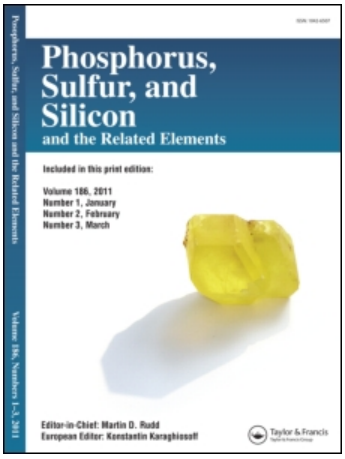

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SYNTHESIS AND REACTIONS OF SOME NEW 6,7-DIHALOQUINOLONES BEARING MERCAPTO GROUPS

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Reaction of the 6-chloro-7-fluoroquinoline ***7*** *with methyl 2-mercaptoacetate, methyl 3-mercaptopropionate, or sodium thiophenolate furnished the quinolone derivatives of 3-carbonylsulfanyl-acetic acid methyl ester* ***8****, the propionoate analogue* ***10****, and 3-carbothioic acid* S*-phenyl ester* ***11*** *respectively. Ester* ***8*** *was converted into the 3-carbothioic acid* S*-carbamoyl derivative* ***9****. Analogously, treatment of the 6,7-diflouroquinolone* ***12*** *with amino or mercapto precursors led to the formation of* ***13*** *and* ***14*** *respectively. Reaction of* ***14*** *with aqueous* NH_3 *or* H_2O_2 */AcOH afforded the acetamide* ***15*** *and the sulfoxide* ***16*** *analogues, respectively. The 5′-thioalkyl-acyclic quinolone nucleosides* ***19*** *and* ***20*** *were obtained from reaction of the mesylate derivative* ***18****, prepared from the free nucleoside* ***17****, with the methanthiolate and thiophenolate anions.*

Quinolone antibacterial agents,[1–3] such as nalidixic acid **1**,[4] norfloxacin **2**,[5] ciprofloxacin (CPFX, **3**),[6] ofloxacin (OFLX, **4**),[7] and sparfloxacin (SPFX, **5**),[8] are major a class of antibacterial drugs. These quinolones show broad-spectrum antibacterial activity and are widely used to treat patients with infections. In addition, some quinolone antibacterial agents play an important role in the cancer chemotherapy, and adriamycin and etoposides[9] are among these quinolones with various cytotoxic activity. Furthermore, some quinolones such as **6** exhibited antiinflammatory activity for treatment of asthma[10] other than antibacterial or anticancer effect. Recently, the incidence of infections by gram-positive and gram-negative bacteria resistant to these

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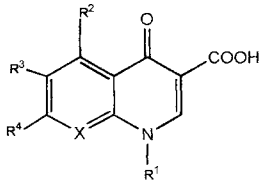
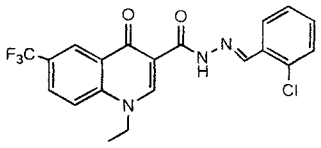




6

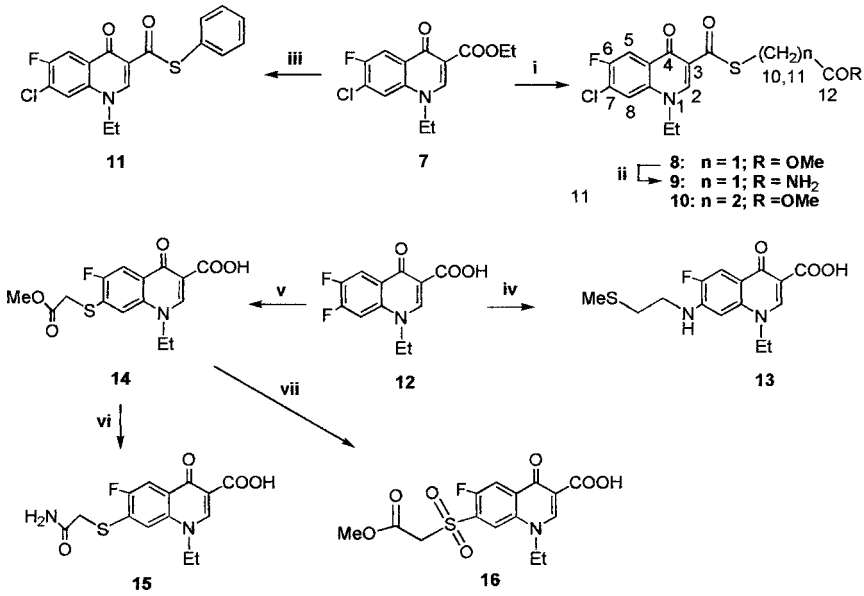
	R^1	R^2	X	R^3	R^4
1. nalidixic acid	Et	N	N	H	Me
2. norfloxacin	Et	H	CH	F	HN⌒N
3. ciprofloxacin	▷—	H	CH	F	HN⌒N
4. ofloxacin	—$OCH_2CH(Me)$—		CH	H	MeN⌒N Me
5. sparfloxacin	▷—	NH_2	CF	F	MeN⌒N Me

FIGURE 1

quinolones has been increasing, so that novel quinolones having higher activity against quinolone-resistant bacteria are required.[11] Nevertheless, some quinolones cause injury to the chromosom of eukaryotic cells.[12] Accordingly, several studies[13] described various modifications in the quinolone ring. For example, substitution with different groups at aromatic ring,[14–17] replacement of the same ring by thiophene moiety,[18–21] introduction of amido group,[10,22,23] at C-3, substitution at N-1 by sugar,[23–25] acyclic moities,[26] or benzyl-1,2,4-triazolo precursors,[27] as well as sugarhydrazone, thiadiazole and oxadiazole precursors[28] at C-3, have been studied. These finding prompted us to optimize the substituents at N-1, C-3, and C-7 by new potential mercapto groups.

RESULTS AND DISCUSSION

Treatment of the quinolone ester **7**[29] with methyl 2-mercaptoacetate, methyl 3-mercapto-propionate or sodium thiophenoate in a 1:3 ratio, using DMF as a solvent at 80°C for 10 h procceded smoothly and furnished the quinolone derivatives of alkyl 3-carbonylsulfanyl esters **8**, **10**, and **11** in yields of 69%, 67%, and 65% respectively. Treatment of **8** with aqueous NH_3 solution at room temperature gave the 3-carbothioic acid *S*-carbamoyl derivative **9** (60%, Scheme 1). The structures of **8–11** were confirmed on the bases of their ^{1}H NMR spectra, which were characterized by the presence of a singlet in the region δ_H 8.96–8.82 (H-2) and two doublets at δ_H 9.12–8.65 with large coupling ($J_{5,F} = 8.9–8.70$)



SCHEME 1 *Reagents and conditions:* (i) methyl 2-mercaptoacetate or methyl 3-mercaptopropionate, DMF, 80°C, 10 h; (ii) aq. NH_3, rt, 10 h; (iii) sodium thiophenolate, DMF, 80°C, 10 h; (iv) (2-methylthio)-ethylamine, pyridine, 100°C, 4 h; (v) methyl 2-mercaptoecetate/NaOMe, pyridine, 5 h, 80°C; (vi) aq. NH_3, rt, 8 h; (vii) H_2O_2/AcOH, rt, 20 h.

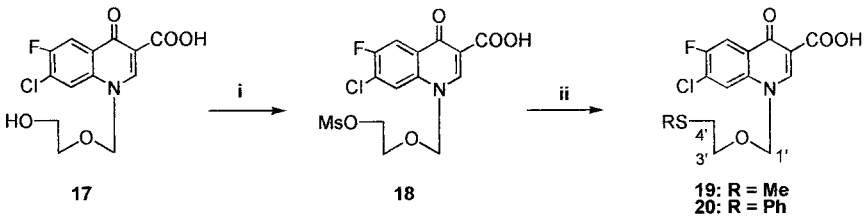
and at δ_H 7.84–7.70 with small coupling constants ($J_{8,F} \sim 5.5$ Hz), assigned to H-5 and H-8, respectively. The CH_2-11 of **8** and **9** appeared as singlets at δ_H 3.76 and 4.01, respectively, and this higher shift might be due to the shielding effect of the amide group. The CH_2-11 and CH_2-12 of **10** appeared as triplets at δ_H 3.69 and 3.60 respectively.

Nucleophilic aromatic substitution at 6,7-difluoroquinolones was regioselective at C-7 in all cases and no C-6 substitution was detected.[30] Therefore, our attempt to substitute the fluorine atom at C-7 of compound **12**[31] by thioalkyl group or alkylamino analogue bearing thio precursor was successful. Thus, treatment of **12** with 2-(methylthio)ethylamine in dry pyridine at 100°C for 5 h gave, after neutralization and purification, the 7-[2-(methylthio)ethylamino)] quinolone **13** (57%). Similarly, treatment of methyl 2-mercaptoacetate with sodium methoxide first, followed by treatment with **12** in a ratio of 3:1 in dry pyridine at 80°C for 5 h, afforded, after purification, the 7-thio-(methyl aceto-*S*-methyl) quinolone analogue **14** (50%, Scheme 1).

Derivatization of the ester group at C-7 of **14** led to a new potential quinolones. Thus, reaction of **14** with aqueous NH_3 solution at room temperature for 8 h gave the 7-thio-(carbamoyl-*S*-methyl) analogue **15** (53%), while, oxidation of **14** with H_2O_2/AcOH at room temperature for 20 h furnished, after purification, sulfone **16** (40%, Scheme 1).

The structures of **13–16** were identified from the ^{1}H NMR and mass spectra. The ^{1}H NMR spectra showed similar signal patterns. The H-2, and H-5 signals appeared as doublets in the region δ_H 9.12–8.58 and 8.25–8.08 respectively. The CH_2 adjacent to the sulfur atom of **13** appeared at lower field (δ_H 2.52) in comparison to those of the same group at **14** and **15**, which resonated at δ_H 3.95 and 3.73 respectively. The difference in the chemical shift might due to the deshielding effect of the ester group around the CH_2 group. Such a difference for the same group of **16** was shown clearly (δ_H 4.20), and this increasing by 0.35 ppm is due to the influence of the sulfoxide group at C-7. The NH_2 group of **15** appeared as a broad singlet at δ_H 6.22.

Recently, some reported acyclic nucleosides bearing quinolone bases exhibited highly antiviral and antibacterial activities.[26] These activity prompted us to select one of these nucleosides, 7-chloro-6-fluoro-1,4-dihydro-1-[(2-hydroxyethoxy)methyl]-4-oxo-quinoline-3-carboxylic acid (**17**), in an attempt to change the $C_{5'}$-OH group by a thio precursors. Thus, mesylation of **17** with methanesulfonyl chloride in dry pyridine at room temperature for 6 h gave, after chromatography, the mesylate derivative **18** (68%). Nucleophilic displacement of the sulfonate group proceeded smoothly by the thio anions. Treatment of **18** with sodium methanthiolate or sodium thiophenolate in DMF at 100°C for 3 h afforded, after chromatographic purification, the 5′-thio-nucleoside analogues **19** and **20** (63% and 56% respectively) (Scheme 2). The structures of **19** and **20** were confirmed by their ^{1}H NMR and mass spectra as well as with a comparison to those of the known acyclic nuceolsides.[26] The H-2 of both **19** and **20** appeared as singlets at δ_H 8.80 and 8.20, respectively, while H-5 and H-8 resonated



SCHEME 2 *Conditions and reagents:* (i) MsCl, pyridine, rt, 6 h; (ii) NaSMe, or NaSPh, DMF; 100°C, 3 h.

as doublets at δ_H 8.21 ($J_{5,F} = 5.8$ Hz), 8.20 ($J_{5,F} = 8.4$ Hz) and 8.00 ($J_{8,F} = 5.8$ Hz), and 7.98 ($J_{8,F} = 5.9$ Hz) respectively. The singlets at δ_H 5.73 and 5.69 were attributed to CH_2-1′ protons, respectively, while the triplets at δ_H 3.79 ($J_{3',4'} = 4.2$ Hz), and δ_H 3.75 ($J_{3',4'} = 4.0$ Hz) were asigned to H-3′ respectively. The H-4′ in both compounds resonated at lower field as triplets (δ_H 2.71 and 2.65 respectively) in comparison to those of the same protons of the mesylate **18** which appeared at higher field (δ_H 4.29). This difference of ~2.60 ppm might due to the the deshielding effect of the thio group around CH_2-4′. The antibacterial screening of the new quinolones is under investigation.

EXPERIMENTAL

General Procedure

Melting points are uncorrected. ^{1}H NMR spectra were recorded at Bruker AC-250, WM-250 spectrometers. Column chromatography was performed on silica gel (70-230 mesh, Merck). EI and FAB mass spectra were recorded on a MAT 312 mass spectrometer using 3-nitrophenol (NBOH) or glycerol as matrices. Some molecular ions were detected by doping the sample with Na^+ ion.

Preparation of 3-Substituted 7-Chloro-6-fluoroquinolones 8, 10, and 11

General Procedure

A suspension of the quinolone ester **7** (0.50 g, 1.79 mmol) in dry DMF (20 ml) and the appropriate substrate (2.0 mmol. aq.) was stirred at 80°C for 10 h. After cooling, the precipitate was separated by filtration, washed with water, then with EtOH, and finally dried at 80–100°C under vaccum to give the desired quinolone.

3-(7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carbonylsulfanyl)acetic Acid Methyl Ester (8)

From methyl-2-mercaptoacetate (0.32 g, 3.58 mmol). Yield: 0.44 g (69%), m.p. 157–159°C (dec). ^{1}H NMR (DMSO-d_6): δ 8.85 (s, 1H, H-2); 8.72 (d, 1H, $J_{5,F} = 8.9$ Hz, H-5); 7.75 (d, 1H, $J_{8,F} = 5.5$ Hz, H-8); 4.48 (q, 2H, $J = 7.0$ Hz, CH_2CH_3); 3.76 (s, 2H, CH_2-11); 3.71 (2, 3H, OMe); 1.58 (t, 3H, CH_2CH_3). Anal. calc. for $C_{15}H_{13}FClNO_4S$ (357.79): C, 50.36; H, 3.66, N, 3.91. Found: C, 50.09; H, 3.54; N, 3.62. MS: m/z (FAB) 358/360 (MH^+).

3-(7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carbonylsulfanyl)propionic Acid Methyl Ester (10)

From methyl 3-mercaptopropionate (0.43 g, 3.58 mmol). Yield: 0.44 g (67%), m.p. 162–165°C (dec). ^{1}H NMR (DMSO-d_6): δ 8.81 (s, 1H, H-2); 8.70 (d, 1H, $J_{5,F} = 8.8$ Hz, H-5); 7.70 (d, 1H, $J_{8,F} = 5.5$ Hz, H-8); 4.40 (q, 2H, $J = 7.0$ Hz, CH_2CH_3); 3.70 (2, 3H, OMe); 3.69 (m, 2H, CH_2-11); 3.60 (m, 2H, CH_2-12); 1.57 (t, 3H, CH_2CH_3). Anal. calc. for $C_{16}H_{15}FClNO_4S$ (371.81): C, 51.81; H, 4.07, N, 3.77. Found: C, 51.57; H, 3.92; N, 3.42. MS: m/z (FAB) 372/374 (MH^+).

7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carbothioic Acid *S*-Carbamoyl Methyl Ester (9)

A solution of **9** (0.20 g, 0.56 mmol) in aqueous NH_3 (10 ml) was stirred at room temperature for 10 h. The solution was evaporated to dryness, and the residue was recrystallized (DMF) to give **10** (0.12 g, 60%), m.p. 184–188°C (dec). ^{1}H NMR (DMSO-d_6): δ 8.82 (s, 1H, H-2); 8.65 (d, 1H, $J_{5,F} = 8.8$ Hz, H-5); 7.70 (d, 1H, $J_{8,F} = 5.6$ Hz, H-8); 4.45 (q, 2H, $J = 7.0$ Hz, CH_2CH_3); 4.02 (s, 2H, CH_2-11); 1.61 (t, 3H, CH_2CH_3). Anal. calc. for $C_{14}H_{12}FClN_2O_3S$ (342.78): C, 49.06; H, 3.53, N, 8.17. Found: C, 48.82; H, 3.42; N, 7.89. MS: m/z (FAB) 343/345 (MH^+).

7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carbothioic Acid *S*-Phenyl Ester (11)

From sodium thiophenolate (0.47 g, 3.58 mmol). Yield: 0.46 g (65%), m.p. 165–168°C (dec). ^{1}H NMR (DMSO-d_6): δ 8.96 (s, 1H, H-2); 9.12 (d, 1H, $J_{5,F} = 8.7$ Hz, H-5); 7.84–7.62 (m, 6H, Ar-H, H-8); 4.59 (q, 2H, $J = 7.0$ Hz, CH_2CH_3); 1.66 (t, 3H, CH_2CH_3). Anal. calc. for $C_{18}H_{13}FClNO_2S$ (361.82): C, 59.75; H, 3.62, N, 3.87. Found: C, 59.52; H, 3.50; N, 3.65. MS: m/z (FAB) 362/364 (MH^+).

1-Ethly-6-fluoro-1,4-dihydro-7-[2-(methylthio)-ethylamino)]-4-oxoquinoline-3-carboxylic Acid (13)

To a suspension of **12** (0.30 g, 1.18 mmol) in dry pyridine (10 ml) was added 2-(methylthio)ethylamine (0.32 g, 3.54 mmol) and heated at 100°C for 4 h. After cooling, water (20 ml) was added, and the solution was acidified with HOAc to pH 6. The precipitated product was collected by filtration and then sequentially washed with water, MeOH, and ether and finally was air dried to give **13** (0.22 g, 57%), m.p. 210–213°C (dec). ^{1}H NMR (DMSO-d_6): δ 14.02 (br s, 1H, CO_2H); 8.58 (s, 1H,

H-2); 8.15 (d, 1H, $J_{5,F} = 8.5$ Hz, H-5); 7.75 (d, 1H, $J_{8,F} = 5.5$ Hz, H-8); 4.85 (br s, 1H, NH); 4.85 (q, 2H, $J = 7.1$ Hz, CH_2CH_3); 3.92 (m, 2H, N—CH_2); 3.80 (m, 2H, S—CH_2); 2.52 (s, 3H, SMe); 1.61 (t, 3H, CH_2CH_3). Anal. calc. for $C_{15}H_{17}FN_2O_3S$ (324.37): C, 55.54; H, 5.28, N, 8.64. Found: C, 55.32; H, 5.20; N, 8.01. MS: m/z (FAB) 325 (MH^+).

1-Ethly-6-fluoro-1,4-dihydro-7-thio-(methyl aceto-*S*-methyl)-4-oxoquinoline-3-carboxylic Acid (14)

A solution of methyl 2-mercaptoacetate (0.38 g, 3.54 mmol) in 0.3 M NaOMe (5 ml) was stirred at room temperature for 30 min to give the sodium thiolate. To this salt was added a suspension of **12** (0.30 g, 1.18 mmol) in dry pyridine (10 ml), and the mixture was heated at 80°C for 5 h. After cooling, the mixture was poured into water (30 ml). The resulting solid was collected by filtration, dried and recrystallized (DMF) using decolorizing carbon to afford **14** (0.19 g, 50%), m.p. 210–213°C, decomp. ^{1}H NMR (DMSO-d_6): δ 14.13 (br s, 1H, CO_2H); 9.12 (s, 1H, H-2); 8.20 (d, 1H, $J_{5,F} = 8.3$ Hz, H-5); 7.81 (d, 1H, $J_{8,F} = 5.3$ Hz, H-8); 4.59 (q, 2H, $J = 7.1$ Hz, CH_2CH_3); 3.95 (s, 2H, S-CH_2); 1.65 (t, 3H, CH_2CH_3). Anal. calc. for $C_{15}H_{14}FNO_5S$ (339.34): C, 53.09; H, 4.16, N, 4.13. Found: C, 52.79; H, 4.08; N, 3.86. MS: m/z (FAB) 340 (MH^+).

1-Ethyl-6-fluoro-1,4-dihydro-7-thio-(carbamoyl-*S*-methyl)-4-oxoquinoline-3-carboxylic Acid (15)

A suspension of **14** (150 mg, 0.44 mmol) in aqueous NH_3 solution (7 ml) was stirred at room temperature for 6 h. The solution was evaporated to dryness, and the residue was co-evaporated with EtOH (3 × 10 ml). The residue was recrystallized (DMF) to give **15** (53 mg, 37%), m.p. 233–237°C. ^{1}H NMR (DMSO-d_6): δ 14.20 (br s, 1H, CO_2H); 9.10 (s, 1H, H-2); 8.25 (d, 1H, $J_{5,F} = 8.6$ Hz, H-5); 7.78 (d, 1H, $J_{8,F} = 5.6$ Hz, H-8); 6.22 (br s, 1H, NH_2); 4.52 (q, 2H, $J = 7.0$ Hz, CH_2CH_3); 3.73 (s, 2H, S-CH_2); 1.56 (t, 3H, CH_2CH_3). Anal. calc. for $C_{14}H_{13}FN_2O_4S$ (324.33): C, 51.85; H, 4.04, N, 8.64. Found: C, 51.66; H, 3.96; N, 8.45. MS: m/z (FAB) 347 (MNa^+).

1-Ethyl-6-fluoro-1,4-dihydro-7-(methylaceto-methylsulfonyl)-4-oxoquinoline-3-carboxylic Acid (16)

A suspension of **14** (150 mg, 0.44 mmol) in H_2O_2/AcOH solution (7 ml) was stirred at room temperature for 20 h. Water (5 ml) was added, and the solution was stirred for 30 min, followed by concentration to 3 ml and cooling at 4°C overnight. The pricipitate was collected by filtration,

washed with water, then with MeOH and finally with ether and was dried at 80°C to give **16** (66 mg, 40%), m.p. 201–204°C. ^{1}H NMR (DMSO-d_6): 14.02 (br s, 1H, CO_2H); 9.15 (s, 1H, H-2); 8.20 (d, 1H, $J_{5,F} = 8.8$ Hz, H-5); 8.15 (d, 1H, $J_{8,F} = 5.7$ Hz, H-8); 4.65 (s, 3H, OMe); 4.62 (q, 2H, $J = 7.0$ Hz, CH_2CH_3); 4.20 (s, 2H, SO_2-CH_2); 1.63 (t, 3H, CH_2CH_3). Anal. calc. for $C_{15}H_{14}FNO_7S$ (371.34): C, 48.52; H, 3.80, N, 3.77. Found: C, 48.20; H, 3.71; N, 3.48. MS: m/z (FAB) 394 (MNa^+).

7-Chloro-6-fluoro-1,4-dihydro-1-[(2-methanesulfonylethoxy)methyl]-4-oxoquinoline-3-carboxylic Acid (18)

To a cooled solution (~4°C) of **17** (0.50 g, 1.58 mmol) in dry pyridine (10 ml) was added methanesulfonyl chloride (0.24 g, 2.05 mmol) dropwise with stirring. After keeping the solution at room temperature for 6 h, the solution was poured onto an ice-bath. The solution was stirred for 30 min and then was partitioned with $CHCl_3$ (3 × 20 ml). The combined organic extracts were washed with a dilute solution (10%) of H_2SO_4 (3 × 20 ml), then diluted aqueous solution (5%) of $NaHCO_3$ (30 ml), and finally was washed with water (20 ml). The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified on short column of silica gel (10 g) using MeOH, in gradient, (0–2%) with $CHCl_3$, to give **18** (0.42 g, 68%) as a solid, m.p. 180–183°C (dec). ^{1}H NMR ($CDCl_3$): δ 8.87 (s, 1H, H-2); 8.24 (d, 1H, $J_{5,F} = 8.5$ Hz, H-5); 8.01 (d, 1H, $J_{8,F} = 5.8$ Hz, H-8); 5.75 (s, 2H, CH_2-1′); 4.29 (t, 2H, $J_{4',5'} = 4.5$ Hz, CH_2-4′); 3.85 (t, 2H, $J_{3',4'} = 4.5$ Hz, CH_2-3′); 3.09 (s, 3H, SO_2Me). Anal. calc. for $C_{14}H_{13}FClNO_7S$ (393.78): C, 42.70; H, 3.57, N, 3.62. Found: C, 42.49; H, 3.68; N, 3.83. MS: m/z (FAB) 394/396 (MH^+).

1-[(2-Alkylthioethoxy)methyl]-7-chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid

General Procedure

To a solution of **18** (150 mg, 0.38 mmol) in DMF (8 ml) was added sodium methanthiolate or sodium thiophenolate (0.60 mmol), and the solution was stirred at 100°C for 3 h. After cooling, the solution was evaporated to dryness, and the residue was partitioned between $CHCl_3$ (3 × 15 ml) and water (20 ml). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was chromatographed on a SiO_2 column (10 g) and eluted, in gradient, with MeOH (0–2%) and $CHCl_3$, to give the desired nucleoside.

7-Chloro-6-fluoro-1,4-dihydro-1-[(2-methylthioethoxy)-methyl]-4-oxoquinoline-3-carboxylic Acid (19)

Yield: 83 mg, (63%), m.p. 164–168°C (dec). ^{1}H NMR ($CDCl_3$): δ 8.80 (s, 1H, H-2); 8.20 (d, 1H, $J_{5,F} = 8.4$ Hz, H-5); 7.98 (d, 1H, $J_{8,F} = 5.9$ Hz, H-8); 5.69 (s, 2H, CH_2-1′); 3.75 (t, 2H, $J_{3',4'} = 4.0$ Hz, CH_2-3′); 2.65 (t, 2H, $J_{4',5'} = 4.0$ Hz, CH_2-4′); 2.60 (s, 3H, SMe). Anal. calc. for $C_{14}H_{13}FClNO_4S$ (345.78): C, 48.63; H, 3.79, N, 4.05. Found: C, 48.42; H, 3.68; N, 3.83. MS: m/z (FAB) 346/348 (MH^+).

7-Chloro-6-fluoro-1,4-dihydro-1-[(2-phenylthioethoxy)-methyl]-4-oxoquinoline-3-carboxylic Acid (20)

Yield: 87 mg, (56%), m.p. 176–179°C (dec). ^{1}H NMR ($CDCl_3$): δ 8.82 (s, 1H, H-2); 8.21 (d, 1H, $J_{5,F} = 8.5$ Hz, H-5); 8.00 (d, 1H, $J_{8,F} = 5.8$ Hz, H-8); 7.83–7.63 (m, 5H, Ph—H); 5.73 (s, 2H, CH_2-1′); 3.79 (t, 2H, $J_{3',4'} = 4.2$ Hz, CH_2-3′); 2.71 (t, 2H, $J_{4',5'} = 4.2$ Hz, CH_2-4′). Anal. calc. for $C_{19}H_{15}FClNO_4S$ (407.85): C, 55.95; H, 3.71, N, 3.43. Found: C, 55.74; H, 3.64; N, 3.22. MS: m/z (FAB) 408/410 (MH^+).

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