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Bedaquiline: An In-Depth Exploration into Its Antitubercular Significance

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Abstract

Tuberculosis is still a leading infectious disease and a major threat to public health. Although there has been a slow decrease in the incidence over years, its "hard to kill nature" is responsible of about 2 million deaths in HIV infected individuals annually. Bedaquiline, a Diaryl-Quinoline drug was fast-track approved as an orphan drug to combat drug resistance. It shows potent activity against Mycobacterium tuberculosis by interfering with the production of ATP. The main mechanism of action of Bedaquiline involves binding to the F_0 domain of the ATP synthase complex and prevents its function, thereby inhibiting the oxidative phosphorylation of the cell ultimately inhibition of ATP generation. In an era of growing resistance and considering the suboptimal efficacy and toxicity of current MDR-TB regimens, Bedaquiline represents a significant contribution to the existing resources of anti-TB drugs, particularly in endemic areas of the world. This paper aims to provide an overview of the drug Bedaquiline, its mechanism of action, microbiology, pharmacokinetics and pharmacodynamics, the chemistry and SAR and design strategies for novel analogues.

Keywords: Tuberculosis, bedaquiline, ATP synthase, diarylquinolines, World Health Organization

INTRODUCTION

Tuberculosis (TB), caused by Mycobacterium tuberculosis is still a leading infectious killer worldwide, responsible for about 2 million deaths in HIV infected individuals annually. According to the World Health Organization (WHO), in 2021, 10.6 million individuals became ill with TB and 1.6 million died [1, 2]. Despite being preventable one of the main reasons for its "hard to kill" nature is because of the ability of the microbe to become metabolically inactive, undetectable by diagnostic tests and immune response [3]. The other major problem in TB is the continuous rise in drug-resistant TB (MDR and XDR-TB) may be due to frequent use of inadequate treatment regimens [1, 4]. Multi-Drug-Resistant TB (MDR-TB) refers to resistance of first line drugs (at least Isoniazid and Rifampicin) while Extensively Drug-Resistant TB (XDR-TB) refers to MDR-Tb with resistance to second line injectables (at least three, i.e., Capreomycin, Kanamycin and Amikacin) and any fluroquinolones [5, 6]. To combat drug resistance, a novel Diaryl-Quinoline drug: Bedaquiline was fast-tracked for approval by the FDA and was approved on 28thDecember 2012 as an "orphan drug" to treat adults with MDR pulmonary TB in combination with other anti-Tb drugs when an effective treatment cannot be provided (last line drug). It was formerly known as TMC207 and was developed J&J's research subsidiary, Tibotec (Tibotec Research and Development, Mechelen, Belgium, and Yardley, PA, USA) [4, 7].

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BEDAQUILINE

Bedaquiline is a first-in-class diaryl-quinoline which shows potent activity against Mtb (both drug sensitive and drug-resistant strains) in vitro with minimum inhibitory concentration (MIC) of 0.002–0.013 µg/mL and in in-vivo studies the drug

eradicates persistent TB infections and completely prevented disease relapse in mice [7, 8]. BDQ displays bactericidal activity and sterilizing against dormant Mtb. A multi-drug anti-tuberculosis regimen with bedaquiline is a helpful addition, especially for patients who have run out of other medication alternatives (Figure 1) [9, 10].

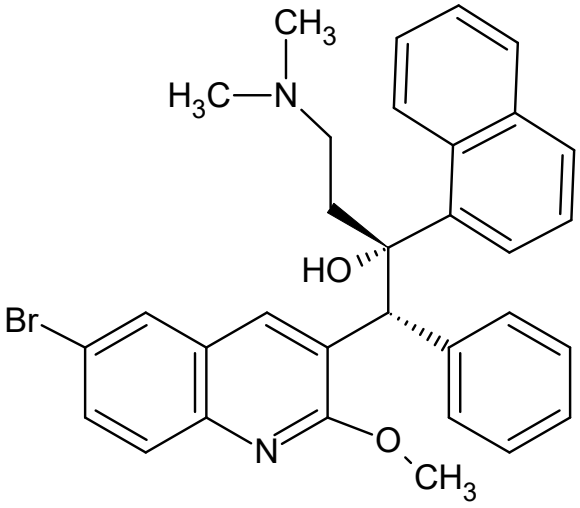

Figure 1. Structure of bedaquiline.

ATP production is essential for Mtb growth and survival in its dormant, non-growing condition. BDQ to exert its anti-mycobacterial effect, it interferes with mycobacterial F-ATP synthase activity, ATP production is inhibited, which results in the depletion of bacterial ATP. BDQ is a highly efficacious drug with both pharmacological and toxicological liabilities. The drug has high lipophilicity (cLogP = 7.25), due to which accumulation can take place within the tissues via phospholipidosis and this contributes to long terminal half-life [11].

MECHANISM OF ACTION

ATP synthesis in Mycobacterium occurs through a complex metabolic pathway, i.e., by oxidative phosphorylation (Figure 2) [12]. The two ways by which bacteria produce ATP is by oxidative phosphorylation route or substrate-level phosphorylation of fermentable carbon sources. *M. tuberculosis* and related mycobacterial strains reportedly require oxidative phosphorylation for development, as shown by high-density mutagenesis and deletion mutant investigation studies [13, 14]. This is because they appear to be unable to obtain enough energy by substrate-level phosphorylation. In oxidative phosphorylation, the protein complexes of the respiratory chain create a proton motive force (PMF) across a bio membrane; ATP synthase then uses the energy of this PMF to produce ATP For *M. tuberculosis* to grow and survive, the input of electrons, preservation of the proton motive force, and the ultimate phase, ATP production, are all essential [15].

ATP GENERATION

NADH dehydrogenase feeds electrons from NADH into the electron transport chain, which lowers the menaquinone pool (MK/MKH2). The type I NADH dehydrogenase, which is the mitochondrial complex I homologue in *M. tuberculosis*, is not necessary for growth. Type II NADH dehydrogenase (NDH-2) is found in *M. tuberculosis* in two copies. Alternative electron donors, such as succinate dehydrogenase (SDH), can also diminish the menaquinone pool. Two succinate dehydrogenase enzymes (SDH-1 and SDH-2) and one fumarate reductase, which catalyzes the opposite reaction, are present in *M. tuberculosis*. The cytochrome bc_1 complex can receive electrons from the menaquinone pool. In mycobacteria, the cytochrome bc_1 complex joins forces with the terminal oxidase of the cytochrome aa_3 subfamily to produce a super complex that transports electrons to oxygen. A cytochrome bd-type terminal oxidase, which directly takes electrons from the menaquinone pool, is an

alternative method of reducing oxygen. Protons are pumped across the membrane during electron transport along the respiratory chain, creating a proton motive force (PMF). The ATP synthase enzyme can utilize the PMF's energy to create ATP (Figures 2–6) [12].

This force causes the central stalk subunits and of the F-ATP synthase to rotate, which in turn causes ATP synthesis to occur at the enzyme's $\alpha_3\beta_3$ catalytic headpiece through the central stalk subunits γ and ε [16–20].

Small-molecule inhibitors can be used to block the synthesis of ATP, restrict respiratory electron transport, or damage the proton motive force by targeting the above mentioned functions of oxidative phosphorylation [16].

F1F0-ATPASE SYNTHASE

The peripheral F1 subcomplex, which contains the nucleotide binding sites, and the membrane-embedded F0 subcomplex, through which protons flow, are the two subcomplexes that constitute up ATP synthase. It has eight different subunits, namely $\alpha_3\ \beta_3\ \gamma\ \delta\ \varepsilon$ a $b_2\ c_{10}$. ATP synthesis occurs because of addition to binding to the c subunit of the enzyme. It has been demonstrated that BDQ is also able to block mycobacterial F-ATP synthase by targeting its subunit. The proton motive force through F0 stimulates the rotation of the cylindrical ring of subunits c and coupling that rotation to the catalytic b subunit of the F1 domain. The cytoplasmic sector F1 of this complex enzyme is made up of five subunits (α_3, β_3, γ, δ and ε), whereas the membrane sector F0 is made up of three subunits (a, b_2, and $c_{10–15}$) [21].

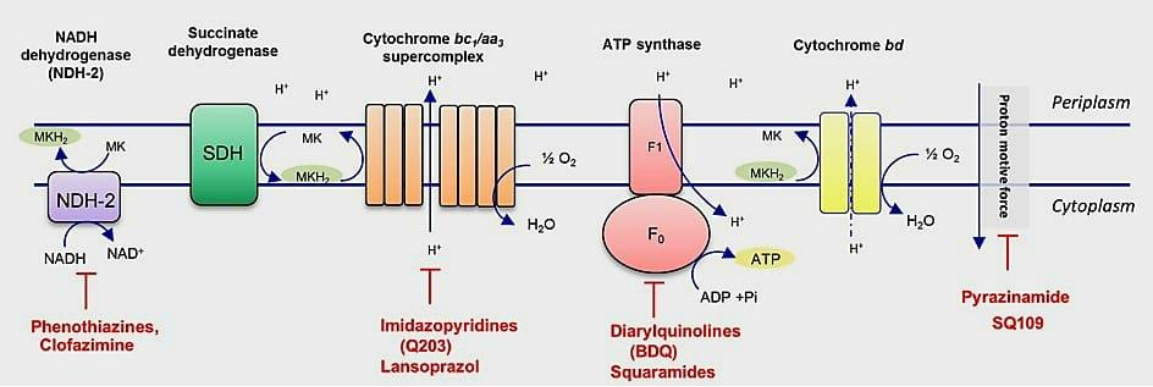

Figure 2. Oxidative phosphorylation in Mycobacterium tuberculosis.

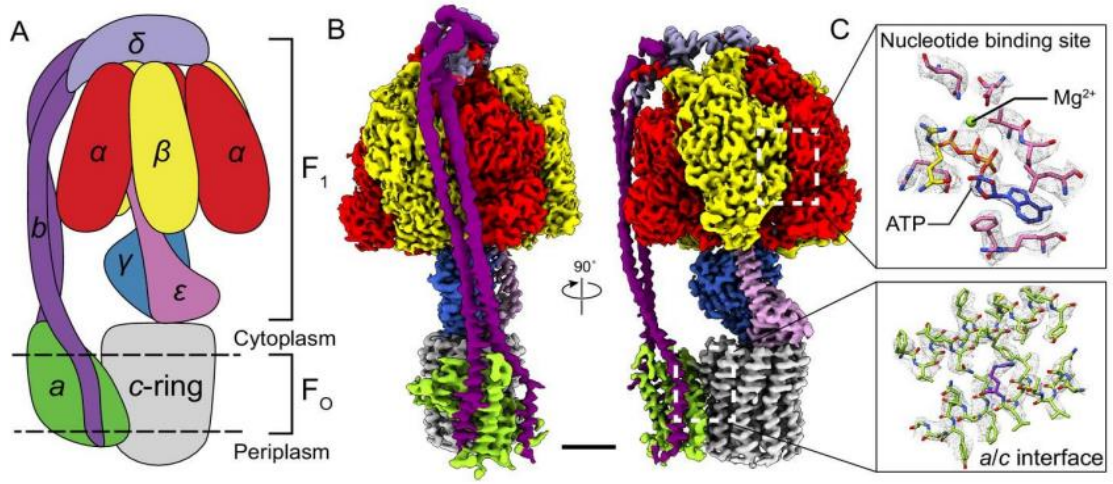

Figure 3. ATP synthase, an enzyme located in the inner membrane of mitochondria, generates energy to fuel the catabolic and anabolic reactions of growing mycobacterial cells.

SUBUNIT C OF THE ATP SYNTHASE

The primary transmembrane subunit of V-type, A-type, and F-type synthases is subunit C of the Fo/Vo complex. The Fo/Vo/Ao rotor is made up of oligomeric c rings that are formed by the subunits, whose precise numbers differ significantly depending on the enzyme [21].

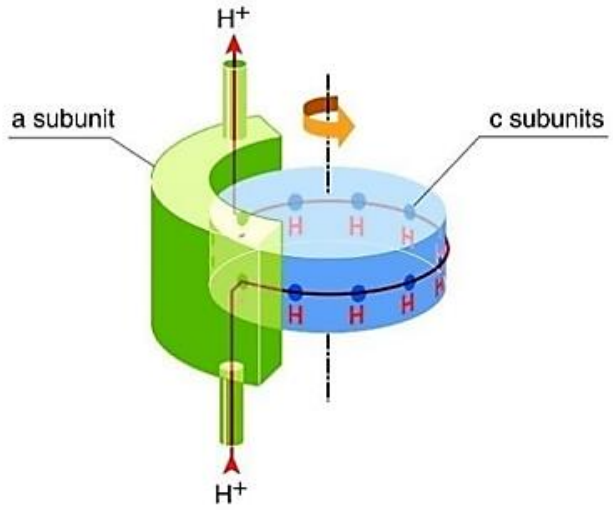

Figure 4. Subunit c of ATP synthase.

BDQ ACTS BY 2 MECHANISMS

- BDQ can bind to the F0 domain of the ATP synthase complex's oligomeric/proteolipid component c and inhibit its activity. (Illustrated below) This entry corresponds to subunit C, which is a component of the F-ATPase F0 complex. The F0 rotor is composed of an oligomeric ring made up of ten C subunits. Because the gamma and epsilon subunits of the F1 complex are permanently bound to the C subunit ring of F0, the flux of protons through the ATPase channel drives the rotation of the C subunit ring, which is related to the rotation of the gamma subunit rotor of the F1 complex. The progressive rotation of the rotor is related to the successive protonation and deprotonation of Asp61 of subunit C [20].
- In addition to binding to the c subunit of the enzyme, it has been demonstrated that BDQ is also able to block mycobacterial F-ATP synthase by targeting its subunit ε. The inhibitory effect is specific for Mycobacteria [22].

MICROBIOLOGY

Bedaquiline, a diarylquinoline, acts mainly against mycobacterial species. MIC ranges of 0.03–0.12 g/ml were reported in the original article by Andries et al. when tested against the reference strain *M. tuberculosis* H37Rv and six other fully susceptible clinical isolates. Similar MICs were found for *M. tuberculosis* strains that were resistant to the most used anti-TB medications, including moxifloxacin, streptomycin, PZA, INH, and RIF. Following, a bigger investigation using 44 MDR and 41 drug-resistant M.TB strains discovered MIC50 values of 0.03 g/ml and 0.06 g/ml. Bedaquiline shows reports of MIC >4.0 µg/ml does not seem to have activity against gram-positive and gram-negative micro-organisms [23, 24].

PHARMACODYNAMICS AND PHARMACOKINETICS

The primary metabolic pathway for bedaquiline results in the formation of the N-monodesmethyl metabolite (M2). Given its lower average human exposure (23% to 31%) and lower antimycobacterial activity (4 to 6-fold lower) compared to the parent compound, M2 is not thought to significantly contribute to clinical efficacy. M2 levels and QT lengthening seemed to be related. Bedaquiline has a

MIC50 of 0.03 g/ml and a minimum inhibitory concentration (MIC) range of 0.002–0.06 g/ml for inhibiting mycobacterial TB. Additionally, bedaquiline is more effective against bacteria with smaller ATP stores, which are typically found in dormant, nonreplicating bacilli [25].

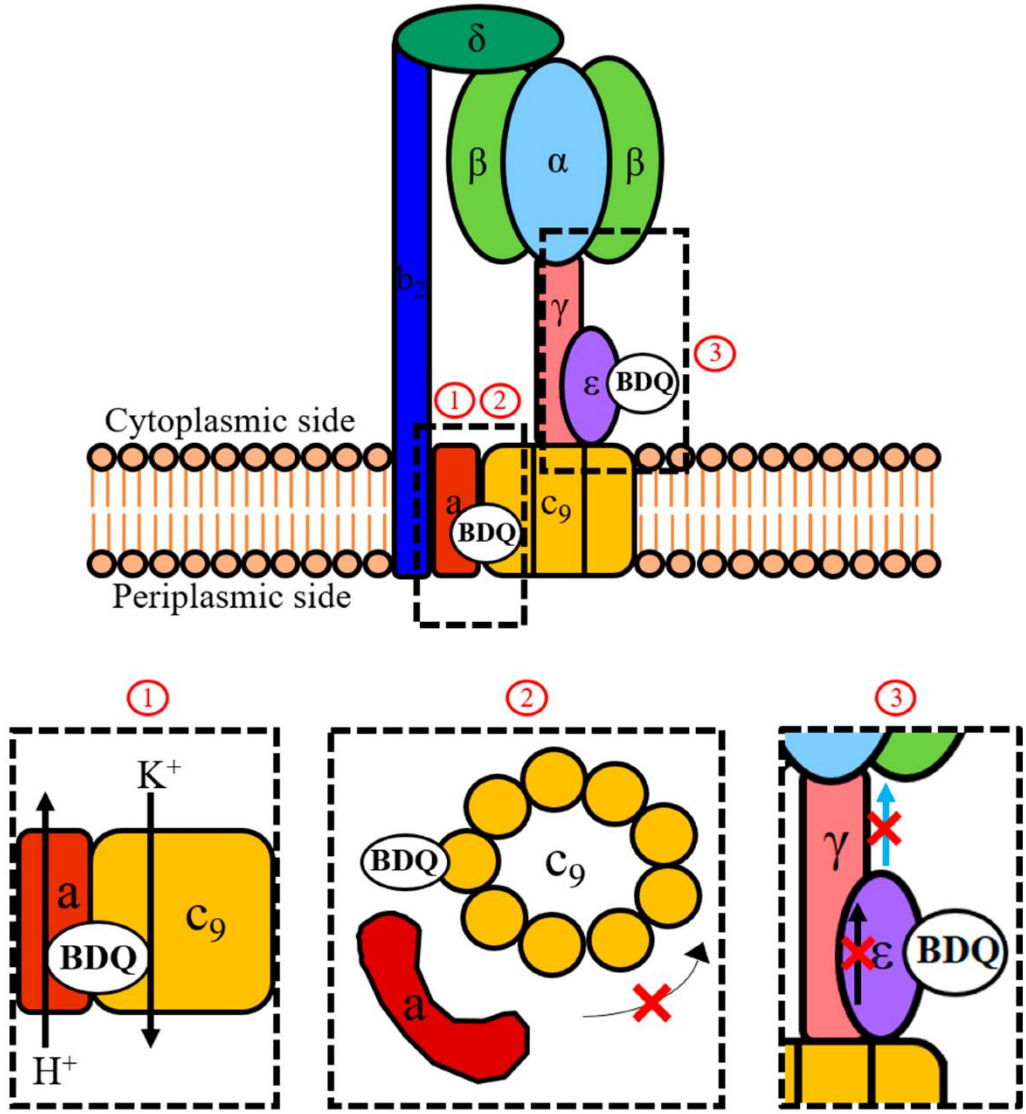

Figure 5. Action of BDQ on ATP synthase.

Adverse Effects of Bedaquiline

Although bedaquiline's innovative mode of action promises to revolutionize the treatment of multi-drug-resistant TB, several serious adverse reactions have limited its clinical use. Many of the documented toxicities of bedaquiline are thought to be the result of its unfavorable physicochemical profile. Most notably, its considerable lipophilicity (cLogP 7.3) causes QT interval prolonging due to inhibition of the hERG cardiac potassium ion channel. Furthermore, bedaquiline has a very long terminal half-life, which increases its ability to accumulate in tissue compartments (Table 1).

CHEMISTRY OF BEDAQUILINE

- *IUPAC name*: (1*R*, 2*S*)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-naphthalen-1-yl-1-phenylbutan-2-ol.
- *Molecular formula*: $C_{32}H_{31}BrN_2O_2$
- *Physicochemical properties* [26]:

Table 1. Physiochemical properties.

S.N.	Property Name	Property Values
1	miLogP	7.10
2	TPSA (Topological Polar Surface Area)	45.59
3	Natoms	37
4	MW (Molecular weight)	555.52
5	nON (Hydrogen Bond Acceptor Count)	4
6	nOHNH (Hydrogen Bond Donor Count)	1
7	Nviolations	2
8	Nrotb (Rotatable Bond Count)	8

Experimental Properties [27]

1. *Color:* White solid.
2. *Melting Point:* 118°C.
3. *Solubility:* Insoluble in water (1.77×10^{-3} mg/L at 25°C).
4. *Specific Optical Rotation:* 166.98 degree at 20°C/D (c = 0.505 in dimethyl formamide).
5. *Dissociation Constants:* pKa1 = 1.57 (imine); pKa2 = 8.91 (amine); pKa3 = 13.61 (hydroxyl).

SAR OF DIARYLQUINOLINES (BEDAQUILINE)

DARQs differ structurally and mechanistically from other quinoline classes, such as mefloquine and its analogues 4-methylquinolines and 4-quinolylhydrazones, as well as fluoroquinolones (including methoxy quinolones). One of the primary structural distinctions between the DARQs and other quinolone or quinoline class is the distinctive character of the functionalized lateral (3') chain borne by the DARQ class [8].

Bedaquiline is Diaryl-Quinoline (DARQ) derivative the main difference is the presence of 2 steriogenic (classified as R and S) centers which led to the formation of four isomers. The (RS, SR) configuration was found to frequently possess greater antibacterial activity than the (RR, SS) configuration (one of the crucial factors is how the asymmetric centers are set up. While the carbon carrying the hydroxyl group should be in the S configuration, the carbon carrying the phenyl substituent should be in the R configuration) [29].

Halogen atoms (electron-withdrawing groups) at the C6 (R^4 in Figure 4) of the quinoline ring produce better outcomes, according to SAR analysis of the diarylquinoline derivatives. In terms of halogens, bromine produces the most powerful molecules. The methyl-oxy group produces the best results among alkyl-oxy groups at the C2 (R^3 in Figure 4) position. It is necessary to have a naphthalene nucleus and an unsubstituted phenyl ring. The activity is decreased when the naphthyl group is substituted with a phenyl ring or another substituted ring system.

The antimycobacterial activity is attributed to both the tertiary alcohol and tertiary amine groups. The effects of substituting non-basic functionality for various amino groups and adding modifications to the dimethylamino group. Antimycobacterial activity was sustained when the amino group was basic (calculated pKa > 8) but diminished with less basic derivatives 40–43 (estimated < pKa 8). The best results are obtained when both groups are methyl. The amine (-NR1, R2) can be a simple alkyl tertiary amine or in the form of cyclic structure (CH_3, CH_2 CH_3, imidazolyl, triazolyl, piperidinyl, etc.). Better outcomes are provided by the two-carbon aliphatic chain that connects the tertiary alcohol and amine groups. Activity declines as the chain length increases or decreases [28, 29].

DESIGN STRATEGIES OF BEDAQUILINE

Bedaquiline has 2 chiral carbons adjacent to each other, these bridges the three aryl rings (core Quinoline moiety, phenyl ring and napthylmethyl ring) and a dimethylaminoethyl moiety. By the SAR of the drug, it was seen that the quinoline moiety and the dimethylamino group are important for the

activity whereas groups, like bromo and hydroxy, were less important and the activity is also related to the spatial arrangement of the segments.

These major fragments can be reattached to the core quinoline moiety to design four series of new analogues while gradually replacing the chiral linkage (Figure 7) [29].

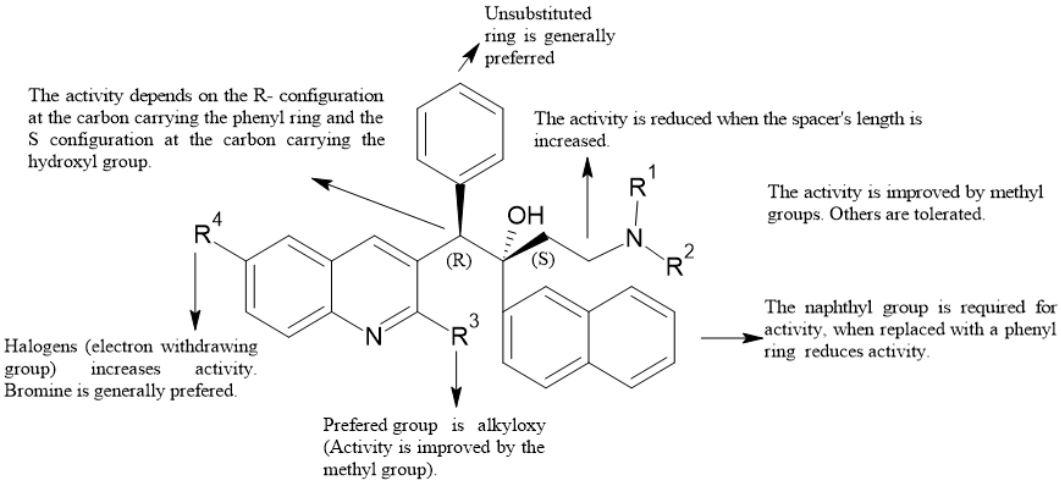

Figure 6. SAR of Diarylquinolines.

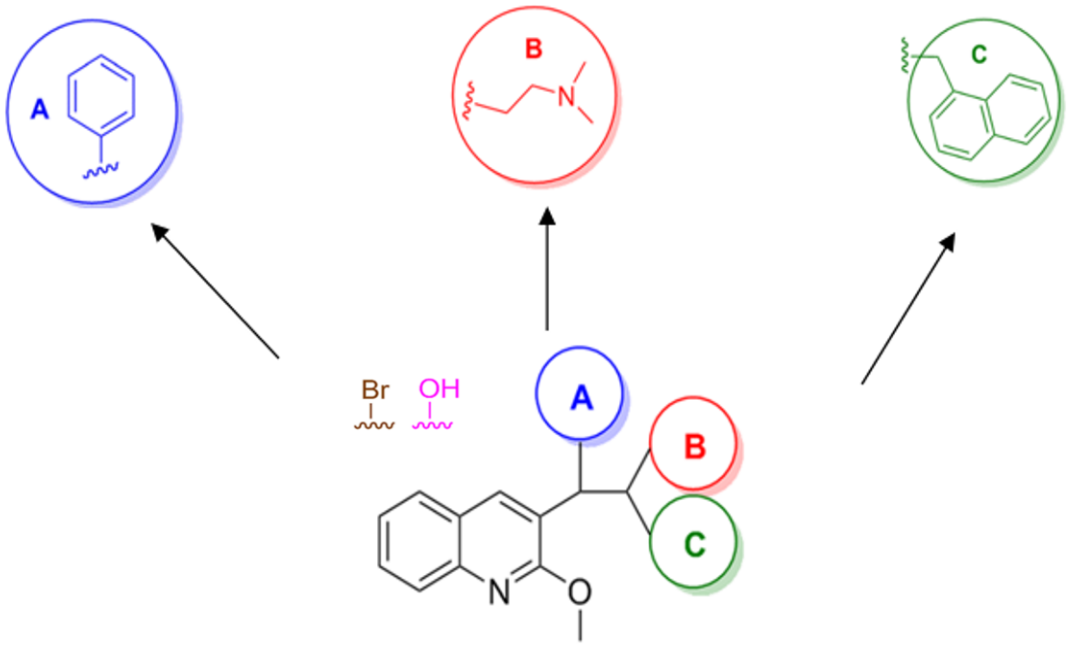

Figure 7. Bedaquiline is divided into the essential group Quinoline moiety, 3 major fragments which can be modified and 2 minor fragments – bromine and hydroxy groups.

Bedaquiline contains 3 aromatic rings namely, a quinoline ring(A), a benzene(B) ring and a naphthalene ring (C) (Figure 8). Modification of A by scaffold hopping strategy was observed to retain anti-tubercular activity but no significant decrease in hERG affinity and modification of B and C ring demonstrated an increased in-vitro potency, most importantly hERG potency therefore reducing the risk of QTc prolongation. On extensive exploration of modification of A ring and further SAR would be useful for the design of DRAQs with less toxicity [30].

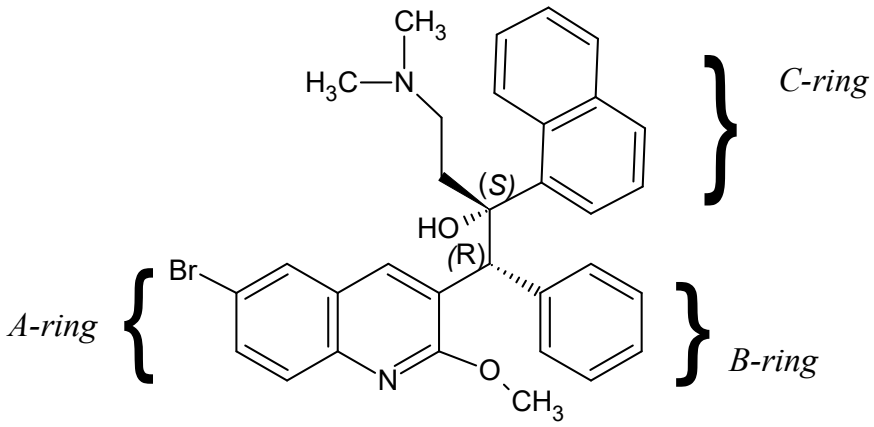

Figure 8. Regions of modification (Ring A, B and C).

CONCLUSIONS

There has been a lack of novel TB medications in the market for almost 30 years, despite the urgent need for agents that can shorten treatment time and cure MDR-TB effectively. Bedaquiline is a breakthrough diaryl-quinolone that effectively treats both drug-sensitive and drug-resistant tuberculosis. Bedaquiline is effective against multiple NTMs, including *M. TB*, *M. avium*, *M. fortuitum*, and *M. ulcerans.* In an era of growing resistance and considering the suboptimal efficacy and toxicity of current MDR-TB regimens, Bedaquiline represents a significant contribution to the existing resources of anti-TB drugs, particularly in endemic areas of the world.

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