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SYNTHESIS AND STRUCTURAL OPTIMIZATION OF 7-(3,3-DISUBSTITUTED-1-PYRROLIDINYL)-1-CYCLOPROPYL-6-FLUORO-1,4-DIHYDRO-8-METHOXY-4-OXO-3-QUINOLINECARBOXYLIC ACIDS AS ANTIBACTERIAL AGENTS

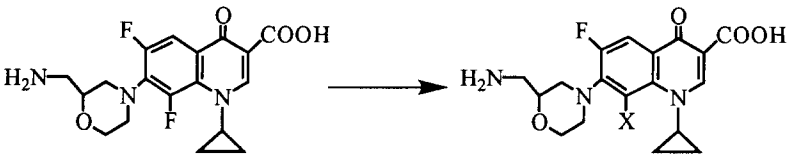
Hiroyuki Kitani*, Tsuyoshi Kuroda, Akihiko Moriguchi, Hideki Ao, Fumihiro Hirayama, Yoshifumi Ikeda, and Takeshi Kawakita.

Research Laboratories, Yoshitomi Pharmaceutical Industries, Ltd., 955 Koiwai, Yoshitomi-cho, Chikujo-gun, Fukuoka 871, Japan.

Abstract: A series of the titled compounds were synthesized and tested for antibacterial activities in comparison with typical fluoroquinolones. (*S*)-3-Aminomethyl-3-fluoromethyl derivative (Y-688) was confirmed to be optimal because of being most active especially against Gram-positive bacteria including fluoroquinolone-resistant strains and showing high photostability.

Fluoroquinolones, synthetic antibacterial agents, are useful for clinical treatment of various infectious diseases. In recent years, many fluoroquinolones bearing a broad antibacterial spectrum have been developed[1]. Some of the agents, however, often exhibit severe phototoxicity[2] (e.g., Erythema, Edema, Eschar, Rash), which is reported to be due to their photodecomposition products[3]. Frequent clinical use of fluoroquinolones brought about an increase in the nosocomial infection by fluoroquinolone-resistant *Staphylococcus aureus* (SA) , in particular some of which are also methicillin-resistant. We previously reported that 7-(2-aminomethyl-4-morpholinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (Y-26611; **1**) exhibited potent antibacterial activity with a wide spectrum[4]. However, photolabile compound **1** showed severe phototoxicity in clinical tests. Matsumoto[2] reported that introduction of a methoxy group into the 8-position of fluoroquinolones improved their photostability. In order to improve the photostability of **1**, we replaced its fluorine atom at the 8-position by other groups (chlorine, hydrogen, and methoxy) (Chart 1). On the other hand, Domagara[1] reviewed that introduction of a 3-aminomethyl-1-pyrrolidinyl moiety into the 7-position of fluoroquinolones enhanced potency against Gram-positive bacteria. As alternative substituents at the 7-position of fluoroquinolones, we designed new 3-substituted-3-aminomethyl-1-pyrrolidinyl moieties (Chart 2) based on the 2-aminomethyl-4-morpholinyl group, and synthesized a series of analogues that show an enhanced antibacterial activity against Gram-positive bacteria including fluoroquinolone-resistant strains.

In this communication, we describe the synthesis and structural optimization of these new fluoroquinolones using the results of *in vitro* antibacterial evaluation.



Y-26611 (1)

Chart 1

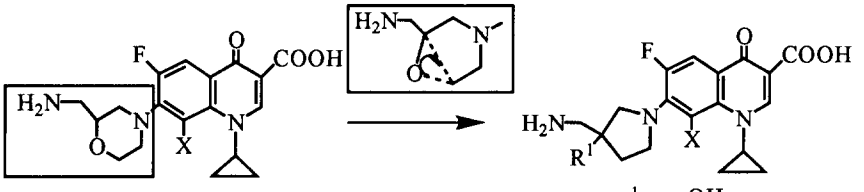


Chart 2

Chemistry: Compounds **2-4** were prepared by coupling of 2-(acetamidomethyl)morpholine[4] with 8-substituted-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid or its difluoroborate followed by deacetylation. Synthetic routes for 3-substituted-3-aminomethylpyrrolidines were shown in Chart 3. For example, 3-aminomethyl-3-hydroxypyrrolidine (**8**) was prepared in accordance with the method A by use of *N*-benzyl-3-oxopyrrolidine (**5**). Through several subroutes summarized in the method B, five pyrrolidine intermediates (**14**,**16**,**19** and **20b-c**) were synthesized by use of diethyl 1-benzyl-2-oxopyrrolidine-4,4-dicarboxylate (**9**)[5]. According to the method C, the pyrrolidine compounds mentioned above were condensed with difluoroborate (**21**) to afford the target fluoroquinolones (**22-27**). Compound **25** was optically separated through its ethyl ester form by using (*R*)- and (*S*)- *O*-methylmandelic acids to give the enantiomers (**28** and **29**).

Results and discussion: Photostabilities[6] of the 8-substituted derivatives were shown in Fig. 1 and their antibacterial activities[7] were listed in Table 1. Among them, compound **4** having a methoxy group at the 8-position were most photostable, but its antibacterial activity was slightly less potent than that of **1**. Antibacterial activities of the 7-substituted-8-methoxy compounds (**22-29**) and some marketed fluoroquinolones are listed in Table 2. Here, 3-aminomethyl-3-hydroxy-1-pyrrolidinyl derivative (**22**) and 3-aminomethyl-3-hydroxymethyl-1-pyrrolidinyl derivative (**23**) were less active than compound **4**. However, displacement of the hydrophilic hydroxy or hydroxymethyl group of **22** or **23** with a small hydrophobic substituent (methyl or fluoromethyl) markedly enhanced the activities not only against Gram-positive bacteria but also against Gram-negative organism. Among the fluoroquinolones tested, **24** and **25** proved to be more active against Gram-positive bacteria including fluoroquinolone and methicillin-resistant SA than the others. In comparison with methyl compound (**24**), fluoromethyl derivative (**25**) was rather superior because of its activity against *Escherichia coli* NIHJ JC-2. However, its *N*-methyl

Fig.1 The stabilities of 8-substituted fluoroquinolones in an aqueous aolution under UV-irradiation

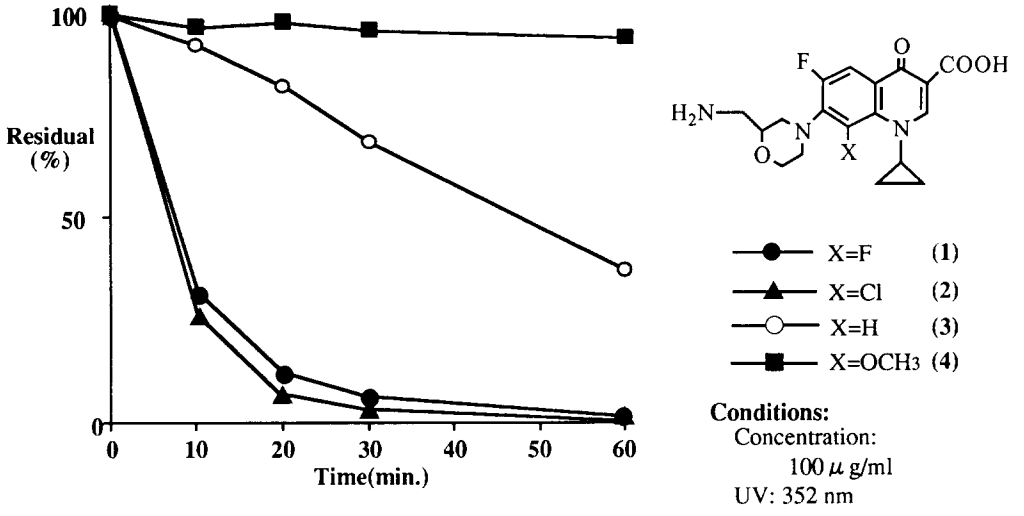
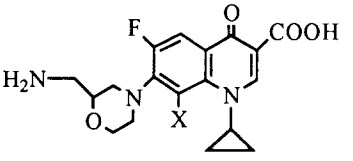


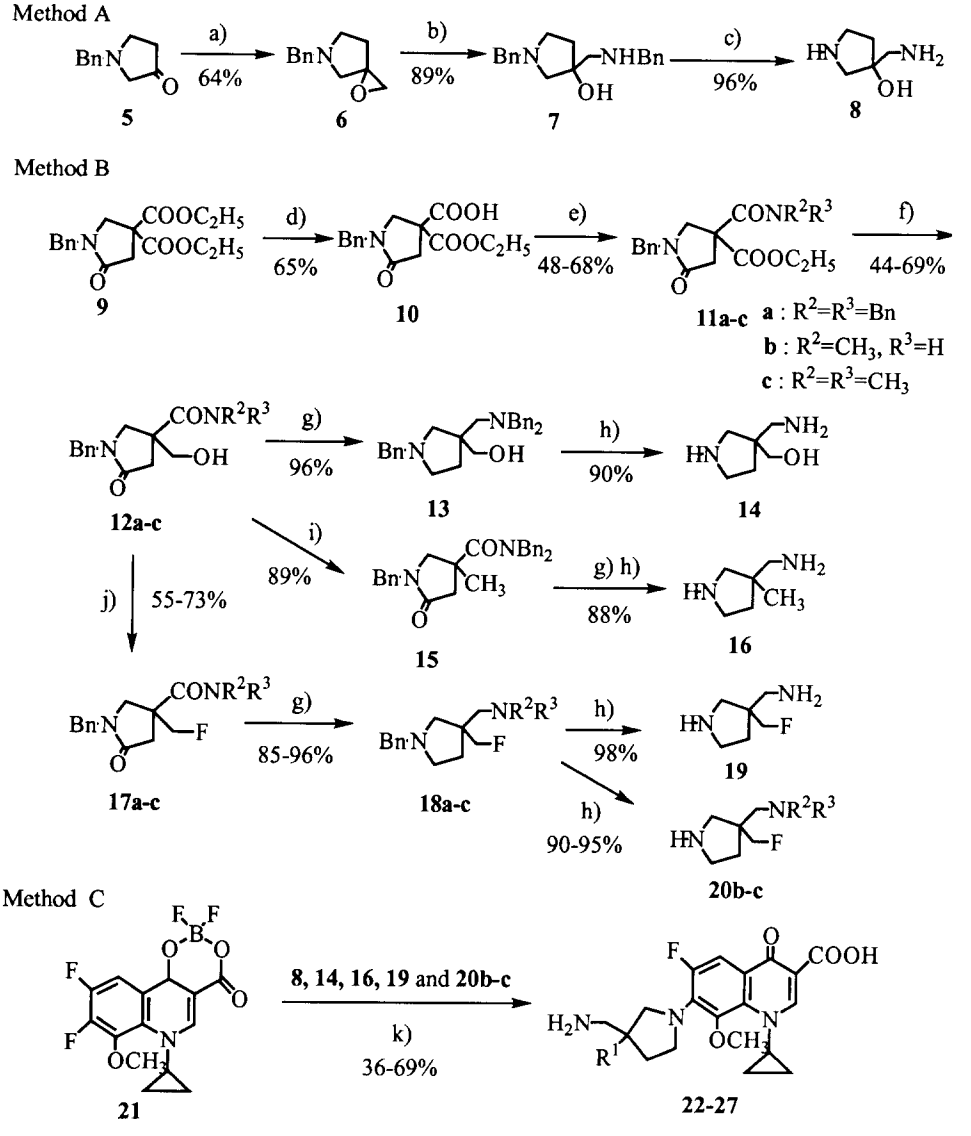
Table 1 Antibacterial activities of 8-substituted fluoroquinolones



Compd. No.	X	mp(℃)	MIC (μg/ml)*		
			S.a.	*S.p.*	*E.c.*
1	F	180-182	0.025	0.10	0.10
2	Cl	265-266	0.012	0.10	0.10
3	H	261-264	0.20	0.39	0.39
4	OCH_3	174-177	0.025	0.20	0.20

* *S.a.* : *Staphylococcus aureus* FDA 209P, *S.p.* : *Streptcoccus pneumoniae* Type III, *E.c.* : *Escherichia coli* NIHJ JC-2

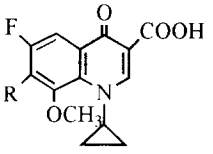
and *N,N*-dimethyl analogues (**26** and **27**) exhibited only limited activities against both Gram-positive and Gram-negative bacteria. Racemate (**25**) was optically separated to examine which is the eutomer between the two isomers (**28** and **29**). As for the activity against fluoroquinolone and methicillin-resistant SA, the *S*-isomer (**28**)[8] was four times as potent as the *R*-isomer (**29**), and was most active against Gram-positive bacteria among the fluoroquinolones tested. Thus, we selected **28** (Y-688) as a candidate for additional biological, physicochemical and pharmaceutical investigation. At the first step of such evaluations, Y-688 was confirmed to be more photostable than the representative fluoroquinolones in the market (Fig.2), suggesting that its potential causing phototoxicity would be obviously diminished in clinical use.

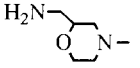
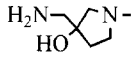
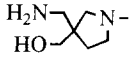
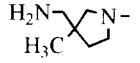
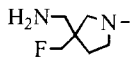
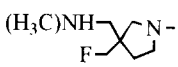
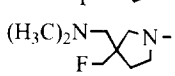
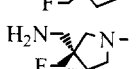
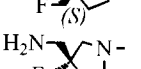


a) $(CH_3)_3SOI$, NaH; b) $BnNH_2$; c) Pd-C, $H_2NNH_2 \cdot H_2O$; d) NaOH; e) R^1R^2NH, HOBt, DCC; f) $NaBH_4$, LiBr; g) $LiAlH_4$; h) 10%Pd-C/H_2; i) 1) $SOCl_2$, 2) Bu_3SnH; j) 1) CH_3SO_2Cl, 2) n-Bu_4NF or KF; k) Et_3N

Chart 3

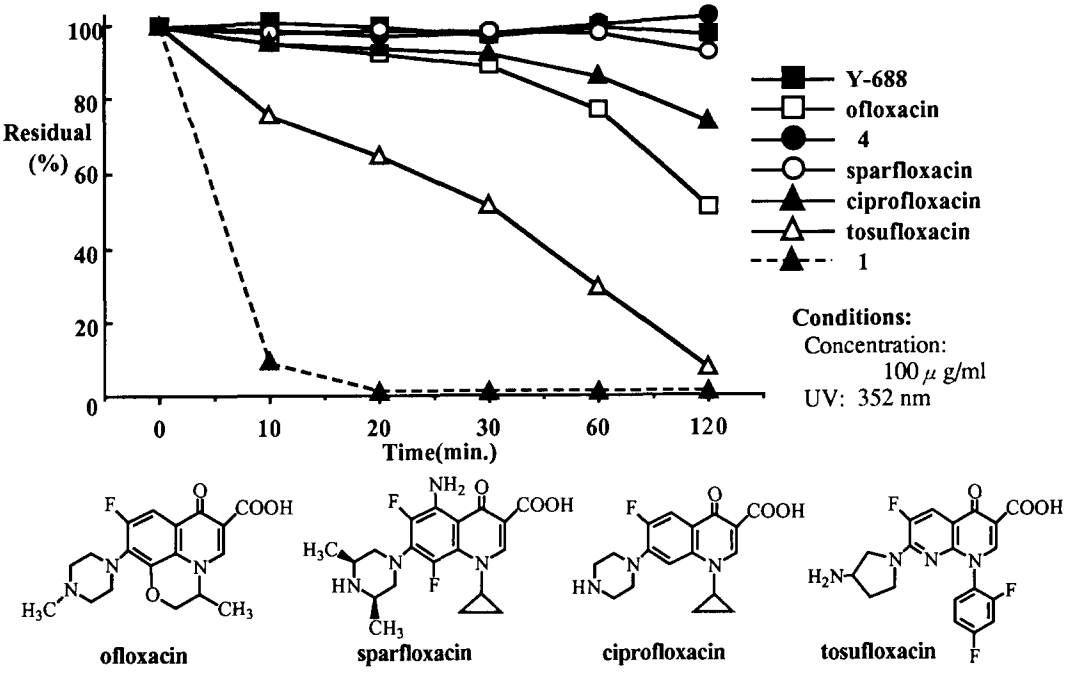
Table 2 Antibacterial activities of 7-substituted 8-methoxyfluoroquinolones



Compd. No.	R	mp(°C)	MIC (μg/ml)*				
			S.a.	*S.a.(R)*	*S.p.*	*E.f.*	*E.c.*
4		174-177	0.025	6.25	0.20	0.05	0.20
22		189-191	0.10	50	0.20	0.20	0.39
23		198-200	0.10	50	0.39	0.20	0.78
24		179-182	0.012	1.56	0.05	0.05	0.10
25		192-194	0.012	1.56	0.05	0.05	0.05
26		165-166	0.025	1.56	0.20	0.05	0.10
27		178-180	0.10	6.25	0.20	0.20	0.39
28(Y-688)		186-188	0.012	0.78	0.05	0.05	0.05
29		187-189	0.012	3.13	0.05	0.05	0.05
ofloxacin			0.20	50	0.78	0.39	0.05
sparfloxacin			0.05	12.5	0.10	0.10	0.025
tosufloxacin			0.025	>25	0.10	0.05	0.025
ciprofloxacin			0.20	>100	0.39	0.20	0.012

* *S.a.* : *Staphylococcus aureus* FDA 209P, *S.a.*(R): *Staphylococcus aureus* No.88 (fluoroquinolone and methicillin-resistant SA), *S.p.* : *Streptcoccus pneumoniae* Type III, *E.f.* : *Enterococcus faecalis* LS-101, *E.c.* : *Escherichia coli* NIHJ JC-2

Fig.2 The stabilities of Y-688 and other fluoroquinolones in aqueous solution under UV-irradiation



Conclusion: A series of new 7-(3-substituted-3-aminomethyl-1-pyrrolidinyl)fluoroquinolone derivatives were synthesized and evaluated for *in vitro* antibacterial activities. From these results, (*S*)-7-(3-aminomethyl-3-fluoromethyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (**28**, Y-688) has been selected as a candidate for further studies.

References and Notes:

1. Domagara, J.M. *J. Antimicrob. Chemother.* **1994**, *33*, 685.
2. Rubinstein, E.; Potgieter, P.; Davey, P.; Norrby, R. *J. Antimicrob. Chemother.* **1994**, *34*, 7.
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5. Engel, W. *Jpn. Kokai Tokkyo Koho,* JP 3-209382, [Chem. Abstr. 115, 159188, 1991].
6. Photostabilities were measured in accordance with literary method; Marutani, K.; Matsumoto, M.; Otabe, Y.; Nagamuta, M.; Tanaka, K.; Miyoshi, A.; Hasegawa, T.; Nagano, H.; Matsubara, S.; Kamide, R.; Yokota, T.; Matsumoto, F.; Ueda, Y. *Antimicrob. Agents Chemother.* **1993**, *37*, 2217.
7. MICs were determined in accordance with the method of the MIC Committee of Japan Society of Chemotherapy; *Chemotherapy*, **1981**, *29*, 76.
8. Data of **28** : $[\alpha]_D = +24.8°$ (c = 1, CH_3COOH). ^{1}H-NMR (CF_3COOD) δ (ppm): 1.15-1.35 (m, 2H), 1.46-1.62 (m, 2H), 2.14-2.35 (m, 2H), 3.80 (s, 3H), 4.05-4.28 (m, 4H), 4.50-4.62 (m, 1H), 4.85 (d, 2H, J = 48.0 Hz), 8.08 (d, 1H, J = 13.0 Hz), 9.32 (s, 1H).

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