SYNTHESIS, SPECTRAL CHARACTERIZATION OF SCHIFF BASE COMPLEXES BASED ON PYRIMIDINE MOIETY WITH MOLECULAR DOCKING WITH BIOMOLECULES

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ABSTRACT

Objective: Aim of this study is to synthesize new bidentate complexes of type MX2nH2O with 4-amino antipyrine and ethyl 4-methyl-2-oxo-6-phenylhexahydropyrimidine-5-carboxylate (DHPM) and to characterize their properties, namely elemental analysis, conductivity measurements, and spectral characteristics and to establish the binding between the Schiff base ligands and complexes with human epidermis cancer cells (Hep-2) through molecular docking.

Method: A new bidentate complexes were synthesized by condensation reaction of MX2nH2O (M = Cu (II), Zn (II), Co (II)) with 4-aminoantipyrine (A) and DHPM in methanol under atmospheric pressure.

Results: All the compounds have been characterized by elemental analysis, conductance measurements, magnetic moments, and spectroscopy techniques such as ultraviolet-visible, infrared (IR), H and 13C nuclear magnetic resonance, and electron spin resonance (ESR). The IR showed that nature of functional group present in the ligand (Lp) acts as neutral bidentate through the azomethane nitrogen atom and carbonyl oxygen moiety and its complexes formation. The ESR spectral data of copper complex provided information about their structure on the basis of Hamiltonian parameters and degree of covalency. The antimicrobial (Escherichia coli, Salmonella typhi, Bacillus subtilis, and aureus) and antifungal (Candida and Aspergillus niger) activities of the complexes were tested against various microorganism by disc diffusion method.

Conclusion: The antimicrobial activity indicates that the metal complexes are more active than the ligand. Molecular docking was used to predict the binding between the Schiff base ligands and complexes with human epidermis cancer cells (Hep-2).

Keywords: Schiff base molecular structure, Nuclear magnetic resonance, Fourier transform infrared, Electron spin resonance study, Molecular docking with biomolecules.

INTRODUCTION

Transition metal (II) ion coordination complexes of well-defined structures and it play an important role in the numerous biological processes that involve electron transfer reaction or the activation of some antitumor activities [1]. Schiff base ligands are significant important stereochemical models in main group and transition metal. It due to their preparative accessibility and structural variety especially of ligands is potentially capable to form stable complexes with metal ions [2]. Schiff bases of 4-aminoantipyrine and its transition metal complexes have various applications [3-5]. Heterocyclic containing dihydropyrimidinone ring is present in a number of pharmacologically and biologically active compounds [6]. Compounds containing benzothiazole derivatives were used as antifungal, anti-inflammatory, anti-HIV, and antiviral activities [7-9]. The numerous biological experiments performed so far suggest that DNA is the primary intracellular target of anticancer drugs because the interaction between small molecules and can induce DNA damages to cause cancer [10,11].

We synthesized and characterized novel Schiff base metal Co (II), Ni (II), Cu (II), and Zn(II) complexes. In the present study, in silico molecular docking studies of ligand and their metal complex against BCL-2 (PDB id: Bcxl: 2YX) have been carried out using Glide module of Schrodinger 2009. The docking studies which are reported in terms of the docking energy score, which means the lower, the score, the better and the interaction. The ligand and metal complexes were individually docked with Laryngeal carcinoma BCL-2 as the target protein.

MATERIAL AND METHODS

Benzaldehyde, ethyl acetoacetate, urea, and metal halide salts were purchased from E Merck chemical company and used without further purification; ethanol refers to absolute ethanol unless otherwise specified. Carbon, hydrogen, and nitrogen were estimated using elemental analyzer Carlo ErbaEA1108 analyzer. Molar conductivity measurements were recorded on ELICO-CM-82 T conductivity Bridge with a cell having cell constant 0.51 and the magnetic moment was carried out using Faraday balance. The IR spectra of the Schiff bases and its complexes were recorded on a Shimadzu-8400 IR spectrophotometer. The 1H nuclear magnetic resonance (NMR) and 13C NMR spectra of ligands were recorded in dimethyl sulfoxide (DMSO)-d6 on a BRUKER 300 MHz spectrometer at room temperature using TMS as an internal reference. Mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer/data system. The ultraviolet (UV)-visible spectra of the complexes were recorded in high-performance liquid chromatography grade DMSO solvent on a Shimadzu-1800 UV-visible spectrophotometer in the region of 200–1100 nm. The electron spin resonance (ESR) spectrum was recorded on Varian-E4K-band electron paramagnetic resonance (EPR) spectrometer, and the fieldset is 3000 G at a modulation frequency of 100 kHz under room temperature using TCE as g marker.

Preparation of Schiff base

An ethanolic solution of 4-aminoantipyrine (2.03 g, 0.01 mol, and 20 mL) was added to the ethanolic solution of ethyl 4-methyl-2-oxo-6-phenylhexahydropyrimidine-5-carboxylate (2.6 g, 0.01 mol, and 20 mL) with constant stirring at 60°C for 4 h. After cooling the solution, the precipitate was separated, filtered, recrystallized...
with ethanol, and dried over anhydrous calcium chloride under vacuum [12] yield 62.9%; m.p. 233°C, the scheme of preparation is given in Scheme 1.

Synthesis of the [M (4-aminoantipyrine-2-oxo-phenyl hexahydropyrimidine-5-carboxylate [APDM]), Cl₂] complexes

The hot alcoholic solution of the M (II) Cl₂.5H₂O (0.01 mol [2.65 g]) was slowly added to the hot alcoholic solution of the ligand (0.02 mol). The resulting mixture was refluxed for 5 h, few drops of very dilute ammonia were added in drops to the reaction. The colored precipitate obtained was separated by filtration, washed with distilled ethanol and ether. The products were dried and stored atmosphere (Scheme 2).

RESULTS AND DISCUSSION

Physical properties

The ligand: (2E)-ethyl 2-{2, 5-dihydro-2,3-dimethyl-5-oxo-1-phenyl-1H-pyrazol-4-ylamino)-1, 2, 3, 4-tetrahydro-6-methyl-4-phenylpyrimidine-5-carboxylate is the ligand (APDM) is yellow colored solids, amorphous in nature stable at room temperature and insoluble in water, slightly soluble in ethanol and acetone and fairly soluble in hot ethanol, CH₃Cl. The complexes of Mn(II), Co(II), Ni(II), Cu(II), and Zn(II), are stable in room temperature. The complexes are fairly soluble in hot ethanol, dimethylformamide, and dimethyl sulfoxide.

Elemental analysis

The analytical data of the metal complexes of ligand (APDM) are presented in Table 1. It may be seen from the table that the experimental values are in fair agreement with the calculated ones. The molecular formula of the ligand and their metal complexes has been suggested according to the above-mentioned data together with those obtained from spectral, conductivity, and magnetic susceptibility of metal complexes.

Fourier transform infrared (FT-IR) spectra of ligand and complexes

The IR spectra provide valuable information regarding the nature of the functional groups present in the ligand and coordination mode of the metal atom with the ligand. The characteristic IR frequencies of the free ligands and their metal (II) complexes are given in Table 2.

In general, the IR spectra of the free ligand showed a broadband around 3425 cm⁻¹ which could be attributed to NH stretching vibration of benzimidazole moiety. The position of this band remained at nearly the same frequency in the spectra of the metal complexes suggesting the absence of the NH group coordination [13]. The stretching frequency of carbonyl group of ligand ν(C=O) at 1702 cm⁻¹ is shifted to lower frequency range 1688–1699 cm⁻¹ and is attributed to complexes formation with metal. Similarly, the frequency corresponding to ν(C=N) at 1647 cm⁻¹ shifted range 1587–1635 cm⁻¹ in complexes [14]. The shifting in wave number and their intensities of referenced bands led to predict the coordination behavior. The spectra of metal complexes also show additional bands in between 617–642 cm⁻¹, 480–583 cm⁻¹, and 317–326 cm⁻¹ which are probably due to the formation of ν(M-O), ν(M-N), and ν(M-Cl) bond, respectively [15,16]. Thus, the IR spectral results provided strong evidence for the complexation of Schiff base with metal ions through bidentate mode by azomethine and carboxyl oxygen groups.
Table 1: Physical and analytical data of the (APDM) ligand and its metal (II) complexes

| Compound | Mol. formula | m.p.(°C) | Found (Calc.)(%) | Molar conductance (cm$^2$ mol$^{-1}$) × 10$^{-3}$ |
|----------|--------------|----------|-----------------|-----------------------------------------------|
| APDM     | C$_8$H$_8$N$_2$O$_3$ | 233      | 66.89 (67.40)   | 6.08 (6.11) 15.89 (15.72) - 13.77 5.40 3 |
| Mn       | Mn(C$_8$H$_8$N$_2$O$_3$)$_2$ | 252      | 59.06           | (5.92) 13.77 5.40 3 |
| (APDM)$_2$ M | Co(C$_8$H$_8$N$_2$O$_3$)$_2$ | 260      | 58.66           | 5.48 (13.71) 5.40 3 |
| (APDM)$_2$ N | Ni(C$_8$H$_8$N$_2$O$_3$)$_2$ | 214      | 59.01           | (5.33) 13.72 (5.77) 5.45 3.15 |
| (APDM)$_2$ C | Cu(C$_8$H$_8$N$_2$O$_3$)$_2$ | 265      | 58.53           | (5.33) 13.72 (5.77) 5.45 3.15 |
| (APDM)$_2$ Z | Zn(C$_8$H$_8$N$_2$O$_3$)$_2$ | 241      | 58.53           | (5.33) 13.72 (5.77) 5.45 3.15 |

APDM: 4-aminooantipyrine-2-oxo-6-phenyl hexahydropyrimidine-5-carboxylate

Table 2: IR spectral data of the (4-aminooantipyrine-2-oxo-6-phenyl hexahydropyrimidine-5-carboxylate) ligand and its complexes

| Compound | $\nu_{CO}$ | $\nu_{CN}$ | $\nu_{NH}$ | N$_{Ni}$ | $\nu_{NH}$ |
|----------|------------|------------|------------|---------|------------|
| L$_i$      | 1702       | 1647       | -          | 3500    | 3300       |
| [MnL$_2$]Cl$_2$ | 1687       | 1617       | 608        | 54.4    | 3500 3200 |
| [CoL$_2$]Cl$_2$ | 1683       | 1602       | 610        | 54.6    | 3400 3100 |
| [NiL$_2$]Cl$_2$ | 1680       | 1599       | 613        | 530     | 3420 3120 |
| [CuL$_2$]Cl$_2$ | 1677       | 1594       | 614        | 557     | 3380 3200 |
| [ZnL$_2$]Cl$_2$ | 1699       | 1615       | 602        | 528     | -          |

$^1$H NMR and $^{13}$C-NMR of 3-aminopropyldimethylethoxysilane (APDM) ligand and its complexes studies

The NMR spectra of free ligands were obtained in CDCl$_3$. The $^1$H NMR spectral data were acquired using a spectrometer. The $^1$H NMR spectra show a multiplet at 6.10–7.52 ppm (m, 10H, Ar) due to phenyl group, -N-CH$_2$ at 2.3 ppm (s,3H), -C-CH at 3.72 ppm (s, 6H, 2 =C-CH$_2$). The signals at 5.137–1.17 ppm (t, 3H, CH at 5.386–5.497 ppm (d, 1H, CH), CH at 4.05–4.07 ppm (q, 2H), and CH$_2$ at 3.13 ppm (m, 2H) all were characteristic of aromatic protons. The signals of the pyrazoline ring carbon appeared at 146.0–143 ppm. The signals due to methyl carbon were observed around 22–19 ppm. The signals appear for C=N and carbon of C=O at 8 165.0–1622 and δ 153.2–1697 ppm, respectively. Thus, NMR information further supports the apprehension of IR results.

Electronic spectra APDM ligand and its complexes studies

The variety of colors among transition metal complexes arises from the electronic transition between the energy levels. The absorption regions, assignments and the geometry of the complexes are given in Table 3. In the electronic spectrum of the ligand, there are two absorption bands around 286–301 nm assigned to n-π* and π-π* transitions. These transitions are also found in the spectra of the complexes, but they are shifted toward longer wavelength from ligand to complex, indicating coordination of ligand to metals through the azomethine moiety.

The electron spectrum showed at 524 nm assigned to $^4B_{1g}$→$^4A_{1g}$ transition. These values suggested a square planar geometry. In the Co (II) complex, the band at 612 nm and 426 nm is attributed to d-d electronic transition type $^4A_{2g}$→$^4T_{2g}$, suggesting square planar about Co ions [20]. The spectrum of Mn(II) complex displays a broad shoulder such as absorption band near 560 nm and a very weak shoulder around 383 nm in ethanol. The high energy band may be due to charge-transfer whereas the band at 560 nm may be assigned to d-d transitions.

The observed diamagnetism and broad medium band at 426 nm in the spectrum of (NiL)$_2$Cl$_2$ were attributed to [d-d] electronic transition type $^4B_{1g}$→$^4A_{1g}$, suggesting a square planar structure [21]. The electronic spectra of Zn (II) complexes give only charge transfer in the range 25000–3421 cm$^{-1}$ due to the (d-d) configuration the metal ions, suggesting tetrahedral structure. On the basis of the above observations and from the diamagnetic nature, UV-visible data, the structure for the complexes could be proposed as follows: A square planar geometry for Ni (II), Mn(II), Co(II), and a tetrahedral geometry for Zn (II) complexes.

ESI mass spectra of APDM ligand and its complexes studies

ESI mass spectra provide a vital clue for elucidating the structure of complexes. It showed a molecular ion peak (M$^+$) m/z at 445.07 which was equivalent to its molecular weight. The base peak at m/z = 187 was due to 4-aminooantipyrine (C$_8$ H$_8$N$_2$ O$_3$) ion. Another intense peak at m/z = 274 was due to (C$_9$ H$_8$ N$_2$ O$_3$)$^+$ ion. The different competitive fragmentation pathways of ligand gave the peaks at different mass numbers at 257, 185, 173, 171, 147, 132, 82, 77, and 56 due to (C$_8$ H$_8$ N$_2$ O$_3$)$^+$; (C$_7$ H$_8$ N$_2$ O$_3$)$^+$; (C$_7$ H$_7$ N$_2$ O$_3$)$^+$; (C$_7$ H$_6$ N$_2$ O$_3$)$^+$; (C$_7$ H$_5$ N$_2$ O$_3$)$^+$; (C$_6$ H$_4$ N$_2$ O$_3$)$^+$; (C$_5$ H$_3$ N$_2$ O$_3$)$^+$; and (C$_4$ H$_2$ N$_2$ O$_3$)$^+$ ions, respectively. The intensity of these peaks reflected the stability and abundance of the ions [22]. The spectrum of (MnL)$_2$Cl$_2$(CoL)$_2$Cl$_2$ and (CuL)$_2$Cl$_2$ showed a molecular ion peak (M$^+$) m/z at 1048.78, 1052.76, and 1057.30, respectively, that was equivalent to their molecular weight. All these fragments lead to the formation of the species [ML$_2$]Cl$^+$ which further undergo demetallation to yield the species ($^+$) Cl$^-$ gave the fragment ion peak; at m/z 461. Thus, the data obtained from mass spectra confirmed the stoichiometry of metal (1:2) ratio and in good agreement with the micro-analytical data. The discussion suggests that the mass spectra data are correlated with elemental analyses and from the molar conductance data are found that all the complexes are non-electrolytes.

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Table 3: Electronic spectral data of the Schiff bases and their metal complexes

| Compound | Absorption maxima (nm) | Band assignment | Magnetic moment B.M | Geometry          |
|----------|------------------------|-----------------|---------------------|-------------------|
| Ligand   | 242                    | \(\pi-\pi^*\)   | -                   | -                 |
|          | 301                    | n-\pi^*         | -                   | -                 |
| [CuL\(_2\)] | 296                    | INCT            | -                   | Diamagnetic       |
|          | 325                    | INCT            | -                   | Square Planar     |
|          | 426                    | \(^1A_g-^1A_g\) | -                   | Tetrahedral       |
|          | 556                    | \(^1B_{1g}-^1E_g\) | -                   | Tetrahedral       |
| [MnL\(_2\)] | 383                    | \(\beta\)       | Diamagnetic         | Tetrahedral       |
|          | 560                    | \(\alpha\)      |                     |                   |
| [CoL\(_2\)] | 293                    | INCT            | -                   | Diamagnetic       |
|          | 324                    | INCT            | -                   | Tetrahedral       |
|          | 426                    | \(^1A_g-^1B_{1g}\) | -                   | Tetrahedral       |
|          | 612                    | \(^3A_{1g}-^1E_g\) | -                   | Tetrahedral       |
| [NiL\(_2\)] | 296                    | INCT            | Diamagnetic         | Square Planar     |
|          | 325                    | INCT            |                     |                   |
|          | 426                    | \(^1A_g-^1A_g\) |                     |                   |
|          | 556                    | \(^1B_{1g}-^1A_g\) | -                   |                   |

Fig. 1: Electron paramagnetic resonance spectra of Cu(4-amino antipyro-2-oxo-6-phenyl hexa hydro pyrimidine-5-carboxylate)\(_2\) complex in solid at (a) 300 K, dimethyl sulfoxide (b) 300 K, and (c) 77 K

ESR spectrum copper (II) complex

The ESR spectrum of copper (II) complex has been studied and depicted in Fig. 1. The \(g||\) and \(g\perp\) values have been found to be 2.04351 and 2.15835, respectively. The \(g_{un}\) was calculated to be 2.12007. The Cu (II) complex shows reversed axial (compressed octahedral) with \(g|| < g\perp\). The trend \(g|| < g\perp\) showed that the electron is delocalized in \(dz^2\) orbital of the ground state of Cu (II). In this case \(g|| < g\perp\), distortion occurs by compression. The parameter \(G\), determined as \(G\perp = (g\perp - 2\times 0.023) + 3/7 (g|| - 2\times 0.023) + 0\times 04\), was calculated to be 2.12007. The \(g\perp\) value is less than 4 suggesting considerable interaction in the solid state. No band corresponding to \(M_s = \pm 2\) transition was observed in the spectrum ruling out any Cu–Cu interaction. The observed values, it is clear that \(g|| < g\perp\), which indicate that the structure is square-planar and that the unpaired electron is predominantly in the \(dx^2-y^2\) orbital [23,24]. The molecular orbital coefficients, \(a_2\) (covalent in-plane s-bonding) and \(b_2\) (covalent in-plane p-bonding) were calculated using the following equations.

\[\alpha^2 = - (\alpha||/0.036) + |g|| - 2\times 0.023| + 3/7 (g\perp - 2\times 0.023) + 0\times 04\]

\[\beta^2 = |g|| - 2\times 0.023| E/-60\alpha^2\]

Docking studies of ligand and their metal complex

In the present study, in silico molecular docking studies of ligand and their metal complex against BCL-2 (PDB id: Bcl-xl: 2YXJ) have been carried out using Glide module of Schrodinger. The docking studies which are reported in terms of the docking energy score, which means the lower; the score; the better; and the interaction. In the ligand, [Zn (APDM)\(_2\)]Cl\(_2\) and [Cu(APDM)\(_2\)]Cl\(_2\), were individually docked with [Laryngeal carcinoma] BCL-2 as the target protein. Docking results of a best complex of these compounds with their key active site residues interaction are tabulated in Table 4. From the table, these compounds exhibit better docking scores (−7.92 and −6.52) and glide energies (−58.60 and−53.25), respectively. Based on the docking score, the glide energy, and key active site interactions, the metal complexes show better binding affinity compared to ligand inhibit. Molecular docking studies show that these metal complexes bind well in the active site pocket of BCL-2 (PDB id: Bcl-xl: 2YXJ) and interacts with the active site amino acid residues. In ligand, nitrogen atoms N1 interact with Glu 129(A) at distance of 2.90 Å and also O\(_F\) interact with Arg 139(A) at a distance of 2.73 Å which is shown in Fig. 2. Docking score −7.92 of Tetrahedral [Zn (APDM)\(_2\)]Cl\(_2\), Oxygen atom O\(_F\) interacts with of Try195 (A) at a distance of 2.11 Å, Asn136 (A) at a distance 3.28Å, and 05 Arg136(A) at a distance 3.11Å. The compound CuL\(_2\) has a better binding interaction with Bcl-xl: 2YXJ protein and it exhibited the docking score −6.52 with a −53.25 kcal/mol. The hydroxyl group of the amino acid Tyr 101(A) made hydrogen bond interaction with the O6 of compound CuL\(_2\) (O6−OH)(Try 101).
and bonding distance is 2.95 Å. Similarly, carbonyl group involves hydrogen bond interaction with Arg 139 (A), and bond distance is 2.93 Å (Fig. 3).

**CONCLUSION**

A new bidentate complex was synthesized by a condensation reaction with transition metal (II) complexes and pyrimidine-based ligand. To evaluate biological modal with the BCL-2 molecular docking model suggested that compound Cu (II) and Zn (II) complexes act as potent BCL-2 amino acid residues inhibitor as well as in vitro anticancer agent. Overall, the compounds have designed from the parent ligand APDM with Zn (APDM) showed activity in most of the studies. The present research could be useful to develop the in vivo studies of the synthesized compounds.

**AUTHOR’S CONTRIBUTIONS**

Corresponding author has done all the work, interpreted the data, and written the manuscript.

**CONFLICTS OF INTEREST**

All authors have none to declare.
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