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PREPARATION, CHARACTERIZATION, AND BIOLOGICAL RELEVANCE OF Co, Ni, and Zn COMPLEXES DERIVED FROM 6,6'-((1*E*,1'*E*)-((1,3-PHENYLENEBIS(METHYLENE)) BIS(AZANYLYLIDENE))BIS(METHANYLYIDENE))-BIS(2,4-DIBROMOPHENOL)

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ABSTRACT

Synthesis of three metal complexes, Co(II), Ni(II),and Zn(II) by using novel Schiff base as 6,6'((1E,l'E)-((1,3phenylenebis(methylene))bis(azanylylidene))bis(methanylylidene))bis(2,4dibromophenol).All these complexes were characterized using ^{1}H NMR, FTIR, XRD, and TGA. The Complexes synthesized metal ion: ligand ratio 1:1.The Schiff base ligand and their metal complexes were screened for antibacterial, and antifungal activity tested, and compared with the standard. The anticancer activity of Schiff base and their metal complexes tested against MCF -7 human breast cell line shows moderate to good activity. The antioxidant activity of Schiff bases and metal complex tested shows moderate activity.

Keywords: Schiff Base, Metal Complexes, XRD, TGA, Antimicrobial, Anticancer, Antioxidant Activity.
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INTRODUCTION

The Azomethine group of Schiff bases contains a lone pair of electronsin the sp^2 hybridized orbital of a nitrogen atom. Schiff bases in combination with one or more donor atoms close to the azomethine group have good chelating ability. Schiff bases are proven as interesting ligands in coordination chemistry.[1,2] Schiff bases are important compounds owing to their wide range of biological activities and industrial applications. They have been found to possess pharmacological activities such as antibacterial[3-7] antifungal,[8] anticancer,[9] anti-HIV,[10]antitubercular,[11]antiviral,[12]anti-inflammatory,[14]anticonvulsant[14],andantimalarial.[15]Metalcomplexes of Schiff bases are used as catalysts in various organic transformations.[16]The survey of this literature studied that several synthesized Schiff bases with substituted salicylaldehyde, aromatic and aliphatic amines have been prepared.[17,18] However literature study reveals that less work has been done with present Co(II),Ni(II), and Zn(II) complexes of Schiff bases prepared from substituted salicylaldehyde with a meta-xylene diamine. In the present work, we synthesized a novel Schiff base prepared from the condensation of substituted salicylaldehyde with meta xylylidene amine and its metal complexes like Co(II), Ni(II),and Zn(II). All the synthesized metal complexes are characterized by spectral techniques. We also studied their antimicrobial, anticancer, and antioxidant activity.

EXPERIMENTAL

Materials and Methods

All reagents were purchased from SD fine and used without further purification. Melting points of the products were determined on a digital melting point apparatus (Optics Technology) using capillaries open

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at one end and were uncorrected. Progress of the reaction was monitored on silica gel-coatedaluminum thin-layer chromatography (TLC) plates. Visualization was made with UV light (254nm and 365nm). The IR spectra of synthesized compounds were recorded on a Bruket IFS 66V spectrometer with KBr pellets. ^{1}H NMR spectrums were recorded on a BRUCKUR 400 MHz spectrometer using TMS as an internal standard. Mass spectrums of ligands were recorded on the VG 7070H mass spectrometer.

General Procedure for the Synthesis of Schiff Bases

The new Schiff bases were synthesized by condensing the substituted salicylaldehyde with m-xylene diamine in (2:1). The mixture was dissolved in 15-20 mL ethanol and added 2-3 drops of acetic acid, heated under reflux conditions for 3 hr. The yellow color precipitate was obtained and filtered. The yellow product was purified by recrystallization from hot ethanol.[19]

Spectral Analysis of Schiff Base

6,6^1-((1*E*,1'*E*)-((l,3-phenylenebis(methylene))bis(azanylylidene))bis(methanylylidene))bis(2,4-di-bromophenol):-

Yield 68 %; MP. - 150°C; FT-IR (KBr, cm-^{1}): - 3036, 1659, 1589, 127l. ^{1}H-NMR (400 MHz, DMSO-d_6): - δH 8.13 (s, 2H, Ar-OH), δH 7.25 - 7.68 (m, 10H, Ar-H), δH 8.38 (s, 2H,-CH=),δH 4.80 (s,2H,-CH_2- N). ^{13}C-NMR (DMSO-d_6): - δC 163.08(-CH=N), δC 161.34, δC 126.56 (phenyl), δC 52.06 (-CH_2-N). (+) ESI-HRMS m/z: calculated for [$C_{22}H_{16}BuN_2O_2$] 599.99; observed for [$C_{22}H_{16}BuN_2O_2$] 560.

Where-M=Metal (Co, Ni, Zn), R^1 = Br, R^2 = H, R^3 = Br

Spectral Analysis of Metal Complex of Cobalt

Yield 56 %; MP. - 348°C, FT-IR (KBr, cm-^{1}): - 3418, 2283, 1605, 1436, 1150, 576. ^{1}H-NMR (400 MHz, DMSO-d_6): - δH 8.30 (s, 2H, HC=), δH 7.9 - 7.2 (m, 10H, Ar-H), δH 4.83 (s, 2H, - CH2-N). (+) ESI-HRMS m/z: calculated for [$C_{22}H_{14}O_2N_2Br_4Co$] 712; observed for [$C_{22}H_{14}O_2N_2Br_4Co$] 712.71.

Spectral Analysis of the Metal Complex of Nickel

Yield 62 %; MP. - 360°C, FT-IR (KBr, cm-^{1}): - 3415, 2360, 1613, 1431, 1219, 592. ^{1}H-NMR (400 MHz, DMSO-d_6): - δH 8.13 (s, 2H, HC=N), δH 7.9-7.3 (m, 10H, Ar-H), δH 4.13 (s, 2H, -CH2-N). (+) ESI-HRMS m/z: calculated for [$C_{22}H_{14}O_2N_2Br_4Ni$] 711; observed for [$C_{22}H_{14}O_2N_2Br_4Ni$] 711.71.

Spectral Analysis of Metal Complex of Zinc

Yield 68 %; MP. -282°C, FT-IR (KBr, cm-^{1}): - 3410, 2359, 1630, 1445, 1290, 685. ^{1}H-NMR (400 MHz, DMSO-d_6): - δH 9.73 (s, 2H, HC=), δH 7.9 - 7.3 (m, 10H, Ar-H), δH 4.92 (s, 2H, -CH2-N). MF, C22H14O_2NiBr$_4$Zn (+) ESI-HRMS m/z: calculated for [$C_{22}H_{14}O_2N_2Br_4Zn$] 717; observed for [$C_{22}H_{14}O_2N_2Br_4Zn$] 717.71.

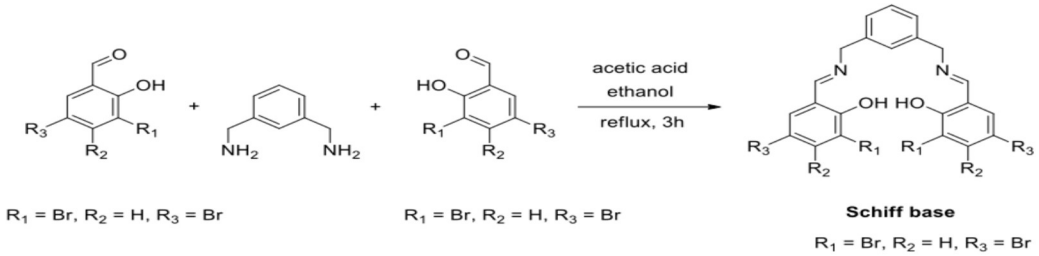
RESULTS AND DISCUSSION

Synthesis of Schiff bases containing metal complexes was carried out by the process described below. The Schiff base ligand (10 mmol) was dissolved in 20 mL absolute ethanol. A metal salt (10 mmol) solution in 30 mL absolute ethanol was added into the above Schiff base ligand solution under constant stirring. The reaction metal-ligand molar ratio was 1:1 in all the cases. The resultant reaction mixture was refluxed for 3 hr, and a precipitated product was obtained. The red-brown colored filtered product was dried at room temperature.

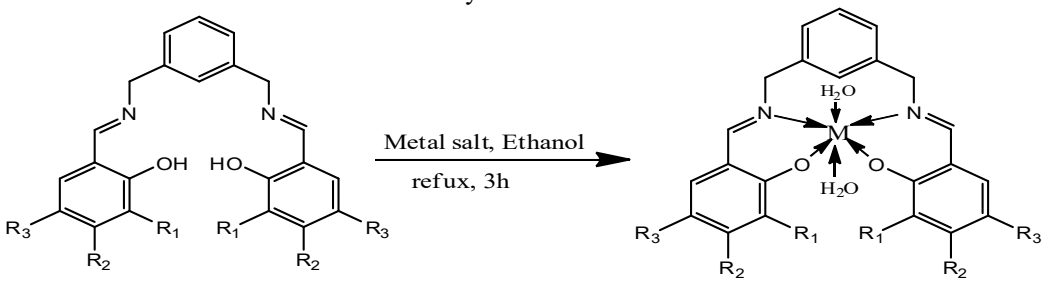
XRD Analysis

The XRD analysis study synthesized transition metal complexes that were used to determine the particle size of complexes and by using this XRD study to determine their nature, finding the possibility of the crystalline amorphous compound. The particle size of prepared complexes was calculated by using Scherer's formula D=Kλ/βcosθ, where K is constant and the value is 0.94, D is particle size, λ is wavelength X-ray radiation, β is the full width at half maximum of the peak and θ is diffraction angle. The interplanar spacing d is calculated by using Bragg's equation nλ=2dsinθ.

The mean particle size of the complex is in the range of 6.19 to 60.93 nm. All the XRD patterns of the complex show a sharp crystalline peak.[20]



Scheme-1: Synthesis of Schiff Base



Scheme-2: Synthesis of Metal Complex

Thermal Analysis

Thermal analysis study of synthesized complexes was carried out using a TGA thermograph or curve. TGA curves of all complexes exhibited weight loss in two or three different steps. In the first steps loss of coordinated water molecules was observed at 120 to 200°C. The second major weight loss was observed because of bromides and organic moiety and in the last step, 25-40 % weight loss was observed beyond 450°C due to loss of Schiff base. The metal oxide was lost finally beyond 650 °C temperature. All the complexes were found to be thermally stable compounds.[21]

Table-1

	Complex Reflexes	20	FWHM	D in mm	D is location Density	Micro strain	Relative intensity
L2M 1	Peak 1	8.3152	0.1586	50.24	3.961E-04	6.899E-04	42.96
	Peak 2	9.7098	0.4884	l6.33	3.749E-03	2.122E-03	41.37
	Peak 3	13.2908	0.2l18	37.78	7.00?E-04	9..175E-04	45.16
	Peak 4	14.58	0.1315	60.93	2.694E-04	5.689E-04	100
	Peak 5	18.74	0.501	16.08	3.869E-03	2.156E-03	62.98
	Peak 6	20.26	0.7039	11.47	7.602E-03	3.022E-03	74.55
	Peak 7	22.33	0.5465	14.82	4.551E-03	2.338E-03	82.92
	Peak 8	23.38	1.3105	6.19	2.607E-02	5.597E-03	82.57
	Peak 9	25.39	0.2003	40.67	6.045£-04	8.522E-04	82.71
	Peak 10	27.34	0.4411	18.54	2.908E-03	1.869E-04	65.67
	Peak 11	31.68	0.4634	17.83	3.147E-03	1.944E-03	54.13

Biological Activity

Antibacterial *(E.coli, B. subtilis, S. typhiand S. aureus)* activity was evaluated by agar cup method. Diameter zone of inhibition in mm for antibacterial activity data Table-2.

Table-2: Antimicrobial Activity of Synthesized Compounds

Entry		*E.coil*	*B.subtilis*	*S. Typhi*	*S.aureus*
I	Schiff base	12	15	13	15
2	The metalcomplex of cobalt	04	07	07	10
3	The metal complex of Nickel	03	06	04	07

4	The metal complex of zinc	05	05	05	06
5	Standard	08	25	21	30

Ligands: - ve, no. antibacterial activity, Zone of inhibition in mm

Anticancer Activity of Synthesized Compounds Against MCF-7 Cell Line (Human Breast Cancer)

The anticancer activity of synthesized compounds against the MCF-7 cell line [16-17] (human breast cancer) was shown above in Table-3.

Table-3: Anticancer Activity of Synthesizes Schiff Base & Metal Complex Compounds Against MCF-7 Cell Line (In Human Breast Cancer)

Entry	Sample Code	% Inhibition
I	Control	-
2	Standard(5 FU20ug/ml)	52.48
3	SchiffbaseorL2	09.38
4	L2M1	94.57
5	L2M2	85.81
6	L2M3	86.68

Antioxidant (DPPH Radical Scavenging Activity)

Molecule1,l-diphenyl-2-picrylhydrazyl (α,α-diphenyl-picrylhydrazyl;DPPH) is characterized as a stable free radical by virtue of the delocalization of this electron over the molecule as a whole, so that the molecule does not dimerize, as would be the case with most other free radicals. The delocalization of electrons also gives rise to the deep violet color, characterized by an absorption band in ethanol solution centered at about 517 nm. When a solution of DPPH is mixed with that of a substrate (AH) that can donate a hydrogen atom, then this gives to the reduced form with the loss of this violet color. The ability of these compounds to scavenge DPPH radical was assessed using Manzocco and Sambath Kumar method[22] with modification. Briefly, 1 mL of synthesized compounds as l mM was mixed with 3.0 m MDPPH (0.5 mmol/L in methanol), and the resultant absorbance was recorded at 517 nm after 30 min incubation at 37 °C. The percentage of antioxidant or radical scavenging activity was calculated by using the following formula.[20-21]Antioxidant activity (%) = [(AC-AS)/ AC] x I00 where AC is the absorbance of DPPH and AS is the absorbance reaction mixture (DPPH with sample). The antioxidant activities of the schiff bases are expressed in comparison with ascorbic acid as standard. Antioxidant activity of Schiff base showed poor activity compounds compared to that of standard (ascorbic acid) the results are reported in Table-4.

Table-4: Antioxidant Activity of Synthesized Compounds of Schiff Base and Metal Complex

S.No.	Sample Code	ABSat 517 nm	Activity (%)
I	Blank	1.43	-
2	Standard	0.13	90.90
3	Schiff base	0.39	37.06
4	L2Ml	0.423	ND
5	L2M2	0.333	8.38
6	L2M3	0.337	17.40

The Schiff bases were obtained in good yields from the condensation reaction of halo-substituted salicylaldehyde and m- xylylene diamine (Scheme-l)and purified by hot ethanol. The purity of the compound was checked by TLC. The compounds were characterized by ^{1}HNMR and structures of the Schiff bases were elucidated on the basis of spectroscopic data. The molecular ion peaks in the mass spectra of Schiff bases conformed to the calculated molecular masses. In IR spectra of the compound serves the disappearance of the band about 1700cm^{-1} attributed to the carbonyl group (C=O) and the appearance of a band in the region 1659-1607 cm^{-1}assigned to the azomethine (HC=N) band thereby indicating the formation of the Schiff bases. The characteristic band in the region3082-2979 cm-^{1}is assigned to phenolic (OH)with intermolecular N-HO hydrogen bonding. The H_2C-N bands are observed in the region at 1285-1208cm^{-1}.^{1}H-NMR spectra of Schiff bases showed a singlet at8.13ppm originating from the phenolic OH, azomethine proton (HC=N) appeared

at its expected value of 8.49-8.23 ppm, and (H_2C-N) appeared at its expected value4.83-4.72 ppm, while the azomethine carbon resonated at about 163.08-165.78 ppm in ^{13}C-NMR spectra. The IR spectrum of Schiff base shows OH stretching at 3036 cm-^{1}whereas complex molecules show it around 3400 cm^{-1}. In IR spectra of the Schiff base-metal complex molecule shows a new metal-N coordinate bond stretching at 657 cm^{-1}. Therefore, the Schiff base-metal complex structure is confirmed. In ^{1}HNMR spectra azomethine proton (HC=N) appeared at its expected value of 8.49-8.23 ppm in the Schiff base and in a metal complex of cobalt is 9.72 ppm. There is a downfield shift in the complex as compared to the Schiff base ligand in ^{1}H NMR spectrums. So, the structure is confirmed by H^{1} NMR spectra.The results show that the Schiff base compound shows significant activity against *B. subtilis, S. typhi,S. aureus,* and *E.colias* compared with standard, and metal complexes show moderate activity as compared with standard. All synthesized Schiff bases were screened for their antioxidant activity. DPPH assay was performed to messmate the ability of the Schiff bases to scavenge the DPPH free radicals. The color change produced by free radical scavenging, results in a change in absorbance. Among these compounds, Schiff base and prepared metal complexes show poor activity. But the metal complex of cobalt does not show activity as compared to the standard. The results are summarized in Table-3. The Schiff base and metal complex of cobalt also shows the anticancer activity of human beings of especially the MCF-7 cell line i.e., breast cancer result shows that Schiff base shows poor activity but metal complexes show good activity as compared with the standard cell lines.

CONCLUSION

In the present study, we synthesized new Schiff base and their metal complex with cobalt and they were characterized through elemental analysis, melting point, IR, ^{1}H NMR, and ^{13}CNMR spectroscopic technique, from this data, structures of Schiff base have been confirmed. The results indicate mild to moderate antibacterial activity. The Schiff base compounds showed significant activity & metal complex showed poor activity as compared to the Schiff base. Synthesized Schiff base& metal complex were screened for their antioxidant activity. The result was not good for a metal complex of cobalt but the Schiff base have a good result as compared to the standard. The Schiff base shows very poor activity & metal complexes show significant anticancer activity as compared with the standard.

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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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[RJC- 8220/2022]