Antimicrobial salicylaldehyde Schiff bases: Synthesis, characterization and evaluation

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Abstract: As the pathogens soon develop resistance to the existing antibiotics, the demand for new and more effective anti-microbial agents is a continuous phenomenon. In this paper we are reporting synthesis and spectral data of eight Schiff bases of salicylaldehyde with different amines, and evaluation of their anti-microbial activities against different bacterial strains. The bases were synthesized by reflux method, and their structures were determined based FT-IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectrometric data. The Schiff bases synthesized included 2-{[(*Z*)-(2-hydroxyphenyl) methylidene] amino}benzoicacid (SB1), 4-{[(*Z*)-(2-hydroxyphenyl) methylidene] amino} benzoic acid (SB2),2-[(naphthalene-2-ylimino)methyl] phenol(SB3),2-2'-[benzene-1,4-diylbis(nitrilomethylylidene)]diphenol (SB4), 2-2'-[benzene-1,2-diylbis (nitrile-(*E*)-methylylidene)]diphenol (SB5), 2-[(2-phenylhydrazineylidene)methyl]phenol (SB6), 2-2'-[ethene-1,2-diylbis(iminomethanediyl)]diphenol (SB7) and 2-[(*Z*)-(phenylimino)methyl]phenol (SB8). The anti-microbial activities of synthesized Schiff bases were determined in terms of zones of inhibition and minimum inhibitory concentrations (MICs). All the bases showed moderate to good activities against all the tested microorganisms. The MICs of most compounds were 100-200µg/mL against different microorganisms. However, it was 50µg/mL for SB1 against *P. aeruginosa* (1), SB3 against *P. aurantiaca, P. aeruginosa* (1), *E. coli* (2), *S. typhi* (2) and *C. freundii*, SB4against *E. coli* (2), *S. typhi* (1) and *S. maltophilia*, SB5 against *K. pneumoniae* and *S. typhi* (2), SB6 against *P. aeruginosa* (3) and *C. freundii*, SB7 against *E. cloacae* and *A. lipoferum*, andSB8against *E. coli* (2). Considerably active bases may prove to be potential candidates for future antibiotic drugs.

Keywords: Salicylaldehyde, Schiff bases, spectroscopic, anti-microbial activity.

INTRODUCTION

Synthesis of numerous Schiff bases, the chemical compounds with azomethine, $R_2C=N-$, functionality, have been reported since their first discovery by the German chemist Hugo Schiff in 1864 (Schiff, 1864; Kumar *et al*., 2009; Arulmurugan *et al*., 2010; Parakash *et al*., 2011; Cleiton *et al*., 2011). However, the bioactivities of many of them are yet to be studied. A Schiff base is synthesized by the reaction of a primary amine with an aldehyde or a ketone, and those formed from aromatic amines and carbonyl compounds are particularly stable due to resonance. The Schiff bases derived from salicylaldehyde, which has the structural moiety common with acetyl salicylate, a celebrated drug, have been reported to have considerable bioactivities (Pessoa *et al*., 2000; Liu *et al*., 2004; Redayan, 2012). Schiff bases have been reported to possess different bioactivities including antimicrobial (Sithambaram *et al*., 2006; Pannerselvam *et al*., 2005; Gulcan *et al*., 2012; Raman *et al*., 2008; Baluja *et al*., 2009). The Schiff bases of salicylaldehyde and its derivatives have also been prepared and found active against different pathogens (Islam *et al*., 2002; Shi *et al*., 2007; Ispir, 2009).

Since the pathogens causing infectious diseases soon develop resistance to the existing antibiotics, the discovery of new anti-microbial agents is in a constant demand (Anderson, 2003; Maeda *et al*., 2011; Souli *et al*., 2008), and Schiff bases constitute one of the classes of chemical compounds which hold great promise and are, thus, the subject of extensive investigation.

In view of the fact, we planned to synthesize Schiff bases of salicylaldehyde with different amines and to study their anti-microbial activities. Since Schiff base synthesis is a reversible process, conditions have to be optimized to maximize the yield, which often pose a serious challenge. Equally stimulating is the purification and recrystallization of the product.

MATERIALS AND METHODS

Chemicals and equipment

Salicylaldehyde and most amines were purchased from Merck, however, 2-aminobenzoic acid and 4-aminobenzoic acid from BDH. All other reagents were of analytical grade. The standard antibiotics Amoxylin, Cefixime and Levofloxacin were purchased from the local market. Melting points were determined on Gallenkamp melting point apparatus and were uncorrected. The FT-IR and UV-Vis spectra were respectively recorded on Varian 640-IR Spectrometer (cm^{-1}) and UVD-3200 Spectrometer at Forman Christian College, Lahore, Pakistan. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on Bruker400-MHz NMR Spectrometer, while the mass spectra on Varian

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MAT 312 Mass Spectrometer at HEJ Research Institute of Chemistry, Karachi, Pakistan.

Synthesis of Schiff Bases

The Schiff bases described in this paper were synthesized by refluxing stoichiometric amounts of salicylaldehyde and each of the amines at 60-80°C for 3 h. Methanol was used as solvent while glacial acetic acid was employed as catalyst. The progress of reaction was monitored by thin layer chromatography (TLC) on alumina plates. The Schiff bases were obtained as coloured precipitates which were filtered and washed with distilled water. Recrystallization from methanol or ethanol afforded crystals of compounds designated as SB1-SB8.

Anti-microbial Studies

Microorganisms

Anti-microbial activities of the Schiff bases were studied against a number of bacterial strains including *Klebsiella pneumonia, Enterobacter cloacae, Pseudomonas aurantiaca, Pseudomonas aeruginosa* (3 strains), *Escherichia coli* (3 strains), *Salmonella typhi* (2 strains), *Azospirillum lipoferum, Citrobacter freundii, Achromobacter xylosoxidans, Stenotrophomonas maltophilia* and *Enterobacter aerogenes*. The microbial strains were obtained from Biotechnology laboratories, Forman Christian College University, Lahore. All bacterial cultures were stored at -20°C until utilized.

Zones of Inhibition

Agar well diffusion method was employed to determine the zones of inhibition following standard protocol (CLSI, 2005; Ahmed *et al*., 2012; Kumar *et al*., 2012). Solutions of the compounds were prepared in DMSO. The bacterial inoculums were uniformly swabbed on a Mueller-Hinton Agar plates. In the dried agar, three wells of 7 mm diameter each were dug 33 mm apart from one another using a sterile cork borer. Into each well, 100µL of the test compound was poured and, for diffusion to take place, allowed to stand for 1h. The plates were then incubated at 37°C for 24h, after which the zones of inhibition were measured.

Minimum Inhibitory Concentration (MIC)

The agar dilution method was used to evaluate MIC, or the minimum inhibitory concentration, values of the Schiff bases and the standard antibiotics according to the methods based on National Committee for Clinical Laboratory Standards (NCCLS, 2006; Kumar *et al*., 2012). Solutions of different concentrations (50-250µg/mL) of each base were prepared by serial dilution in Mueller-Hinton Agar (MHA). Bacterial strains were then poured into the wells dug into the agar and the plates were kept in an incubator at 37°C for 24 h before noting the minimum concentrations of each base proved lethal to different bacterial strains.

RESULTS

Eight Schiff bases of salicylaldehyde were synthesized with different primary amines using reflux method. Solvent extraction and chromatographic techniques were used to purify the bases and their structures were determined on the bases of spectroscopic data. The anti-microbial activities of the bases were evaluated against a number of bacteria strains. Structures of the bases are given in table 1.

Structure elucidation

SB1: 2-{[(Z)-(2-Hydroxyphenyl)methylidene]amino} benzoic acid

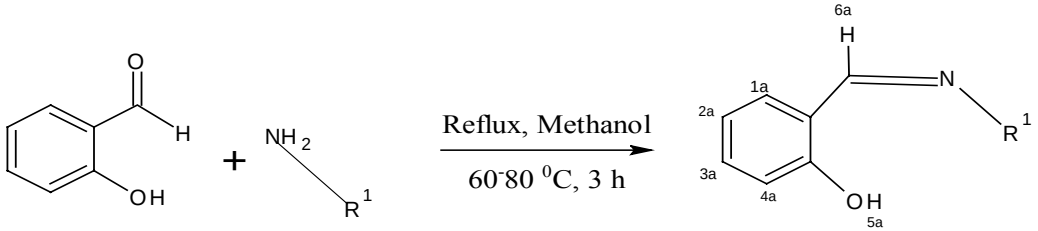
M.P: 140°C; yield (87%); molecular mass: 241.2469; IR (KBr): υ (cm^{-1}) =1663 (C=N). ^{1}H NMR (400 MHz, DMSO), (δppm): 11.6 (s, 1H,H-11b), 8.98 (s,1H,H-6a), 8.01 (1H, H-7b),7.86(1H, H-9b), 7.5(2H, H-10b, H-8b), 7.45(1H, H-1a), 7.20(1H, H-3a), 6.95(1H, H-2a), 6.72(1H, H-4a), 4.89 (1H, H-5a). ^{13}C-NMR(DMSO), δ: 170.9, 161.5, 160.7 (-CH=N-), 155.4, 135.6, 133.1,130, 129.5, 128, 122.3, 122.1, 119, 117, 116.MS (m/z): 241 [M^{+}]

SB2: 4-{[(Z)-(2-Hydroxyphenyl)methylidene]amino} benzoic acid

M.P: 135 °C; yield (89.5%); molecular mass: 241.2469; IR (KBr): υ (cm^{-1}) =1658 (C=N). ^{1}H NMR (400 M Hz, DMSO), (δppm): 12.9 (s,1H,H-11b), 8.85 (s,1H,H-6a), 8.02-7.99 (2H, H-9b, H-10b),7.71-7.69(2H, H-8b H-7b), 7.45(1H, H-1a), 7.12(1H, H-3a), 6.98(1H, H-2a), 6.74(1H, H-4a), 5.44 (1H, H-5a). ^{13}C-NMR (DMSO), δ: 172.3, 161.9, 160.5 (-CH=N-), 158.7, 133.1, 132.4(2C), 129.5, 128, 127.4 (2C), 119, 117.3, 116.MS (m/z): 241 [M^{+}].

SB3: 2-[(Naphthalene-2-ylimino)methyl]phenol

M.P: 255-260°C; yield (79%); molecular mass: 247.1971; IR (KBr): υ (cm^{-1})=1658 (C=N). ^{1}H NMR(400 M Hz, $CDCl_3$), (δppm): 8.5(-N=C-H), 7.7(4H,H-7b,8b,11b,12b), 7.45 (s,1H,H-1a), 7.3 (3H, H-1b,H-9b, H-10b),7.12(1H, H-3a), 6.90(1H, H-2a), 6.76(1H, H-4a), 4.66 (1H, H-5a).



^{13}C-NMR ($CDCl_3$), δ: 162.3, 159.5 (-CH=N-), 151.4, 135, 133, 132.7, 131.5, 129.2 (2C), 128.9, 126.8 (2C), 122.4, 119.8, 119.2, 118.4, 115.7.MS (m/z): 247 [M^+].

SB4: 2-2'-[Benzene-1,4-diylbis(nitrilomethylylidene)] diphenol

M.P: 210-215°C; yield (77%); molecular mass: 316.3602; IR (KBr): υ (cm^{-1}) =1665 (C=N). ^{1}HNMR (400 M Hz, CD_3OD), (δppm): 8.74 (2H, -N=C-H), 7.89 (4H, H-7b, H-8b, H-9b, H-10b), 7.45 (2H, H-1a, H-1a') 7.13(2H, H-3a, H-3a'), 6.89 (2H, H-2a, 2a'), 6.76 (2H, H-4a, 4a'), 4.5 (2H, H-5a, H-5a'), 5.2 (1H, H-5a). ^{13}C-NMR(CD_3OD), δ: 161.8, 160.2 (-CH=N-), 152.4 (2C), 132.7, 129.7, 124.5 (4C), 122.4, 118.3, 117.0.MS (m/z): 316 [M^+].

Table 1: Structures, molecular formulas and molecular masses of the Schiff bases of salicylaldehyde with different amines and IR absorption of C=N, and chemical shift of azomethine proton.

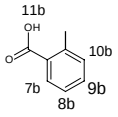
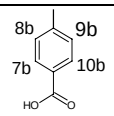
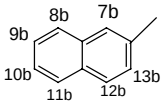
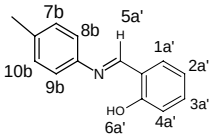
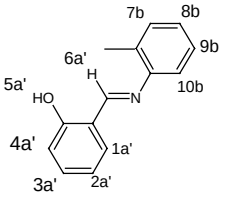
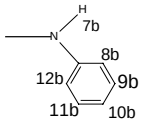
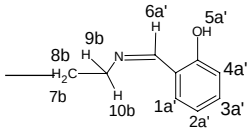
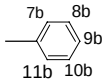
Compound	Substituent (R^1)	Molecular formula	Molecular mass	IR υ(cm^{-1}) C=N	^{1}H NMR H-C=N (ppm)
SB1		$C_{14}H_{11}NO_3$	241.2469	1663	8.98
SB2		$C_{14}H_{11}NO_3$	241.2469	1658	8.85
SB3		$C_{17}H_{13}NO$	247.1971	1658	8.50
SB4		$C_{20}H_{16}N_2O_2$	316.3602	1665	8.74
SB5		$C_{20}H_{16}N_2O_2$	316.3602	1653	8.65
SB6		$C_{13}H_{12}N_2O$	212.2518	1658	8.46
SB7		$C_{16}H_{16}N_2O_2$	268.3162	1650	8.14
SB8		$C_{13}H_{11}NO$	197.2371	1655	8.57

Table 2: Antibacterial activities (zones of inhibition in mm) of salicylaldehyde derived Schiff bases and standard antibiotics against different bacterial strains. Dimethyl sulfoxide was used as the negative control*

Bacterial strains	** A [a]	C [b]	L [c]	SB1	SB2	SB3	SB4	SB5	SB6	SB7	SB8
Klebsiella pneumoniae	23.5	24.0	21.0	23.0	18.0	25.6	22.5	25.5	22.5	24.3	-----
Enterobacter cloacae	19.0	20.0	29.5	18.5	-------	17.0	20.0	21.5	26.0	28.2	20.0
Enterobacter aerogenes	20.5	23.0	29.0	21.5	-------	19.5	24.5	19.4	23.5	18.0	22.5
Pseudomonas aurantiaca	21.5	27.0	31.0	25.1	17.5	32.5	19.5	19.0	------	------	23.5
Pseudomonas aeruginosa (1)	17.5	25.5	29.0	21.7	-------	20.5	24.5	24.3	20.0	20.0	25.4
Pseudomonas aeruginosa (2)	25.5	30.0	20.5	19.6	16.5	26.0	19.8	-------	21.0	------	22.6
Pseudomonas aeruginosa (3)	26.0	22.0	27.0	26.0	24.5	22.5	-------	-------	17.0	27.3	24.5
Pseudomonas sp.	28.0	30.5	20.0	21.0	21.5	20.0	18.5	28.5	18.0	21.0	-----
Escherichia coli (1)	25.0	13.0	19.5	-------	-------	21.0	23.5	-------	------	23.5	24.5
Escherichia coli (2)	32.0	16.0	20.5	27.0	18.5	26.0	28.5	-------	------	22.0	29.5
Escherichia coli (3)	21.0	29.5	25.5	-------	-------	18.0	29.0	-------	24.0	------	-----
Salmonella typhi (1)	29.5	28.5	30.0	25.3	23.0	24.5	-------	23.0	20.7	20.6	23.5
Salmonella typhi (2)	31.0	31.0	22.0	-------	17.5	-------	18.5	18.5	21.6	23.5	18.5
Azospirillum lipoferum	29.0	35.5	30.5	19.0	16.0	24.5	28.0	-------	23.5	24.5	19.0
Rhizobium sp.	20.5	31.0	13.0	24.3	-------	29.5	24.0	23.5	20.0	27.0	17.0
Citrobacter freundii	27.0	27.0	16.0	29.6	16.0	25.4	26.5	17.5	19.5	------	18.5
Achromobacter xylosoxidans	20.0	21.5	29.5	23.5	25.5	22.6	23.5	26.0	------	26.0	-----
Stenotrophomonas maltophilia	19.5	27.5	28.5	18.5	21.5	20.0	-------	-------	21.0	------	-----

Table 3: Minimum inhibitory concentrations (MIC values) of salicylaldehyde Schiff bases against different bacterial strains

Bacterial strains	MIC values (µg/mL)							
	SB1	SB2	SB3	SB4	SB5	SB6	SB7	SB8
Klebsiella pneumoniae	150	250	100	250	50	250	100	100
Enterobacter cloacae	200	200	100	100	100	100	50	150
Enterobacter aerogenes	250	200	150	100	200	100	150	150
Pseudomonas aurantiaca	250	250	50	150	200	250	200	200
Pseudomonas aeruginosa (1)	50	100	50	100	150	200	250	250
Pseudomonas aeruginosa (2)	100	100	200	200	100	100	250	200
Pseudomonas aeruginosa (3)	200	250	200	200	100	50	250	100
Escherichia coli (1)	200	100	200	200	200	250	100	200
Escherichia coli (2)	150	150	50	50	150	250	200	50
Escherichia coli (3)	300	150	200	100	300	250	100	200
Salmonella typhi (1)	250	200	100	50	250	200	100	200
Salmonella typhi (2)	200	200	50	100	50	200	200	100
Azospirillum lipoferum	150	200	150	100	150	100	50	250
Citrobacter freundii	100	100	50	150	200	50	100	250
Achromobacter xylosoxidans	100	100	150	250	150	200	200	200
Stenotrophomonas maltophilia	150	250	100	50	200	200	200	200

SB5: 2-2'-[Benzene-1,2-diylbis(nitrilo(E) methylylidene)]diphenol

M.P: 240-243°C; yield (73%); molecular mass: 316.3602;IR (KBr): υ (cm^{-1}) =1653 (C=N). ^{1}H NMR (400 M Hz, $CDCl_3$), (δppm): 8.65(2H, -N=C-H), 7.94 (4H, H-7b, H-8b, H-9b, H-10b), 7.45 (2H, H-1a,H-1a') 7.25(2H, H-3a, H-3a'), 6.89 (2H, H-2a,2a'), 6.79 (2H, H-4a,4a'), 4.6 (2H, H-5a,H-5a'), 5.14 (1H, H-5a) ^{13}C-NMR($CDCl_3$), δ: 162, 161.1 (-CH=N-), 145.5 (2C), 132.7, 129.9 (2C) 129.4, 123.8 (2C), 122.4, 118.3, 117.0.MS (m/z): 316 [M^+].

SB6: 2-[(2-Phenylhydrazineylidene)methyl]phenol

M.P: 190-198°C; yield (73%); molecular mass: 212.2518; IR (KBr): υ (cm^{-1}) = 1658 (C=N). ^{1}HNMR(400 M Hz, $CDCl_3$), (δppm): 8.46(-N=C-H) 7.45 (1H, H-1a),7.27 (1H,H-3a), 7.18 (2H, H-9b, H-11b), 6.95(1H, H-4a), 6.84 (1H, H-2a), 6.78 (1H, H-10b), 6.64 (2H, H-8b, 12b), 5.3(1H, H-5a), 4.85 (1H, H-7a), 5.37 (1H, H-5a). ^{13}C-NMR($CDCl_3$), δ: 161.4, 147.2 (-CH=N-), 144.6, 131.8, 131.2,129.4 (2C), 122.7, 118.9, 120, 115.8, 115.5(2C).MS (m/z): 212 [M^+].

SB7: 2-2'-[Ethene-1,2-diylbis(iminomethanediyl)] diphenol

M.P: 140-144°C; yield (73%); molecular mass: 268.3162;IR (KBr): υ (cm^{-1}) =1650 (C=N). ^{1}H NMR (400 M Hz, $CDCl_3$), (δppm): 8.14 (2H, -N=C-H), 7.39 (2H, H-4a, H-4a'), 7.1 (2H, 2a, 2a'), 6.9 (2H, 3a, 3a'), 6.79 (2H, 1a, 1a'), 5.15 (2H, 5a, 5a'), 3.89-3.95 (4H, 7b, 8b, 9b, 10b). ^{13}C-NMR ($CDCl_3$), δ: 160.6 (2C, -CH=N-), 159.7,132.4, 130.7, 123.3, 118.5, 117.0, 69.3 (2C). MS (m/z): 268 [M^+].

SB8: 2-[(Z)-(Phenylimino)methyl]phenol

M.P: 140-144°C; yield (73%); molecular mass: 197.2371;IR (KBr): υ (cm^{-1}) =1655 (C=N). ^{1}H NMR(400 M Hz, $CDCl_3$), (δppm): 8.57 (-N=C-H), 7.6 (1H, H-4a), 7.6-7.45 (5H, 7b, 8b, 9b, 10b,11b), 7.1 (1H, 2a), 6.9 (1H, 3a), 6.79 (1H, 1a), 4.94 (1H, 5a). ^{13}C-NMR ($CDCl_3$), δ: 161.6, 160.3 (-CH=N-), 154.4, 132.4, 131.1 (2C), 128.6, 122.4, 121.8 (2C), 119.8, 118.4, 115.7.MS (m/z): 197 [M^+].

Anti-microbial Studies

Anti-microbial activities of all the bases were evaluated in terms of Zones of Inhibition and MIC values and the results are presented in table 2 and table 3, respectively. In this study, three different antibiotic medicines, Amoxylin, Cefixime and Levofloxacin, were used as standards to have a comparison of the toxicity of the synthesized Schiff bases. Different bacterial strains showed different sensitivities against these drugs. The different response of the different strains of the same species of bacteria towards the standard antibiotics and the Schiff bases showed different degrees of resistance that these microorganisms have developed.

DISCUSSION

The structures of the Schiff bases were elucidated on the bases of spectroscopic data. The molecular ion peaks in the mass spectra of bases conformed to the calculated molecular masses. In ^{1}H NMR spectra the characteristic azomethine proton (H-C=N) appeared at its expected value (8.14-9.98 ppm), while the azomethine carbon resonated at about 160 ppm in the ^{13}C NMR spectra (Azam *et al*., 2007). The C=N stretching absorption occurred in its normal region of 1650 cm^{-1} in the IR

spectra which confirmed the structures (Tantaru *et al*., 2010). ^{1}H and ^{13}C NMR assignments are shown in Results above (Kumar et al., 2010; Shi *et al*., 2007; Parekh *et al*., 2005). Most bases showed moderate to very good anti-microbial activities. An estimate of the relative toxicity of these bases in comparison with the standard antibiotics can be had from the tables 2 and 3. The base SB1 displayed moderate efficacy against most of the tested strains. However, it was more potent against *P. aurantiaca, P. aeruginosa* (3), *E. coli* (2) and *C. freundii,* with zone of inhibition (ZOI, mm) of 25.1±0.13, 26.0±2.01, 27.0±2.50 and 29.6±1.55, respectively. These results are significant as they are comparable to those of standard drugs. SB2 showed high toxicity against *P. aeruginosa* (3), *A. xylosoxidans* and *S. typhi* (1) with efficacy comparable to that of standard antibiotics. SB3 showed significant toxicity against a number of microorganisms including *P. aurantiaca, K. pneumoniae*, *P. aeruginosa* (2) and *E. coli* (2). The Schiff base SB4 had remarkable efficacy against strains of *E. coli*, *P. aeruginosa* (1), *A. lipoferum*, *C. freundii*, *A. xylosoxidans* and *E. aerogenes.* The Schiff base SB5 was effective against *K. pneumoniae, P. aeruginosa* (1) and *A. xylosoxidans.* SB6 was toxic against *E. cloacae, E. coli* (3) and *E. aerogenes.* SB7 showed very good effectiveness against *K. pneumoniae*, *E. cloacae*, *P. aeruginosa* (3), *E. coli* (1), and *A. xylosoxidans*. The compound SB8 exhibited considerable efficacy against *E. cloacae*, *P. aurantiaca, P. aeruginosa* (1), *P. aeruginosa* (2), *E. coli* (1), *E. coli* (2) and *E. aerogenes.* The ZOI higher than 24 should be regarded as highly significant, between 20-24, as moderately significant, while less than 20 as less significant. Variation in efficacy of compounds is due to variation in their structures.

The minimum concentrations sufficient to kill the microorganisms for most compounds were 100-200 µg/mL. However, some compounds were toxic even at a lower concentration. SB1 against *P. aeruginosa* (1), SB3 against *P. aurantiaca, P. aeruginosa* (1)*, E. coli* (2), *S. typhi* (2), *C. freundii,* SB4 against *E. coli* (2), *S. typhi (1), S. maltophilia,* SB5against *K. pneumoniae* and *S. typhi* (2),SB6 against *P. aeruginosa* (3), *C. freundii,* SB7 against *E. cloacae* and *A. lipoferum*, and SB8 against *E. coli* (2) was 50µg/mL.

The difference in susceptibility of different strains of a microorganism against standard antibiotics as well as the Schiff bases showed different levels of resistance that they have developed.

CONCLUSION

In the present study, Schiff bases of salicylaldehyde with different primary amines were prepared and characterized on the bases of spectroscopic data. The bases exhibited considerable anti-microbial activities against a number of bacterial strains. Expectedly, various strains of bacteria exhibited different susceptibility against the standard antibiotic and the Schiff bases which showed difference in the resistance, which the microorganisms have developed. Further studies may prove some of these bases as suitable candidates for future antibiotics particularly useful for topical application against infections caused by different pathogens.

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