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Synthesis, Characterization and Antibacterial Activity of Novel Schiff Bases Bearing Thiazole Ring

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ABSTRACT

*The synthesis of thiazole-iminine derivatives **8a-8j** was prepared in five steps from commercially available ethylacetoacetate as starting material. Condensation of thiourea and ethylacetoacetate in presence of N-bromsuccinimide gave ethyl 2-amino-4-methylthiazole-5-carboxylate **3.** Sequential reaction of diazoti zation, Suzuki reaction and nitro reduction resulted in the formation of the key amine intermediate ethyl 2-(4-aminophenyl)-4-methylthiazole-5-carboxylate **6**. Condensation of amine **6** with aromatic and hetero aromatic aldehydes **7a-7j** gave rise to thiazole-imine derivatives **8a-8j** in quantitative yields. The structures of the newly synthesized **8a-8j** were established on the basis of the spectroscopic techniques like ^{1}H NMR, mass and IR data. Compounds **8a-8j** was evaluated for antibacterial screening. Most of the compounds within the series exhibited good to moderate antibacterial activity.*

Keywords: Antibacterial activity, Diazotization, Ethylacetoacetate, Suzuki reaction, Synthesis.

INTRODUCTION

Due to the rapid development of bacterial resistance to antibacterial agents, it is vital to discover novel scaffold for the design and synthesis of the new antibacterial agents to help in the battle against pathogenic microorganisms. Much research has been carried out with the aim to discover the therapeutic values of thiazole derivatives. A number of these compounds are today's blockbusters of the antibacterial market due to their therapeutic efficacy having tolerable side-effects and thus, challenging the predominance of well established β-lactam antibiotics which are becoming more prone to the resistant pathogenic bacteria [1]. Antimicrobial activity of thiazole derivatives has been extensively studied by many researchers [2-4]. Thiazoles are important class of heterocyclic compounds and are found to exhibit various pharmacological activities namely anti-inflammatory, antimicrobial [5, 6], antitumor [7], anticonvulsant [8], analgesic [9], and anticancer agents [10]. It has been observed over the years that thiazole nucleus possess different biological activities such as antihypertensive, anti-inflammatory, anti-schizophrenic, antibacterial, anti-HIV, hypnotic, anti-allergic and more recently analgesic fibrinogen receptor antagonists with antithrombotic activity that are inhibitors of bacterial DNA gyrase B and antitumor and cytotoxic activities [11]. Furthermore, these classes of compounds are found in many potent biologically active molecules such as Fentiazac, Meloxicam [12-14], Nizatidine [15] and Sulfathiazole. The present paper describes the

synthesis and antibacterial activity of some novel thiazole-imine derivatives **8a-8j**. The newly synthesized compounds were characterized by spectroscopic techniques like ^{1}H NMR, IR and mass data.

MATERIALS AND METHODS

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 (m.p). 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-300MHz/ 500 MHz instrument used to record ^{1}H NMR spectra. Chemical shifts values are measured in terms of δ ppm (parts per million) with reference to tetramethylsilane (TMS) as internal standard. The following notations *viz.*, singlet-s, doublet-d, double doublet-dd, and multiplet-m was used for the signals that has appeared in the proton NMR spectrum and the coupling constant value was measured in terms of Hz.

Preparation of ethyl 2-amino-4-methylthiazole-5-carboxylate (3): To a stirred solution of ethyl acetoacete (10g, 76.84 mmol) in toluene (125 mL) was added thiourea (5.84g, 76.72 mmol), NBS (13.65g, 76.68 mmol) and catalytic amount of benzoyl peroxide (0.5g). The reaction mixture was refluxed for 4.5 h. The solvent was removed under vacuum and residue was dissolved in water and neutralised with potassium carbonate and filtered and air-dried to obtain a pale yellow solid. The crude compound was utilised in the next step without further purification. Yellow solid; Yield: 11.0 g, 78.5%; M.p: 176-177 ^{o}C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 7.66 (brs, 2H), 4.14 (q, J = 6.9 Hz, 2H), 2.37 (s, 3H0, 1.24 (t, J = 6.9 Hz, 3H); ESI-MS: m/z 186.9 $(M+H^+)$.

Preparation of ethyl 2-bromo-4-methylthiazole-5-carboxylate (4): To a mixture of compound **3** (20g, 96.15 mmol), copper sulphate (71.88 g, 287.88 mmol), sodium bromide (37.5g, 364.65 mmol) in 9 M sulphuric acid (480 mL, in an ice salt bath at –5 ^{o} C) and a pre cooled solution of sodium nitrite (13.2g, 191.30 mmol) in water (40 mL) was added drop wise over a period of 30 min. The internal temperature was maintained below 0 °C during the addition. After being stirred at 0 °C for 30 min, the reaction mixture was gradually warmed to room temperature and stirred for 3 h. The mixture was then diluted with of water (300 mL) and extracted with diethyl ether (400 mL). The organic layer was washed with water (200 mL), brine solution (200 mL), dried over anhydrous sodium sulphate and evaporated under reduced pressure to obtain crude compound. The crude compound was purified by column chromatography (silica gel: 60–120 mesh, eluant: chloroform) to afford compound **4**. Yellow solid; Yield: 10 g, 40.0%; M.p.: 68-69 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 4.30 (q, J = 7.2 Hz, 2H), 2.72 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ESI-MS: m/z 249.9 $(M+H)^+$.

Preparation of ethyl 4-methyl-2-(4-nitrophenyl)thiazole-5-carboxylate (5): To a stirred solution of 4-nitro-phenyl boronate (12g, 48.20 mmol) in dioxane was added 5-bromo thiazole (12g, 48.20 mmol), $Pd(PPh_3)_4$ (2.78g, 2.40 mmol) and cesium carbonate (31.4g, 96.40 mmol). The reaction mixture was heated to 100 °C and maintained for 6 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (600 mL) and of water (500 mL). The organic layer was separated and washed with water (2 X 50 mL), brine solution (2 X 50 mL), dried over anhydrous sodium sulphate and evaporated under vacuum to obtain crude compound. The crude compound was purified by column chromatography (silica gel:60–120 mesh, eluant: chloroform) to afford compound **5**. Yellow solid; Yield:13 g, 47%; M.p.: 108-109 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.32 (d, J = 9.0 Hz, 2H), 8.15 (d, J = 9.0 Hz, 2H), 4.40 (q, J = 7.2 Hz, 2H), 2.82 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H); ESI-MS: m/z 293.1 $(M+H)^+$.

Preparation of ethyl 2-(4-aminophenyl)-4-methylthiazole-5-carboxylate (6): To a stirred solution of ethanol (180 mL) containing compound **8** (13 g, 44.52 mmol) was added $SnCl_2.2H_2O$ (35.15g, 155.70

mmol) and concentrated HCl (26 mL). The reaction mixture was stirred at room temperature for 3.5 h. The reaction mass was cooled to room temperature and diluted with ethyl acetate (600 mL) and water (500 mL). The pH was adjusted to 12–13 with 20% aqueous sodium hydroxide solution (200 mL). The precipitated inorganic salts were filtered through Celite bed and organic layer was washed with water (2 X 250 mL), brine solution (2 X 100 mL) and dried over anhydrous sodium sulphate and evaporated to compound **6**. Yellow solid; Yield: 10.7 g, 84%; M.p.: 138–141 °C; FT-IR (KBr pellet): ν_{max} 3433, 3339, 3226, 2928, 1686, 1640, 1603, 1525, 1412, 1371, 1315, 1272 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 7.62 (d, J = 8.8 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H), 5.90 (s, 2H), 4.22 (q, J = 7.2 Hz, 2H), 2.62 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ESI-MS: m/z 263.2 $(M+H)^+$.

General procedure for the preparation of Schiff's bases derived from ethyl 2-(4-aminophenyl)-4-methylthiazole-5-carboxylate 8a to 8j: To a stirred solution of amine **6** (50 mg, 0.190 mmol) in ethanol was added Aromatic/Hetero aromatic aldehydes **7a to 7j** (0.190 mol) followed by anhydrous sodium sulphate (0.380 mmol) and stirred at room temperature for 10 h. The hot homogenous solution was filtered and cooled to 5 ^oC to isolate the corresponding imines **8a -8j** in quantitative yields.

Ethyl 2-((*E*)-4-(3,4,5-trimethoxybenzylideneamino)phenyl)-4-methylthiazole-5-carboxylate (8a): Off-White solid; Yield: 84%; M.p.: 136-137 °C; FT-IR (KBr pellet): ν_{max} 2985, 2935, 2831, 1708, 1624, 1591, 1500, 1431, 1369, 1327, 1267, 1122, 1091, 1006, 835, 756, 727, 621, 497, 352 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 9.60 (s, 1H), 8.04 (J = 8.2 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.30 (s, 2H), 4.30 (q, J = 5.8 Hz, 2H), 3.84 (s, 6H), 3.78 (s, 3H), 2.70 (s, 3H), 1.30 (t, J = 5.8 Hz, 3H); ESI-MS: m/z 441.4 [M+1].

Ethyl 2-((*E*)-4-(4-(methylsulfonyl)benzylideneamino)phenyl)-4-methylthiazole-5-carboxylate (8b): Yellow solid; Yield: 80%; M.p.: 135-136°C; FT-IR (KBr pellet): ν_{max} 3010, 2978, 2927, 2854, 1708, 1697, 1625, 1595, 1568, 1525, 1469, 1435, 1404, 1365, 1317, 1309, 1263, 1199, 1168, 1141, 1136, 1095, 1004, 958, 883, 846, 763, 692, 530, 503, 441 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 8.82 (s, 1H), 8.22 (J = 7.2 Hz, 2H), 8.14-8.10 (m, 4H), 7.40 (d, J = 7.2 Hz, 2H), 4.30 (q, J = 6.8 Hz, 2H), 3.30 (s, 3H), 2.72 (s, 3H), 1.30 (t, J = 6.8 Hz, 3H); ESI-MS: m/z 429.4 [M+1].

Ethyl 2-((*E*)-4-(4-bromobenzylideneamino)phenyl)-4-methylthiazole-5-carboxylate (8c): Pale yellow solid; Yield: 88%; M.p.: 116-118 °C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 8.74 (s, 1H), 8.10 (J = 7.8 Hz, 2H), 7.96 (d, J = 7.8 Hz, 2H), 7.78 (d, J = 7.2 Hz, 2H), 7.40 (d, J = 7.8 Hz, 2H), 4.36 (q, J = 6.8 Hz, 2H), 2.74 (s, 3H), 1.30 (t, J = 6.8 Hz, 3H); ESI-MS: m/z 429.3 [M+].

Ethyl 2-((*E*)-4-(4-nitrilebenzylideneamino)phenyl)-4-methylthiazole-5-carboxylate (8d): Off-White; Yield: 88%; M.p.: 128–129 °C; FT-IR (KBr pellet): ν_{max} 2991, 2222, 1693, 1627, 1589, 1560, 1508, 1436, 1369, 1328, 1273, 1172, 1099, 1043, 1002, 844, 758, 648, 586, 553, 362 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 8.80 (s, 1H), 8.18 (J = 7.8 Hz, 2H), 8.14 (d, J = 7.8 Hz, 2H), 8.0 (d, J = 7.2 Hz, 2H), 7.42 (d, J = 7.2 Hz, 2H), 4.30 (q, J = 7.6 Hz, 2H), 2.76 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ESIMS: m/z 417.0 $(M+H)^+$.

Ethyl 2-((*E*)-4-(4-nitrobenzylideneamino) phenyl)-4-methylthiazole-5-carboxylate (8e): Yellow solid; Yield: 86%; M.p.: 108–109 °C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 8.40 (s, 1H), 8.22 (J = 7.8 Hz, 2H), 8.12 (d, J = 7.8 Hz, 2H), 7.88 (d, J = 7.2 Hz, 2H), 7.62 (d, J = 7.2 Hz, 2H), 4.34 (q, J = 7.6 Hz, 2H), 2.78 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ESIMS: m/z 396.1 $(M+H)^+$.

Ethyl 2-((*E*)-4-((5-nitrothiophen-3-yl) methyleneamino) phenyl)-4-methylthiazole-5-carboxylate (8f): Yellow solid; Yield: 84%; M.p.: 115–116 °C; FT-IR (KBr pellet): ν_{max} 3086, 2995, 2904, 1683, 1622, 1587, 1508, 1436, 1373, 1328, 1269, 1195, 1161, 1070, 1045, 1001, 964, 856, 833, 808, 758, 752, 648, 607, 582, cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 8.70 (s, 1H), 8.58 (J = 5.2 Hz, 1H), 8.40 (d, J = 5.2 Hz, 1H), 8.10 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 7.6 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 2.70 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H); ESI-MS: m/z 401.9 [M+1].

Ethyl 2-((*E*)-4-((5-nitrothiophen-2-yl)methyleneamino)phenyl)-4-methylthiazole-5-carboxylate (8g): Pale yellow solid; Yield: 80%; M.p.: 90–91°C; FT-IR (KBr pellet): ν_{max} 3084, 2993, 2906, 1687, 1620, 1584, 1511, 1432, 1370, 1326, 1266, 1191, 1165, 1068, 1042, 1008, 962, 854, 832, 810, 754, 750, 644, 602, 580 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 8.76 (s, 1H), 8.62 (J = 5.2 Hz, 1H), 8.44 (d, J = 5.2 Hz, 1H), 8.16 (d, J = 7.6 Hz, 2H), 7.44 (d, J = 7.6 Hz, 2H), 4.36 (q, J = 7.2 Hz, 2H), 2.70 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ES-IMS: m/z 401.9 [M+1].

Ethyl 2-((*E*)-4-((quinoxalin-2-yl)methyleneamino)phenyl)-4-methylthiazole-5-carboxylate (8h): Yellow solid; Yield: 92%; M.p.:98–99 °C; FT-IR (KBr pellet): ν_{max} 3346, 2985, 1693, 1587, 1485, 1436, 1406, 1367, 1328, 1265, 1118, 1093, 1039, 1002, 970, 894, 837, 759, 584, 408, 374 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 9.62 (s, 1H), 8.90 (s, 1H), 8.28 (t, J = 8.2 Hz, 2H), 8.10 (d, J = 7.2 Hz, 2H), 7.98 (d, J = 7.8 Hz, 2H), 7.58 (d, J = 7.8 Hz, 2H), 4.30 (q, J = 7.2 Hz, 2H), 2.70 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ESIMS: m/z 403.0 $(M+H)^+$.

Ethyl 2-((*E*)-4-((quinolin-4-yl)methyleneamino)phenyl)-4-methylthiazole-5-carboxylate (8i): Pale-yellow solid; Yield: 80%; M.p.: 119-120 °C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 8.98 (s, 1H), 8.08-8.01 (m, 2H), 7.86-7.60 (m, 3H), 7.70 (d, J = 6.4 Hz, 1H), 7.66-7.60 (m, 1H), 7.42 (d, J = 6.6 Hz, 1H), 7.0 (d, J = 7.2 Hz, 2H), 4.30 (q, J = 5.8 Hz, 2H), 2.70 (s, 3H), 1.30 (t, J = 5.8 Hz, 3H); ESI-MS: m/z 401.4 [M+1].

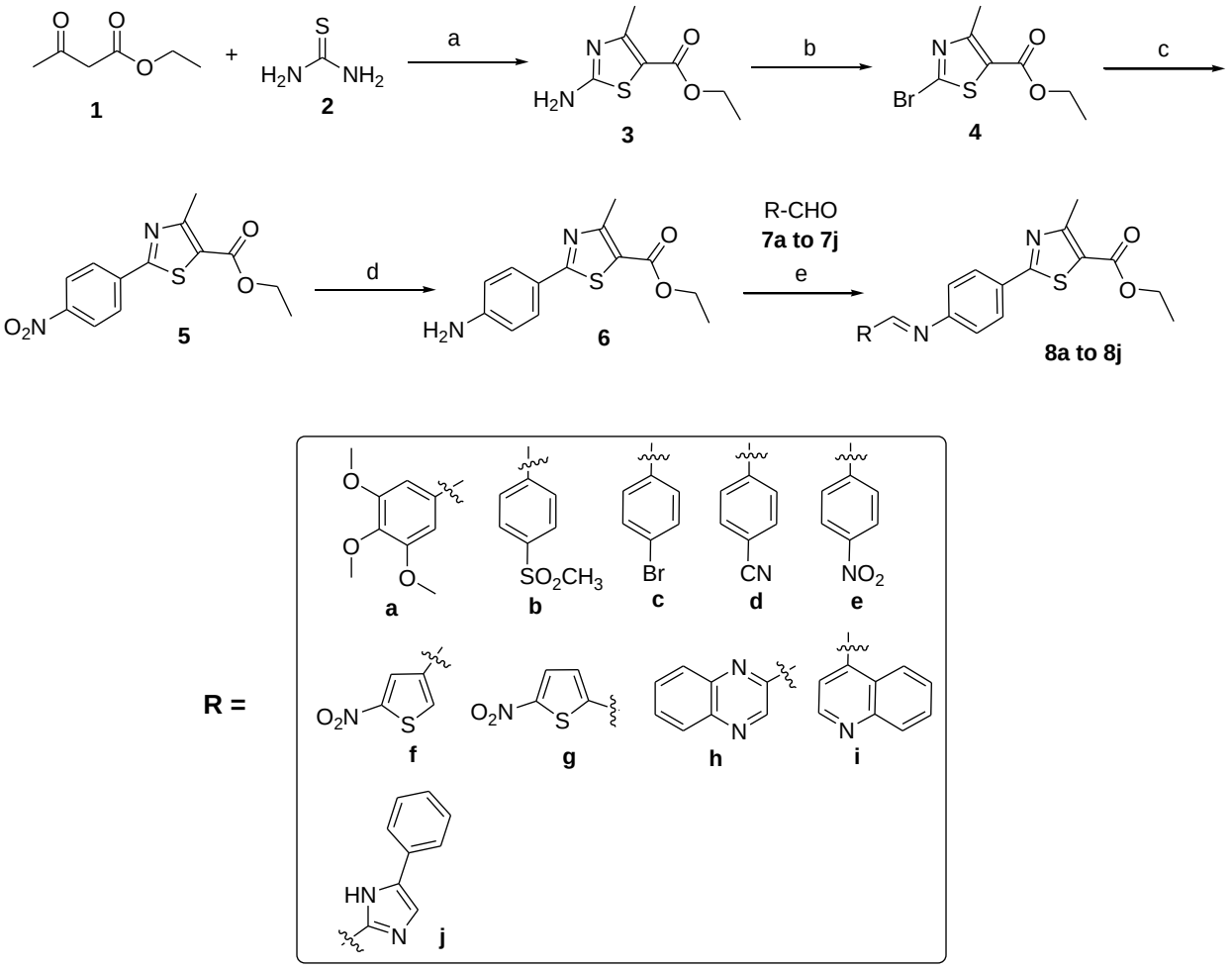
Ethyl 2-((*E*)-4-((5-phenyl-1H-imidazol-2-yl)methyleneamino)phenyl)-4-methylthiazole-5-carboxylate (8j): Pale-yellow solid; Yield: 82%; M.p.: 143-14 °C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 8.70 (s, 1H), 8.40 (s, 1H), 8.06-8.04 (m, 4H), 7.94-7.80 (m, 3H), 7.40 (d, J = 7.6 Hz, 2H), 7.10 (s, 1H), 4.30 (q, J = 6.2 Hz, 2H), 2.70 (s, 3H), 1.30 (t, J = 6.2 Hz, 3H); ESI-MS: m/z 401.4 [M+1]

Biological Assay: The synthesized thiazole-imine derivatives 8a -8j 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 [16, 17]. The compounds were dissolved in dimethylsulphoxide at 250 µg/mL concentrations and the standard antibacterial drug, Ciprofloxacin 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 thiazole-imine derivatives **8a-8j** is illustrated in scheme 1. Condensation of ethylacetoacetate with thiourea in presence of N-bromo succinimide and benzoylperoxide in toluene at reflux for 4.5h gave ethyl 2-amino-4-methylthiazole-5-carboxylate **3**. Diazotization of amine **3** in presence of NaBr, $CuSO_4$ in H_2SO_4 at 0^{o}C to room temperature for 3h gave ethyl 2-bromo-4-methylthiazole-5-carboxylate **4**. Suzuki reaction of thiazole bromide **4** with 4-nitro-phenyl bromate in presence of Pd $(PPh_3)_4$ and Cs_2CO_3 in dioxane at 100^{o}C for 6h gave ethyl 4-methyl-2-(4-nitrophenyl) thiazole-5-carboxylate **5**. Nitro reduction of compound **5** in presence of $SnCl_2$ in ethanol in presence of conc;HCl resulted in the formation of key intermediate ethyl 2-(4-aminophenyl)-4-methylthiazole-5-carboxylate **6**. Condensation of **6** with aromatic and heteroaromatic aldehydes **7a -7j** in presence of sodium sulphate in ethanol at room temperature for 1h gave the corresponding thiazole-imine derivatives **8a-8j** in quantitative yields. The structural assignment of the newly synthesized thiazole-imines **8a-8j** 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 **6**) are in agreement with the desired structures. As a representative example, the ^{1}H NMR ethyl 2-((*E*)-4-(4-nitrilebenzylideneamino)phenyl)-4-methylthiazole-5-carboxylate is interpreted here: The proton signal resonating at 8.80 ppm as singlet corresponds to the characteristic

imine (-C=NH-), while the protons resonating at 8.18 ppm, 8.14 ppm as doublets with two proton integration corresponds to the 4-cyano phenyl ring. The protons of the aromatic ring flanked to thiazole ring were resonated at 8.0 ppm and 7.42 ppm as doublets with two proton integration. The aliphatic protons resonating in the region 2.76 ppm (singlet), 4.30 ppm (quartet) and 1.35 ppm (triplet) corresponds to -CH_3 and –$COOCH_2$-CH_3 respectively.



Scheme 1: Synthesis of Thiazole-imine derivatives **8a – 8j**

Reaction conditions: a) Benzoyl peroxide, NBS, Toluene, reflux, 4.5 h; b) $NaNO_2$, NaBr, $CuSO_4$, 9M H_2SO_4,Water, 0^{o}C-R.T., 3h; c) 4-nitro-Phenyl boronate, $Pd(PPh_3)_4$, Cs_2CO_3, dioxane,100^{o}C, 6h; d) $SnCl_2.2H_2O$, conc. HCl, Ethanol, R.T., 3.5 h; e) R-CHO (**7a-j**), Na_2SO_4, Ethanol, R.T., 10 h.

Antibacterial Activity: The results of antibacterial activity are expressed in terms of zone of inhibition and presented in **table 1**. In case of *Escherichia coli and Pseudomonas aeruginosa (Gram positive bacteria)*: The antibacterial activity was classified as good activity (22-27 mm), moderately active (19-21 mm), and weakly active (< 19 mm). Compounds **8h**, **8i** and **8j** exhibited good antibacterial activity and the compounds **8f** and **8g** showed moderate antibacterial activity while the compounds **8a**, **8b** and **8d** displayed weak antibacterial activity. In case of Gram negative bacteria also, compounds **8a-8j** exhibited similar trends of antibacterial activity as that for Gram positive bacteria.

Table 1: Antibacterial Activity of Thiazole-Imine derivatives **8a-8j**

Compound No.	*Gram negative bacteria*		*Gram positive bacteria*	
	E. coli	***P. aeruginosa***	***S.aureus***	***S.pyogenes***
	Zone of inhibition (mm)			
8a	14	12	10	11
8b	16	13	12	10
8c	-	-	-	-
8d	13	14	13	11
8e	-	-	-	-
8f	19	18	16	18
8g	20	20	17	17
8h	25	23	18	19
8i	26	25	21	19
8j	27	24	20	18
Standard drug*	28	27	22	22

*Ciprofloxacin: (Conc. 250 µg mL^{-1}); --: no activity

APPLICATIONS

The newly synthesized thiazole-iminine derivatives **8a-8j** was found to display good to moderate antibacterial activity and the chances of becoming these compounds as a potential active pharmacophore is high. A further structural activity studies and exploring the various biological activities is the future scope of the work.

CONCLUSIONS

Synthesis of some novel thiazole-iminine derivatives **8a-8j** was prepared in five steps from commercially available ethylacetoacetate as starting material. These compounds were screened against a panel of four bacterial strains viz., *Staphylococcus aureus and Staphylococcus pyogenes, Escherichia coli and Pseudomonas aeruginosa*. Compounds **8h**, **8i** and **8j** exhibited good antibacterial activity and the compounds **8f** and **8g** showed moderate antibacterial activity while the compounds **8a**, **8b** and **8d** displayed weak antibacterial activity.

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