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MEDICINAL CHEMISTRY AND DEVELOPMENT OF ANTITUBERCULAR DRUGS

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ABSTRACT: Tuberculosis (TB) is an ancient disease that has caused inestimable suffering and claimed millions of lives over the centuries. Resistant strains of *Mycobacterium tuberculosis* have slowly emerged especially in developing countries due to the lack of health care organisation in order to provide the long and costly treatment adapted to patients. In fact, 90% of all TB cases occur in the developing world. People with HIV/AIDS are especially susceptible to tuberculosis due to lack of immune system. Tuberculosis has been treated with combination therapy for over fifty years. Drugs are not used singly (except in latent TB or chemoprophylaxis), and regimens that use only single drug result in the rapid development of resistance and treatment failure.

INTRODUCTION: Tuberculosis (TB), an airborne infectious disease caused predominantly by *Mycobacterium tuberculosis* (*Mtb*), is a global health problem and a leading cause of death among adults in the developing world.

According to the World Health Organization (WHO), one third of the world's population is infected with *Mycobacterium tuberculosis* (*Mtb*). In 2008, there were an estimated about 9.4 million incident cases of TB, 11.1 million prevalent cases of TB, 1.3 million deaths from TB among HIV-negative people and an additional 0.52 million TB deaths among HIV-positive people¹.

Owing to population growth, the number of new cases arising each year is increasing globally, posing a continued health and financial burden in various parts of the world, particularly Asia and Africa. When coupled with the emergence of multidrug-resistant strains of *Mycobacterium tuberculosis* (MDR-TB), the scale of the problem becomes clear, as it will inevitably become even more difficult to treat TB in the future. It is now more than a decade since the World Health Organization declared TB "a global health emergency"².

Treatment of tuberculosis is protracted and burdensome. Tuberculosis control is further complicated by the synergy between tuberculosis and HIV/AIDS and by the development of multi-drug resistant tuberculosis (MDR-TB), which can be defined as strains that are resistance to at least isoniazid and rifampicin, important first line drugs used in TB treatment³.

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Another serious problem, in the context of MDR-TB, is the XDR-TB [abbreviation for extensively drug-resistant tuberculosis (TB), defined as multidrug-resistant tuberculosis plus resistance to a fluoroquinolone and an injectable second-line drug (capreomycin, kanamycin, or amikacin)], has recently emerged as a public health threat.⁴ Furthermore, common HIV/AIDS anti-retroviral therapies are not compatible with the current TB regimen because of shared drug toxicities and drug interactions, for example, as a consequence of rifampicin-induced cytochrome P₄₅₀ activation⁵. This has spurred new efforts to find new anti-tuberculosis drug candidates with novel modes of action, develop pipelines for drug discovery and development and, in particular, try to find new regimens that can considerably shorten the duration of effective therapy which would improve patient compliance and slow down the emergence of drug resistant strains⁶⁻⁷.

The biology of *Mycobacterium tuberculosis*: *M. tuberculosis*, the agent of human TB, was discovered in 1882 by Robert Koch and for a long time called after his name (the *Koch bacillus*). *Mycobacterium* genus are slow growing, aerobic Gram-positive bacteria that share the property of acid-fastness (Ziehl-Neelsen staining), due to their mycolic acid rich cell wall structure. The genus *Mycobacterium* includes the highly pathogenic organisms that cause tuberculosis, *Mycobacterium tuberculosis* (*M. tuberculosis*) and sometimes *M. bovis* and *M. leprae* (leprosy)⁸.

Tuberculosis (TB) is an infectious disease caused spread almost exclusively by airborne transmission. Although the disease can affect any site in the body, it most often affects the lungs. When persons with pulmonary TB cough, they produce TB bacteria containing tiny droplets which can remain suspended in the air for prolonged periods of time. Anyone who breathes air that contains these droplet nuclei can become infected with TB.

The cell wall of *Mycobacterium* species in its full structural and functional integrity is essential for its growth and survival in the infected host. In fact, some of the most effective anti-mycobacterial drugs including isoniazid and ethambutol are known to inhibit the biogenesis of cell wall dominated by covalently linked mycolic acids, arabinogalactan and peptidoglycan (AGP), the mycolic acids of which are

complemented by glycolipids such as α , α -trehalose monomycolate (TMM)⁸. This mycolic acid based permeability barrier shields the organism from environmental stress and contributes to disease persistence and the refractoriness of *M. tuberculosis* to many antibiotics. One of the most prominent macromolecular entities of mycobacterial cell wall is arabinan, a common constituent of both arabinogalactan (AG) and lipoarabinomannan (LAM). In the chemical setting of the mycolyl-arabinogalactan-peptidoglycan complex, AG forms an integral part of cell wall proper, whereas LAM, based on a phosphatidylinositol anchor, apparently exists in a state of flux.

LAM is an essential part of the cell envelope, which lacks covalent association with the cell wall core. Anchored in the cell membrane and traversing the cell wall, as well appearing as an excretory product, LAM has been implicated as a key surface molecule in host-pathogen interactions. The biosynthetic pathways leading to formation of the key mycobacterial cell wall components AG and mycolic acids are the targets for the rational design of new anti-tubercular agents.

The determination of the complete genome sequence of *M. tuberculosis*⁹ has had a profound effect on researchers in the TB field.

Multidrug resistant tuberculosis (MDR-TB): It refers to the simultaneous to at least Isoniazid (INH) and Rifampicin (RIF) with or without resistance to other drugs. Multidrug-resistance arises from the sharing of genes between different species or genera generally mediated by small pieces of extra-chromosomal DNA known as transposons or plasmids¹⁰.

Some antibiotics can actually induce the transfer of these resistance genes. Alternatively, as with the problematic multidrug-resistant *M. tuberculosis* (MDR-TB) strains accumulation of multiple point mutations in the chromosomal DNA can take place¹¹. Contamination of some commercial antibiotic preparations with the DNA (containing the inherent resistance genes) of the organisms that produce the antibiotic has been implicated as a source of drug resistance genes. The presence of DNA encoding drug resistance in antibiotic preparations has been proposed as a factor in the rapid development of multidrug resistance in bacteria¹².

Extensively Drug Resistant Tuberculosis (XDR-TB): XDR-TB, defined as extensively drug-resistant tuberculosis are cases of TB disease in persons whose *M. tuberculosis* isolates were resistant to isoniazid and rifampin and at least three of the six main classes of second-line drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine and *p*-aminosalicylic acid)¹³. XDR-TB is related to the poor management of multidrug resistant tuberculosis cases (which in turn is the consequence of poorly managed susceptible TB)¹⁴.

As per the new definition of XDR-TB it is defined as the MDR-TB that is resistant to quinolones and also to any one of kanamycin, capreomycin or amikacin. The principles of treatment of MDR-TB and for XDR-TB are the same. The main difference is that XDR-TB is associated with a much higher mortality rate than MDR-TB, because of a reduced number of effective treatment options. The epidemiology of XDR-TB is currently not well studied, but it is believed that XDR-TB does not transmit easily in healthy populations, but is capable of causing epidemics in populations which are already stricken by HIV and therefore more susceptible to TB infection¹⁵.

Transmission and Pathogenesis: A microbe becomes a pathogen when its biochemical pathways, either individually or acting in concert with one another, causes disease in a host. *M. tuberculosis* is an intracellular pathogenic bacterium, which has developed sophisticated mechanisms to survive inside host monocellular phagocytic cells and thus evade the immune system.

TB bacilli usually multiply first in the macrophages in the lung alveoli and alveolar ducts and in draining lymph nodes. Infected macrophages eventually get killed, progressively creating a primary tubercle. Delayed cutaneous hypersensitivity develops and together with other cellular immune reactions leads to the caseous necrosis of the primary complex. CD4+ T-cells accumulate in great numbers in the early granulomatous lesions, where they are later joined by CD8+T-cells.

Bacilli eventually spread to many parts of the body such as liver, spleen, meninges, bones, kidneys and lymph nodes, where they can either be a source of over disseminated TB or, more commonly, remain dormant.

CD4+ T-cells play a major role in containment of infection: progressive TB is usually associated with a Th2 T-cell response, whereas a pure Th1 response mediates protection. Th1 type cytokines, notably IFN- γ and TNF- α , are instrumental in walling off *M. tuberculosis* inside granulomatous lesions and controlling the evolution of the disease¹⁶.

In addition, T cells expressing a $\gamma\delta$ T-cell receptor with specificity for small phosphorylated ligands and T-cells with specificity for glycolipids are stimulated. Individuals with deficient IFN- γ signaling suffer from rapid evolution of the disease. Treatment with anti-TNF- α antibodies readily leads to tuberculosis reactivation in patients with rheumatoid arthritis^{17,18}.

Granulomas persist for years and efficiently contain *M. tuberculosis* in a state of dormancy, as long as the host remains immunocompetent¹⁹. Occasional decline in cell-mediated immunity leads to reactivation tuberculosis, most frequently seen in adults as a pulmonary disease with infiltration or cavity in the apex of the lung. This is the most infectious form of TB²⁰.

Current Anti-tuberculosis drugs: Currently, TB chemotherapy is made up of a cocktail of first-line drugs, isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB), given for six months. If the 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, that are generally either less effective or more toxic with serious side effects²¹ (**table 1**).

The WHO-recommended DOTS (directly observed treatment, short course) anti-TB therapy involves the administration of four drugs: isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB) or streptomycin (SM).

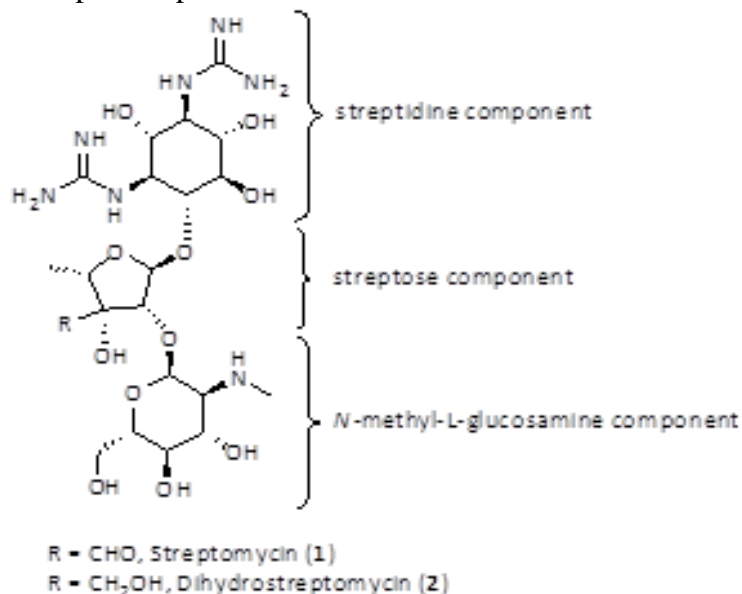
Treatment with these so called first-line drugs is carried out initially over two months, leading to the destruction of bacteria in all growth stages, after which treatment continues with RIF and INH alone for four months, where any residual dormant bacilli are eliminated by RIF and any remaining RIF-resistant mutants are killed by INH²².

TABLE 1: TARGETS AND MODE OF ACTION OF CURRENT TB DRUGS

Drug (Year of discovery)	Effect on bacterial cell	Mechanism of action	Targets
Streptomycin (1943)	Bacteriostatic	Inhibition of protein synthesis	Ribosomal S 12 protein of 30S rRNA
PAS (1944)	Bacteriostatic	Inhibition of folic acid & iron Metabolism	Unknown
Isoniazid (1951)	Bactericidal	Inhibition of cell wall mycolic acid & other multiple effects on DNA, lipids & carbohydrate & NAD metabolism	Primary acyl carrier protein reductase (InhA)
Pyrazinamide (1952)	Bactericidal	Disruption of membrane transport & energy depletion	Membrane energy metabolism
Cycloserine (1952)	Bacteriostatic	Inhibition of peptidoglycan synthesis	D-alanine recimase
Ethionamide (1956)	Bacteriostatic	Inhibition of mycolic acid synthesis	Acyl carrier protein reductase (InhA)
Kanamycin (1957)	Bactericidal	Inhibition of protein synthesis	Ribosomal S 12 protein 16S rRNA
Ethambutol (1961)	Bacteriostatic/ Bactericidal	Inhibition of cell wall arabinogalactan synthesis	Arabinosyl transferase
Quinolones (1963)	Bactericidal	Inhibition of DNA replication & transcription	DNA gyrase
Rifampin (1966)	Bactericidal	Inhibition of RNA synthesis	RNA polymerase β subunit

Streptomycin (1943): Streptomycin (1), an aminoglycoside antibiotic derived from *Streptomyces griseus* was the first antibiotic remedy for tuberculosis. It is made up of three components streptidine, streptose and *N*-methyl-L-glucosamine. Because of its poor absorbance from gastrointestinal tract it is administered intramuscularly and very occasionally by intrathecal route. It has an MIC value of 1 $\mu\text{g/ml}$ with 50-60% plasma protein bound

and a half-life of 5- 7 hr. It penetrates the inner membrane of *M.tuberculosis* and interferes with the binding of formyl-methionyl-tRNA to the 30S subunit of the ribosome. Different synthetic derivatives of streptomycin (dihydrostreptomycin, 2) have been synthesized and evaluated against *M. tuberculosis* (Fig. 1)^{23, 24} and was found to have almost the same antibacterial activity as the parent compound²⁵.

**FIG. 1: STRUCTURE OF STREPTOMYCIN (1) AND DIHYDROSTREPTOMYCIN (2)**

4-Aminosalicylic acid (PAS, 1944): 4-Aminosalicylic acid (3), commonly known as PAS was used as an oral TB therapy reported in 1946, although it was synthesized long before²⁶.

It is available in the form of sodium and calcium salt. *p*-aminosalicylic acid acts as an inhibitor of *M. tuberculosis* by impairing folate synthesis. It is occasionally used in the regimens for the treatment of TB caused by MDR-TB²⁷.

The mode of action of this drug is still unclear but it is suggested that it interferes with the salicylate-dependent biosynthesis of the iron chelating mycobactins involved in iron assimilation²⁸. It is thought to act via NF- κ B (nuclear factor-kappa B) inhibition and free radical scavenging (Fig. 2).

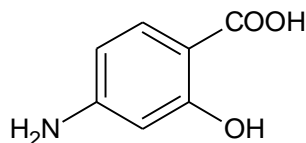


FIG. 2: 4-AMINOSALICYLIC ACID (3)

Isoniazid (INH, 1952):

1. Isoniazid (4) also known as isonicotinylhydrazine (INH) was discovered in 1952 and is a highly potent drug for the treatment of tuberculosis.²⁹ It is highly selective, acts almost exclusively against the *M. tuberculosis* complex and produces side effects in only 5% of patients. It is orally active and exhibits bacteriostatic action on the resting bacilli and has very low MICs (0.02-0.06 μ g/ml)³⁰ against these pathogens. INH is available in tablets, syrup and injectable forms (given intramuscularly and intravenously). It inhibits the synthesis of mycolic acids (long chain α -branched β -hydroxylated fatty acids) in *M. tuberculosis* by affecting the enzyme mycolate synthetase, which is unique for mycobacteria (Fig. 3)^{31, 22}.

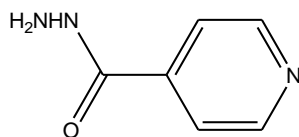


FIG. 3: ISONIAZID (4)

Isoniazid (4) is a prodrug and must be activated by bacterial catalase. INH enters the mycobacterial cell by passive diffusion³³. Recent developments have shown that peroxidative activation of isoniazid by the mycobacterial enzyme KatG generates isonicotinic acyl anion or radical that form adducts with NAD⁺ and NADP⁺. This complex will bind tightly to ketoenoylreductase known as InhA and prevents access of the natural enoyl-AcpM substrate. This mechanism inhibits the synthesis of mycolic acid in the mycobacterial cell wall.

Pyrazinamide (PZA, 1970): Pyrazinamide (5) is a derivative of nicotinamide, is first line drug of short course tuberculosis therapy (Fig. 4). It is active against semi dormant bacilli not affected by any other drug and is used only in combination with other drugs such as isoniazid and rifampin and shortens the therapy period to 6 months^{34, 35}. PZA in conjunction with rifampin is a preferred treatment for latent tuberculosis³⁶. The drug has no significant bactericidal effect and is thought to act by sterilizing effect, killing persisting semi-dormant bacilli in the lungs³¹.

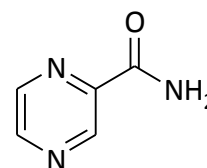


FIG. 4: PYRAZINAMIDE (5)

Resistance to PZA is usually accompanied by mutation in the *pncA* gene responsible for the production of pyrazinamidase³⁷. Some pyrazinoic esters have also been reported to possess good anti-tubercular activities³⁸.

Cycloserine (1955): D-Cycloserine (6), chemically defined as D-4-amino-3-isooxazolidone, is a structural analogue of amino acid D-alanine, is derived from *Streptomyces orchidaceus* and is active against a broad spectrum of bacteria, including *M. tuberculosis*³⁹ at concentrations of 5-20 μ g/ml. 6 is well absorbed and distributed throughout the body following oral administration (Fig. 5).

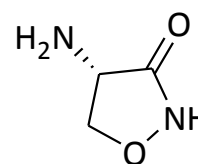


FIG. 5: D-CYCLOSERINE (6)

It blocks peptidoglycan biosynthesis by inhibiting the enzyme D-alanine racemase and D-alanyl alanine synthetase⁴⁰, enzyme necessary for the synthesis of UDP-muramyl-pentapeptide. Microorganisms treated with cycloserine accumulate a muramic-uridine-nucleotide-peptide, which differs from that produced by mycobacteria in the absence of terminal D-alanine dipeptide⁴¹. Cycloserine (6) produces severe side effects in the central nervous system that can also generate psychotic states with suicidal tendencies and epileptic convulsion.

Ethionamide (ETH, 1966): Ethionamide (7) is a derivative of isonicotinic acid and is bacteriostatic in nature (Fig. 6).

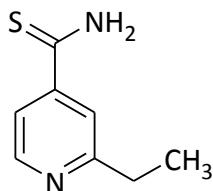


FIG. 6: ETHIONAMIDE (7)

ETH is useful for treating drug-resistant tuberculosis, but it causes frequent toxic side effects such as anorexia, vomiting, dysgeusia, neurological reactions and reversible hepatitis. In the last six years it was confirmed that this compound is a prodrug and is oxidized by ETH A (a flavoprotein monooxygenase)^{42, 43}. Oxidation of ethionamide by ETH A enzyme leads to a sulfinic acid which is likely to be further transformed to an amide and alcohol⁴³. Moreover, it had been known that the sulfinic acid produced was as active on mycobacterial growth *in vitro* as ethionamide^{44, 45, 46}.

Kanamycin (1957): Kanamycin (8) sulfate is an aminoglycoside antibiotic and is used either as orally or intravenously (Fig. 7). It is isolated from *Streptomyces kanamyceticus*⁷⁶. It affects the 30S ribosomal subunit and prevents the translation of RNA.

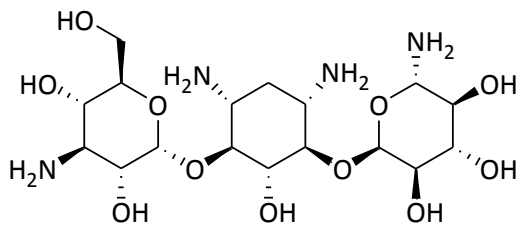


FIG. 7: KANAMYCIN (8)

Ethambutol (EMB, 1968): Commonly abbreviated EMB (9), is a synthetic amino alcohol (ethylene diamino-di-1-butanol)^{47, 48}. It is orally effective bacteriostatic anti-mycobacterial drug that is active against most strains of Mycobacterium (Fig. 8). It disrupts arabinogalactan synthesis by inhibiting the enzyme arabinosyl transferase. Mycolic acids attach to the 5'-hydroxyl groups of D-arabinose residues of arabinogalactan and form mycolyl-arabinogalactan-peptidoglycan complex in the cell wall. Disruption of the arabinogalactan synthesis inhibits the formation of this complex and leads to increased permeability of the cell wall⁴⁹.

The exact mechanism of action of EMB is still not known completely and probability of its interference in the synthesis of proteins and nucleic acids as antimetabolite is also documented. The genes *embAB* of *M. avium* encode the drug target for EMB, the arabinosyl transferase responsible for the polymerization of arabinose into the arabinan of arabinogalactan and overproduction of this ethambutol-sensitive target leads to EMB resistance⁵⁰.

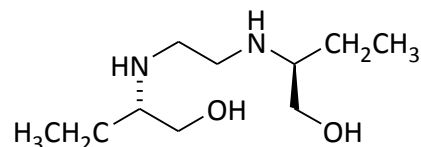
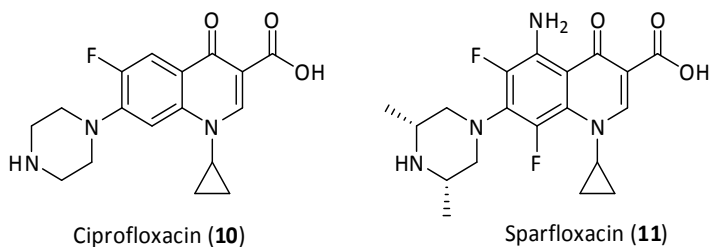


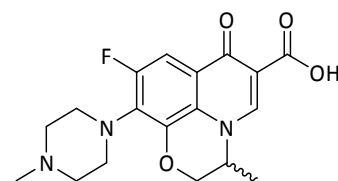
FIG. 8: ETHAMBUTOL (9)

Quinolones (1963): Fluoroquinolones (FQ), synthetic derivatives of nalidixic acid, display broad-spectrum anti-mycobacterial activity^{51, 52}. It has good *in vitro* potency with MIC 1µg/ml⁸⁶. These compounds have a good distribution throughout the body tissues and fluids following oral administration. The main effects of fluoroquinolones involve the interaction of the drugs with DNA-gyrase and DNA-topoisomerase IV⁴⁹⁻⁵³. Derivatives recognized with activity against mycobacteria are ciprofloxacin (10), sparfloxacin (11), ofloxacin (12a), levofloxacin (12b) etc (Fig. 9). Moxifloxacin (BAY 12-8039) is an 8-methoxyquinolone and is one of the most active quinolones against bacteria with resistance to penicillins and macrolides, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *M. tuberculosis*^{54, 55, 56}.



Ciprofloxacin (10)

Sparfloxacin (11)



R/S = Ofloxacin (12a)

S = Levofloxacin (12b)

FIG. 9: STRUCTURE OF QUINOLINE DERIVATIVES (10, 11, 12A & 12B)

Rifamycin derivatives (RIF, 1966): Rifampicin (**13**, INN) or rifampin (USAN) is a bactericidal antibiotic drug belongs to rifamycin group of semisynthetic antibiotics isolated from *Streptomyces mediterranei* (**Fig.10**)⁵⁷.

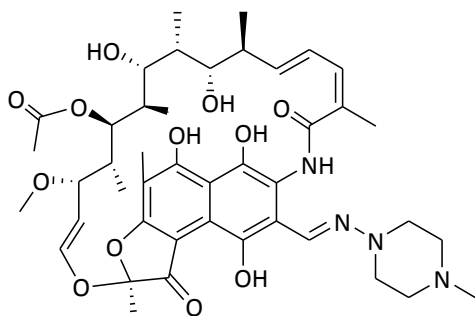


FIG. 10: RIFAMPICIN (13)

It is characterized by chromophoric naphthoquinone group spanned by a long aliphatic bridge and are potent inhibitors of prokaryotic DNA-dependent RNA polymerase, an enzyme necessary for RNA synthesis⁵⁸. RIF acts by inhibiting DNA-dependent RNA polymerase in bacterial cells by binding its beta-subunit resulting in the formation of a stable complex leading to suppression of transcription to RNA and subsequent translation to proteins. More specifically, the beta-subunit of this complex enzyme is the site of the action of the drug, although RIF binds only to the holoenzyme⁵⁹. To avoid rapid development of bacterial resistance

rifampicin is recommended in combination with other first line agents either isoniazid or ethambutol. RIF inhibits *M. tuberculosis* at concentrations ranging from 0.1 to 0.2 µg/ml⁶⁰.

Drugs currently in clinical evaluation for TB: Drug classes currently are evaluated in the clinic for their potential contribution to shortening treatment of active TB fall into two categories: (i) those already used in either first- or second-line TB treatment, or (ii) those that have completely novel mechanisms of action for TB. The former includes rifamycins, fluoroquinolones, and oxazolidinones. The latter includes nitroimidazoles, diarylquinolines, ethylene diamines, and pyrroles.

First- and second-line TB drug classes undergoing new clinical evaluation for a TB indication:

Rifamycin derivatives: Rifamycins, in particular rifampicin (**13**), are currently a cornerstone of first-line TB drug treatment, are now being re-explored for use at relatively high dosages^{61, 62}. Rifamycin derivatives, such as rifalazil (**14**, RLZ, also known as **KRM1648** or benzoxazinorifampicin), rifabutin (**15**) and rifapentine (**16**) have been synthesized to improve antimycobacterial activity and prolong half-life (**Fig. 11**).

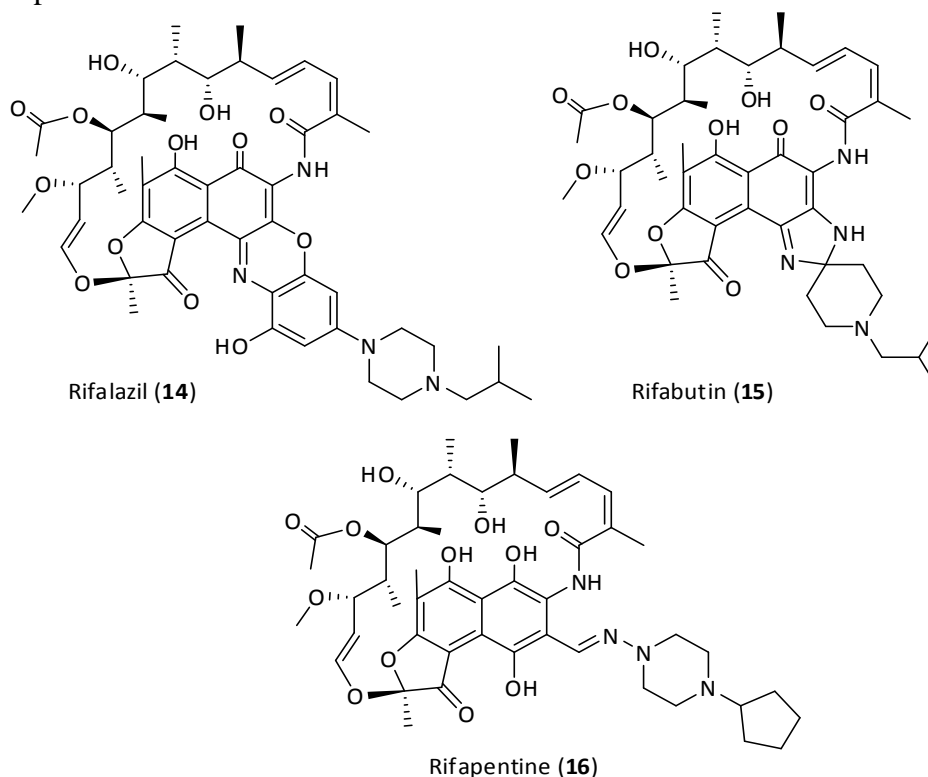


FIG. 11: RIFAMYCIN DERIVATIVES (14, 15 & 16)

Rifapentine (**16**) was approved by the FDA in 1998 appears to be safe and well-tolerated at once-weekly dosing and is currently being evaluated in Phase III efficacy trials for treatment of latent tuberculosis⁶³. Previously, relatively high intermittent doses of rifamycins have occasionally led to toxicities, primarily a flu-like syndrome, but this appears to be less of a problem when the rifamycin is dosed daily, and also less of an issue with rifapentine (**16**) than with rifampicin (**13**).

The underlying mechanism of the rifamycin-associated flu-like syndrome has not been definitively elucidated, although it is believed to be an immunoallergic response⁶². RLZ (**14**) is a new semi synthetic rifamycin derivative with a long half-life, which is highly active against a range of intracellular bacteria including *M. tuberculosis*, *Mycobacterium avium*, and *Helicobacter pylori*⁶⁴ and is more active than RIF or rifabutin against *M. tuberculosis* in mice both *in vitro* and *in vivo*⁶⁵.

RIF-resistant strains confer cross-resistance to all rifamycins, including RLZ⁶⁶, limiting the use of RLZ in the treatment of RIF-resistant TB.

Fluoroquinolones: The most efficacious of the fluoroquinolones against *M. tuberculosis* appear to be the 8-methoxy fluoroquinolones, gatifloxacin (**17**, GATI) and moxifloxacin (**18**, MXF) have a longer half-life and are more active against *M. tuberculosis* than ofloxacin and ciprofloxacin (**Fig. 12**)^{67, 68}.

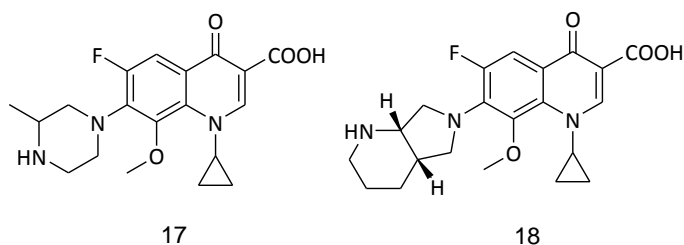


FIG. 12: STRUCTURE OF GATIFLOXACIN (17) AND MOXIFLOXACIN (18)

Each of these drugs is currently being evaluated in a Phase III pivotal trial for its ability to substitute for either ethambutol (GATI; MXF) or INH (MXF) in first-line TB treatment and to shorten therapy to four months from the current standard of six to nine months^{69, 70}. Combination therapy with MXF seems to be as effective as current standard drug combinations⁷¹.

Oxazolidinones: Oxazolidinones are a new class of compounds inhibits protein synthesis at an early stage by binding to 23S rRNA of the 50S ribosomal subunit. Linezolid is the first oxazolidinone to be developed and approved by the FDA to treat single- or multiple-resistant Gram-positive bacterial infections⁷². Concerning the use of this class against tuberculosis, many active compounds were found^{73, 74, 75}. However; the long term use of linezolid (**26**) may be plagued with forbidding side effects including anemia and peripheral neuropathy^{76, 77}. Two novel oxazolidinones, **Ranbezolid/RBx7644 (19)** and **RBx8700 (20)**, were active against MDR-TB and tubercle bacilli inside macrophages (**Fig.13**)⁷⁸.

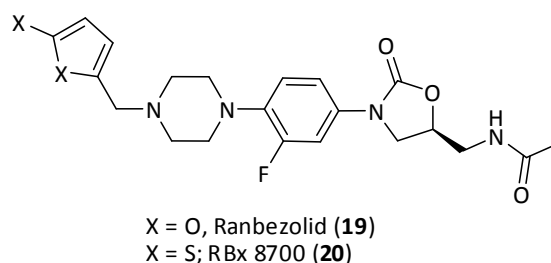


FIG. 13: STRUCTURE OF OXAZOLIDINONES (19 & 20)

Drug classes with novel mechanisms of action undergoing clinical evaluation for a TB indication:

Nitroimidazoles: Two novel nitroimidazoles are currently in clinical development: **PA-824 (21)** and **OPC67683 (22, Fig. 14)**.

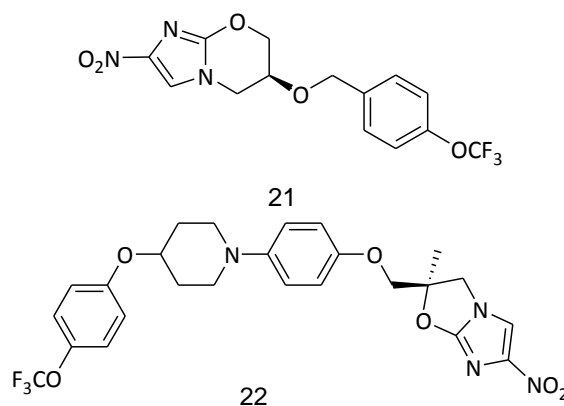


FIG.14. STRUCTURE OF PA-824 (21) AND OPC67683 (22)

PA824 (21) is highly active with MIC as low as 0.015–0.250 µg/ml against *M. tuberculosis* and MDR-TB and is currently undergoing Phase II clinical trials⁷⁹.

The mechanism of action of PA-824 is two-fold, as it inhibits *M.tb* cell wall lipid and protein synthesis; however, since this drug is also active against non-replicating bacteria it appears that inhibition of cell wall biosynthesis cannot be its sole mode of action. PA-824 is, in fact, a prodrug that is metabolized by *M. tb* before it can exert its effect and that may probably involve the bioreduction of its aromatic nitro group to a reactive nitro radical anion intermediate⁸⁰.

OPC-67683 (22) exhibits excellent *in vitro* activity against drug-susceptible and resistant *M. tb* strains and does not show cross-resistance with antituberculosis drugs⁸¹. It inhibits the synthesis of mycolic acid at the stage of methoxy-mycolic and the keto-mycolic acid syntheses (like INH)⁸².

Diarylquinolines (DARQ's): A series of diarylquinolines (DARQ's) has been developed by the Johnson and Johnson group that exhibit potent *in vitro* activity against *M.tb*⁸³. Modification of diarylquinolines led to the identification of diarylquinoline **R207910 (23)** (also known as **J compound** and **TMC207**) as the most potent, with minimum inhibitory concentration (MIC) of 0.003 µg/ml for *M. smegmatis* and 0.030 µg/ml for *M. tuberculosis* (**Fig. 15**)⁸⁴.

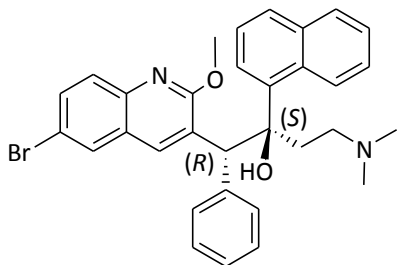


FIG. 15: STRUCTURE OF R207910/TMC207 (23)

TMC207 (23) exhibits excellent activity against drug susceptible, MDR and XDR *M.tb* strains, with no cross-resistance to current first-line drugs⁸⁵.

It acts by blocking the function of an essential membrane-bound enzyme that makes adenosine triphosphate (ATP). The two mutations affect the membrane-spanning α helices of the ATP synthase c subunit and may restrict binding of R207910 (**23**) to the enzyme. Although biochemical confirmation is now required, it is possible that the drug impedes assembly of the mobile disk or interferes with its rotational properties, leading to inadequate synthesis of ATP.

Structure of ATP synthase: ATP synthase is a biological rotary motor made up of two major structural domains, F₀ and F₁ (**Fig. 16**)⁸⁶. F₁ domain is composed of nine subunits (α 3, β 3, γ , δ , ϵ) and is located in the cytoplasm; the F₀ domain spans the cytoplasmic membrane, includes one a subunit, two b subunits, and 9 to 12 c subunits arranged in a symmetrical disk. The F₀ and F₁ domains are linked by central stalks (subunits γ and ϵ) and peripheral stalks (subunits b and δ). The proton-motive force fuels the rotation of the transmembrane disk and the central stalk, which in turn modulates the nucleotide affinity in the catalytic β subunit, leading to the production of ATP. The c subunit has a hairpin structure with two α helices and a short connecting loop.

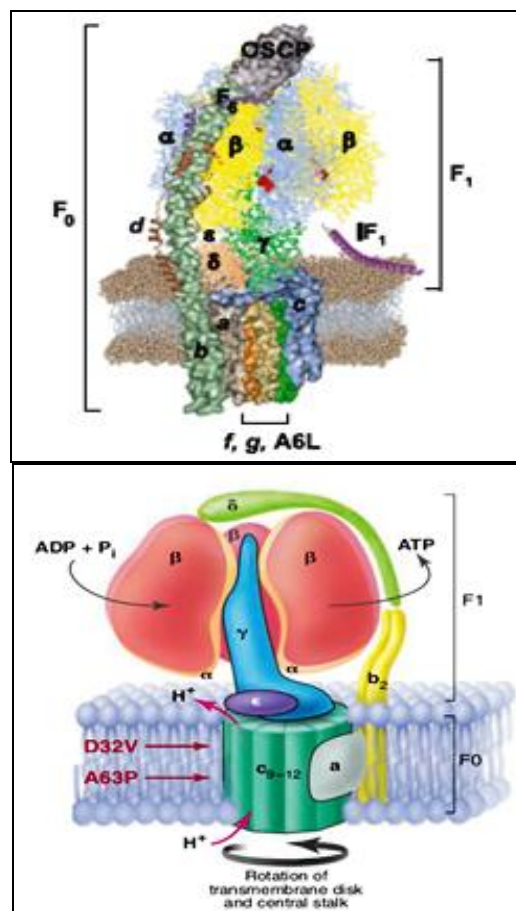


FIG. 16: ATP-SYNTHASE

Mode of action: TMC207 (**23**) acts by inhibiting Mycobacterium membrane-bound ATP synthase. This unique mechanism of action offers great potential as there is little similarity between the mycobacterial and human proteins encoded by the *atpE* gene that codes for the c subunit of ATP synthase, which has been identified as the specific target of TMC207⁸⁷.

A number of mutations (I66M and A63P) have been identified in the c subunit of TMC207-resistant strains^{87, 88} near the glutamate residue E61, which is

involved in proton transport and is necessary for the synthesis of ATP (**Fig.17**)⁸⁹.

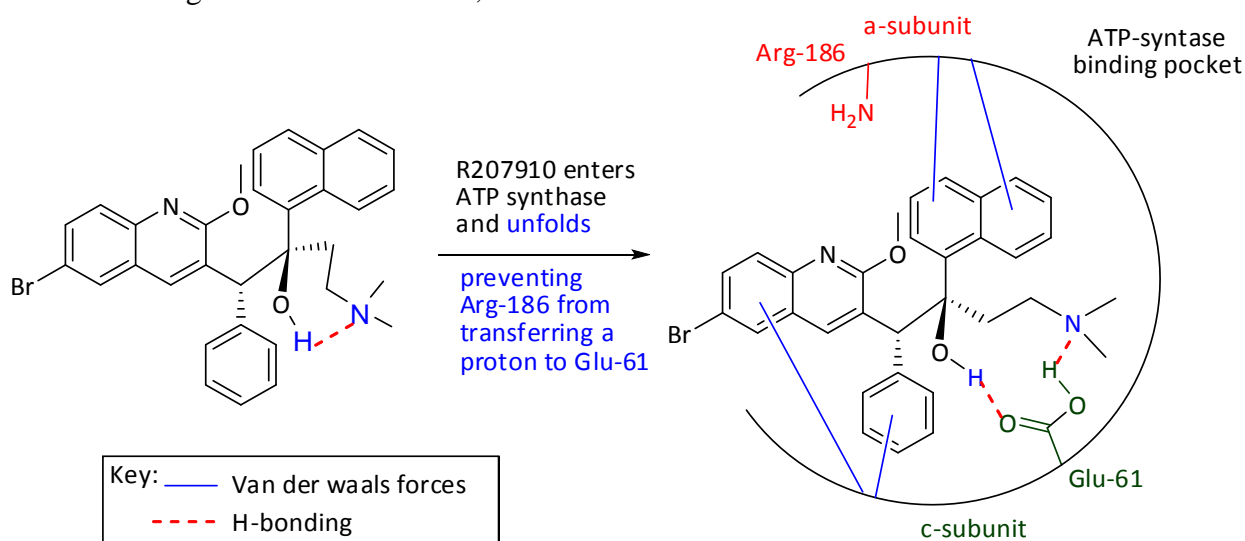


FIG. 17: MODE OF ACTION OF TMC207

Molecular modelling studies of *M.tb* ATP synthase have characterized the binding site of **TMC207** and suggested its probable mechanism of action. Normally, the sidechain of Arg-186 in the a-subunit adopts an extended conformation that reaches towards Glu-61 in the c-subunit to transfer a proton. This event leads to a conformational change in the c-subunit, making Arg-186 adopt a compact conformation and initiating a 308° rotation of the c-subunit. It is believed that the molecular mechanism of action of **TMC207** is to mimic the side chain of Arg-186⁸⁹. **TMC207** adopts a folded conformation in solution before binding owing to intramolecular hydrogen bonding⁹⁰. The lack of a cavity large enough to accommodate the bulky dimethyl amino

group of **TMC207** prevents the necessary rotation required for proton transfer, blocking ATP production.

Several potent quinoline-based anti-TB compounds, bearing an isoxazole containing side-chain have been identified. The most potent compounds, **24** and **25**, exhibited submicromolar activity against the replicating bacteria (R-TB), with minimum inhibitory concentrations (MICs) of 0.77 and 0.95 μM , respectively⁹¹. Also, **24** and **25** were shown to retain their anti-TB activity against rifampin, isoniazid, and streptomycin resistant *M.tb* strains (**Fig. 18**).

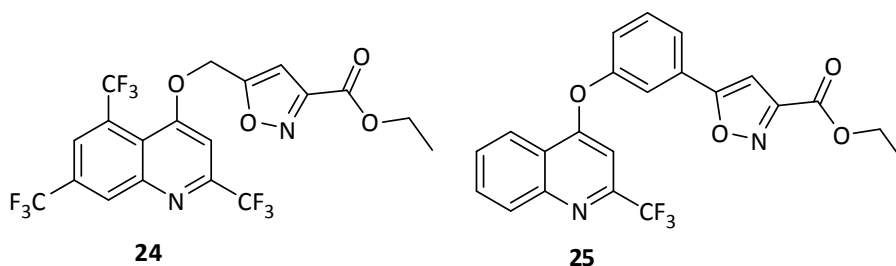


FIG.18. STRUCTURE OF POTENT QUINOLINE-BASED ANTI-TB COMPOUNDS (24 & 25)

A series of 4-quinolylylhydrazones was synthesized and tested *in vitro* against *Mycobacterium tuberculosis*, most showed 100% inhibitory activity at a concentration of 6.25 $\mu\text{g/ml}$. The most potent compound **26** exhibited 100% inhibition at concentration of 2.6 $\mu\text{g/ml}$ (**Fig.19**)⁹².

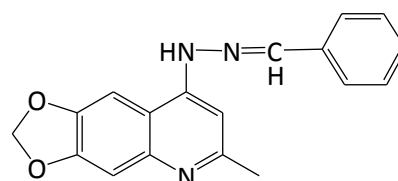


FIG. 19: STRUCTURE OF 4-QUINOLYLHYDRAZONE DERIVATIVE (26)

A new series of 20 quinoline derivatives possessing triazolo, ureido and thioureido substituents was synthesized. Compounds **27**, **28** and **29** inhibited *Mycobacterium tuberculosis* H37Rv up to 96%, 98% and 94% respectively, at a fixed concentration of 6.25 µg/ml.

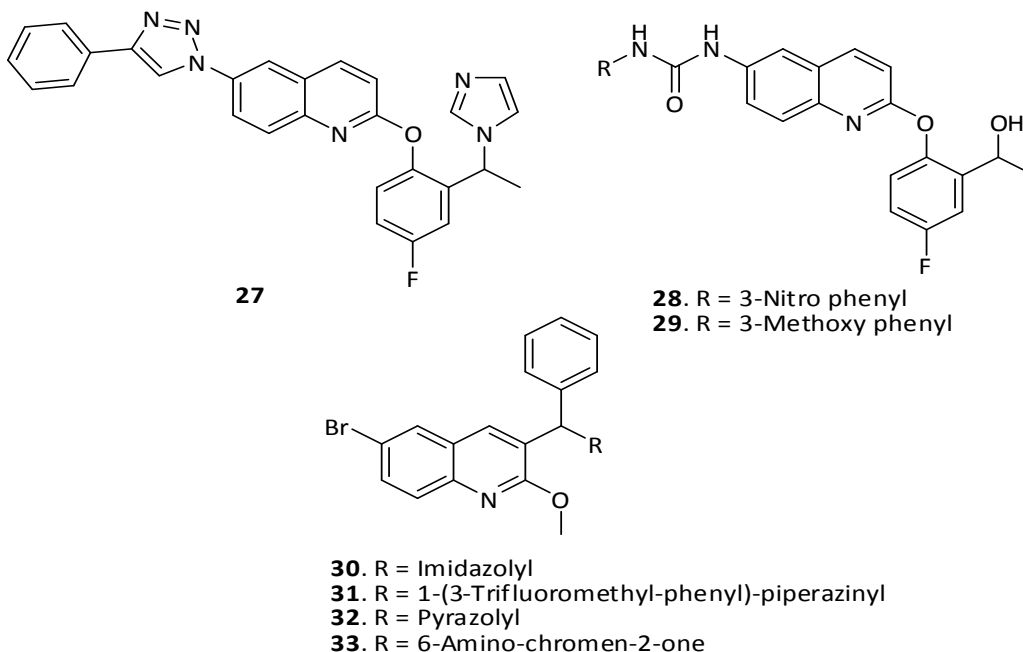


FIG. 20: STRUCTURE OF QUINOLINE DERIVATIVES (27-33)

Ethylene diamines: From the structure of ethambutol (**9**), a modern chemical approach was undertaken leading to the synthesis of many chemical libraries of diaminated analogues.⁹⁴ Remarkably, **SQ109** (**34**) turned out to be a very efficient antimycobacterial, also effective on MDR strains (**Fig. 21**). Moreover, the favorable pharmacological properties of compound **32**⁹⁵ as well as a synergistic effect with other antituberculosis drugs⁹⁶ should lead to clinical trials which were scheduled to start in 2006.

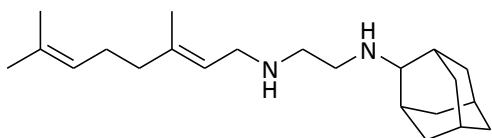


FIG. 21: STRUCTURE OF SQ109 (**34**)

The exact mechanism of action of **34** is not known, although it is believed to target cell wall synthesis in a different manner to EMB as **SQ109** is active against EMB-resistant strains, suggesting the existence of a different specific target or activation pathway.

Several 3-benzyl-6-bromo-2-methoxy-quinolines derivatives; **30**, **31**, **32** and **33** have shown 92-100% growth inhibition of mycobacterial activity, with minimum inhibitory concentration (MIC) of 6.25 µg/ml (**Fig.20**). Molecular modelling and docking studies on well-known diarylquinoline antitubercular drug R207910 (**23**) showed the presence of phenyl, naphthyl and halogen moieties seems critical⁹³.

CONCLUSION: Tuberculosis (TB) is presenting new challenges as a global public health problem, especially due to HIV co-infection, multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis*. The TB drugs currently in use were developed 40 years ago and there is a great need for new new, shorter treatment regimens. In the long term, the availability of more new drugs should play an important role in reducing the global TB burden. Current research involves finding better and more effective drugs that reduce time of treatment, reduce toxicity associated with drugs and provide backup measures in case of drug resistance.

The approaches include: chemical modification of existing drugs (such as rifampin, fluoroquinolones and macrolides); the identification of drug targets (such as persistence genes) using microarray analysis and molecular biology tools; structure based drug design and *in vitro* and *in vivo* screening to identify new drugs; evaluation of novel drug combinations; and the order of drugs given in treatment.

This review has summarized the global disease burden of TB, existing drugs, drugs under clinical trials and their possible targets. Promising leading chemical entities has also been addressed.

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