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Boronic-aurone Derivatives as Anti-Tubercular Agents: Design, Synthesis and Biological Evaluation

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Abstract

Purpose: Current study involved the design, synthesis and biological evaluation of novel boronic-aurones as anti-tubercular agents targeting inhibition of antigen 85, enzymatic complex involved in synthesis of mycobacterial cell wall. To minimize the probability of a single mutation leading to resistance, it is important to target multiple enzymes implicated in mycobacterium cell wall biosynthesis. Hence, new synthetics were virtually screened against both antigen 85 and enoyl-[acyl-carrier-protein] reductase (InhA).

Methods: Using a structure-based approach, new boronic aurone derivatives were designed to target both antigen 85 and InhA, synthesized and screened for anti-tuberculosis activity against *Mycobacterium smegmatis*. Minimum inhibitory concentration (MIC) was determined using resazurin-based assay.

Results: Compound CF1 was the most active boronic aurone analog, with MIC of 0.083 mg/mL; followed by CF2 with MIC of 0.100 mg/mL. AL10 and AL11 both exhibited the same MIC of 0.125 mg/mL. Although AL10 and AL11 scored higher in terms of binding affinity during molecular docking, CF2 and CF1 both exhibited higher anti-mycobacterial activity, showing the importance of hydroxyl groups on aurone core.

Conclusion: This study demonstrates, for the first time, that anti-tuberculosis activity of boronic-aurone derivatives is significant enough, compared to isoniazid, to warrant further investigation.

Keywords: Aurones; Anti-tuberculosis agents; Drug resistant tuberculosis; Boronic acids; *Mycobacterium smegmatis*; *Mycobacterium tuberculosis*; Resazurin-based assay; Antigen 85; Isoniazid

Introduction

Caused by *Mycobacterium tuberculosis (MTB),* tuberculosis (TB) has continued to pose major health challenges worldwide. Increasing incidence of drug resistance and co-infection with HIV/AIDS are making clinical management of the disease more difficult. An estimated 1.4 million people are reported to die annually from the disease across the globe [1]. In addition, about one-third of the world population is believed to be infected with latent form of *MTB* [2,3]. Approximately 13% (1.1 million) of the 8.6 million people who developed TB in 2012 were HIV positive. Of the 1.3 million deaths attributable to TB in 2012, 320 000 deaths were from people living with HIV/AIDS [2]. Hence, TB continues to be a major cause of death for people living with HIV/AIDS.

Inappropriate use of antibiotics by patients undergoing treatment for drug-susceptible active TB often leads to development of drug-resistant strains, including multi-drug resistant TB (MDRTB). Additionally, combined effect of potentially severe side effects and required prolonged use make patient compliance to treatment regimen very difficult, leading to more cases of drug resistance [4]. Further complicating the control and management of TB is the high cost associated with second-line drugs used for treating MDRTB. In 2012 alone, 170,000 deaths were reported globally from MDRTB, while 450,000 new cases were recorded [1,2].

There is therefore a continuing need to develop new TB drugs that are relatively cheap, have less severe side effects, with the potential to sidestep current mode of resistance to existing therapeutics. In the current study, therefore, we report on the design, synthesis, and biological evaluation of anti-tubercular activity of new boronic aurones against *M. smegmatis*, using a structure-based approach targeting antigen 85 (Ag85) and Enoyl-[acyl-carrier-protein] reductase (InhA). *M. smegmatis* does not require specialized containment facilities, grows relatively fast, and is a good predictor of activity against drug-resistant TB [5-8]. Since, *M. smegmatis* is known to exhibit natural resistance to isoniazid (INH) and rifampicin (RMP) [5-7]; we have chosen to screen new synthetics against *M. smegmatis* as a good surrogate for both drug-susceptible and drug-resistant TB strains. The objective of this study then is to demonstrate the anti-tuberculosis effects of different boronic-aurone derivatives using a structure-based design approach. To our knowledge, this is the first report on boronic-aurones as potential anti-tuberculosis agents.

Design of boronic-aurones

Antigen 85 (Ag85), an enzymatic complex comprising of three related acyl transferase enzymes (Ag85A, Ag85B and Ag85C), is critical for the survival of *MTB* in host macrophage due to its role in maintenance of hydrophobic cell wall through mycolation activity [9-11]. Since Ag85 is extracellularly located, it presents an opportunity to reduce the effect of bacterial active efflux and drug-modifying enzymes that act intracellularly to contribute to antibiotic evasion [12,13]. Finally, the fact that Ag85 is not found in humans increases the chance to develop drugs that select for Ag85 with possibility of reduced side effects [10,12]. Therefore, Ag85 is increasingly being targeted in the quest for development of novel TB drugs.

Boronic acid derivatives have been shown to be effective protease inhibitors, especially against serine β-lactamases [14]. Compared to

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other β-lactamase inhibitors in clinical use, boronic acid derivatives work through a novel mechanism in which boron forms a reversible dative bond with the β-lactamase through enzymatic serine hydroxyl group. Furthermore, this dative complex is not hydrolyzed by the enzyme, and therefore serves as a competitive inhibitor. Hence, boronic acids are transition-state analogues which lack the β-lactam recognition moiety and are therefore chemically distinct enough to avoid existing resistance mechanisms [14,15].

Therefore, adopting existing catalytic models using available X-ray structure of Ag85 [4,10], we have designed a short library of new boronic aurone derivatives (Figure 1) that could bind to the active site of Ag85C and form a dative intermediate capable of competitively inhibiting acyltransferase activity of antigen 85C. Studies have already shown that the catalytic triad of both serine protease (Ser-His-Asp) and Ag85 (Ser-His-Glu) have similar charge relay system, and share Ser124 in common [13,16]. Based on this, it is proposed that boronic aurone derivatives will serve as a competitive inhibitor of the Antigen 85 enzyme of *MTB* by acting as a transition-state analog, in which Ser124 of Ag85 could be trapped by similar mechanism.

As structural isomers of flavones, aurones are naturally occurring flavonoids which play important role in pigmentation of flowers in which they occur. Aurones have been shown to have a wide range of biological activity, including anti-inflammatory and antimicrobial activity [17,18]. The biological activities of aurones have been demonstrated to be affected by the number of hydroxyl groups present on the rings [19]. Previous studies have also shown that the active site of Ag85 shows fairly good tolerance for a number of substrates capable of fitting into the trehalose monomycolate-binding pocket [4,9-13]. Therefore, boronic-aurones were designed in such a way that the aurone core will fit into the carbohydrate-binding pocket, being similar to trehalose, while the boronic acid moiety will bind in the mycolate-binding loop.

Since multidrug resistant strains of *MTB* are resistant to INH and RMP, our running hypothesis is that drugs that effectively inhibit the Enoyl-[acyl-carrier-protein] reductase (InhA), with a different mechanism of action from that of INH's role on the same enzyme, may circumvent this resistance. Indeed, studies seem to bear out this rationale [20,21]. Therefore, to minimize the probability of a single mutation leading to resistance, we have argued elsewhere [4] that it may be beneficial to target multiple enzymes representing metabolic "hubs" which are essential for multiple biosynthetic pathways involved in mycobacterium cell wall synthesis. It is for this reason that we also virtually screened proposed analogs for binding affinity to InhA, in addition to probing their affinity for Ag85.

Materials and Methods

Materials

All chemicals were sourced directly from manufacturers through VWR International, and used without further purification. *M. smegmatis* (ATCC 607) was purchased from American Type Culture Collection Company (ATCC). Fresh stock of drugs and chemicals were prepared and used fresh for each experiment. Original stock of new synthetics was prepared in dimethyl sulfoxide (DMSO) or water at 10 mg/mL. For INH, original stock was prepared in DMSO at 1 mg/mL.

Chemistry

Adapting published protocols [22], synthesis of all four boronic aurones (Figure 1) were carried out using microwave assisted Claisen-Schmidt condensation reaction as shown in Scheme 1. To a solution of substituted benzofuran-3(2H)-one 1 (1 equiv) dissolved in 95% ethanol (10 mL) was added aqueous solution of sodium hydroxide (10 mol%). Substituted 4-formylyphenyl boronic-acid derivatives **2** (1 equiv) was then added. Reaction mixture was thoroughly swirled, and irradiated in a microwave at 288 W (30% of output power) at 60 second intervals to avoid charring. The reaction progress was monitored by thin layer chromatography, TLC (chloroform: methanol, 9:1). When completed,

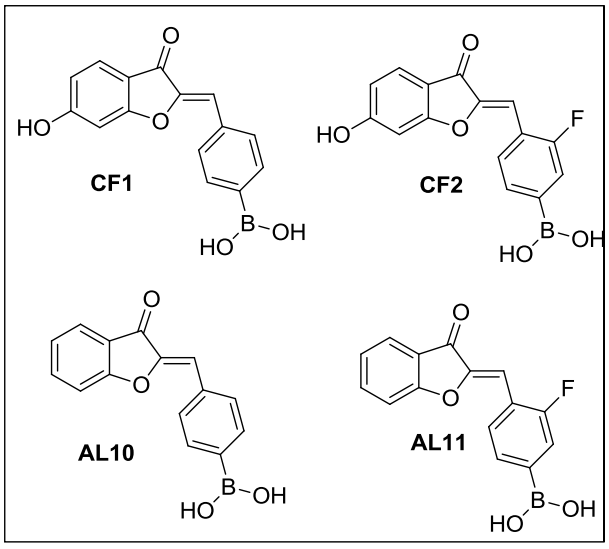
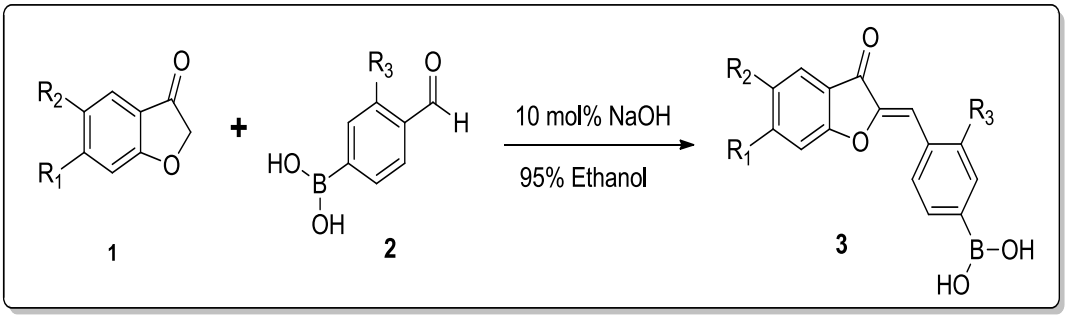


Figure 1: Structure of proposed synthetic boronic-aurone analogs. **CF1**=boronic-aurone with 6-hydroxyl group, **CF2**=boronic-aurone with 6-hydroxyl and 2□-fluoro groups, **AL10**=boronic aurone lacking both 6-hydroxyl and 2□-fluoro moiety, and **AL11**=boronic-aurone with only 2□-fluoro substitution.



Scheme 1: Synthetic scheme for boronic-aurone analogs, using microwave-assisted Claisen-Schmidt condensation reaction.

reaction mixture was cooled to room temperature. The crude solid was filtered, dried, and purified by gradient column chromatography (hexane: ethyl acetate) to yield pure product **3**, in moderate yields (49-55% yield, Table 1). Spectroscopic analysis (^{1}H and ^{13}C NMR) and high resolution mass spectrometry show that expected compounds were successfully synthesized (see supporting documents).

Biology

Fresh isolates of *Mycobacterium smegmattis* (ATCC 14468) were cultured in Middlebrook 7H11 agar for every experiment. Bacterial cultures were diluted to an optical density, OD_{595}=0.01, at 4.7×10^{-5} colony forming units (CFU). Preparation of 7H10 Middlebrook Agar medium for *M. smegmatis* growth followed protocols provided by manufacturer, Difco™ Middlebrook. After all plates were filled, they were stacked upright and left out in room temperature for one day to solidify, and then stored at 4°C. Using aseptic methods and manufacturer's instructions, Middlebrook 7H9 Broth was prepared and stored at 4°C before using in bacterial cultures.

Disc diffusion assays were prepared as previously reported [13]. *M. smegmatis* ATCC 14468 was inoculated into Middlebrook 7H9 containing 0.2% glycerol and ADC enrichment, respectively. The inocula was incubated at 37.5°C for approximately 24 h. The bacteria was plated on agar (Middlebrook 7H10 containing 0.5% glycerol and OADC enrichment) using cotton-tipped applicator. 10 µL of each drug solution was applied to 6 mm sterile paper disks. The plates were incubated for 24 h at 37°C. Using a ruler, diameter of zone of inhibition (DZI) was measured

The resazurin microtiter assay (REMA) was performed in 7H9 medium containing Middlebrook broth and 0.5% glycerol and supplemented with oleic acid, albumin, dextrose, and catalase (Difco™) as previously reported [23-25]. Clear 96-well plates were inoculated with 100 µL of drug diluted with 90 µl of 7H9 medium and 10 µL DMSO (giving essentially 50 µL of drug). Serial twofold dilutions of each drug in 100 µL of 7H9 medium were prepared at concentrations of 0.5 to 0.0039 mg/mL for all drugs, and 0.05 to 0.00039 mg/mL for INH. Growth controls containing no antibiotic and sterility controls without inoculation were also included (Figure 2). To the column containing the control with no bacteria, 10 µL DMSO and 190 µL 7H9 medium was added. To the column containing the control with no drug, 10 µL DMSO, 90 µL 7H9 medium, and 100 µL of bacteria culture were added. Finally, 200 µL of sterile deionized water was added to the outer perimeter wells to prevent evaporation during incubation of the plate. The lid was placed back on the plates and partially sealed with parafilm to allow for air circulation. The plates were incubated at 37°C for 3-4 days. After incubation, the plates were removed and 10 µL of resazurin was added to each well that contained bacteria. More water was added to the outer perimeter wells when necessary. The plates were reincubated at 37°C for 24-48 hours and visually assessed for color development. A change from blue to pink indicates reduction of resazurin to resorufin, and therefore an indication of bacterial growth. The MIC was defined as the lowest drug concentration that prevented this color change, by direct visual examination.

Compound (3):	*Percent Yield*	*Physical state*	*R_f values*
CF1	55.46%	Yellow solid	0.78
CF2	52.16%	Orange solid	0.625
AL10	49.27%	Yellow solid	0.714
AL11	51.31%	Yellow oily solid	0.731

Table 1: Synthetic yield for boronic-aurone derivatives. **CF1**=boronic-aurone with 6-hydroxyl group, **CF2**=boronic-aurone with 6-hydroxyl and 2□-fluoro groups, **AL10**=boronic aurone lacking both 6-hydroxyl and 2□-fluoro moiety, and **AL11**=boronic-aurone with only 2□-fluoro substitution.

Results

Molecular docking

Molecular docking of ligands into active site of target was carried out with 1-Click Docking tool [26], a web-based docking application based on Autodock Vina configuration [27]. Virtual screening was done by docking selected ligands differently into the active site of InhA receptor (PDB id=2nsd; resolution of 1.900) and antigen 85C receptor (PDB id=1va5; resolution of 2.020). Since our internal docking experiment shows that docking results obtained with either AutoDockVina directly or the 1-Click Docking application were almost identical, we have chosen to use the 1-Click Docking application due to the fact that it is easier and meets our current needs. Since AutoDock and all applications based on it do not recognize boron atom [28], we substituted boron with nitrogen. Molecular graphics and analyses were performed with the UCSF Chimera package [29]. Chimera is developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco (supported by NIGMS P41-GM103311).

The best fit pose with the lowest binding energy from initial molecular docking is chosen (Figure 2), and the binding affinity for each ligand with antigen 85C and InhA is reported in kcal/mol (Table 2). The binding affinity for AL10 and AL11 which lack the 6-hydroxy moiety was much better in both enzymes in terms of lowest binding energy and number of hydrogen bonding interactions, compared to CF1 and CF2 (Figure 2 and Table 2). For example, there were two hydrogen bonding interactions between CF2 ligand's boronic-hydroxyl group and Ile 20 (1.980Å), and between carbonyl group of ligand with Lys 164 (2.121Å) of InhA. On the other hand, there were three hydrogen bonding interactions between AL11 and protein residues two boronic hydroxyl groups with Gly 13 (2.244Å) and one hydroxyl group and Ala 21 (1.997Å).

Minimum inhibitory concentration (MIC)

Results of resazurin-based assay were visually ascertained by noting change in color from blue to pink indicating reduction of resazurin to resorufin, and therefore an indication of bacterial growth. The MIC was determined as the lowest drug concentration that prevented this color change, by direct visual examination. MIC results are given in Table 3 and Figure 3; showing that CF1 was the most active boronic aurone analog, with MIC of 0.083 mg/mL and ZOI of 15 mm. This is followed by CF2 having MIC of 0.100 mg/mL and ZOI of 13 mm. AL10 and AL11 both exhibited same MIC of 0.125 mg/mL and ZOI of 12 mm.

Discussion

Biological evaluation of boronic aurones was done using microtiter resazurin-based (Alama blue) assay. The utility of Alamar Blue as a phenotypic high-throughput cell viability screen for identification of potentially new TB leads for screening of clinical isolates of *MTB* has been demonstrated [23,24], among others. In addition, several studies have also shown the reliability of Alamar blue cell viability assay for detection of drug resistant *MTB* [25,30].

The resazurin-based assay is a simple, inexpensive, and effective method with very high diagnostic accuracy, and lends itself to easy use in countries or even laboratories with limited resources [23,24]. Whole-cell screening is getting renewed attention in the drug discovery process compared to target-based method [31,32]. Adopting whole-cell phenotypic screening approach, even for rationally designed ligands, has the unique advantage that it is able to interrogate all biochemical targets simultaneously in a specific physiological environment;

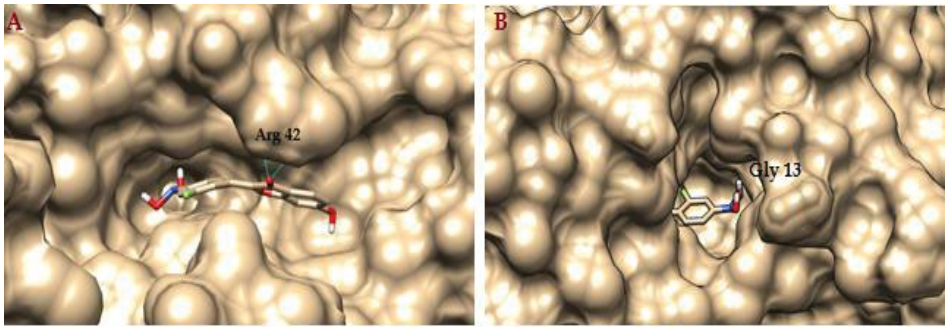


Figure 2: A. **CF2** docked into Ag85C (PDB id=1va5; resolution of 2.020); **B**. **AL11** docked into InhA (PDB id=2nsd; resolution of 1.900).

Compound	Ag85C Binding Affinity (kcal/mol)	InhA Binding Affinity (kcal/mol)
CF1	−8.0	−8.3
CF2	−8.0	−8.5
AL10	−8.8	−9.1
AL11	−8.8	−9.3

Table 2: Binding affinity of synthetic ligands with Antigen 85C and InhA. **CF1**=boronic-aurone with 6-hydroxyl group, **CF2**=boronic-aurone with 6-hydroxyl and 2'-fluoro groups, **AL10**=boronic aurone lacking both 6-hydroxyl and 2'-fluoro moiety, and **AL11**=boronic-aurone with only 2'-fluoro substitution.

particularly during the early phases of the preclinical drug discovery process [31,32]. To underscore the importance of this approach, the first FDA approved antitubercular drug in over 40 years, bedaquiline [33], and others in advanced clinical development (Delamanid, Sutezolid and SQ109) were discovered through phenotypic screening [34,35]. It appears that no truly new anti-TB lead have successful emerged from target-based discovery approach. It is for that reason that we adopted the Alamar Blue microtiter assay as a quick, reliable, screening protocol for this study.

Although AL10 and AL11 scored higher in terms of binding affinity for active sites of both InhA and Ag85C in the virtual molecular docking studies than CF2 and CF1 (Table 2), it is interesting that both CF2 and CF1 exhibited higher anti-mycobacterial activity (Table 3 and Figure 3). An important structural difference between CF1 and CF2 on one hand, and AL10 and AL11 on the other is the presence of 6-hydroxyl group on phenyl ring in the former. This suggests that although introducing more hydrophobic groups may be important, presence of hydroxyl groups appears to be a stronger contributing factor towards aurone activity [18,19]. Compared to NIH with MIC of 0.013 mg/mL, CF1 and CF2 with MICs of 0.083 mg/mL and 0.100 mg/mL respectively exhibit fairly significant anti-tubercular activity. This shows that boronic-aurone derivatives are potentially important class of compounds in search of new anti-tuberculosis leads.

Conclusion

This study demonstrates the utility of boronic aurones as potential anti-tubercular agents for the first time, as far as we know. Adopting an initial structure-based approach, new boronic aurones derivatives were designed using Ag85C and InhA as potential targets. New boronic-aurone derivatives were successfully synthesized, characterized and evaluated for anti-tuberculosis activity against *M. smegmatis* using both Alamar Blue and Kirby-Bauer disk assays. CF1 was the most active boronic aurone analog, with MIC of 0.083 mg/ml and ZOI of 15; followed by CF2 with MIC of 0.100 mg/ml and ZOI of 13 mm. AL10

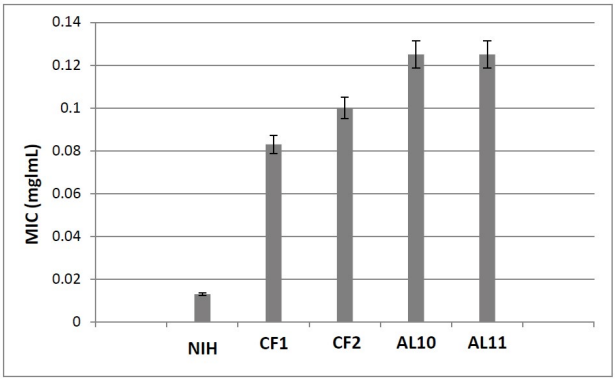


Figure 3: Error bars showing MIC for novel boronic-aurones compared to NIH. CF1=boronic-aurone with 6-hydroxyl group, CF2=boronic-aurone with 6-hydroxyl and 2'-fluoro groups, AL10=boronic aurone lacking both 6-hydroxyl and 2'-fluoro moiety, and AL11=boronic-aurone with only 2'-fluoro substitution.

Compound	ZOI (*mm*)	MIC (*mg/mL*)
CF1	15	0.083
CF2	13	0.100
AL10	12	0.125
AL11	12	0.125
NIH	34	0.013
DMSO	0	*n/a*

Table 3: Zone of inhibition (ZOI) and minimum inhibitory concentration (MIC) for boronic-aurones. **CF1**=boronic-aurone with 6-hydroxyl group, **CF2**=boronic-aurone with 6-hydroxyl and 2'-fluoro groups, **AL10**=boronic aurone lacking both 6-hydroxyl and 2'-fluoro moiety, and **AL11**=boronic-aurone with only 2'-fluoro substitution.

and AL11 both exhibited the same MIC of 0.125 mg/ml and ZOI of 12 mm. Taken together, this study makes an important contribution as it demonstrates that anti-tuberculosis activity of boronic-aurone derivatives is significant enough to merit serious consideration as new anti-tubercular leads. Future research direction includes investigation of structure-activity relationship studies involving substituent group modification, starting with CF1.

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