

## Synthesis of Possible Metabolites of 1-Cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic Acid (Grepafloxacin, OPC-17116)

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**Grepafloxacin (1-cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, OPC-17116) (1) exhibits potent and broad-spectrum *in vitro* and *in vivo* antibacterial activity. In order to identify the structures of the metabolites of grepafloxacin, 17 possible metabolites were prepared. Among them, 6 compounds were found to be actual metabolites (2a, b, 4a, b and 6a, b) of grepafloxacin in rats, dogs and/or humans. The antibacterial activities of these metabolites were found to be weaker than that of grepafloxacin.**

**Key words** metabolite; grepafloxacin; quinolone carboxylic acid; 1-cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid; antibacterial activity; antibacterial agent

The quinolone carboxylic acid derivative ( $\pm$ )-1-cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (Grepafloxacin, OPC-17116) (1), a new antibacterial agent, was synthesized by Miyamoto and co-workers.<sup>1)</sup> Grepafloxacin (1) is characterized by possessing a methyl group at the C-5 position on the quinolone ring and exhibits potent antibacterial activity against gram-positive and gram-negative bacteria. It was found that 1 was distributed to various tissues, especially the lungs, in a pharmacokinetic study.<sup>2)</sup> The metabolism of quinolone carboxylic acids, nadifloxacin, ciprofloxacin, enoxacin and lomefloxacin, has been studied.<sup>3)</sup> In order to identify the metabolites of 1, 17 possible metabolites (2a, b, 3a—d, 4a, b, 5a, b, 6a, b, 7a—c and 8a, b) were synthesized (Fig. 1). These are the piperazine ring-cleaved products (2a, b, 3a—d and 4a, b),

the oxidized derivatives (5a, b and 6a, b) at the methyl group on the piperazine ring and the 5-methyl group on the quinolone ring, and others (7a—c and 8a, b). We wish to report here the synthesis of these compounds and the antibacterial activities of the actual metabolites (2a, b, 4a, b and 6a, b).<sup>2,4)</sup>

### Synthesis

Compounds 2a, b, 3a—d, 4a, b and 5a—c were synthesized as shown in Chart 1. Condensation of the borate complex 9<sup>5)</sup> with various amines in dimethyl sulfoxide (DMSO) afforded the corresponding 7-aminoquinoline derivatives 2a, b, 5a, c, 10 and 11. The 7-ethylenediamino derivative 2a hydrochloride was prepared by deprotection of the *N*-*tert*-butoxycarbonyl (Boc) group with 1 N HCl in EtOH in 66% yield from 9.

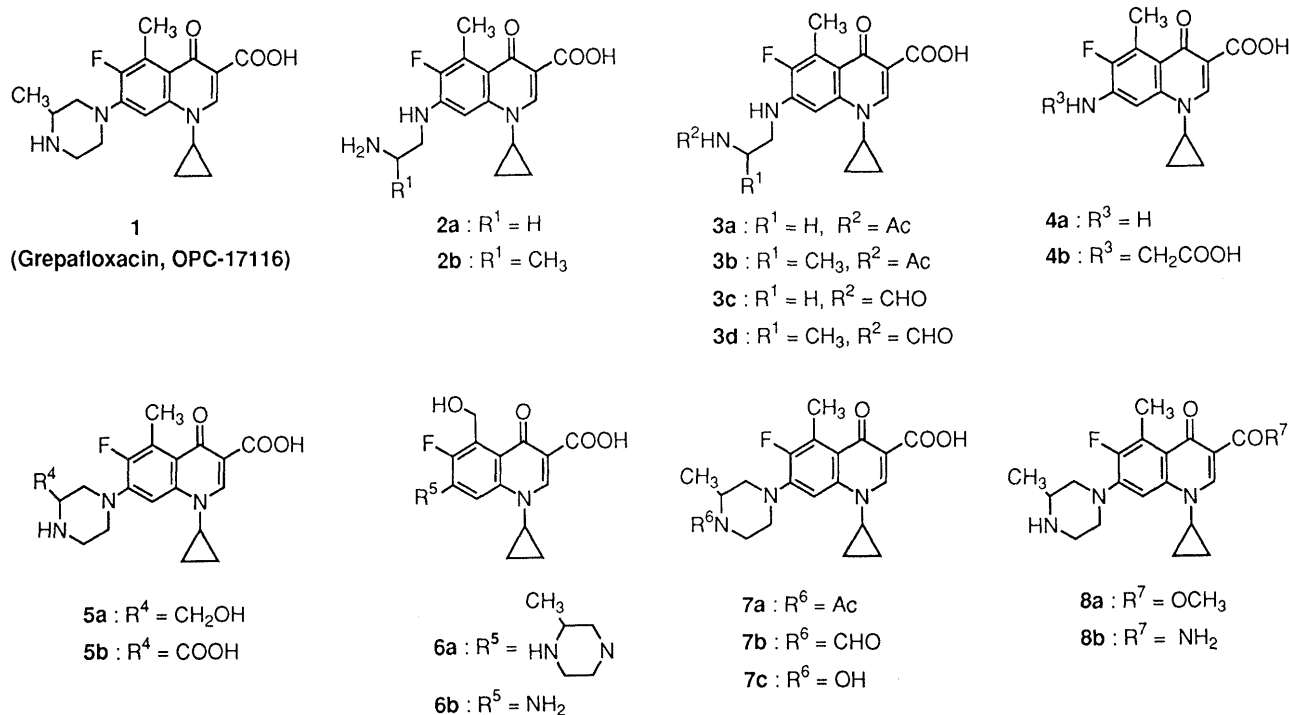


Fig. 1

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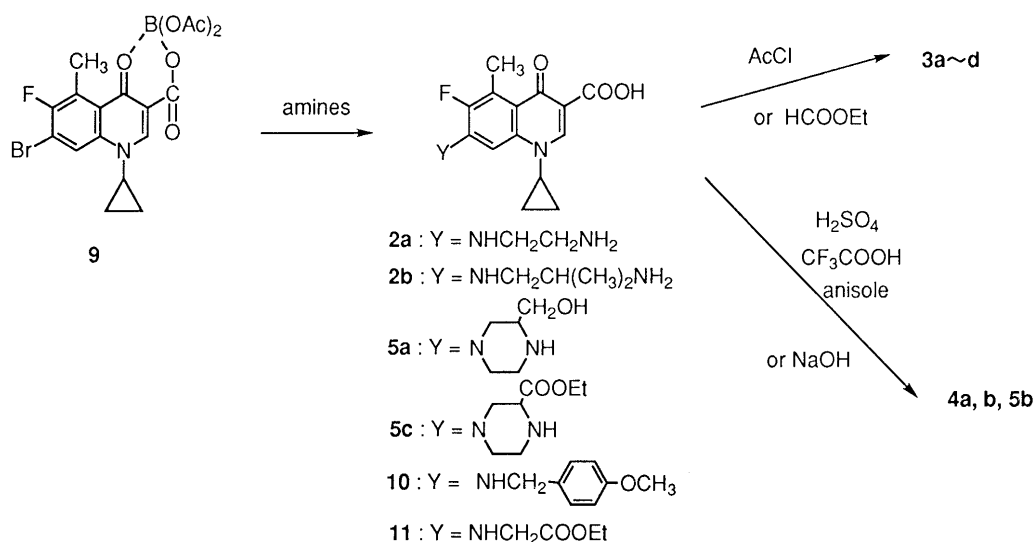
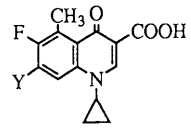


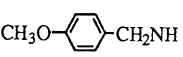


Chart 1

Table 1. Yields and Physical Data for 7-Substituted 1-Cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-4-oxo-3-quinolinecarboxylic Acids



Compd. No.	Y	Yield (%) <sup>a)</sup>	mp (°C)	Appearance (Recrystn. solv.)	Formula	Analysis (%)		
						Calcd	(Found)	
						C	H	N
2a · HCl	HCl · H <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> NH	66	289—291 (dec.)	Colorless needles (EtOH-H <sub>2</sub> O)	C <sub>16</sub> H <sub>18</sub> FN <sub>3</sub> O <sub>3</sub> · HCl · H <sub>2</sub> O	51.41 (51.74)	5.66 (5.67)	11.24 (11.31)
2a	H <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> NH	89	261—263 (dec.)	Pale yellow powder (DMF-H <sub>2</sub> O)	C <sub>16</sub> H <sub>18</sub> FN <sub>3</sub> O <sub>3</sub>	60.18 (59.82)	5.68 (5.72)	13.16 (13.04)
2b · HCl	HCl · H <sub>2</sub> NCH(CH <sub>3</sub> )CH <sub>2</sub> NH	36	298—299 (dec.)	Pale yellow needles (EtOH-H <sub>2</sub> O)	C <sub>17</sub> H <sub>20</sub> FN <sub>3</sub> O <sub>3</sub> · HCl	54.59 (54.43)	5.79 (5.76)	11.23 (11.18)
2b	H <sub>2</sub> NCH(CH <sub>3</sub> )CH <sub>2</sub> NH	91	238—239	White powder (EtOH)	C <sub>17</sub> H <sub>20</sub> FN <sub>3</sub> O <sub>3</sub>	57.45 (57.20)	6.37 (6.03)	11.82 (11.75)
						Water content 1.1% corrected		
5a <sup>b)</sup>		11	219—221	Yellow powder (MeOH)	C <sub>19</sub> H <sub>22</sub> FN <sub>3</sub> O <sub>4</sub> · 1/4H <sub>2</sub> O	60.07 (60.12)	5.97 (5.92)	11.06 (11.15)
5c <sup>b)</sup>		50		Yellow oil	C <sub>21</sub> H <sub>24</sub> FN <sub>3</sub> O <sub>5</sub>			
10		68	171—175	Yellow powder (MeOH)	C <sub>22</sub> H <sub>21</sub> FN <sub>2</sub> O <sub>4</sub>	66.66 (66.21)	5.34 (5.09)	7.07 (7.08)
11 <sup>c)</sup>	EtOOCCH <sub>2</sub> NH	35		Pale brown powder	C <sub>18</sub> H <sub>19</sub> FN <sub>2</sub> O <sub>5</sub>			

<sup>a)</sup> Isolated yield from **9**. <sup>b)</sup> These starting materials (2-hydroxymethylpiperazine and 2-ethoxycarbonylpiperazine) were prepared by the method described in reference 5. <sup>c)</sup> This **11** was used in the next step without further purification.

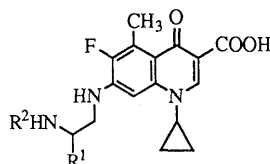
The desired compound **2a** was obtained by neutralization of the hydrochloride with sodium carbonate in water in 89% yield.

Acetylation of **2a** hydrochloride with acetyl chloride in the presence of 1 N NaOH in acetone gave the acetate **3a** in 22% yield. Formylation of **2a** hydrochloride with ethyl formate in the presence of triethylamine (Et<sub>3</sub>N) in *N,N*-dimethylformamide (DMF) afforded **3c** in 71% yield.

(2-Methyl)ethylenediamine series **3b** and **d** were also prepared by the same methods as described above.

Hydrolysis of **10** with concentrated sulfuric acid in the presence of trifluoroacetic acid in anisole afforded the 7-amino derivative **4a** in 51% yield. The carboxylic acid derivatives **4b** and **5b** were obtained by hydrolysis of the esters **11** and **5c** with NaOH in 12 and 45% overall yields from **9**, respectively.

Table 2. Yields and Physical Data for 7-Substituted Amino 1-Cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-4-oxo-3-quinolinecarboxylic Acids



Compd. No.	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	mp (°C)	Appearance (Recrystn. solv.)	Formula	Analysis (%)		
							Calcd	(Found)	
							C	H	N
<b>3a</b>	H	Ac	22	225—256	Colorless needles (EtOH)	C <sub>18</sub> H <sub>20</sub> FN <sub>3</sub> O <sub>4</sub> · 3/2H <sub>2</sub> O	55.66 (55.52)	5.97 (6.02)	10.82 (10.82)
<b>3b</b>	CH <sub>3</sub>	Ac	71	237—238	Pale yellow powder (MeOH-Et <sub>2</sub> O)	C <sub>19</sub> H <sub>22</sub> FN <sub>3</sub> O <sub>4</sub>	60.79 (60.65)	5.91 (6.04)	11.19 (11.20)
<b>3c</b>	H	CHO	71	286—289.5	Pale yellow needles (DMF-H <sub>2</sub> O)	C <sub>17</sub> H <sub>18</sub> FN <sub>3</sub> O <sub>4</sub>	58.78 (58.51)	5.22 (5.27)	12.10 (11.93)
<b>3d</b>	CH <sub>3</sub>	CHO	74	229—230.5	White powder (MeOH-Et <sub>2</sub> O)	C <sub>18</sub> H <sub>20</sub> FN <sub>3</sub> O <sub>4</sub>	59.83 (59.59)	5.58 (5.55)	11.63 (11.60)

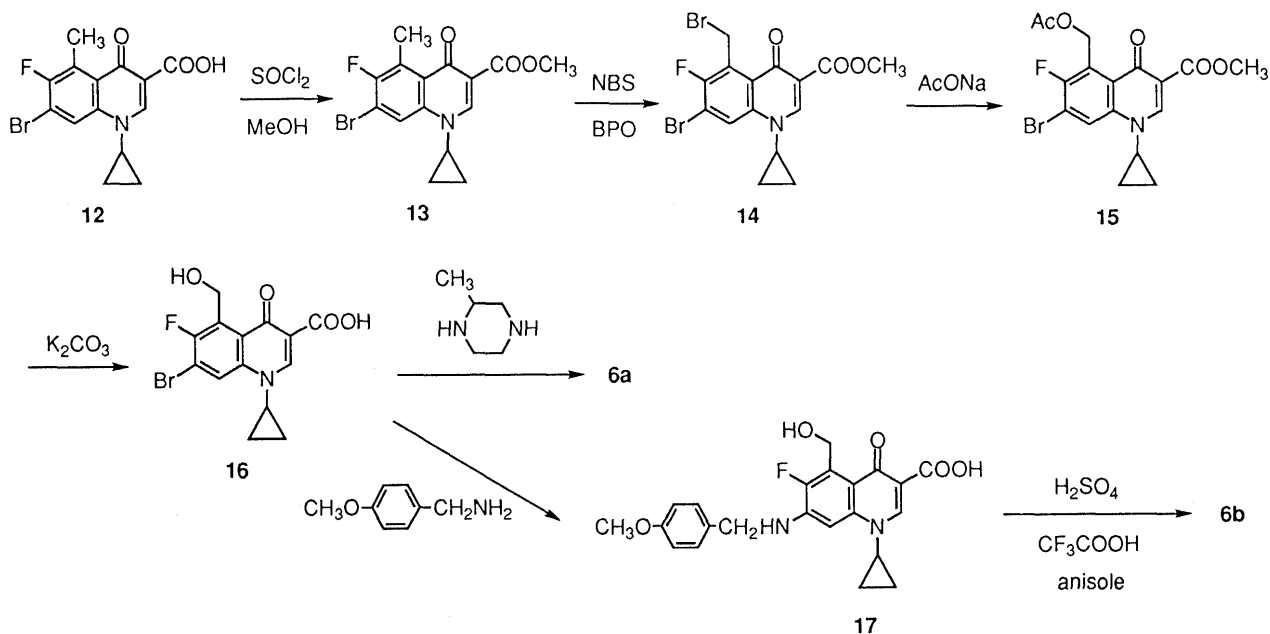


Chart 2

The synthetic route to the 5-hydroxymethyl quinolone derivatives **6a** and **b** is illustrated in Chart 2. The key intermediate **16** was prepared from **12**<sup>5)</sup> in four steps. Esterification of **12** with thionyl chloride-methanol afforded the methyl ester **13** in 97% yield, and this was reacted with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide (BPO) in carbon tetrachloride (CCl<sub>4</sub>) to give the 5-bromomethyl derivative **14** in 53% yield. Treatment of **14** with sodium acetate in DMF gave the 5-acetoxymethyl derivative **15** in 70% yield. This product was hydrolyzed with 10% aqueous potassium carbonate in MeOH to afford **16** in 94% yield. The target compound **6a** was prepared by condensation of **16** with 2-methylpiperazine in pyridine in 60% yield. Compound **6b** was synthesized from **16** by a procedure similar to that used for **4a**.

The syntheses of **7a, b** and **8a, b** were readily accomplished from the mother compound **1** hydrochloride as shown in Chart 3. The acetyl derivative **7a** and formyl

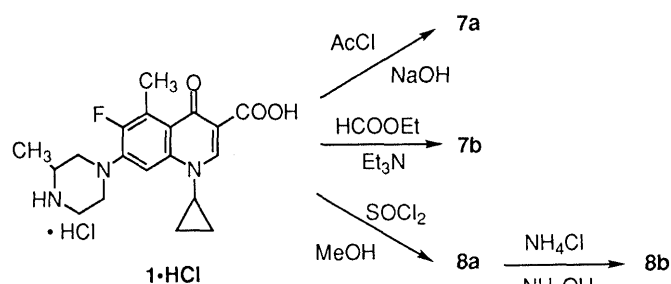


Chart 3

derivative **7b** were synthesized by procedures similar to that used for **3a** and **c**, respectively. The methyl ester **8a** was prepared by esterification of **1** hydrochloride with thionyl chloride-methanol in 77% yield, and the carboxamide **8b** was prepared by ammonolysis of **8a** with 28% ammonia solution in the presence of ammonium chloride in DMF in 55% yield.

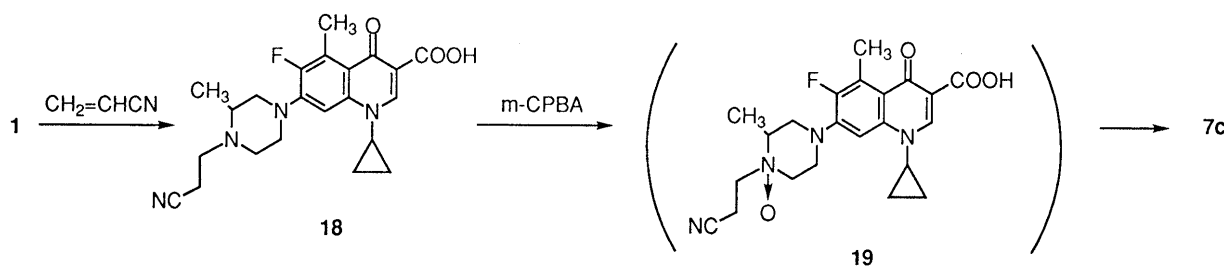


Chart 4

Preparation of 4-hydroxypiperazine derivative 7c is illustrated in Chart 4. Michael addition of 1 with acrylonitrile in CHCl<sub>3</sub> and MeOH provided the corresponding 4-(2-cyanoethyl)piperazine derivative 18 in 94% yield. Oxidation of 18 with *m*-chloroperbenzoic acid (*m*-CPBA) in CHCl<sub>3</sub> afforded the N-oxide 19, which spontaneously transformed to 7c in 54% yield by reverse Michael addition.<sup>3,4)</sup>

### Biological Results

The antibacterial activities against gram-positive and gram-negative bacteria were measured *in vitro* by the serial agar dilution method.<sup>7)</sup> The antibacterial activities of all actual metabolites 2a, b, 4a, b and 6a, b were found to be lower than that of 1.

### Conclusion

Among the 17 compounds prepared in this study, compounds 2a, b, 4a, b and 6a, b were found to be identical with the actual metabolites based on comparisons of the nuclear magnetic resonance (NMR) spectra, mass spectra (MS) and high-performance liquid chromatographic (HPLC) behavior. All the actual metabolites had very weak antibacterial activities. It is considered that the contribution of the metabolites to the activity of the mother compound 1 is small. The 4'-*O*-glucuronide of 7c was isolated from biological fluids of monkey and human.<sup>4)</sup> Therefore, 7c is presumed to be a metabolic intermediate though 7c itself was not found. The mother compound 1 was mainly metabolized at the methylpiperazine ring or the 5-methyl group on the quinoline ring. Compound 2 was the main metabolite in humans and the other metabolites were conjugated derivatives of 1.<sup>4)</sup>

### Experimental

Melting points were determined with a Yamato MP-21 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IR-810 spectrometer. NMR spectra were recorded on a Bruker AC-200 spectrometer. MS were obtained on a Shimadzu GCMS-QP-1000 instrument. Silica gel (Merck Art 7734) was used for column chromatography. Preparative thin layer chromatography (PLC) was carried out on plates (20 × 20 cm, 0.5 mm, thickness) precoated with silica gel (60F<sub>254</sub>, Merck Art 5744).

The yields, melting points and elemental analysis data of 2a, b·HCl, 2a, b, 5a, c, 10 and 11 are listed in Table 1. The <sup>1</sup>H-NMR, IR and MS data are listed in Table 3.

**7-[(2-Aminoethyl)amino]-1-cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-4-oxo-3-quinolinecarboxylic Acid (2a)** A Typical Procedure: A mixture of borate complex (9) (48.21 g, 103 mmol) and [*N*-(*tert*-butoxycarbonyl)amino]ethylamine<sup>8)</sup> (57.52 g, 359 mmol) in DMSO (635 ml) was stirred at 100–110 °C for 22 h. The reaction mixture was allowed to cool to 50 °C and poured into ice-water. The precipitated crystals were suspended in EtOH (700 ml) and water (200 ml), and 6N HCl (150 ml) was added dropwise to the suspension. The mixture was stirred at 70–75 °C for 2 h, then the solvent was evaporated off. The residue was

collected by filtration and washed with CH<sub>2</sub>Cl<sub>2</sub>. Recrystallization from EtOH–H<sub>2</sub>O gave 2a·HCl (48.10 g, 66%) as colorless needles, mp 289–291 °C (dec.). Sodium carbonate (0.24 g, 2.25 mmol) was added to a stirred solution of 2a·HCl (1.07 g, 3 mmol) in water (220 ml), and the mixture was stirred at room temperature for 2 h. The precipitated crystals were collected by filtration. Recrystallization from DMF–H<sub>2</sub>O gave 2a (0.85 g, 89%) as a pale yellow powder, mp 261–263 °C (dec.).

Compounds 2b·HCl, 2b, 5a, c, 6a, 10, 11 and 17 were obtained by a similar procedure to that described for 2a.

**6a:** 60% yield, pale yellow needles from EtOH–H<sub>2</sub>O, mp 155–157 °C. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 1.05 (3H, d, *J*=6.02 Hz), 1.10–1.45 (4H, m), 2.75–3.10 (5H, m), 3.45–3.70 (2H, m), 3.75–3.95 (1H, m), 4.82 (1H, t, *J*=6.60 Hz), 4.95–5.15 (2H, m), 7.55 (1H, d, *J*=7.98 Hz), 8.70 (1H, s). IR (KBr): 3400, 1619, 1579, 1466, 1294 cm<sup>-1</sup>. MS *m/z* (%): 375 (87, M<sup>+</sup>), 329 (89), 287 (58), 57 (59), 45 (54), 44 (100). Anal. Calcd for C<sub>19</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub>·3/2H<sub>2</sub>O: C, 56.71; H, 6.26; N, 10.44. Found: C, 56.72; H, 5.92; N, 10.40.

**17:** 41% yield, brown prisms from MeOH, mp 215–219 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.85–1.10 (2H, m), 1.10–1.25 (2H, m), 3.25–3.45 (1H, br), 3.81 (3H, s), 4.53 (2H, d, *J*=5.34 Hz), 5.30 (2H, s), 5.54 (1H, br s), 6.90 (2H, d, *J*=11.64 Hz), 6.91 (1H, d, *J*=8.02 Hz), 7.29 (2H, d, *J*=11.64 Hz), 8.71 (1H, s), 15.30 (1H, s). IR (KBr): 3430, 1718, 1630, 1523, 1458, 1383, 1325, 1302, 1246, 833 cm<sup>-1</sup>. MS *m/z* (%): 412 (10, M<sup>+</sup>), 366 (20), 311 (28), 309 (25), 277 (25), 231 (59), 121 (100). Anal. Calcd for C<sub>22</sub>H<sub>21</sub>FN<sub>2</sub>O<sub>4</sub>·1/2H<sub>2</sub>O: C, 62.70; H, 5.26; N, 6.65. Found: C, 62.91; H, 5.08; N, 6.65.

**7-[(2-Acetylamino)ethyl]amino]-1-cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-4-oxo-3-quinolinecarboxylic Acid (3a)** Acetyl chloride (55 mg, 0.7 mmol) was added dropwise to a stirred and ice-cooled solution of 2a·HCl (0.18 g, 0.5 mmol) in 1N NaOH (1.5 ml, 1.5 mmol), water (3 ml) and acetone (2 ml). The reaction mixture was stirred at 0 °C for 3 h and at room temperature for 3 h, then poured into 10% aqueous citric acid, and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were dried over MgSO<sub>4</sub>, and the solvent was evaporated off *in vacuo*. Recrystallization from EtOH gave 3a (40 mg, 22%) as colorless needles, mp 255–256 °C.

Compounds 3b and 7a were obtained by a similar procedure to that described for 3a.

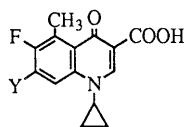
**7a:** 84% yield, a white powder from MeOH–Et<sub>2</sub>O, mp 235–237 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.10–1.25 (2H, m), 1.38 (3H, d, *J*=6.40 Hz), 1.40–1.60 (2H, m), 2.17 (3H, s), 2.82 (3H, d, *J*=3.08 Hz), 2.80–3.30 (3H, m), 3.40–4.20 (4H, m), 4.55–5.10 (1H, m), 7.28 (1H, d, *J*=7.44 Hz), 8.73 (1H, s), 15.55 (1H, s). IR (KBr): 3440, 1723, 1644, 1623, 1428, 1339, 1228 cm<sup>-1</sup>. MS *m/z* (%): 402 (41), 401 (44, M<sup>+</sup>), 41 (100), 355 (30), 221 (36), 70 (61), 43 (61), 42 (45), 41 (100). Anal. Calcd for C<sub>21</sub>H<sub>24</sub>FN<sub>3</sub>O<sub>4</sub>: C, 62.83; H, 6.03; N, 10.47. Found: C, 62.92; H, 6.05; N, 10.47.

**1-Cyclopropyl-1,4-dihydro-6-fluoro-7-[(2-formylamino)ethyl]amino]-5-methyl-4-oxo-3-quinolinecarboxylic Acid (3c)** Ethyl formate (6 ml) was added to a stirred solution of 2a·HCl (50 mg, 0.141 mmol) and Et<sub>3</sub>N (43 mg, 0.423 mmol) in DMF (3 ml), and the mixture was stirred at 70 °C for 6 h. The solvent was evaporated off and the residue was dissolved in CHCl<sub>3</sub>. The extracts were washed with 20% aqueous citric acid and water, and dried over MgSO<sub>4</sub>. After evaporation of the solvent, the residue was recrystallized from DMF–H<sub>2</sub>O to give 3c (35 mg, 71%) as pale yellow needles, mp 286–289.5 °C.

Compounds 3d and 7b were obtained by a similar procedure to that described for 3c.

**7b:** 73% yield, colorless needles from CH<sub>2</sub>Cl<sub>2</sub>–Et<sub>2</sub>O, mp 275–277 °C (dec.). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.10–1.30 (2H, m), 1.30–1.70 (2H, m), 2.85 (3H, d, *J*=3.24 Hz), 2.80–3.20 (2H, m), 3.30–4.10 (5H, m), 4.20–4.90 (1H, m), 7.28 (1H, d, *J*=7.26 Hz), 8.10 (0.45H, s) and 8.21 (0.55H, s), 8.76 (1H, s), 15.48 (1H, s). IR (KBr): 3450, 1722, 1675, 1621,

Table 3. Spectral Data for 7-Substituted 1-Cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-4-oxo-3-quinolinecarboxylic Acids



Compd. No.	Y	<sup>1</sup> H-NMR (solvent) $\delta$ ppm ( <i>J</i> in Hz)	IR (KBr) $\text{cm}^{-1}$	MS <i>m/z</i> (%)
2a · HCl	HCl · H <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> NH	(DMSO- <i>d</i> <sub>6</sub> ) 1.00—1.20 (2H, m), 1.30—1.50 (2H, m), 2.74 (3H, d, 3.04), 3.00—3.25 (2H, br), 3.50—3.70 (2H, m), 3.70—3.85 (1H, m), 7.00—7.20 (1H, br), 7.10 (1H, d, 7.82), 8.00 (3H, br s), 8.57 (1H, s), 16.06 (1H, s)	3422, 3284, 2990, 1680, 1621, 1526, 1468, 1313	319 (100, M <sup>+</sup> ), 276 (22), 275 (55), 273 (30), 245 (46), 220 (20)
2a	H <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> NH	(DMSO- <i>d</i> <sub>6</sub> ) 1.05—1.15 (2H, m), 1.25—1.40 (2H, m), 2.71 (3H, d, 3.04), 2.81 (2H, t, 6.70), 6.85—7.00 (1H, br), 7.07 (1H, d, 7.86), 8.53 (3H, s)	3342, 2975, 1628, 1567, 1515, 1365, 1304	319 (100, M <sup>+</sup> ), 289 (17), 275 (31), 273 (34), 272 (25), 245 (47), 243 (16), 216 (25)
2b · HCl	HCl · H <sub>2</sub> NCH(CH <sub>3</sub> )CH <sub>2</sub> NH	(DMSO- <i>d</i> <sub>6</sub> ) 1.05—1.20 (2H, m), 1.28 (3H, d, 5.72), 1.30—1.50 (2H, m), 2.74 (3H, d, 3.02), 3.40—3.70 (1H, m), 3.70—3.90 (1H, m), 7.12 (1H, d, 7.88), 7.14 (1H, br), 8.08 (3H, br), 8.57 (1H, s), 16.05 (1H, s)	1627, 1526, 1461, 1322, 1219	333 (9, M <sup>+</sup> ), 290 (17), 272 (18), 216 (13), 44 (100)
2b	H <sub>2</sub> NCH(CH <sub>3</sub> )CH <sub>2</sub> NH	(DMSO- <i>d</i> <sub>6</sub> ) 1.00—1.20 (5H, m), 1.25—1.40 (2H, m), 2.73 (3H, d, 2.94), 3.00—3.50 (5H, br), 3.60—3.80 (1H, br), 6.85—7.05 (1H, br), 7.06 (1H, d, 7.88), 8.54 (1H, s)	3562, 1627, 1586, 1515, 1310	333 (52, M <sup>+</sup> ), 290 (100), 272 (90), 271 (16), 245 (15), 244 (15), 243 (31), 217 (18), 216 (15)
5a <sup>a)</sup>		(DMSO- <i>d</i> <sub>6</sub> ) 1.00—1.25 (2H, m), 1.25—1.50 (2H, m), 2.50—3.10 (5H, m), 2.75 (3H, d, 3.22), 3.30—3.90 (5H, m), 4.72 (1H, t, 5.70), 7.45 (1H, d, 8.10), 8.62 (1H, s)	3310, 1728, 1628, 1512, 1462, 1379, 1270	375 (30, M <sup>+</sup> ), 344 (31), 303 (41), 259 (49), 163 (72), 47 (100), 44 (58), 43 (86)
5c <sup>a)</sup>		(CDCl <sub>3</sub> ) 1.00—1.25 (2H, m), 1.33 (3H, t, 7.14), 1.30—1.55 (2H, m), 2.76 (3H, d, 3.22), 3.00—3.60 (6H, m), 3.65—3.85 (2H, m), 4.26 (2H, q, 7.14), 7.34 (1H, d, 7.60), 8.68 (1H, s), 15.50—16.50 (1H, d, 7.58)		418 (35), 417 (100, M <sup>+</sup> ), 373 (28), 344 (83), 303 (56), 300 (38), 259 (92), 245 (33), 149 (29), 56 (78), 41 (43)
10		(DMSO- <i>d</i> <sub>6</sub> ) 0.85—1.10 (2H, m), 1.10—1.25 (2H, m), 2.82 (3H, d, 3.04), 3.15—3.35 (1H, m), 3.81 (3H, m), 4.49 (2H, d, 5.34), 5.15—5.35 (1H, m), 6.86 (1H, d, 7.50), 6.91 (2H, d, 8.72), 7.29 (2H, d, 8.72), 8.65 (1H, s), 16.00 (1H, s)	3430, 1718, 1630, 1523, 1458, 1302, 1246, 833	396 (13, M <sup>+</sup> ), 352 (9), 350 (8), 122 (10), 121 (100), 91 (9), 78 (10), 77 (10)
11 <sup>b)</sup>	EtOOCCH <sub>2</sub> NH	(CDCl <sub>3</sub> ) 1.10—1.25 (2H, m), 1.25—1.45 (5H, m), 2.84 (3H, d, 3.00), 3.35—3.60 (1H, m), 4.06 (2H, d, 5.24), 4.31 (2H, q, 7.14), 5.35—5.50 (1H, br), 6.86 (1H, d, 7.46), 8.72 (1H, s), 15.86 (1H, s)		

a) These starting materials (2-hydroxymethylpiperazine and 2-ethoxycarbonylpiperazine) were prepared by the method described in reference 6. b) This **11** was used in the next step without further purification.

1462, 1434, 1266  $\text{cm}^{-1}$ . MS *m/z* (%): 387 (100, M<sup>+</sup>), 343 (46), 341 (88), 70 (52), 44 (61), 42 (46), 41 (44). *Anal.* Calcd for C<sub>20</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub>: C, 62.01; H, 5.72; N, 10.85. Found: C, 61.69; H, 5.63; N, 10.87.

The yields, melting points and elemental analysis data of **3a**, **b**, **c** and **d** are listed in Table 2. The <sup>1</sup>H-NMR, IR and MS data are listed in Table 4.

**7-Amino-1-cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-4-oxo-3-quinolinecarboxylic Acid (4a)** Trifluoroacetic acid (5 ml) and concentrated H<sub>2</sub>SO<sub>4</sub> (0.5 ml) were added to a stirred suspension of **10** (80 mg, 0.2 mmol) in anisole (5 ml), and the mixture was stirred at 120 °C for 7 h. After evaporation of the trifluoroacetic acid, 10% aqueous KOH (10 ml) was added to the residue, and the whole was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The aqueous layer was separated, acidified by addition of concentrated HCl (10 ml), and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were dried over MgSO<sub>4</sub>, and concentrated to dryness *in vacuo*. The residue was recrystallized from DMF-H<sub>2</sub>O to give **4a** (28 mg, 51%) as a white powder, mp > 300 °C. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 1.05—1.20 (2H, m), 1.20—1.35 (2H, m), 2.72 (3H, d, *J* = 3.04 Hz), 3.55—3.75 (1H, m), 6.66 (1H, br s), 7.29 (1H, d, *J* = 8.10 Hz), 8.52 (1H, s), 16.13 (1H, s). IR (KBr): 3430, 3342, 1650, 1616, 1484, 1433, 1374  $\text{cm}^{-1}$ . MS *m/z* (%): 333 (52, M<sup>+</sup>), 290 (100), 272 (90), 271 (16), 245 (15), 244 (15), 243 (31), 217 (18), 216 (52). *Anal.* Calcd for C<sub>14</sub>H<sub>13</sub>FN<sub>2</sub>O<sub>3</sub>: C, 60.87; H, 4.74; N, 10.14. Found: C, 60.93; H, 4.65; N, 10.11.

Compound **6b** was obtained by a similar procedure to that described for **4a**.

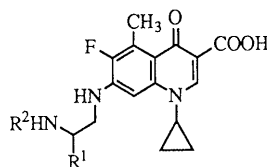
**6b**: 35% yield, a pale brown powder from DMF-H<sub>2</sub>O, mp

291—294 °C (dec.). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 1.05—1.45 (4H, m), 3.55—3.80 (1H, m), 4.75—5.00 (3H, br), 6.60—7.00 (2H, br), 7.40 (2H, d, *J* = 8.02 Hz), 8.59 (1H, s), 15.66 (1H, s). IR (KBr): 3346, 3232, 1732, 1655, 1624, 1474, 1458, 1334, 1024  $\text{cm}^{-1}$ . MS *m/z* (%): 292 (25, M<sup>+</sup>), 247 (16), 246 (100), 217 (10), 202 (10), 189 (17), 149 (11), 122 (14), 107 (12). *Anal.* Calcd for C<sub>14</sub>H<sub>13</sub>FN<sub>2</sub>O<sub>4</sub>: C, 57.53; H, 4.48; N, 9.58. Found: C, 57.22; H, 4.17; N, 9.44.

**7-[(Carboxymethyl)amino]-1-cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-4-oxo-3-quinolinecarboxylic Acid (4b)** A mixture of **11** (2.91 g, 8.3 mmol) and 5*N* NaOH (10 ml) in EtOH (30 ml) was gently refluxed with stirring for 3 h. After evaporation of the solvent, 10% aqueous citric acid (3 ml) was added to the residue, which was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were washed with water, dried over MgSO<sub>4</sub>, and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, eluent, CH<sub>2</sub>Cl<sub>2</sub>: MeOH: AcOH = 10: 1: 0.1) to give **4b** (0.96 g, 35%) as a pale yellow powder. Recrystallized from DMF-H<sub>2</sub>O as a pale yellow powder, mp 303—304 °C (dec.). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 1.10—1.20 (2H, m), 1.20—1.40 (2H, m), 2.74 (3H, d, *J* = 2.70 Hz), 3.65 (1H, br), 4.04 (1H, br s), 6.99 (1H, d, *J* = 7.88 Hz), 7.14 (1H, br), 8.54 (1H, s), 16.09 (1H, s). IR (KBr): 3460, 1738, 1622, 1526, 1462  $\text{cm}^{-1}$ . MS *m/z* (%): 334 (69, M<sup>+</sup>), 290 (64), 289 (28), 288 (100), 245 (29), 216 (32), 214 (22). *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>FN<sub>2</sub>O<sub>5</sub>: C, 57.49; H, 4.52; N, 8.38. Found: C, 57.26; H, 4.53; N, 8.26.

Compound **5b** was obtained by a similar procedure to that described for **4b**.

Table 4. Spectral Data for 7-Substituted Amino 1-Cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-4-oxo-3-quinolinecarboxylic Acids



Compd. No.	R <sup>1</sup>	R <sup>2</sup>	<sup>1</sup> H-NMR (solvent) δ ppm ( <i>J</i> in Hz)	IR (KBr) cm <sup>-1</sup>	MS <i>m/z</i> (%)
3a	H	Ac	(CDCl <sub>3</sub> ) 1.05—1.15 (2H, m), 1.35—1.55 (2H, m), 2.04 (3H, s), 2.81 (3H, d, <i>J</i> = 3.06), 3.49 (2H, t, 5.92), 3.57 (2H, t, 5.92), 5.30—5.50 (1H, br), 5.85—6.05 (1H, br), 7.11 (1H, d, 7.58), 8.69 (1H, s), 16.05 (1H, s)	3308, 1622, 1530, 1470, 1452, 1379, 1316	362 (41), 361 (100, M <sup>+</sup> ), 317 (58), 315 (63), 245 (93), 44 (49), 43 (57), 41 (55)
3b	CH <sub>3</sub>	Ac	(CDCl <sub>3</sub> ) 1.00—1.20 (2H, m), 1.31 (3H, d, 6.76), 1.40—1.50 (2H, m), 2.03 (3H, m), 2.81 (3H, d, 3.06), 3.10—3.30 (1H, m), 3.45—3.65 (2H, m), 4.20—4.40 (1H, m), 5.35—5.50 (1H, m), 5.56 (1H, d, 6.74), 7.23 (1H, d, 7.66), 8.68 (1H, s), 16.07 (1H, s)	3356, 1705, 1641, 1532, 1462	376 (30), 375 (88, M <sup>+</sup> ), 331 (32), 329 (26), 272 (37), 271 (60), 245 (46), 44 (100)
3c	H	CHO	(DMSO- <i>d</i> <sub>6</sub> ) δ: 1.05—1.25 (2H, m), 1.25—1.50 (2H, m), 2.73 (3H, d, 2.73), 3.00—3.50 (4H, m), 3.60—3.85 (1H, m), 7.09 (1H, br), 7.21 (1H, d, 7.92), 7.95 (1H, d, 1.62), 8.26 (1H, s), 8.55 (1H, s), 16.14 (1H, s)	3320, 1681, 1628, 1532, 1461, 1318	361 (100, M <sup>+</sup> ), 303 (64), 301 (73), 245 (82), 216 (25), 91 (35), 44 (57), 41 (52)
3d	CH <sub>3</sub>	CHO	(CDCl <sub>3</sub> ) 1.00—1.20 (2H, m), 1.31 (3H, d, 6.76), 1.40—1.50 (2H, m), 2.03 (3H, m), 2.81 (3H, d, 3.06), 3.10—3.30 (1H, m), 3.45—3.65 (2H, m), 4.20—4.40 (1H, m), 5.35—5.50 (1H, m), 5.56 (1H, d, 6.74), 7.23 (1H, d, 7.66), 8.68 (1H, s), 16.07 (1H, s)	3356, 1705, 1641, 1532, 1462	376 (30), 375 (88, M <sup>+</sup> ), 331 (32), 329 (26), 272 (37), 271 (60), 245 (46), 44 (100)

**5b:** 90% yield, a white powder from MeOH, mp 271—273 °C (dec.). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 1.05—1.20 (2H, m), 1.20—1.40 (2H, m), 2.76 (3H, d, *J* = 2.76 Hz), 2.70—4.00 (8H, m), 7.46 (1H, d, *J* = 7.96 Hz), 8.61 (1H, s). IR (KBr) 3445, 1739, 1622, 1564 cm<sup>-1</sup>. MS *m/z* (%): 358 (23, M<sup>+</sup>) 346 (31), 343 (56), 259 (43), 149 (21), 56 (58), 44 (100). Anal. Calcd for C<sub>19</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>5</sub> · 1/2H<sub>2</sub>O: C, 57.28; H, 5.31; N, 10.55. Found: C, 57.58; H, 5.01; N, 10.57.

**Methyl 7-Bromo-1-cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-4-oxo-3-quinolinecarboxylate (13)** Thionyl chloride (9.0 ml, 125 mmol) was added dropwise to a stirred and ice-cooled suspension of **12** (17.01 g, 50 mmol) in MeOH (200 ml), and the reaction mixture was refluxed with stirring for 4 h. After evaporation of the solvent, the residue was poured into ice-water. The precipitated crystals were collected by filtration. Recrystallization from CH<sub>2</sub>Cl<sub>2</sub>-MeOH gave **13** (17.15 g, 97%) as colorless needles, mp 244—246 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.05—1.20 (2H, m), 1.30—1.50 (2H, m), 2.89 (3H, d, *J* = 2.62 Hz), 3.30—3.45 (1H, m), 3.92 (3H, s), 8.03 (1H, d, *J* = 5.92 Hz), 8.52 (1H, s). IR (KBr) 1697, 1637, 1474, 1449, 1435, 1259, 1242 cm<sup>-1</sup>. MS *m/z* (%): 355 (48), 353 (47, M<sup>+</sup>), 295 (100), 294 (33), 293 (99), 267 (16), 265 (16), 145 (17). Anal. Calcd for C<sub>15</sub>H<sub>13</sub>BrFNO<sub>3</sub>: C, 50.87; H, 3.70; N, 3.95. Found: C, 50.56; H, 3.37; N, 3.91.

Compound **8a** was obtained by a similar procedure to that described for **13**.

**8a:** 77% yield, a white powder from MeOH-Et<sub>2</sub>O, mp 210—212 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.05—1.25 (2H, m), 1.19 (3H, d, *J* = 6.38 Hz), 1.25—1.45 (2H, m), 2.48 (1H, t, *J* = 10.30 Hz), 2.84 (3H, d, *J* = 3.23 Hz), 2.85—3.25 (4H, m), 3.30—3.45 (1H, m), 3.45—3.60 (2H, m), 3.92 (3H, s), 7.19 (1H, d, *J* = 7.63 Hz), 8.49 (1H, s). IR (KBr): 3450, 3314, 1727, 1632, 1478, 1272 cm<sup>-1</sup>. MS *m/z* (%): 373 (100, M<sup>+</sup>), 318 (21), 317 (100), 56 (16), 42 (25), 41 (21). Anal. Calcd for C<sub>20</sub>H<sub>24</sub>FN<sub>3</sub>O<sub>3</sub>: C, 64.33; H, 6.48; N, 11.25. Found: C, 63.87; H, 6.51; N, 11.19.

**Methyl 7-Bromo-5-bromomethyl-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-3-quinolinecarboxylate (14)** A mixture of **13** (11.73 g, 40 mmol), NBS (8.54 g, 48 mmol) and benzoyl peroxide (0.97 g, 4 mmol) in CCl<sub>4</sub> (400 ml) was refluxed for 6 h. After removal of the precipitates by filtration, the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, eluent, CH<sub>2</sub>Cl<sub>2</sub>: MeOH = 50:1) to give **14** (9.09 g, 53%) as a yellow powder. Recrystallized from CH<sub>2</sub>Cl<sub>2</sub> as colorless needles, mp 194—198 °C (dec.). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.05—1.20 (2H, m), 1.30—1.50 (2H, m), 3.35—3.50 (1H, m), 3.93 (3H, s), 5.50 (2H, d, *J* = 2.84 Hz), 8.21 (1H, d, *J* = 6.02 Hz), 8.56 (1H, s). IR (KBr): 1730, 1628, 1470, 1445, 1264 cm<sup>-1</sup>. MS *m/z* (%): 435 (26), 433 (53), 431 (26, M<sup>+</sup>), 375 (50), 373 (100), 371 (52), 353 (62), 351 (55), 145

(68), 82 (88), 81 (59), 80 (91). Anal. Calcd for C<sub>15</sub>H<sub>12</sub>Br<sub>2</sub>FNO<sub>3</sub>: C, 41.60; H, 2.79; N, 3.23. Found: C, 41.74; H, 2.76; N, 3.27.

**Methyl 5-Acetoxyethyl-7-bromo-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-3-quinolinecarboxylate (15)** A mixture of **14** (4.56 g, 12.2 mmol) and sodium acetate (2.00 g, 24.4 mmol) in DMF (50 ml) was stirred at 90 °C for 1.5 h. After evaporation of the solvent, the residue was poured into ice-water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were dried over MgSO<sub>4</sub> and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, eluent, CH<sub>2</sub>Cl<sub>2</sub>: MeOH = 50:1) to give **15** (3.50 g, 70%) as a pale brown powder. Recrystallization from MeOH as yellow needles, mp 224—227 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.10—1.20 (2H, m), 1.30—1.50 (2H, m), 2.06 (3H, s), 3.35—3.50 (1H, m), 3.91 (3H, s), 5.92 (2H, d, *J* = 2.86 Hz), 8.26 (1H, d, *J* = 5.94 Hz), 8.55 (1H, s). IR (KBr): 3670, 1736, 1624, 1474, 1444, 1268, 1246, 1230 cm<sup>-1</sup>. MS *m/z* (%): 413 (14), 411 (13, M<sup>+</sup>), 371 (28), 370 (58), 369 (57), 368 (54), 338 (98), 336 (100), 311 (33), 309 (35), 294 (10). Anal. Calcd for C<sub>17</sub>H<sub>15</sub>BrFNO<sub>5</sub>: C, 49.53; H, 3.67; N, 3.40. Found: C, 49.03; H, 3.33; N, 3.22.

**7-Bromo-1-cyclopropyl-1,4-dihydro-6-fluoro-5-hydroxymethyl-4-oxo-3-quinolinecarboxylic Acid (16)** A mixture of **15** (1.73 g, 4.2 mmol) and 10% aqueous K<sub>2</sub>CO<sub>3</sub> (18 ml) in MeOH (60 ml) was stirred at room temperature overnight. After evaporation of the solvent, the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were washed with 10% aqueous citric acid and water, and dried over MgSO<sub>4</sub>. The extracts were concentrated to dryness *in vacuo*, and the residue was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>-MeOH to give **16** (1.40 g, 94%) as colorless needles, mp 241—244 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.15—1.35 (2H, m), 1.45—1.60 (2H, m), 3.55—3.75 (1H, m), 4.60 (1H, t, *J* = 8.16 Hz), 5.10 (2H, dd, *J* = 2.44, 8.16 Hz), 8.40 (1H, d, *J* = 5.82 Hz), 8.94 (1H, s), 14.40 (1H, m). IR (KBr): 1736, 1618, 1514, 1439, 1329, 1029 cm<sup>-1</sup>. MS *m/z* (%): 357 (10), 355 (11, M<sup>+</sup>), 312 (16), 311 (99), 310 (22), 309 (100), 282 (11), 280 (12), 252 (10), 173 (14), 172 (12), 133 (10). Anal. Calcd for C<sub>14</sub>H<sub>11</sub>BrFNO<sub>4</sub>: C, 47.21; H, 3.11; N, 3.93. Found: C, 46.94; H, 3.11; N, 4.02.

**1-Cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxamide (8b)** A mixture of **8a** (0.11 g, 0.3 mmol), NH<sub>4</sub>Cl (19 mg, 0.36 mmol) and 25% aqueous NH<sub>4</sub>OH (2 ml) in DMF (2 ml) was stirred at 110 °C for 6 h in an autoclave tube. The reaction mixture was poured into ice-water. The resulting precipitates were collected by filtration and recrystallized from MeOH-Et<sub>2</sub>O to give **8b** (60 mg, 55%) as a pale yellow powder, mp 213—214 °C. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 0.95—1.20 (2H, m), 1.03 (3H, d, *J* = 6.20 Hz), 1.20—1.40 (2H, m), 2.03—2.65 (1H, m), 2.74 (3H, d, *J* = 3.04 Hz), 2.70—3.15 (4H,

m), 3.35—3.60 (2H, m), 3.60—3.80 (1H, m), 7.35 (1H, d,  $J=8.20$  Hz), 7.38 (1H, br s), 8.57 (1H, s), 9.29 (1H, d,  $J=3.00$  Hz). IR (KBr): 3450, 3314, 1727, 1632, 1478, 1272  $\text{cm}^{-1}$ . MS  $m/z$  (%): 358 (23,  $M^+$ ), 303 (21), 302 (100), 70 (11). Anal. Calcd for  $\text{C}_{19}\text{H}_{23}\text{FN}_4\text{O}_2 \cdot \text{H}_2\text{O}$ : C, 60.62; H, 6.69; N, 14.88. Found: C, 60.70; H, 6.51; N, 14.97.

**7-[4-(2-Cyanoethyl)-3-methyl-1-piperazinyl]-1-cyclopropyl-1,4-dihydro-6-fluoro-5-methyl-4-oxo-3-quinolinecarboxylic Acid (18)** A mixture of **1** (0.54 g, 1.5 mmol) and acrylonitrile (0.79 ml, 12 mmol) in  $\text{CHCl}_3$  (5 ml) and MeOH (5 ml) was refluxed with stirring for 20 h. The mixture was concentrated to give a white solid, which was collected by filtration and washed with MeOH. The solid was recrystallized from DMF– $\text{H}_2\text{O}$  to give **18** (0.58 g, 94%) as a white powder. mp 197—198 °C.  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ )  $\delta$ : 1.10 (3H, d,  $J=5.78$  Hz), 1.00—1.25 (2H, m), 1.25—1.45 (2H, m), 2.50—3.30 (9H, m), 2.75 (3H, d,  $J=2.77$  Hz), 3.40—3.60 (2H, m), 3.70—3.90 (1H, m), 7.46 (1H, d,  $J=8.04$  Hz), 8.63 (1H, s), 15.69 (1H, s). MS  $m/z$  (%): 413 (26), 412 (100,  $M^+$ ), 372 (26), 368 (34), 366 (39), 303 (69), 259 (41), 242 (21), 109 (34), 84 (47), 71 (33), 70 (26). Anal. Calcd for  $\text{C}_{22}\text{H}_{25}\text{FN}_3\text{O}_4$ : C, 64.66; H, 6.11; N, 13.58. Found: C, 64.07; H, 5.97; N, 13.58

**1-Cyclopropyl-1,4-dihydro-6-fluoro-7-(4-hydroxy-3-methyl-1-piperazinyl)-5-methyl-4-oxo-3-quinolinecarboxylic Acid (7c)** *m*-Chloroperbenzoic acid (80%, 55 mg, 0.255 mmol) was added to a stirred solution of **18** in  $\text{CHCl}_3$  (10 ml) at 0 °C. The reaction mixture was stirred at room temperature, and the solvent was evaporated off. The residue was purified by column chromatography (silica gel, eluent,  $\text{CH}_2\text{Cl}_2$ :MeOH=30:1) to give **7c** (30 mg, 53%) as a white powder. Recrystallized from  $\text{CH}_2\text{Cl}_2$ –MeOH as a white powder, mp 205—207 °C.  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ )  $\delta$ : 1.11 (3H, d,  $J=5.50$  Hz), 1.10—1.40 (4H, m), 2.50—2.90 (2H, m), 2.76 (3H, d,  $J=3.14$  Hz), 3.00—3.50 (4H, m), 3.60—3.90 (2H, m), 7.45 (1H, d,  $J=7.96$  Hz), 8.17 (1H, s), 8.63 (1H, s), 15.70 (1H, s). IR (KBr): 3420, 1705, 1618, 1512, 1450, 1379, 1260  $\text{cm}^{-1}$ . MS  $m/z$  (%): 375

(35,  $M^+$ ), 359 (45), 316 (93), 303 (82), 259 (100), 70 (93), 44 (76). Anal. Calcd for  $\text{C}_{19}\text{H}_{22}\text{FN}_3\text{O}_4$ : C, 60.79; H, 5.91; N, 11.19. Found: C, 60.68; H, 6.07; N, 11.12.

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