Journal of Molecular Structure 1239 (2021) 130493

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstr

Unveiling *p*-quinone methide (QM) chemistry to synthesize bedaquiline (TMC 207) like architectures

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ARTICLE INFO

Article history:
Received 8 February 2021
Revised 6 April 2021
Accepted 12 April 2021
Available online 24 April 2021

ABSTRACT

Bedaquiline (TMC 207) is the first FDA-approved drug to combat multidrug-resistant (MDR) tuberculosis. Herein, we disclosed hydroacylation (tandem C–H activation/C–C bond formation/aromatization) catalyzed by Wilkinson catalyst on quinoline containing new *para*-quinone methides to simplify the construction of diverse bedaquiline analogs with reduction of steps. Direct installation of three crucial aryl rings in hydroacylation giving rise to α-disubstituted aryl ketone can provide a series of bedaquiline analogs.

1. Introduction

Tuberculosis (TB) is a contagious, deadly disease caused by *Mycobacterium tuberculosis* (Mtb) that spreads through air and has become a serious global health issue [1,2]. Most of these infections are asymptomatic, a situation known as latent tuberculosis, and almost 10% of these latent infections will progress to the active disease [3]. Especially in Asia and African subcontinent, around 10.0 million people became ill with TB and 1.3 million (HIV-negative) died from TB in 2017 according to WHO statistics [4,5]. The emergence of multidrug-resistant tuberculosis (MDR-TB) [6] and extensive-drug resistant tuberculosis (XDR-TB) [7] has reduced the use of presently available medicines, such as isoniazid, rifampin, pyrazinamide, ethambutol and streptomycin [8]. Therefore, an urgent need to discover and develop new anti-TB drugs for the treatment of TB is necessary.

Bedaquiline (TMC207), which targets the adenosine triphosphate synthase (ATPase) of *M. tuberculosis*, [9] was approved by the U.S. Food and Drug Administration (FDA) in 2012 for the therapy of MDR-TB [10]. Diarylquinolines (DARQs), which were highly effective against MDR-TB, were discovered in 1996 by Janssen Pharmaceuticals [11]. After careful evaluation of 70,000 compounds against the Mtb surrogate *Mycobacterium smegmatis*, they have identified a DARQ fragmented hit (**1**). Janssen's initial hit molecule then optimized through chemical synthesis to develop another DARQ derivative Bedaquiline (**2**) with promising anti-tubercular activity (MIC- 0.06 μg/ml) in its (2*R*, 3*S*) enantiomeric form (Fig. 1) [12].

Despite its novel mode of action and potent activity, bedaquiline has some adverse side-effects like nausea, joint and chest pain and headache. TMC 207 is vindicated to be a weak human ether-a-go-go related gene (hERG) potassium (K^+) channel blocker which can cause prolongation of the heart QT interval, thus disturbing normal functioning of heart [13]. Several studies suggested that the relatively high lipophilicity of bedaquiline (ClogP-7.3) is a major source of its hERG mediated toxicity.

During development of Bedaquiline, researchers have carefully analyzed the structure-activity relationship (SAR) as reported by Janssen Pharmaceuticals [14]. Chattopadhyaya's group also have great contribution to probing the SAR of bedaquiline by dividing bedaquiline into four hemispheres and modifying every hemisphere to evaluate the biologically active motifs [15–19]. After that in 2015, Li and co-workers have reported naphthylated analog of bedaquiline [20]. Actually they replaced the quinoline ring with a naphthalene ring, leading to a new type of triarylbutanol skeleton.

From synthetic point of view, Janssen Pharmaceuticals prepared bedaquiline analogues by employing a moisture sensitive LDA-mediated addition of 3-benzylquinolines to ethyl-amino substituted aryl ketone [12]. To the best of our knowledge, hitherto three alternative asymmetric synthesis of bedaquiline are known. First one has been reported by Shibasaki's group [21], second one has been reported by Chandrasekhar's group [22] and third one has been reported by Naicker's group [23]. Later, Jonathan B. Baell's group discovered new synthetic pathways to facilitate the preparation of bedaquiline and its analogues [24]. In 2020, one review has

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https://doi.org/10.1016/j.molstruc.2021.130493
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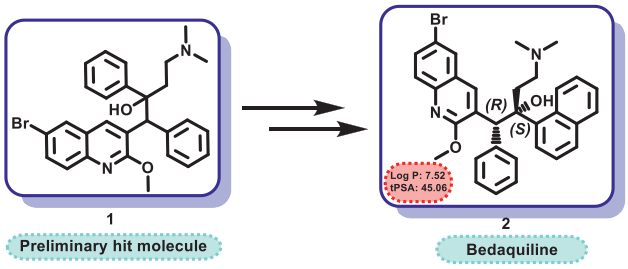


Fig. 1. Janssen developed bedaquiline from preliminary hit molecule.

appeared based on the synthetic approaches towards bedaquiline and its derivatives reported by Calvert *et al.* [25].

Recently, quinone methides (QMs), also known as methylene quinines and quinine methines, are considered to be one of the highly reactive intermediates that have been widely exploited [26]. They are classified into two types namely, 1,2-quinone methides or "*o*"-quinone methides (*o*-QMs) and 1,4-quinone methides or "*p*"-quinone methides (*p*-QMs). Aromatization is the driving force for their unique reactivity towards various nucleophiles, and therefore, these compounds act as valuable synthons for various biologically significant molecules.[27] Currently, *p*-QMs based chemistry is also well known for making various biologically active frameworks. Our goal is to construct anti-tubercular drug TMC207 like new skeleton using novel *p*-QM as a useful synthon that enabled the incorporation of three crucial aryl rings in one reaction as well as installation of various amine and hydroxyl functionality into the pharmacophore of Bedaquiline.

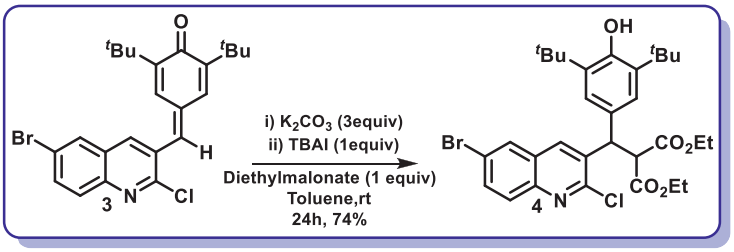
2. Result and discussion

The aim of this investigation was the invention of alternative pathways towards the synthesis of library of bedaquiline analogues that might help to explore new drug candidate in future. To achieve this, quinoline containing *p*-QM **3** was identified as a key starting material in the synthetic pathway, providing substrates that could be further elaborated to get bedaquiline like molecules. Our first approach towards bedaquiline analogues was designed to facilitate the incorporation of the diethyl 2-(naphthalen-1-yl) malonate moiety from the corresponding aryl halide. Initially, we carried out synthesis with *p*-QM **3** and diethylmalonate as a model reaction by using K_2CO_3 in toluene at RT for 24h. After completion of the reaction, we got the diaryl methine (**4**) as a product with 70% yield (Scheme 1). With this acceptable reaction conditions in hand, we then tried to achieve our next target. Primarily, this approach was conducted in a step-wise fashion. To explore this, a suitable coupling partner (**5**) was prepared from 1-bromonaphthalene and diethylmalonate using $Pd(dba)_2$ as a catalyst. (See supporting information ESI).

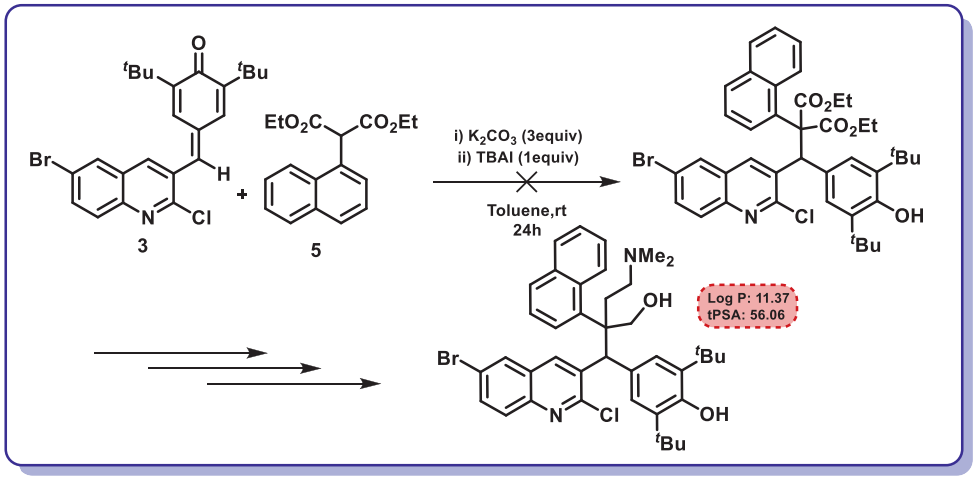
Employing potassium carbonate to generate the 1, 3-diethoxy-2-(naphthalen-1-yl)-1, 3-dioxopropan-2-ide from diethyl 2-(naphthalen-1-yl) malonate, a metal-free 1, 6-addition reaction between *p*-QM **3** and the anion was attempted (Scheme 2). But unfortunately, this reaction did not work to afford the desired product. This is perhaps because of steric hindrance on methine carbon atom. Heating the reaction mixture and employing various bases also did not yield any positive results. Our final target was to introduce $-CH_2OH$ in place of hydroxyl group of bedaquiline through *p*-QM chemistry which will provide enough chemical space and optimization and subsequent application for patents. Unsuccessful approach revoked our thought process to synthesize different kind of bedaquiline analogs by using another approach given below.

Our second approach towards bedaquiline analogs was designed to simplify the incorporation of amine moiety in place of hydroxyl group of bedaquiline to have another hydrophilic functionality as well as scope for formation of salts thereafter. Moreover, introduction of amine containing quaternary center in bedaquiline molecule is not covered in the literature. In this context, we have chosen O-Donell Schiff's base [28] (**6**) as another coupling partner which will couple with *p*-QM **3** and thus will give the corresponding adduct by following few steps. To persue this, we have prepared two types of O-Donell's Schiff bases following literature known procedures. Benzophenone imine reacted with glycine ethyl ester hydrochloride or L-alanine ethyl ester hydrochloride in DCM for 20h at rt to furnish O-Donell's Schiff bases (**6**) in excellent yields (See ESI). A second strategy to access bedaquiline analogues from *p*-QM **3** was then developed with the key reaction being the Cs_2CO_3 mediated 1, 6- addition of *p*-QM **3** with ethyl 2-((diphenylmethylene) amino) acetate (**6a**) derived from glycine ethyl ester hydrochloride as a model reaction (Scheme 3).

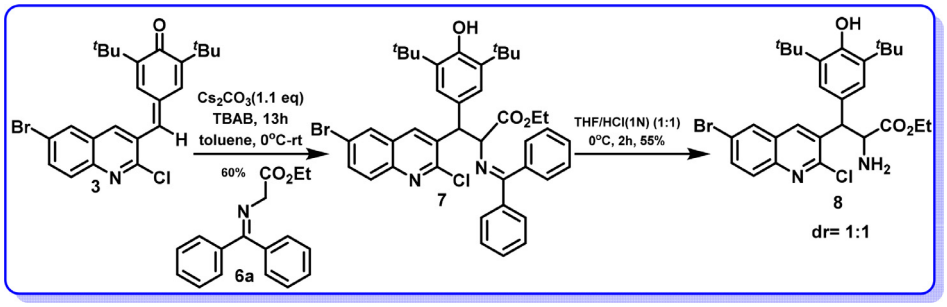
Initially, 2-((diphenylmethylene) amino) acetate (**6a**) was reacted with *p*-QM **3** in the presence of 1.1 equiv of Cs_2CO_3 to afford the ethyl 3-(6-bromo-2-chloroquinolin-3-yl)-3-(3, 5-di-tert-butyl-4-hydroxyphenyl)-2-((diphenylmethylene) amino) propanoate (**7**) in 60% yield. Then the imine (**7**) was readily converted to corresponding amine derivative (**8**) by acidification with 55% yield. After getting this positive result, we tried to incorporate a small methyl group to amine carbon to make it quaternary center in the amine derivative (**8**). To get this, we have already prepared the starting material ethyl (*R*)-2-((diphenylmethylene) amino) propanoate (**6b**) by literature known procedure (See supporting information). Unfortunately, the same reaction did not proceed when we performed the reaction with ethyl (*R*)-2-((diphenylmethylene) amino) propanoate. This is perhaps due to the steric hindrance, that's why the negative ion on center carbon atom of ethyl (*R*)-2-((diphenylmethylene) amino) propanoate perhaps did not generate for further reactions. In this case also, we had tried various methods (Cs_2CO_3, n-BuLi, t-BuLi, LiHMDS etc.) to generate the negative ion on the particular center but was not successful. With this observation, we tried to introduce naphthyl group in place of the methyl group of O-Donell's Schiff base to get naphthylated analog, but it was not fruitful either. So, with this model reaction (Scheme 3), we attempted to elaborate it to make amine-containing de-naphthylated bedaquiline analog in a stepwise manner (Scheme 4).



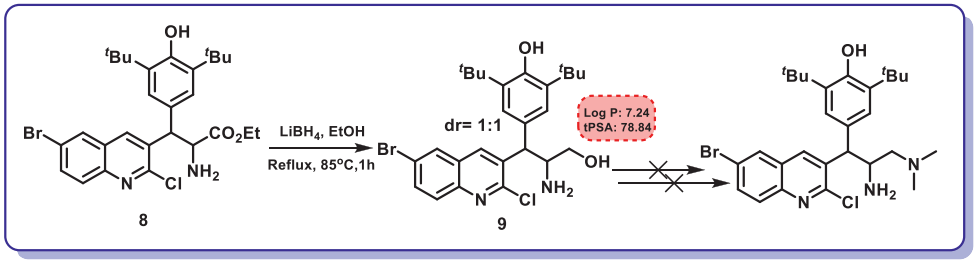
Scheme 1. Synthesis of diaryl methine from 3.



Scheme 2. Metal-free approach for the synthesis of bedaquiline analog.



Scheme 3. Synthesis of amino functionalized bedaquiline analog



Scheme 4. Metal-free approach for the synthesis of amine containing bedaquiline analog.

Initially, formation of compound **8** from compound **3** was described earlier (Scheme 3). Now, amine derivative (**8**) underwent reduction by $LiBH_4$ in ethanol under reflux for 1 h at 85 °C to give amino alcohol (**9**) with 52% yield. Unluckily, further synthetic transformation from amino alcohol (**9**) was not successful.

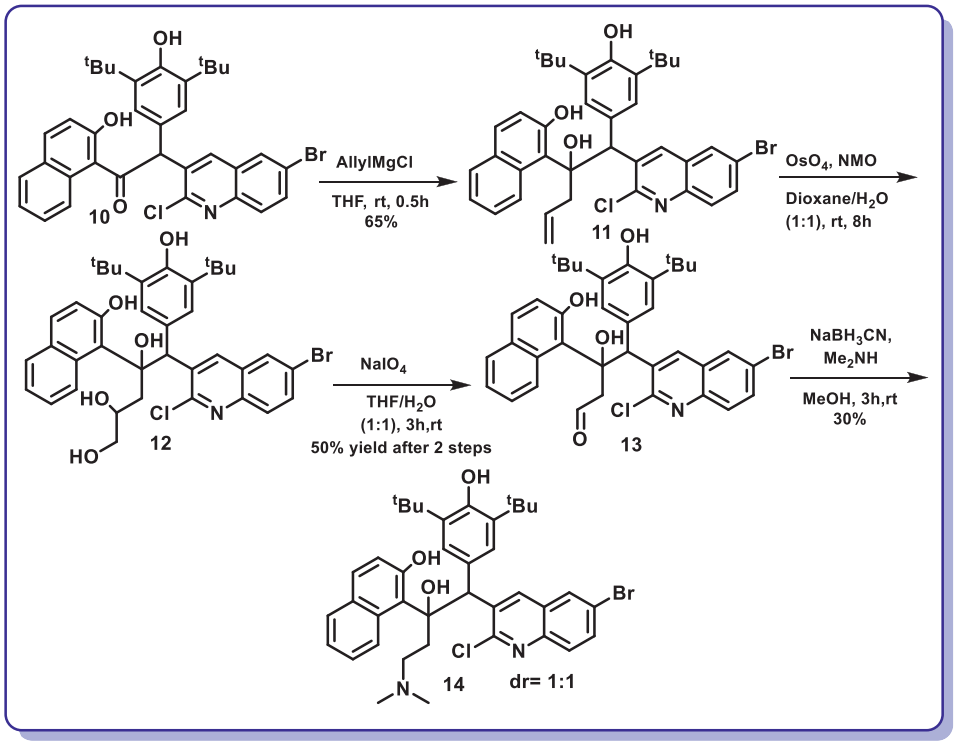
Our next plan was to synthesize trihydroxylated bedaquiline analog from *p*-QM **3** with the key reaction being the rhodium-catalyzed hydroacylation of *p*-QM **3** with 2-hydroxynaphthaldehyde. In that case, we optimized the hydroacylation reaction with *p*-QM **3** and 2-hydroxynaphthaldehyde by using various Rhodium catalysts in different solvents. We have used dppf, PPh_3 as ligand and CsF, DIPEA, CsOAc, as additives. Preliminary attempts using $Rh_2(OAc)_4$ as a catalyst and dppf as a ligand in the presence of CsF in THF at 100 °C led to the hydroacylation product **10** in 20% yield (Table 1, entry 1). When we changed the catalyst from Rh_2 $(OAc)_4$ to [Rh Cp^*Cl_2], then the reaction did not work properly (Table 1, Entry-2). After that, we choose a commercially available catalyst $[Rh(COD)Cl]_2$ for next screening in different solvents. In that case reaction furnished the required product in 30-35% yield (Table 1, Entry-3,4). Delighfully, a significant improvement was noticed when DCE/H_2O (1:1) was employed as solvent system (Table 1, Entry-5). Other additives such as CsOAc, DIPEA were also tested and exhibited inferior performance (Table 1, Entry-6, 7, 10). The yield was further improved to 66%, when PPh_3 was chosen as ligand (Table 1, Entry-8). Finally, a significant improvement was observed when we did not use any ligand. After overall screening, we got the best yield with use of Wilkinson catalyst in 1:1 DCE/H_2O (entry-9, Table 1).

Using this reaction condition in hand, *p*-QM **3** was reacted with 2-hydroxynaphthaldehyde in presence of 2.5 mol% of Wilkinson catalyst in 1:1 DCE/H_2O under reflux condition for 8h to construct α-disubstituted aryl ketone (**10**) through a tandem C–H activation/C–C bond formation/aromatization process in 70% yield. We could achieve the α-disubstituted aryl ketone (**10**) having requisite functionalities like bedaquiline in a single step from easily accessible **3** without any trouble. Smooth tandem C–C bond formation can easily give a chemical library based on bedaquiline. We characterized compound **10** by analysis of proton and [13] C NMR spectra. Some of the characteristic peaks have appeared with methine proton (C-H) at 6.18 ppm, quinoline protons at ~8.46-

Table 1
Optimization of the reaction conditions.

Entry[a]	catalyst	ligand	Additive	Solvent	Yield(%)[b]
1	Rh_2 (OAc)$_4$	dppf	CsF	THF	20
2	[Rh Cp*Cl_2]	dppf	CsF	CH_3CN	trace
3	[Rh (COD)Cl]$_2$	dppf	CsF	DCM	30
4	[Rh (COD)Cl]$_2$	dppf	CsF	DCE	35
5	[Rh (COD)Cl]$_2$	dppf	CsF	DCE/H_2O(1:1)	50
6	[Rh (COD)Cl]$_2$	dppf	DIPEA	DCE/H_2O (1:1)	trace
7	[Rh (COD)Cl]$_2$	dppf	CsOAc	DCE/H_2O (1:1)	10
8	[Rh (COD)Cl]$_2$	PPh_3	CsF	DCE/H_2O (1:1)	66
9[c]	**Rh (PPh_3)$_3$Cl**	**-**	**CsF**	**DCE/H_2O (1:1)**	**70**
10	[Rh (COD)Cl]$_2$	(±)-BINAP	CsF	DCE/H_2O (1:1)	trace

[a] Reaction conditions: **3** (0.24 mmol), 2-hydroxynaphthaldehyde (0.2 mmol), catalyst (2.5 mol %), additive (0.2 mmol) in solvent (2 mL) at 100 °C for 24 h under argon atmosphere.
[b] Isolated yields.
[c] without ligand and within 8 h.



Scheme 5. Synthesis of trihydroxylated bedaquiline analog.

8.12 ppm region and phenolic O–H (2,6-ditertbutylphenol) proton at 6.65 ppm. We assigned all carbons of **10** in [13] C spectra of supporting information.

After obtaining the α-disubstituted aryl ketone (**10**), we turned our attention to elaborate that ketone to insert the dimethylethylamino chain. Although analogous transformations have been previously reported, [29] optimization of this pathway was still necessary to identify reproducible and high-yielding reaction conditions. So, we followed the following synthetic procedures to complete the synthesis (Scheme 5).

The initial step involved the allylation of ketone (**10**) to afford the tertiary allyl alcohol (**11**) via Grignard reaction conditions. It was proposed that due to the acidity of the α-proton of the ketone, basic Grignard reagents led to deprotonation and enolization of the ketone before 1, 2-addition to the carbonyl group could occur. That is why Chandrasekhar *et al.* has reported this transformation by using freshly prepared allyl-ZnBr, because Organo-zinc compounds are non-basic reagents and would not promote enolization. But in our case, enolization did not happen under Grignard reaction conditions. We got our desired allylated product (**11**) as racemates by using 15 equiv of allyl-MgCl in dry THF for half an hour at rt with 65% yield (after column chromatography). Allylated product **11** which upon treatment with OsO_4 and NMO in dioxane/water system afforded the diol **12** as racemates which was used without further purification in next step. Diol **12** underwent periodate oxidation in THF/H_2O combination to give trihydroxy containing aldehyde **13** as racemates in 50% yield. In the last step, reductive amination of aldehyde **13** with dimethyl amine by sodium borohydride in methanol for 3h constructed the final amine containing bedaquiline analog **14** as a diastereomeric mixture (1:1 ratio). In that case, we did not get the α-disubstituted aryl ketone **10** back during reductive amination. We had also attempted reduction process on triaryl aldehyde **13**. But particularly, in this reaction so many spots were generated in the TLC within 5 min. It was

Table 2
Evaluation of compounds against *Mycobacterium tuberculosis* $H_{37}R_a$ with MIC (μM).

Code	MIC (μM)
10	>32
11	>32
13	>50
14	>32
8	>32
3	> 50 µM
Bedaquiline	0.06 µM

very difficult to isolate the corresponding alcohol product. That is why we choose the reductive amination process instead of reduction followed by tosylation and amination. As a result, steps also were decreased compared to the literature procedures. All compounds (11, 13 & 14) were fully characterized by proton and carbon spectra. Compound no **13** has a sharp signal of aldehyde proton at 10.19 ppm and methine proton at 5.79-5.80 ppm as a diastereoisomer with ratio 1:1. Final compound **14** also has some characteristic signals like methine proton at 5.99 ppm, methyl proton at 1.58 ppm and tertbutyl protons at 1.27 ppm. Diastereomeric ratio of final compound **14** was calculated from proton NMR that we have already shown in supporting information file.

The aim of this study was therefore to simplify the chemical synthesis of bedaquiline to work toward new, alternative leads. Once these simplified scaffolds are achieved, they will be used to improve pharmacokinetic properties to decrease the adverse side effects of bedaquiline. The success of bedaquiline has originated significant interest in the development of improved analogues. While the potency of drugs for TB often positively correlates with their lipophilicity (likely due to the very lipophilic cell wall of the bacterium), the extremely high lipophilicity of TMC207 may also lead to the induction of phospholipidosis and to overproportional drug accumulation in tissues (as suggested by its long terminal half-life). To address these concerns, a study of related derivatives in which the hydroxyl group replaced by amino functionality is going on in our lab. The potential utility of amino group perhaps will be lowering lipophilicity while largely retaining good anti-mycobacterial potency against *M. tb*. The synthesized bedaquiline analogs were dissolved in DMSO (Stock con. 10 mM) and seeded in MB7H9 medium (100 μl volume) enriched with ADC (10% v/v) with decreasing double dilutions starting with 50 μM (for 250 μl volume) in 96 well plate. 150 μl of culture (*Mycobacterium tuberculosis H37Ra*, 106 CFU/ml) was added to each well and the efficacy of compounds were evaluated against *Mycobacterium tuberculosis* $H_{37}R_a$ using MABA assay and 90% inhibitory concentrations were calculated by plotting fluorescence values using Microsoft excel template with testing of maximum conc. at 50 μM (Table 2). The preliminary results (fluorescence) were measured at 530±25 nm and 590 ± 25 nm for excitation and emission respectively in Synergy Biotek plate reader.

However, to the best of our knowledge, these types of molecules were earlier not reported from the analogous series of Bedaquiline. Further finding of new chemical space around bedaquiline using this chemistry via construction of α-disubstituted aryl ketone through hydroacylation reaction catalyzed by Wilkinson catalyst is currently underway and their biological results will be the subject matter of future reports.

3. Conclusion

To enable the preparation of novel pharmaceutical agents for the treatment of MDR-TB that displays improved safety profiles, novel synthetic routes to access bedaquiline analogues were required. The new process has some advantages. First, we have avoided the use of conventional, moisture sensitive LDA method which was used in the synthesis of bedaquiline previously to get tri-substituted ethane like skeleton. Second, 1, 6- addition of aldehyde to *p*-QM gives direct installation of three crucial aryl rings in one shot which may give rise to α-disubstituted aryl ketone like molecules very easily. Third, our case went through reductive amination which resulted into reduction of two steps. We reported new synthetic pathways to expedite the construction of bedaquiline analogs using *p*-Quinone methide chemistry and preliminary results presented.

Credit author statement

Deblina Roy, Experimental methodology with Conceptualization, Writing- Original draft preparation

Kasim Ali, Performed preliminary experiments

Gautam Panda Conceptualization, Writing- Reviewing and Editing and Supervision

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank Department of Science & Technology , New Delhi, India (DST; CRG/2019/000489) for financial support. Instrumental facilities from SAIF, CDRI are highly appreciated. We also thank Ashok Kumar Sharma for some preliminary experiment of this manuscript. Preliminary bioevaluation from Dr. B N Singh, CDRI is highly acknowledged. This has CDRI communication no 10230.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.130493.

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