Research Article

Selected Therapeutic Targets of Tuberculosis: An Overview

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ABSTRACT

Tuberculosis (TB) remains one of the deadliest infectious diseases for humans. Approximately eight million people develop active disease each year and between two and three million cases of active disease result in death. Identification of new drug targets is vital for the advancement of drug discovery against Mycobacterium tuberculosis, especially given the increase of resistance worldwide to first- and second-line drugs. Since the determination of the Mycobacterium tuberculosis genome sequence, various groups have used the genomic information to identify and validate targets as the basis for the development of new anti-tubercular agents. This review surveys several newly identified targets as well as those that have been revisited in the past few years, and the levels to which they have been validated to demonstrate their potential role in improving chemotherapy against TB.

Keywords: Antitubercular agents, Chemotherapy, Mycobacterium tuberculosis, Tuberculosis.

INTRODUCTION

Tuberculosis

Every year worldwide more than 9 million new cases of tuberculosis reported. Incidence is declining at a rate of less than 1% per year. Around 2 million people die from tuberculosis infection every year. Worldwide burden of tuberculosis has stimulated much interest in research for new approaches to the management of this disease.[1] *Mycobacterium tuberculosis (M. tuberculosis)* causes tuberculosis and is a very important pathogen of humans.

Tuberculosis kills more people than ever, with the increasing number of HIV-infected individuals.[2] One third of the world's population currently infected and new infections occur every second, which results in new tuberculosis infection around 1% of the world population every year.[3] According to studied facts around newly acquired infections between 2002 and 2010 would be 1 billion persons, of these, 150 million will get sick and 36 million will die of tuberculosis. *Mycobacterium tuberculosis* is related and associated with other species of mycobacteria, referred to as the Mycobacteria Tuberculosis Complex (MTB complex). MTB complex includes; *M. bovis*, (including the vaccination strain BCG) *M. tuberculosis, M. africanum, M. microti*, and *M. canettii.*[4] These grouping is based on several parameters which include the analysis of antigenic extracts, target epitopes for monoclonal antibodies and antigenic Historically, the diagnosis and treatment of M. tuberculosis has been difficult, because of its peculiarities; it has a high concentration of lipids in the cell wall, which makes it impermeable to stains and dyes, requiring special staining techniques for microscopic observation, resistant to many antibiotics, resistant to osmotic lysis via complement deposition, as well as resistant to lethal oxidation and survival inside macrophages, making it possible to undergo a long period of latency. Unlike many pathogenic bacteria, *M. tuberculosis* also grows slowly, making culture and susceptibility testing time consuming.[5]

Basic facts about TB

Mycobacterium tuberculosis

TB is a bacterial disease caused by *Mycobacterium tuberculosis* (and occasionally by *Mycobacterium bovis* and *Mycobacterium africanum*). These organisms are also known as tubercle bacilli (because they cause lesions called tubercles) or as acid-fast bacilli (AFB). When sputum containing tubercle bacilli is stained with certain dyes and examined under the microscope, the bacilli look red. This is because they are acid-fast (they have kept the dye even after being washed with acid and alcohol). Tubercle bacilli can remain dormant in tissues and persist for many years.[6-7]

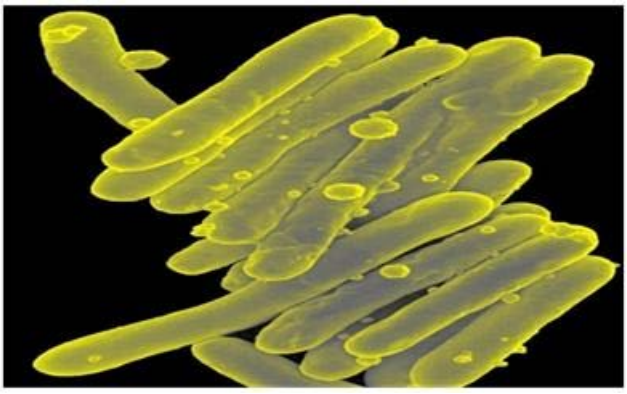


Figure 1: *Mycobacterium tuberculosis*[8]

Tuberculous infection and tuberculosis

Tuberculous infection occurs when a person carries the tubercle bacilli inside the body, but the bacteria are in small numbers and are dormant. These dormant bacteria are kept under control by the body's defences and do not cause disease. Many people have tuberculous infection and are well. Tuberculosis is a state in which one or more organs of the body become diseased as shown by clinical symptoms and signs. This is because the tubercle bacilli in the body have started to multiply and become numerous enough to overcome the body's defences.[7]

Sources of infection

The most important source of infection is the patient with TB of the lung, or pulmonary TB (PTB), and who is coughing. This person is usually sputum smear-positive. Coughing produces tiny infectious droplet nuclei (infectious particles of respiratory secretions usually less than 5 µm in diameter and containing tubercle bacilli). A single cough can produce 3000 droplet nuclei. Droplet nuclei can also be spread into the air by talking, sneezing, spitting and singing, and can remain suspended in the air for long periods. Direct sunlight kills tubercle bacilli in 5 minutes, but they can survive in the dark for long periods. Transmission therefore generally occurs indoors. Droplet nuclei are so small that they avoid the defences of the bronchi and penetrate into the terminal alveoli of the lungs, where multiplication and infection begin. Two factors determine an individual's risk of exposure: the concentration of droplet nuclei in contaminated air and the length of time he or she breathes that air. TB of cattle (bovine TB) occurs in some countries. Milk-borne *M. bovis* may infect the tonsils presenting as scrofula (cervical lymphadenitis), or the intestinal tract, causing abdominal TB.[7]

Routes by which TB is not transmitted

TB is not transmitted through food and water or by sexual intercourse, blood transfusion, or mosquitoes.[7]

Risk of infection

An individual's risk of infection depends on the extent of exposure to droplet nuclei and his or her susceptibility to infection. The risk of infection of a susceptible individual is high with close, prolonged, indoor exposure to a person with sputum smear-positive PTB. The risk of transmission of infection from a person with sputum smear-negative PTB is low, and even lower from someone with extra pulmonary TB (EPTB).[7]

Risk of progression of infection to disease

Infection with *M. tuberculosis* can occur at any age. Once infected with *M. tuberculosis*, a person can stay infected for many years, probably for life. The vast majority (90%) of people without HIV infection who are infected with *M. tuberculosis* do not develop TB. In these, asymptomatic but infected individuals, the only evidence of infection may be a positive tuberculin skin test. Infected persons can develop TB at any time. The disease can affect most tissues and organs, but especially the lungs. The chance of developing disease is greatest shortly after infection and steadily lessens as time goes by. Infected infants and young children are at greater risk of developing disease than older people because they have an immature immune system. TB is also more likely to spread from the lungs to other parts of the body in this age group. Children who develop disease usually do so within two years following exposure and infection. Most do not develop disease in childhood but may do so later in life. Various physical or emotional stresses may trigger progression of infection to disease. The most important trigger is weakening of immune resistance, especially by HIV infection.[7]

Treatment of tuberculosis:

Treatment of tuberculosis divided in following class.

First line Treatment

All first-line anti-tuberculous drug names have a standard three-letter and a single-letter abbreviation:[9]

- Ethambutol (E)
- Isoniazid (INH or H,)
- Pyrazinamide (Z)
- Rifampicin (R)
- Streptomycin (S)

Second line Treatment

These drugs have either low antitubercular efficacy or high toxicity or both; are used in special circumstance only.[9]

- Thiacetazone (Tzn)
- Para amino salicylic acid (PAS)
- Ethionamide (Etm)
- Cycloserine (Cys)
- Kanamycin (Kmc)
- Amikacin (Am)
- Capreomycin (Cpr)

Newer drugs[9]

- Ciprofloxacin
- Ofloxacin
- Clarithromycin
- Azithromycin
- Rifabutin

DOTS

DOTS (directly observed treatment, short-course), is the name given to the World Health Organization-

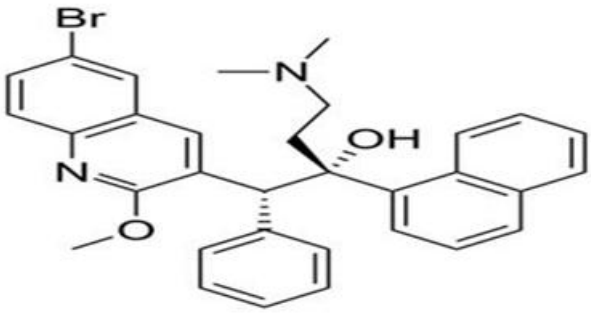
recommended tuberculosis control strategy that combines five components:

- Government commitment (including both political will at all levels, and establishing a centralized and prioritized system of TB monitoring, recording and training)
- Case detection by sputum smear microscopy
- Standardized treatment regimen directly observed by a healthcare worker or community health worker for at least the first two months
- A regular drug supply
- A standardized recording and reporting system that allows assessment of treatment results.

The first WHO endorsed DOTS-Plus programmes began in 2000. At that time, the Green Light Committee (GLC) was established to promote access to high quality second-line drugs for appropriate use in TB control programmes. DOTS-Plus pilot projects have demonstrated the feasibility and effectiveness of MDR-TB treatment in less affluent countries. In 2002, the Global Fund to fight AIDS, TB, and Malaria (GFATM) started financing TB control programmes, including MDR-TB, thus greatly reducing the economic barrier to MDR3TB control. Since then, DOTS-Plus projects have multiplied rapidly. By the end of 2007, 67 projects in 52countries approved by the GLC, with a cumulative total of over 30,000 MDR-TB patients, had been launched world wide, many of them with financial support from the GFATM. Based on data and experience from these projects, practices and further scientific evidence have emerged regarding services for MDR-TB. DOTS-Plus programmes can and should strengthen the basic DOTS strategy.[10-11]

New Approach

R207910:- Bedaquiline (also known as Sirturo, TMC207 or R207910) affects the proton pump for ATP synthase, which is unlike the quinolones, whose target is DNA gyrase.[12]



(1*R*,2*S*)-1-(6-Bromo-2-methoxy-3-quinolyl)-4-dimethylamino-2-(1-naphthyl)-1-phenyl-butan-ol

The standard regimen

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 drugs result in the rapid development of resistance and treatment failure. The rationale for using multiple drugs to treat TB is based on simple probability.[13]

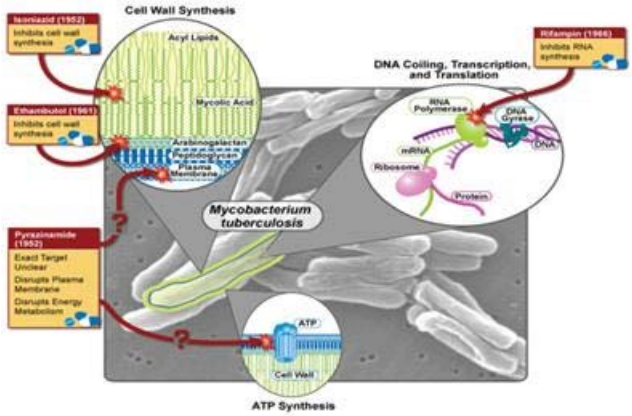


Figure 2: First-Line Treatment of Tuberculosis (TB) for Drug-Sensitive TB[11]

Therapeutic Targets

Cell wall biosynthesis related targets

Cell wall biosynthesis is a particularly good source of molecular targets because the biosynthetic enzymes do not have homologues in the mammalian system.[12] The cell wall of *M. tuberculosis* is very important for its survival with in constrained conditions such as those inside of human macrophages. The biosynthesis of the cell wall components involves many important stages and different enzymes that are absent in mammals and could be attractive drug targets.[14-16] Recently, the 2C-methyl-D-erytrol 4-fosphate (MEP) pathway was found as a potential drug target since the end product of the pathway leads to the formation of isoprenoids, which are responsible for the synthesis of several cell wall components.[17-18] Peptidoglycan biosynthesis is another source of potential drug targets. For instance, alanine racemase and D-Ala-D-Ala-ligase catalyze the first and second committed steps in bacterial peptidoglycan biosynthesis, and since these steps are essential for important polymers, they are good drug targets.[19-20]

Mycolic acid biosynthesis related targets

The mycobacteria lipid metabolism, mycolic acids are essential structural components of the mycobacterial cell wall.[11] The early stage of fatty acid biosynthesis, which generates the precursors of mycolic acids, is a rich source of antibacterial targets.[20] It is also the site of action of INH and ethionamide.[21-22] *M. tuberculosis* has both types of fatty acids synthase (FAS) systems found in nature, FAS-I and FAS-II. FAS I is the system responsible for de novo synthesis of C16-C26 fatty acids and the FAS II system extends these fatty acids up to C56 chains to make precursors of mycolic acids, which are essential for growth. Since enoil-ACP reductase (InhA) is the target of INH, it is reasonable to assume that all steps in the FAS-II pathway will be essential for the viability of *M.*

tuberculosis. Many of the individual enzymes of the FAS-II system have been expressed, purified and characterized.[23-30]

Energy production related targets

Isocitrate lyase (ICL) is an important enzyme in this category and also an important drug target. ICL is involved in energy production via the metabolism of acetyl-CoA and propionial CoA of the glyoxilate pathway. Inactivation of the *icl* gene leads to attenuation of both persistent and virulent strains of *M. tuberculosis.*[31-32]

Amino acid biosynthesis related drug targets

Amino acid biosynthesis is another important target for developing anti-TB drugs. The shikimate pathway is very important and is involved in the synthesis of aromatic amino acids in algae, fungi, bacteria, and higher plants; however, it is absent in the mammalian system.[32] The final product of the shikimate pathway, chorismate, is a key biosynthetic intermediate involved in generating aromatic amino acids and other metabolites. The entire pathway is essential in *M. tuberculosis.*[33] This feature makes the pathway an attractive target for developing anti-TB drugs with minimum cross reactivity.[34] Other enzymes of this pathway are also likely to be essential, and shikimate dehydrogenase[35], and 5-enolpyruvylshikimate 3-phosphate synthase[36] have been characterized Drug Development – A Case Study Based Insight into Modern Strategies 210 in detail. The biosynthesis of non-aromatic amino acids is also emerging as a potential drug target. The impact of amino acids such as lysine[37], proline, tryptophan and leucine[38] is evident from the fact that knocked out *M. tuberculosis* strains of the genes required for amino acid biosynthesis showed less virulence.[39-40] Another attractive target of the lysine biosynthesis pathway is the enzyme dihydrodipicolinate reductase, for which potent inhibitors have been identified.[41]

Cofactor-related drug targets

Several cofactor biosynthetic pathways and pathways requiring some cofactors are good candidates for identification of new drug targets. Folate derivatives are cofactors utilized in the biosynthesis of essential molecules including purines, pyrimidines, and amino acids. While bacteria synthesize folate de novo, mammals must assimilate preformed folate derivatives through an active transport system Dihydrofolate reductase, which catalyses the reduction of dihydrofolate to tetrahydrofolate, a key enzyme In folate utilization whose inhibition may affect the growth of *M. tuberculosis* , and dehydropteroate synthase are validated targets of the widely used antibacterial sulfonamide, trimethoprim.[42-44] Two enzymes involved in the de novo biosynthesis of NAD that affects the NADH/NAD+ ratio upon which *M. tuberculosis* is dependent, have been studied as possible drug targets.[45] Genomic analysis studies have suggested that the riboflavin biosynthesis pathway is essential in *M. tuberculosis* and the lumazine synthase pathway has been validated as a target for anti-TB drug discovery.[46-47]

DNA metabolism

Differences in mammalian and mycobacterial thymidin monophosphate kinase have been studied and exploited in an attempt to find selective inhibitors for this drug target.[48-49] Other targets are ribonucleotide reductases that catalyze the first committed step in DNA synthesis and have differences with corresponding mammalian enzyme.[50-51] DNA ligases that play an important role in the replication and repair of DNA, are classified as NAD+ or ATP dependent. NAD+ dependent ligases are only found in some viruses and eubacteria. LigA is essential for growth of *M. tuberculosis* and inhibitors that distinguish between the two types of ligases and have anti-TB activity have been identified.[52-53] DNA gyrase has also been validated as a target for *M. tuberculosis*, since this is the only type II topoisomerase that it possesses. Its inhibition by fluoroquinolones results in highly mycobactericidal activity.[54]

Menaquinone biosynthesis

It appears that menaquinone is the only quinone in *M. tuberculosis*, so its biosynthesis is essential for growth. The menaquinone pathway is not present in humans, and bacterial homologues of MenA-E and MenH have been described in *M. tuberculosis*, so this pathway is another promising drug target.[55]

Other potential drug targets in M. tuberculosis

The tubercle bacillus produces no less than 20 cythochrome p450 enzymes, some of which appear to play essential roles.[56] Antifungal azole drugs target these enzymes and the cytochrome p450 homologues in the bacteria. Drugs like miconazole and clotrimazole are active against *M. tuberculosi.*[57-58] Subsequent crystallization studies of the *M. tuberculosis* cytochrome p450 enzyme system evoked studies to evaluate new drugs.[59] Peptide deformylase inhibitors may be effective against *M. tuberculosis* since peptide deformylase catalyzes the hydrolytic removal of the B-terminal formyl group from nascent proteins. It is a metalloprotease essential for maturation of nascent polypeptides in bacteria but not essential for humans, making it an attractive target for antibacterial drug development.[60]

Future prospects

A major concern arisen recently is the threat of latent infection in a person exposed to a source case infected with multidrug-resistant strain of M. tuberculosis (MDR-TB). As nearly 440 000 cases of MDR-TB corresponding to nearly 5% of all incident TB cases occurred in 2008 , this concern is likely to attract greater attention in the near future. Only scant information is available in this setting as there have been no randomized controlled trials to assess the effectiveness of specific regimens.[61-62] A 6 to 12 month regimen of a fluoroquinolone + pyrazinamide or ethambutol + pyrazinamide is recommended by CDC.

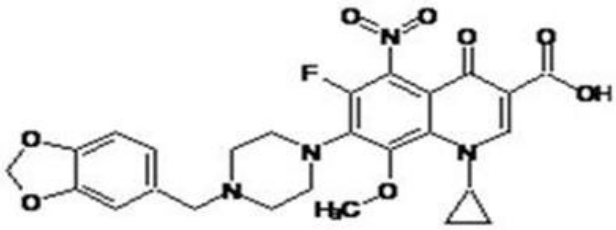
However, the effectiveness and optimal duration of these regimens is largely unknown as they are very poorly tolerated.[63]

The newer drugs that are in different stages of development may offer better alternatives for the treatment of both, active TB disease as well as Latent tuberculosis infection (LTBI). The new generation fluoroquinolones such as moxifloxacin have excellent (bactericidal) activity against M. tuberculosis and may be more effective in the treatment of LTBI than older drugs of the same class.[64-65] In experimental animal model of latent infection, the once weekly regimen of rifapentine + moxifloxacin for 3 months was found to be as effective as daily therapy with isoniazid for 9 months.[66] The PA-824, a nitroimidazo- oxazine, is another promising compound that is active against MDR-TB strains and is also active against non-replicating persistent bacteria, making it an ideal drug candidate for the treatment of LTBI. The treatment regimen containing PA-824, moxifloxacin, and pyrazinamide was highly effective in murine model oftuberculosis.[67] The OPC-67683, a nitroimidazo-oxazone, is another promising new compound that shows promising results against tuberculosis in mice.[68] A diarylquinoline (R207910 also known as TMC207) has shown more potent early bactericidal activity than INH during early phase of infection and higher bactericidal activity late in infection than RMP alone and thus mayprovide another option for the treatment of LTBI . Another promising drug is SQ109 (1,2-ethylenediamine) that is structurally related to ethambutol but is more potent.[69-70] It is expected that some of these new drugs will provide additional options for the treatment of LTBI in the near future. Another approach that is actively being pursued for controlling development of active disease in persons with LTBI is development of novel vaccines that may prevent TB disease reactivation by efficiently containing the pathogen in a latent state in infected individuals.[71-72] More than 10 vaccine candidates have entered clinical trials in the past few years.[69] Two of these vaccine candidates are recombinant M. bovis BCG constructs designed to improve the antigenicity and/or immunogenicity of the current BCG vaccine.[73-74] Another seven subunit vaccines are being tested in clinical trials and are being used as booster vaccines designed to reorient the immune response after priming with recombinant BCG vaccines. Three of the subunit vaccines are incorporated in viral carriers while the other four subunit vaccines are being delivered through adjuvant formulations.[70,75-76] The recombinant BCG and booster subunit vaccines are designed to be given prior to M. tuberculosis infection to sustain latent infection and either prevent or delay the reactivation of latent infection by inducing a memory T cell response that resists exhaustion and suppression.[70] Other vaccine candidates under development include further modifications such as inclusion of dormancy-regulated genes to improve the efficacy of BCG replacement vaccine candidates for post-exposure vaccination of latently infected individuals.[77-78]

A drawback of the above vaccines is that they prevent or delay the reactivation of dormant infection but do not eradicate the pathogen. However, attempts are now underway to combine the antigens of metabolically active (such as secreted proteins) and dormant (such as dormancy regulated genes) state of M. tuberculosis in both, the recombinant BCG and subunit booster vaccines to achieve sterile eradication of the pathogen.[79-82]

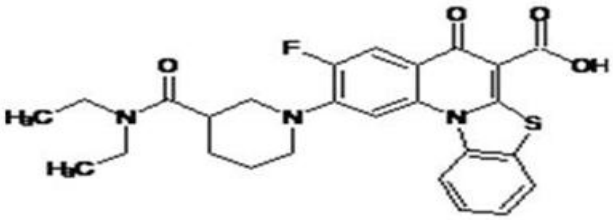
Literature of review

Senthilkumar, P. et al. synthesized a series of 36 compound containing 1-cyclopropyl-1, 4-dihydro-6-fluoro-7-(substituted secondary amino)-8-methoxy -5-(sub)-4-oxoquinoline-3-carboxylicacids having antitubercular activity against *Mycobacterium tuberculosis* H37Rv (MTB). Activity of all compounds was measured as MIC value. In the series the compound with substitution at C-5 position on quinoline ring with NO_2 group and other substitution at C-7 position on quinoline ring with 1-(1,3-benzodioxol-5-ylmethyl)-4-methylpiperazine gave 7-(4-((Benzo[d][1,3] dioxol-5-yl)methyl)piperazin-1-yl)- 1- cyclopropyl-1,4 dihydro-6-fluoro-8- methoxy-5- nitro-4- oxoquinoline- 3-carboxylic acid (Structure 01) as the potent compound of the series. The activity of potent compound was found to be 0.35µM and it was evaluated by agar dilution method.[83]



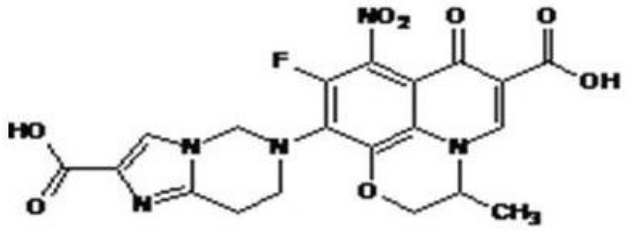
Structure 01

Dinakaran, M. et al. synthesized a series of 34 compound containing 2-(sub)-3-fluoro/nitro-5, 12-dihydro-5-oxobenzothiazolo [3, 2-a] quinoline-6-carboxylic acid having antitubercular activity against *Mycobacterium tuberculosis* H37Rv (MTB). In the series the compound with substitution at C-6 position on quinoline ring with fluorine group and other substitution at C-7 position on quinoline ring with *N*, *N*-diethylpiperidine-3-carboxamide gave 2-(3-(Diethylcarbamoyl) piperidin-1-yl)-3-fluoro-5, 12-dihydro-5- oxobenzothiazolo [3,2-a]quinoline-6-carboxylicacid (Structure 02) as the potent compound of the series. Activity of all compounds was measured as MIC value. It was evaluated by agar dilution method and activity was found to be 0.18µM.[84]



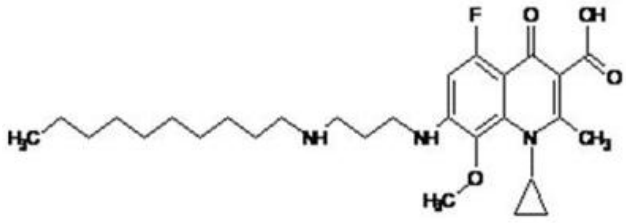
Structure 02

Dinakaran, M. et al. synthesized a series of 30 compound containing. 9-fluoro-2,3-dihydro-8,10-(mono/di-sub)-3-methyl-8-nitro-7-oxo-7H[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylicacids having antitubercular activity against *Mycobacterium tuberculosis* H37Rv (MTB). Activity of all compounds was measured as MIC value. In the series the compound with substitution at C-7 position on quinoline ring with NO2 group and other substitution at C-9 position on quinoline ring with 5, 6, 7, 8-tetrahydroimidazo[1,2-*c*]pyrimidine-2-carboxylic acid gave 10-(2-carboxy-7,8-dihydroimidazo[1,2-*c*]pyrimidin-6(5*H*)-yl)-9-fluoro-3-methyl-8-nitro-7-oxo-2,3-dihydro-7*H*1,4]oxazino[2,3,4*ij*]quinoline-6-carboxylic acid (Structure 03) as the potent compound of the series. It was evaluated by agar dilution method and activity was found to be 0.19µM.[85]



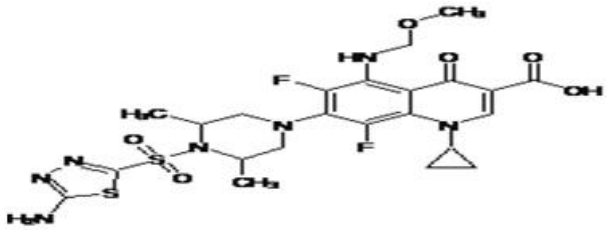
Structure 03

De Almeida, M. V. et al. synthesized a series of 25 compound containing.1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid having antitubercular activity against *Mycobacterium tuberculosis* H37Rv (MTB). Activity of all compounds was measured as MIC value. In the series the compound with substitution at C-7 position on quinoline ring with ethyl group gave 1-cyclopropyl-5-fluoro-8-methoxy-2-methyl-4-oxo-1, 4 dihydroquinoline, N-decylpropane-1, 3 diamine-3-carboxylic acid (Structure 04) as the potent compound of the series. Activity of all compounds was measured as MIC value. It was evaluated by Middle brook 7H9 agar medium and activity was found to be 0.31 µg/Ml.[86]



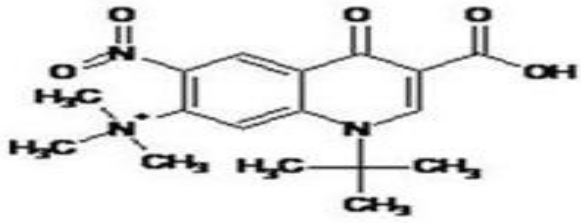
Structure 04

Talath, S.; Gadad synthesized a series of 6 compound containing 7-[4-(5-amino-1,3,4thiadiazole-2-sulfonyl)]-1-piperazinyl fluoroquinolonic derivatives having antitubercular activity against *Mycobacterium tuberculosis* H37Rv (MTB). Activity of all compounds was measured as MIC value. In the series the compound with substitution at C-5 and C-8 on quinoline ring with $NHCOCH_3$ and Fluorine and other substitution on piperazine ring with methyl group at C-3 and C-5 gave 5-Amino-7-[4-(5-amino-[1, 3, 4]-thiadiazole-2-sulfonyl) - 3′, 5′-dimethylpiperazin-1 -yl]-1-cyclopropyl-6, 8-difluoro-4-oxo-1, 4-dihydro-quinoline-3-carboxyl (Structure 05) as the potent compound of the series. It was evaluated by broth micro dilution method and activity was found to be 1 µg/Ml.[87]



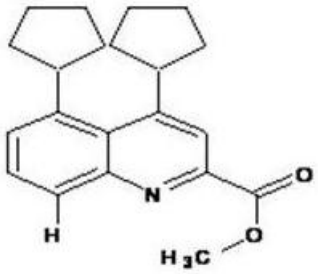
Structure 05

Artico, M. et al. Synthesized a series of 8 compound containing 6, 7-diamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid having antitubercular activity against Mycobacterium tuberculosis H37Rv (MTB). Activity of all compounds was measured as MIC value. In the series the compound with same substitution at N-1 and C-7 position on quinoline ring with t-butly gave 1-*tert*-butyl-3-carboxy-*N*, *N*, *N*-trimethyl-6-nitro-4-oxo-1, 4- dihydroquinolin-7-aminium (Structure 06) as the potent compound of the series. It was evaluated by MTT method and activity was found to be 0.5 µg/mL.[88]



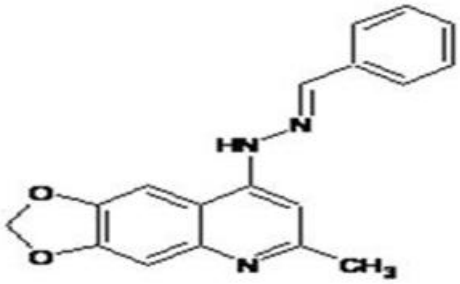
Structure 06

Vaitilingam, B. et al. synthesized a series of 46 compound containing 1-cyclopropyl-1,4-dihydro-6-fluoro-7-(substituted secondary amino)-8-methoxy -5-(sub)-4-oxoquinoline-3-carboxylic acids having antitubercular activity against *Mycobacterium tuberculosis* H37Rv (MTB). In the series the compound with same substitution at C-4, C-5 position on quinoline ring with cyclopentane group and other substitution at C-8 position on quinoline ring with Hydrogen gave methyl 4, 5-dicyclopentylquinoline-2-carboxylate (Structure 07) as the potent compound of the series. It was evaluated by broth micro diluation assay method and activity of all compounds was measured as MIC value and activity was potent compound 1.00 µM.[89]



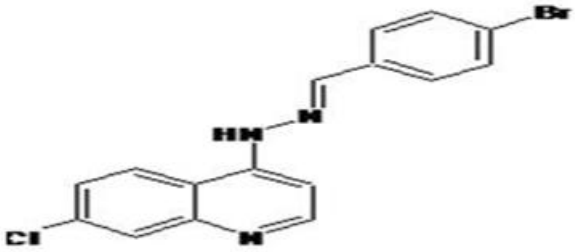
Structure 07

Gemma, S. et al. synthesized a series of 58 compound containing 4-quinolylhydrazone having antitubercular activity against *Mycobacterium tuberculosis* H37Rv (MTB). Activity of all compounds was measured as MIC value. In the series the compound with substitution at C-2 position on quinoline ring with CH_3 group and other substitution at C-4 position on quinoline ring with Benzene gave 8-(2E)-2-benzylidenehydrazinyl-6-methyl- 1, 3- diazole (4, 5-g) quinoline(Structure 08) as the potent compound of the series. It was evaluated by Microplate Alamar Blue Assay (MABA) and activity was found to be 2.6µM.[90]



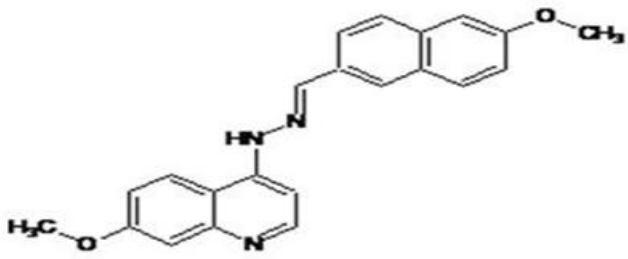
Structure 08

André, L. P. et al. synthesized a series of 21 compound containing 7-chloro-4-quinolinylhydrazones derivatives having antitubercular activity against *Mycobacterium tuberculosis* H37Rv (MTB). Activity of all compounds was measured as MIC value. In the series the compound with substitution at C-1, C-2, C-4, C-5 position on quinoline ring with Hydrogen and other substitution at C-3 position on quinoline ring with Bromine gave 4-(2E)-2-(4-bromobenzylidene) Hydrazinyl-7-chloroquinoline (Structure 09) as the potent compound of the series. It was evaluated by Microplate Alamar Blue Assay (MABA) and activity was found to be of the potent compound 2.5µM.[91]



Structure 09

Savini, L. et al. synthesized a series of 56 compound containing 4-quinolylhydrazones derivatives having antitubercular activity against *Mycobacterium tuberculosis* H37Rv (MTB). Activity of all compounds was measured as MIC value. In the series compound with substitution at C-2 position on quinoline ring with Hydrogen and other substitution at C-4, C-7 position on quinoline ring with 2-OCH3–naphthyl, 7-OCH3 gave 7-methoxy-4{(2E)-2-[(6methoxynaphthalen-2-yl) methylidene] hydrazinyl (Structure 10) as the potent compound of the series. It was evaluated by Microplate Alamar Blue Assay (MABA) and activity was found to be 6.25 µM.[92]



Structure 10

CONCLUSION

Current available treatment for tuberculosis takes too long to be effective and requires too many medications. Sensitive disease treatment requires around 6-9 months whereas treatment of drug-resistant TB is even lengthier, taking 18-24 months or longer. Second-line drugs are also much more toxic and more expensive too than the standard first-line anti TB-regimen. Current first-line treatment regimens are not compatible with certain common antiretroviral (ARV) therapies used to treat HIV/AIDS. Therefore, new drugs are needed that will be effective in treating children, and latent TB infection (an asymptomatic infection), and will be compatible with antiretroviral therapy. New regimens need to be affordable and easily managed in the field. The introduction of new drugs, preferably with novel mechanisms of action, which will be active against current drug-resistant strains, and fewer TB drug side effects, will hopefully allow for a shorter TB regimen for both drug-sensitive and drug-resistant disease. Shortening treatment to four or two months or even less should increase cure rates, improve patient adherence, and lessen the likelihood of bacterial strains developing drug resistance.

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