New Fluoroquinolones: A Class of Potent Antibiotics

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Abstract: The discovery of antibiotics opened a new era in the treatment against several pathogenic microorganisms that can disable or kill humans. The appearance of the fluoroquinolones (based on nalidixic acid, 4-quinolone-3-carboxylates), in the early 1980`s, gave a new impetus in the treatment of infectious diseases. Despite these favourable properties, the earlier fluoroquinolones had limited potency against some clinically important organisms, especially Gram-positive pathogens so that the development of resistance to these organisms has become a serious problem. Thus the development of new fluoroquinolones with a better pharmacokinetic profile, potency, broad spectrum of activity, solubility, prolonged serum half-life and oral and parenteral routes of administration has been a major focus on recent research. The increasing interest in this class led me to review the promising new fluoroquinolones in clinical trials.

Keywords: Fluoroquinolones, fluorine, microbiological activity, antibiotics.

INTRODUCTION

The fluorine atom is an important element in drug design due to its electronic, lipophilic and steric parameters as high electronegativity, very low polarizability, solubility, hydrogen-bonding, relatively small size and steric effects. These important properties of fluorine can modulate both pharmacodynamic and pharmacokinetic effects of drugs with impact on biological activity [1]. The effects of fluorine on biological activity can be seen in the market (delete in) in of a large number of drugs against different diseases (Fig. **1**). An important class of the fluorine compound is the fluoroquinolones (7-fluoro-4-oxo-1,4 dihydro-quinoline-3-carboxylic acid), (Fig. **1**) a potent class of antibacterial agents with a broad spectrum of activity against Gram-positive, Gram-negative and mycobacterial organisms as well as anaerobes with great therapeutic potential, particularly those caused by organism resistant to other classes of antibacterial drugs. The aim of this review is to highlight the history, biologic activity and synthesis of the new fluoroquinolones.

MECHANISM OF ACTION AND RESISTANCE

In 1975, Smith and workers showed that nalidixic acid, 1-ethyl-4-oxo-1,8-naphthyridin-3-carboxylic acid (Fig. **2**) acts by inhibiting an important enzyme for bacterial multiplication. This enzyme was purified in 1976 by Gellert and workers and named DNA gyrase (topoisomerase II) an essential enzyme involved in the replication, transcription and reparation of the bacterials DNA. DNA gyrase is composed of a tetramer of two GyrA and GyrB subunits each. Specifically, fluoroquinolones inhibit DNA gyrase bacterial type II and topoisomerase IV [2-6] (Fig. **2**). Topoisomerase IV is composed of a tetramer of two ParC and ParE subunits each. Topoisomerase IV is responsible for decatenation, that is removing the interlinking of daughter chromosomes, thereby allowing segregation into two daughter cells at the end of the replication round. After the use of nalidixic acid in 1962, bacterials showed a fast resistance to the older fluoroquinolones whereas topoisomerase IV is basically the primary target in Gram-positive bacteria with important implications in the development of resistance [7,8]. The efficacy of the new fluoroquinolones against resistant strains is due to their dual activity inhibiting both DNA gyrase bacterial type II and topoisomerase IV that limit the emergence of fluoroquinolones resistance (Fig. **2**).

A BRIEF HISTORY OF THE FLUORO-QUINOLONES

The history of fluoroquinolones began when Lescher, in 1962 [9], discovered, accidentally, nalidixic acid, 1-ethyl-4-oxo-1,8-naphthyridin-3-carboxylic acid (Fig. **2**) as a by-product during the synthesis of the antimalarial compound chloroquine (Fig. **3**). In 1963 nalidixic acid was approved by the FDA for the treatment of urinary tract infections with a moderate activity on Gram-negative bacteria. In 1970´s the quinolones cinoxacin, oxolinic acid and pipemidic acid (Fig. **3**) were employed with a little improvement in comparison with nalidixic acid. However, it was only during the 1980´s with the combination of a fluorine atom at position 6 and piperazinyl group at position 7 in the norfloxacin (Fig. **3**) that the importance of quinolones started [10-12]. This combination produced a broad spectrum of activity and better pharmacokinetic profile against Gram-negatives and some Gram-positives bacteria with antibacterial activities 1000 times more potent that those observed in the nalidixic acid.

After the discovery of Norfloxacin, a number of structure-activity relationships (SAR) (Fig. **4**) have been examined for the fluoroquinolone nucleus that produced new compounds of this class with further improvements, such as the solubility, antimicrobial activity, prolonged serum half-life, favorable adverse effect profiles and both oral and parenteral

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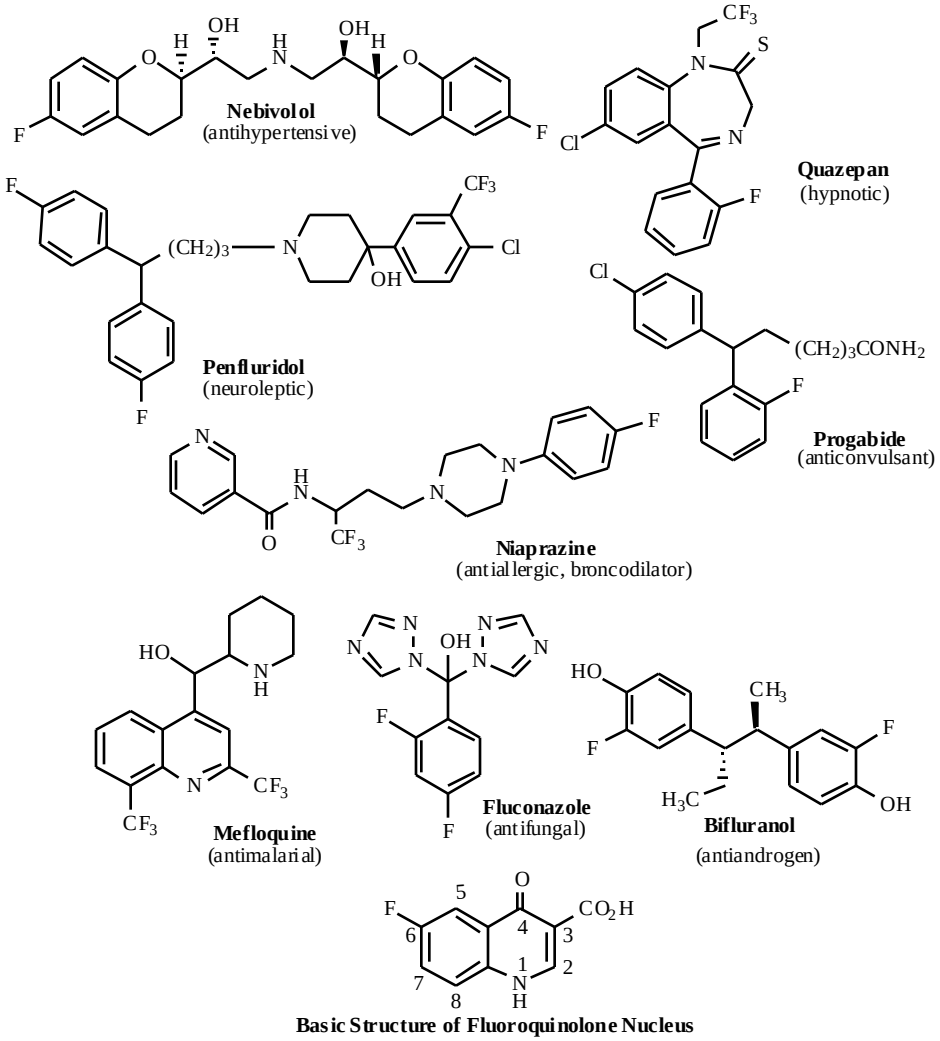
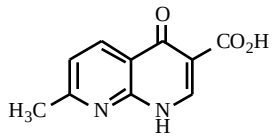


Fig. (1). Examples of fluorinated drugs and the basic structure of fluoroquinolone nucleus.

routes of administration [13-34]. Due to their efficacy, fluoroquinolones open a new era in the treatment of infectious diseases and today they are useful classes of synthetic antibacterial agents in clinical use.



Nalidixic acid

1-ethyl-4-oxo-1,8-naphthyridin-3-carboxylic acid
Year of FDA approval - 1963
Uncomplicated urinary tract infections

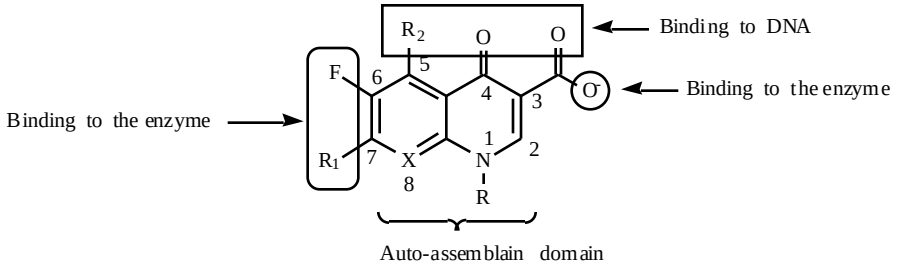


Fig. (2). Structure of nalidixic acid and the bacterial activity of fluoroquinolones by their inhibition of bacterial DNA gyrase and topoisomerase IV enzymes.

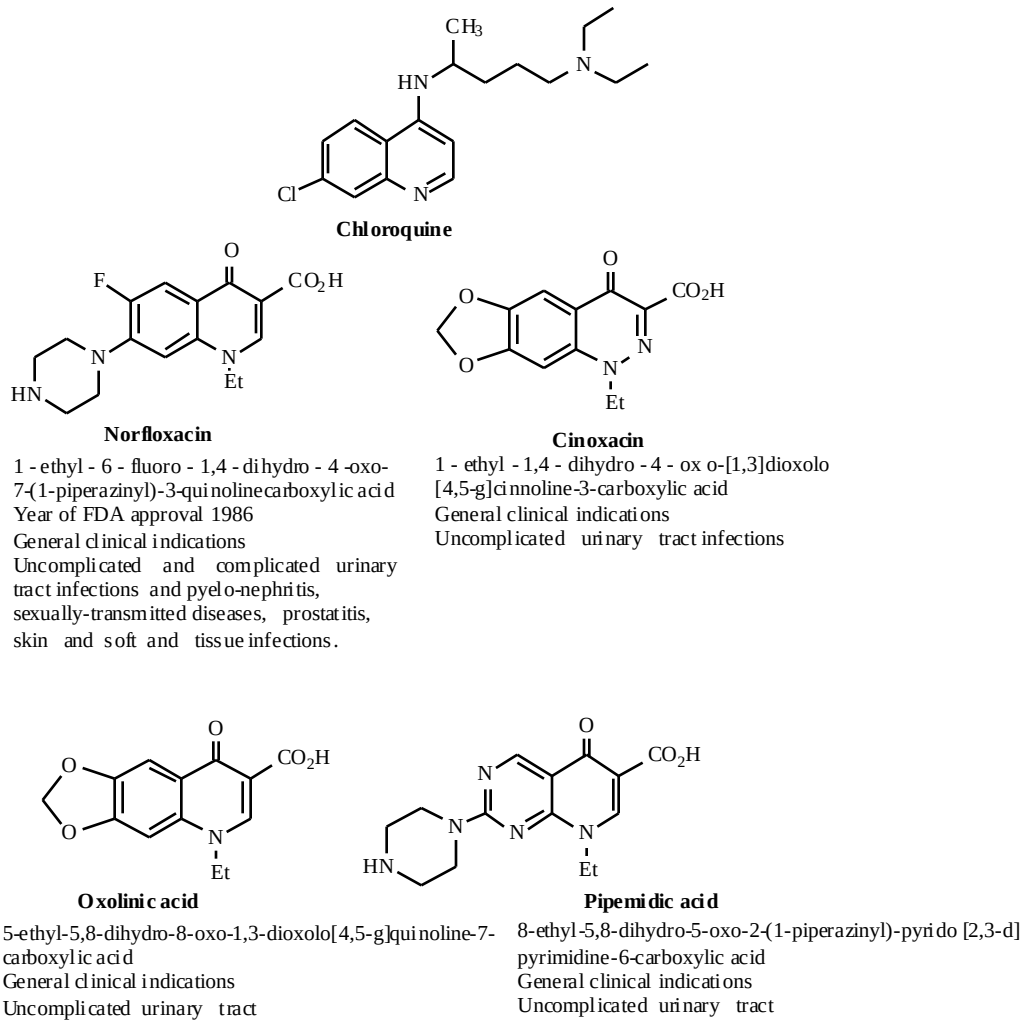


Fig. (3). Structure of chloroquine, norfloxacin, cinoxacin, oxolinic acid and pipemidic acid.

NEW FLUOROQUINOLONES

Basically the fluoroquinolones can be grouped in four generations. The first generation is represented by nalidixic acid and cinoxacin (Fig. **2** and **3**), the second one by norfloxacin (Fig. **3**), ciprofloxacin, ofloxacin, enoxacin and lomefloxacin, the third one by levofloxacin, sparfloxacin and gatifloxacin and, finally, the fourth generation is represented by moxifloxacin and trovafloxacin (Fig. **5**).

Recently, the fourth generation fluoroquinolones have attracted much attention due their fewer toxic effects, improved pharmacokinetic properties and extensive and potent activity against Gram-positive and Gram-negative bacteria, including resistant strains when compared with the earlier fluoroquinolones because they attack both DNA gyrase and topoisomerase IV [36]. Due to their excellent results a number of new forth generation fluoroquinolones have been discovered and will be covered in this review.

GARENOXACIN (BMS-284756 AND T3811)

Garenoxacin (1-cyclopropyl-8-difluoromethoxy)-7-[(1R)-(1-methyl-2,3-dihydro-1H-5-isoindolyl]-4-oxo-1,4-dihydro-

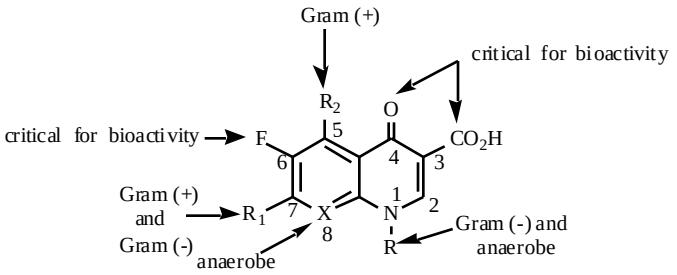
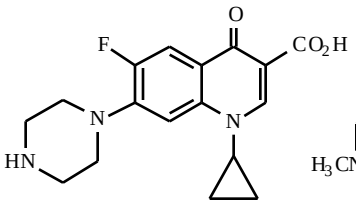
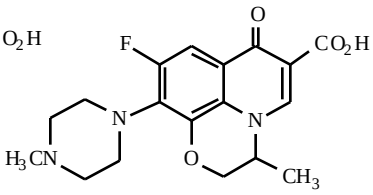


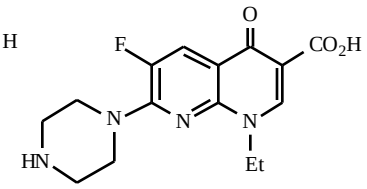
Fig. (4). Structure-activity relationships in fluoroquinolone nucleus.



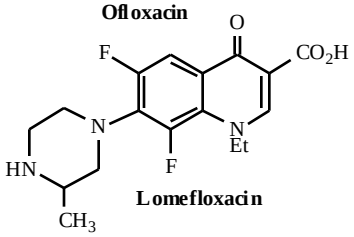
Ciprofloxacin



Ofloxacin



Enofloxacin



Lomefloxacin

Second Generation

1) **Ciprofloxacin** - 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid. Year of FDA approval - 1987.

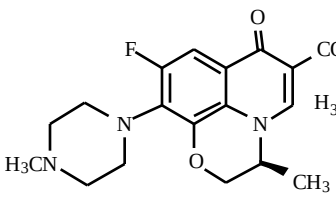
2) **Ofloxacin** - 9-fluor-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido [1,2,3,de]-1,4-benzoxazine-6-carboxylic acid.
Year of FDA approval - 1990.

3) **Enofloxacin** - 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid. Year of FDA approval - 1991.

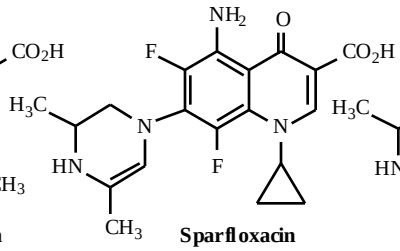
4) **Lomefloxacin** - (+-)-1-ethyl-6,8-difluoro,1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid. Year of FDA approval - 1992.

General clinical indications

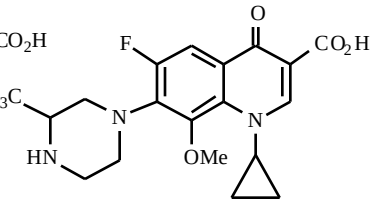
Uncomplicated and complicated urinary tract infections and pyelo-nephritis, sexually-transmitted diseases, prostatitis, skin and soft and tissue infections.



Levofloxacin



Sparfloxacin



Gatifloxacin

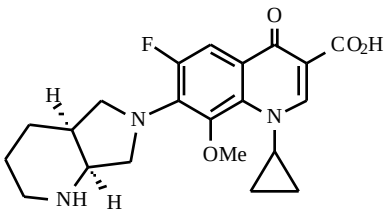
Third Generation

1) **Levofloxacin** - (S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid.
Year of FDA approval - 1996.

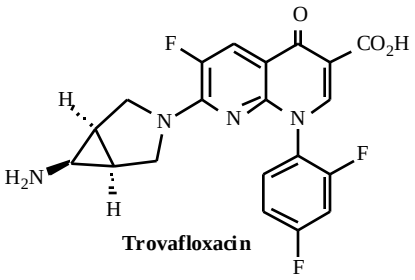
2) **Sparfloxacin** - cis-5-amino-1-cyclopropyl-7-(3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro- 4-oxo-3- quinolinecarboxylic acid.
Year of FDA approval - 1996.

3) **Gatifloxacin** - (+-)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4- oxo-3-quinolinecarboxylic acid.
Year of FDA approval - 1999.

General clinical indications Community-acquired pneumonia and acute exacerbations of chronic bronchitis.



Moxifloxacin



Trovafloxacin

Forth Generation

1) **Moxifloxacin** - 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H- pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid.
Year of FDA approval 1999.

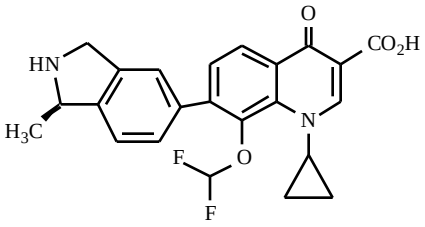
2) **Trovafloxacin** - (1α,5α,6α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid. **General clinical indications** Similar as the first to the third ones.

Fig. (5). The structures of second to fourth generations of fluoroquinolones.

Table 1. Spectrum of Fluoroquinolones Activity

Drug	Gram-positive	Gram-negative	Anaerobic species	STD organism	Pseudomonas species
Trovafloxacin	++	+++	+++	+++	++
Moxifloxacin	++	+++	++	+++	++
Gatifloxacin	++	+++	+	+++	++
Sparfloxacin	++	+++	+	+++	-
Levofloxacin	++	+++	+	+++	+++
Ciprofloxacin	+	++++	-	++	++++
Ofloxacin	+	+++	-	+++	+++

3-quinolinecarboxylic acid methane-sulfonate monohydrateý (Fig. **6**) is a new fluoroquinolone [37,38]. Garenoxacin displays excellent activity against a broad range of anaerobic pathogens and also against gram-positives microorganisms in comparison with the new fluorquinolones, which, in general, are predominantly active against Gram-negative pathogens. Garenoxacin also shows excellent oral bioavailability, potentials to prevent resistance development, toxicities and safety profiles [39-43].



Garenoxacin

Fig. (6). Structure of garenoxacin.

An important review was made by George G. Zhanel [44] that covers the *in vitro* microbiological activities of some the existing fluoroquinolones in comparison to garenoxacin. In general, garenoxacin showed great improvement against respiratory tract pathogens that was demonstrated by its low MIC_{90}s (Table **2**).

Recently, the *in vitro* activity of garenoxacin against *Staphyloccus aureus* and others clinically important gram-positive pathogens has been demonstrated by different groups. In the case of the *in vitro* efficacy against wild type *Staphyloccus aureus strains*, garenoxacin demonstrated better results in comparison with the others fluoroquinolones (Table **3**) [44].

DW-116

DW-116 [1-(5-fluoro-2-pyridyl)—fluoro-7-(4-methyl-1-piperazinyl)1,4-dihydro-4-oxoquinolone-3-carboxylic acid] (Fig. **7**) is a new fluoroquinolone developed by Dong-Wha Pharmaceutical Industry Co. (Anyang, Korea). The pharmacokinetics studies of DW-116 have shown a longer half-life, better absorption and higher drug concentration in tissue than the other fluoroquinolones. However, in despite of its good activity and profile, DW-116 may cause direct developmental toxicity in pregnant rats [45].

GEMIFLOXACIN (LB20304A OR SB-265805)

Gemifloxacin (Fig. **8**) is a new fluoroquinolone that possesses a pyrolidine ring in C-7 position, which bears an alkyloxime substituent in the 4-position and an aminomethyl substituent in the C-3 position [46,47]. This fluoroquinolone is extremely potent antimicrobial activity against both Gram-negative and Gram-positive organisms including resistant strains with remarkable activity against respiratory tract infections, such as *Monaxella catarrhalis*, *Haemophilu influenza* and *Str. pneumoniae*. For example, gemifloxacin particularly has the advantage against multi-drug resistant *S. pneumoniae* with the lowest MIC_{90} (4-64 lower) compared with ciprofloxacin and levofloxacin

Table 2. *In Vitro* Activities of Different Fluoroquinolones Against Respiratory Pathogens

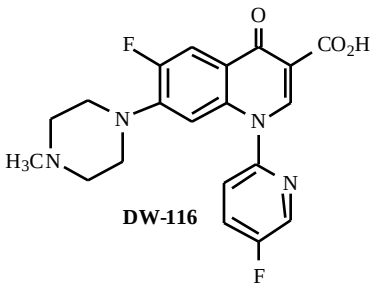
Respiratory pathogens (MIC_{90}; μg/ml)	Fluoroquinolones				
	Cipro	Levo	Gati	Moxi	Gareno
Mycoplasma Pneumoniae	1.4	0.05-1	0.25	0.12	0.06
Chlamydophila pneumoniae	1.0	0.5-1	0.25	0.06	0.008
Legionella pneumophila	0.03	0.016	0.03	0.016	0.06
Moraxella catarrhalis	0.03	0.06	0.03	0.12	0.03
Haemophilus influenzae	0.015	0.03	0.015	0.06	0.03
Streptococcus pneumoniae	2	1	0.5	0.25	0.03-0.06

Table 3. ***In Vitro*** **Activities of Different Fluoroquinolones Against Gram-Positive Cocci**

Fluorquinolone (MIC_{90}; μg/ml)[a]	MSSA	MRSA-CS	MRSA-CR	MRSA
Garenoxacin	0.03	0.12	4	2
Trovafloxacin	0.03	-	-	2
Moxifloxacin	0.06	0.25	8	2
Gatifloxacin	0.25	0.25	16	-
Levofloxacin	0.25	-	-	8
Ciprofloxacin	0.5	1	>32	32

[a]MSSA, methicillin-susceptible *S. aureus*; MRSA-CS, methicillin-resistant *S. aureus*, ciprofloxacin susceptible (MIC ≤ 2 μg/ml); MRSA-CR, methicillin-resistant *S. aureus*, ciprofloxacin resistant (MIC ≤ 4 μg/ml); MRSA, methicillin-resistant *S.aureus* (includes ciprofloxacin-susceptible and – resistant strains).

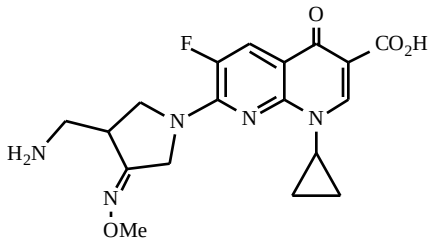
including the penicilin-resistant, macrolide-resistant, cipro-resistant and levofloxacin non-susceptible strain. In rats, gemifloxacin showed good bioavailablity (F = 95%), long serum half-life (t = 2.62 h) and it is well absorbed (AUC = 8.5 mg h/ml). Studies that have been made in dogs with gemifloxacin showed that it has a much longer serum half-life (t = 5.12 h) than ciprofloxacin (t = 1.7 h) [46,47].



DW-116

Fig. (7). Structure of DW-116.

Ball and co-workers have demonstrated that 320 mg of gemifloacin (equivalent to 400mg mesylate salt), that possess a better physicochemical properties, such as high water solubility and stability) administrated in 6775 patients once daily for between 5 and 14 days had a good margin of safety and tolerability profile similar to the others fluoroquinolones, β-lactam and macrolides.

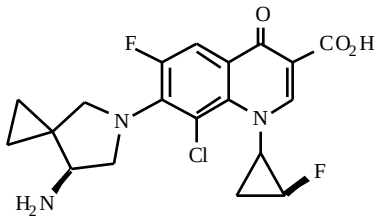


Gemifloxacin

Fig. (8). Structure of gemifloxacin.

SITAFLOXACIN (DU 6859)

The new N1-cyclopropyl fluoroquinolone Sitafloxacin (Fig. **9**) with chemical name (-)-7-[(7S)-7-amino-5-azaspiro [48-52] heptan-5-yl]-8-chloro-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid is being developed by Daiichi Pharmaceutical Co. Ltd. This fluoroquinolone is characterised by a cis-oriented (1R, 2S)-2-fluorocyclopropylamine moiety that is very important for reducing side effects and increasing pharmacokinetic profile. In comparison with some other currently fluoroquinolones, sitafloxacin has been shown to improve its antibacterial activity against Gram-positive, Gram-negative and anaerobic organisms with very potent bacterial activity against methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Bacteroides spp* [48-52]. This fluoroquinolone has also been shown to be effective against pneumonia caused by *Legionella pneumophila* and *S. pneumoniae* in mice, *Mycoplasma pneumoniae* in golden hamsters and *P. aeruginosa* in immunosuppressed guinea pigs [48-52]. The once-daily oral administration of sitafloxacin was designed at a dose of 200 mg, resulting in a mean C_{max} of 1.86 mg/L with a reported t1/2 in plasma of 4.6 h [48-52]. Recently sitafloxacin has been under phase III trials in Japan with oral and injectable formulations and this new fluoroquinolone is expected to be launched in 2006 [48-52].

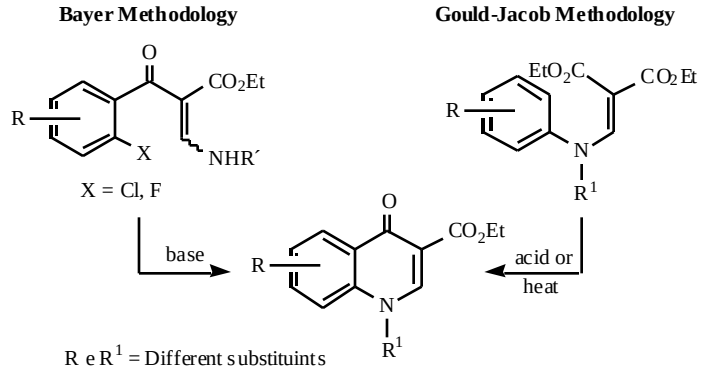


Sitafloxacin

Fig. (9). Structure of sitafloxacin

SYNTHETIC METHODOLOGIES FOR PREPARATION OF NEW FLUOROQUINOLONES

Basically, there are two principal strategies for the construction of the quinolin-4-one nucleus both proceeding *via* enaminones intermediates, the Bayer and the Gould-Jacobs route [53] (Scheme **1**). In the route developed by chemists at Bayer AG, [54-55] the quinolone nucleus is formed by base-induced cyclisation of 2-(2-halobenzoyl)-3-aminoacrylates. Gould-Jacobs cyclisation employs a thermal or acid-catalysed [56] of anilinomethylene malonates. This cyclisation is essentially a modification of the classical Conrad-Limpach synthesis of 4-quinolones from anilines and acetoacetic esters [57].



Scheme 1. Principal strategies for the construction of the quinolin-4-one nucleus.

SYNTHESIS OF SUBSTITUENTS AT THE C-7 POSITION

The optimum substituent at the C-7 position is crucial for the biological activity with impact on the potency, spectrum, solubility, pharmacokinetics and activity against resistant pathogens in the older and newer fluoroquinolones. Basically, the majority of fluoroquinolone C-7 substituents can be organized in three main categories: the piperazinyl, pyrrolidinyl and piperidinyl type side chains with different substituents (Fig. **10**).

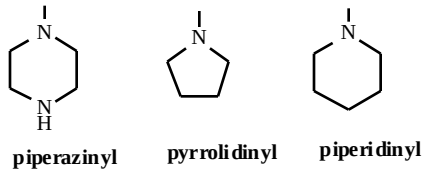
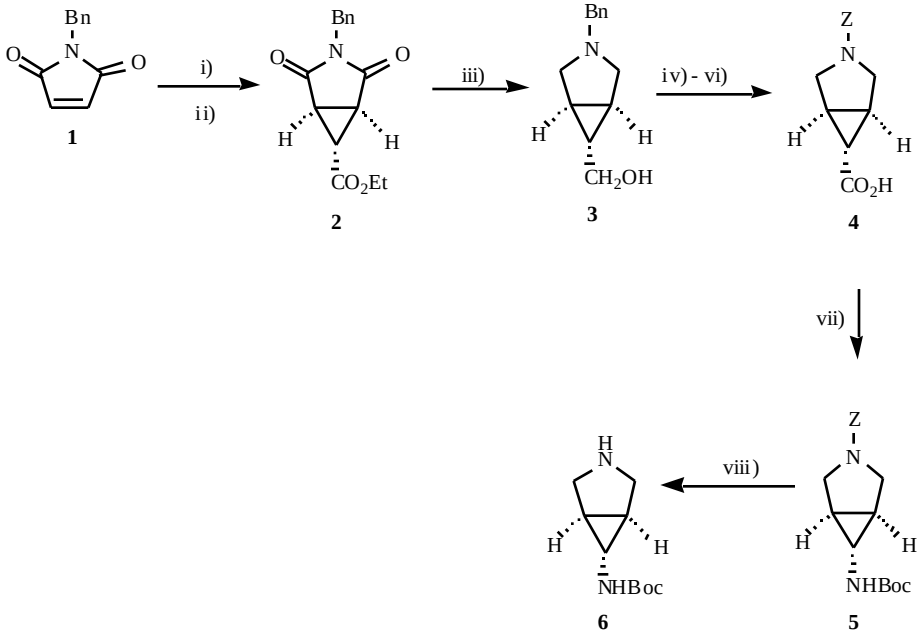


Fig. (10). Structure of the substituent at the C-7 position in the nucleus of fluoroquinolones: piperazinyl, pyrrolidinyl and piperidinyl.

Pyrrolidinyl System

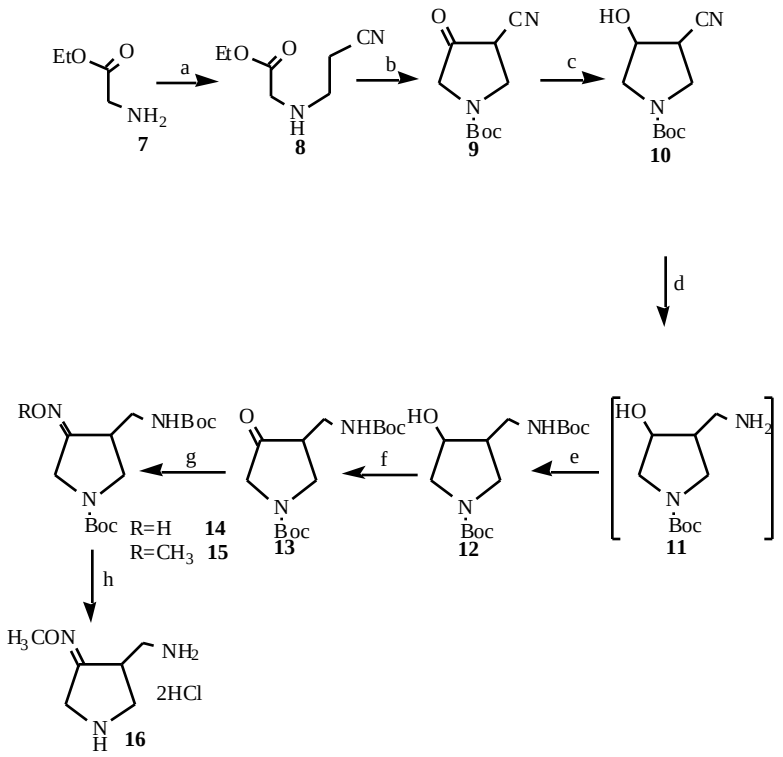
The pyrrolidinyl-based fluoroquinolones are presented in different new compounds of this class and display a more balanced spectrum against Gram-negative and Gram-positive bacterial, including resistant pathogens, such as the new fluoroquinolones trovafloxacin [58,59] (Fig. **5**), gemifloxacin [45] (Fig. **8**) and sitafloxacin [60] (Fig. **9**).

The synthesis of the pyrrolidinyl system in the trovafloxacin [58,59] was synthesized in eight steps (about 10% overall yield) from commercial *N*-benzylmaleimide **1** (Scheme **2**). The first step was the preparation of the 3-azabicyclo[3.1.0]hexane-6-carboxylic ethyl ester **2** in presence of the ethyl diazoacetate followed by heating the reaction (185^0C) for two hours. The group ester was reduced using $LiAlH_4$ followed by benzyl deprotection in presence of hydrogen and palladium, protection and oxidation using Jones reagent to furnish the intermediate **4**. The carboxylic acid **4** was transformed in amine and after Boc protection and deprotection using hydrogen and palladium the pyrrolinidyl system **6** was produced.



(i) N_2CHCO_2Et, Et_2O, rt, 23h; (ii)185°C, 2h; (iii) $LiAlH_4$, THF, reflux, 48h; (iv) H_2 – Pd-C, MeOH, 0°C, 23h; (v) K_2CO_3, ClC(O)OCH_2Ph (ZCl), 1:1 dioxane-H_2O, rt 15h; (vi) Jones reagent, acetone, 0^0C, then rt, 2h; (vii) *t*-BuOH, NEt_3, $(PhO)_2P(O)N_3$, reflux, 44h; (viii) $(Boc)_2O$, NEt_3, 9:1 dioxane – H_2O, rt, 4h (ix) H_2 – Pd-C, MeOH, 0°C, 5h.

Scheme 2. Synthesis of pyrrolidinyl system in trovafloxacin.



(a) CH_2CHCN, NaOH, 60 °C; (b) $(t\text{-BOC})_2O$, $CHCl_3$, then NaOEt, EtOH, reflux; (c) $NaBH_4$, EtOH, 0^0C; (d) $LiAlH_4$, THF, -5°C; (e) $(t\text{-BOC})_2O$, $NaHCO_3$, dioxane-H_2O; (f) pyridine-SO_3.Et_3N, DMSO, 5°C; (g) $RONH_2$.HCl, $NaHCO_3$, EtOH-THF; (h) HCl, MeOH, 0°C.

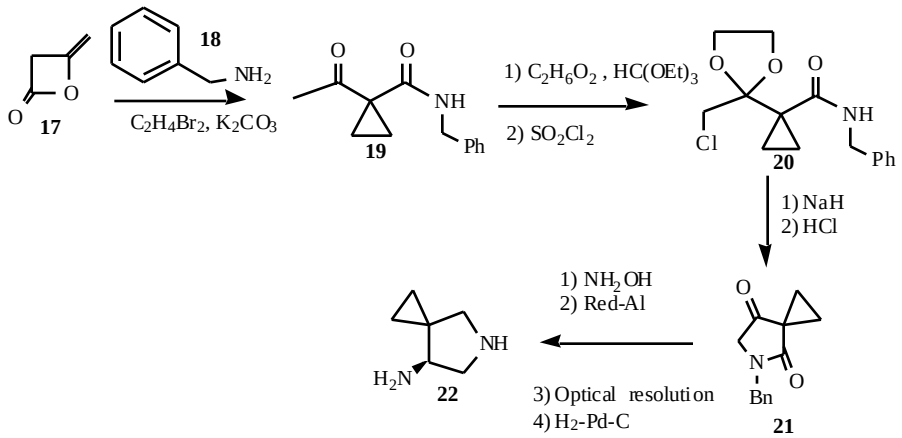
Scheme 3. Synthesis of methyloxime aminomethyl pyrrolidine in the C-7 position on gemifloxacin.

Methyloxime aminomethyl pyrrolidine present in the C-7 position on the gemifloxacin (Fig. **8**) is a key factor for its broad spectrum of activity. The synthesis of this fragment [46] (Scheme **3**) is based on the amino ester **7**. After condensation with acrylonitrile, Boc protection and cyclization furnished the intermediate **9**. This intermediate, after reduction in presence of sodium borohydride, lithium aluminum hydride and Boc protection, produced the compound **12** that was transformed in the intermediate key **16** after oxidation, oxime transformation and Boc deprotection.

The spiro-aminopyrrolidine **22**, the substituent of the C-7 position of sitafloxacin [60] (Fig. **9**) was synthesized (Scheme **4**) from diketene **17**, which was converted in the β-ketoamide **19**. After cyclopropanation of active methylene, the ketone was protected, converted in to chloride **20** and cyclised to the dioxopyrrolidine derivative **21** that was finally transformed to the spiro-aminopyrrolidine **22** (Scheme **4**).

CONCLUSION

The new fluoroquinolones have attracted much attention due to their fewer toxic effects, improved pharmacokinetic properties, ease of dosing, high concentration in respiratory secretions and extensive and potent activity against Gram-positive, Gram negative and mycobacterial organisms as well as anaerobes, including resistant strains. Based on the



Scheme 4. Synthesis of the spiro-aminopyrrolidine in the C-7 position of sitafloxacin.

SAR studies, new fluoroquinolones still have been planned and synthesized searching for more efficient compounds in the treatment of infectious diseases.

REFERENCES

[1] Smart, B. E. Journal of Fluorine Chemistry, **2004**, 109, 3.
[2] Drlica, K.; Zhao, X. *Microbiol. Mol. Biol. Ber.*, **1997**, *61*, 377.
[3] Barrett, J.F.; Sutcliffe, J.A.; Gootz, T.D. *Antimicrob. Agents. Chemother.*, **1990**, *34*, 1.
[4] Gellert, M.; Mizuuchi, K.; O´Dea, M.H.; Itoh, T.; Tomizawa, J.L. *Proc. Natl. Acad., Sci., USA* **1976**, *73*, 3872.
[5] Kato, J.; Nishimura, Y.; Imamura, R.; Niki, H.; Hiraga, S.; Suzuki, H. *Cell*, **1990**, *63*, 393.
[6] Christian, J. S. *Infec. Dis. Update*, **1996**, *3*, 87.
[7] Blondeau, J.M. *Clin. Ther*., **1999**, *21*, 3.
[8] Dougherty, T. J.; Beaulieu, D.; Barret, J. F. *DDT*, **2001**, *6*, 529.
[9] Lescher, G.Y.; Froelich, E.D.; Gruet, M.D.; Bailey, J.H.; Brundage, R.P. *J. Med. Pharmaceut. Chem.*, **1962**, *5*, 1063.
[10] Stratlon, S. *Clin. Ther*., **1992**, *14***,** 348.
[11] Appelbaum, P.C.; Hunter, P.A. *Int. J. Antimicrob. Ag.*, **2000**, *16*, 5.
[12] Sharma, A. K.; Khosla, R.; Kelaand, A. K.; Mehta, V. L. *Indian Journal Pharmacology*, **1999**, *26*, 249.
[13] Albrecht, R. *Prog. Drug. Res.*, **1977**, *21*, 9.
[14] Chu, D.T.; Fernandes, P.B. *Antimicrob. Agents Chemother.*, **1989**, *33*, 131.
[15] Matsumoto, J.I.; Nishimura, Y.; Minamida, A. *Chem. Pharm. Bull*., **1988**, *36*, 1223.
[16] Klopman, G.; Macina, O.; Levinson, M.E.; Rosenkraz, H.S. *Antimicrob. Agents Chemother.*, **1987**, *31*, 1831.
[17] Fujita, T. *The role of QSAR in drug design: fact or fantasy?*, Jolles, G.; Wooldridge, K.R.H., Academic Press: New York, **1984**.
[18] Chu, D.T; Fernandes, P.B. *Advances in Drug Research*, Academic Press: New York, **1991**, vol. 21, 39.
[19] Remuzon, P.; Bouzard, D.; Cesare, P.D.; Essiz, M.; Jacquet, J.P.; Kiechel, J.R.; Ledoussal, B.; Kessler R.E.; Fung-Tonc, J. *J. Med. Chem.*, **1991**, *34*, 29.
[20] Ohta, M.; Koga, H. *J. Med. Chem.*, **1991**, *34*, 131.
[21] Chu, D.T.; Nordeen, C.W.; Hardy, D.J.; Swanson, R.N.; Giardina, W.J.; Pernet, A.G.; Plattner, J.J. *J. Med. Chem.*, **1991**, *34*, 168.
[22] Kiely, J.S.; Hutt, M.P.; Culbertson, T.P.; Bucsh, R.A.; Worth, D.F.; Lesheski, L.E.; Gogliotti, R.D.; Sesnie, J.C.; Solomon, M.; Mich, T.F. *J. Med. Chem.*, **1991**, *34*, 656.
[23] Gootz, T.D.; Brighty, K.E. *Med. Res. Rev.*, **1996**, *16*, 433.
[24] Chu, D.T.W.; Fernandes, P.B. *Adv. Drug. Res.*, **1991**, *21*, 39.
[25] Asahima, Y. Ishizaki, T.; Suzue, S. *Prog. Drug. Res.*, **1992**, *38*, 57.
[26] Ma, Z.; Chu, D.T.W.; Cooper, C.S.; Li, Q.; Fung, A.K.L.; Wang, S.; Shen, L.L.; Flamm, R.K.; Nillus, A.M.; Alder, J.D.; Meulbroek, J.A.; Or, Y.S. *J. Med. Chem.*, **1999**, *42*, 4202.
[27] Jung, J.C.; Baek, S.; Park, O. S. *Il Farmaco*, **2001**, *56*, 665.
[28] Hubschwerlen, C.; Specklin, J. L.; Sigwalt, C.; Schroeder, S.; Locher, H. H. *Bioorg. Med. Chem. Lett.*, **2003**, *11*, 2313.
[29] Hubschwerlen, C.; Specklin, J. L.; Baeschlin, D. K.; Borer, Y.; Haefeli, S.; Sigwalt, C.; Schroeder, S.; Locher, H. H. *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 4229.
[30] Kerns, R. J.; Rybak, M. J.; Kaatz, G. W.; Vaka, F.; Cha, R. Grucz, R. G.; Diwadkar, V. U.; Ward, T. D. *Bioorg. Med. Chem. Lett*., **2003**, *13*, 1745.
[31] Hu, X. E.; Kim, N. K.; Gray, J. L.; Almstead, J. I. K.; Seibel, W. L.; Ledoussal, B. *J. Med. Chem.*, **2003**, *46*, 3655.
[32] Rameshkumar, N.; Ashokkumar, M.; Harihara, E.; Subramanian, H.; Ilavarasan, R.; Sridhar, S. K. *Eur. J. Med. Chem*., **2003**, *38*, 1001.
[33] Gordeev, M. F.; Hackbarth, C.; Barbachyn, M. R.; Banitt, L. S.; Gage, J. R.; Luehr, G. W.; Gomez, M.; Trias, J.; Morin, S. E.; Zurenko, G. E.; Parker, C. N.; Evans, J. M.; White, R. J.; Patel, D. V. *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 4213.
[34] Mather, R.; Karenchak, L. M.; Romanowski, E. G.; Kowalski, R. P. *American Journal of Ophthalmology*, **2002**, 463.
[35] Kowalski, R. P.; Dhaliwal, D. K.; Karenchak, L. M.; Romanowski, E. G.; Mah, F. S.; Ritterband, D. C.; Gordon, J. *American Journal of Ophthalmology*, **2003**, 501.
[36] Blondeau, J.M. *Clin. Ther*., **1999**, *21*, 3. b) Dougherty, T. J.; Beaulieu, D.; Barret, J. F. *DDT*, **2001**, *6*, 529.
[37] Takata, M.; Mitsuyama, J.; Yamshiro, Y.; Araki, H.; Yamada, H.; Hayakawa, H.; Todo, Y.; Minami, S.; Watanabe, Y.; Narita, H. *Abstract of the 37th Interscience Conference on Antimicrob. Agents Chmother*. American Society for Microbiology, DC, **1997**.
[38] Fung-Tomc, J. C.; Minassian, B.; Kolek, B.; Huczko, E.; Aleksunes, L.; Stickle, T.; Gradelski, E.; Vaera, L.; Bonner, D. P. *Antimicrob. Agents Chemother.*, **2000**, *44*, 3351.
[39] Jones, R. N.; Biedenbach, D. J. *Diagnostic Microbiology and Infectious Disease*, **2003**, *45*, 273.
[40] Kirby, J. T.; Mutnick, A. H.; Jones, R. N.; Biedenbach, D. J.; Pfaller, M. A. *Diagnostic Microbiology and Infectious Disease*, **2002**, *43*, 303.
[41] Fung-Tomc, Grandelski, E.; Valera, L.; Huczko, V. E.; Bonner, D. P. *International Journal of Antimicrobial Agents*, **2002**, *20*, 57.
[42] Roblin, P. M.; Reznik, T.; Hammershlag, M. R. *International Journal of Antimicrobial Agents*, **2003**, *21*, 578.
[43] Zhao, X.; Nathan, E.; Rosenthal, N. P.; Kreiwirth, B.; Drlica, K. *Antimicrobial Agents and Chemotherapy*, **2003**, 1023.
[44] Zhanel, G. G. *Clinicl Microbiology Newsletter*, **2003**, *25*, 153.
[45] Kim, J. C.; Shin, D. H.; Ahn, T. H.; Kang, S. S.; Song, S. W.; Han, J.; Kim, C. Y.; Ha, C. S.; Chung, M. K. *Food and Chemical Toxicology*, **2003**, *41*, 637.
[46] Hong, C.Y. *Il Farmaco*, **2001**, *56*, 41.
[47] Choi, D. R.; Shin, J. H.; Yang, J.; Yoon, S. H. *Bioorg. Med. Chem. Lett*., **2004**, *14*, 1273.
[48] Schmitz, F. J.; Fluit, A. C.; Milatovic, D.; Verhoel, J.; Heinz, H. P.; Brisse, S. *Journal of Antimicrobial Chemotherapy*, **2000**, *46*, 109.
[49] Milatovic, D.; Schmitz, F. J.; Brisse, S.; Verhoef, J.; Fluit, A. C. *Journal of Antimicrobial Chemotherapy*, **2000**, *44*, 1102.
[50] Onodera, Y.; Uchida, Y.; Tanaka, M.; Sato, K. *Journal of Antimicrobial Chemotherapy*, **1999**, *44*, 533.
[51] Giamarellou-Bourgoulis, E. J.; Sambatakou, H.; Grecka, P.; Chryssouli, Z.; Giamarellou, H. *Diagnostic Microbiology and Infectious Diseases*, **1999**, *34*, 301.
[52] Adis Comments; *Drugs in R&D*, **2003**, *4*, 61.
[53] Radl, S.; Bouzard, D. *Heterocycles*, **1992**, *34*, 2143.
[54] Grohe, K.J. *Prakt. Chem.*, **1993**, *335*, 397.
[55] Grohe, K.J.; Heitzer, H. *Liebigs Ann. Chem.*, **1987**, 29.
[56] Gould, R.J.; Jacobs, W.A. *J. Am. Chem. Soc.*, **1939**, *61*, 2890.
[57] Conrad, M.; Limpach, L. *Ber.*, **1887**, *20*, 944.
[58] Anquetin, G.; Rouquayrol, M.; Mahmoudi, N.; Santillana-Hayat, M.; Gozalbes, R.; Greiner, J.; Farhati, K.; Derouin, F.; Guedj, R.; Vierling, P. *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 2273.
[59] Brighty, K. E. U.S. Patent 5,229,396, 1992.
[60] Kimura, Y.; Atarashi, S.; Kawakami, K.; Sato, K.; Hayakawa, I. *J. Med. Chem.*, **1994**, *37*, 3344.