

Synthesis and antitubercular activity of lipophilic moxifloxacin and gatifloxacin derivatives

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Abstract—Fluoroquinolone (FQ) has a broad spectrum of activity against several bacteria, mycobacteria, parasites, and other diseases. Moxifloxacin and gatifloxacin are a new generation of fluoroquinolone agents with improved activity against Gram-negative and positive bacteria. As lipophilicity is an important consideration in the design and activity of novel antibacterial agents, we report in this work the synthesis and biological evaluation of 12 lipophilic moxifloxacin or gatifloxacin derivatives, by reaction of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid **13** with several *N*-monoalkyl 1,2-ethanediamine or 1,3-propanediamine.

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The discovery of the FQs during the 1980s improved the treatment of infectious diseases, due to their fewer toxic side effect. This class of compounds has, when compared to the previous existing bactericidal drugs, enhanced pharmacokinetics properties and extensive and potent activity against various parasites, bacteria, and mycobacteria, including resistant strains.¹ This class of antibiotics is the first-line therapy for complicated urinary tract and bacterial diarrhea. They are also alternative agents for the treatment of many sexually transmitted diseases, as well as osteomyelitis, some cases of wound infection, and selected respiratory infections.¹ The history of quinolones began in 1962,² when Leshner accidentally discovered the nalidixic acid, 1-ethyl-1,4-dihydro-7-methyl-1,8-naphthylidene-3-carboxylic acid, as by-product of the synthesis of the antimalarial compound chloroquine. In 1963, the nalidixic acid was approved by The Food and Drug Administration (FDA) for the treatment of urinary tract infection. However, the importance of the FQs started in the early

1980s with the discovery that a combination of a fluorine atom at position 6 and a piperazinyl group at position 7 resulted in a broad and potent antimicrobial activity, producing the norfloxacin, the first of a new generation of FQs antibacterials.³ This combination produced a broad spectrum of activity and better pharmacokinetic profile against Gram-negative, Gram-positive bacteria, and mycobacteria with antibacterial activities 1000 times more potent than those observed in the nalidixic acid.

After the discovery of the norfloxacin, structure–activity relationships (SAR) analysis of the fluoroquinolonic nucleus led to the development of new derivatives with better solubility, higher antimicrobial activity, prolonged serum half-life, fewer adverse side effects, and both oral and parenteral routes of administration.^{1,4} The quinolones can be classified in four generations. The first generation is represented by nalidixic acid and cinoxacin, the second one by norfloxacin, ciprofloxacin (Fig. 1), ofloxacin, enoxacin, and lomefloxacin, the third one by levofloxacin, sparfloxacin, and gatifloxacin (Fig. 1) and, finally, the fourth generation is represented by moxifloxacin (Fig. 1) and trovafloxacin.⁴ The bactericidal activity generated by FQs is caused by the inhibition of two bacterial enzymes: DNA gyrase and topoisomerase IV enzymes. DNA gyrase (topoisomerase II) is an

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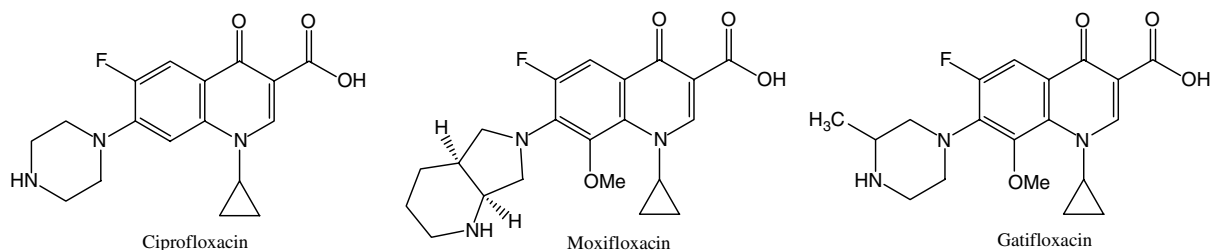


Figure 1. Structure of some fluoroquinolones.

essential enzyme involved in the replication, transcription, and repair of the bacterial DNA and topoisomerase IV is an enzyme responsible for the separation of daughter DNA strands during bacterial cell division. In Gram-negative organisms DNA gyrase is the primary target, in the case of topoisomerase IV the Gram-positive bacteria are the most affected ones.¹

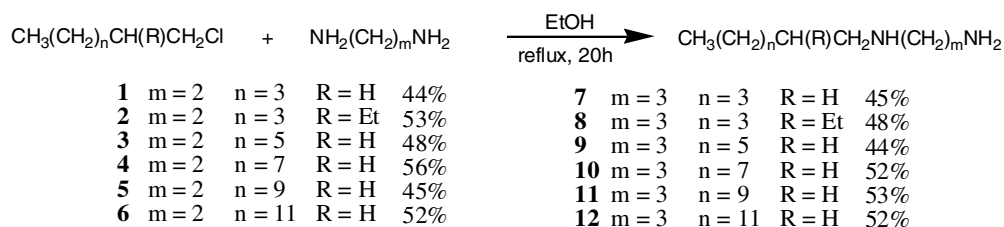
It was observed that C-8 halogen and methoxy FQs derivatives are more active against resistant *M. tuberculosis* than the C-8 H compound ciprofloxacin.^{1,5–10} Moxifloxacin and gatifloxacin are 8-methoxy-fluoroquinolones with enhanced anti-Gram-positive activity in vitro compared with other fluoroquinolones of second generation such as ciprofloxacin and ofloxacin.^{5–8} Moxifloxacin was recently suggested by the American Thoracic Society to be used against tuberculosis.^{1,9} Modification of the substituents at the C-7 position of fluoroquinolone ring could affect the pharmacokinetic profile and the spectrum of activity of this class of antibiotics. A vast number of quinolones differing by the C-7 substituent were prepared aiming at the establishment of structure/antibacterial and antituberculosis relation-

ships.¹⁰ Mycobacteria have lipid-rich cell walls and lipophilicity is an important consideration in the design of novel analogs.¹¹

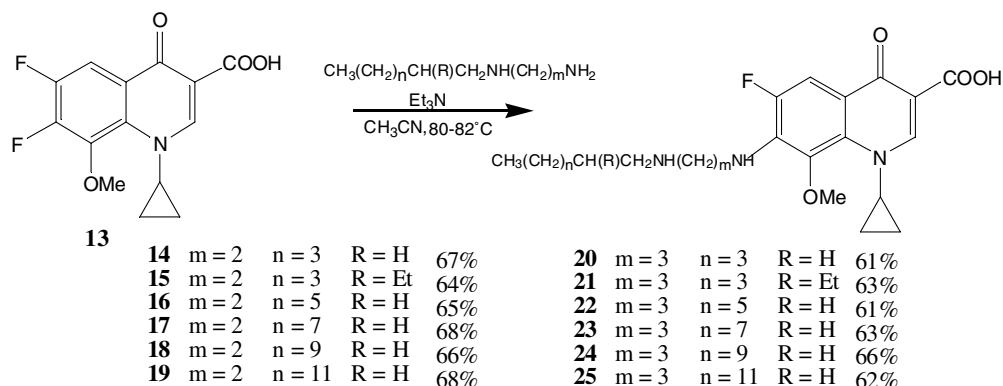
In this context, this work describes the synthesis and antitubercular evaluation of 12 lipophilic moxifloxacin or gatifloxacin analogs. We recently described the synthesis and anti-TB activity of some *N*-acyl diamine derivatives.¹² Furthermore, Shoaib described the antibacterial activity of 1,3-propanediamine fluoroquinolone derivatives.¹³

In this work, we planned the substitution of the 1,2-diamine moiety present in the moxifloxacin or gatifloxacin structure by *N*-alkylated 1,2-ethanediamine or 1,3-propanediamine. The new compounds were prepared by reaction of fluoride **13** with different *N*-alkyl-1,2-ethanediamine or 1,3-propanediamine (Schemes 1 and 2).

The synthesis of different moxifloxacin or gatifloxacin derivatives has been achieved by a simple method described in the general procedure.^{14,15} The *N*-alkyl-diamines were prepared in 44–56% yields by reaction of



Scheme 1.



Scheme 2.

Table 1. In vitro antitubercular activities

Compound	MIC ($\mu\text{g/mL}$)
14	5
15	0.62
16	12.5
17	0.62
18	1.25
19	6.25
20	50
21	2.5
22	1.25
23	0.31
24	0.62
25	0.62
Rifampicin	1.0
Gatifloxacin	0.1

different alkyl chlorides with 1,2-ethanediamine or 1,3-propanediamine (Scheme 1).¹⁴ The low yield in the preparation of *N*-alkyl-diamines is due to the formation of the corresponding *N,N'*-dialkyl-diamines. The reaction between fluoroquinolone intermediate **13**, which was furnished by Xiamen Mchem Pharma group (Xiamen, China), and the respective *N*-alkyl-diamines **1–12** afforded the desired fluoroquinolone derivatives **14–25** in 61–68% yields (Scheme 2).¹⁵

The activity of the compounds against *M. tuberculosis* virulent strain H37Rv was determined in vitro as previously described¹⁶ (Table 1). The minimum inhibitory concentration (MIC), concentration that inhibits the colony, forming ability of *M. tuberculosis*, was determined by incorporating decreasing concentrations of the test compound in Middle brook 7H9 agar medium. MIC values represent means of three separate experiments. Compound **23** inhibited bacterial growth at 0.31 $\mu\text{g/mL}$, whereas compounds **15**, **17**, **24**, and **25** inhibited growth at a concentration of 0.62 $\mu\text{g/mL}$.

The size of the spacer seems to be important: all 1,3-propanediamine derivatives had higher MIC than the 1,2-ethanediamine derivatives with the same alkyl chain. In the two series the best activity was displayed by compounds **17** (MIC 0.62 $\mu\text{g/mL}$) and **23** (MIC 0.31 $\mu\text{g/mL}$), both having a 10 carbon alkyl chain, which would be the ideal length. Compounds **14** and **20**, with shorter alkyl chains, exhibited moderate activities (MIC = 50 $\mu\text{g/mL}$). Ramificated compound **15** showed a better activity (MIC 0.62 $\mu\text{g/mL}$) than its linear analog **16** (MIC 12.5 $\mu\text{g/mL}$), maybe due to its volume. In the propanediamine series, the linear compound **22** was more active than the ramificated analog **21**.

In summary, this work describes the synthesis, characterization, and anti-TB evaluation of 12 lipophilic moxifloxacin or gatifloxacin derivatives, by reaction of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid **13** with several *N*-alkyl-1,2-ethanediamine or 1,3-propanediamine. The minimum inhibitory concentration (MIC) against *M. tuberculosis* demonstrated that compound **23** inhibited growth at 0.31 $\mu\text{g/mL}$, whereas compounds **15**, **17**, **24**, and **25** inhibited growth at 0.62 $\mu\text{g/mL}$ concentration. It seems that

the antitubercular activity depends on the alkyl chains, size or ramification. Ideal chain contains 10 carbon atoms, which could be a good starting point to find new lead compounds.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.07.073.

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- General procedure for the preparation of *N*-alkyl-1,2-ethanediamine and *N*-alkyl-1,3-propanediamine. To a solution of 1,2-ethanediamine or 1,3-propanediamine (100 mmol) in 50 mL of ethanol at reflux was slowly added the alkyl chloride (50 mmol). The reaction mixture

was maintained under reflux during 24 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: dichloromethane:methanol) furnishing compounds **1–12** in 44–56% yield.

15. General procedure for the preparation of fluoroquinolone derivatives. A solution of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid **13** (1.0 mmol), *N*-alkyl-1,2-ethanediamine or *N*-alkyl-1,3-propanediamine (1.0 mmol), and triethylamine (1 mmol)

in 5 mL of CH₃CN was refluxed for 24 h. The white precipitate was removed by filtration, washed with CH₃CN, recrystallized, and dried in vacuo to give the desired compounds **14–25** in 61–68% yield.

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