Inorganic Chemistry Communications 23 (2012) 78–84

Contents lists available at SciVerse ScienceDirect

Inorganic Chemistry Communications

journal homepage: www.elsevier.com/locate/inoche

Synthesis, DNA binding and antiproliferative activity of ternary copper complexes of moxifloxacin and gatifloxacin against lung cancer cells

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ARTICLE INFO

Article history:
Received 25 March 2012
Accepted 12 June 2012
Available online 19 June 2012

Keywords:
Copper-complex
Moxifloxacin
Gatifloxacin
DNA binding
Apoptosis

ABSTRACT

Mixed ligand Cu(II) complexes of third generation fluoroquinolone antibacterial agents moxifloxacin (MFL) and gatifloxacin (GFL) have been synthesized and characterized spectroscopically. The complexes have been found to bind DNA by intercalative mode and the DNA binding constants K_b and K_{sv} have been determined by absorption measurements and florescence quenching experiments respectively. The anti-proliferative and apoptosis inducing activity of the mixed ligand copper complexes against human lung carcinoma cells(A-549) was determined adopting MTT-assay, other specific staining techniques and DNA ladder. All the complexes have been shown to be cytotoxic towards A549 lung cancer cells. The complexes have been shown to bring about apoptosis of the cancerous cells.

Quinolone-based drugs are well-known DNA damaging agents acting against bacteria through disrupting bacterial DNA gyrase and topoisomerase IV enzymes which are functional analogues of eukaryotic topoisomerase II [1]. These drugs exert their topoisomerase II inhibitory activity by intercalation inducing scission of double stranded DNA along with G-2 arrest and induction of apoptosis. Intercalation with double stranded DNA manifests through high cytotoxicity towards interacting cells [2]. In recent years, newer fluoroquinolones have been developed with significantly improved efficacy against Gram-positive organisms, causing lung infections, particularly against pneumococci. These fluoroquinolones are active against bacteria causing atypical pneumonia, against penicillin sensitive as well as resistant pneumococci and against β-lactamase producing and non-producing *Haemophilius influenza* [3]. Certain key advantages of fluoroquinolone therapy include facile penetration into inflammatory fluids and attainment of higher concentration in the cell than serum levels. Concentration of fluoroquinolones in the lung reaches around 4-fold higher than serum levels [4].

Moxifloxacin is a member of fluoroquinolones family, which has been studied for its antibacterial activity, especially against respiratory diseases. Kraseman and group [5] have shown that the compound is highly effective in treatment against pneumonia infection. In addition, it was found to inhibit bacterial growth in clinical isolates of penicillin susceptible as well as resistant pnemococci. [6]. Murata and co-workers have studied another synthetic quinolone derivative, viz., HSR-903, which has been shown to selectively accumulate in the lung tissues in rat models *in vivo*. A comparative study which included levofloxacin, ciprofloxacin, and lomefloxacin also has shown that HSR-903 accumulates more efficiently in the lung tissue [7]. Emami and co-workers have synthesized a series of functionalized *N*-(2 oxyiminoethyl) piperazinyl quinolones, which exhibit antiproliferative effects against variety of cell lines including A549 lung cancer [8]. Due to their ability to inhibit DNA repair activity through blocking of topoisomerase II [9–13] fluoroquinolones have also been examined in colon cancer [10], bladder cancer [14] and leukemia [12] respectively.

Metal complexation plays an important role in the anticancer activities of quinolone compounds and the topic has been reviewed extensively by Turel [15]. Padhye et al. have described a neutral dimeric copper complex of sparfloxacin, which exhibited considerable anti-proliferative activity against hormone independent BT20 breast cancer cells [16]. Li et al. have examined the anti-proliferative activity of the ternary copper complexes of ofloxacin and levofloxacin with 2,2′-bipyridyl/1, 10-phenanthroline as ancillary ligands against HL-60 (human acute myeloid leukemia) cell lines wherein those with 1,10-phenanthroline as ancillary ligands were found to be more active than the free ligands [17].

Gatifloxacin (GFL) and moxifloxacin (MFL) are the third generation fluoroquinolones with a broad spectrum of antibacterial activity including activity against penicillin resistant *Streptococcus pneumonia*. Recently Patel and co-workers have studied Cu(II) and Pt(II) complexes of gatifloxacin for its DNA binding activity along with *in vitro* antibacterial studies [18,19]. In the present work we have

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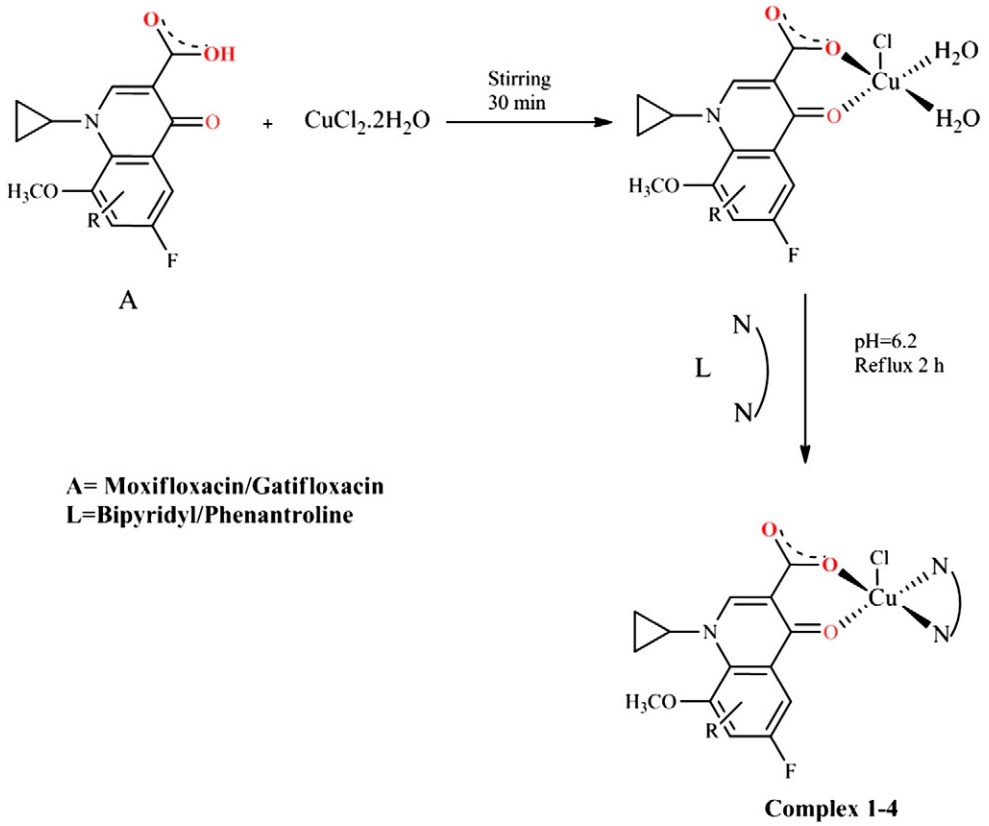
doi:10.1016/j.inoche.2012.06.013



Scheme 1. Schematic representation of synthesis of complexes 1–4.

examined the DNA-binding activity of ternary copper(II) complexes of moxifloxacin and gatifloxacin along with their antiproliferative activities against A-549 lung cancer cell line.

The compounds were synthesized as shown in Scheme 1. A methanolic solution of fluoroquinolone (GFL/MFL) (1.5 mmol) in presence of sod. methoxide (1.5 mmol) was added to a methanolic solution of $CuCl_2.2H_2O$(1.5 mmol) and stirred for 30 min, followed by addition of a methanolic solution of the neutral bidentate ligand (phenanthroline/bipyridyl) (1.5 mmol). The pH was adjusted to 6.2 using dilute solution of sod. methoxide. The resulting solution was refluxed for 2 h on a steam bath, followed by concentrating it to half of its volume. The microcrystalline product of green color obtained was washed with ether and dried. The complexes were characterized by physico-chemical and spectroscopic techniques and the general composition of the complexes was derived as $[Cu(A)(L)Cl].5H_2O$, where A = moxifloxacin/gatifloxacin and L = nitrogen donor ancillary ligands phenanthroline/bipyridyl, from the data obtained (Table S1) since no single crystals of the complexes suitable for the X-ray determination could be isolated. The proposed structures of the complexes are given in Fig. S1 (Supplementary data).

The ESI–MS spectra of complexes 1–4 showed molecular ion peaks at m/z 656.4 [M + 1], 680.4 [M + 1], 653.13 [M+] and 629.13 [M+] that are equivalent to their molecular weights. The m/z values of all complexes confirm the stoichiometry of the complexes as $[Cu(A)(L)Cl].5H_2O$ which was in good agreement with that obtained from microanalytical data (Table S1). The ESI–MS spectra of complexes are given in Fig. S2.

The infrared spectra of synthesized complexes 1–4 exhibited major changes compared to the free ligands in the fingerprint region. The strong bands at 1720 cm^{-1} and 1625 cm^{-1} in the spectrum of gatifloxacin and moxifloxacin are assigned to pyridone carbonyl and carboxyl stretches respectively. On complexation with copper ions, the carboxylate stretching frequency has been replaced with two

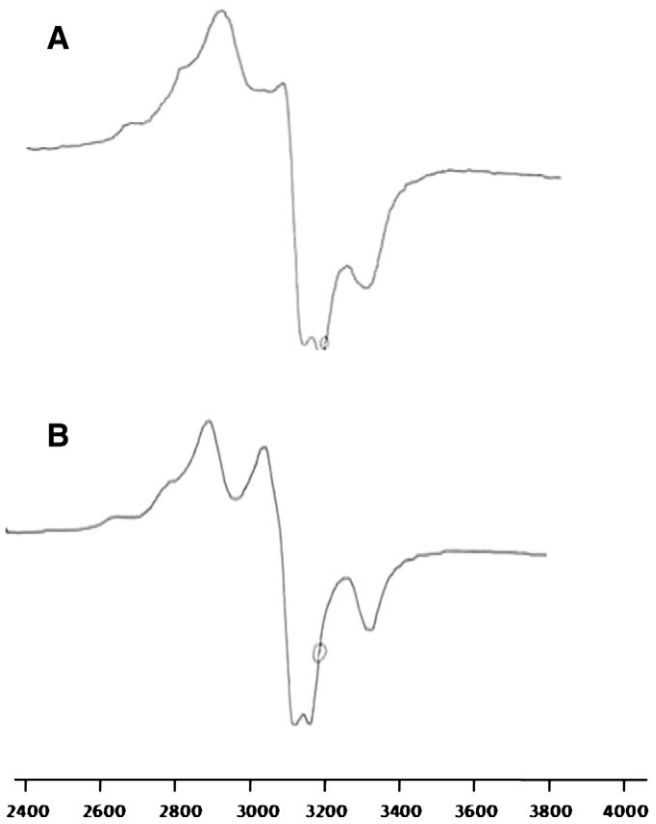


Fig. 1. EPR spectra of the complexes (A) $[Cu(MFL)(By)].5H_2O$ and (B) $[Cu(GFL)(Phe)].5H_2O$ EPR conditions: Temperature, 10 K; microwave power, 5.0 mW; Modulation amplitude, 1 G; microwave frequency, 9.1 GHz.