Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Design of 7-amino-6-chloro-3*H*-imidazo[4,5-*b*]pyridine scaffold from 5-chloro-2,4-diaminopyrimidine pharmacophore: Identification of potent inhibitors of Anaplastic Lymphoma Kinase

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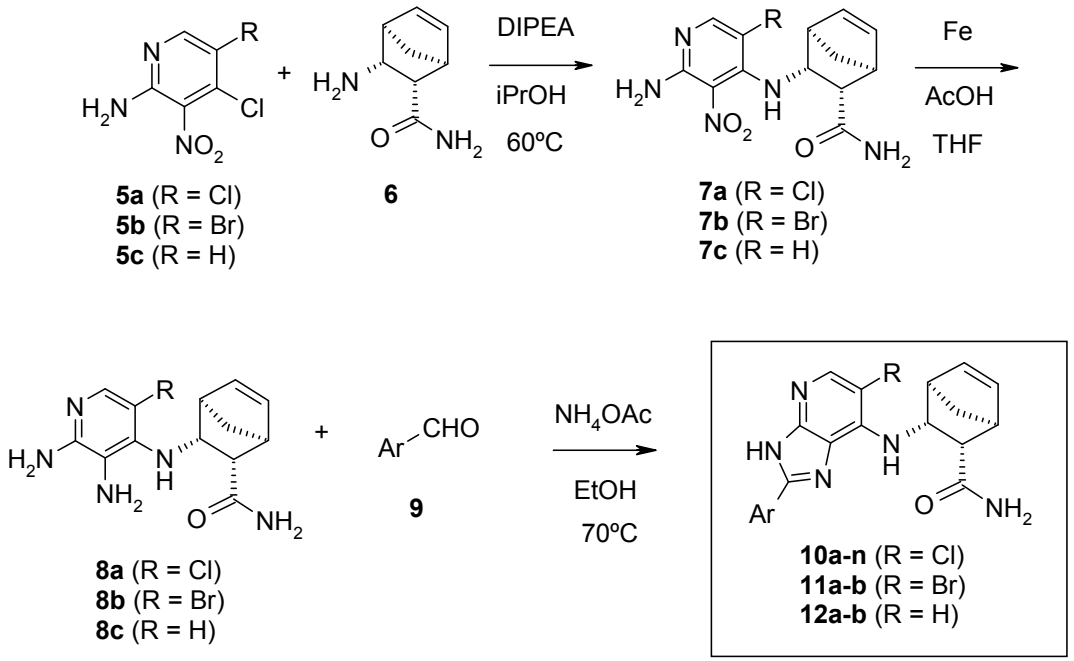
Supplementary Information

General: All commercial reagents and solvents were used as received, unless otherwise indicated. ^{1}H-NMR spectra were recorded on a Bruker Avance spectrometer at 400 MHz, in the solvent indicated, with tetramethylsilane as an internal standard. To asses the purity of the final compounds, analytical HPLC was run on a Zorbax RX-C8, 5 × 150 mm column, eluting with a 10-100% gradient mixture of acetonitrile and water containing 0.1% trifluoroacetic acid, over 5 minutes; purity, determined from the UV peak area, was ≥ 95%, unless indicated otherwise. UV detection was set at 254 and 290 nm wavelengths. Second HPLC purity assessment and low resolution mass spectroscopy (LC/MS) data were recorded on either of the following instruments: a Waters Aquity Ultra Performance LC coupled with Micromass LC-ZQ 2000 quadrupole mass spectrometer [2.1 mm x 50 mm Waters Aquity UPLC BEH C18 1.7 μm column; target column temperature 45°C; run time 2 minutes; flow rate 0.600 mL/min; and solvent mixture of 5% (0.1% formic acid/water): 95% (acetonitrile/0.1% formic acid)], or a Bruker Esquire 200 ion trap. High resolution mass spectrometry was performed on a Waters Synapt G2 Q-TOF mass spectrometer by positive ion electrospray using leucine-enkephalin as a lock-mass standard. Automated column chromatography (SiO_2) was performed on CombiFlash Companion instruments (ISCO, Inc.). Melting points were taken on a Mel-Temp apparatus and are uncorrected.



Experimental Procedures and analytical data for **7a-c**, **8a-c**, **10a-n**, **11a-b**, **12a-b**:

(1S,2S,3R,4R)-3-(2-Amino-5-chloro-3-nitro-pyridin-4-ylamino)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (7a). 4,5-Dichloro-3-nitro-pyridin-2-ylamine (1.01g, 4.86 mmol) and (1S,2S,3R,4R)-3-amino-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide trifluoroacetic acid salt (1.5g, 5.5 mmol) were combined with N,N-diisopropylethylamine (3.3g, 26 mmol) in isopropanol (15 mL) and heated at 60°C overnight. The reaction was permitted to cool to room temperature and the orange solid which had formed was isolated by filtration. The solid was washed with 3 mL cold isopropanol and was dried in an air stream to afford 1.493g (95%) of **7a**. ^{1}H-NMR ($CDCl_3$) δ 7.82 (broad s, 1H), 6.54 (broad s, 2H), 6.30-6.28 (m, 1H), 6.224-6.21 (m, 1H), 5.71 (broad s, 1H), 5.47 (broad s, 1H), 4.30 (m, 1H), 3.09 (s, 1H), 2.80 (s, 1H), 2.56 (d, *J*

= 6.8 Hz, 1H), 2.44 (d, *J* = 9.7 Hz, 1H), 1.71 (d, *J* = 9.3 Hz, 1H). LC/MS (ESI+) *m/z* 323.94 (M+H)+.

(1S,2S,3R,4R)-3-(2-Amino-5-bromo-3-nitro-pyridin-4-ylamino)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (7b) was prepared using the exact same procedure as **7a. 7b** was isolated as an orange solid (88% yield). ^{1}H-NMR ($CDCl_3$) δ 9.86 (broad s, 1H), 7.78 (d, J = 5.9 Hz, 1H), 6.37-6.34 (m, 1H), 6.27-6.24 (m, 1H), 6.19-6.16 (m, 1H), 5.77 (broad s, 1H), 5.45 (broad s, 1H), 3.92 (broad s, 1H), 3.07 (broads, 1H), 2.72 (broad s, 1H), 2.56 (d, *J* = 7.9 Hz, 1H), 2.41 (d, *J* = 9.6 Hz, 1H), 1.68 (d, *J* = 9.6 Hz, 1H). LC/MS (ESI+) *m/z* 368, 370 (M+H)+.

(1S,2S,3R,4R)-3-(2-Amino-3-nitro-pyridin-4-ylamino)-bicyclo[2.2.1]hept- 5-ene-2-carboxylic acid amide (7c) was prepared using the exact procedure used to synthesize **7a**. **7c** was isolated as yellow/orange solid (80% yield). ^{1}H-NMR ($CDCl_3$) 7.29 (s, 1H), 7.53 (broad s, 1H), 6.33 (broad s, 2H), 6.27-6.24 (m, 1H), 6.19-6.16 (m, 1H), 5.77 (broad s, 1H), 5.45 (broad s, 1H), 3.92 (broad s, 1H), 3.07 (broads, 1H), 2.72 (broad s, 1H), 2.56 (d, *J* = 7.9 Hz, 1H), 2.41 (d, *J* = 9.6 Hz, 1H), 1.68 (d, *J* = 9.6 Hz, 1H). LC/MS (ESI+) *m/z* 368, 370 (M+H)+.

(1S,2S,3R,4R)-3-(2,3-Diamino-5-chloro-pyridin-4-ylamino)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (8a). (1S,2S,3R,4R)-3-(2-Amino-5-chloro-3-nitro-pyridin-4-ylamino)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (100 mg, 0.3 mmol) was dissolved in a mixture of tetrahydrofuran (1 mL) and acetic acid (1.6 mL). Powdered

iron (121 mg, 2.2 mmol) was added and the mixture was stirred at 30°C for four hours. Two drops of water were added and the suspended solids removed by filtration. The solid was washed with ethyl acetate (5 mL) and the combined filtrates were portioned between ethyl acetate and saturated sodium bicarbonate solution. The organics were extracted with ethyl acetate (3 X 25 mL), dried (sodium sulfate) and concentrated. Purification was effected via ISCO chromatography (12g SiO_2 cartridge, gradient elution: 0 to 15% MeOH/dichloromethane) to afford 77 mg (80%) of the title compound as a tan solid. ^{1}H-NMR (CDCl3): 7.49 (s, 1H), 6.18-6.20 (m, 4H), 6.09 (m, 1H), 4.51 (d, *J* = 11.1 Hz, 1H), 4.09 (broad s, 2H), 3.79 (7, *J* = 9.4 Hz, 1H), 2.97 (s, 1H), 2.64 (s, 1H), 2.53 (d, *J* = 8.2 Hz, 1H), 2.32 (d, *J* = 9.2 Hz, 1H), 2.06 (s, 1H), 1.66 (d, *J* = 9.2 Hz, 1H). LC/MS (ESI+) *m/z* 294.99 (M+H)+.

(1*S*,2*S*,3*R*,4*R*)-3-(2,3-diamino-5-bromo-pyridin-4-ylamino)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (8b) was synthesized using the exact same procedure as **8a**. **8b** was isolated as a tan foam (74% yield). ^{1}H-NMR (DMSO-d_6) δ 7.52 (s, 1H), 7.38 (s, 1H), 6.94 (s, 1H), 6.20 (dd, *J* = 5.7, 2.9 Hz, 1H), 6.07 (dd, *J* = 5.7, 3.0 Hz, 1H), 5.46 (s, 2H), 4.22 (broad s, 2H), 4.08 (d, *J* = 12.0 Hz, 1H), 3.71-3.66 (m, 1H), 2.75 (s, 1H), 2.41 (d, *J* = 8.8 Hz, 1H), 2.31(s,1 H), 1.41 (d, *J* = 8.8 Hz, 1H). LC/MS (ESI+) *m/z* 338, 340 (M+H)+.

(1S,2S,3R,4R)-3-(2,3-Diamino-pyridin-4-ylamino)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (8c) was synthesized using the exact same procedure as **8a**. **8c** was isolated as a white solid (68% yield). ^{1}H-NMR (DMSO-d_6) δ 7.50 (s, 1H), 7.28 (d, *J*

= 5.0 Hz, 1H), 6.93 (s, 1H), 6.26 (broad absorption, 3H), 6.03 (d, *J* = 5.0 Hz, 1H), 5.49 (d, *J* = 9.2 Hz, 1H), 5.02 (broad s, 2H), 3.51 (t, *J* = 8.3 Hz, 1H), 3.29 (s, 1H), 2.78 (s, 1H), 2.62 (s, 1H), 2.22 (d, *J* = 8.7 Hz, 1H), 2.00(s,1 H), 1.36 (d, *J* = 8.2 Hz, 1H). LC/MS (ESI+) did not ionize.

General procedure for synthesis of imidazopyridine compounds: Diamine (1 eq) and aldehyde (1.1 eq) were dissolved in ethanol (4 mL/mmol substrate) and treated with ammonium acetate (1.25 eq.) and the mixture heated to 70^{o}C overnight. The reaction was concentrated and the organics were partitioned between dichloromethane and saturated sodium bicarbonate solution (50 mL each). Concentration of the organics followed by reverse phase HPLC (gradient elution with MeCN mobile phase in water) afforded desired fractions which were subjected to lyophilization or were partitioned between saturated aq. Sodium bicarbonate and ethyl acetate to afford the free base following drying and concentration.

(1*S*,2*S*,3*R*,4*R*)-3-[6-Chloro-2-(4-methoxy-phenyl)-3H-imidazo[4,5-b]pyridin-7-ylamino]-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (10a) isolated as a white lyophilized powder (6 mgs, 16% yield) as the trifluoroacetic acid salt. ^{1}H-NMR ($CDCl_3$) δ 15.54 (broad s, 1H) 8.23 (d, *J* = 7.8 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 2H), 7.79 (s, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.52-6.50 (m, 1H), 6.43-6.41 (m, 1H), 5.86 (broad s, 1H), 5.46 (broad s, 1H), 5.39 (t, *J* = 7.5 Hz, 1H), 3.91 (s, 3H), 3.17 (s, 1H), 3.05 (s, 1H), 2.68 (d, *J* = 8.5 Hz, 1H), 2.33 (d, *J* = 9.5 Hz, 1H), 1.68 (d, *J* = 9.5 Hz, 1H). LC/MS (ESI+) *m/z*

410.15 (M+H)+, purity >95%. HPLC purity 95%. High resolution mass spectrum *m/z* 410.1378 [$(M+H)^+$ calc'd for $C_{22}H_{20}ClN_5O_2$ 410.1384].

(1*S*,2*S*,3*R*,4*R*)-3-[6-chloro-2-(3-methoxy-phenyl)-3H-imidazo[4,5-b]pyridin-7-ylamino]-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (10b) isolated as a white lyophilized powder as the trifluoroacetic acid salt (10 mgs, 34% yield). ^{1}H-NMR ($CDCl_3$) δ 15.77 (broad s, 1H) 8.43 (d, *J* = 8.2 Hz, 1H), 7.80 (s, 1H), 7.67-7.65 (m, 2H), 7.44 (t, *J* = 8.2 Hz, 1H), 7.06-7.03 (m, 1H), 6.51-6.49 (m, 1H), 6.43-6.40 (m, 1H), 5.93 (broad s, 1H), 5.55 (broad s, 1H), 5.36 (t, *J* = 7.7 Hz, 1H), 3.93 (s, 3H), 3.17 (s, 1H), 3.05 (s, 1H), 2.69 (d, *J* = 7.7 Hz, 1H), 2.32 (d, *J* = 9.9 Hz, 1H), 1.67 (d, *J* = 9.9 Hz, 1H). LC/MS (ESI+) *m/z* 409.95 (M+H)+, purity >95%. HPLC purity 98%. High resolution mass spectrum *m/z* 410.1381 [$(M+H)^+$ calc'd for $C_{22}H_{20}ClN_5O_2$ 410.1384].

(1*S*,2*S*,3*R*,4*R*)-3-[6-Chloro-2-(2-methoxy-phenyl)-3H-imidazo[4,5-b]pyridine-7-ylamino]-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (10c) isolated as a white lyophilized powder (45 mgs, 96% yield) as the trifluoroacetic acid salt. ^{1}H-NMR ($CDCl_3$) δ 13.89 (broad s, 1H) 8.31 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.84 (s, 1H), 7.48-7.46 (m, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.50-6.48 (m, 1H), 6.44-6.41 (m, 1H), 6.07 (broad s, 1H), 5.60 (broad s, 1H), 5.39 (t, *J* = 7.7 Hz, 1H), 4.15 (s, 3H), 3.16 (s, 1H), 3.01 (s, 1H), 2.73 (d, *J* = 8.0 Hz, 1H), 2.33 (d, *J* = 9.0 Hz, 1H), 1.67 (d, *J* = 9.4 Hz, 1H). LC/MS (ESI+) *m/z* 410.16 (M+H)+, purity >95%. HPLC purity 97%. High resolution mass spectrum *m/z* 410.1381 [$(M+H)^+$ calc'd for $C_{22}H_{20}ClN_5O_2$ 410.1384].

(1*S*,2*S*,3*R*,4*R*)-3-[6-chloro-2-(3-morpholin-4-yl-phenyl)-3H-imidazo[4,5-b]pyridin- 7-ylamino]-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (10d) isolated as a pale yellow lyophilized powder as a trifluoroacetic acid salt (8 mgs, 20% yield). ^{1}H-NMR ($CDCl_3$) δ 15.96 (broad s, 1H) 8.37 (d, *J* = 8.3 Hz, 1H), 7.83 (s, 1H), 7.71 (s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 8.3 Hz, 1H), 7.06 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.49-6.46 (m, 1H), 6.43-6.41 (m, 1H), 6.07 (broad s, 1H), 5.86 (broad s, 1H), 5.37 (t, *J* = 7.8 Hz, 1H), 3.96-3.96 (m, 4H), 3.35-3.32 (m, 4H), 3.17 (s, 1H), 3.03 (s, 1H), 2.71 (d, *J* = 8.0 Hz, 1H), 2.31 (d, *J* = 9.5 Hz, 1H), 1.67 (d, *J* = 9.3 Hz, 1H). LC/MS (ESI+) *m/z* 465.16 (M+H)+, purity 96%. HPLC purity 95%. High resolution mass spectrum *m/z* 465.1807 [$(M+H)^+$ calc'd for $C_{24}H_{26}ClN_6O_2$ 465.1806].

(1*S*,2*S*,3*R*,4*R*)-3-[6-Chloro-2-(4-morpholin-4-yl-phenyl)-3H-imidazo[4,5-b]pyridin-7-ylamino]-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (10e) isolated as a pale yellow lyophilized powder (28 mgs, 64% yield). ^{1}H-NMR ($CDCl_3$) δ 15.43 (broad s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.9 Hz, 2H), 7.77 (s, 1H), 7.02 (d, *J* = 8.9 Hz, 2H), 6.51-6.49 (m, 1H), 6.426.40 (m, 1H), 5.91 (broad s, 1H), 5.53 (broad s, 1H), 5.40 (t, *J* = 8.0 Hz, 1H), 3.90 (t, *J* = 4.9 Hz, 4H), 3.30 (t, *J* = 4.9 Hz, 4H), 3.17 (s, 1H), 3.04 (s, 1H), 2.68 (d, *J* = 7.9 Hz, 1H), 2.38 (d, *J* = 9.6 Hz, 1H), 1.67 (d, *J* = 9.6 Hz, 1H). LC/MS (ESI+) *m/z* 465.18 (M+H)+, purity >95%. HPLC purity 99%. High resolution mass spectrum *m/z* 465.1805 [$(M+H)^+$ calc'd for $C_{24}H_{26}ClN_6O_2$ 465.1806].

(1*S*,2*S*,3*R*,4*R*)-3-{6-Chloro-2-[4-(4-methyl-piperazin-1-yl)-phenyl]-3H-imidazo[4, 5-b]pyridin-7-ylamino}-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (10f) isolated as an off-white lyophilized powder as a trifluoroacetic acid salt (50.24 mgs, 88% yield) ^{1}H-NMR ($CDCl_3$) δ 15.58 (broad s, 1H) 8.36 (d, *J* = 8.1 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 2H), 7.78 (s, 1H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.49-6.47 (m, 1H), 6.42-6.40 (m, 1H), 5.99 (s, 1H), 5.61 (s, 1H), 5.35 (t, *J* = 8.4 Hz, 1H), 3.38-3.93 (m, 8H), 3.17 (s, 1H), 3.04 (broad absorption, 1H), 3.02 (s, 1H), 2.91 (s, 3H), 2.69 (d, *J* = 8.1 Hz, 1H), 2.31 (d, *J* = 9.3 Hz, 1H), 1.67 (d, *J* = 9.6 Hz, 1H). LC/MS (ESI+) *m/z* 478.14 (M+H)+, purity 99%. HPLC purity 99%. High resolution mass spectrum *m/z* 478.2118 [$(M+H)^+$ calc'd for $C_{25}H_{29}ClN_7O$ 478.2122].

(1*S*,2*S*,3*R*,4*R*)-3-[6-Chloro-2-(1-methyl-1H-pyrazol-4-yl)-3H-imidazo[4,5-b]pyridin-7-ylamino]-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (10g) isolated as a white lyophilized powder as a trifluoroacetic acid salt (40.1 mgs, 88% yield). ^{1}H-NMR ($CDCl_3$) δ 8.26 (d, *J* = 8.3 Hz, 1H), 8.26 (d, *J* = 9.5 Hz, 1H), 7.78 (s, 1H), 6.47-6.44 (m, 1H), 6.416.39 (m, 1H), 5.99 (s, 1H), 5.70 (s, 1H), 5.31 (t, *J* = 8.2 Hz, 1H), 4.02 (s, 3H), 3.16 (s, 1H), 3.00 (s, 1H), 2.68 (d, *J* = 7.6 Hz, 1H), 2.30 (d, *J* = 9.5 Hz, 1H), 1.66 (d, *J* = 9.5 Hz, 1H). LC/MS (ESI+) *m/z* 384.16 (M+H)+, purity 99%. HPLC purity >99%. High resolution mass spectrum *m/z* 384.1337 [$(M+H)^+$ calc'd for $C_{18}H_{19}ClN_7O$ 384.1340].

(1*S*,2*S*,3*R*,4*R*)-3-[6-Chloro-2-(1-piperidin-4-yl-1H-pyrazol-4-yl)-3H-imidazo[4, 5-b]pyridin-7-ylamino]-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (10h) isolated

as a tan solid (770 mgs, 99%). MP 203-205 ^{o}C; ^{1}H-NMR (methanol-d_4) δ 8.27 (s, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 6.44-6.42 (m, 1H), 6.39-6.37 (m, 1H), 5.32 (d, *J* = 8.3 Hz, 1H), 4.87 (s, 3H), 4.45-4.40 (m, 1H), 3.35-3.30 (m, 2H), 3.28-3.24 (m, 2H), 2.98 (s, 1H), 2.90-2.72 (m, 4H), 2.36 (d, *J* = 8.2 Hz, 1H), 2.20-2.18 (m, 2H), 2.07-2.05 (m, 2H), 1.57 (d, *J* = 9.5 Hz, 1H). LC/MS (ESI+) *m/z* 452.9 (M+H)+, purity >95%. HPLC purity 98%. High resolution mass spectrum *m/z* 453.1911 [(M+H)$^{+}$ calc'd for $C_{26}H_{26}ClN_8O$ 453.1918].

(1*S*,2*S*,3*R*,4*R*)-3-[6-Chloro-2-(2-methoxy-4-morpholin-4-yl-phenyl)-3H-imidazo[4, 5-b]pyridin-7-ylamino]-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (10i) isolated as a yellow lyophilized powder (47.5 mgs, 90% yield). ^{1}H-NMR ($CDCl_3$) δ 13.72 (broad s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.81 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 6.62 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.4-6.46 (m, 2H), 6.40 (dd, *J* = 5.5, 2.9 Hz, 1H), 5.95 (broad s, 1H), 5.48 (broad s, 1H), 5.42 (t, *J* = 8.0 Hz, 1H), 4.15 (s, 3H), 3.91 (t, *J* = 4.8 Hz, 4H), 3.33 (t, *J* = 4.8 Hz, 4H), 3.16 (s, 1H), 3.02 (s, 1H), 2.71 (d, *J* = 7.1 Hz, 1H), 2.34 (d, *J* = 9.5 Hz, 1H), 1.69 (d, *J* = 9.2 Hz, 1H). LC/MS (ESI+) *m/z* 495.17 (M+H)+, purity >95%. HPLC purity 97%. High resolution mass spectrum *m/z* 495.1905 [(M+H)$^{+}$ calc'd for $C_{25}H_{28}ClN_6O_3$ 495.1911].

(1*S*,2*S*,3*R*,4*R*)-3-{6-Chloro-2-[2-methoxy-4-(4-methyl-piperazin-1-yl)-phenyl]- 3H-imidazo[4,5-b]pyridin-7-ylamino}-bicyclo[2.2.1]hept-5-ene-2-carboxylic (10j) isolated as a yellow lyophilized powder as the trifluoroacetic acid salt (37.3 mgs, 62% yield). ^{1}H-NMR ($CDCl_3$) δ 13.76 (broad s, 1H), 8.21 (d, *J* = 8.7 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 6.62 (d, *J* = 9.0 Hz, 1H), 6.47 (s, 1H), 6.47-6.43 (m, 1H), 6.42

(broad s, 1H), 6.07 (broad s, 1H), 5.40 (t, *J* = 9.0 Hz, 1H), 4.11 (s, 3H), 3.65-3.90 (m, 4H), 3.40-3.60 (m, 2H), 3.16 (s, 1H), 3.05-3.02 (m, 1H), 2.99 (s, 1H), 2.92 (s, 3H), 2.72 (d, *J* = 8.3 Hz, 1H), 2.32 (d, *J* = 9.0 Hz, 1H), 1.80-2.10 (broad absorption, 2H), 1.68 (d, *J* = 9.0 Hz, 1H). LC/MS (ESI+) *m/z* 508.14 (M+H)+, purity 95%. HPLC purity 95%. High resolution mass spectrum *m/z* 508.2220 [$(M+H)^+$ calc'd for $C_{26}H_{31}ClN_7O_2$ 508.2228].

(1*S*,2*S*,3*R*,4*R*)-3-{6-Chloro-2-[2-methoxy-4-(4-morpholin-4-yl-piperidin-1- yl)-phenyl]-3H-imidazo[4,5-b]pyridin-7-ylamino}-bicyclo[2.2.1]hept-5-ene- 2-carboxylic acid amide (10k) isolated as a yellow/gold lyophilized powder as the trifluoroacetic acid salt (80.8 mgs, 75% yield). ^{1}H-NMR (DMSO-d_6) δ 12.50 (broad s, 1H), 9.85 (broad s, 1H), 8.09 (s, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.83 (broad s, 1H), 7.29 (s, 1H), 6.77 (d, *J* = 8.9 Hz, 1H), 6.66 (s, 1H), 6.38 (s, 2H), 5.17-5.14 (m, 1H), 3.95-4.30 (m, 7H), 3.69 (t, *J* = 11.9 Hz, 2H), 3.51-3.48 (m, 3H), 3.17-3.10 (m, 2H), 2.82-2.96 (m, 4H), 2.63 (d, *J* = 8.1 Hz, 1H), 2.11-2.26 (m, 3H), 2.08 (s, 1H), 1.69 (m, 2H), 1.41 (d, *J* = 8.6 Hz, 1H). LC/MS (ESI+) *m/z* 578.25 (M+H)+, purity >95%. HPLC purity 97%. High resolution mass spectrum *m/z* 578.2650 [$(M+H)^+$ calc'd for $C_{30}H_{36}ClN_7O_3$ 578.2646].

(1*S*,2*S*,3*R*,4*R*)-3-(6-Chloro-2-{2-methoxy-4-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-phenyl}-3H-imidazo[4,5-b]pyridin-7-ylamino)-bicyclo[2.2.1]hept-5- ene-2-carboxylic acid amide (10l) isolated as a yellow/gold colored foam/solid (59 mgs, 60% yield). ^{1}H-NMR ($CDCl_3$) δ 10.62 (broad s, 1H), 8.22 (d, *J* = 8.9 Hz, 1H), 7.98 (s, 1H), 6.69-6.64 (m, 2H), 6.50 (s, 1H), 6.3-6.32 (m, 2H), 5.07-5.19 (m, 2H), 4.03 (s, 3H), 3.90 (d, *J* = 12.4 Hz, 2H), 3.49 (s, 2H), 3.17 (s, 1H), 2.91-2.89 (m, 4H), 2.66-2.64 (m, 4H),

2.50-2.43 (m, 4H), 2.33-2.30 (m, 1H), 2.31 (s, 3H), 1.97 (d, *J* = 12.4 Hz, 2H), 1.60-1.79 (m, 3H). LC/MS (ESI+) *m/z* 591.25 (M+H)+, purity 96%. HPLC purity 96%. High resolution mass spectrum *m/z* 591.2957 [$(M+H)^+$ calc'd for $C_{31}H_{40}ClN_8O_2$ 591.2963].

(1*S*,2*S*,3*R*,4*R*)-3-[6-Chloro-2-(2-methoxy-4-morpholin-4-ylmethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-ylamino]-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (10m) is olated as a white lyophilized powder as the trifluoroacetic acid salt (62.3 mgs, 65% yield). ^{1}H-NMR ($CDCl_3$) δ 13.88 (broad s, 1H), 8.26-8.23 (m, 2H), 7.77 (s, 1H), 7.18 (s, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.43-6.40 (m, 3H), 5.81 (s, 1H), 5.29 (t, *J* = 8.7 Hz, 1H), 4.53 (d, *J* = 13.0 Hz, 1H), 4.10-3.94 (m, 10H), 3.70-3.66 (m, 1H), 3.37-3.33 (m, 1H), 3.16 (s, 1H), 2.92 (s, 1H), 2.77 (d, *J* = 8.0 Hz, 1H), 2.38 (d, *J* = 8.1 Hz, 1H), 1.63 (d, *J* = 9.3 Hz, 1H). LC/MS (ESI+) *m/z* 509.16 (M+H)+, purity 95%. HPLC purity 95%. High resolution mass spectrum *m/z* 509.2058 [$(M+H)^+$ calc'd for $C_{26}H_{30}ClN_6O_3$ 509.2068].

(1*S*,2*S*,3*R*,4*R*)-3-{6-Chloro-2-[2-methoxy-4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-3H-imidazo[4,5-b]pyridin-7-ylamino}-bicyclo[2.2.1]hept-5-ene-2- carboxylic acid amide (10n) isolated as a yellow solid (95 mgs, 50% yield). ^{1}H-NMR ($CDCl_3$) δ 10.83 (broad s, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H), 7.12-7.10 (m, 2H), 6.05 (broad s, 1H), 6.38-6.22 (m, 2H), 5.57 (d, *J* = 8.7 Hz, 1H), 5.31 (s, 1H), 5.30 (broad s, 1H), 5.20 (t, *J* = 8.0 Hz, 1H), 4.07 (s, 3H), 3.58 (s, 2H), 3.17 (broad s, 1H), 2.91 (broad s, 1H), 2.86 (dd, *J* = 8.1, 1.3 Hz, 1H), 2.57-2.43 (broad absorption, 8H), 2.34 (d, *J* = 9.8 Hz, 1H), 2.31 (s, 3H), 1.74 (d, *J* = 9.8 Hz, 1H). LC/MS (ESI+) *m/z* 522.19 (M+H)+,

purity >95%. HPLC purity 98%. High resolution mass spectrum *m/z* 522.2380 [$(M+H)^+$ calc'd for $C_{27}H_{33}ClN_7O_2$ 522.2384].

(1*S*,2*S*,3*R*,4*R*)-3-[6-bromo-2-(4-morpholin-4-yl-phenyl)-3H-imidazo[4,5-b]pyridin-7-ylamino]-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (11a) isolated as an off-white solid (45 mgs, 75% yield). MP 283-284 ºC. ^{1}H-NMR (DMSO-d_6) δ 12.97 (s, 1H), 8.22 (s, 1H), 8.00 (d, J = 7.8 Hz, 2H), 7.93 (s, 1H), 7.65 (s, 1H), 7.11 (s, 1H), 7.03 (d, J = 7.8 Hz, 2H), 6.98 (d, J = 9.0 Hz, 1H), 6.36 (broad s, 1H), 6.33 (broad s, 1H), 5.27 (t, J = 8.3 Hz, 1H), 3.77 (broad s, 4H), 2.88 (s, 1H), 2.77 (s, 1H), 2.62 (d, J = 7.8 Hz, 1H), 2.26 (broad s, 4H), 1.39 (d, J = 7.8 Hz, 1H). LC/MS (ESI+) *m/z* 509, 511 (M+H)+, purity 90%. HPLC purity 90%. High resolution mass spectrum *m/z* 509.1298 [$(M+H)^+$ calc'd for $C_{24}H_{26}BrN_6O_2$ 509.1301].

(1*S*,2*S*,3*R*,4*R*)-3-{6-Bromo-2-[4-(4-methyl-piperazin-1-yl)-phenyl]-3H-imidazo[4,5-b]pyridin-7-ylamino}-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (11b) isolated as a white solid (30 mgs, 49% yield). MP 215-218 ºC. ^{1}H-NMR (DMSO-d_6) δ13.02 (s, 1H), 7.99-7.97 (m, 3H), 7.73 (s, 1H), 7.20 (s, 1H), 7.07 (d, J = 8.2 Hz, 2H), 6.99 (d, J = 8.8 Hz, 1H), 6.36 (broad s, 2H), 5.29 (t, J = 8.8 Hz, 1H), 3.28-3.25 (broad absorption, 4H), 2.88 (broad s, 1H), 2.75 (broad s, 1H), 2.65 (d, J = 8.2 Hz, 1H), 2.47-2.43 (broad absorption 4H), 2.24 (d, J = 8.8 Hz, 1H), 1.38 (d, J = 8.8 Hz, 1H). LC/MS (ESI+) *m/z* 522, 524 (M+H)+, purity >95%. HPLC purity >95%. High resolution mass spectrum *m/z* 444.2507 [$(M+H)^+$ calc'd for $C_{25}H_{29}BrN_7O$ 444.2512].

(1*S*,2*S*,3*R*,4*R*)-3-[2-(4-Morpholin-4-yl-phenyl)-3H-imidazo[4,5-b]pyridin-7-ylamino]-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (12a) isolated as a white solid (24 mgs, 29% yield). MP 240-244 ºC. ^{1}H-NMR (DMSO-d_6) δ 12.83 (s, 1H), 8.00 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 4.9 Hz, 1H), 7.66 (s, 1H), 7.16 (s, 1H), 7.06 (d, J = 8.2 Hz, 2H), 6.77 (d, J = 8.2 Hz, 1H), 6.38 (d, J = 5.7 Hz, 1H), 6.33 (s, 2H), 3.88 (broad s, 1H), 3.76 (s, 4H), 3.31(s, 3H), 2.87 (s, 1H), 2.75 (s, 1H), 2.60 (d, J = 8.0 Hz, 1H), 2.24 (d, J = 8.7 Hz, 1H), 1.42 (d, J = 8.04 Hz, 1H). LC/MS (ESI+) *m/z* 431 (M+H)+, purity >95%. HPLC purity >95%. High resolution mass spectrum *m/z* 431.2198 [(M+H)$^+$ calc'd for $C_{24}H_{27}N_6O_2$ 431.2195].

(1*S*,2*S*,3*R*,4*R*)-3-{2-[4-(4-Methyl-piperazin-1-yl)-phenyl]-3H-imidazo[4,5- b]pyridin-7-ylamino}-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide (12b) isolated as a white solid (16 mgs, 19% yield). MP 220-222 ºC. ^{1}H-NMR (DMSO-d_6) δ 12.81 (s, 1H), 7.98 (d, J = 7.5 Hz, 2H), 7.86 (d, J = 5.1 Hz, 1H), 7.66 (s, 1H), 7.16 (s, 1H), 7.04 (d, J = 7.7 Hz, 2H), 6.75 (d, J = 8.0 Hz, 1H), 6.38 (d, J = 5.5 Hz, 1H), 6.33 (s, 2H), 3.88 (broad s, 1H), 3.25 (broad absorption 4H), 2.87 (s, 1H), 2.75 (s, 1H), 2.60 (d, J = 8.2 Hz, 1H), 2.46 broad absorption, 4H), 2.23 (broad absorption, 4H), (d, J = 8.2 Hz, 1H). LC/MS (ESI+) *m/z* 444 (M+H)+, purity >95%. HPLC purity >95%. High resolution mass spectrum *m/z* 444.2507 [(M+H)$^+$ calc'd for $C_{25}H_{29}N_7O$ 444.2512].

Cytochrome P450 Inhibition Protocols

P450 inhibition assay was conducted with pooled human liver microsomes (XenoTech LLC, Lenexa, KS) to metabolize P450 probe substrates (phenacetin for CYP1A2, diclofenac for CYP2C9, S-mephenytoin for CYP2C19, dextromethorphan for CYP2D6, testosterone and midazolam for CYP3A4). The test compounds were dissolved in DMSO at the concentration of 15 mM and were serially diluted to achieve the final concentration of 30, 10, 3.33, 1.11, 0.37, and 0.12 μM. The diluted test compounds are added to the reaction mixture containing 50 mM phosphate buffer pH 7.4, 5 mM of $MgCl_2$, varied amount of human liver microsomes and its corresponding probe substrate. The reactions are initiated by the addition of 2mM NADPH (Sigma, St. Louis, MO) and incubated at 37^0C for the optimized time. After incubation, the reactions are terminated with ice-cold acetonitrile and centrifuged. The supernatant were transferred to a 384-well plate and injected into LC/MS/MS for quantitation. IC_{50} values are calculated for each test compound. In each experiment, miconazole is also included as positive control and QC.