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MOLECULAR DOCKING INVESTIGATIONS OF THIOSEMICARBAZONE Cu(II) and Zn(II) METAL COMPLEXES AGAINST EGFR, HER2, AND IKK-β TARGET PROTEINS: SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING

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ABSTRACT

Cu(II) and Zn(II) complexes of Schiff bases produced from thiosemicarbazone with Anthracene, indole, pyrimidines, and chromones have been synthesized and physiochemically characterized. Among the synthesized ligands L1-L4, the first three ligands behave as uninegative bidentate ones towards Cu(II) and Zn(II) metals, whereas the L4 ligand behaves as a uninegative tridentate one. The structure and bonding properties of the complexes have been investigated using electronic and HRMS-spectral data. All the ligands and complexes were tested for their anti-cancer and anti-bacterial activities. Docking studies demonstrated that Cu(II) and Zn(II) complexes interacted favorably with the EGFR, HER2, and IKK-β receptors.

Keywords: Thiosemicarbazide, Metal complexes, Anti-cancer activity, Anti-bacterial activity, EGFR, Molecular docking

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INTRODUCTION

Cancer has long been one of the country's biggest serious health problems, with millions of deaths as a result. Cancer surpassed cardiovascular diseases as the country's greatest cause of death by 2010, and this trend is predicted to continue, with global cancer diagnoses and deaths expected to more than double by 2030.[1] Cancer of the cervix is the fourth highest cause of death in women. In 2018, over 570 000 new cases of cervical cancer were recorded around the world.[2] Because of their importance in the area of pharmaceuticals as well as their wide range of biological uses, the synthesis of Schiff base metal complexes always appears to be significant.[3] The condensation of an aromatic or aliphatic primary amine with a carbonyl molecule produces this important class of synthetic compounds.[4] These are the most popular ligands for stabilizing metal ions in various oxidation states.[5] They may form complexes with a variety of metal ions[6] and the resultant complexes are used as efficient catalysts; DNA/protein binders antitumors and antibacterial drugs.[7] For example, a variety of thiosemicarbazone Schiff base analogs has demonstrated a wide range of chemotherapeutic activities as well as biological activities such as antibacterial[9], antitumor[8], cytotoxicity, and antiviral properties.[10] Metal ion linkage can improve the biological properties of these thiosemicarbazone ligands.[11] Anthracene hybrids are the most important class of ligands with strong intrinsic fluorescence characteristics, and they have been studied for their binding capacity to DNA as potential chemotherapeutics.[12] It has been shown to be useful in the treatment of psoriasis.[13] Because of their physiological and biological activities such as antibacterial, antifungal, and anticonvulsant properties, Chromones and their complexes are also considered a significant family of biologically active compounds.Despite of ligation potentiality associated with thiosemicarbazone derivatives and their metal complexes herein, we describe the synthesis, structural elucidation, antimicrobial, and anticancer activities and molecular docking studies of Cu and Zn complexes of

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thiosemicarbazone Schiff bases namely, anthracene thiosemicarbazone (ATSC=L1), indole thiosemicarbazone (ITSC=L2), piperidinone thiosemicarbazone (PTSC=L3), and chromone thiosemicarbazone (CTSC=L4) ligands.

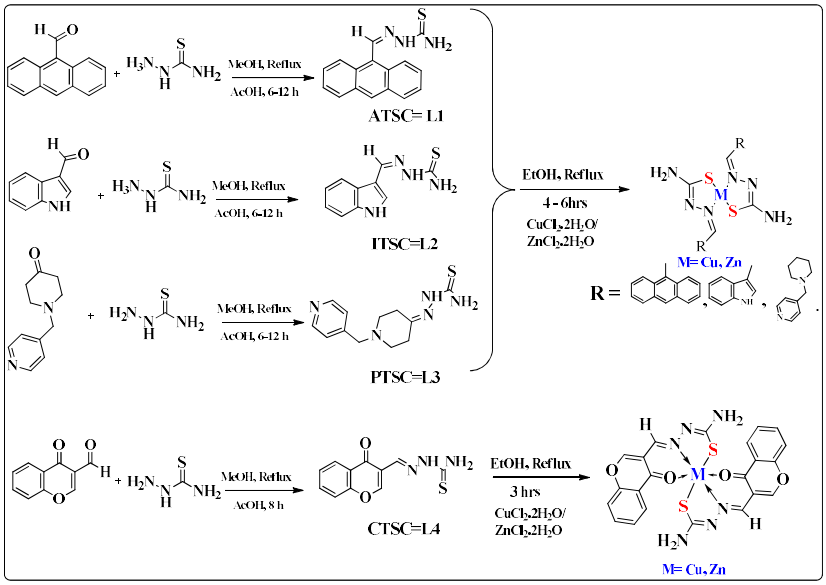
EXPERIMENTAL

Material and Methods

To perform the reaction, AR or BDH-grade chemicals and solvents were used. The melting points were determined in open capillaries without being modified. On plates of prepared silica gel, TLC was used to investigate the compound for the end of the reaction. Using the KBr pellets approach, the IR spectrum of the complexes and ligands was recorded on FT-IR Shimadzu IR affinity–I 8,000 spectrophotometer in the region of 4000-400 cm^{-1}. Using a Bruker Avance II 500 MHz NMR spectrometer, NMR spectra in $CDCl_3$ and DMSO-d_6 were recorded with TMS as a standard solution. On a Uv-vis-NIR Varian Cary 5000 spectrometer, the electronic spectra were measured in dimethylformamide. The elemental analysis was done by using Perkin-Elmer 2400. An ESI–mass spectrometer was used to obtain the mass spectra.

Synthesis of Ligands

Synthesis of anthracene thiosemicarbazone L1 (ATSC) was done by taking a mixture of thiosemicarbazide and 9-anthraldehyde in 15 ml of methanol with a few drops of glacial acetic acid under reflux for 4 hrs. The compound was cooled and the solid that separated during the reflux was filtered, rinsed with cold MeOH and EtOH, and vacuum dried. It was then recrystallized using hot MeOH. The remaining ligands (L2-L4) were also synthesized by using the same synthetic protocol. In order to develop Zn(II) and Cu(II) complexes, respective metal chlorides and ligands were mixed in an ethanolic solution in a 1:2 mol ratio. The contents were refluxed for about 4-6 hrs at 60 ºC. The separated product is filtered, and rinsed with H_2O, then soaked in EtOH and dried in the air.[14]



Scheme-1: Synthesis of Ligands and Metal Complexes

RESULTS AND DISCUSSION

All the metal complexes synthesized as discovered should be colored, stable at ambient temperature, and soluble in solvents such as DMF, DMSO, MeOH, and EtOH. The mass spectral data and elemental analysis data were presented in Table-1 which demonstrates that the values are in excellent conformity with those calculated ones for the proposed molecular formula, indicating that the complexes have 1:2 metal-ligand molar ratios.[15] The ligand HRMS revealed an $[M + H]^+$ peak at m/z 280.12. This is the same as the molecular mass of the ligand (279.36). The high-resolution mass spectra of Zn(II) and Cu(II) complexes also reveal that the mass spectra of the $[Zn(ATSC)_2]$ complex show a peak at 620.08 which

can be assigned to the fragments [Zn (II) complex+1]$^+$ (peak at 621.088) (Fig.-1). The molecular ion peak values are almost equal to the calculated molecular weights of the compounds.

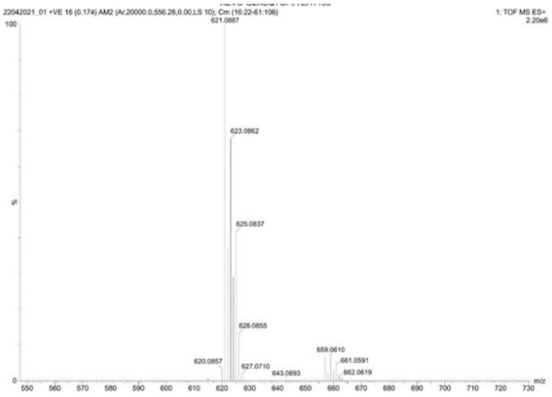


Fig.-1: HRMS Spectrum of [Zn(ATSC)$_2$] Complex

Table-1: Mass and Elemental Analysis Data

Compounds	M.W.	M.P. (°C)	Color (Yield %)	Elemental Analysis found (Calc.) [%]			
				C	H	N	M
[$C_{16}H_{13}N_3S$ (ATSC) +1]$^+$	280.12	212	Yellow (78%)	68.42 (68.79)	4.58 (4.69)	15.00 (15.04)	-- --
$C_{10}H_{10}N_4S$ (ITSC)	218.27	212	Brown (65%)	54.90 (55.02)	4.58 (4.62)	25.43 (25.65)	-- --
$C_{13}H_{18}N_4S$ (PTSC)	262.12	212	cream (71%)	59.60 (59.51)	6.89 (6.91)	21.13 (21.35)	-- --
$C_{11}H_{11}N_3S$ (CTSC)	247.04	218	Yellow (77%)	53.36 (53.43)	3.56 (3.67)	16.87 (16.99)	-- --
[Zn(ATSC)$_2$ +1]$^+$	621.088	254	Yellow (60%)	61.55 (61.78)	3.95 (3.89)	13.46 (13.51)	10.45 (10.51)
[Cu(ATSC)$_2$]	619.08	259	Green (55%)	61.67 (61.97)	3.80 (3.90)	13.43 (13.55)	10.15 (10.25)

Infrared Spectral

The IR spectra of the metal complexes and ligands are compared to learn more about the nature of the functional groups that are coordinated to the metal atom.[16] The data infrared spectrum was presented in Table-2. A sharp band corresponding to $\upsilon_{C=O}$[17] of chromone ligands CTSC was observed at around 1638 cm^{-1}. This band is marginally lower shifted in their metal complexes, indicating carbonyl oxygen involvement in coordination. Furthermore, all four ligands L1-L4 reveal a band corresponding to azomethine nitrogen HC=N- at 1564-1591 cm^{-1}. In all of the complexes, this band was also lower Schifted, indicating that azomethine nitrogen was involved in the coordination. The band corresponding to υ_{S-H} at 2600-2550 cm^{-1} was not revealed by the ligands suggesting that this group has undergone tautomerism.[18] A band attributable to the C=S group at 836-908 cm^{-1} was observed in ligands, but it vanished completely in the complexes, and a new band corresponding to M-S stretching vibration was observed in the region 724-722 cm^{-1}.[19] Because the thioamide functional group in the ligand can exist in thione and thiol forms, this shows that tautomerisms have occurred and the thiol is deprotonated prior to coordination. Thus the ligands (L_1, L_2, and L_3) act as mono-negative bidentate ones towards Cu(II) and Zn(II) complexes coordinating through azomethine nitrogen, and thio keto sulphur. Whereas the ligand L_4 acts as a mono-negative tridentate one towards Cu(II) and Zn(II) complexes coordinating through carbonyl oxygen, azomethine nitrogen, and thio keto sulpher.

Table-2: Selected Infrared Data of the Metal Complexes and its Ligands

Compound	υ(N-H)	υ(C=O)	υ (C=N)	υ (C=S)	υ (M-N)	υ(M-S)
ATMSC	3193	-	1583	908	-	-

ITSC	3449 3309	-	1591	836	-	-
PTSC	3386 3197	-	1591	857	-	-
CTSC	3432 3241	1638	1564	849	-	-
$[Zn(ITSC)_2]$	3425 3174	-	1556	-	606	724
$[Cu(ITSC)_2]$	3373 3189	-	1551	-	595	755
$[Zn(CTSC)_2]$	3433 3245	1601	1565		620	765
$[Cu(CTSC)_2]$	3265 3184	1617	1549		563	772

Electronic Spectral Data

The stereochemistry of metal ions in complexes can be determined using the electromagnetic spectra of the complexes.[20] The complexes and ligands' UV-visible spectra were recorded in DMF. The ligands electronic spectra revealed two bands at 264–243 nm and 330–289 nm, which correspond to the n–π* and π–π* transitions. The spectra of complexes in the DMF solvent showed three bands. Intra-ligand transitions appeared in two bands of about 256–292 and 301–348 nm. The band in the 418–488 nm range was ascribed to LMCT transitions, indicating complex formation.[21,22] As a result, the complexes have octahedral and square planar structures with ligands L1-L4. The copper complexes display bands at 710 nm and 580 nm, caused by the $^2A_{1g}(D)\rightarrow{}^2B_{1g}(\upsilon_1)$, $^2E_g(D)\rightarrow{}^2B_{1g}$ (υ_2) transitions.[23] The square planar structure of Cu(II) is confirmed by the magnetic moment and spectral data. The diamagnetic mononuclear Zn(II) complex produced only intra-ligand transitions at 281 nm and 352 nm with a mononuclear tetrahedral shape surrounding the central metal atom. The absorption band at 418-488 nm in the Zn(II) complex could be attributed to LMCT transitions.[24] The Cu(II) complex ESR spectra are anisotropic in nature in that each of them has two peak envelops, one of small intensity appearing as shoulders towards the low field and the other of large intensity towards the high field. The small intensity envelope has been resolved into three or four segments due to Cu(I=3/2) hyperfine interaction while the large intensity one remains unresolved. The ESR and EPR parameters for the complexes have been calculated using appropriate methods and equations[25] and are presented in Table-3.

Table-3: Cu(II) Complexes EPR Spectral Data

Complex	$g_{\|}$	$g_{\perp}$	g_{av}
Complex $Cu(L1)_2$	2.124	2.123	2.185
Complex $Cu(L2)_2$	2.212	2.056	2.032
Complex $Cu(L3)_2$	2.215	2.076	2.132
Complex $Cu(L4)_2$	2.199	2.134	2.190

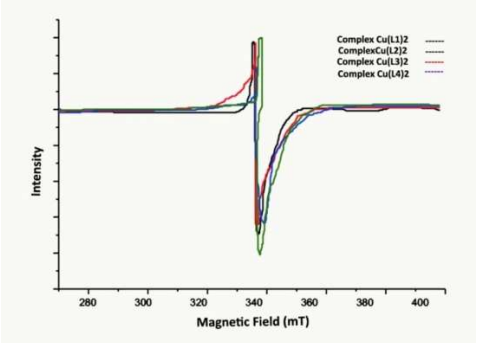


Fig.-2: Metal Complexes (1-4) X-Band EPR Spectra

In all situations, $g_{\|} > g_{\perp} > 2$ indicates that the $^2B_{1g}$ is the ground state due to a single electron present in the $dx^2\text{-}y^2$ orbital, which is an attribute but is able for an elongated octahedral structure.[26]

NMR Spectra

The NMR spectrum of the ligands was recorded in DMSO-d_6 solvent. The ligand L_1: ^{1}H NMR spectra of singlet signals revealed –N=NH- proton at δ 11.70 ppm, -CH=N- proton at δ 9.34 ppm, -NH_2 protons at δ 8.69 ppm, and anthracene C10 proton at 7.76 ppm, with the remaining protons are aromatic regions (Fig.-3). ^{13}C NMR spectrum reveals major signals at δ 178.49 ppm for –C=S carbon, δ 142.64 ppm for –CH=N- carbon, and the remaining carbons are aromatic regions (Fig.-4).

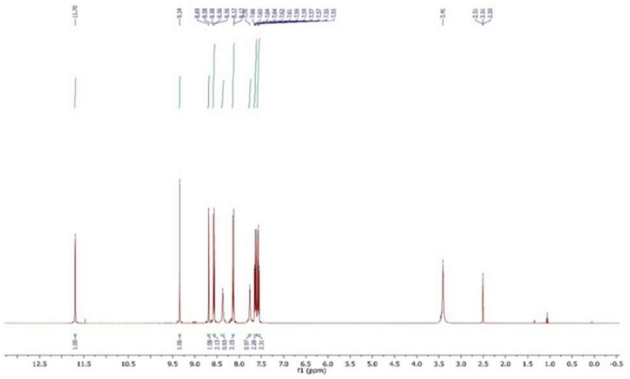


Fig.-3: Proton NMR Spectrum of Ligand L_1

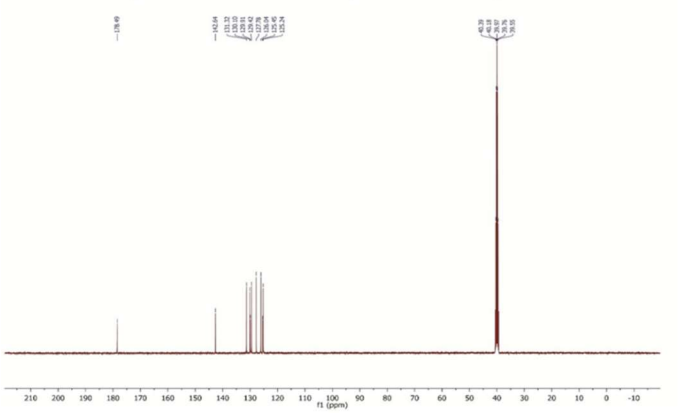


Fig.-4: ^{13}Carbon NMR Spectrum of Ligand L1

Biological Activity: Cancer Activity

The synthesized ligands and all the Zn(II) and Cu(II) complexes were examined for their anticancer activity against the growth of the cancer cell lines, such as cervical-cancer cell line (HeLa) and breast cancer cell line (MCF-7) and a regular embryonic kidney cell line (HEK293). Cisplatin was taken as a reference drug[27], by using the MTT method. The MTT assay data were presented in micromolar units and displayed in terms of IC_{50} values in Table-4.

Table-4: Cytotoxic Activities of Synthesized Metal (II) Complexes (Cu and Zn) and Ligands on Cancer Cell Lines HeLa and MCF-7 [*in vitro* (IC_{50}μM)][a]

S. No.	Ligands/Complexes	MCF-7	HeLa	HEK293
1.	ATSC	80.23 ± 0.65	93.43 ± 0.52	ND
2.	[Zn(ATSC)$_2$]]	19.31 ± 0.72	18.45 ± 1.34	92.54 ± 1.32
3.	[Cu(ATSC)$_2$]	60.06 ± 0.43	85.36 ± 1.01	ND
4.	ITSC	53.69 ± 0.30	65.47 ± 0.76	ND
5.	[Zn(ITSC)$_2$]	61.23 ± 1.02	76.99 ± 0.72	ND
6.	[Cu(ITSC)$_2$]	11.09 ± 1.25	12.31 ± 1.07	99.45 ± 0.54
7.	PTSC	79.11 ± 0.43	91.53 ± 0.43	ND
8.	[Zn(PTSC)$_2$]	53.84 ± 0.45	65.28 ± 1.06	ND
9.	[Cu(PTSC)$_2$]	86.14 ± 0.48	78.13 ± 1.45	ND
10.	CTSC	90.04 ± 0.45	83.76 ± 0.87	ND

11.	$[Zn(CTSC)_2]$	57.29 ± 0.89	45.43 ± 0.74	ND
12.	$[Cu(CTSC)_2]$	20.79 ± 0.43	22.55 ± 1.51	91.65± 0.68
standard	Cisplatin	4.31 ± 0.81	3.48 ± 0.354	ND

[a] Values are expressed as mean ± SEM. ND not determined

The survival curves for MCF-7 and HeLa cell lines were produced by graphing the relation between surviving fraction and drug concentration (Fig.-5). The findings proved that the complex $[Cu(ITSC)_2]$ displayed the most potent activity against the MCF-7 and HeLa with IC_{50} values of 11.09 ± 1.25 µM, and 12.31 ± 1.07 µM, respectively, which is closely related to the referenced drug cisplatin (IC_{50} = 4.31 ± 0.81 µM and 3.48 ± 0.354 µM) and $[Cu(CTSC)_2]$ and $[Zn(ATSC)_2]$ complexes also shown moderate activity with IC_{50} values for 19.31 ± 0.72 µM and 18.45 ± 1.34 µM, and 20.79 ± 0.43 µM and 22.55 ± 1.51µM, respectively. The remaining ligands and complexes displayed less activity against the tested cell lines. Furthermore, we examined the anticancer activity of the active complexes $[Cu(ITSC)_2]$, $[Cu(CTSC)_2]$, and $[Zn(ATSC)_2]$ against HEK293 normal cancer cell line (IC_{50} values of 99.45 ± 0.54 µM, 91.65± 0.68 µM, and 92.54 ± 1.32 µM). The active complexes ($Cu(ITSC)_2$, $Cu(CTSC)_2$, and $Zn(ATSC)_2$) had no effect on the viability of the normal cell line, showing that the complexes are not toxic.

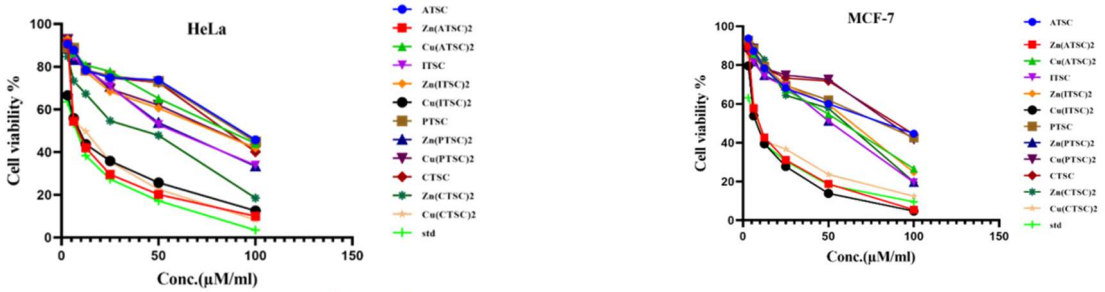


Fig.-5: Survival Curves of Cell Lines: (a) MCF-7, (b) HeLa

Antibacterial Activity

Metal complexes and ligands were tested for antibacterial activity against two gram-positive bacteria, *Bacillus-subtilis*, and *Staphylococcus aureus*, *as well as against* two gram-negative bacteria, *Klebsiella pneumoniae,* and *Escherichia-coli*. For comparison, streptomycin was used as a reference drug.[28] The MIC (minimum inhibition concentration) values for all the synthesized complexes were determined by the Broth dilution approach (Suggested by ESCMID). Based on the antibacterial activity results in Table-5, the complex $[Cu(CTSC)_2]$ has displayed excellent inhibition against four tested strains with MIC values of 12.5 µg/mL (*S. aureus*), 6.25 µg/mL (*B. subtilis*), 6.25 µg/mL (*K. pneumonia*) and 12.5 µg/mL (*E. coli*), respectively. The complex $Zn(CTSC)_2$ showed good activity against *K. pneumonia* (6.25 µg/mL), and *E. coli* (12.5 µg/mL). The remaining complexes and ligands showed good to moderate activity, respectively. The presence of a chromone ring in both complexes influenced the antibacterial activity of the complexes $[Cu(CTSC)_2]$ and $[Zn(CTSC)_2]$.

Table-5: Most Activity (antibacterial) of Ligands and Zn (II) and Cu (II) Complexes

	MIC(µg/mL)			
Ligands/Complex	S. *Aureus*	B. *Subtilis*	K. *pneumoniae*	E. *Coli*
$[Zn(ITSC)_2]$	12.5	25	25	50
PTSC	25	12.5	25	100
$[Cu(PTSC)_2]$	12.5	50	50	12.5
$[Zn(CTSC)_2]$	12.5	12.5	6.25	12.5
$[Cu(CTSC)_2]$	12.5	6.25	6.25	12.5
Streptomycin	6.25	3.125	1.562	6.25

Molecular Docking

The docking research was conducted to evaluate the biological data achieved and to determine how the active molecules bind to their intracellular targets EGFR, HER-2, and IKK-ß. These three targets play a major role in the spreading of disease. The protein receptors EGFR, and HER2 are attractive targets in

cancer disease. The cell-surface receptor in the EGFR. This survives on the cell surface and is fueled by the binding of certain ligands. Overexpression of EGFR has been linked to a variety of tumors, notably glioblastoma, anal cancers, lung squamous-cell, carcinoma, neck and head epithelian tumors.[29] The human epidermal growth factor receptor (HER/EGFR/ERBB) group HER2. Over-expression of this oncogene has been associated with the growth and progress of several aggressive malignancies, including breast, ovarian[30], stomach, lung adenocarcinoma, and uterine cancer. We chose the EGFR and HER2 proteins as target receptors for these reasons. IKK-β is a protein part of the IκB kinase enzyme complex; this is a part of the intracellular signaling pathway induced by cytokines that are involved in the initiation of immunological responses. Following a stroke, IKK-β plays a significant role in brain cells. As a finding, we picked EGFR [PDB ID: 4HJ0], HER2 [PDB: 3POZ], and IKK-ß [PDB: 4KIK] as biological targets for our synthetic compound docking studies. RSC PDB (www.rscb.org) was used to obtain the crystallographic 3D structure of the proteins. The output was exported to PyMol program for a detailed study of the complex's interaction with the receptor binding site.

The docking scores were used to estimate the free energy of binding (BE) of the complexes and details are displayed in Table-6 to 8. The EGFR, HER2, and IKK-β receptors were chosen as the target proteins in this study. A mononuclear complex of $[Cu(L2)_2]$ and $[Zn(L1)_2]$ interacted strongly with the target proteins. The ligands and their Zn(II), Cu(II) metal complexes were compared to well-known EGFR inhibitors like Gefitinib, Erlotinib, and Lapatinib[31] against the EGFR target, as well as their corresponding binding energies, which were reported in Table-6. These findings are very similar to those of an in vitro cancer cell-based assay. The lowest binding energies were -10.32 kcal/mol for $[Cu(L2)_2]$ and -10.32 kcal/mol for $[Zn(L1)_2]$. The complex $[Cu(L2)_2]$ has strong interactions through 6 hydrogen bonds with key amino acids such as ASP831, THR766 (2 hydrogen bonds), ARG817 (2 hydrogen bonds), LUE764, ASP831 with thiosemicarbazide N atoms and sulfur atoms and the remaining all are hydrophobic interactions as shown in Fig.-3. The complex $[Zn(L1)_2]$ also has two H-bonds with key amino acids ASP831 by N atom on the imine group, as illustrated in Fig.-4. In the case of the HER2 target protein, $[Cu(L2)_2]$ and $[Zn(L1)_2]$ are the best inhibitors compared with the remaining complexes. $[Zn(L1)_2]$ have the lowest binding energy -11.43 K.cal/mol and 3 strong hydrogen bonds with the following amino acid residues ASP800(2), ASN842. Other approaches include π-π stacking and hydrophobic interactions. $[Cu(L2)_2]$ complex having the binding energy -10.51 K.cal/mol and having four hydrogen bonding interactions with the following amino acids MET793, GLN791(2), and ASN842 by strong hydrogen bonds. Remaining all are the hydrophobic and π-π stacking approaches. Similarly, the same study has done against the IKK-β receptors, and the complexes $[Zn(L1)_2]$ and $[Cu(L2)_2]$ showed the best interactions with target proteins having binding energies -9.39 K.cal/mol and -8.43 K.cal /mol. $[Zn(L1)_2]$ and $[Cu(L2)_2]$ each having the four hydrogen bonding interactions with LYS44, GLU61(2), GLU149 amino acids. Remaining all are the hydrophobic and π-π stacking approaches. The most effective docking poses and inhibitory potencies of synthesized complexes and conventional inhibitors against the protein EGFR were compared. In comparison to reference compounds, the complexes have low binding energy.

The binding energy of the reference inhibitor Gefitinib was -8.07 kcal/mol, with one H-bond between the morpholine ring on the O atom and the amino acid residue ARG817 and all other interactions being hydrophobic. When compared to conventional inhibitors, $[Cu(L2)_2]$ and $[Zn(L1)_2]$ complexes show strong interactions with target proteins. For all target proteins, $Zn(L1)_2]$ and $[Cu(L2)_2]$ complexes have shown potent inhibiting capability compared with other Zn(II) and Cu(II) metal complexes.

Table-6: Binding Energies of Ligand and its Metal Complexes Against Protein Receptor EGFR

Compound	Binding energy (kcal/mol)	No. of hydrogen bonds	Residues involved in hydrogen bonding (Bond length (Å))
$[Zn(L1)_2]$	-10.32	2	ASP831(2)
$[Cu(L2)_2]$	-10.32	6	ASP831, THR766(2), ARG817(2), LUE764
Gefitinib	-8.07	1	ARG817 (2.224)
Erlotinib	-8.51	1	MET769 (2.111)
Lapatinib	-8.45	4	LYS721 (1.819, 2.333), MET769 (2.461), ARG817 (2.718)

Table-7: Binding Energy, Residues Involved in Hydrogen Bonding, and Hydrogen Bonds of Most Active Zn(II) and Cu(II) Inhibitors Against Protein Receptor HER2 [PDB: 3POZ]

Compound	Binding energy (kcal/mol)	No. of hydrogen bonds	Residues involved in hydrogen bonding
$[Zn(L1)_2]$	-11.43	3	ASP800(2), ASN842
$[Cu(L2)_2]$	-10.51	4	MET793, GLN791(2), ASN842

Table-8: Binding Energy, and Residues Involved in Hydrogen and Bonding Hydrogen Bonds of Most Active Zn(II) and Cu(II) Inhibitors Against Protein Receptor IKK-ß [PDB: 4KIK]

Compound	Binding energy (kcal/mol)	No. of hydrogen bonds	Residues involved in hydrogen bonding
$[Zn(L1)_2]$	-9.39	4	LYS44, GLU61(2), GLU149
$[Cu(L2)_2]$	-8.43	4	LYS44, GLU61(2), GLU97

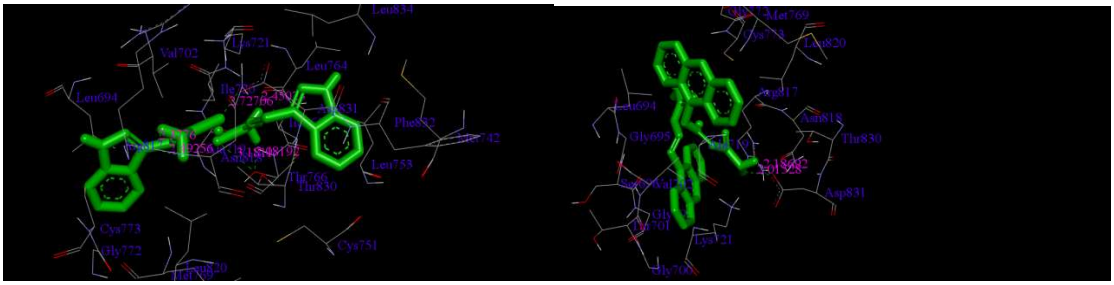


Fig.-3 and 4: Three-dimensional Conformation of Complex $[Cu(L2)_2]$, $[Zn(L1)_2]$ Docked with EGFR Target

CONCLUSION

The metal complexes of L1-L3 with Cu(II) and Zn(II) are square planers in geometry, according to analytical and spectroscopic data. Whereas the metal complexes Cu(II) and Zn(II) of the L4 ligand are octahedral in geometry. The $Cu(L2)_2$ complex displayed excellent cytotoxicity with IC_{50} values 11.09 ± 1.25 µM and 12.31 ± 1.07 µM against MCF-7 and HeLa. Whereas $Cu(L4)_2$ and $Zn(L1)_2$ showed moderate to good activity. The antibacterial activity results exhibit that the metal complexes and ligands displayed better activities against all the tested strains, whereas the complexes $Cu(L4)_2$ showed excellent inhibition. Molecular docking experiments were done against the EGFR, HER2, and IKK-β target proteins. Towards these 3 target proteins, only two complexes $Cu(L2)_2$ and $Zn(L1)_2$ Showed strong interaction with the lowest binding energies -10.32 kcal/mol and -10.32 kcal/mol against the EGFR target and with the other two protein targets also the above two complexes shown strong interactions. The anticancer studies of the complexes are in agreement with docking results.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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