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Research Article

Design, Synthesis and Antibacterial Activity of 1-(8-(Ayloxy)-2-(Trifluoromethyl) Imidazo [1, 2-Apyrazin-6-Yl) Ethan-1-Amine Derivatives

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ABSTRACT

A series of novel 1-(8-(ayloxy)-2-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl)ethan-1-amine derivatives (11a-h) were synthesized by the O-alkylation of 1-(8-chloro-2-(trifluoromethyl) imidazo[1,2-a]pyrazin-6-yl)ethan-1-amine (9) with corresponding aryl alcohols (10a-h) in the presence of K_2CO_3. Reacion of commercially available ethyl 2-amino-2-thioxoacetate with triethyl oxonium hexafluoro phosphate gave ethyl 2-(ethylthio)-2-iminoacetat, which was reacted with 3-amino-1,1,1-trifluoropropan-2-one hydrochloride to afford ethyl 4-(trifluoromethyl)-1H-imidazole-2-carboxylate. Protection of (tert-butoxycarbonyl) alanine with ethyl chloroformate, and treated with diazomehane obtained tert-butyl (4-diazo-3-oxobutan-2-yl) carbamate. Tert-butyl (4-bromo-3-oxobutan-2-yl) carbamate was obtained by the reaction of compound 5 with 48% hydrogen bromide. Compound 3 was treated with compound to give 1-(3-((tert-butoxycarbonyl) amino)-2-oxobutyl)-4-(trifluoromethyl)-1*H*-imidazole-2-carboxylic acid. Cyclizaion of compound using ammonium bicarbonate gave tert-butyl (1-(8-oxo-2-(trifluoromethyl)-7,8-dihydroimidazo[1,2-a]pyrazin-6-yl) ethyl) carbamate, which was chlorinated by phosphorus oxychloride afforded 1-(8-chloro-2-(trifluoromethyl) imidazo [1,2-a]pyrazin-6-yl) ethan-1-amine. All the newly synthesized compounds were characterized by analytical spectral techniques, like ^{1}H NMR, and LCMS, and also evaluated their antibacterial activity.

Keywords: 6-(1-aminoethyl)-2-(trifluoromethyl) imidazo [1,2-a] pyrazin-8-ol; Aryl alcohols; O-alkylation and antibacterial activity

INTRODUCTION

Imidazo [1,2-*a*] pyrazine is a familiar auspicious fused heterocyclic nuclei containing five membered imidazole and six membered pyrazine ring with viaduct head nitrogen atom. Imidazo [1,2-*a*] pyrazine nuclei derivatives are play significant role in medicinal and drug discovery chemistry because of its diverse biological activitives, such as antibacterial [1], antiulcer [2], anticancer [3], antihypertensive [4], antiinflammatory [5], antimalarial cardiac stimulating, uterine relaxant antidepressant hypoglycemic activity moothmusclerelaxant antibronchospastic In addition, it's also exhibit photophysical properties like chemiluminescence and bioluminescence Many researcher reported the synthesis of imidazo [1,2-*a*] pyrazines and its evaluation to diverse biological activities. In vew of above importance, we have synthesized a series of novel 1-(2-(tert-butyl)-8-chloroimidazo [1,2-a] pyrazin-6-yl) ethan-1-amine derivatives and evaluated their antibacterial activity. All synthesized compounds were characterized by ^{1}H NMR, and mass spectroscopy. To the best of my knowledge, nobody has not been reported these compounds till now.

MAERIALS AND MEHODS

All the solvents, reagents and chemicals were purchased from Merck (Mumbai, India), Lancaster chemical (Mumbai, India), Sigma Aldrich (Hyderabad, India), and SD fine chemicals and used directly without purification. Melting points were recorded on Mel-Temp apparatus. All the NMR spectra were recorded on Bruker 400 MHz spectrometer. The compounds were dissolved in $CDCl_3$ and DMSO-d_6; the chemical shifts were referenced to TMS. Coupling constants were calculated in hertz (Hz) and finally the mass spectra were recorded on Agilent LC/MSD SL 1100 instrument.

Synthesis of ethyl 2-(ethylthio)-2-iminoacetate

To a solution of ethyl thioxamate (1.0 g, 7.50 mmol) in dry tetrahydrofuran (25 mL) was added triethyl oxonium hexafluoro phosphate (2.0 g, 8.25 mmol) at 0°C, and the reaction mixture was stirred at room temperature for 2 h. After completion of reaction, excess solvent was concentrated under reduced pressure to afford ethyl 2-(ethylthio)-2-iminoacetate 2 (900 mg, 74%).

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Synhesis of ethyl 4-(trifluoromethyl)-1H-imidazole-2-carboxylate

To a solution of ethyl 2-(ethylthio)-2-iminoacetate 2 (1.0 g, 6.20 mmol) in AcOH (4 mL) were added 3-amino-1,1,1-trifluoropropan-2-one hydrochloride (1.21 g, 7.44 mmol) and freshly prepared sodium ethoxide (634 mg, 9.3 mmol) at room temperature, the resulting reaction mixture was stirred at 50°C for 2 h. After completion of reaction, the mixture was diluted with water and extracted by ethyl acetate. Organic layer was dried over anhydrous sodium sulphate and evaporated. The obtained crude compound was purified by flash column chromatography to afford ethyl 4-(trifluoromethyl)-1*H*-imidazole-2-carboxylate (800 mg, 63%) as thick gummy.

^{1}H NMR (300 MHz, DMSO-d6): 13.2 (s, 1H), 7.10 (s, 1H), 4.30 (q, *J* = 6.9 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); LCMS: 97% (m/z =209.04 [M+H]+)

Synhesis of 1-(3-((tert-butoxycarbonyl) amino)-2-oxobutyl)-4-(trifluoromethyl)-1H-imidazole-2-carboxylic acid

To a solution of ethyl 4-(trifluoromethyl)-1*H*-imidazole-2-carboxylate (1.5 g, 7.20 mmol) in THF (30 mL) was added sodium hydride (263 mg, 11.46 mmol) at 0°C, and stirred for 30 min. Then, added tert-butyl (4-bromo-3-oxobutan-2-yl) carbamate (2.23 g, 8.40 mmol) to the reaction mixture. The resulting reaction was stirred at rate for 2 h. After completion of reaction, quenched with ice cold water and extracted by ethyl acetate. Organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford 1-(3-((tert-butoxycarbonyl) amino)-2-oxobutyl)-4-(trifluoromethyl)-1*H*-imidazole-2-carboxylic acid (2.0 g, 76%) as a thick gummy compound.

^{1}H NMR (300 MHz, DMSO-d6,): 7.33 (s, 1H), 7.2 (s, 1H), 5.35 (s, 2H), 4.15 (m, 2H), 3.98 (q, *J* = 6.6 Hz, 1 H), 1.4 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.24 (d, J=6.3 Hz, 3H) LCMS: 92% (m/z =366.10 [M+H]+)

Synthesis of tert-butyl (1-(8-oxo-2-(trifluoromethyl)-7,8-dihydroimidazo[1,2-a]pyrazin-6-yl) ethyl) carbamate

To a solution of 1-(3-((tert-butoxycarbonyl) amino)-2-oxobutyl)-4-(trifluoromethyl)-1*H*-imidazole-2-carboxylic acid (2.00 g, 5.47 mmol) in MeOH (10 mL) was added ammonium carbonate (1.56 g, 16.41) at room temperature. The resulting reaction mixture was irradiated in microwave at 50°C for 2 h. After completion of reaction (by TLC), the reaction mixture was diluted with water and extracted by ethyl acetate. Organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The obtained crude compound was purified by flash column chromatography to tert-butyl (1-(8-oxo-2-(trifluoromethyl)-7,8-dihydroimidazo[1,2-a] pyrazin-6-yl)ethyl)carbamate 8 (1.0 g, 55%) as a thick liquid.

^{1}H NMR (300 MHz, DMSO-d6): 10.8 (s, 1H), 7.5 (s, 1H), 7.2 (s, 1H), 7.0 (s, 1H), 4.80 (m, 1H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.4 (s, 9H); LCMS: 94% (m/z = 347.13 [M+H]+).

Synthesis of 1-(8-chloro-2-(trifluoromethyl) imidazo[1,2-a] pyrazin-6-yl)ethan-1-amine

Tert-butyl (1-(8-oxo-2-(trifluoromethyl)-7,8-dihydroimidazo[1,2-a] pyrazin-6-yl)ethyl)carbamate 8 (1.0 g, 2.88 mmol) was taken in 50 mL RB flask was added Phosphorus oxychloride (10 mL) at 0°C, and the mixture was heated at 100°C for 1 h. After completion of reaction, the reaction mixture was poured into ice cold water and basified with saturated bicarbonate solution, and extracted by ethyl acetate. Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure gave 1-(8-chloro-2-(trifluoromethyl) imidazo [1,2-a]pyrazin-6-yl)ethan-1-amine 9 (470 mg, 64%) as a thick gummy.

^{1}H NMR (300 MHz, DMSO-d6,): 8.5 (s, 1H), 7.85 (s, 1H), 3.92 (q, *J* = 6.9 Hz, 1 H), 1.91 (br s, 2 H), 1.25 (d, *J* = 6.6 Hz, 3H); LCMS: 90% (m/z = 265.05 [M+H]+).

Synhesis of 1-(8-((1-methyl-1H-1,2,4 -triazol-5-yl)methoxy)-2-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl)ethan-1-amine (Genaral procedure, 11a)

To a solution of 1-methyl-1*H*-1,2,4 -triazol-5-yl) methanol (100 mg, 0.88 mmol) in DMF (3 mL) were added) potassium carbonate (242 mg, 1.76 mmol) and1-(8-chloro-2-(trifluoromethyl) imidazo[1,2-a] pyrazin-6-yl)ethan-1-amine **9** (408 mg, 088 mmol) at room temperature. The resulting reaction mixture was stirred at 80 °C for 4 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with water and extracted by ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to get the crude product. The crude product was purified by flash chromatography to afford **1**-(8-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-2-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl) ethan-1-amine **11a** (100 mg, 33%) as thick yellow compound.

^{1}H NMR (300 MHz, DMSO-d^6) δ: 8.4 (s, 1H), 8.2 (s, 1H), 7.82 (s, 1H), 5.29 (s, 2H), 3.90 (q, *J* = 6.9 Hz, 1 H), 3.6 (s, 1H), 1.92 (br s, 2 H), 1.24 (d, *J* = 6.6 Hz, 3H); LCMS: 96% (m/z = 342.29 [M+H]+).

1-(8-(pyrazin-2-ylmethoxy)-2-(trifluoromethyl) imidazo [1,2-a]pyrazin-6-yl)ethan-1-amine (11b)

^{1}H NMR (300 MHz, DMSO-d6,) δ: 8.8 (d, 2H),8.7(s, 1H), 8.4 (s, 1H), 7.80 (s, 1H), 5.21 (s, 2H), 3.98 (q, *J* = 6.9 Hz, 1H), 2.0 (br s, 2H),1.24 (d, *J* = 6.6 Hz, 3H); LCMS: 95% (m/z = 339.26 [M+H]+)

1-(8-((5-bromopyridin-2-yl) methoxy)-2-(trifluoromethyl) imidazo [1,2-a]pyrazin-6-yl)ethan-1-amine (11c)

^{1}H NMR (300 MHz, DMSO-d6,): 8.8 (s, 1H), 8.5 (s, 1H), 8.3(d, 1H), 7.85 (s, 1H), 7.7 (d, 1H), 5.3 (s, 2H), 3.96 (q, *J* = 6.9 Hz, 1H), 1.94 (br s, 2 H), 1.26 (d, *J* = 6.6 Hz, 3H); LCMS: 97% (m/z = 417.17 [M+H]+)

1-(8-((4-methylthiazol-2-yl) methoxy)-2-(trifluoromethyl) imidazo[1,2-a]pyrazin-6-yl)ethan-1-amin (11d)

^{1}H NMR (300 MHz, DMSO-d6,): 8.48 (s, 1H), 7.84 (s, 1H), 5.15 (s, 2H), 3.95 (q, *J* = 6.9 Hz, 1 H), 2.25(s, 3H), 1.96 (br s, 2 H), 1.27(d, *J* = 6.6 Hz, 3H); LCMS: 96% (m/z = 358.36 [M+H]+).

1-(8-((3-(methylthio) benzyl) oxy)-2-(trifluoromethyl) imidazo[1,2-a]pyrazin-6-yl)ethan-1-amine (11e)

^{1}H NMR (300 MHz, DMSO-d6,): 8.52 (s, 1H), 7.88 (s, 1H), 7.5 (d, 1H), 7.32 (m, 1H), 7.25 (d, 1H), 5.12 (s, 2H), 3.96 (q, *J* = 6.9 Hz, 1 H), 1.97 (br s, 2 H), 1.27 (d, *J* = 6.6 Hz, 3H); LCMS: 96% (m/z = 383.10 [M+H]+)

1-(8-((4-bromo-2-(trifluoromethoxy) benzyl) oxy)-2-(tert-butyl) imidazo[1,2-a] pyrazin-6-yl) ethan-1-amine (10f)

^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 8.45 (s, 1H), 7.83 (s, 1H), 7.62

(s, 2H), 7.52 (s, 1H), 5.20 (s, 2H), 1.91 (br s, 2 H), 1.27 (d, *J* = 6.6 Hz, 3H); LCMS: 95% (m/z = 499.02 [M+H]+)

1-(8-((6-bromopyridin-2-yl) methoxy)-2-(trifluoromethyl) imidazo[1,2-a]pyrazin-6-yl)ethan-1-amine (11g)

^{1}H NMR (400 MHz, DMSO d_6) δ: 8.4 (s, 1H), 7.86 (s, 1H), 7.8 (t, *J* = 7.8 Hz, 1H), 7.6 (d, *J* = 8.0 Hz, 1H), 7.3 (d, *J* = 7.2 Hz, 1 H), 5.32 (s, 2H), 3.95 (q, *J* = 6.6 Hz, 1H), 1.90 (br s, 2H), 1.27 (d, *J* = 6.8 Hz, 3H); LCMS: 95% (m/z = 416.01 [M+H]+)

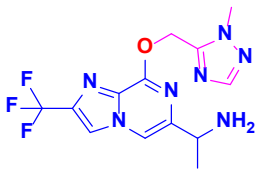
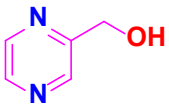
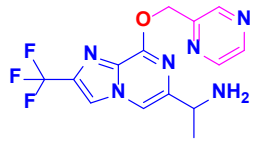
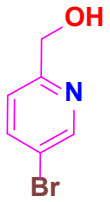
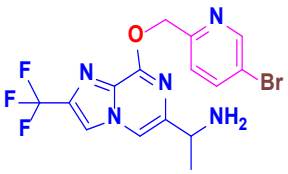
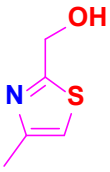
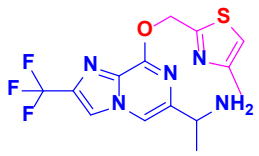
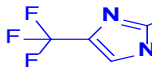
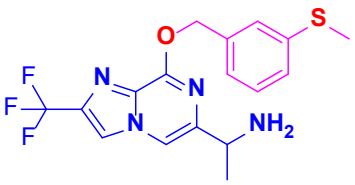
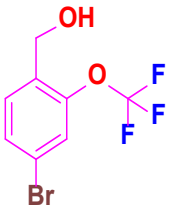
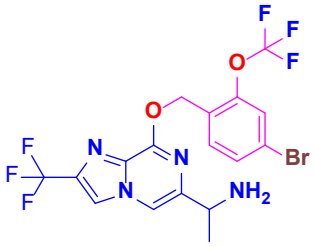
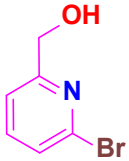
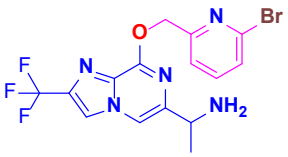
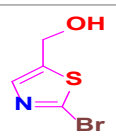
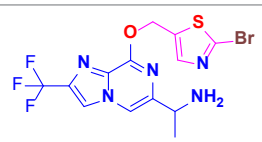
1-(8-((2-bromothiazol-5-yl) methoxy)-2-(trifluoromethyl) imidazo[1,2-a]pyrazin-6-yl)ethan-1-amine (11h)

^{1}H NMR (300 MHz, DMSO-d_6): 8.4 (s, 1H), 7.84 (s, 1H) 7.6 (s, 1H), 5.15 (s, 2H), 3.90 (q, *J* = 6.8 Hz, 1H), 1.90 (s, 2H), 1.26 (d, *J* = 6.6 Hz, 3H); LCMS: 97% (m/z = 421.96 [M+H] +) (Table 1).

Antibacterial activity

All the newly synthesized titled compounds (11a-h) were screened for their antibacterial activity activity against two gram positive

Table1: Synthesized compounds (11a –h).

SNO	Various acids (9a-h)	Products (10a-h)	Time (h)	Yield (%)
1			4	62
2			5	50
3			6	48
4			5	58
5			5	56
6			4	49
7			5	19
8			5	20

bacterial strains (*S. aureus, B. Subtill*), two gram negative bacterial strains (*Pseudomonas E. coli*) using agar-well diffusion method at various concentrations (10, 20 ug/mL). Streptomycin was used as standard control drug. From the (Table 2) it is clear that, most of the synthesized titled compounds displayed moderate to good activities against the specific microbial strain. Among the synthesized compounds 11(a-h), the moieties 11a, 11b, and 11g displayed good activity and the moieties (11c, 11d and 11h) showed comparable activity with the reference drug streptomycin against the tested bacterial strains.

RESULTS AND DISCUSSION

The synthetic approaches are depicted in (Figure 1) for the required target compounds. 6-(1-aminoethyl)-2-(trifluoromethyl) imidazo[1,2-a]pyrazin-8-ol was synthesized in 7 steps, Initially commercially available ethyl 2-amino-2-thioxoacetate was treated with triethyl oxonium hexafluoro phosphate to give ethyl 2-(ethylthio)-2-iminoacetate, it was reacted with 3-amino-1,1,1-trifluoropropan-2-one hydrochloride in the presence of sodium ethoxide and acetic acid to obtain ethyl 4-(trifluoromethyl)-1*H*-imidazole-2-carboxylate. Compound 3 was reacted with tert-butyl (4-bromo-3-oxobutan-2-yl) carbamate in the presence of sodium hydride to yield 1-(3-((tert-butoxycarbonyl) amino)-2-oxobutyl)-4-(trifluoromethyl)-1*H*-imidazole-2-carboxylic acid. Cyclizaion of compound 7 with ammonium carbonate to result tert-butyl (1-(8-oxo-2-(trifluoromethyl)-7,8-dihydroimidazo[1,2-a]pyrazin-6-yl) ethyl) carbamate, which was chlorinated with phosphorous oxychloride to form 1-(8-chloro-2-trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl) ethan-1-amine. Tert-butyl (4-bromo-3-oxobutan-2-yl) carbamate was synthesized according to the literature procedure. Finally, the desired target compounds were synthesized by the reaction of 1-(8-chloro-2-(trifluoromethyl) imidazo [1,2-a] pyrazin-6-yl)ethan-1-amine with aryl alcohols in the presence of K_2CO_3. All the final compounds are isolated good yield expect 11g and 11h. 1-(8-chloro-2-(trifluoromethyl) imidazo[1,2-a]pyrazin-6-yl)ethan-1-amine reacted with (6-bromopyridin-2-yl) methanol (10g) to from desired product along with undesired product, (6-(1-((6-(hydroxymethyl)pyridin-2-yl)amino) ethyl)-2-(trifluoromethyl) imidazo[1,2-a] pyrazin-8-ol. Similarly, 10h also form undesired product, (2-(tert-butyl)-6-(1-((5-(hydroxymethyl) thiazol-2-yl) amino) ethyl) imidazo [1,2-a] pyrazin-8-ol. All the final synthesized compounds were characterized by ^{1}H NMR and mass spectra and spectral studies are described in the experimental section.

Table 2: Antibacterial activity of synthesized compounds.

Compounds	Gram Positive bacteria				Gram Negative bacteria			
	S.aureus		*B.Subtills*		*Pseudomonas*		*E.coli*	
	10 ug/mL	20 ug/mL	10 ug/mL	20 ug/mL	10 ug/mL	20 ug/mL	10 ug/mL	20 ug/mL
11a	9.5	15.5	11.5	19	10.5	18	10.5	19.5
11b	10.5	16.5	11.5	19	11.5	18.5	11.5	17
11c	8.5	13.5	9	16	8	15.5	8	15.5
11d	9.5	14..5	10.5	17	9.5	16.5	9.5	18.5
11e	6.5	10	7	11.5	6	10	6.5	12.5
11f	7.5	10.5	7.50.	11.5	8	12.5	6.5	14.5
11g	12	17	12.5	21	12.5	20	12.5	21.5
11h	11.5	17.5	13.5	20.5	13.5	20.5	13	20
Streptomycin	9	15	11	18	10	17	10	18

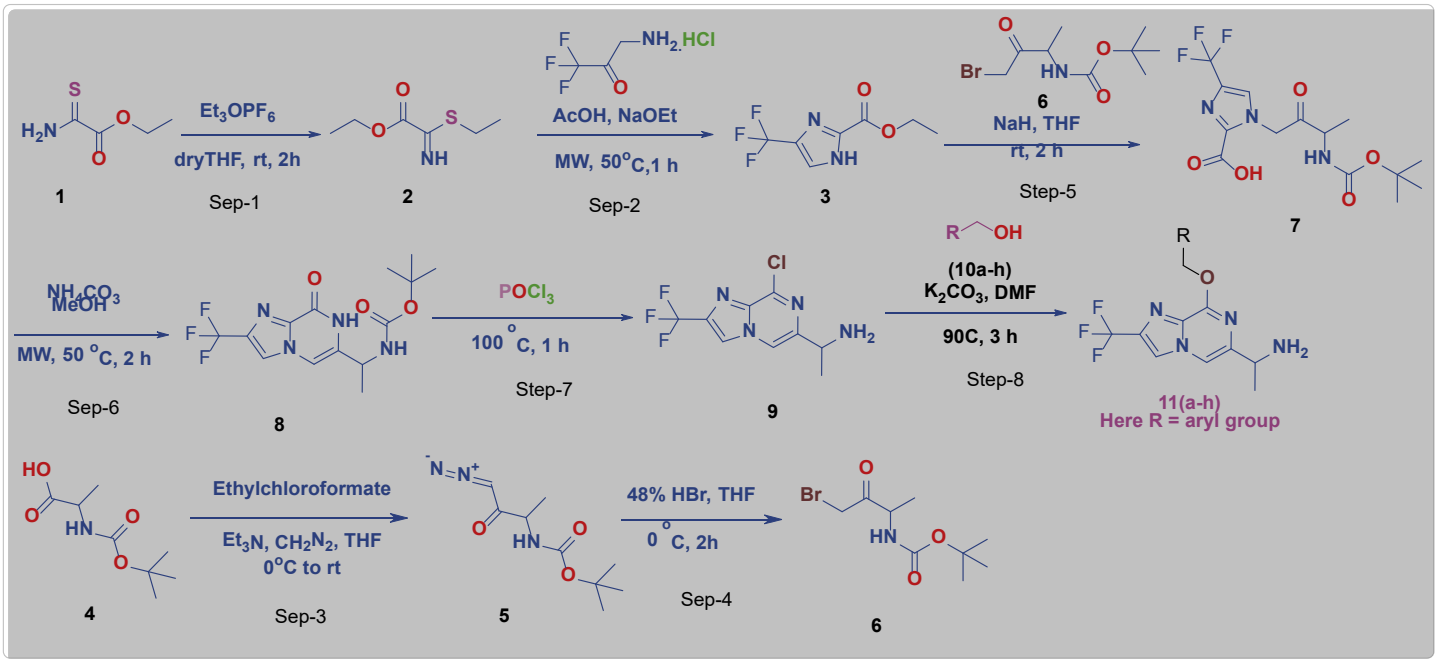


Figure 1: Synthesis of 1-(8-(ayloxy)-2-(trifluoromethyl) imidazo [1, 2-a] pyrazin-6-yl) ethan-1-amine derivatives.

CONCLUSION

In conclusion, we reported a series novel 1-(8-(ayloxy)-2-(trifluoromethyl) imidazo [1,2-a]pyrazin-6-yl) ethan-1-amine derivatives (11a-h) were synthesized by multi step process with commercially available starting material. All synthesized compounds were examined antibacterial activity. Among them compounds 11a, 11b, and 11g exhibited potent activity against the tested bacterial strains.

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