Bull. Chem. Soc. Ethiop. **2008**, 22(3), 459-464. ISSN 1011-3924
Printed in Ethiopia

SHORT COMMUNICATION

SYNTHESES AND SPECTRAL STUDIES OF NOVEL CIPROFLOXACIN DERIVATIVES

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(Received December 31, 2007; revised June 17, 2008)

ABSTRACT. Reaction of 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (ciprofloxacin) with thiazole/benzothiazole diazonium chloride afforded piperazine substituted ciprofloxacin derivative. The acid part of these derivatives was further condensed with various β-diketones to get 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(thiazol-2-yldiazenyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid derivatives (**5a-e**) and 7-(4-(benzo[d]thiazol-2-yldiazenyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid derivatives (**5f-j**). Structures of these compounds were established on the basis of spectral studies.

KEY WORDS: Ciprofloxacin, Thiazole, Benzothiazole, β-Diketone

INTRODUCTION

Ciprofloxacin (**1**) [1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydro quinoline-3-carboxylic acid] is a fluoroquinolone antibacterial agent, which is widely used in human and veterinary medicines [1]. It is one of the drugs used in the treatment of infections due to *Bacillus anthracis* (i.e., anthrax infections) [2]. Because of this, study of fluoroquinolones is generating immense interest among scientists all over the world. There are studies on the modified pharmacological and toxicological properties of these drugs in the form of novel derivatives [3-6].

Quinolones consist of a bicyclic ring structure (Figure 1) in which there is a substitution at position N-1, with various moieties. Most of the current agents have a carboxyl group at position 3, a keto group at position 4, a fluorine atom at position 6 and a nitrogen heterocycle moiety at the C-7 position [7]. The quinolones exert their antibacterial action by interfering with the function of two bacterial type-II topoisomerase enzymes, DNA gyrase and topoisomerase IV [8]. Structure-activity relationship (SAR) studies and the known drug target have facilitated the development of new more potent quinolones with broader spectrum activity, better pharmacokinetics and good tolerability. The SARs of quinolones have been the subject of extensive review [9-11]. In general, β-keto carboxylic acid moiety is required for hydrogen bonding interactions with DNA bases in the single-stranded regions of double helix of DNA created by the action of the enzyme, and therefore it is essential (Figure 1).

The substituent at N-1 and C-8 positions should be relatively small and lipophilic to enhance self-association [12-13]. Groups at C-5 and C-6 have also been optimized in which an amino and fluoro substituent, respectively, at C-5 and C-6 appear to be the best. The nature of substituent at C-7 position has a great impact on potency, spectrum, solubility and pharmacokinetics. Almost all quinolones have nitrogen heterocycles linked to the C-7 position of quinolone ring through the heterocyclic nitrogen [12-13]. Extensively investigated substituent at C-7 are piperazin-1-yl and its 4-substituted derivatives. Ciprofoxacin (**1**), norfoxacin (**2**) and enoxacin (**3**) are characterized by having a piperazine moiety at C- 7, which represents a site amenable to significant modification (Figure 2).

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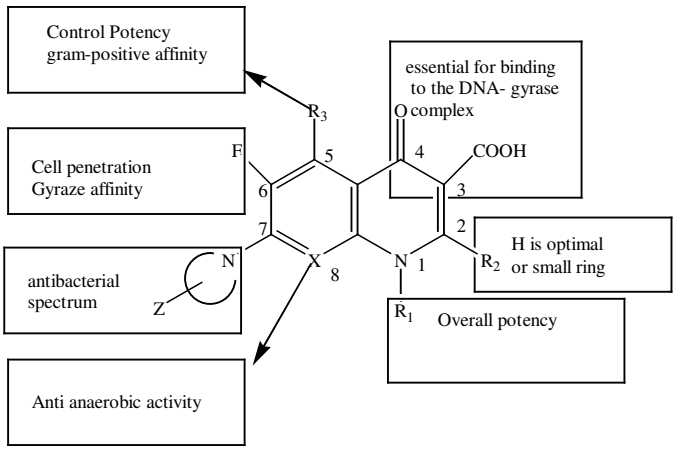
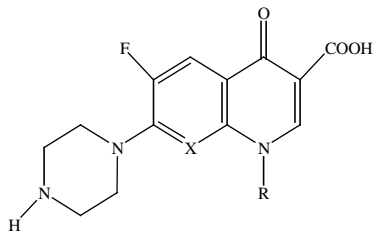


R_1 = Et, cyclopropyle, halo substituted aromatic ring, etc; R_2 = H, -SMe, Or R_1 and R_2 may join to form a ring; R_3 = H, -NH_2, -OMe; X = N, CH, CF, C-OMe, or X and R_1 may join to form a ring; Z = attached group to cycloalkylamine ring

Figure 1. Structural features and common pharmacophor of quinolone antibacterial.



(**1**) Ciprofloxacin; R = cyclopropyle, X = CH, (**2**) Norfloxacin; R = ethyl, X = CH, (**3**) Enoxacin; R = ethyl, X = N

Figure 2. Structure of Ouinolone.

Thiazole moiety has diverse utility as antimicrobial [14], antioxidant [15], CNS agent [16], anti-methicillin-resistant *Staphylococcus aureus* (MRSA) activity and reduced toxicity [17]. The thiazole derivatives act as in vitro anti-HIV activity and antiretroviral agents [18]. Thiazole moiety containing compounds showed the activities against methicillin-resistant *Staphylococcus aureus* (MRSA) [17].

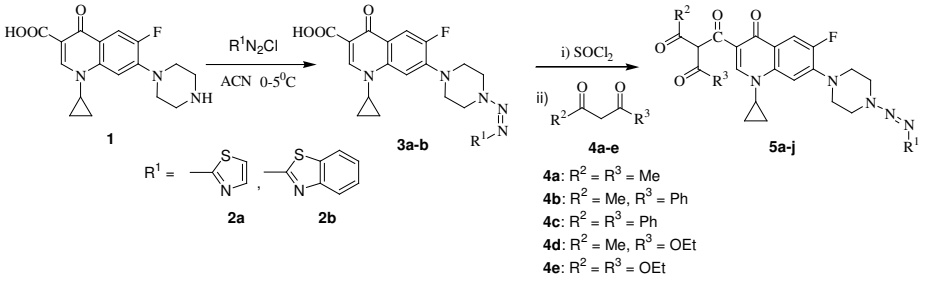
β-Dicarbonyl derivative constitute an important class of compounds, which serve as a precursor [19] of various pharmaceutically useful heterocyclic compounds, and complexes [20, 21]. β-Dicarbonyl compounds are very important chemotherapeutic agents [22]. During recent years a number of quinolones with substitution on piperazine ring at C-7 position of the basic structure of quinolones were synthesized and evaluated for antibacterial activities [23-24]. Inspired by the previous research and in continuation of our research [25], in this paper we report the synthesis and spectral studies of a series of β-dicarbonyl derivatives of 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

EXPERIMENTAL

Microanalysis for C, H, and N was performed using Perkin-Elmer analyzer 2400. Infra red (IR) spectra were recorded using KBr disk on a Nicolet-Megna FT-IR spectrometer. Melting points were determined using open capillary tube method and are uncorrected. ^{1}H NMR spectra were recorded at model DRX-300 at 300.13 MHz, using TMS as an internal standard. Purity of the compounds was tested by pre-coated Silica Gel 60 F254 TLC plates from E. Merck.

*General method for diazo substitution (**3a-b**).* A mixture of ciprofloxacin (**1**) (1.65 g, 5.0 mmol) and sodium bicarbonate (1.0 g, excess) in acetonitrile (10 mL) was stirred at 50 °C for 2 h. Reaction mixture was cooled to 0 °C and thiazole/benzothiazole diazonium chloride (5.0 mmol) was added. The mixture was stirred for 5 h at 0-5 °C. Volatiles were removed under reduced pressure and the residue was partitioned between chloroform/water. The organic layer was separated, washed with water and dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography to afford (**3a-b**).

*General method for preparation of 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(thiazol-2-yldiazenyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid derivatives (**5a-j**).* Compound (**3a-b**) was dissolved in thionyl chloride and refluxed for 4 h to get acid chloride derivative (**3a-b**). Excess thionyl chloride was removed under reduced pressure and sodium salt of β-diketones (prepared using NaOMe and β-diketone (**4a-d**) under N_2 atmosphere) was added and stirred overnight at RT. Reaction mixture was quenched with ice-cold water and stirred for 30 min. The precipitate was filtered and washed with acetone to get (**5a-j**), which were further purified through column chromatography in chloroform-acetone 50:50 mixture.



Scheme I

RESULTS AND DISCUSSION

A series of 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(thiazol-2-yldiazenyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid derivatives (**5a-e**) and 7-(4-(benzo[d]thiazol-2-yldiazenyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid derivatives (**5f-j**) were synthesized in moderate yields using the synthetic route outlined in Scheme I. Structures of the synthesized compounds were established on the basis of IR, ^{1}H NMR, spectral data and elemental analyses (Table 1 and 2). Ciprofloxacin was treated with thiazole/benzothiazole diazonium chloride in presence of base to give piperazine substituted ciprofloxacin derivatives (**3a-b**). The acid part of these derivatives was converted to acid chloride using thionyl chloride, which further condensed with various diketone (**4a-d**) to get (**5a-j**).

Table 1. Substitution pattern and physical properties for novel ciprofloxacin derivatives (**3a-b, 5a-j**).

Cpd. No.	Substitution		M.P. (°C)	Yield (%)	Molecular formula	Elemental data: calculated (found) %		
	R^2	R^3				C	H	N
3a	--	--	145	57	$C_{20}H_{19}FN_6O_3S$	54.29 (54.20)	4.33 (4.30)	18.99 (18.95)
3b	--	--	164	55	$C_{24}H_{21}FN_6O_3S$	58.53 (58.50)	4.30 (4.30)	17.06 (17.00)
5a	CH_3	CH_3	184	61	$C_{25}H_{25}FN_6O_4S$	57.24 (57.20)	4.80 (4.80)	16.02 (16.00)
5b	CH_3	C_6H_5	178	62	$C_{30}H_{27}FN_6O_4S$	61.42 (61.40)	4.64 (4.60)	14.33 (14.30)
5c	C_6H_5	C_6H_5	203	59	$C_{35}H_{29}FN_6O_4S$	64.80 (64.80)	4.51 (4.50)	12.96 (12.95)
5d	CH_3	OC_2H_5	224	53	$C_{26}H_{27}FN_6O_5S$	56.31 (56.30)	4.91 (4.90)	15.15 (15.15)
5e	OC_2H_5	OC_2H_5	158	58	$C_{27}H_{29}FN_6O_6S$	55.47 (55.45)	5.00 (5.00)	14.38 (14.35)
5f	CH_3	CH_3	180	50	$C_{29}H_{27}FN_6O_4S$	60.62 (60.60)	4.74 (4.72)	14.63 (14.60)
5g	CH_3	C_6H_5	174	58	$C_{34}H_{29}FN_6O_4S$	64.14 (64.10)	4.59 (4.55)	13.20 (13.20)
5h	C_6H_5	C_6H_5	196	52	$C_{39}H_{31}FN_6O_4S$	67.03 (63.00)	4.47 (4.45)	12.03 (12.00)
5i	CH_3	OC_2H_5	228	54	$C_{30}H_{29}FN_6O_5S$	59.59 (59.55)	4.83 (4.80)	13.90 (13.90)
5j	OC_2H_5	OC_2H_5	162	58	$C_{31}H_{31}FN_6O_6S$	58.66 (58.65)	4.92 (4.90)	13.24 (13.20)

Table 2. Spectral data of synthesized novel ciprofloxacin derivatives **(3a-b, 5a-j).**

Cpd. No.	IR (KBr) cm^{-1}	^1H NMR ($CDCl_3$/DMSO-d_6) (δ ppm)
3a	3490, 3085, 2914, 1720, 1580, 1429, 690	1.55 (4H, m, CH_2-CH_2), 3.7 (1H, s, N-CH), 3.8 (8H, m, N-CH_2-CH_2-N), 7.15 (1H, d, C_8-H), 7.32 (1H, d, C_5-H), 7.69 (1H, s, C_2-H), 7.5 (1H, d, CH), 8.1 (1H, d, CH), 11.2 (1H, s, COOH)
3b	3480, 3095, 2920, 1715, 1585, 1426, 670	1.52 (4H, m, CH_2-CH_2), 3.6 (1H, s, N-CH), 3.9-4.1 (8H, m, N-CH_2-CH_2-N), 7.25 (1H, d, C_8-H), 7.36 (1H, d, C_5-H), 7.76 (1H, s, C_2-H), 7.4-7.6 (4H, m, Ar-H), 11.2 (1H, s, COOH)
5a	3090, 2918, 1710, 1582, 1430, 680	1.54 (4H, m, CH_2-CH_2), 2.72 (6H, s, $COCH_3$), 3.5 (1H, s, N-CH), 3.8 – 4.0 (8H, m, N-CH_2-CH_2-N), 5.36 (1H, s, >CH), 7.22 (1H, d, C_8-H), 7.36 (1H, d, C_5-H), 7.88 (1H, s, C_2-H), 7.52 (1H,d, CH) 8.12 (1H, d, CH)
5b	3075, 2928, 1718, 1579, 1431, 683	1.53 (4H, m, CH_2-CH_2), 2.72 (3H, s, $COCH_3$), 3.6 (1H, s, N-CH), 3.8 (8H, m, N-CH_2-CH_2-N), 5.35 (1H, s, >CH), 7.18 (1H, d, C_8-H), 7.35 (1H, d, C_5-H), 7.86 (1H, s, C_2-H), 7.4-7.5 (5H, m, Ar-H), 7.54 (1H, d, CH), 8.02 (1H, d, CH)
5c	3080, 2924, 1711, 1583, 1421, 690	1.48 (4H, m, CH_2-CH_2), 3.5 (1H, s, N-CH), 3.87-4.01 (8H, m, N-CH_2-CH_2-N), 5.34 (1H, s, >CH), 7.20 (1H, d, C_8-H) 7.32 (1H, d, C_5-H), 7.92 (1H, s, C_2-H), 7.4-7.5 (10H, m, Ar-H), 7.54 (1H, d, CH), 8.02 (1H, d, CH)
5d	3085, 2914, 1720, 1580, 1429, 688	1.50 (4H, m, CH_2-CH_2), 2.13 (3H, t, CH_2-CH_3), 2.71 (3H, s, $COCH_3$) 3.6 (1H, s, N-CH), 3.8 (8H, m, N-CH_2-CH_2-N), 4.0 (2H, q, O-CH_2) 5.33 (1H, s, >CH), 7.17 (1H, d, C_8-H) 7.36 (1H, d, C_5-H), 7.76 (1H, s, C_2-H), 7.54 (1H, d, CH), 8.02 (1H, d, CH)
5e	3080, 2922, 1723, 1578, 1424, 682	1.51 (4H, m, CH_2-CH_2), 2.14 (6H, t, CH_2-CH_3), 3.7 (1H, s, N-CH), 3.8 (8H, m, N-CH_2-CH_2-N), 3.9 (4H,q, O-CH_2), 5.30 (1H, s, >CH), 7.18 (1H, d, C_8-H), 7.29 (1H, d, C_5-H), 7.65 (1H, s, C_2-H), 7.54 (1H, d, CH) 8.02 (1H, d, CH)
5f	3090, 2918, 1717, 1579, 1419, 692	1.52 (4H, m, CH_2-CH_2), 2.72 (6H, s, $COCH_3$), 3.5 (1H, s, N-CH), 3.9-4.0 (8H, m, N-CH_2-CH_2-N), 5.35 (1H, s, >CH), 7.28 (1H, d, C_8-H), 7.35 (1H, d, C_5-H), 7.80 (1H, s, C_2-H), 7.4-7.6 (4H, m, Ar-H)
5g	3084, 2921, 1715, 1584, 1422, 693	1.54 (4H, m, CH_2-CH_2), 2.72 (3H, s, $COCH_3$), 3.6 (1H, s, N-CH), 3.9-4.1 (8H, m, N-CH_2-CH_2-N), 5.36 (1H, s, >CH), 7.29 (1H, d, C_8-H) 7.35 (1H, d, C_5-H), 7.80 (1H, s, C_2-H), 7.4-7.6 (9H, m, Ar-H)
5h	3083, 2920, 1722, 1581, 1423, 697	1.53 (4H, m, CH_2-CH_2), 3.6 (1H, s, N-CH), 3.8-3.9 (8H, m, N-CH_2-CH_2-N), 5.39 (1H,s, >CH), 7.28 (1H, d, C_8-H) 7.36 (1H, d, C_5-H), 7.78 (1H, s, C_2-H), 7.5-7.6(14H,m, Ar-H)

5i	3083, 2918, 1712, 1583, 1431, 685	1.55 (4H, m, CH_2-CH_2), 2.13 (3H, t, CH_2-CH_3), 2.71 (3H, s, $COCH_3$), 3.6 (1H, s, N-CH), 3.9-4.1 (10H, m, N-CH_2-CH_2-N, O-CH_2), 5.37 (1H, s, >CH), 7.29 (1H, d, C_8-H) 7.35 (1H, d, C_5-H), 7.80 (1H, s, C_2-H), 7.4-7.6 (4H, m, Ar-H)
5j	3079, 2920, 1718, 1576, 1422, 689	1.53 (4H, m, CH_2-CH_2), 2.12 (6H, t, CH_2-CH_3), 3.6 (1H, s, N-CH), 3.8 (8H, m, N-CH_2-CH_2-N), 3.9 (4H, q, O-CH_2), 5.36 (1H, s, >CH), 7.27 (1H, d, C_8-H), 7.32 (1H, d, C_5-H), 7.81 (1H, s, C_2-H), 7.4-7.6 (4H, m, Ar-H)

The in vitro antibacterial activities of the compound in this study were determined by conventional agar dilution method. The in vitro antibacterial activity of quinolone against several gram positive bacteria (*Staphylococcus aureus* ATCC 6538, *Bacillus subtilus* PTCC 1032 and *Staphylococcus epidermidis* ATCC 12228) and gram negative bacteria (*Escherichia coli* ATTC 8739, *Klebsiella pneumonia* ATTC 10031 and *Pseudomonas aerumonia* ATCC 9027) are summarized in Table 3. The data of ciprofloxacin is included for comparison.

Table 3. The in vitro antibacterial activities [(a)].

Compounds	MIC [(b)] (μg/mL)					
	Gram- positive organism			Gram -negative organism		
	Sa	Bs	Se	Ec	Ks	Pa
5a	0.06	0.015	0.03	0.06	0.015	0.50
5b	0.25	0.03	0.125	0.50	0.06	4.0
5c	2.0	0.50	4.0	8.0	0.50	>8.0
5d	0.25	0.06	0.125	0.5	0.06	2.0
5e	4.0	1.0	0.50	2.0	1.0	4.0
5f	0.125	0.015	0.03	0.125	0.03	1.0
5g	0.5	0.03	0.125	1.0	0.06	2.0
5h	2.0	0.125	1.0	8.0	1.0	4.0
5i	0.25	0.06	0.25	0.25	0.06	2.0
5j	4.0	1.0	2.0	4.0	2.0	>8.0
Cipro[(c)]	0.5	0.015	0.25	0.125	0.03	1.0

[(a)] Structures are shown in Table I. [(b)] The MIC (minimum inhibitory concentration) values by the conventional agar dilution. [(c)] Ciprofloxacin the reference drug. Sa = *Staphylococcus aureus* ATCC 6538. Bs = *Bacillus subtilus* PTCC 1032. Se = *Staphylococcus epidermidis* ATCC 12228. Ec = *Escherichia coli* ATTC 8739. Kp = *Klebsiella pneumonia* ATTC 10031. Pa = *Pseudomonas aerumonia* ATCC 9027.

The MIC (minimum inhibitory concentration) of the test derivatives against staphylococcus strain indicates that most compounds possessed a better activity with respect to the reference drug. Compound **5a** was the most active compound against *S. aureus*, its activity was found to be 16-times better than reference drug. Derivative **5a** and **5f** were the most active against *S. epidermidis* showing the MIC values of 0.03 μg/mL where activities found to be 16-fold more than the reference drug.

Antibacterial screening of compound **5a–j** against *B. subtilusb* indicate that compound **5a** and **5f** possessed a significant activity. Generally, most compounds showed poor activity against gram-negative bacteria. However, compound **5a** was the most potent against of gram-negative bacteria. Activity of compound **5f** was found to be comparable to those of reference drug.

In conclusion, we have described the synthesis and antibacterial evaluation of a new series of diketone derivatives of thiazole and benzothiazole derivative of ciprofloxacin. Preliminary results indicate that most compounds demonstrate comparable or better activities against gram-positive bacteria and poor activities against gram-negative bacteria.

AKNOWLEDGEMENTS

Authors are thankful to the Head Department of Chemistry, University of Rajasthan, Jaipur (India) for providing necessary laboratory facilities and spectral data.

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