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A Practical Route to C-8 Substituted Fluoroquinolones

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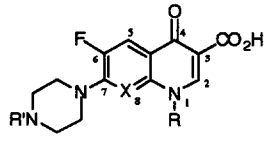
Abstract: *The ortho metalation of N-(tert-butoxycarbonyl)-3,4-difluoroaniline, with t-BuLi at -78°C in THF occured regioselectively at C-2 position. The resulting lithiated species reacted with a variety of electrophiles to give 2-substituted-3,4-difluoroanilines in good yields after hydrolysis. These compounds have been readily transformed into C-8 substituted fluoroquinolones. The nucleophilic substitution at C-7 by piperazines and the alkylation at N-1 on these quinolones have also been performed.*

Introduction

In recent years, many molecular modifications of the parent structures of quinolones have been carried out in order to develop agents with higher potency and broader bacterial coverage[1]. In fact, almost all clinically useful quinolones bear a fluorine atom at the C-6 position and a nitrogen heterocycle, usually a piperazine ring, at the C-7 position. These antibacterial agents, generally known as fluoroquinolones, are now a major class of antiinfectives with significant potential for continued development[2]. Notable examples are Norfloxacin, Pefloxacin, Enoxacin, Ciprofloxacin, Amifloxacin, Ofloxacin and Fleroxacin (Figure 1).



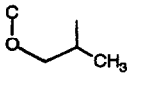
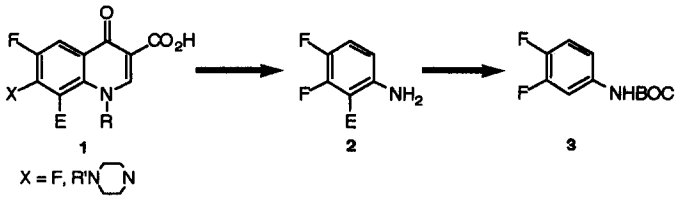
	X	R	R'
Norfloxacin	CH	CH_2CH_3	H
Perfloxacin	CH	CH_2CH_3	CH_3
Enoxacin	N	CH_2CH_3	H
Ciprofloxacin	CH	c-C_3H_5	H
Amifloxacin	CH	$NHCH_3$	CH_3
Fleroxacin	CF	CH_2CH_2F	CH_3
Ofloxacin			CH_3

Figure 1. Clinically significant quinolone antibacterials

In order to perform wider structure-activity studies, the development of general synthetic methods for the preparation of differently substituted quinolones is highly desirable. We wish to report herein a general method of synthesis of fluoroquinolones substituted at the C-8 position from commercially available 3,4-difluoroaniline. This starting material is currently used for the preparation of some important C-8 unsubstituted quinolones such as Pefloxacin and Norfloxacin.

Scheme 1 briefly shows our retrosynthetic plan. It was expected that C-8 substituted quinolones **1** would be easily prepared from 2-substituted-3,4-difluoroanilines **2** according to the Gould-Jacobs reaction sequence[3] for the construction of the quinolone ring. This sequence involves condensation with diethyl ethoxymethylenemalonate and intramolecular Friedel-Crafts acylation as the main steps. An attractive general route to the synthesis of the key intermediates **2** would be the regioselective C-2 ortho metalation[4] of the N-BOC derivative of 3,4-difluoroaniline (**3**) and its further reaction with electrophiles. This approach would be based on the cooperative metalation effects of the strong ortho directing NHBOC group[5] and the weaker ortho directing ability of F[6].

Scheme 1

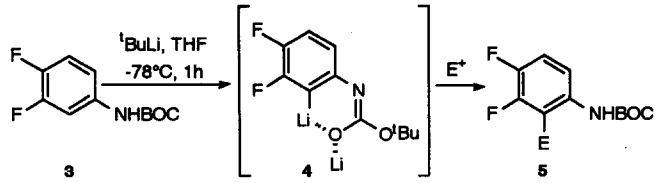


Results and Discussion

The required compound, N-(*tert*-butoxycarbonyl)-3,4-difluoroaniline (**3**), was readily prepared by reaction of 3,4-difluroaniline with di-*tert*-butyl dicarbonate in refluxing THF (97% yield). When a solution of **3** in THF was treated with 2.2 equiv. of *t*-BuLi at -78°C for 1 h a pale yellow solution was formed that after quenching with an excess of D_2O gave regioselectively and quantitatively the deuterated compound **5a** (Table 1, entry a). This result shows that under these conditions[7] a complete ortho deprotonation occurs at C-2 with subsequent formation of the metalated anion **4**. This carbanion also reacted, under very mild conditions, with a wide variety of electrophiles, such as 1,2-dibromoethane[8] (entry b), methyl disulfide (entry c), MeI (entry d), DMF (entry e), acetaldehyde (entry f) and cyclohexanone (entry g) to give the expected products **5**. Excellent yields were obtained after chromatography (78-94%). In all cases the reaction was highly regioselective (the C-6 substituted isomers were not detected by ^1H NMR). On the other hand, when dianion **4** was quenched with acetaldehyde or cyclohexanone and the reaction mixture was left at room temperature overnight, cyclization of the primary product (**5f** or **5g**) occurred spontaneously to give the benzoxazinone derivative **6** in good yield (Scheme 2).

With C-2 substituted carbamates **5** in hand we undertook their transformation into C-8 substituted quinolones **1**. The overall sequence from compounds **5c, 5d** and **5h** (the latter obtained by reduction of **5e** with $NaBH_4$) is depicted in Scheme 3. Acid deprotection of BOC-derivatives **5** (HCl, Et_2O, reflux) afforded the substituted fluoroanilines **2** (80-87% yield) whose condensation with diethyl ethoxymethylenemalonate, at

Table 1: Regioselective preparation of N-BOC-2-substituted-3,4-difluoroanilines **5**

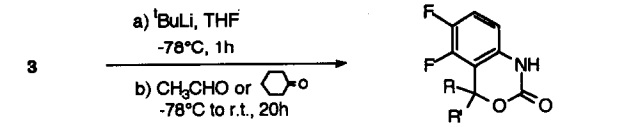


3 4 5

Entry	Electrophile (Conditions)	E	Product	Yield (%)[a]
a	D_2O (10eq, -78°C, 10min)	D	**5a**	94
b	$BrCH_2CH_2Br$ (3eq, -78° to 0°C, 1h)	Br	**5b**	79
c	$(MeS)_2$ (3eq, -78° to 0°C, 90min)	SMe	**5c**	94
d	MeI (1eq, -78° to 0°C, 2h)	Me	**5d**	85
e	DMF (3eq, -78° to 0°C, 90min)	CHO	**5e**	83
f	CH_3CHO (3eq, -78° to -20°C, 90min)	$CH(OH)CH_3$	**5f**	78
g	 (3eq, -78° to -20°C, 3h)		**5g**	85

[a] Yield in pure isolated product after chromatography.

Scheme 2

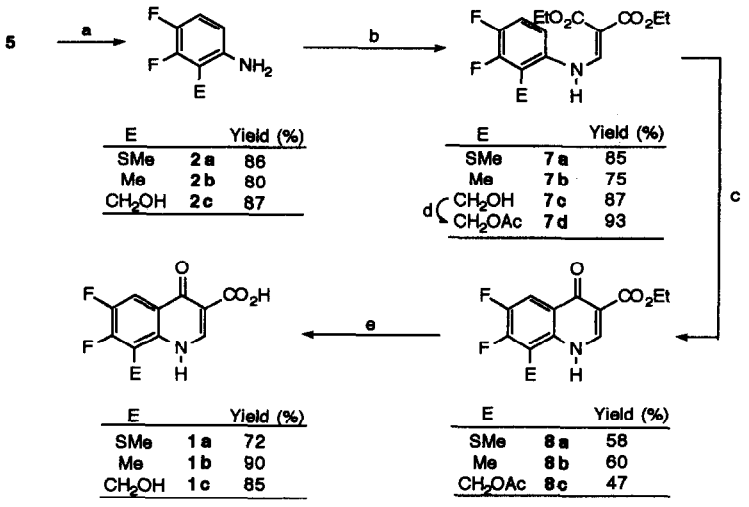


R = Me R' = H **6a** 74%
R = R' = -$(CH_2)_5$- **6b** 80%

110°C, gave enamines **7** in good yields (75-87%). Intramolecular acylation of **7a, 7b** and **7d** (the alcohol **7c** was protected as its acetate **7d**) by heating at 220°C in diphenyl ether[3] led to the formation of ethyl 4-oxoquinoline-3-carboxylic esters **8** (47-60% yield) which were hydrolyzed under basic conditions (NaOH, 100°C) to the corresponding free carboxylic acids (quinolones **1**, 72-90% yield).

Finally, we attempted nucleophilic substitution at C-7 and alkylation at N-1 in order to achieve the usual pattern of substitution of quinolone antibacterials (Figure 1). However, the nucleophilic substitution of fluorine at C-7 position by different piperazines[9] was not successful on quinolones **1**. Fortunately, satisfactory results were obtained when these reactions were carried out starting from their ethyl esters precursors **8** (Scheme 4). Thus, the reaction of **8a** with N-methyl piperazine in DMSO at 110°C yielded exclusively the C-7 substituted compound **8d** (72%), which was hydrolyzed in acid conditions (HCl, AcOH, 100°C) to afford the 7-piperazinyl quinolone **1d** (58%). Regarding the alkylation at N-1 position we observed a competition between N- and O-ethylation in quinolone **8a**, which was very dependent on the nature of the base and the ethylating agent. For instance, whereas ethylation of **8a** with K_2CO_3/EtI in DMF[10] at 90°C for 5 days gave exclusively

Scheme 3



E		Yield (%)
SMe	**2a**	86
Me	**2b**	80
CH_2OH	**2c**	87

E		Yield (%)
SMe	**7a**	85
Me	**7b**	75
CH_2OH	**7c**	87
CH_2OAc	**7d**	93

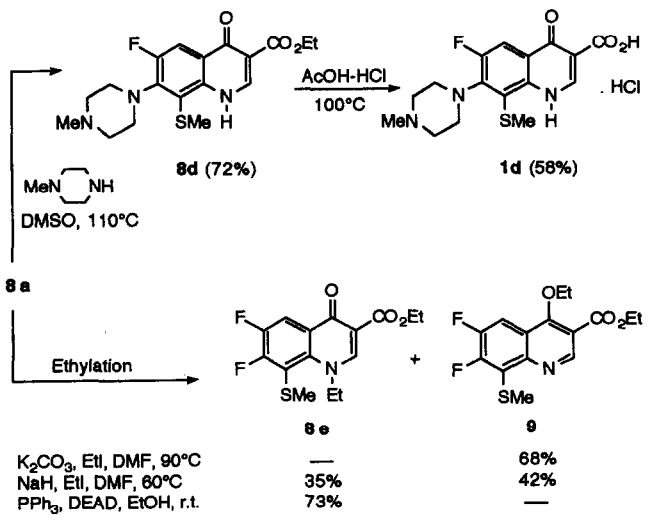
E		Yield (%)
SMe	**1a**	72
Me	**1b**	90
CH_2OH	**1c**	85

E		Yield (%)
SMe	**8a**	58
Me	**8b**	60
CH_2OAc	**8c**	47

(*a*) HCl (c), Et_2O, r.t.; (*b*) $EtOCH{=}C(CO_2Et)_2$, 110°C; (c) Ph_2O, 220°C; (d) Ac_2O, Py, r.t.; (e) NaOH, EtOH-H_2O, 100°C.

the O-ethylated quinoline **9** in 68% yield (20% of unreacted **8a** was recovered), its ethylation with PPh_3/DEAD/EtOH in CH_2Cl_2 at r.t. gave selectively the N-ethylated quinolone **8e** in good yield (73% after purification). An intermediate situation was observed when **8a** was ethylated with NaH/EtI in DMF, under these conditions 35% of **8e** and 42% of **9** were obtained after chromatography.

Scheme 4



	8e	**9**
K_2CO_3, EtI, DMF, 90°C	—	68%
NaH, EtI, DMF, 60°C	35%	42%
PPh_3, DEAD, EtOH, r.t.	73%	—

In summary, the ortho metalation of N-BOC-3,4-difluoroaniline with *t*-BuLi in THF at -78°C is completely regioselective. The C-2 substituted N-BOC anilines **5**, obtained after reaction with electrophiles, can be readily applied to the synthesis of a wide range of C-8 substituted fluoroquinolones.

Experimental Section

Melting points are uncorrected. IR spectra were recorded as thin films from $CHCl_3$ or nujol (only strong absortions are reported. ^1H NMR spectra were taken at 200 MHz, on a Bruker WP-200-SY, in the solvents indicated. High resolution mass spectra were recorded under e.i. at 70 eV. All reagents or solvents were used as comercial grades, except THF which was distilled from Na/benzophenone and DMF which was distilled from CaH_2. Flash column chromatography was performed on silica gel Merck-60 (230-430 mesh).

N-(*tert*-butoxycarbonyl)-3,4-difluoroaniline (3). A solution of 1.30 g (10.1 mmol) of 3,4-difluoroaniline and 2.42 g (11.1 mmol) of di-*tert*-butyldicarbonate in 10 ml of dry THF was heated at 60°C for 15 h. The solvent was removed in vacuo and the residue was dissolved in 15 ml of ethyl acetate. The solution was washed successively with 1 % HCl (2 x 10 ml) and 5 % $NaHCO_3$ (2 x 10 ml). The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The residue was recrystallized from hexane to give 2.24 g (97%) of carbamate **3**, m.p.135-137°C; ^1H NMR ($CDCl_3$) δ: 7.43 (ddd, 1H, J = 12.3, 7.5 and 2.6 Hz, ArH), 7.05 (m, 1H, ArH), 6.90 (m, 1H, ArH), 6.48 (broad s, 1H, NH), 1.52 (s, 9H, ^{t}Bu); IR (nujol) 3300, 2880, 2800, 1690, 1610, 1430, 1390, 1370, 1290, 1170; MS *m/e* 229 (M^+, 10), 173 (37), 129 (43), 101 (13), 86 (18), 84 (22), 59 (20), 57 (100); Anal. Calcd. for $C_{11}H_{13}F_2NO_2$: C, 57.64; H, 5.67; N, 6.11. Found: C, 57.63; H, 5.56; N, 6.06.

General procedure for dilithiation of 3 and further reaction with electrophiles. A 1.6 M solution of *tert*-butyllithium in hexane (22.5 ml, 33.0 mmol) was added slowly to a solution of **3** (3.43 g, 15.0 mmol) in dry THF (40 ml) maintained at -78°C under argon. After 1 h at -78°C the appropriate electrophilic reagent was added and the solution was allowed to warm to the temperature for the reaction time indicated in Table 1. Then, saturated NH_4Cl (15 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 15 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give crude products **5a-g** which were purified by flash chromatography.

2-Deutero-3,4-difluoro-N-(*tert*-butoxycarbonyl)aniline (5a). 3.24 g, 94 % (eluent: hexane/ethyl acetate 6/1), m.p.124-126°C; ^1H NMR ($CDCl_3$) δ: 7.05 (m, 1H, ArH), 6.9 (ddd, 1H, J = 8.6, 4.3 and 1.4 Hz, ArH), 6.48 (broad s, 1H, NH), 1.51 (s, 9H, ^{t}Bu); IR (nujol) 3300, 2880, 2800, 1690, 1610, 1430, 1390, 1370, 1290, 1170; Anal. Calcd. for $C_{11}H_{12}DF_2NO_2$: C, 57.39; H, 6.09; N, 6.09. Found: C, 57.42; N, 5.65; N, 6.27.

2-Bromo-3,4-difluoro-N-(*tert*-butoxycarbonyl)aniline (5b). 3.06 g, 66% (eluent: hexane/ethyl acetate 30/1), m.p.56-57°C; ^1H NMR ($CDCl_3$) δ: 7.29 (ddd, 1H, J = 9.4, 4.6 and 2.3 Hz, ArH), 7.12 (m, 1H, ArH), 6.88 (broad s, 1H, NH), 1.53 (s, 9H, ^{t}Bu); IR (nujol) 3340, 2950, 2840, 1745, 1700, 1590, 1510, 1400, 1370, 1270, 1150; Anal. Calcd. for $C_{11}H_{12}BrF_2NO_2$: C, 42.85; H, 4.05; N, 4.51. Found: C, 42.86; H, 4.22; N, 4.54.

3,4-Difluoro-2-methylthio-N-(*tert*-butoxycarbonyl)aniline (5c). 3.88 g, 94% (eluent: hexane/ethyl acetate 25/1), m.p.53-54°C; ^1H NMR ($CDCl_3$) δ: 7.95 (ddd, 1H, J = 9.2, 4.6 and 1.9 Hz, ArH), 7.75 (broad s, 1H, NH), 7.12 (m, 1H, ArH), 2.36 (s 3H, SCH_3) 1.53 (s, 9H, ^{t}Bu); IR (nujol) 3360, 2910, 2840, 1730,

1700, 1580, 1500, 1450, 1390, 1270, 1220, 1160; MS *m/e* 275 (M^+, 32), 202 (30), 175 (81), 160 (60), 57 (100); HRMS Calcd. for $C_{12}H_{15}F_2NO_2S$ 275.0791. Found 275.0793.

3,4-Difluoro-2-methyl-N-(*tert*-butoxycarbonyl)aniline (5d). 3.10 g, 85% (eluent: hexane/ethyl acetate 20/1), m.p.97-98°C; ^1H NMR ($CDCl_3$) δ: 7.30 (m, 1H, ArH), 6.96 (m, 1H, ArH), 6.19 (broad s, 1H, NH), 2.19 (d, 3H, J = 2.6 Hz, CH3), 1.51 (s, 9H, ^{t}Bu); IR (nujol) 3340, 2945, 2850, 1650, 1510, 1500, 1440, 1370, 1290, 1250, 1150; Anal. Calcd. for $C_{12}H_{15}F_2NO_2$: C, 59.26; H, 6.17; N, 5.76. Found: C, 59.42; H, 6.04; N, 5.74.

2,3-Difluoro-6-(*tert*-butoxycarbamoyl)benzaldehyde (5e). 3.20 g, 83% (eluent: hexane/ethyl acetate 20/1), m.p.130-131°C; ^1H NMR ($CDCl_3$) δ: 10.42 (broad s, 1H, NH), 10.39 (s, 1H, CHO), 8.25 (ddd, 1H, J = 9.5, 4.2 and 2.1 Hz, ArH), 7.40 (m, 1H, ArH), 1.55 (s, 9H, ^{t}Bu); IR (nujol) 3285, 2940, 2840, 1730, 1670, 1660, 1595, 1370, 1300, 1240, 1210, 1170; MS *m/e* 257 (M^+, 8), 201 (18), 184 (12), 157 (29), 129 (30), 86 (34), 84 (57), 69 (11), 57 (100); Anal. Calcd. for $C_{12}H_{13}F_2NO_3$: C, 56.03; H, 5.58; N, 5.45. Found: C, 55.89; H, 5.86; N, 5.47.

3,4-Difluoro-2-(1-hydroxyethyl)-N-(*tert*-butoxycarbonyl)aniline (5f). 3.19 g, 78% (eluent: hexane/CH_2Cl_2 2/1), m.p.114-115°C; ^1H NMR ($CDCl_3$) δ: 8.47(broad s, 1H, NH), 7.71 (ddd, 1H, J = 9.2, 4.1 and 1.6 Hz, ArH), 6.96 (m, 1H, ArH), 5.47 (q, 1H, J = 6.7 Hz, C<u>H</u>OH), 2.49 (broad s, 1H, OH), 1.55 (d, 3H, J = 6.7 Hz, CH_3) and 1.51 (s, 9H, ^{t}Bu); IR (nujol) 3410, 3310, 2930, 2840, 1690, 1600, 1530, 1415, 1360, 1270, 1160; MS m/e 327 (M^+, 16), 271 (65), 253 (86), 236 (21), 227(34), 209 (100), 180 (36), 166 (80); HRMS Calcd. for $C_{13}H_{17}F_2NO_3$ 273.1176. Found 273.1172.

3,4-Difluoro-2-(1-hydroxycyclohexyl)-N-(*tert*-butoxycarbonyl)aniline (5g). 4.17 g, 85% (eluent: hexane/CH_2Cl_2 2/1), m.p.156-157°C; ^1H NMR ($CDCl_3$) δ: 9.51 (broad s, 1H, NH), 7.82 (ddd, 1H, J = 9.3, 5.1 and 2.3 Hz, ArH), 7.00 (m, 1H, ArH), 2.30-1.25 (m, 10H, cyclohexyl), 1.59 (s, 9H, ^{t}Bu); IR (nujol) 3405, 3240, 2920, 2840, 1675, 1595, 1500, 1400, 1360, 1270, 1160; MS *m/e* 273 (M^+, 22), 217 (68), 199 (12), 182 (45), 173 (40), 155 (100), 127 (19), 69 (16), 57 (40); HRMS Calcd. for $C_{17}H_{23}F_2NO_3$ 327.1646. Found 327.1649.

General procedure for the preparation of trisubstituted anilines 2. Concentrated HCl (20 ml) was added to a solution of the corresponding carbamate **5** (4.17 mmol) in Et_2O (42 ml) and the resulting mixture was vigorously stirred at room temperature for 40 min.-17h. 2M NaOH was added until pH>10 and the mixture was extracted with Et_2O (3 x 15 ml). The combined organic layers were washed with H_2O (2 x 10 ml), dried (Na_2SO_4) and evaporated. As soon as the crude anilines **2** were purified by chromatography (hexane/ethyl acetate 1/2 as eluent) they were used in the following reaction due to their limited stability.

3,4-Difluoro-2-methylthioaniline (2a). 628 mg, 86% (reaction time: 17 h); ^1H NMR ($CDCl_3$) δ: 6.93 (m, 1H, ArH), 6.42 (ddd, 1H, J = 9.1, 4.1 and 2.0 Hz, ArH), 4.29 (broad s, 2H, NH_2), 2.32 (s, 3H, SCH_3).

3,4-Difluro-2-methylaniline (2b). 476 mg, 80% (reaction time: 40 min); ^1H NMR ($CDCl_3$) δ: 6.80 (m, 1H, ArH), 6.35 (m, 1H, ArH), 3.55 (broad s, 2H, NH_2), 2.10 (d, 3H, J = 2.1 Hz, CH_3).

3,4-Difluoro-2-hydroxymethylaniline (2c). 577 mg, 87% (reaction time: 40 min); ^1H NMR ($CDCl_3$) δ: 6.92 (m, 1H, ArH), 6.38 (ddd, 1H, J = 8.4, 3.8 and 2.1 Hz, ArH) 4.75 (d, 2H, J = 2.0 Hz, CH_2OH) 3.5-2.5 (broad s, 3H, NH_2 and OH).

General procedure for the preparation of methylenemalonates 7. A mixture of diethyl ethoxymethylenemalonate (10.64 ml, 3.18 mmol) and aniline **2** (3.18 mmol) was heated at 110°C. After 2 h the mixture was cooled to room temperature and hexane (10 ml) was added. The resulting precipitate was filtered

off, washed with hexane, and dried. This crude malonate **7** was used in the following reaction without further purification.

Diethyl (3,4-difluoro-2-methylthioanilinyl)methylenemalonate (7a). 0.93 g, 85% (reaction time: 2.30 h), m.p.88-89°C; ^{1}H NMR ($CDCl_3$) δ: 11.54 (d, 1H, J = 13.7 Hz, NH), 8.47 (d, 1H, J = 13.7 Hz, HC=C), 7.20 (m, 1H, ArH), 7.01 (ddd, 1H, J = 9.3, 4.1 and 1.8 Hz, ArH), 4.35 (q, 2H, J = 7.1 Hz, CH_2), 4.26 (q, 2H, J = 7.1 Hz, CH_2), 2.43 (s, 3H, SCH_3), 1.39 (t, 3H, J = 7.1 Hz, CH_3), 1.34 (t, 3H, J = 7.1 Hz, CH_3); IR (nujol) 2910, 2840, 1665, 1630, 1580, 1440, 1390, 1285, 1250, 970, 880, 790; Anal. Calcd. for $C_{15}H_{17}F_2NO_4S$: C, 52.03; H, 4.92; N, 4.11. Found: C, 52.17; H, 4.93; N, 4.05.

Diethyl (3,4-difluoro-2-methylanilinyl)methylenemalonate (7b). 0.75 g, 75% (reaction time: 1.30 h), m.p.103-104°C; ^{1}H NMR ($CDCl_3$) δ: 11.10 (d, 1H, J =13.1 Hz, NH), 8.41 (d, 1H, J = 13.1 Hz, HC=C), 7.07 (m, 1H, ArH), 6.94 (ddd, 1H, J = 9.1, 4.2 and 1.6 Hz ArH), 4.32 (q, 2H, J = 7.1Hz, CH_2), 4.25 (q, 2H, J = 7.1 HZ, CH_2), 2.31 (d, 2H, J = 2.2 Hz, CH_3), 1.39 (t, 3H, J = 7.1 Hz, CH_3), 1.33 (t, 3H, J = 7.1 Hz, CH_3); IR (nujol) 2910, 2840, 1670, 1630, 1600, 1460, 1380, 1250, 1090, 1020, 1000, 790; Anal. Calcd. for $C_{15}H_{17}F_2NO_4$: C, 57.61; H, 5.44; N, 4.38. Found C, 57.51; H, 5.43; N, 4.47.

Diethyl (3,4-difluoro-2-hydroxymethylanilinyl)methylenemalonate (7c). 0.91 g, 87% (reaction time: 1 h), m.p.133-134°C; ^{1}H NMR ($CDCl_3$) δ: 11.49 (d, 1H, J= 13.5 Hz, NH), 8.40 (d, 1H, J = 13.5 Hz, HC=C), 7.18 (m, 1H, ArH), 7.01 (ddd, 1H, J = 9.0, 3.9 and 1.8 Hz, ArH), 4.87 (d, 2H, J = 2.1 Hz, $C\underline{H_2}OH$), 4.31 (q, 2H, J = 7.0 Hz, CH_2), 4.25 (q, 2H, J = 7.0 Hz, CH_2), 2.85 (broad s, 1H, OH), 1.37 (t, 3H, J = 7.0 Hz, CH_3), 1.33 (t, 3H, J = 7.0 Hz, CH_3); IR (nujol) 3360, 2910, 2840, 1670, 1630, 1580, 1450, 1400, 1285, 1250, 1110, 970, 790; Anal. Calcd. for $C_{15}H_{17}F_2NO_5$: C, 54.63; H, 5.16; N, 4.12. Found: C, 54.71; H, 5.17; N, 4.25.

Diethyl (2-acetoxymethyl-3,4-difluoroanilinyl)methylenemalonate (7d). To a solution of 1.23 g (3.75 mmol) of **7c** in 1.25 ml (15.00 mmol) of pyridine was added at room temperature 0.35 ml (3.75 mmol) of acetic anhydride.The resulting mixture was stirred for 90 minutes, then a solution of 10% HCl was added until pH 2-3.The mixture was extracted with CH_2Cl_2 (3 x 5 ml), the combined organic layers were washed with 5% $NaHCO_3$ (2 x 5 ml), dried ($MgSO_4$) and evaporated to afford 1.29 g (93%) of **7d**, m.p.107-108°C; ^{1}H NMR ($CDCl_3$) δ: 11.32 (d, 1H, J = 13.5 Hz, NH), 8.35 (d, 1H, J = 13.5 Hz, HC=C), 7.23 (m, 1H, ArH), 6.98 (ddd, 1H, J = 9.1, 4.1 and 1.9 Hz, ArH), 5.20 (d, 2H, J = 2.0 Hz, $C\underline{H_2}OAc$), 4.31 (q, 2H, J = 7.0 Hz, CH_2), 4.25 (q, 2H, J = 7.0 Hz, CH_2), 2.20 (s, 3H, CH_3CO), 1.37 (t, 3H, J = 7.0 Hz, CH_3) 1.33 (t, 3H, J = 7.0 Hz, CH_3); IR ($CHCl_3$) 2910, 1680, 1640, 1600, 1490, 1370, 1220, 1180, 1110, 795; Anal. Calcd. for $C_{17}H_{19}F_2NO_5$: C, 54.99; H, 5.12; N, 3.77. Found: C, 54.96; H, 5.35; N, 3.41.

General procedure for the preparation of quinolone ethyl esters 8. The methylenemalonate **7** (3.00 mmol) was added to diphenyl ether (6 ml) and the mixture was heated at 220°C for 1-10 h. The solution was cooled to room temperature and the resulting precipitate was filtered off, washed with hexane, and dried. The crude ester **8** was used in the following reaction without further purification.

Ethyl 6,7-difluoro-1,4-dihydro-8-methylthio-4-oxoquinoline-3-carboxylate (8a). 520 mg, 58% (reaction time: 10 h), m.p.267-270°C; ^{1}H NMR ($CDCl_3$) δ: 9.46 (s, 1H, HC=C), 8.45 (t, 1H, J = 8.2 Hz, ArH), 4.74 (q, 2H, J = 8.2 Hz, CH_2), 2.64 (s, 3H, SCH_3), 1.57 (t, 3H, J = 7.2 Hz, CH_3); IR (nujol) 2920, 2840, 1680, 1650, 1590, 1450, 1370, 1260, 1230; Anal. Calcd. for $C_{13}H_{11}F_2NO_3S$: C, 52.17; H,3.68; N, 4.68. Found: C, 51.81; H, 3.67; N, 4.33.

Ethyl 6,7-difluoro-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (8b). 481 mg, 60% (reaction time: 6 h), m.p.289-291°C; ^{1}H NMR ($CDCl_3$) δ: 9.34 (s, 1H, HC=C), 8.28 (t, 1H, J = 8.3 Hz, ArH), 4.69 (q, 2H, J = 7.2 Hz, CH_2), 2.75 (d, 2H, J = 2.3 Hz, CH_3), 1.53 (t, 3H, J = 7.2 Hz, CH_3); IR (nujol) 2920, 2850, 1700, 1630, 1590, 1480, 1460, 1380, 1300, 1190, 1110; Anal. Calcd. for $C_{13}H_{11}F_2NO_3$: C, 58.43; H, 4.12; N, 5.24. Found: C, 57.93; H, 4.10; N, 5.12.

Ethyl 8-acetoxymethyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (8c). 458 mg, 47% (reaction time: 1 h), m.p.245-250°C; ^{1}H NMR ($CDCl_3$) δ: 9.13 (s, 1H, HC=C), 8.12 (t, 1H, J = 8.7 Hz, ArH), 5.82 (d, 2H, J = 2.0 Hz, CH_2OAc), 4.51 (q, 2H, J = 7.0 Hz, CH_2), 2.11 (s, 3H, CH_3CO_2), 1.47 (t, 3H, J = 7.0 Hz, CH_3).

Ethyl 6-fluoro-7-(4-methyl-1-piperazinyl)-1,4-dihydro-8-methylthio-4-oxoquinoline-3-carboxylate (8d). 0.28 ml (2.57 mmol) of N-methylpiperazine were added to a solution of 0.31 g (1.03 mmol) of ester **8a** in 12 ml of DMSO. The resulting solution was heated at 110°C for 13 h.The solvent was removed by distillation in vacuo (0.1 mm Hg) and the residue was treated with Et_2O (10 ml). The precipitate was filtered off and purified by flash chromatography (CH_2Cl_2 / MeOH 7/1) to give 0.28 g (72%) of **8d**, m.p.250-251°C (dec.); ^{1}H NMR (CF_3CO_2D) δ: 9.32 (s, 1H, HC=C), 8.27 (d, 1H, J = 11.4 Hz, ArH), 4.68 (q, 2H, J = 7.2 Hz, CH_2O), 4.1-3.3 (m, 8H, NCH_2), 3.15 (s, 3H, NCH_3), 2.39 (s, 3H, SCH_3), 1.53 (t, 3H, J = 7.2 Hz, CH_3); IR (nujol) 2910, 2840, 1690, 1600, 1580, 1530, 1450.

General procedure for the preparation of quinolones 1. A mixture of ester **8** (2.50 mmol), EtOH (22ml) and 2M NaOH (4.5 ml) was refluxed for 3-17 h. The solution was cooled to room temperature and acidified with 1% HCl. The resulting precipitate was filtered off, washed with H_2O and dried. The crude quinolone **1** was purified by recrystallization.

6,7-Difluoro-1,4-dihydro-8-methylthio-4-oxoquinoline-3-carboxylic acid (1a). 0.49 g, 72% (reaction time : 17 h), m.p.289-291°C (recrystallized from DMF); ^{1}H NMR (CF_3CO_2D) δ: 9.51(s, 1H, HC=C), 8.41(t ,1H, J = 8.7 Hz, ArH), 2.62 (s, 3H, SCH_3); IR (nujol) 3100, 2910, 2840, 1700, 1625, 1460, 1370, 1220, 1100, 910, 800; Anal. Calcd. for $C_{11}H_7NO_3S$: C, 48.71; H, 2.58; N, 5.17. Found C, 48.32; H, 2.49; N,4.96.

6,7-Difluoro-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid (1b). 0.53 g, 90% (reaction time : 6.3 h), m.p.>300°C (dec.) (recrystallized from DMF); ^{1}H NMR (CF_3CO_2D) δ: 9.44 (s, 1H, HC=C), 8.32 (t, 1H, J = 8.7 Hz, ArH), 2.79 (s, 3H, CH_3); IR (nujol) 3100, 3060, 2910, 2840, 1700, 1620, 1570, 1470, 1380, 1360, 1220, 1005, 985, 800; Anal. Calcd. for $C_{11}H_7F_2NO_3$: C, 55.23; H, 2.93; N, 5.86. Found C, 54.98; H, 2.66; N, 5.75.

6,7-Difluoro-8-hydroxymethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (1c). 0.54 g, 85% (reaction time: 3 h), m.p.267-270°C (recrystallized from Toluene/ DMF 20/1); ^{1}H NMR (CF_3CO_2D) δ: 9.60 (s, 1H, HC=C), 8.57 (t, 1H, J = 8.7 Hz, ArH), 5.70 (s, 2H, CH_2OH); IR (nujol) 3200, 3100, 3040, 2910, 2840, 1685, 1620, 1465, 1370, 1235, 1000, 1040, 1010, 970; Anal. Calcd. for $C_{11}H_7F_2NO_4$: C, 51.76; H, 2.74; N, 5.49. Found: C, 52.01; H, 2.82; N, 4.92.

6-Fluoro-7-(4-methyl-1-piperazinyl)-1,4-dihydro-8-methylthio-4-oxoquinoline-3-carboxylic acid hydrochloride (1d). 0.38 g (1 mmol) of ester **8d** was dissolved in 30 ml of a (1:4) mixture of acetic acid and concentrated HCl. The solution was refluxed at 110°C for 18 h and after cooling to room temperature, the precipitate was filtered off, washed successively with H_2O and Et_2O and dried. The crude acid was recrystallized from DMF:toluene to yield 0.20 g (58%) of **1d**, m.p.289-290°C; ^{1}H NMR (CF_3CO_2D) δ: 9.32

(s, 1H, HC=C), 8.28 (d, 1H, J = 11.5 Hz, ArH), 4.1-3.3 (m, 8H, NCH_2), 3.16 (s, 3H, NCH_3), 2.42 (s, 3H, SCH_3);

Ethylation of quinolone 8a.

Method A: To a solution of 229 mg (1 mmol) of **8a** in 4 ml of dry DMF was added 60 mg (1.5 mmol) of 60% NaH in oil. The solution was stirred for 15 min at room temperature. Then, 0.41 ml (5mmol) of EtI was added and the solution was heated at 60 °C for 3 h. H_2O (5 ml) was added and the mixture was extracted with Et_2O (3 x 10 ml). The combined organic layers were dried and evaporated. The crude product was purified by flash chromatography (Cl_2CH_2/hexane 1/1) to give 114 mg (35%) of N-ethylated quinolone **8e** and 137 mg (42%) of O-ethylated quinoline **9**.

Method B: A solution of 60 µl (0.41mmol) of DEAD in 0.5 ml of dry THF was added dropwise to a solution of 100 mg (0.33 mmol) of quinolone ester **8a** and 0.1 g (0.41 mmol) of triphenylphosphine in 1 ml of dry THF. The solution was stirred overnight at room temperature. The solvent was removed in vacuo and Et_2O was added to the residue to precipitate triphenylphosphine oxide and diethyl hydrazinedicarboxylate which were filtered off. The filtrate was evaporated and purified by flash chromatography (CH_2Cl_2) to give 79 mg (73%) of **9**.

Ethyl 6,7-difluoro-1,4-dihydro-N-ethyl-8-methylthio-4-oxoquinoline-3-carboxylate (8e). m.p.44-46°C; ^1H NMR ($CDCl_3$) δ: 9.23 (s, 1H, HC=C), 7.91 (t, 1H, J = 8.5 Hz, ArH), 4.46 (q, 2H, J = 7.1 Hz, CH_2), 4.33 (q, 2H, J = 7.1 Hz, CH_2), 2.69 (d, 3H, J = 2.4 Hz, SCH_3), 1.53 (t, 3H, J = 7.1 Hz, CH_3), 1.44 (t, 3H, J = 7.1 Hz, CH_3); IR ($CHCl_3$) 2960, 1700, 1580, 1480, 1460, 1420, 1250, 1220, 1180, 1080, 1010, 880; Anal. Calcd. for $C_{15}H_{15}F_2NO_3S$: C, 55.09; H, 4.59; N, 4.28. Found: C, 54.83; H, 4.59; N, 4.04.

6,7-Difluoro-3-ethoxycarbonyl-4-ethoxy-8-methylthioquinoline (9). m.p.113-115°C; ^1H NMR ($CDCl_3$) δ: 8.46 (s, 1H, ArH), 8.36 (t, 1H, J = 8.7 Hz, ArH), 4.87 (q, 2H, J = 7.1 Hz, CH_2), 4.41 (q, 2H, J = 7.1 Hz, CH_2), 2.48 (s, 3H, SCH_3), 1.47 (t, 3H, J = 7.1 Hz, CH_3), 1.42 (t, 3H, J = 7.1 Hz, CH_3); IR ($CHCl_3$) 2980, 1715, 1680, 1620, 1600, 1435, 1305, 1175, 1075, 870; MS *m/e* 327 (M^+, 25), 282 (14), 255 (100), 212 (9), 182 (4), 151 (8), 113 (5); Anal. Calcd. for $C_{15}H_{15}F_2NO_3S$: C, 55.09; H, 4.59; N, 4.28. Found: C, 55.40; H, 4.73; N, 3.97.

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References and Notes

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9.- No substitution at all was detected when quinolones **1** were treated with N-methyl piperazine in DMSO at 110-150°C. Under these conditions a slow decarboxylation reaction was observed.

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