Supporting Information

Discovery of Phenylamino-pyridine Derivatives as Novel HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors

Junwon Kim,[a] Doohyun Lee,[a] Changmin Park,[a] Wonyoung So,[a] Mina Jo,[a] Taedong Ok,[a] Jeongjin Kwon,[a] Sunju Kong,[c] Suyeon Jo,[a] Youngmi Kim,[b] Jihyun Choi,[a] Hyoung Cheul Kim,[a] Yoonae Ko,[b] Inhee Choi,[b] Youngsam Park,[d] Jaewan Yoon,[d] Moon Kyeong Ju,[d] Junghwan Kim,[d] Sung-Jun Han,[d] Tae-Hee Kim,[e,j] Jonathan Cechetto,[e] Jiyoun Nam,[f] Peter Sommer,[g] Michel Liuzzi,[h] Jinhwa Lee,[i] Zaesung No*[,i]

[a] Medicinal Chemistry 2, [b] Medicinal Chemistry 1, [c] Medicinal Chemistry 3, [d] Drug Biology Group, [e] Screening Technology Platforms Group, [f] DMPK Group, [g] Cell Biology of Retroviruses Group, [h] Early Discovery Program, [i] Late Discovery Program, Institut Pasteur Korea (IP-K), Sampyeong-dong 696, Bundang-gu, Seongnam-si, Gyeonggi-do 463-400, Republic of Korea
[j] Department of Biotechnology, College of Life Science and Biotechnology, Yonsei University, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-749, Republic of Korea
[*] Corresponding author. Tel.: +82-31-8018-8160 fax: +82-31-8018-8015; e-mail: noxide@ip-korea.org

Contents

Biological Assays

HIV full replication assay.
CEMx174-LTR-GFP cells (clone CG8) were seeded with a microplate dispenser (WellMate; Thermo Scientific Matrix; U.S.A.) at a density of 4,000 cells/well into 384-well glass plates (Evotec. Hamburg, Germany) pre-dispensed with 10 μL of compound diluted in DMSO and incubated for 1 h at 37 °C, 5% CO_2. Then cells were infected with HIV-1_{LAI} at a multiplicity of infection (MOI) of 3 and incubated for 5 days at 37 °C, 5% CO_2. Fluorescence intensities were the determined using a multilabel plate reader (Victor3; PerkinElmer, Inc.; U.S.A.). And see Sommer, P.; Vartanian, J. P.; Wachsmuth, M.; Henry, M.; Guetard, D.; Wain-Hobson, S. *J. Mol. Biol.* **2004**, *344*, 11.

HIV-1 RT activity assay
The p66 and p51, two subunits of HIV RT, were amplified by PCR with N-terminal 6×His tag using the HIV-1 derived pol protein gene (Gene bank accession number, AY181196.1) as a template and subcloned into pET-28a and pET-15b (Novagen), respectively. The ClaI/ApaI fragment of pET-15b-p51 was ligated to SphI/ApaI digested pET-28a-p66. As a result, fusion plasmid bearing two subunits with their own 6×His tag and T7 promoter was generated.
The plasmid was transformed into E. coli strain, Rosetta DE3 pLysS, and protein expression was induced by 0.1 mM IPTG for 15 h at 25 °C. Overexpressed heterodimeric protein was purified by AKTA purification system (GE healthcare).
Enzyme activity assay was performed based on the scintillation proximity assay (SPA) technique. According to the kinetic analysis, Km value of HIV-RT against dTTP was 4.39 μM. Each reaction consist of 2 ng enzyme, 4 μM dTTP, 0.4 μCi tritium labeled dTTP, 40 μg SPA bead (GE healthcare), and 0.4 μL poly(A)-oligo(dT) (9A/mL) in a total volume of 40 μL with buffer (55mM Tris-Cl, pH 7.8, 30 mM KCl, 30 mM $MgCl_2$, 1 mM DTT, 0.01% Triton X-100, 50 mM EGTA, 0.1mg/ml BSA). The final DMSO concentration was maintained at 1%. After pre-incubation of enzyme and compound for 30 min at 24 °C, reaction mixture was added and incubated for 60 min at 37 °C. Reaction was terminated by addition of 80 μL of 0.12 M EDTA. The signal was counted using MicroBeta2 detector (Perkin Elmer).

Experimental Procedures

General Information

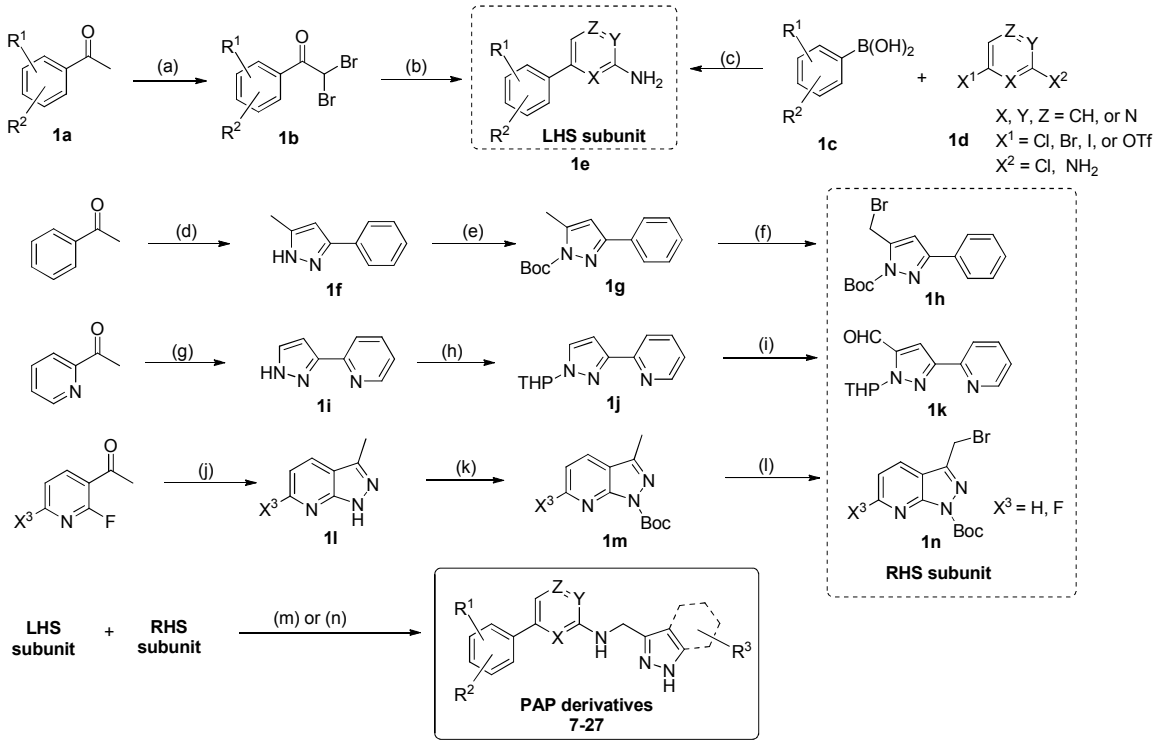
All reactions were carried out under an argon atmosphere in flame-dried glassware with magnetic stirring. THF, CH_2Cl_2, Et_2O, and CH_3CN were purified by passage through a bed of activated alumina.[1] Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.[2] Purification of reaction products was carried out by flash chromatography using silica gel 60 (Merck, 230-400 mesh). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F_{254} plates (Merck). Visualization was accomplished with UV light and iodine or potassium permangenate stain followed by heating. Infrared spectra were recorded on a Varian 3100 FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Varian 400 MHz spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration). Proton-decoupled ^{13}C-NMR spectra were recorded on a Varian 100 MHz spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm or DMSO-*d*6 at 2.50 ppm). LC/MS data were obtained using a Waters 2695 LC and Micromass ZQ spectrometer. The purity of all biologically tested compounds was $\geq$ 95 % by HPLC. Yields refer to purified products and are not optimized.

[1] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometal.* **1996**, *15*, 1518-1520.

[2] Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals;* 3rd Ed., Pergamon Press, Oxford. 1988.

General Procedures for the Synthesis of Substituted Phenylaminopyridine (PAP) derivatives 7–27[a]

The target phenylaminopyridine (PAP) compounds (Tables 1 and 2) were synthesized according to the general routes. The left hand side (LHS) subunits **1e** were prepared mainly from two methods: (i) triazine ring formation from readily available α,α-dibromo acetophenone derivatives **1b** *via* nucleophilic displacement with excess morpholine and then condensation with aminoguanidine in MeOH in the presence of AcOH[3] or (ii) direct Suzuki coupling reaction between boronic acid **1c** and heteroaryl halide/triflate **1d**.[4] For the synthesis of the right hand side (RHS) subunits (**1h**, **1k**, and **1n**), either radical bromination of substituted pyrazole **1g** /pyrazolopyridine **1m** with NBS in the presence of AIBN to give halogenated methyl pyrazole/pyrazolopyridine or deprotonation with *n*-BuLi with THP-protected pyrazole **1j** followed by treatment with DMF to generate formylated pyrazole **1k** was utilized.[5] The final coupling of two subunits was achieved in a straightforward fashion by *N*-alkylation or reductive amination methods. Subsequent deprotection of Boc/THP groups under acidic condition afforded targeted PAP derivatives (**7–27**).

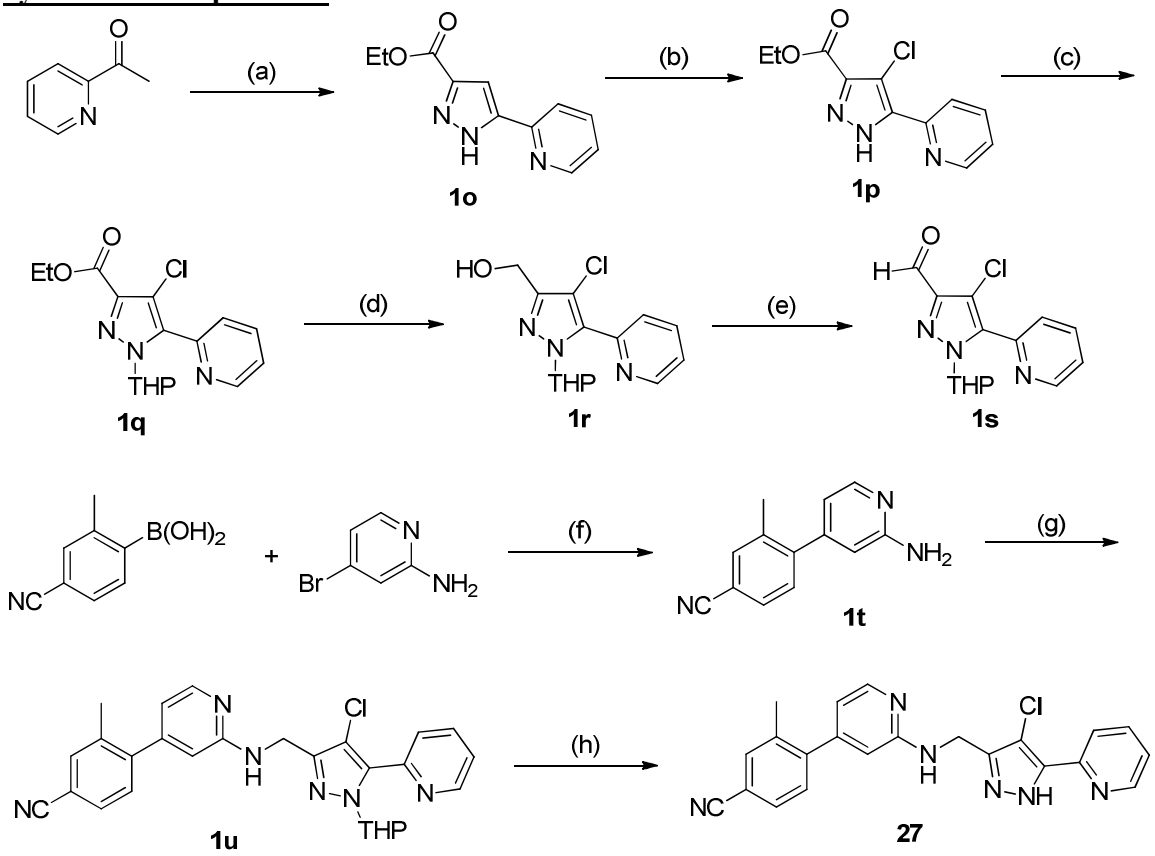


[a] Reagent and conditions: (a) phenyltrimethylammonium tribromide (PTT), THF, 25 °C, overnight; (b) (i) morpholine, THF, 25 to 65 °C, 24 h; (ii) aminoguanidine bicarbonate (AGB), AcOH, MeOH, reflux, 24 h; (c) $Pd(PPh_3)_4$, sat. K_2CO_3, toluene/EtOH, 120 °C, overnight; (d) (i) LiHMDS, toluene, acid chloride, 0 °C, 1 min, then AcOH; (ii) $NH_2NH_2{\cdot}H_2O$, THF/EtOH, reflux, 1 h; (e) Boc_2O, Et_3N, DMAP, CH_3CN, 25 °C, 1 h; (f) NBS, AIBN, $ClCH_2CH_2Cl$, 90 °C, 2 h; (g)

[3] Limanto, J.; Desmond, R. A.; Gauthier, D. R.; Devine, P. N.; Reamer, R. A.; Volante, R. P. A regioselective approach to 5-substituted-3-amino-1,2,4-triazines. *Org. Lett.* **2003**, *5*, 2271-2274.
[4] Kotha, S.; Lahiri, K.; Kashinath, D. Recent applications of the Suzuki-Miyaura cross-coupling reaction in organic synthesis. *Tetrahedron* **2002**, *58*, 9633-9695.
[5] McLaughlin, M.; Marcantonio, K.; Chen, C.-y.; Davies, I. W. A Simple, Modular Method for the Synthesis of 3,4,5-Trisubstituted Pyrazoles *J. Org. Chem. 2008*, *73*, 4309-4312.

(i) DMFDMA, toluene, 100 °C, 48 h; (ii) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, overnight; (h) DHP, TFA, toluene/CH_3CN, 80 °C, 24 h; (i) *n*-BuLi, THF, 0 °C, 10 min, then DMF; (j) $NH_2NH_2{\cdot}H_2O$, ethylene glycol, 165 °C; (k) Boc_2O, Et_3N, DMAP, CH_3CN, 25 °C, 1 h; (l) NBS, AIBN, $ClCH_2CH_2Cl$, 90 °C, 2 h; (m) (i) **1e**, LiHMDS, THF, 0 °C, 1 h, then RHS subunit; (ii) 4N HCl (2 eq.), dioxane, 25 °C, 1 h; (n) (i) **1e**, **1k**, AcOH, THF, molecular sieve, 25 °C, 5 h; (ii) $NaBH(OAc)_3$, 25 °C, overnight; (iii) HCl, MeOH, 25 °C, 3 h.

Synthesis of compound 27



Reagents and conditions: (a) (i) NaOEt, EtOH, diethyl oxalate , 25 °C, 20 h; (ii) H_2NNH_2, H_2O/EtOH, reflux, 2 h, 69% over 2 steps; (b) NCS, CCl_4, DMF, 55 °C, 15 h, 86%; (c) DHP, TFA, CH_3CN/toluene, 100 °C, 6 h, 42%; (d) LAH, THF, 0 °C, 30 min, 58%; (e) Dess-Martin Periodinane, CH_2Cl_2, 25 °C, 3 h, 91%; (f) $Pd(dppf)Cl_2$, Na_2CO_3, DME/H_2O, 140 °C, 2 h, 70%; (g) $NaBH(OAc)_3$, AcOH, 1,2-dichloroethane, 25 °C, 24 h, 50%; (h) HCl, MeOH, 40 °C, 15 h, 82%

Ethyl 5-(pyridin-2-yl)-1*H*-pyrazole-3-carboxylate (1o).
To a solution of diethyl oxalate (14.0 mL, 100 mmol) in EtOH (100 mL) at 25 °C was added a solution of NaOEt (41 mL, 21 wt. % in EtOH, 110 mmol), followed by a solution of 2-acetylpyridine (11.5 mL, 100 mmol) in EtOH (20 mL). The resulting mixture was stirred overnight at 25 °C. The reaction mixture was quenched by the addition of 2.4 N HCl (40 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed successively with water and brine and dried over $MgSO_4$. After filtration and concentration *in vacuo*, ethyl 2,4-dioxo-4-(pyridin-2-yl)butanoate (20 g, 90%) was isolated as a brown solid and used in the following step without further purification.

To a solution of ethyl 2,4-dioxo-4-(pyridin-2-yl)butanoate (20 g, 90.4 mmol) in EtOH (150 mL) was added hydrazine monohydrate (4.4 mL, 90.4 mmol), and the reaction mixture was refluxed for 3 h. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was diluted with Et_2O and washed successively with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give ethyl 5-(pyridin-2-yl)-1*H*-pyrazole-3-carboxylate **1o** (15.0 g, 69%) as a pale yellow solid, which is used in the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.23 (bs, 1H), 8.64 (d, *J* = 4.4 Hz, 1H), 7.34 (m, 2H), 7.57 (m, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 149.4, 148.1, 137.4, 123.3, 120.5, 106.4, 61.1, 14.2; LRMS (electrospray) *m/z* calculated for $C_{11}H_{11}N_3NaO_2$ $[M+Na]^+$ 240.07, found 239.87.

Ethyl 4-chloro-5-(pyridin-2-yl)-1*H*-pyrazole-3-carboxylate (1p)
A solution of ethyl 5-(pyridin-2-yl)-1*H*-pyrazole-3-carboxylate **1o** (4.00 g, 18.4 mmol), *N*-chlorosuccinimide (3.69 g, 27.6 mmol) in CH_3CN/DMF (25 mL/5 mL) was heated to 55 °C for 15 h. The reaction mixture was concentrated under reduced pressure, and then the residue was diluted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give ethyl 4-chloro-5-(pyridin-2-yl)-1*H*-pyrazole-3-carboxylate **1p** (4.00 g, 86%) as a light brown solid, which is used in the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.35 (bs, 1H), 8.65 (m, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.86 (dt, *J* = 8.0, 1.7 Hz, 1H), 7.36-7.33 (m, 1H), 4.46 (t, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.33 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 149.5, 146.3, 137.9, 124.2, 121.5, 111.2, 61.5, 14.4; LRMS (electrospray) *m/z* calculated for $C_{11}H_{11}ClN_3O_2$ $[M+H]^+$ 252.05, found 251.83.

Ethyl 4-chloro-5-(pyridin-2-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carboxylate (1q).
To a solution of ethyl 4-chloro-5-(pyridin-2-yl)-1*H*-pyrazole-3-carboxylate **1p** (4.00 g, 15.9 mmol) in CH_3CN/toluene (1:1, 40 mL) was added 3,4-dihydro-2*H*-pyran (13.6 mL, 149 mmol) and TFA (0.5 mL, 6.53 mmol). The reaction mixture was heated to 100 °C for 8 h. After cooling to 25 °C, the reaction mixture was concentrated under reduced pressure, and then the residue was purified by flash column chromatography to give the desired carboxylate **1q** (2.62 g, 42%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 4.8 Hz, 1H), 7.85 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.35 (dd, *J* = 7.6, 4.8 Hz, 1H), 5.95 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 3.95-3.88 (m, 1H), 3.43 (dt, *J* = 11.2, 2.8 Hz, 1H), 2.44-2.56 (m, 1H), 2.11-1.88 (m, 1H), 1.70-1.44 (m, 3H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 149.3, 147.0, 140.1, 139.1, 136.8, 125.7, 123.8, 112.6, 85.9, 67.8, 61.3, 28.9, 24.8, 22.4, 14.6; LRMS (electrospray) *m/z* calculated for $C_{16}H_{18}ClN_3NaO_3$ $[M+Na]^+$ 358.09, found 357.85.

(4-Chloro-5-(pyridin-2-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)methanol (1r).
To a 0 °C solution of ester **1q** (2.18 g, 6.50 mmol) in THF (40 mL) was added $LiAlH_4$ (7.8 mL, 1.0 M in THF, 7.80 mmol). The resultant mixture was stirred at 0 °C for 1 h. The reaction was quenched by the slow addition of sat. NH_4Cl. The aqueous layer was extracted with EtOAc, dried over $MgSO_4$. After filtration and concentration *in vacuo*, the residue was purified by flash column chromatography to give alcohol **1r** (1.11 g, 58%) as a white waxy solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 4.8, 1H), 7.85 (dt , *J* = 7.8, 1.6 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.35 (dd, *J* = 7.6, 4.8 Hz, 1H), 5.86 (dd, *J* = 10.6, 2.4 Hz, 1H), 4.77 (d, *J* = 6.4 Hz, 2H), 3.99 (d, *J* = 11.6 Hz, 1H), 3.48 (dt, *J* = 11.4, 2.4 Hz, 1H), 2.52-2.40 (m, 1H), 2.33 (t, *J* = 6.4 Hz, 1H), 2.14-1.96 (m, 2H), 1.74-1.62 (m, 2H), 1.56-1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 148.5, 147.5, 138.8, 136.8, 125.4, 123.5, 109.0, 85.4, 68.1, 57.1, 29.5, 24.9, 22.8; LRMS (electrospray) *m/z* calculated for $C_{14}H_{16}ClN_3NaO_2$ $[M+Na]^+$ 316.08, found 315.87.

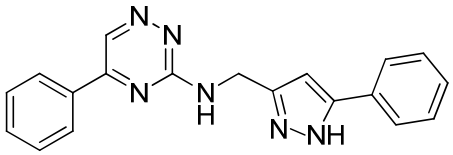
4-Chloro-5-(pyridin-2-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carbaldehyde (1s).
To a solution of alcohol **1r** (1.11 g, 3.70 mmol) in CH_2CI_2 (13 mL) was added Dess-Martin periodinane (2.04 g, 4.81 mmol). The reaction was stirred vigorously for 3 h at room temperature. The reaction mixture was diluted with Et_2O and filtered through a pad of celite. After concentration *in vacuo*, the residue was purified *via* flash column chromatography to give the desired aldehyde **1s** (1.01 g, 91%) as a waxy solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78-8.76 (m, 1H), 7.88 (dt, *J* = 7.7, 1.9, Hz, 1H), 7.78-7.74 (m, 1H), 7.40 (ddd, *J* = 7.6, 5.2, 1.2 Hz, 1H), 6.04 (dd, *J* = 9.4, 2.6 Hz, 1H), 3.88-3.80 (m, 1H), 3.50-3.44 (m, 1H), 2.52-2.40 (m, 1H), 2.17-2.05 (m 2H), 1.78-1.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.3, 149.9, 146.3, 145.0, 140.3, 136.9, 125.8, 124.0, 110.9, 85.9, 67.9, 29.1, 24.7, 22.2; LRMS (electrospray) *m/z* calculated for $C_{14}H_{14}ClN_3NaO_2$ $[M+Na]^+$ 314.07, found 313.82.

4-(2-Aminopyridin-4-yl)-3-methylbenzonitrile (1t)
To a solution of (4-cyano-2-methylphenyl)boronic acid (3.43 g, 20.2 mmol), 4-bromopyridin-2-amine (3.00 g, 16.8 mmol) in 1,2-dimethoxy ethane/water was added [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (366 mg, 0.50 mmol) and sodium carbonate (3.56 g, 33.6 mmol). The mixture was degassed by gently bubbling nitrogen and then heated at 140 °C for 2 h. The mixture was cooled to 25 °C and the insoluble material was removed by filtration through a pad of celite. The filtrate was concentrated *in vacuo* to remove solvents and then the residue was treated with excess ice-water. The precipitate was filtered and rinsed with water. After drying *in vacuo*, the crude product was washed with EtOAc and dried to give aminopyridine **1t** (2.46 g, 70%) as a gray solid, which did not require further purification: ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.97 (d, *J* = 5.2 Hz, 1H), 7.77 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 6.44 (d, *J* = 5.2 Hz, 1H), 6.38 (s, 1H), 6.07 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 159.9, 148.1, 147.9, 144.6, 136.4, 133.8, 129.74, 129.71, 118.6, 111.9, 110.6, 107.3, 19.5; LRMS (electrospray) *m/z* calculated for $C_{13}H_{12}N_3$ $[M+H]^+$ 210.10, found 209.86.

4-(2-((4-Chloro-5-(pyridin-2-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)methylamino)pyridin-4-yl)-3-methylbenzonitrile (1u).
To a solution of 4-chloro-5-(pyridin-2-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazole-3-carbaldehyde **1s** (209 mg, 0.717 mmol) in 1,2-dichloroethane (10 mL)/AcOH (5 drops) was added 4-(2-aminopyridin-4-yl)-3-methylbenzonitrile **1t** (100 mg, 0.478 mmol) at 25 °C. The solution was stirred for 1 h and $NaBH(OAc)_3$ (213 mg, 0.956 mmol) was added. After stirring for 16 h at 25 °C, the reaction was carefully quenched with H_2O and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography to give coupled product **1u** (116 mg, 50%) as a waxy solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.4 Hz, 1H), 8.16 (d, *J* = 5.2 Hz, 1H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.53 (s, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.34-7.31 (m, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 6.49 (d, *J* = 5.2 Hz, 1H), 6.47 (s, 1H), 5.84 (dd, *J* = 9.8, 2.2 Hz, 1H), 5.34 (bs, 1H), 4.10 (d, *J* = 6.8 Hz, 2H), 3.95 (d, *J* = 12.0 Hz, 1H), 3.45 (t, *J* = 11.2 Hz, 1H), 2.48-2.38 (m, 1H), 2.28 (s, 3H), 2.06-1.89 (m, 2H), 1.70-1.54 (m, 2H), 1.54-1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 149.9, 149.2, 148.3, 147.4, 146.1, 145.0, 138.9, 136.87, 136.84, 133.9, 129.9, 129.6, 125.3, 123.5, 118.9, 113.4, 111.7, 109.0, 107.2, 85.2, 68.0, 38.5, 29.4, 24.9, 22.8, 20.2; LRMS (electrospray) *m/z* calculated for $C_{27}H_{26}ClN_6O$ $[M+H]^+$ 485.19, found 484.94.

4-(2-((4-Chloro-5-(pyridin-2-yl)-1*H*-pyrazol-3-yl)methylamino)pyridin-4-yl)-3-methylbenzonitrile (27)
To a flask containing 4-(2-((4-chloro-5-(pyridin-2-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-3-yl)methylamino)pyridin-4-yl)-3-methylbenzonitrile **1u** (100 mg, 0.206 mmol) was added a solution of HCl (1.28 N in MeOH, 5 mL, 6.4 mmol, prepared by reaction between AcCl and

MeOH) at 25 °C. The resulting solution was heated at 40 °C for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and cautiously basified with sat. $NaHCO_3$. The mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography to give the desired compound **27** (68 mg, 82%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.30 (bs, 1H), 8.68 (d, *J* = 4.4 Hz, 1H), 8.09 (d, *J* = 5.6 Hz, 1H), 7.95 (m, 2H), 7.81 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.41 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.03 (m, 1H), 6.54 (m, 2H), 4.53 (d, *J* = 5.2 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, THF-d_8) δ 158.4, 151.3, 150.4, 149.3, 146.6, 146.0, 145.3, 140.0, 137.8, 137.7, 134.8, 130.9, 130.5, 123.9, 121.4, 119.1, 113.5, 113.2, 109.4, 107.3, 38.0, 20.3; LRMS (electrospray) *m/z* calculated for $C_{22}H_{18}ClN_6$ $[M+H]^+$ 401.13, found 401.43.



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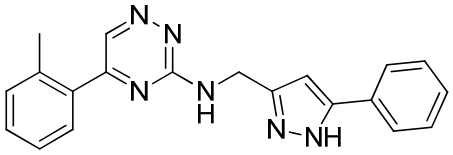
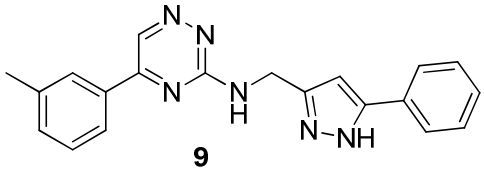
5-Phenyl-*N*-((5-phenyl-1*H*-pyrazol-3-yl)methyl)-1,2,4-triazin-3-amine (7)
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (d, *J* = 12 Hz, 1H), 8.21 (d, *J* = 6.8 Hz, 2H), 7.66 (d, *J* = 6.8 Hz, 2H), 7.56-7.55 (m, 3H), 7.36-7.25 (m, 3H), 6.59 (s, 1H), 4.66 (d, *J* = 21.6 Hz, 2H); TLC R_f (*n*-Hexanes:EtOAc 1:1) = 0.42.



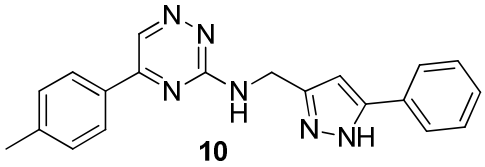
8

***N*-((5-Phenyl-1*H*-pyrazol-3-yl)methyl)-5-*o*-tolyl-1,2,4-triazin-3-amine (8)**
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 0.5H), 12.76 (s, 0.5H), 8.83 (d, *J* = 10.4 Hz, 1H), 8.24 (bs, 1H), 7.69 (d, *J* = 16.8 Hz, 2H), 7.51 (d, *J* = 6.8 Hz, 1H), 7.48-7.25 (m, 6H), 6.54 (d, *J* = 16.8 Hz, 1H), 4.62 (s, 2H), 2.42 (s, 3H); TLC R_f (CH_2Cl_2: MeOH 9:1) = 0.45.



9

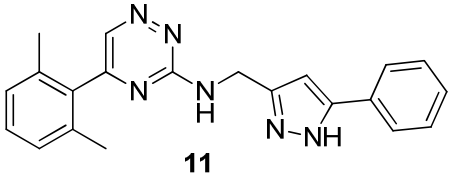
***N*-((5-Phenyl-1*H*-pyrazol-3-yl)methyl)-5-*m*-tolyl-1,2,4-triazin-3-amine (9)**
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 0.5H), 12.82 (s, 0.5H), 9.27 (s, 1H), 8.04 (s, 1H), 8.01 (d, *J* = 7.2 Hz, 1H), 7.72 (m, 2H), 7.47-7.38 (m, 5H), 7.28 (m, 1H), 6.62 (s, 1H), 4.68 (s, 2H), 2.35 (s, 3H); TLC R_f(CH_2Cl_2:MeOH 20:1) = 0.22.



10

***N*-((5-Phenyl-1*H*-pyrazol-3-yl)methyl)-5-*p*-tolyl-1,2,4-triazin-3-amine (10)**

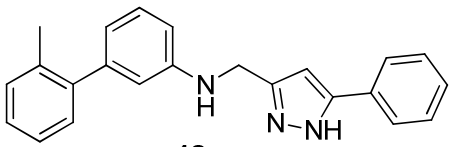
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 9.22 (d, J = 13.6 Hz, 1H), 8.09 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 19.6 Hz, 2H), 7.36-7.21 (m, 4H), 6.56 (s, 1H), 4.62 (d, J = 21.2 Hz, 2H), 2.35 (s, 3H); LRMS (electrospray) *m/z* calculated for $C_{20}H_{19}N_6$ $[M+H]^+$ 343.17, found 343.16.



11

5-(2,6-Dimethylphenyl)-*N*-((5-phenyl-1*H*-pyrazol-3-yl)methyl)-1,2,4-triazin-3-amine (11)

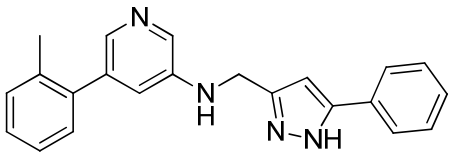
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 8.60 (s, 1H), 7.69 (d, J = 7.2 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.30-7.23 (m, 2H), 7.13 (d, J = 7.6 Hz, 2H), 6.54 (s, 1H), 4.60 (s, 2H), 2.01 (s, 6H) ; TLC R_f(CH_2Cl_2:MeOH 20:1) = 0.24.



12

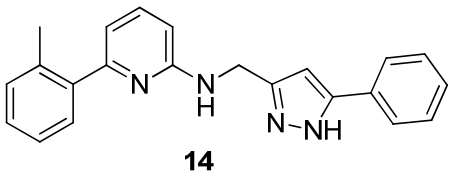
2'-Methyl-*N*-((5-phenyl-1H-pyrazol-3-yl)methyl)biphenyl-3-amine (12)

^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 7.16-7.11 (m, 5H), 6.67 (d, J = 8.0 Hz, 1H), 6.59-6.53 (m, 3H), 4.36 (s, 2H), 2.14 (s, 3H); TLC R_f (*n*-Hexanes: EtOAc 2:1) = 0.34; LRMS (electrospray) *m/z* calculated for $C_{23}H_{22}N_3$ $[M+H]^+$ 340.18, found 340.17.



13

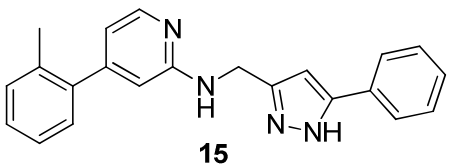
^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (d, J = 2.4 Hz, 1H), 7.70 (m, 3H), 7.40 (t, J = 7.2 Hz, 2H), 7.32 (d, J = 7.2 Hz, 1H), 7.24-7.19 (m, 3H), 7.14 (d, J = 7.2 Hz, 1H), 6.99 (s, 1H), 6.60 (s, 1H), 4.42 (s, 2H), 2.15 (s, 3H); TLC R_f(CH_2Cl_2:MeOH 20:1) = 0.28.



14

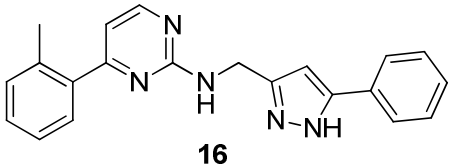
***N*-((5-Phenyl-1*H*-pyrazol-3-yl)methyl)-6-*o*-tolylpyridin-2-amine (14)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 2H), 7.49-7.42 (m, 2H), 7.37-7.34 (m, 2H), 7.29-7.24 (m, 4H), 6.74 (d, J = 7.2 Hz, 1H), 6.45 (s, 1H), 6.40 (d, J = 8.4, 1H), 4.56 (d, J = 5.2, 2H), 2.40 (s, 3H); TLC R_f (*n*-Hexanes:EtOAc 2:1) = 0.22.



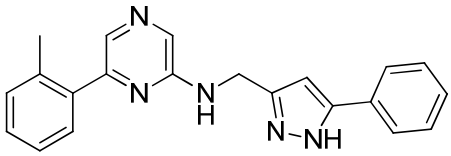
15

***N*-((5-Phenyl-1*H*-pyrazol-3-yl)methyl)-4-*o*-tolylpyridin-2-amine (15)**
^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (d, *J* = 4.0 Hz, 1H), 7.70-7.67 (m, 2H), 7.37-7.35 (m, 2H), 7.30-7.29 (m, 1H),7.23-7.13 (m, 4H), 6.58 (s, 1H), 6.54 (d, *J* = 5.2 Hz, 1H), 6.50 (s, 1H), 4.55 (s, 2H), 2.20 (s, 3H); TLC R_f (*n*-Hexanes:EtOAc 1:2) = 0.21.



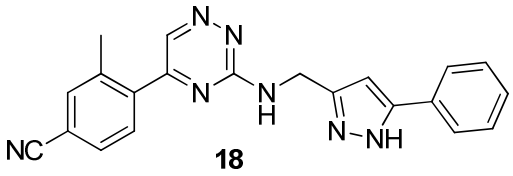
16

***N*-((5-Phenyl-1*H*-pyrazol-3-yl)methyl)-4-*o*-tolylpyrimidin-2-amine (16)**
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 5.2 Hz, 1H), 7.80 (d, *J* = 6.8 Hz, 2H), 7.42-7.22 (m, 7H), 7.16 (d, *J* = 5.2 Hz, 1H), 6.63 (s, 1H), 5.51 (s, 2H), 2.34 (s, 3H); TLC R_f(*n*-Hexanes:EtOAc 1:2) = 0.19.



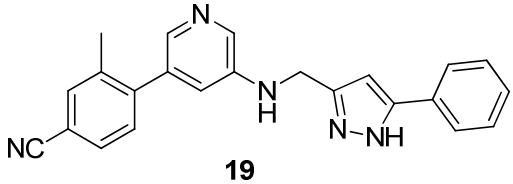
17

***N*-((5-Phenyl-1*H*-pyrazol-3-yl)methyl)-6-*o*-tolylpyrazin-2-amine (17)**
^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (s, 1H), 7.73 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.40-7.27 (m, 7H), 6.59 (s, 1H), 4.53 (s, 2H), 2.30 (s, 3H); TLC R_f(*n*-Hexanes:EtOAc 1:2) = 0.24.



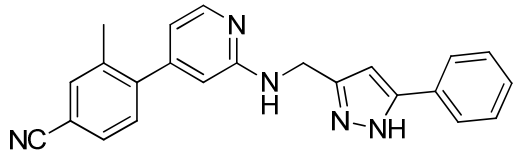
18

3-Methyl-4-(3-((5-phenyl-1*H*-pyrazol-3-yl)methylamino)-1,2,4-triazin-5-yl)benzonitrile (18)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.57-7.52 (m, 3H), 7.38-7.28 (m, 3H), 6.52 (s, 1H), 4.81 (s, 2H), 2.45 (s, 3H); TLC R_f (CH_2Cl_2:MeOH 10:1) = 0.33; LRMS (electrospray) *m/z* calculated for $C_{21}H_{17}N_7$ $[M+H]^+$ 367.41, found 367.94.



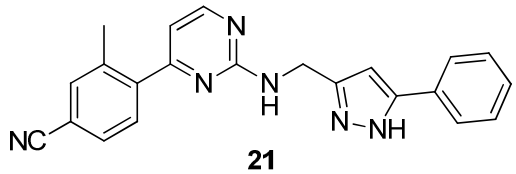
19

3-Methyl-4-(5-((5-phenyl-1*H*-pyrazol-3-yl)methylamino)pyridin-3-yl)benzonitrile (19)
^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.71-7.63 (m, 5H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.41-7.29 (m, 5H), 7.00 (t, *J* =2.2 Hz, 1H), 6.60 (s, 1H), 4.42 (s, 2H), 2.19 (s, 3H); TLC R_f (CH_2Cl_2:MeOH 20:1) = 0.20.



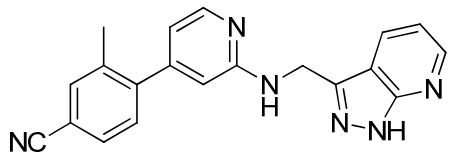
20

3-Methyl-4-(2-((5-phenyl-1*H*-pyrazol-3-yl)methylamino)pyridin-4-yl)benzonitrile (20)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 5.2 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.54 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.25 (d, *J* = 9.2 Hz, 1H), 6.55 (dd, *J* = 6.4, 2.4 Hz, 1H), 6.51 (s, 1H), 6.35 (s, 1H), 4.62 (d, *J* = 4.8 Hz, 2H), 2.26 (s, 3H); TLC R_f(CH_2Cl_2:MeOH 20:1) = 0.28.



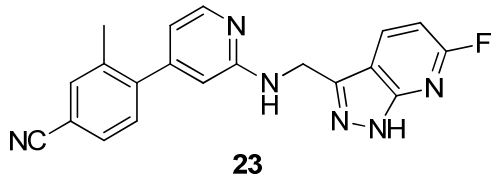
21

3-Methyl-4-(2-((5-phenyl-1*H*-pyrazol-3-yl)methylamino)pyrimidin-4-yl)benzonitrile (21)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.8 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 4.8 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.50 (s, 1H), 4.70 (d, *J* = 6.4 Hz, 2H), 2.43 (s, 3H); TLC R_f(*n*-Hexanes:EtOAc 1:1 with 0.5% MeOH) = 0.10.



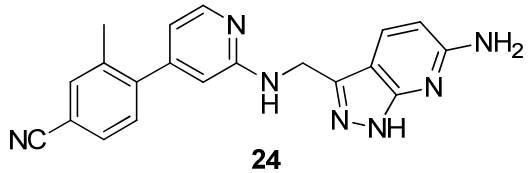
22

4-(2-((1*H*-Pyrazolo[3,4-*b*]pyridin-3-yl)methylamino)pyridin-4-yl)-3-methylbenzonitrile (22)
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.36 (s, 1H), 8.46 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.25 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.07 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.78 (s, 1H), 7.70 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.22 (m, 1H), 7.12 (dd, *J* = 8.0, 4.4 Hz, 1H), 6.49 (d, *J* = 1.6 Hz, 1H), 6.48 (s, 1H), 4.80 (s, 2H), 2.20 (s, 3H); TLC R_f(CH_2Cl_2:MeOH 19:1) = 0.16.



23

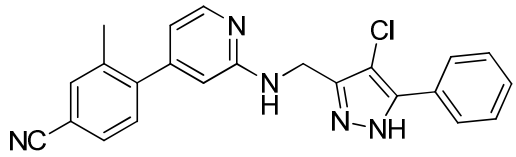
4-(2-((6-Fluoro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methylamino)pyridin-4-yl)-3-methylbenzonitrile (23)
^{1}H NMR (400 MHz, $CDCl_3$ with 20% CD_3OD) δ 8.16 (t, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 4.8 Hz, 1H), 7.41 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 6.40-6.39 (m, 1H), 6.30 (s, 1H), 4.72 (s, 2H), 2.04 (s, 3H); TLC R_f (CH_2Cl_2:MeOH 20:1) = 0.47; LRMS (electrospray) *m/z* calculated for $C_{20}H_{15}FN_6$ $[M+H]^+$ 358.37, found 359.01.



24

4-(2-((6-Amino-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)methylamino)pyridin-4-yl)-3-methylbenzonitrile (24)

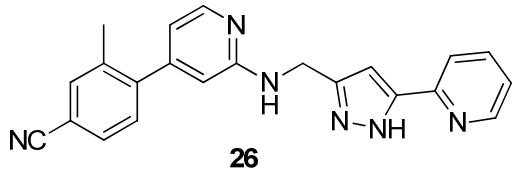
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 6.0 Hz, 1H), 7.77 (s, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.05 (t, J = 6.0 Hz, 1H), 6.47-6.46 (m, 2H), 6.23 (d, J = 8.8 Hz, 1H), 6.19 (s, 1H), 4.60 (d, J = 5.6 Hz, 2H), 2.20 (s, 3H); TLC R_f (CH_2Cl_2:MeOH 20:1) = 0.38; LRMS (electrospray) *m/z* calculated for $C_{20}H_{17}N_7$ $[M+H]^+$ 355.40, found 355.88.



25

4-(2-((4-Chloro-5-phenyl-1*H*-pyrazol-3-yl)methylamino)pyridin-4-yl)-3-methylbenzonitrile (25)

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.70 (bs, 1H), 8.16 (d, J = 5.2 Hz, 1H), 7.83 (d, J = 6.8 Hz, 2H), 7.56 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.41 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 6.57 (dd, J = 5.2, 1.2 Hz, 1H), 6.43 (s, 1H), 5.60 (bs, 1H), 4.59 (d, J = 5.6 Hz, 2H), 2.29 (s, 3H); LRMS (electrospray) *m/z* calculated for $C_{23}H_{19}ClN_5$ $[M+H]^+$ 400.13, found 400.30.



26

3-Methyl-4-(2-((5-(pyridin-2-yl)-1*H*-pyrazol-3-yl)methylamino)pyridin-4-yl)benzonitrile (26)

^{1}H NMR (400 MHz, $CDCl_3$ with 20% CD_3OD) δ 8.49 (d, J = 4.8 Hz, 2H), 8.04 (d, J = 5.6 Hz, 2H), 7.73-7.70 (m, 1H), 7.49-7.31 (m, 2H), 7.22-7.19 (m, 2H), 6.72 (s, 1H), 6.47 (d, J = 5.6 Hz, 1H), 4.53 (s, 2H), 2.20 (s, 3H); TLC R_f (CH_2Cl_2:MeOH 20:1) = 0.56.