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Synthesis and antibacterial activities of new quinolone derivatives utilizing 1-azabicyclo[1.1.0]butane

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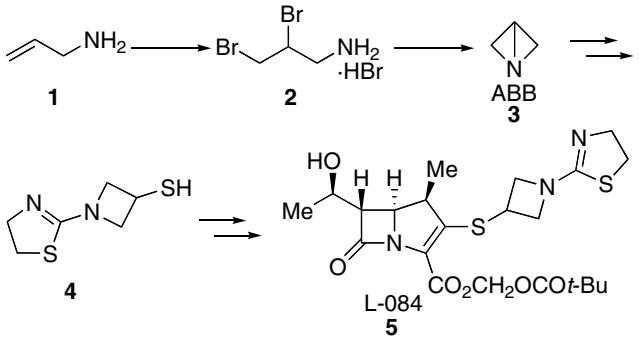
Abstract—The ring-opening reactions of 1-azabicyclo[1.1.0]butane **3** with thiols **6a–f** gave 3-sulfenylazetidine derivatives **7a–f** in 50-92% yields. Treatment of **3** with aromatic amines **11a–e** and dibenzylamine **11f** in the presence of $Mg(ClO_4)_2$ afforded the corresponding 3-aminoazetidine derivatives **12a–f** in 24–53% yields. These azetidine derivatives were introduced into the C7 position of a quinolone nucleus **8** to afford the corresponding fluoroquinolones **9a–f** and **13a–f** in 21–83% yields. Some of them exhibited superior antibacterial activity against quinolone-susceptible MRSA in comparison with clinically used fluoroquinolones, such as levofloxacin, ciprofloxacin, and gatifloxacin.

In recent years, we established an efficient method for synthesizing a strained molecule, 1-azabicyclo[1.1.0]butane (ABB) **3**, starting from allylamine **1** via 2,3-dibromopropylamine hydrobromide **2**, and reported its application to the synthesis of several 3-monosubstituted and 1,3-disubstituted azetidine derivatives.[1] We also reported a practical synthesis of 1-(1,3-thiazolin-2-yl)azetidine-3-thiol **4** as the fascinating pendant moiety of a new oral 1β-methylcarbapenem antibiotic, L-084 **5**, as shown in Scheme 1.[2] This expeditious construction method for 3-monosubstituted azetidine derivatives employing ABB **3** seemed useful also for developing new quinolone antibiotics. This prompted us to develop new quinolones utilizing the azetidine derivatives, in which the C7 substituents of fluoroquinolone carboxylic acids play important antibacterial roles.[3] Herein, we describe a convenient method of synthesizing several 3-sulfenyl- and 3-aminoazetidine derivatives utilizing **3**, and we discuss the syntheses and antibacterial activities of new quinolone antibiotics incorporating these azetidine derivatives to the C7 position. Although several examples of 7-azetidinylquinolones have been reported,[4]



Scheme 1. Synthetic route for ABB **3** and pendant molecule **4** of L-084 **5**.

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 may enhance their antibacterial activities against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa.*

A THF solution of ABB **3**, obtained by treatment of 2,3-dibromopropylamine hydrobromide with *n*-BuLi at −78 °C in THF followed by codistillation with THF,[2a]

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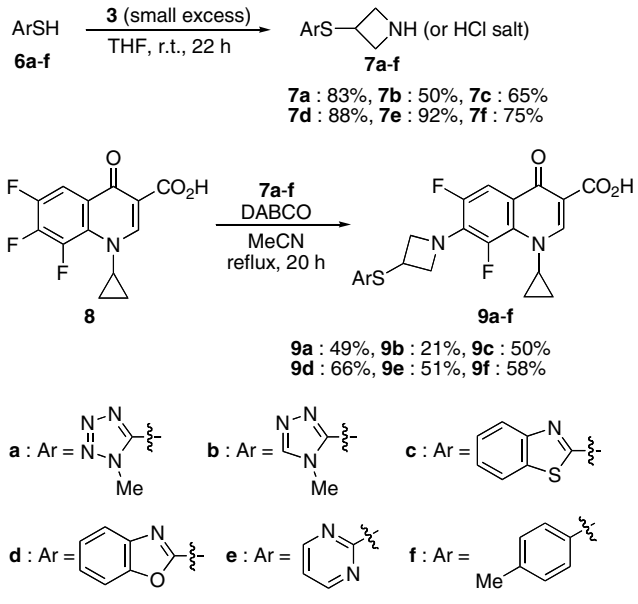
was employed for the synthesis of 3-sulfenyl- and 3-amino-substituted azetidine derivatives. First, we carried out the synthesis of the fluoroquinolones bearing 3-sulfenylazetidine derivatives as follows. The ring-opening reaction of small excess ABB **3** with several heterocyclic thiols **6a**–**e** and *p*-toluenethiol **6f** in THF at room temperature for 22 h proceeded smoothly to furnish the desired corresponding 3-sulfenylazetidine derivatives **7a**–**f** in 50–92% yields, as shown in Scheme 2. Compounds **7c**–**f** were purified as hydrochlorides in the treatment of the crude products with 2 N hydrogen chloride in diethyl ether because of their instability during chromatographic purification on a silica gel column. The structures of 3-sulfenylazetidine derivatives **7a**–**f** were assigned by their characteristic ^{1}H NMR spectra and by high-resolution MS analysis. We chose readily accessible compound **8** as a quinolone nucleus, obtained from the Grohe–Heitzer reaction procedure[5] using 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.[3f] Thus, treatment of quinolone nucleus **8** with 1.2 mol equiv of 3-sulfenylazetidine derivatives **7a**–**f** in the presence of 3.0 mol equiv of 1,4-diazabicyclo[2.2.2]octane (DABCO) in MeCN under reflux for 20 h afforded the corresponding 7-(3-sulfenylazetidin-1-yl)fluoroquinolone carboxylic acids **9a**–**f** in 21–66% yields (Scheme 2).

The structure of product **9b** was precisely determined by X-ray crystallographic analysis (Fig. 1).[6] Other products were assigned as structures **9a** and **9c**–**f**, based on the spectroscopic and elemental analyses in comparison with those of **9b**.

To determine the azetidine ring's effect on antibacterial activity in comparison with that of **9a**, we prepared sulfenyl-C7-substituted fluoroquinolone **10**. Similar treatment of the quinolone nucleus **8** with 1.0 mol equiv of 5-mercapto-1-methyltetrazole in the presence of 3.0 mol equiv of DABCO in MeCN under reflux gave **10** in a 53% yield, as shown in Scheme 3.



Scheme 2. Synthesis of 3-sulfenylazetidine and new quinolone derivatives.

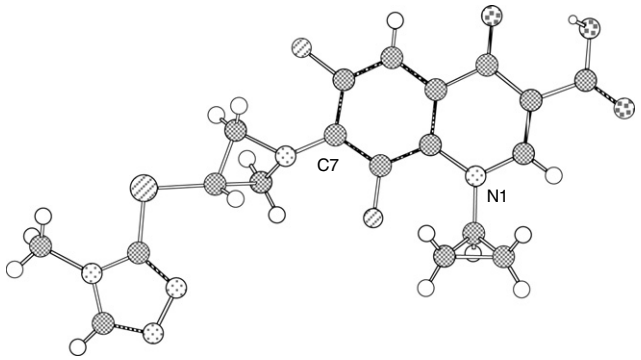
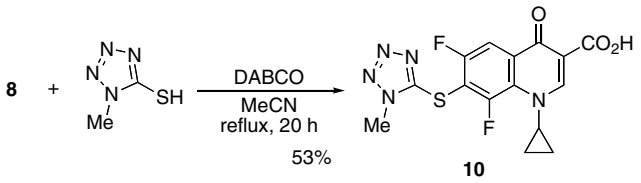
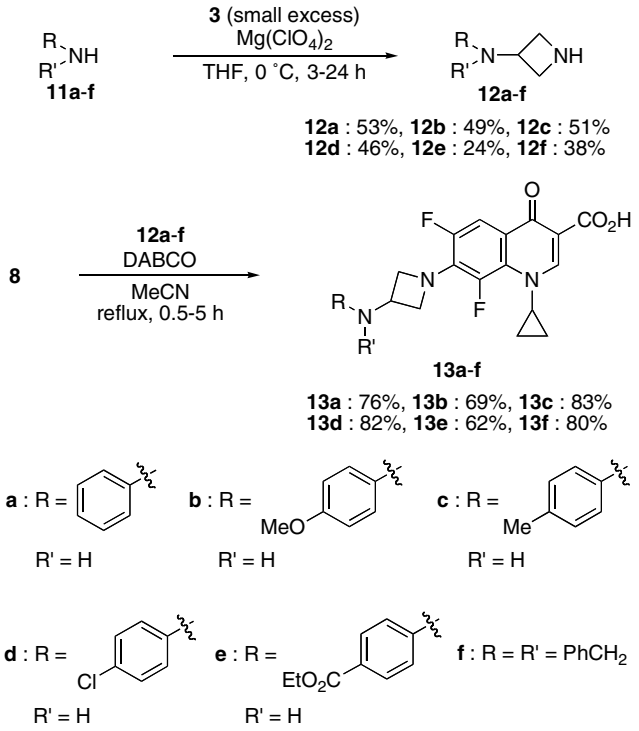


Figure 1. Computer-generated drawing from X-ray coordinates of compound **9b**.



Scheme 3. Synthesis of 7-sulfenylquinolone **10**.

Subsequently, we attempted the similar ring-opening reaction of **3** with aniline **11a** without an additive to the case of thiols **6a**–**f**, but the desirable reaction did not proceed even under the reflux conditions. We then examined in detail the ring-opening reaction of **3** with aniline **11a** in the presence of various Lewis acids such as $Mg(ClO_4)_2$, $BF_3{\cdot}OEt_2$, $Zn(OTf)_2$, $Mg(OTf)_2$, $Cu(OTf)_2$, TMSOTf, $Yb(OTf)_3$, $Hf(OTf)_4$, $Zn(ClO_4)_2{\cdot}6H_2O$, $LiClO_4$, etc., in THF at 0 °C for 1–24 h to give 3-anilinoazetidine **12a** in 1–61% yields together with 13–97% recoveries of aniline. After an exhaustive investigation, $Mg(ClO_4)_2$ was shown to be relatively suitable for the ring-opening reactions of **3** with aniline. Thus, we adopted $Mg(ClO_4)_2$ as the additive for the ring-opening reaction of **3** with several amines because of its good solubility in THF, fewer byproducts, and low cost. A small amount of excess **3** was allowed to react with aromatic amines **11a**–**e** and dibenzylamine **11f** in the presence of 2.0 mol equiv of $Mg(ClO_4)_2$ in THF at 0 °C for 3–24 h to give the corresponding 3-aromatic aminoazetidines **12a**–**e** in 24–53% yields and 3-dibenzylaminoazetidine **12f** in 38% yield,[7] respectively, as shown in Scheme 4. The structures of 3-aromatic aminoazetidine and 3-dibenzylaminoazetidine derivatives **12a**–**f** were assigned by their characteristic ^{1}H NMR spectra and other spectroscopic analyses. Then, 1.2 mol equiv of compounds **12a**–**f** were treated with compound **8** in the presence of 3.0 mol equiv of DABCO in MeCN under reflux for 0.5–5 h to furnish the corresponding 7-(3-aminoazetidinyl)fluoroquinolone carboxylic acids **13a**–**f** in 62–83% yields, as shown in Scheme 4. The structures of **13a**–**f**



Scheme 4. Synthesis of 3-aminoazetidine and new quinolone derivatives.

were assigned by the spectroscopic and elemental analyses in comparison with those of **9b**.

The minimum inhibitory concentrations (MICs) of the synthesized compounds **9a**–**f**, **10**, and **13a**,**f** against several representative Gram-positive and Gram-negative bacteria utilizing a conventional agar dilution procedure[8] are summarized in Table 1, along with the data for levofloxacin (LVFX), ciprofloxacin (CPFX), and gatifloxacin (GFLX) for comparison.[9] The compounds **9a**–**f** bearing 3-sulfenylazetidines as the C7 substituent of **8** exhibited moderate antibacterial activities against each species of bacteria. The antibacterial activities (except for those against *Escherichia coli*) of **9e** are somewhat potent among the 7-(3-sulfenylazetidin-1-yl)-fluoroquinolone series compounds **9a**–**f**. The antibacterial activities of **9e** against quinolone-susceptible and quinolone-resistant MRSA species were shown to be superior to those of LVFX, CPFX, and GFLX, but its activity against Gram-negative bacteria (e.g., *E. coli*) was low. Compound **9a**, bearing the 3-(1-methyltetrazol-5-yl)thioazetidine moiety at the C7 position of the fluoroquinolone carboxylic acid, exhibited more potent activities against Gram-positive bacteria than compound **10** bearing the (1-methyltetrazol-5-yl)thio group alone without the azetidine moiety. Compounds **9a**,**b** and **10** were affected by AcrAB, an efflux system of *E. 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 **13a** displayed fairly potent antibacterial activities against Gram-positive bacteria, compound **13f**, having a large substituent at the C3 position of the azetidine ring, exhibited remarkably weak activities.

Because **13a** exhibited significantly potent activities against Gram-positive bacteria (Table 1), we focused on the para-substituent mode of the phenyl group of 3-anilinoazetidine derivative at the C7 position of the fluoroquinolone carboxylic acid. Then, compounds **13a**–**e** together with LVFX were subjected to the antibacterial screening test, as shown in Table 2. The results showed that the antibacterial spectra of **13a**–**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 **13b** exhibited 4-fold better activity against *Staphylococcus pneumoniae* than **13a**. Compounds **13a**–**e** was more potent than LVFX against quinolone-susceptible and -intermediate MRSA. These compounds did not show considerable antibacterial activities against quinolone-resistant MRSA or *P. aeruginosa*.

Table 1. Antibacterial activity of 7-azetidinylquinolones and clinically used antibiotics (MIC, μg/mL)

Compound	*S. aureus*[a]	*S. aureus*[b]	*S. aureus*[c]	*E. faecalis*	*S. pneumoniae*	*M. catarrhalis*	*H. influenzae*	*E. coli*[d]	*E. coli*[e]	*P. aeruginosa*
9a	0.125	2	>32	1	2	0.063	<0.008	0.125	1	8
9b	0.25	4	>16	1	2	0.123	⩽0.008	0.25	1	8
9c	1	4	32	4	4	0.5	0.5	8	8	>32
9d	1	2	32	2	2	0.5	0.5	8	8	>32
9e	0.063	1	32	0.25	1	0.063	⩽0.008	1	1	8
9f	2	32	>32	16	32	2	0.25	32	32	>32
13a	0.031	0.5	32	0.25	0.5	0.031	<0.008	0.5	0.5	8
13f	>64	>64	>64	>64	>64	>64	8	64	>64	>64
10	16	>16	>16	>16	>16	4	0.125	1	16	>16
LVFX[f]	0.5	8	>128	2	2	0.063	⩽0.008	0.031	0.031	0.5
CPFX[f]	1	16	>64	2	4	0.063	⩽0.008	⩽0.008	⩽0.008	0.25
GFLX[f]	0.25	2	>128	1	0.5	0.063	⩽0.008	0.063	0.063	1

[a] Quinolone-susceptible MRSA.
[b] Quinolone-intermediate MRSA.
[c] Quinolone-resistant MRSA.
[d] Without AcrAB.
[e] With AcrAB.
[f] LVFX, levofloxacin; CPFX, ciprofloxacin; GFLX, gatifloxacin.

Table 2. Antibacterial activity of 7-azetidinylquinolones and a clinically used antibiotic (MIC, μg/mL)

Compound	*S. aureus*[a]	*S. aureus*[b]	*S. aureus*[c]	*E. faecalis*	*S. pneumoniae*	*M. catarrhalis*	*H. influenzae*	*E. coli*[d]	*E. coli*[e]	*P. aeruginosa*
13a	0.016	0.5	>64	0.5	0.25	0.016	⩽0.008	0.031	0.25	4
13b	0.031	0.25	16	0.25	0.063	0.031	⩽0.008	0.031	0.25	4
13c	0.031	0.5	16	0.5	0.5	0.031	⩽0.008	0.063	0.5	16
13d	0.063	1	16	1	0.5	0.063	⩽0.008	0.125	1	>16
13e	0.031	1	>16	2	0.125	0.125	⩽0.008	0.25	2	>16
LVFX[f]	0.5	4	>128	2	1	0.063	0.016	0.016	0.016	0.5

[a] Quinolone-susceptible MRSA.
[b] Quinolone-intermediate MRSA.
[c] Quinolone-resistant MRSA.
[d] Without AcrAB.
[e] With AcrAB.
[f] LVFX, levofloxacin.

In conclusion, we have demonstrated a convenient synthesis of 3-sulfenylazetidine derivatives **7a**–**f** and 3-aminoazetidine derivatives **12a**–**f** utilizing ABB **3**. Several azetidine derivatives were successfully introduced into fluoroquinolone carboxylic acid **8** to give the corresponding fluoroquinolone antibiotics **9a**–**f** and **13a**–**f**. Most of the synthesized fluoroquinolones exhibited more potent antibacterial activities against Gram-positive bacteria than against Gram-negative bacteria. Especially, compounds **13a**–**e** were fairly potent against quinolone-susceptible MRSA in comparison with the activities of clinically used fluoroquinolones, such as LVFX.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.11.048.

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6. X-ray data for **9b**: $C_{19}H_{17}F_2N_5O_3S$, $M_W = 433.43$, colorless block, monoclinic, Space group $P2_1/n$(#14), $a = 16.030(3)$ Å, $b = 7.443(2)$ Å, $c = 16.844(4)$ Å, $\beta = 112.74(2)°$, $V = 1853.4(7)$ Å^3, $Z = 4$, $R = 0.063$, $Rw = 0.061$. CCDC-623357 (**9b**) contains the supplementary crystallographic date for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Date Centre via www.ccdc.cam.ac.uk/date_request/cif.
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