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Synthesis of Quinolone Analogues: 7-[(2S, 4R)-2-Aminomethyl-4-hydroxypyrrolidin-1-yl] Quinolones

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Abstract: New quinolone derivatives of 7-[(2S, 4R)-2-aminomethyl-4-hydroxypyrrolidin-1-yl] quinolone-3-carboxylic acids were synthesized by condensation of 7-halo substituted quinolone-3-carboxylic acids with (2S, 4R)-2-aminomethyl-4-hydroxypyrrolidine. These compounds were characterized by FAB-MS and ^{1}H NMR.

Keywords: Pyrrolidine, quinolone, synthesis.

Quinolone antibacterial agents have emerged as one of the dominant classes chemotherapeutic drugs for the treatment of various bacterial infections[1]. We have focused our attention on the modification of the C-7 basic group of the quinolone which has been most varied. In 1987, Uno *et al.*[2] reported that 3-hydroxypyrrolidine quinolones showed more active antibacterial activities than Norfloxacin *in vivo*. In 1998, Fujita *et al.*[3] reported that 2-aminomethylpyrrolidine quinolones have the same antibacterial activities *in vitro* against Gram-positive and Gram-negative bacteria by contrast with spafloxcin. So our interest was directed to the synthesis of 2-aminomethyl-4-hydroxypyrrolidine quinolones and their antibacterial activities.

Chemistry

As shown in **Scheme 1**, we used compound **1** as the starting material, compounds **2** and **3** were synthesized according to literature[4~5]. **3** reacted with benzyl chloride to give **4**, and then reduction of the carbonyl gave **5**. The resulting amine **5** was protected by a Boc group using di-*tert*-butyl dicarbonate (Boc_2O), which produced the Boc protected compound **6**. Finally, the Bz protective group of **6** was removed by H_2/Pd-C10% to give the new pyrrolidine compound **7**.

The coupling reactions of the new pyrrolidine derivatives with various quinolone and naphthyridone nuclei (**8a-e**) according to well-established literature procedures (**Scheme 2)**[6]. The Boc protecting group was removed using CH_3OH/CH_3COCl and the final products **9a-e** was got.

In total, we have synthesized five new target compounds. The structures of all the

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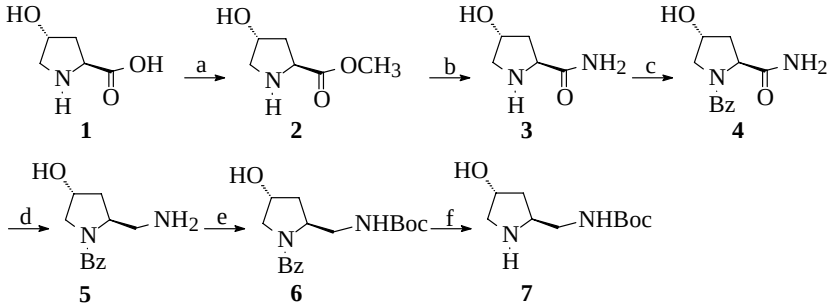
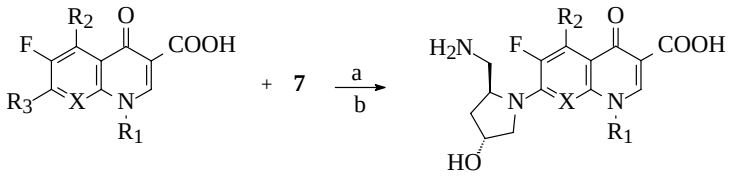
Scheme 1



a: HCl, CH_3OH; b: NH_4OH, r.t.; c: $PhCH_2Cl$, K_2CO_3; d: LAH, THF, 60℃, 82%;

e: $(Boc)_2O$, CH_3OH, r.t., 81%; f: 10% Pd/C/H_2, 3× 10^3Kpa, 50℃, 72%

Scheme 2



8a-8e **9a-9e**

a: CH_3CN, Et_3N, r.t.; b: CH_3OH, CH_3COCl, r.t.

8a: R_1=  , R_2=H, R_3=Cl, X=N

8b: R_1=  , R_2=H, R_3=Cl, X=N

8c: R_1=  , R_2=H, R_3=F, X=C-H

8d: R_1, X=  , R_2=H, R_3=F

8e: R_1=  , R_2=NH_2, R_3=F, X=C-F

9a: R_1=  , R_2=H, X=N, 71%

9b: R_1=  , R_2=H, X=N, 58%

9c: R_1=  , R_2=H, X=C-H, 50%

9d: R_1, X=  , R_2=H, 26%

9e: R_1=  , R_2=NH_2, X=C-F, 26%

target compounds were confirmed by ^{1}H NMR and FAB-MS (data shown in **Table 1**).

Antibacterial Activity

Using ciprofloxcin and gatifloxacin as contrast, we tested the antibacterial-activity *in vitro* of the target compounds with some clinical separated pathogens, quality control strains and standard strains. The target compounds **9a-e** were dissolved in H_2O and to be carried to test MICs using double dilution method. The results were shown in **Table 2**. The activities of **9a-e** were less than ciprofloxcin and gatifloxacin.

It seems that the large volume of R group in the C-2 pyrrolidine position decreased the activity.

Table 1 ^{1}H NMR and FAB-MS data of target compounds

Entry	^{1}H NMR δ (CF_3COOD, ppm),	FAB-MS *m/z*
9a	2.20-2.35 (m, 2H, Pyrrolidine C_3-2H), 3.16-4.46 (m, 5H, Pyrrolidine C_2 -C<u>H</u>$_2$-NH_2, Pyrrolidine C_5-2H, Pyrrolidine C_4-OH), 4.55 (br, 1H, Pyrrolidine C_2-H), 4.80 (s, 1H, Pyrrolidine C_4-H), 7.17-7.58 (m, 3H, Ph-3H), 8.23 (d, 1H, J=10.8 Hz, C_5-H), 9.14 (s, 1H, C_2-H)	435 (M^++1)
9b	1.22-1.53 (m, 4H, cyclopropyl 2×CH_2), 2.41-2.63 (m, 2H, Pyrrolidine C_3-2H), 3.73-4.29 (m, 6H, Pyrrolidine C_2-<u>H</u>-C<u>H</u>$_2$-NH_2, Pyrrolidine C_5-2H, Pyrrolidine C_4-OH), 4.91-5.24 (m, 2H, Pyrrolidine C_4-H, cyclopropyl CH), 8.19 (d, 1H, J=11.1 Hz, C_5-H), 8.17 (s, 1H, C_2-H)	363 (M^++1)
9c	1.26-1.62 (m, 4H, cyclopropyl 2×CH_2), 2.48-2.68 (m, 2H, Pyrrolidine C_3-2H), 3.69-4.28 (m, 6H, Pyrrolidine C_2-<u>H</u>-C<u>H</u>$_2$-NH_2, Pyrrolidine C_5-2H, Pyrrolidine C_4-OH), 4.92-5.11 (m, 2H, Pyrrolidine C_4-H, cyclopropyl CH), 7.62 (s, 1H, C8-H), 8.15(d, 1H, J=11.7 Hz, C_5-H), 9.18 (s, 1H, C_2-H)	362 (M^++1)
9d	1.76 (s, 3H, C_3-CH_3), 2.25-2.61 (m, 2H, Pyrrolidine C_3-2H), 3.35-3.71 (m, 2H, Pyrrolidine C_2-C<u>H</u>$_2$-NH_2), 4.01-5.41 (m, 8H, Pyrrolidine C_5-2H, Pyrrolidine C_2-<u>H</u>, Pyrrolidine C_4-OH, C_2-2H, C_3-H, Pyrrolidine C_4-H), 7.94 (br, 1H, C_5-H), 9.18 (br, 1H, C_2-H)	378 (M^++1)
9e	1.34-1.48 (m, 4H, cyclopropyl 2×CH_2), 2.27-2.63 (m, 2H, Pyrrolidine C_3-2H), 3.61-4.38 (m, 6H, Pyrrolidine C_2-<u>H</u>-C<u>H</u>$_2$-NH_2, Pyrrolidine C_5-2H, Pyrrolidine C_4-OH), 4.88-5.19 (m, 2H, Pyrrolidine C_4-H, cyclopropyl CH), 9.08 (s, 1H, C_2-H)	395 (M^++1)

Table 2 The antibacterial activity *in vitro* of target compounds

Strain	MIC (μg/mL)						
	9a	**9b**	**9c**	**9d**	**9e**	Gatifloxacin	Ciprofloxacin
S.pneumoniae 9798	>64	>64	>64	>64	>64	0.25	4
S. pyogenes *A* 12	>64	>64	>64	>64	64	0.5	1
S. aureus ATCC 25923	>64	>64	>64	>64	>64	0.5	0.25
S. aureus 9616	>64	>64	>64	>64	64	0.25	0.5
S.epidermidis 9726	>64	>64	>64	>64	16	1	4
E. Coli ATCC 25922	>64	>64	>64	>64	16	0.03	0.03
E. Coli 834	>64	>64	>64	>64	16	0.12	0.06
P. aeruginosa 17	>64	64	>64	>64	>64	1	0.25
K. pneumoniae 14	>64	>64	>64	>64	8	0.03	0.03
Bacillus proteus 9	>64	64	>64	>64	>64	0.5	0.25

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