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Discovery of gemifloxacin (Factive, LB20304a): a quinolone of a new generation

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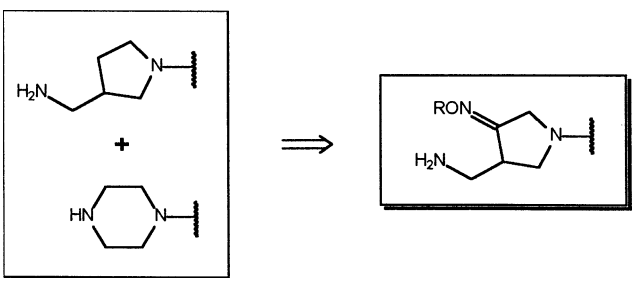
Abstract

Novel quinolone antibacterials, which bear an alkyloxime substituent in the 4-position and an aminomethyl substituent in the 3-position of the pyrrolidine ring, have been designed and synthesized. These fluoroquinolones were found to possess extremely potent antimicrobial activity against Gram-positive organisms including resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA). Among these compounds our development candidate, Gemifloxacin (Factive, LB20304a), showed the best in vivo efficacy and pharmacokinetic profile in animals, as well as good safety pharmacological properties. Gemifloxacin was found to be especially effective against respiratory tract infections that account for over 70% of all infections. With once-a-day dosage, potency against respiratory tract infections such as chronic bronchitis and pneumonia was ensured without any significant side effect. In December 1999, Gemifloxacin filed a NDA for marketing approval to the US Food and Drug Administration.

Keywords: Antibacterial agents; Gemifloxacin; Quinolones; Oxime-functionalized pyrrolidine

Most of the quinolones currently on the market or under development have only moderate activity against many Gram-positive cocci, including *Staphylococci* and *Streptococci*. This insufficient activity has not only limited their use in infections caused by these organisms, such as respiratory tract infections, but has also been believed to be one of the reasons for the rapidly developing quinolone resistance. Therefore, recent efforts have been directed toward the synthesis of new quinolone antibacterials that can provide improved Gram-positive antibacterial activity, while retaining the good Gram-negative activity of ciprofloxacin. As part of an ongoing program to find potent, orally active, broad-spectrum antibacterial agents that display strong Gram-positive activity, we have focused our attention on the modification of the C-7 basic group of the quinolone. From our own research in C-7 amine modifications of the quinolones, we were able to conclude that an aminomethyl group on the pyrrolidine ring was essential for good in vitro (especially Gram-positive) activity.



Since our goal was the discovery of new quinolone antibacterial agents with both strong Gram-positive activity and improved physical properties, we designed novel pyrrolidines that possessed both an alkyloxime substituent and an aminomethyl substituent in the ring.

This structural modification of the pyrrolidine ring was expected to allow modulation of the physical properties of the corresponding quinolones while retaining the strong biological activity of the unsubstituted amino- or aminomethyl-pyrrolidine-containing compounds, thereby possibly improving their pharmacokinetic properties and in vivo potency.

In this symposium, we wish to describe the design and synthesis of oxime-functionalized pyrrolidine derivatives and a series of novel fluoroquinolone compounds containing these amines at the 7-position. The

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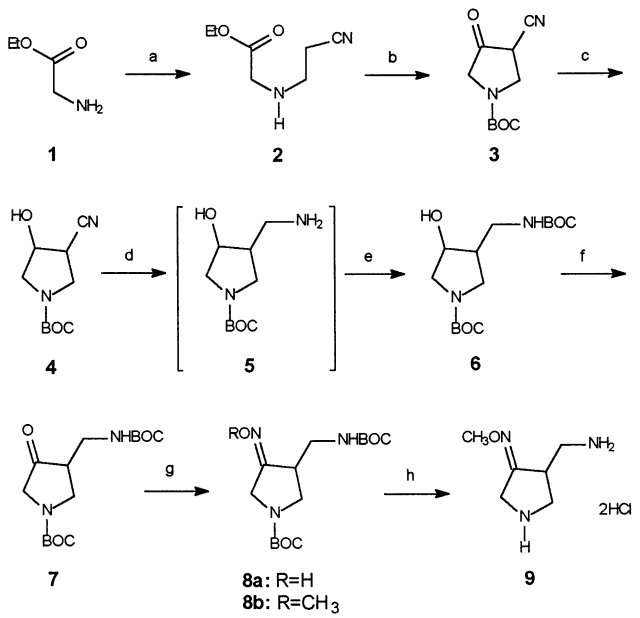
novel pyrrolidines are structurally unprecedented, having an alkyloxime group at the 4-position and an aminomethyl substituent at the 3-position of the ring.

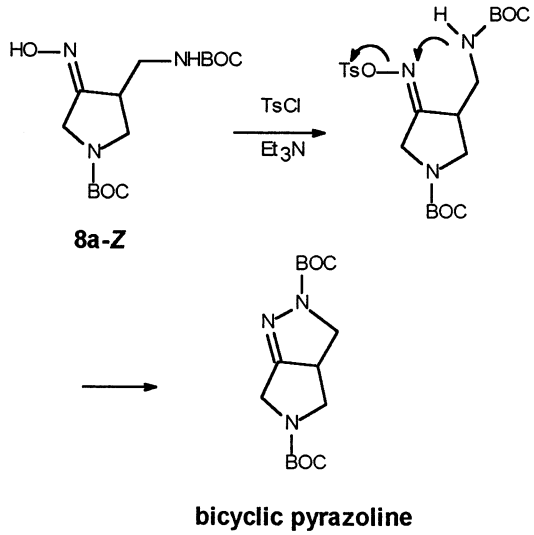
We also report herein the excellent antibacterial activity data of the new quinolones and the structure–activity relationship (SAR) of the pyrrolidinyl group. Finally, we have included the pharmacokinetic profile in animals of the development candidate gemifloxacin and its in vivo efficacy data.

The synthesis of the noted pyrrolidine derivatives is straightforward starting from ethyl glycine and outlined in Scheme 1. Dieckman cyclization of ester **2** nicely produced the pyrrolidine ring and reduction of the cyano group yielded the aminomethyl group; finally, the oxime group was introduced through ketone **7** without any difficulty.

The *Z* configuration of the oxime of **8b** was confirmed by means of a chemical transformation. When compound **8a** was treated with tosyl chloride (TsCl) and triethylamine in methylene chloride, clean formation of the bicyclic pyrazoline was observed. Since only the *Z*-tosylate can produce the bicyclic pyrazoline, the stereochemistry of **8b** can be surmised to be *Z*. The *Z* configuration of **8b** was further confirmed by X-ray crystallography of the final compound (the X-ray structure was presented during the symposium).



Scheme 1. Synthesis of 3-alkyloxime-4-aminomethylpyrrolidine derivative. Reagents: (a) CH_2CHCN, NaOH, 60°C; (b) $(t\text{-}BOC)_2O$, $CHCl_3$, then NaOEt, EtOH, reflux; (c) $NaBH_4$, EtOH, 0°C; (d) LAH, THF, −5°C; (e) $(t\text{-}BOC)_2O$, $NaHCO_3$, Dioxane-H_2O; (f) Pyridine-$SO_3{\cdot}Et_3N$, DMSO, 5°C; (g) $RONH_2{\cdot}HCl$, $NaHCO_3$, EtOH-THF, 40°C; (h) Acetyl chloride, MeOH, 0°C.



The coupling reactions of the pyrrolidine salt **9** and various quinolone or naphthyridone nuclei to give rise to final compounds followed the well-established literature procedures.

The novel quinolones containing the pyrrolidines thus obtained were found to have excellent antibacterial activities against not only Gram-negative strains, but also Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (table of data presented during the symposium). They showed very strong activity against Gram-positive bacteria such as *S. aureus*, *Streptococcus epidermidis* and *Bacillus subtilis*, with MIC values being mostly less than 0.008 μg/ml. The novel quinolones were especially potent against methicillin-resistant *S. aureus* (MRSA, 16–256-fold enhancement compared with ciprofloxacin) and methicillin-resistant *Str. epidermidis* (MRSE, 32–512-fold enhancement compared with ciprofloxacin), against which ciprofloxacin was virtually ineffective (MIC 64 μg/ml and 128 μg/ml, respectively).

Variations at the C-8 position of the quinolone nucleus in this study included fluorine, chlorine, nitrogen, methoxy, and hydrogen substitution. The activity imparted to the substituted quinolone ring by the C-8 substituent was in the order

$$F(C_5\text{–}NH_2) > F(C_5\text{–}H) > \text{naphthyridine} > Cl = OMe = H$$

against Gram-positive organisms. In the case of Gram-negative strains, the activity was in the order

$$F(C_5\text{–}NH_2) > \text{naphthyridine} = F(C_5\text{–}H) > H > Cl > OMe$$

It is also interesting to note that the naphthyridone-type compounds showed comparable potency to its C_8–F quinolone counterparts. These results are unexpected based on the SARs for other quinolones. It has been generally accepted that in vitro activities of naphthyridone compounds are often intrinsically lower than their C_8–F and C_8–Cl quinolone counterparts, although

Table 1
Pharmacokinetic data[a] for gemifloxacin, des-oximino compound, and ciprofloxacin in rat[b] and dog[c]

Animal	Compound	Route	AUC (μg h/ml)	Half-life (h)	C_{max} (μg/ml)	T_{max} (h)	Bioavailability F (%)
Rat	Gemifloxacin	po	8.50	2.33	2.44	0.33	95.3
	Des-oximino	po	0.38	2.20	0.30	0.17	10.1
	Ciprofloxacin	po	2.59	1.87	0.90	0.11	45.4
Dog	Gemifloxacin	po	7.55	5.12	1.34	1.13	71
	Des-oximino	ND	ND	ND	ND	ND	ND
	Ciprofloxacin	po	4.54	1.70	0.91	1.12	75

[a] ND: not determined.
[b] SD rat; dose: 20 mg/kg.
[c] Dose: 4 mg/kg.

Table 2
In vivo efficacy of gemifloxacin, des-oximino compound, and ciprofloxacin against systemic infection in mice

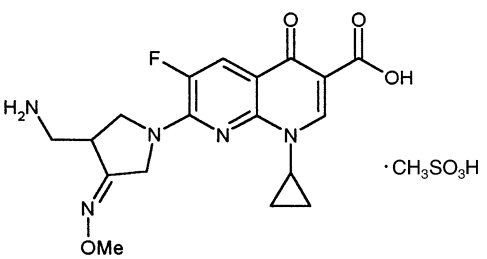
Infected bacteria	Compound[a]	MIC (μg/ml)	ED_{50} [b] (mg/kg)	95% confidence limit (mg/kg)
S. aureus giorgio	Gemifloxacin	≤0.008	1.17	0.52–2.10
	Des-oximino	0.031	8.03	–[c]
	Ciprofloxacin	0.13	6.05	1.60–14.2
Str. epneumoniae 77A	Gemifloxacin	0.016	ND[d]	0.78–17.20
	Des-oximino	0.063	0.5	ND[d]
	Ciprofloxacin	7.64	>200	
P. aeruginosa 1912E	Gemifloxacin	0.25	2.08	0.76–4.94
	Des-oximino	0.5	29.75	–[c]
	Ciprofloxacin	0.13	2.34	0.51–11.98
E. coli 851E	Gemifloxacin	≤0.008	0.47	0.00–1.54
	Des-oximino	0.031	>13.5	
	Ciprofloxacin	≤0.008	0.20	0.01–0.54

[a] Antimicrobial agents were administrated twice orally at 1 and 4 h after infection.
[b] 50% effective dose.
[c] Confidence limits could not be calculated.
[d] ND: not determined.

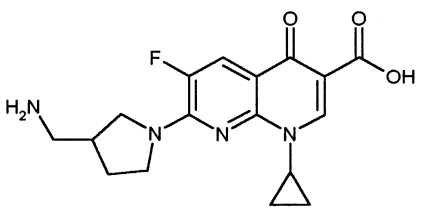
naphthyridones have been reported to have toxicological advantages compared with their quinolone analogs.

The size and lipophilicity of the alkyl group of the oxime moiety were considered to be key factors in determining antibacterial activity. We have briefly investigated the SAR of the alkyloxime group. In order to demonstrate that the newly incorporated oxime moiety is playing the critical role, we also synthesized the des-oximino compound and compared its activity with our novel oxime-derivatized quinolones (table of data presented during the symposium).

Among these novel quinolones with excellent in vitro activity, gemifloxacin (Factive, LB20304a), which has a naphthyridone nucleus and methyloxime group, exhibited the best in vitro potency and most favorable pharmacokinetic profile in animals after oral administration (Table 1). In rats, this compound was well absorbed (AUC = 8.5 mg h/ml), showed good bioavailablity (F = 95%) and long serum half-life (t = 2.62 h). Furthermore, in dogs gemifloxacin was found to have much longer serum half-life (t = 5.12 h) than ciprofloxacin



gemifloxacin (Factive)



des-oximino compound

($t = 1.7$ h). This long serum half-life in rats and dogs was expected to be applicable to human pharmcokinetics, which is good enough for a once-a-day dose.

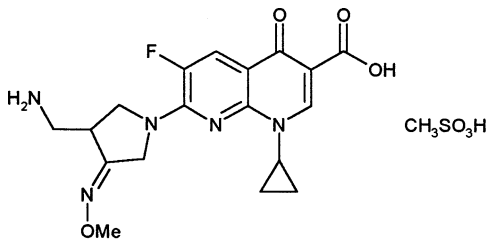
Also, the importance of the oxime group in pharmacokinetics was clearly demonstrated by comparing gemifloxacin with the des-oximino compound. Dramatic improvement in AUC and bioavailability in rats was observed.

Mouse protection tests were used to evaluate the in vivo efficacy of gemifloxacin, with the compound being administered orally (Table 2). The efficacy of this compound was tested against four representative strains: *S. aureus* and *Streptococcus pneumoniae* were selected for Gram-positive bacteria, and *Pseudomonas aeruginosa* and *Escherichia coli* were chosen for Gram-negative bacteria.

In vivo efficacy is well reflected in in vitro inhibitory activity. The ED_{50} of gemifloxacin against *S. aureus* was 1.17 mg/kg with a 95% confidence limit of 0.52–2.10 mg/kg per day, which was about six times stronger than ciprofloxacin (ED_{50} of 6.05 mg/kg) and seven times more potent than the des-oximino compound (ED_{50} of 8.03 mg/kg). Gemifloxacin showed at least a 20-fold enhancement (ED_{50} of 7.64 mg/kg) in activity compared with ciprofloxacin ($ED_{50} > 200$ mg/kg) against *Str. pneumoniae*. The ED_{50} value of gemifloxacin (2.08 mg/kg) was somewhat better than that of ciprofloxacin (2.34 mg/kg) against the Gram-negative strain *P. aeruginosa*, whereas it was 15 times better than the des-oximino compound (ED_{50} of 29.75 mg/kg). Although gemifloxacin exhibited a little lower in vivo efficacy than ciprofloxacin (ED_{50} of 0.47 mg/kg versus 0.20 mg/kg, respectively), it was far more effective against *E. coli* than the des-oximino compound ($ED_{50} > 13.5$ mg/kg).

Gemifloxacin was found to possess an excellent activity against key respiratory tract pathogens such as *Str. pneumoniae*, *Haemophilus influenza*, and *Moraxella catarrhalis* (table of data presented during the symposium). These results suggest a great potential for this compound in the treatment of common respiratory tract infections.

In conclusion, we have designed and synthesized novel quinolone agents derivatized by oxime-substituted aminomethyl pyrrolidines. They were found to possess very potent antibacterial activities against both Gram-negative and Gram-positive organisms, including methicillin-resistant *S. aureus* (MRSA).



gemifloxacin (Factive)

Among these compounds, gemifloxacin showed an excellent in vitro and in vivo efficacy, and good pharmacokinetic profile. As a methanesulfonate form, this compound also has good physicochemical properties, such as high water solubility and stability. The remarkable effects of the newly introduced oxime functional group on biological activity and pharmacokinetic profiles in animals were clearly demonstrated by direct comparison of gemifloxacin with its des-oximino compound.

Based on these promising results, gemifloxacin has been advanced to further studies, and has finished preclinical and phase I clinical trials.

In 1997 gemifloxacin had been licensed out to SmithKline Beecham for worldwide development and commercialization. SmithKline Beecham, after successfully completing phase II and III clinical trials involving more than 8000 patients in 40 countries, filed a new drug application with the FDA in 1999, and are currently waiting for marketing approval.