RESEARCH ARTICLE

Design, Synthesis, and Evaluation of Erlotinib–Metal Complexes for Enhanced Anticancer Efficacy

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ABSTRACT

Erlotinib, a known tyrosine kinase inhibitor (TKI), has played a vital role in the management of non-small cell lung cancer (NSCLC) and pancreatic cancer. Despite its therapeutic success, challenges such as low aqueous solubility, reduced bioavailability, and emerging drug resistance limit its long-term clinical use. In response to these concerns, the present study explores a novel approach—forming metal complexes of Erlotinib with selected transition metals—to potentially improve its pharmacological profile. The drug was initially characterized through UV-visible and FTIR spectroscopy to ensure structural integrity and purity. Metal complexation was achieved by reacting a mildly alkaline ethanolic solution of Erlotinib with ethanolic solutions of metal chlorides, namely $CuCl_2$, $FeCl_3$, $ZnCl_2$, $MgCl_2$, and $MnCl_2$. The process involved dropwise addition of metal solutions with continuous stirring, followed by an incubation period that facilitated the formation of stable complexes. Shifts in λmax values and unique mass spectral fragmentation patterns confirmed the successful coordination of metal ions with Erlotinib. By altering the drug's electronic environment through metal binding, the study demonstrates a promising pathway to enhance Erlotinib's physicochemical and therapeutic characteristics. The outcomes encourage further pharmacological exploration and suggest that metal complexation may help address some of the limitations associated with Erlotinib monotherapy**.**

Keywords: Erlotinib, Metal Complex, EGFR Inhibitor, UV Spectroscopy, Mass Spectrometry, Anticancer Drug Design
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INTRODUCTION

Erlotinib (Fig.1) has emerged as a widely recognized anticancer drug due to its ability to inhibit the epidermal growth factor receptor (EGFR), a critical driver in the progression of several cancers, including non-small cell lung cancer (NSCLC) and pancreatic cancer[1-4]. While it offers significant clinical benefits, patients often face setbacks due to drug resistance and limited bioavailability over prolonged treatments. As a result, researchers have been exploring new ways to enhance Erlotinib's effectiveness and sustainability in cancer therapy[5]. One such promising strategy involves forming complexes of Erlotinib with transition metals like platinum, copper, ruthenium, and zinc. These metal complexes have been shown to influence the pharmacokinetic and pharmacodynamic properties of drugs—improving their solubility, cellular uptake, and even their ability to induce apoptosis by generating reactive oxygen species (ROS)[6,7]. Additionally, metal coordination can alter the drug's interaction with biomolecular targets, making it more difficult for cancer cells to develop resistance[8].

Over the past decade, several studies have reported that metal–Erlotinib complexes demonstrate superior anticancer potential compared to Erlotinib alone. These complexes often show increased DNA-binding affinity, mitochondrial disruption, and inhibition of enzymes like topoisomerase, all of which contribute to enhanced cytotoxicity in cancer cells[9-12]. For instance, copper- and zinc-based Erlotinib complexes have shown promise against resistant cancer cell lines, suggesting that metal coordination may revitalize the clinical performance of the parent drug[11,12]. In light of these developments, this review aims to explore the current progress in the design and biological evaluation of metal–Erlotinib complexes. By analyzing their mechanisms of action, structural characteristics, and anticancer potential, we hope to shed light on how these innovative compounds could shape the future of targeted cancer therapy[13].

MATERIALS AND METHOD

Chemicals

Erlotinib hydrochloride (Aarjey Healthcare Pvt. Ltd., India) was used as the model anticancer agent for complexation studies.

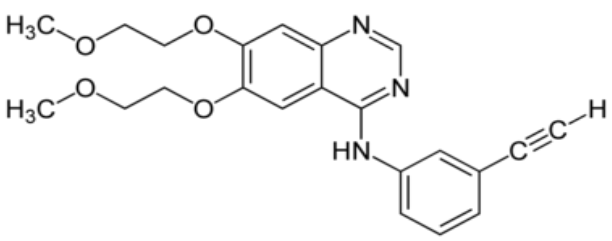

Figure 1: Chemical Structure of Erlotinib

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Table 1: Absorbance values and concentration of solutions

Concentration (µg/mL)	Absorbance
0	00
5	0.783
10	0.849
15	0.942
20	0.991
25	1.138
30	1.217

Table 2: The lambda max values of metal complexes

Sample name	Lambda max (nm)
Erlotinib	341.78
Mg_Er_Complex	345.16
Mn_Er_Complex	357.36
Cu_Er_Complex	350.04
Fe_Er_Complex	349.87
Zn_Er_Complex	348.88

Metal salts including $CuCl_2$, $ZnCl_2$, $FeCl_3$, $MnCl_2$, and $MgCl_2$ were purchased from SD Fine-Chem and Loba Chemie. Analytical-grade solvents such as methanol and ethanol were obtained from Merck, while 0.1 N HCl and NaOH pellets were sourced from HiMedia.

Instruments

UV-Visible spectrophotometer (Shimadzu UV-1800) was used to detect λmax shifts confirming complex formation. FTIR spectrophotometer (Bruker Alpha II) helped identify ligand-metal interactions. Melting points were recorded using Veego apparatus, while a digital pH meter (Eutech Instruments) ensured optimal reaction conditions. All reactions were carried out on a magnetic stirrer with heating (REMI), and sample weights were measured using a Shimadzu analytical balance.

METHODOLOGY

Drug Characterization and Calibration Curve Development

Table 3: The mass analysis of metal-complexes

Sample	Peak value	Corresponds to
Erlotinib	394.02	Molecular ion peak $[C_{22}H_{23}N_3O_4]$
Mg_Er_	418.02	Molecular ion peak $[C_{22}H_{23}N_3O_4]Mg$
Complex	395.17	Erlotinib ion $[C_{22}H_{25}N_3O_4]^{2+}$
	25.09	Mg^{2+}
Mn_Er_	448.67	Molecular ion peak $[C_{22}H_{23}N_3O_4]Mn$
Complex	395.51	Erlotinib ion $[C_{22}H_{25}N_3O_4]^{2+}$
	55.38	Mn^{2+}
Cu_Er_	455.99	Molecular ion peak $[C_{22}H_{23}N_3O_4]Cu$
Complex	395.55	Erlotinib ion $[C_{22}H_{25}N_3O_4]^{2+}$
	64.66	Cu^{2+}
Fe_Er_	450.78	Molecular ion peak $[C_{22}H_{23}N_3O_4]Fe$
Complex	396.01	Erlotinib ion $[C_{22}H_{25}N_3O_4]^{2+}$
	55.89	Fe^{2+}
Zn_Er_	457.98	Molecular ion peak $[C_{22}H_{23}N_3O_4]Zn$
Complex	395.47	Erlotinib ion $[C_{22}H_{25}N_3O_4]^{2+}$
	65.66	Zn^{2+}

Erlotinib was subjected to UV-visible spectrophotometric analysis to determine its λmax. A stock solution was prepared in methanol, diluted with 0.1 N HCl, and scanned between 200–400 nm. A λmax of 340 nm was observed. A series of standard dilutions (5–30 µg/mL) were used to construct a calibration curve correlating absorbance to concentration[14].

FTIR Spectroscopy

The drug was analyzed using FTIR spectroscopy (Bruker Alpha II) to confirm functional groups. This analysis helped ensure that the chemical structure of Erlotinib was intact before initiating complexation[15-19].

Preparation of Erlotinib–Metal Complexes

A 0.01 M solution of Erlotinib in ethanol was alkalinized with NaOH. Separately, 0.01 N ethanolic metal chloride solutions (Cu, Fe, Zn, Mg, Mn) were prepared. Each metal solution was added gradually to the Erlotinib solution under

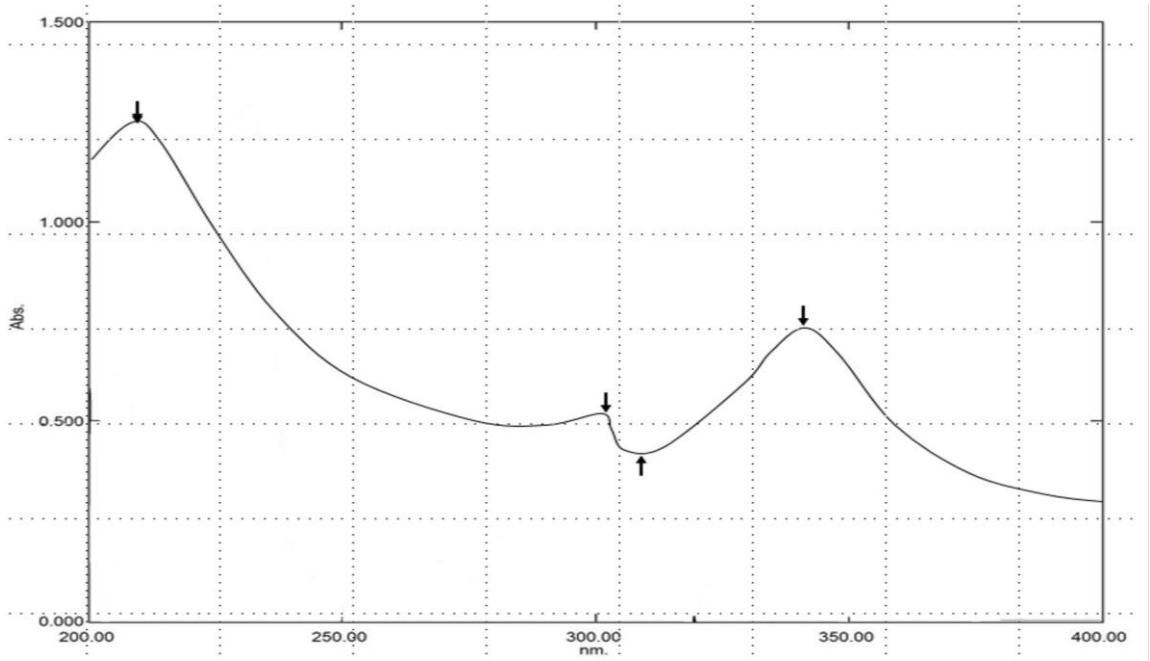


Figure 2: The lambda max value of Erlotinib was found to be 340 nm in 0.1N HCl

stirring. The mixture was stirred for 72 hours and left undisturbed for 7–10 days, allowing complex precipitation, which was filtered and vacuum-dried[20-21].

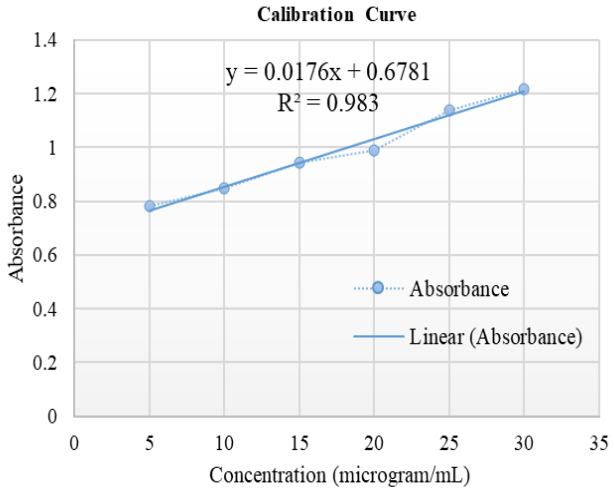


Figure 3: Calibration curve of Erlotinib

UV-Vis Analysis of Metal Complexes

Post-synthesis, each metal complex was scanned using UV spectroscopy to monitor shifts in λmax. These changes in absorption indicated successful metal binding and electronic interaction with Erlotinib's molecular structure[22-24].

Mass Spectrometric Analysis

Mass spectrometry was used to confirm the formation of complexes. Each compound displayed distinct molecular ion peaks, and altered fragmentation patterns compared to the pure drug, affirming metal coordination[25-30].

RESULTS AND DISCUSSION

UV Spectroscopic Analysis of Pure Erlotinib

The UV-visible spectroscopic evaluation of Erlotinib in 0.1 N HCl revealed a distinct absorption maximum at 340 nm. This peak corresponds to the π→π* transition typically associated with the aromatic structure present in Erlotinib. To ensure linearity and reproducibility, standard solutions were prepared in concentrations ranging from 5 to 30 µg/mL.

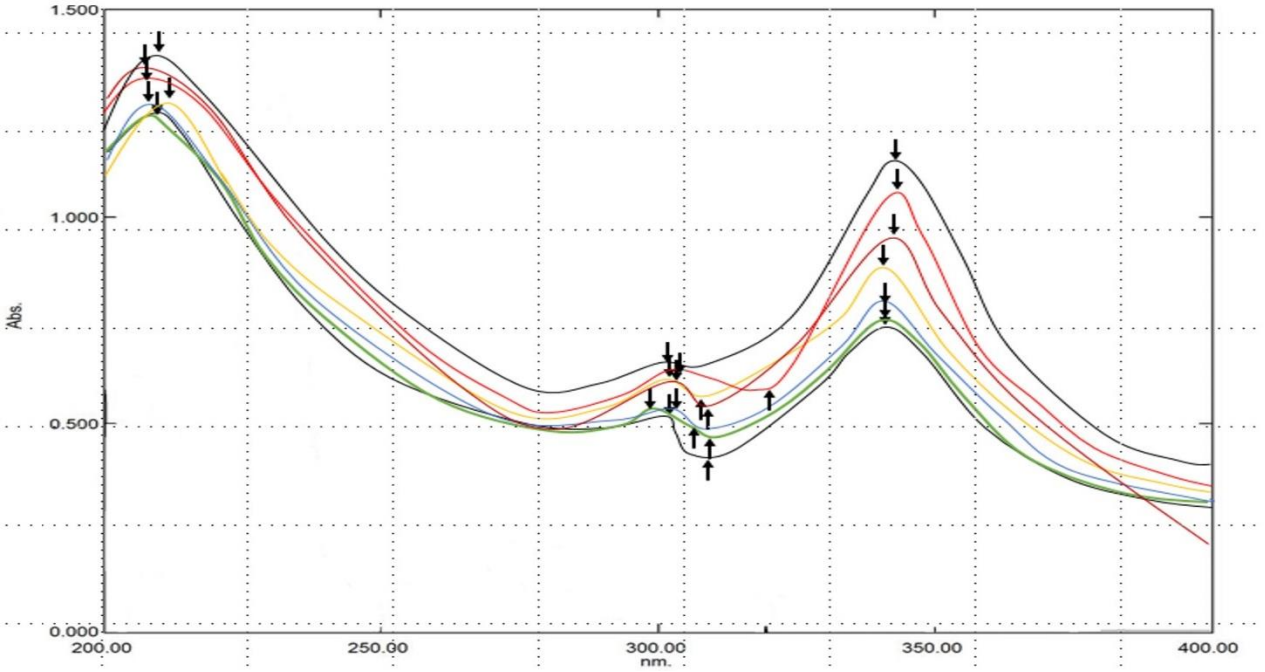


Figure 4: The overlain UV graph of Erlotinib

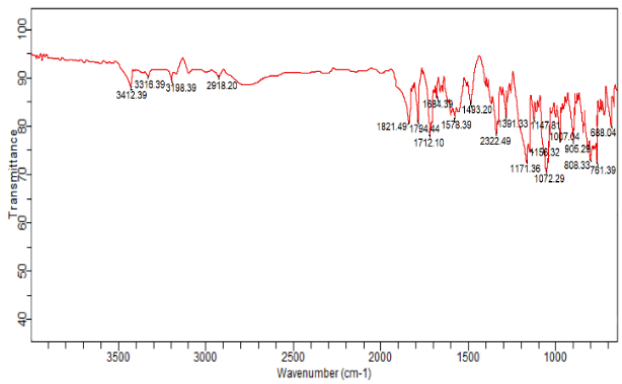
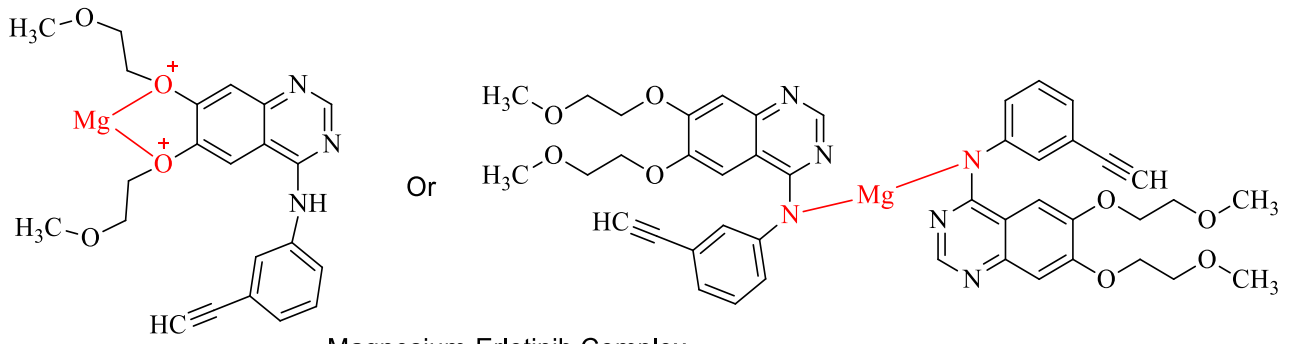
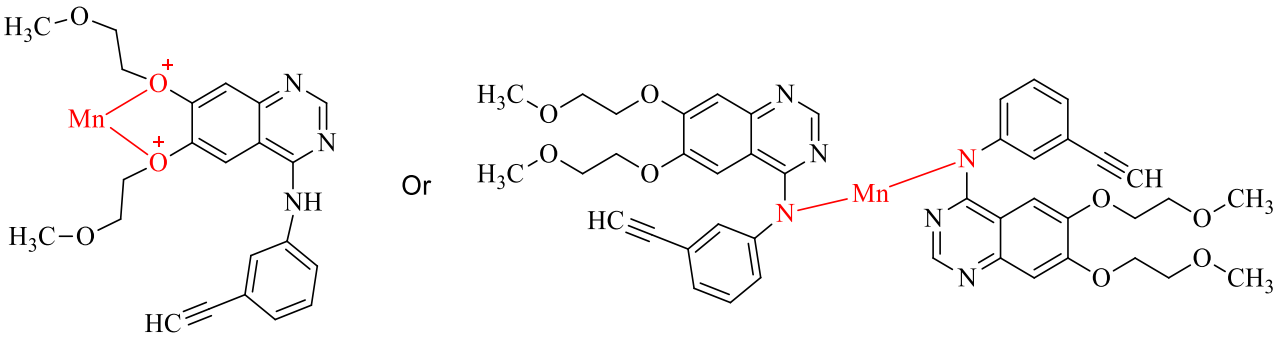


Figure 5: FTIR spectra of Pure Erlotinib

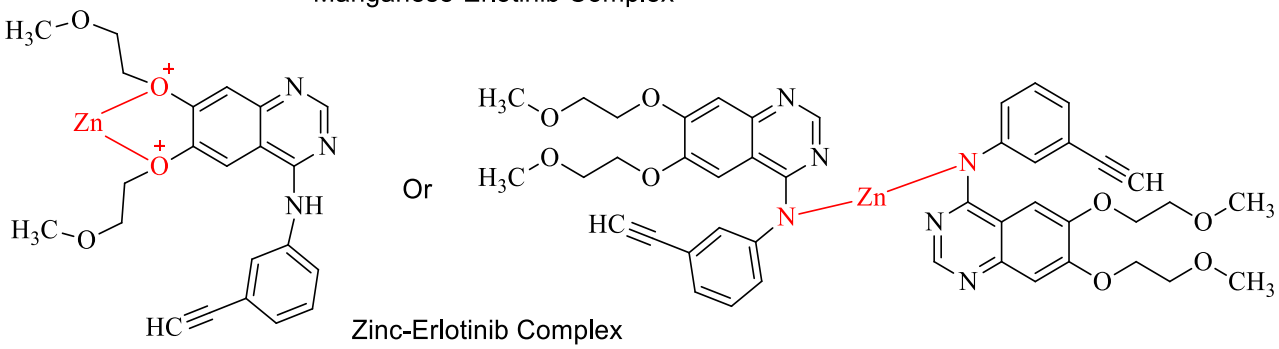
Figure 6: The working images of prepared metal complex solutions and drug solution



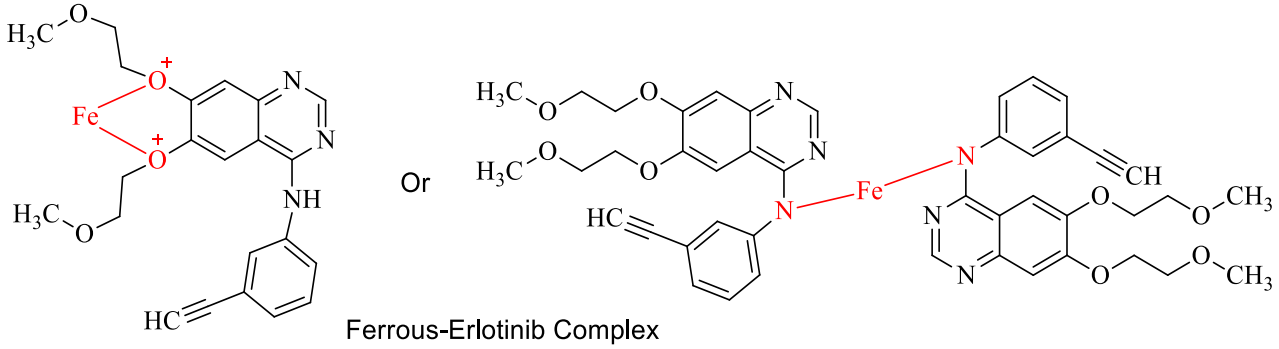
Magnesium-Erlotinib Complex



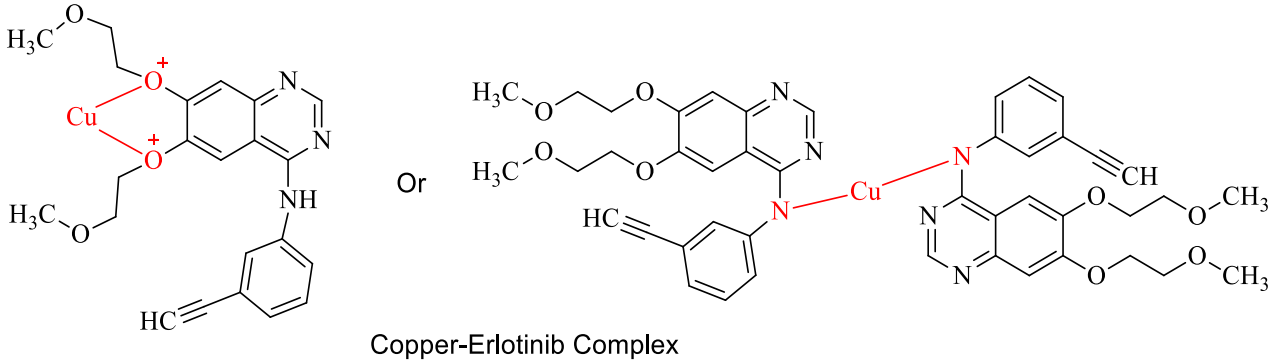
Manganese-Erlotinib Complex



Zinc-Erlotinib Complex



Ferrous-Erlotinib Complex



Copper-Erlotinib Complex

Figure 7: The structure of Erlotinib-metal complex

The absorbance values showed a consistent linear relationship with concentration, confirming the validity of the λmax value and setting the foundation for comparison with metal complexes. The UV graph is depicted in Figure 2. The concentrations and absorbance values are tabulated in Table 1. The calibration curve and overlain graph are given in Figures 3 and 4, respectively.

FTIR Characterization of Pure Drug

The FTIR spectrum of Erlotinib was analyzed to verify its structural integrity before proceeding with complexation (Fig.5).

Key absorption bands were observed that matched well with expected functional groups in the molecule. Peaks indicating –NH stretching, aromatic ring vibrations, and C–N/C=O stretches were identifiable. These spectral features served as reference markers for identifying changes post-metal coordination, providing insight into the nature of bonding in the complexes.

Structural Representation of Erlotinib–Metal Complexes

The working images of prepared metal complex solutions and drug solution are given in Figure 6. Figure 7 illustrates the proposed coordination structures of Erlotinib with five different metal ions—magnesium, manganese, zinc, iron (ferrous), and copper.

In each case, the metal ion forms a stable complex by coordinating with nitrogen atoms on the quinazoline moiety and possibly oxygen atoms on the side chain of Erlotinib. These interactions likely enhance the electronic properties of the molecule and influence its binding affinity to biological targets such as EGFR.

The bidentate nature of Erlotinib allows it to act as a chelating ligand, stabilizing the metal center and facilitating enhanced bioactivity. The structural representations show both possible coordination geometries—one through nitrogen donor atoms and another involving both nitrogen and oxygen, providing insight into the flexibility of Erlotinib as a ligand and supporting its potential for improved pharmacological efficacy when complexed with transition metals.

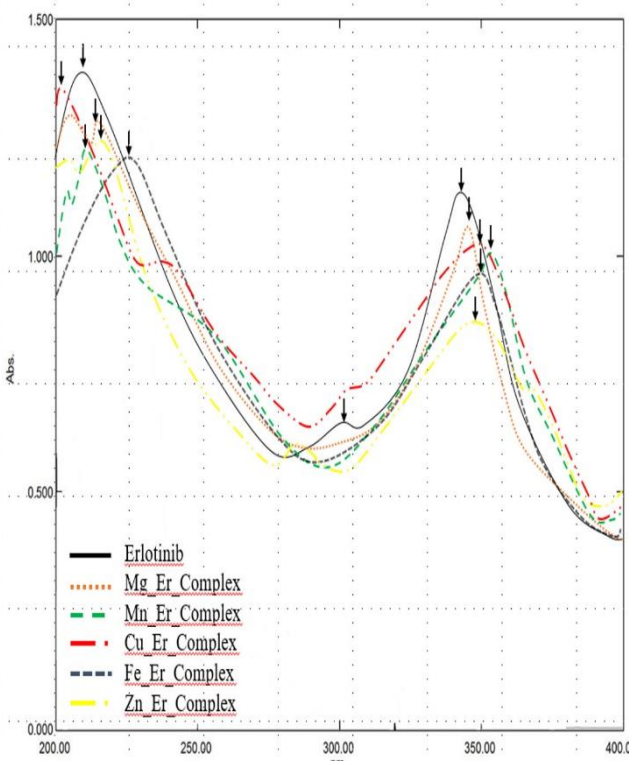


Figure 8: The UV graphs of metal complexes

UV Analysis of Metal Complexes

The metal complex solution were prepared and scanned in UV in the range of 200-400 nm. The obtained overlain graph of UV is depicted in Figure 8. The UV graph indicate formation of metal complex as each one displayed different lambda max value and graph pattern compare to pure drug. The lambda max values of all the metal complexes and pure drug are tabulated in Table 2.

Mass Analysis of Metal Complexes

Mass spectrometric analysis provided further evidence of successful complex formation. For each metal–drug complex, a prominent molecular ion peak was observed, corresponding to the combined mass of Erlotinib and the respective metal ion.

For instance, the Cu–Erlotinib complex displayed a peak at m/z 455.99, suggesting the presence of a mono-ligated species.

Fragmentation patterns supported the structural assumptions, with peaks indicating partial breakdown into constituent parts, thus confirming the identity and stoichiometry of the complexes. From Mass analysis, the different fragments in the spectrum indicate the formation of metal complexes.

The mass spectra of Erlotinib and Erlotinib-metal complexes are depicted in Figure 9, and the analysis presented in Table 3.

CONCLUSION

The study presents a promising approach to enhancing the anticancer potential of Erlotinib by forming coordination complexes with essential metal ions such as magnesium, manganese, copper, iron, and zinc. These metal–drug complexes were successfully synthesized and characterized using techniques like UV-visible spectroscopy and mass spectrometry, confirming the interaction between Erlotinib's functional groups and the metal centers. The nitrogen atoms of the quinazoline ring and possibly oxygen atoms from the side chains played a key role in forming stable bidentate complexes, which may significantly alter the drug's pharmacological behavior.

Such modifications have the potential to improve Erlotinib's solubility, stability, and biological activity, thereby addressing challenges like drug resistance and limited bioavailability.

By enhancing its interaction with target proteins such as EGFR, these metal complexes could pave the way for more effective cancer therapies.

The findings from this study provide a strong basis for further biological evaluation and pharmacodynamic studies to fully understand the therapeutic value of these complexes.

If proven effective in biological models, metal–Erlotinib complexes could offer a new avenue in the design of targeted anticancer agents with superior clinical performance.

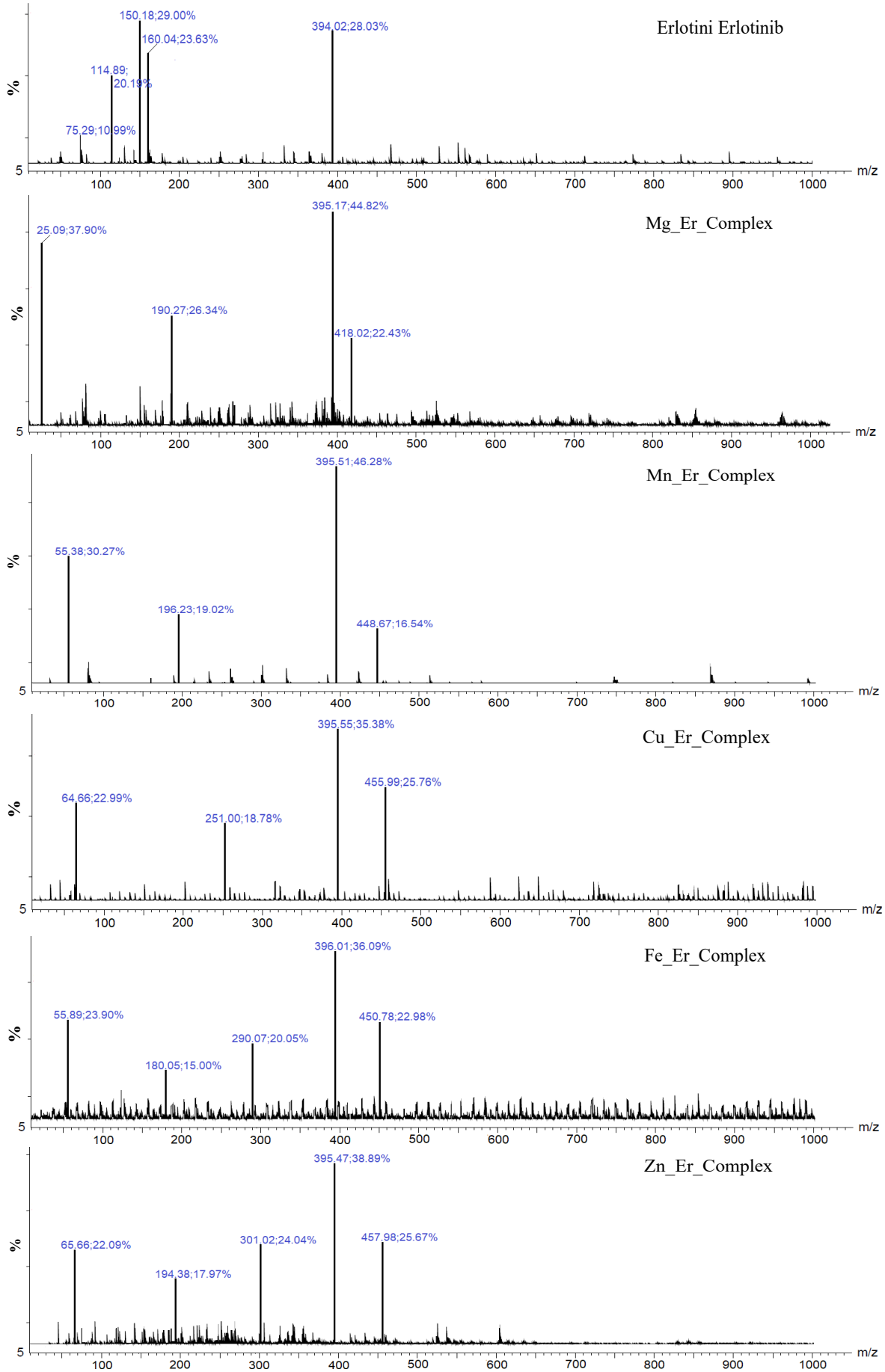


Figure 9: The Mass spectrum of Erlotinib and Erlotinib-metal complex

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