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Synthesis and Spectral Study of Novel Norfloxacin Derivatives

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Abstract: Reaction of [1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinolone-3-carboxylic acid (norfloxacin) with thiazole / benzothiazole diazonium chloride to get new piperazine substituted norfloxacin derivative. These norfloxacin derivatives were further condensed with various β -diketone to get novel acid derivatives of 1-Ethyl-6-fluoro-4-oxo-7-[4 (thiazol-2-ylidiazenyl)-piperazin-1-yl]-1,4-dihydro-quinoline-3-carboxylic acid (6a-e) and 7-(4-(benzo[d]thiazol-2-ylidiazenyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid (6 f-j). Structures of these compounds were established on the basis of spectral studies *viz.* IR, ^1H NMR *etc.*

Keyword: Norfloxacin, β -Diketone, Thiazole, Benzothiazole

Introduction

The earliest antibacterial agents to be used clinically in the 1920 were the synthetic sulfonamides. Since then, quinolones were the only synthetic agents that play a major role in the treatment of bacterial community or hospital-acquired diseases. The excellent pharmacokinetic properties, high antimicrobial activity, and few side effects that most quinolones demonstrate explain their widespread use in clinical practice¹ The compounds have had good success against gram-negative bacteria, but resistance of Gram-positive pathogens, such as *Staphylococcus aureus*, has become a problem²⁻⁸. In addition, certain adverse events (*e.g.* CNS side effects, phototoxicity, and arthropathy) became apparent, although the more serious events are rare⁹⁻¹⁰. Thus, despite many advances in the fluoroquinolone field, there exists a continuous need for novel quinolones to overcome the limitations of existing drugs.

The 1,4-dihydro-4-oxopyridine-3-carboxylic acid associated with a 5,6-fused aromatic ring is the common chemical feature of bactericidal quinolones. In the resulting bicyclic ring, the 1, 5, 6, 7, and 8-positions are the major targets of chemical variation but, synthetic efforts for improved potency have been the main focus on 7-position¹¹⁻¹². Both activity spectrum and kinetic profile can be controlled at C-7. The most common substituents are cyclic amino groups, for example, piperazine or pyrrolidine rings; other groups have been less successful. Piperazine rings are particularly common (*e.g.* ciprofloxacin, norfloxacin or enoxacin) and confer potency against gram-negative bacteria¹¹⁻¹². The first generation of 7-piperazinyl quinolones, exemplified by ciprofloxacin, norfloxacin, and enoxacin, have high activity against Gram-negative species and atypicals, but moderate activity against Gram-positive bacteria². In this paper we report the synthesis and the spectral study of novel β -dicarbonyl derivative of [1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinolone-3-carboxylic acid (norfloxacin).

Structure of norfloxacin

Experimental

All the melting points are uncorrected (Table 1). Using Perkin-Elmer CHNS/O analyzer 2400 carried out the elemental analysis. Infrared spectra were recorded in KBr (AR) pellets on a Nicolet-Magna-FT-IR 550 spectrometer. ¹H NMR spectra were recorded on model DRX 300 at 300.13 MHz in DMSO-D₆ solvent; using TMS as internal standard ¹H NMR spectra were recorded at room temperature and 2 mg/mL. The purity of compounds was tested by pre coated silica gel 60F254 TLC plates from E. Merck in different solvent systems.

General method of preparation of diazo derivatives (3a-b)

A mixture of norfloxacin (1.655 g, 0.005 mol) and sodium bicarbonate (1.0 g, excess) in 10 mL of acetonitrile was stirred at 50°C for 4 hour. Reaction mixture was cooled to 0°C and diazonium chloride of 2-aminothiazole (0.5 g, 0.005 mol)/2-aminobenzothiazole (0.75 g, 0.005 mol) (2a-b) was added. The mixture was stirred at magnetic stirrer for 5 hours at 0-5°C. Acetonitrile was removed under reduced pressure and the solid residue was partitioned between chloroform/water. The organic layer was dried by sodium sulphate, recrystallized in hexane acetone mixture. The purity of compound was checked by TLC in chloroform: acetone: 50:50 mixture.

General method for preparation of 1-ethyl-6-fluoro-4-oxo-7-(4-(thiazol-2-yl)diazenyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid derivatives (6a-j)

Compound (3a-b) was dissolved in thionyl chloride and refluxed for 4 hours to get acid chloride derivative (4a-b). Excess thionyl chloride was removed under reduced pressure and sodium salt of β -diketones (prepared using NaOMe and β -diketone (5a-e) under N₂ 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 (6a-j), which were further purified through column chromatography in some cases.

Scheme 1

Results and Discussion

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

Table 1. Substitution pattern and physical properties for novel norfloxacin derivatives (3a-b, 6a-j)

S. No	R ₂	R ₃	m.p. °C	Yield	Molecular formula	Elemental data Calculated (Found) %		
						C	H	N
3a	--	--	142	51	C ₁₉ H ₁₉ FN ₆ O ₃ S	53.01(53.0)	4.45(4.40)	19.52(19.50)
3b	--	--	154	56	C ₂₃ H ₂₁ FN ₆ O ₃ S	57.49(57.47)	4.41(4.40)	17.49(17.47)
6a	CH ₃	CH ₃	190	54	C ₂₄ H ₂₅ FN ₆ O ₄ S	56.24(56.20)	4.92(4.90)	16.40(16.38)
6b	CH ₃	C ₆ H ₅	180	52	C ₂₉ H ₂₇ FN ₆ O ₄ S	60.62(60.60)	4.74(4.72)	14.63(14.62)
6c	C ₆ H ₅	C ₆ H ₅	206	53	C ₃₄ H ₂₉ FN ₆ O ₄ S	64.14(64.13)	4.59(4.58)	13.20(13.19)
6d	CH ₃	OC ₂ H ₅	214	54	C ₂₅ H ₂₇ FN ₆ O ₅ S	55.34(55.32)	5.02(5.00)	15.49(15.48)
6e	OC ₂ H ₅	OC ₂ H ₅	154	62	C ₂₆ H ₂₉ FN ₆ O ₆ S	54.54(54.52)	5.10(5.09)	14.68(14.67)
6f	CH ₃	CH ₃	175	58	C ₂₈ H ₂₇ FN ₆ O ₄ S	59.77(59.76)	4.84(4.83)	14.94(14.92)
6g	CH ₃	C ₆ H ₅	182	54	C ₃₃ H ₂₉ FN ₆ O ₄ S	63.45(63.44)	4.68(4.67)	13.45(13.44)
6h	C ₆ H ₅	C ₆ H ₅	193	57	C ₃₈ H ₃₁ FN ₆ O ₄ S	66.46(66.45)	4.55(4.54)	12.24(12.23)
6i	CH ₃	OC ₂ H ₅	218	55	C ₂₉ H ₂₉ FN ₆ O ₅ S	58.77(58.76)	4.93(4.92)	14.18(14.17)
6j	OC ₂ H ₅	OC ₂ H ₅	171	58	C ₃₀ H ₃₁ FN ₆ O ₆ S	57.87(57.85)	5.02(5.00)	13.50(13.49)

Table 2.

Comp	IR (KBr) cm ⁻¹	¹ H NMR (CDCl ₃ /DMSO-d ₆) δ ppm
3a	3495,3080,2920,1725,1581,1428, 691	1.29(3H, t, CH ₃) 3.4 (2H, q, CH ₂) 3.8 (8H, m, N-CH ₂ -CH ₂ N), 7.45 (1H, d, C ₈ -H) 7.63 (1H,d, C ₅ -H), 7.80 (1H,s, C ₂ -H), 7.52 (1H,d, CH) 8.1 (1H,d, CH). 11.2 (1H,s, COOH)
3b	3483, 3085, 2923,1725,1584,1423,672	1.24(3H, t, CH ₃) 3.42 (2H, q, CH ₂) 3.9-4.1 (8H, m, N-CH ₂ -CH ₂ N), 7.50 (1H, d, C ₈ -H) 7.63 (1H,d, C ₅ -H), 7.78 (1H,s, C ₂ -H), 7.4-7.6(4H,m, Ar-H). 11.2 (1H,s,COOH)
6a	3090, 2921,1715,1585,1432,684	1.22 (3H, t, CH ₃) 2.72 (6H, s, COCH ₃) 3.42 (2H, q, CH ₂) 3.9 –4.0 (8H,m, N-CH ₂ -CH ₂ N), 5.38 (1H,s, >CH) 7.42 (1H,d,C ₈ -H) 7.56 (1H,d,C ₅ -H),7.88 (1H,s, C ₂ -H),7.50(1H,d, CH) 8.16(1H,d, CH)
6b	3085,2921,1723,1580,1432,670	1.25 (3H, t, CH ₃) 2.72(3H,s ,COCH ₃) 3.38(2H, q, CH ₂), 3.9-4.0 (8H,m, N-CH ₂ -CH ₂ N), 5.32(1H,s,>CH)7.38 (1H,d,C ₈ -H) 7.65 (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) 8.12(1H,d, CH)
6c	3081,2922, 1721,1591,1423, 685	1.20 (3H, t, CH ₃) 3.41 (2H, q, CH ₂), 3.87-4.01 (8H,m, N-CH ₂ -CH ₂ N), 5.44(1H,s, >CH), 7.40 (1H,d, C ₈ -H) 7.62 (1H,d, C ₅ -H), 7.92 (1H,s, C ₂ -H), 7.45-7.55(10H,m, Ar-H) 7.58(1H,d, CH) 8.14(1H,d, CH)
6d	3080,2914,1719,1578, 1424,688	1.23 (3H, t, CH ₃) 2.13(3H,t, CH ₂ -CH ₃) 2.71(3H,s, COCH ₃) 3.42 (2H, q, CH ₂), 3.8 (8H,m, N-CH ₂ -CH ₂ N), 4.0 (2H,q,O-CH ₂) 5.30 (1H,s, >CH), 7.47 (1H,d,C ₈ -H) 7.66 (1H,d,C ₅ -H),7.76 (1H,s,C ₂ -H),7.54(1H,d, CH) 8.11(1H,d, CH)

Contd...

6e	3080,2921,1720,1575, 1424,681	1.25 (3H, t, CH ₃) 2.14(6H,t,CH ₂ -CH ₃), 3.45 (2H, t, CH ₂) 3.8–4.0 (8H,m, N-CH ₂ -CH ₂ N), 3.9 (4H, q, O-CH ₂) 5.32 (1H,s, >CH), 7.48 (1H,d,C ₈ -H) 7.69 (1H,d, C ₅ -H),7.75 (1H,s, C ₂ -H),7.55 (1H,d, CH) 8.09(1H,d, CH)
6f	3094,2918, 1714,1580,1418,690	1.19 (3H, t, CH ₃) 2.72(6H, s, COCH ₃), 3.42 (2H, q, CH ₂) 3.9-4.0 (8H,m, N-CH ₂ -CH ₂ N), 5.33(1H,s, >CH 7.48(1H,d, C ₈ -H) 7.65 (1H,d, C ₅ -H), 7.82 (1H,s, C ₂ -H), 7.4-7.6 (4H,m, Ar-H).
6g	3080,2920,1713,1581, 1420,691	1.20 (3H, t, CH ₃) 2.72(3H, s, COCH ₃), 3.44 (2H, q, CH ₂) 3.9-4.1 (8H,m, N-CH ₂ -CH ₂ N), 5.35 (1H,s, >CH 7.49(1H,d, C ₈ -H) 7.65 (1H,d, C ₅ -H), 7.83 (1H,s, C ₂ -H), 7.4-7.6(9H,m, Ar-H).
6h	3082,2920,1720,1582, 1422,692	1.24 (3H, t, CH ₃), 3.40 (2H, q, CH ₂) 3.8-3.9 (8H, m, N-CH ₂ -CH ₂ N), 5.36 (1H,s, >CH) 7.48 (1H,d, C ₈ -H) 7.65 (1H,d, C ₅ -H), 7.78 (1H,s, C ₂ -H), 7.5-7.6(14H,m, Ar-H).
6i	3084, 2917,1721,1581, 1432,681	1.20 (3H, t, CH ₃) 2.13(3H,t, CH ₂ -CH ₃) 2.71(3H,s ,COCH ₃), 3.42 (2H, q, CH ₂) 3.8-4.1 (10H,m, N-CH ₂ -CH ₂ N,O-CH ₂), 5.40(1H,s, >CH) 7.35 (1H,d,C ₈ -H) 7.65 (1H,d,C ₅ -H),7.81 (1H,s,C ₂ -H),7.4-7.6(4H,m,Ar-H).
6j	3080, 2922,1719,1578, 1420,690	1.25 (3H, t, CH ₃) 2.12(6H,t, CH ₂ -CH ₃) 3.45 (2H, q, CH ₂),3.8–4.0 (12H,m, N-CH ₂ -CH ₂ N & O-CH ₂), 5.37(1H,s, >CH) 7.47(1H,d,C ₈ -H) 7.62 (1H,d,C ₅ -H),7.81 (1H,s,C ₂ -H),7.5-7.6(4H,m,Ar-H).

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