Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *86* (2) 153–164 (2021)
JSCS–5411
Original scientific paper

Synthesis, characterization, antimicrobial screening and cytotoxic properties of Cu(II) and Zn(II) complexes with a bidentate hydroxylated 1,3-diaryl-2-propene-1-one ligand

PRAVINKUMAR PATIL[1] and SAINATH ZANGADE[2]*

[1]*Research Laboratory, Department of Chemistry, N.E.S. Science College, Nanded-431605 (MS), India and* [2]*Department of Chemistry, Madhavrao Patil, ACS College, Palam, Dist. Parbhani-431720 (MS), India*

(Received 1 September, revised 14 October, accepted 2 November 2020)

Abstract: A series of binary metal complexes (halo, hydroxyl and methoxy substituted bis(2-(E)acryloyl)naphthalen-1-yl)oxy)Cu(II) and Zn(II) (**C1**––**C10**)) of Cu^{2+} and Zn^{2+} ions derived from bi-coordinated hydroxylated 1,3--diaryl-2-propene-1-ones were synthesized. The newly synthesized metal complexes were structurally determined by FT-IR, ^{1}H-NMR, ^{13}C-NMR, ESR spectral, XRD and TGA analyses. The FT-IR and ESR studies demonstrated that interactions between metal ions with ligands occur through carbonyl oxygen and deprotonated hydroxyl oxygen and correspond to square-planar geometry for all complexes. The metal complexes were screened *in-vitro* and evaluated for their antimicrobial and cytotoxic activities. The complexes **C1** and **C4** showed significant antimicrobial activity while the remaining complexes showed moderate antimicrobial activity against the tested pathogens. The complexes were evaluated for cytotoxic activity against the organism *Artemia salina.* Complexes **C2**–**C5** exhibited LC_{50} values of 630.45, 969.99, 921.94 and 918.41 μM mL^{-1}, respectively. Furthermore, the complexes were evaluated for their anticancer activity against the liver cancer cell line Hep G2 in comparison with the 5-fluorouracil standard. Complex **C5** showed a significant IC_{50} value of 58.94 μg mL^{-1}. Therefore, the present study is useful for the development of a new class of antimicrobial and anticancer agents.

Keywords: metal complexes; 1,3-diaryl-2-propene-1-one derivatives; antimicrobial activity; cytotoxicity; anticancer activity.

INTRODUCTION

1,3-Diaryl-2-propene-1-ones are recognized as chalcones. Chalcones occur in nature in many plants or are synthesized in laboratories. They serve as biogenic key precursors of flavonoids in higher plants.[1–3] The presence of two elec-

* Corresponding author E-mail: drsbz@rediffmail.com
https://doi.org/10.2298/JSC200901068Z

trophilic reaction centres enables them to participate in the synthesis of heterocyclic compounds.[4] They demonstrate a wide range of biological activities, such as antiviral,[5] anti-inflammatory, anticancer, antimicrobial,[6] antioxidant[7] and antimalerial activities.[8] The biological activity of chalcones may be due to the presence of a reactive keto vinyl group that demonstrates static properties against pathogens.[9]

Chalcones contain an α,β-unsaturated carbonyl system with a reactive ketoethylenic group. The presence of an α,β-unsaturated carbonyl system makes chalcones very important in organic chemistry.[10] The versatility of chalcones arises from their distinctive combination of functional groups. Chalcones and their derivatives can act as chelating agents towards metals to form stable complexes. They are well known as effective metal ion chelators to form metal-coordinated compounds. They provide three centres to interact with metals, *i.e.*, functional groups present on the aromatic ring, the keto–enol moiety and the olefinic moiety.[11] The heterodiene molecular functionalities form stable complexes with transition and non-transition elements.[12]

In recent years, there have outstanding developments in several areas of pharmaceutical science. The wide range of biological activities associated with chalcone-based complexes has explored their therapeutic potentials.[13–14] Transition metal complexes as medicinal compounds posses a great diversity in their action, such as anticancer, antiviral, antimalarial, antitubercular, anti-amoebic,[15] anti-infective[16] and antidiabetic properties.[17,18] Metal ions play essential roles in biological processes. Thus, on coordination, ligands could increase their bioactive profile or some inactive ligand could posses medicinal properties.[19] Copper plays a key role in several enzymes and coenzyme in biochemical processes, because of its bio-essentiality, its complexes are expected to be less toxic in recent medicinal complexes.[20] Zinc is another important transition metal in living organism that plays a critical role in physiological processes.[21] Zinc can adopt different geometries with different coordination numbers; they have good pharmacological profiles[22] as anti-radio agents and tumour photosensitizes.[23,24] Zinc complexes have been used for the treatment of Alzheimer disease.[25] In view of the above importance of metal complexes, first metal complexes of Cu(II) and Zn(II) ions were synthesised and then their antimicrobial and cytotoxic activities evaluated.

EXPERIMENTAL

Chemical material and methods

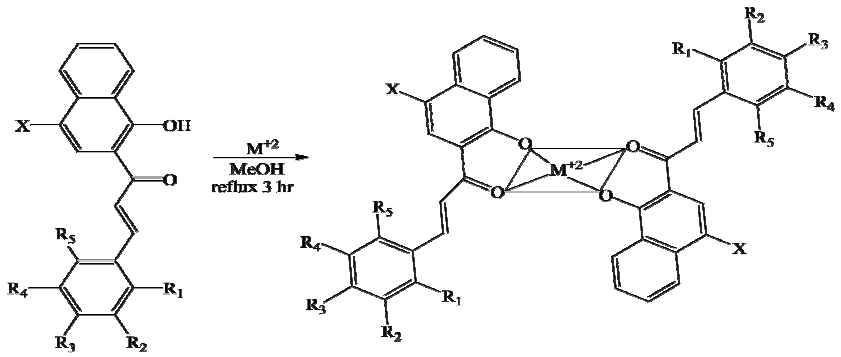
Starting materials, solvents and reagents were purchased from commercial sources and used without purification. FTIR spectra were recorded as KBr pellets on a Perkin Elmer System 2000. ^{1}H-NMR and ^{13}C-NMR spectra were acquired on a Bruker Avance NEO500 spectrometer at 500 and 125 MHz, respectively. XRD was performed on an Ultima IV, Rigaku Corporation, X-ray diffractometer. TGA analysis was realised on a Mettler Toledo instru-

ment under an inert atmosphere. ESR analysis was performed on an ESR-JEOL, JES-FA200 ESR spectrometer with the X band (8.75–9.65 GHz) at room temperature.

The preparation of 1,3-diaryl-2-propene-1-ones ligands were reported in a previous work.[26]

*Synthesis of [Cu(Ln)$_2$]and [Zn(Ln)$_2$] complexes (**C1**–**C10**)*

A warm methanolic solution of metal chloride ($CuCl_2 \cdot 2H_2O$ and $ZnCl_2$ (0.25 mmol, 10 mL)) was added drop wise under constant stirring to a sodium methoxide solution (at pH 7.0–8.0) of ligand 2′-hydroxy chalcones (0.50 mmol, 20 mL). Then, the resultant reaction mixture was refluxed continuously for 3 h. On cooling the solution to room temperature, a brown solid mass separated which was filtered and washed with warm methanol and stored in a $CaCl_2$ desiccator (Scheme 1, Table I). All the complexes gave satisfactory characterization data.



Scheme 1. Representation of the synthesis of Cu(II) and Zn(II) square planar complexes **C1**–**C10**.

TABLE I. Synthesized Cu(II) and Zn(II) complexes

Complex	X	R_1	R_2	R_3	R_4	R_5
C1 : [Cu(L_1)$_2$]	I	OH	I	H	I	H
C2 : [Cu(L_2)$_2$]	Br	H	H	Cl	H	H
C3 : [Cu(L_3)$_2$]	Br	Cl	H	H	H	Cl
C4 : [Cu(L_4)$_2$]	Br	Cl	H	Cl	H	H
C5 : [Cu(L_5)$_2$]	Br	H	OH	OH	H	H
C6 : [Zn(L_6)$_2$]	Br	H	H	OCH_3	H	H
C7 : [Zn(L_7)$_2$]	Br	H	H	Br	H	H
C8 : [Zn(L_8)$_2$]	Br	H	H	OH	H	H
C9 : [Zn(L_9)$_2$]	Br	H	H	F	H	H
C10 : [Zn(L_{10})$_2$]	I	H	OH	OH	H	H

Antimicrobial activity

In-vitro antimicrobial activity of compounds was evaluated by the Agar cup plate method against the Gram-positive bacteria *Staphylococcus aureus* (ATCC6538) and Gram-negative bacteria *Escherichia coli* (ATCC8739), and the yeast *Candida albicans* (ATCC10231). The activity was evaluated against the antibacterial standard drug ampicillin and the antifungal standard drug fluconazole. Stock solutions of each complex and the standard drugs were pre-

pared in dimethyl sulfoxide to obtain a concentration of 1 mg mL^{-1}. The bacterial slant was incubated at 35 °C for 24 h. Soyabean casein in digest agar media and fungal slant was incubated at 25 °C for 72 h in sabourauds dextrose agar media. After incubation, the well grown slant was inoculated in saline solution and adjusted to a viable count of 10^7 colony forming unit (CFU mL^{-1}). These culture suspensions were inoculated on Mueller–Hinton agar and 100 µL of sample solution was added to each well created on plates with a cork borer. Standard drug controls and a blank control were run for each test. Then the plates were incubated at 35 °C for 24 h for the bacteria and for the yeast and mould at 25 °C for 48 h to examine the zone of inhibition. All the experiments were performed in triplicate and the average zone of inhibition is reported.

The minimum inhibitory concentration of each complex was evaluated against the standard concentrations. The different concentrations of sample and standard of 1, 0.5, 0.25 and 0.12 mg mL^{-1} were prepared in dimethyl sulfoxide by serial dilution. A volume of 100 µL was added into each well. Standard and blank controls were run for each test. After incubation, the lowest concentration of test solution with no visually detectable bacterial growth was considered as the minimum inhibitory concentration.

Cytotoxic activity

In-vitro cytotoxic activity was screened against the organism *Artemia salina*. Test solutions with concentrations 1, 10, 100 and 1000 µM mL^{-1} were prepared in dimethyl sulfoxide. Brine solution 0.1 mL and 10 shrimps were added in different test tubes. Each test tube was treated with test solutions of different concentrations, except the blank control. The blank control and test solutions were incubated at room temperature (28–30 °C) under strong aeration conditions for 24 h. After incubation, the nauplii were counted in the stem of capillary against a light background. The percentage mortality was obtained using the following formula:

$$\text{Mortality, \%} = 100(\text{Total nauplii} - \text{Alive nauplii})/\text{Total nauplii}$$

The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay was performed against the liver cancer cell line Hep G2. The assay was evaluated against a standard 20 µg mL^{-1} solution of 5-fluorouracil prepared in dimethyl sulfoxide. Test solutions with concentrations of 200, 400, 600, 800 and 1000 µg mL^{-1} were prepared in dimethyl sulfoxide. Cell line (HepG2) at a concentration of 10^4 cells per well was cultured in 100 µL culture medium in 96 well flat bottom microplates. Controls were run to determine the control cell survival and the percentage of live cells after culture. Control wells containing DMSO (0.2 % in PBS) and cell line and all sample wells in triplicate were incubated in a 5 % CO_2 incubator for 24 h at 37 °C. After incubation, the medium was completely removed and 20 µL of MTT reagent (5 mg mL^{-1} in PBS) was added to each well. Then the cells were incubated for 4 h at 37 °C in a CO_2 incubator. The resulting formazan crystals were dissolved in 200 µL DMSO and the absorbance was measured spectrophotometrically at 550 nm after 10 min incubation at 37 °C. The inhibition induced by each tested compound at the indicated concentrations was calculated using the following formula:

$$\text{Inhibition, \%} = 100(\text{Control absorbance} - \text{Test absorbance})/\text{Control absorbance}$$

RESULTS AND DISCUSSIONS

The Cu(II) and Zn(II) metal complexes were synthesized by the general procedure mentioned above in the experimental section. All the metal complexes were brown coloured and stable towards air and moisture at room temperature.

All these metal complexes are insoluble in most organic solvents except DMSO and DMF.

FT-IR Spectra

FT-IR analysis of the complexes was performed using the KBr pellet technique. The observed results were compared with those of the ligands and are tabulated in Table II. The –OH group in the ligands was confirmed by the presence of corresponding stretching bands at around 3234–3431 cm^{-1} whereas this characteristics band disappeared on complex formation. This is due to deprotonation of the hydroxyl proton and coordination of the central metal ion through the oxygen. The presence of surface or uncoordinated water molecule in the complex was confirmed by the presence of a broad band in the range 3234–3432 cm^{-1}. The vibrational bands observed in the ligands and complexes in the range 1523––1644 cm^{-1}, 1433–1607 and 1207–1294 cm^{-1} confirmed the presence of C=O, C=C and C–O groups, respectively. While the band observed around 468–602 cm^{-1} arises from metal–oxygen bond stretching (M–O) in the formed complexes. The data for the FT-IR analysis of the ligands and synthesized complexes are presented in Table II.

TABLE II. IR frequencies (cm^{-1}) of the ligands and their complexes; * – characteristics IR stretching frequencies of ligand[26]

Ligand and complex	Bond					
	OH	H_2O	C=O	C=C	C–O	M–O
L_1*	3418.97	–	1627.99	1576.87	1268.25	–
C1 : $[Cu(L_1)_2]$	–	3434.8	1643.2	1433.0	1207.2	558.3
L_2*	3415.02	–	1630.88	1576.87	1293.33	–
C2 : $[Cu(L_2)_2]$	–	3410.6	1523.5	1491.2	1256.5	526.5
L_3*	3234.8	–	1624.7	1591.0	1266.80	–
C3 : $[Cu(L_3)_2]$	–	3463.7	1635.1	1606.2	1255.7	599.4
L_4*	3400.00	–	1621.4	1590.20	1266.00	–
C4 : $[Cu(L_4)_2]$	–	3463.8	1633.8	1572.7	1251.2	601.9
L_5*	3431.00	–	1625.40	1591.50	1266.40	–
C5 : $[Cu(L_5)_2]$	–	3416.3	1611.8	1585.5	1253.5	594.1
L_9*	3432.0	–	1625.2	1606.20	1262.30	–
C9 : $[Zn(L_9)_2]$	–	3434.6	1635.1	1547.5	1249.8	468.7

Powder X-ray diffraction analysis

The X-ray powder diffraction analysis was performed on an X-ray powder diffractometer with the scanning mode parameters: $2\theta/\theta$, scanning type; continuous, X-ray; 40 kV/20 mA, fixed monochromator within the 2θ range 10 to 90° at a step 0.02°. To observe the novelty of the synthesized complexes, a comparison was made between the observed patterns and reported patterns with peak search method. The measurements showed peaks present at different 2θ

values. From these values, the grain size, dislocation density, strain and unit cell parameters were calculated and are given in Table III.

TABLE III. Crystal data and structure refinement for bis((4-bromo-2-((E)-3-(4-chlorophenyl)acryloyl)naphthalen-1-yl)oxy)copper(II) (**C2**) and bis((4-bromo-2-((E)-3-(4-fluorophenyl)acryloyl)naphthalen-1-yl)oxy)zinc(II) (**C9**)

Complex	$[Cu(C_{19}H_{11}O_2BrCl)_2]$	$[Zn(C_{19}H_{11}O_2BrF)_2]$
Empirical formula	Cu ($C_{38}H_{22}O_4Br_2Cl_2$)	Zn($C_{38}H_{22}O_4Br_2F_2$)
Formula weight	836.84	805.76
Temperature, K	298	298
Crystal system	Cubic	Cubic
Space group	*Fm–3m*	*Fm–3m*
a / Å	5.6384	5.6382
b / Å	5.6384	5.6382
c / Å	5.6384	5.6382
α / °	90	90
β / °	90	90
γ / °	90	90
Volume, Å^3	179.25	179.23
Z	4	4
ρ_{calc} / g cm^{-3}	31.009	29.860
μ / cm^{-1}	330.933	164.189
Crystallite size, nm	29.76360	30.54437
Dislocation density, nm^{-2}	1.12883	1.07186
Micro strain	6.63928	8.52797

Thermogravimetric analysis

The TGA analyses were performed on a Mettler Toledo instrument under an inert atmosphere. From the thermogram, it can be seen that a first weight loss step was observed in the range 30–100 °C. The weight loss continued gradually in second step in the range 100–800 °C. Weight loss in first step was due to the loss of uncoordinated water molecule then further weight loss in second step was due to the removal of ligands from the metal atom. The final residue was undetermined. Thus, the thermograms of studied complexes showed that almost all the complexes started to lose weight at a relatively high temperature, indicating the absence of coordinated water.

Magnetic moments

Zn(II) is diamagnetic, the Cu(II) complexes are paramagnetic and exhibit magnetic moments at room temperature in the solid state. The Cu(II) complexes showed magnetic moments in the range 1.84–1.95 BM, suggesting one electron in a square planar environment.

ESR analysis

The ESR analysis of the synthesized complexes was performed at room temperature. From the spectrum, the calculated value of $g_{\|}$ and $g\perp$ are respectively 2.2497 and 2.0972, and 2.0509 and 2.0066 for the C1 and C9 complexes respectively. The trend $g_{\|} > g\perp > g_e$ observed for the complexes indicates that the observed complexes have square planar geometry and that the unpaired electron lies in a $dx^2–y^2$ orbital.

^{1}H-NMR and ^{13}C-NMR analysis

In the ^{1}H-NMR analysis, peaks observed at δ values 7.760–8.578 ppm indicate the presence of aromatic protons and the peaks present at δ = 7.110 ppm and δ = 7.740 ppm revealed olefinic H_α and H_β protons, respectively, with a coupling constant value of 16 Hz. The peak present at δ 5.4 ppm indicates the presence of a phenolic –OH group. While the absence of a characteristic peak at δ = 14.0 ppm for 2′-hydroxynapthyl proton confirms the formation of the complexes. In the ^{13}C-NMR analysis, the peaks observed in the δ value range 100 to 183 ppm indicate the presence of aromatic and olefinic carbons, the peak present at δ 188 ppm indicates the presence of a carbonyl carbon and the peak present at 89 ppm indicates the presence of a C–I bond.

Antimicrobial activity

The *in-vitro* antimicrobial activity of the complexes and their ligands are presented in Table IV.

TABLE IV. Antimicrobial activity of the complexes and their ligands; * – growth inhibitory activity of ligand against the tested pathogens[26]

Compound	*S. aureus*		*E. coli*		*C. albicans*	
	Average zone of inhibition, mm	Activity index	Average zone of inhibition, mm	Activity index	Average zone of inhibition, mm	Activity index
L_1*	–	1.2471	–	0.8358	–	1.03132
C1 : $[Cu(L_1)_2]$	19.84	1.3018	12.97	0.9120	18.63	1.14505
L_2*	–	0.5914	–	0.8749	–	0.82447
C2 : $[Cu(L_2)_2]$	11.37	0.7460	13.95	0.9810	19.64	1.20712
L_3*	–	0.8131	–	0.6981	–	0.86288
C3 : $[Cu(L_3)_2]$	14.70	0.9645	11.25	0.7911	15.33	0.94222
L_4*	–	0.7841	–	0.8309	–	0.84220
C4 : $[Cu(L_4)_2]$	14.15	0.9284	13.55	0.9528	15.92	0.97848
L_5*	–	0.8218	–	0.7096	–	0.77069
C5 : $[Cu(L_5)_2]$	14.91	0.9783	13.49	0.9486	17.48	1.07437
L_9*	–	0.5920	–	0.6826	–	0.76950
C9 : $[Zn(L_9)_2]$	11.14	0.7309	12.69	0.8924	15.17	0.93239
DMSO	No zone	–	No zone	–	No zone	–
Ampicilin	15.24	–	14.22	–	–	–
Fluconazole	–	–	–	–	16.27	–

Complexes **C1**, **C4** and **C5** exhibit potent antimicrobial activity against the tested pathogens, complexes **C2** and **C9** display significant antibacterial activity against *Echerchia coli* and antifungal activity against *Candida albicans*, while complex **C3** showed moderate antifungal activity against the pathogen *Candida albicans*. The activity of all complexes was enhanced compared to those of the corresponding ligands. This is because the synthesized complexes are bi-coordinated, and their ligands are associated with multiple halogen or hydroxyl substituents. These substituent supports boost the pharmacological activity.

The minimum inhibitory concentrations of complexes were determined using concentrations of 1.0, 0.5, 0.25 and 0.12 mg mL^{-1}. The observed *MIC* values of complexes and respective ligands are presented in Table V. The complexes **C1** and **C4** exhibited a significant *MIC* value of 0.12 mg mL^{-1} against all pathogens. The complex **C2** and **C5** show a significant *MIC* value of 0.12 mg mL^{-1} against the pathogen *E. coli* and *C. albicans.* The complexes **C3** and **C9** shows a moderate *MIC* value of 0.25 mg mL^{-1} against the pathogen *E. coli* and *C. albicans.* All complexes showed improved *MIC* values with respect to their respective ligands The increased potency is due to the presence of pharmacological active halogens or hydroxyl substituents in the ligands.

TABLE V. *MIC* values (mg mL^{-1}) of complexes and their ligands; a positive sign (+) indicates growth on the plate, a negative sign (–) indicates no growth on the plate; * – *MIC* mg mL^{-1} displayed by the ligands[26]

Ligand and complex	Pathogen											
	S. aureus				*E. coli*				*C. albicans*			
	1.0	0.5	0.25	0.12	1.0	0.5	0.25	0.12	1.0	0.5	0.25	0.12
L_1*	–	–	–	–	–	–	–	+	–	–	–	–
C1 : $[Cu(L_1)_2]$	–	–	–	–	–	–	–	–	–	–	–	–
L_2*	–	–	+	+	–	–	–	+	–	–	–	+
C2 : $[Cu(L_2)_2]$	–	–	+	+	–	–	–	–	–	–	–	–
L_3*	–	–	–	+	–	–	+	+	–	–	–	+
C3 : $[Cu(L_3)_2]$	–	–	–	+	–	–	–	+	–	–	–	+
L_4*	–	–	+	+	–	–	–	+	–	–	–	+
C4 : $[Cu(L_8)_2]$	–	–	–	–	–	–	–	–	–	–	–	–
L_5*	–	–	–	+	–	–	+	+	–	–	+	+
C5 : $[Cu(L_5)_2]$	–	–	–	+	–	–	–	–	–	–	–	–
L_9*	–	+	+	+	–	+	+	+	–	+	+	+
C9 : $[Zn(L_9)_2]$	–	–	+	+	–	–	–	+	–	–	–	+
Ampicilin	–	–	–	+	–	–	–	+				
Fluconazole									+	+	+	+

Cytotoxic activity

In a previous work, a series of ligand was synthesized with different substituent and their biological activity were examined. It was observed that some of them showed significant biological activity. The metal ion plays a significant role

in a bioactive profile. Upon coordination of the ligand with a metal ion, the bioactive profile may be enhanced and so it was our interest to evaluate those complexes which are associated with previously studied biological active ligands. Hence, complexes **C1**–**C5** and **C9** were selected for evaluation and their activities were studied and compared in the respective tables.

The cytotoxic activity of the synthesized complexes was screened in terms of their effect on live cells of the organism *Artemia salina*. Cytotoxic activity was evaluated in percentage mortality after treatment of test solution of different concentrations on live cells of *A. salina.* All the complexes displayed significant cytotoxic activity. The observed results are given in Table VI. Complexes **C3–**–**C5** demonstrated LC_{50} values of 630.45, 969.99, 921.24 and 918.41 μM mL^{-1}, respectively. These values show that **C2**–**C5** are more potent than **C1** and **C9**. Complexes **C2**–**C4** contain –Cl and –Br substituents at the *ortho* and *para* position of the aromatic ring, whereas **C5** has –OH at the *meta/para* position of the aromatic ring and –Br substituent at the *para* position of the naphthyl moiety. Complexes **C1** and **C9** possess –OH, –I and –Br, –F substituent, respectively, are potentially active. All complexes are associated with a copper metal ion except complex **C9** that is associated with a zinc metal ion. From these observations, it could be concluded that complexes associated with a copper metal ion and the substituents –Cl, Br, –OH may lead to significant cytotoxic activity.

TABLE VI. Cytotoxic activity in terms of percentage mortality; ND – not detected; * – cytotoxicity and LC_{50} shown by the ligands[26]

Complex	Mortality, %				LC_{50} / μM mL^{-1}
	Sample concentration, μM mL^{-1}				
	1	10	100	1000	
L_1*	70	70	80	80	ND
C1 : $[Cu(L_1)_2]$	70	70	80	90	ND
L_2*	30	40	40	50	997.14
C2 : $[Cu(L_2)_2]$	30	30	40	60	630.45
L_3*	90	90	100	100	ND
C3 : $[Cu(L_3)_2]$	30	30	40	50	969.99
L_4*	90	80	100	100	ND
C4 : $[Cu(L_4)_2]$	40	40	50	50	921.94
L_5*	100	100	100	100	ND
C5 : $[Cu(L_5)_2]$	30	40	50	50	918.41
L_9*	90	90	100	100	ND
C9 : $[Zn(L_9)_2]$	90	90	100	100	ND

MTT Assay

The *in-vitro* anticancer activity was evaluated by the MTT assay. The growth inhibitory activity of complexes was determined against the liver cancer cells (HepG2). All complexes displayed inhibitory activity against liver cancer

cells. The complexes **C2**–**C5** were showed IC_{50} values of 392.64, 896.64, 490.40 and 58.94 μg mL^{-1}, respectively (Table VII). These values specify that the **C2**–**C5** complexes are more potent than the **C1** and **C9** complexes. The complexes **C2**–**C4** have –Cl and –Br substituents at the *ortho* and *para* position of the aromatic ring, whereas **C5** has –OH at the meta/para position of the aromatic ring and a –Br substituent at the *para* position of the naphthyl moiety. The complexes **C1**and **C9** possessing –OH, –I and –Br, –F substituents at the respective position showed moderate activity. All complexes associated with a copper metal ion and complex **C9**, which is associated with the zinc metal ion, show potency in anticancer activity. From these observations, it was concluded that the complexes associated with the copper metal ion and the attached substituents –Cl, Br, –OH may lead to significant anticancer activity.

TABLE VII. The IC_{50} values of the complexes and their ligands; standard, 5-flurouracil: 97.22 μM mL^{-1}; * – The IC_{50} values shown by the ligands[26]

Complex	IC_{50} / μM mL^{-1}	Ligand	IC_{50}* / μM mL^{-1}
C1 : $[Cu(L_1)_2]$	>1000	L_1	ND
C2 : $[Cu(L_2)_2]$	392.64	L_2	416.66
C3 : $[Cu(L_3)_2]$	896.64	L_3	ND
C4 : $[Cu(L_4)_2]$	490.40	L_4	536.66
C5 : $[Cu(L_5)_2]$	58.94	L_5	91.85
C9 : $[Zn(L_9)_2]$	>1000	L_9	ND

CONCLUSIONS

Novel Cu(II) and Zn(II) complexes with hydroxylated 1,3-diaryl-2-propene--1-ones ligands were synthesized. All the metal complexes were characterized by various spectroscopic and analytical techniques. The data suggested a square planar structure of Cu(II) and Zn(II) complexes with 1:2 (metal:ligand) stoichiometry. Their *in-vitro* antimicrobial activity was evaluated by the agar cup plate method against gram positive bacteria *Staphylococcus aureus* and Gram-negative bacteria *Echerchia coli* and the yeast *Candida albicans*. All complexes showed enhanced antimicrobial activity than its ligands. The complexes **C1** and **C4** showed the significant activity with *MIC* values of 0.12 mg mL^{-1} against all the tested pathogens. The complexes **C2** and **C5** showed significant activity with *MIC* values of 0.12 mg mL^{-1} against the *E. coli* and *C. albicans* and the complexes **C3** and **C9** showed moderate activity with *MIC* values of 0.25 mg mL^{-1} against *E. coli* and *C. albicans*. Their anticancer activity was evaluated against a liver cancer cell line. The complex **C5** showed significant activity with an IC_{50} value 58.94 μg mL^{-1}, while complexes **C2–C4** showed moderate activity with IC_{50} values 392.64, 896.64 and 490.40 μg mL^{-1}, respectively. Hence, the complexes contained pharmacological active substituents, such as hydroxyl, chloro and bromo at the *ortho* and *para* positions of the aromatic ring, shows potentially

antimicrobial and anticancer activity. Therefore, this synthetic methodology and antimicrobial results serve as preliminary screening for the development of new antimicrobial and anticancer agents by new complex synthesis.

SUPPLEMENTARY MATERIAL

Additional data are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/index, or from the corresponding author on request.

Acknowledgments. The authors are very thankful to Panjab University, Chandigarh for the Instrumental Analysis and Radial micro biotech services, Karad, Satara for determination of the biological activity.

ИЗВОД

СИНТЕЗА, КАРАКТЕРИЗАЦИЈА, АНТИМИКРОБНА И ЦИТОТОКСИЧНА ИСПИТИВАЊА КОМПЛЕКСА БАКРА(II) И ЦИНКА(II) СА ХИДРОКСИЛОВАНИМ БИДЕНТАТНИМ 1,3-ДИАРИЛ-2-ПРОПЕН-1-ОН ЛИГАНДИМА

PRAVINKUMAR PATIL[1] и SAINATH ZANGADE[2]

[1]*Research Laboratory, Department of Chemistry, N.E.S. Science College, Nanded-431605(MS), India и*
[2]*Department of Chemistry, Madhavrao Patil, ACS College, Palam, Dist. Parbhani-431720 (MS), India*

Описана је синтеза различитих бинарних комплекса метала (халоген, хидроксил и метокси супституисани бис(2-(*E*)-акрилоил)нафтален-1-ил)окси)-бакар(II) и цинк(II), **C1**–**C10**) који садрже хидроксиловане бидентатно координоване 1,3-диарил-2-пропен-1--он лиганде. Синтетисани комплекси су структурно окарактерисани помоћу FT-IR, ^{1}H--NMR, ^{13}C-NMR, ESR спектроскопије, XRD и TGA анализе. На бази FT-IR и ESR испитивања потврђено је да су лиганди преко карбонилног и депротонованог хидроксилног атома кисеоника бидентатно координовани за јоне метала и да сви комплекси имају квадратно-планарну геометрију. Извршена су *in-vitro* испитивања антимикробне и цитотоксичне активности комплекса. Комплекси **C1** и **C4** су показали значајну антимикробну активност, док је активност осталих комплекса била осредња. Испитивана је цитотоксична активност комплекса према *Artemia salina*. За комплексе **C2**–**C5** добијене су следеће IC_{50} вредности: 630,45, 969,99, 921,94 и 918,41 μM mL^{-1}. Поред тога, испитивана је антитуморска активност комплекса према туморској ћелијској линији јетре (Hep G2), при чему је комплекс **C5** показао највећу активност у односу 5-флуороурацил стандард (IC_{50} = 58,94 μg mL^{-1}). Добијени резултати су од значаја за развој нове класе антимикробних и антитуморских агенаса.

(Примљено 1. септембра, ревидирано 14. октобра, прихваћено 2. новембра 2020)

REFERENCES

1. W. Dan, J. Dai, *Eur. J. Med. Chem*. 187 (2019) 111980 (https://doi.org/10.1016/j.ejmech.2019.111980)
2. A. M. Asiri, S. A. Khan, *Molecules* **16** (2011) 523 (https://doi.org/10.3390/molecules16010523)
3. D. Kakati, J. C. Sarma, *Chem. Cent. J.* **5** (2011) 1 (http://dx.doi.org/10.1186/1752-153X-5-8)
4. H. Albuquerque, C. Santos, J. Cavaleiro, A. Silva, *Curr. Org. Chem.* **18** (2014) 2750 (https://doi.org/10.2174/1385272819666141013224253)
5. J. S. Biradar, B. S. Sasidhar, R. Parveen, *Eur. J. Med. Chem.* **45** (2010) 4074 (https://doi.org/10.1016/j.ejmech.2010.05.067)

6. B. P. Bandgar, S. S. Gawande, *Bioorgan. Med. Chem.* **18** (2010) 2060 (https://doi.org/10.1016/j.bmc.2009.12.077)
7. P. S. Bhale, H. V. Chavan, S. B. Dongare, S. N. Shringare, Y. B. Mule, S. S. Nagane, B. P. Bandgar, *Bioorg. Med. Chem. Lett.* **27** (2017) 1502 (https://doi.org/10.1016/j.bmcl.2017.02.052)
8. M. Liu, P. Wilairat, M. L. Go, *J. Med. Chem.* **44** (2001) 4443 (http://dx.doi.org/10.1021/jm0101747)
9. F. M. Atlam, M. N. El-Nahass, E. A. Bakr, T. A. Fayed, *Appl. Organomet. Chem.* **32** (2018) 1 (https://doi.org/10.1002/aoc.3951)
10. P. Patil, G. Bhopalkar, S. Zangade, *Curr. Microwave Chem.* **7** (2020) 145 (https://doi.org/10.2174/2213335607666200129113827)
11. C. Sulpizio, J. Breibeck, A. Rompel, *Coord. Chem. Rev.* **374** (2018) 497 (https://doi.org/10.1016/j.ccr.2018.05.023)
12. J. Johnson, A. Yardily, *J. Coord. Chem.* **72** (2019) 2437 (https://doi.org/10.1080/00958972.2019.1669022)
13. D. Krajčiová, M. Melník, E. Havránek, A. Forgácsová, P. Mikuš, *J. Coord. Chem.* **67** (2014) 1493 (https://doi.org/10.1080/00958972.2014.915966)
14. L. Dkhar, V. Banothu, E. Pinder, R. M. Phillips, W. Kaminsky, M. R. Kollipara, *Polyhedron* **185** (2020) 114606 (https://doi.org/10.1016/j.poly.2020.114606)
15. D. K. Mahapatra, S. K. Bharti, V. Asati, S. K. Singh, *Eur. J. Med. Chem.* **174** (2019) 142 (https://doi.org/10.1016/j.ejmech.2019.04.032)
16. S. Shukla, A. P. Mishra, *Arab. J. Chem.* **12** (2019) 1715 (https://doi.org/10.1016/j.arabjc.2014.08.020)
17. N. Patel, A. K. Prajapati, R. N. Jadeja, I. P. Tripathi, N. Dwivedi, *J. Coord. Chem.* **73** (2020) 1131 (https://doi.org/10.1080/00958972.2020.1774562)
18. A. Levina, P. A. Lay, *Dalton Trans.* **40** (2011) 11675 (https://doi.org/10.1039/C1DT10380F)
19. O. I. Edozie, O. J. Godday, A. K. Chijioke, I. O. Uchenna, N. F. Chigozie, *Bull. Chem. Soc. Ethiop*. **34** (2020) 83 (https://dx.doi.org/10.4314/bcse.v34i1.8)
20. M. Iqbal, S. Ali, M. Tahir, M. Haleem, H. Gulab, N. Shah, *J. Serb. Chem. Soc.* **85** (2020) 203 (https://doi.org/10.2298/JSC1904230651)
21. A. D. Cort, P. De Bernardin, G. Forte, F. Y. Mihan, *Chem. Soc. Rev.* **39** (2010) 3863 (http://dx.doi.org/10.1039/B926222A)
22. C. T. Liu, A. A. Neverov, R. S. Brown, *J. Am. Chem. Soc.* **130** (2008) 13870 (http://dx.doi.org/10.1021/ja805801j)
23. S. J. Hosseinimehr, S. Emami, S. M. Taghdisi, S. Akhlaghpoor, *Eur. J. Med. Chem.* **43** (2008) 557 (https://dx.doi.org/10.1016/j.ejmech.2007.04.013)
24. Y. Q. Liu, X. M. Luo, H. J. Jiang, Z. Q. Zhang, *Russ. J. Coord. Chem. (Khimiya)* **44** (2018) 317 (https://dx.doi.org/10.1134/S1070328418050032)
25. S. Liu, W. Cao, L. Yu, W. Zheng, L. Li, C. Fan, T. Chen, *J. Chem. Soc. Dalton Trans.* **42** (2013) 5932 (http://dx.doi.org/10.1039/C3DT33077J)
26. P. Patil, P. A. Khan, S. Zangade, *Curr. Chem. Lett.* **9** (2020) 1838 (http://www.growingscience.com/ccl/Vol9/ccl_2020_5.pdf).