Research and Development of Quinolones in Daiichi Sankyo Co., Ltd.

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Quinolones, which are antimicrobials first launched in the 1960s, have exhibited expanded significance in the clinical setting roughly every two decades. The first-generation quinolones were used for the treatment of intestinal and urinary tract infections because of their antimicrobial efficacy against Gram-negative bacteria. During the 1980s, quinolones emerged as broad-spectrum "new quinolones." During the 2000s, quinolones were used for the treatment of a wide variety of infectious diseases, mainly respiratory tract infections, as "respiratory quinolones." During these periods, innovative quinolones representative of each period were produced. Daiichi Pharmaceutical Co., Ltd. (currently Daiichi Sankyo Co., Ltd.) has continued the discovery and research and development of quinolones for more than 40 years, and has released four quinolones, including three in-house development products and one licensed-in product, that have been highly acknowledged by healthcare professionals who treat bacterial infections all over the world.

This document describes the basic concept of drug discovery research of Daiichi's three original quinolones, i.e., ofloxacin, levofloxacin, and sitafloxacin, particularly from the perspective of medicinal chemistry.

Introduction

In 1910, the German bacteriologist Paul Ehrlich and his student Sahachiro Hata developed salvarsan, an agent effective in the treatment of syphilis, and this was the world's first synthetic chemotherapeutic agent. Humans thus became able to create treatments for bacterial infections.

In 1929, Alexander Fleming isolated penicillin, the world's first antibiotic, from *Penicillium notatum*. Howard Florey and other physicians began to use penicillin in the clinical setting, and in this way completely changed clinical treatment of bacterial infections. Around the same time, the first sulfa drug was synthesized, and streptomycin (an antituberculosis agent), tetracycline, and other antibiotics with excellent antimicrobial efficacy were found one after another. Treatment of infectious diseases has thus advanced significantly, however, as early as the middle of the 20th century, the development of resistant bacteria that reduce the efficacy of these antibiotics became a significant concern.

At that time, Sterling-Winthrop Inc. in the USA found that a chloroquinoline derivative produced during the manufacturing of chloroquine, an antimalarial agent, had antimicrobial activity. Through research on this derivative, they found nalidixic acid (NA), the first quinolone type compound, in 1962 (Figure 1) (1). Since nalidixic acid has a naphthyridine ring in its basic structure, exerts antimicrobial activity mainly against Gram-negative bacteria, and is effective against bacteria resistant to sulfa drugs and other antibiotics, it attracted attention as a new synthetic antimicrobial agent with a unique chemical structure.

Daiichi Pharmaceutical Co., Ltd. (currently

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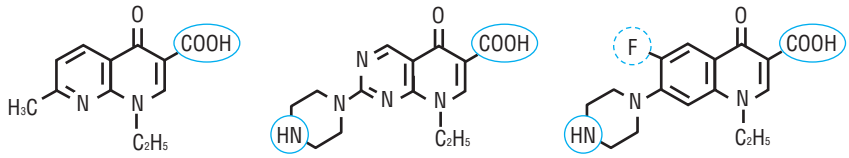
Figure 1. Chemical structures of nalidixic acid, pipemidic acid, and norfloxacin



Nalidixic acid (NA) | Pipemidic acid (PPA) | Norfloxacin (NFLX)

Acidic type | Zwitter type

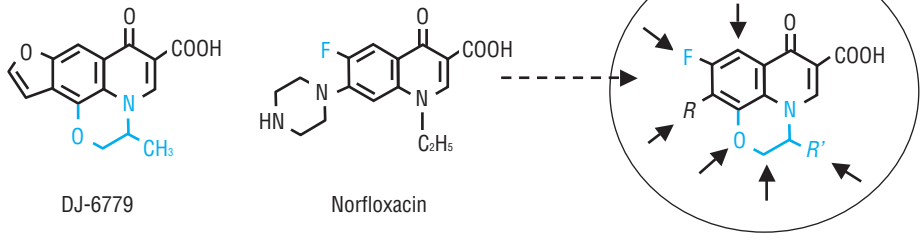
Daiichi Sankyo Co., Ltd.) concluded a contract with Sterling-Winthrop Inc. to introduce nalidixic acid into Japan, and launched it with the trade name of Wintomylon® for the treatment of enteric infection and urinary tract infection (UTI) in 1964.

From acidic quinolones to zwitterionic quinolones—launching ofloxacin

After the release of nalidixic acid in Japan, Daiichi Pharmaceutical began to develop its own acidic quinolones with higher antimicrobial activities and broader antimicrobial spectra using nalidixic acid as the prototype. During a 15-year period, over 1,000 acidic compounds were synthesized. Although compounds with better antimicrobial activities were obtained, they were only effective against Gram-negative bacteria and metabolically unstable. No compounds with physicochemical characteristics sufficient for oral administration were obtained.

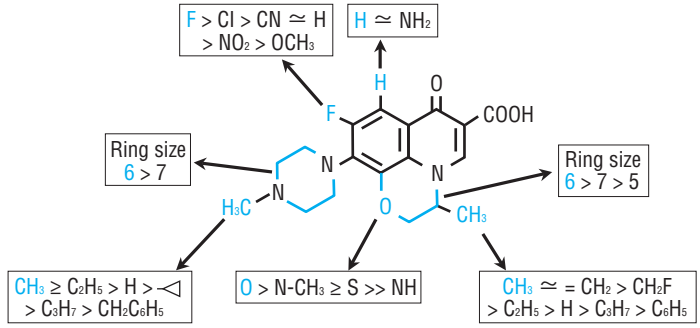
Pipemidic acid (PPA), discovered in 1972, and norfloxacin (NFLX), in 1978 (Figure 1), are zwitter type compounds containing an amino substituent with excellent tissue penetration and urinary excretion not achievable with acidic quinolones ("old quinolones"). In particular, norfloxacin, a compound containing fluorine that exhibits good antimicrobial activity against Gram-positive bacteria, was expected to be beneficial in the treat-

Figure 2. Derivatization of pyridobenzoxazine molecule



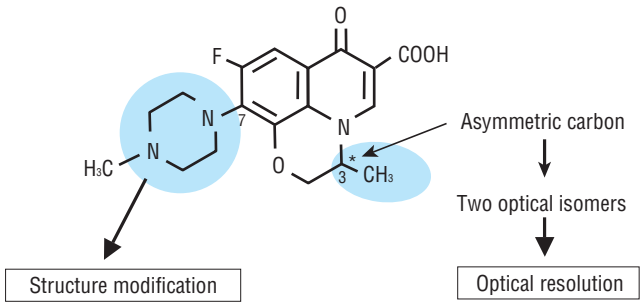
DJ-6779 | Norfloxacin | Pyridobenzoxazine molecule

Figure 3. Structure-activity relationship of ofloxacin structure



Ofloxacin (OFLX)

Figure 4. Modification of ofloxacin chemical structure



ment of respiratory tract infections (RTIs). Daiichi Pharmaceutical, which had reached the limits of R&D of acidic quinolones, became aware of the importance of physicochemical characteristics, especially the tissue penetration of compounds in the body, and changed its targets from acidic to zwitter quinolones ("new quinolones" or "fluoroquinolones"). The company incorporated its abundant findings on structure-activity relationships of acidic quinolones in R&D on zwitter quinolones. From among several candidate structures, the company selected a pyridobenzoxazine skeleton, the basic structure of DJ-6779, which was poorly absorbed following oral administration but exhibited the most potent antimicrobial activities with the widest antimicrobial spectrum among the acidic compounds tested. Daiichi Pharmaceutical developed a lead compound by adding characteristic structures of norfloxacin (fluorine plus amino substituent) to the pyridobenzoxazine skeleton, and produced various analogues called fluoroquinolones (Figure 2 and Figure 3). Among them was ofloxacin (OFLX), which exceeds norfloxacin in all microbiologically significant respects and exhibits high blood concentration, extensive urinary excretion, good tissue penetration, and a broad antimicrobial spectrum covering Gram-positive bacteria (Figure 3) (2).

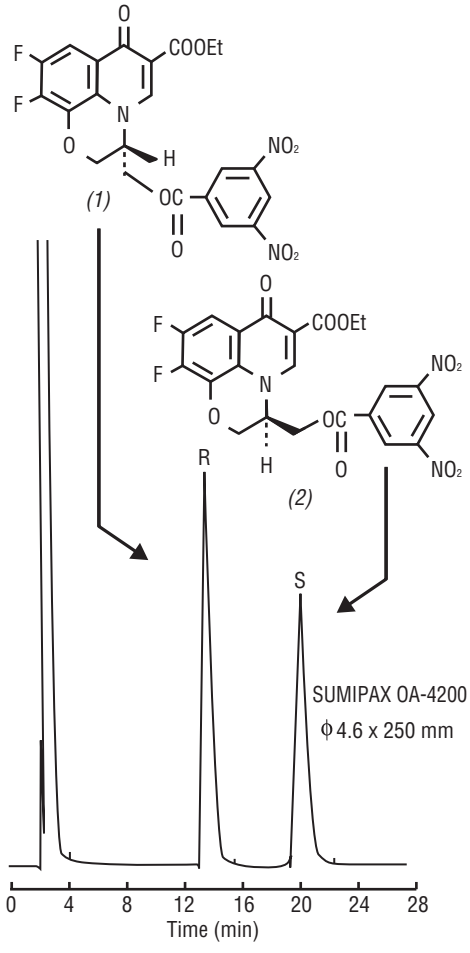
Ofloxacin was released in Japan with the trade name of Tarivid® in 1985, and was then launched in the USA and Europe. This drug is the first export product of Daiichi Pharmaceutical. Although ofloxacin was not the world's first new quinolone, it was approved as a drug for the treatment of various infectious diseases including lower RTIs, and became Daiichi's first successful new quinolone to achieve almost all goals of research.

Introduction of stereochemistry and optical resolution—development of levofloxacin

Before and after the release of ofloxacin, other companies released new quinolones such as norfloxacin, enoxacin, and ciprofloxacin, and the global competition in the quinolone market became fierce. In Daiichi Pharmaceutical, calls for next-generation quinolones with a pyridobenzoxazine structure increased.

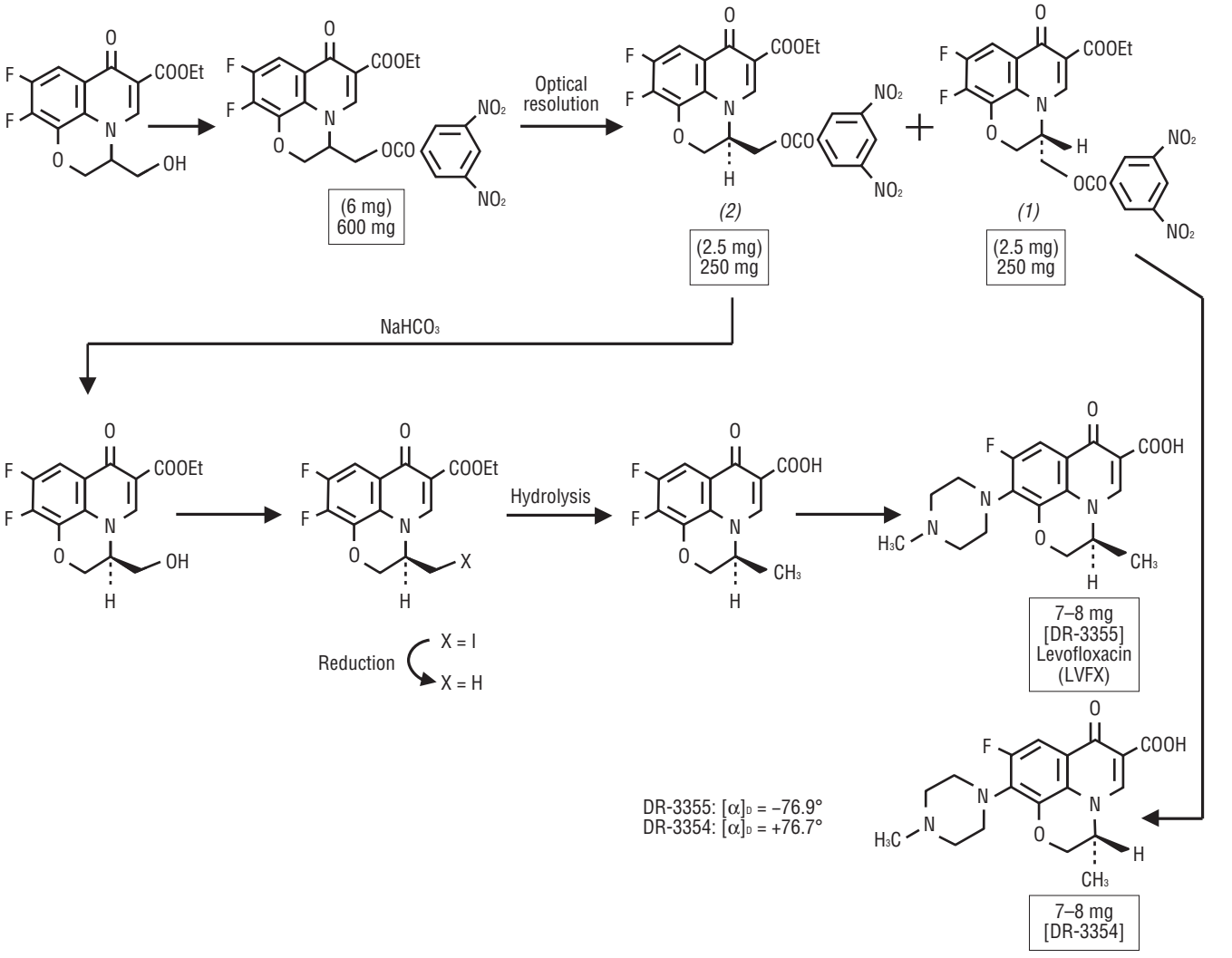
At that time, we knew that the ofloxacin molecule had two possible modifications (Figure 4). The first is further modification of the amino substituent at position 7. The second, the carbon

Figure 5. HPLC chart of optical active 3,5-dinitrobenzoyl derivatives



Abbreviation: HPLC = high-performance liquid chromatography.

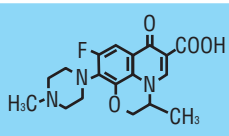
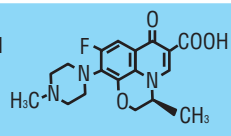
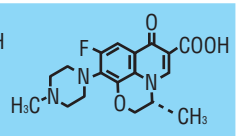
Figure 6. Optical resolution and synthetic pathway to two enantiomers of ofloxacin



at position 3, is a chiral carbon, meaning that two enantiomers are present in terms of the spatial position of the methyl group. Ofloxacin is a racemic compound of two enantiomers that would subsequently be separated. None of the acidic and zwitter quinolones available for human use at that time had asymmetric carbons. Ofloxacin was the first racemic quinolone for which stereochemical research would prove fruitful.

Following successful development of ofloxacin, Daiichi Pharmaceutical attempted to separate enantiomers using various techniques including diastereomer methods, but could not separate them. At that time, the development of chiral columns for high-performance liquid chromatography (HPLC) advanced (3), and various columns were introduced. These columns use optically active polymers as the stationary phase, in which racemic compounds travel differently through the optically active environment and can then be separately eluted based on differences in affinity. We attempted to separate several ofloxacin analogues using some commercially available columns, and found that a newly synthesized 3,5-dinitrobenzoyl derivative could be clearly separated into two enantiomers *(1)*, *(2)* when a specific chiral column is used (Figure 5). However, the column was designed specifically for analytical use, and chiral columns for fractionation able to yield ample amounts (about 10 mg) of enantiomers for analysis of physicochemical characteristics and antimicrobial activities were not available at that time. We asked the manufacturer of the column to produce fraction columns containing the same stationary phase, while we specified suitable eluting conditions in terms of solvent, flow rate, and temperature among other parameters to ensure good separation of enantiomers by HPLC. With this technique, however, we could only run about 6 mg of a 3,5-dinitrobenzoyl derivative to sepa-

Table 1. Characteristics of ofloxacin and its two enantiomers, DR-3355 and DR-3354

	 Ofloxacin (racemate)	 DR-3355 (levofloxacin)	 DR-3354
Antibacterial activity (standard strains)		MIC (μg/ml)	
Staphylococcus aureus	0.39	0.20	25.0
Staphylococcus epidermidis	0.39	0.39	25.0
Streptococcus pyogenes	3.13	1.56	>100
Streptococcus faecalis	3.13	1.56	>100
Escherichia coli	≤0.05	≤0.05	0.39
Proteus vulgaris	≤0.05	≤0.05	0.39
Klebsiella pneumoniae	0.10	≤0.05	1.56
Enterobacter cloacae	≤0.05	≤0.05	0.78
Serratia marcescens	0.10	≤0.05	1.56
Pseudomonas aeruginosa	0.20	0.10	6.25
Toxicity in mice (IV, single)			
Mortality (200 mg/kg)	2/5	0/5	3/5
LD_{50} (mg/kg)	208	248	163
Physicochemical properties			
Optical rotation $[a]_D^{23}$ (0.05N NaOH)	—	–76.9°	+76.7°
Melting point (℃)	260–270	225–229	226–230
Partition coefficient (P')[a]	4.95	5.1	5.1
Solubility in H_2O (mg/ml)	2,400	24,500	25,800

[a] $CHCl_3$/0.1 M of phosphate buffer (pH 7.4).
Abbreviations: MIC = minimum inhibitory concentration, IV = intravenous.

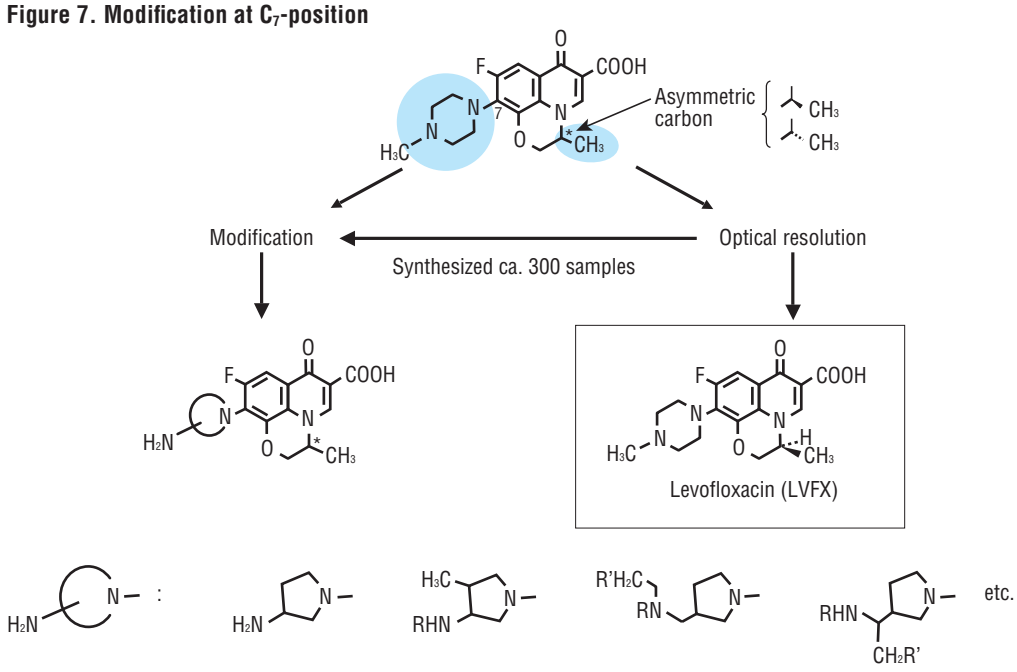
rate the two enantiomers, into about 2.5 mg each, over 1.5 to 2 hours of elution. We repeated the elution over about one month to obtain 250 mg of each enantiomer *(1)* and *(2)*. Using these enantiomers, we finally succeeded in obtaining the enantiomers of ofloxacin, DR-3354 and DR-3355, with optical purities of nearly 100% (Figure 6) (4, 5). X-ray crystal structure analysis of an intermediate compound obtained through a different route revealed that DR-3355 is *(S)*-ofloxacin (4), which was later termed levofloxacin (LVFX).

Evaluation of the antimicrobial activities of ofloxacin, DR-3354, and DR-3355 (levofloxacin) revealed that DR-3355 exhibited antimicrobial activity twice that of ofloxacin in most strains used, while the antimicrobial activity of DR-3354 was 1/10 to 1/100 that of DR-3355 (Table 1), suggesting that the active enantiomer of ofloxacin is DR-3355. In an acute toxicity study in mice, the LD_{50} of DR-3354 was lower than that of DR-3355, suggesting that DR-3354 was a major cause of adverse drug reactions to ofloxacin. Further studies on effects of these substances on arousal of rats and cats and convulsions in mice also revealed that the effects were smallest with DR-3355 and largest with DR-3354, and the strength of effects of ofloxacin was intermediate between the two enantiomers. The water solubilities of DR-3354 and DR-3355 are as high as 25 mg/ml, about 10-fold that of ofloxacin. Injectable DR-3355 was therefore considered feasible (Table 1).

DR-3354 and DR-3355 in amounts sufficient for these non-clinical studies could not be obtained with the chiral column technique. Techniques to obtain several to several hundred grams of DR-3355 such as the proline method (4), the enzyme method (6), and asymmetric synthesis (7) were investigated to ensure rapid progress of non-clinical studies.

Regarding the other point at which modification is possible, the amino substituent at position 7, other companies reported that a five-membered aminopyrrolidine ring improves antimicrobial activities against Gram-positive bacteria (8, 9). Based on these reports, we synthesized about 300 compounds using various aminopyrrolidine groups. However, though antimicrobial activities were increased by inserting aminopyrrolidine groups, we could not obtain any substances acceptable in terms of physicochemical properties and toxicity (Figure 7). As a result of the above-

Figure 7. Modification at C_7-position



described investigations, DR-3355 (levofloxacin) was finally selected as a post-ofloxacin quinolone to be investigated in clinical studies.

Clinical research was initiated in 1987 and proceeded smoothly. In December 1993, levofloxacin was launched in Japan with the trade name of Cravit®. As the world's first optically active quinolone, Daiichi Pharmaceutical launched levofloxacin in Asian countries (from 1994) and licensed it out in the USA and European countries (launched from 1997 to 1998). As of 2010, levofloxacin is available in more than 120 countries due to expansion of its sales network throughout the world (Figure 8). In Japan, levofloxacin was approved at a dose of 100 to 200 mg three times daily, while in the USA clinical development of levofloxacin was started at 500 mg once daily according to pharmacokinetic/pharmacodynamic (PK/PD) modeling, which was new at that time (10). The regimen of 500 mg once daily has become the world standard for levofloxacin therapy (in Japan, the 500 mg once-daily dose was approved in 2009). Because of its broad safety margin, levofloxacin has been approved for use at a dose of 750 mg once daily in the USA and Asian countries* and at 500 mg twice daily in Europe.

Levofloxacin is being used as a blockbuster drug with the best sales in the world market of all original antimicrobial agents in the treatment of infectious diseases throughout the world.

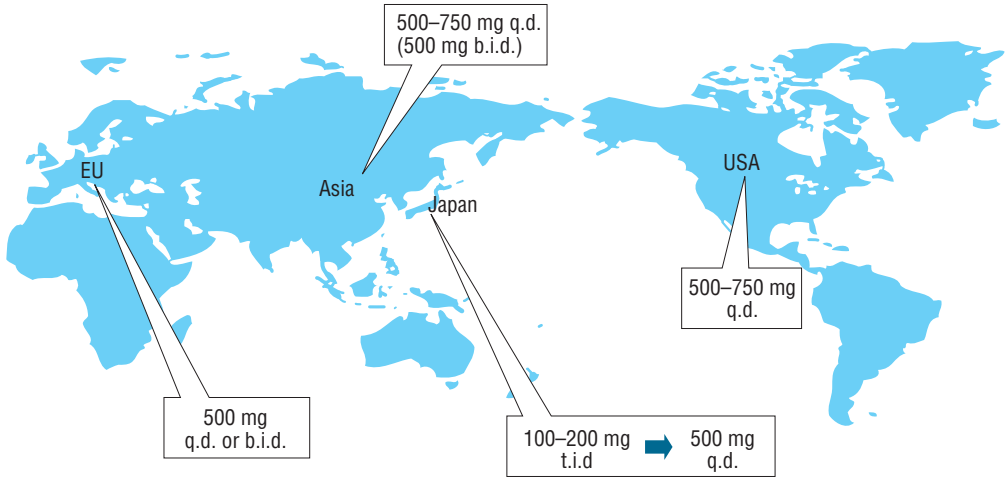
Challenge to severe and intractable infectious diseases—selection of sitafloxacin

Although levofloxacin was acknowledged to be an ultimate quinolone, other pharmaceutical companies were working hard to develop and launch quinolones with higher antimicrobial activities against Gram-positive bacteria and excellent efficacy in the treatment of severe RTIs. Daiichi Pharmaceutical also needed to take a further step in creating completely new quinolones not containing the pyridobenzoxazine structure used as the basis of its quinolone development.

The PK of quinolones would depend on the combination of their basic structure and types of substituents, and differences in PK affect the incidence and types of adverse drug reactions. Selection of suitable chemical structures is facilitated if there are specific criteria for selection of promising compounds. From the launch of ofloxacin, Daiichi Pharmaceutical measured the apparent partition coefficients (P') of quinolones in $CHCl_3$/0.1 M phosphate buffer as a parameter of lipophilicity, and found that quinolones with a P' of 2–5 would be well absorbed after oral administration and rarely cause adverse drug reactions in the central nervous system (CNS) (compounds with P' < 2 are poorly absorbed after oral administration, and compounds with P' > 5 may frequently cause adverse CNS effects). The company used this as a criterion for selection in the discovery of new-generation quinolones. Levofloxacin, a compound with P' = 5, is at the upper limit of

* In some Asian countries, a dose of 500 mg twice daily has been approved.

Figure 8. Global development of levofloxacin[a]

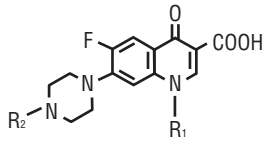


[a] Marketed in more than 120 countries in the world.
Abbreviations: q.d. = once daily, b.i.d. = twice daily, t.i.d. = three times daily.

favorable lipophilicity.

It was generally believed that inclusion of fluorine would increase the lipophilicity of a compound, though Daiichi Pharmaceutical found, through its abundant data on P' of many quinolones, that quinolones become more lipophilic when one or more hydrogen atoms of the aromatic ring are substituted with a fluorine atom, but became less lipophilic when one or more hydrogen atoms of the aliphatic chain are replaced by a fluorine atom (11). We first investigated the usefulness of a new fluorine-containing substituent created by substitution with fluorine of the cyclopropyl substituent at position 1 of ciprofloxacin (CPFX), which exhibits excellent antimicrobial activity against Gram-negative bacteria including *Pseudomonas aeruginosa*. Two pairs of quinolone analogues containing *cis*- and *trans*-

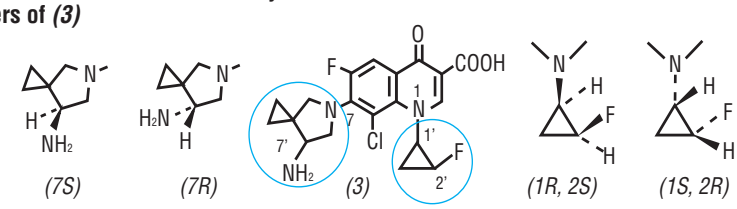
Table 2. Influence of fluorine atom at $C_{2'}$-position of cyclopropyl substituent on antibacterial activity and lipophilicity of the molecule



Configuration of fluorine atom							
	R_1		 *cis*	 *trans*		 *cis*	 *trans*
	R_2	H	H	H	CH_3	CH_3	CH_3
		CPFX					
Antibacterial activity (standard strains)		MIC (μg/ml)					
Escherichia coli		≤0.05	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05
Pseudomonas aeruginosa		≤0.05	≤0.05	0.1	≤0.05	≤0.05	0.39
Staphylococcus aureus		0.1	0.1	0.78	0.2	0.1	0.78
Enterococcus faecalis		0.78	1.56	12.5	0.78	0.78	12.5
Partition coefficient (P')[a]							
		0.89	0.16	—	20.0	7.10	10.7

[a] $CHCl_3$/0.1 M of phosphate buffer (pH 7.4).
Abbreviations: MIC = minimum inhibitory concentration, CPFX = Ciprofloxacin.

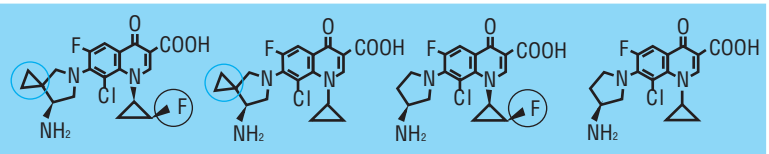
Table 3. Influence of the stereochemistry of N_1- and C_7-substituents on antibacterial activity among four optical isomers of *(3)*



Compound	Configuration		*In vitro* antibacterial activity: MIC (μg/ml)							
	1', 2'	7'	*S. a.*	*S. e.*	*S. p.*	*E. f.*	*E. c.*	*S. m.*	*K. p.*	*P. a.*
DU-6859a[a]	*cis (1R, 2S)*	*(S)*	0.008	0.063	0.031	0.25	0.008	0.031	0.031	0.125
DU-6856	*cis (1S, 2R)*	*(S)*	0.016	0.063	0.063	0.25	0.016	0.063	0.031	0.25
DU-6857	*cis (1R, 2S)*	*(R)*	0.063	0.25	0.5	1	0.031	0.063	0.063	0.25
DU-6858[b]	*cis (1S, 2R)*	*(R)*	0.063	0.25	0.25	1	0.063	0.125	0.125	0.5
LVFX			0.25	0.5	1	2	0.031	0.125	0.063	0.5
CPFX			0.25	0.5	1	2	0.008	0.063	0.031	0.125

[a] Sitafloxacin.
[b] Enantiomer of DU-6859a.
Abbreviations: MIC = minimum inhibitory concentration, *S. a.* = *Staphylococcus aureus* 209P, *S. e.* = *Staphylococcus epidermidis* 56500, *S. p.* = *Streptococcus pneumoniae* J24, *E. f.* = *Enterococcus faecalis* ATCC 19443, *E. c.* = *Escherichia coli* KL16, *S. m.* = *Serratia marcescens* 10100, *K. p.* = *Klebsiella pneumoniae* Type 1, *P. a.* = *Pseudomonas aeruginosa* PAO1, LVFX = Levofloxacin, CPFX = Ciprofloxacin.

Table 4. Influence of the stereochemistry of N_1- and C_7-substituents on product properties

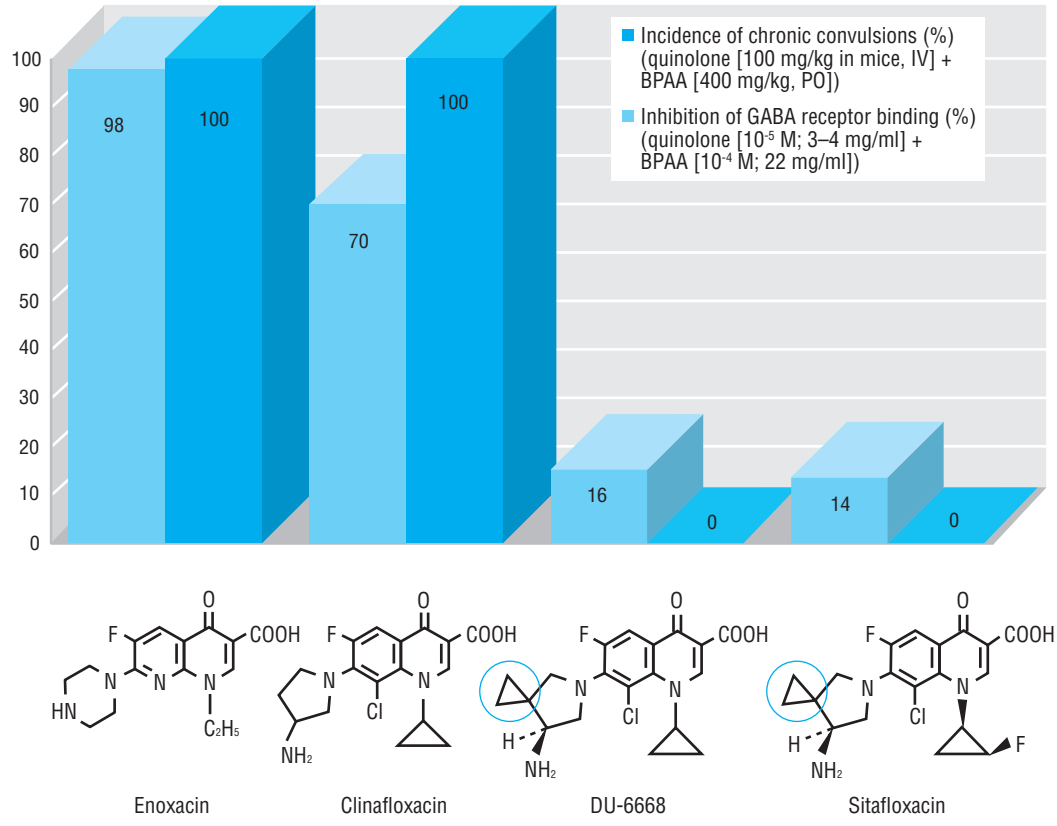


	DU-6859a (Sitafloxacin)	DU-6668	DU-6611	Clinafloxacin (*S*-form)
Antibacterial activity (standard strains)	MIC (μg/ml)			
Escherichia coli	≤0.003	0.006	0.006	≤0.003
Pseudomonas aeruginosa	0.05	0.1	0.025	0.1
Staphylococcus aureus	0.006	0.006	0.012	0.025
Enterococcus faecalis	0.1	0.1	0.2	0.2
Micronucleus test				
	Negative	Positive	Negative	Positive
Partition coefficient (P')[a]				
	3.1	11.1	0.58	2.3

[a] $CHCl_3$/0.1 M of phosphate buffer (pH 7.4).
Abbreviation: MIC = minimum inhibitory concentration.

1-amino-2-fluorocyclopropane groups were synthesized and compared with the corresponding analogue not substituted with fluorine in terms of antimicrobial activities and lipophilicity (Table 2). The *cis*-compounds exhibited antimicrobial activities similar to the non-fluorine compounds, while the *trans*-compounds exhibited poor activities against Gram-positive bacteria. As in the case of levofloxacin, it was speculated that the stereochemical environment around position 1 affected antimicrobial activities. P' were 0.89 and 20 in non-fluorine compounds, 0.16 and 7.10 in *cis*-compounds, and not determined and 10.7 in *trans*-compounds. Introduction of fluorine in the cyclopropyl group resulted in a substantial decrease in lipophilicity. It was therefore concluded that *cis*-1-amino-2-fluorocyclopropane was a promising substituent at position 1 for maintaining favorable antimicrobial activity, although this required careful stereochemical consideration

Figure 9. The effects of spirocyclopropane ring on quinolone-induced convulsions



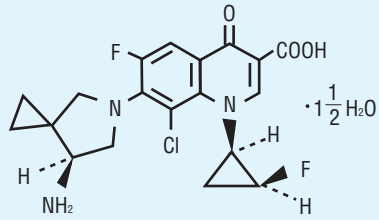
Abbreviations: IV = intravenous, PO = orally, BPAA = biphenyl acetic acid, GABA = γ-aminobutyric acid.

(11).

Using the quinolone structure with the *cis*-fluorocyclopropyl group, compounds containing different substituents at position 7 were synthesized. Among five-membered aminopyrrolidine groups investigated, 3-amino-4-spirocyclopropylpyrrolidine, which contains a spirocyclic structure consisting of two carbon rings linked by a common carbon atom, was the best substituent in terms of yielding a substantial increase in antimicrobial activity against Gram-positive bacteria and appropriate lipophilicity, and compound *(3)* was selected as a candidate molecule (Table 3). Since the substituent at position 1 has two asymmetric carbon atoms and that at position 7 has one asymmetric carbon atom, compound *(3)* has 8 (2^3=8) optical isomers. Because the *cis*-position had already been selected for the substituent at position 1, four optical isomers of the *cis*-compound were synthesized and compared. Antimicrobial activities were most favorable for DU-6859a (sitafloxacin [STFX]) (Table 3) (12). Comparisons in terms of lipophilicity and induction of micronuclei were made among DU-6859a, DU-6668 (a compound with no fluorine atom at position 1 and excellent antimicrobial activities similar to DU-6859a), DU-6611 (substituent at position 7 not a spiro type), clinafloxacin (development of it at Warner-Lambert Co. was discontinued later), and sitafloxacin with a P' of 3.1 and no abnormal findings in micronucleus tests was selected as a compound for clinical development (Table 4). The results indicated that inclusion of a fluorine atom in the substituent at position 1 affected lipophilicity and prevented the induction of micronuclei. Quinolones such as nalidixic acid and enoxacin may induce convulsions, and this had been considered a class effect. Comparison of enoxacin, clinafloxacin, DU-6668, and sitafloxacin in terms of convulsion-inducing activity revealed that the presence of a cyclopropane ring in the substituent at position 7 significantly decreased the incidence of convulsions. It appeared that the cyclopropane ring of sitafloxacin and DU-6668 caused steric hindrance with the binding of these quinolones to γ-aminobutyric acid (GABA) receptors, and thereby decreased CNS activation (Figure 9).

The results of clinical studies of sitafloxacin in various infectious diseases in Japan demonstrated that it exerted excellent antimicrobial activity against Gram-positive bacteria and also exhibited

Figure 10. Characteristics of sitafloxacin



Sitafloxacin hydrate (STFX)
Gracevit®

(-)-7-[(7*S*)-7-Amino-5-azaspiro[2.4]heptan-5-yl]-8-chloro-6-fluoro-1-[(1*R*,2*S*)-2-fluoro-1-cyclopropyl]-1,4-dihydro-4-oxo-3-quinoline-carboxylic acid sesquihydrate

- Broad antimicrobial spectrum and potent antimicrobial activities against aerobic and anaerobic Gram-negative and -positive bacteria and atypical bacteria
- Effective against fluoroquinolone-resistant bacteria
- Appropriate lipophilicity ensuring good oral absorption and low incidence of CNS adverse effects
- Excellent clinical efficacy in patients with severe infection, recurrent/recrudescent infection, or infection with bacteria resistant to other agents
- A promising new-generation fluoroquinolone

Abbreviation: CNS = central nervous system.

more potent antimicrobial activity against Gram-negative bacteria than ciprofloxacin, and yielded excellent bacterial eradication rates and clinical effects. Daiichi Pharmaceutical submitted an application for approval of oral sitafloxacin (50 to 100 mg twice daily) in 2006 and obtained approval in January 2008 for the treatment of 14 infectious diseases including chronic RTIs and complicated UTIs. In June 2008, sitafloxacin was launched with the trade name of Gracevit® in Japan as a next-generation quinolone. In foreign countries, Phase I studies of oral sitafloxacin (500 mg) and injectable sitafloxacin (400 mg) as well as Phase II studies of injectable sitafloxacin in Caucasian participants demonstrated favorable PK of oral sitafloxacin and excellent clinical effects in patients with severe infections (13–16).

Since the minimum inhibitory concentrations (MICs) of sitafloxacin for anaerobes as well as drug-resistant bacteria such as penicillin-resistant pneumococci, quinolone-resistant *Escherichia coli*, and multidrug-resistant *P. aeruginosa* are sufficiently low (17–19), sitafloxacin is expected to function as a key drug in the treatment of severe or intractable infections due to these organisms in Japan and the world (Figure 10) (20).

Safety evaluation

Several review articles have been published on the safety of quinolones (21–23). Quinolones may induce various clinically significant adverse drug reactions such as prolongation of the QT interval, disturbances of blood glucose, liver toxicity and skin rash, and many quinolones have been withdrawn from the market or had their market size decreased after warnings on serious adverse drug reactions were included in their package inserts. However, the risk of serious adverse drug reaction is not high with ofloxacin, levofloxacin, and sitafloxacin, and the safety profile of levofloxacin has been established internationally. The number of patients prescribed sitafloxacin is still not large, and patient data need to be accumulated further to evaluate the safety of this drug.

Conclusions

It is extremely difficult to create substances that will pass screening and investigations and finally prove usable as drugs. During quinolone research for nearly a half century, Daiichi Sankyo Co., Ltd. has found many promising candidate substances for transfer to the process of clinical development, and launched three quinolones, i.e., ofloxacin, levofloxacin, and sitafloxacin. The largest, and indeed never-ending challenge in the development of antimicrobial drugs is the emergence of drug-resistant bacteria. Medicinal chemists thus have the responsibility to continuously seek not only next-generation quinolones, but also novel antimicrobial chemotherapeutic agents with new mechanisms of action.

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