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Digest

Synthetic approaches towards bedaquiline and its derivatives

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ABSTRACT

Bedaquiline is a diarylquinoline drug that demonstrates potent and selective inhibition of mycobacterial ATP synthase, and is clinically administered for the treatment of multi-drug resistant tuberculosis. Due to its excellent activity and novel mechanism of action, bedaquiline has been the focus of a number of synthetic studies. This review will discuss these synthetic approaches, as well as the synthesis and bioactivity of the numerous derivatives and molecular probes inspired by bedaquiline.

Introduction

Tuberculosis (TB), caused by the pathogen *Mycobacterium tuberculosis*, has been a major cause of mortality in humans for millennia, and is currently one of the top ten causes of death worldwide.[1] The incidence of drug-resistant TB is especially concerning, and has been exacerbated by the dearth of new treatment options developed for this disease over the last half century.[2] In 2012 the FDA approved bedaquiline (BDQ, also referred to in the literature as Sirturo, TMC207 and R207910) for the treatment of multidrug-resistant TB, the first new drug to be approved for this disease in forty years.[3] BDQ is a diarylquinoline drug (Fig. 1), which exerts a novel mechanism of action, namely inhibition of mycobacterial ATP synthase.[4–12] It displays excellent activity against both drug-sensitive and drug-resistant TB strains,[4] and was recently added to the World Health Organization's list of essential medicines.[13]

The purpose of this review is to examine the literature around the synthesis of BDQ and its derivatives. These studies can be broadly grouped into four areas: (1) literature syntheses of BDQ, (2) structure-activity-relationship (SAR) studies around the diarylquinoline structure, (3) the synthesis of simplified BDQ analogues, and (4) elaboration of BDQ to generate molecular probes. Some studies nominally describing analogues of BDQ were deemed to have insufficient structural similarity with the parent compound to be discussed in detail in this review.[14–17] Readers interested in the pharmacology, microbiology and clinical efficacy of BDQ are encouraged to read one of the many excellent reviews that address these topics.[18–22]

Literature syntheses of bedaquiline

The first synthesis of BDQ was carried out at Johnson & Johnson as part of a search for novel diarylquinoline compounds active against tuberculosis (Scheme 1).[4,23,24] The synthetic strategy was highly convergent, enabling the synthesis of over 200 diarylquinolines, from which BDQ emerged as the front-runner.[8] While this synthetic route was excellent for quickly generating a library of diverse diarylquinolines, the isolated yield for the most active *R,S* enantiomers was low due to the uncontrolled nature of the final deprotonation/carbonyl addition reaction between **1** and **2** and the difficult separation of BDQ from the undesired stereoisomers **3–5**.

This reaction has been heavily optimised for the purpose of industrial-scale synthesis, giving an overall yield of 12% following selective crystallisation of the undesired *S,S/R,R* isomers **3** and **4**, chiral resolution using phosphoric acid **6**, and a desalting step, which also liberates the chiral phosphoric acid **6** for recycling (Scheme 2).[25,26] A final step delivers BDQ as its stable, non-hygroscopic, water soluble fumarate salt.[27]

The first enantioselective synthesis of BDQ was accomplished by the Shibasaki group in 2010.[28] This route made use of two key stereoselective steps – an enantioselective proton migration catalysed by an yttrium•**7** complex to install the *gem*-diaryl stereocentre in **8**, and a diastereoselective allylation to install the tertiary alcohol in **9** (Scheme 3). Six subsequent steps were required to obtain the target compound, giving an overall yield of 5% from commercially available starting materials.[28]

Shortly thereafter the group of Chandrasekhar disclosed a route to BDQ based around a Sharpless asymmetric epoxidation strategy

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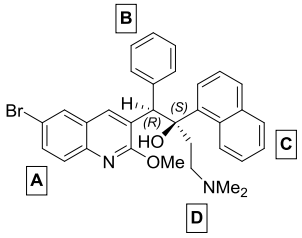


Fig. 1. The structure of BDQ, with the diarylquinoline A/B/C/D nomenclature used throughout this review.

(Scheme 4).[29] The key epoxidation step gave **10** with good yield and enantioselectivity, however the authors were not able to accomplish a diastereoselective allylation of ketone **11**, and therefore BDQ was produced as a (separable) mixture with diastereomer **4**. It is noteworthy that this approach delivered multigram quantities of the target compound in an overall yield of 12% from commercially available aldehyde **12**.

A patent filed in 2017 demonstrated that the addition of chiral amino alcohols improves stereoselectivity in the final coupling step between **1** and **2** (Scheme 5).[30] These amino alcohols also facilitate the separation of BDQ and its enantiomer. Naicker and co-workers recently reported the use of a chiral lithium amide for this step.[31] While stereoselective deprotonation could not be realised using this approach, diastereoselectivity could be improved, albeit with reduced overall product yield. Separation of BDQ and its enantiomer was accomplished using supercritical fluid chromatography. Both approaches suffer from low overall conversion, and the increased cost associated with the use of chiral reagents.

A patent was filed in 2014 disclosing an alternative approach towards BDQ using unsaturated ketone **13** as the electrophile (Scheme 6).[32] Diastereoselectivity is improved with this approach, giving vinyl amine mixture **14a/b** in 57% yield. Hydrogenation of this mixture followed by chiral resolution gives BDQ in 19% overall yield from **1** and **13**, as compared to 12% reported for the original approach.[25]

BDQ is synthesised industrially using the low-cost, stereo-random route outlined in Scheme 2. While this route has been impressively optimised, it nonetheless produces large amounts of the undesired BDQ isomers. An interesting approach towards recycling these undesired isomers has been reported, using a base catalysed carbon-carbon bond cleavage reaction to regenerate **1** and **2** (Scheme 7).[33] Yields of **1** and **2** as high as 90% could be accomplished within 1 h at room temperature, using the mixture of undesired BDQ isomers **3–5**.

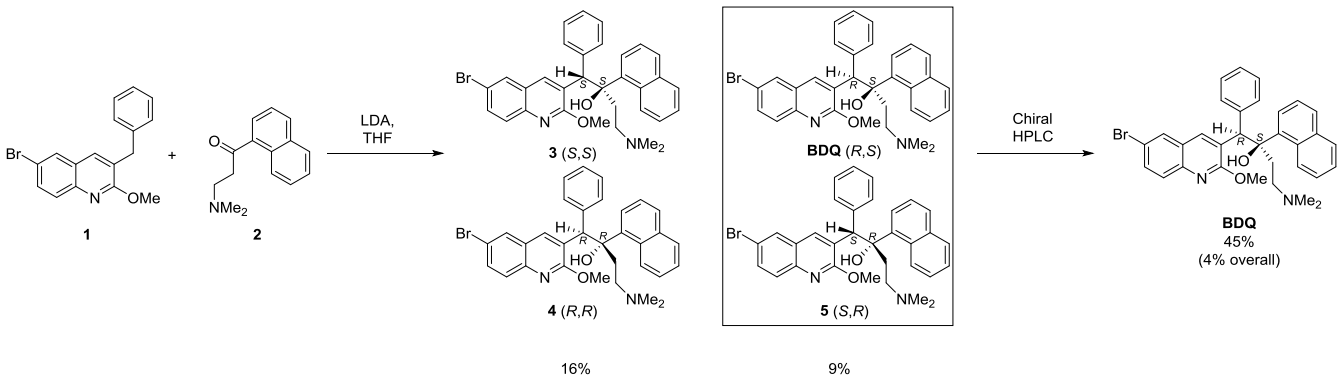
Diarylquinoline SAR studies

Li and co-workers carried out a study into the synthesis of BDQ analogues wherein the quinoline A-ring is replaced with a naphthalene (Scheme 8).[34,35] Similar activities were observed to BDQ for a number of analogues (e.g. **15–17**),[34] indicating that the quinoline ring may not be essential for activity. The stereoselective synthesis of **17**, the closest analogue to BDQ, was carried out following an analogous route to that reported by Chandrasekhar,[29] and the stereoselectivity of the key asymmetric step (epoxide opening of **18** to give diol **19**) was rigorously confirmed.[35] No results have been disclosed about the pharmacokinetic effect of replacing a quinoline ring with a naphthalene, in what is already a highly lipophilic compound.

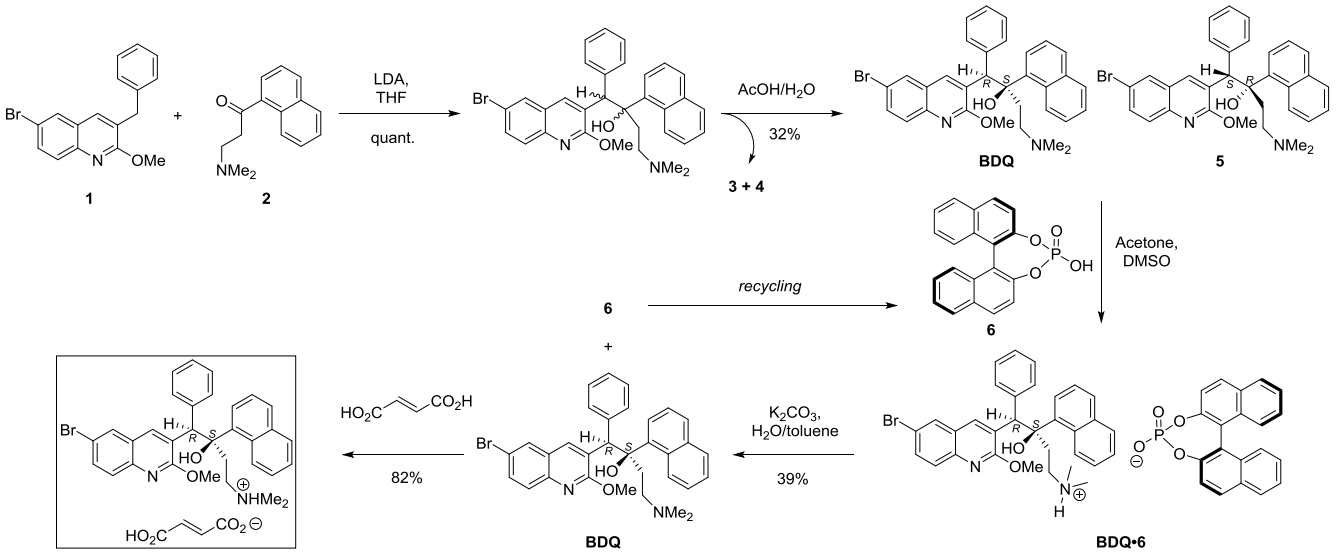
Omel'kov and co-workers reported the synthesis of three BDQ derivatives with modification at the quinoline 2- and 6-positions (Scheme 9).[36] The reaction between benzylquinolines **20a-c** and unsaturated ketone **13**[32] was unsuccessful, giving instead dimerized products **21a-c**. Reaction between **20a-c** and saturated ketone **2** proceeded in moderate yield, to give diastereomeric mixtures of BDQ analogues **22a-c**. Separation of **22a** (R = Br) into its *R,S/S,R* and *R,R/S,S* stereoisomers was achieved, however resolution of the enantiomers was not reported. Upon conversion to its citrate salt, compound **22a** demonstrated moderate anti-tuberculosis activity (*R,S/S,R* diastereomer = 3.125 μg/mL, *R,R/S,S* diastereomer = 6.25 μg/mL).

BDQ is a potent inhibitor of *Mycobacterial* ATP synthase, however it shows minimal inhibition of this enzyme in other pathogenic bacteria.[4] A collaboration between Johnson & Johnson and the Vrije Universiteit Amsterdam was thus established to investigate the possibility of modifying the BDQ structure to find an ATP synthase inhibitor active against a range of Gram-positive and Gram-negative bacteria.[37] More than 700 BDQ derivatives were synthesised, with the structure–activity relationship studies mainly focused on modifying the chain length between the basic nitrogen and the hydroxyl group and/or the C-ring and the hydroxyl group (compounds **23–26**, Fig. 2). The most promising antibacterial activity was observed against *Streptococcus pneumoniae* (compounds **23–25**) and *Staphylococcus aureus* (compounds **23**, **24**, and **26**), with similar activity to levofloxacin. Compounds **23** and **24** were shown to rapidly kill *S. aureus*, and compounds **23–25** were all shown to selectively inhibit ATP synthesis in *S. aureus* and *E. coli* in comparison to human cells, although selectivity was modest. Significant human plasma protein binding limited the clinical usefulness of this class of compounds, however this study nonetheless constitutes a significant proof-of-concept for the development of ATP synthase inhibitors as broad-spectrum antibiotics.[12]

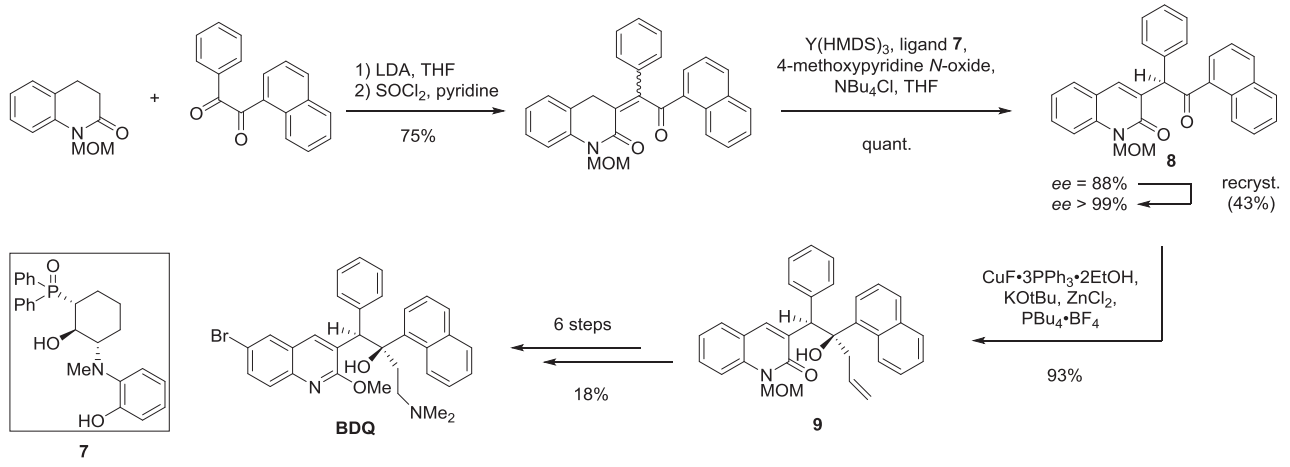
While BDQ has proven itself to be an important new drug in the fight against TB, it nonetheless has a number of shortcomings, most



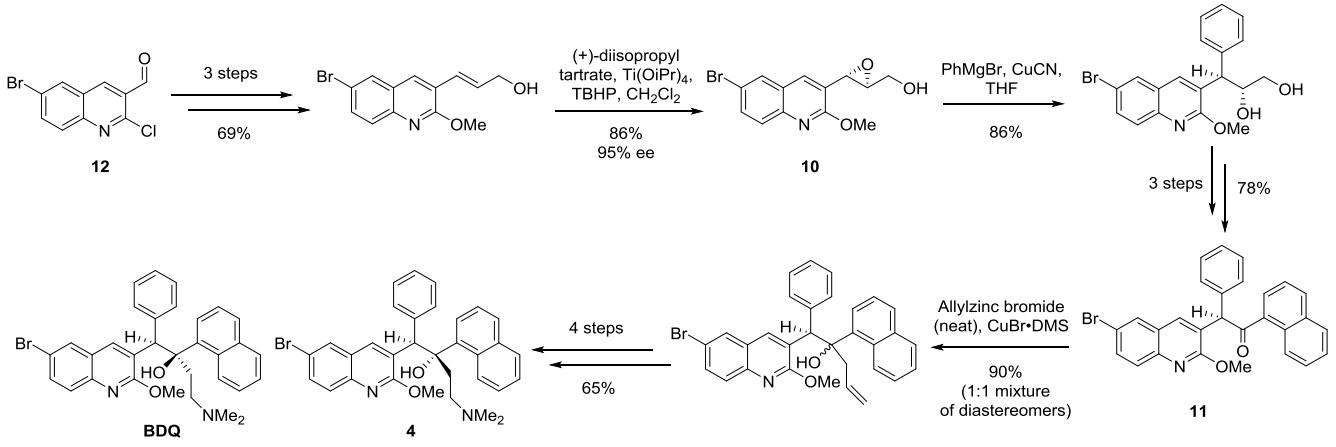
Scheme 1. Original BDQ synthesis.



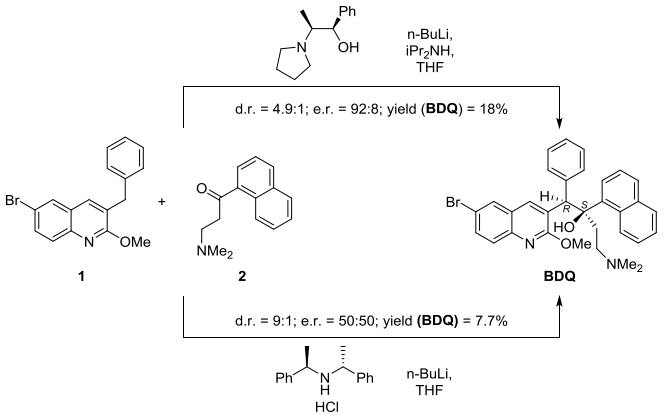
Scheme 2. Industrial synthesis of BDQ.



Scheme 3. Shibasaki's enantioselective synthesis of BDQ.



Scheme 4. Chandrasekhar's asymmetric synthesis of BDQ.

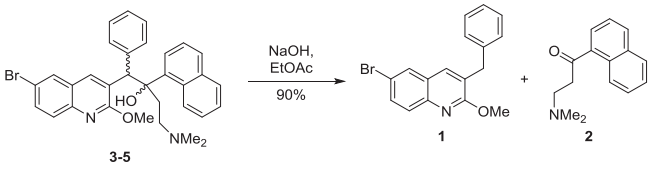


Scheme 5. Asymmetric synthesis of BDQ using lithium alkoxides and lithium amides.

prominently its high lipophilicity, which may lead to undesired accumulation in some tissues, and potent inhibition of the hERG potassium channel, which can lead to arrhythmia.[19] To address these shortcomings, a thorough SAR study was initiated by Denny and co-workers, resulting in a series of publications.[38–43] A number of key findings were disclosed: replacement of the A-ring bromo-substituent with a cyano group gave good reduction in lipophilicity with only a small reduction in potency (Fig. 3, 27 vs **28**);[38] replacement of the phenyl B-ring with a pyridyl derivative (**29**, **30**), or the naphthalene C-ring with heterocycles (**31**, **32**), can also reduce lipophilicity while maintaining potency;[39–41] hERG channel inhibition can be overcome in compounds that have improved lipophilicity and activity (**32**, **TBAJ-876**).[42,43] The most promising compound of this series (**TBAJ-876**) has demonstrated impressive *in vivo* activity in a mouse model[42] and inhibits mycobacterial ATP synthase more strongly than BDQ.[44] Interestingly, **TBAJ-876** maintains excellent bactericidal activity despite the fact that its lower lipophilicity excludes it from exerting BDQ's secondary mode of action, protonophore activity,[45–47] and this compound has also demonstrated activity against *Mycobacterium abscessus*, which is a cause of severe lung disease.[48]

Synthesis of simplified and/or modified bedaquiline analogues

While the diarylquinoline scaffold is relatively simple, the

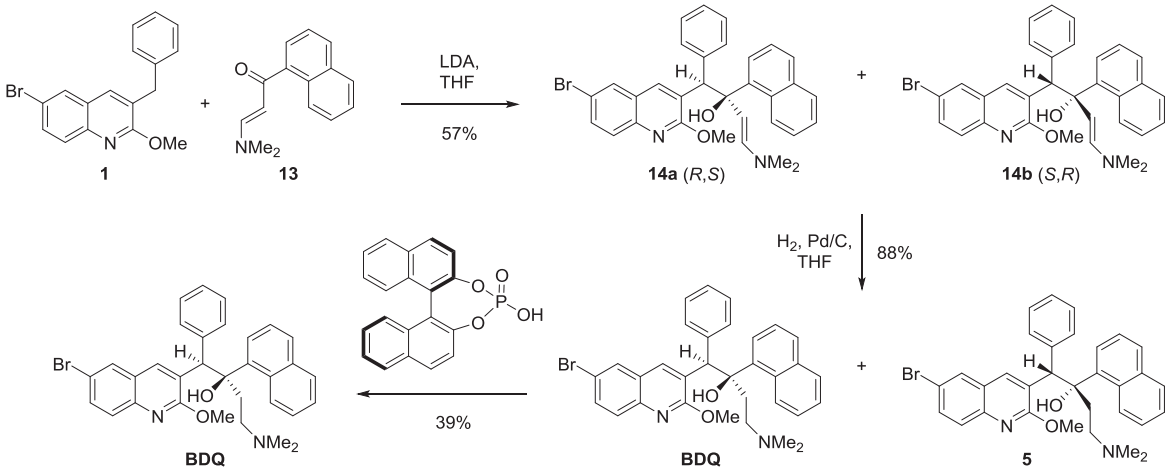


Scheme 7. Recycling of **1** and **2** from undesired BDQ isomers **3–5.**

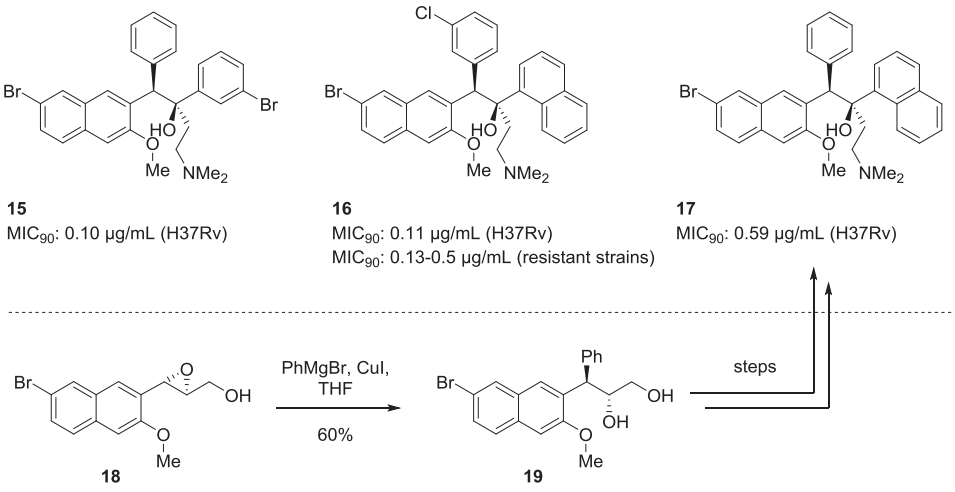
installation of the two congested, contiguous stereocentres is a non-trivial task, as has been demonstrated by the effort required to access BDQ stereoselectively.[28,29,31] If a simplified analogue were able to maintain good potency and selectivity against *M. tuberculosis*, this would likely translate into a more cost-effective product that would in turn be more accessible to lower-income tuberculosis victims.[2] As such, a number of groups have attempted to simplify the BDQ structure in the hopes of finding a potent, readily synthesised analogue.

The group of Chattopadhyaya released the first investigation into compounds conceptually derived from the BDQ skeleton (Fig. 4).[49–54] Most compounds were only loosely based on the BDQ scaffold, with the 3-benzylquinoline motif (rings A and B) the only generally conserved fragment. Compounds **33** and **34** demonstrated moderate activity with low cytotoxicity.[49] Modification of the quinoline 2- and 6-positions also gave moderately active compounds **35** and **36**, with higher cytotoxicity observed.[50] 4-Alkarylquinoline derivatives (e.g. **37**) showed very weak inhibition, while the related naphthalene derivatives (e.g. **38**) were significantly more potent.[51] Some conformationally constrained A/B ring derivatives were also investigated, and the 2-imidazolyl derivatives (**39** and **40**) and fused tetrazole derivative **41** showed good potency, along with low cytotoxicity (for **41**) and more desirable clogP values (3.7–4.9 vs 7.25 for BDQ).[52,53] Further activity improvements to these compounds were enabled by their derivatisation as esters, giving potent inhibitors **42** and **43**, albeit with significantly increased cytotoxicity and lipophilicity.[54]

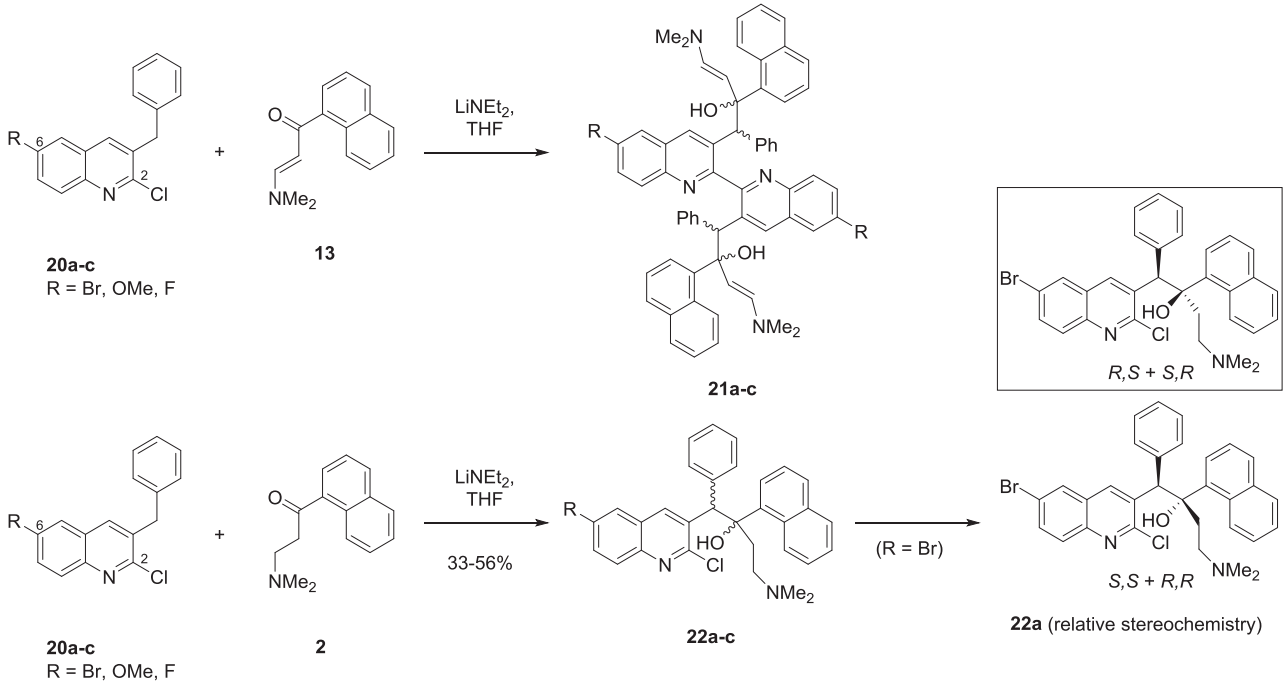
A similar investigation into conformationally constrained BDQ analogues was published by Kalia and co-workers in 2015 (Fig. 5).[55] The C-ring was fused to the D-chain, giving a partially separable mixture of diastereomers (e.g. **44**), all of which were found to have only weak anti-tuberculosis activity (MIC ≥ 6 μg/mL). Constrained macrocyclic analogue **45** displayed good potency against ATP synthase (10 nM vs 2.5 nM for BDQ), however it was not tested for its anti-tuberculosis activity. The most promising non-constrained bis-quinoline derivative, **46**, demonstrated both good ATP synthase inhibition, good



Scheme 6. Improved synthesis of BDQ via unsaturated ketone **13.**



Scheme 8. Activity and stereoselective synthesis of naphthalene BDQ analogues.



Scheme 9. Synthesis of 2-chloroquinoline BDQ derivatives.

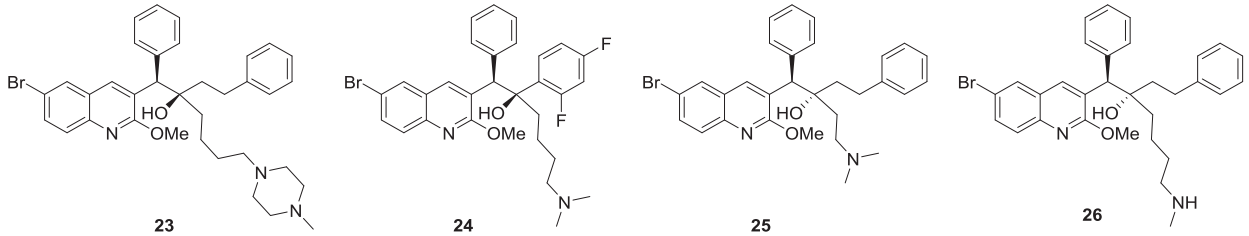


Fig. 2. Representative examples of BDQ analogues targeting non-Mycobacterium pathogens.

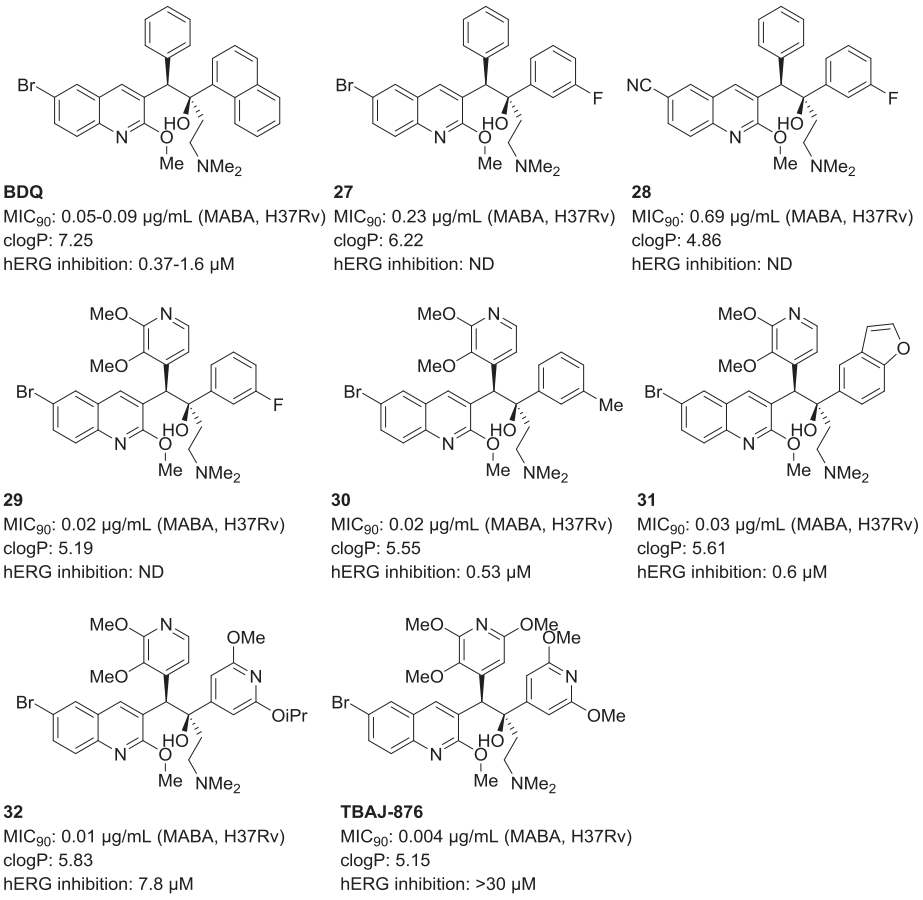


Fig. 3. SAR studies carried out by Denny and co-workers.

anti-tuberculosis activity and low cytotoxicity. Reasonable activity against resistant TB strains was also observed (MIC = 3.12 μM). The separation of the enantiomers of **46** was not reported, however it would be anticipated that one enantiomer is significantly more active, as has generally been observed for diarylquinolines.

As the controlled formation of the two stereocentres in BDQ are the key challenges associated with its synthesis, an investigation was made by Yin and co-workers into analogues that arranged the key A-D fragments (quinolyl, phenyl, naphthyl and alkylamine, or analogues thereof) in such a manner that no chiral centres were present (Scheme 10).[56] The best analogues obtained (**47**–**50**) were synthesised in two steps from commercially available intermediate **51**. These compounds had activity in the high nanomolar range and, significantly, retained activity against isoniazid and rifampicin resistant strains. Interestingly, **48** and **49** demonstrated some inhibition of ATP synthase, albeit much weaker than BDQ, however **50** displayed only very weak inhibition and **47** did not inhibit the enzyme at all, which may imply that **47** could retain activity in strains which have developed resistance to BDQ. Given the simplicity of the synthetic route towards these compounds in comparison with BDQ, these results are noteworthy.

Investigations into simplifying the synthesis of BDQ analogues were carried out by Baell and co-workers (Scheme 11). A number of approaches were detailed, based around efficient palladium-catalysed syntheses of the triarylketone intermediate **52**.[57] Elaboration of this intermediate into debromo-BDQ **53** was demonstrated, and this approach was also shown to be useful for the generation of other BDQ analogues **54** and **55**. No anti-tuberculosis activity data was given for the synthesised compounds.

A recent study has investigated the anti-mycobacterial activity of a range of BDQ triazole derivatives **56** (Fig. 6).[58] While a large range of compounds could be rapidly synthesised by a click reaction between azide **57** and a range of alkynes, none showed promising activity against *M. bovis* (MIC = 30–170 μM).

Elaboration of bedaquiline

The potency and specificity of BDQ for *M. tuberculosis* strains renders it an excellent scaffold for the generation of tool compounds for *in vivo* tuberculosis studies. The first publication investigating this concept was the fluorescent labelling of BDQ by Slotweg and co-workers (Fig. 7).[59] Compound **58** was prepared using a Sonogashira coupling with intact BDQ, and although **58** had significantly reduced anti-tuberculosis activity (IC_{50} ~ 2 μM), it was nonetheless deemed sufficiently active for potential bioimaging purposes. When a longer linker was used between the drug and the fluorophore, lower anti-tuberculosis activity was observed, further indicating that the ATP synthase binding pocket does not accommodate steric bulk at this position. The synthesis of radiolabelled BDQ (**59**) for PET imaging was successfully carried out by Jain and co-workers by exchange of $^{79/81}$Br with radioactive ^{76}Br.[60] The potential of **59** in imaging tuberculosis infection was demonstrated by the generation of 2D autoradiographs in infected mice.

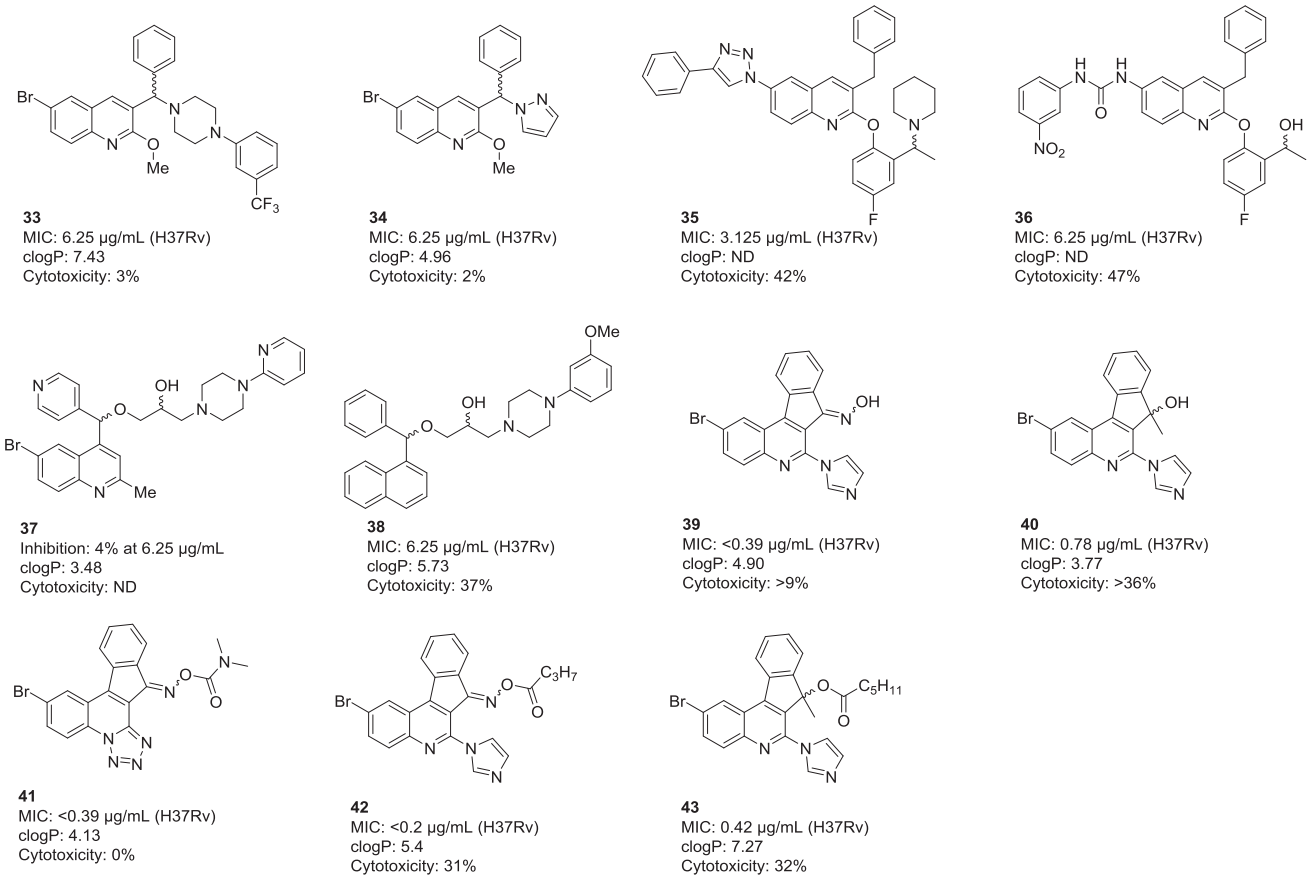


Fig. 4. Synthesis of BDQ-inspired anti-tuberculosis compounds **33–43**. Cytotoxicity = percentage loss of murine macrophage cell viability 72 h after a 10 μg/mL dose.

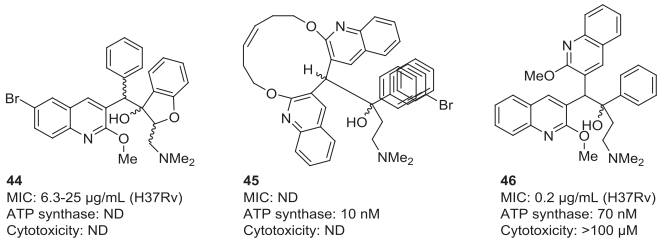


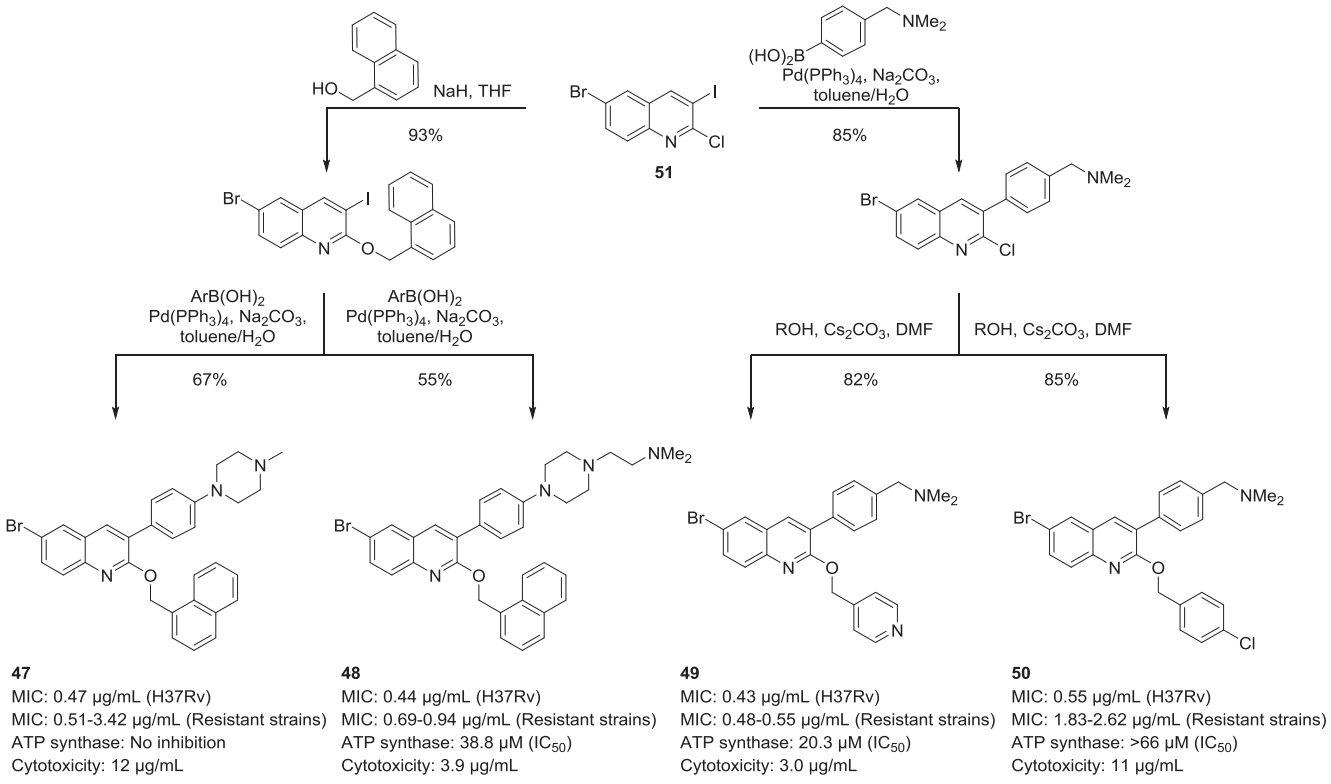
Fig. 5. Synthesis of constrained and non-constrained BDQ analogues. Cytotoxicity = dose causing 50% loss of murine macrophage cell viability.

Conclusion and future directions

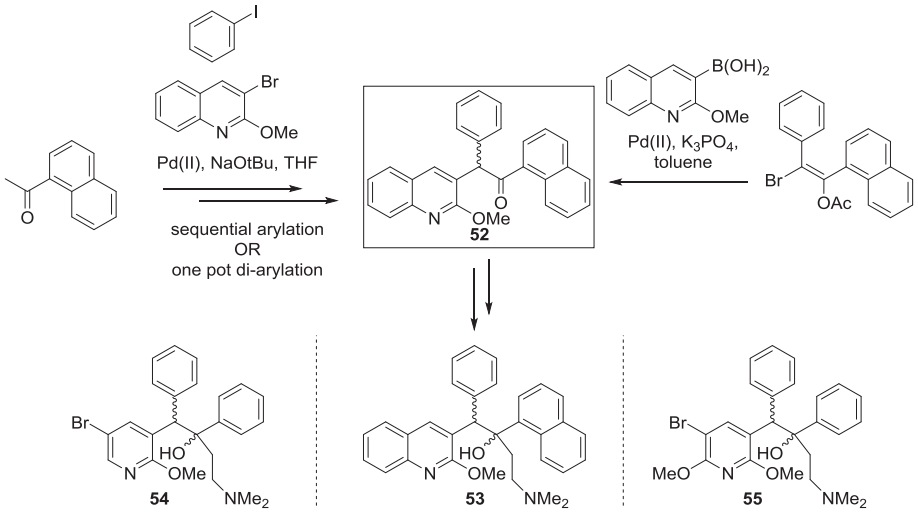
The introduction of BDQ into the arsenal of anti-tuberculosis agents has heralded a new era in the treatment of multi-drug resistant TB. Given the severity of side effects often observed for alternative treatment options,[61] it is unsurprising that patients, advocates, and policy-makers are calling for more widespread access to BDQ.[2,62] Of course, no compound is without its drawbacks: in the case of BDQ these include hERG channel inhibition and very high lipophilicity, as well as a synthetic route that delivers the target compound as a mixture of stereoisomers, thereby lowering the overall yield and increasing BDQ's manufacturing costs. Also of concern are reports detailing the emergence of BDQ-resistant TB strains.[63] It is encouraging that some of the studies cited in this review have been able to make improvements in these areas: the side effects associated with BDQ have been impressively reduced in TBAJ-876[42–44,46] and the recently disclosed approach of recycling undesired BDQ stereoisomers could contribute to lowering production costs.[33] In spite of these advances, further research into the synthesis of BDQ and its analogues is certainly needed. In particular, further optimisation of TBAJ-876 could be beneficial to identify a compound with logP reduced to within the optimal range for a TB treatment (clogP < 4)[64] without compromising activity. Research into analogues which maintain activity against the most commonly observed resistant mutants, e.g. *atp*E mutants,[65,66] would also be valuable. Further studies into high-yielding, cost-effective asymmetric syntheses of BDQ and its analogues should also be prioritised. While investigations into simplified mimics of BDQ have generated a number of interesting compounds, these new chemical classes will also need to be rigorously analysed to confirm whether activity against ATP synthase is retained, or if an alternative mechanism of action is being exerted. Finally, further research into the use of BDQ as a scaffold for the development of molecular probes (such as **58** and **59**)[59,60] should prove useful for the further study of tuberculosis, thereby aiding in the development of the next generation of treatments for this disease.

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.



Scheme 10. Synthesis and activity of simplified BDQ analogues. Cytotoxicity = dose causing 50% reduction in Vero cell growth.



Scheme 11. Approaches to BDQ analogues based around Pd-catalysed coupling reactions.

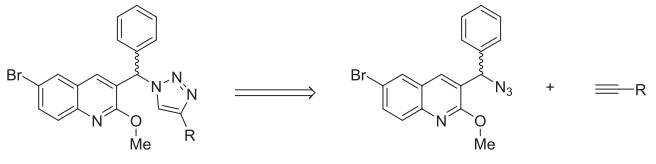


Fig. 6. Click chemistry approach to BDQ analogues **56.**

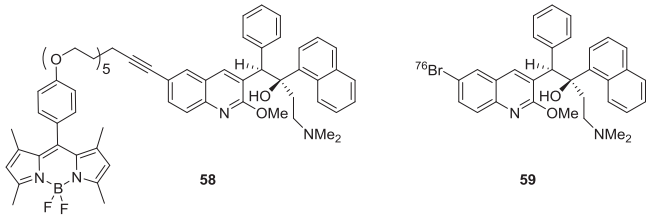


Fig. 7. Molecular probes **58** and **59** derived from BDQ.

References

1. The top 10 causes of death. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed November 11, 2019.
2. Global Tuberculosis Report. Geneva: World Health Organisation; 2019. https://www.who.int/tb/publications/global_report/en/. Accessed November 12, 2019.
3. Cox E, Laessig K. FDA approval of bedaquiline — The benefit–risk balance for drug-resistant tuberculosis. *N Engl J Med.* 2014;371(8):689–691. https://doi.org/10.1056/NEJMp1314385.
4. Andries K. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. *Science.* 2005;307(5707):223–227. https://doi.org/10.1126/science.1106753.
5. Petrella S, Cambau E, Chauffour A, Andries K, Jarlier V, Sougakoff W. Genetic basis for natural and acquired resistance to the diarylquinoline R207910 in Mycobacteria. *Antimicrob Agents Chemother.* 2006;50(8):2853–2856. https://doi.org/10.1128/AAC.00244-06.
6. Koul A, Dendouga N, Vergauwen K, et al. Diarylquinolines target subunit c of mycobacterial ATP synthase. *Nat Chem Biol.* 2007;3(6):323–324. https://doi.org/10.1038/nchembio884.
7. de Jonge MR, Koymans LHM, Guillemont JEG, Koul A, Andries K. A computational model of the inhibition of Mycobacterium tuberculosis ATPase by a new drug candidate R207910. *Proteins Struct Funct Bioinforma.* 2007;67(4):971–980. https://doi.org/10.1002/prot.21376.
8. 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(11):1345–1360. https://doi.org/10.4155/fmc.11.79.
9. Segala E, Sougakoff W, Nevejans-Chauffour A, Jarlier V, Petrella S. New mutations in the Mycobacterial ATP synthase: New insights into the binding of the diarylquinoline TMC207 to the ATP synthase C-ring structure. *Antimicrob Agents Chemother.* 2012;56(5):2326–2334. https://doi.org/10.1128/AAC.06154-11.
10. Preiss L, Langer JD, Yildiz Ö, et al. Structure of the mycobacterial ATP synthase F_o rotor ring in complex with the anti-TB drug bedaquiline. *Sci Adv.* 2015;1(4):e1500106https://doi.org/10.1126/sciadv.1500106.
11. Cholo MC, Mothiba MT, Fourie B, Anderson R. Mechanisms of action and therapeutic efficacies of the lipophilic antimycobacterial agents clofazimine and bedaquiline. *J Antimicrob Chemother.* 2017;72(2):338–353. https://doi.org/10.1093/jac/dkw426.
12. Narang R, Kumar R, Kalra S, et al. Recent advancements in mechanistic studies and structure activity relationship of F_oF_1 ATP synthase inhibitor as antimicrobial agent. *Eur J Med Chem.* 2019;182:111644https://doi.org/10.1016/j.ejmech.2019.111644.
13. World Health Organization Model List of Essential Medicines, 21st List. Geneva: World Health Organisation; 2019.
14. Khan SR, Singh S, Roy KK, Akhtar MS, Saxena AK, Krishnan MY. Biological evaluation of novel substituted chloroquinolines targeting mycobacterial ATP synthase. *Int J Antimicrob Agents.* 2013;41(1):41–46. https://doi.org/10.1016/j.ijantimicag.2012.09.012.
15. Geng Y, Li L, Wu C, et al. Design and stereochemical research (DFT, ECD and crystal structure) of novel bedaquiline analogs as potent antituberculosis agents. *Molecules.* 2016;21(7) https://doi.org/10.3390/molecules21070875.
16. Wang Z, Li L, Zhou Z, Geng Y, Chen Y, Sun T. Design, synthesis, configuration research, and *in vitro* antituberculosis activities of two chiral naphthylamine substituted analogs of bedaquiline: The stereochemistry of two chiral bedaquiline analogs. *J Heterocycl Chem.* 2017;54(2):1024–1030. https://doi.org/10.1002/jhet.2670.
17. Jiang S, Wu C, Yu J, Sun T, Guo X. Separation of eight bedaquiline analogue diastereomers by HPLC on an immobilized polysaccharide-based chiral stationary phase. *Chirality.* 2019;31(1):72–78. https://doi.org/10.1002/chir.23037.
18. Chahine EB, Karaoui LR, Mansour H. Bedaquiline: A novel diarylquinoline for multidrug-resistant tuberculosis. *Ann Pharmacother.* 2014;48(1):107–115. https://doi.org/10.1177/1060028013504087.
19. 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):123–144. https://doi.org/10.1007/s40121-013-0009-3.
20. Pontali E, Sotgiu G, D'Ambrosio L, Centis R, Migliori GB. Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence. *Eur Respir J.* 2016;47(2):394–402. https://doi.org/10.1183/13993003.01891-2015.
21. Chan B, Khadem TM, Brown J. A review of tuberculosis: Focus on bedaquiline. *Am J Health Syst Pharm.* 2013;70(22):1984–1994. https://doi.org/10.2146/ajhp130199.
22. van Heeswijk RPG, Dannemann B, Hoetelmans RMW. Bedaquiline: a review of human pharmacokinetics and drug–drug interactions. *J Antimicrob Chemother.* 2014;69(9):2310–2318. https://doi.org/10.1093/jac/dku171.
23. Andries K, Van Gestel J. Use of substituted quinoline derivatives for the treatment of drug resistant mycobacterial diseases. December 2005. https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2005117875. Accessed November 20, 2019.
24. Van Gestel J, Guillemont J, Venet M, et al. Quinoline derivatives and their use as mycobacterial inhibitors. February 2004. https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2004011436. Accessed November 20, 2019.
25. Porstmann F, Horns S, Bader T. Process for preparing (alpha S, beta R)-6-bromo-alpha-[2-(dimethylamine)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol. November 2006. https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2006125769&_cid=P21-K6BIDD-70598-1. Accessed February 7, 2020.
26. Guillemont J, Meyer C, Koul A, Andries K. Diastereomers, enantiomers and bioactivity. TMC207: A new candidate for the treatment of tuberculosis. In: Carreira EM, Yamamoto H, eds. Comprehensive Chirality. Amsterdam: Elsevier; 2012:54-69. doi:10.1016/B978-0-08-095167-6.00107-5.
27. Hegyi JF, Aelterman W, Lang Y, et al. Fumarate salt of (alpha S, Beta R)-6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol. June 2008. https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2008068231&_cid=P21-K6BI9U-69654-1. Accessed February 7, 2020.
28. Saga Y, Motoki R, Makino S, Shimizu Y, Kanai M, Shibasaki M. Catalytic asymmetric synthesis of R207910. *J Am Chem Soc.* 2010;132(23):7905–7907. https://doi.org/10.1021/ja103183r.
29. Chandrasekhar S, Babu GSK, Mohapatra DK. Practical syntheses of (2S)-R207910 and (2R)-R207910. *Eur J Org Chem.* 2011;2011(11):2057–2061. https://doi.org/10.1002/ejoc.201001720.
30. 赵学清, 黄杨威, 郑治尧, 林燕琴, 陈忠. 用于合成(1R,2S)-贝达喹啉的手性诱导剂. June 2017. https://patents.google.com/patent/CN106866525A/en?oq=CN106866525A. Accessed February 24, 2020.
31. Lubanyana H, Arvidsson PI, Govender T, Kruger HG, Naicker T. Improved synthesis and isolation of bedaquiline. *ACS Omega.* 2020;5(7):3607–3611. https://doi.org/10.1021/acsomega.9b04037.
32. 李建其, 刘育, 邴绍昌, et al. Preparation method for bedaquiline. November 2015. https://patents.google.com/patent/CN105085395A/en. Accessed November 20, 2019.
33. Kong D-L, Huang Y, Ren L-Y, Feng W-H. A highly efficient way to recycle inactive stereoisomers of bedaquiline into two previous intermediates via base-catalyzed Csp3-Csp3 bond cleavage. *Chin Chem Lett.* 2015;26(6):790–792. https://doi.org/10.1016/j.cclet.2015.04.013.
34. Li S, Zhong W, Liu P, et al. Aromatic butan-2-ol compounds, preparation methods and uses thereof. November 2011. https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2011143932&_cid=P21-K6BILN-73044-1. Accessed February 7, 2020.
35. Qiao C-J, Wang X-K, Xie F, Zhong W, Li S. Asymmetric synthesis and absolute configuration assignment of a new type of bedaquiline analogue. *Molecules.* 2015;20(12):22272–22285. https://doi.org/10.3390/molecules201219846.
36. Omel'kov AV, Fedorov VE, Stepanov AA. New 1-(2-chloroquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ols with antituberculosis activity. *Russ Chem Bull.* 2019;68(10):1908–1918. https://doi.org/10.1007/s11172-019-2646-5.
37. Balemans W, Vranckx L, Lounis N, et al. Novel antibiotics targeting respiratory ATP synthesis in Gram-positive pathogenic bacteria. *Antimicrob Agents Chemother.* 2012;56(8):4131–4139. https://doi.org/10.1128/AAC.00273-12.
38. Tong AST, Choi PJ, Blaser A, et al. 6-Cyano analogues of bedaquiline as less lipophilic and potentially safer diarylquinolines for tuberculosis. *ACS Med Chem Lett.* 2017;8(10):1019–1024. https://doi.org/10.1021/acsmedchemlett.7b00196.
39. Choi PJ, Sutherland HS, Tong AST, et al. Synthesis and evaluation of analogues of the tuberculosis drug bedaquiline containing heterocyclic B-ring units. *Bioorg Med Chem Lett.* 2017;27(23):5190–5196. https://doi.org/10.1016/j.bmcl.2017.10.042.
40. Sutherland HS, Tong AST, Choi PJ, 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):1797–1809. https://doi.org/10.1016/j.bmc.2018.02.026.
41. Blaser A, Sutherland HS, Tong AST, et al. Structure-activity relationships for unit C pyridyl analogues of the tuberculosis drug bedaquiline. *Bioorg Med Chem.* 2019;27(7):1283–1291. https://doi.org/10.1016/j.bmc.2019.02.025.
42. Sutherland HS, Tong AST, Choi PJ, et al. 3,5-Dialkoxypyridine analogues of bedaquiline are potent antituberculosis agents with minimal inhibition of the hERG channel. *Bioorg Med Chem.* 2019;27(7):1292–1307. https://doi.org/10.1016/j.bmc.2019.02.026.
43. Sutherland HS, Tong AST, Choi PJ, Blaser A, Franzblau SG, Cooper CB, et al. Variations in the C-unit of bedaquiline provides analogues with improved biology and pharmacology. *Bioorg Med Chem.* 2020;28(1):115213. https://doi.org/10.1016/j.bmc.2019.115213.
44. Sarathy JP, Ragunathan P, Shin J, et al. TBAJ-876 retains bedaquiline's activity against subunits c and ε of Mycobacterium tuberculosis F-ATP synthase. *Antimicrob Agents Chemother.* 2019;63(10).. https://doi.org/10.1128/AAC.01191-19.
45. Hards K, Robson JR, Berney M, et al. Bactericidal mode of action of bedaquiline. *J Antimicrob Chemother.* 2015;70(7):2028–2037. https://doi.org/10.1093/jac/dkv054.
46. Sarathy JP, Ragunathan P, Cooper CB, Upton AM, Grüber G, Dick T. TBAJ-876 displays bedaquiline-like mycobactericidal potency without retaining the parental drug's uncoupler activity. *Antimicrob Agents Chemother.* 2019. https://doi.org/10.1128/AAC.01540-19.
47. Sarathy JP, Gruber G, Dick T. Re-understanding the mechanisms of action of the anti-mycobacterial drug bedaquiline. *Antibiotics.* 2019;8(4):261. https://doi.org/10.3390/antibiotics8040261.
48. Sarathy JP, Ganapathy US, Zimmerman MD, Dartois V, Gengenbacher M, Dick T. TBAJ-876, a 3,5-dialkoxypyridine analogue of bedaquiline, is active against Mycobacterium abscessus. *Antimicrob Agents Chemother.* 2020. https://doi.org/10.1128/AAC.02404-19.
49. Upadhayaya RS, Vandavasi JK, Vasireddy NR, Sharma V, Dixit SS, Chattopadhyaya J. Design, synthesis, biological evaluation and molecular modelling studies of novel quinoline derivatives against Mycobacterium tuberculosis. *Bioorg Med Chem.* 2009;17(7):2830–2841. https://doi.org/10.1016/j.bmc.2009.02.026.
50. Upadhayaya RS, Kulkarni GM, Vasireddy NR, 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):4681–4692. https://doi.org/10.1016/j.bmc.2009.04.069.
51. Upadhayaya RS, Vandavasi JK, Kardile RA, et al. Novel quinoline and naphthalene derivatives as potent antimycobacterial agents. *Eur J Med Chem.* 2010;45(5):1854–1867. https://doi.org/10.1016/j.ejmech.2010.01.024.
52. Upadhayaya RS, Lahore SV, Sayyed AY, et al. Conformationally-constrained indeno [2,1-c]quinolines – a new class of anti-mycobacterial agents. *Org Biomol Chem.*

2010;8(9):2180–2197. https://doi.org/10.1039/B924102G.
53. Upadhayaya RS, Lahore SV, Sayyed AY, et al. Synthesis and structure of azole-fused indeno[2,1-c]quinolines and their anti-mycobacterial properties. *Org Biomol Chem.* 2010;8(24):5661–5673. https://doi.org/10.1039/C0OB00445F.
54. Upadhayaya RS, Shinde PD, Kadam SA, et al. Synthesis and antimycobacterial activity of prodrugs of indeno[2,1-c]quinoline derivatives. *Eur J Med Chem.* 2011;46(4):1306–1324. https://doi.org/10.1016/j.ejmech.2011.01.053.
55. Kalia D, Anil Kumar KS, Meena G, et al. Synthesis and anti-tubercular activity of conformationally-constrained and bisquinoline analogs of TMC207. *MedChemComm.* 2015;6(8):1554–1563. https://doi.org/10.1039/C5MD00131E.
56. He C, Preiss L, Wang B, et al. Structural simplification of bedaquiline: The discovery of 3-(4-(*N*, *N*-dimethylaminomethyl)phenyl)quinoline-derived antitubercular lead compounds. *ChemMedChem.* 2017;12(2):106–119. https://doi.org/10.1002/cmdc.201600441.
57. Priebbenow DL, Barbaro L, Baell JB. New synthetic approaches towards analogues of bedaquiline. *Org Biomol Chem.* 2016;14(40):9622–9628. https://doi.org/10.1039/C6OB01893A.
58. Ramprasad J, Kumar Sthalam V, Linga Murthy Thampunuri R, et al. Synthesis and evaluation of a novel quinoline-triazole analogs for antitubercular properties via molecular hybridization approach. *Bioorg Med Chem Lett.* 2019;29(20)::126671https://doi.org/10.1016/j.bmcl.2019.126671.
59. Rombouts JA, Veenboer RMP, Villellas C, et al. Synthesis, characterization and biological activity of fluorescently labeled bedaquiline analogues. *RSC Adv.* 2016;6(110):108708–108716. https://doi.org/10.1039/C6RA22693K.
60. Ordonez AA, Carroll LS, Abhishek S, et al. Radiosynthesis and PET bioimaging of ^{76}Br-bedaquiline in a murine model of tuberculosis. *ACS Infect Dis.* 2019;5(12):1996–2002. https://doi.org/10.1021/acsinfecdis.9b00207.
61. Reuter A, Tisile P, von Delft D, et al. The devil we know: Is the use of injectable agents for the treatment of MDR-TB justified? *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis.* 2017;21(11):1114–1126. https://doi.org/10.5588/ijtld.17.0468.
62. Johnson & Johnson must halve price of lifesaving TB drug bedaquiline | MSF. Médecins Sans Frontières (MSF) International. https://www.msf.org/johnson-johnson-must-halve-price-lifesaving-tb-drug-bedaquiline. Accessed January 23, 2020.
63. Nguyen TVA, Anthony RM, Bañuls A-L, et al. Bedaquiline resistance: Its emergence, mechanism, and prevention. *Clin Infect Dis.* 2018;66(10):1625–1630. https://doi.org/10.1093/cid/cix992.
64. Lakshminarayana SB, Huat TB, Ho PC, et al. Comprehensive physicochemical, pharmacokinetic and activity profiling of anti-TB agents. *J Antimicrob Chemother.* 2015;70(3):857–867. https://doi.org/10.1093/jac/dku457.
65. Zimenkov DV, Nosova EY, Kulagina EV, et al. Examination of bedaquiline- and linezolid-resistant Mycobacterium tuberculosis isolates from the Moscow region. *J Antimicrob Chemother.* 2017;72(7):1901–1906. https://doi.org/10.1093/jac/dkx094.
66. Huitric E, Verhasselt P, Koul A, Andries K, Hoffner S, Andersson DI. Rates and mechanisms of resistance development in Mycobacterium tuberculosis to a novel diarylquinoline ATP synthase inhibitor. *Antimicrob Agents Chemother.* 2010;54(3):1022–1028. https://doi.org/10.1128/AAC.01611-09.