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Original article

Schiff Base-Benzil of Iron (III), Cerium (IV) and Thorium (IV) Mixed Ligand Chelates: Preparation, Spectral Characterization, Antitumor Activity and Molecular Docking Studies

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Abstract
In the following study, Schiff base formed from the condensation of 2-hydroxyacetophenone and L-alanine as the main ligand (HL1) and benzil compound as secondary ligand were entered into the formation of three new combined ligand chelates of Fe(III), Ce(IV), and Th(IV) ions. The fashioned chelates were characterized through using numerous analytical and spectroscopic equipment. The analytical techniques showed a non-electrolytic nature character for all chelates; moreover, the CHNS elemental analyses exhibited the formation of the mixed ligand chelates in a 1:1:1 [ML1L2] ratio. Meanwhile, the infrared spectral information showed the bonding of the metal ions with the active organizations present within the free ligands (-C=N, NH2, -OH). Also, the electronic spectral results displayed the proper geometrical structures for the mixed ligand chelates. In vitro antitumor activity of a few synthesized compounds with human Hepatocellular Carcinoma cells (Hep-G2) was tested. Additionally, the molecular docking ligand interactions have been evaluated.

Keywords. Schiff Base, Mixed Ligand Chelates, Benzil, Antitumor, Molecular Docking.

Introduction

Schiff base complexes are widely recognized for their versatile coordination abilities, forming stable chelates with various transition metal ions [1, 2]. These complexes have been extensively studied due to their interesting geometries, electronic properties, and potential applications in catalysis, medicine, and material science [3, 4]. Previous studies have explored the binding behavior of amino acids with metallic ions, highlighting their significant role in understanding metal–protein interactions [5]. Schiff bases containing oxygen and nitrogen atoms have been reported to exhibit remarkable utility in various fields, including organic synthesis, medicinal chemistry, and industrial applications [6, 7]. Benzil, an α-diketone known as diphenylethane-1,2-dione [$C_{14}H_{10}O_2(PhCO)_2$], can condense with amines to form diketimine ligands [3]. Both benzil and its metal complexes have demonstrated important applications in organic chemistry [8, 9]. Previous research has reported the synthesis and characterization of mixed-ligand complexes of Fe(III) and Cu(II) derived from catechol and benzil, providing insights into their geometrical structures [10, 11]. Additionally, studies have described the preparation and investigation of Schiff base complexes derived from 4,4′-methylenedianiline, ethanolamine, and benzil [7]. Hepatocellular carcinoma (HCC) remains one of the most formidable health challenges worldwide, ranking among the leading causes of cancer-related mortality [12]. This malignancy affects individuals indiscriminately, regardless of age, gender, or ethnicity, and is often diagnosed at advanced stages due to its aggressive nature and high metastatic potential [13]. The elevated mortality rate associated with HCC is largely attributed to its rapid progression and propensity to form intrahepatic and extrahepatic metastases, making the targeting of molecular mechanisms underlying tumor dissemination a critical focus in therapeutic development [14]. The etiology of HCC is multifactorial, encompassing both genetic and environmental determinants. Genetic alterations, whether inherited or acquired early during development, can disrupt cellular proliferation and apoptotic pathways, predisposing individuals to hepatic tumorigenesis.

Mutations in key genes such as TP53, BRCA1, and BRCA2 have been implicated in heightened susceptibility to liver cancer [15]. Moreover, oncogenesis may originate from monoclonal, multiclonal, or mixed clonal populations, reflecting the interplay between accumulated genetic changes and a permissive microenvironment conducive to tumor growth. In recent years, computational chemistry and biology have emerged as indispensable tools in cancer research and drug discovery, offering predictive insights that significantly reduce the time, cost, and resources associated with conventional experimental approaches [16]. Among these computational strategies, molecular docking plays a pivotal role in identifying potential therapeutic candidates by evaluating the binding interactions between chemical compounds and critical protein targets involved in HCC progression [17].

Building on this approach, the present study focuses on the design and synthesis of three novel mixed-ligand metal chelates formed between a Schiff base, benzil, and selected metal ions. The structures of these complexes were thoroughly characterized using a variety of analytical and spectroscopic techniques to ensure precise structural elucidation. Their antitumor activities were evaluated against several human cancer cell lines, including colon carcinoma (HCT-116), hepatocellular liver carcinoma (HepG2), and breast

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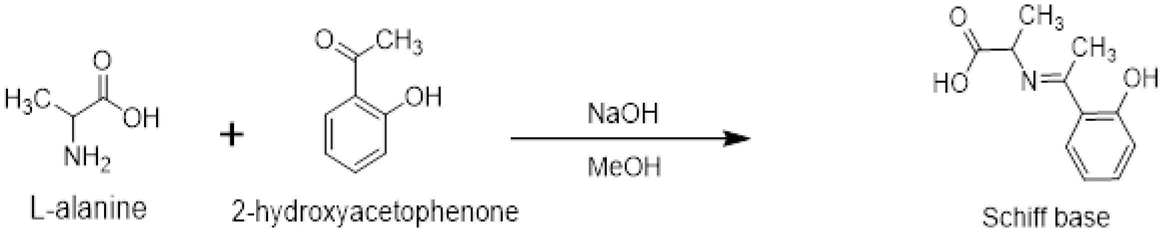
carcinoma (MCF-7), with particular emphasis on HepG2 cells. Furthermore, molecular docking studies were conducted using AutoDock 4.2 software to investigate the interactions of the synthesized complexes with the tyrosine kinase receptor (PDB ID: 1M17). This integrated experimental and computational approach provides a comprehensive assessment of the compounds' structural features and their potential efficacy as anti-HCC agents.

Material and Methods

All chemicals used in this investigation were of pure grade (BDH or Aldrich). Include: 2-hydroxyacetophenone, l-alanine, benzil, DMF, DMSO, NaOH, methanol, ethanol, $FeCl_3.6H_2O$, $Ce(SO_4)_2.4H_2O$, $Th(NO_3)4.4H_2O$, and distilled water [18]. The CHNS analysis for the prepared chelates was made on a 2400-CHN elemental analyzer. The molar conductivity was determined in DMF on the CMD-650 digital conductivity meter, Benghazi University [19]. The magnetic moment measurements were done by using the Gouy balance method. The infrared spectra were carried out on an IFS-25 DPUS/IR spectrometer. NMR spectra were recorded on a Varian Gemini 200–200 MHz spectrometer using TMS as an internal standard in DMSO-d6. The electronic and mass spectra were recorded on a Perkin-Elmer Lambda-365 spectrophotometer and a Shimadzu QP-2010 Plus spectrometer, respectively [20].

Preparation of the amino acid Schiff base

The amino acid Schiff base (Scheme-1) was prepared as follows: NaOH (0.4 g, 1mmole) was dissolved in methanol (25 mL), and L-alanine (0.89 g, 1 mmole) was added to it. The mixture was stirred at room temperature for 5 min [21]. When the mixture became homogeneous, 2-hydroxyacetophenone (1.36 g, mmole) was added. After 2 min., the mixture was evaporated to 20% of its original volume, and acetic acid (1 mL) was added immediately [6]. After 2 h, a yellow product was formed, filtered off, washed, dried, and recrystallized from methanol to provide an excellent (85%) yield of pure crystals [22].



Scheme 1. Formation structure of Schiff base

Preparation of mixed ligand chelates

These mixed ligand chelates under investigation were prepared by adding of 25 mL of a methanolic solution of the HL1(2.07g, 0.01mole) to 0.01mole of the desired metal salts $FeCl_3.6H_2O$, $Ce(SO_4)4.4H_2O$, $Th(NO_3)_4.4H_2O$ (2.70, 4.04 and 5.52 g), respectively, in the same volume of the solvent followed by adding 10% sodium hydroxide solution to adjust the pH to 8 at which the chelates were separated[23]. The obtained reaction mixtures were stirred and refluxed for 1.5 h, and then the second ligand of 25 mL of a methanolic solution of benzil (L2) (0.01 mole, 2.10 g) was added dropwise as a secondary ligand. The obtained mixtures were further refluxed for an extra 3h, then filtered. The resulting precipitates were washed several times with hot ethanol and dried in air [18].

Determination of sample cytotoxicity on cells (MTT protocol)

Cell line and culturing

The human hepatocellular liver carcinoma (HEPG-2) cell line was used for this study. The 96-well tissue culture plate was inoculated with 1 X 105 cells / mL (100 µL/ well) and incubated at 37°C for 24 h to develop a complete monolayer sheet. Growth medium was decanted from 96-well microtiter plates after a confluent sheet of cells was formed, cell monolayer was washed twice with wash media. Two-fold dilutions of the tested sample were made in RPMI medium with 2% serum (maintenance medium). 0.1 mL of each dilution was tested in different wells, leaving 3 wells as controls, receiving only maintenance medium. The plate was incubated at 37°C and examined. Cells were checked for any physical signs of toxicity, e.g., partial or complete loss of the monolayer, rounding, shrinkage, or cell granulation. MTT solution was prepared (5 mg/mL in PBS) (BIO BASIC CANADA INC). 20 µL MTT solutions were added to each well. Place on a shaking table, 150 rpm for 5 min, to thoroughly mix the MTT into the media. Incubate (37 °C, 5% CO_2) for 1-5h to allow the MTT to be metabolized. Dump off the media. (Dry plate on paper towels to remove residue if necessary [24]. Re-suspend formazan (MTT metabolic product) in 200 µL DMSO. Place on a shaking table, 150 rpm for 5min, to thoroughly mix the formazan into the solvent. Read optical density at 560 nm and subtract background at 620 nm. Optical density should be directly correlated with cell quantity [25].

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Molecular docking study

The Molecular Operating Environment (MOE) 2009.10 program was used in a molecular docking study [26]. Docking studies were done to assess the binding free energy of the inhibitor inside the macromolecule. The Dock scoring in MOE software was done utilizing the London dG scoring function, and the Force-field has been improved to check that refined poses meet the specified conformations. Auto rotatable bonds were allowed; the best ten binding poses were analyzed to analyze for achieving the best score. To compare the docking poses to the ligand in the co-crystallized structure, and to obtain RMSD of the docking pose database browser was used.

Preparation of compounds and the target EGFR tyrosine kinase receptor.

The compounds contributed in this study as ligands were studied for their binding affinity to the tyrosine kinase receptor (EGFR). To build a three-dimensional model of the structures, the molecular builder tool in MOE was used. Energy minimization was carried out through Force-Field MMFF94X. Optimization was carried out using a gradient of 0.001 for determining the lowest energy conformation with the most favorable geometry. The crystal structure of c-kit receptor protein-tyrosine kinase in complex was picked up from the Protein Data Bank (PDB) (PDB code: 1M17). Partial charges and a hydrogen atom were put onto the protein with the protonation 3d application in MOE.
RESULTS and Discussion.

Physical properties, microanalysis, and molar conductivity

The Schiff bases and their mixed ligand complexes with the mentioned metal ions were synthesized in powder form with high melting points (Table 1). The amino acid Schiff base is soluble in alcohols, DMSO, or DMF solvents, but not in water; meanwhile, the synthesized mixed ligand complexes are not soluble in alcohols, but they are partially soluble in DMF and DMSO-d_6. All the compounds are stable in air [4]. The CHNS elemental analysis data of the Schiff base and its mixed ligand chelates agree with the suggested compositions. This means that the Schiff base is formed (scheme 1) and their mixed ligand chelates were also formed in a 1:1:1[M: L1:L2] ratio [27]. The obtained molar conductivity values in DMF solvent reveal the existence of a non-electrolyte in nature, indicating that there are no anions outside the coordination sphere [8]

Table 1. Some physical properties, microanalysis, and molar conductivity of mixed ligand chelates

Compounds	**M. wt**	**Color**	**Microchemical analyses Calcd. Found**				**^m; Ω^{-1} cm^2mol^{-1}**	**μ B.M**
			C%	**H%**	**N%**	**S%**		
HL1; ($C_{11}H_{13}NO_3$)	207	Daffodil	63.77 64.20	6.28 5.21	6.76 6.25	----	–	---
$[Fe(L1)(L2)(OH)].H_2O$	506	syrup	59.29 60.19	5.34 5.01	2.77 3.00	----	0.000503	6.40
$[Ce(L1)(L2)(SO_4)(H_2O)].H_2O$	687	Butter	43.67 43.90	4.08 4.00	2.03 3.00	4.66 5.08	0.001119	0.00
$[Th (L1)(L2)(NO_3)_2].2H_2O$	807	Banana	37.17 37.65	3.47 3.02	5. 20 6.00	---	0.000584	0.00

Infrared spectra

The IR spectral results of Schiff base compound (HL1), benzil, and mixed ligand chelates are listed in Table 2, and their spectra are shown in (Fig.1). In the spectra of the Schiff base, the strong broad band appearing at 3441cm^{-1} is due to O-H vibration of the phenolic [28]. This band vanished due to the complexation with a metal ion. The same spectrum shows a band at 1605cm^{-1} corresponding to the formation of the azomethine group (C=N) [10]. The same spectrum also exhibits a band at 3094 cm^{-1} assigned to uCOOH vibration [29]. In the infrared spectra of $[Fe(L1)(L2)(OH)].H_2O$,$[Ce(L1L2)(SO_4)(H_2O)].H_2Oand[Th(L1L2)(NO_3)_2]$. $(H_2O)_2$ mixed ligand chelates, the band at 1605cm-1, analogous to the azomethine u(C=N) group in the free Schiff base, associated with the azomethine group shows changes in its place in all mixed ligand chelates, indicating its coordination with the metal ions [30].

In the free benzil compound, the band in the range at 1660 cm-1 of the C=O group is shifted from its original position to a new position in the infrared spectra of three mixed ligand chelates, confirming its chelation to the metal ions via oxygen atom [31]. The -OH stretching vibration of the free Schiff base (3441 cm^{-1}) is not detected in the IR spectra of the mixed ligand chelates, implying deprotonation of the hydroxyl group and formation of M-O bonds [14]. The same spectra display a band at 462,463,548 cm^{-1}due to u(M-N) vibrations of all mixed ligand chelates, whereas the bands of 602, 633,633 cm^{-1} are attributed to u(M-O) vibrations of the three mixed ligand chelates [32]. The spectrum of Ce(IV) mixed ligand chelate shows three bands at 1204, 1134, 1065 cm^{-1}, which do not exist in the free ligands, indicating the presence of bidentate character of the coordinated sulphate chelation [16]. Meanwhile, the spectrum of Th(IV) mixed ligand chelate exhibits

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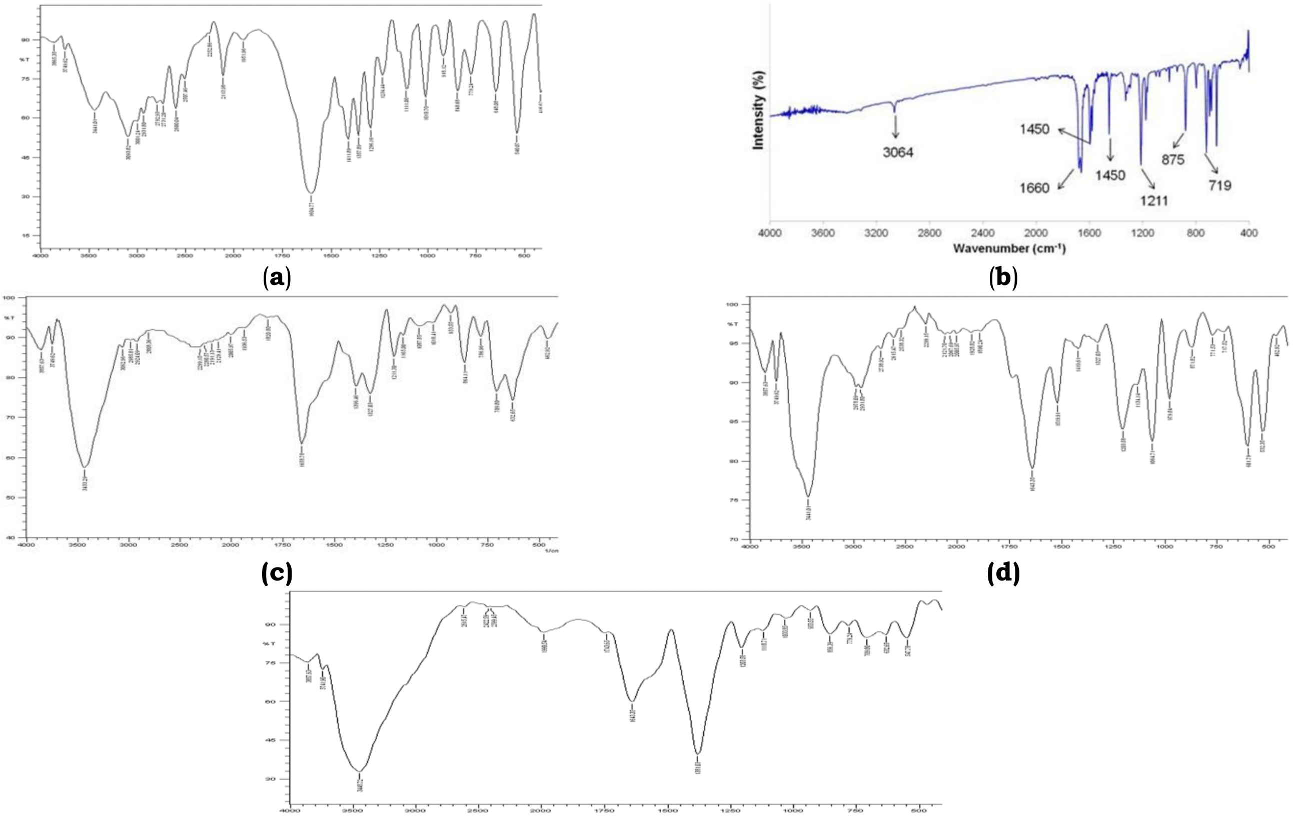
bands at 1203, 1034, 779 cm^{-1} are attributed to the presence of nitrate group vibration [17]. The bands observed in the spectra of all mixed ligand chelates in the range of 3549-3433 cm-1 significantly support the existence of lattice water molecules,[18] whereas the bands in the range of 871-718 cm^{-1} in the spectrum of Ce(IV) mixed ligand chelate are due to the existence of coordinated water molecule [33].

Table 2. Characteristic infrared absorption frequencies (cm^{-1}) of the Schiff base and mixed ligand chelates

Compounds	u (OH) (H_2O) u	u (C=N)	u (C=O)	u (M-O)	u (M-N)
HL1; ($C_{11}H_{13}NO_3$)	3441	1605	---	---	---
[Fe(L1)(L2)(OH)].H_2O		----	1660		-
[Ce(L1)(L2)(SO_4)(H_2O)].H_2O	3433	1659	1744	633	462
[Th (L1)(L2)(NO_3)$_2$].2H_2O	3441	1643	1760	602	463



(**a**) (**b**) (**c**) (**d**) (**e**)

Figure 1. Infrared spectra of (a) the Schiff base (HL1); (b) benzil; (c) [Fe(L1)(L2)(OH)]·H_2O chelate; (d) [Ce(L1)(L2)(SO_4)(H_2O)]·H_2O chelate; and (e) [Th(L1)(L2)(NO_3)$_2$]·2H_2O chelate

^{1}H&^{13}CNMR spectra of Schiff base

The 1HNMR spectrum of the Schiff base was obtained in DMSO- *d$_6$* solution as a solvent at room temperature using TMS as an internal reference. In the present study, the ^{1}HNMR spectral signals are depicted in Fig. 2a. The resonance of protons has been assigned on the basis of their integration and multiplicity pattern. The ^{1}HNMR spectrum of Schiff base shows two signals at 4.1 and 7.73ppm, the first signal attributed to the presence of -OH proton in phenyl ring and -COOH group in amino acid, also the signals at 1.2, 2.3, 3.2, and 2.5 ppm are due to the existence of methyl groups and DMSO-*d$_6$* solvent, respectively [20]. The aromatic protons have been resonated in the region at 6.4-7.5 ppm [34]. 13C NMR spectrum of the Schiff base has been recorded in DMSO-d6 as a solvent. Fig.2b exhibits a chemical shift at (170.82) ppm refers to the imine carbon atom (C=N) group [22]. While the chemical shift at (173.19 ppm) is attributed to the carboxylic carbon atom COOH group, and signals at 57.62, 19.94, and 14.23 ppm are assigned to carbons of methyl groups [35]. Signals that are associated with the aromatic carbons have been detected at a range of 113.02-133.40 ppm, and a signal at 169. 96ppm may be due to carbon of the C-OH phenolic group [36]. The signal observed at 39.50 ppm leads to DMSO- *d$_6$* [37].

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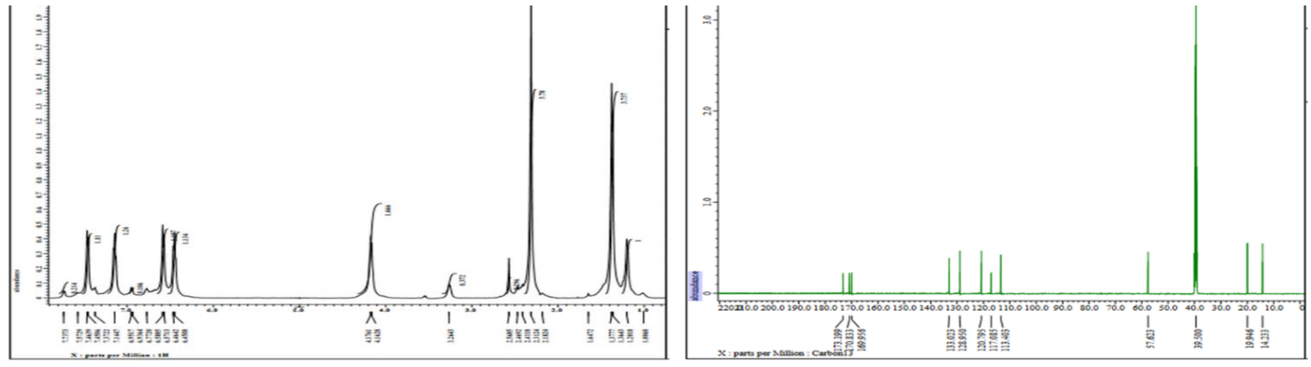


(**a**) (**b**)

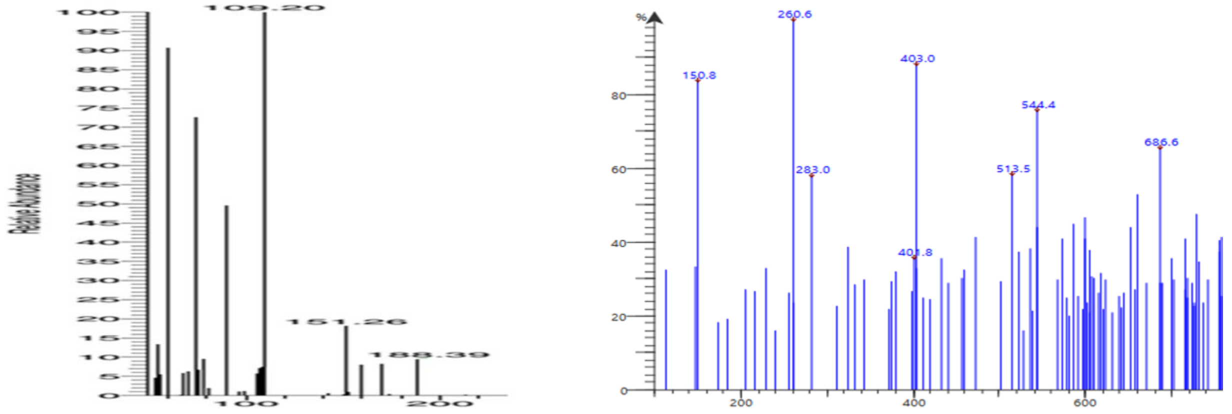
Figure 1. NMR spectra of the Schiff base (HL1): (a) ^1H NMR; (b) ^{13}C NMR

Mass spectra of Schiff base and thorium mixed ligand chelate

The mass spectral data of Schiff base HL1(Fig.3) and $[Th(L1)(L2)(NO_3)_2]\ 2H_2O$ mixed ligand chelate are listed in (Table 3).

Table 1. Mass spectral fragmentations of the Schiff base (HL1) and thorium mixed ligand chelate

Compounds	Fragmented ion	m\z+ Value
HL1; ($C_{11}H_{13}NO_3$)	$C_{11}H_{13}NO_3$	207
	$C_{11}H_{10}NO_2$	188
	$C_8H_9NO_2$	151
	C_7H_9O	109
	C_7H_7	91
$[Th(L1)(L2)(NO_3)_2](H_2O)_2$	$C_{25}H_{25}N_3O_{13}Th$	807
	$C_{22}H_{19}N_2O_9Th$	687
	$C_{19}H_{16}NO_4Th$	544
	$C_{17}H_{16}N_3O_3Th$	514
	$C_{12}H_{11}OTh$	403
	$C_{11}H_3O$	151



(**a**) (**b**)

Figure 3. Mass spectra of (a) the Schiff base (HL1) and (b) the Th(IV) mixed-ligand chelate $[Th(L1)(L2)(NO_3)_2]\cdot 2H_2O$

Electronic spectra and magnetic moments

The electronic spectral data of the Schiff base and mixed ligand chelates are listed in (Table 4) and their spectra are shown in (Figs.4). The spectrum of the Schiff base (HL1) exhibits absorption bands at 260nm (38711cm^{-1}) and 313 nm (31949cm^{-1}) corresponding to $\pi\rightarrow\pi^*$ (phenyl ring) and $n\rightarrow\pi^*$ transition, respectively [38]. The electronic absorption spectrum of the Iron(III) mixed ligand chelate exhibits a band at 274nm(36496cm^{-1}), which is assigned to a charge transfer transition [28]. The observed magnetic moment of the mixed ligand chelate is 6.40 B.M [39]. The nature of the band and the magnetic moment value support the existence of an octahedral geometry involving sp3d2 hybridization in the Iron(III) ion[29]. The electronic spectra of cerium(IV) and thorium(IV) mixed ligand chelates show typical two absorptions at 283nm (35336cm^{-1}) and 262nm (38168cm-1) are attributed to $\pi\rightarrow\pi^*$. The shifts in these bands indicate that the ligand conjugation changes after coordination with the metal [30,31]. Because of the effective shielding of the 4f and 5f orbitals by the 6s, 6p or 7s, 7p octet, and consequently, minimum ligand field perturbation of

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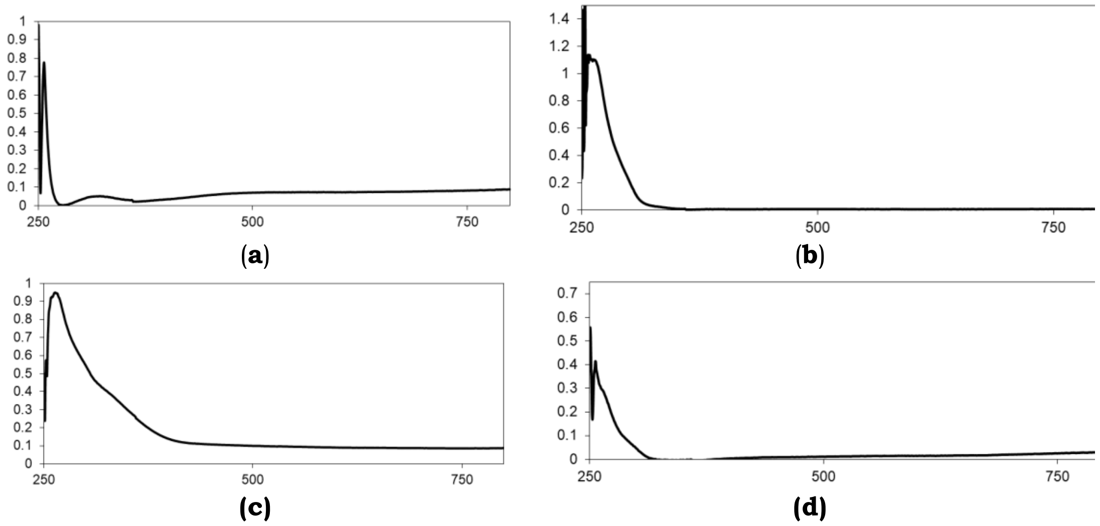
the electronic energy levels in rare earth metals. The spectra of Ce(IV) and Th(IV) mixed ligand chelates display the characteristic bands due to f-f transition. Thus, Ce(IV) and Th(IV) have no clear transitions in the region of 500-700 nm(20000-14286cm^{-1}) because the f–f bands are sharp and line-like [40].



(**a**) (**b**)

(c) **(d)**

Figure 4. Electronic spectra of (a) the Schiff base (HL1); (b) [Fe(L1)(L2)(H_2O)]·H_2O chelate; (c) [Ce(L1)(L2)(SO_4)(H_2O)]·H_2O chelate; and (d) [Th(L1)(L2)(NO_3)$_2$]·2H_2O chelate.

Table 4. Electronic spectral of the Schiff base (HL1) and thorium mixed ligand chelat

Compounds	**λ nm (cm^{-1})**	**assignment**
HL1; ($C_{11}H_{13}NO_3$)	260nm(38462cm^{-1}) 313nm (31949 cm^{-1}	,$^{*}\pi\rightarrow\pi$ n→ π^{*}
[Fe(L1)(L2)(OH)].H_2O	274nm(36496cm^{-1})	CT
[Ce(L1)(L2)(SO_4)(H_2O)]. H_2O	283nm (35336cm^{-1}) 500-700nm(16667-14286cm^{-1})	$\pi\rightarrow\pi^{*}$ f-f transitions
[Th(L1)(L2)(NO_3)$_2$].2H_2O	262nm (38168cm^{-1}) 500-700nm(16667-14286cm^{-1})	$\pi\rightarrow\pi^{*}$ f-f transitions

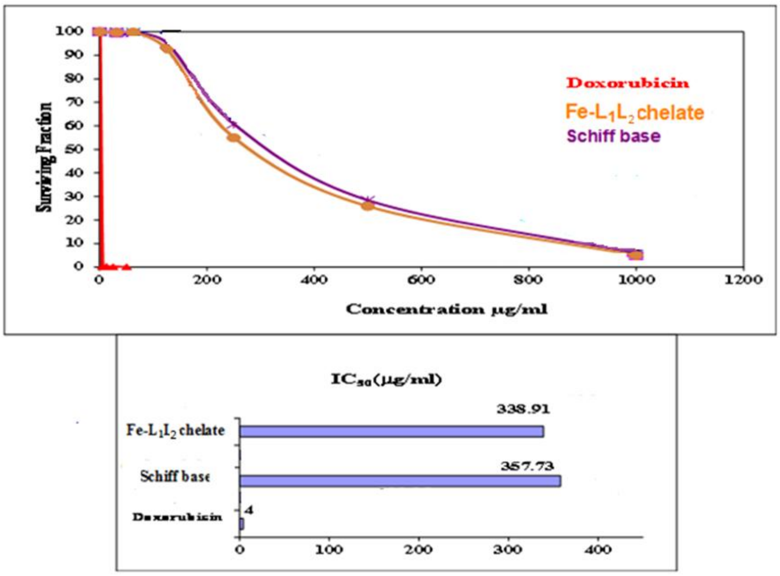


Figure 5. The surviving fraction of compounds against HepG2 liver cells

In this study, the resulting data explained 6-coordinate chelate of Fe(III), 8 8-coordinate chelate of Ce(III), and 9-coordinate chelate of Th(IV) mixed ligand chelates as shown below:

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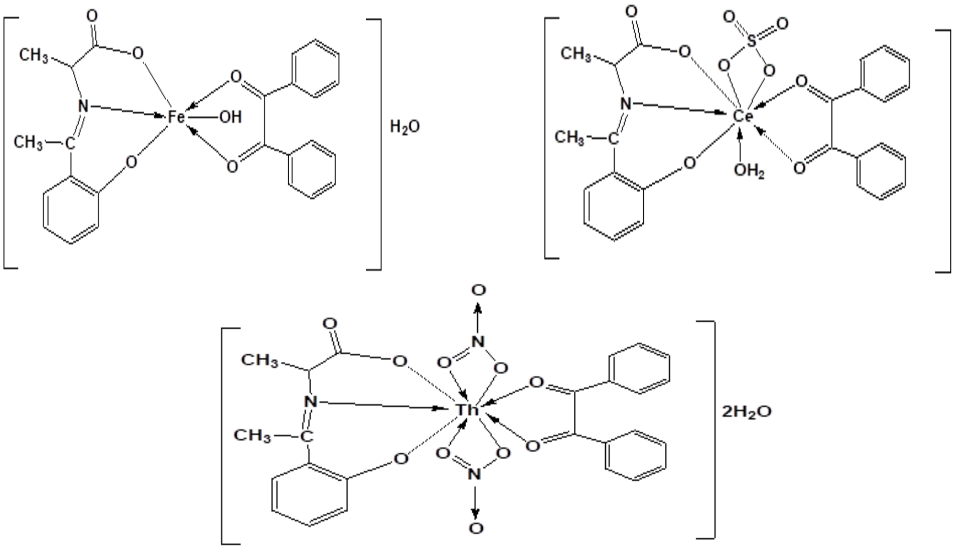

Figure 6. The suggested structures of the Fe(III), Ce(IV), and Th(IV) chelates

Antitumor activity

The in vitro growth inhibitory activity of the prepared Schiff base and iron mixed ligand chelate was evaluated against the HEPG-2 cell line, along with the standard anticancer drug doxorubicin, to assess cell proliferation. The inhibitory activities of compounds against HEPG-2 cell lines were shown in Fig.5. After incubation with chelates, a decrease in cell proliferation was observed. The IC_{50} values of the tested compounds were determined and compared with doxorubicin. The analysis of the obtained IC_{50} values reveals that the iron (III) chelates exerted superior activity in comparison to the free Schiff base. The activity of the ligand is enhanced upon chelate formation of Fe(III). The higher conjugation in the ligand skeleton as a result of the chelation process may be the reason for increased activity upon chelate formation [33]. The obtained results are consistent with the previously published work of metal chelates, which were tested in vitro for their antitumor activities against the Hep G-2 cell line [34]. The high activity of Fe(III)-chelate may be attributed to the positive charge of the metal, increasing the acidity of the coordinated ligand that bears protons, causing stronger hydrogen bonds, which enhance the biological activity.

Molecular docking studies

The molecular docking in this study was performed for the Schiff base and iron(III) mixed ligand chelate(Fig.7) as representative examples to compare their results with the experimental IC_{50} values. The scoring energy and root-mean-square deviation values are represented in (Table 5). Theoretically, the solvent contact of ligand and Fe-L1L2 chelate shows a decrease in scoring energy values, and consequently, it was expected to give a decrease in their true experimental cytotoxic results [41]. But the experimental results, as discussed before, revealed a lower IC50 for Fe-L1L2 chelate than ligand. The best cytotoxic results are explained in the cytotoxic study part, especially the higher conjugation in Fe-L1L2 chelate overcomes the expected solvent contact effect [42].

Table 5. Binding affinity of Schiff base and iron mixed ligand chelate against EGFR tyrosine kinase receptor (PDB Code: 1M17)

Antitumor docking 1M17	
Compound	Scoring energy (RMSD)
Schiff base	-4.10(2.36)
Fe-L1L2 chelate	-4.40(2.2)

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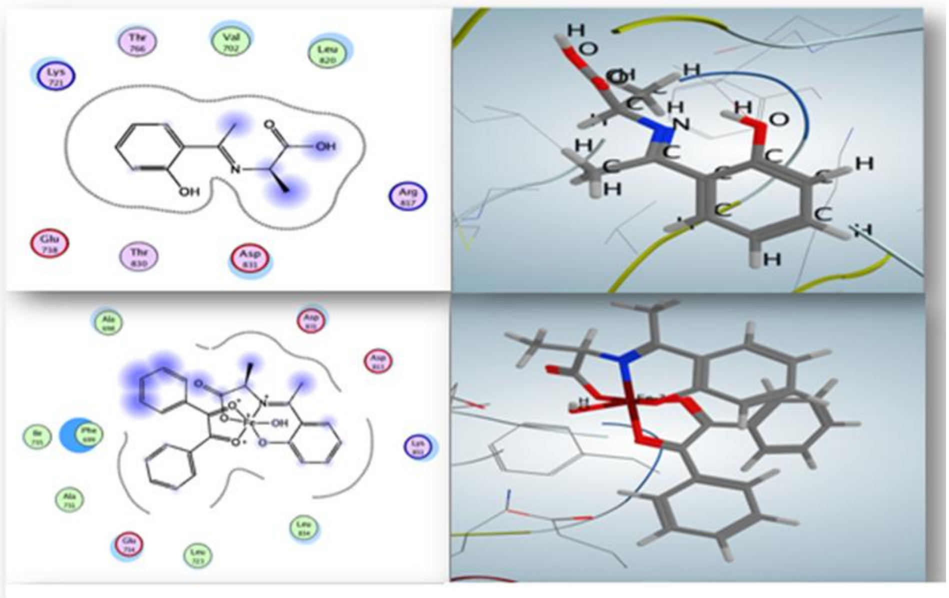

Figure 7. 2D and 3D Binding affinity of Schiff base and iron mixed ligand chelate against EGFR tyrosine kinase receptor (PDB Code: 1M17), respectively

Conclusion

Three novel mixed-ligand chelates of Fe(III), Ce(IV), and Th(IV) were successfully synthesized using a Schiff base derived from 2-hydroxyacetophenone and L-alanine with benzil as a secondary ligand. Spectroscopic and analytical data confirmed their formation in a 1:1:1 [M: L1: L2] ratio with octahedral geometry and non-electrolytic behavior. Coordination occurred through azomethine nitrogen and phenolic oxygen sites. The Fe(III) complex exhibited the highest antitumor activity against HepG2 cells, surpassing the free Schiff base, likely due to increased conjugation and polarity upon chelation. Molecular docking studies with the EGFR tyrosine kinase receptor (PDB: 1M17) supported these findings, indicating favorable binding affinity. Overall, the Fe(III) Schiff base–benzil chelate demonstrates promising potential as a lead compound for hepatocellular carcinoma therapy.

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Conflicts of Interest

The authors declare no conflicts of interest.

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