

Preparation, characterization and biological relevance of Cr,Mn and Cu complexes synthesized from 6,6'-((1E,1'E)-((1,3-phenylenebis(methylene))bis(azanylylidene))bis(methanylylidene))bis(2,4-dibromophenol)

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Abstract

A synthesis of transition metal complexes of Cr (II), Mn (II) and Cu (II) from 6,6'-((1E,1'E)-((1,3-phenylenebis(methylene))bis(azanylylidene))bis(methanylylidene))bis(2,4-dibromophenol) have been synthesized and characterized by ¹H NMR, IR spectral studies. FTIR spectra confirms that the ligand co-ordinates metal ion to form complex via oxygen and nitrogen atom of the phenolic group and azomethine group respectively. The spectroscopic studies suggested the octahedral structure of Chromium complex, Mn Complex, and Copper Complex have square planar structure. The spectroscopic data of complexes is in agreement with their structure in which N₂O₂ group act as tetra-dentate ligand and two chlorides as a mono-dentate ligands.

Keywords: Transition metal complex, Schiff base ligand, Characterization

Introduction

More than 150 years ago Hugo Schiff prepared compounds with azomethine group by condensation of primary amine and carbonyl compound which are now a days commonly referred as Schiff bases [1]. Azomethine group of Schiff bases contain a lone pair of electrons in the sp² hybridized orbital of nitrogen atom. Schiff bases on combination with one or more donor atoms close azomethine group have good chelating ability. Schiff bases are proven as interesting ligands in coordination chemistry [2].

The Schiff bases are the 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, 6], antifungal [7], anticancer [8], anti-HIV [9], antitubercular [10], antiviral [11], antiinflammation [12], anticonvulsant [13] and antimalarial [14]. Metal complexes of Schiff bases are used as catalyst in various organic transformations [15].

The presence of various substituents in the phenyl rings of aromatic Schiff bases are responsible for antifungal activity, which changes depending upon the type of substituent present on the aromatic rings.

In view of these above biological importance of Schiff bases, we have synthesized some new Schiff bases and metal complexes of these novel Schiff bases and evaluated their bioactivity. New Schiff bases were synthesized by refluxing the reaction mixture of m-xylylene diamine with halogen substituted salicylaldehyde in ethanol in the presence of glacial acetic acid.

The entire synthesized compounds were characterized on the basis of their IR, ¹H NMR spectra and halogen, nitrogen analysis. The antibacterial activity of compound was evaluated by Agar cup method respectively. In this study Schiff base metal complexes are widely studied subject due to their industrial and biological applications. Literature reports suggest that some drugs show enhanced activity when administered as a metal complex rather than as an organic compound. The synthesis of novel Schiff bases complex becomes wide spread due to their potential application in chemistry, biochemistry, medicine.

Experimental

Materials and reagents

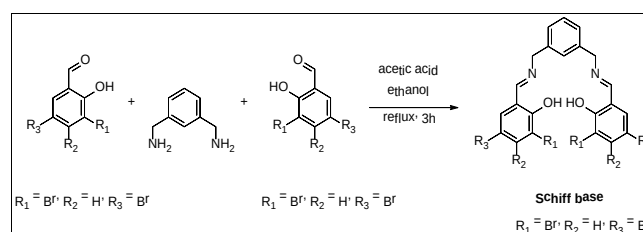
Chemicals like meta-xylylene diamine purchased from sigma Aldrich, salicylaldehyde from SD Fine and Cobalt salt from were used to prepare metal complex and other reagents were of analytical grade.

Physical measurements

The melting points were taken in open capillary tube and were uncorrected. The IR spectra of the compounds were recorded on a Bruker IFS 66V spectrometer with KBr pellets [1]. H NMR spectrums were recorded on a Gemini 200 MHz spectrometer using TMS as an internal standard and Mass spectra of ligand were recorded on VG 7070H mass spectrometer. The purity of the compounds was checked by TLC on silica gel plates and the spots were developed in iodine chamber.

Synthesis of Schiff base

The new Schiff bases were synthesized by condensing the substituted salicylaldehyde and m-xylylene diamine in a 2:1 proportion. The mixture was dissolved in 15-20 ml ethanol with the addition of 2-3 drops of acetic acid and heated under reflux condition for 3h. The yellow colour precipitate obtained was filtered. The yellow product was purified by recrystallization from hot ethanol.



Scheme: Synthesis of Schiff bases.

Spectral analysis of Schiff base

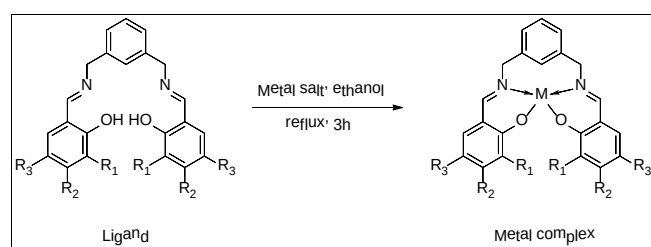
6,6'-((1*E*,1'*E*)-((1,3-phenylenebis(methylene))bis(azanylylidene))bis(methanylylidene)) bis(2,4-dibromophenol)

Yield 68%, mp 150 °C; IR (KBr) cm^{-1} : 3036 (OH), 1659 (HC=N), 1589 (C = C), 1271 ($\text{H}_2\text{C} - \text{N}$); ^1H NMR (CDCl_3) δ : 13.45 (2H, s, Ar – OH), 7.25- 7.68 (10H, m, Ar-H), 8.38 (s, 2H, -CH=N), 4.80 (s, 2H, - CH_2 -N). ^{13}C NMR (CDCl_3) δ ppm: 52.06 (- CH_2 -N), 126.56 (phenyl), 163.08 (-CH=N), 161.34, 163.57. EIMS: m/z $[\text{M}]^+$ calculated for $\text{C}_{22}\text{H}_{16}\text{Br}_4\text{N}_2\text{O}_2$: 599.99; found: 560

Synthesis of metal complex

Synthesis of Schiff base metal complexes were carried out by the process as described below.

The Schiff base ligand (10 mmol) was dissolved in 20 ml absolute ethanol. A solution metal salt (10 mmol) in 30 ml absolute ethanol was added in to the above Schiff base ligand solution under constant stirring. In all the cases the reaction metal ligand molar ratio was 1:1. The resultant reaction mixture was refluxed for 3h and obtained precipitated product. The precipitate of product was filtered. The red brown coloured filtered product was dried at room temperature.



Scheme: Synthesis of metal complex Scheme

Where- M = Metal (Cr,Mn,Cu), $\text{R}^1 = \text{Br}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Br}$

Spectral analysis of metal complexes

Spectral analysis of metal complex of Chromium

Yield 64%, mp 348 °C; IR (KBr) cm^{-1} : 3402 (OH), 2280(HC=N), 1631-1446 (C=C), 1165 ($\text{H}_2\text{C}-\text{N}$), 576 (Cr-N); MF $\text{C}_{22}\text{H}_{14}\text{O}_2\text{N}_2\text{Br}_4\text{Cr}$

Spectral analysis of metal complex of Magnese

Yield 68%, mp 360 °C; IR (KBr) cm^{-1} : 3421 (OH), 2320(HC=N), 1631-1446(C=C), 1221.51 ($\text{H}_2\text{C}-\text{N}$), 685 (Mn-N); MF $\text{C}_{22}\text{H}_{14}\text{O}_2\text{N}_2\text{Br}_4\text{Mn}$

Spectral Analysis of metal complex of Copper

Yield 68%, mp 282 °C; IR (KBR) cm^{-1} : 3418(OH), 2352(HC=N), 1631-1445 (C=C), 1289, (CH_2 -N), 684Cu-N); ; MF $\text{C}_{22}\text{H}_{14}\text{O}_2\text{N}_2\text{Br}_4\text{Cu}$.

Biological activity

Antibacterial (*E. coli*, *B. subtilis*, *S. typhi* and *S. aureus*) activity were evaluated by agar cup method. Diameter zone of inhibition in mm for antibacterial activity data Table 1.

Table 1: Antimicrobial activity of synthesized compound

Sr. No		<i>E. coli</i>	<i>B. subtilis</i>	<i>S. typhi</i>	<i>S. aureus</i>
1	Schiff base	12	15	13	15
2	Metal complex of Chromium	09	08	01	11
3	Metal complex of Magnese	10	08	04	11
4	Metal complex of Copper	08	07	04	08
5	Standard	08	25	21	30

Ligands: -ve, no antibacterial activity

Zone of Inhibition: --mm

Anticancer Activity

Experimental procedure:

- Cells were incubated at a concentration of 1×10^4 cells/ml in culture medium for 24 h at 37 °C and 5% CO_2 .
- Cells were seeded at a concentration (70 μl) 10^4 cells/well in 100 μl culture medium and 100 μl sample of LM series in (1000 $\mu\text{g/ml}$) into micro plates respectively (tissue culture grade, and 96 wells).
- Control wells were incubated with DMSO (0.2% in PBS) and cell line. All samples were incubated in triplicate. Controls were maintained to determine the control cell survival and the percentage of live cells after culture.
- Cell cultures were incubated for 24 h at 37°C and 5% CO_2 in CO_2 incubator (Thermo scientific BB150)
- After incubation, the medium was completely removed and Added 20 μl of MTT reagent (5 mg/min PBS).
- After addition of MTT, cells incubated for 4 hrs. at 37 °C in CO_2 incubator.
- Observed the wells for formazan crystal formation under microscope. The yellowish MTT was reduced to dark coloured formazan by viable cells only.
- After removing the medium completely. Added 200 μl of DMSO (kept for 10 min) and incubate at 37 °C (wrapped with aluminium foil).
- Triplicate samples were analysed by measuring the absorbance of each sample by a micro plate reader 5 fluorouracil at a wavelength of 490 nm.

Anticancer activity of synthesizes compounds against MCF-7 cell line (human breast cancer):

Anticancer activity of synthesizes compounds against MCF-7 cell line ^[16, 17] (human breast cancer) were shown in table 2.

Table 2: Anticancer activity of synthesizes Schiff base & metal complex compounds against MCF-7 cell line (human Breast cancer)

Sr. No.	Sample Code	% inhibition
1	Control	
2	Standard (5 FU20 $\mu\text{g/ml}$)	52.48
3	Schiff base or L2	09.38
4	L2 M1	87.89
5	L2M2	—
6	L2M3	80.72

Antioxidant (DPPH radical scavenging activity)

The molecule 1,1-diphenyl-2-picrylhydrazyl (α , α -diphenyl- β -picrylhydrazyl; DPPH)

is characterized as a stable free radical by virtue of the delocalization of the spare 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 electron also gives rise to the deep violet colour, characterized by an absorption band in ethanol solution centred 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 colour.

The ability of compounds to scavenge DPPH radical was assessed using Sambath Kumar and co-workers method and Manzocco and co-workers method¹⁹ with modification. Briefly, 1 ml of synthesized compounds as 1 mM was mixed with 3.0 mM DPPH (0.5 mmol/L in methanol), the resultant absorbance was recorded at 517 nm after 30 min incubation at 37 °C. The percentage antioxidant or radical scavenging activity was calculated by using the following formula.²⁰⁻²¹ Antioxidant activity (%) = [(AC-AS) / AC] x 100 where AC is absorbance of DPPH and AS is 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 compound as compared to that of standard (ascorbic acid) the results are reported in Table 3.

Table 3: Antioxidant activity of synthesized compounds of Schiff base and metal complex

Sr. No.	Sample Code	ABS at 517 nm	Activity (%)
1	Blank	1.43	-
2	Standard	0.13	90.90
3	Schiff base	0.39	37.06
4	L2M1	0.298	26.96
5	L2M2	0.375	08.08
6	L2M3	0.368	09.80

Result and Discussion

The Schiff bases were obtained in good yields from condensation reaction of halo substituted salicylaldehyde and m- xyllylene diamine (Scheme 1) and purified by hot ethanol. The purity of the compound was checked by TLC. The compounds were characterized by elemental n structures of the Schiff bases were elucidated on the bases 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 compounds reveals the disappearance of the band about 1700 cm⁻¹ attributed to the carbonyl group (C=O) and appearance of a band in the region 1659-1607 cm⁻¹ assigned to the azomethine (HC=N) band thereby indicating formation of the Schiff bases. The characteristic band in the region 3082-2979 cm⁻¹ are assigned to phenolic (OH) with intermolecular N---HO hydrogen bonding. The H₂C-N bands are observed in the region at 1285-1208 cm⁻¹. 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 Schiff base-metal complex molecule shows new metal-N coordinate bond stretching at 657 cm⁻¹. Therefore, the Schiff base-metal complex structure is confirmed.

The results show that Schiff base compound shows significant activity against *B. subtilis*, *S. typhi*, *S. aureus* and *E. coli* as compared with standard and metal complexes shows moderate activity as compared with standard.

All the synthesized Schiff bases were screened for their antioxidant activity. DPPH assay was performed to measure the ability of the Schiff bases to scavenge the DPPH free radicals. Colour change produced by free radical scavenging, result a change in absorbance. Among these compounds Schiff base have good Antioxidant activity as comparatively prepared metal complexes. Table 3.

The Schiff base shows Poor Anti Cancer activity on MCF 7 cell line and metal complex Chromium shows good anticancer activity as Compared to other of human being of specially 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 standard cell line.

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] C NMR 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 Schiff base. Synthesized Schiff base & metal complex were screened for their antioxidant activity. The result was not good for metal complex of cobalt but Schiff base have good result as compared to standard. The Schiff base shows very poor activity & metal complexes show significant anticancer activity as compared with standard.

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