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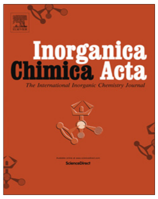

Research paper

Synthesis, characterization and biological studies on Ni^{II} and Cu^{II} complexes of two novel α,β-unsaturated 1,3-diketones related to curcuminoids

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ABSTRACT

Microwave assisted synthesis of two novel α,β-unsaturated 1,3-diketones, their mononuclear Ni^{II} and Cu^{II} complexes, characterization, results on DNA binding activities, short term *in vitro* and *in vivo* antitumor activities were reported. The ligands are structurally related to curcuminoids and exhibited significant antitumor activity against Dalton's lymphoma ascites cells. The ligands were found to be existing in their enolic form and metal complexes have 1:2 metal ligand stoichiometry evidenced by electronic, IR, ^{1}H NMR, ^{13}C NMR and FAB mass spectral data. The DNA binding properties of ligand and metal complexes were studied by absorption titrations and by viscosity measurements with calf thymus DNA. The intrinsic binding constants of copper(II) complexes are slightly higher than complexes of same metals reported in the literature. Interaction of copper(II) complexes were found to be higher than that of nickel(II) complexes and free ligands. The copper(II) complexes of the ligands were found to be more effective towards Dalton's lymphoma ascites cells in both *in vitro* and *in vivo* studies.

1. Introduction

Literature is extensive on the chemistry and application of 1,3-diketones and their metal chelates [1,2]. The application of certain lanthanide 1,3-diketonates as NMR shift reagents has become an extremely useful technique to organic chemists for structural elucidation. The yellow pigment curcumin present in the roots and shoots of herbaceous plant *Curcuma Longa* L (turmeric) and several other related curcuma species of the family *Zingiberaceae* is a typical 1,7-diaryl substituted α,β-unsaturated 1,3-diketone exerting a wide range of pharmacological activities including antioxidative, anti-inflammatory and anticancer activities [3–7]. However, clinical application of curcumin in antitumor therapy has been greatly limited by its rapid metabolism, low absorption and poor stability *in vivo* [8]. In order to enhance the biological properties and antitumor activity of curcumin, a large number of curcumin derivatives and analogues have been designed and synthesized through structural modifications such as variation of the aromatic rings and their substituents or replacing the heptadione bridge chain of curcumin by other linkers [9–11]. Metal chelation can cause drastic changes in the biological activity of many organic compounds and during recent years, metal complexes of biologically active ligands [12–14] have received much attention. In the present investigation, two novel α,β-unsaturated 1,3-diketones with a cyclopentane ring incorporated to enolizable β-diketone moiety synthesized from 2-acetylcyclopentanone and *o*-substituted benzaldehyde by exposing to microwave radiation and their $[ML_2]$ mononuclear Ni^{II} and Cu^{II} complexes were characterized by different physicochemical methods. Copper(II) complexes have attracted considerable attention as antitumor candidates in recent years because copper is an essential micronutrient that participates in several biological processes like mitochondrial respiratory reactions, cellular stress response, antioxidant, etc., [15,16] and hence it may be less toxic than non-essential metals like platinum [17]. Nickel(II) forms an essential component of several enzymes, viz. urease, carbon monoxide dehydrogenase and hydrogenase [18]. In view of the increasing interest in copper(II) and nickel(II) complexes [19–24], the free ligands and their complexes were analysed for their DNA binding properties with calf thymus DNA and screened for both *in vitro* and *in vivo* antitumor activity against Dalton's lymphoma ascites cells.

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2. Experimental

2.1. Materials and methods

2-Acetylcyclopentanone, tris(hydroxymethyl)aminomethane (Tris) and Calf thymus (CT) DNA were procured from Sigma Aldrich, USA. Solvents and other chemicals used were of analytical reagent grade procured from commercial sources and used without any further purification. Solvents used were purified by standard procedures [25].

Carbon and hydrogen were analyzed on an Elemental Vario EL CHN analyzer and metal contents of the complexes were determined using standard methods. The electronic spectra of the ligands and complexes and other UV–Vis measurements were recorded using model Jasco V – 550 UV visible spectrophotometer in $CHCl_3$ and DMSO. The IR spectra were recorded in the region 4000–250 cm^{-1} on a model Jasco FTIR-4100 Fourier transform infrared spectrophotometer in KBr discs. The ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a model Bruker Avance III, 400 MHz FT NMR spectrometer. Mass spectra were recorded on a model JEOL/SX-102 MS (FAB using argon and 3-nitrobenzyl alcohol as the matrix). The mass spectrometer was operated with accelerating voltage 10 kV in the positive ion mode. Molar conductivity measurements were recorded on an ELICO-CM-82 T conductivity bridge with a cell having cell constant 0.51 cm^{-1}.

Dalton's lymphoma ascites (DLA) cells were obtained from the Cancer Research Institute, Mumbai, India. DLA was maintained as ascites tumours in Swiss albino mice, purchased from Kerala Agricultural University, Thrissur, Kerala. They were fed with normal mouse chow (Lipton India) and water *ad libitum*.

2.2. Preparation of ligands

The conventional synthesis of curcumin derivative involves condensation between aromatic aldehyde and 2,4-pentadione – boric oxide complex in ethyl acetate medium [26]. Use of boron-based protection of the 1,3-diketone circumvents the Knoevenagel condensation at C-3 (active methylene group) and facilitates aldol condensations at C-1 and C-5 of 2,4-pentadione successively via the dienolate [27,28]. The procedure involves stirring of the reaction mixture for 3–4 h, giving a mixture of mono and bis condensation products from which the desired product is separated by column chromatography [26,29]. The microwave assisted synthesis exclusively gives the bis condensation product in a short time of 3 min. A typical procedure for the synthesis is given below.

2-Acetylcyclopentanone (20 mmol) was mixed with the boron oxide (20 mmol) in a 100 mL Erlenmeyer flask. The appropriate aromatic aldehyde (40 mmol), acetic acid (100 mg), and morpholine (100 mg) were then added. The reaction mixture was irradiated with the microwave at 70 W for 3 min. The flask was cooled to room temperature and then methanol (50 mL) was added. This mixture was then sonicated for 30–40 min. The fine powder so obtained was filtered and washed with cold methanol. The compounds were recrystallized from hot benzene to obtain chromatographically pure material.

2.2.1. HL^1

74.0%, M wt. 362 Da, m.p. 176 °C, Yellow solid, *Anal.* Calc. for $C_{23}H_{22}O_4$(%): Calc. C (76.22), H (6.12). Found: C (76.34), H (6.51); I.R. (KBr Pellets, cm^{-1}): 1592, ν(C=O) carbonyl, 1342, ν_{as}(C–C–C), 941 ν(CH=CH–)trans,; UV–Vis ($CHCl_3$, nm) 261 ($\pi \rightarrow \pi^*$), 446 ($n \rightarrow \pi^*$); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 14.33 (s, –OH enolic, 1H), 2.73–2.81 (s, ring, 4H), 6.67,6.98 (d, alkenyl,2H), 6.82–7.79 (m, aromatic, vinylic, 9H), δ 3.82 (s, methoxy,6H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm): δ 24.37,27.61 (aliphatic), 179.83,194.77 (carbonyl), 117.89–167.25 (aromatic); MS-EI: m/z = 362.19 $[M]^+$,345.24 $[M-OH]^+$, 213.16 $[M-C_9H_9O_2]^+$, 103.09 $[M-C_{15}H_{15}O_4]^+$,91.08 $[M-C_{16}H_{15}O_4]^+$,77.06 $[M-C_{17}H_{17}O_4]^+$.

2.2.2. HL^2

71.0%, M wt. 330 Da, m.p. 172 °C, Yellow solid, *Anal.* Calc. for $C_{23}H_{22}O_2$(%): Calc. C (83.60), H (6.71). Found: C (83.51), H (6.19); I.R. (KBr Pellets, cm^{-1}): 1587, ν(C=O) carbonyl, 1435, ν_{as}(C–C–C), 921 ν(CH=CH–)trans,; UV–Vis ($CHCl_3$, nm) 257 ($\pi \rightarrow \pi^*$), 434 ($n \rightarrow \pi^*$); ^1H NMR (400 MHz,$CDCl_3$, ppm): δ 14.17 (s, –OH enolic, 1H), 2.76–2.84 (s, ring, 4H), 6.79,6.94 (d, alkenyl,2H), 7.11–7.42 (m, aromatic, vinylic, 9H), δ 2.26 (s, methyl,6H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm): δ 23.47,28.79 (aliphatic), 187.45,195.31 (carbonyl), 121.72–147.63 (aromatic); MS-EI: m/z = 330.75 $[M]^+$, 313.70 $[M-OH]^+$, 211.46 $[M-C_8H_6OH]^+$,197.45 $[M-C_9H_8OH]^+$,171.35 $[M-C_{10}H_7O_2]^+$,105.31 $[M-C_{15}H_{13}O_2]^+$,91.26 $[M-C_{16}H_{15}O_2]^+$,77.24 $[M-C_{17}H_{17}O_2]^+$.

2.3. Preparation of Ni^{II} and Cu^{II} complexes

Metal complexes of the ligands were prepared by refluxing a methanolic solution of the metal(II) acetate (1 mmol) and the ligand (2 mmol) for ~2 h. The solution was concentrated to half of its volume and cooled to room temperature. The precipitated complexes were filtered, washed with methanol and recrystallized from hot methanol.

2.3.1. $[NiL^1_2]$

63.0%, M wt. 781.51 Da, m.p. 168 °C, Brown solid, *Anal.* Calc. for $C_{46}H_{42}O_8Ni$(%): Calc. C (70.70), H (5.42), Ni (7.51). Found C (70.21), H (5.23), Ni (7.43); I.R. (KBr Pellets, cm^{-1}): 1634,1524 ν(C=O) metal chelated carbonyl, 1432, ν(C=C)phenyl, 1272, ν(C=C)alkenyl, 1264, ν_{as}(C–C–C)chelate ring, 1141, ν_{as}(C–C–C)chelate ring 963 ν(CH=CH–)trans, 467, ν(M–O)chelate ring; UV–Vis ($CHCl_3$, nm) 254 ($\pi \rightarrow \pi^*$), 458 ($n \rightarrow \pi^*$); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 2.74–2.84 (s, ring, 8H), 6.71–6.84 (d, alkenyl, 4H), 7.21–7.64 (m, aromatic, vinylic, 18H), δ 3.78(s, methoxy,12H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm): δ 25.61–31.94 (aliphatic), 162.64,190.38 (carbonyl), 116.64–159.68 (aromatic).

2.3.2. $[NiL^2_2]$

64.0%, M wt. 717.52 Da, m.p. 172 °C, Brown solid, *Anal.* Calc. for $C_{46}H_{42}O_4Ni$(%): Calc. C (77.00), H (5.90), Ni (8.18). Found: C (77.24), H (5.68), Ni (8.35); I.R. (KBr Pellets, cm^{-1}): 1647,1538 ν(C=O) metal chelated carbonyl, 1476, ν(C=C)phenyl, 1316, ν(C=C)alkenyl, 1226, ν_{as}(C–C–C)chelate ring, 1138, ν_{as}(C–C–C)chelate ring 958 ν(CH=CH–)trans, 458, ν(M–O)chelate ring; UV–Vis ($CHCl_3$, nm) 268 ($\pi \rightarrow \pi^*$), 476 ($n \rightarrow \pi^*$); ^1H NMR (400 MHz,$CDCl_3$, ppm): δ 2.81–2.89 (s, ring, 8H), 6.28–6.74 (d, alkenyl, 4H), 7.34–7.85 (m, aromatic, vinylic, 18H), δ 2.25 (s, methyl, 12H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm): δ 26.38–32.68 (aliphatic), 163.84–194.76 (carbonyl), 114.38–159.73 (aromatic).

2.3.3. $[CuL^1_2]$

67.0%, M wt. 786.37 Da, m.p. 152 °C, Brown solid, *Anal.* Calc. for $C_{46}H_{42}O_8Cu$(%): Calc. C (70.26), H (5.38), Cu (8.08). Found: C (70.14), H (5.27), Cu (8.16); I.R. (KBr Pellets, cm^{-1}): 1602,1551 ν (C=O) metal chelated carbonyl, 1454, ν(C=C)phenyl, 1445, ν (C=C)alkenyl, 1284, ν_{as}(C–C–C)chelate ring, 1123, ν_{as}(C–C–C)chelate ring 934 ν(CH=CH–)trans, 507, ν(M–O)chelate ring; UV–Vis ($CHCl_3$, nm) 251 ($\pi \rightarrow \pi^*$), 448 ($n \rightarrow \pi^*$); MS-EI: m/z = 787 $[M+2]^+$, 785 $[M]^+$, 423 $[M-C_{23}H_{22}O_4]^+$, 361 $[M-C_{23}H_{21}O_4Cu]^+$,238 $[M-C_{35}H_{31}O_6]^+$,224 $[M-C_{36}H_{33}O_6]^+$.