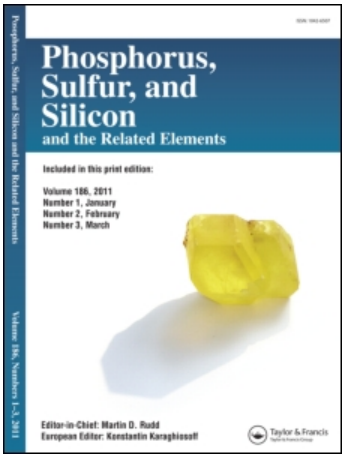

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Synthesis of Thio Analogues of Quinolone Antibacterials

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Synthesis of Thio Analogues of Quinolone Antibacterials

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A facile and rapid synthesis of thio compounds, analogues to ciprofloxacin, and norfloxacin is described.

Keywords Antibacterial; ciprofloxacin; norfloxacin; quinolons

Ciprofloxacin **1** is a widely prescribed fluoroquinolone antiinfection drug.[1] The fluoroquinolones possess a broad spectrum of activity against Gram-negative and Gram-positive bacteria. They exert this antibacterial effect by binding to the bacterial type Π, topoisomerase enzymes DNA gyrase, and topoisomerase III.[2,3] Structurally, fluoroquinolones are characterized by a fluoro substituent in the 6 position of quinolone system.[4] By structure-activity relationships, it has been shown that sulfur atom makes the activity of quinolones twice.[5] Promoted with this idea in order to synthesis more active fluoroquinolones and for our continuous interest in chemistry of sulfur and nitrogen heterocycles,[6] in this communication we wish to report our result from the reaction of 1-substituted-6-fluoro-7-chloro-1,4-dihydro-4-oxoquinolone-3- carboxylic acid **3** with various heterocyclic system under thermal conditions. Compound **3** (R = cyclopropyl or ethyl) was treated with 6-methyl-2-thiouracil **4** and 6-methyl-3-thio-5-oxo-1,2,4-triazine **5** under basic conditions. The progress of the reaction was monitored by TLC. In a various basic and reflux condition, the reactions proceeded slowly and mixture of products was detected. The use of borate as a fluoroborate complex of a quinolone carboxylic acid in order to obtain a

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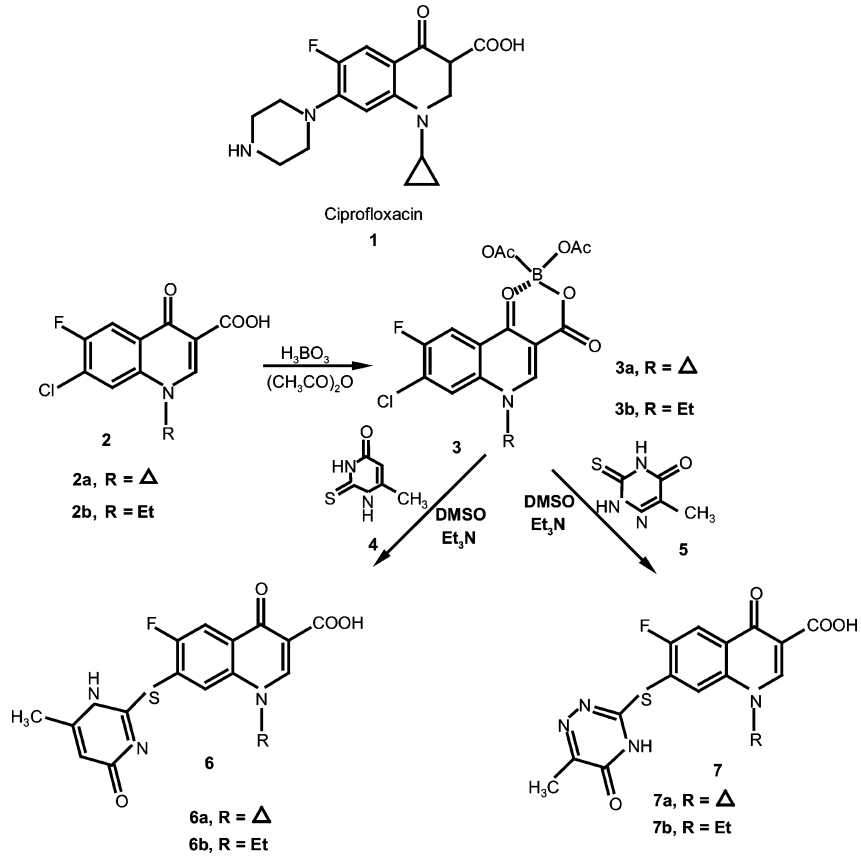
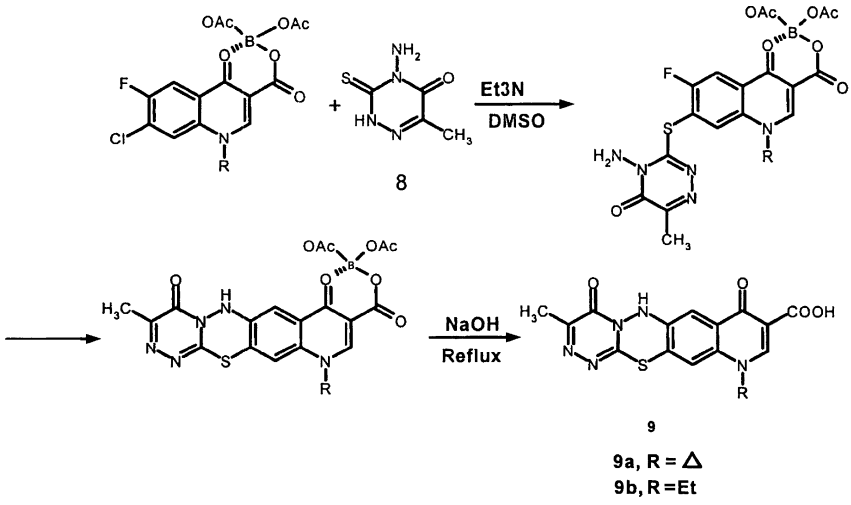
pure fluoro derivative in the reaction of acid **2** with various nucleophils has been reported.[7] Compounds **2a** and **2b** reacted with boric acid triacetate in an acetic acid medium to obtain a compound of the formula **3a** and **3b** in almost quantitative yields. These compounds (**3a** and **3b**) reacted with thiopyrimidine **4** and thio-1,2,4-triazine **5** in DMSO in the presence of triethyl amine to obtain the complex, which was refluxed in NaOH, to get the pure products. These products were identified by spectroscopic data to be the result of a substitution of thiolate in a heterocyclic system with fluorine in acids **2a** and **2b** to afford compounds **6a** and **6b** and **7a** and **7b**, respectively (Scheme 1).



SCHEME 1

When 4-amino-6-methyl-3-thio-1,2,4-triazine-5-one **8** reacted with **3b** under the mentioned condition, a single compound was obtained. The spectroscopic and analytical data proved that in this reaction,

the bidentate nucleophile **8** has substituted fluorine and chlorine of **2b** to afford a novel heterocyclic system, 1,2,4-triazino[3,4-b]1,3,4 thiadizino[5,6-g] quinolone **9** (Scheme 2).



SCHEME 2

EXPERIMENTAL

Melting points were recorded on a 9100 electrothermal melting point apparatus. The IR spectra were obtained on a Brucker Tensor 27 FTIR. The ^{1}HNMR (90 MHz) spectra were recorded on a Brucker DRX-90-AVANCE. Microanalysis was performed by Heroeus CHN-O-rapid.

Synthesis of 1-Substituted-6-fluoro-7- thio Substituted-1,4-dihydro-4-oxo Quinoline-3-carboxylic Acid (6a, 6b, 7a, and 7b): General Procedure

Boric acid (9.3 g, 0.15 mol) in acetic anhydride (54.1 g, 0.53 mol) was stirred for 30 min at 80°C. An appropriate acid, **2a** or **2b** (0.1 mol), was added to this solution and mixture was refluxed for 2 h. To this reaction mixture, water (100 mL) was added. The precipitated solid was filtered and washed with water to afford the corresponding boron complex (1 mmol), which then reacted with an appropriate thio heterocycles, **4** or **5** (1.1 mmol) in a mixture of triethyl amine (1 mL, 2 mmol) and DMSO (5 mL) for 5 h at 60°C. The progress of the reaction was

monitored by TLC using ethylacetate/n-hexan (3:1) as an eluent. After completion of the reaction, water (3 mL) was added and cooled to 0°C. The precipitated solid was filtered and washed with a mixture of water and acetone to afford the corresponding 7-thioheterocyclic substituted derivatives.

Selected Data for 6b

Yield: 82%, M.P. 275°C (decomposed), ^{1}HNMR δ (d_6DMSO) 1.3 (t, 2H, Me), 2 (s, 1H, Me), 4.7 (q, 2H, CH_2), 5.7(s, 1H, vinylic proton), 8.2 (d, 1H, aromatic proton) 8.6 (d, 1H, aromatic proton), 9 (s, 1H, vinylic proton), 13.1 (S, 1H, OH).

Selected Data for 7a

Yield: 67%, M.P. 250°C (decomposed), ^{1}HNMR δ (d_6-DMSO) 0.5 (m, 4H, CH_2), 1.3 (m, 1H, CH), 1.7 (s, 3H, Me), 7.4 (d, 1H, aromatic proton), 7.6 (d, 1H, aromatic proton), 7.9 (s, 1H, vinylic proton), 13.7 (s, 1H, OH).

Selected Data for 7b

Yield: 76%, M.P. 270°C (decomposed), ^{1}HNMR δ (d_6-DMSO), 1.3 (t, 3H, Me), 2.1 (s, 1H, Me), 4.5 (q, 2H, CH_2), 8.3 (d, 1H, aromatic proton), 8.7 (d, 1H, aromatic proton), 9.1 (s, 1H, vinylic proton), 14.8 (s, 1H, OH).

Selected Data for 9a

Yield: 78%, M.P. 285°C (decomposed), ^{1}HNMR δ (d_6DMSO) 1.4 (m, 4H, Me), 1.7 (s, 1H, Me), 4.1 (m, 1H, CH), 8.2 (d, 1H, aromatic proton) 8.6 (d, 1H, aromatic proton), 9.1 (s, 1H, vinylic proton), 14.3 (s, 1H, OH).

Selected Data for 9b

Yield: 74%, M.P. 280°C (decomposed), ^{1}HNMR δ (d_6-DMSO), 1.4 (t, 3H, Me), 2.1 (s, 3H, Me), 4.6 (q, 2H, CH_2), 8.1 (d, 1H, aromatic proton), 8.3 (d, 1H, aromatic proton), 8.9 (s, 1H, vinylic proton), 14.5 (s, 1H, OH), IR(KBr-Pellet) 3426, 3060, 2988, 2934, 2653, 1721, 1610, 1578, 1507, 1455, 1305, 1295, 1048, 751 cm^{-1}; Anal. Calc. for $C_{16}H_{13}N_5O_4S$: C, 51.6; H, 3.7; N, 18; O, 17.8; S, 8.7. Found: C, 51.3; H, 3.5; N, 18.2; O, 18.6; S, 8.4.

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