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6-Cyano Analogues of Bedaquiline as Less Lipophilic and Potentially Safer Diarylquinolines for Tuberculosis

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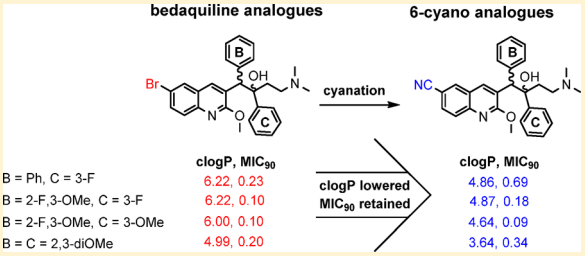
Supporting Information

ABSTRACT: Bedaquiline (**1**) is a new drug for tuberculosis and the first of the diarylquinoline class. It demonstrates excellent efficacy against TB but induces phospholipidosis at high doses, has a long terminal elimination half-life (due to its high lipophilicity), and exhibits potent hERG channel inhibition, resulting in clinical QTc interval prolongation. A number of structural ring A analogues of bedaquiline have been prepared and evaluated for their anti-*M.tb* activity (MIC_{90}), with a view to their possible application as less lipophilic second generation compounds. It was previously observed that a range of 6-substituted analogues of **1** demonstrated a positive correlation between potency (MIC_{90}) toward *M.tb* and drug lipophilicity. Contrary to this trend, we discovered, by virtue of a clogP/*M.tb* score, that a 6-cyano (CN) substituent provides a substantial reduction in lipophilicity with only modest effects on MIC values, suggesting this substituent as a useful tool in the search for effective and safer analogues of **1**.



KEYWORDS: *Bedaquiline, diarylquinoline, tuberculosis, ATP synthase, hERG, lipophilicity*

Novel drugs that can reduce the treatment time for tuberculosis (TB) are vital, particularly in cases of multi- and extensively drug resistant tuberculosis (MDR-TB and XDR-TB).[1] Ideally, new TB drugs are effective against drug-resistant and drug-sensitive TB, well tolerated, suitable for once daily oral dosing, and compatible with antiretroviral therapies for individuals coinfected with HIV. After several decades without the approval of a new class of drug for TB, the diarylquinoline (DARQ) bedaquiline (TMC207, Sirturo, Janssen Pharmaceuticals; **1**, Figure 1) was approved by the US Food and Drug Administration in December 2012 for use in pulmonary multidrug resistant (MDR) TB. Bedaquiline has a novel mechanism of action, through inhibition of the mycobacterial ATP synthase enzyme.[2] Improved outcomes were seen when bedaquiline was added to standard therapy regimens for MDR-TB in a Phase II registration trial.[3] Other multidrug trials are in progress, with positive results being reported for a bedaquiline/pretomanid/pyrazinamide (BPaZ) combination therapy phase IIa trial.[4,5] Bedaquiline shows inhibition of the hERG cardiac potassium channel, with the concomitant risk of QTc prolongation.[6] This raises concerns about potential interactions with other drugs that also prolong the QTc interval (fluoroquinolones, clofazimine) in MDR-TB patients.[7]

It is also very lipophilic (measured log P 7.25), which may contribute to its induction of phospholipidosis, seen at high doses in preclinical models.[8] Its high lipophilicity may also

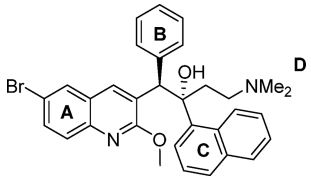


Figure 1. Structure of bedaquiline (**1**).

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contribute to bedaquiline's long terminal elimination half-life,[9] which may lead to tissue overproportional accumulation at high doses or with daily dosing. Due to these pharmacokinetic properties, bedaquiline is currently dosed three times per week, following a period of once daily loading. Additionally, due to the possibility of tissue overproportional accumulation, efficacy has not been thoroughly explored at higher doses.[10] These observations suggest that less lipophilic analogues of bedaquiline would be of potential interest, to reduce the potential for tissue overproportional accumulation and hence to increase suitability for once daily dosing.

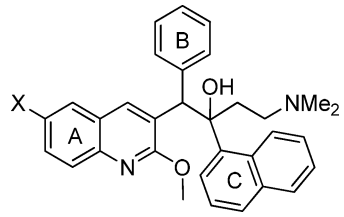
Bedaquiline emerged from a whole-cell screen of 70,000 library compounds against the nonpathogenic *M.smegmatis* strain of TB,[11] where the racemic mixture (comprising four diastereomers) was shown to have useful activity against both *M.smegmatis* and *M.tuberculosis* (*M.tb*), with the *R,S* enantiomer being the most potent. A structure−activity relationship (SAR) study of about 200 analogues of **1** (as mixtures of *RR,SS* or *RS,SR* diastereomers) against *M.smegmatis* showed a rank order correlation between *M.smegmatis* and *M.tb*, with the latter about 10-fold more resistant. The SAR study[11] showed that the dimethylaminoethyl side chain was near optimal for activity, with weaker bases being less effective. This is consistent with later crystallographic studies[12] of **1** bound to its major target (the c subunit of the ATP synthase Fo moiety), where the dimethylaminoethyl unit making a H-bond to Glu65 in the ion-binding site of the enzyme, anchoring the rest of the molecule to make multiple additional hydrophobic contacts. The study also evaluated eight analogues of **1** with differing substituents at the 6-position of the methoxyquinoline ring, including compounds **1**, **2**, **5**, and **6** in Table 1 below (mostly as *RS,SR* diastereomer mixtures). The authors noted that while substituents generally improved potency over the unsubstituted parent (**2**), there seemed to be little electronic effect, with the IC_{90}s of the 6-substituted compounds within a 2-fold range compared with the lead compound (**1**).[11]

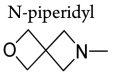
In the present Letter, we expand the range of 6-substituents in this series, across a number of modified B and C ring scaffolds, seeking more polar alternatives to Br that provide analogues of bedaquiline with similar potency of *M.tb* inhibition.

The 6-Br compounds in Tables 1 and 2 were primarily synthesized following a route described previously,[11] from appropriate benzylquinoline A/B units and 3-(dimethylamino)-1-phenylpropan-1-one C/D units (Scheme 1). While there have been two reported asymmetric syntheses of bedaquiline,[13,14] these syntheses are lengthy and nonconvergent, calling for stepwise installation of the B, C, and D units, and were not suitable for a medicinal chemistry SAR program. Our synthetic efforts utilized some expedient synthetic routes to a range of bedaquiline analogues, mainly by employing some common intermediates (e.g., functionalized A/B units where X = Br, I). Tables 1 and 2 report a vast number of DARQ analogues with combinations of various A/B and C/D units, and their building blocks are detailed in the Supporting Information. However, we highlight in Scheme 1 the key reactions for the preparation of a subset of the compounds most relevant to this study.

The majority of final DARQ compounds (including all 6-Br in Table 2) was synthesized via condensation of the appropriate A/B unit and C/D unit (Scheme 1). C/D units were prepared in one step via Mannich reaction of appropriate acetophenones. The DARQ product was formed in one step as a racemic mixture of four diastereomers, and the desired *RS,SR*

Table 1. 6-Substituted Quinoline Analogues of Bedaquiline



#	X	clogP[a]	π	σ_p	MIC_{90}[b] (μg/mL)	hERG IC_{50}[c] (μM)
1	Br	7.25	0.86	0.23	0.09	1.6
2	H	6.37	0.0	0.0	1.9	1.6
3	I	7.51	1.12	0.18	0.20	
4	Cl	7.10	0.71	0.23	0.71	6.9
5	F	6.53	0.14	0.06	0.94	
6	Me	6.86	0.56	-0.17	1.74	4.3
7	Et	7.39	1.02	-0.15	0.23	
8	cyclopropyl	7.31	1.14	-0.21	0.13	
9	C≡CH	6.63	0.40	0.23	0.48	
10	C≡CMe	7.16	0.80	0.03	6.1	7.9
11	$CH=CH_2$	7.09	0.82	-0.02	1.9	
12	CH=NOH	6.45	-0.38	0.10	6.0	3.5
13	CH=NOMe	6.46	0.40	0.30	0.21	2.2
14	CH_2NMe_2	6.20	0.60	0.01	3.7	4.8
15	CH_2NH_2	5.32	-0.10	-0.11	>12	1.7
16	CH_2OH	5.33	-1.03	0.00	1.6	10
17	CH_2COMe	5.66	0.10	-0.05	>7.0	10
18	CF_3	7.31	0.88	0.54	0.38	
19	OCF_3	7.74	1.04	0.35	0.24	
20	$CONMe_2$	5.08	-0.70	0.36	2.2	6.3
21	COOH	4.11	-0.32	0.45	>6.7	10
22	NH_2	5.82	-1.23	-0.66	1.9	
23	N-cyclobutyl	6.49	0.80	-0.85	0.48[d]	
24	N-cyclopentyl	7.05	1.10	-0.85	1.7	
25	N-piperidyl	7.61	1.40	-0.85	0.67[d]	
26		6.06	-0.27	-0.50	0.71[d]	

[a]clogP calculated by ChemDraw Ultra v13.0 (CambridgeSoft). [b]MIC_{90} (mg/mL); minimum inhibitory concentration for 90% inhibition of growth of *M.tb* strain H37Rv, determined under aerobic (MABA)[20] conditions. Each value is the mean of at least two independent determinations. [c]IC_{50} (μM). [d]Data for *R,S* enantiomer.

diastereomer was isolated by supercritical fluid HPLC at BioDuro LLC (Beijing). A wide range of yields were observed for the key condensation reaction, even when the A-ring substituent remained constant (e.g., X = Br, 20−77%; A = spiromorpholine, 16−75%). Moreover, the yield appeared to also be dependent on B-ring substituents, with the 2-F, 3-OMe substituent seemingly preferred over its 3-F and 2,3-diOMe counterparts.

Cyano DARQs (**28**, **33**, **37**, **45**, **53**, **56**, and **59**) were prepared from their corresponding bromides (**27**, **32**, **36**, **44**, **52**, **55**, and **58**) via a Pd-catalyzed cyanation.[15] Cyanation conditions were optimized using various palladium sources and ligands. The purity of tris(dibenzylideneacetone)-dipalladium(0) was variable from several commercial sources and was repurified before use.[16] The order of addition of reagents was also crucial, with addition of cyanide source (zinc cyanide) to a preheated mixture (50 °C) of other reagents critical for high yields and complete conversion to products.[15]

For substituents other than cyano, common intermediates of A/B units where X = Br, I allowed the introduction of amine or sulfamide substituents to the 6-position of the A-ring via

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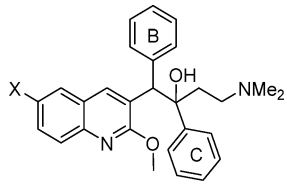
Table 2. Comparison of Different 6-Quinoline Substituents on Modified B/C Scaffolds



#	B-ring substituent	C-ring substituent	X	clogP[a]	MIC_{90}[b]	clog P/*M.tb* score[c]
1	H	1-naphthyl	Br	7.25	0.09	
27	H	3-F	Br	6.22	0.23	
28			CN	4.86	0.69	3.0
29			C≡CH	5.60	0.36	4.8
30			$NMeSO_2Ph$	6.39	4.1[d]	−0.04
31			$NMeSO_2NMe_2$	4.20	5[d]	0.42
32	3-F	3-OCF_3	Br	7.25	0.25	
33			CN	5.89	0.47	6.2
34			$N(CH_2CH_2)_2O$	6.22	0.85	1.7
35			Cl	7.10	0.09	−0.94
36	2-F, 3-OMe	3-F	Br	6.22	0.10	
37			CN	4.87	0.18	17
38			X[e]	5.04	0.51[d]	2.9
39			$N(CH_2CH_2)_2S$	6.03	0.19[d]	2.1
40			$N(CH_2CH_2)_2SO_2$	4.23	>5[d]	0.41
41			$N(CH_2CH_2)_2SO$	4.31	>5[d]	0.39
42			SMe	6.03	0.13[d]	6.3
43			SO_2Me	4.11	2.3[d]	0.96
44	2-F, 3-OMe	3-OCF_3	Br	7.11	0.09	
45			CN	5.75	0.26	8.0
46			X[e]	5.92	0.77	1.8
47			$N(CH_2CH_2)_2O$	6.08	0.14	21
48			$N(CH_2CH_2)_2NH$	6.07	0.66	1.8
49			Npiperidyl	7.46	2.3	−0.16
50			F	6.39	0.21	6.0
51			OCF_3	7.60	1.1	−0.51
52	2-F, 3-OMe	3-OMe	Br	6.00	0.10	
53			CN	4.64	0.09	−130.0[f]
54			X[e]	4.81	0.87[d]	1.5
55	2-F, 3-OMe	3-Cl	Br	6.79	0.07	
56			CN	5.44	0.13	23
57			X[e]	5.61	0.31[d]	4.9
58	2-F, 3-OMe	3-Me	Br	6.58	0.04	
59			CN	5.22	0.09	30
60			X[e]	5.39	1.1[d]	1.1
61	2,3-diOMe	3-F	Br	5.48	0.04	
62			CN	4.12	0.17	11
63			X[e]	4.29	0.66	1.9
64			$N(CH_2CH_2)_2S$	5.28	0.28[d]	0.83
65			$N(CH_2CH_2)_2SO_2$	3.49	>5[d]	0.40
66			$N(CH_2CH_2)_2SO$	3.57	4.8[d]	0.40
67			$NMeSO_2NMe_2$	3.45	1.13[d]	1.9
68	2,3-diOMe	2,3-diOMe	Br	4.99	0.20	
69			CN	3.64	0.34	9.6
70			$N(CH_2CH_2)_2O$	3.97	2.5	0.44
71			Cl	4.84	0.25	3.0
72	2,3-diOMe	3-OCF_3	Br	6.36	0.09	
73			CN	5.01	0.21	11
74			X[e]	5.18	0.75	1.8
75			$N(CH_2CH_2)_2O$	5.34	0.68	1.7

[a]clogP calculated by ChemDraw v.13.0 (CambridgeSoft). [b]MIC_{90} (in μg/mL) for inhibition of *M.tb*. [c]clog P/*M.tb* score = $clogP_{(Br)} - clogP_{(Xsub)}/MIC_{90(Xsub)} - MIC_{90(Br)}$. [d]Data for *R,S* enantiomer. [e]For X, see compound **26** in Table 1. [f]This value was not included as a data point for Figure 2, as the CN analogue was more potent than the Br, producing a negative score.

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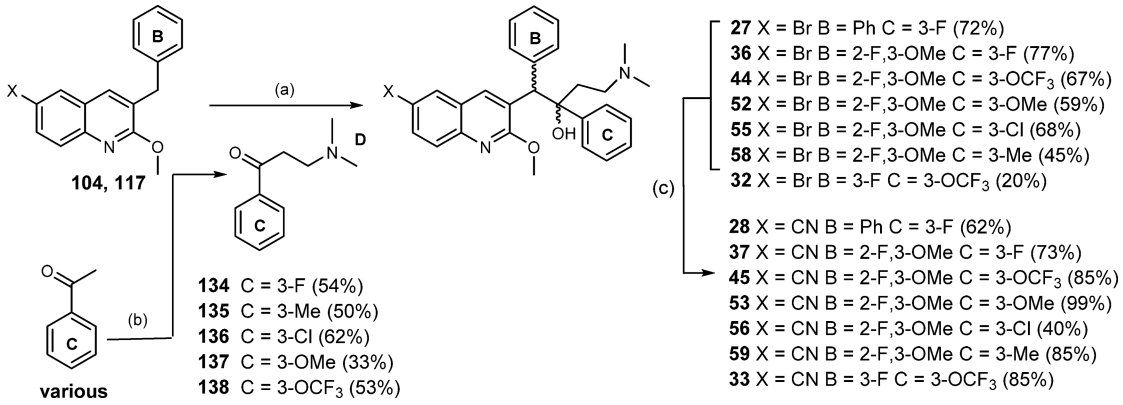
Scheme 1. Syntheses of a Representative Subset of Mannich Bases and Diarylquinoline Analogues[a]



[a]Reagents and conditions: (a) (i) $HN(iOPr)_2$ or TMP, *n*-BuLi, THF, −40 °C, 0.25 h; (ii) **103**−**132**, THF, −78 °C, 1.5 h; (iii) **133**−**139**, THF, −78 °C, 4 h; (b) acetophenone, CH_2O, $Me_2NH{\cdot}HCl$, c.HCl, EtOH, 90 °C, 18 h; (c) P(*o*-tol)$_3$, Zn, $Zn(CN)_2$, $Pd_2(dba)_3$, DMF, 50 °C, 5−18 h.

Buchwald coupling (**107**−**110**, **121**−**127**, and **131**−**132**) or Ullmann type reaction (**113** and **128**), respectively (see Supporting Information). Other reactions such as Suzuki coupling with the 6-bromo A/B unit afforded a 6-cyclopropyl derivative (**112**).

Alternatively, DARQ compounds were directly functionalized at the 6-position of the A-ring. An amino substituent was accessed via hydrolysis of imine (**22**), whereas silanes were reduced to form alkynes (**9** and **29**) or further down to ethyl substituents (**7**). Thio-based DARQs were oxidized to sulfoxides (**41** and **66**) or sulfones (**40**, **43**, and **65**) using *m*-chloroperoxybenzoic acid (*m*-CPBA) or *N*-methylmorpholine *N*-oxide (NMO), respectively.

As the preparation of bedaquiline (**1**) has been reported previously, its synthesis has not been described here. The syntheses of compounds **2**, **4**, **6**, **10**−**14**, **16**, **20**, and **21** were conducted by Janssen Pharmaceutica (Belgium) previously[17−19] and so are not reported in the Supporting Information.

Table 1 shows the structures and physicochemical and biological properties of bedaquiline (**1**) and 25 analogues bearing a wide variety of different 6-substituents. For the majority of the compounds, MIC_{90} values were determined for inhibition of *M.tb* (strain H37Rv) under aerobic conditions (MABA assay[20]). The majority of the compounds were evaluated as the *RS*,*SR* diastereomers, but a few (**23**, **25**, **26**; noted) were available only as the pure *R*,*S* enantiomer.

Representative examples (as pure *R*,*S*-enantiomers) were also evaluated for their ability to inhibit potassium ion through the hERG potassium ion channel.[21,22] While some compounds showed less potent hERG inhibition, there was no significant correlation seen between any 6-substituent properties and hERG inhibitory potency.

Calculations show a modest correlation of lower MIC_{90} with higher overall lipophilicity (measured as 6-substituent π values) (eq 1) but not with substituent electronic properties. The latter suggests there is little 6-substituent interaction with the enzyme active site, consistent with the crystal structure of **1** bound to the c subunit of *M.phlei*.[12]

$$\log(MIC_{90}) = -0.43(\pm 0.14)\pi + 0.19(\pm 0.11)$$
$$n = 26\ R = 0.52\ S = 0.51\ P = 0.007\ F2, 25 = 8.8 \qquad (1)$$

No correlation was seen between 6-substituent properties and hERG IC_{50} values.

In Table 2 we extend these studies on the suitability of different 6-substituents to ten sets of compounds containing a variety of other substituents in the B and C units of the bedaquiline structure. The aim was to seek more polar 6-substituents that would contribute to lowering overall drug lipophilicity and potentially hERG inhibition while (in spite of the overall trend shown by eq 1) not adversely affecting potency (MIC_{90}) against *M.tb*. We have measured this by calculating the expression [clog P/*M.tb* score] for each compound (eq 2)

$$\text{clog } P/M.\ tb \text{ score} = \frac{\text{clogP(Br)} - \text{clogP(Xsub)}}{MIC_{90}(\text{Xsub}) - MIC_{90}(\text{Br})} \qquad (2)$$

This is the ratio of the difference in overall lipophilicity over the difference in MIC_{90} value for each compound, averaged over all the compounds containing that substituent. The more positive the value of the ratio for a particular substituent, the better it fulfills the desired role. Figure 2 shows that, by this

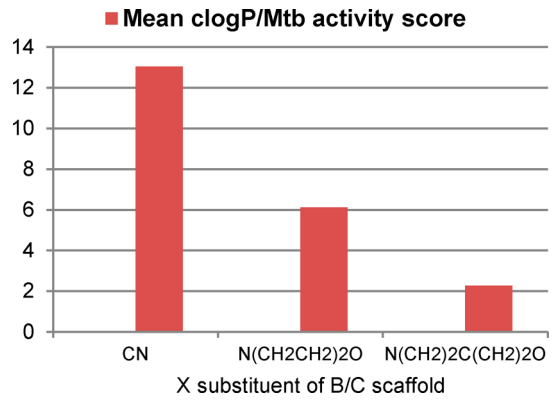


Figure 2. Mean lipophilicity/*M.tb* activity score of most suitable X substituents (cf. with X = Br).

measure, the polar but strongly electron-withdrawing CN substituent is the most preferable of the 6-substituents studied, with the highest average clog P/*M.tb* score of 13 (albeit ranging widely from 3 to 30). Across the 10 individual Br/CN sets in Table 2, the CN compounds had an average MIC of 0.25 μM (only 2-fold greater than the average 0.12 μM MIC for the corresponding Br compounds), but with an average clogP 1.5 log units lower than that of their Br counterparts (4.9 versus

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6.4). Thus, CN is suggested as an accessible and stable 6-substituent across a range of analogues to substantially lower lipophilicity with minimal effects on MIC_{90}.

Table 2 also reveals preliminary SAR information from variations of B/C units. With X = Br or CN (the preferred 6-substituents), a comparison of the MIC_{90} across different B-units suggests that the disubstituted B-units (2-F, 3-OMe, and 2,3-diOMe) may be more favorable than the monosubstituted ones, showing similar potency as **1**. Changing from a bicyclic naphthalene C-unit to a 3-substituted phenyl ring (as well as a 2,3-diOMe phenyl) were found to be tolerated. A few examples of these B/C scaffolds with a 6-CN substituent afforded comparable potencies to **1**, which warrant further investigation into other combinations of B/C units with a 6-CN quinoline scaffold that may further lower both lipophilicity and MIC_{90}.

The results of Table 1 suggest that, for a range of 6-substituted analogues of **1**, there is a positive correlation between potency (MIC_{90}) toward *M.tb* and drug lipophilicity, as has been observed previously. Despite this, in Table 2, we show that a 6-cyano (CN) substituent provides a substantial reduction in lipophilicity with only modest effects on MIC_{90} values, by determining the ratio of the difference in overall lipophilicity over the difference in MIC_{90} value for compounds. This is a valuable new substituent to use in the search for effective but less lipophilic and potentially safer analogues of **1**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.7b00196.

Routes and conditions for the synthesis of A/B and C/D intermediates; general chemistry methods; representative procedures for the syntheses of 6-bromo, 6-cyano, and 6-morpholino analogues of bedaquiline (PDF)

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All of the authors contributed to the writing of this manuscript.

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Notes

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■ ABBREVIATIONS

DARQ, diarylquinoline; DIPEA, diisopropylethylamine; *M.tb*, *Mycobacterium tuberculosis*; DMAP, *N*,*N*-dimethyl-4-aminopyridine; DMDS, dimethyl disulfide; *M. smegmatis*, *Mycobacterium smegmatis*; MABA, microplate alamar blue assay; MDR-TB, multidrug resistant tuberculosis; TMP, tetramethylpiperidine; XDR-TB, extensively drug resistant tuberculosis

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