Syntheses of 6-Fluoro-7-piperazin-1-yl-9-cyclopropyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione and 6-Fluoro-7-piperazin-1-yl-9-*p*-fluorophenyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione [1]

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The syntheses of 6-fluoro-7-piperazin-1-yl-9-cyclopropyl (or 9-*p*-fluorophenyl)-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-diones as well as novel synthesis of isothiazolo-3(2*H*)-one system are described. Key steps include the regiospecific displacement of a sulfinyl group and the amination of the resultant mercapto derivative followed by an intramolecular nucleophilic displacement cyclization reaction to generate the novel 2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione nucleus.

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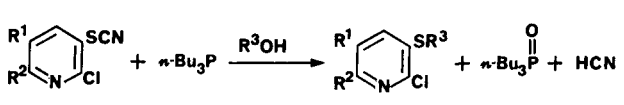
The recent discoveries of many potent clinically important antibacterial quinolones such as norfloxacin **1** [2], ciprofloxacin **2** [3], temafloxacin **3** [4], and ofloxacin **4** [5] have stimulated considerable interest in the synthesis of 1,4-dihydro-4-oxoquinoline-3-carboxylic acid derivatives. Ciprofloxacin is the most active *in vitro* marketed antibacterial quinolone. The structure-activity relationships, relative antibacterial activities and synthetic chemistry associated with these antibacterials have been reviewed [6]. Several interesting novel 6, 7, and 9 substituted quinolone analogues have recently been published [7]. During our research on the syntheses of novel 3-carboxylic acid modified quinolone derivatives as antibacterial agents, we discovered that isothiazolo derivative **5**, designated as A-62824, possesses antibacterial activity 4-10 times more potent than Ciprofloxacin **2** [8]. Although the isothiazolo-[5,4-*b*]quinoline ring system is known [9], compound **5** represents a new quinolone system providing a synthetic challenge. In this paper, we would like to report our general synthetic methodology for the preparation of 7-amino-isothiazolo derivatives and, particularly, the syntheses of 6-fluoro-7-piperazin-1-yl-9-cyclopropyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione (**5**) and 6-fluoro-7-piperazin-1-yl-9-*p*-fluorophenyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione (**6**) which is also a potent antibacterial agent [8].

The chemistry of isothiazol-3(2*H*)-one system as well as 1,2-benzisothiazol-3(2*H*)-one has been reviewed [10,11]. Benzisothiazol-3(2*H*)-ones are generally prepared by two well established routes [12] utilizing 2,2′-dithiodibenzoic acid as starting materal. Treatment of the acid with thionyl chloride yields the 2,2′-dithiodibenzoyl chloride which can be converted to the diamide. Bromination of the 2,2′-dithiobis (benzamides) and subsequent heating in acetic acid affords the desired compound. Alternatively, halogenation of the acid chloride can precede amidation and cyclization. A recent attractive synthesis utilized methyl 2-mercapto benzoate **7** as starting material [13]. It involved a sulfenyl halide intermediate **8** which was obtained by oxidation of the thiol to disulfide and followed by halogenation. Amidation of **8** yielded the cyclization product **9**. This approach, however, cannot be used for the preparation of **9** where R is hydrogen, since amidation of **8** with ammonia generally yielded disulfenamide [13,14]. This limitation precluded our use of this approach to synthesize the 2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione system.

Our synthetic pathway to the desired compounds was designed so as to generate a key intermediate having the novel tetrahydroisothiazoloquinolone ring system with a leaving group at C-7. In this way displacement at C-7 with different amines would produce many derivatives for biological evaluation. Because of the uncertainty about the stability of the isothiazolo ring C, we initially required an intermediate which could allow for addition of the C-7 amino group prior to or following construction of the C ring. The 7-fluoro-2-methylthio derivative **10** was chosen as this intermediate, since it can provide effective control of the regiochemistry of amine addition. Displacement of the fluorine atom at C-7 in **10** by piperazine will yield quinolone **12**, which upon subsequent oxidation of the C-2 methylthio group will allow for the second displacement and formation of ring C. Alternatively, initial oxidation of **10** followed by C-2 displacement and C ring formation will generate the 2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione heterocycle **11**. The fluorine at C-7 can be displaced by piperazine to yield the desired product **13** (Scheme I).

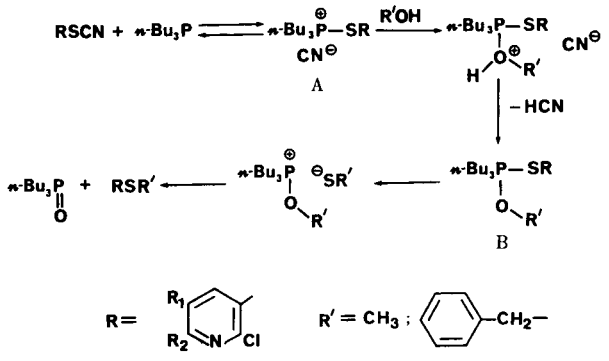
Scheme I



During our chemical investigation on the synthesis of this new heterocycle, we discovered a novel and efficient

method for the formation of isothiazolo-3(2*H*)-one ring by aminating a thiol followed by intramolecular cyclization. This synthetic methodology together with the syntheses of **5** and **6** are outlined in Scheme II.

Scheme II



Treatment of the ethyl 2,4,5-trifluorobenzoylacetate (**14**) with one molar equivalent of sodium hydride in dimethylformamide (DMF) and cyclopropyl isothiocyanate (**15a**) at 20° yielded the condensation product **16a** which, without isolation, was allowed to react with methyl iodide at room temperature to yield the enaminoketo ester **17a** (64%). This enaminoketo ester exists exclusively in one isomeric form (either *trans* or *cis*) as revealed by its ^{1}H nmr spectrum having only one singlet at δ 2.52 (corresponding to the methylthio group) as well as one set of quartet at δ 3.94 (corresponding to the methylene protons of the ethyl group). Similar treatment of the benzoylacetate **14** with *p*-fluorophenyl isothiocyanate (**15b**) at 35° yielded the ethyl 3-*p*-fluoroanilino-3-methylthio-2-(2,4,5-trifluoro)benzoylacrylate (**17b**). It is important to note that the reaction temperature and the time previous to the addition of methyl iodide is very critical. At higher reaction temperature or longer reaction time, a substantial amount of side-product was formed from an intramolecular displacement of the C-2 fluorine by the thiolate anion. Lower temperature and shorter reaction time results in poorer yields with much unreacted **14**.

Intramolecular nucleophilic displacement cyclization [15] of **17a** or **17b** with 1 molar equivalent of sodium hydride in tetrahydrofuran (THF) at reflux yielded ethyl 1-cyclopropyl-2-methylthio-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**10a**) (mp 137.5°, 81%) or ethyl 1-*p*-fluorophenyl-2-methylthio-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**10b**) (mp 167°, 75%). The methylthio derivative **10a** was subjected to piperazine displacement in order to assess the competitive reactivity of the C-7 fluorine atom and C-2 methylmercapto group. As expected, displacement of **10a** with piperazine in pyridine at 60° yielded exclusively ethyl 1-cyclopropyl-2-methylthio-6-fluoro-7-piperazin-1-yl-1,4-dihydro-4-oxoquinoline-3-carboxylate (**12**) (R = C-C_3H_5) (mp 177-178°, 96%). Its ^{1}H nmr spectrum showed the presence of a singlet at δ 2.54 (corresponding to the C-3 methylthio protons). Although chemical manipulation of **12** (R = c-C_3H_5) can lead to compound **5**, we chose to explore the chemistry of the methylthio derivative **10a** to generate the required heterocyclic ring first since **11a** can afford many 7-amino derivatives for biological evaluation.

Oxidation of the 3-carboxylic ester **10a** or **10b** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in methylene chloride at room temperature yielded ethyl 1-cyclopropyl-2-methylsulfinyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**18a**) (mp 207°, 93%) or ethyl 1-*p*-fluorophenyl-2-methylsulfinyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**18b**) (mp 205-206°, 95%). Regiospecific displacement of the sulfinyl group of the sulfoxide **18a** with sodium hydrosulfide in aqueous THF yielded ethyl 1-cyclopropyl-2-mercapto-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**19a**) (mp 93°, 87%). Its ^{1}H nmr spectrum showed the absence of a singlet at δ 2.5-3.5 region (a singlet at δ 3.17 corresponding to the sulfinyl protons was present in the sulfoxide **18a**) confirming that the methyl sulfinyl group was being displaced instead of the C-7 fluorine atom. It was apparent that the sulfinyl group was a better leaving group than the C-7 fluorine atom even though the C-7 fluorine atom in 1,4-dihydro-4-oxoquinoline-3-carboxylates is known to be very susceptible for nucleophilic displacement. Hence the intermediate **10a** or **10b** indeed provided us the flexibility we wanted. Similar reaction of the sulfoxide **18b** with sodium hydrosulfide yielded ethyl 1-*p*-fluorophenyl-2-mercapto-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**19b**) (mp 159-161°, 86%).

Hydroxylamine-*O*-sulfonic acid is a versatile synthetic reagent for amination and other transformations [16], and thiols are known to yield hydrosulfamines [17] when treated with this reagent. Treatment of **19a** with hydroxylamine-*O*-sulfonic acid in the presence of sodium bicarbonate in aqueous THF at room temperature yielded the hydrosulfamine **20a** which then cyclized *in situ* to give the desired heterocycle, 6,7-difluoro-9-cyclopropyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione (**11a**) (mp >250°, 85%). Similar treatment of **19b** with hydroxylamine-*O*-sulfonic acid yielded the *p*-fluorophenyl isothiazolo derivative **11b** (mp 249°, 85%). This amination and subsequent intramolecular cyclization of α-mercaptocarboxylic acid esters by hydroxylamine-*O*-sulfonic acid to produce the isothiazolo ring represents an efficient and novel method for the preparation of isothiazol-3(2*H*)-ones.

Displacement of **11a** with an excess of piperazine in pyridine at 70° yielded 6-fluoro-7-piperazin-1-yl-9-cyclopropyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione (**5**) (91%) indicating that the isothiazolo moiety in this new heterocycle is stable towards organic base.

Treatment of **11b** with piperazine in pyridine produced the corresponding piperazine salt of the *p*-fluorophenyl derivative **6**. The antibacterial activities of **5** and **6** were previously disclosed [8].

In summary, we have discovered an efficient route to 2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione system utilizing novel methodology for the preparation of isothiazol-3(2*H*)-one system *via* the amination of α-mercaptocarboxylic acid ester.

EXPERIMENTAL

Melting points were taken in a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed by the Abbott analytical department. The ^{1}H nmr spectra were obtained on a General Electric QE 300 spectrometer using tetramethylsilane as an internal standard. The ^{1}H nmr peaks were designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Mass spectra were recorded on a Kratos MS-50 mass spectrometer at Abbott Laboratories. The ir spectra were recorded on a Perkin-Elmer Model 710 A infrared spectrometer. The ir, nmr, and ms data of all compounds were consistent with assigned structures. Solutions were dried over magnesium sulphate. E. Merck silica gel (230-400 mesh) obtained from VWR Scientific was used for column chromatography and yields of the reactions were not optimized.

Ethyl 3-Cyclopropylamino-3-methylthio-2-(2,4,5-trifluoro)benzoylacrylate (**17a**).

Sodium hydride (1.3 g of Aldrich 60% sodium hydride in mineral) was added slowly under nitrogen atmosphere to an ice-cooled solution of 7.6 g (30.9 mmoles) of ethyl 2,4,5-trifluorobenzoyl acetate and 3.38 g (34.1 mmoles) of *N*-cyclopropyl isothiocyanate (**15a**) in 50 ml of DMF. After the addition of sodium hydride was complete, the reaction mixture was allowed to warm to ambient temperature (~20°) and stirred at ambient temperature for 22.5 hours. Methyl iodide (2.1 ml, 33.7 mmoles) was added to the reaction mixture at ambient temperature. After 17 hours, glacial acetic acid (1 ml) was added and the solvent was removed *in vacuo*. The residue was dissolved in methylene chloride and the methylene chloride solution was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with 1.5% ethyl acetate in methylene chloride to give an oily compound **17a** (7 g, 64%); ^{1}H nmr (deuteriochloroform): δ 0.86 (m, 2, CH_2), 0.95 (t, J = 7 Hz, 3, ethyl CH_3), 0.97 (m, 2, CH_2), 1.58 (bs, 1, NH), 2.52 (s, 3, SCH_3), 3.01 (m, 1, CH), 3.95 (q, J = 7 Hz, 2, ethyl CH_2), 6.88 (m, 1, aromatic H), 7.29 (m, 1, aromatic H).

By using the above procedure, using *N*-*p*-fluorophenyl isothiocyanate (**15b**) instead of **15a** and heating the mixture at 35° instead of 20° for the first part of the reaction, ethyl 3-*p*-fluorophenyl-3-methylthio-2-(2,4,5-trifluoro)benzoylacrylate (**17b**) was prepared in 86% yield; ^{1}H nmr (deuteriochloroform): δ 0.90 (t, J = 7 Hz, 3, ethyl CH_3), 1.91 (s, 3, SCH_3), 2.27 (m, 1, NH), 4.02 (q, J = 7 Hz, 2, ethyl CH_2), 7.27 (m, 6 , aromatic H).

Anal. Calcd. for $C_{19}H_{15}F_4NO_3S$: C, 55.21; H, 3.63; N, 3.39. Found: C, 55.03; H, 3.69; N, 3.37.

Ethyl 1-Cyclopropyl-2-methylthio-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**10a**).

To a solution of 20.3 g (56.5 mmoles) of ethyl 3-cyclopropylamino-3-methylthio-2-(2,4,5-trifluoro)benzoylacrylate (**17a**) in 350 ml of THF was added 2.3 g of 60% sodium hydride in mineral oil. The reaction mixture was heated at reflux for 48 hours and then 2.5 ml of glacial acetic acid was added. The solvents were removed *in vacuo* and the residue was dissolved in methylene chloride. The methylene chloride solution was washed with water, dried over anhydrous magnesium sulfate and concentrate *in vacuo*. The residue was crystallized from ether to give the ethyl 1-cyclopropyl-2-methylthio-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**10a**), (15.5 g, 81%) mp 137.5°; ^{1}H nmr (deuteriochloroform): δ 1.10 (m, 2, CH_2), 1.41 (t, J = 7 Hz, 3, ethyl CH_3), 1.49 (m, 2, CH_2), 2.57 (s, 3, SCH_3), 3.28 (m, 1, CH), 4.43 (q, J = 7 Hz, 2, ethyl CH_2), 7.68 (m, 1, aromatic H), 8.11 (m, 1, aromatic H).

Anal. Calcd. for $C_{16}H_{15}F_2NO_3S \cdot 0.5\ H_2O$: C, 55.17; H, 4.59; N, 4.02. Found: C, 55.41; H, 4.51; N, 3.89.

By using a similar procedure, using ethyl 3-*p*-fluoroanilino-3-methylthio-2-(2,4,5-trifluoro)benzoylacrylate (**17b**) instead of **17a**, ethyl 1-*p*-fluorophenyl-2-methylthio-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**10b**) was prepared in 75% yield, mp 167°; ^{1}H nmr (deuteriochloroform): δ 1.37 (t, J = 7 Hz, 3, ethyl CH_3), 2.30 (s, 3, SCH_3), 4.47 (q, J = 7 Hz, 2, ethyl CH_2), 6.52 (m, 1 aromatic H), 7.40 (d, 4, aromatic H), 8.15 (m, 1, aromatic H).

Anal. Calcd. for $C_{19}H_{14}F_3NO_3S$: C, 58.02; H, 3.56; N, 3.56. Found: C, 58.09; H, 3.56; N, 3.41.

Ethyl 1-Cyclopropyl-2-methylthio-6-fluoro-7-piperazin-1-yl-1,4-dihydro-4-oxoquinoline-3-carboxylate (**12**).

Piperazine (1.97 g, 22.9 mmoles) was added to a solution of ethyl 1-cyclopropyl-2-methylthio-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**10a**) in pyridine (10 ml) at 60°. After 18 hours under nitrogen atmosphere at 60°, the solvent was removed by distillation at reduced pressure. The residue was dissolved in methylene chloride and washed with sodium bicarbonate solution, dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a solid. Ether was added in and the mixture was filtered yielding ethyl 1-cyclopropyl-2-methylthio-6-fluoro-7-piperazin-1-yl-1,4-dihydro-4-oxoquinoline-3-carboxylate (**12**) (2.24 g, 96%), mp 177-178°; ^{1}H nmr deuteriochloroform): δ 1.07 (m, 2, CH_2), 1.39 (t, J = 7 Hz, 3, ethyl CH_3), 1.46 (m, 2, CH_2), 1.88 (bs, 1, NH), 2.54 (s, 3, SCH_3), 3.11 (m, 4, NCH_2), 3.24 (m, 4, NCH_2), 3.29 (m, 1, CH_2), 4.41 (q, J = 7 Hz, ethyl CH_2), 7.22 (d, J_{H-F} = 7.5 Hz, 1, aromatic H), 7.89 (d, J_{H-F} = 12 Hz, 1, aromatic H).

Anal. Calcd. for $C_{20}H_{24}FN_3O_3S \cdot 0.5\ H_2O$: C, 57.97; H, 6.04; N, 10.14. Found: C, 57.69; H, 5.85; N, 9.91.

Ethyl 1-Cyclopropyl-2-methylsulfinyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**18a**).

To a solution of 5.11 g (15.1 mmoles) of ethyl 1-cyclopropyl-2-methylthio-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**10a**) in 250 ml of methylene chloride was added 3.17 g (14.7 mmoles) of 3-chloroperoxybenzoic acid (Aldrich 80%). After being stirred at ambient temperature for 1.5 hours, the solution was washed with dilute sodium bicarbonate solution (3 g in 100 ml) and then sodium bisulfite solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was crystallized from diethyl ether to give 4.95 g

(93%) of ethyl 1-cyclopropyl-2-methylsulfinyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**18a**), mp 207°; ^{1}H nmr (deuteriochloroform); δ 0.99 (m, 2, CH_2), 1.39 (t, J = 7 Hz, 3, ethyl CH_3), 1.53 (m, 2, CH_2), 3.17 (s, 3, $SOCH_3$), 3.19 (m, 1, CH), 4.43 (m, 2, ethyl CH_2), 7.67 (m, 1, aromatic H), 8.14 (m, 1, aromatic H).

Anal. Calcd. for $C_{16}H_{15}F_2NO_4S \cdot 0.25\ H_2O$: C, 53.41; H, 4.31; N, 3.89. Found: C, 53.49; H, 4.39; N, 3.75.

By using a similar procedure with **10b**, ethyl 1-*p*-fluorophenyl-2-methylsufinyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**18b**) was prepared in 95% yield, mp 205-206°; ^{1}H nmr (deuteriochloroform): δ 1.41 (t, J = 7 Hz, 3, ethyl CH_3), 2.96 (s, 3, $SOCH_3$), 4.46 (q, J = 7 Hz, 2, ethyl CH_2), 6.46 (m, 1, aromatic H), 7.36 (m, 4, aromatic H), 8.21 (m, 1, aromatic H).

Anal. Calcd. for $C_{19}H_{14}F_3NO_4S$: C, 55.75; H, 3.42; N, 3.42. Found: C, 55.38; H, 3.40; N, 3.33.

Ethyl 1-Cyclopropyl-2-mercapto-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**19a**).

To a solution of 2 g (5.63 mmoles) of ethyl 1-cyclopropyl-2-methylsulfinyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**18a**) in 75 ml of THF was added 6.74 ml of 0.92 *N* sodium hydrosulfide in THF. After being stirred at ambient temperature for 4 hours, the reaction mixture was diluted with 300 ml of water and extracted with ether once. The aqueous portion was acidified with 10 ml of 1*N* hydrochloric acid at ice temperature and the resultant solution was extracted with methylene chloride. The solution was dried over magnesium sulfate and evaporated under reduced pressure to a residue which was crystallized from ether/hexane yielding 1.6 g of ethyl 1-cyclopropyl-2-mercapto-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**19a**) (88%) mp 93°; ^{1}H nmr deuteriochloroform): δ 0.98 (m, 2, CH_2), 1.46 (t, J = 7 Hz, 3, ethyl CH_3), 1.54 (m, 2, CH_2), 3.24 (m, 1, CH), 4.48 (q, J = 7 Hz, 2, ethyl CH_2), 7.72 (m, 1, aromatic H), 7.91 (m, 1, aromatic H).

Anal. Calcd. for $C_{15}H_{13}F_2NO_3S \cdot 0.25\ H_2O$: C, 54.62; H, 4.10; N, 4.24. Found: C, 54.88; H, 3.94; N, 4.04.

By using a similar procedure with **18b**, ethyl 1-*p*-fluorophenyl-2-mercapto-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**19b**) was prepared in 86% yield, mp 159-161°; ^{1}H nmr (deuteriochloroform): δ 1.42 (t, J = 7 Hz, 3, ethyl CH_3), 4.49 (q, J = 7 Hz, 2, ethyl CH_2), 6.36 (m, 1, aromatic H), 7.16 (m, 2, aromatic H), 7.27 (m, 2, aromatic H), 7.98 (m, 1, aromatic H), 13.0 (s, 1, SH).

Anal. Calcd. for $C_{18}H_{12}F_3NO_3S$: C, 56.99; H, 3.17; N, 3.69. Found: C, 56.98; H, 3.28; H, 3.57.

6,7-Difluoro-9-cyclopropyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]-quinoline-3,4-dione (**11a**).

To a solution of ethyl 1-cyclopropyl-2-mercapto-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**19a**) (735 mg, 2.25 mmoles) in 20 ml THF was added sodium bicarbonate solution (1.71 g in 30 ml water), followed by the addition of 895 mg (7.87 mmoles) of hydroxylamine-*O*-sulfonic acid. After being stirred at ambient temperature for 3 hours, the reaction mixture was diluted with water and filtered. The aqueous filtrate was extracted with ether once and acidified with 15 ml 1*N* hydrochloric and filtered. The combined residue was boiled in methanol. The suspension was cooled and filtered to give 565 mg (85%) of 6,7-difluoro-9-cyclopropyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]-quinoline-3,4-dione (**11a**), mp >250°; ^{1}H nmr (DMSO-d_6): δ 1.16 (m, 2, CH_2), 1.33 (m, 2, CH_2), 3.49 (m, 1, CH), 8.0 (m, 1, aromatic H), 8.19 (m, 1, aromatic H).

Anal. Calcd. for $C_{13}H_8F_2N_2O_2S \cdot 0.5\ H_2O$: C, 51.69; H, 2.97; N, 9.24. Found: C, 51.46; H, 2.70; N, 9.20.

By using a similar procedure with **19b**, 6,7-difluoro-9-*p*-fluorophenyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione (**11b**) was prepared in 85% yield, mp 249°; ^{1}H nmr (DMSO-d_6): δ 6.98 (m, 1, aromatic H), 7.56 (m, 2, aromatic H), 7.78 (m, 2, aromatic H), 8.17 (m, 1, aromatic H).

6-Fluoro-7-piperazin-1-yl-9-cyclopropyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione (**5**).

To a suspension of 436 mg (1.48 mmoles) of 6,7-difluoro-9-cyclopropyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione (**11a**) in 9 ml of pyridine at 70° was added 755 mg (8.78 mmoles) of piperazine. After a few minutes, a clear solution was formed. After being stirred for 2 days at 70°, the reaction mixture was cooled to ambient temperature and filtered. The solid was washed with ether and then cold water to give 480 mg (91%) of 6-fluoro-7-piperazin-1-yl-9-cyclopropyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione (**5**), mp >275°; ^{1}H nmr (perdeuterioacetic acid): δ 1.36 (m, 2, CH_2), 1.48 (m, 2, CH_2), 3.37 (m, 1, CH), 3.60 (m, 4, NCH_2), 3.60 (m, 4, NCH_2), 7.52 (bd, 1, aromatic H), 7.89 (d, $J_{H\text{-}F}$ = 12 Hz, 1, aromatic H).

Anal. Calcd. for $C_{17}H_{17}FN_4O_2S \cdot 0.3\ H_2O$: C, 55.97; H, 4.83; N, 14.94. Found: C, 55.84; H, 4.83; N, 15.36.

Similarly prepared was the piperazine salt of 6-fluoro-7-piperazin-1-yl-9-*p*-fluorophenyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]-quinoline-3,4-dione (**6**), mp 251-252° dec; ^{1}H nmr (DMSO-d_6): δ 2.70 (bs, 8, NCH_2), 2.77 (m, 4, NCH_2), 2.86 (m, 4, NCH_2), 7.38 (m, 1, aromatic H), 7.56 (m, 2, aromatic H), 7.73 (m, 2, aromatic H), 7.84 (d, $J_{H\text{-}F}$ = 12 Hz, 1, aromatic H), 8.57 (m, 1, NH).

Anal. Calcd. for $C_{20}H_{16}F_2N_4O_2S \cdot C_4H_{10}N_2 \cdot 0.5\ H_2O$: C, 56.36; H, 5.28; N, 16.44. Found: C, 56.22; H, 5.10; N, 16.15.

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