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Synthesis and Characterization of *N*-(3-(8-bromoimidazo [1, 2-a]pyridin-2-yl)-4-fluorophenyl)benzamide Derivatives

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ABSTRACT: *Synthesis of five member heterocyclic compounds such as oxadiazoles, triazoles, and imidazoles are important for medical, biological and material science owing to their wide range of application. Herein reported the synthesis and characterization of new N-(3-(8-bromoimidazo[1, 2-a]pyridin-2-yl)-4-fluorophenyl)benzamidederivatives.*

Imidazoles are an important class of heterocyclic chemistry, they possess a significant role in biological and chemical area. Herein, express the route of newly synthesized imidazole derivatives. Mixture of concentrated sulfuric acid and nitric acid was used for inserting the nitro group on the commercially available 1-(2-fluorophenyl)ethanone (1). Synthesized nitro compound-2 was further treated with phenyl trimethyl ammonium tribromide at room temperature for 2h to obtain the 2-bromo-1-(2-fluoro-5-nitrophenyl)ethanone (3). 3-bromopyridine-2-amine (3a) and compound-3 were used for construction of imidazole ring derivative (4) using sodium bicarbonate and ethanol at 80°C for 3h. 8-bromo-2-(2-fluoro-5-nitrophenyl)imidazo[1,2-a]pyridine (4) was converted to corresponding amine (5) using the ammonium chloride, Zinc dust, tetrahydrofuan, methanol and water at 1 bar hydrogen atmosphere. The active intermediate of 3-(8-bromoimidazo[1,2-a]pyridin-2-yl)-4-fluoroaniline (5) was further coupled with different types of aromatic acid compounds (5a-5e) using the 1-ethyl-3-(3-dimethylaminopropyl carbodiimide, hydroxyl benzotriazole, diisopropylethylamine and N,N-dimethylformamide at room temperature to furnish the final compounds (6a-6e)(Figure-2). All synthesized compounds were confirmed by analytical techniques such as ^{1}H-NMR, ^{13}C-NMR, FT-IR and LCMS.

KEYWORDS: *(2-fluoro-phenyl)ethanone,phenyl trimethyl ammonium tribromide, 3-bromopyridine-2-amine, zinc dust, ammonium chloride.*

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I. INTRODUCTION:

Imidazopyridine is one the significant fused bicyclic heterocycles and it is acknowledged as a “drug prejudice” scaffold due to its broad range of applications in the medicinal chemistry. Among the various imidazopyridine derivatives, the imidazo[1,2-a]pyridine piece is the very important in the area of natural products and pharmaceuticals. The imidazo[1,2-a]pyridine is a well-known privileged fused heterocyclic motif containing five membered imidazole and six membered pyridine 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[1] (an antiulcer drug-brand name is Solimidin), zolpidem[2] (ahypnotic drug), and Linaprazan[3](Potassium-competitive acid blocking (P-CAB) activity) (Figure-1).

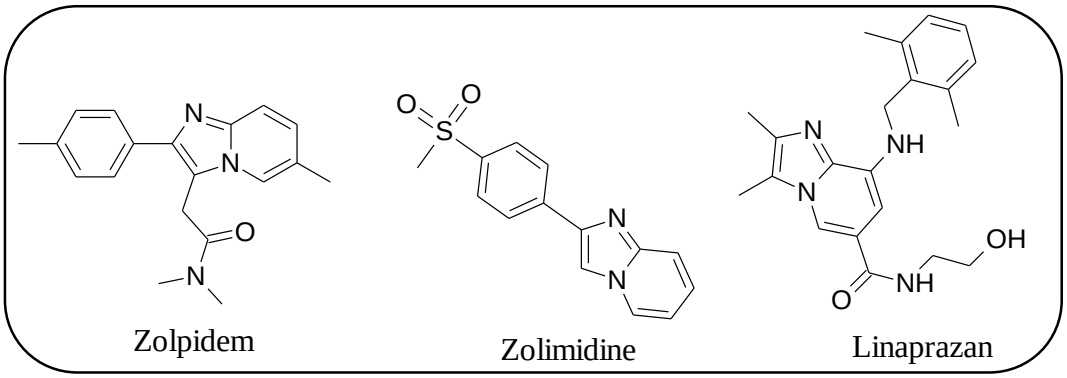


Figure-1: Chemical structures of imidazo[1,2-a]pyridine derivative drugs

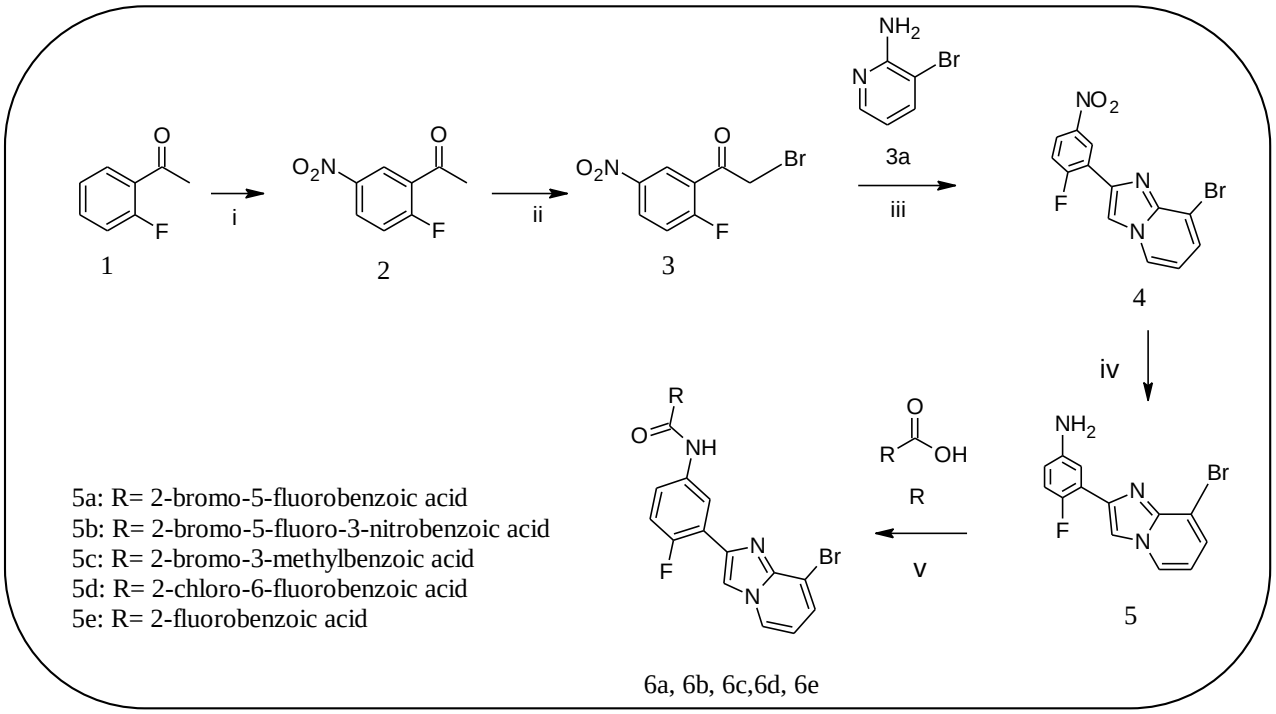


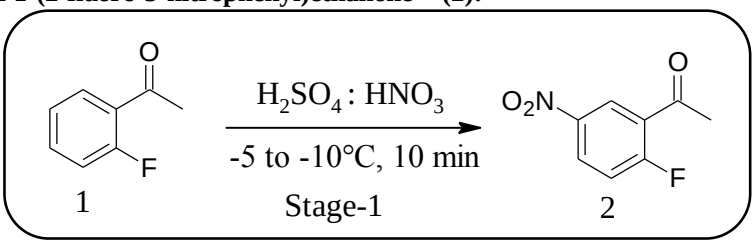
Figure-2:Synthetic scheme & reaction conditions: i) H_2SO_4,HNO_3, -5°C to -10°C, 10 min; ii) Phenyl trimethyl ammonium tribromide, DCM, RT, 2h; iii) 3-bromopyridine-2-amine, $NaHCO_3$, ethanol,80°C, 3h; iv) Ammonium chloride, Zinc, THF, MeOH, Water, 1h, RT; v) N,N-dimethylformamide, EDC.HCl, HOBT,DIPEA, 1h, RT

II. EXPERIMENTAL SECTION:

2.1. Reagents and Instrumentation:

All reagents were purchased from Merck, Aldrich suppliers and used without further purification. The NMR spectra were recorded on a BrukerAvance 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.

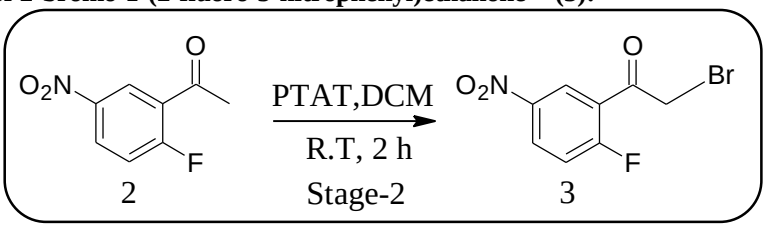
2.2. Synthesis of 1-(2-fluoro-5-nitrophenyl)ethanone[4,5] (2):



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 color stirred suspension, a mixture of Con. sulfuricacid : Con. nitric acid (14 mL: 8 mL) was added drop wise 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 that complete consumption of starting material, the reaction mixture was drop wise poured into ice cold water (500 mL, 50 V). The yellow color precipitated solid was filtered and washed with water (50 mL, 5V). The yellowcolor solid was diluted in dichloromethane (100 mL, 10V) and washed with brine solution (50 mL, 5V). The organic layer was concentrated at -30°C to -35°C and co-evaporated with hexane solvent (50 mL, 5V). The yellow color 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 color solid was filtered and washed with hexane (20 mL, 2V) then dried under vacuum to afford the pale yellow solid (11 g, 83%).

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) (Figure-3 to 4).

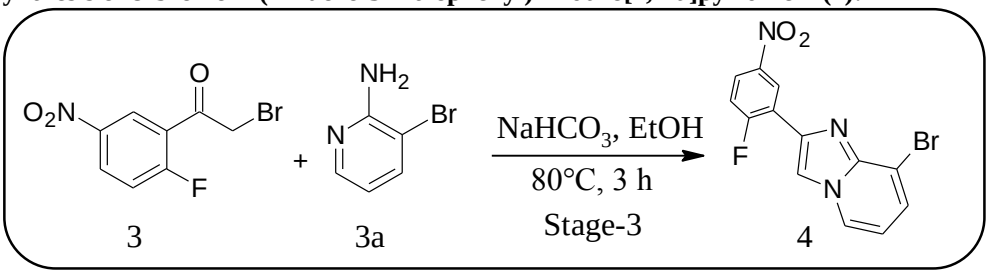
2.3. Synthesis of 2-bromo-1-(2-fluoro-5-nitrophenyl)ethanone[6,7] (3):



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 phenyl trimethyl ammonium tribromide (24.63 g, 0.0655mol) in 3 equal lots in the period of 10 min time interval at same temperature. The reaction mixture slowly warmed to room temperature and stirred for 2h. The reaction mixture was monitored by TLC/LCMS. After completion of starting material the reaction mixture was quenched with ice cold water (250 mL, 25V) and stirred for 10 min. Two layers were separated and organic layer was washed with 10% sodium bicarbonate solution (100 mL, 10V) and brine solution (100 mL, 10 V). The organic layer was concentrated at -30°C to -35°C and obtained as yellow color gammy solid. This solid was dissolved 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%)

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/z262(Figure-5 to 7).

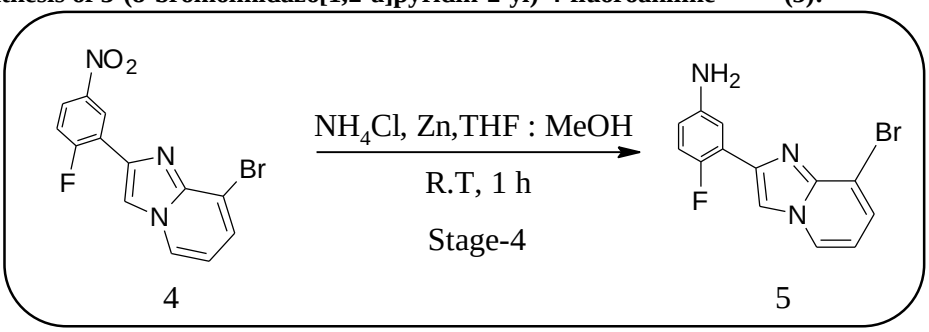
2.4. Synthesis of 8-bromo-2-(2-fluoro-5-nitrophenyl)imidazo[1,2-a]pyridine[8,9] (4):



2-bromo-1-(2-fluoro-5-nitrophenyl)ethanone (8 g, 0.0305 mol) and 3-bromopyridine-2-amine (5.81 g, 0.335 mol) were diluted in ethanol (80 mL, 10 V). To the above clear solution was added sodium bicarbonate (7.7 g, 0.015 mol) at room temperature. The pale yellow color clear solution was heated to 80°C and stirred for 3h under closed condition (after 2h onwards the reaction mixture was becoming pale yellow clear solution to pale yellow color suspension). The progress of reaction mixture was monitored by TLC/LCMS. After 3h, complete consumption of starting material was observed by TLC.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 to 5°C. The precipitated solid was filtered and dried under vacuum to afford the pale yellow solid (5.6 g, 54%).

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-*d6*): 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 (Figure-8 to 11).

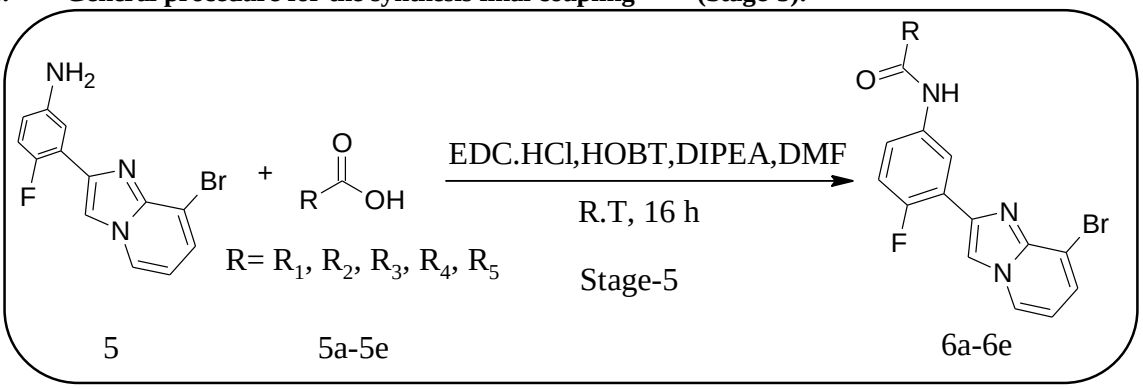
2.5. Synthesis of 3-(8-bromoimidazo[1,2-a]pyridin-2-yl)-4-fluoroaniline[10,11,12] (5):



To a stirred solution of 8-bromo-2-(2-fluoro-5-nitrophenyl)imidazo[1,2-a]pyridine (4 g, 0.0118mol)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 tetrahydrofuran and methanol solvent. The residue was diluted in 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(50-60) % of ethyl acetate in hexane. The column eluted solvent was concentrated under reduced pressure to get the yellow solid (2.2 g, 61%).

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-*d6*): 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 (Figure-12 to 15).

2.6. General procedure for the synthesis final coupling[13,14,15](Stage-5):



Compound-5a(1.5 eq.) and*N*,*N*-dimethylformamide (0.9 mL, 3 V) were taken in the round bottom flask, to this clear solution 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.5 eq.), hydroxybenzotriazole (0.1 eq.) and diisopropylethylamine (3.0 eq.) were added at room temperature and stirred for 15 min. To this yellow color clear solution wasadded 3-(8-bromoimidazo[1,2-a]pyridin-2-yl)-4-fluoroaniline (0.3 g, 0.97 mmol, 1.0 eq., Compound-5) 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 methyl tert-butyl ether (5 V) and stirred for 15 min at room temperature then filtered the solid and dried under vacuum to get the corresponding products as a solid.

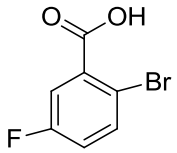
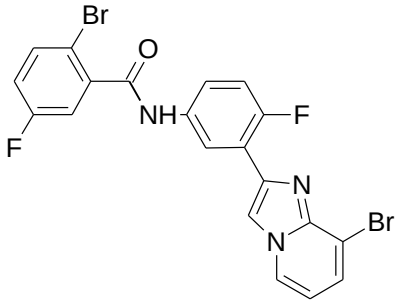
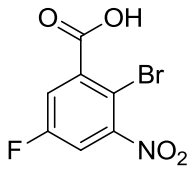
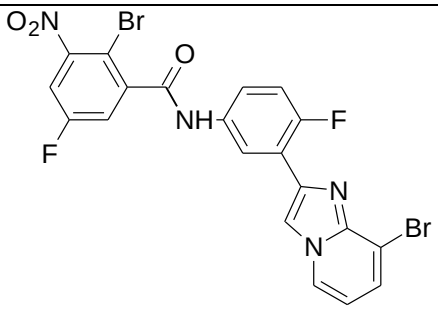
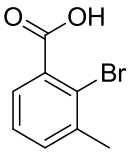
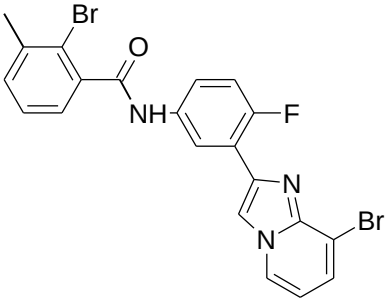
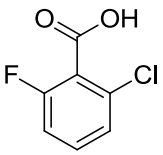
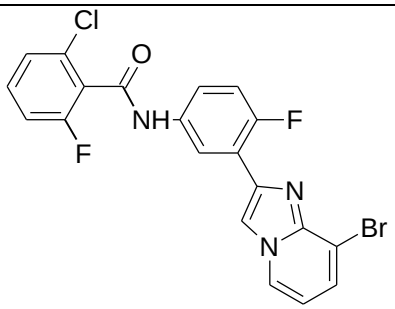
2-bromo-*N*-(3-(8-bromoimidazo[1,2-a]pyridin-2-yl)-4-fluorophenyl)-5-fluorobenzamide (6a):IR (cm^{-1}): 3153 (Amide), 3053 (Aromatic C-H),1672 (C=0), 1501 (Aromatic), 1204 (Aromatic amine), 821 (Bromo); ^{1}H-NMR (400 MHz, DMSO-d_6) : δ 10.80 (s, 1H), 8.62 (d, J = 6.4 Hz, 1H); 8.56 (dd, J = 2.4, 4 Hz, 2H); 7.87 (dd, J = 4.4,5.2 Hz, 2H); 7.66 (dd, J =7.6,3.2Hz, 2H); 7.38 (m, 2H); 6.89 (t, J = 7.2 Hz, 1H); LC-MS: [m+1] 508.0 (Figure-16 to 18).

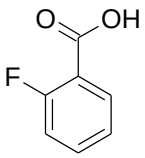
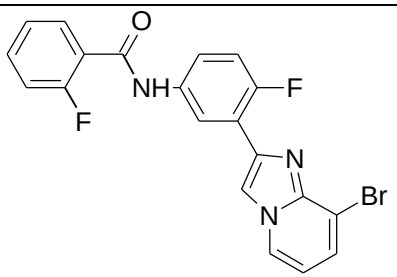
2-bromo-*N*-(3-(8-bromoimidazo[1,2-a]pyridin-2-yl)-4-fluorophenyl)-5-fluoro-3-nitrobenzamide (6b):IR (cm^{-1}): 3151 (Amide), 3090 (Aromatic C-H),1668 (C=0), 1533 (Aromatic), 1361 (Nitro), 1219 (Aromatic amine), 781 (Bromo); ^{1}H-NMR (400 MHz, DMSO-d_6) : δ 10.97 (s, 1H), 8.66 (t, J = 4 Hz, 1H); 8.59 (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-*d6*): 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 (Figure-19 to 22).

2-bromo-*N*-(3-(8-bromoimidazo[1, 2-a]pyridin-2-yl)-4-fluorophenyl)-3-methylbenzamide (6c): 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 = 6.4Hz, 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-*d6*): 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 (Figure-23 to 26).

***N*-(3-(8-bromoimidazo[1, 2-a]pyridin-2-yl)-4-fluorophenyl)-2-fluorobenzamide (6d):**
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 = 7.2Hz, 1H); 7.63 (dd,J = 1.2 Hz, 1H); 7.39 (m, 3H);6.89 (t, J = 6.8Hz, 1H); ^{13}C-NMR (400 MHz, DMSO-*d6*): 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 (Figure-27 to 30).
***N*-(3-(8-bromoimidazo[1,2-a]pyridin-2-yl)-4-fluorophenyl)-2-chloro-6-fluorobenzamide (6e):**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 = 6.4Hz, 1H); 7.57 (d,J = 6.4 Hz, 1H); 7.47 (d, J = 7.6 Hz, 1H);7.39 (d, J = 8.4Hz, 2H);6.88 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-*d6*): 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(Figure-31 to 34).

Table 1: Chemical synthesis of Imidazo[1,2-a] pyridazine derivatives

Entry	Benzoic acid derivatives (5)		Imidazo[1,2-a] pyridazine derivatives (6)		Yield (%)
1		5a		6a	51%
2		5b		6b	45%
3		5c		6c	60%
4		5d		6d	62%

5		5e		6e	56%

III. RESULTS AND DISCUSSION:

The synthesis ofimidazo[1,2-a]pyridine analogues 5a-5e 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 given 83% good yield. Subsequent reduction of the nitro group (2) in dichloromethane was treated with phenyl trimethyl ammonium tribromide at0 ^oC to -5 ^oC for 10 min to make a brominated compoundwith 50% yield. The 2-bromo-1-(2-fluoro-5-nitrophenyl)ethanone (3), 3-bromopyridine-2-amine and $NaHCO_3$ under reflux condition in ethanol gave the cyclisation compound (4) in 54% yield. This compound (4) wasreduced with Zn dust and NH_4Cl at room temperature condition in a mixture of THF:MeOH to given 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-5e in moderate to excellent yields.

IV. CONCLUSION:

In conclusion, we have designed and synthesized the newlysubstituted imidazo[1,2-a] pyridazine derivatives by coupling with 3-(8-bromoimidazo[1,2-a]pyridin-2-yl)-4-fluoroaniline (5) and different substituted benzoic acids (5a-5e). All synthesized compounds were characterized through spectral analysis.

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