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Pyrroloquinolones and pyrazoloquinolones as potential antibacterial agents. Synthesis and antibacterial activity *

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Summary — Diethyl 1-cyclopropyl-5,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3,6-dicarboxylate **4** as a key-intermediate was synthesized via the Dieckmann reaction. The reaction of **4** with nucleophiles proceeded regioselectively at C-5. Facile cyclization between the C-5 and C-6 side chains of the resulting products gave novel pyrroloquinolones **10** and **12** and pyrazoloquinolones **15**. They were converted into a series of cyclic amino-substituted pyrroloquinolones **17–21** and pyrazoloquinolones **22–24**, and their in vitro antibacterial activities were tested. 1*H*-Pyrrolo[2,3-*f*]quinolone **17a** and 2*H*-pyrrolo[3,4-*f*]quinolone **21a** exhibited a potent in vitro antibacterial activity.

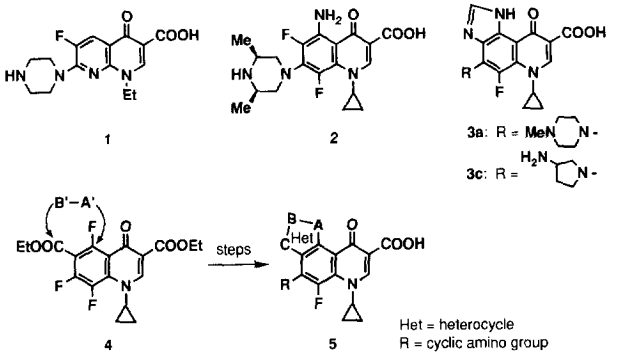
quinolone / 1*H*-pyrrolo[2,3-*f*]quinolone / 2*H*-pyrrolo[3,4-*f*]quinolone / 1*H*-pyrazolo[3,4-*f*]quinolone / antibacterial activity

Introduction

A class of synthetic quinolone antibacterial agents is widely utilized for chemotherapy against bacterial infectious diseases, inhibiting bacterial DNA topoisomerase II (DNA gyrase) and IV [3], and thereby killing bacteria. Most of newer quinolones are those of fluorinated 4-oxo-1,8-naphthyridine-3-carboxylic acids (eg, enoxacin **1** [4, 5]) and 4-oxoquinoline-3-carboxylic acids (eg, sparfloxacin **2** [6]); these possess a fluorine atom at C-6 and a cyclic amino group at C-7 of the bicyclic heterocycle. Their potent antibacterial activity with a broad antibacterial spectrum has provoked the interest of many medicinal chemists [7].

In our previous paper [2], we reported the synthesis and antibacterial activity of quinolones **3a,c** without a fluorine atom at C-6 of their quinoline rings [8, 9]. These compounds exhibited a potent in vitro activity. Their oral efficacies, however, were less than those expected from their in vitro activity, mainly because of poor absorption from animal digestive tracts.

To examine the activity of compounds replaced with a different heterocycle instead of the imidazole ring of



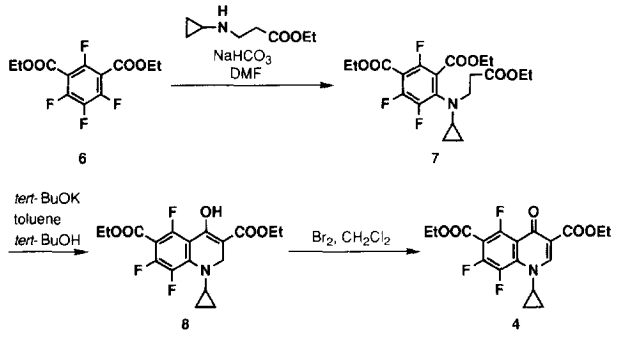
3a,c, a new type of tricyclic quinolone derivative represented by the general structure **5** was synthesized, in which components A and B represent an appropriately substituted nitrogen or carbon. This paper describes the synthesis and the structure–antibacterial activity relationships of compounds **5**.

Chemistry

Compounds **5** were thought to be accessible from quinolone-3,6-dicarboxylate **4** as a common key intermediate because of the following reason. The C-5

* This paper is part 18 in a series *Pyridone carboxylic acids as antibacterial agents*. For part 17 see reference [1], for part 16 see reference [2].

fluorine of 5,6,7,8-tetrafluoroquinolone-3-carboxylate is known to be the most reactive against a nucleophilic attack of primary or secondary amines in an aprotic solvent [6, 10]. Accordingly, the substitution would proceed predominantly at C-5 of **4** on treatment with nucleophiles. Thus, the nucleophilic attack of a group A' to C-5 of **4** and subsequent cyclization would proceed and form the five-membered heterocycle represented as 'Het' in the general structure **5**. To the best of our knowledge, this type of method for formation of these heterocycles has not been studied.

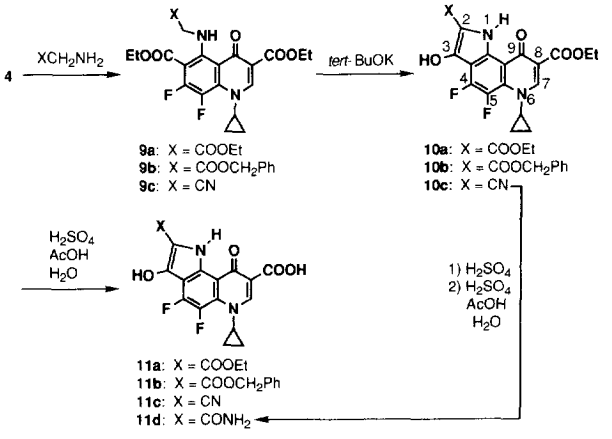


Scheme 1.

The intermediate **4** was derived from diethyl 2,4,5,6-tetrafluoroisophthalate **6** via three steps (scheme 1). Ethyl 3-(cyclopropylamino)propionate was regioselectively introduced to C-4 of **6**, giving the triester **7**. The structure of **7** was confirmed by its ^{19}F-NMR spectrum, which showed three double doublet peaks at −149.95, −132.78 and −117.86 ppm due to three unequivalent fluorines of **7**. The Dieckmann reaction of **7** proceeded successfully with potassium *tert*-butoxide as a non-nucleophilic base in a mixture of *tert*-butanol and toluene to give 2,3-dihydroquinoline **8** in 84% yield through two steps from **6**. Oxidation of **8** was achieved by bromine and gave the quinolone **4** in 65% yield.

In the field of antibacterial quinolone chemistry, the Dieckmann reaction has been adopted thus far in the synthesis of naphthyridones such as nalidixic acid [11], enoxacin **1** [5], and enoxacin-related compounds [12]. Simple non-fluorinated quinolones have also been prepared by the Dieckmann reaction followed by the electrooxidation [13]. The synthesis of **4** is the first example of an application of the Dieckmann reaction to a synthesis of fluorinated quinolones.

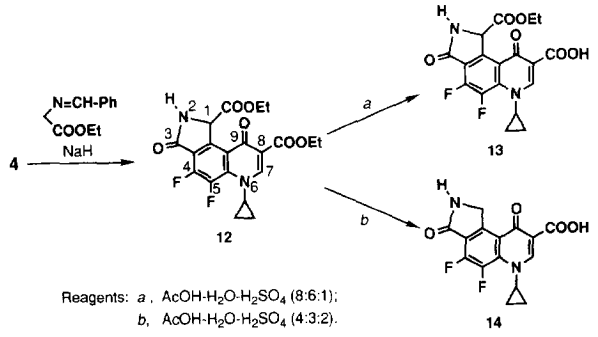
1*H*-Pyrrolo[2,3-*f*]quinolones **11a–d** were prepared by the route shown in scheme 2. As expected, the regioselective substitution proceeded predominantly at the C-5 position on treating with **4** with ethyl and benzyl esters of glycine and aminoacetonitrile in chloroform or toluene and gave **9a,b,c**, respectively, in high yields. The assigned structures of **9a,b,c** were confirmed by their ^{19}F-NMR spectra; the coupling constants between two fluorines of **9a,b,c** are 21.9, 22.1 and 21.6 Hz, respectively, which lie in the general range for fluorine–fluorine *ortho*-coupling constants (*ortho*-, *meta*-, and *para*-coupling constants betwen two fluorines are generally 19–23, 0–11 and 5–9 Hz, respectively [14]). The compounds **9a,b,c** were then treated with potassium *tert*-butoxide, thus giving the corresponding 1*H*-pyrrolo[2,3-*f*]quinolones **10a,b,c**. The conversion of the esters **10a,b,c** to the carboxylic acids **11a,b,c** proceeded in high yields by acidic hydrolysis. During these reaction processes, the ester or nitrile group at C-2 of **10a,b,c** remained unchanged. The nitrile moiety of the cyanoester **10c** was hydrolyzed to the amide group with concentrated sulfuric acid and its ester moiety was subsequently hydrolyzed on heating in an equivolume mixture of acetic acid, water, and concentrated sulfuric acid to give **11d** in 80% yield.



Scheme 2.

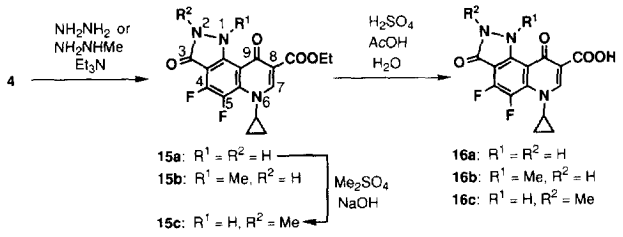
2*H*-Pyrrolo[3,4-*f*]quinolones **13** and **14** were synthesized according to the route shown in scheme 3. The reaction of **4** with the carbanion generated from *N*-benzylidene glycine ethyl ester in toluene at room temperature gave the lactam **12** as expected. This reaction involves the regioselective attack of the carbanion to C-5 of **4**, followed by elimination of the benzylidene protective group and subsequent cyclization, or vice versa. The assigned structure of **12** was supported by ^{19}F-NMR spectrum ($J_{4F\text{-}5F}$ = 18.5 Hz) [14]. The hydrolysis of the diester **12** gave the carboxylic acid **13** or **14** depending on the amount of sulfuric acid in the reaction medium consisting of a mixture of sulfuric acid, acetic acid, and water.

1*H*-Pyrazolo[3,4-*f*]quinolones **16a–c** were prepared by the route shown in scheme 4. The treatment of **4** with hydrazine and methylhydrazine gave 1*H*-pyrazolo[3,4-*f*]quinolones **15a** and **15b** in 99 and 79%



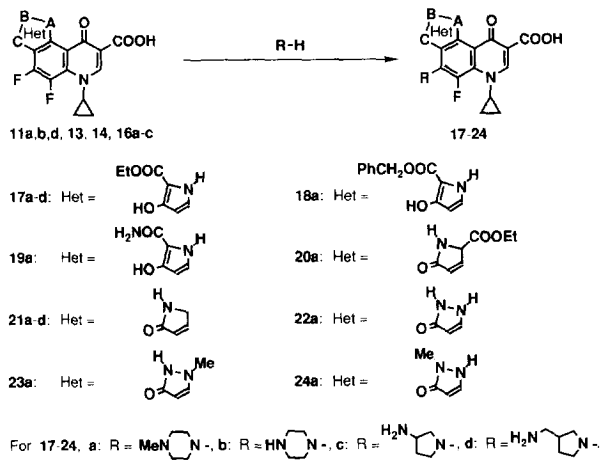
Scheme 3.

yields, respectively. The coupling constants between two fluorines of **15a,b** supported that hydrazines attacked preferentially the C-5 position of **4** (**15a**: $J_{4F\text{-}5F}$ = 20.2 Hz; **15b**: $J_{4F\text{-}5F}$ = 21.3 Hz) [14]. The 2-methyl derivative **15c**, an isomer of **15b**, was obtained in 41% yield by methylation of **15a** with dimethyl sulfate. The ^{1}H-NMR signals due to the methyl groups of **15b,c** were observed at δ 3.96 and 3.45 ppm, respectively, supporting the positions of the methyl groups. (The chemical shifts are well in accordance with the literature data for the methyl groups of more simple pyrazole derivatives; the methyl proton at N-1 of 3-hydroxy-1,5-dimethylpyrazole (model compound for the enol form of **15b**) appeared at δ 3.57 ppm and the methyl proton at N-1 of 1,2,3-trimethylpyrazolin-5-one (model compound for **15c**) appeared at δ 3.21 ppm in their ^{1}H-NMR spectra [15]). 1*H*-Pyrazolo[3,4-*f*]-quinolones **15a–c** were converted by the conventional hydrolysis to the corresponding carboxylic acids **16a–c** in almost quantitative yields.



Scheme 4.

The representative cyclic amines were introduced to C-4 of the tricyclic compounds **11a,b,d, 13, 14**, and **16a–c** in refluxed acetonitrile or heated pyridine to give **17–24** (scheme 5 and table I). The reaction of the cyanocarboxylic acid **11c** with *N*-methylpiperazine resulted in decomposition.



Scheme 5.

Table I. Physical data for the 4,5-disubstituted pyrrolo- and pyrazoloquinolones.

Compound[a]	*Mp (°C) (recrystallization solvent)*	*Yield (%)*	*Formula*
17a	266–267 dec (CHCl$_3$/EtOH)	74	$C_{23}H_{25}FN_4O_6$
17b	202–203 dec (AcOH/NH$_4$OH)	45	$C_{22}H_{23}FN_4O_6 \cdot 1/4H_2O$
17c	215–217 dec (CHCl$_3$/EtOH)	69	$C_{22}H_{23}FN_4O_6 \cdot 1/4H_2O$
17d	222–224 dec (AcOH/NH$_4$OH)	70	$C_{23}H_{25}FN_4O_6 \cdot 1/4H_2O$
18a	257–259 dec (CHCl$_3$/EtOH)	33	$C_{28}H_{27}FN_4O_6$
19a	230–233 dec (DMF/EtOH)	37	$C_{21}H_{22}FN_5O_5 \cdot 3/4H_2O$
20a	271–272 dec (CH_2Cl_2/EtOH)	46	$C_{23}H_{25}FN_4O_6$
21a	284–285 dec (CHCl$_3$/EtOH)	82	$C_{20}H_{21}FN_4O_4$
21b	> 300 dec (AcOH/EtOH)	61	$C_{19}H_{19}FN_4O_4 \cdot H_2O$
21c	255–258 dec (AcOH/NH$_4$OH)	18	$C_{19}H_{19}FN_4O_4 \cdot H_2O$
21d	270–275 dec (AcOH/NH$_4$OH)	45	$C_{20}H_{21}FN_4O_4 \cdot 1/2H_2O$
22a	297–299 dec (CHCl$_3$/EtOH)	26	$C_{19}H_{20}FN_5O_4 \cdot 1/4H_2O$
23a	> 300 dec (DMF/EtOH)	64	$C_{20}H_{22}FN_5O_4$
24a	280–295 dec (EtOH/*i*-Pr$_2$O)	20	$C_{20}H_{22}FN_5O_4$

[a]Compounds **17b,d**, **21c**, and **21d** were purified by reprecipitation, by treating with an acid and subsequently with a base or vice versa.

Pharmacology

The in vitro antibacterial activity of compounds **17–24** was tested against one Gram-positive (*Staphylococcus aureus* 209P JC-1) and two Gram-negative bacteria (*Escherichia coli* NIHJ JC-2 and *Pseudomonas aeruginosa* 12) as representatives. The results are summarized in table II, which includes data for enoxacin **1**, sparfloxacin **2** and **3a,c** for comparison.

Biological results and discussion

First we compared the antibacterial activity of the 4-methyl-1-piperazinyl derivatives (series **a**) of **17–24**. Ethoxycarbonyl compound **17a** was two- to fourfold more potent against three bacteria than the more bulky benzyloxycarbonyl compound **18a**. Carbamoyl compound **19a** was still less potent than benzyloxycarbonyl compound **18a**. In respect of 2*H*-pyrrolo[3,4-*f*]quinolones **20a** and **21a**, removal of the ethoxycarbonyl group at C-1 of **20a** (giving **21a**) enhanced activity four to eight times. Introduction of a methyl substituent to C-1 or C-2 of 1*H*-pyrazolo[3,4-*f*]quinolone **22a**, giving **23a** or **24a**, resulted in deteriorating activity. The results, expect for the activity of **19a**, suggest that the presence of bulky substituents at the position 1 or 2 on the newly formed heterocycles causes a decrease in activity.

Among the series **a** of **17–24**, 1*H*-pyrrolo[2,3-*f*]-quinolone **17a** and 2*H*-pyrrolo[3,4-*f*]quinolone **21a** were relatively potent. Although **17a** and **21a** were two- to eight fold less potent than **3a,c**, their activity was comparable to that of enoxacin **1**. 1*H*-Pyrrolo[2,3-*f*]-quinoline-8-carboxylic acids **17** and 2*H*-pyrrolo[3,4-*f*]-quinoline-8-carboxylic acids **21** were therefore thought to be nuclei favorable for further modification of the substituents on them.

For a further study on the structure–activity relationships, the 4-methyl-1-piperazinyl groups of **17a** and **21a** were replaced with 1-piperazinyl (**17b** and **21b**), 3-amino-1-pyrrolidinyl (**17c** and **21c**), and 3-aminomethyl-1-pyrrolidinyl groups (**17d** and **21d**, respectively) and the antibacterial activities of the resultant compounds were examined. Among 1*H*-pyrrolo[2,3-*f*]quinolones **17a–d**, the activity against the three bacteria decreased in the order of 4-methyl-1-piperazinyl (**17a**) ≥ 1-piperazinyl (**17b**) > 3-amino-1-pyrrolidinyl (**17c**) ≥ 3-aminomethyl-1-pyrrolidinyl (**17d**) derivatives. Of the 2*H*-pyrrolo[3,4-*f*]quinolones **21a–d**, the activity against Gram-negative bacteria was in a similar decreasing order to that as in **17a–d**, whereas the activity against Gram-positive bacteria was arranged in the decreasing order of 4-methyl-1-piperazinyl (**21a**) = 3-aminomethyl-1-pyrrolidinyl (**21d**) > 1-piperazinyl (**21b**) = 3-amino-1-pyrrolidinyl (**21c**) derivatives. As a result, the exchange of the 4-methyl-1-piperazinyl groups of **17a** and **21a** for other cyclic amino groups (yielding **17b–d** and **21b–d**, respectively) caused a decrease in in vitro activity.

Conclusion

We developed a novel method for construction of the heterocycles fused to a quinolone ring; the method involves the regioselective substitution of the C-5 fluorine of quinolone **4** with several carbon- or nitrogen-nucleophiles. 1*H*-Pyrrolo[2,3-*f*]quinolones **17–19**, 2*H*-pyrrolo[3,4-*f*]quinolones **20a** and **21a–d**, and 1*H*-pyrazolo[3,4-*f*]quinolones **22a–24a** were prepared by this method. Among **17–24**, compounds **17a** and **21a** were roughly equipotent to enoxacin **1** but did not exceed the 1*H*-imidazo[4,5-*f*]quinolones **3a,c** in in vitro antibacterial activity.

Experimental protocols

Chemistry

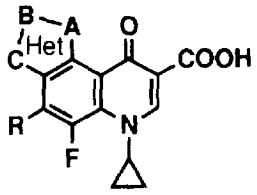
All melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Jasco A-102 or Perkin Elmer 1600 Series FTIR spectrophotometer. ^{1}H-NMR spectra were taken at 80 MHz on a Varian FT-80A spectrometer unless otherwise indicated, at 200 MHz on a Varian Gemini-200 spectrometer, or 300 MHz on a Varian XL-300 spectrometer. Chemical shifts are expressed in ppm (δ) with tetramethylsilane as an internal standard. ^{19}F-NMR spectra were measured at 282 MHz with a Varian XL-300 spectrometer; chemical shifts are expressed in ppm (δ) with hexafluorobenzene (δ = −162.9) as an internal standard. Electron-impact (EI) and atmospheric pressure chemical ionization (APCI) mass spectra were obtained on a Jeol JMS D-300 and Hitachi M-1000 LC API mass spectrometer, respectively. The spectral data for all compounds were consistent with assigned structures.

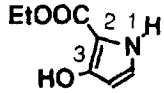
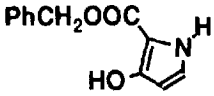
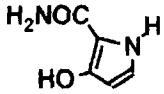
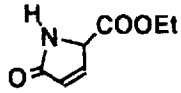
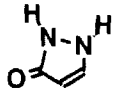
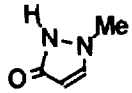
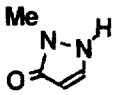
Piperazine, 1-methylpiperazine, and 3-aminopyrrolidine were purchased from commercial suppliers. 3-Aminomethylpyrrolidine was prepared by reduction of the nitrile group of 1-benzyl-3-cyanopyrrolidine [16] with hydrogen over Raney Ni, followed by deprotection of the benzyl group by hydrogenolysis over 5% Pd-C.

Diethyl 4-[N-cyclopropyl-N-(2-ethoxycarbonyl-1-ethyl)]amino-2,5,6-trifluoroisophthalate 7

A mixture of diethyl 2,4,5,6-tetrafluoroisophthalate **6** [17] (234 g, 0.795 mol), ethyl 3-(cyclopropylamino)propionate [12] (250 g, 1.59 mol), $NaHCO_3$ (134 g, 1.59 mol), and *N,N*-dimethylformamide (DMF) (900 mL) was heated at 110 °C for 3 h. The mixture was cooled, treated with charcoal, and then filtered. The filtrate was concentrated in vacuo to leave a crude product, which was taken up with dilute AcOH and extracted with toluene. The organic layer was washed successively with dilute AcOH, water, and brine and then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave 341 g (quantitative yield) of **7** as an oil. IR (neat) cm^{-1}: 1730, 1630. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.45–0.55, 0.60–0.70 (both 2H,

Table II. Antibacterial activity of the 4,5-disubstituted pyrrolo- and pyrazoloquinolones.



Compound	*Het*	*R*[a]	*Minimum inhibitory concentration*[b] *(μg/mL)*		
			S aureus 209P JC-1	*E coli NIHJ JC-2*	*P aeruginosa 12*
17a		a	0.39	0.2	1.56
17b		b	0.78	0.2	3.13
17c		c	1.56	1.56	25
17d		d	1.56	6.25	100
18a		a	1.56	0.78	3.13
19a		a	3.13	1.56	25
20a		a	1.56	0.39	3.13
21a		a	0.39	0.05	0.78
21b		b	1.56	0.39	12.5
21c		c	1.56	0.39	25
21d		d	0.39	1.56	50
22a		a	1.56	0.39	1.56
23a		a	6.25	0.39	6.25
24a		a	1.25	1.56	6.25
3a		a	0.2	0.05	0.2
3c		c	0.05	0.025	0.2
1	Enoxacin		0.78	0.2	0.78
2	Sparfloxacin		0.05	0.0125	0.39

[a] a = MeN⟨⟩N-, b = HN⟨⟩N-, c = H_2N⟨⟩N-, d = H_2N⟨⟩N-. [b] See *Experimental protocols.*

m, cyclopropyl CH_2CH_2), 1.22, 1.36, 1.38 (each 3H, t, J = 7.0 Hz, 3 x CH_2CH_3), 2.64 (2H, t, J = 7.0 Hz, NCH_2CH_2CO), 2.65–2.75 (1H, m, cyclopropyl CH), 3.59 (2H, t, J = 7.0 Hz, NCH_2CH_2CO), 4.11, 4.34, 4.40 (each 2H, q, J = 7.0 Hz, 3 x CH_2CH_3). ^{19}F-NMR ($CDCl_3$) δ: –149.95 (1F, br dd, J_{2F-5F} = 12.1, J_{5F-6F} = 19.9 Hz, 5-F), –132.78 (1F, dd, J_{2F-6F} = 0.8, J_{5F-6F} = 19.9 Hz, 6-F), –117.86 (1F, dd, J_{2F-6F} = 0.8, J_{2F-5F} = 12.1 Hz, 2-F). EIMS *m/z*: 431 (M+), 402, 386.

Diethyl 1-cyclopropyl-5,7,8-trifluoro-1,2-dihydro-4-hydroxyquinoline-3,6-dicarboxylate ***8***

To a solution of **7** (341 g, 0.792 mol) in a mixture of *tert*-BuOH (340 mL) and toluene (1.70 L) was added *tert*-BuOK (88.9 g, 0.792 mol) under ice-cooling. The reaction mixture was stirred for 20 min under ice-cooling, acidified with dilute HCl, and the product was extracted with toluene. The organic layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo to leave an oil, which was crystallized from *n*-hexane. The crystal was collected by filtration, washed with *n*-hexane, and dried to give 257 g (84% from **6**) of **8**, mp 105–108 °C (recrystallized from Et_2O/*n*-hexane). IR (KBr) cm^{-1}: 1705, 1655, 1630. ^{1}H-NMR (80 MHz, $CDCl_3$) δ: 0.5–1.0 (4H, m, cyclopropyl CH_2CH_2), 1.36, 1.38 (both 3H, t, J = 7.0 Hz, 2 x CH_2CH_3), 2.8–3.2 (1H, m, cyclopropyl CH), 4.14 (2H, s, 2-H), 4.28, 4.37 (both 2H, q, J = 7.0 Hz, 2 x CH_2CH_3). EIMS *m/z*: 385 (M+), 366, 357. Anal $C_{18}H_{18}F_3NO_5$ (C, H, F, N).

Diethyl 1-cyclopropyl-5,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3,6-dicarboxylate ***4***

To a solution of **8** (242 g, 0.630 mol) in CH_2Cl_2 (480 mL) was added Br_2 (39.0 mL, 121.0 g, 0.757 mol) dropwise during a period of 8 min under ice-cooling and the resulting mixture was stirred for an additional 10 min under ice-cooling. EtOH (500 mL) and then Et_3N (242 mL) were added therein. The solvents were distilled off under atmospheric pressure, and water was added. The resulting solid was collected by filtration, washed successively with water, EtOH, and iso-Pr_2O, and then dried to give 156 g (65%) of **4**, mp 184–185 °C (recrystallized from $CHCl_3$/EtOH). IR (KBr) cm^{-1}: 1730, 1645, 1605. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 1.05–1.20 (4H, m, cyclopropyl CH_2CH_2), 1.27, 1.32 (both 3H, t, J = 7.0 Hz, 2 x CH_2CH_3), 3.90–4.05 (1H, m, cyclopropyl CH), 4.22, 4.41 (both 2H, q, J = 7.0 Hz, 2 x CH_2CH_3), 8.41 (1H, s, 2-H). ^{19}F-NMR ($CDCl_3$) δ: –149.75 (1F, br dd, J_{5F-8F} = 16.1Hz, J_{7F-8F} = 19.5 Hz, 8-F), –129.50 (1F, dd, J_{5F-7F} = 2.5 Hz, J_{7F-8F} = 19.5 Hz, 7-F), –113.41 (1F, dd, J_{5F-7F} = 2.5 Hz, J_{5F-8F} = 16.1Hz, 5-F). EIMS *m/z*: 383 (M+), 364, 338. Anal $C_{18}H_{16}F_3NO_5$ (C, H, F, N).

Diethyl 5-(ethoxycarbonyl, benzyloxycarbonyl, and cyano)-methylamino-1-cyclopropyl-7,8-difluoro-1,4-dihydro-4-oxoquinoline-3,6-dicarboxylates ***9a–c***

A suspension of **4** (15.00 g, 39.2 mmol), glycine ethyl ester hydrochloride (6.00 g, 43.0 mmol), K_2CO_3 (11.89 g, 86.2 mmol) in $CHCl_3$ (150 mL) was heated to reflux for 2 h and then cooled. The insoluble materials were filtered off. The filtrate was concentrated in vacuo to leave a residue, which was triturated with EtOH. The solid was collected by filtration, washed successively with EtOH and iso-Pr_2O, and then dried to give 17.35 g (95%) of **9a**, mp 158–159 °C (recrystallized from $CHCl_3$/EtOH). IR (KBr) cm^{-1}: 1750, 1725, 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.0–1.4 (4H, m, cyclopropyl CH_2CH_2), 1.28, 1.38, 1.41 (each 3H, t, J = 7.0 Hz, 3 x CH_2CH_3), 3.6–4.0 (1H, m, cyclopropyl CH), 3.89 (2H, s, $NHCH_2CO$), 4.21, 4.36, 4.41 (each 2H, q, J = 7.0 Hz, 3 x CH_2CH_3), 8.36 (1H, s, 2-H). ^{19}F-NMR ($CDCl_3$) δ: –163.11 (1F, dddd, J_{7F-8F} = 21.9 Hz, J_{7F-H} = 2.0, 2.0, 6.0 Hz, 8-F), –130.57 (1F, d, J_{7F-8F} = 21.9 Hz, 7-F). EIMS *m/z*: 466 (M+), 437, 421. Anal $C_{22}H_{24}F_2N_2O_7$ (C, H, F, N).

According to the same method, compound **4** (4.00 g, 10.4 mmol) was allowed to react with *para*-toluenesulfonic acid salt of glycine benzyl ester (8.00 g, 23.7 mmol) in toluene (40 mL) to give 4.65 g (84%) of **9b**, mp 113–114 °C (recrystallized from $CHCl_3$/EtOH). IR (KBr) cm^{-1}: 1750, 1700, 1635. ^{1}H-NMR ($CDCl_3$) δ: 0.9–1.4 (4H, m, cyclopropyl CH_2CH_2), 1.36, 1.38 (both 3H, t, J = 7.0 Hz, 2 x CH_2CH_3), 3.6–4.1 (1H, m, cyclopropyl CH), 3.95 (2H, s, $NHCH_2CO$), 4.36 (2 x 2H, q, J = 7.0 Hz, 2 x CH_2CH_3), 5.17 (2H, s, OCH_2Ph), 7.32 (5H, s, Ph), 8.35 (1H, s, 2-H). ^{19}F-NMR ($CDCl_3$) δ: –162.87 (1F, br dd, J_{H-8F} = 6.0 Hz, J_{7F-8F} = 22.1 Hz, 8-F), –130.51 (1F, dd, J_{H-7F} = 1.5 Hz, J_{7F-8F} = 22.1 Hz, 7-F). EIMS *m/z*: 528 (M+), 483, 437. Anal $C_{27}H_{26}F_2N_2O_7$ (C, H, F, N).

According to the same method, compound **4** (10.00 g, 26.1 mmol) was allowed to react with aminoacetonitrile hydrochloride (5.50 g, 59.4 mmol and after 6 h, an additional 5.27 g, 57.0 mmol) in toluene (100 mL) to give 8.98 g (82%) of **9c**, mp 161–163 °C (recrystallized from EtOH). IR (KBr) cm^{-1}: 1720, 1700, 1640. ^{1}H-NMR ($CDCl_3$) δ: 0.9–1.4 (4H, m, cyclopropyl CH_2CH_2), 1.39, 1.44 (both 3H, t, J = 7.0 Hz, 2 x CH_2CH_3), 3.7–4.1 (1H, m, cyclopropyl CH), 4.16 (2H, s, $NHCH_2CN$), 4.38, 4.48 (2H, q, J = 7.0 Hz, 2 x CH_2CH_3), 8.42 (1H, s, 2-H), 11.45 (1H, br s, NH). ^{19}F-NMR ($CDCl_3$) δ: –159.14 (1F, br dd, J_{H-8F} = 6.0 Hz, J_{7F-8F} = 21.6 Hz, 8-F), –128.33 (1F, d, J_{7F-8F} = 21.6 Hz, 7-F). EIMS *m/z*: 419 (M+), 390, 374. Anal $C_{20}H_{19}F_2N_3O_5$ (C, H, F, N).

Ethyl 2-(ethoxycarbonyl, benzyloxycarbonyl, and cyano)-6-cyclopropyl-4,5-difluoro-6,9-dihydro-3-hydroxy-9-oxo-1H-pyrrolo[2,3-f]quinoline-8-carboxylates ***10a–c***

To a stirred solution of **9a** (17.35 g, 37.2 mmol) in a mixture of *tert*-BuOH (35 mL) and tetrahydrofuran (170 mL) was added *tert*-BuOK (4.60 g, 41.0 mmol) under ice-cooling. The reaction mixture was stirred for 20 min under ice-cooling, diluted with ice water, and acidified with dilute HCl. The resulting solid was collected by filtration, washed successively with water, EtOH, and iso-Pr_2O, and then dried to give 14.16 g (91%) of **10a**, mp 241–243 °C (recrystallized from $CHCl_3$/EtOH). IR (KBr) cm^{-1}: 3360, 1690, 1670, 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.0–1.4 (4H, m, cyclopropyl CH_2CH_2), 1.32, 1.38 (both 3H, t, J = 7.5 Hz, 2 x CH_2CH_3), 3.8–4.3 (1H, m, cyclopropyl CH), 4.25, 4.38 (both 2H, q, J = 7.5 Hz, 2 x CH_2CH_3), 8.48 (1H, s, 7-H), 9.4 (1H, br s, OH), 10.90 (1H, br s, NH). EIMS *m/z*: 420 (M+), 374. Anal $C_{20}H_{18}F_2N_2O_6$ (C, H, F, N).

In the same procedure, compound **9b** (4.13 g, 7.82 mmol) gave 2.18 g (58%) of **10b**, mp 186–187 °C (recrystallized from $CHCl_3$/EtOH). IR (KBr) cm^{-1}: 3378, 1694, 1677, 1609. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.1–1.4 (4H, m, cyclopropyl CH_2CH_2), 1.43 (3H, t, J = 7.5 Hz, CH_2CH_3), 3.9–4.1 (1H, m, cyclopropyl CH), 4.45 (2H, q, J = 7.5 Hz, CH_2CH_3), 5.40 (1H, s, OCH_2Ph), 7.35–7.50 (5H, m, Ph), 8.22 (1H, br s, OH), 8.65 (1H, s, 7-H), 11.24 (1H, br s, NH). APCIMS *m/z*: 483 (M+ + 1). Anal $C_{25}H_{20}F_2N_2O_6$ (C, H, F, N).

In the same procedure, compound **9c** (8.66 g, 20.7 mmol) gave 7.18 g (93%) of **10c**, mp 275–279 °C (dec, recrystallized from $CHCl_3$/EtOH). IR (KBr) cm^{-1}: 3344, 2219, 1727, 1704, 1643, 1605. ^{1}H-NMR (DMSO-d_6) δ: 1.0–1.4 (4H, m, cyclopropyl CH_2CH_2), 1.32 (3H, t, J = 7.0 Hz, CH_2CH_3), 3.9–4.3 (1H, m, cyclopropyl CH), 4.26 (2H, q, J = 7.0 Hz, CH_2CH_3), 8.50 (1H, s, 7-H), 10.7 (1H, br s, OH), 12.35 (1H, br s, NH). EIMS *m/z*: 373 (M+), 345, 327. Anal $C_{18}H_{13}F_2N_3O_4$ (C, H, F, N).

*2-(Ethoxycarbonyl, benzyloxycarbonyl, and cyano)-6-cyclopropyl-4,5-difluoro-6,9-dihydro-3-hydroxy-9-oxo-1H-pyrrolo[2,3-f]-quinoline-8-carboxylic acids **11a–c***

A suspension of **10a** (6.89 g, 16.4 mmol) in a mixture of AcOH, water, and H_2SO_4 (8:6:1, v/v, 67 mL) was heated to reflux for 2 h. The mixture was diluted with ice water. The precipitates were collected by filtration, washed successively with water, EtOH, and iso-Pr_2O, and then dried to give 6.04 g (94%) of **11a**, mp > 300 °C (dec, recrystallized from DMF/EtOH). IR (KBr) cm^{-1}: 3430, 1730, 1690. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 1.1–1.4 (4H, m, cyclopropyl CH_2CH_2), 1.37 (3H, t, J = 7.0 Hz, CH_2CH_3), 4.1–4.3 (1H, m, cyclopropyl CH), 4.39 (2H, q, J = 7.0 Hz, CH_2CH_3), 8.78 (1H, s, 7-H), 10.72 (1H, br s, NH), 14.4 (1H, br s, COOH). EIMS *m/z*: 392 (M^+), 346. Anal $C_{18}H_{14}F_2N_2O_6$ (C, H, F, N).

In the same procedure, compound **10b** (1.00 g, 2.07 mmol) gave 914 mg (97%) of **11b**, mp 270–272 °C (dec, recrystallized from $CHCl_3$/EtOH). IR (KBr) cm^{-1}: 3400, 1720, 1680, 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.0–1.4 (4H, m, cyclopropyl CH_2CH_2), 4.0–4.4 (1H, m, cyclopropyl CH), 5.41 (2H, s, OCH_2Ph), 7.2–7.6 (5H, m, Ph), 8.74 (1H, s, 7-H), 10.72 (1H, br s, NH), 14.3 (1H, br s, COOH). EIMS *m/z*: 454 (M^+), 410, 363. Anal $C_{23}H_{16}F_2N_2O_6$ (C, H, F, N).

In the same procedure, compound **10c** (1.75 g, 4.69 mmol) gave 1.45 g (89%) of **11c**, mp > 300 °C (recrystallized from DMF/EtOH). IR (KBr) cm^{-1}: 3401, 2216, 1711, 1666. ^{1}H-NMR (DMSO-d_6) δ: 1.2–1.4 (4H, m, cyclopropyl CH_2CH_2), 4.0–4.4 (1H, m, cyclopropyl CH), 8.74 (1H, s, 7-H), 12.30 (1H, br s, NH), 14.6 (1H, br s, COOH). EIMS *m/z*: 345 (M^+), 327, 301. Anal $C_{16}H_9F_2N_3O_4$ (C, H, F, N).

*2-Carbamoyl-6-cyclopropyl-4,5-difluoro-6,9-dihydro-3-hydroxy-9-oxo-1H-pyrrolo[2,3-f]quinoline-8-carboxylic acid **11d***

A solution of **10c** (2.00 g, 5.36 mmol) in H_2SO_4 (10 mL) was heated at 100 °C for 40 min and then cooled. Ice water (10 mL) and AcOH (10 mL) were added to the mixture under ice-cooling. The resulting mixture was heated at 100 °C for 1 h, cooled, and diluted with water. The resulting solid was collected by filtration, washed successively with water, EtOH, and iso-Pr_2O, and then dried to give 1.56 g (80%) of **11d**, mp > 300 °C (recrystallized from DMF/EtOH). IR (KBr) cm^{-1}: 3453, 3346, 1729, 1658, 1635. ^{1}H-NMR (DMSO-d_6) δ: 1.0–1.5 (4H, m, cyclopropyl CH_2CH_2), 4.0–4.4 (1H, m, cyclopropyl CH), 8.2 (2H, br s, $CONH_2$), 8.62 (1H, s, 7-H), 10.8 (1H, br s, 3-OH), 11.5 (1H, br s, 1-H), 14.65 (1H, br s, COOH). EIMS *m/z*: 363 (M^+), 320. Anal $C_{16}H_{11}F_2N_3O_5$•1/4H_2O (C, H, F, N).

*Diethyl 6-cyclopropyl-4,5-difluoro-1,3,6,9-tetrahydro-3,9-dioxo-2H-pyrrolo[3,4-f]quinoline-1,8-dicarboxylate **12***

To a suspension of NaH (60% in mineral oil, 3.79 g, 94.8 mmol) in toluene (300 mL) was added dropwise a solution of *N*-benzylidene glycine ethyl ester [18] (18.10 g, 94.8 mmol) in toluene (30 mL) during a period of 2 min under ice-cooling. Compound **4** (16.50 g, 43.1 mmol) was added to the mixture under ice-cooling and the whole mixture was stirred for 18 h at room temperature. The mixture was poured into ice water and the product was extracted twice with $CHCl_3$. The combined organic layers were washed with dilute AcOH, dried over Na_2SO_4, and concentrated in vacuo to leave a solid, which was triturated with iso-Pr_2O. The solid was collected by filtration, washed successively with EtOH and iso-Pr_2O, and then dried to give 8.72 g (48%) of **12**, mp 237–239 °C (recrystallized from $CHCl_3$/EtOH). IR (KBr) cm^{-1}: 3347, 1726, 1685, 1651. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.15–1.25, 1.25–1.40 (both 2H, m, cyclopropyl CH_2CH_2), 1.28, 1.38 (both 3H, t, J = 7.0 Hz, 2 x CH_2CH_3), 3.94–4.06 (1H, m, cyclopropyl CH), 4.22 (2H, q, J = 7.0 Hz, CH_2CH_3), 4.35, 4.40 (both 1H, dq, J = 10.0, 7.0 Hz, CH_2CH_3), 5.86 (1H, d, J = 1.3 Hz, 1-H), 8.64 (1H, s, 7-H). ^{19}F-NMR ($CDCl_3$) δ: −143.24 (1F, br d, $J_{4F\text{-}5F}$ = 18.5 Hz, 5-F), −136.53 (1F, d, $J_{4F\text{-}5F}$ = 18.5 Hz, 4-F). EIMS *m/z*: 420 (M^+), 374, 347. Anal $C_{20}H_{18}F_2N_2O_6$ (C, H, F, N).

*6-Cyclopropyl-1-ethoxycarbonyl-4,5-difluoro-1,3,6,9-tetrahydro-3,9-dioxo-2H-pyrrolo[3,4-f]quinoline-8-carboxylic acid **13***

Using the same method for the hydrolysis of **10a** to **11a**, compound **12** (17.7 g, 46.2 mmol) was hydrolyzed to give 9.96 g (51%) of **13**, mp 286–288 °C (recrystallized from $CHCl_3$/EtOH). IR (KBr) cm^{-1}: 3302, 1740, 1723. ^{1}H-NMR (DMSO-d_6) δ: 1.0–1.5 (4H, m, cyclopropyl CH_2CH_2), 1.18 (3H, t, J = 7.0 Hz, CH_2CH_3), 3.9–4.4 (1H, m, cyclopropyl CH), 4.11 (2H, q, J = 7.0 Hz, CH_2CH_3), 5.74 (1H, d, J = 1.0 Hz, 1-H), 8.78 (1H, s, 7-H), 9.7 (1H, br s, NH). EIMS *m/z*: 392 (M^+), 374, 319. Anal $C_{18}H_{14}F_2N_2O_6$ (C, H, F, N).

*6-Cyclopropyl-4,5-difluoro-1,3,6,9-tetrahydro-3,9-dioxo-2H-pyrrolo[3,4-f]quinoline-8-carboxylic acid **14***

Using the same method for the hydrolysis of **10a** to **11a**, compound **12** (7.52 g, 17.9 mmol) was treated with a mixture of AcOH, water, and H_2SO_4 (4:3:2, v/v, 75 mL) to give 5.51 g (96%) of **14**, mp > 300 °C (recrystallized from DMF/EtOH). IR (KBr) cm^{-1}: 3340, 1720, 1710, 1615. ^{1}H-NMR (DMSO-d_6) δ: 1.1–1.4 (4H, m, cyclopropyl CH_2CH_2), 4.0–4.4 (1H, m, cyclopropyl CH), 4.83 (2H, s, 2 x 1-H), 8.78 (1H, s, 7-H), 9.00 (1H, br s, NH), 14.15 (1H, br s, COOH). EIMS *m/z*: 320 (M^+), 302, 276. Anal $C_{15}H_{10}F_2N_2O_4$ (C, H, F, N).

*Ethyl 6-cyclopropyl-4,5-difluoro-2,3,6,9-tetrahydro-3,9-dioxo-1H-pyrazolo[3,4-f]quinoline-8-carboxylate **15a** and ethyl 6-cyclopropyl-4,5-difluoro-2,3,6,9-tetrahydro-1-methyl-3,9-dioxo-1H-pyrazolo[3,4-f]quinoline-8-carboxylate **15b***

A mixture of **4** (2.00 g, 5.22 mmol), NH_2NH_2•H_2O (450 mg, 8.99 mmol), Et_3N (1.6 mL), CH_2Cl_2 (20 mL), and EtOH (20 mL) was stirred for 3 h at room temperature. The resulting solid was collected by filtration, washed successively with EtOH and $CHCl_3$, and then dried to give 1.80 g (99%) of **15a**, mp 281–286 °C (dec, recrystallized from DMF/EtOH). IR (KBr) cm^{-1}: 3600, 3270, 1720, 1640. ^{1}H-NMR (DMSO-d_6) δ: 1.0–1.4 (4H, m, cyclopropyl CH_2CH_2), 1.22 (3H, t, J = 7.0 Hz, CH_2CH_3), 3.8–4.4 (1H, m, cyclopropyl CH), 4.26 (2H, q, J = 7.0 Hz, CH_2CH_3), 8.50 (1H, s, 7-H), 11.10 (1H, br s, NH), 12.55 (1H, br s, NH). ^{19}F-NMR (DMSO-d_6) δ: −154.64 (1F, br d, $J_{4F\text{-}5F}$ = 20.2 Hz, 5-F), −138.09 (1F, d, $J_{4F\text{-}5F}$ = 20.2 Hz, 4-F). EIMS *m/z*: 349 (M^+), 303. Anal $C_{16}H_{13}F_2N_3O_4$•1/4H_2O (C, H, F, N).

In the same method, compound **4** (1.00 g, 2.61 mmol) was treated with $MeNHNH_2$ (132 mg, 2.87 mmol) to give 746 mg (79%) of **15b**, mp 266–269 °C (dec, recrystallized from $CHCl_3$/EtOH). IR (KBr) cm^{-1}: 1720, 1690, 1645. ^{1}H-NMR (DMSO-d_6) δ: 0.9–1.4 (4H, m, cyclopropyl CH_2CH_2), 1.30 (3H, t, J = 7.0 Hz, CH_2CH_3), 3.96 (3H, s, NCH_3), 4.24 (2H, q, J = 7.0 Hz, CH_2CH_3), 8.43 (1H, s, 7-H), 11.23 (1H, br s, NH). ^{19}F-NMR (DMSO-d_6) δ: −156.23 (1F, br d, $J_{4F\text{-}5F}$ = 21.3 Hz, 5-F), −139.37 (1F, d, $J_{4F\text{-}5F}$ = 21.3 Hz, 4-F). EIMS *m/z*: 363 (M^+), 362, 334. Anal $C_{17}H_{15}F_2N_3O_4$ (C, H, F, N).

*Ethyl 6-cyclopropyl-4,5-difluoro-2,3,6,9-tetrahydro-2-methyl-3,9-dioxo-1H-pyrazolo[3,4-f]quinoline-8-carboxylate **15c***

Dimethyl sulfate (0.50 mL, 0.67 mg, 5.3 mmol) was added to a solution of **15a** (1.30 g, 3.72 mmol) and NaOH (300 mg, 7.5 mmol) in water (13 mL) at room temperature. The resulting mixture was stirred for 2.5 h and diluted with water. The resul-

ting solid was collected by filtration, washed successively with water and EtOH, and then recrystallized from $CHCl_3$/EtOH to give 550 mg (41%) of **15c**, mp 295–298 °C (dec, recrystallized from $CHCl_3$/EtOH). IR (KBr) cm^{-1}: 3150, 1730, 1660, 1640. ^1H-NMR (DMSO-d_6) δ: 1.0–1.4 (4H, m, cyclopropyl CH_2CH_2), 1.25 (3H, t, J = 7.0 Hz, CH_2CH_3), 3.45 (3H, s, NCH_3), 3.7–4.3 (1H, m, cyclopropyl CH), 4.25 (2H, q, J = 7.0 Hz, CH_2CH_3), 8.47 (1H, s, 7-H), 12.13 (1H, br s, NH). EIMS *m/z*: 363 (M^+), 317. Anal $C_{17}H_{15}F_2N_3O_4$ (C, H, F, N).

6-Cyclopropyl-4,5-difluoro-2,3,6,9-tetrahydro-3,9-dioxo-1H-pyrazolo[3,4-f]quinoline-8-carboxylic acid ***16a*** *and 1-methyl- and 2-methyl-6-cyclopropyl-4,5-difluoro-2,3,6,9-tetrahydro-3,9-dioxo-1H-pyrazolo[3,4-f]quinoline-8-carboxylic acids* ***16b*** *and* ***16c***

In the same method for the hydrolysis of **10a** to **11a**, compound **15a** (800 mg, 2.29 mmol) was treated and gave 700 mg (95%) of **16a**, mp > 300 °C (recrystallized from DMF/EtOH). IR (KBr) cm^{-1}: 3450, 3380, 1720, 1645. ^1H-NMR (DMSO-d_6) δ: 1.0–1.4 (4H, m, cyclopropyl CH_2CH_2), 3.9–4.4 (1H, m, cyclopropyl CH), 8.74 (1H, s, 7-H), 12.70 (1H, br s, NH), 14.60 (1H, br s, COOH). EIMS *m/z*: 321 (M^+), 306, 277. Anal $C_{14}H_9F_2N_3O_4$ (C, H, F, N).

In the same method for the hydrolysis of **10a** to **11a**, compound **15b** (445 mg, 1.23 mmol) was treated and gave 396 mg (96%) of **16b**, mp > 300 °C (recrystallized from DMF/EtOH). IR (KBr) cm^{-1}: 1720, 1600. ^1H-NMR (NaOD/D_2O) δ: 1.0–1.4 (4H, m, cyclopropyl CH_2CH_2), 3.7–4.3 (1H, m, cyclopropyl CH), 3.73 (3H, s, NCH_3), 8.38 (1H, s, 7-H). EIMS *m/z*: 335 (M^+), 334, 316. Anal $C_{15}H_{11}F_2N_3O_4$ (C, H, F, N).

In the same method for the hydrolysis of **10a** to **11a**, compound **15c** (500 mg, 1.38 mmol) was treated and gave 450 mg (98%) of **16c**, mp > 300 °C (recrystallized from $CHCl_3$/EtOH). IR (KBr) cm^{-1}: 3330, 1730, 1675, 1640. ^1H-NMR (DMSO-d_6) δ: 1.1–1.4 (4H, m, cyclopropyl CH_2CH_2), 3.47 (3H, s, NCH_3), 3.9–4.3 (1H, m, cyclopropyl CH), 8.70 (1H, s, 7-H), 12.20 (1H, br s, NH), 14.35 (1H, br s, COOH). EIMS *m/z*: 335 (M^+), 317, 291. Anal $C_{15}H_{11}F_2N_3O_4$ (C, H, F, N).

6-Cyclopropyl-2-ethoxycarbonyl-5-fluoro-6,9-dihydro-3-hydroxy-4-(4-methyl-1-piperazinyl)-9-oxo-1H-pyrrolo[2,3-f]quinoline-8-carboxylic acid ***17a***

A mixture of **11a** (1.00 g, 2.55 mmol), 1-methylpiperazine (765 mg, 7.65 mmol) in acetonitrile (20 mL) was heated to reflux for 10 min. The mixture was concentrated in vacuo to give a residue, which was triturated with EtOH. The solid was collected by filtration, washed successively with EtOH and iso-Pr_2O, and then dried to afford 1.03 g of crude crystals, which were recrystallized from $CHCl_3$/EtOH to give 889 mg (74%) of **17a**. IR (KBr) cm^{-1}: 3407, 1731, 1670, 1621. ^1H-NMR (200 MHz, DMSO-d_6) δ: 1.0–1.3 (4H, m, cyclopropyl CH_2CH_2), 1.35 (3H, t, J = 7.0 Hz, CH_2CH_3), 2.28 (3H, s, NCH_3), 2.3–2.7, 3.3–3.6 (both 4H, m, 2 x NCH_2CH_2N), 4.1–4.3 (1H, m, cyclopropyl CH), 4.37 (2H, q, J = 7.0 Hz, CH_2CH_3), 8.65 (1H, s, 7-H), 9.3 (1H, br s, OH), 10.7 (1H, br s, NH), 14.8 (1H, br s, COOH). EIMS *m/z*: 472 (M^+), 443.

According to the same method, compounds **17b–d**, **18a**, **22a**, **23a**, and **24a** were prepared from **11a**, **11b**, **16a–c**, respectively (scheme 5 and table I).

6-Cyclopropyl-4,5-difluoro-1,3,6,9-tetrahydro-4-(4-methyl-1-piperazinyl)-3,9-dioxo-2H-pyrrolo[3,4-f]quinoline-8-carboxylic acid ***21a***

A mixture of **14** (175 mg, 0.547 mmol), 1-methylpiperazine (164 mg, 1.64 mmol) in pyridine (3.5 mL) was heated at 100 °C for 1 h. The mixture was concentrated in vacuo to give a residue that was triturated with EtOH. The solid was collected by filtration, washed successively with EtOH and iso-Pr_2O, and then dried to afford 190 mg of crude crystals, which was recrystallized from $CHCl_3$/EtOH to give 179 mg (82%) of **21a**. IR (KBr) cm^{-1}: 3300, 1685, 1610. ^1H-NMR (CD_3COOD) δ: 1.0–1.5 (4H, m, cyclopropyl CH_2CH_2), 2.98 (3H, s, NCH_3), 3.1–4.5 (5H, m, 2 x NCH_2CH_2N and cyclopropyl CH), 4.93 (2H, s, 1-H), 8.95 (1H, s, 7-H). EIMS *m/z*: 386 (M^+), 369, 343.

According to the same method, compounds **19a**, **20a**, and **21a–d** were prepared from **11d**, **13**, and **14**, respectively (scheme 5 and table I).

Pharmacology. In vitro antibacterial activity

According to the assay method recommended by the MIC Committee of the Japan Society of Chemotherapy [19], the MIC was determined by the twofold agar dilution method using Mueller-Hinton agar (pH 7.4, Difco); the bacterial inocula contained approximately 10^6 colony-forming units and the bacterial growth was observed after a 20 h incubation at 37 °C.

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