

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,900

Open access books available

124,000

International authors and editors

140M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.

For more information visit [www.intechopen.com](http://www.intechopen.com)



# Antitubercular Drugs Development: Recent Advances in Selected Therapeutic Targets and Rational Drug Design

Virgilio Bocanegra-García<sup>4</sup>, Abraham García<sup>2</sup>, Jose Prisco Palma-Nicolás<sup>3</sup>,  
Isidro Palos<sup>1</sup> and Gildardo Rivera<sup>4</sup>

<sup>1</sup>Universidad Autónoma de Tamaulipas, Reynosa,

<sup>2</sup>Facultad de Ciencias Químicas, Universidad Autónoma de Nuevo León, Monterrey,

<sup>3</sup>Instituto de Fisiología Celular, Universidad Nacional Autónoma de México DF,

<sup>4</sup>Centro de Biotecnología Genómica, Instituto Politécnico Nacional, Reynosa,  
México

## 1. Introduction

*Mycobacterium tuberculosis*, the causative agent of tuberculosis (TB), is a remarkably successful pathogen that has latently infected a third of the world population (Zhang et al., 2006). Infection occurs via aerosol, and inhalation of a few droplets containing *M. tuberculosis* bacilli is enough for lung infection (Hassan et al., 2006). After infection, *M. tuberculosis* pathogenesis occurs in two stages. The first is an asymptomatic state that can persist for many years in the host, called latent TB. The second stage requires only a weakened immune response to become activated (Zhang, 2004), then the bacteria begins replicating and causing characteristic symptoms such as cough, chest pain, fatigue and unexplained weight loss. If left untreated, the disease eventually culminates in death. The emergence of Human Immunodeficiency Virus (HIV) and the resultant Acquired Immune Deficiency Syndrome (AIDS) pandemic underlined the importance of reactivation of the disease and its potentially catastrophic outcome since over 50% of deaths among HIV-infected patients results from co-infection with *M. tuberculosis* with the two pathogens inducing each other's replication, thus accelerating the collapse of the immune system (Cole & Alzari, 2007).

While it is impossible to determine the exact number of cases, the latest World Health Organization (WHO) survey estimates that close to 2 million deaths occur every year, that there are approximately 8 million new cases annually, and that every third individual on the planet has been exposed to or infected by *M. tuberculosis* (Dye, 2006; Cole & Alzari, 2007).

Although TB can be treated and even cured with chemotherapy, treatment is exceedingly lengthy and takes 6-9 months (Blumberg, et al., 2003). In addition to significant toxicity, lengthy therapy also causes poor patient compliance, which is a frequent cause for selection of drug resistant and often deadly multidrug resistant TB (MDR-TB) bacteria (Zang et al., 2006).

Currently, TB chemotherapy is made up of a cocktail of first-line drugs, isoniazid (INH), Rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB), which are given for six

months (Blumberg et al., 2006). If this treatment fails as a result of bacterial drug resistance or intolerance to one or more drugs, second-line drugs are used, such as *para*-aminosalicylate (PAS), kanamycin, fluoroquinolones, capreomycin, ethionamide and cycloserine. These are generally less effective or more toxic with serious side effects (Blumberg et al., 2006). This second-line treatment can also result ineffective since MDR-strains that exhibit resistance to these second-line drugs are currently on the rise (Zhang & Amzel, 2002)

Treatment is also made quite difficult by the presence of metabolically silent, persistent or dormant bacteria within host lesions. These are not susceptible to the anti-mycobacterial drugs that usually kill growing but not persistent bacteria (Zhang, 2004). While there are many reasons for drug resistance, including prescription of inadequate regimens, an uncertain drug supply, and ineffective drugs, duration of lengthy treatments is one of the major contributors because some TB patients prematurely stop their therapy after an initial, rapid health improvement, thereby favoring the emergence of drug-resistant strains (Cole & Alzari, 2007)

## 2. Anti-TB drug targets

Despite the relative efficacy of current treatment, the various antibiotics that constitute first- and second-line drugs for TB therapy target only a small number of core metabolic processes such as Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) synthesis, cell wall synthesis, and energy metabolism pathways (Zhang, 2005). New classes of drugs with additional drug targets that are difficult to overcome by mutation are urgently needed (Hansan et al., 2006). Desirable new targets should be involved in vital aspects of bacterial growth, metabolism and viability whose inactivation would lead to bacterial death or an inability to persist, thus therapy could be shortened and drug resistant strains could be eliminated or drastically reduced (Mdluli & Spigelman, 2006; Duncan, 2004). Moreover, targets involved in the pathogenesis of the disease process should also be considered for drug development (Zhang et al., 2006; Palomino et al., 2009).

The discovery of the complete genome sequence of TB bacteria helped to identify several important drug targets (Cole et al., 1998). Various groups have used this genomic information to identify and validate targets as the basis for development of new Anti-TB agents. Besides, mycobacterial genetic tools, such as transposon mutagenesis, gene knockout, and gene transfer, greatly facilitate target identification.

### 2.1 Cell wall biosynthesis related targets

Cell wall biosynthesis is a particularly good source of molecular targets because the biosynthetic enzymes do not have homologues in the mammalian system (Mdluli & Spigelman, 2006). The cell wall of *M. tuberculosis* is very important for its survival within constrained conditions such as those inside of human macrophages. The biosynthesis of the cell wall components involves many important stages and different enzymes that are absent in mammals and could be attractive drug targets (Khasnobis et al., 2002; Brennan & Crick, 2007; Sarkar & Suresh, 2011). Recently, the 2C-methyl-D-erytrotol 4-fosphate (MEP) pathway was found (Eoh et al., 2009) as a potential drug target since the end product of the pathway leads to the formation of isoprenoids, which are responsible for the synthesis of several cell wall components (Mahapatra et al., 2005; Anderson et al., 1972).

Peptidoglycan biosynthesis is another source of potential drug targets. For instance, alanine racemase and D-Ala-D-Ala-ligase catalyze the first and second committed steps in bacterial

peptidoglycan biosynthesis, and since these steps are essential for important polymers, they are good drug targets. Both alanine racemase and D-Ala-D-Ala ligase are inhibited by D-cycloserine, a second line anti-TB drug (Strych et al., 2001; Feng & Barletta, 2003).

Another good drug target is the pyridoxal 5'-phosphate containing enzyme Alr that catalyzes the racemization of L-Alanine into D-Alanine, a major component in the biosynthesis of peptidoglycan (LeMagueres et al., 2005).

Arabinogalactan biosynthesis, a novel arabinofuranosyl transferase that catalyzes the addition of the first key arabinofuranosyl residue of the galactan core, is not sensitive to EMB, but is essential for viability (Sasseti et al., 2003). The ribosyltransferase that catalyzes the first committed step in the synthesis of decaprenyl-phosphoryl-D-arabinose, the lipid donor of mycobacterial d-arabinofuranosyl residues, has also recently been characterized and shown essential for growth (Huang et al., 2005)

## 2.2 Mycolic acid biosynthesis related targets

Within the mycobacteria lipid metabolism, mycolic acids are essential structural components of the mycobacterial cell wall (Brennan, 2003). The early stage of fatty acid biosynthesis, which generates the precursors of mycolic acids, is a rich source of antibacterial targets (Heath et al., 2001). It is also the site of action of INH and ethionamide (Quemard et al., 1995; Larsen et al., 2002). *M. tuberculosis* has both types of fatty acids synthase (FAS) systems found in nature, FAS-I and FAS-II. FAS I is the system responsible for de novo synthesis of C16-C26 fatty acids and the FAS II system extends these fatty acids up to C56 chains to make precursors of mycolic acids, which are essential for growth.

Since enoil-ACP reductase (InhA) is the target of INH, it is reasonable to assume that all steps in the FAS-II pathway will be essential for the viability of *M. tuberculosis*. Many of the individual enzymes of the FAS-II system have been expressed, purified and characterized (Kremer et al., 2001; Choi et al., 2000; Scardale et al 2001; Benerjee et al 1998; Marrakchi et al., 2002; Marrakchi et al., 2000; Slayden & Barry, 2002).

## 2.3 Energy production related targets

Isocitrate lyase (ICL) is an important enzyme in this category and also an important drug target. ICL is involved in energy production via the metabolism of acetyl-CoA and propionyl CoA of the glyoxylate pathway. Inactivation of the *icl* gene leads to attenuation of both persistent and virulent strains of *M. tuberculosis*. However, *M. tuberculosis* has a salvage pathway, so a suitable anti-TB drug for this target must address both the main and salvage pathways (McKinney et al., 2000; Savi et al., 2008)

## 2.4 Amino acid biosynthesis related drug targets

Amino acid biosynthesis is another important target for developing anti-TB drugs. The shikimate pathway is very important and is involved in the synthesis of aromatic amino acids in algae, fungi, bacteria, and higher plants; however, it is absent in the mammalian system (Sarkar & Suresh, 2011). The final product of the shikimate pathway, chorismate, is a key biosynthetic intermediate involved in generating aromatic amino acids and other metabolites. The entire pathway is essential in *M. tuberculosis* (Parish & Stoker 2002). This feature makes the pathway an attractive target for developing anti-TB drugs with minimum cross reactivity (Ducati et al., 2007). Other enzymes of this pathway are also likely to be essential, and shikimate dehydrogenase (Magalhaes et al., 2002), and 5-enolpyruvylshikimate 3-phosphate synthase (Oliverira et al., 2001) have been characterized

in detail. The biosynthesis of non-aromatic amino acids is also emerging as a potential drug target. The impact of amino acids such as lysine (Pavelka & Jacobs, 1999), proline, tryptophan and leucine (Smith et al., 2001) is evident from the fact that knocked out *M. tuberculosis* strains of the genes required for amino acid biosynthesis showed less virulence (Pavelka et al., 2003; Smith et al., 2001). Another attractive target of the lysine biosynthesis pathway is the enzyme dihydrodipicolinate reductase, for which potent inhibitors have been identified (Paiva et al., 2001).

### 2.5 Cofactor-related drug targets

Several cofactor biosynthetic pathways and pathways requiring some cofactors are good candidates for identification of new drug targets. Folate derivatives are cofactors utilized in the biosynthesis of essential molecules including purines, pyrimidines, and amino acids. While bacteria synthesize folate de novo, mammals must assimilate preformed folate derivatives through an active transport system (Mdluli & Spigelman, 2006). Dihydrofolate reductase, which catalyses the reduction of dihydrofolate to tetrahydrofolate, a key enzyme in folate utilization whose inhibition may affect the growth of *M. tuberculosis* (Gerum et al., 2002), and dehydropteroate synthase are validated targets of the widely used antibacterial sulfonamide, trimethoprim (Huovinen et al., 1995).

Two enzymes involved in the de novo biosynthesis of NAD that affects the NADH/NAD<sup>+</sup> ratio upon which *M. tuberculosis* is dependent, have been studied as possible drug targets (Bellinzoni et al., 2002). Genomic analysis studies have suggested that the riboflavin biosynthesis pathway is essential in *M. tuberculosis* (Morgunova et al., 2005) and the lumazine synthase pathway has been validated as a target for anti-TB drug discovery.

### 2.6 DNA metabolism

Differences in mammalian and mycobacterial thymidin monophosphate kinase have been studied and exploited in an attempt to find selective inhibitors for this drug target (Haouz et al., 2003; Vanheusden et al., 2002). Other targets are ribonucleotide reductases that catalyze the first committed step in DNA synthesis and have differences with corresponding mammalian enzymes (Yang et al., 1994; Yang et al., 1997); DNA ligases, that play an important role in the replication and repair of DNA, are classified as NAD<sup>+</sup> or ATP dependent. NAD<sup>+</sup> dependent ligases are only found in some viruses and eubacteria (Mdluli & Spigelman, 2006). LigA is essential for growth of *M. tuberculosis* (Gong et al., 2004) and inhibitors that distinguish between the two types of ligases and have anti-TB activity have been identified (Srivastava et al., 2005). DNA gyrase has also been validated as a target for *M. tuberculosis*, since this is the only type II topoisomerase that it possesses (Cole et al., 1998). Its inhibition by fluoroquinolones results in highly mycobactericidal activity.

### 2.7 Menaquinone biosynthesis

It appears that menaquinone is the only quinone in *M. tuberculosis*, so its biosynthesis is essential for growth. The menaquinone pathway is not present in humans, and bacterial homologues of MenA-E and MenH have been described in *M. tuberculosis*, so this pathway is another promising drug target (Meganathan, 2001).

### 2.8 Other potential drug targets in *M. tuberculosis*

The tubercle bacillus produces no less than 20 cytochrome p450 enzymes, some of which appear to play essential roles (Cole & Alzari, 2007). Antifungal azole drugs target these

enzymes and the cytochrome p450 homologues in the bacteria. Drugs like miconazole and clotrimazole are active against *M. tuberculosis* (McLean et al., 2007; Ahmad et al., 2006; Sun et al., 1999 TD). Subsequent crystallization studies of the *M. tuberculosis* cytochrome p450 enzyme system evoked studies to evaluate new drugs (Leys et al., 2003).

Peptide deformylase inhibitors may be effective against *M. tuberculosis* since peptide deformylase catalyzes the hydrolytic removal of the B-terminal formyl group from nascent proteins. It is a metalloprotease essential for maturation of nascent polypeptides in bacteria but not essential for humans, making it an attractive target for antibacterial drug development (Teo et al., 2006); however, it has little effect on slow growing TB bacteria (Khasnobis et al., 2002).

Another important set of emerging drug targets are the components of the siderophore biosynthesis of *M. tuberculosis* (Monfeli et al., 2007). Upon infection, as a part of the defense mechanism, the host has several mechanisms to withdraw or control the free extracellular, as well as intracellular, iron concentration (Weinberga & Miklossy, 2008; Ferreras et al., 2005). Mycobacteria have an unusual reliance on serine/threonine protein kinases as the main component of signal transduction pathways (Av-Gay & Everett, 2000), and there is considerable activity around this transduction system since some of these enzymes are essential for growth (Fernandez et al., 2006). *M. tuberculosis* synthesizes mycothiol in a multistep process involving four enzymatic reactions for protection against the damaging effects of reactive oxygen species. This pathway is absent in humans, and it has been shown to be essential to *M. tuberculosis* (Sareen et al., 2003).

### 3. Rational drug design

One of the design strategies for new anti-TB compounds is based on the development of analogs of first-line and/or second line drugs. In this section we review the strategies employed and analyze structure-activity relationships (SAR), which have led to the development of new anti-TB agents. In addition, we review new pharmacophore groups. One problem that must be considered in the design of anti-TB compounds is that there is a subpopulation of bacteria in a persistent non-replicating state. This is considered a major contributing factor to long drug treatments for TB. For this reason, it is important to determine if compounds have potential activity against these bacteria at the onset of design. We should also consider the physicochemical properties that directly affect the pharmacokinetics and pharmacodynamics of drugs. An example of this is the influence of stereoisomers on biological activity, because individual enantiomers have significant differences in activity, although sometimes the activity of some enantiomers cannot be explained.

#### 3.1 Isoniazid derivatives

One of the strategies frequently used in medicinal chemistry to develop new drugs is "hybridization", a method that has been proposed particularly for new anti-TB drugs. An example is the design of molecules based on INH or PZA, incorporating NR1R2 groups derived from a second anti-TB molecule or possibly other nucleophilic groups to provide anti-TB activity. With special interest compounds 1 and 2 (figure 1) were obtained. These could be considered prodrugs because they contain two conventional drugs that are bound by a CH fragment. Although the results of activity are very similar to those presented by INH and PZA, the hydrolysis of new compounds ensures prolonged release of the active drugs (Imramovsky et al., 2007).

A variety of compounds derived from INH that include mostly a hydrazine fragment have been determined. Following this strategy and considering the inclusion of an oxadiazole moiety, Navarrete et al, developed new agents with high anti-TB activity (3, figure 1). Due to the substitution in 5-position on the oxadiazole ring, the compounds obtained showed high lipophilicity, hypothesizing that this lipophilicity could facilitate passage of these compounds through the *M. tuberculosis* bacterial membrane (Navarrete-Vazquez et al., 2007). Also, structural modification of the hydrazide moiety on INH (4, figure 1) provided lipophilic adaptations of the drug that blocked the N-acetylation process, obtained high levels of *in vitro* activity against *M. tuberculosis* and macrophages infected, as well as low toxicity (Hearn et al., 2009).

Another strategy in drug design is the formation of molecules that mimic the natural substrate of an enzyme. Delaine et al designed a new series of bi-substrate-type inhibitors based on a covalent association between molecules mimicking the INH substrate and the NAD cofactor that could provide compounds with a high affinity and selectivity for the INH catalytic site (5 and 6, figure 1). In these compounds, the authors determined that incorporating a lipophilic component into the nicotinamide hemiamidal framework provides more active derivatives (Delaine et al., 2010).

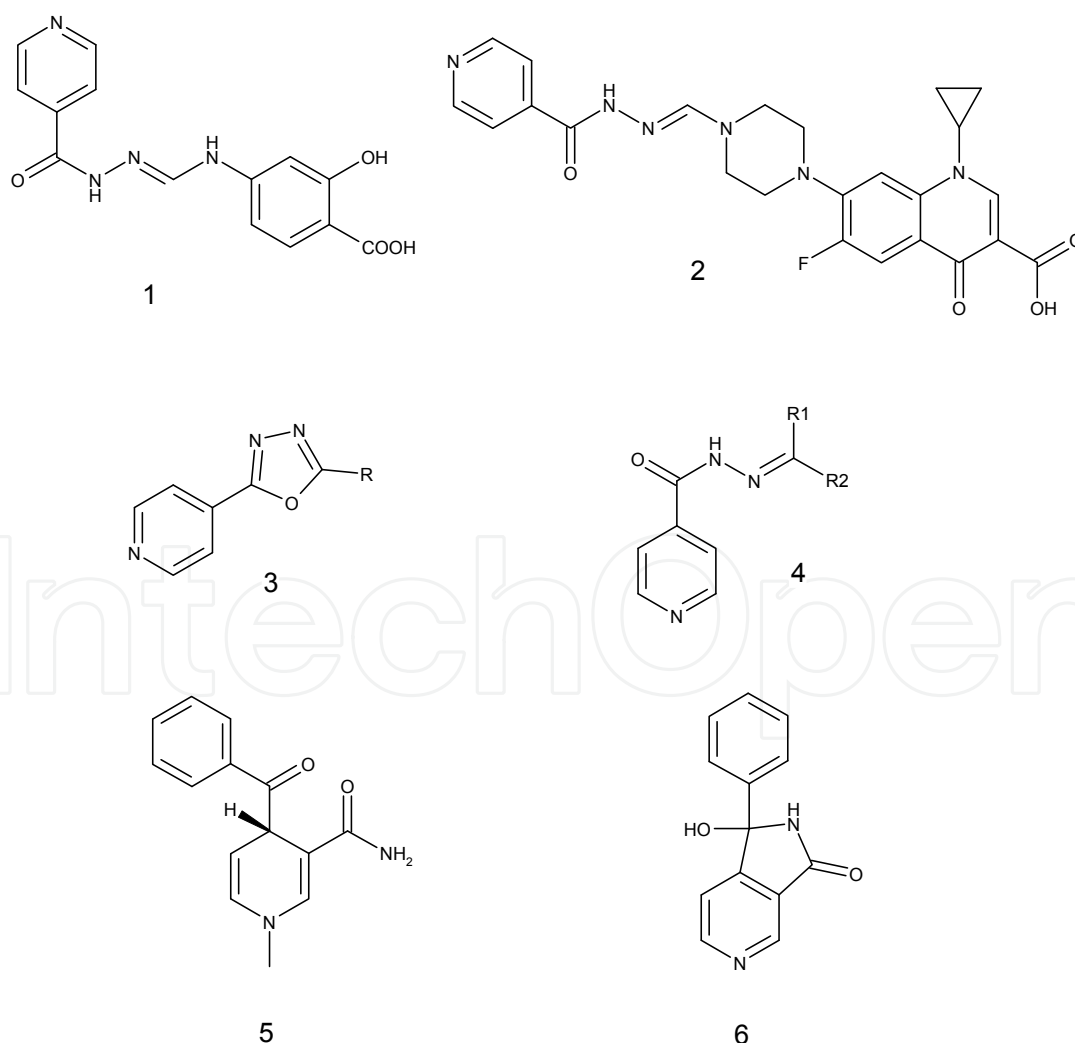


Fig. 1. Structure of compounds derivatives of anti-TB first line drugs.

### 3.2 Ethambutol derivatives

Amino alcohols that include EMB, which is used for pharmacological TB treatment, are an important class of compounds with various applications. This compound has been widely studied determining that the 1,2-ethylenediamine moiety is the EMB pharmacophore, possibility due to chelate bond formation with divalent metal ions such as copper. Based on EMB, a second-generation agent has been developed, a compound called SQ109 (7, figure 2), which is being tested in clinical trials. It is a drug that exhibits potent activity against *M. tuberculosis* strains, including multidrug resistant strains *in vitro* and *in vivo*. Unfortunately, SQ109 has poor bioavailability of only 12% and 3.8% in rats and dogs, respectively. Studies indicate that this compound undergoes oxidation, epoxidation and *N*-dealkylation, which cause its low bioavailability; therefore strategies have been designed to improve its bioavailability minimizing this first-pass effect. Prodrugs based on carbamate groups are a good option for reducing this effect. Considering this Meng and colleagues developed a new series of analogues based on carbamate prodrugs of SQ109 (8, figure 2) that provide good chemical stability as substrates of plasma esterase. The results of bioavailability of these compounds show a five-fold increase of the SQ109 reference compound (Meng et al., 2009). Alternatively, Zhang has carried out the synthesis of new analogues of S2824 (9, figure 2), a second-generation compound derived from EMB. The results show that new analogues with a homopiperazine ring (10, figure 2) have high *in vitro* activity against both sensitive and drug-resistant *M. tuberculosis* strains (Zhang et al., 2009).

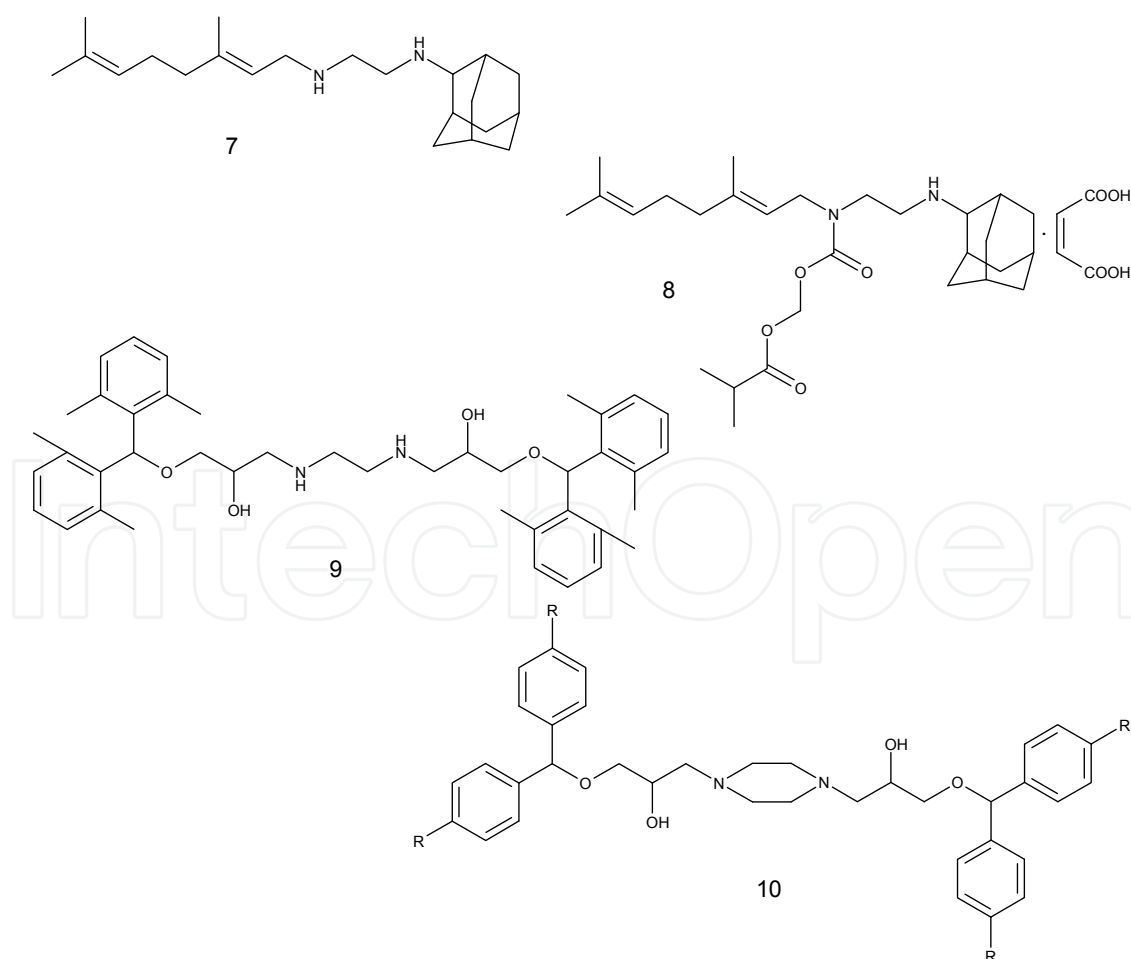


Fig. 2. Structure of SQ109 and analogs.



In the design of new 1,2-diamine derivatives (11, figure 3) compounds with 35 times more activity than EMB have been synthesized. Interestingly, studies show that they do not have the same target as EMB. An SAR analysis has determined that the presence of an  $\beta$ -hydroxy group on the amine increases anti-TB activity; however, the distance between oxygen and nitrogen atoms in EMB are the same as between both atoms in the hydroxyethylamine suggesting a good relationship between both structures (12, figure 3). In a new series of EMB analogs obtained by Cunico et al, it was determined that the sulfonamide moiety reduces activity against *M. tuberculosis*, and that the amino alcohol moiety on hydroxyethylsulfonamide is crucial for anti-TB activity, where the presence of a carbamate moiety leads to a loss of activity. Consistent with this, it has been reported that if compounds lose the basicity of the amino group (12, figure 3), this results in a loss of activity (Cunico et al., 2011). Finally, EMB has served as a proposal for tripartite hybridization (chloroquine, isoxyl and ethambutol) for the development of new anti-TB agents (13, figure 3), which exhibit high activity against *M. tuberculosis* (Nava-Zuazo et al., 2010).

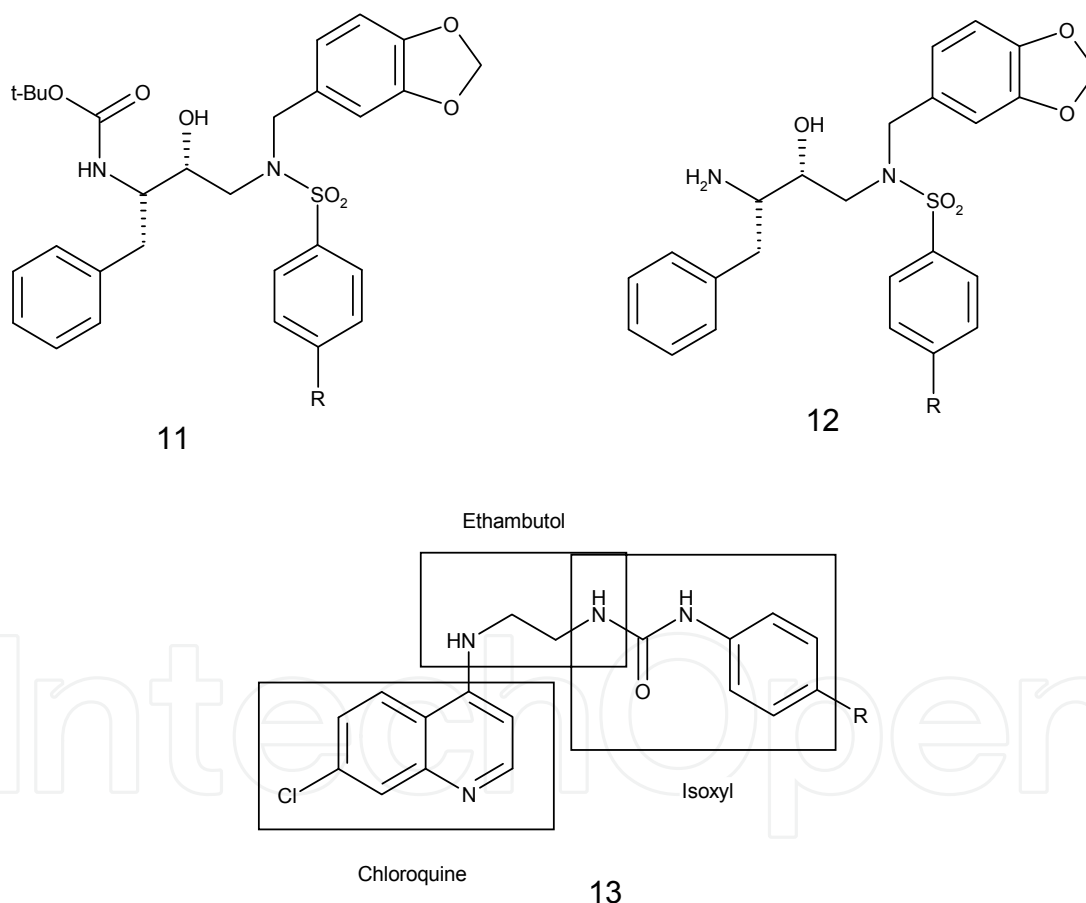


Fig. 3. Ethambutol analogs as anti-TB agents.

### 3.3 Salicylanilides derivatives

salicylanilides (SAL) derivatives have been of great interest in medicinal chemistry, although their mechanism of action still unknown. It is postulated that they serve as epidermal growth factor receptor protein kinase (EGFR PTK) inhibitors. Such compounds have generally been designed to compete with adenosine triphosphate (ATP) in binding

with the catalytic domain of tyrosine kinase. Recent studies specify that selective inhibitors of interleukin-12p40 production also have a specific role in the initiation, expansion, and control of the cellular response to TB. Following the development of SAL derivatives, Imramovský's group obtained a series of compounds (14, figure 4) with activity similar to INH. Through a SAR study, they established that positions R1 and R2 showed Cl and Br atoms that are necessary for high activity against TB and that the benzyl and isopropyl substituent at R3 increases activity (Imramovský et al., 2009).

In addition, in various SAL derivatives that have been developed it has been shown that electron withdrawing groups on the salicyloyl ring and hydrophobic groups on the anilide ring, as well as the 2-hydroxy group, are essential for optimal antimicrobial effect. Halogen-substituted SAL in both parties maintains the requirements and forms of more active derivatives that show anti-TB activity. However, its unsuitable physical properties led to the generation of prodrugs of SAL derivatives with better bioavailability, and due to a high degree of lipophilicity, more efficient transport through *M. tuberculosis* cell membranes. Considering this, Imramovský and colleagues obtained compounds (15, figure 4) with interesting activity against *M. tuberculosis*. They showed a level of inhibition of 89%-99% and an MIC of 3.13  $\mu\text{g}/\text{mL}$ . Although, they demonstrated that lipophilicity is a secondary parameter in anti-TB activity, they also demonstrated that in these compounds the stereoisomer effect is important for anti-TB activity; however, in this case the difference is not determined for individual R/S isomers (Imramovský et al., 2009).

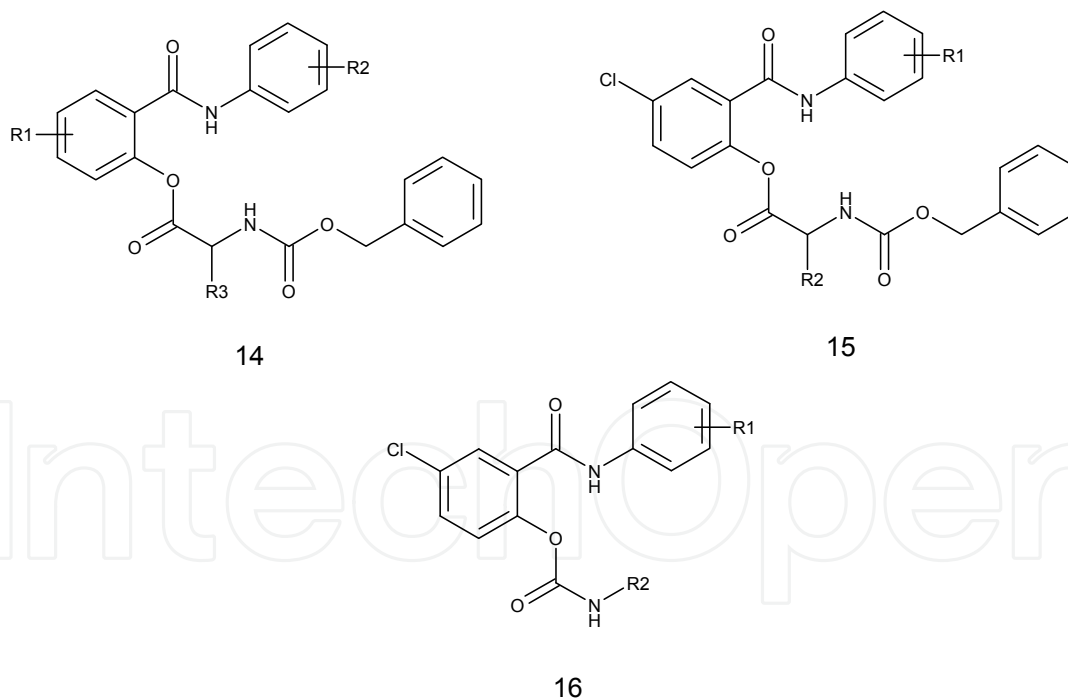


Fig. 4. General structure of salicylanilides derivatives with anti-TB activity.

Using the hybridization strategy, Ferriz et al obtained a new series of derivatives with SAL and carbamate groups, which have been used as antibacterial and antiviral agents. Thus the hybridization of two moieties could produce a new series with changes in their pharmacokinetic and pharmacodynamic properties. Ferriz et al postulated that carbamate could be protecting these molecules against first-pass metabolism, increasing their activity

profile. The series obtained show that Cl atoms at 3 and 4-position on the aniline ring increase *M. tuberculosis* biological activity. Interestingly, the presence of an alkyl chain also increases the biological activity of these compounds, which suggests the importance of carbamate group (16, figure 4). Although these kinds of compounds are consistent with the Lipinski rules, it is speculated that due to their high lipophilicity, these molecules have high permeability, making their release more effective (Ferriz et al., 2009).

Another strategy using SAL derivatives has been the formation of cyclic derivatives, which could serve as antibacterial agents with a dual inhibition system. Thus, following this design strategy a new series of benzoxazinediones derivatives was obtained, where a thioxo group replaced one or two oxo groups. The substitution of an oxo group by the thioxo group (17, figure 5) strongly increased anti-TB activity, although a second substitution with the thioxo group had only a small effect on activity (18, figure 5) (Petrlikova et al., 2010).

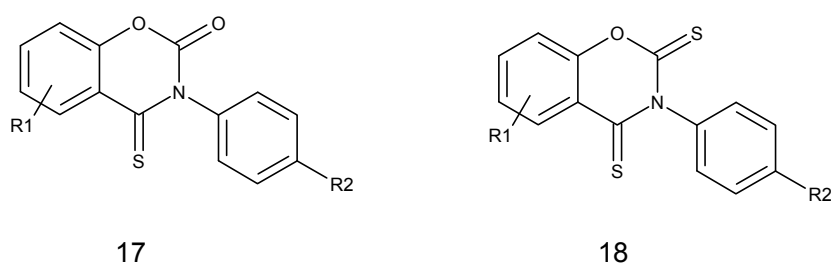


Fig. 5. General structure of 1,3-benzoxazine derivatives.

### 3.4 Quinoline derivatives

A quinoline ring is one of the moieties frequently used in new drug design. It has been considered a pharmacophore for the design of anti-TB agents. Diarilquinoline, denominated TMC207 (19, figure 6), is an adenosine ATP synthase inhibitor that is one of the most important quinoline derivatives with anti-TB activity. TMC207 is currently in Phase II clinical trials. Also, butanamide has been established as an important pharmacophore with good antibacterial activity and the carbohydrazone moiety is also known as a pharmacophore group. Based on the above, the design of new quinoline derivatives with active carbohydrazine and butanamide moieties in 3 and 4-position, respectively, has been carried out. The SAR study of these compounds shows that the presence of a trifluoromethyl group at 8-position increases activity; however, the introduction of a fluoro group in 6-position partially decreases activity (20, figure 6) considering these type of compounds non-toxic (Eswaran et al., 2009). Following the development of mefloquine analogs (21, figure 6) in a series of compounds (22, figure 6), good anti-TB activity has been attributed to the presence of pharmacologically active heterocyclic groups such as pyrazole, imidazole, and indole rings on the quinoline ring. Surprisingly, compounds with a heteroaromatic pyrazole ring have activity against resistant strains, which can be attributed to the presence of substituents (electron donating groups) that stabilize the pyrazole ring, making the quinoline ring a more active entity (Eswaran et al., 2010).

The conformational restriction-like strategy in flexible drugs is extensively used in medicinal chemistry. This helped determine steric requirements of receptor-drug interaction and identification of new structures with high efficiency and selectivity. Based on this, Goncalves et al studied the conformational restriction of the piperidiny ring of mefloquine through the construction of an oxazolidine ring and different substituents on the phenyl ring (23, figure 6).

Conformational restriction showed that the introduction of an oxazolidine core in the mefloquine structure enhances anti-TB activity. Although, the activity of these compounds is affected by substituents on the aromatic ring bound to C-17 of the oxazolidenyl nucleus. Compounds that show hydroxyl or methoxyl groups, which are both electron donors and capable of forming strong hydrogen bonds, in general are active. In contrast, with one exception, compounds with nitro or halogenated groups (electron withdrawing groups and capable of forming only weak hydrogen bonds), are inactive (Goncalves et al., 2010). Thus, mefloquine has been used to design anti-TB agents. Modifications in previous reports included introduction of a hydrazone linker into mefloquine at 4-position, substitution of a piperidine ring with a piperazine ring and extension of the basic terminus of the piperazine ring at 4-position. Additionally, isoxazole is emerging as one of the most powerful hits in high-throughput screening (HTS) against *M. tuberculosis*. Both types of compounds show an aromatic ring, a two-atom linker and a five or six member ring. Hybridization strategies have been the basis for the design of new chemical entities by Mao et al (24, figure 6). One problem that has been detected in this type of compounds is poor penetration of acid derivatives through the *M. tuberculosis* cell wall. It is suggested that these compounds may act as prodrugs when ester derivatives generate acid derivatives (24, figure 6). SAR studies of these compounds show that when a methyl group replaces a trifluoromethyl group, it is 10 times less active, suggesting that electronic effects may play an important role in anti-TB activity. Additionally, steric effects can affect anti-TB activity. Subsequently, making use of drug design strategies, the authors included ester bioisosteres, such as amides and oxadiazole, although none of these bioisosteres showed better activity than ester derivatives. It was determined that 2 and 8-trifluoromethyl groups on quinoline ring (24, figure 6) are essential for anti-TB activity against replicative bacteria (Mao et al., 2009).

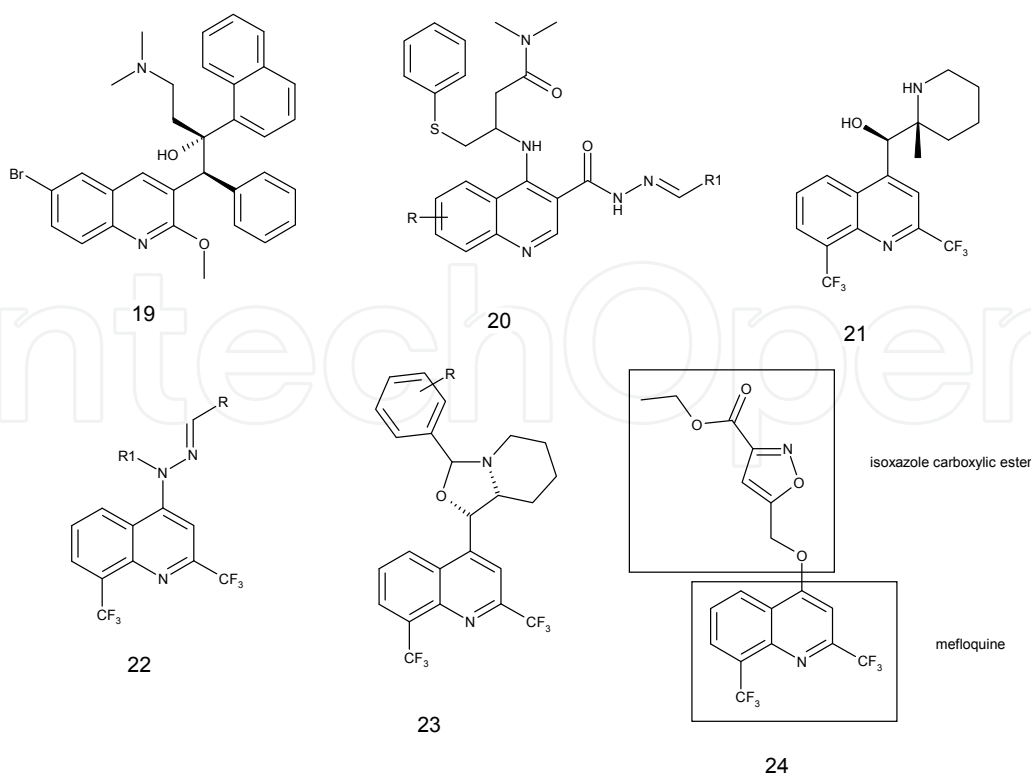


Fig. 6. Quinoline as scaffold for designing new anti-TB agents.

Isoxazole derivatives have also been reported as anti-TB agents, in particular compound 25 (figure 7) with an activity of 2.9  $\mu\text{M}$ , which is comparable to INH and (RIF) (Kini et al., 2009). Thus, quinoline and oxazole ring hybridization has been used to develop a series of new anti-TB agents (26, figure 7) which have good activity due to the presence of aryl substituents at 2-position on quinoline ring. SAR studies show that the introduction of a 1,3-oxazole ring significantly increases activity, obtaining compounds that are more potent than INH (Eswaran et al., 2009). In search of a new moiety that confers anti-TB activity with low cytotoxicity, Yang and colleagues reported methoxybenzofuro[2,3-b]quinoline derivatives (27, figure 7), compounds that have a potent *M. tuberculosis* growth inhibition of 99% at low concentrations (0.20  $\mu\text{g}/\text{mL}$ ) and very low cytotoxicity against VERO cells with an Inhibitor concentration 50 (IC<sub>50</sub>) value of > 30.00  $\mu\text{g}/\text{mL}$  (Yang et al., 2009).

Several studies have analyzed modifications in the quinolone ring, mainly at 3, 6 and 7-position. Wube et al proposed a new strategy for anti-TB agent development. They made a modification in the 2-position, including an aliphatic side chain with various degrees of unsaturation, lengths chains, and double bond positions (28, figure 7). Their results showed that increasing the chain length enhances anti-TB activity, showing optimal activity with 14 C atoms. If there is an increase of more carbon atoms in the chain, activity decreases dramatically. This behavior has also been described for ciprofloxacin derivatives where lipophilicity could play an important role in anti-TB activity. Other research has determined that the saturated aliphatic chain has less activity than unsaturated analogues. This means that unsaturation of an aliphatic chain is an essential structure for *in vitro* anti-TB activity (Wube et al., 2010).

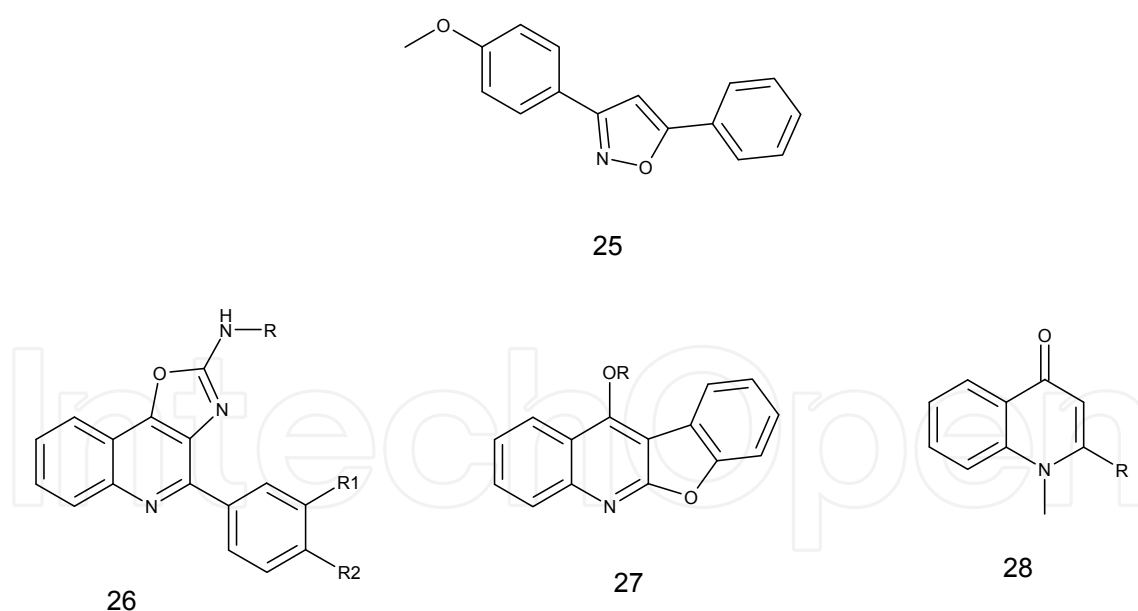


Fig. 7. Quinoline and oxazole derivatives as anti-TB agents.

On the other hand, both phenazine and quinoxaline rings are considered bioisosteres of the quinoline ring. In this focus, phenazine derivatives are a class of useful compounds for new anti-TB agent development, particularly Tubermicyn B and Clofazimine (phenazine derivatives). Likewise, De Logu et al developed new agents that show activity (29, figure 8) in a concentration range of 0.19 to 3.12 mg/L against *M. tuberculosis*-resistant clinical isolates. Interestingly, they found that this series of compounds were ineffective in

inhibiting the growth of INH resistant strains. Compounds that had exocyclic groups, which confer different lipophilic and electronic properties, but with a size similar to INH, such as the phenylamide methyl lipophilic group in 4-position, were the most active. In contrast, the same group in 3-position reduced activity 100-fold. Also, phenazine derivatives with electron withdrawing groups in 2 and 3-position have values with similar biological activity. These results show the importance of the aryl moiety as a pharmacophore for phenazinecarboxamide anti-TB agents. While phenazine's mechanism of action is still unknown, it is hypothesized that it could act as a cellular superoxide bismutase inhibitor. We know that the compound Lomofungin (1-carbomethoxy-5-formyl-4,6,8-trihydroxyphenazine) is capable of inhibiting DNA-dependent RNA polymerase, with both options being possible mechanisms of action of phenazine derivatives (De Logu et al., 2009). Quinoxalines are compounds with a broad spectrum of biological activities. Quinoxaline-*N*-oxide derivatives are known as *M. tuberculosis* bioreductor agents. In this type of compounds missing *N*-oxide groups have led to the loss of anti-TB activity. In this sense, Monge's group developed over 500 derivatives of quinoxaline (30, figure 8), demonstrating the importance of this group for generating a new class of anti-TB drugs. Interestingly, this research group determined that the quinoxaline compounds obtained have activity on non-replicating bacteria, which could lead to shorter anti-TB therapies (Vicente et al., 2008). Finally, a compound denominated ER-2 is a new analogue of quinoline derivatives (31, figure 8) that is a gyrase supercoiling inhibitor that has potency similar to Ciprofloxacin with a minimum inhibitory concentration 90 (MIC90) of 0.5 µg/mL (Sainath et al, 2009).

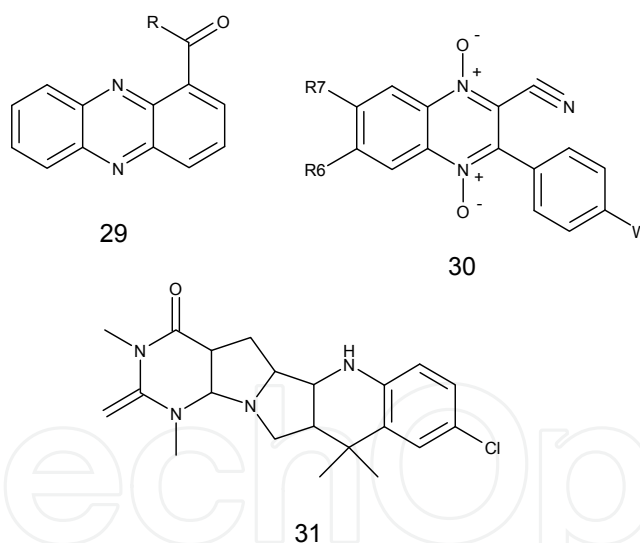


Fig. 8. General structure of phenazine-1-carboxamides, quinoline and quinoxaline derivatives.

### 3.5 Azoles derivatives

One of the most important strategies for effective anti-TB agent design has been the development of cell wall biosynthesis inhibitors. Azole derivatives have shown interesting anti-TB antimicrobial activity, inhibiting the bacteria by blocking lipid biosynthesis and/or additional mechanisms. Thus, by hybridization of 1,2,4-triazoles and a thiazole moiety, new anti-TB agents were discovered (32, figure 9). These molecules with a highly electronegative part at the sulfhydryl groups have emerged as new anti-TB compounds. Particularly, Schiff

bases derivatives probably due to its ability to increase penetration into the bacterial cell (Shiradkar et al, 2006).

Benzimidazole is an important pharmacophore in drug discovery. Gill et al propose 1,2,3-triazole and benzimidazole ring hybridization as design strategies of new anti-TB agents. They have also considered the use of electron withdrawing groups in the benzimidazole ring, which are present in molecules with anti-TB activity. They obtained compound 33 (figure 9) that could be considered a lead series. Their optimization led to determine that substitutions with electron withdrawing groups produce a loss of anti-TB activity (Gill et al., 2008). A new strategy of hybridization between benzimidazole and a 1,2,4-triazole ring has obtained a series of compounds (34, figure 9). Using a SAR study, it was determined that these compounds enhance biological activity by increasing electronegativity of the molecule, but surprisingly when a trifluoromethyl group (high electronegativity) was introduced, it produced a substantial loss of activity, which could be due to a delay in intracellular transport (Jadhav et al., 2009). Following with the use of a benzimidazole ring as a drug design, Klimešova and cols replaced a nitrogen atom with a corresponding oxygen atom (isosteric) (35, figure 9) to obtain a series of benzylsulfanyl benzoxazole derivatives. They consider alkylsulfanyl derivatives of pyridine, benzimidazole and tetrazole as new anti-TB agents, which present anti-TB activity due to the presence of the alkylsulfanyl group bound to an electron deficient carbon atom in the heterocycle ring. Thus, a SAR study of these compounds indicates that anti-TB activity is attributed to the presence of a benzyl moiety at 2-position on the benzoxazole ring, denoting that anti-TB activity is not affected by electron withdrawing or electron donating substituents on the benzyl moiety. It is important to note that the presence of two nitro groups on benzyl led to the most active compound (MIC 2  $\mu\text{mol/L}$ ), which may be related to compounds such as PA-824 and OPC-67683, that also show nitro groups. Research postulated as a mechanism of action the generation of active species that act on biochemical targets. Additionally, regression coefficient values for log P show that anti-TB activity increases when lipophilicity decreases (Klimesova et al., 2008).

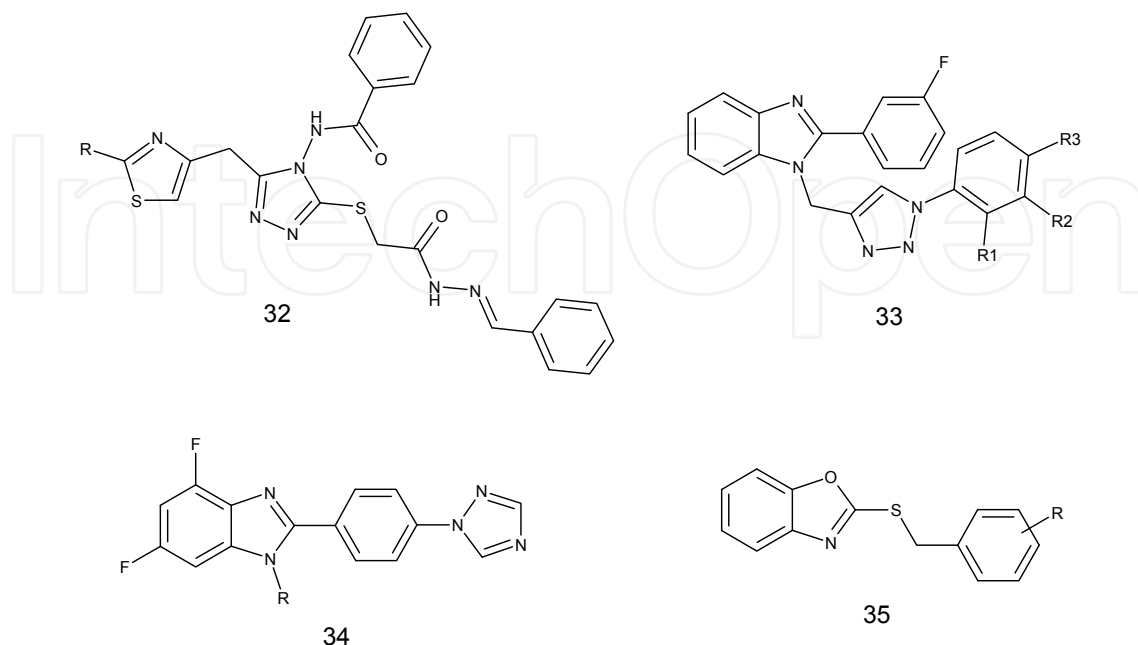


Fig. 9. Triazole and benzimidazole scaffold for designing new anti-TB agents.

Another strategy using 1,2,4-triazole and 1,3,4-thiadiazole rings, led to the development of new anti-TB agents (36, figure 10). Guzeldemerci et al obtained compounds that inhibit 90% *M. tuberculosis* with a concentration greater than 6.25  $\mu\text{g}/\text{mL}$ . In addition, the benzothiazole moiety has been recognized for anti-TB design. Both benzothiazole and 1,2,4-triazole moiety were considered to obtain new structures based on hybridization (37, figure 10). Benzothiazole derivatives with 4-methoxy groups showed the best anti-TB activity; however, compounds obtained by hybridization with the 1,2,4-triazole-benzothiazole moiety with the best activity were those with an electron withdrawing substituent (Cl) on the benzothiazole ring (Patel et al., 2010).

Another moiety considered in anti-TB agent design has been isopropylthiazole. Based on this a series of isopropylthiazole derived triazolothiadiazoles, triazolothiadiazines derivatives, and mannich bases were developed. The SAR study of the thiadiazoles series (38, figure 10) shows that these compounds have excellent activity against *M. tuberculosis* when they have fluorinated (highly electronegative) substituents that increase molecule lipophilicity, producing hydrophobic molecule interactions with specific binding sites on either receptors or enzymes (Suresh Kumar et al., 2010).

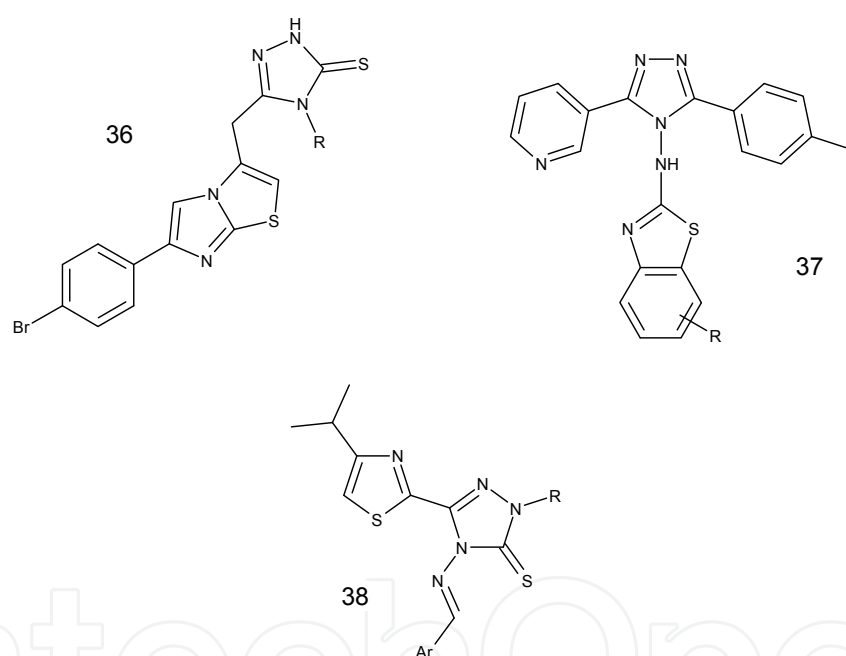


Fig. 10. Triazole derivatives as anti-TB agents.

One of the strategies employed in the development of new drugs is *in silico* screening based on drug structure, structural data of protein and a virtual library of compounds. With this strategy Izumizono et al identified 5 classes of compounds that have an affinity for the active site of enoyl-acyl carrier protein reductase. They determined that these compounds have a structural skeleton of dibenzofuran, acetoamide, triazole, furyl and methoxy phenyl groups (figure 11) that completely inhibit *M. vanbaalenii* growth with no toxic effect on mammalian cells. Binding mode prediction determined that compounds 39, 40 and 41 form common hydrogen bonds with amino acid Lys 165 of the active site of the reductase protein. Lys 165 is an amino acid residue that is known to form hydrogen bonds with INH. This shows that hydrogen bond formation with Lys 165 tends to be effective in the design of new drugs. In drug-interaction, the triazole group of compound 39 forms hydrogen binds with



the active site, and the methoxy and sulfonyl groups in compound 40 and the sulfonyl group in compound 41, respectively, form hydrogen bonds with Lys 165 (Izumizono et al., 2011).

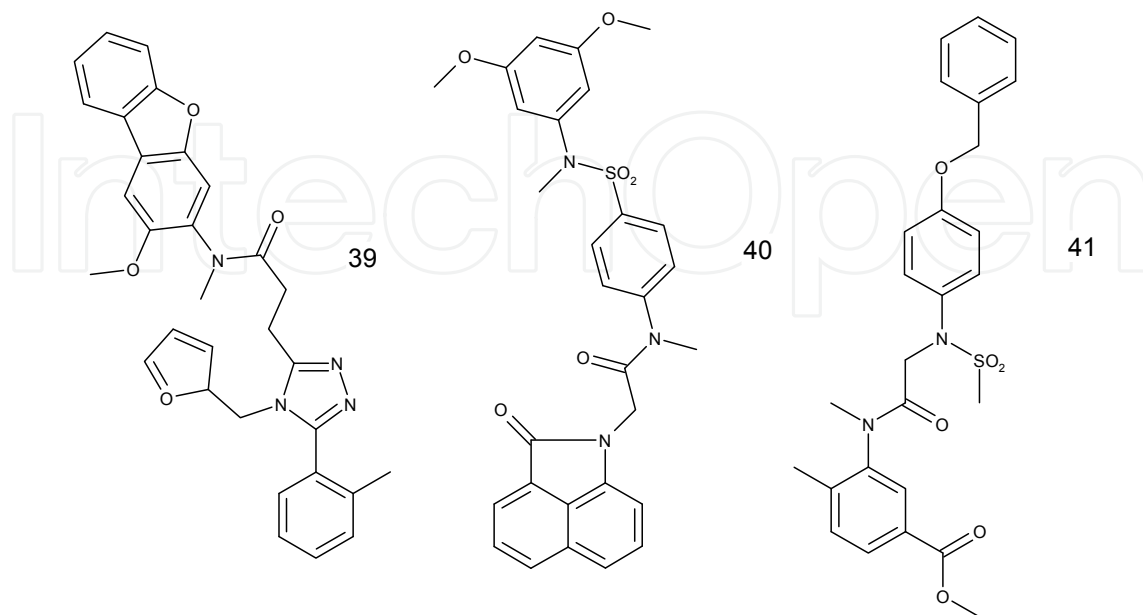


Fig. 11. Dibenzofurane, triazole, methylphenyl and acetamide moiety in compounds with anti-TB activity.

Other derivatives of azoles are pyrazoles. Their activity has been tested against *M. tuberculosis*. SAR studies show that the presence of a *para*-chlorobenzoyl moiety in C4-position on the pyrazole ring is essential for anti-TB activity. Results of a series of pyrazole derivatives, generally show that cyclohexylthio substituted pyrazole derivatives are more active than arylthio substituted systems. An excellent activity is presented when a *para*-nitrophenylthio ring is incorporated on a pyrazole ring (42, figure 12) (Manikannan et al, 2010).

Thiazoles are compounds that contains sulfur and nitrogen atom in its structure, and have been the basis of clinically used compounds. Therefore Samadhiya and colleagues consider it a basis of anti-TB agent design. In one study, which synthesized a series of new thiazoles (43, figure 12), it was demonstrated through SAR analysis that compounds with nitro groups show greater biological activity on *M. tuberculosis* than compounds with Cl and Br atoms, although these derivatives (Cl and Br) have better activity than other compounds. Finally, they found that the activity of the compound depends on the nature of the substituent groups (electron withdrawing) with the following sequence  $\text{NO}_2 > \text{Cl} > \text{Br} > \text{OCH}_3 < \text{OH} > \text{CH}_3$  (Samdhiya et al., 2010).

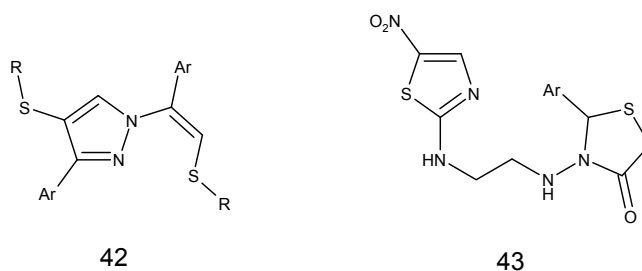


Fig. 12. General structure of pyrazoles and thiazoles derivatives as anti-TB agents.

On the other hand, hybridization of Spiro compound and pyrrolo[2,1-b ]thiazole, an unusual ring with different biological properties, particularly permitted the obtention of pyrrolothiazoles derivatives (44, figure 13) that present a MIC of 0.007  $\mu\text{M}$  against *M. tuberculosis*, being more potent than INH and Ciprofloxacin (Karthikeyan et al., 2010) .

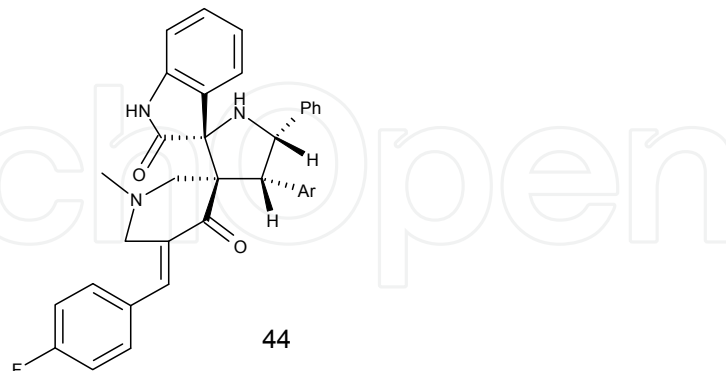


Fig. 13. Spiro-pyrrolothiazoles derivative with anti-TB activity.

### 3.6 Hydrazides/hydrazones derivatives

Hydrazide/hydrazone is a class of compounds that have been considered for new anti-TB drug design. An example is diflunisal, a hydrazide/hydrazone derivative, which has dual effect acting with antimicrobial/anti-inflammatory properties. Furthermore, in thiazolyldiazone derivatives, SAR studies have found that substitutions on the phenyl ring affect anti-TB activity (45, figure 14) (Turan-Zitouni et al., 2008). Another example of a thiazolyldiazine is compound 46 (figure 14), which has high anti-TB activity with a  $\text{IC}_{50}$  of 6.22  $\mu\text{g}/\text{mL}$  and low toxicity ( $\text{CC}_{50} > 40 \mu\text{g}/\text{mL}$ ). Here, a pyridyl moiety plays a direct role related to anti-TB activity (Turan-Zitouni et al, 2010). Pyridine is a moiety known in the design of anti-TB agents. Considering this, and using hybridization technique, Sankar et al developed a series of compounds with potential anti-TB activity (47, figure 14), although in many cases as this, the use of this technique did not produce any agent with excellent activity against *M. tuberculosis* (Sankar et al, 2010).

New designs have been made by molecular hybridization of E-cinamic acid and guanylhydrazones. Based on an empirical analysis of SAR, Bairwa and colleagues determined that electronic and steric parameters have an important role in the activity of these compounds on *M. tuberculosis* (48, figure 14). They remain the basis of new anti-TB agents (Bairwa et al, 2010).

### 3.7 Nitrogen heterocyclic derivatives

Purines are an important group in the design of anti-TB agents. In these compounds (49, figure 15), activity depends on the substituents present in C2, C6 and N9 of the purine ring (Correia et al., 2009). In 6,9-disubstituted purine derivatives, activity increases substantially when a Cl atom is introduced in the 2-position. Interestingly, purine derivatives with thienyl substituents exhibit better activity in non-replicating bacteria, although in these compounds a Cl atom in 2-position is not beneficial for activity. Additionally, it has been determined that purine N-9 is important for activity, in the case of purine C-8, an atom can be exchanged without losing activity and a change in purine N-7 results in a loss of activity, although there are 7-deazapurines derivatives (50, figure 15) that could be compared with RIF (Khoje et al., 2010).

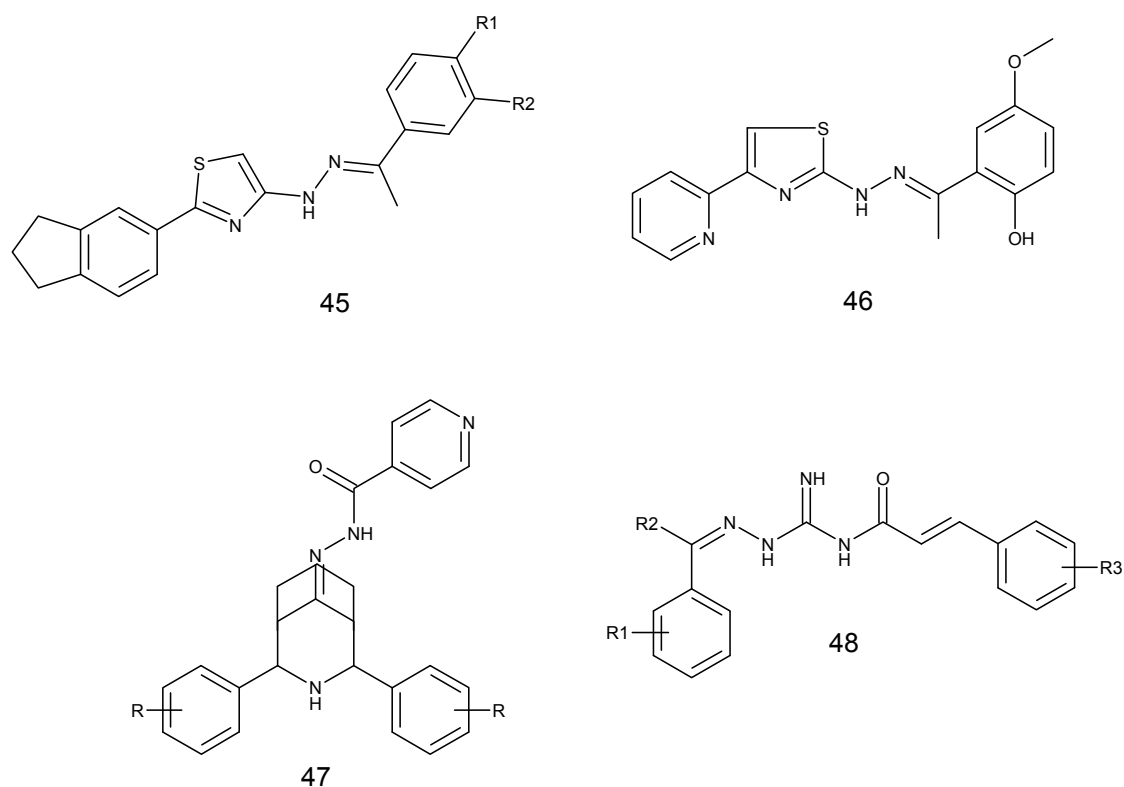


Fig. 14. Hydrazone derivatives as anti-TB agents.

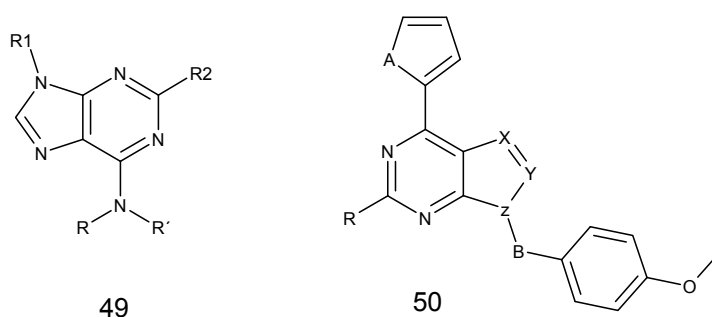


Fig. 15. Purine derivatives as anti-TB agents.

Heterocycles with one nitrogen atom, especially pyrimidines have potential therapeutic applications as anti-TB agents, but there are few reports. For this reason, the design of new pyrimidine derivatives is a viable option (51, figure 16). However, neither compound has an activity comparable to reference drugs, although it has been described that the substituent nature in 2-position can modulate cytotoxic activity (Singh et al, 2011).

On the other hand, thymidine monophosphate kinase of *M. tuberculosis* (TMPKmt) is a prominent target for the development of anti-TB drugs. TMPK is the last specific enzyme for dTTP synthesis and is a key enzyme in *M. tuberculosis* metabolism. This enzyme is different from human enzyme analogs (22% homology). TMPK inhibitors have been developed with single or multiple chemical modifications of the pyrimidine moiety and thymidylate sugar. In particular benzyl-thymine derivatives have been remarkable TMPK inhibitors, which has led to the proposal of new modifications such as: chain length in *para*-position on the benzyl ring, saturation of the alkyl chain, functionalization of the chain group and substitution at 5-

position of the core base. This has led to more selective compounds on TMKP that correspond to benzyl-pyrimidines substituted by a chain length of 4 carbons and a terminal carboxylic acid function. Docking of molecule 52 (figure 16) on TMPKmt showed that the hydrogen of the thymine and acid group can interact with Arg95 (Gasse et al., 2008).

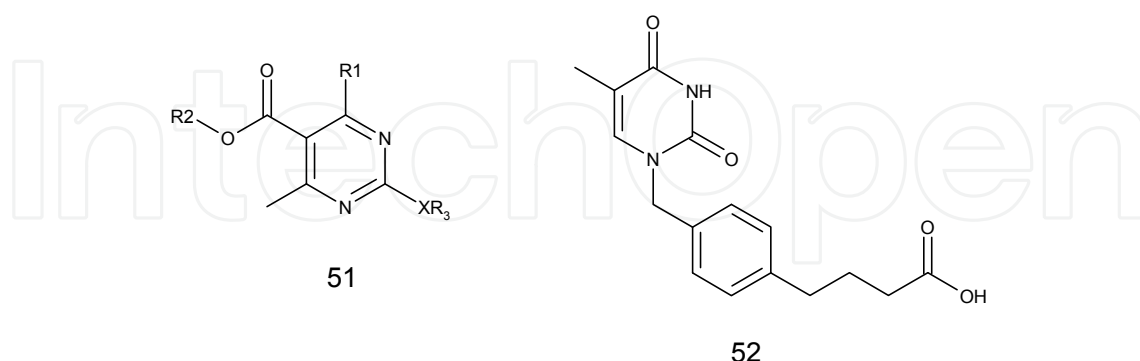


Fig. 16. General structure of pyrimidine derivatives as anti-TB agents.

Pyridine derivatives have also been described as anti-TB agents, an example is compound 53 (figure 17), which presents inhibitory activity with an IC<sub>50</sub> value of 0.38  $\mu$ M, suggesting that its possible mechanism of action is through glutamine synthetase inhibition. This would be the first inhibitor compound not derived from amino acids (Odell et al, 2009). Another series of pyridine derivatives were developed by Fassihi et al who synthesized compound 54 (figure 17), a potent anti-TB agent with activity similar to RIF. The results of these compounds showed that an imidazole group as a substituent is equivalent to a nitro phenyl group, which has been reported in anti-TB agents derived from 1,4-dihydropyridinecarboxamides (Fassihi et al., 2009).

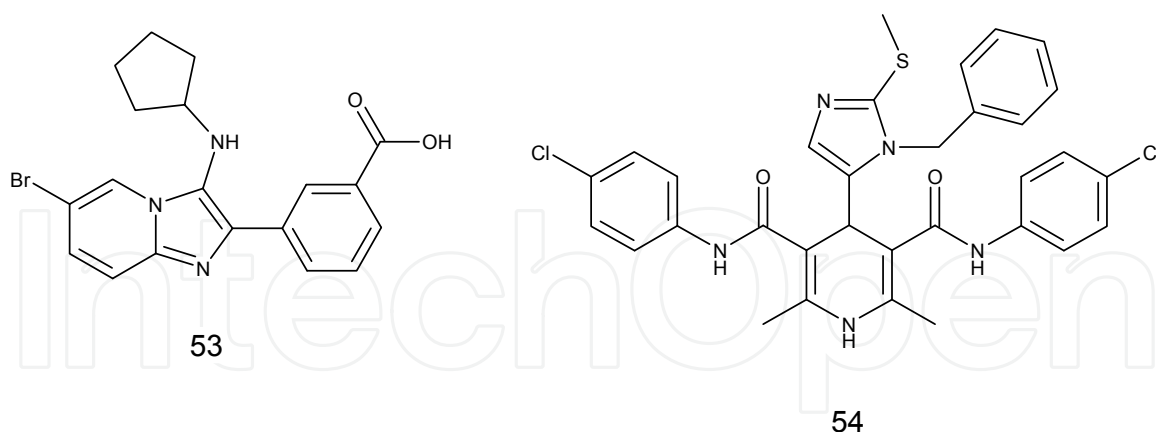


Fig. 17. Pyridine derivatives with potential activity anti-TB.

Another important heterocyclic for the design of anti-TB agents is the pyridazine moiety. In these compounds a relationship between Br, Cl and CH<sub>3</sub> substituents, respectively, with Br and vinyl has been found with a favorable anti-TB activity. In these compounds there is an influence of the substituents X in *para*-position on the aromatic ring, where the activity is increased in the following order: CH<sub>3</sub> < Cl < Br with the activity being affected by the R<sub>1</sub> substituents, where the most active compounds have a CH<sub>3</sub> group (55, figure 18) (Mantu et al., 2010).

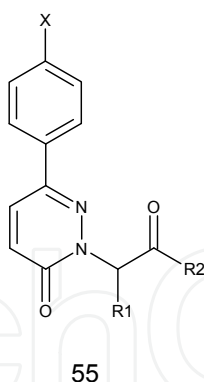


Fig. 18. *N*-substituted-pyridazinones derivatives.

### 3.8 Other derivatives

Several studies indicate that thiosemicarbazone derivatives can be used in TB therapy and prophylaxis. Previous studies of 1*H*-2-thiosemicarbazoneindolinone derivatives indicate that halogenation of R1, elongation of the alkyl chain in R2, substitutions of the alkyl chain in R2 with cyclohexyl or phenyl, and the presence of a substituent in R3, are more efficient for increasing anti-TB activity, while R1 substitutions with a nitro group produce the most active compounds. The presence of a morpholine ring in Schiff bases substituted in R1 with a nitro group also has a significant impact on anti-TB activity. The results of biological activity of this new series indicate that the elongation of the alkyl chain increases activity. This enhanced activity is related to lipophilicity properties and confirmed by values of Log P compounds. Also, replacement of the alkyl chain in R2 and phenyl unsubstituted cyclohexyl has led to more active compounds (56, figure 19). The absence of substitutions at N1 on the indole ring and increased lipophilicity appear to be responsible for high activity against *M. tuberculosis* (Guzel et al., 2008). An example of thiosemicarbazone-derived compounds that have exhibited important anti-TB activity with an IC<sub>50</sub> value of 2.59 μM/mL, is compound 57 (figure 19) (Karali et al., 2007).

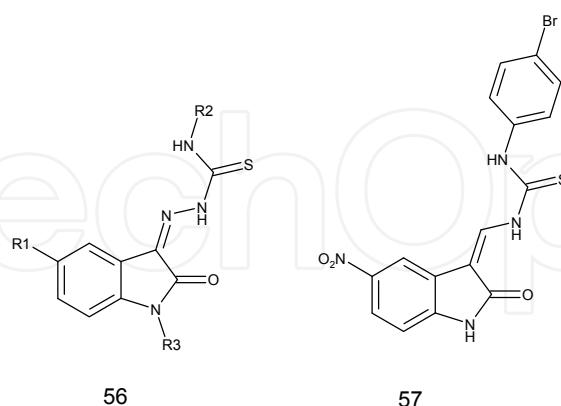


Fig. 19. General structure of 1*H*-indole-2,3-dione 3-thiosemicarbazone with anti-TB activity.

Other moieties used in the design of anti-TB agents are phenazine and benzothiadiazine. In particular, benzothiadiazine 1,1-dioxide constituents are an important class of anti-TB agents (58, figure 20). A SAR study of this series of compounds indicates that the furan/thiophene group linked to benzothiadiazine through a methylene bridge exhibits good activity against TB. It is important to point out that a conjugated thiophene derivative shows moderate

activity and is enhanced when it presents a nitrofuran group. However, elimination of the methylene group with a carbonyl group leads to a dramatic loss of activity. Finally, Kamal et al postulated piperazine-benzothiadiazine with methylene linkage (59, figure 20) as an attractive moiety for the design of anti-TB agents (Kamal et al., 2010).

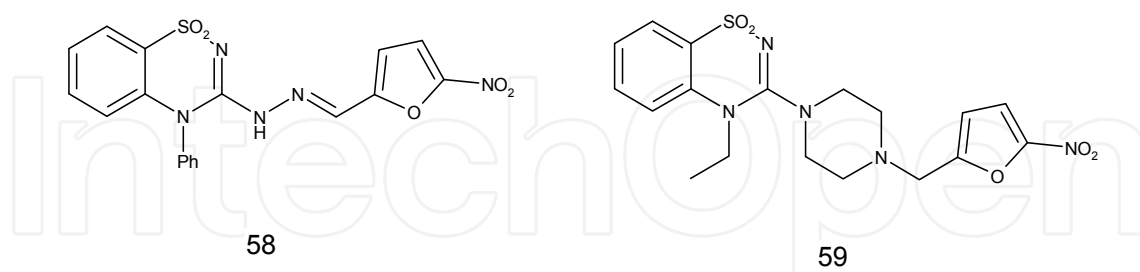


Fig. 20. Benzothiadiazine derivatives as anti-TB agents.

The creation of a hybrid compound has been a frequent strategy for the design of anti-TB agents. One example is compound 60 (figure 21), formed from dibenzofuran and 2,2-dimethylpyran subunits. SAR studies and modifications of benzofurobenzopyran have demonstrated less active compounds such as compound 61, where the furan B ring is replaced by an ether linker, a single carbon-carbon bond, a carbonyl group, a hydroxymethylene or a methylene group. Even modifications such as acylation and bromination in 5-position on the C ring have produced inactive compounds, thus, it has been suggested as a basis for the pharmacophore structure of compound 60. In this sense, Termenzi et al has carried out the synthesis of more derivatives of compound 60, finding that substitutions with a hydroxy, methoxy, or halogen group on benzofurobenzopyran increases anti-TB activity. Although, hydroxy compounds with good activity showed, unfortunately, cytotoxic activity on VERO cells. Halogenated compounds with a Cl or Br atom in 8, 9 and 11-position, exhibit increased potency compared with compound 60. SAR analysis shows that electronic effects of substituents on the A ring play a dramatic role in anti-TB activity. In addition, potency was significantly decreased when the A ring was substituted by an electron withdrawing group. In contrast, electron donating group substitutions such as hydroxy or methoxy show a significant increase in activity (62, figure 21). While all compounds showed a possible mechanism of action of interaction with lipid biosynthesis of the *M. tuberculosis* cell wall, a specific compound was an epoxy-mycolate synthesis inhibitor (Termentzi et al., 2010).

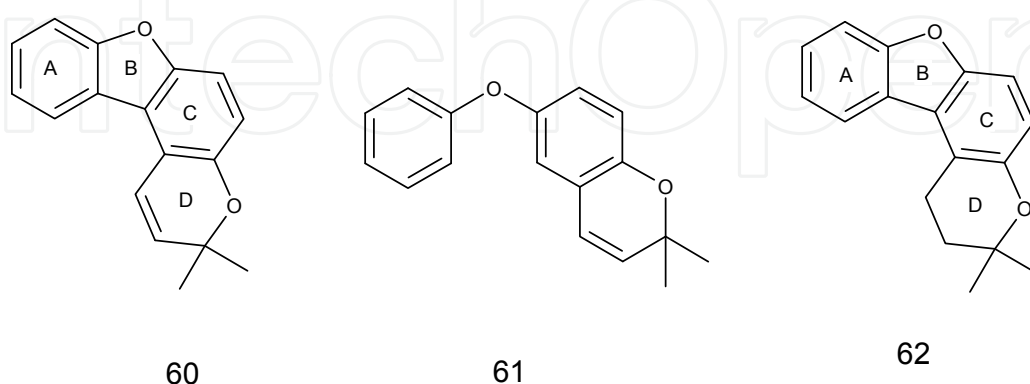
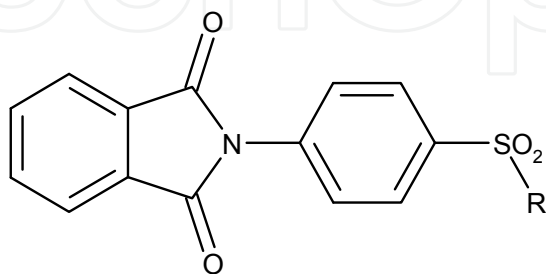


Fig. 21. Structure of benzofurobenzopyrane as anti-TB agents.

Other compounds containing a phthalimide moiety have been described as biophoro to design new prototypes of drug candidates with different biological activities. It has been

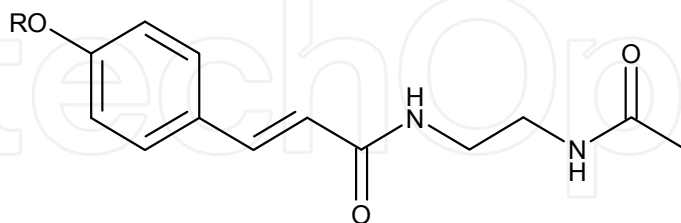
shown that hybridization of both phthalimide (Thalidomide) and sulfonamide (Dapsone) moiety leads to compounds with activity against *M. leprae*. In this sense, the design of new products such as anti-TB agents is interesting. SAR study of a series of derivatives showed that if the pyrimidine ring is substituted in any position or changed by an isosteric, this decreases activity on *M. tuberculosis*. Amino group substitutions by another phthalimide ring also lead to a decrease in anti-TB activity (63, figure 22). Modifications in the pyridine ring decrease anti-TB activity. Introduction of a phthalimide group by molecular hybridization did not produce compounds with an activity similar to INH; however, it allows for compounds with MIC values similar to PZA (Santos et al., 2009).



63

Fig. 22. Phthalimide derivatives as anti-TB agent.

Among families of compounds that act as inhibitors of the FAS-II system we can mention diphenyl ether systems that interact with enzyme-cofactor binary complex, but, recently new compounds such as indols, benzofuran and cinnamic acid derivatives have been reported. Development of new cinnamic acid derivatives would focus on more specific FAS-II inhibitors. From a series of compounds developed (figure 23) it was determined that addition of an alkyl chain increases anti-TB activity. The best results are associated with an acceptable lipophilicity parameter that appears when a geranyl chain is incorporated. This led to compound 64, the most active substance with an MIC of 0.1  $\mu\text{g}/\text{mL}$  (Yoya et al., 2009).



64

Fig. 23. Cinnamic derivatives.

It has also been shown that amide derivatives of fatty acids have anti-TB activity. Due to their nature these compounds are designed to penetrate bacterial cells, which can be useful for studying the mechanism of INH resistance as this can also be due to factors such as mutations in unknown genes, decreased permeability, or increased efflux (D'Oca et al., 2010).

#### 4. Drugs in clinical trials

In drug design, bicyclic nitroimidazofurane derivatives that have anti-TB activity, such as CGI-17341 (65, figure 24) have been developed; however, this compound is mutagenic. This has led to the development of PA-824 (66, figure 24), which is currently in phase II clinical studies and has a long half-life. Its mechanism of action is to inhibit *M. tuberculosis* cell wall lipids and protein synthesis; however, it also inhibits non-replicating bacteria. Additionally, it was reported that PA-824 is a prodrug that is metabolized by *M. tuberculosis* before exercising its effect and may involve bioreduction of aromatic nitro groups to generate a radical intermediate nitro.

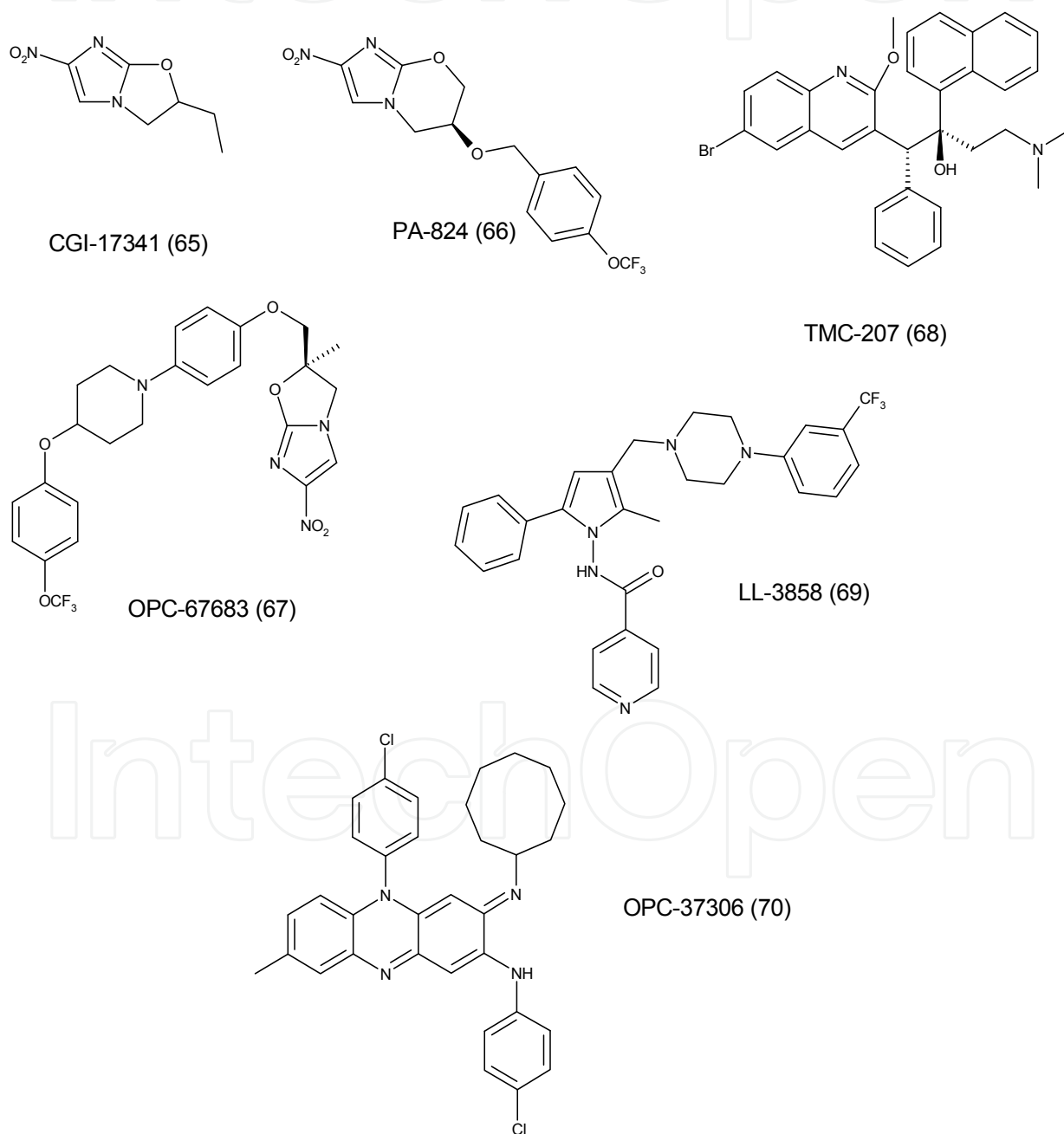


Fig. 24. Anti-TB compounds in clinical trials.



The interest in derived oxazoles as anti-TB compounds led to the development of OPC-67683 (67, figure 24), which has excellent activity *in vitro* in sensitive and resistant *M. tuberculosis* strains. It has a long half-life and its mechanism of action involves inhibition of the synthesis of keto-mycolic, and methoxy-mycolic acid, although is possible another possible mechanism of action or interaction with another drug target in *M. tuberculosis*. OPC-67683 also acts as a prodrug, since *M. tuberculosis* metabolizes it and produces as a product desnitro-imidazooxazole metabolite.

TMC207 (68, figure 25) is a quinoline derivative with potent anti-TB activity in susceptible, DR and XDR strains. It is well absorbed in humans with a long half-life and is currently in phase II clinical studies. Its mechanism of action involves inhibition of ATP synthase that binds the *M. tuberculosis* membrane and there is a synergistic effect between TMC207 and PZA. Other compounds with very promising anti-TB activity are LL-3858 and OPC-37306 (69 and 70, figure 25) (Rivers et al., 2008). Some other examples of anti-TB compounds in clinical trials are showed in table 1 (Janin, 2007; Palomino et al., 2009; Shi & Sugawara, 2010)

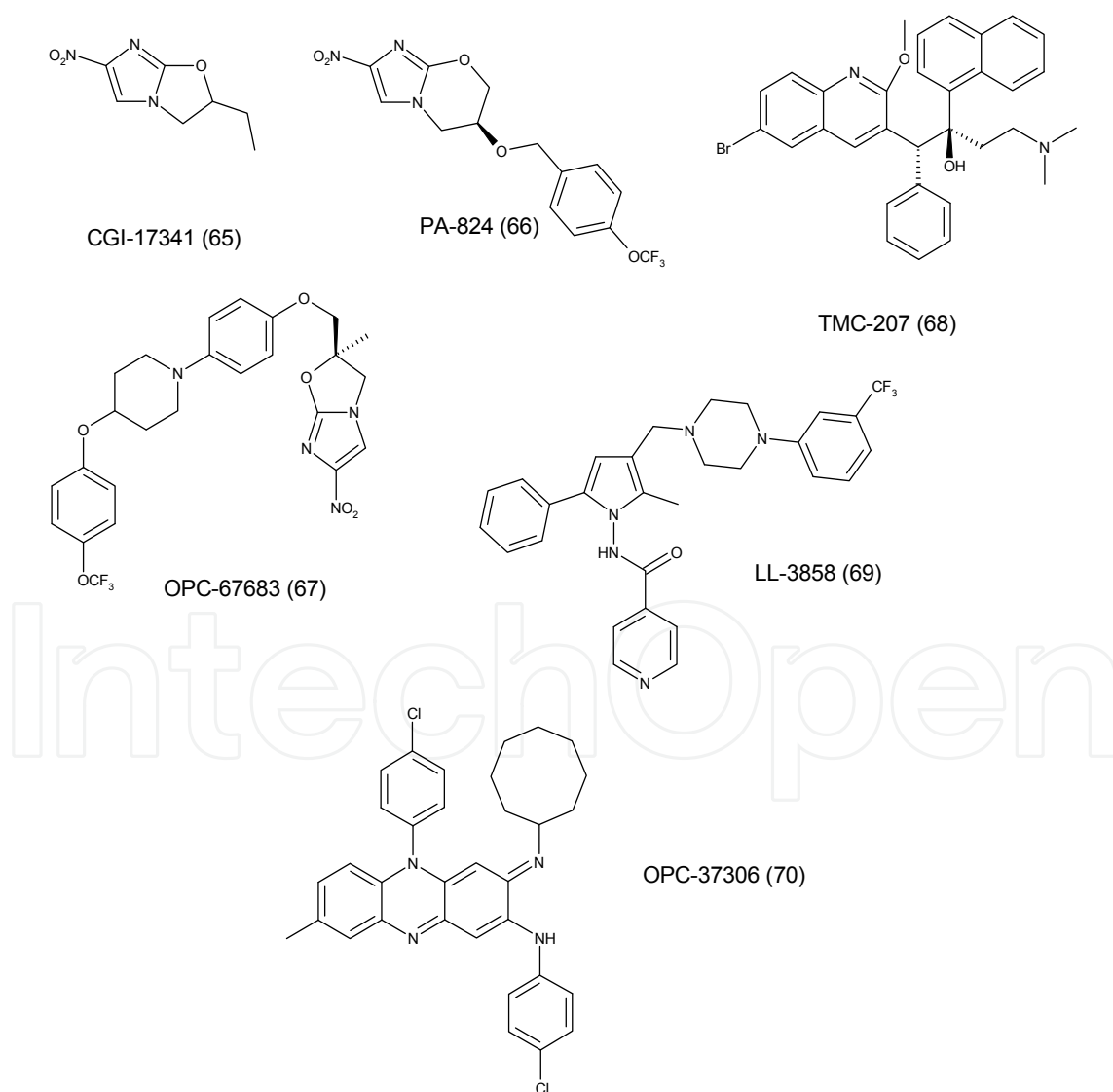


Fig. 25. Anti TB compounds in clinical trials.

| Compound               | Funding              | Target                        | Mechanism of action  | Resistance mechanisms                       | Clinical trial phase |
|------------------------|----------------------|-------------------------------|--|---|----------------------|
| a) Nitroimidazoxacines |                      |                               |  |   |                      |
| PA-824                 | GATB                 | F420 dependent nitroreductase | Inhibition of proteins and cell wall biosynthesis                | Rv0407, Rv3547, Rv3261 and Rv3262 mutations | II                   |
| OPC-67683              | Otsuka               | Nitroreductase                | Inhibition of mycolic acid and cell wall biosynthesis            | Rv3547 mutations                            | II                   |
| b) Fluoroquinolones    |                      |                               |  |   |                      |
| Moxifloxacin           | Bayer, CDC, NIH, FDA | DNA girase                    | Inhibition of DNA biosynthesis                                   | <i>gyrA</i> mutations                       | III                  |
| Gatifloxacin           | NIH                  | DNA girase                    | Inhibition of DNA biosynthesis                                   | <i>gyrA</i> mutations                       | III                  |
| c) Diarilquinolines    |                      |                               |  |   |                      |
| TMC207                 | Tibotec              | F1F0 ATP sintetase            | Inhibition of ATP synthesis and disruption of membrane potential | <i>atpE</i> mutations                       | II                   |
| d) Oxazolidinones      |                      |                               |  |   |                      |
| Linezolid              | NIH, Pfizer          | Ribosome                      | Inhibition of protein biosynthesis                               | rRNA 23S mutations                          | Pre-trial            |
| e) Dietilamins         |                      |                               |  |   |                      |
| SQ109                  | Sequella             | Un known                      | Inhibition of cell wall biosynthesis                             | Unknown                                     | I/II                 |
| f) Pirrols             |                      |                               |  |   |                      |
| LL3858                 | Lupin                | Unknown                       | Unknown  | Unknown                                     | I                    |

Table 1. Some compounds under clinical trials

## 5. Conclusion

Tuberculosis remains the leading infectious disease worldwide, despite the availability of TB chemotherapy and the BCG vaccine. This is further demonstrated by the fact that half a year of treatment with multiple drugs is needed. Recent genetic and genomic tools as well as high-throughput screening, and structure-based drug design strategies have allowed the discovery of new anti-TB drugs. These are increasingly receiving more attention, and a large number of new compounds or derivatives from existing drugs are under investigation. With this and a better understanding of the unique biology of TB, more targets will be validated, and hopefully a pattern will emerge that will help us reach the goals of more potent compounds that allow multiple stages and drug targets to be addressed.

## 6. References

- Ahmad, Z., Sharma, S., Khuller, GK., Singh, P., Faujdar, J., Katoch, VM. (2006). Antimycobacterial activity of econazole against multidrug-resistant strains of *Mycobacterium tuberculosis*. *International Journal of Antimicrobial Agents*, Vol. 28, No.6, (Dec 2006), pp. 543-544. ISSN: 0924-8579.
- Anderson, RG., Hussey, H., Baddiley, J. (1972). The mechanism of wall synthesis in bacteria. The organization of enzymes and isoprenoid phosphates in the membrane. *The Biochemical Journal*. Vol. 127, No. 1 (Mar 1972), pp. 11-25. ISSN: 0264-6021.
- Av-Gay, Y., Everett, M. (2000). The eukaryotic-like Ser/Thr protein kinases of *Mycobacterium tuberculosis*. *Trends in Microbiology*, Vol. 8, No.5, (May 2000), pp. 238-244. ISSN: 0966-842X.
- Bairwa, R., Kakwani, M., Tawari, NR., Lalchandani, J., Ray, MK., Rajan, MG., Degani, MS. (2010). Novel molecular hybrids of cinnamic acids and guanylhydrazones as potential antitubercular agents. *Bioorganic & Medicinal Chemistry Letters*, Vol.20, No.5 (Jan, 2010), pp. 1623-1625, ISSN 0960-894X.
- Banerjee, A., Sugantino, M., Sacchetti, J.C., Jacobs, WR. Jr. (1998). The mabA gene from the inhA operon of *Mycobacterium tuberculosis* encodes a 3-ketoacyl reductase that fails to confer isoniazid resistance. *Microbiology*, Vol. 144, No.10,(Oct 1998), pp. 2697-2704. ISSN: 1350-0872.
- Bellinzoni, M., De Rossi, E., Branzoni, M., Milano, A., Peverali, FA., Rizzi, M., Riccardi, G. (2002). Heterologous expression, purification, and enzymatic activity of *Mycobacterium tuberculosis* NAD(+) synthetase. *Protein Expression and Purification*. Vol. 25, No.3, (Aug 2002), pp. 547-557. ISSN: 1046-5928.
- Betts, JC., McLaren, A., Lennon, MG., Kelly, FM., Lukey, PT., Blakemore, SJ., Duncan, K. (2003). Signature gene expression profiles discriminate between isoniazid-, thiolactomycin-, and triclosan-treated *Mycobacterium tuberculosis*. *Antimicrobial Agents and Chemotherapy*. Vol. 47, No.9, (Sep 2003), pp. 2903-2913. ISSN: 1073-449X.
- Blumberg, HM., Burman, WJ., Chaisson, RE., Daley, CL., Etkind, SC., Friedman, LN., Fujiwara, P., Grzemska, M., Hopewell, PC., Iseman, MD., Jasmer, RM., Koppaka, V., Menzies, RI., O'Brien, RJ., Reves, RR., Reichman, LB., Simone, PM., Starke, JR., Vernon, AA. (2003). American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *American Journal of Respiratory and Critical Care Medicine*. Vol. 167, No.4, (Feb 2003), pp. 603-662. ISSN: 1073-449X.
- Brennan, PJ., Crick, DC. (2007). The cell-wall core of *Mycobacterium tuberculosis* in the context of drug discovery. *Current Topics in Medicinal Chemistry*, Vol. 7, No.5, (Feb 2007), pp. 475-88. ISSN: 1568-0266.
- Choi, KH., Kremer, L., Besra, GS., Rock, CO. (2000). Identification and substrate specificity of beta -ketoacyl (acyl carrier protein) synthase III (mtFabH) from *Mycobacterium tuberculosis*. *The Journal Biological Chemistry*, Vol. 275, No.36, (Sep 2000), pp. 28201-28207. ISSN: 0021-9258.
- Cole, ST., and Alzari PM. (2007) Towards new tuberculosis drugs. *Biochemical Society Transactions*, Vol. 35, Part 5 (Sep 2007), pp. 1321-1324. ISSN: 0300-5127.
- Cole, ST., Brosch, R., Parkhill, J., Garnier, T., Churcher, C., Harris, D., Gordon, SV., Eiglmeier, K., Gas, S., Barry, CE. 3rd, Tekaia, F., Badcock, K., Basham, D., Brown,

- D., Chillingworth, T., Connor, R., Davies, R., Devlin, K., Feltwell, T., Gentles, S., Hamlin, N., Holroyd, S., Hornsby, T., Jagels, K., Krogh, A., McLean, J., Moule, S., Murphy, L., Oliver, K., Osborne, J., Quail, MA., Rajandream, MA., Rogers, J., Rutter, S., Seeger, K., Skelton, J., Squares, R., Squares, S., Sulston, JE., Taylor, K., Whitehead, S., Barrell, BG. (1998). Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. *Nature*, Vol. 393, No.6685, (Jun 1998), pp 537-544. ISSN: 0028-0836.
- Correia C., Carvalho MA., Proenca MF. (2009). Synthesis and in vitro activity of 6-amino-2,9-diarylpurines for *Mycobacterium tuberculosis*. *Tetrahedron*, Vol.65, No.34, (Aug, 2009), pp. 6903-6911, ISSN 0040-4020.
- Cunico, W., Gomes CR., Ferreira, ML., Ferreira, TG., Cardinot, D., de Souza, MV., Lorengo, MC. (2011). Synthesis and anti-mycobacterial activity of novel amino alcohol derivatives. *European Journal of Medicinal Chemistry*. Vol.46, No.3, (Mar, 2011), pp. 974-978, ISSN 0223-5234.
- D'Oca, Cda R., Coelho, T., Marinho, TG., Hack, CR., Duarte, Rda C., da Silva, PA., D'Oca, MG. (2010). Synthesis and antituberculosis activity of new fatty acid amides. *Bioorganic & Medicinal Chemistry Letters*, Vol.20, No.17, (Jul, 2010), pp. 5255-5257, ISSN 0960-894X.
- De Logu, A., Palchykovska, LH., Kostina, VH., Sanna, A., Meleddu, R., Chisu, L., Alexeeva, IV., Shved, AD. (2009). Novel N-aryl- and N-hetryl phenazine-1-carboxamide as potential targets for the treatment of infections sustained by drug-resistant and multidrug-resistant *Mycobacterium tuberculosis*. *International Journal Of Antimicrobial Agents*. Vol.33, No.3 (Dec, 2008), pp. 223-229, ISSN 0924-8579.
- Delaine, T., Bernades-Genisson, V., Quemard, A., Constant, P., Meunier, B., Bernadou, J. (2010). Development of isoniazid-NAD truncated adduct embedding a lipophilic fragment as potential bi-substrate InhA inhibitors and antimycobacterial agents. *European Journal of Medicinal Chemistry*, Vol.45, No. 10, (Oct, 2010), pp. 4554-4561, ISSN 0223-5234.
- Ducati, RG., Basso, LA., Santos, DS. (2007). Mycobacterial shikimate pathway enzymes as targets for drug design. *Current Drug Targets*, Vol. 8, No. 3 (Mar 2007), pp. 423-35. ISSN: 1389-4501.
- Duncan, K. (2004). Identification and validation of novel drug targets in tuberculosis. *Current Pharmaceutical Design*, Vol. 10, No.26, (Sep 2004) pp. 3185-94. ISSN: 1381-6128
- Dye C. (2006). Global epidemiology of tuberculosis. *Lancet*, Vol. 367, No.9514, (Mar 2006), pp.938-40. ISSN: 0140-6736.
- Eoh, H., Brennan, PJ., Crick, DC. (2009). The *Mycobacterium tuberculosis* MEP (2C-methyl-d-erythritol 4-phosphate) pathway as a new drug target. *Tuberculosis* (Edinburg, Scotland). Vol. 89, No. 1 (Jan 2009), pp. 1-11. ISSN:1472-9792.
- Eswaran, S., Adhikari, AV., Chowdhury, IH., Pal, NK., Thomas, K. (2010). New quinoline derivatives: synthesis and investigation of antibacterial and antituberculosis properties. *European Journal Of Medicinal Chemistry*, Vol.45, No.8, (Apr, 2010), pp. 3374-3383, ISSN 0223-5234.
- Eswaran, S., Adhikari, AV., Kumar, R. (2010). New 1,3-oxazolo[4,5-c]quinoline derivatives: Synthesis and evaluation of antibacterial and antituberculosis properties. *European*

- Journal of Medicinal Chemistry*, Vol.45, No.3, (Nov, 2009), pp. 957-966, ISSN 0223-5234.
- Eswaran, S., Adhikari, AV., Pal, NK., Chowdhury, IH. (2010). Design and synthesis of some new quinoline-3-carbohydrazone derivatives as potential antimycobacterial agents. *Bioorganic & Medicinal Chemistry Letters*, Vol.20, No.3, (Dec, 2009), pp. 1040-1044, ISSN 0960-894X.
- Fassihi A., Azadpour Z., Delbari N., Saghaie L., Memarian HR., Sabet R., Alborzi A., Miri R., Pourabbas B., Mardaneh J., Mousavi P., Moeinifard B., Sadeghi-aliabdi, H. (2009). Synthesis and antitubercular activity of novel 4-substituted imidazolyl-2,6-dimethyl-N3,N5-bisaryl-1,4-dihydropyridine-3,5-dicarboxamides. *European Journal of Medicinal Chemistry*, Vol.44, No.8, (Mar, 2009), pp. 3253-3258. ISSN 0223-5234.
- Feng, Z., Barletta, RG. (2003). Roles of *Mycobacterium smegmatis* D-alanine:D-alanine ligase and D-alanine racemase in the mechanisms of action of and resistance to the peptidoglycan inhibitor D-cycloserine. *Antimicrobial Agents and Chemotherapy*, Vol. 47, No. 1 (Jan 2003), pp. 283-291 ISSN: 0066-4804.
- Fernandez, P., Saint-Joanis, B., Barilone, N., Jackson, M., Gicquel, B., Cole, ST., Alzari, PM. (2006). The Ser/Thr protein kinase PknB is essential for sustaining mycobacterial growth. *Journal of Bacteriology*, Vol. 188, No.22, (Nov 2006), pp. 7778-7784. ISSN: 0021-9193.
- Ferreras, JA., Ryu, JS., Di Lello, F., Tan, DS., Quadri, LE. (2005). Small-molecule inhibition of siderophore biosynthesis in *Mycobacterium tuberculosis* and *Yersinia pestis*. *Nature Chemical Biology*, Vol. 1, No.1, (Jun 2005), pp. 29-32. ISSN: 1552-4450.
- Ferriz, JM., Vavrova, K., Kunc, F., Imramovsky, A., Stolarikova, J., Vavrikova, E., Vinsova, J. (2010). Salicylanilide carbamates: Antitubercular agents active against multidrug-resistant *Mycobacterium tuberculosis* strains. *Bioorganic & Medicinal Chemistry*, Vol.18, No.3, (Dec, 2009), pp. 1054-1061, ISSN 0968-0896.
- Gasse, C., Douguet, D., Huteau, V., Marchal, G., Munier-Lehmann, H., Pochet, S. (2008). Substituted benzyl-pyrimidines targeting thymidine monophosphate kinase of *Mycobacterium tuberculosis*: Synthesis and in vitro anti-mycobacterial activity. *Bioorganic & Medicinal Chemistry*, Vol. 16, No.11, (Apr, 2008), pp. 6075-6085, ISSN 0968-0896.
- Gerum, AB., Ulmer, JE., Jacobus, DP., Jensen, NP., Sherman, DR., Sibley, CH. (2002). Novel *Saccharomyces cerevisiae* screen identifies WR99210 analogues that inhibit *Mycobacterium tuberculosis* dihydrofolate reductase. *Antimicrobial Agents and Chemotherapy*, Vol. 46, No.11, (Nov 2002), pp. 3362-3369. ISSN: 0066-4804.
- Gill, C., Jadhav, G., Shaikh, M., Kale, R., Ghawalkar, A., Nagargoje, D., Shiradkar, M. (2008). Clubbed [1,2,3] triazoles by fluorine benzimidazole: A novel approach to H37Rv inhibitors as a potential treatment for tuberculosis. *Bioorganic & Medicinal Chemistry Letters*, Vol.18, No.23, (Oct, 2008), pp. 6244-6247, ISSN 0968-0896.
- Goncalves, RS., Kaiser, CR., Lourenco, MC., de Souza, MV., Wardell, JL., Wardell, SM., da Silva, AD. (2010). Synthesis and antitubercular activity of new mefloquine-oxazolidine derivatives. *European Journal of Medicinal Chemistry*. Vol.45, No.12, (Sep, 2010), pp. 6095-6100, ISSN 0223-5234.
- Gong, C., Martins, A., Bongiorno, P., Glickman, M., Shuman, S. (2004). Biochemical and genetic analysis of the four DNA ligases of mycobacteria. *The Journal of Biological Chemistry*, Vol. 279, No.20, (May 2004), pp. 20594-20606. ISSN: 0021-9258.

- Güzel, O., Karali, N., Salman, A. (2008). Synthesis and antituberculosis activity of 5-methyl/trifluoromethoxy-1H-indole-2,3-dione 3-thiosemicarbazone derivatives. *Bioorganic & Medicinal Chemistry*, Vol.16, No.19, (Aug, 2008), pp. 8976-8987, ISSN 0968-0896.
- Haouz, A., Vanheusden, V., Munier-Lehmann, H., Froeyen, M., Herdewijn, P., Van Calenbergh, S., Delarue, M. (2003). Enzymatic and structural analysis of inhibitors designed against *Mycobacterium tuberculosis* thymidylate kinase. New insights into the phosphoryl transfer mechanism. *The Journal of Biological Chemistry*, Vol. 278, No. 7, (Feb 2003), pp. 4963-4971. ISSN: 0021-9258.
- Hasan, S., Daugelat, S., Rao, PS., Schreiber, M. (2006). Prioritizing genomic drug targets in pathogens: application to *Mycobacterium tuberculosis*. *PLoS Computational Biology*, Vol. 2, No.6, (Jun 2006) Epub 2006: ISSN: 1553-734X.
- Hearn MJ., Cynamon MH., Chen MF., Coppins R., Davis J., Joo-On Kang, H., Noble A., Tu-Sekine B., Terrot MS., Trombino D., Thai M., Webster ER., Wilson, R. (2009). Preparation and antitubercular activities in vitro and in vivo of novel Schiff bases of isoniazid. *European Journal of Medicinal Chemistry*, Vol.44, No.10, (Oct, 2009), pp. 4169-4178, ISSN 0223-5234.
- Heath, RJ., White, SW., Rock, CO. (2001). Lipid biosynthesis as a target for antibacterial agents. *Progress in Lipid Research*. Vol. 40, No.6, (Nov 2001), pp. 467-497. ISSN: 0163-7827.
- Huang, H., Scherman, MS., D'Haese, W., Vereecke, D., Holsters, M., Crick, DC., McNeil, MR. (2005) Identification and active expression of the *Mycobacterium tuberculosis* gene encoding 5-phospho- $\alpha$ -D-ribose-1-diphosphate: decaprenyl phosphate 5-phosphoribosyltransferase, the first enzyme committed to decaprenylphosphoryl-D-arabinose synthesis. *The Journal Biological Chemistry*, Vol. 280, No. 26 (Jul 2005), pp. 24539-24543. ISSN: 0021-9258.
- Huovinen, P., Sundström, L., Swedberg, G., Sköld, O. (1995). Trimethoprim and sulfonamide resistance. *Antimicrobial Agents and Chemotherapy*, Vol. 39, No.2, (Feb 1995), pp. 279-289. ISSN: 0066-4804.
- Imramovsky, A., Polanc, S., Vinsova, J., Kočevar, M., Jampilek, J., Reckova, Z., Kaustova, J. (2007). A new modification of anti-tubercular active molecules. *Bioorganic & Medicinal Chemistry*, Vol.15, No.7, (Apr, 2007), pp. 2551-2559, ISSN 0968-0896.
- Imramovsky, A., Vinsova J., Ferriz, JM., Buchta, V., Jampilek, J. (2009). Salicylanilide esters of N-protected amino acids as novel antimicrobial agents. *Bioorganic & Medicinal Chemistry Letters*, Vol.19, No.2, (Nov, 2008), pp. 348-351, ISSN 0968-0896.
- Imramovsky, A., Vinsova, J., Ferriz, JM., Dolezal, R., Jampilek, J., Kaustova, J., Kunc, F. (2009). New antituberculotics originated from salicylanilides with promising in vitro activity against atypical mycobacterial strains. *Bioorganic & Medicinal Chemistry*, Vol.17, No.10, (May, 2010), pp. 3572-3579, ISSN 0968-0896.
- Izumizono, Y., Arevalo, S., Koseki, Y., Kuroki, M., Aoki, S. (2011). Identification of novel potential antibiotics for tuberculosis by in silico structure-based drug screening. *European Journal of Medicinal Chemistry*, Vol.46, No.5, (Feb, 2011), pp. 1849-1856, ISSN 0223-5234.
- Jadhav GR., Shaikh MU., Kale RP., Shiradkar MR., Gill, CH. (2009). SAR study of clubbed [1,2,4]-triazolyl with fluorobenzimidazoles as antimicrobial and antituberculosis

- agents. *European Journal of Medicinal Chemistry*, Vol.44, No.7, (Dec, 2008), pp. 2930-2935, ISSN 0223-5234.
- Janin YL. (2007). Antituberculosis drugs: ten years of research. *Bioorganic and Medicinal Chemistry*, Vol. 15, No.7, (Apr 2007), pp. 2479-2513. ISSN: 0968-0896.
- Kamal, A., Shett, RVCRCNC., Azeeza, S., Ahmed, SK., Swapna, P., Reddy, AM., Khan, IA., Sharma, S., Abdullah, ST. (2010). Anti-tubercular agents. Part 5: Synthesis and biological evaluation of benzothiadiazine 1,1-dioxide based congeners. *European Journal of Medicinal Chemistry*, Vol.45, No.10, (Jul, 2010), pp. 4545-4553, ISSN0223-5234.
- Karali, N., Gürsoy, A., Kandemirli, F., Shvets, N., Kaynak, FB., Özbey., Kovalishyn, V., Dimoglo, A. (2007). Synthesis and structure-antituberculosis activity relationship of 1H-indole-2,3-dione derivatives. *Bioorganic & Medicinal Chemistry*, Vol.15, No.17, (Jun, 2007), pp. 5888-5904, ISSN 0968-0896.
- Karthikeyan, SV., Bala, BD., Raja, VP., Perumal, S., Yogeewari, P., Sriram, D. (2010). A highly atom economic, chemo-, regio and stereoselective synthesis and evaluation of spiro-pyrrolothiazoles as antitubercular agents. *Bioorganic & Medicinal Chemistry Letters*, Vol. 20, No.1, (Oct, 2009), pp. 350-353, ISSN 0960-894X.
- Khasnobis, S., Escuyer, VE., Chatterjee, D. (2002). Emerging therapeutic targets in tuberculosis: post-genomic era. *Expert Opinion on Therapeutic Targets*, Vol. 6, No.1, (Feb 2002), pp. 21-40. ISSN: 1472-8222.
- Khoje, AD., Kulendrn, A., Charnock, C., Wan, B., Franzblau, S., Gundersen, LL. (2010). Synthesis of non-purine analogs of 6-aryl-9-benzylpurines, and their antimycobacterial activities. Compounds modified in the imidazole ring. *Bioorganic & Medicinal Chemistry*, Vol.18, No.20, (Aug, 2010), pp. 7274-7282, ISSN 0968-0896.
- Kini SG., bhat AR., Bryant B., Williamson J., Dayan FE. (2009). Synthesis, antitubercular activity and docking study of novel cyclic azole substituted diphenyl ether derivatives. *European Journal of Medicinal Chemistry*, Vol.44, No.2, (May, 2008), pp. 492-500, ISSN 0223-5234.
- Klimesova, V., Koci, J., Waisser, K., Kaustova, J., Mollmann, U. (2009). Preparation and in vitro evaluation of benzylsulfanyl benzoxazole derivatives as potential antituberculosis agents. *European Journal of Medicinal Chemistry*, Vol.44, No.5, (Jul, 2008), pp. 2286-2293, ISSN 0223-5234.
- Kremer, L., Nampoothiri, KM., Lesjean, S., Dover, LG., Graham, S., Betts, J., Brennan, PJ., Minnikin, DE., Loch, C., Besra, GS. (2001). Biochemical characterization of acyl carrier protein (AcpM) and malonyl-CoA:AcpM transacylase (mtFabD), two major components of *Mycobacterium tuberculosis* fatty acid synthase II. *The Journal Biological Chemistry*, Vol. 276, No.30, (Jul 2001), pp. 27967-27974. ISSN: 0021-9258.
- Larsen, MH., Vilchèze, C., Kremer, L., Besra, GS., Parsons, L., Salfinger, M., Heifets, L., Hazbon, MH., Alland, D., Sacchettini, JC., Jacobs, WR Jr. (2002). Overexpression of inhA, but not kasA, confers resistance to isoniazid and ethionamide in *Mycobacterium smegmatis*, *M. bovis* BCG and *M. tuberculosis*. *Molecular Microbiology*, Vol. 46, No.2, (Oct 2002), pp. 453-466. ISSN: 0950-382X.
- LeMagueres, P., Im, H., Ebalunode, J., Strych, U., Benedik, MJ., Briggs, JM., Kohn, H., Krause, KL. (2005). The 1.9 Å crystal structure of alanine racemase from *Mycobacterium tuberculosis* contains a conserved entryway into the active site. *Biochemistry*, Vol. 44, No.5, (Feb 2005), pp. 1471-1481. ISSN: 0006-2960.

- Leys, D., Mowat, CG., McLean, KJ., Richmond, A., Chapman, SK., Walkinshaw, MD., Munro, AW. (2003). Atomic structure of *Mycobacterium tuberculosis* CYP121 to 1.06 Å reveals novel features of cytochrome P450. *The Journal Biological Chemistry*, Vol. 278, No.7, (Feb 2003), pp. 5141-5147. ISSN: 0021-9258.
- Magalhães, ML., Pereira, CP., Basso, LA., Santos, DS. (2002). Cloning and expression of functional shikimate dehydrogenase (EC 1.1.1.25) from *Mycobacterium tuberculosis* H37Rv. *Protein Expression and Purification*, Vol. 26, No.1, (Oct 2002), pp. 59-64. ISSN: 1046-5928.
- Mahapatra, S., Yagi, T., Belisle, JT., Espinosa, BJ., Hill, PJ., McNeil, MR., Brennan, PJ., Crick, DC. (2005). Mycobacterial lipid II is composed of a complex mixture of modified muramyl and peptide moieties linked to decaprenyl phosphate. *Journal Bacteriology*, Vol. 187, No.8, (Apr 2005), pp.2747-2757. ISSN: 0021-9193.
- Manikannan, R., Venkatesan, R., Muthusubramanian., Yogeewari, P., Sriram, D. (2010). Pyrazole derivatives from azines of substituted phenacyl aryl/cyclohexyl sulfides and their antimycobacterial activity. *Bioorganic & Medicinal Chemistry Letters*, Vol.20, No.23, (Oct, 2010), pp. 6920-6924, ISSN 0960-894X.
- Mantu, D., Luca, MC., Moldoveanu, C., Zbancioc, G., Mangalagiu, II. (2010). Synthesis and antituberculosis activity of some new pyridazine derivatives. Part II. *European Journal of Medicinal Chemistry*. Vol.45, No.11, (Aug, 2010), pp. 5164-5168, ISSN 0223-5234.
- Mao, J., Yuan, H., Wang, Y., Wan, B., Pak, D., He, R., Franzblau, SG. (2010). Synthesis and antituberculosis activity of novel mefloquine-isoxazole carboxylic esters as prodrugs. *Bioorganic & Medicinal Chemistry Letters*, Vol.20, No.3, (Nov, 2009), pp. 1263-1268, ISSN 0960-894X.
- Marrakchi, H., Ducasse, S., Labesse, G., Montrozier, H., Margeat, E., Emorine, L., Charpentier, X., Daffé, M., Quémard, A. (2002). MabA (FabG1), a *Mycobacterium tuberculosis* protein involved in the long-chain fatty acid elongation system FAS-II. *Microbiology*, Vol. 148, No.4, (Apr 2002), pp. 951-960. ISSN: 1350-0872.
- Marrakchi, H., Lanéelle, G., Quémard, A. (2000). InhA, a target of the antituberculous drug isoniazid, is involved in a mycobacterial fatty acid elongation system, FAS-II. *Microbiology*, Vol. 146, No.2, (Feb 2000), pp. 289-296. ISSN: 1350-0872.
- McKinney, JD., Hönerzu Bentrup, K., Muñoz-Eliás, EJ., Miczak, A., Chen, B., Chan, WT., Swenson, D., Sacchettini, JC., Jacobs, WR Jr., Russell, DG. (2000). Persistence of *Mycobacterium tuberculosis* in macrophages and mice requires the glyoxylate shunt enzyme isocitrate lyase. *Nature*, Vol. 406, No.6797, (Aug 2000), pp. 735-738. ISSN: 0028-0836 EISSN: 1476-4687.
- McLean, KJ., Dunford, AJ., Neeli, R., Driscoll, MD., Munro, AW. (2007). Structure, function and drug targeting in *Mycobacterium tuberculosis* cytochrome P450 systems. *Archives of Biochemistry and Biophysics*, Vol. 464, No.2, (Aug 2007), pp. 228-240. ISSN: 0003-9861.
- Mdluli, K., Spigelman, M. (2006). Novel targets for tuberculosis drug discovery. *Current Opinion Pharmacology*, Vol. 6, No.5, (Oct 2006), pp. 459-467. ISSN: 1471-4892.
- Meganathan, R. (2001). Biosynthesis of menaquinone (vitamin K2) and ubiquinone (coenzyme Q): a perspective on enzymatic mechanisms. *Vitamins & Hormones*, Vol. 61, No.173, (Aug 2001), pp. 173-218. ISSN: 0083-6729.



- Meng, Q., Luo, H., Lu, Y., Li, W., Zhang, W., Yao, Q. (2009). Synthesis and evaluation of carbamate prodrugs of SQ109 as antituberculosis agents. *Bioorganic & Medicinal Chemistry Letters*, Vol.19, No.10, (May, 2009), pp. 2808-2810, ISSN 0960-894X.
- Monfeli, RR., Beeson, C. (2007). Targeting iron acquisition by *Mycobacterium tuberculosis*. *Infectious Disorders- Drug Targets*, Vol. 7, No.3, (Sep 2007), pp. 213-220. ISSN: 1871-5265.
- Morgunova, E., Meining, W., Illarionov, B., Haase, I., Jin, G., Bacher, A., Cushman, M., Fischer, M., Ladenstein, R. (2005). Crystal structure of lumazine synthase from *Mycobacterium tuberculosis* as a target for rational drug design: binding mode of a new class of purinetrione inhibitors. *Biochemistry*, Vol. 44, No.8, (Mar 2005), pp. 2746-2758. ISSN: 0006-2960,
- Navarrete-Vázquez, G., Molina-Salinas, GM., Duarte-Fajardo, ZV., Vargas-Villarreal, J., Estrada-Soto, S., Gonzalez-Salazar, F., Hernandez-Nuñez, E., Said-Fernández, S. (2007). Synthesis and antimycobacterial activity of 4-(5-substituted-1,3,4-oxadiazol-2-yl)pyridines. *Bioorganic & Medicinal Chemistry*, Vol.15, No.16, (Aug, 2007), pp. 5502-5508, ISSN 0968-0896
- Nava-Zuazo, C., Estrada-Soto, S., Guerrero-Alvarez, J., Leon-Rivera, I., Molina-Salinas, GM., Said-Fernández, S., Chan-Bacab, MJ., Cedillo-Rivera, R., Moo-Puc, R., Mirón-Lopez, G., Navarrete-Vázquez, G. (2010). Design, synthesis and in vitro anti protozoal, antimycobacterial activities of N-{2-[(7-chloroquinolin-4-yl)amino]ethyl} ureas. *Bioorganic & Medicinal Chemistry*, Vol.18, No.17, (Sep, 2010), pp. 6398-6403, ISSN 0968-0896.
- Odell LR., Nilsson MT., Gising J., Lagerlund O., Muthas D., Nordqvist A., Karlen A., Larhed M. (2009). Functionalized 3-amino-imidazol[1,2-a]pyridines: A novel class of drug-like *Mycobacterium tuberculosis* glutamine synthase inhibitors. *Bioorganic & Medicinal Chemistry Letters*, Vol.19, No.16, (Jun, 2009), pp. 4790-4793, ISSN 0960-894X.
- Oliveira, JS., Pinto. CA., Basso. LA., Santos. DS. (2001). Cloning and overexpression in soluble form of functional shikimate kinase and 5-enolpyruvylshikimate 3-phosphate synthase enzymes from *Mycobacterium tuberculosis*. *Protein Expression and Purification*, Vol. 22, No.3, (Aug 2001), pp. 430-435. ISSN: 1046-5928.
- Paiva, AM., Vanderwall, DE., Blanchard, JS., Kozarich, JW., Williamson, JM., Kelly TM. (2001). Inhibitors of dihydrodipicolinate reductase, a key enzyme of the diaminopimelate pathway of *Mycobacterium tuberculosis*. *Biochimica et Biophysica Acta*, Vol. 1545, No. (Feb 2001), pp. 67-77. ISSN: 0006-3002.
- Palomino, JC., Ramos, DF., da Silva PA. (2009). New anti-tuberculosis drugs: strategies, sources and new molecules. *Current Medicinal Chemistry*, Vol. 16, No.15, (Jan 2009), pp. 1898-1904. ISSN: 0929-8673.
- Parish, T., Stoker, NG. (2002). The common aromatic amino acid biosynthesis pathway is essential in *Mycobacterium tuberculosis*. *Microbiology*, Vol. 148, No.10, (Oct 2002), pp. 3069-3077. ISSN: 1350-0872.
- Patel, NB., Khan, RH., Rajani, SD. (2010) Pharmacological evaluation and characterizations of newly synthesized 1,2,4-triazoles. *European Journal of Medicinal Chemistry*, Vol.45, No.9, (Jun, 2010), pp. 4293-4299, ISSN 0223-5234.
- Pavelka, MS Jr., Chen, B., Kelley, CL., Collins, FM., Jacobs, Jr WR Jr. (2003). Vaccine efficacy of a lysine auxotroph of *Mycobacterium tuberculosis*. *Infection and Immunity*, Vol. 71, No.7, (Jul 2003), pp. 4190-4192. ISSN: 0019-9557.

- Pavelka, MS Jr., Jacobs, WR Jr. (1999). Comparison of the construction of unmarked deletion mutations in *Mycobacterium smegmatis*, *Mycobacterium bovis* bacillus Calmette-Guérin, and *Mycobacterium tuberculosis* H37Rv by allelic exchange. *Journal of Bacteriology*, Vol. 181, No.16, (Aug 1999), pp.4780-4789. ISSN: 0021-9193.
- Petrlikova, E., Waissner, K., Divisova, H., Husakova, P., Vrabcova, P., Kunes, J., Kolar, K., Stolarikova, J. (2010). Highly active antimycobacterial derivatives of benzoxazine. *Bioorganic & Medicinal Chemistry*, Vol. 18, No.23, (Oct, 2010), pp. 8178-8187, ISSN 0968-0896.
- Quémard, A., Sacchettini, JC., Dessen, A., Vilcheze, C., Bittman, R., Jacobs, WR Jr., Blanchard, JS. (1995). Enzymatic characterization of the target for isoniazid in *Mycobacterium tuberculosis*. *Biochemistry*, Vol. 26, No.8243, (Jul 1995), pp. 8235-8241. ISSN: 0006-2960.
- Rivers, EC., Mancera, RL. (2008). New anti-tuberculosis drugs in clinical trials with novel mechanisms of action. *Drug Discovery Today*, Vol.13, (Oct, 2008), pp. 1090-1098, ISSN 1359-6446.
- Sainath, SR., Raghunathan, R., Ekambaram, R., Raghunathan, M. (2009). In vitro activities of the newly synthesised ER-2 against clinical isolates of *Mycobacterium tuberculosis* susceptible or resistant to antituberculosis drugs. *International Journal of Antimicrobial Agents*, Vol.34, No.5, (Jul, 2009), pp. 451-453, ISSN 0924-8579.
- Samadhiya, P., Sharma, R., Srivastava, SK. Srivastava, SD. (2011). Synthesis and biological evaluation of 4-thiazolidinone derivatives as antitubercular and antimicrobial agents. *Arabian Journal of Chemistry*, doi: 10.1016/j.arabjc.2010.11.015, (Dec, 2010), ISSN 1878-5352.
- Sankar, C., Pandiarajan, K. (2010). Synthesis and anti-tubercular and antimicrobial activities of some 2r,4c-diaryl-3-azabicyclo[3.3.1]nonan-9-one *N*-isonicotinylhydrazone derivatives. *European Journal of Medicinal Chemistry*, Vol.45, No.11, (Aug, 2010), pp. 5480-5485, ISSN 0223-5234.
- Santos, JL., Yamasaki, PR., Chin, CM., Takashi, CH., Pava,n FR., Leite, CQF. (2009). Synthesis and in vitro anti *Mycobacterium tuberculosis* activity of a series of phthalimide derivatives. *Bioorganic & Medicinal Chemistry*, Vol.17, No.11, (May, 2009), pp. 3795-3799, ISSN 0968-0896.
- Sareen, D., Newton, GL., Fahey, RC., Buchmeier, NA. (2003). Mycothiol is essential for growth of *Mycobacterium tuberculosis* Erdman. *Journal of Bacteriology*, Vol. 185, No.22, (Nov 2003), pp. 6736-6740. ISSN: 0021-9193.
- Sarkar, S., Suresh, MR. (2001). An overview of tuberculosis chemotherapy - a literature review. *Journal of Pharmacy and Pharmaceutical Sciences*, Vol. 14, No.2, (Jul 2011), pp. 148-161. ISSN: 1482-1826.
- Sassetti, CM., Boyd, DH., Rubin, EJ. (2003). Genes required for mycobacterial growth defined by high density mutagenesis. *Molecular Microbiology*, Vol. 48, No.1, (Apr 2003), pp. 77-84. ISSN: 0950-382X.
- Savvi, S., Warner, DF., Kana, BD., McKinney, JD., Mizrahi, V., Dawes, SS. (2008). Functional characterization of a vitamin B12-dependent methylmalonyl pathway in *Mycobacterium tuberculosis*: implications for propionate metabolism during growth on fatty acids. *Journal of Bacteriology*, Vol. 190, No.11, (Jun 2008), pp. 3886-3895. ISSN: 0021-9193.

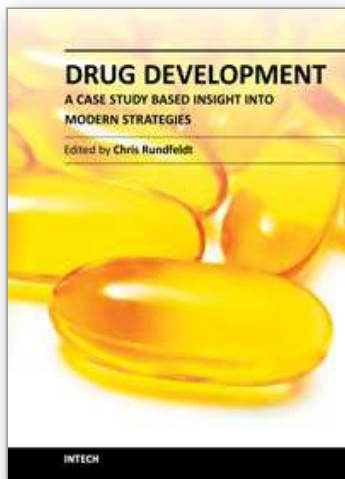
- Scarsdale, JN., Kazanina, G., He, X., Reynolds, KA., Wright HT. (2001). Crystal structure of the *Mycobacterium tuberculosis* beta-ketoacyl-acyl carrier protein synthase III. *The Journal of Biological Chemistry*, Vol. 276, No.23, (Jun 2001), pp. 20516-20522. ISSN: 0021-9258.
- Shi, R., Sugawara, I. (2010). Development of new anti-tuberculosis drug candidates. *The Tohoku Journal of experimental medicine*, Vol. 22, No.2, (Feb 2010), pp. 97-106. ISSN: 0040-8727
- Shiradkar, M., Suresh Kumar, GV., Dasari, V., Tatikonda, S., Akula, KC., Shah, R. (2007). Clubbed triazoles: A novel approach to antitubercular drugs. *European Journal of Medicinal Chemistry*, Vol.42, No.6, (Dec, 2006), pp. 807-816, ISSN 0223-5234.
- Singh, K., Singh, K., Wan, B., Franzblau, S., Chibale, K., Balzarini, J. (2011). Facile transformation of biginelli pyrimidin-2(1H)-ones to pyrimidines. In vitro evaluation as inhibitors of *Mycobacterium tuberculosis* and modulators of cytostatic activity. *European Journal of Medicinal Chemistry*, Vol.46, No.6, (Mar, 2011), pp. 2290-2294, ISSN 0223-5234.
- Slyden, RA., Barry, CE 3rd. (2002). The role of KasA and KasB in the biosynthesis of meromycolic acids and isoniazid resistance in *Mycobacterium tuberculosis*. *Tuberculosis (Edinburg, Scotland)*. Vol. 82, No.4, (Jan 2002), pp. 149-160. ISSN: 1472-9792.
- Smith, DA., Parish, T., Stoker, NG., Bancroft, GJ. (2001). Characterization of auxotrophic mutants of *Mycobacterium tuberculosis* and their potential as vaccine candidates. *Infection and Immunity*, Vol. 69, No.2, (Feb 2001), pp. 1142-1150. ISSN: 0019-9567.
- Srivastava, SK., Tripathi, RP., Ramachandran, R. (2005). NAD<sup>+</sup>-dependent DNA Ligase (Rv3014c) from *Mycobacterium tuberculosis*. Crystal structure of the adenylation domain and identification of novel inhibitors. *The Journal of Biological Chemistry*, Vol. 280, No.34, (Aug 2005), pp. 30273-30281. ISSN: 0021-9258.
- Strych, U., Penland, RL., Jimenez, M., Krause, KL., Benedik, MJ. (2001). Characterization of the alanine racemases from two mycobacteria. *FEMS Microbiology Letters*, Vol. 196, No.2, (Mar 2001), pp. 93-98. ISSN: 1574-6968.
- Sun, Z., Zhang, Y. (1999). Antituberculosis activity of certain antifungal and antihelmintic drugs. *Tubercle and Lung Disease*, Vol. 79, No.5, (Jan 1999), pp. 319-320. ISSN: 0962-8479.
- Suresh Kumar GV., Rajendra Prasad, Y., Mallikarjuna, BP., Chandrashekar, SM. (2010). Synthesis and pharmacological evaluation of clubbed isopropylthiazole derived triazolothiadiazoles, triazolothiadiazines and mannich bases as potential antimicrobial and antitubercular agents. *European Journal of Medicinal Chemistry*, Vol.45, No.11, (Aug, 2010), pp. 5120-51299, ISSN 0223-5234.
- Teo, JW., Thayalan, P., Beer, D., Yap, AS., Nanjundappa, M., Ngew, X., Duraiswamy, J., Liung, S., Dartois, V., Schreiber, M., Hasan, S., Cynamon, M., Ryder, NS., Yang, X., Weidmann, B., Bracken, K., Dick, T., Mukherjee, K. (2006). Peptide deformylase inhibitors as potent antimycobacterial agents. *Antimicrobial Agents and Chemotherapy*, Vol. 50, No.11, (Nov 2006), pp. 3665-3673. ISSN: 0066-4804.
- Termentzi, A., Khouri, I., Gaslonde, T., Prado, S., Saint-Joanis, B., Bardou, F., Amanatiadou, EP., Vizirianakis, I., Kordulakova, J., Jackson, M., Brisch, R., Janin, YL., Daffe, M., Tillequin, F., Michel, S. (2010). Synthesis, biological activity and evaluation of the mode of action of novel antitubercular benzofurobenzopyrans substituted on A

- ring. *European Journal of Medicinal Chemistry*, Vol.45, No.12, (Oct, 2010), pp. 5833-5847, ISSN 0223-5234.
- Turan-Zitouni, G., Kaplancikli, Z.A., Ozdemir, A. (2010). Synthesis and antituberculosis activity of some *N*-pyridyl-*N*-thiazolyldiazine derivatives. *European Journal of Medicinal Chemistry*, Vol.45, No.5, (Jan, 2010), pp. 2085-2088, ISSN 0223-5234.
- Turan-Zitouni, G., Ozdemir, A., Kaplancikli, Z.A., Benkli, K., Chevallet, P., Akalin, G. (2008). Synthesis and antituberculosis activity of new thiazolyldiazone derivatives. *European Journal of Medicinal Chemistry*, Vol.43, No.5, (Jul, 2007), pp. 981-985, ISSN 0223-5234.
- Vanheusden, V., Munier-Lehmann, H., Pochet, S., Herdewijn, P., Van Calenbergh, S. (2002). Synthesis and evaluation of thymidine-5'-O-monophosphate analogues as inhibitors of *Mycobacterium tuberculosis* thymidylate kinase. *Bioorganic and Medicinal Chemistry Letters*, Vol.12, No.19, (Oct 2002), pp. 2695-2698. ISSN: 0960-894X.
- Vicente, E., Perez-Silanes, S., Lima, L.M., Ancizu, S., Burguete, A., Solano, B., Villar, R., Aldana, I., Monge, A. (2009). Selective activity against *Mycobacterium tuberculosis* of new quinoxaline 1,4-di-*N*-oxides. *Bioorganic & Medicinal Chemistry*, Vol.17, No.1, (2008), pp. 385-389, ISSN 0968-0896.
- Weinberg, E.D., Miklossy J. (2008). Iron withholding: a defense against disease. *Journal of Alzheimer's Disease*, Vol. 13, No.4, (May 2008), pp. 451-463. ISSN: 1387-2877.
- Wube, A.A., Hufner, A., Thomaschitz, C., Blunder, M., Kollroser, M., Bauer, R., Bucar, F. (2011). Design, synthesis and antimycobacterial activities of 1-methyl-2-alkenyl-4(1H)-quinolones. *Bioorganic & Medicinal Chemistry*, Vol.19, No.1, (Nov, 2010), pp. 567-579, ISSN 0968-0896.
- Yang, C.L., Tseng, C.H., Chen, Y.L., Lu, C.M., Kao, C.L., Wu, M.H., Tzeng, C.C. (2010). Identification of benzofuro[2,3-*b*]quinoline derivatives as a new class of antituberculosis agents. *European Journal of Medicinal Chemistry*, Vol.45, No.2, (Nov, 2009), pp. 602-607 ISSN 0223-5234.
- Yang, F., Curran, S.C., Li, L.S., Avarbock, D., Graf, J.D., Chua, M.M., Lu, G., Salem, J., Rubin, H. (1997). Characterization of two genes encoding the *Mycobacterium tuberculosis* ribonucleotide reductase small subunit. *Journal of Bacteriology*, Vol. 179, No. 20 (Oct 1997), pp. 6408-6415. ISSN: 0021-9193.
- Yang, F., Lu, G., Rubin, H. (1994). Isolation of ribonucleotide reductase from *Mycobacterium tuberculosis* and cloning, expression, and purification of the large subunit. *Journal of Bacteriology*, Vol. 176, No.21, (Nov 1994), pp. 6738-6743. ISSN: 0021-9193.
- Yoya, G.K., Bedos-Belval, F., Constante, P., Duran, H., Daffe, M., Balatas, M. (2009). Synthesis and evaluation of a novel series of pseudo-cinnamic derivatives as antituberculosis agents. *Bioorganic & Medicinal Chemistry Letters*, Vol.19, No.2, (Nov, 2008), pp. 341-343, ISSN 0960-894X.
- Zhang, X., Hu, Y., Chen, S., Luo, R., Yue, J., Zhang, Y., Duan, W., Wang, H. (2009). Synthesis and evaluation of (S,S)-N,N'-bis[3-(2,2',6,6'-tetramethylbenzhydryloxy)-2-hydroxypropyl]-ethylenediamine (S2824) analogs with anti-tuberculosis activity. *Bioorganic & Medicinal Chemistry Letters*, Vol.19, No.21, (Nov, 2009), pp. 6074-6077, ISSN 0960-894X.
- Zhang, Y. (2004). Persistent and dormant tubercle bacilli and latent tuberculosis. *Frontiers Bioscience*, Vol. 1. No. 9, (May 2004), pp. 1136-1156. ISSN: 1093-9946.

- Zhang, Y. (2005). The magic bullets and tuberculosis drug targets. *Annual Review Pharmacology and Toxicology*, Vol. 45, (Feb 2005), pp. 529-564. ISSN: 0362-1642.
- Zhang, Y., Amzel, LM. (2002). Tuberculosis drug targets. *Current Drug Targets*, Vol. 3, No. 2 (Apr 2002), pp. 131-154. ISSN: 1389-4501.
- Zhang, Y., Post-Martens, K., Denkin, S. (2006). New drug candidates and therapeutic targets for tuberculosis therapy. *Drug Discovery Today*, Vol. 11, No. 1, (Jan 2006), pp. 21-27. ISSN: 1359-6446.

IntechOpen

IntechOpen



## **Drug Development - A Case Study Based Insight into Modern Strategies**

Edited by Dr. Chris Rundfeldt

ISBN 978-953-307-257-9

Hard cover, 654 pages

**Publisher** InTech

**Published online** 07, December, 2011

**Published in print edition** December, 2011

This book represents a case study based overview of many different aspects of drug development, ranging from target identification and characterization to chemical optimization for efficacy and safety, as well as bioproduction of natural products utilizing for example lichen. In the last section, special aspects of the formal drug development process are discussed. Since drug development is a highly complex multidisciplinary process, case studies are an excellent tool to obtain insight in this field. While each chapter gives specific insight and may be read as an independent source of information, the whole book represents a unique collection of different facets giving insight in the complexity of drug development.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Virgilio Bocanegra-García, Abraham García, Jose Prisco Palma-Nicolás, Isidro Palos and Gildardo Rivera (2011). Antitubercular Drugs Development: Recent Advances in Selected Therapeutic Targets and Rational Drug Design, Drug Development - A Case Study Based Insight into Modern Strategies, Dr. Chris Rundfeldt (Ed.), ISBN: 978-953-307-257-9, InTech, Available from: <http://www.intechopen.com/books/drug-development-a-case-study-based-insight-into-modern-strategies/antitubercular-drugs-development-recent-advances-in-selected-therapeutic-targets-and-rational-drug-d>

**INTECH**  
open science | open minds

### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen