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Pharmacological and spectral studies of synthetic biomimetic copper complexes derived from 3-hydroxyflavone derivatives as anti-inflammatory agents

K. Nagashri ^a, J. Joseph ^{a,*}, C. Justin Dhanaraj ^b

^a Department of Chemistry, Noorul Islam Centre for Higher Education (Noorul Islam University), Kumaracoil 629 180, India

^b Department of Chemistry, Anna University Tirunelveli, University VOC College of Engineering, Thoothukudi, India

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Abstract Novel biomimetic ligands were synthesized by the condensation of 3-hydroxyflavone, 2-aminophenol(L¹)/2-aminobenzoic acid (L²) and-aminothiazole (L³). Their Cu(II) complexes have also been synthesized and characterized on the basis of ¹H NMR, IR, UV–Vis spectra, elemental analyses, molar conductivity, ESR, electrochemical behaviour and thermal analyses. The antimicrobial activities (MIC values) of the ligands, copper complexes and standard drugs have been evaluated using the serial dilution technique against the bacterial species *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris* and *Pseudomonas aeruginosa* and fungal species *Aspergillus niger*, *Rhizopus stolonifer*, *Aspergillus flavus*, *Rhizoctonia bataicola* and *Candida albicans*. The anti-inflammatory and SOD activities of the investigated compounds are also promising and allow the selection of a lead compound for further biological studies.

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1. Introduction

Flavones occupy a special place in the realm of natural and synthetic organic chemistry owing to their useful biological activities such as anti-oxidant (Rice-Evans, 2001), Anxiolytic (De Almeida et al., 2009), anti-cancer (Liu et al., 1992), analgesic (Shin et al., 1999), and anti-microbial (Sohel et al., 2006). During the past few years various methods have been reported for the synthesis of flavones (Diana, 2000; Kumar and Perumal, 2007; Ballesteros et al., 1995).

The copper is an essential micronutrient for feeding and a cofactor of several enzymes involved in oxidative metabolism like β -hydroxylases, quercetinase, ceruloplasmine, cytochrome oxidase, monoaminoxidase, superoxydismutase, ascorbic acid oxidase and tyrosinase (Berdanier et al., 1999; Brill et al., 1964 and Frieden et al., 1965). The catalytical role of these en-

* Corresponding author. Tel.: +91 09629474150; fax: +91 4562230414.

E-mail address: chem_joseph@yahoo.co.in (J. Joseph).

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zymes is a two-step process, i.e., the reduction of Cu^{2+} ion to Cu^+ and the fixation of molecular oxygen (Halfen et al., 1996). The copper(II) complexes of multidentate Schiff base ligands have played a vital role in the development of coordination chemistry (Chiari et al., 2001; Swearingen and West, 2001).

A range of monocarboxylic acids are known to have a variety of pharmacological effects. Salicylic acid and its derivatives, for example, have been shown to possess anti-inflammatory and antitumour activity (Sorenson, 1976). Upon coordination to a suitable metal centre, the biologically active carboxylic acids often become more effective and desirable drugs (Sorenson, 1989). The carboxylate group is an important class of ligands in inorganic and bioinorganic chemistry, metal complexes containing monocarboxylic acids are well known, and the publication of many structurally characterised examples of this class of compound has demonstrated its versatility as an inner-sphere ligand (Mehrotra and Bohra, 1983).

As part of our continuous investigations, we report here the synthesis, structural aspects and biological studies of copper(II) complexes of the above said Schiff base ligands. The anti-inflammatory activity of the ligands and their complexes has also been studied.

2. Experimental

Analytical grade chemicals commercially available purchased from BDH, Aldrich, Fischer etc were used for synthesis and solvents were purified by standard methods.

Micro analytical data and FAB Mass spectra of the compounds were recorded at the Regional Sophisticated Instrumentation Center, Central Drug Research Institute (RSIC, CDRI), Lucknow. The amount of copper present in the copper complexes was estimated using AAS. The NMR spectra of the ligands were recorded using TMS as internal standard. Chemical shifts (δ) are expressed in units of parts per million relative to TMS. The FAB mass spectrum of the ligands and their complexes were recorded on a JEOL SX 102/DA-6000 mass spectrometer/data system using argon/xenon (6 kV, 10 mA) as the FAB gas. The accelerating voltage was 10 kV and the spectra were recorded at room temperature using m-nitrobenzylalcohol (NBA) as the matrix. Molar conductance of the copper complexes was measured in DMSO solution using a coronation digital conductivity metre. The IR spectra of the ligands and their copper complexes were recorded on a Perkin-Elmer 783 spectrophotometer in 4000–200 cm^{-1} range using KBr disc. Electronic spectra were recorded with a Systronics 2201 Double beam UV-Vis, spectrophotometer in the 200–1100 nm region. The magnetic susceptibility values were calculated using the relation $\mu_{\text{eff}} = 2.83 (\chi_{\text{m}} \cdot T)$. The diamagnetic corrections were made by Pascal's constant and $\text{Hg}[\text{Co}(\text{SCN})_4]$ was used as a calibrant. The ESR spectra of the copper complexes were recorded at 300 and 77 K on a Varian E112 X-band spectrometer. Cyclic voltammetric measurements were performed using a glassy carbon working electrode, Pt wire auxiliary electrode and an Ag/AgCl reference electrode. Tetra-butylammoniumperchlorate (TBAP) was used as the supporting electrolyte. All solutions were purged with N_2 for 30 min prior to each set of experiments. The computer controlled X-ray diffractometer system JEOL JDX 8030 was used to record powder data for the copper complexes, at the Central Electrochemical Research Institute, Karaikudi.

2.1. Preparation of Ligand (L^1-L^3)

Equimolar amount of 3-hydroxyflavone and o-aminophenol (L^1)/o-aminobenzoic acid (L^2)/o-aminothiazole (L^3) was dissolved in ethanol (40 mL). Acetic acid (1.0 mL) was added to this solution. The solution was stirred for 3 h and the precipitate was formed. The precipitate was filtered and washed with water and ethanol.

L^1 : Yield: 60%. Anal. Calcd for $\text{C}_{21}\text{H}_{15}\text{NO}_3$: C, 76.58; H, 4.59; N, 4.25. Found: C, 76.64; H, 4.62; N, 4.28. FAB mass spectrometry (FAB-MS), m/z 330 $[\text{M} + 1]$. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 6.6–7.8 (13H, m, Ar-H) and 11.2 and 10.8 (2H, s, O–H, D_2O exchangeable, 3-hydroxyflavone and o-aminophenol moieties). $^{13}\text{C-NMR}$ (400 MHz, CDCl_3 , ppm): 150.8 (C-2), 140.6 (C-3), 153.8 (C-4), 112.8(C-5), 145.6 (C-6), 124.4 (C-7), 126.9 (C-8), 156.6 (C-9), 118.8 (C-10), 133.6 (C-1'), 124.3 (C-2', 6'), 126.5 (C-3', 5'), 126.4 (C-4'), 130.6 (C-1''), 115.2 (C-2''), 120.6 (C-3''), 119.2 (C-4''), 126.2 (C-5'') and 140.8 (C-6'').

L^2 : Yield: 65%. Anal. Calcd for $\text{C}_{22}\text{H}_{15}\text{NO}_4$: C, 73.94; H, 4.23; N, 3.91. Found: C, 73.98; H, 4.26; N, 3.98. FAB mass spectrometry (FAB-MS), m/z 358 $[\text{M} + 1]$. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 6.7–7.9 (12H, m, Ar-H), 11.6 and 10.4 (2H, $^{13}\text{C-NMR}$ (400 MHz, CDCl_3 , ppm): 149.4 (C-2), 110.2 (C-3), 154.5 (C=N), 115.6 (C-5), 146.4 (C-6), 122.8 (C-7), 126.4 (C-8), 152.6 (C-9), 119.9 (C-10), 132.5 (C-1'), 125.4 (C-2', 6'), 127.6 (C-3', 5'), 126.5 (C-4'), 148.6 (C-1''), 113.4 (C-2''), 132.6 (C-3''), 116.5 (C-4''), 128.9 (C-5''), 140.8 (C-6'') and 168.2 (COOH).

L^3 : Yield: 62%. Anal. Calcd for $\text{C}_{18}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$: C, 67.49; H, 3.78; N, 8.75. Found: C, 67.42; H, 3.72; N, 8.69. Fast atom bombardment mass spectrometry (FAB-MS), m/z 322 $[\text{M} + 1]$. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 5.9–7.9 (13H, m, Ar-H), 12.9 and 10.8 (2H, s, S–H & O–H, D_2O exchangeable). $^{13}\text{C-NMR}$ (400 MHz, CDCl_3): 149.4 (C-2), 110.2 (C-3), 154.5 (C=N), 115.6 (C-5), 147.4 (C-6), 122.6 (C-7), 126.9 (C-8), 154.6 (C-9), 121.9 (C-10), 132.5 (C-1'), 125.4 (C-2', 6'), 127.6 (C-3', 5'), 126.5 (C-4'), 158.6 (C-11), 103.4 (C-12) and 148.9 (C-13).

2.1.1. Preparation of copper complexes of Ligands (L^1-L^3)

The ligand (s) (0.05 mM) and copper acetate (0.05 mM) were dissolved in acetone (20 mL). Under stirring, triethylamine (0.075 mM) was then dropped to the mixture with caution. After stirring for 4 h at room temperature, the precipitate was separated, purified by washing several times with acetone and dried in vacuum.

Complex of L^1 : Yield: 74%. Anal. Calcd for $\text{CuC}_{21}\text{H}_{17}\text{NO}_4$: C, 61.36; H, 4.17; N, 3.41, Cu, 15.47. Found: C, 61.31; H, 4.15; N, 3.36; Cu, 15.43. FAB mass spectrometry (FAB-MS), m/z 411 $[\text{M} + 1]$. μ_{eff} (BM) = 1.92; Λ_{m} ($\text{mho cm}^2 \text{ mol}^{-1}$) = 24.

Complex of L^2 : Yield: 79%. Anal. Calcd for $\text{CuC}_{22}\text{H}_{17}\text{NO}_5$: C, 60.18; H, 3.91; N, 3.19, Cu, 14.49. Found: C, 60.14; H, 3.86; N, 3.15; Cu, 14.43. FAB mass spectrometry (FAB-MS), m/z $[\text{M} + 1]$. μ_{eff} (BM) = 2.06; Λ_{m} ($\text{mho cm}^2 \text{ mol}^{-1}$) = 29.

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