

Promising Drugs Against Tuberculosis

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Abstract: Tuberculosis (TB) is an important public health problem worldwide due to AIDS epidemic, the advent of multidrug resistant strains (MDR) and the lack of new drugs in the market. TB is responsible for almost 3 millions deaths each year. According to WHO (World Health Organization), which declared tuberculosis a global health emergency in 1993, tuberculosis, without a coordinated control effort, will infect an estimated 1 billion people by 2020, killing 70 million. In spite of this problem, there is a lack of development of new TB drugs. For example, it has been nearly 35 years since the introduction of a new class of compounds for the treatment of TB. Thus, there is an urgent need for new drugs to fight against this disease. Considering that, this review aims promising drug candidates that are in development against TB.

Keywords: Tuberculosis, drugs, antimycobacterial activity.

INTRODUCTION

Nowadays, tuberculosis (TB) is becoming a worldwide problem. This contagious disease is transmitted through the air and it is caused by the bacterium *Mycobacterium tuberculosis*, which can attack different organs of human body. However, it most commonly affects the lungs, which is responsible for more than 75 percent of cases. The common symptoms of this disease are prolonged cough, chest pain, and hemoptysis, fever, chills, night sweats, appetite loss, weight loss, and easy fatigability. Different factors are responsible for the resurgence of TB, such as people infected with HIV virus, immigration, war, famine, homelessness, the lack of new drugs and multi-drug-resistant tuberculosis (MDR TB) due to inconsistent or partial treatment. Considering TB problems, the World Health Organization declared this disease a global health emergency in 1993 [1].

According to statistics, one-third of the world's population is currently infected with the TB bacillus totaling up almost three million deaths each year. Each year, 8 million people worldwide develop active TB and almost 3 million die. The population infected at present is: Africa (35%); Americas (18%); Eastern Mediterranean (29%); Europe (15%); South-east Asia (44%) and Western Pacific (35%). Statistical dates demonstrate that without a coordinated control effort, tuberculosis will infect an estimated 1 billion people by 2020, killing 70 million [1].

TUBERCULOSIS TREATMENT

The standard first-line treatment against active TB is a combination of the drugs rifampicin, isoniazid, pyrazinamide, and ethambutol (Fig. 1) and (Table 1) given in combination over six to nine months. The combinations are

very important to prevent the emergence of multiple drug-resistant organisms, which can lead to an ineffective treatment. A typical treatment for a non-drug resistant strain of TB is two months of isoniazid, pyrazinamide, ethambutol and rifampin followed by four months of rifampin and isoniazid. WHO strongly recommends the use of fixed-dose combination tablets for TB treatment (Table 2). The minor and major side-effects of antituberculosis drugs are described in (Table 3).

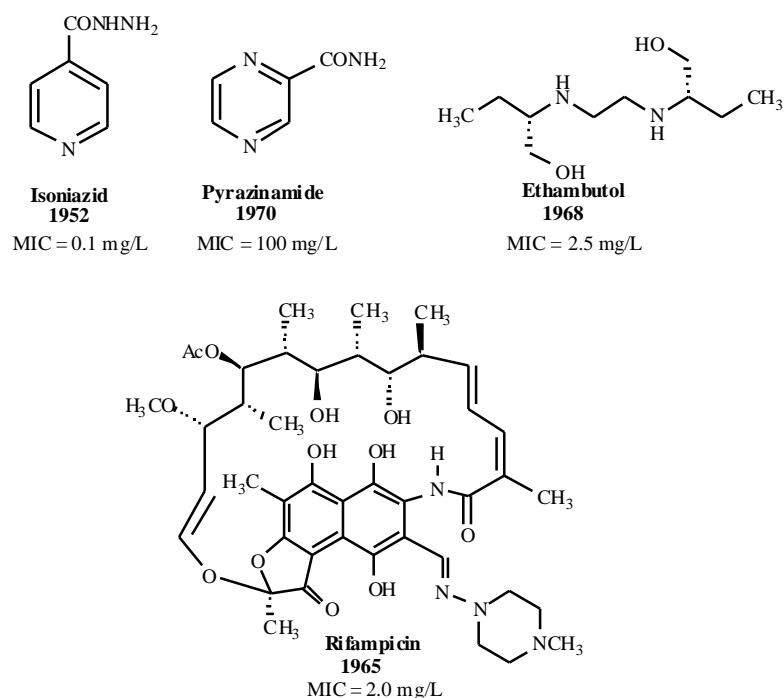
MULTI-DRUG RESISTANT (MDR) TB

Multi-Drug Resistant (MDR) TB is normally defined as a patient who has active tuberculosis with resistant bacilli at least to both rifampicin and isoniazid and this patient needs to be treated intensively and for up to 24 months with regimen based on other antituberculosis drugs. The factors that contribute to MDR-TB are interrupted, erratic or inadequate therapy, as well as an inadequate public health system. The cost to treat MDR-TB are 1400 times the cost of regular treatment and according WHO, there are 300,000 new cases per year of MDR-TB worldwide. Nowadays, there are 79% of MDR-TB resistant to at least three out of the four main drugs used to treat TB. The drugs normally used to treat MDR-TB are amikacin, capreomycin, ciprofloxacin, cycloserine, ethionamide, kanamycin, ofloxacin, *p*-aminosalicylic acid and protonamide (Fig. 2) and (Table 4).

According to WHO, the re-treatment regimen should include at least four drugs never used by the patient, including an injectable amikacin, capreomycin or kanamycin and a fluoroquinolone. Pyrazinamide and ethambutol can be added in the treatment because of the lower probability of resistance than other essential drugs (Table 5).

There are three basic factors involved in the development of new tuberculosis drugs; to reduce the total duration of treatment, to improve the MDR TB and to provide more effective treatment of latent tuberculosis infection [2,3]. However, in spite of the worldwide problem caused by TB,

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MIC - Minimal inhibitory concentration of antibiotic that inhibits a bacterium.

Fig. (1). Essential antituberculosis drugs.

Table 1. Essential Antituberculosis Drugs

Drugs Abbreviations	Recommended dosage (dose range) in mg/Kg Daily	Dose Form
Isoniazid (I)	5 (4-6)	Tablet 100, 300 mg
Rifampicin (R)	10 (8-12)	tablet or capsule 150, 300 mg
Pyrazinamid (P)	25 (20-30)	tablet 400 mg
Ethambutol (E)	15 (15-20)	tablet 100, 400 mg

WHO/CDS/TB/2003.313 Treatment of tuberculosis: guidelines for national programmes, third edition revision approved by STAG, June 2004.

Table 2. Fixed-Dose Combination of Drugs

Drug	Dose form	Strength for daily use	Strength for use 3 times weekly
I + R	tablet	75 mg + 150 mg	150 mg + 150 mg
	tablet or pack of granules ^a	150 mg + 300 mg 30 mg + 60 mg	60 mg + 60 mg
I + E	tablet -	150 mg + 400 mg	-
I + R + P	tablet	75 mg + 150 mg + 400 mg	150 mg + 150 mg + 150 mg
	tablet or pack of granules ^a	30 mg + 60 mg + 150 mg	-
I + R + P + E	tablet	75 mg + 150 mg + 400 mg + 275 mg	-

From essential drugs: WHO Model List (revised in December, 1999). In: *WHO drug information*, 1999, 13(4):249-262.

^aFor pediatric use.

Table 3. Symptom-Based Approach to Side-Effects of Antituberculosis Drugs

Drug	Side-effects	Management
	Minor	Continue anti-TB drugs
P and R	Anorexia, nausea, abdominal pain	Give drugs with small meals or last thing at night
P	Joint pains	Aspirin
I	Burning sensations in the feet	Pyridoxine 100 mg daily
R	Orange-red urine	This commonly happens and is normal
	Major	Stop responsible drug(s)
R	Shock, purpura, acute renal failure	Stop rifampicin
E	Visual impairment	Stop ethambutol
I, R	Ichting, skin rash	Stop anti-TB drug
I, R, P	Jaundice (other causes excluded) hepatitis	Stop anti-TB drug

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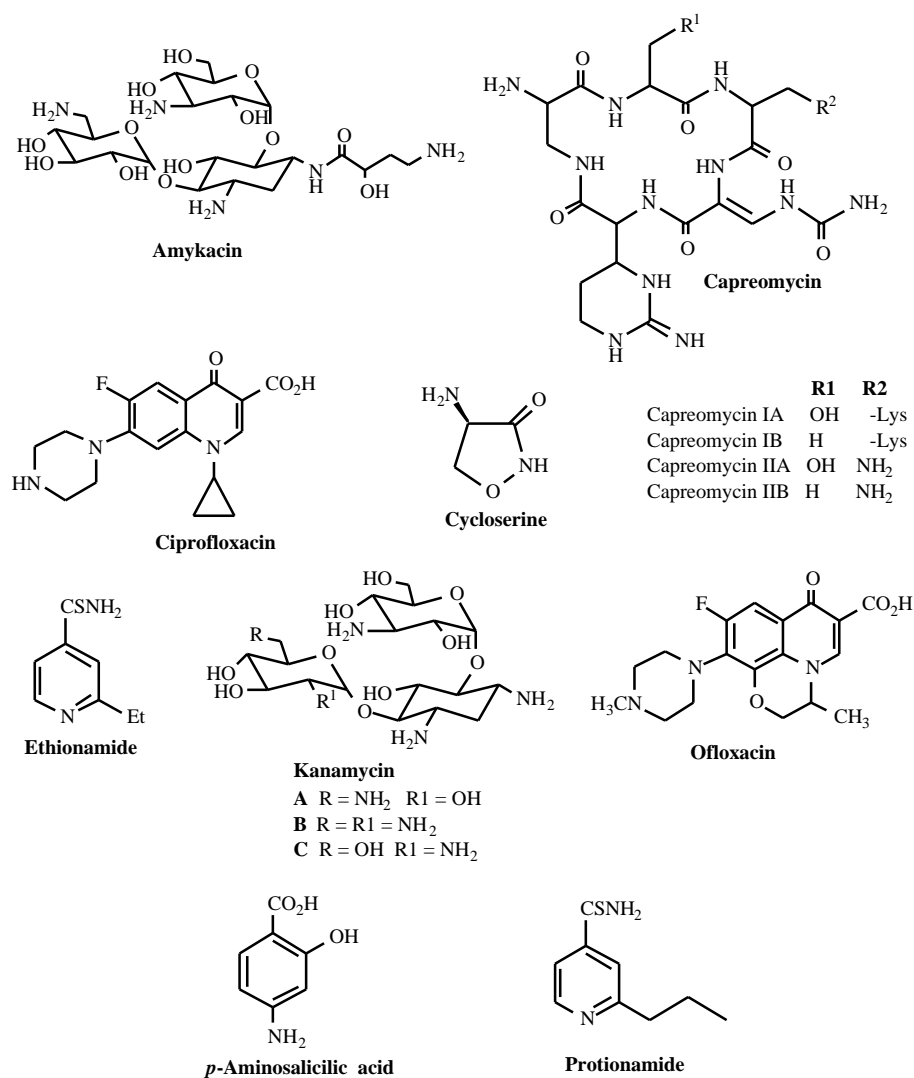


Fig. (2). Second-line antituberculosis drugs.

Table 4. Second-Line Antituberculosis Drugs

Drug	Mode of action	Recommended Daily Dosage		
		Average (mg/Kg)	Minimum (mg)	Maximum (mg)
Amikacin (A)	bactericidal	15	750	1000
Capreomycin (Cm)	bactericidal	15	750	1000
Ciprofloxacin (Cx)	bactericidal	10-20	1000	1500
Cycloserine (Cs)	bacteriostatic	10-20	500	750
Ethionamide (Et)	bactericidal	10-20	500	750
Kanamycin (Km)	bactericidal	15	750	1000
Ofloxacin (O)	bactericidal	7.5-15	600	800
<i>p</i> -Aminosalicylic acid (PAS)	bacteriostatic	150	8g	12g
Protionamide (Pt)	bactericidal	10-20	500	750

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Table 5. Suggested Treatment Regimens

Susceptibility to	Initial Phase		Continuation Phase	
	Drug	Duration	Drug	Duration
Resistance to H+R	S ^a +Et+Q ^b +Z +/- E	at least 6 months	Et+Q+Z +/- E	12-18 months
Resistance to all Essential drugs	1 injectable + 1 fluoroquinolone+ 2 of these 3 oral drugs: PAS, Et, Cs	at least 6 months	the same drug except injec- table	18 months

^a if resistance to S is confirmed, replace this drug with Km, Am or Cm.

^bFluoroquinolone (Q) (ciprofloxacin or ofloxacin).

WHO/CDS/TB/2003.313 Treatment of tuberculosis: guidelines for national programmes, third edition revision approved by STAG, June 2004.

unfortunately the development of new drugs for the treatment of tuberculosis has been slow [4-6]. Due to the importance of new drugs in this field, the aim of this review is to highlight the promising candidates drugs against TB.

ANTI-TB DRUGS

Nowadays, there are different classes of compounds under research and development to obtain new drugs against TB. For example, thiolactomycin and analogs, ethambutol analogs, mefloquine and analogs, deazapteridines, 9-benzylpurines, benzoxazines, diterpenoids, imidazo (4,5-c)pyridines, tryptanthrin and analogs, clofazimine and others phenazines, 1,2,4 triazoles, isoniazid analogs, fulleropyrrolidines, toluidine derivatives, saccharides, quinolones, oxazolidinones and miconazole analogues, as well as the natural product calanolide [7]. In recent patent, there are also new classes with TB activity, such as pyrrolidine-2,5-dione and piperidine-2,6-dione derivatives [8], sulpho compounds [9], halogenated *p*-aminosalicylic acid and thioacetazone [10] and *p*-guanidinosalicylate sodium hydrochloride [11].

RIFAMYCINS

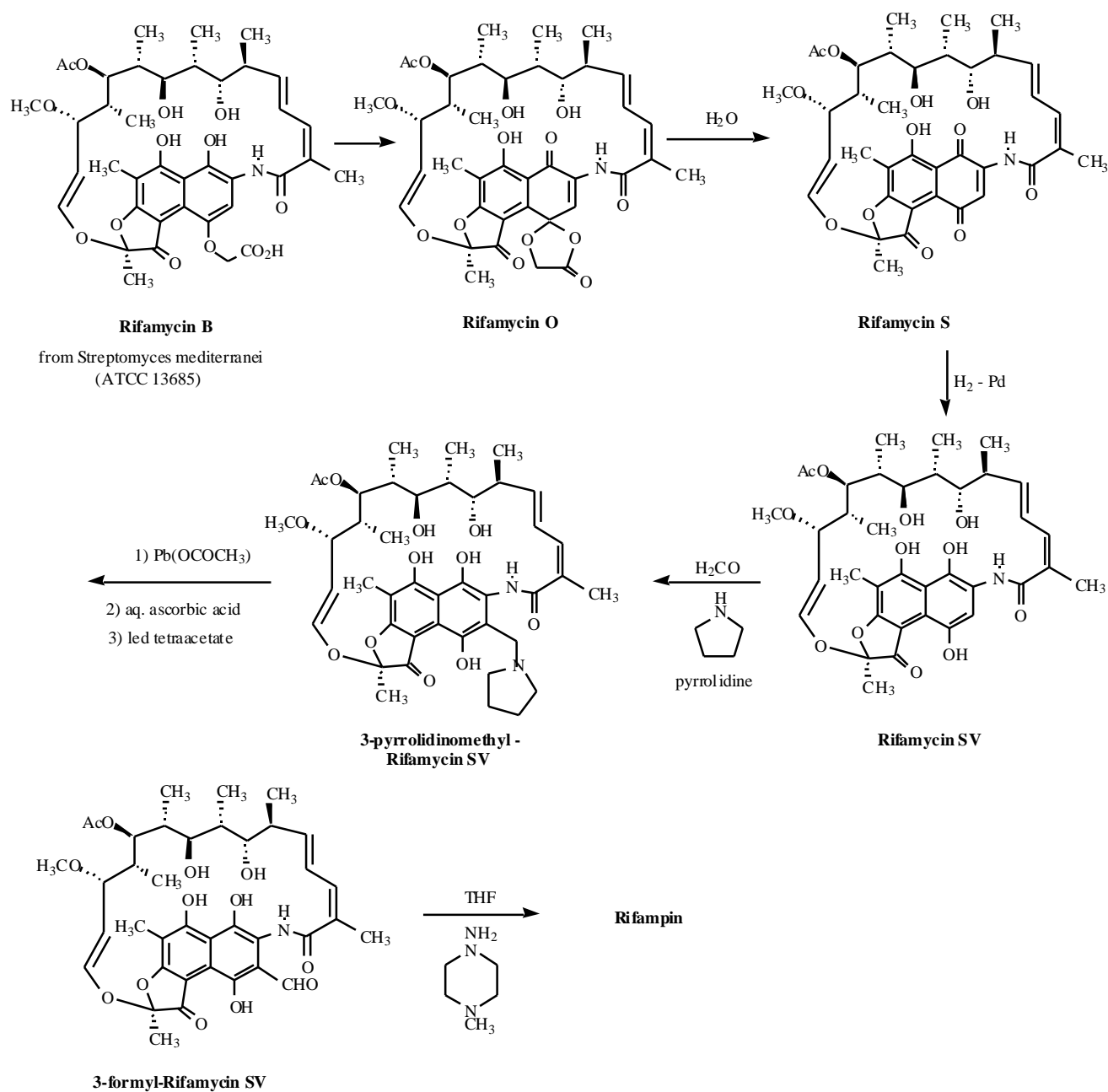
General Information

Rifamycins are a group of anti-bacterial agents characterized by a chromophoric naphthohydroquinone group spanned by a long aliphatic bridge, which belong to the family of ansamycins antibiotics [12]. Rifampin (USAN) or rifampicin (INN) (Fig. 1) is the most important drug of this group in TB treatment.

This semisynthetic antibiotic is produced from fermentation broth of *Streptomyces mediterranei* (Scheme 1) and it shows better activity against Gram-positive and negative bacteria in comparison with the other rifamycins, specially against mycobacteria with excellent oral bioavailability [13-15].

Mechanism of Action

Rifampin became clinically available in 1966 and it is responsible for the reduction of the duration of therapy, from 12 to 6 months, when combined with others drugs, as well as from 9 to 2 or 3 months in latent infection. Its mechanism of



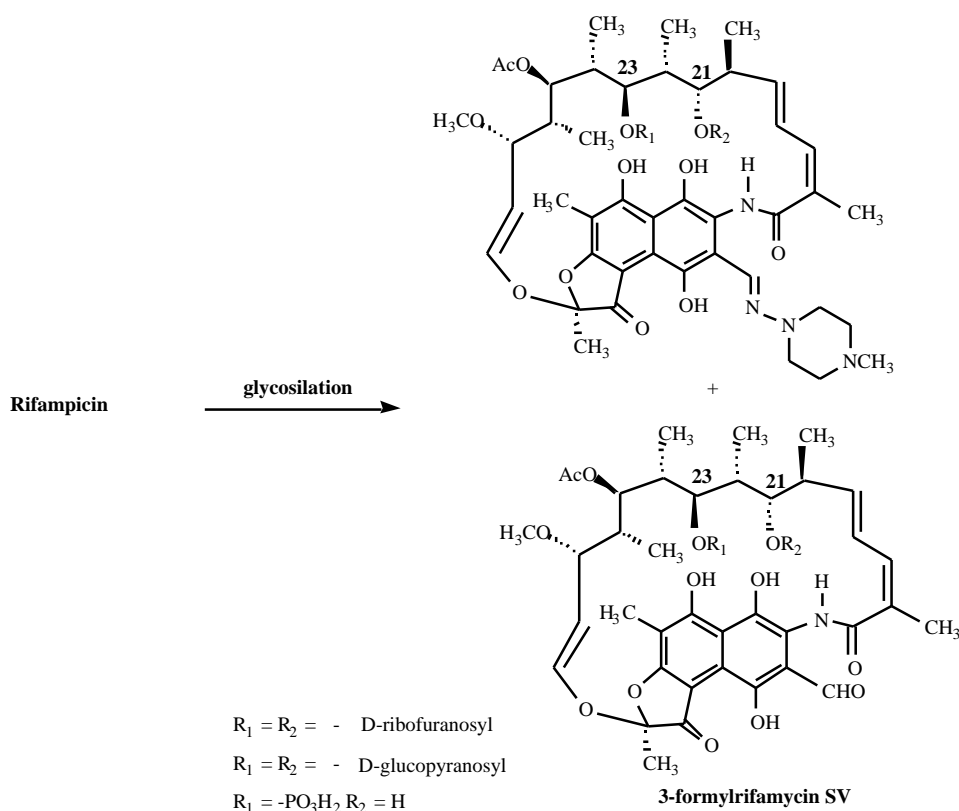
Scheme 1. Semisynthetic synthesis of rifampin.

action is based on the inhibition of bacterial DNA-dependent RNA polymerase, which produces essential proteins and it is responsible to copy their own genetic information, the DNA. Despite the importance of rifampin in the TB treatment, the emergence of different rifampicin-resistant bacteria, increase the problems to global tuberculosis control [16]. This resistance occurs during therapy against active tuberculosis and normally arises from mutations in the beta subunit of the ribosomal polymerase gene (*rpoB*). The inactivation of rifampicin by different rifampicin-resistant bacteria is due to the glycosylation or phosphorylation of rifampicin and 3-formylrifamycin SV in the C₂₁ and C₂₃ position (Scheme 2) [12].

Due to the rifampicin-resistance and in search for more potent drugs with lesser side effects, other semisynthetic rifampin analogues have been introduced for clinical use, such as rifapentine, rifalazil, rifabutin and rifametan.

Rifapentine

After a thirty years gap, in which no new TB drug was introduced in the market, Rifapentine (Fig. 3) [17] was developed by Hoechst Marion Roussel under the trade name Priftin. This cyclopentyl-substituted rifampicin was approved by FDA in 1998 and it possesses the same broad



Scheme 2. Inactivation of rifampicin by different rifampicin-resistant bacteria.

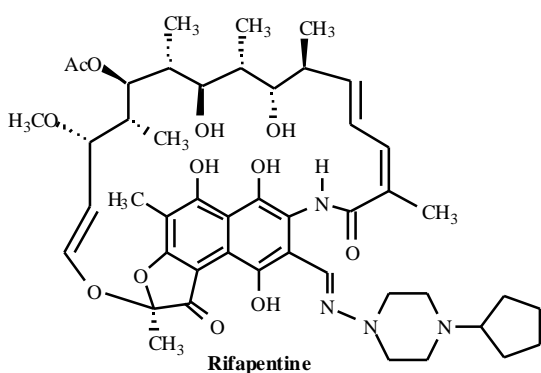


Fig. (3). Structure of rifapentine.

spectrum activity than rifampin. However, an important difference between both rifamycins is the elimination half-life of rifapentine, which is almost 4 fold greater in humans than rifampin. This can be explained by the higher lipophilicity, which facilitates tissue penetration of this drug, as well as the lack of biotransformation to antimicrobially inactive metabolites.

Rifalazil

The benzoxazinorifamycin, common known as Rifalazil or (KRM 1648) (Fig. 4) is also a semisynthetic analog of rifampin [18] produced by Kaneka Corporation that possesses potent bactericidal activity against *M. tuberculosis*

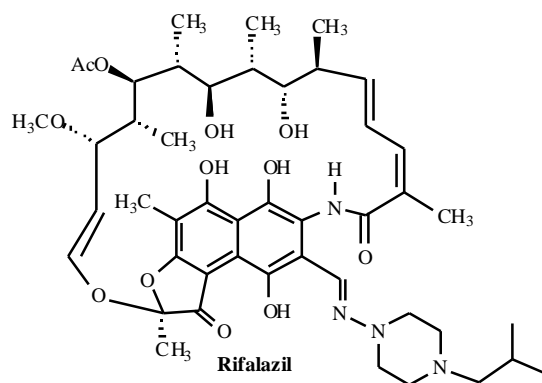


Fig. (4). Structure of rifalazil.

in vitro and *in vivo*. Studies *in vitro* have shown that rifalazil is 64-fold more active than rifampin against different *M. tuberculosis* strains. Rifalazil also presents good oral activity against *M. tuberculosis* both in animal and humans with a long half-life of about 60h. This rifamycin was in Phase II clinical trials, however, due to severe side effects in the fourth day of Phase II trial, the development of rifalazil was aborted.

Rifabutin

Rifabutin (Fig. 5) [19] is the first rifamycin approved by FDA for the prevention of MAC (*Mycobacterium avium*

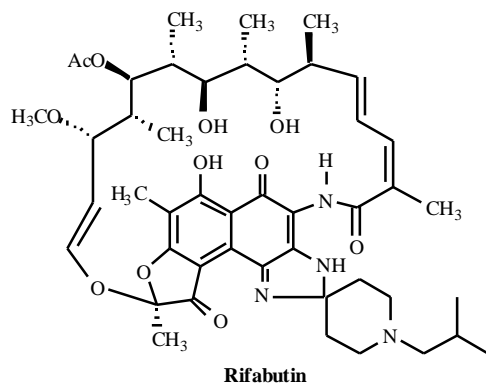


Fig. (5). Structure of rifabutin.

complex) disease in people with advanced HIV infection. People with MAC present fatigue, weight loss, abdominal pain, night sweats, fever, and liver dysfunction and it can contribute to death. This rifamycin is used in combination with others drugs, such as ciprofloxacin, ethambutol, amikacin, azithromycin and clarithromycin. Rifabutin is manufactured by Adria Laboratories, Columbus, Ohio, with the brand name Mycobutin.

Rifametane

The semisynthetic analog of rifampin, rifametane (SPA-S-565) (Fig. 6) has been developed by Societa Prodotti Antibiotici (SPA), Milan, Italy. The phase I pharmacokinetic study of rifametane was conducted in 8 healthy male volunteers with a 300 mg single oral compared with 300 mg of conventional rifampicin [20]. The pharmacokinetic profiles of rifametane were significantly more favorable than those of rifampicin. Currently, SPA is collaborating with Glaxo India to advance rifametane into phase II trials.

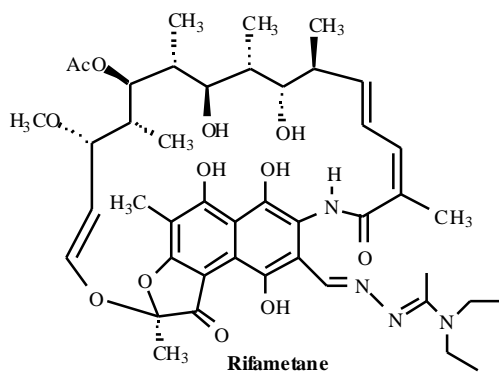


Fig. (6). Structure of rifametane.

FLUOROQUINOLONES

Fluoroquinolones (7-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid), (Fig. 7) are an important class of fluorine compounds. This class possesses a potent antibacterial activity with a broad spectrum of activity against Gram-positive, Gram-negative and mycobacterial organisms as

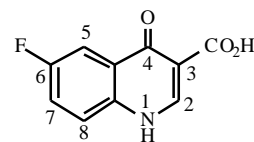


Fig. (7). Basic structure of fluoroquinolones nucleus.

well as anaerobes with great therapeutic potential, particularly those caused by organism resistant to other classes of antibacterial drugs [21]. The importance of the fluoroquinolones in the fight against infectious diseases began during the 1980's when the norfloxacin was discovered. This compound has presented broad spectrum of activity and better pharmacokinetic profile against Gram-negative and some Gram-positive bacteria due to the combination of a fluorine atom at position 6 and piperazinyl group at position 7. After this important discovery, a large number of fluoroquinolones have been synthesized with further improvement, such as the solubility, antimicrobial activity, prolonged serum half-life, lesser adverse side effects and both oral and parenteral routes of administration. In this context, ciprofloxacin, ofloxacin, enoxacin, lomefloxacin, levofloxacin and sparfloxacin (Fig. 8) [21] can be pointed out.

At present, much attention has been paid to the newer fluoroquinolones commonly classified in fluoroquinolones of fourth generation due to their fewer toxic effects, improved pharmacokinetic properties and extensive and potent activity against Gram-positive and Gram-negative bacteria, including resistant strains when compared with the earlier fluoroquinolones. Their advantages can be explained by their mechanism of action [22,23]. The inhibition of bacterial multiplication caused by fluoroquinolones is in general due to the inhibition of two bacterial enzymes: DNA gyrase (topoisomerase II) and topoisomerase IV enzymes. DNA gyrase is an essential enzyme involved in the replication, transcription and reparation of the bacterial DNA. In the case of topoisomerase IV enzyme, it is responsible for decatenation, that is removing the interlinking of daughter chromosomes, thereby allowing segregation into two daughter cells at the end of the replication round. For the Gram-negative organisms, DNA gyrase is the primary target, while in the Gram-positive bacteria, topoisomerase IV is the most affected [22,23]. The efficacy of the new fluoroquinolones in comparison with the earlier fluoroquinolones is due to their dual activity inhibiting both DNA gyrase bacterial type II and topoisomerase IV, which limits also the emergence of fluoroquinolones resistance. As examples of this class can be mentioned gatifloxacin, moxifloxacin and trovafloxacin (Fig. 9) [21].

Moxifloxacin

The fluoroquinolone moxifloxacin (BAY12-8039) developed by Bayer [24,25], possesses excellent activity against a variety of different types of bacteria, which causes infections, such as pneumonia, bronchitis and sinusitis. Their excellent activity against *M. tuberculosis in vivo* and *in vitro* in different studies can be compared with other known fluoroquinolones (Table 6) [26]. For example, in comparison

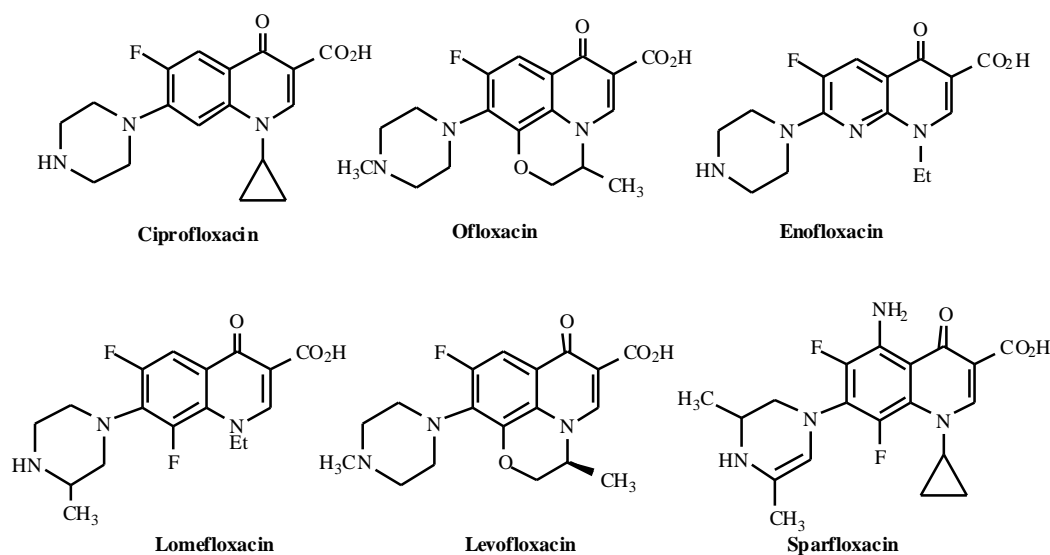


Fig. (8). Structure of some fluoroquinolones.

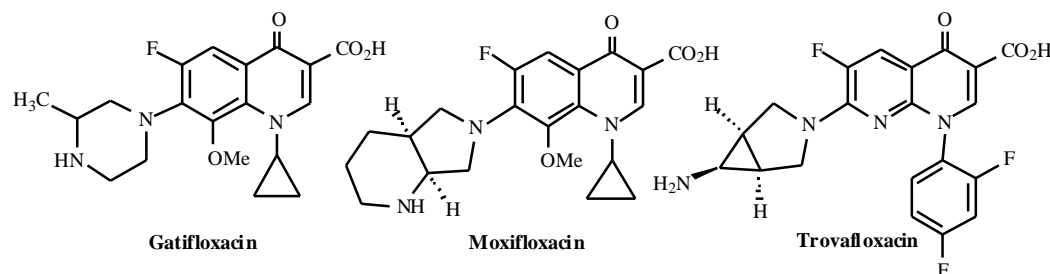


Fig. (9). Structure of gati, moxi and trovafloxacin.

Table 6. Moxifloxacin Compared with other Known Fluoroquinolones

DRUG	Tablet	MIC ₉₀	AUC	t _{1/2}	C _{max}
Moxifloxacin	400 mg	0.25	45-51	12	5
Gatifloxacin	400 mg	0.25	29-40	08	5
Sparfloxacin	400 mg	0.5	41-54	20	1
Levofloxacin	500 mg	1.0	34	07	6

with levofloxacin and ofloxacin (Fig. 8) against rifampicin-tolerant bacteria, moxifloxacin is much more effective with better bactericidal and sterilizing activity. Moxifloxacin has also excellent oral bioavailability and long t_{1/2} and the elimination half-life of the drug in man is about 12 hours in comparison with 1 to 2 hours for isoniazid. Because of its good results, moxifloxacin is under clinical studies for TB treatment.

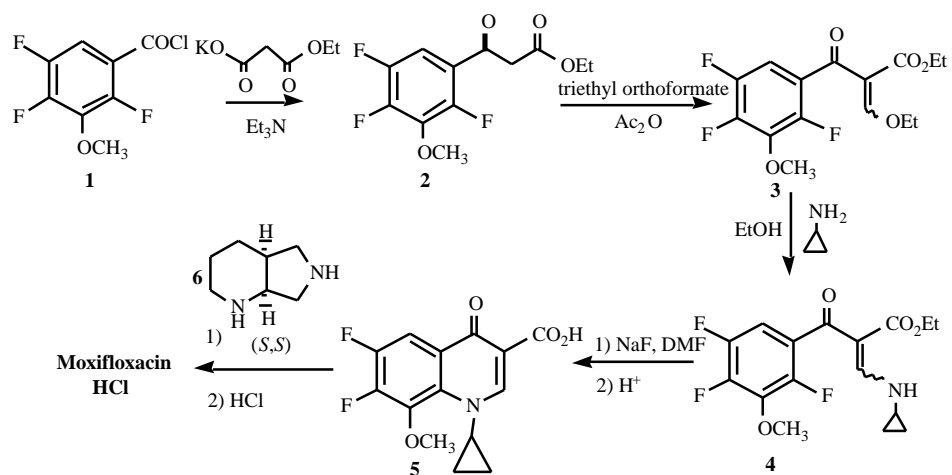
The synthesis of moxifloxacin (Scheme 3) [27] is based on the acid chloride 1 as the starting material, which was transformed into the -Ketoester 2 and subsequently converted to its ethoxyacrylate derivative 3. Treatment of this ethoxy acrylate derivative with the cyclopropylamine gave the enamine 4. Cyclization of the enamine and

hydrolysis gave the 4-oxoquinoline-3-carboxylic acid 5. The substitution of fluorine atom at the C-7 position by bicyclo 6, which was prepared (Scheme 4) using pyridine-2,3-carboxylic acid 7 as starting material gave moxifloxacin.

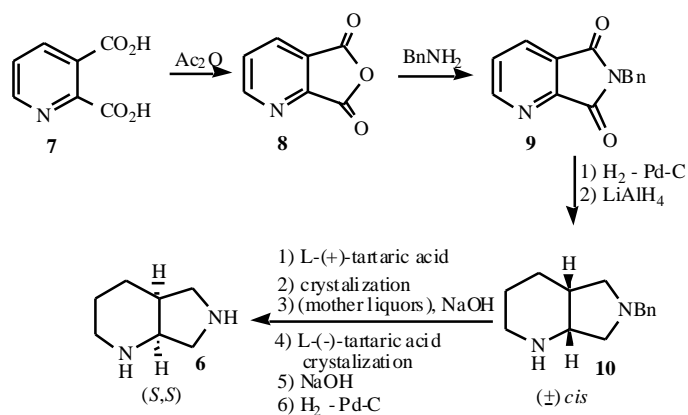
Due to the importance of the fluoroquinolones in the fight against tuberculosis, others fluoroquinolones and quinolones have been under preclinical and clinical study such as, PD 161148, CS-940, sitafloxacin, gemifloxacin and T-3811ME (Fig. 10) [7].

Linezolid

Oxazolidinones represent the first new class of antibacterial drugs in the last 35 years [28,29]. The history of



Scheme 3. Synthesis of moxifloxacin.



Scheme 4. Synthesis of bicyclo 6 present in moxifloxacin structure.

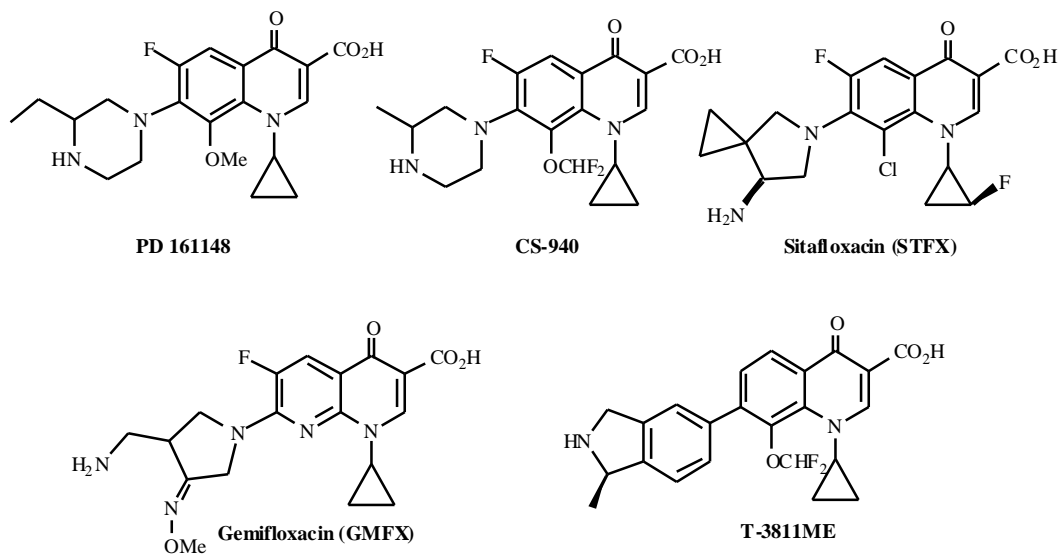


Fig. (10). Structures of some fluoroquinolones and quinolone under study against tuberculosis.

oxazolidinones as drug started in 1978, when a patent of El DuPont de Nemours & Co., Inc. reported a series of 5-(halomethyl)-3-aryl-2-oxazolidinones with biological activity against certain plant pathogen [30]. After this discovery, (5*R*)-(hydroxymethyl)-3-aryl-2-oxazolidinone, S-6123 (Fig. 11) was reported to have weak *in vitro* activity against human pathogens. The optimization of this compound led in 1987 to the discovery of two compounds DuP 721 and DuP 105 (Fig. 11), which possessed parentally and oral activity [30]. However, due to their toxicity, the development of these compounds was aborted. In spite of these problems, Upjohn Laboratories (latterly Pharmacia Corporation, Peapack, NJ) and Pfizer continued to study this class of compounds and in 1996, two non-toxic derivatives U-100592 and U-100766 (Fig. 9) were reported [30]. They were also named eperzolid and linezolid, respectively. Linezolid was developed by Pharmacia Corporation, Peapack, NJ with the brand name Zyvox in oral and intravenous formulations [31]. This compound, approved by FDA in 2000 is used to treat infections caused by Gram-positive strains, which are resistant to different antibacterial drugs, such as vancomycin and penicillin. However, it has limited activity against Gram-negative bacteria. This class possesses new mechanisms of action based on block protein synthesis by stopping translation at the initiation step, which involves the binding of *N*-formylmethionyl-tRNA to the 70S ribosome [31]. Oxazolidinones possess promising activity against *M. tuberculosis* especially for the treatment of multi-drug resistant strains with MIC₉₀ *in vitro* from 0.5 to 2.0 mg/l and inhibition of growth in murine model. The use of linezolid in humans with MDR-TB reported in 2003 by Hadjiangelis and co-workers was effective [32]. A recent study made by Lippe and co-workers showed the efficacy and safety of linezolid in patients with MDR-TB in ten patients treated with this drug in combination with others TB drugs [33].

The synthesis of linezolid (Scheme 5) [30] was based on the coupling between morpholine **11** and 3,4-difluoronitrobenzene **12**, which selectively afforded the *p*-substituted nitrobenzene **13**, which after reduction and attachment of a carbobenzyoxy (Cbz) activating group produce the

intermediate **15**. This intermediate in the presence of *n*-BuLi followed by addition of (*R*)-glycidyl butyrate furnished (5*R*)-(hydroxymethyl)-2-oxazolidinone **16** in 85% yield and high enantiomeric excess >99.7% ee. The hydroxyl group was mesylated to produce the compound **17**, which was displaced with sodium azide on laboratory scale or potassium phthalimide on large scale to furnish the compound **18**. Finally, linezolid was obtained after reduction of azide group followed by acetylation of amino group.

PA-824

PA-824 (Fig. 10) is a nitroimidazole developed by PathoGenesis Inc in 1995 for cancer treatment [34]. However, due to its promising TB activity reported in 2000 and to the decision taken by Chiron, which bought PathoGenesis Inc in 2000, of not to continue the development of PA-824. Due to this decision, TB Alliance and Chiron signed a license agreement that gave TB Alliance rights to develop this molecule. PA-824 showed potent *in vitro* activity against *M. tuberculosis* with MIC of 0.03-0.2 µg/mL [34]. This compound also possesses high activity in mice with no toxicity in rodent models, as well as excellent sterilize activity compared with isoniazid and rifampin. The mechanism of action of this prodrug, which requires activation, is due to a flavinoid known as F-420 cofactor, which activates PA-824, which subsequently inhibits the synthesis of protein and cell wall lipids. Due to its important results, PA-824 is under clinical phase.

CURRENT & FUTURE DEVELOPMENTS

The worldwide problem caused by TB and the lack of new drugs in the market makes it imperative to have new drugs to fight efficiently against the rapid spread of multi-drug resistant TB strain against all major antituberculosis drugs in the market. In this context, there is an urgent need for TB drugs with fewer toxic side effects, improved pharmacokinetics properties, extensive and potent activity against Gram-positive and Gram-negative bacteria, including resistant strains and drugs able to reduce the total duration of treatment.

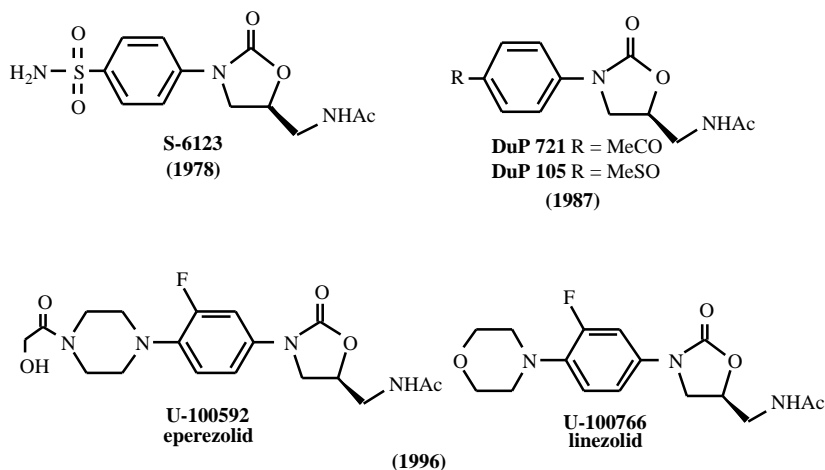
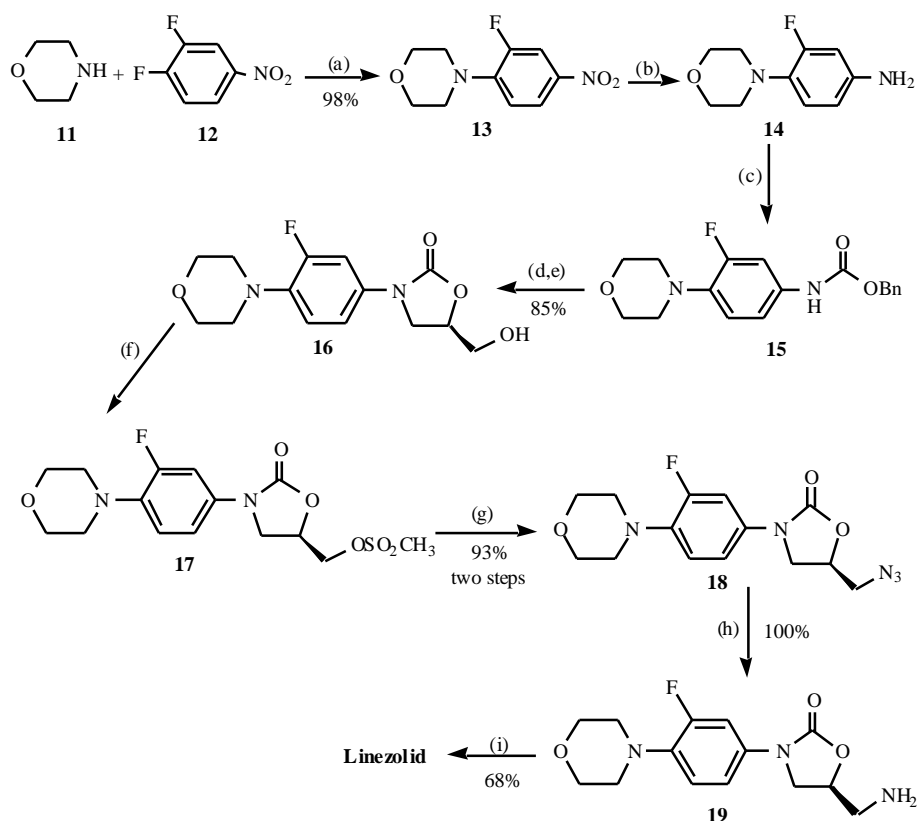


Fig. (11). Structures of some important linezolid.



(*i*-Pr)₂EtN, EtOAc; b) HCO₂NH₄, 10% Pd-C, THF-MeOH; c) CBzCl, NaHCO₃ or NaCO₃, acetone-H₂O; d) *n*-BuLi, THF, 78°C; e) (*R*)-glycidyl butyrate; f) MsCl, Et₃N, CH₂Cl₂; g) NaN₃, DMF, 75°C; h) 10% Pd-C, H₂, EtOAc; i) Ac₂O, pyr.

Scheme 5. Synthesis of linezolid.

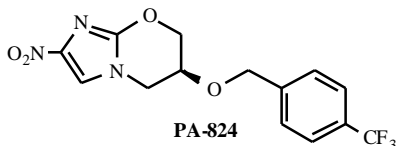


Fig. (12). Structure of PA-824.

REFERENCES

- [1] <http://www.who.int/tb/en/>
- [2] O'Brien RJ, Nunn PP. The need for new drugs against tuberculosis. Obstacles, opportunities and next steps. *Am J Respir Crit Care Med* 2001; 162: 1055-8.
- [3] Mukherjee JS, Rich ML, Socci AR, Joseph JK, Viru FA, Shin SS, Furin JJ, Becerra MC, Barry DJ, Kim JY, Bayona J, Farmer P, Fawzi MCS, Seung KJ. Programmes and principles in treatment of multidrug-resistant tuberculosis. *Lancet* 2004; 363: 474-81.
- [4] O'Brien RJ, Vernon AA. New tuberculosis drug development. How can we do better? *Am J Respir Crit Care Med* 1998 157: 1705-7.
- [5] Duncan K, Barry III CE. Prospects for new antitubercular drugs. *Curr Opin Microbiol* 2004; 7: 460-5.
- [6] Zhang Y, Amzel LM. Tuberculosis Drug Targets. *Curr Drug Targets* 2002; 3: 131-154.
- [7] Hudson, A, Imamura, T, Gutteridge, W, Kanyok, T, Nunn, P. The current anti-TB drug research and development pipeline. 2003; http://www.who.int/tdr/publications/publications/anti-tb_drug.htm.
- [8] Balganes, M., Ethiraj, K., Ganguly, B. *et al.*: WO9965483A1 (1999).
- [9] Townsend, C.A., Dick, J.D., Pasternack, G.R., Kuhajda, F.P., Parrish, N.M.: US6713654B1 (2004).
- [10] Kobarfard, F., Kauffman, J.M.: US0114531A1 (2003).
- [11] Gembitskij, P.A., Efimov, K.M., Martynenko, S.V.: RU2237658C1 (2003).
- [12] Floss HG, Yu TW. Rifamycin – Mode of action, resistance and biosynthesis. *Chem Rev* 2005; 105: 621-32.
- [13] Shichiri, M., Tanaka, Y.: EP1516620A4 and EP1516620A1 (2005).
- [14] Rangdao, Z.: CN1358724A (2002).
- [15] Nicola, M., Piero, S.: US3342810 (1967).
- [16] Cahisson RE. Treatment of chronic infections with rifamycins: Is resistance likely to follow? *Antimicrobi Agents Chemother* 2003; 3037-9.
- [17] Cricchio, R., Arioli, V.: DE2608218A1 (1976).
- [18] Yamne, T., Hashizume, T., Yamashida, K., Hosoe, K., Kuze, F., Watanabe, K.: US4983602 (1991).
- [19] Marsili, L., Rossetti, V., Pasqualucci, C.: US4219478 (1980).
- [20] Potkar, C., Gogtav, N., Kshirsagar, NA, Ajav, S, Cooverji, ND, Bruzzese, T. Phase I pharmacokinetic study of a new 3-azinomethyl-rifamycin (rifametan) as compared to rifampicin. *Chemotherapy* 1999; 45: 147-53.
- [21] Da Silva, AD, De Almeida, MV, De Souza, MVN, Couri, MRC. Biological Activity and Synthetic Methodologies for the Preparation of Fluoroquinolones, A class of Potent Antibacterial Agents. *Curr Med Chem* 2003; 10: 21-39.
- [22] Drlica K, Zhao X. DNA gyrase, Topoisomerase IV, and the 4-quinolones. *Microbiol Mol Biol Rev* 1997, 61: 377-92.
- [23] Mitscher LA. Topoisomerase Inhibitors: Quinolone and Pyridone Antibacterial Agents *Chem Rev* 2005; 105: 559-92.

- [24] Gehring, R., Mohrs, K., Heilman, W., Diehl, H.: DE19751948A1 (1999).
- [25] Grunenberg, A., Bosche, P.: DE19546249A1 (1997).
- [26] Gosling RD, Ulso LO, Sam NE, *et al.* The Bacterial Activity of Moxifloxacin in Patients with Pulmonary Tuberculosis. *Am J Respir Crit Med Care* 2003, 168:1342.
- [27] Petersen, U., Krebs, A., Schenke, T. *et al.*: DE4208792A1 (1993).
- [28] Bozdogan B, Appelbaum PC. Oxazolidinones: activity, mode of action and mechanism of resistance. *Int J Antimicrob Agents* 2004; 23: 113-9.
- [29] Zurenko GE, Gibson JK, Shinabarger DL, Aristoff PA, Ford CW, Tarpley WG. Oxazolidinones: a new class of antibacterials. *Int J Antimicrob Agents* 2004; 23: 113-9.
- [30] Brickner SJ, Hutchinson, DK, Barbachym, MR, *et al.* Synthesis and antibacterial activity of U-100592 and U-100766, two oxazolidinone antibacterial agents for the potential treatment of multidrug-resistant gram-positive bacterial infections. *J Med Chem* 1996; 39: 673-9.
- [31] Ross JE, Anderegg TR, Sader HS, Fritsche TR, Jones RN. Trends in linezolid susceptibility patterns in 2002: Reports from the worldwide Zyvox annual appraisal of potency and spectrum program. *Diag Microbiol Infect Dis* 2005; 52: 53-8.
- [32] Hadjiangelis NO, Leibert E, Harkin TJ. Linezolid: a promising new agent for multidrug resistant tuberculosis treatment. *Am J Respir Crit Care Med* 2003, 167: A868.
- [33] Lippe B, Sandven P, Brubakk O. Efficacy and safety of linezolid in multidrug resistant tuberculosis (MDR-TB) – a report of ten cases. *J Infections* 2005; 1-5.
- [34] Stover CK, Warrenner P, VanDevanter DR, *et al.* A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. *Nature* 2000; 405: 962-6.