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Zinc (II) complexes derived from ibuprofen Schiff base ligands: synthesis, characterization, and biological activity

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Abstract: The produced Ibuprofen derivative, Ibuprofen hydrazide and 2-hydroxy-1-naphthaldhyde to form HL_1 and Ibuprofen hydrazide and 5-bromosalicylaldehyde to form HL_2 ligand, was reacted with Zn(II) ions complexes under experimental conditions to produce the ZnL_1 and ZnL_2 complexes. The ligands and their complexes were characterised using elemental analyses (C,H,N), FT-IR, electronic spectra, magnetic moments, molar ratio measurements, and molar conductance tests. The in-vitro cytotoxic activity of the new ligand and their complexes was also investigated against colon cancer cells (HCT-116 cell line), breast cancer cells (MCF-7 cell line), and hepatic cancer cells (MCF-8 cell line). Ibuprofen Schiff base ligands and their complexes wer tested in-vitro against bacterial pathogens and fungi. Synthetic compounds and the conventional antibiotic Gentamycin were tested in vitro against two Gram positive bacteria (*S. aureus* and *B. subtilis*) and two Gram negative bacteria (*E. coli* and *P. vulgaris*). In vitro antifungal potency, the new Schiff base ligands and their complexes were tested against two fungus, *C. albicans* and *A. fumigatus*, and compared to Ketoconazole, a common antifungal drug.

Keywords: Schiff base, Zn complexes, Ibuprofen, anti-bacterial.

1 Introduction

Due to their advantageous characteristics, the Schiff bases are a target for numerous synthetic approaches and play a significant role in medicinal chemistry [1]. The use of Schiff bases as ligands in the medical field, especially in diagnostics, has been demonstrated. These substances have a variety of donor sites and a propensity to chelate several different metal ions [2]. The antibacterial, antifungal, antidiabetic, tumor-fighting, antiproliferative, anticancer, anticorrosive, and anti-inflammatory properties of Schiff bases are among their biological effects. [3]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and their derivatives have shown a diversity of structural and physicochemical features when utilised as ligands to produce therapeutic transition metal complexes [4]. The most popular NSAIDs that can act as ligands for metal complexes are naproxen, ibuprofen, and aspirin because of their medicinal use and biocompatibility. A product of propionic acid, ibuprofen is an NSAID [5]. NSAIDs have several side effects, the majority of which are related to the gastrointestinal, renal, and cardiovascular systems . This side effect of NSAIDs can cause major problems ranging from lesions to diaphragm disease, which is characterized by a narrowing of the lumen.

Due to its anti-inflammatory, antipyretic, and analgesic properties, it is commonly used to treat fever, pain, and inflammatory conditions including rheumatoid arthritis. Most of the negative effects that NSAIDs have on the cardiovascular, renal, and gastrointestinal systems [6]. Major issues can result from this NSAID side effect, including lesions and the A narrowing of the lumen is a defining characteristic of diaphragm illness. Therefore, one of the most important tasks in the field of drug research today is to produce bioactive chemicals with low side effects, particularly those that can be utilised as anti-inflammatory medications. Antibacterial, antifungal, anti-tumor, and antiviral properties of metal complexes [7]. When a metal ion and a ligand engage, a variety of coordination numbers, oxidation states, and geometries can be produced. To create innovative drugs with high activity and minimal toxicity, ligand-metal coordination is a method. In light of this, We are enthusiastic to make new metal complexes of the water-insoluble Ibuprofen Schiff bases with the metal salt of Zn and analyse their pharmacological characteristics, including their cytotoxic and antibacterial potencies. The ibuprofen Schiff base ligands and their ZnL_1 and ZnL_2 complexes are synthesised in this paper [8].

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2 Experimental

All chemicals (materials, solvents, and reagents) utilised in this study were purchased from Merck, Fluka, and Sigma-Aldrich and used without further purification.

2.1. Instrumentation and Materials

The analytical reagent grade of all regents, and metal salt $Zn(NO_3)_2.6H_2O$ should be used exactly as directed. Ibuprofen, 2-hydroxy-1-naphthaldhyde, and 5-bromosalicylaldehyde are all available from Sigma Aldrich. A Gallen Kamp (UK) device was used to record the melting points of all the compounds created. An elemental analyzer made by Perkin-Elmer, model 240 ^{0}C, was used to gather micro analytical data (C,H,N). The infrared spectra of the synthesized ligands and their complexes was acquired on an FT-IR Alpha Bruker using Platinum-Ate with KBr pellets in the 400–4000 cm^{-1} range with a resolution of 4 cm^{-1}. A Bruker Biospin NMR spectroscopy magnet system model 400 MHz and deuterated dimethyl sulfoxide (DMSO) as the solvent were used to record the ligand's ^{1}HNMR. The Jenway conductivity/TDS metre model 4510 is the tool used to measure the molar conductivity of 10^{-3} M metal complexes in DMF at room temperature. Pascal's constants and $Hg[Co(SCN)_4]$ were used to calibrate the diamagnetic adjustments, and Gouy's balance was used to record the complexes' magnetic susceptibilities. The absorbance of ZnL_1 and ZnL_2 complexes was measured at 1×10^{-3} M at various pH . Britton universal buffers were used to check the pH readings. A Jenway pH metre was used to measure the pH.

2.2. Synthesis ibuprofen ethyl ester

Ibuprofen (0.01 mol, 2.06 g), absolute ethanol (20 ml), and the catalyst sulphuric acid are combined in a round-bottomed flask (0.5 ml). The solution was then refluxed for a further 12 hours. Following the procedure, the liquid's pH was adjusted to 8 by neutralising it with 10 % sodium bicarbonate. Anhydrous magnesium sulphate was used to extract and dry 30 mL of dichloromethane. Rf value for n-hexane (3:7) and ethyl acetate is 0.65. Yield: (91%) light yellow oil at 263–265 °C with an Rf value of 0.65 for ethyl acetate:n-hexane (3:7). cm^{-1} IR spectrum: 1735 (CO), 1165 (C-O ester) [9].

2.3. Synthesis ibuprofen hydrazide

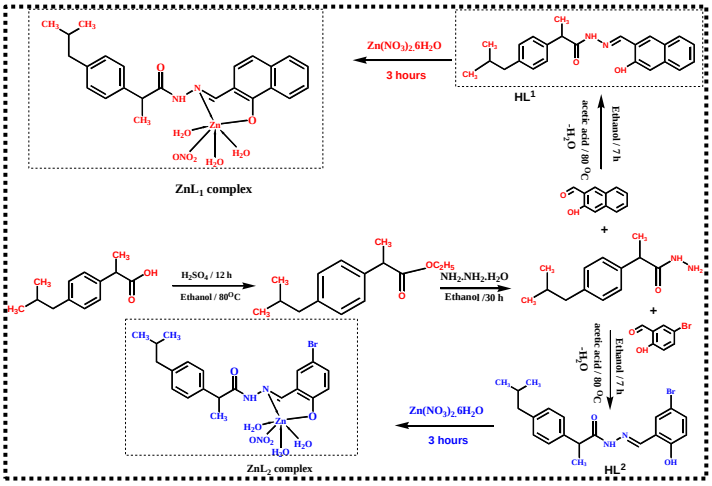
Ibuprofen ethyl ester (0.02 mol), 99 percent hydrazine hydrate (0.1 ml), and 30 ml 100% ethanol were added to a 100 ml round-bottomed flask. Then, for 10 hours, the reaction mixture was refluxed. Its concentration has reduced it to about a quarter of its initial size. Ibuprofen hydrazide was the result, and it was purified as a white crystal using ice-cold water. White crystal, m.p. 73-74 degrees Celsius, yield: 89 percent. Rf value (ethyl acetate: n-hexane 3:7) is 0.83, and the IR (KBr) spectrum has the following cm^{-1} values: 1685 (CO amide), 3313, and 3278. (assym. & sym.NH_2) [10].

2.4. Synthesis of Schiff base

Scheme 1 shows the synthetic of HL_1 and HL_2 Schiff bases ligands by mixing 1.10145 g of Ibuprofen hydrazide (5 mmol) with 1.006 g of 5 bromo salicylaldehyde (5 mmol) for HL_2 and 0.861 g of 2-hydroxy-1-naphthaldhyde (5 mmol) for HL_1 in 30 mL ethanol with stirring and reflux for three hours at 60 °C with the addition of drops of acetic acid as a catalyst till the production of Green precipitat. The precipitate was then filtered, washed, and dried in vacuo over anhydrous $CaCl_2$. For HL_2 the empirical formula was Molecular Formula $C_{20}H_{25}BrN_2O_2$; m. p. 163°C; solubility: ethanol; molecular weight: 405.3 g/mol. For HL_1 empirical formula was $C_{24}H_{26}N_2O_2$; m.p. 172 ºC; soluble in ethanol; molecular weight: 374.01 g / mol. [11].

2.5. Synthesis of Zn(II) Schiff base complexes

In flasks containing 20 mL ethanol, 1 mmol of HL_1 and HL_2 Schiff base ligands were combined with equimolar quantities of metal salt $Zn(NO_3)_2.6H_2O$ (1 mmol, 0.29749 g). stirring was used to mix the solution combinations. ZnL_1 and ZnL_2 complexes were isolated, filtered, washed with ethanol, dried in vacuo under anhydrous $CaCl_2$, and then submitted to various types of analysis after 3 hours [12].



Scheme 1: The scheme of synthesis of the HL_1, HL_2, ZnL_1 and ZnL_2 ibuprofen Schiff base complexes.

2.6. Complex stability in solution

In solution, ZnL_1 and ZnL_2 complexes' molar mass and stability were investigated. This was accomplished using Job's methods (continuous variation and mole ratio). After giving the reaction mixtures (M & L) time to equilibrate, the absorbance of each combination was measured. The ligand mole fraction ([L]/[L]+[M]) or molar ratio ([L]/[M]) were therefore calculated from the absorbance of each solution [13].

2.7. Biological studies

2.7.1. Antimicrobial activity

2.7.1.1. Antibacterial activity

The well diffusion method and standard agar were used to test the compounds' antibacterial activity against two types of Gram-positive bacteria (*B. subtills* and *S. aureus*) and two types of Gram-negative bacteria (*E. coli* and *P. vulgaris*). All compounds were dissolved in DMSO, a negative control, at concentrations of 15 and 25 mg/mL, and none of the organisms were inhibited by it. Tests were conducted twice to obtain an average value. The results were contrasted with those of the reference medication Gentamycin, and the clear inhibition zone around each distance was quantified (in mm) [**14**].

2.7.1.2. Anti-fungal activity

The ligands and their complexes were examined using the disc diffusion method for antifungal activity against two species of fungi (*Candida albicans* and *Aspergillus fumigatus*) in comparison to the common antifungal medication Ketoconazole [**15**]. The literature indicates that a single-spore isolation strategy was used for fungal purification culture. Based on the diameter of inhibitory zones, anti-fungal susceptibility testing was conducted on fungus strains belonging to the Albicans and non-Albicans species. [**16**]

2.7.2. Anticancer activity

The absorbance or optical density (O.D.) of each well was measured spectrophotometrically at 564 nm using a "ELIZA" micro plate reader (Meter tech. 960, "USA") (nm). On (HCT-116 cell line), (MCF-7 cell line), and (MCF-8 cell line), the cytotoxic activity of the HL_1 and HL_2 ligands and its metal complexes was examined (HepG-2 cell line). The in vitro process was assessed using the Sulfo-Rhodamine-B stain (SRB). Cells were placed in a 96-multiwell plate with 104 cells per well for 24 hours prior to processing with the complexes to promote cell attachment to the plate wall [**17**]. In DMSO, the test substances were exposed to the cell monolayer at different concentrations (0, 1, 2.5, 5, and 10 μM). Monolayer cells were grown with the complexes for 48 hours at 37 °C and 5 % CO_2. After 48 hours, cells were fixed, cleaned, and stained with Sulfo-Rhodamine-B dye. Acetic acid was used to remove any excess stain, and Tris EDTA buffer was used to remove any remaining stain. Color intensity was evaluated using an ELISA reader. Using the IC50 value and the percentage change in the value, the potency of a molecule was calculated (Vinblastine standard). The inhibitory concentration percent (IC %) was obtained using equation (1) [**18**].

$$\text{IC (\%)} = \frac{Control_{OD} - compoud_{OD}}{Control_{OD}} \times 100 \qquad \textbf{(1)}$$

3. Result and discussion

In ethanol, the Ibuprofen hydrazide combines with 5-Bromosalicylaldehyde HL_2 and 2-hydroxy-1-naphthaldhyde to create HL_1 ligands, which reacts with Zn(II) ion to form solid complexes. To classify the obtained complex, we employed elements analysis, molar conductivity, magnetic susceptibilit, IR, UV-Vis and ^{1}HNMR.

3.1. FT-IR Spectral Studies

The FT-IR spectra can be used to distinguish between the functional groups of the ligands and to show how those groups interact with the primary metal ions of the complexes that are created. Graphical representations of the characteristic IR spectral bands of the HL_2 ligand and its ZnL2 metal chelate are presented. The IR spectra of the ligand showed a peak at 1662 cm^{-1}, which is associated with the v(CH= N) vibration; however, coordination with metal ions caused this peak to shift to 1619 cm^{-1} in the complexes [**19**]. The spectra of the complexes showed a reduced shift of the (OH) vibrations from their initial existence at 1541 and 3195 cm^{-1} in the ligand spectrum and the removal of v(C=N) (in the ibuprofen hydrazide ring). The HL_1 Ligand, however, contained two faint bands at 2986 and 3047 cm^{-1} that suggested the presence of intermolecular hydrogen bonding (-NH-O-) between the phenolic (-OH) and the ibuprofen hydrazide nitrogen (-C=N), which might have produced either enol-isomers or keto-isomers. Additionally, the v(C-O)vibration in the complex was drastically moved from the range of 1267 cm^{-1} as shown in the ligand spectra to the region of 1227 cm^{-1}. These results show that the ligand binds to all metal ions in a mono-negative tridentate manner. The isolated complexes' anions were specifically described as follows: The mono-dentate coordination was indicated by the ZnL_2 complex's vas(NO_3) and vs(NO_3) vibrations at 1354 and 1387 cm^{-1}, respectively. at 929 cm^{-1} [**20**]. The HL_1 Ligand, however, contained two faint bands at 2986 and 3047 cm^{-1} that suggested the presence of intermolecular hydrogen bonding (-NH-O-) between the phenolic (-OH) and the ibuprofen hydrazide nitrogen (-C=N), which might have produced either enol-isomers or keto-isomers. Additionally, the v(C-O)vibration in the complex was drastically moved from the range of 1267 cm^{-1} as shown in the ligand spectra to the region of 1227 cm^{-1}. These results show that the ligand binds to all metal ions in a mono-negative tridentate manner. The isolated complexes' anions were specifically described as follows: The mono-dentate coordination was indicated by the ZnL1 complex's vas(NO_3) and vs(NO_3) vibrations at 1354 and 1387 cm^{-1}, respectively, at 929 cm^{-1} [21], Figure 1.

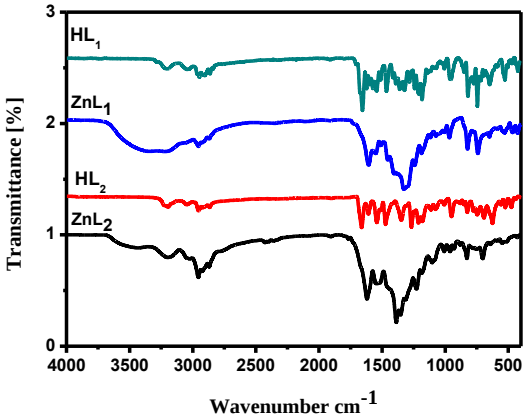


Fig. 1: FT- IR of the ligands and their complexes.

3.2. ^{1}H NMR of the ligands

The NMR spectra are used to identify a newly synthesised ligands and their diamagnetic metal complexes. Tetra methyl silane (TMS) is used as an internal standard in the ^{1}H NMR spectra of the ligand (HL_2) and its diamagnetic complex ZnL_2, which are recorded in DMSO-d6. The proton (-CH=N-), which was seen in the ligand's ^{1}HNMR spectra as a strong singlet signal at about δ 9.21 ppm, was identified. The numerous signals observed between δ 7.10 and δ 7.88 ppm are caused by aromatic protons. The sharp singlet at δ 11.23 and δ 11.9 ppm is caused by the ligand's (-NH- bond) and phenolic proton. The chemical ZnL_2's ^{1}H NMR spectra in DMSO-d6 were also obtained.Figure 2 [22] Tetramethyl silane (TMS) is used as an internal standard in the ^{1}H NMR spectra of the ligand (HL_1) and its diamagnetic complex ZnL_1 recorded in DMSO-d6 to ascertain the structure of the ligand and its complex. The proton (-CH=N-) has a strong singlet signal in the ligand's ^{1}H-NMR spectrum at about 9.21 ppm. The multiple signals observed between 7.11 and 8.22 ppm are caused by aromatic protons. The sharp singlet detected at 12.8 ppm and 11.86 ppm is due to the phenolic proton and (-NH- bond) of the ligand. For DMSO-d6.

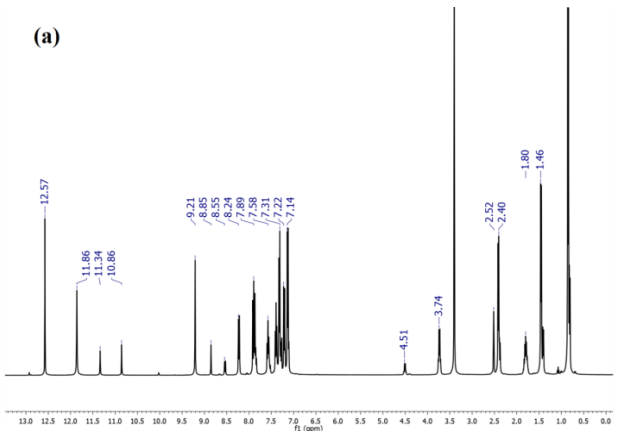


Fig. 2: The ^{1}H NMR of the **HL_1** ligand

3.3. Molar conductivity and elemental analysis

Tabulated data for the ligands and their complexes included physical characteristics, microanalytical information, and molar conductance values. According to the results, the molar ratio of all the chelates under study was 1:1 (M:L). Complexes with molar conductivities of 1 10-3 M were discovered to be non-conducting. (15.21-12.22 Ω-1mol-1cm2). Table 1

Table 1: Physicochemical properties of the HL_1 and HL_2 ligands and its complexes; color, melting point (m. p oC/ dec. temp.), M. wt. and magnetic moment (μ eff, B.M).

Compound formula	Color	M.P °C / Dec. Temp	μ_{eff} *(B.M.)*	M. wt.	Analysis: Calc (Found)		
					C(%)	H(%)	N(%)
HL_1 $C_{24}H_{26}N_2O_2$	Gray green	172	-	374.01	76.91 (77.04)	6.9 (6.9)	7.48 (7.28)
ZnL_1 $C_{24}H_{31}N_3O_8Zn$	Dark brown	>300	Dia	554.62	51.89 (52.17)	5.59 (5.7)	7.57 (7.82)
HL_2 $C_{20}H_{25}BrN_2O_2$	Green	163	-	405.3	59.26 (59.10)	6.22 (6.51)	6.91 (6.58)
ZnL_2 $C_{20}H_{30}N_3O_8ZnBr$	Brown	>300	Dia	585.8	41.01 (41.06)	5.16 (5.32)	7.17 (7.22)

3.4. Electronic Spectra

The findings of various structural inspection methods are typically evaluated using the molecule electronic absorption spectra. Electronic spectrum measurements were utilized to determine the stereochemistry of metal ions in the complex based on the positions and quantity of d-d transition peaks. The electronic absorption spectra of the HL_2 ligand and its complex were listed at wavelengths between 800 and 200 nm while the temperature was 298 K. The n→π∗ transition brought on by the Schiff base ligand's imine activity is responsible for the ligand's absorption bands in the UV-Vis region about 390 nm. The complexes' absorption bands with a maximum wavelength of 440 nm are designated as the site of charge transfer from the Schiff base ligand to the metal ion. Figure 3, [23].

The HL_1 ligand exhibits absorption bands in the UV–

Vis region at 280 nm, which is referred to $\pi - \pi*$ and at 384 nm, which is attributed to the $n \rightarrow \pi*$ transition resulting from the Schiff base ligand's imine activity. Charge transfer from the Schiff base ligand to the metal ion is allocated to the absorption bands of complexes at λ_{max}= 448 nm.

3.5. Stability range of the complexes

Figure 4 displays the remarkable stability of new complexes at a variety of pH value. As a result, the pH range for various implementations of the new metal chelates should be between 5 and 11 [24].

3.6. Stoichiometry of complexes

Using the spectrophotometric Job's method of continuous variation, the stoichiometry of the two complexes were calculated as in Figure 5 . The continuous variation curve showed maximum absorbance at mole fraction X ligand ≈ 0.5, showing 1:1 (M:L) molar ratio coordination between the metal ion and the ligands [25].

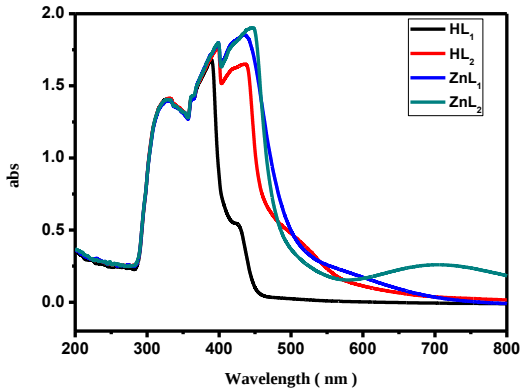


Fig. 3: Electronic spectra of **HL_1, HL_2** and its metal complexes in DMF at 298 K.

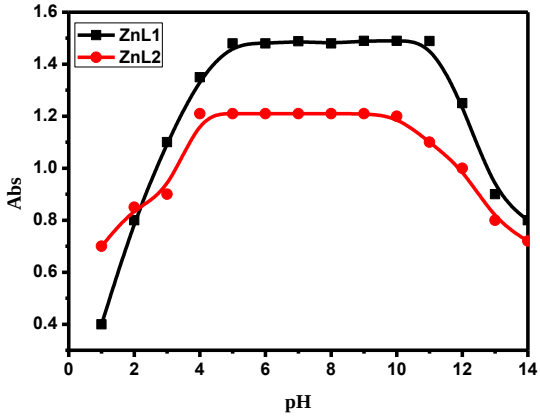


Fig. 4: pH profile of the **ZnL_1** and **ZnL_2** complexes in DMF at different pH values.

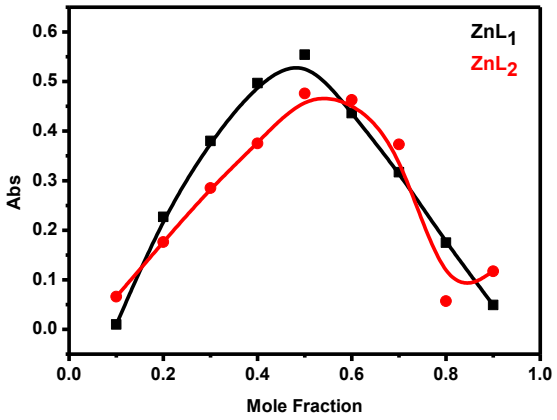


Fig. 5: Complexes stoichiometry by job method for the prepared complexes.

3.7. Antimicrobial activity

The free ligands and their metal complexes were assessed against bacterial and fungal species by measuring the size of the bacteriostatic diameter. According to the findings, which are displayed in Figure 6, the tested chemicals significantly inhibited a range of bacteria and fungus [26].

3.7.1. Antibacterial activity

S. aureus and *B. subtilis* and two Gram negative bacteria were evaluated in vitro against synthetic chemicals and the traditional antibiotic Gentamycin. The agar well diffusion method was used to assess the antibacterial activity of substances. In terms of antibacterial activity, mononuclear metal complexes outperformed the Schiff base (HL_1 and HL_2), and their metal complexes were more potent against Gram-positive than Gram-negative bacteria when compared to free ligands. In terms of antibacterial activity, the mononuclear ZnL_2 metal complex was superior to the ZnL_1 metal complex. It was also discovered that the ZnL_2 metal complex displayed greater antipathogenic activity toward Gram-positive bacteria than Gram-negative bacteria when compared to the ZnL_1 metal complex [27].

3.7.2. Antifungal activity

The novel Schiff base ligands (HL_1 and HL_2) and their complexes were examined for their in vitro antifungal potency against the fungi *C. albicans* and *A. fumigatus* and compared to the common antifungal medication ketoconazole. Figure 6 demonstrates that metal complexes have stronger antifungal effects than Schiff base (HL_1 and HL_2) ligands. The ZnL_2 complex has the best activity against A. fumigatus and is the most effective against all the investigated fungi [28].

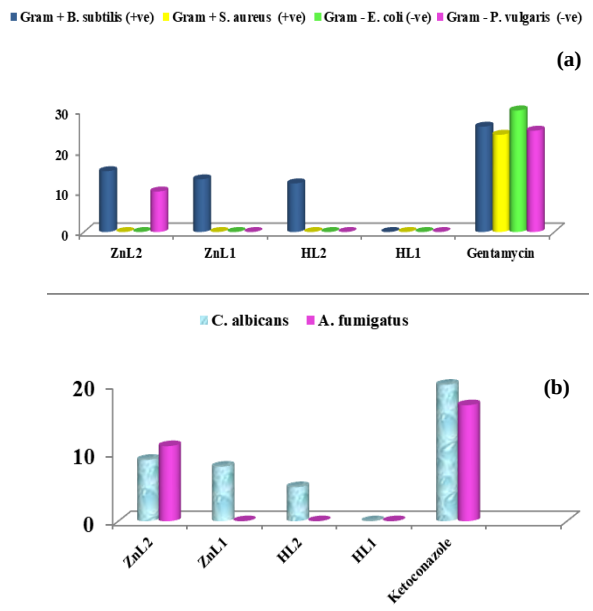


Fig. 6: Histogram showing the comparative antimicrobial activities of the HL_1 and HL_2 ligands and their ZnL_1 and ZnL_2 complexes compared to gentamycin and ketoconazole with a concentration of 25 mg /ml.

3.8. Cytotoxic evaluation for the complexes

Three human cancer cells—HCT-116, MCF-7, and HepG-2—were used in the investigation of the anticancer activities of the HL_1, HL_2, ZnL_1, and ZnL_2 complexes. Vinblastine served as the reference medication, and the corresponding IC_{50} values were determined. Furthermore, the new complexes were more susceptible to cytotoxicity against HepG-2 compared to the other cancer cells (MCF-7 and HCT-116). Surprisingly, the ZnL_2 complex outperformed other complexes and free Schiff base ligands in cytotoxicity tests against all three cell types tested. Its IC_{50} values against the three cancer cell lines are very comparable to the IC_{50} values of vinblastine, ZnL_2 has (5.5, 5.9 and 6.31 µM) where vinblastine IC_{50} values were (4.46, 5.25 and 4.10 µM) against MCF-7, HCT-116 and HepG-2 respectively, the ZnL_2 complex performed better than other complexes and free Schiff base ligands [**29**], Figure 7.

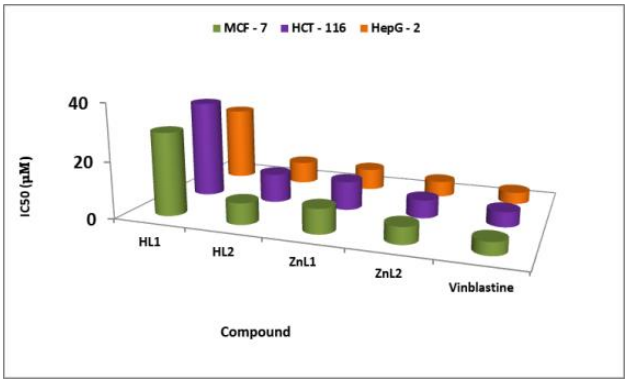


Fig. 7: IC_{50} values for HL_1 and HL_2 Ligands and their complexes compared to vinblastine drug against HepG-2, HCT – 116, MCF – 7.

4 Conclusion

New Schiff bases are Synthesized from ibuprofen hydrazide and 5-Bromosalicylaldehyde to form HL_2 and from ibuprofen hydrazide and 2-hydroxyl-1-naphthaldehyde to form HL_1 and characterized using different analytical and spectroscopic techniques. Zn metal salt was coordinated with the two Schiff base ligands and formed new complexes (ZnL_1 and ZnL_2) and confirmed by different techniques as electronic spectra, IR and ^{1}HNMr . In vitro antibacterial and antifungal activities revealed that the new compounds exhibit promising bioactivities against the tested pathogens. In addition, the new compounds were tested against the HCT 116, HepG 2, and MCF7 cell lines to see if they inhibited cell proliferation. The cytotoxic of the new complexes follows the order $ZnL_2 > ZnL_1 > HL_2 > HL_1$.

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