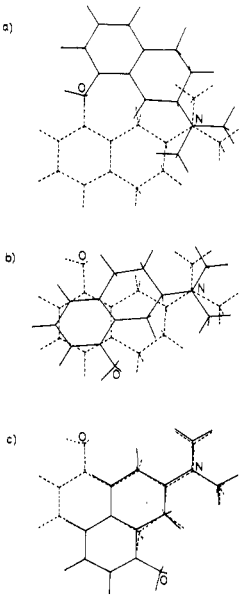

Figure 11. Extreme computer-generated best fits of conformation I of (2*R*)-1 (dashed lines) with the enantiomeric conformation of (2*S*)-1 (solid lines): (a) fit of the nitrogens, the N-electron pairs, and the hydroxyl groups; (b) fit of the nitrogens, the N-electron pairs, and the midpoints of the aromatic rings; (c) fit (C4a, C5, nitrogens, and N-electron pairs were fitted) based on a structural comparison with *d*-LSD (see text).

The other two extreme fittings of the enantiomers of 1 (Figure 11) are more attractive. When only the aromatic rings, the nitrogens, and the N-electron pairs are included in the fit, the main difference between the structures is the different location of the phenolic groups. The third mode of fitting (Figure 11) is based on the assumption that the aromatic ring of (2*R*)-1 would interact with the same portion of the 5-HT receptors as the benzene ring of **14** or *d*-LSD, whereas the benzene ring of (2*S*)-1 would assume a relative location similar to that of the pyrrole ring of **14** or *d*-LSD. This structural comparison is contradicted by several reports which indicate that the pyrrolethylamine moiety is the dopaminergic pharmacophore of LSD and related ergolines.[51] It is noteworthy, however, that the two latter modes of fitting seem to rationalize both the low stereoselectivity of **1** and the opposite stereoselectivities of **2** and **15**;[49,50] when (2*R*,3*S*)-**15** is fitted with (1*S*,2*R*)-**2** as above, the C3-methyl group of (2*R*,3*S*)-**15** adopts a similar relative position as the C1-methyl group of (1*S*,2*R*)-**2**.[49]

Additional studies of stereochemically well-defined 5-HT-receptor agonists should make it possible to assess the relevance of these structural comparisons.

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Supplementary Material Available: Positional and thermal parameters, bond lengths, and bond angles (2 pages). Ordering information is given on any current masthead page.

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Studies on Prodrugs. 7. Synthesis and Antimicrobial Activity of 3-Formylquinolone Derivatives

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Several 3-formylquinolone derivatives (**8a–c**) were synthesized to assay the antibacterial activity both in vitro and in vivo. In vitro, all of the compounds **8a–c** showed lower activity than that of the corresponding 3-carboxyl compounds **1a–c**, and in vivo, they showed higher activity than that of compounds **1a–c**. After oral administration of 3-formyl compounds **8a–c** to mice, the compounds were rapidly metabolized into 3-carboxyl compounds **1a–c**. In particular, the 3-formyl derivative (**8a**) of norfloxacin (NFLX, **1a**) gave a 2-fold higher serum level than that of NFLX and functioned as a prodrug of NFLX.

In 1979, norfloxacin (NFLX, **1a**) was synthesized as a new quinolone by Koga et al.[1] Several related new quinolones, including ciprofloxacin (CPFX, **1b**)[2] and pefloxacin (PFLX, **1c**),[3] have also been developed. On comparison with conventional compounds[4] such as nalidixic acid, piromidic acid, and pipemidic acid, the new quinolones exhibited marked and broad antibacterial activities against Gram-positive and Gram-negative bacteria.[2,3,5] Although NFLX is strongly active in test systems in vitro, it was found there was still room for improvement in the activity after oral administration.[6] We have applied a prodrug technique to NFLX and have recently reported N-masked NFLX prodrugs (**2**[7] and **3**[8], Chart I) to propose that both an increase of oral absorbability by N-masked

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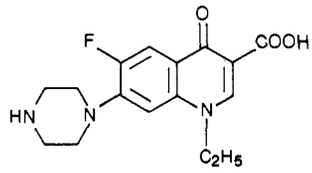
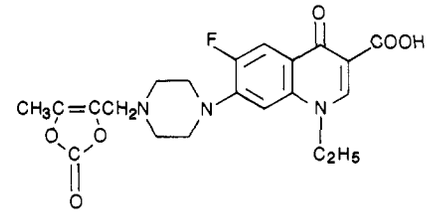
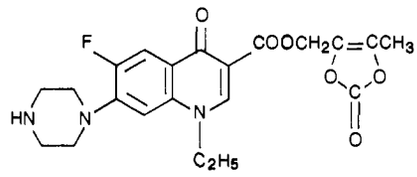
Chart I



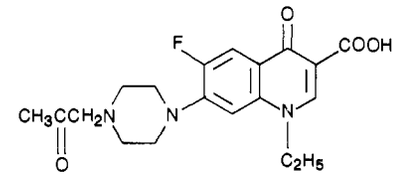
1a (NFLX)



2 (N-masked NFLX)



4 (NFLX ester)



3 (N-masked NFLX)

NFLX and a production of active NFLX by metabolism can make an important contribution to enhancing the activity in vivo. Other workers[9] who prepared the tioxacin ester concluded that the activity in vivo was insignificant. We also prepared the NFLX ester[7] **4**, NFLX (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, to confirm that it was poorly effective as a prodrug. There would be two types of ineffective derivatives among these esters. One was too stable to liberate the parent compound smoothly after absorption, and the other was too unstable before absorption. Our compound **4** has been assumed to be latter one.

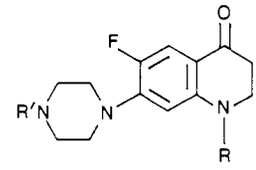
On the basis of many studies of metabolism, it has been found that a formyl group is spontaneously metabolized into the corresponding carboxyl group by oxidative enzymes.[10] And also the Schiff base of salicylaldehyde was previously reported to be a prodrug of salicylic acid as it was oxidized rapidly in vivo to the acid.[11] However, there are no reports in the literature on a prodrug technique that uses 3-formylquinolones.

Consequently, we focused our interest on the prodrug technique of new quinolones and the biological transformation of formyl groups and now report the design and synthesis of an orally active novel series of 3-formylquinolone derivatives (**8a–c**). Furthermore, their serum levels after oral administration in mice were measured, and their antibacterial activities were assayed in vitro and in vivo.

Chemistry

The 3-carboxyquinolones **1a–c** were synthesized in accordance with the methods of several reports.[1-3] Few cases of the preparation of 3-formylquinolones have been reported,[10b] e.g., one is the oxidation of the 3-(hydroxymethyl)quinolones. We have now found a unique and simple synthetic pathway from the 3-carboxyquinolones **1a–c** to the corresponding 3-formylquinolones **8a–c** (Scheme I). In this pathway, 1,2,3,4-tetrahydroquinolones **5a–c** were prepared by a novel reduction and a subsequent decarboxylation of 3-carboxyquinolones **1a–c**. For the 1,2,3,4-tetrahydroquinolone skeleton, the preparation from the aniline derivatives as starting materials had been reported,[12] but the conversion from the 3-carboxyquinolones is unknown, and relatively little evidence exists for the reduction of 3-carboxyquinolones **1a–c**. A reduction of compounds **1a–c** with sodium borohydride in methanol, followed by acid-catalyzed decarboxylation, gave compounds **5a–c** in good yields (Table I).

Table I. Physical Data of 1,2,3,4-Tetrahydroquinolines **5a–c**



compd	R	R′	mp, °C	formula[a]	yield, %
5a	C_2H_5	H	55–58	$C_{15}H_{20}N_3OF$	68
5b	c-C_3H_5	H	99–103	$C_{16}H_{20}N_3OF$	72.7
5c	C_2H_5	CH_3	112–115	$C_{16}H_{22}N_3OF\cdot H_2O$	76.2

[a] The analyses for C, H, and N were within ±0.4% of the theoretical values.

On the other hand, formylation of cyclic ketones is well known and has been usually carried out with an excess of sodium methoxide and ethyl formate.[13] In a similar manner, the formyl group could be introduced into the 3-position of compounds **5a–c** but with formylation at the 4-position of the piperazinyl group of compounds **5a–b** as well. Without the isolation of compounds **6a–c**, the 2,3-double bond was reintroduced by oxidation with manganese dioxide in methanol to obtain the 3-formyl-7-(4-formyl-1-piperazinyl)quinolones **7a,b** and compound **8c** in favorable yields, respectively (Table II). The compounds **7a,b** were hydrolyzed in 1 N hydrochloric acid to prepare the 3-formylquinolones **8a–b**. Compound **8b** was isolated similarly to CPFX as a monohydrochloride.

Biological Results and Discussion

The antibacterial activity in vitro against Gram-positive and Gram-negative bacteria was tested for compounds **1a–c** and **8a–c**. The available results are summarized in Table III. 3-Formyl compounds **8a–c** showed lower activity against all bacteria than the corresponding 3-

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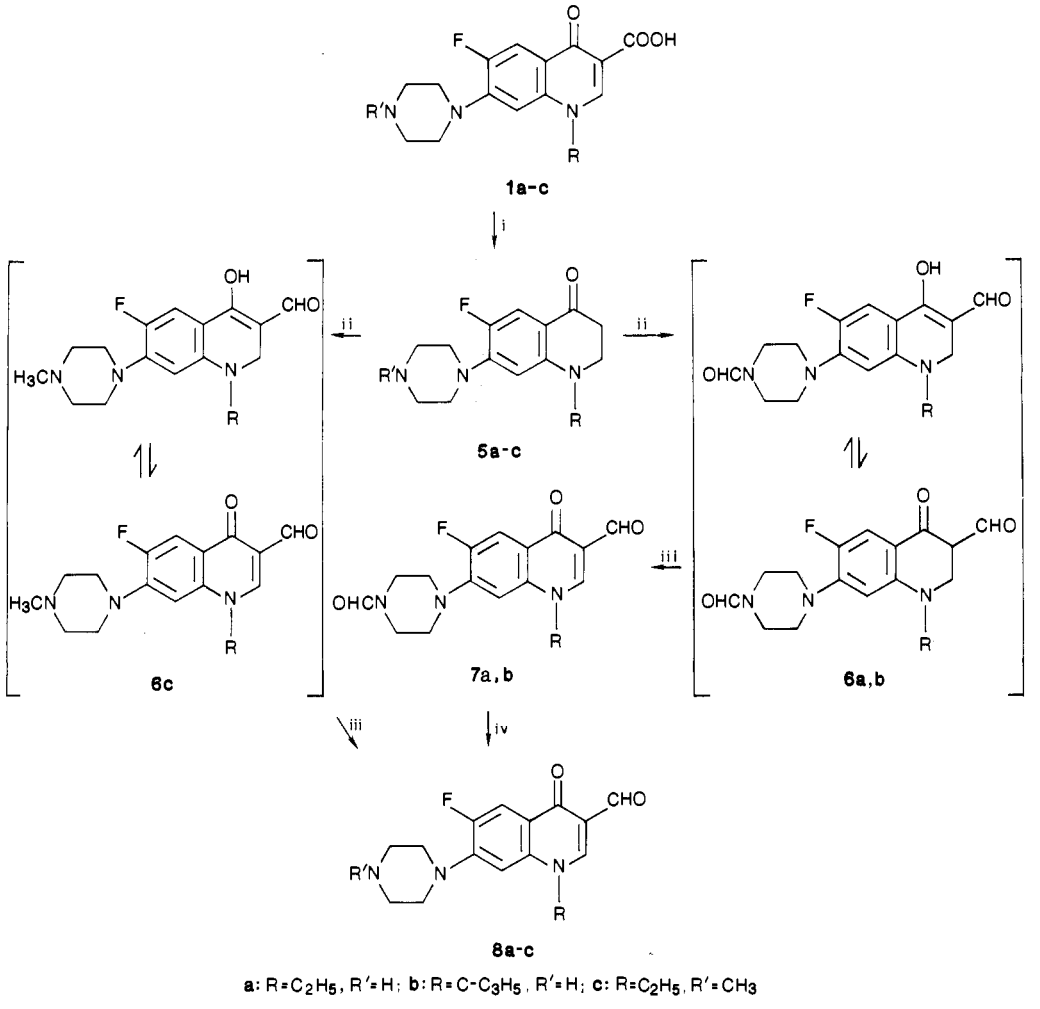
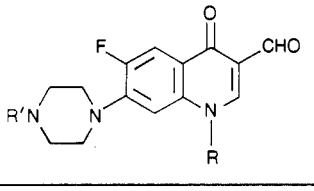
Scheme I[a]



a: R = C_2H_5, R′ = H; **b**: R = c-C_3H_5, R′ = H; **c**: R = C_2H_5, R′ = CH_3

[a] (i) $NaBH_4$, *p*-TsOH; (ii) $NaOCH_3$, $HCOOC_2H_5$; (iii) $MnO_2/MeOH_3$; (iv) 3 N HCl/EtOH.

Table II. Physical Data of 3-Formyl-4-oxoquinolines **7a,b** and **8a–c**



compd	R	R′	mp, °C	recrystn solvent[a]	formula[b]	yield, %
7a	C_2H_5	CHO	241–245	A	$C_{17}H_{18}N_3O_3F·0.5H_2O$	72
7b	c-C_3H_5	CHO	268–272	A	$C_{18}H_{18}N_3O_3F·0.75H_2O$	51.8
8a	C_2H_5	H	161–163	A	$C_{16}H_{18}N_3O_2F·0.75H_2O$	34.7
8b	c-C_3H_5	H	269–273 dec	B	$C_{17}H_{18}N_3O_2F·HCl$	61.8
8c	C_2H_5	CH_3	229–234	C	$C_{17}H_{20}N_3O_2F·0.25H_2O$	49.5

[a] A, EtOAc/EtOH; B, $CHCl_3$/EtOH; C, $CHCl_3/Et_2O$. [b] The analyses for C, H, and N were within ±0.4% of the theoretical values.

Table III. Antibacterial Activity of Compounds **1a–c** and **8a–c**

compd	microorganism[a]							ED_{50}[b] (*E. coli* KC-14), mg/kg oral
	Sa	Bs	Ec	Kp	Sm	Pv	Pa	
1a (NFLX)	0.20	0.20	0.10	0.05	0.20	0.05	0.78	7.68 (5.82–10.1)
8a	100<	12.5	12.5	3.12	100<	6.25	100<	2.53 (1.63–3.93)
1b (CPFX)	0.20	0.05	0.006	0.10	0.10	0.025	0.39	0.84 (0.60–1.17)
8b	25	6.25	3.13	12.5	12.5	3.13	50	0.49 (0.29–0.84)
1c (PFLX)	0.39	0.20	0.20	0.05	0.39	0.05	1.56	1.67 (1.19–2.35)
8c	12.5	3.13	6.25	1.56	12.5	1.56	25<	0.84 (0.60–1.17)

[a] Microorganism: Sa, *Staphylococcus aureus* FDA207PJC-1; Bs, *Bacillus subtilis* ATCC6633; Ec, *Escherichia coli* KC-14; Kp, *Klebsiella pneumonia* PCI602; Sm, *Serratia marcescens* IAM1184; Pv, *Proteus vulgaris* OX-19; Pa, *Pseudomonas aeruginosa* E-2. [b] 95% confidence limit.

Table IV. Serum Levels of 1a and 8a after Oral Administration in Mice

compd	0.5	1.0	2.0	4.0	AUC[a]
1a (50 mg/kg, po)					
1a (NFLX)	0.57 ± 0.10[b]	0.44 ± 0.16	0.19 ± 0.08	0.08 ± 0.03	0.98
8a (50 mg/kg, po)[c]					
8a	nd[d]	nd	nd	nd	
1a (NFLX)	1.13 ± 0.36	0.80 ± 0.16	0.30 ± 0.10	0.15 ± 0.03	1.77

[a] Areas under the concentration/time, μg/mL per hour, elution solvent; 5% AcOH/MeOH (70/30). [b] Standard deviation. [c] A dose equivalent to 50 mg/kg of 1a. [d] nd, not detected.

carboxyl compounds **1a–c**. 3-Formyl compounds **8a–c** were tested by oral administration on a systemic infection due to *Escherichia coli* KC-14 in mice and compared with the corresponding 3-carboxyl compounds **1a–c**. The evaluated medium effective dose values (ED_{50}) are presented in Table III. Although the 3-formyl compounds **8a–c** showed lower activity in vitro than the corresponding 3-carboxyl compounds **1a–c** against *E. coli* KC-14, all of the 3-formyl compounds **8a-c** exhibited higher activity in vivo than **1a–c**. The enhancement of the activity of 3-formyl compounds **8a–c** in vivo may be assumed by the following possibility: an increase of oral absorbability and a production of some active species in vivo after oral administration. If our designed formyl compounds **8a–c** were well absorbed after oral administration and were oxidized in vivo, the potent 3-carboxyl compounds **1a–c** would be liberated in high concentration. In order to clarify those points, we studied the blood level and the biological transformation of compound **8a**. First, the stability of **8a** at pH 7.4 and 37 °C was determined by high-performance liquid chromatography (HPLC). As a result, compound **8a** was found to be stable at physiological pH. The serum specimens were collected at regular time intervals, 0.5, 1.0, 2.0, and 4.0 h after oral administration of compounds **1a** and **8a**, and the concentrations of some species in serum were measured individually by HPLC (Table IV). The 3-formyl derivative **8a** of NFLX was converted into NFLX in vivo, while no other metabolites and **8a** could be detected in serum, as shown in Table IV. The serum levels of NFLX from compound **8a** were at all times about 2-fold higher than those of NFLX after oral administration. This corresponds to the activity in vivo outlined in Table III. The bioavailability of compound **8b** after oral administration may be assumed to be analogous to that of compound **8a**. As shown in Table III, PFLX (**1c**), that is an *N*-methyl NFLX, exhibited somewhat lower activity in vitro than NFLX, but 4.6-fold higher activity against *E. coli* KC-14 in vivo. Recently, we have also reported the increase of oral absorbability and the enhancement of the activity of N-masked NFLX's[7,8] in vivo.

On the other hand, PFLX and the 3-formyl compound **8c** were compared on systemic infection due to *E. coli* KC-14 in mice. The result is particularly interesting; namely, the 3-formyl compound **8c** exhibited 2-fold higher activity in vivo than PFLX. In the case of 3-formylquinolone derivatives **8a–c**, it became clear that the conversion from the carboxyl group to the formyl group at the 3-position in the quinoline skeleton increased the oral absorbability of the quinoline agent and the serum level of the active specimens **1a–c**. 3-Formyl compounds **8a–c** are well absorbed compared to 3-carboxyl compounds **1a–c**, possibly due to the increase of lipophilicity or the lack of its amphoteric nature. In order to clarify those points, we measured the log *P* values[14] of compounds **1a** and **8a**. As a result, **1a** and **8a** were found to have similar log *P* values (−0.57 and −0.58, respectively). The higher bioavailability of formyl derivatives **8a–c** may be due to a desirable change in physical and chemical properties by the lack of their amphoteric nature compared to the parent zwitterionic compounds **1a–c**. In the in vitro experiments, it has been demonstrated that oxidative metabolism of drugs proceeds extensively in liver homogenate and more or less in lung and kidney.[15] Our case may be similar, but we have no supporting data.

Few detailed studies have been reported, on which the formyl group functioned as the promoiety of a prodrug, but this paper has presented definitive evidence that the 3-formyl compounds **8a–c** function as prodrugs of NFLX (**1a**), CPFX (**1b**), and PFLX (**1c**), respectively, in mice. This fact opens the possibility for other similar drug design.

Experimental Section

Melting points were determined on a Yamato capillary melting point apparatus, Model MP-21, and all melting points are uncorrected. ^{1}H NMR spectra were determined at 100 MHz on a Nihon Denshi PS-100 NMR spectrometer with tetramethylsilane as an internal standard. All compounds were analyzed for C, H, and N, and the values were within ±0.4% of the calculated theoretical ones.

In Vitro Antibacterial Activity. According to the method of Goto et al.,[16] the MIC's (minimum inhibitory concentrations) of compounds tested in this study were determined by the serial 2-fold dilution technique, with Mueller-Hinton agar. The inoculum size was approximately 10^6 cfu/mL. The concentrations of compounds in the plates ranged from 0.006 to 100 μg/mL. MIC was defined as the lowest concentration of a compound that prevented visible growth of bacteria after incubation at 37 °C for 18 h.

In Vivo Efficacy on Systemic Infections. In vivo assay was carried out according to the general method.[17] Groups of 10 male ddY mice (20 ± 2 g) were infected with bacteria. A 0.5-mL volume of a bacterial dilution, corresponding to 10 or 100 times higher than the 50% lethal dose, was inoculated intraperitoneally. The test compounds were suspended in 0.5% sodium (carboxymethyl)cellulose and administered orally at 1 h postinfection. Survival rates were evaluated after 1 week.

Oral Absorbability Test. Serum patterns of compounds 1a–c and **8a–c** were determined by HPLC. Test compounds were suspended in 0.5% sodium (carboxymethyl)cellulose and administered orally at a dose of 50 mg/kg. After 0.5, 1.0, 2.0, and 4.0 h, the mice were killed by bleeding. The collected blood was centrifuged, and the test serum was adjusted. A HPLC machine was equipped with a Hitachi Model 655 pump; a Shimadzu Model SPD-2A spectrophotometric detector (at 280 nm) and YMC A-312 ODS column were used. The mobile phase consisted of 5.0% aqueous acetic acid/acetonitrile (70/30 v/v), and the flow rate was 2.0 mL/min.

1-Ethyl-6-fluoro-4-oxo-7-piperazinyl-1,2,3,4-tetrahydroquinoline (5a). General Procedure. 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazinylquinoline-3-carboxylic acid[1] (**1a**; 10 g,

(14) P is the partition coefficient between 1-octanol and pH 7 buffer solution.

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31.3 mmol) was suspended in dry methanol (450 mL), and sodium borohydride (4.8 g, 127 mmol) dissolved in dry methanol (50 mL) was added slowly. The reaction mixture, after addition of a catalytic amount of *p*-toluenesulfonic acid monohydrate, was heated at 65 °C for 30 min. The solvent was removed in vacuo, and the residue was extracted with chloroform. The extract was washed with water, dried over $MgSO_4$, concentrated to give the crude oil, and chromatographed on a column of silica gel with chloroform/ethyl acetate (3/1 v/v) as an eluent under medium pressure to give **5a** (5.9 g, 68%) of yellow prisms: mp 55–58 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3 H), 2.25 (m, 1 H), 2.60 (dd, 2 H), 3.18 (m, 8 H), 3.40 (q, 2 H), 3.46 (dd, 2 H), 6.15 (d, 1 H), 7.50 (d, 1 H). Anal. ($C_{15}H_{20}N_3OF$) C, H, N.

1-Cyclopropyl-6-fluoro-4-oxo-7-piperazinyl-1,2,3,4-tetrahydroquinoline (5b). 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazinylquinoline-3-carboxylic acid[2] (**1b**; 1.3 g, 3.9 mmol) was reduced by the above procedure and recrystallized from chloroform/ethyl ether to give **5b** (0.8 g, 72.7%) of yellow crystals: mp 99–103 °C; ^{1}H NMR ($CDCl_3$) δ 0.80 (m, 4 H), 1.87 (m, 1 H), 2.50 (m, 1 H), 2.60 (dd, 2 H), 3.15 (m, 8 H), 3.51 (dd, 2 H), 6.75 (d, 1 H), 7.54 (d, 1 H). Anal. ($C_{16}H_{20}N_3OF$) C, H, N.

1-Ethyl-6-fluoro-7-(4-methyl-1-piperazinyl)-4-oxo-1,2,3,4-tetrahydroquinoline (5c). 1-Ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid[3] (**1c**; 1.5 g, 4.5 mmol) was reduced by the above procedure and recrystallized from ethyl acetate/ethanol to give **5c** (1.0 g, 76.2%) as yellow prisms: mp 112–115 °C; ^{1}H NMR ($CDCl_3$) δ 1.18 (t, 3 H), 2.30 (s, 3 H), 2.40–2.75 (m, 6 H), 3.00–3.60 (m, 8 H), 6.05 (d, 1 H), 7.45 (d, 1 H). Anal. ($C_{16}H_{22}N_3OF·H_2O$) C, H, N.

1-Ethyl-6-fluoro-1,4-dihydro-3-formyl-7-(4-formyl-1-piperazinyl)-4-oxoquinoline (7a). General Procedure. Sodium methoxide (0.775 g, 14 mmol) and ethyl formate (1.05 g, 14.2 mmol) were added slowly to a solution of **5a** (1 g, 3.6 mmol) in dichloromethane (200 mL), and the mixture was stirred at room temperature overnight. Ice water (200 mL) was then added, the aqueous layer was separated, and the organic layer was washed twice with dilute sodium hydroxide. The aqueous layer and alkaline extracts were combined, washed once with dichloromethane, and acidified with 3 N HCl. The oily precipitate was extracted with dichloromethane, washed with saturated sodium chloride solution, and dried, and the solvent was removed to give **6a** (0.94 g) as a brownish oil, which was dissolved in methanol (50 mL) and stirred with an excess amount of manganese dioxide at room temperature for 16 h. The undissolved substance was filtered, concentrated, and recrystallized from ethyl acetate to give **7a** (0.86 g, 72% based on **5a**) as colorless needles: mp 241–245 °C; ^{1}H NMR ($CDCl_3$) δ 1.55 (t, 3 H), 3.0–3.90 (m, 8 H), 4.24 (q, 2 H), 6.80 (d, 1 H), 8.04 (d, 1 H), 8.10 (s, 1 H), 8.20 (s, 1 H), 10.36 (s, 1 H). Anal. ($C_{17}H_{18}N_3O_3F·0.5H_2O$) C, H, N.

1-Cyclopropyl-6-fluoro-1,4-dihydro-3-formyl-7-(4-formyl-1-piperazinyl)-4-oxoquinoline (7b). Via the general procedure described above, a mixture of sodium methoxide (0.19 g, 3.5 mmol), ethyl formate (0.26 g, 3.5 mmol), and **5b** (0.26 g, 0.9 mmol) was worked up to give **7b** (0.16 g, 51.8% based on **5b**) as pale yellow crystals: mp 268–272 °C; ^{1}H NMR ($CDCl_3$) δ 1.00–1.50 (m, 4 H), 3.10–3.50 (m, 4 H), 3.51–3.95 (m, 5 H), 7.35 (d, 1 H), 8.00 (d, 1 H), 8.13 (s, 1 H), 8.35 (s, 1 H), 10.34 (s, 1 H). Anal. ($C_{18}H_{18}N_3O_3F·0.75H_2O$) C, H, N.

1-Ethyl-6-fluoro-3-formyl-1,4-dihydro-4-oxo-7-piperazinylquinoline (8a). General Procedure. The suspension of **7a** (0.82 g, 2.47 mmol) in 3 N HCl (5 mL) was allowed to reflux with stirring for 30 min and stood at room temperature for a while to give a white solid. The solid was collected by filtration and dissolved in a small amount of water. The acidic solution was neutralized with 3 N NaOH, and the obtained solid was extracted with chloroform, dried over $MgSO_4$, concentrated, and recrystallized from ethyl acetate/ethanol to give **8a** (0.52 g, 34.7%) as colorless needles: mp. 161–163 °C; ^{1}H NMR ($CDCl_3$) δ 1.60 (t, 3 H), 2.90–3.40 (m, 8 H), 4.25 (q, 2 H), 6.82 (d, 1 H), 8.10 (d, 1 H), 8.26 (s, 1 H), 10.40 (s, 1 H). Anal. ($C_{16}H_{18}N_3O_2F·0.75H_2O$) C, H, N.

1-Cyclopropyl-6-fluoro-3-formyl-1,4-dihydro-4-oxo-7-piperazinylquinoline (8b). Via the general procedure described above, the suspension of **7b** (0.15 g, 0.43 mmol) in 3 N HCl (1.2 mL) was allowed to reflux to give **8b** (0.095 g, 61.8%) as a pale yellow powder as a monohydrochloride: mp 269–273 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.00–1.50 (m, 4 H), 3.10–3.45 (m, 4 H), 3.50–3.90 (m, 5 H), 7.35 (d, 1 H), 8.00 (d, 1 H), 8.35 (s, 1 H), 10.34 (s, 1 H). Anal. ($C_{17}H_{18}N_3O_2F·HCl·0.25H_2O$) C, H, N.

1-Ethyl-6-fluoro-3-formyl-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxoquinoline (8c). Via the general procedure for **7a** described above, a mixture of sodium methoxide (0.74 g, 13.7 mmol), ethyl formate (1.0 g, 13.5 mmol), and **5c** (1.0 g, 3.4 mmol) was worked up to give **8c** (0.54 g, 49.5% based on **5c**) as pale yellow needles: mp 229–234 °C; ^{1}H NMR ($CDCl_3$) δ 1.50 (t, 3 H), 2.36 (s, 3 H), 2.48–2.64 (m, 4 H), 3.28–3.44 (m, 4 H), 4.36 (q, 2 H), 6.81 (d, 1 H), 8.08 (d, 1 H), 8.22 (s, 1 H), 10.38 (s, 1 H). Anal. ($C_{17}H_{20}N_3O_2F$) C, H, N.

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