Research Article

Synthesis and Antibacterial Evaluation of Some New Schiff Bases

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ABSTRACT

An innovative protocol to the synthesis of this material emerged on exploring the potential of the various form of benzoic acid on its reaction with 3-hydroxy-4-methoxybenzaldehyde and 2-amino benzoic acid. Various Schiff bases are formed as the same process named as 2-(3-hydroxy-4-methoxybenzylideneamino)benzoic acid, (E)-2-(2-carboxybenzylideneamino)benzoic acid, (E)-2-(pyridin-2-ylmethyleneamino)benzoic acid, (E)-2-((2,5-dihydrothiazol-2-ylimino)-methyl)benzoic acid, (E)-2-(3-hydroxy-4-methylbenzyl ideneamino)benzoic acid etc. The structure of the compounds had been established on the basis of IR, ^{1}H NMR, and MS spectral data. The explorations of the biological properties of the compounds are mentioned in this paper.

Keywords: 3-hydroxy-4-methoxybenzaldehyde, 2-amino benzoic acid, Schiff Bases, Spectral Studies, Anti-Bacterial studies.

INTRODUCTION

Schiff bases form a significant class of compounds in medicinal and pharmaceutical chemistry with several biological applications that include antibacterial,[1-6] antifungal[3-6] and antitumor activity.[7, 8] They also serve as a back bone for the synthesis of various heterocyclic compounds. Schiff bases are the compounds containing azimethine group (-HC=N-). These are the condensation products of ketones or aldehydes with primary amines and were first reported by Hugo Schiff in 1864. Now a day, Schiff bases are used as intermediates for the synthesis of amino acids or as ligands for preparation of metal complexes having a series of different structures.

A large number of Schiff bases and their complexes have been studied for their interesting and important properties, e.g., their ability to reversibly bind oxygen,[9] catalytic activity in hydrogenation of olefins[10] and transfer of an amino group,[11] photochromic properties,[12] and complexing ability towards some toxic metals.

There are wide applications of Schiff bases and their metal chelates in biological systems[13], catalysis, dying processes[14, 15] and analytical applications, the spectral studies of the Schiff bases containing a heterocyclic ring are comparatively minor.[16,17] An interesting application of Schiff bases is their use as an effective corrosion inhibitor, which is based on their ability to spontaneously form a monolayer on the surface to be protected. Many commercial inhibitors include aldehydes or amines, but presumably due to the C=N bond the Schiff bases function more efficiently in many cases.[18]

A Schiff base behaves as a flexidentate ligand and commonly coordinates through the O atom of the deprotonated phenolic group and the N atom of azomethine group. Schiff base ligands have significant importance in chemistry; especially in the development of Schiff base complexes, because Schiff base ligands are potentially capable of forming stable complexes with metal ions.[19] Many Schiff base complexes show excellent catalytic activity in various reactions at high temperature (>100 °C) and in the presence of moisture. Over the past few years, there have been many reports on their applications in homogeneous and heterogeneous catalysis, hence the need for a review article highlighting the catalytic activity of Schiff base complexes realized.[20] Today, Schiff bases are used as intermediates for the synthesis of amino acids or as ligands for preparation of metal complexes having a series of different structures. This paper presents a series of new Schiff bases with a potential biological activities.[19]

MATERIALS AND METHODS

Experimental section

Melting points were taken in open capillaries and are uncorrected. Purity of compounds was monitored on silica gel 'G' coated TLC plates. IR spectra were recorded on Schimadzu FTIR-8400S Spectrometer in KBr, ^{1}HNMR spectra were taken in $CDCl_3$+$DMSOd_6$ on BRUKER AVANCE II 400 NMR Spectrometer using TMS as an internal standard and Mass spectra were recorded on a Joel SX-102 (EI/CI/FAB) mass spectrometer.

Preparation of new Schiff bases (1-8)

Synthesis of 2-(3-hydroxy-4-methoxybenzylideneamino) benzoic acid (1):

Isovanillin (1.52g, 10 mmol), Anthranillic acid (1.37g, 10 mmol) and triethylamine (1ml, 10 mmol) were mixed in 50 ml ethanol in a round flask. The mixture was refluxed with agitation for 4 h at 323 K to give a yellow precipitate. After filtration and washing the precipitate with ethanol, a pure Schiff base ligand, 2-(3-hydroxy-4-methoxybenzylideneamino) benzoic acid (yield: 0.25 g, 66%) was obtained.

IR (KBr, cm^{-1}): 3370(COOH str), 1606 (C=N str), 1939 (C=O str), 3500 (OH str), 1586 (C=C str), 2700 (OCH_3 str), 1250 (C-N str); ^{1}H-NMR: 5.35 (s, OH), 7.61 -8.21 (m, 4H, Ar-H), 11.0 (s, OH,) 6.89-7.40 (m, 3H, Ar-H), 3.83 (s, CH_3); m/z: 271.08 (100.0%), 272.09 (16.5%), 273.09 (2.1%).

Synthesis of (E)-2-(2-carboxybenzylideneamino) benzoic acid (2):

Anthranillic acid (1.37g, 10 mmol), 2-Carboxy benzaldehyde (1.50g, 10 mmol) and triethylamine (1 ml, 10 mmol) were mixed in 50 ml ethanol in a round flask. The mixture was refluxed with agitation for 4 h at 323 K to give a yellow precipitate. After filtration and washing the precipitate with ethanol, a pure Schiff base ligand, (E)-2-(2-carboxybenzylideneamino) benzoic acid (yield: 0.32 g, 74%) was obtained.

IR (KBr, cm^{-1}): 1483 (C=N str), 1678 (C=O str), 3350 (COOH str), 1582 (C=C str),1262 (C-N str); ^{1}H-NMR: 11.0 (s, OH), 7.66 -8.20 (m, 4H, Ar-H), 7.73-8.37 (m, 4H, Ar-H), 11.0 (s, OH), 8.64 (s, CH); m/z: 269.07 (100.0%), 270.07 (16.7%), 271.08 (1.3%).

Synthesis of (E)-2-(pyridin-2-ylmethyleneamino) benzoic acid (3):

Anthranillic acid (1.37g, 10 mmol), Pyridine 2-Carboxyaldehyde (1.07g, 10 mmol) and triethylamine (1 ml, 10 mmol) were mixed in 50 ml ethanol in a round flask. The mixture was refluxed with agitation for 4 h at 323 K to give a yellow precipitate. After filtration and washing the precipitate with ethanol, a pure Schiff base ligand, (E)-2-(pyridin-2-ylmethyleneamino) benzoic acid (yield: 0.37 g, 75%) was obtained.

IR (KBr, cm^{-1}): 1611 (C=N str), 1923 (C=O str), 3288 (COOH str), 1506 (C=C str),1278 (C-N str); ^{1}H-NMR: 11.0 (s, OH), 7.66 -8.21 (m, 4H, Ar-H), 7.64-8.65 (m, 4H, Ar-H), 8.40 (s, CH); m/z: 226.07 (100.0%), 227.08 (14.3%), 228.08 (1.4%).

Synthesis of (E)-2-((2,5-dihydrothiazol-2-ylimino) methyl)benzoic acid (4):

2-Amino thiazole (1.00g, 10 mmol), 2-carboxy benzaldehyde (1.50g, 10 mmol) and triethylamine (1 ml, 10 mmol) were mixed in 50 ml ethanol in a round flask. The mixture was refluxed with agitation for 4 h at 323 K to give a yellow precipitate. After filtration and washing the precipitate with ethanol, a pure Schiff base ligand, (E)-2-((2,5-dihydrothiazol-2-ylimino)methyl)benzoic acid (yield: 0.20 g, 61%) was obtained.

IR (KBr, cm^{-1}): 1483 (C=N str), 1796 (C=O str), 1592 (C=C str), 3206 (COOH str), 1273 (C-N str), 1326 (s, C-S); ^{1}H-NMR: 11.0 (s, OH), 7.73 -8.37 (m, 4H, Ar-H), 8.74 (s, CH), 4.2 (s, CH), 3.10 (s, CH_2) , 7.50 (s, CH); m/z: 234.05 (100.0%), 235.05 (12.9%), 236.04 (4.5%), 236.05 (1.2%).

Synthesis of (E)-2-(3-hydroxy-4-methylbenzyl ideneamino) benzoic acid (5):

Anthranilic acid (1.37 g, 10 mmol), 4-hydroxy 3-metyl benzaldehydes (1 ml, 10 mmol) and triethylamine (1 ml, 10 mmol) were mixed in 50 ml ethanol in a round flask. The mixture was refluxed with agitation for 4 h at 323 K to give a yellow precipitate. After filtration and washing the precipitate with ethanol, a pure Schiff base ligand, (E)-2-(3-hydroxy-4-methylbenzylideneamino) benzoic acid (yield: 0.90 g, 68%) was obtained.

IR (KBr, cm^{-1}): 1483 (C=N str), 1592 (C=C str), 3206 (COOH str), 1273 (C-N str), ^{1}H-NMR: 11.0 (s, OH), 7.66 -8.21 (m, 4H, Ar-H), 7.11 (s, CH,), 7.27 (s, CH,), 7.34 (s, CH,), 8.66 (s, CH), 2.15 (s, CH_3), 5.35 (s, OH); m/z: 255.09 (100.0%), 256.09 (16.7%), 257.10 (1.3%).

Synthesis of (E)-1-(5-chloro-2-(3-hydroxy-4-methoxybenzylideneamino) phenyl)-2, 2, 2-triflr - uorethanone (6):

Vanillin (1.52g,10mmol), 1-(2-amino-5-chlorophenyl)-2,2,2,-trifluroethane-1,1-diol hydrochlo-ride (2.76g, 10 mmol) and triethylamine (1 ml, 10 mmol) were mixed in 50 ml ethanol in a round flask. The mixture was refluxed with agitation for 4 h at 323 K to give a yellow precipitate. After filtration and washing the precipitate with ethanol, a pure Schiff base ligand, (E)-1-(5-chloro-2-(3-hydroxy-4-methoxybenzylideneamino) phenyl)-2, 2, 2-triflr - uorethanone (yield: 1.10 g, 79%) was obtained.

IR (KBr, cm^{-1}): 1444 (C=N str), 1649 (C=O str), 3131 (OH str), 1584 (C=C str), 2700 (OCH_3 str), 1142 (C-N str); ^{1}H-NMR: 5.35 (s, OH), 6.89 -7.40 (m, 4H, Ar-H), 7.38-7.86 (m, 3H, Ar-H), 3.83 (s, CH_3), 8.66 (s, CH); m/z: 357.04 (100.0%), 359.04 (34.0%), 358.04 (17.5%), 360.04 (5.6%).

Synthesis of (E)-1-(5-chloro-2-(pyridin-2-ylmethyl eneamino) phenyl)-2, 2, 2-trifluoroethanon -e (7):

Pyridine 2-Carboxyaldehyde (1.07g, 10 mmol), 1-(2-amino-5-chlorophenyl 2, 2, 2, trifluroethane-1, 1-diol hydrochloride, triethylamine (1 ml, 10 mmol) were mixed in 50 ml ethanol in a round flask. The mixture was refluxed with agitation for 4 h at 323 K to give a yellow precipitate. After filtration and washing the precipitate with ethanol, a pure Schiff base ligand, (E)-1-(5-chloro-2-(pyridin-2-ylmethyleneamino) phenyl)-2, 2, 2-trifluoroethanone (yield: 0.25 g, 69%) was obtained.

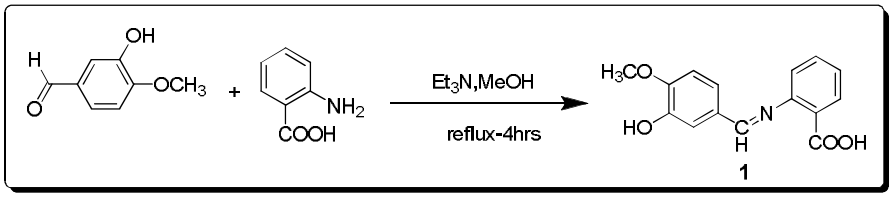
IR (KBr, cm^{-1}): 1387 (C=N str), 1615 (C=O str), 1560 (C=C str), 1178 (C-CF_3 str), 1273 (C-N str); ^{1}H-NMR: 7.38 -7.86 (m, 3H, Ar-H), 7.65-8.65 (m, 4H, Ar-H), 8.40 (s, CH); m/z: 312.03 (100.0%), 314.02 (32.0%), 313.03 (15.3%), 315.03 (4.9%), 314.03 (1.4%).

Synthesis of (E)-6-(4-chloro-1-(2, 5-dihydrothiazol-2-yl)-3-oxoazetidin-2-ylidene) cyclohexa-1,3-dienecarboxylic acid (8):

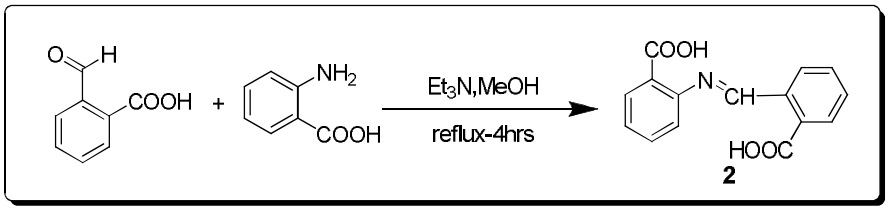
A mixture of Schiff base (3.10gr, 0.01mol) in benzene was taken in a 50ml round bottom flask. It was added to bromoacetyl bromide (2.02g, 0.01mol), triethylamine hydrochloride (1.01gr, 0.01mol) were added slowly. It was refluxed for 15-16hrs. The triethylamine hydrochloride was formed during the reaction, was removed and the benzene was distilled off to get the product. The crude product obtained was recrystallised from ethanol a pure Schiff base ligand (yield: 3.50 g, 72%) was obtained.

IR (KBr, cm^{-1}): 1483 (C=N str), 1796 (C=O str), 1592 (C=C str), 3206 (COOH str), 1273 (C-N str), 1326 (s, C-S); 1690 (s, Azitidinone ring); ^{1}H-NMR: 11.0 (s, OH), 8.30 (s, H), 7.50 (s, CH), 3.10 (s, CH_2), 5.66 (s, H), 6.16 (s, H), 3.7 (s, CH), 5.47 (s, CH); m/z: 310.02 (100.0%), 312.01 (36.5%), 311.02 (15.1%), 313.02 (5.2%), 312.02 (1.7%), 314.01 (1.5%).

Synthesis of new Schiff bases (1-8):



Scheme-1



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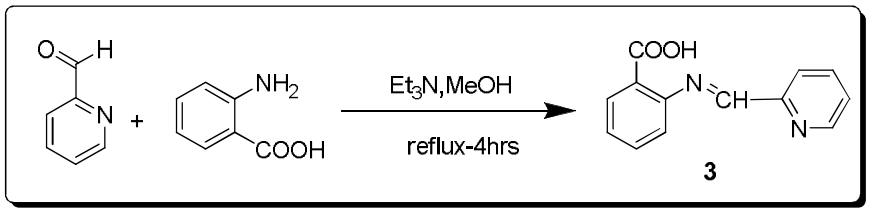

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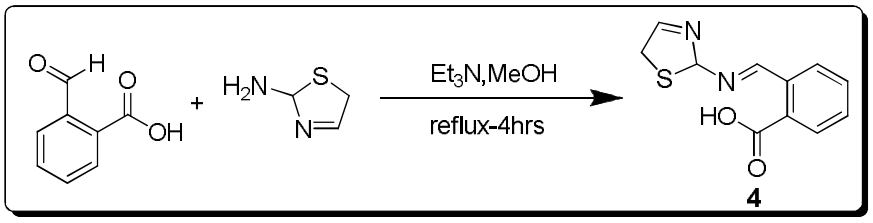
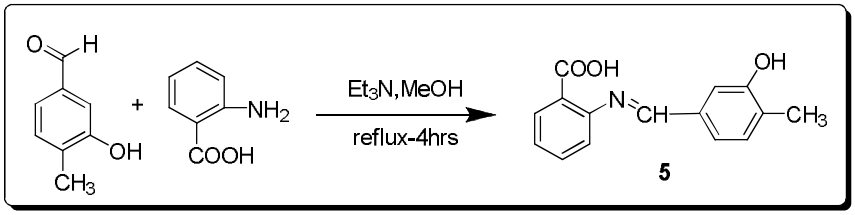
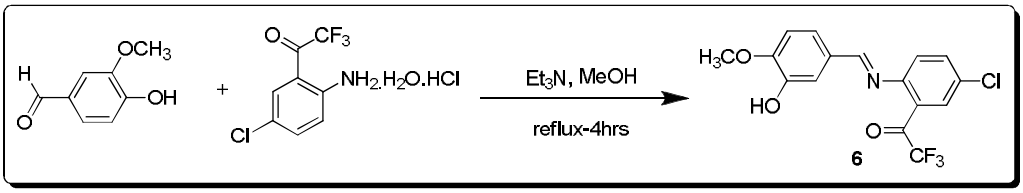


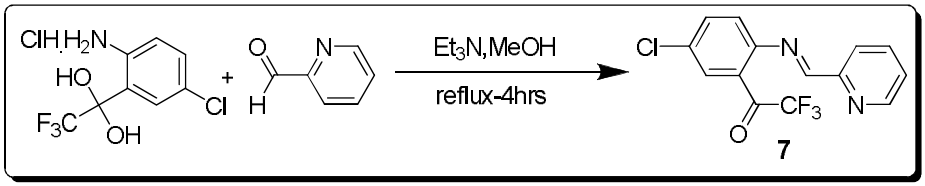
Scheme-4



Scheme-5



Scheme-6



Scheme-7

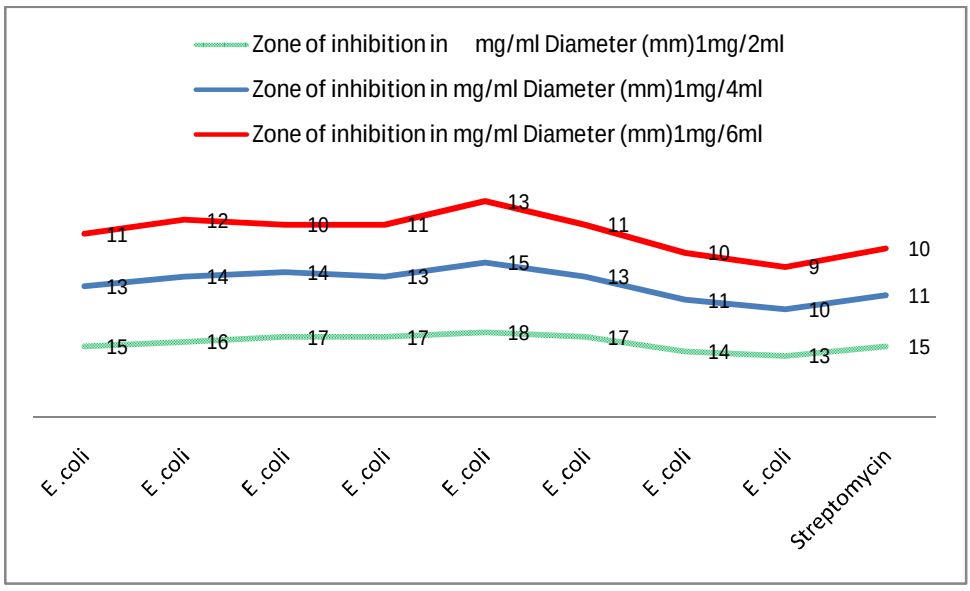
Scheme-8

Table 1: Physical and analytical data of Schiff bases (1-8)

Molecular Formula	M.W.	Yield (%)	M.P.(°C)	Elemental Analysis Cal/exp.			
				C	H	N	S
$C_{15}H_{13}NO_4$	271.27	65	188-189	66.41/66.07	4.83/4.85	5.16/5.18	-
$C_{15}H_{11}NO_4$	269.25	57	205-208	66.91/66.57	4.12/4.14	5.20/5.22	-
$C_{13}H_{10}N_2O_2$	226.23	60	302-308	69.02/68.67	4.46/4.48	12.38/12.44	-
$C_{11}H_{10}N_2O_2S$	234.27	70	198-202	56.39/56.10	4.30/4.32	11.96/11.90	13.69/13.75
$C_{13}H_{10}N_2O_3$	255.27	65	178-182	70.58/70.93	5.13/5.15	5.49/5.51	-
$C_{16}H_{14}ClF_3NO$	357.71	50	138-142	53.72/53.98	3.10/3.12	3.92/3.93	-
$C_{14}H_8ClF_3N_2O$	312.67	68	176-180	53.78/53.51	2.58/2.60	8.96/9.004	-
$C_{13}H_{11}ClN_2O_3S$	310.76	62	222-225	50.24/49.98	3.57/3.59	9.01/9.05	10.32/10.37

Table 2: Results of Screening antibacterial activity of products 1-9 of 1,5-Benzodiazepene in mg/ml.

New Schiff bases	Tested Bacteria	Zone of inhibition in Diameter (mm) [1mg/2ml]	Zone of inhibition in Diameter (mm) [1mg/4ml]	Zone of inhibition Diameter (mm) 1mg/6ml
1	E .coli	15	13	11
2	E .coli	16	14	12
3	E .coli	17	14	10
4	E .coli	17	13	11
5	E .coli	18	15	13
6	E .coli	17	13	11
7	E .coli	14	11	10
8	E .coli	13	10	9
9	Streptomycin	15	11	10
10	Control	-	-	-



Graph 1: Anti-bacterial Activities

Biological Activity

The synthesized Schiff bases were screened for antibacterial activity.

Antibacterial Studies

The synthesized Schiff bases, their derivatives and their metal complexes were screened for their antibacterial activity against the bacterial species, E. coli.

The paper disc diffusion method was used for the determination of the antibacterial activity.

Preparation of Discs

The ligand complex (20 mg to 80mg) in DMF (0.01 ml) was applied on a paper disc, [prepared from blotting paper (3 mm diameter)] with the help of a micropipette.

The discs were left in an incubator for 48 h at 37' C and then applied on the bacteria grown agar plates.

Preparation of Agar Plates

Minimal agar was used for the growth of specific bacterial species. For the preparation of agar plates for E.coli, MacConkey agar (50g), obtained from Merck Chemical Company, was suspended in freshly distilled water (I L). It was allowed to soak for 15 minutes and then boiled on a water bath until the agar was completely dissolved. The mixture was autoclaved for 15 minutes at 120' C and then poured into previously washed and sterilized Petri dishes and stored at 40' C for inoculation.

Procedure of Inoculation

Inoculation was done with the help of a platinum wire loop which was made red hot in a flame, cooled and then used for the application of bacterial strains.

Inoculation of Discs

A sterilized forceps was used for the application of paper disc on then already inoculated agar plates. When the discs were applied, they were incubated at 37°C for 24 h. The zone of inhibition was then measured (diameter in mm) around the disc.

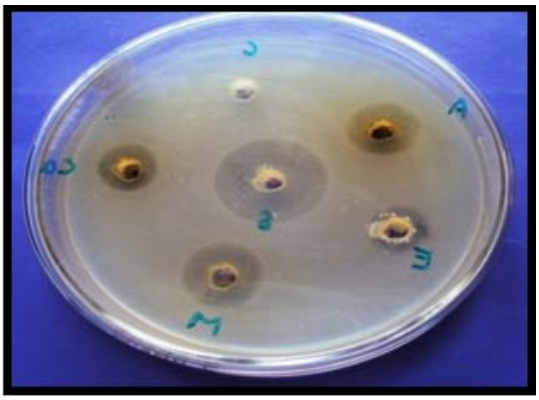


Figure 1: Showing zone of inhabitation against, Streptomycin and *E. coli*

[S - Standard (Streptomycin); **C** – Control (Solvent); **E** - 20 mg of sample (A) -Soluble in DMF, **Ca** - 40 mg of sample (A), **M** - 60 mg of sample (A).]

RESULTS AND DISCUSSION

Various Schiff bases are synthesized by 2-amino benzoic acid with the help of catalyst and solvent Et_3N /MeOH. These Schiff bases have reversible nature of synthesized Schiff bases reaction. All the synthesized compounds (1-8) were purified by successive recrystallization using ethanol. The purity of the synthesized compounds was checked by performing TLC. The structures of the synthesized compounds were determined on the basis of their FTIR and ^{1}HNMR data.

All the synthesized Schiff bases (1-8) show the antibacterial activities. The antibacterial activity was evaluated against pathogenic strain *E.coli*. The zone of inhibition and activity index were determined by comparison with the standard drug *streptomycin*. The outcome of this study is presented in table-2. The antibacterial screening against *E.coli* showed that amongst the compounds (1-8), the compound (5) displayed highest activity in (mg/2ml, mg/4ml, mg/6ml) and compound (8) displayed lowest activity. The remaining compounds showed moderate activity.

CONCLUSION

Various Schiff bases were synthesized by the analytical and spectral techniques. These compounds exhibited significant activity against all the tested microorganisms.

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