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SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF BENZIMIDAZOLE INCORPORATED PYRAZOLE DERIVATIVES

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Abstract: A series of novel 2-(2-aryl-1*H*-benzo[*d*]imidazol-1-yl)-*N*′-((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)acetohydrazide derivatives containing imidazole incorporated pyrazole moieties were synthesized by the condensation of pyrazole derivatives with imdazole hydrazide derivatives in the presence of acetic acid in good yields. These compounds were screened for their antibacterial activity by using standard drug Ciprofloxacin. One of the compounds exhibited better activity against *E. coli* with zone of inhibition 16 mm.

Keywords: Pyrazole, Imidazole, Antibacterial activity, Ciprofloxacin, Vilsmeier Haack reaction.

Introduction:

The pyrazole ring is a prominent structural motif found in numerous pharmaceutically active compounds. This is mainly due to its ease of preparation and pharmacological activity. Many pyrazole derivatives are known to possess a wide range of bioactivities such as anti-inflammatory [i, ii], analgesic [iii, iv], antibacterial [v, vi], antifungal [vii] and anticancer [viii]. Some biologically important drugs containing pyrazole such as Zaleplon, Zoniporide, Celecoxib and Acomplia are also available.

In addition, benzimidazole ring is also an important pharmacophore in modern drug discovery. The synthesis of novel benzimidazole derivatives remain as a main focus of medicinal research. Several benzimidazole derivatives had been proven to possess bioactivities such as antiviral [ix], antihypertensive [x], antitumor [xi], antiproliferative [xii], antimicrobial [xiii], antioxidant and antiglycation [xiv].

A large number of reports were there on the synthesis and biological activities especially antibacterial activity of pyrazole and imidazole derivatives [xv-xvii]. Herein, we have

synthesized a novel series of 1,3-diaryl pyrazole derivatives bearing imidazoles and evaluated their antibacterial activity.

Experimental:

All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (mesh); spots were visualized with UV light. Merck silica gel (60-120 mesh) was used for column chromatography. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 MHz NMR spectrometer in $CDCl_3$/DMSO solution using TMS as an internal standard. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Agilent 1100 LC/MSD instrument with method API-ES at 70 eV.

Synthesis of acetophenone phenyl hydrazones (2a-e)

A mixture of appropriate ketone (**1a-e**) (1 mmol) and phenyl hydrazine (1 mmol) in ethanol was refluxed in the presence of few drops of glacial acetic acid for 2 h. The progress of reaction was monitored by TLC using n-hexane: ethyl acetate (7:3) as a mobile phase. The mixture was cooled and the solid product obtained was filtered, washed with water and recrystallized from ethanol.

(Z)-1-(1-(4-nitrophenyl)ethylidene)-2-phenylhydrazine (2a)

Red solid, Yield: 90%, mp: 128-130 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3H), 6.95 (t, J = 7.32 Hz, 1H), 7.20-7.22 (m, 2H), 7.32 (t, J = 7.9 Hz, 2H), 7.60 (s, 1H), 7.92 (d, J = 9.0 Hz, 2H), 8.22 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.9, 113.4, 121.1, 123.6, 125.6, 129.3, 137.8, 144.2, 145.0, 159.5; LCMS (positive ion mode) (*m/z*): 256.2 $[M+H]^+$ for $C_{14}H_{13}N_3O_2$.

(Z)-1-phenyl-2-(1-phenylethylidene)hydrazine (2b)

White solid, Yield: 88%, mp: 117-119 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H), 7.02 (t, J = 7.50 Hz, 1H), 7.32-7.35 (m, 4H), 7.42-7.45 (m, 1H), 7.45 (s, 1H), 7.56 (d, J = 8.76 Hz, 2H), 7.73 (d, J = 8.74 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.4, 112.6, 120.5, 122.9, 124.5, 129.8, 136.7, 145.3, 146.4, 160.2; LCMS (positive ion mode) (*m/z*): 211.3 $[M+H]^+$ for $C_{14}H_{14}N_2$.

(Z)-1-(1-(4-chlorophenyl)ethylidene)-2-phenylhydrazine (2c)

White solid, Yield: 92%, mp: 120-122 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H), 7.14-7.26 (m, 5H), 7.65 (s, 1H), 7.69 (d, J = 8.56 Hz, 2H), 7.84 (d, J = 8.57 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.3, 113.2, 120.6, 123.5, 124.2, 129.5, 136.5, 144.6, 145.7, 160.1; LCMS (positive ion mode) (*m/z*): 245.2 $[M+H]^+$ for $C_{14}H_{13}ClN_2$.

(Z)-1-(1-(4-fluorophenyl)ethylidene)-2-phenylhydrazine (2d)

White solid, Yield: 91%, mp: 118-120 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3H), 7.15 (d, J = 7.56 Hz, 2H), 7.25-7.32 (m, 3H), 7.67 (s, 1H), 7.75 (d, J = 8.46 Hz, 2H), 7.83 (d, J = 8.47 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.3, 115.7, 121.4, 123.9, 125.3, 129.7, 137.2, 145.2, 146.5, 160.5; LCMS (positive ion mode) (*m/z*): 229.3 $[M+H]^+$ for $C_{14}H_{13}FN_2$.

(Z)-1-(1-(4-methoxyphenyl)ethylidene)-2-phenylhydrazine (2e)

White solid, Yield: 89%, mp: 125-127 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H), 4.12 (s, 3H), 7.25-7.34 (m, 5H), 7.54 (s, 1H), 7.68 (d, J = 8.72 Hz, 2H), 7.75 (d, J = 8.75 Hz,

2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.9, 114.8, 122.5, 123.7, 125.8, 129.4, 137.5, 145.3, 147.8, 160.2; LCMS (positive ion mode) (*m/z*): 241.4 $[M+H]^+$ for $C_{15}H_{16}N_2O$.

Synthesis of 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes (3a-e)

To an ice cold of dimethyl formamide (10 ml), $POCl_3$ (3 mmol) was added drop wise with continuous stirring over a period of 30 min. Stirring was continued for further 60 min, keeping the reaction temperature at 0 ^oC. Then acetophenone phenyl hydrazone derivative (**2a-e)** (1 mmol) was then added and the reaction mixture was allowed to attain room temperature. The mixture was then refluxed for 5 h, allowed to cool and poured onto ice. The mixture was neutralized with saturated sodium bicarbonate solution. The solid product obtained was filtered, washed with water and recrystallized from methanol. The completion of reaction was monitored by TLC using n-hexane: ethyl acetate (7:3) as a mobile phase.

3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3a)

Grey solid, Yield: 78%, mp: 135-137 ^oC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.09 (d, J = 8.69 Hz, 2H), 7.51 (d, J = 7.85 Hz, 2H), 7.88-7.92 (m, 5H), 8.55 (s, 1H), 10.14 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 115.8, 120.5, 123.9, 124.5, 129.4, 130.3, 130.5, 131.5, 138.6, 155.7, 160.1, 186.2; LCMS (positive ion mode) (*m/z*): 294.12 $[M+H]^+$ for $C_{16}H_{11}N_3O_3$.

1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (3b)

Off-white solid, Yield: 82%, mp: 129-131 ^oC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.14-7.19 (m, 3H), 7.36 (d, J = 7.92 Hz, 2H), 7.53-7.58 (m, 5H), 8.63 (s, 1H), 10.19 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 114.8, 121.5, 122.5, 123.5, 129.8, 130.1, 130.3, 131.9, 136.6, 158.7, 161.1, 185.1; LCMS (positive ion mode) (*m/z*): 249.05 $[M+H]^+$ for $C_{16}H_{12}N_2O$.

3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3c)

Off-white solid, Yield: 75%, mp: 128-130 ^oC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.13 (d, J = 8.69 Hz, 2H), 7.57 (d, J = 7.85 Hz, 2H), 7.91-7.94 (m, 5H), 8.45 (s, 1H), 10.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 116.8, 121.5, 123.2, 124.8, 127.4, 129.5, 130.8, 131.7, 138.6, 156.7, 160.6, 185.2; LCMS (positive ion mode) (*m/z*): 283.10 $[M+H]^+$ for $C_{16}H_{11}ClN_2O$.

3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3d)

Off-white solid, Yield: 79%, mp: 134-136 ^oC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.15 (d, J = 8.69 Hz, 2H), 7.63 (d, J = 7.85 Hz, 2H), 7.81-7.85 (m, 5H), 8.57 (s, 1H), 10.12 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 115.9, 120.5, 123.9, 124.4, 127.4, 129.5, 130.8, 131.7, 138.6, 156.7, 160.6, 185.2; LCMS (positive ion mode) (*m/z*): 267.10 $[M+H]^+$ for $C_{16}H_{11}FN_2O$.

3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3e)

Off-white solid, Yield: 74%, mp: 136-138 ^oC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.87 (s, 3H), 7.03 (d, J = 8.69 Hz, 2H), 7.38 (d, J = 7.39 Hz, 1H), 7.51 (t, , J = 7.85 Hz, 2H), 7.78-7.80 (m, 4H), 8.52 (s, 1H), 10.04 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.9, 114.8, 120.3, 122.9, 124.4, 128.4, 130.2, 130.8, 131.8, 139.6, 155.1, 161.1, 185.7; LCMS (positive ion mode) (*m/z*): 279.15 $[M+H]^+$, 301.10 $[M+Na]^+$ for $C_{17}H_{14}N_2O_2$.

Synthesis of 2-aryl-1*H*-benzo[*d*]imidazoles (5a-c)

To a solution of o-phenylenediamine (1 mmol) in 20 ml of DMF, a suspension of appropriate aldehyde (1 mmol) **(4a-c)** and sodium metabisulfite (2 mmol) in 50 ml of DMF was added. The heterogeneous mixture was stirred at 110 ^oC for 4 h. After completion of reaction

monitored by TLC, the mixture was cooled and poured onto a lot of ice. A large amount of solid would emerge and was filtered to give the corresponding benzimidazole derivative.

2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazoles (5a)
Grey solid, Yield: 89%, mp: 175-177 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.24 (d, J = 8.52 Hz, 2H), 7.43 (t, J = 8.70 Hz, 2H), 7.65 (d, J = 8.43 Hz, 2H), 8.23-8.25 (m, 2H), 10.35 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 115.2, 116.5, 121.9, 126.8, 137.5, 148.3, 159,2, 163.8; LCMS (positive ion mode) (*m/z*): 229.2 $[M+H]^+$ for $C_{13}H_9ClN_2$.

2-(4-fluorophenyl)-1*H*-benzo[*d*]imidazoles (5b)
Grey solid, Yield: 89%, mp: 177-180 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.22 (d, J = 8.20 Hz, 2H), 7.40 (t, J = 8.82 Hz, 2H), 7.60 (d, J = 8.23 Hz, 2H), 8.20-8.24 (m, 2H), 10.38 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 114.8, 116.0, 122.1, 128.6, 138.8, 150.1, 161.7, 164.2; LCMS (positive ion mode) (*m/z*): 213.3 $[M+H]^+$ for $C_{13}H_9FN_2$.

2-(p-tolyl)-1*H*-benzo[*d*]imidazoles (5c)
Grey solid, Yield: 82%, mp: 172-175 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H), 7.18 (dd, J = 2.74 Hz, 3.05 Hz, 2H), 7.33 (d, J = 7.78 Hz, 2H), 7.57 (dd, J = 2.44 Hz, 3.20 Hz, 2H), 8.04 (d, J = 7.78 Hz, 2H), 10.39 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.5, 113.8, 115.7, 122.0, 127.5, 138.2, 148.6, 160.5, 163.9; LCMS (positive ion mode) (*m/z*): 209.2 $[M+H]^+$ for $C_{14}H_{12}N_2$.

Synthesis of ethyl 2-(2-aryl-1*H*-benzo[*d*]imidazol-1-yl)acetates (6a-c)
To a solution of compound (1 mmol) (**5a-c)** in acetone, potassium carbonate (2 mmol) and bromo ethyl acetate (1.2 mmol) were added and the mixture was refluxed for 2 h. The completion of reaction was monitored by TLC using hexane: ethyl acetate (7:3) as a mobile phase. After completion of reaction, the mixture was poured into crushed ice and the formed precipitate was filtered and dried. The product was recrystallized by using ethanol as a solvent.

Ethyl 2-(2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)acetate (6a)
Brown solid, Yield: 78%, mp: 180-182 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.38 (t, J = 7.92 Hz, 3H), 4.32 (q, J = 8.0 Hz, 2H), 4.67 (s, 2H), 7.22-7.26 (m, 2H), 7.35 (d, J = 7.34 Hz, 2H), 7.49 (d, J = 7.45 Hz, 2H), 7.74 (d, J = 8.20 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.9, 45.9, 60.7, 109.5, 114.6, 119.2, 121.6, 125.9, 132.4, 134.5, 142.7, 151.6, 162.8, 163.9, 167.6; LCMS (positive ion mode) (*m/z*): 315.2 $[M+H]^+$ for $C_{17}H_{15}ClN_2O_2$.

Ethyl 2-(2-(4-fluorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)acetate (6b)
Grey solid, Yield: 75%, mp: 184-186 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (t, J = 7.92 Hz, 3H), 4.27 (q, J = 8.0 Hz, 2H), 4.72 (s, 2H), 7.19-7.24 (m, 2H), 7.39 (d, J = 7.34 Hz, 2H), 7.58 (d, J = 7.45 Hz, 2H), 7.78 (d, J = 8.20 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.7, 46.1, 61.8, 109.0, 115.8, 119.7, 122.6, 125.5, 131.0, 135.5, 142.4, 152.6, 162.2, 164.7, 167.3; LCMS (positive ion mode) (*m/z*): 299.03 $[M+H]^+$ for $C_{17}H_{15}FN_2O_2$.

Ethyl 2-(2-(p-tolyl)-1*H*-benzo[*d*]imidazol-1-yl)acetate (6c)
Grey solid, Yield: 78%, m.p: 181-183 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (t, J = 7.2 Hz, 3H), 2.43 (s, 3H), 4.25 (q, J = 7.2 Hz, 2H), 4.87 (s, 2H), 7.26-7.34 (m, 5H), 7.59 (d, J = 8.0 Hz, 2H), 7.83-7.85 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.1, 22.9, 46.5, 61.8,

109.6, 119.9, 123.1, 126.5, 129.2, 129.4, 129.7, 135.8, 140.4, 142.5, 154.1, 167.5; LCMS (positive ion mode) (*m/z*): 295.0 $[M+H]^+$ for $C_{18}H_{18}N_2O_2$.

Synthesis of 2-(2-aryl-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazides (7a-c)

To a solution of compound (**6a-c**) (1 mmol) in ethanol, hydrazine hydrate (4.5 mmol) was added and the reaction mixture was refluxed for 2 h. After completion of reaction, the mixture was cooled to room temperature and then poured into crushed ice. The formed precipitate was filtered, dried and recrystallized from ethanol.

2-(2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (7a)

Grey solid, Yield: 85%, mp: 215-218 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 4.25 (s, 2H), 4.85 (s, 2H), 7.23-7.26 (m, 3H), 7.45-7.48 (m, 1H), 7.75-7.77 (d, J = 8.5 Hz, 2H), 7.89-7.93 (d, J = 8.5 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 44.7, 109.1, 115.4, 117.9, 121.6, 124.9, 131.2, 134.8, 141.5, 152.6, 161.1, 163.8, 165.9; LCMS (positive ion mode) (*m/z*): 301.0 $[M+H]^+$ for $C_{15}H_{13}ClN_4O$.

2-(2-(4-fluorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (7b)

Off-white solid, Yield: 82%, mp: 218-220 ^oC ^1H NMR (400 MHz, DMSO-d_6): δ 4.22 (s, 2H), 4.81 (s, 2H), 7.25-7.30 (m, 3H), 7.40-7.43 (m, 1H), 7.72-7.75 (d, J = 8.2 Hz, 2H), 7.87-7.91 (d, J = 8.2 Hz, 2H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 44.5, 108.9, 114.4, 117.8, 121.4, 124.7, 130.2, 134.6, 140.9, 151.6, 160.2, 163.5, 165.1; LCMS (positive ion mode) (*m/z*): 285.2 $[M+H]^+$ for $C_{15}H_{13}FN_4O$.

2-(2-(p-tolyl)-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (7c)

Off-white solid, Yield: 87%, mp: 220-225 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 2.15 (s, 3H), 4.21 (s, 2H), 4.73 (s, 2H), 7.27-7.30 (m, 3H), 7.43-7.48 (m, 1H), 7.73-7.77 (d, J = 8.2 Hz, 2H), 7.87-7.92 (d, J = 8.2 Hz, 2H), 9.69 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 44.8, 108.7, 113.2, 116.5, 121.8, 125.7, 130.8, 134.9, 141.9, 150.5, 159.2, 162.5, 165.5; LCMS (positive ion mode) (*m/z*): 281.2 $[M+H]^+$ for $C_{16}H_{16}N_4O$.

Synthesis of 2-(2-aryl-1*H*-benzo[*d*]imidazol-1-yl)-*N'*-((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)acetohydrazide (8a-o)

A mixture of 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**3a-e**) (1 mmol) and 2-(2-aryl-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (**7a-c**) (1 mmol) in ethanol were refluxed for 2 h. After completion of reaction the mixture was cooled to room temperature and poured onto crushed ice. The formed precipitate was filtered, dried and purified by column chromatography using chloroform and methanol mixture as a mobile phase.

(E)-2-(2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)-N'-((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)acetohydrazide (8a)

Brown solid, Yield: 74%, mp: 210-212 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 4.50 (s, 2H), 6.56 (d, J = 7.42 Hz, 2H), 6.70 (d, J = 8.25 Hz, 2H), 6.75 (d, J = 8.80 Hz, 2H), 6.82-6.86 (m, 2H), 7.10 (d, J = 7.98 Hz, 2H), 7.22-7.17 (m, 4H), 7.37 (d, J = 3.85 Hz, 2H), 7.40 (s, 1H), 7.48-7.52 (m, 1H), 8.25 (s, 1H), 10.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.63, 110.1, 116.6, 118.2, 118.5, 121.6, 122.2, 122.9, 126.8, 128.3, 128.9, 129.0, 129.3, 129.9, 130.3, 133.1, 134.1, 136.5, 138.1, 141.6, 146.5, 148.1, 151.7, 167.2; LCMS (positive ion mode) (*m/z*): 576.0 $[M+H]^+$ for $C_{31}H_{22}ClN_7O_3$.

(E)-2-(2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)-N'-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)acetohydrazide (8b)
White solid, Yield: 74%, mp: 215-217 ^{o}C; ^{1}H NMR (400 MHz,$CDCl_3$): δ 5.20 (s, 2H), 7.30-7.34 (m, 5H), 7.45-7.49 (m, 5H), 7.58-7.60 (m, 2H), 7.69 (d, J = 8.31 Hz, 2H), 7.76 (d, J = 7.82 Hz, 2H), 7.84-7.86 (m, 2H), 8.09 (s, 1H), 8.25 (s, 1H), 9.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.2, 109.9, 119.6, 120.4, 123.2, 123.6, 124.2, 124.5, 127.0, 127.7, 128.9, 129.1, 129.4, 129.7, 129.8, 130.9, 132.3, 134.5, 138.8, 143.1, 148.4, 153.2, 158.0, 166.2; LCMS (positive ion mode) (*m/z*): 531 $[M+H]^+$ for $C_{31}H_{23}ClN_6O$.

(E)-N'-((3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-(2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (8c)
White solid, Yield: 71%, mp: 215-218 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.22 (s, 2H), 7.28-7.31 (m, 4H), 7.36 (d, J = 7.58 Hz, 2H), 7.46-7.50 (m, 5H), 7.54 (d, J = 8.43 Hz, 2H), 7.69 (d, J = 8.55 Hz, 2H), 7.75 (d, J = 8.68 Hz, 2H), 8.1 (s, 1H), 8.24 (s, 1H), 10.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.2, 116.0, 119.7, 120.4, 123.0, 123.2, 127.3, 127.9, 129.2, 129.4, 129.7, 129.9, 130.2, 131.0, 134.5, 136.5, 138.3, 143.6, 144.3, 146.9, 151.9, 163.5, 164.4, 166.2; LCMS (positive ion mode) (*m/z*): 565 $[M+H]^+$ for $C_{31}H_{22}Cl_2N_6O$.

(E)-2-(2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)-N'-((3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)acetohydrazide (8d)
White solid, Yield: 72%, mp: 216-218 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.25 (s, 2H), 7.29-7.33 (m, 4H), 7.39 (d, J = 7.58 Hz, 2H), 7.45-7.48 (m, 5H), 7.56 (d, J = 8.43 Hz, 2H), 7.72 (d, J = 8.55 Hz, 2H), 7.77 (d, J = 8.68 Hz, 2H), 8.15 (s, 1H), 8.25 (s, 1H), 10.21 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 39.5, 115.8, 120.1, 120.7, 121.5, 123.7, 127.5, 127.7, 128.6, 128.9, 129.5, 129.8, 131.5, 132.1, 134.7, 135.6, 137.7, 142.3, 143.6, 147.8, 152.9, 161.5, 164.5, 166.8; LCMS (positive ion mode) (*m/z*): 549.1 $[M+H]^+$ for $C_{31}H_{22}ClFN_6O$.

(E)-2-(2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)-N'-((3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)acetohydrazide (8e)
Off-white solid, Yield: 73%, mp: 220-225 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.8 (s, 3H), 5.18 (s, 2H), 7.04 (d, J = 8.69 Hz, 2H), 7.14 (d, J = 8.69 Hz, 1H), 7.32-7.35 (m, 3H), 7.41 (t, J = 7.39 Hz, 2H), 7.68-7.69 (m, 2H), 7.77-7.79 (m, 3H), 7.88 (d, J = 8.54 Hz, 1H), 7.97 (d, J = 7.62 Hz, 2H), 8.03 (d, J = 7.78 Hz, 1H), 8.21 (s, 1H), 8.60 (s, 1H), 10.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.7, 56.9, 116.7, 117.3, 119.5, 120.3, 123.4, 126.9, 127.5, 128.7, 129.3, 129.5, 130.1, 130.8, 131.9, 133.7, 134.2, 136.6, 136.9, 142.3, 145.4, 147.9, 151.8, 152.6, 168.8; LCMS (positive ion mode) (*m/z*): 561.2 $[M+H]^+$ for $C_{32}H_{25}ClN_6O_2$.

(E)-2-(2-(4-fluorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)-N'-((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)acetohydrazide (8f)
Brown solid, Yield: 69%, mp:215-217 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.20 (s, 2H), 7.18 (t, J = 8.64 Hz, 2H), 7.27-7.31 (m, 6H), 7.49 (t, J = 7.88 Hz, 2H), 7.59-7.62 (m, 2H), 7.72-7.74 (m, 3H), 7.85-7.88 (m, 2H), 8.12 (s, 1H), 8.25 (s, 1H), 10.15 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 39.3, 109.8, 114.8, 116.7, 119.5, 119.8, 121.7, 123.5, 126.2, 127.3, 128.4, 128.9, 129.6, 131.1, 131.4, 132.6, 134.8, 137.1, 139.6, 142.8, 151.6, 153.5, 161.4, 168.7; LCMS (positive ion mode) (*m/z*): 560.1 $[M+H]^+$ for $C_{31}H_{22}FN_7O_3$.

(E)-N'-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-(2-(4-fluorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (8g)

Off-white solid, Yield: 72%, mp: 205-207 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.18 (s, 2H), 7.16 (t, J = 8.64 Hz, 2H), 7.26-7.31 (m, 6H), 7.46 (t, J = 7.88 Hz, 2H), 7.56-7.58 (m, 2H), 7.72-7.76 (m, 4H), 7.82-7.85 (m, 2H), 8.09 (s, 1H), 8.22 (s, 1H), 10.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.8, 109.6, 115.8, 116.1, 119.2, 119.8, 122.8, 123.2, 126.0, 127.3, 128.4, 128.5, 129.5, 131.3, 131.4, 132.0, 134.1, 136.2, 139.2, 142.7, 152.6, 153.3, 162.4, 168.5; LCMS (positive ion mode) (*m/z*): 515 $[M+H]^+$ for $C_{31}H_{23}FN_6O$.

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(E)-N'-((3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-(2-(4-fluorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (8h)

White solid, Yield: 72%, mp: 210-212 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.20 (s, 2H), 7.18 (t, J = 8.6 Hz, 2H), 7.24-7.28 (m, 2H), 7.29-7.31 (m, 3H), 7.36 (d, J = 7.47 Hz, 1H), 7.47 (t, J = 7.05 Hz, 2H), 7.52 (d, J = 8.39 Hz, 2H), 7.73-7.76 (m, 4H), 7.79 (s, 1H), 7.84 (d, J = 8.08 Hz, 1H), 8.22 (s, 1H), 10.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 38.9, 110.6, 115.7, 116.5, 118.2, 119.5, 121.4, 124.2, 126.7, 127.5, 128.3, 129.5, 130.4, 131.3, 131.7, 132.5, 134.6, 136.7, 139.3, 143.9, 151.6, 154.5, 161.4, 168.6; LCMS (positive ion mode) (*m/z*): 549 $[M+H]^+$ for $C_{31}H_{22}ClFN_6O$.

(E)-N'-((3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-(2-(4-fluorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (8i)

Off-white solid, Yield: 68%, mp: 205-207 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (s, 2H), 6.93 (t, J = 8.62 Hz, 2H), 7.16 (t, J = 8.62 Hz, 2H), 7.26-7.30 (m, 4H), 7.47 (t, , J = 8.00 Hz, 2H), 7.51-7.54 (m, 2H), 7.72-7.75 (m, 4H), 7.79 (s, 1H), 7.82-7.84 (m, 1H), 8.20 (s, 1H), 10.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.8, 109.5, 115.5, 115.8, 115.9, 116.1, 119.3, 120.0, 122.8, 123.2, 126.9, 127.5, 129.4, 129.6, 130.3, 130.4, 131.3, 131.4, 132.8, 134.2, 138.2, 139.1, 163.0, 165.9; LCMS (positive ion mode) (*m/z*): 533 $[M+H]^+$ for $C_{31}H_{22}F_2N_6O$.

(E)-2-(2-(4-fluorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)-N'-((3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)acetohydrazide (8j)

White solid, Yield: 75%, mp: 215-217 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 3H), 5.41 (s 2H), 6.99 (d, J = 8.69 Hz, 2H), 7.34-7.37 (m, 1H), 7.51-7.55 (m, 4H), 7.62-7.66 (m, 5H), 7.71-7.74 (m, 3H), 7.92 (d, J = 8.69 Hz, 2H), 8.16 (s, 1H), 8.98 (s, 1H), 10.32 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.2, 55.1, 110.6, 113.9, 115.7, 116.0, 116.4, 118.5, 119.0, 122.1, 122.6, 124.5, 126.8, 128.2, 129.7, 131.2, 136.5, 137.7, 138.9, 142.3, 151.1, 152.6, 159.5, 161.3, 167.8; LCMS (positive ion mode) (*m/z*): 545.1 $[M+H]^+$ for $C_{32}H_{25}FN_6O_2$.

(E)-N'-((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-(2-(p-tolyl)-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (8k)

Brown solid, Yield: 68%, mp: 200-202 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39 (s, 3H), 5.22 (s, 2H), 7.27-7.30 (m, 5H), 7.38 (t, J = 7.35 Hz, 2H), 7.50 (t, J = 7.90 Hz, 3H), 7.61 (d, J = 7.93 Hz, 2H), 7.76-7.78 (m, 3H), 8.06 (d, J = 7.95 Hz, 2H), 8.25 (s, 1H), 8.70 (s, 1H), 10.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.1, 38.5, 109.2, 116.0, 119.0, 119.4, 122.4, 122.7, 123.3, 127.4, 127.8, 128.4, 128.8, 129.1, 129.3, 133.8, 135.9, 137.5, 138.2, 138.6, 140.0, 142.4, 147.3, 154.0, 168.2; LCMS (positive ion mode) (*m/z*): 556.1 $[M+H]^+$ for $C_{32}H_{25}N_7O_3$.

(E)-N'-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-(2-(p-tolyl)-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (8l)

White solid, Yield: 75%, mp: 190-195 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 5.18 (s, 2H), 7.24-7.30 (m, 8H), 7.46 (t, J = 7.94 Hz, 2H), 7.56 (d, J = 7.80 Hz, 2H), 7.64 (d, J = 8.06 Hz, 2H), 7.75 (d, J = 7.58 Hz, 2H), 7.80-7.84 (m, 2H), 8.09 (s, 1H), 8.19 (s, 1H), 10.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 38.5, 109.3, 115.5, 118.9, 119.5, 122.3, 122.6, 126.9, 128.1, 128.2, 128.9, 129.1, 129.2, 131.7, 133.8, 136.0, 138.3, 138.9, 139.7, 142.5, 152.3, 154.1, 165.6, 168.2; LCMS (positive ion mode) (*m/z*): 511 $[M+H]^+$ for $C_{32}H_{26}N_6O$.

(E)-N'-((3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-(2-(p-tolyl)-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (8m)

Off-white solid, Yield: 73%, mp: 200-202 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 5.18 (s, 2H), 7.16 (d, 2H, J = 8.54 Hz), 7.26-7.29 (m, 7H), 7.45-7.48 (m, 2H), 7.50 (d, J = 8.39 Hz, 2H), 7.63 (d, J = 8.08 Hz, 2H), 7.72 (d, J = 7.93 Hz, 2H), 7.76 (s, 1H), 8.16 (s, 1H), 10.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 38.8, 109.6, 115.9, 119.1, 119.7, 122.6, 122.9, 126.8, 127.3, 127.7, 128.5, 129.2, 129.5, 129.7, 130.6, 134.6, 136.3, 138.6, 139.1, 140.2, 142.7, 151.0, 154.4, 168.7; LCMS (positive ion mode) (*m/z*): 545 $[M+H]^+$ for $C_{32}H_{25}ClN_6O$.

(E)-N'-((3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-(2-(p-tolyl)-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (8n)

Off-white solid, Yield: 69%, mp: 195-197 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 5.21 (s, 2H), 7.25-7.29 (m, 7H), 7.34 (d, J = 7.47 Hz, 1H), 7.46 (t, J = 7.85 Hz, 2H), 7.52-7.55 (m, 2H), 7.63 (d, J = 8.08 Hz, 2H), 7.73 (d, J = 7.78 Hz, 2H), 7.82 (d, J = 6.86 Hz, 1H), 8.09 (s, 1H), 8.18 (s, 1H), 10.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 38.8, 109.6, 115.3, 115.8, 119.1, 119.8, 122.6, 122.9, 126.9, 127.3, 128.2, 128.8, 129.2, 129.5, 130.3, 134.1, 136.3, 138.6, 139.1, 140.1, 142.8, 154.4, 165.9, 168.7; LCMS (positive ion mode) (*m/z*): 529 $[M+H]^+$ for $C_{32}H_{25}FN_6O$.

(E)-N'-((3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-2-(2-(p-tolyl)-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (8o)

Off-white solid, Yield: 67%, mp: 205-207 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40 (s, 3H), 3.77 (s, 3H), 5.28 (s, 2H), 6.91 (d, , J = 8.52 Hz, 2H), 7.25-7.32 (m, 6H), 7.45 (t, , J = 7.97 Hz, 2H), 7.58-7.66 (m, 4H), 7.73-7.79 (m, 3H), 8.17 (s, 1H), 8.42 (s, 1H), 10.35 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.2, 37.2, 54.2, 111.6, 112.8, 115.9, 116.5, 116.9, 117.8, 119.4, 121.2, 122.6, 124.7, 125.8, 128.6, 129.7, 132.5, 135.5, 137.3, 138.4, 141.2, 151.8, 152.7, 159.9, 162.1, 167.5; LCMS (positive ion mode) (*m/z*): 541.1 $[M+H]^+$ for $C_{33}H_{28}N_6O_2$.

Antibacterial activity

Antimicrobial activity has been conducted by measuring Zone of inhibition. The medium used in this experimentation are Nutrient Agar (HiMedia Laboratories Pvt. Ltd., Mumbai., India) for bacteria grown at 28˚C for 24 h. Agar disk-diffusion testing was developed by N.G. Heatley in 1940. 28 g Nutrient agar medium was weighed and suspended in 1lit of distilled water in a conical flask. The conical flask further plugged with Nonabsorbent cotton bung. The medium was then sterilized by autoclaving at 15-lbf/in^2 pressure for 20 min. Sterilized Nutrient agar medium was poured into Petri plates and allow for solidifying. 50 µg/ml discs were prepared for testing efficiency of compounds (**8a-o**) by using Whatman no1 filter paper. One strip of Ciprofloxacin (standard) was placed aseptically to the central part of each plate.

They were incubated for about 24 h at 32 ± 2°C. After 24 h the plates were examined and the diameter of zones of inhibition was accurately measured.

Results and discussion

The synthesis of target pyrazolyl-imidazole derivatives was carried out as outlined in the **Scheme.** In the present investigation 3-substituted-1*H*-pyrazole-4-carbaldehydes (**3a-e**) were synthesized by the Vilsmayer Haack reaction of semicarbazones [xviii]. Condensation reactions between benzene-1,2-diamine and the appropriate carboxylic acids (**4a-c**) yielded benzo[d]imidazoles (**5a-c**) where various substitutions, including alkyls and halides, were introduced at 2C-position of the imidazole ring system [xix]. Imidazole ester derivatives (**6a-c**) were obtained by refluxing with bromomethyl acetate in the presence of base potassium carbonate. Then hydrazide derivatives (**7a-c**) were prepared by treating with hydrazine hydrate. Final derivatives (**8a-o**) were synthesized by the condensation of pyrazole derivatives (**3a-e**) with imidazole derivatives (**7a-c**) in the presence of acetic acid.

All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, mass spectral analysis. The formation of compounds (**3a-e**) was confirmed by the appearance of a singlet in the range of δ 10.04 - 10.19 ppm due to aldehyde proton in ^{1}H NMR spectrum. Similarly compound **3a** gives a signal at 186.2 ppm in ^{13}C NMR spectrum due to carbonyl carbon.

A singlet at δ 4.87 ppm due to methylene in ^{1}H NMR spectrum indicates the formation of imidazoles ester derivatives (**6c**). The formation of hydrazides (**7a-c**) from ester derivatives (**6a-c**) was confirmed by the disappearance of triplet and quartet corresponding to ethoxy protons in ^{1}H NMR spectrum. It was also confirmed by the appearance of a peak [M+H]+ with m/z value 285.2 for compound **7b**.

The formation of derivatives (**8a-o**) was confirmed by the shielding of aldehyde proton in ^{1}H NMR spectrum. The ^{1}H NMR spectrum of compound **8j** showed a singlet at δ 3.75 ppm due to $-OCH_3$ group and a singlet at δ 5.41 ppm assigned to methylene protons. The remaining aromatic protons appear in the range of δ 6.99-8.16 ppm. The imine proton and -NH proton appears at δ 8.98 and 10.32 ppm respectively. Similarly in it's ^{13}C NMR spectrum, aliphatic carbons appear at δ 38.2 and 55.1 ppm and a signal at δ 167.8 ppm corresponds to carbonyl carbon. Almost similar patterns were observed in ^{1}H and ^{13}C NMR spectra of rest of the compounds (**8a-o**). Further the mass spectrum of compound **8j** showed a peak at *m/z* 545.1 which corresponds to $[M+H]^{+}$.

Antibacterial activity

All the target compounds (**8a-o**) were evaluated *in vitro* for their antibacterial activities against *Bacillus subtilis* (MTCC 441) and *Staphylococcus aureus* (MTCC 731) as Gram positive strains and *Escherichia coli* (MTCC 443) and *Klebsiella pneumonia* (MTCC 741) as Gram negative strains by using standard drug Ciprofloxacin. The antibacterial activities of the tested compounds were evaluated using the Agar disk diffusion method and the results were recorded for each tested compound as the diameter of inhibition zones of bacterial growth surrounding the well in millimeters. The obtained results were represented in the **Table**.

From these values, it could be noticed that only compounds **8f**, **8j** and **8k** showed activity against *B. subtilis, S. aureus* and *E. coli.* None of the compounds exhibited activity against *K. pneumonia.* Out of these three compounds (**8f**, **8j** and **8k**) maximum activity was observed

for compound **8j** against *S. aureus, B. subtilis* and *E. coli* with zone of inhibition values of 10, 11 and 16 mm respectively. Compounds **8f**, **8j** and **8k** showed better activity against *E. coli*, moderate activity against *B. subtilis* and *S. aureus*. From these results, it can be understood that compound **8j** was found to be a good antibacterial agent.

Conclusion

We have synthesized a series of novel pyrazole-imidazole derivatives (**8a-o**) by condensation of pyrazole derivatives which are prepared by "Vilsmeier Haack" reaction with imdazole hydrazide derivatives in the presence of acetic acid in good yields. All the final derivatives were characterized by ^{1}H NMR, ^{13}C NMR and mass spectra. These compounds were also evaluated for antibacterial activity. Among all the compounds, highest antibacterial activity was observed for compound **8j** with zone of inhibition 16 mm. So, compound **8j** was considered as a potential antibacterial agent.

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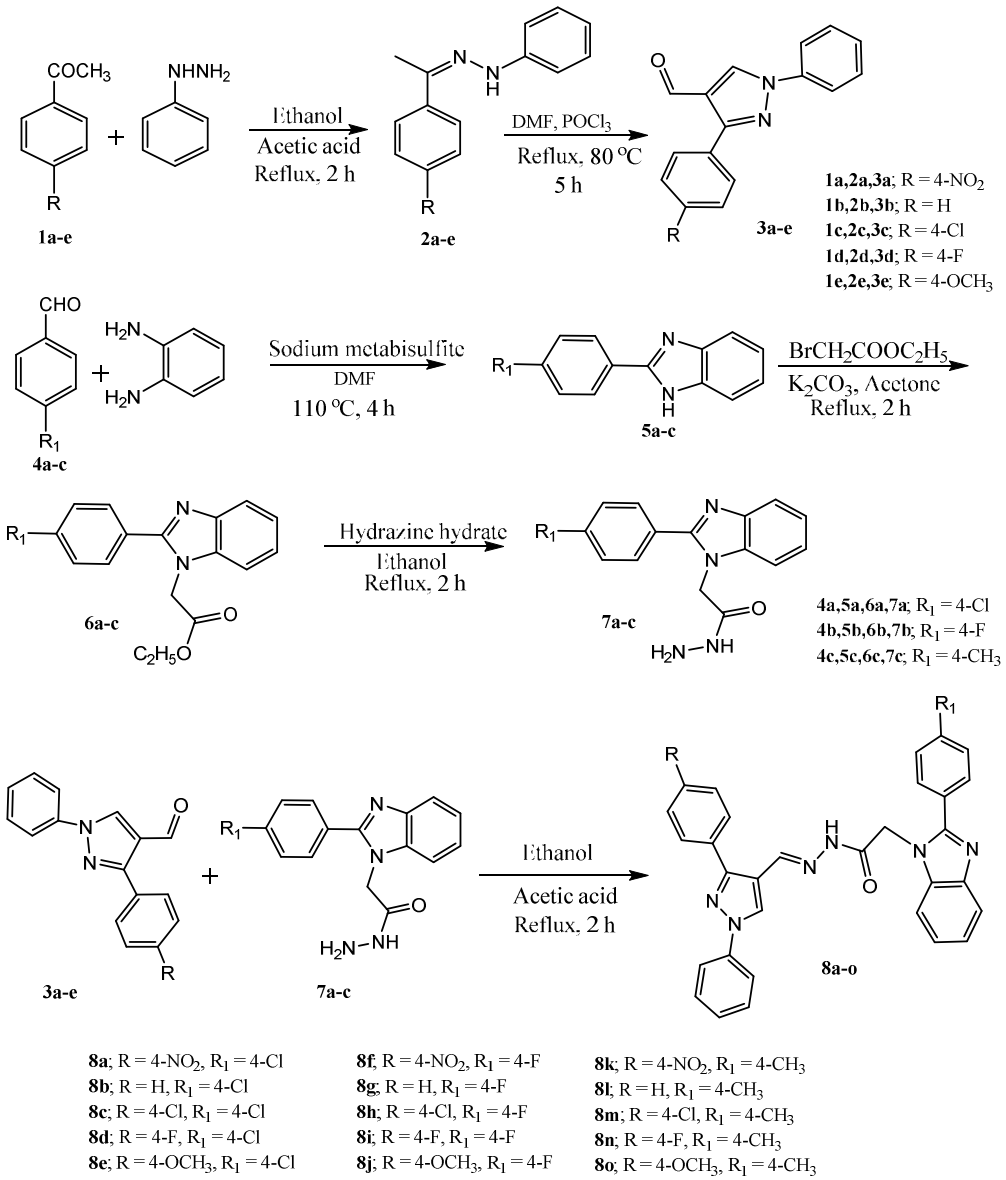
Scheme



8a; R = 4-NO_2, R_1 = 4-Cl
8b; R = H, R_1 = 4-Cl
8c; R = 4-Cl, R_1 = 4-Cl
8d; R = 4-F, R_1 = 4-Cl
8e; R = 4-OCH_3, R_1 = 4-Cl
8f; R = 4-NO_2, R_1 = 4-F
8g; R = H, R_1 = 4-F
8h; R = 4-Cl, R_1 = 4-F
8i; R = 4-F, R_1 = 4-F
8j; R = 4-OCH_3, R_1 = 4-F
8k; R = 4-NO_2, R_1 = 4-CH_3
8l; R = H, R_1 = 4-CH_3
8m; R = 4-Cl, R_1 = 4-CH_3
8n; R = 4-F, R_1 = 4-CH_3
8o; R = 4-OCH_3, R_1 = 4-CH_3

Table

Compound	Zone of inhibition (mm)			
	Gram-positive bacteria		Gram-negative bacteria	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Klebsiella pneumonia*
8a	-	-	-	-
8b	-	-	-	-
8c	-	-	-	-
8d	-	-	-	-
8e	-	-	-	-
8f	8	8	12	-
8g	-	-	-	-
8h	-	-	-	-
8i	-	-	-	-
8j	11	10	16	-
8k	10	9	15	-
8l	-	-	-	-
8m	-	-	-	-
8n	-	-	-	-
8o	-	-	-	-
Ciprofloxacin	37	38	28	32

Antibacterial activity of synthesized compounds **(8a-o)**

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