SUPPLEMENTARY METHODS

1. Genomics Institute of the Novartis Research Foundation (GNF) chemical library

The GNF chemical library consists of ~3 million low molecular weight compounds.

2. High throughput screening (HTS) campaigns and hit identification

The high throughput screens were performed using 1,536 well polystyrene solid bottom white microplates (Greiner Bio-One). The GNF chemical library was tested against *L. donovani*, *T. brucei* and *T. cruzi* in whole-cell growth inhibition screens at single compound concentrations specified in sections below describing individual parasite screens. Parasite proliferation protocols described in the Methods section were optimized for 1,536 well plate assay format to provide optimal assay window and Z-factor. Primary hits included compounds that reduced growth of parasites by more than 50% relative to the relevant DMSO controls.

2.1. *Leishmania donovani* HTS

Leishmania donovani MHOM/SD/62/1S-CL2D axenic amastigotes in cell suspension were dispensed into 1,536-well assay plates (2,000 parasite cells in 5 μL of medium) and library compounds dissolved in DMSO were added to 4 μM final concentration (0.4% final DMSO concentration). After 48 hour incubation at 37 ^{o}C, parasite viability was assessed using the CellTiter-Glo Luminescent Cell Viability Assay (Promega) as described previously[32]. Compounds causing more than 50% reduction in parasite viability were considered hits. Identified hits were subsequently evaluated in the screening assay in triplicates at 4 μM compound concentration. Compounds that inhibited *L. donovani* growth in at least two replicates were considered confirmed hits.

2.2. *Trypanosoma brucei* HTS

Trypanosoma brucei Lister 427 bloodstream trypomastigotes in cell suspension were dispensed into 1,536-well assay plates (900 parasite cells in 7 μL of medium) and library compounds dissolved in

DMSO were added to 7 μM final concentration (0.7% final DMSO concentration). After 48 hour incubation at 37 ^{o}C, parasite viability was assessed using the CellTiter-Glo Luminescent Cell Viability Assay (Promega) as described previously[32]. Compounds causing more than 50% reduction in parasite viability were considered hits. Identified hits were subsequently evaluated in the screening assay in triplicates at 7 μM compound concentration. Compounds that inhibited *T. brucei* growth in at least two replicates were considered confirmed hits.

2.3. *Trypanosoma cruzi* HTS

A suspension of mouse fibroblast 3T3 cells was dispensed into 1,536-well assay plates (750 cells in 5 μL of medium). After overnight incubation at 37 ^{o}C, adhered 3T3 cells were infected with *T. cruzi* trypomastigotes (2,500 trypomastigotes per well in 3 μL of medium) and library compounds dissolved in DMSO were added to 6.3 μM final concentration (0.63% final DMSO concentration). After an additional 96 hour incubation at 37 °C, parasite viability was assessed using the BetaGlo Luminiscent Assay (Promega) as described previously[32]. Compounds causing more than 50% reduction in parasite viability were considered hits. Because of a large number of screen hits, we further followed upon only on a small subset of hits that were also identified as confirmed hits in *L. donovani* and *T. brucei* high throughput screens. Out of 93 such hits, 77 compounds were confirmed to be selective pan-kinetoplastid inhibitors (*L. donovani*, *T. brucei*, *T. cruzi* EC_{50} values < 10 μM, selectivity index relative to 3T3 CC_{50}> 5).

3. Chemical synthesis

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Removal of solvent under reduced pressure refers to distillation using Büchi rotary evaporator attached to a vacuum pump (~3 mm Hg). Products obtained as solids or high boiling oils were dried under vacuum (~1 mm Hg). Purification of compounds by high pressure liquid chromatography was achieved using a Waters 2487 series with Ultra 120 5 μm C18Q column with a linear gradient from

10% solvent A (acetonitrile with 0.035% trifluoroacetic acid) in solvent B (water with 0.05% trifluoroacetic acid) to 90% A in four minutes, followed by two and half minute elution with 90% A.

^{1}H NMR spectra were recorded on Bruker XWIN-NMR (400 MHz or 600 MHz). Proton resonances are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). ^{1}H NMR data are reported as multiplicity (s - singlet, d - doublet, t - triplet, q - quartet, quint - quintet, sept - septet, dd - doublet of doublets, dt - doublet of triplets, bs - broad singlet), number of protons and coupling constant in Hertz. For spectra obtained in $CDCl_3$, DMSO-d_6, CD_3OD, the residual protons (7.27, 2.50 and 3.31 ppm respectively) were used as the reference.

Analytical thin-layer chromatography (TLC) was performed on commercial silica plates (Merck 60-F 254, 0.25 mm thickness); compounds were visualized by UV light (254 nm). Flash chromatography was performed either by CombiFlash® (Separation system Sg. 100c, ISCO) or using silica gel (Merck Kieselgel 60, 230-400 mesh). Agilent 1100 series liquid chromatograph/ mass selective detector (LC/ MSD) was used to monitor the progress of reactions and check the purity of products using 254 nm and 220 nm wavelengths, and electrospray ionization (ESI) positive mode. Mass spectra were obtained in ESI positive mode. Elemental analyses were carried out by Midwest microlabs LLC, Indianapolis.

3.1. Synthesis of GNF5343

GNF5343 is a commercially available compound and was purchased from Chembridge laboratories (catalogue # 5840200).

3.2. Synthesis of GNF6702; N-(4-fluoro-3-(6-(pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)phenyl)-2,4-dimethyloxazole-5-carboxamide

3.2.1. Synthesis of 2-fluoro-5-nitrobenzoyl chloride (1)

A solution of 2-fluoro-5-nitrobenzoic acid (50 g, 270 mmol) in thionyl chloride (100 mL) was heated to 80 °C and stirred for 4 hours. The mixture was allowed to cool down to room temperature and the solvent was removed to give compound **1** (54 g, 98% yield).

3.2.2. Synthesis of 2-(2-fluoro-5-nitrobenzoyl)hydrazine-1-carboximidamide (2)

To a solution of aminoguanidine carbonate (36.2 g, 266 mmol) in dry toluene (300 mL) at 0 °C, was added compound **1** (54 g, 0.266 mol) over 30 minutes. The mixture was stirred at room temperature for 12 hours. The formed precipitate was removed by filtration, and the residue was treated with H_2O (400 mL) and made alkaline with sodium carbonate. The solid was collected and recrystallized from water to obtain compound **2** (62 g, 97% yield). M/Z 241.1 (M+1).

3.2.3. Synthesis of 5-(2-fluoro-5-nitrophenyl)-4H-1,2,4-triazol-3-amine (3)

A solution of compound **2** (62 g, 0.257 mol) in H_2O (800 mL) was stirred for 8 hours at 100 °C. After cooling, the obtained solid was filtered, and the cake was washed with H_2O (100 mL), tetrahydrofuran (100 mL), and dried to give compound **3** (34 g, 51% yield). ^{1}H NMR (400 MHz, DMSO) 12.42 (s, 1H), 8.74 (dd, J = 6.27, 3.01 , 1H), 8.26 (dt, J = 8.97, 3.42 , 1H), 7.57 (t, J = 9.54 , 1H), 6.29 (s, 2H).

3.2.4. Synthesis of 2-(2-fluoro-5-nitrophenyl)-6-(pyridin-2-yl)-[1,2,4]triazolo[1,5-a] pyrimidine (4)

To a solution of compound **3** (1 g, 4.48 mmol) in acetic acid (20 mL) 2-(pyridin-2-yl)malonaldehyde (0.8 g, 5.376 mmol) was added at room temperature. The mixture was heated to 100 °C and stirred for 4 hours. The mixture was allowed to cool to room temperature before adding water (50 mL), filtered, and the filter cake was washed with saturate sodium bicarbonate solution (100 mL), H_2O (100 mL), and tetrahydrofuran (100 mL) and dried under vacuum to give compound **4** (0.9 g, 60% yield). ^{1}H NMR (400 MHz, DMSO) 10.13 (d, J = 2.01 ,1H), 9.68 (d, J = 2.01 , 1H), 9.09- 9.02 (m, 1H), 8.77 (d, J = 4.27 , 1H), 8.28-8.19 (m, 1H), 8.15-7.96 (m, 2 H), 7.77 (t, J = 9.54 , 1H), 7.56-7.43 (m, 1H).

3.2.5. Synthesis of 4-fluoro-3-(6-(pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)aniline (5)

To a solution of compound **4** (0.15 g, 0.443 mmol) in tetrahydrofuran (5 mL) was added Raney Nickel (0.2 g) and ZnI_2 (71 mg) at room temperature. The mixture was stirred under H_2 (50 psi) at 25 °C for 2.5 hours. The mixture was diluted with methanol (10 mL) and filtered. The solvent was removed and the crude product was washed with methanol (5 mL x 2) and dried under vacuum to give compound **5** (90 mg, 66% yield). ^{1}H NMR (400 MHz, DMSO) 10.01-10.06 (m, 1H), 9.62-9.58 (m, 1H), 8.73-8.78 (m, 1H), 8.24-8.20 (m, 1H), 8-02-7.96 (m, 1H), 7.57-7.47 (m, 2H), 7.08-7.05 (m, 1H), 6.76-6.70 (m, 1H), 5.24 (s, 2H) M/Z 307.01 (M+1).

3.2.6. Synthesis of N-(4-fluoro-3-(6-(pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)phenyl)-2,4-dimethyloxazole-5-carboxamide (GNF6702; 6)

To a solution of 2,4-dimethyloxazole-5-carboxylic acid (40.6 mg, 0.28 mmol) in dimethylformamide (5 mL) was added HATU (118.6 mg, 0.31 mmol) and DIEA (72.4 mg, 0.56 mmol) at room temperature. The mixture was stirred for 30 min, the intermediate **5** (80 mg, 0.26 mmol) was added at room temperature. The mixture was stirred for 3 hours, water (10 mL) was added, the mixture was filtered, and the filter cake was washed with H_2O (5 mL x 2), tetrahydrofuran (5 mL x 2) and purified by HPLC to give product **6** (33 mg, 31% yield). ^{1}H NMR (400 M, MeOD) 9.84 (d, J = 2.4, 1H), 9.61 (d, J = 2.3, 1H), 8.76 (dt, J = 4.8, 1.4, 1H), 8.54 (dd, J = 6.4, 2.7, 1H), 8.12 (dt, J = 8.0, 1.1, 1H), 8.00 (td, J = 7.8, 1.8, 1H), 7.93 (ddd, J = 8.9, 4.1, 2.7, 1H), 7.49 (ddd, J = 7.5, 4.9, 1.0, 1H), 7.34 (dd, J = 10.4, 9.0, 1H), 2.57 (s, 3H), 2.48 (s, 3H). M/Z= 430.13 (M+1).

3.3. Synthesis of GNF3943; Isopropyl (2-(2-chloro-5-(furan-2-carboxamido)phenyl)-1H-imidazo[4,5-b]pyridin-6-yl)carbamate

3.3.1. Synthesis of 2-chloro-5-(furan-2-carboxamido)benzoic acid (7)

To a suspension of 5-amino-2-chlorobenzoic acid (13.7 g, 79.85 mmol, 1.00 equiv) in tetrahydrofuran (100 mL) was added furan-2-carbonyl chloride (11.5 g, 88.10 mmol, 1.10 equiv) at 0 °C. The ice bath

was then removed and the reaction was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum and diluted with DCM. The solid was collected by filtration to give 17 g (80%) of 2-chloro-5-(furan-2-amido)benzoic acid (**7**) as a gray solid.

3.3.2. Synthesis of *N*-(4-chloro-3-[6-nitro-1*H*-imidazo[*4,5-b*]pyridin-2-yl]phenyl)furan-2-carboxamide (8)

A mixture of 5-nitropyridine-2,3-diamine (6 g, 38.93 mmol, 1.00 equiv) and 2-chloro-5-(furan-2-amido)benzoic acid (**7**) (10.4 g, 39.15 mmol, 1.00 equiv) in polyphosphoric acid (PPA) (100 mL) was stirred overnight at 130 °C. The reaction was then poured into water/ice and the pH value of the mixture was adjusted to 9 with sodium carbonate. The solids were collected by filtration and applied onto a silica gel column with ethyl acetate/petroleum ether (3/1) to give 3.9 g (26%) of *N*-(4-chloro-3-[6-nitro-1*H*-imidazo[*4,5-b*]pyridin-2-yl]phenyl)furan-2-carboxamide (**8**) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 10.50 (s, 1H), 9.19 (d, *J* = 2.6 Hz, 1H), 8.73 (s, 1H), 8.43 (d, *J* = 2.6 Hz, 1H), 8.03 – 7.90 (m, 4H), 7.61 (d, *J* = 8.9 Hz, 1H), 7.41 (d, *J* = 3.6 Hz, 1H), 6.79 – 6.67 (m, 1H). MS *m*/*z* 383.9 $(M+H)^+$.

3.3.3. Synthesis *N*-(3-[6-amino-1*H*-imidazo[*4,5-b*]pyridin-2-yl]-4-chlorophenyl)furan-2-carboxamide (9)

To a suspension of *N*-(4-chloro-3-[6-nitro-1*H*-imidazo[*4,5-b*]pyridin-2-yl]phenyl)furan-2-carboxamide (3.9 g, 10.16 mmol, 1.00 equiv) in ethanol (50 mL) was added $SnCl_2 \cdot 2H_2O$ (3.4 g, 15.04 mmol, 1.48 equiv) and the resulting mixture was heated to reflux overnight. The reaction mixture was concentrated under vacuum and diluted with H_2O. The pH value of the mixture was adjusted to 9 with saturated sodium carbonate. The solids were collected by filtration and applied onto a silica gel column with ethyl acetate/PE (3/1) to give 1.95 g (54%) of *N*-(3-[6-amino-1*H*-imidazo[*4,5-b*]pyridin-2-yl]-4-chlorophenyl)furan-2-carboxamide (**9**) as a yellow solid. ^{1}H-NMR: (CD_3OD, 400 MHz): 8.16 (d, *J* = 2.4

Hz, 1H), 7.97-8.10 (m, 2H), 7.78 (d, *J* = 0.8 Hz, 1H), 7.65 (d, *J* = 20.0 Hz, 1H), 7.31-7.41 (m, 2H), 6.68 (dd, *J* = 3.6, 2.0 Hz, 1H. MS $(M+H)^+$=354.

3.3.4. Synthesis of Isopropyl (2-(2-chloro-5-(furan-2-carboxamido)phenyl)-1H-imidazo[4,5-b]pyridin-6-yl)carbamate (**GNF3943**) (**10**)

To a 20 mL vial was transferred N-(3-(6-amino-1H-imidazo[4,5-b]pyridin-2-yl)-4-chlorophenyl)furan-2-carboxamide **9** (80 mg, 0.225 mmol) in dimethylformamide (4 mL) followed by addition of pyridine (2 drops), and the reaction mixture was stirred at 0 °C for 10 minutes. At this point was added isopropyl carbonochloridate (1 M solution in toluene, 1.45 mmols, 6.4 eq). The reaction mixture was stirred overnight while slowly warming up to room temperature. The presence of desired peak (M+H (440)) was confirmed by LC/MS. The reaction mixture was then quenched with saturated sodium carbonate solution to neutralize the extra acid chloride and to make the solution basic (pH 8-9). The reaction was extracted with ethyl acetate (3x10 mL), and the resulting organics were dried over sodium sulfate, filtered, and dried under vacuum. The resulting residue was purified via ISCO column chromatography using (0-100% ethyl acetate/hexane) to provide 53 mg, 0.119 mmol, 53% of the desired compound. ^{1}H NMR (400 MHz, MeOD) δ 8.28 (d, *J* = 22.1, 2H), 8.10 (s, 1H), 7.88 (s, 1H), 7.67 (d, *J* = 1.0, 1H), 7.51 (d, *J* = 8.8, 1H), 7.24 – 7.16 (m, 1H), 6.56 (dd, *J* = 1.7, 3.5, 1H), 4.91 (dt, *J* = 6.2, 12.5, 1H), 1.24 (d, *J* = 6.2, 6H). M/Z=440.1(M+1)

3.4. Synthesis of GNF8000; isopropyl (2-(2-fluoro-5-(furan-2-carboxamido)phenyl) imidazo[1,2-a]pyrimidin-6-yl)carbamate

3.4.1. Synthesis of 1-(2-fluoro-5-nitrophenyl)ethan-1-one (11)

A 3,000 mL three necked flask equipped with a mechanic stirrer was charged with concentrated H_2SO_4 (720 mL) and cooled to -40 °C. 1-(2-fluorophenyl)ethanone (180 g, 1.3 mol) was added, followed by addition of a mixture of fuming HNO_3 (106.2 mL) in concentrated H_2SO_4 (260 mL) dropwise over 45

minutes. This mixture was stirred at this temperature for 15 minutes, poured into ice (8 kg), and extracted with ethyl acetate (2000 mL x 2). The combined ethyl acetate layer was washed with saturated $NaHCO_3$ solution (800 mL x 3), brine (800 mL), dried with anhydrous sodium sulfate, and concentrated under vacuum. The residue was crystallized with petroleum ether to give compound **11** (200 g, yield: 84%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 9.29 Hz, 1H), 8.33-8.48 (m, 1H), 8.78 (dd, *J* = 6.15, 2.89 Hz, 1H).

3.4.2. Synthesis of 2-bromo-1-(2-fluoro-5-nitrophenyl)ethan-1-one (12)

To a solution of compound **11** (126 g, 0.688 mol) in acetic acid (860 mL) and 40% HBr solution (825.6 mL) at 0 °C, was added a solution of Br_2 (110 g, 0.688 mol) in acetic acid (344 mL) in one portion. This mixture was stirred at room temperature overnight, diluted with water (3000 mL), and extracted with 50% ethyl acetate/petroleum ether (1500 mL x 2). The combined organic layer was washed with a saturated $NaHCO_3$ solution (1000 mL x 2), brine (1000 mL), dried with anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (20% EA/PE) to give the compound **12** (150 g, yield: 83%) as a white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (dd, *J* = 5.90, 2.89 Hz, 1H), 8.42-8.58 (m, 1H), 7.42 (t, *J* = 9.29 Hz, 1H), 4.52 (d, *J* = 2.01 Hz, 2H).

3.4.3. Synthesis of Isopropyl (2-aminopyrimidin-5-yl)carbamate (13)

A suspension of 5-nitropyrimidine-2-amine (1 eq.) and Pd/C (0.05 eq.) in ethanol (0.1 mM) was stirred under hydrogen atmosphere overnight at room temperature to give of 2,5-diaminopyrimidine. The mixture was then filtered and concentrated under vacuum. The residue (1 eq.) was subjected to coupling with isopropylcarbonochloridate (1.5 eq.) in anhydrous pyridine (0.3 mM) overnight at room temperature. The mixture was concentrated under vacuum, and the residue was extracted with ethyl acetate, washed with brine, dried over anhydrous MgSO4 (s), filtered and concentrated under vacuum to give **13** as a yellow solid. m/z (ESI): 196 ($M + H^+$).

3.4.4. Synthesis of isopropyl (2-(2-fluoro-5-nitrophenyl)imidazo[1,2-a]pyrimidin-6-yl)carbamate (**14**)

Into a 500 mL round-bottom flask, was placed 2-bromo-1-(2-fluoro-5-nitrophenyl)ethan-1-one **12** (30 g, 114.49 mmol, 1 eq.), propan-2-yl N-(2-aminopyrimidin-5-yl)carbamate (11.2 g, 57.08 mmol, 0.5 eq.) and acetone (200 mL). The resulting solution was stirred overnight at 70 °C. The reaction mixture was cooled down and the solids were collected by filtration resulting in 15 g (36%) of propan-2-yl N-[2-(2-fluoro-5-nitrophenyl)imidazo[1,2-a]pyrimidin-6-yl]carbamate (**14**) as a brown solid.

3.4.5. Synthesis of isopropyl (2-(5-amino-2-fluorophenyl)imidazo[1,2-a]pyrimidin-6-yl)carbamate (**15**)

Into a 1 L round-bottom flask was placed tetrahydrofuran (500 mL), Raney Ni (15 g) and propan-2-yl N-[2-(2-fluoro-5-nitrophenyl)imidazo[1,2-a]pyrimidin-6-yl]carbamate **14** (8 g, 22.26 mmol, 1 eq.). The resulting solution was stirred overnight at room temperature under an atmosphere of hydrogen. The solids were filtered out, and washed with methanol (200 mL x 4). The resulting mixture was concentrated under vacuum to give 7 g (95%) of propan-2-yl N-[2-(5-amino-2-fluorophenyl)imidazo[1,2-a]pyrimidin-6-yl]carbamate (**I5**) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 9.24 (s, 1H), 8.46-8.47 (m, 1H), 8.26-8.28 (m, 1H), 7.51-7.53 (m, 1H), 6.96-7.02 (m, 1H), 6.55-6.59 (m, 1H), 4.89-4.98 (m, 1H), 3.17 (s, 2H), 1.07-1.30(m, 6H). MS *m/z*= 330 (M+1).

3.4.6. Synthesis of isopropyl (2-(2-fluoro-5-(furan-2-carboxamido)phenyl) imidazo[1,2-a]pyrimidin-6-yl)carbamate (GNF8000) (16)

In a 40 mL vial, pyridine (10 mL) was added to intermediate **15** (0.5 g, 1.518 mmol) to give a yellow solution. To this solution was added furan-2-carbonyl chloride (0.198 g, 1.518 mmol) at 0 °C and the resulting mixture was stirred for 1 hour. The reaction mixture was quenched with 60 mL of water and extracted with ethyl acetate. The same step was repeated once more time to remove any extra pyridine.

All organic phases were combined, dried over sodium sulfate and purified by flash chromatography to give product **16** (ethyl acetate/methanol= 0-10%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 10.06 (s, 1H), 9.36 (s, 1H), 8.69 (dd, *J* = 2.8, 6.9 Hz, 1H), 8.56 (d, *J* = 2.7 Hz, 1H), 8.45 (d, *J* = 4.2 Hz, 1H), 8.02 (d, *J* = 1.0 Hz, 1H), 7.95-7.85 (m, 1H), 7.46 (d, *J* = 3.4 Hz, 1H), 7.37 (dd, *J* = 9.0, 10.9 Hz, 1H), 6.78 (dd, *J* = 1.7, 3.5 Hz, 1H), 5.00 (dt, *J* = 6.3, 12.5 Hz, 1H), 1.35 (d, *J* = 6.2 Hz, 6H). MS *m/z* = 424 (M+1).

3.5. Synthesis of GNF3849; N-(4-fluoro-3-(6-phenyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)phenyl)-2,4-dimethyloxazole-5-carboxamide

3.5.1. Synthesis of 2-(2-fluoro-5-nitrophenyl)-6-phenyl-[1,2,4]triazolo[1,5-a]pyrimidine (17)

To a solution of compound **3** (0.5 g, 2.24 mmol) in AcOH (5 mL) was added 2-phenylmalonaldehyde (0.39 g, 2.7 mmol). The mixture was then heated to 100 °C and stirred for 4 hours. The mixture was allowed to cool to room temperature, water (10 mL) was added, the solids filtered, and the filter cake was washed with tetrahydrofuran, and dried under vacuum to give compound **17** (0.36 g, 48% yield). ^{1}H NMR (400 MHz, DMSO) 9.93 (d, *J* = 2.4, 1H), 9.38 (d, *J* = 2.8, 1H), 8.90 (s, 1H), 7.93 (d, *J* = 7.78, 2H), 7.69 (d, *J* = 8.53, 1H), 7.61-7.50 (m, 2H), 7.31 (t, *J* = 7.40, 1H), 6.88 (s, 1H).

3.5.2. Synthesis of 4-fluoro-3-(6-phenyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)aniline (18)

To a solution of compound **17** (2.5 g, 7.4 mmol) in tetrahydrofuran (200 mL) was added ZnI_2 (1.2 g, 3.7 mmol) and Raney Nickel (3.5 g). This mixture was stirred at room temperature for 4 hour under H_2 at 50 psi, then the mixture was filtrated and washed with methanol (20 mL) to give compound **18** (2.0 g, 87% yield). ^{1}H NMR (400 MHz, DMSO) 9.81 (d, *J* = 2.4, 1H), 9.27 (d, *J* = 2.8, 1H, 7.90 (d, *J* = 7.6, 2H), 7.58-7.53 (m, 2H), 7.45-7.50 (m, 2H), 7.09-7.05 (m, 1H), 6.74-6.70 (m, 1H), 5.22 (s, 2H). M/Z 306.1 ($M+H^+$).

3.5.3. Synthesis of N-(4-fluoro-3-(6-phenyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)phenyl)-2,4-dimethyloxazole-5-carboxamide (GNF3849) (19)

To a solution of 2,4-dimethyloxazole-5-carboxylic acid (0.56 g, 3.9 mmol) in dimethylformamide (30 mL) was added DIEA (0.85 g, 6.66 mmol) and HATU (1.5 g, 3.9 mmol). This mixture was stirred at room temperature for 30 minutes, then compound **18** (1.0 g, 3.28 mmol) was added. The mixture was then stirred at room temperature for 4 hours, diluted with water (50 mL) and extracted with tetrahydrofuran/ ethyl acetate (100 mL /50 mL), the organic layer was dried over sodium sulfate and concentrated to give the crude product. It was purified by HPLC to give product **19** (0.91 g, yield, 65%) as a white solid. ^{1}H NMR (400 MHz, MeOD) 9.49 (d, *J* = 2.4, 1H), 9.22 (d, *J* = 2.4, 1H), 8.51 (dd, *J* = 6.4, 2.8, 1H), 7.90 (ddd, *J* = 8.9, 4.2, 2.8, 1H), 7.86-7.76 (m, 2H), 7.63-7.55 (m, 2H), 7.54-7.45 (m, 1H), 7.32 (dd, *J* = 10.4, 9.0, 1H), 2.56 (s, 3H), 2.47 (s, 3H). M/Z= 429.2 ($M+H^{+}$).

3.6. Synthesis of GNF2636; isopropyl (2-(2-chloro-5-(furan-2-carboxamido)phenyl)imidazo[1,2-a]pyrimidin-6-yl)carbamate

3.6.1. Synthesis of isopropyl (2-(2-chloro-5-nitrophenyl)imidazo[1,2-a]pyrimidin-6-yl)carbamate (20)

Into a 500-mL round-bottom flask, was placed **13** (1.75 g, 6.3 mmol, 1.2 equiv), acetone (400 mL) and 2-bromo-1-(2-chloro-5-nitrophenyl)ethan-1-one (1.0 g, 5.3 mmol). The resulting solution was stirred overnight at 70 °C. The reaction mixture was cooled, the solvent evaporated, the resulting material suspended in methanol, and then solids collected by filtration resulting in product **20** (0.75 g, 38% yield). 1H NMR (400 MHz, DMSO-D6) δ 10.08 (s, 1H), 9.34 (s, 1H), 9.08 (s, 1H), 8.86 (s, 1H), 8.56 (s, 1H), 8.19 (d, J = 8.7, 1H), 7.88 (d, J = 8.8, 1H), 4.95 (m, 1H), 1.30 (m, 6H). MS m/z (ESI) = 377 (M +).

3.6.2. Synthesis of isopropyl (2-(5-amino-2-chlorophenyl)imidazo[1,2-a]pyrimidin-6-yl)carbamate (21)

In a round-bottom flask, **20** (300 mg, 0.77 mmol) was taken up in methanol (20 mL) and SnCl2 (3 equivalents) was added. The resulting mixture was stirred for 2 hours at reflux. The reaction mixture was concentrated under vacuum and the crude material was purified by flash column chromatography (hexane/ ethyl acetate solvent system followed by DCM/methanol solvent system) resulting in **21** (265 mg, 96%) as a yellow solid. 1H-NMR: (300 MHz, MeOD): 9.30 (s, 1H), 8.51 (d, J = 2.1 Hz, 1H), 8.37 (s, 1H), 7.37 (d, J = 1.8 Hz, 1H), 7.23 (d, J = 6.6 Hz, 1H), 6.72-6.74 (m, 1H), 5.01-5.07 (m, 1H), 1.24-1.36 (m, 6H). MS m/z = 346 (M+H+).

3.6.3. Synthesis of isopropyl (2-(2-chloro-5-(furan-2-carboxamido)phenyl)imidazo[1,2-a] pyrimidine-6-yl)carbamate (GNF2636) (22)

To a suspension of compound **21** (20 mg, 0.06 mmol) in pyridine (2 mL) in a vial was added 2-furoyl chloride (1.5 equivalents) at room temperature. After stirring overnight, the reaction was concentrated and the resulting residue was purified by prep HPLC to afford the product **22** (5 mg, 19% yield). 1H NMR (400 MHz, methanol-*d*4) δ9.57 (s, 1H), 8.76 (d, *J* = 2.6 Hz, 1H), 8.52 (s, 1H), 8.31 (d, *J* = 2.6 Hz, 1H), 7.89 – 7.69 (m, 2H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 3.5 Hz, 1H), 6.68 (dd, *J* = 3.5, 1.7 Hz, 1H), 5.14 – 4.97 (m, 1H), 1.35 (d, *J* = 6.3 Hz, 6H). MS *m/z* = 440.2 (M+H).