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Synthesis and antibacterial activity of 7-(substituted)aminomethyl quinolones

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Abstract—A series of 7-(substituted)aminomethyl quinolones was synthesized and evaluated for antibacterial activity. Derivatives with (monoalkyl)aminomethyl substituent at C-7 displayed high in vitro activities comparable to Lomefloxacin against gram-negative organisms, whereas those bearing a [(substituted)phenyl]aminomethyl side chain at C-7 demonstrated good activities against gram-positive organisms as potent as Lomefloxacin and Vancomycin.

Increasing multidrug-resistant pathogens have become a serious problem particularly during the last decade.[1] A more controlled usage of these drugs may be a way to partially counterbalance this challenge. However, the design of new agents active against resistant organism remains of critical importance. In the field of quinolone antibacterial agents, the new generation of quinolones achieved significant improvement over the last generation in terms of potency, spectrum and pharmacodynamic properties,[2] but these agents faced a rapid emergence of resistance from gram-positive organisms.[3] Therefore, enhancing the potency of quinolones especially against gram-positive organism becomes more and more urgent recently.[4]

While almost all of the nitrogen heterocycles evaluated at C-7 of quinolone are linked to the quinoline ring through the heterocylic nitrogen, the exact role of this nitrogen has not yet been unequivocally defined.[5] Pazufloxacin is a well-known quinolone antibacterial agent possessing an aminocyclopropyl at C-7 linked through a carbon rather than nitrogen to the quinoline nucleus (Fig. 1).[6] More recently, nonfluorine quinolones such as T-3912, bearing a carbon bonded aromatic substituent at C-7, have been reported to displayed substantial level of activity especially against gram-positive organisms.[7] The less availability of agents possessing nitrogen-containing carbo- or heterocyclic rings directly attached to C-7 through a carbon-carbon bond could be the result of the scarceness of efficient methodologies for their preparation. We report herein the synthesis and antibacterial activities of a series of agents with a carbon bonded side chain at C-7 of quinolone.

7-Aminomethyl derivative **1** (Fig. 1 and Table 1) was designed first as stated previously for preliminary study. Biological test indicated it displayed high antibacterial potency against gram-negative organisms. Therefore similar heterocyclic amine side chains as that of **2** and **3** were introduced to mimic the frequently employed side chain in marketed quinolones, but these derivatives did not exhibit antibacterial potency as high as that of **1**. And then secondary alkylamine side chains were designed to investigate the influence of the substitution

Table 1. Structure of 7-(substituted)aminomethyl quinolone derivatives **1**–**16** (Fig. 1)

Compd	R_1	R_2	Compd	R_1	R_2
1	H	H	**9**	Phenyl	H
2	Piperazinyl[a]		**10**	4-Chlorophenyl	H
3	4-Methylpiperazinyl[a]		**11**	3-Chlorophenyl	H
4	Et	H	**12**	4-Fluorophenyl	H
5	*n*-Pr	H	**13**	3-Chloro-4-fluorophenyl	H
6	*i*-Pr	H	**14**	4-Methylphenyl	H
7	Cyclopropyl	H	**15**	3,4-Dimethylphenyl	H
8	*n*-Bu	H	**16**	4,6-Dimethyl-pyridin-2-yl	H

[a] = R_1R_2N.

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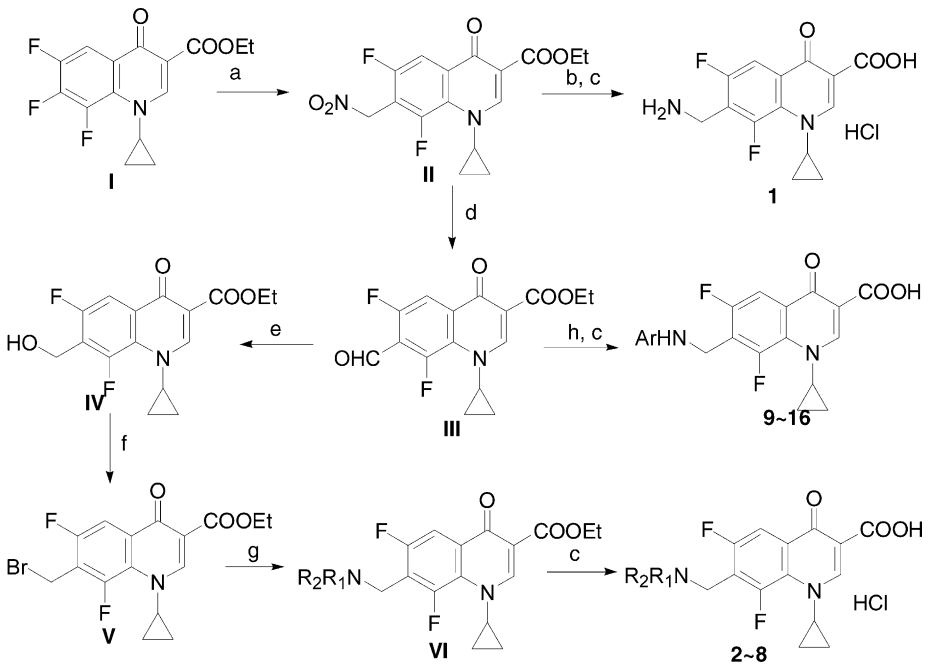

Scheme 1. (a) CH_3NO_2, NaH, DMSO; (b) Pd/C, EtOH; (c) HOAc/HCl; (d) $KMnO_4$, $Na_2B_4O_7$, $MeOH/H_2O$; (e) $NaBH_4$, MeOH; (f) PBr_3, DCM; (g) R_1R_2NH, CH_3CN; (h) $NaCNBH_3$.

Table 2. In vitro antibacterial activity of 7-(substituted)aminomethyl quinolone derivatives **1–16**

Compd	MIC, μg/mL					
	Gram-positive organism			Gram-negative organism		
	S. aureus	*S. epidermidis*	*S. pneumoiae*	*S. boydii*	*K. pneumoniae*	*S. citrobacter*
LMFLX[a]	0.78	0.78	0.195	0.098	0.098	0.098
VCMC[b]	0.39	0.78	0.098	>6.25	>6.25	>6.25
FCPFLX[c]	0.195	0.39	0.049	0.049	0.049	0.049
1	12.5	12.5	0.78	0.098	0.098	0.098
2	6.25	6.25	6.25	0.78	0.195	0.195
3	12.5	12.5	1.56	1.56	1.56	1.56
4	>6.25	>6.25	0.78	≤0.049	≤0.049	≤0.049
5	>6.25	>6.25	3.13	0.195	0.39	0.195
6	>6.25	>6.25	1.56	0.195	0.098	0.098
7	3.13	6.25	0.195	0.098	≤0.049	≤0.049
8	>6.25	>6.25	3.13	0.39	≤0.049	0.098
9	0.78	1.56	0.049	0.39	0.78	0.39
10	0.39	1.56	≤0.049	1.56	1.56	1.56
11	0.195	1.56	≤0.049	0.78	1.56	1.56
12	0.78	1.56	0.049	0.195	0.78	0.39
13	0.39	1.56	0.39	1.56	1.56	0.78
14	0.39	1.56	0.049	0.39	1.56	0.78
15	0.39	0.78	0.098	1.56	1.56	1.56
16	0.39	1.56	0.098	0.39	0.78	0.78

[a] Lomefloxacin.
[b] Vancomycin.
[c] 8-Fluorociprofloxacin.

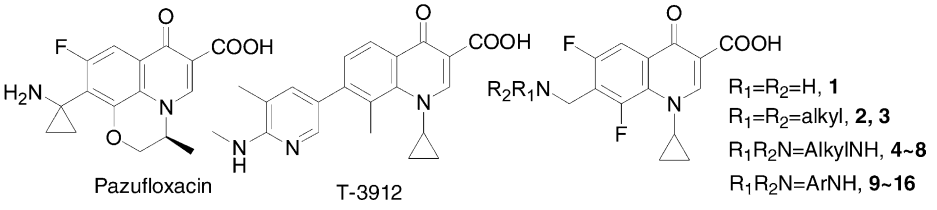

Figure 1.

on the nitrogen of 7-aminomethyl upon the biological activity. On the other hand, hydrophobic moiety as aromatic ring at C-7 was reported to be favorable in increasing the activity of quinolone against gram-positive organism,[2] therefore aromatic amine side chain were designed in order to obtain more potent antibacterial agents.

The synthesis of 7-(substituted)aminomethyl quinolone derivatives is illustrated in Scheme 1. There are only few methods for construction of carbon–carbon bond at C-7 of quinolones. Nitromethyl quinolone derivative **II** was achieved following the method we reported previously.[8] It served as the critical intermediate in the synthesis of all new derivatives in this project. Catalytic hydrogenation of **II** followed by acidic hydrolysis afforded compound **1**. Oxidizing the nitronate of **II** in methanol by aqueous $KMnO_4$ gave the formyl derivative **III**,[9] which was reduced with $NaBH_4$ to give **IV**. **IV** was brominated with PBr_3 in methylene chloride. Treatment of **V** with appropriate amine followed by hydrolysis provided expected compounds **2–8**. Reductive amination of **III** with appropriate aromatic amine followed by hydrolysis afforded compounds **9–16**.

The minimum inhibitory concentrations (MICs) of 7-(substituted)aminomethyl quinolones against several representative gram-negative and gram-positive organisms are summarized in Table 2 along with data of the 7-piperazinyl analogue (8-fluorociprofloxacin), Lomefloxacin and Vancomycin for comparison. MICs were determined by agar dilution method as outlined by the National Committee for Clinical Laboratory Standards. The MIC was defined as the lowest concentration resulting in inhibition of visible bacterial growth after incubation at 37 °C for 18–24 h.

Compound **1** exhibited high activity comparable to the reference agent Lemofloxacin against gram-negative organisms. **4** and **7** were more active than Lemofloxacin against all of the gram-negative organisms tested. **9–16** displayed potent activities against gram-positive organisms. SAR indicated that saving at least one hydrogen atom on the nitrogen of aminomethyl at C-7 of quinolone is favorable for potent activity. Introduction of different substituent on this nitrogen affected activity and selectivity substantially. Derivatives with small alkyl on this nitrogen showed high gram-negative potency while arylation at this nitrogen increased their activities against gram-positive organisms greatly.

In conclusion, a series of 7-(substituted)aminomethyl quinolones was synthesized and evaluated for antibacterial activity. Most of the new compounds demonstrated high in vitro antibacterial activity. Among them, **1**, **4** and **7** exhibited the most significant activities against gram-negative organisms, which were equivalent to or slightly more potent than that of Lomefloxacin. Those derivatives with aromatic substituent on the nitrogen of 7-aminomethyl demonstrated significant activities as potent as Lomefloxacin and Vancomycin against gram-positive organisms.

References and notes

1. Witte, W. *J. Antimicrob. Chemother*. **1999**, *44A*, 1.
2. Beermann, D.; Kuhlmann, J.; Dalhoff, A.; Zeiler, H. J. *Quinolone Antibacterials*; Springer: New York, 1998.
3. Hooper, D. C. *Lancet Infect. Dis*. **2002**, *2*, 530.
4. Dougherty, T. J.; Beauliu, D.; Barrett, J. F. *Drug Dicovery Today* **2001**, *6*, 529.
5. Laborde, E.; Kiely, J. S.; Culberston, T. P.; Lesheski, L. E. *J. Med. Chem*. **1993**, *36*, 1964.
6. Fukuoka, Y.; Ikeda, Y.; Yamashiro, Y.; Takahata, M.; Todo, Y.; Narita, H. *Antimicrob. Agents Chemother*. **1993**, *37*, 384.
7. Yamakawa, T.; Mitsuyama, J.; Hayashi, K. *J. Antimicrob. Chemother*. **2002**, *49*, 455.
8. Zhang, Z.; Zhou, W. *Chin. J. Pharm* **2002**, *33*, 209.
9. Steliou, K.; Poupart, M. A. *J. Org. Chem*. **1985**, *50*, 4971.