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## Quinolone Compounds with Activity Against Multidrug-Resistant Gram-Positive Microorganisms

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Additional information is available at the end of the chapter

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### Abstract

The emergence of resistance to antimicrobial agents is a global public health problem. Some microorganisms may develop resistance to a single antimicrobial agent (or related class of agent), while others develop resistance to several antimicrobial agents or classes. These organisms are often referred to as multidrug-resistant or MDR strains. Identification of new molecules that show activity against multidrug-resistant microorganisms and its development on a new antimicrobial drug, would be an important step in the fight against antimicrobial resistance. This paper presents experimental data regarding the synthesis of several quinolones. The novel compounds having quinolone structure were synthesized by Gould-Jacobs method. Their structure has been determined and confirmed by the following physicochemical methods: elemental analysis, IR spectral analysis, H-NMR, C-NMR, UV, thin layer chromatography. The new compounds have been evaluated for „in vitro” activity by determining minimum inhibitory concentration against a variety of bacteria. Some of new quinolones, which showed a good activity, have been tested against 30 strains of methicillin resistant *Staphylococcus aureus* isolated in the Microbiology Laboratory of INBI Prof. “Dr. Matei Bals” during 2012. The minimum inhibitory concentration (MIC) of the isolates have been determined by agar plate Mueller Hinton (bioMerieux) dilution method using the reference strain *Staphylococcus aureus* ATCC 29213. The 30 strains of isolated have been also tested for susceptibility to ciprofloxacin, levofloxacin and imipenem by Etest method. Based on the “in vitro” studies, the quinolone FPQ-30 appears to be a promising compound, all strains isolates were inhibited at a concentration of 8 µg/ml.

**Keywords:** Quinolones, fluoroquinolones, antimicrobial agents, Methicillin-resistant *Staphylococcus aureus*

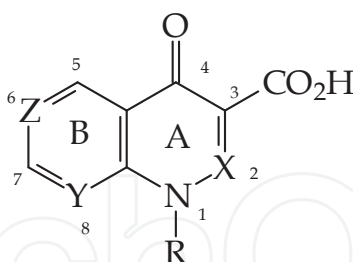
## 1. Introduction

The emergence of resistance to antimicrobial agents is a global public health problem. Some microorganisms may develop resistance to a single antimicrobial agent (or a related class of agents), while others develop resistance to several antimicrobial agents or classes. These organisms are often referred to as multidrug-resistant or MDR strains. Identification of new molecules that show activity against multidrug-resistant microorganisms and its development into a new antimicrobial drug would be an important step in the fight against antimicrobial resistance.

The discovery of fluoroquinolones after 1980 represented a decisive step forward for chemical anti-infectious therapy. A large number of fluoroquinolones are used today in medical practices and some of them are deemed by leading pharmacologists to be of vital importance to anti-infectious therapy.

## 2. Tendencies and strategies in the field of quinolones

The basic structure of quinolones (Figure 1) [9], is a bicyclic structure that contains a ring type A 4-pyridinone combined with an aromatic or heteroaromatic ring B. According to the nature of atoms symbolized by X, Y, Z, they can be defined as four subfamilies: naphthyridine 1-8, cinnoline, pyrido-2,3-pyrimidines, and quinolone.



naphthyridines : X=Z=H; Y=N  
 cinnolin: X=N; Y=Z=H  
 pyrido-2,3-pyrimidine: X=H; Y=Z=N  
 quinolones : X=Y=Z= H

**Figure 1.** Basic structure of quinolones.

The structural modifications of the core of the quinolone influence the antimicrobial activity

### 2.1. Position 1

Research has been oriented in several directions:

- Introducing an unsubstituted or substituted alkyl:  $R_1$  = methyl [32], ethyl [32, 28], *isopropyl* [28, 48, 1], *tert*-butyl [48, 14], fluoroethyl [28], hydroxyethyl [38], chloroethyl [38];
- Introduction of a vinyl, allyl [38, 32];
- Introduction of alkylamino groups [65];
- Introduction of a cyclopropyl [38, 56, 57, 49] or cyclobutyl [49, 1];
- Introducing mono or disubstituted phenyl [38, 7, 46, 49];
- Introduction of a five-membered aromatic heterocycles: pyrrolyl, [34].

Usually, the most active compounds contain the ethyl substituent in position 1. Using a STERIMOL program, Fujita (1984), based on a set of five parameters that characterize the shape and size of a substituent and following a quantitative analysis of the relationship between chemical structure and biological activity on a set of N-1 allyl and alkyl derivatives have deduced the optimum length of the substituent in position 1 is 0.42 nm [9, 58], which corresponds to the ethyl substituent. In general, the most active components contain in position 1 an ethyl substituent. These studies have already been confirmed by the results achieved with quinolones that are used in therapeutic practice: nalidixic acid, oxolinic acid, norfloxacin, pefloxacin, quinolones that have an ethyl substituent in N-1 position.

In Table 1 is presented the antimicrobial activity for the 1-substituted quinolones against gram positive and gram negative microorganisms. By comparison, data are entered for norfloxacin ( $R_1$  = ethyl) and ciprofloxacin ( $R_1$  =  $c\text{-C}_3\text{H}_5$ ).

Replacing ethyl substituent with:

- Sterically comparable substituents (2-fluoroethyl and vinyl) lead to compounds with comparable activity on gram negative bacteria, while replacing with substituent steric hindrance effect more or less pronounced (methyl, 2 hydroxy-ethyl, n-propyl, allyl, benzyl, cyclopropyl-methyl) leads to decreased activity of “in vitro”.
- *Tert*-butyl substituent leads to compounds that possess good antimicrobial activity against *Staphylococcus aureus*, while against gram negative microorganisms, the activity is comparable to the reference compound (norfloxacin). Increasing the number of carbon atoms (number of carbon atoms > 4) results in decreased antimicrobial activity. The replacement of a hydrogen by fluorine atom leads to the increase of antibacterial activity two to three times compared to the compound where  $R_1$  = *tert*-butyl, while introducing more fluorine atoms leads to a decrease in the antimicrobial activity.

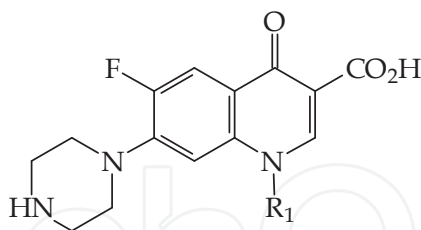
In series N-1 cyclopropyl (ciprofloxacin), the substituent from N-1 position has a larger volume than the ethyl. This is contrary to the concept of the steric volume. High antimicrobial activity of the ciprofloxacin may be caused by this hyperconjugation or self-association properties induced by the cyclopropyl. For compounds that present in this position, a cycloalkyl with a number of carbon atoms of more than 3 (cyclobutyl, cyclopentyl) the antimicrobial activity is much reduced compared to ciprofloxacin.

The following are relevant for the chemical structure–biological activity relationships:

- The nature of the substituent introduced in the alkyl moiety at N-1 position of quinolone: the fluorine atom has benefic influence on the antimicrobial activity;
- The position where the substituents are introduced in the alkyl moiety: substituents in position 1 of the alkyl moiety have positive influence on antimicrobial activity;
- The number of substituents placed on the alkyl moiety: increasing the number of substituents leads to decreased antimicrobial activity;
- Presence of cis-trans stereoisomers: cis derivatives are more active against gram positive bacteria than the trans derivatives, while the activity is comparable against gram negative bacteria.

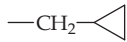
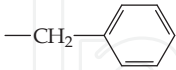


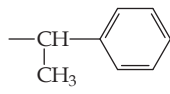


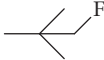
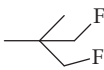

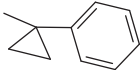

Relevant for the chemical structure–biological activity relationships are to:





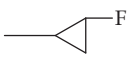



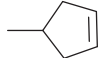

- Nature of the substituent introduced in the alkyl moiety at N-1 position of quinolone: the fluorine atom has benefic influence on the antimicrobial activity;
- The position where the substituents are introduced in the alkyl moiety: substituents in position 1 of the alkyl moiety have positive influence on antimicrobial activity;
- The number of substituents placed on the alkyl moiety: increasing the number of substituents leads to decreased antimicrobial activity;
- Presence of cis-trans stereoisomers: cis derivatives are more active against gram positive bacteria than the trans derivatives, while the activity is comparable against gram negative bacteria.



**Figure 2.** Quinolones with an aliphatic substituent in N-1 position.

R <sub>1</sub>	Minimum inhibitory concentration (µg/ml)			Reference
	<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
-CH <sub>3</sub>	6.25	0.39	1.56	(Koga et al. 1980)
-C <sub>2</sub> H <sub>5</sub> (Norfloxacin)	0.39	0.05	0.39	(Koga et al. 1980)
-CH=CH <sub>2</sub>	3.13	0.10	0.39	(Koga et al. 1980)
n-C <sub>3</sub> H <sub>7</sub>	1.56	0.20	3.13	(Koga et al. 1980)

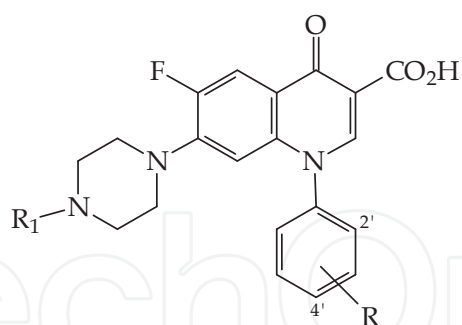
R <sub>1</sub>	Minimum inhibitory concentration (µg/ml)			Reference
	<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
	1.00	0.50	4.00	(Bouzard et al. 1989)
	1.56	0.78	1.56	(Koga et al. 1980) (Bouzard et al. 1989)
	1.00	0.50	1.00	(Bouzard et al. 1989)
	0.50	0.13	0.50	(Bouzard et al. 1989)
	4.00	2.00	32.00	(Bouzard et al. 1989)
	0.25	0.06	0.50	(Remuzon et al. 1991)
	0.25	0.50	4.00	(Bouzard et al. 1989)
	0.13	0.016	0.25	(Remuzon et al. 1991)
	1.00	0.13	1.00	(Remuzon et al. 1991)
-CH <sub>2</sub> CH <sub>2</sub> F	1.56	0.10	0.78	(Koga et al. 1980)
-CH <sub>2</sub> CH <sub>2</sub> OH	1.56	0.39	3.13	(Koga et al. 1980)
-NH-CH <sub>3</sub>	1.95	1.00	1.00	(Koga et al. 1980) (Wentland et al. 1984)
-CH <sub>2</sub> -CH=CH <sub>2</sub>	3.13	0.20	1.56	(Koga et al. 1980)
 (Ciprofloxacin)	0.13	0.03	0.013	(Chu&Fernandes 1991)
	0.13	0.13	4.00	(Bouzard et al. 1989)
	0.25	0.06	0.50	(Bouzard et al. 1989)

R <sub>1</sub>	Minimum inhibitory concentration (µg/ml)			Reference
	<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
 (trans)	1.00	0.06	2.00	(Bouzard et al. 1989)
 (cis)	0.13	0.13	1.00	(Bouzard et al. 1989)
	1.00	1.00	32.00	(Bouzard et al. 1989)
 (cis)	0.10	≤0.05	≤0.05	(Youichi et al. 1994) (Shongo et al. 1993)
 (trans)	0.78	≤0.05	0.10	(Youichi et al. 1994) (Shongo et al. 1993)
	0.50	0.13	1.00	(Bouzard et al. 1989)
	4.00	2.00	32.00	(Bouzard et al. 1989)
	0.50	0.25	8.00	(Bouzard et al. 1989)
	2.00	1.00	8.00	(Bouzard et al. 1989)
	8.00	2.00	63.00	(Bouzard et al. 1989)

**Table 1.** MIC values (µg/ml) for quinolones with an aliphatic substituent in N-1 position

It is obvious that the volume of the substituent at position N-1 is not the only factor influencing the antibacterial activity of the quinolones. There are other factors that have a considerable influence on biological activity such as, for example, the effects of conjugation, conformational effects. This has been demonstrated by the synthesis of compounds containing aryl substituents in N-1 position [32, 7, 8, 46].

In Table 2 are presented data on the antimicrobial activity of 7-piperazinyl and 7- (4-methylpiperazinyl)-quinolone derivatives having substituted or unsubstituted aryl substituents in N-1 position.



**Figure 3.** Aryl-quinolones.

Compound	R	R <sub>1</sub>	Minimum inhibitory concentration ( $\mu\text{g/ml}$ )			Reference
			<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
Norfloxacin			0.39	0.05	0.39	2
1	H	H	0.20	0.78	0.78	(Chu et al. 1985)
Sarafloxacin	4-F	H	0.20	0.05	0.39	(Chu et al. 1985)
2	H	CH <sub>3</sub>	0.78	0.78	6.20	(Chu et al. 1985)
3	2-F	CH <sub>3</sub>	1.56	0.78	6.20	(Chu et al. 1985)
4	3-F	CH <sub>3</sub>	12.50	6.20	50.00	(Chu et al. 1985)
Difloxacin	4-F	CH <sub>3</sub>	0.20	0.20	1.56	(Chu et al. 1985)
5	4-Br	CH <sub>3</sub>	3.10	6.20	50.00	(Chu et al. 1985)
6	4-Cl	CH <sub>3</sub>	1.56	1.56	12.50	(Chu et al. 1985)
7	4-OH	CH <sub>3</sub>	0.05	0.10	0.39	(Chu et al. 1985)
8	4-OCH <sub>3</sub>	CH <sub>3</sub>	1.50	50.00	200.00	(Chu et al. 1985)
9	4-CH <sub>3</sub>	CH <sub>3</sub>	1.56	1.56	12.50	(Chu et al. 1985)
10	3,4-OCH <sub>2</sub> O-	CH <sub>3</sub>	0.75	0.78	6.20	(Chu et al. 1985)
11	2-F,4v-F	CH <sub>3</sub>	0.10	0.20	1.56	(Chu et al. 1985)
12	2'-CH <sub>3</sub>	CH <sub>3</sub>	3.10	1.56	25.00	(Chu et al. 1985)
13	2-CH <sub>3</sub> ,4CH <sub>3</sub>	CH <sub>3</sub>	100.00	100.00	100.00	(Chu et al. 1985)
14	4-NO <sub>2</sub>	CH <sub>3</sub>	64.00	8.00	128.00	(Radl & Zikan 1989)
15	4-NH <sub>2</sub>	CH <sub>3</sub>	2.00	1.00	32.00	(Radl & Zikan 1989)

**Table 2.** The “in vitro” antibacterial activity of 1-aryl-quinolones



For 7-*piperazinyl quinolones*, the introduction of an unsubstituted aryl affords a compound (compound 1 – Table 2) with good antimicrobial activity “in vitro” against *S. aureus* being more active than the reference compound, norfloxacin.

The presence of a substituent on the aryl nucleus leads to improved antimicrobial activity, e.g. a fluorine atom (sarafloxacin) in the 4-position of the phenyl ring.

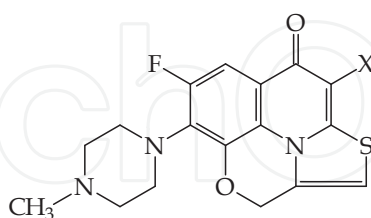
In the series 7-(4-methyl-piperazinyl)-1-aryl-quinolones the best results are obtained when in position 4 is located a fluorine atom (for example, difloxacin) or -OH (compound 7). Good results are also obtained in the case of two substituents present (positions 2 and 4) on the aryl nucleus (R = F) (compound 11).

## 2.2. Position 2

Some changes were explored for this position [9]. Replacing the carbon atom of oxolinic acid with a nitrogen atom (which led to cinoxacin) has resulted in improved pharmacokinetic properties, but has led to decreased antimicrobial activity “in vitro”. Significant reductions in bacterial activity were also observed in the case of 2-aza-4-quinolones derivatives from norfloxacin and pefloxacin. The introduction of substituents on the carbon atom in position 2, for example, hydroxy, methyl, methylthio, etc., leads to the inactivation of the quinolone compounds.

## 2.3. Position 3

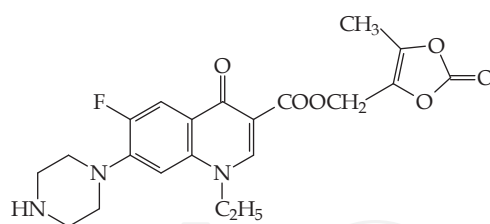
In the quinolone molecule, combination between carboxyl group from 3 position and ketone group in 4 position, is considered necessary for binding to DNA gyrase, while the presence of carboxyl group in 3 position is essential for antimicrobial activity. Modification of carboxyl groups, generally leads to obtaining biologically inactive compounds (Figure 4) [62]. The exceptions are groups that can be converted “in vitro” to the carboxyl function.



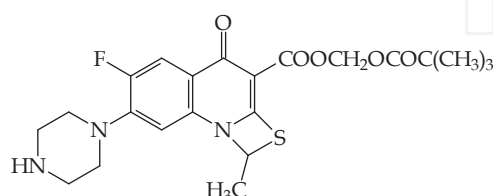
**Figure 4.** X = H, 4b: X = SO<sub>3</sub>H

The researches regarding changes of the substituent in the 3 position of quinolone, followed to obtain:

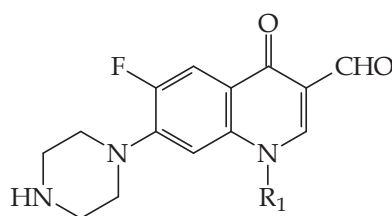
- Compounds presenting free carboxyl group;
- Bioreversible compounds (prodrugs) ester (Figures 5, 6), [59, 51], which easily hydrolyzed in the body releasing the carboxyl group;



**Figure 5.** Methyl-2-oxo-1,3-dioxol-4-yl ethyl ester

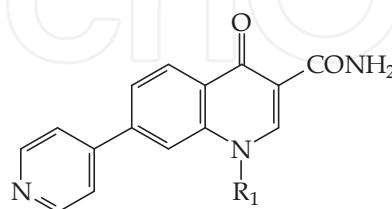


**Figure 6.** Pivaloiloxymethyl ester



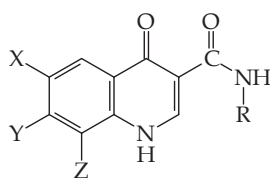
**Figure 7.**  $R_1$  = ethyl, cyclopropyl,  $R$  = H, methyl

- Bioreversible derivatives (prodrugs) - 3-formyl-quinolone (Figure 7) [31];
- Quinolone-3-carboxamide: (Wetland et al. 1993), (Sajay et al. 2000).



**Figure 8.**  $R_1$  = alkyl, mono or disubstituted phenyl

Both types of structures (Figures 8 and 9) have been hydrolyzed in the body; carboxyl group has been generated; and through this the biological activity was explained, with the observation that the time to reach that MICs is greater.



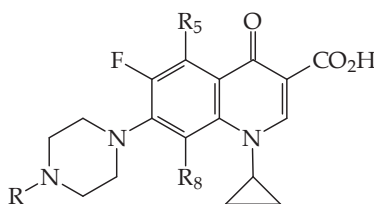
**Figure 9.** X = H, Cl, F, NO<sub>2</sub>, Y = H, Cl, NO<sub>2</sub>, Z = H, CH<sub>3</sub>, F, R = cyclopropyl, n-octyl, (N, N-diethylamino-1-methyl) butyl

## 2.4. Position 4

The quinolone structure requires the presence of the ketone group in position 4. Replacing this ketone group, the 4-thiooxo or 4-sulfonyl groups led to obtaining inactive compounds [9].

## 2.5. Position 5

In position 5 of the quinolones various groups were introduced, such as nitro (Domagala et al. 1988) unsubstituted or substituted amino [27, 16, 36] [17], alkyl [23, 25], halogen [35, 36], mercapto [35, 36], hydroxy [36, 17], alkoxy or tioalcooxi [35, 36]



**Figure 10.** Substituted quinolones.

R	R <sub>5</sub>	R <sub>8</sub>	Minimum inhibitory concentration (µg/ml)			Reference
			<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
H	H	H	0.2	0.013	0.4	(Domagala et al.1991)(*)
H	NH <sub>2</sub>	H	0.025	0.013	0.8	(Domagala et al.1991)(*)
H	NH <sub>2</sub>	F	0.013	0.013	0.025	(Domagala et al.1991)(*)
			0.013	0.013	0.025	(Domagala et al.1988)(*)
			0.050	0.0063	0.1	(Myamoto et al. 1990) 74(**)
H	CH <sub>3</sub> NH	F	0.2	0.1	1.6	(Domagala et al.1988)(*)
H	AcNH	F	>25	>25	>25	(Domagala et al.1988)(*)
H	NH <sub>2</sub>	Cl	0.025	0.025	0.8	(Domagala et al.1991)(*)
H	HO	H	0.2	0.025	0.4	(Domagala et al.1991)(*)

R	R <sub>5</sub>	R <sub>8</sub>	Minimum inhibitory concentration ( µg/ml)			Reference
			<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
H	HO	F	0.2 0.2	0.05 0.025	0.8 0.39	(Myamoto et al. 1990) (**)
H	CH <sub>3</sub>	H	0.025	0.013	0.2	(Hagen et al. 1991) (*)
H	CH <sub>3</sub>	F	0.025	0.025	0.2	(Hagen et al. 1991) (*)
H	CH <sub>3</sub>	Cl	0.025	0.025	0.2	(Hagen et al. 1991) (*)
H	C <sub>2</sub> H <sub>5</sub>	H	6.30	0.4	12.5	(Hagen et al. 1991) (*)
H	F	F	0.2	0.0125	0.39	(Myamoto et al. 1990) (**)
H	Cl	F	0.1	0.0125	0.39	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	H	F	0.2	0.025	0.39	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	F	F	0.39	0.05	0.78	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	Cl	F	0.2	0.025	0.78	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	Br	F	0.39	0.05	0.78	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	HO	F	0.2	0.05	0.78	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	CH <sub>3</sub> O	F	25	0.2	12.5	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	PhCH <sub>2</sub> O	F	6.25	1.56	6.25	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	HS	F	3.13	0.39	12.5	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	CH <sub>3</sub> S	F	3.13	0.2	12.5	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	4-CH <sub>3</sub> OPhCH <sub>2</sub> S	F	100	12.5	>100	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	NH <sub>2</sub>	F	0.1	0,0125	0.2	(Domagala et al.1988)( *)
			0.013	0.025	0.1	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	CH <sub>3</sub> NH	F	0.78	0.1	1.56	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> N	F	25	3,3	50	(Domagala et al.1988)
			>25	>25	>25	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	PhCH <sub>2</sub> NH	F	0.78	0.78	3.13	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	HOCH <sub>2</sub> CH <sub>2</sub> NH	F	0.39	0.5	0.78	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> NH	F	6.25	0.05	0.78	(Myamoto et al. 1990) (**)
CH <sub>3</sub>	pyrrolyl	F	3.13	0.39	12.5	(Myamoto et al. 1990) (**)

Ciprofloxacin ; \* *S. aureus* UC 76 ; \* *E. coli* Vogel; \* *P. aeruginosa*.UI-18; \*\**S. aureus* 209P JC-1 ; \*\**E. coli* NIIIJ JC-2; \*\**P. aeruginosa* 12

**Table 3.** The “in vitro” antibacterial activity of 5-substituted quinolones

In the series of *1-cyclopropyl-7-piperazinyl quinolones*, the influence of the substituent in position 5 on the antimicrobial activity is manifested as follows:

- The introduction of unsubstituted amino group when  $R_8 = H$  leads to increased antibacterial activity against gram positive only, while when  $R_8 = F$  or  $Cl$  leads to the increase of antibacterial activity on gram positive and gram negative microorganisms.
- The introduction of substituted amino group leads to the lowering of antimicrobial activity on the entire microbial spectrum.
- The introduction of the hydroxy group ( $R_8 = H, F$ ), does not produce any change in the antibacterial activity.
- The introduction of the methyl group ( $R_8 = H, F, Cl$ ) causes increased activity on the entire microbial spectrum.
- The introduction of an alkyl radical having a carbon number greater than 2 leads to decreased antimicrobial activity.
- The introduction of a halogen atom:
- For  $R_5 = F$  ( $R_8 = F$ ) – the antimicrobial activity remains unchanged on the entire microbacterial spectrum.
- For  $R_5 = F$  ( $R_8 = F$ ) – antibacterial activity is improved against gram positive bacteria).

In the series of *1-cyclopropyl-7-(4-methyl-piperazinyl)-quinolones*, the influence of the substituent in position 5 on the antimicrobial activity is manifested as follows:

- The introduction of an unsubstituted amino group ( $R_8 = F$ ) leads to increased antibacterial activity against gram positive and gram negative microorganisms; the alkylation of the amino group leads to the lowering of antimicrobial activity on the entire microbial spectrum, the decrease being dependent on the size of the alkyl group (especially dialkylating lead to a loss of antibacterial activity).
- The introduction of a halogen atom (fluorine or bromine) ( $R_8 = F$ ) leads to the slight decrease of activity compared to the unsubstituted compound; the introduction of a chlorine atom decreases antibacterial activity only against *Pseudomonas aeruginosa*.
- The introduction of a hydroxy group does not modify the biological activity. The introduction of a methoxy or benzyloxy group leads to decreasing of the antimicrobial activity against all tested microorganisms.
- The introduction of a mercapto group leads to a considerable decrease of the antimicrobial activity on the entire microbial spectrum. The same decrease is found in the case of methylthio group.
- The presence of a bulky substituent leads to the loss of biological activity against all microorganisms tested.

### 2.5.1. In conclusion

In the case of 1-cyclopropyl-7-piperazinyl-quinolones, antibacterial activity increases according to the nature of the substituent in position 5, in the following order:

For  $R_8 = H$  :  $RO < HO < NH_2 < CH_3$ ;

For  $R_8 = F$  :  $HO \leq F \leq Cl < CH_3 < F$

In the case of 1-cyclopropyl-7-(4-methyl-piperazinyl)-8-fluoro-quinolones, antibacterial activity increases according to the nature of the substituent in position 5, in the following order:

$R_2N < RH < SH < RO < RNH < Br F \leq HO \leq Cl < NH_2$

### 2.6. Position 6

The nature of the substituent from this position influences the inhibition activity of DNA gyrase and cell penetration.

In this position the following substituents have been introduced: H, F, Cl, Br,  $CH_3$ ,  $NO_2$ ,  $NH_2$  [32, 5, 7, 34, 29, 4, 5].

The introduction of a fluorine atom in this position has lead to a spectacular increase of the antibacterial activity, compared to unsubstituted compound ( $R_6 = H$ ) (activity of norfloxacin against *E. coli*  $R_6 = F$ , is 16 times higher than the nonfluorinated compound in position 6) (Table 6).

Regarding the importance of the presence of fluorine atom in position 6 of the quinolone, other authors (Ledoussant et al. 1992) have reported that this is essential for the activity of the quinolone compounds.

$R_6$	Minimum inhibitory concentration ( $\mu g / ml$ )			Reference
	<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
H	12.50	0.78	3.13	(Koga et al. 1980)
F: Norfloxacin	0.39	0.05	0.39	(Koga et al. 1980)
Cl	1.56	0.20	3.13	(Koga et al. 1980)
Br	3.13	0.39	1.50	(Koga et al. 1980)
$CH_3$	3.13	0.39	6.25	(Koga et al. 1980)
$SCH_3$	25.00	0.78	12.50	(Koga et al. 1980)
$COCH_3$	100.00	100.00	100.00	(Koga et al. 1980)
CN	12.50	0.39	6.25	(Koga et al. 1980)
$NO_2$	25.00	0.78	12.50	(Koga et al. 1980)

**Table 4.** The “in vitro” antibacterial activity of 6 substituted quinolones

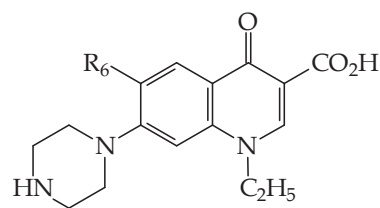
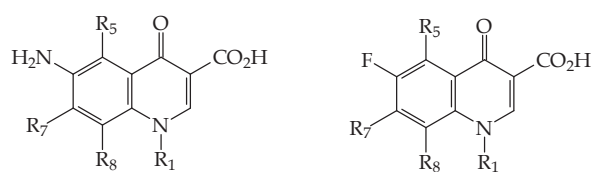


Figure 11. Substituted quinolones.

There have been synthesized compounds containing an amino group at position 6 [3-5]. A direct comparison between 6-amino-quinolones and 6-fluoro-quinolones shows a decrease of antimicrobial activity of 6-amino-quinolones of about 28–300 times (Table 7). The antimicrobial activity of 6-amino-quinolones can be improved by optimizing the chemical structure through the introduction of various substituents in other positions of the quinolones core.

	R <sub>1</sub>	R <sub>5</sub>	R <sub>7</sub>	R <sub>8</sub>	Minimum inhibitory concentration (µg/ml)			Reference
					<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
1 a	-c-C <sub>3</sub> H <sub>5</sub>	H	Piperazinyl	H	0.25	64.00	2.00	(Cechetti et al. 1995)
2 a	-c-C <sub>3</sub> H <sub>5</sub> <i>ciprofloxacin</i>	H	Piperazinyl	H	0.12	0.03	0.06	(Cechetti et al. 1995)
1 b	-c-C <sub>3</sub> H <sub>5</sub>	H	4-Methyl-piperazinil	H	0.25	2.00	4.00	(Cechetti et al. 1995)
1 c	-c-C <sub>3</sub> H <sub>5</sub>	H	Tiomorpholiny	F	0.12	0.25	4.00	(Cechetti et al. 1995)
1 d	-c-C <sub>3</sub> H <sub>5</sub>	NH <sub>2</sub>	4-Methyl-piperazinyl	H	128	16	128	(Cechetti et al. 1995)
1 e	-c-C <sub>3</sub> H <sub>5</sub>	NH <sub>2</sub>	4-Methyl-piperazinyl	F	2	0.03	4	(Cechetti et al. 1995)
1 f	-c-C <sub>3</sub> H <sub>5</sub>	H	4-Methyl-piperazinyl	F	4	1	2	(Cechetti et al. 1995)
1 g	t-Bu	H	4-Methyl-piperazinyl	H	2	0.06	2	(Cechetti et al. 1995)
1 h	4-FC <sub>6</sub> H <sub>4</sub>	H	4-Methyl-piperazinyl	H	8	0.12	8	(Cechetti et al. 1995)

Table 5. The “in vitro” antibacterial activity of 6-amino-quinolones.



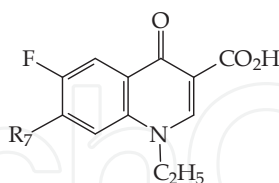
**Figure 12.** Amino-quinolones and 6-fluoro-quinolones.

## 2.7. Position 7

Modifications in position 7 have been the most intensively studied; studies have shown that the nature of the substituent from this position has a great influence on the biological potential, antibacterial spectrum, solubility, and on the pharmacokinetics (bioavailability). Research has been focused in the following areas: introduction of piperazinyl, mono or disubstituted piperazinyl, morpholinyl or thiomorpholinyl, pyrrolidinyl, piperidinyl, azetidiny, bicyclic heterocycles, 4-pyridinyl.

Influence of the nature of the substituent in position 7 on the antibacterial activity is closely related to the nature of the substituents from the other positions of the quinolones core, especially the nature of the substituents at the nitrogen in position 1.

For *1-ethyl-6-fluoro-7-substituted-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid* (Table 6), it was observed that the best influence on antimicrobial activity is the introduction of a piperazinyl group (norfloxacin). Introducing the piperazinyl group in position 7 of the quinolone ring leads to a product with a higher antibacterial potential. The antibacterial spectrum of norfloxacin includes both gram positive and gram negative bacteria, in particular more strains of *P. aeruginosa*.



**Figure 13.** Ethyl-7-substituted-quinolones.

R <sub>7</sub>	Minimum inhibitory concentration (μg/ml)			Reference
	<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
Chlor	12.50	1.56	100.00	(Koga et al.1980)
Methyl	6.25	0.39	5000	(Koga et al.1980)
Amino	100.00	3.13	100.00	(Koga et al.1980)



R <sub>7</sub>	Minimum inhibitory concentration (µg/ml)			Reference
	<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
Methylamino	12.50	3.10	100.00	(Koga et al.1980)
Dimethylamino	0.78	0.39	50.00	(Koga et al.1980)
S(CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>	25.00	0.80	3.10	(Chu & Fernandes 1991)
Piperazinyl (norfloxacin)	0.39	0.05	0.39	(Koga et al.1980)
4-Methyl-piperazinyl	0.39	0.10	1.56	(Koga et al.1980)
4-Allyl-piperazinyl	0.39	0.39	6.25	(Koga et al.1980)
4-Benzyl-piperazinyl	0.39	0.79	50.00	(Koga et al.1980)
4- (4-Nitro-benzyl) -piperazinyl	1.56	6.25	100.00	(Koga et al.1980)
4- (4-Amino-benzyl) -piperazinyl	0.39	0.39	12.50	(Koga et al.1980)
4-Benzoyl-piperazinyl	1.56	3.13	25.00	(Koga et al.1980)
4- (2-Hydroxyethyl) piperazinyl	0.78	0.10	6.25	(Koga et al.1980)
3- (Hydroxymethyl) piperazinyl	8.00	2.00	64.00	(Ziegler et al. 1990)
3-Fluoromethyl-piperazinyl	0.12	0.12	32.00	(Ziegler et al. 1990)
3-Difluoromethyl-piperazinyl	0.12	0.50	32.00	(Ziegler et al. 1990)
Morpholinyl	0.78	0.20	12.50	(Koga et al.1980)
Thiomorpholinyl	0.06	1.60	12.50	(Chu & Fernandes 1991)
1-Piperidinyl	0.78	1.56	50.00	(Koga et al.1980)
4-Hydroxy-piperidinyl	0.39	0.39	6.25	(Koga et al.1980)
4-Dimethylamino-piperidinyl	0.39	0.10	3.13	(Koga et al.1980)
Pyrrolidinyl	0.20	0.39	12.50	(Koga et al.1980)
Pyrrolidyl	0.40	1.60	12.50	(Chu & Fernandes 1991)
Thiazolidinyl	0.20	0.20	3.10	(Chu & Fernandes 1991)
1-Imidazolyl	0.25	1.56	12.50	(Toshio et al. 1987)
1-Pyrazolyl	6.25	12.50	25.00	(Toshio et al. 1987)
1-Pyrrolyl	0.39	3.13	12.50	(Toshio et al. 1987)
1,2,4-Triazol-4-yl	25.00	25.00	25.00	(Toshio et al. 1987)
3-Amino-3-methyl-1-azetidiny	0.50	0.50	2.00	(Toshio et al. 1987)

**Table 6.** The “in vitro” antibacterial activity of 1-ethyl-7-substituted-quinolones.

For 1-cyclopropyl-6-fluoro-7-substituted-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (Table 7) it was observed:

- Introducing a piperazinyl moiety (ciprofloxacin) yields a compound with a higher antibacterial potential; a similar antibacterial activity is obtained in the case where R<sub>7</sub> is 3-methyl-piperazinyl (Compound 1B);
- Introducing the pyrrolidinyl moiety (4A-4E compounds) gives a good bacterial activity on the entire bacterial spectrum, especially in the case of compound 4A where R<sub>7</sub> = 3-amino-pyrrolidinyl;
- Introducing an azetidiny moiety (Compound 8A) leads to an approximately twofold increase in activity against gram positive bacteria compared to ciprofloxacin; activity against gram negative microorganisms is 4-15 times lower. Introduction of a substituent on the azetidiny moiety offers compounds with increased activity in the following order: 8I(aminomethyl) ≈ 8J(thia) < 8D(ethylamino) < 8E(dimethylamino) < 8C(methylamino) < 8B(amino). For the 7-(3,3-di-azetidiny)-quinolone, antibacterial activity increases in the following order: 8K (aminomethyl) ≈ 8L (ethylaminomethyl) < 8H (dimethylamino) < 8C (methylamino) < 8F (amino). In conclusion, the activity “in vitro” of the compounds 8B and 8F increases on the entire bacterial spectrum and can be compared with that of ciprofloxacin. For compounds where R<sub>7</sub> are 3-amino-2-methyl-azetidiny (compounds 9A–9H), the effect given by the stereochemistry of the substituents in the azetidiny moiety has been studied. The activity “in vitro” of the compound trans-7-(3-amino-2-methyl-azetidiny) quinolone 9A can be compared favorably with the activity of 3-monosubstituted-azetidiny, 3,3-disubstituted-azetidiny and ciprofloxacin.

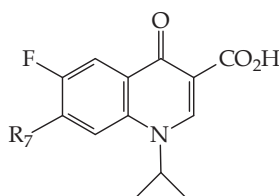
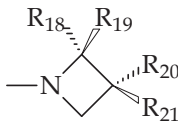
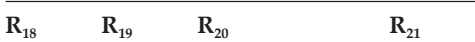


Figure 14. Cyclopropyl-7-substituted-quinolones.

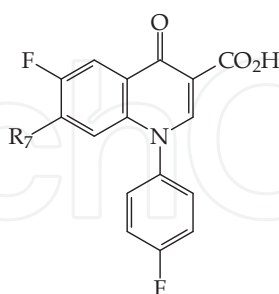
Comp.	R <sub>7</sub>	Minimum inhibitory concentration			Reference
		(µg/ml)			
		<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
1A	Piperazinyl (ciprofloxacin)	0.13	0.03	0.13	(Bouzard et al. 1989)
1B	3-Methyl-piperazinyl	0.12	0.015	0.25	(Ziegler et al. 1990)
1C	3-Fluoromethyl-piperazinyl	0.12	0.06	2.00	
2A	Morpholinyl	0.05	0.20	1.56	(Kazico et al. 1993)
2B	3-Aminomethyl-morpholinyl	0.20	0.20	1.56	

Comp.	R <sub>7</sub>	Minimum inhibitory concentration			Reference
		(µg/ml)			
		<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
3A	Homopiperazinyl	0.25	0.03	1.00	(Ziegler et al. 1990)
3B	3-Hydroxy-homopiperazinyl	4.00	0.25	2.00	
3C	3-Fluoro-homopiperazinyl	0.25	0.03	2.00	
4A	3-Amino-pyrrolidinyl	0.025	0.025	0.1-0.2	(Domagala et al.1993)
4B	3-Aminomethyl-pyrrolidinyl	0.006	0.05	0.80	
4C	3-Methylamino-pyrrolidinyl	0.025	0.10	0.80	
4D	3-Thia-pyrrolidinyl	0.013	0.20	1.6	
4E	3-Aminomethyl-3-methyl-pyrrolidinyl	0.013	0.20	0.80	
5	3-Hydroxy-pyrrolidinyl	<0.015	<0.015	0.125	(Petersen & Grohe 1992)
6	3-Oxo-pyrrolidinyl	1.56	6.20	100.00	(Cooper et al. 1992)
7A	3-Amino-4-trans-cyclopropyl-pyrrolidinyl	<0.025	0.05	0.80	(Bush et al. 1993)
7B	3-Amino-4-trans-(trans-2-CO <sub>2</sub> Et)-cyclopropyl- pyrrolidinyl	0.20	0.20	3.10	
8A	Azetidinyl	0.06	0.12	2.00	(Frigola et al. 1993)
8B	3-Amino-azetidinyI	0.25	0.03	0.25	
8C	3-Methylamino-azetidinyI	0.25	0.03	0.50	
8D	3-Ethylamino-azetidinyI	0.25	0.06	2.00	
8E	3-Dimethylamino-azetidinyI	0.12	0.06	2.00	
8F	3-Methyl-3-amino-azetidinyI	0.12	0.06	0.50	
8G	3-Methylamino-3-methyl-azetidinyI	0.25	0.06	2.00	
8H	3-Dimethylamino-3-methyl-azetidinyI	0.25	0.25	4.00	
8I	3-Aminoethyl-azetidinyI	0.50	0.12	1.00	
8J	3-Thia-azetidinyI	0.50	0.25	4.00	
8K	3-Aminomethyl-3-methyl-azetidinyI	0.25	0.12	1.00	(Frigola et al. 1994)
8L	3-Thia-3-methyl-azetidinyI	0.25	0.12	4.00	
9					
					

Comp.	R <sub>7</sub>	Minimum inhibitory concentration					Reference
		(μg/ml)					
		<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>			
9A	CH <sub>3</sub>	H	H	NH <sub>2</sub>	0,12.	0.03	0.25
9B	CH <sub>3</sub>	H	NH <sub>2</sub>	H	0.12	0.06	0.50
9C	C <sub>2</sub> H <sub>5</sub>	H	NH <sub>2</sub>	H	0.25	0.12	2.00
9D	H	CH <sub>3</sub>	NH <sub>2</sub>	CH <sub>3</sub>	0.25	0.06	2.00
9E	H	CH <sub>3</sub>	NHCH <sub>3</sub>	H	0.12	0.06	0.50
9F	H	CH <sub>3</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	H	0.25	0.50	4.00
9G	H	CH <sub>3</sub>	CH <sub>2</sub> NH <sub>2</sub>	H	0.25	0.12	2.00
9H	H	CH <sub>3</sub>	CH <sub>2</sub> NHC <sub>2</sub> H <sub>5</sub>	H	0.25	0.12	4.00

**Table 7.** The “in vitro” antibacterial activity of 1-cyclopropyl-7-substituted-quinolones.

For 1-(*p*-fluorophenyl)-7-substituted-quinolones (Table 8), it is observed that the introduction of substituents: 3-methyl-piperazinyl (4), 4-amino-piperazinyl (8), 3 amino-pyrrolidinyl (17), and 3-methyl-2-amino-pyrrolidinyl (20) has the effect of extending of the antibacterial spectrum on both gram positive and gram negative bacteria, while introducing morpholinyl groups (10), thiomorpholinyl (11), 4-hydroxy-piperidinyl (13), pyrrolidinyl (15), 3-hydroxy-pyrrolidinyl (compound 16) leads to the increase of antibacterial activity against gram positive bacteria, comparable with the antibacterial activity of the sarafloxacin and difloxacin. It should be noted that the introduction of the methyl group in position 5 of 3-amino-pyrrolidinyl substituent (compound 17) leads to obtaining a compound (20) with a high solubility in water and with excellent efficacy in oral administration.



**Figure 15.** *p*-Fluorophenyl)-7-substituted-quinolones.

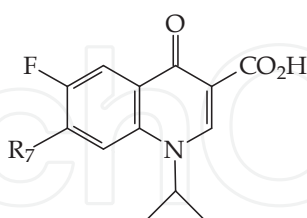
Structural changes were focused on replacing the nitrogen atom of the heterocyclic substituent with a sp<sup>2</sup> or sp<sup>3</sup> hybridized carbon atom. All new compounds have a high activity both “in vitro” and “in vivo”. The potential of these compounds is relatively dependent on the size of the ring and the hybridization of the carbon atom through which it connects with the quinolone. 1-Piperazino moiety can be substituted with 4-piperidinyl (compound 1, Table 9) with

	R <sub>7</sub>	Minimum inhibitory concentration (µg/ml)			Reference
		<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
1	Piperazinyl (sarafloxacin)	0.20	0.05	0.39	(Chu et al. 1985)
2	4-Methyl-piperazinyl (difloxacin)	0.20	0.20	1.56	(Chu et al. 1985)
3	4-Butyl-piperazinyl	0.78	1.56	12.50	(Chu et al. 1985)
4	3-Methyl-piperazinyl	0.20	<0.05	0.78	(Chu & Fernandes 1991)
5	3,5-Dimethyl-piperazinyl	0.39	<0.05	1.56	(Chu & Fernandes 1991)
6	3-Fluoromethyl-piperazinyl	0.25	0.25	2.00	(Domagala et al. 1988)
7	3-Oxo-piperazinyl	0.20	0.20	1.56	(Chu et al. 1985)
8	4-Amino-piperazinyl	0.39	0.20	0.78	(Chu & Fernandes 1991)
9	Homopiperazinyl	0.79	0.20	1.56	(Chu et al. 1985)
10	Morpholinyl	0.10	0.39	3.10	(Chu et al. 1985)
11	Thiomorpholinyl	0.05	0.78	3.10	(Chu et al. 1985)
12	Piperidinyl	0.20	1.56	6.20	(Chu et al. 1985)
13	4-Hydroxy-piperidinyl	0.10	0.39	6.20	(Chu et al. 1985)
14	4-Dimethylamino-piperidinyl	0.39	0.73	3.10	(Chu et al. 1985)
15	Pyrrolidinyl	0.10	0.78	1.56	(Chu et al. 1985)
16	3-Hydroxy-pyrrolidinyl	0.10	0.20	3.10	(Chu et al. 1985)
17	3-Amino-pyrrolidinyl	0.10	<0.05	0.78	(Chu & Fernandes 1991)
18	3-Methylamino-pyrrolidinyl	0.20	<0.05	1.56	(Chu & Fernandes 1991)
19	3-Dimethylamino-pyrrolidinyl	0.78	<0.05	6.25	(Chu & Fernandes 1991)
20	3-Methyl-3-amino-pyrrolidinyl	0.05	0.02	0.78	(Rosen et al. 1988)
21	Trans (3-amino-2-methyl) -azetidiny	0.25	0.12	1.00	(Domagala et al. 1988)
22	3-Amino-3-methyl-azetidiny	0.12	0.12	2.00	(Domagala et al. 1988)
6-Fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acids substituted in position 7 with bioisosteric non-basic groups.					

**Table 8.** The “in vitro” antibacterial activity of 1-(*p*-fluorophenyl)-7-substituted-quinolones.

4-(1,2,3,6-tetrahydropyridinyl) (compound 2), while the 3-amino-pyrrolidinyl moiety can be substituted with 3-amino-cyclopentanyl (compound 3). For the compounds 1 and 2, the nature of isosteric atom that replaces the nitrogen atom in position 1 of the piperazinyl moiety influences the antimicrobial activity “in vitro” as follows: while this sp<sup>2</sup> hybridized atom (through which connects the quinolone nucleus) leads to compounds (2) with activity comparable to ciprofloxacin, the presence of carbon sp<sup>3</sup> leads to decreased activity “in vitro” of about 4–12 times. Replacement of the 3-amino-1-pyrrolidinyl (compound B) with 3-amino-1-

cyclopentanyl (compound 3) results in a decrease in antimicrobial activity. In general, the piperazinyl moiety in position 7 has a favorable influence at the “in vitro” activity, but 7-substituted piperazinyl quinolones do not have a good availability.



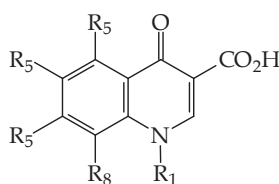
**Figure 16.** Cyclopropyl-quinolones substituted in position 7 with bioisosteric non-basic groups.

Compound	R <sub>7</sub>	Minimum inhibitory concentration ( µg / ml)			Reference
		<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	
A		0.13	0.03	0.13	(Bouzard et al. 1989)
1		0.80	0.20	1.60	(Laborde et al. 1993)
2		0.10	0.025	0.80	(Laborde et al. 1993)
B		0.025	0.025	0.20	(Laborde et al. 1993)
3		0.10	0.10	0.80	(Laborde et al. 1993)

**Table 9.** The “in vitro” antibacterial activity of 1-cyclopropyl-quinolones substituted in position 7 with bioisosteric non-basic groups.

## 2.8. Position 8

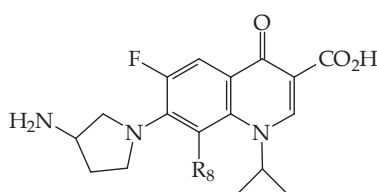
The most famous modifications of the 8 position of the quinolone are X = CH or N (naphthyr- idines). However, compact and lipophilic groups: X = CR<sub>8</sub>, where R<sub>8</sub> = fluorine [16, 17, 25, 54], trifluoromethyl [52] and methoxy [22, 55] have gained ground due to the positive influence they have on the antibacterial activity.



$R_8 = \text{F, Cl, OCH}_3 > \text{H, CF}_3 > \text{methyl, vinyl, propargyl}$

**Figure 17.** Influence of the nature of the substituent at 8 position on the antimicrobial activity.

In general, the introduction of a fluorine atom in 8 position leads to increased antibacterial activity against gram negative microorganisms, while introducing the methoxy group increase the activity only against the gram positive bacteria.



**Figure 18.** Cyclopropyl-8-substituted quinolones.

$R_8$	Minimum inhibitory concentration ( $\mu\text{G} / \text{ML}$ ) geometric mean	
	Gram (-)organisms	Gram (+)organisms
H	0.09	0.14
F	0.04	0.03
OMe	0.07	0.03
Cl	0.03	0.04
$\text{NO}_2$	0.46	0.92
$\text{NH}_2$	0.53	0.06
$\text{CF}_3$	0.20	0.20
SMe	0.20	0.06

**Table 10.** The “in vitro” antibacterial activity 8 substituted quinolones.

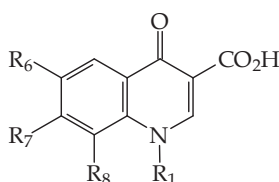
The compounds containing a chlorine atom in 8 position [30, 25, 17] are very active, as well as analogs containing fluorine or methoxy moiety [22, 55]. The introduction of bulky substituents, e.g., ethyl, reduces the antibacterial activity against gram negative (if a comparison with 8-methoxy-quinolones is made). Quinolones having a halogen atom, fluorine or chlorine in 8

position, show the phototoxicity; the introduction of trifluoromethyl group [52] leads to reduced cytotoxicity. Alkylation of carbon in position 8 is tolerated, especially if the substituent is lipophilic and has a small volume. Thus the introduction of the methyl group [4, 5] leads to compounds with modest antibacterial activity. Instead, amino, nitro, hydroxy substituents lead to loss of antibacterial activity (Dax 1997).

### 3. New compounds: synthesis, structure and antimicrobial activity

#### 3.1. Structure of the new compounds

A series of 4-oxo-1,4-dihydro-quinoline-3-carboxylic acids was synthesized. (Figure 19) (Table 11). Their structure has been determined and confirmed by the following physicochemical methods: elemental analysis, IR spectral analysis, H-NMR, C-NMR, UV, thin layer chromatography.



**Figure 19.** Structure of 4-oxo-1,4-dihydro-quinoline-3-carboxylic acids.

Quinolones	R <sub>1</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>8</sub>	m.p. (°C)	Reference
FPQ 24 C <sub>18</sub> H <sub>21</sub> FN <sub>2</sub> O <sub>3</sub>	Ethyl	F	3-Methyl-piperidin-1-yl	H	189.4	Pintilie et al. (2009b)
FPQ 30 C <sub>18</sub> H <sub>20</sub> ClFN <sub>2</sub> O <sub>3</sub>	Ethyl	F	3-Methyl-piperidin-1-yl	Cl	163-165.3	Pintilie et al. (2014a)
FPQ 32 C <sub>17</sub> H <sub>19</sub> FN <sub>2</sub> O <sub>3</sub>	Ethyl	F	Piperidin-1-yl	H	202.4-204.4	Pintilie & Nita (2011a)
FPQ 33 C <sub>17</sub> H <sub>18</sub> ClFN <sub>2</sub> O <sub>3</sub>	Ethyl	F	Piperidin-1-yl	Cl	186-191.2	Pintilie & Nita (2011a)
Q 83 C <sub>18</sub> H <sub>21</sub> FN <sub>2</sub> O <sub>3</sub>	Ethyl	F	4-Methyl-piperidin-1-yl	H	235-237	Pintilie et al. (2003b)
Q 85 C <sub>18</sub> H <sub>20</sub> ClFN <sub>2</sub> O <sub>3</sub>	Ethyl	F	4-Methyl-piperidin-1-yl	Cl	201-202.5	Pintilie et al. (2003b)
FPQ 35 C <sub>16</sub> H <sub>17</sub> FN <sub>2</sub> O <sub>3</sub>	Ethyl	F	Pyrrolidin-1-yl	H	336.6-337.9	Pintilie & Nita (2011a)
FPQ 36	Ethyl	F	Pyrrolidin-1-yl	Cl	214.5-217.8	Pintilie & Nita (2011a)



Quinolones	R <sub>1</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>8</sub>	m.p. (°C)	Reference
C <sub>16</sub> H <sub>16</sub> ClFN <sub>2</sub> O <sub>3</sub>						
FPQ 25 C <sub>16</sub> H <sub>17</sub> FN <sub>2</sub> O <sub>4</sub>	Ethyl	F	Morpholin-1-yl	H	257.4-258.7	Pintilie et al. (2009b)
FPQ 28 C <sub>16</sub> H <sub>16</sub> ClFN <sub>2</sub> O <sub>4</sub>	Ethyl	F	Morpholin-1-yl	Cl	244.6-244	Pintilie et al. (2014a)
NF C <sub>16</sub> H <sub>18</sub> FN <sub>3</sub> O <sub>3</sub>	Ethyl	F	Piperazin-1-yl	H	218-220	Pintilie et al. (2014b)
AcNF C <sub>18</sub> H <sub>20</sub> FN <sub>3</sub> O <sub>4</sub>	Ethyl	F	4-Acetyl-piperazin-1-yl	H	297.8-299.9	Pintilie et al. (2014b)
AcFPQ 50 C <sub>18</sub> H <sub>19</sub> ClFN <sub>3</sub> O <sub>4</sub>	Ethyl	F	4-Acetyl-piperazin-1-yl	Cl	255.7-258.2	Pintilie et al. (2014b)
FPQ 50 C <sub>16</sub> H <sub>17</sub> ClFN <sub>3</sub> O <sub>3</sub>	Ethyl	F	Piprazin-1-yl	Cl	227-230	Pintilie et al. (2014b)
PF C <sub>17</sub> H <sub>20</sub> FN <sub>3</sub> O <sub>3</sub>	Ethyl	F	4-Methyl-piperazin-1-yl	H	269.2-272.8	Pintilie et al. (2014b)
FPQ 51 C <sub>17</sub> H <sub>19</sub> ClFN <sub>3</sub> O <sub>3</sub>	Ethyl	F	4-Methyl-piperazin-1-yl	Cl	219.6-221	Pintilie et al. (2014b)
FPQ 27 C <sub>17</sub> H <sub>20</sub> FN <sub>2</sub> O <sub>3</sub>	Ethyl	F	3-Methyl-piperazin-1-yl	H	177.6-180.6	Pintilie et al. (2014a)
AcFPQ 27 C <sub>19</sub> H <sub>22</sub> FN <sub>3</sub> O <sub>4</sub>	Ethyl	F	4-Acetyl-3-methyl-piperazin-1-yl	H	247.5-248.9	Pintilie & Nita (2011a)
AcFPQ29 C <sub>19</sub> H <sub>21</sub> ClFN <sub>3</sub> O <sub>4</sub>	Ethyl	F	4-Acetyl-3-methyl-piperazin-1-yl	Cl	262.7-264.8	Pintilie & Nita (2011a)
FPQ29 . HCl C <sub>17</sub> H <sub>29</sub> ClFN <sub>2</sub> O <sub>3</sub> . HCl	Ethyl	F	3-Methyl-piperazin-1-yl	Cl	280-283	Pintilie & Nita (2011a)
6CIPQ 24 C <sub>18</sub> H <sub>21</sub> ClN <sub>2</sub> O <sub>3</sub>	Ethyl	Cl	3-Methyl-piperidin-1-yl	H	216.4-218.4	Pintilie et al. (2009b)
6CIPQ 30 C <sub>18</sub> H <sub>20</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	Ethyl	Cl	3-Methyl-piperidin-1-yl	Cl	190.3-192.2	Pintilie & Nita (2011b)
6CIPQ 32 C <sub>17</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>3</sub>	Ethyl	Cl	Piperidin-1-yl	H	234.6-236.4	Pintilie & Nita (2011b)
6CIPQ 33 C <sub>17</sub> H <sub>18</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	Ethyl	Cl	Piperidin-1-yl	Cl	214.6-216.3	Pintilie & Nita (2011b)
PQ 80 C <sub>18</sub> H <sub>21</sub> ClN <sub>2</sub> O <sub>3</sub>	Ethyl	Cl	4-Methyl-piperidin-1-yl	H	262.5-264.4	Pintilie & Nita (2011b)
PQ87 C <sub>18</sub> H <sub>20</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	Ethyl	Cl	4-Methyl-piperidin-1-yl	Cl	152.3-154.9	Pintilie & Nita (2011b)
6CIPQ 35 C <sub>17</sub> H <sub>18</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	Ethyl	Cl	Pyrrolidin-1-yl	H	312.3-315.5	Pintilie & Nita (2011b)

Quinolones	R <sub>1</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>8</sub>	m.p. (°C)	Reference
6CIPQ 36 C <sub>17</sub> H <sub>18</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	Ethyl	Cl	Pyrrolidin-1-yl	Cl	172.4-176.1	Pintilie & Nita (2011b)
6CIPQ 25 C <sub>16</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>4</sub>	Ethyl	Cl	Morpholin-1-yl	H	267,1-269,2	Pintilie et al. (2009b)
6CIPQ 28 C <sub>16</sub> H <sub>16</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub>	Ethyl	Cl	Morpholin-1-yl	Cl	213.9-216.7	Pintilie & Nita (2011b)
NCIX C <sub>16</sub> H <sub>18</sub> ClN <sub>3</sub> O <sub>3</sub>	Ethyl	Cl	Piperazin-1-yl	H	226.8-228.5	Pintilie et al. (2014b)
AcNCIX C <sub>18</sub> H <sub>20</sub> ClN <sub>3</sub> O <sub>4</sub>	Ethyl	Cl	4-Acetyl-piperazin-1-yl	H	306-310	Pintilie et al. (2014b)
Ac6CIPQ 50 C <sub>18</sub> H <sub>19</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>4</sub>	Ethyl	Cl	4-Acetyl-piperazin-1-yl	Cl	260.1-263.7	Pintilie et al. (2014b)
6CIPQ 50 C <sub>16</sub> H <sub>17</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>3</sub>	Ethyl	Cl	Piperazin-1-yl	Cl	228.2-230.4	Pintilie et al. (2014b)
PCIX C <sub>17</sub> H <sub>20</sub> ClN <sub>3</sub> O <sub>3</sub>	Ethyl	Cl	4-Methyl-piperazin-1-yl	H	253.7-258.2	Pintilie et al. (2014b)
6CIPQ 51 C <sub>17</sub> H <sub>19</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>3</sub>	Ethyl	Cl	4-Methyl-piperazin-1-yl	Cl	223.4-226	Pintilie et al. (2014b)
6CIPQ 27 C <sub>17</sub> H <sub>20</sub> ClN <sub>3</sub> O <sub>3</sub>	Ethyl	Cl	3-Methyl-piperazin-1-yl	H	170.5-171.4	Pintilie et al. (2009b)
Ac6CIPQ 27 C <sub>19</sub> H <sub>22</sub> ClN <sub>3</sub> O <sub>4</sub>	Ethyl	Cl	4-Acetyl-3-methyl-piperazin-1-yl	H	275-276	Pintilie et al. (2014 b)
Ac6CIPQ 29 C <sub>19</sub> H <sub>21</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>4</sub>	Ethyl	Cl	4-Acetyl-3-methyl-piperazin-1-yl	Cl	210.3-211.7	Pintilie et al. (2014b)
6CIPQ 29 C <sub>17</sub> H <sub>19</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	Ethyl	Cl	3-Methyl-piperazin-1-yl	Cl	278.5-282	Pintilie et al. (2014b)

**Table 11.** Oxo-1,4-dihydro-quinoline-3-carboxylic acids synthesized.

### 3.2. Synthesis pathway

The synthesis of the novel quinolones followed a Gould–Jacobs cyclization process (Scheme 1). Appropriate unsubstituted aniline (1) is reacted with diethylethoxy methylene malonate (EMME) to produce the resultant anilinomethylenemalonate. A subsequent thermal process induces Gould–Jacobs cyclization to afford the corresponding 4-hidroxy-quinoline-3-carboxylate ester (2). The following operation is the alkylation of the quinolone, which is usually accomplished by reaction with a suitable alkyl halide or dialkyl sulphates to produce the qinolone-3-carboxylate ester (3). The final manipulation is acid or basic hydrolysis to cleave the ester generating the biologically active free carboxylic acid (4). The biologically active free carboxylic acid (4) was also obtained from the corresponding 4-hidroxy-quinoline-3-carboxylate ester (2) by alkylation with dialkyl sulphates in presence of alkali, for example, the reaction

it can conveniently be carried out in aqueous 40% sodium hydroxide solution. The displacement of 7-chloro group with a heterocyclic yielded compounds (5). 8-Chloro-quinoline-3-carboxylic acid (8) was synthesized from 8-unsubstituted quinoline-3-carboxylic acid (5) by chlorination with sulfuryl chloride (when  $R_7 = 4$ -methyl-piperazine). When  $R_7 = 3$ -methyl-piperazine or piperazine, it is necessary to protect the nitrogen atom from piperazine group. After chlorination and hydrolysis, the final compound (8) is obtained ( $R_7 = 3$ -methyl-piperazine, or piperazine).

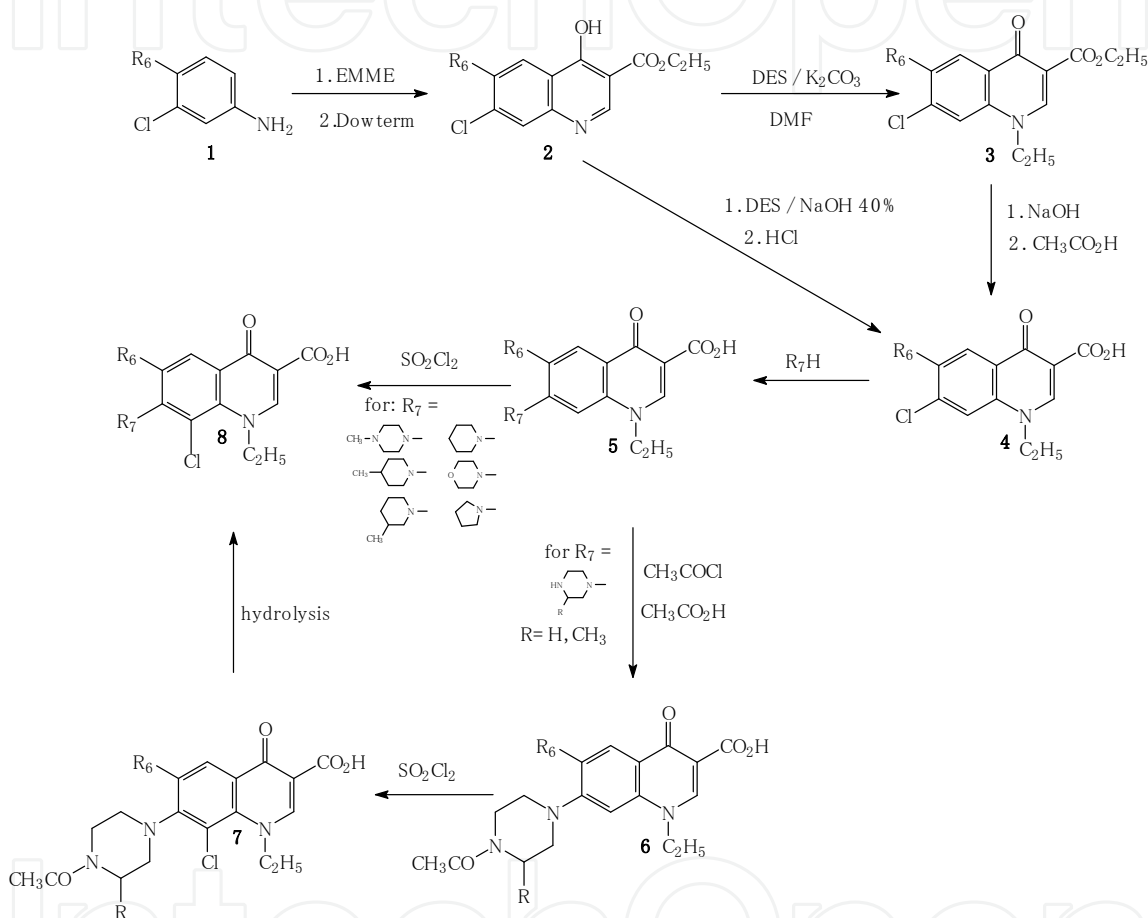


Figure 20. Synthesis of the new quinolones.

### 3.3. Antibacterial activity of the new compounds

The new compounds were evaluated for “in vitro” activity by determining minimum inhibitory concentration against bacteria *E. coli*, *S. aureus*, and *P. aeruginosa*, by agar dilution method (Buiuc 1998) (NCCLS 2003) (Table 12). After analyzing chemical structure–biological activity relationships, it was observed that the presence of chlorine in 8 position of the quinolones core leads to increased antimicrobial activity for the compounds having piperidinyl, morpholinyl, and pyrrolidinyl moiety in 7-position. For 7-piperazinyl quinolones, the chlorine atom from 8-position leads to decreased activity against all the tested strains.

Quinolone	Minimum inhibitory concentration			References
	µg/ml			
	<i>E. coli</i> (a)	<i>S. aureus</i> (b)	<i>P. aeruginosa</i> (c)	
FPQ 24	2.00	0.50	32.00	Pintilie et al. 2009b
FPQ 30	0.32	0.125	1.28	Pintilie & Nita 2011a
FPQ 32	1.00	8.00	8.00	Pintilie & Nita 2011a
FPQ 33	0.32	0.32	1.28	Pintilie & Nita 2011a
Q 83	3,12	1,56	6,25	Pintilie et al. 2003b
Q 85	3,12	0,39	6,25	Pintilie et al. 2003b
FPQ 35	31.25	1.953	">125	Pintilie & Nita 2011a
FPQ 36	15.625	0.244	15.625	Pintilie & Nita 2011a
FPQ 28	0,125	0,06	8,00	Pintilie et al. (2009b)
NF	<0.08	0.32	0.32	Pintilie et al. 2014 b
FPQ 50	2.00	4.00	16.00	Pintilie et al. 2014 b
PF	<0.08	1.28	1.28	Pintilie et al. 2014 b
FPQ 51	2.00	4.00	32.00	Pintilie et al. 2014 b
FPQ 27	0.125	1.00	1.00	Pintilie & Nita 2011a
FPQ 29	0.30	1.21	4.83	Pintilie & Nita 2011a
6CIPQ 24	8,00	2,00	">128	Pintilie et al. (2009b)
6CIPQ 30	8.00	2.56	2.56	Pintilie & Nita 2011b
6CIPQ 33	2.56	2.56	2.56	Pintilie & Nita 2011b
6CIPQ 36	2.56	2.56	2.56	Pintilie & Nita 2011b
6CIPQ 28	1.28	1.28	64	Pintilie & Nita 2011b
NCIX	0.32	1.28	5.12	Pintilie et al. 2014 b
6CIPQ 50	2.00	8.00	32.00	Pintilie et al. 2014 b
PCIX	0.32	1.28	5.12	Pintilie et al. 2014 b
6CIPQ 51	3.906	15.625	62.5	Pintilie et al. 2014 b

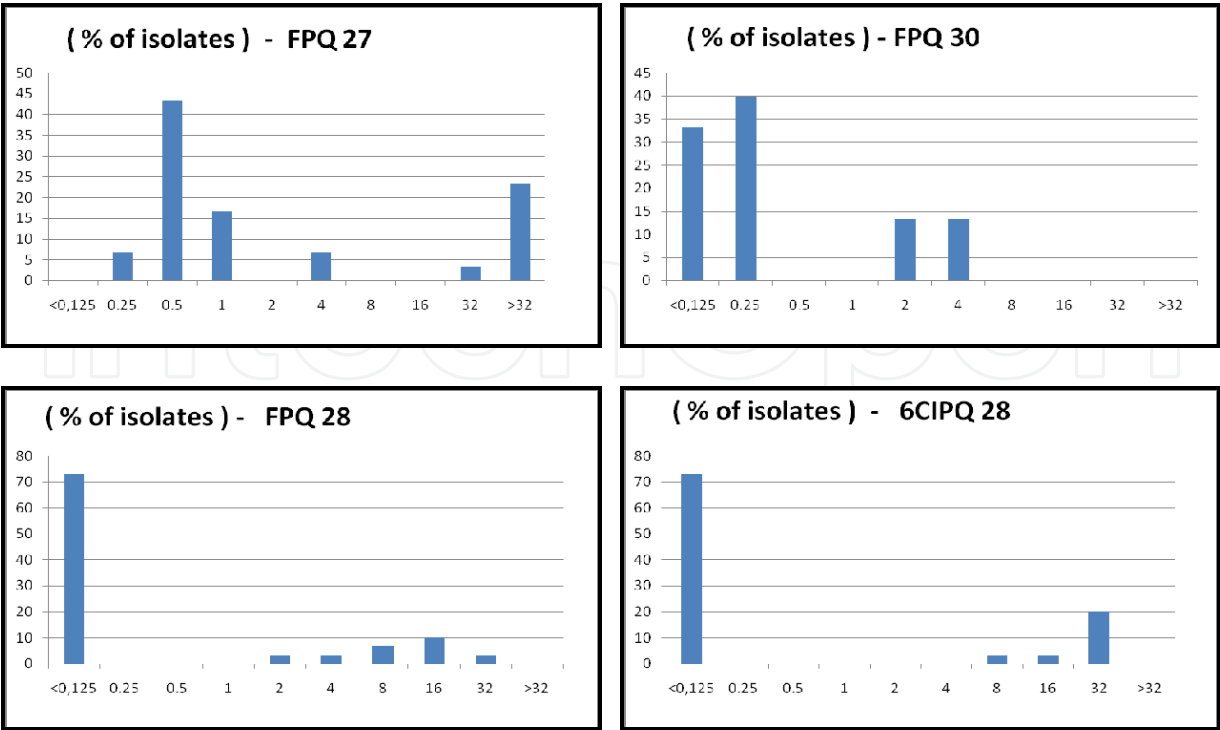
a. *E. coli* ATCC 8739, b. *S. aureus* ATCC 6538, c. *P. aeruginosa* ATCC 9027

a. *E. coli* ATCC 8739, b. *S. aureus* ATCC 6538, c. *P. aeruginosa* ATCC 9027

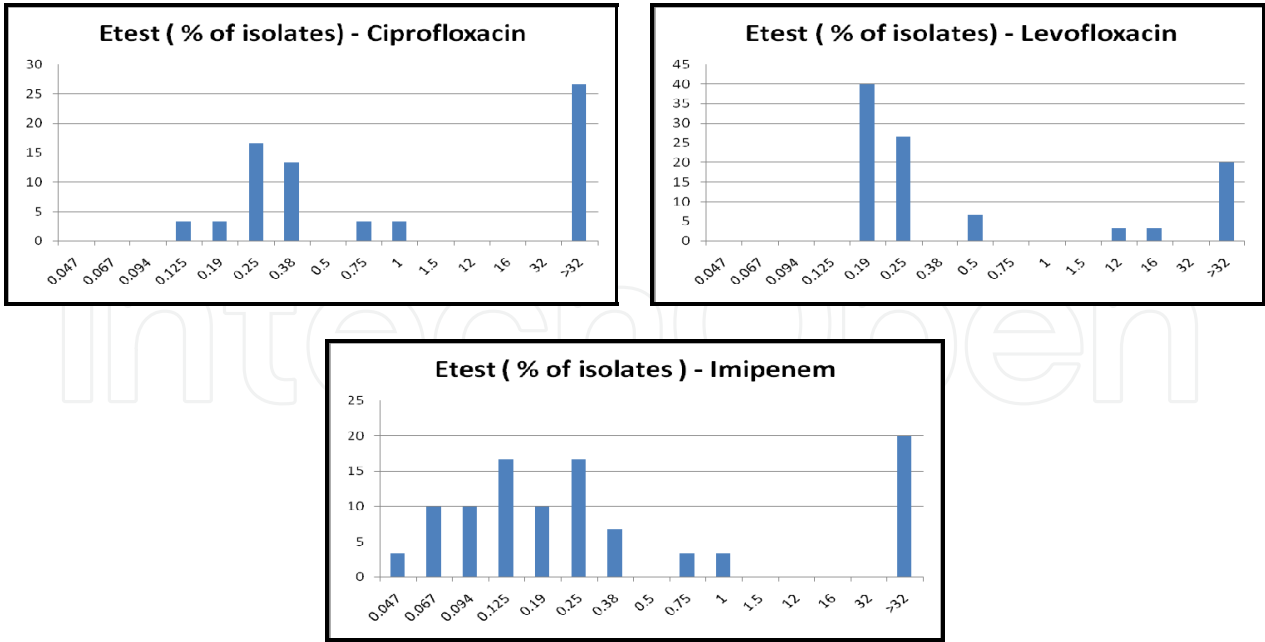
**Table 12.** "In vitro" antibacterial activity of the new quinolones.

### 3.4. Antibacterial activity of the new compounds against methicillin-resistant *S. aureus*

Some of the new quinolones, which showed a good activity, have been tested against 30 strains of methicillin-resistant *S. aureus* isolated in the Microbiology Laboratory of INBI Prof. "Dr. Matei Bals" during 2012. The minimum inhibitory concentration (MIC) of the isolates has been determined by agar plate Mueller Hinton (bioMerieux) dilution method using the reference strain *S. aureus* ATCC 29213. The 30 strains of isolated have been also tested for susceptibility to ciprofloxacin, levofloxacin, and imipenem by Etest method.



**Figure 21.** MIC histograms of 4 quinolones against 30 strains of methicillin-resistant *S. aureus*.



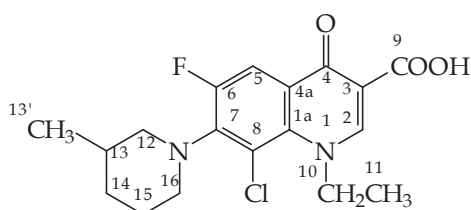
**Figure 22.** MIC histograms of ciprofloxacin, levofloxacin, imipenem against 30 strains of methicillin-resistant *S. aureus*, determined by Etest method.

Base on the “in vitro” studies, the quinolone FPQ-30 appears to be a promising compound; all strains isolates were inhibited at a concentration of 8 µg/ml (Figure 21).

## 4. Conclusion

In conclusion, we have synthesized new quinolone compounds and we have investigated their activity against multidrug-resistant gram positive microorganisms. Of the four compounds, FPQ-30 (Figure 23, 24) showed the best activity; all strains isolates were inhibited at a concentration of 8 µg/ml. The results of the present study indicate the quinolone FPQ-30 appears to be a promising compound.

Its structure has been determined and confirmed by the following physicochemical methods: elemental analysis, IR spectral analysis, H-NMR, C-NMR, UV (Figure 25) and thin layer chromatography.

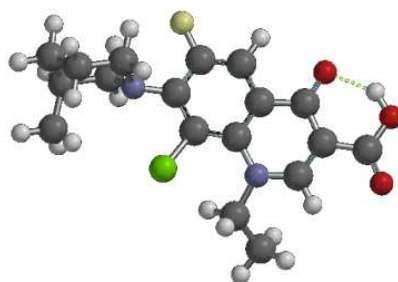


<sup>1</sup>H-NMR(dmso-d<sub>6</sub>, δ ppm, J Hz, T = 333K): 8.88(s, 1H, H-2); 7.93(d, 1H, H-5, <sup>3</sup>J(F-H<sup>5</sup>) = 13.4 Hz); 4.81(q, 2H, H-10, 7.1); 3.28(m, 2H, H-16, H-12); 3.11(dd, 1H, H-12, 10.7, 12.1); 2.81(td, 1H, H-16, 12.1, 2.9); 1.58 ÷ 1.86(m, H, H-13, 2H-14, 1H-15); 1.39(t, 3H, H-11, 7.1); 1.13(qd, 1H, H-15, 10.8, 4.1); 0.88(d, 3H, H-13, 6.4).

<sup>13</sup>C-NMR(dmso-d<sub>6</sub>, δ ppm): 175.89(d, C-4, <sup>4</sup>J(F-C<sup>4</sup>) = 2.8 Hz); 167.30(C-9); 155.83(d, C-6, J(F-C<sup>6</sup>) = 251.1 Hz); 152.45(C-2); 144.37(d, C-7, <sup>2</sup>J(F-C<sup>7</sup>) = 14.3 Hz); 136.46(C-1a); 122.95(d, C-4a, <sup>3</sup>J(F-C<sup>4a</sup>) = 7.1 Hz); 118.93(C-8); 110.79(d, C-5, <sup>2</sup>J(F-C<sup>5</sup>) = 23.4 Hz); 107.67(C-3); 58.70 (d, C-12, <sup>4</sup>J(F-C<sup>12</sup>) = 4.6 Hz); 53.06(C-10); 51.57(d, C-16, <sup>4</sup>J(F-C<sup>16</sup>) = 4.6 Hz); 32.05(C-15); 31.17(C-13); 25.39(C-14); 18.82(C-13); 15.73(C-11).

FT-IR(solid in ATR, ν/cm): 3059m; 2947w; 2925m; 2867w; 2845m; 1719vs; 1616s; 1558s; 1531m; 1489m; 1437vs; 1381m; 1319m; 1294m; 1250m; 1229m; 1208m; 1189m; 1125w; 1101m; 1081m; 1040m; 996w; 968w; 926m; 887m; 857w; 838w; 8.05m; 741w.

**Figure 23.** Ethyl-6-fluoro-7-(4-methyl-piperidinyl)-8-chloro- Optimized molecular structure of FPQ 30



**Figure 24.** dihydro-4-oxo-quinoline-3-carboxylic acid (FPQ 30) with Spartan 14 Software

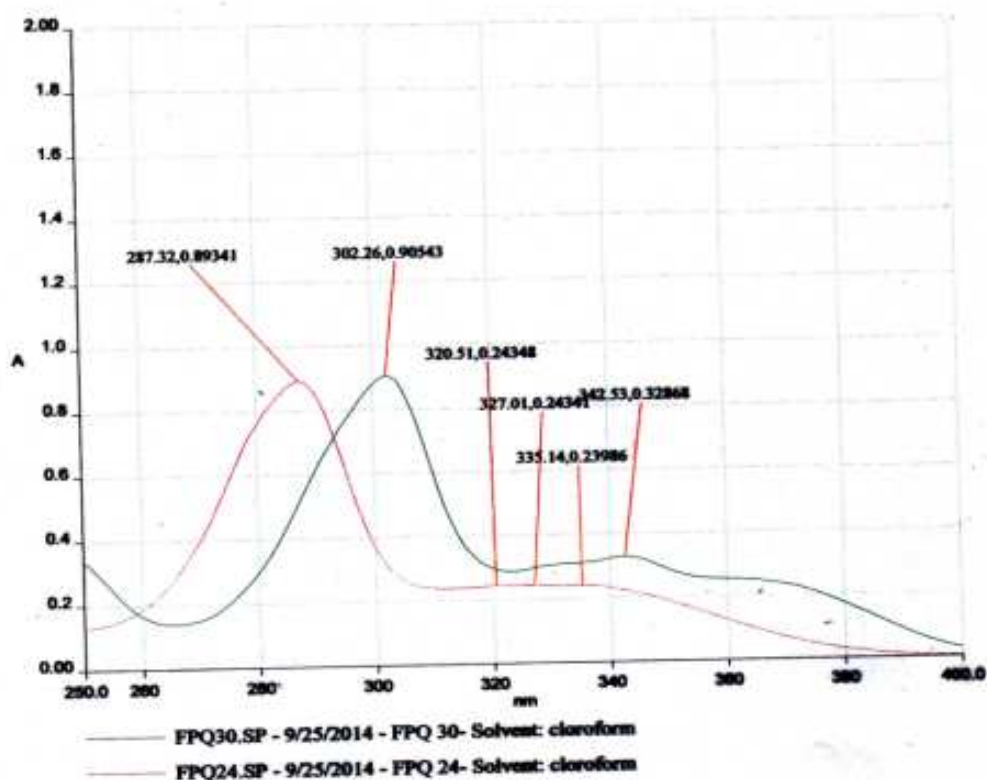


Figure 25. UV absorption spectrum of FPQ-24 and FPQ-30

UV absorption spectra study was carried out using solutions with concentration of 10 mg/ml in chloroform. Interpretation of the UV absorption spectrum has been made in comparison with that of the quinolone compound: 1-ethyl-6-fluoro-7-(3-methyl-piperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (FPQ 24), namely:

- The presence of the quinolone nucleus determines in chloroform the appearance of electronic transitions in the field of 260–310 nm and 320–350 nm.
- The introduction of chlorine atom in 8 position produces a batocroma displacement of the entire spectrum.

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