Quinolone Analogues 10: Synthesis of Antimalarial Quinolones Having Pyridyl Moiety in N1-Side Chain

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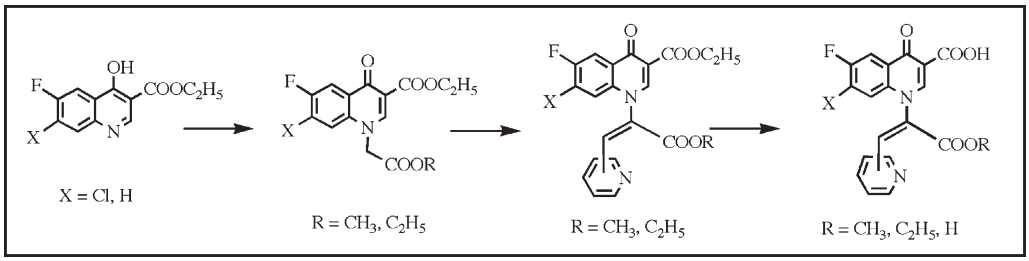

Novel 4-quinolone-3-carboxylates **6,7** and 4-quinolone-3-carboxylic acids **8–11** were synthesized from 4-hydroxyquinoline-3-carboxylates. Ethyl 1-[1-ethoxycarbonyl-2-(4-pyridyl)vinyl]-6-fluoro-4-oxoquinoline-3-carboxylate **7a** was found to show antimalarial activity from the screening data.

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INTRODUCTION

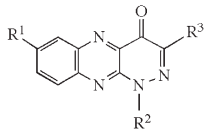
In previous articles [1–9], we reported the synthesis of the 1-alkyl-4-oxopyridazino[3,4-*b*]quinoxalines **1** (Chart 1) as candidates of antibacterial quinolone analogues, in which the 3-H [5], 3-methyl [3], 3-trifluoromethyl [4], and 3-bromo [6] derivatives showed good antibacterial, antifungal, and/or algicidal activities. To search for novel compounds with biological activities, we converted the target ring system from the 4-oxopyridazino[3,4-*b*]quinoxaline to the 4-quinolone nucleus, which was included in the excellent antibacterial agents such as new quinolones. A novel type of new quinolones is still developed nowadays as an antibacterial agents. On the other hand, Wentland et al. [10] reported the antiherpetic activity of the 7-(4-pyridyl)-4-quinolone-3-carboxamide **2** derived from its parent 3-carboxylic acid **3** (Chart 1).

Since quinolone antibacterials have been known to act on the DNA gyrase, some other biological activities such as antifungal and antiviral [10] activities are expected for quinolone analogues. In fact, some of our 1-methyl-4-oxopyridazino[3,4-*b*]quinoxalines **1** (R^1 = Cl, R^2 = CH_3, R^3 = H, CH_3, Br) exhibited antifungal activities in addition to antibacterial activities [9]. In this investigation, we undertook the structural transformation of ordinary new quinolones **4** into compounds **6–11** as shown in Scheme 1. Namely, the C7-basic moiety is shifted to the N1-side chain leading to compound **5**, and the linker part is inserted between the N1 and the basic moiety. Furthermore, a carboxyl group was introduced in the linker part to provide a proximal pair of the acid and base moieties. This article describes the synthesis of compounds **6–11**, some of which are found to exhibit antimalarial activity from the screening data.

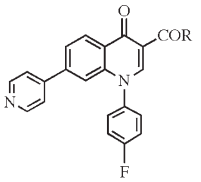
RESULTS AND DISCUSSION

Synthesis of compounds 6–11. The reaction of ethyl 7-chloro-6-fluoro-4-hydroxyquinoline-3-carboxylate **12** [11,12] with methyl bromoacetate or ethyl 6-fluoro-4-hydroxyquinoline-3-carboxylate **13** [11,12] with ethyl

Chart 1



1: 1-Alkyl-4-oxopyridazino[3,4-*b*]quinoxalines
R^1 = H, Cl; R^2 = CH_3, C_2H_5;
R^3 = H, CH_3, CF_3, Br



2: R = NH_2; **3**: R = OH

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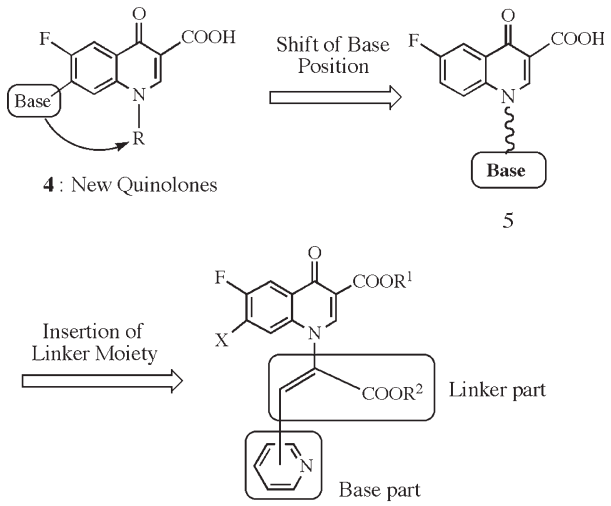
Scheme 1



6a,b: X = Cl; $R^1 = C_2H_5$; $R^2 = CH_3$

7a-c: X = H; $R^1 = R^2 = C_2H_5$

8a,b: X = Cl; R^1 = H; $R^2 = CH_3$

9a-c: X = H; R^1 = H; $R^2 = C_2H_5$

10a,b: X = Cl; $R^1 = R^2$ = H

11a-c: X = H; $R^1 = R^2$ = H

a: 4-Pyridyl; **b**: 3-Pyridyl; **c**: 2-Pyridyl

Table 1

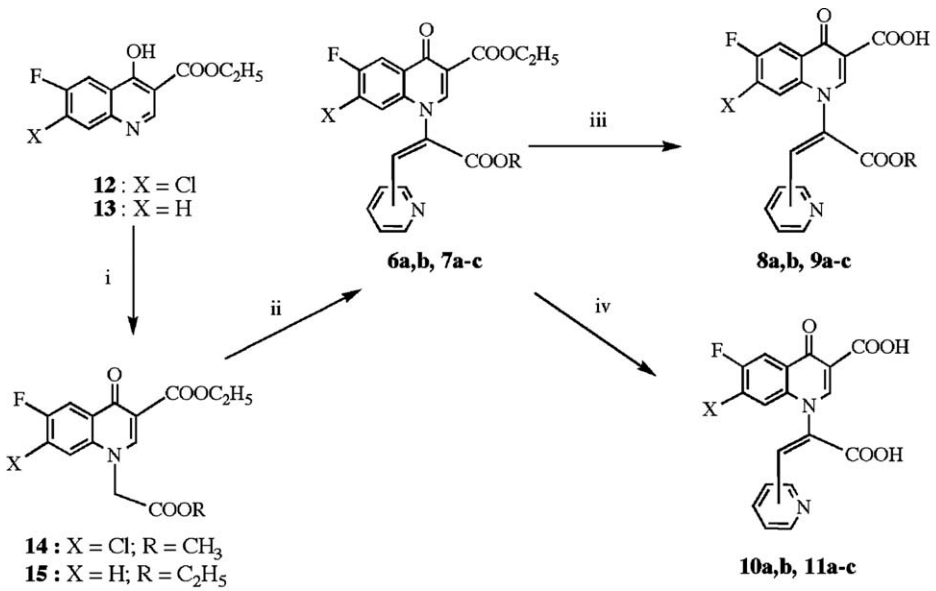
In vitro antimalarial activity for compounds **7**, **9**, and **11**.

Compound	*Plasmodium falciparum*, IC_{50} (μmol)	Mouse FM3A Cell,[a] IC_{50} (μmol)	Chemotherapeutic coefficient
7a	8.2	>24	>2.9
7b	26	100	3.8
9b	29	>100	>3.4
9c	21	>100	>4.8
11b	24	>100	>4.2
11c	21	>100	>4.8

[a] Mouse breast cancer cell, F28-7 strain.

bromoacetate gave the methyl (7-chloro-6-fluoro-4-quinolon-1-yl)acetate **14** or ethyl (6-fluoro-4-quinolon-1-yl)-acetate **15**, respectively (Scheme 2). The reaction of compound **14** with 4- and 3-pyridinecarbaldehydes or the reaction of compound **15** with 4-, 3-, and 2-pyridinecarbaldehydes afforded the methyl 2-(7-chloro-6-fluoroquinolon-1-yl)-3-(4- and 3-pyridyl)acrylates **6a,b** or ethyl 2-(6-fluoroquinolon-1-yl)-3-(4-, 3-, and 2-pyridyl)acrylates **7a–c**, respectively. Reflux of compounds **6a,b** in sulfuric acid/acetic acid/water was clarified to hydrolyze the ethyl ester of quinolone nucleus from the analytical and spectral data, providing the quinolone-3-carboxylic acids **8a,b**, respectively. Similar reaction of

Scheme 2

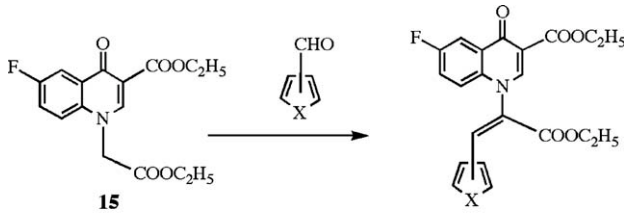


Reagents: i) $BrCH_2COOR$, K_2CO_3 in *N,N*-Dimethylformamide; ii) Pyridinecarbaldehyde, DBU in *N,N*-Dimethylformamide; iii) H_2SO_4, H_2O in CH_3COOH, then NaOH; iv) NaOH, H_2O in EtOH, then HCl

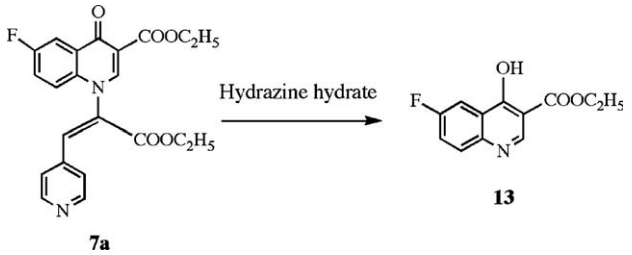
6a,b: X = Cl; R = CH_3 ; **7a-c**: X = H; R = C_2H_5 ; **8a,b**: X = Cl; R = CH_3 ; **9a-c**: X = H; R = C_2H_5 ;

10a,b: X = Cl ; **11a-c**: X = H ; **a**: 4-Pyridyl ; **b**: 3-Pyridyl; **c**: 2-Pyridyl

Scheme 3



Scheme 4



compounds **7a–c** gave the quinolone-3-carboxylic acids **9a–c**, respectively. On the other hand, the hydrolysis of **6a,b** and **7a–c** with sodium hydroxide afforded the dicarboxylic acids **10a,b** and **11a–c**, respectively.

Antimalarial activity. The *in vitro* screening to antimalarial activity was carried out for compounds **6–11** according to a method in literatures [13], and the data are shown in Table 1. The IC_{50} of the diester **7a** was 8.2 μmol to *Plasmodium falciparum*, whose value was referred as effective. The IC_{50} of the diester **7a** to mouse FM3A cell F28-7 strain was 24 μmol, and the chemical therapeutic coefficient was the value of 2.9. The diester **7b** with the 3-pyridyl moiety had a weaker activity than the diester **7a** with the 4-pyridyl moiety. Moreover, compounds with carboxyl group in the quinolone nucleus and/or N1-side chain or compounds with the C7-chlorine atom in the quinolone nucleus represented no antimalarial activity, suggesting the unfavorable effect of such carboxyl group and chlorine atom on the activity.

The 4-pyridyl moiety in the N1-substituent of the diester **7a** was found not to be replaced with the nonbasic moiety. That is, compounds **16–18** (Scheme 3) with furyl or thienyl moiety in the N1-substituent were clarified to exhibit no antimalarial activity.

Trial for modification of compound 7a. An attempt was unsuccessful to convert the ester group into carbohydrazide group to install an additional basic moiety in the N1-side chain of compound **7a**. As shown in Scheme 4, the reaction of compound **7a** with hydrazine hydrate resulted in the bond cleavage between the N1 and acrylate moiety.

Analytical and spectral data. The structural assignment of novel compounds **6–11** was based on the analytical and spectral data. Especially, the NOE spectral data among the vinyl, pyridyl, and quinolone 8-H protons of compounds **7a–c** shown in Table 2 ascertained the presence of the pyridylacrylate moiety in the N1 of the quinolone nucleus. Moreover, the NOE between the vinyl and quinolone 8-H proton signals suggested the *E*-isomer for compounds **6–11** and **16–18**, whereas the NOE between the pyridine 3-H and quinolone 2-H proton signals supported the presence of the *Z*-isomer for compounds **7a** and **9a** (Table 2). There was no difference in the proton chemical shifts between the *E*- and *Z*-isomers in compounds **7a** and **9a**.

In the ^{1}H-NMR spectra of compounds **6b**, **8a**, **11a**, and **17**, two kinds of quinolone 2-H proton signals were observed [14] (Table 3), which would not be due to the presence of the *E*- and *Z*-isomers, because compounds **7a** and **9a** existing as the *E*- and *Z*-isomers in solution exhibited a single quinolone 2-H proton signal.

Table 2

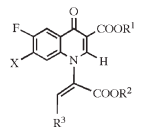
NOE data for compounds **7**, **9**, **11**, and **16–18**.

Radiation	NOE	7a	7b	7c	9a	9b	9c	11b	16	17	18
Vinyl H	Quinolone 8-H	1.2[a]	1.4	1.0	1.6	–	–	–	1.0	1.5	1.1
	Quinolone 2-H	–	2.7	0.6	–	–	–	–	–	–	–
	Pyridyl 4-H	–	2.8	–	–	2.7	–	3.8	–	–	–
	Pyridyl 3-H	8.8	–	6.1	10.9	–	12.0	–	–	–	–
	Pyridyl 2-H	–	8.1	–	–	13.7	–	7.7	–	–	–
	Furyl 3-H	–	–	–	–	–	–	–	3.9	–	–
	Thienyl 4-H	–	–	–	–	–	–	–	–	–	2.5
	Thienyl 3-H	–	–	–	–	–	–	–	–	6.5	–
	Thienyl 2-H	–	–	–	–	–	–	–	–	–	7.4
Pyridyl 3-H	Vinyl H	8.4	–	–	–	–	–	–	–	–	–
	Pyridyl 2-H	17.9	–	–	–	–	–	–	–	–	–
Quinolone 2-H	Pyridyl 3-H	2.3	–	–	2.0	–	–	–	–	–	–

[a] NOE (%) Observed.

Table 3

Compounds showing two kinds of quinolone 2-H proton signals [14].

	Compound	R^1	R^2	R^3	X	Chemical Shift (δ)		
						Quinolone 2-H		Ratio
	**6b**	C_2H_5	CH_3	3-Pyridyl	Cl	8.66	8.60	40 : 60
	8a	H	CH_3	4-Pyridyl	Cl	9.05	8.90	72 : 28
	11a	H	H	4-Pyridyl	H	9.11	9.03	23 : 77
	17	C_2H_5	C_2H_5	2-Thienyl	H	8.59	8.55	45 : 55

Moreover, two kinds of quinolone 2-H, 8-H, vinyl, pyridine 5-H, and ethyl ester CH_2 proton signals were observed in the ^{1}H-NMR spectra of compound **6b**, suggesting the presence of two kinds of isomers [14]. Further investigation to clarify the aforementioned phenomena is in progress, and the results will be reported elsewhere.

The ^{13}C-NMR spectral data are shown in Table 4, which includes the respective carbon chemical shifts of the typical our quinolones **6a**, **7a**, **14**, and **16** assigned by the dHSQC and gHMBC spectral data.

EXPERIMENTAL

All melting points were determined on a Yazawa micro-melting point BY-2 apparatus and are uncorrected. The IR spectra (potassium bromide) were recorded with a JASCO FT/IR-200 spectrometer. The ^{1}H-NMR and dHSOC/gHMBC spectra were measured with a Varian XL-400 and Varian INOVA 600 spectrometers at 400 and 600 MHz, respectively. The chemical shifts are given in the δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

Compounds **12** and **13** were synthesized by a method reported in literatures [11,12], refluxing in diphenyl ether at 250°.

Methyl (7-chloro-3-ethoxycarbonyl-6-fluoro-1,4-dihydro-4-oxoquinolin-1-yl)acetate 14. A mixture of compound **12** (5.0 g, 18.6 mmol), ethyl bromoacetate (5.09 g, 33.5 mmol), potassium carbonate (5.0 g, 36.2 mmol) in dry *N*,*N*-dimethylformamide (200 mL) was heated at 100–120° with stirring for 2 h and filtrated while the mixture was hot. Evaporation of the solvent *in vacuo* gave colorless crystals, which were recrystallized from *N*,*N*-dimethylformamide/ethanol/water to afford colorless needles **14** (5.13 g, 81%); mp: 251–252°; IR: ν 1725 cm^{-1}; ms: m/z 341 (M^+), 343 ($M^+ + 2$); NMR (deuteriodimethyl sulfoxide): 8.73 (s, 1H, 2-H), 8.06 (d, $J = 6.0$ Hz, 1H, 8-H), 8.02 (d, $J = 9.5$ Hz, 1H, 5-H), 5.39 (s, 2H, CH_2), 4.22 (q, $J = 7.0$ Hz, 2H, CH_2), 3.72 (s, 3H, CH_3), 1.27 (t, $J = 7.0$ Hz, 3H, CH_3). Anal. Calcd. for $C_{15}H_{13}ClFNO_5$: C, 52.72; H, 3.83; N, 4.10. Found: C, 52.45; H, 3.94; N, 4.36.

Ethyl (3-ethoxycarbonyl-6-fluoro-1,4-dihydro-4-oxoquinolin-1-yl)acetate 15. A mixture of compound **13** (5.0 g, 21.3 mmol), ethyl bromoacetate (5.33 g, 31.9 mmol), potassium carbonate (4.40 g, 31.9 mmol) in dry *N*,*N*-dimethylformamide (200 mL) was heated at 100–120° with stirring for 2 h and filtrated while the mixture was hot. Then, ethanol (100 mL) was added to the filtrate with stirring, and the solution was allowed to stand at room temperature to precipitate colorless needles **15**, which were collected by suction and then washed with *n*-hexane (5.97 g, 87%); mp: 274–275°; IR: ν 1740, 1720 cm^{-1}; ms: m/z 321 (M^+); NMR (deuteriotrifluoroacetic acid): 9.14 (s, 1H, 2-H), 8.11 (dd, $J = 7.5$, 2.8 Hz, 1H, 5-H), 7.82 (dd, $J = 10.0$, 4.0 Hz, 1H, 8-H), 7.75 (ddd, $J = 10.0$, 7.5, 2.8 Hz, 1H, 7-H), 5.50 (s, 2H, CH_2), 4.42 (q, $J = 7.0$ Hz, 2H, CH_2), 4.16 (q, $J = 7.0$ Hz, 2H, CH_2), 1.24 (t, $J = 7.0$ Hz, 3H, CH_3), 1.08 (t, $J = 7.0$ Hz, 3H, CH_3). Anal. Calcd. for $C_{16}H_{16}ClFNO_5$: C, 59.81; H, 5.02; N, 4.36. Found: C, 59.64; H, 5.09; N, 4.59.

Table 4

^{13}C-NMR spectral data for compounds **6a**, **7a**, **14**, and **16**.

	Compounds			
Carbon	**14**	**6a**	**7a**	**16**
2-C	151.1	149.0	148.5	149.4
3-C	110.5	112.4	111.9	111.3
4-C=O	171.7	171.8	172.4	172.5
4a-C	128.2	127.9	129.2	129.2
5-C	112.6	113.1	111.4	111.1
6-C	154.6	155.0	159.8	159.5
7-C	125.8	126.5	122.0	121.6
8-C	120.3	119.9	120.2	120.2
8a-C	136.9	136.1	135.7	136.5
1N-Methylene	53.5	–	–	–
3-Ester C=O	164.2	163.8	164.0	164.3
Other Ester C=O	168.4	162.9	162.5	163.0
Vinyl 1-C	–	130.3	130.9	123.0
Vinyl 2-C	–	140.0	139.1	128.0
Pyridyl 2,6-C	–	150.9	150.9	–
Pyridyl 3,5-C	–	123.5	123.4	–
Pyridyl 4-C	–	138.0	138.0	–
Furyl 2-C	–	–	–	147.2
Furyl 3-C	–	–	–	121.8
Furyl 4-C	–	–	–	113.5
Furyl 5-C	–	–	–	149.0
CH_3	14.3	14.4	14.1	14.2
	53.6	52.8	14.3	14.4
CH_2	60.5	60.2	60.4	60.2
	–	–	62.6	62.0

Ethyl 7-chloro-6-fluoro-1,4-dihydro-1-[(*Z*)-1-methoxycarbonyl-2-(4- and 3-pyridyl)vinyl]-4-oxoquinoline-3-carboxylates 6a,b. ***General procedure.*** A solution of compound **14** (5.0 g, 14.6 mmol), 4- or 3-pyridinecarbaldehyde (2.50 g, 23.4 mmol), and 1,8-diazabicyclo[5.4.0]-7-undecene (1.19 g, 7.80 mmol) in dry dioxane (100 mL) was refluxed with stirring for 10 h. Acetic acid (5 mL) was added to the solution, and the solvent was evaporated *in vacuo* to give colorless crystals. Recrystallization from dioxane/water afforded colorless needles **6a** or **6b**.

Compound **6a** was obtained in 55% yield (3.48 g); mp 226–227°; IR: ν 1730 cm^{-1}; ms: m/z 430 (M^+), 432 ($M^+ + 2$); NMR (deuteriodimethyl sulfoxide): 8.65 (s, 1H, 2-H), 8.54 (d, $J = 6.5$ Hz, 2H, pyridine 2-H and 6-H), 8.24 (s, 1H, vinylic H), 8.07 (d, $J = 9.0$ Hz, 1H, 5-H), 7.81 (d, $J = 6.0$ Hz, 1H, 8-H), 7.12 (d, $J = 6.5$ Hz, 2H, pyridine 3-H and 5-H), 4.18 (q, $J = 7.0$ Hz, 2H, CH_2), 3.81 (s, 3H, CH_3), 1.22 (t, $J = 7.0$ Hz, 3H, CH_3). Anal. Calcd. for $C_{21}H_{16}ClFN_2O_5 \cdot 1/3H_2O$ [15]: C, 57.74; H, 3.85; N, 6.41. Found: C, 57.79; H, 3.81; N, 6.36.

Compound **6b** was obtained in 61% yield (3.82 g); mp 214–215°; IR: ν 1735, 1720 cm^{-1}; ms: m/z 430 (M^+), 432 ($M^+ + 2$); NMR (deuteriodimethyl sulfoxide): (isomer A) [14] 8.66 (s, 1H, 2-H), 8.29 (s, 1H, vinylic H), 8.08 (d, $J = 9.0$ Hz, 1H, 5-H), 7.81 (d, $J = 6.0$, Hz, 1H, 8-H), 7.41 (ddd, $J = 4.0$, 2.0, 2.0 Hz, 1H, pyridine 4-H), 7.34 (dd, $J = 8.0$, 4.0 Hz, 1H, pyridine 5-H), 8.57–8.52 (m, 2H, pyridine 2-H and 6-H), 4.21 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 4.17 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 3.81 (s, 3H, CH_3), 1.23 (dd, $J = 7.0$, 7.0 Hz, 3H, CH_3); (isomer B) [14] 8.60 (s, 1H, 2-H), 8.22 (s, 1H, vinylic H), 8.08 (d, $J = 9.0$ Hz, 1H, 5-H), 7.73 (d, $J = 6.0$ Hz, 1H, 8-H), 7.41 (ddd, $J = 4.0$, 2.0, 2.0 Hz, 1H, pyridine 4-H), 7.33 (dd, $J = 8.0$, 4.0 Hz, 1H, pyridine 5-H), 8.57–8.52 (m, 2H, pyridine 2-H and 6-H), 4.20 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 4.16 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 3.81 (s, 3H, CH_3), 1.23 (dd, $J = 7.0$, 7.0 Hz, 3H, CH_3). The 5-H, pyridine 4-H, ester methyl proton signals of the above isomers A and B were observed in the same magnetic field. Anal. Calcd. for $C_{21}H_{16}ClFN_2O_5 \cdot 1/2H_2O$ [15]: C, 57.35; H, 3.90; N, 6.37. Found: C, 57.39; H, 3.75; N, 6.42.

Methyl 1-[(*Z*)-1-ethoxycarbonyl-2-(4-, 3-, and 2-pyridyl)-vinyl]-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylates 7a–c. ***General procedure.*** A solution of compound **15** (5.0 g, 15.6 mmol), 4-, 3-, or 2-pyridinecarbaldehyde (2.50 g, 23.4 mmol), and 1,8-diazabicyclo[5.4.0]-7-undecene (1.19 g, 7.80 mmol) in dry dioxane (100 mL) was refluxed with stirring for 10 h. Acetic acid (5 mL) was added to the solution, and the solvent was evaporated *in vacuo* to give colorless crystals. Recrystallization from dioxane/water afforded colorless needles **7a**, **7b**, or **7c**.

Compound **7a** [16] was obtained in 59% yield (3.75 g); mp 226–227°; IR: ν 1725 cm^{-1}; ms: m/z 410 (M^+); NMR (deuteriodimethyl sulfoxide): 8.63 (s, 1H, 2-H), 8.54 (d, $J = 6.0$ Hz, 2H, pyridine 2-H and 6-H), 8.25 (s, 1H, vinylic H), 7.92 (dd, 9.3, 3.0 Hz, 1H, 5-H), 7.58 (ddd, 9.0, 8.0, 3.0 Hz, 1H, 7-H), 7.50 (dd, $J = 9.0$, 4.5 Hz, 1H, 8-H), 7.11 (d, $J = 6.0$ Hz, 2H, pyridine 3-H and 5-H), 4.28 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 4.24 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 4.18 (q, $J = 7.0$ Hz, 2H, CH_2), 1.22 (dd, $J = 7.0$, 7.0 Hz, 3H, CH_3), 1.21 (t, $J = 7.0$ Hz, 3H, CH_3). Anal. Calcd. for $C_{22}H_{19}FN_2O_5$: C, 64.39; H, 4.67; N, 6.83. Found: C, 64.39; H, 4.67; N, 6.86.

Compound **7b** was obtained in 49% yield (3.10 g); mp 140–141°; IR: ν 1725, 1690 cm^{-1}; ms: m/z 410 (M^+); NMR (deuteriodimethyl sulfoxide): 8.65 (s, 1H, 2-H), 8.55 (d, $J = 2.0$ Hz, 1H, pyridine 2-H), 8.53 (dd, $J = 4.5$, 2.0 Hz, 1H, pyridine 6-H), 8.29 (s, 1H, vinylic H), 7.92 (dd, 9.0, 3.0 Hz, 1H, 5-H), 7.57 (ddd, $J = 9.0$, 8.0, 3.0 Hz, 1H, 7-H), 7.50 (dd, $J = 9.0$, 4.5 Hz, 1H, 8-H), 7.39 (ddd, $J = 8.0$, 2.0, 2.0 Hz, 1H, pyridine 4-H), 7.33 (dd, $J = 8.0$, 4.5 Hz, 1H, pyridine 5-H), 4.28 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 4.24 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 4.22 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 4.17 (dq, $J = 11.0$, 7.0 Hz, 1H, methylene CH), 1.23 (dd, $J = 7.0$, 7.0 Hz, 3H, CH_3), 1.22 (dd, $J = 7.0$, 7.0 Hz, 3H, CH_3). Anal. Calcd. for $C_{22}H_{19}FN_2O_5$: C, 64.39; H, 4.67; N, 6.83. Found: C, 64.16; H, 4.67; N, 6.90.

Compound **7c** was obtained in 58% yield (3.73 g); mp 166–167°; IR: ν 1700 cm^{-1}; ms: m/z 410 (M^+); NMR (deuteriodimethyl sulfoxide): 8.56 (s, 1H, 2-H), 8.27 (ddd, $J = 5.0$, 1.5, 0.5 Hz, 1H, pyridine 6-H), 8.24 (s, 1H, vinylic H), 7.99 (dd, $J = 9.0$, 3.0 Hz, 1H, 5-H), 7.83 (ddd, 7.5, 7.5, 1.5 Hz, 1H, pyridine 4-H), 7.69 (ddd, $J = 7.5$, 1.0, 0.5 Hz, 1H, pyridine 3-H), 7.50 (ddd, $J = 9.0$, 8.0, 3.0 Hz, 1H, 7-H), 7.41 (dd, $J = 9.0$, 4.5 Hz, 1H, 8-H), 7.29 (ddd, $J = 7.5$, 5.0, 1.0 Hz, 1H, pyridine 5-H), 4.30 (dq, $J = 10.5$, 7.0 Hz, 1H, methylene CH), 4.25 (dq, $J = 10.5$, 7.0 Hz, 1H, methylene CH), 4.17 (q, $J = 7.0$ Hz, 2H, CH_2), 1.23 (dd, $J = 7.0$, 7.0 Hz, 3H, CH_3), 1.22 (t, $J = 7.0$ Hz, 3H, CH_3). Anal. Calcd. for $C_{22}H_{19}FN_2O_5$: C, 64.39; H, 4.67; N, 6.83. Found: C, 64.00; H, 4.69; N, 6.85.

7-Chloro-6-fluoro-1,4-dihydro-1-[(*Z*)-1-methoxycarbonyl-2-(4- and 3-pyridyl)vinyl]-4-oxoquinoline-3-carboxylic acids 8a,b. ***General procedure.*** A solution of compound **6a** or **6b** (1.0 g, 2.33 mmol) in concentrated sulfuric acid (0.4 mL), water (1.0 mL), and acetic acid (40 mL) was refluxed with stirring for 2 h. The solvent was evaporated *in vacuo* to give an oily product, which was dissolved in ethanol (10 mL) and then neutralized with sodium hydrogen carbonate to afford crystals. The crystals were collected by suction, and then recrystallization from *N*,*N*-dimethylformamide/ethanol/water provided yellow needles **8a** or **8b**.

Compound **8a** was obtained in 87% yield (810 mg); mp 244–245°; IR: ν 1740 cm^{-1}; ms: m/z 402 (M^+), 404 ($M^+ + 2$); NMR (deuteriodimethyl sulfoxide): 14.23 (brs, 1H, COOH), 9.05, 8.90 [14] (s, 1H, 2-H), 8.52 (d, $J = 6.0$ Hz, 2H, pyridine 2-H and 6-H), 8.28 (s, 1H, vinylic H), 8.25 (d, $J = 9.0$ Hz, 1H, 5-H), 8.07 (d, $J = 6.0$ Hz, 1H, 8-H), 7.09 (d, $J = 6.0$ Hz, 2H, pyridine 3-H and 5-H), 3.80 (s, 3H, CH_3). Anal. Calcd. for $C_{19}H_{12}ClFN_2O_5 \cdot 1/5H_2O$ [15]: C, 56.16; H, 3.08; N, 6.89. Found: C, 56.08; H, 3.07; N, 6.93.

Compound **8b** was obtained in 51% yield (470 mg); mp 216–217°; IR: ν 1725 cm^{-1}; ms: m/z 402 (M^+), 404 ($M^+ + 2$); NMR (deuteriodimethyl sulfoxide): 14.22 (brs, 1H, COOH), 9.06 (s, 1H, 2-H), 8.60 (s, 1H, pyridine 2-H), 8.55 (dd, $J = 3.6$, 1.0 Hz, 1H, pyridine 6-H), 8.34 (s, 1H, vinylic H), 8.26 (dd, 9.1, 1.0 Hz, 1H, 5-H), 8.08 (dd, $J = 4.0$, 1.0 Hz, 1H, 8-H), 7.34 (dd, $J = 5.0$, 1.0 Hz, 1H, pyridine 4-H), 7.30 (dd, $J = 5.0$, 3.6 Hz, 1H, pyridine 5-H), 3.82 (s, 3H, CH_3). Anal. Calcd. for $C_{19}H_{12}ClFN_2O_5 \cdot 1/3H_2O$ [15]: C, 55.83; H, 3.12; N, 6.85. Found: C, 55.83; H, 3.11; N, 6.96.

1-[(*Z*)-1-Ethoxycarbonyl-2-(4-, 3-, and 2-pyridyl)vinyl]-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acids 9a–c. ***General procedure.*** A solution of compound **7a**, **7b**, or **7c** (1.0 g, 2.44 mmol) in concentrated sulfuric acid (0.4 mL),

water (1.0 mL), and acetic acid (40 mL) was refluxed with stirring for 2 h. The solvent was evaporated *in vacuo* to give an oily product, which was dissolved in ethanol (10 mL) and then neutralized with sodium hydrogen carbonate to afford crystals. The crystals were collected by suction, and then recrystallization from *N*,*N*-dimethylformamide/ethanol/water provided yellow needles **9a**, **9b**, or **9c**.

Compound **9a** [16] was obtained in 67% yield (620 mg); mp 228–229°; IR: ν 1740, 1720 cm^{-1}; ms: m/z 382 (M^+); NMR (deuteriodimethyl sulfoxide): 14.45 (brs, 1H, COOH), 9.06 (s, 1H, 2-H), 8.51 (d, J = 6.5 Hz, 2H, pyridine 2-H and 6-H), 8.30 (s, 1H, vinylic H), 8.09 (ddd, 9.0, 8.5, 2.0 Hz, 1H, 7-H), 7.77 (dd, 10.0, 2.0 Hz, 1H, 5-H), 7.74 (dd, J = 9.0, 3.5 Hz, 1H, 8-H), 7.07 (d, J = 6.5 Hz, 2H, pyridine 3-H and 5-H), 4.28 (dq, J = 11.0, 7.0 Hz, 1H, methylene CH), 4.24 (dq, J = 11.0, 7.0 Hz, 1H, methylene CH), 1.21 (dd, J = 7.0, 7.0 Hz, 3H, CH_3). Anal. Calcd. for $C_{19}H_{15}FN_2O_5$: C, 62.83; H, 3.95; N, 7.33. Found: C, 62.66; H, 3.98; N, 7.42.

Compound **9b** was obtained in 64% yield (600 mg); mp 168–169°; IR: ν 1725, 1620 cm^{-1}; ms: m/z 382 (M^+); NMR (deuteriodimethyl sulfoxide): 14.48 (brs, 1H, COOH), 9.07 (s, 1H, 2-H), 8.56 (dd, J = 1.5, 1.5 Hz, 1H, pyridine 2-H), 8.52 (dd, J = 4.0, 2.5 Hz, 1H, pyridine 5-H), 8.35 (s, 1H, vinylic H), 8.09 (ddd, 8.5, 8.5, 1.5 Hz, 1H, 7-H), 7.74 (J = 8.5, 6.0, 1.5 Hz, 2H, 5-H and 8-H), 7.28 [(dd, J = 4.0, 1.5 Hz, 1H), (dd, J = 2.5, 1.5 Hz, 1H), pyridine 4-H and 6-H], 4.28 (dq, J = 11.0, 7.0 Hz, 1H, methylene CH), 4.23 (dq, J = 11.0, 7.0 Hz, 1H, methylene CH), 1.22 (dd, J = 7.0, 7.0 Hz, 3H, CH_3). Anal. Calcd. for $C_{19}H_{15}FN_2O_5$: C, 62.83; H, 3.95; N, 7.33. Found: C, 62.57; H, 3.95; N, 7.36.

Compound **9c** was obtained in 70% yield (652 mg); mp 200–201°; IR: ν 1720, 1620 cm^{-1}; ms: m/z 382 (M^+); NMR (deuteriodimethyl sulfoxide): 14.75 (s, 1H, COOH), 8.99 (s, 1H, 2-H), 8.30 (s, 1H, vinylic H), 8.16 (dd, J = 4.5, 2.5 Hz, 1H, pyridine 6-H), 8.06 (dd, J = 8.5, 2.0 Hz, 1H, 5-H), 7.84 (ddd, J = 8.0, 7.0, 2.5 Hz, 1H, pyridine 4-H), 7.80 (dd, J = 8.0, 1.5 Hz, 1H, pyridine 3-H), 7.70 (ddd, J = 7.0, 7.0, 2.0 Hz, 1H, 7-H), 7.66 (dd, J = 7.0, 2.0 Hz, 1H, 8-H), 7.27 (ddd, J = 7.0, 4.5, 1.5 Hz, 1H, pyridine 5-H), 4.30 (dq, J = 11.0, 7.0 Hz, 1H, methylene CH), 4.25 (dq, J = 11.0, 7.0 Hz, 1H, methylene CH), 1.23 (dd, J = 7.0, 7.0 Hz, 3H, CH_3). Anal. Calcd. for $C_{20}H_{15}FN_2O_5$: C, 61.86; H, 4.07; N, 7.21. Found: C, 62.06; H, 3.98; N, 7.28.

1-[(*Z*)-1-Carboxy-2-(4- and 3-pyridyl)vinyl]-7-chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acids 10a,b. ***General procedure.*** A solution of potassium hydroxide (290 mg, 5.13 mmol) in water (2 mL) was added to a solution of compound **6a** or **6b** (1.0 g, 2.33 mmol) in ethanol (40 mL), and the solution was refluxed for 2 h to precipitate crystals. After cooling of the reaction mixture and then neutralization with hydrochloric acid (1 mol solution), the solvent was evaporated *in vacuo* to afford crystals, which were collected by suction. Recrystallization from *N*,*N*-dimethylformamide/ethanol/water gave yellow needles.

Compound **10a** was obtained in 89% yield (800 mg); mp 285–286°; IR: ν 1730 cm^{-1}; ms: m/z 388 (M^+), 390 (M^+ + 2); NMR (deuteriodimethyl sulfoxide): 14.28 (brs, 1H, COOH), 9.01 (s, 1H, 2-H), 8.51 (d, J = 6.5 Hz, 2H, pyridine 2-H and 6-H), 8.25 (d, J = 9.0 Hz, 1H, 5-H), 8.22 (s, 1H, vinylic H), 8.01 (d, J = 6.0 Hz, 1H, 8-H), 7.93 (s, formyl H of *N*,*N*-dimethylformamide), 7.10 (d, J = 6.0 Hz, 2H, pyridine 3-H and 5-H), 2.81 (s, CH_3 of *N*,*N*-dimethylformamide), 2.71 (s, CH_3 of *N*,*N*-dimethylformamide). One of two COOH proton signals was not observed presumably due to flattening. Anal. Calcd. for $C_{17}H_{10}ClFN_2O_5 \cdot 1/3H_2O \cdot 2/3HCON(CH_3)_2$ [15]: C, 56.16; H, 3.08; N, 6.89. Found: C, 56.08; H, 3.07; N, 6.93.

Compound **10b** was obtained in 95% yield (860 mg); mp 284–285°; IR: ν 1720 cm^{-1}; ms: m/z 388 (M^+), 390 (M^+ + 2); NMR (deuteriodimethyl sulfoxide): 14.29 (brs, 1H, COOH), 9.02 (s, 1H, 2-H), 8.56 (d, J = 2.0 Hz, 1H, pyridine 2-H), 8.52 (dd, J = 4.5, 2.0 Hz, 1H, pyridine 6-H), 8.27 (s, 1H, vinylic H), 8.25 (d, J = 9.0 Hz, 1H, 5-H), 7.99 (d, J = 6.0 Hz, 1H, 8-H), 7.33 (ddd, J = 8.0, 2.0, 2.0 Hz, 1H, pyridine 4-H), 7.28 (dd, J = 8.0, 4.5 Hz, 1H, pyridine 5-H). One of two COOH proton signals was not observed presumably due to flattening. Anal. Calcd. for $C_{17}H_{10}ClFN_2O_5$: C, 55.61; H, 2.59; N, 7.21. Found: C, 55.33; H, 2.70; N, 7.23.

1-[(*Z*)-1-Carboxy-2-(4-, 3-, and 2-pyridyl)vinyl]-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acids 11a–c. ***General procedure.*** A solution of potassium hydroxide (300 mg, 5.37 mmol) in water (2 mL) was added to a solution of compound **7a**, **7b**, or **7c** (1.0 g, 2.44 mmol) in ethanol (40 mL), and the solution was refluxed for 2 h to precipitate crystals. After cooling of the reaction mixture and then neutralization with hydrochloric acid (1 mol solution), the solvent was evaporated *in vacuo* to afford crystals, which were collected by suction. Recrystallization from ethanol/water gave analytically pure sample.

Compound **11a** was obtained in 58% yield (500 mg) as yellow needles; mp 270–271°; IR: ν 1720 cm^{-1}; ms: m/z 354 (M^+); NMR (deuteriodimethyl sulfoxide): 14.80 (brs [17], COOH), 14.51 (brs, 1H, COOH), 9.11, 9.03 [14] (s, 1H, 2-H), 8.50 (d, J = 6.0 Hz, 2H, pyridine 2-H and 6-H), 8.26 (s, 1H, vinylic H), 8.08 (dd, 8.5, 2.5 Hz, 1H, 5-H), 7.76 (ddd, 8.5, 8.5, 2.5 Hz, 1H, 7-H), 7.73 (dd, J = 8.5, 4.5 Hz, 1H, 8-H), 7.06 (d, J = 6.0 Hz, 2H, pyridine 3-H and 5-H). Anal. Calcd. for $C_{17}H_{11}FN_2O_5 \cdot H_2O$ [15]: C, 58.07; H, 3.52; N, 7.52. Found: C, 58.34; H, 3.48; N, 7.40.

Compound **11b** was obtained in 73% yield (630 mg) as colorless needles; mp 246–247°; IR: ν 1710 cm^{-1}; ms: m/z 354 (M^+); NMR (deuteriodimethyl sulfoxide): 14.53 (brs, 1H, COOH), 9.04 (s, 1H, 2-H), 8.54 (d, J = 2.0 Hz, 1H, pyridine 2-H), 8.51 (dd, J = 4.0, 2.5 Hz, 1H, pyridine 6-H), 8.31 (s, 1H, vinylic H), 8.09 (ddd, J = 8.5, 8.5, 2.5 Hz, 1H, 7-H), 7.75 (dd, J = 7.0, 2.5 Hz, 1H, 5-H), 7.74 (J = 8.5, 5.0 Hz, 1H, 8-H), 7.29 (ddd, J = 8.0, 2.5, 2.0 Hz, 1H, pyridine 4-H), 7.28 (dd, J = 8.0, 4.0 Hz, 1H, pyridine 5-H). One of two COOH proton signals was not observed presumably due to flattening. Anal. Calcd. for $C_{17}H_{11}FN_2O_5 \cdot 2/5H_2O$ [15]: C, 59.57; H, 3.26; N, 7.81. Found: C, 59.47; H, 3.52; N, 7.67.

Compound **11c** was obtained in 56% yield (480 mg) as colorless needles; mp 242–243°; IR: ν 1715 cm^{-1}; ms: m/z 354 (M^+); NMR (deuteriodimethyl sulfoxide): 14.80 (s, 1H, COOH), 14.05 (brs, 1H, COOH), 8.95 (s, 1H, 2-H), 8.27 (s, 1H, vinylic H), 8.17 (ddd, J = 4.5, 2.0, 0.5 Hz, 1H, pyridine 6-H), 8.06 (dd, J = 8.5, 3.0 Hz, 1H, 5-H), 7.84 (ddd, J = 8.5, 8.0, 2.0 Hz, 1H, pyridine 4-H), 7.76 (dd, J = 8.5, 0.5 Hz, 1H, pyridine 3-H), 7.70 (ddd, J = 9.0, 8.0, 3.0 Hz, 1H, 7-H), 7.66 (dd, J = 9.0, 4.5 Hz, 1H, 8-H), 7.28 (dd, J = 8.0, 4.5 Hz, 1H, pyridine 5-H). Anal. Calcd. for $C_{17}H_{11}FN_2O_5$: C, 61.02; H, 3.13; N, 7.91. Found: C, 60.72; H, 3.30; N, 7.76.

Ethyl 1-[(*Z*)-1-ethoxycarbonyl-2-(2-furyl, 2-thienyl, and 3-thienyl)vinyl]-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylates 16–18. ***General procedure.*** A solution of compound **15** (2.0 g, 6.23 mmol), [furfural (898 mg, 9.35 mmol), thiophene-2-carbaldehyde (1.74 g, 15.6 mmol), or thiophene-3-carbaldehyde (1.74 g, 15.6 mmol)], 1,8-diazabicyclo[5.4.0]-7-undecene (0.3 mL) in dry *N*,*N*-dimethylformamide (30 mL) was refluxed for 2 h with stirring. Evaporation of the solvent *in vacuo* gave an oily substance, which was crystallized from ethanol/water to afford yellow needles **16**, **17**, or **18**.

Compound **16** was obtained in 59% yield (1.46 g); mp 154–155°; IR: ν 1715, 1700 cm^{-1}; ms: m/z 399 (M^+); NMR (deuteriodimethyl sulfoxide): 8.61 (s, 1H, 2-H), 8.08 (s, 1H, vinylic H), 7.92 (dd, 8.5, 3.0 Hz, 1H, 5-H), 7.75 (d, J = 2.0 Hz, 1H, furan 5-H), 7.55 (ddd, J = 9.0, 8.0, 3.0 Hz, 1H, 7-H), 7.42 (dd, J = 9.0, 4.5 Hz, 1H, 8-H), 7.00 (d, J = 3.5 Hz, 1H, furan 3-H), 6.60 (dd, J = 3.5, 2.0 Hz, 1H, furan 4-H), 4.26 (dq, J = 10.0, 6.5 Hz, 1H, methylene CH), 4.21 (dq, J = 10.0, 6.5 Hz, 1H, methylene CH), 4.20 (q, J = 6.5 Hz, 2H, CH_2), 1.24 (dd, J = 6.5, 6.5 Hz, 3H, CH_3), 1.21 (t, J = 6.5 Hz, 3H, CH_3). Anal. Calcd. for $C_{21}H_{18}FNO_6$: C, 63.16; H, 4.54; N, 3.51. Found: C, 63.16; H, 4.56; N, 3.68.

Compound **17** was obtained in 60% yield (1.55 g); mp 182–183°; IR: ν 1720 cm^{-1}; ms: m/z 415 (M^+); NMR (deuteriodimethyl sulfoxide): 8.59, 8.55 [14] (s, 1H, 2-H), 8.55 (s, 1H, vinylic H), 7.94 (dd, 9.0, 3.0 Hz, 1H, 5-H), 7.82 (d, J = 3.5, 1.0 Hz, 1H, thiophene 3-H), 7.78 (dd, J = 5.0, 1.0 Hz, 1H, thiophene 5-H), 7.55 (ddd, J = 9.5, 8.0, 3.0 Hz, 1H, 7-H), 7.43 (dd, J = 9.5, 4.5 Hz, 1H, 8-H), 7.16 (dd, J = 5.0, 3.5 Hz, 1H, thiophene 4-H), 4.26 (dq, J = 10.5, 7.0 Hz, 1H, methylene CH), 4.20 (q, J = 7.0 Hz, 2H, CH_2), 4.19 (dq, J = 10.5, 7.0 Hz, 1H, methylene CH), 1.24 (dd, J = 7.0, 7.0 Hz, 3H, CH_3), 1.22 (t, J = 7.0 Hz, 3H, CH_3). Anal. Calcd. for $C_{21}H_{18}FNO_5S$: C, 60.71; H, 4.37; N, 3.37. Found: C, 60.79; H, 4.31; N, 3.74.

Compound **18** was obtained in 51% yield (1.31 g); mp 180–181°; IR: ν 1710, 1682 cm^{-1}; ms: m/z 415 (M^+); NMR (deuteriodimethyl sulfoxide): 8.59 (s, 1H, 2-H), 8.29 (dd, J = 0.5, 0.5 Hz, 1H, vinylic H), 8.04 (ddd, J = 3.0, 1.5, 0.5 Hz, 1H, thiophene 2-H), 7.94 (dd, J = 9.0, 3.0 Hz, 1H, 5-H), 7.56 (ddd, J = 9.0, 8.0, 3.0 Hz, 1H, 7-H), 7.52 (dd, J = 5.0, 3.0 Hz, 1H, thiophene 5-H), 7.44 (dd, J = 9.0, 4.0 Hz, 1H, 8-H), 6.45 (ddd, J = 5.0, 1.5, 0.5 Hz, 1H, thiophene 4-H), 4.25 (dq, J = 11.0, 7.0 Hz, 1H, methylene CH), 4.19 (q, J = 7.0 Hz, 2H, CH_2), 4.18 (dq, J = 11.0, 7.0 Hz, 1H, methylene CH), 1.24 (dd, J = 7.0, 7.0 Hz, 3H, CH_3), 1.21 (t, J = 7.0 Hz, 3H, CH_3). Anal. Calcd. for $C_{21}H_{18}FNO_5S$: C, 60.71; H, 4.37; N, 3.37. Found: C, 60.68; H, 4.40; N, 3.54.

Conversion of compound 7a into compound 13. A solution of compound **7a** (2.0 g, 4.88 mmol), hydrazine hydrate (700 mg, 14.0 mmol) in dioxane (36 mL)/*N*,*N*-dimethylformamide (24 mL) was refluxed for 2 h with stirring to precipitate colorless needles. After cooling the reaction mixture, crystals were collected by suction and washed with ethanol to give an analytically pure sample **13** (460 mg, 40%).

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[14] Conformational analysis might be necessary for the clarification of such NMR spectral data.

[15] Compounds **6a,b**, **8a,b**, **10a**, and **11a,b** were found to absorb moisture while the procedures of the elemental analyses.

[16] The NOE spectral data (Table 2) showed that compounds **7a** and **9a** were a mixture of the *E*- and *Z*-isomers.

[17] The integral curve of the COOH proton signal was less than 1H size presumably due to flattening by moisture in the sample tube.