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Neutral dimeric copper–sparfloxacin conjugate having butterfly motif with antiproliferative effects against hormone independent BT20 breast cancer cell line

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Abstract

A neutral dimeric copper conjugate of sparfloxacin and its phenanthroline adduct show considerable enhancement in their antiproliferative activities against hormone independent BT20 breast cancer cells.
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Keywords: X-ray crystal structure; Sparfloxacin; Phenanthroline adduct; Copper dimer; Breast cancer

Quinolones represent relatively recently discovered class of antibacterial agents with considerable therapeutic potential and a large number of quinolone compounds have been synthesized [1]. These compounds target the bacterial DNA gyrase enzymes, viz. topoisomerase II in gram-negative bacteria and DNA topoisomerase IV in gram-positive bacteria, respectively [2]. Sparfloxacin is the first marketed aminodifluoroquinolone compound that possesses higher activity against gram-positive species like *S. pneumoniae* as well as the tubercular bacteria *M. tuberculosis* and a vast majority of multidrug drug resistant (MDR) clinical isolates of it [3].

While cytotoxicity represents a serious disadvantage while employing quinolones as antibacterial agents, it becomes a desirable feature when developing them as antiproliferative agents [4]. Thus, use of quinolone compounds as adjuvant therapeutic agents for treating tumors of the bladder and urinary tract is a logical step since the urinary concentration of these quinolones after oral administration are found to be high [5] and they are found to be excreted unchanged. Amongst the fluoroquinolone antibiotics, ciprofloxacin and norfloxacin show growth inhibitory activites against human transitional cell carcinoma of the bladder cell lines, viz. TCCSUP, T24, and J82 [6], MBT-2, HTB9 as well as human leukemia and osteoblast-like MG-63 human osteosarcoma cells.

Earlier work has indicated the inhibitory potential of ciprofloxacin in case of bladder tumour cells and has established the induction of cell cycle arrest at the S/G_2–M checkpoint. It also shows a down regulation of antiapoptotic protein Bcl-2 resulting in alteration of Bax: Bcl-2 ratio in the hormone resistant PC-3 prostate cancer cell line leading to apoptosis [7]. Enoxacin has been shown to possess promising antiproliferative activity against MCF-7 breast cancer cell line by inducing cell cycle arrest at G_2/M phase, thus inhibiting cell growth [8]. Additional target for the quinolone action is thought to be the telomerase enzyme,

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which is activated in a vast majority of tumor cells [9]. Due to adjacent placement of pyridone carbonyl and the carboxylate function, these compounds are also capable of complexing a large number of metal ions [10] and this intrinsic property has been thought to contribute to their biological activity [11]. Most of the studies have involved copper complexes of ciprofloxacin where metal conjugation has been found to result in enhancement of the therapeutic activity of the parent ligands [12]. Similarly the copper conjugate of norfloxacin is shown to have strong inhibitory effects on leukemia HL-60 and liver cancer BEL-7402 cell lines, respectively.

Sparfloxacin **1** (sflx) (Fig. 1) is the first aminodifluoroquinolone currently available in Japan and United States for clinical use. The C-8 fluoro substitution is thought to increase its absorption and plasma half-life [13] and thus contributes to its enhanced activity. Its favorable pharmacokinetic characteristics and bioavailability are encouraging features for its increased use in clinics. Additionally its oral absorption is not affected by ingestion of food, including milk and meals with a high fat content, which makes it an attractive therapeutic agent even in treating tumors.

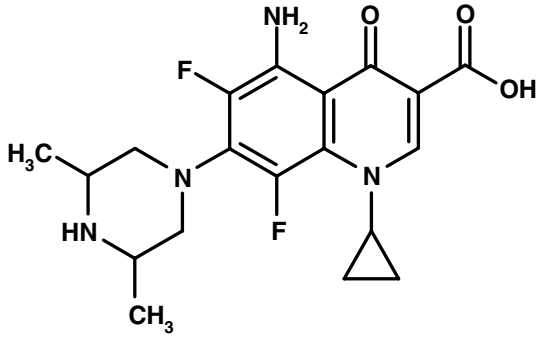

Fig. 1. Chemical structure of sparfloxacin **1** (sflx).

DNA topoisomerase IIα (topoIIα) is a marker of cell proliferation in normal as well as cancerous tissues [14]. It has also been assessed in various solid tumours, e.g. breast cancer, testicular teratoma and transitional cell carcinomas [15]. Several studies indicate that the sensitivity to the topoIIα-inhibitors is directly dependent on the expression level of topoIIα in cancer cells [16]. Recently high expression of topoIIα in breast cancer has been correlated with hormone independent pathway [17]. Fluoroquinolones are known to inhibit topoIIα in mammalian cells. Thus in the present communication we describe synthesis, characterization (as supplementary information) and antiproliferative activity against hormone independent breast cancer cell line BT20 of copper-sflx complex **(2),** with appended ancillary ligands, viz. 2,2'bipyridine **(3)**, 1,10-phenanthroline **(4)** and 4,5-diazafluoren-9-one **(5)**.

The single crystal X-ray structural characterization of the copper complex of **1** reveals it to be a dimeric, neutral molecule having a butterfly like structural scaffold. The dimeric copper complex **(2)** consists of a neutral $[Cu_2(sflx)_2]$ moiety in which both the copper centres have an almost perfect square pyramidal geometry and each is coordinated to four oxygen atoms of two sparfloxacin ligands and the nitrogen atom from the amino group of the adjacent sparfloxacin molecule at the apical position (Fig. 2) [18].

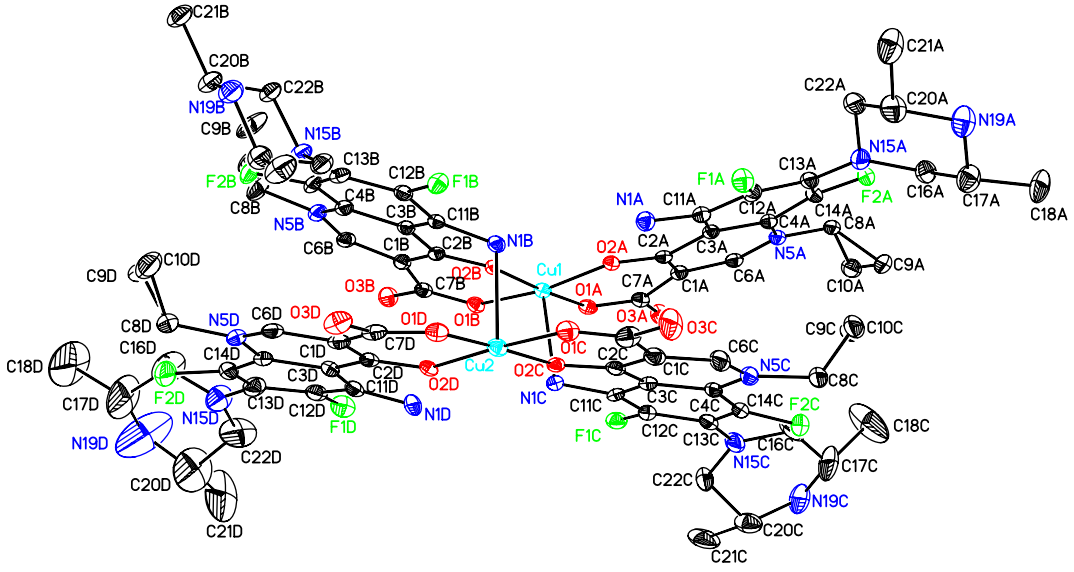

Fig. 2. Single crystal X-ray structure of **2**. Selected bond lengths (Å) and angles (°): Cu(1)–O(1A) −1.904(3), Cu(1)–O(1B) −1.925(3), Cu(1)–O(2A) −1.939(3), Cu(1)–O(2B) −1.928(3), Cu(1)–N(1C) 2.463(4), Cu(2)–O(1C) −1.906(3), Cu(2)–O(1D) −1.932(3), Cu(2)–O(2C) 1.948(3), Cu(2)–O(2D) −1.947(3), Cu(2)–N(1B) −2.518(4); O(1A)–Cu(1)–O(1B) −87.07(14), O(1A)–Cu(1)–O(2B) −5.40(13), O(1B)–Cu(1)–O(2B) −91.59(13), O(1A)–Cu(1)–O(2A) −92.33(13), O(1B)–Cu(1)–O(2A) −170.63(13), O(2B)–Cu(1)–O(2A) −88.27(12), O(1A)–Cu(1)–N(1C) −96.18(13), O(1B)–Cu(1)–N(1C) −100.60(13), O(2B)–Cu(1)–N(1C) −88.40(12), O(2A)–Cu(1)–N(1C) −88.77(13).

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