

Synthesis and Characterization of New Schiff Base Transition Metal Complexes Derived from Drug Together with Biological Potential Study

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Abstract

Purpose: 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 seen as promising alternatives for possible replacement for some of the current drugs. So, we synthesized Schiff base metal complexes in this regard.

Materials and Methods: A series of transition metal(II) complexes of new Schiff base were synthesized by the condensation of sulphadiazine and 2-carboxybenzaldehyde in ethanol.

Results: The Schiff base and transition metal complexes were characterized by using different instrumental techniques like microanalysis, thermogravimetric analysis and spectroscopy. The synthesized ligand and metal complexes were subjected to antibacterial studies. The studies showed the enhance activity of metal complexes against one or more species as compared to the uncomplexed ligand.

Conclusions: The data showed that transition metal complexes have significant improved antibacterial activity than parent drug.

Keywords: Schiff base; Metal complexes; Sulphadiazine; 2-carboxybenzaldehyde; Antibacterial

Introduction

Schiff bases sustain azomethine or imine ($-C=N$) unit. This is the primary condensation of amines with carbonyl compounds and have been reported by Hugo Schiff [1-3]. Schiff bases have a wide variety of applications in different areas such as biological chemistry, organic and inorganic chemistry. The medicinal uses and applications Schiff bases and their metal complexes are of increasing clinical and commercial importance. Schiff bases have picked up significance in medicinal and pharmaceutical field because of an expansive range of biological activities like anti-inflammatory [4-7], analgesic [5-8], antimicrobial [9,10], antispasmodic [11], tuberculosis [12], anti-cancer [13,14], antioxidants [15], anthelmintic [16]. Schiff bases are also administered as catalysts, intermediates in organic synthesis, pigments, dyes, polymeric stabilizers [3] and corrosion inhibitors [17]. On reviewing the literature, it is proved that metal complex exhibits greater biological activity as the free organic compounds [18]. Increase of biological activity reported by the implementation of the transition metals of Schiff bases [19]. Schiff bases have played a significant role in the development of coordination chemistry and have been implicated as an important point in the development of inorganic biochemistry and optical materials [20]. In the search for novel therapy against resistant organism, the modification of existing drug by combination to a metal center has gained attention in recent years [21]. So, we synthesized and characterized transition metal complexes derived from sulphadiazine and 2-carboxybenzaldehyde.

Materials and Methods

Analytical grade chemicals and solvent used in these studies. Sulphadiazine and 2-carboxybenzaldehyde were taken from BDH. Other pure chemicals and solvent were purchased from Alfa Aesar and used without purification.

Preparation of Schiff base

The drug sulphadiazine (2.0 mmole) was dissolved in ethanol (20

cm³). It was mixed with 2-carboxybenzaldehyde (2.0 mmole) dissolved in ethanol 20 cm³. To this sodium hydroxide (1.0 M) was added in order to maintain the pH of the solution at 8-9. The mixture was refluxed for one hour approximately. A clear orange colored solution was obtained. The Schiff base ligand was isolated by crystallization after volume reduction. The crystalline product was dried under vacuum and kept in a desiccator until further use.

Preparation of Schiff base metal complexes

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

Characterization

Microanalysis was performed using usual techniques. Metals were evaluated by atomic absorption spectroscopy. Elemental analyses were determined on a CE-440 Elemental analyzer, FT-IR spectra were recorded with a Perkin Elmer Spectrum-100 spectrometer using KBr disks. NMR spectra were measured on a Jeol ECS 400 spectrometer.

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Mass spectra were measured with the help of Thermo Scientific Exactive TM Plus Orbitrap spectrometer. Thermogravimetric analysis for the complexes was carried out on a SDT-Q600 instrument.

Magnetic moments were determined with Evans balance using anhydrous calcium chloride. Electronic absorption spectra of all the complexes were recorded on a Shimadzu-1800 spectrophotometer. Conductance measurements were taken in DMSO (10^{-3} mol L⁻¹) using an electroconductivity bridge.

Antimicrobial assay

In vitro antimicrobial tests were carried out by agar well diffusion method [22]. The antimicrobial activities of synthesized compounds were investigated against *Escherichia coli*, *Enterobacter aerogenes*, *Staphylococcus aureus*, *Bacillus pumilus*, *Klebsiella oxytoca* and *Clostridium butyrium*.

Results and Discussion

The synthesis of ligand was accomplished by refluxing the drug and aldehyde 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 characterization is done with Elemental analyzer FT-IR, NMR, Mass Spectroscopy, TG and micro-analytical data. The metal complexes of ligand were prepared using metal chloride and ligand in a 2:1 molar ratio. 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. The structure of synthesized Schiff base ligand along with metal complexes were investigated by different techniques and characterized as follows:

Ligand (L. N-4-(2-carboxybenzylideneamino-pyrimidin-2-yl)-benzene sulfonamide)

Yield 70% (White). m. p. (decomp.) 261°C to 264°C. IR (KBr, cm⁻¹) 3255 (OH), 1610 (HC=N azomethine), 1573 (C=N-pyrimidine), 1157(O=S=O), 1087. Anal. Calcd. For C₁₇H₁₄N₄O₃S(382); Calcd: C, 56.48; H 3.66; N, 14.64; Found: C, 56.52; H, 3.49; N, 14.71%.

¹H NMR (DMSO-D₆, δ ppm) 8.43 (-CH=N), 11.4 (OH), 6.99-7.92 (phenyl); ¹³C NMR (DMSO-D₆, δ ppm) 169.3 (-CH=N), 157.8 (pyrimidine), 125-153 (phenyl). MS (EI); m/z (%)=382.0791 [M+].

Copper (II) complexes of L

Yield 72% (Dirty green). m. p. (decomp.) 277°C to 279°C. IR (KBr, cm⁻¹) 3440 (OH), 1624 (HC=N azomethine), 1581 (C=N-pyrimidine), 1126 (O=S=O), 450 (M-N), 365 (M-O).

UV (DMSO) λ_{max} (cm⁻¹) 15336, 28169; B.M (1.69μ_{eff}); molar conductance (15 μS cm⁻¹). Anal. Calcd. For C₃₆H₂₈N₈O₈S₂Cu(864.36); Calcd: C, 49.97; H 3.23; N, 12.95; Cu,7.35; Found: C, 50.10; H, 3.27; N, 12.91; Cu, 7.41%.

Cobalt (II) complexes of L

Yield 75% (Lalic). m. p. (decomp.) 279°C to 282°C. IR (KBr, cm⁻¹) 3340 (OH), 1614 (HC=N azomethine), 1550 (C=N-pyrimidine), 1161 (O=S=O), 408 (M-N), 363 (M-O).

UV (DMSO) λ_{max} (cm⁻¹) 17580, 21735; B.M (4.09μ_{eff}); molar conductance (10 μS cm⁻¹). Anal. Calcd. For C₃₆H₂₈N₈O₈S₂Co(859.75); Calcd: C,50.24; H 3.25; N, 13.02; Co, 6.85; Found: C, 50.32; H, 3.27; N, 13.11; Co, 6.90%.

Zinc (II) complexes of L

Yield 71% (Pale yellow). m. p. (decomp.) 281°C to 284°C. IR (KBr, cm⁻¹) 3455 (OH), 1619 (HC=N azomethine), 1581 (C=N-pyrimidine), 1134 (O=S=O), 410 (M-N), 360 (M-O).

UV (DMSO) λ_{max} (cm⁻¹) 28340; Diamagnetic; molar conductance (8 μS cm⁻¹). Anal. Calcd. For (866.20); Calcd: C, 49.87; H, 3.23; N, 12.93; Zn, 7.54; Found: C, 49.99; H, 3.31; N,12.91; Zn,7.49%.

Nickle (II) complexes of L

Yield 72% (Blue) m. p. (decomp.) 276°C to 278°C. IR (KBr, cm⁻¹) 3340 (OH), 1622 (HC=N azomethine), 1558 (C=N-pyrimidine), 1126 (O=S=O), 412 (M-N), 365 (M-O).

UV (DMSO) λ_{max} (cm⁻¹) 16550, 24270; B.M (2.89μ_{eff}); molar conductance (21 μS cm⁻¹). Anal. Calcd. For (859.51); Calcd: C, 50.26; H, 3.25; N,13.03; Ni, 6.82; Found: C, 50.31; H, 3.35; N,12.97; Ni, 7.05%.

Manganese (II) complexes of L

Yield 71% (Brown). m. p. (decomp.) 279°C to 282°C. IR (KBr, cm⁻¹) 3255 (OH), 1628 (HC=N azomethine), 1577 (C=N-pyrimidine), 1126 (O=S=O), 411 (M-N), 328 (M-O).

UV (DMSO) λ_{max} (cm⁻¹) 15209, 24547; B.M (5.33μ_{eff}); molar conductance (17 μS cm⁻¹). Anal. Calcd. For C₃₆H₂₈N₈O₈S₂Mn (855.75); Calcd: C,50.48; H, 3.27; N, 13.08; Mn, 6.41; Found: C, 50.63; H, 3.33; N,13.11; Mn, 6.54%.

Iron (II) complexes of L

Yield 70% (Peech). m. p. (decomp.) 286°C to 288°C. IR (KBr, cm⁻¹) 3277 (OH), 1622 (HC=N azomethine), 1581 (C=N-pyrimidine), 1157 (O=S=O), 470 (M-N), 366 (M-O).

UV (DMSO) λ_{max} (cm⁻¹) 28250, 31055; B.M (5.55μ_{eff}); molar conductance (16 μS cm⁻¹). Anal. Calcd. For C₃₆H₂₈N₈O₈S₂Fe (856.66); Calcd: C, 50.42; H, 3.26; N, 13.07; Fe, 6.51; Found: C, 51.03; H, 3.51; N, 13.01; Fe, 6.63% (Figure 1).

¹H NMR and ¹³C NMR spectra

¹H NMR and ¹³C NMR spectra were recorded in DMSO. All assignments of the proton and carbon atoms were found in their

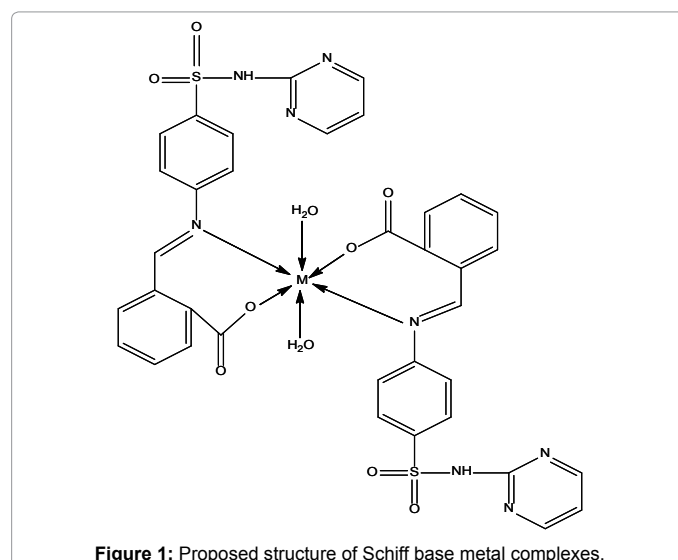


Figure 1: Proposed structure of Schiff base metal complexes.

NO	Metal Chelates	Temperature Range (°C)	Mass Loss % Found (Calculated)	Assignment
1	[Cu(L-H) ₂ (H ₂ O) ₂]	152-270	4.03 (4.16)	Loss of 2H ₂ O
		270-410	33.02 (32.33)	Loss of 2-imino-pyrimidine+Loss of 2SO ₂
2	[Co(L-H) ₂ (H ₂ O) ₂]	162-305	4.44 (4.18)	Loss of 2H ₂ O
		305-450	32.13 (33.51)	Loss of 2-imino-pyrimidine+Loss of 2SO ₂
3	[Zn(L-H) ₂ (H ₂ O) ₂]	153-298	4.01 (4.15)	Loss of 2H ₂ O
		298-420	33.21 (33.26)	Loss of 2-imino-pyrimidine+Loss of 2SO ₂
4	[Ni(L-H) ₂ (H ₂ O) ₂]	144-310	4.22 (4.18)	Loss of 2H ₂ O
		310-430	32.99 (33.52)	Loss of 2-imino-pyrimidine+Loss of 2SO ₂
5	[Mn(L-H) ₂ (H ₂ O) ₂]	153-275	4.14 (4.20)	Loss of 2H ₂ O
		275-425	33.44 (33.67)	Loss of 2-imino-pyrimidine+Loss of 2SO ₂
6	[Fe(L-H) ₂ (H ₂ O) ₂]	151-278	4.33 (4.20)	Loss of 2H ₂ O
		278-420	33.88 (33.63)	Loss of 2-imino-pyrimidine+Loss of 2SO ₂

Table 1: Thermal analysis data of the metal (II) complexes.

Compound (300 µg/mL)	<i>E. coli</i>	<i>E. aerogenes</i>	<i>S. aureus</i>	<i>B. pumilus</i>	<i>K. oxytoca</i>	<i>C. butyrium</i>
[Cu(L) ₂ (H ₂ O) ₂]	29 ± 0.29	19 ± 0.31	30 ± 0.14	17 ± 0.27	18 ± 0.13	27 ± 0.09
[Co(L) ₂ (H ₂ O) ₂]	22 ± 0.21	15 ± 0.28	24 ± 0.19	14 ± 0.24	15 ± 0.18	22 ± 0.11
[Zn(L) ₂ (H ₂ O) ₂]	26 ± 0.19	17 ± 0.23	29 ± 0.22	19 ± 0.18	18 ± 0.21	26 ± 0.17
[Ni(L) ₂ (H ₂ O) ₂]	20 ± 0.09	13 ± 0.19	32 ± 0.26	17 ± 0.11	14 ± 0.26	25 ± 0.21
[Mn(L) ₂ (H ₂ O) ₂]	28 ± 0.12	13 ± 0.25	25 ± 0.17	20 ± 0.15	16 ± 0.11	28 ± 0.29
[Fe(L) ₂ (H ₂ O) ₂]	21 ± 0.18	12 ± 0.15	22 ± 0.11	22 ± 0.19	14 ± 0.13	25 ± 0.24
Ligand	15 ± 0.21	10 ± 0.18	13 ± 0.19	10 ± 0.22	11 ± 0.19	15 ± 0.15
Drug	10 ± 0.15	8 ± 0.20	11 ± 0.22	8 ± 0.16	8 ± 0.28	9 ± 0.17

Zone of inhibition data was shown as mean ± SD. Each experiment was repeated three times.

Table 2: Antibacterial activity of Schiff base ligand and their metal complexes.

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 8.43. ¹³C NMR spectra also verify azomethine peak at δ 169.3. The diamagnetic zinc complex showed a slight change in spectra due to the increased conjugation and coordination to metal ions.

IR spectra

The metal ligand bond was confirmed by comparing the IR spectra of the Schiff base ligand with metal (II) complexes. The FT-IR spectra predicted all the absorption bands of the Schiff base ligand and some new bands at specific frequency confirmed the modes of absorption and the completion of the ligand with the metal ions through nitrogen and oxygen.

A broad band around 3440 cm⁻¹ to 3277 cm⁻¹ showed water molecule in all complexes [23]. The azomethine group of ligand 1610 cm⁻¹ was shifted to higher value (1628 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 ligand and in metal complexes have same frequency. Further conclusive evidence of the coordination of the Schiff-bases with the metal ions was shown by the appearance new bands at 408 cm⁻¹ to 470 cm⁻¹ and 328 cm⁻¹ to 366 cm⁻¹ assigned to the metal nitrogen (M-N) and metal-oxygen (M-O) stretching vibrations, respectively. These bands were absent in the spectra of the free ligands, thus confirming participation of the O and N in the coordination.

Electronic spectra and magnetic susceptibility

The electronic absorption spectra of metal (II) complexes were recorded in 10⁻³ M solutions of each complex in DMSO in the range 2000 cm⁻¹ to 10000 cm⁻¹ at room temperature.

The electronic spectrum of Mn (II) and Fe (II) complexes shows ⁶A_{1g}

→ ⁴A_{1g} (G), ⁶A_{1g} → ⁴A_{1g}, 4E_g and ³A_{2g} (F) → ³T_{1g} (P) and ⁵T_{2g} → ⁵E_g transitions respectively. The magnetic moment values of both complexes support octahedral geometry i.e., 5.33 B.M. and 5.55 B.M.

The electronic absorption spectrum of the Cu (II) complex showed two bands at 15336 cm⁻¹ and 28169 cm⁻¹ corresponding to the transition ²B_{1g} → ²A_{1g}. No spectral bands were found below 10000 cm⁻¹ which supports octahedral geometry. Also, the magnetic moment value (1.69 B.M.) for the Cu (II) appears to be in the octahedral geometry with dx²-y² ground state.

The spectrum of the Ni (II) complex showed d-d bands in the region 16550 cm⁻¹ and 24270 cm⁻¹. These were assigned to the spin-allowed transitions ³A_{2g} (F) → ³T_{1g} (F) and ³A_{2g} (F) → ³T_{1g} (P) respectively, consistent with the octahedral configuration. The magnetic moment (2.89 B.M.) value suggested two unpaired electrons per Ni (II) ion also consistent with an octahedral geometry for the Ni (II) complex.

The electronic spectra of Co (II) complexes in DMSO exhibited bands around 17580 cm⁻¹ and a strong high-energy band at 21735 cm⁻¹ which were assigned to the transitions ⁴T_{1g} (F) → ⁴T_{2g} (F), ⁴T_{1g} (F) → ⁴T_{1g} (P) respectively, for a high-spin octahedral geometry. The magnetic susceptibility measurements (4.09 B.M.) for the solid Co (II) complexes are also indicative of three unpaired electrons per Co (II) ion consistent with their octahedral environment [24-25]. The spectrum of Zn (II) complex exhibited only one band at 28340 cm⁻¹ which was assigned to a ligand → metal charge transfer. The zinc (II) complexes of all ligand were found to be diamagnetic as expected and therefore, their magnetic properties could not be investigated.

Thermal studies

Thermogravimetric analyses (TGA) for the transition metal complexes were done from room temperature to 1000°C. Calculated and found mass losses are shown in Table 1.

Antibacterial activity

All the synthesized metal complexes and Schiff base ligand were tested against *Escherichia coli*, *Enterobacter aerogenes*, *Staphylococcus aureus*, *Bacillus pumilus*, *Klebsiella oxytoca* and *Clostridium butyrium* by agar well diffusion method according to literature. *In vitro* antimicrobial activities were measured from the diameter of clear zones caused by samples against the bacteria under the identical experimental conditions.

In order to clarify role of DMSO, separate studies were carried out with the DMSO and the metal complexes. It was found that they have no effect on the growth of any microorganism taken. DMSO used as a negative control as it did not show any activity against bacteria, so data is not included. Each experiment was repeated three times. All the data was shown as mean \pm SD. The results showed enhanced activity when coordinated with transition metals (Table 2).

Conclusion

On the premise of results got after characterization and antibacterial studies it is obvious that all the synthesized metal complexes demonstrated octahedral geometry and enhanced antibacterial properties against selected microbes. These observations, in accordance with different studies, recommend that metal based drugs have potential as therapeutics.

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