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Antitubercular and fluorescence studies of copper(II) complexes with quinolone family member, ciprofloxacin

G.J. Kharadi*

Shri R. R. Lalan College, Department of Chemistry, Bhuj, Gujarat, India

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ABSTRACT

Four new mixed-ligand complexes of Cu(II) with ciprofloxacin (Cip) and uninegative bidentate ligands have been synthesized and characterized. The structure of mixed-ligand complexes was investigated using spectroscopic method, physicochemical and elemental analyses. The fluorescence spectra of complexes show red shift, which may be due to the chelation by the ligands to the metal ion. It enhances ligand ability to accept electrons and decreases the electron transition energy. Antimycobacterial screening of ligand and its copper compound against *Mycobacterium tuberculosis* shows clear enhancement in the antitubercular activity upon copper complexation.

1. Introduction

The development of metal complexes as artificial nucleases is an area of burgeoning interest. The metal complexes as pharmaceuticals have gained access over traditional organic of gene expression and tools of molecular biology [1]. Derivatives of compounds composed of 3-carboxy-4-oxo-1,4-dihydroquinoline (i.e., 4-quinolones) are active against a wide range of gram-positive and gram-negative organisms. The first member of the quinoline family kept forward for clinical practice was nalidixic acid; it is used for the treatment of urinary tract infections. Major increase in the potency was obtained by addition of fluorine atom on position 6 of the quinoline ring, addition of piperazinyl group on position 7 to enhance permeability and potency [2]. Metal coordination to biologically active molecules can be used as a strategy to enhance their activity and overcome resistance. For instance, metal complexes of thiosemicarbazones can be more active than the free ligand, or they can be employed as a vehicle for activation of the ligand as the cytotoxic agent [3–5]. Saha et al. [6] have shown that the complex of Cu(II) and ciprofloxacin presents a significant enhancement in antitubercular activity. Presumably, the formation of the complex facilitates the intracellular transport of the drug. Copper complexes with fused coumarin derivative and fluroquinolones have not been reported yet, to the best of our knowledge. In this context, the present work describes the synthesis of copper(II) complexes having as ligand (fused coumarin derivative + ciprofloxacin). For the characterization of the compounds the following spectroscopic and analytical techniques were employed: IR and NMR spectroscopy, and thermogravimetric and elemental analyses.

Previously, Kharadi et al., have synthesized a series of fused coumarin derivatives and their transition complexes [7–11]. In order to have further investigation, the coordination abilities and complexation behaviors of coumarin based ligands, we extended the study to the synthesis of new benzo [c] coumarin derivatives and their transition metal complexes. Present work describes antimycobacterial and fluorescence activity of new Cu(II) complexes.

2. Experimental

2.1. Materials

All the chemicals used were of analytical grade. Ciprofloxacin hydrochloride was purchased from Bayer AG (Wyppertal, Germany). Luria broth was purchased from Hi-media Laboratories Pvt. Ltd., India. Agarose was purchased from Sisco Research Lab., India. Acetic acid and EDTA were purchased from SD Fine Chemicals, India. The organic solvents were purified by standard methods [12].

Abbreviations: Cipro, ciprofloxacin; A^n, A^1, A^2, A^3, A^4; A^1, 7-hydroxy-10,11-dihydroindeno[5,4-c]chromen-6(9H)-one; A^2, 7-hydroxy-4-methoxy-10,11-dihydroindeno[5,4-c]chromen-6(9H)-one; A^3, 2-bromo-7-hydroxy-10,11-dihydroindeno[5,4-c]chromen-6(9H)-one; A^4, 5-hydroxy-8,9-dihydrobenzo[f]indeno[5,4-c]chromen-4(7H)-one; D. D. water, double distilled water; Cu(II)-1, $[Cu(A^1)(Cipro)(H_2O)_2]\cdot 3H_2O$; Cu(II)-2, $[Cu(A^2)(Cipro)(H_2O)_2]\cdot 5H_2O$; Cu(II)-3, $[Cu(A^3)(Cipro)(H_2O)_2]\cdot H_2O$; Cu(II)-4, $[Cu(A^4)(Cipro)(H_2O)_2]\cdot 2H_2O$; B.M., Bohr magneton.

* Tel.: +91 02832250117.
E-mail addresses: gaurangkharadi@yahoo.com, drkharadi84@gmail.com

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2.2. Instrumentation

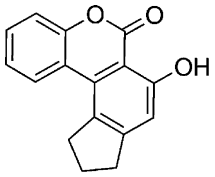
Elemental analyses (C, H, N) were analyzed with the PerkinElmer, USA 2400-II CHN analyzer. FT-IR spectra (4000–400 cm^{-1}) were recorded on Nicolet-400D spectrophotometer using KBr pellets. ^1H NMR spectra were recorded on a model Advance 400 Bruker FT-NMR instrument and DMSO-d_6 used as a solvent. The magnetic moments were obtained by the Gouy's method using mercury tetrathiocyanato cobaltate (II) as a calibrant ($g = 16.44 \times 10^{-6}$ c.g.s. units at 20 °C). Diamagnetic corrections were made using Pascal's constant. The fluorescence behaviors of ligands and their Cu(II) complexes were studied using a Shimadzu RF-1501 Fluorescence Spectrophotometer with Xe arc lamp as the light source at room temperature. The slit width for excitation and emission was 10 nm, and the scan speed was 1200 nm/min. The FAB mass spectrum of the complex was recorded at SAIF, CDRI, Lucknow with JEOL SX-102/DA-6000 mass spectrometer. A simultaneous TG/DTG had been obtained by a model 5000/2960 SDT, TA Instruments, U.S.A. The experiments were performed in N_2 atmosphere at a heating rate of 10 °C min^{-1} in the temperature range 50–800 °C, using Al_2O_3 crucible. The sample sizes are ranged in mass from 4.5 to 10 mg. The DSC was recorded using DSC 2920, TA Instrument, U.S.A. The DSC curves were obtained at a heating rate of 10 °C min^{-1} in N_2 atmosphere over the temperature range of 50–400 °C, using aluminum crucible.

2.3. Preparation of ligands

The uninegative bidentate ligands were synthesized by condensation of various coumarinoyl methyl pyridinium salt (0.004 mol) [13], with cyclopentanone (0.004 mol), in the presence of sodium acetate (0.020 mol) and acetic acid (40 mL).

2.3.1. 7-Hydroxy-10,11-dihydroindeno[5,4-c]chromen-6(9H) -one (A^1)

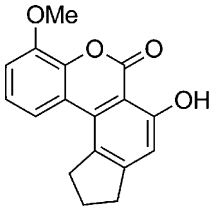
The reaction mixture of 3-coumarinoyl methyl pyridinium salt, cyclopentanone and sodium acetate in acetic acid was stirred for 10 min and then refluxed for 8 h. It was then allowed to cool to room temperature, and poured into cold water (75 mL), the crude solid was extracted with chloroform (3× 30 mL). The combined chloroform extract was washed with water (3× 20 mL). It was dried over anhydrous sodium sulfate. The removal of chloroform under reduced pressure gave a solid product. It was recrystallized from chloroform–hexane to give white crystalline products. M.p. 230–232 °C. Yield 60%. Elemental analysis found (%): C, 72.24; H, 4.98; calculated for $C_{17}H_{14}O_4$(%): C, 72.33; H, 5.00. FT-IR (KBr, cm^{-1}): 3420 υ(O–H), 1605 υ(C=C), 3035 υ(C–H), 2945 υ(C–H) cyclopentane ring, 1675 υ(C=O) α-lactone coumarin. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) = 11.76 (1H, s, –OH proton); 7.74 (1H, d, C_{11} proton); 7.25–7.29 (1H, m, C_{10} proton); 7.05 (1H, d, C_9 proton); 7.01 (1H, s, C_4 proton); 4.00 (3H, s, $–OCH_3$); 3.34 (2H, t, C_3 proton); 3.02 (2H, t, C_1 proton); 2.21 (2H, m, C_2 proton). ^{13}C NMR: 166.00 (CO of coumarin); 161.98 (C_5); 157.00 (C); 150.60 (C); 130.73 (C); 129.84 (C); 129.71 (CH); 126.55 (CH); 124.65 (CH); 119.89 (C); 117.49 (CH); 112.80 (CH); 104.30 (C); 34.66 (C_3); 33.47 (C_1); 25.12 (C_2).



(A^1)

2.3.2. 7-Hydroxy-4-methoxy-10,11-dihydroindeno[5,4-c] chromen-6(9H)-one (A^2)

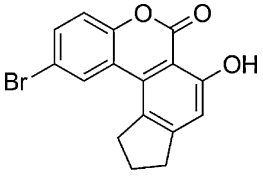
A^2 was synthesized by same method used for A^1 by using 8-methoxy-3-coumarinoyl methyl pyridinium instead of 3-coumarinoyl methyl pyridinium. M.p. 230–232 °C. Yield 60%. Elemental analysis found (%): C, 72.24; H, 4.98; calculated for $C_{17}H_{14}O_4$(%): C, 72.33; H, 5.00. FT-IR (KBr, cm^{-1}): 3420 υ(O–H), 1605 υ(C–C), 3035 υ(C–H), 2945 υ(C–H) cyclohexane ring, 1675 υ(C=O) α-lactone coumarin, 1260 υ(asym. C–O–C), 1050 υ(sym. C–O–C). ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) = 11.76 (1H, s, –OH proton); 7.74 (1H, d, C_{11} proton); 7.25–7.29 (1H, m, C_{10} proton); 7.05 (1H, d, C_9 proton); 7.01 (1H, s, C_4 proton); 4.00 (3H, s, $–OCH_3$); 3.34 (2H, t, C_3 proton); 3.02 (2H, t, C_1 proton); 2.21 (2H, m, C_2 proton). ^{13}C NMR: 166.01 (CO of coumarin), 159.65 (C_6), 150.94 (C), 149.48 (C), 132.86 (C), 131.00 (CH), 129.61 (C), 128.43 (C), 128.22 (CH), 127.13 (CH), 126.04 (CH), 125.32 (CH), 116.69 (CH), 116.60 (CH), 113.96 (C), 106.58 (C), 30.37 (C_2), 29.88 (C_3), 23.99 (C_4), 21.31 (C_1). ^{13}C NMR (400 MHz, DMSO-d_6): δ (ppm) = 165.58 (CO of coumarin); 162.00 (C_5); 157.02 (C); 147.84 (C); 140.48 (C); 131.07 (C); 130.13 (C); 124.14 (CH); 120.73 (C); 118.00 (CH); 112.89 (CH); 111.74 (CH); 104.41 (C); 56.24 (OCH_3); 34.77 (C_3); 33.55 (C_1); 25.19 (C_2).



(A^2)

2.3.3. 2-Bromo-7-hydroxy-10,11-dihydroindeno[5,4-c]chromen-6(9H)-one (A^3)

A^3 was synthesized by same method used for A^1 by using 6-bromo-3-coumarinoyl methyl pyridinium instead of 3-coumarinoyl methyl pyridinium. M.p. 193–195 °C. Yield 63%. Elemental analysis found (%): C, 57.99; H, 3.31; calculated for $C_{16}H_{11}BrO_3$(%): C, 58.03; H, 3.35. FT-IR (KBr, cm^{-1}): 3410 υ(O–H), 1595 υ(C=C), 3040 υ(C–H), 2950 υ(C–H) aliphatic CH_2, 1680 υ(C=O) α-lactone coumarin. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) = 11.60 (1H, s, –OH proton); 8.23 (1H, d, C_{11} proton); 7.56 (1H, d, C_9 proton); 7.24 (1H, d, C_8 proton); 7.03 (1H, s, C_4 proton); 3.31 (2H, t, C_3 proton); 3.03 (2H, t, C_1 proton); 2.24 (2H, m, C_2 proton).^{13}C NMR: 165.86 (CO of coumarin); 165.58 (CO of coumarin); 162.00 (C_5); 157.02 (C); 147.84 (C); 140.48 (C); 131.07 (C); 130.13 (C); 124.14 (CH); 120.73 (C); 118.00 (CH); 112.89 (CH); 111.74 (CH); 104.41 (C); 34.77 (C_3); 33.55 (C_1); 25.19 (C_2).



(A^3)

2.3.4. 5-Hydroxy-8,9-dihydrobenzo[f]indeno[5,4-c] chromen-4(7H)-one (A^4)

A^4 was synthesized by same method used for A^1 by using 5,6-benzo-3-coumarinoyl methyl pyridinium salt instead of 3-coumarinoyl methyl pyridinium. M.p. 140–142 °C. Yield 64%. Elemental analysis found (%): C, 79.41; H, 4.64; calculated for $C_{20}H_{14}O_3$(%): C, 79.46; H, 4.67. FT-IR (KBr, cm^{-1}): 3400 υ(O–H),