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Synthesis of New Fluoroquinolones Containing a *N*-[5-(Fluorobenzylthio)-1,3,4-thiadiazol-2-yl]piperazine moiety

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A series of *N*-[5-(fluorobenzylthio)-1,3,4-thiadiazol-2-yl]-piperazinylquinolones derivatives (**4a-i**) have been synthesized as potential antibacterial agents. The 2-amino-5-(fluorobenzylthio)-1,3,4-thiadiazole derivatives (**6a-c**) were obtained from 5-amino-1,3,4-thiadiazol-2-thiol (**5**). The treatment of compound **5** with fluorobenzyl chloride derivatives afforded *S*-benzyl intermediates **6a-c**. Diazotization of amine **6a-c** with $NaNO_2$ in hydrochloric acid in the presence of copper powder gave the corresponding 2-chloro-5-(fluorobenzylthio)-1,3,4-thiadiazoles (**7a-c**). Reaction of compounds **7a-c** with piperazinyl quinolones (**1-3**) in DMF in the presence of $NaHCO_3$ gave the target compounds **4a-i**. The structure of synthesized compounds was confirmed by elemental analysis, IR and ^{1}H NMR spectra.

Key Words: Fluoroquinolones, *N*-Substituted piperazinyl quinolones, Fluorobenzylthio-1,3,4-thiadiazoles.

INTRODUCTION

Quinolones are synthetic antibacterial compound based on a 4-quinolone skeleton. These compounds (*e.g.*, norfloxacin **1**, ciprofloxacin **2** and enoxacin **3**) have been clinically successful and are used to treat bacterial infections in both community and hospital settings[1-3]. Most of the quinolones currently on the market or under development have only moderate activity against many Gram-positive cocci, including *staphylococci* and *streptococci*[4,5]. This insufficient activity seems to be one of the reasons for the rapidly developing quinolone resistance. Therefore, despite many advances in the fluoroquinolone field, there exists continuous need for novel quinolones with better activity profile, pharmacokinetics and tolerability, to overcome the limitations of existing drugs.

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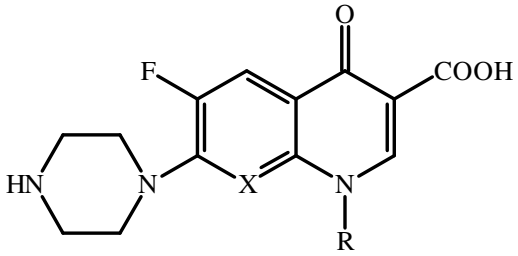


1, Norfloxacin: R = Et, X = CH
2, Ciprofloxacin: R = C=-Pr, X = CH
3, Enoxacin: R = Et, X = N

The antibacterial activity of fluoroquinolones depends not only on the bicyclic heteroaromatic pharmacophore but also on the nature of the peripheral substitutions and their spatial relationship[6]. It has been shown that the inhibition of DNA gyrase and the cell permeability of quinolones are greatly influenced by the nature of the C-7 substitutent[7]. The most common substituents at 7-position of fluoroquinolones are cyclic amino-groups, *e.g.*, piperazine ring[8-12]. Furthermore, it has been proposed that for gram-positive organisms, increasing molecular mass and bulkiness of substituent at C-7 position is not a barrier to penetration[13]. Accordingly, in the present study a number of *N*-substituted piperazinyl quinolones (**4a-i**), that carrying a 5-(fluorobenzylthio)-1,3,4-thiadiazole moiety on piperazine ring have been synthesized as potential antibacterial agents.

EXPERIMENTAL

The melting points were determined on a Kofler hot stage apparatus and uncorrected. Infrared spectra were recorded in KBr pellets on Shimadzu 470 instrument. Proton magnetic resonance spectra were obtained using Bruker FT-80 or Varrian 400 unity plus spectrometers with TMS as internal standard. Chemical shift values are given in δ scale. Column chromatography was performed on (Merck) Silica gel 60 (particle size 0.06-0.20 mm).

Prepration of compounds 6a-c, General procedure: A solution of 0.1 N sodium hydroxide (25 mL) was added to a mixture of 5-amino-1,3,4-thiadiazol-2-thiol (5 mmol), appropriate benzyl halide (5 mmol) and ethanol 80 % (75 mL). The reaction mixture was stirred at room temperature for 24 h and then water was added to the reaction mixture. The precipitate was filtered and washed with water, then crystallized from ethanol to give **6a-c**.

2-Amino-5-(2-fluorobenzylthio)-1,3,4-thiadiazole (6a): Yield 80 %, m.p. 145-146°C. IR (KBr, cm^{-1}): 3312 ν(NH); ^{1}H NMR (80 MHz, DMSO-d_6): δ 4.4 (s, 2H, CH_2), 6.6 (brs, 2H, NH_2), 7.0-7.4 (m, 4H, phenyl).

2-Amino-5-(3-fluorobenzylthio)-1,3,4-thiadiazole (6b): Yield 67 %, m.p. 132-133°C. IR (KBr, cm^{-1}): 3364 ν(NH); ^{1}H NMR (80 MHz, DMSO-d_6): δ 4.3 (s, 2H, CH_2), 6.6 (brs, 2H, NH_2), 6.9-7.4 (m, 4H, phenyl).

2-Amino-5-(4-fluorobenzylthio)-1,3,4-thiadiazole (6c): Yield 87 %, m.p. 149-150°C. IR (KBr, cm^{-1}): 3345 ν(NH); ^{1}H NMR (80 MHz, DMSO-d_6): δ 4.3 (s, 2H, CH_2), 6.5 (brs, 2H, NH_2), 6.9-7.4 (m, 4H, phenyl).

Prepration of compounds 7a-c, General procedure: To a stirring solution of conc. HCl (30 mL) and water (13 mL), containing copper powder (0.5 g), a mixture of compound **6** (10 mmol) and sodium nitrite (1.59 g, 30 mmol) was added in small portions at 0°C. The reaction mixture was allowed to reach room temperature and was stirred for an additional 1 h, then heated at 60°C for 15 min. The cooled reaction mixture was extracted with chloroform (3 × 50 mL).The organic layer was washed with water and dried (sodium sulphate). The solvent was removed under reduced pressure to give crude **7**, which was purified by flash chromatography on silica gel eluting with chloroform to give **7a-c**.

2-Chloro-5-(2-fluorobenzylthio)-1,3,4-thiadiazole (7a): Yield 52 %, oily compound; ^{1}H NMR (80 MHz, $CDCl_3$): δ 4.7 (s, 2H, CH_2), 7.1-7.5 (m, 4H, phenyl).

2-Chloro-5-(3-fluorobenzylthio)-1,3,4-thiadiazole (7b): Yield 42 %, m.p. 35-36°C ; ^{1}H NMR (80 MHz, $CDCl_3$): δ 4.5 (s, 2H, CH_2), 7.0-7.5 (m, 4H, phenyl).

2-Chloro-5-(4-fluorobenzylthio)-1,3,4-thiadiazole (7c): Yield 53 %, m.p. 48-49°C. ^{1}H NMR (80 MHz, $CDCl_3$): δ 4.5 (s, 2H, CH2), 7.0-7.5 (m, 4H, phenyl).

Prepration of 4a-i, General procedure: A mixture of compound **7** (0.5 mmol), piperazinyl quinolone 1-3 (0.5 mmol) and $NaHCO_3$ (42 mg, 0.5 mmol) in DMF (10 mL), was heated at 85-90°C for 12-18 h. After consumption of piperazinyl quinolone (monitored by TLC), H_2O (20 mL) was added and the precipitate was filtered and washed with water to give the crude **4**. The crude product was purified by chromatography on a short silica gel column, eluting with chloroform and ethanol (95:5). The product was crystallized from DMF-H_2O to give **4a-i**.

1-Ethyl-6-fluoro-7-{4-[5-(2-fluorobenzylthio)-1,3,4-thiadiazol-2-yl]-1-piperazinyl}-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (4a): Yield 35 %, m.p. 219-220°C. ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.27 (t, 3H, CH_3, J = 7.0 Hz), 3.42-3.79 (m, 8H, piperazine), 4.32-4.45 (m, 4H, CH_2, CH_2-S), 6.8-7.42 (m, 5H, H-C_8 quinolone and phenyl), 8.13 (d, 1H, H-C_5 quinolone, J = 12.8 Hz), 8.70 (s, 1H, H-C_2 quinolone). Anal. Calcd. for $C_{25}H_{23}F_2N_5O_3S_2$: C 55.24, H 4.26, N 12.88. Found: C 55.55, H 4.10, N 12.93.

1-Ethyl-6-fluoro-7-{4-[5-(3-fluorobenzylthio)-1,3,4-thiadiazol-2-yl]-1-piperazinyl}-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (4b): Yield 40 %, m.p. 181-182°C. ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.22 (t, 3H, CH_3, J = 7.0 Hz), 3.27-3.90 (m, 10H, piperazine and CH_2), 4.36 (s, 2H, CH_2-S), 6.87-7.31 (m, 5H, phenyl and H-C_8 quinolone), 8.10 (d, 1H, H-C_5 quinolone, J = 12.8 Hz), 8.70 (s, 1H, H-C_2 quinolone). Anal. Calcd. for $C_{25}H_{23}F_2N_5O_3S_2$: C 55.24, H 4.26, N 12.88. Found: C 55.63, H 4.14, N 12.71.

1-Ethyl-6-fluoro-7-{4-[5-(4-fluorobenzylthio)-1,3,4-thiadiazol-2-yl]-1-piperazinyl}-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (4c): Yield 45 %, m.p. 221-222°C. ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.61 (t, 3H, CH_3, J = 7 Hz), 3.40-3.76 (m, 8H, piperazine), 4.30-4.38 (m, 4H, CH_2 and CH_2-S), 6.98-7.38 (m, 5H, H-C_8 quinolone and phenyl), 8.12 (d, 1H, H-C_5 quinolone, J = 12.4 Hz), 8.70 (s, 1H, H-C_2 quinolone). Anal. Calcd. for $C_{25}H_{23}F_2N_5O_3S_2$: C 55.24, H 4.26, N 12.88. Found: C 55.51, H 4.15, N 12.62.

1-Cyclopropyl-6-fluoro-7-{4-[5-(2-fluorobenzylthio)-1,3,4-thiadiazol-2-yl]-1-piperazinyl}-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (4d): Yield 41 %, m.p. 184-185°C. IR (KBr, cm^{-1}): 1715 ν(C=O). ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.10-1.55 (m, 4H, cyclopropyl), 3.30-3.84 (m, 9H, piperazine and cyclopropyl), 4.44 (s, 2H, CH_2), 7.05-7.57 (m, 5H, phenyl and H-C_8 quinolone), 8.00 (d, 1H, H-C_5 quinolone, J = 12.8 Hz), 8.73 (s, 1H, H-C_2 quinolone). Anal. Calcd. for $C_{26}H_{23}F_2N_5O_3S_2$: C 56.20, H 4.17, N 12.60. Found: C 56.63, H 4.14, N 12.26.

1-Cyclopropyl-6-fluoro-7-{4-[5-(3-fluorobenzylthio)-1,3,4-thiadiazol-2-yl]-1-piperazinyl}-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (4e): Yield 48 %, m.p. 231-232°C. ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.12-1.52 (m, 4H, cyclopropyl), 3.29-3.78 (m, 9H, piperazine and cyclopropyl), 4.37 (s, 2H, CH_2), 6.97-7.55 (m, 5H, phenyl and H-C_8 quinolone), 8.00 (d, 1H, H-C_5 quinolone, J = 12.8 Hz), 8.73 (s, 1H, H-C_2 quinolone). Anal. Calcd. for $C_{26}H_{23}F_2N_5O_3S_2$: C 56.20, H 4.17, N 12.60. Found: C 56.41, H 4.15, N 12.33.

1-Cyclopropyl-6-fluoro-7-{4-[5-(4-fluorobenzylthio)-1,3,4-thiadiazol-2-yl]-1-piperazinyl}-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (4f): Yield 39 %, m.p. 325-328°C. IR (KBr, cm^{-1}): 3344 ν(OH). ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.12-1.52 (m, 4H, cyclopropyl), 3.30-3.86 (m, 9H, piperazine and cyclopropyl), 4.35 (s, 2H, CH_2), 6.99-7.55 (m, 5H, phenyl and H-C_8 quinolone), 8.00 (d, 1H, H-C_5 quinolone, J = 12.8 Hz), 8.73 (s, 1H, H-C_2 quinolone). Anal. Calcd. for $C_{26}H_{23}F_2N_5O_3S_2$: C 56.20, H 4.17, N 12.60. Found: C 56.53, H 4.12, N 12.24.

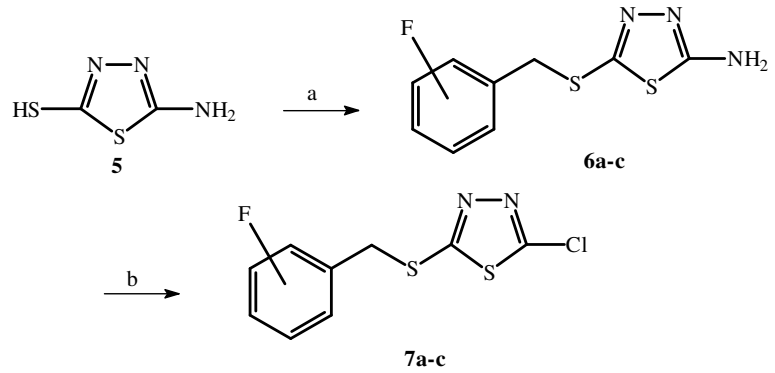
1-Ethyl-6-fluoro-7-{4-[5-(2-fluorobenzylthio)-1,3,4-thiadiazol-2-yl]-1-piperazinyl}-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (4g): Yield 62 %, m.p. 223-224°C. IR (KBr, cm^{-1}): 1725 ν(C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (t, 3H, CH_3, J = 7 Hz), 3.67-4.02 (m, 10H, piperazine and CH_2), 4.43 (s, 2H, CH_2-S), 7.04-7.44 (m, 4H, phenyl), 8.18 (d, 1H, H-C_5 naphthyridine, J = 13.6 Hz), 8.73 (s, 1H, H-C_2 naphthyridine), 14.96 (s, 1H, OH). Anal. Calcd. for $C_{24}H_{22}F_2N_6O_3S_2$: C 52.93, H 4.07, N 15.43. Found: C 52.66, H 4.03, N 15.18.

1-Ethyl-6-fluoro-7-{4-[5-(3-fluorobenzylthio)-1,3,4-thiadiazol-2-yl]-1-piperazinyl}-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (4h): Yield 67 %, m.p. 223-224°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (t, 3H, CH_3), 3.67-4.02 (m, 8H, piperazine), 4.37 (s, 2H, CH_2-S), 4.43 (q, 2H, CH_2), 6.98-7.37 (m, 4H, phenyl), 8.18 (d, 1H, H-C_5 naphthyridine, J = 12.8 Hz), 8.73 (s, 1H, H-C_2 naphthyridine), 14.87 (s, 1H, OH). Anal. Calcd. for $C_{24}H_{22}F_2N_6O_3S_2$: C 52.93, H 4.07, N 15.43. Found: C 52.33, H 4.10, N 15.76.

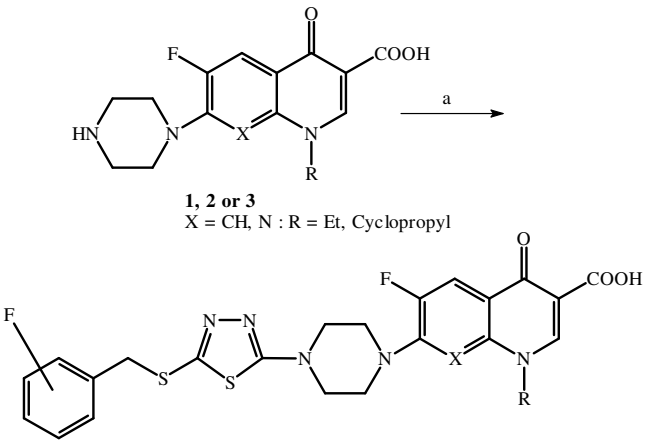
1-Ethyl-6-fluoro-7-{4-[5-(4-fluorobenzylthio)-1,3,4-thiadiazol-2-yl]-1-piperazinyl}-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (4i): Yield 57 %, m.p. 222-223°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (t, 3H, CH_3), 3.65-4.07 (m, 8H, piperazine), 4.36-4.53 (m, 4H, CH_2-S and CH_2), 6.99-7.46 (m, 4H, phenyl), 8.15 (d, 1H, H-C_5 naphthyridine, J = 12.8 Hz), 8.70 (s, 1H, H-C_2 naphthyridine). Anal. Calcd. for $C_{24}H_{22}F_2N_6O_3S_2$: C 52.93, H 4.07, N 15.43. Found: C 52.57, H 4.16, N 15.79.

RESULTS AND DISCUSSION

The synthetic pathway to intermediates **6a-c** and target compounds **4a-i**, are presented in **Schemes I** and **II**.



Scheme-I. Synthesis of intermediates **7a-c**. Reagents and conditions: (a) appropriate benzyl halide, NaOH, EtOH 80 %, room temperature, 24 h; (b) $NaNO_2$, HCl, Cu, 0°C, 1 h, then room temperature, 2 h



Scheme-II. Synthesis of compounds **4a-i**. Reagents and conditions: (a) compounds **7a-c**, $NaHCO_3$, DMF, 85-90°C

The 2-amino-5-(fluorobenzylthio)-1,3,4-thiadiazole derivatives (**6a-c**) were obtained from 5-amino-1,3,4-thiadiazol-2-thiol (**5**). Thus treatment of **5** with benzyl chloride derivatives in presence of NaOH in 80 % ethanol at room temperature afforded *S*-benzyl intermediates **6a-c**[14]. Diazotization of amine **6a-c** with $NaNO_2$ in hydrochloric acid in presence of copper powder gave the corresponding 2-chloro-1,3,4-thiadiazoles (**7a-c**)[14,15]. Reaction of compounds **7a-c** with piperazinyl quinolones **1**, **2** or **3** in DMF in the presence of $NaHCO_3$ at 85-90°C gave compounds **4a-i**[16-18].

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