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Synthesis of novel ciprofloxacin analogues and evaluation of their anti-proliferative effect on human cancer cell lines

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ABSTRACT

A series of twenty two novel 1-cyclopropyl-6-fluoro-4-oxo-7-(4-substituted piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid analogues have been synthesized, characterized (^{1}H NMR, ^{13}C NMR and LCMS) and evaluated for their inhibitory activity on the proliferation of human caucasian acute lymphoblastic leukemia cells (CCRF-CEM), breast adenocarcinoma cells (MDA-MB-468) and human colon carcinoma cells (HCT-116). Among all the synthesized ciprofloxacin analogues **3t** at 50 μM showed comparable potency to doxorubicin (10 μM) in all three cell lines and **3j** inhibited proliferation of MDA-MB-468 up to 35% selectively over other two cell lines.

Cancer is a leading cause of death worldwide. It is a group of diseases characterized by uncontrolled growth. Cancer is the second cause of death in the US.[1] Ciprofloxacin (CP) is one of the broad-spectrum fluoroquinolone (FQ) antibiotics with low side effects.[2] CP exhibited antiproliferative and apoptotic activities in several cancer cell lines such as hormone resistant prostate cancer (HRPC) cell line (PC-3),[3] transitional cell carcinoma cell lines (MBT-2 and T24),[4] colon carcinoma cell lines (CC-531,SW-403 and HT-29),[5] human lymphoidal cell lines (Jurkat),[6] non-small-cell lung cancer cell line (NCI-H460 and A549),[7,8] ovarian cancer cell line (CHO AA8),[9] murine glioma cell line (GL26),[10] bladder cell line (HTB9). CP was also found to exhibit cell cycle arrest at the S/G_2-M checkpoints.[11]

Along with CP, other FQ derivatives like ofloxacin, levofloxacin, enoxacin and fleroxacin were shown to inhibit the growth of transitional cell and bladder carcinoma cell lines.[2] CP enhanced the antiproliferative effect of 5-fluorouracil,[12] used for treatment of colon cancer.[13] FQs inhibit the activity of mammalian DNA topoisomerases I, II and DNA polymerase enzymes involved in supercoiling, transcription, replication and chromosomal separation of prokaryotic DNA.[5,14]

Many reports indicate, antitumor efficacy of FQs can be augmented by increasing the lipophilicity of compounds.[2,15,16] Introducing substituents at C-7 position of camptothecin improved the lipophilicity and this led to the discovery of gimatecan, which is currently in phase II clinical trials.[17] In *bis*-quinolinium compounds, lipophilicity of the substituent enhanced their antiproliferative activity against HT-29 colon cancer cell line.[18] Structure of FQ derivatives as anticancer agents is depicted in Figure 1.[19–21]

CP showed antiproliferative and apoptotic activities on prostate cancer cell lines (PC3) but not on non-tumorigenic prostate epithelial cells (MLC8891).[22] CP can impede the acute and chronic prostate inflammation which is responsible for prostate cancer development.[23] Fruitful anticancer results of lipophilic derivatives of CP have attracted us to investigate new lipophilic derivatives of CP as antitumor agents. Hence, we impelled our research work and synthesized new FQ derivatives as antitumor agents. In the current study, we synthesized 7-(substituted piperazin-1-yl) derivatives of CP. Firstly, 7-(4-(2-chloroacetyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**2**) was synthesized by coupling CP with chloroacetyl chloride as reported earlier[2] and then various substituted piperazines were reacted with **2** to enhance the lipophilicity (Scheme 1).

Acylation of **CP**, **1** with chloroacetyl chloride in CH_2Cl_2 yielded compound **2** in 70% after purification.[2] The series of 1-cyclopropyl-6-fluoro-4-oxo-7-(4-substituted piperazin-1-yl)-1,4-dihydro quinoline-3-carboxylic acid derivatives of **CP** were prepared by

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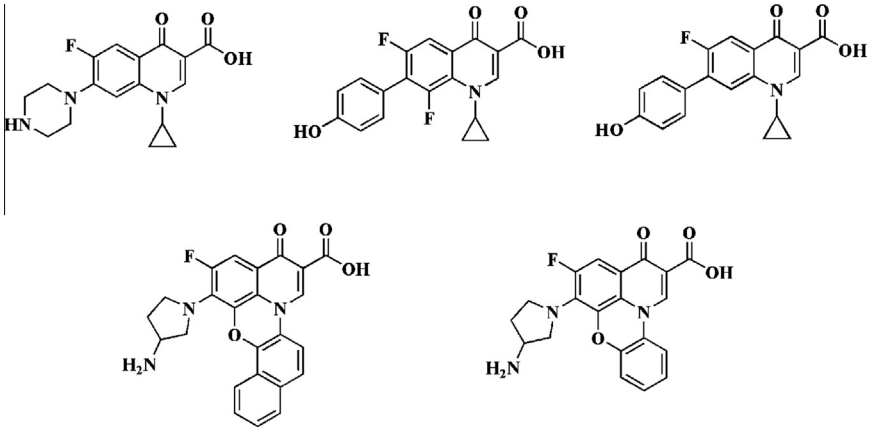
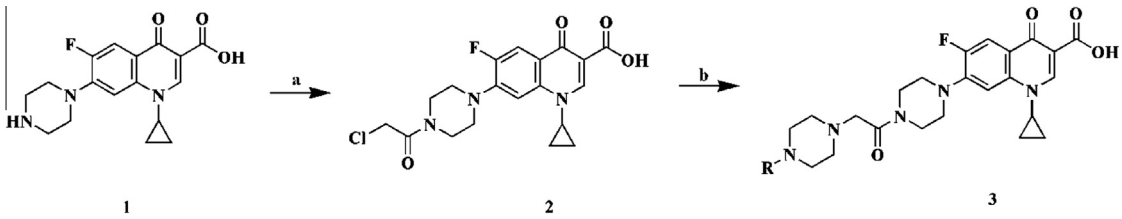
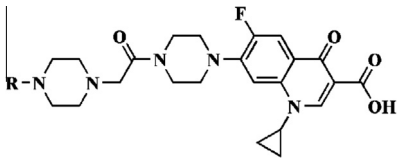


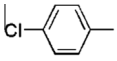
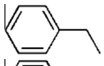
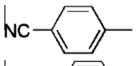
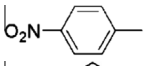
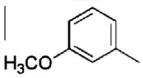
Figure 1. Structures of some fluoroquinolone anticancer agents.



Scheme 1. Reagents and conditions: (a) Et_3N, $ClCH_2COCl$, CH_2Cl_2, 0 °C to rt; (b) Et_3N, KI, substituted piperazines, 125 °C.

Table 1
Synthesized compounds: structure, yield, and lipophilicity (**3a–v**)



Entry	R	Yield (%)	*c*Log *P*[a]
3a		57	−1.20
3b		68	2.54
3c		88	−0.81
3d		89	1.95
3e		88	1.66
3f		95	2.54
3g		68	1.49
3h		92	1.77
3i		87	1.61

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