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A Review on Anti-Tubercular Agents, Their Chemical Structure and Mechanism of Action

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Abstract

M. tuberculosis is a very age old disease also reported from Egyptian mummies fragments of the spinal column 2400 BC. Actual pathological and anatomical description of the disease was reported in the 17th century. In 1882, Robert Koch's scientific brilliance led to the discovery of *M. tuberculosis* as the causative agent of the disease. There are three major approaches have been in practice to prevent TB these are the sanatorium with fresh air, cleanliness and a nutritious diet, vaccination, immunotherapy and chemotherapy. Chemotherapy of TB started in the 1940s. In 1943, anti-TB research resulted in discovery of the active anti-TB agents, and strategies have been devised to treat TB from time to time. A number of agents have been discovered since then, including para-aminosalicylic acid (PAS), isoniazid (INH), pyrazinamide (PZA), cycloserine, ethionamide, rifampicin (RMP), and ethambutol. The majority of these drugs were discovered through broad random screening. In this paper known anti-TB agents and new molecules having anti-TB activity are discussed.

Keywords: Anit-TB, vaccination, chemotherapy.

Introduction

The disease Tuberculosis (TB), caused by a slow growing bacterium *Mycobacterium tuberculosis (M. tb.)* evolved from soil bacterium more than 10,000 years ago. It is a respiratory transmitted infectious disease. There are many known and under clinical trial medicines which are discussed here.

Aim of the Study

The main objective of the paper is to create awareness of current and old medicines of TB in society. In 1939, India established TB association with the objective of providing expert advice on the development of standard methods to deal with the disease; setting up model institutions for training TB workers and education of the public regarding preventive measures.

Known Anti-Tubercular Agents

Streptomycin is an aminoglycoside antibiotic isolated from *Streptomyces griseus* and made of three structural 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. Streptomycin was the first really effective drug against tuberculosis and derivatves of dihydrostreptomycin have also anti TB activities. It has an MIC value of 1µg/ml. It has 50-60 % plasma protein bound with plasma half-life 5-7 hours. It penetrates the inner membrane of *M. tuberculosis* and binds to the 30S subunit of the ribosome. Different synthetic derivatives of streptomycin have been synthesized and
evaluated against *M. tuberculosis.*

Isoniazid is a prodrug that requires activation by the mycobacterial catalase peroxidase enzyme (kat G), which confers sensitivity in *M. tuberculosis* towards INH. It is orally active and exhibits bactereostatic action on the resting bacilli and is highly active against the *M. tuberculosis* complex (*M. tuberculosis, M. bovis, M. atricanum and M. Microti*). It has very low MICs (0.02-0.06 µg/ml) against these pathogens. INH enters the organism by diffusion and oxygen-dependent active transport and it has been reported to have effect on almost every aspect of Mycobacterial metabolism. INH inhibits the mycolic acid biosynthesis in *Mycobacterium tuberculosis* by affecting an enzyme *Mycolate synthetase,*

unique for *Mycobacteri*a.

Rifamycins are a group of semisynthetic antibiotics of rifamycin B, isolated from *Streptomyces mediterrani* with characteristic ansa structure (chromophoric naphthaquinone group spanned by a long aliphatic bridge) which itself has very poor antimicrobial activity. They inhibit prokaryotic DNA-dependent RNA polymerase, an enzyme necessary for RNA synthesis. Rifampin acts on B subunit of this enzyme resulting into formation of stable complex causing inhibition of bacterial RNA synthesis. Mammalian enzymes are not affected by rifampicin and the lipophilic properties of the molecule are important for binding of the drug to the polymerase and its penetration across the Mycobacterial cell wall. To avoid rapid development of bacterial resistance rifampicin is recommended in combination with other first line agents either isoniazid or ethambutol. However, combination of INH and rifampicin may increase risk of hepatotoxicity. Rifampicin is effective against *M. tuberculosis* with MIC ranging from 0.1 to 0.2 µg/ml.

Ethambutol is a synthetic amino alcohol (ethylene diamino-di-1-butanol) orally effective bacteriostatic agent and active against most strains of Mycobacterium. The proposed site of action of this first line drug ranged from trehalose dimycolate, mycolate and glucose metabolism to spermidine biosynthesis. However, recent studies have evidenced the primary site of action to be arabinan biosynthesis both in arabinogalactan and lipoarabinomannan (LAM). Activity of EMB is stereospecific as *dextro* isomer exhibited maximum antitubercular activity (*S, S* form is 600 times more active than *R, R)*. Mechanism of action of EMB is still not known completely, but probably it interferes in the synthesis of proteins and nucleic acids by acting as antimetabolite. Its complex forming ability is also a contributing feature to its bactereostatic activity. Disruption of the arabinogalactan biosynthesis inhibits the formation of this complex and this may lead to increased permeability of the cell wall. It has been suggested that this drug inhibits the enzyme arabinosyl transferase and thereby disrupts the biosynthesis of AG and LAM. Arabinosyl transferase III is responsible for the polymerization of arabinose into arabinan of arabinogalactan during cell wall biosynthesis.

The macrolides comprise a family of antibiotics ranging from erythromycin (1952) to analogs synthesized more recently. Erythromycin is 14 membered macrolide consisting of a macrocyclic lactone ring attached to two sugar residues. Newer derivatives differ from the parent erythromycin in the size and/or substitution pattern of the lactose ring and include; roxithromycin, clarithromycin, azithromycin, rokitamycin and spiramycin. Although some of the macrolides display poor antimicrobial activity against enterobacteria, they can generally be regarded as broad- spectrum agents inhibiting mycobacterial growth also. However, none of them displayed interesting antitubercular activity. A number of semisynthetic derivatives with improved pharmacokinetic properties appear to be promising in the treatment mycobacterial infections particularly those caused by non-tuberculosis species.

A number of diacyl thioureas have shown activity in experimental tuberculosis. One of such agent 4,4'-diisoamyloxydiphenylthiourea (ISO) (4,4'-diisoamyloxydiphenyl thiocarbanitide, isoxyl, thiocarlide) has proved clinically useful. The mode of action of this drug has been shown to be the inhibition of mycolic acid biosynthesis in *M. bovis* during a 6h exposure to 10 µg/ml.

The antimycobacterial activity of p-Amino salicylic acid (PAS) was reported only in 1946 although it was synthesized a long back. It has no effect against other bacteria and it is highly effective against *M. tuberculosis*. Following DOTS it is rarely used today. However, it is occasionally used in the regimens for the treatment of tuberculosis caused by MDR TB The mode of action of this drug is still unclear but it has been suggested that it interferes with the salicylate-dependent biosynthesis of the iron chelating mycobactins involved in iron assimilation.

Pyrazinamide, a structural analog of nicotinamide, is first line drug of short course tuberculosis therapy. It is also active against semidormant bacilli not affected by any other drug and has strong synergy with INH and rifampicin and shortens the therapy period to six months. The drug has no significant bactericidal effect and is thought to act by sterilizing effect. The activity of PZA depends on the presence of bacterial amidase which converts PZA to pyrazinoic acid, the active antituberculosis molecule and this activity is highly specific to *M. tuberculosis*. Mutation in the *pncA* gene responsible for the production of pyrazinamidase has been shown to be the reason for resistance against this drug. Some pyrazinoic esters have also been reported to possess good antitubercular activities.

D-Cycloserine, a structural analogue of amino acid D-alanine, possesses activity against a wide range of bacteria, and inhibits *M. tuberculosis* at concentrations of 5-20 µg/mL. It blocks peptidoglycan biosynthesis by inhibiting the enzyme D-alanine racemase and D-alaninyl alanine synthetase. Microorganisms treated with cycloserine accumulate a muramic-uridine-nucleotide-peptide, which differs from that produced by Mycobacteria in the absence of terminal D-alanine dipeptide. Cycloserine results in the central nervous system toxicity and can also generate psychotic states with suicidal tendencies and epileptic convulsion.

Fluoroquinolone are synthetic derivatives of nalidixic acid and display road-spectrum antimycobacterial activity as ciprofloxacin and ofloxacin used as a part of multi drug regimens, resulted in clinical and microbiological cure of patients infected with *M. tuberculosis* and *M. avium*. Structural modification of FQ to optimize antimycobacterial activity have been extensively carried out to produce candidates which are more efficacious than earlier FQ. Their bactericidal effects involve an interaction of the drugs with DNA-gyrase and DNA –

topoisomerase IV.

New molecules having antitubercular activity

A number of researchers design, synthesize and show that biphenyl analogues of the antitubercular drug PA-824 displayed improved activities when in heterobiaryl one of the phenyl is replaced with 5-membered ring heterocycles. Such type of compounds like 6-[4-{4-(4-methoxyphenoxy) piperidin-1-yl}phenoxy methyl]-6- methyl-2-nitro-6,7-dihydro-5H-pyrrolo [1,2-a] imidazole were formed by coupling of chiral 2-nitroimidazooxazine alcohol with various halomethyl substituted arylheterocycles etc. 1-Methylpyrazole, 1,3-linked pyrazole, 2,4-linked triazole and tetrazole showed higher MIC values.

The long term course of *Mycobacterium tuberculosis* treatment in the case of nonreplicating persistent form of TB (NRP-TB) is the main cause of treatment failure. Therefore 5-[(*E*)-2-arylethanyl]-3-isoxazolecarboxylic acid alkyl ester derivative synthesized and biologically evaluated successfully. Nitazoxamide and its active metabolite kill replicating and nonreplicating *M. tuberculosis* at low µg/ml levels. A series of 2-(hydrazinocarbonyl)-3-aryl-1*H*-indole-5-sulfonamide derived by reaction with 2,4,6-trimethyl pyrylium perchlorate, leading to pyridium derivatives. The new sulphonamide were inhibitors of two β-carbonic anhydrases from *M. tuberculosis,* R_V 1284 and R_V 3273. These compounds show excellent nanomolar inhibitory activity with several subnanomolar inhibitors being reported. R_V 1284 and R_V 3273 have potential to fight against mycobacterial agents with an alternate mechanism of action.

Diarylquinoline (DARQ) is new class of compounds possesses good antimycobacterial properties. A number of DARQ compounds have MIC as low as 0.5 µg/ml against *M. tuberculosis* H37Rv. The active compounds of the series are TMC207 and R207910. Structurally and mechanistically DARQs are different from both flouroquinolones and other quinoline classes including mefloquine and its analogs 4-methylquinolines and 4-quinonylhydrazones. R207910 has unique spectrum of potent and selective antimycobacterial activity *in vitro*. Unlike the lack of resistance with other anti-TB agents R207910 retains activity against (MDR) TB strains. DARQ seems to act by inhibiting the ATP synthase leading to ATP depletion and pH imbalance.

Food and Drug Administration (FDA) developed and approved the first oxazolidinone, Linezolid to treat single and multiple bacterial infections. Linezolid inhibits protein synthesis by binding to 23S rRNA and to the 50 s ribosomal subunit.

Researchers reported that tiamulin and valemulin class of antibiotics can be used in veterinary medicines. Since this class of compounds create interference in protein by binding to the 50S ribosome subunit and therefore stop peptide bond formation.

Oxazolidinone an important anti-TB agent was for the first time discovered by Dupont in 1970. These are totally synthetic orally active anti-bacterial agents e.g. Dup721 (S)-N-[3-(4-acetylphenyl)-2-oxo-oxazolidin-5-ylmethyl] acetamide. Dup721 is active primarily against gram-positive bacteria including multiple resistant strains of Staphylococci. Oxazolidinone derivatives, eperezolid and U-100480 are active against *M. tb*, moderately active against *M. fortuitum* and *Mycobacterium chelonae*, and exhibit good therapeutic efficacy against *M. tb* infection in mice. Oxazolidinone derivative's mechanism of action involve inhibition of protein synthesis by binding to *23S* rRNA and to the 50 s ribosomal subunit.

1, 4 - Dihydropyridine - 3, 5 - dicarbamoyl derivatives having lipophilic groups have significant anti-tubercular activity. In 1,4- dihydropyridine alkyl, aryl esters and diethyl carbamoyl substituent at C-3 and C-5 in DHP ring increase its activity. Nitroimidazole ring present at C-4 position further added its efficacy. *In vitro* antitubercular activity of compounds show that compounds containing aromatic esters are potent than alkyl esters. 3-phenyl propyl substituted ester in the molecule exhibits anti-tubercular activity (MIC 1 µmol/ml) with the reference compound isoniazid (INH) (MIC 1 µmol/ml).

In *M. tuberculosis* siderophore biosynthesis involved the presence of aryl acid adenylating enzymes (AAAE). Amol Gupte et al reported new series of 2-triazole derivatives of 5'-*O*-[*N*-(salicyl) salfamoyl] (Sal AMS) adenosine emerged as a promising inhibitor of diverse bacterial AAAEs and possess whole-cell activity toward both *M. tuberculosis* and *Yersinia* spp. Thorough study of the structure-activity relationships of Sal-AMS revealed that it contains four domains *viz*. aryl, linker, glycosyl and nucleoside. The aryl, linker and glycosyl domain only tolerated conservative modifications whereas the nucleobase express flexibility and provides the greatest opportunities to modify physicochemical and drug disposition properties.

Nitroimidazoles constitute another group of antitubercular agents, (*S*)-2-nitro- 6-substituted-6,7-dihydro- 5H-imidazo[2,1-b][1,3] oxazines have been exclusively explored and found that they can be used as new antituberculars based on their excellent bactericidal properties on aerobic whole cells of *M. tuberculosis.* In *M. tuberculosis* the siderophore biosynthesis is inhibited by 2-triazole derivative of 5-0-[N-(salicyl) sulfamoyl] adenosine (Sal-AMS) antibacterial nucleoside, which act as inhibitors of aryl acid adenylating enzymes (AAAE) involved in siderophore biosynthesis by *M. tuberculosis.*

Natural resources are employed by the researchers as rich source for isolation of medicines since ages. *Sapium haematospermum* plant is the constituent of many *M. tuberculosis* growth inhibitor such as lecheronol A and lecheronol B, an acylated cycloartane and highly oxygenated novel chalconoid. Stemwood of *Cinnmomum kotense* is the large source of antitubercular agents like Kotolactone and Secokotomolide.

A number of novel fluroquinolones have showed antimycobacterial activities like 1-

(cyclopropyl/ 2,4-difluorophenyl/ t-butyl)-1,4-dihydro-6-fluoro-7- (sub secondary amino)-4-oxoquinoline-3-carboxylic acids were synthesized and evaluated for their antimycobacterial *in vitro* and *in vivo* against *M. tuberculosis* $H_{37}R_V$ (MTB), multidrug resistant TB (MDR-TB), *M. smegmatis* and also tested for the ability to inhibit the supercoiling activity of DNA gyrase from *M. smegmatis.*

Antitubercular activity have been shown by Nelfinavir diester derivatives. These are prepared by reacting nelfinavir with two molar amount of an appropriate substituted aromatic/aliphatic acid in the presence of dicyclohexyl carbodiimide as the carboxyl group activator and 4-dimethyl amino pyridine as catalyst. The synthesized compounds were evaluated for their inhibitory effects on *Mycobacterium tuberculosis* $H37R_V$ by agar dilution method.

A new series of quinoline derivatives possessing triazolo, ureido and thioureido substituents have been synthesized and their antimycobacterial properties have been studied. Some of the compounds inhibited *Mycobacterium tuberculosis* H37Rv up to 98% at a fixed concentration of 6.25 µg/mL. Minimum inhibitory concentration of 3.125 µg/mL and 6.25 µg/mL was found. Molecular docking calculations suggest critical hydrogen bonding and electrostatic interactions between polar functional groups (such as quinoline-nitrogen, urea-carbonyl and hydroxyl) of anti-mycobacterial (anti-TB) compounds and amino acids (Arg 186 and Glu 61) of ATP - synthase of *M. tuberculosis*, could be the probable reason for observed anti-mycobacterial action.

Diterpenoids have various medicinal properties therefore it is screened against *M. tuberculosis* It was found that benzooxazole alkaloids isolated from the Indian sea whip *Pseudopterogorgia elisabethae* were tested against the bacterium and it was found that pseudopteroxazole has potent inhibitory activity (97%) at 12.5 µg/ml in *M. tuberculosis.*

Conclusion

In this review global disease burden of TB, recent approaches for its control and drug combinations used for treatment of TB has been discussed. Further work on the molecules described here and others emerging from both screening and focused medicinal chemistry programmes should lead to new clinical agents becoming a reality in the forthcoming years.

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