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New Antitubercular Drugs Designed by Molecular Modification

Jean Leandro dos Santos, Luiz Antonio Dutra,
Thais Regina Ferreira de Melo and Chung Man Chin
School of Pharmaceutical Science – State University of São Paulo (UNESP)
Brazil

1. Introduction

Tuberculosis (TB) is an illness that results from infection with *Mycobacterium tuberculosis* (MTB). This aerobic bacillus have the cell wall with a high lipid content which result in a high degree of lipophilicity and resistance to alcohol, acids, alkali and some disinfectants. TB is the leading worldwide cause of mortality resulting from an infectious bacterial agent. The World Health Organization (WHO) estimates that almost one-third of world's population is infected with MTB, with 8.9-9.9 million incident cases by year (WHO, 2010).

MTB is epidemiologically characterized by high rate infectivity, so the one-third of latent infection population which remains a reservoir from mycobacterium is the major obstacle to the total control of the disease. In normal conditions, the bacteria has the ability to live in balance with immune response but in situations such as genetic impaired, intercurrent diseases (i.e. AIDS), malnutrition and medical interventions could occur an imbalance, and the MTB multiplies rapidly developing the disease (Gideon & Flynn, 2011).

The multidrug-resistant tuberculosis (MDR-TB) is another important problem to control TB worldwide. It has been reported that include patients who have never been treated with any TB drug demonstrated resistance. According to WHO, MDR-TB is responsible for approximately 460 thousand new cases per year and for about 740 thousand new patients infected by both MTB and HIV/AIDS. Recent estimates show that 10% of all new TB infections are resistant to at least one anti-TB drug.

The actual drug therapy for tuberculosis has involved administration of multiple drugs because it was clear that monotherapy led to the development of resistance (Barry & Blanchard, 2010). Short course chemotherapy involves taking isoniazid and rifampicin for 6 months with pyrazinamide and ethambutol supplement in the first 2 months (Ma et al., 2010).

For multidrug-resistance (MDR) and extensively drug resistance (XDR) are used the combination of first line drugs and seconde line drugs as aminoglycosides (amikacyn and kanamycin), polypeptides (capreomicyn, viomycin, envyomicin), fluoroquinolones (ofloxacin, levofloxacin, moxifloxacin, gatifloxacin), thioamides (ethionamide, prothionmide),

cycloserine, terizidone, para-aminosalicylic acid. This chemotherapy is less effective, longer, expensive and more toxic than the short course therapy (Ma et al., 2010).

Third line drugs include rifabutin, macrolides (clarithromycin), linezolid, thiacetazone, thioridazine, arginine, vitamin D are still being developed, have less or unproven efficacy and are very expensive (Laloo & Ambaram, 2010).

Since the discovery of rifampicin in 60' there is no more drugs developed to treat tuberculosis. Considering the increase of resistant the discovery of new antitubercular drugs is urgent. A new anti-TB drug must possess some characteristics such as wide spectrum of action, adequate posology to allow the patient compliance, short duration of treatment and adequate pharmacokinetic properties (half-life, decreased drug-drug interaction among others).

Among the strategies to introduce a new drug in the market, the molecular modification approach has showed to be promising. Several drugs in the market was developed using this strategy. This chapter aiming to discuss some strategies of molecular modification such as prodrug approach, molecular hybridization and biosisoterism in order to design and develop new drugs against M. tuberculosis.

2. Molecular modification

Molecular modification is an chemical alteration in a molecule which could be a lead compound or a drug aiming to enhance its pharmaceutical, pharmacokinetic or pharmacodynamics. This strategy has been used by medicinal chemistry by several years allowing the discovery of many available drugs present in the market. Among molecular modification used we can cite: prodrug approach, molecular hybridization and bioisosterism. Each one of this strategy will be introduced highlighting their application in TB drug discovery.

2.1 Prodrug approach

The first definition of prodrug was introduced by Albert in 1958 which define prodrug as “any compound that undergoes biotransformation prior to exhibit its pharmacological effects” (Albert, 1958). In order to improve this definition, Haper (1959) proposed the term latentiation. Drug latentiation is understood as “the chemical modification of biologically active compound to form a new compound that, upon in vivo enzymatic attack, will liberate the parent compound”. In general the prodrugs could be classified into two main classes: bioprecursors and carrier prodrugs.

Bioprecursors is a molecular modification strategy that generates a new compound-substrate for the metabolizing enzymes that after this biotransformation demonstrate biological activity. This approach generally does not use carriers. Several examples of drugs are available in the market used this strategy such as sulindac, acyclovir, losartan among others (Silva et al., 2005).

Carriers' prodrugs are designed using labile linkage between a carrier group and an active compound. This prodrug after chemical or biological biotransformation releases the parental drug responsible for the biological activity (Figure 01). The prodrug, per se, is usually inactive or less active than parental drug.

The carrier selection could explore two strategies: the first one is use an inactive carrier (non-toxic) and the second one use active compounds in order to obtain synergic effect. In the last strategy we could classified as mutual prodrugs or codrugs. In both situations is expected that then active compound (s) should be release with adequate kinetic hydrolysis reaction (Silva et al., 2005).

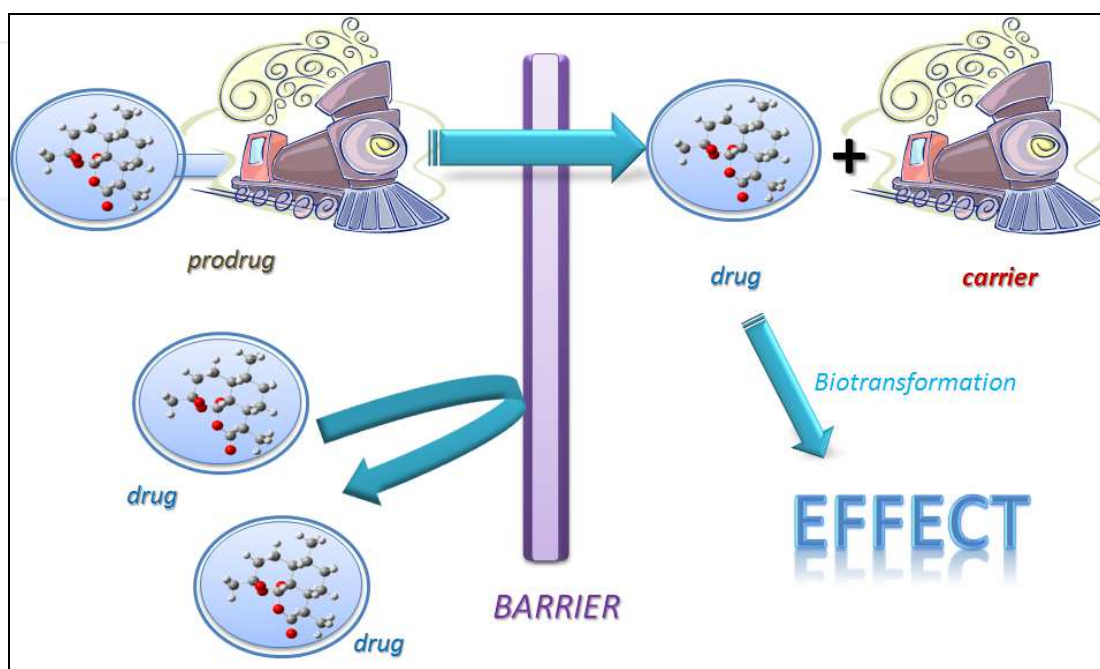


Fig. 1. Prodrug approach. The drug could present some inadequate characteristic related to pharmaceutical, pharmacokinetic or pharmacodynamic phase. As the drug is not able to win barriers due this inadequate characteristic the effect is not observed or is decreased. The use of the prodrug approach can solve this problem. After biotransformation the drug can act demonstrating the optimization of the effect.

The prodrug approach has been used by several researches in order to find new antitubercular compounds (Chung et al., 2007).

Some antitubercular drugs such as pyrazinamide, isoniazide and ethionamide could be considered as bioprecursor prodrugs.

Pyrazinamide is bioconverted by intracellular antimicrobial pyrazinamidase to pyrazinoic acid (Figure 2). This last one can decrease the pH surroundings the *M. tuberculosis* preventing growth. Furthermore, pyrazinoic acid can cross through mycobacterial membrane allows lowering of cytoplasmatic pH leading to the disruption of membrane transport and energy depletion (Zhang, 2005). Pyrazinamide resistance could be found in tubercle bacillus that present mutation encoding pyrazinamide/nicotinamidase (*pncA*).

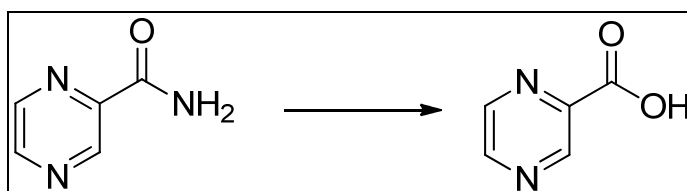


Fig. 2. Pyrazinamide conversion to pyrazinoic acid.

Several pyrazinoic prodrugs with increased lipophilic properties have demonstrated activity against *M. tuberculosis*. Some substituted pyrazinoic esters demonstrated 100-fold more active than pyrazinamide against *M. tuberculosis* with high plasma stability (Figure 3) (Cynamon et al., 1995).

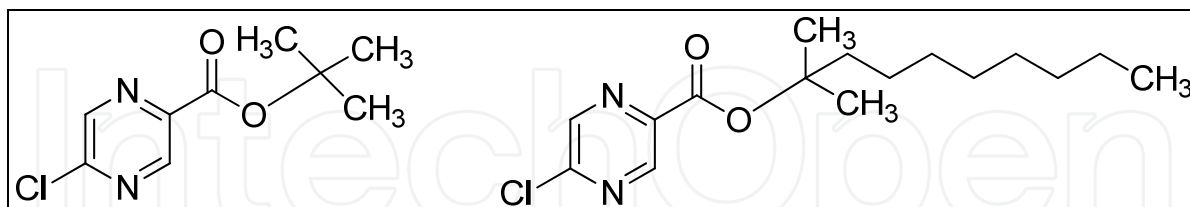


Fig. 3. Chemical structures of some substituted pyrazinoic esters.

Other pyrazinoic and quinoxaline esters derivatives were prepared and evaluated against *M. tuberculosis*. The compounds 4-acetoxybenzyl esters of pyrazinoic acid and 4'-acetoxybenzyl 2-quinoxalinecarboxylate demonstrated MIC values of 1-6,25 µg/mL (Seitz et al., 2002) (Figure 4).

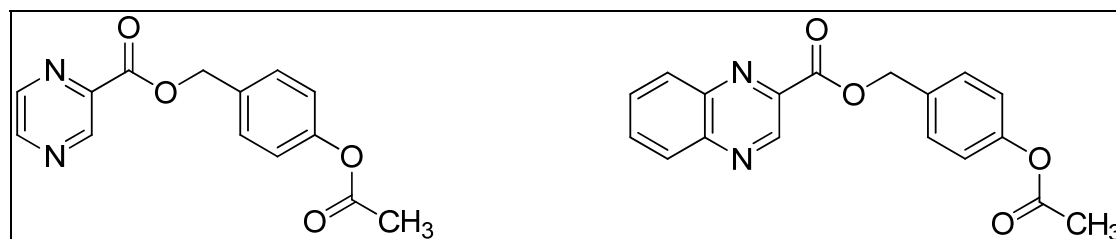


Fig. 4. Pyrazinoic and quinoxaline esters derivatives.

Another interesting study about pyrazinoic prodrugs was performed by Simões and co-workers (2009). The authors synthesized and compared a series of esters and amides prodrugs based on pyrazinamide structure (Figure 5). All compounds demonstrated higher lipophilicity (log P) than pyrazinamide. The esters derivatives demonstrated better in vitro activity against *M. tuberculosis* (MIC = 10-20 µg/mL) than amide derivatives (MIC = > 800 µg/mL) with suitable stability in presence of plasma.



Fig. 5. Ester and amide derivatives of pyrazinoic acid synthesized by Simões and co-workers (2009).

The use of prodrug approach to obtain new esters prodrugs such as pyrazinamide analogues seems to be an important strategy to discovery new drugs with improved pharmacokinetic and pharmacodynamic properties.

The isoniazide, a first line drug to the treatment of *M. tuberculosis*, was discovered in 1950. Isoniazid is a prodrug that is activated through an oxidation reaction catalyzed by the enzyme katG which demonstrate catalase-peroxidase activity. After conversion, the drug is

biotransformed into reactive species capable to acylate an enzyme system found in the mycobacterium. It has been proposed that one of this system is the enzyme inhA which is involved in the biosynthesis of mycolic acids (Mdluli et al., 1996). So, after activation by KatG the isonicotinoyl radical couples with NADH leading to adduct and inhibiting Inha.

One of the most problems with antitubercular therapy is the patient compliance and the long term therapy involving the use of several drugs. In order to decrease problems with therapy adhesion mutual prodrugs (or codrugs) have been reported. Using the prodrug approach it was reported the combination of 4-amino-salicylic acid (PAS) – a second line drug in the treatment, with isoniazide. The PAS treatment presents some inconvenience such as gastrointestinal irritation effects and inadequate bioavailability due to rapid phase II metabolism. In the other hand, isoniazide is rapidly absorbed after oral administration and quickly metabolized to inactive products (acetylhydrazide, diacetylhydrazide, N-acetylisoniazide and hydrazine) (Katleen, 1999). This metabolism reaction (acetylation) is reduce when PAS is previously administered, increasing half-life of isoniazide. So, using the prodrug approach it was proposed the association of both drugs into mutual prodrug in order to reduce gastrointestinal toxicity and extensive metabolism of PAS, reduce intestinal acetylation of isoniazid and increase the duration of drugs actions. All these hypotheses were confirmed after in vitro and in vivo studies (Figure 6) (Prateek et al., 2007).

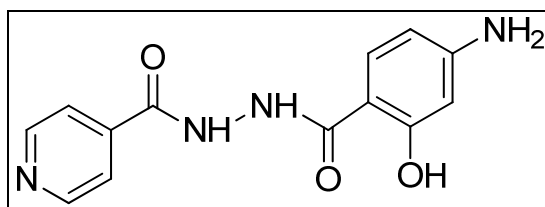


Fig. 6. Chemical structure of the mutual prodrug proposed by Prateek and co-workers (2007).

In order to decrease the toxicity and prolonged half-life of isoniazide, polymeric prodrugs were synthesized and evaluated. Micellar systems of polyethyleneglycol-poly(aspartic acid) copolymer and N-methylene phosphonic chitosan were used as carrier to obtain isoniazid prodrugs. The micellar prodrugs demonstrated activity against *M. tuberculosis* (Silva et al., 2001).

The same polymeric prodrugs approach was also explore to design norfloxacin derivatives. It was considered that the use of mannosyl ligands as carriers that can be used to target macrophages increasing the drug levels in this cell (Gordon & Rabinowitz, 1989; Roseeuw et al., 2003).

Ethionamide is a prodrug which similar mechanism of action of isoniazide. After oxidation by catalase-peroxidase the drug is bioconverted to an active acylating agent, ethionamide sulfoxide, which inactive inhA enoyl reductase (Figure 7) (Johnsson et al., 1995).

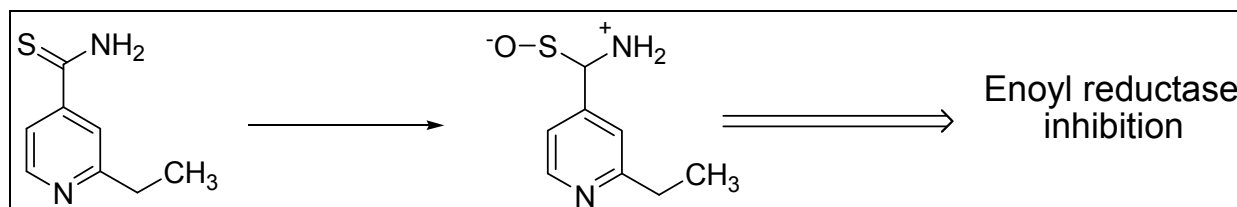


Fig. 7. Mechanism of action of ethionamide.

The association of TB and HIV infection is dramatic. The immune system is weakened in HIV patients allowing reactivation of latent TB and makes these patients more susceptible to drug-resistant strains. It has been estimated that two-thirds of the patients diagnosed with TB are also HIV seropositive (Shindikar, 2005). The usual treatments of HIV use nucleoside analogs (i.e. zidovudine) associated with other drugs. In this context, mutual prodrugs of antimycobacterial agents (such as isoniazid, norfloxacin and ciprofloxacin) and HIV nucleoside analogs (such as zidovudine, stavudine and lamivudine) were synthesized and evaluated. The zidovudine prodrugs were assayed at 6.25 $\mu\text{g/mL}$ against *M. tuberculosis* strain H37Rv and demonstrated 99% inhibition (with fluoroquinolones derivatives) and 90% of inhibition (with isoniazide) (Figure 8). The compounds also have inhibited HIV-1 replication (Sriram et al., 2005; Sriram et al., 2004).

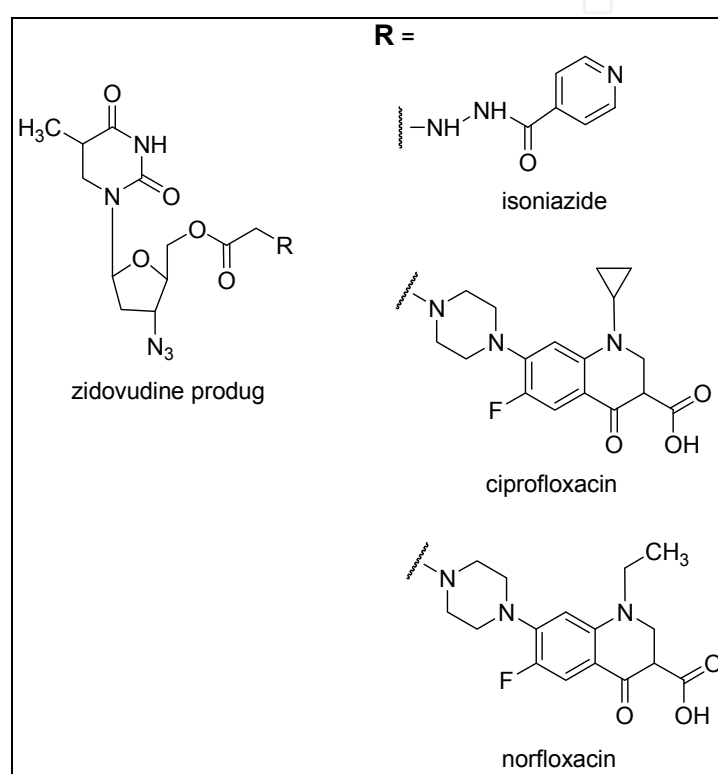


Fig. 8. Zidovudine prodrugs.

2.2 Molecular modification

The “one-target-one-drug” paradigm conducted the drug design on 20th century. Although very drugs used in therapy have been designed using this approach for a one drug for a single target, many diseases remains inadequately treated today. Considering that this approach fails to treat some diseases, the drug discovery explores the hybridization between molecules in order to modulate multiple targets. The molecular hybridization can be useful to improve the main unsuccessful causes of fail in drug discovery such as lack of efficacy and poor safety (Morphy & Rankovic, 2006).

Nowadays there are different approaches to multiple target therapy used mainly in unresponsive patient's conditions such as: a) use of two or more individual tablets (or other formulation); b) use of fixed dose combination therapy which two or more drugs are

combined in a single tablet (or other kind of formulation); c) use of single molecular entity which combine multiple targets actions. The first strategy has the disadvantage of inadequate compliance for the patients once they will have to use several drugs during the day in order to control some symptoms. Example of this kind of situation could be represented by hypertension or diabetes treatment. When someone compares the second and third strategies one important difference is that the use of a single chemical entity reduce the risk of drug-drug interaction and allows obtaining new compounds that can be patented. However, the challenge to design a compound multiple ligand with adequate ratio to different receptors is high. On the other hand, the combination of drugs in the same formulation favours fast development in order to obtain new commercial product by the pharmaceutical companies and it allows prolonged patent life of some old drugs. Superiority of combination and drug-drug interaction studies must be performed in this kind of strategy (Morphy & Rankovic, 2007).

Schematically, the Figure 9 shows the use of molecular hybridization strategy. The drug A interacts only with the receptor A. The drug B interacts only with the receptor B. It is prohibitive the interaction between drug A and receptor B (and vice versa) but is possible to design compounds that can interact with both receptors contributing synergically for a desire effect.

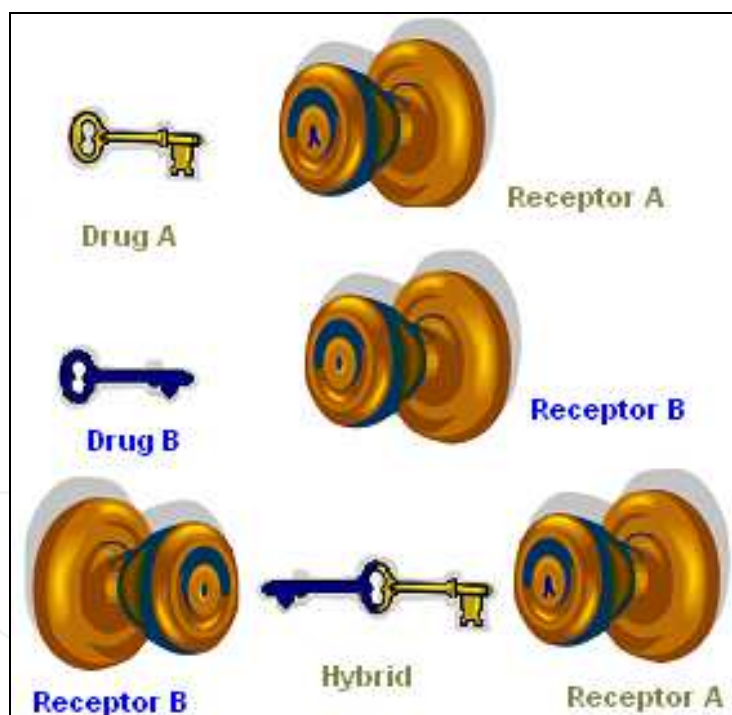


Fig. 9. Molecular hybridization strategy – analogy to “lock-key” model.

The drug design of hybrid compound must consider three different situations: a) the desired subunits are linked by a spacer agent; b) both subunits are linked without spacer agent and they are fused; c) the desired activities are merged in a new structure. The Figure 10 represents these different situations in order to design a new drug.

The combination of multiple actions in the same drug is an interesting strategy in tuberculosis treatment in order to contribute to therapy compliance, improve the activity

and reduce resistance. One fruitful example using this strategy could be represented by Figure 11 which demonstrated the use molecular hybridization of isoniazid and one quinolone derivative to increase the antimycobacterial activity of the novel compounds. This compound was able to maintain high survival rate reducing in vivo the colony-forming unit (CFU) with little few lung lesion and reduce splenomegaly (Shindikar & Viswanathan, 2005).

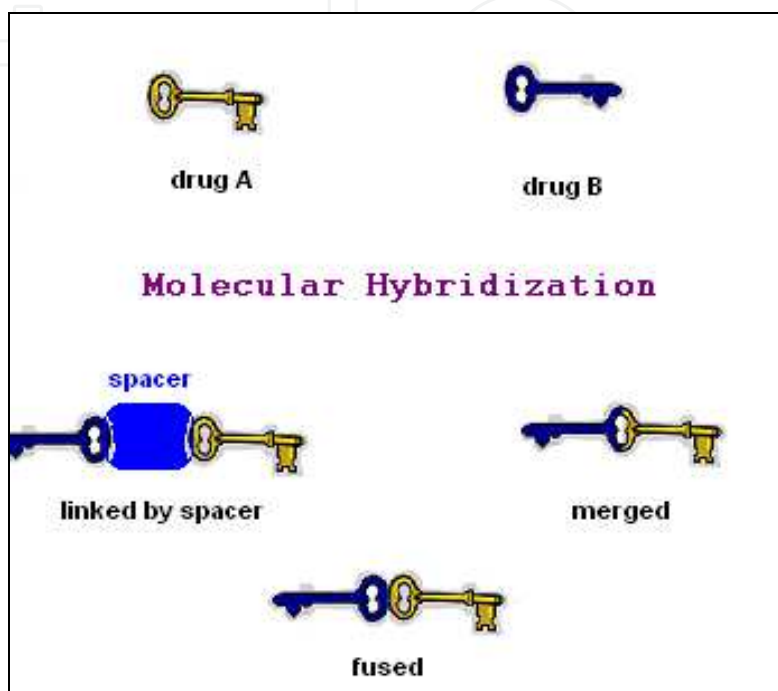


Fig. 10. Different hybrid compounds obtained by molecular hybridization.

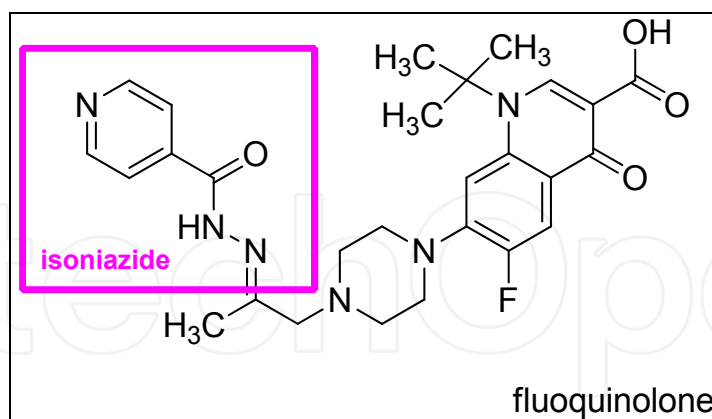


Fig. 11. Molecular hybridization between fluorquinole and isoniazid.

Similar molecular hybridization approach was performed using a fluorquinole derivative and pyrazinamide through Mannich bases. The compounds obtained demonstrated in vitro and in vivo antitubercular activity. The compound presented in the Figure 12 demonstrated higher log P than pyrazinamide. The log P is an important property to be evaluated in novel effective compounds due to lipophilic characteristics of the *M. tuberculosis* wall. In vitro studies showed that the compound was more active than pyrazinamide demonstrating important activity against multi drug resistant *M. tuberculosis*. Furthermore, the compound

was able to decrease thorough in vivo studies the bacterial load in lung and spleen tissues (Sriram et al., 2006). This result shows that the use of this approach can increase the activity of compounds.

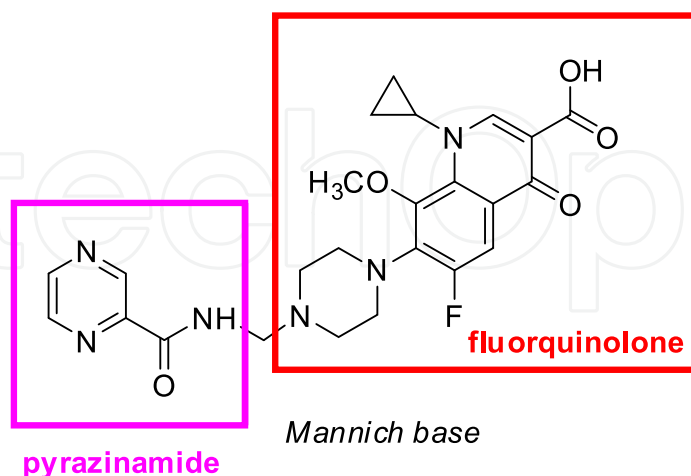


Fig. 12. Molecular hybridization between fluorquinolone and pyrazinamide.

Some phthalimide derivatives obtained through molecular hybridization between thalidomide and dapsone designed to be active against *M. leprae* was evaluated against *M. tuberculosis*. The compounds demonstrated in vitro activity with selective index higher than 80. This hybridization strategy shows to be promising in discovery compounds with wide spectrum of action in *Mycobacterium* sp (Santos et al., 2009).

2.3 Bioisosterism

The term isosterism was first defined by Languimuir in 1919 as atoms or organic or inorganic molecules which possess the same number and/or arrangement of electrons examples such as C=O and N=N; CO₂ and NO₂ (Burger, 1991). Grimm formulated in 1925, the hydride displacement law which explain that the addition of hydrogen to an atom confers properties of the next highest atomic number (i.e. the fluorine anion F⁻ and the hydroxyl anion HO⁻ present some analogies according to Grimm law) (Grimm, 1925). Erlenmeyer proposed the definition of isosteres as elements, molecules or ions which present the same number of electrons at the valence level expanding the definition (Erlenmeyer, 1932).

Currently bioisosteres is understood as groups or molecules which have a chemical and physical similarity producing broadly similar biological effects (Thornber, 1957). Burger classified and subdivided bioisosteres in two broad categories: classic and non-classic (Burger, 1970). The classical bioisosteres is subdivided in: a) monovalent atoms or groups; b) divalent atoms or groups; c) trivalent atoms or groups; tetravalent atoms and e) ring equivalents (Table 1).

The non-classical bioisosteres do not present the steric and electronic definition of classical isosteres, furthermore they do not have the same number of atoms of the substituent or moiety replaced. Among non-classical bioisosteres we could cite: functional groups, non-cyclic or cyclic and retroisosterism.

Monovalent	Divalent	Trivalent	Tetravalent
-OH, -NH2 – CH3, -OR	-CH2-	=CH-	=c=
-F, -Cl, -Br, -I, -SH, -PH2	-O-	=N-	=Si=
-Si3, -SR	-S-	=P-	=N+=
	-Se-	=As-	=As+=
	-Te-	=Sb-	=Sb+=
			=P+=

Table 1. Classic biososteres atoms and groups.

The bioisosterism approach is an important molecular modification tool that allows the discovery of several drugs in the market. The drugs discovered using this strategy that are in the markets usually known as “me too” (Lima & Barreiro, 2005).

This strategy has been used to discovery new compounds to treat tuberculosis. One example is the class of fluoquinolones. Fluoquinolones demonstrated, besides Gram-negative and Gram- positive activity, antitubercular activity. This class of drugs is known to inhibit bacterial DNA replication and transcription by binding to DNA-gyrase-DNA complex. The use of fluorquinolones occurs mainly in patients with multidrug-resistance (MDR). The most actives quinolones for the treatment of TB are: ciprofloxacin, sparfloxacin, ofloxacin, moxifloxacin and levofloxacin (Renau et al., 1996). Studies comparing the bactericidal activity of various fluoroquinolones against Mycobacterium tuberculosis in the latent and exponential growth phases.has demonstrated that most promising drugs are moxifloxacin and levofloxacin (Cremades et al., 2011). All these fluorquinolones drugs were obtained using bioisosteric replacement (Figure 13).

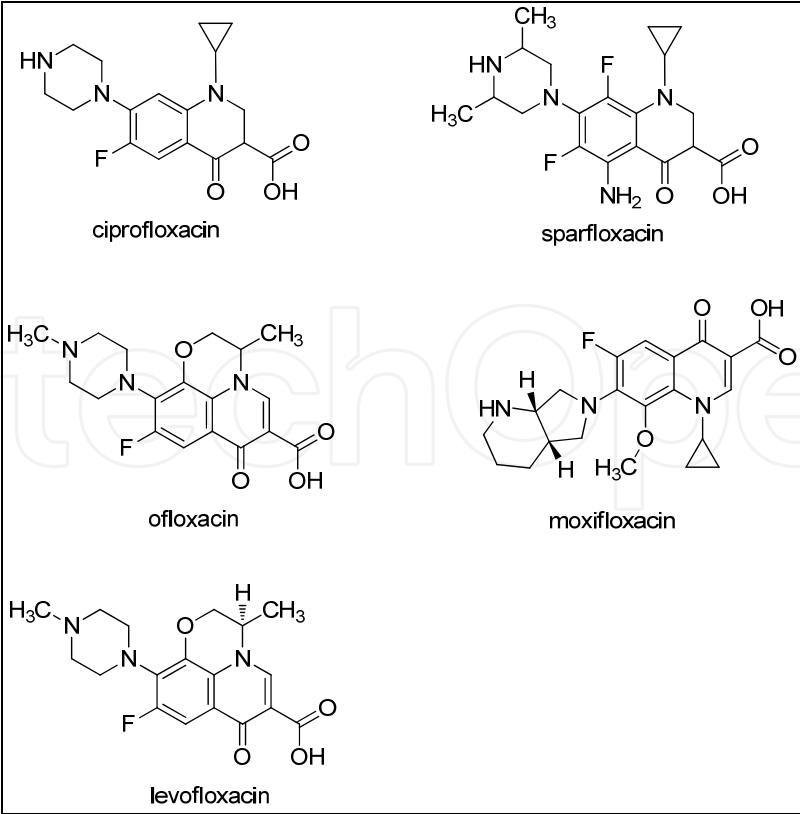


Fig. 13. Fluorquinolones active against Mycobacterium tuberculosis.

Linezolid is oxazolidinone drug belonging of antibacterial agents used in the treatment of nosocomial pneumonia and uncomplicated and complicated skin and soft tissue infections caused by select Gram-positive bacteria (Ford et al., 2001). The drug has been evaluated in the treatment of MDR tuberculosis showing interesting results (Pinon et al., 2010). Based on this interesting result, some oxazolidinone biosisoteres have been developed. PNU-100480 is an analog of linezolid in clinical trial to be used in tuberculosis treatment (Leach et al 2011). Others linezolid derivatives such as radezolid and torezolid are obtained by isosteric replacement and these drugs are under clinical trial (Figure 14) (Leach et al 2011).

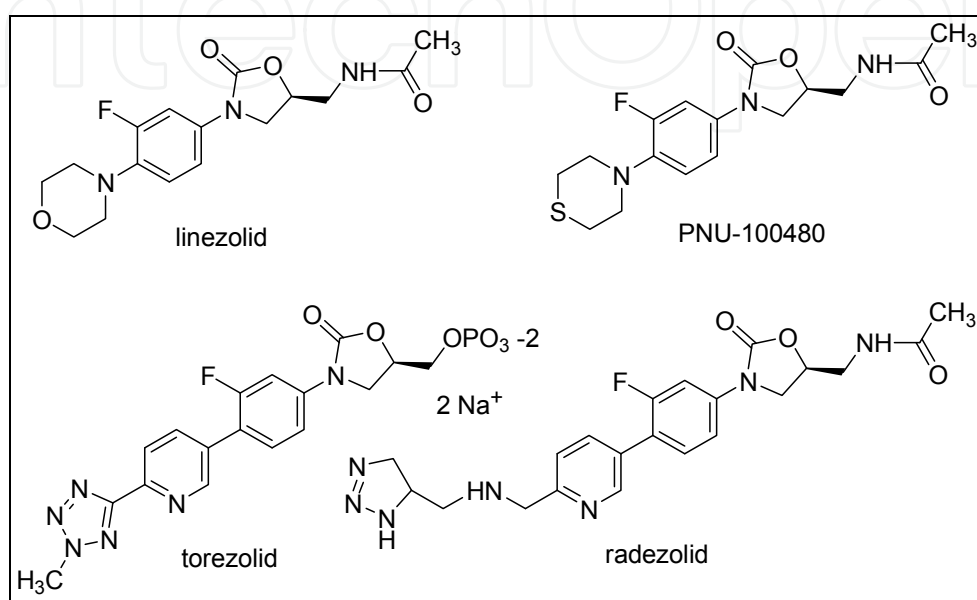


Fig. 14. Chemical structure of linezolid bioisosteric derivatives.

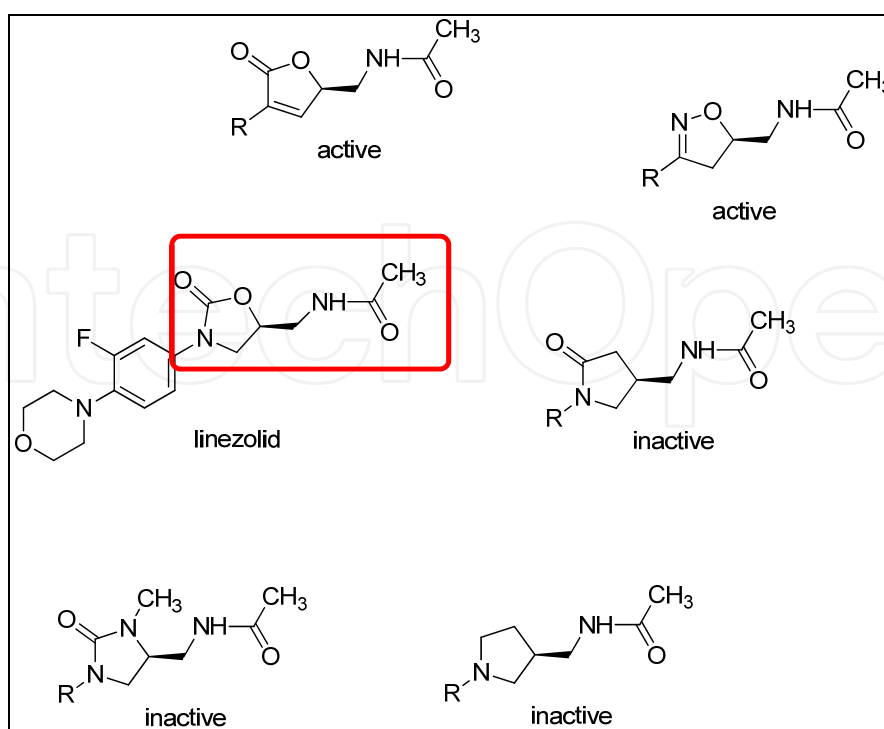


Fig. 15. Some active and inactive oxazolidinone isosteres derivatives.

The isosteric replacement not always leads to equal or more active compounds. Sometimes isosteric replacement leads to inactive compounds. Snyder and co-workers do not found relationship between some heterocyclic rings with oxazolidinone present in linezolid. However, the same authors demonstrate an interesting relationship with other active compounds (Figure 15). In general, with bioisosteric approach it is possible to find at least one (or sometimes more) equivalent systems.

Mycobacterium avium – *intracellulare* complex is one of the most common bacterial opportunistic in patients with AIDS. Clarithromycin and azithromycin are first-line agents for prevention and treatment. They are macrolide antibiotics which bacteriostatic activity due to bind to the 50S ribosomal unit (Wright, 1998). Azithromycin is a bioisoster of clarithromycin (Figure 16).

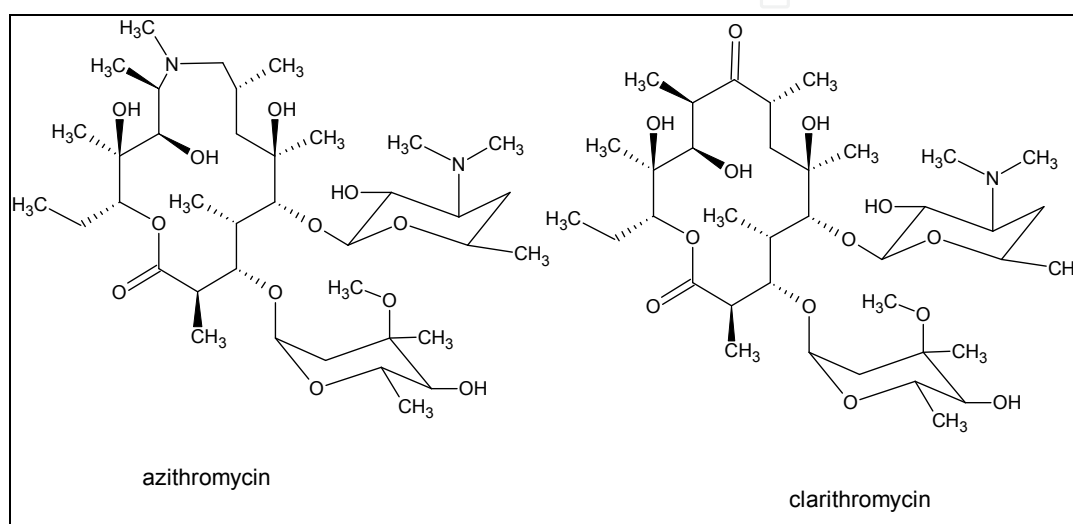


Fig. 16. Chemical structure of azithromycin and clarithromycin.

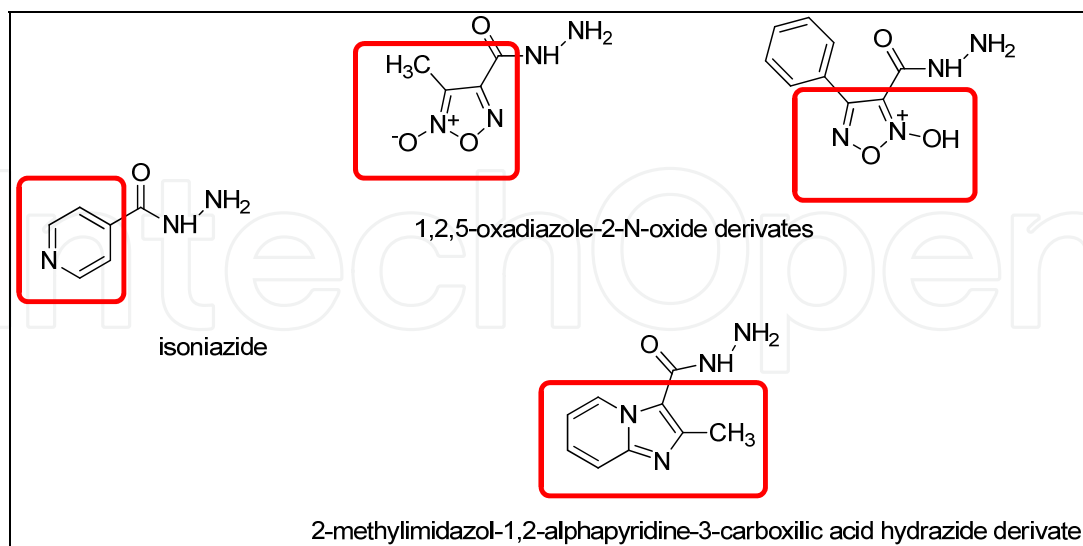


Fig. 17. Ring bioisosteres of pyridine presenting in isoniazid.

Bioisosteres of isoniazid has been designed exploring the bioisosteric replacement of pyridine ring to imidazo[1,2- α]-pyridine. However, the compound 2-methylimidazo[1,2- α]pyridine-3-carboxylic acid hydrazide demonstrate less antitubercular activity than

isoniazide (Kasimogullari & Cesur, 2004). The same results were observed by Santos and co-workers after biosisoteric replacement of pyridine to 1,2,5-oxadiazole-2-oxide (furoxan) (unpublished results) (Figure 17).

3. New drugs candidates for tuberculosis treatment

Tuberculosis drug development efforts have emerged in the last years. Despite the progress, none new drugs were found in this last years. Ryfampicin, discovered 40 years ago, was the last novel antibiotic introduced for the first treatment of tuberculosis. The search for new targets in *M. tuberculosis* that might be inhibited to eliminate all known strains is a global pursuit.

Several targets in *M. tuberculosis* have been reported. The inhibition of these targets could act in the growth and latent phase. Some targets in growth phase are GlgE (maltose metabolism), mycolic acid (mycolic acid metabolism), DprE1/DprE2 (cell wall metabolism), MshC (mycothiol ligase), HisG (histidine biosynthesis), AtpE (ATP synthesis), Def (protein processing), methionine aminopeptidase (protein processing). Some targets of dormant phase are isocitrate lyase (energy metabolism), proteosome complex (protein processing), L,D-transpeptidase (peptidoglycan metabolism), DosR (DevR) (regulation of dormancy) and CarD (stringent response) (Lamichhane, 2011). The most advances in new TB targets identification have been directed by the genome sequence of *M. tuberculosis*, however genome-derived target based approach have had little success until the present moment in the antibacterial class (Payne et al., 2007).

The discovery new antitubercular drugs must possess some desired profile such as: broad spectrum of action acting against MDR-TB and XDR-TB; adequate and shorten treatment duration reducing pill burden in order to reduce numbers of pills taken; adequate pharmacokinetic profile in order to reduce drug-drug interaction (to be administered with HIV drugs), desired target tissue levels and allows long half-life of the drug (Koul et al, 2011).

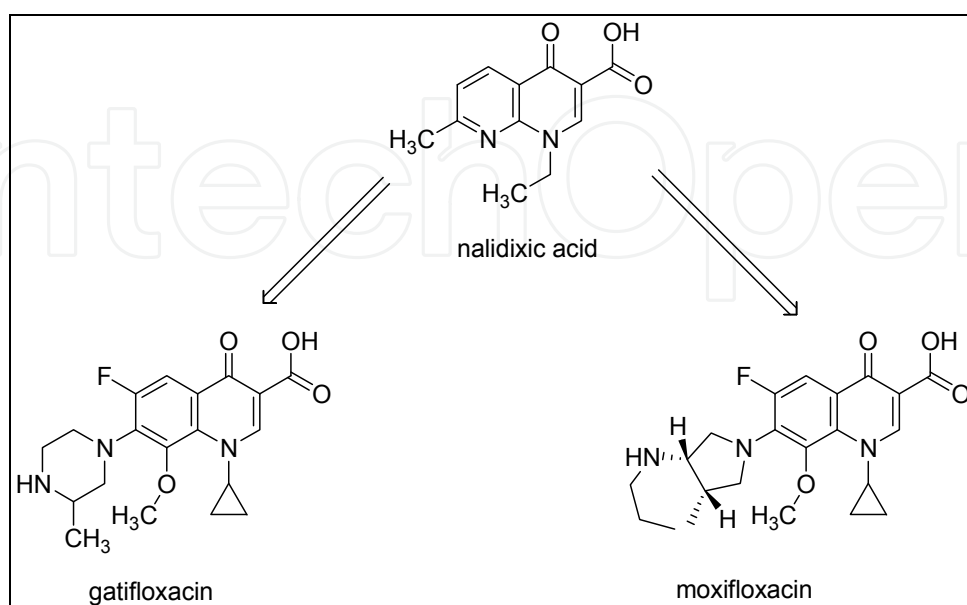


Fig. 18. Moxifloxacin and gatifloxacin designed using naldixic acid scaffold.

Currently the global TB development pipeline has nine candidates in different stages of clinical trial. These pipelines are: PNU 100480 (protein synthesis inhibitor), AZD 5847 (protein synthesis inhibitor), SQ 109 (cell wall and multitarget inhibitor), OPC67683 (cell wall and multitarget inhibitor), PA824 (cell wall and multitarget inhibitor), gatifloxacin (DNA gyrase inhibitor), moxifloxacin (DNA gyrase inhibitor), TMC 207 (ATP synthase inhibitor) and sudoterb (mechanism still unknown). Some of them are active in latent and active form against MDR-TB and XD-TB (Koul et al., 2011).

The most of currently pipeline TB drugs were developed using molecular modifications strategies. The fluorquinolones derivatives gatifloxacin and moxifloxacin were derivatized scaffolds from the parent nalidixic acid using the bioisosterism as molecular modification (Figure 18).

The metronidazole scaffold was used to design PA-824 and OPC-67683 using bioisosterism and molecular hybridization (Figure 19).

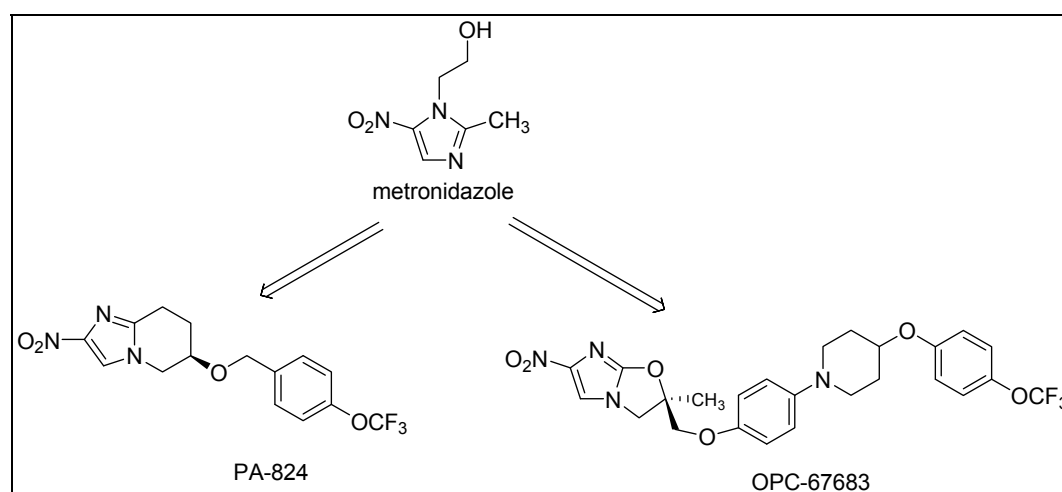


Fig. 19. Nitroimidazole derivatives designed by molecular modification of metronidazole.

The oxazolidinone derivative PNU-100480 was designed using linezolid as parent scaffold. This last one explored the bioisosterism as molecular modification tool (Figure 20).

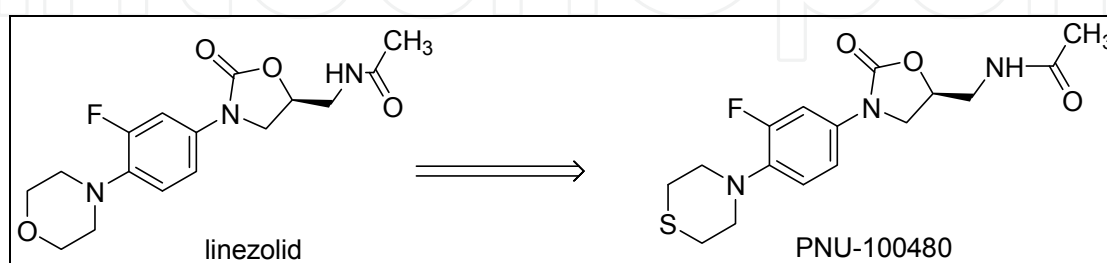


Fig. 20. PNU-100480 derivative of oxazolidinones linezolid.

The second line drug ethambutol was used as scaffold to develop the compound SQ109 using bioisosterism and molecular hybridization (Figure 21).

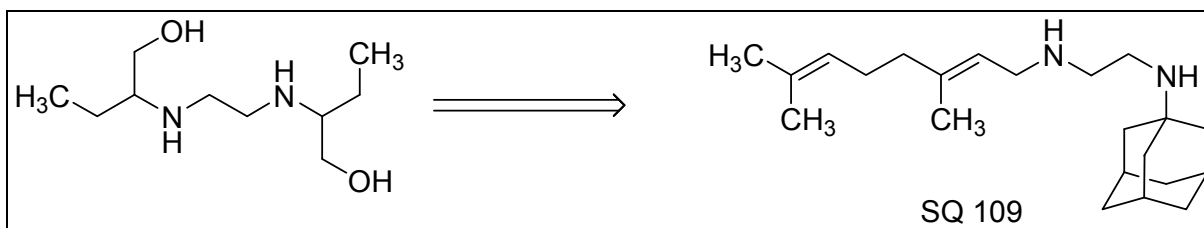


Fig. 21. 1,2-ethylenediamine derivative SQ109 designed from ethambutol.

4. Conclusion

The molecular modification is an important tool to discover new compounds to treat *Mycobacterium tuberculosis* infection. The use of this strategy has allowed finding more active and safe compounds with wide spectrum, acting include against MDR and XDR tuberculosis. The most currently pipeline drugs for TB in clinical trial were developed using molecular modification demonstrating the importance of this strategy in antitubercular drug discovery new agents.

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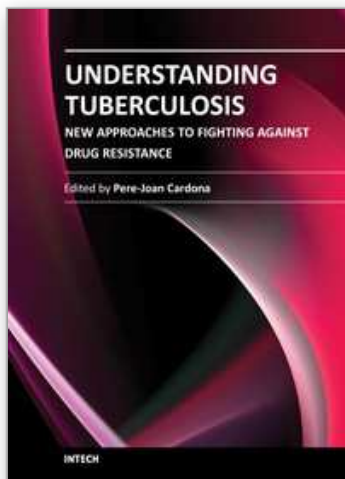
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Understanding Tuberculosis - New Approaches to Fighting Against Drug Resistance

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In 1957, a Streptomyces strain, the ME/83 (S.mediterranei), was isolated in the Lepetit Research Laboratories from a soil sample collected at a pine arboretum near Saint Raphael, France. This drug was the base for the chemotherapy with Streptomycin. The euphoria generated by the success of this regimen led to the idea that TB eradication would be possible by the year 2000. Thus, any further drug development against TB was stopped. Unfortunately, the lack of an accurate administration of these drugs originated the irruption of the drug resistance in Mycobacterium tuberculosis. Once the global emergency was declared in 1993, seeking out new drugs became urgent. In this book, diverse authors focus on the development and the activity of the new drug families.

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Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
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Phone: +86-21-62489820
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