Supporting Information

Optimisation of Imidazo[4,5-*b*]pyridine-based Kinase Inhibitors: Identification of a Dual FLT3/Aurora Kinase Inhibitor as an Orally Bioavailable Preclinical Development Candidate for the Treatment of AML

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4-Chloro-3-nitropyridin-2-amine[35] **(11)**

To a 100 mL round-bottomed flask containing 2-amino-4-chloropyridine (0.480 g, 3.75 mmol) and cooled in an ice bath was added concentrated sulphuric acid (5.4 g). The reaction mixture was stirred for 5 min and then nitric acid (70%; 0.36 g) was added dropwise. The reaction mixture was stirred at 0 ^{o}C for 10 min, then heated to 55 ^{o}C and stirred at this temperature for 1 h. It was cooled to room temperature and diluted with ice-water. The pH was carefully adjusted to ~ 7.5 with 10% aqueous NaOH whereupon a yellow precipitate formed. This was filtered off, washed with water and dried *in vacuo* over P_2O_5. The product was purified by silica column chromatography (elution with DCM) to provide in order of elution: 4-chloro-3-nitropyridin-2-amine as a yellow solid (0.210 g, 32%): ^{1}H-NMR (500 MHz, DMSO-d_6) 6.87 (d, J = 5.2 Hz, 1H, pyridine C-H), 7.21 (s, 2H, NH_2), 8.11 (d, J = 5.2

Hz, 1H, pyridine C-H); and 4-chloro-5-nitropyridin-2-amine (0.080 g, 12%): ^{1}H-NMR (500 MHz, DMSO-d_6) 6.58 (s, 1H, pyridine C-H), 7.58 (s, 2H, NH_2), 8.79 (s, 1H, pyridine C-H).

5-Bromo-4-chloro-3-nitropyridin-2-amine (13)

4-Chloro-3-nitropyridin-2-amine (0.10 g, 0.58 mmol) was dissolved in dry acetonitrile (20 mL). *N*-Bromosuccinimide (0.124 g, 0.70 mmol) was added to the stirred solution, and the reaction mixture heated at 80 ^{o}C for 1 h. Volatiles were removed *in vacuo* and the residue purified by silica column chromatography (elution with DCM) to provide the product as a pale brown powder (0.125 g, 85%). ^{1}H-NMR (500 MHz, DMSO-d_6) 7.35 (s, 2H, NH_2), 8.41 (s, 1H, 6-H).

4,5-Dichloro-3-nitropyridin-2-amine (12)

4-Chloro-3-nitropyridin-2-amine (0.10 g, 0.58 mmol) was dissolved in dry acetonitrile (20 mL). *N*-Chlorosuccinimide (0.094 g, 0.70 mmol) was added to the stirred solution, and the reaction mixture was heated at 80 ^{o}C for 1 h. Volatiles were removed *in vacuo* and the residue purified by silica column chromatography (elution with DCM) to provide the product as a pale brown powder (0.125 g, 85%). ^{1}H-NMR (500 MHz, DMSO-d_6) 7.35 (s, 2H, NH_2), 8.36 (s, 1H, 6-H).

4-(4-Acetylpiperazin-1-yl)benzaldehyde (9b)

To a solution of *tert*-butyl 4-(4-formylphenyl)piperazine-1-carboxylate (0.102 g, 0.35 mmol) in dichloromethane (2.5 mL) was added trifluoroacetic acid (1.0 mL). The reaction mixture

was stirred at room temperature for 1.5 h before being concentrated in vacuo. The resulting residue was dissolved in anhydrous dichloromethane (3.5 mL) under argon, and the solution was cooled to 0 ^{o}C. A solution of acetyl chloride (0.050 g, 0.64 mmol) in anhydrous dichlorometane (1 mL) was then slowly added followed by diisopropylethylamine (0.18 mL, 1.05 mmol). The clear solution was stirred for 4 h under argon and allowed to warm to room temperature. The solvents were removed *in vacuo*, the residue was absorbed on silica gel and placed on a 10 g isolute silica column. Elution with a gradient of ethyl acetate in dichloromethane (20 to 50%) afforded the desired product as a white solid (0.052 g, 64%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.04 (s, 3H, $COCH_3$), 3.39 (t, J = 5.6 Hz, 2H), 3.46 (t, J = 5.6 Hz, 2H) and 3.57 (m, 4H) (piperazine C-H), 7.05 (d, J = 8.9 Hz, 2H) and 7.72 (d, J = 8.9 Hz, 2H) (2,6-C_6H_4 and 3,5-C_6H_4), 9.72 (s, 1H, CHO); LC - MS (ESI, *m/z*): Rt = 1.73 min – 233 [$(M+H)^+$].

1-(4-(4-(6-Bromo-7-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl)phenyl)piperazin-1-yl)ethanone (10b)

To a mixture of 5-bromo-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (0.056 g, 0.14 mmol) and EtOH (6 mL) was added 4-(4-acetylpiperazin-1-yl)benzaldehyde (0.042 g, 0.18 mmol) followed by a freshly prepared aqueous solution of $Na_2S_2O_4$ (1M; 0.56 mL, 0.56 mmol). The reaction mixture was stirred at 80 ^{o}C for 20 h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was absorbed on silica gel, and the free-running powder was placed on a 10 g isolute silica column and eluted with a gradient of methanol (0 to 8%) in ethyl acetate / dichloromethane (v:v; 1:1). After trituration with diethyl ether, the precipitate was collected by filtration and washed with water and diethyl ether to afford the title compound as a pale yellow solid (0.028 g, 35%). ^{1}H-

NMR (500 MHz, DMSO-d_6) 2.05 (s, 3H, $COCH_3$), 2.40 (s, 3H, isoxazole 5-CH_3), 2.62 (br s, 4H), 3.25 (br t, J = 5.0 Hz, 2H), 3.31 (m obscured by water peak), 3.59 (br s, 6H), and 3.62 (br s, 4H) (piperazine C-H and N-CH_2-isoxazole), 6.25 (s, 1H, 4-H isoxazole), 7.08 (d, J = 9.0 Hz, 2H) and 8.04 (d, J = 8.9 Hz, 2H) (2,6-C_6H_4 and 3,5-C_6H_4), 8.18 (s, 1H, imidazo[4,5-*b*]pyridine 5-H), 13.27 (br s, 1H, imidazo[4,5-*b*]pyridine N-H); LC - MS (ESI, *m/z*): Rt = 2.03 min – 579, 581 [$(M+H)^+$, Br isotopic pattern]; HRMS: Found: 579.1819, calculated for $C_{27}H_{32}BrN_8O_2$ $(M+H)^+$: 579.1826.

4-(4-(6-Bromo-7-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl)phenyl)morpholine (10a)

To a mixture of 5-bromo-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (0.060 g, 0.15 mmol) and EtOH (6 mL) was added 4-(morpholin-4-yl)benzaldehyde (0.036 g, 0.19 mmol) followed by a freshly prepared aqueous solution of $Na_2S_2O_4$ (1M; 0.6 mL, 0.6 mmol). The reaction mixture was stirred at 80 ^oC for 18 h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was absorbed on silica gel, and the free-running powder was placed on a 10 g isolute silica column. Elution with a gradient of methanol (0 to 4%) in ethyl acetate / dichloromethane (v:v; 1:1) afforded the title compound as a white solid after trituration with diethyl ether (0.031 g, 39%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.40 (s, 3H, isoxazole 5-CH_3), 2.62 (br s, 4H), 3.24 (br t, J = 4.8 Hz, 4H), 3.62 (br t, J = 4.5 Hz, 4H) and 3.75 (t, J = 5.0 Hz, 4H) (piperazine N-CH and morpholine CH), 3.59 (s, 2H, N-CH_2-isoxazole), 6.25 (s, 1H, 4-H isoxazole), 7.08 (d, J = 9.0 Hz, 2H) and 8.04 (d, J = 8.9 Hz, 2H) (2,6-C_6H_4 and 3,5-C_6H_4), 8.18 (s, 1H, imidazo[4,5-*b*]pyridine 5-H), 13.27 (br s, 1H, imidazo[4,5-*b*]pyridine N-H); LC - MS (ESI, *m/z*): Rt = 2.12 min – 538, 540

[$(M+H)^+$, Br isotopic pattern]; HRMS: Found: 538.1549, calculated for $C_{25}H_{29}BrN_7O_2$ $(M+H)^+$: 538.1561.

4-(4-(2-Methoxyethyl)piperazin-1-yl)benzaldehyde (9d)

To a mixture of 4-bromobenzylaldehyde diethyl acetal (0.518 g, 2.0 mmol) and anhydrous toluene (4 mL) was added 1-(2-methoxyethyl)piperazine (0.345 g, 2.4 mmol) followed by $Pd_2(dba)_3$ (0.018 g, 0.02 mmol), racemic BINAP (0.037 g, 0.06 mmol) and NaO^tBu (0.326 g, 3.4 mmol). The reaction mixture was placed into an oil bath preheated to 100 ^oC and stirred at this temperature for 7.5 h under argon, then allowed to cool to room temperature. Aqueous HCl (1M; 10 mL) was added, the mixture was vigorously stirred for 2.5 h, then the pH adjusted to 13 with aqueous NaOH and extracted with ethyl acetate (3 x 40 mL). The combined organics were dried (Na_2SO_4), concentrated in vacuo and the residue absorbed on silica gel and placed on a 20 g isolute column. Elution with a gradient of methanol (0 to 4%) in ethyl acetate / dichloromethane (v/v; 1:1) afforded the title compound as an oil (0.130 g, 26%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.56 (m, 6H, piperazine C-H and CH_2CH_2OMe), 3.26 (s, 3H, OMe), 3.38 (t, J = 5.0 Hz, 4H, piperazine C-H), 3.48 (t, J = 5.8 Hz, 2H, CH_2OMe), 7.04 (d, J = 8.8 Hz, 2H) and 7.71 (d , J = 8.8 Hz, 2H) (2,6-C_6H_4 and 3,5-C_6H_4), 9.72 (s, 1H, CHO); LC - MS (ESI, *m/z*): Rt = 0.95 min – 249 $(M+H)^+$.

3-((4-(6-Bromo-2-(4-(4-(2-methoxyethyl)piperazin-1-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (10d)

To a mixture of 5-bromo-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (0.052 g, 0.13 mmol) and EtOH (6.0 mL) was added 4-(4-(2-

methoxyethyl)piperazin-1-yl)benzaldehyde (0.042 g, 0.17 mmol) followed by a freshly prepared aqueous solution of $Na_2S_2O_4$ (1M; 0.50 mL, 0.50 mmol). The reaction mixture was stirred at 80 ^oC for 20 h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was absorbed on silica gel, and placed on a 10 g isolute silica column which was eluted with dichloromethane and then a gradient of methanol (2 to 7%) in ethyl acetate / dichloromethane (v:v; 1:1). Fractions containing the product were combined and concentrated *in vacuo*. The resulting solid residue was triturated with diethyl ether, and the title compound was isolated as a white solid by filtration and washed with diethyl ether (2 x 7 mL), water (3 x 2 mL), and diethyl ether (3 x 4 mL) (0.022 g, 25%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.40 (s, 3H, isoxazole 5-CH_3), 2.52 (t, J = 5.7 Hz, 2H, C*H*$_2$CH$_2$OMe), 2.56 (br s, 4H, piperazine C-H), 2.62 (br s, 4H, piperazine C-H), 3.25 (m, 7H, piperazine C-H and OMe), 3.47 (t, J = 5.7 Hz, 2H, CH$_2$C*H*$_2$OMe), 3.59 (s, 2H, N-CH$_2$-isoxazole) 3.62 (br t, J = 4.2 Hz, 4H, piperazine C-H), 6.25 (s, 1H, isoxazole 4-H), 7.05 (d, J = 8.9 Hz, 2H) and 8.02 (d, J = 8.9 Hz, 2H) (2,6-C_6H_4 and 3,5-C_6H_4), 8.17 (s, 1H, imidazo[4,5-*b*]pyridine 5-H), 13.25 (br s, 1H, imidazo[4,5-*b*]pyridine N-H); LC - MS (ESI, *m/z*): Rt = 1.60 min – 595, 597 [$(M+H)^+$, Br isotopic pattern]; HRMS: Found: 595.2132, calculated for $C_{28}H_{36}BrN_8O_2$ $(M+H)^+$: 595.2139.

(*S*)-*tert*-Butyl 3,4-dimethylpiperazine-1-carboxylate (17)

To a solution of (*S*)-*tert*-butyl-3-methylpiperazine-1-carboxylate (349 mg, 1.74 mmol) in MeOH/THF (15 mL each) was added formaldehyde 33% in H_2O (471 μL, 5.23 mmol) followed by $Na(OAc)_3BH$ (369 mg, 1.74 mmol). The reaction was stirred for 18 h before being concentrated *in vacuo* and dry loaded onto silica. Purification was accomplished by flash chromatography on silica gel (3 x 11) eluting with MeOH/CH_2Cl_2 (10-20%) to yield the

title compound (352 mg, 94%). ^{1}H-NMR (500 MHz, $CDCl_3$) 1.02 (d, *J* = 6.2 Hz, 3H, $CHCH_3$), 1.43 (s, 9H, -$C(CH_3)_3$), 2.00 (dqd, *J* = 9.8, 6.2, 3.3 Hz, 1H, C*H*CH_3), 2.13 (td, *J* = 11.5, 3.4 Hz, 1H, CH_2), 2.26 (s, 3H, NCH_3), 2.58 (br s, 1H, CH_2), 2.69 (app d, *J* = 11.5 Hz, 1H, CH_2), 2.99 (t, *J* = 11.5 Hz, 1H, -CH_2), 3.93-3.68 (m, 2H, CH_2); LC - MS (ESI, *m/z*): Rt = 1.20 min - 159 $(M - {}^tBu)^+$.

(*S*)-4-(3,4-Dimethylpiperazin-1-yl)benzaldehyde (9e)

To a solution of (*S*)-*tert*-butyl-3,4-dimethylpiperazine-1-carboxylate (324 mg, 1.51 mmol) in CH_2Cl_2 (40 mL) was added TFA (4.00 mL, 54.0 mmol) and the solution was stirred at room temperature for 2 h. The reaction was concentrated *in vacuo*, azeotroping with toluene (x2), to give a yellow oil. The residue was dissolved in DMSO (3.0 mL) and DIPEA (1.10 mL, 6.04 mmol) was added followed by 4-fluorobenzaldehyde (194 μL, 1.81 mmol). The solution was stirred at 120 °C for 2 h. On cooling the reaction was partitioned between EtOAc/H_2O (100 mL), the separated organic layer was washed with H_2O (100 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude brown oil. Purification was accomplished by flash chromatography on silica gel (3 x 12) eluting with MeOH/CH_2Cl_2 (5%) to yield the title compound (121 mg, 0.550 mmol, 37%) as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) 1.13 (d, *J* = 6.2 Hz, 3H, $CHCH_3$), 2.21 (dqd, *J* = 9.6, 6.2, 3.2 Hz, 1H, CH_2), 2.32 (s, 3H, NCH_3), 2.35 (td, *J* = 11.6, 3.4 Hz, 1H, CH_2), 2.70 (dd, *J* = 12.4, 10.2 Hz, 1H, CH_2), 2.88 (td, *J* = 11.6, 2.9 Hz, 1H, CH_2), 3.08 (td, *J* = 11.9, 3.2 Hz, 1H, CH_2), 3.65 (ddd, *J* = 12.4, 3.0, 2.1 Hz, 1H, CH_2), 3.73 (dq, *J* = 12.4, 2.8 Hz, 1H, CH_2), 6.88 (d, *J* = 8.9 Hz, 2H, CH_{ar}), 7.72 (d, *J* = 8.9 Hz, 2H, CH_{ar}), 9.76 (s, 1H, CH_{ald}); LC - MS (ESI, *m/z*): Rt = 0.97 min - 219 $(M + H)^+$.

(*S*)-3-((4-(6-Chloro-2-(4-(3,4-dimethylpiperazin-1-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (10e)

To a solution of 5-chloro-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (75.0 mg, 0.212 mmol) and (*S*)-4-(3,4-dimethylpiperazin-1-yl)benzaldehyde (48.6 mg, 0.223 mmol) in EtOH (5.1 mL) was added 1M $Na_2S_2O_4$ (0.848 mL, 0.848 mmol, freshly prepared) and the solution was heated to 80 °C and stirred for 16 h whilst being open to air. Once cooled, the reaction was evaporated *in vacuo* and the residue dry loaded onto silica. Purification was accomplished by flash chromatography on silica gel (3 x 12) eluting with 2M methanolic NH_3/CH_2Cl_2 (5-10%) to give a yellow solid. The solid was triturated with hot EtOAc to yield the title compound (35 mg, 0.067 mmol, 32%) as an off white solid. ^{1}H-NMR (500 MHz, DMSO-d_6) 1.08 (d, *J* = 6.2 Hz, 3H, CH_3), 2.17-2.08 (m, 1H, C*H*CH_3), 2.23 (s, 3H, N-CH_3), 2.23-2.28 (m, 1H, CH_2), 2.41 (s, 3H, CH_3), 2.52-2.46 (obs m, 1H, CH_2), 2.64 (br s, 4H, CH_2), 2.90-2.81 (m, 2H, CH_2), 3.60 (s, 2H, CH_2), 3.75-3.64 (m, 6H, CH_2), 6.26 (s, 1H, CH_{ar}), 7.06 (d, *J* = 8.9 Hz, 2H, CH_{ar}), 8.02 (d, *J* = 8.9 Hz, 2H, CH_{ar}), 8.05 (1H, s, CH_{ar}), 13.19 (s, 1H, NH); LC - MS (ESI, *m/z*): Rt = 1.53 min – 521, 523 [$(M + H)^+$, Cl isotopic pattern]; HRMS: Found: 521.2527, calculated for $C_{27}H_{34}N_8OCl$ $(M+H)^+$: 521.2539.

3-Fluoro-4-(4-methylpiperazin-1-yl)benzaldehyde (19a)

A solution of 3,4-difluorobenzaldehyde (0.5g, 3.52 mmol), N-methylpiperazine dihydrochloride (0.60 g, 3.52 mmol) and diisopropylethylamine (1.80 g, 14 mmol) in dimethylsulfoxide (10 mL) was heated at 120 °C for 2 h. The reaction mixture was then cooled to room temperature and partitioned between water (100 mL) and chloroform (60

mL). The aqueous layer was further extracted with ethyl acetate; the organic solutions were combined, dried and concentrated. The crude product was purified by silica column chromatography (1 to 5% methanol in chloroform) to give 0.71 g of the desired product (91%). ^{1}H NMR (500MHz, $CDCl_3$) 2.37 (s, 3 H, NCH_3), 2.62 (t, J = 5.1 Hz, 4H, NCH_2), 3.31 (t, J = 5.1 Hz, 4H, NCH_2), 6.99 (t, J = 7.0 Hz, 1H, ArH), 7.52 (dd, J = 1.8, 13.2 Hz, 1H, ArH), 7.58 (dd, J = 1.9, 8.4 Hz, 1H, ArH), 9.82 (d, J = 2.1 Hz, 1H, CHO); LC - MS (ESI, *m/z*): Rt = 1.08 min, - 223 $(M+H)^+$.

3-((4-(6-Chloro-2-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (20a)

To a mixture of 5-chloro-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (0.07 g, 0.198 mmol) and EtOH (10mL) was added 3-fluoro-4-(4-methylpiperazin-1-yl)benzaldehyde (0.051 g, 0.23 mmol) followed by a freshly prepared aqueous solution of $Na_2S_2O_4$ (1M; 0.6 mL, 0.6 mmol). The reaction mixture was heated at reflux for 24 h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was taken up in chloroform and 10% aqueous sodium bicarbonate. The aqueous layer was further extracted with dichloromethane and the combined organic solutions dried and concentrated. The crude product was purified by silica column chromatography eluting with 2 to 10% methanol in dichloromethane. The pure fractions provided 55 mg of product (53%). ^{1}H-NMR (500 MHz, d_6-DMSO) 2.23 (s, 3H, piperazine N-Me), 2.40 (s, 3H, isoxazole 5-CH_3), 2.63 (br s, 4H, piperazine NCH_2), 3.13 (br s, 4H, piperazine NCH_2), 3.59 (s, 2H, N-CH_2-isoxazole), 3.68 (br s, 4 H, piperazine NCH_2), 6.24 (s, 1H, 4-H isoxazole), 7.15 (t, J = 8.8 Hz, 1H, ArH), 7.95 – 7.86 (m, 2H, ArH), 8.08 (s, 1H, imidazo[4,5-*b*]pyridine 5-H), 13.30 (br s, 1H, imidazo[4,5-

b]pyridine N-H); LC - MS (ESI, *m/z*): Rt = 1.67 min – 525, 527 [$(M+H)^+$, Cl isotopic pattern]; HRMS: Found: 525.2283; calculated for $C_{26}H_{31}ClFN_8O$ $(M+H)^+$: 525.2288

2-Fluoro-4-(4-methylpiperazin-1-yl)benzaldehyde (19b)

A solution of 2,4-difluorobenzaldehyde (0.50 g, 3.52 mmol), *N*-methylpiperazine dihydrochloride (0.6 g, 3.52 mmol) and diisopropylethylamine (1.8 g, 14.0 mmol) in dimethylsulfoxide (10 mL) was heated at 120 ^oC for 2 h. It was then cooled to room temperature and partitioned between water (100 mL) and chloroform (60 mL). The aqueous layer was further extracted with ethyl acetate; the organic solutions were combined, dried and concentrated. The crude was purified by silica column chromatography (1 to 5% methanol in chloroform) to give 0.7 g of product (85%). ^1H NMR (500MHz, $CDCl_3$) 2.37 (s, 3 H, NCH_3), 2.57 (br s, 4H, NCH_2), 3.40 (t, J = 5.2 Hz, 4H, NCH_2), 6.45 (dd, J = 14.5, 2.4 Hz, 1H, ArH), 6.64 (dd, J = 8.9, 2.6 Hz, 1H, ArH), 7.70 (t, J = 8.9 Hz, 1H, ArH), 10.06 (s, 1 H, CHO); LC - MS (ESI, *m/z*): Rt = 1.00 min- 223 $(M+H)^+$.

3-((4-(6-chloro-2-(2-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (20b)

To a mixture of 5-chloro-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (0.1 g, 0.28 mmol) and EtOH (10 mL) was added 2-fluoro-4-(4-methylpiperazin-1-yl)benzaldehyde (0.071 g, 0.32 mmol) followed by a freshly prepared aqueous solution of $Na_2S_2O_4$ (1M; 0.9 mL, 0.9 mmol). The reaction mixture was heated at reflux for 24 h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was taken up in chloroform and 10% aqueous sodium bicarbonate. The aqueous layer was further extracted

with dichloromethane and the combined organic solutions dried and concentrated. The crude product was purified by silica column chromatography eluting with 3 to 10% methanol in chloroform. The pure fractions provided 40 mg of product (27%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.23 (s, 3H, piperazine N-Me), 2.40 (s, 3H, isoxazole 5-CH_3), 2.44 (t, J = 4.9 Hz, 4H, piperazine NCH_2), 2.62 (br s, 4H, piperazine NCH_2), 3.58 (s, 2H, N-CH_2-isoxazole), 3.67 (br s, 4H, piperazine NCH_2), 6.24 (s, 1H, 4-H isoxazole), 6.92 – 6.86 (m, 2H, ArH), 7.90 (t, J = 8.9 Hz, 1H, ArH), 8.08 (s, 1H, imidazo[4,5-*b*]pyridine 5-H), 12.85 (br s, 1H, imidazo[4,5-*b*]pyridine N-H); LC - MS (ESI, *m/z*): Rt = 1.54 min – 525, 527 $(M+H)^+$, Cl isotopic pattern; HRMS: Found: 525.2284; calculated for $C_{26}H_{31}ClFN_8O$ $(M+H)^+$ 525.2288.

2-(3-(6-Chloro-7-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl)phenoxy)-*N*,*N*-dimethylethanamine (20c)

To a mixture of 5-chloro-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (0.054 g, 0.15 mmol) and EtOH (10 mL) was added 3-(2-(dimethylamino)ethoxy)benzaldehyde (0.035 g, 0.18 mmol) followed by a freshly prepared aqueous solution of $Na_2S_2O_4$ (1M; 0.45 mL, 0.45 mmol). The reaction mixture was heated at reflux for 24 h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was taken up in chloroform and 10% bicarbonate. The aqueous layer was further extracted with dichloromethane and the combined organic solutions dried and concentrated. The crude product was purified on an SCX ion-exchange column eluting first with 5% methanol in dichloromethane followed by 1M ammonia in methanol. The pure fractions provided 50 mg of product (66 %). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.28 (s, 6H, NMe_2), 2.40 (s, 3 H, isoxazole 5-CH_3), 2.64 (br s, 4H, piperazine NCH_2), 2.70 (t, J = 5.7 Hz, 2H, CH_2NMe_2), 3.60 (s, 2 H, CH_2-isoxazole), 3.71 (br s, 4H, piperazine NCH_2), 4.15 (t, J = 5.7

Hz, 2H, $ArOCH_2$), 6.24 (s, 1H, 4-H isoxazole), 7.09 – 7.07 (m , 1H, ArH), 7.46 – 7.43 (m, 1H, ArH), 7.78 – 7.75 (m, 2H, ArH), 8.11 (s, 1H, imidazo[4,5-*b*]pyridine 5-H), 13.45 (br s, 1H, imidazo[4,5-*b*]pyridine N-H); LC - MS (ESI, *m/z*): 496, 498 $[(M+H)^+$, Cl isotopic pattern]; HRMS: Found: 496.2217, calculated for $C_{25}H_{31}ClN_7O_2$ $(M+H)^+$: 496.2222

4-(3-(6-Chloro-7-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl)benzyl)morpholine (20e)

To a mixture of 5-chloro-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (0.043 g, 0.12 mmol) and EtOH (5.0 mL) was added 3-(morpholinomethyl)benzaldehyde (0.031 g, 0.15 mmol) followed by a freshly prepared aqueous solution of $Na_2S_2O_4$ (1M; 0.46 mL, 0.46 mmol). The reaction mixture was stirred at 80 ^oC for 20 h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was absorbed on silica gel, and placed on a 10 g isolute silica column. Elution with a gradient of methanol (0 to 6%) in ethyl acetate / dichloromethane (v:v; 1:1) afforded the title compound as a yellow solid after trituration with diethyl ether (0.003 g, 5%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.40 (br s, 7H, piperazine or morpholine C-H and isoxazole 5-CH_3), 2.63 (br s, 4H, piperazine or morpholine C-H), 3.56 (s, 2H, C_6H_4-CH_2-morpholine), 3.60 (m, 6H, piperazine or morpholine C-H and N-CH_2-isoxazole), 3.70 (br s, 4H, piperazine or morpholine C-H), 6.25 (s, 1H, 4-H isoxazole), 7.45 (d, J = 7.3 Hz, 1H, PhH), 7.49 (t, J = 7.3 Hz, PhH), 8.06 (d, J = 7.3 Hz, 1H, PhH), 8.11 (s, 1H) and 8.13 (s, 1H) (PhH and imidazo[4,5-*b*]pyridine 5-H), 13.51 (br s, 1H, imidazo[4,5-*b*]pyridine N-H); LC - MS (ESI, *m/z*): Rt = 1.59 min – 508, 510 $[(M+H)^+$, Cl isotopic pattern]; HRMS: Found: 508.2226, calculated for $C_{26}H_{31}ClN_7O_2$ $(M+H)^+$: 508.2222.

6-Chloro-2-(3-dimethylaminomethyl)phenyl-7-(4-(5-methylisoxazol-3-ylmethyl)piperazin-1-yl)-imidazo[4,5-*b*]pyridine (20d)

To 3-bromomethylbenzaldehyde (124 mg, 0.62 mmol) was added a 2M solution of dimethylamine in THF (1.5 mL, 3.0 mmol). The reaction was stirred at 20 ^{o}C for 1.75 h. The reaction was added to water (10 mL) and the product extracted with ethyl acetate (3 x 5 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and evaporated to leave 3-dimethylaminomethylbenzaldehyde (105 mg). ^{1}H-NMR ($CDCl_3$, 500MHz): 2.27 (s, 6H, Me), 3.51 (s, 2H, CH_2), 7.50 (t, J=7.6 Hz, 1H, aryl CH), 7.61 (d, J=7.6 Hz, 1H, aryl CH), 7.79 (d, J=7.6 Hz, 1H, aryl CH), 7.84 (s, 1H, aryl CH), 10.04 (s, 1H, CHO). To a mixture of 3-dimethylaminomethylbenzaldehyde (34 mg, 0.21 mmol) and 2-amino-5-chloro-4-(4-(5-methylisoxazol-3-yl)methylpiperazin-1-yl)-3-nitropyridine (70.5 mg, 0.20 mmol) in ethanol (1.5 mL) was added freshly prepared 1M sodium dithionite solution (0.7 mL, 0.7 mmol). The reaction was stirred and heated at 75 ^{o}C for 40 h. The reaction was cooled and 5M ammonia solution (0.4 mL) was added and stirred for 15 min. The solid product was filtered off, washed with water (2x2 mL) and dried in vacuum over sodium hydroxide (62 mg, 66%).^{1}H-NMR (500 MHz, DMSO-d_6) 2.20 (s, 6H, NMe_2), 2.40 (s, 3H, Me), 2.64 (m, 4H, piperazine CH_2), 3.49 (s, 2H, CH_2), 3.60 (s, 2H, CH_2), 3.70 (m, 4H, piperazine CH_2), 6.25 (s, 1H, isoxazole CH), 7.42 (d, J = 7.2 Hz, 1H, aryl-H), 7.50 (t, J =7 .7 Hz, 1H, aryl-H), 8.07 (d, J=6.9 Hz, 1H, aryl-H), 8.12 (s, 2H, aryl-H and heteroaryl-H), 13.48 (br s, 1H, NH);LC - MS (ESI, *m/z*): Rt = 1.49 min – 466, 468 [$(M+H)^+$, Cl isotopic pattern]; HRMS: Found: 466.2103, calculated for $C_{24}H_{29}ClN_7O$ $(M+H)^+$: 466.2117; HPLC: Rt = 3.15 min; 92%, λ = 309 nm.

3-((4-(6-Chloro-2-(1-methyl-1*H*-imidazol-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (21b)

To a mixture of 5-chloro-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (0.06 g, 0.17 mmol) and EtOH (10 mL) was added 1-methyl-1*H*-imidazole-2-carbaldehyde (0.022 g, 0.20 mmol) followed by a freshly prepared aqueous solution of $Na_2S_2O_4$ (1M; 0.5 mL, 0.5 mmol). The reaction mixture was heated at reflux for 24 h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was taken up in chloroform and 10% aqueous sodium bicarbonate. The aqueous layer was further extracted with dichloromethane and the combined organic solutions dried and concentrated *in vacuo*. The crude product was purified by silica column chromatography eluting with 1 to 5% methanol in dichloromethane. The pure fractions provided 50 mg of product (71%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.39 (s, 3 H, isoxazole 5-CH_3), 2.63 (br s, 4H, piperazine NCH_2), 3.59 (s, 2H, N-CH_2-isoxazole), 3.71 (br s, 4H, piperazine NCH_2), 4.13 (s, 3H, NCH_3), 6.23 (s, 1H, 4-H isoxazole), 7.13 (s, 1H, CH-imidazole), 7.43 (s, 1H, CH-imidazole), 8.10 (s, 1H, imidazo[4,5-*b*]pyridine 5-H), 13.30 (br s, 1H, imidazo[4,5-*b*]pyridine N-H); LC - MS (ESI, *m/z*): Rt = 2.11 min- 413, 415 [$(M+H)^+$, Cl isotopic pattern]; HRMS: Found: 413.1596, calculated for $C_{19}H_{22}ClN_8O$ $(M+H)^+$: 413.1599.

3-((4-(6-Chloro-2-(furan-3-yl)-3*H*-imidazo[4,5-b]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (21c)

To a mixture of 5-chloro-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (0.058 g, 0.164 mmol) and EtOH (10 mL) was added furan-3-carbaldehyde (0.019 g, 0.2 mmol) followed by a freshly prepared aqueous solution of $Na_2S_2O_4$ (1M; 0.45 mL, 0.45

mmol). The reaction mixture was heated at reflux for 24 h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was taken up in chloroform and 10% aqueous sodium bicarbonate. The aqueous layer was further extracted with dichloromethane and the combined organic solutions dried and concentrated *in vacuo*. The crude product was purified by silica column chromatography eluting with 1 to 3% methanol in dichloromethane. The pure fractions provided 45 mg of product (69%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.40 (s, 3H, isoxazole 5-CH_3), 2.61 (br s, 4 H, piperazine NCH_2), 3.59 (s, 2H, N-CH_2-isoxazole), 3.65 (br s, 4H, piperazine NCH_2), 6.24 (s, 1H, 4-H isoxazole), 7.06 (s, 1H, furan-H), 7.85 (s, 1H, furan-H), 8.09 (s, 1H, imidazo[4,5-*b*]pyridine 5-H), 8.37 (s, 1 H furan-H), 13.30 (br s, 1H, imidazo[4,5-*b*]pyridine N-H); LC - MS (ESI, *m/z*): Rt = 1.82 min – 399, 401 [$(M+H)^+$, Cl isotopic pattern]; HRMS: Found: 399.1334, calculated for $C_{19}H_{20}ClN_6O_2$ $(M+H)^+$: 399.1331.

3-((4-(6-Bromo-2-(2,5-dimethyloxazol-4-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (21d)

To a mixture of 5-bromo-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (0.1 g, 0.25 mmol) and EtOH (15 mL) was added 2,5-dimethyloxazole-4-carbaldehyde (30 mg, 0.32 mmol) followed by a freshly prepared aqueous solution of $Na_2S_2O_4$ (1M; 1.0 mL, 1.0 mmol). The reaction mixture was heated at reflux for 24 h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was taken up in chloroform and 10% aqueous sodium bicarbonate. The aqueous layer was further extracted with dichloromethane and the combined organic solutions dried and concentrated. Ether was added to the residue and a pale white powder precipitated; this was filtered and dried (45 mg). The product was purified on a SCX ion-exchange column to provide the title compound

as an off-white powder after trituration with ether (30 mg, 25%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.39 (s, 3H, isoxazole 5-CH_3), 2.47 (s, 3H, oxazole-CH_3), 2.62 (br s, 4H, piperazine NCH_2), 2.72 (s, 3H, oxazole-CH_3), 3.59 (s, 2H, N-CH_2-isoxazole), 3.63 (br s, 4H, piperazine NCH_2), 6.23 (s, 1H, 4-H isoxazole), 8.18 (s, 1H, imidazo[4,5-*b*]pyridine 5-H), 13.50 (br s, 1H, imidazo[4,5-*b*]pyridine N-H); LC - MS (ESI, *m/z*): Rt = 2.09 min- 472, 474 [$(M+H)^+$, Br isotopic pattern]; HRMS: Found: 472.1089, calculated for $C_{20}H_{23}BrN_7O_2$ $(M+H)^+$: 472.1091.

3-((4-(6-Chloro-2-(5-methylisoxazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (21e)

To a mixture of 5-chloro-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (0.055 g, 0.156 mmol) and EtOH (10 mL) was added 5-methylisoxazole-3-carbaldehyde (0.02 g, 0.18 mmol) followed by a freshly prepared aqueous solution of $Na_2S_2O_4$ (1M; 0.5 mL, 0.5 mmol). The reaction mixture was heated at reflux for 24 h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was taken up in chloroform and 10% aqueous sodium bicarbonate *in vacuo*. The aqueous layer was further extracted with dichloromethane and the combined organic solutions dried and concentrated. The crude product was purified by silica column chromatography eluting with 1 to 5% methanol in dichloromethane. The pure fractions provided 34 mg of product (53%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.40 (s, 3H, isoxazole 5-CH_3), 2.52 (s, 3H, isoxazole-CH_3), 2.62 (br s, 4H, piperazine NCH_2), 3.59 (s, 2H, N-CH_2-isoxazole), 3.70 (br s, 4H, piperazine NCH_2), 6.24 (s, 1H, 4-H isoxazole), 6.82 (s, 1H, 4-H isoxazole), 8.18 (s, 1H, imidazo[4,5-*b*]pyridine 5-H), 13.80 (br s, 1H, imidazo[4,5-*b*]pyridine N-H); LC - MS (ESI, *m/z*): Rt =

1.85 min – 414, 416 [$(M+H)^+$, Cl isotopic pattern]; HRMS: Found: 414.1435, calculated for $C_{19}H_{21}ClN_7O_2$ $(M+H)^+$: 414.1440.

3-((4-(6-Chloro-2-(1-methyl-1*H*-pyrazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (21g)

To 5-chloro-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (48.8 mg, 0.138 mmol) and 1-methylpyrazole-3-aldehyde (17.5 mg, 0.159 mmol) in ethanol (1.1 mL) was added freshly prepared 1 M aqueous sodium dithionite solution (0.55 mL, 0.55 mmol). The reaction was stirred and heated at 75 ^oC for 22 h. The reaction was cooled and 5 M ammonia solution (0.28 mL, 1.4 mmol) was added. The resulting solid was filtered off and washed with water (2 x 2 mL), then dried *in vacuo* over sodium hydroxide to give the title compound (42 mg, 73%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.40 (s, 3H, isoxazole 5-CH_3), 2.61 (m, 4H, piperazine CH_2), 3.59 (s, 2H, N-CH_2-isoxazole), 3.65 (m, 4H, piperazine CH_2), 3.96 (s, 3H, NCH_3), 6.24 (s, 1H, isoxazole 4-H), 6.86 (d, J = 2.2 Hz, 1H, pyrazole H), 7.85 (d, J = 1.9 Hz, 1H, pyrazole H), 8.08 (s, 1H, hetaryl H), 13.32 (s, 1H, N-H); LC - MS (ESI, *m/z*): Rt = 1.66 min – 413, 415 [$(M+H)^+$, Cl isotopic pattern]; HRMS: Found: 413.1589, calculated for $C_{19}H_{22}ClN_8O$ $(M+H)^+$: 413.1600; HPLC: Rt = 4.33 min; 94%, λ = 310 nm.

3-((4-(6-Bromo-2-(1,2,3-thiadiazol-4-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (21f)

To a mixture of 5-bromo-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (0.052 g, 0.131 mmol) and EtOH (10 mL) was added 1,2,3-thiadiazole-4-carbaldehyde (0.018g, 0.16 mmol) followed by a freshly prepared aqueous solution of

$Na_2S_2O_4$ (1M; 0.4 mL, 0.4 mmol). The reaction mixture was heated at reflux for 24 h, then allowed to cool to room temperature and concentrated *in vacuo*. The residue was taken up in chloroform and 10% aqueous sodium bicarbonate. The aqueous layer was further extracted with dichloromethane and the combined organic solutions dried and concentrated *in vacuo*. The crude product was purified on a silica column eluting with 1 to 5% methanol in dichloromethane. The pure fractions provided 30 mg of product (50%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.40 (s, 3H, isoxazole 5-CH_3), 2.64 (br s, 4H, piperazine NCH_2), 3.60 (s, 2H, N-CH_2-isoxazole), 3.68 (br s, 4H, piperazine NCH_2), 6.24 (s, 1H, 4-H isoxazole), 8.32 (s, 1H, imidazo[4,5-*b*]pyridine 5-H), 9.78 (s, 1H, CH of thiadiazole), 14.00 (br s, 1H, imidazo[4,5-*b*]pyridine N-H); LC - MS (ESI, *m/z*): Rt = 1.70 min – 461, 463 [$(M+H)^+$, Br isotopic pattern]; HRMS: Found: 461.0497, calculated for $C_{17}H_{18}BrN_8OS$ $(M+H)^+$: 461.0502.

3-((4-(6-Chloro-2-(1-methyl-1*H*-pyrazol-5-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (21h)

To a solution of 5-chloro-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (75.0 mg, 0.212 mmol) and 1-methyl-1*H*-pyrazole-5-carbaldehyde (50.0 mg, 0.454 mmol) in EtOH (5.0 mL) was added 1M $Na_2S_2O_4$ (0.848 mL, 0.848 mmol, freshly prepared aqueous solution) and the reaction mixture was heated to 80 °C and stirred for 15 h whilst being open to air. Once cooled, the reaction was evaporated *in vacuo* and the residue dry loaded onto silica. Purification was accomplished by flash chromatography on silica gel (3 x 12) eluting with MeOH/CH_2Cl_2 (5%) to yield the title compound (15 mg, 17%) as a pale yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$) 2.43 (d, J = 0.4 Hz, 3H, CH_3), 2.76 (app t, J = 4.2 Hz, 4H, CH_2), 3.67 (s, 2H, CH_2), 3.90 (app s, 4H, CH_2), 4.39 (s, 3H, -NCH_3), 6.07 (s, 1H, CH_{ar}), 6.83 (d, J = 1.9 Hz, 1H, CH_{ar}), 7.62 (d, J = 1.9 Hz, 1H, CH_{ar}), 8.16 (br s, 1H, CH_{ar}),

13.25 (s, 1H, NH); LC - MS (ESI, *m/z*): Rt = 1.82 min – 413, 415 [(M + H)$^+$, Cl isotopic pattern]; HRMS: Found: 435.1417, calculated for $C_{19}H_{21}N_8OClNa$ (M+Na)$^+$: 435.1419.

3-((4-(6-Chloro-2-(1-ethyl-1*H*-pyrazol-4-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (22a)

To a solution of 5-chloro-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (80.0 mg, 0.230 mmol) and 1-ethyl-1*H*-pyrazole-4-carbaldehyde (30.0 mg, 0.240 mmol) in EtOH (5.5 mL) was added 1M aqueous $Na_2S_2O_4$ (0.920 mL, 0.920 mmol, freshly prepared) and the solution was heated to 80 °C and stirred for 18 h whilst being open to air. Once cooled, the reaction was evaporated *in vacuo* and the residue dry loaded onto silica. Purification was accomplished by flash chromatography on silica gel (3 x 12) eluting with MeOH/CH_2Cl_2 (5-7.5%) to yield the title compound (78 mg, 79%) as a pale yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$) 1.55 (t, *J* = 7.3 Hz, 3H, CH_2CH_3), 2.44 (s, 3H, CH_3), 2.73 (app t, *J* = 4.3 Hz, 4H, CH_2), 3.67 (s, 2H, CH_2), 3.81 (br s, 4H, CH_2), 4.23 (q, *J* = 7.3 Hz, 2H, CH_2CH_3), 6.09 (s, 1H, CH_{ar}), 7.96 (br s, 3H, CH_{ar}), 13.83 (s, 1H, NH); LC - MS (ESI, *m/z*): Rt = 1.82 min – 427, 429 [(M + H)$^+$, Cl isotopic pattern]; HRMS: Found: 427.1759, calculated for $C_{20}H_{24}N_8OCl$ (M+H)$^+$: 427.1756.

3-((4-(6-Chloro-2-(1-isopropyl-1*H*-pyrazol-4-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (22b)

To a solution of 5-chloro-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (80.0 mg, 0.230 mmol) and 1-isopropyl-1*H*-pyrazole-4-carbaldehyde (33.2 mg, 0.240 mmol) in EtOH (5.5 mL) was added 1M aqueous $Na_2S_2O_4$ (0.920 mL, 0.920 mmol,

freshly prepared), and the solution was heated to 80 °C and stirred for 18 h whilst being open to air. Once cooled, the reaction was evaporated *in vacuo* and the residue dry loaded onto silica. Purification was accomplished by flash chromatography on silica gel (3 x 12) eluting with MeOH/CH_2Cl_2 (5-7.5%) to yield the title compound (70 mg, 69%) as a pale yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$) 1.57 (d, J = 6.6 Hz, 6H, $CH(CH_3)_2$), 2.43 (s, 3H, CH_3), 2.73 (br s, 4H, CH_2), 3.67 (s, 2H, CH_2), 3.82 (br s, 4H, CH_2), 4.56 (septet, J = 6.6 Hz, 1H, $CH(CH_3)_2$), 6.09 (s, 1H, CH_{ar}), 8.07-7.93 (m, 3H, CH_{ar}), 13.85 (s, 1H, NH); LC - MS (ESI, *m/z*): Rt = 1.90 min – 441, 443 [$(M + H)^+$, Cl isotopic pattern]; HRMS: Found: 463.1732, calculated for $C_{21}H_{25}N_8OClNa$ $(M+Na)^+$: 463.1732.

3-((4-(6-Chloro-2-(1-(2,2-difluoroethyl)-1*H*-pyrazol-4-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (22c)

To a solution of 5-chloro-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (80.0 mg, 0.230 mmol) and 1-(2,2-difluoroethyl)-1*H*-pyrazole-4-carbaldehyde (38.0 mg, 0.240 mmol) in EtOH (5.5 mL) was added 1M aqueous $Na_2S_2O_4$ (0.920 mL, 0.920 mmol, freshly prepared) and the solution was heated to 80 °C and stirred for 18 h whilst being open to air. Once cooled, the reaction was evaporated *in vacuo* and the residue dry loaded onto silica. Purification was accomplished by flash chromatography on silica gel (3 x 12) eluting with MeOH/CH_2Cl_2 (5-7.5%) to yield the title compound (65 mg, 61%) as a pale yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$) 2.44 (s, 3H, CH_3), 2.74 (br s, 4H, CH_2), 3.68 (s, 2H, CH_2), 3.82 (br s, 4H, CH_2), 4.51 (td, J = 13.3, 3.8 Hz, 2H, CH_2CHF_2), 6.10 (s, 1H, CH_{ar}), 6.15 (tt, J = 55.2, 3.8 Hz, 1H, CHF_2), 7.89 (br s, 1H, CH_{ar}), 8.00 (br s, 2H, CH_{ar}), 13.91 (s, 1H, NH); LC - MS (ESI, *m/z*): Rt = 1.82 min – 463, 465 [$(M + H)^+$, Cl isotopic pattern];

HRMS: Found: 485.1388, calculated for $C_{20}H_{21}N_8OClF_2Na$ $(M+Na)^+$: 485.1387.

3-((4-(6-Chloro-2-(3-cyclopropyl-1-methyl-1*H*-pyrazol-4-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methylisoxazole (22e)

To a solution of 5-chloro-4-(4-((5-methylisoxazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (75.0 mg, 0.213 mmol) and 1-methyl-3-isopropyl-1*H*-pyrazole-4-carbaldehyde (33.6 mg, 0.224 mmol) in EtOH (5.0 mL) was added 1M aqueous $Na_2S_2O_4$ (0.850 mL, 0.850 mmol, freshly prepared) and the solution was heated to 80 °C and stirred for 18 h whilst being open to air. Once cooled, the reaction was evaporated *in vacuo* and the residue dry loaded onto silica. Purification was accomplished by flash chromatography on silica gel (3 x 15) eluting with MeOH/CH_2Cl_2 (2.5-4-8%) to yield the title compound (82 mg, 85%) as a pale yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$) 0.97-1.03 (m, 4H, $CH(CH_2)_2$), 2.43 (s, 3H, CH_3), 2.53 (app qn, J = 5.9 Hz, 1H, CH), 2.73 (app t, J = 4.5 Hz, 4H, CH_2), 3.66 (s, 2H, CH_2), 3.82 (br s, 4H, CH_2), 3.87 (s, 3H, NCH_3), 6.06 (d, J = 0.6 Hz, 1H, CH_{ar}), 7.78 (br s, 1H, CH_{ar}), 8.00 (br s, 1H, CH_{ar}), 12.23 (s, 1H, NH); LC - MS (ESI, *m/z*): Rt = 2.04 min – 453, 455 [$(M + H)^+$, Cl isotopic pattern]; HRMS: Found: 475.1737, calculated for $C_{22}H_{25}N_8OClNa$ $(M+Na)^+$: 475.1732.

5-Chloro-4-(4-((4-methyl-1,2,5-oxadiazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (26a)

To a solution of 3-methyl-4-(piperazin-1-ylmethyl)-1,2,5-oxadiazole (114 mg, 0.624 mmol) and 2-amino-3-nitro-4,5-dichloropyridine (150 mg, 0.594 mmol) in *i*PrOH (4.3 mL) was added DIPEA (466 µl, 2.67 mmol). The solution was stirred at 50 °C for 14½ hrs. On

cooling a yellow precipitate dropped out which was filtered, washed with Et_2O, dried *in vacuo* to yield the title compound as a yellow solid (208 mg, 94%). The filtrate was concentrated *in vacuo* and the residue purified by flash chromatography on silica gel (2 x 10) eluting with EtOAc/hexane (30-50%) to yield the title compound (13 mg, 6%) as a yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$) 2.45 (s, 3H, CH_3), 2.66 (br s, 4H, CH_2), 3.19 (app t, J = 4.6 Hz, 4H, CH_2), 3.74 (s, 2H, CH_2C), 5.81 (s, 2H, NH_2), 8.02 (s, 1H, C(Cl)CH); LC (Method C) - MS (ESI, *m/z*): Rt = 2.15 min – 354, 356 [$(M + H)^+$, Cl isotopic pattern].

3-((4-(6-Chloro-2-(1,3-dimethyl-1*H*-pyrazol-4-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-4-methyl-1,2,5-oxadiazole (27a)

To a solution of 5-chloro-4-(4-((4-methyl-1,2,5-oxadiazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (53.0 mg, 0.150 mmol) and 1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (19.5 mg, 0.157 mmol) in EtOH (3.5 mL) was added 1M aqueous $Na_2S_2O_4$ (0.629 mL, 0.629 mmol, freshly prepared) and the solution was heated to 80 °C and stirred for 15 h whilst being open to air. Once cooled, the reaction was evaporated *in vacuo* and the residue dry loaded onto silica. Purification was accomplished by flash chromatography on silica gel (3 x 12) eluting with MeOH/CH_2Cl_2 (5-7.5%) to give an off white solid (48 mg). The solid was further purified by trituration in hot EtOAc to yield the title compound (33 mg, 51%) as an off white solid and a filtrate which upon evaporation *in vacuo* gave the title compound (9 mg, 14%) as a pale yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$) 2.49 (s, 3H, CH_3). 2.61 (s, 3H, CH_3), 2.72 (app t, J = 4.7 Hz, 4H, CH_2), 3.77 (s, 2H, CH_2), 3.82 (app s, 4H, CH_2), 3.92 (s, 3H, NCH_3), 7.83 (s, 1H, CH_{ar}), 8.02 (s, 1H, CH_{ar}), 11.49 (br s, 1H, NH); LC - MS (ESI, *m/z*): Rt = 2.35 min – 428, 430 [$(M + H)^+$, Cl isotopic pattern]; HRMS: Found: 428.1712, calculated for $C_{19}H_{23}N_9OCl$ $(M+H)^+$: 428.1708.

***tert*-Butyl 4-((1,2,4-oxadiazol-3-yl)methyl)piperazine-1-carboxylate (24b)**

To a solution of Boc-piperazine (571 mg, 3.07 mmol) and 3-(chloromethyl)-1,2,4-oxadiazole (400 mg, 3.37 mmol) in CH_2Cl_2 (30 mL) was added triethylamine (1.70 mL, 12.3 mmol). The reaction was stirred for 22 h at 50 °C before being concentrated *in vacuo* to give a crude oily white solid. Purification was accomplished by flash chromatography on silica gel (4 x 12) eluting with MeOH/CH_2Cl_2 (5%) to yield the title compound (555 mg, 67%) as a white solid. ^{1}H-NMR (500 MHz, $CDCl_3$) 1.43 (s, 9H, $C(CH_3)_3$), 2.52 (app t, J = 4.9 Hz, 4H, CH_2), 3.45 (app t, J = 4.9 Hz, 4H, CH_2), 3.78 (s, 2H, CH_2C), 8.71 (s, 1H, CH_{ar}); LC - MS (ESI, *m/z*): Rt = 1.67 min - 213 $(M - {}^tBu)^+$, 169 $(M - Boc)^+$.

4-(4-((1,2,4-Oxadiazol-3-yl)methyl)piperazin-1-yl)-5-chloro-3-nitropyridin-2-amine (26b)

To a solution of *tert*-butyl 4-((1,2,4-oxadiazol-3-yl)methyl)piperazine-1-carboxylate (213 mg, 0.790 mmol) in CH_2Cl_2 (18 mL) was added TFA (1.8 mL, 23.8 mmol) and the solution was stirred at room temperature for 1½ h. The reaction was concentrated *in vacuo*, azeotroping with toluene (x2) and drying in vacuum desiccator (containing KOH) overnight gave a yellow oil (**25b**). The crude oil was dissolved in ^{i}PrOH (4.4 mL) and both 2-amino-3-nitro-4,5-dichloropyridine (190 mg, 0.752 mmol) and DIPEA (520 µl, 3.00 mmol) were added. The solution was stirred at 50 °C for 4 h. On cooling a yellow precipitate formed which was filtered, washed with Et_2O, dried *in vacuo* to yield the title compound as a yellow solid (165 mg, 65%). The filtrate was concentrated *in vacuo* to give 715 mg of an oily yellow solid. Purification was accomplished by flash chromatography on silica gel (4 x 11) eluting with

EtOAc/hexane (40-50%) to yield the title compound (42 mg, 16%) as a yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$) 2.74 (app t, *J* = 4.1 Hz, 4H, -CH_2-), 3.25 (t, *J* = 4.8 Hz, 4H, -CH_2-), 3.85 (s, 2H, -CH_2C-), 5.77 (s, 2H, NH_2), 7.99 (s, 1H, CH_{ar}), 8.72 (s, 1H, -C(Cl)CH-); LC - MS (ESI, *m/z*): Rt = 1.56 min – 340, 342 [$(M + H)^+$, Cl isotopic pattern];

3-((4-(6-Chloro-2-(1,3-dimethyl-1*H*-pyrazol-4-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-1,2,4-oxadiazole (27b)

To a solution of 4-(4-((1,2,4-oxadiazol-3-yl)methyl)piperazin-1-yl)-5-chloro-3-nitropyridin-2-amine (50.0 mg, 0.147 mmol) and 1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (19.2 mg, 0.155 mmol) in EtOH (3.4 mL) was added 1M $Na_2S_2O_4$ (0.588 mL, 0.588 mmol, freshly prepared) and the solution was heated to 80 °C and stirred for 15 h whilst being open to air. Once cooled, the reaction was evaporated *in vacuo* and the residue dry loaded onto silica. Purification was accomplished by flash chromatography on silica gel (2 x 14) eluting with MeOH/CH_2Cl_2 (5-7.5%) to yield the title compound (26 mg, 43%) as a pale yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$) 2.58 (s, 3H, CH_3), 2.81 (app t, *J* = 4.4 Hz, 4H, CH_2), 3.82 (app s, 4H, CH_2), 3.85 (s, 3H, NCH_3), 3.88 (s, 2H, CH_2), 7.62 (br s, 1H, CH_{ar}), 7.87 (br s, 1H, CH_{ar}), 8.74 (s, 1H, CH_{ar}), 13.04 (s, 1H, NH); LC - MS (ESI, *m/z*): Rt = 1.91 min – 414, 416 [$(M + H)^+$, Cl isotopic pattern]; HRMS: Found: 436.1374, calculated for $C_{18}H_{20}N_9OClNa$ $(M+Na)^+$: 436.1372.

2-Amino-5-chloro-4-(4-(5-methyl-1,2,4-oxadiazol-3-yl)methylpiperazin-1-yl)-3-nitropyridine (26c)

1-[(5-Methyl-1,2,4-oxadiazol-3-yl)methyl]piperazine hydrochloride (217 mg, 0.99 mmol) and 2-amino-4,5-dichloro-3-nitropyridine (208 mg, 1.0 mmol) were stirred in 2-propanol (5 mL) and diisopropylethylamine (523 μL, 387 mg, 3.0 mmol) was added. The mixture was stirred and heated at 45 ^{o}C for 23 h. The reaction was cooled and the product filtered off and washed with 2-propanol. Drying in vacuum gave the product (246 mg, 69%). ^{1}H-NMR (500 MHz, $CDCl_3$,) 2.63 (s, 3H, CH_3), 2.77 (br m, 4H, piperazine C-H), 3.29 (m, 4H, piperazine C-H), 3.76 (s, 2H, CH_2), 5.27 (s, 2H, NH_2), 8.02 (s, 1H, pyridine 6-H); LC - MS (ESI, *m/z*): Rt = 1.66 min – 354 $(M + H)^+$, ^{35}Cl isotope.

3-((4-(6-Chloro-2-(1,3-dimethyl-1*H*-pyrazol-4-yl)-3*H*-imidazo[4,5-*b*]pyridin-7-yl)piperazin-1-yl)methyl)-5-methyl-1,2,4-oxadiazole (27c)

To a solution of 5-chloro-4-(4-((5-methyl-1,2,4-oxadiazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (60.0 mg, 0.170 mmol) and 1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (22.2 mg, 0.179 mmol) in EtOH (3.8 mL) was added 1M aqueous $Na_2S_2O_4$ (0.678 mL, 0.678 mmol, freshly prepared) and the solution was heated to 80 °C and stirred for 16 h whilst being open to air. Once cooled, the reaction was evaporated *in vacuo* and the residue dry loaded onto silica. Purification was accomplished by flash chromatography on silica gel (3 x 14) eluting with MeOH/CH_2Cl_2 (5-7.5%) to yield the title compound as a pale yellow solid. Recrystallisation in EtOAc/Et_2O gave the title compound (20 mg, 27%) as an off white solid. The filtrate was concentrated *in vacuo,* to yield an additional amount of title compound (12 mg, 16%) as a pale yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$) 2.60 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 2.81 (app t, J = 4.5 Hz, 4H, CH_2), 3.76 (s, 2H, CH_2), 3.87 (app s, 4H, CH_2), 3.90 (s, 3H, NCH_3), 7.77 (br s, 1H, CH_{ar}), 7.96 (br s, 1H, CH_{ar}), 12.18 (s, 1H, NH); LC - MS (ESI,

m/z): Rt = 1.95 min – 428, 430 [$(M + H)^+$, Cl isotopic pattern]; HRMS: Found: 450.1527, calculated for $C_{19}H_{22}N_9OClNa$ $(M+Na)^+$: 450.1528; HPLC: Rt = 5.90 min: 94%, λ= 309 nm.

tert-Butyl 4-((1-methyl-1*H*-1,2,4-triazol-3-yl)methyl)piperazine-1-carboxylate (24d)

To a solution of Boc-piperazine (217 mg, 1.16 mmol) and 3-(chloromethyl)-1-methyl-1*H*-1,2,4-triazole HCl salt (200 mg, 1.19 mmol) in CH_2Cl_2 (8 mL) was added triethylamine (0.45 mL, 3.24 mmol). The reaction mixture was stirred at room temperature for 20 h and then at 50 °C for 18 h before being concentrated *in vacuo*. Purification of the crude product was accomplished by flash chromatography on silica gel to yield the title compound (290 mg, 89%).^{1}H-NMR (500 MHz, $CDCl_3$) 1.45 (s, 9H, $C(CH_3)_3$), 2.44 (br s, 4H, piperazine N-CH), 3.42 (br t, J = 4.6 Hz, 4H, piperazine N-CH), 3.70 (s, 2H, N*CH*$_2$-triazole), 3.94 (s, 3H, N-CH_3), 7.80 (s, 1H, triazole C-H); LC - MS (ESI, *m/z*): Rt = 1.56 min (absorbs weakly) – 304 $(M+Na)^+$.

5-Chloro-4-(4-((1-methyl-1*H*-1,2,4-triazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (26d)

To a solution of *tert*-butyl 4-((1-methyl-1*H*-1,2,4-triazol-3-yl)methyl)piperazine-1-carboxylate (142 mg, 0.51 mmol) in CH_2Cl_2 (30 mL) was added TFA (3.0 mL) and the solution was stirred at room temperature for 16 h. The reaction was concentrated *in vacuo* to give a yellow oil (**25d**). The crude oil was dissolved in ^{i}PrOH (6.3 mL) and both 2-amino-3-nitro-4,5-dichloropyridine (100 mg, 0.48 mmol) and DIPEA (377 µl, 2.16 mmol) were added, and the reaction mixture was stirred at 50 °C for 4½ hr. On cooling a yellow precipitate

formed which was filtered, washed with ice cold ^{i}PrOH then Et_2O, dried *in vacuo* to yield the title compound as a yellow solid (142 mg, 84%). ^{1}H-NMR (500 MHz, $CDCl_3$) 2.66 (app t, *J* = 4.7 Hz, 4H, CH_2), 3.21 (app t, *J* = 4.7 Hz, 4H, CH_2), 3.78 (s, 2H, CH_2C), 3.98 (s, 3H, CH_3), 5.80 (s, 2H, NH_2), 7.81 (s, 1H, CH_{ar}), 8.03 (s, 1H, C(Cl)CH); LC - MS (ESI, *m/z*): Rt = 1.50 min – 353, 355 [$(M + H)^+$, Cl isotopic pattern].

6-Chloro-2-(1,3-dimethyl-1*H*-pyrazol-4-yl)-7-(4-((1-methyl-1*H*-1,2,4-triazol-3-yl)methyl)piperazin-1-yl)-3*H*-imidazo[4,5-*b*]pyridine (27d)

To a solution of 5-chloro-4-(4-((1-methyl-1*H*-1,2,4-triazol-3-yl)methyl)piperazin-1-yl)-3-nitropyridin-2-amine (45 mg, 0.128 mmol) and 1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (16.6 mg, 0.134 mmol) in EtOH (2.97 mL) was added 1M $Na_2S_2O_4$ (0.589 mL, 0.589 mmol, freshly prepared) and the solution heated to 80 °C, whilst being open to air. After 22 h an additional 4 eq. of 1M aqueous $Na_2S_2O_4$ (0.589 mL, 0.589 mmol, freshly prepared) was added and the reaction heated for a further 67 h. Once cooled, the reaction was evaporated *in vacuo* and the residue dry loaded onto silica. Purification was accomplished by flash chromatography on silica gel (3 x 16) eluting with MeOH/CH_2Cl_2 (5-10%) to yield the title compound (23 mg, 42 % yield) as a pale yellow film. ^{1}H-NMR (500 MHz, $CDCl_3$) 2.59 (s, 3H, CH_3), 2.68 (app s, 4H, CH_2), 3.75 (app s, 4H, CH_2), 3.78 (s, 2H, CH_2), 3.83 (br s, 3H, NCH_3), 4.01 (s, 3H, NCH_3), 7.60 (br s, 1H, CH_{ar}), 7.84 (s, 1H, CHCCl), 7.87 (br s, 1H, CH_{ar}), 13.29 (s, 1H, NH); LC - MS (ESI, *m/z*): Rt = 1.79 min – 427, 429 [$(M + H)^+$, Cl isotopic pattern]; HRMS: Found: 427.1871, calculated for $C_{19}H_{24}N_{10}Cl$ $(M+H)^+$: 427.1868; HPLC: Rt = 5.27 min; 92%, λ = 309 nm.

***tert*-Butyl 4-(pyrimidin-5-ylmethyl)piperazine-1-carboxylate (24f)**

To a solution of 1-Boc-piperazine (0.45 g, 2.40 mmol) in anhydrous dichloromethane (25 mL) was added 5-formylpyrimidine (0.260 g, 2.40 mmol) followed by sodium triacetoxyborohydride (0.600g, 2.76 mmol) and acetic acid (0.144 g, 2.40 mmol). The reaction mixture was stirred at room temperature for 6 h, and then diluted with chloroform (25 mL), washed with a 10% aqueous $NaHCO_3$ solution (2 x 40 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$), and concentrated *in vacuo*. The title compound was obtained as a white solid (0.611 g, 92%). ^{1}H-NMR (500 MHz, DMSO-d_6) 1.38 (s, 9H, $CO_2(CH_3)_3$), 2.32 (t, J = 5.0 Hz, 4H, piperazine N-CH), 3.30 (br s, 4H, piperazine N-CH), 3.53 (s, 2H, N*CH*$_2$-pyrimidine), 8.72 (s, 2H, pyrimidine 4-H and pyrimidine 6-H) 9.09 (s, 1H, pyrimidine 2-H); LC - MS (ESI, *m/z*): Rt = 1.24 min – 223 $(M\text{-}^tBu)^+$, 179 $(M\text{-}BOC)^+$.

5-Chloro-3-nitro-4-(4-(pyrimidin-5-ylmethyl)piperazin-1-yl)pyridin-2-amine (26f)

A solution of *tert*-butyl 4-(pyrimidin-5-ylmethyl)piperazine-1-carboxylate (0.567 g, 2.03 mmol) in TFA (12 mL) and dichloromethane (17 mL) was stirred at room temperature for 2 h and 15 min. The solvents were then removed under reduced pressure and azeotroped with toluene. The resultant residue (**25f**) was dissolved in isopropanol (34 mL), and to this solution 4,5-dichloro-3-nitropyridin-2-amine (0.395 g, 1.90 mmol) was added followed by diisopropylethylamine (1.77 mL, 10.15 mmol). The reaction mixture was stirred at 45 ^oC for 18 h, it was then allowed to cool to room temperature and diluted with isopropanol (20 mL). The yellow precipitate was collected by filtration, washed with isopropanol, diethyl ether, and dried (0.380 g, 54%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.50 (br s, obscured by solvent peak, piperazine N-CH), 3.06 (br s, 4H, piperazine N-CH), 3.59 (s, 2H, N*CH*$_2$-pyrimidine),

7.00 (s, 2H, NH_2), 8.07 (s, 1H, pyridine 6-H), 8.75 (s, 2H, pyrimidine 4-H and pyrimidine 6-H) 9.10 (s, 1H, pyrimidine 2-H); LC - MS (ESI, *m/z*): Rt = 1.16 min – 350, 352 [$(M+H)^+$, Cl isotopic pattern].

6-Chloro-2-(1,3-dimethyl-1*H*-pyrazol-4-yl)-7-(4-(pyrimidin-5-ylmethyl)piperazin-1-yl)-3*H*-imidazo[4,5-*b*]pyridine (27f)

To a mixture of 5-chloro-3-nitro-4-(4-(pyrimidin-5-ylmethyl)piperazin-1-yl)pyridin-2-amine (0.070 g, 0.20 mmol) and EtOH (3.5 mL) was added 1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (0.027 g, 0.22 mmol) followed by a freshly prepared aqueous solution of $Na_2S_2O_4$ (1M; 0.80 mL, 0.80 mmol). The reaction mixture was stirred at 80 ^oC for 18 h, it was then allowed to cool to room temperature, and concentrated *in vacuo*. The resultant residue was absorbed on silica gel, placed on a 10 g isolute silica column which was first eluted with ethyl acetate / dichloromethane (v:v; 1:1), and then 4%, 6%, and 10% methanol in ethyl acetate. The product obtained was triturated with diethyl ether, the yellow precipitate was collected by filtration, and it was successively washed with diethyl ether (2 x 5 mL), water (4 x 3 mL), diethyl ether (3 x4 mL), then dried *in vacuo* over P_2O_5 (0.013 g, 15%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.51 (s, obscured by solvent peak, 3H, pyrazole 3-CH_3), 2.61 (br s, 4H, piperazine N-CH), 3.62 (s, 2H, NCH_2-pyrimidine), 3.69 (s, 4H, piperazine N-CH), 3.84 (s, 3H, pyrazole N-CH_3), 8.02 (s, 1H) and 8.18 (s, 1H) (imidazo[4,5-*b*]pyridine 5-H and pyrazole 5-H), 8.78 (s, 2H, pyrimidine 4-H and pyrimidine 6-H) 9.11 (s, 1H, pyrimidine 2-H), 12.96 (br s, 1H, imidazo[4,5-*b*]pyridine N-H); LC - MS (ESI, *m/z*): Rt = 1.58 min – 424, 426 [$(M+H)^+$, Cl isotopic pattern]; HRMS: Found: 424.1761, calculated for $C_{20}H_{23}ClN_9$ $(M+H)^+$: 424.1760.

***tert*-Butyl 4-(pyrazin-2-ylmethyl)piperazine-1-carboxylate (24g)**

To a solution of 1-Boc-piperazine (0.298 g, 1.60 mmol) in anhydrous dichloromethane (22 mL) was added pyrazine-2-carbaldehyde (0.173 g, 1.60 mmol) followed by sodium triacetoxyborohydride (0.392g, 1.76 mmol) and acetic acid (0.096 g, 1.6 mmol). The reaction mixture was stirred at room temperature for 6.5 h; it was then was diluted with dichloromethane (25 mL) and washed with a 10% aqueous $NaHCO_3$ solution (2 x 35 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$), and concentrated in vacuo to afford the title compound as a yellow oily residue (0.403 g, 91%). ^{1}H-NMR (500 MHz, DMSO-d_6) 1.39 (s, 9H, $CO_2(CH_3)_3$), 2.39 (t, J = 5.2 Hz, 4H, piperazine N-CH_2), 3.32 (t, J = 4.60 Hz, 4H. piperazine N-CH_2), 3.67 (s, 2H, N*CH_2*-pyrazine), 8.53 (d, J = 2.5 Hz, 1H, pyrazine C-H), 8.57 (dd, J = 1.4, 2.2 Hz, 1H, pyrazine C-H), 8.68 (d, J = 1.2 Hz, 1H, pyrazine C-H); LC - MS (ESI, *m/z*): Rt = 1.20 min – 223 [(M-^{t}Bu)$^+$, 80%], 179 (M-BOC)$^+$, 100%].

5-Chloro-3-nitro-4-(4-(pyrazin-2-ylmethyl)piperazin-1-yl)pyridin-2-amine (26g)

A solution of *tert*-butyl 4-(pyrazin-2-ylmethyl)piperazine-1-carboxylate (0.336 g, 1.21 mmol) in TFA (7 mL) and dichloromethane (10 mL) was stirred at room temperature for 2 h. The solvents were then removed under reduced pressure and azeotroped with toluene. The resultant residue (**25g**) was dissolved in isopropanol (20 mL), and to this solution 4,5-dichloro-3-nitropyridin-2-amine (0.235 g, 1.13 mmol) was added followed by diisopropylethylamine (1.07 mL, 6.0 mmol). The reaction mixture was stirred at 45 ^{o}C for 20 h; it was then allowed to cool to room temperature and diluted with isopropanol (10 mL). The yellow precipitate was collected by filtration, washed with isopropanol, diethyl ether, and

dried (0.195 g, 47%). ^{1}H-NMR (500 MHz, DMSO-d_6) 2.58 (br s, 4H, piperazine N-CH), 3.08 (br t, J = 4.4 Hz, 4H, piperazine N-CH), 3.73 (s, 2H, N*CH*$_2$-pyrazine), 6.95 (s, 2H, NH_2), 8.06 (s, 1H, pyridine 6-H), 8.54 (d, J = 2.5 Hz, 1H, pyrazine C-H), 8.58 (dd, J = 1.5, 2.5 Hz, 1H, pyrazine C-H), 8.71 (d, J = 1.3 Hz, 1H, pyrazine C-H); LC - MS (ESI, *m/z*): Rt = 1.16 min – 350, 352 [$(M+H)^+$, Cl isotopic pattern].

6-Chloro-2-(1,3-dimethyl-1*H*-pyrazol-4-yl)-7-(4-(pyrazin-2-ylmethyl)piperazin-1-yl)-3*H*-imidazo[4,5-*b*]pyridine (27g)

To a mixture of 5-chloro-3-nitro-4-(4-(pyrazin-2-ylmethyl)piperazin-1-yl)pyridin-2-amine (0.070 g, 0.20 mmol) and EtOH (3.5 mL) was added 1,3-dimethyl-1*H*-pyrazole-4-carbaldehyde (0.028 g, 0.22 mmol) followed by a freshly prepared aqueous solution of $Na_2S_2O_4$ (1M; 0.90 mL, 0.90 mmol). The reaction mixture was stirred at 80 ^oC for 20 h, it was then allowed to cool to room temperature, and concentrated *in vacuo*. The resultant residue was absorbed on silica gel, placed on a 10 g isolute silica column which was first eluted with ethyl acetate / dichloromethane (v:v; 1:1), then 5%, 10% methanol in ethyl acetate / dichloromethane (v:v; 1:1), and finally 10% methanol in ethyl acetate. The product obtained was triturated with diethyl ether, the yellow precipitate was collected by filtration, and successively washed with diethyl ether (2 x 5 mL), water (4 x 3 mL), diethyl ether (3 x 4 mL), then dried *in vacuo* over P_2O_5 (0.010 g, 12%); ^{1}H-NMR (500 MHz, DMSO-d_6) 2.51 (s, 3H, pyrazole-CH_3), 2.67 (br s, 4H, piperazine N-CH), 3.70 (br t, J = 4.5 Hz, 4H, piperazine N-CH), 3.76 (s, 2H, N*CH*$_2$-pyrazine), 3.84 (s, 3H, pyrazole N-CH_3), 8.02 (s, 1H) and 8.18 (s, 1H) (imidazo[4,5-*b*]pyridine 5-H and pyrazole 5-H), 8.54 (d, J = 2.7 Hz, 1H, pyrazine C-H), 8.60 (m, 1H, pyrazine C-H), 8.74 (d, J = 1.2 Hz, 1H, pyrazine C-H), 12.97 (br s, 1H,

imidazo[4,5-*b*]pyridine N-H); LC - MS (ESI, *m/z*): Rt = 1.60 min – 424, 426 [$(M+H)^+$, Cl isotopic pattern]. HRMS: Found: 424.1758, calculated for $C_{20}H_{23}ClN_9$ $(M+H)^+$: 424.1759.

Table S1: Summary of Crystallographic Analysis of Compound **21a**

Crystals		
Spacegroup		$P4_12_12$
Lattice constants	*a* (Å)	83.56
	b (Å)	83.56
	c (Å)	76.15
	α, β, γ (°)	90.00
Data collection		
X-ray source		DIAMOND I03
Resolution range (Å)		76.25-2.50 (2.64-2.5)
(Highest resolution shell)		
Unique reflections		9,791
Completeness(%)		99.7 (100.0)
Multiplicity		4.0 (4.2)
Rmerge (%)		8.3 (32.7)
I/σ(I)		14.4 (3.5)
Refinement		
Resolution range (Å)		19.80-2.50
*R*factor (%)		20.20
*R*free[a] (%)		26.30
RMSD bonds (Å)		0.008
RMSD angles (°)		1.16
Average B		44.1
Molprobity analysis		
Ramachandran favored (%)		96.7
Ramachandran outliers (%)		0.8
Rotamer outliers (%)		8.6
Clashscore (%)		10.76

[a] Free *R*factor was computed using 5% of the data assigned randomly (Brunger, 1992).

Table S2: Kinase selectivity profiling of compound **27e** in a 442-kinase panel screened at a concentration of 1 μM; KINOMEScan™ technology.

KINOMEscan Gene Symbol	Entrez Gene Symbol	Percent Control
AAK1	AAK1	97
ABL1(E255K)-phosphorylated	ABL1	77
ABL1(F317I)-nonphosphorylated	ABL1	100
ABL1(F317I)-phosphorylated	ABL1	65
ABL1(F317L)-nonphosphorylated	ABL1	100
ABL1(F317L)-phosphorylated	ABL1	89
ABL1(H396P)-nonphosphorylated	ABL1	100
ABL1(H396P)-phosphorylated	ABL1	99
ABL1(M351T)-phosphorylated	ABL1	60
ABL1(Q252H)-nonphosphorylated	ABL1	100
ABL1(Q252H)-phosphorylated	ABL1	84
ABL1(T315I)-nonphosphorylated	ABL1	100
ABL1(T315I)-phosphorylated	ABL1	85
ABL1(Y253F)-phosphorylated	ABL1	100
ABL1-nonphosphorylated	ABL1	94
ABL1-phosphorylated	ABL1	100
ABL2	ABL2	100
ACVR1	ACVR1	90
ACVR1B	ACVR1B	68
ACVR2A	ACVR2A	100
ACVR2B	ACVR2B	72
ACVRL1	ACVRL1	100
ADCK3	CABC1	80
ADCK4	ADCK4	45
AKT1	AKT1	100
AKT2	AKT2	100
AKT3	AKT3	100
ALK	ALK	100
AMPK-alpha1	PRKAA1	2.4
AMPK-alpha2	PRKAA2	0.9
ANKK1	ANKK1	89
ARK5	NUAK1	9.6
ASK1	MAP3K5	100
ASK2	MAP3K6	100
AURKA	AURKA	3.4
AURKB	AURKB	1
AURKC	AURKC	16
AXL	AXL	2.2
BIKE	BMP2K	6.7

BLK	BLK	100
BMPR1A	BMPR1A	62
BMPR1B	BMPR1B	100
BMPR2	BMPR2	100
BMX	BMX	100
BRAF	BRAF	100
BRAF(V600E)	BRAF	100
BRK	PTK6	96
BRSK1	BRSK1	100
BRSK2	BRSK2	100
BTK	BTK	100
CAMK1	CAMK1	100
CAMK1D	CAMK1D	100
CAMK1G	CAMK1G	100
CAMK2A	CAMK2A	95
CAMK2B	CAMK2B	94
CAMK2D	CAMK2D	94
CAMK2G	CAMK2G	100
CAMK4	CAMK4	100
CAMKK1	CAMKK1	100
CAMKK2	CAMKK2	100
CASK	CASK	84
CDC2L1	CDK11B	100
CDC2L2	CDC2L2	100
CDC2L5	CDK13	77
CDK11	CDK19	100
CDK2	CDK2	60
CDK3	CDK3	95
CDK4-cyclinD1	CDK4	76
CDK4-cyclinD3	CDK4	74
CDK5	CDK5	76
CDK7	CDK7	100
CDK8	CDK8	75
CDK9	CDK9	100
CDKL1	CDKL1	100
CDKL2	CDKL2	29
CDKL3	CDKL3	100
CDKL5	CDKL5	99
CHEK1	CHEK1	100
CHEK2	CHEK2	100
CIT	CIT	83
CLK1	CLK1	63
CLK2	CLK2	77
CLK3	CLK3	88
CLK4	CLK4	100

CSF1R	CSF1R	50
CSK	CSK	100
CSNK1A1	CSNK1A1	77
CSNK1A1L	CSNK1A1L	93
CSNK1D	CSNK1D	100
CSNK1E	CSNK1E	99
CSNK1G1	CSNK1G1	100
CSNK1G2	CSNK1G2	96
CSNK1G3	CSNK1G3	100
CSNK2A1	CSNK2A1	97
CSNK2A2	CSNK2A2	67
CTK	MATK	82
DAPK1	DAPK1	80
DAPK2	DAPK2	80
DAPK3	DAPK3	84
DCAMKL1	DCLK1	80
DCAMKL2	DCLK2	100
DCAMKL3	DCLK3	14
DDR1	DDR1	55
DDR2	DDR2	96
DLK	MAP3K12	81
DMPK	DMPK	100
DMPK2	CDC42BPG	100
DRAK1	STK17A	13
DRAK2	STK17B	21
DYRK1A	DYRK1A	82
DYRK1B	DYRK1B	75
DYRK2	DYRK2	100
EGFR	EGFR	100
EGFR(E746-A750del)	EGFR	94
EGFR(G719C)	EGFR	86
EGFR(G719S)	EGFR	100
EGFR(L747-E749del, A750P)	EGFR	100
EGFR(L747-S752del, P753S)	EGFR	42
EGFR(L747-T751del,Sins)	EGFR	97
EGFR(L858R)	EGFR	100
EGFR(L858R,T790M)	EGFR	91
EGFR(L861Q)	EGFR	84
EGFR(S752-I759del)	EGFR	60
EGFR(T790M)	EGFR	82
EIF2AK1	EIF2AK1	100
EPHA1	EPHA1	90
EPHA2	EPHA2	100
EPHA3	EPHA3	100
EPHA4	EPHA4	100

EPHA5	EPHA5	100
EPHA6	EPHA6	100
EPHA7	EPHA7	100
EPHA8	EPHA8	100
EPHB1	EPHB1	100
EPHB2	EPHB2	100
EPHB3	EPHB3	77
EPHB4	EPHB4	100
EPHB6	EPHB6	73
ERBB2	ERBB2	70
ERBB3	ERBB3	95
ERBB4	ERBB4	100
ERK1	MAPK3	100
ERK2	MAPK1	100
ERK3	MAPK6	87
ERK4	MAPK4	96
ERK5	MAPK7	100
ERK8	MAPK15	8.2
ERN1	ERN1	83
FAK	PTK2	95
FER	FER	100
FES	FES	100
FGFR1	FGFR1	62
FGFR2	FGFR2	45
FGFR3	FGFR3	70
FGFR3(G697C)	FGFR3	69
FGFR4	FGFR4	68
FGR	FGR	100
FLT1	FLT1	0.3
FLT3	FLT3	0.4
FLT3(D835H)	FLT3	0.75
FLT3(D835Y)	FLT3	5.6
FLT3(ITD)	FLT3	3.3
FLT3(K663Q)	FLT3	0.8
FLT3(N841I)	FLT3	0
FLT3(R834Q)	FLT3	97
FLT4	FLT4	0
FRK	FRK	100
FYN	FYN	100
GAK	GAK	94
GCN2(Kin.Dom.2,S808G)	EIF2AK4	100
GRK1	GRK1	100
GRK4	GRK4	41
GRK7	GRK7	97
GSK3A	GSK3A	100

GSK3B	GSK3B	68
HCK	HCK	100
HIPK1	HIPK1	66
HIPK2	HIPK2	70
HIPK3	HIPK3	50
HIPK4	HIPK4	85
HPK1	MAP4K1	74
HUNK	HUNK	66
ICK	ICK	92
IGF1R	IGF1R	100
IKK-alpha	CHUK	100
IKK-beta	IKBKB	100
IKK-epsilon	IKBKE	100
INSR	INSR	100
INSRR	INSRR	100
IRAK1	IRAK1	56
IRAK3	IRAK3	16
IRAK4	IRAK4	74
ITK	ITK	100
JAK1(JH1domain-catalytic)	JAK1	46
JAK1(JH2domain-pseudokinase)	JAK1	100
JAK2(JH1domain-catalytic)	JAK2	1.3
JAK3(JH1domain-catalytic)	JAK3	0.85
JNK1	MAPK8	93
JNK2	MAPK9	100
JNK3	MAPK10	100
KIT	KIT	4.6
KIT(A829P)	KIT	64
KIT(D816H)	KIT	71
KIT(D816V)	KIT	9.2
KIT(L576P)	KIT	19
KIT(V559D)	KIT	2.5
KIT(V559D,T670I)	KIT	19
KIT(V559D,V654A)	KIT	83
LATS1	LATS1	89
LATS2	LATS2	77
LCK	LCK	100
LIMK1	LIMK1	58
LIMK2	LIMK2	75
LKB1	STK11	100
LOK	STK10	100
LRRK2	LRRK2	100
LRRK2(G2019S)	LRRK2	85
LTK	LTK	100
LYN	LYN	86

LZK	MAP3K13	88
MAK	MAK	85
MAP3K1	MAP3K1	100
MAP3K15	MAP3K15	66
MAP3K2	MAP3K2	77
MAP3K3	MAP3K3	91
MAP3K4	MAP3K4	94
MAP4K2	MAP4K2	85
MAP4K3	MAP4K3	62
MAP4K4	MAP4K4	88
MAP4K5	MAP4K5	79
MAPKAPK2	MAPKAPK2	100
MAPKAPK5	MAPKAPK5	97
MARK1	MARK1	78
MARK2	MARK2	93
MARK3	MARK3	45
MARK4	MARK4	29
MAST1	MAST1	100
MEK1	MAP2K1	100
MEK2	MAP2K2	100
MEK3	MAP2K3	100
MEK4	MAP2K4	100
MEK5	MAP2K5	58
MEK6	MAP2K6	73
MELK	MELK	100
MERTK	MERTK	100
MET	MET	83
MET(M1250T)	MET	93
MET(Y1235D)	MET	76
MINK	MINK1	84
MKK7	MAP2K7	100
MKNK1	MKNK1	100
MKNK2	MKNK2	46
MLCK	MYLK3	100
MLK1	MAP3K9	15
MLK2	MAP3K10	5.4
MLK3	MAP3K11	9.8
MRCKA	CDC42BPA	40
MRCKB	CDC42BPB	55
MST1	STK4	100
MST1R	MST1R	100
MST2	STK3	100
MST3	STK24	85
MST4	MST4	100
MTOR	MTOR	98

MUSK	MUSK	100
MYLK	MYLK	89
MYLK2	MYLK2	61
MYLK4	MYLK4	94
MYO3A	MYO3A	100
MYO3B	MYO3B	100
NDR1	STK38	86
NDR2	STK38L	90
NEK1	NEK1	82
NEK11	NEK11	100
NEK2	NEK2	100
NEK3	NEK3	100
NEK4	NEK4	82
NEK5	NEK5	23
NEK6	NEK6	100
NEK7	NEK7	100
NEK9	NEK9	79
NIM1	MGC42105	100
NLK	NLK	72
OSR1	OXSR1	66
p38-alpha	MAPK14	71
p38-beta	MAPK11	100
p38-delta	MAPK13	100
p38-gamma	MAPK12	100
PAK1	PAK1	100
PAK2	PAK2	97
PAK3	PAK3	32
PAK4	PAK4	100
PAK6	PAK6	100
PAK7	PAK7	83
PCTK1	CDK16	75
PCTK2	CDK17	97
PCTK3	CDK18	100
PDGFRA	PDGFRA	93
PDGFRB	PDGFRB	4
PDPK1	PDPK1	100
PFCDPK1(P.falciparum)	CDPK1	100
PFPK5(P.falciparum)	MAL13P1.279	100
PFTAIRE2	CDK15	100
PFTK1	CDK14	100
PHKG1	PHKG1	100
PHKG2	PHKG2	100
PIK3C2B	PIK3C2B	100
PIK3C2G	PIK3C2G	100
PIK3CA	PIK3CA	100

PIK3CA(C420R)	PIK3CA	100
PIK3CA(E542K)	PIK3CA	94
PIK3CA(E545A)	PIK3CA	75
PIK3CA(E545K)	PIK3CA	100
PIK3CA(H1047L)	PIK3CA	100
PIK3CA(H1047Y)	PIK3CA	100
PIK3CA(I800L)	PIK3CA	90
PIK3CA(M1043I)	PIK3CA	92
PIK3CA(Q546K)	PIK3CA	76
PIK3CB	PIK3CB	97
PIK3CD	PIK3CD	81
PIK3CG	PIK3CG	100
PIK4CB	PI4KB	100
PIM1	PIM1	100
PIM2	PIM2	100
PIM3	PIM3	100
PIP5K1A	PIP5K1A	16
PIP5K1C	PIP5K1C	84
PIP5K2B	PIP4K2B	28
PIP5K2C	PIP4K2C	80
PKAC-alpha	PRKACA	57
PKAC-beta	PRKACB	48
PKMYT1	PKMYT1	95
PKN1	PKN1	16
PKN2	PKN2	33
PKNB(M.tuberculosis)	pknB	56
PLK1	PLK1	100
PLK2	PLK2	93
PLK3	PLK3	88
PLK4	PLK4	84
PRKCD	PRKCD	100
PRKCE	PRKCE	97
PRKCH	PRKCH	100
PRKCI	PRKCI	97
PRKCQ	PRKCQ	100
PRKD1	PRKD1	100
PRKD2	PRKD2	100
PRKD3	PRKD3	100
PRKG1	PRKG1	100
PRKG2	PRKG2	92
PRKR	EIF2AK2	95
PRKX	PRKX	18
PRP4	PRPF4B	100
PYK2	PTK2B	100
QSK	KIAA0999	100

RAF1	RAF1	69
RET	RET	1.8
RET(M918T)	RET	2
RET(V804L)	RET	2.1
RET(V804M)	RET	22
RIOK1	RIOK1	9.2
RIOK2	RIOK2	97
RIOK3	RIOK3	2.8
RIPK1	RIPK1	78
RIPK2	RIPK2	100
RIPK4	RIPK4	74
RIPK5	DSTYK	100
ROCK1	ROCK1	50
ROCK2	ROCK2	35
ROS1	ROS1	100
RPS6KA4(Kin.Dom.1-N-terminal)	RPS6KA4	62
RPS6KA4(Kin.Dom.2-C-terminal)	RPS6KA4	98
RPS6KA5(Kin.Dom.1-N-terminal)	RPS6KA5	100
RPS6KA5(Kin.Dom.2-C-terminal)	RPS6KA5	100
RSK1(Kin.Dom.1-N-terminal)	RPS6KA1	100
RSK1(Kin.Dom.2-C-terminal)	RPS6KA1	92
RSK2(Kin.Dom.1-N-terminal)	RPS6KA3	84
RSK3(Kin.Dom.1-N-terminal)	RPS6KA2	100
RSK3(Kin.Dom.2-C-terminal)	RPS6KA2	100
RSK4(Kin.Dom.1-N-terminal)	RPS6KA6	66
RSK4(Kin.Dom.2-C-terminal)	RPS6KA6	89
S6K1	RPS6KB1	92
SBK1	SBK1	80
SgK110	SgK110	15
SGK3	SGK3	100
SIK	SIK1	100
SIK2	SIK2	36
SLK	SLK	100
SNARK	NUAK2	32
SNRK	SNRK	100
SRC	SRC	100
SRMS	SRMS	100
SRPK1	SRPK1	7.8
SRPK2	SRPK2	97
SRPK3	SRPK3	39
STK16	STK16	18
STK33	STK33	100
STK35	STK35	75
STK36	STK36	74
STK39	STK39	100

SYK	SYK	100
TAK1	MAP3K7	100
TAOK1	TAOK1	79
TAOK2	TAOK2	73
TAOK3	TAOK3	87
TBK1	TBK1	90
TEC	TEC	100
TESK1	TESK1	87
TGFBR1	TGFBR1	83
TGFBR2	TGFBR2	100
TIE1	TIE1	47
TIE2	TEK	56
TLK1	TLK1	66
TLK2	TLK2	92
TNIK	TNIK	93
TNK1	TNK1	60
TNK2	TNK2	98
TNNI3K	TNNI3K	93
TRKA	NTRK1	80
TRKB	NTRK2	44
TRKC	NTRK3	57
TRPM6	TRPM6	100
TSSK1B	TSSK1B	100
TTK	TTK	100
TXK	TXK	100
TYK2(JH1domain-catalytic)	TYK2	6.2
TYK2(JH2domain-pseudokinase)	TYK2	100
TYRO3	TYRO3	73
ULK1	ULK1	78
ULK2	ULK2	100
ULK3	ULK3	85
VEGFR2	KDR	12
VRK2	VRK2	100
WEE1	WEE1	96
WEE2	WEE2	99
YANK1	STK32A	100
YANK2	STK32B	100
YANK3	STK32C	100
YES	YES1	96
YSK1	STK25	70
YSK4	YSK4	67
ZAK	ZAK	71
ZAP70	ZAP70	100