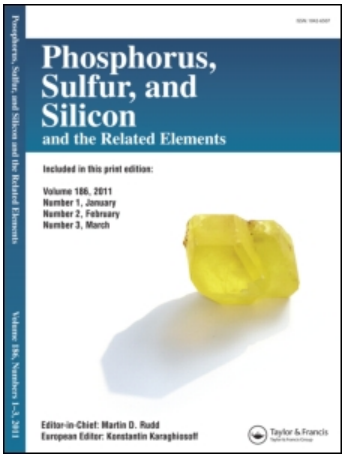

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The Synthesis of the Novel Thio-Quinolone Derivatives

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The boron-chelated carboxylic acids of 7-chloro-6-fluoroquinolones were substituted selectively at C-7 by 2- mercapto benzimidazoles.

Keywords Benzimidazole; fluoroborate complex; fluoroquinolone

The fluoroquinolones such as ciprofloxacine, norfloxacine, and sporfloxacine are totally synthetic antibacterial agents that have gained wide acceptance for use in the treatment of various bacterial infections.[1] Their mode of action is believed to involve the inhibition of bacterial DNA gyrase, an enzyme essential for DNA replication.[2] Moreover, recent studies have identified some quinolones, which also inhibit mammalian topoisomerase-II as potential lead compounds in the development of anticancer drugs.[3] In addition, very recently it has been reported that fluoroquinolone antibacterials having the pyridine carboxylic acid skeleton at the N-1 position show anti-HIV activity.[4] Structurally, fluoroquinolones are characterized by a fluro substitutet in the 6 position of the quinolone system.[5] By structure-activity relationships, it has been shown that a sulfur atom makes the activity of quinolones twice.[6] Prompted with these properties and with the idea of synthesizing more active fluoroquinolones and our continuous interest in the chemistry of sulfur and nitrogen heterocycles,[7] in this communication we wish to report our result from the reaction of 1-substituted-6-fluoro-7-chloro-1,4-dihydro-4-oxo-quinolone-3-carboxylic acid with various heterocyclic systems at r.t.

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Compounds **3a–b** (R = cyclopropyl or ethyl) were treated with 2-mercapto benzimidazole **2a** and 2-mercapto-5-methoxy benzimidazole **2b** under basic conditions. The progress of the reaction was monitored by TLC using ethylacetate and n-heptan (3:1). In various basic and reflux conditions, the reactions proceeded slowly and a mixture of products was detected.

The use of borate as a fluoroborate complex of quinolone carboxylic acid in order to obtain a pure fluoro derivative in the reaction of acids **1** with various nucleophils has been reported.[8]

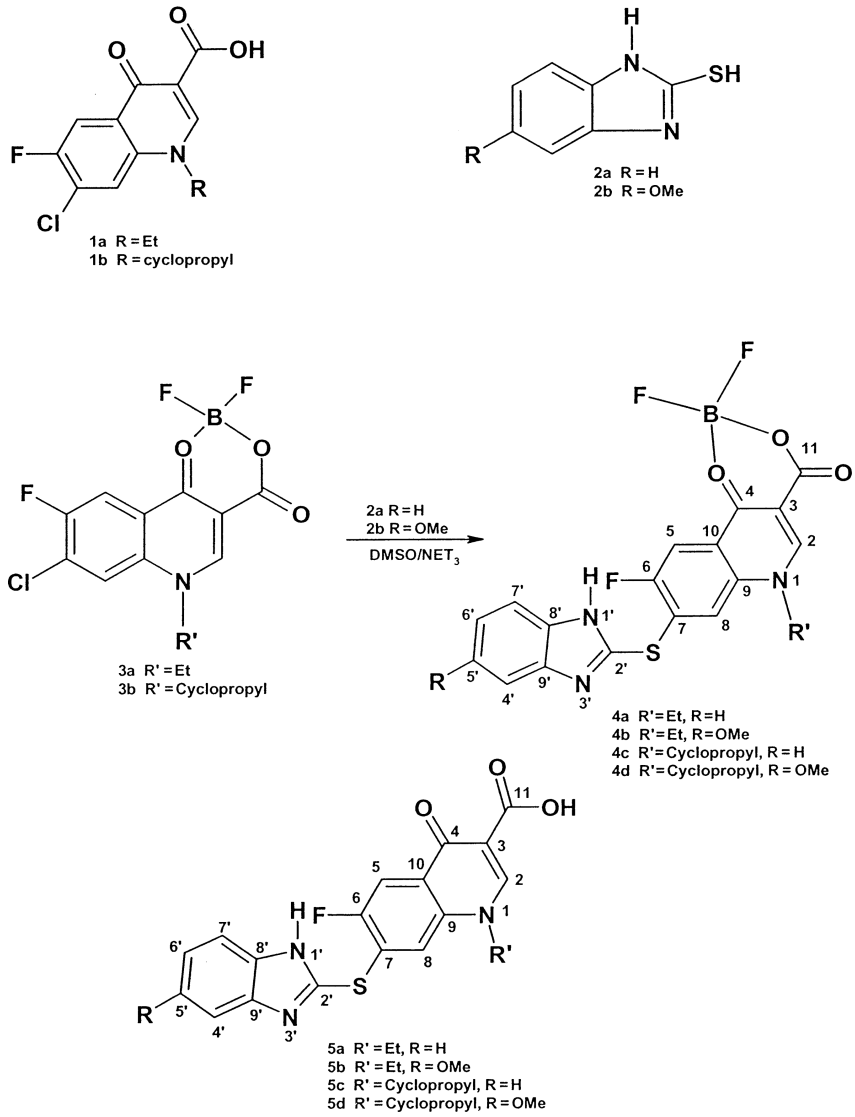
Compounds **1a–b** reacted with boron trifluride etherate in diphenyl ether as a solvent to obtain compounds of the formula **3a–b** in almost quantitative yields. The compounds **3a–b** were caused to react with 2-mercapto benzimidazole **2a** and 2-mercapto-5-methoxy benzimidazole **2b** in DMSO in the presence of triethylamine to obtain compounds **4a–4d**, which were refluxed in NaOH to give the pure quinoline derivatives. These products were identified by spectroscopic data to be the result of the substitution of the thiolate in the heterocyclic system for chlorine in acides **1a–b** to afford compounds **5a–d**, respectively (Scheme 1).

EXPERIMENTAL

The melting points were obtained using an Electrothermal IA 9100 digital melting point apparatus. The IR spectra were recorded on a Bruker (400–4000 Cm^{-1}) spectrometer. ^{1}HNMR spectra were recorded on a 300 MHz spectrometer using TMS as internal standard. Mass spectrometric measurements were made on an Agilent apparatus.

GENERAL PROCEDURE

Boron trifluride etherate in diphenyl ether (1 mmol), an appropriate acid, **1a** or **1b** (1 mmol), and diethylamine (2 mL) in dichloromethane (50 mL) were stirred for 30 min at r.t. The solid was filtered and dried to afford the corresponding boron complex (1 mmol), which then reacted with an appropriate thio heterocycle (**2a–b**) (1 mmol) in a mixture of triethylamine (1 mL) and DMSO (5 mL) for 4 h at r.t. The progress of the reaction was monitored by TLC using ethylacetate/n-hexan (3:1) as an eluent. Upon completion of the reaction, the precipitated solid was filtered and washed with a mixture of water and acetone to afforded the corresponding 7-thioheterocyclic compounds **4a–d**, which were refluxed in NaOH (0.1 M, 20 mL) for 1 h. After cooling, HCl (0.1 M) was added to the mixture. The precipitated solid was collected by filtration and washed with water to obtain **5a–d**.



SCHEME 1

1-ETHYL-6-FLUORO-7-(2-MERCAPTOBENZIMIDAZOLE)-4-OXO-1,4-DIHYDROQUINOLINE-3-CARBOXYLIC ACID 5A

M.p. > 300°C, orange powder, yield 56%, ^{1}HNMR: δ (d_6-DMSO), 1.43 (t, $J = 7$, 3H, CH_3), 4.82 (q, $J = 7$, 2H, CH_2), 7.24 (d, d, $J = 3, 6$, 2H,

H-4′, 7′), 7.55 (m, 2H, H-5′, 6′), 8.38 (d, $J = 9$, 1H, H-5), 8.75 (d, $J = 6$, 1H, H-8), 9.58 (s, 1H, H-2), 13.23 (br, 1H, NH), 14.65 (br, 1H′, COOH). ^{13}C-NMR: δ (d_6-DMSO), 15.05 (CH_3), 49.86 (CH_2), 126.55 (C-8′), 127.78 (C-9′), 153.73 (C-2′), 157.03 (C-6), 165.97 (C-11), 176.99 (C-4). IR (KBr) (υ_{max}, cm^{-1}): 2500–3300 (br, COOH), 3181 (NH, str), 1701 (C=O, str).

1-EETHYL-6-FLUORO-7-(5-METHOXY-2-MERCAPTOBENZIMIDAZOLE)-4-OXO-1,4-DIHYDROQUINOLINE-3-CARBOXYLIC ACID 5B

M.p. = 179°C, yellow orange powder, yield 60%. ^{1}HNMR: δ (d_6-DMSO), 1.30 (t, $J = 7$, 3H, CH_3), 3.66 (s, 3H, OMe), 4.65 (q, 2H, $J = 7$, CH_2), 6.75 (d, d, $J = 2$, 8.7, 1H, H-5′), 6.91 (d, $J = 2$, 1H, H-7′), 7.35 (d, $J = 8.7$, 1H, H-4′), 8.22 (d, $J = 9$, 1H, H-5), 8.48 (d, $J = 6$, 1H, H-8), 9.44 (s, 1H, H-2), 12.98 (br, 1H, NH), 14.86 (br, 1H, COOH). ^{13}CNMR: δ (d_6-DMSO), 14.08 (CH_3), 45.67 (CH_2), 55.47 (OCH_3), 156.21 (C-8′), 159.40 (C-6), 159.69 (C-9′), 165.59 (C-2′), 168.50 (C-5′), 168.5 (C-11), 176.46 (C-4). IR (KBr) (υ_{max}, cm^{-1}): 2500–3600 (br, COOH), 3209 (NH, str), 1700 (C=O, str).

1-CYCLOPROPYL-6-FLUORO-7-(2-MERCAPTOBENZIMIDAZOLE)-4-OXO-1,4-DIHYDROQUINOLINE-3-CARBOXYLIC ACID 5C

M.p. >300°C, orange powder, yield 65%. ^{1}HNMR: δ (d_6-DMSO), 1.01 (m, 2H, cyclopropyl), 1.25 (m, 2H, cyclopropyl), 3.98 (m, 1H, cyclopropyl), 7.31 (d, d, $J = 2$, 8, 2H, H-4′, H-7′), 7.65 (m, 2H, H-5′, H-6′), 8.40 (d, $J = 14$, 1H, H-5), 8.68 (d, $J = 9$, 1H, H-8), 9.19 (s, 1H, H-2). IR (KBr) (υ_{max}, cm^{-1}): 2500–3600 (br, COOH), 3209 (NH, str), 1724 (C=O, str).

1-CYCLOPROPYL-6-FLUORO-7-(5-METHOXY-2-MERCAPTOBENZIMIDAZOLE)-4-OXO-1,4-DIHYDROQUINOLINE-3-CARBOXYLIC ACID 5D

M.p. >300°C, yellow powder, yield 62%. ^{1}HNMR: δ (d_6-DMSO), 1.01 (m, 2H, cyclopropyl), 1.13 (m, 2H, cyclopropyl), 3.85 (m, 1H, cyclopropyl), 3.92 (s, 3H, OMe), 6.95 (d, d, $J = 2$, 8.7, 1H, H-7′), 7.08 (d, $J = 2$, 1H, H-4′), 7.55 (d, $J = 8.7$, 1H, H-4′), 8.26 (d, $J = 14$, 1H, H-5), 8.31 (d, $J = 8$, 1H, H-8), 8.75 (s, 1H, H-2), 14.73 (br, 2H, NH, COOH). ^{13}CNMR: δ (d_6-DMSO), 7.96 (CH_2), 36.3 (CH), 56.12 (OMe), 149.58 (C-7), 149.99 (C-2), 154.38 (C-8′), 158.65 (C-6), 159.51 (C-9′), 164.77 (C-2′), 165.80 (C-11), 168.5 (C-5′), 177.21 (C-4). MS, m/z; M^+, 425 (79), 179 (11), 146 (87). IR

(KBr) (υ_{max}, cm^{-1}): 2500–3300 (br, COOH), 3103 (NH, str), 1725 (C=O, str).

REFERENCES AND NOTES

[1] T. D. Gootz and K. E. Brighty, *Med. Res. Rev.*, **16,** 433 (1996).
[2] B. Liorente, F. Leclerc, and R. Cedergren, *Bioorg. Med. Chem.*, **4,** 61 (1996).
[3] (a) M. P. Wentland, G. Y. Lesher, M. Reuman, M. D Gruett, B. Sing, S. C. Aldous, H. P. Dorff, J. B. Rake, and S. A. Coughlin, *J. Med. Chem.*, **36,** 2801 (1993); (b) S. H. Elsea, N. Osheroff, and J. Nitiss, *J. Biol. Chem.*, **267,** 13150 (1992).
[4] Y. S. Oh, C. W. Lee, Y. H. Chung, S. J. Yoon, and S. H. Cho, *J. Heterocyclic Chem.*, **35,** 541 (1998).
[5] H. Egava and M.K. Shibamaro, *J. Heterocyclic Chem.*, 181 (1987).
[6] S. Gallo, J. Cherabir, A. Mahameud, A. Eyraud, J. M. Pages, and J. Barbe, *International J. Antimicrobial Agent*, **22,** 270 (2003).
[7] (a) M. M. Heravi, M. Bakherad, M. Rahimizadeh, M. Bakavoli, and M. Ghassemzadeh, *Heterocyclic Commun.*, **10,** 335 (2005); (b) M. M. Heravi, N. Ramezanian, M. M. Sadeghi, and M. Ghassemzadeh, *Phosphorus, Sulfur, and Silicon*, **179,** 1469 (2004); (c) M. M. Heravi, A. Kevanloo, M. Rahimizadeh, M. Bakavoli, and M. Ghassemzadeh, *Tettrahedron Lett.*, **45,** 5747 (2004); (d) M. M. Heravi, A. Kevanloo, M. Rahimizadeh, M. Bakavoli, M. Ghassemzadeh, and B. Neumuller, *Tettrahedron Lett.*, **46**, 1607 (2005).
[8] (a) L. S. Sidro, P. A. Ilierto, and D. Antonio, *Span.* E.S. Patent 2007, 280 (1989), 2006, 977 (1989), 2009, 936 (1990), 2009, 963 (1989); (b) R. M. Pulla and CH. N. Venkaiah. US Pat. 0073030 (2004).