Studies on Antibacterial Agents. III.[1] Synthesis and Antibacterial Activities of Substituted 1,4-Dihydro-8-methyl-4-oxoquinoline-3-carboxylic Acids

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A series of substituted 4-oxoquinoline-3-carboxylic acids having a methyl group at the 8-position was prepared and tested for their antibacterial activity. 7-(*trans*-3-Amino-4-methyl-1-pyrrolidinyl)-1-cyclopropyl-1,4-dihydro-6-fluoro-8-methyl-4-oxoquinoline-3-carboxylic acid (21) exhibited highly potent antibacterial activity against both gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa*.

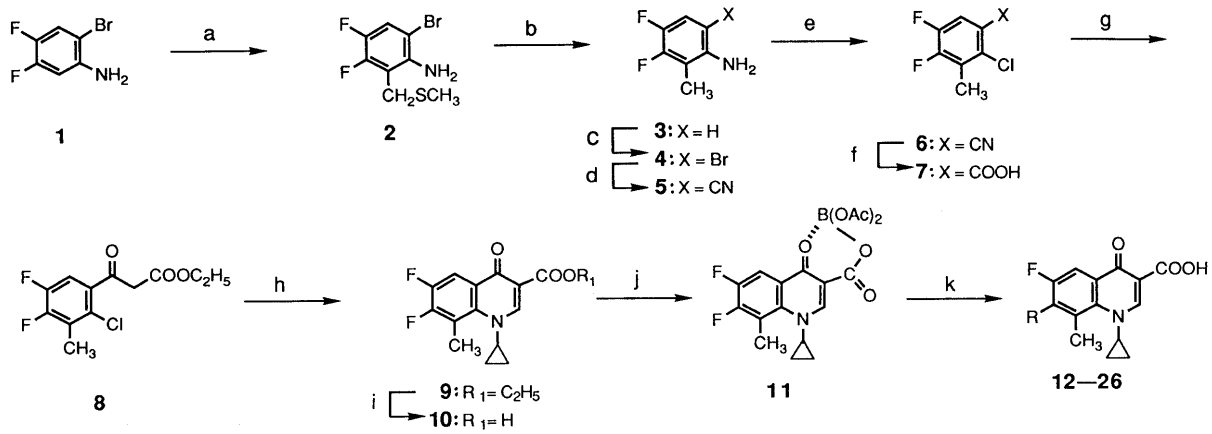
Keywords 4-oxoquinoline-3-carboxylic acid; 8-methylquinoline; methyl group; fluorine; antibacterial activity; *Pseudomonas aeruginosa*

Since nalidixic and (NA)[2] was discovered by Lesher in 1962, a number of the analogues have been synthesized and tested for antibacterial activity. In 1978, we found that 7-chloro-1-ethyl-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid,[3] which was obtained by the modification of NA, had more potent and broad-spectrum antibacterial activity than the corresponding 8-unsubstituted compound. Since then, our interest has been directed to the activity of the compound with a methyl group at the 8-position of quinoline ring. On the other hand, highly potent and broad-spectrum quinolone antibacterial agents such as norfloxacin,[4] ofloxacin (OFLX),[5] enoxacin[6] and ciprofloxacin (CPFX)[7] have florine and cyclic amine as substituents. Therefore, we expected that 8-methylquinolone carboxylic acids with these substituents would show very potent antibacterial activity. However, no method for synthesizing them has yet been disclosed, probably because of the difficulty of preparation.

Now, we wish to report here the synthesis and antibacterial activity of substituted 1-cyclopropyl-6-fluoro-8-methyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid derivatives.

Synthesis

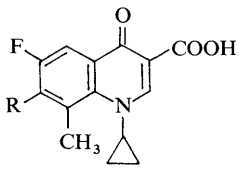
Substituted 8-methyl-4-oxoquinoline-3-carboxylic acid derivatives listed in Table I were synthesized as shown in Chart 1. First, the benzoic acid derivative (**7**) was prepared by a route involving ortho selective alkylation[8] of 2-bromo-4,5-difluoroaniline (**1**).[1] Namely, addition of *N*-chlorosuccinimide (NCS) to a mixture of **1** and dimethyl sulfide at $-15\,^{\circ}C$ in CH_2Cl_2, followed by treatment with triethylamine gave 6-bromo-3,4-difluoro-2-methylthiomethylaniline (**2**). Reductive elimination of a bromine and methylthio group of **2** with activated Raney nickel gave 3,4-difluoro-2-methylaniline (**3**). Compound (**3**) was selectively monobrominated with bromine in AcOH to afford 6-bromo-3,4-difluoro-2-methylaniline (**4**). Treatment of **4** with cuprous cyanide (CuCN) in *N*,*N*-dimethyl formamide (DMF) gave 6-cyano-3,4-difluoro-2-methylaniline (**5**) in 81% yield. Diazotization of **5** with sodium nitrite ($NaNO_2$) in AcOH, followed by treatment with cuprous chloride (CuCl) provided 2-chloro-4,5-difluoro-3-methylbenzonitrile (**6**). Hydrolysis of **6** with 50% H_2SO_4 gave 2-chloro-4,5-difluoro-3-methylbenzoic acid (**7**), which was a key intermediate for the synthesis of the quinoline ring. Condensation of acid chloride of **7** with ethoxymagnesium malonic ester, followed by heating with *p*-toluenesulfonic acid (*p*-TsOH) in water gave ethyl 2-chloro-4,5-difluoro-3-methylbenzoylacetate (**8**). Then, treatment of **8** with acetic anhydride and triethyl orthoformate, followed by addition of cyclopropylamine in EtOH and successive cyclization with 60% NaH gave ethyl 1-cyclopropyl-6,7-difluoro-1,4-

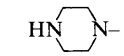
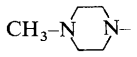
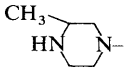
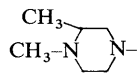
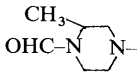
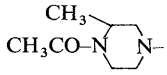
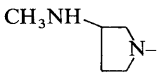
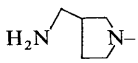
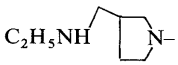
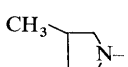
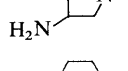
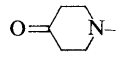
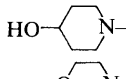
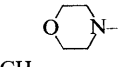
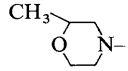


a, (1) CH_3SCH_3, NCS (2) Et_3N; b, Raney Ni; c, Br_2, AcONa; d, CuCN; e, (1) $NaNO_2$ (2) CuCl; f, H_2SO_4; g, (1) $SOCl_2$(2) $EtOMgCH(COOC_2H_5)_2$ (3) *p*-T_sOH; h, (1) Ac_2O, $CH(OC_2H_5)_3$ (2) $C_3H_5NH_2$ (3) NaH; i, HCl; j, H_3BO_3, Ac_2O; k, RH

Chart 1

TABLE I. Substituted 1,4-Dihydro-8-methyl-4-oxoquinoline-3-carboxylic Acids



Compd.	R	Recryst. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
12		DMF	38	291—294 (dec.)	$C_{18}H_{20}FN_3O_3 \cdot 2H_2O$	56.68 (56.44	6.34 6.21	11.02 10.98)
13		EtOH	41	219—220.5	$C_{19}H_{22}FN_3O_3$	63.50 (63.77	6.17 6.17	11.69 11.76)
14		EtOH	36	206—208	$C_{19}H_{22}FN_3O_3$	63.50 (63.44	6.17 6.05	11.69 11.61)
15		AcOEt	48[a]	181—183	$C_{20}H_{24}FN_3O_3$	64.33 (64.32	6.48 6.56	11.25 11.25)
16		MeOH	47[a]	236—239	$C_{20}H_{22}FN_3O_4 \cdot 1/4H_2O$	61.29 (61.34	5.79 5.73	10.72 10.84)
17		MeOH	48[a]	219—221	$C_{21}H_{24}FN_3O_4$	62.83 (62.83	6.03 5.83	10.47 10.31)
18		EtOH	32	185.5—187.5 (dec.)	$C_{19}H_{22}FN_3O_3 \cdot HCl \cdot H_2O$	55.14 (54.83	6.09 5.97	10.15 10.23)
19		AcOEt–MeOH	28	196—198	$C_{19}H_{22}FN_3O_3 \cdot HCl \cdot H_2O$	55.14 (55.48	6.09 5.81	10.15 10.11)
20		CH_3CN–MeOH	33	267—270 (dec.)	$C_{21}H_{26}FN_3O_3 \cdot HCl \cdot 1/4H_2O$	58.88 (58.82	6.47 6.33	9.81 9.83)
21	 *trans*	AcOEt–EtOH	31	268—270 (dec.)	$C_{19}H_{22}FN_3O_3 \cdot HCl$	57.65 (57.43	5.86 5.92	10.61 10.58)
22	 *cis*	AcOEt–MeOH	28	206—208	$C_{19}H_{22}FN_3O_3 \cdot HCl \cdot 2H_2O$	52.79 (52.57	6.07 5.86	9.73 9.53)
23		$CHCl_3$–EtOH	26	247—250	$C_{19}H_{19}FN_2O_4 \cdot 1/4H_2O$	62.89 (62.95	5.42 5.25	7.72 7.74)
24		$CHCl_3$–EtOH	35	234—236	$C_{19}H_{21}FN_2O_4 \cdot 1/4H_2O$	63.32 (63.52	5.87 5.79	7.77 7.70)
25		EtOH	44	227.5—228	$C_{18}H_{19}FN_2O_4$	62.42 (62.03	5.53 5.85	8.09 7.98)
26		AcOH–EtOH	42	199.5—201	$C_{19}H_{21}FN_2O_4$	63.32 (63.25	5.87 5.89	7.77 7.59)

a) Yield from **14**.

dihydro-8-methyl-4-oxoquinoline-3-carboxylate (**9**). Hydrolysis of **9** gave the acid derivative (**10**) in good yield. Treatment of **10** with cyclic amine in *N*-methylpyrrolidinone at 150 °C gave 7-substituted compound in poor yield, probably because of the steric effect of a methyl group at the 8-position. Therefore, we prepared a chelate compound (**11**) in order to activate the 7-position of quinoline ring. Namely, treatment of **10** with boric acid in acetic anhydride[9] gave **11** in good yield. The desired 7-substituted derivatives (**12**—**26**) were obtained by treatment of **11** with various cyclic amines in CH_3CN at 60 °C.

Biological Result

Compounds (**12**—**26**) were tested for *in vitro* antibacterial activity against gram-positive (*Staphylococcus aureus* 209p, *Streptococcus pyogenes* IFD 12580) and gram-negative bacteria (*Escherichia coli* NIHJ JC-2, *Pseudomonas aeruginosa* ATCC 10145 and *Acinetobacter calcoaceticus* AC-54) by serial dilution method.[10] The results are summarized in Table II; the antibacterial activity of CPFX and OFLX are included for comparison. 8-Methyl compound (**12**) showed more potent activity against gram-positive bacteria than the corresponding 8-unsubstituted compound (CPFX), but slightly less activity against *Ps. aeruginosa*. The substitution of hydrogen of the piperazine group (**14**) by acyl group (**16** and **17**) and the introduction of 4-hydroxypiperidine (**24**) and morpholine (**25**) at the 7-position increased the activity against gram-positive bacteria, particularly *S. aureus*, but they caused a decrease in the activity against gram-negative

TABLE II. *In Vitro* Antibacterial Activity (Minimum Inhibitory Concentration, μg/ml)

Compd.	Microorganism[a]				
	Sa	Ef	Ec	Pa	Ac
12	0.1	0.39	0.024	0.39	0.2
13	0.1	0.39	0.024	0.78	0.05
14	0.1	0.39	0.024	0.39	0.1
15	0.1	0.78	0.024	1.56	0.05
16	0.024	0.2	0.39	6.25	0.39
17	0.05	0.39	0.78	12.5	1.56
18	0.024	0.2	≤0.006	0.39	0.05
19	≤0.006	0.024	0.012	0.39	0.05
20	≤0.006	0.05	0.012	0.78	0.05
21	0.024	0.1	≤0.006	0.1	0.024
22	0.024	0.1	0.012	0.2	0.05
23	≤0.006	0.2	0.1	1.56	0.2
24	0.012	0.1	0.1	1.56	0.2
25	0.012	0.1	0.1	0.78	0.1
26	0.012	0.2	0.2	0.78	0.39
CPFX	0.2	0.78	0.024	0.2	0.39
OFLX	0.2	1.56	0.1	1.56	0.39

a) Sa, *Staphylococcus aureus* 209p; Ef, *Enterococcus faecalis* IFD 12750; Ec, *Escherichia coli* NIHJ JC-2; Pa, *Pseudomonas aeruginosa* ATCC 10145; Ac, *Acinetobacter calcoaceticus* AC-54.

bacteria. The compounds (**18**—**22**) with substituted pyrrolidine group markedly enhanced gram-positive activity.

Among them, Compound (**21**) exhibited highly potent activity against both gram-positive and gram-negative bacteria, including *Ps. aeruginosa*.

Experimental

All the melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 or Bruker AC-200 NMR spectrometer using tetramethylsilane as internal standard.

6-Bromo-3,4-difluoro-2-methylthiomethylaniline (2) NCS (6.2 g, 46 mmol) was added portionwise to a mixture of 2-bromo-4,5-difluoroaniline (6.0 g, 46 mmol) and dimethyl sulfide (2.9 g, 46 mmol) in dry CH_2Cl_2 (120 ml) at −15 °C. After the addition, triethylamine (4.6 g, 46 mmol) was added to the mixture and refluxed for 14 h. After cooling, the reaction mixture was washed with 10% NaOH and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 5 : 1) and recrystallized from hexane to give **2** (4.2 g, 54%) as colorless prisms, mp 58—59 °C. NMR ($CDCl_3$) δ: 2.02 (3H, d, J = 1.0 Hz), 3.76 (2H, d, J = 1.8 Hz), 4.47 (2H, br s), 7.24 (1H, dd, J = 8.2, 11.3 Hz). *Anal.* Calcd for $C_8H_8BrF_2NS$: C, 35.84; H, 3.01; N, 5.22. Found: C, 35.67; H, 2.92; N, 5.27.

3,4-Difluoro-2-methylaniline (3) A suspension of **2** (26.7 g, 0.1 mol) and activated Raney Ni (110 ml) in EtOH (500 ml) was refluxed for 1 h. After cooling, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and distilled under reduced pressure to give **3** (11.4 g, 80%), bp 92 °C (12 mmHg). NMR ($CDCl_3$) δ: 2.08 (3H, d, J = 1.8 Hz), 3.54 (2H, br s), 6.23—6.58 (1H, m), 6.82 (1H, dt, J = 6.1, 8.9 Hz). *Anal.* Calcd for $C_7H_7F_2N$: C, 58.74; H, 4.93; N, 9.79. Found: C, 58.69; H, 4.85; N, 9.97.

6-Bromo-3,4-difluoro-2-methylaniline (4) A solution of bromine (17.6 g, 0.11 mol) in AcOH (30 ml) was added dropwise to a mixture of **3** (14.3 g, 0.1 mol) and sodium acetate (9.4 g, 0.11 mol) in AcOH (80 ml) below 20 °C. The reaction mixture was concentrated *in vacuo*, basified with 10% NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and then concentrated. The residue was distilled under reduced pressure to give **4** (17.1 g, 77%) as colorless oil, bp 83 °C (0.5 mmHg). NMR ($CDCl_3$) δ: 2.14 (3H, d, J = 2.2 Hz), 3.97 (2H, br s), 7.15 (1H, t, J = 8.8 Hz). *Anal.* Calcd for $C_7H_6BrF_2N \cdot 1/2\ H_2O$: C, 36.39; H, 3.05; N, 6.06. Found: C, 36.44; H, 2.97; N, 6.12.

6-Cyano-3,4-difluoro-2-methylaniline (5) A mixture of **4** (1.8 g, 8.1 mmol) and CuCN (1.1 g, 12 mmol) in DMF (10 ml) was heated at 150 °C for 5h. The reaction mixture was cooled at 80 °C and poured into a solution of ethylenediamine (0.7 g, 12 mmol) in water (10 ml) with vigorous stirring. The suspension was extracted with ethyl acetate. The ethyl acetate solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent, CH_2Cl_2: hexane = 1 : 1) and recrystallized from hexane–ethyl acetate to give **5** (1.1 g, 81%) as colorless needles, mp 114—116 °C. NMR ($CDCl_3$) δ: 2.13 (3H, d, J = 2.2 Hz), 4.37 (2H, br s), 7.09 (1H, t, J = 8.8 Hz). *Anal.* Calcd for $C_8H_6F_2N_2$: C, 57.15; H, 3.60; N, 16.66. Found: C, 57.27; H, 3.40; N, 16.76.

2-Chloro-4,5-difluoro-3-methylbenzonitrile (6) A solution of **5** (19.0 g, 0.11 mol) in AcOH (190 ml) was added dropwise to a solution of $NaNO_2$ (9.3 g, 0.13 mol) in concentrated H_2SO_4 (91 ml) at 40 °C. The mixture was stirred for 30 min and then added to a solution of CuCl (37.0 g, 0.37 mol) in concentrated HCl (370 ml) at room temperature. The reaction mixture was heated at 80 °C for 30 min, then poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (eluent, CH_2Cl_2 : hexane = 1 : 1). Recrystallization from hexane gave **6** (13.4 g, 63%) as colorless needles, mp 59—61 °C. NMR ($CDCl_3$) δ: 2.41 (3H, d, J = 2.2 Hz), 7.40 (1H, t, J = 8.4 Hz). *Anal.* Calcd for $C_8H_4ClF_2N$: C, 51.23; H, 2.15; N, 7.47. Found: C, 51.21; H, 2.03; N, 7.44.

2-Chloro-4,5-difluoro-3-methylbenzoic Acid (7) A solution of **6** (4.0 g, 21 mmol) in 60% H_2SO_4 was heated at 150 °C for 3 h. The mixture was poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated. The residue was recrystallized from ethyl acetate–hexane to give **7** (4.0 g, 91%) as colorless needles, mp 121—122 °C. NMR ($CDCl_3$) δ: 2.41 (3H, d, J = 2.8 Hz), 7.74 (1H, dd, J = 8.2, 10.1 Hz), 10.44 (1H, br s). *Anal.* Calcd for $C_8H_5ClF_2O_2$: C, 46.51; H, 2.44. Found: C, 46.79; H, 2.73.

Ethyl 2-Chloro-4,5-difluoro-3-methylbenzoylacetate (8) A mixture of **7** (7.5 g, 34 mmol) and thionyl chloride (15 ml, 0.21 mol) was heated at 80 °C for 1 h, and then concentrated *in vacuo*. A few drops of carbon tetrachloride was added to a suspension of magnesium (0.9 g, 38 mmol) in EtOH (2 ml). When the reaction started, a solution of diethyl malonate (5.8 g, 38 mmol) in EtOH (3.6 ml) and toluene (15 ml) was added dropwise to the suspension below 60°C. After stirring at room temperature for 30 min, the reaction mixture was cooled at 0 °C. Acid chloride obtained above was added dropwise to the mixture and stirred at room temperature for 30 min. A solution of concentrated H_2SO_4 (1 ml) in water (8 ml) was then added under ice-cooling. The organic layer was separated, washed with 2% sodium bicarbonate and concentrated *in vacuo*. A solution of *p*-TsOH (80 mg) in water (21 mg) was added to the residue, and then the mixture was refluxed for 3 h. After cooling, the mixture was extracted with ether. The ether solution was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (eluent, CH_2Cl_2: hexane = 1 : 4) to give **8** (8.0 g, 80%) as colorless oil. NMR ($CDCl_3$) δ: 1.34 (3H, t, J = 7.2 Hz), 2.38 (3H, d, J = 2.6 Hz), 4.28 (2H, q, J = 7.2 Hz), 5.49 (1H, s), 7.26 (1H, t, J = 9.3), 12.46 (1H, s). *Anal.* Calcd for $C_{12}H_{11}ClF_2O_3$: C, 52.10; H, 4.01. Found: C, 51.95; H, 4.38.

Ethyl 1-Cyclopropyl-6,7-difluoro-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (9) A mixture of **8** (3.9 g, 14 mmol), acetic anhydride (3.4 g, 33 mmol) and triethyl orthoformate (3.1 g, 21 mmol) was heated at 150 °C for 1 h, and then concentrated *in vacuo*. EtOH (50 ml) was added to the residue. Cyclopropylamine (1.2 g, 21 mmol) was added dropwise to the EtOH solution at room temperature and stirred for 30 min. The mixture was concentrated *in vacuo*, and then dry dioxane (30 ml) was added to the residue. 60% NaH (0.6 g, 15 mmol) was added portionwise to the dioxane solution at room temperature, and the mixture was heated at 100 °C for 1 h. After cooling, the reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated. The residue was recrystallized from EtOH to give **9** (2.8 g, 65%) as colorless needles, mp 214—215 °C. NMR ($CDCl_3$) δ: 0.97—1.10 (2H, m), 1.18—1.32 (2H, m), 1.40 (3H, t, J = 7.1 Hz), 2.78 (3H, d, J = 3.1 Hz), 3.90—4.01 (1H, m), 4.38 (2H, q, J = 7.1 Hz), 8.12 (1H, t, J = 9.6 Hz), 8.66 (1H, s). *Anal.* Calcd for $C_{16}H_{15}F_2NO_3$: C, 62.54; H, 4.92; N, 4.56. Found: C, 62.83; H, 4.96; N, 4.61.

1-Cyclopropyl-6,7-difluoro-1,4-dihydro-8-methyl-4-oxo-quinoline-3-carboxylic Acid (10) A mixture of **9** (2.6 g, 8.5 mmol), concentrated HCl (7 ml) and 90% AcOH (26 ml) was refluxed for 2 h. After cooling, the resulting precipitate was collected by filtration to give **10** (2.1 g, 89%) as colorless needles, mp 240—243 °C. NMR (DMSO-d_6) δ: 1.01—1.28 (4H, m), 2.81 (3H, d, J = 3.4 Hz), 4.28—4.42 (1H, m), 8.04 (1H, t, J = 9.6 Hz), 8.80 (1H, s), 14.97 (1H, br s). *Anal.* Calcd for $C_{14}H_{11}F_2O_3$: C, 60.22; H, 3.97; N, 5.02. Found; C, 60.08; H, 4.00; N, 4.80.

1-Cyclopropyl-6,7-difluoro-1,4-dihydro-8-methyl-4-oxo-quinoline-3-

carboxylic Acid B(OCOCH$_3$)$_2$Chelate (11) Boric acid (4.4 g, 71 mmol) was added portionwise to acetic anhydride (160 ml) at 70 °C during 2 h. **10** (16.4, 59 mmol) was added to the clear solution, and the mixture was heated at 90 °C for 15 min. The reaction mixture was concentrated *in vacuo*, and isopropylether was added to the residue. The resulting precipitates were collected by filtration to give **11** (23.6 g, 99%) as white powder, which was used in the next reaction step without further purification. NMR (CDCl$_3$) δ: 1.13—1.60 (4H, m), 2.03 (6H, s), 2.97 (3H, d, J=3.4 Hz), 4.30—4.58 (1H, m), 8.23 (1H, t, J=8.8 Hz), 9.32 (1H, s).

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic Acid (14) A mixture of **11** (4.1 g, 10 mmol) and 1-benzyl-2-methylpiperazine (7.6 g, 40 mmol) in dry CH_3CN (80 ml) was stirred at 60 °C for 15 h. The mixture was concentrated *in vacuo*. A mixture of concentrated HCl (5 ml) and acetone (30 ml) was added to the residue, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated, and then water was added to the residue. The resulting precipitates were filtered off and the filtrate was neutralized to pH=7.5 with 2% $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (eluent, CH_2Cl_2: MeOH=20:1) to give N-benzyl compound, which was stirred with 10% Pd–C (0.2 g) in AcOH (20 ml) at 70 °C for 1 h under atmospheric pressure of hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off and the filtrate was adjusted to pH=7.5 with 2% $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was concentrated, and the residue was collected by filtration and recrystallized from EtOH to give **14** (1.3 g, 36%). NMR (CDCl$_3$) δ: 0.87—1.00 (2H, m), 1.11 (3H, d, J=5.4 Hz), 1.18—1.33 (2H, m), 2.75 (3H, s), 2.90—3.50 (7H, m), 4.01—4.18 (1H, m), 7.93 (1H, d, J=12.0 Hz), 8.90 (1H, s). The melting point and elemental analysis data are given in Table I.

Compounds (**12** and **13**) were obtained by the same procedure as described for **14**; the yield, melting point and elemental analysis data are listed in Table I.

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-7-(3,4-dimethyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic Acid (15) A mixture of **14** (0.4 g, 1.1 mmol), sodium acetate (0.4 g, 5 mmol), 90% formic acid (3 ml) and 37% formalin (3 ml) was refluxed for 5 h. After cooling, the reaction mixture was poured into ice-water, adjusted to pH=7.5 with 2% $NaHCO_3$ and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated. The residue was recrystallized from ethyl acetate to give **15** (0.2 g, 48%) as pale yellow powder. NMR (CDCl$_3$) δ: 0.85—1.05 (2H, m), 1.12 (3H, d, J=6.2 Hz), 1.15—1.33 (2H, m), 2.38 (3H, s), 2.32—2.60 (2H, m), 2.76 (3H, s), 2.85—3.28 (4H, m), 3.40—3.68 (1H, m), 4.02—4.22 (1H, m), 7.88 (1H, d, J=12.0 Hz), 8.88 (1H, s), 14.75 (1H, br s). The melting point and elemental analysis data are given in Table I.

1-Cyclopropyl-6-fluoro-7-(4-formyl-3-methyl-1-piperazinyl)-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic Acid (16) A mixture of acetic anhydride (2.2 ml, 23 mmol) and formic acid (1.7 ml, 45 mmol) was heated at 50°C for 20 min, then **14** (0.4 g, 1.1 mmol) was added to the mixture, and the mixture was heated at 80 °C for 2 h. After cooling, the reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated. The residue was recrystallized from MeOH to give **16** (0.2 g, 47%) as white powder. NMR (CDCl$_3$) δ: 0.85—1.12 (2H, m), 1.15—1.35 (2H, m), 1.41 (1.2H, d, J=6.8 Hz), 1.50 (1.8H, d, J=6.8 Hz), 2.85 (3H, s), 2.90—4.22 (7.6H, m), 4.62—4.81 (0.4H, m), 7.96 (1H, d, J=12.0 Hz), 8.10 (0.4H, s), 8.23 (0.6 H, s), 8.92 (1H, s), 14.6 (1H, br s). The melting point and elemental analysis data are given in Table I.

7-(4-Acetyl-3-methyl-1-piperazinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic Acid (17) Acetic anhydride (0.3 ml, 3.2 mmol) was added to a solution of **14** (0.3 g, 0.8 mmol) in 10% NaOH (5 ml) at room temperature, and the mixture was stirred for 1 h. The reaction mixture was acidified with AcOH, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (eluent, CH_2Cl_2) and recrystallized from MeOH to give **17** (0.16 g, 48%) as white powder. NMR (CDCl$_3$) δ: 0.80—1.55 (7H, m), 2.17 (3H, s), 2.85 (3H, s), 2.91—3.85 (6H, m), 4.02—4.22 (1H, m), 4.44—4.68 (0.5 H, m), 4.80—5.05 (0.5 H, m), 7.96 (1H, d, J=12.0 Hz), 8.92 (1H, s), 14.61 (1H, br s). The melting point and elemental analysis data are given in Table I.

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-7-(3-methylamino-1-pyrrolidinyl)-4-oxoquinoline-3-carboxylic Acid (18) A mixture of **11** (16.3 g, 40 mmol) and 3-(*N*-*tert*-butoxycarbonyl-*N*-methyl)aminopyrrolidine (16.0 g, 80 mmol) in dry acetonitrile (320 ml) was stirred at 60 °C for 15 h. The mixture was poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (eluent, CH_2Cl_2: MeOH=20:1) to give *tert*-butoxycarbonylamine compound, which was refluxed with 10% HCl (70 ml) for 30 min. The reaction mixture was concentrated, and the residue was recrystallized from MeOH to give **18** (5.3 g, 32%). NMR (DMSO-d_6) δ: 0.82—1.02 (2H, m), 1.13—1.38 (2H, m), 2.05—2.45 (2H, m), 2.62 (3H, s), 2.65 (3H, s), 3.42—3.95 (5H, m), 4.25—4.42 (1H, m), 7.76 (1H, d, J=13.4 Hz), 8.79 (1H, s), 9.33 (2H, br s), 15.01 (1H, s). The melting point and elemental analysis data are given in Table I.

Compounds (**19**—**26**) were obtained by the same procedure as described for **18**; the yield, melting point and elemental analysis data are listed in Table I.

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