6N-aryl-2-aminobenzimidazoles: Novel, Efficacious, Antimalarial leadcompounds

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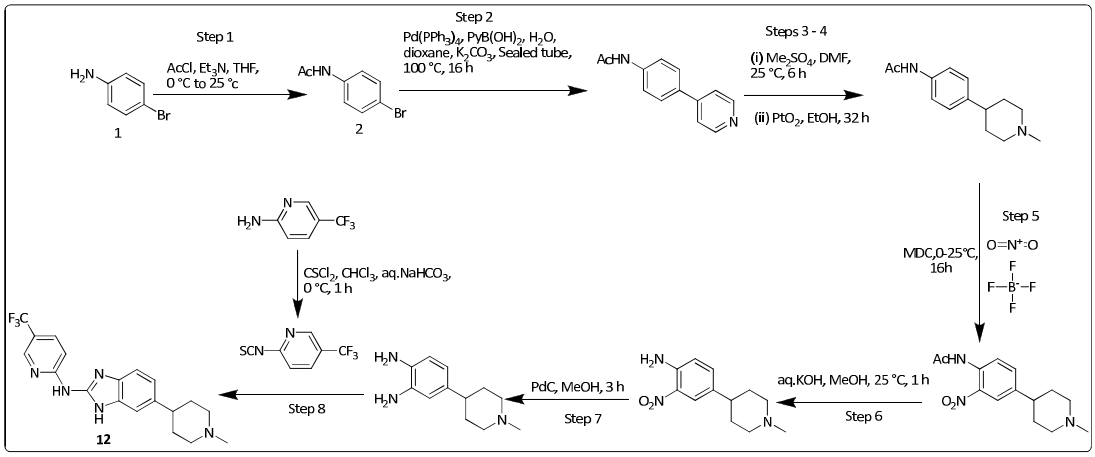
Supporting information

1. **Synthetic schemes and procedures for intermediates and final compounds**
2. Synthetic schemes and procedures for intermediates and final compounds

6-(1-Methylpiperidin-4-yl)-N-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]imidazol-2-amine (12):



Step 1: N-(4-Bromophenyl)acetamide

To the solution of 4-bromoaniline (6g, 0.03529 mole) in dry THF (120 mL) was added TEA (19.67 mL, 0.1411 mole) followed by acetylchloride (5 mL, 0.07058 mole) at 0°C. The resulting solution was allowed to stir at RT for 16 h. The reaction mixture was concentrated to remove THF, added water (100 mL) to the residue and filtered, washed with pet ether and dried to give N-(4-bromophenyl) acetamide as pale yellow solid. Yield: 6 g (79%). LCMS m/z: 216.3 (M+2).

Step 2: N-(4-(Pyridin-4-yl)phenyl)acetamide

To the solution of N-(4-bromophenyl)acetamide (6 g, 0.02803 mole) in dioxane:water (4:1, 60 mL) in a sealed tube was added pyridine-4-boronic acid (4.13 g, 0.03363 mole), K_2CO_3 (7.74 g, 0.05606 mole) and the resulting solution was degassed with nitrogen followed by addition of tetrakis (triphenylphosphine) palladium (0) (1.61 g, 0.001401 mole) and stirred at 100°C for 16 h. The reaction mixture was filtered through celite, washed with ethylacetate (25 mL) and the filtrate was concentrated to remove dioxane. The residue was triturated with

water (50 mL), filtered, washed with ether and dried to give N-(4-(pyridin-4-yl)phenyl)acetamide as dark brown solid. Yield: 4 g (67%). LC-MS: m/z 213.25 (M+1) 400 MHz, DMSO-d6: δ 10.12 (s, 1H), 8.58 (d, J = 8.0 Hz, 2H), 7.66-7.78 (m, 6H), and 2.07 (s, 3H).

Step3-4: N-(4-(1-Methylpiperidin-4-yl)phenyl)acetamide:

To the solution of N-(4-(pyridin-4-yl)phenyl)acetamide (4 g, 0.01884 mole) in dry DMF (60 mL) was added dimethyl sulfate (2.68 mL, 0.02826 mole) and the resulting solution was stirred at RT for 12 h. Completion of the reaction was monitored by LCMS. Ether (25 mL×2) was added to the reaction mixture stirred and decanted to remove DMF. Ethanol (25 mL) was added to the gummy solid, stirred and the solid precipitated was filtered under cold conditions. It was washed with ether and dried to give the quaternary salt as a brown solid. This solid (5.37 g, 0.02363 mole) was suspended in dry ethanol (75 mL), added PtO_2 (0.268 g, 0.00118 mole) and hydrogenated using balloon pressure for 12 h. Completion of the reaction was monitored by LCMS. The reaction mixture was filtered through celite, washed with methanol (20 mL), water (10 mL) and the filtrate was concentrated to remove ethanol and methanol. The resulting water layer was basified with 30% NaOH and extracted with DCM (50mL×2). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give N-(4-(1-methylpiperidin-4-yl)phenyl)acetamide as a white solid. Yield: 4 g (73%). LC-MS: m/z 233 (M+1). ^{1}H NMR: 300 MHz, $CDCl_3$: δ 7.41 (dd, J = 2.0, 9.00Hz, 2H), 7.25 (s, 1H), 7.17 (dd, J = 2.1, 6.0 Hz, 2H), 2.97 (dd, J = 3.0, 12.0 Hz, 2H), 2.37-2.50 (m, 2H), 2.16 (s, 3H), 2.09 (s, 3H), 1.94-2.05 (m, 2H), and 1.81-1.82 (m, 3H)

Step 5: N-(4-(1-Methylpiperidin-4-yl)-2-nitrophenyl)acetamide:

To the stirred solution of N-(4-(1-methylpiperidin-4-yl)phenyl)acetamide (4 g, 0.01724 mole) in dry DCM (100 mL) was added Nitronium tetrafluoroborate (4.57 g, 0.03448 mole)

portion wise at 0°C and the resulting solution was stirred at 25°C for 12h. Completion of the reaction was monitored by LCMS. The reaction mixture was diluted with DCM (100 mL), washed with saturated bicarbonate solution, water, brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography using 4-5% MeOH in DCM as an eluent to give N-(4-(1-methylpiperidin-4-yl)-2-nitrophenyl)acetamide as a white solid. Yield: 3.4 g (71%). LCMS: m/z 278.4 (M+1). ^{1}H NMR:300 MHz, DMSO-d_6: δ 10.16 (s, 1H), 7.73 (s, 1H), 7.55-7.58 (m, 1H), 7.47-7.50 (m, 1H), 2.83-2.87 (m, 2H), 2.48-2.58 (m, 1H), 2.18 (s, 3H), 2.02 (s, 3H), 1.92-1.96 (m, 2H), and 1.64-1.75 (m, 4H).

Step 6: 4-(1-Methylpiperidin-4-yl)-2-nitroaniline:

To the solution of N-(4-(1-methylpiperidin-4-yl)-2-nitrophenyl)acetamide (3.43 g, 0.01238 mole) in methanol (70 mL) was added 30% KOH solution (5.8 mL, 0.03095 mole) and stirred at RT for 3 h. The reaction mixture was concentrated to remove methanol, diluted with water and extracted with DCM (50 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give 4-(1-methylpiperidin-4-yl)-2-nitroaniline as a pale yellow solid which was used for next step without further purification. Yield: 2.7 g (92%). LCMS: m/z 236.4 (M+1). ^{1}H NMR: 400 MHz, DMSO-d_6: δ 7.74 (s, 1H), 7.31-7.36 (m, 3H), 6.97 (d, J = 12.00 Hz, 1H), 2.82-2.84 (m, 2H), 2.33-2.39 (m, 1H), 2.17 (s, 3H), 1.89-1.94 (m, 2H), 1.68-1.71 (m, 2H), and 1.57-1.61 (m, 2H).

Step 7: 4-(1-Methylpiperidin-4-yl)benzene-1,2-diamine:

To the solution of 4-(1-methylpiperidin-4-yl)-2-nitroaniline (2.7 g, 0.01148 mole) in EtOAc : MeOH (50 mL, 1:1) was added 10% Pd/C (540 mg) and hydrogenated using balloon pressure for 3 h. The reaction mixture was filtered through celite, washed with methanol (50 mL) and the filtrate was concentrated to remove methanol. The crude product was used as such for the next step without further purification. Yield: 2.48 g (crude).

2-Isothiocyanato-5-(trifluoromethyl)pyridine:

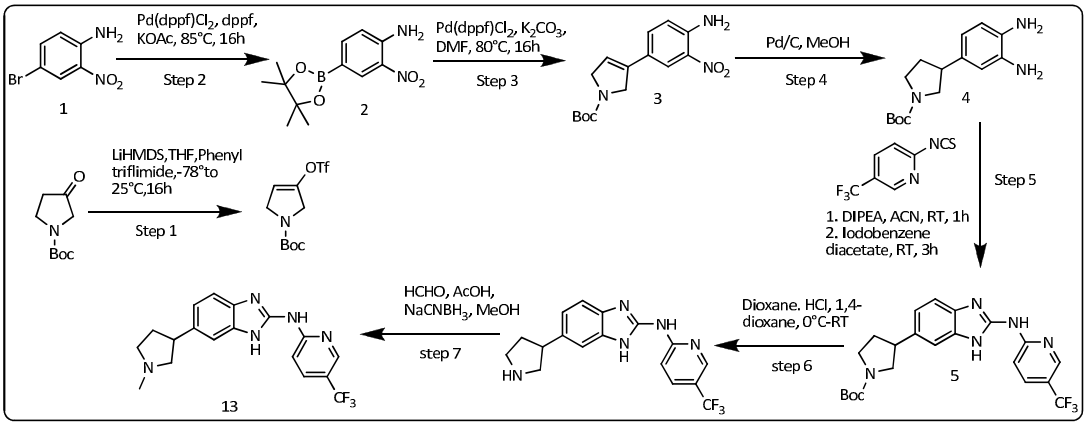
To the solution of 5-(trifluoromethyl)pyridin-2-amine (7.5 g, 0.04118 mole) in $CHCl_3$:H_2O (150 ml, 1:1) was added sodium bicarbonate (6.75 g, 0.08216 mole) followed by addition of thiophosgene (3.76 mL, 0.0494 mole) at 0°C. The reaction mixture was allowed to stir at 0°C for 1.5 h. Organic layer was separated and aqueous layer was extracted with DCM (50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated (bath temperature below 45°C). The crude product was purified by column chromatography using 5% EtOAc in pet ether as an eluent to give -isothiocyanato-5-(trifluoromethyl)pyridine as a red oil, which can be stored below -10°C for a period of 10-15 days. Yield: 4.5 g (59%). ^{1}H NMR: 400 MHz, CDCl3: δ 8.71-8.71 (m, 1H), 7.95-7.99 (m, 1H), and 7.20 (dd, J = 8.00 Hz, 1H).

Step 8: 6-(1-Methylpiperidin-4-yl)-N-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]-imidazol-2-amine (12):

To the solution of 4-(1-methylpiperidin-4-yl)benzene-1,2-diamine (2.48 g, 0.01208 mole) in dry THF (50 mL) in a sealed tube was added 2-isothiocyanato-5-(trifluoromethyl)-pyridine (2.96 g, 0.01450 mole), followed by EDCI (4.66 g, 0.02416 mole) and stirred at 100°C for 12 h. The reaction mixture was concentrated to remove THF, added water and extracted with DCM (50 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was triturated with acetonitrile (20 mL), cooled, filtered, washed with cold CH_3CN (10 mL), ether and dried to give 6-(1-methylpiperidin-4-yl)-N-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]imidazol-2-amine as off white solid .Yield: 2.4 g (52%). HRMS for$C_{19}H_{20}F_3N_5$[M+H]$^+$:376.17666.^{1}H NMR: 400 MHz, MeOD: δ 8.67 (s, 1H), 7.95-7.98 (m, 1H), 7.37-7.41 (m, 2H), 7.18 (dd, J = 2.1, 8.0 Hz, 1H), 7.06-7.09

(m, 1H), 3.15-3.18 (m, 2H), 2.68-2.76 (m, 4H), 2.49 (s, 3H), 2.41-2.46 (m, 1H), and 1.93-1.99 (m, 4H). HPLC purity: 98 %.

6-(1-Methylpyrrolidin-3-yl)-N-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]imidazol-2-amine (13):



Step 1: Tert-butyl 3-(((trifluoromethyl)sulfonyl)oxy)-2,5-dihydro-1H-pyrrole-1-carboxylate:

To a solution of tert-butyl 3-oxopyrrolidine-1-carboxylate (5.0 g, 27 mmol) in tetrahydrofuran (50 mL) at -78 °C is added 1M solution of sodium hexamethyldisilazane in tetrahydrofuran (50 mL) and the resulting mixture is stirred for 30 minutes. A solution of N-phenyl-bis-trifluoro methane sulfonimide (10.7 g, 30.0 mmol) in tetrahydrofuran (100 mL) is then added slowly to the reaction. The mixture is warmed to 0 °C and stirred for 2 h. Ice-water (100 mL) is added to the reaction mixture and the mixture is diluted with ethylacetate. The layers are separated and the aqueous layer is extracted with ethylacetate. The combined organic phase is dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material is purified via neutral alumina chromatography using 10% ethylacetate in petroleum ether as the eluent to afford the desired product as white gummy solid. Yield: 3.6 g (42.35%). 300 MHz, $CDCl_3$: δ 5.71-5.77 (m, 1H), 4.22-4.25 (m, 4H), and 1.57 (s, 9H).

Step2: 2-Nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

To a solution of 4-bromo-2-nitrobenzenamine (4 g, 18.43 mmol) in 1 ,4-dioxane (100 mL) was added KOAc (5.4 g, 55.02 mmol), Pd(dppf)Cl_2 (405 mg, 0.55 mmol), dppf (307 mg, 0.55 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (5.15 g, 20.28 mmol) under nitrogen purging for 10 mins. The resulting solution was stirred for 16 h at 85°C. Then the reaction was quenched by the addition of water (200 mL), extracted with ethylacetate (3 x 80 mL), dried over anhydrous ssodium sulfate, and concentrated under vacuum to give a residue, which was purified by silica gel column chromatography (50% DCM in pet ether) to afford 2-nitro-4-(4,4,5,5- tetramethyl- 1 ,3,2-dioxaborolan-2-yl)aniline as a yellow solid. Yield: 3.5 g (71.5%). LCMS: m/z 265.2 (M+1). ^{1}H NMR 300 MHz, DMSO-d_6: δ 8.25 (s, 1H), 7.69 (s, 2H), 7.53 (d, J = 1.3 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), and 1.26 (s, 12H).

Step 3: Tert-butyl 3-(4-amino-3-nitrophenyl)-2,5-dihydro-1H-pyrrole-1-carboxylate

A solution of 2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.5 g, 1.89 mmol) in anhydrousDMF (25 mL) was purged with nitrogen for 10 minutes. (tert-butyl 3-(((trifluoromethyl)sulfonyl)-oxy)-2,5-dihydro-1H-pyrrole-1-carboxylate (0.72 g, 2.27 mmol), dry potassium carbonate (0.602 g,4.35 mmol) were added under purging. Finally Pd(dppf)Cl_2 (0.092 g, 0.113 mmol) was added and heated to 80°C for 16 h. The reaction mixture was concentrated under reduced pressure. The crude product obtained was purified by column chromatography with 30% EtOAc in pet ether as eluent to get dark brown solid and used directly for next step. Yield: 0.31 g (53.7%).

Step 4:Tert-butyl 3-(3,4-diaminophenyl)pyrrolidine-1-carboxylate

To the solution oftert-butyl 3-(4-amino-3-nitrophenyl)-2,5-dihydro-1H-pyrrole-1-carboxylate (0.35 g, 1.14 mmol) in DCM:MeOH (10 mL) was added 10% Pd/C (100 mg) and

hydrogenated under hydrogen balloon pressure for 3 h. The reaction mixture was filtered through celite, washed with methanol (10 mL) and the filtrate was concentrated to remove methanol. The crude product was used as such for the next step without further purification. Yield: 0.292 g (92.1%). LCMS: m/z 279.2 (M+2).

Step 5: Tert-butyl 3-(2-((5-(trifluoromethyl)pyridin-2-yl)amino)-1H-benzo[d]imidazol-6-yl)-pyrrolidine-1-carboxylate

To the solution of tert-butyl 3-(3,4-diaminophenyl)pyrrolidine-1-carboxylate (0.292 g, 1.05 mmol) in acetonitrile (10 mL) was added 2-isothiocyanato-5-(trifluoromethyl)pyridine (0.214 g, 1.05 mmol) and diisopropylethylamine (0.625 mL, 3.79 mmol) stirred at RT for 1 h. Then Iodo benzenediacetate (0.813 g. 2.52 mmol) was added and stirred at RT for 3 h. The reaction mixture was concentrated to remove acetonitrile and the crude obtained was purified by column chromatography with 10% MeOH in DCM-saturated with ammonia as eluent to get tert-butyl 3-(2-((5-(trifluoromethyl)pyridin-2-yl)amino)-1H-benzo[d]imidazol-6-yl)pyrrolidine-1-carboxylate as off white solid. Yield: 0.090 (19.1%)**.** LCMS: m/z 448.2 (M+1). ^{1}H NMR400 MHz, DMSO-d_6: δ 12.01 (s, 1H), 11.27 (s, 1H), 8.62 (s, 1H), 8.09 (q, J = 2.0 Hz, 1H), 7.36-7.47 (m, 3H), 7.06 (d, J = 7.6 Hz, 1H), 3.71-3.75 (m, 1H), 3.49 (s, 3H), 3.16-3.25 (m, 1H), 2.13 (m, 1H), 1.90-2.01 (m, 1H), and 1.42 (s, 9H).

Step 6: 6-(Pyrrolidin-3-yl)-N-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]imidazol-2-amine

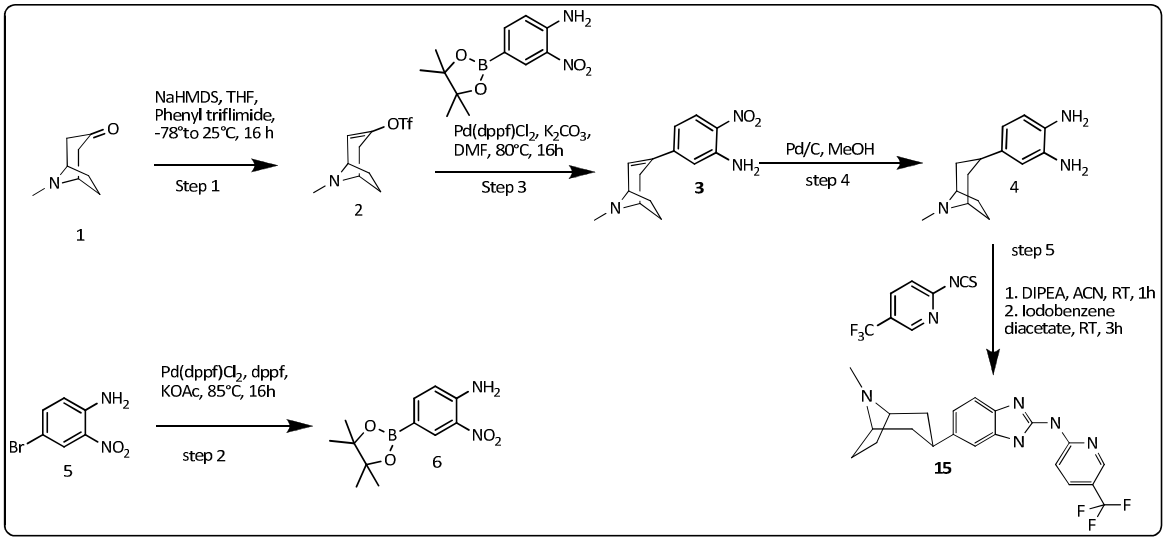
To a solution of tert-butyl 3-(2-((5-(trifluoromethyl)pyridin-2-yl)amino)-1H-benzo[d]imidazol-6-yl)pyrrolidine-1-carboxylate (0.21 g, 0.561 mmol) in 1,4-dioxane (10 mL) was added HCl in 1,4-dioxane solution (10 mL, 3N) at 0°C and stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure diluted with 10% MeOH in DCM and basified with solid sodium bicarbonate and filtered. The

filtrate was concentrated under reduced pressure. The residue was taken in 1% MeOH in DCM and filtered to remove the solid sodium bicarbonate, filtrate concentrated under reduced pressure to obtain 6-(pyrrolidin-3-yl)-N-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]imidazol-2-amine as brown color solid. Yield: 0.16 g (59.2%). LCMS: m/z 348.2 (M+1). ^{1}H NMR 300 MHz, DMSO-d6: δ 11.94 (s, 1H), 11.14 (s, 1H), 9.02 (s, 1H), 8.59 (s, 1H), 8.07 (d, J = 5.9 Hz, 1H), 7.39-7.49 (m, 3H), 7.03 (d, J = 8.1 Hz, 1H), 3.40-3.70 (m, 3H), and 3.07 (m, 4H).

Step 7: 6-(1-Methylpyrrolidin-3-yl)-N-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]imidazol-2-amine (13)

To a solution of 6-(pyrrolidin-3-yl)-N-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]imidazol-2-amine (0.16 g, 0.48 mmol) in methanol (10 mL) was added formaldehyde (0.036 g, 0.48 mmol, 40%) and glacial acetic acid (2 drops) stirred at room temperature for 2 h. Then sodium cyanoborohydride was added and stirred at 20°C for 16 h. Reaction mixture was concentrated under reduced pressure and purified by column chromatography using 5% MeOH in DCM as eluent to obtain the crude product which was again purified in preparative HPLC to get 6-(1-methylpyrrolidin-3-yl)-N-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]imidazol-2-amine as a TFA salt which was taken in 10% MeOH in DCM and washed with 10% aqueous sodium bicarbonate solution. The organic layer was separated dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain 6-(1-methylpyrrolidin-3-yl)-N-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]imidazol-2-amine as off white solid. Yield: 0.024 g (13.87%). HRMS for$C_{18}H_{18}F_3N_5[M+H]^+$:362.15897.^{1}H NMR (400 MHz), MeOD: δ 8.66 (s, 1H), 7.94-7.97 (m, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.16 (m, 1H), 7.10 (t, J = 1.6 Hz, 1H), 3.67 (s, 1H), 3.55 (t, J = 8.8 Hz, 1H), 3.20 (t, J = 8.4 Hz, 1H), 2.97-2.99 (m, 1H), 2.78-2.81 (m, 1H), 2.50 (s, 3H), 2.40-2.42 (m, 1H), and 2.02-2.05 (m, 2H). HPLC purity: 97.87%.

6-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-N-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]imidazol-2-amine (15)



Step 1: (1R,5S)-8-Methyl-8-azabicyclo[3.2.1]oct-2-en-3-yl trifluoromethanesulfonate

To the solution of 8-methyl-8-azabicyclo[3.2.1]octan-3-one (9.35 g, 67.2 mmol) in dry THF (100 mL) was added sodium bis(trimethylsilyl)amide in tetrahydrofuran (73.9 mL, 73.9 mmol) at -78°C stirred for 10 mins. N-phenylbis(trifluoromethanesulfonamide) (24.0 g, 67.2 mmol) in tetrahydrofuran (100 mL) was added at -78° C, The reaction mixture was allowed to come to room temperature slowly and was stirred over night. Aqueous sodium hydroxide (0.1 M, 350 mL) was added and the mixture was extracted twice with ethylacetate (150 mL). The crude product was purified by column chromatography using 10-30% EtOAc in pet ether as eluent to give (1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-2-en-3-yl trifluoromethanesulfonate as a brown oil. Yield: 6.6 g (36%). ^{1}H NMR 400 MHz, $CDCl_3$: δ 5.87 (d, J = 5.6 Hz, 1H), 3.49-3.56 (m, 2H), 2.83-2.89 (m, 1H), 2.47 (s, 3H), 2.23-2.30 (m, 2H), 2.06-2.19 (m, 1H), 1.96-2.02 (m, 2H), and 1.80-1.86 (m, 1H).

Step 2: 2-Nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

To a solution of 4-bromo-2-nitrobenzenamine (4 g, 18.43 mmol) in 1 ,4-dioxane (100 mL) was added KOAc (5.4 g, 55.02 mmol), Pd(dppf)Cl_2 (405 mg, 0.55 mmol), dppf (307 mg, 0.55 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (5.15 g, 20.28 mmol) under nitrogen purging for 10 minutes. The resulting solution was stirred for 16 h at 85°C. Then the reaction was quenched by the addition of water (200 mL), extracted with ethylacetate (3 x 80 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum to give a residue, which was purified via silica gel chromatography (50% DCM in pet ether) to afford 2-nitro-4-(4,4,5,5- tetramethyl- 1 ,3,2-dioxaborolan-2-yl)aniline as a yellow solid. Yield: 3.5 g (71.5%). LCMS: m/z 265.2 (M+2). ^{1}H NMR 300 MHz, DMSO-d_6: δ 8.25 (s, 1H), 7.69 (s, 2H), 7.53 (d, J = 1.3 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), and 1.26 (s, 12H).

Step 3: 5-((1R,5S)-8-Methyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-nitroaniline

A solution of 2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.46 g, 5.0 mmol) in anhydrous DMF (30 mL) was purged with nitrogen for 10 mins. (1R,5S)-8-methyl-8-azabicyclo[3.2.1]-oct-2-en-3-yl trifluoromethanesulfonate (1.5 g, 5.0 mmol), dry potassiumcarbonate (1.74 g, 12.0 mmol) were added under purging. Finally Pd(dppf)Cl_2 (0.135g, 0.16 mmol) was added and heated at 80°C for 16 h. The reaction mixture was concentrated under reduced pressure. The crude obtained was purified by column chromatography with 30% EtOAc in pet ether as eluent to get dark brown solid. Yield: 1.2 g (83%). LCMS: m/z 260.4 (M+1). ^{1}H NMR 400 MHz, DMSO-d_6: δ 7.93 (s, 1H), 7.60-7.66 (m, 2H), 7.02 (d, J = 12.0Hz, 1H), 3.98-4.07 (m, 2H), and 1.89-1.97 (m, 4H).

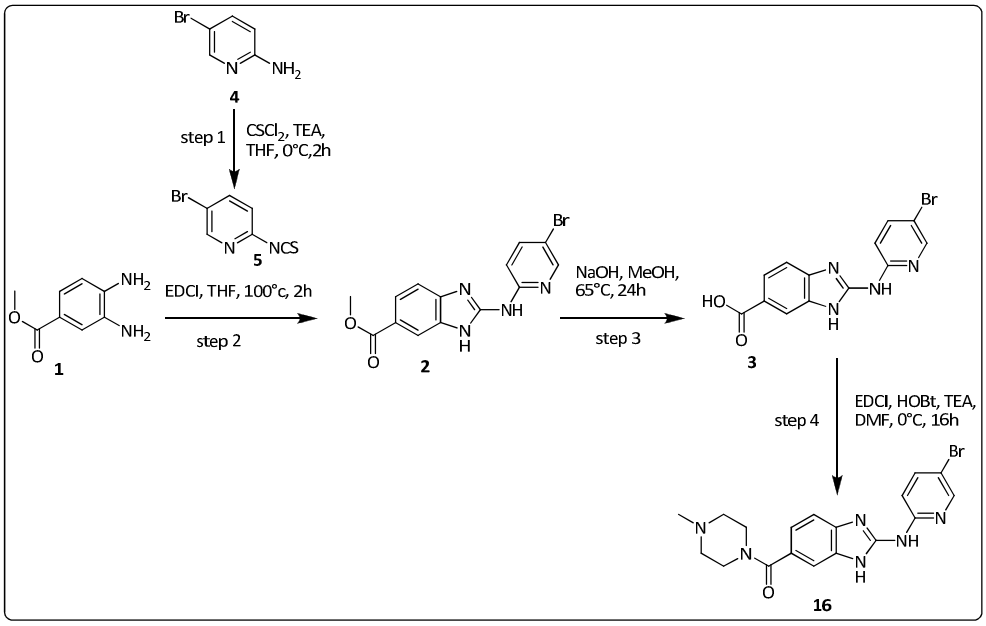
Step 4: 4-((1R,5S)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)benzene-1,2-diamine

To the solution of 5-((1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)-2-nitroaniline (1.2 g, 0.004 mol) in DCM:MeOH (120 mL) was added 10% Pd/C (500 mg) and hydrogenated using balloon pressure for 3 h. The reaction mixture was filtered through celite, washed with methanol (10 mL) and the filtrate was concentrated to remove methanol. The crude product was used as such for the next step without further purification. Yield: 0.9 g (84%). LCMS: m/z 233.2 (M+2). ^{1}H NMR 400 MHz, DMSO-d_6: δ 6.92-7.03 (m, 3H), 3.84 (s, 2H), 3.38 (s, 2H), 3.05-3.15 (m, 1H), 2.58-2.62 (m, 3H), 2.20-2.34 (m, 4H), and 1.99-2.02 (m, 2H).

Step 5: 6-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-N-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]-imidazol-2-amine (15)

To the solution of 4-((1R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)benzene-1,2-diamine (0.50 g, 2.1 mmol) in acetonitrile (10 mL) was added 2-isothiocyanato-5-(trifluoromethyl)pyridine (0.441 g, 2.1 mmol) and diisopropylethylamine (0.350 mL, 4.3 mmol) stirred at RT for 1 h. Then Iodobenzenediacetate (1.39 g. 4.3 mmol) was added and stirred at RT for 3 h. The reaction mixture was concentrated to remove acetonitrile and the crude obtained was purified by column chromatography with 10% MeOH in DCM-saturated with ammonia as eluent to get 6-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-N-(5-(trifluoromethyl)pyridin-2-yl)-1H-benzo[d]imidazol-2-amine as off white solid. Yield: 0.05 g (5.7%). ^{1}H NMR 400 MHz, DMSO-d_6: δ 11.42 (s, 2H), 8.59 (s, 1H), 8.06 (d, J = 8.52 Hz, 1H), 7.47 (d, J = 8.64 Hz, 1H), 7.32 (t, J = 8.44 Hz, 2H), 6.99 (d, J = 8.12 Hz, 1H), 3.20 (s, 2H), 3.04 (d, J = 8.24 Hz, 1H), 2.31-2.36 (m, 2H), 2.18 (s, 3H), 2.01 (d, J = 3.92 Hz, 2H), and 1.47 (d, J = 7.08 Hz, 3H). HPLC purity: 94.6%.

(2-((5-Bromopyridin-2-yl)amino)-1H-benzo[d]imidazol-6-yl)(4-methylpiperazin-1-yl)methanone(16)



Step 1: 5-Bromo-2-isothiocyanatopyridine

To the solution of 5-bromopyridin-2-amine (1.0g, 5.7 mmol) in anhydrous THF (10 mL) was added triethylamine (1.75 mL, 12.7 mmol) and then at 0°C was added thiophosgene (0.697 g, 6.0 mmol) in THF (5 mL) was added dropwise and stirred for 3 h at 0°C. 10 g of celite was added to the reaction mixture and evaporated to dryness. The residue was purified by column chromatography using 5% EtOAc in pet ether as eluent to obtain 5-bromo-2-isothiocyanatopyridine as yellow solid. Yield: 0.52 g (43.3%). LCMS: m/z 215 (M+2). ^{1}H NMR 400 MHz, DMSO-d_6: δ 8.62 (d, J = 2.5 Hz, 1H), 8.19 (dd, J = 2.5, 8.4 Hz, 1H), and 7.39 (d, J = 8.5 Hz, 1H).

Step 2: Methyl 2-((5-bromopyridin-2-yl)amino)-1H-benzo[d]imidazole-6-carboxylate

To a solution of methyl 3,4-diaminobenzoate (0.4 g, 2.40 mmol) in THF (10 mL) were added 5-bromo-2-isothiocyanatopyridine (0.518 g, 2.40 mmol) and EDC.HCl (0.923 g, 4.81 mmol)

at room temperature. The resulting mixture was subjected to microwave irradiation in a sealed tube at 100°C for 2h. The product formation was confirmed by LCMS. The solvent was evaporated to dryness and residue was recrystallised from DCM and MeOH to obtain methyl 2-((5-bromopyridin-2-yl)amino)-1H-benzo[d]-imidazole-6-carboxylate as off white solid. Yield: 0.37 g (44.2%). LCMS: m/z 349.2 (M+2). ^{1}H NMR 300 MHz, DMSO-d_6: δ 12.13 (s, 1H), 11.00 (s, 1H), 8.37 (d, J = 2.1 Hz, 1H), 8.09 (s, 1H), 7.95 (t, J = 2.2 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.42 (s, 1H), 7.29 (s, 1H), and 3.83 (s, 3H).

Step 3: 2-((5-Bromopyridin-2-yl)amino)-1H-benzo[d]imidazole-6-carboxylic acid

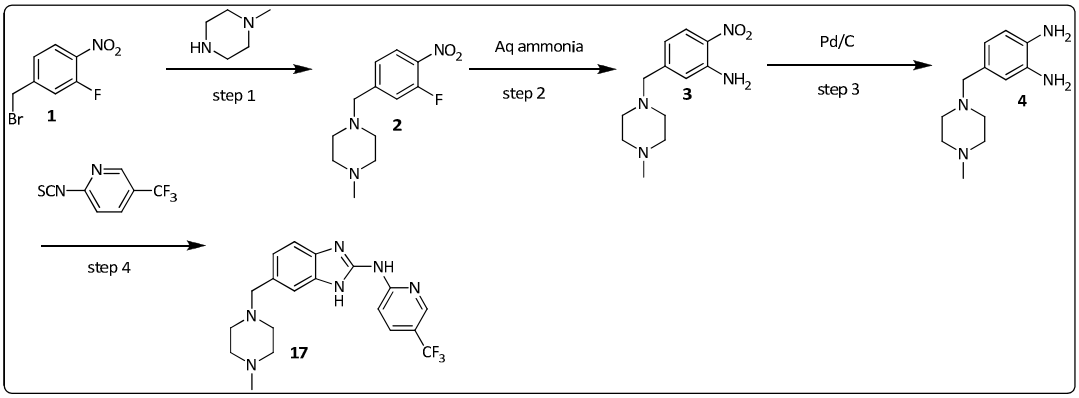
To a suspension of 2-((5-bromopyridin-2-yl)amino)-1H-benzo[d]imidazole-6-carboxylate (0.3 g, 0.86 mmol) in methanol was added sodium hydroxide solution. The resulting mixture was refluxed for 24h. The reaction mixture was cooled and evaporated to dryness. The residue was taken in water and acidified to pH 2 using conc. HCl and filtered to obtain 2-((5-bromopyridin-2-yl)amino)-1H-benzo[d]imidazole-6-carboxylic acid as white solid. Yield: 0.28 g (97.5%). LCMS: m/z 333 (M+1). ^{1}H NMR 400 MHz, DMSO-d_6: δ 12.64 (s, 1H), 8.45 (d, J = 2.4 Hz, 1H), 8.11 (d, J = 0.8 Hz, 1H), 8.04 (dd, J = 2.8, 9.0 Hz, 1H), 7.81 (dd, J = 1.2, 8.2 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), and 7.36 (t, J = 6.8 Hz, 1H).

Step 4:(2-((5-Bromopyridin-2-yl)amino)-1H-benzo[d]imidazol-6-yl)(4-methylpiperazin-1-yl)methanone (16)

To a solution of 2-((5-bromopyridin-2-yl)amino)-1H-benzo[d]imidazole-6-carboxylic acid (0.29 g, 0.87 mmol) in DMF (20 mL) were added EDC.HCl (0.250 g, 1.30 mmol), HOBt (0.176 g, 1.30 mmol) and Triethylamine (0.241mL, 1.74 mmol). To this clear solution was added N-methyl piperazine (0.176 g, 1.30 mmol) and stirred at room temperature for 16 h. The product formation was confirmed by LCMS. The solvent was evaporated to dryness and residue was Purified by column chromatography using 10% MeOH in DCM as eluent to

obtain (2-((5-bromopyridin-2-yl)amino)-1H-benzo[d]imidazol-6-yl)(4-methylpiperazin-1-yl)methanone as white solid. Yield: 0.049 g (11.35%). ^{1}H NMR 400 MHz, DMSO-d_6: δ 11.97 (s, 1H), 10.87 (s, 1H), 8.38 (d, J = 2.2 Hz, 1H), 7.96 (dd, J = 2.5, 8.8 Hz, 1H), 7.33-7.53 (m, 3H), 7.10 (s, 1H), 3.54 (s, 4H), 2.40 (s, 4H), and 2.25 (s, 3H). HPLC purity: 98.13 %.

6-((4-Methylpiperazin-1-yl)-N-(5-trifluoromethyl) pyridine-2-yl)-1H-benzo(d)imidazol-2-amine (17)



Step 1: 1-(3-Fluoro-4-nitrobenzyl)-4-methylpiperazine

To the solution of 4-(bromomethyl)-2-fluoro-1-nitrobenzene (2.47 g, 0.0105 mol) in DCM (50 mL) was added DIPEA (3.65 mL, 0.0157 mole) and 1-methylpiperazine (1.162 g, 0.0116 mol) at RT. Then the resulting solution was stirred at RT for 1 h. After the completion of the reaction, reaction mass was diluted with DCM, water and the organic layer was separated. Then organic layer was dried over Na_2SO_4 and concentrated to get brown solid. The crude material was directly taken to next step without further purification. Yield: 1.5 g (45%). ^{1}H NMR: 400 MHz, DMSO-d_6: δ 8.11 (m, 1H), 7.93 (s, 1H), 7.42 (m, 1H), 3.56 (s, 2H), 2.48-2.49 (m, 8H), and 2.14 (s, 3H),.

Step 2: 5-((4-Methylpiperazin1-yl)-2-nitroaniline

To the solution of 1-(3-fluoro-4-nitrobenzyl)-4-methylpiperazine (1.5 g, 0.0059 mole) in ethanol (15 mL) was added aqueous ammonia (30 mL) at RT. Then reaction mass was stirred at 80-85°C in a sealed tube for 16h. TLC checked, after the completion of the reaction, reaction mass was evaporated completely to get brown solid. This was directly taken to next step without further purification. Yield: 1.2 g (Crude). LCMS [M+1] 251.2.

Step 3:4-((4-Methylpiperazin-1-yl)methyl)benzene-1,2-diamine:

To a solution of nitro compound **3** (1.2 g, 0.00479 mo) in methanol-ethyl acetate (1:1 mixture, 15 mL) was added palladium (10%) on carbon (cat. amount). The mixture was stirred under hydrogen atmosphere for 16 h. The suspension was filtered out. The filtrate was concentrated to obtain crude diamine. Yield: 1.0 g (63%). LCMS [M+1] 221.2.

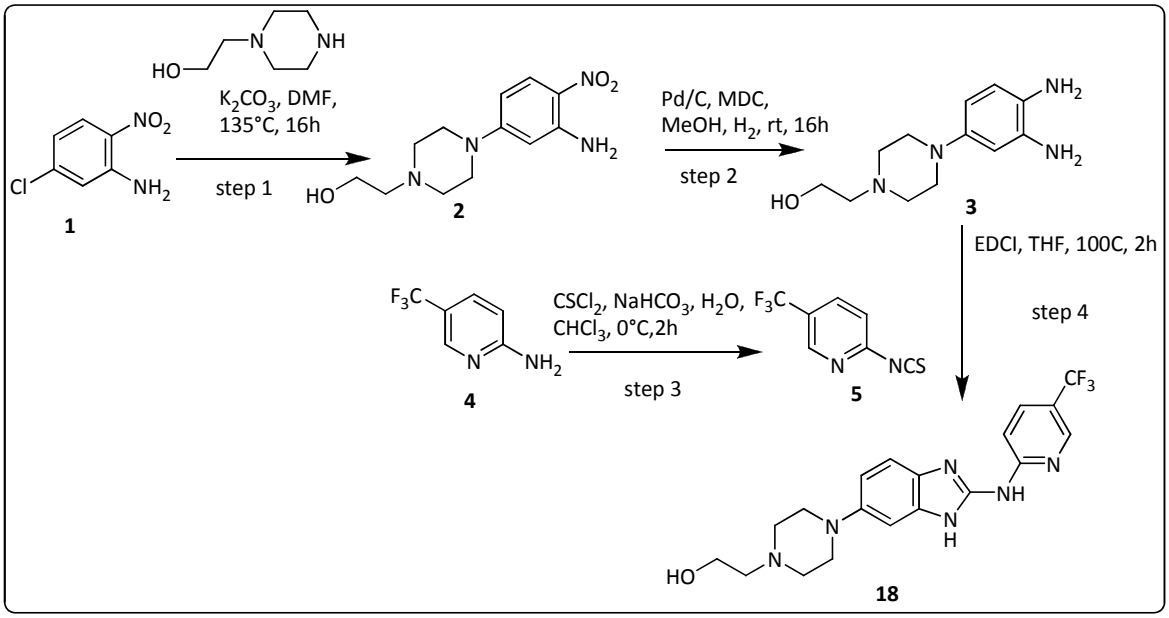
2-Isothiocyanato-5-(trifluoromethyl)pyridine

To the solution of 5-(trifluoromethyl)pyridin-2-amine (7.5 g, 0.04118 mole) in $CHCl_3$:H2O (150 mL, 1:1) was added sodium bicarbonate (6.75g, 0.08216 mole) followed by addition of thiophosgene (3.76 mL, 0.0494 mole) at 0°C. The reaction mixture was allowed to stir at 0°C for 1.5 h. Organic layer was separated and aqueous layer was extracted with DCM (50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated (bath temperature below 45°C). The crude product was purified by column chromatography using 5% EtOAc in pet ether as an eluent to give -isothiocyanato-5-(trifluoromethyl)pyridine as a red oil, which can be stored below -10°C for a period of 10-15 days. Yield: 4.5 g (59%).

Step 4: 6-((4-Methylpiperazin-1-yl)-N-(5-trifluoromethyl) pyridine-2-yl)-1H-benzo(d)imidazol-2-amine (17)

To the solution of 4-((4-methylpiperazin-1-yl)methyl)benzene-1,2-diamine (0.5 g, 0.00226 mole) in dry THF (15 mL) in a microwave was added 2-isothiocyanato-5-(trifluoromethyl)-pyridine (0.556 g, 0.00272 mole), followed by EDCI (0.866 g, 0.00452 mole) and stirred at 100°C for 2 h. The reaction mixture was concentrated to remove THF, added water and extracted with DCM (25 mL×2). The combined organic layer was washed with water, brine, dried over Na2SO4 and concentrated. The crude product was purified by column chromatography using 2-3% MeOH in DCM as an eluent to give 6-((4-methylpiperazin-1-yl)-N-(5-trifluoromethyl) pyridine-2-yl)-1H-benzo(d)imidazol-2-amine as off white solid. Yield: 0.12 g (82%). HRMS for $C_{19}H_{21}F_3N_6$ $[M+H]^+$: 391.18625. ^{1}H NMR: 400 MHz, DMSO-d_6: δ 8.70 (s, 1H), 8.22 (d, J = 8.00 Hz, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.44 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 3.45 (s, 2H), 3.38-3.44 (m, 4H), 3.08-3.17 (m, 4H), and 2.50 (s, 3H). HPLC 98.43 %.

2-(4-(2-((5-(Trifluoromethyl)pyridin-2-yl)amino)-1H-benzo[d]imidazol-6-yl)piperazin-1-yl)ethan-1-ol (18)



Step 1: 2-(4-(3-Amino-4-nitrophenyl)piperazin-1-yl)ethan-1-ol

To the solution of 5-chloro-2-nitroaniline (2.0 g, 11.0 mmol) in anhydrous DMF (20 mL) were added tert-butyl 2-(piperazin-1-yl)ethan-1-ol (2.26 g, 17.0 mmol) and potassium carbonate (4.80 g, 34.0 mmol). The resulting mixture was heated at 120°C for 16 h. The reaction mixture was quenched over water and extracted with EtOAc. The organic layer was separated dried over anhydrous sodiumsulphate and concentrated under reduced pressure to get dark brown solid which was washed with EtOAc to obtain 2-(4-(3-amino-4-nitrophenyl)piperazin-1-yl)ethan-1-ol as a yellow solid. Yield: 1.1 g (33.3%). LC-MS: m/z 267.4 (M+1). ^{1}H NMR 300 MHz, DMSO-d_6: δ 7.78 (d, J = 9.7 Hz, 1H), 7.25 (s, 1H), 6.37 (dd, J = 2.6, 9.9 Hz, 1H), 6.19 (d, J = 2.4 Hz, 1H), 4.44 (t, J = 5.3 Hz, 1H), 3.51 (q, J = 6.0 Hz, 2H), 3.29 (q, J = 5.0 Hz, 4H), and 2.40 (t, J = 6.3 Hz, 4H).

Step 2: 2-(4-(3,4-Diaminophenyl)piperazin-1-yl)ethan-1-ol

To a solution of 2-(4-(3-amino-4-nitrophenyl)piperazin-1-yl)ethan-1-ol (0.5 g, 1.87 mmol) in methanol : DCM (30 mL) was added palladium (10%) on carbon (0.2 g). The mixture was stirred under hydrogen atmosphere for 2 h. The suspension was filtered through celite and filtrate was concentrated under reduced pressure to obtain 2-(4-(3,4-diaminophenyl)piperazin-1-yl)ethan-1-ol which was taken to next step without further purification. Yield: 0.3 g (68.18%). %). LC-MS: m/z 237.4 (M+1).

Step 3: 2-Isothiocyanato-5-(trifluoromethyl)pyridine

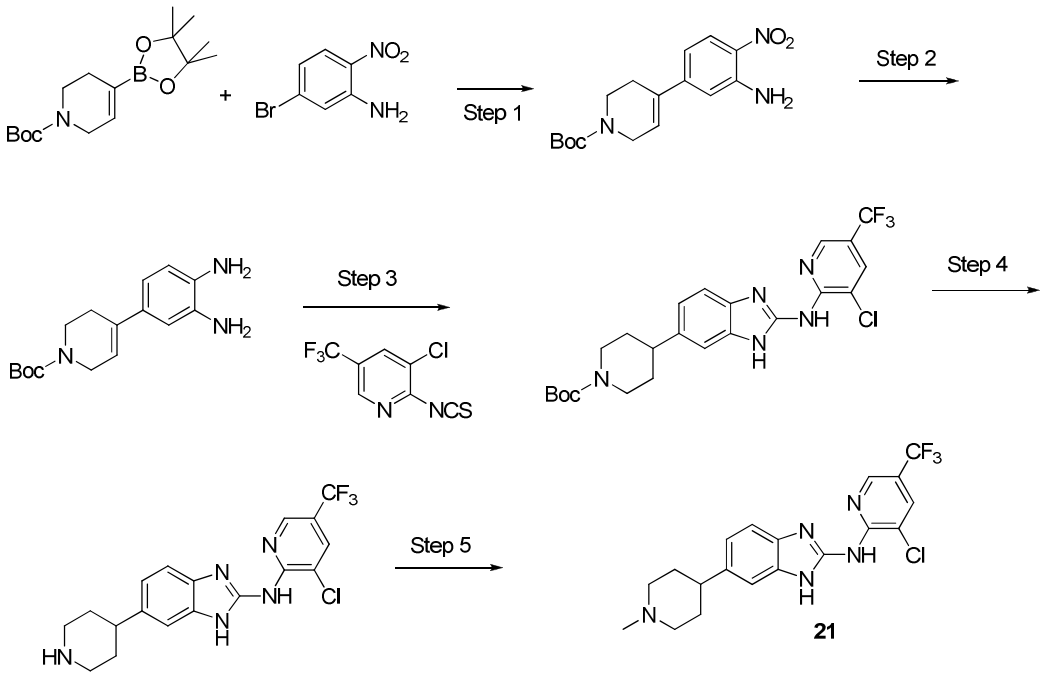
To the solution of 5-(trifluoromethyl)pyridin-2-amine (20 g, 12.3 mmol) in chloroform (100 mL) was added aqueous sodium bicarbonate (72.5 g, 6.4 mmol, 100 mL H_2O) and then at 0°C was added thiophosgene (9.4 mL, 12.3 mmol) dropwise and stirred for 2 h at 0°C. The reaction mixture was diluted with cold water and extracted in DCM. The organic layer was

separated dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain dark brown liquid which was passed through neutral alumina column using pet ether as eluent to obtain 2-isothiocyanato-5-(trifluoromethyl)pyridine as light yellow liquid. Yield: 16 g (64%). ^{1}H NMR 400 MHz, DMSO-d_6: δ 8.87 (d, J = 2.0 Hz, 1H), 8.14-8.17 (m, 1H), and 8.02 (d, J = 8.4 Hz, 1H).

Step 4:2-(4-(2-((5-(Trifluoromethyl)pyridin-2-yl)amino)-1H-benzo[d]imidazol-6-yl)piperazin-1-yl)ethan-1-ol (18)

To a solution of 2-(4-(3,4-diaminophenyl)piperazin-1-yl)ethan-1-ol (0.3 g, 1.26 mmol) in THF (10 mL) were added 2-isothiocyanato-5-(trifluoromethyl)pyridine (0.259 g, 1.36 mmol) and EDC.HCl (0.486 g, 2.53 mmol) at room temperature. The resulting mixture was subjected to microwave irradiation in a sealed tube at 100°C for 2 h. The product formation was confirmed by LCMS. The solvent was evaporated to dryness. The crude obtained was purified by column chromatography using 5% MeOH in DCM as eluent to obtain 2-(4-(2-((5-(trifluoromethyl)pyridin-2-yl)amino)-1H-benzo[d]imidazol-6-yl)piperazin-1-yl)ethan-1-ol as off white solid. Yield: 0.040 g (7.7%). %). ^{1}H NMR 400 MHz, DMSO-d_6: δ 11.59 (s, 1H), 10.80 (s, 1H), 8.58 (s, 1H), 8.04 (t, J = 1.96Hz, 1H), 7.45 (d, J = 8.16Hz, 1H), 7.27 (d, J = -2.04Hz, 1H), 6.98 (s, 1H), 6.79 (t, J = 2.0Hz, 1H), 4.48 (d, J = 7.1 Hz, 1H), 3.55 (d, J = 4.8 Hz, 2H), 3.08 (s, 4H), and 2.62 (s, 4H). HPLC purity: 95.94 %.

N-(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)-6-(1-methylpiperidin-4-yl)-1H-benzo[d]imidazol-2-amine (21)



Step 1: Tert-butyl 4-(3-amino-4-nitrophenyl)-5,6-dihydropyridine-1(2H)-carboxylate

In a biotage microwave reaction tube, 3,6-Dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid, pinacolester (712 mg, 2.30 mmol), 4-Bromo-2-nitrobenzenamine (500 mg, 2.30 mmol),1,1'-Bis(diphenylphosphino)ferrocenedichloropalladium(II) (190 mg, 0.23 mmol),CsF (1050 mg, 6.91 mmol) was taken in methanol (5 ml).The RM was subjected to MW power of 400W 120°C for 20'.The LCMS was checked showed the formation of required mass. The RM was passed through flow and the filtrate was chromatographed using dcm methanol to obtain tert-butyl 4-(4-amino-3-nitrophenyl)-5,6-dihydropyridine-1(2H)-carboxylate (720 mg, 98 %). MS (ES+), (M+H)+ = 319 for $C_{16}H_{21}N_3O_4$.

Step 2: Tert-butyl 4-(3,4-diaminophenyl)-5,6-dihydropyridine-1(2H)-carboxylate

In a 100ml RB flask,tert-butyl 4-(4-amino-3-nitrophenyl)-5,6-dihydropyridine-1(2H)-carboxylate (736 mg, 2.30 mmol) was dissolved in methanol (30 ml) and Pd/C (24.53 mg, 0.23 mmol) was added and stirred under hydrogen atmosphere (balloon) at RT for 13 hours.

Reaction mixture was filtered through sintered funnel and washed with methanol and concentrated under vacuum to gettert-butyl 4-(3,4-diaminophenyl)piperidine-1-carboxylate (640 mg, 95 %) which was taken for further step without purification. LCMS confirmed the product. MS (ES+), (M+H)+ = 291 for $C_{16}H_{25}N_3O_2$.

Step 3: **Tert-butyl 4-(2-(3-chloro-5-(trifluoromethyl)pyridin-2-ylamino)-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate**

3-chloro-2-isothiocyanato-5-(trifluoromethyl)pyridine (294 mg, 1.23 mmol)was added to the tert-butyl 4-(3,4-diaminophenyl)piperidine-1-carboxylate (359 mg, 1.23 mmol) in acetonitrile (10 ml).Complete conversion to the corresponding monothiourea was confirmed by LCMS(30-60 min). DIEA (0.430 ml, 2.46 mmol) was added to this reaction mixture followed by the portion wise addition of Iodobenzenediacetate (476 mg, 1.48 mmol) over a period of 10-15 min. The conversion of the thiourea to benzimidazole was observed within 5-10 min with concomitant precipitation of sulphur. The reaction mixture was allowed to stand, and the precipitated sulphur was filtered. The organic Layer was concentrated and chromatographed using dcm methanol to obtain the compound which was given for Gilson purification to obtain tert-butyl 4-(2-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate (387 mg, 63.3 %). LC-MS (M+H)+: 455 for $C_{23}H_{25}ClF_3N_5O_2$.

Step 4: N-(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)-6-(piperidin-4-yl)-1H-benzo[d]imidazol-2-amine

In a 50ml RB flask, tert-butyl 4-(2-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-1H-benzo[d]imidazol-6-yl)piperidine-1-carboxylate (387 mg, 0.78 mmol) was taken in dioxane

(5 ml). The RM was stirred at room temperature for 2 hrs. The LCMS was checked showed the formation of required mass. The RM was evaporated and given for Gilson prep purification to obtain N-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-6-(piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (235 mg, 66.1 %). LC-MS (M+H)+: 397 for $C_{18}H_{17}ClF_3N_5$.

Step 5: N-(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)-6-(1-methylpiperidin-4-yl)-1H-benzo[d]imidazol-2-amine (21)

In a 25 ml glass reaction vial N-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-6-(piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (200 mg, 0.51 mmol) was taken in DCM (2 ML). N,N'-diisopropylethylamine (0.352 mL, 2.02 mmol) was added and stirred for 5 min. The solvent was evaporated under vacuum. To this resultant crude, ethanol (2 mL) was added and followed by addition of Formaldehyde (0.044 mL, 0.66 mmol). After 10 min stirring, Sodium cyanoborohydride (31.8 mg, 0.51 mmol) was added one portion and stirred for 30 min. The reaction was monitored by LCMS. The profile showed completion of reaction. The RM was evaporated and taken in sodium bicarbonate solution, the solid obtained was filtered. The residue was chromatographed using dcm : methanol and little ammonia afforded N-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-6-(1-methylpiperidin-4-yl)-1H-benzo[d]imidazol-2-amine (45.0 mg, 21.73 %).^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.55 - 1.87 (m, 4 H) 1.91 - 2.08 (m, 2 H) 2.14 - 2.26 (m, 3 H) 2.82 - 2.95 (m, 2 H) 7.01 - 7.07 (m, 1 H) 7.15 - 7.20 (m,1 H) 7.22 - 7.29 (m, 1 H) 7.92 - 8.12 (m, 1 H) 8.33 - 8.53 (m, 1 H) 12.08 - 12.47 (m, 2 H). HPLC purity: 98 %.