

Supporting Information

Identification of C-2 Hydroxyethyl

Imidazopyrrolopyridines as Potent JAK1 Inhibitors with Favorable Physicochemical Properties and High Selectivity over JAK2

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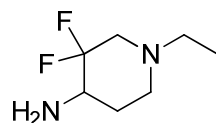
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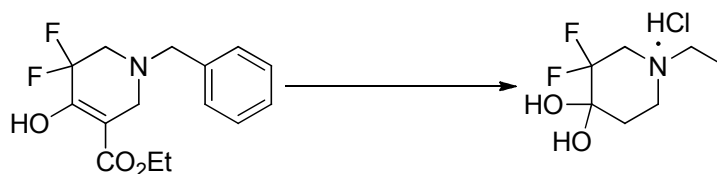
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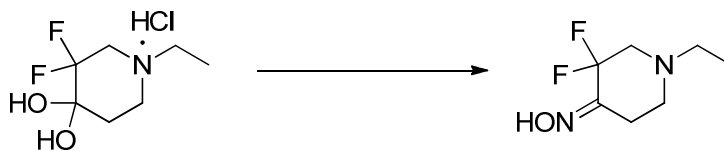
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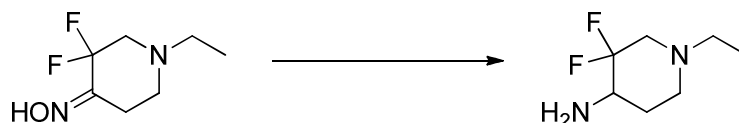
(±)-1-Ethyl-3,3-difluoropiperidin-4-amine (16a)



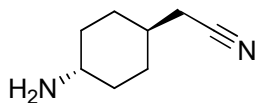
1-Ethyl-3,3-difluoropiperidine-4,4-diol hydrochloride. A solution of 1-benzyl-5,5-difluoro-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate [Prepared as described in: Shirakami, S.; Inoue, T.; Mukoyoshi, K.; Nakajima, Y.; Usuda, H.; Hamaguchi, H.; Higashi, Y.; Hatanaka, K. EP2123651, **2009**.] (59.5 g, 0.20 mol) in EtOAc (600 mL) was degassed and charged with acetaldehyde (13.2 g, 0.30 mol) and 10% palladium on activated carbon (6.0 g). The reaction mixture was allowed to stir for three h under an atmosphere of hydrogen, then filtered through Celite and concentrated under vacuum. The residue was immediately taken up into a 3 N solution of aqueous hydrochloric acid (470 mL) and heated to reflux for four h. The reaction mixture was cooled to room temperature and concentrated under vacuum to yield 43.5 g of the title compound as a pale yellow powder (100%). ¹H NMR (400 MHz, D₂O) δ 3.86 – 3.74 (m, 1H), 3.60 – 3.42 (m, 2H), 3.38 – 3.09 (m, 3H), 2.12 (d, *J* = 6.0 Hz, 2H), 1.25 (t, *J* = 6.0 Hz, 3H).



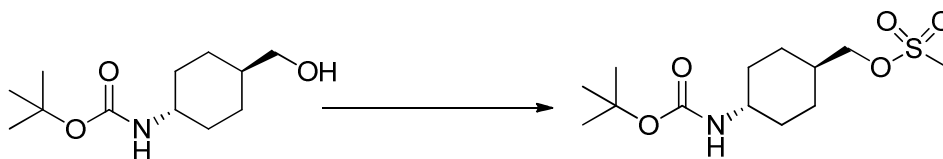
1-Ethyl-3,3-difluoropiperidin-4-one oxime. To a suspension of 1-ethyl-3,3-difluoropiperidine-4,4-diol hydrochloride (10.2 g, 46.9 mmol) in EtOH (80 mL) was added aqueous hydroxylamine solution (50% by weight, 3.58 mL, 58.4 mmol) and stirred for 16 h. The thick precipitate was dissolved with the addition of EtOH (20 mL) and heating. The solution was cooled to room temperature, then to 0 °C. The precipitated solid was collected by filtration and dried under vacuum to yield 8.27 g (99%) of the title compound as a white solid. ¹H NMR (400 MHz, D₂O) δ 4.07 – 3.86 (m, 2H), 4.58 – 3.49 (m, 2H), 3.30 (q, *J* = 7.3 Hz, 2H), 3.21 – 2.98 (m, 2H), 1.38 (t, *J* = 7.3 Hz, 3H).



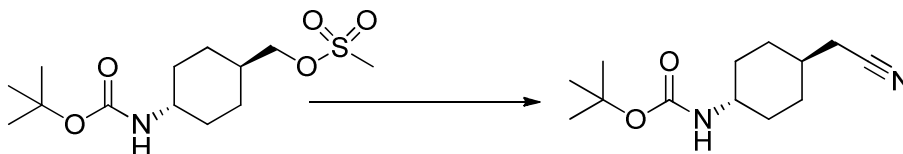
(±)-1-Ethyl-3,3-difluoropiperidin-4-amine (16a). To a solution of 1-ethyl-3,3-difluoropiperidin-4-one oxime (6.19 g, 34.7 mmol) in tetrahydrofuran (300 mL) was added a 1 M solution of lithium aluminum hydride in tetrahydrofuran (69.4 mL, 69.4 mmol) at 0 °C. The reaction mixture was stirred for 16 h, gradually warming to room temperature. The reaction mixture was quenched by dropwise addition of a 1 N aqueous solution of sodium potassium tartrate (70 mL) and left to stir for an additional 18 h. The resulting white slurry was extracted twice with EtOAc (50 mL) and twice with DCM (50 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum to yield 4.71 g of the title compound as a pale yellow oil (83%). ¹H NMR (400 MHz, CDCl₃) δ 3.16 – 3.01 (m, 2H), 2.84 – 2.72 (m, 2H), 2.52 – 2.38 (m, 2H), 2.20 – 2.01 (m, 2H), 1.93 – 1.82 (m, 1H), 1.58 – 1.43 (m, 1H), 1.04 (t, *J* = 8.0 Hz, 3H).



2-(trans-4-Aminocyclohexyl)acetonitrile (33a).



(*trans*-4-((*tert*-Butoxycarbonyl)amino)cyclohexyl)methyl methanesulfonate. A solution of *tert*-butyl (*trans*-4-(hydroxymethyl)cyclohexyl)carbamate (3.49 g, 15.0 mmol) in DCM (50 mL) was treated with pyridine (4.98 mL, 60.8 mmol). The mixture was cooled to 0 °C and methanesulfonyl chloride (2.36 mL, 30.4 mmol) was added dropwise over 5 minutes. The mixture was stirred at 23 °C for 5 h. The mixture was then concentrated under vacuum. The residue was partitioned between EtOAc and water (50 mL), then layers were separated, and the aqueous phase was re-extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried with sodium sulfate, filtered, and concentrated under vacuum. The residue was triturated with cyclohexane then dried under vacuum to give a white solid. Further purification by column chromatography on silica gel (eluting with 1:1 cyclohexane/EtOAc) gave 4.17 g (90%) of the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 4.37 (br s, 1H), 4.02 (d, *J* = 6.5 Hz, 2H), 3.39 (br s, 1H), 3.00 (s, 3H), 2.11 – 2.00 (m, 2H), 1.91 – 1.81 (m, 2H), 1.77 – 1.64 (m, 1H), 1.43 (s, 9H), 1.18 – 1.05 (m, 4H).

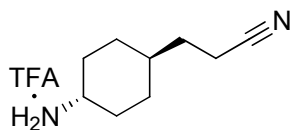


***tert*-butyl (*trans*-4-(Cyanomethyl)cyclohexyl)carbamate.** A mixture of (*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)methyl methanesulfonate (0.93 g, 3.00 mmol) and sodium cyanide (0.44 g, 9.00 mmol) in DMSO (10 mL) was stirred at 90 °C for 4 h. After cooling to room temperature, the mixture was partitioned between EtOAc and brine (20 mL each), the layers were separated, and the

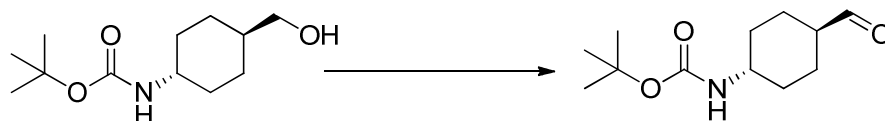
aqueous phase was re-extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried with sodium sulfate, filtered, and concentrated under vacuum to give 0.72 g (100%) of the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 4.38 (br s, 1H), 3.45 – 3.33 (m, 1H), 2.26 (d, *J* = 6.8 Hz, 2H), 2.10 – 2.02 (m, 2H), 1.96 – 1.87 (m, 2H), 1.71 – 1.57 (m, 1H), 1.45 (s, 9H), 1.26 – 1.03 (m, 4H).



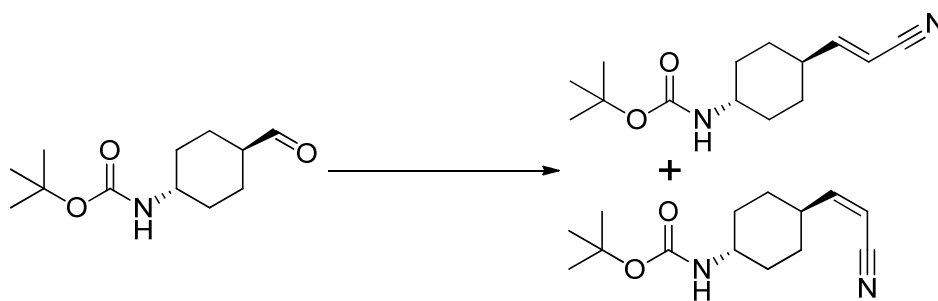
2-(*trans*-4-Aminocyclohexyl)acetonitrile (33a). A solution of *trans tert*-butyl (*trans*-4-(cyanomethyl)cyclohexyl)carbamate (0.71 g, 3.00 mmol) in DCM (15 mL) was treated with trifluoroacetic acid (2 mL). The mixture was stirred at 23 °C for 2.5 h, then concentrated under vacuum. The residue was purified by column chromatography using an Isolute SCX-2 cartridge (eluting with MeOH then 2 M NH₃ in MeOH). The relevant fractions were combined and concentrated under vacuum to afford 0.40 g (97%) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 3.52 – 3.42 (m, 2H), 2.69 – 2.60 (m, 1H), 2.26 (d, *J* = 6.5 Hz, 2H), 1.94 – 1.83 (m, 4H), 1.70 – 1.57 (m, 1H), 1.24 – 1.06 (m, 4H).



3-(*trans*-4-Aminocyclohexyl)propanenitrile trifluoroacetic acid salt (34a).



***tert*-butyl (*trans*-4-Formylcyclohexyl)carbamate.** A mixture of *tert*-butyl (*trans*-4-(hydroxymethyl)cyclohexyl)carbamate (10.0 g, 43.7 mmol) in DCM (225 mL) was treated with DMSO (75 mL) and then cooled to 0 °C. DIPEA (30.4 mL, 0.17 mol) was added followed by dropwise addition of a fine suspension of sulfur trioxide pyridine complex (27.8 g, 0.17 mol) in DMSO (75 mL). The mixture was stirred at 23 °C for 10 minutes and then 1N aqueous hydrochloric acid solution (200 mL) was added with cooling in an ice bath. The phases were separated and the aqueous layer was extracted with DCM (2 x 100 mL) and the combined organic phases were washed with brine (100 mL), dried with sodium sulfate, filtered, and concentrated under vacuum. Trituration with pentane gave 9.36 g (94%) of the title product as a white solid which was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ 9.62 (d, J = 1.9 Hz, 1H), 4.40 (br s, 1H), 3.51 – 3.28 (m, 1H), 2.20 – 1.99 (m, 4H), 1.44 (s, 9H), 1.38 (m, 2H), 1.16 (m, 2H).

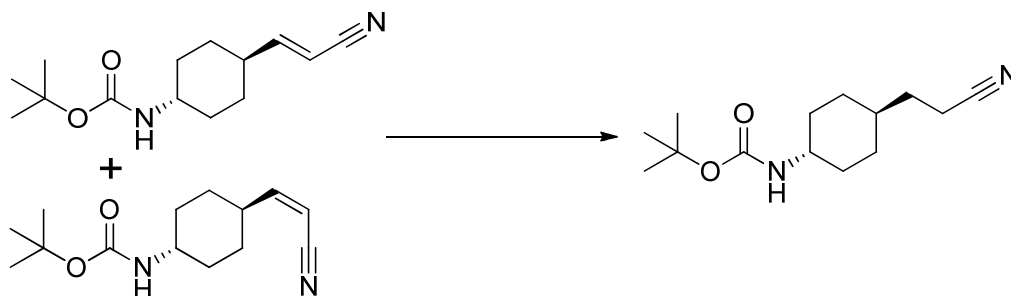


***tert*-butyl (*trans*-4-((*E*)-2-Cyanovinyl)cyclohexyl)carbamate and *tert*-butyl (*trans*-4-((*Z*)-2-Cyanovinyl)cyclohexyl)carbamate.** To a suspension of potassium *tert*-butoxide (5.54 g, 49.5 mmol) in dry THF (110 mL) at 0 °C, diethyl cyanomethyl phosphonate (8.00 mL, 49.5 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 hour. A solution of *tert*-butyl (*trans*-4-formylcyclohexyl)carbamate (9.36 g, 41.2 mmol) in dry THF (290 mL) was added slowly over ~15 min, then the cooling bath was removed and the mixture was stirred at 23 °C for 1 h. EtOAc (200 mL) and water (100 mL) were added and the phases were separated. The aqueous phase was extracted with

EtOAc (2 x 100 mL), and the combined organic phase was washed with 10% aqueous citric acid solution, saturated sodium hydrogen carbonate solution, and brine (100 mL each), dried with sodium sulfate, filtered, and concentrated under vacuum to give 12.6 g (>100%) of the title products as a golden oil (~ 1:2 mixture of E- and Z- isomers), which was contaminated with some phosphonate residues. The golden oil crystallized almost immediately and was used in the next step without further purification.

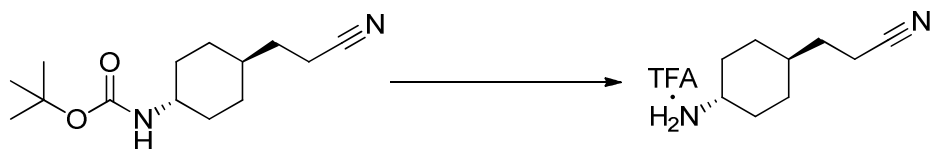
E-isomer: ^1H NMR (400 MHz, CDCl_3) δ 6.64 (dd, $J = 16.5, 6.9$ Hz, 1H), 5.29 (dd, $J = 16.5, 1.5$ Hz, 1H), 4.39 (m, 1H), 4.26 (m, 1H), 3.52 – 3.28 (m, 1H), 2.08 (m, 2H), 1.83 (m, 2H), 1.44 (s, 9H), 1.35 – 1.10 (m, 4H).

Z-isomer: ^1H NMR (400 MHz, CDCl_3) δ 6.28 (dd, $J = 10.9, 9.9$ Hz, 1H), 5.25 (dd, $J = 10.9, 0.6$ Hz, 1H), 4.39 (m, 1H), 4.26 (m, 1H), 3.52 – 3.28 (m, 1H), 2.08 (m, 2H), 1.83 (m, 2H), 1.44 (s, 9H), 1.35 – 1.10 (m, 4H).

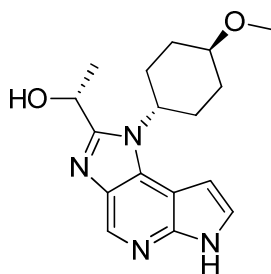


tert-butyl (*trans*-4-(2-Cyanoethyl)cyclohexyl)carbamate. A mixture of tert-butyl (*trans*-4-((*E*)-2-cyanovinyl)cyclohexyl)carbamate and tert-butyl (*trans*-4-((*Z*)-2-cyanovinyl)cyclohexyl)carbamate (4.00 g, 16.0 mmol) in EtOH (50 mL, IMS grade) under nitrogen was treated with 10% palladium/carbon (1.60 g, 1.50 mmol palladium). The mixture was purged with hydrogen gas and was stirred under an atmosphere of hydrogen (balloon) for 64 h. The mixture was filtered through Celite® and the filtrate was concentrated under vacuum. Purification by column chromatography on silica gel (EtOAc/cyclohexane 1:3) gave 2.68 g (76% over 3 steps) of the title

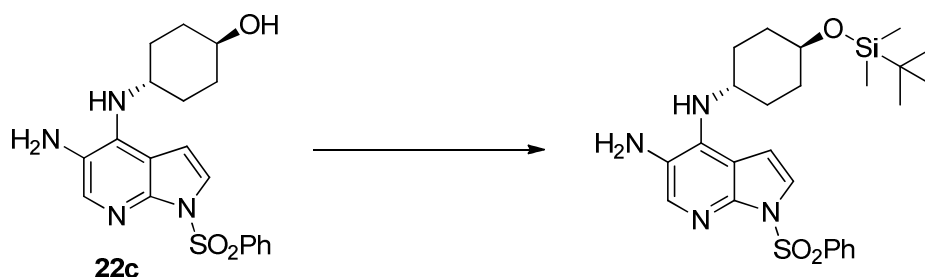
compound as an off-white solid. ^1H NMR (400 MHz, CDCl_3) δ 4.37 (br s, 1H), 3.38 (br s, 1H), 2.36 (t, $J = 7.3$ Hz, 2H), 2.03 (m, 2H), 1.79 (m, 2H), 1.56 (q, $J = 7.1$ Hz, 2H), 1.44 (s, 9H), 1.36 (m, 1H), 1.19 – 0.98 (m, 4H).



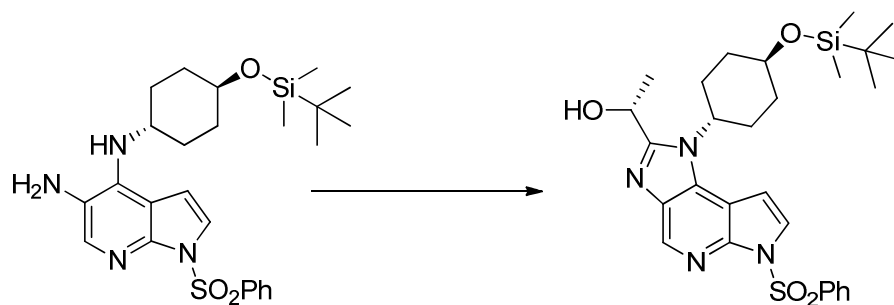
3-(*trans*-4-Aminocyclohexyl)propanenitrile trifluoroacetic acid salt (34a). A solution of *tert*-butyl (*trans*-4-(2-cyanoethyl)cyclohexyl)carbamate (2.68 g, 10.6 mmol) in DCM (30 mL) was treated with trifluoroacetic acid (30 mL) and the mixture was stirred at 23 °C for 30 min then concentrated under vacuum. Toluene (30 mL) was added to the residue, then the mixture was concentrated under vacuum (repeated three times). The resulting oil was triturated with diethyl ether, then dried under vacuum to give 2.75 g (97%) of the title compound as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.88 (br s, 3H), 3.01 (m, 1H), 2.37 (t, $J = 7.3$ Hz, 2H), 2.08 (m, 2H), 1.89 (m, 2H), 1.59 (q, $J = 7.1$ Hz, 2H), 1.49 – 1.35 (m, 3H), 1.04 (m, 2H).



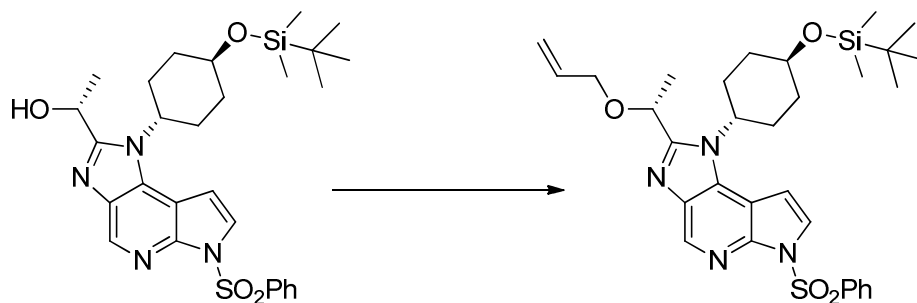
(*R*)-1-(1-(*trans*-4-Methoxycyclohexyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)ethanol (25).



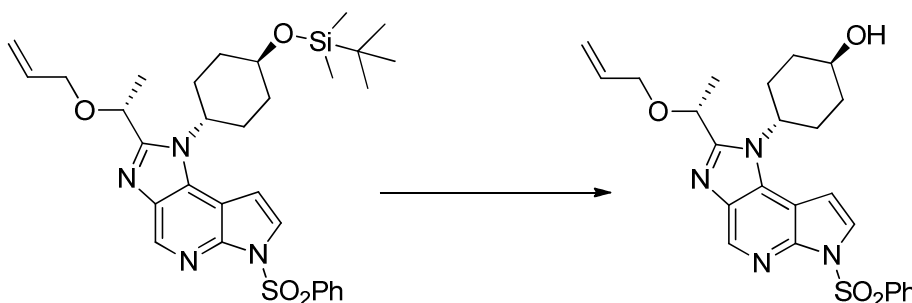
N⁴-(*trans*-4-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine-4,5-diamine. 2,6-lutidine (6.0 mL, 51.8 mmol) was added to a solution of *trans*-4-((5-amino-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)amino)cyclohexanol (**22c**) (prepared by methods similar to **21c**) (5.00 g, 13.0 mmol) in DCM (50 mL). The mixture was cooled to 0 °C and *tert*-butyldimethylsilyl triflate (8.90 mL, 38.9 mmol) was added dropwise. The mixture was allowed to return to room temperature and stirred for 16 h. The mixture was concentrated under vacuum, then the residue was dissolved in MeOH (10 mL). This mixture was stirred at room temperature for 90 min, then concentrated under vacuum. The residue was suspended in water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed sequentially with 10% aqueous citric acid solution, saturated aqueous NaHCO₃ solution, and brine (1 x 50 mL each), then dried (Na₂SO₄), filtered, and concentrated under vacuum. Purification by column chromatography on silica gel (gradient: DCM to 25% EtOAc in DCM) gave 3.09 g (48%) of the title compound as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.00 (m, 2H), 7.66 (d, *J* = 7.4 Hz, 1H), 7.55 (m, 3H), 7.45 (d, *J* = 4.2 Hz, 1H), 6.72 (d, *J* = 4.3 Hz, 1H), 5.05 (d, *J* = 8.4 Hz, 1H), 4.33 (s, 2H), 3.66 (m, 2H), 1.91 (m, 2H), 1.81 (m, 2H), 1.44 (m, 2H), 1.32 (m, 2H), 0.86 (s, 9H), 0.05 (s, 6H). LCMS (method LCMS12, ESI): RT = 3.99 min, *m/z* = 501.1 [M+H]⁺.



(R)-1-(1-(*trans*-4-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-6-(phenylsulfonyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)ethanol. (*R*)-(+)-Lactamide (1.65 g, 18.5 mmol) was dissolved in THF (28 mL) and triethyloxonium tetrafluoroborate (3.52 g, 18.5 mmol) was added. The mixture was stirred for 3 h at room temperature, then concentrated under vacuum. The residue was dissolved in EtOH (14 mL, IMS grade) and added to a suspension N⁴-(*trans*-4-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine-4,5-diamine (3.09 g) in EtOH (42 mL, IMS grade). The mixture was stirred at 75 °C for 3 h, then cooled and concentrated under vacuum. The residue was dissolved in absolute EtOH (42 mL), and a further portion of (*R*)-(+)-Lactamide (1.65 g, 18.5 mmol) and triethyloxonium tetrafluoroborate (3.52 g, 18.5 mmol) premixed as above was added as a solution in absolute EtOH (14 mL). The resulting mixture was stirred at 75 °C for 45 min, then cooled to room temperature. Saturated aqueous NaHCO₃ solution (30 mL) was added and the mixture extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), then dried (Na₂SO₄), filtered, and concentrated under vacuum. Purification by column chromatography on silica gel (gradient: 3:1 cyclohexane: [1:1 DCM: EtOAc] to 1:4 cyclohexane: [1:1 DCM: EtOAc] to 1:1 DCM: EtOAc) gave 3.31 g (97%) of the title compound as an off-white solid, which was used directly in the next step without further purification. LCMS (method LCMS12, ESI): RT = 4.70 min, *m/z* = 555.3 [M+H]⁺.

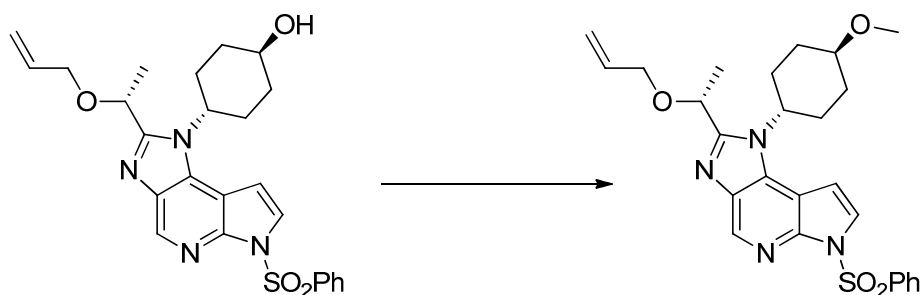


2-((*R*)-1-(Allyloxy)ethyl)-1-(*trans*-4-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-(phenylsulfonyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine. (*R*)-1-(1-(*trans*-4-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-(phenylsulfonyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)ethanol (1.00 g, 1.81 mmol) was dissolved in THF (10 mL) and allyl *tert*-butyl carbonate (1.42 g, 8.05 mmol) was added. The mixture was evacuated and purged with nitrogen (\times 3). Palladium tetrakis(triphenylphosphine) (105 mg, 0.081 mmol) was added and the mixture heated at 85 °C under nitrogen for 1 h. The mixture was concentrated, then purification by silica gel chromatography (gradient: cyclohexane to 1:2 EtOAc: cyclohexane) gave 715 mg (66%) of the title compound as an off-white solid. LCMS (method LCMS12, ESI): RT = 5.36 min, m/z = 595.4 [M+H]⁺.



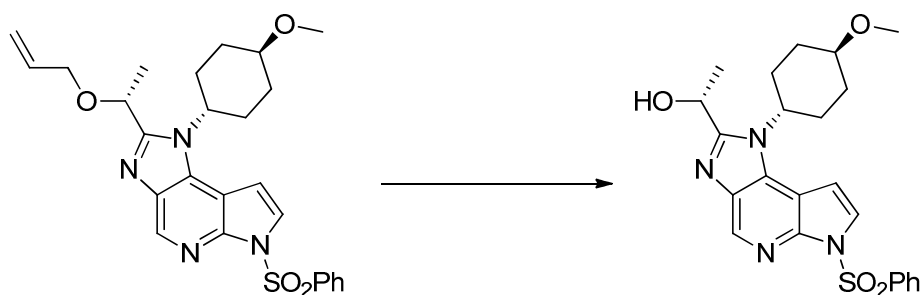
***trans*-4-(2-((*R*)-1-(Allyloxy)ethyl)-6-(phenylsulfonyl)imidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(*6H*)-yl)cyclohexanol.** 2-((*R*)-1-(allyloxy)ethyl)-1-(*trans*-4-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-6-(phenylsulfonyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine (710 mg) was dissolved in EtOH (10 mL, IMS grade) and 37% aqueous HCl (100 μ L) was

added. The mixture was stirred at room temperature for 1 h, then a further 100 μ L of HCl was added. The mixture was stirred for a further 90 min, then concentrated under vacuum. The residue was triturated with cyclohexane then dried under vacuum to give 490 mg (85%) of the title compound as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.72 (s, 1H), 8.13 (m, 2H), 7.99 (d, $J = 4.1$ Hz, 1H), 7.71 (t, $J = 7.4$ Hz, 1H), 7.61 (t, $J = 7.7$ Hz, 2H), 7.07 (d, $J = 4.2$ Hz, 1H), 5.88 (m, 1H), 5.26 (dd, $J = 17.0, 2.0$ Hz, 1H), 5.13 (m, 2H), 4.79 (d, $J = 4.3$ Hz, 1H), 4.71 (m, 1H), 3.99 (d, $J = 5.1$ Hz, 2H), 3.81 (m, 1H), 2.23 (m, 2H), 2.04 (m, 2H), 1.85 (m, 2H), 1.63 (d, $J = 6.3$ Hz, 3H), 1.43 (m, 2H). LCMS (method LCMS12, ESI): RT = 3.31 min, $m/z = 481.4$ $[\text{M}+\text{H}]^+$.

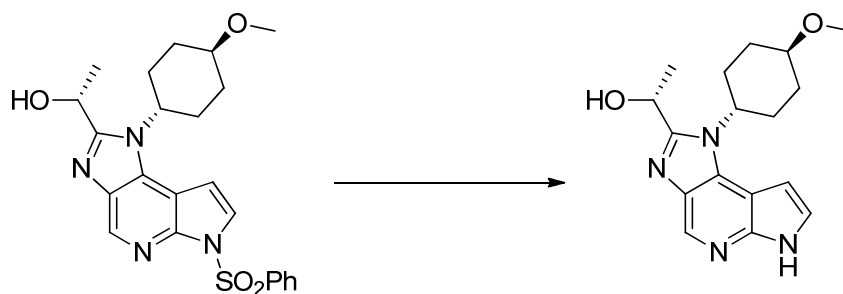


2-((*R*)-1-(Allyloxy)ethyl)-1-(*trans*-4-methoxycyclohexyl)-6-(phenylsulfonyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine. A mixture of *trans*-4-(2-((*R*)-1-(allyloxy)ethyl)-6-(phenylsulfonyl)imidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(*6H*)-yl)cyclohexanol (240 mg, 0.50 mmol), 2,6-di-*tert*-butyl-4-methyl piperidine (360 mg, 1.75 mmol) and silver trifluoromethane sulfonate (400 mg, 1.55 mmol) in dry DCM (2 mL) was cooled to 0 $^{\circ}\text{C}$. Iodomethane (102 μ L, 1.63 mmol) was added and the reaction mixture stirred for 3 h at 0 $^{\circ}\text{C}$, followed by 16 h at room temperature. The reaction mixture was diluted with DCM (10 mL), washed with 10% aqueous citric acid solution, saturated aqueous sodium bicarbonate solution, and brine (5 mL each), dried over sodium sulfate, filtered and the filtrate evaporated under vacuum. The residue was purified by column chromatography on silica gel (gradient: 0 to 70% EtOAc in DCM) to afford 140 mg (57%) of the title compound as a white foam. ^1H NMR (400

MHz, CDCl₃) δ 8.88 (s, 1H), 8.23 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.85 (d, *J* = 4.1 Hz, 1H), 7.56 (m, 1H), 7.47 (m, 2H), 6.86 (d, *J* = 4.1 Hz, 1H), 5.85 (m, 1H), 5.26 (m, 1H), 5.18 (dd, *J* = 10.5, 1.6 Hz, 1H), 5.01 (q, *J* = 6.8 Hz, 1H), 4.96 (m, 1H), 3.96 (m, 2H), 3.46 (m, 4H), 2.35 (m, 4H), 2.02 (m, 1H), 1.90 (m, 1H), 1.71 (d, *J* = 6.8 Hz, 3H), 1.48 (m, 2H). LCMS (method LCMS11, ESI): RT = 3.65 min, *m/z* = 495.3 [M+H]⁺.



(*R*)-1-(1-(*trans*-4-Methoxycyclohexyl)-6-(phenylsulfonyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)ethanol. A mixture of 2-((*R*)-1-(allyloxy)ethyl)-1-(*trans*-4-methoxycyclohexyl)-6-(phenylsulfonyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine (120 mg, 0.24 mmol) and 1,3-dimethylbarbituric acid (190 mg, 1.21 mmol) was dissolved in dry THF (2 mL) under argon. Tetrakis(triphenylphosphine) palladium (0) (28.0 mg, 0.024 mmol) was added and the reaction mixture heated at 70 °C for 2 h. The solvent was concentrated under vacuum and the resulting residue purified by column chromatography on silica gel (gradient: 0 to 5% MeOH in DCM) to afford 88.0 mg of the title compound as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.70 (s, 1H), 8.13 (m, 2H), 7.97 (d, *J* = 4.1 Hz, 1H), 7.70 (m, 1H), 7.61 (m, 2H), 7.10 (d, *J* = 4.2 Hz, 1H), 5.75 (m, 1H), 5.14 (m, 1H), 4.84 (m, 1H), 3.54 (m, 1H), 3.33 (s, 3H), 2.21 (m, 4H), 1.94 (m, 2H), 1.61 (d, *J* = 6.4 Hz, 3H), 1.39 (m, 2H). LCMS (method LCMS12, ESI): RT = 2.88 min, *m/z* = 455.2 [M+H]⁺.



(R)-1-(1-(*trans*-4-Methoxycyclohexyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)ethanol (25). Aqueous sodium hydroxide (1 mL of 1 M solution) was added to a solution of (R)-1-(1-(*trans*-4-methoxycyclohexyl)-6-(phenylsulfonyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-2-yl)ethanol (88.0 mg, 0.19 mmol) in a 1:1 mixture of THF:MeOH (1 mL), and the mixture was stirred at room temperature for 64 h. The solvent was evaporated under vacuum to a small volume, then DCM (10 mL) was added. The organic layer was washed with saturated sodium bicarbonate solution and brine (5 mL each), dried over sodium sulfate, filtered, and concentrated under vacuum to afford 58.0 mg (97%) of the title compound as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.85 (s, 1H), 8.54 (s, 1H), 7.47 (t, *J* = 3.0 Hz, 1H), 6.69 (m, 1H), 5.66 (d, *J* = 6.7 Hz, 1H), 5.12 (m, 1H), 4.84 (m, 1H), 3.54 (m, 4H), 2.39 (m, 2H), 2.24 (m, 2H), 1.94 (m, 2H), 1.63 (d, *J* = 6.5 Hz, 3H), 1.40 (m, 2H). LCMS (method LCMS11, ESI): RT = 2.34 min, *m/z* = 315.5 [M+H]⁺.

In vitro microsome metabolic stability experiments were carried out as described in:

Halladay, J. S.; Wong, S.; Jaffer, S. M.; Sinhababu, A. K.; Khojasteh-Bakht, S. C. Metabolic stability screen for drug discovery using cassette analysis and column switching. *Drug Metab. Lett.* **2007**, *1*, 67–72.

In vitro hepatocyte metabolic stability experiments were carried out as described in:

The metabolic stability of test compounds (1 μM test concentration) was determined in human, Sprague–Dawley rat, CD-1 mouse, beagle dog, and cynomolgus monkey, cryopreserved primary hepatocytes (CellzDirect Invitrogen Corporation, Durham, NC, USA, pooled donors). Incubations (final incubation volume = 250 μL) were performed at 37 °C under an atmosphere of 95%/5% CO_2/O_2 using 0.5 million cells mL^{-1} in hepatocyte incubation media (In Vitro Technologies, Baltimore, MD, USA). 50- μL aliquots (cells and media) were taken at zero, 1, 2 and 3 h following the start of the incubation and quenched using 100 μL of ice-cold acetonitrile. The resulting samples were centrifuged at 3000 g for 10 min. Supernatant (90 μL) was diluted in water (180 μL) and the percent remaining test compound was assessed by LC/MS/MS. All incubations were performed in quadruplicate.

Reversible CYP inhibition experiments were carried out as described in:

Halladay, J. S.; Delarosa, E. M.; Tran, D.; Wang, L.; Wong, S.; Khojasteh-Bakht, S. C. High-throughput, 384-well, LC-MS/MS CYP inhibition assay using automation, cassette-analysis technique, and streamLined data analysis. *Drug Metab. Lett.* **2011**, 5, 220–230.

Time-dependent CYP inhibition experiments were carried out as described in:

(a) Mukadam, S.; Tay, S.; Tran, D.; Wang, L.; Delarosa, E. M.; Khojasteh, S. C.; Halladay, J., S.; Kenny, J. R. Evaluation of Time-Dependent Cytochrome P450 Inhibition in a High-Throughput, Automated Assay: Introducing a Novel Area Under the Curve Shift Approach. *Drug Metab. Lett.* **2012**, 6, 43–53.

(b) Obach, R. S.; Walsky, R. L.; Venkatakrishnan, K. Mechanism-based inactivation of human cytochrome p450 enzymes and the prediction of drug-drug interactions. *Drug Metab. Dispos.* **2007**, *35*, 246–255.

MDCK permeability experiments were carried out as described in:

(a) Plise, E. G.; Sindelar, E.; Duck, B.; Cheong, J.; Sodhi, J.; Salphati, L. Fully Automated 24-Well Madin-Darby Canine Kidney (MDCK) Permeability Assay Utilizing the Hamilton Microlab Star Liquid handling Platform. AAPS Annual Meeting 2009.

AAPS Abstract: http://www.aapsj.org/abstracts/AM_2009/AAPS2009-001769.PDF

Hamilton Robotics website:

http://www.hamiltonrobotics.com/fileadmin/user_upload/prodb/app_notes/Metabolomics/Genentech2.pdf

(b) Irvine, J. D.; Takahashi, L.; Lockhart, K.; Cheong, J.; Tolan, J. W.; Selick, H. E.; Grove, J. R. MDCK (Madin-Darby canine kidney) cells: a tool for membrane permeability screening. *J. Pharm. Sci.* **1999**, *88*, 28–33.

In vivo PK experiments were carried out as follows:

The pharmacokinetics of test compounds were evaluated following a single intravenous bolus (IV) of solution at a dose of 0.2 – 1 mg/kg and oral administration (PO) of solution/suspension at doses of 1 – 5 mg/kg in male cynomolgus monkey, beagle dogs, or sprague dawley rats using a parallel study design. Blood samples for the IV dose group were collected prior to administration (predose) and at 0.033, 0.083, 0.25, 0.5, 1, 3, 6, 9 and 24 h post dose. Blood samples for PO dose groups were collected prior to administration (predose) and at 0.083, 0.25, 0.5, 1, 3, 6, 9 and 24 h post dose. For the IV group, urine

was collected from each animal at predose and from 0 – 6 and 6 – 24 h post dose. The vehicle used for IV dose groups was a combination of PEG400 with citrate buffer (pH_{5.0}) or PEG400 with DMSO/H₂O, and for PO groups was MCT. Plasma and urine concentrations were quantitated at Genentech Inc. using a non-validated LC/MS/MS method. The lower limit of quantitation (LLOQ) of the plasma and urine assays was 0.005 µM. PK parameters were determined by non-compartmental methods using WinNonlin (version 5.2, Pharsight Corporation, Mountain View, CA).

JAK Enzyme Assays were carried out as follows:

The activity of the isolated recombinant JAK1, JAK2 or TYK2 kinase domain was measured by monitoring phosphorylation of a peptide derived from JAK3 (Val-Ala-Leu-Val-Asp-Gly-Tyr-Phe-Arg-Leu-Thr-Thr, fluorescently labeled on the N-terminus with 5-carboxyfluorescein) using the Caliper LabChip technology (Caliper Life Sciences, Hopkinton, MA). Alternatively, the activity of the isolated JAK3 kinase domain was measured by monitoring phosphorylation of a different peptide derived from JAK3 (Leu-Pro-Leu-Asp-Lys-Asp-Tyr-Tyr-Val-Val-Arg, fluorescently labeled on the N-terminus with 5-carboxyfluorescein) using the same Caliper LabChip technology. To determine inhibition constants (K_i), compounds were diluted serially in DMSO and added to 50 µL kinase reactions containing purified enzyme (1.5 nM JAK1, 0.2 nM JAK2, 5nM JAK3 or 1 nM TYK2), 100 mM HEPES buffer (pH 7.2), 0.015% Brij-35, 1.5 µM peptide substrate, ATP (5 µM for JAK3, 25 µM for JAK1, JAK2, and TYK2), 10 mM MgCl₂, 4 mM DTT at a final DMSO concentration of 2%. Reactions were incubated at 22 °C in 384-well polypropylene microtiter plates for 30 minutes and then stopped by addition of 25 µL of an EDTA containing solution (100 mM HEPES buffer (pH 7.2), 0.015% Brij-35, 150 mM EDTA), resulting in a final EDTA concentration of 50 mM. After termination of the kinase reaction, the proportion of phosphorylated product was determined as a fraction of total peptide substrate using the Caliper LabChip 3000 according to the manufacturer's specifications. K_i values were then determined

using the Morrison tight binding model (Morrison, J.F., Biochim. Biophys. Acta. 185:269-296 (1969); William, J.W. and Morrison, J.F., Meth. Enzymol., 63:437-467 (1979)) modified for ATP-competitive inhibition [$K_i = K_{i,app} / (1 + [ATP] / K_{m,app})$].

JAK Pathway Assay in Cell Lines were carried out as follows:

Inhibitor potency (EC_{50}) was determined in cell-based assays designed to measure JAK1, JAK2 and TYK2 dependent STAT phosphorylation. TF-1 cells, obtained from the American Type Culture Collection (ATCC; Manassas, VA) were used to measure JAK1 dependent STAT3 phosphorylation downstream of IL-6 stimulation and JAK2 dependent STAT5 phosphorylation downstream of erythropoietin (EPO) stimulation. Prior to use in the assays, TF-1 cells were starved of GM-CSF overnight in OptiMEM (Life Technologies, Grand Island, NY) supplemented with 0.5% charcoal/dextran stripped fetal bovine serum (FBS), 0.1 mM non-essential amino acids (NEAA), and 1 mM sodium pyruvate. NK92 cells (ATCC) were used to measure TYK2 dependent STAT4 phosphorylation downstream of IL-12 stimulation. NK92 cells were starved of IL-2 overnight in RPMI with 10% charcoal/dextran stripped FBS. The assays were run in a 384-well format in serum free RPMI medium using 100,000 cells per sample. Test compounds were serially diluted 1:2 in DMSO and then diluted 1:50 in RPMI just before use. Diluted compounds were added 1:10 to the cells, for a final DMSO concentration of 0.2%, and incubated for 20 min at 37 °C. Cells were stimulated with human recombinant cytokine, 30 ng/mL IL-6 (Invitrogen, Carlsbad, CA), 10 U/mL EPO (Invitrogen), or 30 ng/mL IL-12 (R&D, Minneapolis, MN), for 30 min (IL-6) or 45 min (EPO and IL-12) at 37 °C. The reactions were stopped by the addition of 10x lysis buffer (Cell Signaling Technologies, Danvers, MA) and the resultant samples were frozen at -80 °C. Compound mediated inhibition of pSTAT3, pSTAT5 and pSTAT4 was measured in the cell lysates using Meso Scale Discovery (MSD) technology

(Gaithersburg, MD). EC₅₀ values were determined as the concentration of compound required for 50% inhibition of STAT phosphorylation relative to that measured for the DMSO control.

Human whole blood assays were carried out as follows:

Compound potency was determined in whole blood by measuring JAK1-dependent STAT3 phosphorylation downstream of IL-6 stimulation. Blood was collected in citrate and dispensed into a 384-well microtiter plate. As above, test compounds were serially diluted in DMSO, diluted 1:50 in RPMI and added 1:10 to the blood sample for a final DMSO concentration of 0.2%. Blood was incubated with compound for 20 min at 37 °C and then stimulated with IL-6 (300 ng/mL) for 45 min at 37 °C. The reactions were stopped by the addition of 10x lysis buffer and the resultant samples were frozen at -80 °C. Compound mediated inhibition of pSTAT3, was measured in the lysates using MSD technology.

The CIA efficacy study of compound **31** in the rat was carried out as follows:

6-week-old female Lewis rats were obtained from Harlan Sprague Dawley, Livermore, California. The experiment was conducted in compliance with National Institute of Health Guide for the Care and Use of Laboratory Animals and was approved by the Genentech Institutional Animal Care and Use Committee.

Lewis rats were immunized i.d. at the base of the tail with 400 µg bovine collagen type II (CII, Chondrex) emulsified in 400 µl incomplete Freund's adjuvant (IFA) on day 0. On day 6, rats received a booster injection of 400 µg CII in 400 µl IFA and were allowed to develop disease.

To assess efficacy animals were randomized based on clinical arthritis scores and start treatment at day 10 after immunization. A dose response of JAK1 inhibitor, compound **31**, comparing to vehicle was

performed. The JAK1 inhibitor was formulated in corn oil and administered PO daily at dosages of 20mg/kg, 100mg/kg and 500mg/kg until termination at day 20.

Rats were examined 3 times per week for clinical signs of joint inflammation and edema in each paw. Edema of the ankle joint was assessed with a caliper (CD-6” CSX, Mitutoyo) under light anesthesia.

Study design:

The number of rats per group is as follows: G1 = 5, G2 – G4 = 9 each, G5 = 3.

G1: Immunized and treated with corn oil vehicle 1 mL PO QD.

G2: Immunized and treated with compound **31**, 20 mg/kg in corn oil vehicle 1 mL PO QD.

G3: Immunized and treated with compound **31**, 100 mg/kg in corn oil vehicle 1 mL PO QD.

G4: Immunized and treated with compound **31**, 500 mg/kg in corn oil vehicle 1 mL PO QD.

G5: Naïve, non-diseased controls

PK analysis:

3 rats from groups 3, 4 and 5 will be bled for plasma PK analysis.

Day 10: Blood sample (200ul) will be collected via tail vein at 0.5, 2hr post-dose for plasma PK.

Day 11: Blood sample (200ul) will be collected via tail vein at 24hr post day 10 dose for plasma PK.

Day 20: Blood samples (200ul) will be collected via tail vein at 30 min, 2 and 4 hrs post-dose for PK.

Day 21: Terminal blood samples (200ul) will be collected at 24 h post day 20 dose for plasma PK. The rats will be euthanized after the terminal bleeds.

hERG assays were carried out as follows:

The in vitro potential for hERG (human ether-a-go-go-related gene) potassium channel current inhibition was assessed according to the study site standard procedures (ChanTest, Cleveland, OH). In brief, hERG inhibition (% max) was determined in hERG-expressing HEK-293 cells (n=2 /concentration) using the automated PatchXpress 7000A system (Molecular Devices, Sunnyvale, CA) for 5 minutes after adding the test article. IC₅₀ values were calculated based on hERG inhibition at test article concentrations of 0.01, 0.1, 1, 10, 30, and 100 μ M.

Protein expression, purification for X-ray crystallography, crystallization and X-ray structure determination were carried out as described in:

Kulagowski, J. J.; Blair, W.; Bull, R. J.; Chang, C.; Deshmukh, G.; Dyke, H. J.; Eigenbrot, C.; Ghilardi, N.; Gibbons, P.; Harrison, T. K.; Hewitt, P. R.; Liimatta, M.; Hurley, C. A.; Johnson, A.; Johnson, T.; Kenny, J. R.; Bir Kohli, P.; Maxey, R. J.; Mendonca, R.; Mortara, K.; Murray, J.; Narukulla, R.; Shia, S.; Steffek, M.; Ubhayakar, S.; Ultsch, M.; van Abbema, A.; Ward, S. I.; Waszkowycz, B.; Zak, M. Identification of Imidazo-pyrrolopyridines as Novel and Potent JAK1 Inhibitors. *J. Med. Chem.* **2012**, *55*, 5901–5921.

Data reduction and final refinement statistics appear in Table S1.

Table S1: Data Collection and Refinement for JAK1 and JAK2 Complexes

	cmpd31/JAK2 PDB 4IVA	cmpd31/JAK1 PDB 4IVB	cmpd33/JAK1 PDB 4IVC	cmpd34/JAK1 PDB 4IVD
<i>Data collection</i>	APS 21-IDD	ALS 5.0.2	APS 22-ID	APS 22BM
space group	P2 ₁	P2 ₁	P2 ₁	P2 ₁
unit cell (\AA , °)	<i>a</i> = 42.25, <i>b</i> = 69.30,	<i>a</i> =42.92, <i>b</i> =173.5,	<i>a</i> = 42.33, <i>b</i> = 172.9,	<i>a</i> = 42.80, <i>b</i> = 173.6,
	<i>c</i> = 50.91	<i>c</i> =44.54	<i>c</i> = 44.12	<i>c</i> =44.63
	β = 101.0	β =94.29	β = 94.75	β = 94.53

V_M ($\text{\AA}^3/\text{Dalton}$)	2.3	2.5	2.5	2.5
Resolution (\AA)	50 – 1.5 (1.55 - 1.50)	50 – 1.90 (1.97 – 1.90)	50 – 2.35 (2.43 – 2.35)	50 – 1.93 (2.00 - 1.93)
Rsym ^b	0.049 (0.259)	0.072 (0.497)	0.089 (0.375)	0.098 (0.558)
Num. observations	170096	182532	74432	173963
Unique reflections	45972	49333	26579	48323
Completeness (%) ^b	96.8 (87.5)	97.6 (94.8)	98.1 (97.3)	99.6 (100.0)
$I/\sigma I$ ^b	26 (4.3)	17 (2.6)	10 (2.3)	12 (2.4)
Wilson B (\AA^2)	16	27	38	24
<i>Refinement</i>				
Resolution (\AA)	50 – 1.50	50 – 1.90	50.0 – 2.35	50 – 1.93
No. reflections ($F > 0\sigma(F)$)	45968	49321	25726	48317
Final R, R_{FREE}	0.175, 0.192	0.181, 0.221	0.197, 0.263	0.202, 0.247
Molecules/asym. unit	1	2	2	2
protein residues	291	575	575	574
solvent molecules	280	311	159	327
atoms	2272	5102	4884	5063
Mean B-factor (\AA^2) ^d	21/16/30/22	46/17/38/45	41/16/33/40	33/16/34/33
Rmsd bonds (\AA)	0.007	0.008	0.008	0.007
Rmsd angles ($^\circ$)	1.2	1.2	1.2	1.1
NCS rmsd coords (\AA)	–	0.14	0.21	0.08
Num. TLS groups	0	4	4	0
Ramachandran (%)	99.0/1.0/0	98.8/1.2/0	98.6/1.4/0	98.9/1.1/0

^b In parenthesis, for the highest resolution shell.

^d protein/ligand/solvent/all atoms

Measured thermodynamic solubility (pH_{7.4} and pH_{2.0}) experimental procedures:

A standard curve for each compound tested was prepared as follows: A 10 mM stock solution in DMSO was prepared. The DMSO stock was then serially diluted with a 1:1 mixture of acetonitrile/water to concentrations of 200 μM , 20 μM , and 2 μM to provide standard samples. The UV absorbance at a wavelength of 254 nm was then measured using a LC/UV method for each of the standard samples to make a calibration curve. The testing sample was then prepared as follows: 0.45 mL of phosphate buffered saline (PBS, pH = 7.4), or phosphate buffered saline containing HCl (PBS/HCl, pH = 2.0) was added to 2 mg of solid test sample in a Whatman UniPrep filter vial. The vial was shaken for 24 h at room temperature, then the aqueous mixture was filtered. The filtrate was diluted 10-fold with PBS or PBS/HCl buffer and an aliquot was then injected onto a LC/UV instrument. The

UV absorbance of the test sample at 254 nm was measured and compared with its calibration curve to determine the concentration and, hence, the aqueous solubility of the test sample.

Table S2. Analytical LCMS and SFC conditions

Method	Instrument	Column brand	Column diameter (mm)	Column length (mm)	Column particle size (µm)	Column temperature (°C)	Mobile phase: A	Mobile phase: B	Gradient	Flow rate (mL/min)	UV Detection Wavelength (nm)	run length (min)	Mass spectrometer	Ionization	Scan range (AMU)
LCMS1	Waters Acquity UPLC	Acquity BEH C18 or Acquity BEH Shield RP18	2.1	50	1.7	40	water with 0.05% TFA	acetonitrile with 0.05% TFA	A:B = 98:2 (0.6 min); 98:2 - 2:98 (over 16 min); 2:98 (1.2 min); 2:98 - 98:2 (over 1.2 min)	0.6	200-400	20.0	Waters Micromass LCT Premier XE Q-TOF	ESI*	80-1300
LCMS2	Shimadzu HPLC	Waters Sunfire C18	4.6	50	3.5	25	water with 0.1% formic acid	acetonitrile with 0.1% formic acid	A:B = 90:10 (0.3 min); 90:10 - 10:90 (over 1.2 min); 10:90 - 5:95 (over 1.0 min); 5:95 - 10:90 (over 0.2 min)	2.0	214 and 254	2.5	Shimadzu LCMS-2020 (single quadrupole)	ESI*	60-800
LCMS3	HPLC Agilent 1200	Agilent SB C18	2.1	30	1.8	25	water with 0.05% TFA	acetonitrile with 0.05% TFA	A:B = 97:3 (0.3 min); 95:3 - 5:95 (over 6.5 min); 5:95 (1.5 min); 5:95 - 97:3 (over 0.1 min)	0.4	254	10.0	Agilent 6140 Quadrupole LC/MS	ESI*	90-1300
LCMS4	Waters Acquity UPLC	Acquity UPLC BEH C18	2.1	30	1.7	40	water with 0.1% formic acid	acetonitrile with 0.1% formic acid	A:B = 95:5 - 5:95 (over 1.4 min); 5:95 (0.3 min)	0.8	220 and 254	1.7	Waters SQ	ESI*	100 - 800
LCMS5	Waters Acquity UPLC	Acquity UPLC BEH C18	2.1	50	1.7	40	water with 0.05% TFA	acetonitrile with 0.05% TFA	A:B = 98:1 - 2:98 (over 17 min); 2:98 (1.5 min)	0.6	254	18.5	Waters LCT Premier XE	ESI*	100 - 800
LCMS6	Shimadzu HPLC	Phenomenex Onyx Monolithic C18	4.6	50		25	water with 0.0375% TFA	acetonitrile with 0.0375% TFA	A:B = 95:5 - 15:85 (over 4.0 min); 15:85 (0.5 min)	3.0	214 and 254	4.5	Waters SQ	ESI*	150-1250
LCMS7	Waters Acquity UPLC	Acquity BEH C18 or Acquity BEH Shield RP18	2.1	100	1.7	40	water with 0.1% formic acid	acetonitrile with 0.1% formic acid	A:B = 95:5 (0.4 min); 95:5 - 5:95 (over 5.6 min); 5:95 (0.8 min); 5:95 - 95:5 (over 1.2 min)	0.4	220 and 254	8.0	Waters Micromass ZQ2000 quadrupole	ESI*	110 - 800
LCMS8	Agilent 1200 HPLC	Agilent SD-C18	2.1	30	1.8	40	water with 0.05% trifluoroacetic acid	acetonitrile with 0.05% trifluoroacetic acid	A:B = 97:3 - 5:95 (over 8.5 min); 5:95 (2.5 min)	0.7	220 and 254	11.0	Agilent quadrupole 6140	ESI*	110 - 800
LCMS9	Agilent 1200 HPLC	Agilent SD-C18	3.0	100	3.5	40	water with 0.05% trifluoroacetic acid	acetonitrile with 0.05% trifluoroacetic acid	A:B = 98:2 - 2:98 (over 25.5 min); 2:98 (4.5 min)	0.7	220 and 254	30.0	Agilent quadrupole 6140	ESI*	110 - 800
LCMS10	Waters 1525 HPLC	Phenomenex Luna C18(2)	4.6	30	3.0	25	water with 0.1% formic acid	acetonitrile with 0.1% formic acid	A:B = 95:5 (0.5 min); 95:5 - 5:95 (over 4.0 min); 5:95 (1.0 min); 5:95 - 95:5 (over 0.5 min)	2.0	220 and 254	6.0	Waters ZMD quadrupole	ESI*	110 - 800
LCMS11	Hewlett Packard HP1100 HPLC	Phenomenex Luna C18(2)	4.6	30	3.0	25	water with 0.1% formic acid	acetonitrile with 0.1% formic acid	A:B = 95:5 (0.5 min); 95:5 - 5:95 (over 4.0 min); 5:95 (1.0 min); 5:95 - 95:5 (over 0.5 min)	2.0	220 and 254	6.0	Waters ZMD single quadrupole	ESI*	100 - 800
LCMS12	Hewlett Packard 1050 HPLC	Phenomenex Luna C18(2)	4.6	30	3.0	25	water with 0.1% formic acid	methanol with 0.1% formic acid	A:B = 95:5 (0.5 min); 95:5 - 5:95 (over 4.0 min); 5:95 (1.0 min); 5:95 - 95:5 (over 0.5 min)	2.0	220 and 254	6.0	Finnigan AQA single quadrupole	ESI*	110 - 800
SFC1	Berger Analytical SFC/MS	Luxcellulose-1	4.6	50	3.0	40	Carbon dioxide	Ethanol with 0.1% NH ₄ OH	isocratic, A:B = 80:20	5.0	230-254	2.5	Waters ZQ quadrupole	ESI*	110 - 800
SFC2	Berger Analytical SFC/MS	Chiralpak AS	4.6	50	3.0	40	Carbon dioxide	Methanol with 0.1% NH ₄ OH	isocratic, A:B = 90:10	5.0	230-254	2.5	Waters ZQ quadrupole	ESI*	110 - 800

Table S3. Off-Target Kinase data of **21, 26, 29, 31, 33, 34**; % Inhibition shown

Example	21		26		29		31		33		34	
Concentration tested (μM)	0.15	1.0	0.10	1.0	0.10	1.0	0.10	1.0	0.010	0.10	0.015	0.15
Fold over K_i	53x	355x	130x	1300x	50x	500x	53x	530x	85x	850x	43x	430x
# Non-JAK inhibited >50%	1	15	2	17	0	1	0	2	2	21	4	38
Kinases Tested												
Abl	6.5	12.1	1.7	-0.3	7.7	-6.6	-10.4	-4	-1.3	7	-9.9	9.6
ACVR1B	-16.1	1.7	8.9	7.5	-5.1	-9.1	2	9.7	-3.8	-3.3	-1.1	0.5
AKT1	0.9	4.7	-4.3	-7.7	5	-6.5	0.8	-7.9	4	3.3	2	-2
AKT2	-0.6	5.3	0	-2.3	9.4	-3.6	5.7	5.4	1.2	5.3	4.5	4.3
AKT3	3	2.1	1.5	0.4	3.3	-5.5	-0.3	1.4	-3.9	3.2	2.6	6
ALK	6.2						14.9		2.4		11.1	10.1
ALK2	9.9	4.2	1.1	13.8	2.1	1.1	-3.4	3.3	9.8	5.4	-2.3	24.6
Arg	5.2	18.4	-0.1	-0.6	12.6	10.9	10.8	-5.8	5.5	13.9	8	7.8
ARK5	45.8	69.7	21.1	54.5	19.5	27.3	8.8	36.1	7.9	63.1	13.2	66.8
ASK1	2.8	38.6	6.4	11.1	2	0.8	2	12.9	1.6	22.5	6.1	45.2
Aurora_A	11.2	32.4	19.8	54.7	6.4	8	3.1	29.9	15.4	75.5	6.2	56.1
Aurora_B	15.1	34.4	1	13.7	18.3	14.7	10.4	10.5	21	67	10.4	46.5
Aurora_C	5	22.6	5.5	27.1	4	-2.8	5.8	16.8	9.9	39.3	3.5	40
Axl	12.6	23.8	8	32.4	15.3	-2.9	5.2	12.6	3.5	33.5	4.9	51.3
B-Raf	41.1	10.4	13.3	6.7	7.7	-5.4	14.5	27.1	3.8	17.8	11.9	48.8
Blk	11.1	6.1	9.3	22.1	8.4	13	4.2	7.3	13.1	32.2	5.9	24.3
Bmx	4.4	11.8	1.7	7	4.8	-2.9	13.7	12.1	17.9	7.2	15.4	10.1
Brk	5.1	5.1	1.9	4.6	8.9	-7.8	5.4	8.2	-15.4	11.5	3.3	6.1
BrSK1	14.2	32.5	36	78.9	18	40.1	7.5	42.5	23.7	83.4	20.4	92.1
BTK	2.6	1.8	9.3	1.5	8.5	-6.6	-3	6.3	-0.5	7.9	-4.8	-10.9
CaMKI	23.2	-16.9	-3.3	8.8	-16.8	-20.5	-3.3	-18.6	-28	-2.5	-6.5	-10.1
CaMKI_delta	-0.4	6.8	6.8	6.9	14.1	9.2	14.1	4.3	11.1	13.8	21.3	13.2
CamKII_alpha	11.6	9.7	2.4	4.5	8	3.8	7.6	5.4	6.8	4.3	9.6	17.4
CaMKII_beta	-3.1	11.5	0	8.6	6.2	-0.8	1.3	10	13.3	2.9	10.9	4.7

CamKII_delta		-3.5	8.3	6	7.3	5.7	7.1	7.3	9.2	4.3	7.7	27.9	12.4
CamKIV		25.4	2.9	15.8	7.1	11.2	-2.4	-1.3	17.8	14.8	16.1	-4.8	3.3
CAMKK1		8.1	25.5	-2.3	-6.8	1.1	-0.4	-1.9	-3.3	-1.6	-9.9	-2.5	-4.5
CAMKK2		6.7	12.6	-12.2	-9.2	-0.6	11.2	-3	-0.8	1.1	-1.8	-1.1	-0.9
CDK1/cyclinB		4	5.8	7.4	8	14.7	6.8	2.5	3.9	3	7.5	0.8	5.4
CDK2/cyclinA		10.2	8.9	7.3	12.5	26.4	12.7	0.5	10.2	10.4	22.8	7.1	37.2
CDK5/p25		-6.6	8.1	1.5	3.1	11.9	-4.5	0.9	4.3	-1.2	12.1	0.2	2.9
CDK5/p35		-6.9	7.2	1.7	4.9	8.9	2.3	3.1	3.1	3.1	11.3	2.1	13.4
CDK7/cyclinH		-7.2	5.6	-3	-0.6	-2.8	3.9	-7.5	1.1	-1.3	-0.5	-6.4	-6.6
CDK8/cyclinC		4.2	13.6	-1.3	2.1	8	0.3	-3.7	2.5	0.5	-1.3	-1.5	-2.7
CDK9/cyclinK		9.4	0.9	-7.7	-7.2	4.3	3.1	-6.1	3.1	2	-2.9	-3.8	0.8
CDK9/cyclinT1		-1.1	11.8	0.5	13.8	4.9	5.8	-0.5	14.4	-2.6	3.4	-8.4	5.7
CHK1		37.2	8.6	3.8	9.8	0.3	-4.3	5.2	-6.5	6.6	11.8	1.5	6.4
CHK2		1.6	3.9	1.3	2.4	8.9	-9.8	5.8	2.4	2.6	8.4	3.5	12.4
CK1_alpha1		-0.4	4.3	-18.3	-17.5	3.4	0.9	5.3	15.6	1.9	5.1	10.6	0.3
CK1_delta		4.1	4.4	-2.7	-1.9	5.3	0.1	1	1	4.8	3.7	0.7	1.1
CK1_epsilon1		5.9	2.3	0.5	-3.3	11	-1	6.6	-0.6	5.3	7.3	5.8	-0.5
CK1_gamma1		-2.4	-1.3	-0.6	-1.5	-1.4	5.7	8.5	-4.7	0.1	-0.4	3.8	-5.9
CK1_gamma2		0.6	4.2	5.3	6.5	4.8	0.1	0	7.9	11.4	4.8	1.3	3.1
CK1_gamma3		1.7	1.8	7.5	5.8	1.8	3.8	-0.3	8.8	3.9	5.2	-2.7	-4.5
CK2_alpha1		6.8	3.9	11.2	11.7	19.1	2.1	7.8	8.1	6	17.6	5.1	0.8
CK2_alpha2		-0.5	4.8	9.3	7.7	-2.7	1.6	5.3	11.4	2.6	0.1	5.9	3
CLK1		6.8	0.9	12.1	7.6	8.8	7.4	9.2	9.7	4.3	3	5.9	13
CLK2		4	16.9	3.5	10.2	8.9	3.1	2.3	5.4	-0.4	14.6	2.6	26.9
CLK3		3.5	12.9	3.4	4.9	11.8	8.8	8	5.8	4.5	12.9	10.2	3.9
Cot		23.8	14.3	21.4	21.1	26.5	-10.6	-1.4	8.8	8.5	33.1	18.1	54.2
CSF1R		68.2	74.3	25.6	45.5	12.6	2	13.8	74.9	20.9	61.8	-2.8	66.2
CSK		0.5	1.8	5.7	4.8	12.3	-1	7.8	15.1	18.6	7.9	10.7	2.9
DAPK1		-1.8	-8.2	1.5	35.1	0.8	8.8	-1.9	26.4	-5.9	2.2	-2.3	21.7
DCAMKL2		8.2	4.1	4.2	7	11.1	0.9	2.9	4.3	5.8	11	5.1	0.5
DDR2		-2.7	8.9	-4.2	-1.1	-8.7	2.9	-0.8	-1.3	0.8	-8	0.7	-2.4
DMPK		9.6	35.5	6.5	31.2	1.9	23	4	14.6	1.3	15.1	8.8	62.3
DRAK1		8.8	5.2	6.9	37.1	4.6	10.9	-5.7	-4	-1	23.8	66.5	68

DYRK1A		0.9	4.7	1	2.4	4	5.8	0.7	1.9	4	9.8	0.5	10.4
DYRK1B		-14.2	8.1	1.4	2.8	3.6	-2.6	-2.7	3.8	4.5	6.2	-2.5	13.1
DYRK3		-1.8	2.4	1.1	1.3	5.2	-3.3	-9.2	-1.2	6.3	2.5	-3	2.3
DYRK4		-3.2	-0.4	-2.3	-2	3.6	-0.8	2.9	0.3	-2.5	0.9	2.5	-1.6
eEF-2K		5.3	-1.1	3.2	2.4	3.7	-0.8	6	6.2	6.2	2.8	8.7	1.2
EGFR		4.8	2.3	-15.7	-16.9	8.1	4.2	-7.2	-6.8	6.3	2.4	-5.6	2.3
EGFR(L858R)		0.8	10.6	-0.3	-0.9	5.7	-0.8	0.4	4.7	-5	3.4	0.2	8.3
EphA1		12.6	16.9	11.5	21.9	19	7.3	-7.2	16.4	-5.2	20	-3.8	14.2
EphA2		4.3	0.1	4.8	8.6	7.9	-7.3	-1.8	2.6	4.4	8.8	-0.3	5.4
EphA3		8.2	6.3	0.2	-3.9	11.4	6.3	2.7	2.5	-3.2	4.7	1.3	-3.6
EphA4		4.6	7.2	4.1	6.1	8.6	1.6	0	10	1	8.4	-1.1	12.9
EphA5		6.7	2.2	-2.2	-1.9	6.8	3.2	-4.1	-2.1	13.5	10.7	2.5	7.1
EphA7		9.3	9.9	4.4	15.1	15.4	4.6	0.8	6.8	1.3	13.1	1.5	9.5
EphA8		24.7	6	1.3	1.4	9.3	0.6	1	4.7	-4.7	4.8	-0.4	-9.3
EphB1		0.7	8.9	6.1	12.9	5.3	4.5	0.8	6.4	4.8	10.5	0.7	5.4
EphB2		4	0.8	4.7	8.5	17	4.8	1.6	11.9	7.4	10.6	2.4	4
EphB3		4.9	6.5	1.4	1.5	7.2	-2.3	-0.3	3	3.6	3.6	0.2	0.4
EphB4		10.3	4.9	6.1	5.2	4.2	-6.2	-5.1	9.3	8.6	10.9	-0.5	1.8
ErbB2		5.1	2.2	-2.3	1.1	6.9	-9.8	10.4	-1.9	13.9	19.5	7.2	3.9
ErbB4		4	1.3	11.8	12.3	6.3	2.2	2.5	5.5	-1	18.7	3.1	0.2
ERK1		34.2	4.6	18.9	20	13.8	7.7	1.6	13.9	7.8	17.1	2.5	34.9
ERK2		15.1	0.1	2.8	3.2	9.9	6.5	0.7	1.1	6.8	7	2	2.8
FAK		-3.5	7	2.8	3.6	16.4	1.7	0.8	8.3	7.5	14.4	2	-4
FAK2		4	4	3.7	3.6	6.3	-8.1	3.2	14	15.2	4	5.6	10.7
Fer		-8.4	24.1	10.1	38.1	8.1	1.1	1	21.7	5.5	30.3	2	37.5
Fes		-6.8	21.5	4	4.5	8.1	4.2	-11.4	0.8	14.3	8.8	-8.4	-5
FGFR1		11.1	16.9	12.4	49	7.2	15.2	6.1	9.1	19.3	55.1	6.5	31.1
FGFR2		3	44.5	21.4	58	12.7	22.3	11.4	19	20.8	70.7	21.9	64.5
FGFR3		15.1	15.7	14.2	25.9	13.7	5	7.4	15.6	14.2	38.8	16.1	28.4
FGFR3(K650E)		9.7	37.3	24.4	49	7.4	16.6	10.6	19.4	8.5	60.8	13.1	61.5
FGFR4		6.6	4.3	21.9	40.7	-4.8	-4.6	3.2	21.3	23.3	26.6	6.1	14.3
Fgr		6.2	-0.1	2.5	7.4	7.4	8.9	3.8	6.5	11.9	12.7	6.1	22.2
Flt1		10.4	13.6	7.8	24.6	6.1	0.5	5.4	11.6	9.1	19.7	15.4	57.3

Flt3		31.1	61.3	41.3	79.5	20.4	15.1	5.8	33.8	50.3	85.6	24.7	94.7
Flt3(D835Y)		24.6	62	45.2	85.6	1.5	21.4	21.7	46.5	29.4	84.7	54.4	95.5
Flt4		25.1	69.8	49	84.8	14.1	29.5	8.2	47.5	39.5	90.1	43.5	97.3
Frk		6.6	-3.1	0.3	2	13.9	1.5	10.4	1.3	14.4	14.5	12.9	20.3
Fyn		-3.7	3.6	5.3	10.9	10.2	9.2	4	8.4	4.9	19.1	3.6	16.6
GCK		-11.9	19.1	0.7	6.8	2.2	15.4	10.2	5.4	-0.8	-0.4	9.3	40
GRK2		3.5	1.5	2.6	3.5	7.3	0.3	-3.3	7.9	9.3	5.8	-2.8	-1.7
GRK3		-1.9	0.4	-0.6	-3	0.6	3.3	3.4	1	6.5	0.4	5.2	-9.9
GRK4		10.7	7.7	13.4	-2.8	1	4	2.6	-9.8	-6.5	6.8	1	-3.9
GRK5		-6.6	-1.3	-5.1	-7.2	-3	-0.9	-4	-2.1	0	-2.9	-3.8	-2.4
GRK6		5.8	-2.1	2.9	3.1	2	-10.1	-8.1	4.9	-0.8	-0.2	-8.7	1.9
GRK7		5.4	5	1.1	4.5	0.8	-3.3	0.6	4.7	4	5.2	0.1	12.8
GSK3_alpha		15.9	8.7	9.6	12.2	10.4	11.4	4.7	9.4	7.8	15.8	8.5	49.9
GSK3_beta		13.8	7.6	-3	0.3	8.1	6.2	-6.7	-1.7	0.1	18.3	5.5	49
Haspin		4	-12.9	1.1	9.6	14.4	5.5	-3.7	-6.7	-7.8	-0.7	0.1	16.1
Hck		8.1	3	10.1	13.6	19.2	9.9	6.8	18.3	0.8	18.9	12.7	14.5
HIPK1		9.1	7.2	1.6	0.3	5.3	0.4	1.1	2.5	0.6	-1.6	-4.3	4.3
HIPK2		4.8	6.1	2.5	1.6	7.5	0.2	0.9	1.7	2.2	5.2	1	1.8
HIPK4		6.7	8.4	1.5	2.9	10.6	6	-1.1	0.8	4.5	12.3	2	2.3
Hyl		-3	5.5	2.3	2.2	7	0.9	9.6	6	12.2	8.8	11.4	0.3
IGF1R		0	7.3	25.8	22.8	10.4	3	1.8	20	7	12.1	1.1	6.8
IKK_alpha		5.1	-8.8	-3.1	-5.7	7.8	0.5	4.4	9	-0.2	6	3.9	33.5
IKK_beta		2.4	10.4	4.9	11.6	3.1	3	-2.9	8	3.5	12.9	-0.1	21.8
IKK_epsilon		3.8	3.8	4.7	7.8	10.6	-5.2	3.5	10.3	0.4	13.1	11.6	22.6
InsR		6.8	7.2	0.3	1.9	13.4	-4.2	-3.4	6.4	-4.5	9.9	1.1	1.6
IRAK1		2.3	13.3	-2.5	17.2	7.5	-0.9	11.4	-7.1	8.6	45.5	12.6	41.5
IRAK4		3.6	-1	-1.8	-1	6.7	5.2	-7.7	-1.8	-3.2	5.7	-5.8	11.4
IRR		6	12.3	5.7	7.6	12.7	4.7	7.6	11.6	-1.4	14.8	10.2	10.9
Itk		6.8	5.1	6.5	6.7	5.8	-3.2	2.9	11.7	15	-5.3	6.9	8.1
JAK1		94.5	100.1	96.1	98.8	91.8	100.9	90.4	97.8	103.2	99.5	92.9	104.4
JAK2		62.8	79.7	80.4	96.8	44.4	75.3	18.3	71.6	72.4	97	39.1	88.3
JAK3		30.1	76.6	51.4	82.9	47.5	85.4	13.6	44.2	39.7	86.9	25.9	81
JNK1_alpha1		-8.2	4.7	9.6	12.4	7.6	11.6	-23.6	4.9	-9.4	24.6	3	7.3

JNK2		-10.7	0.1	5.1	-14.2	6.8	0.7	9.9	12.2	1.8	16.6	3.3	-2.5
JNK3		-1	13.9	7.1	7	4.2	-2.8	-6.7	16.2	5	10.4	-6.1	7.1
KDR		25.2	65.8	37.9	77.7	15.4	6.7	12.6	32.9	32.5	80	21.2	97.3
KHS1		7.5	-6.5	-5	6.8	1.2	3.1	-8.6	0.1	8.8	12.6	-4.2	44.6
Kit		5.9	3.2	11.3	14.4	13.4	-1.1	3.5	16.1	-0.4	9.8	1	12.8
Kit(T670I)		13.3	5.5	0	-4	12.9	10.4	9.9	8.1	0	14.4	6.9	13.1
Kit(V654A)		13.9	5.2	8.4	12.5	13.4	2.8	3.7	4.7	-1.2	1.5	3.9	2.9
Lck		7.2	14.7	11.9	18.3	-2.3	15	7.8	-2.8	20.4	-13.1	-20.3	24.7
LIMK1		12.5	6.2	3.6	10.4	0.3	0.9	2.1	9.3	-2.4	7.9	0.5	-0.3
LIMK2		9.1	8.8	7.4	5.4	0.6	2.6	-8.4	-1.5	0.8	1	-7.2	-10.3
LRRK2		37.5	78	12.6	65.3	18.4	47.4	22.7	35.8	20.1	83.5	38.8	89.7
LRRK2(G2019S)		44.3	74.1	35.9	76	27.9	71.9	32.7	47.5	60.7	90.4	60.8	95.3
LTK		3.2	14.9	1.6	1.9	9.9	-3.7	12.1	5.9	-7.4	17.3	6.1	14.8
Lyn		8.4	8.6	9	19.9	12.7	12.5	25.5	5.7	11.7	18.7	26.9	12.5
LynB		8.7	16	21.3	28.6	6.3	5.7	-8.6	23.6	22.1	13.4	-1.9	17.6
MAP4K4		9.6	14.2	-7.4	29.9	22.8	42	33.3	30.3	-4.7	24.8	8.9	61.5
MAPKAPK2		5	6.8	3.4	11.8	7.1	4.1	-0.8	10.1	7	9.4	2.5	-2
MAPKAPK3		1.5	-4	3.3	4.3	6.4	-0.6	3	3	5.9	6.4	2.1	4.2
MARK1		18.9	11.1	16.6	34.3	15	24.6	-4.6	9.8	16.1	22.1	2.1	28.5
MARK2		14.2	21.9	23.6	51.3	18.8	41.9	9.9	6.4	8	32	10.9	42.4
MARK3		6.3	30.1	10	33	4.4	34.8	14.1	-1.5	10.7	21.9	10.1	40.7
MARK4		-0.9	5.6	9.8	33.5	13.4	34	1.3	7.1	9.3	28.4	1.1	37.5
MEK1		6.7	5.8	13.1	15.4	5.2	-7.8	28.4	43.5	15.7	39.9	21.4	64.3
MEK2		13.7	27.4	10.2	13.6	3.8	8.8	20.8	27.9	-2.4	20.4	10.8	47.3
MEK3		26.1	9.1	-5.4	1.2	-11.8	5.3	-2.3	4.7	-11.7	-6.3	-3.2	13.6
MEKK2		12.3	61.4	7.8	53.3	10.9	15.1	13.6	42.4	8.8	52.4	29.2	86.6
MEKK3		5.4	57.5	20.8	43.6	7.1	0.6	9	35.2	4.4	21.6	16.3	80.7
MELK		6.5	28.6	12.8	33.8	14.9	22.3	-1.1	21.6	14.8	43.1	10.1	67.5
Mer		5.8	11.4	2.5	9.8	9.4	4.1	5.7	8.6	5.8	21.4	4	22.9
Met		13.5	-2.5	7	4.2	8.9	8.6	5.9	15.1	22	20.4	-0.5	17.7
Met(1250T)		2.3	9.3	3.8	-10.4	6	4.5	-3.7	8.3	1.5	7.8	-2.9	14.6
Mink1		38.9	1.9	19.4	19.6	2	35.9	10.1	31.4	5.3	28.3	12.3	37.8
MKK6		4.9	0.8	4.8	4.4	4.7	-1.6	3.1	14.9	1.3	14.6	0.1	15.5

MKK6(S207E,T211E)		6.7	3.6	-0.8	6.6	18.9	3.8	-5.7	7.2	3.8	1.7	-0.9	21
MLCK		-1.4	3	-1.9	0.7	3.6	3	-7	1.4	-1.6	0.4	-4.7	2
MLCK2		5.8	4	-2.1	5.8	12.1	-3.5	-1	2.7	3.6	5	3.3	34.5
MLK1		0	5.8	4.6	12.8	0.5	-9.3	1.8	-5.2	-11.6	5.2	-3	35.9
MLK2		5.8	18.4	-1.8	14	5.6	5.5	4.3	3.4	7.8	1.8	9.6	42.6
MLK3		2.7	9.1	-0.3	9.6	-2.4	6.7	-4	1.2	1.6	3.4	-2.3	12.5
MRCK_alpha		8.6	4	5.3	4.5	1.6	12.8	0.7	5.9	3.6	8.3	1.4	2.4
MRCK_beta		9.8	6.2	-7.1	-17.6	5.4	-1.9	-4.5	-1.8	8.6	10.4	-2.9	16.9
MSK1		-1.9	2	5.9	8.9	10.9	1.9	2.9	10.7	6.7	11.5	3.7	8.6
MSK2		3.3	-0.4	7.8	14	13.1	7.8	2.6	10.4	17.1	12.8	1.6	17.1
MSSK1		2.5	-0.5	15.4	12.4	13.6	-9.4	6.7	13.9	4.3	16.3	11.9	7.2
MST1		15.9	55.5	17.6	42.9	11.7	33.2	1.9	26.8	6.5	34.5	18.9	92.8
MST2		31.7	60.2	20.8	48.3	20.1	39.8	11.2	27.9	9.7	52.8	30.8	93.9
MST3		4.2	6.8	7.1	11.7	8.2	6.9	15.1	2.9	-8.7	13.5	19.9	-26.9
MST4		4	18.9	-0.7	-11.8	14.6	7.7	-1.3	-0.4	-7.6	6.1	-1.1	-7.4
mTOR		16.2	-2.4	2.6	3.1	-8.8	-10.4	1.1	-0.2	-9.7	-5.6	0.1	0.4
MuSK		-4.4	8.7	0.3	2.6	16.5	-7.8	1.2	4	16.1	12.4	7	-2
NEK1		5.3	4.9	9.2	7.8	4.4	-6.1	5.5	-0.6	-14.8	3.1	4	9.6
NEK2		-3.9	-1.4	6.6	4.2	8	6.2	-7	11.8	4.3	6	-6.3	6.6
NEK4		5	6.6	5.3	6.8	7.5	-2.4	4.2	10.3	4.7	8.7	4.3	-0.3
NEK6		10.1	8.6	-6.2	-5.8	6	2.9	11.6	4.8	3.6	1.8	7.7	-1.6
NEK7		10.4	-2.6	11.2	9.3	7.2	-0.6	0	10.8	0.2	5.3	0.3	-2.5
NEK9		-3.1	5.3	-0.7	3.8	0	7.1	3.1	10.1	-4	0.9	-0.7	-9.1
NIK		3.7	11.4	-0.2	-5.8	-0.2	4.8	-3.4	1.4	4.6	3.6	-2.1	3.3
NLK		13.8	0.3	-2.5	-2.9	0.7	1.6	-1.7	3.5	5.7	6.9	0.5	-4.9
p38_alpha		-1.9	5.5	8.5	8.7	1	-3.2	11.9	8.9	7	9.9	2.5	-0.4
p38_alpha(direct)		0.3	-2.6	-12.2	-12.6	12.8	-4	1.8	4.3	5.6	11.7	1.2	0.6
p38_beta		7.3	11.6	11.6	11.7	11.4	-7.2	4.9	14.6	13.6	8.5	5.3	-0.8
p38_delta		3.1	5.3	5.4	8.3	14.5	6.6	4.4	8.4	6.7	13.9	4.3	6.3
p38_gamma		1.9	4.7	4.6	7.8	15.5	4.7	9.6	7.5	6.2	11.9	8.1	5
p70S6K		3.6	10.4	5.3	11.1	9.1	4.5	8.1	10.4	-2.1	19.1	5	35.5
PAK1		4.9	1.8	12.2	13.9	19.5	-1.8	11.7	17.2	19.7	5.1	8	18.1
PAK2		4	6.2	9.3	8	12.4	0.4	-4.7	15.4	9.2	14.9	10.9	3.1

PAK3		-4.3	1.3	17.8	3.7	14.9	14.9	9.3	5.1	10.9	21.3	18.1	6.3
PAK4		0.5	2.9	2.9	5.4	2.5	-4.6	-21	-4.1	9.1	0.6	-20.1	-1
PAK6		4.9	5.3	8.6	5.8	21.8	12.8	20	5.6	10.6	11.1	19.7	-1.1
PAK7		-11.1	12.7	-0.3	1.5	8.8	7.8	3.5	3.3	2.8	9.3	5.4	-4.5
PASK		2.2	12.5	11.9	9.9	4.3	-2.9	-6.9	12.5	-2	-4.6	-5.5	8.6
PDGFR_alpha		8.9	22.9	27.7	64.6	17.7	10.5	8.2	24.8	15.1	58	10.9	89.7
PDGFR_alpha(D842V)		18.8	33.7	34	66.9	5.8	9.4	4.2	17.1	17.6	61.6	33.5	98.6
PDGFR_alpha(T674I)		26.8	21	16.7	32.5	15.5	-5.3	20.6	18.5	7	23.3	25.8	70.6
PDGFR_alpha(V561D)		19.6	62.3	62.8	90.9	8.8	33.5	14.5	54.6	35.3	85.2	53.4	104.7
PDGFR_beta		7.2	11.9	5.4	25.9	9.4	0.7	6.3	11.1	3.6	22.8	12	32.6
PDK1		19	11.9	11.8	22.3	14.4	17	16.9	17.8	5.5	23.6	17.3	34.3
PDK1(direct)		7.2	37	6.2	43.5	4.6	17.4	-22.1	16.6	5.9	46.5	-13.4	75.2
PhK_gamma1		-0.8	-1.2	8.1	12.5	0.6	5.8	7	15.6	7	3.5	10.5	9.6
PhK_gamma2		8.4	0.8	5.1	3.1	8.4	3.5	8.8	1.5	7.8	7.7	7.8	5.1
PI3K-A		6.2	-8.9	-8.2	10.6	-16.2	1	-9.8	9.3	-6.8	4.6	-3.7	-9.2
PI3K-D		-8	-3	6.5	3.9	-5.4	6	-19.5	9.3	-4.9	0.1	4	-17.9
PI3K-G		13.7	6.1	-1.3	-2.4	-0.4	-0.5	20.3	-4.8	-12.1	-2.8	19.2	0.7
PI3KC2a		-6.8	2.5	-2.1	2.7	-1.4	1.5	1	-2.6	-8.6	-7.8	1.6	8.3
PI3KC2b		11.4	-2.3	5.5	17.3	-14.8	-7.7	1.7	-1.1	-4.3	3.5	4.3	-0.3
PI3KC3_hVPS34		-6.3	1	1.3	3.9	10.4	-4.8	-3	-2.1	-23.8	9.1	2.7	-4
PI4Ka		0.5	-6	-2.6	2.3	8.6	-3.9	4.2	1.1	-0.9	5.1	1.9	2
PI4Kb		-10.4	-10	-2.3	-0.5	-7.8	3.4	21.1	-6.5	-13.2	-14.4	-0.7	11.8
PIM1		11.6	-5.1	7.7	5.3	3.5	0.1	-13.6	7.3	-0.6	16.8	3.4	11.7
PIM2		4	6.3	1.8	2.5	-0.3	-2.2	-2.5	14.1	5.3	-0.8	2.9	9.3
PKA		3.4	13.4	1	1.3	1.8	2.5	-4	-0.3	0.3	5.1	-4.3	10.4
PKC_alpha		-1.3	9.6	7.9	9.3	23.4	13.8	8.8	10.1	9.1	-6.7	7.8	8.6
PKC_beta1		10.8	-5.5	-0.1	11.1	11.6	6.9	17.5	7	-7.3	-13.1	15.9	18.2
PKC_beta2		8.1	17.2	4	11.2	19	11.1	10.8	7.5	10.9	11.2	-10.2	20
PKC_delta		13.8	13.4	10.3	15.3	17.9	32.1	3.2	8.4	3.9	-9.3	5.8	19
PKC_epsilon		20.8	6	2.3	7.9	11.8	8.3	11.3	-1	8.1	-9.4	9.9	11.7
PKC_eta		4.8	3.5	17.8	7.5	22.6	10.3	-2.6	9.5	5.5	-8.6	0.1	7.5
PKC_gamma		21.1	-0.7	2.5	18.8	32.8	22.6	12.4	12.9	9.7	16.9	14.3	20.9
PKC_iota		-3.5	-5.1	20.1	16.8	19.9	14.4	0.8	25.6	5.8	-14.7	1.9	10.4

PKC_theta		15.5	-8.4	5.9	-0.2	19.7	26.6	24.5	6.5	4.1	0.7	23.3	16.6
PKC_zeta		8.3	12.8	15.4	14.8	15.2	5.3	-7.3	20.9	6.3	-13.1	-8	2.4
PKD1		16.9	45	10.6	22.1	18.5	11.8	-1	12.3	15.3	38.5	6.8	67.1
PKD2		18.4	22.5	5.6	24.6	16.1	7.6	5.6	4.8	3.4	34.7	12.5	62
PKD3		9.3	20.6	16.6	35.5	13.3	1.3	17.1	8.7	15.1	32	31.8	65.5
PKG1_alpha		-0.7	1.7	5.3	4.2	8.8	2	-6	1.1	3.8	9.7	-2.3	1.2
PKG2		4.7	3.3	1.1	4.4	12.2	-4.2	6.4	2.4	5.3	13.2	3.6	9.5
PLK1		4	11.7	15.3	14.7	8.6	-7.9	2.6	10.5	6.8	9.4	2.4	2
PLK2		14	14.7	7.9	3.7	17.5	-1.6	6.7	13.1	8.1	16.4	6.6	-7.7
PLK3		9.1	4.6	-2.8	-0.1	-10.8	42.3	-4.7	-4.2	-2.5	-4.5	-12.8	-5.6
PRAK		1.1	9.4	4.7	3.9	6.5	2.5	6.2	10.1	7	10.2	8.1	1.1
PRK1		-2.5	-2.4	16.2	28.1	12.8	8.8	-5	11.3	10.7	25.4	-4.5	27.5
PRKAA1		6	1.3	1.1	7.7	4.3	10.2	-4.3	0.9	-0.3	16.1	-8	13.8
PRKAA2		3.9	15.8	10	16.4	11.9	9.8	6.6	13.8	14	25.9	5.6	18.5
PrKX		-5.8	1.3	10.4	13.5	13.4	4.5	13.4	15.6	5.9	16.4	11.4	9.3
RAF1(Y340D,Y341D)		10.5	18.5	24.2	25.1	27.8	-8	7.7	29	3	35	7.3	44.8
Ret		31.3	71.1	71.3	89.9	13.6	41.4	20	49.2	33.8	84.6	37.9	90.9
RIPK2		9.4	2.9	-2	-0.8	-2.4	1.5	-7.9	-1.1	1.7	-4.9	-6.6	5.4
ROCK1		3.6	-0.8	6.7	9.3	-2.5	3	-16.6	5.8	17.4	10.2	-12.1	7.3
ROCK2		-4.9	1.6	5.8	9.9	-0.2	9.4	13.9	7.4	2.1	2.6	5.4	1.9
Ron		-1.9	11.4	3.1	3.3	7.5	3.9	13.1	5.4	3	5.8	9.1	17
Ros		3.4	20.5	11.3	27.8	17.5	0	-11.8	21.9	1.2	25.4	-8.3	29.3
Rse		8.4	7.2	5.8	13.8	11.2	8.2	-0.8	2.3	10.1	21	2.2	6.3
Rsk1		11.5	26.3	7.3	26.5	2.6	15.4	7.5	11.7	2.7	10.6	4.7	41.8
Rsk2		5.5	18.3	8	23	7.8	11.4	13.7	16.4	5.4	22.5	7.6	48.8
Rsk3		33	53.8	10.8	47	12.6	16.3	31.1	35.8	11.5	53.9	32	88
Rsk4		25.2	50.3	6.7	44	12.2	24.6	21.3	33	15.1	41.3	7.1	72.9
SGK1		12.8	17.8	-0.3	5.5	12.4	6.2	0.3	1.3	7.7	10.7	-0.3	22.6
SGK2		2	13.2	1	5.8	8	-11.9	5.4	4.3	1	9.2	12.7	3.7
SGK3		9.3	20.4	4.2	7.5	10.2	-4.2	7	10.9	4.6	0.6	4.1	6.7
SIK2		13	4.2	11.5	38.5	12.8	18.9	8.1	5.3	11.8	32.8	8.4	47.1
skMLCK		3.8	5	5	6.6	13.4	2.3	-8.2	9.9	6.9	15.3	-4.8	2.6
SLK		5.2	25.6	9.4	13.2	1	21.9	-0.1	8.7	2.2	9.9	6.9	58.6

SPHK1		-12.1	-13.7	11.1	11.1	-7.9	-1.6	-0.1	11.2	-11.3	1.9	-5.2	-7.5
SPHK2		-18.9	9.8	-8.3	-17.1	3.7	-10.1	13.4	-7.3	-9.3	22.4	13.7	-10.9
Src		18.6	14.5	4.5	8.6	5.3	14	3.6	8.4	9.6	-6.8	-2.8	-1
Src_N1		9.9	19.4	6.3	7.6	8.8	16	3.6	8.6	7.4	9.1	3.4	10.9
Srm		17	28.5	1.6	5.5	12.8	-4.8	11.5	8.4	4.5	14.6	6.1	21.7
SRPK1		3.3	3.5	21.4	20.7	11.4	7.9	2.8	11.2	3.2	15.1	2.5	2.8
SRPK2		3.3	-3.5	4.9	3.5	0.6	-0.7	-1.8	6	2.8	9.6	-4.9	-1.4
STK16		12.2	17.3	17.4	50.6	6.2	8.2	-0.3	-4.7	-8.1	18.4	8.3	69.1
STK33		3.9	3.2	9.9	3.2	0.3	-0.6	-2.5	-2.5	0.6	-2.2	-0.8	2.9
Syk		2.9	4.9	20.6	15.4	6.3	-0.3	-1.5	11.4	18.6	5	0	-0.3
TAK1-TAB1		5	5.4	4.3	0	-3	1.6	11.6	8.6	-5	11.5	13.4	47
TAO1		-0.4	-3.5	2.9	2	0.9	-5.2	7.7	6.8	1.6	13.8	9	13.9
TAO3		3.1	6.5	3.4	6.5	-11.9	5	6.1	7.8	-0.3	-9.4	9.9	15.2
TBK1		7.2	42.5	27.1	42.5	22.4	45.4	9.8	20.5	5.3	40.5	46.3	90.2
TEC		-9.9	5.9	-0.7	0.3	-3.3	7.3	8.9	4.6	-1.5	-1.1	10.6	6.7
Tie2		2.3	6.6	4.4	2.7	7.8	-17.4	1.3	-1.2	-5.2	19.3	4.4	4
TNK2		3.2	6	2.2	3.8	1.1	1.5	0.5	2.6	1.3	7.6	1.1	7.4
TrkA		40.5	-14.4	32.6	31.4	18.7	21.4	35.6	35	-8.2	28.4	35.8	19.8
TrkB		11.9	18.2	8.9	18.9	11.7	-9.8	0	19.3	6.6	32.4	5.3	28.8
TrkC		1.8	37.9	13.4	27.9	22.8	9.9	7.7	28.1	9.8	38.3	12.9	48.2
TSSK1		4.5	11.4	16.8	27.9	10.7	7.6	-2.2	15.6	10.9	17.6	3.8	31.5
TSSK2		-1.8	10.2	9.1	9.7	15.7	3.7	-10.8	11.6	12	18.4	-6.5	6.3
TTK		2.1	7	5.3	10.4	-8.1	2.2	2.3	-10.9	3.6	-10.9	1.1	6.4
TYK2		54.6	90.1	99.4	101.9	71.3	94.1	57.5	94.6	98	103.3	64.8	95.5
WEE1		13.4	-1.5	15.2	7.5	3.1	3	-11.9	-11.9	5.7	4.7	-6.3	0.1
WNK2		-0.9	1.9	-4.5	-3.8	-7.8	-2.8	-12.8	3.7	2.5	1.6	-13.1	2.9
Yes		3.7	6.3	6.3	8.9	14.6	13.9	6.7	11.9	9.2	20.8	26.1	10.8
YSK1		6.5	19.6	5.5	15.8	5	0.8	-4	16	2.1	11.1	-4.8	-4.8
ZAK		11.1	1.5	1.2	0.9	-1.6	-3.8	-3.4	2.3	2.5	-1.3	-2.4	0.3
ZAP-70		16.7	8.2	4.8	1.2	2	8.4	-5.8	4.5	-1.4	5.9	-3	3.3
ZIPK		0.1	4.5	8.7	29.4	3.3	0.4	1.1	4.4	4.8	8.5	-0.5	10.4

Table S4. Tabulated Compound Structures and Data used to Produce Graphs in Figure 2 of Manuscript^a

Compound (smiles)	Stereochemistry comment	Whole blood EC ₅₀ (µM)	IL-6 pSTAT3 EC ₅₀ (µM)	Whole Blood Shift	cLogD _{7.4}	MDCK P _{app} A:B (x 10 ⁶ cm/s)	TPSA (Å ²)	Measured HLM CL _{int} (mL min ⁻¹ kg ⁻¹)	Calculated probability of HLM stability	%F, Rat	In vivo rat CL (mL min ⁻¹ kg ⁻¹)	Rat %PPB	AUC Rat (µM·h)	AUC _{unbound} Rat (µM·h)
<chem>C(N1CCC[C@H](C1)n2cnc3cnc4[nH]c cc4c23)c5ccccc5</chem>	single known enantiomer	6.143	1.11	5.5	2.8	16.1	49							
<chem>C1CNC[C@@H](C1)n2cnc3cnc4[nH]c cc4c23</chem>	single known enantiomer				8.50E-04		58							
<chem>O=C(CC#N)N1CC C[C@H](C1)n2cnc3 cnc4[nH]ccc4c23</chem>	single known enantiomer	0.491	0.18	2.7	0.62	0.3	90	10.5	0.64	4.6	84.5	42	0.059	0.034
<chem>N#CCCN1CCC[C@ H](C1)n2cnc3cnc4[nH]ccc4c23</chem>	single known enantiomer		0.708		0.67		73	12	0.67					
<chem>C(N1CCC[C@@H](C1)n2cnc3cnc4[nH]c cc4c23)c5ccccc5</chem>	single known enantiomer				2.8		49	16	0.37					
<chem>CC(C)(C)OC(=O)N 1CC(C1)n2cnc3cnc 4[nH]ccc4c23</chem>					1.9		76	10	0.62					
<chem>C(N1CCC(CC1)n2c nc3cnc4[nH]ccc4c2 3)c5ccccc5</chem>		0.472	0.086	5.5	1.9	32.3	49	13.3	0.46	0.6	170	88.6	0.000	0.000
<chem>C(N1CC[C@H](C1) n2cnc3cnc4[nH]ccc 4c23)c5ccccc5</chem>	single known enantiomer	4.411	0.685	6.4	2.3		49	12	0.38					
<chem>C(N1CC(C1)n2cnc 3cnc4[nH]ccc4c23) c5ccccc5</chem>					1.9		49	13	0.46					
<chem>C1C[C@H](CN(C1) c2ccccc2)n3cnc4cn c5[nH]ccc5c34</chem>	single known enantiomer				3.3		49	18	0.37					
<chem>O=C(CC#N)N1CC C(CC1)n2cnc3cnc4 [nH]ccc4c23</chem>			10		0.62		90	8.5	0.69					

<chem>O=C(CC#N)N1CC[C@H](C1)n2cnc3cnc4[nH]ccc4c23</chem>	single known enantiomer		4.41		0.2		90	9.9	0.7					
<chem>O=C(CC#N)N1CC(C1)n2cnc3cnc4[nH]ccc4c23</chem>					-0.22		90	9.6	0.73					
<chem>C(N1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23)c5ccnc5</chem>	single known enantiomer				1.7		62	16	0.42					
<chem>CC(=O)N1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23</chem>	single known enantiomer				0.89		66	12	0.72					
<chem>CS(=O)(=O)N1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23</chem>	single known enantiomer	1.411	0.309	4.6	0.3		83	10	0.8					
<chem>O=C(N1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23)c5ccccc5</chem>	single known enantiomer				2.1		66	13	0.47					
<chem>N#Cc1ccc(CN2CC[C@H](C2)n3cnc4cnc5[nH]ccc5c34)c1</chem>	single known enantiomer	2.483	0.218	11.4	2.5		73	14	0.55					
<chem>N#Cc1ccccc1CN2CC[C@H](C2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				2.5		73	18	0.43					
<chem>C(N1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23)c5cncnc5</chem>	single known enantiomer				0.96		75	15	0.54					
<chem>C1C[C@H](CN(C1)c2ccncc2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				0.39		62	9.6	0.53					
<chem>C1C[C@H](CN(C1)c2ccncc2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				1.7		75	13	0.54					
<chem>C(N1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23)c5occc5</chem>	single known enantiomer				0.57		75	14	0.46					
<chem>Cn1ccnc1CN2CCC[C@H](C2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				0.5		67	15	0.61					
<chem>O=C(N1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23)c5ccnc5</chem>	single known enantiomer				0.94		79	12	0.57					
<chem>N#Cc1cccc(CN2CC[C@H](C2)n3cnc4cnc5[nH]ccc5c34)c1</chem>	single known enantiomer	2.532	0.369	6.9	2.5		73	16	0.49					
<chem>NC(=O)CN1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23</chem>	single known enantiomer				0.35		92	8.5	0.73					

<chem>C(N1CCC[C@H](C1)n2cnc3cnc4[nH]c4c23)c5ccnc5</chem>	single known enantiomer				0.66		75	9.5	0.54					
<chem>CN(C)CC(=O)N1C CC[C@H](C1)n2cn c3cnc4[nH]ccc4c23</chem>	single known enantiomer				1.2		70	0.2	0.7					
<chem>N#Cc1ccc(CN2CC C(CC2)n3cnc4cnc5 [nH]ccc5c34)cc1</chem>		1.147	0.041	27.9	2.4		73	10	0.61					
<chem>N#Cc1cccc(CN2CC C(CC2)n3cnc4cnc5 [nH]ccc5c34)c1</chem>		0.305	0.02	15	2.1	2.2	73	9.9	0.56	42	33	81.7	1.210	0.221
<chem>O=C(N1CCC(CC1)n2cnc3cnc4[nH]ccc4c23)c5ccccc5</chem>					0.94		79	14	0.66					
<chem>O=C(N1CCC(CC1)n2cnc3cnc4[nH]ccc4c23)c5ccccc5</chem>			1.347		2.1		66	10	0.56					
<chem>N#CCCN1CCC(CC1)n2cnc3cnc4[nH]c4c23</chem>		0.159	0.043	3.7	0.64	8.2	73	5	0.73	48	96.4	39.4	0.636	0.385
<chem>CN(C)C(=O)CN1C CC[C@H](C1)n2cn c3cnc4[nH]ccc4c23</chem>	single known enantiomer				1.1		70	12	0.74					
<chem>CS(=O)(=O)CCN1C CC[C@H](C1)n2cn c3cnc4[nH]ccc4c23</chem>	single known enantiomer		0.575		0.023		83	12	0.79					
<chem>COCCN1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23</chem>	single known enantiomer				1.2		58	11	0.67					
<chem>COc1ccc(CN2CCC[C@H](C2)n3cnc4cnc5[nH]ccc5c34)cc1</chem>	single known enantiomer				2.8		58	15	0.35					
<chem>C(N1CCC(CC1)n2cnc3cnc4[nH]ccc4c23)c5ccccc5</chem>		0.646	0.197	3.3	1.1		62	5.3	0.51					
<chem>Fc1cccc(CN2CCC[C@H](C2)n3cnc4cnc5[nH]ccc5c34)c1</chem>	single known enantiomer				3		49	17	0.38					
<chem>CN(C)CC(=O)N1C CC(CC1)n2cnc3cnc4[nH]ccc4c23</chem>			5.592		1.1		70	9.7	0.78					
<chem>CC(N1CCC(CC1)n2cnc3cnc4[nH]ccc4c23)c5ccccc5</chem>	Racemic		0.157		2.7		49	15	0.58					
<chem>C1CN(CCC1n2cnc3cnc4[nH]ccc4c23)c5ccccc5</chem>					1.7		75	10	0.55					

<chem>CN(C)C(=O)CN1C CC(CC1)n2cnc3cnc 4[nH]ccc4c23</chem>					1		70	9.6	0.81					
<chem>CS(=O)(=O)N1CCC (CC1)n2cnc3cnc4[n H]ccc4c23</chem>		0.342	0.136	2.5	0.29	1.2	83	8.4	0.86	30	38.3	44.4	1.070	0.595
<chem>CS(=O)(=O)CCN1C CC(CC1)n2cnc3cnc 4[nH]ccc4c23</chem>			1.045		0.02	0.5	83	11	0.87					
<chem>C(N1CCC(CC1)n2c nc3cnc4[nH]ccc4c2 3)c5cncnc5</chem>		0.524	0.35	1.5	0.82		75	5.3	0.62					
<chem>O=S(=O)(N1CCC(C C1)n2cnc3cnc4[nH] ccc4c23)c5ccccc5</chem>			0.536		2.3		83	14	0.5					
<chem>COCCN1CCC(CC1 n2cnc3cnc4[nH]cc c4c23</chem>		0.424	0.152	2.8	0.3	3.4	58	6.1	0.74					
<chem>O=S(=O)(N1CCC(C C1)n2cnc3cnc4[nH] ccc4c23)c5ccc(cc5) C#N</chem>		2.259	0.271	8.3	2		107	13	0.56					
<chem>C1CN(CCC1n2cnc 3cnc4[nH]ccc4c23) c5ncccn5</chem>					1.8		75	15	0.51					
<chem>O=S(=O)(N1CCC[C @H](C1)n2cnc3cnc 4[nH]ccc4c23)c5cc ccc5</chem>	single known enantiomer				2.3		83	16	0.4					
<chem>O=S(=O)(N1CCC[C @H](C1)n2cnc3cnc 4[nH]ccc4c23)c5cc c(cc5)C#N</chem>	single known enantiomer		1.163		2		107	17	0.49					
<chem>Fc1cccc(CN2CCC (CC2)n3cnc4cnc5[n H]ccc5c34)c1</chem>			0.032		2.7		49	13	0.46					
<chem>Cn1cc(CN2CCC(C C2)n3cnc4cnc5[nH] ccc5c34)cn1</chem>					-0.047		67	9	0.68					
<chem>O=S(=O)(C1CC1)N 2CCC(CC2)n3cnc4 cnc5[nH]ccc5c34</chem>			0.148		1.2		83	11	0.71					
<chem>O=S(=O)(C1CC1)N 2CCC[C@H](C2)n3 cnc4cnc5[nH]ccc5c 34</chem>	single known enantiomer				1.2		83	11	0.61					
<chem>C1C[C@H](CN(C1) C2COC2)n3cnc4cn c5[nH]ccc5c34</chem>	single known enantiomer				1		58	11	0.71					
<chem>C1CN(CCC1n2cnc 3cnc4[nH]ccc4c23) c5cncnc5</chem>			0.444		1.4		75	12	0.55					

<chem>O=S(=O)(N1CCC(C1)n2cnc3cnc4[nH]ccc4c23)c5cccc(c5)C#N</chem>			0.122		2	2	107	9.2	0.53	19	40.9	82.4	0.381	0.067
<chem>O=C(Cc1cccc1)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>			0.549		2.6		66	14	0.31					
<chem>O=C(CN1CCC(CC1)n2cnc3cnc4[nH]ccc4c23)c5cccc5</chem>			0.118		2.8		66	14	0.41					
<chem>C1CC(CCN1)n2cnc3cnc4[nH]ccc4c23</chem>			1.397		-0.91		58							
<chem>O=C(C1CC1)N2CC[C@H](C2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer		0.595		1.5	6.3	66	7.5	0.5	27	68.8	61.7	0.426	0.163
<chem>O=C(CS(=O)(=O)c1cccc1)N2CCC[C@H](C2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				1.4	0.8	100	12	0.41					
<chem>O=C(CN1CCOCC1)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>					0.85		79	11	0.65					
<chem>CN1CCC[C@H]1C(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer		7.966		1.4		70	4.8	0.78					
<chem>CS(=O)(=O)CC(=O)N1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23</chem>	single known enantiomer				-0.45		100	7.6	0.84					
<chem>C(Cc1cccc1)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>			0.148		1.9		49	12	0.5					
<chem>C(N1C2CCC1CC(C2)n3cnc4cnc5[nH]ccc5c34)c6cccc6</chem>	mixture of diastereomers				2.2		49	13	0.34					
<chem>Cc1nc2cnc3[nH]ccc3c2n1C4CCN(Cc5cccc5)CC4</chem>		1.231	0.035	35.3	2.3	17.4	49	13.5	0.38					
<chem>O=C(Nc1cccc1)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>					2.6		78	9	0.55					
<chem>CC(C)CC(=O)N1CCC(CC1)n2cnc3cnc4[nH]ccc4c23</chem>			1.794		2.3		66	15	0.49					
<chem>Cn1ccc1C(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>					1.2		84	9.9	0.65					
<chem>C1CC(CCO1)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>					0.12		58	8.9	0.74					

Cc1nc2cnc3[nH]ccc3c2n1C4CCN(CC4)S(=O)(=O)C			0.415		0.65	1.3	83	5.8	0.85	21	35.5	56.8	0.583	0.252
Cc1nc2cnc3[nH]ccc3c2n1C4CCNCCC4		1.593	0.247	6.5	-0.62	0.4	58	8.6	0.92	4.3	42.8	36.5	0.215	0.137
O=S(=O)(N1CCC(C1)n2cnc3cnc4[nH]ccc4c23)c5cccn5			0.431		1.2		96	13	0.57					
FC(F)(F)S(=O)(=O)N1CCC(CC1)n2cnc3cnc4[nH]ccc4c23			0.304		2.4		83	9.6	0.6					
C(N1CCC(CC1)n2cnc3cnc4[nH]ccc4c23)c5cccn5			0.244		-0.18		75	15	0.57					
CS(=O)(=O)c1ccc(CN2CCC(CC2)n3cnc4cnc5[nH]ccc5c34)c1			0.187		1.2	7.7	83	15	0.54					
C(N1CCC(CC1)n2cnc3cnc4[nH]ccc4c23)c5cncn5		1.193	0.199	6	-0.1	7.2	75	8.7	0.59	80	83.3	56.2	0.965	0.423
C1CC2CC(CC1N2)n3cnc4cnc5[nH]ccc5c34	mixture of diastereomers				-0.85		58	13	0.84					
N#Cc1cccc(n1)N2CC(CC2)n3cnc4cnc5[nH]ccc5c34			0.066		2.3		86	14	0.52					
N#Cc1ccc(nc1)N2CC(CC2)n3cnc4cnc5[nH]ccc5c34					2.3	5.5	86	9.3	0.57	26	8.68	95.7	3.530	0.152
N#Cc1ccnc(c1)N2CC(CC2)n3cnc4cnc5[nH]ccc5c34			0.235		2.2		86	14	0.62					
CS(=O)(=O)N1C2CC1CC(C2)n3cnc4cnc5[nH]ccc5c34	mixture of diastereomers		0.516		0.61		83	11	0.68					
N#CCCN1C2CCC1CC(C2)n3cnc4cnc5[nH]ccc5c34	mixture of diastereomers		0.103		1.2		73	13	0.64					
C(N1CCC(CC1)n2cnc3cnc4[nH]ccc4c23)c5cncs5			0.034		1.4		62	8.4	0.58					
CS(=O)(=O)N[C@@H]1CC[C@H](CC1)n2cnc3cnc4[nH]ccc4c23			0.696		1.5	0.4	92	9	0.87					
CC(=O)N[C@@H]1CC[C@H](CC1)n2cnc3cnc4[nH]ccc4c23			1.536		1.3	0.5	75	10	0.76					

<chem>CC(C)(C)OC(=O)N[C@@H]1CC[C@H](CC1)n2cnc3cnc4[nH]ccc4c23</chem>		3.518	0.185	19	3.1	11.2	84	9.8	0.57					
<chem>N[C@@H]1CC[C@H](CC1)n2cnc3cnc4[nH]ccc4c23</chem>		3.265	0.343	9.5	-0.77	0.2	72	6.4	0.74	0.2	64.6	31.3	0.088	0.060
<chem>O=C(N[C@@H]1CC[C@H](CC1)n2cnc3cnc4[nH]ccc4c23)c5ccccc5</chem>			0.089		3.1		75	13	0.55					
<chem>N#Cc1cccc(CN[C@@H]2CC[C@H](CC2)n3cnc4cnc5[nH]ccc5c34)c1</chem>			0.178		2.9		82	13	0.72					
<chem>O=C(CC1CC1)N2CC[C@H](C2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer		0.212		1.7		66	13	0.4					
<chem>O=C(N1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23)C5(CC5)C#N</chem>	single known enantiomer		0.159		1		90	14	0.59					
<chem>O=C(Cc1cccc1)N2CCC[C@H](C2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				2.6		66	15	0.25					
<chem>C[C@H]1C[C@H](CCN1Cc2cccc2)n3cnc4cnc5[nH]ccc5c34</chem>	single known isomer		0.08		2.2		49	17	0.4					
<chem>C[C@@H]1C[C@H](CCN1Cc2cccc2)n3cnc4cnc5[nH]ccc5c34</chem>	single known isomer		0.17		2.2		49	15	0.4					
<chem>O=C(CN1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23)c5ccccc5</chem>	single known enantiomer				3.1		66	17	0.34					
<chem>CC1(C)CC1C(=O)N2CCCC(C2)n3cnc4cnc5[nH]ccc5c34</chem>	mixture of diastereomers				2.1		66	15	0.47					
<chem>CC1(CC1)C(=O)N2CCC[C@H](C2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer		0.346		1.7		66	12	0.5					
<chem>FC(F)(F)C1(CC1)C(=O)N2CCC[C@H](C2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				1.9		66	13	0.43					
<chem>C[C@H]1C[C@H](CCN1)n2cnc3cnc4[nH]ccc4c23</chem>	single known isomer				-0.55		58	8.3	0.84					
<chem>C[C@@H]1C[C@H](CCN1)n2cnc3cnc4[nH]ccc4c23</chem>	single known isomer				-0.55		58	1.4	0.84					
<chem>C(Cc1cccc1)N2CC[C@H](C2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				3.2		49	19	0.42					

<chem>FC1CC1C(=O)N2C CCC(C2)n3cnc4cnc 5[nH]ccc5c34</chem>	single known enantiomer		0.175		1.3		66	11	0.48					
<chem>O=C([C@@H]1CC CN1Cc2ccccc2)N3 CCC(CC3)n4cnc5c nc6[nH]ccc6c45</chem>	single known enantiomer				3		70	18	0.31					
<chem>CCS(=O)(=O)N1CC C(CC1)n2cnc3cnc4 [nH]ccc4c23</chem>			0.107		0.89	4.9	83	9.7	0.79	49	36.6	48.6	1.390	0.714
<chem>COCC(=O)N1CCC(CC1)n2cnc3cnc4[n H]ccc4c23</chem>					0.95		76	13	0.63					
<chem>CC(=O)N1CC[C@ H](C1)n2cnc3cnc4[nH]ccc4c23</chem>	single known enantiomer		6.297		0.47		66	8.5	0.79					
<chem>O=C(Cc1ccccc1)N2 CC[C@H](C2)n3cnc 4cnc5[nH]ccc5c34</chem>	single known enantiomer		2.664		2.1		66	8.6	0.27					
<chem>O=S(=O)(N1CC[C@ H](C1)n2cnc3cnc 4[nH]ccc4c23)c5cc ccc5</chem>	single known enantiomer		0.594		1.9		83	15	0.5					
<chem>O=C1CC(CCN1Cc 2ccccc2)n3cnc4cnc 5[nH]ccc5c34</chem>	Racemic		1.622		1.8		66	13	0.36					
<chem>Cc1nc2cnc3[nH]ccc 3c2n1[C@@H]4CC CN(Cc5ccccc5)C4</chem>	single known enantiomer		0.307		3.1		49	15	0.28					
<chem>Cc1nc2cnc3[nH]ccc 3c2n1C4CCN(CCC #N)CC4</chem>		0.144	0.026	5.5	1	5.1	73	8.6	0.68	53	54.8	49.2	1.040	0.528
<chem>CC(C)(C#N)C(=O) N1CC[C@H](C1)n2 cnc3cnc4[nH]ccc4c 23</chem>	single known enantiomer				1.1		90	9.6	0.69					
<chem>CN(C)CC(=O)N1C C[C@H](C1)n2cnc3 cnc4[nH]ccc4c23</chem>	single known enantiomer				0.77		70	9.3	0.77					
<chem>O=S(=O)(C1CCCC 1)N2CCC(CC2)n3c nc4cnc5[nH]ccc5c3 4</chem>			0.242		2		83	11	0.59					
<chem>Cc1nc2cnc3[nH]ccc 3c2n1C4CCOCC4</chem>		0.768	0.993	0.8	1.5	14.3	55	13	0.59					
<chem>OCCN1CC[C@H](C1)n2cnc3cnc4[nH] ccc4c23</chem>	single known enantiomer				0.13		69	13	0.85					
<chem>CC(C)(O)CN1CC[C@ H](C1)n2cnc3cnc 4[nH]ccc4c23</chem>	single known enantiomer				0.88		69	11	0.82					

<chem>OCC(=O)N1CCC(C1)n2cnc3cnc4[nH]ccc4c23</chem>			3.1		0.34	0.4	87	11	0.86					
<chem>CC(N(C)C)C(=O)N1CCC(CC1)n2cnc3cnc4[nH]ccc4c23</chem>	Racemic				0.87		70	9.2	0.79					
<chem>O=C(CN1CCCCC1=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>					0.89		87	12	0.55					
<chem>CC(C)(C)OC(=O)N1CCC[C@@H]1C(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				2.9		96	12	0.5					
<chem>CC(C)(C)OC(=O)N1CCC[C@H]1C(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				2.9		96	10	0.5					
<chem>CC(C)(C)OC(=O)N1CC(F)(F)C[C@H]1C(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				3		96	13	0.49					
<chem>CC(C)(C)OC(=O)N1CCCC1(C)C(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				3.2		96	18	0.47					
<chem>C1CNC[C@H](C1)n2cnc3cnc4[nH]ccc4c23</chem>	single known enantiomer				8.50E-04		58							
<chem>Cc1nc2cnc3[nH]ccc3c2n1[C@@H]4CC[C@@H](O)CC4</chem>		0.538	0.267	2	1.9	2.1	66	11	0.8					
<chem>Cc1nc2cnc3[nH]ccc3c2n1C4CCC5CC(=O)NC5C4</chem>	racemic, cis		10		1		75	11	0.7					
<chem>CC(C)NC(=O)[C@@H]1CC[C@H](CC1)n2cnc3cnc4[nH]ccc4c23</chem>					2.3		75	7.3	0.55					
<chem>O=C([C@@H]1CC[C@H](CC1)n2cnc3cnc4[nH]ccc4c23)N5CCOCC5</chem>					1.3		76	10	0.5					
<chem>O=C([C@H]1CCCCN1)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				-0.21		78	12	0.86					
<chem>O=C([C@@H]1CCCN1)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				-0.21		78	10	0.86					
<chem>FC1(F)CN[C@@H](C1)C(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				1.2		78	13	0.53					
<chem>CC1(CCCN1)C(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>	racemic				0.11		78	10	0.84					

<chem>CN1CCC[C@@H]1C(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				1.4		70	6.8	0.78					
<chem>Cc1nc2cnc3[nH]ccc3c2n1[C@@H]4CCN4</chem>	single known enantiomer				0.43		58	6.6	0.87					
<chem>O=C1CCC(CN1Cc2ccccc2)n3cnc4cnc5[nH]ccc5c34</chem>	racemic				1.8		66	12	0.32					
<chem>CS(=O)(=O)N1CC[C@H](C1)n2cnc3cnc4[nH]ccc4c23</chem>	single known enantiomer				-0.13		83	10	0.85					
<chem>O=S(=O)(Cc1ccccc1)N2CC[C@H](C2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer				1.5		83	18	0.54					
<chem>O=C(CN1CCCC1=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>					0.47		87	11	0.65					
<chem>CC(C)(C#N)C(=O)N1CCC(CC1)n2cnc3cnc4[nH]ccc4c23</chem>					1.6	4.5	90	7.1	0.68					
<chem>O=C1CC2CCC(CC2N1)n3cnc4cnc5[nH]ccc5c34</chem>	racemic, cis		8.046		0.66		75	12	0.7					
<chem>Cc1nc2cnc3[nH]ccc3c2n1[C@@H]4CC[C@H](O)CC4</chem>		0.952	0.248	3.8	1.9	4.8	66	8.1	0.8	63	100	69.5	0.777	0.237
<chem>N#CCCN1CC[C@H](C1)n2cnc3cnc4[nH]ccc4c23</chem>	single known enantiomer				0.25		73	9.5	0.71					
<chem>CN(C)CCC(=O)N1CCC(CC1)n2cnc3cnc4[nH]ccc4c23</chem>					-0.3		70	3.2	0.8					
<chem>O=S(=O)(Cc1ccccc1)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>		1.44	0.171	8.4	1.9		83	15	0.54					
<chem>CC(C)(C)OC(=O)N1CCC(Cn2cnc3cnc4[nH]ccc4c23)CC1</chem>					2.9		76	17	0.4					
<chem>C(C1CCNCC1)n2cnc3cnc4[nH]ccc4c23</chem>					-1.1		58	1.6	0.81					
<chem>CC(C)N1CCC[C@H]1C(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer	9.916	6.322	1.6	1.9	0.7	70	11	0.69					
<chem>Cc1nc2cnc3[nH]ccc3c2n1[C@@H]4C[C@H]5CC[C@H](C4)N5Cc6ccccc6</chem>	single known isomer				2.7		49	14	0.24					

<chem>Cc1nc2cnc3[nH]ccc3c2n1[C@@H]4CCCN(C4)C(=O)CC#N</chem>	single known enantiomer	0.197	0.132	1.5	0.98	0.3	90	9.7	0.6	6.9	71.3	22.2	0.102	0.079
<chem>Cc1nc2cnc3[nH]ccc3c2n1[C@@H]4CC[C@@H](N)CC4</chem>		1.095	0.54	2	-0.41	0.4	72	0.6	0.76					
<chem>Cc1nc2cnc3[nH]ccc3c2n1[C@H]4CCCN4</chem>	single known enantiomer				0.43	0.8	58	2.9	0.87					
<chem>Cc1nc2cnc3[nH]ccc3c2n1C4CCOC4</chem>	single unknown isomer (enantiomer of below)		0.893		1.5		55	11	0.49					
<chem>Cc1nc2cnc3[nH]ccc3c2n1C4CCOC4</chem>	single unknown isomer (enantiomer of above)	0.89	0.346	2.6	1.5	7.8	55	10	0.49					
<chem>C1CCC(CNC1)n2cnc3cnc4[nH]ccc4c23</chem>	single unknown isomer (enantiomer of below)				0.19		58	5.8	0.78					
<chem>C1CCC(CNC1)n2cnc3cnc4[nH]ccc4c23</chem>	single unknown isomer (enantiomer of above)	3.791	0.42	9	0.19	8.1	58	2	0.78	93	60.3	43.3	2.050	1.162
<chem>Cc1nc2cnc3[nH]ccc3c2n1C4CCOC5C(=O)NC5C4</chem>	cis, single unknown isomer (enantiomer of below)		4.828		1	0.2	75	9.4	0.7					
<chem>Cc1nc2cnc3[nH]ccc3c2n1C4CCOC5C(=O)NC5C4</chem>	cis, single unknown isomer (enantiomer of above)				1		75	11	0.7					
<chem>N#CCCN[C@@H]1CC[C@H](CC1)n2cnc3cnc4[nH]ccc4c23</chem>		0.592	0.435	1.4	0.79	1.5	82	4.8	0.81	28	117	19.9	0.263	0.211
<chem>CC(=O)N[C@@H]1CC[C@H](CC1)n2c(C)nc3cnc4[nH]ccc4c23</chem>		2.862	3.552	0.8	1.7	0.5	75	8	0.75					
<chem>NC1CCCC(C1)n2cnc3cnc4[nH]ccc4c23</chem>	single unknown stereoisomer				-0.27		72	13	0.73					
<chem>NC1CCCC(C1)n2cnc3cnc4[nH]ccc4c23</chem>	single unknown stereoisomer				-0.27		72	13	0.73					

NC1CCCC(C1)n2cnc3cnc4[nH]ccc4c23	single unknown stereoisomer				-0.27		72	6.4	0.73					
NC1CCCC(C1)n2cnc3cnc4[nH]ccc4c23	single unknown stereoisomer				-0.27		72	8.3	0.73					
O=C(CC#N)N1CC(C)(CC1)n2cnc3cnc4[nH]ccc4c23	racemic	0.859	1.067	0.8	1	0.6	90	11	0.66					
O=C([C@@H]1CC(C)N1)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34	single known enantiomer				0.94		93	12	0.6					
O=C1CCC(CN1)n2cnc3cnc4[nH]ccc4c23	racemic				-0.092		75	10	0.76					
CC1CCN(Cc2ccccc2)CC1n3cnc4cnc5[nH]ccc5c34	cis, racemic		0.476		3.1		49	15	0.32					
Cc1nc2cnc3[nH]ccc3c2n1C4CCN(Cc5ccccc5)CC4		0.489	0.118	4.1	1.5		62	13	0.44					
CN1CCC[C@H]1C(=O)N2CCC(CC2)n3c(C)nc4cnc5[nH]ccc5c34	single known enantiomer				1.8		70	6.6	0.8					
Cc1nc2cnc3[nH]ccc3c2n1C4CCc5[nH]ncc5C4	racemic	1.476	0.463	3.2	1.9		75	8.8	0.47					
CCN1CCC(CC1)n2cnc3cnc4[nH]ccc4c23			0.518		-0.021		49	7.4	0.79					
C(N1CCCC(C1)n2cnc3cnc4[nH]ccc4c23)c5ccccc5	racemic				0.96		62	13	0.45					
Cc1nc2cnc3[nH]ccc3c2n1C4CCc5cn[nH]c5C4	racemic				1.9		75	1.2	0.42					
C1CNCCC(C1)n2cnc3cnc4[nH]ccc4c23	racemic				-0.74		58	15	0.86					
O=C(Cc1cccc(c1)C#N)N2CC[C@H](C2)n3cnc4cnc5[nH]ccc5c34	single known enantiomer				1.9		90	13	0.4					
O=C(Cc1ccc(cc1)C#N)N2CC[C@H](C2)n3cnc4cnc5[nH]ccc5c34	single known enantiomer				1.8		90	11	0.45					
O=S(=O)(N1CC[C@H](C1)n2cnc3cnc4[nH]ccc4c23)c5ccc(cc5)C#N	single known enantiomer				1.6	5.7	107							

<chem>O=S(=O)(N1CC[C@H](C1)n2cnc3cnc4[nH]ccc4c23)c5ccc(cc5)C#N</chem>	single known enantiomer		0.621		1.6		107							
<chem>N#Cc1ccc(CN2CC[C@H](C2)n3cnc4cnc5[nH]ccc5c34)cc1</chem>	single known enantiomer		1.633		2.1		73	12	0.57					
<chem>N#Cc1cccc(CN2CC[C@H](C2)n3cnc4cnc5[nH]ccc5c34)c1</chem>	single known enantiomer		0.801		2.1		73							
<chem>CN1CCN(CC(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34)C1</chem>					0.52		73							
<chem>CS(=O)(=O)c1ccc(cc1)S(=O)(=O)N2CC(C(C2)n3cnc4cnc5[nH]ccc5c34</chem>			4.502		1.1		118	9.1	0.64					
<chem>Cc1nc2cnc3[nH]ccc3c2n1C4CCNCC4F</chem>	cis, racemic	1.852	1.197	1.5	0.46	1.9	58	1	0.69					
<chem>CC(C)(C)OC(=O)N[C@@H]1CC[C@@H](CC1)n2cnc3cnc4[nH]ccc4c23</chem>			0.499		3.1		84							
<chem>N[C@@H]1CC[C@@H](CC1)n2cnc3cnc4[nH]ccc4c23</chem>		0.647	0.26	2.5	-0.77		72	4.1	0.74					
<chem>CC(C)(C)OC(=O)N1CCC(C1)n2cnc3cnc4[nH]ccc4c23</chem>	trans, racemic	1.221	0.091	13.5	2.7	10.1	84	4.2	0.63					
<chem>NC1CCC(C1)n2cnc3cnc4[nH]ccc4c23</chem>	trans, racemic				-0.66		72							
<chem>FC(F)(F)c1nc(CN2CCC(CC2)n3cnc4cnc5[nH]ccc5c34)cs1</chem>		0.406	0.052	7.8	2.5		62	9.1	0.48					
<chem>FC(F)(F)CC(=O)N1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23</chem>	single known enantiomer	0.609	0.234	2.6	1.7	2.7	66	3.6	0.43					
<chem>CC(C)(C#N)C(=O)N1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23</chem>	single known enantiomer		0.341		1.6		90	5.5	0.63					
<chem>CC1CN(Cc2cccc2)CCC1n3cnc4cnc5[nH]ccc5c34</chem>	cis, racemic		0.032		2.3		49							
<chem>Cc1nc2cnc3[nH]ccc3c2n1[C@H]4CCC[C@@H](O)C4</chem>	single stereoisomer. Cis. Absolute stereochemistry unknown. Enantiomer of below.		0.311		1.9	4.9	66	8.6	0.79					

<chem>Cc1nc2cnc3[nH]ccc3c2n1[C@@H]4CC[C@H](O)C4</chem>	single stereoisomer. Cis. Absolute stereochemistry unknown. Enantiomer of above.				1.9		66	12	0.79					
<chem>Cc1nc2cnc3[nH]ccc3c2n1[C@@H]4CC[C@H](O)C4</chem>	single known stereoisomer	0.226	0.087	2.6	1.9	7	66	3.4	0.79	74	43.1	49.1	2.144	1.091
<chem>Cc1nc2cnc3[nH]ccc3c2n1[C@H]4CC[C@H](O)C4</chem>	single known stereoisomer		0.191		1.9		66	6.8	0.79					
<chem>O=C1CCCN1c2ccc(cc2)S(=O)(=O)N3CCC(CC3)n4cnc5cnc6[nH]ccc6c45</chem>					1.9		104	12	0.5					
<chem>C1c1cc(ccc1S(=O)(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34)C#N</chem>			0.114		2.8		107	18	0.52					
<chem>Cc1onc(C)c1S(=O)(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>					0.91		109	13	0.6					
<chem>Cc1nn(C)cc1S(=O)(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>					1.1	1.4	101	8.4	0.71					
<chem>C(C1CCNC1)n2cnc3cnc4[nH]ccc4c23</chem>	racemic				-1.6		58							
<chem>Cc1nc2cnc3[nH]ccc3c2n1C4CCCC4</chem>		0.405	0.103	3.9	2.9	19.9	46	11	0.35					
<chem>N#CCCNC1CCC(C1)n2cnc3cnc4[nH]ccc4c23</chem>	trans, racemic		0.28		0.47		82	0.4	0.81					
<chem>N#Cc1ccc(N[C@@H]2CC[C@H](CC2)n3cnc4cnc5[nH]ccc5c34)nc1</chem>			0.158		3.1		95	5.9	0.57					
<chem>Fc1cncc(CN2CCC(CC2)n3cnc4cnc5[nH]ccc5c34)c1</chem>		0.428	0.08	5.3	1.8		62	9.9	0.52					
<chem>N#Cc1cccc(CN2CCC(CC2)n3cnc4cnc5[nH]ccc5c34)n1</chem>		0.563	0.144	3.9	1		86	5	0.61					
<chem>CC(CC#N)N1CCC(CC1)n2cnc3cnc4[nH]ccc4c23</chem>	racemic				0.88	6.9	73	8.5	0.73					
<chem>CC1CNCCC1n2cnc3cnc4[nH]ccc4c23</chem>	cis, racemic				-0.53		58	0.1	0.85					

<chem>CC1CN(Cc2cccc2)CCC1n3c(C)nc4cn5[nH]ccc5c34</chem>	cis, racemic		0.04		2.7		49	16	0.27					
<chem>CC1CN(Cc2cccc2)CCC1n3cnc4cnc5[nH]ccc5c34</chem>	trans, racemic		0.122		2.3		49	14	0.38					
<chem>Cc1nc(cn1C)S(=O)(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>					1.1		101	4	0.64					
<chem>N#CCC1(COC1)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>		0.087	0.118	0.7	-0.22	1.7	82	4.7	0.67					
<chem>FC1CNCCC1n2cnc3cnc4[nH]ccc4c23</chem>	cis, racemic				0.15		58	9.3	0.68					
<chem>Cc1nc2cnc3[nH]ccc3c2n1C4CCC(F)(F)CC4</chem>			0.34		3		46	10	0.6					
<chem>CC(C)OC(=O)N[C@@H]1CC[C@H](CC1)n2cnc3cnc4[nH]ccc4c23</chem>		1.71	0.434	3.9	2.7		84	2.2	0.62					
<chem>COC(=O)N[C@@H]1CC[C@H](CC1)n2cnc3cnc4[nH]ccc4c23</chem>		1.669	0.361	4.6	1.9	5.3	84	0.6	0.65					
<chem>O=C(N[C@@H]1CC[C@H](CC1)n2cnc3cnc4[nH]ccc4c23)OCC5CC5</chem>		1.083	0.335	3.2	2.7	12.8	84	1.8	0.52	91	15.5	84.4	5.700	0.889
<chem>N#Cc1cc(CN2CCC(CC2)n3cnc4cnc5[nH]ccc5c34)ccn1</chem>		0.576	0.187	3.1	1.4	10.5	86	5.9	0.6	48	176	58.6	0.483	0.200
<chem>FC(F)(F)c1ccc(CN2CCC(CC2)n3cnc4cnc5[nH]ccc5c34)n1</chem>		1.609	0.217	7.4	2.1		62	7.4	0.56					
<chem>O=C(C1CCC1)N2CC[C@H](C2)n3cnc4cnc5[nH]ccc5c34</chem>	single known enantiomer		0.308		1.9		66	6.9	0.45					
<chem>O=C(N1CCC[C@H](C1)n2cnc3cnc4[nH]ccc4c23)C5(CCC5)C#N</chem>	single known enantiomer		0.191		1.5		90	6.6	0.55					
<chem>CC(C)(C)OC(=O)N1CCC(C)(CC1)n2cnc3cnc4[nH]ccc4c23</chem>			1.961		3.4		76	9.8	0.48					
<chem>CC(C)(C)OC(=O)N1CC(C1)n2cnc3cnc4[nH]ccc4c23</chem>	mixture of diastereomers		0.257		2.2	7	84	6.2	0.69					
<chem>CC1(CCNCC1)n2cnc3cnc4[nH]ccc4c23</chem>			0.884		-0.43		58	0.6	0.86					

<chem>N#CCCN[C@@H]1CC[C@@H](CC1)n2cnc3cnc4[nH]ccc4c23</chem>					0.79		82	2.6	0.81					
<chem>NC1CC(C1)n2cnc3cnc4[nH]ccc4c23</chem>	mixture of diastereomers				-0.16		72							
<chem>CS(=O)(=O)N[C@@H]1CC[C@@H](CC1)n2cnc3cnc4[nH]ccc4c23</chem>			1.343		1.5	0.5	92	6.4	0.87					
<chem>CC1(CCN(Cc2cncnc2)CC1)n3cnc4cnc5[nH]ccc5c34</chem>		1.795	0.673	2.7	1.5	5.9	75	9.7	0.64					
<chem>CC1CN(CCC#N)C(CC1)n2cnc3cnc4[nH]ccc4c23</chem>	trans, racemic	0.293	0.055	5.3	0.96	4.9	73	2.4	0.68					
<chem>CC1CNCCCC1n2cnc3cnc4[nH]ccc4c23</chem>	trans, racemic				-0.53		58	6.9	0.85					
<chem>CC1CN(CCC#N)C(CC1)n2cnc3cnc4[nH]ccc4c23</chem>	cis, racemic	0.043	0.035	1.2	0.96		73	0.2	0.68					
<chem>CN1CCCC[C@@H]1C(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>	single known stereoisomer	4.517	1.813	2.5	2	0.4	70	5.9	0.71					
<chem>CN1CCCC[C@@H]1C(=O)N2CCC(CC2)n3cnc4cnc5[nH]ccc5c34</chem>	single known stereoisomer				2		70	5.3	0.71					
<chem>CCN1CC[C@@H]([C@@H](F)C1)n2c(C)nc3cnc4[nH]ccc4c23</chem>	single known stereoisomer	0.752	0.149	5	1.6	12.7	49	7.3	0.47					
<chem>CCN1CC[C@@H]([C@@H](F)C1)n2cnc3cnc4[nH]ccc4c23</chem>	single known stereoisomer				1.2		49	2.6	0.56					
<chem>Cc1nc2cnc3[nH]ccc3c2n1C4CCNCC4F</chem>	single stereoisomer. cis. Absolute stereochemistry unknown.				0.46	2.2	58							
<chem>Cc1nc2cnc3[nH]ccc3c2n1C4CCNCC4F</chem>	single stereoisomer. trans. Absolute stereochemistry unknown. Enantiomer of below.	0.236	0.293	0.8	0.46	4.6	58	0.3	0.69					
<chem>Cc1nc2cnc3[nH]ccc3c2n1C4CCNCC4F</chem>	single stereoisomer. trans. Absolute stereochemistry unknown. Enantiomer of above.	0.184	0.057	3.2	0.46	5	58	3	0.69	172	40.3	78.1	5.340	1.169

<chem>C1COCC(C1)n2cnc3cnc4[nH]ccc4c23</chem>	single unknown isomer. enantiomer of below.				1.2		55							
<chem>C1COCC(C1)n2cnc3cnc4[nH]ccc4c23</chem>	single unknown isomer. enantiomer of above.		0.456		1.2		55							
<chem>C1CC(CCO1)n2cnc3cnc4[nH]ccc4c23</chem>					1.2		55							
<chem>Cc1nc2cnc3[nH]ccc3c2n1C4CCc5[nH]ncc5C4</chem>	single unknown stereoisomer. enantiomer of below.		0.582		1.9	1.1	75	1.5	0.47					
<chem>Cc1nc2cnc3[nH]ccc3c2n1C4CCc5[nH]ncc5C4</chem>	single unknown stereoisomer. enantiomer of above.		0.524		1.9		75	0.3	0.47					

^aCompounds synthesized by the methods reported in:

- (a) Zak, M.; Mendonca, R.; Balazs, M.; Barrett, K.; Bergeron, P.; Blair, W. S.; Chang, C.; Deshmukh, G.; DeVoss, J.; Dragovich, P. S.; Eigenbrot, C.; Ghilardi, N.; Gibbons, P.; Gradl, S.; Hamman, C.; Hanan, E. J.; Harstad, E.; Hewitt, P. R.; Hurley, C. A.; Jin, T.; Johnson, A.; Johnson, T.; Kenny, J. R. Koehler, M. F. T.; Bir Kohli, P.; Kulagowski, J. J.; Labadie, S.; Liao, J.; Liimatta, M.; Lin, Z.; Lupardus, P. J.; Maxey, R. J.; Murray, J. M.; Pulk, R.; Rodriguez, M.; Savage, S.; Shia, S.; Steffek, M.; Ubhayakar, S.; Ultsch, M.; van Abbema, A.; Ward, S. I.; Xiao, L.; Xiao, Y. Discovery and optimization of C-2 methyl imidazopyrrolopyridines as potent and orally bioavailable JAK1 inhibitors with selectivity over JAK2. *J. Med. Chem.* **2012**, *55*, 6176 – 6193.
- (b) Kulagowski, J. J.; Blair, W.; Bull, R. J.; Chang, C.; Deshmukh, G.; Dyke, H. J.; Eigenbrot, C.; Ghilardi, N.; Gibbons, P.; Harrison, T. K.; Hewitt, P. R.; Liimatta, M.; Hurley, C. A.; Johnson, A.; Johnson, T.; Kenny, J. R.; Bir Kohli, P.; Maxey, R. J.; Mendonca, R.; Mortara, K.; Murray, J.; Narukulla, R.; Shia, S.; Steffek, M.; Ubhayakar, S.; Ultsch, M.; van Abbema, A.; Ward, S. I.; Waszkowycz, B.; Zak, M. Identification of Imidazo-pyrrolopyridines as Novel and Potent JAK1 Inhibitors. *J. Med. Chem.* **2012**, *55*, 5901–5921.
- (c) Babu, S.; Bergeron, P.; Dragovich, P.; Dyke, H. J.; Gibbons, P.; Gradl, S.; Hanan, E.; Hurley, C.; Johnson, T.; Koehler, M.; Kulagowski, J. J.; Labadie, S.; Lyssikatos, J. P.; Mendonca, R.; Pulk, R.; Ward, S.; Waszkowycz, B.; Zak, M. Tricyclic heterocyclic compounds, compositions and methods of use thereof. WO2011086053, **2011**.

Table S5. Biochemical JAK3 and TYK2 K_i values of **1 – 34**

Ex	JAK3 K_i (nM) ^a	TYK2 K_i (nM) ^a
1	0.4	7.3
2	540	375
3	250	290
4	4.9	3.4
5	13	1.9
6	20	8.1
7	69	46
8	23	2.9
9	32	72
10	120	35
11	32	10
12	50	20
13	17	4.3
14	18	14
15	23	23
16	5.3	25
17	83	67
18	520	350
19	100	74
20	340	180
21	110	31
22	150	40
23	51	37
24	60	5.4
25	430	13
26	76	3.4
27	110	5.3
28	46	73
29	53	20
30	98	6.8
31	280	12
32	2.1	0.8
33	5.9	0.4
34	7.8	1.7

^aArithmetic mean of at least three separate runs ($n \geq 3$).