

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado
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ASUNTO	Radicación	10-000239
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	
	Folios	19

215436

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☐	Cap. I	☐ Cap. II ☐

No. Solicitud Internacional PCT/JP2008/060804
Fecha de Presentación Internacional 06/Junio/2008

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 126 a 258	04/Enero/2010
Reivindicaciones:	Folios 259 a 253	04/Enero/2010
Prioridad:	US 2007-150819	06/Junio/2007

2. Análisis de la Prioridad

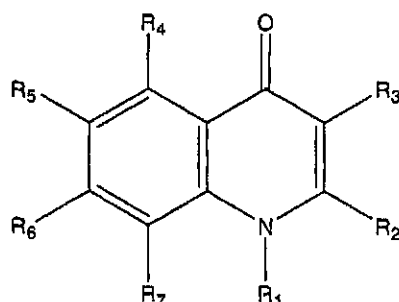
Se acepta la reivindicación de prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Compuesto de quinolona el cual suprime la progresión de disfunción neurológica al inhibir la progresión crónica de la enfermedad de Parkinson o proteger las neuronas de dopamina de la etiología de la enfermedad" modificado (Fl. 281 y 282)

El problema planteado en esta solicitud consiste en la necesidad de suministrar nuevos compuestos derivados de quinolona para el tratamiento de la enfermedad de Parkinson.

Para resolver este problema técnico la solicitud en estudio proporciona compuestos de la fórmula (I) para el tratamiento de la enfermedad de Parkinson.



Fórmula I

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07D407/04, C07D409/04, C07D215/233.

4. Excepción a la Patentabilidad (Art 20 D486 literal d)

Las reivindicaciones 5 a 8 y 10 están relacionadas con un método de tratamiento, el cual no es patentable de acuerdo con el Art 20 literal d. Aunque, las reivindicaciones 5 a 8 se encabezan por un compuesto (agente terapéutico), su contenido se refiere al método terapéutico, por lo tanto, no se consideran patentables.

5. Reivindicaciones relativas a un uso (Art 14 D 486)

El uso de la reivindicación 9 no es patentable, de acuerdo con el Art 14.

6. De la Solicitud de Patente

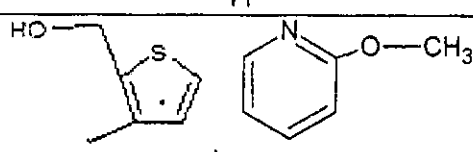
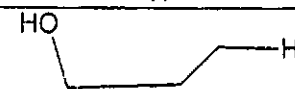
Reivindicaciones (Art 30 D 486, Art 22 PCT)

En las reivindicaciones 1 y 2 el término "opcionalmente", no es claro porque hace eventual la sustitución de los grupos funcionales y no permite distinguir la invención del estado de la técnica. Se sugiere sustituirlo por un rango concreto.

Las reivindicaciones 5 a 8 no están redactadas con la siguiente estructura: preámbulo-conector-parte característica. La redacción de estas reivindicaciones no cumple con la estructura porque se encabezan así: agente profiláctico, a continuación sigue un conector, en seguida una palabra que corresponde a la enfermedad que trata el compuesto; luego un segundo conector: que comprende y por último la categoría de la invención (producto: quinolona).

De acuerdo a lo anterior, se sugiere que el solicitante corrija la redacción y que se ajuste a la estructura preámbulo-conector- parte característica. El preámbulo es lo que identifica la categoría de invención (producto o procedimiento), el conector es por ejemplo "que comprende" y la parte característica es la que define el objeto de la invención en términos de sus elementos esenciales.

En la definición de los radicales más representativos de la fórmula (I), de acuerdo con lo que se encuentra debidamente sustentado en el capítulo descriptivo, se encuentra que siempre varían entre los siguientes grupos funcionales:

Radical	Soporte en la descripción
R ¹	H
R ²	H
R ³	
R ⁴	F
R ⁵	H
R ⁶	H
R ⁷	

Por lo tanto se sugiere al solicitante presentar una generalización razonable y eliminar aquellas definiciones que exceden el sustento descriptivo.

7. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de prioridad (06/Junio/2007) y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	US6645983	Pharmaceutical compositions comprising 4-quinolones for treating cancers	11/Noviembre/2003
D2	WO/0226713	Antiparasitic Compounds	04/Abril/2002

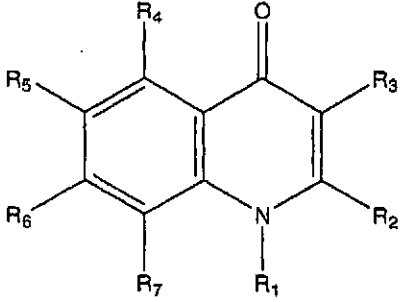
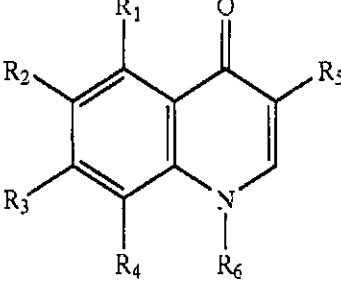
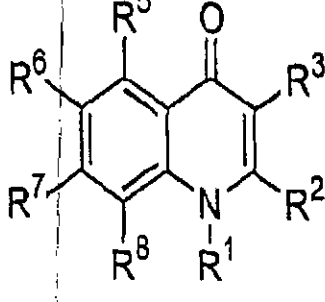
D1<http://www.google.com/patents/US6645983?printsec=claims&dq=US6645983&ei=J2ctUPTAC6mryQHTmYC4AQ#v=onepage&q=US6645983&f=false>
Divulga compuestos 4-quinolonas para ser usados en el tratamiento del cáncer (columna 1 a 2, 9, 127 y 128).
D2http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2008150029A1&KC=A1&FT=D&ND=3&date=20081211&DB=EPODOC&locale=en_EP
Divulga compuestos derivados de quinolonas pertenecientes a la fórmula IB para ser usados como antiparasitarios (Pág. 2 a 4 y 116 a 118).

8. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en un compuesto de quinolona representado por la fórmula general (I) donde: (Fl. 259 a 261).

Comparación de las **características técnicas esenciales**, con las del Estado de la Técnica:

Características esenciales	D1	D2
<u>Compuesto de fórmula I</u> 	<u>Compuestos de fórmula I</u> 	<u>Compuestos de fórmula IB</u> 
R ¹ = H	R ⁶ = H	R ¹ = H
R ² = H	H	R ² = H
R ³ = tienilo, pirididilo, fenilo sustituido por alcoxi, amino, halo, entre otros.	R ⁶ = fenilo	R ³ = arilo, heterociclo de 5 a 10 miembros con 1 a 3 heteroátomos (O, N, S), sustituido por alcoxi, amino, halo, entre otros.
R ⁴ = H	R ¹ = H	R ⁶ = H
R ⁵ = H, halógeno	R ² = H	R ⁶ = H, halógeno
R ⁶ = H	R ³ = H	R ⁷ = H
R ⁷ = alcoxi inferior	R ⁴ = alcoxi inferior	R ⁸ = alcoxi inferior

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1.

D1 divulga los compuestos 4-quinolonas para ser usados en el tratamiento del cáncer (columna 1 a 2, 127 y 128).

D2 divulga los compuestos derivados de quinolonas pertenecientes a la fórmula IB para ser usados como antiparasitarios (Pág. 2 a 4 y 116 a 118).

La diferencia entre la invención, definida en la reivindicación 1 y el compuesto de D1 consiste en que la invención tiene el grupo funcional halógeno en el radical R5.

La diferencia entre la invención, definida en la reivindicación 1 y el compuesto de D2 consiste en que la invención tiene los anillos heterocíclicos específicos.

No se evidencia que por el hecho de tener el grupo funcional halógeno en el radical R5, se tenga un efecto técnico inesperado.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: “cómo modificar los compuestos de fórmula I conocidos en D1 para conseguir compuestos quinolona alternativos”.

Sin embargo, es conocido en el documento D2 el grupo funcional halógeno en el radical R5 porque el documento divulga los radicales F, Cl, Br y I en la posición R6 o el radical equivalente al radical R5 de la invención. Adicionalmente es conocido en el diseño de moléculas nuevas que la modificación del núcleo quinolona se ha realizado en el carbono 3, 5 y 8 para evaluar la actividad farmacológica.¹

1 Monique I. Andersson. Development of the quinolones. *Journal of Antimicrobial Chemotherapy* (2003) 51, Suppl. S1, 1–11. http://jac.oxfordjournals.org/content/51/suppl_1/1.full.pdf
Primer Artículo 45- Expediente 10-000239

En consecuencia, la persona del oficio normalmente versada en la materia, estaría motivada a emplear radicales pertenecientes al grupo funcional halógeno en el radical equivalente a R5. Por lo cual se considera obvia.

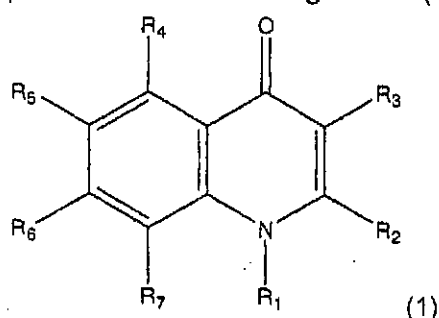
Conclusión:

La reivindicación 1 no cumple con el requisito de nivel inventivo (Art. 18).

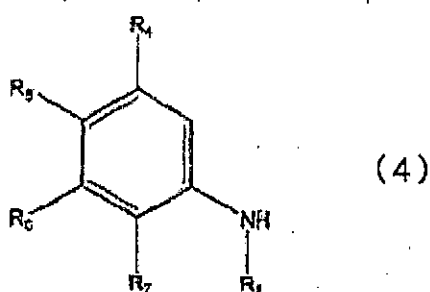
Puesto que las reivindicaciones dependientes 2 a 4 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

Novedad (Art 16 D486)

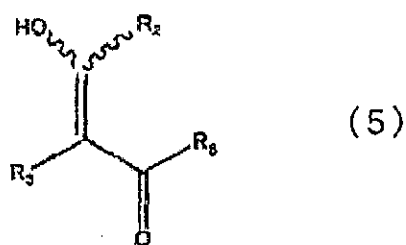
La reivindicación 11 consiste en un proceso para producir un compuesto de quinolona de fórmula general (1)



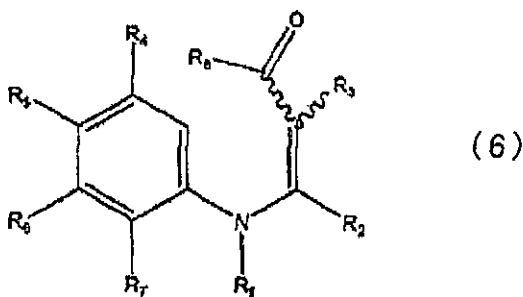
o una sal del mismo, en donde R1, R2, R3, R4, R5, R6 y R7 se definen cada uno anteriormente en la reivindicación 1, que comprende hacer reaccionar un compuesto representado por la fórmula general (4)



en donde R1, R4, R5, R6 y R7 se definen cada uno anteriormente en la reivindicación 1, con un compuesto representado por la fórmula general (5)



en donde R2 y R3 se definen cada uno anteriormente en la reivindicación 1, y R8 representa un grupo alcoxi inferior, dando por lo tanto un compuesto intermedio representado por la fórmula general (6)



en donde R1, R2, R3, R4, R5, R6 y R7 se definen cada uno anteriormente y se somete el compuesto resultante a una reacción de ciclización

Comparación de las **características técnicas esenciales**, con las del Estado de la Técnica:

Características esenciales	D1
proceso para producir un compuesto de quinolona de fórmula general (1) que comprende	proceso para producir un compuesto de quinolona de fórmula general (1) que comprende
hacer reaccionar compuesto representado por la fórmula general (4) (4) en donde R1, R4, R5, R6 y R7 se definen cada uno anteriormente en la reivindicación 1, con un compuesto representado por la fórmula general (5) (5) en donde R2 y R3 se definen cada uno anteriormente en la reivindicación 1, y R8 representa un grupo alcoxi inferior, dando por lo tanto un compuesto intermedio representado por la fórmula general (6) (6) en donde R1, R2, R3, R4, R5, R6 y R7 se definen cada uno anteriormente y se somete el compuesto resultante a una reacción de ciclización	toluene reflux diphenyl ether biphenyl

Las características técnicas esenciales del método de preparación de un compuesto de la reivindicación 11 habían sido divulgadas previamente en D1 (Columna 9), el cual da a conocer un método de preparación a partir de una amina aromática y una molécula que tiene dos grupos funcionales carbonilos terminales, asimismo se divulga que estos carbonilos pueden convertirse fácilmente en un hidroxilo (Columna 10). De igual manera en la descripción de la presente solicitud se divulga en el esquema de reacción que el grupo funcional hidroxilo terminal unido al doble enlace presenta tautomerismo ceto-enol, por lo tanto la molécula que reacciona con la amina aromática puede presentar dos formas: enol y carbonilo (Fl. 146, Pág. 21) tal como se presenta en el cuadro anterior. Asimismo, se definen las etapas de reacción pero con la ventaja que el documento D1 divulga las condiciones de reacción (reflujo) para producir los compuestos equivalentes al compuesto de la reivindicación 11.

En consecuencia, la reivindicación 11 no es nueva, según lo divulgado en el documento D1.

9. Conclusión

Los requisitos de patentabilidad de la presente solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US6645983	1 a 4 11	Nivel inventivo Novedad
D2	WO/0226713	1 a 4	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

04 SET. 2012

Elaborado por: Ruth Angélica Lizarazo Pedraza
Revisado por: Consuelo Leguizamón Leguizamón

Development of the quinolones

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Since their discovery in the early 1960s, the quinolone group of antibacterials has generated considerable clinical and scientific interest. Nalidixic acid, the first quinolone to be developed, was obtained as an impurity during the manufacture of quinine. Since this time, many derivatives have been synthesized and evaluated for their antibacterial potency. Two major groups of compounds have been developed from the basic molecule: quinolones and naphthyridones. Manipulations of the basic molecule, including replacing hydrogen with fluorine at position 6, substituting a diamine residue at position 7 and adding new residues at position 1 of the quinolone ring, have led to enhanced antibacterial efficacy. In general these compounds are well tolerated. However, some of these structural changes have been found to correlate with specific adverse events: the addition of fluorine or chlorine at position 8 being associated with photo-reactivity, e.g. Bay y 3118 and sparfloxacin; and the substitution of an amine or a methyl group at position 5 having a potential role in QTc prolongation, e.g. sparfloxacin and grepafloxacin. Progressive modifications in molecular configuration have resulted in improved breadth and potency of *in vitro* activity and pharmacokinetics. One of the most significant developments has been the improved anti-Gram-positive activity of the newer compounds, such as moxifloxacin and garenoxacin. In the current millennium, these new agents may play an important role in the treatment of respiratory infections.

Keywords: quinolones, pharmacokinetics, pharmacodynamics, drug development

Introduction

Quinolones have been the centre of considerable scientific and clinical interest since their discovery in the early 1960s. This is because they potentially offer many of the attributes of an ideal antibiotic, combining high potency, a broad spectrum of activity, good bioavailability, oral and intravenous formulations, high serum levels, a large volume of distribution indicating concentration in tissues and a potentially low incidence of side-effects. Much research has attempted to make these potential attributes real. Nalidixic acid was the first quinolone to be developed (Table 1), but it took more than a decade before additional compounds, such as flumequin, norfloxacin and enoxacin became available for clinical use. The main use for all these agents was the treatment of urinary tract infection. In the late 1980s more systemically active drugs, such as ciprofloxacin and ofloxacin, were marketed. Recently, there has been a considerable increase in the number of agents that are in development, and to date over 10 000 molecules have

been patented. This review will trace the development of quinolones from their sole use as treatment for urinary tract infections, via systemic use, to those agents whose primary use is for the treatment of respiratory tract infections. This development may be described in terms of structures, potency, pharmacokinetics and pharmacodynamics, and finally indications and clinical use.

Structural developments

Quinolones were derived from quinine. Figure 1 shows the basic fluoroquinolone molecule or 'pharmacore'.¹ The addition of a fluorine molecule at position 6 was one of the earliest changes to the structure. This single alteration provides a more than 10-fold increase in gyrase inhibition and up to 100-fold improvement in MIC. Two major groups have been developed from the basic structure: quinolones and naphthyridones.^{1–5} The presence of a nitrogen at position 8 identi-

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Table 1. Chronology of quinolones that reached the UK market

Date	Quinolone
1960–1969	nalidixic acid
1970–1975	cinoxacin
1975–1985	norfloxacin
1985–1990	ciprofloxacin, ofloxacin
1990–1995	temafloxacin, sparfloxacin
1995–2000	grepafloxacin, levofloxacin, trovafloxacin
2000–2005	moxifloxacin, possibly gemifloxacin and garenoxacin in 2003 or later

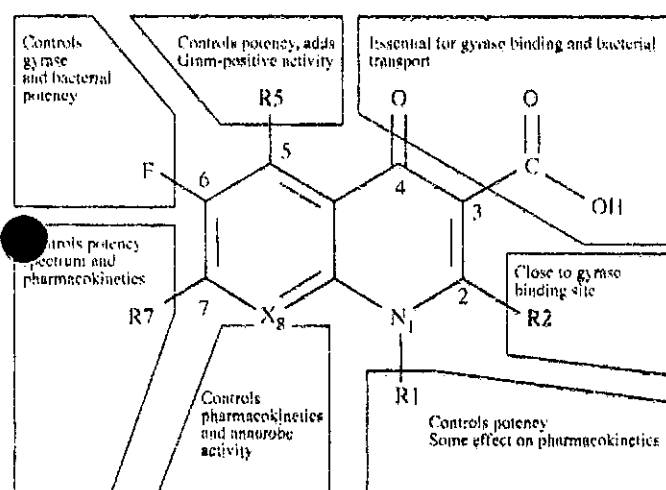


Figure 1. Structure of the quinolone and naphthyridone molecule. In molecules where X is a carbon atom, the molecule is a quinolone (cinoxacin, norfloxacin, ofloxacin, ciprofloxacin, temafloxacin, sparfloxacin, grepafloxacin, levofloxacin, clinafloxacin, moxifloxacin, gatifloxacin). Where X is a nitrogen atom the molecule is a naphthyridone (nalidixic acid, enoxacin, tosufloxacin, trovafloxacin, gemifloxacin). Adapted from Domagala (1994).²

ifies the naphthyridones, a carbon and associated group at position 8 identifies the quinolones.^{1–5}

The quinolones and naphthyridones were further enhanced by the addition of groups to the N₁, C-5 and C-7 positions of their respective basic molecules. The addition of piperazine to the C-7 position (e.g. norfloxacin) improves activity against Gram-negative organisms. There are data to suggest that a piperazine ring may play a role in inhibiting efflux mechanisms, thereby improving the potency of these drugs. The structure of norfloxacin illustrates these developments and subsequent to this all quinolones (except garenoxacin) have a fluorine at position 6 and many have six-membered rings at position C-7 (Figure 2). The presence of a pyrrolidinyl group at position C-7 (e.g. clinafloxacin) improves activity against

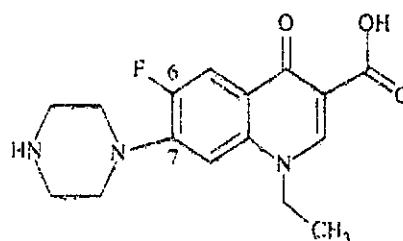


Figure 2. Modifications of quinolone structures: norfloxacin. In all subsequent molecules, except garenoxacin, fluorine was retained at position 6. A six-membered ring at position 7 is found in ciprofloxacin, temafloxacin, sparfloxacin, ofloxacin and levofloxacin.

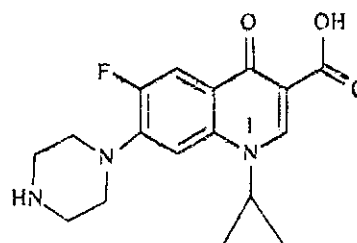


Figure 3. Modification of quinolone structures: ciprofloxacin. A cyclopropyl group at position 1 is found in sparfloxacin, grepafloxacin, clinafloxacin, gatifloxacin, moxifloxacin and garenoxacin.

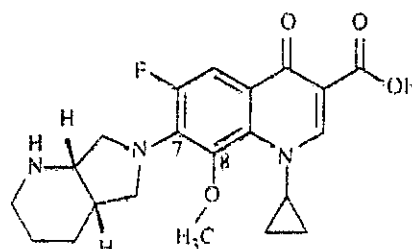


Figure 4. Modification of quinolone structures: moxifloxacin. A five-membered ring or azabicyclo rings at position 7 are found in clinafloxacin and trovafloxacin (five-membered ring) or moxifloxacin and garenoxacin (azabicyclo rings). A methoxy group at position 8 is found in moxifloxacin and gatifloxacin. A difluoromethyl ether (OHF₂) group is found at position 8 in garenoxacin.

Gram-positive organisms. In addition to piperazine at the C-7 position, a cyclopropyl group was introduced to the N₁ position and is best exemplified by ciprofloxacin, which was first synthesized in 1983 (Figure 3). This increases the potency of the drug and many subsequent quinolones have a cyclopropyl group (e.g. grepafloxacin, moxifloxacin, gatifloxacin and garenoxacin; Figure 4). The addition of a 2,4-difluorophenyl group at position 1 (e.g. trovafloxacin) also improves potency, especially in improving activity against anaerobes.

A number of other structural manipulations have been tried to improve the anti-Gram-positive activity of fluoroquinolones. One of the first additions was an NH₂ group at position

Development of the quinolones

C-5, which resulted in a general increase in anti-Gram-positive activity. This is seen with sparfloxacin which otherwise has a very similar structure to ciprofloxacin. Sparfloxacin also has a fluorine at position C-6, a piperazine at position C-7 and is alkylated. Grepafloxacin is also substituted at position C-5 but by a CH_3 group and has improved anti-Gram-positive potency compared with ciprofloxacin. The substituents at position C-7 are associated with a number of key attributes, such as antibacterial spectrum, bioavailability and side-effects. The most common substituents are cyclic amino groups, for example piperazine or pyrrolidine rings; other groups have been less successful. Piperazine rings are particularly common (e.g. norfloxacin, enoxacin or ciprofloxacin) and confer potency against Gram-negative bacteria. The addition of methyl groups can improve both oral absorption and *in vivo* activity. However, the improved activity against Gram-positive bacteria can sometimes be at the expense of activity against *Pseudomonas aeruginosa*.

Pyrrolidine rings (five-membered) are also common substituents at position 7, and are associated with enhanced potency against Gram-positive bacteria. However, this group is associated with low water solubility and low oral bioavailability so *in vivo* activity may be compromised. Introduction of methyl groups on the pyrrolidine ring helps to overcome some of these physical properties. Gemifloxacin, a naphthyridone, is a good example of the advantages and disadvantages associated with a pyrrolidine ring at position 7.⁶ The addition of azabicyclo groups onto position 7 has resulted in agents (moxifloxacin and trovafloxacin) with significant anti-Gram-positive activity, marked lipophilicity and half-lives of >10 h.^{7,8}

Manipulation of the group at position 8 has also been shown to play a role in altering oral pharmacokinetics, broadening the spectrum of activity and reducing the selection of mutants.⁹⁻¹³ Whilst alkylation has been shown to increase further anti-Gram-positive activity, it also improves tissue penetration and extends the half-life by increasing lipophilicity, as with grepafloxacin, levofloxacin and sparfloxacin.

The structural changes to the quinolone molecule and correlation with adverse events are now well documented.^{3,14} Photo-reactivity is probably most influenced by position 8, with fluorine or chlorine producing most phototoxic potential (e.g. lomefloxacin, clinafloxacin, Bay y 3118 and sparfloxacin) and methoxy groups the least (e.g. moxifloxacin or garifloxacin). Garenoxacin has fluorine incorporated through a C-8 difluoromethyl ether linkage as there is no fluorine at C-6. It has been suggested that substitution at position 5 may have a role in QTc prolongation as those agents that have been associated with significant problems, such as sparfloxacin and grepafloxacin, have either a NH_2 or a CH_3 group in this position.^{15,16}

Much speculation has also surrounded the likely structural correlates of the haemolytic uraemic-like syndrome caused

by temafloxacin,¹⁷ hepatic eosinophilia caused by trovafloxacin,¹⁸ pulmonary interstitial eosinophilia and other immunological side-effects caused by tosufloxacin¹⁹ and gemifloxacin, and the hypoglycaemia seen with temafloxacin and clinafloxacin.^{18,20,21} Although a number of these agents are naphthyridones (trovafloxacin, tosufloxacin and gemifloxacin) others are fluoroquinolones (temafloxacin), hence it is unclear whether this difference is relevant. A more powerful association is that of the 2,4-difluorophenyl group at position 1, as this is shared by trovafloxacin, temafloxacin and tosufloxacin¹ but not by gemifloxacin.⁶ A further hypothesis is that metabolites of these agents (as yet not fully identified), which share common structures, may be responsible for some of the immunologically mediated adverse events seen with these drugs.

The naphthyridones can be modified by the addition of cyclopropyl groups in the same way as the quinolones. A five-membered ring has been added to the molecule of gemifloxacin at position 7. Trovafloxacin has an azabicyclo ring, which improves anti-Gram-positive activity, increases the half-life and results in resistance to efflux pumps.⁸

Developments in potency

The development of these agents can be described in terms of their potency against Gram-positive, Gram-negative or atypical bacteria. In terms of anti-Gram-negative potency, as indicated by MIC_{90} s, the activity of quinolones against Enterobacteriaceae such as *Escherichia coli* and *Klebsiella* spp. has not changed significantly since the development of norfloxacin (Table 2).^{6,22-31} In terms of their MIC_{90} s, the early drugs (nalidixic acid and cinoxacin) did not have very good anti-pseudomonal potency. In general, the newer agents have improved activity against pathogens such as *Mycoplasma pneumoniae* and other atypical bacteria, and some have improved activity against Gram-negative anaerobes, such as *Bacteroides fragilis* (Tables 2 and 3). However, many of the newer agents, such as garifloxacin, gemifloxacin, garenoxacin and moxifloxacin, are not as potent as ciprofloxacin against *P. aeruginosa*.

One of the more interesting developments in terms of potency is the area of anti-Gram-positive activity. Although it is unlikely any fluoroquinolone will have activity against ciprofloxacin-resistant *Staphylococcus aureus*, a major development has been in the activity of these drugs against ciprofloxacin-sensitive *S. aureus*, *Streptococcus pneumoniae* and Group A streptococci.^{10,12,32-35} This is one of the key advances in terms of the development of these agents.

Table 4^{22-31,36-39} lists the fluoroquinolones on the basis of their MIC_{90} s for five Gram-positive species. Nalidixic acid, cinoxacin and enoxacin have no activity at all, whereas gemifloxacin has an MIC_{90} of 0.03 mg/L for *S. pneumoniae*, and is

Table 2. Development of quinolone potency against Gram-negative bacteria

Quinolone	MIC ₉₀ (mg/L)						
	<i>E. coli</i>	<i>Klebsiella</i> spp.	<i>Enterobacter/</i> <i>Citrobacter</i> spp.	<i>Serratia</i> spp.	<i>Haemophilus</i> <i>influenzae</i>	<i>P. aeruginosa</i>	<i>B. fragilis</i>
Nalidixic acid	8	16	>64	>64	2	>64	>64
Cinoxacin	8	8	>64	>64	2	>64	>64
Enoxacin	0.25	2	1	4	0.12	2	>64
Norfloxacin	0.12	0.5	0.25	2	0.06	2	>64
Ciprofloxacin	0.03	0.25	0.12	0.5	0.03	1	16
Ofloxacin	0.12	0.5	0.5	1	0.03	4	16
Levofloxacin	0.12	0.25	0.5	0.5	0.03	2	8
Temafloxacin	0.06	0.5	0.5	0.5	0.03	1	4
Trovafloxacin	0.06	0.25	0.06	1	0.01	1	0.25
Clinafloxacin	0.01	0.03	0.12	0.25	0.01	0.5	0.25
Sparfloxacin	0.06	0.5	0.5	4	0.03	4	4
Grepafloxacin	0.06	0.12	0.5	2	0.01	8	8
Moxifloxacin	0.06	0.12	1	2	0.06	8	1
Gatifloxacin	0.06	0.25	0.5	1	0.03	4	1
Gemifloxacin	0.03	0.25	0.5	2	0.06	4	ND
Garenoxacin	0.06	0.5	1.0	2	0.03	16	1

Table 3. Development of quinolone potency against atypical bacteria

Quinolone	MIC ₉₀ (mg/L)				
	<i>Legionella pneumophila</i>	<i>M. pneumoniae</i>	<i>Chlamydia</i> spp.	<i>Mycoplasma hominis</i>	<i>Ureaplasma urealyticum</i>
Nalidixic acid	0.25	>64	>64	>64	>64
Enoxacin	0.12	4	8	8	16
Norfloxacin	0.06	16	16	8	16
Ciprofloxacin	0.01	2	2	1	4
Ofloxacin	0.03	2	2	0.5	1
Levofloxacin	0.01	1	1	0.25	1
Trovafloxacin	0.01	0.25	0.12	0.5	0.5
Clinafloxacin	0.008	0.03	0.12	0.03	0.12
Sparfloxacin	0.06	0.5	0.5	0.5	0.5
Grepafloxacin	0.01	0.5	0.12	0.12	0.5
Moxifloxacin	0.01	0.12	0.12	0.06	0.25
Gatifloxacin	0.01	0.12	0.25	0.12	0.25
Gemifloxacin	0.008	0.12	0.06	0.01	0.25
Garenoxacin	0.008	0.06	0.016	0.03	0.06

equivalent to the earlier compounds in terms of activity against the majority of Gram-negatives (Table 2). The activity against enterococci is less clearly defined because different species are often classified together, and the proportions of *Enterococcus faecium* and *Enterococcus faecalis* are not provided. This is important as *E. faecium* is more resistant than *E. faecalis*.

Developments in pharmacodynamics and pharmacokinetics

Pharmacokinetics (PK) refers to changes in drug concentration as the drug moves through the body, whilst pharmacodynamics (PD) refers to how the drug action changes with concentration or dose.

Development of the quinolones

Table 4. Development of quinolone potency against Gram-positive bacteria

Quinolone	MIC ₉₀ (mg/L)				
	<i>S. aureus</i> (methicillin sensitive)	<i>S. pneumoniae</i>	Group A streptococci	<i>Enterococcus</i> spp.	<i>Clostridium</i> <i>perfringens</i>
Nalidixic acid	>64	>64	>64	>64	>64
Cinoxacin	>64	>64	>64	>64	>64
Enoxacin	2	64	64	8	>64
Ciprofloxacin	1	2	1	4	0.5
Ofloxacin	0.5	2	2	2	1
Levofloxacin	0.25	1	1	2	0.5
Temafloxacin	0.25	0.5	0.5	2	1
Sparfloxacin	0.12	0.5	1.0	2	0.25
Grepafloxacin	0.12	0.25	1.0	4	1
Gatifloxacin	0.25	0.25	0.25	1	0.5
Trovafoxacin	0.03	0.12	0.25	1	0.25
Moxifloxacin	0.06	0.12	0.25	2	0.25
Clinafloxacin	0.06	0.12	0.06	0.25	0.12
Gemifloxacin	0.06	0.03	0.06	4	ND
Garenoxacin	0.03	0.12	0.25	0.5	0.25

Table 5. Development of quinolone pharmacokinetics

Quinolone	Dose (g) (frequency per day)	C _{max} (mg/L)	AUC (mg·h/L)	Half-life (h)	Protein binding (%)	Elimination route
Nalidixic acid	1 (×4)	variable	variable	1.5	90	renal
Enoxacin	0.5 (×2)	1.5	19	2	60	renal
Enoxacin	0.6 (×1)	3.7	29	6	70	renal
Norfloxacin	0.4 (×2)	1.5	10	3	15	renal and hepatic
Ciprofloxacin	0.75 (×2)	3.5	30	4	40	renal and enteral
Ofloxacin	0.4 (×2)	4.8	64	6	40	renal
Levofloxacin	0.5 (×1)	5.2	48	7	40	renal
Temafloxacin	0.6 (×2)	7.0	134	8	25	renal
Trovafoxacin	0.3 (×1)	2.5	40	12	85	hepatic
Clinafloxacin	0.2 (×2)	1.6	18	6	40	renal
Sparfloxacin	0.4 (×1)	1.0	20	18	40	renal and hepatic
Grepafloxacin	0.4 (×1)	1.4	14	14	50	hepatic
Moxifloxacin	0.4 (×1)	3.1	30	13	50	hepatic
Gatifloxacin	0.4 (×1)	4.0	37	9	20	renal
Gemifloxacin	0.32 (×1)	1.0	9	7	60	renal and other
Garenoxacin	0.4 (×1)	5.8	59	15	87	renal and other

Nalidixic acid is a drug that is excreted in urine and has very variable systemic absorption. Essentially it is not a systemic drug, but a urinary agent. Over time, larger serum area under the curve (AUC) or peak serum (C_{max}) values are consistently seen as the quinolones have developed, and oral absorption has markedly improved compared with that of nalidixic acid (Table 5).^{6,30,31,40,41} The half-life of these agents has also tended to increase as structural modifications have been made

to the molecule. However, since the activity of quinolones is concentration dependent, meaning that the extent of bacterial killing increases as drug concentrations increase, and they have a prolonged post-antibiotic effect (PAE),⁴² a long half-life is not an absolute prerequisite for once-daily dosing.^{14,43,44} No trend in protein binding has become apparent over time with some agents having a binding of <30% (norfloxacin, temafloxacin and gatifloxacin) and others >70% (nalidixic

Table 6. Development of quinolone pharmacodynamics against Gram-negative pathogens

AUC/MIC (total)	<i>E. coli</i>	<i>H. influenzae</i>	<i>P. aeruginosa</i>
<12.5	nalidixic acid	nalidixic acid	nalidixic acid, enoxacin, norfloxacin, sparfloxacin, grepafloxacin, moxifloxacin, gatifloxacin, gemifloxacin, garenoxacin
12.5–25			cinoxacin, ofloxacin
25–50			ciprofloxacin, levofloxacin, trovafloxacin, clinafloxacin
50–100	norfloxacin		
>100	all others	all others	temafloxacin

Table 7. Development of quinolone pharmacodynamics against Gram-positive pathogens

AUC/MIC (total)	<i>S. aureus</i>	<i>S. pneumoniae</i>	Group A streptococci
<12.5	nalidixic acid, cinoxacin, norfloxacin	nalidixic acid, cinoxacin, enoxacin, norfloxacin	nalidixic acid, cinoxacin, enoxacin, norfloxacin
12.5–25	enoxacin	ciprofloxacin	sparfloxacin, grepafloxacin
25–50	ciprofloxacin	ofloxacin, levofloxacin, grepafloxacin	ciprofloxacin, ofloxacin, levofloxacin
50–100		sparfloxacin	
>100	ofloxacin, levofloxacin, temafloxacin, trovafloxacin, clinafloxacin, grepafloxacin, moxifloxacin, gatifloxacin, gemifloxacin, garenoxacin	temafloxacin, trovafloxacin, clinafloxacin, moxifloxacin, gatifloxacin, gemifloxacin, garenoxacin	temafloxacin, trovafloxacin, clinafloxacin, moxifloxacin, gatifloxacin, gemifloxacin, garenoxacin

acid, enoxacin, trovafloxacin and garenoxacin). Non-renal clearance seems to have become a feature of a number of the newer agents (e.g. trovafloxacin, grepafloxacin, moxifloxacin and garenoxacin), although many fluoroquinolones and naphthyridones are eliminated primarily by metabolism and renal clearance (glomerular filtration and active tubular secretion). Clearly, a high free-drug C_{max} and AUCs, combined with lower MIC, are a significant advance because they will have the effect of increasing the value of C_{max}/MIC or AUC/MIC ratios.

There is always a certain amount of debate as to whether the C_{max}/MIC or the AUC/MIC is more important in terms of fluoroquinolone bacteriological and clinical outcomes in man. This is probably not important because the co-variable nature of these two pharmacokinetic parameters makes it difficult to identify which one is dominant in determining microbiological and clinical outcome. In general, agents with large AUC also have high C_{max} concentrations. The other area of considerable pharmacodynamic debate has been what breakpoint or critical PK/PD ratio is required to optimize microbiological or clinical outcomes. For example, if there is a range of values, the bigger numbers are more likely to be predictive of good clinical outcome in terms of the microbiology

and the emergence of resistance.⁴⁵ At present it is reasonable to assume that almost all the drugs that have AUC/MIC ratios >100 are likely to have useful activity against Enterobacteriaceae and *P. aeruginosa*, while a target of free AUC/MIC of 30–40 is required for *S. pneumoniae*.⁴⁶

For predicting efficacy against most infections, pharmacodynamic variables (for example, AUC/MIC or C_{max}/MIC) are driven by changes in potency, much more than they are driven by changes in pharmacokinetics. The MIC changes are sometimes 100-fold between agents, whereas the pharmacokinetic changes are probably at most five-fold between any of these agents. For example, as ciprofloxacin has an AUC/MIC between 25 and 50 for the therapy of *P. aeruginosa*, it can be anticipated that levofloxacin, trovafloxacin and clinafloxacin will have similar activity to ciprofloxacin against *P. aeruginosa* (Table 6).^{47,48} In contrast, some of the newer drugs, such as grepafloxacin, moxifloxacin, gatifloxacin, sparfloxacin, gemifloxacin or garenoxacin, together with some of the older urinary drugs like norfloxacin, are unlikely to have significant clinical activity against *P. aeruginosa* at present doses. Pharmacodynamics would predict that all but the very early quinolones will have good clinical activity

Table 8. Proposed classification of fluoroquinolones

Agents	Activity	Clinical applications
Urinary agents (1960–1985) nalidixic acid cinoxacin enoxacin norfloxacin	activity against common Enterobacteriaceae, short serum half-lives, renal elimination	main use in UTI
Gram-negative systemic agents (1985–1995) ciprofloxacin ofloxacin levofloxacin	wide activity against Gram-negatives, including <i>P. aeruginosa</i> , marginal activity against Gram-positives, longer serum half-lives	widely used against tissue-based and urinary infections
Broad spectrum systemic agents (1990–2000) temafloxacin clinafloxacin trovafloxacin	wide activity against Gram-negatives, including <i>P. aeruginosa</i> for some agents, and Gram-positives, for some agents long serum half-lives, some activity against anaerobes	widely used against a broad range of tissue- based infections
Respiratory agents (1995 onwards) levofloxacin sparfloxacin grepafloxacin moxifloxacin gatifloxacin gemifloxacin garenoxacin	wide activity against Enterobacteriaceae, active against Gram-positives, especially <i>S.</i> <i>pneumoniae</i> , active against atypical bacteria, variable activity against anaerobes, long serum half-life	main use in respiratory tract infection

against *E. coli* and *H. influenzae* causing systemic infection (Table 6).

With respect to the Gram-positive organisms, it is clear that the urinary drugs are not going to have useful clinical activity against *S. pneumoniae*, *S. aureus* or *Streptococcus pyogenes* (Table 7). Whereas with ofloxacin, levofloxacin, grepafloxacin and sparfloxacin, AUC/MIC ratios of >25 are beginning to predict clinically useful outcomes for non-immunocompromised patients with mild to moderate community-acquired disease. In the context of immunocompromised patients (those with co-morbidity or ITU patients) or in order to prevent the emergence of resistance, ratios should probably be higher. The more recently developed fluoroquinolones, such as trovafloxacin, gatifloxacin, gemifloxacin, moxifloxacin and garenoxacin, are likely to have useful clinical activity against *S. pneumoniae*, a prediction now supported by clinical trials data in community-acquired pneumonia⁴⁹ and acute exacerbation of chronic bronchitis (AECB).^{50,51} The small amount of existing clinical data also implies that these agents are clinically active against ciprofloxacin-susceptible *S. aureus* and Group A streptococci.^{32–35,52}

Toxicology

Many of the more recently developed quinolones do not have the toxicological disadvantages of the earlier compounds, for example the QTc prolongation that has limited the use of sparfloxacin and grepafloxacin. Other effects include a haemolytic uraemic-like syndrome with temafloxacin,¹⁷ a metallic taste with grepafloxacin,⁵³ hepatitis with trovafloxacin,⁵⁴ unexpected hypoglycaemia with clinafloxacin and temafloxacin,^{21,55,56} a number of immunologically mediated adverse events with tosufloxacin,¹⁸ and an immune-mediated rash in young women with gemifloxacin.⁶ To date there are little toxicological data on garenoxacin.

Indications and use

The pharmacokinetic and *in vitro* potency profiles of fluoroquinolones determine the areas of clinical use. This has shifted from agents used predominantly for the treatment of urinary tract infections in the 1960s/70s, to more systemic use in the 1980s/90s, and in the current millennium, to the treatment of respiratory tract infections. Sparfloxacin and grepafloxacin

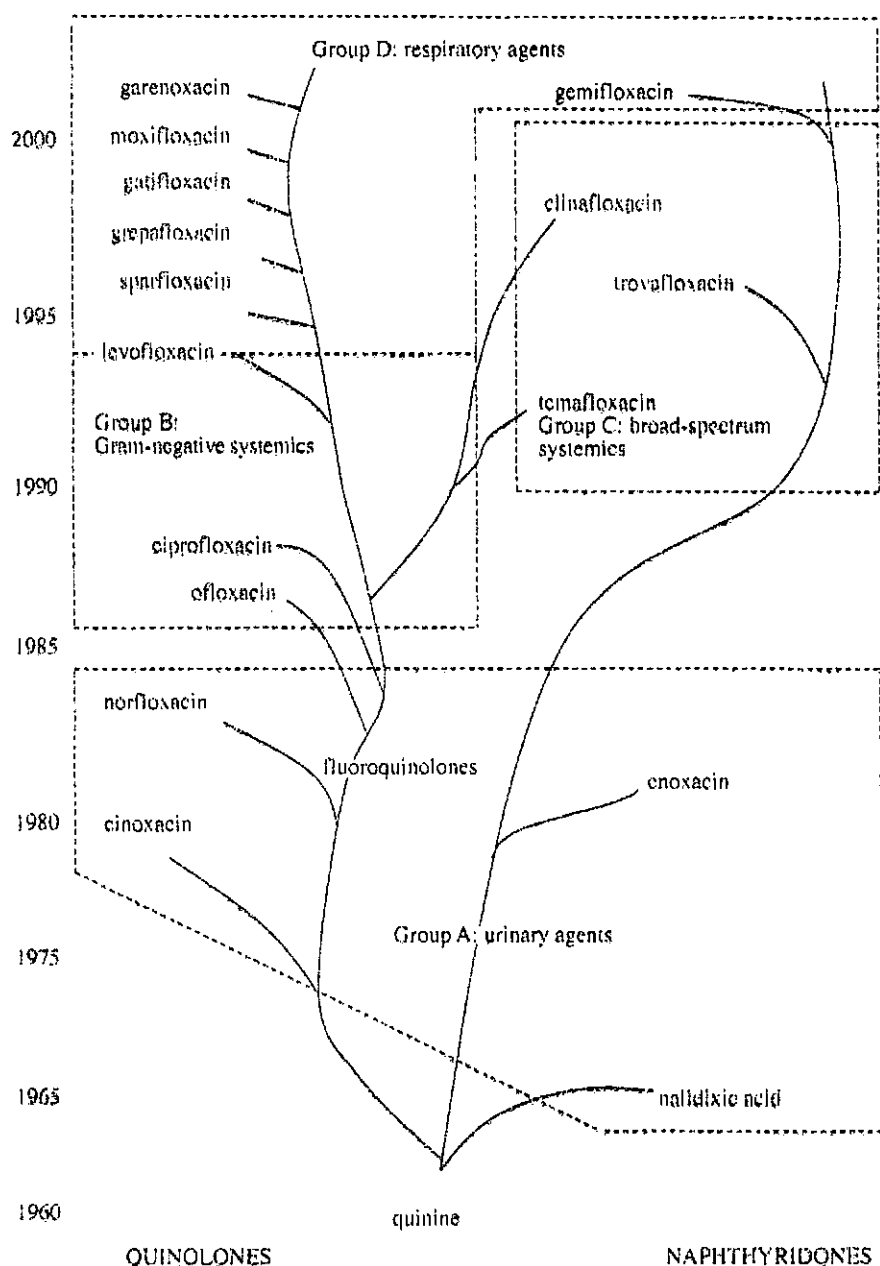


Figure 5. Development of quinolones.

floxacin were the first agents to focus on the respiratory tract, exploiting their activity against *S. pneumoniae* and atypical organisms. More recently a further group of agents (moxifloxacin, gatifloxacin, gemifloxacin and garenoxacin) with more convincing potential in the respiratory tract have been developed. Thus development has moved from the urinary to the respiratory tract via a miscellaneous group of systemic indications. Levofloxacin is one example of a drug where there is a wide range of potential uses, but in terms of marketing the main focus appears to be respiratory.

On this basis, quinolones can be classified into four groups according to clinical use, potency, pharmacokinetics and

pharmacodynamics. The first group consists of urinary agents that are, in general, the older drugs which are active against the common Enterobacteriaceae and tend to have short half-lives and renal elimination (Table 8). The second group includes the anti-Gram-negative systemic agents such as ciprofloxacin, levofloxacin and ofloxacin which, according to their pharmacokinetics and activity, indicate that they can be used for Gram-negative infection and as anti-pseudomonal agents. There is, however, debate about their use in various areas of Gram-positive infection. The third group, of which trovafloxacin and temafloxacin are the best examples, have sufficiently broad activity in terms of anti-Gram-negative,

anti-Gram-positive, antipseudomonal and anti-anaerobic activity, to indicate their use for a wide range of tissue-based infections. The fourth group includes the respiratory agents, some of which are also in other categories. These drugs have activity against *S. pneumoniae* and atypical organisms, but are less active against *P. aeruginosa*. Some of these agents, such as moxifloxacin and garenoxacin, may be as active as trovafloxacin against anaerobes, suggesting that with time, their clinical indications may expand beyond the respiratory area. The nomenclature of the quinolones is complex, and these agents have also been classified in terms of generation⁵⁷ (discussed in this supplement in the article by P. Ball). However, whichever classification is used, it is clear that these agents are not a homogeneous group of antibiotics, and that important differences exist between them.

Conclusions

Modifications in the basic structure of quinolones have increased their antibacterial spectrum and potency, as well as improving bioavailability, making quinolones useful agents in the treatment of urinary, systemic and respiratory tract infections. An 'evolutionary' tree is shown in Figure 5. However, safety concerns continue with some members of this class and have resulted in the withdrawal of some agents after marketing (temafloxacin, grepafloxacin, sparfloxacin, trovafloxacin) or others in late development (clinafloxacin and gemifloxacin). It is still unclear as to which structure-function relationships have resulted in these problems, so despite a good deal of progress being made in terms of *in vitro* activity and pharmacodynamics, progress in the area of toxicology has been erratic.

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