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A Review On Current Status Of ATP Synthase Inhibitors As Anti-Tuberculosis Agents

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Abstract:
Tuberculosis (TB) remains a global health crisis, aggravated by multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of Mycobacterium tuberculosis. Traditional therapies are losing efficacy, highlighting the urgent need for novel drug targets. The mycobacterial ATP synthase, essential for energy metabolism in both replicating and dormant bacilli, has emerged as a promising target. Inhibitors such as diarylquinolines (e.g., bedaquiline), along with novel quinolines, squaramides, and imidazo[1,2-a]pyridine ethers, demonstrate potent activity and offer structural diversity for drug development. These advances underscore ATP synthase inhibition as a paradigm shift in TB chemotherapy, enabling more effective strategies against resistance.
Keywords: *Tuberculosis; Multidrug resistance; ATP synthase; Diarylquinolines; Quinolines; Squaramides*

1. INTRODUCTION

Tuberculosis (TB) is a persistent infectious disease predominantly caused by Mycobacterium tuberculosis, a slow-growing, acid-fast bacillus characterized by a distinctive lipid-rich cell wall that provides resistance to many environmental stressors and antimicrobial drugs. Although treatable and preventive, tuberculosis remains a significant worldwide health challenge, especially in low- and middle-income nations [1]. The World Health Organization (WHO) ranks tuberculosis (TB) among the ten foremost causes of mortality globally and identifies it as the primary cause of death attributable to a single infectious agent, exceeding even HIV/AIDS. The disease mostly impacts the lungs (pulmonary TB), however extrapulmonary symptoms may affect lymph nodes, bones, meninges, kidneys, and other organs. Tuberculosis is transmitted via airborne droplets, rendering it extremely contagious in densely populated or resource-constrained environments [2].

Tuberculosis continues to be a significant global public health issue. Recent WHO data indicate that roughly 10.6 million individuals contracted tuberculosis in 2022, resulting in almost 1.3 million fatalities related to the disease. The burden is disproportionately allocated, with nations in South-East Asia, Africa, and the Western Pacific representing the majority of cases. India accounts for around 25% of the global tuberculosis incidence [3]. Multiple risk factors, including HIV co-infection, diabetes, malnutrition, tobacco use, and inadequate living conditions, markedly elevate susceptibility. Drug-resistant tuberculosis presents a further epidemiological challenge. Multidrug-resistant tuberculosis (MDR-TB), characterized by resistance to at least isoniazid and rifampicin, has been documented in more than 150 countries. Extensively drug-resistant tuberculosis (XDR-TB), which exhibits resistance to fluoroquinolones and at least one second-line injectable antibiotic, in addition to isoniazid and rifampicin, exacerbates treatment results. Drug-resistant strains of tuberculosis are linked to extended treatment periods, increased toxicity, and diminished cure rates [4-7].

The advent of anti-tuberculosis chemotherapy in the mid-20th century transformed TB treatment. The initial efficacious medication was streptomycin, identified in 1943, which markedly decreased mortality yet swiftly resulted in resistance when administered as monotherapy. Isoniazid and para-aminosalicylic acid (PAS) were created in the 1950s, establishing combination therapy as the foundation of tuberculosis management to avert resistance. Rifampicin, introduced in the 1960s, significantly improved therapy efficacy. Ethambutol and pyrazinamide subsequently concluded the "first-line" arsenal [8,9]. The conventional treatment protocol devised in the 1980s, referred to as short-course chemotherapy,

incorporated isoniazid, rifampicin, pyrazinamide, and ethambutol during an initial intense phase lasting two months, succeeded by a continuation phase of isoniazid and rifampicin for four months. This six-month treatment protocol is the benchmark for drug-susceptible tuberculosis and has attained elevated cure rates with consistent adherence. Nonetheless, prolonged treatment duration, hepatotoxicity, and the development of resistance have prompted the pursuit of enhanced therapeutic options.

The escalating menace of MDR-TB and XDR-TB has prompted the advancement of novel pharmaceuticals and therapeutic protocols. Bedaquiline, a diarylquinoline launched in 2012, specifically targets mycobacterial ATP synthase and constitutes the first new class of tuberculosis drugs in more than forty years [10,11]. Delamanid, a nitroimidazole derivative, impedes mycolic acid production and demonstrates efficacy against resistant strains [12,13]. Pretomanid, a nitroimidazole licensed in 2019, is utilized in combination therapies for extremely resistant tuberculosis [14,15]. Linezolid, an oxazolidinone antibiotic initially designed for Gram-positive infections, has been repurposed for tuberculosis and is progressively integrated into multidrug-resistant tuberculosis regimens [16,17]. These novel medicines, frequently utilized alongside enhanced background treatments, have reduced therapy durations and enhanced outcomes for resistant instances. Moreover, initiatives are underway to reduce the duration of treatment for drug-susceptible tuberculosis. Regimens incorporating rifapentine and moxifloxacin have shown promise in shortening therapy to four months while maintaining comparable efficacy to the standard six-month regimen. Notwithstanding these advancements, accessibility and cost continue to pose challenges in several high-burden nations.

The unique physiology of M. tuberculosis offers multiple potential drug targets [18]. Classical drugs act on essential biosynthetic pathways (Table 1):

Table 1: Drugs targets for tuberculosis

S. No	**Drug target**	**Description**
1	Cell wall synthesis inhibitors	Isoniazid and ethambutol inhibit mycolic acid and arabinogalactan synthesis, respectively.
2	RNA synthesis inhibitor	Rifampicin binds to DNA-dependent RNA polymerase, blocking transcription.
3	Energy metabolism inhibitors	Pyrazinamide disrupts membrane energetics and transport, while bedaquiline inhibits ATP synthase.
4	Protein synthesis inhibitors	Streptomycin and other aminoglycosides target the ribosome, while linezolid inhibits the 50S ribosomal subunit.

Novel targets under exploration include enzymes involved in lipid metabolism, virulence factors such as serine/threonine kinases, regulatory proteins controlling dormancy, and pathways responsible for persistence inside macrophages. Host-directed therapies, which aim to modulate the host immune response rather than the bacterium itself, are also being investigated as adjunctive strategies to shorten therapy and reduce relapse.

ATP synthase is a crucial enzyme complex in Mycobacterium TB that facilitates the synthesis of adenosine triphosphate (ATP) via proton translocation across the cell membrane. In contrast to numerous bacteria, *M. tuberculosis* predominantly depends on oxidative phosphorylation for energy production, rendering ATP synthase an essential element for life, even during latent infection [19]. This reliance presents a distinctive druggable target, as the blockage of ATP generation swiftly depletes cellular energy, resulting in bacterial mortality. Bedaquiline, the inaugural diarylquinoline, selectively targets the c subunit of the *M. tuberculosis* ATP synthase proton pump. Bedaquiline binds to the c-ring, obstructing proton flow, which disrupts the proton motive force and ceases ATP generation. Authorized in 2012, it became the inaugural innovative tuberculosis medication in over forty years and has greatly enhanced results for multidrug-resistant tuberculosis (MDR-TB). Resistance to bedaquiline has been observed with increasing frequency. Mutations in the atpE gene, which encodes the c component of ATP synthase, confer

significant resistance by diminishing drug binding affinity. Moreover, mutations in the transcriptional regulator Rv0678, which governs the MmpS5-MmpL5 efflux pump system, result in enhanced efflux and low-to-moderate resistance. The advent of resistance mechanisms highlights the necessity for diligent management, regular susceptibility testing, and combination therapy to maintain the efficacy of bedaquiline [20-22].

The importance of ATP synthase and resistance to its newest developed inhibitor warrants a review on current status of the compounds which have been identified as ATP synthase inhibitors in the latest literature. This review accounts for the latest developments in the field of ATP synthase inhibitors.

2. ATP synthase

Adenosine triphosphate (ATP) is comprised of the molecule adenosine bound to three phosphate groups. Adenosine is a nucleoside consisting of the nitrogenous base adenine and the five-carbon sugar ribose. Adenosine Triphosphate (ATP), commonly termed "molecular currency" for intracellular energy transmission, serves as a chemical fuel that drives numerous biological processes. ATP synthesis is the fundamental energy-producing process present in all biological forms. ATP (Figure 1) serves as the energy source for nearly all cellular metabolic pathways. In an ATP (a multifunctional ester) molecule, two high-energy phosphate bonds, known as phosphoanhydride bonds, account for its elevated energy content. Adenosine diphosphate (ADP) serves as a substrate for ATP synthesis and is a byproduct of its hydrolysis. ADP enhances respiration (oxidative metabolism)-the degradation of ATP elevates ADP levels, subsequently activating the mechanisms that supply energy for ATP synthesis [23].

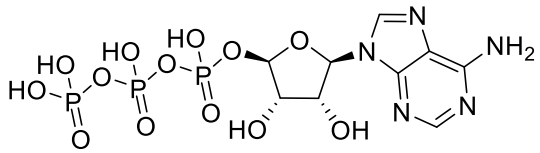


Figure 1: Chemical structure of Adenosine Triphosphate

3. Physiology and working of ATP synthase

ATP production is the most prevalent chemical reaction inside the biological realm. ATP is produced from its precursor, ADP, by ATP synthases. These enzymes are located in the cristae and inner membrane of mitochondria, the thylakoid membrane of chloroplasts, and the plasma membrane of bacteria [24]. ATP synthase is the final enzyme in the oxidative phosphorylation pathway that utilizes electrochemical energy to facilitate ATP synthesis [25,26]. Typically, it is widely accepted that ATP synthesis takes place in mitochondria. In bacteria and archaea that lack mitochondria, ATP synthase is located in their plasma membrane. Mycobacterial ATP synthase is found embedded in the bacterial plasma membrane, specifically within the cell membrane. Bacterial ATP synthase comprises a membrane-embedded F_0 sector with a subunit composition of $a_1b_2c_{10-15}$ and a hydrophilic F_1 component, consisting of subunits $\alpha 3\beta 3\gamma\delta\varepsilon$. Mitochondrial ATP synthase has several additional peripheral subunits alongside the eight core subunits observed in bacteria [27,28]. The translocation of ions, primarily protons, through F_0 induces the rotation of the oligomeric c ring subunit, which is linked to the rotation of subunits γ and ε. The rotation of subunit γ inside the $\alpha_3\beta_3$ hexamer of F_1 subsequently facilitates ATP production [29-31]. Although the fundamental architecture of ATP synthase and its rotational catalysis mechanism are seemingly maintained across the three domains of life, ATP synthases from certain organisms exhibit specialized characteristics that may reflect adaptations to specific environmental conditions. Thes studies have shown that there exists certain divergence in the structure of human and mycobacterial ATPase [32]. The membrane domain of mycobacterial ATP synthase is integrated inside the inner plasma membrane, whereas the catalytic F_1-domain of the enzyme protrudes into the bacterial cytoplasm, connected to the membrane domain by a central stalk and a peripheral stalk (PS). Similar to other ATP synthases found in eubacteria, chloroplasts, and mitochondria, the enzyme utilizes a proton-motive force (pmf) across the inner membrane space (IMS) produced by respiration to facilitate the synthesis of ATP from adenosine diphosphate (ADP) and inorganic phosphate in the F_1 domain by a mechanical rotational process. The mycobacterial rotor has a membrane-anchored ring of nine c-subunits, connected to an

elongated central stalk formed by single copies of the γ- and ε-subunits. The central stalk is ubiquitous among all F-type ATP synthases and extends into the spherical component of the F_1-domain, which comprises an assembly of three α-subunits and three β-subunits arrayed alternately around the central axis. The rotation of the asymmetrical rotor induces a sequence of conformational alterations in the three catalytic sites, located at three of the six interfaces between α- and β-subunits, resulting in the sequential binding of the substrates ADP and phosphate, the synthesis of ATP, and ultimately the release of ATP. Each 360° rotating cycle generates three ATP molecules [33-35].

4. ATP synthase inhibitors

In Mycobacterium TB, ATP synthase is an essential enzyme that is responsible for the production of ATP through the process of oxidative phosphorylation.

It is a promising pharmacological target for latent tuberculosis because, unlike many other bacterial enzymes, this ATP synthase is important even during non-replicating persistence. This makes it a suitable candidate for treatment. Through the inhibition of this enzyme, the loss of energy leads to a bactericidal action. Some of the chemical classes inhibiting ATP synthase have been discussed below,

4.1 Diarylquinolines (DARQs)

As a result of the global burden of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis, the discovery of therapeutic medicines with novel modes of action has become necessary. Diarylquinolines, also known as DARQs, are a revolutionary class of anti-tuberculosis medications. They are distinguished by their specific inhibition of the mycobacterial ATP synthase. Bedaquiline (Figure 2), which is also referred to as R207910 or TMC207, is the first-in-class DARQ and represents the first new anti-TB medicine class to be released in more than four decades [36,37]. DARQs operate by specifically binding to the c-subunit (c-ring) of the F_1F_0-ATP synthase, thereby obstructing proton translocation and inhibiting ATP synthesis. This blockade inhibits the enzymatic rotor mechanism that facilitates energy generation in Mycobacterium tuberculosis, resulting in bactericidal effects [38,36]. Structural studies have demonstrated that bedaquiline extensively encircles the c-ring, establishing multiple interactions that contribute to its strong and specific binding. DARQs, such as bedaquiline, demonstrate efficacy against both actively replicating and non-replicating (latent) M. tuberculosis, providing therapeutic benefits compared to conventional medications. Bedaquiline has notably accelerated sputum culture conversion and enhanced outcomes in patients with MDR-TB in clinical trials, leading to its incorporation in various WHO-recommended regimens [39]. Challenges continue to exist. Bedaquiline is linked to QT interval prolongation and various cardiac issues, requiring vigilant patient monitoring. Resistance may arise from mutations in the atpE gene, which impact the c-subunit, or through the activation of drug efflux mechanisms [40]. In response to these challenges, second-generation DARQs, including TBAJ-587 and TBAJ-876, have been developed. The analogues exhibit structural modifications that decrease lipophilicity and cardiotoxicity (e.g., reduced hERG inhibition), while demonstrating enhanced potency (e.g., lower MIC_{90}) and superior pharmacokinetic profiles. Studies conducted *in vitro* and using murine models indicate improved efficacy, with several now advancing to early clinical trials [41,42].

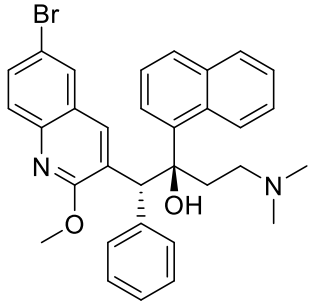
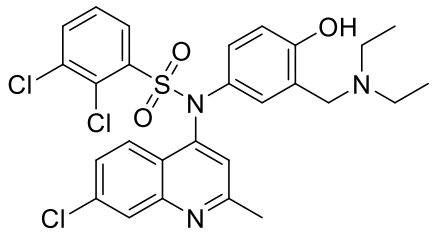


Figure 2: Chemical structure of bedaquiline

Singh et al. designed, synthesized, and evaluated a series of eighteen novel compounds for their activity against *Mycobacterium smegmatis* ATPase [43]. The measured ATPase inhibitory activities (IC_{50}) of these compounds varied from 0.36 to 5.45 μM. The lead compound (1) was N-(7-chloro-2-methylquinolin-4-yl)-

N-(3-((diethylamino)methyl)-4-hydroxyphenyl)-2,3-dichlorobenzenesulfonamide which showed no cytotoxicity (CC_{50} >300 μg/mL). The compound (1) showed notable anti-mycobacterial activity (mycobacterial and mammalian IC_{50} of 0.51 μM and > 100 μM) and selectivity >200) which inhibited the complete growth of replicating Mycobacterium tuberculosis H37Rv at 3.12 μg/mL. Furthermore, it also demonstrated a bactericidal effect, achieving approximately 2.4 $\log_{10}$ reductions in CFU in the hypoxic culture of nonreplicating *M. tuberculosis* at a concentration of 100 μg/mL, in contrast to the positive control isoniazid, which resulted in approximately 0.2 log10 reduction in CFU at 5 μg/mL (50-fold of its MIC). The pharmacokinetics of compound (1) following oral and intravenous administration in male Sprague–Dawley rats demonstrated rapid absorption and distribution, with a slow elimination phase. In a murine model of chronic tuberculosis, (1) demonstrated a 2.12 $\log_{10}$ reduction in colony-forming units (CFU) in both the lung and spleen at a dosage of 173 μmol/kg, compared to the untreated control group of Balb/C male mice infected with replicating *M. tuberculosis* H37Rv. The *in vivo* efficacy of (1) is at least twice that of the control drug ethambutol [43].



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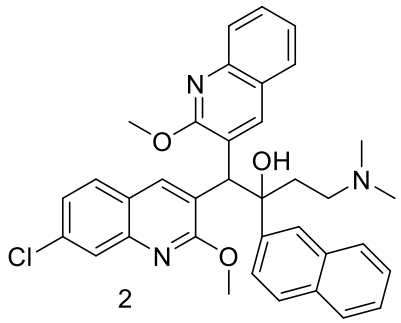
Kalia et al. synthesized conformationally-constrained bisquinoline analogs of TMC207 [44]. The study showed that making the lateral chain of the drug rigid by linking it to an adjacent phenyl substituent resulted in a decrease in activity while replacing a phenyl substituent of TMC207 with a quinoline moiety gave bisquinolines which demonstrated potent antitubercular activity in *in vitro* experiments, in *ex vivo* mouse bone marrow macrophage assays, and also in *in vivo* mouse model of the disease. The most active compound (2) showed ATP synthase inhibitory activity of 0.001 μM with antitubercular activity (MIC of 0.70 μM) against H_{37}Rv strain. The compound (2) also showed low cytotoxicity of >100 μM in VERO cells and mouse macrophages.



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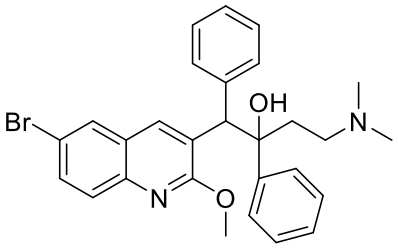
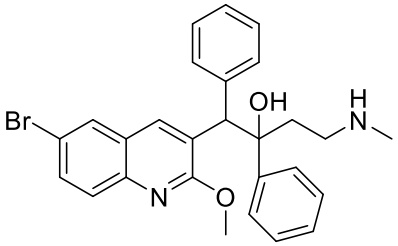
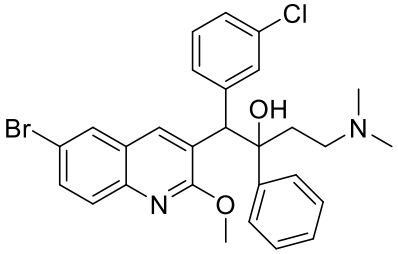
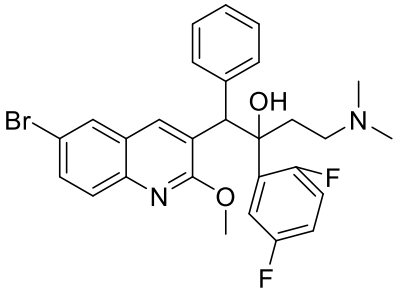
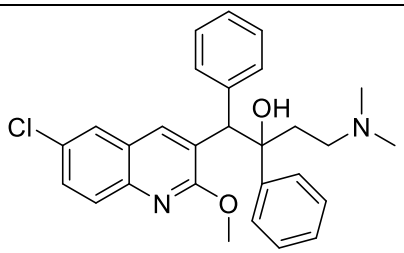
Guillemont et al. designed a large set of TMC207 derivatives by modifying its structural features. The designed molecules are shown in Table 2 [45].

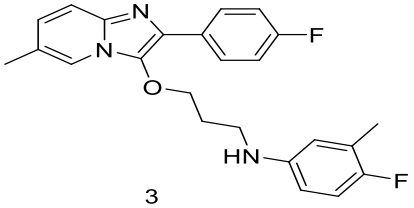
Table 2: Designed DARQs based on the modification of TMC207.

S. No	**Modification**	**Structure**	**Activity *Mycobacterium smegmatis* IC_{90} (μg/ml)**

1	Modulation of the chain lengthening		0.16
2	Modulation of the basic moiety		0.02
3	Substitution of the first phenyl ring of the lateral chain		0.004
4	Modulation of the second phenyl ring of the lateral chain		0.003
5	Substitution on the quinoline core		0.06

4.2 Imidazo[1,2-a]pyridine ethers

Tantry et al. discovered imidazo[1,2-a]pyridine ethers as ATP synthase inhibitors. The modification involved the alteration in the ether side chain. The most active compound (3) showed the IC_{50} value of 0.005 μM against Mycobacterium ATP synthase, MIC value of 0.03 μM with cytotoxicity index of 1050 [46].



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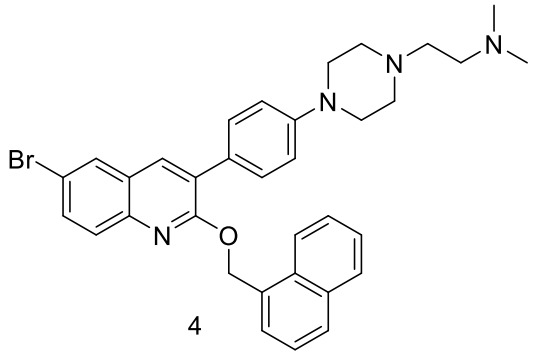
4.3 Quinoline derivatives

He et al. synthesized some quinoline derivatives out of which compound (4) showed MIC value of 0.73 μM and CC_{50} value of 6.6 μM. The compound also showed ATP synthase inhibitory activity in the range of 20-40 μM [47].



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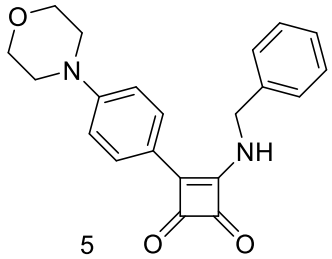
4.4 Squaramides

Tantry et al. also identified some squaramide derivatives with ATP synthase activity (IC_{50}) of 0.03 μM and MIC value of 0.5 μM [46].



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5. CONCLUSIONS

Tuberculosis continues to be a global health threat, complicated by the dual burden of HIV and rising drug resistance. While traditional anti-TB drugs laid the foundation for effective treatment, challenges in adherence, toxicity, and resistance have highlighted the need for new therapeutic approaches. Recent drugs such as Bedaquiline, delamanid, and pretomanid, along with repurposed antibiotics like linezolid, have expanded treatment options, especially for resistant forms. The emergence of resistance to traditional and current drugs warrants the search of new targets which could lead to identification of new chemical entities. The most promising target for the inhibition of mycobacterial growth is ATP synthase. There have been several attempts to synthesize inhibitors of ATP synthase which resulted in Bedaquiline. The resistance to Bedaquiline prompts the search for new ATP synthase inhibitors belonging to the class of diaryl quinolines, quinolines, pyridine ethers, and squaramides. The study of these classes reveals important SAR characteristics which may be helpful in designing new compounds. Advances in drug discovery are increasingly targeting unique aspects of mycobacterial physiology and host-pathogen interactions, raising hope for shorter, safer, and more effective regimens. Nevertheless, success in combating TB will depend not only on novel drugs but also on strengthening health systems, ensuring equitable access, and integrating preventive measures.

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