Synthesis, Pharmacokinetics, and Biological Activity of a Series of New Pyridonecarboxylic Acid Antibacterial Agents Bearing a 5-Fluoro-2-pyridyl Group or a 3-Fluoro-4-pyridyl Group at N-1

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The 1-(5-fluoro-2-pyridyl) or 1-(3-fluoro-4-pyridyl) group was introduced in the syntheses of new pyridonecarboxylic acid antibacterial agents. 1-(5-Fluoro-2-pyridyl)-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxoquinolone-3-carboxylic acid **7b** (DW-116) showed a moderate *in vitro* antibacterial activity but it was found to have very excellent pharmacokinetic profiles so that **7b** (DW-116) showed dramatic increased *in vivo* efficacy.

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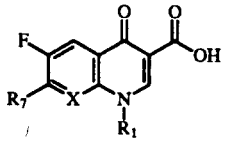
Fluoroquinolone antibacterial agents continue to show the promise of being an important class of therapeutically useful drugs. In recent years, the emergence of compounds such as ciprofloxacin [1], ofloxacin [2], and tosufloxacin [3] is a clear example. In this paper, the quinolones can mean both quinolones and naphthyridones or quinolones only. Most of these agents, which have a strong and broad spectrum antibacterial activity, have been modified mainly at the N-1 and C-7 positions in the quinolone nucleus to increase the activity.

The quinolones having aromatic groups at N-1 are interesting and well-known because they display not only the good antibacterial activities in spite of their bulky size, but also the good pharmacokinetics which is generally known to have an effect on *in vivo* activity. The most successful quinolones belonging to this category are tosufloxacin and temafloxacin [4]. These two quinolones have the characteristic substituents of a 2,4-difluorophenyl group at N-1 (Figure 1). Recently, the quinolone agents with a fluoroheteroaromatic group at N-1 were synthesized [5,6] but were not a success as drugs.



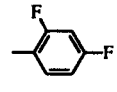
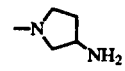
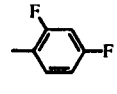
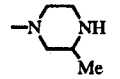
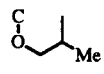
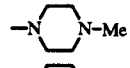
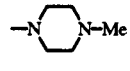
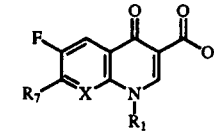
Compound	X	R_1	R_7
Tosufloxacin	N		
Temafloxacin	CH		
Ofloxacin			
Pefloxacin	CH	—Et	

Figure 1

Based on the relationship of the structure and the activity of a good aromatic group such as 2,4-difluorophenyl group introduced into N-1, we decided to prepare compounds bearing a 2,4-disubstituted 6-membered-heteroaromatic group at N-1, one of which substituent is nitrogen in the ring and the other is fluorine, because a fluorine atom would be essential to display the antibacterial activity and expected to have a good effect on pharmacokinetic profiles together with a nitrogen atom in the ring.

As revealed in ofloxacin [7], pefloxacin [8], and temafloxacin [9], the introduction of alkylpiperazine derivatives



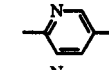
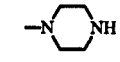
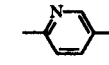
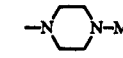
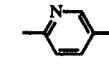
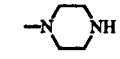
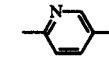
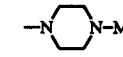
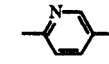
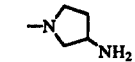
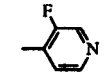
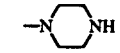
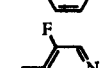
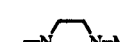
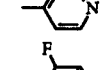
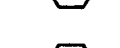
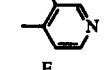
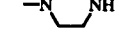
Compound	X	R_1	R_7
1	CH		
2	CH		
3	N		
4	N		
5	N		
6	CH		
7	CH		
8	N		
9	N		

Figure 2

into C-7 position generally exhibits good pharmacokinetics. In order to make better antibacterial agents with excellent pharmacokinetic profiles, therefore, our concern has been focused on piperazine derivatives as a C-7 substituent.

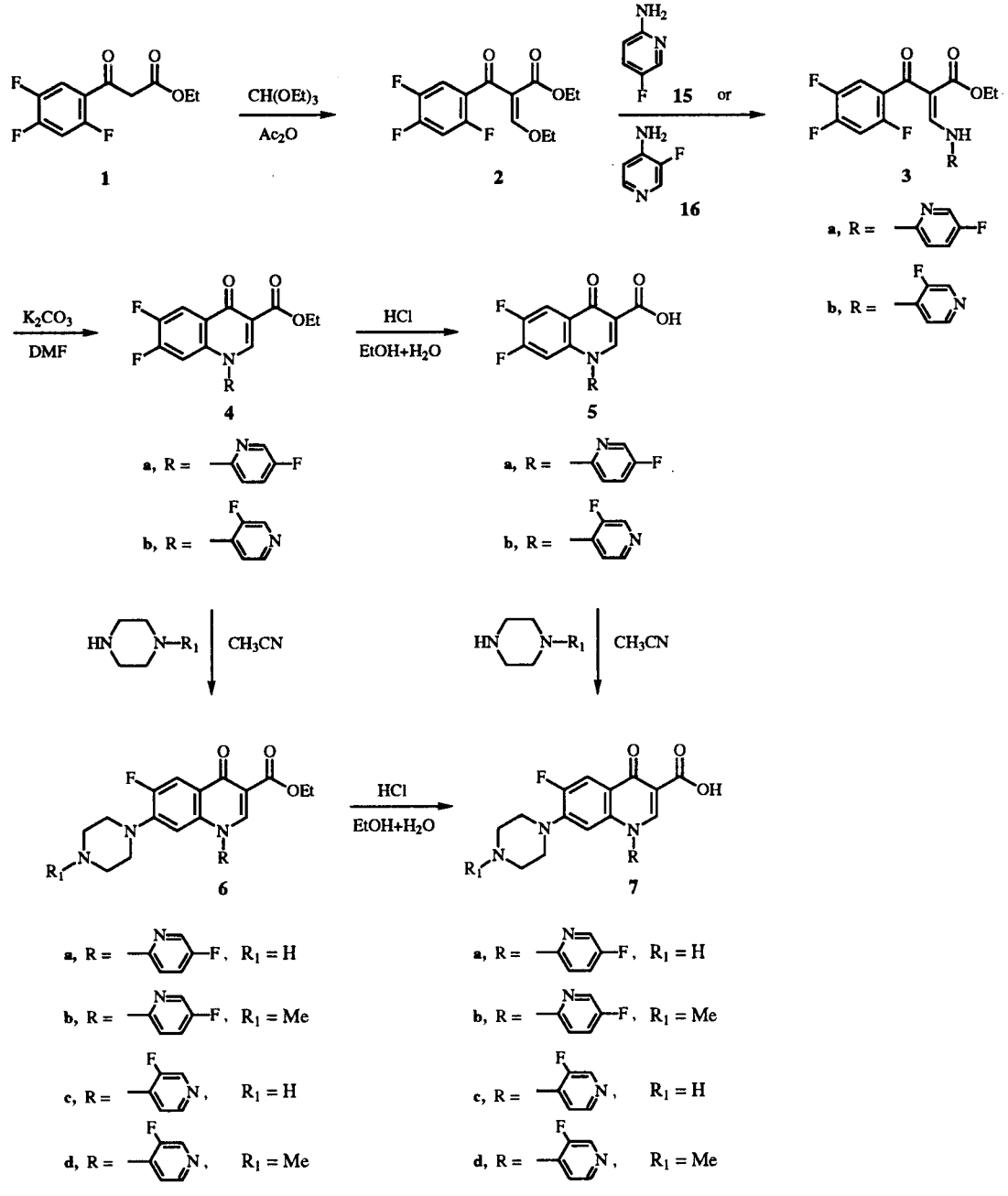
In this paper, we describe the synthesis of new quinolones with their biological activity (MIC and ED_{50}) and pharmacokinetic profiles. As shown in Figure 2, our quinolones have 5-fluoro-2-pyridyl group or 3-fluoro-4-pyridyl group at N-1 and piperazine, *N*-methylpiperazine or 3-aminopyrrolidine group at C-7.

Chemistry.

First of all, 2-amino-5-fluoropyridine **15** and 4-amino-3-fluoropyridine **16** were prepared by a modification of the procedures described by Hand, *et al.* [10] and Talik, *et al.* [11], respectively and identified by comparing their melting points and ^1H nmr data with those reported in literature.

To obtain the compounds with a quinolone structure moiety (Scheme 1), ethyl 2,4,5-trifluorobenzoylacetate **1** was prepared according to the procedure of Chu, *et al.* [12]. The treatment of **1** with triethyl orthoformate in acetic anhydride

Scheme 1



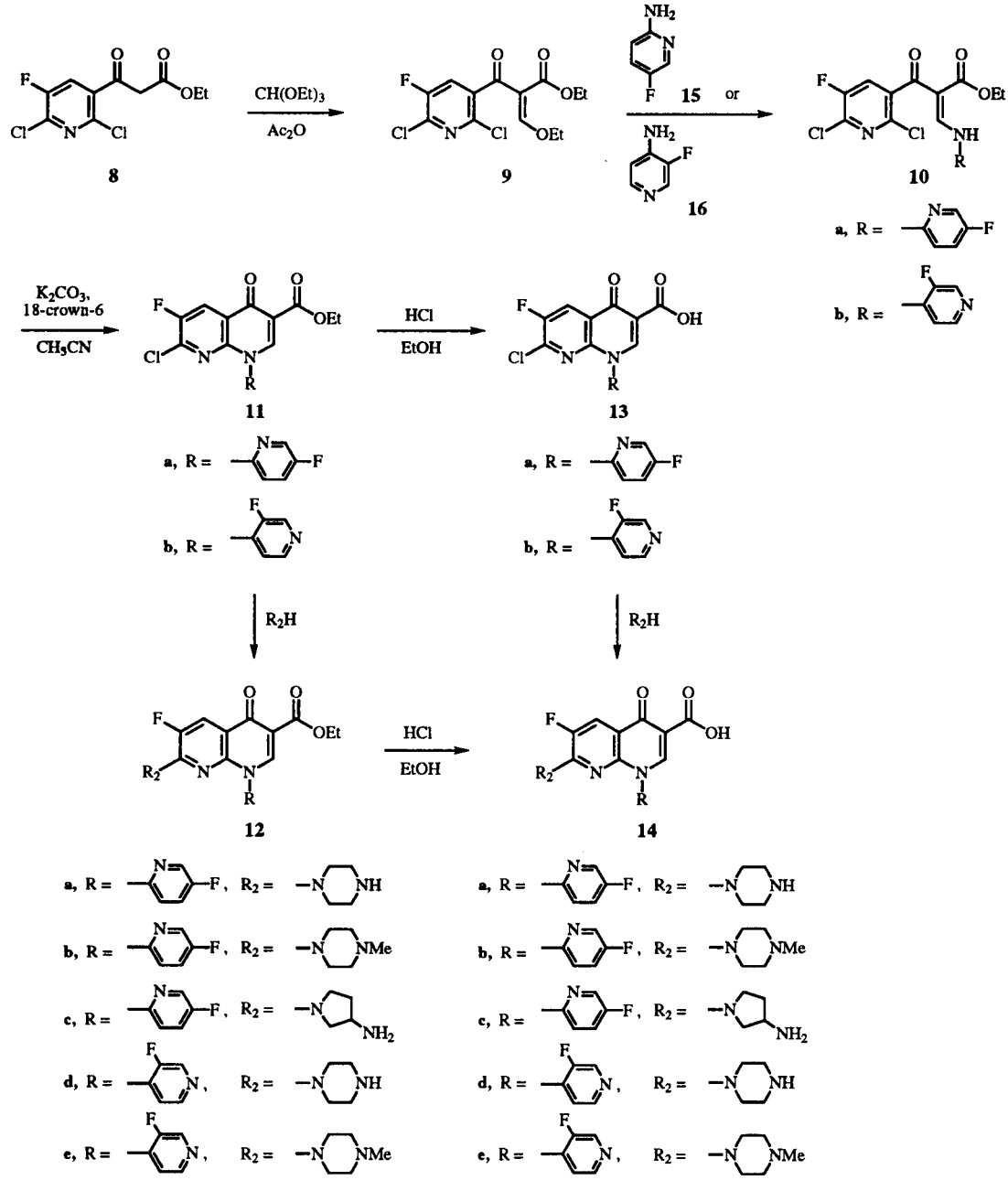
afforded ethyl 2,4,5-trifluorobenzoylethoxyacrylate **2**. After the solvent was evaporated, crude **2**, not further purified, was treated with **15** and **16** to afford acrylate derivatives **3a** and **3b** with potassium carbonate in *N,N*-dimethylformamide gave corresponding cyclized compounds **4a** and **4b** in good yield (98% and 97%, respectively).

The final products **7a-d** could be obtained from **4a-b** in good yield (83-92%) by acid hydrolysis followed by introducing piperazinyl moieties into C-7 position.

Although final products could be obtained by introducing piperazinyl moieties into **4a-b** before hydrolysis, the yield was somewhat lower than that by the former method. This phenomena coincides with the fact that the ethoxycarbonyl group at C-3 of the quinolone nucleus reduces the reactivity of the fluorine atom at C-7 toward cyclic amines compared with free carboxyl group at C-3.

As the synthetic starting material for the compounds of the 1,8-naphthyridone structure moiety (Scheme 2), ethyl 2-(2,6-dichloro-5-fluoronicotinoyl)acetate **8** was used, which was prepared according to the procedure of Chu, *et al.* [12]. Nicotinoylacrylate derivatives **10a-b** were prepared from **8** *via* ethoxyacrylate **9** by the same procedure as that

Scheme 2



for synthesis of **3** from **1**. Cyclization of **10a-b** with potassium carbonate in *N,N*-dimethylformamide was performed to afford cyclized products **11a-b** in poor yield due to side reactions. It may probably be one reason why the chlorine atom at C-7 of the 1,8-naphthyridone structure is more active than the fluorine atom at C-7 of the quinolone structure. Therefore, the reaction conditions, potassium carbonate in *N,N*-dimethylformamide were replaced with potassium carbonate and 18-crown-6 in acetonitrile. Under these conditions, the cyclization reaction went smoothly and in good yield (90-93%).

To obtain the final products **14a-e** from **11a-b**, hydrolyis and introduction of cyclic secondary amines such as piperazinyl derivatives and an 3-aminopyrrolidine group into C-7 were performed according to the procedures used in the synthesis of **7a-d**. In this case, the procedure of introducing amines before hydrolysis afforded the products in good yield, which means that the chlorine atom C-7 in the 1,8-naphthyridone structure is even more active than the fluorine atom at C-7 in quinolone structure.

Biological Results.

In Table 1 are summarized the *in vitro* antibacterial activity of the quinolones bearing a 5-fluoro-2-pyridyl group **15** or a 3-fluoro-4-pyridyl group **16** at the N-1 position.

Table 1

In vitro Antibacterial activity: MICμg/ml [a]

Compound	Organism Str. [b]	St. [c]	E. [d]	P. [e]	Sa. [f]	K. [g]	En. [h]
7a	3.125	1.563	0.098	0.781	0.195	0.025	0.195
7b (DW-116)	6.25	0.781	0.195	3.125	0.195	0.025	0.195
7c	3.125	6.250	0.195	3.125	0.391	0.098	0.781
7d	12.500	12.500	0.391	6.250	0.781	0.195	1.563
14a	6.250	3.125	0.195	1.563	0.195	0.049	0.195
14b (DW-135)	12.500	0.781	0.195	3.125	0.195	0.025	0.195
14c	1.563	0.391	0.049	0.391	0.049	0.013	0.098
14d	6.250	0.781	0.195	6.250	0.195	0.049	0.195
14e	12.500	1.563	0.195	6.250	0.391	0.098	0.391
Ofloxacin	0.781	0.195	0.013	0.781	0.049	0.007	0.049

[a] MIC (minimum inhibitory concentrations) were determined by the agar dilution method. Inoculation was perfomed with one loopful 10^7 cells per ml. [b] *Streptococcus pyogens* 77 A. [c] *Staphylococcus aureus* 503. [d] *Esherichia coli* 078. [e] *Pseudomonas aeruginosa 1592 E.* [f] *Salmonella typhimurium.* [g] *Klebsiella oxytoca 1082 E.* [h] *Enterobacter cloacae p 99.*

As shown in Table 1, none of the compounds showed a minimum inhibitory concentration at the level of the reference drug, ofloxacin. Among them, **14c** showed good antibacterial activity but it was found to have very poor absorption (data not shown). Although **7b** (DW-116) and **14b** (DW-135) exhibited a moderate antibacterial activity, they are far more excellent in their pharmacokinetic profiles (especially $t_{1/2}$ and AUC, see Table 2) than ofloxacin which is generally known to have good pharmacokinetic profiles.

Table 2

Pharmacokinetic Parameters of **7b** (DW-116), Ofloxacin, and **14b** (DW-135) in Rats

Parameters	DW-116 [a] **7b**	Ofloxacin [a]	DW-135 **14b**
Dose (mg/kg)	17.93	19.74	20.00
Cmax (μg/ml)	9.0 ±2.295	9.28 ±2.041	9.25 ±5.397
Tmax (hours)	0.5	0.25	0.5
$t_{1/2}$ (hours)	3.32	2.49	7.00
AUC_t° [b] (μg•hr/ml)	36 47	29.28	77.20
Total AUC (μg•hr/ml)	42.74	31.58	85.71

[a] Calculated as anhydrous free base. [b] **7b** (DW-116) and Ofloxacin (t = 9), **14b** (DW-135) (t = 24).

Table 3

The *in vivo* efficacy (ED_{50} mg/kg) [a] of **7b** (DW-116)

Orgamsms	Drugs	Inoculum Size (cells/mouse)	MIC (μg/ml)	ED_{50} (mg/kg)
S. aureus Smith	**7b** (DW-116)	6.9×10^6	0.39	5.368 [b] (3.311-7.305) [c]
	Ofloxacin		0.2	6.694 (5.798-7.997)
E. Coli O-444	**7b** (DW-1 16)	6.5×10^5	0.012	0.737 (0.562 - 0.963)
	Ofloxacin		0.006	1.147 (0.877-1.441)

[a] Median effective dose. [b] ED_{50}: calculated by Prohibit method. [c] 95% confidence limit. Compounds were administered twice orally at one and four hour after infection.

Table 3 shows the *in vivo* and *in vitro* antibacterial activities of **7b**. As shown in Table 3, the in vitro activity of **7b** was about 2 to 4 times lower than that of ofloxacin. However, its *in vivo* efficacy (ED_{50}) was similar to that of ofloxacin, which is undoubtedly considered to be the result from its excellent pharmacokinetics.

Conclusively, **7b** is chosen to be a promising candidate as an once-a-day-drug with the good *in vivo* efficacy. More detailed *in vivo* data of **7b** will be reported elsewhere.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared (ir) spectra were recorded on a Unicam Mattson 1000 FT-IR spectrometer (potassium bromide pellets). The ^1H nmr spectra were recorded at 250 MHz

on a Bruker ARX AC 250 spectrometer. Chemical shifts are reported in delta units relative to tetramethylsilane. Mass spectra (ms) were recorded on a Mass VG trio 2000 mass spectrometer. Electron impact (EI) mass spectra were recorded on a Elemental Vario EL.

Ethyl 3-(5-Fluoro-2-pyridyl)-2-(2,4,5-trifluorobenzoyl)acrylate (**3a**).

In a typical procedure, **3a, 3b, 10a, 10b**, a mixture of ethyl 2,4,5-trifluorobenzoylacetate **1** (10 g, 41 mmoles) and triethylorthoformate (11.5 ml, 69 mmoles) in acetic anhydride (11.5 ml) was heated to reflux for 15 hours. The solvent was removed by distillation and the residue was cooled to 10°. To a cooled residue was added ethanol (50 ml), and then 2-amino-5-fluoropyridine **15** (5.01 g, 45 mmoles) was added portionwise. The reaction mixture was stirred at -10-25° for 4 hours and the resulting solid was filtered, washed with ethanol, and dried to afford **3a** (13.68 g, 91%), mp 130-132°; ir (potassium bromide): 1674, 1643, 1605, 1566, 1481, 1219 cm^{-1}; ^1H nmr (deuteriochloroform): δ (two sets of signals) 1.00 and 1.16 (t, 3H, J = 7.14 Hz, ethyl CH_3), 4.11 (q, 2H, J = 7.14 Hz, ethyl CH_2 signal overlap), 6.82-7.04 (m, 2H, aromatic H, pyridyl CHC=N), 7.23-7.52 (m,2H, aromatic H, pyridyl CFCH), 8.22 and 8.26 (d, 1H, J = 2.83 Hz, pyridyl NCHCF), 8.95 and 9.14 (d, 1H, J = 12.76 Hz, vinyl H); ms: (EI) m/z: 368 (M^+), 303, 276, 159 (base), 96.

Anal. Calcd. for $C_{17}H_{12}N_2O_3F_4$: C, 55.44; H, 3.28; N, 7.61. Found: C, 55.52; H, 3.15; N, 7.63.

Ethyl 3-(3-Fluoro-4-pyridyl)-2-(2,4,5-trifluorobenzoyl)acrylate (**3b**).

Using the procedure above, the treatment of ethyl 2,4,5-trifluorobenzoylacetate **1** with triethyl orthoformate in acetic anhydride afforded intermediate **2**. Being not further purified, **2** was treated with 4-amino-3-fluoropyridine **16** in ethanol to afford **3b** (85%), mp 129-131°; ir (potassium bromide): 3070, 1697, 1620, 1435, 1281 cm^{-1}; ^1H nmr (deuteriochloroform): δ (two sets of signals) 1.02 and 1.16 (t, 3H, J = 7.15 Hz, ethyl CH_3), 4.15 (q, 2H, J = 7.15 Hz, ethyl CH_2, signal overlap), 6.90 (m, 1H, aromatic H), 7.27-7.52 (m, 2H, aromatic H, pyridyl NCH), 8.28-8.55 (m, 3H, vinyl H, pyridyl NCHCF, CHCCF), 11.14 and 12.14 (d, 1H, J = 13.24 Hz, NH); ms: (EI) m/z: 368 (M^+), 303, 276, 159 (base), 96.

Anal. Calcd. for $C_{17}H_{12}N_2O_3F_4$: C, 55.44; H, 3.28; N, 7.61. Found: C, 55.61; H, 3.44; N, 7.58.

Ethyl 3-(5-Fluoro-2-pyridyl)amino-2-(2,6-dichloro-5-fluoronicotinoyl)acrylate (**10a**).

Using the procedure above, the treatment of ethyl 2,6-dichloro-5-fluoronicotinoylacetate **8** with triethyl orthoformate in acetic anhydride afforded intermediate **9**. Being not further purified, **9** was treated with 2-amino-5-fluoropyridine **15** to afford **10a** (87%), mp 105-107°; ir (potassium bromide): 3440, 1697, 1620, 1481, 1396, 1265 cm^{-1}; ^1H nmr (deuteriochloroform): δ (two sets of signals) 0.92 and 1.14 (t, 3H, J = 7.10 Hz, ethyl CH_3), 4.10 (q, 2H, J = 7.10 Hz, ethyl CH_2, signal overlap), 7.04 (m, 1H, pyridyl CHC=N), 7.37-7.53 (m, 2H, nicotinyl H, pyridyl CHCF), 8.25 and 8.29 (d, 1H, J = 2.90 Hz, pyridyl CFCHN), 9.20 and 9.25 (d, 1H, J = 12.63 Hz, vinyl H), 11.41 and 12.62 (d, 1H, J = 12.63 Hz, NH); ms: (EI) m/z: 402 (M^+), 366, 320, 96 (base).

Anal. Calcd. for $C_{16}H_{11}N_3O_3F_2Cl_2$: C, 47.78; H, 2.76; N, 10.45. Found: C, 47.90; H, 2.88; N, 10.33.

Ethyl 3-(3-Fluoro-4-pyridyl)amino-2-(2,6-dichloro-5-fluoronicotinoyl)acrylate (**10b**).

Using the procedure above, the treatment of ethyl 2,6-dichloro-5-fluoronicotinoylacetate **8** with triethylorthoformate in acetic anhydride afforded intermediate **9**. Being not further purified, **9** was treated with 4-amino-3-fluoropyridine **16** to afford **10b**, which also being not further purified, was cyclized to afford **11b**.

Ethyl 1-(5-Fluoro-2-pyridyl)-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3 carboxylate (**4a**).

A mixture of ethyl 3-(5-fluoro-2-pyridyl)amino-2-(2,4,5-trifluorobenzoyl)acrylate **3a** (10 g, 27 mmoles) and potassium carbonate (5.63 g, 41 mmoles) in *N,N*-dimethylformamide (50 ml) was heated at 80-90° for 2.5 hours. After cooling to room temperature, water (55 ml) was added to the mixture. The resulting light yellow solid was collected by filtration, washed with 25% aqueous ethanol, and dried to afford **4a** (9.27 g, 98%), mp 210-212°; ir (potassium bromide): 3425, 3070, 1705, 1620, 1497, 1466, 1227 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.37 (t, 3H, J = 7.10 Hz, ethyl CH_3), 4.37 (q, 2H, J = 7.10 Hz, ethyl CH_2), 6.96 (m, 1H, pyridyl CHC=N), 7.57 (m, 1H, pyridyl CHCF), 7.77 (m, 1H, C_8-H), 8.28 (m, 1H, C_5-H), 8.56 and 8.57 (s, 2H, pyridyl CFCHN, C_2-H); ms: (EI) m/z: 348 (M^+), 303, 275, 221 (base), 96.

Anal. Calcd. for $C_{17}H_{11}N_2O_3F_3$: C, 58.63; H, 3.18; N, 8.04. Found: C, 58.60; H, 3.40; N, 7.95.

Ethyl 1-(3-Fluoro-4-pyridyl)-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**4b**).

Using the procedure above, cyclization of ethyl 3-(3-fluoro-4-pyridyl)amino-2-(2,4,5-trifluorobenzoyl)acrylate **3b** with potassium carbonate in *N,N*-dimethylformamide afforded **4b** (97%), mp 212°; ir (potassium bromide): 3440, 1736, 1597, 1504, 1335, 1288 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (t, 3H, J = 7.14 Hz, ethyl CH_3), 4.38 (q, 2H, J = 7.14 Hz, ethyl CH_2), 6.70 (m, 1H, pyridyl CHCCF), 7.51 (m, 1H, C_8-H), 8.28 (m, 1H, pyridyl CHN), 8.36 (s, 1H, pyridyl NCHCF), 8.76 (d, 1H, $J_{H\text{-}F}$ = 5.06 Hz, C_5-H), 8.85 (s, 1H, C_2-H); ms: (EI) m/z: 348 (M^+), 303, 276 (base), 96.

Anal. Calcd. for $C_{17}H_{11}N_2O_3F_3$: C, 58.63; H, 3.18; N, 8.04. Found: C, 58.71; H, 3.37; N, 8.28.

1-(5-Fluoro-2-pyridyl)-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**5a**).

To a suspension of ethyl ester **4a** (9 g, 29 mmoles) in ethanol (70 ml) was added 3 *N* hydrochloric acid solution (45 ml) and the mixture was refluxed for 5 hours. After cooling to 10°, the resulting solid was filtered, washed with 50% aqueous ethanol, and dried to afford **5a** (8.19 g, 99%), mp 278-280°; ir (potassium bromide): 3448, 3062, 1735, 1619, 1504, 1465 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid) δ 7.31-7.38 (m, 1H, pyridyl CHC=N), 7.89-8.09 (m, 2H, pyridyl CHCF, C_8-H), 8.60 (dd, 1H, $J_{H\text{-}F}$ = 8.60 Hz, $J_{H\text{-}F}$ = 7.93 Hz, C_5-H), 8.66 (d, 1H, J = 2.75 Hz, pyridyl CFCHN), 9.44 (s, 1H, C_2-H); ms: (El) m/z: 320 (M^+), 276 (base), 223, 96.

Anal. Calcd. for $C_{15}H_7N_2O_3F_3$: C, 56.26; H, 2.20; N, 8.75. Found: C, 56.17; H, 2.45; N, 8.83.

1-(3-Fluoro-4-pyridyl)-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**5b**).

Using the procedure above, hydrolysis of **4b** in ethanol with 3 *N* hydrochloric acid afforded **5b** (98%), mp 271-273°; ir (potassium bromide): 3440, 1720, 1628, 1497, cm^{-1}; ^1H nmr (deuteriotri-

fluoroacetic acid): δ 7.29-7.35 (m, 1H, pyridyl CHCCF), 8.39-8.46 (m, 1H, C_8-H), 8.58-8.63 (m, 1H, pyridyl NCH), 9.22 (d, 1H, J_{H-F} = 5.86 Hz, C_5-H), 9.29 (s, 1H, C_2-H), 9.34 (d, 1H, J = 2.70 Hz, pyridyl NCHCF); ms: (EI) m/z: 320 (M^+), 276 (base), 248, 96.

Anal. Calcd. for $C_{15}H_7N_2O_3F_3$: C, 56.26; H, 2.20; N, 8.75. Found: C, 56.35; H, 2.39; N, 8.80.

1-(5-Fluoro-2-pyridyl)-6-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Monohydrochloride Salt (**7a**).

In a typical procedure **7a-7d**, a mixture of 4-oxoquinoline-3-carboxylic acid derivative **5a** (1 g, 3.1 mmoles) and piperazine (565 mg, 6.6 mmoles) in acetonitrile (10 ml) was heated to reflux for 7 hours. After cooling to 10°, the resulting light yellow solid was collected by filtration and washed with ethanol. To a dispersion of this obtained solid was added ethanol (5 ml) and 6 *N* hydrochloric acid solution (2.2 ml) and the mixture was stirred at room temperature for 6 hours. After cooling to 10°, the resulting solid was filtered, washed with ethanol, and dried to afford monohydrochloride salt **7a** (1.1 g, 83%), mp 300° dec; ir (potassium bromide): 3440, 1720, 1628, 1466 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 3.60 (bs, 4H, piperazinyl CH_2), 3.73 (bs, 4H, piperazinyl, CH_2), 6.73 (bs, 1H, C_8-H), 8.01 (bs, 2H, pyridyl CHCHCF), 8.26 (d, 1H, J_{H-F} = 12.28 Hz, C_5-H), 8.63 (s, 1H, pyridyl NCHCF), 9.24 (s, 1H, C_2-H); ms: (EI) m/z: 386 (M^+), 342 (base), 300, 96.

Anal. Calcd. for $C_{19}H_{16}N_4O_3F_2$ HCl: C, 53.97; H, 4.05; N, 13.25. Found: C, 54.18; H, 4.11; N, 13.11.

1-(5-Fluoro-2-pyridyl)-6-fluoro-7-(4-methyl-1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Monohydrochloride Salt (**7b**).

Using the procedure above, treatment of 4-oxoquinolinecarboxylic acid derivative **5a** with 1-methylpiperazine in acetonitrile afforded **7b** (91%), mp >250° dec; ir (potassium bromide): 3425, 1736, 1628, 1466 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 3.05 (s, 3H, NCH_3), 3.37 (m, 2H, piperazinyl CH_2), 3.58 (m, 2H, piperazinyl CH_2), 3.76 (m, 2H, piperazinyl CH_2), 3.95 (m, 2H, piperazinyl CH_2), 6.77 (d, 1H, J = 6.60 Hz, C_8-H), 8.03 (m, 2H, pyridyl CHCHCF), 8.28 (d, 1H, J_{H-F}) = 12.38 Hz, C_5-H), 8.66 (s, 1H, pyridyl NCHCF), 9.26 (s, 1H, C_2-H); ms: (EI) m/z: 400 (M^+), 356, 284, 96, 70 (base).

Anal. Calcd. for $C_{20}H_{18}N_4O_3F_2$ HCl: C, 54.99; H, 4.38; N, 12.83. Found: C, 54.91; H, 4.25; N, 12.68.

1-(3-Fluoro-4-pyridyl)-6-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Monohydrochloride Salt (**7c**).

Using the procedure above, the treatment of 4-oxoquinolinecarboxylic acid derivative **5b** with piperazine in acetonitrile afforded **7c** (89%), mp 284-286°; ir (potassium bromide): 3425, 1736, 1628, 1497, 1458 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 3.63 (m, 4H, piperazinyl CH_2), 3.85 (m, 4H, piperazinyl CH_2), 6.81 (m, 1H, C_8-H), 8.34 (d, 1H, J_{H-F} = 10.02 Hz, C_5-H), 8.82 (m, 1H, pyridyl CHCCF), 9.17-9.62 (m, 3H, pyridyl CHNCH, C_2-H); ms: (EI) m/z: 386 (M^+), 342, 300 (base), 96.

Anal. Calcd. for $C_{19}H_{16}N_4O_3F_2$ HCl: C, 53.97; H, 4.05; N, 13.25. Found: C, 53.79; H, 4.30; N, 13.08.

1-(3-Fluoro-4-pyridyl)-6-fluoro-7-(4-methyl-1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Monohydrochloride Salt (**7d**).

Using the procedure above, the treatment of 4-oxoquinolinecarboxylic acid derivative **5b** with 1-methylpiperazine in acetonitrile afforded **7d** (92%), mp 274-276°; ir (potassium bromide): 3417, 1728, 1628, 1466 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 3.04 (s, 3H, NCH_3), 3.36 (m, 2H, piperazinyl CH_2), 3.50-3.80 (m, 4H, piperazinyl CH_2), 4.02 (m, 2H, piperazinyl CH_2), 6.80 (m, 1H, C_8-H), 8.30 (d, 1H, J_{H-F} = 12.21 Hz, C_5-H), 8.78 (m, 1H, pyridyl CHCCF), 9.20-9.48 (m, 3H, pyridyl CHNCH, C_2-H); ms: (EI) m/z: 400 (M^+), 356, 285, 96, 71 (base).

Anal. Calcd. for $C_{20}H_{18}N_4O_3F_2$ HCl: C, 54.99; H, 4.38; N, 12.83. Found: C, 54.85; H, 4.57; N, 12.66.

Ethyl 1-(5-Fluoro-2-pyridyl)-6-fluoro-7-chloro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**11a**).

A mixture of nicotinoylacrylate derivative **10a** (10 g, 25 mmoles), potassium carbonate (5.16 g, 3.17 mmoles) and 18-crown-6 (1.97 g, 7.5 mmoles) in acetonitrile (50 ml) was heated to reflux for 2 hours. After cooling to room temperature, water was added to the mixture. The resulting light yellow solid was collected by filtration, washed with 25% aqueous ethanol, and dried to afford **11a** (8.41 g, 93%), mp 230°; ir (potassium bromide): 3448, 3055, 1705, 1651, 1605, 1466, 1242 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (t, 3H, J = 7.11 Hz, ethyl CH_3), 4.39 (q, 2H, J = 7.11 Hz, ethyl CH_2), 7.67-7.73 (m, 2H, pyridyl CHCHCF), 8.47-8.50 (m, 2H, pyridyl CFCHN, C_5-H), 8.97 (s, 1H, C_2-H); ms: (EI) m/z: 365 (M^+), 293 (base), 96.

Anal. Calcd. for $C_{16}H_{10}N_3O_3F_2Cl$: C, 52.55; H, 2.76; N, 11.49. Found: C, 52.71; H, 2.58; N, 11.66.

Ethyl 1-(3-Fluoro-4-pyridyl)-6-fluoro-7-chloro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**11b**).

Using the procedure above, cyclization of nicotinoyl acrylate derivative **10b** with potassium carbonate and 18-crown-6 in acetonitrile afforded **11b** (90%), mp 226°; ir (potassium bromide): 3432, 1689, 1650, 1604, 1411, 1280 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (t, 3H, J = 7.09 Hz, ethyl CH_3), 4.38 (q, 2H, J = 7.09 Hz, ethyl CH_2), 7.43-7.49 (m, 1H, pyridyl CHCCF), 8.45 (d, 1H, J = 7.13 Hz, pyridyl NCH), 8.52 (s, 1H, pyridyl NCHCF), 8.69 (d, 1H, J = 4.77 Hz, C_5-H), 8.77 (s, 1H, C_2-H); ms: (EI) m/z: 365 (M^+), 293 (base), 96.

Anal. Calcd. for $C_{16}H_{10}N_3O_3F_2Cl$: C, 52.55; H, 2.76; N, 11.49. Found: C, 52.44; H, 2.96; N, 11.22.

1-(5-Fluoro-2-pyridyl)-6-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Monohydrochloride Salt (**14a**).

In a typical procedure, **14a-14e**, a mixture of ethyl ester **11a** (1.0 g, 2.7 mmoles) and piperazine (491 mg, 5.7 mmoles) in acetonitrile (10 ml) was warmed at 35° for 6 hours. After cooling to room temperature, the resulting light yellow solid was collected by filtration, washed with ethanol, and dried to afford **12a**. To a dispersion of this obtained solid was added ethanol (5 ml) and 6 *N* hydrochloric acid solution (2.2 ml) and the mixture was refluxed for 6 hours. After cooling to room temperature, the resulting white powder was collected by filtration, washed with ethanol, and dried to afford monohydrochloride salt **14a** (0.88 g, 76%), mp >300°; ir (potassium bromide): 3448, 1728, 1628, 1434 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 3.59 (bs, 4H, piperazinyl CH_2), 4.23 (bs, 4H, piperazinyl CH_2), 8.01 (bs, 2H, pyridyl CHCHCF), 8.29 (d, 1H, J_{H-F} = 12.43 Hz, C_5-H), 8.63 (s, 1H, pyridyl CFCHN), 9.33 (s, 1H, C_2-H); ms: (EI) m/z: 387 (M^+), 343, 319 (base), 96.

Anal. Calcd. for $C_{18}H_{15}N_5O_3F_2$ HCl: C, 51.01; H, 3.81; N, 16.53. Found: C, 51.15; H, 3.72; N, 16.31.

1-(5-Fluoro-2-pyridyl)-6-fluoro-7-(4-methyl-1-piperazinyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Monohydrochloride Salt (**14b**).

Using the procedure above, **14b** was obtained in 98% yield *via* **12b**, mp 275-277°; ir (potassium bromide): 3518, 3433, 1728, 1643, 1473 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 3.03 (s, 3H, NCH_3), 3.29 (m, 2H, piperazinyl CH_2), 3.76 (m, 4H, piperazinyl CH_2), 4.74 (m, 2H, piperazinyl CH_2), 8.03 (m, 2H, pyridyl CHCHF), 8.32 (d, 1H, J_{H-F} = 9.65 Hz, C_5-H), 8.63 (s, 1H, pyridyl NCHCF), 9.34 (s, 1H, C_2-H); ms: (EI) m/z: 401 (M^+), 357, 313, 96, 70 (base).

Anal. Calcd. for $C_{19}H_{17}N_5O_3F_2$ HCl: C, 52.12; δ 4.14; N, 16.00. Found: C, 52.33; H, 4.41; N, 16.09.

1-(5-Fluoro-2-pyridyl)-6-fluoro-7-(3-amino-1-pyrrolidinyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Monohydrochloride Salt (**14c**).

Using the procedure above, **14c** was obtained in 75% yield *via* **12c**, mp 208-210°; ir (potassium bromide): 3417, 1720, 1635, 1466 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 2.32-2.79 (m, 2H, pyrrolidinyl CH_2), 3.60-4.12 (m, 2H, pyrrolidinyl CH_2), 4.25-4.72 (m, 3H, pyrrolidinyl CH, CH_2), 8.04 (m, 2H, pyridyl CHCHF), 8.15 (d, 1H, J_{H-F} = 11.16 Hz, C_5-H), 8.66 (s, 1H, pyridyl NCHCF), 9.28 (s, 1H, C_2-H); ms: (EI) m/z: 387 (M^+), 343 (base), 299, 96.

Anal. Calcd. for $C_{18}H_{15}N_5O_3F_2$ HCl: C, 51.01; H, 3.81; N, 16.53. Found: C, 50.92; H, 3.58; N, 16.37.

1-(3-Fluoro-4-pyridyl)-6-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Monohydrochloride Salt (**14d**).

Using the procedure above, **14d** was obtained in 84% yield *via* **12d**, mp 273-275° dec; ir (potassium bromide): 3409, 1727, 1635, 1442 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 3.62 (m, 4H, piperazinyl CH_2), 4.26 (m, 4H, piperazinyl CH_2), 8.30 (d, 1H, J_{H-F} = 12.10 Hz, C_5-H), 8.78 (m, 1H, pyridyl CHCCF), 9.24 (m, 1H, pyridyl NCH), 9.36 (m, 2H, pyridyl NCHCF, C_2-H); ms: (EI) m/z: 387 (M^+), 343, 301 (base), 96.

Anal. Calcd. for $C_{18}H_{15}N_5O_3F_2$ HCl: C, 51.01; H, 3.81; N, 16.53. Found: C, 51.24; H, 3.63; N, 16.77.

1-(3-Fluoro-4-pyridyl)-6-fluoro-7-(4-methyl-1-piperazinyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Monohydrochloride Salt (**14e**).

Using the procedure above, **14e** was obtained in 85% yield *via* **12e**, mp 275°; ir (potassium bromide): 3448, 1736, 1635, 1450 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 3.05 (s, 3H, NCH_3), 3.34 (m, 2H, piperazinyl CH_2), 3.80 (m, 4H, piperazinyl CH_2), 4.71 (m, 2H, piperazinyl CH_2), 8.30 (d, 1H, J_{H-F} = 12.58 Hz, C_5-H), 8.75 (m, 1H, pyridyl CHCCF), 9.19-9.48 (m, 3H, pyridyl NCH, NCHCF, C_2-H); ms: (EI) m/z: 401 (M^+), 357, 287, 70 (base).

Anal. Calcd. for $C_{19}H_{17}N_5O_3F_2$ HCl: C, 52.12; H, 4.14; N, 16.00. Found: C, 52.19; H, 4.02; N, 16.21.

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