

Supporting Information

Design and Synthesis of Novel Amino-triazine Analogs as Selective Bruton's Tyrosine Kinase Inhibitors for Treatment of Rheumatoid Arthritis

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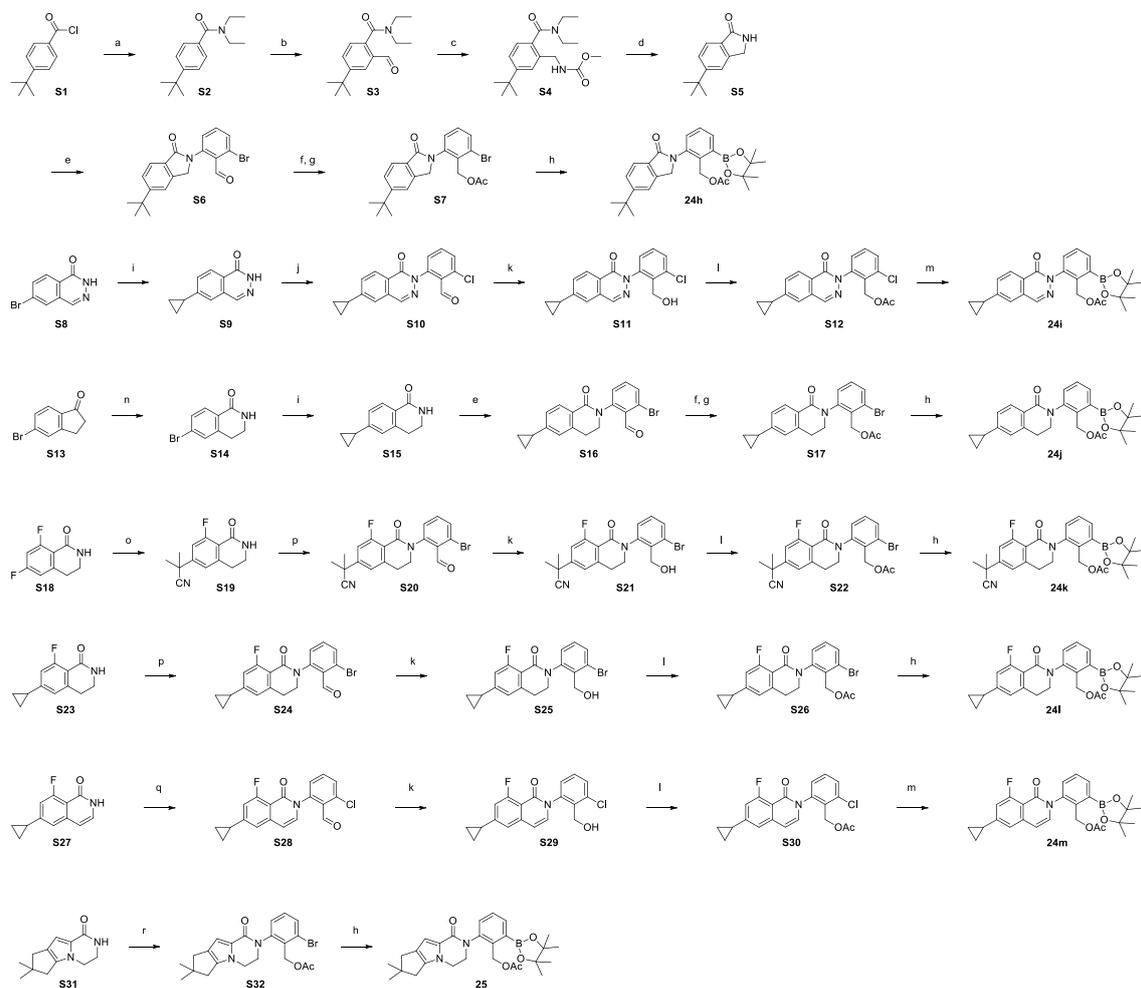
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Scheme S1: Preparation of boronate esters **24h-m** and **25**^a



^a Reagents and conditions: (a) diethylamine, TEA, DCM, rt; (b) TMEDA, sec.-BuLi, DMF, THF, -70 °C; (c) methyl carbamate, TFA, triethylsilane, ACN, 130 °C; (d) 2M-LiOH aq., THF, MeOH, 110 °C; (e) 2,6-dibromobenzaldehyde, Pd₂(dba)₃, xantphos, Cs₂CO₃, DOX, 110 °C; (f) NaBH₄, THF, MeOH, 0 °C; (g) acetyl chloride, TEA, DCM, 0 °C; (h) bis(pinacolato)diboron, Pd(dppf)-CH₂Cl₂, potassium acetate, DOX, 80 °C; (i) cyclopropylboronic acid, tricyclohexylphosphine, PdOAc₂, K₃PO₄, water, toluene, 105 °C; (j) 2-chloro-6-fluorobenzaldehyde, Cs₂CO₃, ethoxytrimethylsilane, DMF, 60 °C; (k) NaBH₄, DCM, 2-PrOH, 0 °C; (l) acetyl chloride, pyridine, DCM, 0 °C; (m) bis(pinacolato)diboron, Pd(dba)₂, X-Phos, potassium acetate, DOX, 60 °C; (n) methansulfonic acid, NaN₃, dichloromethane, 0 °C; (o) isobutyronitrile, KHMDs, THF, rt; (p) 2,6-dibromobenzaldehyde, CuI, NaHCO₃, DMSO, 110 °C; (q) 2-bromo-6-chlorobenzaldehyde, CuI, K₂CO₃, DMF, 120 °C; (r) 2,6-dibromobenzyl acetate, Pd₂(dba)₃, xantphos, Cs₂CO₃, DOX, 120 °C;

4-(tert-Butyl)-N,N-diethylbenzamide (S2). To a solution of diethylamine (7.91 ml, 77 mmol) in DCM (51 mL) was added TEA (4.6 mL, 37.7 mmol) and cooled with an ice bath. To this solution, 4-

(*tert*-butyl)benzoyl chloride **S1** (10 ml, 51.2 mmol) was added dropwise, and the mixture was stirred at room temperature for 1 h. The reaction mixture was added water and extracted with ethyl acetate (3×250 mL). The organic layer was washed with 1N hydrochloric acid solution, water, saturated NaHCO₃ aq. and brine, then the organic layer was dried over sodium sulfate, and concentrated to afford a crude **S2** (13 g, 55.7 mmol, quantitative yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.34 (m, 2H), 7.36 – 7.25 (m, 2H), 3.68 – 3.40 (m, 2H), 3.42 – 3.08 (m, 2H), 1.32 (s, 9H), 1.31 – 1.04 (m, 6H).

4-(*tert*-Butyl)-*N,N*-diethyl-2-formylbenzamide (S3). Under nitrogen atmosphere, TMEDA (4.85 mL, 32.1 mmol) was dissolved in THF (49 mL) and cooled to -70 °C. To this solution, 1.08 M *sec*-butyl lithium solution in THF (29.8 mL, 32.1 mmol) was added dropwise and the mixture was stirred at -70 °C for 20 min. To this solution, solution of **S2** (6 g, 25.7 mmol) in THF (15.3 mL) was added dropwise and stirred for 20min at -70 °C. DMF (5.97 ml, 77 mmol) was added dropwise and the reaction mixture was stirred for 70min at -70 °C. The reaction mixture was warmed up to -30 °C, and quenched with 4M-HCl (100 ml). The mixture was extracted with ethyl acetate (3×150 mL) and the combined organic layers were washed with water, saturated NaHCO₃ aq. and brine. The organic layer was dried over sodium sulfate. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate to afford **S3** (1.58 g, 6.05 mmol, 23.51% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 10.05 (s, 1H), 7.95 (dd, *J* = 2.1, 0.4 Hz, 1H), 7.66 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 3.62 (q, *J* = 7.1 Hz, 2H), 3.14 (q, *J* = 7.1 Hz, 2H), 1.36 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H).

5-(*tert*-Butyl)-2-(diethylcarbamoyl)benzylcarbamate (S4). To a solution of **3S** (1.58 g, 6.05 mmol) in acetonitrile (15.78 mL) was added methyl carbamate (0.908 g, 12.09 mmol), TFA (0.931 ml, 12.09 mmol) and triethylsilane (1.931 ml, 12.09 mmol). The mixture was heated in the microwave reactor at 130 °C for 90 min. The reaction mixture was diluted with 1M NaOH aq., and extracted with ethyl acetate (3×50 mL). The combined the organic layers were washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated to afford **S4** (1.677 g, 5.23 mmol, 87% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.39 (m, 1H), 7.30 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 5.62 (s, 1H), 4.27 (s, 2H), 3.65 (s, 3H), 3.56 (q, *J* = 6.7 Hz, 2H), 3.20 (q, *J* = 7.1 Hz, 2H), 1.31 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H).

5-(*tert*-Butyl)isoindolin-1-one (S5). To a solution of **S4** (1.67 g, 5.21 mmol) in THF (10 mL) was added MeOH (10 mL) and 2M-LiOH aq. The mixture was heated in the microwave reactor at 110 °C for 150 min. The reaction mixture was added 2M-HCl (10 mL), and extracted with ethyl acetate (3×25 mL). The combined the organic layers were washed successively with water, saturated NaHCO₃ aq.

and brine. The organic layer was dried over sodium sulfate. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate to afford **S5** (400 mg, 2.114 mmol, 40.6% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.84 – 7.74 (m, 2H), 7.57 – 7.47 (m, 2H), 4.46 (s, 2H), 1.37 (s, 9H).

2-Bromo-6-(5-(tert-butyl)-1-oxoisindolin-2-yl)benzaldehyde (S6). A mixture of **S5** (1 g, 5.28 mmol), 2,6-dibromobenzaldehyde (3.07 g, 11.62 mmol), Pd₂(dba)₃ (48 mg, 0.053 mmol), xantphos (61 mg, 0.106 mmol) and Cs₂CO₃ (3.44 g, 10.57 mmol) in 1,4-dioxane (50 mL) was degassed with N₂ for 5 min. The mixture was heated 110 °C for 90 min. The reaction was added water, and extracted with ethyl acetate (2×50 mL). The combined organic layers were washed by water, and concentrated. The residue was purified by flash column chromatography using ethyl acetate in hexane as eluent to afford **S6** (983 mg, 2.64 mmol, 50%). ¹H NMR (400 MHz, Chloroform-*d*) δ 10.27 – 10.21 (m, 1H), 7.71 – 7.50 (m, 3H), 7.50 – 7.40 (m, 2H), 7.36 – 7.29 (m, 1H), 4.87 – 4.80 (m, 2H), 1.38 (s, 9H).

2-Bromo-6-(5-(tert-butyl)-1-oxoisindolin-2-yl)benzyl acetate (S7). To a solution of **S6** (800 mg, 2.149 mmol) in THF (20 mL) and MeOH (5 mL) was NaBH₄ (122 mg, 3.22 mmol) at 0 °C and then stirred for 60 min at rt. The reaction was quenched with water, and extracted with ethyl acetate (2×50 mL). The combined organic layers were washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated, and the residue was diluted with DCM (20 mL). To this solution, TEA (0.599 ml, 4.30 mmol) and AcCl (0.306 ml, 4.30 mmol) were added and then stirred for 60min at 0 °C. The reaction was added water, and extracted with ethyl acetate (2×100 mL). The combined organic layers were washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated, and the residue was purified by flash column chromatography using ethyl acetate in hexane as eluent to afford **S7** (856 mg, 2.056 mmol, 95%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.01 – 7.82 (m, 1H), 7.71 – 7.62 (m, 2H), 7.62 – 7.49 (m, 1H), 7.48 – 7.41 (m, 1H), 7.37 – 7.27 (m, 1H), 5.20 (s, 2H), 4.82 – 4.73 (m, 2H), 1.98 (s, 3H), 1.40 (s, 9H).

2-(5-(tert-Butyl)-1-oxoisindolin-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate (24h). To a solution of **S7** (330 mg, 0.793 mmol) in 1,4-dioxane (5.3 mL) was added bis(pinacolato)diboron (403 mg, 1.585 mmol), PdCl₂(dppf)-CH₂Cl₂ Adduct (64.7 mg, 0.079 mmol) and potassium acetate (233 mg, 2.378 mmol), and the mixture was stirred for 16hr at 80 °C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, then the organic layers were dried over sodium sulfate, and concentrated. The crude material was purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate to afford **24h** (213 mg, 0.46 mmol, 58%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.99 – 7.94 (m, 1H), 7.89 – 7.82 (m, 1H), 7.72 – 7.62 (m, 2H), 7.61 – 7.56 (m, 1H), 7.35 – 7.29 (m,

1H), 5.20 (s, 2H), 4.75 (s, 2H), 1.98 (s, 3H), 1.40 – 1.39 (m, 21H).

6-Cyclopropylphthalazin-1(2H)-one (S9). To a mixture of **S8** (1.0 g, 4.44 mmol), cyclopropylboronic acid (0.573 g, 6.67 mmol), tricyclohexylphosphine (0.125 g, 0.444 mmol), and K_3PO_4 (1.886 g, 8.89 mmol) in toluene (20 mL) and water (1.5 mL) was added $PdOAc_2$ (0.200 g, 0.889 mmol) and the mixture was stirred at 105 °C for 1 day. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, then the organic layers were dried over sodium sulfate, and concentrated. The crude residue was triturated with isopropylether and ethylacetate to afford **S9** (393 mg, 1.899 mmol, 42.7%) as pale yellow powder. 1H NMR (400 MHz, $DMSO-d_6$) δ 12.52 (s, 1H), 8.25 (d, $J = 0.6$ Hz, 1H), 8.08 (d, $J = 8.2$ Hz, 1H), 7.60 (d, $J = 1.7$ Hz, 1H), 7.56 (dd, $J = 8.3, 1.8$ Hz, 1H), 2.14 (tt, $J = 8.4, 5.0$ Hz, 1H), 1.16 - 1.07 (m, 2H), 0.90 - 0.82 (m, 2H).

2-Chloro-6-(6-cyclopropyl-1-oxophthalazin-2(1H)-yl)benzaldehyde (S10). To the mixture of **S9** (186 mg, 1.0 mmol), 2-chloro-6-fluorobenzaldehyde (174 mg, 1.100 mmol), and Cs_2CO_3 (195 mg, 0.600 mmol) in DMF (2 mL) was added ethoxytrimethylsilane (0.312 ml, 2.0 mmol), and the mixture was stirred at 60 °C for 2 hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, then the organic layers were dried over sodium sulfate, and concentrated. The crude residue was purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate to afford **S10** (114 mg, 0.351 mmol, 35%) as colorless powder. 1H NMR (400 MHz, $DMSO-d_6$) δ 10.18 (d, $J = 0.5$ Hz, 1H), 8.48 (d, $J = 0.8$ Hz, 1H), 8.13 (d, $J = 8.3$ Hz, 1H), 7.85 - 7.69 (m, 3H), 7.69 - 7.59 (m, 2H), 2.23 - 2.15 (m, 1H), 1.21 - 1.11 (m, 2H), 0.95 - 0.86 (m, 2H).

2-(3-Chloro-2-(hydroxymethyl)phenyl)-6-cyclopropylphthalazin-1(2H)-one (S11). To a solution of **S10** (113 mg, 0.348 mmol) in DCM (1 mL) and 2-Propanol (0.5 mL) was $NaBH_4$ (6.58 mg, 0.174 mmol) at 0 °C and then stirred for 30 min at room temperature. The reaction was quenched with water, and extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated to afford **S11** (111 mg, 0.336 mmol, 97%). 1H NMR (400 MHz, $DMSO-d_6$) δ 8.44 (d, $J = 0.7$ Hz, 1H), 8.16 (d, $J = 8.3$ Hz, 1H), 7.71 (d, $J = 1.7$ Hz, 1H), 7.64 (dd, $J = 8.3, 1.8$ Hz, 1H), 7.59 (dd, $J = 8.0, 1.3$ Hz, 1H), 7.47 (t, $J = 8.0$ Hz, 1H), 7.38 (dd, $J = 7.9, 1.3$ Hz, 1H), 4.88 - 4.74 (m, 1H), 4.43 (s, 2H), 2.19 (ddd, $J = 8.3, 5.0, 3.3$ Hz, 1H), 1.22 - 1.10 (m, 2H), 0.96 - 0.84 (m, 2H).

2-Chloro-6-(6-cyclopropyl-1-oxophthalazin-2(1H)-yl)benzyl acetate (S12). To a solution of **S11** (111 mg, 0.340 mmol) in DCM (3 mL) was added Acetyl chloride (0.036 ml, 0.510 mmol) and pyridine

(0.082 ml, 1.019 mmol) at 0 °C and then stirred for 2 hr at room temperature. The reaction mixture was diluted with water and extracted with chloroform. The combined organic layers were washed successively with water and brine, then the organic layers were dried over sodium sulfate, and concentrated. The crude residue was triturated with isopropylether to afford **S12** (102 mg, 0.277 mmol, 81%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.45 (d, *J* = 0.7 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.73 - 7.62 (m, 3H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.47 (dd, *J* = 7.9, 1.3 Hz, 1H), 5.04 (s, 2H), 2.19 (ddd, *J* = 8.3, 5.0, 3.4 Hz, 1H), 1.78 (s, 3H), 1.22 - 1.11 (m, 2H), 0.95 - 0.86 (m, 2H).

2-(6-Cyclopropyl-1-oxophthalazin-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate (24i). A mixture of **S12** (100 mg, 0.271 mmol) and bis(pinacolato)diboron (138 mg, 0.542 mmol), potassium acetate (80 mg, 0.813 mmol), and X-Phos (12.93 mg, 0.027 mmol) in 1,4-dioxane (2 mL) was degassed with N₂ for 5 min. To this mixture, Pd(dba)₂ (7.8 mg, 0.014 mmol) was added and stirred for 16 hr at 60 °C. The reaction mixture was diluted with ethyl acetate and insoluble materials were filtered off. The filtrate was washed with water and dried over sodium sulfate, filtered and concentrated. The crude material was purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate to afford **24i**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.47 - 8.41 (m, 1H), 8.20 - 8.12 (m, 1H), 7.92 (s, 1H), 7.80 (dd, *J* = 2.58, 6.28 Hz, 1H), 7.73 - 7.60 (m, 2H), 7.59 - 7.48 (m, 1H), 5.13 - 5.08 (m, 2H), 2.24 - 2.14 (m, 1H), 1.75 (s, 3H), 1.31 (s, 12H), 1.22 - 1.09 (m, 2H), 0.95 - 0.86 (m, 2H).

6-Bromo-3,4-dihydroisoquinolin-1(2H)-one (S14). To a solution of **S13** (5 g, 23.69 mmol) in DCM (40 ml) was added metahanesulfonic acid (20 ml, 308 mmol) at 0 °C. To this solution, sodium azide (2.5 g, 38.5 mmol) was added in portion and stirred for 30 min at 0 °C. The reaction mixture was added 20%-NaOH aqueous and extracted with DCM. The combined organic layers were washed successively with water and brine. The organic layer was dried over sodium sulfate. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate to afford **S14** (2.12 g, 9.38 mmol, 39.6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.01 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.61 - 7.56 (m, 1H), 7.54 (dt, *J* = 8.2, 1.4 Hz, 1H), 3.36 (ddd, *J* = 6.9, 6.2, 2.9 Hz, 2H), 2.91 (t, *J* = 6.6 Hz, 2H).

6-Cyclopropyl-3,4-dihydroisoquinolin-1(2H)-one (S15). Following the procedures described for **S9**, substituting **S14** for **S8**, the title compound **S15** was obtained. Yield: 49%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.77 (d, *J* = 7.1 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.03 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.97 (d, *J* = 1.7 Hz, 1H), 3.36 - 3.33 (m, 2H), 2.84 (t, *J* = 6.6 Hz, 2H), 1.94 (tt, *J* = 8.3, 5.0 Hz, 1H), 1.06 - 0.94 (m, 2H), 0.77 - 0.68 (m, 2H).

2-Bromo-6-(6-cyclopropyl-1-oxo-3,4-dihydroisoquinolin-2(*1H*)-yl)benzaldehyde (S16).

Following the procedures described for **S6**, substituting **S15** for **S5**, the title compound **S16** was obtained. Yield: 36%. ¹H NMR (400 MHz, Chloroform-*d*) δ 10.21 (d, *J* = 0.64 Hz, 1H), 8.10 – 7.88 (m, 1H), 7.72 – 7.50 (m, 1H), 7.51 – 7.19 (m, 2H), 7.10 – 6.99 (m, 1H), 6.99 – 6.76 (m, 1H), 3.94 (t, *J* = 6.50 Hz, 2H), 3.20 – 3.15 (m, 2H), 2.01 – 1.87 (m, 1H), 1.13 – 0.96 (m, 2H), 0.86 – 0.71 (m, 2H).

2-Bromo-6-(6-cyclopropyl-1-oxo-3,4-dihydroisoquinolin-2(*1H*)-yl)benzyl acetate (S17).

Following the procedures described for **S7**, substituting **S16** for **S6**, the title compound **S17** was obtained. Yield: 67%. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.03 – 7.90 (m, 1H), 7.64 – 7.55 (m, 1H), 7.54 – 7.19 (m, 2H), 7.08 – 6.99 (m, 1H), 6.94 – 6.89 (m, 1H), 5.33 – 5.01 (m, 2H), 4.06 – 3.90 (m, 1H), 3.83 – 3.69 (m, 1H), 3.34 – 3.21 (m, 1H), 3.05 – 2.92 (m, 1H), 2.05 (s, 3H), 2.01 – 1.88 (m, 1H), 1.10 – 0.94 (m, 2H), 0.83 – 0.73 (m, 2H).

2-(6-Cyclopropyl-1-oxo-3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate (24j). Following the procedures described for **24h**, substituting **S17** for **S7**, the title compound **24j** was obtained. Yield: 81%. LCMS (*m/z*): mass was calculated for C₂₇H₃₂BNO₅ requires 461.2, found 462.3 [M+H]⁺.

2-(8-Fluoro-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpropanenitrile (S19). To a mixture of **S18**¹ (3.0 g, 16.38 mmol) and isobutyronitrile (5.88 ml, 65.5 mmol) in THF (40 ml) was added 1M-KHMDS in THF (34.4 ml, 34.4 mmol). The reaction mixture was stirred for overnight at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, then the organic layers were dried over sodium sulfate, and concentrated. The crude residue was purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate to afford **S19** (315 mg, 1.356 mmol, 8%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.20 (dq, *J* = 1.6, 0.8 Hz, 1H), 7.10 (dd, *J* = 11.9, 1.9 Hz, 1H), 6.15 (s, 1H), 3.54 (ddd, *J* = 6.8, 6.0, 3.3 Hz, 2H), 3.11 – 2.87 (m, 2H), 1.73 (s, 6H).

2-(2-(3-Bromo-2-formylphenyl)-8-fluoro-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpropanenitrile (S20). Under nitrogen atmosphere, a mixture of **S19** (315 mg, 1.356 mmol), 2,6-dibromobenzaldehyde (716 mg, 2.71 mmol), sodiumbicarbonate (228 mg, 2.71 mmol), and CuI (258 mg, 1.356 mmol) in DMSO (3 ml) was stirred at 110 °C for 1day. The mixture was diluted with water and ethyl acetate, and the liberated solids were filtered off. The filtrate was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, then the organic layers were dried over sodium sulfate, and concentrated. The crude residue was purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate to afford **S20** (297 mg, 0.715 mmol,

52.7%). ¹H NMR (400 MHz, Chloroform-*d*) δ 10.25 (d, *J* = 0.6 Hz, 1H), 7.62 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.22 (dq, *J* = 1.5, 0.8 Hz, 1H), 7.10 (dd, *J* = 11.8, 1.9 Hz, 1H), 3.94 (s, 2H), 3.27 (d, *J* = 127.5 Hz, 2H), 1.74 (s, 6H).

2-(2-(3-Bromo-2-(hydroxymethyl)phenyl)-8-fluoro-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpropanenitrile (S21). Following the procedures described for **S11**, substituting **S20** for **S10**, the title compound **S21** was obtained. Yield: quant. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.64 (dd, *J* = 1.27, 7.97 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.24 – 7.18 (m, 1H), 7.14 (dd, *J* = 1.87, 11.80 Hz, 1H), 4.80 – 4.58 (m, 2H), 4.12 – 3.98 (m, 1H), 3.83 – 3.69 (m, 1H), 3.40 – 3.03 (m, 3H), 1.76 (s, 6H).

2-Bromo-6-(6-(2-cyanopropan-2-yl)-8-fluoro-1-oxo-3,4-dihydroisoquinolin-2(*1H*)-yl)benzyl acetate (S22). Following the procedures described for **S12**, substituting **S21** for **S11**, the title compound **S22** was obtained. Yield: 99%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.63 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.25 – 7.21 (m, 2H), 7.12 (dd, *J* = 11.7, 2.0 Hz, 1H), 5.31 – 5.17 (m, 2H), 4.01 – 3.91 (m, 1H), 3.83 – 3.74 (m, 1H), 3.39 – 3.28 (m, 1H), 3.13 – 3.04 (m, 1H), 2.06 (s, 3H), 1.75 (s, 6H).

2-(6-(2-Cyanopropan-2-yl)-8-fluoro-1-oxo-3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate (24k). Following the procedures described for **24h**, substituting **S22** for **S7**, the title compound **24k** was obtained. Yield: 80%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.83 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.33 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.22 (d, *J* = 1.9 Hz, 1H), 7.11 (dd, *J* = 11.8, 1.9 Hz, 1H), 5.51 (d, *J* = 11.6 Hz, 1H), 5.21 (d, *J* = 11.7 Hz, 1H), 3.99 – 3.89 (m, 1H), 3.83 – 3.73 (m, 1H), 3.38 – 3.26 (m, 1H), 3.13 – 3.03 (m, 1H), 2.00 (s, 3H), 1.56 (s, 6H), 1.37 – 1.31 (m, 12H).

2-Bromo-6-(6-cyclopropyl-8-fluoro-1-oxo-3,4-dihydroisoquinolin-2(*1H*)-yl)benzaldehyde (S24). Following the procedures described for **S20**, substituting **S23**² for **S19**, the title compound **S24** was obtained. Yield: 51%. ¹H NMR (400 MHz, Chloroform-*d*) δ 10.21 (d, *J* = 0.6 Hz, 1H), 7.58 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.25 – 7.21 (m, 1H), 6.73 (s, 1H), 6.68 (dd, *J* = 12.2, 1.7 Hz, 1H), 3.90 (s, 2H), 3.17 (d, *J* = 126.5 Hz, 2H), 1.89 (ddd, *J* = 13.4, 8.6, 5.0 Hz, 1H), 1.12 – 1.03 (m, 2H), 0.77 (dt, *J* = 6.8, 4.8 Hz, 2H).

2-(3-Bromo-2-(hydroxymethyl)phenyl)-6-cyclopropyl-8-fluoro-3,4-dihydroisoquinolin-1(*2H*)-one (S25). Following the procedures described for **S11**, substituting **S24** for **S10**, the title compound **S25** was obtained. Yield: quant. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.62 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.29 – 7.23 (m, 1H), 7.18 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.78 – 6.68 (m, 2H), 4.74 – 4.68 (m, 2H), 4.05 –

3.94 (m, 1H), 3.74 - 3.64 (m, 1H), 3.44 - 3.33 (m, 1H), 3.27 - 3.16 (m, 1H), 3.06 - 2.96 (m, 1H), 1.96 - 1.87 (m, 1H), 1.14 - 1.05 (m, 2H), 0.82 - 0.74 (m, 2H).

2-Bromo-6-(6-cyclopropyl-8-fluoro-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)benzyl acetate (S26).

Following the procedures described for **S12**, substituting **S25** for **S11**, the title compound **S26** was obtained. Yield: 90%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.88 (dd, *J* = 8.0, 1.2 Hz, 0H), 7.60 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.23 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.76 - 6.66 (m, 2H), 5.37 - 4.98 (m, 2H), 3.92 (ddd, *J* = 12.0, 10.6, 4.1 Hz, 1H), 3.73 (dt, *J* = 12.1, 5.3 Hz, 1H), 3.25 (ddd, *J* = 15.7, 10.6, 5.1 Hz, 1H), 2.98 (dt, *J* = 15.8, 4.8 Hz, 1H), 1.90 (ddd, *J* = 8.4, 5.0, 3.4 Hz, 1H), 1.55 (s, 3H), 1.15 - 0.99 (m, 2H), 0.82 - 0.71 (m, 2H).

2-(6-Cyclopropyl-8-fluoro-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate (24I).

Following the procedures described for **24h**, substituting **S26** for **S7**, the title compound **24I** was obtained. Yield: 87%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.81 (dd, *J* = 1.46, 7.37 Hz, 1H), 7.45 - 7.34 (m, 1H), 7.32 (dd, *J* = 1.46, 7.89 Hz, 1H), 6.76 - 6.65 (m, 2H), 5.51 (d, *J* = 11.62 Hz, 1H), 5.21 (d, *J* = 11.59 Hz, 1H), 3.97 - 3.84 (m, 1H), 3.79 - 3.67 (m, 1H), 3.30 - 3.17 (m, 1H), 3.03 - 2.91 (m, 1H), 1.99 (s, 3H), 1.94 - 1.85 (m, 1H), 1.36 - 1.32 (m, 12H), 1.12 - 1.02 (m, 2H), 0.81 - 0.72 (m, 2H).

2-Chloro-6-(6-cyclopropyl-8-fluoro-1-oxoisoquinolin-2(1H)-yl)benzaldehyde (S28).

A mixture of **S27**² (2.5 g, 12.30 mmol), 2-bromo-6-chlorobenzaldehyde (3.51 g, 15.99 mmol) and CuI (0.469 g, 2.460 mmol) in DMF (30 mL) was degassed with N₂ for 5 min. The mixture was heated 120 °C for 20 hr. The reaction mixture was diluted with THF (100 mL) then filtered through celite pad. The filtrate was evaporated to remove THF, and then diluted with diethylether and water. The liberated solids were formed and collected by filtration to afford **S28** (2.13 g, 6.23 mmol, 50.7% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.18 (s, 1H), 7.84 - 7.78 (m, 1H), 7.75 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.27 (d, *J* = 1.6 Hz, 1H), 7.00 (dd, *J* = 13.3, 1.6 Hz, 1H), 6.64 (dd, *J* = 7.5, 2.1 Hz, 1H), 2.14 - 2.00 (m, 1H), 1.15 - 1.04 (m, 2H), 0.94 - 0.82 (m, 2H).

2-(3-Chloro-2-(hydroxymethyl)phenyl)-6-cyclopropyl-8-fluoroisoquinolin-1(2H)-one (S29).

Following the procedures described for **S11**, substituting **S28** for **S10**, the title compound **S29** was obtained. Yield: 96%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.60 - 7.49 (m, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.15 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.08 - 6.97 (m, 2H), 6.83 (dd, *J* = 12.7, 1.7 Hz, 1H), 6.51 (dd, *J* = 7.4, 2.1 Hz, 1H), 4.77 - 4.60 (m, 1H), 4.46 (dd, *J* = 12.1, 2.1 Hz, 1H), 3.37 (dd, *J* = 11.0, 2.5 Hz, 1H), 2.01 (td, *J* = 8.2, 4.0 Hz, 1H), 1.18 - 1.12 (m, 2H), 0.89 - 0.80 (m, 2H).

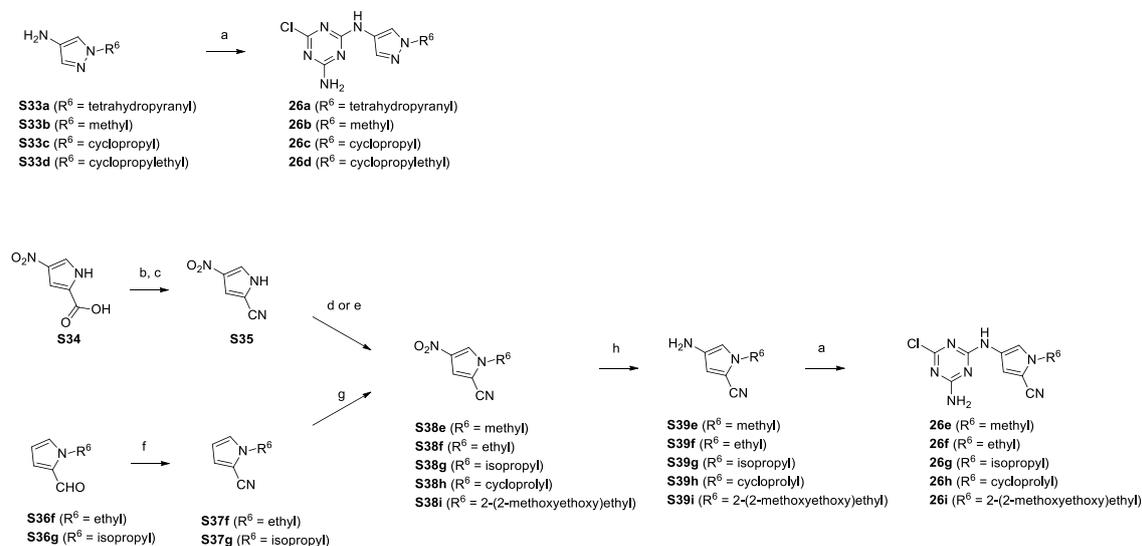
2-Chloro-6-(6-cyclopropyl-8-fluoro-1-oxoisoquinolin-2(*IH*)-yl)benzyl acetate (S30). Following the procedures described for **S12**, substituting **S29** for **S11**, the title compound **S30** was obtained. Yield: 66%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.53 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.22 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.09 – 6.95 (m, 2H), 6.80 (dd, *J* = 12.7, 1.7 Hz, 1H), 6.43 (dd, *J* = 7.5, 2.1 Hz, 1H), 5.25 (d, *J* = 12.4 Hz, 1H), 4.98 (d, *J* = 12.3 Hz, 1H), 2.03 – 1.96 (m, 1H), 1.18 – 1.06 (m, 2H), 0.90 – 0.79 (m, 2H).

2-(6-Cyclopropyl-8-fluoro-1-oxoisoquinolin-2(*IH*)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate (24m). Following the procedures described for **24h**, substituting **S30** for **S7**, the title compound **24m** was obtained. Yield: 71%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.80 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.59 – 7.51 (m, 1H), 7.46 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.33 – 7.23 (m, 2H), 6.99 (dd, *J* = 13.2, 1.7 Hz, 1H), 6.58 (dd, *J* = 7.4, 2.1 Hz, 1H), 5.20 (d, *J* = 11.8 Hz, 1H), 4.95 (d, *J* = 11.9 Hz, 1H), 2.12 – 2.01 (m, 1H), 1.83 (s, 3H), 1.31 (s, 12H), 1.14 – 1.04 (m, 2H), 0.91 – 0.83 (m, 2H).

2-Bromo-6-(7,7-dimethyl-1-oxo-3,4,7,8-tetrahydro-*IH*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2(6*H*)-yl)benzyl acetate (S32). A mixture of **S31**³ (400 mg, 1.96 mmol), 2,6-dibromobenzyl acetate (1.6 g, 5.88 mmol), Pd₂(dba)₃ (449 mg, 0.49 mmol) and xantphos (283 mg, 0.49 mmol) and Cs₂CO₃ (1.6 g, 4.9 mmol) in 1,4-dioxane (30 mL) was degassed with N₂ for 5 min. The mixture was heated 120 °C for 16 hr. The reaction mixture was filtered through celite and concentrated. The crude residue was purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate to afford **S32** (340 mg, 0.784 mmol, 40%). LCMS (*m/z*): mass was calculated for C₂₁H₂₃BrN₂O₃ requires 430.1, found 432.0 [M+H]⁺.

2-(7,7-Dimethyl-1-oxo-3,4,7,8-tetrahydro-*IH*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2(6*H*)-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl acetate (25). Following the procedures described for **24h**, substituting **S32** for **S7**, the title compound **25** was obtained. Yield: 96%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.65 – 7.63 (m, 1H), 7.46 – 7.43 (m, 2H), 6.48 (s, 1H), 5.29 – 5.25 (m, 1H), 4.97 – 4.93 (m, 1H), 4.18 – 4.06 (m, 4H), 2.55 (s, 2H), 2.40 (s, 2H), 1.93 (s, 3H), 1.30 (s, 12H), 1.20 (s, 6H). LCMS (*m/z*): mass was calculated for C₂₇H₃₅BN₂O₅ requires 478.3, found 479.0 [M+H]⁺.

Scheme S2: Preparation of chlorotriazine intermediates **26a-i**^a



^a Reagents and conditions: (a) 4,6-dichloro-1,3,5-triazin-2-amine, DIEA, THF, 0 °C; (b) CDI, ammonia, THF, rt; (c) T3P, TEA, ethyl acetate, rt; (d) alkyl halide, NaH, DMF, 0 °C; (e) cyclopropylboronic acid, Na₂CO₃, 2,2'-bipyridine, Cu(AcO)₂, DCE, 75 °C; (f) NH₂OH HCl, NMP, 110 °C; (g) HNO₃, Ac₂O, 0 °C; (h) HCl, Pd-C, EtOH, 1,4-dioxane, rt.

6-Chloro-N²-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-1,3,5-triazine-2,4-diamine (26a).

A solution of 4,6-dichloro-1,3,5-triazin-2-amine (5 g, 30.3 mmol) in THF (100 mL) was cooled with an ice bath. To this solution, DIEA (10.59 ml, 60.6 mmol) and **S33a** (7.09 g, 42.4 mmol) were added. The mixture was stirred at 0 °C for 1 hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, then the organic layers were dried over sodium sulfate, and concentrated. The crude solids were washed with chloroform to afford **26a** (6 g, 20.29 mmol, 66.9%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.95 (s, 1H), 8.10 (s, 1H), 7.65 – 7.48 (m, 3H), 5.39 – 5.27 (m, 1H), 3.96 – 3.87 (m, 1H), 3.68 – 3.53 (m, 1H), 1.99 – 1.83 (m, 2H), 1.76 – 1.45 (m, 4H).

6-Chloro-N²-(1-methyl-1H-pyrazol-4-yl)-1,3,5-triazine-2,4-diamine (26b). Following the procedures described for **26a**, substituting **S33b** for **S33a**, the title compound **26b** was obtained. Yield: 60%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.89 (s, 1H), 7.91 (s, 1H), 7.56 - 7.49 (m, 3H), 3.79 (s, 3H).

6-Chloro-N²-(1-cyclopropyl-1H-pyrazol-4-yl)-1,3,5-triazine-2,4-diamine (26c). Following the procedures described for **26a**, substituting **S33c** for **S33a**, the title compound **26c** was obtained. Yield: 42%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.89 (s, 1H), 8.00 (s, 1H), 7.63 - 7.49 (m, 2H), 7.46 (s, 1H), 3.73 - 3.59 (m, 1H), 1.06 - 0.89 (m, 4H).

6-Chloro-N²-(1-(1-cyclopropylethyl)-1H-pyrazol-4-yl)-1,3,5-triazine-2,4-diamine (26d).

Following the procedures described for **26a**, substituting **S33d** for **S33a**, the title compound **26d** was obtained. Yield: 71%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.88 (s, 1H), 8.01 (s, 1H), 7.55 – 7.44 (m, 3H), 3.67 – 3.49 (m, 1H), 1.48 (d, *J* = 6.70 Hz, 3H), 1.28 – 1.12 (m, 1H), 0.63 – 0.52 (m, 1H), 0.51 – 0.36 (m, 1H), 0.36 – 0.24 (m, 2H).

4-Nitro-1H-pyrrole-2-carbonitrile (S35). To a solution of **S34** (1.0g, 6.41 mmol) in THF (32 mL) was added CDI (1.247 g, 7.69 mmol) and stirred for 1 hr at room temperature. To this solution, 28% ammonia solution was added stirred for 1 day at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, then the organic layers were dried over sodium sulfate, and concentrated. The residue was diluted with ethyl acetate (32 mL) then added TEA (1.786 mL, 12.81 mmol) and T3P (7.54 mL, 12.81 mmol) at room temperature. The mixture was stirred at room temperature for 1 day. The reaction mixture was quenched by sat-NH₄Cl and extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, then the organic layers were dried over sodium sulfate, and concentrated. The crude residue was purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate to afford **S35** (400 mg, 0.878 mmol, 45%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.51 (s, 1H), 8.28 (d, *J* = 1.71 Hz, 1H), 7.67 (d, *J* = 1.68 Hz, 1H).

1-Methyl-4-nitro-1H-pyrrole-2-carbonitrile (S38e). To a solution of **S35** (500 mg, 3.65 mmol) in DMF (10 ml) was added NaH (219 mg, 5.47 mmol) and stirred for 30 min at room temperature. To this mixture, MeI (0.456 ml, 7.29 mmol) was added stirred for overnight at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, then the organic layers were dried over sodium sulfate, and concentrated. The residue was triturated with isopropyl ether to afford **S38e** (458 mg, 3.03 mmol, 83%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.35 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.72 (d, *J* = 1.9 Hz, 1H), 3.83 (d, *J* = 0.5 Hz, 3H).

4-Amino-1-methyl-1H-pyrrole-2-carbonitrile (S39e). To a solution of **S38e** (100 mg, 0.662 mmol) in ethanol (2 mL) and 1,4-dioxane (1 mL) was added 10%-Pd/C (40 mg, 0.038 mmol) and 3 drops of 6M HCl. The reaction mixture was vigorously stirred H₂ atmosphere at room temperature for 1.5 hr. The reaction mixture was filtered through celite, and the filtrate was concentrated to afford **S39e** (80 mg, 0.660 mmol, quantitative yield.). ¹H NMR (400 MHz, Chloroform-*d*) δ 6.36 (d, *J* = 2.0 Hz, 1H), 6.30 (d, *J* = 2.0 Hz, 1H), 3.66 (s, 3H), 3.09 – 2.91 (m, 2H).

4-[(4-Amino-6-chloro-1,3,5-triazin-2-yl)amino]-1-methyl-1*H*-pyrrole-2-carbonitrile (26e).

Following the procedures described for **26a**, substituting **S39e** for **S33a**, the title compound **26e** was obtained. Yield: 62%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.98 (s, 1H), 7.54 (s, 2H), 7.44 (d, *J* = 1.81 Hz, 1H), 6.99 (d, *J* = 1.84 Hz, 1H), 3.72 (s, 3H).

1-Ethyl-1*H*-pyrrole-2-carbonitrile (S37f). To a solution of **S36f** (2.3 g, 18.68 mmol) in NMP (18.7 mL) was added hydroxylamine hydrochloride (1.557 g, 22.41 mmol) and stirred for 2 hr at 110 °C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, then the organic layers were dried over sodium sulfate, and concentrated. The crude residue was purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate to afford **S37f** (1.64 g, 13.65 mmol, 73%). ¹H NMR (400 MHz, Chloroform-*d*) δ 6.86 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.78 (dd, *J* = 4.0, 1.6 Hz, 1H), 6.16 (dd, *J* = 4.0, 2.6 Hz, 1H), 4.10 (q, *J* = 7.3 Hz, 2H), 1.47 (t, *J* = 7.3 Hz, 3H).

1-Ethyl-4-nitro-1*H*-pyrrole-2-carbonitrile (S38f). To a solution of **S37f** (0.7 g, 5.83 mmol) in acetic anhydride (58 mL) was slowly added nitric acid (0.26 ml, 5.83 mmol) at 0 °C and then stirred for 1 hr. The reaction mixture was poured into ice-water (200 mL) and slowly alkalified by NaOH. The solution was extracted with diethyl ether. The combined organic layers were washed successively with water, sat-NaHCO₃ and brine, then the organic layers were dried over sodium sulfate, and concentrated. The crude residue was purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate to afford **S38f** (505 mg, 3.06 mmol, 52%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 1.8 Hz, 1H), 7.32 (d, *J* = 1.8 Hz, 1H), 4.18 (q, *J* = 7.3 Hz, 2H), 1.57 (t, *J* = 7.3 Hz, 3H).

4-Amino-1-ethyl-1*H*-pyrrole-2-carbonitrile (S39f). Following the procedures described for **S39e**, substituting **S38f** for **S38e**, the title compound **S39f** was obtained. Yield: quant. ¹H NMR (400 MHz, Chloroform-*d*) δ 6.41 (d, *J* = 2.0 Hz, 1H), 6.29 (d, *J* = 2.0 Hz, 1H), 3.97 (q, *J* = 7.3 Hz, 2H), 3.01 (s, 2H), 1.41 (t, *J* = 7.3 Hz, 3H).

4-[(4-Amino-6-chloro-1,3,5-triazin-2-yl)amino]-1-ethyl-1*H*-pyrrole-2-carbonitrile (26f).

Following the procedures described for **26a**, substituting **S39f** for **S33a**, the title compound **26f** was obtained. Yield: 89%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.00 (s, 1H), 7.56 (s, 2H), 7.52 (d, *J* = 1.8 Hz, 1H), 6.98 (d, *J* = 1.8 Hz, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H).

1-Isopropyl-1*H*-pyrrole-2-carbonitrile (S37g). Following the procedures described for **S37f**, substituting **S36g** for **S36f**, the title compound **S37g** was obtained. Yield: 72%. ¹H NMR (400 MHz, Chloroform-*d*) δ 6.92 (dd, *J* = 2.7, 1.6 Hz, 1H), 6.78 (dd, *J* = 3.9, 1.6 Hz, 1H), 6.18 (dd, *J* = 3.9, 2.7

Hz, 1H), 4.60 – 4.50 (m, 1H), 1.51 (d, $J = 6.7$ Hz, 6H).

1-Isopropyl-4-nitro-1H-pyrrole-2-carbonitrile (S38g). Following the procedures described for **S38f**, substituting **S37g** for **S37f**, the title compound **S37g** was obtained. Yield: 50%. ^1H NMR (400 MHz, Chloroform- d) δ 7.73 (d, $J = 1.81$ Hz, 1H), 7.32 (d, $J = 1.82$ Hz, 1H), 4.60 (hept, $J = 6.72$ Hz, 1H), 1.59 (d, $J = 6.70$ Hz, 6H).

4-Amino-1-isopropyl-1H-pyrrole-2-carbonitrile (S39g). Following the procedures described for **S39e**, substituting **S38g** for **S38e**, the title compound **S39g** was obtained. Yield: quant. ^1H NMR (400 MHz, Chloroform- d) δ 6.45 (dd, $J = 21.7, 2.0$ Hz, 1H), 6.29 (d, $J = 2.0$ Hz, 1H), 4.43 (dt, $J = 13.4, 6.7$ Hz, 1H), 3.04 – 2.96 (m, 2H), 1.44 (d, $J = 6.7$ Hz, 6H).

4-[(4-Amino-6-chloro-1,3,5-triazin-2-yl)amino]-1-isopropyl-1H-pyrrole-2-carbonitrile (26g). Following the procedures described for **26a**, substituting **S39g** for **S33a**, the title compound **26g** was obtained. Yield: 89%. ^1H NMR (400 MHz, DMSO- d_6) δ 9.98 (s, 1H), 7.64 – 7.59 (m, 1H), 7.58 – 7.52 (m, 2H), 6.93 (d, $J = 1.8$ Hz, 1H), 4.51 – 4.36 (m, 1H), 1.46 (d, $J = 6.7$ Hz, 6H).

4-Amino-1-cyclopropyl-1H-pyrrole-2-carbonitrile (S38h). Under nitrogen atmosphere, a mixture of **S35** (1.0 g, 7.29 mmol), cyclopropylboronic acid (1.253 g, 14.59 mmol), sodium carbonate (1.546 g, 14.59 mmol), 2,2'-bipyridine (1.139 g, 7.29 mmol) and copper (II) acetate (1.325 g, 7.29 mmol) in dichloroethane (36 ml) was stirred at 75 °C for 4 hr. The reaction mixture was diluted with ethyl acetate then filtered through celite pad. The filtrate was washed successively with water and brine, then the organic layers were dried over sodium sulfate, and concentrated. The crude residue was purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate to afford **S38f** (107 mg, 0.604 mmol, 8%). ^1H NMR (400 MHz, Chloroform- d) δ 7.66 (dd, $J = 1.8, 0.6$ Hz, 1H), 7.29 (d, $J = 1.8$ Hz, 1H), 3.58 - 3.46 (m, 1H), 1.29 - 1.23 (m, 2H), 1.18 - 1.12 (m, 2H).

4-Amino-1-cyclopropyl-1H-pyrrole-2-carbonitrile (S39h). Following the procedures described for **S39e**, substituting **S38h** for **S38e**, the title compound **S39h** was obtained. Yield: 92%. LCMS (m/z): mass was calculated for $\text{C}_8\text{H}_9\text{N}_3$ requires 147.1, found 148.1 $[\text{M}+\text{H}]^+$.

4-[(4-Amino-6-chloro-1,3,5-triazin-2-yl)amino]-1-cyclopropyl-1H-pyrrole-2-carbonitrile (26h). Following the procedures described for **26a**, substituting **S39h** for **S33a**, the title compound **26h** was obtained. Yield: 70%. ^1H NMR (400 MHz, DMSO- d_6) δ 9.95 (s, 1H), 7.67 – 7.62 (m, 1H), 7.57 – 7.52 (m, 1H), 7.43 (d, $J = 1.84$ Hz, 1H), 6.91 (d, $J = 1.84$ Hz, 1H), 3.57 – 3.47 (m, 1H), 1.09 – 0.99 (m, 4H).

1-(2-(2-Methoxyethoxy)ethyl)-4-nitro-1*H*-pyrrole-2-carbonitrile (S38i). To a solution of **S35** (300 mg, 2.188 mmol) in DMF (9.1 ml) was added NaH (131 mg, 3.28 mmol) and stirred for 30 min at room temperature. To this mixture, 1-bromo-2-(2-methoxyethoxy)ethane (357 μ l, 2.63 mmol) was added stirred for overnight at room temperature. The reaction mixture was diluted with water (300 mL) and extracted with ethyl acetate (3 \times 150 mL). The combined organic layers were washed successively with water and brine, then the organic layers were dried over sodium sulfate, and concentrated. The crude residue was purified by flash chromatography on silica gel, eluted with hexane/ethyl acetate to afford **S38i** (407 mg, 1.701 mmol, 78%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 1.8 Hz, 1H), 7.32 (d, *J* = 1.8 Hz, 1H), 4.31 – 4.21 (m, 2H), 3.89 – 3.80 (m, 2H), 3.69 – 3.58 (m, 2H), 3.58 – 3.48 (m, 2H), 3.38 (s, 3H).

4-Amino-1-[2-(2-methoxyethoxy)ethyl]-1*H*-pyrrole-2-carbonitrile (S39i). Following the procedures described for **S39e**, substituting **S38i** for **S38e**, the title compound **S39i** was obtained. Yield: 98%. ¹H NMR (400 MHz, Chloroform-*d*) δ 6.53 (d, *J* = 2.0 Hz, 1H), 6.32 (d, *J* = 2.0 Hz, 1H), 4.09 (t, *J* = 5.4 Hz, 2H), 3.74 (t, *J* = 5.4 Hz, 2H), 3.61 – 3.55 (m, 2H), 3.55 – 3.49 (m, 2H), 3.37 (s, 3H).

4-[(4-Amino-6-chloro-1,3,5-triazin-2-yl)amino]-1-[2-(2-methoxyethoxy)ethyl]-1*H*-pyrrole-2-carbonitrile (26i). Following the procedures described for **26a**, substituting **S39i** for **S33a**, the title compound **26i** was obtained. Yield: 68%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.99 (s, 1H), 7.76 – 7.13 (m, 3H), 7.03 (d, *J* = 1.8 Hz, 1H), 4.20 – 4.11 (m, 2H), 3.76 – 3.66 (m, 2H), 3.57 – 3.45 (m, 2H), 3.47 – 3.36 (m, 2H), 3.22 (s, 3H).

The following in vitro ADMET studies were performed by Shanghai Chempartner Co., Ltd.

Microsomal stability assay. The 30 μL of 100 mM potassium phosphate buffer containing 1.0 mM EDTA, 1.5 μM test compounds and 0.75 mg/mL microsomes was incubated at 37 °C for 10 min. To this solution, 15 μL of 6 mM NADPH solution in 100 mM potassium phosphate buffer was added and incubated at 37 °C for 30 min. At the end of incubation, the reactions were stopped by adding ACN. The samples were centrifuged for 10 min, and the supernatant was diluted with ultra pure water and then the amount of compounds remaining in the samples were determined by LC-MS/MS.

Aqueous solubility assay. The 10 mM solution of reference (Propranolol, Ketoconazole and Tamoxifen) and test compound solutions were added into the 100 mM phosphate buffer (pH 7.4). The mixture was shaken for 1 hr (1000 rpm) at room temperature and then centrifuged (10 min, 12000 rpm) to precipitate insoluble particles. The supernatants of the solutions were transferred to new tubes and the concentrations of the test compound were determined by LC-UV or LC-MS/MS.

hERG assay. Patch-clamp assays were performed using CHO cells stably expressing the hERG potassium channel using the automated patch-clamp system QPatch (Sophion). The cells were voltage clamped at a holding potential of -80 mV. The hERG current was activated by depolarizing at +20 mV for 5 sec, after which the current was taken back to -50 mV for 5 sec. to remove the inactivation and observe the deactivating tail current. The maximum amount of tail current size was used to determine hERG current amplitude. Six doses (30, 10, 3, 1, 0.3 and 0.1 μM) were chosen to obtain fitting curves and IC_{50} . Final DMSO concentration was 0.1% except for 30 μM which is 0.3%. Doses for IC_{50} evaluation of positive control cisapride were 3, 1, 0.3, 0.1, 0.03, and 0.01 μM . After achieving break-in (whole-cell) configuration, the cells were recorded for 120 sec. to assess current stability. The voltage protocol described above was then applied to the cells every 20 sec throughout the whole procedure. After allowing the current to stabilize for 3 minutes, compound was applied. Compound solution was added and the cells were kept in the test solution until the compound's effect reached a steady state or for a maximum of 3 min. Positive control cisapride was used in the experiments to test the same batch of cells used for test compounds to ensure the normal response and the good quality of the cells.

Kinase selectivity panel assay. Kinase panel assay (QuickScout™) of **4b** was conducted at 0.3 μM by Contract Research Department of Carina Biosciences Inc..

The detailed experimental procedure is available at https://www.carnabio.com/output/pdf/ProfilingProfilingBook_en.pdf.

Table S1: Kinase Selectivity Data of **4b**.

Kinase	% inhibition at 0.3μM		
	compound 4b	compound 4e	Ibrutinib
ABL	-2.3	-3.1	2.4
ABL(E255K)	-4.2	-6.5	-2.7
ABL(T315I)	-6.2	-4.7	-0.5
ACK	-7.2	-5.2	11.7
ALK	-6.6	-3.5	-1.8
ALK(F1174L)	-2.6	-3.0	-0.5
ALK(L1196M)	-3.7	-3.2	-1.1
ALK(R1275Q)	-1.9	-2.9	0.4
EML4-ALK	-8.5	-6.6	-5.0
NPM1-ALK	-2.8	-1.9	-1.6
ARG	-3.7	-5.5	1.4
AXL	-7.7	-3.8	1.7
BLK	4.9	5.9	102.7
BMX	80.0	84.3	103.4
BRK	-9.0	-7.8	95.0
BTK	107.5	106.1	104.3
CSK	-7.7	-9.7	98.9
DDR1	-7.3	-6.0	7.6
DDR2	-7.2	-3.1	4.9
EGFR	-2.8	-2.3	100.7
EGFR(d746-750)	-1.1	-2.2	52.8
EGFR(d746-750/T790M)	-2.3	-0.5	19.4
EGFR(L858R)	-1.9	-2.6	79.0
EGFR(L861Q)	-1.2	-1.2	88.2
EGFR(T790M)	-3.9	-3.0	66.9
EGFR(T790M/L858R)	-2.0	-0.7	38.1
EPHA1	-6.3	-6.5	11.7

EPHA2	-6.9	-7.9	-5.6
EPHA3	-3.0	-4.6	-7.1
EPHA4	-9.6	-12.3	-3.9
EPHA5	-15.1	-13.1	3.1
EPHA6	-6.7	-6.9	60.5
EPHA7	-11.2	-8.6	-2.3
EPHA8	-4.3	-8.5	20.5
EPHB1	-8.9	-11.8	-1.9
EPHB2	-7.0	-5.5	3.2
EPHB3	-13.8	-15.2	-1.7
EPHB4	-7.6	-8.0	6.0
FAK	-11.4	-9.5	-2.6
FER	-2.0	3.5	0.1
FES	-2.4	0.4	-0.5
FGFR1	2.7	-6.5	33.9
FGFR1(V561M)	7.5	-11.4	NA
FGFR2	-3.9	-4.4	50.8
FGFR3	-3.6	-1.6	49.1
FGFR3(K650E)	-2.6	-1.6	23.8
FGFR3(K650M)	-5.9	-7.0	6.6
FGFR4	-3.6	-1.0	13.7
FGFR4(N535K)	-1.9	-2.7	-0.5
FGFR4(V550E)	-4.2	-3.7	-1.8
FGFR4(V550L)	-3.6	-2.9	0.7
FGR	0.7	3.3	97.2
FLT1	-0.3	0.7	39.0
FLT3	-11.7	-6.6	35.2
FLT4	-1.1	1.3	68.2
FMS	-2.7	-1.0	5.1
FRK	-1.2	1.2	80.7
FYN	-2.3	0.1	94.0
HCK	3.6	1.6	97.7
HER2	-2.7	-1.2	100.3
HER4	-4.0	0.2	98.8
IGF1R	-5.0	-4.5	-4.6

INSR	-3.6	-1.8	-2.6
IRR	-3.8	-2.2	3.1
ITK	17.9	20.2	73.5
JAK1	-7.1	-5.4	-2.0
JAK2	-5.5	-0.8	-0.6
JAK3	-8.2	-4.9	67.1
KDR	-5.7	-2.3	40.0
KIT	-3.4	-0.7	27.8
KIT(D816V)	-0.4	-1.0	-0.8
KIT(T670I)	-2.2	-1.3	-1.5
KIT(V560G)	-2.9	-3.7	-1.5
KIT(V654A)	-3.8	-3.7	-0.5
LCK	-0.9	-0.3	100.8
LTK	-3.0	-2.5	0.0
LYNa	0.8	7.2	92.7
LYNb	-5.9	-3.2	96.8
MER	-6.7	-3.6	-4.1
MET	-9.8	-6.5	11.8
MET(Y1235D)	0.1	2.1	0.1
MUSK	-2.0	0.0	-0.7
PDGFR α	0.4	0.1	73.3
PDGFR α (T674I)	-7.3	-2.1	2.7
PDGFR α (V561D)	-0.4	2.5	60.3
PDGFR β	-3.8	-1.1	21.1
PYK2	-4.9	-5.6	-1.4
RET	-4.5	-4.5	64.1
RET(G691S)	-0.1	-0.1	59.3
RET(M918T)	-3.0	-2.1	34.3
RET(S891A)	2.5	0.2	56.3
RET(Y791F)	-1.2	-5.3	60.9
RON	-10.9	-8.2	-3.9
ROS	-4.7	-5.1	-3.1
SRC	8.9	10.8	80.3
SRM	-11.7	-14.6	97.1
SYK	21.2	-15.5	-9.2

TEC	99.5	99.2	103.6
TIE2	-7.3	-12.0	2.8
TNK1	-3.7	-4.8	-2.4
TRKA	-4.9	-0.5	12.4
TRKB	-2.2	0.0	5.6
TRKC	-4.2	0.1	7.3
TXK	-7.4	-7.2	99.5
TYK2	-6.8	-4.2	-7.1
TYRO3	-11.0	-3.2	-0.1
YES	6.9	8.0	97.2
YES(T348I)	1.6	-0.5	NA
ZAP70	-7.0	-6.4	0.7
AKT1	-4.5	-6.2	-4.0
AKT2	-3.1	-3.2	-4.5
AKT3	-9.0	-7.7	-2.0
AMPK α 1/ β 1/ γ 1	-6.9	-8.6	0.7
AMPK α 2/ β 1/ γ 1	-2.5	-3.2	-0.1
AurA	-3.5	-4.5	7.4
AurA/TPX2	-3.4	-3.9	-4.2
AurB	-5.0	0.8	0.4
AurC	-8.0	1.6	-1.3
BMPR1A	0.3	-7.7	-5.5
BRAF	7.0	-5.4	-5.6
BRAF(V600E)	-0.8	-7.0	4.9
BRSK1	-0.6	0.0	-0.9
BRSK2	-2.4	-1.3	2.8
CaMK1 α	-5.7	-4.1	-1.5
CaMK1 δ	-2.4	-0.7	-5.8
CaMK2 α	-3.0	-3.8	-5.2
CaMK2 β	-4.9	-1.8	-3.6
CaMK2 γ	-3.1	-2.6	-4.8
CaMK2 δ	-3.5	-1.5	-3.5
CaMK4	-6.6	-5.3	-1.8
CDC2/CycB1	-5.0	-5.2	-5.5
CDC7/ASK	-6.9	-5.9	-9.6

CDK2/CycA2	-6.9	-7.4	-4.6
CDK2/CycE1	-1.3	16.6	0.8
CDK3/CycE1	-10.6	-10.7	-4.6
CDK4/CycD3	-2.4	-0.2	8.4
CDK5/p25	-4.3	-6.8	-3.0
CDK6/CycD3	-0.6	-2.2	-0.4
CDK7/CycH/MAT1	-6.7	-8.0	-3.7
CDK9/CycT1	-16.1	-11.0	-2.7
CGK2	-4.2	-4.0	-5.2
CHK1	-42.5	-1.4	-0.8
CHK2	-3.6	-3.4	1.9
CK1 α	-9.1	-18.2	-20.4
CK1 γ 1	-0.8	-1.8	-1.5
CK1 γ 2	1.2	-1.3	-1.1
CK1 γ 3	-0.3	-1.1	0.3
CK1 δ	-0.3	3.9	-0.5
CK1 ϵ	-7.9	-9.9	25.6
CK2 α 1/ β	-8.2	-7.5	-11.6
CK2 α 2/ β	-4.8	-3.0	-4.7
CLK1	-1.3	-3.9	-6.1
CLK2	-3.6	-1.4	-2.8
CLK3	0.8	1.1	-1.8
COT	15.2	6.1	1.2
CRIK	-6.6	-6.1	-2.5
DAPK1	-5.9	-7.2	2.0
DCAMKL2	-6.2	-4.3	-1.8
DLK	7.6	-0.7	5.4
DYRK1A	-3.8	-2.1	-3.8
DYRK1B	2.1	2.3	-4.6
DYRK2	0.0	-4.8	-7.5
DYRK3	1.1	-2.8	-2.7
EEF2K	-4.9	-6.1	-1.3
Erk1	-5.6	-7.2	0.2
Erk2	-2.5	-3.6	-3.8
Erk5	-9.8	-9.3	-3.4

GSK3 α	-2.8	-4.5	-2.0
GSK3 β	2.9	-7.1	-7.0
Haspin	-0.2	0.1	-5.6
HGK	-7.6	-5.0	-6.2
HIPK1	2.0	-2.8	-3.3
HIPK2	-5.8	-7.4	-1.8
HIPK3	-5.9	-1.9	-1.9
HIPK4	-10.0	-7.4	2.2
IKK α	9.5	7.7	-9.4
IKK β	-9.0	-7.7	0.8
IKK ϵ	-10.2	-11.9	-5.4
IRAK1	1.5	-12.5	-0.6
IRAK4	-12.7	-10.1	-1.9
JNK1	-1.8	0.8	-2.5
JNK2	-2.2	-1.5	-4.2
JNK3	-0.1	2.0	-2.5
LATS2	-4.8	-4.3	-2.3
LIMK1	-2.1	-5.8	6.1
LKB1	1.9	2.2	1.6
LOK	-10.1	-6.8	-0.2
MAP2K1	-8.3	-2.2	20.6
MAP2K2	-4.1	-7.3	22.8
MAP2K3	6.5	0.4	4.9
MAP2K4	-5.0	-3.2	1.8
MAP2K5	-18.5	-18.3	-1.4
MAP2K6	2.1	1.5	10.6
MAP2K7	0.0	-5.6	35.1
MAP3K1	8.4	-10.4	-18.9
MAP3K2	4.3	-0.2	27.2
MAP3K3	-3.2	-22.7	37.1
MAP3K4	-16.0	-5.3	-2.2
MAP3K5	0.1	-6.7	42.6
MAP4K2	0.1	-3.0	1.4
MAPKAPK2	-1.8	-25.3	2.1
MAPKAPK3	1.7	-2.5	0.6

MAPKAPK5	-4.4	-4.4	-1.5
MARK1	-0.4	-1.9	-5.2
MARK2	-1.7	-14.3	1.8
MARK3	-2.0	-3.7	-1.1
MARK4	6.7	-4.1	3.3
MELK	-3.4	-6.1	3.4
MGC42105	0.9	-2.5	-1.2
MINK	-3.6	-3.7	-4.1
MLK1	-21.7	-16.6	-15.0
MLK2	-4.6	-2.3	16.6
MLK3	1.9	0.2	-22.7
MNK1	-5.2	-6.3	0.0
MNK2	-1.5	-2.3	0.5
MOS	4.6	2.2	3.8
MRCK α	-0.5	-1.2	0.0
MRCK β	-3.9	-3.3	3.5
MSK1	-0.6	-1.8	-3.3
MSK2	-4.3	-3.2	-3.0
MSSK1	-3.7	-1.0	-1.7
MST1	-7.6	-4.9	0.5
MST2	5.2	2.7	2.0
MST3	-2.4	-1.2	3.7
MST4	-5.3	0.6	-1.1
NDR1	-3.2	-4.4	-5.2
NDR2	-3.6	-3.8	-4.2
NEK1	-7.0	-7.7	0.4
NEK2	-1.4	-0.8	-4.7
NEK4	-3.2	1.3	-4.4
NEK6	-4.4	-3.5	0.8
NEK7	-4.0	-4.2	-0.9
NEK9	-3.0	-2.8	-3.8
NuaK1	-9.8	-3.5	1.9
NuaK2	-6.2	-3.1	2.1
p38 α	-2.2	-5.5	-3.6
p38 β	-4.4	-4.3	-1.8

p38 γ	-3.4	-0.4	-1.6
p38 δ	-0.4	0.3	-0.9
p70S6K	-0.9	-3.5	3.1
p70S6K β	23.0	-7.5	-0.3
PAK1	-10.9	-2.4	-6.2
PAK2	-34.4	-33.6	0.2
PAK4	-13.1	2.1	-4.9
PAK5	-3.8	-2.8	-3.6
PAK6	-3.0	-3.0	-11.2
PASK	-4.4	-3.5	0.8
PBK	-7.4	-2.3	-0.5
PDHK2	-3.1	-0.4	5.1
PDHK4	-4.6	-3.4	-2.8
PDK1	-8.6	-6.0	-8.9
PEK	-2.5	-4.8	11.1
PGK	-3.8	-3.8	-5.3
PHKG1	-5.0	-5.3	-1.2
PHKG2	0.0	-5.0	-2.0
PIM1	-9.2	-11.6	0.1
PIM2	-8.9	-1.0	4.9
PIM3	-1.2	0.0	0.7
PKAC α	-1.1	-8.4	-3.4
PKAC β	0.1	-3.1	-4.2
PKAC γ	-7.2	-4.2	-7.1
PKC α	-1.7	-1.8	4.2
PKC β 1	1.3	0.0	-1.0
PKC β 2	2.3	-3.4	1.1
PKC γ	-0.7	-1.5	-1.1
PKC δ	1.0	-3.8	4.4
PKC ϵ	-6.0	-0.9	2.0
PKC ζ	-1.9	-2.0	-0.4
PKC η	3.4	2.4	1.3
PKC θ	5.0	-6.1	1.2
PKC ι	-3.0	2.1	2.2
PKD1	0.2	3.1	-1.9

PKD2	-11.0	-13.8	2.7
PKD3	3.8	1.5	-6.9
PKN1	0.7	0.7	2.6
PKR	12.4	6.6	-2.5
PLK1	-6.1	-7.9	3.4
PLK2	1.8	1.7	6.0
PLK3	-6.1	-3.2	-3.9
PLK4	1.6	9.6	7.9
PRKX	-3.1	-3.1	-6.5
QIK	-4.0	-2.5	-5.9
RAF1	10.0	0.8	6.0
ROCK1	-1.3	-1.7	-3.8
ROCK2	1.1	-3.4	-1.6
RSK1	3.8	-1.6	-2.7
RSK2	-2.5	-5.2	1.5
RSK3	0.5	-2.9	0.4
RSK4	-4.4	-4.1	-2.6
SGK	-4.8	-6.1	-1.2
SGK2	0.2	-3.9	2.5
SGK3	-2.7	-1.8	2.2
SIK	-3.0	-2.5	-2.6
skMLCK	-5.9	-6.2	-2.6
SLK	-18.3	-6.6	-0.1
SRPK1	-4.8	-6.6	5.5
SRPK2	-0.4	-2.7	-1.0
TAK1-TAB1	16.7	1.7	-7.9
TAOK2	-1.3	-0.3	-3.0
TBK1	-4.8	-1.3	-1.9
TNIK	-2.6	-2.0	-2.1
TSSK1	-10.7	-7.9	-5.3
TSSK2	-11.2	3.2	-1.2
TSSK3	-3.7	3.5	8.4
TTK	14.0	5.6	-4.8
WEE1	-8.5	-7.8	-1.4
WNK1	-2.0	-1.9	-2.6

WNK2	-5.5	-6.5	-1.9
WNK3	-3.5	-3.9	-1.1
PIK3CA/PIK3R1	7.0	3.6	20.4
SPHK1	-13.6	-7.9	-1.3
SPHK2	-1.2	-6.4	-5.3

REFERENCES

- (1). Ernst, J. T.; Neubert, T.; Liu, M.; Sperry, S.; Zuccola, H.; Turnbull, A.; Fleck, B.; Kargo, W.; Woody, L.; Chiang, P.; Tran, D.; Chen, W.; Snyder, P.; Alcacio, T.; Nezami, A.; Reynolds, J.; Alvi, K.; Goulet, L.; Stamos, D. Identification of novel HSP90 α/β isoform selective inhibitors using structure-based drug design. Demonstration of potential utility in treating CNS disorders such as Huntington's disease. *J. Med. Chem.* **2014**, *57*, 3382-3400.
- (2). Lou, Y.; Han, X.; Kuglstatler, A.; Kondru, R. K.; Sweeney, Z. K.; Soth, M.; McIntosh, J.; Litman, R.; Suh, J.; Kocer, B.; Davis, D.; Park, J.; Frauchiger, S.; Dewdney, N.; Zecic, H.; Taygerly, J. P.; Sarma, K.; Hong, J.; Hill, R. J.; Gabriel, T.; Goldstein, D. M.; Owens, T. D. Structure-based drug design of RN486, a potent and selective Bruton's tyrosine kinase (BTK) inhibitor, for the treatment of rheumatoid arthritis. *J. Med. Chem.* **2015**, *58*, 512–516.
- (3). Crawford, J. J.; Johnson, A. R.; Misner, D. L.; Belmont, L. D.; Castanedo, G.; Choy, R.; Coraggio, M.; Dong, L.; Eigenbrot, C.; Erickson, R.; Ghilardi, N.; Hau, J.; Katewa, A.; Kohli, P. B.; Lee, W.; Lubach, J. W.; McKenzie, B. S.; Ortwine, D. F.; Schutt, L.; Tay, S.; Wei, B.; Reif, K.; Liu, L.; Wong, H.; Young, W. B. Discovery of GDC-0853: A potent, selective, and noncovalent Bruton's tyrosine kinase inhibitor in early clinical development. *J. Med. Chem.* **2018**, *61*, 2227-2245.