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Synthesis, Characterization, Antimicrobial and Anticancer Activity of New Bidentate Schiff Base Ligand and their Transition Metal(II) Complexes

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The metal(II) complexes were synthesized by addition of corresponding MCl_2 (M = Mn^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) with 1,2-*bis*(1*H*-pyrrol-2-ylmethylene)diazane in methanol. The ligand acts as a bidentate as confirmed from the mass, IR, UV, NMR and EPR spectral studies. The Schiff base ligand forms hexa-coordinated complexes having octahedral geometry for Mn(II), Ni(II), Zn(II) and Cu(II) complexes. The metal complexes showed an excellent antimicrobial activity spectrum *in vitro* against both Gram-negative (*Klebsiella pneumoniae* and *Acinetobacter baumannii*), Gram-positive (*Staphylococcus aureus* and *Enterococcus faecalis)* and human pathogenic bacteria isolates. To find the binding affinity with protein BSA kinase, for that molecular docking studies were also carried for all the four synthesized metal(II) complexes. The anticancer activity of the synthesized metal(II) complexes was also screened against the three human tumor cell lines MCF7 human breast adenocarcinoma cell line, CaSki human caucasian cervical epidermoid carcinoma and HCT116 human colon cancer cell lines. The present study showed that Zn(II) complex showed potent inhibition by the ratio of 80% as compared to the inhibition in the normal cells (L-6).

Keywords: Schiff bases, Metal complexes, Antibacterial activity, Anticancer activity, Docking study.

INTRODUCTION

For several years, metal complexes have been receiving the substantial attentions in the field of material science and biological systems due to their interesting characteristic properties [1-4]. Many researchers [5-8] have reported several non-platinum metal complexes, which have wide range of oxidation states and are proposed as chemotherapeutic drugs. Many of metal complexes have an ability to reduce the tumor mass and seems hopeful for their *in vitro* and *in vivo* properties such as cytostasis activity [9-12].

Due to the presence of two nitrogen and one oxygen atoms, pyrrole derivatives are frequently found as constituents of various synthetic drugs including BM212 (mycobacterium), atorvastatin (a cholesterol-lowering agent) and anthelmintic pyrvinium (nonsteroidal anti-infammatory drugs) [13-15]. Pyrrole moiety is an entity of great interest and the synthesis of its derivatives from long-past and recent years has received the attention of synthetic and medicinal chemists to create new derivatives and explore their biological and pharmacological potentials [16-20].

Due to the immense chelating behaviour and the flexibility of the Schiff bases ligands always attracted a considerable interest due to its different properties [21]. Recently, metal based compounds has been growing demand for the cancer treatment. Due to intimate of cancer, to greater extent, the level of metal based compounds *in vitro* cytotoxic effect are exhibited, predominantly which are synthesized recently [22,23]. In addition, ligand substitutions and the modifications of existing chemical structures led to the synthesis of a wide range of metal-based compounds, some of which have confirmed an enhanced cytotoxic profile. The objective of this work, while focusing more on newly designed metal based compounds and their cytotoxic effect on the cancer cell line, as well as on new approach to metal-based drug design in cancer therapy. Hence, we synthesized the new pyrrole-based Schiff base ligand, which contains additional donor sites. The Schiff base were synthesized by the condensation of 1,2-*bis*-(1*H*-pyrrol-2-ylmethylene)diazane with 5-bromosalicylaldehyde. Using this ligand, a new series of manganese(II), nickel(II), copper(II) and zinc(II) complexes

were synthesized. *in vitro* Anticancer activities of the metal(II) complexes have been screened against the three human tumor cell lines CaSki human caucasian cervical epidermoid carcinoma, MCF7 human breast adenocarcinoma cell line and HCT116 human colon cancer cell lines. In addition, molecular docking analysis of selected compounds on protein BSA kinase were also carried out for confirming the experimental observations.

EXPERIMENTAL

The chemicals *viz*. 2-pyrrole carboxaldehyde, hydrazine, 5-bromosalicylaldehyde and metal(II) chloride (M = Mn^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) were procured from the commercial sources and of the highest available purity. ^{1}H & ^{13}C NMR spectra were determined in DMSO (internal standard TMS) on Bruker spectrometer. IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer using KBr pellets in the range of 4000-400 cm^{-1}. The ESI mass spectra were recorded on a Thermo Scientific Orbitrap Elite mass spectrometer. The UV-vis spectra were recorded on a Cary 100 version 11.1 spectrophotometer using DMSO as solvent. Electron paramagnetic resonance (EPR) spectra of complexes were recorded on JES-X310 X-band EPR Spectrometer at room temperature.

Synthesis of pyrrole-based ligand (HL): Under nitrogen atmosphere, an ethanolic solution (30 mL) of 5-bromosalicylaldehyde (5 mmol) was slowly added to an ethanolic solution (30 mL) of (1*H*-pyrrole-2-yl)methylene)hydrazine (5 mmol) with constant stirring in the presence of acetic acid (3 drops) as a catalyst. The stirring was continued for 1 h and then refluxed for 8 h. Finally, the product was collected by filtration, washed with ethanol and dried in vacuum (**Scheme-I**).

General procedure for the synthesis of pyrrole-based bidentate metal(II) complexes: An ethanolic solution (30 mL) of $NiCl_2$ (0.29 g, 1.2 mmol), $CuCl_2$ (0.29 g, 1.2 mmol), $ZnCl_2$ (0.36 g, 1.2 mmol), $MnCl_2$ (0.36 g, 1.2 mmol) was added to an equimolar amount of appropriate ligand (1.2 mmol) in ethanol (30 mL) with constant stirring while a colour change was immediately observed. The stirring was continued for 30 min and refluxed on an oil bath for additional 3 h, filtered while hot and the filtrate was allowed to stand at room temperature for a few days. The solid complexes obtained were recrystallized by using hot ethanol (**Scheme-I**).

Antimicrobial assay

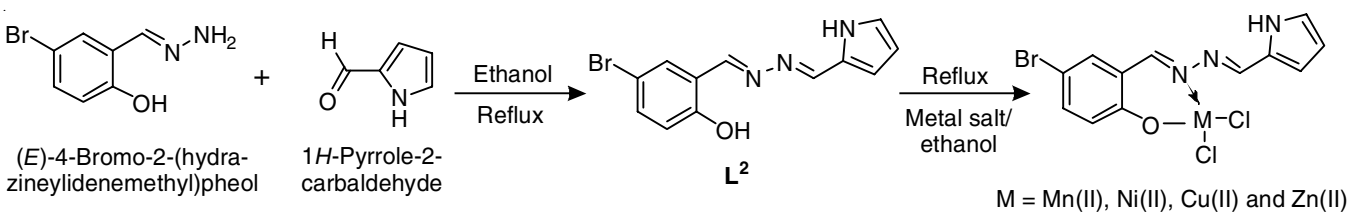
Microorganisms: A four bacteria were tested for their susceptibility against the synthesized metal(II) compounds. The strains were obtained from ATCC culture collection center and maintained in our laboratory. They were *Enterococcus faecalis* ATCC, *Staphylococcus aureus* ATCC29213, Methicillin resistant *Staphylococcus aureus* (MRSA) ATCC33591, *Klebsiella pneumoniae* ATCCBAA-1705, *Acinetobacter baumannii* ATCC19606. The bacteria were grown at 37 ºC and maintained on nutrient agar slants and finally stored at 4 ºC.

Disc diffusion assay and determination of minimum inhibitory concentration (MIC): The MCF7 human breast adenocarcinoma cell line, CaSki human caucasian cervical epidermoid carcinoma and HCT116 human colon cancer cell lines were procured from National Centre for Cell Sciences (NCCS), Pune, India and maintained in Dulbeco's modified Eagles medium (Gibco, Invitrogen). The cell line was cultured in DMEM supplemented with 10% FBS, L-glutamine, sodium bicarbonate along with penicillin (100 U/mL), streptomycin (100 µg/mL) and amphoteracin B (2.5 µg/mL). Cultured cell lines were kept at 37 ºC in a humidified 5% CO_2 incubator (NBS Eppendorf, Germany). The qualitative viability of cells were evaluated by direct observation of cells by inverted phase contrast microscope. The quantitative cytotoxic experiments were evaluated by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Two days old confluent monolayer of cells were trypsinized and suspended in 10% growth medium, seeded in 96 well micro plate and incubated at 37 ºC in a 5% CO_2 incubator. Metal(II) complex sample (1 mg/mL) was prepared in DMSO and filtered through 0.22 µm syringe filter to ensure the sterility. After 24 h, the growth medium was removed, freshly prepared compounds were serially diluted to 100 µg, 50 µg, 25 µg, 12.5 µg and 6.25 µg in 100 µL of 5% DMEM. Each concentration of 100 µL were added in triplicates to the respective wells and incubated at 37 ºC in a humidified 5% CO_2 incubator.

Cytotoxic assay by MTT method: Entire plate was observed after 24 h of treatment in an inverted phase contrast tissue culture microscope (Olympus CKX41 with Optika Pro5 CCD camera) and microscopic observation were recorded as images. Any detectable changes in the morphology of the cells, such as rounding or shrinking of cells, granulation and vacuolization in the cytoplasm of the cells were considered as indicators of cytotoxicity.

After 24 h of incubation, the samples from experimental wells were removed and 30 µL of reconstituted MTT solution was added to all wells and then incubated at 37 ºC in a humidified 5 % CO_2 incubator for 4 h. Following to incubation, the supernatant was removed and the absorbance values were measured by using microplate reader at a wavelength of 540 nm. The percentage of growth inhibition was calculated using the formula:

$$\text{Viability (\%)} = \frac{\text{Mean OD samples}}{\text{Mean OD of control group}} \times 100$$



(*E*)-4-Bromo-2-(hydrazineylidenemethyl)pheol

1*H*-Pyrrole-2-carbaldehyde

Scheme-I: Preparations of ligand (L^2) and metal complexes [Mn(II), Ni(II), Cu(II) and Zn(II]

Molecular docking studies: In this study, the docking of the synthesized metal(II) complexes into the receptor bovine serum albumin preferred in order to predict the binding site inside the target protein. Initially, the protein structure of BSA (PDB ID: 3V03) downloaded from the protein data bank (http://www.rcsb.org) and removing water molecules beyond 3 Å to the protein and hydrogen atoms were added to the protein. Thereafter, the minimization was carried out using force field OPLS-2005 until it reached a cutoff of 0.01 Å RMSD. The 2D structures of the metal(II) complexes were drawn using ChemDraw Ultra 12.0 software. Chem3D Ultra 12.0 was used to convert the 2D structures into three-dimensional (3D) and the energy was minimized using the semi-empirical AM1 method and converted into PDB format suitable for docking program using OPENBABEL. The docking results were visualized with help of PyMOL visualizer.

Bovine serum albumin receptor (BSA): Bovine serum albumin (BSA) has been widely used as a template to synthesize nanostructures [24,25]. Hence, the synthesized metal(II) complexes were evaluated for the binding affinity of BSA receptor (PDB 3V03) for the purpose of both investigates the interaction between studied complexes and BSA receptor and for lead optimization.

RESULTS AND DISCUSSION

The reaction of Schiff base with MCl_2 (M = Mn^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) resulted in the formation of ($MLCl_2$) (**Scheme-I**). The physico-analytical data of the synthesized metal(II) complexes are given in Table-1.

FT-IR spectra: The FT-IR spectrum of the synthesized metal(II) complexes (M = Mn^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}) shows the strong absorptions in the range at 1602.18-1596.90 cm^{-1}, which indicate the presence of azomethine (CH=N) group (Fig. 1). The broad –OH stretching frequency did not appeared in range of 3208.98-3190.21 cm^{-1}, which clearly indicated that all the OH groups involved in the metal(II) complexes. The charac-teristic of aromatic stretching frequency absorption at 1512.37-1441.50 cm^{-1} was also observed in the complexes. The result are summarized in Table-2.

TABLE-2
FT-IR SPECTRAL DATA OF THE SYNTHESIZED BIDENTATE METAL(II) COMPLEXES

Complexes	ν(C=N)	ν(C=C)Ar	ν(M-N)	ν(M-O)
[$MnLCl_2$]	1618.21	1462.88	599.56	483.09
[$NiLCl_2$]	1596.90	1512.37	599.55	526.41
[$CuLCl_2$]	1602.18	1441.90	585.97	454.81
[$ZnLCl_2$]	1603.78	1442.90	565.97	456.80

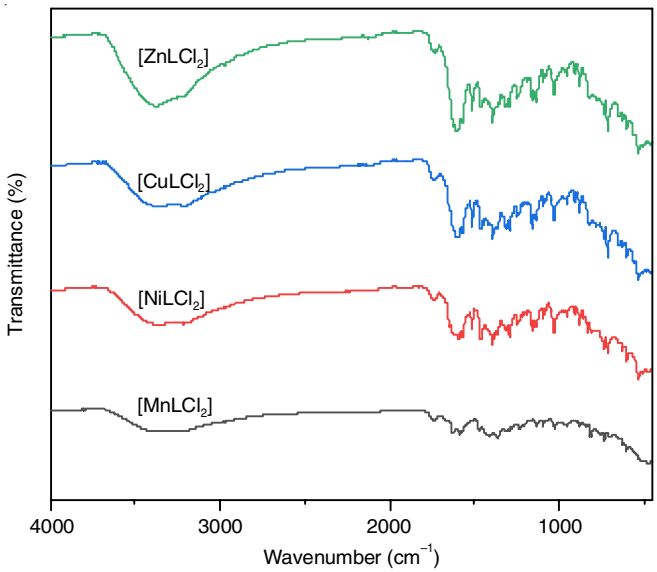


Fig. 1. FT-IR spectra of the synthesized metal(II) complexes (M = Mn^{2+}; Ni^{2+}; Cu^{2+} and Zn^{2+})

^{1}H & ^{13}C NMR spectra: The ^{1}H NMR (400 MHz) spectrum of Zn(II) complex exhibits a signal at 11.7 ppm, which indicates the presence of pyrrole NH protons and singlet which appeared at 8.8 ppm shows the azomethine protons. The aromatic ring protons of the synthesized ligand resonate between at 6.10 ppm to 7.86 ppm (Fig. 2a). The ^{13}C NMR (100 MHz) spectrum of Zn(II) complex (Fig. 2b) exhibits various signals and chemical shifts, the signal which disappeared at 161.97 ppm indicate that –OH group involved in the complex formation and the signal appears at 151.05 ppm is attributed due to the presence of azomethine carbon. The aromatic ring signals resonate between 110.19-127.79 pmm.

UV-visible spectra: The UV-visible spectra of the synthesized metal(II) complexes recorded in the region 200-900 nm range using methanol as solvent. The absorption band appeared in the 200-300 nm range indicates the π-π* and n-π* transition. The existence of band between 300-400 nm range attribute to ligand to metal charge transfer (LMCT) (Table-3). Moreover, Ni(II) and Cu(II) complexes showed two weak absorptions in the range 500-700 nm range, which confirmed square planar geometry of metal complexes (Fig. 3). The Mn(II) and Zn(II) did not show any band in the visible region due half-filled and completely filled electronic configuration of metal complexes, respectively (Fig. 3).

Molecular docking study: The binding interaction of the ligand and its metal(II) complexes with target protein is shown in Fig. 4, respectively and the docking parameters values are

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF METAL(II) COMPLEXES

Complex	m.f.	Colour	m.w. (g/mol)	m.p. (°C)	Yield (%)	Elemental analysis (%): Found (calcd.)		
						C	H	N
HL	$C_{12}H_{11}N_3O$	Brown	213.24	> 121	86	67.59 (67.01)	5.20 (5.1)	14.38 (14.39)
[$MnLCl_2$]	$C_{12}H_9N_3OBrCl_2Mn$	Brown	415.97	> 300	81	33.98 (34.57)	2.08 (2.18)	9.86 (10.08)
[$NiLCl_2$]	$C_{12}H_9N_3OBrCl_2Ni$	Dark brown	418.52	> 300	79	34.08 (34.26)	2.02 (2.16)	9.21 (9.99)
[$CuLCl_2$]	$C_{12}H_9N_3OBrCl_2Cu$	Dark brown	423.23	> 300	82	32.38 (33.87)	1.90 (2.13)	9.49 (9.87)
[$ZnLCl_2$]	$C_{12}H_9N_3OBrCl_2Zn$	Black	426.01	> 300	76	33.35 (33.72)	2.02 (2.12)	9.22 (9.83)

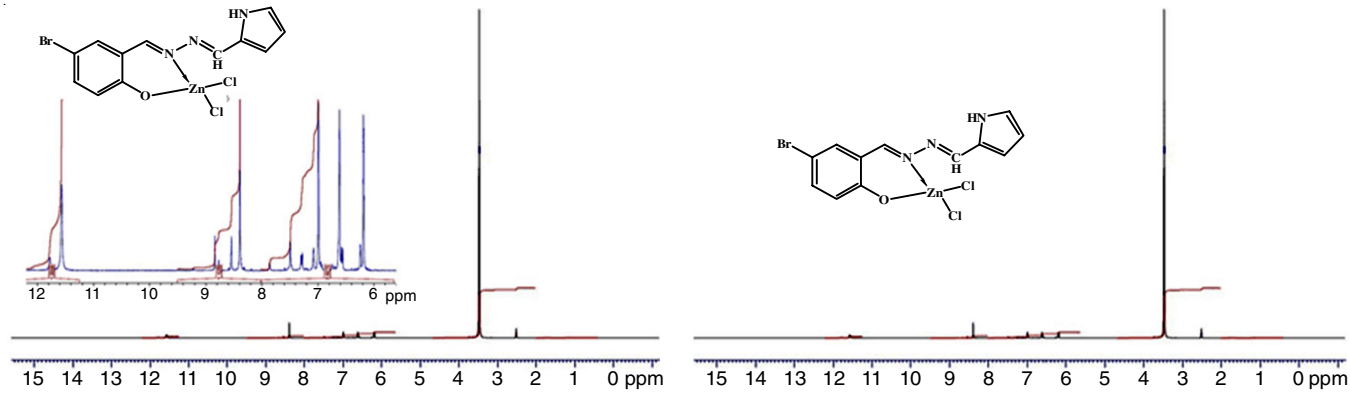


Fig. 2. ^{1}H and ^{13}C NMR spectra of Zn(II) complex

TABLE-3
UV-VISIBLE SPECTRAL DATA OF THE SYNTHESIZED BIDENTATE METAL(II) COMPLEXES

Complexes	UV-visible spectral data (λ_{max}, nm)	
	Charge transfer	*d-d*
$[MnLCl_2]$	227 (π–π*); 298 (n–π*); 385 (LMCT)	–
$[NiLCl_2]$	247 (n–π*); 330 (LMCT)	560, 672
$[CuLCl_2]$	266 (n–π*); 398 (LMCT)	577, 691
$[ZnLCl_2]$	283 (n–π*); 382 (LMCT)	–

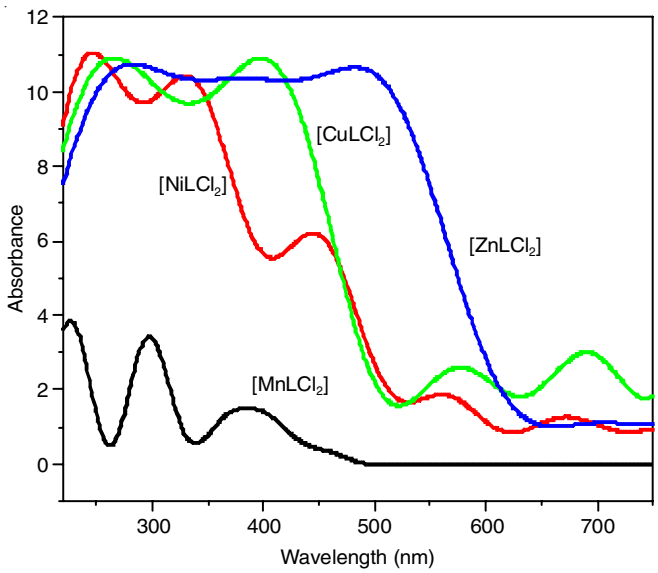


Fig. 3. UV-visible spectra of the synthesized metal(II) complexes (M = Mn^{2+}; Ni^{2+}; Cu^{2+} and Zn^{2+})

summarized in Table-4. It is clear that the active sites of docked protein well-stabilized by H-bond, π-π stacking interactions and hydrophobic contacts. The ligand and its metal(II) complexes showed the binding energy values found to be -6.113, -2.668, -4.815, -4.701 and -4.733 kcal/mol. When the docking scores value is more negative, the binding nature of complex with receptor is greater. Based on above facts, Zn(II) complex showed the highest docking affinity compared to other synthesized complexes.

Antimicrobial activity: In antibacterial activity assay by disc diffusion method, among the synthesized metal(II) complexes, zinc(II) complex showed the maximum inhibition zone against all the tested pathogens MRSA, *Staphylococcus aureus*, *Enterococcus faecalis, Klebsiella pneumoniae* and *Acinetobacter baumannii* and the inhibition diameter is depicted in Table-5. Further, MIC experiments revealed that among the synthesized metal(II) complexes, zinc(II) complex showed a MIC value of 8 µg/mL against MRSA, *Staphylococcus aureus* and *Enterococcus faecalis* and 16 µg/mL against *Klebsiella pneumoniae* and *Acinetobacter baumannii*.

Toxicity towards cancer cell lines: The cytotoxic viability index was examined using MTT assay of the synthesized metal(II) complexes. The increasing concentrations favour the antiproliferation of MCF7 human breast adenocarcinoma cell line, CaSki human caucasian cervical epidermoid carcinoma and HCT116 human colon cancer cell lines. Zinc(II) complex showed a potent cytotoxicity over 20.64 ± 0.72% death of MCF7 cells at the initial treatment concentration of 6.25 µg/mL and the same concentration showed 20.23 ± 0.83% and 9.5 ± 0.72% against CaSki and HCT116 cells (Fig. 5). The

TABLE-4
DOCKING PARAMETERS OF THE SYNTHESIZED BIDENTATE LIGAND AND ITS METAL(II) COMPLEXES WITH BSA RECEPTOR

Complexes	Docking score (kcal mol^{-1})	Active sites with a mode of interaction		
		H-bond	π-π stacking	Hydrophobic contacts
HL	-6.113	VAL 899	–	ILE 888, LEU 889, ILE 892, VAL 898, VAL 899, VAL 914, VAL 916, LEU 1019, CYS 1024, ILE 1025, ILE 1044, CYS 1045, PHE 1047
$[MnLCl_2]$	-2.668	–	–	CYS 817, ALA 881, ILE 888, LEU 889, ILE 892, LEU 1019, CYS 1024, ILE 1025
$[NiLCl_2]$	-4.733	ASP 1046	–	ALA 844, PHE 845, ALA 881, LEU 1049, ALA 1050, ILE 1053, TYR 1054, TYR 1059, ALA 1065, LEU 1067
$[CuLCl_2]$	-4.701	ASP 1046	–	ALA 844, PHE 845, ALA 881, LEU 1049, ALA 1050, ILE 1053, TYR 1054, TYR 1059, ALA 1065, LEU 1067
$[ZnLCl_2]$	-4.815	ASP 1046	HIE 1026	CYS 817, ALA 881, ILE 888, LEU 889, ILE 892, VAL 898, VAL 899,LEU 1019, CYS 1024, ILE 1025, ILE 1044, CYS 1045

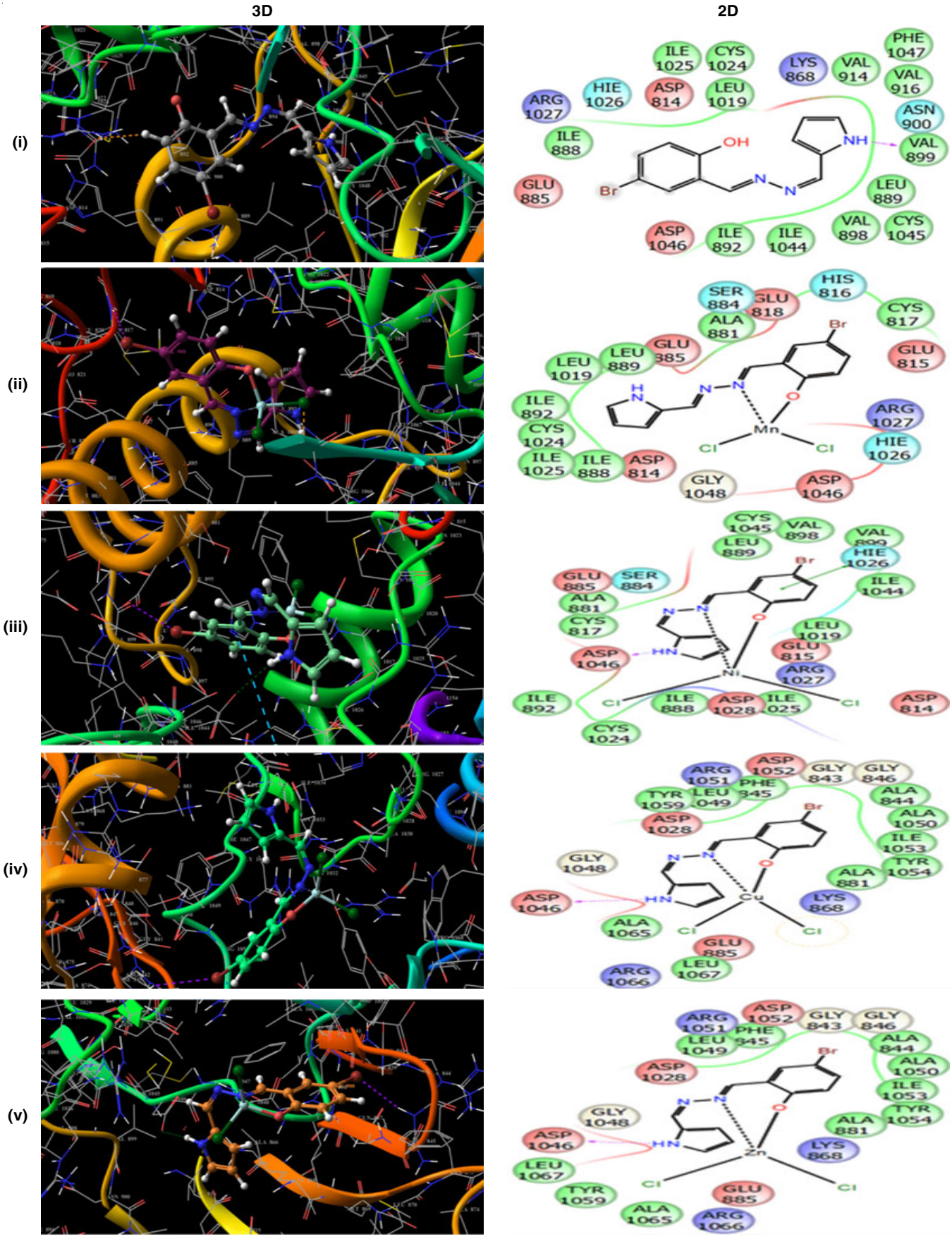


Fig. 4. 3D & 2D representation of ligand (i) and its metal(II) complexes (ii) Mn^{2+}, (iii) Ni^{2+}, (iv) Cu^{2+} and (v) Zn^{2+} located in the active sites of BSA receptor

TABLE-5
ANTIBACTERIAL ACTIVITY DATA THE SYNTHESIZED METAL(II) COMPLEXES

Samples	Zone of inhibition (mm)				
	E. faecalis	*S. aureus*	*K. pneumoniae*	*A. baumannii*	MRSA
$[MnLCl_2]$	–	–	–	–	–
$[NiLCl_2]$	–	–	–	–	–
$[CuLCl_2]$	–	–	–	–	–
$[ZnLCl_2]$	6	3	8	4	3

photomicrographs (Fig. 6) showed the different cytotoxic morphologies of condensed nuclei, membrane blebbing, cell shrinkage, apoptotic cells, bubbling and echinoid spikes. Zinc(II) complex exhibited LC_{50} value of 37.23, 38.54 and 27.29 µg/mL against MCF7 human breast adenocarcinoma cell line, CaSki human caucasian cervical epidermoid carcinoma and HCT116 human colon cancer cell lines (Table-6).

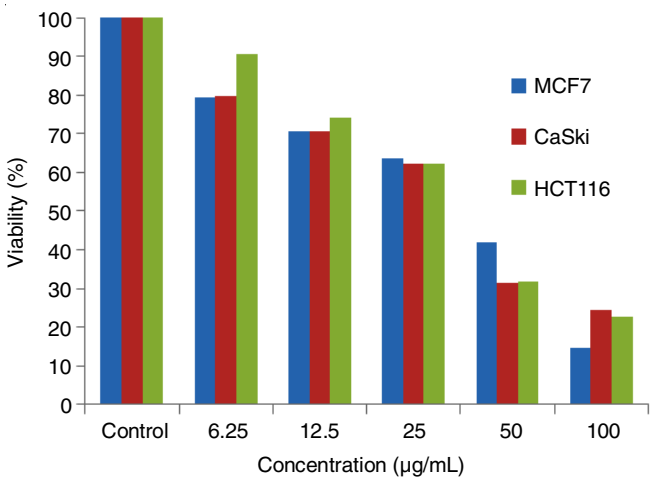


Fig. 5. MTT assay of the synthesized zinc(II) complex against MCF7 human breast adenocarcinoma cell line, CaSki human caucasian cervical epidermoid carcinoma and HCT116 human colon cancer cell lines

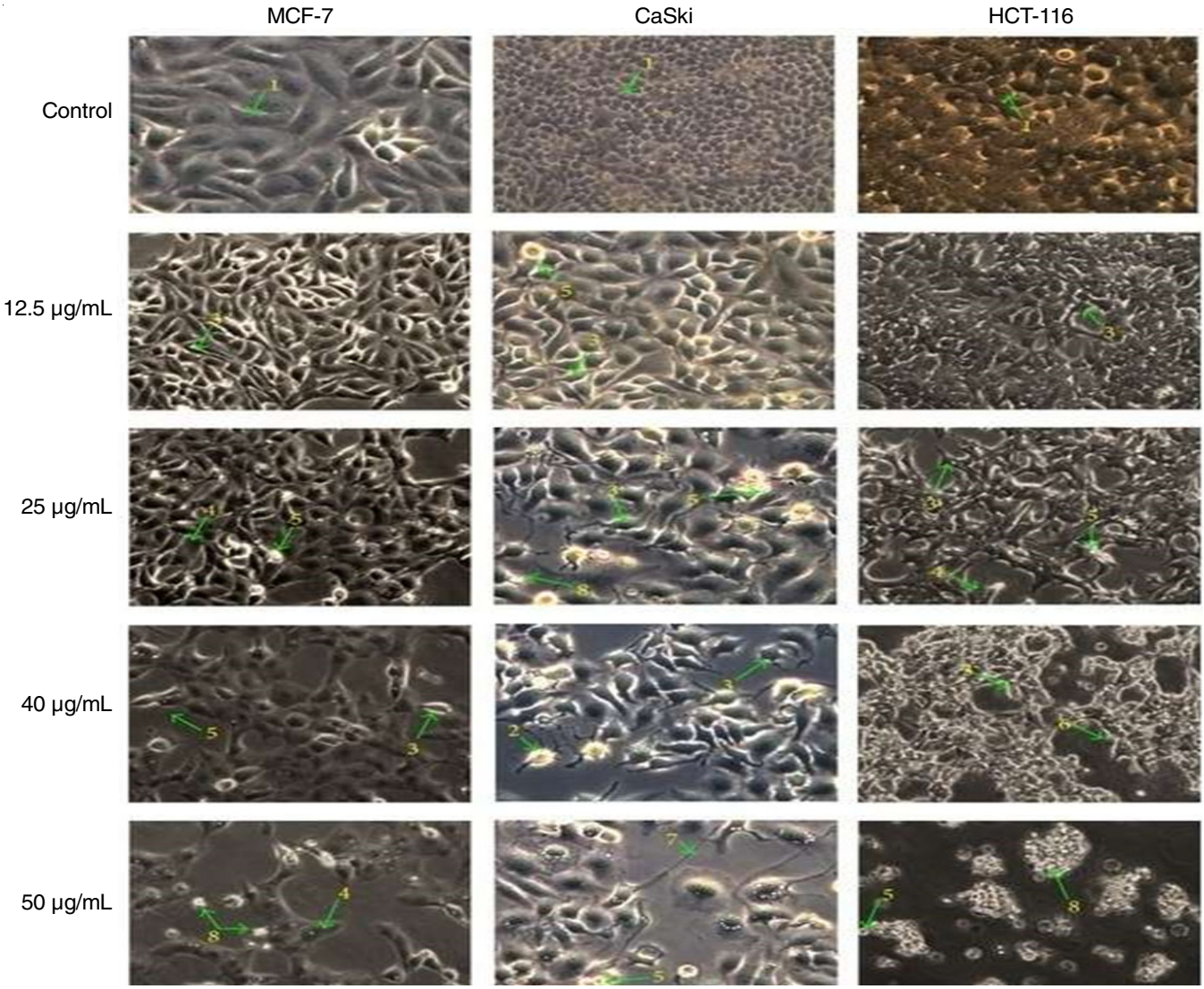


Fig. 6. MTT based antiproliferative photomicrographs of synthesized zinc(II) complex on MCF7 human breast adenocarcinoma cell line, CaSki human caucasian cervical epidermoid carcinoma and HCT116 human colon cancer cell lines after 24 h incubation under the phase contrast microscope. Arrows indicates (1) control cell (2) condensed nuclei (3) cell shrinkage (4) membrane blebbing (5) apoptotic bodies (6) bubbling and (7) echinoid spikes

TABLE-6
CYTOTOXIC ACTIVITY OF THE Zn(II) COMPLEX AGAINST MCF7, CaSki AND HCT116 CELL LINES

Concentration of Zn^{2+} complex (µg/mlL)	Survival (%)		
	MCF7	CaSki	HCT116
Control	100	100	100
6.25	79.35	79.78	90.50
12.5	70.67	70.71	74.16
25	63.68	62.14	62.19
50	41.87	31.50	31.68
100	14.72	24.36	22.75

Conclusion

In the present study, Mn(II), Ni(II), Cu(II) and Zn(II) complexes derived from bidentate pyrrole-based ligand have been synthesized and characterized on the basis of spectroscopic studies. The data from electronic spectra and magnetic moment measurement typically supported the square planar geometry for nickel(II) and copper(II) complexes while zinc(II) complex were assigned with tetrahedral geometry. Cytotoxicity studies revealed the Zn(II) complex have been found to exhibit cytotoxicity towards three cancer cell lines including MCF7 human breast adenocarcinoma cell line, CaSki human caucasian cervical epidermoid carcinoma and HCT116 human colon cancer cell lines. The antimicrobial activity along with cytotoxicity results suggested that Zn(II) complex could be used as an effective metal-based anticancer drug. Further, *in vivo* experiments in relevance to anticancer activity of these complexes can be considered as future perspectives.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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