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Synthesis of Schiff bases of naphtha[1,2-*d*]thiazol-2-amine and metal complexes of 2-(2'-hydroxy)benzylideneaminonaphthothiazole as potential antimicrobial agents

AZAM Faizul[†1,2], SINGH Satendra[3], KHOKHRA Sukhbir Lal[1], PRAKASH Om[1]

([1]*Department of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, Haryana 136119, India*)

([2]*Faculty of Pharmacy, Seventh of October University, P.O. Box 2909, Misurata, Libya*)

([3]*Dr. B. R. Ambedkar Center for Biomedical Research, University of Delhi, Delhi 110007, India*)

[†]E-mail: faizulazam@gmail.com

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Abstract: Objective: A series of 2-benzylideneaminonaphthothiazoles were designed and synthesized incorporating the lipophilic naphthalene ring to render them more capable of penetrating various biomembranes. Methods: Schiff bases were synthesized by the reaction of naphtha[1,2-*d*]thiazol-2-amine with various substituted aromatic aldehydes. 2-(2'-Hydroxy)benzylideneaminonaphthothiazole was converted to its Co(II), Ni(II) and Cu(II) metal complexes upon treatment with metal salts in ethanol. All the compounds were evaluated for their antibacterial activities by paper disc diffusion method with Gram positive *Staphylococcus aureus* and *Staphylococcus epidermidis* and Gram negative *Escherichia coli* and *Pseudomonas aeruginosa* bacteria. The minimum inhibitory concentrations of all the Schiff bases and metal complexes were determined by agar streak dilution method. Results: All the compounds moderately inhibited the growth of Gram positive and Gram negative bacteria. In the present study among all Schiff bases 2-(2'-hydroxy)benzylideneaminonaphthothiazole showed maximum inhibitory activity and among metal complexes Cu(II) metal complex was found to be most potent. Conclusion: The results obtained validate the hypothesis that Schiff bases having substitution with halogens, hydroxyl group and nitro group at phenyl ring are required for the antibacterial activity while methoxy group at different positions in the aromatic ring has minimal role in the inhibitory activity. The results also indicated that the metal complexes are better antibacterial agents as compared to the Schiff bases.

Key words: Schiff bases, Metal complexes, Antimicrobial
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INTRODUCTION

The development of bacterial resistance to available antibiotics and increasing incidence of multi resistant bacterial infections in hospitals and in the community has necessitated the search for new antibacterial agents to treat the bacterial infection (Harbarth *et al*., 2001; Mitscher *et al*., 1999). It has long been known that metal ions are involved in biological processes of life through bonding to the hetero atoms of the heterocyclic residues of biological molecules i.e., proteins, enzymes and nucleic acids etc. (Erwin and Omoshile, 1995). Various cobalt, nickel and copper metal complexes were reported to have antimicrobial activities (El-Ayaan and Abdel-Aziz, 2005; Sonmez *et al*., 2006). Schiff bases are characterized by the −N=CH− (imine) group which is important for elucidating the mechanism of transamination and racemisation reactions in biological systems (Lau *et al*., 1999) and are also known to have biological activities such as antimicrobial (Fioravanti *et al*., 1995; El-Masry *et al*., 2000; Pandeya *et al*., 1999), antifungal (Singh and Dash, 1998), antitumor (Desai *et al*., 2001) and herbicidal (Samadhiya and Halve, 2001). Schiff bases continue to occupy an important position as ligands in metal coordination chemistry (Wu *et al*., 2004; Aydogan *et al*., 2001), even almost a century since their discovery.

Moreover, the incorporation of transition metal into Schiff bases enhances the biological activity of

the ligand and decreases the cytotoxic effects of both the metal ion and ligand on the host (Trávníček *et al*., 2001). Thiazoles and their derivatives form a part of vitamin B_1 and coenzyme carboxylase (Schrauzer and Kohnle, 1964). They represent a very interesting class of compounds because of their wide applications as antimicrobial (Chohan *et al*., 2003; Vicini *et al*., 2003), anti-inflammatory (Geronikaki *et al*., 2003), anti-degenerative (Panico *et al*., 2003) and anti-HIV (Maass *et al*., 1993) activities. In continuation of our work on thiazole derivatives (Amir and Azam, 2004a) and Schiff bases (Amir and Azam, 2004b) we have synthesized new Schiff bases of naphtha[1,2-*d*]thiazol-2-amine purposely to combine the lipophilicity of naphthalene moiety to enhance membrane permeability with thiazole ring and azomethine linkage to study their effect on pathogenic strains of Gram positive and Gram negative bacteria. The Co(II), Ni(II) and Cu(II) metal complexes of the 2-(2'-hydroxy) benzylideneaminonaphthothiazole were prepared. All the compounds were screened for their antibacterial activity. We presented some part of this work earlier (Luthra *et al*., 2006).

MATERIALS AND METHODS

Chemistry

Synthetic starting material, reagents and solvents were of analytical reagent grade or of the highest quality commercially available and were purchased from Aldrich Chemical Co. (USA) and Merck Chemical Co. (USA) and were dried when necessary. The progress of the reactions was monitored by thin layer chromatography with F_{254} silica-gel precoated sheets (Merck Chemical Co., USA) using chloroform/methanol (98/2, v/v) as eluent; UV light and iodine vapours were used for detection. IR spectra were recorded, as KBr pellets, on a Schimadzu FT-IR spectrophotometer with wave numbers given in cm^{-1}. Electron ionization (EI) mass spectra were obtained on Jasco Model (JASCO International Co. Ltd., Japan). ^1H NMR spectra, in DMSO-d_6 solution, were recorded on a Bruker AC 300 instrument at 298 K. Chemical shifts were reported as δ relative to TMS as internal standard. Melting points (°C) were determined with an open glass capillary tube and uncorrected. Elemental analysis was performed in the analytical laboratory of University Science Instrumentation Centre, University of Delhi on Perkin Elmer 240 instrument (PerkinElmer Life and Analytical Sciences Inc., USA). The found values for C, H, N and S were always 0.4% of the theoretical ones.

Synthesis of naphtha[1,2-*d*]thiazol-2-amine (Fig.1): It was synthesized according to the method in (Mehra and Zaman, 1978) and recrystallized from acetonitrile (m.p. 190~192 °C, Lit 190 °C).

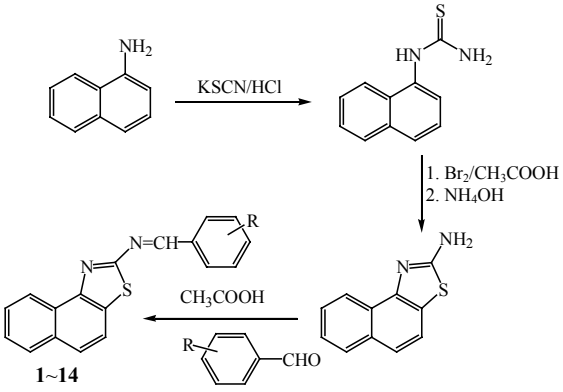


Fig.1 Scheme for synthesis of Schiff bases

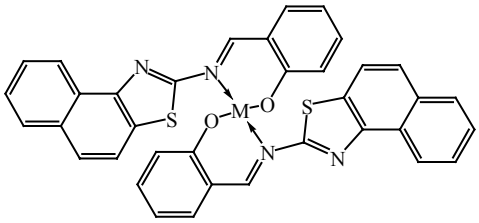
General method for the synthesis of Schiff bases (compounds **1**~**14**, Fig.1): Naphtha[1,2-*d*]thiazol-2-amine (0.01 mol, 2.0 g) was dissolved in 20 ml of glacial acetic acid. Substituted aromatic aldehyde (0.01 mol) in 10 ml glacial acetic acid was added dropwise with stirring and the reaction mixture was heated to reflux for over 8 h.

After completion of reaction, it was poured onto crushed ice, the solid thus obtained was filtered, washed with water and recrystallized from ethanol. Physical characterization of synthesized compounds is given in Table 1.

General method for the preparation of metal complexes (Fig.2): The ligand, 2-(2'-hydroxy)benzylideneaminonaphthothiazole (0.610 g, 2 mmol) was dissolved in 30 ml of absolute ethanol and a solution of the metal salts (1 mmol) in 10 ml of ethanol was added dropwise to the ligand solution with continuous stirring and the mixture was refluxed overnight. The pH of the solutions was adjusted to 5~6 by adding a Na_2CO_3 suspension in ethanol. Then the volume of the solutions was reduced to about 10 ml and complexes were precipitated with dry diethyl ether (15 ml). The precipitate was filtered, washed with water and cold ethanol, then dried at room temperature.

Table 1 Physical characterization of the synthesized compounds

Compound	R	Molecular formula	m.p. (°C)	Yield (%)	R_f	Nitrogen estimation (%)	
						Calculated	Found
1	H	$C_{18}H_{12}N_2S$	144	48	0.52	9.71	9.58
2	2-Cl	$C_{18}H_{11}ClN_2S$	152	64	0.68	8.68	10.02
3	4-Cl	$C_{18}H_{11}ClN_2S$	262	68	0.67	8.68	9.98
4	4-Br	$C_{18}H_{11}BrN_2S$	162	61	0.70	7.63	7.39
5	4-F	$C_{18}H_{11}FN_2S$	272	56	0.74	9.14	9.26
6	2-OH	$C_{18}H_{12}N_2OS$	266	72	0.79	9.20	9.01
7	4-OH	$C_{18}H_{12}N_2OS$	166	68	0.80	9.20	9.47
8	2-NO_2	$C_{18}H_{11}N_3O_2S$	170	59	0.43	12.60	12.51
9	3-NO_2	$C_{18}H_{11}N_3O_2S$	188	54	0.46	12.60	12.84
10	4-OCH_3	$C_{19}H_{14}N_2OS$	192	73	0.59	8.80	9.12
11	3-OCH_3, 4-OH	$C_{19}H_{14}N_2O_2S$	164	71	0.82	8.38	8.03
12	3,4-OCH_3	$C_{20}H_{16}N_2O_2S$	198	65	0.65	8.04	7.91
13	2,5-OCH_3	$C_{20}H_{16}N_2O_2S$	270	58	0.67	8.04	8.22
14	3,4,5-OCH_3	$C_{21}H_{18}N_2O_3S$	236	62	0.72	7.40	7.56



M=Co(II), Ni(II), Cu(II)

Fig.2 Supposed structure of the metal complexes

Subsequently, the precipitate was dissolved in 15 ml of $CHCl_3$ and reprecipitated with diethyl ether (15 ml), then washed with ether several times, and dried in vacuo at 60 °C.

Physical characterization of synthesized complexes is given in Table 2. Table 3 lists characteristic IR bands of the ligand and its complexes as KBr pellets.

The spectral data of the synthesized compounds (Schiff bases) were as follows:

Compound **1**: IR (KBr, υ cm^{-1}) 3010 (Ar-H stretch), 1608 (N=CH stretch azomethine), 1510 (C=N stretch thiazole), 684 (C-S-C stretch); ^{1}H NMR (DMSO d_6, δ) 7.47~7.89 (m, 11H, ArH), 9.12 (s, 1H, N=CH); EI-MS *m*/*z* (M^+) 288.

Compound **2**: IR (KBr, υ cm^{-1}) 2990 (Ar-H stretch), 1620 (N=CH stretch azomethine), 1508 (C=N stretch thiazole), 682 (C-S-C stretch); ^{1}H NMR (DMSO d_6, δ) 7.28~7.86 (m, 10H, ArH), 8.91 (s, 1H, N=CH); EI-MS *m*/*z* (M^+) 323.

Compound **3**: IR (KBr, υ cm^{-1}) 2998 (Ar-H stretch), 1613 (N=CH stretch azomethine), 1520 (C=N stretch thiazole), 690 (C-S-C stretch); ^{1}H NMR (DMSO d_6, δ) 7.70~7.85 (m, 10H, ArH), 9.02 (s, 1H, N=CH); EI-MS *m*/*z* (M^+) 323.

Compound **4**: IR (KBr, υ cm^{-1}) 3008 (Ar-H stretch), 1617 (N=CH stretch azomethine), 1513 (C=N stretch thiazole), 684 (C-S-C stretch); ^{1}H NMR (DMSO d_6, δ) 7.62~7.85 (m, 10H, ArH), 8.82 (s, 1H, N=CH); EI-MS *m*/*z* (M^+) 367.

Compound **5**: IR (KBr, υ cm^{-1}) 3040 (Ar-H stretch), 1618 (N=CH stretch azomethine), 1505 (C=N stretch thiazole), 688 (C-S-C stretch); ^{1}H NMR (DMSO d_6, δ) 7.20~8.08 (m, 10H, ArH), 8.52 (s, 1H, N=CH); EI-MS *m*/*z* (M^+) 306.

Compound **6**: IR (KBr, υ cm^{-1}) 3460 (O-H stretch), 2992 (Ar-H stretch), 1607 (N=CH stretch azomethine), 1509 (C=N stretch thiazole), 685 (C-S-C stretch); ^{1}H NMR (DMSO d_6, δ) 7.37~7.89 (m, 10H, ArH), 8.98 (s, 1H, N=CH); EI-MS *m*/*z* (M^+) 304.

Compound **7**: IR (KBr, υ cm^{-1}) 3466 (O-H stretch), 2999 (Ar-H stretch), 1623 (N=CH stretch azomethine), 1518 (C=N stretch thiazole), 686 (C-S-C stretch); ^{1}H NMR (DMSO d_6, δ) 7.45~7.80 (m, 10H, ArH), 9.04 (s, 1H, N=CH); EI-MS *m*/*z* (M^+) 304.

Compound **8**: IR (KBr, υ cm^{-1}) 3012 (Ar-H stretch), 1609 (N=CH stretch azomethine), 1501 (C=N stretch thiazole), 687 (C-S-C stretch); ^{1}H NMR (DMSO d_6, δ) 7.59~7.89 (m, 10H, ArH) 9.10 (s, 1H, N=CH); EI-MS *m*/*z* (M^+) 333.

Table 2 Physical characterization of 2-(2'-hydroxy)benzylideneaminonaphthothiazole (ligand) and its complexes with Co(II), Ni(II) and Cu(II)

Compound	Molecular formula	*FW* (g/mol)	Colour	m.p. (°C)	Yield (%)	Nitrogen estimation (%)	
						Calculated	Found
LH	$C_{18}H_{12}N_2SO$	304.37	Yellow	266	72	9.20	9.01
CoL_2	$C_{36}H_{22}N_4S_2O_2Co$	665.67	Orange	312	53	8.42	8.54
NiL_2	$C_{36}H_{22}N_4S_2O_2Ni$	665.44	Red	286	38	7.42	7.51
CuL_2	$C_{36}H_{22}N_4S_2O_2Cu$	670.27	Red	272	42	8.36	8.19

Table 3 Characteristic IR bands (cm^{-1}) of the ligand and its complexes as KBr pellets

Compound	υ(O-H)	υ(C=N) thiazole	υ(C=N) azomethine	υ(C-S-C) thiazole
LH	3460	1509	1607	685
CoL_2	−	1507	1588	683
NiL_2	−	1508	1586	685
CuL_2	−	1506	1587	684

Compound **9**: IR (KBr, υ cm^{-1}) 3018 (Ar-H stretch), 1618 (N=CH stretch azomethine), 1511 (C=N stretch thiazole), 681 (C-S-C stretch); ^{1}H NMR (DMSO d_6, δ) 7.24~7.92 (m, 10H, ArH), 8.99 (s, 1H, N=CH); EI-MS *m*/*z* (M^+) 333.

Compound **10**: IR (KBr, υ cm^{-1}) 2995 (Ar-H stretch), 1614 (N=CH stretch azomethine), 1504 (C=N stretch thiazole), 688 (C-S-C stretch); ^{1}H NMR (DMSO d_6, δ) 4.15 (s, 3H, 4-OCH_3), 7.29~8.11 (m, 10H, ArH), 8.67 (s, 1H, N=CH); EI-MS *m*/*z* (M^+) 318.

Compound **11**: IR (KBr, υ cm^{-1}) 3462 (O-H stretch), 3018 (Ar-H stretch), 1620 (N=CH stretch azomethine), 1512 (C=N stretch thiazole), 684 (C-S-C stretch); ^{1}H NMR (DMSO d_6, δ) 3.97 (s, 3H, 3-OCH_3), 6.97~7.85 (m, 9H, ArH), 8.78 (s, 1H, N=CH); EI-MS *m*/*z* (M^+) 334.

Compound **12**: IR (KBr, υ cm^{-1}) 3014 (Ar-H stretch), 1611 (N=CH stretch azomethine), 1515 (C=N stretch thiazole), 689 (C-S-C stretch); ^{1}H NMR (DMSO d_6, δ) 3.89 (s, 6H, 3,4-OCH_3), 7.22~7.98 (m, 9H, ArH), 8.86 (s, 1H, N=CH); EI-MS *m*/*z* (M^+) 348.

Compound **13**: IR (KBr, υ cm^{-1}) 3022 (Ar-H stretch), 1619 (N=CH stretch azomethine), 1522 (C=N stretch thiazole), 687 (C-S-C stretch); ^{1}H NMR (DMSO d_6, δ) 4.23 (s, 6H, 2,5-OCH_3), 7.69~8.13 (m, 9H, ArH), 8.91 (s, 1H, N=CH); EI-MS *m*/*z* (M^+) 348.

Compound **14**: IR (KBr, υ cm^{-1}) 3019 (Ar-H stretch), 1611 (N=CH stretch azomethine), 1508 (C=N stretch thiazole), 689 (C-S-C stretch); ^{1}H NMR (DMSO d_6, δ) 3.99 (s, 9H, 3,4,5-OCH_3), 7.14~7.94 (m, 8H, ArH), 8.83 (s, 1H, N=CH); EI-MS *m*/*z* (M^+) 378.

Antimicrobial acivity

The antibacterial activity of all the synthesized compounds was tested against *Staphylococcus aureus* (ATCC 6571), *Staphylococcus epidermidis* (ATCC 155), *Escherichia coli* (ATCC 10418) and *Pseudomonas aeruginosa* (ATCC 10662) using nutrient agar medium (Hi-Media Laboratories, India) by the method of Tandon *et al*.(2005). The sterilized (autoclaved at 120 °C for 30 min) medium (40~50 °C) was inoculated (1 ml/100 ml of medium) with the suspension (105 CFU/ml) of the microorganism (matched to McFarland barium sulphate standard) and poured into a petridish to a depth of 3~4 mm. The paper impregnated with the test compounds (50 μg/ml in dimethyl formamide) was placed on the solidified medium. The plates were preincubated for 1 h at room temperature and incubated at 37 °C for 24 h. Neomycin was used as standard for antibacterial activity. The observed zone of inhibition is presented in Table 4. Minimum inhibitory concentration (MIC) of the test compounds was determined by agar streak dilution method. A stock solution of the synthesised compound (50 μg/ml) in dimethyl formamide was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile nutrient agar. A specified quantity of the medium (40~50 °C) containing the compound was poured into a petridish to a depth of 3~4 mm and allowed to solidify. Suspension of the microorganism was prepared to contain approximately 105 CFU/ml and applied to plates with serially diluted compounds in dimethyl formamide to be tested and incubated at 37 °C for 24 h. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria on the plate. The observed inhibition of growth in mm and MIC in μg/ml are presented in Table 4.

Table 4 Antimicrobial activity of the synthesized compounds

Compound	In vitro activity-zone of inhibition in mm (MIC in μg/ml)			
	Staphylococcus aureus	*Staphylococcus epidermidis*	*Escherichia coli*	*Pseudomonas aeruginosa*
1	10 (30)	10 (44)	11 (39)	9 (49)
2	8 (35)	9 (44)	8 (43)	10 (32)
3	10 (43)	8 (36)	9 (32)	9 (42)
4	9 (47)	10 (38)	8 (36)	10 (45)
5	9 (39)	11 (45)	11 (34)	10 (43)
6	13 (33)	14 (31)	14 (26)	13 (38)
7	10 (45)	8 (49)	9 (41)	8 (39)
8	10 (36)	11 (39)	12 (33)	10 (41)
9	12 (28)	10 (34)	10 (26)	9 (36)
10	9 (31)	8 (32)	9 (39)	10 (44)
11	10 (36)	11 (38)	9 (43)	9 (33)
12	7 (39)	7 (42)	8 (46)	6 (37)
13	7 (55)	8 (49)	9 (44)	8 (50)
14	6 (48)	6 (42)	7 (56)	6 (48)
CoL_2	15 (36)	16 (38)	16 (32)	14 (38)
NiL_2	17 (40)	16 (36)	16 (28)	15 (30)
CuL_2	17 (28)	18 (34)	17 (32)	16 (30)
Neomycin (30 μg/disc)	24 (0.3)	26 (0.2)	25 (0.3)	23 (0.4)
Dimethyl formamide	–	–	–	–

RESULTS AND DISCUSSIONS

In the IR spectra of the Schiff bases absence of C=O and NH_2 peaks and appearance of C=N (azomethine) peaks indicate that the expected imino compound was formed by condensation from naphtha[1,2-*d*]thiazol-2-amine and various substituted aromatic aldehydes and it was also shown that there are no residual starting materials left as well. The IR spectra of the metal complexes showed that the band at 1607 cm^{-1} assigned to the υ(C=N azomethine) vibration of the ligand 2-(2'-hydroxy)benzylideneaminonaphthothiazole was shifted to lower frequency after complexation to 1588, 1586 and 1587 cm^{-1} for the Co(II), Ni(II) and Cu(II) complexes respectively. This shift indicates coordination of the ligand to the metal atoms by the nitrogen of azomethine (Nakamura *et al*., 1979). The ligand's O-H stretching vibration at 3460 cm^{-1} disappeared on complexation with Co(II), Ni(II) and Cu(II). This also indicates that the OH group deprotonates on complexation. The practically unchanged υ(C=N thiazole) at 1509 cm^{-1} and υ(C-S-C) at 685 cm^{-1} of the thiazole ring confirmed that the thiazole group itself does not coordinate to metal atoms by either nitrogen or sulphur atoms.

Two bands at 352 and 414 nm are observed in the electronic spectra of the ligand. The band at 352 nm is attributed to $\pi\rightarrow\pi^*$ transitions in the aromatic ring and the C=N chromophore. The second band at 414 nm is assigned to the $n\rightarrow\pi^*$ transition. Fig.2 shows the tentative geometry of the complexes; the ligand acts as bidentate ligand with −O and =N sites and forms a dimeric complex with Co(II), Ni(II) and Cu(II). In the UV-visible spectra of the Cu(II) complex, a broad band at 437 nm and a shoulder at 480 nm were observed which may be assigned to $^2B_{1g}\rightarrow{}^2B_{2g}$ and $^2B_{1g}\rightarrow{}^2A_{1g}$ transition in a tetragonal field, respectively (Alvarez *et al*., 1990; Cervera *et al*., 1997). The UV-visible spectra of the Co(II) complex show two bands, one at 360 nm and the other at 452 nm, which may be assigned to $^4A_2\rightarrow{}^4T_1(F)$ and $^4A_2\rightarrow{}^4T_1(P)$ transitions in tetrahedral complexes, respectively (West, 1962). The electronic spectrum of the Ni(II) complex has two bands, one at 370 nm and the other at 486 nm, which may be assigned to $^3T_1(F)\rightarrow{}^3T_1(P)$ and $^3T_1(F)\rightarrow{}^3T_2(F)$ transitions. From these transitions of the Ni(II) complex, the structure

of the Ni(II) complex can be assigned to tetrahedral geometry (Bosnich, 1968). Based on the above results the supposed structure of the metal complex is given in Fig.2.

All the compounds moderately inhibited the growth of Gram positive and Gram negative bacteria. The antibacterial activity was evaluated by measuring the zone of inhibition in mm. In the present study, among all Schiff bases 2-(2'-hydroxy)benzylideneaminonaphthothiazole showed maximum inhibitory activity and among metal complexes Cu(II) metal complex was found to be most potent. The compounds containing methoxy group at different positions of the aromatic ring showed less inhibition in microorganisms growth whereas compounds having halogens, hydroxyl and nitro group showed good inhibitory activity. The results are summarized in Table 4.

CONCLUSION

We have prepared and characterized the substituted Schiff bases of naphtha[1,2-*d*]thiazole-2-amine and the metal complexes of 2-(2'-hydroxy)benzylideneaminonaphthothiazole with Co(II), Ni(II) and Cu(II). The compounds exhibited reasonable antibacterial activity as compared to standard drug.

The results obtained validate the hypothesis that Schiff bases having substitution with halogens, hydroxyl group and nitro group at phenyl ring are required for the antibacterial activity while methoxy group at different positions in the aromatic ring has minimal role in the inhibitory activity. The results also indicated that the metal complexes are better antibacterial agents as compared to the Schiff bases.

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