Synthesis of New Quinolone Antibiotics Utilizing Azetidine Derivatives Obtained from 1-Azabicyclo[1.1.0]butane

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A series of 3-sulfenylazetidine derivatives 5a—f were synthesized *via* the ring-opening reactions of 1-azabicyclo[1.1.0]butane (ABB, 3) with thiols 4a—f in 50—92% yields. Treatment of ABB (3) with aromatic amines 9a—e and dibenzylamine (9f) in the presence of $Mg(ClO_4)_2$ afforded the corresponding 3-aminoazetidine derivatives 10a—f in 24—65% yields. *N*-Benzyl-3-bromoazetidine (13), which was obtained by the reaction of ABB (3) with benzyl bromide, gave 3-aliphatic amino-substituted azetidine derivatives 15a, b. Novel fluoroquinolones 7a—f, 11a—f, 16a, b and 25a—c were obtained by the introduction of these azetidine derivatives into the C7 position of a quinolone nucleus 6 and N1-heterocyclic quinolones 21a—c in 21—83% yields. Some of them exhibited a greater antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) in comparison with that of clinically used fluoroquinolone, levofloxacin (LVFX).

Key words azabicyclobutane; azetidine; new quinolone; antibacterial agent; methicillin-resistant *Staphylococcus aureus*

Although 1-azabicyclo[1.1.0]butane (ABB, **3**) proved to be the unique molecule bearing the highly strained bicyclic structure, little attention has been paid to the unusual ring system.[1—10] Specifically, the synthetic utility of ABB (**3**), which must be useful for the preparation of various 1,3-disubstituted and 3-monosubstituted azetidines,[1,9,10] has scarcely reported because of its synthetic difficulty due to the remarkably strained structure. These azetidine moieties have often been found in many natural products[11] and biologically active compounds such as carbapenems[1] and new quinolone antibiotics.[12—15] 1,3,3-Trinitroazetidine (TNAZ),[16,17] an insensitive high explosive, was also synthesized by using ABB (**3**). In recent years, we established an efficient method for synthesis of ABB (**3**) starting from allylamine (**1**) *via* 2,3-dibromopropylamine hydrobromide (**2**), and reported its application to the synthesis of several azetidine derivatives, as shown in Chart 1.[9] We also reported a practical synthesis of 1-(1,3-thiazolin-2-yl)azetidine-3-thiol as the fascinating pendant moiety of a new oral 1β-methylcarbapenem antibiotic, L-084 by starting from ABB (**3**).[1] This expeditious construction method for 3-monosubstituted azetidine derivatives employing ABB (**3**) seemed to be useful also for developing new quinolone antibiotics.

Fluoroquinolones have been developed and are widely used clinically. This is because they have potent, a broad spectrum of antibacterial activities, and few side effects.[18—22] However, increasingly multidrug-resistant pathogens, especially methicillin-resistant *Staphylococcus aureus* (MRSA), have become a serious problem particularly during the last decade.[23] The resistance levels to quinolones are as yet relatively low but are steadily increasing.[24] Therefore new antibacterial agents have become increasingly urgent. This prompted us to develop new quinolones utilizing the azetidine derivatives, in which the C7 substituents of fluoroquinolone carboxylic acids play important antibacterial roles.[18—22] Previously, we communicated synthesis and antibacterial activities of new quinolone derivatives utilizing ABB (**3**).[10]

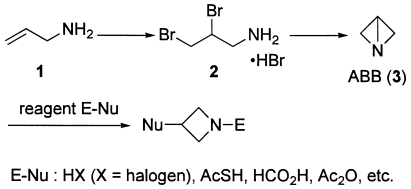

Chart 1. Synthetic Route for ABB (**3**) and Its Reaction Mode with Reagent E-Nu

We now describe, in detail, a convenient method of synthesizing several 3-sulfenyl- and 3-aminoazetidine derivatives utilizing ABB (**3**), and we discuss the synthesis and antibacterial activities of new quinolone antibiotics incorporating these azetidine derivatives to the C7 position. Although several examples of 7-azetidinylquinolones have been reported,[12—15] there have been not many prominent quinolone antibiotics bearing the azetidinyl substituent groups thus far. We envisaged that the introduction of azetidine derivatives onto the C7 position of the quinolone nucleus might enhance their antibacterial activities against MRSA.

Results and Discussion

A tetrahydrofuran (THF) solution of ABB (**3**), obtained by treatment of 2,3-dibromopropylamine hydrobromide (**2**) with *n*-BuLi at −78 °C in THF followed by codistillation with THF,[1] was employed for the synthesis of 3-sulfenyl- and 3-amino azetidine derivatives **5a**—**f** and **10a**—**f**.[10] The synthesis of the fluoroquinolones bearing 3-sulfenylazetidine derivatives was performed in a following manner. Namely, the ring-opening reaction of small excess ABB (**3**) with several heterocyclic thiols **4a**—**e** and *p*-toluenethiol (**4f**) was carried out in THF at room temperature. The reaction proceeded smoothly to furnish the desired corresponding 3-sulfenylazetidine derivatives **5a**—**f** in 50—92% yields, as shown in Table 1. Compounds **5c**—**f** were purified as the hydrochlorides by treatment of the crude products with 2 N HCl in Et_2O because of their instability during chromatographic purifica-

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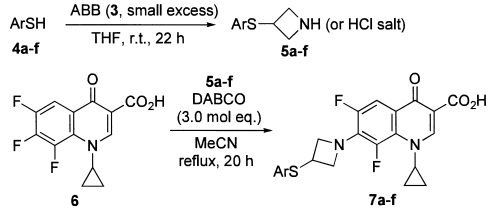
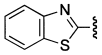
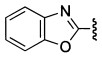
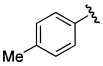
Table 1. Synthesis of 3-Sulfenylazetidines **5a**—**f** and New Quinolone Derivatives **7a**—**f**



	Ar	Yield (%)[a] of **5a**—**f**		Yield (%)[a] of **7a**—**f**	
a		**5a**	83	**7a**	49
b		**5b**	50	**7b**	21
c		**5c**	65[b]	**7c**	50
d		**5d**	88[b]	**7d**	66
e		**5e**	92[b]	**7e**	51
f		**5f**	75[b]	**7f**	58

a) Isolated yield. *b*) Isolated yield as the HCl salt.

tion on a silica gel column. The structures of 3-sulfenylazetidine derivatives **5a**—**f** were determined by their characteristic ^{1}H-NMR spectra and high-resolution MS analysis (see Experimental). In all the sulfenylation reactions, ABB (**3**) must play an important role as a base [*e.g.*, 3-phenyl-1-azabicyclo[1.1.0]butane: $pK_a(H_2O)=7.3$, benzenethiol: $pK_a(H_2O)=6.6$][7,25] to heterocyclic thiols and benzenethiols. The resulting anionic thio group can smoothly attack the C3 position of ABB (**3**) followed by cleavage of the highly strained N1–C3 σ-bond to furnish each corresponding 3-sulfenylazetidine derivative. Subsequently, we chose readily accessible compound **6** as a quinolone nucleus, obtained from the Grohe–Heitzer reaction procedure[26—30] employing 2,3,4,5-tetrafluorobenzoic acid and cyclopropyl amine, because the cyclopropyl group was widely used as an N1 substituent for the quinolone antibiotics, which generally provided wide and potent antibacterial activities.[22] The compound **6** was treated with 3-sulfenylazetidine derivatives **5a**—**f** in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) in MeCN under reflux to give the corresponding 7-(3-sulfenylazetidin-1-yl)fluoroquinolone carboxylic acids **7a**—**f** in 21—66% yields (Table 1). The structure of product **7b** was precisely determined by X-ray crystallographic analysis (Fig. 1).[31] Other products were shown to be structures **7a** and **7c**—**f**, based on the spectroscopic and elemental analyses in comparison with those of **7b**.

To determine the azetidine ring's effect on antibacterial activity in comparison with that of **7a**, sulfenyl-C7-substituted fluoroquinolone **8** was prepared by similar treatment of the compound **6** with 5-mercapto-1-methyltetrazole (**4a**) in the presence of DABCO in MeCN under reflux, as shown in Chart 2.

Subsequently, we attempted the similar ring-opening reaction of ABB (**3**) with aniline (**9a**) without an additive to the

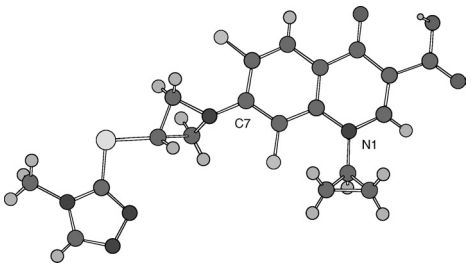


Fig. 1. Computer-Generated Drawing from X-Ray Coordinates of Compound **7b**

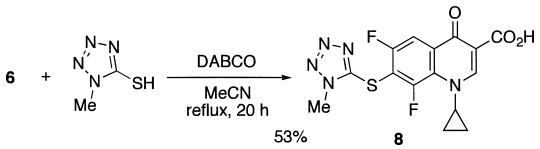
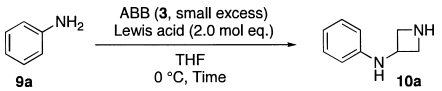


Chart 2. Synthesis of 7-Sulfenylquinolone **8**

Table 2. Reaction of ABB (**3**) with Aniline in the Presence of Various Lewis Acids



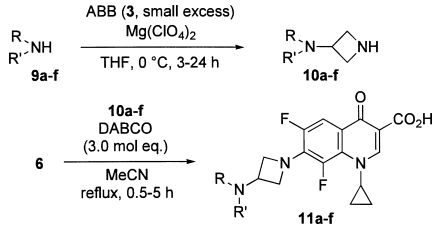
Entry	Lewis acid	Time (h)	Yield (%)[a,b]	Recovery (%)[b] of aniline
1	$BF_3\cdot OEt_2$	3	29	51
2	TMSOTf	3	38	25
3	$Zn(OTf)_2$	1	61	20
4	$Mg(OTf)_2$	2	59	25
5	$Cu(OTf)_2$	3	52	15
6	$Yb(OTf)_3$	2	57	18
7	$Hf(OTf)_4$	2	36	16
8	$Zn(ClO_4)_2\cdot 6H_2O$	3	57	13
9	$Mg(ClO_4)_2$	3	61	21
10	$LiClO_4$	3	1	97
11	$MgCl_2$	24	7	85
12	$TiCl_4$	24	11	89
13	$AlCl_3$	24	18	71

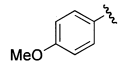
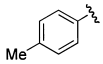
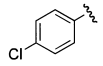
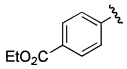
a) Based on aniline. *b*) Determined by HPLC analysis.

case of thiols **4a**—**f**, but the desirable reaction did not proceed even under the reflux conditions. Then, we tried activation of ABB (**3**) with Brønsted acids (CSA, TFA) in the presence of aniline (**9a**), but an unknown polymer was obtained instead of the desired 3-anilinoazetidine (**10a**). Thus, we examined in detail the ring-opening reaction of ABB (**3**) with aniline (**9a**) in the presence of various Lewis acids, as shown in Table 2.

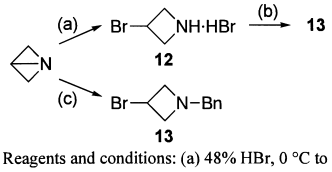
When $BF_3\cdot OEt_2$ or trimethylsilyl trifluoromethanesulfonate (TMSOTf) was employed, a polymer was formed together with 3-anilinoazetidine (**10a**) in 29 or 38% yield (Entries 1, 2). The similar reaction was attempted using $Zn(OTf)_2$ in THF at 0 °C for 1 h to give 3-anilinoazetidine (**10a**) in 61% yield (Entry 3). However, the results using other Lewis acids such as $Mg(ClO_4)_2$, $Mg(OTf)_2$, $Cu(OTf)_2$, $Yb(OTf)_3$, $Hf(OTf)_4$, $Zn(ClO_4)_2\cdot 6H_2O$, and $LiClO_4$ were not improved (Entries 4—10). Lewis acids having chloride anion such as $MgCl_2$, $TiCl_4$, and $AlCl_3$ decreased the yield of **10a** as opposed to the case of $Zn(OTf)_2$ or $Mg(ClO_4)_2$ (Entries 3,

Table 3. Synthesis of 3-Aminoazetidines **10a**—**f** and New Quinolone Derivatives **11a**—**f**



	R	R′	Yield (%)[a] of **10a**—**f**		Yield (%)[a] of **11a**—**f**	
a		H	**10a**	53 (65)[b]	**11a**	76
b		H	**10b**	49 (61)[b]	**11b**	69
c		H	**10c**	51	**11c**	83
d		H	**10d**	46	**11d**	82
e		H	**10e**	24	**11e**	62
f	Bn	Bn	**10f**	38	**11f**	80

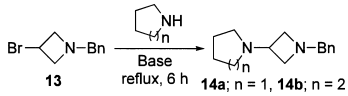
a) Isolated yield. *b*) Reaction was carried out using 1.2 mol eq. of $Mg(ClO_4)_2$ in MeCN as a cosolvent.



Reagents and conditions: (a) 48% HBr, 0 °C to r.t., 30 min, 61%; (b) BnBr, K_2CO_3, DMF, 3.5 h, 39 %; (c) BnBr, reflux, 6 h, 61%

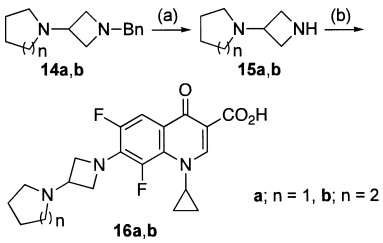
Chart 3. Synthesis of *N*-Benzyl-3-bromoazetidine **13**

Table 4. Reaction of **13** with Cyclic Aliphatic Amines



Entry	*n*	Base	Solvent	Yield (%)[a]
1	1	Et_3N	MeCN	62
2	1	$KHCO_3$	MeCN	41
3	1	$NaHCO_3$	MeCN	59
4	1	K_2CO_3	MeCN	73
5	1	$CsCO_3$	MeCN	55
6	1	K_2CO_3	DMF	60
7	1	K_2CO_3	DMF/H_2O	52
8	1	K_2CO_3	THF	9
9	2	K_2CO_3	MeCN	66

a) Isolated yield.



Reagents and conditions: (a) n = 1 : i) 2N HCl/ether, MeOH, r.t., 20 min, ii) $Pd(OH)_2$/C, H_2, EtOH/H_2O, r.t., 50 h, or n = 2 : $Pd(OH)_2$/C, H_2, EtOH/H_2O, 50°C, 24 h; (b) **6**, DABCO, MeCN, reflux, 2 h, n = 1 : 61% from **14a**, n = 2 : 63% from **14b**

Chart 4. Synthesis of New Quinolone Derivatives **16a**, **b**

9, 11—13). After detailed investigation, $Mg(ClO_4)_2$ was shown to be relatively suitable for the ring-opening reactions of ABB (**3**) with aniline (**9a**). Thus, we chose $Mg(ClO_4)_2$ as the additive for the ring-opening reaction of ABB (**3**) with several amines because of its good solubility in THF, fewer by-products, and low cost.

A small amount of excess ABB (**3**) was allowed to react with aromatic amines **9a**—**e** and dibenzylamine (**9f**) in the presence of 2.0 mol eq of $Mg(ClO_4)_2$ in THF at 0 °C for 3—24 h to furnish the corresponding 3-aromatic aminoazetidines **10a**—**e** in 24—53% yields and 3-dibenzylaminoazetidine (**10f**) in 38% yield, respectively, as shown in Table 3. When the ring-opening reaction was carried out employing a reduced amount (1.2 mol eq) of $Mg(ClO_4)_2$ and MeCN as a cosolvent, the yields of **10a**, **b** were improved (**10a**: 65% yield, **10b**: 61% yield). Unfortunately, the ring opening reaction of ABB (**3**) with aliphatic amines in the presence of $Mg(ClO_4)_2$ resulted in production of an unknown polymer. The structures of **10a**—**f** were assigned by their characteristic ^{1}H-NMR spectra and other spectroscopic analyses (see Experimental). Then, compounds **10a**—**f** were treated with compound **6** in the presence of DABCO in MeCN under reflux to afford the corresponding 7-(3-aminoazetidinyl)fluoroquinolone carboxylic acids **11a**—**f** in 62—83% yields, as shown in Table 3. The structures of **11a**—**f** were assigned by the spectroscopic and elemental analyses in comparison with those of **7b**.

The reaction of ABB (**3**) with cyclic aliphatic amines was investigated as follows. Since the desirable reaction did not proceed under the same conditions as described in Table 3, we focused on *N*-benzyl-3-bromoazetidine (**13**)[8] which can be exploited to synthesize various azetidine derivatives *via* suitable nucleophilic substitution reaction. The compound **13** was obtained *via* two steps of reactions involving the ring-opening reaction of ABB (**3**) with HBr to give 3-bromoazetidine hydrobromide (**12**) followed by benzyl protection of the N1 group, but this reaction procedure resulted in a low yield (24% total yield). We carefully examined the reaction conditions to obtain **13** from ABB (**3**) by one step of reaction. Thus, treatment of ABB (**3**) with benzyl bromide under reflux afforded the desired compound **13** in 61% yield (Chart 3).

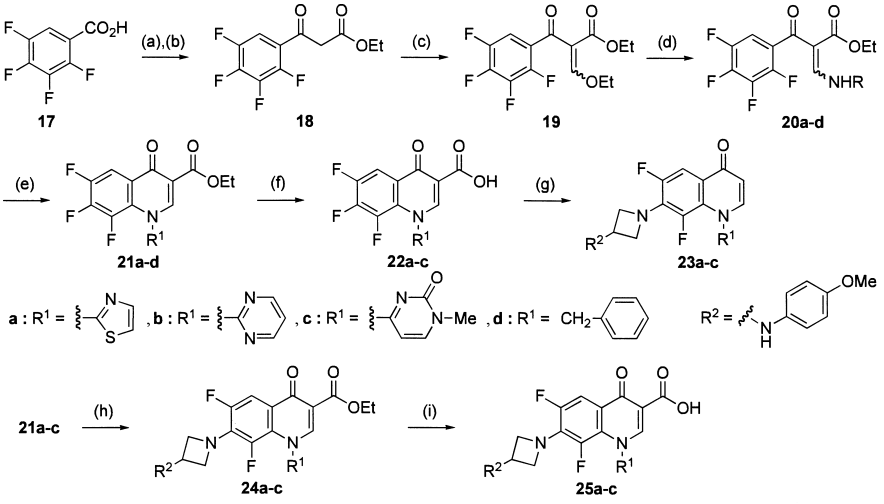
Several reactions of **13** with pyrrolidine were carried out in the presence of various bases in some solvents under reflux, as shown in Table 4. We realized that K_2CO_3 was a good reagent for this substitution reaction (Entry 4) in comparison with other bases (Entries 1—3, 5). Based on screening the reaction solvents, MeCN seemed to be suitable (Entries 4, 6—8).

Thus, compounds **14a**, **b** were subjected to hydrogenolysis of the benzyl group on $Pd(OH)_2$/C to give **15a**, **b**, which were

allowed to react with **6** to afford the corresponding 7-azetidinyl quinolones **16a**, **b** in 61% yield from **14a** and in 63% yield from **14b**, respectively, as shown in Chart 4. The structures were shown to be **16a**, **b** on the basis of their spectroscopic data.

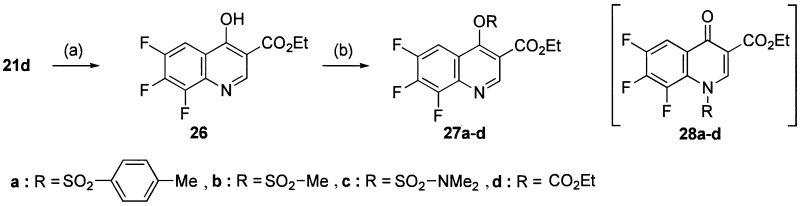
Kuramoto *et al.* reported that the potency order of C7 substituent for 1-cyclopropyl quinolones was as follows: pyrrolidine>piperazine, azetidine.[32] On the other hand, the order for 1-aminodifluorophenyl and 1-aminodifluoropyridyl quinolones was reverse to that for 1-cyclopropyl quinolones: azetidine>piperazine, pyrrolidine.[32] In addition, 1-aminodifluorophenyl and 1-aminodifluoropyridyl quinolones caused mild phototoxicity, despite the substitution of a halogen atom at the C8 position.[33] Therefore, we attempted syntheses of N1-heterocyclic quinolones, as shown in Chart 5. Namely, 2,3,4,5-tetrafluorobenzoic acid **17** was converted to the known compound **19** *via* β-keto ester **18** by exploiting known reactions.[34] The crude product **19** was treated with various amines, such as 2-aminothiazole, 2-aminopyrimidine, 4-amino-1-methylcytosine, and benzylamine in EtOH or CH_2Cl_2 to give the corresponding enamines **20a**—**d**. Treatment of the crude enamines **20a**—**d** with K_2CO_3 in *N*,*N*-dimethylformamide (DMF) afforded cyclized products **21a**—**d** in 43—63% yields. Hydrolysis of **21a**—**c** in 6 N HCl and AcOH at 100 °C gave the corresponding carboxylic acids **22a**—**c** in 67—95% yields. Reaction of **22a**—**c** with 3-(4-methoxyanilino)azetidine (**10b**) in the presence of DABCO in MeCN under reflux afforded decarboxylated products **23a**—**c** in 54—83% yields. This easy decarboxylation outcome of **22a**—**c** can be explained in terms of fairly strong electron-withdrawing effect of the heterocyclic N1 moiety. Although we attempted the nucleophilic substitution reactions of **22a**—**c** without decarboxylation by derivatizing to their boron difluoride intermediates or by the method in the presence of LiCl,[15] desirable products **25a**—**c** have never been obtained. On the other hand, treatment of **21a**—**c** with 3-(4-methoxyanilino)azetidine (**10b**) at room temperature or 40 °C in MeCN afforded 7-azetidinylquinolone ethyl esters **24a**—**c** in 56—78% yields. Alkaline hydrolysis of **24a**—**c** followed by acidification with AcOH provided the desired N1-heterocyclic-7-azetidinyl quinolones **25a**—**c** in 48—80% yields, as shown in Chart 5.

Since any quinolone antibiotic bearing the sulfonamide or carbamate moiety at the N1 position has been unknown, we have done such an attempt as follows. The benzyl (Bn) group of compound **21d** (see Chart 5) was removed by hydrogenolysis on Pd/C at room temperature to give compound **26** in 98% yield. Treatment of **26** with *p*-toluenesulfonyl chloride, methanesulfonyl chloride, *N*,*N*-dimethylsulfamoyl chloride, and ethyl chloroformate gave compound **27a**—**d** in 54%—quantitative yields instead of N1-substituted products **28a**—**d**, as shown in Chart 6.



Reagents and conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, r.t., 18 h; (b) Ethylhydrogen malonate, *n*-BuLi, THF, -78 °C to -5 °C, 1 h, 68% (from **17**); (c) $HC(OEt)_3$, Ac_2O, 135 °C, 5 h; (d) R^1NH_2 (R^1 = thiazol-2-yl, pyrimidin-2-yl, 1-methylcytosin-4-yl, benzyl), EtOH or CH_2Cl_2, r.t., 1-25 h; (e) K_2CO_3, DMF, r.t., 15-22 h, **21a**: 58%, **21b**: 63%, **21c**: 43%, **21d**: 53% (3 steps); (f) 6N HCl, AcOH, 100 °C, 30 min-2 h, **22a**: 77%, **22b**: 95%, **22c**: 67%; (g) **10b**, DABCO, MeCN, reflux, 0.5 h-16 h, **23a**: 65%, **23b**: 54%, **23c**: 83%; (h) **10b**, DABCO, MeCN, r.t. or 40 °C, 9-45 h, **24a**: 63%, **24b**: 78%, **24c**: 67%; (i) (1) NaOH, EtOH, r.t. or LiOH, THF/H_2O, 0 °C; (2) AcOH/H_2O, r.t., 2-6 h, **25a**: 80%, **25b**: 62%, **25c**: 48%

Chart 5. Synthesis of N1-Heterocyclic Quinolones



Reagents and conditions: (a) H_2, Pd/C, EtOH, r.t., 20 h, 98%; (b) RCl (R = *p*-toluenesulfonyl, methanesulfonyl, *N*,*N*-dimethylsulfamoyl, ethoxycarbonyl), Et_3N, CH_2Cl_2, 1.5-3 h, **27a**: quant, **27b**: quant, **27c**: 54%, **27d**: 94%

Chart 6. Reaction of **21d** with *p*-Toluenesulfonyl Chloride and the Related Chlorides

The structure of product **27a** was precisely determined by X-ray crystallographic analysis, as represented in Fig. 2. Other products **27b**—**d** were determined as the aromatized quinoline structures based on their spectroscopic analyses in comparison with those of **27a**.[35)]

The minimum inhibitory concentrations (MICs) of the synthesized compounds **7a**—**f**, **8**, and **11a**, **f** against several representative Gram-positive and Gram-negative bacteria utilizing a conventional agar dilution procedure[36)] are listed in Table 5, along with the data for levofloxacin (LVFX) for comparison.[37,38)] The compounds **7a**—**f** bearing 3-sulfenylazetidines as the C7 substituent of **6** exhibited moderate antibacterial activities against each species of bacteria. The antibacterial activities (except for those against *Escherichia coli*) of **7a**, **b** and **7e** are somewhat potent among the 7-(3-sulfenylazetidin-1-yl)fluoroquinolone series compounds **7a**—**f**. The antibacterial activities of **7e** against methicillin-susceptible *Staphylococcus aureus* (MSSA) and MRSA species (*S. aureus* 1—4 in Table 5), some of which have amino acid mutation in GyrA of DNA gyrase and ParC of topoisomerase IV, were shown to be superior to those of LVFX. However, its activity against Gram-negative bacteria (except for *Haemophilus influenzae*) was low. Compound **7a**, bearing the 3-(1-methyltetrazol-5-yl)thioazetidine moiety at the C7 position of the fluoroquinolone carboxylic acid **6**, exhibited more potent activities against Gram-positive bacteria than those of compound **8** bearing the (1-methyltetrazol-5-yl)thio group alone without the azetidine moiety. Compounds **7a**, **b** and **8** were affected by AcrAB, an efflux system of *Escherichia coli*, which seemed to be changeable by the basicity of the substituent groups at the C7 position. While 7-(3-anilinoazetidin-1-yl)fluoroquinolone carboxylic acid **11a** displayed fairly potent antibacterial activities against Gram-positive bacteria, compound **11f**, having a large substituent at the C3 position of the azetidine ring, exhibited remarkably reduced activities.

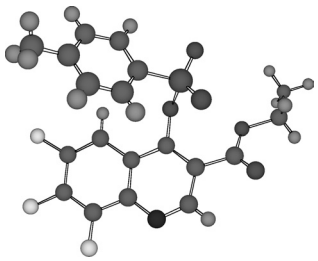


Fig. 2. Computer-Generated Drawing from X-Ray Coordinates of Compound **27a**

Because **11a** exhibited significantly potent activities against Gram-positive bacteria (Table 5), compounds **11a**—**e** together with LVFX were subjected to the antibacterial screening test, as shown in Table 6. The test results showed that the antibacterial spectra of **11a**—**e** do not differ much and that the effects of mutation as well as those of the efflux system seem to be similar among these antibiotics. However, their potencies differed only slightly. Compound **11b** exhibited four-fold better activity against *Staphylococcus pneumoniae* (*S. pneumoniae* R6 and 3—7 in Table 6), such as penicillin-susceptible *Staphylococcus pneumoniae* (PSSP) and penicillin-resistant *Staphylococcus pneumoniae* (PRSP) having amino acid mutation in GyrA and ParC, than **11a**. Compounds **11a**—**e** were more potent than LVFX against quinolone-susceptible and -intermediate MRSA (*S. aureus* 1 and 3 in Table 6). These compounds did not show considerable antibacterial activities against quinolone-resistant MRSA (*S. aureus* 4) or *Pseudomonas aeruginosa*, as shown in Table 6.

Table 5. Antibacterial Activity of 7-Azetidinylquinolones and Levofloxacin

Strain	Characteristics[a)]	Amino acid mutation		MIC[b)] (μg/ml)									
		DNA gyrase	Topoisomerase IV	**7a**	**7b**	**7c**	**7d**	**7e**	**7f**	**11a**	**11f**	**8**	LVFX[c)]
S. aureus ATCC29213	MSSA			0.125	0.125	0.5	1	0.063	2	0.016	>64	16	0.25
S. aureus 1	MRSA			0.125	0.25	1	1	0.063	2	0.031	>64	16	0.5
S. aureus 2	MRSA	GyrA; E88K	ParC; S80F	2	4	4	2	1	32	0.5	>64	>16	8
S. aureus 3	MRSA	GyrA; S84L	ParC; S80Y	2	2	4	2	1	32	0.5	>64	>16	4
S. aureus 4	MRSA	GyrA; S84L, E88K	ParC; S80F, E84K	>32	>16	32	32	32	>32	32	>64	>16	>128
E. faecalis ATCC19433				1	1	4	2	0.25	16	0.25	>64	>16	2
E. faecium ATCC19434				4	8	32	32	4	>32	4	>64	>16	4
S. pneumoniae 1	PSSP			2	2	4	2	1	32	0.5	>64	>16	2
S. pneumoniae 2	PRSP	GyrA; wt	ParC; wt	2	2	2	2	1	32	0.5	>64	>16	2
H. influenzae Rd		GyrA; wt	ParC; wt	0.031	0.016	1	1	0.031	2	0.016	16	0.125	0.016
H. influenzae 1	Δ acrB	GyrA; wt	ParC; wt	≤0.008	≤0.008	0.5	0.5	≤0.008	0.25	≤0.008	8	0.125	≤0.008
H. influenzae 2	BLNAR			0.031	0.016	1	1	0.031	0.5	0.016	32	0.25	0.016
M. catarrhalis				0.063	0.125	0.5	0.5	0.063	2	0.031	>64	4	0.063
K. pneumoniae				2	2	32	8	2	>32	1	>64	16	0.125
E. coli 1				1	2	16	8	1	32	1	>64	8	0.063
E. coli 2				1	1	8	8	1	32	0.5	>64	16	0.063
E. coli 3	Δ acrAB			0.125	0.25	8	8	1	32	0.5	64	1	0.031
P. aeruginosa PAO1				8	8	>32	>32	8	>32	8	>64	>16	0.5
P. aeruginosa 1		GyrA; T83I		>32	>16	>32	>32	>32	>32	>128	>64	>16	16
P. aeruginosa 2		GyrA; T83I	ParC; S87L	>32	>16	>32	>32	>32	>32	>128	>64	>16	64
P. aeruginosa 3		GyrA; T83I, D87G	ParC; S87L	>16	>16	>32	>32	>32	>32	>128	>64	>16	>128

a) MSSA: methicillin-susceptible *Staphylococcus aureus*, MRSA: methicillin-resistant *Staphylococcus aureus*, PSSP: penicillin-susceptible *Staphylococcus pneumoniae*, PRSP: penicillin-resistant *Staphylococcus pneumoniae*, BLNAR: β-lactamase negative anpicilline-resistant *Haemophilus influenzae*. *b*) MIC: minimum inhibitory concentration against microorganisms. *c*) LVFX: levofloxacin.

Table 6. Antibacterial Activity of 7-Azetidinylquinolones and Levofloxacin

Strain	Characteristics[a]	Amino acid mutation		MIC[b] (μg/ml)					
		DNA gyrase	Topoisomerase IV	**11a**	**11b**	**11c**	**11d**	**11e**	LVFX[c]
S. aureus 1	MRSA			0.016	0.031	0.031	0.063	0.031	0.5
S. aureus 3	MRSA	GyrA; S84L	ParC; S80Y	0.5	0.25	0.25	0.5	1	4
S. aureus 4	MRSA	GyrA; S84L, E88K	GyrA; S80F, E85K	>64	16	16	16	>16	>128
E. faecalis ATCC19433				0.5	0.25	0.5	1	2	2
E. faecium ATCC19434				8	4	8	16	16	4
S. pneumoniae R6				0.25	0.063	0.5	0.5	0.125	1
S. pneumoniae 3	PSSP	GyrA; S81F	ParC; D83N	2	0.5	2	4	1	16
S. pneumoniae 4	PRSP	GyrA; S81F	ParC; wt	2	0.25	4	4	1	8
S. pneumoniae 5		GyrA; S81L	ParC; K137L	0.25	0.125	0.25	0.5	1	16
S. pneumoniae 6		GyrA; wt	ParC; S79F	0.5	0.125	0.5	1	0.125	2
S. pneumoniae 7		GyrA; S81F	ParC; S79F	4	0.5	8	16	1	16
H. influenzae Rd		GyrA; wt	ParC; wt	0.016	0.016	0.031	0.063	0.031	0.016
H. influenzae 1	Δ acrB	GyrA; wt	ParC; wt	≤0.008	≤0.008	≤0.008	≤0.008	≤0.008	0.016
H. influenzae 3		GyrA; S84L		0.5	0.5	1	1	0.5	0.125
H. influenzae 4		GyrA; S84L	ParC; S84R, E88K	1	0.5	2	4	2	0.5
H. influenzae 5		GyrA; S84L, D88A	ParC; S84R	32	8	>16	>16	>16	4
M. catarrhalis				0.016	0.031	0.031	0.063	0.125	0.063
K. pneumoniae				1	1	2	4	16	0.125
E. coli 2				0.25	0.25	0.5	1	2	0.063
E. coli 3	Δ acrAB			0.031	0.031	0.063	0.125	0.25	0.016
P. aeruginosa PAO1				4	4	16	>16	>16	0.5
P. aeruginosa 1		GyrA; T83I		>64	>16	>16	>16	>16	16
P. aeruginosa 3		GyrA; T83I, D87G	ParC; S87L	>64	>16	>16	>16	>16	>128

a) MSSA: methicillin-susceptible *Staphylococcus aureus*, MRSA: methicillin-resistant *Staphylococcus aureus*, PSSP: penicillin-susceptible *Staphylococcus pneumoniae*, PRSP: penicillin-resistant *Staphylococcus pneumoniae*. *b*) MIC: minimum inhibitory concentration against microorganisms. *c*) LVFX: levofloxacin.

Table 7. Antibacterial Activity of 7-Azetidinylquinolones and Levofloxacin

Strain	Characteristics[a]	Amino acid mutation		MIC[b] (μg/ml)						
		DNA gyrase	Topoisomerase IV	**16a**	**16b**	**25a**	**25b**	**25c**	**11b**	LVFX[c]
S. aureus ATCC29213	MSSA			0.25	0.12	4	>64	16	≤0.008	0.25
S. aureus 1	MRSA			0.25	0.25	16	>64	16	0.016	0.25
S. aureus 2	MRSA	GyrA; E88K	ParC; S80F	8	4	>64	>64	>64	0.12	8
S. aureus 3	MRSA	GyrA; S84L	ParC; S80Y	4	2	>64	>64	>64	0.25	4
S. aureus 4	MRSA	GyrA; S84L, E88K	ParC; S80F, E84K	>64	>64	>64	>64	>64	16	>64
E. faecalis ATCC19433				2	1	64	>64	>64	0.12	2
E. faecium ATCC19434				16	8	>64	>64	>64	2	4
S. pneumoniae 1	PSSP			2	2	>64	>64	>64	0.12	1
S. pneumoniae 2	PRSP	GyrA; wt	ParC; wt	1	0.5	32	>64	>64	0.03	0.5
S. pneumoniae 3	PSSP	GyrA; S81F	ParC; D83N	16	8	>64	>64	>64	0.25	16
S. pneumoniae 4	PRSP	GyrA; S81F	ParC; wt	32	16	>64	>64	>64	0.25	8
S. pneumoniae 8		GyrA; S81Y		32	32	>64	>64	>64	1	32
H. influenzae Rd		GyrA; wt	ParC; wt	0.016	≤0.008	2	>64	4	0.016	0.016
H. influenzae 1	Δ acrB	GyrA; wt	ParC; wt	≤0.008	≤0.008	0.12	>64	0.5	≤0.008	≤0.008
H. influenzae 5		GyrA; S84L, D88A	ParC; S84R	16	8	>64	>64	>64	8	4
H. influenzae 6		GyrA; 85Adelete, D88Y	ParC; S84R	16	8	>64	>64	>64	8	4
M. catarrhalis				0.06	0.06	4	>64	16	0.03	0.06
E. coli 2				0.25	0.06	>64	>64	>64	0.25	0.06
E. coli 3	Δ acrAB			≤0.008	≤0.008	4	>64	8	0.016	0.016
P. aeruginosa PAO1				4	1	>64	>64	>64	2	0.5
P. aeruginosa 1		GyrA; T83I		64	64	>64	>64	>64	>64	16
P. aeruginosa 3		GyrA; T83I, D87G	ParC; S87L	>64	>64	>64	>64	>64	>64	>64

a) MSSA: methicillin-susceptible *Staphylococcus aureus*, MRSA: methicillin-resistant *Staphylococcus aureus*, PSSP: penicillin-susceptible *Staphylococcus pneumoniae*, PRSP: penicillin-resistant *Staphylococcus pneumoniae*. *b*) MIC: minimum inhibitory concentration against microorganisms. *c*) LVFX: levofloxacin.

Compounds **16a**, **b** and **25a**—**c** together with **11b** and LVFX were subjected to the antibacterial screening test, as shown in Table 7. The compounds **16a**, **b** exhibited comparable antibacterial activities with those of LVFX against both Gram-positive and Gram-negative bacteria. The antibacterial activities of **16a**, **b** seemed to be similar to those of **11b** against Gram-negative bacteria and to be 4—64 times lower than those of **11b** against Gram-positive bacteria. On the other hand, N1-heterocyclic quinolones **25a**—**c** did not show activities.

In conclusion, this work demonstrated a convenient synthesis of 3-sulfenylazetidine derivatives **5a**—**f** and 3-aminoazetidine derivatives **10a**—**f** utilizing ABB (**3**). *N*-Benzyl-3-bromoazetidine (**13**) was readily prepared by treatment of **3** with benzyl bromide, and exploited for the synthesis of 3-pyrrolidine and 3-piperidine-substituted azetidine derivatives **15a**, **b**. Several azetidine derivatives were successfully introduced into fluoroquinolone carboxylic acid **6** to give the corresponding fluoroquinolone antibiotics **7a**—**f**, **11a**—**f**, and **16a**, **b**. Most of the series of fluoroquinolones exhibited more potent activity profiles versus Gram-positive bacteria than versus Gram-negative bacteria. In particular, compounds **11a**—**e** exhibited the fairly potent activities against quinolone-susceptible and intermediate MRSA in comparison with the activities of a clinically used fluoroquinolone, LVFX. Although we synthesized 7-azetidinylquinolones **25a**—**c** bearing N1-heterocyclic groups, their antibacterial activities were remarkably weak.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-420 IR Fourier transform spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-AL300 (300 MHz) or JEOL JNM-AL400 (400 MHz) spectrometer. ^{13}C-NMR spectra were recorded on a JEOL JNM-AL300 (75 MHz) or JEOL JNM-AL400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are given in δ values (ppm) using tetramethylsilane (TMS) as an internal standard. Electron impact (EI)-MS and FAB-MS were recorded on a JEOL JMS SX-120A spectrometer. Electron spray ionization (ESI)-MS were recorded on a Waters LCT Premier spectrometer. Elementary combustion analyses were determined by a Yanaco CHN CORDER MT-5. All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F_{254}). Column chromatography was carried out on silica gel [Kanto Chemical 60N (spherical, neutral); 63—210 μm] or basic alumina (Merck 1076; 90 active basic). X-Ray crystal structure data were collected using a Rigaku RAXIS-RAPID diffractometer. All reagents were used as purchased.

Procedure (A) for the Preparation of 3-Sulfenylazetidines 5 To a solution of 5-mercapto-1-methyltetrazole (**4a**, 141.1 mg, 1.21 mmol) in THF (5 ml) was added dropwise ABB (**3**, *ca.* 0.1 mol/l in THF, 14.5 ml, *ca.* 1.45 mmol)[1] at −5 °C. After being stirred at room temperature for 24 h, the reaction mixture was evaporated *in vacuo* to give an oily residue, which was purified by column chromatography on silica gel with $CHCl_3$–MeOH (10 : 1, v/v) to afford **5a** (173.0 mg, 83%) as a colorless oil.

3-(1-Methyltetrazol-5-yl)thioazetidine (**5a**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.10 (br s, 1H), 3.75 (m, 2H), 3.94 (s, 3H), 4.19 (m, 2H), 4.68 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 33.3, 39.3, 54.1, 153.0; EI-MS Calcd for $C_5H_9N_5S$ MW 171.0579, Found *m/z* 171.0580 (M^+).

3-(4-Methyl-4*H*-1,2,4-triazol-5-yl)thioazetidine (**5b**): Pale yellow oil. ^{1}H-NMR (400 MHz, CD_3OD) δ: 3.61 (m, 2H), 3.68 (s, 3H), 4.02 (m, 2H), 4.44 (m, 1H), 8.52 (s, 1H); ^{13}C-NMR (75 MHz, CD_3OD) δ: 32.11, 32.13, 41.0, 54.9, 147.6, 151.0; EI-MS Calcd for $C_6H_{10}N_4S$ MW 170.0626, Found *m/z* 170.0615 (M^+).

Procedure (B) for the Preparation of 3-Sulfenylazetidines 5 To a solution of 2-mercaptobenzothiazole (**4c**, 203.6 mg, 1.22 mmol) in THF (5 ml) was added dropwise ABB (**3**, *ca.* 0.1 mol/l in THF, 14.5 ml, *ca.* 1.45 mmol)[1] at −5 °C. After being stirred at room temperature for 24 h, the reaction mixture was added dropwise to 2 N HCl in Et_2O at 0 °C with stirring. The precipitate was collected by filtration and washed subsequently with THF, $CHCl_3$, and Et_2O to afford **5c** (204.2 mg, 65%) as a white powder.

3-(Benzo[*b*]thiazol-2-yl)thioazetidine Hydrochloride (**5c**): White powder (MeOH), mp 124—125.5 °C; ^{1}H-NMR (400 MHz, CD_3OD) δ: 4.25—4.40 (m, 2H), 4.58—4.77 (m, 2H), 4.82—4.91 (m, 1H), 7.32—7.56 (m, 2H), 7.86—7.97 (m, 2H); ^{13}C-NMR (75 MHz, CD_3OD) δ: 37.9, 53.5, 122.5, 122.7, 126.0, 127.5, 136.3, 154.1, 164.7; IR (KBr) 2942, 1426, 1310 cm^{-1}; FAB-MS Calcd for $C_{10}H_{11}N_2S_2$ MW 223.0360, Found *m/z* 223.0364 (M^+-Cl).

3-(Benzo[*b*]oxazol-2-yl)thioazetidine Hydrochloride (**5d**): White powder (MeOH); mp 138—139.5 °C; ^{1}H-NMR (400 MHz, CD_3OD) δ: 4.34—4.49 (m, 2H), 4.58—4.73 (m, 2H), 4.74—4.85 (m, 1H), 7.28—7.43 (m, 2H), 7.53—7.71 (m, 2H); ^{13}C-NMR (75 MHz, CD_3OD) δ: 36.7, 53.2, 111.2, 119.7, 125.9, 126.0, 142.6, 153.1, 163.2; IR (KBr) 2855, 1600, 1504, 1454 cm^{-1}; FAB-MS Calcd for $C_{10}H_{11}N_2OS$ MW 207.0604, Found *m/z* 207.0592 (M^+-Cl).

3-(Pyrimidin-2-yl)thioazetidine Hydrochloride (**5e**): Pale yellow powder (MeOH); mp 118—120 °C (dec.); ^{1}H-NMR (400 MHz, CD_3OD) δ: 4.11—4.29 (m, 2H), 4.54—4.74 (m, 3H), 7.21—7.30 (m, 1H), 8.60—8.66 (m, 2H); ^{13}C-NMR (75 MHz, CD_3OD) δ: 35.8, 53.3, 119.1, 159.3 171.3; IR (KBr) 2958, 2291, 1596, 1518 cm^{-1}; FAB-MS Calcd for $C_7H_{10}N_3S$ MW 168.0605, Found *m/z* 168.0595 (M^+-Cl).

3-*p*-Tolylthioazetidine Hydrochloride (**5f**): White powder (MeOH); mp 123.5—124.5 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 3.86—4.13 (m, 2H), 4.14—4.44 (m, 3H), 7.14 (d, J=8.0 Hz, 2H), 7.23 (d, J=8.0 Hz, 2H), 9.36 (br s, 1H); IR (KBr) 2970, 2360, 1894, 1496, 1435 cm^{-1}; FAB-MS Calcd for $C_{10}H_{14}NS$ MW 180.0854, Found *m/z* 180.0847 (M^+-Cl); *Anal.* Calcd for $C_{10}H_{14}ClNS$: C, 55.67; H, 6.54; N, 6.49. Found: C, 55.76; H, 6.54; N, 6.40.

Typical Procedure for the Preparation of New Quinolone 7 To a solution of 1-cyclopropyl-4-oxo-6,7,8-trifluoro-1,4-dihydroquinoline-3-carboxylic acid (**6**, 207.0 mg, 0.73 mmol) and **5a** (150.0 mg, 0.88 mmol) in MeCN (3 ml) was added DABCO (245.7 mg, 2.19 mmol) at room temperature. The mixture was refluxed for 22 h and cooled in an ice bath. The precipitate was collected by filtration and washed subsequently with H_2O, EtOH, and Et_2O to afford **7a** (155.1 mg, 49%) as colorless needles.

1-Cyclopropyl-6,8-difluoro-7-[3-(1-methyltetrazol-5-ylthio)azetidine-1-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**7a**): Colorless needles (THF–MeOH–$CHCl_3$); mp 249—249.5 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.07—1.39 (m, 4H), 3.85—3.96 (m, 1H), 3.98 (s, 3H), 4.47—4.64 (m, 2H), 4.65—4.82 (m, 1H), 4.99—5.11 (m, 2H), 7.81 (dd, J=1.5, 12.5 Hz, 1H), 8.70 (s, 1H), 14.74 (s, 1H); IR (KBr) 2650, 1723, 1627, 1474 cm^{-1}; FAB-MS Calcd for $C_{18}H_{17}F_2N_6O_3S$ MW 435.1041, Found *m/z* 435.1051 (M^++H); *Anal.* Calcd for $C_{18}H_{16}F_2N_6O_3S$: C, 49.55; H, 3.76; N, 19.14. Found: C, 49.77; H, 3.71; N, 19.35.

1-Cyclopropyl-6,8-difluoro-7-[3-(4-methyl-4*H*-1,2,4-triazol-5-ylthio)azetidine-1-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**7b**): Colorless prisms (THF–MeOH–$CHCl_3$); mp 255—256.5 °C (dec.); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.05—1.34 (m, 4H), 3.64 (s, 3H), 3.85—3.99 (m, 1H), 4.40—4.57 (m, 2H), 4.59—4.74 (m, 1H), 4.92—5.12 (m, 2H), 7.82 (d, J=12.5 Hz, 1H), 8.18 (s, 1H), 8.72 (s, 1H), 14.80 (s, 1H); IR (KBr) 2503, 1712, 1620, 1466 cm^{-1}; FAB-MS Calcd for $C_{19}H_{18}F_2N_5O_3S$ MW 434.1119, Found *m/z* 434.1098 (M^++H); *Anal.* Calcd for $C_{19}H_{17}F_2N_5O_3S$: C, 52.48; H, 3.94; N, 15.99. Found: C, 52.65; H, 3.95; N, 16.16.

7-[3-(Benzo[*b*]thiazol-2-ylthio)azetidine-1-yl]-1-cyclopropyl-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**7c**): Colorless powder (THF–MeOH–$CHCl_3$); mp 246—247 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.09—1.31 (m, 4H), 3.85—3.97 (m, 1H), 4.48—4.62 (m, 2H), 4.76—4.90 (m, 1H), 4.97—5.14 (m, 2H), 7.30—7.39 (m, 1H), 7.40—7.50 (m, 1H), 7.75—7.93 (m, 3H), 8.72 (s, 1H), 14.80 (s, 1H); IR (KBr) 2876, 1725, 1626, 1456 cm^{-1}; FAB-MS Calcd for $C_{23}H_{18}F_2N_3O_3S_2$ MW 486.0786, Found *m/z* 486.0758 (M^++H); *Anal.* Calcd for $C_{23}H_{17}F_2N_3O_3S_2$: C, 56.69; H, 3.67; N, 8.35. Found: C, 56.90; H, 3.53; N, 8.65.

7-[3-(Benzo[*b*]oxazol-2-ylthio)azetidine-1-yl]-1-cyclopropyl-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**7d**): Colorless needles (THF–MeOH–$CHCl_3$); mp 253.5—254 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.02—1.35 (m, 4H), 3.79—4.03 (m, 1H), 4.44—4.64 (m, 2H), 4.65—4.88 (m, 1H), 4.96—5.17 (m, 2H), 7.27—7.39 (m, 2H), 7.40—7.53 (m, 1H), 7.54—7.70 (m, 1H), 7.82 (d, J=12.5 Hz, 1H), 8.70 (s, 1H), 14.79 (s, 1H); IR (KBr) 2720, 1719, 1627, 1461 cm^{-1}; FAB-MS Calcd for $C_{23}H_{18}F_2N_3O_4S$ MW 470.0972, Found *m/z* 470.0986 (M^++H); *Anal.* Calcd for $C_{23}H_{17}F_2N_3O_4S$: C, 58.64; H, 3.72; N, 8.80. Found: C, 58.84; H, 3.65; N, 8.95.

1-Cyclopropyl-6,8-difluoro-4-oxo-7-[3-(pyrimidin-2-ylthio)azetidine-1-yl]-1,4-dihydroquinoline-3-carboxylic Acid (**7e**): Pale yellow needles (THF–MeOH–$CHCl_3$); mp 210 °C (dec.); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.05—1.38 (m, 4H), 3.85—3.99 (m, 1H), 4.38—4.53 (m, 2H), 4.57—4.72 (m, 1H), 4.90—5.11 (m, 2H), 7.01—7.12 (m, 1H), 7.82 (dd, J=1.6, 12.6 Hz, 1H), 8.49—8.63 (m, 2H), 8.71 (s, 1H), 14.84 (s, 1H); IR (KBr) 2718, 1724, 1626 cm^{-1}; FAB-MS Calcd for $C_{20}H_{17}F_2N_4O_3S$ MW 431.0965, Found *m/z* 431.0989 (M^++H); *Anal.* Calcd for $C_{20}H_{16}F_2N_4O_3S$: C, 55.53; H, 3.79; N, 12.82. Found: C, 55.81; H, 3.75; N, 13.02.

1-Cyclopropyl-6,8-difluoro-4-oxo-7-(3-*p*-tolylthioazetidine-1-yl)-1,4-dihydroquinoline-3-carboxylic Acid (**7f**): Colorless needles (acetone–Et_2O); mp 211.5—212 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.03—1.31 (m, 4H), 2.35 (s, 3H), 3.84—3.99 (m, 1H), 4.13—4.25 (m, 1H), 4.31—4.46 (m, 2H),

4.78—4.92 (m, 2H), 7.15 (d, J=8.0 Hz, 2H), 7.25 (d, J=8.0 Hz, 2H), 7.78 (dd, J=1.6, 12.6 Hz, 1H), 8.70 (s, 1H), 14.84 (s, 1H); IR (KBr) 2681, 1724, 1620, 1462 cm^{-1}; FAB-MS Calcd for $C_{23}H_{21}F_2N_2O_3S$ MW 443.1253, Found m/z 443.1241 (M^++H); *Anal.* Calcd for $C_{23}H_{20}F_2N_2O_3S$: C, 62.31; H, 4.55; N, 6.33. Found: C, 62.43; H, 4.56; N, 6.33.

1-Cyclopropyl-6,8-difluoro-7-(1-methyltetrazol-5-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (8) To a solution of 1-cyclopropyl-4-oxo-6,7,8-trifluoro-1,4-dihydroquinoline-3-carboxylic acid (**6**, 141.6 mg, 0.50 mmol) and 5-mercapto-1-methyltetrazole (58.1 mg, 0.50 mmol) in MeCN (7 ml) was added DABCO (336.5 mg, 1.50 mmol) at room temperature. The mixture was refluxed for 20 h and cooled in an ice bath. The precipitate was collected by filtration and washed with H_2O, EtOH, and Et_2O. The crude solid was recrystallized from THF–MeOH–$CHCl_3$ to afford **10** (100.3 mg, 53%) as a white powder. mp 218—218.5 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.23—1.35 (m, 4H), 4.02—4.04 (m, 1H), 4.18 (s, 3H), 8.14 (dd, J=2.0, 8.1 Hz, 1H), 8.90 (s, 1H), 13.99 (s, 1H); ESI-MS Calcd for $C_{15}H_{12}F_2N_5O_3S$ MW 380.0629, Found m/z 380.0631 (M^++H); *Anal.* Calcd for $C_{15}H_{11}F_2N_5O_3S$: C, 47.49; H, 2.92; N, 18.46. Found: C, 47.39; H, 3.21; N, 18.16.

Typical Procedure for the Preparation of 3-Amino Azetidine 10 To a solution of aniline (0.09 ml, 1.00 mmol) and ABB (**3**, *ca.* 0.1 mol/l in THF, 10.3 ml, *ca.* 1.2 mmol)[1)] in THF was added a suspension of $Mg(ClO_4)_2$ (446.4 mg, 2.00 mmol) in THF (5 ml) at 0 °C. After being stirred at 0 °C for 3 h, 6 N NaOH was added to the reaction mixture and then extracted with $CHCl_3$. The organic layer was washed with brine and then dried over anhydrous $MgSO_4$. Evaporation *in vacuo* afforded a crude product, which was purified by column chromatography on basic alumina with $CHCl_3$–MeOH (10 : 1, v/v) to give **10a** (78.6 mg, 53%) as a pale yellow amorphous powder.

3-Anilinoazetidine (**10a**)[39)]: Pale yellow amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.05 (br s, 1H), 3.40—3.60 (m, 2H), 3.82—4.00 (m, 2H), 4.03 (br s, 1H), 4.26—4.59 (m, 1H), 6.47—6.57 (m, 2H), 6.66—6.84 (m, 1H), 7.07—7.24 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 48.13, 55.0, 112.8, 117.7, 129.1, 146.4; IR (KBr) 2933, 1602, 1498, 1317 cm^{-1}; EI-MS Calcd for $C_9H_{12}N_2$ MW 148.1002, Found m/z 148.1000 (M^+).

3-(4-Methoxyanilino)azetidine (**10b**): Pale yellow amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.91 (br s, 1H), 3.48 (m, 2H), 3.74 (s, 3H), 3.92 (m, 2H), 4.31 (m, 1H), 6.51 (d, J=9.0 Hz, 2H), 6.78 (d, J=9.0 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 49.3, 55.4, 55.7, 114.4, 115.0, 140.7, 152.5; IR (KBr) 3255, 2931, 1508, 1251, 1166, 1039, 821 cm^{-1}; EI-MS Calcd for $C_{10}H_{14}N_2O$ MW 178.1106, Found m/z 178.1088 (M^+).

3-(*p*-Tolylamino)azetidine (**10c**): Pale yellow amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.79 (br s, 1H), 2.23 (s, 3H), 3.48 (m, 2H), 3.92 (m, 2H), 4.34 (m, 1H), 6.46 (d, J=8.2 Hz, 2H), 6.99 (d, J=8.2 Hz, 2H); ^{13}C-NMR (75 MHz, CD_3OD) δ: 32.1, 32.1, 41.0, 54.9, 147.6, 151.0; IR (KBr) 3289, 2931, 1878, 1619, 1525, 1261, 985, 808 cm^{-1}; EI-MS Calcd for $C_{10}H_{14}N_2$ MW 162.1157, Found m/z 162.1166 (M^+).

3-(4-Chloroanilino)azetidine (**10d**): Pale yellow amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.79 (br s, 1H), 3.48 (m, 2H), 3.93 (m, 2H), 4.30 (m, 1H), 4.06 (br s, 1H), 6.44 (d, J=8.6 Hz, 2H), 7.11 (d, J=8.6 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 48.5, 55.1, 114.1, 122.5, 129.2, 145.2; IR (KBr) 3289, 2946, 1872, 1596, 1490, 1259, 985, 815 cm^{-1}; EI-MS Calcd for $C_9H_{11}ClN_2$ MW 182.0611, Found m/z 182.0597 (M^+).

3-(4-Ethoxycarbonylanilino)azetidine (**10e**): Pale yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.36 (t, 3H), 1.79 (br s, 1H), 3.52 (m, 2H), 3.97 (m, 2H), 4.31 (q, 2H), 4.41 (m, 1H), 6.48 (d, J=8.7 Hz, 2H), 7.87 (d, J=8.7 Hz, 2H); IR (neat) 3357, 2950, 1693, 1604, 1527, 1274, 1174, 1105 cm^{-1}; EI-MS Calcd for $C_{12}H_{16}N_2O_2$ MW 220.1212, Found m/z 220.1193 (M^+).

3-Dibenzylaminoazetidine (**10f**): Pale yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.61—2.05 (m, 1H), 3.30—3.42 (m, 2H), 3.42—3.57 (m, 6H), 3.57—3.69 (m, 1H), 7.18—7.42 (m, 10H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 52.9, 55.1, 57.9, 127.0, 128.1, 129.0, 138.6; IR (neat) 3289, 3060, 2943, 2866, 1603, 1493, 1454, 1367 cm^{-1}; EI-MS Calcd for $C_{17}H_{20}N_2$ MW 253.1705, Found m/z 253.1706 (M^+).

Typical Procedure for the Preparation of New Quinolone 11 To a solution of 1-cyclopropyl-4-oxo-6,7,8-trifluoro-1,4-dihydroquinoline-3-carboxylic acid (**6**, 120.2 mg, 0.42 mmol) and **10a** (62.9 mg, 0.42 mmol) in MeCN (6 ml) was added DABCO (142.8 mg, 1.27 mmol) at room temperature. The mixture was refluxed for 0.5 h and cooled in an ice bath. The precipitate was collected by filtration and then washed with H_2O, EtOH, and Et_2O to afford **11a** (130.9 mg, 76%) as a pale yellow powder.

7-(3-Anilinoazetidin-1-yl)-1-cyclopropyl-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**11a**): Pale yellow powder (THF–MeOH–$CHCl_3$); mp 278 °C (dec.); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.05—1.33 (m, 4H), 3.84—4.00 (m, 1H), 4.12—4.23 (m, 1H), 4.24—4.36 (m, 2H), 4.41—4.54 (m, 1H), 4.78—4.95 (m, 2H), 6.53—6.66 (m, 2H), 6.75—6.87 (m, 1H), 7.17—7.29 (m, 2H), 7.79 (d, J=12.2 Hz, 1H), 8.70 (s, 1H), 14.87 (s, 1H); IR (KBr) 2642, 1724, 1624, 1466 cm^{-1}; FAB-MS Calcd for $C_{22}H_{20}F_2N_3O_3$ MW 412.1485, Found m/z 412.1473 (M^++H); *Anal.* Calcd for $C_{22}H_{19}F_2N_3O_3$: C, 64.23; H, 4.66; N, 10.21. Found: C, 64.10; H, 4.96; N, 10.12.

1-Cyclopropyl-6,8-difluoro-7-[3-(4-methoxyanilino)azetidine-1-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**11b**): White powder (DMF); mp 261—262 °C (dec.); ^{1}H-NMR (400 MHz, DMSO) δ: 1.09—1.21 (m, 4H), 3.65 (s, 3H), 4.05 (m, 1H), 4.17 (m, 2H), 4.30 (m, 1H), 4.77 (m, 2H), 5.93 (d, J=6.1 Hz, 1H), 6.51 (d, J=8.6 Hz, 2H), 6.76 (d, J=8.6 Hz, 2H), 7.73 (m, 1H), 8.59 (s, 1H); IR (KBr) 3407, 2360, 1725, 1629, 1517 cm^{-1}; FAB-MS Calcd for $C_{23}H_{22}F_2N_3O_4$ MW 442.1578, Found m/z 442.1549 (M^++H); *Anal.* Calcd for $C_{23}H_{21}F_2N_3O_4 \cdot 1/2H_2O$: C, 61.33; H, 4.92; N, 9.33. Found: C, 61.60; H, 4.86; N, 9.50.

1-Cyclopropyl-6,8-difluoro-4-oxo-7-[3-(*p*-tolylamino)azetidine-1-yl]-1,4-dihydroquinoline-3-carboxylic Acid (**11c**): White powder (DMF); mp 253—255 °C (dec.); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.10—1.28 (m, 4H), 2.27 (s, 3H), 3.91 (m, 1H), 4.05 (m, 1H), 4.26 (m, 2H), 4.43 (m, 1H), 4.84 (m, 2H), 6.51 (d, J=8.1 Hz, 2H), 7.05 (d, J=8.1 Hz, 2H), 7.79 (m, 1H), 8.69 (s, 1H), 14.88 (s, 1H); IR (KBr) 3361, 1722, 1629, 1525, 1471 cm^{-1}; FAB-MS Calcd for $C_{23}H_{22}F_2N_3O_3$ MW 426.1629, Found m/z 426.1639 (M^++H).

7-[3-(4-Chloroanilino)azetidine-1-yl]-1-cyclopropyl-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**11d**): Pale yellow powder (DMF); mp 286—288 °C (dec.); ^{1}H-NMR (400 MHz, DMSO) δ: 1.10—1.20 (m, 4H), 4.06 (m, 1H), 4.20 (m, 2H), 4.34 (m, 1H), 4.79 (m, 2H), 6.56 (m, 3H), 7.15 (d, 2H), 7.74 (m, 1H), 8.60 (s, 1H), 15.01 (s, 1H); IR (KBr) 3409, 3048, 2360, 1722, 1629 cm^{-1}; FAB-MS Calcd for $C_{22}H_{19}ClF_2N_3O_3$ MW 446.1083, Found m/z 446.1083 (M^++H); *Anal.* Calcd for $C_{22}H_{18}ClF_2N_3O_3$: C, 59.27; H, 4.07; N, 9.42. Found: C, 58.98; H, 4.28; N, 9.50.

1-Cyclopropyl-6,8-difluoro-7-[3-(4-ethoxycarbonylanilino)azetidine-1-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**11e**): White powder (DMF); mp 261—263 °C (dec.); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.12—1.29 (m, 4H), 1.37 (t, 3H), 3.91 (m, 1H), 4.28—4.38 (m, 4H), 4.52 (m, 1H), 4.73 (m, 1H), 4.88 (m, 2H), 6.56 (d, J=8.9 Hz, 2H), 7.76 (m, 1H), 7.92 (d, J=8.9 Hz, 2H), 8.66 (s, 1H), 14.86 (s, 1H); IR (KBr) 3369, 2979, 2360, 1729, 1698 cm^{-1}; FAB-MS Calcd for $C_{25}H_{24}F_2N_3O_5$ MW 484.1684, Found m/z 484.1646 (M^++H); *Anal.* Calcd for $C_{25}H_{23}F_2N_3O_5$: C, 62.11; H, 4.80; N, 8.69. Found: C, 61.82; H, 4.79; N, 8.72.

1-Cyclopropyl-7-(3-dibenzylaminoazetidin-1-yl)-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**11f**): Pale yellow powder (THF–MeOH); mp 213—215 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.08—1.29 (m, 4H), 3.60 (s, 4H), 3.71—3.82 (m, 1H), 3.83—3.95 (m, 1H), 4.16—4.27 (m, 2H), 4.34—4.45 (m, 2H), 7.19—7.40 (m, 10H), 7.77 (d, J=12.5 Hz, 1H), 8.69 (s, 1H), 14.90 (s, 1H); FAB-MS Calcd for $C_{30}H_{28}F_2N_3O_3$ MW 516.2084, Found m/z 516.2099 (M^++H); *Anal.* Calcd for $C_{30}H_{27}F_2N_3O_3$: C, 69.89; H, 5.28; N, 8.15. Found: C, 69.59; H, 5.52; N, 8.08.

Synthesis of *N*-Benzyl-3-bromoazetidine 13 To ABB (**3**, *ca.* 0.1 mol/l in THF, 100 ml, *ca.* 10 mmol)[1)] was added dropwise a HBr (48% in H_2O, 3.6 ml, 32 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. The reaction mixture was evaporated *in vacuo* to give a residue, which was washed with $CHCl_3$ and crystallized from MeOH–AcOEt to give compound **12** (1.4 g, 61%) as colorless needles.

Method (A): To a solution of **12** (506.7 mg, 2.36 mmol) and potassium carbonate (678 mg, 4.9 mmol) in DMF (2.3 ml) was added benzyl bromide (278 ml, 2.36 mmol) at room temperature. After being stirred at room temperature for 3.5 h, the reaction mixture was treated with water and then extracted with $CHCl_3$. The extract was dried over anhydrous $MgSO_4$. Evaporation *in vacuo* afforded a crude product, which was purified by column chromatography on silica gel with *n*-hexane–AcOEt (4 : 1, v/v) to yield **13** (205.4 mg, 39%) as a colorless oil.

Method (B): To ABB (**3**, *ca.* 0.1 mol/l in THF, 125 ml, *ca.* 12.5 mmol)[1)] was added dropwise benzyl bromide (1.5 ml, 12.5 mmol) at 0 °C, and the mixture was stirred under reflux for 6 h. The reaction mixture was evaporated *in vacuo* to give an oily residue, which was purified by column chromatography on silica gel with *n*-hexane–AcOEt (4 : 1, v/v) to yield **13** (1.72 g, 61%) as a colorless oil.

3-Bromoazetidine Hydrobromide (**12**): Colorless needles, mp 119 °C; ^{1}H-NMR (400 MHz, CD_3OD) δ: 4.26 (m, 2H), 4.74 (m, 2H), 4.8—5.0 (m, 1H); IR (KBr) 3003, 2881, 2630, 1441, 1338, 1269, 1229 cm^{-1}. EI-MS Calcd for C_3H_7NBr MW 134.9684, M+2 136.9663, Found m/z 134.9684 (M^+), 136.9684 (M^++2). *Anal.* Calcd for $C_3H_7NBr_2$: C, 16.61; H, 3.25; N, 6.46. Found: C, 16.60; H, 3.21; N, 6.47.

N-Benzyl-3-bromoazetidine (**13**): Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.44 (m, 2H), 3.69 (s, 2H), 3.88 (m, 2H), 4.48 (m, 1H), 7.21—

7.39 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 34.4, 63.5, 64.8, 127.2, 128.1, 128.3, 128.3, 128.6, 137.3; ESI-MS Calcd for $C_{10}H_{13}BrN_2$ MW 226.0231, Found *m/z* 226.0224 (M^++H).

Reaction of 13 with Aliphatic Amines To a solution of **13** (989 mg, 4.37 mmol) and potassium carbonate (1.8 g, 13.1 mmol) in MeCN (5 ml) was added pyrrolidine (1.1 ml, 13.1 mmol) at room temperature. After being stirred at 80 °C for 6 h, the reaction mixture was evaporated *in vacuo* to give an oily residue, which was purified by column chromatography on silica gel with $CHCl_3$–MeOH (10 : 1, v/v) to yield **14a** (689 mg, 73%) as a pale yellow oil.

1-Benzylazetidin-3-ylpyrrolidine (**14a**)[40,41]: Pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.76—1.80 (m, 4H), 2.39—2.41(m, 4H), 3.00—3.12 (m, 3H), 3.46 (m, 2H), 3.57 (s, 2H), 7.24 (m, 5H); ^{13}C-NMR (75 MHz, CD_3OD) δ: 23.4, 51.3, 54.6, 59.6, 63.8, 126.9, 128.3, 128.5, 138.2; ESI-MS Calcd for $C_{14}H_{21}N_2$ MW 217.1705, Found *m/z* 217.1707 (M^++H).

1-Benzylazetidin-3-ylpiperidine (**14b**)[40]: Pale yellow oil; ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.37—1.50 (m, 2H), 1.58 (m, 4H), 1.84—2.05 (m, 1H), 2.05—2.34 (m, 3H), 2.85—3.00 (m, 3H), 3.46—3.54 (m, 2H), 3.65 (s, 2H), 7.20—7.40 (m, 5H); ^{13}C-NMR (75 MHz, CD_3OD) δ: 23.3, 24.6, 49.7, 50.1, 50.7, 52.7, 57.2, 58.1; IR (neat) 3062, 3027, 2952, 2873, 2823, 2696, 1706, 1606, 1494, 1475, 1454 cm^{-1}; ESI-MS Calcd for $C_{15}H_{23}N_2$ MW 231.1861, Found *m/z* 231.1867 (M^++H).

1-Cyclopropyl-6,8-difluoro-4-oxo-7-(3-pyrrolidinoazetidin-1-yl)-1,4-dihydroquinoline-3-carboxylic Acid (16a) To a solution of **14a** (358.8 mg, 1.66 mmol) in MeOH (3 ml) was added 2 N HCl in Et_2O (0.8 ml) at 0 °C with stirring. The precipitate was collected by filtration under argon to afford **14a**·HCl (318.6 mg) as a yellow amorphous powder. This amorphous powder was dissolved in EtOH–H_2O (1 : 7) (4 ml) and hydrogenated over 20% $Pd(OH)_2$/C (31 mg, 10% w/w) at 50 °C for 50 h with stirring. The catalyst was filtered out, and evaporation *in vacuo* afforded **15a** (256.4 mg) as a yellow solid. To a solution of the yellow solid **15a** (256.4 mg) and **6** (356.8 mg, 1.26 mmol) in MeCN (18 ml) was added DABCO (424 mg, 3.78 mmol) at room temperature. The mixture was refluxed for 2.5 h and cooled in an ice bath. The precipitate was collected by filtration and then washed with MeCN, H_2O, EtOH, and Et_2O to afford **16a** (300.1 mg, 61% in two steps) as pale yellow needles. mp 240 °C (dec.); ^{1}H-NMR (400 MHz, DMSO) δ: 1.16 (m, 4H), 1.72 (m, 4H), 2.47 (m, 4H), 3.37 (m, 1H), 4.00—4.08 (m, 1H), 4.21—4.29 (m, 2H), 4.45—4.52 (m, 2H), 7.70 (m, 1H), 8.58 (s, 1H), 15.01 (s, 1H); IR (KBr) 3083, 2933, 2784, 1722, 1627, 1529, 1475, 1417, 1326, 1160 cm^{-1}; ESI-MS Calcd for $C_{20}H_{22}F_2N_3O_3$ MW 390.1629, Found *m/z* 390.1626 (M^++H).

1-Cyclopropyl-6,8-difluoro-4-oxo-7-(3-piperidinoazetidin-1-yl)-1,4-dihydroquinoline-3-carboxylic Acid (16b) A solution of **14b** (724 mg, 3.1 mmol) in EtOH–H_2O (2 : 7) (9 ml) was hydrogenated over 20% $Pd(OH)_2$/C (70 mg, 10% w/w) at 50 °C for 24 h with stirring. The catalyst was filtered out, and evaporation *in vacuo* afforded **15b** (377.1 mg) as a pale yellow oil. To a solution of the yellow oil **15b** (105.4 mg, *ca.* 0.67 mmol) and **6** (212.9 mg, 0.75 mmol) in MeCN (11 ml) was added DABCO (253 mg, 2.25 mmol) at room temperature. The mixture was refluxed for 2.5 h and cooled in an ice bath. The precipitate was collected by filtration and then washed with MeCN, H_2O, EtOH, and Et_2O to afford **16b** (218.4 mg, 63% in two steps) as colorless needles. mp 242 °C (dec.) (THF); ^{1}H-NMR (400 MHz, DMSO) δ: 1.16 (m, 4H), 1.34—1.47 (m, 2H), 1.47—1.60 (m, 4H), 2.15—2.38 (m, 4H), 3.20 (m, 1H), 4.00—4.11 (m, 1H), 4.16—4.26 (m, 2H), 4.40—4.52 (m, 2H), 7.71 (m, 1H), 8.59 (s, 1H), 15.01 (s, 1H); IR (KBr) 3083, 2933, 2807, 2360, 1727, 1629, 1550, 1494, 1461, 1324 cm^{-1}; ESI-MS Calcd for $C_{21}H_{24}F_2N_3O_3$ MW 404.1786, Found *m/z* 404.1787 (M^++H); *Anal.* Calcd for $C_{21}H_{23}F_2N_3O_3$: C, 62.52; H, 5.75; N, 10.42. Found: C, 62.39; H, 5.82; N, 10.35.

Typical Procedure for the Preparation of 21 To a solution of 2,3,4,5-tetrafluorobenzoic acid (5.8 g, 30 mol) in CH_2Cl_2 (45 ml) was added oxalyl chloride (2.8 ml). The mixture was treated with few drops of dry DMF and stirred at room temperature for 18 h. Concentration, a toluene chase, and reconcentration gave the crude acid chloride. According to literature,[34] ethyl hydrogen malonate (7.9 g, 60 mol) was converted to the dilithium salt in THF (120 ml) with *n*-BuLi (1.56 mol/l, 76.9 ml, 120 mmol) at −78 °C. After being stirred at −5 °C for 1 h, the acid chloride (prepared above) in THF (16 ml) was added. The reaction mixture was stirred at −78 °C for 1 h and poured into 1 N HCl. The water layer was extracted with CH_2Cl_2 and dried over anhydrous $MgSO_4$. Evaporation *in vacuo* afforded a crude product, which was purified by column chromatography on silica gel with *n*-hexane–AcOEt (9 : 1, v/v) to obtain **18** (5.35 g, 68%) as a white solid.

Triethyl orthoformate (6.8 ml, 40.9 mmol) and acetic anhydride (7.2 ml, 76.3 mmol) was added to **18** (7.2 g, 27.3 mmol). After being stirred under reflux for 5 h, the reaction mixture was concentrated *in vacuo* to give a yellow oil **19**. To a solution of **19** in EtOH (9.9 ml) was added 2-aminothiazole (346.5 mg, 3.46 mmol) at 0 °C. After being stirred at room temperature for 25 h, the reaction mixture was concentrated *in vacuo* to give an enamine **20**. Potassium carbonate (509.6 mg, 3.69 mmol) was added to the solution of **20** in dioxane (10 ml). After being stirred at room temperature for 18 h, the reaction mixture was poured into cold water and acidified with 1 N HCl. The organic layer was extracted with $CHCl_3$ and dried over anhydrous $MgSO_4$. Evaporation *in vacuo* afforded a crude product, which was purified by column chromatography on silica gel with AcOEt–$CHCl_3$ (1 : 3, v/v) to yield **21a** (326.6 mg, 29% in three steps) as colorless plates.

Ethyl 6,7,8-Trifluoro-4-oxo-1-(thiazol-2-yl)-1,4-dihydroquinoline-3-carboxylate (**21a**)[27,42]: Colorless plates (THF); mp 177 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.40 (t, *J*=7.3 Hz, 3H), 4.40 (q, *J*=7.3 Hz, 2H), 7.59 (d, *J*=3.5 Hz, 1H), 7.81 (d, *J*=3.5 Hz, 1H), 8.15 (m, 1H), 8.49 (s, 1H); IR (KBr) 3434, 3033, 1722, 1729, 1619, 1575, 1481, 1348 cm^{-1}; EI-MS Calcd for $C_{15}H_9F_3N_2O_3S$ MW 354.0286, Found *m/z* 354.0317 (M^+); *Anal.* Calcd for $C_{15}H_9F_3N_2O_3S$: C, 50.85; H, 2.56; N, 7.91. Found: C, 50.73; H, 2.70; N, 7.87.

Ethyl 6,7,8-Trifluoro-4-oxo-1-(pyrimidin-2-yl)-1,4-dihydroquinoline-3-carboxylate (**21b**): Colorless needles (THF); mp 209 °C (dec.); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.40 (t, *J*=7.1 Hz, 3H), 4.41 (q, *J*=7.1 Hz, 2H), 7.47 (m, 1H), 8.12 (m, 1H), 8.88 (d, 2H), 9.02 (s, 1H); IR (KBr) 3073, 1695, 1629, 1575, 1515, 1486, 1402 cm^{-1}; EI-MS Calcd for $C_{16}H_{10}F_3N_3O_3$ MW 349.0674, Found *m/z* 349.0704 (M^+); *Anal.* Calcd for $C_{16}H_{10}F_3N_3O_3$: C, 55.02; H, 2.89; N, 12.03. Found: C, 54.89; H, 3.42; N, 11.87.

Ethyl 6,7,8-Trifluoro-1-(1-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (**21c**): Pale peach powder (THF); mp 249 °C (dec.); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.39 (t, *J*=7.1 Hz, 3H), 3.70 (s, 3H), 4.39 (q, *J*=7.1 Hz, 2H), 6.38 (dd, 1H), 7.91 (d, 1H), 8.11 (m, 1H), 8.83 (s, 1H); IR (KBr) 3097, 2992, 1718, 1685, 1619, 1536, 1486, 1405, 1348 cm^{-1}; FAB-MS Calcd for $C_{17}H_{13}F_3N_3O_4$ MW 380.0858, Found *m/z* 380.0876 (M^+ + H); *Anal.* Calcd for $C_{17}H_{12}F_3N_3O_4 \cdot 1/4H_2O$: C, 53.20; H, 3.28; N, 10.95. Found: C, 53.38; H, 3.55; N, 10.79.

Ethyl 1-Benzyl-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**21d**): Colorless needles (THF); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.42 (t, *J*=7.3 Hz, 3H), 4.42 (q, *J*=7.3 Hz, 2H), 5.53 (s, 2H), 7.14 (d, 2H), 7.34—7.40 (m, 3H), 8.18 (m, 1H), 8.54 (s, 1H); IR (KBr) 3072, 2992, 1729, 1677, 1656, 1614, 1484 cm^{-1}; EI-MS Calcd for $C_{19}H_{14}F_3NO_3S$ MW 361.0926, Found *m/z* 361.0904 (M^+); *Anal.* Calcd for $C_{19}H_{14}F_3NO_3S$: C, 63.16; H, 3.89; N, 3.88. Found: C, 63.08; H, 3.89; N, 3.81.

Typical Procedure for the Preparation of 22 To a solution of **21a** (94.0 mg, 0.27 mmol) in acetic acid (0.5 ml) was added 6 N HCl (0.27 ml). After being stirred at 100 °C for 2 h, the reaction mixture was poured into cold water. The precipitate was collected by filtration and then washed with H_2O, EtOH, and Et_2O to afford **22a** (67.7 mg, 77%) as a pale amorphous yellow powder.

6,7,8-Trifluoro-4-oxo-1-(thiazol-2-yl)-1,4-dihydroquinoline-3-carboxylic Acid (**22a**): Pale yellow amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, *J*=3.4 Hz, 1H), 7.84 (d, *J*=3.4 Hz, 1H), 8.20 (m, 1H), 8.81 (s, 1H), 13.76 (br s, 1H); IR (KBr) 3060, 2717, 2358, 1743, 1614, 1571, 1492, 1444, 1421, 1326, 1253, 1174, 1108, 1037 cm^{-1}; ESI-MS Calcd for $C_{13}H_5F_3N_2O_3SNa$ MW 348.9871, Found *m/z* 348.9863 (M^++Na).

6,7,8-Trifluoro-4-oxo-1-(pyrimidin-2-yl)-1,4-dihydroquinoline-3-carboxylic Acid (**22b**): Pale yellow amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.50 (t, *J*=4.9 Hz, 1H), 8.18 (m, 1H), 8.92 (d, *J*=4.9 Hz, 2H), 9.22 (s, 1H), 13.87 (br s, 1H); IR (KBr) 3064, 2740, 1722, 1617, 1581, 1560, 1496, 1461, 1411, 1328, 1255, 1184, 1112, 1043 cm^{-1}; ESI-MS Calcd for $C_{14}H_7F_3N_3O_3$ MW 322.0440, Found *m/z* 322.0418 (M^++H).

6,7,8-Trifluoro-1-(1-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (**22c**): Pale peach amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.74 (s, 3H), 6.35 (d, *J*=6.8 Hz, 1H), 8.05 (d, *J*=6.8 Hz, 1H), 8.16 (m, 1H), 8.93 (s, 1H), 13.68 (br s, 1H); IR (KBr) 3070, 2830, 2358, 1735, 1587, 1506, 1388, 1321, 1290, 1249, 1186, 1103, 890, 804 cm^{-1}; ESI-MS Calcd for $C_{15}H_9F_3N_3O_4$ MW 352.0545, Found *m/z* 352.0528 (M^++H).

Typical Procedure for the Preparation of 23 To a solution of **22a** (120.2 mg, 0.42 mmol) and 3-aminoazetidine (**11b**) (62.9 mg, 0.42 mmol) in MeCN (6 ml) was added 1,4-diazabicyclo[2.2.0]octane (142.8 mg, 1.27 mmol). After being stirred under reflux for 0.5 h, the resulting precipitate was collected by filtration and then washed with MeCN, H_2O, EtOH, and Et_2O to afford **23a** (130.9 mg, 76%) as a yellow amorphous powder.

6,8-Difluoro-7-[3-(methoxyanilino)azetidin-1-yl]-1-(thiazol-2-yl)quinolin-4(1*H*)-one (**23a**): Yellow amorphous powder; ^{1}H-NMR (400 MHz,

$CDCl_3$) δ: 3.75 (s, 3H), 3.79 (br s, 1H), 4.01—4.08 (m, 2H), 4.26—4.32 (m, 1H), 4.60—4.67 (m, 2H), 6.21 (d, J=8.1 Hz, 1H), 6.50 (d, J=8.8 Hz, 2H), 6.79 (d, J=8.8 Hz, 2H), 7.45 (d, J=3.7 Hz, 1H), 7.47 (d, J=8.1 Hz, 1H), 7.70 (d, J=3.7 Hz, 1H), 7.77 (m, 1H); IR (KBr) 3110, 3035, 2360, 1720, 1621, 1575, 1481, 1405, 1348, 1299 cm^{-1}; ESI-MS Calcd for $C_{22}H_{19}F_2N_4O_2S$ MW 441.1197, Found m/z 441.1183 (M^++H).

6,8-Difluoro-7-[3-(methoxyanilino)azetidin-1-yl]-1-(pyrimidin-2-yl)-quinolin-4(1*H*)-one (**23b**): Yellow amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.75 (s, 3H), 3.83 (br s, 1H), 4.02—4.10 (m, 2H), 4.25—4.35 (m, 1H), 4.60—4.68 (m, 2H), 6.25 (d, J=8.1 Hz, 1H), 6.52 (d, J=8.8 Hz, 2H), 6.79 (d, J=8.8 Hz, 2H), 7.31 (t, J=4.9 Hz, 1H), 7.76 (m, 1H), 8.04 (d, J=8.1 Hz, 1H), 8.78 (d, J=4.9 Hz, 2H); IR (KBr) 3318, 2940, 2871, 1617, 1571, 1523, 1479, 1409, 1344, 825 cm^{-1}; ESI-MS Calcd for $C_{23}H_{20}F_2N_5O_2$ MW 436.1585, Found m/z 436.1597 (M^++H).

6,8-Difluoro-7-[3-(methoxyanilino)azetidin-1-yl]-1-(1-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)quinolin-4(1*H*)-one (**23c**): Yellow amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.63 (s, 3H), 3.76 (s, 3H), 3.90 (br s, 1H), 4.07—4.17 (m, 2H), 4.29—4.40 (m, 1H), 4.66—4.75 (m, 2H), 6.2—6.3 (m, 2H), 6.53 (d, J=8.8 Hz, 2H), 6.81 (d, J=8.8 Hz, 2H), 7.70—7.78 (m, 2H) , 8.05 (m, 1H); IR (KBr) 3342, 2950, 1670, 1612, 1515, 1467, 1419, 1340, 1257 cm^{-1}; ESI-MS Calcd for $C_{24}H_{22}F_2N_5O_3$ MW 466.1691, Found m/z 466.1696 (M^++H).

Typical Procedure for the Preparation of 24 To a solution of **21a** (200.5 mg, 0.57 mmol) in MeCN (5 ml) was added **10b** (201.7 mg, 1.13 mmol). After being stirred at room temperature for 9 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with AcOEt–$CHCl_3$ (1 : 3, v/v) to yield **24a** (179.6 mg, 63%) as a pale yellow powder.

Ethyl 6,8-Difluoro-7-[3-(methoxyanilino)azetidin-1-yl]-4-oxo-1-(thiazol-2-yl)-1,4-dihydroquinoline-3-carboxylate (**24a**): Pale yellow powder ($CHCl_3$); mp 186—187 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.37 (t, J=7.1 Hz, 3H), 3.75 (s, 3H), 4.01—4.11 (m, 2H), 4.25—4.33 (m, 1H), 4.58—4.69 (m, 2H), 6.50 (d, J=8.8 Hz, 2H), 6.78 (d, J=8.8 Hz, 2H), 7.50 (d, J=3.7 Hz, 2H) , 7.74 (d, J=3.7 Hz, 2H) , 7.83 (m, 1H) , 8.35 (s, 1H); IR (KBr) 3295, 3079, 2360, 1619, 1579, 1508, 1467, 1428, 1342, 1251, 1147, 821 cm^{-1}; ESI-MS Calcd for $C_{25}H_{23}F_2N_4O_4S$ MW 513.1408 Found m/z 513.1396 (M^++H); *Anal.* Calcd for $C_{25}H_{22}F_2N_4O_4S$: C, 58.59; H, 4.33; N, 10.93. Found: C, 58.26; H, 4.16; N, 10.67.

Ethyl 6,8-Difluoro-7-[3-(methoxyanilino)azetidin-1-yl]-4-oxo-1-(pyrimidin-2-yl)-1,4-dihydroquinoline-3-carboxylate (**24b**): Pale yellow crystals ($CHCl_3$); mp 208—209 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.39 (t, J=7.1 Hz, 3H), 3.75 (s, 3H), 4.02—4.11 (m, 2H), 4.26—4.34 (m, 1H), 4.38 (q, J=7.1 Hz, 3H), 4.59—4.69 (m, 2H), 6.51 (d, J=8.8 Hz, 2H), 6.79 (d, J=8.8 Hz, 2H), 7.39 (m, 1H), 7.84 (m, 1H), 8.83 (m, 3H); IR (KBr) 3866, 3338, 3052, 2696, 2832, 1731, 1697, 1616, 1515, 1467, 1407 cm^{-1}; ESI-MS Calcd for $C_{26}H_{24}F_2N_5O_4$ MW 508.1796 Found m/z 508.1747 (M^++H); *Anal.* Calcd for $C_{26}H_{23}F_2N_5O_4$: C, 61.53; H, 4.57; N, 13.80. Found: C, 61.48; H, 4.82; N, 13.46.

Ethyl 6,8-Difluoro-7-[3-(methoxyanilino)azetidin-1-yl]-4-oxo-1-(1-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)-1,4-dihydroquinoline-3-carboxylate (**24c**): This compound was not isolated.

Typical Procedure for the Preparation of 25 To a solution of **24a** (22.3 mg, 0.0435 mmol) in EtOH was added 1 N NaOH (0.3 ml). After being stirred at room temperature for 5 h, the reaction mixture was poured into cold water. The precipitate was collected by filtration and then washed with H_2O, EtOH, and Et_2O to afford **25a** as sodium salt (31.3 mg). This salt was dissolved in water and acetic acid (10 μl, 0.16 mmol), and then stirred at room temperature for 4 h. The reaction mixture was poured into cold water and the precipitate was collected by filtration and then washed with H_2O, EtOH, and Et_2O to afford **25a** (24.8 mg, 97 %).

6,8-Difluoro-7-[3-(methoxyanilino)azetidin-1-yl]-4-oxo-1-(thiazol-2-yl)-1,4-dihydroquinoline-3-carboxylic Acid (**25a**): Pale yellow amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.75 (s, 3H), 4.01—4.21 (m, 2H), 4.25—4.37 (m, 1H), 4.64—4.78 (m, 2H), 6.48 (dd, J=2.2 Hz, 6.6 Hz, 2H), 6.79 (dd, J=2.2 Hz, 6.6 Hz, 2H), 7.51 (d, J=3.7 Hz, 1H), 7.53 (m, 1H), 7.76 (d, J=3.7 Hz, 1H), 10.04 (s, 1H); IR (KBr) 3363, 2948, 2360, 1671, 1619, 1513, 1467, 1428, 1294, 1257, 1141, 1118, 1033 cm^{-1}; ESI-MS Calcd for $C_{23}H_{19}F_2N_4O_4S$ MW 485.1095 Found m/z 485.1075 (M^++H).

6,8-Difluoro-7-[3-(methoxyanilino)azetidin-1-yl]-4-oxo-1-(pyrimidin-2-yl)-1,4-dihydroquinoline-3-carboxylic Acid (**25b**): Pale yellow amorphous powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.74 (s, 3H), 4.02—4.16 (m, 2H), 4.21—4.33 (m, 1H), 4.59—4.72 (m, 2H), 6.47 (dd, J=2.2, 8.8 Hz, 2H), 6.78 (dd, J=2.2, 8.8 Hz, 2H), 7.43 (m, 1H), 7.53 (m, 1H), 8.89 (m, 2H), 10.05 (s, 1H); IR (KBr) 3338, 3052, 2969, 2832, 2360, 1733, 1697, 1619, 1573, 1515, 1469, 1407 cm^{-1}; ESI-MS Calcd for $C_{24}H_{20}F_2N_5O_4$ MW 480.1483 Found m/z 480.1467 (M^++H).

6,8-Difluoro-7-[3-(methoxyanilino)azetidin-1-yl]-4-oxo-1-(1-methyl-2-oxo-1,2-dihydropyrimidin-2-yl)-1,4-dihydroquinoline-3-carboxylic Acid (**25c**): Pale yellow powder (EtOH–$CHCl_3$); mp 228 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.65 (s, 3H), 3.75 (s, 3H), 4.11—4.21 (m, 2H), 4.28—4.36 (m, 1H), 4.68—4.76 (m, 2H), 6.50 (dd, J=2.2, 6.6 Hz, 2H), 6.62 (m, 1H), 6.80 (dd, J=2.2, 6.6 Hz, 2H), 7.49 (m, 1H), 7.78 (m, 1H), 10.01 (s, 1H); IR (KBr) 3334, 2942, 2360, 1664, 1617, 1531, 1459, 1344, 1294, 1236, 1126, 825 cm^{-1}; ESI-MS Calcd for $C_{25}H_{22}F_2N_5O_5$ MW 510.1589 Found m/z 510.1582 (M^++H); *Anal.* Calcd for $C_{25}H_{21}F_2N_5O_5$: C, 58.94; H, 4.15; N, 13.75. Found: C, 58.65; H, 4.45; N, 13.47.

Ethyl 6,7,8-Trifluoro-4-hydroxyquinoline-3-carboxylate (26) A solution of **21d** (203.4 mg, 0.56 mmol) in EtOH (5.6 ml) was hydrogenated over 10% Pd/C (67.8 mg, 30% w/w) at room temperature for 20 h with stirring. The catalyst was filtered out, and the filtrate was concentrated to afford **26** (149.2 mg, 98%) as a white powder. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.49 (t, J=7.3 Hz, 3H), 4.54 (q, J=7.3 Hz, 2H), 7.89 (m, 1H), 9.15 (s, 1H), 12.46 (s, 1H); IR (KBr) 3077, 2996, 2360, 1714, 1581, 1498, 1378 cm^{-1}; FAB-MS Calcd for $C_{12}H_9F_3NO_3$ MW 272.0535, Found m/z 272.0518 (M^++H); *Anal.* Calcd for $C_{12}H_8F_3NO_3$: C, 53.15; H, 2.97; N, 5.16. Found: C, 53.11; H, 3.09; N, 5.18.

Typical Procedure for the Preparation of 27 To a solution of **26** (500 mg, 1.84 mmol) in CH_2Cl_2 (16 ml) was added *p*-toluenesulfonyl chloride (527 mg, 2.77 mmol) and triethylamine (0.5 ml, 3.69 mmol) at 0 °C. After being stirred at room temperature for 1.5 h, the reaction mixture was poured into water. The organic layer was extracted with $CHCl_3$ and dried over anhydrous $MgSO_4$. Evaporation *in vacuo* afforded a crude product, which was purified by column chromatography on silica gel with *n*-hexane–AcOEt (2 : 1, v/v) to yield **27a** (739.5 mg, quant.) as a colorless plates.

Ethyl 4-Tosyloxy-6,7,8-trifluoroquinoline-3-carboxylate (**27a**): Colorless plates (THF); mp 149—151 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (t, J=7.1 Hz, 3H), 2.49 (s, 3H), 4.43 (q, J=7.1 Hz, 2H), 7.12—7.17 (m, 1H), 7.38 (d, J=8.4 Hz, 2H), 7.77 (d, J=8.4 Hz, 2H), 9.34 (s, 1H); IR (KBr) 3446, 1731, 1648, 1596, 1508 cm^{-1}; *Anal.* Calcd for $C_{19}H_{14}F_3NO_5S$: C, 53.65; H, 3.32; N, 3.29. Found: C, 53.62; H, 3.37; N, 3.18.

Ethyl 4-Mesyloxy-6,7,8-trifluoroquinoline-3-carboxylate (**27b**): Colorless needles (THF); mp 118 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.47 (t, J=7.1 Hz, 3H), 3.62 (s, 3H), 4.50 (q, J=7.1 Hz, 2H), 8.02 (m, 1H), 9.40 (s, 1H); IR (KBr) 3025, 1727, 1606, 1504, 1442, 1274 cm^{-1}; EI-MS Calcd for $C_{13}H_{10}F_3NO_5S$ MW 349.0232, Found m/z 349.0223 (M^+).

Ethyl 4-Dimethylsulfamoyloxy-6,7,8-trifluoroquinoline-3-carboxylate (**27c**): Colorless plates (THF); mp 115—116 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.46 (t, J=7.1 Hz, 3H), 3.18 (s, 6H), 4.49 (q, J=7.1 Hz, 2H), 7.87 (m, 1H), 9.26 (s, 1H); IR (KBr) 2985, 1735, 1648, 1608, 1511, 1373 cm^{-1}; EI-MS Calcd for $C_{14}H_{13}F_3N_2O_5S$ MW 378.0497, Found m/z 378.0490 (M^+); *Anal.* Calcd for $C_{14}H_{13}F_3N_2O_5S$: C, 44.45; H, 3.46; N, 7.40. Found: C, 44.50; H, 3.41; N, 7.36.

Ethyl 4-Ethoxycarbonyloxy-6,7,8-trifluoroquinoline-3-carboxylate (**27d**): Colorless needles (THF); mp 86—86.5 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.38—1.50 (m, 6H), 4.37—4.50 (m, 4H), 7.74 (m, 1H), 9.43 (s, 1H); IR (KBr) 3081, 2981, 1770, 1722, 1652, 1508, 1398 cm^{-1}; EI-MS Calcd for $C_{15}H_{12}F_3NO_5$ MW 343.0668, Found m/z 343.0699 (M^+).

***In Vitro* Antibacterial Activity** The minimum inhibitory concentrations (MICs) were determined using the agar dilution method as described by the Japan Society of Chemotherapy.[36] The MIC was defined as the lowest drug concentration of the test compound that prevented visible growth on the plate.

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