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Preparation and Characterization of Schiff Base Ligand (E)-2-(2-Oxoindolin-3-Ylidene) Hydrazine-1- Carbothioamide and its Metal Complexes with Study of Their Impact on the Division of Lymphocyte Cells of Humans

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Abstract

This research involves the synthesis of the Schiff base ligand (E)-2-(2-oxoindolin-3-ylidene)hydrazine-1-carbothioamide (L^M) from the reaction of indoline-2,3-dione with thiosemicarbazide and characterization using ^{1}HNMR, UV-Vis, FT-IR, spectroscopy and C.H.N. This Schiff base ligand utilized for the synthesizing of its metal ions complexes from its reaction with several compounds ($CoCl_2.6H_2O$, $NiCl_2.6H_2O$, $CuCl_2.2H_2O$, and $ZnCl_2$). The prepared complexes $[M(L^M)_2]Cl_2$ characterized using various techniques such as: FTIR, UV-Vis, A. A spectroscopy, molar conductivity and magnetic susceptibility. Both the Schiff base ligand and the complexes tested for their biological activity against the Lymphocyte cells of humans in order to measure the Mitotic Index. The results showed that the effect of Zinc and Copper complexes on the rate of division of lymphocyte cells was higher compare with the effect of the Cobalt, Nickel complexes and the Schiff base ligand utilizing a concentration of 100 µg/mL at 15 minutes of exposure. From that it can be infer that the Copper and Zinc

complexes were the closest to colchicine for stopping lymphocyte division in the equatorial phase.

Keywords: Thiosemicarbazide, Colchicine, Mitotic Index, Transition elements.

Introduction

Heterocyclic compounds importance are primarily used as drugs, antioxidants, corrosion, inhibitors, copolymers, and dying materials. They use to synthesize other organic materials, including compounds for some natural products, antibiotics like penicillin and alkaloids such as morphine and heterocyclic moiety [1]. Indole is a heterocyclic compounds formes from pyroyl ring fusion with benzene ring [2]. Indole is a major component for hormones of natural plant, in addition that, it plays an important role in the animals' biochemistry [3]. Isatin is made up of indole nucleus and two types of carbonyl groups, keto and lactam group, it was discovered 150 years ago by Erdman and Laurent in 1841[4]. Isatin and its derivatives are widely used as substrates for the synthesis of pharmaceuticals as well as starting materials for the synthesis of heterocyclic compounds due to their wide range of biological and pharmacological properties [5]. Generally, Schiff bases formed from condensation reaction of a primary amine and an aldehyde or ketone, those are from aromatic aldehydes are more stable than those of aliphatic aldehydes which are comparatively more unstable and are easily polymerized. The existence of an electron lone pair on the atom of nitrogen for the azomethine is of large chemical and biological prominence. Schiff bases over the years have played an animated role as chelating ligands in coordination chemistry, because of their immutability with different oxidation and reduction conditions difference, as well as the imine ligands are considered the borderline between soft and hard Lewis bases [6]. Schiff bases complexes can be used in different applications like medicinal and pharmaceutical fields, industrial and bioinorganic chemistry, catalytic properties, and material science [7].

Lymphocytes are cells that circulate in our blood that are part of the immune system because lymphocytes are the cells that determine the specificity of the immune response to infectious microorganisms and cancer and other foreign substances. In human adults, lymphocytes make

up roughly 20 to 40 percent of the total number of white blood cells [8]. A deviation in lymphocytes number from the reference values indicate an abnormal state and hence, require immediate diagnosis. Therefore, proper interpretation of lymphocytes abnormalities in the lymphocytosis form and lymphopaenia would help a clinician in the appropriate description, diagnosis and management of pathological and physiological cases [9]. This study measured the ability of the synthesized ligand and its complexes on Mitotic Index in the lymphocytes cells of humans.

Materials and Methods

The materials used in the study were Indolin-2,3-dione, Zinc chloride anhydrous and Acetic acid (99% purity, Aldrich), Thiosemicarbazide (98% purity, Aldrich), Cobalt chloride hexahydrate (96% purity, Aldrich), Nickel chloride hexahydrate (99% purity, Fluka), copper chloride dihydrate (99% purity, ACS), Dimethyl sulphoxide DMSO (98% purity, BDH). Sodium Bicarbonate (96% purity, BDH),

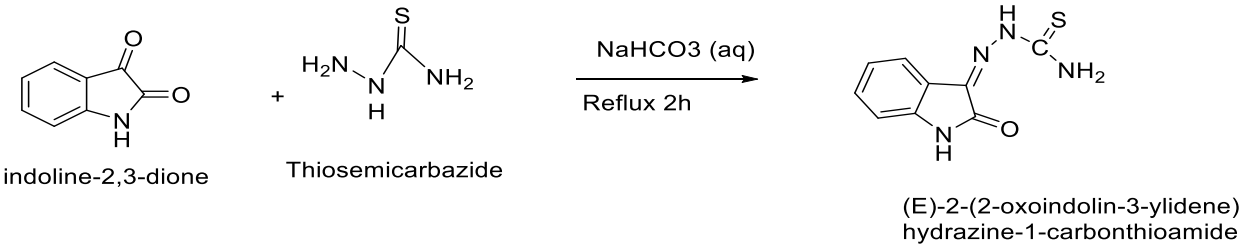
The instrumentations utilized in this study were Melting point SMP10, FTIR spectrophotometer PERKIN ELMER SPEACTUM-65 using a KBr disc in the range 4000-400, NMR spectrophotometer Bucker Bio Spin GmbH, NMR spectrometer recorded in d^6-DMSO. UV-Vis spectrophotometer UV-160 A Shimadzu using 1.0 cm quartz cell at room temperature range of wavelength 200-1000 nm. The elemental analysis C.H.N EM-017 mth instrument, atomic absorption Shimadzu Atomic Absorption 680 Flam Spectrophotometer, and Balance Magnetic Susceptibility Model MSB-MKI to determine magnetic Susceptibility using the Faradays method. The molar conductivity (Λ_m) of the complexes were registered at (25 ºC) for (0.001 M) solution of the samples in DMSO using conductivity meter, inolab / Germany.

Procedure

Synthesis of the Schiff base ligand (L^M)

Dissolve Indoline-2,3-dione (0.85 g, 5.8 mmol) in an aqueous solution of sodium bicarbonate (1.18 g, 14.1 mmol) in 80 mL water. Thiosemicarbazide (0.60 g, 6.6 mmol) was added to this solution and the mixture refluxed for 2 h. The reaction completion checked utilizing TLC (mobile phase, 1ethyl acetate: 3 hexane). After cooling down of solution to the room

temperature acidified with acetic acid in the second day and left overnight [10]. The precipitate filtered, washed with water and dried in air. Scheme (1) shows the preparation method. The result was a yellow precipitate; Yield (51%); m. p=245-248 ºC; Anal. Calc. for $C_9H_8N_4OS$ (220.25), C (49.08), H (3.66), N (25.44). Found: C (49.38), H (3.76), N (25.66); ^{1}H-NMR (400 MHz) δ (ppm): 12.48 (s, 1H, N*H*–C=O), 11.21 (s, 1H, N*H*–C=S), 9.06 (s, 1H, N*H*$_2$), 8.69 (s, 1H, N*H*$_2$), 7.66- 6.91 (m, 4H, Ar-*H*). ^{13}C-NMR (100 MHz) δ (ppm): 179.12 (NH–*C*=S), 163.09 (NH–*C*=O), 142.81 (*C*=N), 132.49, 131.71, 122.83, 121.42, 120.44 and 111.49 (Ar-H). FT-IR (cm^{-1}): 3421 and 3337(NH_2), 3264 (N–H hydrazide), 3165 (N-H amide), 3063(C–H aromatic), 1673 (C=O), 1623 (C=N); UV/Vis in nm (cm^{-1}): π→π*= 273 (36630) and 296 (33783), n→π*= 369 (27100).



Scheme 1: The synthetic pathway of (L^M) Schiff base ligand

Synthesis of [M (L^M)$_2$]Cl_2 Complexes

The complexes [M(L^M)$_2$]Cl_2 were synthesized by gradual addition of one equivalent of transition element ions (0.44 mmol) dissolved in 10 ml of ethanol to two equivalents of the Schiff base ligand (0.2 gm, 0.88 mmol) dissolved in 20 ml of ethanol. A few drops of potassium hydroxide (5%) added to the solution. Later, the mixture refluxed for two hours in a water bath at 78° C, then the solvent partially evaporated, and the precipitate was filtered off, washed with water and dried.

The complex of [Co(L^M)$_2$]Cl_2**:** 38 % black precipitate; m. p (200-203 ºC) decomposition; Anal. Calc. for $C_{18}H_{16}Cl_2CoN_8O_2S_2$ (570.33), C (37.87), H (2.80), N (19.63), Co (10.33), Found: C (38.17), H (2.92), N (19.85), Co (10.48); μ_{eff} (B. M) = 6.36; Λ in DMSO solvent = 76 cm^2.ohm^{-1}. mol^{-1}; FT-IR spectrum (cm^{-1}): 3428 (NH_2), 1746 (C=O), 1617 (C=N), 681 (Co-N), 408

(Co-O); UV-Vis in nm (cm^{-1}): Intra ligand= 269 (37174, 288 (34722) and 328 (30487), charge transfer= 399 (25062), $\upsilon_3 = {}^4T_1g_{(F)} \rightarrow {}^4T_1g_{(p)}$= 583 (17152).

The complex of $[Ni(L^M)_2]Cl_2$: 38% brown precipitate ; m.p (> 300 ºC) decomposition; Anal. Calc. for $C_{18}H_{16}Cl_2NiN_8O_2S_2$ (570.09), C (37.88); H (2.80); N (19.64); Ni (10.29), Found: C (38.01); H (2.96); N (19.81); Ni (10.52); μ_{eff} (B.M) = 2.71; Λ in DMSO solvent = 74 $cm^2.ohm^{-1}.mol^{-1}$; FT-IR spectrum (cm^{-1}): 3361 (NH_2), 3278 (N-H hydrazide), 3164 (N-H amide), 1692 (C=O), 1672 (C=N), 643 (Ni-N), 498 (Ni-O); UV-Vis in nm (cm^{-1}): Intra ligand= 266 (37593) and 364 (27472), MLCT= 444 (22522), $\upsilon_2 = {}^3A_2g \rightarrow {}^3T_1g_{(F)}$ = 744 (13440), $\upsilon_1 = {}^3A_2g \rightarrow {}^3T_2g_{(F)}$ =983 (10172).

The complex of $[Cu(L^M)_2]Cl_2$: 65% brown precipitate ; m.p (280-282 ºC) decomposition; Anal. Calc. for $C_{18}H_{16}Cl_2CuN_8O_2S_2$ (574.94), C (37.56); H (2.78); N (.48); Cu (11.05), Found: C (37.78); H (2.98); N (19.56); Cu (11.98); μ_{eff} (B. M) = 1.61; Λ in DMSO solvent =69 $cm^2.ohm^{-1}.mol^{-1}$; FT-IR spectrum (cm^{-1}): 3418 and 3353 (NH_2), 3230 (N-H hydrazide), 3152 (N-H amide), 1703 (C=O), 1600 (C=N), 625 (Cu-N), 449 (Cu-O); UV-Vis in nm (cm^{-1}): Intra ligand= 272 (36764) and 296(33783), charge transfer = 374 (26737), $\upsilon = {}^2E_g \rightarrow {}^2T_2g$ = 737 (13568).

The complex of $[Zn(L^M)_2]Cl_2$: 39% light yellow precipitate ; m. p (290-293 ºC) decomposition; Anal. Calc. for $C_{18}H_{16}Cl_2ZnN_8O_2S_2$ (576.78), C (37.44); H (2.77); N (19.41); Zn (11.33), Found: C (37.97); H (2.90); N (19.66); Zn (11.98); μ_{eff} = 0.00 B. M; Λ in DMSO solvent = 82 $cm^2.ohm^{-1}.mol^{-1}$; FT-IR spectrum (cm^{-1}): 3493 and 3437 (NH_2), 3369 (N-H hydrazide), 3151(N-H amide), 1692 (C=O), 1614 (C=N), 644 (Zn-N), 494 (Zn-O); UV-Vis in nm (cm^{-1}): Intra ligand= 265 (37735) and 344 (29069), charge transfer= 430 (23255).

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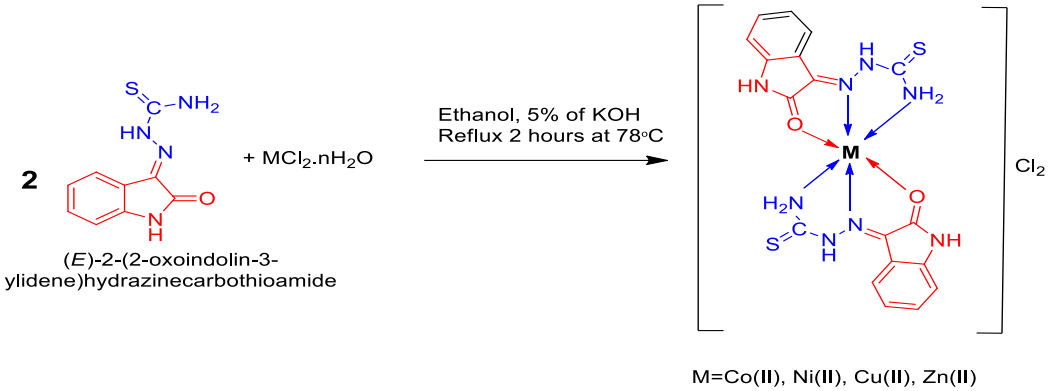

(*E*)-2-(2-oxoindolin-3-ylidene)hydrazinecarbothioamide

Scheme 2. The synthetic pathway of $[M(L^{M})_2]Cl_2$ Complexes

Biological activity of the synthesized compounds

The investigation into the impact of both the ligand and its complexes on lymphocytes involved short-term culture, following the methodology outlined by Verma and Babu [11]. Random blood samples collected from individuals across various age groups using a 5ml heparin solution-filled medical syringe for each participant. These blood samples utilized in the subsequent experiments.

1. Blood and prepared compound transplantation:

Inject 0.2 mL of each compound into the complete plant medium PMRI-1640, considering the final mixture volume. Subsequently, 0.5 mL of blood added to each tube using a 5 ml syringe. Following this, 0.1 mL of lymphocytes added and thoroughly mixed with the medium. The tubes incubated at a tilted angle at 37 °C for 72 hours, with periodic mixing of the content every 12 hours. One of the tubes designated as the control and left without the addition of any prepared compound to serve as a reference for comparison.

2. Harvesting of Cell:

A volume of 0.1 mL of colchicine, with a concentration of 100 µg/mL introduced into the control tube 15 minutes before concluding the initial culture period. In contrast, the treated tubes did not receive any colchicine. Subsequently, all tubes returned to the incubator. After incubation, the tubes underwent centrifugation at 1500 rpm for 10 minutes, resulting in the

removal of the supernatant. The resulting precipitate thoroughly mixed with the remaining culture medium. To each tube, 5-10 mL of 0.075 M hypotonic solution was gradually added and gently warmed with intermittent shaking, using a water bath set at 37 °C for 30 minutes. Following this, the tubes were subjected to centrifugation at 1500 rpm for 10 minutes, and the supernatant was discarded.

3. Fixation, Washing, Dropping, Pigmentation, microscopy, and Mitotic Index

The fixation process was repeated until the suspension displayed a distinct color. The precipitate was re-suspended by adding 1 mL of the fixative, and the mixture was stored at -20°C. Clean, chilled, and moisture-free glass slides were prepared, and the cells were thoroughly mixed before being dispensed onto the cold slides using a Pasteur pipette from a distance of 0.5-1m. The slides then left to air-dry. Subsequently, they stained with a Giemsa stain prepared in a warm Sorensen buffer solution at a 4:1 ratio for 2-3 minutes, washed with Sorensen buffer, and allowed to dry. The stained slides examined under a light microscope to determine the Mitotic Index (MI), calculated by the following equation [12]:

(MI) = {The number of dividing cells \ The total number of cells is 1000}*100

Statistical analysis:

Statistical analysis of the results conducted utilizing the experiment of Duncan Multiplex, and significant differences were noted at an eventuality level of $P < 0.05$.

Results and Discussion

Characterization of the Schiff base ligand and the complexes

Nuclear Magnetic Resonance (NMR) spectrum of the L^M Schiff base ligand.

The ^{1}H-NMR spectrum of the **Schiff base** ligand, as depicted in Figure 1, exhibits single peaks at 12.48 and 11.21 ppm, corresponding to the protons of the NH amide and hydrazide respectively. While the signals at 9.06 ppm and 8.69 ppm assigned to the two protons of the amine group. Additionally, signals within the range of 7.66 to 6.91 ppm attributed to the aromatic ring protons. ^{13}C-NMR spectra of the ligand as depicted in Figure 2, confirmed ^{1}H NMR results. A signal appeared at 179.12 ppm which attributed to carbon atom of (C=S) and

a signal at 163.09 ppm which attributed to carbon atom of carbonyl group. In addition a peak at 142.81 ppm attributed to carbon atoms of (C=N) and six signals at 132.49, 131.71, 122.83, 121.42, 120.44 and 111.49 belonged to carbon atoms of aromatic ring[13-15]. Consequently, the observed hydrogen and carbon atoms count in the NMR spectrum aligns with the anticipated structure of the synthesized ligand.

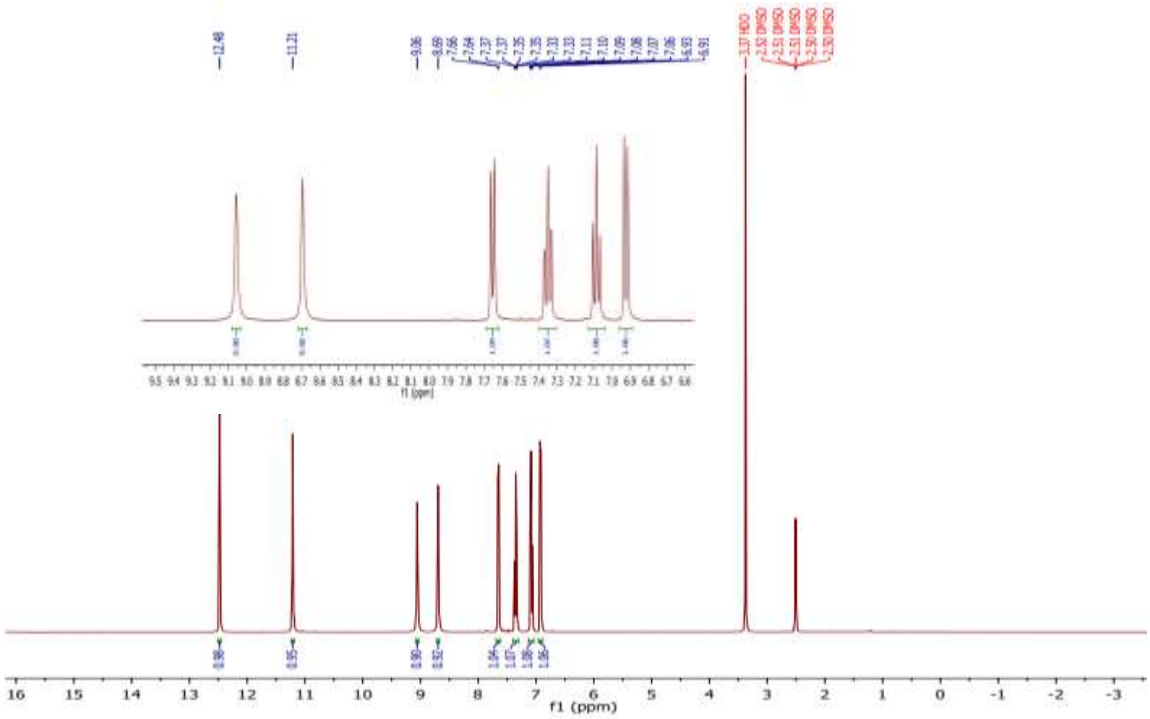

Figure 1: ^{1}H-NMR spectrum of L^{M} Schiff base ligand

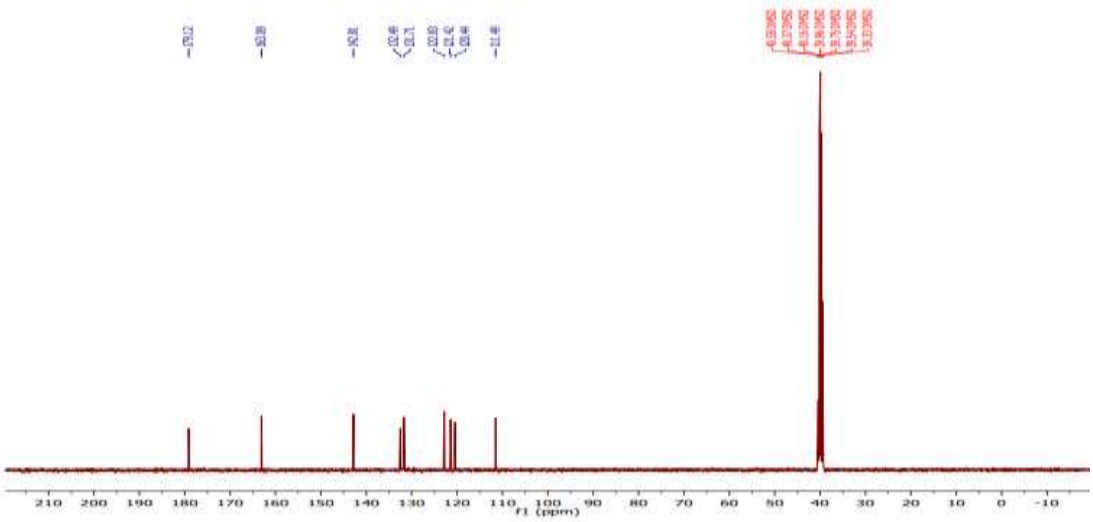

Figure 2: ^{13}C-NMR spectrum of L^M Schiff base ligand

FT-IR and UV/Vis spectra of L^M Schiff base ligand and the complexes

Figure 3 show the FT-IR spectrum of L^M Schiff base ligand that show absorption bands at 3421 cm^{-1} and 3337 cm^{-1} referring to the stretching vibration of the N–H bond for NH_2 group, and absorption band at 3264 cm^{-1} and 3165 refers to the stretching vibration of NH hydrazide and amide groups respectively. The absorption band at 1701 cm^{-1} that attributed to the stretching vibration of a carbonyl group. In addition, the occurrence of absorption band at 1623 cm^{-1} assign to C=N group [16, 17]. All these bands refer to the formation of L^M Schiff base ligand.

The FT-IR spectra of complexes exhibit shifts in the stretching vibrations of (NH_2), (C=O), and (C=N) groups compared to the ligand spectrum. This shift gives evidence on the coordinated the nitrogen and oxygen atoms of (NH_2), (C=N) and (C=O), groups from the ligand into the metal ion. As well as, weak intensity bands in the range of 625-681 cm^{-1} suggest stretching vibrations of M-N, while bands in the range of 408-498 cm^{-1} indicate stretching vibrations of M-O for the complexes [18, 19]. The experimental section includes illustrated FT-IR spectra data for the ligand and its complexes.

The UV/Vis spectrum of L^M ligand Figure 4 displays three distinct bands at 273 nm ($\pi \rightarrow \pi^*$), 296 nm ($\pi \rightarrow \pi^*$), and 369 nm ($n \rightarrow \pi^*$). When examining the spectra of the complexes, a

notable shift in the band positions relative to those of the free ligand observed. Additionally, new bands of low intensity emerge in the visible region, assigned to d-d transitions, providing clear evidence of a metal-ligand coordination and a complex formation. Notably, the complex $[Zn(L^M)_2]Cl_2$ does not exhibit an absorption band in the visible region, because the d orbital is filled with electrons and absence of d-d electronic transitions for d^{10} system. However, a proportional change in the band positions contrasted to those of the ligand suggests coordination between Zn and the ligand. The experimental section includes illustrated UV-Vis spectra data, along with the assigned transitions, for both the ligand and its complexes[20-23].

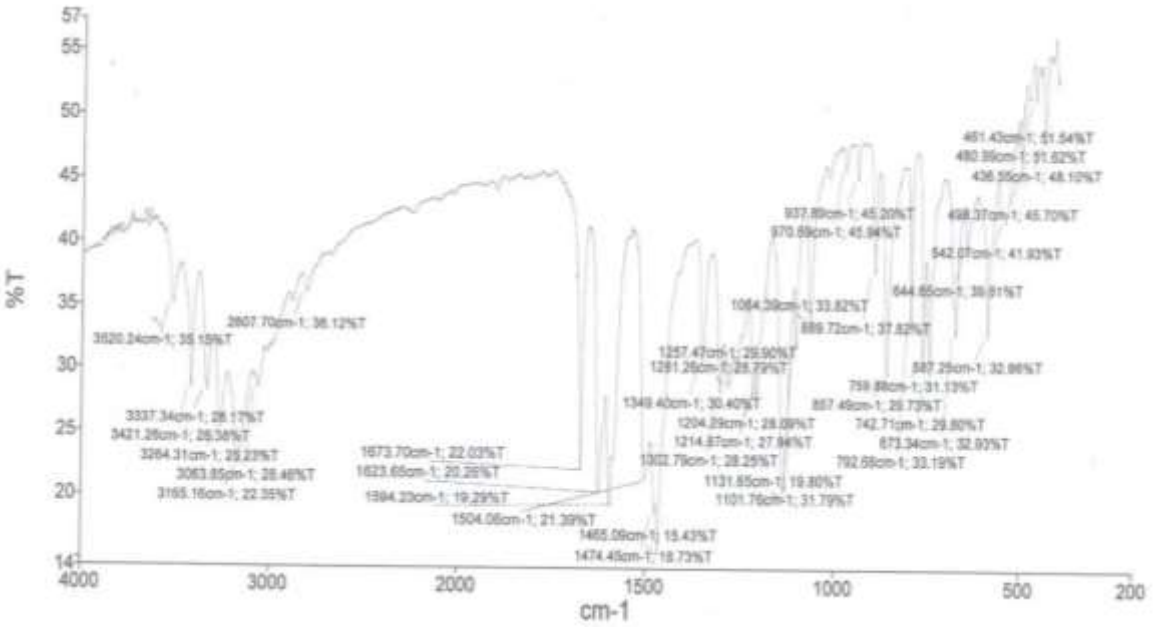

Figure 3: FTIR spectrum of L^M Schiff base ligand

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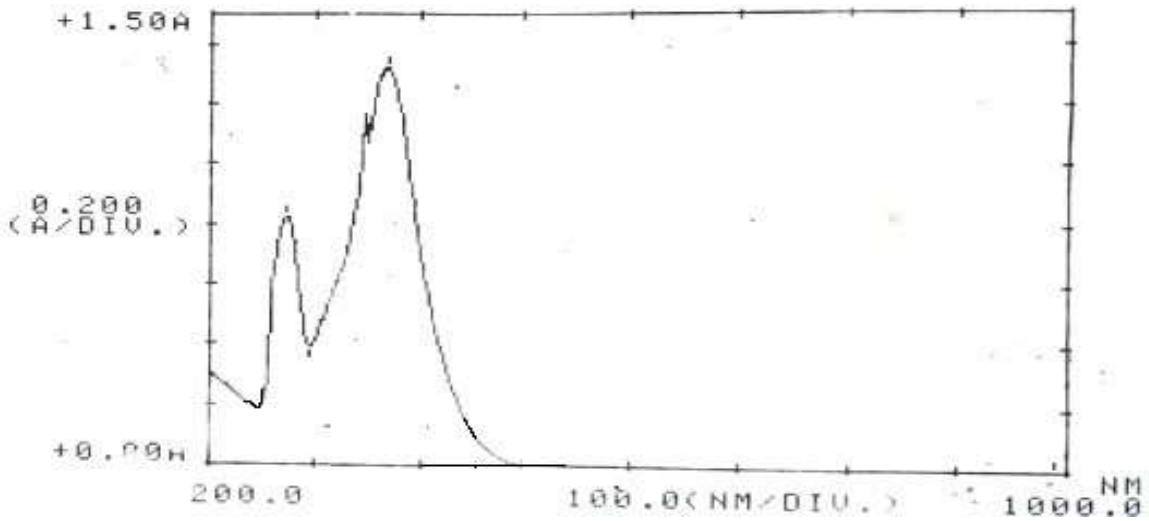

Figure 4: UV/Vis spectrum of L^M Schiff base ligand

Elemental analysis, atomic absorption, magnetic susceptibility, and molar conductivity for the complexes

The experimental results, including elemental analysis and atomic absorption measurements, align with the proposed structures of the new synthesized complexes of the L^M ligand with Co (II), Ni (II), Cu (II), and Zn (II) as illustrated in experimental section. Furthermore, the molar conductivity of the complexes falls within the range of 69-82 $cm^2.ohm^{-1}.mol^{-1}$, indicating their conductivity in a 1:2 ratio. This suggests the existence of two ions of chloride outside the coordination sphere in the complexes, confirming the proposed structures as $[M(C_9H_8N_4OS)_2]Cl_2$. As for magnetic susceptibility data, further details provided in the experimental section. [μ_{eff}= 1.69 for Cu(II), 2.79 for Ni(II), 6.63 for Co(II) and 0.00 for Zn(II)] refers to paramagnetic properties of high spin octahedral complexes except the Zn(II) complex shows diamagnetic properties [24, 25].

Lymphatic Cell interaction with the Schiff base Ligand and its complexes

In order to study the effect of the synthesized Schiff base ligand and its complexes on the specified cells in human blood, a specific procedure followed as explained previously and the results shown in Table 1 and Figure 5 below. In this procedure, the Colchicine, ligand and its

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complexes applied on Lymphatic Cell in metaphase in human blood. The ratios of blocked cells in the metaphase at the concentrations of 100 µg/mL were 4.33%, 1.45%, 2.21%, 1.97%, 4.10%, and 4.24% for Colchicine, L^M, $[Co(L^M)_2]Cl_2$, $[Ni(L^M)_2]Cl_2$, $[Cu(L^M)_2]Cl_2$, and $[Zn(L^M)_2]Cl_2$ respectively. The results showed that the complexes of copper and zinc had a high percentage and closer to the control while the Schiff base ligand, cobalt and nickel complexes has a lower value comparing with the control.

Table 1: The Mitotic Index of the Schiff base Ligand and the complexes

Compound in concentration 100 µg/mL	**Mitotic Index (MI %) M±SD**
Colchicine	4.33 ± 0.01 a
L^M	1.45 ± 0.11 d
$[Co(L^M)_2]Cl_2$	2.21 ± 0.08 c
$[Ni(L^M)_2]Cl_2$	1.97 ± 0.15 d
$[Cu(L^M)_2]Cl_2$	4.10 ± 0.10 a
$[Zn(L^{M-})_2]Cl_2$	4.24 ± 0.18 a

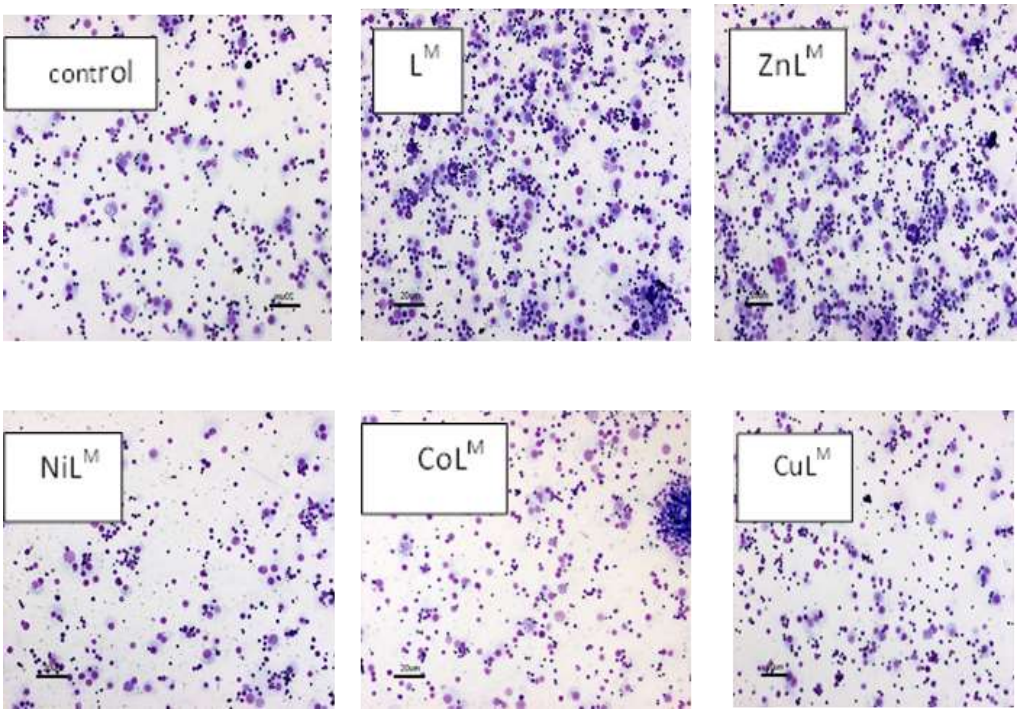

Figure 5: Cell lymphocyte interaction with the control, Schiff base Ligand and the complexes of Zn, Ni, Co and Cu.

Conclusion

The Schiff base ligand (E)-2-(2-oxoindolin-3-ylidene)hydrazine-1-carbothioamide (L^M) synthesized through a condensation reaction involving indoline-2,3-dione with thiosemicarbazide. The newly prepared complexes synthesized and characterized by various techniques such as FTIR, UV-Vis, atomic absorption spectroscopy, magnetic susceptibility and molar conductivity. The molar conductivity of the complexes indicating their conductivity in a 1:2 ratio. This suggests the presence of two ions of chloride outside the coordination sphere in the complexes, confirming the octahedral shape of the proposed structures as $[M(C_9H_8N_4OS)_2]Cl_2$. The biological activity assessment of the ligand and its complexes on the Mitotic Index in human lymphocyte cells, conducted at a 15-minute exposure time, indicated an increasing inhibition rate in the order of L^M < $[Ni(L^M)_2]Cl_2$ < $[Co(L^M)_2]Cl_2$ < $[Cu(L^M)_2]Cl_2$ < $[Zn(L^M)_2]Cl_2$< Colchicine. This suggests that the Schiff base ligand was the lowest effective and its complexes are more effective in halting lymphocyte division during the equatorial phase.

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Conflict of interest: The authors declare that there is no conflict of interest.

Ethical clearance: Ethical approval was not required for this review.

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