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ARTICLE

Synthesis, characterization and antibacterial activity of ethylene di-amine and 2-hydroxybenzadehyde Schiff base and its metal complexes

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Abstract
A number of modern techniques have been developed for the synthesis of Schiff bases. We reported the synthesis of ethylene di-amine and 2-hydroxybenzadehyde Schiff base (SB) via the condensation method. To remove phenolic hydrogen to form Schiff base it was reacted with sodium hydroxide and then treated with M(II) chloride (M=Fe, Cu, Zn, Ni and Sn) to fabricate their respective metal complexes**.** The synthesis of SB metal complexes and detailed functional group characterization were validated via Fourier transform infrared (FT-IR) spectroscopy. In the final SB, FT-IR results revealed a vibrational peak at 1614 cm^{-1}, which was credited to the –C=N part. The absence of a vibration band for –OH vibration on 1613 cm^{-1} and the presence of a novel band in the 659 to 586 cm^{-1} range were due to the metal-oxygen bond, confirming the synthesis of metal complexes. The Schiff base showed high antibacterial activity against *E. coli, Pseudomonas aeruginosa, Salmonella typhi, S.aureus* and *Bacillus* whereas *Streptococcus* was found resistant. Cu, Fe and Sn coordination improved Schiff base activity while Ni coordination did not affect the activity. Similarly, Fe and Sn complex had no effect on *E. coli*. In comparison with standard Ciprofloxacin, the activities of respective metal complexes were low.
Keywords: Ethylene di-amine and 2-hydroxybenzadehyde Schiff base; metal complex of Schiff base; FT-IR; antibacterial activity; standard ciprofloxacin.

1. Introduction

In 1864, a German chemist named Hugo Schiff developed Schiff base (SB) by condensing primary amines and aldehyde [1]. The following compound, R1R2C=NR3, is known as an SB since R1 is an aryl group, R2 is a hydrogen atom, and R3 is an aryl or alkyl group, which is also known as a Schiff base. SBs with aryl substituents are the most stable and easy to synthesize, whereas those with alkyl substituent's are more unstable [2]. SBs and their metal complexes have been used since the mid-nineteenth century. Jorgensen and Warner, the two physicists, addressed the role of SBs and their metal complexes in coordination chemistry [3]. From salicyl aldehyde SBs and their substituted analogues, Pfeiffer and his colleagues built a chain of complexes [4]. The development of SBs complexes, their chelation properties, and stereochemistry are all studied [5]. These are generally bidentate, tridentate, tetradentate or polydentate ligands and form stable complexes with transition metals by forming five or six member ring at the condensation site[6].

1.1 SB metal complexes and their properties

SB based complexes have earned a vital position in coordination chemistry. In this connection, S and N have been the key elements in the coordination chemistry related biomolecules [7]. SB metal complexes have some intriguing properties of chelation [8, 9] oxygen affinity [10] and hence can be used as a catalyst and in the processing of dyes [11].

1.2 SBs and their metal complexes' biological significance

Malaria is a parasitic disease caused by the Plasmodium genus that kills one million people per year [12]. More than 500 million people are affected according to WHO data, with 90 percent of those affected being children from Sub-Saharan Africa. For controlling malaria, SB based molecules have been effectively applied, especially their Ruthenium complexes from aryl and ferrocyl groups [13]. The development of drug resistance against available antibiotic drugs has been a growing concern for the researcher. This has also led to a significant rise in the mortality rate [14]. SBs made from 2-hydroxy-1-napth-aldehyde and alpha amino-acids possessed exceptional antibacterial action. Apart from these, SBs resulting from salicylaldehyde show strong antibacterial activity against *Mycobacterium tuberculosis* [15].

Some SBs and their complexes like N-salicylidene-2-hydroxyaniline and 3-Fluro salicylaldehydeOxo vanadium (IV) have also been reported with promising antifungal activity. Similarly, SB derived from chitosanareis effective against *Botrytis cinerrea* and *Colletotrichumlagenarrium*[16]. SBs produced from isatin and bisisatin. Abacavir (Ziagen), a pro-drug, has been shown to have potent antiviral and anti-HIV properties [17]. Furthermore, SBs of 2-phenylquinazoline-4(3)H-one have been shown to have potent antiviral properties against corona virus, influenza, and HSV types 1 and 2 [18]. In addition to these activities, SBs have been shown to possess anticancer (Cumarin and pyrazole) [19]. 2, 6-dichloroanilino and 4 amino, 5-di methyl and similarly, some SBs possess activities against insects like bollworm (o-vanillin and its metal complexes). SBs derivative from o-vanillin and their metal complexes have anti-bollworm properties [20].

Hydrazine carboxoamide and metal complexes of di-oxo Manganese have the anti-fertility ability to alter reproductive physiology [21]. Some of the SBs possess anti-allergic, analgesic, radical scavenging and anti-oxidative activities [22]. Attributed to these reports of SBs against various biotic cultures, herein we report the synthesis of ethylene di-amine and 2-hydroxybenzadehyde Schiff base and its metal complexes and their activities analysis against biological cultures. Fourier transform infrared (FT-IR) spectroscopy was used to classify the prepared SBs, which aided in the interpretation of the experimental findings.

2. Materials and Methods

2.1 Reagents

Sodium Hydroxide (NaOH), 2 hydroxy-Benzaldehyde, Ethylene-diamine, Iron (II) chloride (FeCl2), Copper (II) chloride (CuCl2),Tin (II) chloride (SnCl2), Zinc Chloride (ZnCl2), Nickel (II) chloride (NiCl2), Ethanol, Methanol, and Chloroform, Except for metal chloride salt, which was purchased from Sigma Aldrich, these chemicals were extremely pure and purchased from Fluka.

2.2 Methods

The condensation method was used to synthesize SB and its metal complexes while the antibacterial properties of these compounds were investigated using the agar well diffusion process.

2.3 Instruments

By using an electrochemical melting point apparatus, the difference in melting points of precursors and final products was calculated. FT-IR was used to analyze the chemistry and nature of bands and functional groups noted in a range of 4000 to 400cm^{-1} by using KBr-disc methods.

2.3 Synthesis of SB and respective metal complexes

The synthesis of SB and its metal complexes are schematically shown in Figure 1.

2.4 Synthesis of 2,2’ (1E, 1E’)-(ethane-1,2-diylbis (azan-1-yl-1-yidene) bis(methan-1-yl-1ylidene)-diphenol

First, ethylene diamine was reacted in 1:2 ratios with 2 hydroxy Benzaldehyde in a two-necked flask linked to a reflex condenser and Deane-Stark apparatus.

The extra solvent was evaporated while the methanol was refluxed for 3-4 hours, and the yields were washed away by ethanol and re-crystallized with chloroform. Figure 2 depicts the chemical reaction for SB synthesis.

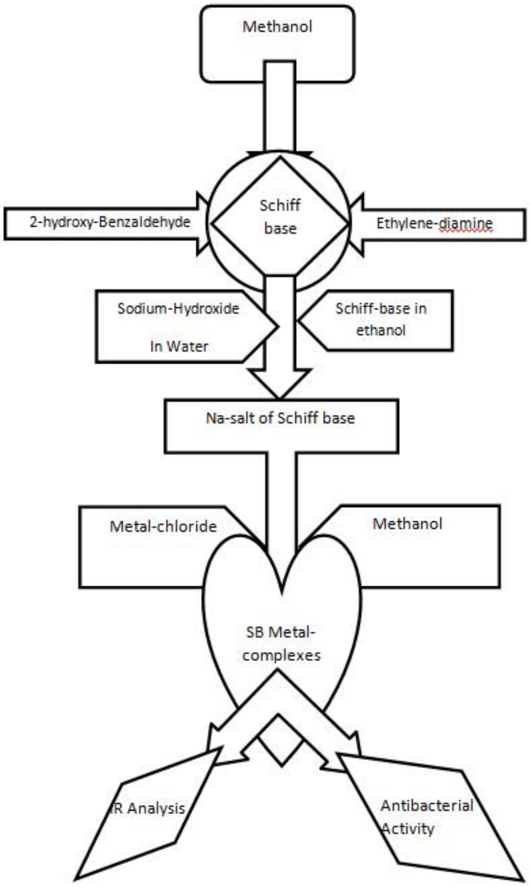


Figure 1: Overall pattern adopted throughout this study

2.5 Synthesis of the Sodium salt of SB

The solutions were combined with intense stirring and continuous heating for 1 hour after sodium hydroxide and SB were dissolved in water and ethanol in 1:2 ratios. The solvents were evaporated at 120°C, leaving a white substance that was cleaned, collected then preserved for coming experimentations. Figure 3 illustrates the chemical reaction of SB sodium salt.

2.6 SB synthesis of copper complex

Copper (II) chloride was added in a 1:2 ratio to a hot methanolic solution of SB-Na salt, then the mixture was refluxed for 6-7 hours and then chilled overnight while the additional solvent was vaporized under reduced pressure. With the aid of chloroform, the finished product was re-crystallized.

2.7 Synthesis of the iron complex with SB

For the Creation of the SB-iron complex, a similar procedure was followed as that for the copper complex, and the reaction scheme is summarized in figure 5.

2.8 Nickel complex synthesis with SB

The nickel complex of SB was prepared by applying an equimolar solution of Nickel (II) chloride to a hot methanolic solution of SB-Na salt and refluxing it for 6-7 hours. With the aid of chloroform, the finished product was re-crystallized. Figure 6 shows the chemical reaction.

2.9 Synthesis of Tin and Zn complexes with SB

Similar procedures for the preparation of Sn and Zn complexes with SB were followed while their respective reaction schemes are shown in Figures 7 and 8.

2.10 Anti-bacterial activities evaluation

The anti-bacterial activity of SB and respective complexes were used against Gram-positive bacteria such as *Bacillus cereus*, *Staphylococcus aureus, Streptococcus*, and Gram-negative bacteria such as *Bacillus subtilis*, *Escherichia c*oli, *Pseudomonas aeruginosa* and *Salmonella typh)*. Bacterial cultures were inoculated on media, and SB and their metal complexes solutions were poured into these cultures under aerobic condition and incubated for 24 hours at 37°C. The plates were analyzed for inhibition zones after 24 hours (IZ).

3. Results and discussion

The SB was synthesized by condensing ethylene-di-amine with 2-hydroxy-benzaldehyde (salicyl-aldehyde) in 1:2 ratios, and then react it with various metal salts to make its metal complexes. The empirical and structural formula of SB and its metal are summarized in Table 1.

3.1 SB and its metal complexes physical parameters

The Schiff base has a melting point of 113 to 115°C, while its metal complexes have a melting point of 262-293°C.Table no 2 lists the physical characteristics of SBs

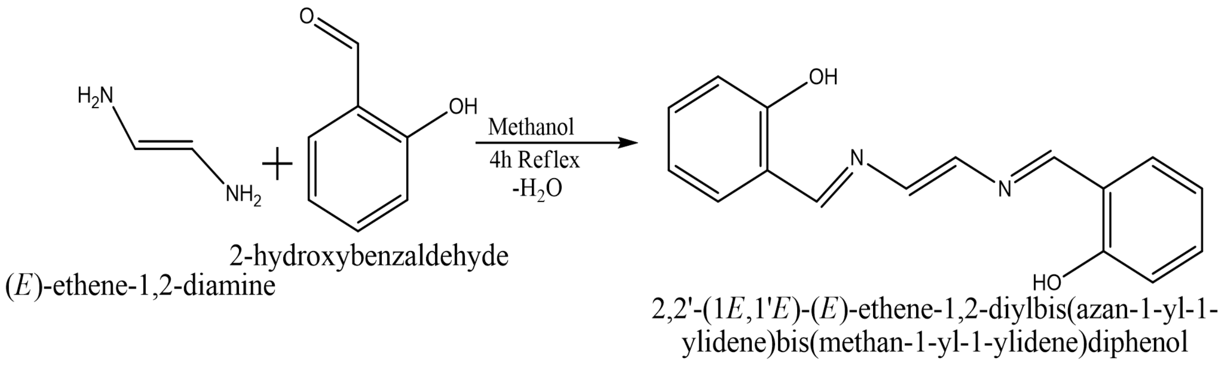


Figure 2: Chemical reaction for the synthesis of 2,2'(1E, 1E')-(ethane-1,2-diylbis (azan-1-yl-1-yidene)bis(methan-1-yl-1ylidene)-diphenolpreparation

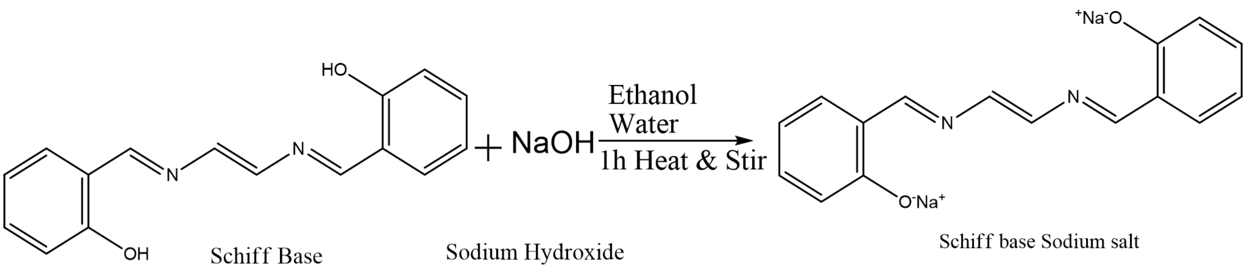


Figure 3: Schiff base reaction with sodium salt

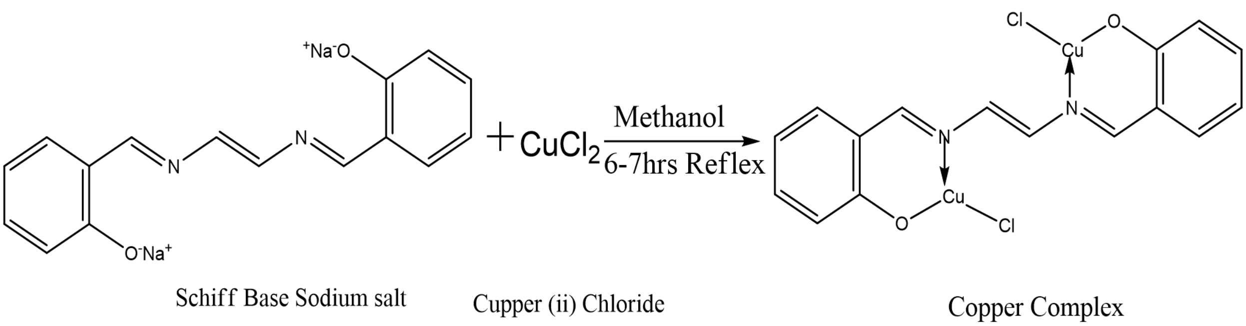


Figure 4: Schiff base Na-salt with copper chloride reaction

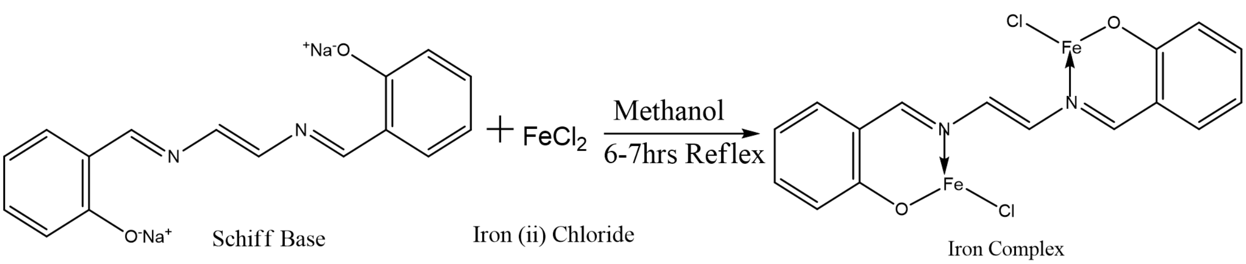


Figure 5: Schiff base with Iron chloride reaction

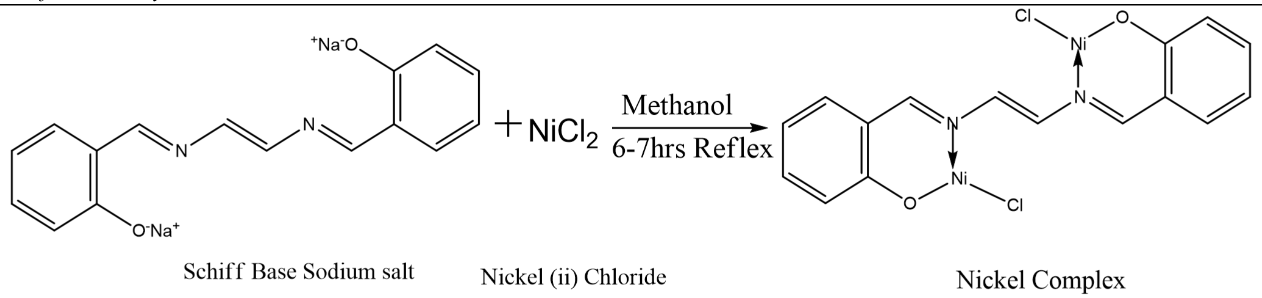


Figure 6: Schiff base Na-salt with Nickel chloridereaction

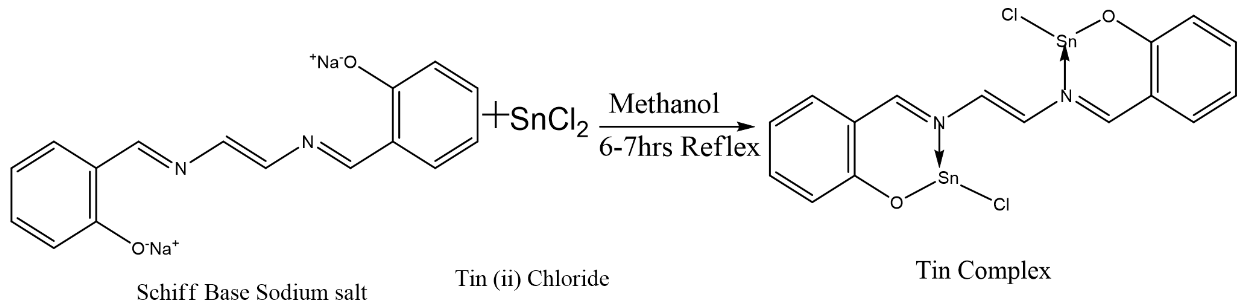


Figure 7: Schiff base Na-salt with Tin chloride reaction

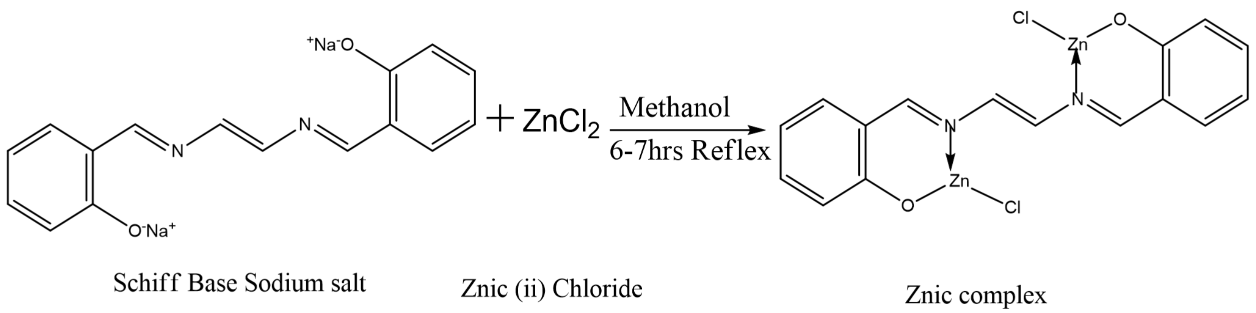


Figure 8: Schiff base Na-salt with Zn chloride reaction

and their complexes, such as color, melting point, molecular weight, and physical state. FT-IR in the range of 4000-400 cm^{-1} was used to perform spectroscopic analysis of SB and metal complexes, yielding valuable information about the chemistry and functional groups of different SBs and their corresponding complexes. Table 3 shows some of the most significant FT-IR bands of the synthesized SBs and metal complexes.

3.2 FT-IR characterization of SBs and their respective metal complexes

FT-IR research revealed a new vibration peak at 1614 cm^{-1} assigned to –C=N-, created by the reaction of ethylene diamine's amine (-NH2) and carbonyl-group (-C=O) of 2-hydroxyl-benzaldehyde. The hydroxyl group was attributed to a strong band in the FT-IR spectra of SB in the range of 3578-3450 cm^{-1} (-OH). The absorption bands at 3086, 1588 and 1436 cm-1 were attributed to the carbon-hydrogen and aromatic carbon-carbon (C=C) double bonds correspondingly, while the absorption band at 1249 cm^{-1} was attributed to a carbonyl group. The existence, absence, and shifting of certain bands in FT-IR analysis determined the active preparation of SBs and their metal complexes. The absence of a vibration band for –OH vibration at 1614 cm-1 and the occurrence of a new band in the series of 659-586 cm^{-1} were due to the formation of metal complexes, confirming their synthesis [23]. Further groups at 536-516 cm^{-1} and 439-406 cm^{-1} are attributable to metal-chloride band, and imin- nitrogen similar by metal ion (N →M) as well confirmed the successful synthesis of metal complexes [24]. The shifting of the band for the imine group (-C=N-) to a lower wave number due to the shifting of electron density from

Nitrogen to metals ions in the FT-IR spectra of metal complexes is a clear confirmation of metal nonmetal coherence and production of metal complexes.

3.3 Anti-bacterial action

The synthesized compounds were dissolved in DMSO with a 1:10 ratio to test the biological activity of SB and its metal complexes. After 24 hours of incubation at 37°C, the diameter of IZ is visually determined. The PC was Ciprofloxacin, and the NC was DMSO.

3.4 Antibacterial activity of synthesized compounds against *Escherichia coli, streptococcus and Bacillus cereus*

By using the good diffusion process, the SB and its metal complexes were added to the cultures above. The synthesized complexes were effective against *E. coli* and *Bacillus cereus*, but had no effect on *Streptococcus* growth, which was unaffected by any metal complexes except SB, which has negligible activity. The IZ measures are tabulated in table 4.

Table 1: Titles, empirical and structural formulation of SBs and respective metal complexes

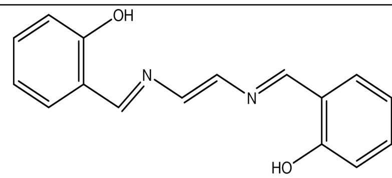
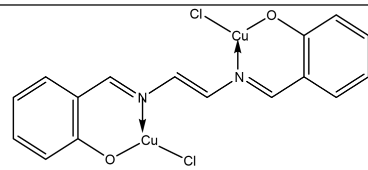
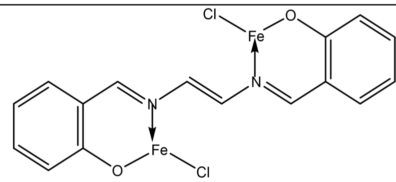
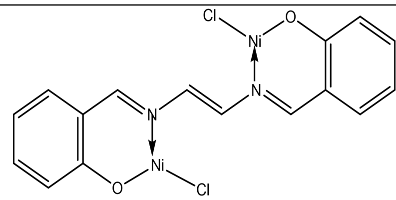
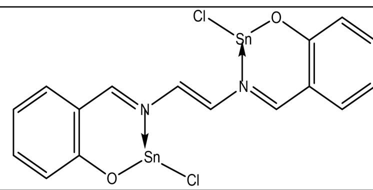
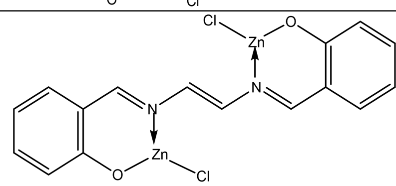
Serial	Titles	Empirical formulation	Structural formulation
1	2, 2'- (1E,1E)- (ethane- 1,2-diylbis(azan-1yl-1-ylidene)bis-(methan-1yl-1ylidene)-diphenol	$C_{16}H_{14}N_2O_2$	
2	(2- (E-(2- (E- 2-hydroxy benzalieneamine)ethylimino)methyl) phenoxy)di-cupper (II) di-chloride	$C_{16}H_{12}C_{12}Cu_2N_2O_2$	
3	(2-(E-(2-(E-2-hydroxybenzalieneamine)-ethylimino)methyl)phenoxy)di-iron (II) di-chloride	$C_{16}H_{12}C_{12}Fe_2N_2O_2$	
4	(2-(E-(2-(E-2-hydroxybenzalieneamine)-ethylimino)methyl) phenoxy)di-nickel (II) dichloride	$C_{16}H_{12}C_{12}Ni_2N_2O_2$	
5	(2-(E-(2- (E-2-hydroxybenzalieneamine)-ethylimino)methyl)phenoxy)di-tin (II) dichloride	$C_{16}H_{12}C_{12}Sn_2N_2O_2$	
6	(2-(E- (2-(E-2-hydroxybenzalieneamine)-ethylimino)methyl)phenox) di-zinc (II) dichloride	$C_{16}H_{12}C_{12}Zn_2N_2O_2$	

Table 2: SBs and their metal complexes physical parameters

Serial	Molecular-Formulas	Physical-state	Color	Molecular weight(g/mol)	Melting point(˚C)	Yield%
1	$C_{16}H_{14}N_2O_2$	Solid	Yellowish	227.28	114-116	88
2	$C_{16}H_{12}C_{12}Cu_2N_2O_2$	Solid	Light blue	462.26	234-236	77
3	$C_{16}H_{12}C_{12}Fe_2N_2O_2$	Solid	Brownish	446.83	292-294	72
4	$C_{16}H_{12}C_{12}Ni_2N_2O_2$	Solid	Green	452.58	268-270	76
5	$C_{16}H_{12}C_{12}Sn_2N_2O_2$	Solid	White	573.56	207-209	68
6	$C_{16}H_{12}C_{12}Zn_2N_2O_2$	Solid	White	466.02	228-230	77

Table 3: FT-IR statistics of SBs and their metal complexes

S.No	Complexes	-O- H	=C –H Aro	-C= N	-C =C Aro	=C –O	M –O	M- N	N→ M
1	SB	3579-3451	3086	1614	1589 1437	1249			
2	Cu(ll)	-	3095	1598	1539 1406	1227	586	516	406
3	Fe(ll)	-	3109	1586	1545 1391	1231	616	551	439
4	Ni(ll)	-	3131	1571	1569 1376	1211	659	511	426
5	Sn(ll)	-	3111	1585	1581 1372	1222	650	536	411
6	Zn(ll)		3127	1579	1576 1381	1216	631	523	416

Table 4: IZ of synthesized complexes against *E. coli, streptococcus and bacillus cereus*

Esherichia Coli				
Serial	**Complexes**	**Dilution 1:10**	**Ciprofloxacin(Positive control)**	**DMSO(Negative control)**
1	SB	6mm	19.6mm	0 mm
2	Cu- complex	4.4mm		
3	Fe-Complex	Resistant		
4	Ni-complex	3.7mm		
5	Sn-complex	Resistant		
6	Zn-complex	4.2mm		
Streptococcus				
1	SB	0.5mm	14mm	0mm
2	Cu-complex	Resistant		
3	Fe-complex	Resistant		
4	Ni-complex	Resistant		
5	Sn-complex	Resistant		
6	Zn-complex	Resistant		
Bacillus Cereus				
1	SB	5.1mm	15.4mm	0mm
2	Cu-complex	2.7mm		
3	Fe-complex	6.7mm		
4	Ni-complex	4.1mm		
5	Sn-complex	3.7mm		
6	Zn-complex	5.2mm		

Table 5: IZ of SBs and its metal complexes against *Staphylococcus Aureus, pseudomonas aeuroginosa and salmonella typhi*

Staphylo-coccus aureus				
Serial	**Complexes**	**Dilution 1:10**	**Ciprofloxacin (Positive control)**	**DMSO (Negative control)**
1	SB	3.1mm	15.6mm	0mm
2	Cu-complex	6.3mm		
3	Fe-complex	3mm		
4	Ni-complex	2.3mm		
5	Sn-complex	2.6mm		
6	Zn-complex	4.3mm		
Pseudomonas aeuroginosa				
1	SB	3.2mm	16.3mm	0mm
2	Cu-complex	3.1mm		
3	Fe-complex	7.3mm		
4	Ni-complex	2.3mm		
5	Sn-complex	4mm		
6	Zn-complex	3mm		
Salmonella typhi				
1	SB	3.7mm	12.4mm	0mm
2	Cu-complex	4.5mm		
3	Fe-complex	7.1mm		
4	Ni-complex	3.2mm		
5	Sn-complex	3.4mm		
6	Zn-complex	2.7mm		

The copper complex has high activity against *staphylococcus aureus*, followed by zinc complex, and Ni complex has low activity, while the iron complex has high activity against *Pseudomonas aeuroginosa* and *salmonella typhi*, as shown in Table 5.

The Agar well diffusion method was used to design an in-vitro antibacterial study of SBs and their metal complexes for some specific bacteria [25].

The impact of the synthesized SBs and their metal complexes against the growth of *streptococcus* was negligible; however marginal activity shown by some SBs was greatly dependent on the central metal atoms upon coordination with SB against *Bacillus Anthraces.* After reacting iron with SB, the activity of the iron complex increased, while the zinc complex has the same activity as pristine SB. The cell wall surrounded by a lipid membrane favored the route of lipid-soluble constituents which is a vital aspect of controlling anti-microbial action. The IZ showed that the copper complex has the highest activity against *Staphylococcus aureus*, followed by the Zinc complex, and Ni complex has the lowest activity among the synthesized compounds. The iron complex possesses high activity as related to other synthesized compounds upon exposure to *Pseudomonas aeruginosa*. The activity of SB was enhanced by coordinating Fe and Sn metals while it remained unaffected by the addition of other metal ions.

SBs and their metal complexes inhibited the growth of *Salmonella typhi* as iron complex has high activity with IZ of 7mm followed by copper complex with IZ 4.3 mm while zinc complex with 2.6 mm IZ has the least activity. The coordination of SB with transition metal complexes is the main reason for the increased activity [26]. The different variations in the activity of complexes may be due to the impermeability of microbe's cells or can be the difference in ribosomes in microbial cells [27].

4. CONCLUSION

This study focused on the synthesis of SBs and their metal complexes which were in turn applied for the treatment of various pathogenic bacteria as tested by standard biotic cultures and their results were compared with standard antibiotics (Ciprofloxacin). With the exception of *streptococcus*, which showed resistance, the SBs and their metal complexes exhibited strong anti-bacterial activity against selected bacteria. Metal complexes synthesized with SBs may be a feasible alternative to currently available antibiotics.

Authors Contribution

M.J and M.H supervised the research work and has the main idea and wrote the manuscript. ZY and ZQ revised the manuscript and provided suggestions.

Conflicts of Interest

The authors declare no conflict of interest. All the authors approved the submission of the manuscript.

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Data Availability statement

The data presented in this study are available on request from the corresponding author.

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