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Synthetic Study on Novel Immunosuppressant KF20444

Iwao Chujo,* Yoshiaki Masuda, Kenji Fujino, Sachiko Kato, Takehiro Ogasa, Shin-ichiro Mohri and Masaji Kasai

Sakai Research Laboratories, Kyowa Hakko Kogyo Co., Ltd., 1-1-53, Takasu-cho, Sakai, Osaka 590–8554, Japan

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Abstract—The two new synthetic routes to 6,7-dihydro-10-fluoro-3-(2-fluorophenyl)-5*H*- benzo[6,7]cyclohepta[1,2-*b*]-quinoline-8-carboxylic acid (**1**), a novel immunosuppressant KF20444, are described. The seven-membered ring construction from 2-[4-(2-fluorophenyl)phenyl]-3-(2-carboxyethyl)-4-chloromethyl-6-fluoroquinoline (**17c**) was achieved by intramolecular Friedel–Crafts reaction under acidic conditions as the key step. Subsequently, the oxidation of 4-chloromethyl group followed by reduction of carbonyl group on the seven-membered ring afforded **1**. This route provides a new method for the synthesis of **1**.

Introduction

Immunosuppressive drugs have assumed a critical role in the suppression of tissue rejection reaction, allowing life-saving organ transplantation to become almost routine.[1] Brequinar sodium,[2] undergoing clinical trials for the prevention of organ transplant rejection,[3] is a inhibitor (K_i of 12 nM) of dihydroorotate dehydrogenase (DHO-DH), which is the controlling step in de novo pyrimidine nucleotide biosynthesis.[4,5] 6,7-Dihydro-10-fluoro-3- (2-fluorophenyl)-5*H*-benzo[6,7]cyclohepta[1,2-*b*]quinoline-8-carboxylic acid (**1**; KF20444), tetracyclic analogue of Brequinar with trimethylene bridge, has more potent inhibitory activity (K_i of 4.6 nM) against DHO-DH.[6–8] KF20444 has been found to display a more potent immunosuppressive effect than Brequinar sodium,[8–11] and will be a useful immunosuppressant.

The structure–activity relationship (SAR) studies revealed that the activity depended on the bridged ring size between quinoline nucleus and biphenyl moiety. The series of seven-membered ring compounds showed high activities,[6,7] and the most promising compound, KF20444, was selected for further evaluation. It has been reported on the construction of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]quinoline-8-carboxylic acid framework[12,13] as well as 5,6-dihydro-3-benz[c]acridine-7-carboxylic acid framework.[12–19] They all utilized the Pfitzinger reaction[20] of the 1-benzosuberone or α-tetralone derivatives with isatine to constitute these structure (Scheme 1).

The synthetic route of KF20444 also adapted the same strategy to prepare the substrate for SAR studies.[6,7] Therefore, 7-(2-fluorophenyl)-1-benzosuberone (**2**) was chosen as a key intermediate and treatment of **2** with 5-

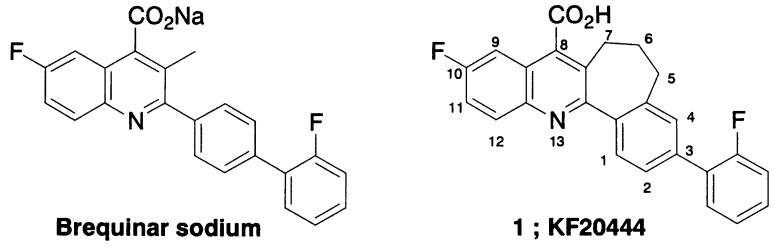

Figure 1.

*Corresponding author. Tel.: +81-722-23-5583; fax: +81-722-27-7214; e-mail: iwao.chujo@kyowa.co.jp

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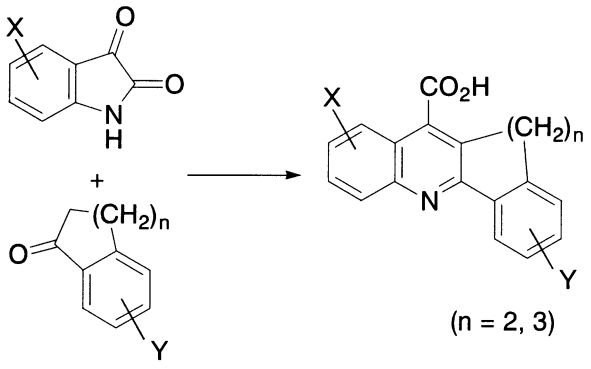
fluoroisatin (**3**) under Pfitzinger reaction conditions produced KF20444 (Scheme 2).

Taking into account the large-scale synthesis for the further evaluation, there were several issues, for instance use of heavy metal reagent and low temperature reaction, low yield in several steps, and difficulties in isolation and purification of some intermediates owing to oily compounds included key intermediate **2**. Therefore, we decided to investigate alternative strategy for the construction of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]quinoline-8-carboxylic acid framework. In our strategy, the quinoline skeleton would be produced before the construction of carbon seven-membered ring to avoid the oily intermediate **2**, then the ring closure by intramolecular Friedel–Crafts reaction would afford the 6,7-dihydro-5*H*- benzo[6,7]cyclohepta[1,2-*b*]quinoline-8-carboxylic acid framework. After that, the reduction of the carbonyl group at seven-membered ring would produce KF20444 (Scheme 3).

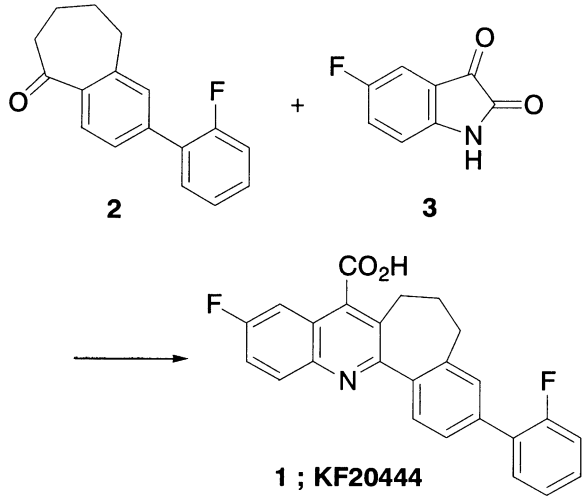
Result and Discussion

The 4-quinolinecarboxylic acid derivative **5** was easily synthesized from commercially available 2-fluorobiphenyl (**7**). Friedel–Crafts reaction of **7** with methyl 5-chloro-5-oxovalerate followed by Pfitzinger reaction with 5-fluoroisatin (**3**)[21–24] under the basic conditions afforded 4-quinolinecarboxylic acid derivative **5** in good yield. First, we tried the cyclization reaction of **5** in acidic conditions without protection of the carboxyl group at the 4-position on the quinoline. However, the decarboxylation and subsequent cyclization occurred, and the undesirable product **10** was obtained exclusively. The diester derivative **9** gave the same result (Scheme 4).

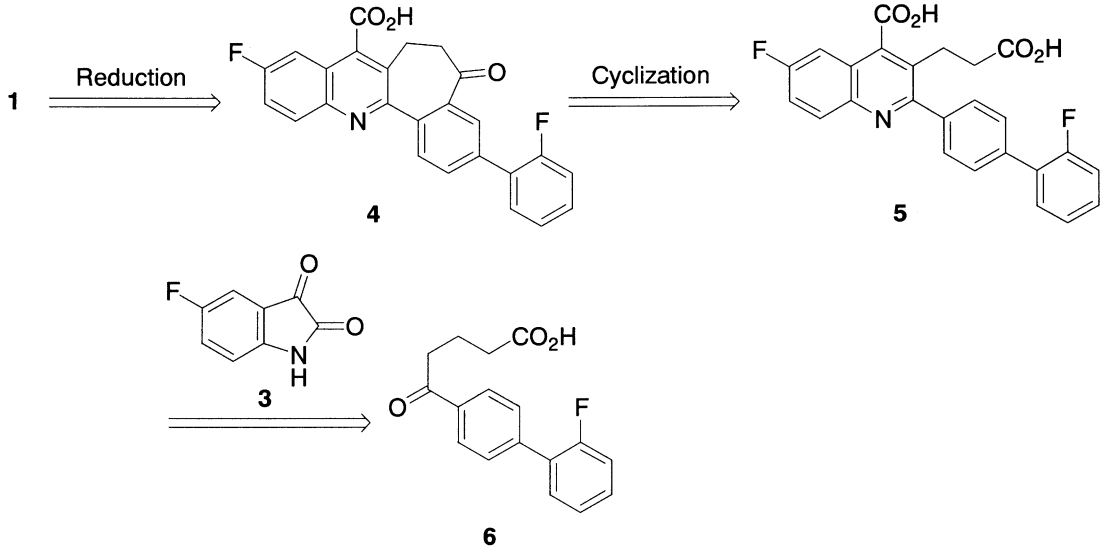
To avoid the decarboxylation, the carboxyl group at the 4-position was converted into the various amide groups. The selective amidation of the carboxyl group at the 4-position on the quinoline was achieved by taking advantage of differences of reactivity between these two



Scheme 1.



Scheme 2.



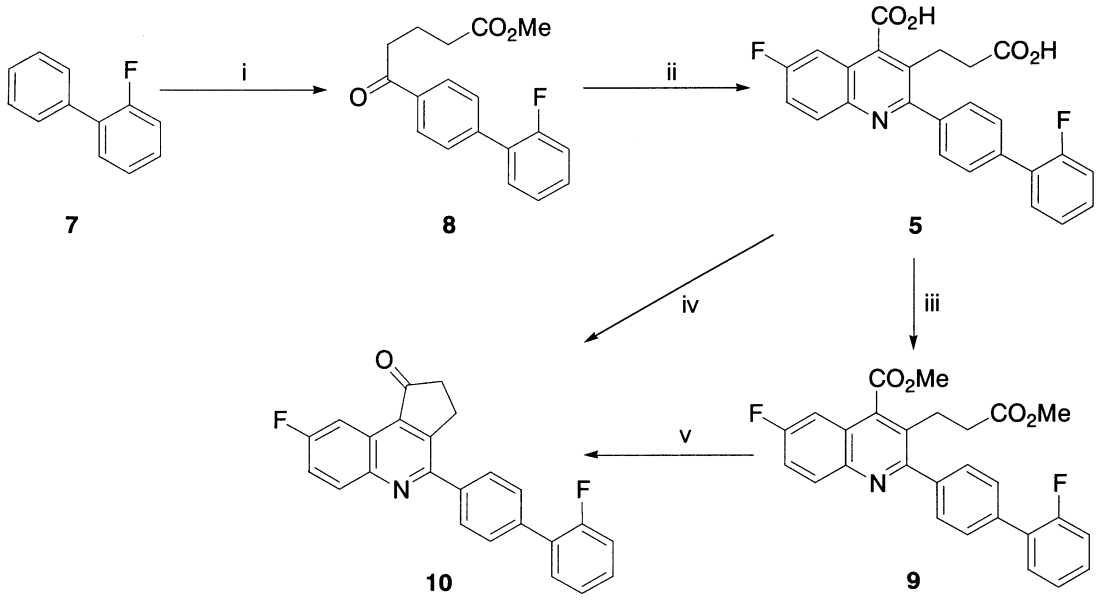
Scheme 3. Synthetic strategy of KF20444.

carboxyl groups. Thus, without DMF, the monoester **11** was obtained exclusively by the treatment of dicarboxylic acid **5** with thionyl chloride (2.1 equiv) followed by methanol. On the other hand, by the treatment with thionyl chloride and catalytic amount of DMF after the esterification of the side chain, the acid chloride at the 4-position was obtained. Then the in situ treatment of the acid chloride with adequate amine gave the amides. The hydrolysis of the methyl ester on the side chain afforded desired amide derivatives **12a–d** (Scheme 5).

The ring closure reaction of piperidine amide derivatives **12a** with trifluoromethanesulfonic acid gave the desired products **13a** along with the dimer **14a** and the decarboxylation/cyclization product **10** (Table 1). When the cyclization reaction was carried out with methanesulfonic acid or polyphosphoric acid (PPA), undesired compound **10** was obtained exclusively. The seven-membered ring closure reaction was promoted under highly diluted conditions, and the yield of **13a** increased with suppression of the formation of **14a**. On the other hand, the reaction of *N*-monosubstituted amides **12b–d** gave more complex mixture and resulted low yield (16–19%) compared with the piperidine amide **12a**. In these *N*-monosubstituted amides, the steric hindrance of *N*-alkyl group did not affect the yield of the cyclization reaction. Even though the yield of the product **13a** was not satisfactory (42%), the piperidine amide derivative **12a** gave the best result.

Then, we tried to convert the octylamide derivative **13b** to KF20444 (Scheme 6). The attempts to reduce the carbonyl group on the seven-membered ring with hydrogenation, Wolff–Kishner reduction, or silane reduction with triethylsilane were unsuccessful. Yet it gave a hydroxy derivative mainly. These results promoted us to reduce carbonyl group in stepwise. A treatment of **13b** with sodium borohydride, followed by hydriodic acid and acetic anhydride[25,26] gave the desired product **15b** successfully. Finally, KF20444 was obtained by treating **15b** with sodium nitrite and acetic anhydride, followed by potassium hydroxide.[27–29]

Although we obtained KF20444 by these procedures, we made further efforts to improve the yield of seven-membered ring closure reaction, in which the carboxyl

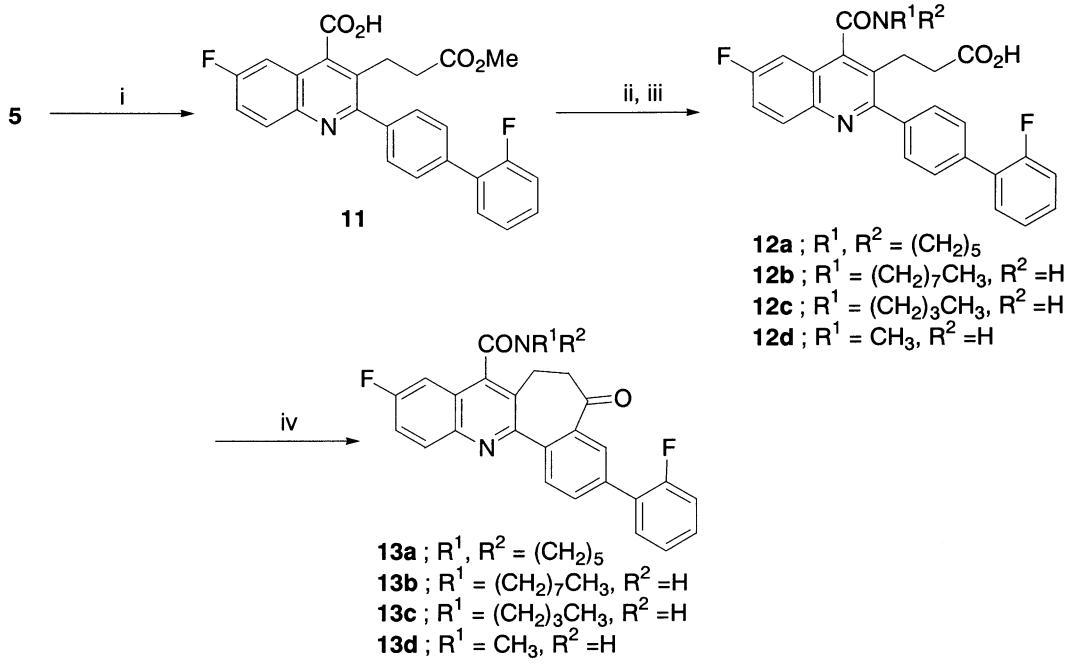


Scheme 4. Reagents: (i) $MeO_2C(CH_2)_3COCl$, $AlCl_3$, $ClCH_2CH_2Cl$, 5 °C, 75%; (ii) **3**, KOH, EtOH, dioxane, H_2O, 55 °C, 89%; (iii) $SOCl_2$, DMF, toluene, 50 °C, then MeOH, Et_3N, 46%; (iv) TfOH, 60 °C, 71%; (v) TfOH, 70 °C, 65%.

Table 1. Cyclization of 4-quinolinecarboxamide derivaitves **12a–d**

Entry	Substrate	Conditions				**13** Yield (%)[b,c]	Ratio[c,d]		
		Acid	Concd (g/L)[a]	Temp. (°C)	Time (h)		**13**	**14**	**10**
1	**12a**	TfOH	50	110	17	14	25	22	2
2	**12a**	TfOH	10	130	9	42	61	13	2
3	**12a**	MsOH	10	130	8	N.D.	N.D.	N.D.	60
4	**12a**	PPA	10	100	16	N.D.	N.D.	N.D.	87
5	**12b**	TfOH	10	130	4	16	19	12	27
6	**12c**	TfOH	10	130	10	16	not determined		
7	**12d**	TfOH	10	130	4	18	not determined		

[a]Calculated by weight of substrate (f)/volum of acid (mL).
[b]Isolated yield.
[c]N.D.; not detected.
[d]Ratios of the reaction mixture were determined by HPLC (area %).



Scheme 5. Reagents: (i) $SOCl_2$, toluene, 50 °C, then MeOH, 0 °C, 99%; (ii) $SOCl_2$, DMF, toluene, 60 °C, then R_1R_2NH, Et_3N, rt; (iii) aq NaOH, MeOH, 50 °C, 43–83%; (iv) (see Table 1).

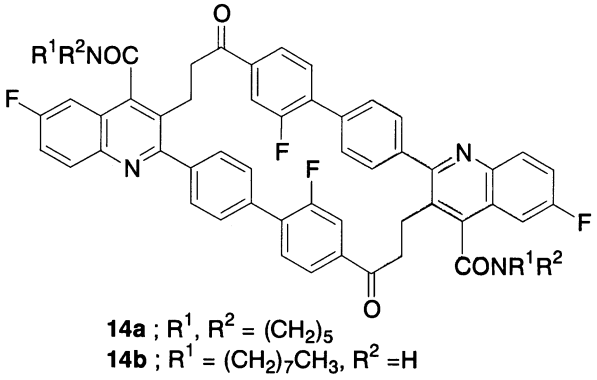
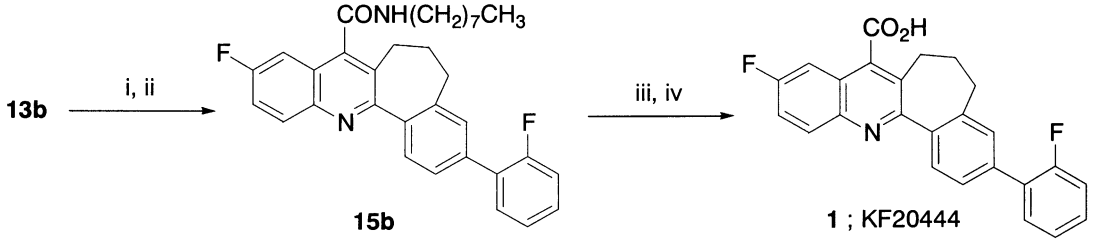


Figure 2.

group at the 4-position of quinoline ring was converted into the other functional groups. The 4-hydroxymethyl derivative **16a** was synthesized by the treatment of the monoester **11** with thionyl chloride, followed by reduction with sodium borohydride in THF. Reactions of **16a** with sodium hydride and iodomethane, or thionyl chloride gave the 4-methoxymethyl derivative **16b** or the 4-chloromethyl derivative **16c**, respectively. A treatment of **16c** with sodium borohydride in DMF produced the 4-methyl derivative **16d**. Hydrolysis of the methyl ester on **16a–d** with aqueous sodium hydroxide or concd hydrochloric acid gave the corresponding carboxylic acids **17a–d** (Scheme 7).

The cyclization reaction of **17a–d** was investigated next (Table 2). The reaction of chloromethyl derivative **17c** and methyl derivative **17d** with trifluoromethanesulfonic acid gave desired products in good yield. On the other hand, the reaction of the hydroxymethyl compound **17a** resulted in low yield because the lactone **19** was formed mainly, and the methoxymethyl compound **17b** gave the complex mixture. Although the cyclization reaction proceeded under other conditions (PPA or methanesulfonic acid), the yields of the desired products were not so good as with trifluoromethanesulfonic acid (Scheme 8).

Then the chloromethyl derivative **18c** was converted into KF20444 (Scheme 9). The replacement of chlorine to oxygen functionality proceeded successfully by the substitution with sodium acetate in acetic acid. Under basic conditions, however, decomposition of the substrate occurred, and it resulted in the low yield of the



Scheme 6. Reagent: (i) NaBH, MeOH, 5 °C; (ii) 57% HI, Ac_2O, AcOH, 100 °C, 96%; (iii) $NaNO_2$, Ac_2O, AcOH, rt; (iv) KOH, EtOH, 80 °C, 74%.

replacement. The hydrolysis of the acetoxy group by aqueous sodium hydroxide afforded the hydroxymethyl derivative **18a**. An oxidation of the hydroxymethyl group into the carboxyl group proceeded directly with chromium oxide under Jones oxidation condition and gave the carboxylic acid **4** in 86% yield. However, to avoid the use of heavy metal reagents, we established the stepwise oxidation method under mild reaction conditions. The hydroxymethyl derivative **18a** was oxidized into the aldehyde **21** with acetic anhydride and dimethylsulfoxide, then the treatment with sodium chlorite[30–32] afforded the carboxylic acid **4** in 88% yield. Because of the low solubility of the carboxylic acid **4,** the carboxyl group was converted into the methyl ester

Table 2. Investigation of cylization reaction of **17a–d**

Entry	Substrate	X	Conditions[a]		**18** Yield (%)[b]
			Acid	Time (h)	
1	**17a**	CH_2OH	TfOH	5	13[c]
2	**17b**	CH_2OMe	TfOH	2	Complex mixture[d]
3	**17c**	CH_2Cl	TfOH	2	81
4	**17c**	CH_2Cl	MsOH	8	No reaction
5	**17c**	CH_2Cl	PPA	20	21
6	**17d**	Me	TfOH	4	72
7	**17d**	Me	PPA	11	28

[a]Reaction was carried out at 130 °C in 10 g/L concentration.
[b]Isolated yield.
[c]The lactone **19** was main product.
[d]The lactone **19** was obtained in 27% yield.

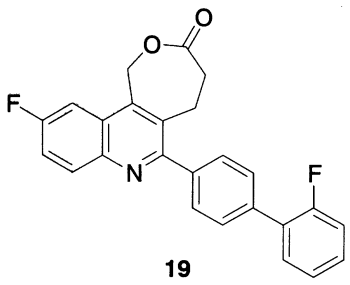


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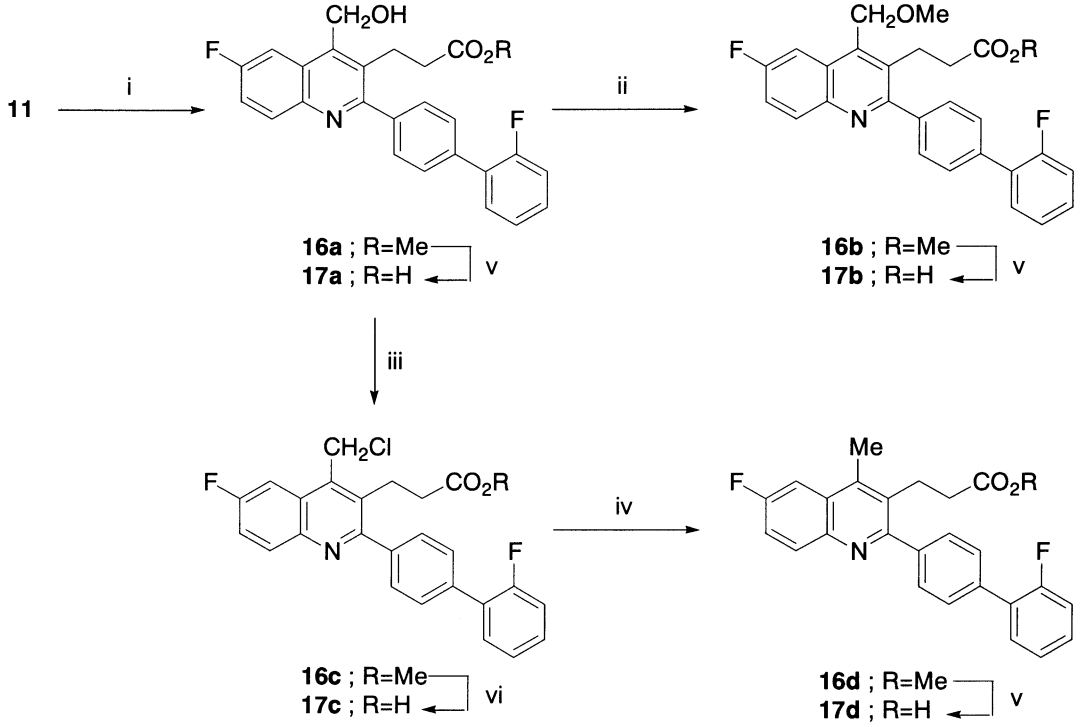
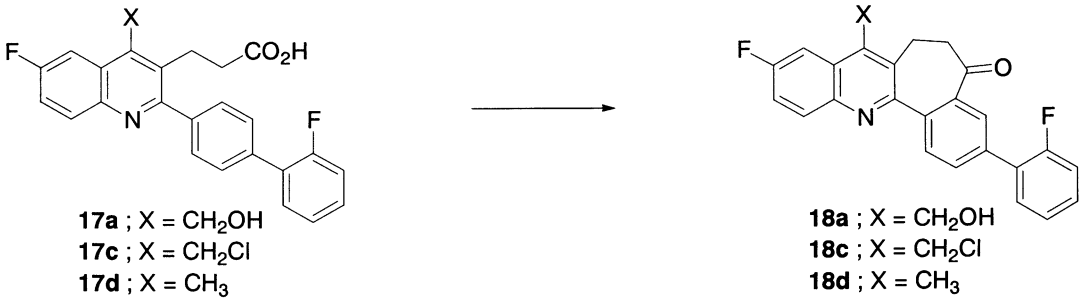
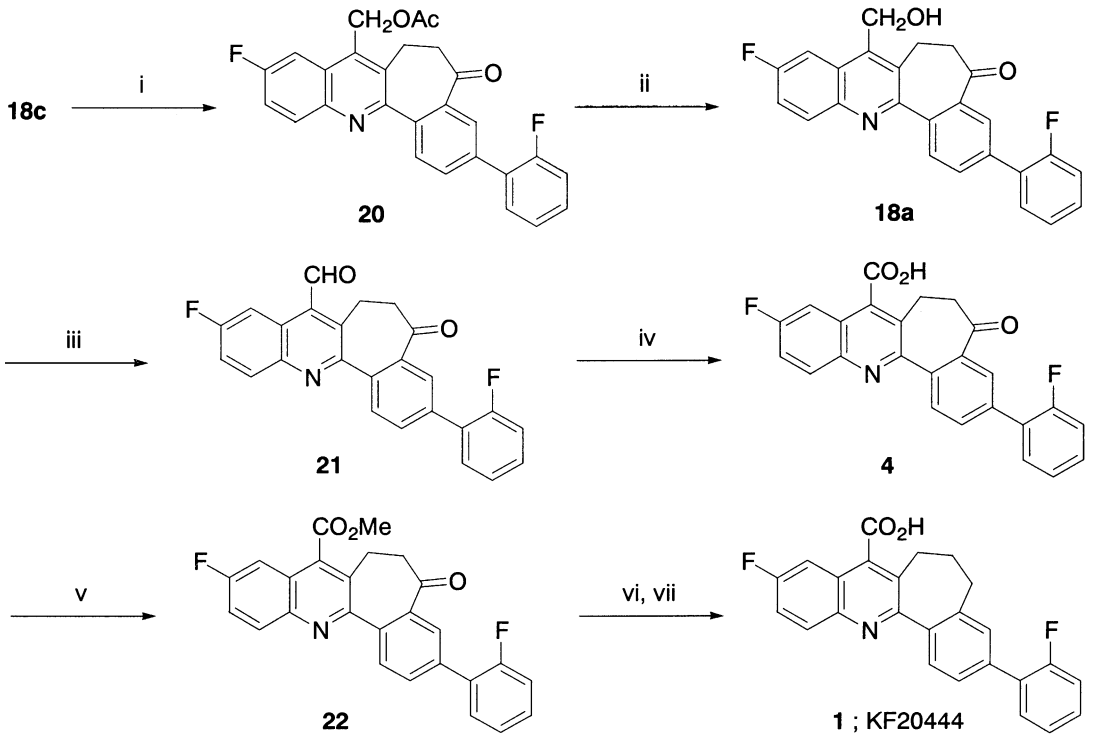
Figure 3.



Scheme 7. Reagents: (i) $SOCl_2$, DMF, toluene, 55 °C, then $NaBH_4$, THF, rt, 75%; (ii) MeI, NaH, DMF, 5 °C, 94%; (iii) $SOCl_2$, $ClCH_2CH_2Cl$, rt, 99%; (iv) $NaBH_4$, DMF, rt, 91%; (v) aq NaOH, MeOH, 55 °C, 99%; (vi) concd HCl, AcOH, 55 °C, 98%.



Scheme 8.



Scheme 9. Reagents: (i) AcONa, AcOH, 110 °C; (ii) aq NaOH, MeOH, rt, 97% from **18c**; (iii) Ac_2O, DMSO, rt, 90%; (iv) 87% $NaClO_2$, NaH_2PO_4, DMSO, H_2O, rt, 98%; (v) MeI, K_2CO_3, acetone, 45 °C, 77%; (vi) $NaBH_4$, MeOH, rt; (vii) 57% HI, Ac_2O, AcOH, 110 °C, 73% from **21**.

group by a treatment with iodomethane and potassium carbonate to afford the methyl ester **22**. Finally, the reduction of the carbonyl group on the seven-membered ring was accomplished by the same procedure already established in the reduction of amide derivatives. Thus, the treatment of **22** with sodium borohydride, followed by hydriodic acid and acetic anhydride afforded KF20444 in 73% yield from **22**.

Conclusions

In conclusion, we have established two new synthetic routes of KF20444 (**1**) in which the seven-membered ring closure reaction of 4-*N*-octylcarbamoyl or 4-chloromethyl quinoline derivatives was the key step. In the former route, the total yield from **7** is too poor (6.2%), because of the low yield in seven-membered ring closure reaction, to utilize it for the large scale synthesis. In the latter route, the yields in every step are more than 70% and the total yield was improved to 19%. Additionally, according to this route, all intermediates are isolated as crystals, and it does not need to use the heavy metal reagent and the low temperature reaction. We expect this route to provide a new method for the production of **1** in large-scale. Further work is required to develop this route, because our results are in early stage for the improvement on the synthetic method of **1**.

Experimental

5-Fluoroisatin was synthesized according to the described methods.[21–24] All other reagents were purchased from commercial suppliers and used without further purification. TLC analysis was carried out on silica gel 60 F-254 plates (0.1 mm, Merck) with iodine and/or UV detection. Chromatographic separation was made on silica gel columns (Wako-gel C-200, 75–150 mesh). HPLC was carried out with Hitachi instrument (detector L-4000H, pump L-6000, oven L-5025, recorder D-2500) and measured with 254 nm. Melting points were measured on a Mettler FP61 melting point apparatus and uncorrected. IR spectra were measured on a Horiba FT-200 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded using JEOL JNM-400 (400 MHz) and Bruker AC-300 (300 MHz) spectrometers using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS-D300 and micromass LCT spectrometers.

Methyl 4-[4-(2-fluorophenyl)benzoyl]butylate (8). Methyl 5-chloro-5-oxovalerate (21.0 g, 128 mmol) was added dropwise to a mixture of 2-fluorobiphenyl (20.0 g, 116 mmol), $AlCl_3$ (31.0 g, 232 mmol) and $ClCH_2CH_2Cl$ (60 mL) at 5 °C. The mixture was stirred at 5 °C for 8 h and then poured into 6 mol/L HCl (280 mL). The organic layer was washed with 2 mol/L HCl then brine, and dried over $MgSO_4$. After filtration and evaporation, the resulting residue was crystallized from *i*-PrOH (140 mL) to afford the ester **8** (26.2 g, 75%).

Mp 75–76 °C (decomp); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.10 (2H, m), 2.49 (2H, t, $J=7.2$ Hz), 3.09 (2H, t, $J=7.2$ Hz), 3.69 (3H, s), 7.14–7.27 (2H, m), 7.33–7.40 (1H, m), 7.45 (1H, dt, $J=7.7$, 1.8 Hz), 7.65 (1H, ddd, $J=1.6$, 1.8,

6.7 Hz), 8.04 (1H, ddd, J = 1.8, 1.9, 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.1, 33.9, 38.3, 52.3, 117.0 (J = 22.6 Hz), 125.3 (J = 3.8 Hz), 128.6 (J = 13.1 Hz), 128.9, 129.9 (J = 3.2 Hz), 130.6 (J = 8.3 Hz), 131.3 (J = 3.1 Hz), 136.5, 141.3 (J = 0.8 Hz), 160.5 (J = 248.8 Hz), 174.5, 199.7; MS m/z 300 (M^+), 269, 241, 227, 214, 199, 171; HR-MS [ESI(+)] calcd for $C_{18}H_{18}FO_3$ (M + H): 301.1240, found 301.1240.

2-[4-(2-Fluorophenyl)phenyl]-3-(2-carboxyethyl)-6-fluoroquinoline-4-carboxylic acid (5). A solution of the ester **8** (10.1 g, 33.5 mmol) in EtOH (80 mL) and dioxane (40 mL) was added dropwise to a mixture of 5-fluoroisatin **3** (8.30 g, 50.3 mmol), KOH (13.3 g, 201 mmol) and water (20 mL) at room temperature. The mixture was stirred at 55 °C for 13 h. After cooling and evaporation of EtOH, water (150 mL) and Et_2O (75 mL) were added to the residue, then the aqueous layer was separated. AcOH (40 mL) and water (50 mL) were added to the aqueous layer, and the mixture was stirred at 5 °C for 2 h. The precipitated solid was filtered and dried under reduced pressure to yield 14.0 g of the crude product. The crude product was recrystallized from AcOEt (140 mL) to afford the dicarboxylic acid **5** (12.9 g, 89%).

Mp 220–221 °C (decomp); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.28–2.34 (2H, m), 2.99–3.04 (2H, m), 7.28–7.33 (2H, m), 7.38–7.42 (1H, m), 7.47 (1H, dd, J = 2.8, 9.8 Hz), 7.56–7.73 (6H, m), 8.09 (1H, dd, J = 5.5, 9.2 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 26.8, 35.2, 109.6 (J = 22.9 Hz), 117.2 (J = 22.5 Hz), 120.5 (J = 25.8 Hz), 124.7 (J = 10.2 Hz), 126.1 (J = 3.4 Hz), 127.9, 128.7 (J = 12.9 Hz), 129.5, 129.6 (J = 2.7 Hz), 129.9, 130.8 (J = 8.1 Hz), 131.8 (J = 3.1 Hz), 132.9 (J = 9.3 Hz), 135.9, 140.8, 144.1, 160.2 (J = 246.1 Hz), 160.5 (J = 2.6 Hz), 161.0 (J = 245.6 Hz), 170.5, 174.2; MS m/z 433 (M^+), 388, 342; HR-MS [ESI(+)] calcd for $C_{25}H_{18}F_2NO_4$ (M + H):434.1204, found 434.1199.

Methyl 2-[4-(2-fluorophenyl)phenyl]-3-[(2-methoxycarbonyl)ethyl]-6-fluoroquinoline-4-carboxylate (9). DMF (0.11 mL, 1.38 mmol) and $SOCl_2$ (2.71 mL, 37.4 mmol) were added to a suspension of dicarboxylic acid **5** (3.00 g, 6.92 mmol) in toluene (90 mL) at room temperature. The mixture was stirred at 50 °C for 2 h. After cooling, MeOH (5.61 mL, 138.0 mmol) and Et_3N (14.8 mL, 104.0 mmol) were added, and the resulting mixture was stirred at room temperature for 30 min. After quenching with water, the reaction mixture was extracted with AcOEt. The extract was washed with 6 mol/L HCl, brine, and dried over $MgSO_4$. After filtration and evaporation, the residue was recrystallized from MeOH (10 mL) to afford the diester **9** (1.46 g, 46%).

Mp 126–127 °C (decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.42–2.48 (2H, m), 3.16–3.21 (2H, m), 3.59 (3H, s), 4.11 (3H, s), 7.15–7.22 (1H, m), 7.26 (1H, dd, J = 1.3, 7.5 Hz), 7.32–7.49 (2H, m), 7.50–7.54 (2H, m), 7.59 (2H, dd, J = 1.8, 6.5 Hz), 7.70 (2H, dd, J = 1.5, 8.3 Hz), 8.15 (1H, dd, J = 5.4, 9.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.0, 35.1, 52.5, 53.7, 108.8 (J = 23.7 Hz), 116.9 (J = 22.7 Hz), 120.9 (J = 25.8 Hz), 125.0 (J = 10.3 Hz), 125.2 (J = 3.6 Hz), 129.1 (J = 13.2 Hz), 129.3, 130.0 (J = 8.4 Hz), 130.1 (J = 2.9 Hz), 130.2, 131.4 (J = 3.3 Hz), 133.1 (J = 9.4 Hz), 137.0, 139.7, 139.8, 144.4, 160.0 (J = 2.9 Hz), 160.5 (J = 248.4 Hz), 161.9 (J = 249.7 Hz), 168.5, 173.0; MS m/z 461 (M^+), 430, 402, 369, 342; HR-MS [ESI(+)] calcd for $C_{27}H_{22}F_2NO_4$ (M + H): 462.1517, found 462.1526.

4-[4-(2-Fluorophenyl)phenyl]-3-[(2-methoxycarbonyl)ethyl]-6-fluoroquinoline-4-carboxylic acid (11). $SOCl_2$ (4.04 g, 34.0 mmol) was added to a suspension of dicarboxylic acid **5** (7.00 g, 16.2 mmol) in toluene (220 mL) at room temperature. The mixture was stirred at 50 °C for 3 h. After cooling and adding MeOH (13 mL), the reaction mixture was stirred at 0 °C for 3 h. The precipitated solid was filtered and dried under reduced pressure to yield monoester **11** (7.20 g, 99%).

Mp 243–244 °C (decomp); ^{1}H NMR (CD_3OD, 300 MHz) δ 2.51 (2H, brt, J = 8.1 Hz), 3.21 (2H, brt, J = 8.1 Hz), 3.52 (3H, s), 7.14–7.29 (2H, m), 7.32–7.39 (1H, m), 7.50–7.78 (7H, m), 8.05(1H, dd, J = 5.3, 9.2 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 25.6, 33.6, 50.5, 108.3 (J = 23.2 Hz), 115.4 (J = 23.0 Hz), 119.4 (J = 26.4 Hz), 124.0 (J = 3.4 Hz), 124.1 (J = 9.3 Hz), 127.2, 127.8 (J = 13.2 Hz), 128.3, 128.5 (J = 3.0 Hz), 129.0 (J = 8.4 Hz), 130.0 (J = 9.1 Hz), 130.1 (J = 3.1 Hz), 130.2, 136.1, 138.5, 142.5, 159.5 (J = 247.0 Hz), 159.5, 160.6 (J = 247.9 Hz), 170.8, 172.6; MS m/z 447 (M^+), 402, 388, 342; HR-MS [ESI(+)] calcd for $C_{26}H_{20}F_2NO_4$ (M + H): 448.1360, found 448.1378.

Typical procedure for the synthesis of 2-[4-(2-fluorophenyl)phenyl]-3-(2-carboxyethyl)-quinoline-4-carboxamide derivatives (12a–d) from monoester 11. DMF (0.1 equiv) and $SOCl_2$ (4.0 equiv) were added to a suspension of the monoester **11** in toluene at room temperature. The mixture was stirred at 60 °C for 1 h. After cooling to 5 °C, Et_3N (15.0 equiv) and amine R^1R^2NH (4.0 equiv) were added. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. After quenching with water and 1 mol/L HCl, the reaction mixture was extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, the residue was dissolved in MeOH, and to this solution was added 1 mol/L NaOH at room temperature. The mixture was stirred at 50 °C for 4 h. After quenching with water and 1 mol/L HCl, the mixture was extracted with AcOEt. The extract was washed with brine, and dried over $MgSO_4$. After filtration and evaporation, the amide derivatives (**12a–d**) were isolated by silica gel column chromatography (toluene–AcOEt).

Piperidino-2-[4-(2-fluorophenyl)phenyl]-3-(2-carboxyethyl)-6-fluoroquinoline-4-carboxamide (12a). Yield 43%. Mp 176–178 °C (hexane/AcOEt = 1:1, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48 (1H, brs), 1.72–1.77 (4H, m), 2.63 (1H, ddd, J = 5.1, 11.8, 16.8 Hz), 2.93 (1H, ddd, J = 5.1, 11.8, 16.9 Hz) 2.94–3.04 (1H, m), 3.14–3.24 (4H, m), 3.73–3.79 (1H, m), 4.01–4.05 (1H, m) 7.13–7.21 (1H, m), 7.24 (1H, dd, J = 1.3, 7.5 Hz), 7.30–7.38 (2H, m), 7.45–7.52 (2H, m), 7.57 (2H, dd, J = 1.8, 6.5 Hz), 7.68 (2H, dd, J = 1.5, 8.2 Hz), 8.15 (1H, dd, J = 5.4, 9.2 Hz);

^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.1, 26.4, 26.5, 27.2, 34.6, 43.3, 48.6, 108.6 (J = 23.0 Hz), 117.0 (J = 22.6 Hz), 121.0 (J = 25.8 Hz), 125.1 (J = 9.8 Hz), 125.2 (J = 3.7 Hz), 128.9, 129.1 (J = 13.1 Hz), 129.3, 130.0, 130.1 (J = 3.0 Hz), 131.5 (J = 3.3 Hz), 133.1 (J = 9.3 Hz), 137.0, 139.8, 143.2 (J = 5.7 Hz), 144.3, 160.6 (J = 248.3 Hz), 160.5 (J = 2.8 Hz), 161.9 (J = 249.9 Hz), 166.7, 177.2; MS m/z 500 (M^+), 455, 372, 342; HR-MS [ESI(+)] calcd for $C_{30}H_{27}F_2N_2O_3$ (M + H): 501.1990, found 501.1977.

***N*-Octyl-2-[4-(2-fluorophenyl)phenyl]-3-(2-carboxyethyl)-6-fluoroquinoline-4-carboxamide (12b).** Yield 76%. Mp 201–202 °C (toluene, decomp); ^{1}H NMR ($CDCl_3$-CD_3OD, 300 MHz) δ 0.90 (3H, t, J = 6.8 Hz), 1.20–1.43 (10H, m), 1.66–1.76 (2H, m), 2.44 (2H, brs), 3.19 (2H, t, J = 8.1 Hz), 3.54 (2H, t, J = 7.1 Hz), 7.19 (1H, ddd, J = 1.2, 8.2, 10.8 Hz), 7.27 (1H, dt, J = 1.3, 7.5 Hz), 7.34–7.41 (1H, m), 7.44–7.56 (3H, m), 7.60 (2H, d, J = 8.3 Hz), 7.72 (2H, dd, J = 1.5, 8.3 Hz), 8.09 (1H, dd, J = 5.3, 9.2 Hz); MS m/z 544 (M^+), 498, 371, 342; HR-MS [ESI(+)] calcd for $C_{33}H_{35}F_2N_2O_3$ (M + H): 545.2616, found 545.2626.

***N*-Butyl-2-[4-(2-fluorophenyl)phenyl]-3-(2-carboxyethyl)-6-fluoroquinoline-4-carboxamide (12c).** Yield 83%. Mp 238–240 °C (AcOEt, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (3H, t, J = 7.3 Hz), 1.40–1.50 (2H, m), 1.60–1.70 (2H, m), 2.44 (2H, brs), 3.19 (2H, t, J = 7.7 Hz), 3.53–3.60 (2H, m), 6.53 (1H, brt, J = 5.7 Hz), 7.14–7.26 (2H, m), 7.32–7.39 (1H, m), 7.42–7.51 (3H, m), 7.56 (2H, d, J = 8.3 Hz), 7.67 (2H, dd, J = 1.5, 8.3 Hz), 8.11 (1H, dd, J = 5.5, 9.0 Hz); MS m/z 488 (M^+), 443, 371, 342; HR-MS [ESI(+)] calcd for $C_{29}H_{27}F_2N_2O_3$ (M + H: 489.1990, found 489.1986.

***N*-Methyl-2-[4-(2-fluorophenyl)phenyl]-3-(2-carboxyethyl)-6-fluoroquinoline-4-carboxamide (12d).** Yield 77%. Mp 243–244 °C (AcOEt, decomp); ^{1}H NMR ($CDCl_3$–CD_3OD, 300 MHz) δ 2.41 (2H, brs), 3.11 (3H, s), 3.18 (2H, t, J = 7.7 Hz), 7.19 (1H, ddd, J = 1.2, 8.2, 10.8 Hz), 7.26 (1H, dt, J = 1.2, 7.5 Hz), 7.35–7.41 (1H, m), 7.43–7.55 (3H, m), 7.60 (2H, d, J = 8.2 Hz), 7.71 (2H, dd, J = 1.4, 8.2 Hz), 8.10 (1H, dd, J = 5.4, 9.2 Hz); MS m/z 446 (M^+), 399, 371, 342; HR-MS [ESI(+)] calcd for $C_{26}H_{21}F_2N_2O_3$ (M + H): 447.1520, found 447.1538.

2-[4-(2-Fluorophenyl)phenyl]-3-(2-methoxycarbonylethyl)-4-hydroxymethyl-6-fluoroquinoline (16a). DMF (0.6 mL) and $SOCl_2$ (2.12 g, 17.8 mmol) were added to a suspension of monoester **11** (2.00 g, 4.47 mmol) in toluene (60 mL) at room temperature. The mixture was stirred at 55 °C for 2 h. After cooling, water (50 mL) was added, and the organic layer was washed with brine and dried over $MgSO_4$. After filtration and evaporation, the resulting residue was dissolved in THF (40 mL). To this solution was added $NaBH_4$ (0.34 g, 8.94 mmol) at 0 °C and the mixture was stirred at room temperature for 1.5 h. After quenching with water (40 mL) and 1 mol/L HCl (40 mL), the mixture was extracted with $CHCl_3$. The extract was washed with brine and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue ($CHCl_3$/AcOEt = 16:1) gave the alcohol **16a** (1.46 g, 75%).

Mp 189–192 °C (AcOEt, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.46 (2H, t, J = 7.2 Hz), 3.26 (1H, t, J = 5.8 Hz), 3.35, (2H, t, J = 7.2 Hz), 3.55 (3H, s), 5.18 (2H, d, J = 5.8 Hz), 7.15–7.27 (2H, m), 7.32–7.39 (1H, m), 7.43–7.59 (4H, m), 7.64–7.71 (2H, m), 7.90 (1H, dd, J = 2.7, 10.4 Hz), 8.11 (1H, dd, J = 5.6, 9.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.0, 34.2, 51.9, 57.8, 108.1 (J = 23.1 Hz), 116.2 (J = 22.6 Hz), 119.3 (J = 25.7 Hz), 124.5 (J = 3.7 Hz), 127.5 (J = 9.7 Hz), 128.4 (J = 14.7 Hz), 128.6, 129.2, 129.3 (J = 2.9 Hz), 130.6, 130.7 (J = 3.4 Hz), 132.3 (J = 9.3 Hz), 135.9, 140.3, 143.1 (J = 5.7 Hz), 143.8, 159.8 (J = 248.2 Hz), 159.8 (J = 2.8 Hz), 161.0 (J = 247.9 Hz), 173.6; MS m/z 433 (M^+), 401, 375, 356; HR-MS [ESI(+)] calcd for $C_{26}H_{22}F_2NO_3$ (M + H): 434.1568, found 434.1559.

2-[4-(2-Fluorophenyl)phenyl]-3-(2-methoxycarbonylethyl)-4-methoxymethyl-6-fluoroquinoline (16b). MeI (0.65 mL, 10.4 mmol) and NaH (62% dispersion in mineral oil, 121 mg, 3.12 mmol) were added to a solution of the alcohol **16a** (900 mg, 2.08 mmol) in DMF (18 mL) at 5 °C, and the mixture was stirred for 2 h. After quenching with 1 mol/L HCl (4 mL) and water (60 mL), the reaction mixture was extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue (toluene/AcOEt = 10:1) gave the methyl ether **16b** (876 mg, 94%).

Mp 203–204 °C (toluene, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.48 (2H, brt, J = 8.3 Hz), 3.29 (2H, brt, J = 8.3 Hz), 3.59 (3H, s), 3.62 (3H, s), 4.91 (2H, s), 7.15–7.27 (2H, m), 7.32–7.39 (1H, m), 7.43–7.57 (4H, m), 7.69 (2H, dd, J = 1.5, 8.1 Hz), 7.75 (1H, dd, J = 2.7, 10.5 Hz), 8.12 (1H, dd, J = 5.7, 9.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.9, 35.2, 51.7, 59.1, 67.4, 107.7 (J = 23.1 Hz), 116.2 (J = 22.7 Hz), 119.3 (J = 25.7 Hz), 124.4 (J = 3.7 Hz), 127.8 (J = 9.9 Hz), 128.5 (J = 13.4 Hz), 128.6, 129.1, 129.2 (J = 3.1 Hz), 130.8 (J = 3.4 Hz), 132.0, 132.5 (J = 9.3 Hz), 135.9, 140.2, 140.3, 143.8, 159.8 (J = 248.1 Hz), 159.9 (J = 2.8 Hz), 161.0 (J = 247.6 Hz), 172.6; MS m/z 447 (M^+), 416, 360; HR-MS [ESI(+)] calcd for $C_{27}H_{24}F_2NO_3$ (M + H): 448.1724, found 448.1706.

2-[4-(2-Fluorophenyl)phenyl]-3-(2-methoxycarbonylethyl)-4-chloromethyl-6-fluoroquinoline (16c). $SOCl_2$ (0.69 g, 5.83 mmol) was added dropwise to a solution of the alcohol **16a** (1.26 g, 2.91 mmol) in $ClCH_2CH_2Cl$ (25 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. After quenching with water (20 mL), the reaction mixture was neutralized with $NaHCO_3$ and separated. The organic layer was washed with brine and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue ($CHCl_3$) gave the chloride **16c** (1.31 g, 99%).

Mp 129–131 °C ($CHCl_3$, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.49–2.55 (2H, m), 3.29–3.34 (2H, m), 3.62 (3H, s), 5.09 (2H, s), 7.15–7.28 (2H, m), 7.32–7.40 (1H, m), 7.47–7.59 (4H, m), 7.68–7.76 (3H, m), 8.16 (1H, dd, J = 5.6, 9.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.7,

34.3, 37.9, 51.8, 107.1 (J = 23.3 Hz), 116.2 (J = 22.7 Hz), 119.7 (J = 25.7 Hz), 124.4 (J = 3.7 Hz), 126.6 (J = 9.6 Hz), 128.4 (J = 12.5 Hz), 128.5, 129.2, 129.3 (J = 3.1 Hz), 130.7 (J = 3.3 Hz), 131.5, 133.0 (J = 9.4 Hz), 136.1, 139.8, 139.9, 143.9, 159.8 (J = 248.2 Hz), 160.0 (J = 2.8 Hz), 161.2 (J = 249.2 Hz), 172.4; MS m/z 451 [M^+ (Cl^{35})], 416, 392, 356; HR-MS [ESI(+)] calcd for $C_{26}H_{21}ClF_2NO_2$ (M + H): 452.1229, found 452.1237.

2-[4-(2-Fluorophenyl)phenyl]-3-(2-methoxycarbonylethyl)-4-methyl-6-fluoroquinoline (16d). $NaBH_4$ (92 mg, 2.43 mmol) was added to a solution of the chloride **16c** (1.00 g, 2.21 mmol) in DMF (25 mL), and the mixture was stirred at room temperature for 2 h. After quenching with 2 mol/L HCl (4.9 mL), the reaction mixture was extracted with AcOEt. The extract was washed with brine and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue (toluene/AcOEt = 40:1) gave the 4-methyl derivative **16d** (0.84 g, 91%).

Mp 179–181 °C (toluene, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.42–2.48 (2H, m), 2.71 (3H, s), 3.20–3.26 (2H, m), 3.62 (3H, s), 7.15–7.26 (2H, m), 7.31–7.38 (1H, m), 7.41–7.45 (1H, m), 7.49 (1H, dd, J = 2.1, 7.6 Hz), 7.53–7.56 (2H, m), 7.63 (1H, dd, J = 2.8, 10.4 Hz), 7.68 (2H, dd, J = 1.5, 8.1 Hz), 8.11 (1H, dd, J = 5.7, 9.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.7, 25.3, 34.2, 51.7, 107. (J = 22.6 Hz), 116.1 (J = 23.6 Hz), 118.9 (J = 25.7 Hz), 124.4 (J = 3.6 Hz), 128.2 (J = 9.3 Hz), 128.5, 128.6 (J = 12.0 Hz), 129.1, 129.2 (J = 3.0 Hz), 130.5, 130.7 (J = 3.1 Hz), 132.6 (J = 9.4 Hz), 135.7, 140.5, 141.7 (J = 5.6 Hz), 143.1, 159.7 (J = 2.7 Hz), 159.8 (J = 248.3 Hz), 160.5 (J = 247.1 Hz), 172.5; MS m/z 417 [M^+ (Cl^{35})], 386, 358; HR-MS [ESI(+)] calcd for $C_{26}H_{22}F_2NO_2$ (M + H): 418.1619, found 418.1603.

Typical procedure for the synthesis of carboxylic acid (17a, 17b, 17d) from methyl ester (16a, 16b, 16d). To a solution of the methyl ester **16** in MeOH (3.3%) was added 1 mol/L aqueous NaOH (2.0 equiv), and the mixture was stirred at 55 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. Water and 1 mol/L HCl (2.0 equiv) were added to the residue, and the mixture was extracted with ethyl AcOEt. The extract was washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure to afford the carboxylic acid **17**.

2-[4-(2-Fluorophenyl)phenyl]-3-(2-carboxyethyl)-4-hydroxymethyl-6-fluoroquinoline (17a). Yield 99%. Mp 186–189 °C (AcOEt, decomp); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.41 (2H, brt, J = 8.3 Hz), 3.14 (2H, brt, J = 8.3 Hz), 4.99 (2H, s), 7.33–7.39 (2H, m), 7.43–7.53 (1H, m), 7.60–7.72 (6H, m), 7.91–8.07 (2H, m); MS m/z 419 (M^+), 401, 356, 306; HR-MS [ESI(+)] calcd for $C_{25}H_{20}F_2NO_3$ (M + H): 420.1411, found 420.1426.

2-[4-(2-Fluorophenyl)phenyl]-3-(2-carboxyethyl)-4-methoxymethyl-6-fluoroquinoline (17b). Yield 99%. Mp 224–226 °C (AcOEt, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.46–2.52 (2H, m), 3.24–3.29 (2H, m), 3.56 (3H, s), 4.89 (2H, s), 7.14–7.26 (2H, m), 7.31–7.38 (1H, m), 7.43–7.58 (4H, m), 7.67 (2H, dd, J = 1.5, 8.3 Hz), 7.74 (1H, dd, J = 2.7, 10.4 Hz), 8.12 (1H, dd, J = 5.6, 9.2 Hz); MS m/z 433 (M^+), 388, 360; HR-MS [ESI(+)] calcd for $C_{26}H_{22}F_2NO_3$ (M + H): 434.1568, found 434.1560.

2-[4-(2-Fluorophenyl)phenyl]-3-(2-carboxyethyl)-4-methyl-6-fluoroquinoline (17d). Yield 99%. Mp 238–239 °C (AcOEt, decomp); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.36 (2H, brt, J = 8.2 Hz), 2.69 (3H, s), 3.09 (2H, brt, J = 8.2 Hz), 7.32–7.39 (2H, m), 7.43–7.49 (1H, m), 7.57–7.69 (6H, m), 7.91 (1H, dd, J = 2.4, 9.7 Hz), 8.01 (1H, dd, J = 5.8, 9.1 Hz); MS m/z 403 (M^+), 358, 308; HR-MS [ESI(+)] calcd for $C_{25}H_{20}F_2NO_2$ (M + H): 404.1462, found 404.1473.

2-[4-(2-Fluorophenyl)phenyl]-3-(2-carboxyethyl)-4-chloromethyl-6-fluoroquinoline (17c). To a solution of the methyl ester **16c** (700 mg, 1.55 mmol) in AcOH (28.0 mL) was added concd HCl (7.0 mL) and the mixture was stirred at 55 °C for 2 h. After cooling to room temperature, water (200 mL) was added, and the mixture was neutralized with $NaHCO_3$. The mixture was extracted with AcOEt. The extract was washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure to afford the carboxylic acid **17c** (667 mg, 98%).

Mp 194–197 °C (AcOEt, decomp); ^{1}H NMR ($CDCl_3$–CD_3OD, 300 MHz) δ 2.51 (2H, brt, J = 8.2 Hz), 3.29 (2H, brt, J = 8.2 Hz), 5.14 (2H, s), 7.17–7.29 (2H, m), 7.34–7.41 (1H, m), 7.52 (2H, dd, J = 1.7, 8.1 Hz), 7.58 (2H, d, J = 8.0 Hz), 7.73 (2H, dd, J = 0.8, 7.6 Hz), 7.79 (1H, dd, J = 2.6, 10.1 Hz), 8.13 (1H, dd, J = 5.6, 9.2 Hz); MS m/z 437 [M^+ (Cl^{35})], 401, 356, 306; HR-MS [ESI(+)] calcd for $C_{25}H_{19}ClF_2NO_2$ (M + H): 438.1072, found 438.1082.

Reaction of dicarboxylic acid 5 with TfOH. {2,3-dihydro-2-[4-(2-fluorophenyl)phenyl]-8-fluoro-1*H*-cyclopenta[*c*]quinoline-1-one (10)}. The dicarboxylic acid **5** (100 mg, 0.23 mmol) was dissolved into TfOH (2.0 mL), and the mixture was stirred at 60 °C for 7 h. After cooling, the resulting mixture was poured into water and neutralized with Na_2CO_3, then extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue (hexane/AcOEt = 5:1) gave the decarboxylated/cyclized product **10** (61 mg, 71%).

Mp 206–207 °C (toluene, decomp); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.88–2.90 (2H, m), 3.44–3.47 (2H, m), 7.19 (1H, ddd, J = 1.2, 8.3, 10.7 Hz), 7.26 (1H, dt, J = 1.2, 7.8 Hz), 7.34–7.40 (1H, m), 7.52 (1H, dt, J = 2.0, 7.8 Hz), 7.55 (1H, ddd, J = 2.9, 8.2, 9.2 Hz), 7.75 (2H, dd, J = 1.5, 8.6 Hz), 7.97 (2H, d, J = 8.6 Hz), 8.25 (1H, dd, J = 5.5, 9.2 Hz), 8.69 (1H, dd, J = 2.9, 9.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2, 36.8, 107.6 (J = 24.0 Hz), 116.3 (J = 22.3 Hz), 120.1 (J = 25.6 Hz), 123.0 (J = 11.6 Hz), 124.6 (J = 3.3 Hz), 128.4 (J = 13.2 Hz), 128.8, 129.4, 129.5 (J = 9.9 Hz), 130.7 (J = 3.3 Hz), 132.1 (J = 9.9 Hz), 137.0, 137.8, 138.2 (J = 6.6 Hz), 145.1, 148.8, 156.7 (J = 3.3 Hz), 159.9 (J = 248.1 Hz), 162.6 (J = 251.4 Hz),

207.3; MS *m/z* 371 (M^+), 342, 248; HR-MS [ESI(+)] calcd for $C_{24}H_{16}F_2NO$ (M+H): 372.1200, found 372.1189.

Reaction of diester 9 with TfOH. The diester **9** (50 mg, 0.11 mmol) was dissolved into TfOH (1.0 mL), and the mixture was stirred at 70 °C for 9 h. After cooling, the resulting mixture was poured into water and neutralized with Na_2CO_3, then extracted with AcOEt. The extract was washed with water, brine and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue (hexane/AcOEt = 5:1) gave the decarboxylated/cyclized product **10** (26 mg, 65%).

Reaction of carboxylic acid 12a with TfOH. {Piperidino-6,7-dihydro-10-fluoro-3-(2-fluorophenyl)-5-oxo-5*H*-benzo[6,7]cyclohepta-[1,2-*b*]quinoline-8-carboxamide (13a)}. The carboxylic acid **12a** (100 mg, 0.20 mmol) was dissolved into TfOH (10 mL), and the mixture was stirred at 130 °C for 9 h. After cooling, the resulting mixture was poured into water and neutralized with Na_2CO_3, then extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue (toluene/AcOEt = 1:1) gave the cyclized product **13a** (40 mg, 42%), dimer **14a** (12 mg, 12%) and decarboxylated/cyclized product **10** (2 mg, 3%).

Cyclized product **13a**: mp 228–229 °C (hexane, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43–1.50 (2H, m), 1.73–1.81 (4H, m), 2.95–3.13 (1H, m), 3.14–3.22 (5H, m), 3.86–4.02 (2H, m), 7.16–7.29 (2H, m), 7.32–7.42 (2H, m), 7.46–7.56 (2H, m), 7.92–7.96 (2H, m), 8.13 (1H, d, *J* = 8.6 Hz), 8.20 (1H, dd, *J* = 5.4, 9.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.8, 26.0, 26.4, 27.2, 43.0, 45.7, 48.4, 108.5 (*J* = 23.0 Hz), 116.8 (*J* = 22.2 Hz), 120.7 (*J* = 25.7 Hz), 124.8 (*J* = 9.9 Hz), 125.1 (*J* = 3.6 Hz), 127.9 (*J* = 13.1 Hz), 128.7, 129.7, 130.4 (*J* = 8.2 Hz), 131.1 (*J* = 3.1 Hz), 131.7, 133.3 (*J* = 9.4 Hz), 133.7 (*J* = 3.5 Hz), 137.3, 138.1, 138.7, 140.9 (*J* = 5.9 Hz), 145.2, 157.3 (*J* = 2.9 Hz), 160.3 (*J* = 248.7 Hz), 161.9 (*J* = 250.5 Hz), 166.1, 203.8; MS *m/z* 482 (M^+), 398, 368, 342; HR-MS [ESI(+)] calcd for $C_{30}H_{25}F_2N_2O_2$ (M+H): 483.1884, found 483.1871.

Dimer **14a**: ^{1}H NMR (acetone-d_6, 300 MHz) δ 1.42–1.55 (4H, m), 1.68–1.85 (8H, m), 2.98–3.13 (4H, m), 3.29 (4H, brt, *J* = 4.5 Hz), 3.38–3.53 (4H, m), 3.88–4.02 (4H, m), 7.32 (2H, dd, *J* = 8.6, 10.8 Hz), 7.43 (2H, dd, *J* = 2.6, 9.7 Hz), 7.62–7.69 (2H, m), 7.73–7.78 (6H, m), 7.85–7.91 (6H, m), 8.14 (2H, dd, *J* = 5.5, 9.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.1, 25.3, 26.5, 27.2, 38.5, 43.2, 48.6, 108.6 (*J* = 23.0 Hz), 117.6 (*J* = 22.8 Hz), 120.8 (*J* = 25.7 Hz), 124.9 (*J* = 10.0 Hz), 128.4 (*J* = 13.5 Hz), 129.2, 129.6, 129.7, 130.1, 130.7 (*J* = 4.6 Hz), 133.1 (*J* = 9.2 Hz), 134.3 (*J* = 3.3 Hz), 135.5, 140.7, 140.9, 143.2 (*J* = 5.7 Hz), 144.4, 144.5, 159.8 (*J* = 2.7 Hz), 161.9 (*J* = 249.9 Hz), 163.2 (*J* = 257.5 Hz), 166.6, 197.6; MS (SIMS) *m/z* 1053 (M+H), 926, 898.

Reaction of carboxylic acid 12b with TfOH. {*N*-Octyl-6,7-dihydro-10-fluoro-3-(2-fluorophenyl)-5-oxo-5*H*-benzo[6,7]-cyclohepta[1,2-*b*]-quinoline-8-carboxamide (13b)}. The carboxylic acid **12b** (500 mg, 0.92 mmol) was dissolved into TfOH (50 mL), and the mixture was stirred at 130 °C for 4 h. After cooling, the resulting mixture was poured into water and neutralized with Na_2CO_3, then extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue (hexane/AcOEt = 4:1) gave the cyclized product **13b** (76 mg, 16%), dimer **14b** (52 mg, 12%) and decarboxylated/cyclized product **10** (76 mg, 22%).

Cyclized product **13b**: mp 181–182 °C (hexane/AcOEt = 4:1, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (3H, brt, *J* = 6.6 Hz), 1.23–1.43 (10H, m), 1.62–1.73 (2H, m), 3.09 (2H, brs), 3.22 (2H, brt, *J* = 5.8 Hz), 3.62 (2H, q, *J* = 6.6Hz), 6.08 (1H, brt, *J* = 5.8 Hz), 7.17–7.29 (2H, m), 7.36–7.40 (1H, m), 7.44–7.56 (3H, m), 7.90 (1H, s), 7.92 (1H, dd, *J* = 1.7, 9.8 Hz), 8.10 (1H, d, *J* = 8.0 Hz), 8.16 (1H, dd, *J* = 5.5, 9.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.6, 25.3, 27.0, 29.1, 29.2, 29.6, 31.7, 40.0, 45.6, 108.1 (*J* = 23.2 Hz), 116.3 (*J* = 22.5 Hz), 120.0 (*J* = 25.8 Hz), 124.4 (*J* = 10.0 Hz), 124.6 (*J* = 3.7 Hz), 127.2 (*J* = 13.0 Hz), 128.8 (*J* = 2.7 Hz), 129.3, 129.9 (*J* = 8.3 Hz), 130.5 (*J* = 3.0 Hz), 130.9, 132.4 (*J* = 9.3 Hz), 133.1 (*J* = 3.3 Hz), 136.5, 137.5, 138.2, 140.9 (*J* = 5.8 Hz), 144.5, 156.5 (*J* = 2.8 Hz), 159.8 (*J* = 248.8 Hz), 161.1 (*J* = 250.3 Hz), 166.6, 204.3; MS *m/z* 526 (M^+), 398, 370, 342; HR-MS [ESI(+)] calcd for $C_{33}H_{33}F_2N_2O_2$ (M+H): 527.2510, found 527.2514.

Dimer **14b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (6H, brt, *J* = 6.4 Hz), 1.20–1.46 (20H, m), 1.65–1.75 (4H, m), 2.89–3.10 (4H, m), 3.25–3.62 (8H, m), 6.18 (2H, brt, *J* = 5.7 Hz), 7.20–7.33 (2H, m), 7.35–7.43 (4H, m), 7.51–7.90 (12H, m), 8.16 (2H, dd, *J* = 5.3, 9.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.4, 25.3, 27.2, 29.2, 29.3, 29.7, 38.5, 42.3, 46.6, 108.4 (*J* = 22.9 Hz), 117.6 (*J* = 23.9 Hz), 120.7 (*J* = 25.6 Hz), 124.7 (*J* = 9.8 Hz), 128.3 (*J* = 13.5 Hz), 129.3, 129.5, 129.8, 130.6, 130.7 (*J* = 4.9 Hz), 133.0 (*J* = 9.3 Hz), 134.1 (*J* = 3.3 Hz), 135.5, 140.6, 140.8, 143.0 (*J* = 5.6 Hz), 143.1, 144.3, 159.6 (*J* = 2.8 Hz), 161.9 (*J* = 249.9 Hz), 163.2 (*J* = 257.7 Hz), 168.3, 197.5; MS (SIMS) *m/z* 941 (M+H), 814, 784.

Reaction of carboxylic acid 12c with TfOH. {*N*-Butyl-6,7-dihydro-10-fluoro-3-(2-fluorophenyl)-5-oxo-5*H*-benzo[6,7]-cyclohepta[1,2-*b*]-quinoline-8-carboxamide (13c)}. The carboxylic acid **12c** (667 mg, 1.36 mmol) was dissolved into TfOH (66 mL), and the mixture was stirred at 130 °C for 10 h. After cooling, the resulting mixture was poured into water and neutralized with Na_2CO_3, then extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue (toluene/AcOEt = 10:1) gave the cyclized product **13c** (121 mg, 16%). (We did not try to isolate the other product).

Mp 243–244 °C (hexane/AcOEt = 4:1, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (3H, t, *J* = 7.3 Hz), 1.42–1.51 (2H, m), 1.62–1.73 (2H, m), 3.05 (2H, brs), 3.18 (2H, brt, *J* = 6.6 Hz), 3.59 (2H, q, *J* = 6.5 Hz), 6.29

(1H, brt, $J=5.7$ Hz), 7.15–7.29 (2H, m), 7.34–7.60 (3H, m), 7.69, (1H, dd, $J=1.5$, 8.2 Hz), 7.86 (1H, brt, $J=1.3$ Hz), 7.91 (1H, dt, $J=8.1$, 1.8 Hz), 8.07 (1H, d, $J=8.1$ Hz), 8.13 (1H, dd, $J=5.3$, 9.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 20.2, 25.4, 31.6, 39.8, 45.6, 108.1 ($J=23.2$ Hz), 116.2 ($J=22.5$ Hz), 120.1 ($J=25.8$ Hz), 124.5 ($J=10.2$ Hz), 124.6 ($J=3.6$ Hz), 127.3 ($J=13.1$ Hz), 128.4, 128.9 ($J=2.7$ Hz), 129.9 ($J=8.3$ Hz), 130.6 ($J=3.1$ Hz), 130.9, 132.5 ($J=9.3$ Hz), 133.1 ($J=3.4$ Hz), 136.6, 137.6, 138.3, 140.8 ($J=5.8$ Hz), 144.6, 156.6 ($J=2.6$ Hz), 159.8 ($J=248.7$ Hz), 161.2 ($J=250.4$ Hz), 166.6, 204.1; MS m/z 470 (M^+), 398, 368, 342; HR-MS [ESI(+)] calcd for $C_{29}H_{25}F_2N_2O_2$ (M + H): 471.1884, found 471.1896.

Reaction of carboxylic acid 12d with TfOH. {*N*-Methyl-6,7-dihydro-10-fluoro-3-(2-fluorophenyl)-5-oxo-5*H*-benzo[6,7]-cyclohepta-[1,2-*b*]quinoline-8-carboxamide (13d)}. The carboxylic acid **12d** (100 mg, 0.22 mmol) was dissolved into TfOH (10 mL), and the mixture was stirred at 130 °C for 4h. After cooling, the resulting mixture was poured into water and neutralized with Na_2CO_3, then extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue (hexane/AcOEt = 3:2) gave the cyclized product **13d** (18 mg, 18%). (We did not try to isolate the other product).

Mp 240–241 °C (hexane/AcOEt = 1:2, decomp); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.95 (3H, d, $J=4.6$ Hz), 3.08 (4H, brs), 7.36–7.54 (4H, m), 7.67 (1H, dt, $J=1.7$, 7.8 Hz), 7.75 (1H, dt, $J=2.9$, 8.5 Hz), 7.79 (1H, brt, $J=1.5$ Hz), 8.00 (1H, dt, $J=8.1$, 1.7 Hz), 8.10 (1H, d, $J=8.1$ Hz), 8.21 (1H, dd, $J=5.4$, 9.3 Hz), 8.81 (1H, brq, $J=4.6$ Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 25.1, 25.8, 45.2, 108.3 ($J=22.3$ Hz), 116.3 ($J=22.3$ Hz), 119.9 ($J=25.6$ Hz), 124.4 ($J=9.9$ Hz), 125.2 ($J=3.3$ Hz), 126.7 ($J=13.2$ Hz), 128.2 ($J=3.3$ Hz), 129.3, 130.4 ($J=8.3$ Hz), 130.7 ($J=2.5$ Hz), 130.9, 132.4 ($J=9.1$ Hz), 132.4, 136.2, 136.5, 138.5, 142.0 ($J=5.0$ Hz), 144.0, 156.3 ($J=2.5$ Hz), 159.1 ($J=246.5$ Hz), 160.4 ($J=247.3$ Hz), 166.1, 204.0; MS m/z 428 (M^+), 413, 398, 370; HR-MS [ESI(+)] calcd for $C_{26}H_{19}F_2N_2O_2$ (M + H): 429.1415, found 429.1431.

Reaction of carboxylic acid 17a with TfOH. {6,7-Dihydro-10-fluoro-3-(2-fluorophenyl)- 5-oxo-8-chloromethyl-5*H*-benzo[6,7]cyclohepta-[1,2-*b*]quinoline (18a)}. The carboxylic acid **17a** (610 mg, 1.45 mmol) was dissolved into TfOH (61 mL), and the mixture was stirred at 130 °C for 5h. After cooling, the resulting mixture was poured into water and neutralized with Na_2CO_3, then extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue (toluene/AcOEt = 5/1) gave the cyclized product **18a** (61 mg, 10%) and lactone **19** (210 mg, 36%).

Cyclized product **18a**: mp 208–211 °C (hexane/AcOEt = 2:1, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.02 (1H, brs), 3.06–3.10 (2H, m), 3.38–3.42 (2H, m), 5.21 (2H, s), 7.17–7.29 (2H, m), 7.35–7.42 (1H, m), 7.45–7.56 (2H, m), 7.82 (1H, dd, $J=2.7$, 10.3 Hz), 7.88 (1H, brt, $J=1.5$ Hz), 7.93 (1H, dt, $J=8.1$, 1.8 Hz), 8.12 (1H, d, $J=8.0$ Hz), 8.17 (1H, dd, $J=5.6$, 9.2 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.8, 45.8, 55.8, 108.5 ($J=23.1$ Hz), 116.3 ($J=22.3$ Hz), 119.1 ($J=26.0$ Hz), 125.2 ($J=3.5$ Hz), 126.7 ($J=12.8$ Hz), 127.1 ($J=9.9$ Hz), 127.8 ($J=3.0$ Hz), 130.4 ($J=8.2$ Hz), 130.7 ($J=2.9$ Hz), 130.8, 132.2 ($J=2.8$ Hz), 132.4, 132.5, 136.3, 137.1, 138.6, 142.8 ($J=5.8$ Hz), 144.2, 156.6 ($J=2.6$ Hz), 159.2 ($J=246.7$ Hz), 160.2 ($J=245.1$ Hz), 204.7; MS m/z 401 (M^+), 384, 370, 306, 276; HR-MS [ESI(+)] calcd for $C_{25}H_{18}F_2NO_2$ (M + H): 402.1306, found 402.1313.

Lactone **19**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.09–3.14 (2H, m), 3.32 (2H, brt, $J=6.7$ Hz), 5.80 (2H, s), 7.16–7.29 (2H, m), 7.33–7.41 (1H, m), 7.46–7.58 (4H, m), 7.63 (1H, dd, $J=2.6$, 10.4 Hz), 7.70 (2H, dd, $J=1.6$, 8.2 Hz), 8.19 (1H, dd, $J=5.7$, 9.2 Hz); MS m/z 401 (M^+), 372, 356, 306; HR-MS [ESI(+)] calcd for $C_{25}H_{18}F_2NO_2$ (M + H): 402.1306, found 402.1298.

Reaction of carboxylic acid 17b with TfOH. The carboxylic acid **17b** (140 mg, 0.32 mmol) was dissolved into TfOH (14 mL), and the mixture was stirred at 130 °C for 2h. After cooling, the resulting mixture was poured into water and neutralized with Na_2CO_3, then extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue (toluene/AcOEt = 3:1) gave the lactone **19** (35 mg, 27%) as the only isolable product.

Reaction of carboxylic acid 17c with TfOH. {6,7-dihydro-10-fluoro-3-(2-fluorophenyl)- 5-oxo-8-chloromethyl-5*H*-benzo[6,7]cyclohepta-[1,2-*b*]quinoline (18c)}. The carboxylic acid **17c** (2.00 g, 4.57 mmol) was dissolved into TfOH (200 mL), and the mixture was stirred at 130 °C for 2 h. After cooling, the resulting mixture was poured into water and neutralized with Na_2CO_3, then extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue ($CHCl_3$) gave the cyclized product **18c** (1.55 g, 81%).

Mp 214–216 °C (toluene/AcOEt = 10:1, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.11–3.15 (2H, m), 3.36–3.40 (2H, m), 5.05 (2H, s), 7.16–7.29 (2H, m), 7.35–7.42 (1H, m), 7.49–7.56 (2H, m), 7.72 (1H, dd, $J=2.6$, 10.0 Hz), 7.91–7.93 (1H, m), 7.94 (1H, dt, $J=8.1$, 1.8 Hz), 8.12 (1H, d, $J=8.0$ Hz), 8.20 (1H, dd, $J=5.6$, 9.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.3, 37.4, 45.3, 107.0 ($J=23.5$ Hz), 116.3 ($J=22.5$ Hz), 119.7 ($J=25.8$ Hz), 124.6 ($J=3.7$ Hz), 126.3 ($J=9.6$ Hz), 127.4 ($J=13.3$ Hz), 128.9 ($J=2.7$ Hz), 129.8 ($J=8.3$ Hz), 130.6 ($J=3.1$ Hz), 130.9, 132.6, 133.1, 133.3 ($J=9.5$ Hz), 137.2, 137.6, 137.7 ($J=6.0$ Hz), 138.2, 144.8, 156.9 ($J=3.0$ Hz), 159.8 ($J=248.9$ Hz), 161.4 ($J=249.8$ Hz), 203.8; MS m/z 419 (M^+ (Cl^{35})), 384, 290; HR-MS [ESI(+)] calcd for $C_{25}H_{17}ClF_2NO$ (M + H): 420.0967, found 420.0971.

Reaction of carboxylic acid 17d with TfOH. {6,7-Dihydro-10-fluoro-3-(2-fluorophenyl)-5-oxo-8-methyl-5*H*-benzo[6,7]cyclohepta[1,2-*b*]-quinoline (18d)}. The carboxylic acid **17d** (2.00 g, 4.96 mmol) was dissolved into TfOH (200 mL), and the mixture was stirred at 130 °C for 4 h. After cooling, the resulting mixture was poured into water and neutralized with Na_2CO_3, then extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue (toluene/AcOEt = 10:1) gave the cyclized product **18d** (1.38 g, 72%).

Mp 241–242 °C (hexane/AcOEt = 3:1, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.71 (3H, s), 3.02–3.06 (2H, m), 3.29–3.33 (2H, m), 7.16–7.27 (2H, m), 7.33–7.40 (1H, m), 7.43–7.55 (2H, m), 7.64 (1H, dd, J = 2.7, 10.4 Hz), 7.88 (1H, brs), 7.92 (1H, dt, J = 8.2, 1.6 Hz), 8.12 (1H, d, J = 8.1 Hz), 8.13 (1H, dd, J = 5.6, 9.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 24.4, 45.2, 107.6 (J = 22.7 Hz), 116.2 (J = 22.5 Hz), 118.9 (J = 25.6 Hz), 124.5 (J = 3.8 Hz), 127.5 (J = 13.1 Hz), 128.2 (J = 9.3 Hz), 128.6 (J = 2.6 Hz), 129.7 (J = 8.2 Hz), 130.6 (J = 3.1 Hz), 130.7, 131.4, 132.8 (J = 9.3 Hz), 133.0 (J = 3.4 Hz), 137.2, 137.9, 138.3, 139.5 (J = 5.7 Hz), 144.2, 156.5 (J = 2.8 Hz), 159.8 (J = 248.6 Hz), 160.8 (J = 247.6 Hz), 204.5; MS m/z 385 (M^+), 357, 290; HR-MS [ESI(+)] calcd for $C_{25}H_{18}F_2NO$ (M + H): 386.1356, found 386.1342.

***N*-Octyl-6,7-dihydro-10-fluoro-3-(2-fluorophenyl)-5*H*-benzo[6,7]cyclohepta[1,2-*b*]-quinoline-8-carboxamide (15b)**. $NaBH_4$ (9.0 mg, 0.22 mmol) was added to a solution of the ketone **13b** (117 mg, 0.22 mmol) in MeOH (12 mL) at 5 °C. The mixture was stirred at room temperature for 1 h. After quenching with acetone (1.0 mL), the reaction mixture was concentrated under reduced pressure, and water was added to the residue. The mixture was extracted with AcOEt, and the extract was washed with brine and dried over Na_2SO_4. After filtration and evaporation, the residue was dissolved in AcOH (2.0 mL). Then Ac_2O (2.0 mL) and HI (57%, 4.0 mL) were added to this solution at room temperature, and the mixture was stirred at 100 °C for 3 h. After cooling and quenching with 10% aqueous $Na_2S_2O_5$ (10 mL), the mixture was neutralized with $NaHCO_3$, then extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. After filtration and evaporation, chromatographic separation of the residue (toluene/AcOEt = 20:1) gave the carboxamide **15b** (108 mg, 96%).

Mp 149–150 °C (toluene, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87–0.91 (3H, m), 1.15–1.52 (10H, m), 1.58–1.73 (2H, m), 2.24–2.31 (2H, m), 2.64–2.76 (4H, m), 3.59 (2H, brq, J = 6.9 Hz), 6.01 (1H, brt, J = 5.7 Hz), 7.15–7.27 (2H, m), 7.31–7.38 (1H, m), 7.44–7.53 (4H, m), 7.63 (1H, dt, J = 7.9, 1.4 Hz), 7.87 (1H, d, J = 7.9 Hz), 8.16 (1H, dd, J = 5.4, 10.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.6, 27.0, 27.6, 29.1, 29.2, 29.7, 31.0, 31.5, 31.7, 40.1, 108.1 (J = 23.2 Hz), 116.2 (J = 22.8 Hz), 119.4 (J = 25.7 Hz), 124.4 (J = 3.7 Hz), 124.6, 127.8 (J = 2.7 Hz), 128.2, 128.6 (J = 13.4 Hz), 129.0, 129.2 (J = 7.8 Hz), 129.8, 130.7 (J = 3.3 Hz), 132.3 (J = 9.2 Hz), 137.1, 138.9, 139.0, 140.8 (J = 5.5 Hz), 144.1, 144.1, 159.6 (J = 2.8 Hz), 159.8 (J = 248.1 Hz), 160.9 (J = 248.7 Hz), 167.1; MS m/z 512 (M^+), 384, 356; HR-MS [ESI(+)] calcd for $C_{33}H_{35}F_2N_2O$ (M + H): 513.2717, found 513.2705.

6,7-Dihydro-10-fluoro-3-(2-fluorophenyl)-5-oxo-8-hydroxymethyl-5*H*-benzo[6,7]cyclo-hepta[1,2-*b*]quinoline (18a). AcONa (527 mg, 6.42 mmol) was added to a solution of the chloride **18c** (350 mg, 0.83 mmol) in AcOH (17.5 mL). The mixture was stirred at 110 °C for 22 h. After cooling and quenching with water (100 mL), the reaction mixture was neutralized with $NaHCO_3$, then extracted with AcOEt. The extract was washed with water, brine and dried over $MgSO_4$. After filtration and evaporation, MeOH (16 mL) and 1 mol/L NaOH (0.85 mL) were added to the residue. The resulting mixture was stirred at room temperature for 2 h. Then water (100 mL) was added, and the mixture was extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue (toluene/AcOEt = 1:1) gave the alcohol **18a** (323 mg, 97%).

6,7-Dihydro-10-fluoro-3-(2-fluorophenyl)-5-oxo-8-formyl-5*H*-benzo[6,7]cyclohepta[1,2-*b*]-quinoline (21). Ac_2O (0.24 mL, 2.49 mmol) was added to a solution of the alcohol **18a** (200 mg, 0.50 mmol) in DMSO (6.0 mL) at room temperature. The mixture was stirred at room temperature for 17 h. After cooling to 0 °C, MeOH (1 mL) was added, and the mixture was stirred for 2 h. Water (20 mL) was added to the mixture, and the mixture was extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue (toluene/AcOEt = 10:1) gave the aldehyde **21** (180 mg, 90%).

Mp 185–189 °C (toluene, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.15–3.19 (2H, m), 3.49–3.58 (2H, m), 7.17–7.30 (2H, m), 7.34–7.43 (1H, m), 7.51–7.60 (2H, m), 7.92 (1H, brt, J = 1.5 Hz), 7.96 (1H, dt, J = 8.1, 1.8 Hz), 8.15 (1H, d, J = 8.1 Hz), 8.23 (1H, dd, J = 5.5, 9.2 Hz), 8.26 (1H, dd, J = 2.8, 10.5 Hz), 11.02 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.1, 45.4, 107.6 (J = 24.6 Hz), 116.3 (J = 22.5 Hz), 120.2 (J = 25.9 Hz), 124.4 (J = 10.8 Hz), 124.6 (J = 3.7 Hz), 127.3 (J = 13.1 Hz), 128.9 (J = 2.7 Hz), 129.9 (J = 8.4 Hz), 130.6 (J = 3.0 Hz), 131.0, 132.9 (J = 9.6 Hz), 133.2 (J = 3.6 Hz), 134.4 (J = 6.1 Hz), 134.8, 136.3, 137.9, 138.3, 145.2, 157.7 (J = 3.0 Hz), 159.8 (J = 248.8 Hz), 162.3 (J = 251.1 Hz), 192.6, 203.5; MS m/z 399 (M^+), 370, 276; HR-MS [ESI(+)] calcd for $C_{25}H_{16}F_2NO_2$ (M + H): 400.1149, found 400.1157.

6,7-Dihydro-10-fluoro-3-(2-fluorophenyl)-5-oxo-5*H*-benzo[6,7]cyclohepta[1,2-*b*]quinoline-8-carboxylic acid (4). A solution of $NaH_2PO_4 \cdot H_2O$ (72 mg, 0.46 mmol) in water (1.0 mL) was added to a suspension of the aldehyde **21** (80 mg, 0.20 mmol) in DMSO (8.0 mL) at room

temperature. Then 87% $NaClO_2$ (83 mg, 0.80 mmol) was added dropwise to the mixture for 5 min. The resulting mixture was stirred at room temperature for 2 h, and water (20 mL) and 1 mol/L HCl (1 mL) were added. The mixture was extracted with AcOEt, and the extract was washed with water, brine, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure to afford the carboxylic acid **4** (81 mg, 98%).

Mp 285–290 °C (AcOEt, decomp); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.07–3.16 (4H, m), 7.34–7.42 (2H, m), 7.47–7.52 (1H, m), 7.57 (1H, dd, J = 2.8, 9.8 Hz), 7.67 (1H, dt, J = 1.7, 7.9 Hz), 7.73–7.80 (2H, m), 7.99 (1H, dt, J = 8.2, 1.7 Hz), 8.10 (1H, d, J = 8.2 Hz), 8.21 (1H, dd, J = 5.6, 9.2 Hz); MS m/z 415 (M^+), 370, 320; HR-MS [ESI(+)] calcd for $C_{25}H_{16}F_2NO_3$ (M + H): 416.1098, found 416.1087.

Methyl 6,7-dihydro-10-fluoro-3-(2-fluorophenyl)-5-oxo-5*H*-benzo[6,7]cyclohepta[1,2-*b*]-quinoline-8-carboxylate (22). Na_2CO_3 (40 mg, 0.29 mmol) and MeI (82 mg, 0.59 mmol) were added to a suspension of the carboxylic acid **4** (81 mg, 0.20 mmol) in acetone (8.1 mL) at room temperature. The mixture was stirred at 45 °C for 5 h. After cooling, water (30 mL) and 1 mol/L HCl (1 mL) were added to the reaction mixture. The mixture was extracted with AcOEt, and the extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, chromatographic separation of the residue (toluene/AcOEt = 20:1) gave the methyl ester **22** (64 mg, 77%).

Mp 209–212 °C (toluene, decomp); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.12–3.21 (4H, m), 4.13 (3H, s), 7.17–7.29 (2H, m), 7.35–7.42 (1H, m), 7.45 (1H, dd, J = 2.7, 9.5 Hz), 7.50–7.57 (2H, m), 7.92–7.96 (2H, m), 8.14 (1H, dd, J = 0.4, 7.9 Hz), 8.20 (1H, dd, J = 5.5, 9.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.3, 45.3, 53.0, 108.3 (J = 23.7 Hz), 116.3 (J = 22.5 Hz), 120.2 (J = 25.8 Hz), 124.3 (J = 10.3 Hz), 124.6 (J = 3.6 Hz), 127.4 (J = 13.1 Hz), 129.0 (J = 2.7 Hz), 129.9 (J = 8.4 Hz), 130.4, 130.6 (J = 3.0 Hz), 130.9, 132.7 (J = 9.5 Hz), 133.2 (J = 3.5 Hz), 136.5, 136.8 (J = 5.8 Hz), 137.7, 138.4, 144.7, 156.7 (J = 3.0 Hz), 159.8 (J = 248.7 Hz), 161.4 (J = 250.3 Hz), 167.4, 203.7; MS m/z 429 (M^+), 414, 398, 370, 334; HR-MS [ESI(+)] calcd for $C_{26}H_{17}F_2NO_3$ (M + H): 430.1255, found 430.1268.

6,7-Dihydro-10-fluoro-3-(2-fluorophenyl)-5*H*-benzo[6,7]cyclohepta[1,2-*b*]quinoline-8-carboxylic acid (1, KF20444). From the carboxamide **15b**: $NaNO_2$ (38 mg, 0.55 mmol) was added to a solution of the carboxamide **15b** (57 mg, 0.11 mmol) in a mixture of AcOH (0.6 mL) and Ac_2O (3.0 mL) at 5 °C. The mixture was stirred at room temperature overnight. After quenching with water (40 mL) and neutralization with Na_2CO_3, the mixture was extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, a saturated ethanolic solution of KOH (2.0 mL) was added to the residue, and the mixture was stirred at 80 °C for 3 h. After cooling, EtOH was removed under reduced pressure. Water (60 mL) and Et_2O (40 mL) were added to the residue, and the mixture was stirred at room temperature, then separated. The aqueous layer was adjusted to pH 2.0 with 2 mol/L HCl and extracted with AcOEt. The extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, $CHCl_3$ (3.0 mL) was added to the residue and stirred at 5 °C. The precipitated solid was filtered and dried under reduced pressure to afford KF20444 (33 mg, 74%).

From the methyl ester **22**: $NaBH_4$ (13 mg, 0.35 mmol) was added to a suspension of the methyl ester **22** (70 mg, 0.16 mmol) in MeOH (7.0 mL) at 5 °C. The mixture was stirred at room temperature for 2.5 h. After quenching with acetone (2.0 mL) and evaporation, to the residue were added water (15 mL) and 1 mol/L HCl (2 mL). The mixture was extracted with AcOEt and the extract was washed with water, brine, and dried over $MgSO_4$. After filtration and evaporation, the residue was dissolved in AcOH (4.0 mL), then Ac_2O (4.0 mL) and HI (57%, 4.0 mL) were added to this solution at room temperature. The mixture was stirred at 110 °C for 5 h. After cooling and quenching with 5% aqueous $Na_2S_2O_5$ (50 mL), the mixture was extracted with AcOEt. The organic layer was washed with water, brine and dried over Na_2SO_4. After filtration and evaporation, CH_2Cl_2 (7.0 mL) was added to the residue and stirred at room temperature. The precipitated solid was filtered and dried under reduced pressure to afford KF20444 (47 mg, 73%).

Mp 230–234 °C (CH_2Cl_2, decomp); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.20–2.27 (2H, m), 2.56–2.68 (4H, m), 7.33–7.40 (2H, m), 7.43–7.51 (1H, m), 7.56–7.66 (4H, m), 7.75 (1H, dt, J = 2.8, 8.8 Hz), 7.86 (1H, d, J = 7.9 Hz), 8.21 (1H, dd, J = 5.6, 9.2 Hz); MS m/z 401 (M^+), 356, 306, 259; HR-MS [ESI(+)] calcd for $C_{25}H_{18}F_2NO_2$ (M + H): 402.1306, found 402.1307.

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