



Investigation of Metal(II)-Curcumin-Glycine Complexes: Preparation, Structural Characterization and Biological Activities

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ABSTRACT

A novel Schiff base obtained from curcumin and glycine was prepared and it was reacted with Co, Ni, Cu and Zn metals in order to form the stable metal complexes and characterized by elemental analysis, magnetic, molar conductance, IR, UV-Vis., ¹H NMR and PXRD. The data shows that the complexes have the structure [M(II)-(cur-gly)H₂O] system. Electronic and magnetic data suggest a tetrahedral geometry for Co, Ni and Zn except Cu complex has a square planar geometry. The antimicrobial activity of cur-gly and its metal chelates were confirmed against the bacterial species as *E. coli*, *P. aeruginosa*, *Enterococcus*, *B. cereus* and *S. aureus* species. Antifungal activity was screened against *C. albicans*, *C. parapsilosis* and *A. flavus*. Metal chelates indicate excellent antimicrobial activity than their parent cur-gly and DNA photo cleavage activity shows that metal chelate effectively cleave the pUC 18 DNA.

Keywords: Curcumin, Schiff base, UV-Vis, Glycine, Antimicrobial activity, DNA cleavage.

INTRODUCTION

Since the cumulative recognition role of metal complexes in biological systems are widely studied in Schiff bases. The ligands are able to coordinate with metals through imine nitrogen and to the aldehyde or ketone.¹ 1,7-bis(4-hydroxy 3-methoxyphenyl)-1,6-hepta-diene-3,5-dione has a specific conjugated β-diketone moiety and act as an influential natural chelating agent as an

strong antioxidant² than Vitamin E. Over the past years complexation with metals has fascinated much consideration necessities for the treatment of Alzheimer's diseases.^{3,4} Curcumin compounds have good combination with other anticancer therapies have been described to prevent the clonogenicity of cancer cells and induce anti-proliferative, apoptotic effects on drug-resistant and sphere-forming cancer cells expressing stem cell-like signs as well as converse the chemoresistance. Amino acids cur-gly



form stable compounds and also inhibits the growth of bacterial and fungal strains after complexation.^{5,6} Present investigation⁷ deals with the preparation of the ligand resulting from curcumin-glycine (cur-gly) and containing Co(II), Ni(II), Cu(II) and Zn(II) complexes and their structural characterization was carried by using various instrumental techniques. The antimicrobial activities and DNA cleavage of cur-gly and its metal(II) complexes have been investigated systematically.

MATERIALS AND METHODS

Materials

The AR grade reagents, chemicals including curcumin, glycine, EtOH, methanol, Co/Ni/Cu/Zn(II) chloride salts were used. All chemicals and solvents were acquired from Merck. Infrared spectrum was recorded on SHIMADZU FT-IR Affinity-1 spectrophotometer by potassium bromide pellet disc method. UV-Vis. studies were carried out on SHIMADZU1800 spectrophotometer between 200-1100 nm by using suitable solvent. ¹H-NMR of Zn(II)-cur-gly complexes and cur-gly were recorded Bruker Drx-300 MHz NMR spectrometer using DMSO-d₆ solvent and Tetramethyl silane as internal

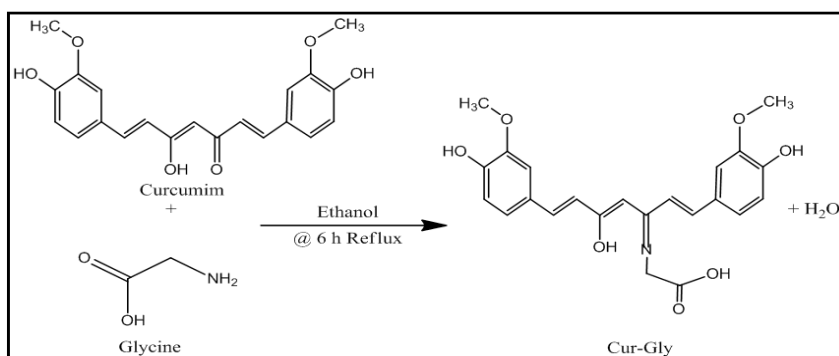
standard. Magway MSB Mk 1 Magnetic susceptibility balance was used to carry out the magnetic moment measurements at room temperature.

Preparation of cur-gly

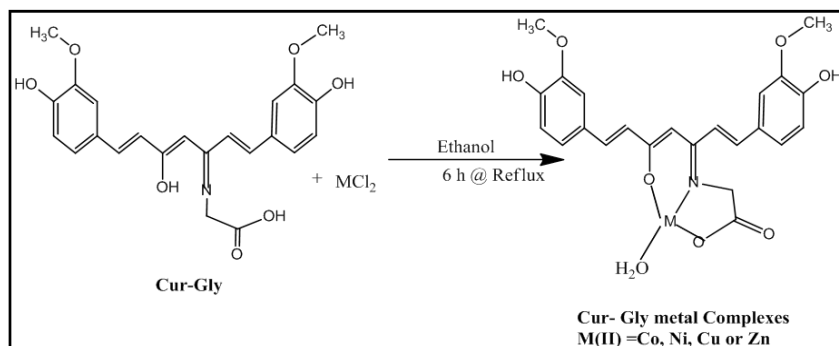
An ethanolic solution of curcumin (0.368 g, 0.001 mol), glycine (0.075 g, 0.001 mol) was added dropwise followed by 3 drops of glacial acetic acid and heated under reflux about 3-5 h on a hot plate at 55-60°C. The resulting solution was reduced to one-third. Dark yellow precipitate was formed, filtered off washed with ethanol and finally dried over fused CaCl₂.^{8,9} The preparation route of cur-gly is outlined in Scheme 1.

Preparation of metal complexes [M(II)-(cur-gly)H₂O]

An ethanolic solution of CoCl₂.6H₂O, NiCl₂.6H₂O, CuCl₂.2H₂O and ZnCl₂.H₂O (1 mmol) with an aqueous EtOH solution (15 mL) of cur-gly (1 mmol) was refluxed for about 5 hour. Then the reaction mixture was concentrated to 10 mL on a boiling water bath and then cooled at room temperature¹⁰. The solid product formed was filtered, washed with EtOH and recrystallized from methanol. The proposed reaction pathway is shown in Scheme 2.



Scheme 1. Synthetic route of cur-gly



Scheme 2. Synthetic route of [M(II)-(cur-gly)H₂O]

Antimicrobial studies

The *In vitro* antimicrobial activity of cur-gly and [M(II)-(cur-gly)H₂O] in DMSO were studied against the bacterial species such as *P. aeruginosa*, *E. coli*, *Enterococcus*, *B. cereus* and *S. aureus* and fungal species like *C. albicans*, *C. parapsilosis* and *A. flavus* by Kirby–Bauer disk diffusion^{11,12} technique.

Kirby–Bauer method was used to shade the antimicrobial (bacterial & fungal) activity. Plates were incubated for 16 to 18 h at 35–37°C aerobically for fastidious organisms. The zones of diameters were reserved to the nearest mm with vernier calipers or a thin insincere mm scale values. The point of abrupt diminution of evolution, which in most circumstances resembles with the idea of complete embarrassment growth, was takes as the zone control.

DNA cleavage studies

Plasmid University of California, DNA models for the cur-gly and [M(II)-(cur-gly)H₂O] were evaluated by agar gel-electrophoresis technique based on procedure described in the literature. Test trials (100 mg/mL) were ready with DMSO solvent; about 5 µL of the plasmid was subjected to the test solution and incubated on behalf of 1.5 h, 37°C.

About 10 µL of sample/ plasmid (Bromophenol blue dye, 5: 1 molar ratio) was overloaded sensibly into the electrophoresis compartment wells alongside with a standard DNA indication following the Tris-acetate buffer (4.84 g, Trisbase, pH~8; 0.5 M, [CH₂N(CH₂CO₂H)₂]₂/1 L). Finally encumbered onto the agar gel (1% gel, 10 µg/mL, ethidium bromide). Gel covering the compound samples were linked to power supply of 100 V for about forty five min., PUC18-DNA possess in the UV-trans-illuminator existed experimental to govern the extent of DNA cleavage analysis.¹³

RESULTS AND DISCUSSION

Characterization of cur-gly and its [M(II)-(cur-gly)H₂O] complexes

The [M(II)-(cur-gly)H₂O] complexes, where M(II)=Co/Ni/Cu/Zn are stable at room temperature and soluble in some selected suitable organic solvents such as EtOH, CH₃CN, DMSO, CHCl₃ and DMF. The cur-gly and [M(II)-(cur-gly)H₂O] were accomplished in respectable yield and have the melting point ~200°C. The physico-chemical statistics of cur-gly and [M(II)-(cur-gly)H₂O] are formulated in Table 1.

Table 1: Physical parameters of cur-gly and [M(II)-(cur-gly)H₂O] complexes

Compounds	Molecular formula	Colour	Yield(%)	Molar conductance(Ω ⁻¹ cm ² mol ⁻¹)
cur-gly	C ₂₃ H ₂₃ O ₇ N	dark yellow	75	-
[Co(II)-(cur-gly)H ₂ O]	C ₂₃ H ₂₃ O ₈ NCo	brown	73	11
[Ni(II)-(cur-gly)H ₂ O]	C ₂₃ H ₂₃ O ₈ NNi	brown	80	8
[Cu(II)-(cur-gly)H ₂ O]	C ₂₃ H ₂₃ O ₈ NCu	dark brown	70	9
[Zn(II)-(cur-gly)H ₂ O]	C ₂₃ H ₂₃ O ₈ NZn	colourless	72	12

Elemental analysis

The analytical data of cur-gly and [M(II)-(cur-gly)H₂O] are tabulated in Table 2. The elemental analysis supports good agreement with the molecular

formula assigned to the cur-gly and [M(II)-(cur-gly)H₂O]. The calculated and experimental data matches well with the prepared compounds. Moreover, all metal complexes have 1:1 [M:L] stoichiometric ratio.

Table 2: Analytical data of cur-gly and [M(II)-(cur-gly)H₂O] complexes

Compounds	Found (Cald.) (%)			
	C	H	N	Metal
cur-gly	64.94 (64.96)	5.45 (5.42)	3.29 (3.21)	-
[Co(II)-(cur-gly)H ₂ O]	55.21 (55.21)	4.63 (4.23)	2.80 (2.69)	11.78 (11.32)
[Ni(II)-(cur-gly)H ₂ O]	55.24 (55.29)	4.64 (4.23)	2.80 (2.82)	11.74 (11.30)
[Cu(II)-(cur-gly)H ₂ O]	54.71 (54.67)	4.59 (4.27)	2.77 (2.74)	12.58 (12.00)
[Zn(II)-(cur-gly)H ₂ O]	54.52 (54.69)	4.57 (4.14)	2.76 (2.64)	12.90 (12.40)

Molar conductance

The physical molar conductance data of 0.001 mol solution of [M(II)-(cur-gly)H₂O] complexes in EtOH are provided in the Table 1. Low molar conductivity data [M(II)-(cur-gly)H₂O] complexes in the range of 8-12 Ω⁻¹cm²mol⁻¹ suggests their non-electrolytic behaviour for the prepared [M(II)-(cur-gly)H₂O] complexes.¹⁴

Infrared spectra

The IR spectrum provides respected evidence concerning the nature of the useful group coordinated to the metal atom. In cur-gly, the infrared spectrum showed a medium intensity band favoured at 1610 cm⁻¹ may be consigned to ν(C=N) stretching vibration.¹⁵ In the Mid IR spectrum cur-gly band is found at 3120 cm⁻¹ is ascribed to -NH₂ stretching vibration. The bands appeared at 1589 and 1483 cm⁻¹ of cur-gly corresponds to carboxylate asymmetric ν_{as}(COO⁻) and symmetric ν_{sy}(COO⁻)

stretching frequencies.^{16,17} In complexes, the ν(C=N) cm⁻¹ band was shifted to lower wavenumber 1610-1570 cm⁻¹ specifies the coordination of azomethine nitrogen atom with metal ion. In metal complexes the asymmetric ν_{sym}(COO⁻) and symmetric ν_{asym}(COO⁻) stretching bands shifted to lower wave frequency region designates from 1510 and 1402 cm⁻¹ respectively, which reveals the materialization of a bond between metal and carboxylate O atom. The IR spectra of all M(II)-(cur-gly)H₂O complexes containing hydration and or coordination water molecules display bands seen at 3487-3354 cm⁻¹ due to ν(O-H) vibration mode of the H₂O molecules. Therefore the fourth position would be occupied by water molecule in the metal complexes. IR spectra of the complexes also show new peaks at 474-450 cm⁻¹ and 560-568 cm⁻¹ region due to the formation of M-N, and M-O bond. Some important IR spectral assignments of cur-gly and its M(II)-(cur-gly)H₂O complexes is provided in Table 3.

Table 3: Important selected IR bands of cur-gly and [M(II)-(cur-gly)H₂O].

Compounds	IR assignments, wavenumber (cm ⁻¹)				
	ν(C=N)	ν(M-N)	ν(M-O)	νs(COO)	νas(COO)
cur-gly	1610	-	-	1483	1589
[Co(II)-(cur-gly)H ₂ O]	1570	450	560	1408	1523
[Ni(II)-(cur-gly)H ₂ O]	1573	451	568	1417	1513
[Cu(II)-(cur-gly)H ₂ O]	1587	474	562	1402	1510
[Zn(II)-(cur-gly)H ₂ O]	1590	459	563	1413	1519

PNMR spectra

PNMR spectra of cur-gly and its [Zn(II)-(cur-gly)H₂O] were studied in DMSO-d₆ solvent. PNMR spectra of (a) cur-gly and (b) [Zn(II)-(cur-gly)H₂O] are given in Fig. 1. PNMR spectra of cur-gly displays a peak at δ 12.34 ppm which may be attributable to the enolic -OH group of curcumin moiety. These PNMR spectral signals vanished in all complexes due to the deprotonation of OH group. The azomethine proton of the zinc complex

appeared δ 9.67 ppm indicating complexation of nitrogen atom of the azomethine with Zn(II) ion. The peaks at δ 6.05 ppm in Schiff base and the complex are assignable to two phenolic -OH group in the curcumin moiety^{18,19} which suggested that they are not involved in the coordination. The multi signals within the range δ 6.73–7.56 ppm are assigned to the aromatic protons of ring in metal(II) complexes δ 3.34-3.83 ppm for asymmetric proton while the CH₂ protons are shown in the δ 2.50 ppm.

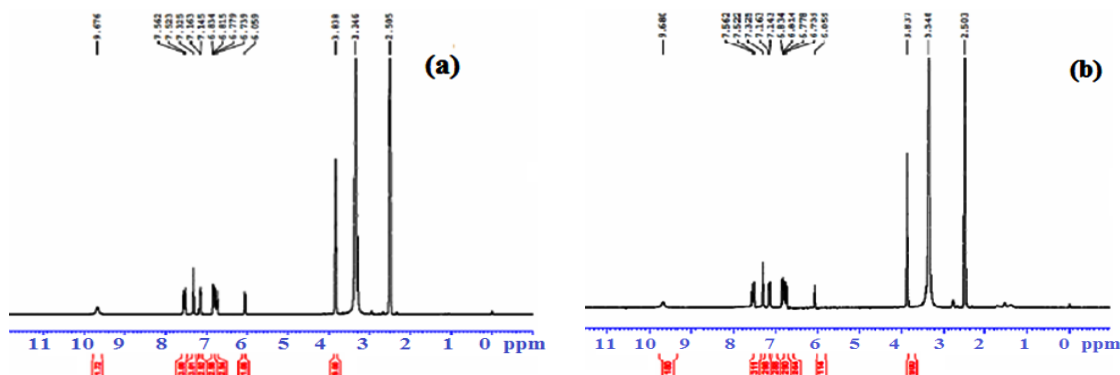


Fig. 1. PNMR spectra of (a) cur-gly and (b) [Zn(II)-(cur-gly)H₂O]

Electronic absorption spectral analysis

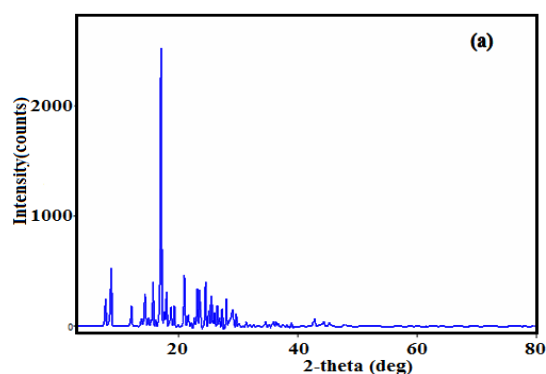
UV-Vis. spectrum of cur-gly exhibited a band centered at 330 nm, which is the characteristic transition of $n \rightarrow \pi^*$ agrees to azomethine moiety. This spectral electronic band may be shifted to higher absorption wavelength region demonstrating the status of coordination. The electronic spectra of [Co(II)-(cur-gly)H₂O] and [Ni(II)-(cur-gly)H₂O] displays a broad absorption spectral band regions ensued at 620 and 615 nm respectively may be attributed to ${}^4A_{2g} \rightarrow {}^4T_{1g}$ transition, propose tetrahedral geometrical environment for these complexes. The [Cu(II)-(cur-gly)H₂O] demonstrated a broad band concentrated around 670 nm corresponds to ${}^2B_{1g} \rightarrow {}^2A_{1g}$ transition proposes square planar geometrical behaviour for this complex. The [Zn(II)-(cur-gly)H₂O] is diamagnetic and favours four coordinated^{20,21} tetrahedral geometry would be desirable for this complex. Electronic spectral data [M(II)-(cur-gly)H₂O] are listed in Table 4.

Table 4: Electronic data of [M(II)-(cur-gly)H₂O]

Complexes	λ_{\max} (nm)	Transitions	Geometry
[Co(II)-(cur-gly)H ₂ O]	620	${}^4A_{2g} \rightarrow {}^4T_{1g}$	Tetrahedral
[Ni(II)-(cur-gly)H ₂ O]	615	${}^4A_{2g} \rightarrow {}^4T_{1g}$	Tetrahedral
[Cu(II)-(cur-gly)H ₂ O]	670	${}^2B_{1g} \rightarrow {}^2A_{1g}$	Square planar
[Zn(II)-(cur-gly)H ₂ O]	330	No d-d	Tetrahedral

Magnetic moment studies

The observed magnetic susceptibility value



of [Co-(cur-gly)H₂O] and [Ni-(cur-gly)H₂O] systems are observed at 4.0 and 3.9 B.M. respectively, corresponds to tetrahedral geometry for these complex systems.²² Normally square planar [Cu(II)-(cur-gly)H₂O] exhibit magnetic moments in the range 1.8-2.1 B.M. The observed magnetic moment value of [Cu(II)-(cur-gly)H₂O] is 1.9 B.M., which is the characteristic for square planar geometry of the [Cu(II)-(cur-gly)H₂O]. Magnetic measurements and visible spectral data provide sufficient support in assigning the geometry of the metal complexes.

Powder XRD

The PXRD patterns of cur-gly and its [Cu(II)-(cur-gly)H₂O] complex are measured in the range $2\theta = 0-80^\circ$, Fig. 2(a, b). By Scherer's equation, $d_{\text{XRD}} = 0.89\lambda/\beta\cos\theta$, the average grain size dXRD was calculated, 'd' characterizes the average grain size phases under examination. 'λ' indicate the wavelength of X-ray beam used. 'β' is the full-width half maxima of diffraction, and 'θ' is the Bragg's angle. From the XRD patterns, the average grain size for cur-gly and [Cu(II)-(cur-gly)H₂O] are 67 nm and 50 nm respectively for the above mentioned compounds. XRD patterns subsequently on complexation, the particle size decreases, indicate that the metal-ligand coordination.

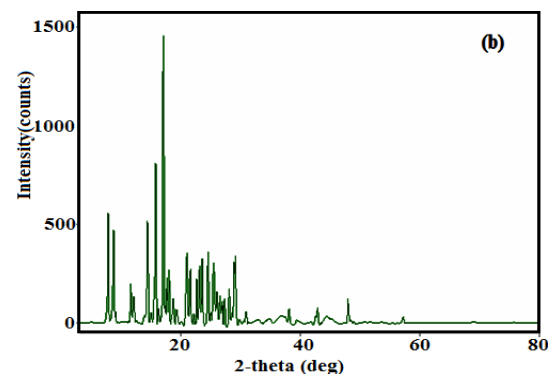


Fig. 2. Powder XRD pattern of (a) cur-gly and (b) [Cu(II)-(cur-gly)H₂O]

Biological Studies

Antimicrobial activity

Antibacterial activity of cur-gly and [M(II)-(cur-gly)H₂O] complexes have been assessed by measuring the zone of growth inhibition against *E. coli*, *P. aeruginosa*, *Enterococcus*, *B. cereus* and *S. aureus*. The antifungal activity was screened against *C. albicans*, *C. parapsilosis* and *A. flavus*.

Biological activities of cur-gly and its complexes are summarized in Table 5 and the results infer that Co and Cu metal complexes have more inhibition towards *S. aureus* and [Cu(II)-(cur-gly)H₂O] has added inhibition towards *E. coli*. Ni, Cu and Zn have more inhibition towards *C. parapsilosis*. Cur-gly and its [M(II)-(cur-gly)H₂O] were compared its shows that, the metal chelates are more effectively inhibits

the microorganism than their parent cur-gly against the same microorganism under indistinguishable experimental conditions. Complexation increases the polarity of metal ion by the partial distribution of its

positive charge with donor groups in complexes. This increases the lipophilic environment of the central metal atom which ultimately favours its permeation through the lipid level of the cell membrane.²³⁻²⁶

Table 5: Antibacterial activities of cur-gly and its [M(II)-(cur-gly)H₂O]

Microbial species	cur-gly	Zone of inhibition (mm)				Standard Amikacin	
		Co	Ni	Cu	Zn		
Bacterial	<i>P. aeruginosa</i>	8	10	11	9	9	24
	<i>S. aureus</i>	9	15	9	16	13	23
	<i>E. coli</i>	11	13	10	15	10	20
	<i>Enterococcus</i>	-	14	9	13	10	18
	<i>B. cereus</i>	-	12	10	12	11	28
	<i>C. albicans</i>	10	11	-	11	-	18
Fungal	<i>C. parapsilosis</i>	-	-	14	11	12	14
	<i>A. flavus</i>	-	-	-	-	-	8

DNA Cleavage

The pUC18 (Plasmid University of California) DNA using agarose gel electrophoresis experiment was conducted in the present investigation at 37°C using our synthesized cur-gly and its [M(II)-(cur-gly)H₂O] in existence of hydrogen peroxide as an oxidant. It is shown in Fig. 3, some complexes exhibit cleavage activity in presence of hydrogen peroxide at the low concentration levels. In Lane 1 shows the control DNA. Lane 2 does not display any substantial cleavage of pUC18 DNA even on longer exposure time interval.²⁷⁻³¹ From the figure observed result shows, the metal complexes of [Zn(II)-(cur-gly)H₂O] and [Ni(II)-(cur-gly)H₂O] effectively cleaved the supercoiled plasmid DNA pUC18.

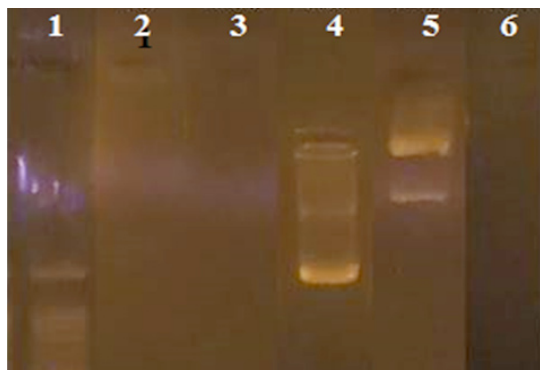


Fig. 3. DNA Cleavage of cur-gly and its [M(II)-(cur-gly)H₂O]

Lane 1 Marker DNA control

Lane 2 Plasmid DNA + cur-gly

Lane 3 Plasmid DNA + [Co(II)-(cur-gly)H₂O]

Lane 4 Plasmid DNA + [Zn(II)-(cur-gly)H₂O]

Lane 5 Plasmid DNA + [Cu(II)-(cur-gly)H₂O]

Lane 6 Plasmid DNA + [Ni(II)-(cur-gly)H₂O]

CONCLUSION

Metal(II) complexes of imine-linked cur-gly has been synthesized and characterized. The experimental and theoretical results shows that the cur-gly is complexed to metal ions via azomethine N atom, carboxylate O atom. Geometrical structures are found to be tetrahedral for [Co(II)-(cur-gly)H₂O], [Ni(II)-(cur-gly)H₂O] and [Zn(II)-(cur-gly)H₂O], square planar for [Cu(II)-(cur-gly)H₂O]. The crystalline nature and crystallite size have been obtained from PXRD analysis. The antimicrobial activity and DNA cleavage study revealed that all [M(II)-(cur-gly)H₂O] exhibit good activities as compared to cur-gly.

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Conflicts of Interest

The authors declare no conflict of interest.

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