



J. Serb. Chem. Soc. 89 (2) 165–175 (2024)
JSCS–5713

Anticancer activity of Schiff base ligand (*E*)-4-((5-chloro-2-hydroxybenzylidene)amino)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one and its Co(II), Cu(II) and Zn(II) metal complexes

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(Received 3 August, revised 11 September, accepted 21 November 2023)

Abstract: A series of transition metal complexes of Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and VO(II) have been prepared by using the Schiff base ligand (L) derived from 4-aminoantipyrine and 5-chlorosalicylaldehyde. The structural properties of Schiff base ligand were characterized by mass, FT-IR, UV–Vis, ¹H-NMR spectroscopy, etc. Also, metal complexes were studied by P-XRD, elemental analysis, thermogravimetric studies along with various biological activities. The micro analytical data revealed that, the metal complexes have 1:1 stoichiometry composition of M:L. Generally, it is observed that prepared metal complexes show better antifungal, antibacterial and anticancer activities than its Schiff base ligand.

Keywords: Schiff base ligand; metal complexes; 5-chlorosalicylaldehyde; 4-aminoantipyrine.

INTRODUCTION

The Schiff bases can be synthesized by the condensation of the primary amines (R–NH₂) with carbonyl compounds (>C=O). Biological assessment of these Schiff base ligands is enhanced on undergoing complexation with transition metal ions.^{1,2} The derivatives (metal complexes) which are synthesized by transition metals are known to play a vital biological role and can be used in chemotherapy.^{3–5} Among the transition metal-supported drugs, the cisplatin (Cis-Pt (NH₃)₂Cl₂) was the inorganic compound which was firstly utilized in the medication or treatment of cancer. However, cisplatin was first inorganic compound but its clinical utilization had limitations due to rise of drug resistance.⁶ Surplus limitation of platinum-supported drug comprised their cytotoxic assessment in blooming tissues.^{7,8} As a result, compounds with more substantial discretion and

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<https://doi.org/10.2298/JSC230803092S>

anti-proliferative assessment, than platinum-supported drugs are essential for the medication of solid tumours. Antithesis to platinum, copper is a trace element that is essential to human body. Numerous fundamental proteins and enzymes impose the activation and participation on trace amount of copper.^{9,10}

Derivatives of 4-aminoantipyrine are known to exhibit analgesic,^{11,12} anti-inflammatory effects,^{13,14} antibacterial,¹⁵ antifungal¹⁶ and antimicrobial activities,¹⁷ also utilized as hair colour additives¹⁸ and to potentiate the local anaesthetic effect of lidocaine.^{19,20} These compounds have been utilized in spectrophotometric determination of metal ions. Many of these reagents give intense colours with transition metal ions, providing sensitive probes and some of them can also coordinate to rare earth ions to form metal complexes with interesting structures.²¹

In this present context we have synthesized Schiff base ligand from 5-chlorosalicylaldehyde and 4-aminoantipyrine and its metal complexes. These have been characterized and analysed by mass, ¹H-NMR, FT-IR spectroscopy, P-XRD and studied by anticancer, antifungal and antibacterial assessments.

EXPERIMENTAL

Material and methods

All the chemicals of analytical grade were used. 5-Chlorosalicylaldehyde and 4-aminoantipyrine purchased from Spectrochem Pvt. Ltd. Solvents like ethanol, ethyl acetate, petroleum ether, *n*-hexane were purchased from local provider and purified by standard procedures. Thin layer chromatography (TLC) plate pre-coated with silica gel on aluminium sheet was used to detect the completion of reaction with system of *n*-hexane and ethyl acetate. ¹H-NMR spectra of Schiff base ligand (L) recorded on Bruker 500 MHz ¹H-NMR instrument in CDCl₃ as solvent. EI-MS spectra recorded on a Bruker compass data analysis 4.2. The prepared Schiff base ligand and its metal complexes confirmed by FTIR spectra with KBr disc on Bruker Alpha T FTIR spectrophotometer. The electronic spectra recorded on Perkin Elmer UV-spectrophotometer. Thermal analysis of the complexes performed on TA instruments Trios V4.4.0.41128 TG/DSC thermal system under nitrogen atmosphere. The powder XRD was carried out on Rigaku-Japan Miniflex 600 instrument.

Analytical and spectral data of the synthesized compounds are given in the Supplementary material to this paper.

The biological activity

We have studied synthesized ligand and its metal complexes against the biological activities like anticancer, antibacterial and antifungal activity. From the observation we found that metal complexes shows better results as compared to ligand.

Anticancer activity

Anticancer activity of the Schiff base ligand (L) and metal complexes (M) were tested by using SRB assay on MCF-7 human breast cancer cell line. The growing cell line used medium of L-glutamine and 10 % fetal bovine serum and inoculated in incubator at temperature 37 °C, 5 % CO₂ and 95 % air and 100 % relative humidity for 24 h. The L and M dissolved in up to 1 mg/ml of DMSO and diluted in water at up to 100 µg/ml and added into the microtiter wells, incubated for 48 h. the process was finished by adding trichloroacetic acid (TCA) and cell line

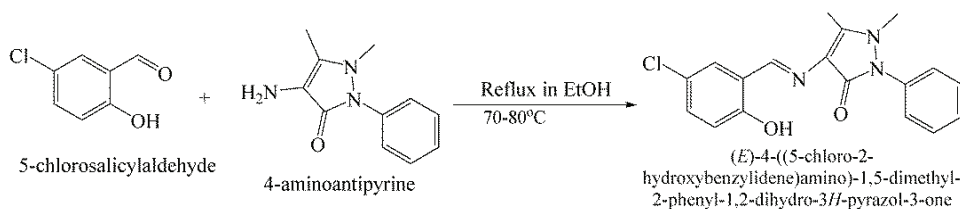
fixed, incubated at 4 °C for 1 h. synthesis of sulforhodamine B (SRB) solution 1 % of acetic acid used for removal of unbound dye incubated at room temperature for 20 min. Bounded dye stain was eluted with 10 mM trizma base. Absorbance was measured at a wavelength of 540 nm and reference wavelength of 690 nm against standard 5-fluorouracil.

Antimicrobial activity

Firstly, preparation of Mueller–Hinton agar (MHA) and potato dextrose agar (PDA) medium sterilized by autoclaving for 15 min, then prepared McFarland turbidity standards by utilising 0.5 ml of 1.175 % barium chloride dihydrate ($\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$) solutions were added to 99.5 ml of 0.18 mol/L sulfuric acid with constant stirring. Petri dishes containing Mueller–Hinton agar plus potato dextrose were inoculated by swabbing with standardized bacterial and fungal inoculums. Then application of sample to inoculated agar plate and plates were placed in an incubator already set to 30 °C. After 24 h, each plate was carefully observed, we found that inhibition zone uniformly circular with lawn of growth, the inhibition zone of diameter measured by unaided eye. The zones are measured in millimetre by utilizing sliding callipers on the back of inverted petri dish.

Synthesis of Schiff base ligand (L)

The (*E*)-4-((5-chloro-2-hydroxybenzylidene)amino)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one was prepared by using well known method.²² 5-chlorosalicylaldehyde (1.56 g, 0.01 mol) and 4-aminoantipyrine (2.03 g, 0.01 mol) were dissolved in hot ethanol. This mixture was refluxed for 45 min at 70–80 °C after time span temperature was reduced to ambient and yellow precipitation was observed. The mixture was filtered, washed with mild ethanol and dried under vacuum.²³ (Scheme 1)



Scheme 1. Synthesis of Schiff base ligand (L).

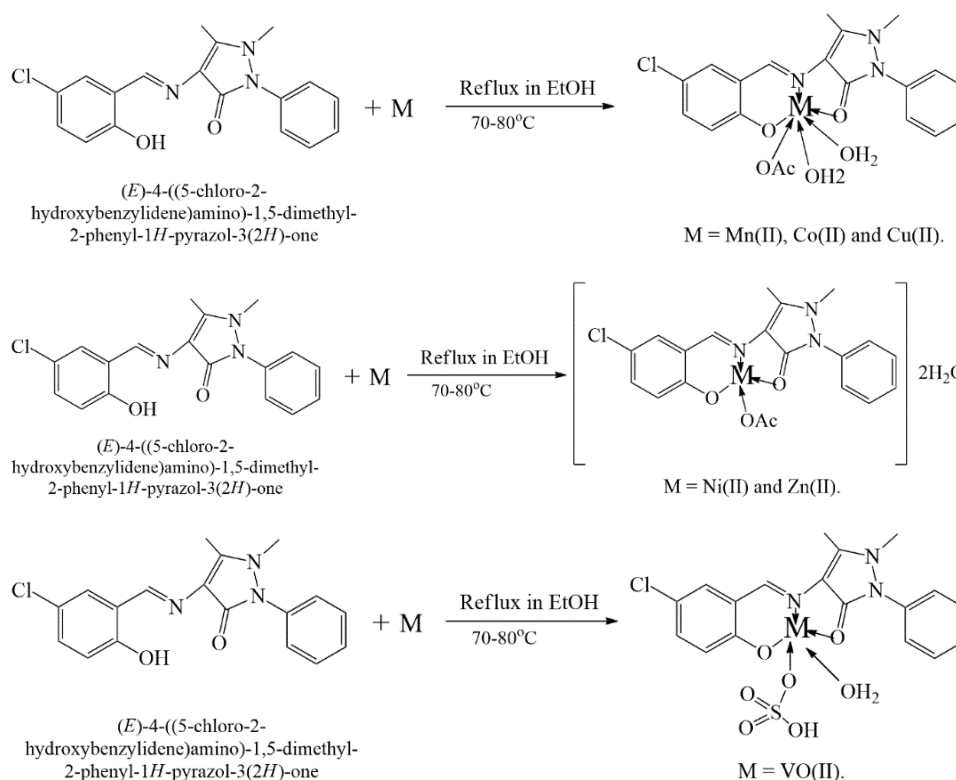
Synthesis of metal complex (M)

In the preparation of the metal complexes, the ligand and the metals were mixed in 1:1 mole ratio using necessary quantity of ethanol. Hot ethanolic solution of Schiff base ligand (0.01 mol) and hot ethanolic solution of corresponding metal salts (0.01 mol) were mixed together and refluxed for 2–3 h. Coloured solid metal complexes were obtained. The products were filtered, washed with cold ethanol and dried under vacuum. (Scheme 2).

RESULTS AND DISCUSSION

The synthesized Schiff base ligand and its metal complexes were analysed by using sophisticated instruments for the various spectroscopic analytical techniques like FTIR, MS and $^1\text{H-NMR}$, and studied by biological activities like anticancer, antifungal and antibacterial. All complexes have different colours than ligand, are insoluble in ethyl alcohol and methyl alcohol and soluble in

DMSO and DMF. The physical and analytical data of ligand and its transition metal complexes are given in Table S-I of the Supplementary material.



Scheme 2. Synthesis of metal complexes.

¹H-NMR spectra of Schiff base ligand(L)

¹H-NMR (400 MHz, chloroform-*d*) $\delta = 13.37$ ppm (*s*, 1H) indicates presence of hydrogen bonding between carbonyl group of 4-aminoantipyrine and hydroxy group of salicylaldehyde.²⁴ $\delta = 9.78$ ppm (*s*, 1H) belongs to azomethine group, $\delta 7.58$ – 7.49 ppm (*m*, 2H) belongs to hydrogen of benzene ring, $\delta 7.46$ – 7.35 ppm (*m*, 3H), $\delta = 7.33$ ppm (*d*, $J = 2.6$ Hz, 1H) indicates meta coupling, $\delta 7.32$ – 7.21 ppm (*m*, 1H), 6.92 ppm (*d*, $J = 8.8$ Hz, 1H), 3.23 ppm (*s*, 3H) are due to N–CH₃, whereas $\delta 2.45$ ppm (*s*, 3H) belongs to C–CH₃.

Mass spectra of Schiff base ligand (L)

In the mass spectrum of ligand, the molecular ion peak was observed at m/z 342 and 343 ($M+1$) which is in good agreement with the molecular weight of the

proposed structure. There are several other peaks also observed which show fragmentation of ligand.

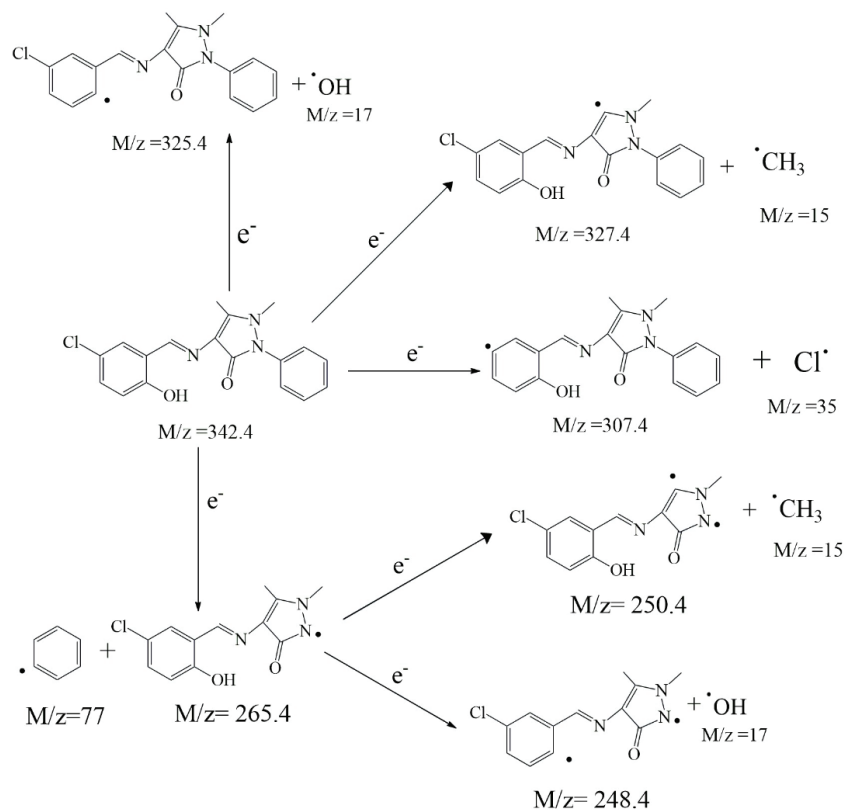


Fig. 1. Fragmentation of Schiff base ligand (L).

FTIR of Schiff base ligand (L) and its metal complexes (M)

The infrared spectra of ligand were recorded on Bruker Alpha T FTIR spectrophotometer and some of the selective bands are shown in Table I. On complexation, the C=N band is shifted to lower frequency corresponding to free ligand, indicating that azomethine group is formed.^{25,26} and nitrogen atom of the azomethine group is coordinated to the metal ion.^{27,28} Carbonyl group of Schiff base ligand exhibit band at 1639 cm^{-1} and in metal complexes, it is shifted to lower frequency by $30\text{--}55\text{ cm}^{-1}$, indicating that the participating carbonyl oxygen is in coordination with metal.^{28,29} In a Schiff base ligand, a band is observed at 3304 cm^{-1} which corresponds to the hydroxy group. In all metal complexes hydroxy group band has disappeared indicating coordination of oxygen atom with central metal ion. A band observed at 1262 cm^{-1} in ligand corresponds to the phenolic C–O group and in all metal complexes this band is shifted to lower

frequency in the range of 1230–1174 cm^{-1} and is further evidence of the formation of metal complexes.³⁰ From above data it is clear that imine nitrogen, carbonyl oxygen and hydroxy oxygen take part in the coordination with central metal ion. The band at 480–495 cm^{-1} is due to M–N vibration. The band at 669–684 cm^{-1} is due to C–Cl vibration.

TABLE I. FT-IR data of Schiff base ligand and its metal complexes.

No.	Compound	–OH	Azomethine, C=N	4-AAP, C=O	M–O	C–O	M–N	C–Cl
1.	L	3304	1563	1639	–	1262	–	684
2.	Mn(II) complex	–	1556	1616	588	1174	497	669
3.	Co(II) complex	–	1556	1637	588	1230	489	669
4.	Ni(II) complex	–	1562	1627	590	1226	491	673
5.	Cu(II) complex	–	1521	1608	619	1174	495	657
6.	Zn(II) complex	–	1535	1624	588	1178	480	677
7.	VO(II) complex	–	1438	1585	605	1193	443	768

Electronic spectra of Schiff base ligand (L) and its metal complexes (M)

The electronic spectra of Schiff base ligand and its metal complexes were recorded in DMSO at concentration of $\approx 5 \times 10^{-4}$, molar range of 50000 to 16666 cm^{-1} .^{23,31,32} Electronic spectral data of ligand and its metal complexes are represented in Table II.

TABLE III Electronic spectral data

No.	Compound	λ_{max} nm	Absorption band cm^{-1}	Proposed transition	Molar conductance $\text{S mol}^{-1} \text{cm}^2$
1.	L	350	28571	$n \rightarrow \pi^*$	4.6
		300	33333	$\pi \rightarrow \pi^*$	
2.	Mn(II)	365	27397	MLCT	6.7
3.	Co(II)	420	23809	${}^4T_{1g} \rightarrow {}^4T_{2g}$	5.2
		375	26666	${}^4T_{1g} \rightarrow {}^4T_{1g(P)}$	
		320	31250	${}^4T_{1g} \rightarrow {}^4A_{2g}$	
4.	Ni(II)	425	23539	${}^3A_{2g} \rightarrow {}^3T_{2g}$	4.3
		360	27777	${}^3A_{2g} \rightarrow {}^3T_{1g(f)}$	
		324	30864	${}^3A_{2g} \rightarrow {}^3T_{1g(P)}$	
5.	Cu(II)	430	29441	${}^2E_g \rightarrow {}^2T_{2g}$	5.1
		400	25000	${}^2E_g \rightarrow {}^2T_{2g}$	
		340	23255	LMCT	
6.	Zn(II)	355	28169	MLCT	4.8
		470	21276	${}^2B_2 \rightarrow {}^2A_1$	
7.	VO(II)	435	22948	${}^2B_2 \rightarrow {}^2B_1$	4.4
		365	27397	${}^2B_2 \rightarrow {}^2E$	

Thermogravimetric analysis

The thermal stability of metal complexes, synthesized from Schiff base ligand, were investigated by varying the temperature range from 50 to 800 °C. With the help of thermal gravimetric analysis (TGA), it is found that the metal complexes decompose in two steps. In the first step, the two coordinated water molecules are removed in the temperature range 50 to 205 °C and the ligand molecule is removed in the 250–580 °C range along with acetate ion for Mn(II), Co(II) and Cu(II) complexes, two lattice water molecules are removed in the temperature range 50 to 215 °C then ligand molecule is removed in the 250–605 °C range along with acetate ion for Ni(II) and Zn(II) complexes and one coordinated sulphate and one coordinated water molecule are removed in the temperature range 50 to 205 °C and ligand molecule is removed in the 260–518 °C range for VO(II) complex. In all metal complexes the mass of the final residue corresponds to stable metal oxides.²⁷ Thermogravimetric data of transition metal complexes are given in Table III.

TABLE III. Thermogravimetric data

No.	Compound	TG range °C	Mass loss % (Calc.)	Cmpd. decomposition	Metallic residue
1.	Mn(II) complex	55–210	7.81(7.34)	2 H ₂ O	MnO
		260–590	79.05(78.17)	Acetate + L	
2.	Co(II) complex	55–205	7.47(7.28)	2 H ₂ O	CoO
		255–565	78.05(77.53)	Acetate + L	
3.	Ni(II) complex	50–180	7.418(7.30)	2H ₂ O	NiO
		255–530	85.03(84.02)	Acetate + L	
4.	Cu(II) complex	50–200	7.09 (7.22)	2 H ₂ O	CuO
		250–580	77.10(76.91)	Acetate + L	
5.	Zn(II) complex	50–215	7.04(7.21)	2 H ₂ O	ZnO
		250–604	78.95(79.75)	Acetate + L	
6.	VO(II) complex	50–205	20.82(21.64)	H ₂ O + SO ₄	VO
		260–518	66.04(65.49)	Ligand	

Powder X-ray diffraction

The P-XRD of metal complexes derived from ligand were scanned in 2θ range 20–80° at wavelength of 1.540 Å for the prediction of cell parameter, crystal system, lattice parameter etc. From the observed data we have found that the metal complexes of Co(II), Ni(II) and VO(II) have monoclinic crystal system, Mn(II) and Zn(II) orthorhombic crystal system and Cu(II) hexagonal crystal system.^{26,27} The XRD diffractograms exhibit the crystalline nature of metal complexes.³⁴ The Powder XRD data of metal complexes are given in Table S-II of the Supplementary material.

Biological studies of Schiff base ligand (L) and its metal complexes (M)

Antimicrobial activities. The Schiff base ligand and metal complexes were investigated against antifungal and antibacterial activities.³⁵ The observation suggest that the metal complexes are more active than the Schiff base ligand (L).

Antifungal activity. The ligand and its metal complexes were evaluated for their antifungal activity against *Penicillium chrysogenum*, *Trichoderma viride* and *Aspergillus niger* fungi by using well known disc diffusion method. For the purification culture of fungi, we have used a single-spore isolation technique according to the literature procedure.¹⁵ This antifungal susceptibility testing was performed on the basis of diameter of inhibition zones against albicans and on albicans strains of fungi.^{36,37}

The antifungal activity of the imine metal complexes has been assessed for their potential application in the region of medicinal bioinorganic chemistry. All related tests were performed using disc diffusion method, under the same experimental conditions and against the same organisms, the results are given in Table IV. It was found that some metal complexes show better antifungal activity than corresponding ligand.

Antibacterial activity. The antibacterial activity of the synthesized ligand and its metal complexes were screened against gram positive and gram negative bacteria using disc diffusion method. From findings, it is clear that some metal complexes exhibit greater inhibition zone than that of ligand.^{38,39} The findings of antimicrobial activities of ligand and its metal complexes are given in Table IV.

TABLE IV. Results of antibacterial and antifungal activities; interpretation key: – resistant, up to 8 mm, intermediate sensitive, 8–12 mm, sensitive, 12–18 mm, highly sensitive, ≥ 18 mm

Test organism	Zone of inhibition (diameter in mm)						
	Ligand(L)	Mn(II)	Co(II)	Ni(II)	Cu(II)	Zn(II)	VO(II)
Antibacterial activity							
<i>Staphylococcus aureus</i>	–	10	9.5	–	–	–	–
<i>Bacillus subtilis</i>	–	–	12.5	–	9	–	–
<i>Klebsiella pneumoniae</i>	–	–	13.5	–	10	11	–
<i>Pseudomonas aeruginosa</i>	–	10.5	13	–	–	10	11
Antifungal activity							
<i>P. chrysogenum</i>	–	–	15	–	20	12	–
<i>T. viride</i>	–	–	22.5	–	10	8	–
<i>A. niger</i>	–	–	12	–	15	8	–

Anticancer activity

The anticancer activity of the prepared ligand (L) and metal complexes (M) were determined using technique of the sulpho-rhodamine-B-stain (SRB) assay on MCF-7 human breast cancer cell line in comparison to 5-fluorouracil as a

standard and it was observed that activity of all the tested compounds is less than that of standard but greater than that of Schiff base ligand (L), Table V.⁴⁰

TABLE V. Results of anticancer activity

No.	Test Compound	Concentration, $\mu\text{g/mL}$	Inhibition, %
1.	5-Fluorouracil (standard)	20	69.66
2.	L ₁	100	32.69
3.	Co(II)	100	56.04
4.	Cu(II)	100	57.06
5.	Zn(II)	100	62.72

CONCLUSION

In the course of our research we have synthesized the Schiff base ligand along with its metal complexes. Based on all spectroscopic techniques, ligand shows tridentate character. The metals Co(II), Ni(II) and VO(II) show monoclinic crystal system, Mn(II) and Zn(II) show orthorhombic and Cu(II) shows hexagonal crystal system. From the biological studies of metal complexes, it was found that some metal complexes show better antibacterial and antifungal activities than ligand, and all metal complexes show better anticancer activities than ligand.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: <https://www.shd-pub.org.rs/index.php/JSCS/article/view/12524>, or from the corresponding author on request. CCDC 2269543-2269546.

Acknowledgments. The authors are gratefully acknowledging University Grant Commission (UGC) for financial assistance, as well as we are very thankful to the Principal, Balbhim Arts, Science & Commerce College, Beed (MS) for providing research laboratory.

ИЗВОД

АНТИТУМОРСКА АКТИВНОСТ ШИФОВЕ БАЗЕ (E)-4-((5-ХЛОРО-2-ХИДРОКСИ-БЕНЗИЛИДЕНЕ)АМИНО)-1,5-ДИМЕТИЛ-2-ФЕНИЛ-1H-ПИРАЗОЛ-3(2H)-ОН КАО ЛИГАНДА И ОДГОВАРАЈУЋИХ КОМПЛЕКСА СО(II), CU(II) И ZN(II)

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Синтетисана је серија комплекса јона прелазних метала, Mn(II), Co(II), Ni(II), Cu(II), Zn(II) и VO(II), који као лиганд садрже Шифову базу (L), која представља дериват од 4-аминоантипирина и 5-хлоросалицилалдехида. Структурне карактеристике Шифове базе су одређене применом масене спектрометрије, као и FT-IR, UV-Vis и ¹H-NMR спектроскопије. Поред наведених спектроскопских метода, за карактеризацију комплекса употребљени су P-XRD, елементална микроанализа и термогравиметријска мерења. Испитивана је антимикуробна и антитуморска активност претходно наведених једињења. На основу резултата аналитичких испитивања закључено је да су у комплексима јон метала и лиганд (L) координовани у 1:1 молском односу. Нађено је да су испи-

тивани комплекси показали бољу антибактеријску, антигљивичну и антитуморску активност у односу на Шифову базу (L).

(Примљено 3. августа, ревидирано 11. септембра, прихваћено 21. новембра 2023)

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