

SYNTHESIS, CHARACTERIZATION AND *IN VITRO* BIOLOGICAL STUDIES OF NOVEL SCHIFF BASE AND ITS TRANSITION METAL COMPLEXES DERIVED FROM SULPHADOXINE

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Abstract

The new series of coordination transition metal complexes were prepared from Schiff base obtained from sulphadoxine and thiophene-2-carboxaldehyde. The structural investigation of Schiff base and their complexes were characterized by different instrumental procedures like microanalysis, spectroscopic and thermogravimetric examination. The integrated Schiff base ligand and transition metal complexes were subjected to antibacterial and antifungal activities. The studies demonstrated the enhanced activity of metal complexes against reported microbes when compared with free ligand.

Rezumat

O nouă serie de combinații complexe ale unor metale tranziționale a fost sintetizată pornind de la baza Schiff obținută din sulfadoxină și tiopen-2-carboxaldehidă. Structurile bazei Schiff și a complexelor au fost caracterizate prin diferite procedee instrumentale cum ar fi microanaliza, spectroscopia și termogravimetria și au fost investigate activitățile lor antibacteriene și antifungice. Studiile au demonstrat o activitate antimicrobiană superioară a complexelor metalice în comparație cu ligandul liber.

Keywords: Schiff base, metal complex, sulphadoxine, thiophene-2-carboxaldehyde, Antibacterial activity.

Introduction

Recently, the significance of metal ions to the key elements of living life forms has turned out to be progressively clear. Thus, the field of bioinorganic science is currently creating at a fast pace. New models for complex natural structures and processes are being formulated and studied [1]. Many drugs have improved pharmacological properties when forming metal complexes. The Schiff base metal chelates have gained attention in fields like medicine and pharmaceutical because of wide spectrum of biological activities such as anti-inflammatory drugs [2-4], antimicrobial [5-10], antispasmodic [11], tuberculosis [12], anti-cancer [13-14], antioxidants [15] and anthelmintic [16]. Aside from biological activities, Schiff bases are additionally utilized as catalysts [17-20], dyes and pigments [21-22], polymers [23-24] and corrosion inhibitors [25-27]. Schiff base assumed an impact part in the improvement of coordination science and were included as key point in the advancement of inorganic biochemistry and optical materials [28]. In the quest for novel treatment against safe life form, the alteration of existing medication by mix to a metal focus has picked up consideration as of late. Thus metal-based drug is viewed as promising

options for possible substitution for current drugs. Here we report preparation, characterization and biological studies of new Schiff base transition metal complexes obtained from sulphadoxine and thiophene-2-carboxaldehyde.

Materials and Methods

Analytical grade chemicals and solvents were used in these studies. Sulphadoxine and thiophene-2-carboxaldehyde were obtained from BDH. Other pure chemicals and solvent were purchased from Alfa Aesar and used without further purification. Microanalysis was performed utilizing normal strategies. Metals in the complexes were assessed by atomic absorption spectroscopy. Basic investigations were resolved on a CE-440 Elemental analyser. FT-IR spectra were recorded with a Perkin Elmer Spectrum-100 spectrometer utilizing KBr pallets. NMR spectra were measured on a Jeol ECS 400 spectrometer. Mass spectra were done with the assistance of Thermo Scientific Exactive TM Plus Orbitrap spectrometer. Thermogravimetric examination for the buildings was completed on a SDT-Q600 instrument. Magnetic moments were estimated using Evans balance with anhydrous calcium chloride. Electronic absorption

spectra of all the metal complexes were recorded on a Shimadzu-1800 spectrophotometer. The solutions of metal complexes of concentration (10^{-3} mol/L) were prepared and dimethyl sulphoxide (DMSO) was used as a solvent for conductance measurements using conductivity meter (4510-Jenway).

Preparation of Schiff base ligand

Sulphadoxine (2.0 mmol) was dissolved in 2.0 mL of (1N) sodium hydroxide. To the obtained solution an ethanolic solution of pyridoxal hydrochloride (2.0 mmol) was added and refluxed for one hour. A clear orange coloured solution was collected for isolation of Schiff base ligand by crystallization. The crystalline product was dried under vacuum and kept in a desiccator for further use.

Preparation of Schiff base metal complexes

The ligand (L) and chloride salt of copper(II), cobalt(II), zinc(II), nickel(II), manganese(II), iron(II) were dissolved in ethanol separately and after that mixed together in a 2:1 ratio. The reaction mixture was then refluxed for 1.0 h. After preparation, the coloured precipitate of Schiff base metal complexes were filtered off, washed with water, ethyl alcohol and dried under reduced pressure at room temperature.

Biological assay

In vitro antimicrobial and antifungal tests were estimated by agar well diffusion method [29]. The antimicrobial activities of the synthesized compounds were investigated against *Escherichia coli*, *Enterobacter aerogenes*, *Staphylococcus aureus*, *Bacillus pumilus*, *Klebsiella oxytoca* and *Clostridium butyrium*. *Mucor* and *Aspergillus niger* were used for the antifungal studies.

Results and Discussion

The synthesis of ligand was accomplished by refluxing the sulphadoxine and thiophene-2-carboxaldehyde in a molar ratio 1:1 in ethanol. The metal complexes of ligand were prepared using metal chloride and ligand in a 2:1 molar ratio. The structure elucidation was done with Elemental analyzer FT-IR, NMR, mass spectroscopy, TG and micro-analytical data. All the metal complexes are amorphous solids and have decomposition point. They are insoluble in water, organic solvents, partially soluble in acetone and completely soluble in DMF and DMSO. Molar conductance values (89-151 $\mu\text{S}/\text{cm}$) point out the electrolytic nature of metal complexes. The structures of the synthesized Schiff base ligand along with metal complexes were investigated by different techniques.

Schiff base Ligand: [*N*-4-(thiophene-2-yl-methyleneamino)-(5,6-dimethoxy-4-pyrimidine) benzene sulfonamide.]

Yield 75% (Off white). M. P. 166-169 $^{\circ}\text{C}$. IR (KBr, cm^{-1}) 3241 (NH), 1622 (HC=N-azomethine), 1581 (C=N-pyrimidine), 1124 (O=S=O), 1095 (C-N).

Anal. Calcd. For $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}_4\text{S}_2$ (405.06); Calcd: C, 50.43; H 4.20; N, 13.84; Found: C, 50.58; H 4.42; N, 13.77 %.

^1H NMR (DMSO- D_6 , δ ppm) 8.76 (-CH=N), 6.51-8.07 (phenyl); ^{13}C NMR (DMSO- D_6 , δ ppm) 164.2 (-CH=N), 160.6 (pyrimidine), 122.1-149.1 (phenyl). MS (EI); m/z (%) = 405.0361 [M^+].

Copper (II) complex

Colour; Blue, Yield 69%, Decomp. Point; 277-280 $^{\circ}\text{C}$. IR; (KBr, cm^{-1}) 3230 (OH), 1625 (HC=N azomethine), 1579 (C=N- pyrimidine), 1124 (O=S=O), 501 (M-N), 345 (M-O). UV; (DMSO) λ_{max} (cm^{-1}) 15345, 25651; B.M; (1.97 μ_{eff}), Molar conductance (121 $\mu\text{S cm}^{-1}$)

Anal. Calcd. For $\text{C}_{34}\text{H}_{32}\text{N}_8\text{O}_8\text{S}_4\text{Cu}$ (908.50); Calcd: C, 44.90; H 3.52; N, 12.32; Cu, 6.99%, Found: C, 45.09; H, 3.57; N, 12.38; Cu, 6.96%.

Cobalt (II) complex

Colour; Pink, Yield; 71% Decomp. Point; 271-274 $^{\circ}\text{C}$, IR; (KBr, cm^{-1}) 3225 (OH), 1624 (HC=N azomethine), 1577 (C=N- pyrimidine), 1118 (O=S=O), 499 (M-N), 362 (M-O), UV; (DMSO) λ_{max} (cm^{-1}) 17580, 25641; B.M; (4.77 μ_{eff}), Molar conductance; (92 $\mu\text{S cm}^{-1}$).

Anal. Calcd. For $\text{C}_{34}\text{H}_{32}\text{N}_8\text{O}_8\text{S}_4\text{Co}$ (903.89); Calcd: C, 45.13; H, 3.54; N, 12.38; Co, 6.51% Found: C, 45.22; H, 3.57; N, 12.39; Co, 6.49%.

Zinc (II) complex

Colour; Pale Yellow, Yield; 85 %, Decomp. Point 274-279 $^{\circ}\text{C}$. IR; (KBr, cm^{-1}) 3225 (OH), 1625 (HC=N azomethine), 1578 (C=N- pyrimidine), 1144 (O=S=O), 493 (M-N), 344 (M-O), UV; (DMSO) λ_{max} (cm^{-1}) 29380, Diamagnetic; Molar conductance; (89 $\mu\text{S cm}^{-1}$).

Anal. Calcd. For $\text{C}_{34}\text{H}_{32}\text{N}_8\text{O}_8\text{S}_4\text{Zn}$ (910.34); Calcd: C, 44.81; H 3.51; N, 12.30; Zn, 7.18 % Found: C, 44.94; H, 3.47; N, 12.31; Zn, 7.13 %.

Nickle (II) complex

Colour; Bluish green, Yield; 70 %, Decomp. Point; 271-273 $^{\circ}\text{C}$. IR; (KBr, cm^{-1}) 3226 (OH), 1624 (HC=N azomethine), 1571 (C=N- pyrimidine), 1179 (O=S=O), 491 (M-N), 324 (M-O), UV; (DMSO) λ_{max} (cm^{-1}) 14700, 24345; B.M; (3.01 μ_{eff}), Molar conductance; (103 $\mu\text{S cm}^{-1}$),

Anal. Calcd. For $\text{C}_{34}\text{H}_{32}\text{N}_8\text{O}_8\text{S}_4\text{Ni}$ (903.65); Calcd: C, 45.15; H, 3.54; N, 12.38; Ni, 6.49 %, Found: C, 45.19; H, 3.55; N, 12.44; Ni, 6.55 %.

Manganese (II) complex

Color; Off-white, Yield; 71 % Decomp. Point 266-267 $^{\circ}\text{C}$. IR; (KBr, cm^{-1}) 3237 (OH), 1626 (HC=N azomethine), 1573 (C=N- pyrimidine), 1177 (O=S=O), 501 (M-N), 360 (M-O), UV; (DMSO) λ_{max} (cm^{-1}) 17880, 24630; B.M; (4.59 μ_{eff}), Molar conductance; (112 $\mu\text{S cm}^{-1}$)

Anal. Calcd. For $\text{C}_{34}\text{H}_{32}\text{N}_8\text{O}_8\text{S}_4\text{Mn}$ (899.89), Anal. Calcd: C, 45.33; H, 3.55; N, 12.44; Mn, 6.10 % Found: C, 45.37; H, 3.61; N, 12.49; Mn, 6.24 %.

Iron (II) Complexes of Ligand

Color; Peach, Yield 85% Decomp. Point 268-272 $^{\circ}\text{C}$. IR (KBr, cm^{-1}) 3232 (OH), 1624 (HC=N

azomethene), 1569 (C=N- pyrimidine), 1141 (O=S=O), 489 (M-N), 348 (M-O). UV (DMSO) $\lambda_{\max}(\text{cm}^{-1})$ 29673, 31440; B.M (5.36 μ_{eff}); molar conductance (151 $\mu\text{S cm}^{-1}$).

Anal.Calcd.For $\text{C}_{34}\text{H}_{32}\text{N}_8\text{O}_8\text{S}_4\text{Fe}$ (900.80); Calcd: C, 45.29; H 3.55; N, 12.40; Fe, 6.19 Found: C, 45.22; H 3.51; N, 12.61; Fe, 6.13 %.

NMR Spectra

^1H NMR and ^{13}C NMR spectra were taken in d_6 -DMSO. The peaks of all the proton and carbon atoms were fixed in their expected region. The NMR spectra of Schiff base ligand was confirmed the absence of aldehyde peak at δ 9-10 and presence of azomethine at δ 8.76. ^{13}C NMR spectra also verify azomethine peak at δ 164.2. The diamagnetic zinc complex showed a slight change in spectra because of increased conjugation and coordination to metal ions.

FTIR Spectra

The metal ligand bond was verified by comparing the IR spectra of the Schiff base ligands with metal (II) complexes. The FTIR spectra predicted all the absorption bands of the Schiff base ligands and some new bands at specific frequency confirmed the modes of absorption and the complexation of the ligands with the metal ions through nitrogen and oxygen. The azomethine group of ligand 1622 cm^{-1} was shifted to higher value (1626 cm^{-1}) in all the complexes thus suggested the coordination of metal to ligand bond through azomethine(HC=N). Absorption bands of the sulfonamides moiety in the synthesized ligands and in metal complexes have same frequency. Further definitive proof of the coordination of the Schiff-bases with the metal ions was confirmed by the appearance of new bands at 489-501 cm^{-1} and 348-362 cm^{-1} designated to the metal nitrogen (M-N) and metal-oxygen (M-O) extending vibrations, respectively [30]. These bands were not present in the spectra of the free ligands, therefore affirming the presence of O and N in the coordination.

Electronic spectra and magnetic susceptibility

The electronic absorption spectra of transition metal(II) complexes were recorded in 10^{-3} M

solutions of each complex in DMSO in the range 2000-10000 cm^{-1} at room temperature.

The electronic absorption spectrum of the Cu(II) complex showed two bands at 15345 cm^{-1} and 25651 cm^{-1} corresponding to the transition $^2\text{B}_{1g} \rightarrow ^2\text{A}_{1g}$. No spectral bands were found below 10000 cm^{-1} which supported the octahedral geometry of the complex. Also, the magnetic moment value (1.97 B.M) for the Cu(II) complexes suggests the octahedral geometry with $dx^2 - y^2$ ground state.

The electronic spectra of Co(II) complexes in DMSO exhibited bands around 17,580 cm^{-1} and a strong high-energy band at 25641 cm^{-1} designed $^4\text{T}_{1g}(\text{F}) \rightarrow ^4\text{T}_{2g}(\text{F})$, $^4\text{T}_{1g}(\text{F}) \rightarrow ^4\text{T}_{1g}(\text{P})$ transitions respectively, for a high-spin octahedral geometry. The magnetic susceptibility measurements (4.77 B.M) for the solid Co(II) complexes are also indicative of three unpaired electrons per Co(II) ion consistent with their octahedral environment.

The spectrum of Zn(II) complex exhibited only one band at 29,380 cm^{-1} which was assigned to a ligand \rightarrow metal charge transfer. The zinc (II) complexes of ligand were observed to be diamagnetic obviously and in this manner, their magnetic properties could not be calculated.

The spectrum of the Ni(II) complex showed d-d bands in the region 14700 and 24,345 cm^{-1} showed the spin-allowed transitions $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{1g}(\text{F})$ and $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{1g}(\text{P})$, respectively with the octahedral configuration. The magnetic moment (3.01 B.M) value recommended two unpaired electrons Ni(II) ion also consistent with an octahedral geometry for the Ni(II) complex.

The electronic spectrum of Mn (II) and Fe(II) complexes shows $^6\text{A}_{1g} \rightarrow ^4\text{A}_{1g}(\text{G})$, $^6\text{A}_{1g} \rightarrow ^4\text{A}_{1g}4\text{E}_g$ and $^3\text{A}_{2g}(\text{F}) \rightarrow ^3\text{T}_{1g}(\text{P})$ and $^5\text{T}_{2g} \rightarrow ^5\text{E}_g$ transitions respectively. The magnetic moment values of both complexes supports octahedral geometry i.e. 4.59 B.M and 5.36 B.M [31-32].

Thermal studies

Thermogravimetric analyses (TGA) for the transition metal complexes were done from room temperature to 1000 $^\circ\text{C}$. Calculated and found mass losses are shown in Table below.

Table 1

Thermal Analysis Data of the Metal(II) Complexes

S. No.	Metal Chelates	Temperature Range($^\circ\text{C}$)	Mass Loss % Found (Calculated)	Assignment
1	[Cu(L-H) ₂ (H ₂ O) ₂]	120-230	4.32(3.96)	Loss of 2H ₂ O
		230-470	44.78(44.52)	Loss of L ₁
2	[Co(L-H) ₂ (H ₂ O) ₂]	135-235	4.18(3.98)	Loss of 2H ₂ O
		235-400	44.98(44.74)	Loss of L ₁
3	[Zn(L-H) ₂ (H ₂ O) ₂]	150-233	4.33(3.95)	Loss of 2H ₂ O
		233-455	45.13(44.43)	Loss of L ₁
4	[Ni(L-H) ₂ (H ₂ O) ₂]	118-230	4.45(3.98)	Loss of 2H ₂ O
		230-460	44.98(44.76)	Loss of L ₁
5	[Mn(L-H) ₂ (H ₂ O) ₂]	145-240	4.25(4.00)	Loss of 2H ₂ O
		240-475	45.25(44.94)	Loss of L ₁
6	[Fe(L-H) ₂ (H ₂ O) ₂]	115-227	4.32(3.99)	Loss of 2H ₂ O
		227-465	45.36(44.90)	Loss of L ₁

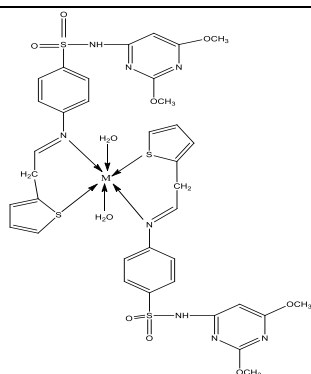


Figure 1

Proposed structure of Schiff base metal(II) complexes where M= Cu (II), Co (II), Mn (II), Fe (II), Ni (II), Zn (II)

Biological activities

Antimicrobial and antifungal activity of all the synthesized transition metal complexes and Schiff base ligand were tested against *Escherichia coli*, *Enterobacter aerogenes*, *Staphylococcus aureus*, *Bacillus pumilus*, *Klebsiella oxytoca*, *Clostridium butyrium*, *Aspergillus niger* and *Mucor*. The results showed enhanced activity when coordinated with transition metals (Table 2). This enhancement in activity of the metal complexes as compared to free ligand can be explained by chelation therapy. The metal complexes were found to be active against *Aspergillus niger* and *Mucor* whereas parent drug and ligand showed no antifungal activity.

Table II

Antibacterial and antifungal activity of Schiff base ligand and their metal complexes (zone of inhibition; 350 $\mu\text{g mL}^{-1}$)

Compounds	<i>E. coli</i> (mm)	<i>E. aerogenes</i> (mm)	<i>S. aureus</i> (mm)	<i>B. pumilus</i> (mm)	<i>K. oxytoca</i> (mm)	<i>C. butyrium</i> (mm)	<i>A. niger</i> (mm)	<i>Mucor</i> (mm)
[Cu(L) ₂ (H ₂ O) ₂]	28 ± 0.31	17 ± 0.27	28 ± 0.29	17 ± 0.15	18 ± 0.26	25 ± 0.21	15 ± 0.19	17 ± 0.18
[Co(L) ₂ (H ₂ O) ₂]	17 ± 0.28	15 ± 0.18	20 ± 0.21	14 ± 0.16	15 ± 0.20	20 ± 0.25	11 ± 0.22	12 ± 0.12
[Zn(L) ₂ (H ₂ O) ₂]	24 ± 0.23	17 ± 0.24	25 ± 0.19	19 ± 0.25	19 ± 0.11	24 ± 0.16	16 ± 0.23	15 ± 0.17
[Ni(L) ₂ (H ₂ O) ₂]	19 ± 0.19	15 ± 0.22	19 ± 0.09	16 ± 0.23	14 ± 0.14	22 ± 0.14	13 ± 0.29	12 ± 0.23
[Mn(L) ₂ (H ₂ O) ₂]	16 ± 0.25	13 ± 0.19	18 ± 0.12	15 ± 0.11	15 ± 0.18	19 ± 0.16	12 ± 0.18	12 ± 0.29
[Fe(L) ₂ (H ₂ O) ₂]	20 ± 0.15	12 ± 0.15	17 ± 0.18	14 ± 0.17	14 ± 0.15	17 ± 0.22	12 ± 0.22	11 ± 0.21
Ligand	14 ± 0.18	10	13	11	10	14	-	-
Drug	11 ± 0.21	8 ± 0.18	11 ± 0.19	9 ± 0.22	9 ± 0.21	11 ± 0.21	-	-

Conclusions

The results obtained after investigation demonstrated that derivatization of Schiff base with certain transition metal (II) ions, the antibacterial activities were enhanced against chosen bacterial strains. The metal complexes additionally demonstrated action against *Aspergillus niger* and *Mucor* though parent drug and ligand showed no antifungal activity. These observations were in accordance with different studies, already reported that metal based drugs have more potential as therapeutics.

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