# Studies on Pyridonecarboxylic Acids. 1. Synthesis and Antibacterial Evaluation of 7-Substituted-6-halo-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acids[1]

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A series of [1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acids and their esters were prepared and evaluated for antibacterial activity. The derivatives with a hydrogen or methyl group at C-1, fluorine at C-6, and piperazinyl or 4-methyl-1-piperazinyl group at C-7 showed superior in vitro antibacterial activity, and the derivatives with 4-methyl-1-piperazinyl group at C-7 had potent in vivo activity. Compound **29a** (NM394) showed excellent in vitro antibacterial activity and low toxicity but poor absorption from the gastrointestinal tract. Compound **29ee** (NM441), an *N*-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl] derivative of **29a**, was found to possess a favorable pharmacokinetic profile and oral activity superior to that of ciprofloxacin in experimental animals.

Recently many clinically useful therapeutic agents, collectively known as quinolones, such as norfloxacin (**1**),[2] enoxacin (**2**),[3] ofloxacin (**3**),[4] ciprofloxacin (**4**),[5] lomefloxacin (**5**),[6] and tosufloxacin (**6**),[7] have attracted increased attention as a source of new antibacterial agents. A large number of tricyclic analogues which contain a three-atom bridge connecting the vicinal positions of quinolones with the exception of the C-2 position, have also recently been reported to be good antibacterial agents, i.e., oxolinic acid (**7**),[8] tioxacin (**8**),[9] flumequine (**9**),[10] and ofloxacin (**3**).

Until recently little attention was paid to the role of the C-2 substituents of the quinolones in antibacterial activity since the introduction of a methyl group at C-2 resulted in completely inactive compounds, i.e., 1-ethyl-2-methyl-6,7-(methylenedioxy)-4-quinoline-3-carboxylic acid (**10**)[11] and 2,7-dimethyl-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthylidine-3-carboxylic acid (**11**).[12] Although it was not clear why compound **10** and **11** lost their antibacterial activity, it was suggested that the coplanarity of the C-3 carboxyl and C-4 carbonyl groups of the quinolone ring was inhibited by the steric bulk of the methyl group and that the interaction between the drug and target enzyme was weakened.[13] This suggestion led us to believe that minimization of the steric hindrance of the C-2 substituent exerting toward the C-3 carboxyl group can lead to active antibacterial agents. Therefore we designed the tricyclic structure **12** as shown in Figure 1, which has a bridge connecting the quinolone N-1 and C-2 positions, to see how antibacterial activity would be affected by prohibiting the free rotation of the C-2 substituent in the quinolone.

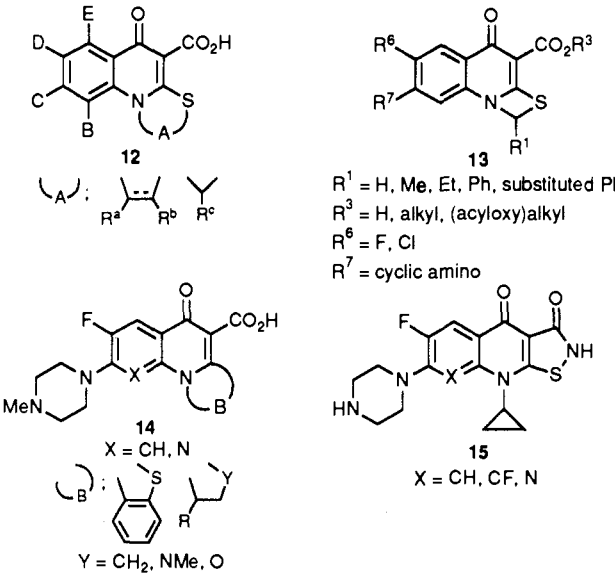


**Figure 1.**

(1) This work was presented in part at the 29th Interscience Conference on Antimicrobial Agents and Chemotherapy, Houston, Sept 17–20, 1989; 10th Symposium on Medicinal Chemistry, Kyoto, Nov 30–Dec 1, 1989; 109th Annual Meeting of Japan Pharmaceutical Society, Nagoya, April 4–6, 1989.

(2) Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Irikura, T. Structure–Activity Relationships of Antibacterial 6,7- and 7,8-Disubstituted 1-Alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic Acids. *J. Med. Chem.* **1980**, *23*, 1358–1363.

(3) Matsumoto, J.; Miyamoto, T.; Minamida, A.; Nishimura, Y.; Egawa, H.; Nishimura, H. Pyridonecarboxylic Acids as Antibacterial Agents. 2. Synthesis and Structure–Activity Relationships of 1,6,7-Trisubstituted 1,4-Dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids, Including Enoxacine, a New Antibacterial Agent. *J. Med. Chem.* **1984**, *27*, 292–301.

(4) Sato, K.; Matsuura, Y.; Inoue, M.; Une, T.; Osada, Y.; Ogawa, H.; Mitsuhashi, S. In Vitro and In Vivo Activity of DL-8280, a New Oxazine Derivative. *Antimicrob. Agents Chemother.* **1982**, *22*, 548–553.

(5) Wise, R.; Andrews, J. M.; Edwards, L. J. In Vitro Activity of Bay 09867, a New Quinoline Derivative, Compared with Those of Other Antimicrobial Agents. *Antimicrob. Agents Chemother.* **1983**, *23*, 559–564.

(6) Katoh, H.; Ogawa, N.; Koshinaka, E.; Suzuki, T.; Yagi, N. Eur. Patent Appl. EP 140116, 1985.

(7) Narita, H.; Konishi, Y.; Nitta, J.; Nagai, H.; Kobayashi, J.; Watanabe, Y.; Minami, S.; Saikawa, I. Pyridonecarboxylic Acids as Antibacterial Agents. IV. Synthesis and Structure-Activity Relationship of 7-Amino-1-aryl-6-fluoro-4-quinoline-3-carboxylic Acids. *Yakugaku Zasshi* **1986**, *106*, 795–801.

(8) (a) Agui, H.; Mitani, T.; Nakashita, M.; Nakagome, T. Studies on Quinoline Derivatives and Related Compounds. I. A New Synthesis of 1-Alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids. *J. Heterocycl. Chem.* **1971**, *8*, 357–365. (b) Kaminsky, D.; Meltzer, R. I. Quinoline Antibacterial Agents. Oxolinic Acid and Related Compounds. *J. Med. Chem.* **1968**, *11*, 160–163.

(9) Dohmori, R.; Kadoya, S.; Takamura, I.; Suzuki, N. *Chem. Pharm. Bull.* **1976**, *24*, 130–135. Ibid. **1976**, *24*, 136–146.

(10) Gerster, J. F. U.S. Patent 3896131.

(11) (a) Agui, H.; Mitani, T.; Izawa, A.; Komatsu, T.; Nakagome, T. Studies on Quinoline Derivatives and Related Compounds. 5. Synthesis and Antimicrobial Activity of Novel 1-Alkoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids. *J. Med. Chem.* **1977**, *20*, 791–796. (b) Mitscher, L. A.; Gracey, H. E.; Clark, J. W., III; Suzuki, J. Quinolone Antimicrobial Agents. 1. Versatile New Synthesis of 1-Alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids. *J. Med. Chem.* **1978**, *21*, 485–489.

(12) Nishigaki, S.; Mizushima, N.; Yoneda, F.; Takahashi, H. Synthetic Antibacterials. 3. Nitrofurylvinyl-1,8-naphthylidine Derivatives. *J. Med. Chem.* **1971**, *14*, 638–640.

(13) Koga, H. Structure-Activity Relationships and Drug Design of the Pyridonecarboxylic Acid Type (Nalidixic Acid Type) Synthetic Antibacterial Agents. *Kagaku no Ryoiki, Zokan.* **1982**, *136*, 177–202.

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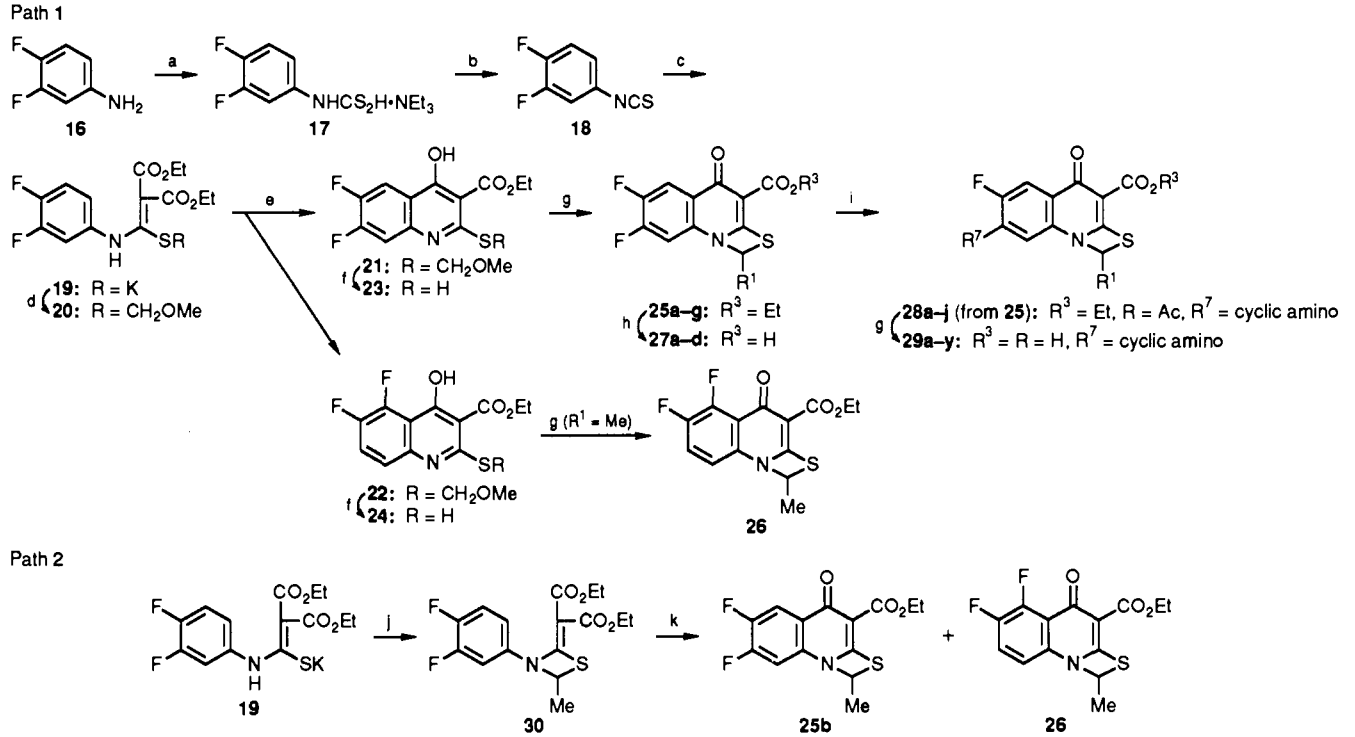
**Scheme I** [a]




[a] (a) $CS_2$, $NEt_3$; (b) $ClCO_2Et$, $CHCl_3$; (c) $CH_2(CO_2Et)_2$, KOH, dioxane, (d) $ClCH_2OMe$, $NEt_3$, toluene; (e) heat, $Ph_2O$; (f) $H^+$, EtOH; (g) $R^1CHX_2$ (X = Br, I), $K_2CO_3$, DMF; (h) KOH, $H_2O$; (i) cyclic amine, $NEt_3$, DMF (or Py); (j) $CH_3CHBr_2$, $K_2CO_3$, DMF; (k) heat, PPE.

With this idea, we synthesized a series of 4-oxo-4*H*-[1,3]-thiazeto[3,2-*a*]quinoline-3-carboxylic acids[14] and 5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic acids.[15] In this paper we report the syntheses and antibacterial activity of 7-substituted-6-halo-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acids and esters (**13**). The title compounds were found to possess excellent antibacterial activity. These compounds have a [1,3]thiazetidine moiety which is fused to the quinolone N-1 and C-2 positions, and the sulfur atom in the C-2 position is thought to have little steric effect on the C-3 carboxyl group. With respect to C-2 substituents, a comparison of our biological result with that of C-2-methylquinolone[11,12] indicates that the steric hindrance to the C-3 carboxyl group should have a large effect on antibacterial activity. After completion of our work, several syntheses of tricyclic quinolones which contain a three-atom bridge connecting the C-2 and either N-1 (**14**)[16a-c] or C-3 (**15**)[16d] were reported.

## Chemistry

The [1,3]thiazeto[3,2-*a*]quinolone-3-carboxylic acids and their analogues were synthesized as illustrated in Schemes I, II, and III. As shown in Scheme I, path 1, treatment of 3,4-difluoroa··line (**16**) with carbon disulfide in the presence of triethylamine gave triethylammonium dithiocarbamate (**17**), which was treated with ethyl chloroformate to give isothiocyanate **18**.[17] Reaction of **18** with diethyl malonate in the presence of KOH in dioxane yielded the potassium salt of methylenemalonate **19**, which was converted to methoxymethyl thioether **20**[18] by treatment with chloromethyl methyl ether. Cyclization was performed in the usual manner:[19] purified **20** was heated in diphenyl ether to afford quinoline **21** along with a small amount of the isomer **22**. The structures of **21** and **22** were determined by converting them to **25b** and **26**, respectively. The methoxymethyl group of **21** was removed with acid to give the key intermediate, ethyl 2-mercaptoquinoline-3-carboxylate **23**. Treatment of **23** with 1,1-dibromoethane in the presence of potassium carbonate yielded 6,7-difluoro[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate **25b**. By using the same procedure, 5,6-difluoro derivative **26** was prepared from **22**. The $^1H$ NMR

(14) (a) Matsumura, S.; Kise, M.; Ozaki, M.; Tada, S.; Kazuno, K.; Watanabe, H.; Kunimoto, K.; Tsuda, M. Japan Patent Kokai 57-136588. (b) Enomoto, H.; Kise, M.; Ozaki, M.; Kitano, M.; Morita, I. Japan Patent Kokai 58-103393. (c) Kise, M.; Kitano, M.; Morita, I. Japan Patent Kokai 58-105965.

(15) (a) Kise, M.; Kitano, M.; Ozaki, M.; Kazuno, K.; Shirahase, I.; Tomii, Y.; Segawa, J. Japan Patent Kokai 63-107990. (b) Kise, M.; Kitano, M.; Ozaki, M.; Kazuno, K.; Matsuda, M.; Shirahase, I.; Tomii, Y. Japan Patent Kokai 1-230584. (c) Kise, M.; Kitano, M.; Ozaki, M.; Kazuno, K.; Matsuda, M.; Shirahase, I. Japan Patent Kokai 1-294680. (d) Segawa, J.; Kitano, M.; Kazuno, K.; Tsuda, M.; Shirahase, I.; Ozaki, M.; Matsuda, M.; Kise, M. Studies of Pyridonecarboxylic Acids. 2. Synthesis and Antibacterial Activity of 8-Substituted-7-fluoro-5-oxo-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic acids. *J. Heterocycl. Chem.*, in press.

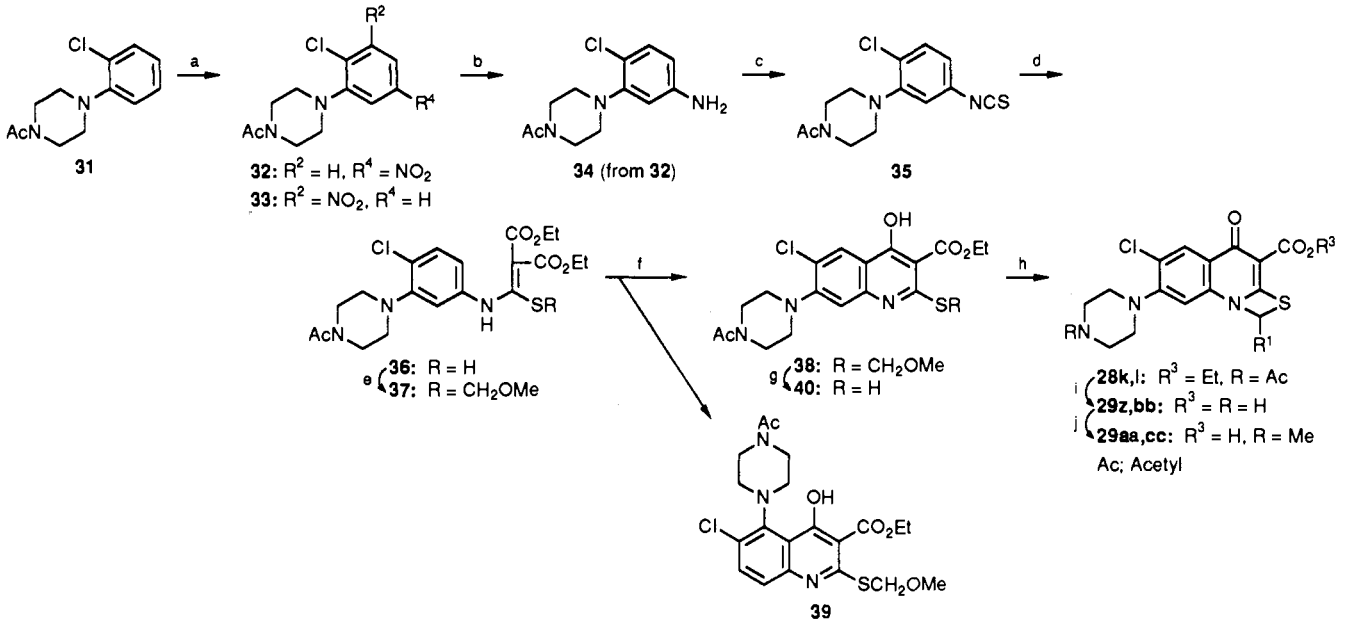
(16) (a) Chu, D. T. W.; Fernandes, P. B.; Pernet, A. G. Synthesis and Biological Activity of Benzothiazolo[3,2-*a*]quinolone Antibacterial Agents. *J. Med. Chem.* **1986**, *29*, 1531–1534. (b) Chu, D. T. W.; Claiborne, A. K. Short Synthesis of 1,2,3,5-Tetrahydro-5-oxopyrrolo[1,2-*a*]quinoline-4-carboxylic Acid and 1,2,3,4-Tetrahydro-6*H*-6-oxopyrido[1,2-*a*]quinoline-5-carboxylic Acid Derivatives. *J. Heterocycl. Chem.* **1987**, *24*, 1537–1539. (c) Kondo, H.; Taguchi, M.; Inoue, Y.; Sakamoto, F.; Tsukamoto, G. Synthesis and Antibacterial Activity of Thiazolo-, Oxazolo-, and Imidazolo-[3,2-*a*][1,8]naphthylidenecarboxylic Acids. *J. Med. Chem.* **1990**, *33*, 2012–2015. (d) Chu, D. T. W.; Claiborne, A. K. Practical Synthesis of Iminochlorothioformates: Application of Iminochloroformates in the Synthesis of Novel 2,3,4,9-Tetrahydroisothiazolo[5,4-*b*][1,8]naphthylidine-3,4-diones and 2,3,4,9-tetrahydroisothiazolo[5,4-*b*]quinoline-3,4-dione Derivatives. *J. Heterocycl. Chem.* **1990**, *27*, 1191–1195.

(17) (a) Hodgkins, J. F.; Reeves, W. P. The Modified Kaluza Synthesis. III. The Synthesis of Some Aromatic Isothiocyanates. *J. Org. Chem.* **1964**, *29*, 3098–3099. (b) Moore, M. L.; Crossley, F. S. Methyl Isothiocyanate. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. 3, pp 599–600.

(18) These compounds exist as a mixture of tautomers in $CDCl_3$ solution. Walter, W.; Meyer, H. W. Imine-enamine tautomerism. IV. Thioimidate/ketene S,N-acetal tautomerism. *Liebigs Ann. Chem.* **1975**, 19–35.

(19) Albrecht, R. Development of Antibacterial Agents of the Nalidixic Acid Type. *Prog. Drug Res.* **1977**, *21*, 9–104.

**Scheme II** [a]




[a] (a) concentrated $H_2SO_4$, $HNO_3$; (b) $H_2$; (c) $CSCl_2$, $NEt_3$, $CHCl_3$; (d) $CH_2(CO_2Et)_2$, KOH, dioxane; (e) $ClCH_2OMe$, $NEt_3$, toluene; (f) heat, $Ph_2O$; (g) $H^+$, EtOH; (h) $R^1CHX_2$ (X = Br, I), $K_2CO_3$, DMF; (i) HCl, EtOH; (j) HCHO, $HCO_2H$.

spectrum (in DMSO-$d_6$) of **25b** shows signals at $\delta$ 7.60 (dd, $J$ = 6 and 11 Hz) for the proton at C-8 and $\delta$ 7.88 (dd, $J$ = 9 and 11 Hz) at C-5, while that of **26** shows signals at $\delta$ 7.20 (ddd, $J$ = 2,4, and 9 Hz) for the proton at C-8 and $\delta$ 7.77 (ddd, $J$ = 8, 9, and 10 Hz) at C-7. Several [1,3]-thiazeto[3,2-*a*]quinoline carboxylate derivatives (**25a,c–g**) were prepared from **23** and alkylidene dihalides.[20] Hydrolysis of compounds **25a–d** with aqueous KOH provided the corresponding carboxylic acids **27a–d**. An alternative pathway for **25b** and **26** is shown in Scheme I, path 2. Treatment of **19** with 1,1-diiodoethane afforded the thiazetidine derivative **30**, which was cyclized by heating in polyphosphate ester (PPE) to give **25b** and the isomer **26** in approximately 10:3 ratio. 7-Substituted-6-fluoro-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acids (**29a–y**) were synthesized from **25a–g** or **27a–d**. Thus, treatment of **25a–g** with cyclic amines in pyridine or dimethylformamide in the presence of triethylamine gave 7-cyclic amino 3-esters (**28a–j**), which were subjected to saponification with aqueous KOH to give **29a,u–y**. Compounds **29b–t** were obtained from **27a–d** and cyclic amines. In addition, 6-chloro-7-piperazinyl derivatives (**29z–cc**) were synthesized from 1-acetyl-4-(2-chlorophenyl)piperazine (**31**)[21] by the route depicted in Scheme II. Nitration of **31** afforded **32** and the isomer **33** in approximately 52:1 ratio. Reduction of **32** followed by treatment with thiophosgene[22] yielded isothiocyanate **35**, which was converted to methoxymethyl thioether **37**[18] via **36**. Compound **37** was cyclized by heating in diphenyl ether to yield quinoline **38** and the isomer **39** in approximately 56:1 ratio.[23] Deprotection of methoxymethyl moiety of **38** gave 2-mercaptoquinoline **40**, which was treated with alkylidene dihalides to afford ethyl [1,3]thiazeto[3,2-*a*]-quinoline-3-carboxylates **28k,l**. Hydrolysis of these esters with aqueous hydrochloric acid yielded 7-piperazinyl-3-carboxylic acids **29z,bb**, which were converted to 7-(4-methyl-1-piperazinyl) analogues **29aa,cc** by treatment with formic acid and formaldehyde.[24] The in vivo efficacy of most 7-piperazinyl derivatives in the infection models did not reflect their in vitro activity. Therefore, we planned to modify 7-piperazinyl and 3-carboxyl groups to improve absorption.[25,26] As shown in Scheme III, part 1, treatment of 7-piperazinyl-3-carboxylic acids **29a,u** with 4-(bromomethyl)-5-methyl-1,3-dioxol-2-one (DMDO-Br)[25] in dimethylformamide in the presence of potassium hydrogen carbonate gave 7-[4-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-1-piperazinyl]-3-carboxylic acids **29ee,ff**. As shown in Scheme III, part 2, treatment of 6,7-difluoro esters **25b,d** with 1-acetonylpiperazine yielded 7-(4-acetonyl-1-piperazinyl) esters **41f,41h**. Treatment of **29a** with acetonyl bromide gave 7-(4-acetonyl-1-piperazinyl)-3-carboxylic acid derivative **29dd**, which was converted to (pivaloyloxy)-methyl ester **41g** by treatment with chloromethyl pivalate. As shown in Scheme III, part 3, a variety of esters were prepared by transesterification of **25b** or esterification of

(20) (a) Letsinger, R. L.; Kammeyer, C. W. The preparation of Ethylidene Iodide. *J. Am. Chem. Soc.* **1951**, *73*, 4476. (b) Pross, A.; Sternhell, S. Oxidation of Hydrazones with Iodine in the Presence of Base. *Aust. J. Chem.* **1970**, *23*, 989–1003. (c) Friedrich, E. C.; Falling, S. N.; Lyons, D. E. A Convenient Synthesis of Ethylidene Iodide. *Synth. Commun.* **1975**, *5*, 33–36.

(21) Pollard, C. B.; Wicker, Jr. T. H. Derivatives of Piperazine. XXIV. Synthesis of 1-Arylpiperazines and Amino Alcohol Derivatives. *J. Am. Chem. Soc.* **1954**, *76*, 1853–1855.

(22) Dyer, E.; Johnson, T. B. Nitro and Amino Triphenylguanidines. *J. Am. Chem. Soc.* **1932**, *54*, 777–787.

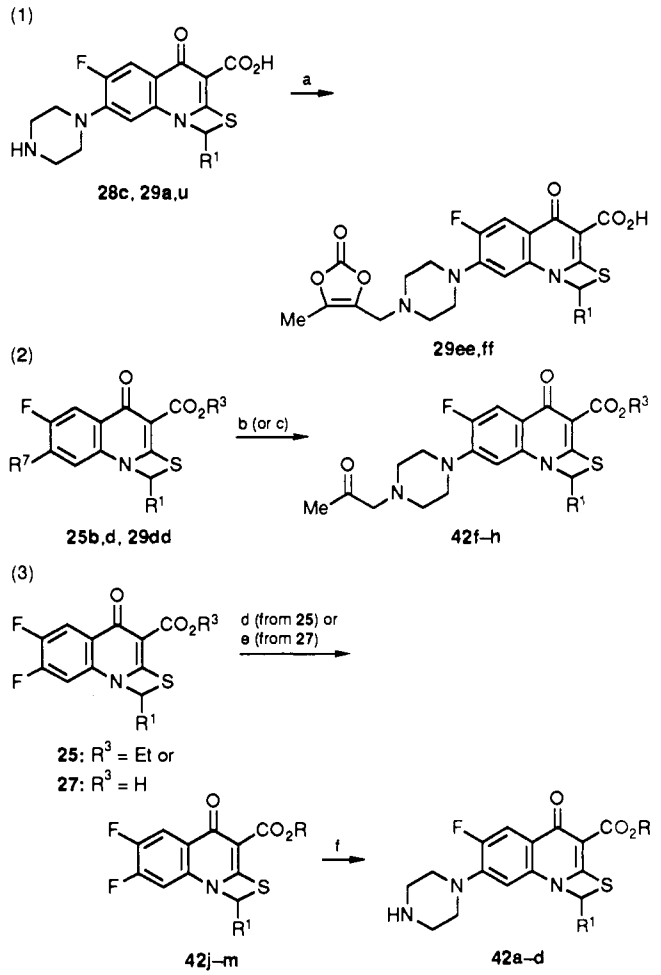
(23) Cooper, C. S.; Klock, P. L.; Chu, D. T. W.; Fernandes, P. B. The Synthesis and Antibacterial Activities of Quinolones Containing Five- and Six-Membered Heterocyclic Substituents at the 7-Position. *J. Med. Chem.* **1990**, *33*, 1246–1252.

(24) (a) Moore, M. L. The Leuckart Reaction. *Org. React.* **1949**, *5*, 301–330. (b) Quin, L. D.; Shelburne, F. A. Rearrangement of Some Piperidine *N*-Oxides to Hexahydro-1,2-oxazepines. *J. Org. Chem.* **1965**, *30*, 3135–3138.

(25) (a) Sakamoto, F.; Ikeda, S.; Kondo, H.; Tsukamoto, G. Studies on Prodrugs. IV. Preparation and Characterization of N-(5-Substituted 2-oxo-1,3-dioxol-4-yl)methyl Norfloxacin. *Chem. Pharm. Bull.* **1985**, *33*, 4870–4877. (b) Sakamoto, F.; Ikeda, S.; Tsukamoto, G. Studies on Prodrugs. II. Preparation and Characterization of (5-Substituted 2-oxo-1,3-dioxol-4-yl)methyl Esters of Ampicillin. *Chem. Pharm. Bull.* **1984**, *32*, 2241–2248.

(26) Kondo, H.; Sakamoto, F.; Kodera, Y.; Tsukamoto, G. Studies of Prodrugs. 5. Synthesis and Antimicrobial Activity of *N*-(Oxoalkyl)-norfloxacion. Derivatives. *J. Med. Chem.* **1986**, *29*, 2020–2024.

**Scheme III** [a]




(a) DMDO-Br, $KHCO_3$, DMF; (b) 1-acetonylpiperazine, $K_2CO_3$, DMF; (c) $ClCH_2COCMe_3$; (d) ROH, $H^+$; (e) KOH, $H_2O$, alkyl or (acyloxy)alkyl halide, $K_2CO_3$, DMF; (f) piperazine, DMF.

**27b**, followed by the nucleophilic substitution reaction at C-7 with piperazine.

## Biological Results and Discussion

Compounds **29a–cc** were evaluated for in vitro antibacterial activity against a variety of organisms. The minimum inhibitory concentrations (MICs) of these compounds against several Gram-positive and Gram-negative bacteria compared to those of ofloxacin (**3**) and ciprofloxacin (**4**) are listed in Table IV.

Variation of the C-1 substituent of the thiazetoquinolones significantly influenced their activity. For those analogues (**29b, 29s, 29t, 29v**) with a 4-methylpiperazinyl group at C-7, the in vitro activity decreased as the size of the C-1 substituent increased [i.e. H (**29s**) > Me (**29b**) > Et (**29t**), Ph (**29v**)]. However, for those analogues (**29a, 29r, 29u**) with a 1-piperazinyl group at C-7, the activity decreased in the order Me (**29a**) > Ph (**29u**) > H (**29r**). Hence, although 1-phenyl analogues **29u** and **29v** are generally less active than 1-methyl analogues **29a** and **29b**, the steric bulk of the C-1 substituent alone does not always determine the biological activity. It is characteristic that the 1-hydrogen analogues **29r** and **29s** have a markedly reduced activity against *Micrococcus luteus* in vitro. Substitution on the 1-phenyl ring does not enhance the activity. Thus, the 1-(4-fluorophenyl) analogue **29w** has about the same activity as **29u**, while the 1-(2-fluorophenyl) analogue **29x** and the 1-(2,4-difluorophenyl) analogue **29y** have much less activity than **29u** and **29v**, respectively. This finding is different from the general trend that the 1-(2-fluorophenyl) derivative is more potent than the 1-phenyl analogue as reported by Chu.[27]

A comparison of the in vitro antibacterial activity of 6-fluoro analogues **29a, 29b, 29r**, and **29s** with that of 6-chloro analogues (**29z–cc**) indicates that the replacement of fluorine with chlorine results in reduced activity. This result is in agreement with the generally accepted SAR of the substitution in the C-6 position.[19]

In regard to substitutions in the C-7 position, 7-pyrrolidinyl, 7-piperidinyl, 7-morpholino, and 7-thiomorpholino analogues **29k, 29l, 29n**, and **29o** show good in vitro antibacterial activity. They display more potent activity than **29a** and **29b** against Gram-positive bacteria but less activity against Gram-negative bacteria, especially against *Pseudomonas aeruginosa*. In general, replacing the basic nitrogen of the 4-position of the piperazinyl group with a nonbasic atom resulted in slightly improved activity against Gram-positive bacteria and slightly decreased activity against Gram-negative bacteria.[27] 7-(3-oxo-1-piperazinyl), 7-imidazolyl, and 7-homopiperazinyl analogues **29j, 29q**, and **29p** have weak in vitro activity.

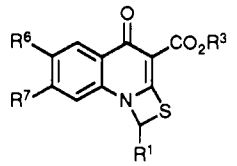
For those analogues (**29a–h**) with piperazine or N-substituted piperazine at C-7, the in vitro activity against Gram-negative bacteria decreases as the size of the 4-substituent increases (i.e. **29a, 29b > 29c, 29e ≥ 29d ≥ 29f > 29h > 29g**). However, against Gram-positive bacteria, the order is very different: i.e. **29h > 29e > 29d, 29c ≥ 29b ≥ 29a, 29f > 29g**; 7-(4-Acetyl-1-piperazinyl) analogue (**29i**) shows reduced activity. Thus, 7-piperazinyl and 7-(4-methyl-1-piperazinyl) analogues **29a** and **29b** have the most potent and balanced in vitro activity against both Gram-positive and Gram-negative bacteria.

In general, compounds with a hydrogen or methyl group at C-1, fluorine at C-6, and piperazinyl or 4-methyl-1-piperazinyl at C-7 have the greatest in vitro activity against both Gram-positive and Gram-negative bacteria.

The efficacy of selected compounds against systemic infections caused by *Escherichia coli* and *P. aeruginosa* in mice is shown in Table V. 7-(4-methyl-1-piperazinyl) analogues **28g, 29b**, and **29s** show good in vivo potency against both organisms. However, 7-piperazinyl analogue **29a** has only weak in vivo potency, although it possesses potent in vitro activity against both *E. coli* and *P. aeruginosa*. Among various 7-(4-substituted-1-piperazinyl-3-carboxylic acid and ester analogues prepared to improve the in vivo efficacy of 7-piperazinyl analogues, 7-(4-acetonyl-1-piperazinyl) analogue **41f** and 7-[4-(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl] analogue **29ee** have the best in vivo potency. Ethyl ester analogues **28g** and **41f** have good in vivo potency. In these studies, **29a** (NM394) was found to possess broad and potent in vitro antibacterial activity against both Gram-positive and Gram negative bacteria and low toxicity, but it is poorly absorbed from the gastrointestinal tract. **29ee** {NM441: 7-[4-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-1-piperazinyl] analogue of **29a**} was found to have a favorable pharmacokinetic profile and better oral efficacy than ciprofloxacin in experimental animals. Therefore, compound **29ee** was finally selected for extensive biological evaluation. It is

(27) Chu, D. T. W.; Fernandes, P. B.; Claiborne, A. K.; Pihuleac, E.; Nordeen, C. W.; Maleczka, Jr., R. E.; Pernet, A. G. Synthesis and Structure-Activity Relationships of Novel Arylfluoroquinoline Antibacterial Agents. *J. Med. Chem.* **1985**, *28*, 1558–1564.

**Table I.** Synthesis and Physical Data of the Thiazetoquinolone-3-carboxylic Acids and Their Ethyl Esters



| no. | $R^1$ | $R^3$ | $R^6$ | $R^7$ | procedure[a] | yield, %[b] | mp (°C) | formula[c] |
|---|---|---|---|---|---|---|---|---|
| **25a** | H | Et | F | F | A | 83 | 240–247 dec | $C_{13}H_8F_2NO_3S$ |
| **25b** | Me | Et | F | F | A | 47 | 200–202 | $C_{14}H_{11}F_2NO_3S$ |
| **25c** | Et | Et | F | F | A | 12 | 175–178 | $C_{15}H_{15}F_2NO_3S$ |
| **25d** | Ph | Et | F | F | A | 82 | 173–175 | $C_{19}H_{15}F_2NO_3S$ |
| **25e** | 4-F-Ph | Et | F | F | A | 42 | 177–190 | $C_{19}H_{12}F_3NO_3S$ |
| **25f** | 2-F-Ph | Et | F | F | A | 83 | 216–217 | $C_{19}H_{12}F_3NO_3S$ |
| **25g** | 2,4-$F_2$-Ph | Et | F | F | A | 87 | 203–206 | $C_{19}H_{11}F_4NO_3S$ |
| **27a** | H | H | F | F | A | 97 | 241–255 dec | $C_{11}H_5F_2NO_3S$ |
| **27b** | Me | H | F | F | A | 93 | 269–272 dec | $C_{12}H_7F_2NO_3S$ |
| **27c** | Et | H | F | F | A | 96 | 250–251 dec | $C_{13}H_8F_2NO_3S$ |
| **27d** | Ph | H | F | F | A | 72 | 221–224 dec | $C_{17}H_8F_2NO_3S \cdot {}^1/_4H_2O$ |
| **28a** | H | Et | F | P[d] | A | 34 | >300 dec | $C_{17}H_{18}FN_3O_3S \cdot {}^1/_4H_2O$ |
| **28b** | H | Et | F | 4-Me-P | A | 60 | 260–265 dec | $C_{18}H_{20}FN_3O_3S \cdot {}^1/_2H_2O$ |
| **28c** | Me | Et | F | P | A | 84 | 230 | $C_{18}H_{20}FN_3O_3S \cdot {}^6/_5H_2O$ |
| **28d** | Me | Et | F | 4-Me-P | A | 75 | 223–225 | $C_{19}H_{22}FN_3O_3S \cdot {}^1/_2H_2O$ |
| **28e** | Et | Et | F | 4-Me-P | A | 30 | 211–212 | $C_{20}H_{24}FN_3O_3S \cdot {}^1/_3H_2O$ |
| **28f** | Ph | Et | F | P | A | 73 | 189–191 | $C_{23}H_{22}FN_3O_3S \cdot {}^4/_3H_2O$ |
| **28g** | Ph | Et | F | 4-Me-P | A | 67 | 208 | $C_{24}H_{24}FN_3O_3S \cdot {}^3/_5H_2O$ |
| **28h** | 4-F-Ph | Et | F | 4-Me-P | A | 42 | 121.5 | $C_{24}H_{23}F_2N_3O_3S \cdot {}^1/_2H_2O$ |
| **28i** | 2-F-Ph | Et | F | 4-Me-P | A | 78 | 198–201 | $C_{24}H_{23}F_2N_3O_3S$ |
| **28j** | 2,4-$F_2$-Ph | Et | F | 4-Me-P | A | 60 | 212–214 | $C_{24}H_{22}F_3N_3O_3S$ |
| **28k** | H | Et | Cl | 4-acetyl-P | B | 80 | 266–268 dec | $C_{19}H_{20}ClN_3O_4S \cdot {}^1/_2H_2O$ |
| **28l** | Me | Et | Cl | 4-acetyl-P | B | 56 | 260–262 dec | $C_{20}H_{22}ClN_3O_4S \cdot {}^1/_4H_2O$ |

[a] Refers to the general method used and is described in the Experimental Section. [b] Yields were not optimized. [c] C, H, and N analyses were within ±0.4% of the theoretical values. [d] P stands for a piperazinyl group.

presently being tested in clinical studies. Details of the antibacterial and pharmacokinetic properties of **29a** and **29ee** were presented in part at the 29th Interscience Conference on Antimicrobial Agents and Chemotherapy (Houston, TX) and reported.[28]

## Experimental Section

**In Vitro Antibacterial Activity.** According to the method of the MIC Committee of the Japan Society of Chemotherapy,[29] the MIC (in μg/mL) was determined by the 2-fold agar dilution method using Sensitivity Test agar (Nissui; Tokyo, Japan); the bacterial inocula contained approximately $10^6$ colony-forming units/mL and the bacterial growth observed after 20 h of incubation at 37 °C.

**In Vivo Efficacy on Systemic Infections.** Seven male mice (ddY, 20 ± 2 g, Japan SLC Inc., Shizuoka, Japan) were used for each dose of a drug. *E. coli* KC-14 ($4.3 \times 10^4$ cfu/mL) and *P. aeruginosa* E-2 ($2.88 \times 10^5$ cfu/mL) were suspended in 5% gastric mucin. A 0.5-ml volume of bacterial suspension was challenged intraperitoneally. Drugs were suspended in 0.5% HPC-SL (hydroxypropylcellulose type SL) and administered orally 2 h (in case of *E. coli* KC-14) or 1 h (in case of *P. aeruginosa* E-2) after challenge. The 50% effective doses were calculated by the Probit method from the survival rates at 7 days after infection.

**Acute Toxicity on Oral Administration to Mice.** A suspension of **29ee** in 0.5% HPC-SL was administered orally to Slc:SD (Japan SLC Inc.) rats (male: 141–168 g body weight, female: 113–127 g body weight, five per group). Seven days later, $LD_{50}$ values were determined by the method of Weil.[30]

**Chemistry.** All melting points were determined in capillary tubes on a Büchi melting point apparatus and were uncorrected. Elemental analyses were performed on a Yanaco CHN Corder MT-3 elemental analyzer, and C,H,N values were within ±0.4% of the theoretical values. $^1$H NMR spectra were recorded on either a 200-MHz Varian XL-200 or 60-MHz Hitachi R-24-B spectrometer using tetramethylsilane as internal standard, and chemical shifts are given in ppm (δ). $^1$H NMR spectra of all compounds obtained were consistent with assigned structures. IR spectra were recorded on a Shimadzu IR-453-U-03 spectrometer. High-resolution mass spectra were recorded on a JEOL JMS-SX102 spectrometer at 70 eV ionization potential. HPLC analyses were carried out with Shimadzu LC-6A liquid chromatograph. Column chromatography separations were carried out on either Wako Gel C-200 or C-300. Yields are of purified products and are not optimized. The characteristics of synthesized compounds are summarized in Tables I, II and III. The oils are characterized by $^1$H NMR data.

**Procedure A-(1). 3,4-Difluorophenyl Isothiocyanate (18).** To a stirred solution of 200 g (1.55 mol) of 3,4-difluoroaniline (16) and 470 g (4.64 mol) of triethylamine was added dropwise 130 g (1.7 mol) of carbon disulfide under ice cooling. The reaction mixture was allowed to stand at the same temperature overnight. The resulting precipitate was collected by filtration, washed with benzene and ether, and dried to give 449 g (95%) of triethylammonium (3,4-difluorophenyl)dithiocarbamate (17) as a colorless powder, which, without further purification, was suspended in 800 mL of $CHCl_3$ and 163 g (1.61 mol) of triethylamine. To this suspension was added dropwise 175 g (1.61 mol) of ethyl chloroformate with stirring under ice cooling. After stirring at room temperature for 3.5 h, the reaction mixture was poured into ice–water and extracted with *n*-hexane. The organic layer was washed with dilute aqueous HCl and water, dried, and concentrated to dryness under reduced pressure to afford a crude oil, which was chromatographed on silica gel with *n*-hexane to give 186 g (74% from 16) of 18: bp 68–70 °C (4 mmHg); IR 2050, 1600, 1500 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 6.75–7.30 (m, 3 H, aromatic); MS *m/z* 171 ($M^+$).

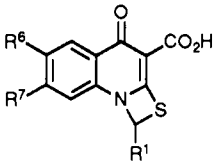
**Diethyl [[(3,4-Difluorophenyl)amino][(methoxymethyl)thio]methylene]malonate (20).** To a stirred suspension of 6.6

(28) (a) Ozaki, M.; Matsuda, M.; Tomii, Y.; Kimura, K.; Segawa, J.; Kitano, M.; Kise, M.; Shibata, K.; Otsuki, M.; Nishino, T. In Vivo Evaluation of NM441, a New Thiazeto-Quinoline Derivative. *Antimicrob. Agents Chemother.* **1991**, *35*, 2496–2499. (b) Ozaki, M.; Matsuda, M.; Tomii, Y.; Kimura, K.; Kazuno, K.; Kitano, M.; Kise, M.; Shibata, M.; Otsuki, M.; Nishino, T. In Vitro Antibacterial Activity of a New Quinolone, NM394. *Antimicrob. Agents Chemother.* **1991**, *35*, 2490–2495.

(29) MIC Committee of the Japan Society of Chemotherapy. *Chemotherapy (Tokyo)* **1981**, *29*, 76.

(30) Weil, C. S. Tables for convenient calculation of median-effective dose ($LD_{50}$ or $ED_{50}$) and instructions in their use. *Biometrics* **8**, 249–263.

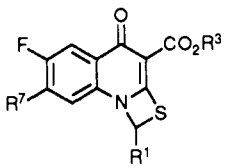
Table II. Synthesis and Physical Data of the Thiazetoquinoline-3-carboxylic Acids



| no. | $R^1$ | $R^6$ | $R^7$ | procedure[a] | yield, %[b] | mp (°C) | formula[c] |
|---|---|---|---|---|---|---|---|
| **29a** | Me | F | P[d] | A | 92 | 215–218 dec | $C_{18}H_{18}FN_3O_3S\cdot^6/_4H_2O$ |
| **29b** | Me | F | 4-Me-P | A | 70 | 262 dec | $C_{17}H_{18}FN_3O_3S$ |
| **29c** | Me | F | 4-Et-P | A | 70 | 211–214 dec | $C_{18}H_{20}FN_3O_3S\cdot HF\cdot^1/_4H_2O$ |
| **29d** | Me | F | 4-*i*-Pr-P | A | 77 | 227–228 dec | $C_{19}H_{22}FN_3O_3S\cdot^1/_4H_2O$ |
| **29e** | Me | F | 4-allyl-P | A | 73 | 216–218 dec | $C_{19}H_{20}FN_3O_3S$ |
| **29f** | Me | F | 4-$HOCH_2CH_2$-P | A | 43 | 230–232 dec | $C_{18}H_{20}FN_3O_4S\cdot^3/_4H_2O$ |
| **29g** | Me | F | 4-Ph-P | A | 52 | 267–269 dec | $C_{22}H_{20}FN_3O_3S$ |
| **29h** | Me | F | 4-(*p*-$NH_2$-benzyl)-P | A | 18 | 209–211 dec | $C_{23}H_{23}FN_4O_3S$ |
| **29i** | Me | F | 4-acetyl-P | A | 68 | 263–265 dec | $C_{18}H_{18}FN_3O_4S\cdot^1/_4H_2O$ |
| **29j** | Me | F | 3-oxo-P | A | 46 | 254–256 dec | $C_{18}H_{14}FN_3O_4S\cdot^1/_2H_2O$ |
| **29k** | Me | F | pyrrolidinyl | A | 68 | 275–277 dec | $C_{16}H_{15}FN_2O_3S$ |
| **29l** | Me | F | piperizinyl | A | 65 | 246–248 dec | $C_{17}H_{17}FN_2O_3S$ |
| **29m** | Me | F | 4-HO-piperizinyl | A | 77 | 266–268 dec | $C_{17}H_{17}FN_2O_4S$ |
| **29n** | Me | F | morpholino | A | 63 | 250–252 dec | $C_{15}H_{15}FN_2O_4S$ |
| **29o** | Me | F | thiomorpholino | A | 63 | 258–260 dec | $C_{15}H_{15}FN_2O_3S_2$ |
| **29p** | Me | F | homopiperazinyl | A | 60 | 158–164 dec | $C_{18}H_{20}FN_3O_3S$ |
| **29q** | Me | F | imidazolyl | A | 77 | 248–251 dec | $C_{15}H_{10}FN_3O_3S\cdot^1/_4H_2O$ |
| **29r** | H | F | P | A, C | 37 | >300 dec | $C_{15}H_{14}FN_3O_3S\cdot HCl\cdot H_2O$ |
| **29s** | H | F | 4-Me-P | A, C | 38 | >300 dec | $C_{18}H_{18}FN_3O_3S$ |
| **29t** | Et | F | 4-Me-P | A | 43 | 233–234 dec | $C_{15}H_{20}FN_3O_3S\cdot^1/_4H_2O$ |
| **29u** | Ph | F | P | A | 41 | 210–230 dec | $C_{21}H_{18}FN_3O_3S\cdot^1/_2H_2O$ |
| **29v** | Ph | F | 4-Me-P | A | 87 | 216–217 dec | $C_{22}H_{20}FN_3O_3S\cdot^1/_2H_2O$ |
| **29w** | 4-F-Ph | F | P | A | 87 | 298–304 dec | $C_{21}H_{17}F_2N_3O_3S\cdot H_2O$ |
| **29x** | 2-F-Ph | F | P | A | 48 | 203–205 dec | $C_{22}H_{18}F_2N_3O_3S$ |
| **29y** | 2,4-$F_2$-Ph | F | 4-Me-P | A | 70 | 209–211 dec | $C_{24}H_{22}F_3N_3O_3S$ |
| **29z** | H | Cl | P | B | 48 | 235–240 dec | $C_{15}H_{14}ClN_3O_3S\cdot^1/_2H_2O$ |
| **29aa** | H | Cl | 4-Me-P | B | 29 | 220–230 dec | $C_{18}H_{16}ClN_3O_3S\cdot H_2O$ |
| **29bb** | Me | Cl | P | B | 59 | >300 dec | $C_{18}H_{16}ClN_3O_3S\cdot^1/_2H_2O$ |
| **29cc** | Me | Cl | 4-Me-P | B | 53 | 257–259 dec | $C_{17}H_{16}ClN_3O_3S$ |
| **29dd** | Me | F | 4-acetonyl-P | A | 53 | 208–209 dec | $C_{18}H_{20}FN_3O_4S\cdot^1/_2H_2O$ |
| **29ee** | Me | F | 4-DMDO-P[e] | A | 64 | 220 dec | $C_{21}H_{20}FN_3O_6S$ |
| **29ff** | Ph | F | 4-DMDO-P | A | 34 | 201–202 dec | $C_{26}H_{22}FN_3O_6S\cdot^3/_4H_2O$ |

[a–d] See Table I, footnotes a–d. [e] DMDO stands for (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group.

Table III. Synthesis and Physical Data of the Thiazetoquinoline-3-carboxylic Esters



| no. | $R^1$ | $R^3$ | $R^7$ | yield, %[b] | mp (°C) | formula[c] |
|---|---|---|---|---|---|---|
| **41a** | Me | Me | P[d] | 76 | 208 dec | $C_{17}H_{18}FN_3O_3S\cdot^2/_5H_2O$ |
| **41b** | Me | *i*-Pr | P | 70 | 220 dec | $C_{18}H_{22}FN_3O_3S\cdot^1/_2H_2O$ |
| **41c** | Me | *n*-Bu | P | 63 | 212–213 dec | $C_{20}H_{24}FN_3O_3S\cdot^1/_4H_2O$ |
| **41d** | Me | hydroxyethyl | P | 77 | 164–168 dec | $C_{18}H_{20}FN_3O_4S\cdot^3/_2H_2O$ |
| **41e** | Me | Pom[a] | P | 18 | 211–214 dec | $C_{22}H_{26}FN_3O_3S\cdot^1/_4H_2O$ |
| **41f** | Me | Et | 4-acetonyl[e]-P | 55 | 196–199 dec | $C_{21}H_{24}FN_3O_3S\cdot^1/_4H_2O$ |
| **41g** | Me | Pom | 4-acetonyl-P | 63 | 132–134 | $C_{25}H_{30}FN_3O_6S\cdot^1/_4H_2O$ |
| **41h** | Ph | Et | 4-acetonyl-P | 48 | 190–191 | $C_{26}H_{26}FN_3O_4S$ |
| **41i** | Me | Et | 4-DMDO[f]-P | 66 | 241–243 dec | $C_{23}H_{24}FN_3O_6S$ |
| **41j** | Me | Me | F | 82 | 202–209 | $C_{18}H_8F_2NO_3S\cdot^1/_4H_2O$ |
| **41k** | Me | *i*-Pr | F | 79 | 206–208 | $C_{15}H_{18}F_2NO_3S\cdot^1/_2H_2O$ |
| **41l** | Me | *n*-Bu | F | 83 | 163–165 | $C_{16}H_{15}F_2NO_3S$ |
| **41m** | Me | hydroxyethyl | F | 88 | 224 dec | $C_{14}H_{11}F_2NO_4S$ |

[a] Pom stands for a pivaloyloxymethyl group. [b–d] See Table I, footnotes b–d. [e] Acetonyl stands for 2-oxopropyl group. [f] See Table II, footnote e.

g (0.118 mol) of powdered KOH in 200 mL of dioxane was added dropwise 18.9 g (0.118 mol) of diethyl malonate. After stirring at room temperature for 30 min, 17.6 g (0.118 mol) of 18 was added gradually to this mixture under ice cooling. The reaction mixture was allowed to stand at 4 °C for 15 h. The resulting precipitate was collected by filtration, washed with ether, and dried to afford the potassium salt of diethyl [[(3,4-difluorophenyl)amino]mercaptomethylene]malonate (19). To a solution of 19 in DMF (100 mL) was added dropwise 9.5 g (0.118 mol) of chloromethyl methyl ether under ice cooling. After stirring at the same temperature for 1.5 h, the reaction mixture was warmed gradually to room temperature and was stirred for an additional 2 h. The reaction mixture was then poured into water and extracted with $CHCl_3$. The organic layer was washed with water, dried over $MgSO_4$, and concentrated to dryness under reduced pressure. The residue was chromatographed on silica gel with *n*-hexane to give 36.2 g (94%) of 20: IR 1730, 1575 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.2–1.4 (m, 6 H, $CH_2CH_3$), 3.20 [s, a/(a+b) × 3 H,

Table IV. In Vitro Antibacterial Activity[a] (MIC) μg/mL

| | Gram-positive organisms | | Gram-negative organisms | | | | |
|---|---|---|---|---|---|---|---|
| no. | *Staphylococcus* aureus 209P JC-1 | *Micrococcus luteus* ATCC 9341 | *Escherichia coli* NIH JC-2 | *Klebsiella pneumoniae* K-1966 | *Serratia marcescens* IFO 3736 | *Shigella flexneri* 2a EW-10 | *Pseudomonas aeruginosa* E-2 |
| **29a** | 0.05 | 0.78 | 0.0125 | ≃0.006[d] | 0.05 | ≃0.006 | 0.2 |
| **29b** | 0.1 | 1.56 | 0.025 | 0.025 | 0.05 | 0.0125 | 0.39 |
| **29c** | 0.1 | 1.56 | 0.05 | 0.05 | 0.1 | 0.025 | 0.78 |
| **29d** | 0.05 | 3.13 | 0.2 | 0.025 | 0.39 | 0.025 | 1.56 |
| **29e** | 0.05 | 1.56 | 0.05 | 0.05 | 0.19 | 0.025 | 0.78 |
| **29f** | 0.1 | 0.78 | 0.1 | 0.1 | 0.39 | 0.05 | 1.56 |
| **29g** | 3.13 | 12.5 | >100 | >100 | >100 | >100 | >100 |
| **29h** | 0.05 | 0.39 | 0.2 | 0.2 | 1.56 | 0.1 | 3.13 |
| **29i** | 0.2 | 3.13 | 0.78 | 0.39 | 1.56 | 0.39 | 6.25 |
| **29j** | 0.39 | 3.13 | 0.39 | 0.2 | 3.13 | 0.1 | 6.25 |
| **29k** | 0.05 | 0.78 | 0.2 | 0.1 | 0.78 | 0.1 | 0.39 |
| **29l** | 0.2 | 3.13 | 0.78 | 0.39 | 3.13 | 0.78 | 1.56 |
| **29m** | 0.1 | 1.56 | 0.39 | 0.05 | 0.78 | 0.2 | 0.78 |
| **29n** | 0.1 | 1.56 | 0.1 | 0.1 | 0.39 | 0.1 | 0.39 |
| **29o** | 0.025 | 0.78 | 0.2 | 0.2 | 0.39 | 0.1 | 0.39 |
| **29p** | 0.1 | 3.13 | 0.2 | 0.2 | 0.39 | 0.1 | 3.13 |
| **29q** | 0.39 | 6.25 | 0.2 | 0.1 | 0.78 | 0.1 | 3.13 |
| **29r** | 0.05 | 25 | 0.1 | 0.05 | 0.1 | 0.025 | 0.78 |
| **29s** | 0.05 | 12.5 | 0.0125 | 0.025 | 0.05 | 0.006 | 0.39 |
| **29t** | 0.2 | | | | 0.78 | | |
| **29u** | 0.2 | 3.13 | 0.025 | 0.025 | 0.05 | 0.025 | 0.2 |
| **29v** | 0.39 | 6.25 | 0.2 | 0.2 | 0.39 | 0.2 | 1.56 |
| **29w** | 0.2 | 1.56 | 0.025 | 0.0125 | 0.39 | 0.025 | 0.39 |
| **29x** | 1.56 | 12.5 | 0.39 | 0.78 | 12.5 | 0.78 | 3.13 |
| **29y** | 1.56 | 6.25 | 0.39 | 0.78 | 12.5 | 0.78 | 3.13 |
| **29z** | 0.2 | 6.25 | 0.39 | 0.2 | 0.2 | 0.1 | 6.25 |
| **29aa** | 0.2 | 6.25 | 0.2 | 0.2 | 0.39 | 0.1 | 1.56 |
| **29bb** | 0.1 | 1.56 | 0.05 | 0.025 | 0.1 | 0.0125 | 1.56 |
| **29cc** | 0.2 | 3.13 | 0.1 | 0.025 | 0.1 | 0.1 | 1.56 |
| **3**[b] | 0.39 | 3.13 | 0.1 | 0.025[d] | 0.39 | 0.1 | 1.56 |
| **4**[c] | 0.1 | 1.56 | 0.0125 | ≃0.006[d] | 0.1 | ≃0.006 | 0.2 |

[a] See the Experimental Section. [b] Ofloxacin. [c] Ciprofloxacin. [d] IFO3512.

Table V. Oral Efficacy on Systemic Infections in Mice

| | $ED_{50}$[a] mg/kg po (95% confidence limits) | | $LD_{50}$[b] mg/kg |
|---|---|---|---|
| no. | *E. coli* KC-14 | *P. aeruginosa* E-2 | |
| **28g** | 0.89 (0.55–1.35) | 18.13 (14.94–22.01) | |
| **29b** | 0.97 (0.62–1.47) | 8.84 (6.19–12.63) | |
| **29s** | 1.77 (1.11–2.71) | 16.42 (2.39–26.58) | |
| **29ee** | 0.35 (0.25–0.55) | 8.02 (6.21–9.90) | >5000 |
| **41f** | 0.78 (0.33–1.32) | 27.01 (20.86–49.53) | |
| **3**[c] | 0.55 (0.50–0.60) | 23.01 (17.78–29.91) | |
| **4**[d] | 0.45 (0.35–0.60) | 9.01 (6.93–10.96) | |

[a,b] See the Experimental Section. [c] Ofloxacin. [d] Ciprofloxacin.

$OCH_3$], 3.38 [s, b/(a+b) × 3 H, $OCH_3$], 4.1–4.4 (m, 4 H, $CH_2CH_3$), 4.59 [s, a/(a+b) × 2 H, $SCH_2$], 4.86 [s, b/(a+b) × 2 H, $SCH_2$], 5.02 [s, b/(a+b) × 1 H, CH], 6.5–7.2 (m, 3 H, aromatic), 10.5 [s, a/(a+b) × 1 H, NH]. Anal. ($C_{16}H_{19}F_2NO_5S$) C, H, N.

**Ethyl 6,7-Difluoro-4-hydroxy-2-[(methoxymethyl)thio]-quinoline-3-carboxylate (21) and Ethyl 5,6-Difluoro-4-hydroxy-2-[(methoxymethyl)thio]quinoline-3-carboxylate (22).** A solution of 95.9 g (0.256 mol) of **20** in 250 mL of diphenyl ether was heated at 240 °C for 5 min with stirring. After cooling, the reaction mixture was chromatographed on silica gel with 5% EtOAc in *n*-hexane to give 48.5 g (58%) of **21** as a colorless powder. Compound **21**: mp 126–129 °C; IR 1640, 1590 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.54 (t, 3 H, $J$ = 8 Hz, $CH_2CH_3$), 3.46 (s, 3 H, $OCH_3$), 4.57 (q, 2 H, $J$ = 8 Hz, $CH_2CH_3$), 5.46 (s, 2 H, $SCH_2O$), 7.57 (dd, 1 H, $J$ = 8 and 12 Hz, 8-H), 7.84 (dd, 1 H, $J$ = 8 and 12 Hz, 5-H), 13.12 (s, 1 H, OH). Anal. ($C_{14}H_{15}F_2NO_4S$) C, H, N.

Elution also afforded 3.7 g (4%) of **22** as colorless needles. Compound **22**: mp 140–141 °C; $^1H$ NMR ($CDCl_3$) δ 1.55 (t, 3 H, $J$ = 8 Hz, $CH_2CH_3$), 3.46 (s, 3 H, $OCH_3$), 4.58 (q, 2 H, $J$ = 8 Hz, $CH_2CH_3$), 5.47 (s, 2 H, $SCH_2O$), 7.47–7.68 (m, 2 H, aromatic), 13.63 (s, 1 H, OH). Anal. ($C_{14}H_{13}F_2NO_4S$) C, H, N.

**Ethyl 6,7-Difluoro-4-hydroxy-2-mercaptoquinoline-3-carboxylate (23).** To a stirred suspension of 195 g (0.592 mol) of **21** in 1 L of EtOH was added dropwise 600 mL of 35% hydrochloric acid at room temperature. After stirring for 2 h, the reaction mixture was poured into ice–water. The resulting solid was collected by filtration, washed with water thoroughly, dried, and recrystallized from DMF–$CHCl_3$ to give 166.6 g (99%) of **23** as yellow crystals: mp 200–202 °C dec; IR 3000, 1640, 1590, 1515 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 1.63 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 4.78 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 7.71 (dd, 1 H, $J$ = 6 and 9 Hz, 8-H), 8.27 (dd, 1 H, $J$ = 8 and 9 Hz, 5-H). Anal. ($C_{12}H_9F_2NO_3S$) C, H, N.

**Ethyl 5,6-Difluoro-4-hydroxy-2-mercaptoquinoline-3-carboxylate (24).** By using the same procedure, compound **24** was prepared from **22** in 97% yield. Compound **24**: mp 179 °C dec; IR 2920, 1650, 1630, 1610, 1585, 1500, 1420 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 1.64 (t, 3 H, $J$ = 8 Hz, $CH_2CH_3$), 4.79 (q, 2 H, $J$ = 8 Hz, $CH_2CH_3$), 7.71 (ddd, 1 H, $J$ = 2, 4 and 9 Hz, 8-H), 7.95 (ddd, 1 H, $J$ = 8, 9 and 10 Hz, 5-H). Anal. ($C_{12}H_9F_2NO_3S$) C, H, N.

**Ethyl 6,7-Difluoro-1-methyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (25b).** To a mixture of 110 g (0.59 mol) of 1,1-dibromoethane, 77.4 g (0.56 mol) of $K_2CO_3$, 4.6 g (0.028 mol) of KI, and 540 mL of DMF was added dropwise a solution of 80 g (0.28 mol) of **23** in 1.4 L of DMF at 105–110 °C with vigorous stirring during 5.5 h. After stirring at the same temperature for 0.5 h, the reaction mixture was concentrated under reduced pressure and poured into ice–water. The precipitate was collected by filtration, washed with water, dried to give a crude solid, which was recrystallized from $CHCl_3$–$CH_3OH$ (10:1) to give 41.2 g (47%) of **25b**: mp 200–202 °C; IR 3450, 3000, 1720, 1610, 1500 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.27 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 2.07 (d, 3 H, $J$ = 7 Hz, 1-$CH_3$), 4.15 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 6.08 (q, 1 H, $J$ = 7 Hz, 1-H), 7.60 (dd, 1 H, $J$ = 6 and 11 Hz, 8-H), 7.88 (dd, 1 H, $J$ = 9 and 11 Hz, 5-H).

**Ethyl 5,6-Difluoro-1-methyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (26).** By using the same procedure, compound **26** was prepared from **24** in 47% yield. Compound **26**: mp 232–234 °C dec; IR $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.26 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 2.04 (d, 3 H, $J$ = 6 Hz, 1-$CH_3$), 4.18 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 6.17 (q, 1 H, $J$ = 6 Hz, 1-H), 7.27 (ddd, 1 H, $J$ = 2, 4 and 9 Hz, 8-H), 7.77 (ddd, 1 H, $J$ = 8, 9 and 10 Hz, 7-H). Anal. ($C_{14}H_{11}F_2NO_3S$) C, H, N.

By using the same procedure, compounds **25a,c–g** were prepared. Compound **25a**: IR 3420, 3050, 1720, 1610, 1545, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 1.54 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 4.67 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 6.17 (s, 2 H, 1-H), 7.62 (1 H, 8-H), 8.34 (1 H, 5-H).

Compound **25c**: IR 3600, 3000, 1730, 1610, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 1.23 (t, 3 H, $J$ = 8 Hz, 1-$CH_2CH_3$), 1.54 (t, 3 H, $J$ = 8 Hz, $CO_2CH_2CH_3$), 2.00–3.30 (m, 2 H, 1-$CH_2CH_3$), 4.64 (q, 2 H, $J$ = 8 Hz, $CO_2CH_2CH_3$), 6.55 (m, 1 H, 1-H), 7.68 (dd, 1 H, $J$ = 6 and 9 Hz, 8-H), 8.32 (dd, 1 H, $J$ = 8 and 9 Hz, 5-H).

Compound **25d**: IR 3010, 2995, 1730, 1610, 1495 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.38 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 4.30 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 6.38 (dd, 1 H, $J$ = 8 and 10 Hz, 8-H) 6.80 (s, 1 H, 1-H), 7.49 (s, 5 H, Ph), 8.03 (dd, 1 H, $J$ = 9 and 10 Hz, 5-H).

Compound **25e**: IR 2980, 1720, 1650, 1590, 1560, 1495, 1425 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.36 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 4.28 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 6.34 (dd, 1 H, $J$ = 7 and 10 Hz, 8-H), 6.76 (s, 1 H, 1-H), 7.11 (dd, 2 H, $J$ = 8 and 9 Hz, 2′-H, 6′-H), 7.55 (dd, 2 H, $J$ = 8 and 5 Hz, 3′-H, 5′-H), 8.01 (dd, 1 H, $J$ = 8 and 11 Hz, 5-H).

Compound **25f**: IR 3450, 2980, 1735, 1670, 1610, 1560, 1495 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.38 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 4.34 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 6.44 (dd, 1 H, $J$ = 7 and 10 Hz, 8-H), 7.01 (s, 1 H, 1-H), 7.05–7.70 (m, 4 H, aromatic), 8.09 (dd, 1 H, J = 8 and 11 Hz, 5-H).

Compound **25g**: IR 3450, 1610, 1500 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.38 (t, 3 H, $J$ = 8 Hz, $CH_2CH_3$), 4.32 (q, 2 H, $J$ = 8 Hz, $CH_2CH_3$), 6.43 (dd, 1 H, $J$ = 6 and 10 Hz, 8-H), 6.98 (s, 1 H, 1-H), 6.75–7.75 (m, 3 H, aromatic), 8.06 (dd, 1 H, $J$ = 8 and 11 Hz, 5-H).

**6,7-Difluoro-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (27a).** To 20 g of fuming sulfuric acid was added portionwise 2.38 g (8 mmol) of **25a** with stirring under ice cooling. After stirring at room temperature overnight, the reaction mixture was poured into ice. The precipitate was collected by filtration, washed thoroughly with water, and dried to give 2.09 g (97%) of **27a**: IR 3070, 1710, 1610, 1490 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 6.19 (s, 2 H, 1-H), 7.20–8.00 (m, 1 H, 8-H), 8.00–8.70 (m, 1 H, 5-H).

By using the same procedure, compounds **27b–d** were prepared from **25b–d**, respectively. Compound **27b**: IR 3010, 1710, 1605, 1485 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 2.39 (d, 3 H, $J$ = 7 Hz, $CH_3$), 6.61 (q, 1 H, $J$ = 7 Hz, 1-H), 7.64 (dd, 1 H, $J$ = 6 and 9 Hz, 8-H), 8.37 (dd, 1 H, $J$ = 8 and 9 Hz, 5-H).

Compound **27c**: IR 3400, 3060, 1700, 1610 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 1.28 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 2.10–3.25 (m, 2 H, $CH_2CH_3$), 6.58 (m, 1 H, 1-H), 7.64 (m, 1 H, 8-H), 8.31 (dd, 1 H, $J$ = 8 and 10 Hz, 5-H).

Compound **27d**: IR 3040, 1700, 1600, 1540, 1490 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 7.03 (dd, 1 H, $J$ = 6 and 9 Hz, 8-H), 7.33 (s, 1 H, 1-H), 7.58 (br s, 5 H, Ph), 8.31 (dd, 1 H, $J$ = 8 and 10 Hz, 5-H).

**Ethyl 6-Fluoro-1-methyl-4-oxo-7-(1-piperazinyl)-4*H*-[1,3]-thiazeto[3,2-*a*] quinoline-3-carboxylate (28c).** To a stirred suspension of 2.5 g (8 mmol) of **25b** in 80 mL of DMF was added dropwise 2.3 g (26.7 mmol) of piperazine. After stirring overnight at room temperature, the reaction mixture was concentrated to dryness under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$–$CH_3OH$ (1:1) to give 2.51 g of **28c** as colorless crystals: IR 3300, 2800, 1720, 1625 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.24 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 2.04 (d, 3 H, $J$ = 6 Hz, $CH_3$), 2.86–2.93 (m, 4 H, piperazine), 3.02–3.31 (m, 4 H, piperazine), 4.07 (br s, 1 H, NH), 4.17 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 6.17 (q, 1 H, $J$ = 6 Hz, 1-H), 6.75 (d, 1 H, $J$ = 8 Hz, 8-H), 7.67 (d, 1 H, $J$ = 15 Hz, 5-H).

By using the same procedure, **28a,b,d–j** were prepared. Staring materials, physical appearance, and spectral data are given below.

Compound **28a**: **25a** and piperazine; colorless crystals; IR 3400, 1705, 1625 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 1.56 (t, 3 H, $J$ = 8 Hz, $CH_2CH_3$), 3.68–3.85 (m, 4 H, piperazine), 3.85–4.02 (m, 4 H, piperazine), 4.68 (q, 2 H, $J$ = 8 Hz, $CH_2CH_3$), 6.15 (s, 2 H, 1-H), 7.15 (d, 1 H, $J$ = 8 Hz, 8-H), 8.17 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **28b**: **25a** and *N*-methylpiperazine; colorless crystals; IR 3400, 1700, 1625, 1595 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 1.56 (t, 3 H, $J$ = 8 Hz, $CH_2CH_3$), 3.20 (s, 3 H, $CH_3N$), 3.40–3.75 (m, 4 H, piperazine), 3.80–4.30 (m, 4 H, piperazine), 4.86 (q, 2 H, $J$ = 8 Hz, $CH_2CH_3$), 6.13 (s, 2 H, 1-H), 7.14 (d, 1 H, $J$ = 7 Hz, 8-H), 8.16 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **28d**: **25b** and *N*-methylpiperazine; colorless crystals; IR 3400, 1710, 1625, 1600 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 1.54 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 2.36 (d, 3 H, $J$ = 7 Hz, 1-$CH_3$), 3.20 (s, 3 H, $CH_3N$), 3.42–3.77 (m, 4 H, piperazine), 3.83–4.18 (m, 4 H, piperazine), 4.65 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 6.56 (q, 1 H, $J$ = 7 Hz, 1-H), 7.09 (d, 1 H, $J$ = 7 Hz, 8-H), 8.19 (d, 1 H, $J$ = 12 Hz, 5-H).

Compound **28e**: **25c** and *N*-methylpiperazine; colorless crystals; IR 2900, 1715, 1625, 1595 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.08 (t, 3 H, $J$ = 8 Hz, 1-$CH_2CH_3$), 1.33 (t, 3 H, $J$ = 8 Hz, $CO_2CH_2CH_3$), 2.00–2.50 (m, 2 H, 1-$CH_2CH_3$), 2.35 (s, 3 H, $CH_3N$), 2.06–2.60 (m, 4 H, piperazine), 3.08–3.24 (m, 4 H, piperazine), 4.29 (q, 2 H, $J$ = 8 Hz, $CH_2CH_3$), 5.77 (m, 1 H, 1-H), 6.26 (d, 1 H, $J$ = 7 Hz, 8-H), 7.88 (d, 1 H, $J$ = 12 Hz, 5-H).

Compound **28f**: **25d** and piperazine; a pale yellow powder; IR 3300, 2800, 1720, 1605 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.22 (t, 3 H, $J$ = 8 Hz, $CH_2CH_3$), 2.74–3.04 (m, 8 H, piperazine), 4.39 (q, 2 H, $J$ = 8 Hz, $CH_2CH_3$), 5.90 (d, 1 H, $J$ = 7 Hz, 8-H), 6.67 (s, 1 H, 1-H), 7.23–7.62 (m, 5 H, Ph), 7.95 (d, 1 H, $J$ = 14 Hz, 5-H).

Compound **28g**: **25d** and *N*-methylpiperazine; a colorless powder; IR 3400, 2800, 1720, 1665, 1610, 1540, 1495 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.42 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 2.31 (s, 3 H, $CH_3N$), 2.42–2.55 (m, 4 H, piperazine), 2.83–3.08 (m, 4 H, piperazine), 4.39 (q, 2 H, $J$ = 7, $CH_2CH_3$), 5.91 (d, 1 H, $J$ = 7 Hz, 8-H), 6.66 (s, 1 H, 1-H), 7.43–7.58 (m, 5 H, Ph), 7.96 (d, 1 H, $J$ = 14 Hz, 5-H).

Compound **28h**: **25e** and *N*-methylpiperazine; a colorless powder; IR 3400, 1720, 1630, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.40 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 2.30 (s, 3 H, $CH_3N$), 2.40–2.56 (m, 4 H, piperazine), 2.62–3.10 (m, 4 H, piperazine), 4.38 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 5.88 (d, 1 H, $J$ = 8 Hz, 8-H), 6.66 (s, 1 H, 1-H), 7.09–7.24 (m, 2 H, aromatic), 7.62–7.50 (m, 2 H, aromatic), 7.93 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **28i**: **25f** and *N*-methylpiperazine; pale yellow crystals; IR 3450, 1710, 1625, 1610, 1595, 1580, 1495 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.40 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 2.31 (s, 3 H, $CH_3N$), 2.44–2.58 (m, 4 H, piperazine), 2.90–3.14 (m, 4 H, piperazine), 4.38 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 6.00 (d, 1 H, $J$ = 6 Hz, 8-H), 7.00 (s, 1 H, 1-H), 7.14–7.30 (m, 2 H, aromatic), 7.22–7.62 (m, 2 H, aromatic), 7.95 (d, 1 H, $J$ = 14 Hz, 5-H).

Compound **28j**: **25g** and *N*-methylpiperazine; colorless crystals; IR 3400, 1730, 1630, 1600, 1495 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.38 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 2.30 (s, 3 H, $CH_3N$), 2.15–2.70 (m, 4 H, piperazine), 2.75–3.20 (m, 4 H, piperazine), 4.33 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 5.92 (d, 1 H, $J$ = 7 Hz, 8-H), 6.93 (s, 1 H, 1-H), 6.70–7.65 (m, 3 H, aromatic), 7.80 (d, 1 H, $J$ = 13 Hz, 5-H).

**6-Fluoro-1-methyl-4-oxo-7-(1-piperazinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (29a).** A mixture of 8.0 g (21 mmol) of **28c**, 4.0 g (71 mmol) of KOH, 60 mL of *tert*-butyl alcohol, and 20 mL of water was heated at 50–60 °C for 1 h with stirring. After cooling, the reaction mixture was poured into ice-water and neutralized with acetic acid. The resulting precipitate was collected by filtration, washed with water, dried, and recrystallized from $CHCl_3$–MeOH to give 6.7 g (88%) of **29a** as pale yellow crystals. Compound **29a**: IR 3400, 1605, 1495 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 2.39 (d, 3 H, $J$ = 7 Hz, $CH_3$), 3.58–3.88 (m, 4 H, piperazine), 3.88–4.18 (m, 4 H, piperazine), 6.58 (q, 1 H, $J$ = 7 Hz, 1-H), 7.10 (d, 1 H, $J$ = 7 Hz, 8-H), 8.21 (d, 1 H, $J$ = 13 Hz, 5-H).

By using the same procedure, compounds **29u–y** were prepared. Starting materials, physical appearance, and spectral data are given below.

Compound **29u**: **28f**; colorless crystals; IR 3400, 1615, 1495 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 3.24–3.86 (m, 8 H, piperazine), 6.52 (d, 1 H, $J$ = 8 Hz, 8-H), 7.37 (s, 1 H, 1-H), 7.65 (s, 5 H, Ph), 8.18 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **29v**: **28g**; colorless crystals; IR 3400, 1710, 1625, 1600, 1495 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 3.14 (s, 3 H, $CH_3N$), 3.23–4.12 (m, 8 H, piperazine), 6.53 (d, 1 H, $J$ = 7 Hz, 8-H), 7.37 (s, 1 H, 1-H), 7.64 (s, 5 H, Ph), 8.19 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **29w**: **28h**; pale yellow crystals; IR 3400, 1620, 1605, 1495 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) δ 3.35–4.05 (m, 8 H, piperazine), 6.53 (d, 1 H, $J$ = 7 Hz, 8-H), 7.27 (dd, 2 H, $J$ = 8 and 8, aromatic), 7.37 (s, 1 H, 1H), 7.70 (dd, 2 H, $J$ = 5 and 8 Hz, aromatic), 8.17 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **29x**: **28l**; colorless crystals; IR 3400, 2800, 1710, 1625, 1600, 1495 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.30 (s, 3 H, $CH_3N$), 2.20–2.65 (m, 4 H, piperazine), 2.95–3.20 (m, 4 H, piperazine), 6.02 (d, 1 H, $J$ = 8 Hz, 8-H), 7.05–7.65 (m, 5 H, aromatic and 1-H), 7.82 (d, 1 H, $J$ = 14 Hz, 5-H).

Compound **29y**: **28j**; colorless crystals; IR 3400, 1700, 1625, 1600, 1500 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.31 (s, 3 H, $CH_3N$), 2.25–2.65 (m, 4 H, piperazine), 2.95–3.25 (m, 4 H, piperazine $CH_2N$), 6.00 (d, 1 H, $J$ = 7 Hz, 8-H), 6.75–7.70 (m, 3 H, aromatic), 7.80 (d, 1 H, $J$ = 14 Hz, 5-H).

**6-Fluoro-1-methyl-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (29b).** To a stirred solution of 14.1 g (0.05 mol) of **27b** in 300 mL of DMF was added dropwise 10.6 g (0.106 mol) of *N*-methylpiperazine under ice cooling. After stirring at room temperature overnight, the reaction mixture was concentrated under reduced pressure. The resulting crystalline solid was treated with acetone, collected by filtration, and washed with acetone, $CHCl_3$, and ether to give 12.63 g (70%) of **29b** as colorless crystals. Compound **29b**: IR 3400, 1705, 1630, 1480 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.39 (d, 3 H, $J$ = 6 Hz, $CH_3$), 3.22 (s, 3 H, $CH_3N$), 3.42–3.84 (m, 4 H, piperazine), 3.84–4.32 (m, 4 H, piperazine), 6.59 (q, 1 H, $J$ = 6 Hz, 1-H), 7.12 (d, 1 H, $J$ = 7 Hz, 8-H), 8.21 (d, 1 H, $J$ = 12 Hz, 5-H).

By using the same procedure, compounds **29c–t** were prepared. Starting materials, physical appearance, and spectral data are given below.

Compound **29c**: **27b** and *N*-ethylpiperazine; pale tan crystals; IR 3400, 1715, 1630, 1605, 1505 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 1.56 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 2.35 (d, 3 H, $J$ = 6 Hz, $CH_3$), 3.20–4.45 (m, 10 H, piperazine and $CH_2CH_3$), 6.54 (q, 1 H, $J$ = 6 Hz, 1-H), 7.07 (d, 1 H, $J$ = 6 Hz, 8-H), 8.16 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **29d**: **27b** and *N*-isopropylpiperazine; pale tan crystals; IR 3400, 1715, 1630, 1610, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 1.67 [d, 6 H, $J$ = 7 Hz, $(CH_3)_2CH$], 2.36 (d, 3 H, $J$ = 7 Hz, $CH_3$), 3.20–4.50 [m, 9 H, piperazine and $CH(CH_3)_2$], 6.54 (q, 1 H, $J$ = 7 Hz, 1-H), 7.03 (d, 1 H, $J$ = 7 Hz, 8-H), 8.15 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **29e**: **27b** and *N*-allylpiperazine; a pale tan powder; IR 3400, 1710, 1630, 1605 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.35 (d, 3 H, $J$ = 7 Hz, $CH_3$), 3.20–4.40 (m, 10 H, piperazine and $NCH_2CH{=}CH$), 5.70–6.00 (m, 3 H, olefinic), 6.55 (q, 1 H, $J$ = 7 Hz, 1-H), 7.07 (d, 1 H, $J$ = 7 Hz, 8-H), 8.17 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **29f**: **27b** and *N*-(2-hydroxyethyl)piperazine; yellow crystals; IR 3530, 3400, 1710, 1630, 1600, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.35 (d, 3 H, $J$ = 6 Hz, $CH_3$), 3.00–4.55 (m, 12 H, piperazine and $OCH_2CH_2N$), 6.54 (q, 1 H, $J$ = 6 Hz, 1-H), 7.05 (d, 1 H, $J$ = 6 Hz, 8-H), 8.17 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **29g**: **27b** and *N*-phenylpiperazine; pale yellow crystals; IR 3400, 1705, 1625, 1600, 1495 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.36 (d, 3 H, $J$ = 6 Hz, $CH_3$), 4.07 (m, 8 H, piperazine), 6.55 (q, 1 H, $J$ = 6 Hz, 1-H), 7.12 (d, 1 H, $J$ = 6 Hz, 8-H), 7.66 (s, 5 H, Ph), 8.18 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **29h**: **27b** and *N*-(*p*-aminobenzyl)piperazine; pale yellow crystals; IR 3350, 1705, 1630, 1600, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.35 (d, 3 H, $J$ = 7 Hz, $CH_3$), 3.20–4.50 (m, 8 H, piperazine), 4.67 (br s, 2 H, $NCH_2Ph$), 6.54 (q, 1 H, $J$ = 7 Hz, 1-H), 7.05 (d, 1 H, $J$ = 7 Hz, 8-H), 7.76 (s, 4 H, aromatic), 8.17 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **29i**: **27b** and *N*-acetylpiperazine; a light gray powder; IR 3400, 1710, 1630, 1600, 1495 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.34 (d, 3 H, $J$ = 7 Hz, $CH_3$), 2.62 (s, 3 H, $COCH_3$), 3.45–4.45 (m, 8 H, piperazine), 6.48 (q, 1 H, $J$ = 7 Hz, 1-H), 6.89 (d, 1 H, $J$ = Hz, 8-H), 8.09 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **29j**: **27b** and 2-oxopiperazine; a pale tan powder; IR 3350, 1625, 1605, 1485 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.43 (d, 3 H, $J$ = 6 Hz, $CH_3$), 3.70–4.30 (m, 4 H, piperazine $NCH_2CH_2N$), 4.50–4.85 (m, 2 H, piperazine $COCH_2N$), 6.58 (q, 1 H, $J$ = 6 Hz, 1-H), 7.05 (d, 1 H, $J$ = 7 Hz, 8-H), 8.18 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **29k**: **27b** and pyrrolidine; a light gray powder; IR 3400, 1690, 1630, 1600, 1505 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.10–2.40 [m, 4 H, pyrrolidine, $C(CH_2)_2C$], 2.33 (d, 3 H, $J$ = 7 Hz, $CH_3$), 3.6–4.0 (m, 4 H, pyrrolidine, $CCH_2NCH_2C$), 6.43 (q, 1 H, $J$ = 7 Hz, 1-H), 6.53 (d, 1 H, $J$ = 7 Hz, 8-H), 7.97 (d, 1 H, $J$ = 14 Hz, 5-H).

Compound **29l**: **27b** and piperazine; pale yellow crystals; IR 3400, 1705, 1600, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.37 (d, 3 H, $J$ = 6 Hz, $CH_3$), 1.60–2.60 (m, 6 H, piperizine $CH_2$), 3.80–4.25 (m, 4 H, piperizine $CH_2N$), 6.66 (q, 1 H, $J$ = 6 Hz, 1-H), 8.22 (d, 1 H, $J$ = 6 Hz, 8-H), 8.50 (d, 1 H, $J$ = 11 Hz, 5-H).

Compound **29m**: **27b** and 4-hydroxypiperizine; pale yellow crystals; IR 3500, 1700, 1600, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.42 (d, 3 H, $J$ = 6 Hz, $CH_3$), 3.50–4.75 (m, 5 H, piperizine $CH_2N$ and piperizine HOCH), 6.62 (q, 1 H, $J$ = 6 Hz, 1-H), 8.78 (d, 1 H, $J$ = 6 Hz, 8-H), 8.40 (d, 1 H, $J$ = 11 Hz, 5-H).

Compound **29n**: **27b** and morpholine; a pale yellow powder; IR 3450, 1710, 1630, 1600, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.36 (d, 3 H, $J$ = 6 Hz, $CH_3$), 3.50–3.95 (m, 4 H, morpholine $CH_2O$), 3.95–4.35 (m, 4 H, morpholine $CH_2N$), 6.53 (q, 1 H, $J$ = 6 Hz, 1-H), 6.97 (d, 1 H, $J$ = 7 Hz, 8-H), 8.12 (d, 1 H, $J$ = 14 Hz, 5-H).

Compound **29o**: **27b** and thiomorpholine; a pale yellow powder; IR 3420, 1720, 1630, 1600, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.37 (d, 3 H, $J$ = 6 Hz, $CH_3$), 2.80–3.35 (m, 4 H, thiomorpholine $CH_2S$), 3.85–4.35 (m, 4 H, thiomorpholine $CH_2N$), 6.54 (q, 1 H, $J$ = 6 Hz, 1-H), 7.32 (d, 1 H, $J$ = 6 Hz, 8-H), 8.20 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **29p**: **27b** and homopiperazine; pale tan crystals; IR 3400, 1710, 1630, 1600, 1500 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.09 (d, 3 H, $J$ = 6 Hz, $CH_3$), 1.80–2.12 (m, 2 H, homopiperazine $CH_2$), 2.32 (s, 3 H, $CH_3N$), 2.50–3.76 (m, 8 H, homopiperazine $CH_2N$), 6.37 (q, 1 H, $J$ = 6 Hz, 1-H), 6.63 (d, 1 H, $J$ = 8 Hz, 8-H), 7.72 (d, 1 H, $J$ = 15 Hz, 5-H), 14.80 (br s, 1 H, $CO_2H$).

Compound **29q**: **27b** and imidazole; colorless crystals; IR 3430, 1695, 1600, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.42 (d, 3 H, $J$ = 6 Hz, $CH_3$), 6.67 (q, 1 H, $J$ = 6 Hz, 1-H), 7.49 (s, 1 H, 8-H), 7.70–8.75 (m, 2 H, 4′-H, 5′-H), 8.40 (d, 1 H, $J$ = 12 Hz, 5-H), 9.29 (s, 1 H, 2′-H).

Compound **29r**: **27a** and piperazine, colorless crystals; IR 3500, 1690, 1620, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 3.70–4.20 (m, 8 H, piperazine), 6.18 (s, 2 H, 1-H), 7.20 (d, 1 H, $J$ = 7 Hz, 8-H), 8.17 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **29s**: **27a** and *N*-methylpiperazine; pale tan crystals; IR 3400, 1710, 1630, 1600, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 3.20 (s, 3 H, $CH_3N$), 3.00–4.55 (m, 8 H, piperazine), 6.09 (s, 2 H, 1-H), 7.07 (d, 1 H, $J$ = 11 Hz, 8-H), 8.11 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **29t**: **27c** and *N*-methylpiperazine; colorless crystals; IR 3400, 1710, 1630, 1600, 1500 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 0.95 (t, 3 H, $J$ = 8 Hz, $CH_2CH_3$), 2.24 (s, 3 H, $CH_3N$), 2.10–2.76 (m, 8 H, piperazine), 3.32 (m, 2 H, $CH_2CH_3$), 6.28 (m, 1 H, 1-H), 6.90 (d, 1 H, $J$ = 7 Hz, 8-H), 7.79 (d, 1 H, $J$ = 14 Hz, 5-H), 14.53 (s, 1 H, $CO_2H$).

**Procedure A, Path 2. Ethyl 6,7-Difluoro-1-methyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (25b) and Ethyl 5,6-Difluoro-1-methyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]-quinoline-3-carboxylate (26).** To a mixture of 1,1-diiodoethane (11.39 g, 40.4 mmol), $K_2CO_3$ (5.58 g, 40.4 mmol), and 30 mL of DMF was added a solution of **19** (9.95 g, 26.9 mmol) in 12 mL of DMF during 0.5 h at 70 °C with vigorous stirring. After stirring for 1 h, the reaction mixture was concentrated to dryness under reduced pressure and extracted with $CHCl_3$. The organic layer was washed with water, dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$ to give 2.22 g (23% from **18**) of diethyl 3-(3,4-difluorophenyl)-4-methyl[1,3]thiazetidin-2-ylidenemalonate (**30**) as a pale yellow oil. Compound **30**: IR 2970, 1720, 1660, 1510 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.8–1.5 (m, 6 H, $CH_2CH_3$), 1.68 (d, 3 H, $J$ = 6.5 Hz, $CH_3$), 3.5–4.6 (m, 4 H, $CH_2CH_3$), 5.42 (q, 1 H, $J$ = 6.5 Hz, 4-H), 6.6–7.5 (m, 3 H, aromatic). Anal. ($C_{16}H_{17}F_2NO_4S$) C, H, N.

A mixture of 973 mg (2.72 mmol) of **30** and 7 mL of PPE was heated at 80 °C for 1.5 h with stirring. After cooling, the reaction mixture was poured into water and extracted with $CHCl_3$. The organic layer was washed with water, dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel with 1% MeOH in $CHCl_3$ to give 350 mg (41% from **18**) of **25b**. Chromatography also gave 103 mg (12% from **18**) of **27**. Compounds **25b** and **27** were identical in all respects with an authentic specimen of **25b** and **27** prepared by the procedure A, path 1.

**Procedure B. 3-(4-Acetyl-1-piperazinyl)-4-chloroaniline (34).** To a stirred suspension of 50.0 g (0.21 mol) of 1-acetyl-4-(2-chlorophenyl)piperazine (**31**)[21] in 190 mL of concentrated sulfuric acid was added dropwise 22.6 g (0.25 mol) of 70% aqueous $HNO_3$ under ice cooling. During the addition, the temperature

was maintained between 5 °C and 10 °C. After all $HNO_3$ was added, the reaction mixture was stirred at 15 °C for 2.5 h and poured into ice. The aqueous mixture was extracted with EtOAc. The organic layer was washed with water, dried, and concentrated to dryness under reduced pressure. The residue was chromatographed on silica gel with 2% MeOH in $CHCl_3$ to give 0.7 g (1.2%) of 1-acetyl-4-(2-chloro-3-nitrophenyl)piperazine (**33**). Chromatography also gave 37.1 g (62.5%) of 1-acetyl-4-(2-chloro-5-nitrophenyl)piperazine (**32**). Compound **32**: mp 117–118 °C; IR 2820, 1625, 1525 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.16 (s, 3 H, $CH_3CO$), 3.02–3.17 (m, 4 H, piperazine), 3.58–3.88 (m, 4 H, piperazine), 7.54 (dd, 1 H, $J$ = 8 Hz and 1 Hz, 3-H), 7.86 (dd, 1 H, $J$ = 3 Hz and 1 Hz, 5-H), 7.88 (dd, 1 H, $J$ = 8 Hz and 3 Hz, 4-H). Anal. ($C_{12}H_{14}ClN_3O_3$) C, H, N.

Compound **33**: mp 84–86 °C; IR 2820, 1635, 1525 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.15 (s, 3 H, $CH_3CO$), 2.96–3.14 (m, 4 H, piperazine), 3.59–3.88 (m, 4 H, piperazine), 7.19 (dd, 1 H, $J$ = 8 Hz and 2 Hz, 5-H), 7.35 (dd, 1 H, $J$ = 8 Hz and 8 Hz, 4-H), 7.43 (dd, 1 H, $J$ = 8 Hz and 2 Hz, 3-H). Anal. ($C_{12}H_{14}ClN_3O_3$) C, H, N.

A mixture of 20.7 g (73 mmol) of **32**, 5.0 g of 10% Pd-C, and 200 mL of EtOH was shaken under $H_2$ gas until the required volume of hydrogen was absorbed. The mixture was filtered to remove the catalyst, and the filtrate was concentrated to dryness in vacuo. The resulting solid was triturated with $Et_2O$ to give 15.4 g (83%) of **34**: mp 132–135 °C; IR 3430, 3310, 3200, 1625, 1590, 1435 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.13 (s, 3 H, $CH_3CO$), 2.88–3.04 (m, 4 H, piperazine), 3.54–3.80 (m, 4 H, piperazine), 6.31–6.36 (m, 2 H, 4-H and 6-H), 7.11 (dd, 1 H, $J$ = 2 Hz and 7 Hz, 3-H). Anal. ($C_{12}H_{16}ClN_3O \cdot {}^5/_{16}H_2O$) C, H, N.

**3-(4-Acetyl-1-piperazinyl)-4-chlorophenyl Isothiocyanate (35).** To a stirred solution of 8.35 g (73 mmol) of thiophosgene in 30 mL of $CHCl_3$ was added dropwise a mixture of 15.36 g (61 mmol) of **34**, 15.4 g (153 mmol) of triethylamine, and 70 mL of $CHCl_3$ below 10 °C. After stirring at room temperature overnight, the reaction mixture was poured into ice–water, washed with dilute aqueous $NaHCO_3$ and water, dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$ to give 11.96 g (66%) of **35**: mp 123–124 °C; IR 2070, 1620, 1580, 1470 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.14 (s, 3 H, $CH_3CO$), 2.8–4.0 (m, 8 H, piperazine), 6.7–7.5 (m, 3 H, aromatic). Anal. ($C_{13}H_{14}ClN_3OS$) C, H, N.

**Diethyl [[3-(4-Acetyl-1-piperazinyl)-4-chlorophenyl]amino]mercaptomethylenemalonate (36).** To a stirred suspension of 1.95 g (41 mmol) of NaH (50% in oil) in 150 mL of distilled THF was added dropwise 6.5 g (41 mmol) of diethyl malonate and then was added a solution of 11.0 g (37 mmol) of **35** in 50 mL of distilled THF under ice cooling. After stirring at room temperature overnight, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in water, neutralized with 5% aqueous HCl, and extracted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and concentrated to dryness in vacuo. The remaining viscous oil was triturated with *n*-hexane, and the resulting solid was collected by filtration and dried to give 14.9 g (88%) of **36**: mp 117–119 °C; IR 3400, 2980, 1740, 1725, 1620 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.33 (t, 6 H, $J$ = 7 Hz, $CH_2CH_3$), 2.14 (s, 3 H, $CH_3CO$), 3.0–4.0 (m, 8 H, piperazine), 4.31 (q, 4 H, $J$ = 7 Hz, $CH_2CH_3$), 7.2–8.0 (m, 3 H, aromatic). Anal. ($C_{20}H_{26}ClN_3O_5S$) C, H, N.

**Ethyl 7-(4-Acetyl-1-piperazinyl)-6-chloro-4-hydroxy-2-[(methoxymethyl)thio]quinoline-3-carboxylate (38).** To a stirred mixture of 14.84 g (32.5 mmol) of **36** 4.90 g (35 mmol) of $K_2CO_3$ and 50 mL of DMF was added dropwise a solution of 2.8 g (35 mmol) of chloromethyl methyl ether with stirring under ice cooling. After stirring at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with water, dried, and concentrated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$ to give 17.51 g of **37** as an oily substance. Compound **37**: IR 2980, 1730, 1650, 1560 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.31 (t, 6 H, $J$ = 8 Hz, $CH_2CH_3$), 2.12 (s, 3 H, $CH_3CO$), 2.7–4.0 (m, 8 H, piperazine), 3.19 [s, a/(a+b) × 3 H, $CH_3O$], 3.32 [s, b/(a+b) × 3 H, $CH_3O$], 4.22 (q, 2 H, $J$ = 8 Hz, $CH_2CH_3$), 4.54 [s, a/(a+b) × 2 H, $SCH_2O$], 4.92 [s, b/(a+b) × 2 H, $SCH_2O$], 4.75 [s, b/(a+b) × 1 H, CH], 6.3–7.5 (m, 3 H, aromatic), 10.53 [s, a/(a+b) × 1 H, NH]. Anal. ($C_{22}H_{30}ClN_3O_6S \cdot H_2O$) C, H, N.

A mixture of 8.61 g (17 mmol) of **37** and 26 g of diphenyl ether was heated at 200–220 °C for 5 min. After cooling, the reaction mixture was chromatographed on silica gel with 0.5% MeOH in $CHCl_3$ to yield 0.09 g (1.1%) of ethyl 5-(4-acetyl-1-piperazinyl)-6-chloro-4-hydroxy-2-[(methoxymethyl)thio]quinoline-3-carboxylate (**39**). Chromatography also gave 4.78 g (61%) of **38**. Compound **38**: mp 181–182 °C; IR 2980, 1720, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.52 (t, 3 H, $J$ = 6 Hz, $CH_2CH_3$), 2.15 (s, 3 H, $CH_3CO$), 2.70–4.10 (m, 8 H, piperazine), 3.45 (s, 3 H, $OCH_3$), 4.53 (q, 2 H, $J$ = 6 Hz, $CH_2CH_3$), 5.45 (s, 2 H, $SCH_2O$), 7.25 (s, 1 H, 8-H), 8.10 (s, 1 H, 5-H). Anal. ($C_{20}H_{24}ClN_3O_5S$) C, H, N. Compound **39**: mp 160–161 °C; IR 2870, 1710, 1650, 1560 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.46 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 2.18 (s, 3 H, $CH_3CO$), 2.90–3.18 (m, 4 H, piperazine), 3.40 (s, 3 H, $OCH_3$), 3.42–4.10 (m, 4 H, piperazine), 4.49 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 5.53 (s, 2 H, $SCH_2O$), 7.51 (d, 1 H, $J$ = 9 Hz, 7-H), 7.78 (d, 1 H, $J$ = 9 Hz, 8-H). Anal. ($C_{20}H_{24}ClN_3O_5S$) C, H, N.

**Ethyl 7-(4-Acetyl-1-piperazinyl)-6-chloro-4-hydroxy-2-mercaptoquinoline-3-carboxylate (40).** A mixture of 4.8 g (10.6 mmol) of **38** and 50 mL of 40% HCl in EtOH was stirred at room temperature overnight. After cooling, the reaction mixture was poured into ice–water and extracted with $CHCl_3$. The organic layer was washed with water, dried, and concentrated to dryness under reduced pressure to give 3.4 g (79%) of **40**: yellow crystals; mp 230–232 °C dec; IR 3420, 2900, 1625, 1565 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 1.27 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 2.06 (s, 3 H, $CH_3CO$), 2.80–4.00 (m, 8 H, piperazine), 4.26 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 7.28 (s, 1 H, 8-H), 8.09 (s, 1 H, 5-H), 12.98 (s, 1 H, OH). Anal. ($C_{16}H_{20}ClN_3O_4S \cdot {}^1/_2H_2O$) C, H, N.

**Ethyl 7-(4-Acetyl-1-piperazinyl)-6-chloro-4-oxo-4*H*-[1,3]-thiazeto[3,2-*a*]quinoline-3-carboxylate (28k).** To a mixture of 2.35 g (9 mmol) of diiodomethane, 2.5 g (18 mmol) of $K_2CO_3$, and 50 mL of dry DMF was added dropwise a solution of 3.0 g (7.3 mmol) of **40** in 30 mL of dry DMF with vigorous stirring at room temperature. After stirring for 1 h, the reaction mixture was concentrated in vacuo at 80 °C. The residual solid was washed with water, dried, and recrystallized from $CHCl_3$–EtOH to give 2.49 g (80%) of **28k** as a colorless powder. Compound **28k**: IR 3450, 1710, 1635, 1590 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 1.54 (t, 3 H, $J$ = 6 Hz, $CH_2CH_3$), 2.63 (s, 3 H, $CH_3CO$), 3.20–4.50 (m, 8 H, piperazine), 4.66 (q, 2 H, $J$ = 6 Hz, $CH_2CH_3$), 6.11 (s, 2 H, 1 H), 7.14 (s, 1 H, 8-H), 8.52 (s, 1 H, 5-H).

By using the same procedure, compound **28l** was prepared from **40** and 1,1-dibromoethane. Compound **28l**: a pale yellow powder; IR 2980, 1710, 1640, 1585 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 1.56 (t, 3 H, $J$ = Hz, $CH_2CH_3$), 2.39 (d, 3 H, $J$ = 7 Hz, 1-$CH_3$), 2.68 (s, 3 H, $CH_3CO$), 3.37–4.43 (m, 8 H, piperazine), 4.66 (q, 2 H, $J$ = 8 Hz, $CH_2CH_3$), 6.56 (q, 1 H, $J$ = 7 Hz, 1-H), 7.10 (s, 1 H, 8-H), 8.56 (s, 1 H, 5-H).

**6-Chloro-1-methyl-4-oxo-7-(1-piperazinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (29bb).** A mixture of 610 mg (1.4 mmol) of **28l**, 12 mL of 5% aqueous HCl, and 3 mL of EtOH was heated at 110 °C for 2 h. After cooling, the reaction mixture was neutralized with 5% aqueous ammonia and the resulting precipitate was collected by filtration and recrystallized from DMF to give 300 mg (59%) of **29bb** as a colorles powder. Compound **29bb**: IR 3500, 1600, 1470 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.10 (d, 3 H, $J$ = 6 Hz, $CH_3$), 2.80–3.32 (m, 8 H, piperazine), 6.41 (q, 1 H, $J$ = 6 Hz, 1-H), 7.01 (s, 1 H, 8-H), 8.10 (s, 1 H, 5-H).

By using the same procedure, compound **29z** was prepared from **28k**. Compound **29z**: a pale yellow powder; IR 3400, 1600, 1470 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 2.85–3.30 (m, 8 H, piperazine), 5.91 (s, 2 H, 1-H), 7.11 (s, 1 H, 8-H), 8.07 (s, 1 H, 5-H).

**6-Chloro-7-(4-methyl-1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid (29aa).** A mixture of 320 mg (0.91 mmol) of **29z**, 1.2 mL of formic acid, and 0.6 mL of formaldehyde (37% solution in water) was heated under reflux for 5 h. The reaction mixture was concentrated to dryness under reduced pressure. The residue was diluted with water and neutralized with $K_2CO_3$. The resulting precipitate was collected by filtration and recrystallized from EtOH to give 100 mg (29%) of **29aa** as a pale yellow powder. Compound **29aa**: IR 3500, 1700, 1600, 1465 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 3.22 (s, 3 H, $CH_3$), 3.32–4.24 (m, 8 H, piperazine), 6.20 (s, 2 H, 1-H), 7.32 (s, 1 H, 8-H), 8.62 (s, 1 H, 5-H).

By using the same procedure, compound **29cc** was prepared from **29bb** in 53% yield. Compound **29cc**: a colorless powder; IR 3420, 1700, 1605 $cm^{-1}$; NMR ($CF_3CO_2D$) $\delta$ 2.40 (d, 3 H, $J$ = 7 Hz, 1-$CH_3$), 3.22 (s, 3 H, $CH_3N$), 3.30–4.30 (m, 8 H, piperazine), 6.63 (q, 1 H, $J$ = 7 Hz, 1 H), 7.29 (s, 1 H, 8-H), 8.64 (s, 1 H, 5-H).

**7-(4-Acetonyl-1-piperazinyl)-6-fluoro-1-methyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (29dd).** To a suspension of 3.0 g (10.5 mmol) of **27b** in 30 mL of DMF was added 3.7 g (26.3 mmol) of *N*-acetonylpiperazine under ice cooling. After stirring for 2 days at room temperature, the reaction mixture was concentrated to dryness under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$–$CH_3OH$ (50:1) to afford a solid, which was recrystallized from EtOH to give 2.25 g (53%) of **29dd** as a pale yellow crystals. Compound **29dd**: IR 3400, 1710, 1625, 1600, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.40 (d, 3 H, $J$ = 6 Hz, 1-$CH_3$), 2.48 (s, 3 H, $CH_3CO$), 3.54–4.20 (m, 8 H, piperazine), 4.57 (s, 2 H, $COCH_2N$), 6.63 (q, 1 H, $J$ = 6 Hz, 1-H), 7.17 (d, 1 H, $J$ = 6 Hz, 8-H), 8.20 (d, 1 H, $J$ = 13 Hz, 5-H).

**(Pivaloyloxy)methyl 7-(4-Acetonyl-1-piperazinyl)-6-fluoro-1-methyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (41g).** To a mixture of 200 mg (0.49 mmol) of **29dd**, 2 mL of DMF, and 68 mg (0.490 mmol) of $K_2CO_3$ was added dropwise 178 mg (0.98 mmol) of chloromethyl pivalate at room temperature. After stirring at 60 °C for several hours and then at room temperature overnight, the reaction mixture was concentrated to dryness under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (30:1) to give 160 mg (63%) of **41g** as pale yellow crystals. Compound **41g**: IR 3400, 1720, 1610, 1500 $cm^{-1}$; $^1H$ NMR ($CDCL_3$) $\delta$ 1.22 [s, 9 H, $COC(CH_3)_3$], 2.10 (d, 3 H, $J$ = 7 Hz, 1-$CH_3$), 2.16 (s, 3 H, $CH_3$-CO), 2.53–3.45 (m, 8 H, piperazine), 3.28 (s, 2 H, $COCH_2N$), 5.90 (s, 2 H, $OCH_2O$), 5.90 (q, 1 H, $J$ = 7 Hz, 1-H), 6.30 (d, 1 H, $J$ = 8 Hz, 8-H), 7.75 (d, 1 H, $J$ = 14 Hz, 5-H).

**Ethyl 7-(4-Acetonyl-1-piperazinyl)-6-fluoro-1-methyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (41f). Method A.** To a stirred solution of 1.0 g (3.2 mmol) of **25b** in 30 mL of DMF was added 0.96 g (6.74 mmol) of acetonylpiperazine. After stirring at 60–70 °C for 5 h, the reaction mixture was concentrated to dryness under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$–MeOH to give 460 mg (33%) of **41f**: IR 3400, 1715, 1600, 1490 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 1.56 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 2.37 (d, 3 H, $J$ = 7 Hz, 1-$CH_3$), 2.48 (s, 3 H, $CH_3CO$), 3.54–4.30 (m, 8 H, piperazine), 4.56 (s, 2 H, $COCH_2N$), 4.68 (q, 2 H, $J$ = 7 Hz, $CH_2CH_3$), 6.58 (q, 1 H, $J$ = 7 Hz, 1-H), 7.09 (d, 1 H, $J$ = 8 Hz, 8-H), 8.19 (d, 1 H, $J$ = 13 Hz, 5-H).

**Method B.** To a solution of **28c** (from 13.0 g of **25b**) in 50 mL of DMF was added 7.0 g (69 mmol) of $NEt_3$ and 7.1 g (52 mmol) of bromoacetone. After stirring for 4 h, the reaction mixture was concentrated to dryness in vacuo. The residue was chromatographed on silica gel with $CHCl_3$–MeOH to give 9.98 g (67%) of **41f** which was identical in all respects with an authentic specimen of **41f** prepared by the method A.

By using the same procedure, compound **41h** was prepared from **25d** in 48% yield. Compound **41h**: colorless crystals: IR 3450, 1720, 1600, 1495 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.41 (t, 3 H, $J$ = 8 Hz, $CH_2CH_3$), 2.16 (s, 3 H, $CH_3CO$), 2.50–2.70 (m, 4 H, piperazine), 2.87–3.14 (m, 4 H, piperazine), 3.28 (s, 2 H, $COCH_2N$), 4.19 (q, 2 H, $J$ = 8 Hz, $CH_2CH_3$), 5.91 (d, 1 H, $J$ = 8 Hz, 8-H), 6.68 (s, 1 H, 1-H), 7.40–7.60 (m, 5 H, Ph), 7.95 (d, 1 H, $J$ = 14 Hz, 5-H).

**Ethyl 6-Fluoro-1-methyl-7-[4-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-1-piperazinyl]-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]-quinoline-3-carboxylate (41i).** To a mixture of 3.88 g (10.3 mmol) of **28c**, 1.23 g (12.3 mmol) of $KHCO_3$, and 20 mL of DMF was added dropwise 2.38 g (12.3 mmol) of DMDO-Br[24] with stirring under ice cooling. The reaction mixture was warmed gradually to room temperature, stirred for 1 h and concentrated to dryness in vacuo. The residue was dissolved in $CHCL_3$, washed with water, dried, and concentrated to dryness in vacuo. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (50:1) to give 3.32 g (66%) of **41i** as a colorless powder. Compound **41i**: IR 3420, 1810, 1720, 1630, 1605, 1495 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 1.51 (t, 3 H, $J$ = 7 Hz, $CH_2CH_3$), 2.30 (s, 3 H, 7-$CH_3$), 2.33 (d, 3 H, $J$ = 6 Hz, 1-$CH_3$), 3.30–4.37 (m, 8 H, piperazine), 4.55 (s, 2 H, 7-$CH_2N$), 4.61 (q, 2 H, $J$ = 7, $CH_2CH_3$), 6.49 (q, 1 H, $J$ = 6 Hz, $CH_2CH_3$), 7.03 (d, 1 H, $J$ = 6 Hz, 8-H), 8.10 (d, 1 H, $J$ = 13 Hz, 5-H).

**6-Fluoro-1-methyl-7-[4-[(5-methyl-2-oxo-1,3-dioxol-4-yl)-methyl]-1-piperazinyl]-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic Acid (29ee).** To a stirred mixture of 2.5 g (7.2 mmol) of **29a**, 0.79 g (7.9 mmol) of $KHCO_3$, and 10 mL of DMF was added a solution of 1.52 g (7.9 mmol) of DMDO-Br in 10 mL of DMF under ice-cooling. After stirring at room temperature for 4–5 h, the reaction mixture was poured into ice–water. The aqueous mixture was neutralized with 3% AcOH (pH 6–7). The resulting precipitate was collected by filtration, washed with water, and dried to afford a solid, which was recrystallized from acetonitrile to give 2.05 g (62%) of **29ee** as a pale yellow powder. Compound **29ee**: IR 3400, 1810, 1705, 1625, 1600, 1495 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.34 (s, 3 H, dioxole $CH_3$), 2.38 (d, 3 H, $J$ = 7 Hz, 1-$CH_3$), 3.55–4.35 (m, 8 H, piperazine), 4.56 (s, 2 H, dioxole $CH_2N$), 6.55 (q, 1 H, $J$ = 7 Hz, 1-H), 7.19 (d, 1 H, $J$ = 7 Hz, 8-H), 8.20 (d, 1 H, $J$ = 12 Hz, 5-H).

By using the same procedure, compound **29ff** was prepared from **29u** in 34% yield. Compound **29ff**: a colorless powder; IR 3400, 1810, 1705, 1625, 1600, 1495 $cm^{-1}$ $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.26 (s, 3 H, $CH_3$), 3.00–4.35 (m, 8 H, piperazine), 4.43 (s, 2 H, dioxole $CH_2$), 6.44 (d, 1 H, $J$ = 6 Hz, 8-H), 7.36 (s, 1 H, 1-H), 7.54 (s, 5 H, Ph), 8.09 (d, 1 H, $J$ = 12 Hz, 5-H).

**Methyl 6,7-Difluoro-1-methyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (41j).** A mixture of 2.0 g (7 mmol) in **27b**, 0.4 g (8.3 mmol) of NaH (50% in oil), and 50 mL of DMF was heated at 50 °C for 1 h with stirring. After cooling, to this mixture was added 1.2 g (8.4 mmol) of methyl iodide. After stirring for 20 h at room temperature, the reaction mixture was poured into ice–water. The resulting precipitate was collected by filtration, washed with water, and dried to afford a crystalline solid, which was chromatographed on silica gel with $CHCl_3$ to yield 1.71 g (82%) of **41j** as a colorless powder; IR 3500, 1725, 1675, 1610, 1495 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.39 (d, 3 H, $J$ = 7 Hz, $CH_3$), 4.21 (s, 3 H, $CO_2CH_3$), 6.60 (q, 1 H, $J$ = 7 Hz, 1-H), 7.62 (dd, 1 H, 8-H), 8.36 (dd, 1 H, $J$ = 8 and 9 Hz, 5-H).

By using the same procedure, compound **41k** was prepared. Compound **41k**: a colorless powder; IR 3450, 1720, 1610, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 1.51 [d, 6 H, $J$ = 6 Hz, $CH(CH_3)_2$], 2.35 (d, 3 H, $J$ = 7 Hz, 1-$CH_3$), 5.5 [m, 1 H, $CH(CH_3)_2$], 6.58 (q, 1 H, $J$ = 7 Hz, 1-H), 7.59 (dd, 1 H, $J$ = 6 and 8 Hz, 8-H), 8.33 (dd, 1 H, $J$ = 8 and 9 Hz, 5-H).

**2-Hydroxyethyl 6,7-Difluoro-1-methyl-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (41m).** A mixture of 4.0 g (13 mmol) of **25b**, 100 mL of ethylene glycol, and 5 drops of concentrated $H_2SO_4$ was heated at 100 °C for 5.5 h with stirring. After being allowed to stand at room temperature overnight, the resulting precipitate was collected by filtration, washed with water, and dried to give 3.69 g (88%) of **41m**: a colorless powder; IR 3410, 1710, 1660, 1605, 1550, 1480 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.41 (d, 3 H, $J$ = 7 Hz, 1-$CH_3$), 4.05–5.05 (m, 4 H, $CO_2CH_2$-$CH_2OH$), 6.61 (q, 1 H, $J$ = 7 Hz, 1-H), 7.62 (dd, 1 H, $J$ = 6 and 9 Hz, 8-H), 8.33 (dd, 1 H, $J$ = 7 and 9 Hz, 5-H).

By using the same procedure, compound **41l** was prepared. Compound **41l**: a colorless powder; IR 3050, 1705, 1605, 1550 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 1.08 [t, 3 H, $J$ = 7 Hz, $(CH_2)_2CH_3$], 1.50–2.05 [m, 4 H, $(CH_2)_2CH_3$], 2.42 (d, 3 H, $J$ = 7 Hz, 1-$CH_3$), 4.68 (t, 2 H, $J$ = 7 Hz, $OCH_2$), 6.64 (q, 1 H, $J$ = 7 Hz, 1-H), 7.69 (dd, 1 H, J = 7 and 9 Hz, 8-H), 8.42 (dd, 1 H, $J$ = 8 and 8 Hz, 5-H).

***n*-Butyl 6-Fluoro-1-methyl-4-oxo-7-(1-piperazinyl)-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (41c).** A mixture of 0.9 g (2.65 mmol) of **41l** 1.0 g (11.6 mmol) of piperazine, and 15 mL of DMF was stirred at room temperature for 15 h. The resulting precipitate was collected by filtration, washed with ether, and then subjected to column chromatography over silica gel to afford a solid, which was recrystallized from *i*-PrOH to give 0.68 g (63%) of **41c** as colorless crystals; IR 3400, 1715, 1625, 1600, 1495 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 0.90–2.20 [m, 7 H, $CH_3(CH_2)_2$], 2.36 (d, 3 H, $J$ = 6 Hz, 1-$CH_3$), 3.50–4.20 (m, 8 H, piperazine), 4.35–4.85 (m, 2 H, $OCH_2$), 6.53 (q, 1 H, $J$ = 6 Hz, 1-H), 7.02 (d, 1 H, $J$ = 7 Hz, 8-H), 8.22 (d, 1 H, $J$ = 12 Hz, 5-H).

By using the same procedure, compounds **41a,b,d** were prepared. Starting materials, physical appearance, and spectral data are given below.

Compound **41a**: **41j** and piperazine; pale yellow crystals; IR 3400, 1725, 1625, 1585, 1490 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.34 (d, 3 H, $J$ = 6 Hz, 1-$CH_3$), 3.45–4.35 (m, 8 H, piperazine), 4.16 (s, 3 H, $CO_2CH_3$), 6.53 (q, 1 H, $J$ = 6 Hz, 1-H), 7.04 (d, 1 H, $J$ = 7 Hz, 8-H), 8.15 (d, 1 H, $J$ = 13 Hz, 5-H).

Compound **41b**: **41k** and piperazine; pale yellow crystals; IR 3400, 1715, 1600, 1495 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 1.25 [d, 6 H, $J$ = 6 Hz, $CH(CH_3)_2$], 2.05 (d, 3 H, $J$ = 6 Hz, 1-$CH_3$), 2.80–3.20 (m, 8 H, piperazine), 4.94–5.08 [m, 1 H, $CH(CH_3)_2$], 6.16 (q, 1 H, $J$ = 6 Hz, 1-H), 6.75 (d, 1 H, $J$ = 8 Hz, 8-H), 7.67 (d, 1 H, $J$ = 14 Hz, 5-H).

Compound **41d**: **41m** and piperazine; yellow crystals; IR 3400, 1710, 1600, 1500 $cm^{-1}$; $^1H$ NMR ($CF_3CO_2D$) $\delta$ 2.35 (d, 3 H, $J$ = 6, 1-$CH_3$), 3.55–4.10 (m, 8 H, piperazine), 4.10–4.95 [m, 4 H, $CO_2(CH_2)_2OH$], 6.55 (q, 1 H, $J$ = 6 Hz, 1-H), 7.05 (d, 1 H, $J$ = 7 Hz, 8-H), 8.15 (d, 1 H, $J$ = 13 Hz, 5-H).

**(Pivaloyloxy)methyl 6-Fluoro-1-methyl-7-(1-piperazinyl)-4-oxo-4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylate (41e).** To a stirred solution of 0.5 g (1.43 mmol) of **29a**, 0.2 g (1.43 mmol) of $K_2CO_3$, and 15 mL of DMF was added 0.215 g (1.43 mmol) of chloromethyl pivalate. After stirring at 60–80 °C for 3 h, the reaction mixture was poured into ice–water. The aqueous solution was acidified with AcOH, washed with EtOAc, made alkaline with $K_2CO_3$, and extracted with EtOAc. The organic layer was washed with water, dried, and concentrated to leave a crude product, which was treated with ether to give 0.12 g (18%) of **41e** as colorless crystals: IR 3320, 2930, 1730, 1710, 1625, 1600, 1500 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.23 [s, 9 H, $(CH_3)_3CCO_2$], 2.10 (d, 3 H, $J$ = 6 Hz, 1-$CH_3$), 2.50–3.50 (m, 8 H, piperazine), 5.87 (q, 1 H, $J$ = 6 Hz, 1-H), 5.88 (s, 2 H, $CO_2CH_2OCO$), 6.28 (d, 1 H, $J$ = 7 Hz, 8-H), 7.76 (d, 1 H, $J$ = 14 Hz, 5-H).

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