Perspectives on the Development of Novel Potentially Active Quinolones Against Tuberculosis and Cancer

V. Facchinetti[1,2], C.R.B. Gomes[2], M.V.N. de Souza[2] and T.R.A. Vasconcelos*[,1]

[1]*Universidade Federal Fluminense, Instituto de Química, Departamento de Química Orgânica, Programa de Pós-Graduação em Química. Outeiro de São João Batista, s/no, Centro, Niterói, 24020-141, Rio de Janeiro, Brazil;* [2]*Fundação Oswaldo Cruz, Instituto de Tecnologia em Fármacos - Farmanguinhos. Rua Sizenando Nabuco 100, Manguinhos, 21041-250, Rio de Janeiro, RJ, Brazil*

Abstract: Quinolones and its derivatives comprise an important group of heterocyclic compounds that exhibit a wide range of pharmacological properties such as antibacterial, antitumor, antiviral, anti-ischemic, antiparasitic and anxiolytic. Persistent efforts have been made over the years to develop novel congeners with superior biological activities and minimal potential for undesirable side-effects. The present review aims to highlight some recent discoveries on the development of novel quinolone-based compounds with potential antitubercular and anticancer activity.

Keywords: Biological activity, cancer, drugs, quinolones, tuberculosis.

INTRODUCTION

Quinolones core structures play an important role in the design of new drugs, since they have been found to possess interesting and diversified pharmacological activities [1]. Although they are well recognized as antimicrobial agents, they are also endowed with antitumor [2], antiviral [3], anti-ischemic [4], antiparasitic [5] and anxiolytic [6] activities. Persistent efforts have been made over the years to develop novel congeners with superior biological activities and minimal potential for undesirable side-effects.

Quinolones consist of a bicyclic structure in which a pyridinic ring is fused to a benzene moiety that possesses an atom of nitrogen at position 1 and a keto group on the pyridinic ring. The most active compounds have a keto group at position 4, a carboxyl group at position 3 and a fluorine atom at position 6 (Fig. **1**).

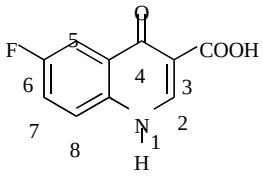

Fig. (1). General structure for 6-fluoro-4-quinolone-3-carboxylic acid nucleus.

The mode of action of quinolone antibacterials involves the inhibition of the bacterial type II DNA topoisomerases, DNA gyrase and topoisomerase IV, responsible for the supercoiling of bacterial DNA. The inhibition of these enzymes causes damages on DNA replication, like uncontrolled mRNA synthesis, and activates mechanisms that lead to apoptosis (Fig. **2**) [7-11]. It was also demonstrated that quinolone derivatives can inhibit mammalian topoisomerase II, one of the targets of DNA-active antitumor agents such as doxorubicin and etoposide. Thus, type II topoisomerases have been also explored as targets for anticancer therapies [1,12,13].

Due to its synthetic versatility, substituents in the 1-, 2-, 5-, 6-, 7-, 8- positions may be varied besides the possibility of functionalization at the carboxylic portion, quinolones are considered as a privileged scaffold that offer enormous scope in the field of medicinal chemistry. The most remarkable methodologies used to synthesize the quinolone scaffold include the Gould-Jacobs reaction, which consists of the condensation of anilines with a malonic ester, such as diethyl ethoxymethylene malonate, followed by thermal cyclization [14] and the Grohe-Heitzer cycloacylation through the reaction of a *β*-ketoester, first elaborated from a substituted benzoic acid or acetophenone, with an ortho ester under dehydrating conditions and subsequent addition-elimination reaction with a primary amine followed by cyclization [15]. Recently, Genelot *et al.* described the selective synthesis of 2-substituted-4-quinolones from carbonylative coupling of 2-iodoanilines with arylacetylenes through a *one-pot two-step multi-catalysis* using sequentially $[PdCl_2(dppp)]$ and $HNEt_2$ as catalysts [16,17].

In this review, we will highlight some recent discoveries on the development of novel quinolone-based compounds with potential antitubercular and anticancer activity, focusing on some synthetic strategies employed in order to obtain new analogues.

ANTITUBERCULAR ACTIVITY

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis*, also known as Koch's

*Address correspondence to this author at the Universidade Federal Fluminense, Instituto de Química, Departamento de Química Orgânica, Programa de Pós-Graduação em Química. Outeiro de São João Batista, s/no, Centro, Niterói, 24020-141, Rio de Janeiro, Brazil; Tel: +552126292230; Fax: +552126292144; E-mail: gqothatyana@vm.uff.br

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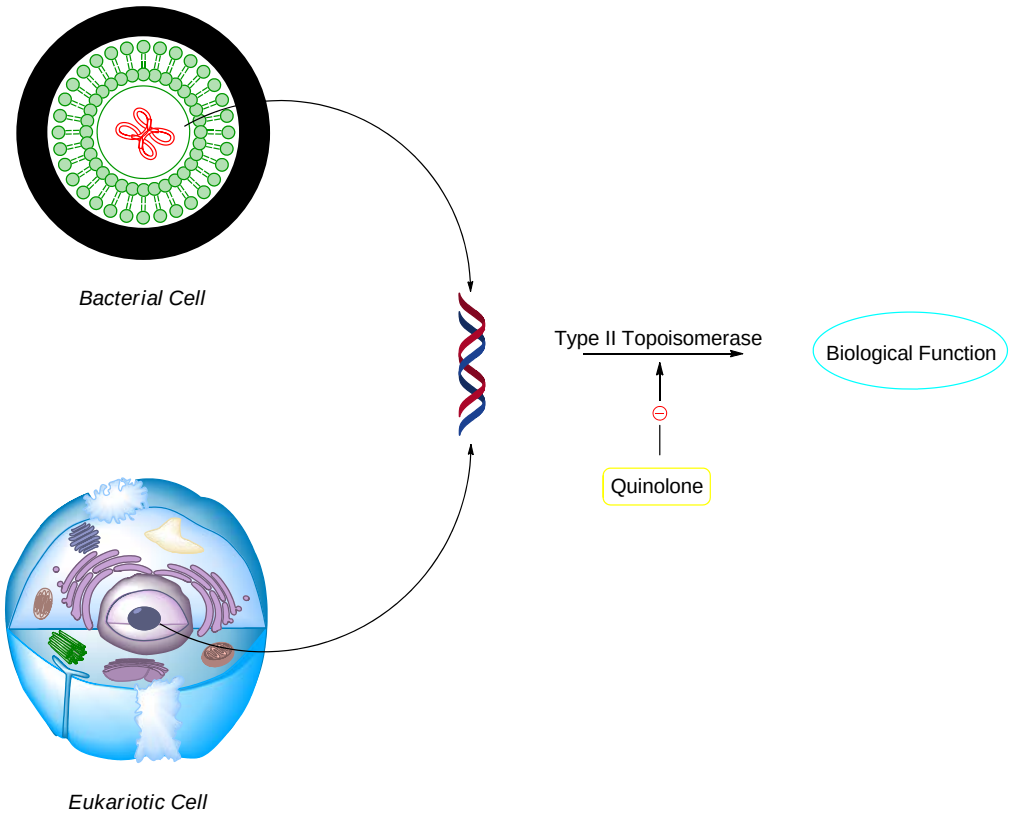


Fig. (2). Mechanism of action involving Type II topoisomerase inhibition.

bacillus. Its transmission occurs from person to person through dispersed contaminated microscopic droplets in air. TB most commonly attacks the lungs, but also can affect any organ of the body. The main symptoms are persistent cough, fever, night sweats, extreme tiredness and weight loss due to the lack of appetite. It is estimated that one-third of the world's population is currently infected with the TB bacillus and among these, 5-10% become sick. According to the World Health Organization (WHO), 1.7 million people died from TB in 2009. In Brazil, Rio de Janeiro is the state with major incidence of this disease, registering approximately 60.000 annual deaths from TB, with 20% of these cases associated to HIV virus co-infection [18,19].

The prevention of TB is achieved through vaccination of newborns with a vaccine called BCG (Bacille Calmette-Guérin). The treatment, that usually lasts 6 to 8 months, preferentially consists in a combination of the four first-line drugs: Isoniazid, Rifampicin, Pyrazinamide and Ethambutol [20].

In the last years, fluoroquinolones have become one of the main classes of chemotherapeutics for the treatment of a variety of bacterial infections (Fig. **3**). Even though they are not officially registered on the FDA for the treatment of tuberculosis, they are being used, according to a WHO recommendation, as second-line medicines in the fight against this disease, mainly due to the advent of multidrug-resistant tuberculosis strains [21-23]. For example, in Brazil, the Health Department recommends the use of Levofloxacin and Ofloxacin in association with other drugs for the treatment of MDR-TB (multidrug-resistant tuberculosis), which is defined as a form of tuberculosis resistant to at least the two main first-line TB drugs - Isoniazid and Rifampicin. Moxifloxacin is considered to be a reserve medicine used only in special cases for the treatment of XDR-TB (extensively drug-resistant tuberculosis), which is also resistant to any fluoroquinolone and any of the second-line anti-TB injectable drugs: Amikacin, Kanamycin or Capreomycin [24]. The use of fluoroquinolones as standard drugs for TB is already under investigation [21,25]. Some of the known drawbacks of antituberculous treatment with quinolones are some relevant drug interactions and the increased toxicity when used with other antituberculous or anti-HIV drugs. Also, several adverse reactions like gastrointestinal problems, cardiac arrhythmias, psychosis and convulsions have been reported. Induced resistance should also be taken into account, considering that this class of compounds is widely prescribed for the treatment of common respiratory, urinary and gastrointestinal tracts and other infections [26,27].

It is noteworthy that different moieties at C-7 position or at N-1 position markedly influence both microbiological and pharmacokinetic properties. For example, compounds with a piperazinyl ring at C-7 position possess better Gram-negative than Gram-positive potency and alkyl chains at N-1 position increase the lipophilicity and the volume of distribution of the compounds [28].

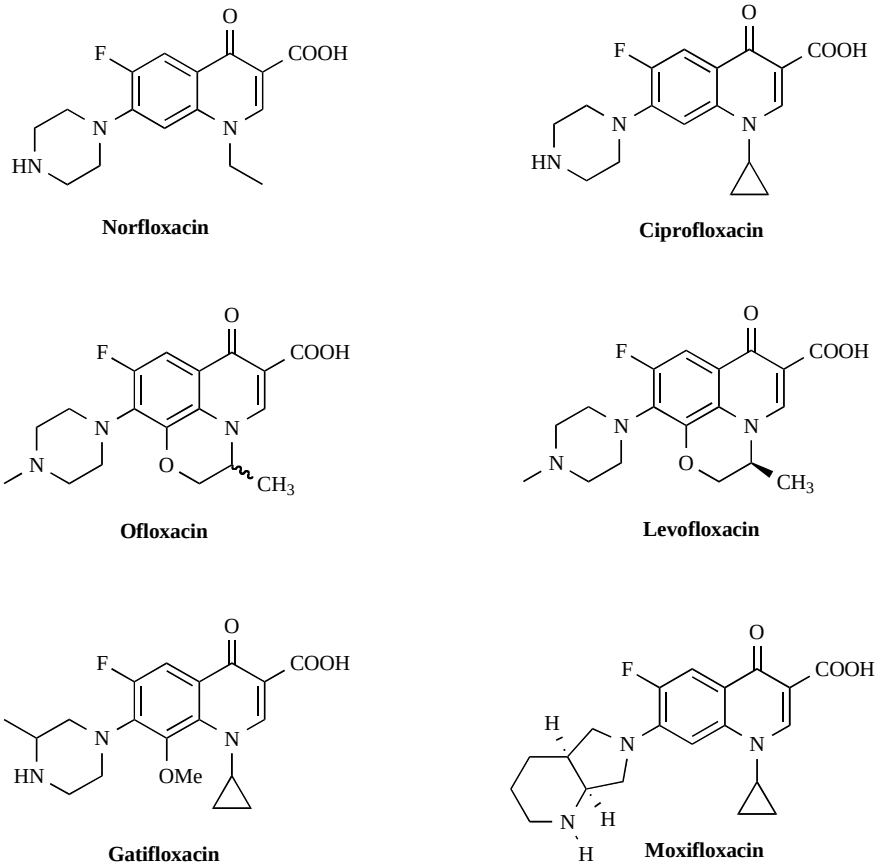


Fig. (3). Main fluoroquinolones in clinical use.

Synthetic Strategies on the Development of Novel Prototypes Against TB

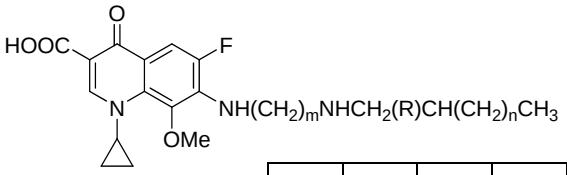
The recent growth of MDR and XDR-TB incidence and the increasing number of HIV-TB association cases demand urgency in the development of new drugs with higher antibacterial potency that would allow a reduction in the cost and in the duration of the treatment [29]. Generally speaking, modifications at C-7 position of the fluoroquinolone core (Fig. **1**) significantly alter the spectrum and the pharmacokinetic profile of this kind of structure. In this context, many researchers have been focusing their efforts on the optimization of second, third and fourth generation fluoroquinolones by attempting various structural modifications at this position [30].

De Almeida *et al.* have synthesized a series of novel Moxifloxacin and Gatifloxacin derivatives containing *N*-alkyl-diamines at C-7 position. Five of the screened substances (**1-5**) exhibited good biological profile against *M. tuberculosis* H37Rv strains (Fig. **4**) being considered by the authors as good leads on the development of novel drugs [31].

Recently, a new series of fifteen ciprofloxacin derivatives containing the isatin nucleus at C-7 position and a methoxy group at C-8 position was reported by Feng and co-workers. The synthesized substances were screened *in vitro* against *M. tuberculosis* H37Rv strains and fourteen of them displayed an improvement in the biological activity when compared to the original drug. The prototypes were also evaluated against MDR-TB strains and the results obtained have shown that substances **6-9** are around 3.5 times more potent *in vitro* than the referred drug Ciprofloxacin (MIC = 24.17 μM, MDR-TB) (Fig. **5**) [22].

The search for compounds with higher potency has also led researchers to modify other positions on the quinolone moiety besides C-7. Considering the *in vitro* and *in vivo* activity of diverse nitro-substituted heterocyclic compounds, Senthilkumar and co-workers attempted to synthesize some series of 6-nitroquinolones derivatives that were screened for their *in vitro* activity against MDR-TB strains resistant to Isoniazid, Rifampicin and Ethambutol and also to the fluoroquinolone Ofloxacin [32]. The reported results indicated the success of this approach, since all eighteen molecules tested have shown improved *in vitro* activity when compared to the drug Gatifloxacin. Compound **10** (Fig. **6**) was 52 times more potent than the reference drug, also displaying good *in vivo* activity. The cytotoxicity associated to these compounds was comparable to that observed on currently marketed fluoroquinolones.

A very similar 6-fluoroquinolones series was previously reported by the same authors [33]. Many of the 6-nitroquinolones tested have shown better *in vitro* results when compared to their 6-fluoro counterparts, a fact that suggests the importance of these compounds on the development of novel leads.

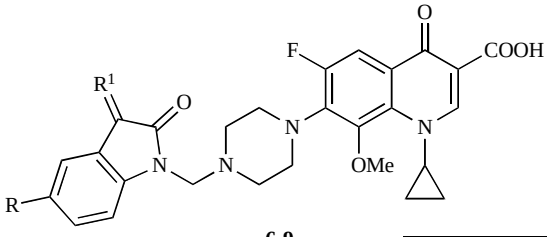


1-5

	m	n	R	MIC[a]
1	2	3	Et	0.62
2	2	7	H	0.62
3	3	7	H	0.31
4	3	9	H	0.62
5	3	11	H	0.62

[a]MIC values are expressed in μg/mL.

Fig. (4). Some derivatives reported by Almeida *et al*. with activity against TB.



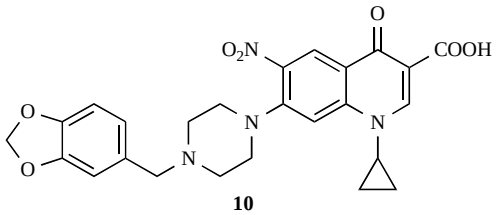
6-9

	R	R'	MIC[a]
6	F	$NOCH_3$	7.05
7	H	$NNHCONH_2$	6.93
8	F	$NNHCONH_2$	6.72
9	H	$NNHCSNH_2$	6.75

[a]MIC values are expressed in μg/mL. MDR-TB 90710 strain

Fig. (5). Isatinic quinolone derivatives with potential activity against TB.

The molecular hybridization strategy can also be used in the search for novel quinolone derivatives with potential activity against *M. tuberculosis*. Recently, a new series of triazoloquinolones have been reported by Carta *et al.* based on the biological activity previously described for benzotriazole derivatives (Fig. **7**) [34].



10
MIC = 0.16 μM
MDR-TB

Fig. (6). 6-nitroquinolone derivative with potent activity against MDR-TB.

Compounds **11**, **12** and **13** have shown promising results *in vitro*, exhibiting high selectivity against the *M. tuberculosis* H37Ra strain (Fig. **8**). According to the authors, the development of novel drugs from these structures could be interesting since their screened spectrum of bacterial activity was very narrow, suggesting specific anti-mycobacterial activity. Compounds with such specificity would not disturb the normal flora and would not induce the selection of resistant strains from other species besides the targeted one [34].

Quinolones containing long aliphatic chains at C-2 position were recently proposed by Wube and co-workers as good leads for the development of novel molecules with a higher potency against TB. The compounds were designed from the core structure of Evocarpin, an alkaloid isolated from *Evodia rutaecarpa* that was previously identified as a good prototype. This approach led to the screening of various novel quinolone derivatives (**14**-**16**) with excellent biological activity against *Mycobacterium smegmatis* (Fig. **9**) [35].

ANTICANCER ACTIVITY

Cancer is a generic term for a large group of diseases that can affect any part of the body. One defining feature of this

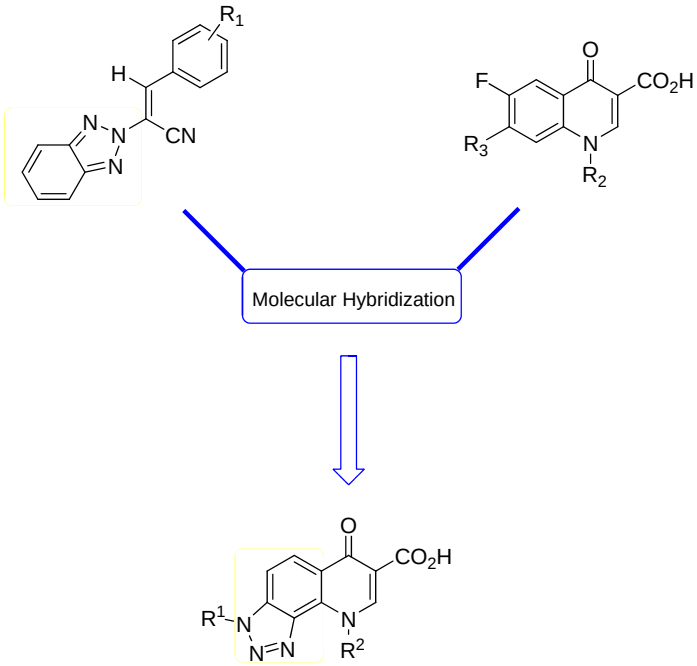
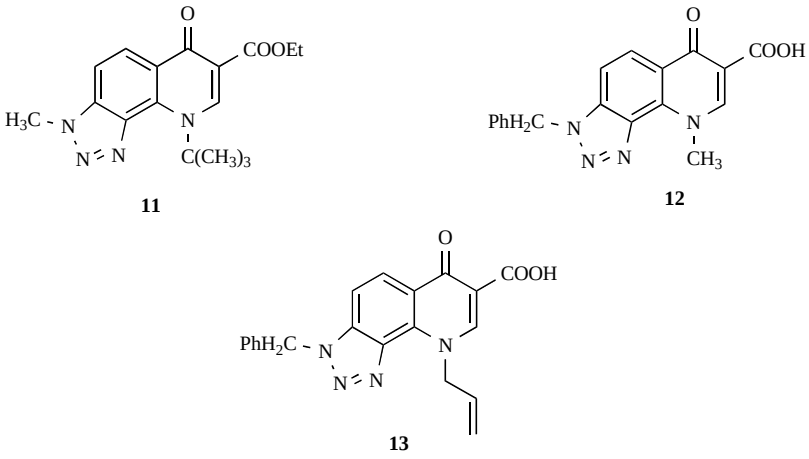
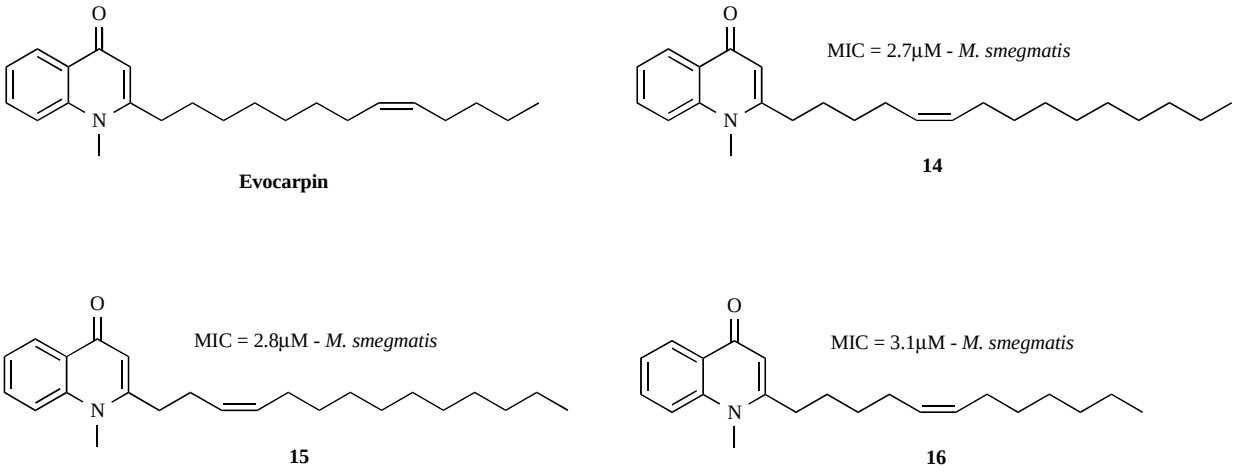


Fig. (7). Molecular planning of the structures proposed by Carta *et al.*

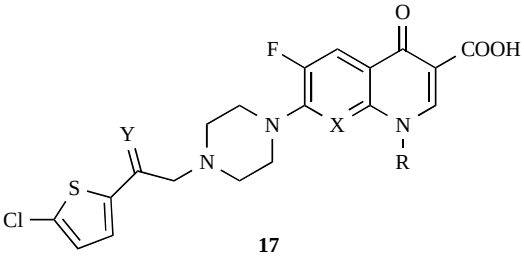


11 **12** **13**

Fig. (8). Triazoloquinolones with antimycobacterial activity.

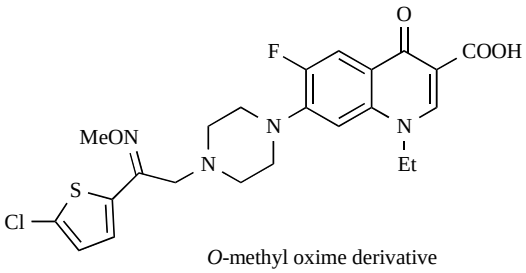


Evocarpin **14** **15** **16**



17

X= CH, N
Y= O, NOH, NOMe, NOBn
R= Et, c-Pr



O-methyl oxime derivative

(IC_{50}= 2.5 μM for MCF-7 cells)

Fig. (10). General structures of *N*-substituted piperazinyl quinolones **17** and the most active one, the *O*-methyl oxime derivative.

Fig. (9). Structures bearing an alkyl chain at C-2 position with activity against *M. smegmatis.*

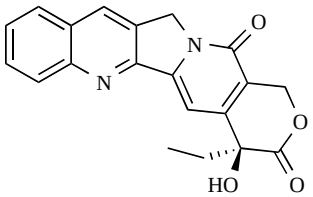
disease is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs [36]. Cancer still remains a threat to men's health, representing the leading cause of death in economically developed countries and the second leading cause of death in developing countries [37]. It is estimated that 12 million people will die from cancer in 2030 [36]. In the last years, many efforts have been made to develop new strategies for finding safe and effective ways for treating this disease, which include an increase in the understanding of the biological process involved in cancer cell survival and also the search for novel chemotherapeutic agents [38]. In this context, the major challenge is the development of more effective and safer drugs for the treatment of cancer. Fluoroquinolones and analogues are also attracting much attention as potential antitumor agents [1,39-41].

Synthetic Strategies on the Development of Novel Anticancer Prototypes

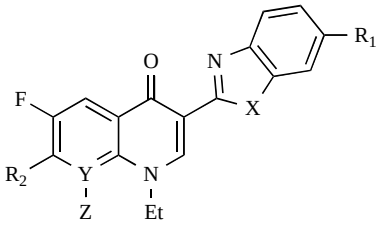
The quinolone-based compounds ability in inhibiting different type II topoisomerase enzymes makes this class of substance an attractive starting point for the design of new anticancer agents [42]. In fact, quinolone derivatives have been extensively explored in the search for new compounds to fight against different types of cancer cells [1,12,43,44].

Based on the knowledge that the nature of the C-7 substituent influences the inhibition of DNA topoisomerases and the cell permeability of quinolones, Foroumadi and co-workers have synthesized a series of *N*-substituted piperazinyl quinolones **17** through the introduction of a 2-(5-chlorothiophen-2-yl)ethyl moiety on the piperazine ring of Ciprofloxacin, Norfloxacin and Enoxacin (Fig. **10**) [12]. The authors observed that the employed modifications changed the biological profile of these quinolones from antibacterials to cytotoxic agents. The most expressive result was obtained for the *O*-methyl oxime derivative (Fig. **10**) that showed 95-fold increased activity in MCF-7 cells (breast cancer) with a IC_{50} value of 2.5 μM, compared to its parent quinolone norfloxacin (IC_{50}= 238 μM).

You *et al.* have described a series of quinolone and naphthyridine derivatives **18** as potential anticancer agents through scaffold modification of camptothecin (CPT), a natural pentacyclic alkaloid that is capable of inhibiting DNA replication causing cell death (Fig. **11**). Thus, they designed the new compounds lacking the lactone ring of CPT and change its rigid framework into a combination of the quinolone core and benzimidazole group or its bioisosters having a single carbon bond [44,45].



Camptothecin (CPT)



18

X= NH; O; S
Y= C; N
Z= H; F; (S)-$CH(CH_3)CH_2O$-
R_1= H; Cl; NO_2; NH_2
R_2= Cl; piperazin1-yl; 3-methylpiperazin1-yl; 4-methylpiperazin1-yl

Fig. (11). Structures of **CPT** and quinolone and naphthyridine derivatives **18**.

The compound that bears the heterocyclic benzoxazole at the 3-position, a 3-methylpiperazin-1-yl side chain at the 7-position and a fluorine atom at 8-position was the most potent derivative assessed against the three cancer cells lines tested, oral epidermal (KB), ovarian (A2780) and hepatocellular (Bel-7402) carcinoma cells lines (Fig. **12**).

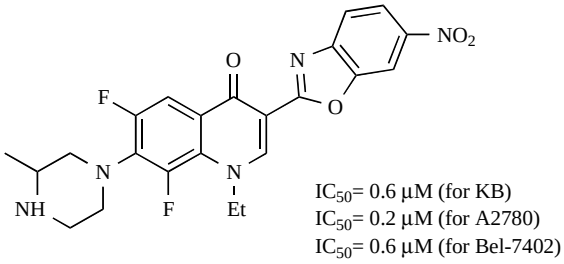


Fig. (12). The most potent quinolone derivative against three cancer cells lines.

It is noteworthy that natural products, such as camptothecin, have been extensively explored as lead compounds for the development of new anti-cancer agents. Constant advances in synthetic methodologies allow modification, removal or introduction of functional groups and stereocenters or more drastic remodeling of the basic scaffold [46].

Synthesis and structure-activity relationships of new quinolone derivatives as potential anticancer agents were reported by Tomita and co-workers [39,40]. In an early work, they proposed a series of 1,7-disubstituted-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids through chemical modifications on the N-1 and C-7 positions. The authors have determined that 6-fluoro-1,4-dihydro-4-oxo-7-(substituted pyrrolidinyl)-1-(2-thiazolyl)-1,8-naphthyridine-3-carboxylic acids were the most active molecules against murine tumor cells *in vitro* as well as *in vivo* tests in mice P388 leukemia models. Compounds **19** and **20** (Fig. **13**) also demonstrated good activity against several human tumor cell lines. Later, the same authors have proposed modifications at C-5, C-6 and C-7 positions of **19** and determined that the presence of the fluorine atom at C-6 position is dispensable for the antitumor activity. For example, the analogue 6-unsubstituted was two times more potent then the 6-fluoro-1,8-naphthyridine **19**, indicating a significant difference in relation to quinolone antibacterials in which the fluorine atom at this position has been shown to be indispensable for enhanced activity. Evaluation of C-7 modifications, further synthesis and in vitro/*in vivo* assay of both optical isomers of the racemic compound **21** showed that (*S*,*S*)-**21** had a considerable cytotoxic activity against murine and human tumor cell lines and also a high water solubility (Fig. **13**).

Compound **21**, lately named Voreloxin, is currently completing Phase 2 clinical trials in acute myeloid leukemia and platinum-resistant ovarian cancer. Hawtin *et al.* established Voreloxin as a first-in-class topoisomerase II poison and inhibitor that intercalates DNA and induces site-selective DNA DSB, G2 arrest and apoptosis [41,47]. Studies have demonstrated that voreloxin may provide clinical advantages over other topoisomerase II poisons that are currently in use.

Recently, our research group reported novel quinolone derivatives containing the benzothiazole moiety as potential antitumorals [48]. Compounds **22** and **23** exhibited good *in vitro* activity against MDAMB-435 (breast cancer) cell lines. Compound **22** also showed moderate *in vitro* activity against HL-60 (leukemia) (Fig. **14**). Further studies are underway in order to elucidate the molecular mechanism underlying the referred compounds toxicity.

PERSPECTIVES

Gatifloxacin and Moxifloxacin, two fluoroquinolone drugs, were repurposed as first line drugs for the treatment of TB and are currently being evaluated in phase III clinical trials as potential substitutes for the older antibiotics Ethambutol (Gatifloxacin and Moxifloxacin) and Isoniazid (Moxifloxacin). It is expected that the introduction of these

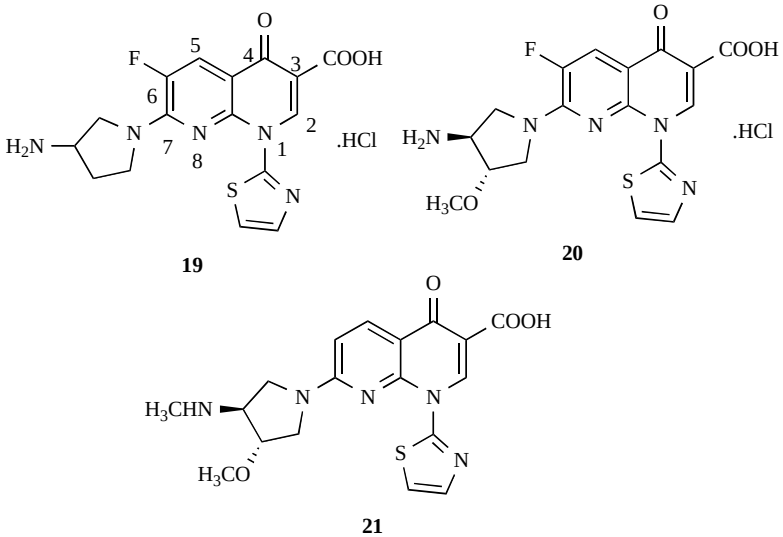
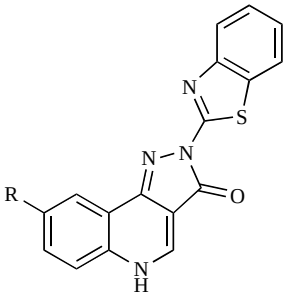


Fig. (13). Analogues of quinolones as potential antitumor agents.



	R
22	Br
23	CH_3

22: IC_{50} = 1.6 μg/mL (MDAMB-435)
3.0 μg/mL (HL-60)
23: IC_{50} = 2.3 μg/mL (MDAMB-435)

Fig. (14). Quinolone derivatives as potential anticancer agents.

drugs in the TB first line treatment will reduce the costs and time needed for cure, which ranges from 6 to 8 months using current chemotherapy. This long time needed for complete cure, plus the severe side effects experienced during treatment are considered to be the main causes for the emergence of multi-drug resistant strain since patients tend to abandon the chemotherapy as soon as the TB symptoms disappear, inducing the selection of MDR-TB and XDR-TB strains. It is estimated that a new treatment regimen with a 4-month duration using those fluoroquinolones will be registered by 2015.

The approval for clinical use of Voreloxin, a quinolone derivative that has no antibacterial activity but exhibits potent cytotoxicity towards eukaryotic cancer cell lines may benefit patients who prove resistant to currently available topoisoimerase II-targeting drugs or encounter unacceptable toxicities. It is also expected that this find can encouraged new further efforts in order to develop safer and more effective topoisomerase II-target cancer therapies.

CONCLUSION

In this review, we have attempted to provide information about some recent approaches in the search for novel quinolone derivatives as potential antitubercular and anticancer agents, focusing on some synthetic strategies employed in order to obtain new analogues. The quinolone-based compounds ability in inhibiting different type II topoisomerase enzymes allied to its synthetic versatility and also the world worry about the alarming statistics related to these two diseases, make this class of substance an attractive starting point for the design of new drugs. Various quinolone-based compounds have been reported with equivalent or better activity than standard drugs and could become a new medicine on the market in the future. Therefore, quinolone derivatives and its analogues represent promising compounds in the search of new lead molecules.

CONFLICT OF INTEREST

None declared.

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