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Review Article

A Review on Anticancer and Antimicrobial Activity of Tetrafluoroquinolone Compounds

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Abstract

The prokaryotic type II topoisomerases (DNA gyrase and topoisomerase IV) and the eukaryotic type II topoisomerases represent the cellular targets for quinolone antibacterial agents and a wide variety of anticancer drugs, respectively. In view of the mechanistic similarities and sequence homologies exhibited by the two enzymes, tentative efforts to selectively shift from an antibacterial to an antitumoral activity was made by a series of functionalized teracyclic fluoroquinolones. Thus, as part of a continuing search for potential anticancer drug candidates in the quinolones series, the interest in cytotoxicity of functionalized tetracyclic fluoroquinolones. The growth inhibitory activities of tetracyclic fluoroquinolones were against cancer cell lines using an *in vitro* cell culture system. Some of tetracyclic fluoroquinolones showed *in vitro* cytotoxic activity. The tetracyclic group of fluoroquinolones series changes the biological profile of quinolones from antibacterial to cytotoxic activity. The tetracyclic fluoroquinolones have excellent potential as a new class of cytotoxic agents.

INTRODUCTION

Fluoroquinolone (FQL), Norfloxacin is an antibacterial agent with potent and broad spectrum activity and several other members of this family (**Figure 1**) have emerged with enhanced activity against Gram positive and anaerobic bacteria and improved pharmacokinetic profile and studied how molecular modifications of the core quinolone structure affect the antibacterial profile and studied the structure–activity relationship (SAR) of quinolones [1,2]. For most of the agents, hydrogen at position 2, a carboxyl group at position 3 and a keto group at position 4 in the bicyclic ring cannot be changed without a significant loss of activity. Furthermore it appears that a cyclopropyl group is optimal at C-1. The fluorine atom at position 6 imparts increased intracellular penetration and enhanced DNA gyrase activity and some efficacy against Gram positive bacteria. It can be considered for the enhanced Gram negative activity, which led to the group of the modern 6-fluoro compounds (second generation quinolones). The substituent at position 7 greatly influences potency, spectrum and safety. A nitrogen heterocyclic moiety is optimal and piperazine, pyrrolidine and their substituted derivatives have been the most successfully employed side chains as evidenced by the compounds. The substituent at C-8, and similarly the substituent at C-5, affects the overall steric configuration and the number of intracellular targets on bacterial type II topoisomerases. A fused ring with a bridge between C-8 and N-1 is found in levofloxacin and Rufloxacin. Last generation FQLs demonstrated the favorable influence of an OCH_3 substituent at position 8 on Gram positive and on anaerobic bacteria. Moreover, the optimal substituent placed on C-8, combined with a bulky addition at C-7 has been shown to markedly reduce the development of FQL resistance in *S. aureus* [3].

Quinolones (e.g. ciprofloxacin **1** and norfloxacin **2**) are a very important family of antibacterial agents that are widely prescribed for the treatment of infections in humans [4]. They corrupt the activities of prokaryotic type II topoisomerases, DNA gyrase and topoisomerase IV, and induce them to kill cells by generating high levels of double-stranded DNA breaks. Type II topoisomerases modulate the topological state of the genetic material by passing an intact DNA helix through a transient double stranded break that they generate in a separate DNA segment [5]. Like bacterial cells, eukaryotic species require a type II topoisomerase, for viability [6]. In addition to the antibacterial quinolones, specific members of quinolone family display high activity against eukaryotic type II topoisomerases, as well as cultured mammalian cells and *in vivo* tumor models [7]. These anticancer quinolones represent a potentially important source of new anticancer agents. Several new quinolones have been synthesized that displayed significant activity against eukaryotic type II topoisomerases [8]. Cancer is known medically

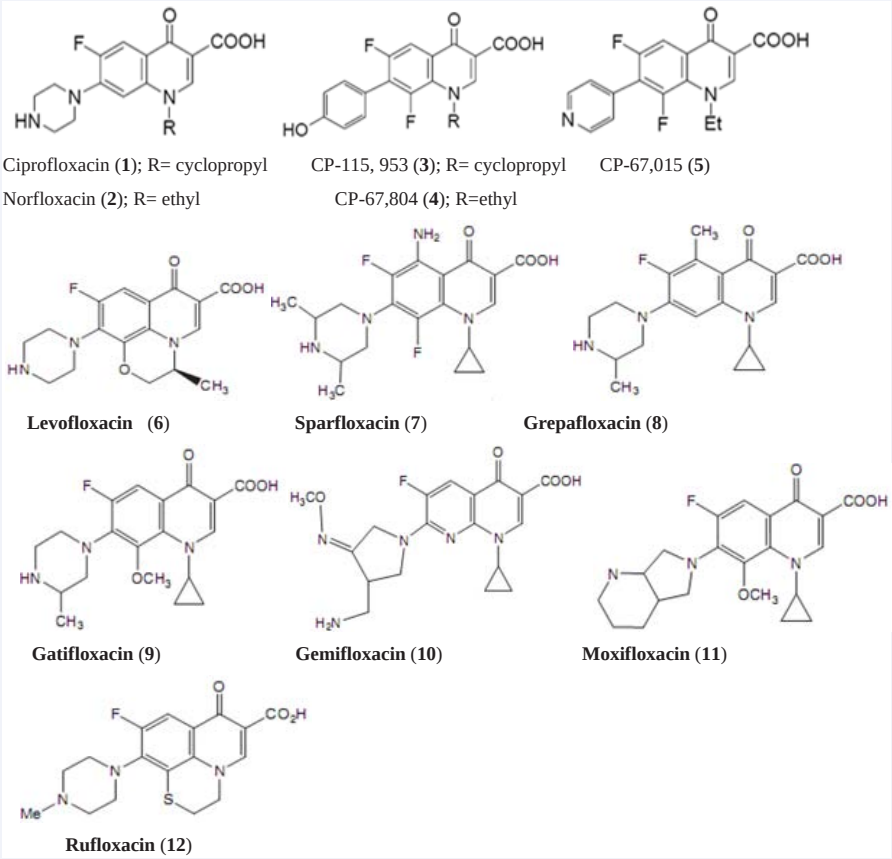

Figure 1 Structures of some fluoroquinolones in clinical use.

as a malignant neoplasm, which includes of various diseases, all involving unregulated cell growth. There are over 200 different known cancers that afflict humans [9]. Quinolones are synthetic antibacterial compounds based on a 4-quinolone skeleton [11]. They have been developed for clinical use in human [12]. These antibiotics exert their effect by inhibition of two type II topoisomerase enzymes, DNA gyrase and topoisomerase IV [14]. DNA topoisomerases are found in both eukaryotic and prokaryotic cells and are target for chemotherapeutic intervention in antibacterial and anticancer therapies [15]. Topoisomerase II plays important roles in a number of fundamental nuclear processes [16] and is essential for the survival of eukaryotic cells [17]. Indeed, DNA topoisomerase II enzyme catalyzes the double-strand breakage of DNA to allow strand passage and thereby control the topology and conformation of DNA [18]. The activities of these drugs correlate with their ability to stabilize covalent enzyme-cleaved DNA complexes that are intermediates in the catalytic cycle of topoisomerase II [19]. Beyond its required physiological functions, the enzyme is a target for some of the most active compounds currently employed for the treatment of human cancers [16, 20]. Among the topoisomerase II-targeted antineoplastic agents in clinical use are etoposide, amsacrine (mAMSA), adriamycin, and mitoxantrone. Since topoisomerase II-targeted drugs act by converting the enzyme into a cellular poison [19], antineoplastic potential is a reflection of the physiological level of the type II enzyme [21]. In view of the mechanistic similarities and sequence homologies exhibited by the prokaryotic type II topoisomerases and the eukaryotic type II topoisomerases, tentative efforts to selectively shift from an antibacterial to an antitumoral activity was made by synthesizing novel classes of quinolones [22]. The majority of quinolones in clinical use belong to the subset fluoroquinolones (FQLs), which have a fluorine atom attached to the central ring system, typically at the C-6 or C-7 positions [15]. FQLs have attracted much attention because of their broad spectrum of activity against various bacteria, mycobacteria and parasites [23]. Indeed, although FQLs are generally classified as broad-spectrum antibacterial agents, due to structural and functional similarities between bacterial DNA gyrase and mammalian topoisomerase II, the cytotoxicities of some of them also evaluated [24,25]. Rational mechanism-based drug design is an efficient route for the discovery of lead compounds [26]. An interesting example is the use of prokaryotic type II topoisomerases (DNA gyrase and topoisomerase IV) and eukaryotic type II topoisomerases as cellular targets in the search for FQLs with anti-bacterial and anticancer activities respectively [27]. In view of the mechanistic similarity and sequence homologies of the two enzymes, many attempts have been made to modify antibacterial FQLs to produce novel antitumor drugs [28,29]. Recently, promising results of tetrafluoroquinolones (TFQLs) have increased our interest in developing such compounds as antitumor FQLs [30]. Structures of selected cytotoxic quinolones **3-5,** which make on the ciprofloxacin **1** or norfloxacin **2** nucleus. These compounds displayed high activity against DNA gyrase or topoisomerase IV,

they are distinguished from the antibacterial quinolones by the presence of an aromatic substituent at the C-7 position [19,31].

A novel series of 8-substituted-9,1-[(N-methylimino) methano]-7-fluoro-5-oxo-5H-thiazolo[3,2-alpha]-quinoline-4-carboxylic acids having a unique thiazolopyrazine-incorporated tetracyclic structure were evaluated against Gram-positive and Gram-negative bacteria. All compounds had more potent activity than ofloxacin, which is one of the most popular quinolones, against Gram-positive and Gram-negative bacteria. The 8-pyrrolidinyl, and 8-morpholino, derivatives showed the most potent activity against Gram-positive bacteria. It is also significant that these compounds showed more potent antibacterial activity against methicillin-resistant *Staphylococcus aureus* isolates (MRSA) than ofloxacin (OFX). The combination of the morpholino group and this unique tetracyclic thiazolopyrazine skeleton contributes to the enhancement of the antibacterial activity against MRSA isolates. The in vivo antibacterial activities of these compounds were limited and depended on the structure of the substituent. The 8-(4-alkyl-1-piperazinyl) derivatives provided good efficacy and exhibited more potent activity [32]. The antibacterial activity of tetracyclic quinolone, against 25 strains of *S. aureus* clinically isolated was determined. The MICs of against both quinolone-susceptible (MIC: norfloxacin (NRFX) less than or equal to 6.25 μg/ml, ciprofloxacin (CPFX) less than or equal to 1.56 μg/ml) and 4 out of 5 NRFX and CPFX moderately resistant strains (MIC: 25 μg/ml less than or equal to NRFX less than or equal to 50 μg/ml, 3.13 μg/ml less than or equal to CPFX less than or equal to 12.5 μg/ml) were 0.05 μg/ml. The quinolone-resistant mutants derived by NRFX. The quinolone-susceptible strain of *S. aureus* was 2.47μg/mg dry cell and the uptake in NRFX and CPFX moderately resistant strains was comparable to that in the quinolones susceptible strain. The tetracyclic quinolone has potent antibacterial activity against quinolone susceptible strains of *S. aureus* and also has potent antibacterial activity against NRFX and CPFX moderately resistant strains [33]. The antibacterial activities of KB-5246, a tetracyclic quinolone, were compared with those of CPFX, OFX, and NRFX demonstrated a broad antibacterial spectrum [5, 34].

Similarly the *S. aureus* and *S. epidermidis* strains resistant to 3.13 μg of NRFX per ml. Among the *S. pneumoniae* and *Enterococcus faecalis* strains resistant to 12.5 μg of norfloxacin per ml [35]. The 6-fluoro-4-oxopyrido [2,3-a] carbazole-3-carboxylic acids and a structurally related 6-fluoro-4-oxothieno [20,30:4,5] pyrrolo [3,2-h] quinolinewas achieved via Stille arylation of 7-chloro-6-fluoro-8-nitro-4-oxoquinoline-3-carboxylate. These new compounds were tested for their in vitro antimicrobial and antiproliferative activity. The ability of 6-fluoro-4-oxopyrido[2,3-a]carbazole-3-carboxylic acids and 6-fluoro-4-oxothieno [20,30:4,5] pyrrolo[3,2-h]quinoline to inhibited the activity of DNA gyrase and topoisomerase IV. The thieno isostere 6-fluoro-4-oxothieno [20,30:4,5]pyrrolo[3,2-h] quinoline emerged as the most active antibacterial, while the 9-fluoro derivative (**13e**) was the most potent against multidrug-resistant (MDR) staphylococci. These compounds displayed growth inhibition against MCF-7 breast tumor and A549 non-small cell lung cancer cells coupled with an absence of cytotoxicity toward normal human-derm fibroblasts (HuDe). One compound was the most active anticancer against MCF-7 cells, with greater potency than ellipticine (IC_{50} 0.8 and 1.6 lM, respectively). The most active compounds in this series show promise as dual acting anticancer and antibacterial chemotherapeutics [28].

Changes in substitution on the quinolone C-7 and C-8 positions appear to play a significant role in the target preference and may offer new insight into the SAR of the FQL antibacterials. The fused ring with a bridge between the critical 7 and 8 positions has not yet been extensively investigated. The heterocycles fused 1-cylopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, some 9-cyclopropyl-4-fluoro-6-oxoimidazo[4,5-h] quinoline-7-carboxylic acids and of 9-cyclopropyl-4-fluoro-6-oxo[1,2,5]thiadiazolo[3,4-h]quinoline-5-carboxylic acid, which is endowed with strong antibacterial activity. Tetracyclic FQLs (**Figure 2**) with variously substituted 1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydropyrido[2,3-a]carbazole-3-carboxylic acids (**13a-e**) and the structurally related 1-cyclopropyl-6-fluoro-4-oxo-4,10-dihydro-1H-thieno[20,30:4,5]pyrrolo[3,2-h]quinoline-3-carboxylic acid (**13f**), a thiophene isostere of **13a** exhibited in vitro antimicrobial and antitumor properties.

The antitumor activity of the tetracyclic fluoroquinolones (TFQL) **13a–f** with 4-quinolone-3-carboxylic acid motif as a multivalent scaffold [36], and the structure of **13a–e** closely resembles the pyrido[4,3-b]carbazole system that constitutes the skeleton of the naturally occurring anticancer ellipticine and its derivatives (**Figure 2**) [37]. Ellipticine **14a**, an alkaloid isolated from Apocynaceae plants such as *Ochrosia elliptica* labil, and several of its derivatives (natural analogs 9-methoxyellipticine **14b**, 9-hydroxyellipticine **14c**, and the isomeric olivacine **15** showed promise in the treatment of osteolytic breast cancer metastases, kidney sarcoma, brain tumors and myeloblastic leukemia [38]. A number of ellipticine analogues have been synthesized with improved cytotoxicity and anticancer activities against a panel of cancer cell lines [39,40]. The derivative 9-hydroxy-2-methylellipticinium acetate **16** (elliptinium acetate), has found application in the treatment of breast, kidney, and thyroid cancer [41]. The interest in ellipticine and its derivatives for clinical purposes is mainly due to their high efficiency against several types of cancer, limited toxic side effects, and complete lack of hematological toxicity. The antiproliferative activity of all compounds was evaluated against MCF-7 (breast), A549 (non-small cell lung cancer) tumor cells, and normal human-derm fibroblasts (HuDe). Compound **13e** have the best antiproliferative activity in comparison to ellipticine. Moreover apoptosis induction and p53 expression were studied to obtain further insight, at the molecular level, into the mechanism of their action.

Antimicrobial activity

The antimicrobial activity of the novel heterocyclic compounds **13a–f** was assayed against Gram positive and Gram negative bacteria, yeasts, and molds. Bearing in mind that the spread of resistant strains reduces the number of available chemotherapeutic agents, MDR bacterial species, such as clinical isolates of quinolone- and penicillin- resistant *S. aureus, Staphylococcus epidermidis, Acinetobacter baumannii, Escherichia coli,* and *Pseudomonas aeruginosa*, were included in the investigation. The inhibitory activity of **13a–f** against bacteria (Table1), together with the results obtained for

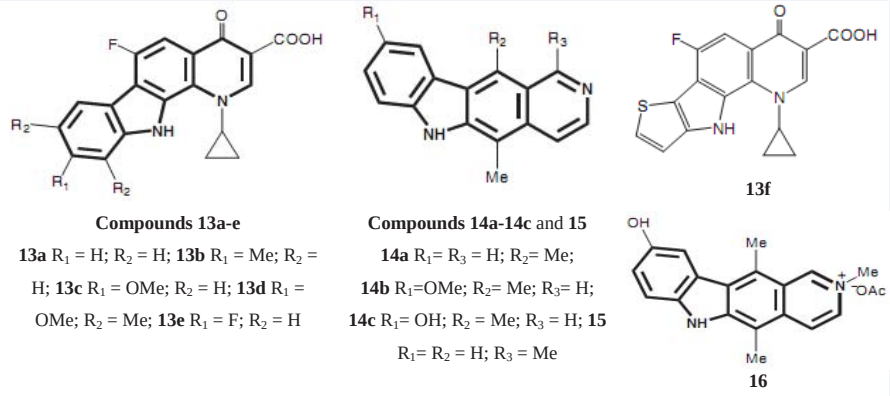

Figure 2 Structure of tetrafluoroquinolones, 6-fluoro-4-oxo-1,4-dihydropyrido[2,3-a] carbazole -3-carboxylic acids (13a–e) and their ethyl esters; Ethyl 4-oxo-4,11-dihydropyrido[2,3-a]carbazole-3-carboxylates (12a–e),(13a-f), ellipticines (14a-c, 16) and olivacine (15).

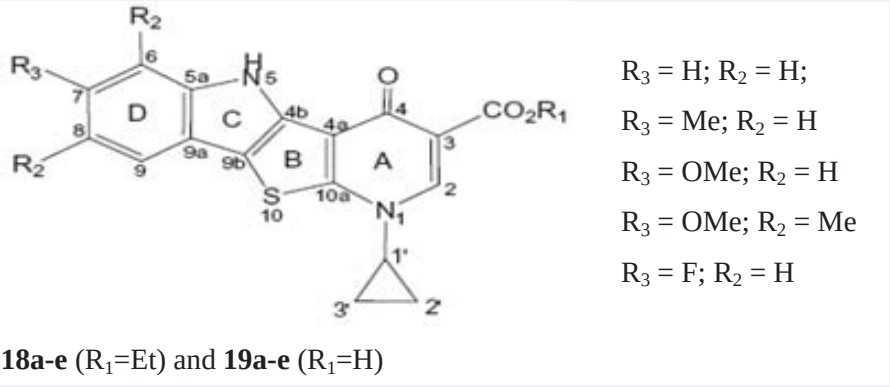

Figure 3 Structures of some tetracyclic fluoroquinolones.

commercial quinolones ciprofloxacin, levofloxacin, moxifloxacin, and gemifloxacin, which were used as reference drugs. All new compounds exhibited strong activity against Bacillus subtilis, the most sensitive microorganism to the tested substances. The MIC of **13a–d** ranged from 0.015 to 0.07 lg/mL and were close to those of standard quinolones, while a higher effect was exerted by **13e** and 13f (MIC 0.003 μg/mL). In addition, **13a** and, **13e–f** showed the best activity against wild staphylococci at the same concentrations observed for the reference drugs. These bacteria were also significantly inhibited by compounds **13c** and **13d**.

Compounds **13e** and **13f** had effective antibacterial properties against both MDR strains of S. aureus and S. epidermidis with MIC values 1.5–12 μg/mL and 3–50 μg/mL, respectively. Compound 13a was also a moderate inhibitor of SAR 72 at 12 μg/mL concentration. It is worth noting that, against the above mentioned staphylococci, 13a and 13f exhibited greater inhibitory activity than that of ciprofloxacin and levofloxacin and comparable to that of moxifloxacin and gemifloxacin, whereas **13e** (MIC 1.5–3 μg/mL) was found to be more potent than all the reference quinolones (MIC from 6to >100 μg/mL). MIC values in Table 1 show that all the tested compounds exhibited relatively better inhibition of Gram positive bacteria than Gram negative ones. Among the latter, Haemophilus influenzae was found to be the most sensitive (MIC 0.015–6 lg/mL) and it was inhibited by **13a** and **13e–f** at the same concentrations of standard quinolones. A lower potency was exhibited by the above mentioned compounds, relative to the standard quinolones, for the inhibition of A. baumannii and E. coli and by **13f** towards *P. aeruginosa*, while no activity was noted against MDR Gram negative strains. Thus, 13f was the most active quinolone against all tested microorganisms, with the exception of MDR staphylococci that were more significantly inhibited by **13e**. In order to reveal potential antifungal properties, the new compounds were tested on *Aspergillus niger, Candida tropicalis*, and *Saccharomyces cerevisiae*, but no activity was observed at, or below, the concentration of 100 lg/mL. Analysis of the SAR shows that the different substituents at ring (D), fused onto the pyrroloquinolone scaffold, affect the antibacterial properties of the substances. Concerning the benzo-fused derivatives, bulky substituents on the benzene ring, such as a lipophilic methyl group or a hydrophilic methoxy group, did not improve the antibacterial activity of the parent analogue **13a**. In fact, MIC values of compound **13a** were always lower than those of compounds **13b–d**. Among these, the methyl derivative **13b** was active only against B. subtilis. Better activity was noted for the methoxy derivative **13c**, which showed excellent inhibition of all wild type Gram positive bacteria tested and Gram negative H. influenzae and also a moderate effect against A. baumannii. As expected, the introduction of two methyl groups in **13c**,that produces **13d**, led to decreased antibacterial activity. It is worth

noting that the most effective compounds contained a fluorine atom. For instance, compound **13e**, bearing fluorine in the para position of the benzene ring, was the most active carbazole derivative. The electronic influence on the antibacterial activity of the selected substituents in the series **13a-e**, can be seen from the favorable effect of the electron-withdrawing fluorine (**13e**) and, conversely, the detrimental action of the electron-donating methyl and methoxy groups (**13b-d**). The SARs analysis of the data showed that the thiophene isosteric replacement of the D benzene moiety played a positive, crucial role in the antibacterial effectiveness of the tested compounds. Hence, **13f** possessed the highest inhibitory properties as compared to the corresponding benzofused derivatives **13a-e**. However, it is noteworthy that, in the case of MDR staphylococci, the presence of a fluoro substituted benzene ring (**13e**) contributed to an activity enhancement, with respect to the thiophene analogue **13f**.

DNA gyrase and topoisomerase IV inhibition: To elucidate the mechanism by which the novel tetracyclic fluoroquinolones (TFQL) induce antibacterial activity, the inhibitory activities of all the compounds 13a–f were examined against DNA gyrase and topoisomerase IV isolated from E. coli (Table 2). Antibacterial quinolones exert their activity by targeting Gram negative bacteria DNA gyrase and Gram positive bacteria topoisomerase IV, and inhibiting DNA replication process. We hypothesized that FQL **13a–f** could afford favorable binding to the DNA–enzyme complex, but surprisingly we found in most cases moderate inhibition of DNA gyrase (compounds **13a–c** and **13e–f** IC_{50} 1.1-4.8 μg/mL) and a weak inhibition of topoisomerase IV (compounds **13a** and **13c–e** IC_{50} 28–48 μg/mL). All of the tested compounds displayed higher IC_{50} values than the reference ciprofloxacin and moxifloxacin, nevertheless most of them (Table 1), exhibit against Gram positive bacteria lower or comparable MICs in respect to that of the reference quinolones. Lack of correlation between the MICs and the IC_{50}s indicates that inhibition of bacterial cell growth, when detected for compounds **13a–f**, was not mainly caused by inhibition of the topoisomerase IV and suggests that other different mechanisms could be involved in the antibacterial effect.

Antitumor activity

The antitumor activity of compounds **13a–f** was assayed with respect to ellipticine by evaluating cell proliferation in MCF-7 breast cancer and in A549 non-small cell lung cancer (NSCLC) cell lines and cell cycle distribution, apoptosis induction and p53 expression in MCF-7 cell line. After 72 h, all the tested compounds showed significant inhibition of cell proliferation in a dose-dependent manner. Ellipticine showed IC_{50} of 1.6 lM. The most interesting compounds (**13c–e**) had comparable IC_{50} to the reference substance, ranging between 0.8 and 2.4 lM against MCF-7 cells and between 3 and 4.9 lM against A549 cells. In contrast, compound 13b showed a reduced effect on cell proliferation against both cell lines (IC_{50} >10 lM). The SARs analysis of showed that among carbazole analogues **13a–e**, a lipophilic and electron-donor substituent, such as a methyl group (**13b**) at the para position of the D benzene ring, significantly decreased the antiproliferative activity on both cell lines (IC_{50} >10 lM). By contrast, substitution of the parent compound 13a with a hydrophilic and electron-donor methoxy group (to give **13c**), resulted in increased potency (IC_{50} 2.4 and 4.9 lM against MCF-7 and A549 cells, respectively), compared to 13a (IC_{50} 3.6 and 6.4 lM against MCF-7 and A549 cells, respectively). Compound **13e**, bearing a fluoro substituent with electron-withdrawing properties, had a fourfold increased potency in breast cells (IC_{50} 0.8 lM) compared to the unsubstituted analogue **13a** (IC_{50} 3.6 lM) and was even more active than the reference ellipticine (IC_{50} 1.6 lM). A significantly increased activity was also observed for **13e** against A549 cells (IC_{50} 3.5 vs 6.4 lM). Interestingly, the 4-methoxy-3,5-dimethyl derivative **13d** was more potent than the 4-methoxy substituted carbazole **13c**, showing that the presence of two small lipophilic and electron-donor methyl groups in the 3 and 5 positions was beneficial. This led us to speculate that the biological target responsible for the antiproliferative activity of

Table 1: Inhibitory activity against Gram positive and Gram negative bacteria, expressed as MIC (μg/mL) Bacteriaa Compound[b]

Bacteria[a]	Compound [b]									
Gram positive	**13a**	**13b**	**13c**	**13d**	**13e**	**13f**	**CIP**	**LEV**	**MOX**	**GEM**
BS	0.015	0.07	0.07	0.07	0.003	0.003	0.03	0.03	0.015	0.007
SA	0.3	>100	3	6	0.07	0.03	0.3	0.07	0.03	0.015
SAR 72	12	—c	>100	>100	1.5	12	100	25	12	6
SAR 4790	>100	>100	>100	>100	>100	>100	>100	100	50	50
SE	0.15	>100	3	25	0.07	0.03	0.07	0.15	0.07	0.015
SER	>100	—	>100	>100	3	50	100	>100	50	50
Gram negative										
AB	12	>100	50	>100	12	3	0.7	0.15	0.15	0.3
ABR	>100	—	>100	—	>100	>100	>100	>100	50	100
EC	50	>100	>100	>100	25	1.5	0.015	0.03	0.03	0.015
ECR	>100	—	—	—	>100	>100	100	25	50	50
HI	0.03	>100	1.5	6	0.15	0.015	0.15	0.15	0.03	0.015
PA	>100	>100	>100	>100	>100	50	0.07	0.3	0.7	0.07
PAR	—	—	—	—	—	>100	25	50	>100	>100

the FQLs/carbazoles under study has two additional drugbinding sites, with two small hydrophobic pockets at the 3 to 5 benzene positions distance. Replacement of the D benzene ring of compound **13a** with its heterocyclic bioisoster thiophene (**13f**) did not significantly modify the antiproliferative activity, further evidence for the bioisosteric equivalence between benzene and thiophene rings. The mechanism responsible for cell growth inhibition, cell cycle distribution was evaluated using flow cytometric analysis in MCF-7 cells. The effect of ellipticine and the most active compound **13e** on MCF-7 cell cycle distribution, cells treated with 5 lM for 24 h were analyzed by flow cytometry.

[a]BS, Bacillus subtilis ATCC 6633; SA, *Staphylococcus aureus* ATCC 6538; SAR 72 and SAR 4790, *Staphylococcus aureus* quinolone- and penicillin-resistant clinical isolates; SE, Staphylococcus epidermidis; SER, Staphylococcus epidermidis quinolone- and penicillin-resistant clinical isolate; AB, Acinetobacter baumannii; ABR, Acinetobacter baumannii quinolone- and penicillin-resistant clinical isolate; EC, Escherichia coli; ECR, Escherichia coli quinolone- and penicillin-resistant clinical isolate; HI, Haemophilus influenzae; PA, Pseudomonas aeruginosa; PAR, Pseudomonas aeruginosa quinolone- and penicillin-resistant clinical isolate. [b]CIP, ciprofloxacin; LEV, levofloxacin; MOX, moxifloxacin; GEM, gemifloxacin. [c]Not tested because inactive against the corresponding quinolone-sensitive microorganism.

Cells were treated with indicated compounds at concentrations ranging from 0.1 to 20 lM for 72 h and then viability was determined by MTT assay. Concentration that inhibits 50% (IC_{50}) (e.g., the point at which viability is 50%) was extrapolated from the dose–response curves. Representative results of at least three independent experiments are reported.

Both ellipticine and **13e** caused a significant increase in the proportion of cells in G2/M phase with a decrease in G0/G1 phase. The treatment of MCF-7 cells with ellipticine and with compound **13e** at 5 lM for 48 h was associated with the induction of cell death. Western blotting analysis revealed that programmed cell death by apoptosis was involved in the loss of viability. The activation and cleavage of caspase 7 (MCF-7 cells are caspase 3 null) was detected in MCF-7 cells treated with ellipticine and with **13e**. In MCF-7 ellipticine treatment resulted in an increase of p53 and KIP1/p27. Ellipticine treatment induced p53 accumulation in MCF-7 cells expressing wild type p53 protein. In contrast, compound **13e** induced only a modest increase of p53 protein, suggesting that other mechanisms were involved in its antiproliferative effect. The compounds were also evaluated against normal humanderm fibroblasts (HuDe) and, as shown in the (Table 3) no effect on cell proliferation and viability was detected until 10 lMindicating a selectivity of action, toward tumor cells coupled with a lack of cytotoxicity towards normal cells. In summary, the selective antiproliferative effect observed for the FQL **13e** as a representative of the novel FQLs with a carbazole core (**13a-e**) or with a bioisosterically thieno related structure (**13f**) seems to be due to multiple mechanisms.

Table 2: Inhibitory activity against DNA gyrase and topoisomerase IV of E. coli, expressed as 50% inhibitory concentration (lg/mL).

Compound	IC50	
	Gyrase[a]	Topoisomerase IV[b]
13[0]	1.7	35
13b	3.0	>300
13c	4.8	48
13d	>30	31
13e	1.8	28
13f	1.1	100
Ciprofloxacin	0.34	4.6
Moxifloxacin	0.85	5.0

Representative results of at least three independent experiments are reported.
[a]E. coli DNA gyrase supercoiling assay.
[b]E. coli topoisomerase IV decatenation assay.

The fluoroquinolones (FQLs) constitute a major class of antibacterial chemotherapeutic agents which have a broad spectrum against Gram positive and Gram negative bacteria [1,3,42] Examples include norfloxacin and ciprofloxacin which were the first two quinolones marketed human use. Since 1986, more than twenty FQLs have been approved by FDA and most of them remain on the market. Several 4-oxothieno[2,3-b]pyridine-5-carboxylic acids, potential bioisosters of quinolone antibacterials. Substitution at the N(7)-position of thienopyridones has been reported for alkyl groups, for example, some compounds exhibited good level of activity against Gram negative bacteria. N(7)-Aryl and -heteroaryl substitution has also been achieved, exemplified by compounds that exhibited good level of activity against Gram negative and Gram positive bacterial strains. In addition, selected N(7)-azacyclohexyl derivatives and related congeners, such as 7-(N,N-dimethylamino) derivative, have been prepared; the latter exhibited good level of activity, especially against *Klebsiella pneumoniae* and *Salmonella paratyphi* A (MIC 0.5 and 1.0 μg/mL, respectively). The 4-oxopyrido [30,20:4,5] thieno[3,2-b]indole-3-carboxylic acids **19a–e** was achieved via Stille arylation of 2-chloro-3-nitro-4-oxothieno[2,3-b] pyridine-5-carboxylate. Thees compounds were tested in vitro antimicrobial and antiproliferative activity. Most of these compounds exhibited very high potency against Gram positive Bacillus subtilis and Bacillus megaterium at concentrations 0.000015–0.007 μg/mL. They also displayed excellent activity towards other Gram positive bacilli and staphylococci and Gram negative Haemophilus influenzae, being in most cases superior or equal to commercial FQLs. Few compounds were inhibitors of the DNA gyrase activity. As concerns antitumor properties, most of compounds showed growth inhibition of MCF-7 breast tumor and A549 non-small cell lung cancer cells with IC_{50} 1.6–2.8 lM and 2.6–6.9 lM, respectively. These compounds are promising as dual acting chemotherapeutics [43].

Table 3: Effects of compounds **13a–f** and ellipticine on MCF-7, A549, and HuDE cell viability.

Compound	IC50 MCF-7 (μM)	IC_{50} A549 (μM)	IC50 HuDe (μM)
13a	3.6 ± 1.09	6.4 ± 1.02 >10	>10
13b	>10	>10	>10
13c	2.4 ± 1.05	4.9 ± 1.01 >10	>10
13d	1.7 ± 1.04	3 ± 1.03 >10	>10
13e	0.8 ± 1.04	3.5 ± 1.05 >10	>10
13f	4.4 ± 1.09	6.4 ± 1.07 >10	>10
Ellipticine	1.6 ± 1.16	3.4 ± 1.04 >10	>10

Some tetracyclic fluoroquinolones (TFQLs) [44], as part of an program aimed at developing novel antibacterial agents such as 4-oxothieno [2,3-b]pyridine-5-carboxylic acid derivatives that are bioisosters of FQL antibacterials. The fused rings with a bridge between the critical C-2 and C-3 positions have not yet been investigated in this 4-oxothieno [2,3-b]pyridine system. The designed compounds are isosteric with pyridocarbazoles, a class to which the natural ellipticine antitumor drug belongs [28]. In vitro evaluation of the antimicrobial and antitumor properties of tetracyclic thienopyridones such as the variously substituted 4-oxopyrido[30,20:4,5]thieno[3,2-b]indole-3-carboxylic acids **19a–e**. 4-oxopyrido [30,20:4,5]thieno[3,2-b] indole-3-carboxylic acids 9a–e and their ethyl esters **18a–e** was achieved by utilizing ethyl 2-chloro-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-b] pyridine-5-carboxylate [5].

Antimicrobial activity

The new thienopyridones **19a–e** were screened for their in vitro antimicrobial activity against model Gram positive and Gram negative bacteria, including **multidrug**-resistant species, yeasts and mould. The MICs are compared with the results obtained for standard antibacterial quinolones ciprofloxacin, levofloxacin, moxifloxacin and gemifloxacin. All the investigated compounds presented remarkable antibacterial properties against Gram positive bacteria, both bacilli and staphylococci, in most cases at concentrations lower than reference drugs. Interestingly, compounds **19a** and **19e** exhibited unprecedented powerful activity at 0.000015μg/mL against *Bacillus megaterium* and *B. subtilis*. These microorganisms were also inhibited by **19b** and **19c** at 0.00003–0.007 μg/mL, so appearing to be the most sensitive strains. Furthermore, compounds 19a–c and 19e displayed excellent activity against other tested bacilli and wild staphylococci. The inhibition of *B. cereus, B. thuringiensis* and *Staphylococcus aureus* was achieved by compounds **19a, 19c** and **19e** at concentrations of 0.003–0.03 μg/mL, generally lower than those of standard quinolones (MICs 0.015–0.3 μg/mL), and also against Staphylococcus epidermidis compounds **19a** and **19e** at 0.03 μg/mL were superior to reference ciprofloxacin, levofloxacin and moxifloxacin (MICs 0.07–0.15 μg/mL). As concerns compound **19d**, it showed significant activity against all tested bacteria at concentrations 1.5–6 μg/mL. Of particular relevance is that thienopyridones exerted strong antibacterial effectiveness against both MDR strains of S. aureus and S. epidermidis, their MICs ranging from 0.7 to 25 μg/mL and displaying for compounds 9a and **19c–e** higher potency as compared to the standard quinolones used in this study. Almost all of the studied thienopyridones exhibited also a marked degree of activity against Gram negative bacteria. Among these, Acinetobacter baumannii and, especially, Haemophilus influenza were found to be more sensitive in comparison to *E. coli* and *P. aeruginosa*. Unsubstituted 9a displayed the highest activity, inhibiting the growth of H. influenzae and A. baumannii at concentrations of 0.03 and 0.07μg/mL, respectively, comparable or lower than those of the reference quinolones. Strong effect was shown by fluoro derivative **19e** at 0.15 μg/mL, while compounds **19b** and **19c** were found to exhibit high to good antibacterial properties (MIC 0.15–3 μg/mL). A significant inhibition was also observed for 9d towards H. influenzae. Only 9a and 9e showed activity against E. coli with MIC values 25–50 lg/mL, higher than those of standard substances. However, none of the tested thienopyridones inhibited *P. aeruginosa* and MDR Gram negative strains even at the higher concentration of 100 μg/mL.

It is worthwhile to note that **19e** was the only compound exhibiting antifungal properties, when compared to the other thienopyridones and quinolones tested. This chemical displayed against yeast Saccharomyces cerevisiae an effect equal to that of standard antifungal miconazole (MIC 12 lg/mL), but it was found to be less active than the reference drug against *Candida tropicalis* and Aspergillus niger (MIC of miconazole 6 and 3 μg/mL, respectively). The SARs analysis of the data reported in Table 4 shows that the thiophene isosteric replacement of the fluorobenzene (ring B) in the tetracyclic structure of fluoroquinolones (TFQLs) played a positive role in the antibacterial effectiveness, with a general increase of activity, especially against bacilli, and including resistant S. aureus and S. epidermidis strains. Overall, **19a**, unsubstituted, and 9e, carrying an electron-withdrawing fluorine group with low bulkiness and a comparable size to the hydrogen atom, showed higher effectiveness against both Gram positive and Gram negative bacteria, as compared to methyl and methoxy substituted thienopyridones **19b–d**. MIC values exhibited by 9e were equal to those of **19a** with a slight enhancement in the activity against Gram positive *B. thuringiensis* and resistant *S. epidermidis* strain and a weak reduction against Gram negative A. baumannii, E. coli and H. influenzae. It is worth noting that fluoro substituted **19e** is also endowed with a certain antifungal activity. The introduction in the para position of the benzene ring D of bulky and electron-donating substituents, such as a hydrophilic methoxy group and, in a more extent, a lipophilic methyl group, leads to comparatively less active compounds **19c** and **19b**. The antibacterial properties of the latters are further considerably reduced in three substituted **19d**, except when MDR *S. aureus* and *S. epidermidis* strains were tested.

[a]BC, Bacillus cereus; BM, *Bacillus megaterium*; BS, *Bacillus subtilis*; BTK, Bacillus thuringiensis var. kurstaki; SA, Staphylococcus aureus; SAR 72 and SAR 4790, *Staphylococcus aureus* quinolone- and penicillin-resistant clinical isolates; SE, Staphylococcus epidermidis; SER, *Staphylococcus epidermidis* quinolone- and penicillin-resistant clinical isolate; AB, Acinetobacter baumannii; ABR, Acinetobacter baumannii quinolone- and penicillin-resistant clinical isolate; EC, Escherichia coli; ECR, Escherichia coli quinolone- and penicillin-resistant clinical isolate; HI, Haemophilus influenzae; PA, *Pseudomonas aeruginosa*; SC, Saccharomyces cerevisiae; CT, Candida tropicalis; AN, Aspergillus niger. [b]CIP, ciprofloxacin; LEV, levofloxacin; MOX, moxifloxacin; GEM, gemifloxacin. [c]Not tested because inactive against the corresponding quinolone-sensitive microorganism.

DNA gyrase and topoisomerase IV inhibition: Bacterial DNA gyrase of Gram negative strains and topoisomerase IV of Gram positive ones are well-characterized clinically validated targets of the quinolone antibacterials [1,3]. Therefore, the enzymatic inhibition of compounds **19a** and **19c**, possessing potent antibacterial activity against a wide spectrum of microorganisms and structurally related to quinolones, was tested against DNA gyrase and topoisomerases IV isolated from E. coli. Data reported in Table 5 show that both the tested compounds displayed inhibitory properties towards DNA gyrase,

Table 4: Inhibitory activity of compounds **19a–e** against bacteria and fungi, expressed as MIC (μg/mL).

Microorganism[a]	Compound[b]								
	19a	19b	19c	19d	19e	CIP	LEV	MOX	GEM
G(+ve) bacteria									
BC	0.007	0.3	0.03	3	0.007	0.3	0.15	0.3	0.07
BM	0.000015	0.007	0.00003	3	5	0.007	0.03	0.003	0.0003
BS	0.000015	0.0003	0.0003	3	0.000015	0.03	0.03	0.015	0.007
BTK	0.007	0.15	0.007	1.5	0.003	0.03	0.07	0.03	0.015
SA	0.003	0.07	0.015	6	0.003	0.3	0.07	0.03	0.015
SAR 72	0.7	12	1.5	3	0.7	100	25	12	6
SAR 4790	>100	>100	>100	>100	>100	>100	100	50	50
SE	0.03	0.3	0.15	3	0.03	0.07	0.15	0.07	0.015
SER	3	25	6	3	1.5	100	>100	50	50
G (-e) bacteria									
AB	0.07	0.7	3	>100	0.15	0.7	0.15	0.15	0.3
ABR	>100	>100	>100	—[c]	>100	>100	>100	50	100
EC	25	>100	>100	>100	50	0.015	0.03	0.03	0.015
ECR	>100	—	—	—	>100	100	25	50	50
HI	0.03	1.5	0.15	6	0.15	0.15	0.15	0.03	0.015
PA	>100	>100	>100	>100	>100	0.07	0.3	0.7	0.07
Fungi									
SC	>100	>100	>100	>100	12	>100	>100	>100	>100
CT	>100	>100	>100	>100	>100	>100	>100	>100	>100
AN	>100	>100	>100	>100	>100	>100	>100	>100	>100

with IC_{50} values 1.0–1.1μg/mL (ciprofloxacin and moxifloxacin IC_{50} 0.34 and 0.85 μg/mL, respectively), whereas they did not inhibit topoisomerases IV up to the concentration of 24 lg/mL. The different target affinity suggests that the great antibacterial potency exhibited by thienopyridones against Gram positive organisms was not due to inhibition of topoisomerases IV and hints that other mechanisms are involved in the antibacterial effect.

Antitumor activity

The antitumor activity of compounds **19a–e** was assayed with respect to ellipticine by evaluating cell proliferation in MCF-7 breast cancer, in A549 non-small cell lung cancer (NSCLC) cell lines and in normal human-derm fibroblasts (HuDe). After 72 h cell viability was determined: against HuDe cells no effect was detected until 10 lM, while against both the tumor cell lines all the tested compounds showed significant inhibition of cell proliferation in a dose dependent manner (**Table 6**). Ellipticine showed IC_{50} of 1.6 lM and 3.4 lM against MCF-7 and A549 cells, respectively. The most potent compounds **19c** and **19e** had comparable IC_{50} to the reference substance, ranging between 1.6 and 1.9 lM against MCF-7 cells, and between 2.6 and 2.7 lM against A549 cells. Compound **19a** showed the lowest effect on cell proliferation against both cell lines (IC_{50} 10 and 5.2 lM against A549 and MCF-7 cells, respectively).

Cells were treated with the indicated compounds at concentrations ranging from 0.1 to 20 lM for 72 h and then viability was determined by MTT assay. Concentration that inhibits 50% (IC_{50}) was extrapolated from the dose–response curves.

DISCUSSION AND CONCLUSION

Novel 1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydropyrido[2,3-a]-carbazole-3-carboxylic acids (**13a–e**) and the structurally related 1-cyclopropyl-6-fluoro-4-oxo-4,10-dihydro-1H-thieno[20,30:4,5] pyrrolo [3,2-h]quinoline-3-carboxylic acid (**13f**) were evaluated for their antibacterial and antiproliferative activity assessed. The six tetracyclic fluoroquinolones (TFQL) exhibited high antibacterial activity against Gram positive strains, including a few resistant ones. Furthermore, most of them had high antiproliferative activity against breast MCF-7 and lung A549 tumor cell lines, and were devoid of cytoxicity against normal cells. **13e** emerged as the most active antibacterial compound against MDR staphylococci and the most potent antiproliferative compound against MCF-7 cells. While the investigation at the molecular level identified only in part the targets and the binding modes of these new molecules need to be further elucidated, the combination of potent activity against Gram positive bacteria and cancer cell lines, the absence of cytoxicity against normal cells, make these agents of interest in the search for potential cancer chemotherapeutics. These compounds, possessing both anticancer and antibacterial activity, have a promising therapeutic potential due to their selective cytoxicity coupled with the ability to reduce the danger of bacterial infections in the frequently immune compromised cancer patient. This is supported by clinical data (Paul, et al., 2007; Cavazzoni, et al.,

Table 5: Inhibitory activity of compounds 9a and 9c against DNA gyrase and topoisomerase IV of E. coli, expressed as 50% inhibitory concentration (lg/mL).

Compound	IC50	
	Gyrase[a]	Topoisomerase IV[b]
19a 1.0 >24	1.0	>24
19c 1.1 >24	1.1	>24
Ciprofloxacin 0.34 4.60	0.34	4.60
Moxifloxacin 0.85 5.00	0.85	5.00

[a]E. coli DNA gyrase supercoiling assay. [b]E. coli topoisomerase IV decatenation assay.

Table 6: Effects of compounds **19a–e** and ellipticine on MCF-7, A549 and HuDE cell lines.

Compound	IC_{50} MCF-7, µM (breast cancer)	IC_{50} A549, µM (NSCLC)	IC_{50} HuDe, µM
19a	5.2 ± 1.09	10 ± 1.04	>10
19b	2.8 ± 1.05	6.9 ± 1.06	>10
19c	1.6 ± 1.04	2.6 ± 1.02	>10
9d	2.5 ± 1.05	4.7 ± 1.05	>10
19e	1.9 ± 1.04	2.7 ± 1.02	>10
Ellipticine	1.6 ± 1.06	3.4 ± 1.04	>10

2004; Cavazzoni, et al., 2008) [45-47], demonstrating a positive effect of quinolone antimicrobials on cancer patients' survival, and makes the multiple targeted approach, as here, a promising avenue for drug development. Novel 1-cyclopropyl-4-oxopyrido [30,20:4,5]thieno[3,2-b]indole-3-carboxylic acids **19a–e** were synthesized and their antimicrobial and antitumor properties assessed. Four of these five tetracyclic thieno[2,3-b]pyridones showed unprecedented powerful activity against B. megaterium and B. subtilis, excellent activity against *S. aureus* and also against Gram negative H. influenzae, in addition to activity against few resistant Gram positive bacteria. Furthermore, these compounds had high anticancer activity against breast MCF-7 and lung A549 tumor cell lines, and were devoid of cytotoxicity against normal cells. The combination of potent activity against bacteria and cancer cell lines, together with the absence of cytotoxicity against normal cells, makes these agents of interest in the search for novel potential antimicrobials able to reduce the danger of bacterial infections in the frequently immune compromised cancer patients [45, 47-51]. In summary, a series of derivatives of teracyclic fluoroquinolone have potential cytotoxic effects. The results obtained showed the test compounds had IC_{50} more than the control drug. Further studies are in progress to evaluate antimicrobial effects of the compounds on Gram positive and Gram-negative bacteria. The aim of this research was to produce novel antitumor FQLs from antibacterial analogs. A series of tetracyclic FQL derivatives were designed. In vitro antimicrobial and antitumor activity against various pathogenic bacteria and cancer cell lines was evaluated. Teracyclic FQLs were particularly active against various pathogenic bacteria and cancer cells and warrant further development.

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