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Review

A structural insight of bedaquiline for the cardiotoxicity and hepatotoxicity

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ABSTRACT

Bedaquiline was approved by USFDA in 2012 for pulmonary MDR-TB. The IC_{50} value of bedaquiline was reported to be remarkably low (25 nM), effectively inhibiting mycobacterial ATP synthase. In addition to these obvious assets of bedaquiline, the potential disadvantages of bedaquiline include inhibition of the hERG (human Ether-à-go-related gene; $KCNH_2$) potassium channel (concurrent risk of cardiac toxicity), hepatic toxicity and possibly phospholipidosis. The current review focuses primarily on the structural part of bedaquiline for the activity-toxicity optimization. This critical analysis of the structure of bedaquiline will help medicinal chemists to synthesize the better modified analouge of bedaquiline with reduced cardiotoxicity, hepatotoxicity potential and improved pharmacokinetics.

1. Introduction

Multi-drug resistant tuberculosis (MDR-TB) is of rising global concern and threatens to undermine increasing endeavours to control the overall spread of tuberculosis (TB) [1,2]. Bedaquiline has recently come out as a new drug to explicitly treat MDR-TB [3]. In spite of being highly effective mere because of its distinct mode of action, Bedaquiline has been linked with major toxicities and thus safety concerns are constraining its clinical utilization [4–6]. The development of bedaquiline, the primary new anti-TB drug commercial in over fourty years secure to revolutionize the treatment of MDR-TB because of its novel mechanism of action towards mycobacterial ATP synthase [7]. Diarylquinoline (DARQs) that were extremely active against MDR-TB was invented in 1996 at Janssen Pharmaceuticals [8]. Janssen's hit-to-lead effort made a series of many hundred DARQ derivatives with *in vitro* activity against Mtb, eventually leading to the identification and development of bedaquiline; the most effective anti-TB agent in its (R,S) enantiomeric type as shown in Fig. 1 [7,8]. Bedaquiline was endorsed by the USFDA in 2012 for explicit use in pulmonary MDR-TB, and shows improved outcomes once it's utilized in combination with standard MDR-TB drugs [9]. An ongoing report, adding bedaquiline to a standard routine for the treatment of MDR-TB demonstrated a positive cost-benefit analysis by minimizing hospital residence [10].

At the molecular level the compound was appeared to restrain the mycobacterial F_1F_o ATP synthase by binding to its membrane-embedded F_o rotor ring as depicted in Fig. 2 [11]. The IC_{50} value of bedaquiline was reported to be remarkably low (25 nM), effectively inhibiting mycobacterial ATP synthase. In addition, the mode of action of bedaquiline is highly target-specific [12,13], since the IC_{50} values for human, bovine and mouse mitochondrial ATP synthases were 20000 times higher [12,13]. In addition to these obvious assets of bedaquiline, the potential disadvantages of bedaquiline include inhibition of the hERG (human Ether-à-go-related gene; KCNH2) potassium channel (concurrent risk of cardiac toxicity) [14], hepatic toxicity [15] and possibly phospholipidosis (related to its high lipophilicity [calculated clogP of 7.25]) [16,17]. There are also potential pharmacokinetic (PK) drug-drug interactions with common TB drug-drugs rifampicin and rifapentine, which are potent inducers of bedaquiline's main metabolizing enzyme CYP3A4 [18,19]. In order to facilitate the effective treatment of MDR-TB, highly active bedaquiline analogues that exhibit an improved safety profile are urgently needed. Following our research into the identification of potential anti-mycobacterial agents [20–23], the current review focuses primarily on the structural part of bedaquiline that is responsible for its activity and toxicity. This critical analysis of the structure of bedaquiline will help medicinal chemists to synthesize the better modified analouge of bedaquiline with reduced cardiotoxicity, hepatotoxicity potential and improved pharmacokinetics.

2. Challenges with bedaquiline

In addition to the standard MDR-TB background therapy, Bedaquiline demonstrated faster bactericidal activity than background therapy alone and was approved in 2012 by the US Food and Drug Administration for the treatment of MDR-TB [24]. It is very lipophilic (measured logP 7.25), however, and probably contributes to its long

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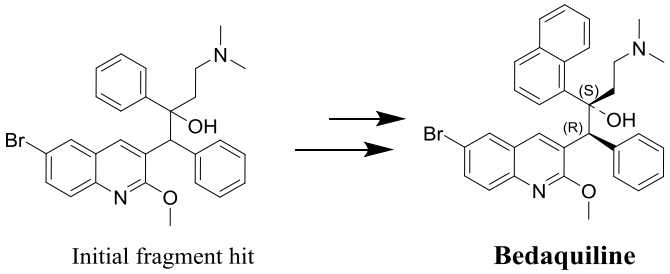

Fig. 1. Janssen developed bedaquiline from an initial fragment screening hit.

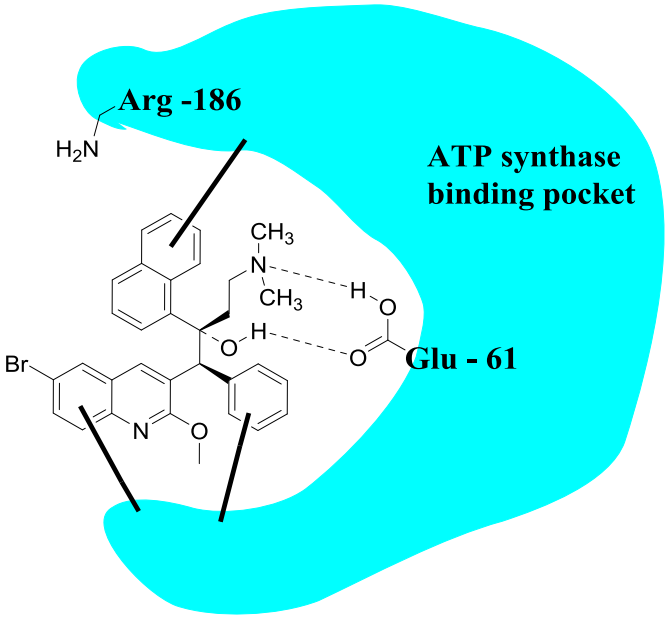

Fig. 2. Binding interaction of bedaquiline with ATP synthase. It inhibits the transfer of proton from Arg-186 to Glu-61 (dotted line indicates: Hydrogen bonding and bold line: vander Waal's forces).

terminal half-life of 5–6 months [25]. The potential for excessively proportional tissue accumulation has limited the full exploration of its possible dose range [26]. In general, highly lipophilic drugs are also prone to liver toxicity [27]. Bedaquiline also shows inhibition of the cardiac potassium channel hERG (human Ether-à-go-Related Gene; KCNH2) with the concomitant risk of delayed ventricular repolarization (QTc interval) and this is a point to be taken into account in the planning of combination regimens with other TB drugs with similar effects (e.g. Clofazimine (fluoroquinolones) (Fig. 3) [28].

3. Structural features of bedaquiline responsible for the activity and toxicity (activity-toxicity optimization)

When we did the literature survey, we observed several reports of optimizing the bedaquiline to minimize the cardiotoxicity and lipid solubility but them at the same time need to compensate with IC_{50} value [29–32]. Therefore, bedaquiline analogs of comparable antibacterial activity but with lower clogP and less potent inhibition of the potassium hERG channel would be of considerable interest. The proper balance of lipid solubility and the basicity of the terminal dimethylamino group is an important factor in the optimization of activity-toxicity for Bedaquiline. Keeping this idea in mind, we first studied the pharmacophoric and structural characteristics of bedaquiline, which are responsible for its activity and potency. Guillemont et al., the pioneer researcher group and inventor of bedaquiline reported the interesting structural features of Diaryl Quinolines (DARQ) [8]. They concluded the structure–activity analysis from more than 200 derivatives tested against *M. Smegmatis* (Figs. 4 and 5).

1) Shortening or the lengthening of the lateral chain (dimethylamino ethyl) did not improve the antimycobacterial activity but more cytotoxicity as lipophilicity of these derivatives increased.
2) The impact of modification to the dimethylamino group located at the end of the lateral chain was evaluated by the introduction of diverse amino groups and replacement with non-basic functionality. When the amino group is basic (calculated pKa > 8) antimycobacterial activity against *M. smegmatis* was retained, whereas with less basic derivatives (calculated pKa < 8) activity decreased. 3) Marked potency differences among diasatereoisomer could be observed with the (*RS*,*SR*) form displaying the highest activity, at

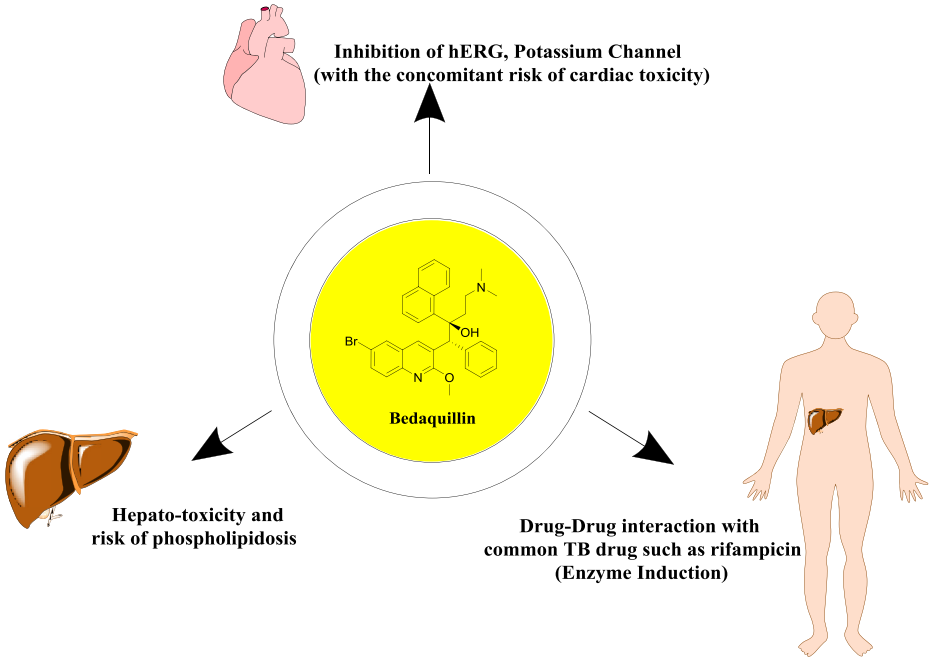

Fig. 3. Challenges associated with bedaquiline.

2) The impact of modification to the dimethylamino group located at the end of the lateral chain was evaluated by the introduction of diverse amino groups and replacement with non-basic functionality. When the amino group is basic (calculated pKa > 8) antimycobacterial activity against *M. smegmatis* was retained, whereas with less basic derivatives (calculated pKa < 8) activity decreased. 3) Marked potency differences among diasatereoisomer could be observed with the (*RS*,*SR*) form displaying the highest activity, at least tenfold more active than the (*RR*,*SS*) form. 4) The presence of a chlorine atom in the meta position of the phenyl ring was preferred over ortho and para positions. 5) Instead of naphthalene, o-fluoro phenyl also showed significant activity. 6) Replacing the bromine atom by an alkyl or an aryl group delivered compound, which displayed a slightly better activity against *M. Smegmatis* [8].

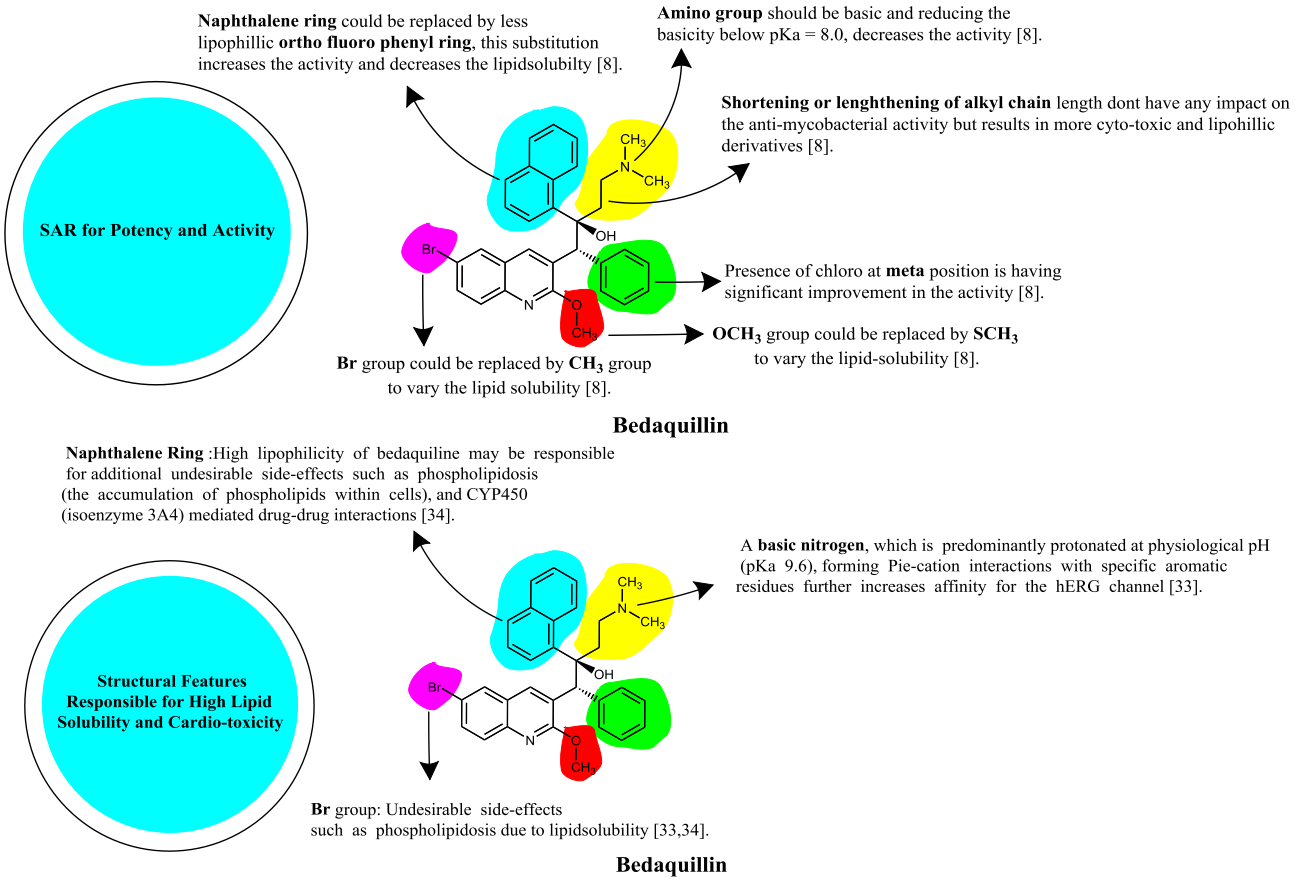

Fig. 4. Structural feature responsible for the activity and toxicity of bedaquiline.

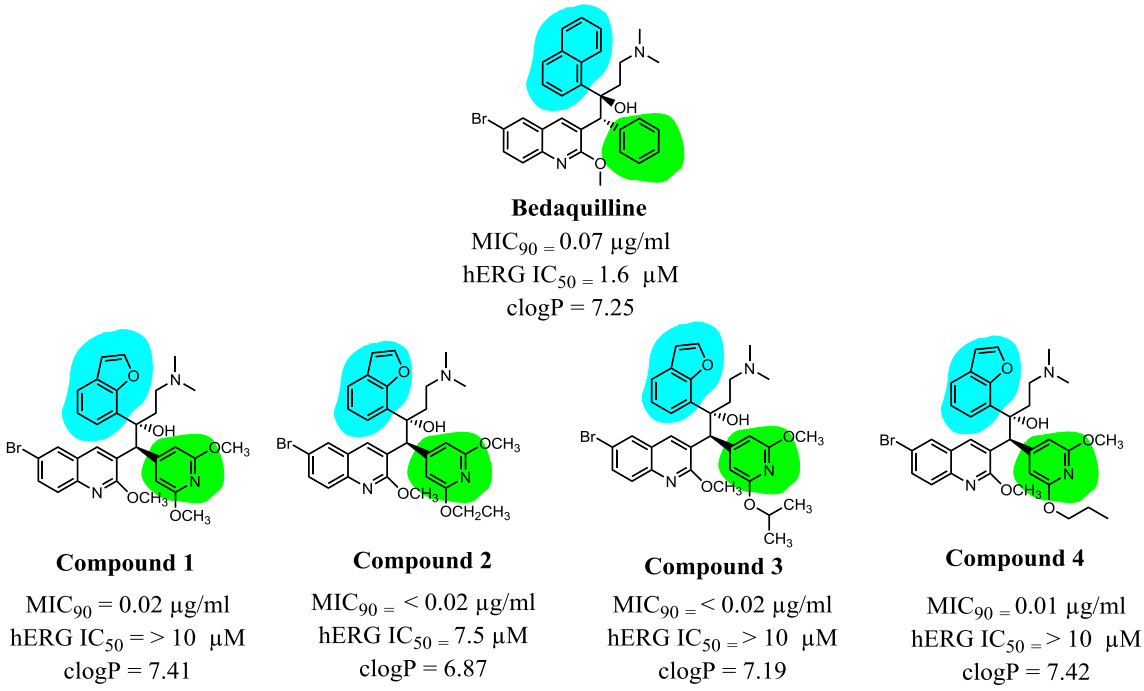

Fig. 5. Naphthalene substituted analouge of bedaquiline.

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We have also collected the information about the functional group

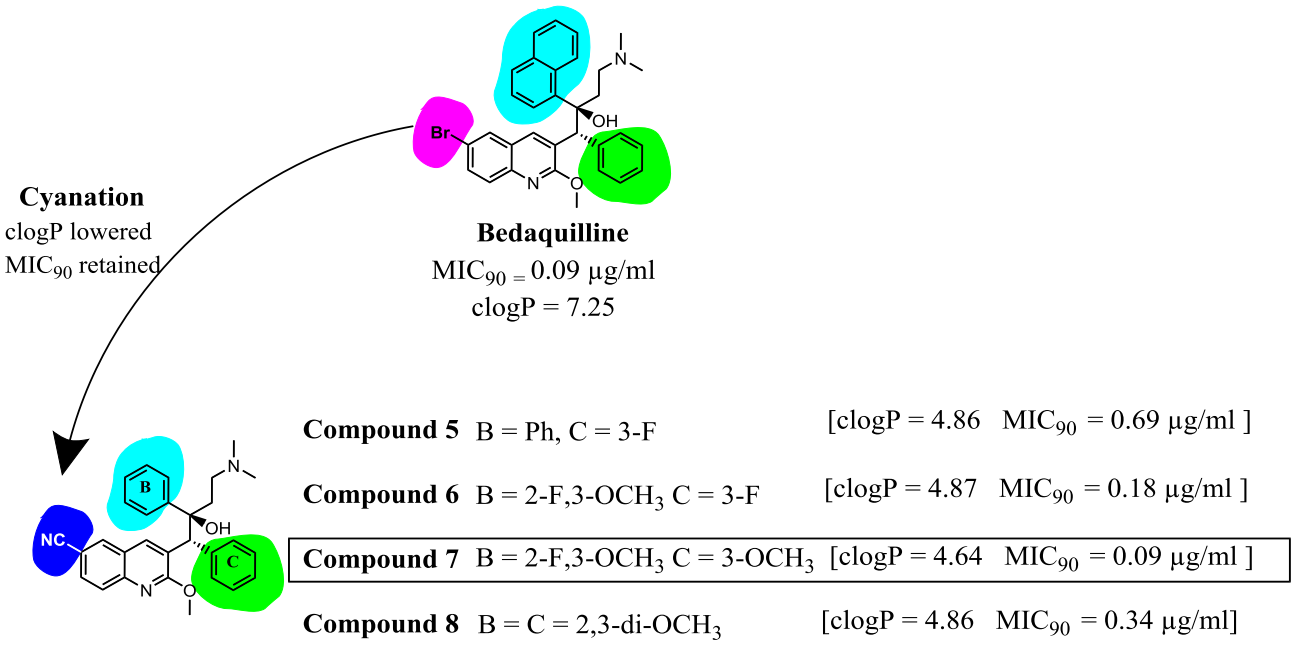

Fig. 6. 6-cyano substituted analouge of bedaquiline.

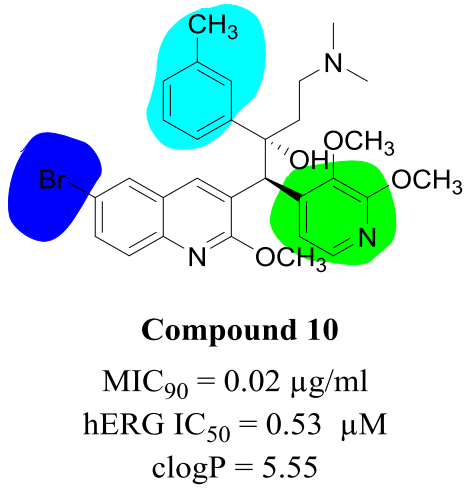

Fig. 7. Anti-mycobacterial potential of compound 10.

responsible for high lipid solubility and cardiotoxicity of bedaquiline [33,34]. Fernandez et al., reported that the basic amine functional group present in bedaquiline, which is predominantly protonated at physiological pH (pKa 9.6), forming π-cation interactions with specific aromatic residues within this region [33], increases the affinity for the hERG channel. In addition to promoting hERG binding, the high lipophilicity of bedaquiline may be responsible for additional undesirable side-effects such as phospholipidosis (phospholipid accumulation in cells), and drug-drug interactions mediated by CYP450 (isoenzyme 3A4), as shown in Fig. 4 [34]. Fox et al., reported recently that *N*-desmethyl metabolite ("M2″) of Bedaquiline is more toxic and less bactericidal [34]. These observations suggest that less lipophilic analogues of bedaquiline would be of considerable interest in reducing the potential for tissue over proportional accumulation and modifying the terminal dimethyl amino group would lessen the affinity with the hERG channel (cardio-toxicity).

We have also collected the information about the functional group responsible for high lipid solubility and cardiotoxicity of bedaquiline [33,34]. Fernandez et al., reported that the basic amine functional group present in bedaquiline, which is predominantly protonated at physiological pH (pKa 9.6), forming π-cation interactions with specific aromatic residues within this region [33], increases the affinity for the hERG channel. In addition to promoting hERG binding, the high lipophilicity of bedaquiline may be responsible for additional undesirable side-effects such as phospholipidosis (phospholipid accumulation in cells), and drug-drug interactions mediated by CYP450 (isoenzyme 3A4), as shown in Fig. 4 [34]. Fox et al., reported recently that *N*-desmethyl metabolite ("M2″) of Bedaquiline is more toxic and less bactericidal [34]. These observations suggest that less lipophilic analogues of bedaquiline would be of considerable interest in reducing the potential for tissue over proportional accumulation and modifying the terminal dimethyl amino group would lessen the affinity with the hERG channel (cardio-toxicity).

4. Recently reported less lipophilic bedaquiline analouge with minimal cardio-toxicity

Several attempts were made by the different Researcher to optimize the Bedaquiline to have minimal lipophilicity and cardio-toxicity. The details of which are discussed below;

Sutherland *et al.*, synthesized the modified derivatives of bedaquiline, where they replaced the naphthalene unit with a range of widely differing lipophilic bicycle heterocycles (4.5-fold range in clogP values) [29]. On average, the biological results of these compounds show a lower clogP limit of around 5.0 for the confinement of potent inhibitory activity (MIC_{90}s) towards the *M. tb*.

Among the synthesized compounds; **1**, **2**, **3** and **4** showed a significant reduction in hERG channel potassium current (hERG IC_{50} = > 10 µM) inhibition compared to bedaquiline (hERG IC50 = 1.6 µM) and anti-TB activity retention as shown in Fig. 5. All four potent compounds had benzofuran substitution, indicating that further exploration of the benzofuran ring could be of interest in order to obtain a better Bedaquiline analog with minimal cardiotoxicity. They also investigated the impact of CN substitution at 6th quinoline ring position and confirmed their ability to reduce overall drug lipophilicity (thus contributing to desirable physiochemical properties) without compromising *in vivo* efficacy.

Tong *et al.*, synthesized the 6-cyano (**Compound 7**) analouge of the bedaquiline and reported the significant decrease in lipophilicity (clogP = 4.64) with just humble impacts on MIC (0.09 µg/ml) values as

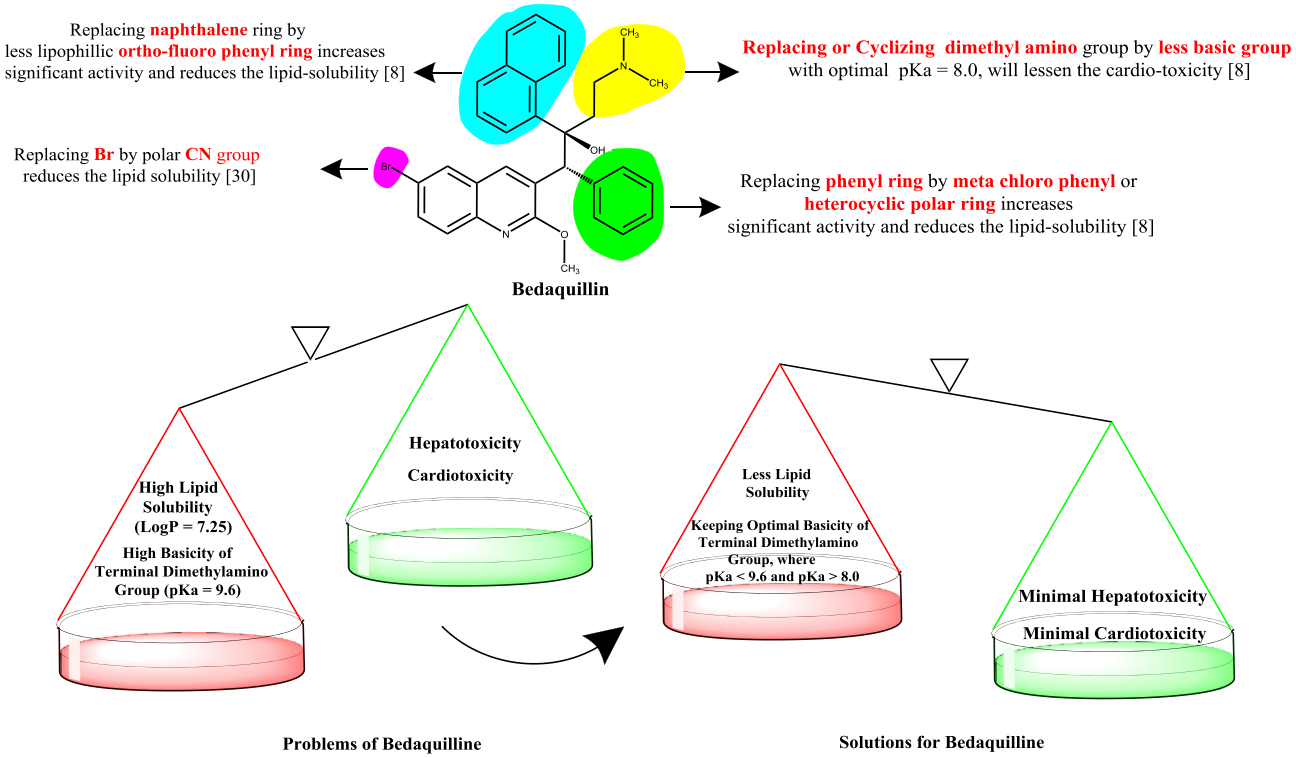

Fig. 8. Activity-toxicity optimization of Bedaquiline.

shown in Fig. 6 [30].

This is a crucial new substitute for the efficient but less lipophilic and potentially safer Bedaquiline analogs.

Choi et al., synthesized and evaluated bedaquiline analogs, in which the phenyl unit was substituted by monocyclic lipophilic heterocycles (thiophenes, furans, pyridines) [32]. While a broad positive correlation was expected between lipophilicity and anti-tubercular activity, the 4-pyridyl analouge (**Compound 10**) additionally contributed to antibacterial potency. Most of the synthesized compounds were polar and had higher clearance rates than bedaquiline, and their oral bioavailability was acceptable, but their hERG liability improved slightly (Fig. 7).

5. Discussion and future perspectives

It could be deduced from the literature review that the appropriate balance of lipid solubility and basicity of the terminal dimethylamino group could solve hepatotoxicity and cardiotoxicity problems associated with Bedaquiline and make it an appropriate candidate for treatment of MDR - TB. Based on these chemical characteristics (activity and toxicity), the designing of the new bedaquiline analouge in which the cyano group at the 6th position of the quinolines, which is more polar than the bromine and also retained the activity would be preferable to reduce lipid solubility (Fig. 8) [30]. Replacing more lipophilic naphthalene in the side chain with less lipo-phillic rings such as 2-fluoro-phenyl, 2,5-difluro-phenyl, benzofuran and furan would also have had a positive effect on the reduction of LogP. The replacement of the bedaquiline side chain phenyl ring with meta chloro phenyl, 3-pyridine and 4-pyridine ring causes increased activity and reduction of lipid solubility (Fig. 8) [8,29–32]. Fernandez et al., disclosed that the basic amine functional group present in bedaquiline, which is predominantly protonated at physiological pH (pKa 9.6), forming π-cation interactions with specific aromatic residues within this region [33], increases the affinity for the hERG channel. Contrarily Guillemont et al., reported that the basicity of amino group should be more than 8 (pKa > 8) to retain the anti-mycobacterial activity against *M. smegmatis*, whereas with less basic derivatives (calculated pKa < 8) activity decreased [8]. Both the above observations indicate that an appropriate balance of basicity is essential for optimizing activity-toxicity. Therefore, here we suggest that replacing the dimethylamino terminal group of bedaquiline with different functional groups or cycling the dimethylamino terminal nitrogen into the heterocyclic ring to maintain the optimum basicity (pKa greater than 8 and less than 9.6) will reduce the cardiotoxicity (Fig. 8).

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References

[1] WHO. Global control tuberculosis. www.who.int/tb/publications/global_ report/2010/gtbr10.pdf; 2010.
[2] WHO. Stop TB partnership. www.WHO.int/tb/publications/2009/fact sheet_tb_2009update_dec2009.pdf; 2009.
[3] Udwadia ZF, Amale RA, Ajbani KK, et al. Totally drug-resistant tuberculosis in India. Clin Infect Dis 2012;54(4):579–81.
[4] Upadhayaya RS, Kulkarni GM, et al. Design, synthesis and biological evaluation of novel triazole, urea and thiourea derivatives of quinoline against Mycobacterium tuberculosis. Bioorg Med Chem 2009;17(13):4681–92.
[5] Andries K, Verhasselt P, et al. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. Science 2005;307(5707):223–7.
[6] Huitric E, Verhasselt P, et al. In vitro antimycobacterial spectrum of a diarylquinoline ATP synthase inhibitor. Antimicrob Agents Chemother 2007;51(11):4202–4.
[7] Andries K, Verhasselt P, Guillemont J, Göhlmann HW, Neefs JM, Winkler H, Van Gestel J, Timmerman P, Zhu M, Lee E, Williams P. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. Science 2005;307:223–7.
[8] Guillemont J, Meyer C, et al. Diarylquinolines, synthesis pathways and quantitative structure–activity relationship studies leading to the discovery of TMC207. Future Med Chem 2011;3(11):1345–60.
[9] Pym AS, Diacon AH, et al. Bedaquiline in the treatment of multidrug-and extensively drug-resistant tuberculosis. Eur Respir J 2016;47(2):564–74.
[10] Wolfson LJ, Walker A, et al. Cost-effectiveness of adding bedaquiline to drug regimens for the treatment of multidrug-resistant tuberculosis in the UK. PLoS One 2015;10:e0120763.
[11] Preiss L, Lange JD, et al. Structure of the mycobacterial ATP synthase Fo rotor ring

in complex with the anti-TB drug bedaquiline. Sci Adv 2015;1(4):e1500106.
[12] Koul A, Dendouga N, et al. Diarylquinolines target subunit c of mycobacterial ATP synthase. Nat Chem Biol 2007;3(6):323.
[13] Haagsma AC, Podasca I, et al. Probing the interaction of the diarylquinoline TMC207 with its target mycobacterial ATP synthase. PLoS One 2011;6(8):e23575.
[14] Worley MV, Estrada SJ. Bedaquiline: a novel antitubercular agent for the treatment of multidrug-resistant tuberculosis. Pharmacotherapy 2014;34(11):1187–97.
[15] Kakkar AK, Dahiya N. Bedaquiline for the treatment of resistant tuberculosis: promises and pitfalls. Tuberculosis 2014;94(4):357–62.
[16] Diacon AH, Donald PR, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. Antimicrob Agents Chemother 2012;56(6):3271–6.
[17] Guillemont J, Meyer C, et al. Diarylquinolines, synthesis pathways and quantitative structure–activity relationship studies leading to the discovery of TMC207. Future Med Chem 2011;3(11):1345–60.
[18] Svensson EM, Murray S, et al. Rifampicin and rifapentine significantly reduce concentrations of bedaquiline, a new anti-TB drug. J Antimicrob Chemother 2014;70(4):1106–11014.
[19] Mesens N, Verbeeck J, et al. Elucidating the role of M2 in the preclinical safety profile of TMC207. 38th world conference on lung health of the international union against tuberculosis and lung disease. 2007. p. 8–12.
[20] Patel HM, Noolvi MN, et al. Synthesis and antitubercular evaluation of imidazo [2, 1-b][1, 3, 4] thiadiazole derivatives. Arab J Chem 2017;10:S996–1002.
[21] Chaudhari KS, Patel HM, Surana SJ. Pyridines: multidrug-resistant tuberculosis (MDR-TB) inhibitors. Indian J Tuberc 2017;64:119–28.
[22] Chaudhari K, Surana S, et al. Mycobacterium Tuberculosis (MTB) GyrB inhibitors: an attractive approach for developing novel drugs against TB. Eur J Med Chem 2016;124:160–85.
[23] Shaikh MS, Palkar MB, et al. Design and synthesis of novel carbazolo–thiazoles as potential anti-mycobacterial agents using a molecular hybridization approach. RSC Adv 2014;4(107):62308–20.
[24] Pontali E, Sotgiu G, et al. Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence. Eur Respir J 2016;47:394–402.
[25] Kakkar AK, Dahiya N. Bedaquiline for the treatment of resistant tuberculosis: promises and pitfalls. Tuberculosis 2014;94:357–62.
[26] Diacon AH, Donald PR, Pym A, Grobusch M, Patientia RF, Mahanyele R, Bantubani N, Narasimooloo R, De Marez T, Van Heeswijk R, Lounis N. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. Antimicrob Agents Chemother 2012;56:3271–6.
[27] Guillemont J, Meyer C, Poncelet A, Bourdrez X, Andries K. Diarylquinolines, synthesis pathways and quantitative structure–activity relationship studies leading to the discovery of TMC207. Future Med Chem 2011;3:1345–60.
[28] Svensson EM, Murray S, Karlsson MO, Dooley KE. Rifampicin and rifapentine significantly reduce concentrations of bedaquiline, a new anti-TB drug. J Antimicrob Chemother 2014;70:1106–14.
[29] Sutherland HS, Tong AS, et al. Structure-activity relationships for analogs of the tuberculosis drug bedaquiline with the naphthalene unit replaced by bicyclic heterocycles. Bioorg Med Chem 2018;26(8):1797–809.
[30] Tong AS, Choi PJ, et al. 6-Cyano analogues of bedaquiline as less lipophilic and potentially safer diarylquinolines for tuberculosis. ACS Med Chem Lett 2017;8(10):1019–24.
[31] He C, Preiss L, et al. Structural simplification of bedaquiline: the discovery of 3-(4-(N, N-Dimethylaminomethyl) phenyl) quinoline-Derived antitubercular lead compounds. ChemMedChem 2017;12(2):106–19.
[32] Choi PJ, Sutherland HS, et al. Synthesis and evaluation of analogues of the tuberculosis drug bedaquiline containing heterocyclic B-ring units. Bioorg Med Chem Lett 2017;27(23):5190–6.
[33] Fernandez D, Ghanta A, et al. Physicochemical features of the HERG channel drug binding site. J Biol Chem 2004;279(23):10120–7.
[34] Fox GJ, Menzies D. A review of the evidence for using bedaquiline (TMC207) to treat multi-drug resistant tuberculosis. Infect Dis Ther 2013;2(2):123–44.