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Anti-tubercular activity of triazoloquinolone and isoniazid-fluoroquinolones compounds

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ABSTRACT

Quinolone derivative, particularly fluoroquinolones are important synthetic antimicrobial agents. Currently some quinolone derivatives are under investigation for the treatment of multidrug-resistant tuberculosis (MDR-TB) and extensive drug resistance tuberculosis (XDR-TB), and are under investigation as first-line anti-TB drugs. The main biological objective in Mycobacterium tuberculosis is the DNA gyrase, a topoisomerase II encoded by gyrA and gyrB that is necessary to retain the DNA supercoil. Mutations in short regions of DNA gyrase are associated with quinolone resistance and take place in several MDR clinical isolates of M. tuberculosis. The new quinolone derivatives, isoniazid-fluoroquinolones and triazoloquinolone derivatives are representatives of a new class of potent and selective anti-TB agents. The esters of triazoloquinolone derivatives are with absence of cytotoxicity. Furthermore, they are particularly interesting is their activity against MDR-TB and XDR-TB.

Keywords: *Anti-TB, MDR-TB, triazoloquinolones, XDR-TB, DNA gyrase inhibitors.*

1. INTRODUCTION

Tuberculosis (TB) is one of the most widespread infectious diseases, concerning one-third of world's population (about 2 billion people) infected with *Mycobacterium* species, mainly *M. tuberculosis*. Every year, approximately 8 million of the TB infected people develop active TB, and almost 2 million die of the disease and approximately one life is lost due to TB every 15 seconds. According to the 2011 Global TB Control Report of the World Health Organization (WHO), in 2010 650,000 cases of MDR-TB emerged among the world's 12 million prevalent cases of TB [1,2]. Even more terrifying is the appearance of multi drug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) reported in all around the world. The increased number of MDR strains, is closely associated to the growing global HIV/AIDS pandemic [3]. The connection of TB and HIV infections is so dramatic that, in some cases, almost two-thirds of the patients diagnosed with TB are also HIV-1 positive [4], and the risk of developing TB is between 20 and 37 times greater in people living with HIV than among those who do not have HIV infection [5]. TB is the leading cause of death among HIV infected people. TB accounts for more than a quarter of deaths among people living with HIV worldwide [6,7]. Since HIV infection is a major risk factor for the development of active TB which, in turn it is a cofactor in the expansion of HIV infection [8]. The immune suppression linked to HIV infection has also caused the emergence of many infections, like *M. avium complex* (MAC) infections [9-11]. *M. avium complex* (MAC) infections can cause severe

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illness in people with advanced AIDS but rarely affects others [12-14]. Since the introduction of highly active antiretroviral therapy (HAART), the rate of MAC infection has substantially declined. Current treatment of disseminated MAC infection includes the use of macrolides (clarithromycin or azithromycin) in combination with ethambutol, or rifabutin. These drugs increase overall the patients survival time , however treatment must be continued indefinitely in patients with advanced AIDS or discontinued after at least 12 months in those who are also treated with HAART and experience immune reconstitution [15]. Although the introduction of HAART has significantly contributed to reduce the frequency and improve the outcome of MAC infection, this remains an important complication of AIDS for which new therapeutic approaches are needed. One of the main problems faced is that the *in vitro* susceptibility testing results of non-tuberculous mycobacteria do not correspond with how these bacteria respond to treatment in patients [16]. In *M. tuberculosis* the existence of hetero-resistance has also been shown when the presence of mutations associated with resistance to certain drugs is genetically studied [17]. In order to improve these problems, a significant effort is being made to standardize methods of studying the susceptibility of these microorganisms *in vitro*. In the latter editions of the National Committee for Clinical Laboratory Standards (NCCLS), there are also included recommendations to evaluate the *in vitro* activity of *M. chelonae*, *M. abscessus*, *M. fortuitum*, *M. avium complex* (MAC), *M. marinum* and *M. kansasii* [18,19], these systems being already proved to provide acceptable results for of the study of *M. tuberculosis* susceptibility to isoniazid and rifampicin only [20]. In the recent years efforts have been made to standardize the *in vitro* susceptibility tests, especially of *M. tuberculosis* to fluoroquinolones [21]. With regard to non-tuberculous mycobacteria, susceptibility testing for baseline MAC isolates from AIDS patients not previously treated with clarithromycin or azithromycin does not appear to be useful in guiding therapy [22]. Furthermore, the treatments currently used for TB are prolonged and may produce important side effects, especially when the strain is resistant to isoniazid and rifampicin. Therefore, the Global Alliance for Tuberculosis Drug Development recommends that in order to stop the spread of TB it is necessary to develop new fast acting drugs [23]. Moreover, it is very important to try to prevent primary resistance emerging and limit the spread of resistant strains [24], since recently there has been great concern about the increasing spread of MDR strains [25,26].

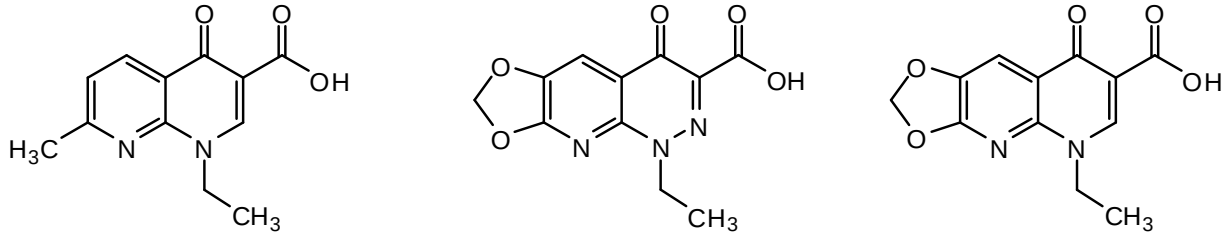
2. THE MOST PROMISING DRUGS

In order to alleviate this problem, many experimental studies have been done and the new fluoroquinolones (moxifloxacin and gatifloxacin) and linezolid have been shown to exhibit good *in vitro* activity against *M. tuberculosis* and against other mycobacteria [27]. The good activity of these compounds has been verified in animal models, and moxifloxacin is known to have potent activity against both actively multiplying and non-actively multiplying tubercle bacilli. Using a murine model, the combination of moxifloxacin, rifampin and pyrazinamide has been seen to reduce the time needed to eradicate *M. tuberculosis* from the lungs of infected mice by up to 2 months when compared to the standard regimen of isoniazid, rifampin and pyrazinamide [27], although this has not been demonstrated in humans [28]. The rapid development of fluoroquinolone resistance in *M. tuberculosis* has also been reported [29]. Linezolid has proved to be useful in the treatment of some cases of MDR-TB, but its prolonged use is frequently associated with toxicity, mainly anaemia and peripheral neuropathy [30]. Some drugs of rifampicin family, such as rifalazil, rifapentin, and rifabutin, have also been proved to be useful. For example, in mouse, rifalazil in combination with isoniazid have been found to be more active than rifampin/ isoniazid [31]. As far as treatment of non-tuberculous mycobacteria is concerned, the new fluoroquinolones exhibit good activity against *M. kansasii* and *M. fortuitum*, and linezolid is active against *M. kansasii* [32]. Latent TB infects one-

third of the world and its treatment may be the basis for controlling this disease in the future, provided that the right drugs are found. With this end in mind, models that attempt to mimic the latent state are being developed [33]. The combination of rifapentine and isoniazid was better tolerated than the combination of rifampin and pyrazinamide and was associated with good protection [34]. In the case of MAC, the efficacy of treatment with azithromycin and thiacetazone is being evaluated, as well as the efficacy of clarithromycin compared with that of azithromycin, and that of the clarithromycin/etambutol combination compared with rifabutin or clofazimine [35,36].

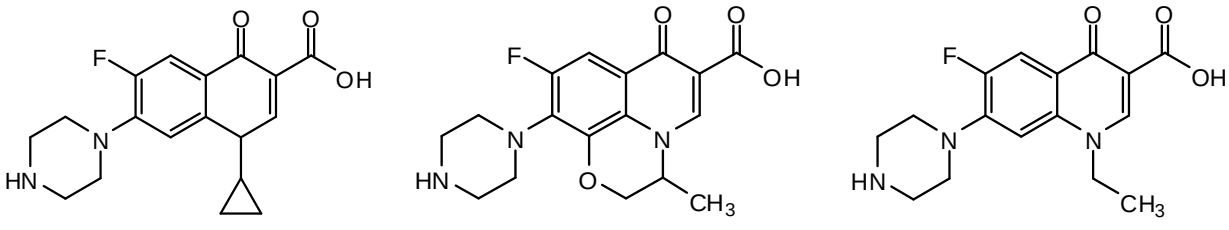
3. CHEMOTHERAPY OF TUBERCULOSIS

Earlier to the beginning of effective chemotherapy of TB, 50% of patients with active pulmonary TB died within 2 years. Since 1940s the introduction of the combination of streptomycin and para-aminosalicylic acid in therapy and successively, the addition of isoniazid, ethambutol, rifampin and pyrazinamide, used in various combinations, resulted in a significant decrease in the mortality. These drugs are recommended as first-line therapy [37]. However, quinolines are classified as second-line drugs, since their use in TB treatment still remains controversial [38]. They are recommended and suggested in managing MDR-TB and XDR-TB, due to the fact that they have a broad and potent spectrum of antimicrobial activity and can also be administered orally, giving a better chance of cure and preventing the development and spread of further resistance [39].

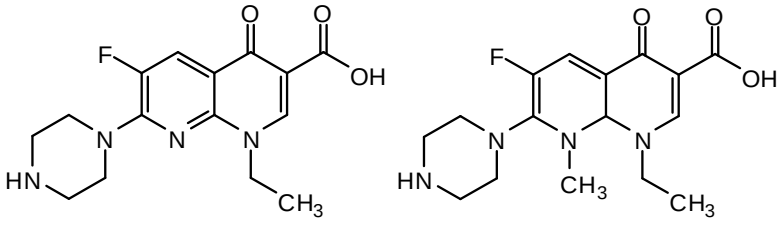


Nalidixic acid **Cinoxacin** **Oxolinic acid**

Figure 1: First generation quinolone compounds

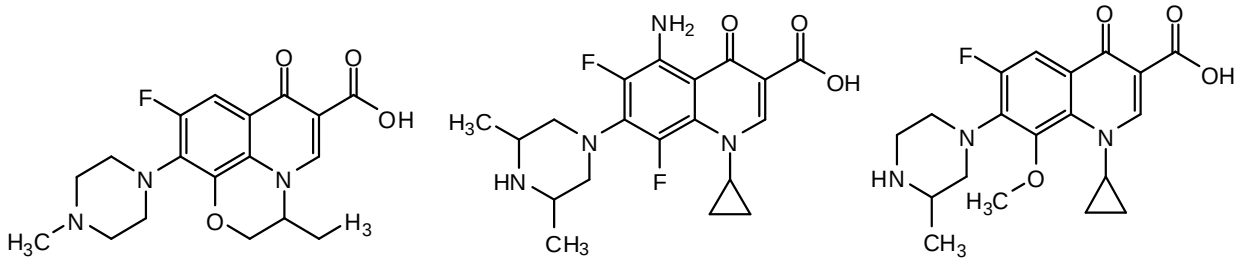


Ciprofloxacin **Ofloxacin** **Norfloxacin**



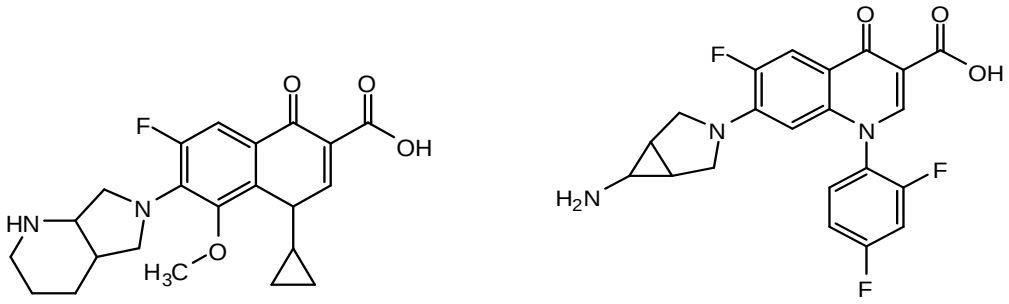
Enoxacin **Lemefloxain**

Figure 2: Second generation quinolone compounds



Levofloxacin **Sparfloxacin** **Gatifloxacin**

Figure 3: Third generation quinolone compounds



Moxifloxacin **Trovafloxacin**

Figure 4: Fourth generation quinolone compounds

The 4-quinolones-3-carboxylic acid, typical of quinolones, have been reported to display "non-classical" biological activities, such as antitumor, anxiolitic, anti-ischemic, anti-HCV-NS3 helicase and NS5B polymerase activities, anti-HSV-1, anti-HIV-1 integrase and CB-2 agonists [40,41]. However, quinolones remain one of the most widely prescribed antibiotics. Generally quinolones are classified in four generations. The first generation is represented by quinolones without fluorine as nalidixic acid, cinoxacin and oxolinic acid (Figure 1); the second one by norfloxacin, ciprofloxacin, ofloxacin, enoxacin and lomefloxacin (Figure 2); the third one by levofloxacin, sparfloxacin and gatifloxacin (Figure 3) and the fourth generation is represented by moxifloxacin and trovafloxacin (Figure 4) [42]. The most recent fluoroquinolones (FQs) are being evaluated as potential anti-TB drugs, also for their potential to shorten TB treatment duration, one of the major strategies for TB control [43,44]. The use of levofloxacin or moxifloxacin for the treatment of XDR-TB, defined as resistance to isoniazid, rifampicin, a FQ and a second-line injectable drug, even when ofloxacin resistance is present [45,46].

4. FLUOROQUINOLONE DERIVATIVES-MODIFICATIONS, RESEARCH TRENDS

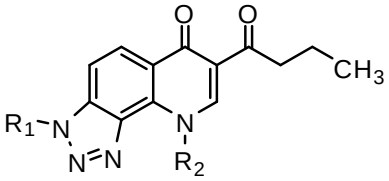
A great amount of work has been done in order to acquire useful knowledge about mechanism of action and resistance to available anti-TB agents. Fluoroquinolones has been one of the most effective anti-TB drugs used in clinical practice. The antimycobacterial pharmacophore moiety of fluoroquinolones have been introduced in a number of various types of molecules to prepare simple or more complicated compounds to improve their activity against *Mycobacteria* sp., and their MDR strains. All these fluoroquinolone molecule modifications are possessing at least medium anti-TB activity. The reported fluoroquinolones derivatives are classified according to their structure.

Table 1: Quinolones that inhibit *M. tuberculosis* DNA gyrase activity and growth (Concentration in µg/mL).

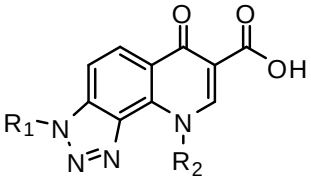
Quinolones	IC_{50}	CC_{50}	MIC	Quinolones	IC_{50}	CC_{50}	MIC
Sparfloxacin	2	5	0.25	**Trovafloxacin**	15	25	16
Sitafloxacin	2.5	2	0.25	**Grepafloxacin**	16	15	1
Clinafloxacin	2.5	5	0.5	**Peflofloxacin**	37	40	8
Gatifloxacin	3	4	0.12	**Tosufloxacin**	37	25	16
Ciprofloxacin	3.5	6	0.5	**Temafloxacin**	40	35	4
Floxifloxacin	4.5	4	0.5	**Flerofloxacin**	45	50	6.25
Levofloxacin	5	12	0.5	**Enofloxacin**	50	25	8
Oflofloxacin	10	20	1	**Oxolinic acid**	300	-	32
Gemifloxacin	11	6	4	**Flumequin**	500	-	64
Garefloxacin	13	15	2	**Pipemidic acid**	1000	-	128
Norfloxacin	14	40	4	**Nalidixic acid**	1100	-	128

5. NEW CLASS OF QUINOLONE DERIVATIVES TRIAZOLOQUINOLONES

Triazolo[4,5-f]quinoline-8-carboxylic acids exhibited *in vitro* antibacterial activity against both gram-positive and gram-negative bacteria. As for the C-5 substituents, a fluorine atom was the most favorable of the three groups, H, F, and Cl [47]. In the last decade, various quinolone compounds have been reported to have antitubercular activity. *M. tuberculosis* isolates expressing resistance to both isoniazid and rifampin are susceptible to fluoroquinolones. The activity of triazolo[4,5-h]quinolone-carboxylic acids, a new class of compounds active against MDR-TB. This novel class of quinolones is endowed with a selective anti-TB activity, coupled with absence of cytotoxicity. The new derivatives showed that the methyl group is the most effective substituent in both N-3 and N-9 positions of the ring system [48]. Quinolone derivatives, 3-methyl-9-substituted-6-oxo-6,9-dihydro-3*H*-[1,2,3]-triazolo [4,5-*h*]quinolone-7-carboxylic acids and their ethyl esters parents (Figure 5; compounds 1-34) have anti-TB activity [49-52].



Compounds 1-17



compounds 18-34

Compound	R_1	R_2	Compound	R_1	R_2
1	CH_3	CH_3	**18**	CH_3	CH_3
2	CH_3	CH_2CH_3	**19**	CH_3	CH_2CH_3
3	CH_3	$CH_2CH_2CH_3$	**20**	CH_3	$CH_2CH_2CH_3$
4	CH_3	$CH_2CH_2CH_2CH_3$	**21**	CH_3	$CH_2CH_2CH_2CH_3$
5	CH_3	$CH_2CH=CH_2$	**22**	CH_3	$CH_2CH=CH_2$
6	CH_3	benzyl	**23**	CH_3	Benzyl
7	CH_3	4-Me-benzyl	**24**	CH_3	4-Me-benzyl
8	CH_3	4-Br-benzyl	**25**	CH_3	4-Br-benzyl
9	CH_3	CH_2CH_2-phenyl	**26**	CH_3	CH_2CH_2-phenyl
10	CH_3	$C(CH_3)_3$	**27**	CH_3	$C(CH_3)_3$
11	CH_3	$CH_2C(CH_3)=CH_2$	**28**	CH_3	$CH_2C(CH_3)=CH_2$
12	CH_3	CH_2-cyclopropyl	**29**	CH_3	CH_2-cyclopropyl

13	CH_3	CH_2-cyclobutyl	**30**	CH_3	CH_2-cyclobutyl
14	CH_2Ph	CH_3	**31**	CH_2Ph	CH_3
15	CH_2Ph	CH_2CH_3	**32**	CH_2Ph	CH_2CH_3
16	CH_2Ph	$CH_2CH=CH_2$	**33**	CH_2Ph	$CH_2CH=CH_2$
17	CH_2Ph	$CH_2CH_2CH_2CH_3$	**34**	CH_2Ph	$CH_2CH_2CH_2CH_3$

Figure 5: Chemical structure of [1,2,3]triazolo[4,5-*h*]quinolone compounds **1-34**

All compounds anti-TB *in vitro* activity have been evaluated in comparison with standard anti-TB drugs. The results showed that [1,2,3] triazolo[4,5- *h*]quinolones exhibited a good anti-TB activity, without cytotoxicity [48]. Compounds **10**, **27** and **31** showed the best activity against mycobacteria. Among them, compound **10** was the most potent against H37Rv and H37Ra (MIC_{90} = 0.5μg/mL), and 11 clinical isolates of MDR-TB (Table 2) [50]. The small, electron donor methyl group in position N3 gave the best results, since the introduction of an increasing steric effect substituent (as the benzyl group) led to a loss of the biological effect, like as more lipophilic and bulking substituents at the N9 position. Lastly, when MICs were determined against gram-positive and gram-negative bacteria and against *Candida sp*. all compounds were inactive (MIC > 64-100μg/mL) [53].

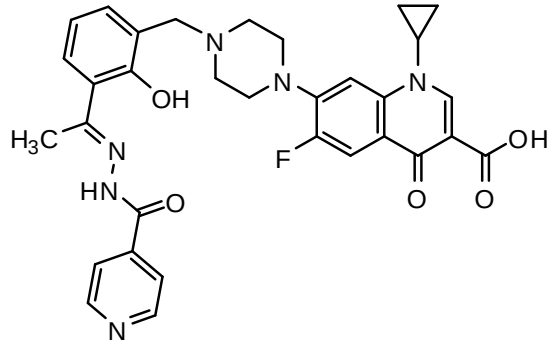
Table 2: *In-vitro* evaluation of triazoloquinolone compounds 10, 27, 31 against *Mycobacterium* (MIC:μg/mL)

Compound	***M. tuberculosis H37Rv***	***M. tuberculosis H37Ra***	***M. smegmatis mc^2 155***	***M. bovis***
10	0.5	0.5	5	4
27	16	8	32	16
31	8	4	32	4
Ethambutol	5	4	0.5	2
Rifampin	<0.5	<0.06	8	-
Streptomycin	1	1	-	-
Ciprofloxacin	0.5	0.5	0.125	0.25

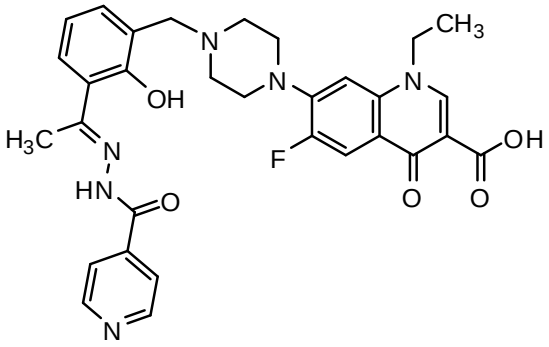
6. ISONIAZID-FLUOROQUINOLONES

The adducts of isoniazid with antibacterial fluoroquinolones **35** and **36** exhibited the MIC value [μmol] of 1.30 and 1.26 respectively. The fluoroquinolone-isoniazid derivatives showed higher activity than the above discussed quinolone-isoniazid derivatives **35** and **36** (fig **5**) [54]. Further indolyl-isoniazid-flouroquinolone derivatives **37-40** were prepared [55]. All compounds are substituted by anti-TB active gatifloxacin at the same time. All compounds **37-40** are more lipophilic than gatifloxacin, which is important for penetration of these com-pounds through bacterial/mycobacterial cell. Assuming the issue of penetration is even more crucial for quinolone activity against *Mycobacteria* sp. All compounds were tested against *M. tuberculosis*, and against MDR-TB and they showed similar activity. According to the results, it can be assumed, that unsubstituted gatifloxacin exhibited higher activity against *M. tuberculosis*, whereas prepared analogues **37-40** (fig **6**) showed good efficacy against MDR-TB strains. All the compounds were also evaluated for their cytotoxicity and all the discussed derivatives were found to be non-toxic until 62.5μg/ml. Combination of isoniazid with other appropriate antibacterial component leads to the prodrugs with prolonged release and possible synergism as compound **41**. Their activities are comparable with fluoroquinolone not only against *M. tuberculosis* H37Rv, but they exhibited activity also against some clinical isolated atypical strains. MIC value of compound **41** (fig **7**) against various mycobacterium were *M. tuberculosis* H37Rv (-μmol/l) *M. tuberculosis* 331/88 (2.0

μmol/l) *M. avium* 330/88 (125 μmol/l) *M. kansasii* 235/80 (2.0 μmol/l) and *M. kansasii* 6509/96 (2.0 μmol/l) [56,57].

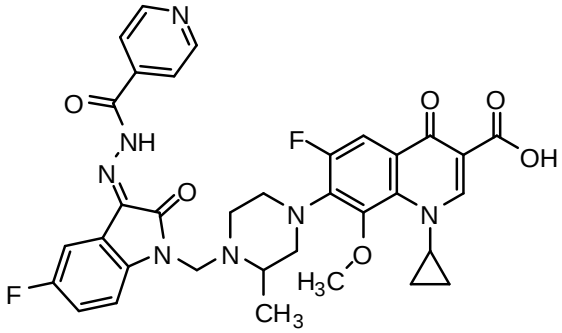


35 (1.30)

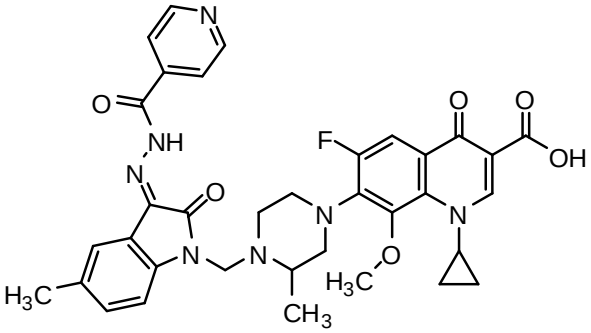


36 (1.26)

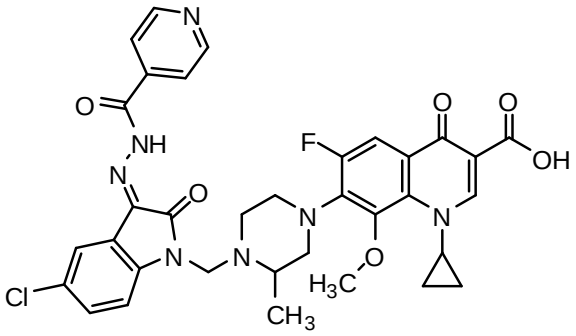
Figure 6: Fluoroquinolone-isoniazide derivatives **35** and **36**



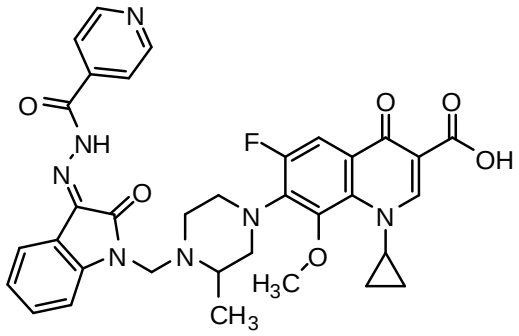
37 (0.78, 0.78)



38 (0.78, 0.78)



39 (0.39, 0.78)



40 (0.20, 0.78)

Figure 7: Indolyl-gatifloxacin-isoniazid derivatives **37-40**, their MIC value against *M. tuberculosis*, and against MDR-TB strains. The MIC value of gatifloxacin was 0.20 μg/ml, or 3.12 μg/ml

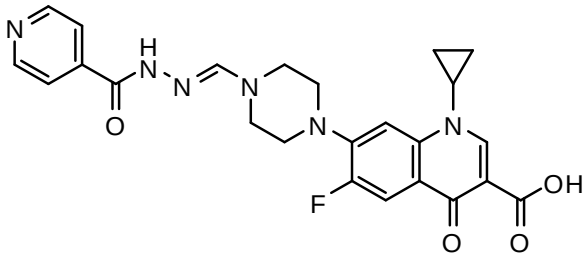


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Figure 8: The antitubercular effect of fluoroquinolone-isoniazid derivatives

7. DISSCUSSION

In view of the persistent drug-resistant (MDR-TB/XDR-TB) problems to currently used anti-TB agents, it is important that new anti-TB agents should address different targets, as those of currently used drugs including the shortening of TB therapy. The unique structure of the mycobacterial cell wall makes it a useful target for drug development and studies can be directed to specific sites. Although one possible long term solution to the problem is a better vaccine, in the short term, the major reliance will be on chemotherapy requiring the development of novel, effective and non-toxic anti-TB agents to control TB. However, in recent years, there is an enhanced activity in the research and development of new drugs for TB. Some compounds are presently in clinical development, while others are being investigated pre-clinically in an attempt to explore new molecules for the target based treatment of TB [1,42,]. Simultaneously, some new targets are being identified and validated for their practical usefulness. The specific goal would be to bring new, affordable TB agents that would reduce duration of treatment, effective against latent infections andagainst MDR-TB/XDR-TB, cheap and easily available [32,58]. Thetriazolo[4,5-*h*]quinolone-carboxylic acid derivatives have specific anti-TB potential. This characteristic is quite relevant in the context of a new anti-TB drug for two main reasons. First, the limited spectrum should not disturb the existing normal flora and, therefore, should likely be better tolerated as compared with wide spectrum existing treatments. Second, the selectivity of the antimicrobial activity should limit the selection of resistant mutants among species that are not specifically targeted by the treatment, therefore reducing the risk of vertical transmission of resistance across species.

8. CONCLUSIONS

The triazolo[4,5-h]quinolone-carboxylic acid derivatives belong to a novel class of quinolones endowed with a selective anti-TB activity. The comparison of the new derivatives with the previous series shows that the methyl group is the most effective substituent in both N-3 and N-9 positions of the ring system. In conclusion, these new quinolones are particularly adapted to be used as anti-TB agents. Finally, the selectivity and the consistent ability to reduce the onset of cross resistance of triazoloquinoles, probably due to their different mechanism of action, lead them to be good candidates for further development of new anti-TB drugs.

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