IJPSR (2024), Volume 15, Issue 6 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 08 November 2023; received in revised form, 03 January 2024; accepted, 05 April 2024; published 01 June 2024

ANTI-TUBERCULAR DRUGS: A REVIEW ON CURRENT TRENDS AND NOVEL DRUGS

A. A. Ankalikar, A. S. Menasinkai, P. M. Ronad *, Anuradha, Rohan Kurbet and Honur Hussen

Department of Pharm-Chemistry, KLE College of Pharmacy, Vidyanagar, Hubli - 580031, Karnataka, India.

Keywords:

Mycobacterium tuberculosis, Bedaquiline, Delamanid, Sutezolid, Marcozinone

Correspondence to Author:
Dr. P. M. Ronad

Professor,
Department of Pharm-Chemistry,
KLE College of Pharmacy,
Vidyanagar, Hubli - 580031,
Karnataka, India.

E-mail: ronadp@gmail.com

ABSTRACT: Tuberculosis remains a challenge globally affecting the health of several individuals globally. The emergence of drug resistant tuberculosis has further increased the threat. Despite having several drugs available the peril of the mycobacterium continues to loom. Across the globe several scientists are putting in efforts to come up with newer drugs with novel mechanism of action and belonging to several old as well as newer chemical classes. This review article delves in detail on each of the newer drugs discovered for the treatment and control of the disease. It begins with highlighting the progress of the diseases and its treatment over the years and then probes in-depth into the novel molecules of drugs discovered for the same. This article thus is a concise landscape which underlines the need of novel drug molecules and further highlights the potential of these newer drugs to combat tuberculosis by controlling the spread, shortening its treatment period, and making the treatment affordable to all.

INTRODUCTION: For time immemorial now we have been knowing that tuberculosis has been into existence. The excavations done at sites in Egypt and Nubia indicate that tuberculosis is older than humans itself. Earlier the disease was known as "phthisis" and was hereditary and non-contagious. It was only during the early 18th century when the industrial development was at boom that the numbers of people suffering from tuberculosis reached epidemic levels making it the most common cause of death. In the year 2021 India reported a whooping 210 per lakh population cases of tuberculosis and about 80,000 people lost their lives to this deadly infectious disease and worldwide 10.6 million people fell ill to TB and 1.4 million of them succumbed to it.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.15(6).1581-90

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.15(6).1581-90

This is in spite of the constant research being done for newer anti-tubercular drugs. Thus, we may say the disease is still a menace for the human kind [1, 2].

Etiology agent and Pathogenesis: The mycobacterial species include a plethora of microorganisms some of which cause different types of diseases in humans. These include Mycobacterium tuberculosis (M. tuberculosis), *M. bovis*, *M. africanum*, *M. microti*, *M. caprae*, *M. pinnipedii*, *M. canetti* and *M. mungi.* Amongst which *M.tuberculosis* is the causative agent of tuberculosis which is also known as tubercle bacilli. In 1882 Robert Koch was successful in isolating the bacilli in pure culture. The bacilli are extremely slow growing which is curved in shape protected with a unique complex cell wall. Lipid complexes like mycolic acids, peptidoglycan or peptidoglycolipids, long chain fatty acids imparting acid fast staining character to the bacilli, sulpholipids, cord factor make the cell wall extremely sturdy and also impart a curved shape to the bacilli. The bacilli are resistant to dehydration the bacilli are aerobic, non-motile non-sporing

microorganism which take 3-6 weeks to grow at 35°C which can be stained with ZN (Ziehl Neelsen) stain [3]. This bacillus causes an airborne infection which spreads when a healthy person inhales the droplet nuclei which contains the tubercle bacilli. These bacilli then get inside the alveoli and further get swallowed by the macrophages which have the capability to destroy them. Either the bacilli multiply intracellularly which get released when the macrophages die, or the bacilli can get killed or destroyed by the macrophages.

The human body on being attacked by the bacilli produces Th1 lymphocytes and macrophages which have bactericidal activity. These cells generate reactive oxygen and nitrogen along with promoting migration of immune cells at infection site and this then leads to formation of a granuloma. The main aim of macrophages as mentioned previously is to eradicate bacilli. However, at times the bacilli grow inside the macrophage, bursts open and further infects other macrophages. At times when the immune system of the individual is strong the bacilli grow inside the system for years without the host showing any symptoms and when the immune system weakens the bacilli multiplication and growth is reactivated. When immuno-compromised patients were observed it was seen that the process of granuloma formation fails to control the growth and there is increase in the number of bacteria seen thus spreading and aggravating the infection. The cell wall of the bacilli also contains another lipid Phthiocerol dimycocerosate which is responsible for TB pathogenesis in lungs. The lipid can alter the physicochemical properties of the host cell membrane facilitating phagocytosis [4, 5].

Epidemiology: Estimates show that around two billion people are infected with the tubercle bacilli (MTb) latently every year and out of these 10% cases become active on weakening of the immune system. In the year 2014-15 the UN and the WHO designed and adapted a strategy to end the TB epidemic aiming first at decreasing the incidences of tuberculosis by 20% and the next target was to reduce or decrease the number of deaths occurring by 35% in the year 2020 when as compared to the base line of deaths which occurred in 2014-15. The most recent Global Tuberculosis Report of 2021 has shown an increase in the number of cases of tuberculosis. As per the 2017 studies of WHO two-third of the world's population is infected or suffering from latent tuberculosis who will start exhibiting symptoms like persistent cough for more than three weeks, infection to the larynx and respiratory tract, fever, associated with weight loss. Further the infection is seen in the chest radiograph as well. Inclusive of infecting the pulmonary site the bacilli have the capability to infect extra pulmonary sites as well like the bones, joints, kidneys, and brain as well [6, 7].

One of the leading causes of death in the late 18th and early 19th century was tuberculosis. The initial drugs discovered were para-Amino salicylic acid in 1945, followed by Isoniazid in 1952 which were inexpensive, safe, and effective. In 1960s Ethambutol was discovered which was a better anti-TB drug much better tolerated than p-Amino salicylic acid. The discovery of Rifampin was a turning point in the treatment of tuberculosis in the 1970s followed by discovery of Pyrizinamide and newer latest drugs Bedaquiline and Delamanid. These discoveries made the tuberculosis situation look winnable causing a decreased attention towards public health and sanitation, irregularity in drug dosage compliance all this leading to the development of multi resistant tuberculosis (MDR-TB) and extensive drug resistant tuberculosis (XDR-TB). The main target in health sector the UN desires to achieve is to end the Tuberculosis epidemic by 2030 however a grave man-made problem in the treatment regimen of tuberculosis is leading to MDR-TB and XDR-TB.

Unprecedented use of first line drugs, poor clinical practices, using these drugs as monotherapy are a sure shot formula for leading a patient to multidrug resistant tuberculosis or MDR-TB. Worldwide over 5,00,000 cases get reported yearly and when these are mishandled followed by erratic use of second-line drug treatment leads to XDR-TB worldwide statistics show reporting of over 35,000 cases yearly of XDR-TB. Identifying that the patient has MDR-TB and XDR-TB is imperative and crucial steppingstone. For this the patient's medical history his previous drug regimen for tuberculosis treatment, drug intolerance if any all these details need to meticulously be noted down so that specific drug resistance can be identified and such a drug can be excluded from the new drug regimen. Along with these radiological studies of the lungs can

supplement and fortify the findings. It's a challenge to treat MDR-TB and XDR-TB which should be carried out under expert medical supervision and should be managed with care. Studies show that the control over MDR-TB and XDR-TB requires a multi drug regimen i.e., four, six or more drugs used in permutation and combination with each other but while administering such a regimen we need to keep in mind that using such multi combination of drugs can lead to high probability of developing intolerance in patients and this could cause or lead to patient noncompliance [8-12].

Other Associated Complications with Tuberculosis: Several associated conditions weaken the immune system and make the individual prone to contracting tuberculosis. Individuals suffering from Crohn's disease, various types of cancer, organ transplants, diabetes mellitus, substance abuse and HIV could be some of the reason that can cause weakening of the immune system further leading to contracting TB or if the person is a latent carrier of TB and becomes immunocompromised the situation can aggravate and the latent TB can turn active. Amongst these HIV is one risk factors which has proven to be the most important predisposing reasons leading to coinfection of TB. The risk of developing TB with HIV is 170 times more when compared to a non-immunocompromised person. The intensity of symptoms and the progress of the TB infection is dependent on the status of immunity of the individual, with decrease in the individuals immunocompetency there is increase in the intensity of the symptoms of TB and the progress of the disease is also rapid. The depletion of CD4+ cells, T cells is rapid along with increase in the levels of pro inflammatory mediators or biomarkers like cytokines, INF-γ, IL-2 and IL-17 [13, 14].

Treatment of Tuberculosis: A lingering threat that always exists for controlling TB is the development of multidrug resistant tuberculosis. Presently the line of tuberculosis treatment has four main drugs used to treat tuberculosis namely, Isoniazid, Rifampicin, Ethambutol and Pyrizinamide. The drug regimen has shown 95% of efficacy in controlling the spread of the disease in the individual patients, however it makes the whole process cumbersome as the treatment regimen is very prolonged. The patients face problems of compliance and toxicity wing to prolonged duration of treatment. Situations pertaining to tuberculosis turned alarming when in 2014 the number of deaths caused due to tuberculosis surpassed the total number of deaths due to HIV worldwide. The first line of treatment which is lengthy cumbersome and unforgiving includes drugs discovered majorly between the 1950s and 1970s. When in the late 21st century MDR TB kicked in the striain of the bacilli had turned resistant to Isoniazid and Rifampicin same time XDR TB was discovered whose patients are resistant to Fluroquinolones. With the advent and progress in the discovery of drugs molecules like Kanamycin, Levofloxacin, Cycolserine Capreomycin, Moxifloxacin, Clofazimine, Linezolid etc for the treatment and damage control of MDR and XDR TB is seen [13-19].

Recent Molecules Evaluated for Tuberculosis: Even after 140 years of discovery by Robert Koch to stain the tubercular bacilli, tuberculosis continues to be a challenge persistently. The discovery of several drug molecules to treat the disease in the early 1940s gave only a temporary relief however at the advent of the 20th century the disease emerged more fiercely in the form of XDR-TB and MDR-TB. Nevertheless, the progress in knowledge about the bacilli, improvised biochemical knowledge and know-how of medicinal chemistry has led onto a pathway of discovering newer drug entities and molecules' which can aid our war to combat the bacilli. Use of the knowledge of bioinformatics, genetic tools, screening of libraries of several compounds, identification of several potential targets has provided us with potentially active compounds which have given us a ray of hope of discovering several newer drugs.

Even the mechanisms' of discovering and identifying newer drugs, their probable mechanism of actions, different assays to evaluate the drug potency has led to discovery of several drug molecules'. Newer assays like Luminescence based low oxygen assay (LORA), Reza zurin microtiter assay (REMA), bioassay guided evaluation of natural compounds are a few methods to name which have aided and catered in the development and discovery of newer drug molecules [20, 21].

Streptomycin: Isolated from *Streptomyces griseus* which is a bacterium the structure of the streptomycin drug shows presence of a triacidic base with an aldose sugar, a hydrophilic drug which is water soluble the high basic nature of the drug is attributed to the presence of two guanidino groups present on streptidine and imparting a strong basic nature to the drug. The discovery of this drug has enabled the treatment of several infectious diseases, including tuberculosis (TB). The drug is effective against both gram positive and gram-negative bacteria hence is titled as a broad-spectrum antibiotic. Belonging to the class of aminoglycoside antibiotics the drug acts as a protein synthesis inhibitor exerting its mechanism of action by binding irreversibly to a small unit i.e., the 16S rRNA present in the 30S ribosomal sub unit, interfering with the activity of the formyl methionyl tRNA which leads to codon misreading further inhibiting protein synthesis and ultimately causing cell death of the mycobacteria. At the 30S ribosomal sub unit the drug specifically binds with the Lysine 42 and lysine 87 along with faulty biosynthesis of fatty acids and lipids. This is followed by causing leakage of K+ ions along with amino acids, nucleotides, oligonucleotides, and other proteins [20-22].

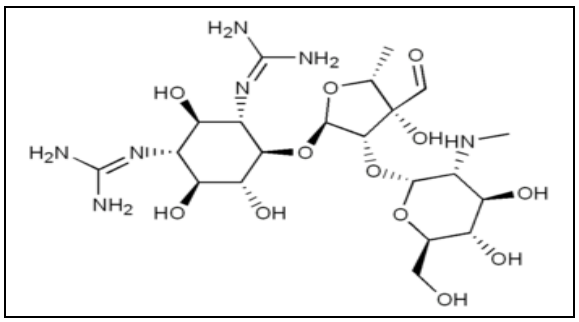

FIG. 1: STREPTOMYCIN

At lower concentrations the drug shows bacteriostatic effect and has broad spectrum of activity as it is effective on gram positive and gram-negative bacteria. The drug is a second choice of treatment after the R.I.P.E. combination (Rifampicin, Isoniazid, Pyrizinamide, Ethambutol) therapy. Due to its poor absorption in the GI tract the drug is administered parentally. The drug is contra indicated in patients with myasthenia gravis and other neuromuscular disorders and it has the common side effects like vertigo, vomiting, fever, and rash along with ear and kidney toxicity. Inspite of the drug having such promising anti-tubercular action the emergence of resistance to the drug has raised concerns. The excessive misuse of the drug, inadequate dosing and incomplete treatment course has led to resistance development. The development of these resistant strains has led to significant threat to public threat. The development of resistance is due to mutations in genome of *M. tuberculosis* in the genes psL, rrs, and gid which stand for codes of enzymes S12 protein, 16S rRNA, and the S-adenosyl methionine dependent 7-methylguanosine methyltransferase, respectively. This resistance threat however is not pictured as a threat but still has played a key role in leading us to the emerging problem of antimicrobial resistant TB [22-30].

Clofazimine: This drug belongs to the class of Riminophenazine compounds which was developed mainly when a dire need for a newer more efficient anti-tubercular drug was anticipated especially as an alternative regimen of treatment. Initially the drug molecule showed activity on *Mycobacterium leprae* and was ruled out to be useful in tuberculosis. However, when the prevalence of MDR TB precipitated, the role and use of Clofazimine was reevaluated. The drugs mode of action involves intracellular redox cycling leading to membrane destabilization caused mainly due to increase in reactive oxygen species. The drug shows synergistic effect when used in combination with Pyrazinamide or with Clarithromycin for the treatment of tuberculosis. The half-life of the drug is found to be approximately 70 days, a long half-life combined with less cost of the drug are its major advantages.

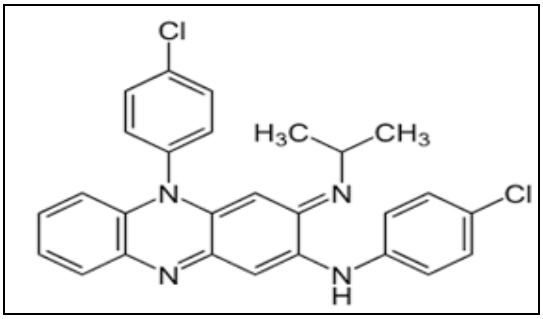

FIG. 2: CLOFAZIMINE

However, the dose intake needs to be monitored when the drug is administered to patients with hepatic impairment. Most common adverse side effects of the drug seen are orange or brown skin pigmentation and discolouration of body fluids and

secretions reversal of which may take months or years. It may also cause dryness of skin and ichthyosis [31-34].

Linezolid: An oxazolidinone antibiotic Linezolid was the first from this class of antibiotics to be introduced as anti-tubercular drug. Discovered in 1996 and approve as a safe drug in the year 2000 by the US FDA. The drug is a bacterial protein synthesis inhibitor, it binds to the 30S and the 50S ribosomal sub units of the bacteria, leading to decrease in length of the bacterial peptide chain, it also decreases the translation reaction rate and thus exerts its anti-mycobacterial effect on the microorganism. Presence of the morpholino group on the 1st ring and the fluoride atom on the 2nd ring enhances the drug activity. For the drug molecule to exert its anti-mycobacterial effect the presence of an electron withdrawing aryl group and the 5-S-configuration is essential for activity.

Presence of extra substituents on the aromatic ring which is present proximally has no effect on the drug activity but alters the drug solubility and the drugs pharmacokinetic properties. The drug has proven to be extremely promising in the treatment of multi drug resistant tuberculosis (MDR-TB) as well as XDR-TB. Other than being useful in the treatment of tuberculosis the drug has several other pharmacological uses *viz:* supressing toxic shock syndrome, necrotizing fasciitis, multiple infections after neurological surgeries, since the drug penetration through the cerebrospinal fluid is good.

It has proven to be useful in treating ventilator-associated pneumonia, catheter-related bacteraemia, *S. aureus* caused endocarditis and it is also at par with the effect of the drug Vancomycin which has been found to be extremely useful in treating MRSA infections. The bioavailability of the drug on oral administration is 100%, its oral absorption is unaffected with the presence of antacids, similarly the drug can be safely co-administered with antibiotic Aztreonam as well as gram negative bacteria antibiotics like Ciprofloxacin, Gentamycin, Meropenem and Ceftazidime. Linezolid also shows no effect or does not hamper the bioavailability and the absorption of aminoglycoside antibiotics, fluroquinolones, β-lactams, antivirals as well as anti-fungal agents. However, precautions are advised when Linezolid needs to be combined with serotonergic therapeutics [27-35].

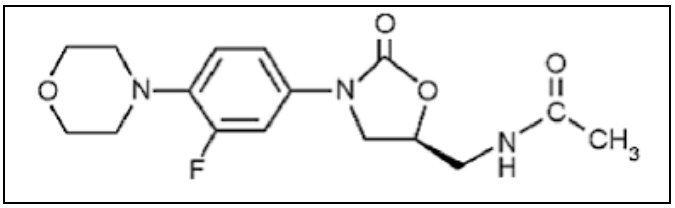

FIG. 3: LINEZOLID

Moxifloxacin: Belonging to the class of fluoroquinolones the drug Moxifloxacin which is a 8-methoxy quinolone with a hydrophobic diazabicyclononyl ring moiety and S, S-configuration at the 7th position has shown promising *in-vitro* as well as *in-vivo* activity against *Mycobacterium tuberculosis* especially in cases which have not responded to first line of treatment or it has been included as a part of treatment for MDR-TB.

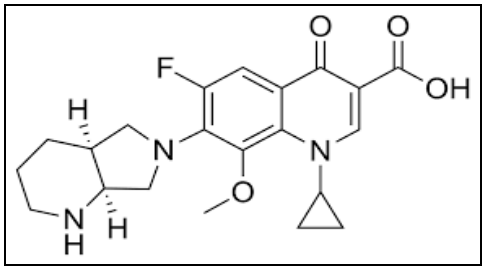

FIG. 4: MOXIFLOXACIN

One of the major concerns of tuberculosis treatment is its duration of treatment. The mycobacterium being a slow growing organism often demands use of anti-tubercular drugs for a prolonged duration leading to decreased compliance, effect on tolerability, safety issues etc. In this regard Moxifloxacin comes in picture as a potential drug with the ability to shorten the duration of action. Quinolones have always been a promising class of anti-TB drugs starting from Rifampicin, this class of drugs are better tolerated, with improved outcomes and have proven to be safe and effective in treatment of MDR TB. The drug has shown promising results in the study wherein it was administered along with other anti-tubercular drugs like Pretomanid, Bedaquiline, Pyrazinamide, or Rifapentine against MDR-TB. This combination although does not shorten the duration of treatment but is effective in patients who have not responded to first line of drugs. Exerting its mycobacterial action by binding to the

topoisomerase enzyme-II (DNA gyrase) inhibiting the process of replication, translation, transcription. Moxifloxacin exerts lethal action by leading to the formation of quinolone-gyrase-DNA complex, leading to DNA fragmentation and Moxifloxacin could kill the mycobacterium which is in dormant state as well thus proving as an aid for eradicating the disease and preventing relapse[35-37].

Bedaquiline:

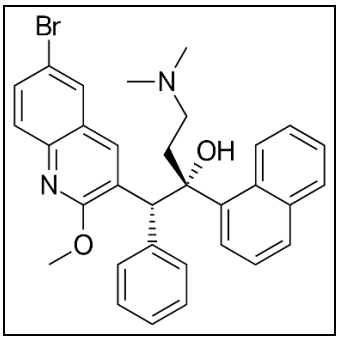

FIG. 5: BEDAQUILINE

Bedaquiline is a diarylquinoline class of drug which was launched in 2012 and targets a new mechanism in the tubercular bacilli i.e., the proton pump of the adenosine triphosphate synthase in the bacilli. The drug is active against both strains of the bacilli the drug-susceptible and drug-resistant isolates.

The treatment of MDR-TB and XDR-TB is expensive time consuming and difficult to manage. There is no however a study and reference available for the use of Bedaquiline along with another anti-TB drug Delmanid available as a handy solution for treating MDR-TB and XDR-TB. The structural studies of the drug show presence of a quinolinic heterocyclic nucleus to which is attached the alcohol and amine side chains, which are responsible for its antimycobacterial activity. The structural formula of the drug prominently shows two parts namely the hydrophobic part which has the group $-N(CH_3)_2$ and the H_2 donor/acceptor. The main target of this drug is to inhibit the action of ATP synthase enzyme responsible for energy metabolism in the mycobacteria and the group $-N(CH_3)_2$ is responsible for this activity. The H2 donor/ acceptor group is responsible for providing stability to the drug molecule. The drug which has a half-life of more than 24 hours is active against both drug susceptible strains and drug resistant strains. The drug is also a promising agent of treatment in individuals suffering from HIV/AIDS and co-infected with tuberculosis and in shortening the treatment time of MDR-TB and XDR-TB. The efficient antimycobacterial activity of the drug is attributed to the diarylquinoline ring and side chain at the N, N dimethyl amino terminal along with the hydroxyl group and naphthalene moiety. and a functionalized lateral chain which contains the teritary amine. The enantiopure compound of the drug has two adjacent chiral carbon atoms, giving a mixture of four isomers and amongst them the enantiomer 1R. 2S stereoisomer is more active which Bedaquiline 38-44 is.

Delamanid:

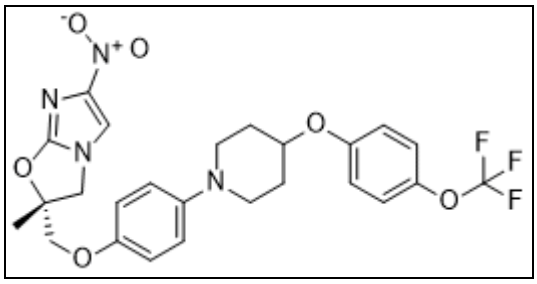

FIG. 6: DELAMANID

The drug is a dihydro-nitroimidazooxazole derivative which received conditional approval for the treatment of MDR and XDR-TB. Delamanid, and its congener Pretomanid (PA-824), belong to the class of bicyclic nitroimidazoles whose initially discovery was as anti-cancer agents but precursor CGI17341 was serendipitously found to have potent bactericidal activity against multidrug resistant Mtb. Delamanid seems to be more active than Pretomanid, and the drugs act by inhibiting the synthesis of mycolic acids by inducing respiratory poisoning. They do so by activating the deazaflavin which is a cofactor F420 and is dependent on nitroreductase enzyme which converts Pretomanid into three primary metabolites. Amongst these metabolites the des-nitroimidazole (des-nitro) derivative is responsible for generating reactive nitrogen species like nitric oxide which causes respiratory poisoning, further decreasing intracellular ATP levels further interfering with the electron flow and ATP homeostasis. The drug also acts by inhibiting the synthesis of methoxy-mycolic and keto-mycolic acid synthesis essential for the cell wall. The drug has shown promising potent activity at the MIC values of 0.006 to 0.024 g/mL.

Since the drug requires activation by mycobacterial F420 depedent nitroreductase enzyme any mutation in the five coenzymes of the F420genes fgd, Rv3547, fbiA, fbiB, and fbiC can lead to resistance development. Thus, we may call Delmanaid drug to be a promising anti-tubercular drug particularly to treat MDR-TB. The drug when administered orally has shown bactericidal property and the clinical efficacy of the drug is also reassuring though limited, and the drug can be a hopeful addition in treating tuberculosis [43-47].

Sutezolid:

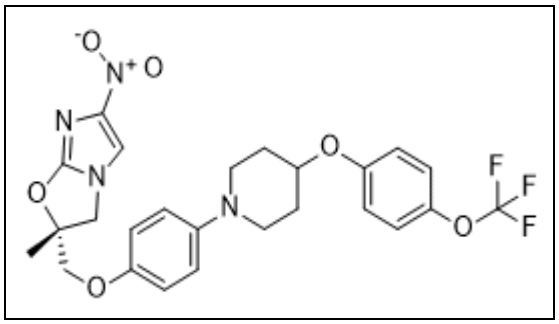

FIG. 7: SUTEZOLID

Sutezolid is an oxazolidinone analogue of linezolid. Oxazolidinediones is a class of five membered heterocyclic compound which has both oxygen and nitrogen atom in the structure with promising broad spectrum of pharmacological properties. Sutezolid which belongs to this class exists in two metabolite forms namely its sulfoxide and sulfone, and both the metabolites have exhibited potent *in-vitro* antibacterial activity against *Mycobacterium tuberculosis*. The drug has shown better activity than linezolid and hence is used in combination with first-line and second-line anti-TB drugs thus exhibiting promising bactericidal activity and also shortening the treatment time. Studies have further proved that Sutezolid is active against drug-susceptible and drug-resistant *Mycobacterium tuberculosis* strains, unlike Linezolid which is only bacteriostatic in action. The drug is known to exert anti-tubercular activity both extracellularly and intracellularly. The intracellulcar bactericidal activity is attributed to the parent molecule while the extracellular bactericidal activity is mainly due to the sulfoxide metabolite. The inducers and inhibitors of cytochrome CYP3A4 affect the concentration of sutezolid and consequently its activity due to the fact that each one of cytochrome CYP3A4 and flavin-containing monooxygenases are responsible for sutezolid metabolism. Resistance to sutezolid was found to be associated with mutations in the 23S rRNA (*rrl*) and the ribosomal protein L3 (RplC). Early bactericidal activity in TB patients showed that sutezolid was generally safe and well tolerated. The only adverse event that was observed was the mild to moderate increase in hepatic alanine aminotransferase enzyme levels. The studies have shown that the drug is well tolerated in treating drug-sensitive tuberculosis. It was found to be well tolerated, safe but still concerns have been expressed on it exhibiting development of peripheral neuropathy on long term use. Regulatory approvals and clinical trials results are awaited especially for it being used against MDR and XDR-TB [48-50].

Macozinone:

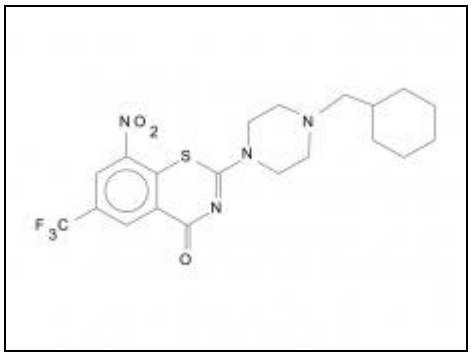

FIG. 8: MACOZINONE

The arise of drug-resistant TB has posed a major challenge, greatly complicating TB management for the individual patient and for health systems. To tackle these challenges scientists across the world have geared up to synthesise and develop newer and novel anti-TB drugs. The nascent stage of new era of anti-TB drugs have shown a ray of hope to tackle and overcome this great scourge of drug-resistant TB. One such newly discovered drug is Macozinone a piperazine-benzothiazinone class of anti-TB drug. The benzothiazinone (BTZ) class of compounds emerged during the study of ditiocarbamate DTC class of compounds which possess antimicrobial activity. Structural studies of the diticarbamates for improvising the selectivity and activity led to the development of the BTZ scaffold of drugs. These BTZ derivatives on being synthesised and tested for their activity against mycobacteria displayed promising MIC values against *M .tuberculosis* including the resistant strains. Further when studied on murine models of

TB the BTZ class of drugs exhibited anti-mycobacterial activity at par with isoniazid. Genetic studies of the drug to estimate the probable mechanism of action showed that this class of drugs cause the epimerization of two major enzymes which play a pivotal role in the cell wall synthesis of the mycobacteria. These two enzymes mainly are decaprenylphosphoryl ribose (DPR) to decaprenylphosphoryl arabinose (DPA). Amongst the two enzymes it was found that the DPR enzyme is predominantly involved in inhibition by undergoing oxidation followed by undergoing reduction of the nitro group to finally inhibit or prevent the synthesis of arabinose polymers bringing about antimycobacterial action. Further studies showcase the in-depth mechanism of action of the drug which comprises of the drug Macozinone covalently binding to DprE1 the flavoenzyme responsible for synthesizing and incorporating the arabinogalactan in the mycobacterial cell wall. Thus, inhibiting the DPA formation and its incorporation in the cell wall eventually leads to bacterial cell death [51-58].

CONCLUSION: Since, the 1940s during which drugs like Isoniazid, p-Aminosalicylic acid, Ethambutol, Pyrizinamide were discovered in a series which was followed up by discovering the use of Rifampicin, antibiotics, and fluroquinolones for treating tuberculosis we have made immense progress. However, in spite of having several drugs for treatment the mycobacterium does not stop in surprising us with newer variants. Keeping these challenges in mind the medical fraternity has been working dedicatedly and tirelessly to combat the disease. In this article we have attempted to give a concise view on the progress that has been made in discovering newer drugs for the treatment of tuberculosis. The scientific fraternity has made promising and significant progress in combating tuberculosis by discovering and designing newer drugs which are tolerable, more effective and target specific. This also speaks volumes about the dedication and diligence of the scientific fraternity to fight this public health concern. The disease treatment has evolved considerably to treat the different variants of mycobacterium making it more manageable. Introduction of fluroquinolones like kanamycin, amikacin in 1970s, antibiotics like Moxifloxacin for treating tuberculosis as second line of drug treatment followed by new drugs like Linezolid, Bedaquiline, Delamanid, Macozinone has played an instrumental role in helping the human kind to combat drug resistant strains as well as shortening the duration of treatment. These novel drugs have improved efficacy, higher curing rates, better patient recovery, improved public health outcomes, being effective on latent tuberculosis and are better tolerated. Thus, these drugs provide hope in tackling the world's most tenacious and widespread public health challenge. As more drugs become available, it will become possible to generate entirely new treatment regimens for TB, which could radically change the approach to drug resistant disease. In the future, as knowledge about these new agents accumulates, we may well find tools to meet the challenges of drug resistant TB [23, 58].

ACKNOWLEDGMENT: The authors would like to thank Principal KLE College of Pharmacy, Hubballi, Karnataka for providing us with this opportunity and facilities to work on this review.

CONFLICTS OF INTEREST: The authors declare there are no conflicts of interest.

REFERENCES:

1. Tuberculosis is one of the top infectious killers in the world[Internet]. www.who.int. Available from https://www.who.int/multi-media/details/global-tuberculosis-report-2022-infographic-1
2. Nerlich AG: Ancient Egyptian prosthesis of the big toe. Lancet 2000; 356: 2176-79.
3. Salo WL, Aufderheide AC, Buikstra J and Holcomb TA: Identification of Mycobacterium tuberculosis DNA in a pre-Columbian Peruvian mummy. Proc Natl Acad Sci U S A [Internet]. 1994; 91(6): 2091–4. Available from: https://pubmed.ncbi.nlm.nih.gov/8134354/
4. Osoba AO: Microbiology of Tuberculosis. In: Tuberculosis. Berlin, Heidelberg: Springer Berlin Heidelberg 2004; 115–32.
5. Grange JM: Tuberculosis. In: Wilson G, Miles A, Parker MT (eds) Topley and Wison's principles of bacteriology, virology and immunity, 7th edn. Arnold, London 1984; 32-35.
6. GTP. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update [Internet]. Who.int. World Health Organization; 2022.Available from: https://www.who.int/publications/i/item/9789240063129.
7. CDC. Extensively drug-resistant tuberculosis—United States, 1993– 2006. MMWR 2007; 56(11): 250–3. www.cdc.gov/mmwr/preview/mmwrhtml/mm5611a3.htm
8. Sasindran SJ and Torrelles JB: Mycobacterium Tuberculosis Infection and Inflammation: what is Beneficial for the Host and for the Bacterium? Front Microbiol [Internet] 2011; 2. Available from: http://dx.doi.org/10.3389/fmicb.2011.00002

9. Flynn JL, Chan J and Lin PL: Macrophages and control of granulomatous inflammation in tuberculosis. Mucosal Immunol [Internet] 2011; 4(3): 271–8. Available from: http://dx.doi.org/10.1038/mi.2011.14
10. Boom WH, Canaday DH, Fulton SA, Gehring AJ, Rojas RE and Torres M: Human immunity to M. tuberculosis: T cell subsets and antigen processing. Tuberculosis (Edinb) [Internet] 2003; 83(1–3): 98–106. Available from: https://www.sciencedirect.com/science/article/pii/S1472979202000549
11. Chandra P, Grigsby SJ & Philips JA: Immune evasion and provocation by Mycobacterium tuberculosis. Nat Rev Microbiol 2022; 20: 750–766. https://doi.org/10.1038/s41579-022-00763-4.
12. Diatlova A, Linkova N, Lavrova A, Zinchenko Y, Medvedev D and Krasichkov A: Molecular markers of early immune response in tuberculosis: Prospects of application in predictive medicine. Int J Mol Sci [Internet]. 2023; 24(17): 13261. Available from: http://dx.doi.org/10.3390/ijms241713261
13. Lyadova I: Inflammation and Immunopathogenesis of Tuberculosis Progression. In: Cardona P-J, editor. Understanding Tuberculosis - Analyzing the Origin of Mycobacterium Tuberculosis Pathogenicity. London, England: In Tech 2012.
14. Rahlwes KC, Dias BRS, Campos PC, Alvarez-Arguedas S and Shiloh MU: Pathogenicity and virulence of Mycobacterium tuberculosis. Virulence [Internet]. 2023 [cited 2023 Dec 31]; 14(1). Available from: http://dx.doi.org/10.1080/21505594.2022.2150449
15. Sasindran SJ and Torrelles JB: Mycobacterium Tuberculosis Infection and Inflammation: what is Beneficial for the Host and for the Bacterium? Front Microbiol 2011; 2: 2.
16. American Thoracic Society and CDC. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000; 161 (4): 1376–1395. http://ajrccm.atsjournals.org/cgi/reprint/161/4/1376
17. Nambuya A, Sewankambo N and Mugerwa J: Tuberculous lymphadenitis associated with human immunodeficiency virus infection in Uganda. J Clin Pathol 1988; 41: 93-6. Guidelines for PMDT in India; 2017. Available at: https://tbcindia.gov.in/index1.php?lang¼1&level¼2&sublinkid¼4780&lid¼3306
18. Prasad R, Verma SK, Sahai S, Kumar S and Jain A: Efficacy, and safety of kanamycin, ethionamide, PAS, and cycloserine in multidrug resistant pulmonary tuberculosis patients. Indian J Chest Dis Allied Sci 2006; 48: 183e186.
19. Wong K, Nguyen J, Blair L, Banjanin M, Grewal B and Bowman S: Pathogenesis of Human Immunodeficiency Virus-Mycobacterium tuberculosis Co-Infection. J Clin Med [Internet]. 2020 [cited 2023 Dec 31]; 9(11):3575. Available from: http://dx.doi.org/10.3390/jcm9113575
20. Dartois VA and Rubin EJ: Anti-tuberculosis treatment strategies and drug development: challenges and priorities. Nat Rev Microbiol 2022; 20: 685–701. https://doi.org/10.1038/s41579-022-00731-y
21. Ejalonibu MA, Ogundare SA, Elrashedy AA, Ejalonibu MA, Lawal MM and Mhlongo NN: Drug discovery for Mycobacterium tuberculosis using structure-based computer-aided drug design approach. Int J Mol Sci [Internet]. 2021; 22(24):13259. Available from: http://dx.doi.org/10.3390/ijms222413259
22. Piergallini TJ, Scordo JM, Pino PA, Schlesinger LS, Torrelles JB and Turner J: Acute inflammation confers enhanced protection against Mycobacterium tuberculosis infection in mice. Microbiol Spectr [Internet]. 2021; 9(1). Available from: http://dx.doi.org/10.1128/spectrum.00016-21
23. Sileshi T, Tadesse E, Makonnen E and Aklillu E: The Impact of First-Line Anti-Tubercular Drugs' Pharmacokinetics on Treatment Outcome: A Systematic Review. Clin Pharmacol. 2021; 13: 1-12. https://doi.org/10.2147/CPAA.S289714
24. Bahuguna A and Rawat DS: An overview of new antitubercular drugs, drug candidates, and their targets. Med Res Rev [Internet]. 2020; 40(1): 263–92. Available from: http://dx.doi.org/10.1002/med.21602
25. Gopal M, Padayatchi N, Metcalfe JZ and MR: O'Donnell Systematic review of clofazimine for the treatment of drug resistant tuberculosis Int J Tuberc Lung Dis 2013; 17(8): 1001–1007. doi:10.5588/ijtld.12.0144.
26. Moss J, Lane MD. Acetyl coenzyme A carboxylase. J Biol Chem [Internet] 1972; 247(16):4944–51. Available from: https://www.sciencedirect.com/science/article/pii/S0021925819449223
27. Khosravi AD, Etemad N, Hashemzadeh M, Khandan Dezfuli S and Goodarzi H: Frequency of Rrs and RpsL Mutations in Streptomycin-Resistant Mycobacterium Tuberculosis Isolates from Iranian Patients. J Glob Antimicrob Resist 2017; 9: 51–56.
28. Honore N, Marchal G and Cole ST: Novel Mutation in 16S RRNA Associated with Streptomycin Dependence in Mycobacterium Tuberculosis. Antimicrob. Agents Chemother 1995; 39: 769–770.
29. Okamoto S, Tamaru A, Nakajima C, Nishimura K, Tanaka Y, Tokuyama S, Suzuki Y and Ochi K: Loss of a Conserved 7-Methylguanosine Modification in 16S RRNA Confers Low-Level Streptomycin Resistance in Bacteria. Mol. Microbiol 2007; 63: 1096–1106.
30. Spies FS, Ribeiro AW, Ramos DF, Ribeiro MO, Martin A, Carlos Palomino J, Lucia Rossetti MR, Eduardo da Silva PA and Zaha A: Streptomycin Resistance and Lineage-Specific Polymorphisms in Mycobacterium Tuberculosis GidB Gene. J Clin Microbiol 2011; 49: 2625–30.
31. Mabhula A and Singh V: Drug-Resistance in: Mycobacterium Tuberculosis: Where We Stand. Medchem comm 2019; 10: 1342–60.
32. Lai YP and Ioerger TR: Exploiting Homoplasy in Genome-Wide Association Studies to Enhance Identification of Antibiotic-Resistance Mutations in Bacterial Genomes. Evol Bioinform 2020; 16: 13–15.
33. Rocha DMGC, Viveiros M, Saraiva M and Osório NS: The neglected contribution of streptomycin to the tuberculosis drug resistance problem. Genes (Basel) [Internet]. 2021 [cited 2023 Nov 8]; 12(12):2003. Available from: https://www.mdpi.com/2073-4425/12/12/2003
34. Yano T, Kassovska-Bratinova S and Teh JS: Reduction of clofazimine by mycobacterial type 2 NADH: quinone oxido-reductase: a pathway for the generation of bactericidal levels of reactive oxygen species. J Biol Chem 2011; 286: 10276–287.
35. Lu Y, Wang B, Zhao WJ, Zheng MQ and Li P, Fu L: A study on the activity of clofazimine with antituberculous drugs against Mycobacterium tuberculosis. Zhonghua Jie He He Hu Xi Za Zhi 2010; 33(9): 675–8.
36. Watkins RR, Lemonovich TL and File TM: An evidence-based review of linezolid for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA): place in therapy. Core Evid 2012; 7: 131–143.
37. Batts DH: Linezolid-a new option for treating Gram-positive infections. Oncology 2000; 14(8-6): 23–29.

38. Ament PW, Jamshed N and Horne JP: Linezolid: its role in the treatment of Gram-positive, drug-resistant bacterial infections. Am Fam Phys 2002; 65(4): 663–670.
39. Shee S, Singh S, Tripathi A, Thakur C, Kumar T A and Das M: Moxifloxacin-mediated killing of Mycobacterium tuberculosis involves respiratory downshift, reductive stress, and accumulation of reactive oxygen species. Antimicrob Agents Chemother [Internet] 2022; 66(9). Available from: http://dx.doi.org/10.1128/aac.00592-22.
40. Pham TDM, Ziora ZM and Blaskovich MAT: Quinolone antibiotics. Medchemcomm [Internet]. 2019 [cited 2023 Dec 31]; 10(10): 1719–39. Available from: https://pubs.rsc.org/en/content/articlelanding/2019/md/c9md00120d
41. Barry VC, Belton JG and Conalty ML: A new series of phenazines (rimino-compounds) with high antituberculosis activity. Nature 1957; 179: 1013–1015.
42. Barry VC, Buggle K, Byrne J, Conalty ML and Winder F: Absorption, distribution, and retention of the rimino compounds in the experimental animal. Ir J Med Sci 1960; 416: 345–352.
43. Barry VC and Conalty ML: Anti-tuberculosis activity in the phenazine series. II. N3-substituted anilinoaposafranines (rimino compounds) and some derivatives. Am Rev Tuberc 1958; 78: 62–73.
44. Chang YT: Chemotherapy of murine leprosy. IV. The effects of amithiozone (TB1/698), p aminosalicylic acid (PAS), B 283 (a phenazine pigment), five antibiotics and three diphenylthiourea compounds on mouse leprosy. Int J Lepr 1955; 23: 167–180.
45. Tasneen R, Li SY and Peloquin CA: Sterilizing activity of novel TMC207- and PA-824-containing regimens in a murine model of tuberculosis. Antimicrob Agents Chemother 2011; 55: 5485–5492.
46. Perrin C, Athersuch K, Elder G, Martin M and Alsalhani A: Recently developed drugs for the treatment of drug-resistant tuberculosis: a research and development case study. BMJ Glob Health 2022; 7(4): 007490. doi: 10.1136/bmjgh-2021-007490. PMID: 35440441; PMCID: PMC9020285.
47. Mukherjee T and Boshoff H: Nitroimidazoles for the treatment of TB: past, present, and future. Future Med Chem 2011; 3(11): 1427–1454.
48. Gurumurthy M, Mukherjee T and Dowd CS: Substrate specificity of the deazaflavin-dependent nitroreductase from Mycobacterium tuberculosis responsible for the bioreductive activation of bicyclic nitroimidazoles. FEBS J 2012; 279(1): 113–125
49. Théoneste Umumararungu, Marie Jeanne Mukazayire, Matabishi Mpenda, Marie Françoise Mukanyangezi, Jean Bosco Nkuranga, Janvier Mukiza, Emmanuel Oladayo Olawode, A review of recent advances in anti-tubercular drug development, Indian Journal of Tuberculosis 2020; 67(4): 539-59.
50. Marco Pieroni Chapter Two - Antituberculosis agents: Beyond medicinal chemistry rules, Editor(s): Kelly Chibale, Annual Reports in Medicinal Chemistry, Academic Press 2019; 52: 27-69.
51. Bandodkar B, Shandil RK, Bhat J and Balganesh TS: Two decades of TB drug discovery efforts—what have we learned? Appl Sci (Basel) [Internet]. 2020; 10(16): 5704. Available from: https://www.mdpi.com/2076-3417/10/16/5704
52. Singh R, Manjunatha U and Boshoff HI: PA-824 kills nonreplicating Mycobacterium tuberculosis by intracellular NO release. Science 2008; 322(5906): 1392–1395.
53. Neres J, Pojer F, Molteni E, Chiarelli LR, Dhar N, Boy-Rottger S, Buroni S, Fullam E, Degiacomi G and Lucarelli AP: Structural basis for benzothiazinone-mediated killing of Mycobacterium tuberculosis. Sci Transl Med 2012; 4: 150ra121.
54. Makarov V, Lechartier B, Zhang M, Neres J, van der Sar AM, Raadsen SA, Hartkoorn RC, Ryabova OB, Vocat A and Decosterd LA: Towards a new combination therapy for tuberculosis with next generation benzothiazinones. EMBO Mol Med 2014; 6: 372–383.
55. Piton J, Vocat A, Lupien A, Foo CS, Riabova O, Makarov, V and Cole ST: Structure-Based drug design and characterization of sulfonyl-piperazine benzothiazinone inhibitors of DprE1 from Mycobacterium tuberculosis. Antimicrob. Agents Chemot 2018; 62.
56. Wolucka BA, McNeil MR, de Hoffmann E Chojnacki T and Brennan PJ: Recognition of the lipid intermediate for arabinogalactan/arabinomannan biosynthesis and its relation to the mode of action of ethambutol on mycobacteria. J Biol Chem 1994; 269: 23328–23335.
57. Trefzer C, Skovierova H, Buroni S, Bobovska A, Nenci S, Molteni E, Pojer F, Pasca MR, Makarov V and Cole ST: Benzothiazinones are suicide inhibitors of mycobacterial decaprenylphosphoryl-Beta-D-ribofuranose 2'-oxidase DprE1. J Am Chem Soc 2012; 134: 912–915.
58. Bahuguna A, Rawat S and Rawat DS: QcrB in mycobacterium tuberculosis: the new drug target of antitubercular agents. Med Res Rev 2021; 41(4): 2565–81. https:// doi.org/10.1002/med.21779
59. Poen S, Nakatani Y, Opel-Reading HK, Lassé M, Dobson RC and Krause KL: Exploring the structure of glutamate racemase from Mycobacterium tuberculosis as a template for antimycobacterial drug discovery. Biochem J 2016; 473(9): 1267–80. https://doi.org/10.1042/BCJ20160186

How to cite this article:
Ankalikar AA, Menasinkai AS, Ronad PM, Anuradha, Kurbet R and Hussen H: Anti-tubercular drugs: a review on current trends and novel drugs. Int J Pharm Sci & Res 2024; 15(6): 1581-90. doi: 10.13040/IJPSR.0975-8232.15(6).1581-90.