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NATURAL ACID-CATALYZED SYNTHESIS OF 6,6'-(((3,3'-DIMETHOXY-[1,1'-BIPHENYL]-4,4'-DIYL)BIS(AZANYLYLIDENE))BIS(METHANYLYLIDENE))BIS(2,4-DICHLOROPHENOL), ITS CONVENTIONALLY SYNTHESIZED METAL COMPLEXES AND THEIR POTENTIAL AS BIOLOGICAL AGENTS

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ABSTRACT

Organic research has recently focused on the development of a more environmentally friendly process that uses alternate reaction media in place of harmful and expensive catalysts. So here a facile protocol was developed for the green synthesis of a novel Schiff base ligand, and the synthesized ligand was characterized using physicochemical techniques. The homobinuclear complexes of synthesized ligands made of Iron (II), Cobalt (II), Manganese (II), Nickel (II), Zinc (II), and Copper (II) were characterized through the FTIR technique after synthesizing them conventionally. The *in-vitro* antimicrobial and antioxidant activities were examined for all the synthesized compounds.

Keywords: Schiff Base; Lemon Juice; Spectral Characterization; Antimicrobial; and Antioxidant.

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INTRODUCTION

The most essential role of green chemistry in synthetic chemistry is to optimize reaction product yield while minimizing side products without utilizing any hazardous chemicals and under particular reaction circumstances, allowing for the least amount of environmental harm.[1–5] Many techniques for the synthesis of Schiff base have been published; however, we want to use eco-friendly procedures and reagents that provide a better yield of product.[6–13] So, here the Schiff base was synthesized by using less organic solvent and acid present in naturally available fruit juice as a biocatalyst in the condensation reaction of 3,5-dichloro salicylaldehyde and o-dianisidine, and the synthesized ligand was characterized using Fourier transform infrared spectroscopy (FTIR), ^{1}H and ^{13}C-Nuclear magnetic resonance (NMR), and Mass spectrometry.[14–19]

Furthermore, we synthesized Cobalt (II), Nickel (II), Zinc (II), Iron (III), Copper (II), and Manganese (II) complexes of ligand using the conventional method and analyzed them by using FTIR. All the synthesized compounds were also investigated for antibacterial and antioxidant efficacy.[20–22]

As a result; the goal of this work is to examine the green synthesis, antioxidant, and antimicrobial properties of the ligand and its complexes with different metals.

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EXPERIMENTAL

Material and Methods

We used all analytical-grade chemicals and solvents exactly as they were provided to us. Using Analab's melting point apparatus the melting point of the synthesized compounds was determined. TLC was used to assess the compound's purity. IR spectra were collected on a PerkinElmer FTIR L160000T spectrometer. The ^{1}H-NMR and ^{13}C-NMR spectra were captured using a JEOL ECZ600R operating at 600 MHz. Mass spectrometry was measured using a Shimadzu LC-MS/MS 8050. Agar well diffusion method was used to determine the antimicrobial activity of the synthesized compounds and their antioxidant activity was tested by following DPPH (1,1- diphenyl picrylhydrazyl) radical scavenging assay and Ferric reducing antioxidant property assay (FRAP).

Green Synthesis of Schiff Base Ligand

3,5-dichloro salicylaldehyde was diluted in a small amount of 100% ethanol and added drop wise while stirring to a beaker containing a solution of 2-dianisidine (5 mmol) in ethanol and then 2 ml of lemon juice was added to this reaction mixture. The reaction mixture was properly mixed by stirring and then allowed to stand at room temperature for about 10 minutes. When 3, 5-dichloro salicylaldehyde and 2-dianisidine reacted a solid orange colored product (SB) was observed. It was then filtered and washed with ethanol and it was recrystallized using DMSO. TLC was carried out using ethyl acetate and hexane (7:3) as a solvent system to monitor the reaction. The product was discovered to be soluble in DMF, DMSO and THF. The synthesis of the ligand is as shown in Fig.-1.

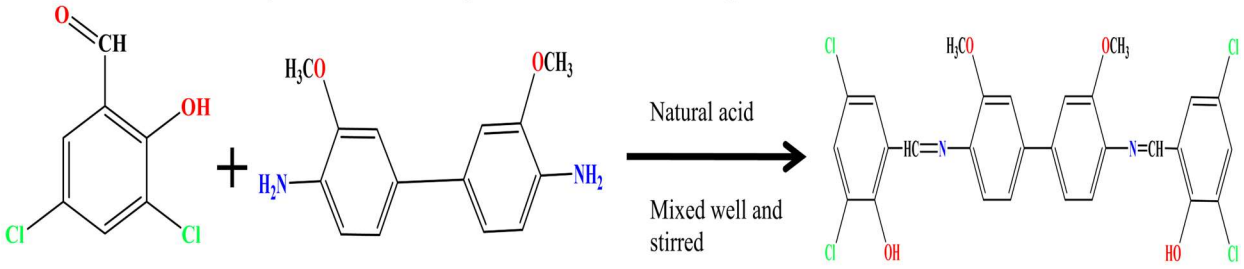


Fig.-1: Synthesis of Schiff Base Ligand Via Green Synthesis (SB)

General Procedure for the Synthesis of Metallic Complexes of Synthesized Ligand

All of the complexes were made by dissolving a (4.0 mmol) sample of hydrated MCl_2 (metal chlorides) in hot water (3 ml) and then adding it to a hot Schiff base (2.0 mmol) solution in DMF (3 ml). For 2 hours the reaction mixture was kept at a constant temperature of 80^0C in water bath. Following filtering the fine solid complexes were collected and given a hot ethanol wash followed by hot water and finally dried in a hot air oven. In the air the complexes were observed to stay stable. Figure-2 illustrates the general synthetic reaction for metal complexes of synthesized ligands.

Spectral Characterization

For the confirmation of the structure of the ligand and its metallic complexes the infrared spectrum of all the synthesized compounds was recorded in the range 450-4000 cm^{-1}. The ^{1}H-NMR and ^{13}C-NMR spectrums were measured in DMSO-d_6 for the structural confirmation of the ligand. Also, for validation of the synthesized ligand its mass spectrum was collected and studied.

Biological Activities

Antimicrobial Activity of Synthesized Compounds

Agar well diffusion assay was used to investigate the *in-vitro* bactericidal activity for all the synthesized compounds.[23–29] For the testing reference microbial species employed were *gram-positive* strains of *S. aureus* and *B. subtilis*, and *gram-negative* strains of *E. coli*.

Antioxidant Activities of Schiff Base Ligands

Free Radical Scavenging Activity

By using the DPPH assay the free radical scavenging activity was evaluated in vitro by taking different concentrations of compounds in the range of 10-1000 µg/ml.[30–33] Ascorbic acid was used as the standard.

Ferric Reducing Antioxidant Power (FRAP) Assay

The FRAP activity was measured in vitro by taking various concentrations of compounds (10-1000 µg/ml).[34–38] Ascorbic acid was employed as a reference standard and the sample mixture without the components was utilized as a control.

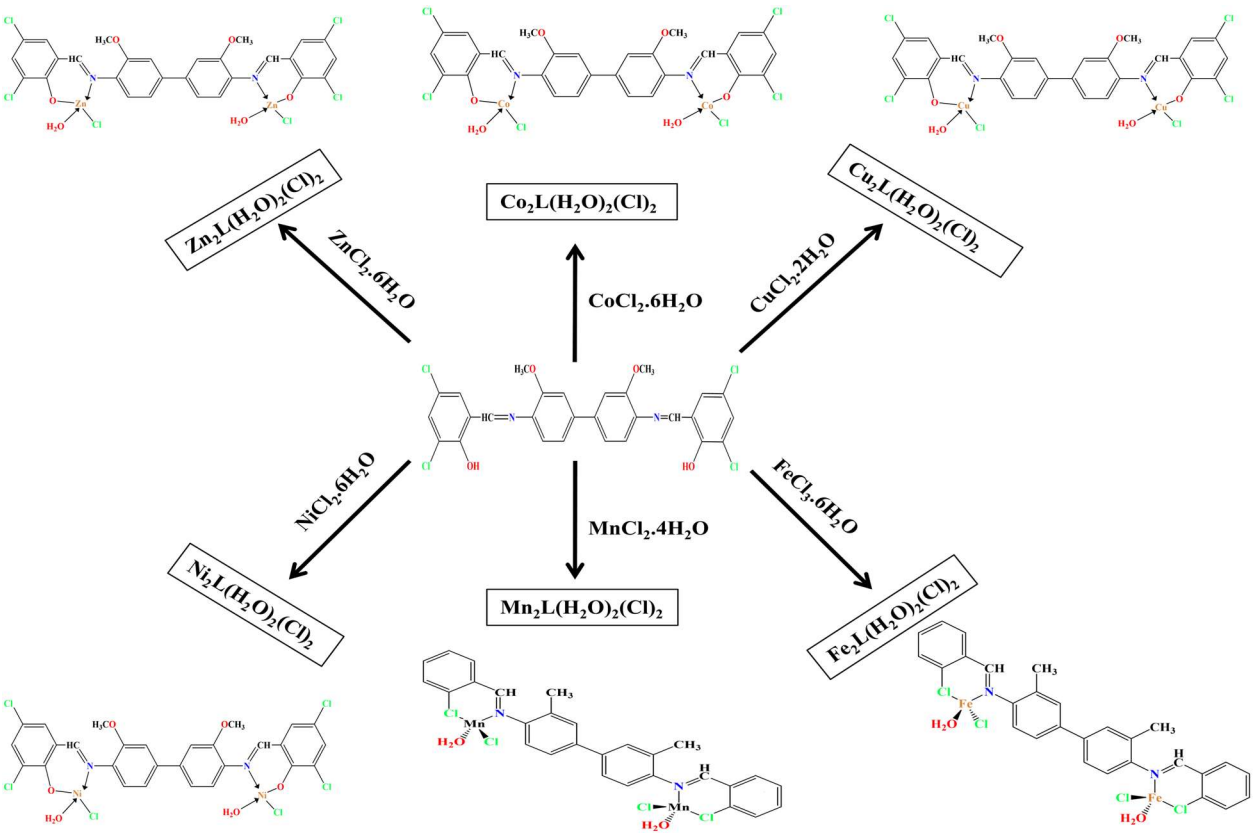
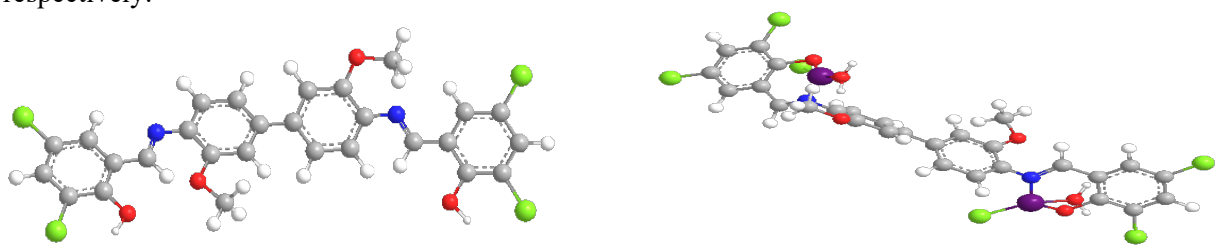


Fig.-2: Synthesis of Schiff Base Metal Complex

RESULTS AND DISCUSSION

The current ligand was produced by the condensation reaction between o-dianisidine and 3, 5-dichloro salicylaldehyde in a 1:2 molar ratio. To examine the structures of the produced Schiff bases ^{1}H NMR, IR, LC-MS/MS, and ^{13}C NMR were utilized also the structures of metallic complexes were confirmed by FTIR. Figure-3(a) and 3(b) represent probable structures for synthesized ligand and metal complex respectively.



3(a) 3(b)

Fig.-3(a): The Proposed 3D Structure of Schiff Base Ligand; 3(b) The Proposed 3D Structure of Metallic Complex [Ball and Stick Model: Red Ball- Oxygen; White Ball- Hydrogen; Violet Ball- Metal; Blue Ball- Nitrogen; Gray Ball- Carbon]

Table-1**:** Physical and Chemical Data of the Synthesized Compounds

Compound	Molecular formula	Molecular weight gm/mole	Colour	Melting point °C	Yield %
Schiff Base Ligand	$C_{28}H_{20}Cl_4N_2O_4$	590.28	Dark red	280	91 %
Cobalt Complex	$C_{28}H_{22}Cl_6Co_2N_2O_6$	813.06	Dark red	310	73 %
Copper Complex	$C_{28}H_{22}Cl_6Cu_2N_2O_6$	822.28	Black	320	79 %
Nickel Complex	$C_{28}H_{22}Cl_6Ni_2N_2O_6$	812.58	Red	300	72 %
Zinc Complex	$C_{28}H_{22}Cl_6Zn_2N_2O_6$	825.95	Dark red	308	77%
Iron Complex	$C_{28}H_{22}Cl_6Fe_2N_2O_6$	806.28	Dark brown	302	69 %
Manganese complex	$C_{28}H_{22}Cl_6Mn_2N_2O_6$	805.07	Dark black	340	74 %

Spectral Characterization Data of Synthesized Compounds

Table-2: ^{1}H-NMR and Mass Spectroscopy Data of Schiff Base Ligand

Compound	^{1}H-NMR	Mass
Schiff base ligand	HC=N (8.5 δ ppm),	m/z = 591
	-OCH_3(3.85 – 3.99),	
	Aromatic protons (7.30 – 7.74),	
	-OH (14.81)	

Table-3: IR Spectral Data for the Developed Compounds

Compound	C=N (cm^{-1})	O-H (cm^{-1})	v(C-O) (cm^{-1})	C-Cl (cm^{-1})	C-H (cm^{-1})	$H4_2O$ (cm^{-1})	Ph-N (cm^{-1})	M-N (cm^{-1})	M-O (cm^{-1})	M-Cl (cm^{-1})
Schiff base ligand	1617	1438	-	757	1720	-	1130	-	-	-
Cobalt complex	1549	-	1320	753	1767	3408	1125	564	645	469
Copper Complex	1551	-	1289	752	1820	3389	1110	582	657	483
Nickel Complex	1561	-	1315	755	1920	3367	1132	571	649	475
Zinc Complex	1555	-	1294	756	1789	3370	1129	569	651	486
Iron Complex	1543	-	1278	751	1865	3378	1123	573	655	498
Manganese complex	1556	-	1325	758	1790	3381	1126	578	661	493

Biological Activities

Antimicrobial Activity of Synthesized Compounds

Figure shows the zone of inhibition values in mm for synthesized ligands which were compared with the inhibition values of standard cefadroxil. Figure-4 shows the antibacterial activity zone of inhibition values for all the synthesized compounds. According to the findings Cobalt and copper complex exhibit the highest antibacterial activity. Schiff base and zinc complex have good antibacterial activity while the remaining complexes exhibit moderate to good antibacterial activity.

Antioxidant Activities of Schiff Base Ligands

Free Radical Scavenging Activity

Figure-5 shows IC_{50} values for all the compounds which are required to scavenge 50% of DPPH free radicals. The following formula was used to calculate the percentage of free radical scavenging or inhibition:

$$\%\ DPPH\ radical\ scavenging\ activity\ = \{(A0 - A1)/A0\} * 100$$

Where, A_0 = Absorbance of control, A_1= Absorbance of test with different concentrations

According to the graph the Zn complex has the highest level of scavenging activity as it requires 362.0 µg/ml to scavenge 50% of DPPH free radicals which is the lowest amount than the requirement of other remaining compounds. The remaining compounds exhibit good to moderate scavenging activity.

Ferric Reducing Antioxidant Power (FRAP) Assay

Figure-6 displays IC_{50} values for all the developed compounds for FRAP activity. The proportion of FRAP activity was calculated using the calculation shown below:

$$\%\ FRAP\ activity\ = \{1 - (A1/A0)\} * 100$$

Where, A0 = Absorbance of control, A1= Absorbance of test with different concentrations

The graph shows that the Zn complex exhibits the strongest FRAP activity because its IC_{50} value is 377.7 µg/ml which is lower than that of the other compounds. The compounds other than the Zn complex have good to moderate FRAP activity.

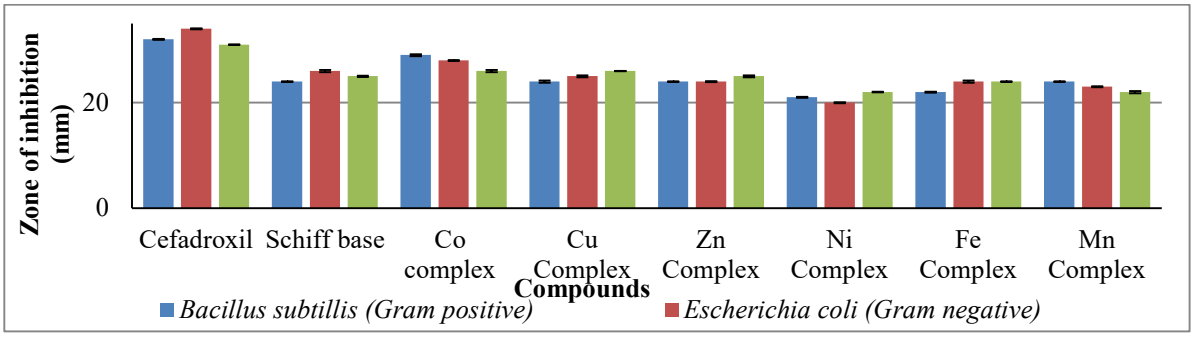


Fig.-4: Antibacterial Activity Zone of Inhibition Values of Schiff Base Ligand and its Metallic Complexes

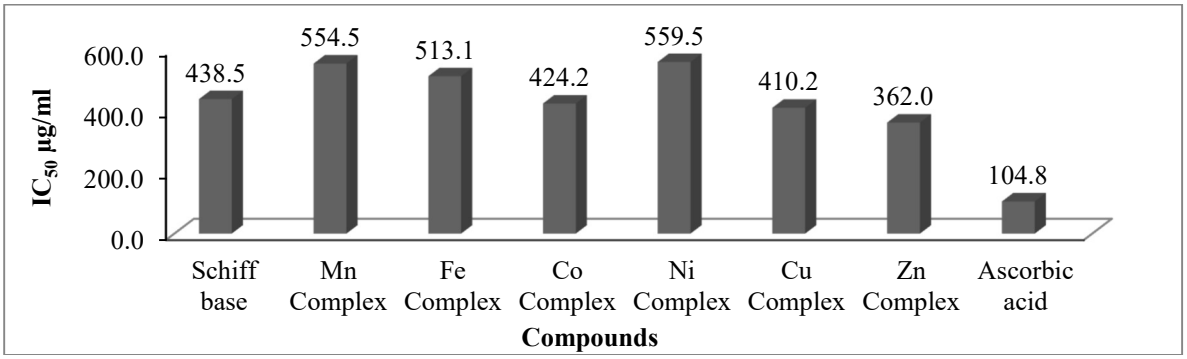


Fig.-5: DPPH Radical Scavenging Activity IC_{50} Values for Schiff Base and its Metal Complexes

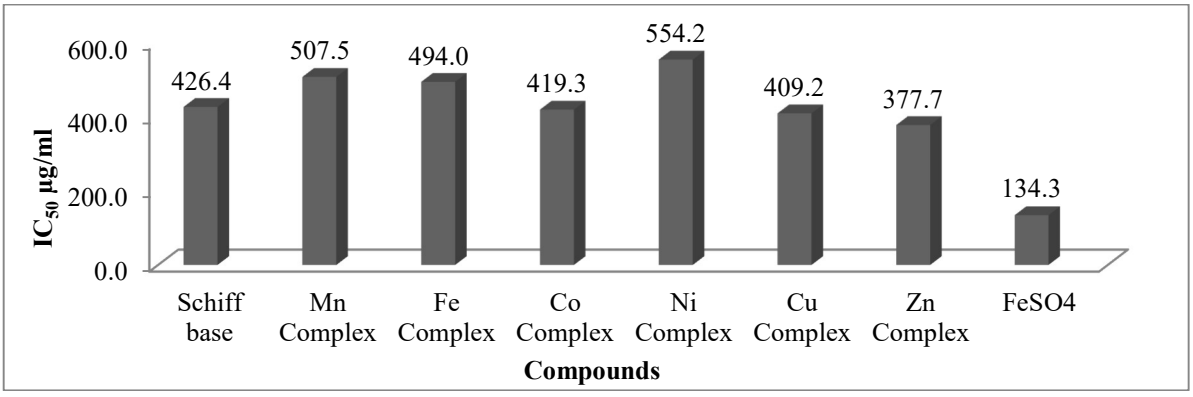


Fig.-6: FRAP Activity IC_{50} Values for Schiff Base and its Metal Complexes

SAR Studies (Structure-Activity Relation)

All the synthesized compounds showed remarkable radical scavenging activity in DPPH and FRAP assays. The inclusion of hydroxy and chloro groups in the aromatic ring may account for the ligand's significant antioxidant activity, which increased with the addition of different metals. Further in the antimicrobial activity investigation, all the compounds showed the significant antimicrobial property. Due to the chlorine group that is present in the aromatic ring, the ligand has good antibacterial activity, and this activity may improve further with the addition of metals. The cobalt, copper, and zinc complexes have potent antibacterial properties, with the cobalt complex displaying the highest level of activity. Even though the basic structure of the Schiff bases is the same in all the compounds, the investigation of their structure-bioactivity relationship it reveals that different substituents present in the phenyl ring influences a massive impact on their biological and physical properties.

CONCLUSION

The researchers found an innovative and environmentally friendly method for producing Schiff bases using lemon juice as a catalyst. Since the method used in this work uses moderate reaction conditions and just minimal experimental setup to provide useful findings, it is safer, cleaner, and more ecologically friendly. Clean reaction profiles, a lack of side reactions, waste minimization, straightforward experimental methodologies, cost-effectiveness, and commercial availability are all advantages of this research work. Moreover, the developed compounds bear excellent to moderate antimicrobial and antioxidant activities.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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