SYNTHESIS OF *N*-(1-AZIRIDINYL)-6-FLUORO-1,4-DIHYDRO-4-OXOQUINOLINE-3-CARBOXYLIC ACIDS

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Abstract - A series of *N*-(1-aziridinyl)quinoline-3-carboxylic acid derivatives (*e.g.* **11a-f, 20a-g, 21a-d**) have been synthesized by insertion reaction of nitrenes (*e.g.* ethyl 7-chloro-6-fluoro-1-nitreno-1,4-dihydro-4-oxoquinoline-3-carboxylate (**9**)) into double bond of different olefins (*e.g.* styrene (**10a**), see Schemes 2 and 4). The nitrenes were formed *in situ* by oxidation of *N*-aminoquinolin-4(1*H*)-one derivatives (**8, 18a,b**) using $Pb(OAc)_4$ as oxidizing agent.

INTRODUCTION

Since the discovery of antibacterial behaviour of nalidixic acid[1] (**1**, Figure 1) a huge work was done to enhance its biological potency by modification of its chemical structure.[2] This activity led to the discovery of the third generation of nalidixic acid (fluoroquinolones) in the early 1980's (introducing a fluorine atom in position 6, a substituted amino group in position 7 and changing of N-8 to CH or CF). Since then more than a dozen representatives of this class have been introduced into the human and veterinary therapy for a broad variety of clinical indications,[3] among others amifloxacin[4] (**2**) and ciprofloxacin[5] (**3**), one of the clinically most successful agents.

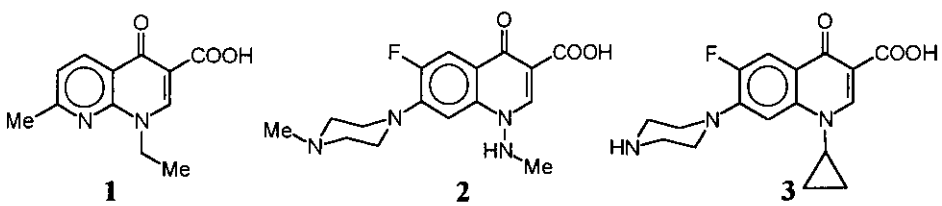


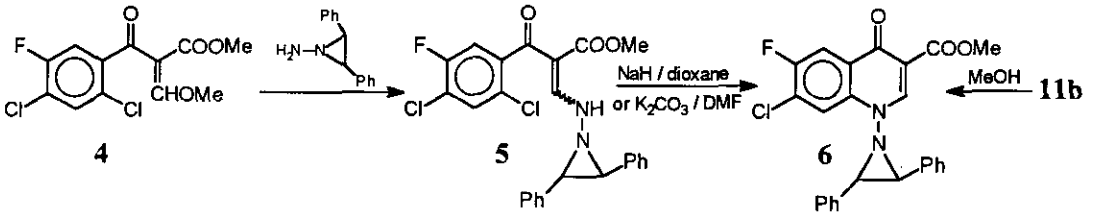
Figure 1

Recently we published[6] the short synthesis and the biological evaluation of the aza analogues of ciprofloxacin, the *N*-(1-aziridinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acids. Now we would like to report the details of the chemical work leading to these derivatives.

RESULTS AND DISCUSSION

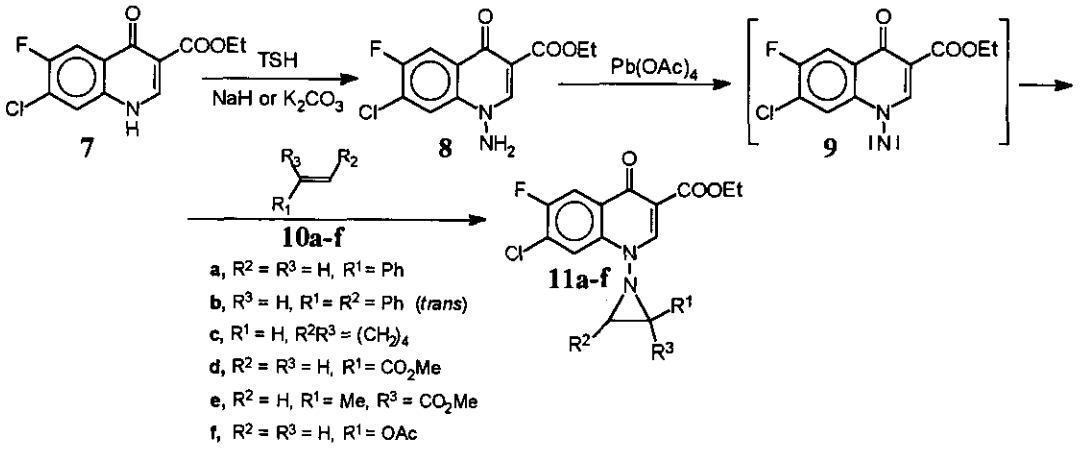
Two main strategies were applied in the course of the synthesis.

1. According to the general procedure of synthesis of different fluoroquinolones[7] (in which substituted amines were reacted with properly substituted benzoyl acrylic acid derivatives, e.g. **4**), the reaction of the 1-amino-*trans*-2,3-diphenylaziridine[8] with methyl 2-(2,4-dichloro-5-fluorobenzoyl)-3-methoxyacrylate (**4**, Scheme 1) was performed.



Scheme 1

The reaction gave the mixture of the possible geometric isomers (**5**, E : Z ≈ 10 : 1) in 52 % yield. The attempted ring closure of **5** under different conditions resulted in a multicomponent mixture, in which the presence of the desired product (**6**) could have been proved by TLC. An authentic sample of **6** was prepared by transesterification of ethyl ester (**11b**), obtained by a different route (see below).



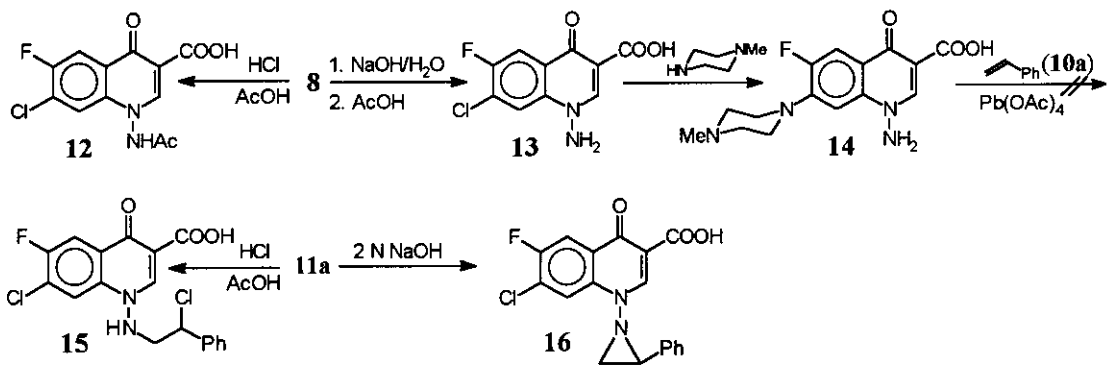
Scheme 2

2. It is known[9] since longer time that nitrenes can be inserted into double bond to form aziridine derivatives. Deshmukh *et al* [10] gave a nice example of the selective aziridination in the course of the synthesis of 1-(1-aziridinyl)quinazolines. On this basis we found promising the aziridination of the *N*-

amino-4-quinolone derivatives. At the same time of our investigations Japanese authors[11] patented the synthesis of 1-(1-aziridinyl)-4-oxoquinoline-3-carboxylates on very similar conception.

Our work started with the *N*-amination of ethyl 7-chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**7**, Scheme 2). It was performed under basic condition (using NaH or K_2CO_3) by *O*-(*p*-toluenesulfonyl)hydroxylamine (TSH)[12] to give the *N*-amino-4-oxoquinoline (**8**). The *N*-amino group of **8** was oxidized by $Pb(OAc)_4$ in dichloromethane in the presence of different olefins (**10a-f**) to afford the 1-(1-aziridinyl) derivatives (**11a-f**) in moderate to good yield.

The exchange of the Cl substituent in position 7 by *N*-methylpiperazine was unsuccessful even at 160 °C both in the case of the *N*-amino derivative (**8**) and the *N*-(1-aziridinyl) derivative (**11a**), therefore the hydrolysis of **8** and **11a** was performed (Scheme 3), because it was observed in similar reactions (L. Vasvári-Debreczy, I. Hermecz, and G. Keresztúri, unpublished results) that the halogen substituent in position 7 of the free 3-acids is more reactive towards amines than that of the ester derivatives.



Scheme 3

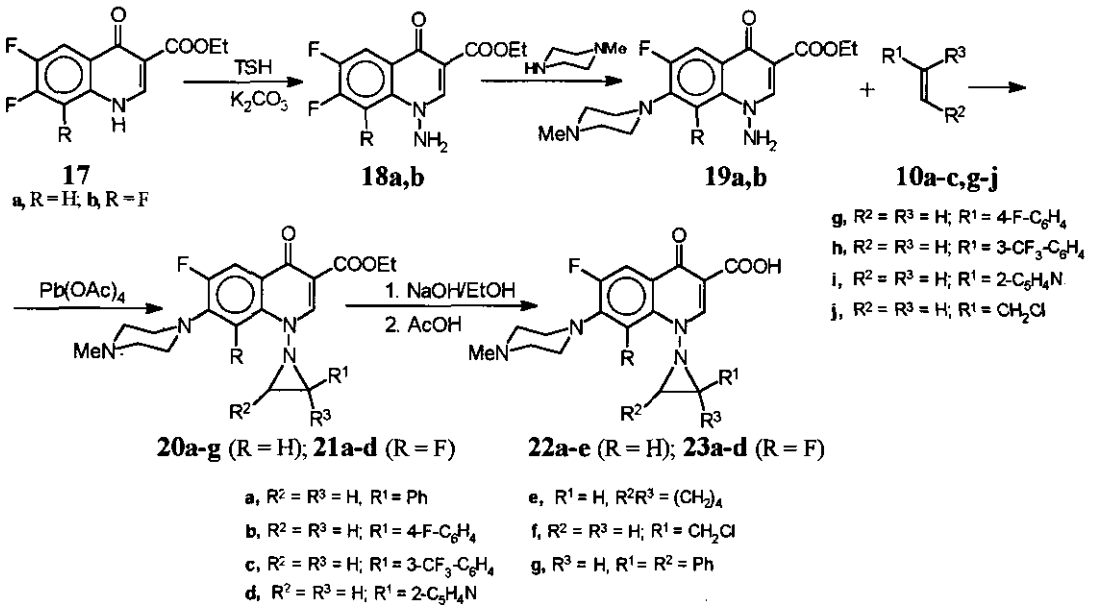
The hydrolysis of the ester moiety of **8** or **11a** was successful both under basic or acidic condition. While the hydrolysis of **8** in AcOH gave surprisingly the *N*-acetyl derivative (**12**); in the case of **11a**, the hydrolysis of the ester group was followed by the opening of the aziridine ring to afford **15**.

Although the Cl substituent of **13** was easily exchanged for *N*-methylpiperazinyl group at 150 °C, the attempted nitrene insertion reaction of the resulted **14** with **10a** (and $Pb(OAc)_4$) was unsuccessful, very probably because of the poor solubility of **14** in suitable solvents (*e.g.* CH_2Cl_2 or $CHCl_3$).

Generally, the fluorine atom is much better leaving group in a nucleophilic reaction than the chlorine atom.[13] That was the reason why the reactions of 6,7-difluoro (**17a**) and 6,7,8-trifluoro (**17b**) derivatives[14] were also studied.

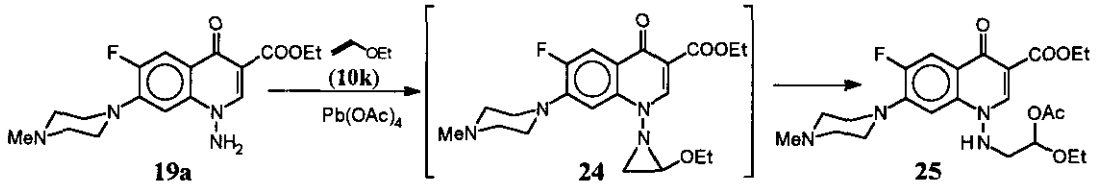
The *N*-amination of **17a,b** (Scheme 4) was performed in DMF using TSH as reagent (similarly as in the case of 7) to give **18a,b** in good yield. The exchange of the fluorine substituent in position 7 of **18a,b** took

place easily in boiling pyridine with *N*-methylpiperazine resulting the *N*-amines (**19a,b**). These latter compounds were then reacted by different olefins (**10a-c,g-j**) in the presence of $Pb(OAc)_4$ to give *N*-(1-aziridinyl)quinoline-3-carboxylate derivatives (**20a-g, 21a-d**). The hydrolysis of the ester moiety was performed in ethanol using aqueous NaOH followed by neutralization with acetic acid then with NH_4OH. Using this procedure, the desired free acids (**22a-e, 23a-d**) were obtained.



Scheme 4

Finally we did an interesting observation in the course of the study of the nitrene insertion reaction of **19a** (Scheme 5) in ethyl vinyl ether (**10k**): instead of the 1-(2-ethoxy)aziridinyl derivative (**24**) the product (**25**) (which contained the opened aziridine ring) was only isolated.



Scheme 5

This observation is an illustration of the fact, that the aziridine ring can be opened not only by strong acids (HCl, see Scheme 3) but in special cases even by acetic acid (during the aziridination reaction). It is in this way understandable, that in certain cases the desired aziridine derivative can be isolated under 50 % yield or - as the example in Scheme 5 shows - its isolation entirely fails.

The structures of the reaction products were elucidated based on elementary analysis data, IR and ^{1}H NMR spectra. The NMR data are summarised in Tables 2 and 3. In compounds (**21a-d**) an unusual further splitting of the H-2' and H-3' (*cis* to each other) signals of the aziridine ring was observed compared to the multiplicity of the same peaks of compounds (**20a-d**). This is thought to be due to a through-space coupling with 8-F. Detailed analysis of this phenomenon and the conformation of the compounds will be published separately (B. Podányi *et al.*, to be published).

EXPERIMENTAL

Melting points were determined by a Büchi apparatus. IR spectra were recorded on Specord IR-75 equipment and ^{1}H-NMR spectra: 100 MHz on Varian XL-100; 400 MHz on Varian VXR-400, Bruker AC-400 and Bruker DRX-400 instruments at ambient temperature using TMS as internal standard. ^{13}C NMR spectra were recorded on a Bruker DRX-400 instrument. The yields of the reactions were not optimized.

***Methyl 2-(2,4-dichloro-5-fluorobenzoyl)-3-methoxyacrylate* (4)**

Methyl orthoformate (1.59 g, 15 mmol) was added dropwise to a stirred suspension of methyl 2-(2,4-dichloro-5-fluorobenzoyl)acetate[15] (2.65 g, 10 mmol) in acetic anhydride (2.55 g, 25 mmol). The mixture was heated and stirred at 105-107 °C for 2 h. The resulting solution was evaporated *in vacuo*. The residue (3.0 g) crystallized in cold methanol (4 mL). The crystals were collected, washed with cold methanol (0.5 mL) and dried to give 1.66 g (54 %) of beige crystals, mp 123-125 °C; IR (KBr): 3080, 3060, 3030, 2961, 1700, 1650, 1580, 1040 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.57 (s, 1H, H-3); 7.43 (d, 1H, H-5', $J_{F,H}$ = 6.3 Hz); 7.19 (d, 1H, H-2', $J_{F,H}$ = 8.4 Hz); 4.11 (s, 3H, $COOCH_3$) 3.70 (s, 3H, 3-OCH_3); Anal. Calcd for $C_{12}H_9O_4Cl_2F$: C, 46.93; H, 2.95; F, 6.19; Cl, 23.08. Found: C, 47.02; H, 2.93; F, 6.09; Cl, 23.28.

***Methyl 2-(2,4-dichloro-5-fluorobenzoyl)-3-[(2,3-trans-diphenylaziridin-1-yl)amino]acrylate* (5)**

To the stirred suspension of **4** (0.9 g, 3 mmol) in dry ethanol (2 mL) and ethyl acetate (2 mL) a solution of 1-amino-*trans*-2,3-diphenylaziridine[8] (0.63 g, 3 mmol) in dry ethanol (10 mL) was added at 10 °C. The mixture was stirred at 10 °C for 4 h and allowed to stay at rt overnight. The orange-red solution was evaporated. The residue was separated on silicagel, using hexane - ethyl acetate eluant to give 0.75 g (51.7 %) of **5** as colourless crystals, mp 61-64 °C. As shown by NMR, the product was a 10 : 1 mixture of the *E* and *Z* geometric isomers; IR (KBr): 3090, 3070, 3035, 2950, 1705, 1620, 1600, 1495, 1270 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *E* isomer: δ 11.67 (d, 1H, NH, $J_{NH,CH}$ = 11.6 Hz); 8.47 (d, 1H, H-acrylic, $J_{NH,CH}$ = 11.6 Hz); 7.50-7.27 (m, 11H, Ph rings and benzoyl H-3); 6.84 (d, 1H, benzoyl H-6, $J_{6,F}$ = 8.4 Hz); 3.82-

3.75 (m, 2H, H-2',3'); 3.54 (s, 3H, OCH_3); Z isomer: δ 9.93 (d, 1H, NH, $J_{NH,CH}$ = 12.0 Hz); 8.34 (d, 1H, H-acrylic, $J_{NH,CH}$ = 12.0 Hz); 7.50-7.27 (m, 11H, Ph rings and benzoyl H-3); 6.97 (d, 1H, benzoyl H-6, $J_{6,F}$ = 8.8 Hz); 3.82-3.75 (m, 2H, H-2', H-3'); 3.38 (s, 3H, OCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) E isomer: 190.4 (s, C=O), 165.8 (s, COO) 158.3 (s, =CH), 156.5 (d, C-5, $J_{C5,F}$ = 249.8 Hz), 141.8 (d, C-2, $J_{C2,F}$ = 5.9 Hz), 135-126 (Ph), 125.2 (d, C-1, $J_{C1,F}$ = 3.6 Hz), 121.2 (d, C-4, $J_{C4,F}$ = 19.2 Hz), 115.1 (d, C-6, $J_{C6,F}$ = 23.8 Hz), 98.8 (s, =C), 54.1, 51.1, 49.6 (each s, OCH_3, CH-CH); Z isomer: 187.6 (s, C=O), 168.1 (s, COO), 157.9 (s, =CH), 135-126 (Ph), 115.9, (d, C-6, $J_{C6,F}$ = 23.7 Hz), 98.7, (s, =C), 53.9, 51.0, 49.5 (each s, OCH_3, CH-CH); Anal. Calcd for $C_{25}H_{19}N_2O_3Cl_2F$: C, 61.86; H, 3.94; N, 5.77. Found: C, 61.51; H, 4.27; N, 5.51.

***Attempts to cyclize* 5 *to* 6**

A. In DMF / K_2CO_3: **5** (0.5 g, 1 mmol) was heated in DMF (5 mL) in the presence of K_2CO_3 (0.14 g, 1 mmol). The temperature was gradually raised and the reaction mixture was checked by TLC, beside an authentic sample of **6** (prepared from **11b**). After 1.5 h of heating at 130 °C a multicomponent mixture was obtained, in which only traces of **6** could have been shown by TLC.

B. In NaH / dioxane: **5** (0.5 g, 1 mmol) dissolved in dry dioxane (2 mL) was added at 10 °C to a stirred suspension of NaH (55 % dispersion in oil; 0.22 g, 5 mmol) in dry dioxane (10 mL). The temperature was gradually raised and the reaction mixture was checked by TLC, beside an authentic sample of **6** (prepared from **11b**). After 2 h heating at 97 °C a multicomponent mixture was obtained, in which only traces of **6** could have been shown by TLC.

***Methyl 7-chloro-6-fluoro-1-(2,3-*trans*-diphenylaziridin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate* (6) *by transesterification of* 11b**

11b (0.5 g, 1.1 mmol) was refluxed in dry methanol (25 mL) for 9 h. The solution was evaporated and the residue was purified on a silicagel 60 column using ethyl acetate as eluant, to obtain 0.30 g (62%) of **6** as white crystals, mp 104-105 °C; IR (KBr): 3060, 3035, 2950, 2930, 2850, 1733, 1695, 1635, 1610, 1545, 1210 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1H, H-2); 8.01 (d, 1H, H-5, $J_{5,F}$ = 9.0 Hz); 7.98 (d, 1H, H-8, $J_{8,F}$ = 6.0 Hz); 7.58-7.50 (m, 5H, Ph); 7.27-7.10 (m, 5H, Ph); 4.57 (d, 1H, H-2', $J_{2',3}$ = 5.3 Hz); 4.08 (d, 1H, H-3', $J_{2',3}$ = 5.3 Hz); 3.92 (s, 3H, OCH_3). Anal. Calcd for $C_{25}H_{18}N_2O_3ClF$: C, 66.84; H, 4.04; N 6.24. Found: C, 66.90; H, 4.22; N, 6.16.

***Ethyl 1-amino-7-chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate* (8)**

A suspension of 7[16] (5.4 g, 20 mmol) in dry DMF (50 mL) was stirred under argon atmosphere with NaH (1 g, 20 mmol; 50 % dispersion in paraffin oil) at 25 °C for 3 h. Freshly prepared TSH[12] (3.8 g, 20 mmol)

in CH_2Cl_2 (100 mL) was added at 0 °C and the reaction mixture was stirred at 25 °C for 20 h. The solid formed was filtered off, washed with water and ethanol to give 4.1 g (72 %) of pale yellow crystals, mp 249-252 °C; IR (KBr): 3290, 3180, 3100, 3040, 2980, 2910, 2850, 1720, 1690, 1640, 1605, 1570, 1520, 1480, 1450 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.60 (s, 1H, H-2); 8.23 (d, 1H, H-8, $J_{8,F}$ = 6.3 Hz); 7.99 (d, 1H, 5-H, $J_{5,F}$ = 9.3 Hz); 6.58 (s, 2H, NH_2); 4.22 (q, 2H, OCH_2, J_{CH_2,CH_3} = 7.1 Hz) 1.28 (t, 3H, CH_3, J_{CH_2,CH_3} = 7.1 Hz); Anal. Calcd for $C_{12}H_{10}N_2O_3ClF$: C, 50.63; H, 3.54; N, 9.84. Found: C, 50.89; H, 3.48; N, 9.71.

***General procedure for synthesis of 7-chloro-6-fluoro-1-(substituted aziridin-1-yl)-4(1H)-quinolones* (11a-f)**

To a suspension of **8** (0.57 g, 2 mmol) in dry CH_2Cl_2 (10 mL), the olefin derivative (**10a-f**, 10 mmol) was added followed by addition of $Pb(OAc)_4$ (1 g, 2.2 mmol) at 25 °C and the suspension was stirred for 5 h (in the case of **10c** for 16 h). Water (20 mL) was added to the reaction mixture and it was extracted with CH_2Cl_2 (6 x 20 mL). The combined organic extract was dried on $MgSO_4$, filtered and evaporated to dryness. The residue was suspended in acetonitrile (2 mL), filtered off and washed with acetonitrile to give the product (**11a-f**). For physical and spectroscopic data see Tables 1, 2 and 3.

***1-Acetamino-7-chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid* (12)**

A solution of **8** (0.28 g, 1 mmol) in AcOH (3.2 mL) and HCl (0.8 mL, 36 %) was refluxed for 3 h then cooled, the precipitate was filtered off, washed with ethanol to give 0.22 g (73 %) of white crystals, mp 212-213 °C; IR (KBr): 3270, 3040, 1700, 1605, 1560, 1540, 1480, 1460, 1420 cm^{-1}; ^{1}H-NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 14.25 (br, 1H, COOH), 11.75 (br, 1H, NH), 8.80 (s, 1H, H-2), 8.15 (d, 1H, H-8 $J_{8,F}$ = 6 Hz), 7.90 (d, 1H, H-5 $J_{5,F}$ = 9 Hz), 2.25 (s, 3H, CH_3); Anal. Calcd for $C_{12}H_8N_2O_4ClF$: C, 48.26; H, 2.70; N, 9.38. Found: C, 48.03; H, 2.64; N, 9.22.

***1-Amino 7-chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid* (13)**

A suspension of **8** (0.3 g, 1.1 mmol) in water (10 mL) was refluxed with NaOH (0.19 g, 4.8 mmol) for 2 h. The solution was cooled, neutralized with AcOH to pH = 7, the precipitate was filtered off, washed with water and ethanol to give 0.26 g (94 %) of white crystals, mp 280-282 °C; IR (KBr): 3330, 3200, 3030, 1710, 1605, 1540, 1500, 1460 cm^{-1}; ^{1}H-NMR (100 MHz, TFA): δ 9.60 (s, 1H, H-2), 8.85 (d, 1H, H-8, $J_{8,F}$ = 6.1 Hz), 8.35 (d, 1H, H-5, $J_{5,F}$ = 9.2 Hz); Anal. Calcd for $C_{10}H_6N_2O_3ClF$: C, 46.80; H, 2.36; N, 10.92. Found: C, 46.53; H, 2.18; N, 10.75.

***1-Amino-6-fluoro-7-(4-methylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid* (14)**

A suspension of **13** (0.2 g, 0.8 mmol) was stirred in *N*-methylpiperazine (3 mL) at 140-150 °C for 4 h. The excess of *N*-methylpiperazine was evaporated *in vacuo*, the residue was suspended in ethanol, filtered off and washed with ethanol to give 0.18 g (66 %) of white crystals, mp 300 °C; IR (KBr): 3170, 1655, 1625, 1580, 1560 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.87 (s, 1H, H-2), 8.42 (d, 1H, H-8, $J_{8,F}$ = 6.3 Hz), 8.18 (d, 1H, H-5, $J_{5,F}$ = 9.1), 6.89 (br, 2H, NH_2), 2.69 (m, 4H, H-2',6'), 2.21 (m, 4H, H-3',5'), 2.11 (s, 3H, NCH_3); Anal. Calcd for $C_{15}H_{17}N_4O_3F$: C, 56.24; H, 5.35; N, 17.49. Found: C, 56.42; H, 5.21; N, 17.28.

7-Chloro-6-fluoro-1-(2-chloro-2-phenylethylamino)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid **(15)**

A solution of **11a** (0.13 g, 0.33 mmol) in acetic acid (1.2 mL) and 36 % HCl (0.8 mL) was refluxed for 6 h and cooled. The precipitate was filtered off, washed with water and ethanol to give 0.1 g (72 %) of yellow needles, mp 225-228 °C; IR (KBr): 3280, 3030, 1710, 1610, 1550, 1510, 1475, 1440 cm^{-1}; ^{1}H-NMR (100 MHz, DMSO-d_6): δ 14.4 (br, 1H, OH), 9.05 (s, 1H, H-2), 8.20 (d, 1H, H-8, $J_{8,F}$ = 6 Hz), 8.10 (d, 1H, H-5, $J_{5,F}$ = 9 Hz), 7.5-7.4 (m, 6H, Ph, NH), 5.20 (t, 1H, H-2' J_{2',CH_2} = 7 Hz), 3.80 (dd, 2H, CH_2 $J_{CH_2,NH}$ = 6 Hz, J_{2',CH_2} = 7 Hz); Anal. Calcd for $C_{18}H_{13}N_2O_3Cl_2F$: C, 54.70; H, 3.32; N, 7.09. Found: C, 54.40; H, 3.15; N, 6.88.

7-Chloro-6-fluoro-1-(2-phenylaziridin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid **(16)**

A suspension of **11a** (0.1 g, 0.25 mmol) in ethanol (1 mL) and 2N aqueous NaOH (0.5 mL) was stirred at 25 °C for 48 h then mixed with water (1 mL), neutralized with acetic acid to pH = 7. The precipitate was filtered off, washed with water and ethanol to give 71 mg (80 %) of pale yellow crystals, mp 280-283 °C; IR (KBr): 3020, 1705, 1620, 1550, 1480, 1460 cm^{-1}; ^{1}H-NMR (100 MHz, DMSO-d_6): δ 8.90 (s, 1H, H-2), 8.20 (d, 1H, H-8 $J_{8,F}$ = 6.2 Hz), 8.10 (d, 1H, H-5 $J_{5,F}$ = 9 Hz), 8.05 (s, 5H, Ph), 3.80-3.00 (m, 3H, H-2',3',3"); Anal. Calcd for $C_{18}H_{12}N_2O_3ClF$: C, 60.26; H, 3.37; N, 7.81. Found: C, 60.03; H, 3.44; N, 7.50.

General procedure for synthesis of 1-amino-4(1H)-quinolones **(18a,b)**

A suspension of **17a** and **17b**[14] (2 mmol), resp. in dry DMF (12 mL) was stirred with K_2CO_3 (0.55 g, 0.4 mmol) at 25 °C for 2 h. Freshly prepared TSH (0.42 g, 2.2 mmol) in CH_2Cl_2 (12 mL) was added at 0 °C and the reaction mixture was stirred at 25 °C for 24 h. The precipitated crystals were filtered off, washed with water and ethanol to give the product.

Ethyl 1-amino-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate **(18a)**

Yield: 74.6 %, mp 163-166 °C; IR (KBr): 3300, 3180, 3050, 2970, 1720, 1640, 1600, 1480, 1440 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 8.61 (s, 1H, H-2), 8.03 (m, 2H, H-5,8) 6.57 (s, 2H, NH_2), 4.22 (q, 2H, OCH_2, J = 7.2 Hz), 1.28 (t, 3H, CH_3, J = 7.2 Hz); Anal. Calcd for $C_{12}H_{10}N_2O_3F_2$ x $0.25H_2O$: C, 52.85; H, 3.88; N, 10.27. Found: C, 52.90; H, 3.83; N, 10.24.

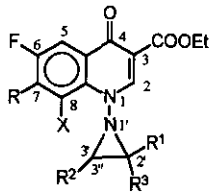
Table 1
Physical and spectroscopic data of compounds (**11a-f, 20a-g** and **21a-d**)

	Yield (%)[a]	Yield Σ (%)	mp (°C)	IR (KBr) (cm^{-1})	Anal. Calcd				Found		
					Formula	C	H	N	C	H	N
11a	70	50[b]	183-186	3100, 3030, 2950, 1720, 1600, 1540, 1450	$C_{20}H_{16}N_2O_3ClF$	62.10	4.17	7.24	62.09	4.13	7.24
11b	45	32[b]	109-111	3100, 3030, 2950, 1720, 1600, 1540, 1450	$C_{26}H_{20}N_2O_3ClF$ x $0.75H_2O$	65.55	4.53	5.88	65.80	4.67	5.56
11c	58	42[b]	228-232	3070, 3020, 2940, 2910, 1720, 1600, 1540	$C_{18}H_{18}N_2O_3ClF$ x $0.75H_2O$	57.15	5.20	7.40	57.04	5.01	7.31
11d	58	42[b]	189-192	3100, 2980, 1740, 1630, 1605, 1540, 1440	$C_{16}H_{14}N_2O_5ClF$	52.12	3.83	7.60	52.38	3.61	7.52
11e	52	37[b]	142-146	3100, 2980, 1720, 1680, 1630, 1600, 1540	$C_{17}H_{16}N_2O_5ClF$	53.34	4.21	7.32	53.19	4.07	7.39
11f	34	24[b]	270-271	3100, 3000, 1760, 1720, 1610, 1590, 1460	$C_{16}H_{14}N_2O_5ClF$	52.12	3.83	7.60	52.34	3.68	7.46
20a	65	37[c]	216-218	3010, 2950, 1725, 1625, 1580, 1530, 1480	$C_{25}H_{27}N_4O_3F$	66.65	6.04	12.44	66.70	5.85	12.51
20b	52	30[c]	215-218	3010, 2950, 2800, 1720, 1620, 1505, 1480	$C_{25}H_{26}N_4O_3F_2$	64.09	5.59	11.96	64.23	5.42	12.08
20c	43	25[c]	192-194	2950, 2800, 1715, 1620, 1500, 1480	$C_{26}H_{26}N_4O_3F_4$	60.23	5.05	10.81	60.08	5.14	10.62
20d	38	22[c]	192-195	2930, 2800, 1720, 1610, 1540, 1480	$C_{24}H_{26}N_5O_3F$	63.85	5.80	15.51	63.58	5.92	15.73
20e	34	19[c]	198-200	2960, 2800, 1710, 1620, 1505, 1420	$C_{23}H_{29}N_4O_3F$	64.47	6.82	13.07	64.28	6.59	13.02
20f	10	6[c]	244-246	3050, 3000, 2960, 1700, 1630, 1580, 1520	$C_{20}H_{24}N_4O_3ClF$	56.80	5.72	13.25	56.51	5.89	12.97
20g	58	33[c]	186-189	3090, 2990, 2960, 2860, 2810, 1720, 1610	$C_{31}H_{31}N_4O_3F$	72.64	6.10	8.20	72.41	6.08	8.35
21a	42	21[d]	188-190	3000, 1720, 1640, 1610, 1550	$C_{25}H_{26}N_4O_3F_2$	64.09	5.59	11.96	63.80	5.35	11.88
21b	48	24[d]	197-200	2800, 1725, 1610, 1520, 1480	$C_{25}H_{25}N_4O_3F_3$	61.72	5.18	11.52	61.42	5.07	11.47
21c	43	22[d]	157-160	2800, 1710, 1680, 1640, 1600, 1460	$C_{26}H_{25}N_4O_3F_5$	58.21	4.70	10.44	58.44	4.52	10.28
21d	52	26[d]	132-135	2940, 2800, 1720, 1610, 1470	$C_{24}H_{25}N_5O_3F_2$ x $1.5H_2O$	58.23	5.40	14.15	58.30	5.51	13.91

[a]Last step. [b]From **7** to **11a-f**. [c]From **17a** to **20a-g**. [d]From **17b** to **21a-d**.

Table 2

^{1}H-NMR data (δ ppm) of compounds (**11a-f**, **20a-g**, **21a-d**, **22a-e** and **23a-d**)



	H-2	H-5	H-8	CO_2Et	H-2'	H-3'	H-3"	MeN-Pip	$R^1(R^2R^3)$
11a[a]	8.68 s	8.06 d	7.86 d	4.32 q, 1.37 t	3.76 dd	3.39 dd	3.06 dd	--	7.48 m
11b[b]	8.75 s	7.79 d	8.37 d	4.23 m 1.27 t	5.48 d	--	4.66 d	--	7.70 m, 7.51 m 7.43 m, 7.41 m 7.17 m
11c[a]	8.48 s	8.11 d	7.92 d	4.34 q, 1.36 t	2.94 s		--	--	2.16 s, 1.45 s
11d[a]	8.51 s	8.10 d	7.11 d	4.35 q, 1.40 t	3.50 dd	3.25 dd	3.10 dd	--	3.92 s
11e[a,c]	8.66 s 8.58 s	8.11 d 8.10 d	8.04 d 7.82 d	4.35 q, 1.39 t	--	3.75 d 3.26 d	3.22 d 3.19 d	--	3.93 s, 3.40 s 1.87 s, 1.27 s
11f[d]	9.02 s	7.91 d	7.92 d	4.23 q, 1.35 t	5.70 dd	3.27 dd	3.06 dd	--	2.25 s
20a[b]	8.62 s	7.74 d	6.86 d	4.23 m 1.30 t	3.63 dd	3.67 dd	3.05 dd	2.78 m, 2.60 m 2.24 m, 2.15 s	7.46 m
20b[b]	8.61 s	7.74 d	6.84 d	4.23 m 1.30 t	3.70 dd	3.66 dd	3.06 dd	2.83 m, 2.66 m 2.28 m, 2.17 s	7.51 m 7.32 m
20c[b]	8.63 s	7.75 d	6.77 d	4.24 m 1.30 t	3.77 dd	3.81 dd	3.17 dd	2.80 m, 2.60 m 2.23 m, 2.14 s	7.9-7.7 m
20d[b]	8.64 s	7.75 d	6.90 d	4.24 m 1.30 t	3.65 dd	3.77 dd	3.22 dd	2.85 m, 2.72 m 2.30 m, 2.17 s	8.64 o, 7.92 td 7.58 dd, 7.46 dd
20e[b]	8.48 s	7.76 d	7.19 d	4.21 q 1.27 t	3.07 m			3.25 m, 2.53 m 2.26 s	2.08 m, 1.32 m
20f[b]	8.59 s	7.76 d	7.31 d	4.21 q, 1.28 t	3.50 m	2.88 dd	2.90 dd	3.27 m, 3.15 m, 2.53 m, 2.25 s	4.10 dd, 3.78 dd
20g[b]	8.42 s	7.58 d	7.20 d	4.13 m 1.22 t	5.26 d	--	4.56 d	3.03 m, 2.43 m 2.23 s	7.68 m 7.55-7.37 m 7.23 m
21a[b]	8.58 s	7.67 dd	--	4.22 m 1.28 t	4.06 ddd	3.39 dt	2.99 dd	3.16 m, 2.35 m 2.20 s	7.38 m
21b[b]	8.58 s	7.67 dd	--	4.22 m 1.28 t	4.09 ddd	3.40 dt	3.00 dd	3.16 m, 2.35 m 2.20 s	7.42m,7.23 m
21c[b]	8.60 s	7.66 dd	--	4.23 m 1.29 t	4.18 ddd	3.51 dt	3.13 dd	3.10 m, 2.30 m 1.29 t	7.82 m, 7.73 m 7.74 m
21d[b]	8.64 s	7.67 dd	--	4.23 m 1.28 t	4.10 ddd	3.41 dt	3.22 dd	3.16 m, 2.36 m 2.21 s	8.56 ddd, 7.83 td, 7.46 dt, 7.36 ddd

	H-2	H-5	H-8	CO_2Et	H-2'	H-3'	H-3"	MeN-Pip	$R^1(R^2R^3)$
22a[a]	8.78 s	7.97 d	6.95 d	--	3.50 m	3.3 m	3.05 m	3.0-2.3 m	7.6-7.5 m
22b[c]	8.88 s	7.88 d	6.93 d	--	3.75 dd	3.80 dd	3.12 dd	2.81 m, 2.72 m, 2.28 m, 2.18 s	7.51 dd, 7.30 t
22c[e]	8.90 s	7.89 d	6.90 d	--	3.88 m		3.18 m	2.90 m, 2.68 m, 2.25 m, 2.18 s	7.85-7.65 m
22d[b]	8.93 s	7.91 d	7.01 d	--	3.86 dd	3.81 dd	3.29 dd	2.92 m, 2.77 m 2.29 m, 2.17 s	8.65 dd, 7.94 td 7.59 dt, 7.48 ddd
22e[b]	8.67 s	7.85 d	7.22 d	--	3.10 s		--	3.29 m, 2.54 m, 2.26 s	2.15 m, 1.35 m
23a[c]	8.82 s	7.86 d	--	--	4.02 m	3.38 m	2.99 m	3.28 m, 2.43 m 2.29 s	7.35 m
23b[b]	8.68 s	7.63 d	--	--	3.94 m	3.26 m	3.26 m	3.19 m, 2.38 m 2.22 s	7.40 m 7.16 m
23c[b]	8.84 s	7.82 d	--	--	4.27 m	3.60 m	3.20m	3.2 m, 2.35 m 2.19 s	7.8-7.5 m
23d[c]	8.90 s	7.83 d	--	--	4.18 m	3.52 m	3.29 m	3.25 m, 2.38 m, 2.25 s	8.58 d, 7.83 dd, 7.50 d, 7.37 dd

[a] 100 MHz, DMSO-d_6 + $CDCl_3$. [b] 400 MHz, DMSO-d_6. [c] The sample is a 1:1 mixture of the *trans* and *cis* substituted izomers of the aziridine ring, therefore two sets of signals were observed. [d] 100 MHz, $CDCl_3$. [e] 400 MHz, DMSO-d_6 + $CDCl_3$.

Table 3

Characteristic coupling constants of selected compounds

Compound	$J_{5,6F}$	$J_{5,8F}$	$J_{8,6F}$	$J_{2',3'}$	$J_{2',3"}$	$J_{3',3"}$	$J_{2',8F}$	$J_{3',8F}$
11b	9.2	--	6.2	--	5.6	--	--	--
20a	13.6	--	7.5	8.4	5.2	2.7	--	--
21a	12.2	1.6	--	8.6	5.8	2.9	2.4	2.9
22d	13.3	--	7.4	8.2	5.6	2.8	--	--

***Ethyl 1-amino-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate* (18b)**

Yield: 82 %, mp 212-214 °C; IR (KBr): 3300, 3180, 3050, 1720, 1640, 1600, 1480, cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 8.47 (s, 1H, H-2), 7.95 (m, 1H, H-5), 6.81 (s, 2H, NH_2), 4.22 (q, 1H, OCH_2, J = 7.2 Hz), 1.28 (t, 1H, CH_3, J = 7.2 Hz); Anal. Calcd for $C_{12}H_9N_2O_3F_3$: C, 50.36; H, 3.17; N, 9.79.

***General procedure for synthesis of 7-(4-methylpiperazin-1-yl)quinolines* (19a,b)**

A suspension of **18a** and **18b** (1 mmol), resp. in dry pyridine (3 mL) was stirred with *N*-methylpiperazine (0.45 g, 0.5 mL, 4.5 mmol) at 130 °C under argon atmosphere for 2 h. The reaction mixture was evaporated *in vacuo* to dryness, the residue was recrystallized from acetonitrile to give the product.

***Ethyl 1-amino-6-fluoro-7-(4-methylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate* (19a)**

Yield: 77 %, mp 240-242 °C; IR (KBr): 3310, 3200, 3000, 2800, 1720, 1640, 1610, 1550 1500, 1440 cm^{-1}; ^{1}H-NMR (100 MHz, TFA): δ 9.46 (s, 1H, H-2), 8.33 (d, 1H, H-8, $J_{8,F}$ = 6 Hz), 8.10 (d, 1H, H-5, $J_{5,F}$ = 9.1 Hz), 4.75 (q, 2H, OCH_2, J_{CH_2,CH_3} = 7.1 Hz), 4.5-3.6 (m, 8H, piperazino), 3.26 (s, 3H, NCH_3), 1.60 (t, 3H, CH_3, J_{CH_2,CH_3} = 7.1 Hz); Anal. Calcd for $C_{17}H_{21}N_4O_3F$: C, 58.61; H, 6.08; N, 16.08. Found: C, 58.84; H, 6.03; N, 15.92.

***Ethyl 1-amino-6,8-difluoro-7-(4-methylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylate* (19b)**

Yield: 61 %, mp 161-163 °C; IR (KBr): 3310, 3200, 3000, 2800, 1720, 1630, 1610, 1550 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.36 (s, 1H, H-2), 7.62 (dd, 1H, H-5, $J_{5,6F}$ = 12.3, $J_{5,8F}$ = 1.5 Hz), 6.71 (br, 2H, NH_2), 4.20 (q, 2H, OCH_2, J_{CH_2,CH_3} = 7.0 Hz), 3.26 (m, 4H, H-2',6'), 2.44 (m, 4H, H-3',5'), 2.23 (s, 3H, NCH_3), 1.27 (t, 3H, CH_3, J_{CH_2,CH_3} = 7.0 Hz); Anal. Calcd for $C_{12}H_{20}N_4O_3F_2$: C, 55.73; H, 5.50; N, 15.29. Found: C, 55.62; H, 5.42; N, 15.08.

Table 4
Physical and IR data of compounds (**22a-e**[a] and **23a-d**[a])

	Yield (%)	mp (°C)	IR (KBr) (cm^{-1})
22a	87	224-225	3400, 3070, 2960, 1720, 1630, 1520, 1490
22b	70	225-229	3400, 2800, 1720, 1620, 1510, 1480
22c	61	219-224	3400, 2800, 1730, 1630, 1480
22d	65	202-204	3410, 2800, 1730, 1630, 1600, 1520, 1470
22e	68	244-245	3420, 2800, 1705, 1630, 1560, 1480, 1410
23a	71	193-197	3400, 2800, 17200, 1640, 1620, 1480
23b	68	230-232	3400, 2800, 17200, 1640, 1620, 1480
23c	70	230-232	3400, 2800, 1720, 1620, 1610, 1540, 1480
23d	52	132-135	3400, 2800, 1720, 1620, 1605, 1540, 1480

[a] Because of the difficulties in the purification, the compounds gave no satisfactory elementary analysis. The structures were supported by IR and ^{1}H-NMR spectroscopy.

***General procedure for synthesis of ethyl 6(8)-(di)fluoro-7-(4-methylpiperazin-1-yl)-1-(substituted aziridine-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylates* (20a-g, 21a-d)**

To a stirred suspension of **19a** and **19b** (1 mmol), resp. and the appropriate olefin (**10a,c,g-j**, 5 mmol) in dry CH_2Cl_2 (5 mL) was dropped a solution of $Pb(OAc)_4$ (0.45 g, 1 mmol) in dry CH_2Cl_2 (5 mL) and the stirring was continued for 12 h at 25 °C. The reaction mixture was mixed with water (10 mL) and extracted with $CHCl_3$ (6 x 5 mL). The combined organic extract was dried on $MgSO_4$, filtered and

evaporated to dryness. The residue was recrystallized from acetonitrile to give the product. For physical and spectroscopic data see Tables 1, 2 and 3.

***General procedure for hydrolysis of esters* (20a-e) *and* (21a-d) *to obtain 6(8)-(di)fluoro-7-(4-methylpiperazin-1-yl)-1-(substituted aziridin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acids* (22a-e) *and* (23a-d)**

A suspension of the appropriate ester (**20a-e** and **21a-d**, resp., 0.2 g) in ethanol (4 mL) was stirred with 2N aqueous NaOH (1.6 mL) at 25 °C for 48 h. Water (2 mL) was added and the reaction mixture was acidified with acetic acid to pH = 6, then made alkaline with 25 % NH_4OH (to pH = 8). The precipitate was filtered off, washed with water to give the product. For physical and spectroscopic data see Tables 2, 3 and 4.

***Ethyl 1-(2-acetoxy-2-ethoxyethylamino)-6-fluoro-7-(4-methylpiperazin-1-yl)-1,4-dihydro-4-oxoquinolinecarboxylate* (25)**

To a stirred suspension of **19a** (0.17 g, 0.5 mmol) and ethyl vinyl ether (**10k**, 0.18 g, 0.24 mL, 2.5 mmol) was dropped a solution of $Pb(OAc)_4$ (0.3 g, 0.56 mmol) in dry CH_2Cl_2 (3 mL) and the stirring was continued for 16 h at 25 °C. The reaction mixture was mixed with water (10 mL) and extracted with CH_2Cl_2 (4 x 5 mL). The combined organic extract was dried on $MgSO_4$, filtered and evaporated to dryness. The residue was suspended in acetonitrile (0.5 mL), filtered off, washed with ether to give 60 mg of pale yellow crystals, mp 147-149 °C; IR (KBr): 3110, 3080, 3040, 2980, 2920, 2830, 2790, 1740, 1700, 1620, 1600, 1580 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.61 (s, 1H, H-2), 7.24 (d, 1H, H-5, $J_{5,F}$ = 13.5 Hz), 7.36 (d, 1H, H-8, $J_{8,F}$ = 7.6 Hz), 7.21 (t, 1H, NH, J_{NH,CH_2} = 4.8Hz), 5.88 (dd, 1H, H-2', $J_{1',2'} = J_{1'',2'}$ = 5.1 Hz), 4.21 (q, 2H, $COOCH_2$, J_{CH_2,CH_3} = 7.1 Hz), 3.62 (m, 1H, H-1'), 3.46 (m, 1H, H-1''), 3.27 (q, 2H, OCH_2 J_{CH_2,CH_3} = 7.0 Hz), 3.23 (m, 4H, piperidino), 2.55 (m, 4H, piperidino), 2.27 (s, 3H, NCH_3), 1.95 (s, 3H, $COCH_3$), 1.28 (t, 3H, CH_3, J_{CH_2,CH_3} = 7.1 Hz), 1.00 (t, 3H, CH_3, J_{CH_2,CH_3} = 7.0 Hz); Anal. Calcd for $C_{23}H_{31}N_4O_6F$: C, 64.17; H, 7.26; N, 13.05. Found: C, 64.25; H, 7.18; N, 12.92.

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