Synthesis and Characterization of N-(3-(8-Bromoimidazo[1, 2-a] pyridin-2-yl)-4-Fluorophenyl)Benzamide Derivatives

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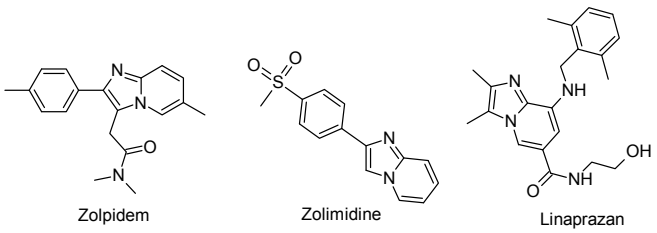
Abstract: We report here the synthesis and characterization of new N-(3-(8-bromoimidazo[1, 2-a]pyridin-2-yl)-4-fluorophenyl)benzamide derivatives. This collection was obtained from 3-(8-bromoimidazo [1,2-a]pyridin-2-yl)-4-fluoroaniline(5). The family of new compounds was characterized by ^{1}H-NMR, ^{13}C-NMR, FT-IR and LC-MS analysis.

Keywords: (2-fluoro-phenyl)ethanone; phenyl trimethyl ammonium tribromide; 3-bromopyridine-2-amine; zinc dust; ammonium chloride

Introduction:

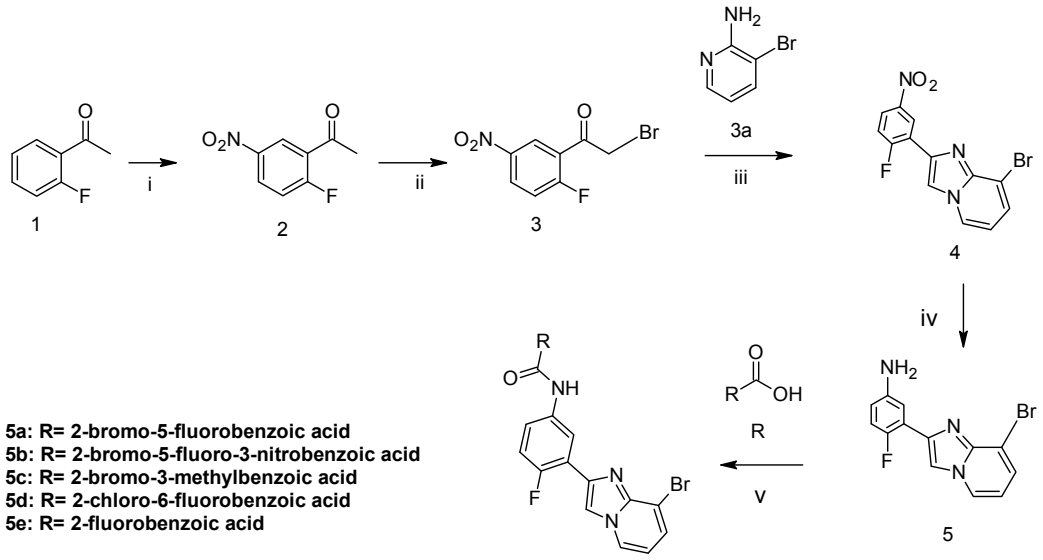
Heterocyclic compounds play important role in synthetic organic chemistry, due to its wide variety of applications in pharmaceutical, veterinary and agrochemical. Imidazo[1,2-a]pyrazine is a well known privileged fused heterocyclic motif containing five membered imidazole and six membered pyrazine ring with bridgehead nitrogen atom. Imidazo[1,2-a]pyridines, a novel class of pharmaceutical compounds exhibit a broad range of biological activities. Besides, imidazo[1,2-a]pyridine scaffold is found in a number of marketed drug formulations, such as zolimidine (an antiulcer drug), zolpidem (ahypnotic drug), and Linaprazan (Potassium-competitive acid blocking (P-CAB) activity).



Reagents and Instrumentation:

All reagents were purchased from Merck and Aldrich and used without further purification. The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). Elemental analysis was performed on a Heraeus CHN-O-Rapid analyzer. TLC was performed on silica gel Polygram SIL G/UV 254 plates.

Scheme 1



Reaction conditions and yields: i) H_2SO_4,HNO_3, -5°C to -10°C, 10 min,83%, ii) Phenyl trimethyl ammonium tribromide, DCM, RT, 2h 50%, iii) 3-bromopyridine-2-amine, $NaHCO_3$, ethanol,80 ^oC, 3h, 54%, iv) Ammonium chloride, Zinc, THF, MeOH, Water, 1h, RT 61%, v) N,N-dimethyl formamide, EDC.HCl, HOBT,DIPEA, 1h, RT 51% (**5a**), 45% (**5b**), 60% (**5c**), 62% (**5d**), 56% (**5e**).

Experimental

General

All reagents were purchased from Merck and Aldrich and used without further purification. The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument. The spectra were measured in DMSO-d6 relative to TMS (0.00 ppm). Elemental analysis was performed on a Heraeus CHN-O-Rapid analyzer. TLC was performed on silica gel Polygram SIL G/UV 254 plates.

Synthesis of 1-(2-fluoro-5-nitrophenyl)ethanone (2): A stirred solution of (2-fluoro-phenyl)ethanone (10 g, 0.0723 mol) in Con sulfuric acid (40 mL, 4V) was cooled to -5°C to -10°C. To this yellow stirred suspension was added drop wise a mixture of Con sulfuric acid : Con nitric acid (14 mL: 8 mL) at same temperature in the period of 30 min. A yellow color thick suspension was stirred for 10 min at same temperature and monitored by TLC /LCMS. After 10 min TLC shows complete consumption of starting material, the reaction mixture was drop wise poured in ice cold water (500 mL, 50 V). The yellow precipitated solid was filtered and washed with water (50 mL, 5V). The yellow solid was taken in dichloromethane (100 mL, 10V) and washed with brine solution (50 mL, 5V). Organic layer was concentrated at -30°C to -35°C and co-evaporated with hexane (50 mL, 5V). The yellow crude solid was suspended in hexane (50 mL, 5V) and cooled to 0°C to 5°C then stirred for 1h at same temperature. The yellow solid was filtered and washed with hexane (20 mL, 2V) then dried under vacuum to afford the pale yellow solid (11 g, 83%).

FT-IR (cm−1): 3079 (Aromatic C-H), 1691 (C=0), 1352 (Nitro), 576 (Halo); ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 8.77 (d, J = 3.2 Hz, 1H); 8.42 (dd, J =3.2, 4, 1H); 7.37 (d, J = 9.2, Hz, 1H); 3.15 (s, 3H). (Fig-1 to 2)

Synthesis of 2-bromo-1-(2-fluoro-5-nitrophenyl)ethanone (3): A stirred solution of 1-(2-fluoro-5-nitrophenyl)ethanone (10 g, 0.0546 mol) in dichloromethane (150 mL, 15V) was cooled to 0°C to -5°C. To this yellow color clear solution was added the phenyl trimethyl ammonium tribromide (24.63 g, 0.0655 mol) in 3 equal lots in the period of 10 min time interval. The reaction mixture slowly warmed to room temperature and stirred for 2h at same temperature.

The reaction mixture was monitored by TLC/LCMS. After completion of starting material the reaction mixture was quenched with ice cold water (250 mL, 25 V). Two layers were separated and organic layer was washed with 10% sodium bicarbonate (100 mL, 10V) and brine solution (100 mL, 10 V). Organic layer was concentrated concentrated at -30°C to -35°C. The yellow gammy solid was taken in methanol (2 mL, 2 V) and cooled to -15°C to -20 °C then stirred for 1h. The precipitated solid was filtered and dried under vacuum to afford the off white solid (7.15 g, 50%)

FT-IR (cm−1): 3080 (Aromatic C-H), 2959 (Alkane), 1697 (C=0), 1346 (Nitro), 597 (Halo); ^{1}H-NMR (400 MHz, $CDCl_3$) : δ 8.84 (d, J = 0.8 Hz, 1H); 8.49 (dd, J =2.8, 1.2, 1H); 7.42 (d, J = 9.2, Hz, 1H); 2.10 (s, 2H); LC-MS: m/z 262. (Fig-3 to 5)

Synthesis of 8-bromo-2-(2-fluoro-5-nitrophenyl)imidazo[1,2-a]pyridine (4): 2-bromo-1-(2-fluoro-5-nitrophenyl)ethanone (8 g, 0.0305 mol) , 3-bromopyridine-2-amine (5.81 g, 0.335 mol) and sodium bicarbonate (7.7 g, 0.015 mol) was taken in ethanol (80 mL, 10 V) at room temperature. The pale yellow color clear solution was heated to 80°C in closed condition and stirred for 3h. The progress of reaction mixture was monitored by TLC/LCMS, after 3h complete consumption of starting material was observed y by TLC. After 2h onwards the reaction mixture was becoming pale yellow clear solution to pale yellow suspension. The reaction mixture was cooled to room temperature and concentrated the ethanol solvent up to 2V level. This residue was poured into ice cold water (160 mL, 20 V) and stirred for 30 min at 0 °C to 5 °C. The precipitated solid was filtered and dried under vacuum to afford the pale yellow solid (5.6 g, 54%).

FT-IR (cm−1): 3088 (Aromatic C-H), 1343 (Nitro), 1250 (Aromatic amine), 709 (Bromo); ^{1}H-NMR (400 MHz, DMSO-d_6) : δ 9.06 (dd, J = 2.8, 3.2 Hz, 1H); 8.67 (d, J= 6.4 Hz, 2H); 8.29 (m, 1H); 7.71 (m, 2H); 6.93 (dd, J=7.6, 6.8 Hz, 1H); ^{13}C-NMR (400 MHz, DMSO-*d_6*): δ = 163.7, 161.2, 144.3, 142.1, 135.7, 128.6, 126.9, 124.7, 123.5, 122.4, 117.7, 115.3 , 113.0,109.9; LC-MS: m/z 337.9 . (Fig- 6 to 9)

Synthesis of 3-(8-bromoimidazo[1,2-a]pyridin-2-yl)-4-fluoroaniline (5): To a solution of 8-bromo-2-(2-fluoro-5-nitrophenyl)imidazo[1,2-a]pyridine (4 g, 0.0118 mol) in tetrahydrofuran:methanol (160 mL:40 mL, 40:10 V) was added zinc dust (3.86 g, 0.059 mol),

ammonium chloride (3.15 g, 0.059 mol) and water (8 mL, 2 V) at room temperature. The reaction mixture was stirred for 1h at room temperature and monitored by TLC/LCMS. After completion of stating material, the reaction mixture was filtered through celite plug. The filtrate was concentrated under reduced pressure to remove the THF and methanol solvent. The residue was diluted with water and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to afford the pale yellow solid. The crude was purified by column chromatography by eluting the 50% to 60% ethyl acetate in hexane. The column eluted solvent was concentrated under reduced pressure to get the yellow solid (2.2 g, 61%).

FT-IR (cm−1): 3400 (Amine), 3200 (Aromatic C-H), 1500 (Aromatic), 1196 (Aromatic amine), 760 (Bromo); ^{1}H-NMR (400 MHz, DMSO-d_6) : δ 8.63 (t, J = 4 Hz, 1H); 8.38 (d, J = 5.2 Hz, 1H); 7.62 (d, J = 7.2 Hz, 1H); 7.53 (dd, J = 3.2, 3.6 Hz, 1H); 6.99 (dd, J = 8.8, 2.4 Hz, 1H); 6.85 (t, J = 7.2 Hz, 1H); 6.54 (m, 1H); 5.16 (s, 2H); ^{13}C-NMR (400 MHz, DMSO-d_6): δ = 153.1, 150.8, 145.2, 141.7, 139.0, 128.6, 127.7, 126.6, 120.6, 115.9 , 114.4, 113.9, 112.6, 109.7, 79.0; LC-MS: [m+1] 307.9. (Fig-10 to 13)

*General procedure for the synthesis final coupling **5a-5e** :*

Compound-5a (1.5 eq) in N,N-dimethylformamide (0.9 mL, 3 V) was added EDC.HCl (1.5 eq), HoBt (0.1 eq) and diisopropylethyl aimne (3.0 eq) at room temperature and stirred for 15 min. To this yellow color clear solution was added 3-(8-bromoimidazo[1,2-a]pyridin-2-yl)-4-fluoroaniline (0.3 g, 0.97 mmol, 1.0 eq) and stirred for 16 h at room temperature. The progress of reaction was monitored by TLC/LCMS. After completion of starting material, the reaction mixture was poured into ice cold water (50 V) and stirred for 30 min. The precipitated solid was filtered and dried under vacuum. The crude material was suspended in MTBE (5 V) and stirred for 15 min at room temperature then filtered the solid and dried under vacuum to get the off white solid.

*2-bromo-N-(3-(8-bromoimidazo[1,2-a]pyridin-2-yl)-4-fluorophenyl)-5-fluorobenzamide **(5a)**:* FT-IR (cm−1): 3153 (Amide), 3053 (Aromatic C-H), 1672 (C=0), 1501 (Aromatic), 1204 (Aromatic amine), 821 (Bromo); ^{1}H-NMR (400 MHz, DMSO-d_6) : δ 10.80 (s, 1H), 8.62 (d, J = 6.4 Hz, 1H); 8.56 (dd, J = 2.4, 4 Hz, 2H); 7.87 (dd, J = 4.4,5.2 Hz, 2H); 7.66 (dd, J =7.6, 3.2 Hz, 2H); 7.38 (m, 2H); 6.89 (t, J = 7.2 Hz, 1H); LC-MS: [m+1] 508.0 . (Fig-14 to 16)

2-bromo-N-(3-(8-bromoimidazo[1,2-a]pyridin-2-yl)-4-fluorophenyl)-5-fluoro-3-nitrobenzamide (**5b**): FT-IR (cm−1): 3151 (Amide), 3090 (Aromatic C-H), 1668 (C=0), 1533 (Aromatic), 1361 (Nitro), 1219 (Aromatic amine), 781 (Bromo); ^{1}H-NMR (400 MHz, DMSO-d_6) : δ 10.97 (s, 1H), 8.66 (t, J = 4 Hz, 1H); 8.59 (d, J = 5.2 Hz, 1H); 7.62 (d, J = 7.2 Hz, 1H); 7.53 (dd, J = 3.2, 3.6 Hz, 1H); 6.99 (dd, J = 8.8, 2.4 Hz, 1H); 6.85 (t, J = 7.2 Hz, 1H); 6.54 (m, 1H); 5.16 (s, 2H); ^{13}C-NMR (400 MHz, DMSO-*d_6*): δ = 159.2, 151.2, 142.0, 141.7, 137.6, 134.9, 128.2, 126.8, 119.4, 116.4 , 114.7, 113.2, 112.7, 109.8, 105.8; LC-MS: [m+1] 553.0 . (Fig-17 to 20)

2-bromo-N-(3-(8-bromoimidazo[1,2-a]pyridin-2-yl)-4-fluorophenyl)-3-methylbenzamide (**5c**): FT-IR (cm−1): 3243 (Amide), 3072 (Aromatic C-H), 1670 (C=0), 1498 (Aromatic), 1357 (Alkane), 1201 (Aromatic amine), 815 (Bromo); ^{1}H-NMR (400 MHz, DMSO-d_6) : δ 10.65 (s, 1H), 8.66 (d, J = 6.4 Hz, 1H); 8.59 (d, J = 2.8 Hz, 1H); 8.50 (d, J = 4.4 Hz, 1H); 8.29 (s, 1H); 7.85 (m, 1H); 7.65 (t, J = 6.4 Hz, 1H); 7.47 (t, J = 2.8 Hz, 1H); 7.41 (m, 3H); 6.88 (t, J = 7.2 Hz, 1H); ^{13}C-NMR (400 MHz, DMSO-*d_6*): δ = 166.2, 154.5, 141.9, 139.7, 138.1, 137.9, 135.5, 131.5, 128.0, 127.4, 126.8, 126.0, 121.1, 120.6, 119.4, 116.4 , 114.6, 112.6, 109.7, 79.1; LC-MS: [m+1] 504.0 . (Fig-21 to 24)

N-(3-(8-bromoimidazo[1, 2-a]pyridin-2-yl)-4-fluorophenyl)-2-fluorobenzamide (**5d**):

FT-IR (cm−1): 3475 (Amide), 3032 (Aromatic C-H), 1660 (C=0), 1496 (Aromatic), 1215 (Aromatic amine), 776 (Bromo); ^{1}H-NMR (400 MHz, DMSO-d_6) : δ 10.68 (s, 1H), 8.67 (d, J = 6.8 Hz, 1H); 8.59 (dd, J = 4 Hz, 1H); 7.90 (d, J = 4.4 Hz, 1H); 7.74 (t, J = 7.2 Hz, 1H); 7.66 (d, J = 7.2 Hz, 1H); 7.63 (dd, J = 1.2 Hz, 1H); 7.39 (m, 3H); 6.89 (t, J = 6.8 Hz, 1H); ^{13}C-NMR (400 MHz, DMSO-*d_6*): δ = 162.8,160.1, 157.6, 154.5, 141.9, 137.9, 135.5, 132.5, 129.9, 128.1, 126.8, 124.5, 121.0, 120.9, 119.6, 116.2 , 115.9, 114. 6, 112.6, 109.7; LC-MS: [m+1] 464.0 . (Fig-25 to 28)

N-(3-(8-bromoimidazo[1,2-a]pyridin-2-yl)-4-fluorophenyl)-2-chloro-6-fluorobenzamide (**5e**): FT-IR (cm−1): 3132 (Amide), 2959 (Aromatic C-H), 1672 (C=0), 1496 (Aromatic), 1235 (Aromatic amine), 769 (Bromo); ^{1}H-NMR (400 MHz, DMSO-d_6) : δ 11.03 (s, 1H), 8.66 (d, J =5.6 Hz, 1H); 8.52 (s, 2H); 7.85 (s, 1H); 7.66 (d, J = 6.4 Hz, 1H); 7.57 (d, J = 6.4 Hz, 1H); 7.47 (d, J = 7.6 Hz, 1H); 7.39 (d, J = 8.4 Hz, 2H); 6.88 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-*d_6*): δ =

160.1, 157.5, 154.7, 141.9, 137.7, 135.0, 131.8, 128.1, 126.8, 125.8, 121.2, 120.3, 119.1, 116.4 , 114.8, 112.7, 109.8; LC-MS: m/z 428.1 . (Fig-29 to 32)

Results and discussion:

The synthesis of imidazo[1,2-a]pyridine analogues 5a-e were obtained starting from 1-(2-fluoro-5-nitrophenyl)ethanone (1) was treated with mixture of Con.H_2SO_4 and Con.HNO_3 at –5 ^oC to -10 ^oC for 30 min to gave 83% good yield. Subsequent reduction of the nitro group (2) in DCM was treated with PTAT at –0 ^oC to -5 ^oC for 10 min to make a brominated compound with 50% yield. The 2-bromo-1-(2-fluoro-5-nitrophenyl)ethanone (3), 3-bromopyridine-2-amine and NaHCo3 under reflux condition in ethanol gave the cyclisation compound (4) in 54% yield. This compound (4) was reduced with Zn dust and NH_4Cl at room temperature condition in a mixture of THF:MeOH to gave a corresponding amine (5) in 61% yield. Coupling of compound (5) with suitable benzoic acids using appropriate coupling agents such as EDC, HOBt, in the presence of Hunig's base furnished the corresponding amide analogues 5a-e in moderate to excellent yields.

Conclusion:

In conclusion, we have designed and synthesized new substituted imidazo[1,2-a] pyridazine derivatives with different substituted benzoic acid couplings with amino compound-5 and characterized through spectral analysis.

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