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Synthesis, characterization and anticancer activity of novel schiff base ligand and its metal complexes

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This work represents the synthesis of a (E)-1-(1-(4-cyanophenyl)ethylidene) thiosemicarbazide ligand and its Mn(II), Co(II) and Cu(II) complexes. ^{1}H NMR, ^{13}C NMR Spectroscopy, IR and mass spectroscopy were some of the physical and spectral characterisation methods used to examine the produced complexes. The azomethine ligand is effective against microbes, but the metal complexes, especially Mn(II) complexes, were shown to be more effective against *Staphylococcus aureus* (*S. aureus*) bacterium. When tested against *Aspergillus fumigatus* (*A. fumigatus*), all of the metal compounds that were produced showed more antifungal effectiveness than when tested against *Candida albicans* (*C. albicans*). The compounds of Mn(II), Co(II) and Cu(II) has showed moderate to excellent efficacy when tested for anticancer properties against several cancer cell lines.

Keywords: Antimicrobial screening, Azomethine, Characteristics, Spectral analysis

Schiff bases are highly desirable among synthetic nitrogen-containing chemicals because they are more likely to interact with transition metals to create coordination complexes[1]. The simplest way to make Schiff base is to employ a carbonyl molecule (aldehyde/ketone) in a condensation reaction with a primary amine[2]. Coordination of ligands from Schiff bases with ions from transition metals produces coordinated compounds with vibrant colours[3]. The capacity of Schiff bases to compound with various metals makes them useful in analytical chemistry, pharmaceutical chemistry, biology, organic chemistry and inorganic chemistry, among other fields[4-9]. The azomethine group (-C=N-) is known to enhance the reliability of Schiff base in medicinal chemistry[10]. This is due to the two electrons on the -N atom, which are actively involved in chelation with transition metal ions[11].

It is well-known that Schiff's base compounds have antimicrobial, antiviral, antioxidant, antitumor, antifungal, anti-cancer, anti-helminthic, anti-tuberculosis, analgesic, DNA binding, and photo-cleavage characteristics. At the same time, the use of anti-microbial medications has grown in prominence during the last several years[12-22]. To stop the development of drug-resistant bacteria in our populations, we must discover new types of antibiotics[23]. Schiff bases containing a nitrogen donor atom are versatile ligands that may be used to synthesize a wide range of transition metal complexes[24]. These complexes have several uses in both organic and inorganic areas[25]. The analysis of ligand and its metal complexes was carried out using ^{1}H NMR, ^{13}C NMR, Mass spectrometry[26-28]. In comparison to the ligand, the results showed that the metal complexes exhibited better antibacterial activities[29].

Materials and Methods

The substances were distilled before to use following standard technique and were of analytical grade. The Elementar Vario EL III analyzer was used for the elemental analysis of CHN. The analyses were repeated twice to guarantee the accuracy of the findings. A Shimadzu 8001-PC FTIR spectrophotometer was used to record the infrared spectra of the KBr pellets. Using a Universal TGA Q50 apparatus, which can heat samples from 30 to 1000°C at a rate of 2°C/min, thermo gravimetric analysis (TGA) was carried out. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz using a Bruker ARX-300 instrument. When compared to tetramethylsilane, the chemical changes in the presence of deuterated DMSO are reported in parts per million (ppm).

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Synthesis and characterization of ligand

The Schiff base ligand (E)-1-(1-(4-cyanophenyl) ethylidene)thiosemicarbazide was prepared by mixing a hot methanolic solution of 4-acetylbenzonitrile (0.02 mol) with thiosemicarbazide (0.02 mol) in an equimolar ratio (1:1:1) and three drops of hydrochloric acid (HCl) on a magnetic stirrer. The mixture was microwaved for 7 min at 85°C. After cooling to ambient temperature, the reaction mixture crystallized overnight. After precipitation, the milky white solid was filtered, rinsed with distilled water and desiccated[30].

White colour, yeild: 82%, $T_{m.p}$: 194-195. IR (KBr) υ: 1700 (CN), 1580 (NH_2), 1276(CS) cm^{-1}. ^1H NMR spectrum, δ, ppm: 9.88 s (1H, NH), 7.86 m (2H, ArH), 7.63 m (2H, Ar-H), 6.73 s (2H, NH_2), 2.07 s (3H, CH_3); ^{13}C NMR spectrum, δ C, ppm: 181.20, 146.09, 139.07, 133.01, 131.63, 119.12, 111.42, 15.45: Mass spectrum: *m*/*z* 218.10, Found: 218.25; Anal. Cacld for $C_{10}H_{10}N_4S$; C 55.02; H 4.62; N 25.67; Found: C 55.05; H 4.63; N 25.69.

Synthesis and characterization of metal complexes

The chemical method involved using suitable solvent to synthesize the ligand and metal complexes. The azomethine ligand and metal salts (Mn(II), Co(II), Cu(II)) were reacted to form various metal compounds in 1:2 M. The following $MnCl_2.4H_2O$, $CoCl_2.6H_2O$ and $CuCl_2.5H_2O$ was added 1:2 M to a methanolic solution of (E)-1-(1-(4-cyanophenyl) ethylidene)thiosemicarbazide. The resultant mixture has been heated for 7-9 and 4-8 min. The TLC studies were used to track the reaction's development. After the reaction, the colored solids were filtered, washed with 50% ethanol and desiccated.

Mn(II) complex

Cream colour, yeild: 83%, $T_{m.p}$: 273-275. IR (KBr)υ: 1650 (CN), 1550 (NH_2), 575 (M-S), 468 (M-N) cm^{-1}. ^1H NMR spectrum, δ, ppm: 9.88 s (2H, NH), 7.96 m (4H, ArH), 7.60 m (4H, Ar-H), 6.73 s (4H, NH_2), 2.06 s (6H, CH_3); ^{13}C NMR spectrum, δ C, ppm: 181.42, 168.72, 146.09, 138.37, 138.20, 132.32, 129.62, 129.56, 115.12, 114.42, 14.41: Mass spectrum: *m*/*z* 562.30, Found: 562.27; Anal. Cacld for $C_{20}H_{20}Cl_2MnN_8S_2$; C 42.71; H 3.58; N 19.92; Found: C 42.75; H 3.60; N 19.95.

Co(II) complex

Brownish colour, yeild: 85%, $T_{m.p}$: 275-277. IR (KBr)υ: 1649 (CN), 1650 (NH_2), 592 (M-S), 437 (M-N) cm^{-1}. ^1H NMR spectrum, δ, ppm: 9.84 s (2H, NH), 7.82 m (4H, ArH), 7.50 m (4H, Ar-H), 6.53 s (4H, NH_2), 2.10 s (6H, CH_3); ^{13}C NMR spectrum, δ C, ppm: 181.42, 181.32, 168.72, 138.37, 138.25, 132.32, 129.62, 129.52, 115.82, 115.56, 114.90, 14.12, 14.08: Mass spectrum: *m*/*z* 565.50, Found: 562.72; Anal. Cacld for $C_{20}H_{20}Cl_2CoN_8S_2$; C 42.41; H 3.56; N 19.78; Found: C 42.45; H 3.60; N 19.82.

Cu(II) complex

Purple colour, yeild: 89%, $T_{m.p}$: 297-299. IR (KBr)υ: 1700 (CN), 1580 (NH_2), 548 (M-S), 419 (M-N) cm^{-1}. ^1H NMR spectrum, δ, ppm: 9.85 s (2H, NH), 7.85 m (4H, ArH), 7.54 m (4H, Ar-H), 6.55 s (4H, NH_2), 2.08 s (6H, CH_3); ^{13}C NMR spectrum, δ C, ppm: 181.45, 165.52, 138.75, 138.55, 131.52, 128.52, 127.42, 117.82, 114.46, 114.20, 14.12, 14.10: Mass spectrum: *m*/*z* 569.70, Found: 569.26; Anal. Cacld for $C_{20}H_{20}Cl_2CuN_8S_2$; C 42.07; H 3.53; N 19.62; Found: C 42.09; H 3.55; N 19.65.

Results and Discussion

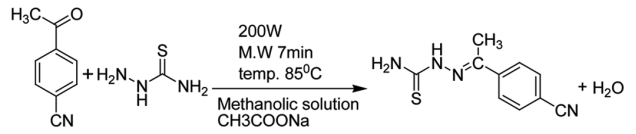
The Schiff base ligand (E)-1-(1-(4-cyanophenyl) ethylidene)thiosemicarbazide was prepared by combining a hot methanolic solution of 4-acetylbenzonitrile (0.02 mol) with a hot methanolic solution of thiosemicarbazide (0.02 mol) in an equimolar ratio (1:1:1), as well as three drops of hydrochloric acid (HCl) while stirring continuously on a magnetic stirrer (Scheme 1). As thiosemicarbazide polymerizes at pH levels greater than 6, the addition of HCl serves to inhibit this process when it comes into contact with a water condenser. The resultant mixture was subjected to 7 min of microwave radiation at 85^0C. Following that, the reaction mixture was allowed to cool to ambient temperature and then left overnight to get compound. The resulting milky white solid was filtered, rinsed with distilled water, and then dried in a desiccator after precipitation. Silica gel is used as a moisture absorber in the desiccator. The yield was expected to be 82%.

In a 1:2 M ratio several metal compounds were synthesized by reacting the azomethine ligand with metal salts (Mn, Co, Cu). The following amounts of $MnCl_2.4H_2O$, $CoCl_2.6H_2O$ and $CuCl_2.5H_2O$ were added to a methanolic solution of (E)-1-(1-(4-cyanophenyl)ethylidene)thiosemicarbazide in a 1:2 M ratio respectively. In Scheme 2, the reaction mixture was subjected to microwave irradiation for durations of 7-9 min and 4-8 min respectively. The progress of

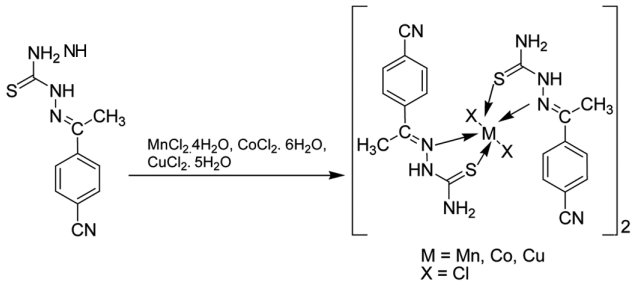
the reaction was monitored by TLC studies. Once the reaction had finished, the colored solids were filtered, rinsed with a 50% ethanolic solution and then dried in a desiccator.

Antimicrobial activity

The synthesized compounds were tested for their antimicrobial properties using two different kinds of tests, one for bacteria and one for fungus[31]. A solution containing 10 mg/mL of Schiff base ligand and its complexes was prepared by dissolving them in methanol. Using Muller Hinton Agar medium and the Disc diffusion technique, we investigated the antibacterial effect of the named compounds against *E. coli* and *S. aureus*[32]. We sterilized the solution at 121°C for 30 min. The nutritional agar was mixed until completely smooth after being mixed with peptone water. The filter paper discs were placed on the SDA plates, and all of the media was transferred to them[33]. After being deposited on individual discs of filter paper the mixture was maintained at 37°C for 24 h. The ligand and its complexes antibacterial activities resulted in the formation of basic circular inhibitory zones[34]. Amoxicillin is the most often used antibacterial medication. The millimeter-scale inhibitory zones of all the complexes



Scheme 1 — Synthesis of (E)-1-(1-(4-cyanophenyl)ethylidene) thiosemicarbazide



Scheme 2 — The synthetic pathway of Schiff base metal complexes

were determined[35,36]. 4-acetyl-benzonitrile thiosemicarbazone served as the ligand against which the outcomes were evaluated. The ligand biological activity is nearer to the some of the metal complexes because of strong interactions with the bacterial and fungal strains leads to more effective binding and biological sites.

The aforementioned compounds were tested for their antifungal activity utilizing a disc diffusion procedure and Sabouraud dextrose agar medium, which is similar to how they are tested for their antibacterial action. The fungus strains used in this investigation were *Aspergillus fumigatus* and *Candida albicans*. We sterilized the medium at 121°C for 30 min[37]. Each compound was placed on its own filter paper disc and left at 37°C for 24 h. Fungi albicans develops at 28°C for 24 h, whereas *A. fumigatus* takes 2-3 days at 37°C[38]. Simple circular inhibitory zones were formed as a result of the antifungal activities of the ligands and complexes (Table 1). Millimeters were used to determine the inhibition zones of each chemical. There was a comparison between the ligand, 4-acetylbenzonitrile thiosemicarbazone and the results of the compound's activity[39,40].

Anticancer activity

The anticancer potential of compounds (Mn(II), Co(II), Cu(II)) was studied by assessing their ability to suppress the proliferation of tumor cell lines in 96-well plates by cell-mediated inhibition of tetrazolium salt to water-insoluble crystal formation doxorubicin was used as a reference. MTT experiments were performed on four distinct human tumor cell lines (A549), Hela (human cervical cancer cells), MDA-MB-231 (human breast adenocarcinoma cells) and HEK 293 (normal human embryonic kidney cell line) to measure cytotoxicity[41,42]. Inhibitory concentration (IC_{50}) values were obtained using dose-response curves constructed from absorbance data. The median and standard deviation of IC_{50} values (in μM) from three different experiments are shown. As indicated in Table 2, the majority of the produced compounds had a considerable cytotoxic impact on all cells[43-45].

Table 1 — Antimicrobial data of ligand and its complexes

Compounds	*E. coli*	*S. aureus*	*C. albicans*	*A. fumigatus*
Ligand	10	12	10	09
Mn(II)	17	18	19	20
Co(II)	16	15	17	13
Cu(II)	13	15	18	14
Amoxicilin	10	11	12	11

Table 2 — *In vitro* anticancer activity of compounds

Compound	IC_{50} Values in μM				
Cell lines	A549	Hela	MDAMB231	MCF-7	HEK 293
Ligand	5.05	2.36	4.25	1.92	>100
Mn(II)	7.05	3.70	4.09	10.27	>100
Co(II)	>100	5.66	4.13	6.13	>100
Cu(II)	13.09	6.88	4.87	>100	>100

Conclusion

A newly synthesized and characterized Azomethine ligand (E)-1-(1-(4-cyanophenyl) ethylidene) thiosemicarbazide and its Mn^{2+}, Co^{2+} and Cu^{2+} metal complexes are detailed in this paper. To determine the structure, a number of spectrum investigations were conducted, including IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy as well as elemental analysis. It was concluded that the ligand was bidentate, having sulfur and azomethine nitrogen atoms bound to metals. Octahedral geometries were shown by the metal complexes. Antimicrobial activity against bacterial strains *S. aureus* and *E. coli* as well as fungal strains *A. fumigatus* and *C. albicans* was tested for in the produced compounds. According to the chelation hypothesis, metal complexes have superior antimicrobial effects compared to ligand. Mn(II), Co(II) and Cu(II) compounds shown moderate to superior anticancer activity against a variety of cancer cell types.

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Conflict of interest

All authors declare no conflicts of interest.

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