We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

3,500
Open access books available

108,000
International authors and editors

1.7 M
Downloads

151
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
1. Introduction

After the concept of selective toxicity in chemotherapy was introduced at the beginning of the 20th century, (Ehrlich, 1913), classes of substances with antibacterial properties, produced by microorganisms or created through synthesis were obtained. After the discovery of penicillin, the first antibiotic introduced in clinical use in man in 1940s, a large number of different types of antibiotics were produced. Antibiotics such as beta-lactams, macrolides, aminoglycosides and tetracyclines were discovered and introduced during an extremely short period. These were obtained either by isolation from fungi or by chemically modification of the naturally isolated substrates. These dominated the antimicrobial industry, while synthetically obtained substances only played a minor role. (Chu & Fernandes, 1991)

In 1962, G. Y. Lesher and his collaborators introduced the first quinolone derivative, nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid), (1, Lesher et al. 1962) which had moderate activity against gram-negative organisms and was used for treating urinary tract infections. In the following years, a large gamma of derivatives from common elements were synthesized, which could be grouped by: cinoline (cinoxacin), pyrido-pyrimidine (pipemidic acid; piromidic acid), naphthyridine (nalidixic acid) and quinolones (oxolinic acid, miloxacin, tioxacin, etc.). These derivatives, with differentiated structures, have 2 common pharmacological properties, which allowed them to be classified as first generation biologically active derivatives with quinolone structure. The two common characteristics for first generation quinolones are:

- a narrow antibacterial spectrum, designed especially for enterobacteriaceae;
- a pharmacokinetic which allows for rapid elimination and reduced tissue absorption, only allowing them to be used as urinary antiseptics.
The success of first generation quinolones spurred the research in this area, which led to the obtainment through synthesis, after 1980, of a new series of compounds with stronger antibacterial properties and a broader spectrum of antibacterial activity which included gram positive and gram negative organisms, and which where defined by their ability to be applied on all localized infections. Koga and his collaborators introduced Norfloxacin into clinical use in 1980, the first quinolone with a fluorine atom substituted at the C-6 position and a piperazine C-7. Norfloxacin (Koga et al. 1980) was the first quinolone with increased antimicrobial activity, acting on a large spectrum of gram positive and gram negative microorganisms, including Pseudomonas aeruginosa.

Research in the field of derivatives with a quinolone structure have lead to new compounds obtained recently, which have been classified as third and fourth generation systemic quinolones, largely effective against Staphylococcus aureus. Their large antibacterial spectrum includes anaerobes, Chlamydia and Mycoplasma. (Brighty & Gootz, 2000)
The four generations have the following common aspects: an identical mechanism of action by inhibition the $A$ subunit of DNA-gyrase, an exclusively chromosomal bacteria resistance and some similar bacteria effects: photo toxicity, neurotoxicity, cartilage toxicity.

Fig. 3. Third- generation quinolones.

Fig. 4. Fourth- generation quinolones.

Until now a large number of antibacterial substances belonging to the above mentioned class have been used in medicine. Quinolones are used when treating infections of the urinary tract, the respiratory tract, intestinal infections, ear/nose/throat infections, STD’s, soft tissue and skin infections, meningitis caused by gram negative and Staphilococci bacteria, liver and bile infections, septicemia and endocarditis, prophylaxis and surgical infections and on patients with immune deficiencies.
The mechanism of action of quinolone antibacterial agents involves the inhibition of DNA gyrase (a bacterial topoisomerase II) resulting in a rapid bactericidal effect.

The antibacterial activity of quinolones (measured in terms of MIC), however, is the result of the combination of bacterial cell penetration and DNA gyrase inhibitory activity. The antibacterial activity of quinolones depends not only on the bicyclic heteroaromatic system combining the 1,4-dihydro-4-pyridine-3-carboxylic acid moiety and an aromatic ring, but also on the nature of the peripheral substituents and their spatial relationships. These substituents exert their influence on bacterial activity by providing additional affinity for bacterial enzymes, enhancing cell penetration or altering the pharmacokinetics.

The research for an ideal quinolone continues worldwide. Such a quinolone must be biologically active on a large spectrum of gram positive and gram negative bacteria, aerobes and anaerobes and mycobacteria, must have as few side effects as possible, excellent solubility in water and oral bioavailability.

In figure 5, the most common synthesized chemical variations obtained during the research for new quinolones with antibacterial activity, are visible.

Fig. 5. Structural variations of the most recent quinolones.
2. Quinolones: Structural features and method of synthesis

2.1 Structural features

Quinolone derivatives are an important class of antibacterial agents with wide action. Basic structure of these compounds (Figure 6) is a bicyclic structure, which contains a ring of type A 4-piridinona combined with aromatic or heteroaromatic ring B. The ring type A 4-piridinona is a ring with absolute necessity: an unsaturation in position 2-3, a free acid function in position 3 and a substituent at nitrogen in position 1.

![Figure 6. Basic structure of quinolones.](image)

2.1.1 Bicyclic quinolones

Position 1

The studies on quinolones indicated that in order for the compound to have antibacterial activity, the N-1 position requires a substituent. Many quinolones contain in N-position: ethyl (norfloxacin, pefloxacin, lomefloxacin), fluoroethyl (fleroxacin), vinyl, chloroethyl, trifluoroethyl, aminoethyl, cyclopropyl (ciprofloxacin), t-butyl, bicyclopentyl, p-fluorophenyl, 2,4-difluorophenyl (Scott 1997)

Position 2

Quinolones contain at C-2 hydrogen (R₂=H). The replacement at hydrogen has generally proven to be disadvantageous. However, some compounds containing a suitable C-1, C-2 ring have recently been shown to possess biological activity. (Figure 7 - Segawa 1992) (Figure 8 - Scott 1997)

![Figure 7. Basic structure of bicyclic quinolones.](image)
**Antimicrobial Agents**

R = H, methyl, ethyl, substituted phenyl

R₆= F, Cl

R₇= heterocycle

Fig. 8. 7-Substituted-6-halo-4-oxo-4H-[1,3]-thiazeto[3,2]quinolin-3-carboxylic acid.

**Position 3**

The C-3 carboxylic acid moiety is most commonly encountered. (Chu & Fernandes 1991). In the late of 1980s, a modification was described that eliminated the need for C-3 carboxylic acid. A fused isothiazolone ring was identified as serving as a carboxylic acid mimic. The compound A-62824 (Figure 9) have been found with biological activity.

Fig. 9. Quinolones with sulfur substituent at C-2.

Fig. 10. A-62824.

**Position 4**

The C-4 oxo group of the quinolones nucleus is generally considered to be essential for antibacterial activity.

**Position 5**

The choice of the C-5 substituent appears to be dictated by the the steric regulations and the nature of the N-1 and C-8 substituent (Chu & Fernandes 1991). (R₅ = methyl, halogen, amino when X = CF).
Position 6

The nature of the C-6 substituent have a great impact on the DNA-gyrase inhibitory activity and cell penetration. (Domagala et al. 1986). The $R_6$ can be H, Cl, F, NO$_2$, NH$_2$, CN, CH$_3$SCH$_3$, COCH$_3$ (Koga et al. 1980)

Position 7

The choice of the C-7 substituent is a key issue which continues to guide the design of new antibacterial quinolones. The $R_7$ can be substituted/unsubstituted piperazines, aminopyrrolidines, aminoalkylypyrrolidines, (Figure 5) (Chu & Fernandes 1991) (Scott 1997).

Position 8

The most common variations at the C-8 position is hydrogen atom (X= CH) or a nitrogen atom (a naphthyridine) (X=N). However, compact, lipophilic group (X = CF, C-F$_3$, CCl, C-OCH$_3$) increase the antibacterial activity. (Chu & Fernandes 1991) (Scott 1997).

2.2 Method of synthesis

Gould-Jacobs method

The quinolones are of synthetic origin. (Chu & Fernandes, 1991). The most common synthetic methodology to prepare quinolone derivatives is Gould-Jacobs method (Figure 11). This method is used mainly for synthesis of compounds with N-1 alkyl substituents, and consists in the condensation of anilines (II) with diethyl ethoxymethylenemalonate (EMME) and cyclization of the obtained anilinomethylenemalonate. Thermal cyclization can be carried out in dioxane (Koga, et al.1980), chlorosulfonic acid, oleum acid or a mixture of chlorosulfonic acid and oleum acid (Saukaita & Gupton, 1996). The key intermediary obtained (IV or X) will undergo an alkylation (Koga et al. 1980), cycloalkylation with bromocyclopropane (Kazimierozaack & Pyznar, 1987), (Sanjose&Ulpiano 1986), or with 1-bromo-1-ethoxy-cyclopropane, arylation with para-nitro-clorofenil or 2,4-dinitro-clorofenil (Raddl & Zikan, 1989) in order to insert the substituent into position 1 of the quinolone nucleus. The ethyl ester (V) undergoes a hydrolysis reaction, and the quinoline-3-carboxylic acid (VI), following regiospecific substitution of the 7-chloro group leads to the final compounds (VIII). Figure 11 illustrates also, methods for synthesis of 1-cyclopropyl-quinolones starting to anilines of formula II. Anilines (II) is reacted with 1-bromo-1-ethoxy-cyclopropane (Ramos & Garcia 1994)(Scriewer et al. 1988) or a cyclopropyl-metalic compound (McGuirk 1989). Alternatively, N-ethyl substituted anilines of formula XV may be formed by reductive amination with an appropriate aldehyde and a suitable reducing agent: diboran, palladium on carbon with hydrogen, sodium borohydride or sodium cyanoborohidride (McGuirk 1989) (Ramos 1994). N-isopropyl substituted quinolones may be form by alkylation with isopropylbromide (Pintilie et al. Sept. 2009), (Pintilie et al, oct.2009),(Pintilie et al. 2010), of compounds IV. (Figure 11).

The modified Gould-Jacobs method will also be used, where the diethyl ethoxymethylenemalonate reacts with monosubstituted N aniline (XVII) (Figure 12). The aniline (XVII) is obtained by reductive amination of ketones and aldehydes with sodium borohydride-acetic acid (Itoh & Kato 1984) or triacetoxyborohydride. (Pintilie et al.2009). (Pintilie et al. 2010).
compound (HOCH=CHOEt) to provide key compound (V). Another synthesis method requires the reaction of isatoic anhydride with sodium ethyl formate (Figure 11). The benzoxazindione (XXII) is then condensed with 2,4,6-trihalobenzoic acid (XX) in reflux with an appropriate amine, and treated with the compound :R_2R_3CO (R_2 = R_3 = Cl, CCl_3 or R_2 = C_1-10 alkyl and R_3 = Cl) to produce benzoxazindione (XXII). The benzoxazindione (XXII) is then treated with the compound HOCH=CHOEt and refluxed with an appropriate amine, and the benzoxazindione (XXII) is then treated with the compound :R_2R_3CO (R_2 = R_3 = Cl, CCl_3 or R_2 = C_1-10 alkyl and R_3 = Cl) to produce benzoxazindione (XXII).
Fig. 12. The modified Gould-Jacobs method.

Fig. 13. Method requires the reaction of isatoic anhydride with sodium ethyl formyl acetate

*Intramolecular nucleophilic displacement cyclization route to quinolones (a)*

An efficient and regiospecific synthesis via an intramolecular nucleophilic displacement cyclization reaction was reported. (Chu, 1985) (Figure 14).

Key compound (III) can be obtained by:

- reaction of benzoic acid chloride (I) with ethyl malonic acid; the compound (II) give the compound (III), (Petersen & Grohe 1984a), (Petersen & Grohe 1984b),
- acetophenone (Ia) is condensed with diethyl carbonate in the presence of sodium hydride (Chu et al. 1985)
Fig. 14. Intramolecular nucleophilic displacement cyclization route to quinolones (a).

Intermediates (III) reacts with acetic anhydride in the presence trietilortoformiate to produce 3-ethoxy-2-benzoyl-ethyl acrylate (IV). Compound (IV) is further reacted with an appropriate amine in dichloromethane at room temperature to provide 3-anilino-2-benzoyl-ethyl acrylate (IVa).

Compound (IVa) can be also obtained directly from benzoic acid chloride (I). (Chu & Fernandes 1991).

Treatment with a base induces cyclization to produce the quinolone (V).
Intramolecular nucleophilic displacement cyclization route to quinolones (b)

A synthesis method similar to that described above is shown in Figure 15. This method involves intramolecular cyclization of the compound (VIII). (Egawa et al. 1987).

Fig. 15. Intramolecular nucleophilic displacement cyclization route to quinolones (b).

2.3 Structure of the new compounds

This paper presents experimental data regarding the synthesis of several quinolones with general formula: (Figure 16)
Fig. 16. The structure of the new compounds.

\[ R_1 = \text{ethyl, isopropyl, 2-buthyl, 2-pentyl, benzyl, alyl, } p\text{-nitro-phenyl, } p\text{-amino-phenyl}; \]
\[ R_6 = \text{hydrogen, fluor, chlor, methyl}; \]
\[ R_7 = \text{3-methyl-piperazinyl, 4-methyl-piperazinyl, piperidinyl, 3-methyl-piperidinyl, } \]
\[ 4\text{-methyl-piperidinyl, pirolidinyl, morpholinyl, homopiperazinyl}; \]
\[ R_8 = \text{hydrogen, chlor, methyl. methoxy, nitro} \]

2.4 Synthesis pathway

The synthesis of the novel quinolones followed a Gould-Jacobs cyclization process (Figure 17). An appropriate unsubstituted aniline (1) is reacted with diethylethoxy methylene malonate (EMME) to produce the resultant anilinomethylene malonate (2). A subsequent thermal process induces Gould-Jacobs cyclization to afford the corresponding 4-hydroxy-quinoline-3-carboxylate ester (3). (R_6 = fluor, chlor, methyl, hydrogen) (Pintilie et al. 2009a) (Pintilie et al. 2009b), (Pintilie et al. 2010).

Fig. 17. Synthesis of the new quinolones.

The following operation is the alkylation of the 4-hydroxy-quinoline-3-carboxylate ester (3), which is usually accomplished by reaction with a suitable alkyl halide, dialkyl sulphates, aril
halide to produce the quinolone 3-carboxylate ester (6). ($R_1 = \text{ethyl, alyl, benzyl, } p$-nitrophenyl) (Pintilie et al. 2003a) (Pintilie et al. 2003b), (Pintilie et al. 2003c) (Pintilie & Nita 2011).

A modified approach resorts to the use of a monosubstitued aniline (4) as a starting material which avoids subsequent N-1-amine alkylation ($R_1 = \text{isopropyl, 2-butyl, 2-pentyl}$). (Pintilie et al. 2009a) (Pintilie et al. 2009b), (Pintilie et al. 2010). A strong acid (such as polyphosphoric acid) is often needed to induce cyclization directly resulting in the formation of N-isopropyl-4-oxo-quinolone-3-carboxylate ester (6) ($R_1 = \text{isopropyl, 2-butyl, 2-pentyl}$). In either case, the final manipulation is acid or basic hydrolysis to cleave the ester generating the biologically active free carboxylic acid (7). The biologically active free carboxylic acid (7) was also obtained from the corresponding 4-hidroxy-quinoline-3-carboxylate ester (3) 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 heterocycle yielded compounds (8).

The synthesis of new 1-aryl quinoline-3-carboxylic acids is according Figure 18. Compound (3) ($R_6 = \text{F,Cl,CH}_3$) is direct N-arylation. Treatment of (3) with potassium carbonate in DMSO and $p$-fluoro-nitrobenzene yielded 9). The esters were hydrolized to the appropiate acids (10) by refluxing with a mixture of hydrochloric and acetic acids. Upon treatment with a heterocycle yielded compounds (11). The 1-$p$ amino-phenyl)-quinoline-3-carboxylic acids (12) can be prepared by a common reduction of nitro group using sodium dithionite.

![Fig. 18. Simthesis of 1-aryl-quinolones.](image-url)

The synthesis of the new 8-substituted quinoline-3-carboxylic acids is according Figure 19. 8-Chloro-quinoline-3-carboxylic acids (13) was synthesized from 8-unsubstituted quinoline-3-carboxylic acids by chlorination with sulphuryl chloride. 8-Methoxy-quinoline-3-carboxylic acids (14) was prepared allowing compound (13) to act with alkali metallic alkolate.

![Fig. 19. Simthesis of the new 8-substituted quinoline-3-carboxylic acids.](image-url)
2.5 New compounds: Structure and antimicrobial activity

2.5.1 Structure of the new compounds

A series of new 4-oxo-1,4-dihydro-quinoline-3-carboxylic acids was synthesized. (Figure 20) (Table 1).

![Chemical structure of new compounds](image)

**Fig. 20. Structure of the new compounds.**

<table>
<thead>
<tr>
<th>Quinolones</th>
<th>R₁</th>
<th>R₆</th>
<th>R₇</th>
<th>R₈</th>
<th>m.p. (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q 83</td>
<td>ethyl</td>
<td>F</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>235-237</td>
<td>Pintilie et al. (2003b)</td>
</tr>
<tr>
<td>Q 85</td>
<td>ethyl</td>
<td>F</td>
<td>4-methyl-piperidin-1-yl</td>
<td>Cl</td>
<td>201-202.5</td>
<td>Pintilie et al. (2003b)</td>
</tr>
<tr>
<td>PQ 1</td>
<td>ethyl</td>
<td>F</td>
<td>4-methyl-piperidin-1-yl</td>
<td>OCH₃</td>
<td>170</td>
<td>Pintilie et al. (2003b)</td>
</tr>
<tr>
<td>PQ 12</td>
<td>iso-propyl</td>
<td>F</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>253</td>
<td>Pintilie et al. (2003b)</td>
</tr>
<tr>
<td>PQ 11</td>
<td>benzyl</td>
<td>F</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>240-242</td>
<td>Pintilie et al. (2003b)</td>
</tr>
<tr>
<td>PQ 4</td>
<td>alyl</td>
<td>F</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>168-170</td>
<td>Pintilie et al. (2003b)</td>
</tr>
<tr>
<td>FFQ 24</td>
<td>ethyl</td>
<td>F</td>
<td>3-methyl-piperidin-1-yl</td>
<td>H</td>
<td>189,4</td>
<td>Pintilie et al. (2009b)</td>
</tr>
<tr>
<td>6ClPQ 24</td>
<td>ethyl</td>
<td>Cl</td>
<td>3-methyl-piperidin-1-yl</td>
<td>H</td>
<td>216,4-218,4</td>
<td>Pintilie et al. (2009b)</td>
</tr>
<tr>
<td>PQ 24</td>
<td>iso-propyl</td>
<td>F</td>
<td>3-methyl-piperidin-1-yl</td>
<td>H</td>
<td>209,1-211,7</td>
<td>Pintilie et al. (2009b)</td>
</tr>
<tr>
<td>PQ 22</td>
<td>iso-propyl</td>
<td>F</td>
<td>3-methyl-piperazin-1-yl</td>
<td>H</td>
<td>215-218</td>
<td>Pintilie et al. (2009b)</td>
</tr>
<tr>
<td>PQ 23</td>
<td>iso-propyl</td>
<td>F</td>
<td>morpholin-1-yl</td>
<td>H</td>
<td>266-268</td>
<td>Pintilie et al. (2009b)</td>
</tr>
<tr>
<td>FFQ 25</td>
<td>ethyl</td>
<td>F</td>
<td>morpholin-1-yl</td>
<td>H</td>
<td>257,4-258,7</td>
<td>Pintilie et al. (2009b)</td>
</tr>
<tr>
<td>6ClPQ 25</td>
<td>ethyl</td>
<td>Cl</td>
<td>morpholin-1-yl</td>
<td>H</td>
<td>267,1-269,2</td>
<td>Pintilie et al. (2009b)</td>
</tr>
<tr>
<td>6ClPQ 27</td>
<td>ethyl</td>
<td>Cl</td>
<td>3-methyl-piperazin-1-yl</td>
<td>H</td>
<td>170,5-171,4</td>
<td>Pintilie et al. (2009b)</td>
</tr>
</tbody>
</table>
Quinolones: Synthesis and Antibacterial Activity

<table>
<thead>
<tr>
<th>Quinolones</th>
<th>R₁</th>
<th>R₆</th>
<th>R₇</th>
<th>R₈</th>
<th>m.p. (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPQ 28</td>
<td>ethyl</td>
<td>F</td>
<td>morpholin-1-yl</td>
<td>Cl</td>
<td>244.6-244</td>
<td>Pintilie et al. (2009b)</td>
</tr>
<tr>
<td>6MeQ 83</td>
<td>ethyl</td>
<td>CH₃</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>240-242</td>
<td>Pintilie et al. (2003a)</td>
</tr>
<tr>
<td>6MePQ 12</td>
<td>isopropyl</td>
<td>CH₃</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>234-235</td>
<td>Pintilie et al. (2003a)</td>
</tr>
<tr>
<td>6MePQ 11</td>
<td>benzyl</td>
<td>CH₃</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>218-220</td>
<td>Pintilie et al. (2003a)</td>
</tr>
<tr>
<td>6MePQ 4</td>
<td>allyl</td>
<td>CH₃</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>244-246</td>
<td>Pintilie et al. (2003a)</td>
</tr>
<tr>
<td>PQ 83</td>
<td>ethyl</td>
<td>H</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>240-242</td>
<td>Pintilie et al. (2003c)</td>
</tr>
<tr>
<td>HPQ 12</td>
<td>isopropyl</td>
<td>H</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>234-235</td>
<td>Pintilie et al. (2003c)</td>
</tr>
<tr>
<td>HPQ 11</td>
<td>benzyl</td>
<td>H</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>218-220</td>
<td>Pintilie et al. (2003c)</td>
</tr>
<tr>
<td>HPQ 4</td>
<td>allyl</td>
<td>H</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>244-246</td>
<td>Pintilie et al. (2003c)</td>
</tr>
<tr>
<td>HPQ 21</td>
<td>isopropyl</td>
<td>H</td>
<td>4-methyl-piperazin-1-yl</td>
<td>H</td>
<td>239-240</td>
<td>Pintilie et al. (2009a)</td>
</tr>
<tr>
<td>HPQ 24</td>
<td>ethyl</td>
<td>H</td>
<td>3-methyl-piperidin-1-yl</td>
<td>H</td>
<td>190,1-192,1</td>
<td>Pintilie et al. (2009a)</td>
</tr>
<tr>
<td>HPQ 25</td>
<td>ethyl</td>
<td>H</td>
<td>morpholin-1-yl</td>
<td>H</td>
<td>267,3-269</td>
<td>Pintilie et al. (2009a)</td>
</tr>
<tr>
<td>HPQ 27</td>
<td>ethyl</td>
<td>H</td>
<td>3-methyl-piperazin-1-yl</td>
<td>H</td>
<td>191,3-192,6</td>
<td>Pintilie et al. (2009a)</td>
</tr>
<tr>
<td>HPQ 31</td>
<td>2-butyl</td>
<td>H</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>181,4-183</td>
<td>Pintilie et al. (2009a)</td>
</tr>
<tr>
<td>HPQ 51</td>
<td>2-pentyl</td>
<td>H</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>138,5-140,5</td>
<td>Pintilie et al. (2009a)</td>
</tr>
<tr>
<td>PQ 3</td>
<td>p-nitrophenyl</td>
<td>F</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>204-206</td>
<td>Pintilie&amp;Nita (2011)</td>
</tr>
<tr>
<td>PQ 7</td>
<td>p-nitrophenyl</td>
<td>F</td>
<td>Homopiperazin-1-yl</td>
<td>H</td>
<td>128-130</td>
<td>Pintilie&amp;Nita (2011)</td>
</tr>
<tr>
<td>6ClCPQ 3</td>
<td>p-nitrophenyl</td>
<td>Cl</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>202-205</td>
<td>Pintilie&amp;Nita (2011)</td>
</tr>
<tr>
<td>6MePQ 3</td>
<td>p-nitrophenyl</td>
<td>CH₃</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>222-224</td>
<td>Pintilie&amp;Nita (2011)</td>
</tr>
<tr>
<td>APQ 3</td>
<td>p-amino-phenyl</td>
<td>F</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>284-285,5</td>
<td>Pintilie&amp;Nita (2011)</td>
</tr>
<tr>
<td>A6MePQ 3</td>
<td>p-amino-phenyl</td>
<td>CH₃</td>
<td>4-methyl-piperidin-1-yl</td>
<td>H</td>
<td>250-253</td>
<td>Pintilie&amp;Nita (2011)</td>
</tr>
</tbody>
</table>

Table 1. 4-Oxo-1,4-dihydro-quinoline-3-carboxylic acids synthesized in this paper.
2.5.2 Antibacterial activity of the new compounds

The new compounds were evaluated for “in vitro” activity by determining minimum inhibitory concentration against bacteria *Escherichia Coli*, *Staphylococcus Aureus* and *Pseudomonas aeruginosa*, by agar dilution method (Buiuc 1998) (NCCLS 2003). (Table 2).

<table>
<thead>
<tr>
<th>Quinolone</th>
<th>Minimum inhibitory concentration µg/ml</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. coli</td>
<td>S. aureus</td>
</tr>
<tr>
<td>Q 83</td>
<td>3,12 (a)</td>
<td>1,56 (c)</td>
</tr>
<tr>
<td>Q 85</td>
<td>3,12 (a)</td>
<td>0,39 (c)</td>
</tr>
<tr>
<td>PQ 1</td>
<td>3,12 (a)</td>
<td>0,78 (c)</td>
</tr>
<tr>
<td>PQ 4</td>
<td>12,5 (a)</td>
<td>1,56 (c)</td>
</tr>
<tr>
<td>FPQ 24</td>
<td>2,00 (a)</td>
<td>0,50 (b)</td>
</tr>
<tr>
<td>6CIPQ 24</td>
<td>8,00 (a)</td>
<td>2,00 (b)</td>
</tr>
<tr>
<td>PQ 24</td>
<td>8,00 (a)</td>
<td>2,00 (b)</td>
</tr>
<tr>
<td>PQ 22</td>
<td>0,50 (a)</td>
<td>4,00 (b)</td>
</tr>
<tr>
<td>6CIPQ 25</td>
<td>4,00 (a)</td>
<td>2,00 (b)</td>
</tr>
<tr>
<td>FPQ 25</td>
<td>0,125 (a)</td>
<td>0,06 (b)</td>
</tr>
<tr>
<td>FPQ 28</td>
<td>0,125 (a)</td>
<td>0,06 (b)</td>
</tr>
<tr>
<td>HPQ 21</td>
<td>8,00 (a)</td>
<td>64,00 (b)</td>
</tr>
<tr>
<td>HPQ 25</td>
<td>8,00 (a)</td>
<td>64,00 (b)</td>
</tr>
<tr>
<td>HPQ 27</td>
<td>&gt;128 (a)</td>
<td>32,00 (b)</td>
</tr>
<tr>
<td>P 3</td>
<td>12,50 (a)</td>
<td>25,00 (c)</td>
</tr>
<tr>
<td>APQ 3</td>
<td>12,50 (a)</td>
<td>0,78 (c)</td>
</tr>
<tr>
<td>PQ 7</td>
<td>12,50 (a)</td>
<td>3,12 (c)</td>
</tr>
</tbody>
</table>

Table 2: “In vitro” antibacterial activity of the new quinolones.

**3. Conclusion**

In conclusion, were synthesized new quinolones and was investigated their antibacterial activity. The results indicate that substituent combinations in the quinolone ring, might produce powerful antibacterial agents such as compound: FPQ-28 (1-ethyl-6-fluoro-7-morpholinyl-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid). (Figure 21) in concordance with the QSARs studies (Tarko et al. 2008). showed excellent “in vitro” activity against *E. Coli* ATCC 25922 (MIC 0,125 µg/mL) and *S.aureus* ATCC29213 (MIC 0,06 µg/mL).
Fig. 21. 1-Ethyl-6-fluoro-7-morpholinyl-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid –FPQ 28

1H-NMR(dmso-d6, δ ppm, J Hz): 8.97(s, 1H, H-2); 8.07(d, 1H, H-5, 11.8); 4.89(q, 2H, H-17, 7.2); 3.82(m, 4H, sist. A2B2, H-13-15); 3.37(m, 4H, sist. A2B2, H-12-16); 1.46(t, 3H, H-18, 7.2).

13C-NMR(dmso-d6, δ ppm, J Hz): 175.56(C-4); 166.12(C-21); 154.95(d, J(13C-19F)=254.8, C-6); 158.37(Cq); 153.04(C-2); 125.94(Cq); 124.76(Cq); 116.86(Cq); 111.57(d, J(13C-19F)=23.5, C-5); 98.35(C-3); 67.23(C-13-15); 53.64(C-12-16); 51.58(Cq); 16.14(C-18).

FT-IR(solid in ATR, νcm⁻¹): 3056; 2957; 2895; 2849; 1717; 1615; 1558; 1532; 1492; 1435; 1376; 1300; 1253; 1207; 1102; 1033; 980; 920; 890; 846; 803; 740; 651; 528; 464.

4. References


*** National Committee on Clinical Laboratory Standards (NCCLS) (2003) *Antimicrobial Susceptibility Standards* (ATS), ed. 2003, for M7 (CMI) şi M100