A SYNTHESIS OF 4-QUINOLONE-3-CARBOXYLIC ACIDS *VIA* PYROLYSIS OF *N*-ARYLDIOXOPYRROLINES

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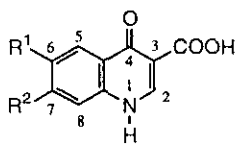
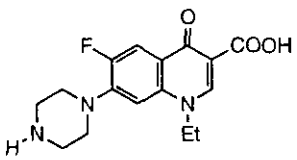
Abstract - A synthesis of 4-quinolone-3-carboxylic acids (**8**) was achieved by pyrolysis of 4,5-dimethoxycarbonyl-1-aryl-1*H*-pyrrole-2,3-diones (**3**) followed by selective demethoxycarbonylation of the resulting 2,3-dimethoxycarbonyl-4-quinolones (**4**) in excellent overall yields.

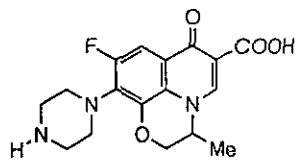
4-Oxo-1,4-dihydroquinoline-3-carboxylic acid (4-quinolone-3-carboxylic acid) is the basic skeleton of antibacterial quinolones such as Norfloxacin and Ofloxacin.[1] There are many reports on the synthesis of 4-quinolone-3-carboxylic acid. The methods can be classified roughly into three types, that is Gould-Jacobs reaction,[2] Biere method[3] and Bayer group's method.[4] The methods utilized a basically same reaction of pyrolysis of appropriate dicarboxylic acid derivatives. On the other hand, 4-quinolones were observed to be formed by pyrolysis of *N*-aryldioxopyrrolines by several workers.[5a-d] However, the reaction has not been applied for the synthetic purpose of 4-quinolones. Here, we describe a synthesis of 4-quinolone-3-carboxylic acids *via* electrocyclic reaction of imino ketene generated by pyrolysis of *N*-aryldioxopyrroline.



4-Quinolone-3-carboxylic acid



Norfloxacin



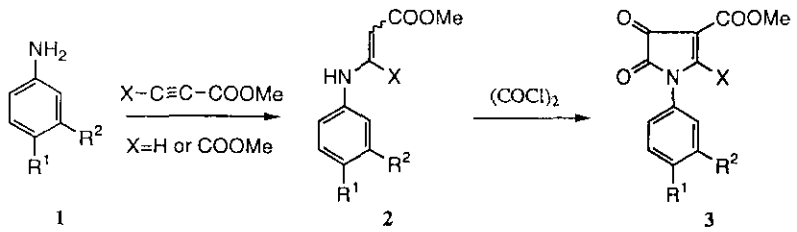
Ofloxacin

Scheme 1

N-Phenyldioxopyrrolines (**3a-h**) were synthesized from anilines (**1a-h**) as shown in Scheme 2. The enamine (**2a**, *E*, *Z* mixture) was prepared from methyl propiolate and aniline (**1a**) according to the known procedure.[6] The enamines (**2b-i**) were prepared by addition of the anilines (**1a-h**) to dimethyl acetylenedicarboxylate. Condensation of **2** with oxalyl chloride at room temperature gave the corresponding *N*-aryldioxopyrrolines (**3a-h**) in excellent overall yields from **1** (Table 1) with exception of **3i**. This condensation reaction was affected by the substituents on the benzene ring.

The enamine (**2h**) bearing two fluorines was needed 48 h to complete the reaction in contrast to those of the enamines (**2a-g**) with non-substituent, OMe or Me groups which completed within several hours. In case of **2i** with a nitro group, the reaction caused extensive decomposition to yield no characterizable product. This decrease of reactivity in the enamines with electron-attractive groups may be attributable to the

decreased basicity of the enamines of which condensation with oxalyl chloride become increasingly difficult.



1 2 3

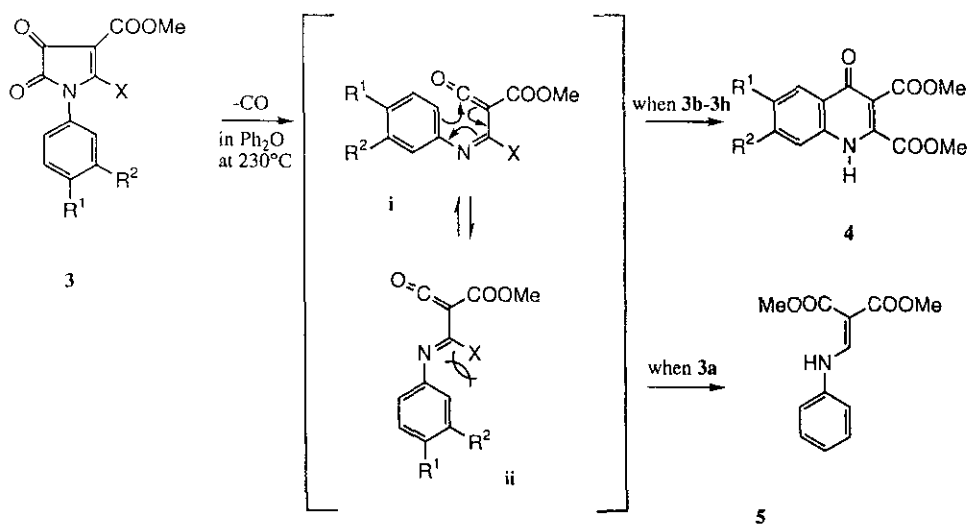
a : R^1=R^2=H
b: R^1=OMe, R^2=H
c: R^1=H, R^2=OMe
d: R^1=R^2=OMe
e: R^1=Me, R^2=H
f: R^1=F, R^2=H
g: R^1=R^2=F
h: R^1=NO_2, R^2=H

For compounds (**2**, **3**, **4** , **7** and **8**)

	R^1	R^2	X
a	H	H	H
b	H	H	COOMe
c	OMe	H	COOMe
d	H	OMe	COOMe
e	OMe	OMe	COOMe
f	Me	H	COOMe
g	F	H	COOMe
h	F	F	COOMe
i	NO_2	H	COOMe

Scheme 2

First of all, conversion of the *N*-aryldioxopyrrolines (**3**) into 4-quinolones (**4**) was carried out by pyrolysis of the dioxopyrroline (**3a**) with a methoxycarbonyl group. However, the reaction on heating in diphenyl ether at 230°C for 0.5 h caused only extensive decomposition to give no characterizable product. Furthermore when the pyrolysis was carried out in *p*-xylene or *o*-dichlorobenzene, the enamino diester (**5**) was obtained in only few percents yield and the desired quinolone (**4a**) was not obtained in any extent. All attempts to prepare **4a** under various pyrolytic conditions failed. On the other hand, the dioxopyrroline (**3b**) with two methoxycarbonyl group underwent the desired reaction under the same conditions to give



3 6 4 5

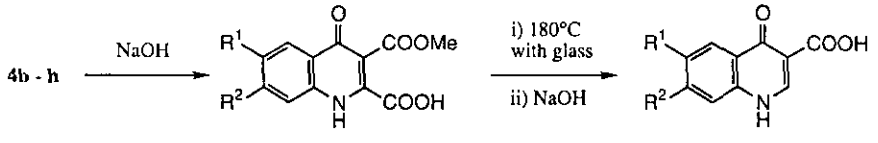
Scheme 3

A : X=H
B : X=COOMe

2,3-dimethoxycarbonyl-4-quinolone (**4b**) in 79% yield. The reaction of the dimethoxycarbonyldioxopyrrolines (**3c-h**) with OMe, Me and F groups on the benzene ring also readily occurred under similar pyrolytic conditions to give the corresponding 4-quinolones (**4c-h**) in good yields (Table 1).

It seems to be rationalized by the stereochemistry of the intermediary formed imino ketene why the dioxopyrroline (**3a**) with a methoxycarbonyl group, in contrast to the reactions of dioxopyrrolines (**3b-i**) bearing two methoxycarbonyl groups, did not form the 4-quinolone (**4a**) as described above. Ziegler *et al.*[5a,5d] proved that the pyrolytic conversion of *N*-aryldioxopyrroline into 4-quinolone proceeds *via* the cyclization of imino ketene formed by cheletropic loss of CO. The imino ketene (**6**) may exist as a mixture of two geometric isomers on respect of the imino double bond. One is a cisoid form (**i**) and the other is a transoid form (**ii**). The 4-quinolone should be formed by the ring closure of the cisoid form since the cyclization is geometrically impossible at the transoid form. In the transoid form (**ii**) of the imino ketene (**6B**) generated from **3b** a large steric repulsion between the benzene ring and the methoxycarbonyl group is present, but in the transoid form (**ii**) of **6A** from **3a** the interaction is absent. Therefore, the imino ketene (**6B**) adopts preferencially the cisoid form (**i**) favored for the cyclization to 4-quinolone, while the imino ketene (**6A**) does preferencially the transoid form (**ii**) unfavored for the cyclization. Furthermore, it is worthwile to note that the cyclization reaction of the imino ketene (**6**) is not affected by the electronic properties of the aromatic ring. This fact suggests that the cyclization proceeds as a concerted 6π electrocyclic reaction and not as an ionic one.

Selective elimination of the COOMe at C-2 from 2,3-dimethoxycarbonyl-4-quinolones (**4**) was achieved by the known procedure developed by Biere *et al.*[3] Treatment of **4** with aqueous NaOH caused selective hydrolysis of the COOMe at C-2 to give the carboxylic acids (**7**) in good yields. Heating of **7** with powdered glass at 180°C caused decarboxylation at C-2 and following hydrolysis of the crude product with aqueous NaOH at 80°C afforded 4-quinolone-3-carboxylic acids (**8**) in good yields. The results were shown in Table 1.



Scheme 4 **7b -h** **8b -h**

Table 1: Yield of Products (%)

	R^1	R^2	X	2	3	4	7	8
a	H	H	H	98	89	-	-	-
b	H	H	COOMe	98	77	79	89	80
c	OMe	H	COOMe	98	58	64	79	82
d	H	OMe	COOMe	95	70	84	85	75
e	OMe	OMe	COOMe	96	99	72	82	81
f	Me	H	COOMe	99	95	90	93	80
g	F	H	COOMe	97	88	89	99	82
h	F	F	COOMe	99	88	62	74	82
i	NO_2	H	COOMe	70	-	-	-	-

EXPERIMENTAL

Unless otherwise stated, the following procedure were adopted. Melting points were determined on a Yanaco micro-melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IR-810 spectrophotometer and data are given in cm^{-1}. UV spectra were recorded on a HITACHI U-2000 and data are given in λmax nm (ε). ^{1}H- and ^{13}C-NMR spectra were taken with a JEOL JNM-EX90, a JEOL JNM-AL300 or a JNM-α500 spectrometer in $CDCl_3$ solutions with TMS as an internal standard and the chemical shifts are given in δ values. MS and HRMS were taken with a JEOL JMS D-300 machine. Elemental analysis was performed with a YANACO MT-3.

Methyl 3-phenylamino-2-propenoate (2a)[6] A mixture of aniline (**1a**, 11.08 g, 0.12 mol) and methyl propiolate (10 g, 0.12 mol) in MeOH (250 mL) was stirred at rt for 12 h. The solvent was concentrated to give the crude product, which was recrystallized from MeOH-hexane. The enamine (**2a**) was yielded (20.63 g, 98%) as colorless needles. mp 151-154°C. IR (KBr): 3240, 1700. ^{1}H-NMR: 9.87 (br d, 1H), 7.41-6.93 (m, 6H), 4.84 (d, *J*=8.3 Hz, 1H), 3.71 (s, 3H). ^{13}C-NMR: 170.7, 143.2, 140.6, 129.7x2, 122.6, 115.4x2, 86.9, 50.6. MS: *m/z* 177 (M^+).

Methyl 3-carbomethoxy-3-arylamino-2-propenoate (2b-2h) (General Procedure)[6a] A mixture of aniline derivative (**1a-1g**, 35 mmol) and dimethyl acetylenedicarboxylate (5 g, 35 mmol) in MeOH (125 mL) was stirred at rt for 0.5-2 h. The solvent was concentrated to give the crude product, which was purified by short SiO_2 column chromatography (AcOEt-hexane=1:1) to yield **2b-2h** (95-99%).

2b: Yellow gum. IR ($CHCl_3$): 1740, 1660, 1620, 1600. ^{1}H-NMR: 9.66 (br s, 1H), 7.29-6.87 (m, 5H), 5.38 (s, 1H), 3.70 (s, 3H), 3.67 (s, 3H). ^{13}C-NMR: 169.8, 164.7, 147.9, 140.2, 129.0x2, 120.6x2, 124.1, 93.5, 52.6, 51.1. HRMS: Calcd for $C_{12}H_{13}NO_4$: 235.0843. Found: 235.0843.

2c: Yellow gum. IR ($CHCl_3$): 1740, 1670, 1620. ^{1}H-NMR: 9.58 (br s, 1H), 6.89-6.79 (m, 4H), 5.29 (s, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.66 (s, 3H). ^{13}C-NMR: 169.9, 164.7, 156.7, 148.9, 133.2, 122.8x2, 114.2x2, 91.5, 55.2, 52.5, 50.9. HRMS: Calcd for $C_{13}H_{15}NO_5$: 265.0947. Found: 265.0942.

2d: Yellow gum. IR ($CHCl_3$): 1740, 1670, 1600. ^{1}H-NMR: 9.63 (br s, 1H), 7.20-6.45 (m, 4H), 5.37 (s, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H). ^{13}C-NMR: 169.7, 164.8, 160.3, 147.9, 141.4, 129.8, 112.8, 109.9, 106.3, 93.6, 55.1, 52.7, 51.1. HRMS: Calcd for $C_{13}H_{15}NO_5$: 265.0951. Found: 265.0959.

2e: Yellow gum. IR ($CHCl_3$): 1740, 1670, 1610. ^{1}H-NMR: 9.58 (br s, 1H), 6.76 (d, *J*=8.4 Hz, 1H), 6.53 (d, *J*=2.5 Hz, 1H), 6.46 (dd, J_1=8.4 Hz, J_2=2.5 Hz, 1H), 5.30 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.74 (s, 3H), 3.68 (s, 3H). ^{13}C-NMR: 170.4, 165.0, 149.3, 149.0, 146.4, 133.8, 113.3, 111.3, 106.0, 92.0, 56.0, 55.8, 52.8, 51.1. HRMS: Calcd for $C_{14}H_{17}NO_6$: 295.1056. Found: 295.1084.

2f: Yellow prisms. mp 90°C. IR (KBr): 3240, 1740, 1670, 1600. ^{1}H-NMR: 9.62 (br s, 1H), 7.09-6.78 (m, 4H), 5.33 (s, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.30 (s, 3H). ^{13}C-NMR: 169.9, 164.9, 148.4, 137.6, 134.0, 129.7x2, 120.8x2, 92.5, 52.7, 51.1, 20.8. HRMS: Calcd for $C_{13}H_{15}NO_4$: 249.1000. Found: 249.1030.

2g: Yellow gum. IR ($CHCl_3$): 1740, 1670, 1620. ^{1}H-NMR: 9.58 (br s, 1H), 7.48-7.00 (m, 4H), 5.39 (s, 1H), 3.73 (s, 3H), 3.68 (s, 3H). ^{13}C-NMR: 169.9, 164.5, 159.8, 148.2, 136.4, 122.9, 122.7, 116.0, 115.7, 93.4, 52.7, 51.1. HRMS: Calcd for $C_{12}H_{12}NO_4F$: 253.0750. Found: 253.0750.

2h: Yellow gum. IR ($CHCl_3$): 3250, 1740, 1670, 1620, 1600. ^{1}H-NMR: 9.55 (br s, 1H), 7.07 (dd, J_1=18.6 Hz, J_2=8.7 Hz, 1H), 6.78-6.71 (m, 1H), 6.65-5.90 (m, 1H), 5.47 (s, 1H), 3.75 (s, 3H), 3.72 (s, 3H) ^{13}C-NMR: 169.7, 164.1, 150.2, 147.4, 147.3, 137.0, 117.4, 116.9, 110.5, 95.1, 52.9, 51.3. HRMS: Calcd for $C_{12}H_{11}NO_4F_2$: 271.0611. Found: 271.0632.

Methyl 3-carbomethoxy-3-(4'-nitorophenyl)amino-2-propenoate (2i) A mixture of *p*-nitroaniline (**1h**, 4.83 g, 35 mmol) and dimethyl acetylenedicarboxylate (5 g, 35 mmol) in MeOH (125 mL)

was refluxed for 2 h. The solvent was concentrated to give the crude product, which was purified by short SiO_2 column chromatography (AcOEt-hexane=1:1) to yield **2i** (6.86 g, 70%) as yellow prisms. mp 120-123°C (lit.,[7] mp 118.5-119.5°C). IR (KBr): 1730. ^{1}H-NMR: 9.80 (br s, 1H), 8.16 (d, *J*=9.1 Hz, 2H), 6.88 (d, *J*=9.1 Hz, 2H). 5.70 (s, 1H), 3.80 (s, 3H), 3.78 (s, 3H). ^{13}C-NMR: 169.2, 163.9, 146.1, 145.1, 143.1, 125.2x2, 118.9x2, 99.6, 53.2, 51.7.

4-Methoxycarbonyl-1-phenyl-1*H*-pyrrole-2,3-dione (3a) Oxalyl chloride (3 mL, 34.4 mmol) was added dropwise to **2a** (3 g, 16.9 mmol) in THF (2 mL)-ether (1L) and the mixture was stirred at rt for 1 h. Dioxane (50 mL) and octane (50 mL) were added to the reaction mixture, then the solvent was removed. The crystalline product was recrystallized from ether-heptane to give **3a** (3.5 g, 89%) as red brown prisms. mp 129-134°C. IR (KBr): 1770, 1740, 1730, 1690. ^{1}H-NMR: 9.04 (s, 1H), 7.46 (br s, 5H), 3.86 (s, 3H). ^{13}C-NMR: 176.8, 165.5, 160.8, 155.1, 134.3, 129.9x2, 128.3, 121.8x2, 105.5, 50.6. MS: *m/z* 231 (M^+).

4,5-Dimethoxycarbonyl-1-aryl-1*H*-pyrrole-2,3-dione (3b-3g) (General Procedure) Oxalyl chloride (3.1 mL, 35.5 mmol) was added dropwise to **2b-2g** (17.6 mmol) in THF (1 mL)-ether (300 mL) and the mixture was stirred at rt for 1-6 h. Dioxane (50 mL) and octane (50 mL) were added to the reaction mixture, then the solvent was removed. The crystalline product was recrystallized from ether-heptane to give **3b-3g** (58-99%).

3b: Orange prisms. mp 156-158°C. IR (KBr): 1780, 1760, 1740, 1710. ^{1}H-NMR: 7.40-7.30 (m, 5H), 3.85 (s, 3H), 3.76 (s, 3H). ^{13}C-NMR: 169.5, 164.1, 162.7, 158.0, 133.2, 129.4x2, 128.6, 126.8x2, 110.3, 86.8, 54.2, 52.4. HRMS: Calcd for $C_{14}H_{11}NO_6$: 289.0585. Found: 289.0580.

3c: Orange prisms. mp 92-94°C. IR (KBr): 1780, 1750, 1730, 1710. ^{1}H-NMR: 7.21-7.18 (m, 2H), 6.98-6.89 (m, 2H), 3.86 (s, 3H), 3.84 (s, 6H). ^{13}C-NMR: 176.5, 167.0, 160.5, 160.2, 159.7, 155.4, 127.9x2, 124.0, 115.0x2, 101.3, 55.5, 53.9, 52.3.

3d: Red brown prisms. mp 124-127°C. ^{1}H-NMR: 7.41-7.35 (m, 1H), 7.01-6.97 (m, 1H), 6.90-6.80 (m, 1H),3.87 (s, 6H), 3.82 (s, 3H). ^{13}C-NMR: 176.4, 166.6, 160.5, 160.2, 159.7, 154.8, 132.7, 130.9, 118.0, 115.7, 112.0, 101.8, 55.5, 53.9, 52.3. HRMS: Calcd for $C_{15}H_{13}NO_7$: 319.0689. Found: 319.0574.

3e: Red brown needles. mp 160-161°C. IR (KBr): 1770, 1760, 1730, 1710. ^{1}H-NMR: 6.93-6.78 (m, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H). ^{13}C-NMR: 176.5, 167.0, 160.2, 159.7, 155.3, 150.1, 149.6, 124.1, 119.0, 111.2, 109.7, 101.4, 56.1, 56.0, 53.9, 52.3. HRMS: Calcd for $C_{16}H_{15}NO_8$: 349.0798. Found: 349.0816.

3f: Orange prisms. mp 156-157°C. IR (KBr): 1780, 1740, 1710. ^{1}H-NMR: 7.28 (d, *J*=8.3 Hz, 2H), 7.16 (d, *J*=8.3 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.40 (s, 3H). ^{13}C-NMR: 176.5, 166.9, 160.2, 159.7, 155.1, 140.2, 130.4x2, 129.0, 126.1x2,101.5, 53.8, 52.3, 21.2. HRMS: Calcd for $C_{15}H_{13}NO_6$: 303.0726. Found: 303.0733.

3g: Yellow prisms. mp 176-179°C. IR (KBr): 1780, 1740, 1730, 1715. ^{1}H-NMR: 7.33-7.03 (m, 4H), 3.85 (s, 6H). ^{13}C-NMR: 176.2, 166.3, 162.9, 160.1, 159.5, 154.9, 128.7, 128.5, 127.5, 117.2, 116.9, 101.9, 54.0, 52.3. HRMS: Calcd for $C_{14}H_{10}NO_6F$: 307.0490. Found: 307.0483.

4,5-Dimethoxycarbonyl-1-(3',4'-difluorophenyl)-1*H*-pyrrole-2,3-dione (3h) Oxalyl chloride (3.1 mL, 35.5 mmol) was added dropwise to **2h** (4.77 g, 17.6 mmol) in THF (1 mL)-ether (300 mL) and the mixture was refluxed for 48 h. Dioxane (50 mL) and octane (50 mL) were added to the reaction mixture, then the solvent was removed. The crystalline product was recrystallized from ether-heptane to give **3h** (5.03 g, 88%) as orange prisms. mp 126-128°C. IR (KBr): 1770, 1740, 1710. ^{1}H-NMR: 7.30 (dd, J_1=18.0 Hz, J_2=8.7 Hz, 1H), 7.22-7.16 (m, 1H), 7.10-7.05 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H). HRMS: Calcd for $C_{14}H_9NO_6F_2$: 325.0398. Found: 325.0434.

Pyrolysis of 3a A solution of **3a** (300 mg, 1.3 mmol) in *o*-dichlorobenzene or *p*-xylene (10 mL) was heated in a sealed tube at 230°C for 0.5 h. The solvent was evaporated and the residue was purified by SiO_2 column chromatography (AcOEt-hexane=1:3) to yield dimethyl 2-phenylaminoethylene-1,1-dicarboxylate (**5**)[8] (45 mg, 15%) as yellow gum. ^{1}H-NMR: 11.05 (br d, *J*=13.4 Hz, 1H), 8.58 (d, *J*=13.4 Hz, 1H), 7.41-7.10 (m, 5H), 3.86 (s, 3H), 3.81 (s, 3H). ^{13}C-NMR: 169.4, 166.0, 152.3, 139.1, 129.9x2, 125.1, 117.3x2, 92.9, 51.6, 51.5. HRMS: Calcd for $C_{12}H_{13}NO_4$: 235.0842. Found: 235.0839.

Pyrolysis of 3b-3h (General Procedure) A solution of **3b-3h** (3.46 mmol) in diphenyl ether (25 mL) was heated in a sealed tube at 230°C for 0.5 h. The reactant was cooled, the resulted precipitate was collected and washed sufficiently with MeOH to yield 2,3-dimethoxycarbonyl-4-quinolone (**4b-4h**) (62-90%).

4b: Colorless prisms. mp 220-223°C (lit., mp 217-218°C[3], mp 224°C[9]). IR (KBr): 1740, 1730. UV (EtOH): 218 (31000), 238 (14600), 251 (16400), 330 (7600), 348 (7800), 364 (4900). ^{1}H-NMR (CDCl$_3$-DMSO-d_6): 12.39 (br s, 1H), 8.12 (d, *J*=8.3 Hz, 1H), 7.92 (d, *J*=8.3 Hz, 1H), 7.75 (m, 1H), 7.43 (m, 1H), 3.97 (s, 3H), 3.79 (s, 3H). ^{13}C-NMR (CDCl$_3$-DMSO-d_6): 174.2, 165.6, 161.9, 139.0, 136.8, 133.1, 125.5, 124.8x2, 119.6, 116.3, 53.8, 52.1. HRMS: Calcd for $C_{13}H_{11}NO_5$: 261.0637. Found: 261.0650.

4c: Colorless prisms. mp 203°C. IR (KBr): 1750, 1740. ^{1}H-NMR (DMSO-d_6): 12.41 (br s, 1H), 7.87 (d, *J*=9.0 Hz, 1H), 7.45 (m, 1H), 7.40 (dd, J_1=9.0 Hz, J_2=3.0 Hz, 1H), 3.94 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H). ^{13}C-NMR (DMSO-d_6): 173.4, 166.0, 162.0, 156.8, 135.6, 133.6, 126.9, 123.9, 121.6, 115.4, 103.9, 55.5, 53.9, 52.2. HRMS: Calcd for $C_{14}H_{13}NO_6$: 291.0741. Found: 291.0741.

4d: Yellow prisms. mp 206-209°C. IR (KBr): 1760, 1750. ^{1}H-NMR (CDCl$_3$-CF$_3$COOD): 8.44 (d, *J*=9.3 Hz, 1H), 7.50 (dd, J_1=9.3 Hz, J_2=2.3Hz, 1H), 7.37 (d, *J*=2.3 Hz, 1H), 4.092 (s, 3H), 4.086 (s, 3H), 4.04 (s, 3H). ^{13}C-NMR (CDCl$_3$-CF$_3$COOD): 171.8, 168.2, 167.1, 16.0.6, 147.1, 141.9, 126.6, 123.4, 114.2, 101.2, 100.1, 56.7, 55.0, 54.8. MS: *m/z* 291 (M^+). *Anal.* Calcd for $C_{14}H_{13}NO_6$: C, 57.73; H, 4.50; N, 4.82. Found: C, 57.66; H, 4.52; N, 4.90.

4e: Pale yellow prisms. mp 128-132°C (decomp). IR (KBr): 1750, 1720. ^{1}H-NMR (CDCl$_3$-CF$_3$COOD): 7.68 (s, 1H), 7.44 (s, 1H), 4.12 (s, 3H), 4.10 (s, 3H), 4.09 (s, 3H), 4.08 (s, 3H). ^{13}C-NMR (CDCl$_3$-CF$_3$COOD): 169.5, 167.2, 160.8, 159.6, 152.8, 144.1, 136.9, 115.2, 101.9, 101.6, 100.1, 57.2, 56.8, 54.9, 54.7. MS: *m/z* 321 (M^+).

4f: Colorless needles. mp 209-211°C. IR (KBr): 1740, 1730, 1720. ^{1}H-NMR (DMSO-d_6): 12.43 (s, 1H), 7.90 (s, 1H), 7.81 (d, *J*=8.4 Hz, 1H), 7.61 (d, *J*=8.4 Hz, 1H), 3.96 (s, 3H), 3.78 (s, 3H), 2.43 (s, 3H). ^{13}C-NMR (DMSO-d_6): 173.8, 166.6, 165.8, 161.9, 137.0, 134.78, 134.75, 125.4, 123.9, 119.5, 115.9, 53.8, 52.1, 20.7. HRMS: Calcd for $C_{14}H_{13}NO_5$: 275.0794. Found: 275.0814. *Anal.* Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.26; H, 4.76; N, 5.28.

4g: Colorless prisms. mp 225-227°C. IR (KBr): 1740. ^{1}H-NMR (DMSO-d_6): 12.59 (br s, 1H), 8.00 (dd, J_1=4.8 Hz, J_2=4.4 Hz, 1H), 7.78-7.65 (m, 2H), 4.00 (s, 3H), 3.82 (s, 3H). HRMS: Calcd for $C_{13}H_{10}NO_5F$: 279.0541. Found: 279.0531. *Anal.* Calcd for $C_{13}H_{10}NO_5F$: C, 55.92; H, 3.61; N, 5.02. Found: C, 55.91; H, 3.60; N, 5.20.

4h: Colorless prisms. mp 231-232°C. IR (KBr): 1750, 1740. HRMS: Calcd for $C_{13}H_9NO_5F_2$: 297.0446. Found: 297.0440. *Anal.* Calcd for $C_{13}H_9NO_5F_2$: C, 52.54; H, 3.05; N, 4.71. Found: C, 52.34; H, 3.10; N, 4.92.

3-Methoxycarbonyl-4-quinolone-2-carboxylic acid (7b-7h) (General Procedure) A mixture of **4b-4h** (1.4 mmol) and NaOH (112 mg, 2.8 mmol) in H_2O (6 mL) was stirred at 60°C for 1 h.

After acidification of the cooled mixture with concentrated HCl, the resulted precipitate was collected. The product was purified by recrystallization with MeOH to give **7b**-**7h** (74-99%).

7b: Colorless prisms. mp 148-150°C (lit.,[3] mp >136°C (decomp)). IR (KBr): 1740, 1730. ^{1}H-NMR (CDCl$_3$-DMSO-d_6): 8.18 (d, J=7.5 Hz, 1H), 7.98 (d, J=8.3 Hz, 1H), 7.82 (t, J=7.2 Hz, 1H), 7.51 (t, J=7.5 Hz, 1H), 3.83 (s, 3H). ^{13}C-NMR (CDCl$_3$-DMSO-d_6): 174.9, 166.5, 162.5, 139.0, 138.5, 133.2, 125.1, 125.0, 124.7, 119.6, 115.4, 52.4. HR-MS: Calcd for $C_{12}H_9NO_5$: 247.0481. Found: 247.0482.

7c: Colorless needles. mp 210°C. IR (KBr): 3550, 1730. ^{1}H-NMR (CDCl$_3$-DMSO-d_6): 7.91 (d, J=9.1 Hz, 1H), 7.57 (d, J=2.9 Hz, 1H), 7.28 (dd J_1=9.1 Hz, J_2=2.9 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H). ^{13}C-NMR (CDCl$_3$-DMSO-d_6): 171.7, 167.5, 162.8, 156.5, 136.0, 133.6, 126.7, 123.4, 121.2, 114.9, 103.5, 55.1, 51.8. HRMS: Calcd for $C_{13}H_{11}NO_6$: 277.0584. Found: 277.0583. *Anal.* Calcd for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05. Found: C, 56.04; H, 3.99; N, 5.29.

7d: Colorless prisms. mp 246-248°C. IR (KBr): 1640. ^{1}H-NMR (CDCl$_3$-DMSO-d_6): 8.23 (d, J=9.1 Hz, 1H), 7.21 (s, 1H), 7.13 (d, J=9.1 Hz, 1H), 3.94 (s, 6H). ^{13}C-NMR (CDCl$_3$-DMSO-d_6): 177.2, 165.9, 163.2, 162.5, 147.5, 139.7, 125.9, 117.0, 116.0, 102.8, 99.3, 54.8, 54.7.

7e: Colorless prisms. mp 210°C. ^{1}H-NMR (CDCl$_3$-CF$_3$COOD): 7.69 (s, 1H), 7.45 (s, 1H), 4.12 (s, 3H), 4.11 (s, 3H), 4.08 (s, 3H). ^{13}C-NMR (CDCl$_3$-DMSO-d_6): 169.9, 167.5, 163.1, 159.5, 152.9, 152.6, 120.0, 115.1, 102.1, 101.3, 99.9, 57.2, 56.9, 54.6.

7f: Colorless prisms. mp 233-235°C. IR (KBr): 3570,1730. ^{1}H-NMR (CDCl$_3$-DMSO-d_6): 8.10 (s, 1H), 7.64 (d, J=8.5 Hz, 1H), 7.49 (d J=8.5 Hz, 1H), 3.93 (s, 3H), 2.47 (s, 3H). ^{13}C-NMR (DMSO-d_6): 174.3, 166.3, 163.0, 137.3, 137.2, 134.6, 134.4, 125.5, 123.9, 119.6, 116.6, 52.1, 20.8. HRMS: Calcd for $C_{13}H_{11}NO_5$: 261.0634. Found: 261.0621. *Anal.* Calcd for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36. Found: C, 59.54; H, 4.30; N, 5.47.

7g: Colorless prisms. mp 270°C. IR (KBr): 1730, 1720. ^{1}H-NMR (CDCl$_3$-DMSO-d_6): 8.10-8.00 (m, 1H), 7.84-7.76 (m, 1H), 7.55-7.41 (m, 1H), 3.84 (s, 3H). HRMS: Calcd for $C_{12}H_8NO_5F$: 265.0387. Found: 265.0389.

7h: Colorless prisms. mp 215-220°C (decomp). IR (KBr): 1710. ^{1}H-NMR (CDCl$_3$-DMSO-d_6): 8.00 (dd, J_1=10.5 Hz, J_2=8.6 Hz, 1H), 7.85 (dd, J_1=11.2 Hz, J_2=6.8 Hz, 1H), 3.88 (s, 3H).

4-Quinolone-3-carboxylic acid (8b-8h) (General Procedure) **7b**-**7h** (0.4 mmol) was heated with powdered glass (300 mg) at 180°C for 20 min. A solution of NaOH (400 mg, 10 mmol) in H_2O (5 mL) was added to the cooled mixture, which was stirred at 80°C for 0.5 h. After filtration of the cooled mixture, the filtrate was acidified with concentrated HCl. The resulted precipitate was collected and recrystallized from MeOH to give **8b**-**8h** (75-82%).

8b: Colorless prisms. mp 267°C (lit.,[3] mp 267°C). ^{1}H-NMR (DMSO-d_6): 13.44 (br s, 1H), 8.90 (s, 1H), 8.31 (dd, J_1=8.3 Hz, J_2=0.9 Hz, 1H), 7.93-7.81 (m, 2H), 7.64-7.58 (m, 1H). ^{13}C-NMR (DMSO-d_6): 178.4, 166.4, 145.2, 139.5, 134.0, 126.2, 125.1, 124.4, 119.7, 107.6. HRMS: Calcd for $C_{10}H_7NO_3$: 189.0426. Found: 189.0432.

8c: Colorless prisms. mp 279-280°C (lit.,[10] mp 259-262°C). ^{1}H-NMR (CDCl$_3$-CF$_3$COOD): 9.27 (s, 1H), 8.09 (d, J=9.4 Hz, 1H), 7.83-7.75 (m, 2H), 4.06 (s, 3H). MS: m/z 219 (M^+).

8d: Colorless prisms. mp 264-267°C (lit.,[11] mp 291°C). IR (KBr): 1700, 1640. ^{1}H-NMR (CDCl$_3$-DMSO-d_6): 8.76 (s, 1H), 8.25 (d, J=9.0 Hz, 1H), 7.21 (d, J=2.4 Hz, 1H), 3.96 (s, 3H). ^{13}C-NMR (CDCl$_3$-DMSO-d_6): 176.7, 167.0, 163.0, 160.6, 143.4, 141.0, 126.1, 117.6, 115.8, 99.4, 55.0. MS: m/z 219 (M^+).

8e: Colorless prisms. mp 282-284°C. IR (KBr): 1700. ^{1}H-NMR (CDCl$_3$-CF$_3$COOD): 9.13 (s, 1H), 7.70 (s, 1H), 7.45 (s, 1H), 4.12 (s, 6H). HRMS: Calcd for $C_{12}H_{11}NO_5$: 249.0635. Found: 249.0614.

8f: Pale yellow prisms. mp 280-282°C. IR (KBr): 1680. ^{1}H-NMR (CDCl3-CF3COOD): 9.37 (s, 1H), 8.37 (s, 1H), 8.10-8.02 (m, 2H), 2.70 (s, 3H). ^{13}C-NMR (CDCl3-CF3COOD): 172.7, 169.9, 165.3, 145.2, 140.2, 142.0, 123.9, 120.5, 120.1, 104.0, 21.7. HRMS: Calcd for $C_{11}H_9NO_3$: 203.0580. Found: 203.0580.

8g: Colorless prisms. mp 287°C. IR (KBr): 1690. ^{1}H-NMR (DMSO-d_6): 14.30 (br s, 1H), 9.06 (s, 1H), 8.09-8.02 (m, 1H), 7.97-7.91 (m, 1H), 7.88-7.80 (m, 1H). ^{13}C-NMR (DMSO-d_6): 177.4, 166.1, 159.6, 144.5, 136.3, 125.8, 122.9, 122.6, 109.3, 107.0. HRMS: Calcd for $C_{10}H_6NO_3F$: 207.0332. Found: 207.0355. *Anal.* Calcd for $C_{10}H_6NO_3F$: C, 57.98; H, 2.92; N, 6.76. Found: C, 57.77; H, 3.18; N, 6.69.

8h: Colorless prisms. mp 289-290°C (lit.,[12] mp 274-276°C). IR (KBr): 1710. ^{1}H-NMR (CDCl3-DMSO-d_6): 13.33 (br s, 1H), 8.17 (dd, J_1=10.2 Hz, J_2=8.3 Hz, 1H), 8.01 (s, 1H), 7.64 (dd, J_1=10.2 Hz, J_2=6.6 Hz, 1H). HRMS: Calcd for $C_{10}H_5NO_3F_2$: 225.0235. Found: 225.0215.

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