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Synthesis, Characterization and Antibacterial Activity of Novel Schiff Bases

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The present work describes the synthesis of novel Schiff bases (**8.1-8.9**) in five steps from diethyl oxalate and acetone as starting materials. Condensation of ethyl 1-(2-aminophenyl)-5-methyl-1H-pyrazole-3-carboxylate (**6**) with aromatic and heteroaromatic aldehydes (**7.1-7.9**) in presence of sodium sulphate at 50 °C in ethanol gave the corresponding imine derivatives (**8.1-8.9**) in quantitative yields. The structure of these compounds was determined by ^{1}H NMR, mass and IR spectral data. These Schiff's bases were further evaluated for antibacterial activity against the selected Gram-positive and Gram-negative bacteria pathogens. The antibacterial activity data revealed that Schiff base embedded with heteroaromatic ring was found to exhibit good antibacterial activity than the aromatic ring.

Keywords: Acetone, Antibacterial activity, Diethyl oxalate, Schiff base, Synthesis.

INTRODUCTION

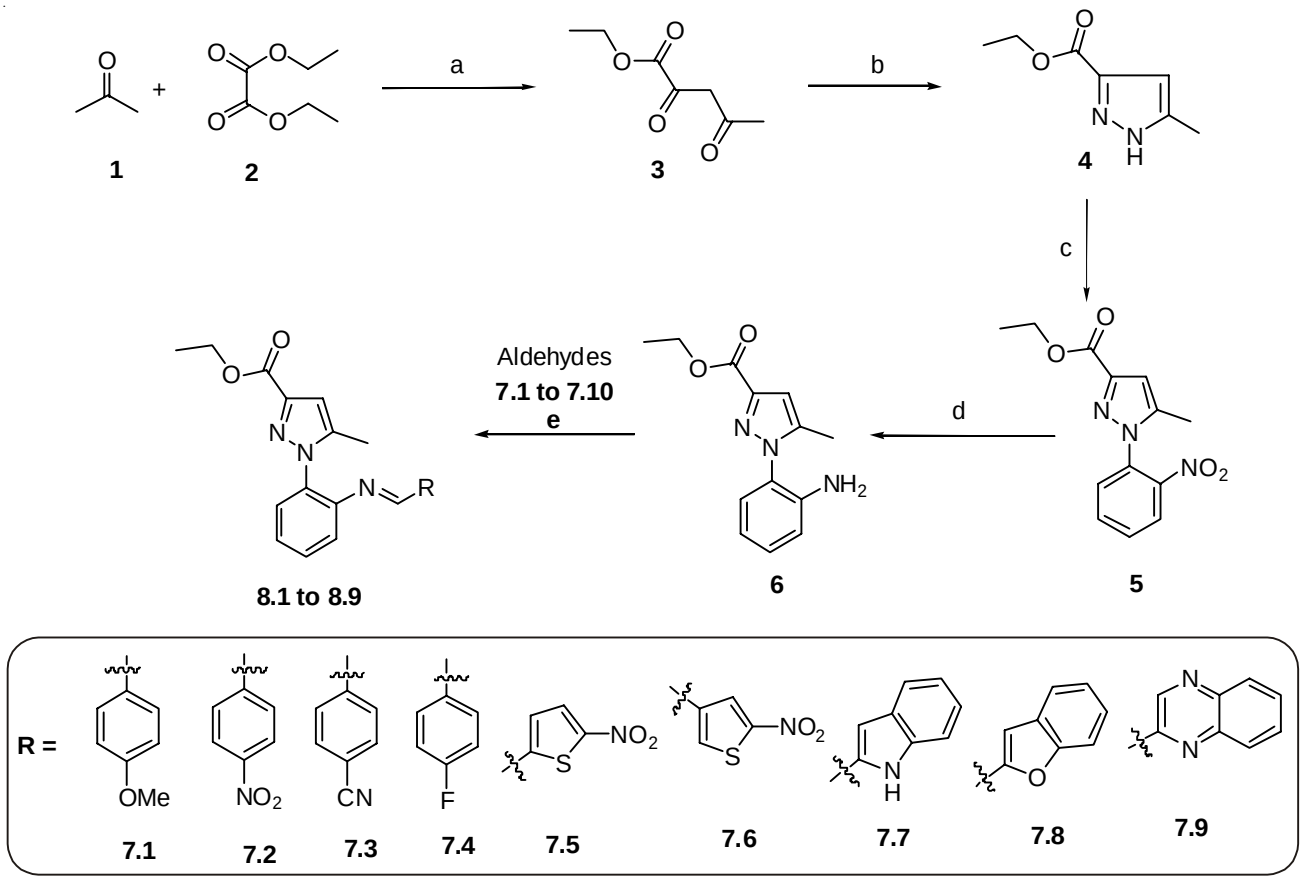
Schiff bases [1-9] are compounds that are represented by the general formula $R_3R_2C{=}NR_1$. The most common method for preparing imines is the original reaction discovered by Schiff [1,3,4,10,11]. Schiff bases are present in various natural, semi-synthetic and synthetic compounds and have been demonstrated to be essential for their biological activities [12,13]. Schiff bases are the important class of compounds owing to their wide range of biological activities and industrial applications. These compounds are now used to formulate anticancer [14], anti HIV [15], antitubercular [16], antiviral [17], antimalarial [18] drugs. Some complexes of Schiff base shows antibacterial and antiviral activity [19,20]. The activity of Schiff bases as antibacterial [21,22], antifungal [23,24], antiviral agents [25] has been extensively studied.

A huge number of antibacterial agents are accessible to handle pathogenic microorganisms in nature. These treatments however could not totally wipe out such organisms, possibly due to the widespread irrational, unscientific and uninterested use of such agents. The survived microorganisms have harmonized the initiative in increasing their own defenses. As a result such drugs steadily mislay their efficiency in action. Replication and overindulge of such drugs often cause harsh environmental pollution. In order to get purge of this situation, it has become a common practice to find out safer, more effectual and low-cost new chemical compounds as antibacterial agents. In the present paper, we report herein a series of Schiff bases with a potential antibacterial activity resulted from the condensation of aromatic and heteroaromatic aldehydes (**7.1-7.9**) with ethyl 1-(2-aminophenyl)-5-methyl-1H-pyrazole-3-carboxylate (**6**) (**Scheme-I**).

EXPERIMENTAL

Standard operating procedures was implemented for the purification of solvents before being utilized for the reactions and work up's. Merck silica gel 60 (230-400 mesh) and Merck pre-coated plates (silica gel 60 F254) was used for the routine column chromatography and visualization of spots (under UV lamp). Mel-temp apparatus was utilized for the determination of melting point. Agilent ion trap MS was utilized for recording the mass spectra. Perkin Elmer FT-IR spectrometer was used for recording the IR data. Varian NMR-300 MHz instrument was used to record ^{1}H NMR spectra.

Ethyl 2,4-dioxopentanoate (3): Sodium metal (1.13 g, 49 mmol) was added to ethanol (25 mL) over a period of 45 min and allowed to maintain at room temperature. To the above mixture, a premixed solution of diethyl oxalate (**2**) (6.6 g, 45.66 mmol) in acetone (**1**) (10 mL) was added over a period of 1 h. After the addition, a thick yellow precipitate was formed which was filtered and dried. The yellow solid was suspended in cold water and acidified with sulphuric acid and extracted with 4 × 25 mL of benzene. The organic layer was washed with water (4 × 20 mL), brine solution (2 × 15 mL), dried over anhydrous sodium sulphate and evaporated to obtain compound **3**. The crude product obtained was used in the next step without further purification. Yellow oily liquid; Yield: 4.33 g, 61 %;



Experimental conditions: a) Sodium metal, diethyloxalate, acetone, room temperature, 1 h; b) Hydrazine-hydrate, 0-5 °C, 1 h; c) 2-Chloro-nitro benzene, Cs_2CO_3, DMF, 90 °C, 4 h; d) H_2, 10 % Pd-C, 40 psi, room temperature, 1 h; e) Aromatic/Heteroaromatic aldehydes **7.1-7.9**, Sodium sulphate, ethanol, 50 °C, 1 h

Scheme-I: Synthesis of novel Schiff bases (**8.1-8.9**)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.36 (s, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 2.24 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ESI MS: *m/z*, 159.0 (M+1).

Ethyl 5-methyl-1H-pyrazole-3-carboxylate (4): Ethyl acetopyruvate (6.26 g, 39.6 mmol) was cooled to 0-5 °C and added hydrazine hydrate (1.86 mL, 39.66 mmol) over a period of 5 min. The reaction mixture was allowed to stir at this temperature for 1 h. The obtained solid was dissolved in ethyl acetate (120 mL), washed with water (3 × 15 mL) followed by brine solution (20 mL). The organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to obtain compound **4**. Pale yellow solid; Yield: 5.3 g, 87 %; m.p.: 81-82 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.90 (brs, 1H), 6.60 (s, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H); ESI MS: *m/z*, 155.2 (M+1).

Ethyl 5-methyl-1-(2-nitrophenyl)-1H-pyrazole-3-carboxylate (5): To a stirred solution of DMF containing 2-chloro nitrobenzene (5.9 g, 37.4), was added cesium carbonate (24.42 g, 74.10 mmol) followed by compound **4** (5.77 g, 37.35 mmol). The reaction mixture was heated to 90 °C for 4 h. The completion of the reaction was monitored by TLC. The reaction mixture was diluted with ethyl acetate (50 mL) and water (100 mL). The organic layer was washed with water (75 mL), brine solution (50 mL), dried over anhydrous sodium sulphate and evaporated under reduced pressure to obtain compound **5**. Yellow crystalline solid; Yield: 6.65 g, 66.5 %; m.p.: 98-99 °C; IR (KBr, ν_{max}, cm^{-1}): 3406, 3097, 2992, 2870, 1717, 1674, 1608, 1525, 1479, 1441, 1379, 1356, 1303, 1235, 1441, 1379, 1356, 1303, 1235, 1165, 11091, 1024, 977, 849, 813, 778, 732, 701, 673, 638, 578, 505, 458, 436; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.70 (td, *J* = 1.5, 7.8, 10.5 Hz, 1H), 7.68 (td, *J* = 1.5, 7.8, 10.5 Hz, 1H), 7.52 (dd, *J* = 1.5, 7.8 Hz, 1H), 6.76 (s, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 2.29 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H); ESI MS: *m/z*, 276.2 (M+1).

Ethyl 1-(2-aminophenyl)-5-methyl-1H-pyrazole-3-carboxylate (6): Compound **5** (5.5 g, 20 mmol) was suspended in ethanol and was charged with 10 % Pd/C under nitrogen atmosphere. The above reaction mixture was hydrogenated at 40 psi for 1 h at room temperature. The reaction mixture was filtered through celite bed and the filtrate was evaporated under reduced pressure to obtain to obtain compound **6**. White amorphous solid; Yield: 4.54 g, 92.2 %; m.p.: 102-104 °C; IR (KBr, ν_{max}, cm^{-1}): 3445, 3335, 2989, 1725, 1625, 1509, 1458, 1424, 1370, 1228; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (t, *J* = 7.8 Hz, 1H), 7.0 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.75 (s, 1H), 6.60 (t, *J* = 7.8 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 3.82 (brs, 2H), 2.02 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ESI MS: *m/z*, 246.0 (M+1).

General experimental procedure for the preparation of imines 8.1-8.9: To a stirred solution of amine (**6**) (100 mg, 0.407 mmol) in ethanol was added amines (**7.1-7.9**) (0.407 mol) followed by anhydrous sodium sulphate (0.407 mmol)

and stirred at 50 °C for 1 h. The hot homogenous solution was filtered and cooled to 5 °C to isolate the corresponding imines (**8.1-8.9**) in quantitative yields.

Ethyl 1-[(*E*)-2-(4-methoxybenzylideneamino)phenyl]-5-methyl-1H-pyrazole-3-carboxylate (8.1): White solid; Yield: 80 %; m.p.: 129-130 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.80 (s, 1H), 8.38 (d, *J* = 7.8 Hz, 2H), 7.98 (d, *J* = 7.6 Hz, 2H), 7.66-7.60 (m, 1H), 7.58-7.46 (m, 3H), 6.72 (s, 1H), 4.18 (q, *J* = 7.6 Hz, 3H), 2.06 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ESI MS: *m/z*, 363.3 (M+1).

Ethyl 1-[(*E*)-2-(4-nitrobenzylideneamino)phenyl]-5-methyl-1H-pyrazole-3-carboxylate (8.2): Yellow solid; Yield: 90 %; m.p.: 80-81 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (s, 1H), 6.80 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.66-7.60 (m, 1H), 7.58-7.46 (m, 3H), 6.72 (s, 1H), 4.22 (q, *J* = 7.6 Hz, 3H), 2.10 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ESI MS: *m/z*, 379.3 (M+1).

Ethyl 1-[(*E*)-2-(4-cyanobenzylideneamino)phenyl]-5-methyl-1H-pyrazole-3-carboxylate (8.2): White solid; Yield: 90 %; m.p.: 80-81 °C; IR (KBr, ν_{max}, cm^{-1}): 3079, 2986, 1717 (C=O), 1622 (-C=N), 1501, 1432, 1377, 1298, 1233, 1156, 1109, 1026, 989, 951, 840, 764, 660; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (s, 1H), 7.98 (d, *J* = 7.6 Hz, 2H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.56-7.42 (m, 3H), 6.70 (s, 1H), 4.20 (q, *J* = 7.6 Hz, 3H), 2.10 (s, 3H), 1.24 (t, *J* = 7.6 Hz, 3H); ESI MS: *m/z*, 359.1 (M+1).

Ethyl 1-[(*E*)-2-(4-fluorobenzylideneamino)phenyl]-5-methyl-1H-pyrazole-3-carboxylate (8.4): White solid; Yield: 90 %; m.p.: 69-70 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.76 (s, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.88 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.50-7.52 (m, 3H), 6.72 (s, 1H), 4.22 (q, *J* = 7.6 Hz, 3H), 2.12 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H); ESI MS: *m/z*, 351.3 (M+1).

Ethyl 1-[(*E*)-2-{(5-nitrothiophen-2-yl)methyleneamino}-phenyl]-5-methyl-1H-pyrazole-3-carboxylate (8.5): Pale-yellow solid; Yield: 85 %; m.p.: 102-103 °C; IR (KBr, ν_{max}, cm^{-1}): 3098, 3050, 2962, 1720 (C=O), 1621 (-C=N), 1598, 1507, 1430, 1376, 1340, 1233, 1158, 1108, 1027, 979, 825, 766, 654; ^{1}HMR (300 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.58 (s, 1H), 8.06 (s, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.52-7.38 (m, 3H), 6.68 (s, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.08 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ESI MS: *m/z*, 385.3 (M+1).

Ethyl 1-[(*E*)-2-{(5-nitrothiophen-3-yl)methyleneamino}-phenyl]-5-methyl-1H-pyrazole-3-carboxylate (8.6): Pale-yellow solid; Yield: 90 %; m.p.: 111-112 °C; IR (KBr, ν_{max}, cm^{-1}): 3037, 2963, 1721 (C=O), 1621 (-C=N), 1506, 1430, 1372, 1336, 1234, 1161, 1107, 1074,1021, 983, 949, 848, 815, 796, 761, 675; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 8.16 (d, *J* = 6.8 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 1H), 7.68-7.62 (m, 1H), 7.58-7.48 (m, 3 H), 6.75 (s, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 2.10 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ESI MS: *m/z*, 385.2 (M+1).

Ethyl 1-[(*E*)-2-{(1H-indol-2-yl)methyleneamino}phenyl]-5-methyl-1H-pyrazole-3-carboxylate (8.7): Yellow solid; Yield: 90 %; m.p.: 120-121 °C; IR (KBr, ν_{max}, cm^{-1}): 3450, 3336, 2929, 2820, 1729 (C=O), 1624 (-C=N), 1514, 1440, 1379, 1233, 1123, 1017, 876, 831, 751, 635; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.18 (brs, 1H), 9.98 (s, 1H), 8.30 (s, 1H), 8.10 (d, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.32-7.28 (m, 3H), 7.14 (d, *J* = 6.8 Hz, 1H), 6.84 (d, *J* = 6.8 Hz, 1H), 6.66 (s, 1H), 6.60 (brs, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 2.10 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ESI MS: *m/z*, 371.1 (M-1).

Ethyl 1-[(*E*)-2-{(benzofuran-2-yl)methyleneamino}-phenyl]-5-methyl-1H-pyrazole-3-carboxylate (8.8): Yellow solid; Yield: 90 %; m.p.: 133-134 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.32-7.28 (m, 3H), 7.16 (d, *J* = 6.8 Hz, 1H), 6.84 (d, *J* = 6.8 Hz, 1H), 6.62 (s, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 2.06 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ESI MS: *m/z*, 373.1 (M+1).

Ethyl 1-[(*E*)-2-{(quinoxalin-2-yl)methyleneamino}-phenyl]-5-methyl-1H-pyrazole-3-carboxylate (8.9): Off-white solid; Yield: 90 %; m.p.: 92-93 °C; IR (KBr, ν_{max}, cm^{-1}): 3141, 2980, 1711 (C=O), 1622 (-C=N), 1597, 1554, 1488, 1436, 1374, 1236, 1161, 1105, 1023, 973, 853, 885, 767, 660; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18 (s, 1H, quinaxaline ring), 8.90 (s, 1H,-N=**CH**-), 8.22-8.12 (m, 2H, quinaxaline ring proton), 7.98 (d, *J* = 7.8 Hz, 2H, quinaxaline ring protons), 7.72 (d, *J* = 7.8 Hz, 2H, phenyl ring protons), 7.62-7.58 (m, 2H, phenyl ring protons), 6.75 (s, 1H, pyrazole ring proton), 4.24 (q, *J* = 7.6 Hz, 2H,-**CH_2**), 2.18 (s, 3H,-**CH_3**), 1.28 (t, *J* = 7.2 Hz, 3H); ESI MS: *m/z*, 386.3 (M+1).

Biological assay: The synthesized imine compounds **8.1-8.9** was screened against the following pathogens (a) *Escherichia coli* (MTCC 443) and (b) *Pseudomonas aeruginosa* (MTCC 424) (Gram-negative); (c) *Staphylococcus aureus* (MTCC 96) and (d) *Streptococcus pyogenes* (MTCC 442) (Gram-positive). The antibacterial activity of the compounds was carried out using agar well diffusion method according to the literature protocol [26,27]. The compounds were dissolved in dimethyl sulphoxide at 250 µg/mL concentrations and the standard antibacterial drug, chloramphenicol was used as the reference antibiotic drug. The antibacterial activity was determined by zones showing complete inhibition (mm). Growth inhibition was calculated with reference to positive control. All the samples were taken in triplicates.

RESULTS AND DISCUSSION

The synthesis of Schiff base derivatives (**8.1-8.9**) is given in **Scheme-I**. Condensation of diethyl oxalate (**2**) with acetone (**1**) in presence of sodium metal at room temperature for 1 h gave ethyl 2,4-dioxopentanoate (**3**). Reaction of compound **3** with hydrazine hydrate at 0-5 °C for 1 h gave ethyl 5-methyl-1H-pyrazole-3-carboxylate (**4**) in 87 % yield. Nucleophilic aromatic substitution of compound **4** with 2-chloro-nitro benzene in presence of Cs_2CO_3 in DMF at 90 °C for 4 h resulted in the formation of ethyl 5-methyl-1-(2-nitrophenyl)-1H-pyrazole-3-carboxylate (**5**). Hydrogenation of compound 5 in presence of 10 % Pd/C at 40 psi gave the corresponding ethyl 1-(2-aminophenyl)-5-methyl-1H-pyrazole-3-carboxylate (**6**) in 92 % yield. Condensation of 5 with aromatic and hetero-aromatic aldehydes (**7.1-7.9**) in presence of sodium sulphate at 50 °C in ethanol gave the corresponding Schiff bases (**8.1-8.9**) in quantitative yields. The structural assignment of the newly synthesized imines (**8.1-8.9**) was determined by the spectroscopic techniques like ^{1}H NMR, IR and mass spectral data. The mass and IR spectral data of all the compounds are in agreement with the desired molecular formulae. Also, the

^{1}H NMR data of all the imine derivatives and its intermediates (compound **1** to **5**) are in agreement with the desired structures. As an example, the ^{1}H NMR interpretation of ethyl 1-((*E*)-2-((quinoxalin-2-yl)methyleneamino)phenyl)-5-methyl-1H-pyrazole-3-carboxylate (**8.9**) is presented here, the protons resonating at 9.18, 8.90 and 6.75 ppm as singlets corresponds to the quinaxaline ring, imine proton and pyrazole ring proton, respectively. The protons resonating at 8.22-7.98 and 7.72-7.58 ppm is assigned for the quinaxaline ring and phenyl ring protons. The protons resonating in the aliphatic region is assigned to groups such-CH_3 and-$COOCH_2CH_3$, thus confirming the structure of compound **8.9**.

Antibacterial activity: The screening results of antibacterial activity of Schiff bases (**8.1-8.9**) are given in Table-1. The antibacterial activity data was determined by measuring the zone of inhibition (ZI) values and was compared with the drug chloramphenicol (at 250 µg/mL, ZI ~ 20-23 mm) against the tested bacterial strains. From Table-1, it is observed that compounds **8.5, 8.6, 8.7, 8.8** and **8.9** showed good antibacterial activity whereas the compounds **8.2, 8.3** and **8.4** showed weak antibacterial activity and the compound **8.1** showed no activity. In general, it is observed that the Schiff derivatives with heteroaromatic ring were found to exhibit good antibacterial activity than the aromatic ring. A further exploratory research work by varying numerous heteroaromatic rings may lead to a suitable antibacterial drug candidate.

TABLE-1
ANTIBACTERIAL SCREENING RESULTS OF IMINES DERIVATIVES (**8.1-8.9**)

Compound No.	Zone of inhibition (mm)[a]			
	Gram-negative bacteria		Gram-positive bacteria	
	E. coli MTCC 443	*P. aeruginosa* MTCC 424	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442
8.1	–	–	–	–
8.2	10	11	9	8
8.3	9	8	8	10
8.4	11	9	9	8
8.5	16	17	18	18
8.6	17	16	17	17
8.7	20	17	18	16
8.8	17	14	13	12
8.9	19	16	17	15
Chloramphenicol Conc. 250 µg/mL	23	21	21	20

[a]Values, including diameter of the well (8 mm), are means of three replicates; [c]No activity.

Conclusion

Synthesis of Schiff bases (**8.1-8.9**) is described utilizing commercially available diethyl oxalate and acetone in five steps. The newly synthesized Schiff bases was characterized and evaluated for antibacterial activity. The screening results of the antibacterial activity revealed that the Schiff bases (**8.1-8.9**) incorporated with heteroaromatic ring exhibited good antibacterial activity when compared to the standard drug chloramphenicol.

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