 °C, 3 h, quantitative; (f) TFA, 0 °C to rt, 16 h, 91%

Chlorination of intermediate **25** followed by reaction with ammonia or methyl amine gave the 4-chloro-3-cinnoline carboxamides **27a-b**. Displacement of the 4-chloro with the previously known[12] chiral amines **34**, **35a** or **35b**, followed by Suzuki coupling with the suitable boronic esters (either previously described or prepared by known methods) gave compounds **8-11**, **13-14**, **16-18**, or the 4-fluoro-3-pyridine intermediates **31-33** (Scheme 2).

These intermediates **31-33** were converted to compounds **12**, **15**, **19-22** by displacement of the fluorine atom with the corresponding alcoholate or amine (Scheme 3).

Scheme 2[a]

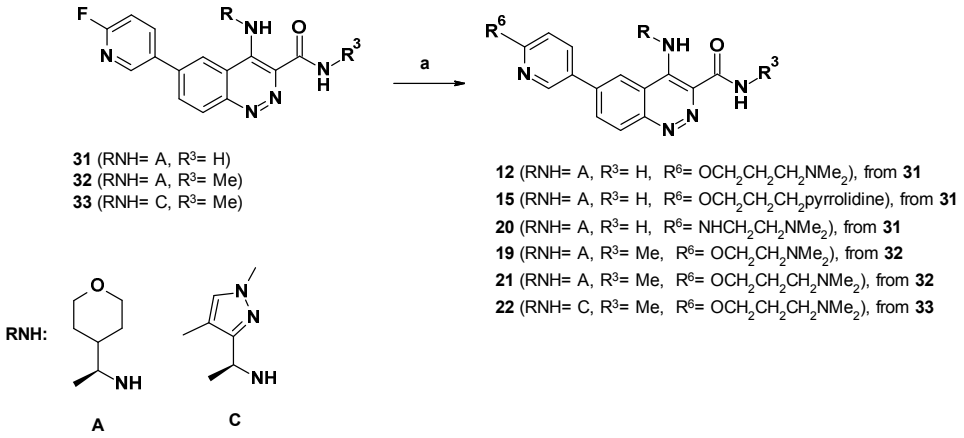


8 (R^3= H, Ar= 3-pyridyl-6-CH_2OMe)
11 (R^3= Me, Ar= 3-pyridyl-6-CH_2OMe)
31 (R^3= H, Ar= 3-pyridyl-6-F)
32 (R^3= Me, Ar= 3-pyridyl-6-F)

9 (R= H, R^3= H, Ar= 3-pyridyl-6-CH_2OMe)
10 (R= Me, R^3= H, Ar= 3-pyridyl-6-CH_2OMe)
13 (R= H, R^3= H, Ar= 3-pyridyl-6-$OCH_2CH_2CH_2NMe_2$)
14 (R= Me, R^3= H, Ar= 3-pyridyl-6-$OCH_2CH_2CH_2NMe_2$)
16 (R= H, R^3= H, Ar= 3-pyridyl-6-$OCH_2CH_2CH_2$-pyrrolidine)
17 (R= Me, R^3= H, Ar= 3-pyridyl-6-$OCH_2CH_2CH_2$-pyrrolidine)
18 (R= H, R^3= H, Ar= 3-pyridyl-6-$OCH_2CH_2NMe_2$)
33 (R= Me, R^3= Me, Ar= 6-F-3-pyridyl)

[a] **Reagents:** (a) $SOCl_2$, cat. DMF, 75-80 °C; NH_4OH, acetone, 0 °C to rt, 30 min, 82% (**27a**) or $MeNH_2$, DIPEA, THF-DCM, 0 °C, 1 h, 79% (**27b**), (b) chiral amine (i.e. **34, 35a** or **35b** as HCl salt), DIPEA, DMA, 90-100 °C; (c) Ar-BPin, Cs_2CO_3, $Pd(PPh_3)_4$ or 2nd Generation X-Phos precatalyst, dioxane-water, 80-100 °C (**8-11, 13-14, 16-18**) or Na_2PdCl_4 (0.05 eq.), $^tBu_2PCH_2CH_2CH_2SO_3H$ (0.1 eq.), 6-F-3-pyridyl-$B(OH)_2$, K_2CO_3, dioxane or AcO^iPr-water, 80-90 °C, 18 h, 73-98% (**31-33**)

Scheme 3[a]



[a] **Reagents:** (a) R^6-H (alcohol), NaH, DMA or THF, rt, then **31**, **32** or **33**, rt or rt to 50 °C (**12, 15, 19, 21-22**); or R^6-H (primary amine), DMSO, 100 °C, 30% (**20**)

General Procedures

All experiments were carried out at ambient temperature under an inert atmosphere. Evaporations were carried out by rotary evaporation or utilising Genevac equipment *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration. Flash chromatography purifications were performed on an automated Armen Glider Flash: Spot II Ultimate (Armen Instrument, Saint-Ave, France) using prepacked Merck normal phase Si60 silica cartridges (granulometry: 15-40 or 40-63 μm) obtained from Merck, Darmstadt, Germany or using Silicycle silica cartridges or Graceresolv silica cartridges. Preparative chromatography was performed on a Waters instrument (600/2700 or 2525) fitted with a ZMD or ZQ ESCi mass spectrometer and a Waters X-Terra or a Waters X-Bridge or a Waters SunFire reverse-phase column (C-18, 5 μm silica, 19 mm or 50 mm diameter, 100 mm length, flow rate of 40 mL/min) using decreasingly polar mixtures of water (containing 1% NH_3 or 0.1% formic acid) and acetonitrile as eluent. Intermediates were not fully purified but their structure and purity were assessed by TLC, NMR, HPLC and mass techniques and are consistent with the proposed structures. The purities of the compounds for biological testing were assessed by NMR, HPLC and mass spectral techniques and are consistent with the proposed structures; purity was at least 95%. Unless stated otherwise, proton magnetic resonance spectra were determined using a Bruker Avance instrument (400 MHz). Measurements were taken at ambient temperature unless otherwise specified. ^{1}H NMR chemical shift values are reported as δ values (ppm) downfield from internal TMS in appropriate organic solutions. The following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublets of doublets; dt, doublet of triplets; bs, broad signal. Analytical HPLC was carried out using an Waters Alliance HT (2790 & 2795) fitted with a Waters ZQ ESCi or ZMD ESCi mass spectrometer and an X Bridge 5μm C-18 column (2.1 x 50 mm) at a flow rate of 2.4 mL/min, using a solvent system of 95% A + 5% C to 95% B + 5% C over 4 minutes, where A = water, B = methanol, C = 1:1 methanol:water (containing 0.2% ammonium carbonate) or by using a

Shimadzu UFLC or UHPLC coupled with DAD detector, ELSD detector and 2020 EV mass spectrometer (or equivalent) fitted with a Phenomenex Gemini-NX C18 3.0 x 50 mm, 3.0 μm column or equivalent (basic conditions) or a Shim pack XR – ODS 3.0 x 50 mm, 2.2 μm column or Waters BEH C18 2.1 x 50 mm, 1.7 μm column or equivalent using a solvent system of 95% D + 5% E to 95% E + 5% D over 4 minutes, where D = water (containing 0.05% TFA), E = MeCN (containing 0.05% TFA) (acidic conditions) or a solvent system of 90% F + 10% G to 95% G + 5% F over 4 minutes, where F = water (containing 6.5 mM ammonium hydrogen carbonate and adjusted to pH10 by addition of NH_3), G = MeCN (basic conditions); detection was by Electrospray Mass Spectrometry and by UV absorbance at a wave length of 254 nm. Accurate mass spectra were recorded on a Thermo LTQ-FT in +ve ion mode with a Thermo Accela pump and a Surveyor PDA + with a CTC autosampler.

Diethyl [(4-bromophenyl)hydrazono]malonate (23)

Diethyloxomalonate (349.3 g, 2.01 mol) was added dropwise to a mixture of 4-bromophenyl hydrazine hydrochloride (448.3 g, 2.01 mol) and 50% aq. EtOH (7.8 L) over 10 minutes and the reaction was stirred at ambient temperature for 18 hours. The reaction was diluted with water (4.9 L), stirred for 30 minutes and then filtered. The solid was washed with water (4 x 500 mL) then dried in a vacuum oven overnight at 40 °C to afford **23** (633 g, 92%), which was used without further purification.

Ethyl 6-bromo-4-oxo-1,4-dihydro-3-cinnolinecarboxylate (24)

A mixture of **23** (633 g, 1.84 mol) and EtOH (1.26 L) was heated to 78 °C. Then 2N aq. NaOH (930 mL, 1.86 mol) was added dropwise over 15 minutes, maintaining the temperature between 75 and 78 °C. Additional 1N aq. NaOH (3.7 L, 3.7 mol) was added over 50 minutes, maintaining the temperature between 75 and 78 °C. The reaction was allowed to cool to ~55 °C and filtered. The filtrate was allowed to cool to ~30 °C and was then added dropwise to a solution of concentrated hydrochloric acid (563 mL, 6.76 mol) and water (5 L) cooled in a bath of isopropyl alcohol / solid carbon dioxide to maintain the temperature below 10 °C. Additional water (1 L) was added; the slurry was stirred for 30 minutes and filtered. The resulting solid was slurried in water (2 L) at ambient temperature for 30 minutes. The suspension was filtered and the solid was dried in a vacuum oven at 45 °C for 6 days to afford crude material (494 g). This material was further purified by suspending in EtOAc (2.47 L) and stirring at ambient temperature for 1 hour. The mixture was filtered, the solid washed with EtOAc (2 x 500 mL) and dried in a vacuum oven overnight at 40 °C to afford [(4-bromophenyl)hydrazono]malonic acid (425 g, 81%).

A mixture of [(4-bromophenyl)hydrazono]malonic acid (170 g, 0.592 mol) and thionyl chloride (510 mL, 7.03 mol) was heated to 40 °C for 44 hours and then allowed to cool. The reaction was diluted with heptane (250 mL), filtered and the solid was washed with heptane (2 x 100 mL) to afford [(4-bromophenyl)hydrazono]malonoyl dichloride (186.5 g, 97%).

$TiCl_4$ (116.7 mL, 1.065 mol) was added to a mixture of [(4-bromophenyl)hydrazono]malonoyl dichloride (328.5 g, 1.014 mol) in nitrobenzene (1.64 L) over 10 minutes. Then the reaction was heated to 120 °C for 20 minutes then to 95 °C and stirred overnight. The reaction was quenched by dropwise addition of 2N aq. NaOH (4 L, 8 mol) and the resulting suspension was stirred for 2 hours. The reaction was filtered twice to remove fine particulates believed to be titanium salts, the filtrate was separated and the aqueous layer was washed with DCM (3 x 300 mL). The aqueous layer was filtered again and the filtrate cooled to 5 °C. The pH of the mixture was adjusted to pH 1 by dropwise addition of concentrated hydrochloric acid and the resulting slurry was stirred for 30 minutes. The mixture was filtered; the solid was washed with water (2 x 100 mL) and dried in a vacuum oven at 40 °C to afford 6-bromo-4-oxo-1,4-dihydro-3-cinnolinecarboxylic acid (102.7 g)

containing significant amounts of inorganic impurities and nitrobenzene impurities. Additional impure 6-bromo-4-oxo-1,4-dihydro-3-cinnolinecarboxylic acid (32.2 g) was isolated, following a slurry of the titanium salts in 1M NaOH (3 L) for 2 hours at ambient temperature, filtration of the mixture twice to remove fine particulates and the subsequent washing of the aqueous layer with DCM (3 x 200 mL), filtration, acidification of the filtrate to pH1 with concentrated hydrochloric acid, stirring for 30 minutes and filtration. The impure 6-bromo-4-oxo-1,4-dihydro-3-cinnolinecarboxylic acid (123.2 g) obtained from the above procedure was processed in 3 separate batches according to the following procedure. The impure 6-bromo-4-oxo-1,4-dihydro-3-cinnolinecarboxylic acid was dissolved in EtOH (~40 volumes) and concentrated sulphuric acid (1.15 equiv.) added. The mixture was heated to 90 °C for 5 hours then allowed to cool to approximately 50 °C. The liquid was removed from insoluble residues by decanting and the residues discarded. The solution was allowed to cool to ambient temperature and stirred for 16 hours. The solid was collected by filtration and washed with a small quantity of cold EtOH to afford **24** (88.1 g over 3 batches, 29.2%) as an orange solid. The filtrates from the 3 procedures were combined and concentrated to approximately 25% of the original volume and cooled to 5 °C to encourage precipitation. The suspension was subsequently stirred at ambient temperature for 16 hours, the solid collected by filtration and washed with a small amount of cold EtOH to afford additional **24** (10.7 g, 3.6%). ^{1}H NMR (DMSO-d_6): 1.29 (3H, t), 4.30 (2H, q), 7.65 (1H, d), 8.00 (1H, dd), 8.18 (1H, d), 14.02 (1H, s); MS-ESI *m/z* 297 $[MH]^+$ $C_{11}H_9BrN_2O_3$ requires 297.

Alternatively, ethyl 6-bromo-4-oxo-1,4-dihydro-3-cinnolinecarboxylate **(24)** was prepared as follows:
TFA (837 mL, 10.9 mol) was added slowly to **26** (160 g, 435 mmol) over a period of 30 minutes at 0 °C under an inert atmosphere. The resulting solution was stirred at ambient temperature for 16 hours then the reaction mixture was poured onto ice-water (2 L). The precipitate was collected by filtration, washed with water (5 x 100 mL) and dried in the vacuum oven to afford **24** (118 g, 91%) as a pale yellow solid, which was used without further purification.

Ethyl 3-[5-bromo-2-(1-pyrrolidinyldiazenyl)phenyl]-3-oxopropionate (26)
1-(2-Amino-5-bromophenyl)ethanone (94.8 g, 443 mmol) was added to 2M hydrochloric acid (700 mL, 1.4 mol) and the resulting mixture was stirred at 60 °C for 2 hours. The mixture was cooled to 0 °C and a solution of sodium nitrite (30.6 g, 443 mmol) in water (100 mL) was added dropwise. After 15 minutes the mixture was filtered, the solid discarded and the filtrate added to a stirred solution of pyrrolidine (31.5 g, 443 mmol) and sodium hydroxide (56.0 g, 1.4 mol) in water (500 mL) at 0 °C. After 15 minutes, the precipitate was collected by filtration, washed with water and dried in the vacuum oven to afford 1-[5-bromo-2-(1-pyrrolidinyldiazenyl)phenyl]ethanone (117 g, 89%) as a red solid, which was used without further purification. ^{1}H NMR (DMSO-d_6): 1.99 (4H, m), 2.54 (3H, s), 3.58 (2H, t), 3.91 (2H, t), 7.37 - 7.66 (3H, m); MS-ESI *m/z* 298 $[MH]^+$, (^{81}Br).
Sodium hydride (55.3 g, 1.38 mol) was added portionwise to a solution of diethyl carbonate (467 g, 3.95 mol) in THF (800 mL) at ambient temperature under an inert atmosphere. A solution of 1-[5-bromo-2-(1-pyrrolidinyldiazenyl)phenyl]ethanone (117 g, 395 mmol) in THF (200 mL) was added slowly over a period of 60 minutes and the resulting mixture stirred at 75 °C for 3 hours. The reaction mixture was allowed to cool then quenched with water (100 mL) and the resulting mixture concentrated under vacuum. The residue was diluted with water (500 mL), extracted with EtOAc (4 x 500 mL), the organic layer dried over Na_2SO_4, filtered and evaporated to afford **26** (168 g, quantitative) as a brown solid, which was used without further purification. ^{1}H NMR (DMSO-d_6): 1.11 (3H, t), 1.93 - 2.04 (4H, m), 3.60

(2H, t), 3.93 (2H, t), 4.03 (2H, q), 4.11 (2H, s), 7.41 (1H, d), 7.61 - 7.64 (2H, m); MS-ESI *m/z* 368 $[MH]^+$ $C_{15}H_{18}BrN_3O_3$ requires 368.

6-Bromo-4-oxo-1,4-dihydro-3-cinnolinecarboxylic acid (25)
2M Aq. sodium hydroxide (375 mL, 747 mmol) was added to a mixture of **24** (44.4 g, 149 mmol) in THF (1 L) and MeOH (100 mL) and the resulting mixture was stirred at 60 °C for 1 hour. Water (600 mL) was added and the mixture was heated at 60 °C for a further 2 hours. The reaction mixture was diluted with water (1.6 L) and the pH adjusted to pH 3 by the addition of 2M hydrochloric acid. The precipitate was collected by filtration, washed with water (1.6 L) and dried under vacuum to afford **25** (38.6 g, 96%) as a beige solid, which was used without further purification. ^{1}H NMR (DMSO-d_6): 7.77 (1H, d), 8.10 (1H, dd), 8.31 (1H, d), 14.14 (1H, s), 14.71 (1H, s); MS-ESI *m/z* 267 $[M-H]^-$ $C_9H_5BrN_2O_3$ requires 267.

6-Bromo-4-chloro-3-cinnolinecarboxamide (27a)
DMF (0.1 mL, 1.24 mmol) was added in one portion to **25** (3.34 g, 12.4 mmol) and thionyl chloride (33 mL, 460 mmol). The resulting mixture was stirred at 80 °C for 3 hours. The resulting mixture was evaporated to dryness and the residue was azeotroped with toluene (3 x 20 mL) to afford crude 6-bromo-4-chloro-3-cinnolinecarbonyl chloride (3.80 g, 100 %). Ammonium hydroxide (35.5 mL, 910 mmol) was added dropwise to 6-bromo-4-chloro-3-cinnolinecarbonyl chloride (3.80 g, 12.4 mmol) in acetone (60 mL) cooled to 0 °C over a period of 10 minutes. The resulting mixture was stirred at room temperature for 30 minutes. The precipitate was collected by filtration, washed with acetone (10 mL) and dried under vacuum to afford **27a** (2.93 g, 82%) as a tan solid, which was used without further purification. ^{1}H NMR (DMSO-d_6, 30 °C): 8.11 (1H, s), 8.26 (1H, dd), 8.41 (1H, s), 8.49 - 8.68 (2H, m); MS-ESI *m/z* 286 $[MH]^+$ $C_9H_5BrClN_3O$ requires 286.

6-Bromo-4-{[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]amino}-3-cinnolinecarboxamide (28a)
DIPEA (4.5 mL, 26 mmol) was added in one portion to **27a** (2.93 g, 10.23 mmol) and (1S)-1-(tetrahydro-2H-pyran-4-yl)ethanamine **34**[12] (as the hydrochloride salt, 1.864 g, 11.25 mmol) in DMA (40 mL). The resulting mixture was stirred at 100 °C for 2 hours. The reaction mixture was diluted with EtOAc (500 mL), and washed sequentially with water (2 x 200 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford **28a** (3.76 g, 97%). ^{1}H NMR (DMSO-d_6): 1.32 (5H, d), 1.59 (2H, dd), 1.76 (1H, s), 3.25 (2H, t), 3.75 - 3.96 (2H, m), 3.99 - 4.14 (1H, m), 7.76 (1H, s), 7.99 (1H, dd), 8.14 (1H, d), 8.34 (1H, s), 8.61 (1H, s), 10.26 (1H, s). MS-ESI *m/z* 381 $[MH]^+$, (^{81}Br) $C_{16}H_{19}BrN_4O_2$ requires 381.

6-[6-(Methoxymethyl)-3-pyridinyl]-4-{[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]amino}-3-cinnolinecarboxamide (8)
Tetrakis(triphenylphosphine)palladium(0) (12 mg, 11 μmol) was added in one portion to **28a** (200 mg, 0.53 mmol), 2-(methoxymethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine[12] (315 mg, 0.63 mmol) and cesium carbonate (430 mg, 1.32 mmol) in 1,4-dioxane (3 mL) : water (0.4 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 18 hours. The reaction mixture was diluted with EtOAc (20 mL), and washed with water (2 x 20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 50 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **8** (11 mg, 5%) as a solid. ^{1}H NMR (500

MHz, DMSO-d_6, 30 °C): 1.31 - 1.47 (5H, m), 1.57 (1H, d), 1.68 (1H, d), 1.78 - 1.85 (1H, m), 3.23 - 3.3 (2H, m), 3.43 (3H, s), 3.84 - 3.92 (2H, m), 4.22 - 4.33 (1H, m), 4.60 (2H, s), 7.59 (1H, d), 7.74 (1H, s), 8.23 - 8.27 (2H, m), 8.32 (1H, d), 8.41 (1H, d), 8.62 (1H, s), 8.99 (1H, dd), 10.35 (1H, s); HRMS-ESI *m/z* 422.2176 $[MH]^+$ $C_{23}H_{27}N_5O_3$ requires 422.2192.

6-Bromo-4-{[(1S)-1-(1-methyl-1H-pyrazol-3-yl)ethyl]amino}-3-cinnolinecarboxamide (29)

27a (0.25 g, 0.87 mmol), (1S)-1-(1-methyl-1H-pyrazol-3-yl)ethanamine **35a**[12] (as the hydrochloride salt, 0.169 g, 1.05 mmol) and DIPEA (0.53 mL, 3.05 mmol) were suspended in DMA (3 mL) and heated at 100 °C for 1 hour. The reaction mixture was diluted with water (200 mL), and extracted with ethyl acetate (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the crude product, which was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH and pure fractions were evaporated to dryness to afford **29** (0.240 g, 73%) as a brown gum. ^{1}H NMR (DMSO-d_6, 30 °C): 1.62 (3H, dd), 3.69 - 3.86 (3H, m), 5.35 (1H, dd), 6.21 (1H, d), 7.62 (1H, d), 7.76 (1H, s), 7.94 (1H, dd), 8.11 (1H, d), 8.56 (1H, d), 8.61 (1H, s), 10.79 (1H, d); MS-ESI *m/z* 377 $[MH]^+$, (^{81}Br) $C_{15}H_{15}BrN_6O$ requires 377.

6-[6-(methoxymethyl)-3-pyridinyl]-4-{[(1S)-1-(1-methyl-1H-pyrazol-3-yl)ethyl]amino}-3-cinnolinecarboxamide (9)

29 (150 mg, 0.40 mmol), 2-(methoxymethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (149 mg, 0.60 mmol), cesium carbonate (96 mL, 1.20 mmol) and tetrakis(triphenylphosphine)palladium(0) (32.3 mg, 0.03 mmol) were suspended in degassed 1,4-dioxane (10 mL) and water (1.1 mL) at ambient temperature. The resulting mixture was degassed, purged with nitrogen and heated at 100 °C for 16 hours. The mixture was allowed to cool, and then was filtered, diluted with diethylether, and washed with water. The resulting organic filtrate was evaporated to dryness. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 50 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluent. Fractions containing the desired compound were evaporated to dryness to afford **9** (65 mg, 39%) as a white solid. ^{1}H NMR (DMSO-d_6, 30 °C): 1.60 (3H, d), 3.43 (3H, s), 3.82 (3H, s), 4.59 (2H, s), 5.49 (1H, m), 6.22 (1H, d), 7.52 (1H, m), 7.62 (1H, d), 7.75 (1H, s), 8.15 (1H, m), 8.19 (1H, m), 8.24 (1H, d), 8.60 (1H, s), 8.63 (1H, s), 8.88 (1H, s), 10.87 (1H, d); MS-ESI *m/z* 418 $[MH]^+$ $C_{22}H_{23}N_7O_2$ requires 418.

6-bromo-4-{[(1S)-1-(1,4-dimethyl-1H-pyrazol-3-yl)ethyl]amino}-3-cinnolinecarboxamide (30a)

27a (0.25 g, 0.87 mmol), (1S)-1-(1,4-dimethyl-1H-pyrazol-3-yl)ethanamine **35b**[12] (as the hydrochloride salt, 0.184 g, 1.05 mmol) and DIPEA (0.53 mL, 3.05 mmol) were suspended in DMA (3 mL) and heated at 100 °C for 1 hour. The reaction mixture was diluted with water (200 mL), and extracted with ethyl acetate (200 mL). The organic was dried over $MgSO_4$, filtered and evaporated. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH and pure fractions were evaporated to dryness to afford **30a** (0.310 g, 91%) as a brown gum. ^{1}H NMR (DMSO-d_6, 30 °C): 1.59 (3H, d), 1.99 - 2.03 (3H, m), 3.70 (3H, s), 5.35 (1H, p), 7.39 (1H, s), 7.75 (1H, s), 7.92 (1H, dd), 8.07 (1H, d), 8.45 (1H, d), 8.60 (1H, s), 10.95 (1H, d); MS-ESI *m/z* 389 $[MH]^+$ $C_{16}H_{17}BrN_6O$ requires 389.

4-{[(1S)-1-(1,4-dimethyl-1H-pyrazol-3-yl)ethyl]amino}-6-[6-(methoxymethyl)-3-pyridinyl]-3-cinnolinecarboxamide (10)

30a (0.30 g, 0.77 mmol), 2-(methoxymethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.288 g, 1.16 mmol), cesium carbonate (185 mL, 2.31 mmol) and tetrakis(triphenylphosphine)palladium(0) (62 mg, 0.05 mmol) were suspended in degassed 1,4-dioxane (10 mL) and water (1.1 mL) at ambient temperature. The resulting mixture was degassed, purged with nitrogen and heated at 100 °C for 16 hours. The mixture was allowed to cool. The mixture was filtered, diluted with diethylether, and washed with water. The resulting organic filtrate was evaporated to dryness. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 50 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **10** (0.310 g, 93%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6, 30 °C): 1.69 (3H, d), 2.00 (3H, s), 3.48 (3H, s), 3.73 (3H, s), 4.65 (2H, s), 5.58 (1H, d), 7.43 (1H, s), 7.63 (1H, d), 7.80 (1H, s), 8.19 - 8.34 (3H, m), 8.64 (1H, d), 8.69 (1H, s), 9.02 (1H, d),11.1 (1H, s); MS-ESI *m/z* 432 $[MH]^+$ $C_{23}H_{25}N_7O_2$ requires 432.

6-bromo-4-chloro-N-methyl-3-cinnolinecarboxamide (27b)

25 (34.3 g, 127 mmol) was suspended in thionyl chloride (343 mL, 4.72 mol) and DMF (1 mL, 13 mmol) added. The resulting mixture was stirred at 75 °C for 16 hours. Then, the mixture was evaporated to dryness and the residue azeotroped three times with toluene. The residue was dissolved in DCM (900 mL). DIPEA (28 mL, 160 mmol) and methylamine (2M in THF, 51 mL, 102 mmol) were added dropwise over 30 minutes at 0 °C under an inert atmosphere. The resulting mixture was stirred for a further 15 minutes at 0 °C, then additional methylamine (2M in THF, 8.3 mL, 17 mmol) was added dropwise. The mixture was stirred for a further 15 minutes at 0 °C then diluted with DCM (700 mL) and washed sequentially with water (800 mL), 0.1 M citric acid (800 mL) and saturated sodium hydrogencarbonate solution (400 mL). The organic layer was filtered through a phase-separating paper, EtOAc (1000 mL) was added and the mixture was concentrated to a 1 L volume. The solid was collected by filtration, washed with a small amount of cold EtOAc and dried to afford **27b** (30.2 g, 79%) as a beige solid used without further purification. ^{1}H NMR (DMSO-d_6): 2.91 (3H, d), 8.26 (1H, dd), 8.52 (1H, d), 8.55 (1H, d), 9.00 (1H, q); MS-ESI *m/z* 300 $[MH]^+$ $C_{10}H_7BrClN_3O$ requires 300.

6-Bromo-N-methyl-4-{[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]amino}-3-cinnolinecarboxamide (28b)

DIPEA (36 mL, 208 mmol) was added to a mixture of **27b** (25.0 g, 83.2 mmol), **34** (as the free base 7.75 g, 60 mmol,) and more of **34** (as the hydrochloride salt, 5.5 g, 33.2 mmol) in DMA (200 mL) and the resulting mixture was stirred at 100 °C for 2 hours before being allowed to cool. This procedure was also performed on 17 g (56.6 mmol) of **27b** using 8.04 g (62.2 mmol) of **34** (free base) and the cooled reaction mixture was combined with that from the previous preparation. The combined reaction mixtures were partitioned between EtOAc (1.5 L) and water (1.5 L) although the addition of DCM (1 L) was required to ensure all material was in solution. The organic extracts were washed with brine (1.5 L), dried over $MgSO_4$, filtered and concentrated to around 200 mL volume at which point precipitation was observed. The solid was collected by filtration, washed with a small amount of EtOAc and dried to afford **28b** (40.1 g, 73%) as a white crystalline solid. A second crop of **28b** (10.4 g, 19%) was obtained by evaporation of the filtrate and trituration with a small amount of EtOAc. ^{1}H NMR (DMSO-d_6): 1.30 (3H, d), 1.33 - 1.42 (2H, m), 1.56 (1H, d), 1.62 (1H, dd), 1.73 - 1.9 (1H, m), 2.87 (3H, d), 3.21 - 3.27 (2H, m), 3.87 – 3.91 (2H, m), 4.08 - 4.12 (1H,

m), 7.99 (1H, dd), 8.15 (1H, d), 8.37 (1H, d), 9.24 (1H, d), 10.24 (1H, br s); MS-ESI *m/z* 395 $[MH]^+$, (^{81}Br) $C_{17}H_{21}BrN_4O_2$ requires 395.

6-[6-(Methoxymethyl)-3-pyridinyl]-N-methyl-4-{[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]amino}-3-cinnolinecarboxamide (11)

28b (0.15 g, 0.38 mmol), 2-(methoxymethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.114 g, 0.46 mmol), cesium carbonate (372 mg, 1.14 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.031 g, 0.03 mmol) were suspended in degassed 1,4-dioxane (10 mL) and water (1.1 mL) at ambient temperature. The resulting mixture was degassed, purged with nitrogen and heated at 90 °C for 16 hours. The mixture was allowed to cool overnight. The mixture was filtered, washing sequentially with water and diethylether. The resulting filtrate was evaporated to dryness. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 50 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **11** (0.100 g, 60 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6, 30 °C): 1.44 (5H, d), 1.64 (1H, m), 1.74 (1H, m), 1.88 (1H, m), 2.94 (3H, d), 3.35 (2H, m), 3.49 (3H, s), 3.94 (2H, m), 4.26 - 4.37 (1H, m), 4.65 (2H, s), 7.64 (1H, d), 8.30 (2H, m), 8.38 (1H, d), 8.47 (1H, d), 9.04 (1H, d), 9.32 (1H, d), 10.39 (1H, s). MS-ESI *m/z* 436 $[MH]^+$ $C_{24}H_{29}N_5O_3$ requires 436.

6-(6-Fluoro-3-pyridyl)-4-[[(1S)-1-tetrahydropyran-4-ylethyl]amino]cinnoline-3-carboxamide (31)

A 1:2 mixture of sodium tetrachloropalladate(II) and 3-(di-*tert*-butylphosphino)propane-1-sulfonic acid (0.05 M in water, 10 mL, 0.50 mmol) was added to **28a** (3.76 g, 9.91 mmol), (6-fluoropyridin-3-yl)boronic acid (1.54 g, 10.9 mmol) and potassium carbonate (4.11 g, 29.7 mmol) in degassed 1,4-dioxane (70 mL) and water (17.5 mL) under an inert atmosphere. The resulting mixture was stirred at 80 °C for 18 hours then allowed to cool. The reaction mixture was diluted with EtOAc (200 mL), and washed sequentially with water (2 x 200 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford **31** (3.39 g, 86 %) as a pale yellow solid. ^{1}H NMR (DMSO-d_6): 1.34 - 1.38 (5H, m), 1.54 (1H, d), 1.65 (1H, d), 1.76 - 1.83 (1H, m), 3.25 (2H, t), 3.8 - 3.95 (2H, m), 4.19 - 4.33 (1H, m), 7.38 (1H, dd), 7.74 (1H, s), 8.21 (1H, d), 8.30 (1H, d), 8.36 (1H, s), 8.44 (1H, td), 8.61 (1H, s), 8.71 (1H, d), 10.34 (1H, s); MS-ESI *m/z* 396 $[MH]^+$ $C_{21}H_{22}FN_5O_2$ requires 396.

6-{6-[3-(Dimethylamino)propoxy]-3-pyridinyl}-4-{[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]amino}-3-cinnolinecarboxamide (12)

A solution of 3-(dimethylamino)-1-propanol (1.3 mL, 11 mmol) in DMA (10 mL) was added dropwise to a stirred suspension of sodium hydride (1.27 g, 31.8 mmol) in DMA (40 mL) at ambient temperature and the resulting suspension was stirred for 20 minutes under an inert atmosphere. **31** (3.14 g, 7.94 mmol) was added and the reaction stirred at ambient temperature for 1 hour and then heated to 50 °C for 10 minutes. The reaction mixture was diluted with DCM (150 mL), and washed sequentially with water (2 x 100 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the crude product which was purified by ion exchange chromatography, using an SCX column eluting with 1M NH_3 in MeOH. The material was further purified by flash silica chromatography, elution gradient 0 to 20% MeOH in DCM, to afford **12** (2.1 g, 55%). ^{1}H NMR ($CDCl_3$): 1.34 - 1.57 (5H, m), 1.62 - 1.93 (3H, m), 1.93 - 2.08 (2H, m), 2.28 (6H, s), 2.41 - 2.53 (2H, m), 3.36 - 3.40 (2H, m), 3.97 - 4.03 (2H, m), 4.08 - 4.20 (1H, m), 4.43 (2H, t), 5.57 (1H, d), 6.89 (1H, d), 7.84 (1H, dd), 7.95 (1H, dd), 8.21 (1H, d), 8.36 - 8.40 (2H, m), 8.44 (1H, d), 10.20 (1H, d). ^{13}C NMR (126 MHz, DMSO-d_6): 18.90, 26.34, 27.17, 28.90,

29.13, 42.15, 45.66, 56.19, 64.70, 67.31, 67.41, 111.48, 117.12, 122.04, 128.60, 130.21, 130.35, 130.72, 136.63, 138.42, 145.77, 145.93, 149.58, 163.82, 168.65; HRMS-ESI *m/z* 479.2762 $[MH]^+$ $C_{26}H_{34}N_6O_3$ requires 479.2771.

6-{6-[3-(Dimethylamino)propoxy]-3-pyridinyl}-4-{[(1S)-1-(1-methyl-1H-pyrazol-3-yl)ethyl]amino}-3-cinnolinecarboxamide (13)

A mixture of **29** (50 mg, 0.13 mmol), N,N-dimethyl-2-{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridinyl]oxy}propanamine **37a**[13] (82 mg, 0.27 mmol), cesium carbonate (87 mg, 0.27 mmol) and 2nd Generation XPhos precatalyst [also known as chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)] (21 mg, 0.03 mmol) in 1,4-dioxane (5 mL) and water (1 mL) was stirred under an atmosphere of nitrogen at 90 °C for 12 hours. The reaction mixture was diluted with water (2 mL) and extracted with EtOAc (5 x 5 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford a yellow oil, which was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length) using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluent. Fractions containing the desired compound were evaporated to dryness to afford **13** (22 mg, 36 %) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6, 22 °C): 1.61 (3H, t), 1.85-1.95 (2H, m), 2.21 (6H, s), 2.46 (2H, t), 3.82 (3H, s), 4.36 (2H, t), 5.46 (1H, p), 6.23 (1H, d), 6.97 (1H, d), 7.62 (1H, d), 7.79 (1H, s), 8.08-8.25 (3H, m), 8.51-8.53 (2H, m), 8.61 (1H, s), 10.82 (1H, d); MS-ESI *m/z* 475 $[MH]^+$ $C_{25}H_{30}N_8O_2$ requires 475.

6-[6-[3-(Dimethylamino)propoxy]-3-pyridyl]-4-[(1S)-1-(1,4-dimethylpyrazol-3-yl)ethylamino]cinnoline-3-carboxamide (14)

A mixture of **30a** (100 mg, 0.26 mmol), **37a** (118 mg, 0.39 mmol), cesium carbonate (251 mg, 0.77 mmol) and $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) in 1,4-dioxane (5 mL) and water (1 mL) under nitrogen was stirred at 80 °C for 12 hours. After cooling, the crude product was purified by preparative HPLC (XSelect CSH Prep C18 OBD column, 5µ silica, 19 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1% formic acid) and MeCN as eluent. Fractions containing the desired compound were evaporated to dryness to afford **14** (25 mg, 20 %) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6, 22 °C): 1.63 (3H, d), 1.82-1.87 (2H, m), 1.94 (3H, s), 2.18 (6H, s), 2.39 (2H, t), 3.69 (3H, s),4.35 (2H, t), 5.50 (1H, p), 6.97 (1H, d), 7.37 (1H,s), 7.75 (1H, d), 8.1-8.3 (3H, m), 8.49 (1H, s), 8.6-8.7 (2H, m),11.0-11.1 (1H, d); MS-ESI m/z 489 $[MH]^+$ $C_{26}H_{32}N_8O_2$ requires 489.

6-{6-[3-(1-Pyrrolidinyl)propoxy]-3-pyridinyl}-4-{[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]amino}-3-cinnolinecarboxamide (15)

A solution of 3-(pyrrolidin-1-yl)propan-1-ol (174 mg, 1.35 mmol) in DMA (6 mL) was added dropwise to a stirred suspension of sodium hydride (154 mg, 3.84 mmol) in DMA (6 mL) at ambient temperature under an inert atmosphere and the resulting suspension stirred for 20 minutes. **31** (380 mg, 0.96 mmol) was then added and the reaction was stirred at ambient temperature for 18 hours. Water (5 mL) was added to the reaction mixture and the crude material purified by ion exchange chromatography, using an SCX column eluting with 1M NH_3 in MeOH. The isolated material was further purified by flash silica chromatography, elution gradient 0 to 15% MeOH in DCM, to afford **15** (353 mg, 73%) as a yellow foam. ^{1}H NMR (DMSO-d_6): 1.32 - 1.41 (5H, m), 1.56 (1H, d), 1.61 - 1.75 (5H, m), 1.76 - 1.82 (1H, m), 1.93 (2H, p), 2.49 - 2.62 (6H, m), 3.22 - 3.33 (2H, m), 3.79 - 3.97 (2H, m), 4.17 - 4.33 (1H, m), 4.39 (2H, t), 6.98 (1H, dd), 7.71 (1H, s), 8.13 - 8.18 (2H, m), 8.24 - 8.36 (2H, m), 8.59 (1H, s), 8.64 (1H, d), 10.27 (1H, d); MS-ESI *m/z* 505 $[MH]^+$ $C_{28}H_{36}N_6O_3$ requires 505.

5-Bromo-2-[3-(1-pyrrolidinyl)propoxy]pyridine (36b)
Sodium hydride (0.591 g, 14.8 mmol) was added portionwise to a solution of 3-(1-pyrrolidinyl)-1-propanol (1.61 g, 12.5 mmol) in THF (20 mL) at 0 °C. Then the mixture was stirred at ambient temperature for 30 minutes. 5-Bromo-2-fluoropyridine (2 g, 11.4 mmol) was added and the resulting mixture stirred at ambient temperature for 2 hours before being quenched by the addition of a saturated aqueous solution of ammonium chloride. The mixture was extracted with EtOAc (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford a pale yellow solid. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM, to afford **36b** (2.70 g, 83%) as a yellow solid. MS-ESI *m/z* 285 $[MH]^+$ $C_{12}H_{17}BrN_2O$ requires 285.

2-[3-(1-Pyrrolidinyl)propoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (37b)
n-Butyl lithium (5.7 mL, 14.2 mmol, 2.5 N in hexanes) was added dropwise to a mixture of **36b** (2.7 g, 9.47 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.64 g, 14.2 mmol) in THF (20 mL) at -78 °C over a period of 10 minutes under an inert atmosphere. The resulting mixture was allowed to warm to ambient temperature and stirred for 12 hours. The reaction mixture was quenched by the addition of a saturated aqueous solution of ammonium chloride and extracted with EtOAc (2 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford the desired material (3.10 g, 99 %) as a yellow oil. The product was used in the next step directly without further purification. ^1H NMR ($CDCl_3$): 1.26-1.41 (12H, m), 1.77-1.80 (4H, m), 1.95-2.04 (2H, m), 2.50-2.58 (4H, m), 2.62 (2H, t), 4.37 (2H, t), 6.69 (1H, d), 7.91 (1H, d), 8.52 (1H, s). MS-ESI *m/z* not detected for $C_{18}H_{29}BN_2O_3$ requires 333; found 251 for $C_{12}H_{19}BN_2O_3$ formula of the corresponding boronic acid requires 251.

4-{[(1S)-1-(1-Methyl-1H-pyrazol-3-yl)ethyl]amino}-6-{6-[3-(1-pyrrolidinyl)propoxy]-3-pyridinyl}-3-cinnolinecarboxamide (16)
$Pd(PPh_3)_4$ (58.5 mg, 0.05 mmol) was added to **37b** (252 mg, 0.76 mmol), **29** (190 mg, 0.51 mmol) and Cs_2CO_3 (330 mg, 1.01 mmol) in 1,4-dioxane (5 mL) and water (1 mL) under nitrogen. The resulting mixture was stirred at 90 °C for 2 hours. The reaction mixture was poured into water (15 mL), extracted with EtOAc (3 x 15 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford the crude product, which was purified by preparative HPLC (XBridge Prep Phenyl OBD column, 5µ silica, 19 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.03 % NH_3) and MeCN as eluent. Fractions containing the desired compound were evaporated to dryness to afford **16** (45 mg, 18 %) as a white solid. ^1H NMR (300 MHz, DMSO-d_6): 1.62 (3H, d) 1.71-1.75 (4H, m), 1.92 (2H, p), 2.41-2.45 (4H, m), 2.55-2.65 (2H, m), 3.82 (3H, s), 4.37 (2H, t), 5.47 (1H, p), 6.23 (1H, d), 6.97 (1H, d), 7.62 (1H, d), 7.78 (1H, d), 8.08-8.25 (3H, m), 8.52-8.56 (2H, m), 8.64 (1H, s), 10.82 (1H, d); MS-ESI *m/z* 501 $[MH]^+$ $C_{27}H_{32}N_8O_2$ requires 501.

4-{[(1S)-1-(1,4-Dimethyl-1H-pyrazol-3-yl)ethyl]amino}-6-{6-[3-(1-pyrrolidinyl)propoxy]-3-pyridinyl}-3-cinnolinecarboxamide (17)
30a (130 mg, 0.33 mmol) was added to **37b** (222 mg, 0.67 mmol), Cs_2CO_3 (326 mg, 1.00 mmol) and $Pd(PPh_3)_4$ (38.6 mg, 0.03 mmol) in 1,4-dioxane (5 mL) and water (1 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 5 hours. The crude product was purified by preparative HPLC (XSelect CSH Prep C18 OBD column, 5µ silica, 19 mm diameter, 150 mm length), using decreasingly polar mixtures of water (containing 0.1%

formic acid) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **17** (50 mg, 29 %) as an off-white solid. ^{1}H NMR (300 MHz, CD_3OD, 22 °C) 1.72 (3H, d) 1.91-1.96 (4H, m), 1.98 (3H, s), 2.10-2.22 (2H, m), 2.91-3.10 (6H, m), 3.80 (3H, s), 4.45 (2H, t), 5.52 (1H, p), 6.92 (1H, d), 7.13 (1H, s), 8.05 (1H, dd), 8.11 (1H, dd), 8.19 (1H, s), 8.40-8.42 (2H, m). MS-ESI *m/z* 515 $[MH]^+$ $C_{28}H_{34}N_8O_2$ requires 515.

2-[(5-Bromo-2-pyridinyl)oxy]-N,N-dimethylethanamine (36c)
2-(Dimethylamino)ethanol (1.6 g, 17.9 mmol) was added slowly to a suspension of sodium hydride (60% in oil, 1.6 g, 40 mmol) in DMF at r.t. The mixture was stirred for 1 h at room temperature. 5-Bromo-2-fluoropyridine (3.52 g, 20.00 mmol) was added to the reaction mixture. The reaction mixture was stirred for 2 hours at r.t., poured into sat. aq. ammonium chloride and extracted with ethyl acetate (200 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. Purification of the crude product by chromatography on silica gel, eluting with 10% methanol in DCM gave **36c** (4 g, 82 %) as a yellow oil. MS-ESI *m/z* 245 $[MH]^+$ $C_9H_{13}BrN_2O$ requires 245.

2-[2-(N,N-dimethylamino)ethoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (37c)
A solution of **36c** (1 g, 4.08 mmol), $(BPin)_2$ (1.55 g, 6.12 mmol), potassium acetate (1.2 g, 12.2 mmol) and $Pd(dppf)Cl_2$ (150 mg, 0.21 mmol) in 1,4-dioxane (10 mL) under an inert atmosphere was heated for 2 h at 80 °C. After cooling, the resulting solution was diluted with 50 mL of petroleum ether. The solids were filtered out and the filtrate was concentrated under vacuum to give **37c** (1.2 g, quantitative), used without further purification. MS-ESI *m/z* 293 $[MH]^+$ $C_{15}H_{25}BN_2O_3$ requires 293.

6-{6-[2-(Dimethylamino)ethoxy]-3-pyridinyl}-4-{[(1S)-1-(1-methyl-1H-pyrazol-3-yl)ethyl]amino}-3-cinnolinecarboxamide (18)
29 (130 mg, 0.35 mmol), **37c** (405 mg, 1.39 mmol), Cs_2CO_3 (228 mg, 0.70 mmol) and $Pd(PPh_3)_4$ (40 mg, 0.03 mmol) in a mixture of water (1 mL) and 1,4-dioxane (5 mL) under an inert atmosphere was stirred for 16 h at 90 °C. The reaction mixture was cooled to room temperature and concentrated under vacuum. The crude reaction mixture was dissolved in DMSO (4 mL) and purified by preparative HPLC (XBridge Shield RP18 OBD column, 5µ silica, 19 mm diameter, 150 mm length) using decreasingly polar mixtures of water (containing 0.03 % NH_3) and MeCN to obtain **18** (34 mg, 21 %) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): 1.61 (3H, m), 2.23 (6H, s), 2.65 (2H, m), 3.82 (3H, s), 4.42 (2H, m), 5.47 (1H, m), 6.23 (1H, m), 6.97 (1H, m), 7.62 (1H, m), 7.77 (1H, s), 8.10-8.25 (3H, m), 8.52 (2H, m), 8.54-8.64 (1H, m), 10.82 (1H, m). MS-ESI *m/z* 461 $[MH]^+$ $C_{24}H_{28}N_8O_2$ requires 461.

6-{6-[2-(Dimethylamino)ethoxy]-3-pyridinyl}-N-methyl-4-{[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]amino}-3-cinnolinecarboxamide (19)
A solution of 2-(dimethylamino)ethanol (0.044 g, 0.49 mmol) in THF (2 mL) was added slowly to a stirred suspension of sodium hydride (0.039 g, 0.98 mmol) in THF (2 mL). The reaction mixture was stirred at ambient temperature for 30 minutes and a solution of **32** (0.100 g, 0.24 mmol) in DMF (1 mL) was then added. The solution was stirred at 50 °C for 16 hours and cooled to room temperature. Water was slowly added and the reaction mixture was diluted with DCM (10 mL). The organic layer was isolated, dried and evaporated to afford the crude product. Purification by flash silica chromatography, elution gradient 0 to

10% MeOH in DCM afforded **19** (0.082 g, 71 %) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 27 °C): 1.3 - 1.42 (5H, m), 1.56 (1H, d), 1.66 (1H, d), 1.73 - 1.86 (1H, m), 2.21 (6H, s), 2.64 (2H, t), 2.86 (3H, d), 3.21 - 3.29 (2H, m), 3.87 (2H, td), 4.19 - 4.3 (1H, m), 4.41 (2H, t), 6.97 (1H, dd), 8.16 (2H, ddd), 8.27 (1H, d), 8.32 (1H, d), 8.62 (1H, dd), 9.19 - 9.31 (1H, m), 10.24 (1H, s). MS-ESI *m/z* 479 $[MH]^+$ $C_{26}H_{34}N_6O_3$ requires 479.

6-(6-{[2-(Dimethylamino)ethyl]amino}-3-pyridinyl)-4-{[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]amino}-3-cinnolinecarboxamide (20)

A mixture of **31** (98 mg, 0.25 mmol), N,N-dimethyl-1,2-ethanediamine (56 mg, 0.64 mmol) in DMSO (1.5 mL) in a 10 mL sealed tube was stirred for 3 min at 100 °C in an oil bath. After cooling, the crude reaction mixture was purified by preparative HPLC (XBridge Shield RP18 OBD column, 5µ silica, 19 mm diameter, 150 mm length) using decreasingly polar mixtures of water (containing 0.03 % NH_3) and MeCN to obtain **20** (35 mg, 30 %) as a yellow solid. ^{1}H NMR (DMSO-d_6): 1.35-1.42 (5H, m), 1.52-1.73 (2H, m), 1.75-1.87 (1H, m), 2.20 (6H, s), 2.35-2.56 (2H, m), 3.21-3.29 (2H, m), 3.41-3.51 (2H, m), 3.80-3.93 (2H, m), 4.18-4.35 (1H, m), 6.55-6.71 (1H, m), 6.71-6.98 (1H, m), 7.63-7.79 (1H, m), 7.80-7.98 (1H, m), 8.18 (1H, m), 8.22-8.35 (2H, m), 8.41-8.56 (1H, m), 8.67 (1H, m), 10.25 (1H, m). MS-ESI *m/z* 464 $[MH]^+$ $C_{25}H_{33}N_7O_2$ requires 464.

6-(6-Fluoro-3-pyridinyl)-N-methyl-4-{[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]amino}-3-cinnolinecarboxamide (32)

A mixture of aq. 2M potassium carbonate (75 mL, 150 mmol), (6-fluoropyridin-3-yl)boronic acid (9.08 g, 64.5 mmol) and **28b** (19.5 g, 49.6 mmol) in isopropyl acetate (550 mL) was purged with nitrogen for 30 minutes. A separate flask was charged with 3-(di-*tert*-butylphosphino)propane-1-sulfonic acid (1.33 g, 4.96 mmol) and sodium tetrachloropalladate(II) (0.729 g, 2.48 mmol) in degassed water (60 mL) and stirred at ambient temperature under an inert atmosphere for 30 minutes. The catalyst solution was added to the main reaction mixture and the mixture was heated at 90 °C for 18 hours under an inert atmosphere before being allowed to cool. The reaction was repeated on an identical scale and the reaction mixture from the two reactions combined. Water (1.2 L) was added and the mixture extracted with EtOAc (3 x 1.5 L). The organic layers were combined, washed with water (2 x 1 L), brine (500 mL), dried over Na_2SO_4 and filtered. The mixture was concentrated to approximately 500 mL volume where precipitation was observed. The mixture was heated to 90 °C, further EtOAc was added (500 mL) followed by the addition of heptane (~1 L), and the mixture allowed to cool with stirring. After 16 hours stirring, the solid precipitate was collected by filtration and washed with approximately 500 mL of 15% EtOAc in heptane. The solid was dried to afford crude material (~31 g) as a yellow crystalline solid which may contain palladium residues. The crude material was dissolved in DCM (400 mL) using sonication to aid dissolution. MP-TMT resin (25 g obtained from Biotage AB, Box 8, 75103 Uppsala, Sweden – catalogue number 801471) was added and the mixture was stirred for 20 minutes before being filtered through a plug of silica. The plug/spent resin was eluted with EtOAc and fractions containing the desired material were combined and concentrated to around 500 mL volume. The resulting suspension was stirred for 16 hours at ambient temperature then the solid collected by filtration, and washed with a small amount of cold EtOAc to afford the desired material (29.8 g, 73%) as a white crystalline solid. ^{1}H NMR (DMSO-d_6): 1.29 - 1.41 (2H, m), 1.36 (3H, d), 1.56 (1H, d), 1.66 (1H, d), 1.74 - 1.88 (1H, m), 2.87 (3H, d), 3.21 - 3.31 (2H, m), 3.83 - 3.93 (2H, m), 4.22 - 4.33 (1H, m), 7.38 (1H, dd), 8.21 (1H, d), 8.30 (1H, d), 8.38 (1H, s), 8.44 (1H, ddd), 8.71 (1H, s), 9.26 (1H, d), 10.32 (1H, br s). MS-ESI *m/z* 410 $[MH]^+$ $C_{22}H_{24}FN_5O_2$ requires 410.

6-{6-[3-(Dimethylamino)propoxy]-3-pyridinyl}-N-methyl-4-{[(1S)-1-(tetrahydro-2H-pyran-4-yl)ethyl]amino}-3-cinnolinecarboxamide (21)

A suspension of sodium hydride (60% dispersion in mineral oil) (10.47 g, 261.8 mmol) and 3-(dimethylamino)propan-1-ol (10.9 mL, 91.6 mmol) in DMA (250 mL) was stirred under nitrogen for 60 minutes. **32** (26.8 g, 65.4 mmol) was added portionwise and additional DMA (20 mL) was used to rinse the reactants into the reaction vessel. The reaction mixture was stirred under nitrogen at ambient temperature for 90 minutes then quenched with the addition of saturated ammonium chloride solution (100 mL). The resulting suspension was concentrated under vacuum (65 °C, 5 mbar). Water (600 mL) was added to the residue and the mixture adjusted to pH 10 with the addition of 2M sodium hydroxide solution. The mixture was extracted with DCM (4 x 500 mL) and the combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was purified by flash silica chromatography, elution gradient 0 to 6% (10:1 MeOH / concentrated aqueous NH_3) in DCM, to afford the desired material (29.85 g) as a pale yellow foam. ^{1}H NMR (DMSO-d_6): 1.28 - 1.41 (2H, m), 1.36 (3H, d), 1.56 (1H, d), 1.67 (1H, d), 1.76 - 1.83 (1H, m), 1.87 (2H, tt), 2.14 (6H, s), 2.35 (2H, t), 2.86 (3H, d), 3.21 - 3.31 (2H, m), 3.80 - 3.95 (2H, m), 4.20 - 4.30 (1H, m), 4.35 (2H, t), 6.97 (1H, d), 8.1 - 8.2 (2H, m), 8.27 (1H, d), 8.32 (1H, s), 8.62 (1H, d), 9.25 (1H, q), 10.25 (1H, d). ^{13}C NMR (126 MHz, DMSO-d_6): 18.94, 26.49, 28.86, 29.16, 42.30, 44.92, 55.76, 56.40, 64.44, 67.30, 67.40, 111.50, 117.14, 122.11, 130.22, 130.82, 136.60, 138.47, 145.77, 145.92, 149.69, 163.73, 164.21, 170.94; HRMS-ESI m/z: 493.2926 $[MH]^+$ $C_{27}H_{36}N_6O_3$ requires 493.2927; enantiopurity: 100% ee (UV max = 280 nm. r.t. 9.94 min, opposite isomer r.t.11.94 min, analytical HPLC Phenomenex Lux C4 column, 5 µm silica, 4.6 mm diameter, 250 mm length, using a 50/50 mixture of heptane/EtOH-MeOH as eluents flow rate 2 mL/min).

6-Bromo-4-[[(1S)-1-(1,4-dimethylpyrazol-3-yl)ethyl]amino]-N-methyl-cinnoline-3-carboxamide (30b)

A mixture of DIPEA (2.6 mL, 15 mmol), **27b** (1.53 g, 4.33 mmol) and **35b** (0.964 g, 4.54 mmol, as the dihydrochloride salt) in DMA (15 mL) was stirred at 90 °C for 2 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 1M NH_3/MeOH and pure fractions were evaporated to dryness. The product was further purified by flash silica chromatography, elution gradient 0 to 7% MeOH in DCM, followed by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 50 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **30b** (0.210 g, 12 %) as a white solid. ^{1}H NMR (DMSO-d_6, 30 °C): 1.60 (3H, d), 1.95 - 2.06 (3H, m), 2.88 (3H, d), 3.70 (3H, d), 5.35 (1H, p), 7.39 (1H, s), 7.91 (1H, dd), 8.08 (1H, d), 8.47 (1H, d), 9.26 (1H, d), 10.91 (1H, d). MS-ESI *m/z* 403 $[MH]^+$ $C_{17}H_{19}BrN_6O$ requires 403.

4-{[(1S)-1-(1,4-Dimethyl-1H-pyrazol-3-yl)ethyl]amino}-6-(6-fluoro-3-pyridinyl)-N-methyl-3-cinnolinecarboxamide (33)

A premixed solution of 3-(di-*tert*-butylphosphino)propane-1-sulfonic acid and sodium tetrachloropalladate(II) (0.5M in water, 2:1 Ligand: Pd, 0.052 mL, 0.026 mmol) was added dropwise to (6-fluoropyridin-3-yl)boronic acid (0.081 g, 0.57 mmol), **30b** (0.210 g, 0.52 mmol) and potassium carbonate (0.216 g, 1.56 mmol) in dioxane (3 mL) and water (0.75 mL) under nitrogen. The resulting solution was stirred at 80 °C for 2 hours and cooled to r.t. The reaction mixture was diluted with EtOAc (20 mL), and washed sequentially with water (10 mL) and saturated brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford **33** (0.215 g, 98 %). ^{1}H NMR ($CDCl_3$, 27 °C): 1.77 (3H, d), 2.10 (3H, s),

3.09 (3H, d), 3.80 (3H, s), 5.41 (1H, p), 7.02 - 7.11 (2H, m), 7.27 (1H, s), 7.90 (1H, dd), 8.20 (1H, td), 8.32 (1H, d), 8.52 (1H, d), 8.62 (1H, d), 11.05 (1H, d). MS-ESI *m/z* 420 $[MH]^+$ $C_{22}H_{22}FN_7O$ requires 420.

6-{6-[3-(Dimethylamino)propoxy]-3-pyridinyl}-4-{[(1S)-1-(1,4-dimethyl-1H-pyrazol-3-yl)ethyl]amino}-N-methyl-3-cinnolinecarboxamide (22)

A solution of 3-(dimethylamino)propan-1-ol (0.026 g, 0.25 mmol) in DMA (1 mL) was added dropwise to a stirred suspension of sodium hydride (0.020 g, 0.50 mmol) in DMA (1 mL) at r.t. The resulting suspension was stirred at room temperature for 20 minutes under nitrogen. **33** (0.070 g, 0.17 mmol) was added and the reaction was stirred at room temperature for 1 hour at 50 °C. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **22** (0.013 g, 15 %). ^1H NMR (500 MHz, DMSO-d_6, 30 °C): 1.69 (3H, d), 1.95 (2H, p), 2.02 (3H, s), 2.22 (5H, s), 2.38 - 2.47 (3H, m), 2.95 (3H, d), 3.76 (3H, s), 4.43 (2H, t), 5.51 - 5.63 (1H, m), 7.03 (1H, d), 7.43 (1H, s), 8.22 (2H, ddd), 8.28 (1H, d), 8.57 (1H, d), 8.68 (1H, d), 9.34 (1H, d), 11.02 (1H, d). MS-ESI *m/z* 503 $[MH]^+$ $C_{27}H_{34}N_8O_2$ requires 503.

PDB ID Codes

The crystal structures of compounds **6** and **7** in PI3Kγ have been deposited under the following codes 5G55[12] and 6GQ7 respectively.

Structure Determination of 6GQ7

Human PI3Kγ (residues 144-1102) with a c-terminal 6-His tag was expressed and purified as previously described.[16] Compound **7** was solubilised in DMSO to 50 mM and added to the protein (at 12 mg/mL in 20 mM Tris pH 7.2, 50 mM ammonium sulfate, 1% betaine, 1% ethylene glycol, 0.02% CHAPS and 2 mM TCEP) to a final concentration of 2 mM. The mixture was left to incubate for 1 h and then centrifuged at 13.000 rpm for 30 min. Hanging drops were set up with a one to one ratio of protein solution and well solution containing 20% PEG3350, 175 mM ammonium sulfate, 10 mM DTT and 100 mM Hepes (pH 7.4–7.9) at 20 °C. Several rounds of optimization and streak seeding improved the quality and size of the crystals. Prior to flash freezing, the crystals were rapidly dipped in a cryo solution consisting of 15% glycerol, 20% PEG3350, 175 mM ammonium sulfate, 10 mM DTT and 100 mM Hepes pH 7.5. X-ray diffraction data were collected at beam line ID23-1 at the European Synchroton Radiation Facility, France. The Complex structure of PI3Kγ was determined by molecular replacement using the program ‘‘Molrep” using internal structures as search model. Manual fitting and inspection of the structure were carried out in the program “Coot” and refinement carried out using the program “Buster”.

Procedures for determination of physicochemical and DMPK properties

$LogD_{7.4}$ was measured as described in: Scott, J. S.; Bowker, S. S.; Brocklehurst, H. S.; Brown, H. S.; Clarke, D. S.; Easter, A.; Ertan, A.; Goldberg, K.; Hudson, J. A.; Kavanagh, S.; Laber, D.; Leach, A. G.; MacFaul, P. A.; Martin, E. A.; McKerrecher, D.; Schofield, P.; Svensson, P. H.; Teague, J. *J. Med. Chem.*, **2014**, *57*, 8984.

Hepatocyte intrinsic clearance was measured as described in:
Temesi, D. G.; Martin, S.; Smith, R.; Jones, C.; Middleton, B. High-throughput metabolic stability studies in drug discovery by orthogonal acceleration time-of-flight (OATOF) with analogue-to-digital signal capture (ADC). *Rapid Commun. Mass Spectrom.* **2010**, *24*, 1730-1736.

Solubility and plasma protein binding was measured according to Buttar, D.; Colclough, N.; Gerhardt, S.; MacFaul, P. A.; Phillips, S. D.; Plowright, A.; Whittamore, P.; Tam, K.; Maskos, K.; Steinbacher, S.; Steuber, H. A combined spectroscopic and crystallographic approach to probing drug−human serum albumin interactions. *Bioorg. Med. Chem.* **2010**, *18*, 7486−7496.

Caco-2 apparent permeability and efflux ratio were measured according to: Fredlund, F.; Winiwarter, S.; Hilgendorf, C. In vitro intrinsic permeability: a transporter-independent measure of Caco-2 cell permeability in drug design and development. *Mol. Pharmaceutics* **2017**, *14*, 1601−1609.

MDCK-MDR1 apparent permeability and efflux ratio were measured as follows:
A confluent monolayer of MDCK-MDR1 cells was established in a 96 well transwell plate. 1 uM compound was added to the apical side (A) of the transwell and the compound quantified on both the apical and basolateral side (B) of the well at 0 and 120 minutes at 37 °C. 1 uM compound is also dosed to the basolateral side of the cell and the compound quantified on both the apical and basolateral side (B) of the well at 0 and 120 minutes at 37 °C. Apparent permeability values are determined for transport in the A to B and B to A direction from this data.

Human liver microsome intrinsic clearance was measured as described in:
The metabolic stability of test compounds was assessed by incubating with human liver microsomes in the presence of NADPH. Incubations were carried out in 96 deep well plates at 37ºC using a CAT orbital shaker heater (Hamilton, UK). Pooled human liver microsomes (BD Gentest Ultrapool 150, final concentration 1 mg/mL in 0.1 M Phosphate buffer) were preincubated with 1 mM NAPDH for 5 min at 37ºC. The reaction was initiated by addition of test compound at a final concentration of 1 μM (final solvent concentrations 0.09% acetonitrile, 0.01% DMSO). Aliquots were removed at 0, 5, 10, 15, 20 and 30 min and quenched with 3 volumes of cold acetonitrile containing an appropriate internal standard. Following 1:1 dilution with water, the quenched incubates were then centrifuged at 3000 rpm for 15 min to remove the precipitated protein. Test compound disappearance was measured by a generic LC-MS/MS method. The Cl_{int} values were calculated using the substrate depletion method as described by Jones and Houston: Jones, H. M.; Houston, J. B. *Drug Metab. Disp.* **2004**, *32*, 973.

hERG was measured according to: Bridgland-Taylor, M. H.; Hargreaves, A. C.; Easter, A.; Orme, A.; Henthorn, D. C.; Ding, M.; Davis, A. M.; Small, B. G.; Heapy, C. G.; Abi-Gerges, N.; Persson, F.; Jacobson, I.; Sullivan, M.; Albertson, N.; Hammond, T. G.; Sullivan, E.; Valentin, J. P.; Pollard, C. E. Optimisation and validation of a medium-throughput electrophysiology-based hERG assay using IonWorks HT. *J. Pharmacol. Toxicol. Methods* **2006**, *54*, 189−199.

Biology

Compounds **8-22** were routinely assessed against ATM and ATR using cell based assays (ATM cell assay: endpoint, phosphorylation of ATM at Ser1981 in HT29 cells[12,13]; ATR cell assay: endpoint, phosphorylation of Chk-1 at Ser345 in HT29 cells[17]). ATM potency was also assessed in a biochemical enzyme assay[12,13] and selectivity across other PIKK kinases was confirmed with biochemical enzyme assays[18,19] (PI3Kα–δ, mTOR, DNAPK) on selected compounds. Selectivity against PI3Ks was also monitored in cell assays (inhibition of AKT phosphorylation at Thr308 in PIK3CA mutant human breast ductal carcinoma BT474 cells, sensitive to PI3Kα inhibition, and at Ser473 in PTEN-null breast adenocarcinoma MDA-MB-468 cells, sensitive to PI3Kβ or mTOR inhibition). [18,19] Kinase selectivity on selected compounds was further assessed using kinase panels.

In vivo SW620 xenograft tumour growth inhibition protocol was published previously.[12]

The ATM results are tabulated below with number of test results (n) and standard deviation (SD)

Compound	ATM cell pIC_{50}	n	SD
8	6.86	4	0.06
9	6.58	3	0.20
10	7.36	3	0.24
11	6.48	7	0.17
12	8.73	11	0.36
13	8.41	4	0.36
14	9.04	4	0.14
15	8.75	4	0.17
16	8.98	4	0.35
17	9.30	4	0.18
18	7.46	2	0.28
19	7.31	3	0.06
20	7.21	3	0.04
21	8.55	13	0.32
22	8.41	3	0.22

expressed as pIC_{50}, n number of tests; SD for standard deviation

Molecular Formula Strings

Compound Id	**Isomeric Smiles**
8	C[C@@H](C1CCOCC1)Nc2c3cc(ccc3nnc2C(=O)N)c4ccc(nc4)COC
9	C[C@@H](c1ccn(n1)C)Nc2c3cc(ccc3nnc2C(=O)N)c4ccc(nc4)COC
10	Cc1cn(nc1[C@H](C)Nc2c3cc(ccc3nnc2C(=O)N)c4ccc(nc4)COC)C
11	C[C@@H](C1CCOCC1)Nc2c3cc(ccc3nnc2C(=O)NC)c4ccc(nc4)COC
12	C[C@@H](C1CCOCC1)Nc2c3cc(ccc3nnc2C(=O)N)c4ccc(nc4)OCCCN(C)C
13	C[C@@H](c1ccn(n1)C)Nc2c3cc(ccc3nnc2C(=O)N)c4ccc(nc4)OCCCN(C)C
14	Cc1cn(nc1[C@H](C)Nc2c3cc(ccc3nnc2C(=O)N)c4ccc(nc4)OCCCN(C)C)C
15	C[C@@H](C1CCOCC1)Nc2c3cc(ccc3nnc2C(=O)N)c4ccc(nc4)OCCCN5CCCC5
16	C[C@@H](c1ccn(n1)C)Nc2c3cc(ccc3nnc2C(=O)N)c4ccc(nc4)OCCCN5CCCC5
17	Cc1cn(nc1[C@H](C)Nc2c3cc(ccc3nnc2C(=O)N)c4ccc(nc4)OCCCN5CCCC5)C
18	C[C@@H](c1ccn(n1)C)Nc2c3cc(ccc3nnc2C(=O)N)c4ccc(nc4)OCCN(C)C
19	C[C@@H](C1CCOCC1)Nc2c3cc(ccc3nnc2C(=O)NC)c4ccc(nc4)OCCN(C)C
20	C[C@@H](C1CCOCC1)Nc2c3cc(ccc3nnc2C(=O)N)c4ccc(nc4)NCCN(C)C
21	C[C@@H](C1CCOCC1)Nc2c3cc(ccc3nnc2C(=O)NC)c4ccc(nc4)OCCCN(C)C
22	Cc1cn(nc1[C@H](C)Nc2c3cc(ccc3nnc2C(=O)NC)c4ccc(nc4)OCCCN(C)C)C

References

(15) Barber, H. J.; Washbourn, K.; Wragg, W. R.; Lunt, E. A new cinnoline synthesis. Part I. Cyclisation of mesoxalyl chloride phenylhydrazones to give substituted 4-hydroxycinnoline-3-carboxylic acids. *J. Chem. Soc.* **1961**, 2828-2843.

(16) Aston, N. M.; Robinson, J. E.; Trivedi, N. Cinnolines compounds as inhibitors of phosphodiesterase type IV (PDE4) *PCT Int. Appl.* (2007), WO2007045861.

(17) Foote, K. M.; Blades, K.; Cronin, A.; Fillery, S.; Guichard, S. S.; Hassall, L.; Hickson, I.; Jacq, X.; Jewsbury, P. J.; McGuire, T. M.; Nissink, J. W.; Odedra, R.; Page, K.; Perkins, P.; Suleman, A.; Tam, K.; Thommes, P.; Broadhurst, R.; Wood, C. Discovery of 4-{4-(3R)-3-Methylmorpholin-4-yl]-6-1-(methylsulfonyl)cyclopropyl]pyrimidin-2-yl}-1H-indole (AZ20): A Potent and Selective Inhibitor of ATR Protein Kinase with Monotherapy in Vivo Antitumor Activity. *J. Med. Chem.* **2013**, *56,* 2125-2138.

(18) Barlaam, B.; Cosulich, S.; Degorce, S. L; Fitzek, M.; Green, S.; Hancox, U.; Lambert-van der Brempt, C.; Lohmann, J.; Maudet, M.; Morgentin, R.; Pasquet, M.; Peru, A.; Plé, P.; Saleh, T.; Vautier, M.; Walker, M.; Ward, L.; Warin, N. Discovery of (R)-8-(1-(3,5-Difluorophenylamino)ethyl)-N,N-dimethyl-2-morpholino-4-oxo-4H-chromene-6-carboxamide (AZD8186): A Potent and Selective Inhibitor of PI3Kβ and PI3Kδ for the Treatment of PTEN-Deficient Cancers. *J. Med. Chem.* **2015**, *58,* 943-962.

(19) Barlaam, B.; Cosulich, S.; Delouvrié, B.; Ellston, R.; Fitzek, M.; Germain, H.; Green, S.; Hancox, U.; Harris, C. S.; Hudson, K.; Lambert-van der Brempt, C.; Lebraud, H.; Magnien, F.; Lamorlette, M.; Le Griffon, A.; Morgentin, R.; Ouvry, G.; Page, K.; Pasquet, G.; Polanska, U.; Ruston, L.; Saleh, T.; Vautier, M.; Ward; L. Discovery of 1-(4-(5-(5-Amino-6-(5-tert-butyl-1,3,4-oxadiazol-2-yl)pyrazin-2-yl)-1-ethyl-1,2,4-triazol-3-yl)piperidin-1-yl)-3-hydroxypropan-1-one (AZD8835): A Potent and Selective Inhibitor of PI3Kα and PI3Kδ for the Treatment of Cancers *Bioorg. Med. Chem. Lett.* **2015**, *25,* 5155-5162.