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Design, Synthesis and Antibacterial Activity of *N*-(3-((4-(6-(2,2,2-Trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-yl)amide Derivatives

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A new series of *N*-(3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-yl)amide derivatives (**10a-h**) were synthesized by the reaction of 3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-amine (**8**) with various carboxylic acids in the presence of T_3P catalyst. The reaction is usually furnished within 60 min with good isolated yields. Coupling of 6-(2,2,2-trifluoroethoxy) nicotinic acid (**1**) with Weinreb amine hydrochloride gave *N*-methoxy-*N*-methyl-6-(2,2,2-trifluoroethoxy) nicotinamide (**2**). Compound **3** was synthesized by the Grignard reaction of compound **2** with methylmagnesium bromide. Bromination of compound **3** with *N*-bromo succinamide to obtain 2-bromo-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethan-1-one (**4**), which was reacted with 2-(3-(((benzyloxy)carbonyl)amino)oxetan-3-yl)acetic acid (**5**) gave 2-oxo-2-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl 2-(3-(((benzyloxy)carbonyl)amino)oxetan-3-yl)acetate (**6**). Compound **7** was synthesized by the cyclization of compound **6** with ammonium acetate. Finally, debenzylation of compound **7** gave 3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-amine (**8**). All the synthesized amide compounds were characterized by analytical spectral techniques, like ^{1}H & ^{13}C NMR and LCMS and also evaluated their antibacterial activity.

Keywords: Pyridine-imidazole derivatives, Imidazole amide derivatives, Antibacterial activity.

INTRODUCTION

From the literature review, pyridine-imidazole and its derivative compounds are key division of heterocycles. Imidazoles nuclei derivatives has shown interesting biological activities such as antibacterial [1,2], antifungal [3,4] antiviral [5], anti-inflammatory [6,7], antiulcer [8], antiprotozoal [9,10], anti-herpes and anti-tumor agents [11]. In addition, these heterocycles include a number of inhibitors of p38 MAP kinases [12-15], which are concerned in a variety of inflammatory and immunological disorders and several derivatives such as etomidate, mitronidazole and ketoconazole, which have found application in drug therapy. Pyridine, pyrimidine, oxazole, isoxazole containg imidazole chemistry has been developed widely and are still being developed presently. There are a number of drugs used clinically [16,17], which comprise imidazole moieties in combination with various heterocyclic rings. In view of the above evidence, in present work, we have synthesized 3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-amide derivatives and evaluated their antimicrobial activities.

EXPERIMENTAL

All the chemicals, solvents and reagents were procured from Sigma-Aldrich (Hyderabad, India), Merck (Mumbai, India), Lancaster chemical (Mumbai, India) and SD fine chemicals and used as such without further purification. All used solvents for spectroscopic and other physical studies were reagent grade and further purified by employing the reported methods. Melting points were recorded on Mel-Temp apparatus. All the infrared spectra of the title compounds were recorded on Brucker Alpha-Eco ATR-FTIR (Attenuated total reflection-Fourier transform infrared) interferometer with single reflection sampling module equipped with KBr crystal. All the NMR spectra were recorded on Bruker 400 MHz and 300 MHz spectrometer operating at 400 MHz and 300 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. 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 *N*-methoxy-*N*-methyl-6-(2,2,2-trifluoroethoxy)nicotinamide (2): To a stirred solution of 6-(2,2,2-trifluoroethoxy)nicotinic acid (**1**) (2.5 g, 11.30 mmol) in DMF (10 mL) were added Weinreb amine hydrochloride (2.35 mL, 16.95 mmol), *N*,O-dimethyl hydroxylamine hydrochloride (1.2 g, 12.43 mmol) and 1-[*bis*(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]-pyridinium 3-oxid hexafluorophosphate, *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methyl-methanaminium hexafluorophosphate *N*-oxide (5.67 g, 14.96 mmol) at room temperature and stirred for 3 h. After completion of the reaction, monitored by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate, dried over sodium sulphate and concentrated under reduced pressure. The obtained crude product was purified by flash chromatography to give *N*-methoxy-*N*-methyl-6-(2,2,2-trifluoroethoxy)nicotin-amide (**2**) (2.5 g, 83%) as a thick gum. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 4.80 (m, 2H), 3.56 (s, 3H), 3.36 (s, 3H); LC-MS: 96% (*m/z* = 265 $[M+H]^+$).

Synthesis of 1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethan-1-one (3): To a solution of *N*-methoxy-*N*-methyl-6-(2,2,2-trifluoroethoxy)nicotinamide (**2**) (2.0 g, 7.57 mmol) in THF (20 mL) was added methyl magnesium bromide (9.0 mL, 9.0 mmol) at 0 ºC and stirred at room temperature for 6 h, the reaction mass was quenched with ammonium chloride solution and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The obtained crude product was purified by flash chromatography to afford 1-(6-(2,2,2-trifluoroethoxy)-pyridin-3-yl)ethan-1-one (1.0 g, 60%) as a thick solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1 H), 8.22 (d, *J* = 8.6 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 4.84 (m, 2H), 2.60 (s, 3H); LC-MS: 96% (*m/z* = 220 0$[M+H]^+$).

Synthesis of 2-bromo-1-(6-(2,2,2-trifluoroethoxy)-pyridin-3-yl)ethan-1-one (4): To a solution of 1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethan-1-one (**3**) (500 mg, 2.28 mmol) in THF (25 mL) was added *N*-bromo succinamide (427 mg, 2.4 mmol) at 0 ºC and stirred at room temperature for 2 h. After completion of reaction, the reaction was quenched with sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The obtained crude product was purified by column chromatography to afford 2-bromo-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethan-1-one (**4**) (350 mg, 44%) as a semi-solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.89 (s, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 7.15 (d, *J* = 8.4 Hz 1H), 5.10 (m, 2H), 4.94 (s, 2H); LC-MS: 95% (*m/z* = 299 $[M+H]^+$).

Synthesis of 2,2-oxo-2-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl-2-(3-(((benzyloxy)carbonyl)amino)oxetan-3-yl)acetate (6): To a solution of 2-bromo-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethan-1-one (**4**) (1.0 g, 3.35 mmol) in dichloromethane (20 mL) were added triethylamine (0.7 mL, 5.02 mmol) and 2-(3-(((benzyloxy)carbonyl)amino)oxetan-3-yl)acetic acid (**5**) (888.65 mg, 3.35 mmol) and the resulting reaction mixture was stirred at room temperature for 12h. After completion of reaction, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The obtained crude product was purified by flash column chromatography to afford 2-oxo-2-(6-(2,2,2-trifluoroethoxy)-pyridin-3-yl)ethyl-2-(3-(((benzyloxy)-carbonyl)amino)oxetan-3-yl)acetate (**6**) (1.2 g, 74.5%) as thick liquid. ^{1}H NMR: (300 MHz, DMSO-d_6): δ 8.86 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.14 (s, 1H), 7.35 (m, 5H), 7.15 (d, *J* = 8.4 Hz, 1H), 5.46 (s, 2H), 5.10 (m, 4H), 4.55 (s, 4H), 3.20 (s, 2H); LC-MS: 95.6% (*m/z* = 483 $[M+H]^+$).

Synthesis of benzyl (3-((4-(6-(2,2,2-trifluoroethoxy)-pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-yl)-carbamate (7): To a solution of 2-oxo-2-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl 2-(3(((benzyloxy)carbonyl)amino)-oxetan-3-yl)acetate (**6**) (800 mg, 1.68 mmol) in toluene was added ammonium acetate (142.4 mg, 1.84 mmol) and the reaction mixture was refluxed for 4 h. After completion of reaction, the reaction was diluted with water and extracted with ethyl acetate. Organic layer was dried over sodium sulphate and concentrated under reduced pressure. The obtained crude product was purified flash chromatography to afford benzyl (3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)-methyl)oxetan-3-yl)carbamate (**7**) (500 mg, 63%) as a thick liquid. ^{1}H NMR: (300 MHz, DMSO-d_6): δ 12.10 (s, 1H), 8.55 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.90 (s, 1H), 7.55 (s, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 5.04 (m, 2H),5.0 (s, 2H), 4.63 (s, 2H), 4.53 (s, 2H), 3.30 (s, 2H); LC-MS: 94% (*m/z* = 463 $[M+H]^+$).

Synthesis of 3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-amine (8): To a solution of benzyl (3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-yl) carbamate (**7**) (500 mg, 1.08 mmol) in ethanol (20 mL) was added 10% Pd/C (50 mg) and the reaction was stirred at room temperature for 3 h under hydrogen balloon pressure. After completion of reaction, the reaction mass was filtered through celite pad and washed with ethanol. Filtrate was concentrated under reduced pressure to afford 3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-amine (**8**) (300 mg, 85%) as a white sticky compound. ^{1}H NMR: (300 MHz, DMSO-d_6): δ 12.5 (s, 1H), 8.80 (s, 2H), 8.53 (s, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.52 (s, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 4.98 (m, 2H), 4.44 (s, 2H), 4.34 (s, 2 H), 3.05 (s, 2 H); ^{13}C NMR: (75 MHz, DMSO-d_6): δ 163.4, 150.2, 142.2, 140.5, 136.4, 125.6, 122.5, 120.8, 114.6, 89.2, 84.0, 59.6 and 45.4; LC-MS: 95% (*m/z* = 329 $[M+H]^+$).

Synthesis of 2-(2-methylpyrimidin-5-yl)-*N*-(3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)-methyl)oxetan-3-yl) acetamide (10a): To a solution of 3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)-methyl)oxetan-3-amine (**8**) (50 mg, 0.152 mmol) in THF (5 mL) were added to 2-(2-methylpyrimidin-5-yl)acetic acid (**9a**) (27.89 mmol, 0.183 mmol), DIPEA (0.05 mL, 0.304 mmol) and propylphosphonic anhydride (T_3P) (0.6 mL, 0.304 mmol) at room temperature and stirred for 2 h. After completion of reaction, the mixture was diluted with water and extracted with

ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The obtained crude compound was purified by flash chromatography gave 2-(2-methylpyrimidin-5-yl)-*N*-(3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-yl) acetamide (**10a**) as a thick liquid. ^{1}H NMR: (300 MHz, DMSO-d_6): δ 12.5 (s, 1H), 8.60 (s, 2H), 8.54 (s, 1H), 8.32 (s, 1H), 8.16 (d, *J* = 8.6 Hz, 1H), 7.54 (s, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 4.94 (m, 2H), 4.40 (s, 2H), 4.34 (s, 2H), 3.45 (s, 2H), 3.05 (s, 2H), 2.61 (s, 3H); ^{1}H NMR: (75 MHz, DMSO-d_6): δ 174.2, 166.4, 163.1, 158.6, 150.2, 143.7, 141.9, 136.6, 128.4, 123.6, 121.5, 120.2, 112.3, 86.4, 83.0, 60.2, 42.3, 40.0 and 22.5; LC-MS: 97% (*m/z* = 463.2 $[M+H]^+$).

Synthesis of *N*-(3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-yl)-2-(2-(trifluoromethyl)pyrimidin-5-yl)acetamide (10b): Off white solid; m.p.: 310-313 ºC; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 12.6 (s, 1H) 8.6 (s, 2H), 8.54 (s, 1H), 8.2 (s, 1H), 8.16 (d, *J* = 8.6 Hz, 1H), 7.54 (s, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 4.94 (m, 2H), 4.40 (s, 2H), 4.34 (s, 2H), 3.45 (s, 2H), 3.05 (s, 2H); ^{1}H NMR: (75 MHz, DMSO-d_6): δ 174.6, 166.5, 163.4, 157.9, 150.6, 144.1, 142.0, 135.9, 127.1, 124.0, 121.1, 120.0, 112.1, 118.6, 87.0, 83.6, 59.8, 41.9 and 39.8; LC-MS: 96% (*m/z* = 516.2 $[M+H]^+$).

Synthesis of 2-(2-methyloxazol-4-yl)-*N*-(3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)-oxetan-3-yl)acetamide (10c): Off white solid; m.p.: 323-326 ºC; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 12.7 (s, 1H), 8.53 (s, 1H), 8.20 (s,1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.8 (s, 1H), 7.52 (s, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 4.98 (m, 2H), 4.44 (s, 2H), 4.34 (d, 2H), 3.5 (s, 2H), 3.05 (s, 2 H); 2.4 (s, 3H); ^{1}H NMR: (75 MHz, DMSO-d_6): 173.0, 165.4, 162.3, 149.2, 142.3, 140.2, 138.6, 135.5, 126.5, 121.3,123.4, 120.6, 111.3, 86.7, 83.1, 59.8, 39.2, 38.0 and 13.9; LC-MS: 95% (*m/z* = 456.2 $[M+H]^+$).

Synthesis of 2-(2-cyclopropyloxazol-4-yl)-*N*-(3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-yl)acetamide (10d): White solid; m.p.: 290-294 ºC; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 12.6 (s, 1H), 8.6 (s, 2H), 8.54 (s, 1H), 8.16 (d, *J* = 8.6 Hz, 1H), 7.54 (s, 1H), 7.4 (s, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 4.94 (m, 2H), 4.40 (s, 2H), 4.34 (s, 2H), 3.45 (s, 2H), 3.05 (s, 2H), 2.61 (s, 3H), 2.1 (m, 1H), 1.05 (m, 4H); ^{1}H NMR: (75 MHz, DMSO-d_6): 173.3, 171,2, 162.5, 149.1, 141.6, 140.2, 138.2, 135.3, 126.4, 123.4, 121.6, 120.2, 111.6, 86.9, 83.5, 59.5, 39.6,10.2 and 8.80; LC-MS: 95% (*m/z* = 4478.2 $[M+H]^+$)

Synthesis of 2-(oxetan-3-yl)-*N*-(3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-yl)acetamide (10e): Thick liquid; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 12.7 (s, 1H), 8.53 (s, 1H), 8.20 (s, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.52 (s, 1 H), 6.97 (d, *J* = 8.4 Hz, 1H), 4.98 (m, 2H), 4.9 (d, 2H), 4.44 (s, 2H), 4.34 (s, 2H), 4.3 (d, 2H), 4.1 (m, 1H), 3.4 (d, 2H), 3.05 (d, 2H); ^{1}H NMR: (75 MHz, DMSO-d_6): 174.2, 162.3, 159.4, 142.3, 141.0, 135.4, 123.6, 121.6, 120.4, 111.6, 86.4, 83.2, 76.4, 59.7, 41.6, 39.3 and 13.1; LC-MS: 96% (*m/z* = 427.1 $[M+H]^+$).

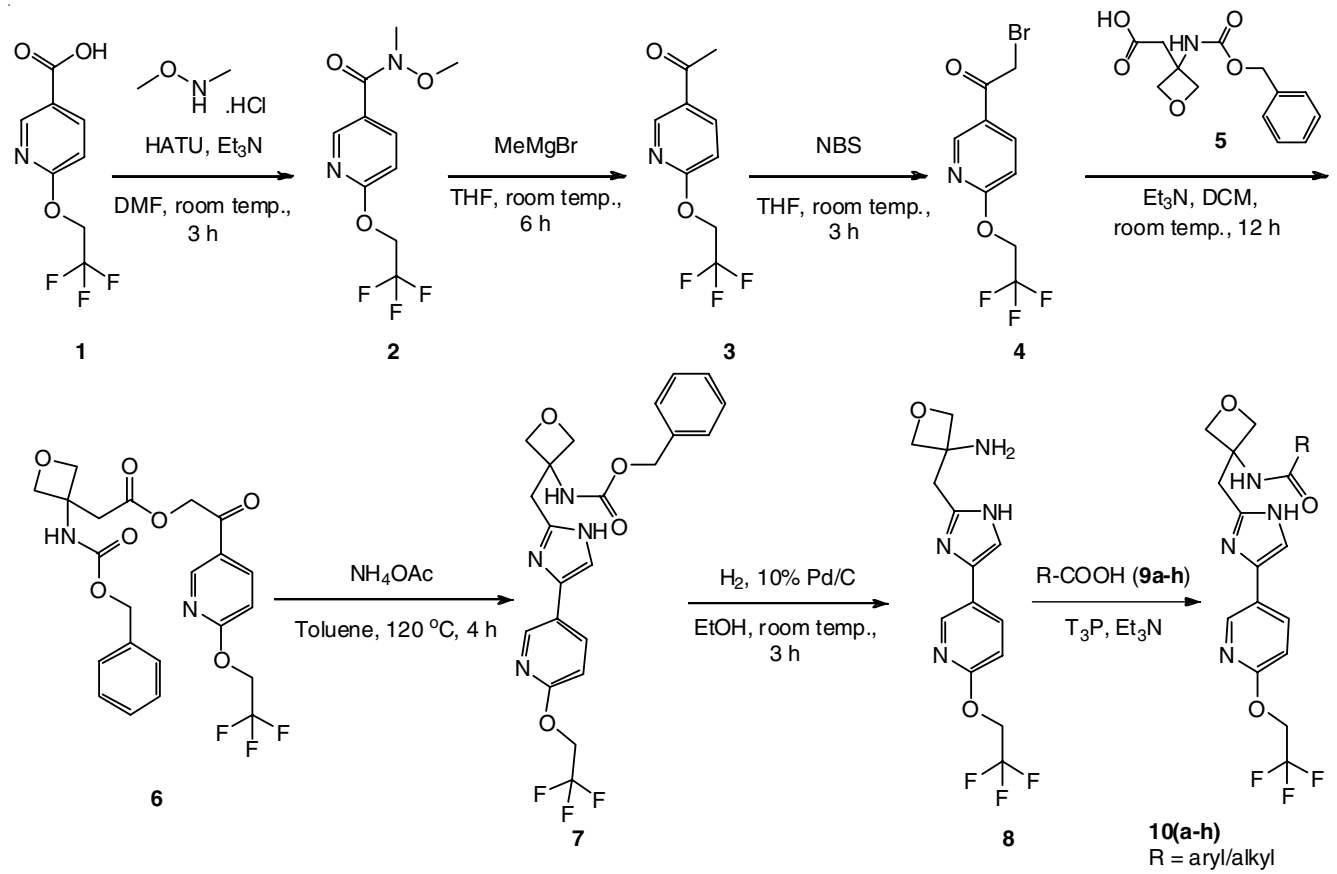
Synthesis of 3-methyl-*N*-(3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1H-imidazol-2-yl)methyl)oxetan-3-yl)-isoxazole-5-carboxamide (10f): White solid; m.p.: 255-258 ºC; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 12.5 (s, 1H), 8.55 (s, 1H), 8.22 (s, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 7.53 (s, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.91 (s, 1H), 4.98 (m, 2H), 4.45 (s, 2H), 4.33 (s, 2H), 3.48 (s, 2H), 2.41 (s, 3H); ^{1}H NMR: (75 MHz, DMSO-d_6): 163.0, 162.1, 161.5, 159.4, 149.4, 142.0, 140.6, 135.7, 123.6, 121.8, 120.3, 111.6, 105.4, 86.4, 83.9, 59.4, 39.6 and 13.6; LC-MS: 96% (*m/z* = 516.2 $[M+H]^+$), LC-MS: 97% (*m/z* = 438.2 $[M+H]^+$).

Synthesis of 2-methyl-*N*-(3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-yl)-oxazole-4-carboxamide (10g): Off white solid; m.p.: 320-323 ºC; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 12.7 (s, 1H), 8.53 (s, 1H), 8.22 (s,1H), 8.12 (d, *J* = 8.6 Hz, 1H), 7.81 (s, 1H), 7.54 (s, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 4.94 (m, 2H), 4.42 (s, 2H), 4.36 (s, 4H), 3.5 (s, 2H), 2.42 (s, 3H); ^{1}H NMR: (75 MHz, DMSO-d_6): 166.4, 163.1, 149.3, 142.4, 140.6, 137.6, 135.4, 123.3, 121.0, 120.2, 111.5, 86.4, 82.6, 58.8, 38.6 and 13.3; LC-MS: 96% (*m/z* = 438.2 $[M+H]^+$).

Synthesis of 3-cyclopropyl-*N*-(3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-yl)isoxazole-5-carboxamide (10h): White coloured solid; m.p.: 288-290 ºC; ^{1}H NMR: (300 MHz, DMSO-d_6): δ 12.4 (s, 1H), 8.55 (s, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 7.53 (s, 1 H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.91 (s, 1H), 4.98 (m, 2H), 4.45 (s, 2H), 4.33 (s, 2H), 3.05 (s, 2H), 2.1 (m, 1H), 1.1 (m, 2H), 0.8 (m, 2H); ^{1}H NMR: (75 MHz, DMSO-d_6): 165.0, 162.3, 160.0, 152.6, 149.5, 142.0, 141.4, 135.6, 123.4, 121.7, 120.8, 112.4,111.2, 86.9, 84.0, 59.1, 39.4, 9.4 and 8.5; LC-MS: 96% (*m/z* = 464.2 $[M+H]^+$).

RESULTS AND DISCUSSION

We reported here a novel amides (**Scheme-I**) directly from different acids and 3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-amine (**8**) by known amide coupling method using T_3P as a catalyst. Initially, we paid attention on the synthesis of 3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-amine (**8**). Commercially available, 6-(2,2,2-trifluoroethoxy) nicotinic acid (**1**) was converted into *N*-methoxy-*N*-methyl-6-(2,2,2-trifluoroethoxy) nicotinamide (**2**) by the reaction with *N,O*-dimethylhydroxylamine hydrochloride in the presence of HATU/Et_3N. Compound **2** was treated with methyl magnesium bromide to give 1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethan-1-one (**3**). Bromonation of compound **3** with *N*-bromo succinamide to afford 2-bromo-1-(6-(2,2,2-trifluoroethoxy)-pyridin-3-yl)ethan-1-one (**4**), which was coupled with 2-(3-(((benzyloxy)carbonyl)amino)oxetan-3-yl)acetic acid (**5**) in the presence of triethyl amine gave 2-oxo-2-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl 2-(3-(((benzyloxy) carbonyl)amino)-oxetan-3-yl)acetate (**6**). Cyclization of compound **6** with ammonium acetate gave benzyl (3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-yl)-carbamate (**7**). De-benzylation of compound **7** using Pd/C, under hydrogen atmosphere afforded 3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-amine (**8**).



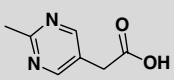
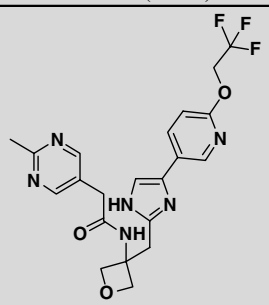
Scheme-I

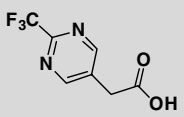
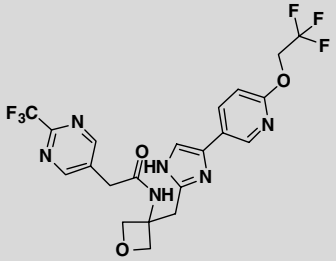
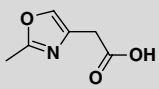
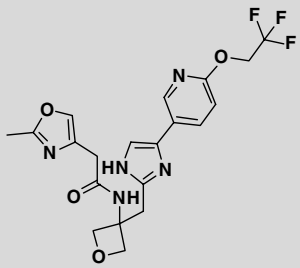
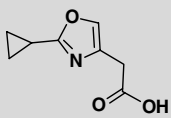
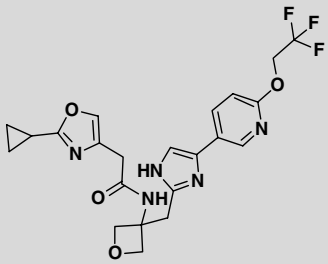
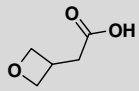
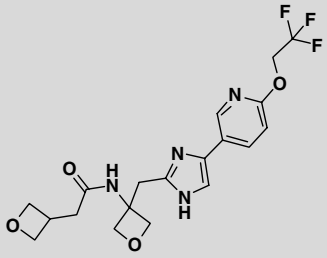
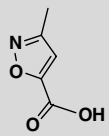
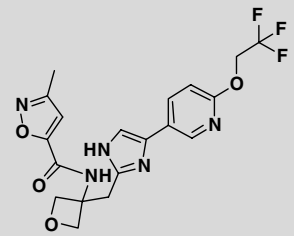
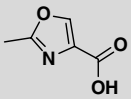
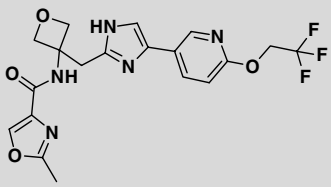
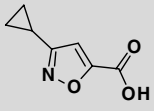
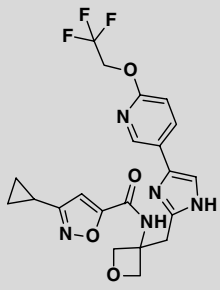
A series of *N*-(3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl) oxetan-3-yl) amide derivatives (**10a-h**) were synthesized by the reaction of 3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl) methyl)-oxetan-3-amine (**8**) with various carboxylic acids (**9a-h**) in the presence of propanephosphonic acid anhydride (T_3P) catalyst.

The reaction is usually finished within 1 h with good isolated yields (Table-1). The IR spectra of 3-((4-(6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-amine displayed characteristic absorption bands for primary amine (-NH_2), imidazole (NH) and ether (C-O) groups at 3445, 3540 and 1155 cm^{-1}, respectively; In the IR, amides **10a**, NH and C=O groups showed absorption bands at 3420 and 1645 cm^{-1}. The ^1H NMR spectra of 3-((4-(6-(2,2,2-trifluoroethoxy)-pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetan-3-amine (**8**), the proton in imidazole (-NH) resonated in downfield at singlet 12.50 and 7.52 ppm other signals at singlet 8.53 and at doublet, 8.10 and 7.22 ppm are attributed to pyridine protons, trifluoro-ethoxy protons resonated at multiplet 4.98 ppm, oxetan mehyl protons displayed at singlet 4.44 and 4.34 ppm and the methyl protons showed resonance signal at singlet 3.05 ppm, In compound **10a**, the amine (-NH) protons in amide resonated at singlet δ 8.20 ppm and pyrimidine ring protons singlet displayed at singlet δ 8.6 ppm.

Antibacterial activity: All the newly synthesized imidazole amide compounds (**10a-h**) were screened for antibacterial activity against *S. aureus*, *E. coli* and *Proteus mirabilis* by agar disc diffusion method. In this method, DMSO was used as solvent

TABLE-1
A NEWLY SYNTHESIZED AMIDE DERIVATIVES (**10a-h**)

Various acids (**9a-h**)	Products (**10a-h**)	Time (min)	Yield (%)
		60	66

		65	62
		55	65
		65	66
		60	62
		50	86
		55	82
		60	80

and the concentration of tested compounds was 10^{-3} M. The results of these studies are listed in Table-2. It is observed that all the tested compounds were active toward *E. coli*, expect **10e**. All the compounds were active towards *S. aureus* and *Proteus mirabilis*, respectively. Compounds **10a** & **10b** showed high inhibition towards *S. aureus*, *E. coli* and *Proteus mirabilis*. In addition, compound **10g** and compounds **10c**, **10d**, **10f** and **10h** showed high inhibition towards *E. coli* and *P. mirabilis*, respectively.

TABLE-2
ANTIBACTERIAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS (**10a-h**)

Compounds	*S. aureus*	*E. coli*	*P. mirabilis*
DMSO	–	–	
10a	+++	+++	+++
10b	+++	+++	+++
10c	++	++	+++
10d	++	++	+++
10e	++	–	++
10f	++	++	+++
10g	++	+++	++
10h	++	++	+++

Zone diameter of growth inhibition: – = no inhibition, + = (3-6) mm ++ = (7-10) nm and +++ = (11-15) nm. Conc. 10^{-3} M

Conclusion

In summary, a series of novel 3-((4-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1*H*-imidazol-2-yl)methyl)oxetanamide derivatives (**10a-h**) were synthesized in multi-step process. All the synthesized amide compounds were tested for their antibacterial activity against the *S. aureus*, *E. coli* and *P. mirabilis* by agar disc diffusion method. Compounds **10a** & **10b** showed high inhibition towards the tested bacteria. In addition, compounds **10g** and **10c**, **10d**, **10f** & **10h** showed high inhibition towards *E. coli* and *P. mirabilis*, respectively.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. Y. Rival, G. Grassy and G. Michel, *Chem. Pharm. Bull. (Tokyo)*, **40**, 1170 (1992); https://doi.org/10.1248/cpb.40.1170
2. M.H. Fisher and A. Lusi, *J. Med. Chem.*, **15**, 982 (1972); https://doi.org/10.1021/jm00279a026
3. Y. Rival, G. Grassy, A. Taudou and R. Ecalle, *Eur. J. Med. Chem.*, **26**, 13 (1991); https://doi.org/10.1016/0223-5234(91)90208-5
4. T. Biftu, D. Feng, M. Fisher, G. Liang, X. Qian, A. Scribner, R. Dennis, S. Lee, P.A. Liberator, C. Brown, A. Gurnett, P.S. Leavitt, D. Thompson, J. Mathew, A. Misura, S. Samaras, T. Tamas, J.F. Sina, K.A. McNulty, C.G. McKnight, D.M. Schmatz and M. Wyvratt, *Bioorg. Med. Chem. Lett.*, **16**, 2479 (2006); https://doi.org/10.1016/j.bmcl.2006.01.092
5. Y. Katsura, S. Nishino, Y. Inoue, M. Tomoi and H. Takasugi, *Chem. Pharm. Bull. (Tokyo)*, **40**, 371 (1992); https://doi.org/10.1248/cpb.40.371
6. E. Abignente, P. De Caprariis, E. Fattorusso and L. Mayol, *J. Heterocycl. Chem.*, **26**, 1875 (1989); https://doi.org/10.1002/jhet.5570260664
7. G.C. Moraski, L.D. Markley, P.A. Hipskind, H. Boshoff, S. Cho, S.G. Franzblau and M.J. Miller, *ACS Med. Chem. Lett.*, **2**, 466 (2011); https://doi.org/10.1021/ml200036r
8. Y. Jiao, B.T. Xin, Y. Zhang, J. Wu, X. Lu, Y. Zheng, W. Tang and X. Zhou, *Eur. J. Med. Chem.*, **90**, 170 (2015); https://doi.org/10.1016/j.ejmech.2014.11.008
9. M.A. Ismail, R.K. Arafa, T. Wenzler, R. Brun, F.A. Tanious, W.D. Wilson and D.W. Boykin, *Bioorg. Med. Chem.*, **16**, 683 (2008); https://doi.org/10.1016/j.bmc.2007.10.042
10. K.S. Gudmundsson and B.A. Johns, *Bioorg. Med. Chem. Lett.*, **17**, 2735 (2007); https://doi.org/10.1016/j.bmcl.2007.02.079
11. Y. Maruyama, K. Anami, M. Terasawa, K. Goto, T. Imayoshi, Y. Kadobe and Y. Mizushima, *Arzneimittel Forsch.,* **31**, 1111 (1981).
12. N. Habersaat, R. Fröhlich and E.-U. Würthwein, *Eur. J. Org. Chem.*, 2567 (2004); https://doi.org/10.1002/ejoc.200400057
13. M. Yamada, T. Yura, M. Morimoto, T. Harada, K. Yamada, Y. Honma, M. Kinoshita and M. Sugiura, *J. Med. Chem.*, **39**, 596 (1996); https://doi.org/10.1021/jm950610n
14. A. Marwaha, P. Singh, M.P. Mahajan and D. Velumurugan, *Tetrahedron Lett.*, **45**, 8945 (2004); https://doi.org/10.1016/j.tetlet.2004.09.119
15. C.W. Derstine, D.N. Smith and J.A. Katzenellenbogen, *J. Am. Chem. Soc.*, **118**, 8485 (1996); https://doi.org/10.1021/ja9614833
16. S. Ohta, T. Osaki, S. Nishio, A. Furusawa, M. Yamashita and I. Kawasaki, *Tetrahedron Lett.*, **41**, 7503 (2000); https://doi.org/10.1016/S0040-4039(00)01283-1
17. P.V. Frank, K.S. Girish and B. Kalluraya, *J. Chem. Sci.*, **119**, 41 (2007); https://doi.org/10.1007/s12039-007-0007-7