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Synthesis, Crystal Structure and Antitumor Activity of Mixed Ligand Coordination Compound of Copper with Norfloxacin and 1, 10-Phen, [Cu (NFLX)(phen)(H_2O)] $NO_3 \cdot 3H_2O$

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Abstract: The mixed ligand coordination compound of copper with norfloxacin (NFLX) and 1, 10-phen has been synthesized and characterized by means of X-ray single crystal diffraction. The structure features of the coordination compound are described. Antibacterial activities of the coordination compound have been tested against different microorganisms. The antitumor activities of the coordination compound on leukemia HL-60 cell line and liver cancer BEL-7402 cell line have been measured, respectively. The results indicated that the coordination compound has strong inhibitory effect on HL-60 and BEL-7402 cell lines.

Keywords: Synthesis, crystal structure, antitumor activity, norfloxacin, coordination compound of copper.

Fluoroquinolones are the widely used antibiotics for treating of numerous diseases[1-4]. Norfloxacin(1-ethyl-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4–dihydroquinoline-3-carboxylic acid, NFLX) is a typical member of this family and its metal coordination compounds have also received much more attention[5-11]. Apart from the synthesis and physicochemical properties of the coordination compounds, their antibacterial properties were also tested[7-13], but there was scare report on antitumor properties of the quinolones metal coordination compounds[14]. Here we report the synthesis of mixed ligand coordination compound of copper with NFLX and 1,10-phen and its X-ray crystal structure, antibacterial and antitumor properties.

Synthesis and Structure Determination

1 mmol $Cu(NO_3)_2 \cdot 3H_2O$ was dissolved in 10 mL of distilled water and 1 mmol 1,10-phen (phen) dissolved in 5mL of ethanol ,which was added to the $Cu(NO_3)_2$ solution. To this mixture was added a solution prepared by dissolving 1 mmol of NFLX in 100 mL of water containing 1mmol NaOH; its pH was adjusted to 7.0～8.0 with HCl. By slow evaporation of the resulting blue solution at room temperature, blue crystals were formed after a period of 1 month and have been submitted to X-ray structure determination.

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All measurements were made on a Bruker Smart CCD X-ray diffractometer with graphic monochromated MoK α (λ=0.71073Å). A total of 6682 independent reflections were collected in the range of 1.59°< θ <28.30° by φ and ω scans technique at 293.5(2) K. The structure was solved by direct methods using SHELXS-97 and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. All calculations were performed using the Bruker SMART crystallographic software.

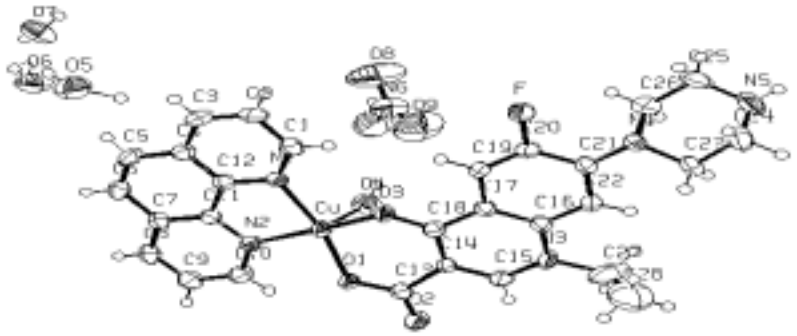
Results and Discussion

An ORTEP diagram of the complex is shown in **Figure 1**. The chemical formula of the complex is $C_{28}H_{33}CuFN_6O_{10}$. The crystal is triclinic, space group P-1, with a=10.5635(8)Å, b= 11.6081(10) Å, c= 13.0896(10) Å; α =78.814(2)°, β= 84.936(2)°, γ=71.933(2)°, V=1496.3(2) Å3, Dc=1.545 g/cm^3, F(000)=722, and Z=2. Final R indices [I>2σ (I)] R1=0.0559, and ω R2 = 0.0841.

The copper atom is five-coordinate with square-based pyramidal geometry and involves two nitrogen atoms from phen, two oxygen atoms from NFLX and one oxygen atom from H_2O occupying the fifth site. There is an aromatic ring stacking effect between NFLX ring and phen ring from another molecule with a distance of about 3.4～3.6 Å. The observed stacking in these molecules are indicative of a π～π interaction at a distance that is similar with those encountered in the base stacking of DNA[15].

The antibacterial activities of both drug ligand and the coordination compound have been assayed against gram-positive and gram-negative bacteria by doubling dilutions method, the coordination compound shows the same minimal inhibitory concentration (MIC) as the corresponding ligand against *S. Aureus*, *M. Lutens*, *E. Coli* and *P. Aeruginosa* bacteria. The antitumor activities of the drug ligand and coordination compound on leukemia HL-60 cell line and liver cancer BEL-7402 cell line have been

Figure 1 The ORTEP plot of [Cu (NFLX)(phen)(H_2O)] $NO_3 \bullet 3H_2O$



measured by using MTT (Methyl- thiazol- tetrozolium) and SRB (Sulphurhodamin B) assay methods, respectively. When the concentration of the coordination compound and drug ligand is 10^{-7}mol • L^{-1}, respectively, inhibitory activities of the coordination compound against liver cancer BEL-7402 cell line is 95.8%, and that of against leukemia HL-60 cell line is 98.4%, and that of drug ligand against HL-60 cell line is 5.1% and against BEL-7402 is 0%. The results indicated that the coordination compound has strong inhibitory effect on HL-60 and BEL-7402 cell lines.

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