Supplemental Data

$^{86}Rb^{+}$Efflux. CHO cells stably expressing KCNQ2/Q3, KCNQ3/Q5 or KCNQ1(KvLQT1)+minK were grown as confluent monolayers in 96-well tissue culture plates (Corning Glassworks, Corning, NY) in minimal essential medium-α with 10% heat-inactivated fetal bovine serum and 400 μg/ml G418. Cells were incubated overnight in growth media containing 1 μCi/ml ^{86}Rb (PerkinElmer Life and Analytical Sciences, Waltham, MA) to permit intracellular uptake of the isotope. At the end of the incubation period, the ^{86}Rb solution was aspirated, and the cells were washed three times with EBSS. The cells were then preincubated for 10 min at room temperature in 100 μl/well EBSS or EBSS containing test compound at concentrations varying from 1 nM to 100 μM. At the end of this period, the supernatant from the wells was aspirated, and 100 μl of EBSS containing a submaximal concentration of KCl (typically 20-40 mM) and the test compound was added to each well. After incubation in the KCl buffer, the solution was removed and placed into the appropriate well of a 96-well counting plate for analysis. Finally, 100 μl of 0.1% SDS was added to each well to lyse the cells. The lysate was also placed in a 96-well counting plate for analysis. Both the efflux and lysate plates were then counted using a Wallac MicroBeta liquid scintillation counter (PerkinElmer Wallac, Gaithersburg, MD). Enhancement of efflux was expressed as a percentage of that induced by the addition of 70 mM KCl. Concentration-response curves were constructed by averaging data from multiple independent assays and fitting the averaged data with a logistic function as described by Response $=\{A_1 - A_2/[(1+x/xo)_p]\} + A_2$ where A_1 is the initial response, A_2 is the final response, x_0 is the midpoint (i.e., EC_{50}), and p is power (slope factor).

***In Vivo* Pharmacokinetic Studies** - Male Sprague Dawley rats were used for pharmacokinetic assays. Three rats were used to obtain plasma samples per time point (0.25, 0.5, 1, 2, 4, 7 and 24 hr). Mean body weights were 225 grams for both the 2 mg/kg PO group and the 2 mg/kg IV group. Plasma concentrations are quantitatively measured by LC-MS/MS. Plasma samples were extracted on-line with a Cohesive 2300 Turbulent Flow system followed by chromatographic separation with an Agilent 1100 LC. Quantitative analysis was performed with mrm detection on a Waters-Micromass Ultima triple quadrupole mass spectrometer. The rate and extent of available drug at the site of action in rats is determined by comparing the estimated AUC (area under the curve) of an IV dose with the AUC of a PO dose. The AUC value is corrected for dose amount in order to normalize the comparison. All calculations are performed with WinNonlin software from Pharsight

Compound Preparation and Administration – Compounds including **51,** were homogenized in 0.5% methyl cellulose and administered orally through a steel 18-gauge rat gavage tube. The vehicle for intravenous administration via tail vein was 25% 1-methyl-2-pyrolidinone in water. The dosing volume was 1 mL/kg for all groups.

In vivo Efficacy Studies (see reference 8)

Rat Maximal Electroshock Seizure (MES) Assay. Male Wistar rats were tested in the MES assay using the electroshock seizure apparatus designed by Walhquist Instrument Co (Salt Lake City, UT). A typical experiment consists of a compound formulated in 0.5% methylcellulose and administered orally in a volume of 1 mL/kg 30 min before electroshock application. The shock level was set at 150 mA, and the duration was set at 0.2 s. A drop of 1% proparacaine solution was placed in each eye, electrodes were placed over the eyes, and shock was administered. Latency to hind limb extension was measured to the nearest 0.1 s. If extension did not occur within 6 s, the animal was scored as protected from seizure and a latency of 6 s was recorded.

Rat Pentylenetetrazol-Induced (PTZ) Seizure Assay. Male Sprague Dawley rats were administered compound orally 30 minutes prior to the s.c. administration of 85 mg/kg pentylenetetrazol (PTZ). Immediately following administration of PTZ the rats were placed into individual plastic observation chambers and the latency to seizure was recorded in minutes. If no tonic-clonic seizure was observed within 15 minutes post-PTZ the animal was considered protected and a latency score of 15 minutes was recorded.

Methods. General Procedures. All reagents and solvents were obtained from commercial sources and used as received. 1H and 13CNMR spectra were obtained with a Varian Inova spectrometer at 300 and 75 MHz, respectively, in the solvent indicated. Coupling constants (J) are in hertz (Hz). Mass spectrometric identification of compounds was performed using standard electrospray ionization methods, MS (ESI), with a Perkin-Elmer SCIEX API 150 EX. Melting points were obtained with a Electrothermal IA9000 digital melting point apparatus. All compounds were assessed as greater than 95% pure by HPLC (C18) on a Michrom Bioresources Magic 2002 system (solvent A = 100% water/1.0mL/L formic acid; solvent B=99%CH3OH/1%water/1.0 mL/L formic acid; gradient of 0% to 100% B over 10 min). CMA80 is solvent mixture that was used as an eluent in chromatography; it is a 2/18/80 mixture of $NH_4OH/CH_3OH/CHCl_3$.

General experimental for Scheme 1 – The benzanilides found in Tables 1 and 2 may be prepared by reacting acid chlorides with aminopyridines in the presence of a tertiary amine base such as triethylamine or pyridine in an organic solvent such as dichloromethane at RT. Commercially available acid chlorides were used when available, The corresponding benzoic acids were converted to the acid chlorides using oxalyl chloride in DCM and cat. DMF.

Synthesis of acid chlorides – Typical procedure - Oxalyl chloride (1.05 mmol) was added dropwise to a stirring suspension of the acid (1 mmol) and DMF (0.1 mmol) in dry DCM (5 mL) at 0 ^{o}C. Once addition was complete the reaction was allowed to warm to RT and stirred for a further 45 min whereupon the reaction was a clear solution. This solution was used in the next step.

Synthesis of Benzanilides - Typical procedure - A solution of acid chloride (1 mmol) in a dry solvent DCM (3 mL) was added drop wise to a stirring solution of amino pyridine (1 mmol) and N, N-diisopropylethylamine (1.2 mmol) in a dry DCM) (5 mL) at RT. The resulting solution was stirred for an additional 1h. If tlc analysis indicated presence of starting aniline the solution was heated at 55^{o}C for another 1h. After cooling to room temperature ethyl acetate (10 mL) was added and the solution washed with water (2 x 10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude material was purified by column chromatography (hexanes/ethyl acetate) or by crystallization (hexane/dichloromethane). The products were typically white solids (50-98%) and all were >95% pure as indicated by HPLC, MS and NMR.

<u>Synthesis of 2-susbtituted-5-aminopyridines – Curtius Reaction.</u>

5-Amino-2-methylpyridine (TFA salt)
A solution of diphenylphosphorylazide (430 μL, 2 mmol), triethylamine (278 μL, 2 mmol) and 6-methyl-nicotinic acid (274 mg, 2 mmol) in t-butanol (30 mL) was heated at reflux for 4h. Cooled to RT and poured into water (50 mL). The organics were extracted with ether (3 x 20 mL), washed with brine (2 x 10 mL) and dried (Na_2SO_4). Column chromatography (1:1 hexane/ethyl acetate) of the boc-protected aminopyridine gave the intermediate as a white solid (156 mg, 38%). The desired 5-amino-2-methylpyridine-TFA salt was generated in situ by stirring in a 20% TFA/DCM solution (2 mL) for 4h. The solution was concentrated under reduced pressure to afford a semi-solid, which was used without further purification.

5-Amino-2-(trifluoromethyl)pyridine (TFA salt).
A solution of diphenylphosphorylazide (644 μL, 3 mmol), triethylamine (417 μL, 3 mmol) and 6-(trifluoromethyl)-nicotinic acid (573 mg, 3 mmol) in t-butanol (50 mL) was heated at reflux for 4h, then cooled to RT and poured into water (50 mL). The organics were extracted with ether (3 x 20 mL), washed with brine (2 x 10 mL) and dried (Na_2SO_4). Column chromatography (1:1 hexane/ethyl acetate) of the boc-protected aniline gave the intermediate as a white solid (389 mg,

50%). The desired 5-amino-2-methylpyridine-TFA salt was generated in situ by stirring in a 20% TFA/DCM solution (2 mL) for 4h. The solution was concentrated under reduced pressure to afford a semi-solid, which was used without further purification.

Preparation of key compounds

5,6-Difluoro-N-(6-fluoro-pyridin-3-yl)-nicotinamide (**5**): mp 135-137 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.58 (1H, brs), 8.52 (1H, s), 8.29-8.23 (1H, m), 8.03-7.97 (1H, m), 7.87-7.82 (1H, m), 7.65-7.56 (1H, m) and 7.19 (1H,dd, J= 8.9, 3.1 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ -73.6 (1F, d, J= 6.5Hz), -132.9 (1H, q, J= 10.7Hz) and –137.1 (1H, q, J= 10.7Hz); MS (ESI) *m/z*: 253.0 $[M+H]^+$.

3,4-Difluoro-N-(6-methyl-pyridin-3-yl)-benzamide (**6**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.42 (1H, brs), 8.73 (1H, d, J = 2.3 Hz), 8.04-7.97 (2H, m), 7.86-7.82 (1H, m), 7.90 (1H, dt, J= 10.4, 8.4 Hz), 7.23 (1H, d, J= 8.5 Hz) and 2.42 (3H, s); ^{19}F NMR (282 MHz, DMSO-d_6) δ -133.1 to -133.3 (1H, m) and –137.1 (1H, q, J= 10.7Hz); MS (ESI) *m/z*: 249.0 $[M+H]^+$.

3,4-Difluoro-N-(6-trifluoromethyl-pyridin-3-yl)-benzamide (**8**): mp 175-176 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.84 (1H, brs), 9.05 (1H, d, J = 1.8 Hz), 8.45 (1H, dd, J= 8.5, 1.9 Hz), 8.07 (1H, ddd, J= 9.9, 7.6, 2.1 Hz), 7.93 (1H, d, J= 8.5 Hz) and 7.89-7.86 (1H, m); ^{19}F NMR (282 MHz, DMSO-d_6) δ -65.7 (3F, s), -132.5 (1F, m) and –137.0 (1F, m); MS (ESI) *m/z*: 303.1 $[M+H]^+$.

N-(6-Chloro-pyridin-3-yl)-3,4-difluoro-benzamide (**12**): mp; 164 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (1H, d, J = 8.7 Hz), 7.59-7.68 (1H, m), 7.84-7.88 (1H, m), 8.03 (1H, ddd, J= 11.3, 7.9, 2.1 Hz), 8.19-8.23 (1H, m), 8.25 (1H, d, J= 2.0 Hz) and 10.64 (1H, s); ^{19}F NMR (282 MHz, DMSO-d_6) δ -112.9 (m), -115.2 (m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 117.9 (dd, J= 18.3, 49.8 Hz), 124.7, 125.7 (dd, J= 3.4, 6.9 Hz), 131.5 (m), 131.9, 135.3, 142.1, 145.0, 149.3 (dd, J= 14.7, 201.0 Hz), 152.8 (dd, J= 12.6, 205.0 Hz), 164.6; MS (ESI) *m/z*: 269.1 $[M+H]^+$.

N-(6-Chloro-pyridin-3-yl)-4-chloro-benzamide (**16**): mp 197-199 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.63 (1H, brs), 8.76 (1H, d, J = 2.6 Hz), 8.22 (1H, dd, J= 8.7, 2.8 Hz), 7.98 (2H, d, J= 8.7 Hz), 7.63 (1H, d, J= 8.7 Hz) and 7.52 (1H, d, J= 8.7 Hz); MS (ESI) *m/z*: 267.0 $[M+H]^+$.

N-(6-Chloro-pyridin-3-yl)-benzamide (**17**): mp 163-164 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.59 (1H, brs), 8.74 (1H, d, J = 2.6 Hz), 8.21 (1H, dd, J= 8.7, 2.8 Hz), 7.94 (1H, s), 7.92 (1H, d, J= 1.6 Hz), 7.59 (1H, d, J= 7.1 Hz) and 7.55-7.49 (3H, m); MS (ESI) *m/z*: 233.0 $[M+H]^+$.

N-(6-chloropyridin-3-yl)-2-fluorobenzamide (**18**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (1H, d, J = 2.6 Hz), 8.54 (1H, bs), 8.33 (1H, dd, J = 2.6, 8.5 Hz), 8.22 (1H, ddd, J = 2.0, 7.9, 9.9 Hz), 7.59-7.64 (1H, m), 7.37-7.42 (2H, m) and 7.27 (1H, ddd, J = 1.1, 8.3, 9.4 Hz); MS (ESI) *m/z*: 251.4 $[M+H]^+$.

N-(6-Chloro-pyridin-3-yl)-3-fluoro-benzamide (**19**): mp 160 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.63 (1H, brs), 8.75 (1H, d, J = 2.8 Hz), 8.20 (1H, dd, J= 8.7, 2.8 Hz), 7.79 (1H, d, J= 7.8 Hz), 7.75 (1H, d, J= 11.1 Hz), 7.62-7.55 (1H, m) and 7.53-7.43 (2H, m); ^{19}F NMR (282 MHz, DMSO-d_6) δ -112.0 (q, 8.5Hz); MS (ESI) *m/z*: 251.0 $[M+H]^+$.

N-(6-Chloro-pyridin-3-yl)-4-fluoro-benzamide (**20**): mp 163-164 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.58 (1H, brs), 8.76 (1H, d, J = 2.6 Hz), 8.22 (1H, dd, J= 8.7, 2.6 Hz), 8.04 (1H, d, J= 8.7 Hz), 8.02 (1H, d, J= 8.7 Hz), 7.51 (1H, d, J= 8.7 Hz) and 7.39 (2H, t, J= 8.8 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ -107.7 (m); MS (ESI) *m/z*: 319.0 $[M+H]^+$.

N-(6-Chloro-pyridin-3-yl)-3-trifluoromethyl-benzamide (**21**): mp 139-140 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (1H, d, J = 8.7 Hz), 7.63 (1H, t, J = 7.8 Hz), 7.82 (1H, d, J= 7.8 Hz), 8.06 (1H, d, J= 7.8 Hz), 8.11 (1H, brs), 8.25 (1H, dd, J = 8.7, 2.9 Hz), 8.36 (1H, s) and 8.50 (1H, d, J= 2.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.6; ^{13}C NMR (75 MHz, DMSO-d_6) δ 124.2, 124.2, 124.6, 129.0, 129.7, 130.6, 130.9, 133.7, 134.6, 141.2 and 164.8; MS (ESI) *m/z*: 301.2 $[M+H]^+$.

N-(6-Chloro-pyridin-3-yl)-3-(trifluoromethyl)-benzamide (**22**): mp 169-170 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.81 (1H, brs), 8.75 (1H, d, J = 2.8 Hz), 8.22 (1H, dd, J= 8.7, 2.8 Hz), 8.13 (1H, d, J= 8.2 Hz), 7.91 (2H, d, J= 8.4 Hz) and 7.52 (2H, d, J= 8.7 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ -61.4 (s); MS (ESI) *m/z*: 301.2 $[M+H]^+$.

Biphenyl-4-carboxylic acid (6-chloro-pyridin-3-yl)-amide (**23**): mp 227-229 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.62 (1H, brs), 8.81 (1H, d, J = 2.3 Hz), 8.26 (1H, dd, J= 8.7, 2.4 Hz), 8.06 (2H, d, J= 8.2 Hz), 7.85 (2H, d, J= 8.2 Hz), 7.75 (2H, d, J= 7.5 Hz), 7.53-7.47 (3H, m) and 7.42 (1H, q, J= 7.1 Hz); MS (ESI) *m/z*: 309.2 $[M+H]^+$.

N-(6-chloropyridin-3-yl)-3-methoxybenzamide (**24**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (1H, J = 2.7 Hz), 8.33 (1H, dd, J = 2.8, 8.7 Hz), 8.04 (1H, bs), 7.38-7.48 (4H, m), 7.17 (1H, ddd, J = 2.9, 4.8, 6.0 Hz) and 3.92 (1H, s); MS (ESI) *m/z*: 263.1 $[M+H]^+$.

N-(6-chloropyridin-3-yl)-3,4-dimethylbenzamide (**25**): ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD) δ 8.49 (1H, d, J = 2.8 Hz), 8.40 (1H, dd, J = 2.7, 8.6 Hz), 7.71 (1H, d, J = 1.7 Hz), 7.66 (1H, dd, J = 1.9, 7.7 Hz), 7.36 (1H, d, J = 8.8 Hz), 7.26 (1H, d, J = 7.7) and 2.35 (6H, s); MS (ESI) *m/z*: 261.4 $[M+H]^+$.

3,4-Dichloro-N-(6-chloro-pyridin-3-yl)-benzamide (**26**): mp 188-189 ^{o}C;^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (1H,d, J = 8.7 Hz), 7.58 (1H, d, J = 9.3 Hz), 7.70 (1H, dd, J= 9.4, 2.0 Hz), 7.90 (1H, brs), 7.96 (1H, d, J= 1.9 Hz), 8.24 (1H, dd, J= 8.7, 2.8 Hz) and 8.48 (1H, d, J=2.8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 124.7, 128.6, 130.2, 131.4, 131.9, 134.8, 135.4, 142.0, 144.9 and 164.0; MS (ESI) *m/z*: 301.1 $[M+H]^+$.

3-Chloro-N-(6-chloro-pyridin-3-yl)-benzamide (**27**): mp 153-154 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.67 (1H, brs), 8.74 (1H, d, J = 2.6 Hz), 8.22 (1H, dd, J= 8.7, 2.8 Hz), 7.99 (1H, d, J= 1.7 Hz), 7.90 (1H, d, J= 7.8 Hz), 7.69 (1H, d, J= 7.1 Hz), 7.58 (1H, t, J= 7.8 Hz) and 7.51 (1H, d, J= 8.7 Hz); MS (ESI) *m/z*: 267.0 $[M+H]^+$.

N-(6-Chloro-pyridin-3-yl)-4-fluoro-3-trifluoromethyl-benzamide (**28**): mp 149-150 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.63 (1H, brs), 8.76 (1H, d, J = 2.6 Hz), 8.22 (1H, dd, J= 8.7, 2.8 Hz), 7.98 (2H, d, J= 8.7 Hz), 7.63 (1H, d, J= 8.7 Hz) and 7.52 (1H, d, J= 8.7 Hz); MS (ESI) *m/z*: 319.1 $[M+H]^+$.

N-(6-Chloro-pyridin-3-yl)-3-fluoro-4-trifluoromethyl-benzamide (**31**): mp 182 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.78 (1H, brs), 8.75 (1H, d, J = 2.3 Hz), 8.37-8.32 (2H, m), 8.22 (1H, dd, J= 8.7, 2.6 Hz), 7.73 (1H, m) and 7.54 (1H, d, J= 8.7 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.1 (3F, m), -110.7 (m); MS (ESI) *m/z*: 319.1 $[M+H]^+$.

N-(6-Chloro-pyridin-3-yl)-3-chloro-4-fluoro-benzamide (**32**): mp 173 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.65 (1H, brs), 8.74 (1H, s), 8.23-8.18 (2H, m), 8.01-7.97 (1H, m), 7.61 (1H, t, J= 9.1 Hz) and 7.52 (1H, d, J= 8.7 Hz): MS (ESI) *m/z*: 285.0 $[M+H]^+$.

N-(6-chloropyridin-3-yl)-3-fluoro-4-methylbenzamide (**33**): ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD) δ 8.50 (1H, dd, J = 0.7, 2.9 Hz), 8.40 (1H, dd, J = 2.9, 8.8 Hz), 7.61-7.65 (2H, m), 7.30-7.39 (2H, m) and 2.38 (3H, d, J = 1.7 Hz); MS (ESI) *m/z*: 265.2 $[M+H]^+$.

N-(6-Chloro-pyridin-3-yl)-4-methylsulfamoyl-benzamide (**35**): mp 186-189 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.78 (1H, brs), 8.77 (1H, d, J= 2.3 Hz), 8.23 (1H, dt, J= 8.7, 2.8 Hz), 8.13 (2H, d, J= 8.4 Hz), 7.99 (1H, d, J= 8.2 Hz), 7.63 (1H, q, J= 5.2 Hz), 7.53 (1H, d, J= 8.7 Hz) and 2.43 (3H, s); MS (ESI) *m/z*: 326.2 $[M+H]^+$.
N-(6-chloropyridin-3-yl)-4-phenoxybenzamide (**36**): ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD) δ 8.49 (1H, dd, J = 0.4, 2.8 Hz), 8.41 (1H, dd, J = 2.7, 8.6 Hz), 7.93 (2H, dd, J = 2.2, 6.8 Hz), 7.35-7.46 (3H, m), 7.23 (1H, t, J = 7.2 Hz) and 7.06-7.12 (4H, m); MS (ESI) *m/z*: 325.2 $[M+H]^+$.

N-(6-chloropyridin-3-yl)-3-fluoro-4-isobutoxybenzamide (**40**): ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD) δ 8.49 (1H, d, J = 2.4 Hz), 8.41 (1H, dd, J = 2.6, 8.6 Hz), 7.73 (2H, dd, J = 1.9,

11.8 Hz), 7.37 (1H, d, J = 8.6 Hz), 7.04 (1H, dd, J = 8.2, 8.2 Hz), 3.88 (2H, d, J = 6.6 Hz), 2.10-2.25 (1H, m) and 1.09 (6H, d, J = 6.8 Hz); MS (ESI) *m/z*: 323.3 $[M+H]^+$.

N-(6-chloropyridin-3-yl)-3-fluoro-4-phenoxybenzamide (**41**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (1H, s), 8.33 (1H, dd, J = 2.4, 8.7 Hz), 7.78 (1H, dd, J = 2.1, 11.3 Hz), 7.65 (1H, d, J = 8.5 Hz), 7.26-7.38 (2H, m), 7.15 (1H, t, J = 7.3 Hz) and 6.96-7.02 (2H, m); MS (ESI) *m/z*: 343.0 $[M+H]^+$.

Preparation of 2-chloro-5-nitro-pyrimidine- 5-Nitro-pyrimidin-2-ylamine (v) (0.98g, 7mmol, 1eq) was added to a stirring mixture of anhydrous copper (II) chloride (1.12g, 8.4mmol, 1.2eq), tert-butylnitrite (1.24mL, 10.5mmol, 1.5eq) and $MgSO_4$ (~300mg) in acetonitrile (40mL) at 65-80^{o}C (bath temperature). After 30min the mixture was cooled to rt and diethyl ether (100mL) was added. The organic layer was separated and washed sequentially with 1N aqueous HCl (2x20mL), H_2O (50mL) and brine (20mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography of the crude material (hexanes/diethyl ether: 3:1) gave the desired product as a pale yellow solid (0.56g, 50%). mp 105-106 ^{o}C; ^{1}H NMR (300 MHz,$CDCl_3$) δ 9.39 (s, 2H).

Preparation of 2-chloro-pyrimidin-5-ylamine- Iron (3.38g, 60 mmol) was added to a boiling solution of 2-chloro-5-nitro-pyrimidine (vi) (2.4g, 15mmol) in ethanol (40mL), H_2O (20mL) and acetic acid (5mL). The mixture was heated at reflux for a further 20 min then cooled to rt and neutralized with saturated aqueous sodium bicarbonate. EtOAc (100mL) was added and the mixture was filtered through a pad of celite. The filtrate was washed with H_2O (50mL) and brine (20mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography of the crude material (hexanes/EtOAc: 1:1to 1:2) gave the desired product as a yellow solid (0.74g, 38%).

Preparation of *N*-(2-chloro-pyrimidin-5-yl)-aryl amides (**50-55**):
The aryl acid chloride (1.1eq) in THF (0.2M) was added to a solution of 2-chloro-pyrimidin-5-ylamine (1 eq) and pyridine (1.2 eq) in THF (0.2M) at rt. After 1h the suspension was diluted with EtOAc (5mL/mmol), washed with H_2O (20mL) and dried (Na_2SO_4). Concentration under reduced pressure followed by column chromatography (hexanes/EtOAc) gave the desired products in high yields (>80%) typically as white solids.

N-(2-Chloro-pyrimidin-5-yl)-3-fluoro-benzamide (**50**): ^{1}H NMR (300 MHz, d_6-DMSO) δ 10.83 (s, 1H), 9.11 (s, 2H), 7.84 (d, J = 7.9 Hz, 1H), 7.79-7.76 (m, 1H), 7.62 (q, J = 8.0 Hz, 1H), 7.50 (dt, J = 8.7, 2.6 Hz, 1H); ^{19}F NMR (282 MHz, d_6-DMSO) δ -111.9 to –112.0 (m); MS(ESI): 249.7[M-H], 251.7[M-H].

N-(2-Chloro-pyrimidin-5-yl)-3,4-difluoro-benzamide (**51**): ^{1}H NMR (300 MHz, d_6-DMSO) δ 10.80 (s, 1H), 9.08 (s, 2H), 8.04-7.98 (m, 1H), 7.88-7.86 (m, 1H), 7.63 (q, J= 8.4Hz, 1H); ^{19}F NMR (282 MHz, d_6-DMSO) δ -132.1 to –132.3 (m), -136.8 to –136.9 (m); MS(ESI): 267.8[M-H], 269.8[M-H].

3-Chloro-N-(2-chloro-pyrimidin-5-yl)-benzamide (**52**): ^{1}H NMR (300 MHz, d_6-DMSO) δ 10.85 (s, 1H), 9.10 (s, 2H), 8.02 (s, 1H), 7.91 (dd, J = 7.8, 1.2 Hz, 1H), 7.72-7.69 (m, 1H), 7.60 (dt, J = 7.8, 0.9 Hz, 1H); MS(ESI): 265.7[M-H], 267.7[M-H], 269.6[M-H].

N-(2-Chloro-pyrimidin-5-yl)-3-trifluoromethyl-benzamide (**53**): ^{1}H NMR (300 MHz, d_6-DMSO) δ 10.95 (s, 1H), 9.10 (s, 2H), 8.29 (s, 1H), 7.26 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.80 (t, J = 7.8 Hz, 1H); ^{19}F NMR (282 MHz, d_6-DMSO) δ -61.2; ; MS(ESI): 299.6[M-H], 301.6[M-H].

4-Chloro-N-(2-chloro-pyrimidin-5-yl)-3-fluoro-benzamide (**54**): ^{1}H NMR (300 MHz, d_6-DMSO) δ 10.86 (s, 1H), 9.09 (s, 2H), 7.90 (d, J = 9.4 Hz, 1H), 7.86-7.79 (m, 1H), 7.83 (s, 1H); ^{19}F NMR (282 MHz, d_6-DMSO) δ -114.6 to –114.7 (m); MS(ESI): 283.7[M-H], 285.7[M-H].

N-(2-Chloro-pyrimidin-5-yl)-3-fluoro-4-methyl-benzamide (**55**): ^{1}H NMR (300 MHz, d_6-DMSO) δ 10.73 (s, 1H), 9.10 (s, 2H), 7.73 (d, J = 8.9 Hz, 2H), 7.48 (t, J= 7.7 Hz, 1H), 2.31 (s, 3H); ^{19}F NMR (282 MHz, d_6-DMSO) δ -115.7; MS(ESI): 263.7[M-H], 265.7[M-H].