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Research Article

Synthesis, Characterization and Antitrypanosomal Activity of Metal Complexes of 2-{(E)-[(4-Bromophenyl)imino]methyl}phenol

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Abstract

The current study investigates the Antileishmanial and cytotoxic activity of synthesized Schiff base ligand 2-{(E)-[(4-bromophenyl)imino]methyl}phenol and their Metal complexes prepared by reflux process**.** Various metal salt is used in complexation like Zn, Cu, Ni, Co and the synthesized compounds is studied structurally with chromatographic technique and checked their solubility in THF, DMSO and CH_3COCH_3. Such compounds show good Anti-leishmanial activity with no Cytotoxicity which exhibited scarcer negative impacts and could serve as effective substances in Antileishmanial and Cytotoxicity.

Keywords: Schiff base metal complexes, structural characterization, anti-leishmanial activity, cytotoxicity.

1. Introduction

Hugo Schiff reported the Schiff base by condensation reaction between aldehyde and amine in 1864.These compounds contain azomethine group (–HC=N–) and acts like Flexi-dentate ligand. Organic reactions that result in the formation of new compounds by joining together at least two atoms are frequently seen in drug development, leading to the formation of molecules with novel biological properties [1], Such alterations are important in many catalytic processes such as oxidation, asymmetric cyclo-propanation, and polymerization [2]. Schiff-bases can serve as ligands with varying numbers of coordination atoms, such as mono, di, tri, or tetradentate ligands, and are capable of forming chelate rings typically consisting of 5 or 6 members when reacting with a transition metal atom [3]. It has been recognized that Schiff bases can create complexes with f-block elements and d-block metals [4]. The Schiff base ligands have the ability to form complexes with a variety of metals, each with unique oxidation states for the metal. Schiff base complexes have numerous applications in catalyzing reactions [4, 5]. Several binuclear and multinuclear transition metal complexes were synthesized, demonstrating a wide range of applications in magneto science, material science, bioinorganic studies, and multi electron redox chemistry [6]. The majority of Schiff bases are known for their synthetic instability and tendency to be involved in various equilibria, such as tautomeric interconversions, hydrolysis, or formation of ionized species [7]. Metal ions can enhance the activity of biologically active compounds. The formation of complexes typically results in Schiff bases compounds being effective and stereo-specific catalysts for various chemical reactions in inorganic and organic chemistry [8]. In Schiff base synthesis, the amine acts as a nucleophile and adds to the carbonyl group through nucleophilic addition [9]. Schiff base metal complexes exhibit superior antibacterial properties when compared to Schiff base ligands. Several Schiff bases containing amino acids such as glycine, phenylalanine, and valine were employed as antibacterial agents [10]. Medicinal scientists are currently interested in enhancing a recently developed chemotherapeutic Schiff base [11].The Schiff bases containing penicillin and heterocyclic units with N, N atoms are considered highly significant in studies due to their antibacterial and surfactant properties [12]. Schiff base ligands are used in antitrypanosomal treatments due to their ability to chelate metal ions (e.g., Zn, Cu, Ni, Co) that are essential for many Trypanosoma enzymes, disrupting

their function. By forming metal-Schiff base complexes, these ligands can induce oxidative stress and interfere with vital metabolic processes, such as enzyme activity and redox balance, impairing the parasite's survival [13]. Additionally, Schiff bases can be designed for selective toxicity, targeting specific trypanosomal enzymes while minimizing damage to host cells. Their ease of synthesis and modification further enhance their potential as effective antitrypanosomal agents, offering a versatile platform for developing novel therapies against trypanosomiasis [14].

1.1. Type of Schiff Bases

1.1.1. Salen Type Ligand

The versatile and successful Salen ligands were first synthesized in 1869, and comprehensive studies were conducted in the 1930s by Pfeiffer and colleagues [15]. Salen-type Schiff bases are renowned for their simple synthesis and capacity to form bonds with a variety of metal atoms, making them one of the most adaptable ligands. Numerous chiral and achiral salen-type ligands with a preference for different metals have been produced through the direct reaction of aldehyde derivatives with different diamines [16].

1.2. Application of Schiff Bases

Schiff bases play a significant role in biology and are utilized for their antibacterial, antifungal, anticancer, antiviral, antiparasitic, and antitumor properties. Schiff bases are frequently used as catalysts in various biological systems and also find use as controllers of plant development, enzymes, insecticides, and more [3]. It has been noted that Schiff bases of chitosan exhibit superior antifungal properties in comparison to acylated chitosan [17].

1.3. Activity of Schiff bases

Aldehydes with one or more halo atoms in their salicylaldehyde derivative show various biological effects like being antifungal and antibacterial [18].

1.4 Leishmaniasis

Leishmaniasis is an illness caused by parasites from the Leishmania genus, which infect vertebrate hosts' macrophages, resulting in effects like skin ulcers, damage to mucous membranes, and overall organ illness [19]. Leishmaniasis, a major health issue, is one of the five common parasitic diseases globally. According to (WHO), approximately two million new cases are reported annually in many non-industrialized countries, affecting twelve million people, with no effective vaccine for Leishmaniasis developed yet. Treatment options for the disease are limited [20]. Leishmaniasis is caused by parasites and includes four main clinical syndromes: cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), visceral leishmaniasis (VL), and post-kala-azar dermal leishmaniasis (PKDL). The incidence of this deadly disease in East Africa still requires monitoring [21].

1.4.2 Cytotoxicity:

Twelve compounds derived from a Schiff base of 4-aminoantipyrine were created. Various biological effects of these compounds were studied, including in vitro antibacterial, antioxidant, and cytotoxic activities. The findings demonstrate varying efficacy of two Schiff bases: one is effective against Faecalis, while the other exhibits antioxidant properties [22]. Cu (II) compounds exhibited biological activity at room temperature were [Cu (N-(2-mercaptophenyl)-2′-pyridylmethylenimine)Cl] (1), [Cu(N-(2-pyridylmethyl)-2-ercaptoaniline) Cl] (2), and [Cu(2,2′-di(pyridyl-2-methyleneimine) diphenyl-disulphide) Cl] Cl (3), (abbreviated as pabt=N-(2-mercaptophenyl)-2′-pyridylmethylenimine, pma = N-(2-pyridylmethyl)-2-mercaptoaniline, pdta = 2,2′-di(pyridyl2-methyleneimine) diphenyl disulfide), indicating their mononuclear nature. One out of the three compounds were found to be orderly. These compounds exhibited effectiveness in breaking down DNA through oxidation and hydrolysis. These Mononuclear Cu (II) complexes demonstrate significant efficacy against Homolysis and cervical cancer HeLa cell line [23]. The condensation reaction of 4-acyl-5-pyrazolones and conjugated diamines produced several active Schiff bases, which can be identified using qualitative and quantitative analysis. Each of these compounds demonstrate antibacterial effects against Bacillus subtilis and Escherichia coli, displaying significant efficacy against Phytophthora infestanse and Aspergillus Niger [24].

2. Experimental Work

2.1. Chemicals and reagents

Salicylaldehyde, Sulfuric acid, 4-bromoaniline, potassium hydroxide, and trimethylamine, along with zinc acetate, cobalt acetate, copper acetate, and nickel acetate, are used alongside CH3OH, CH_3CH_2OH, CH_3COCH_3, $CHCl_3$, n-Hexane, DMF, DMSO, CH_2Cl_2, tetrazolium-dye (MTT), and phosphate buffer saline (FBS). Titron X-100 streptomycin/penicillin were obtained from Riedel de Haen. These transition metal salts were obtained from a source of analytical grade.

2.2. Instrumentation

The Stuart SMP10 Thermo electric instrument is used to determine the melting points of both the ligand and complexes. Employing FTIR spectrophotometer to analyze the compounds' IR spectra. The Nicolet 6700 FTIR spectrophotometer was used to record the infra-red spectra. IR spectral data was collected using an FTS spectrophotometer FTIR machine with a range of 4000-400cm-1 by following standard protocols.

2.3. Synthesis of 2-{(E)-[(4-Bromophenyl) Imino] Methyl} Phenol (H-BIMP)

Schiff base imine compound was produced by reacting salicylaldehyde and 4-bromo aniline in methanol solvent for 2 hours with stirring. 1.7202g of 4-bromoaniline (0.01mol) was dissolved in 15-20ml methanol, followed by the addition of 1.048ml of salicylaldehyde (0.01mol) with a few drops of H_2SO_4. After agitating and stirring for approximately 2 hours, crystals formed in the fresh solution (ligand) of yellow color, which was subsequently dried to yield the final product as shown in Fig no 1. The ligand's melting point ranges from 111°C to 114°C.

2.4. Synthesis of [Cu-BIMP]

During the synthesis of a copper complex, 0.0004mol (0.072652g) of copper acetate and 0.0008mol (0.220g) of ligand are separately dissolved in 20ml of methanol before being combined and stirred for around 4 hours. Following the reaction, the mixture was allowed to crystallize undisturbed at room temperature. Cover the beaker and let it dry; after a few days, brownish crystals of a new complex formed. The Cu complex has a melting point of 250°C.

2.5. Synthesis of [Zn-BIMP]

For the synthesis of Zn complex, 0.0004mol (0.073g) of zinc acetate and 0.0008mol (0.2208g) of the ligand were dissolved in 20ml of methanol each. The two solutions were then mixed together and stirred for about 4 hours. No precipitate was found under the same condition, so we added KOH after 2 hours of reflux to obtain a precipitate of the complex. The combination was heated for 6 hours at 80°C using reflux. After that reaction was finished, the round bottom flask was cooled to room temperature. The remedy was strained into a tiny container and allowed to crystallize overnight at room temperature. The color of the complex remains unchanged after it dries. The complex has a melting point of 298°C.

2.6. Synthesis of [Ni-BIMP]

A quantity of 0.0003mol (0.053g) of nickel acetate is mixed with 20ml of methanol, and separately, 0.0006mol (0.1656g) of the ligand is mixed with 20ml of methanol.

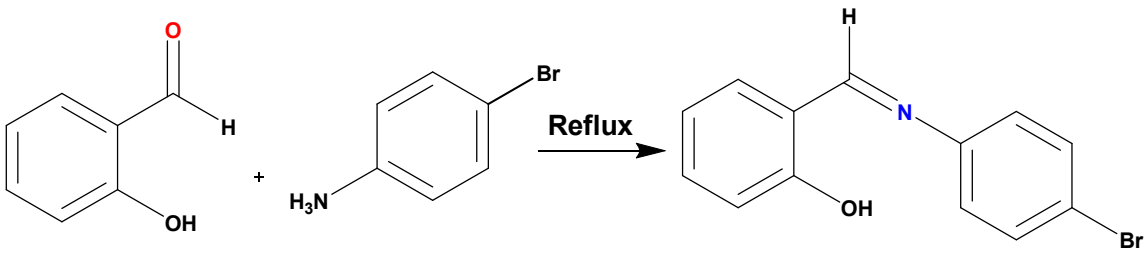

Figure 1. General Reactions for the synthesis of H-BIMP.

The two solutions are then combined and stirred for about 4 hours. No precipitate was observed under the identical conditions, so we introduced KOH and reflux for 2-hour reflux to obtain a precipitate of the complex. The blend was heated under reflux for six hours at 80°C. Once the reaction finished, the round bottom flask was left to cool to room temperature. The solution was poured into a tiny beaker and allowed to crystallize overnight at room temperature. Following dehydration, the color of the compound shifted from yellow to brown. The complex has a melting point of 153°C.

2.7. Synthesis of [Co-BIMP]

A 0.0004mol (0.0708g) of cobalt acetate is dissolved in 20ml of methanol in a beaker, while 0.0008mol (0.220g) of the ligand is dissolved in 20ml of methanol. Both solutions are then combined and stirred for about 4 hours. No precipitation was observed under the same circumstances hence, after a 2-hour reflux, potassium hydroxide was introduced to form a complex precipitation. The mixture was heated under reflux for 6 hours at 80°C. After the reaction was finished, the round bottom flask was cooled to room temperature. The mixture was strained into a tiny container and allowed to crystallize at room temperature overnight, the compounds is synthesized as shown in Fig no 2. Following the absence of moisture, the color of the compound transformed into a deep green shade. The complex has a melting point of 297°C.

2.8. Antileishmanial activity

Discussed the antileishmanial activity of BIMP Schiff base ligand and its Co-BIMP, Ni-BIMP, Cu-BIMP, and Zn-BIMP complexes. The medium containing 10% FBS and 1% antibiotic, like streptomycin/penicillin, was utilized to grow Leishmania tropica promastigotes until the culture reached a density of four to five million per ml. Neubauer is employed to count the culture in a 96-well plate with the testing compound at three different concentrations. The entire culture (106 cells/ml) was added in a volume of 100 microliters to each well of the plate. The plate was then placed in an incubator at 25°C for approximately 72 hours. The viability of the promastigotes of all compounds was evaluated using the tetrazolium-dye (MTT) calorimetric method. A 100µl sample of the entire culture (106 cells/ml) was added to a 96-well plate with three different sections of the screening synthetics. The plate was kept at a temperature of 25°C for a period of 72 hours. The Promastigotes were tested for suitability using the MTT colorimetric procedure with tetrazolium-color. Every individual typically receives 100 µl of MTT dye. After MTT was added, the 96-well plate was left to incubate for 3 hours at 37^{o}C. Finally, a stop solution of 40 µl of DMSO was used. Qualities were measured at 570 nm using an ELISA plate reader.

2.9. Cytotoxicity

A volunteer from the Department of Biotechnology at Abdul Wali Khan University Mardan had 5ml of blood extracted with prior approval from the ethics board. The blood was mixed with Phosphate Buffer Saline (PBS) several times and red blood cells were isolated through centrifugation at 1500rpm for 10 minutes. The blends BIMP, Cu-BIMP, Zn-BIMP, Ni-BIMP, and Co-BIMP were placed in Eppendorf tubes to create three distinct concentrations such as 250ppm, 500ppm, and 1000ppm. Triton X-100 (0.5%) was employed as the positive control while Dimethyl sulfoxide (5%) was used as the negative control. Each of the mixtures was incubated for three hours at 37 degrees Celsius. Following incubation, the sample tubes underwent centrifugation at a speed of 1500rpm for a duration of 10 minutes. Hemolysis was observed with the naked eye, and then 100µl of the supernatant from each sample was added to a 96-well plate to measure the amount of hemoglobin present at 576 nm.

3. Result and discussion

3.1. 4.1 FT-IR characterization

Salicylaldehyde possesses both an imine bonding group and a hydroxyl moiety, both of which directly bond with metal ions. The typical location of the stretching vibration of Salicyldehyde carbonyl is at 1720 cm^{-1}. The carbonyl group of Salicylaldehyde usually absorbs at 1725cm^{-1} but when conjugated with an aromatic compound, such as through the presence of hydrogen bonding, the frequency shifts to a lower position on the spectrum. In the synthesis of the ligand, Salicyldehyde reacts with a primary amine as the second step.

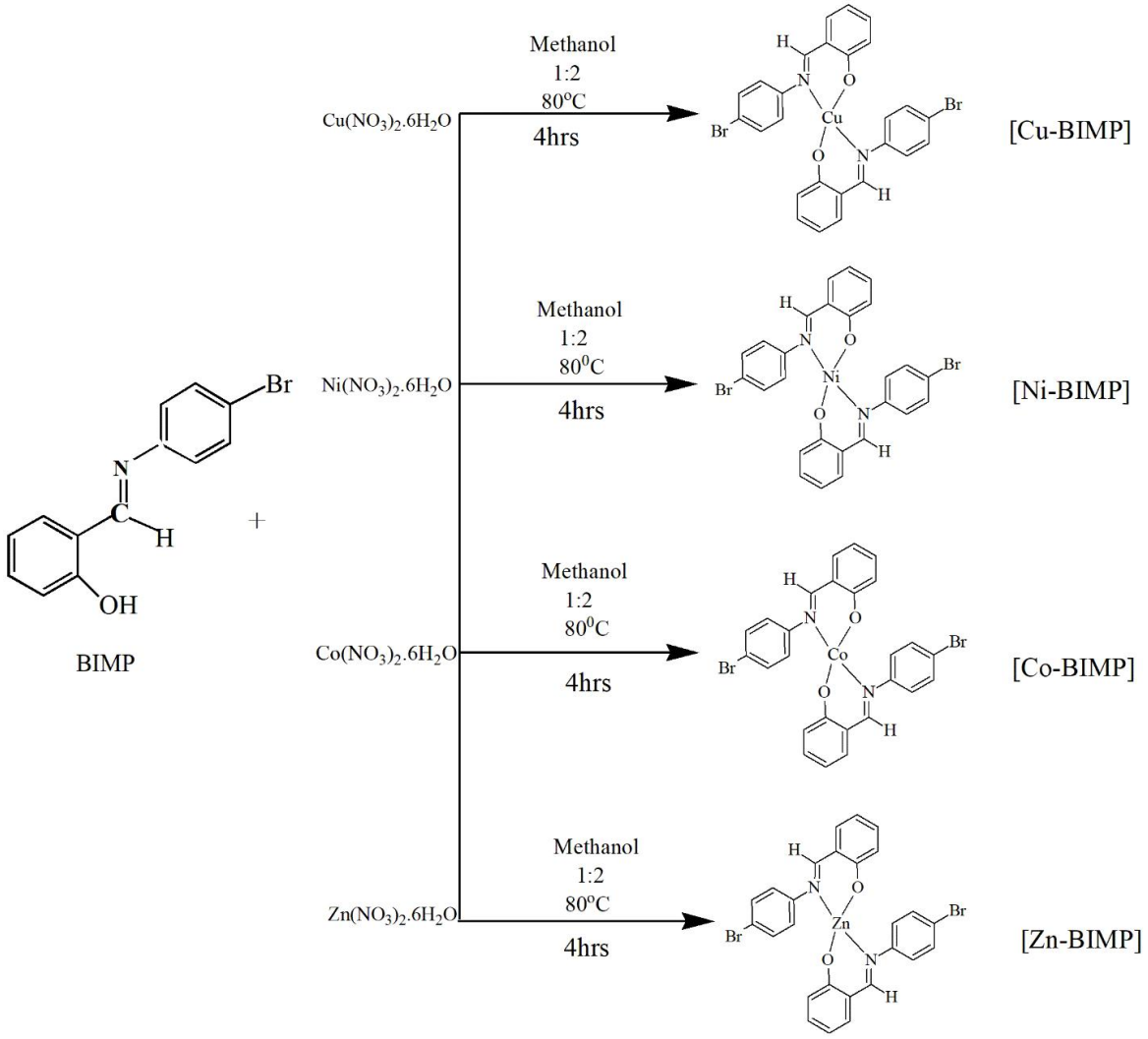

Figure 2. Synthetic protocol for Cu, Ni, Co, Zn with H-BIMP.

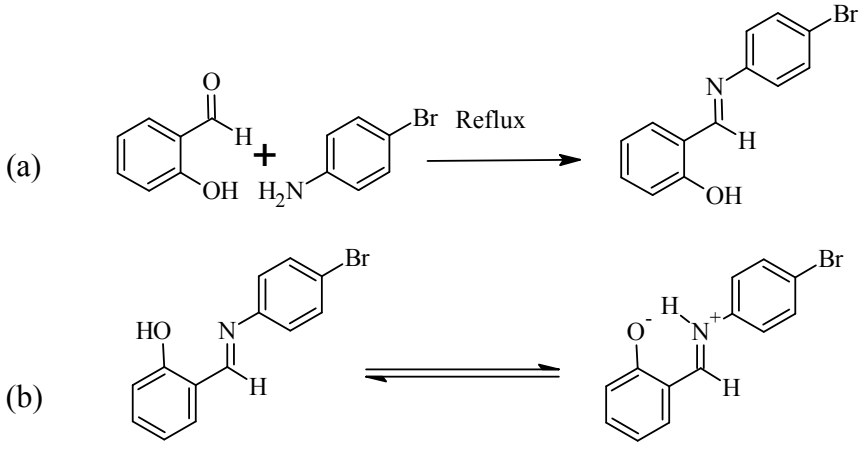

Figure 3. (a) synthesis of H-BIMP Schiff base ligand (b) Intramolecular Hydrogen bonding of H-BIMP Schiff base ligand.

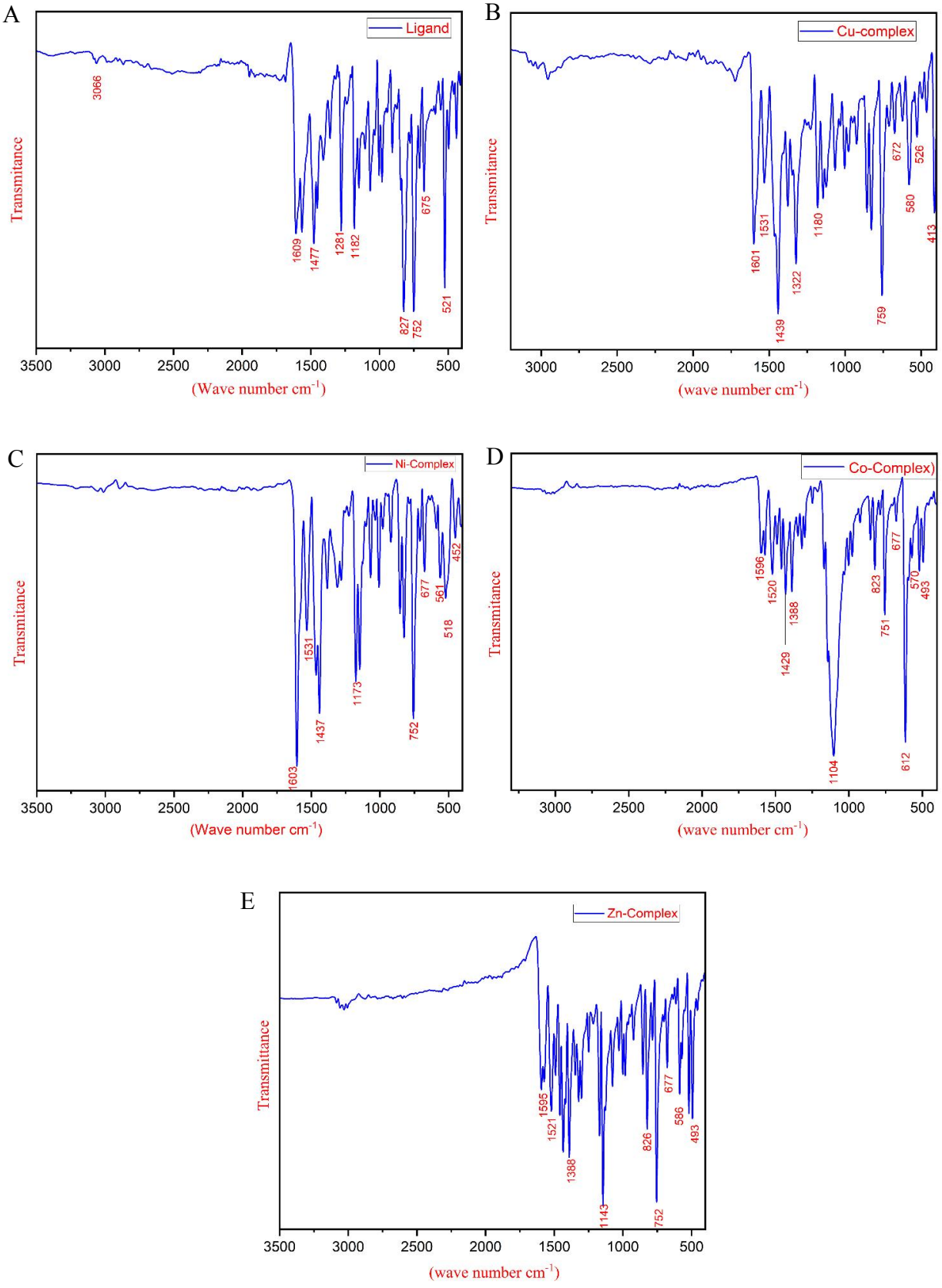

Figure 4. FTIR spectra of (A) H-BIMP, (B) Cu- BIMP, (C) Ni- BIMP, (D) Co- BIMP and (E) Zn- BIMP.

A primary amine contains an NH2 group, which shows a peak at 3066 cm^{-1} on an IR spectrum. Following the creation of the ligand, the IR spectrum indicates the complete disappearance of these NH2 bands. Therefore, it is evident that a new compound is created that produces varying bands in different areas. A band of normal size appeared at 1609 cm^{-1} in the H-BIMP spectrum as shown in Fig no 3. signaling the presence of a new group (N=C) known as azomethine. The lack of detection of the -OH vibration frequency may be attributed to the presence of the hydroxyl group and intramolecular hydrogen bonding. A slight peak at 675cm^{-1} was detected corresponding to the stretching of the C-Br bond.

The FT-IR characterization was utilized to analyze the synthesis of metal complexes with the imine ligand. This study will determine whether the ligand is bound to the metal or not. The ligand is reacted with various transition metal salts such as copper acetate, nickel acetate, cobalt acetate, and zinc acetate. We can examine the formation of metal complexes through both physical and spectral methods. When a ligand is combined with metal salts, a precipitate is produced and the color of the compound changes, indicating that a complex has been formed. Spectroscopic methods are utilized to describe the metal complex that is formed. Spectral methods utilize an infrared spectrophotometer to identify the creation of metal complexes such as Cu-BIMP, Zn-BIMP, Ni-BIMP, and Co-BIMP. Upon examining the IR data of the ligand and metal compounds, we found that a complex had indeed been formed. New compound formation resulted in the creation of additional absorption bands, prompting further research. Upon examination of the IR spectrum of the Ni-BIMP complex, it was observed that the frequencies associated with the coordinating sites shifted from high to low in Ni-BIMP by a difference of 38cm^{-1}. A fresh peak has emerged at 1603cm^{-1} in the spectrum, indicating the formation of Ni-BIMP complex. In addition, some new peaks were also generated, such as the N-M absorption band occurring at 561cm^{-1} and the O-M peak at 452cm^{-1}. It was discovered through this spectral analysis that the complex had been created. The identification of Zn-BIMP can also be validated using IR spectrophotometry, as distinct peaks appear in the tested compound at 1575cm^{-1} indicating the formation of a new compound. The newly formed peak is specifically for the C=N azomethine group It appears, N-M absorption band occurring at 586cm^{-1} and the O-M peak at 456cm^{-1} Analyzing the IR spectrum of the Co-BIMP compound reveals a peak at 1597cm^{-1}, indicating the formation of a new compound. The Azomethine group band emerged at 1596 cm^{-1} in the complex, shifting from high to low frequencies with various differences as shown in Fig no 4. Additional new peaks also appeared, indicating the bonding of the ligand in the metal complex formation. When a ligand binds to a nitrogen donor atom, it produces a peak at 570cm^{-1}, while the oxygen atom from a hydroxyl group produces a peak at 493cm^{-1}. We can easily verify whether the studied compound has been synthesized or not by utilizing the infrared spectrophotometer technique. Likewise, in the IR spectrum of Cu-BIMP, the Azomethine peak was observed around 1601cm^{-1} with a small variation compared to the ligand peak. Several additional bands were also present, as evident from the graph. Examining the IR spectrum reveals a distinctive peak at 526cm^{-1} for the N-metal bond, and an absorption band at the 413cm^{-1} region for the O-metal bond.

3.2. Antileishmanial activity

Screening was conducted for Antileishmanial activity of transition metal complexes formed with Schiff base ligands. The BIMP ligand is a compound with Antileishmanial activity that exhibits effectiveness across all concentrations. At a high concentration of 1000 micrograms/ml, it demonstrates 80% activity against Leishmania. Similar to BIMP, its metal complex also exhibited Antileishmanial activity. Cu-BIMP is effective against leishmania at all concentrations, exhibiting approximately 85% activity at a concentration of 1000 micrograms/mL. Zn-BIMP is another effective compound for treating Leishmaniasis, demonstrating significant levels of activity. At a concentration of 1000 micrograms per milliliter, this compound exhibited almost 90% activity. The Co-BIMP compound shows high activity against Leishmania at every concentration.

Table 1. Characteristic FT-IR bands (cm-1) of the H-BIMP, Cu- BIMP, Ni- BIMP, Co- BIMP, Zn- BIMP.

Compounds	C=N cm^{-1}	O-M cm^{-1}	M-N cm^{-1}	C-Br cm^{-1}	C-OH cm^{-1}
(BIMP)	1609	-	-	675	1477
[Cu-BIMP]	1604	413	526	672	-
[Zn-BIMP]	1595	493	586	677	-
[Ni-BIMP]	1603	452	571	677	-
[Co-BIMP]	1596	493	570	677	-

Table 2. Percentile inhibition of BIMP and M-BIMP towards leishmania.

Compound No	Compound code	1000ug/ml	500ug/ml	250ug/ml
01	Cu- BIMP	84.86	62.46	39.44
02	Ni-BIMP	92.62	64.36	47.97
03	BIMP	79.85	52.48	38.83
04	Co-BIMP	90.20	59.53	48.08
05	Zn-BIMP	77.95	56.78	23.20
06	Cu-BIMP(c)	92.66	55.71	45.23
07	Meltifosine	97.82	97.82	97.82

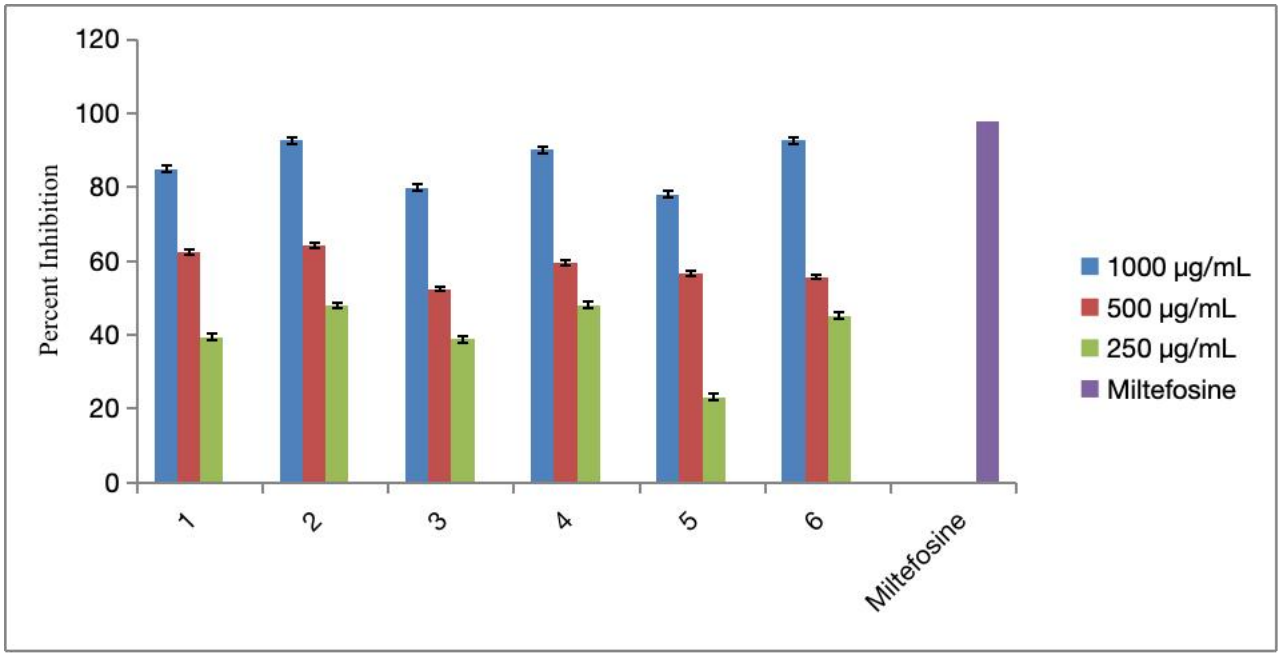

Figure 5. Graph of Antileishmanial activity of H-BIMP and its metal complexes.

Table 3. CC50 values of H-BIMP and its metal complexes

Compound No	Compound code	1000ug/ml	500ug/ml	250ug/ml	CC50ug/ml
01	Cu- BIMP	92.02981651	35.66513761	13.8188073	612.952381
02	NI-BIMP	34.74770642	17.43119266	5.963302752	1424.189189
03	BIMP	36.52522936	17.88990826	6.594036697	1351.871795
04	Co-BIMP	15.76834862	6.594036697	5.103211004	3534.571429
05	Zn-BIMP	23.39449554	10.4357798	4.873853	2150.208333
06	Cu-BIMP(c)	91.51376147	10.7798165	4.357798	628.5746199

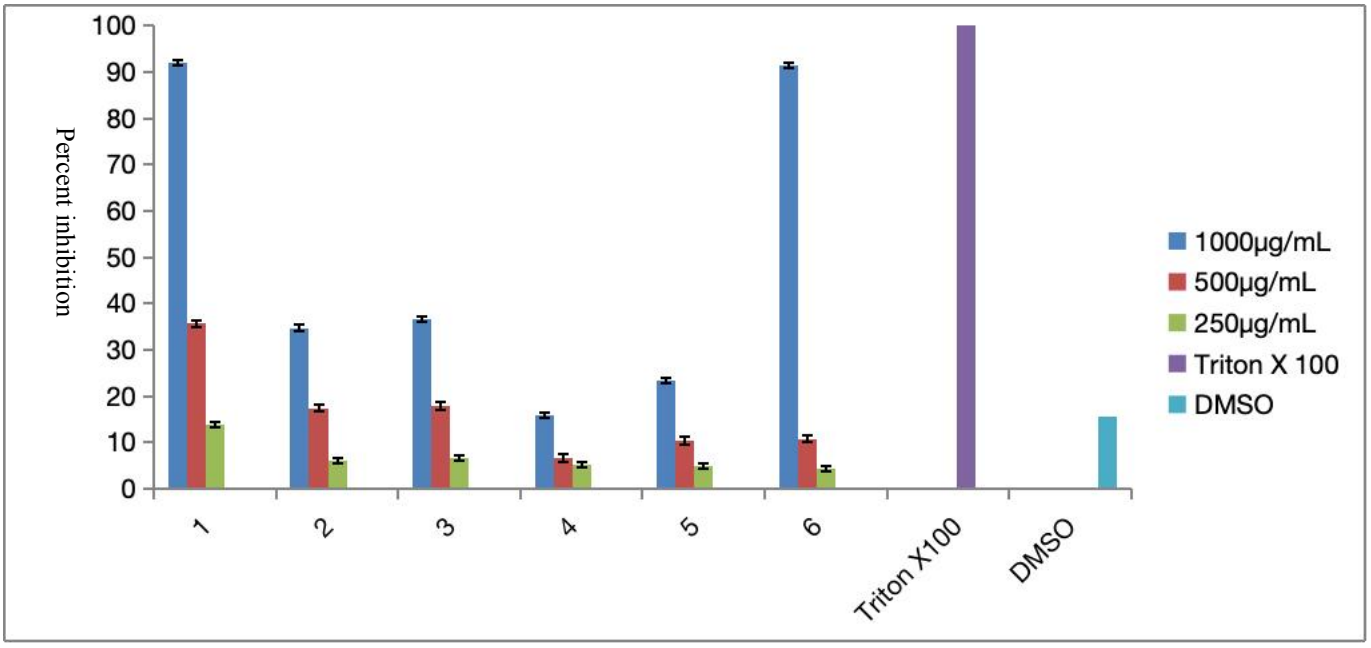

Figure 6. Graph for cytotoxic activity of H-BIMP and its metal complexes.

Table 4. Percent Homolysis values of H-BIMP and its metal complexes.

Compound No	Compound code	1000ug/ml	500ug/ml	250ug/ml
01	Cu-BIMP	92.02981651	33.66513761	13.8188073
02	Ni-BIMP	34.74770642	17.43119266	5.963302752
03	BIMP	36.52522936	17.88990826	6.594036697
04	Co-BIMP	15.76834862	6.594036697	5.103211004
05	Zn-BIMP	23.39449554	10.4357798	4.873853
06	Cu-BIMP(c)	91.51376147	10.7798165	4.357798

The activity of the metal complex with a concentration of 1000 micrograms per milliliter exhibited nearly 90% activity, surpassing all other metal complexes, including the ligand. Ni-BIMP shows lower effectiveness than other metal complexes

in its Antileishmanial activity. T 1000microgram/ml replicate it shown activity of about 80%. Cu-BIMP crystals were screened towards Leishmania, this compound was found extremely good for the inhibition of leishmania. 1000microgram/ml replicate are about 95% active. Overall, the antileishmanial results shown that metal complexes of Schiff base ligand like 2-{(E)-[(4-bromophenyl)imino]methyl}phenol are active because of the presence of Salicyldehyde group as shown in Fig no 5. The presence of metal ion also imparted effects on the overall activity as may be seen in difference of the activity among the metal complexes. Copper and cobalt centered metal complexes were extremely good toward antileishmanial activity.

3.3. Cytotoxicity

Compounds including H-BIMP, Cu-BIMP, Zn-BIMP, Co-BIMP, Ni-BIMP, and Cu-BIMP (crystal) were evaluated for their cytotoxic effects on erythrocytes. The cytotoxicity of all synthesized compounds, including H-BIMP, Cu-BIMP, Zn-BIMP, Co-BIMP, Ni-BIMP, and Cu-BIMP (crystal), was assessed using Tritonx100 as a positive control and DMSO as a negative control, with three replicates per experiment. When these substances are evaluated against tritonx100, they exhibit some level of toxicity. H-BIMP imine ligand is tested on blood cells, at elevated levels these substances display harmful effects on red blood cells. By examining their CC50 values, we can readily study their level of inhibition. H-BIMP demonstrated a CC50 value of 1351ug/ml, suggesting that it is not as toxic to red blood cells as the standard drug as shown in Fig no 6. Substances with a high CC50 value are considered less dangerous, while those with a low CC50 value are more hazardous. Co-BIMIP, Ni-BIMP, and Zn-BIMP exhibited high CC50 values at high concentrations, indicating lower toxicity, while Cu-BIMP and Cu-BIMP(c) showed some harmful effects on RBCs at low CC50 values. All compounds are highly effective at high concentrations, but their toxicity at low concentrations is lower than that of the DMSO negative control. We can conclude from this experimental data that compounds are less toxic if they have a low percentage of Hemolysis and a high CC50 value.

4. Conclusion:

By reacting 4-bromoaniline with salicylaldehyde, the novel Schiff base ligand 2-{(E)-[(4-bromophenyl) imino] methyl} phenol was created using the magnetic reflux method. Spectral methods were used to characterize the produced ligand and its complexes. Schiff base complexes were created by reacting a synthesized imine ligand with transition metal salts. Cu-acetate, Zn-acetate, Co-acetate, and Ni-acetate are salts. The antileishmanial and cytotoxic properties of the synthesized compounds were tested. With no cytotoxicity, the Schiff base ligand and its transition complex are effective antileishmanial.

Authors Contribution

Uzair Khan and Sara Ali conceptualized the study, supervised the research, and contributed to the design of the methodology and manuscript revisions. Zama Jan and Muhammad Jamshed participated in data collection, data analysis, and drafting the manuscript. All authors reviewed and approved the final version of the manuscript. Uzair Khan served as corresponding author and ensured the overall quality and completion of the work.

Conflicts of Interest

There is no conflict of interest between the authors.

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Data Availability statement

The data presented in this study are available on request from the corresponding authors.

Funding

Not applicable

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