Design, synthesis, and biological evaluation of new Benzoxaborole derivatives as potential antimycobacterial agents

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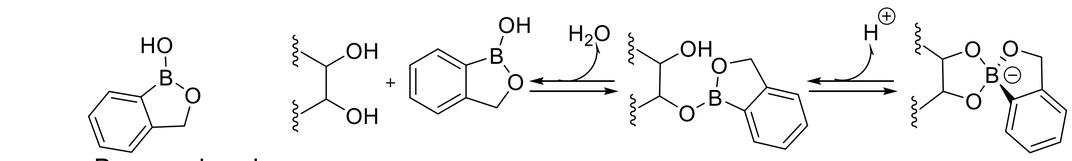
Introduction

Benzoxaborole moiety is an emerging scaffold in development of new antimicrobials after FDA approval of tavaborole as a new drug against onychomycosis. It has been proved, that benzoxaborole moiety may create spiro adducts with diols, therefore it may exhibit oxaborole tRNA trapping mechanism (OBORT).[1]

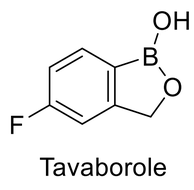


Benzoxaborole
benzo[*c*][1,2]oxaborol-1(3*H*)-ol

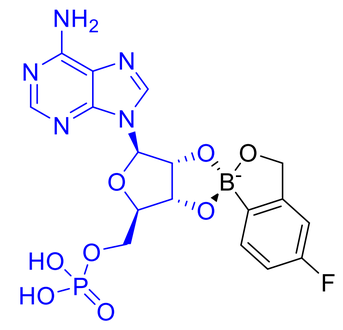
Formation of spiro adduct

Oxaborole tRNA trapping mechanism (OBORT)[2]

- Boron atom forms covalent bonds with the *cis*-diols of the 3´-terminal adenosine nucleotide Ade76 of $tRNA^{Leu}$.
- Resulting adduct traps the 3´ end of tRNA in the editing site in a nonproductive complex.
- This causes inhibition of leucylation and thereby protein synthesis.
- **Inhibits leucyl-tRNA synthetase (LeuRS).**



Tavaborole

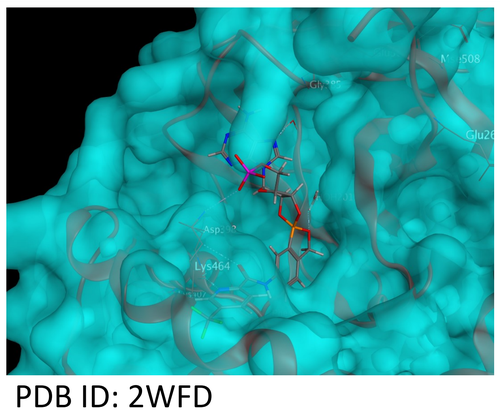


Spiro adduct of AMP with tavaborole

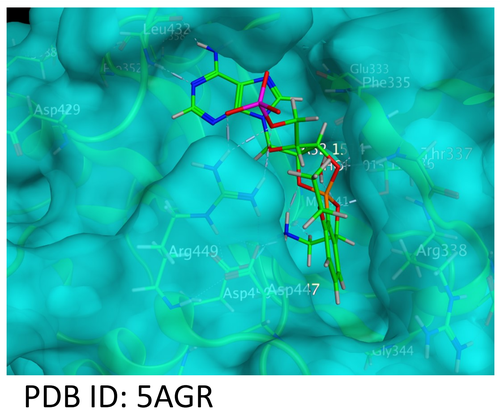
In Silico studies

By superposition of human cytosolic LeuRS and *M. tuberculosis* LeuRS we found out, that there is a key difference between editing site of human (PDB ID: 2WFD) and *M. tuberculosis* LeuRS (PDB ID: 5AGR). Human LeuRS has an extra alfa-helix (R^{457}EKLAEAKEKIYLKGFYE^{474}) that closes over the active site of enzyme. LeuRS of *M. tuberculosis* missing this extra alfa helix, this makes the active pocket wider and leaves space for substitution.

We conclude, that largely substituted benzoxaborole derivatives in position 6 could lead to active and yet selective compounds.



PDB ID: 2WFD

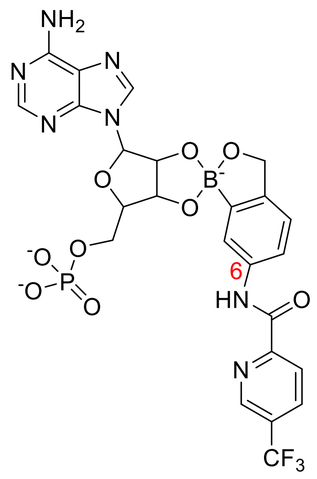


PDB ID: 5AGR

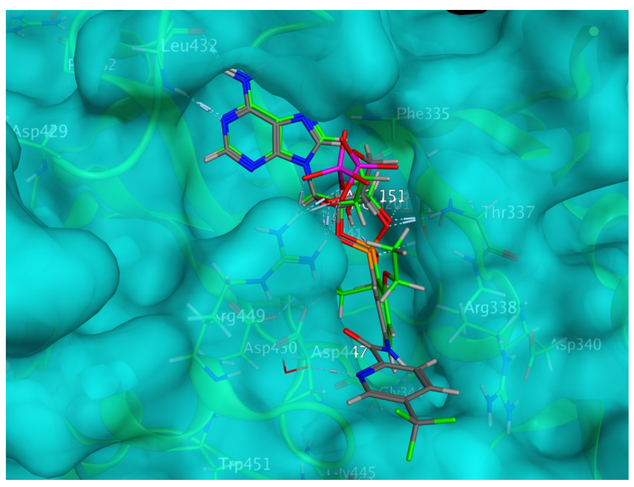
Design of new compounds

According to our hypothesis from *in silico* studies, we have created a library of different largely substituted benzoxaborole derivatives and their adducts with AMP. Template docking proved us that large substitution in position 6 should smoothly fit in active site of LeuRS of *M. tuberculosis* and few heterocyclic candidates showed promising H-bond interaction with Asp447 through water molecule. Interaction with the same amino acid's residue can be observed in series of aminomethyl substituted benzoxaborole derivatives in position 3.[3]

By superpositioning our docking results and human cytosolic LeuRS we observed serious steric clashes with the extra alfa helix.

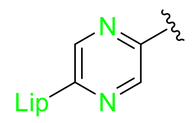


Spiro adduct of AMP and one of our candidates

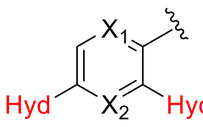


PDB ID: 5AGR (superposition of cocrystalized ligand in green with our docking candidate in gray)

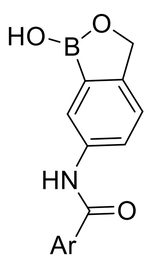
Results and discussion

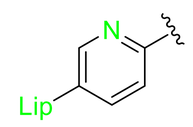


Pyrazine with lipophilic substitution in position 5 leads to increase of activity. Lipophilic substitution in any other position leads to decrease of activity.

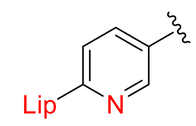


Any hydrophilic sustitution of pyrazine or pyridine ring leads to decrease of activity.

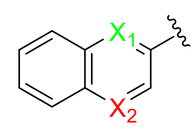




Activity of pyridine derivatives depends on the position of substitution. 2-Pyridyl derivative substituted in position 5 with lipophilic substituents shows high activity.



3-Pyridyl derivative substituted in position 6 with the same substituents shows decreased activity. The same phenomenon can be observed with hydrophilic substitution.



Quinoxaline substitution leads to lost of activity against *Mtb* H37Ra with persisted high activity against *Mtb* H37Ra. Quinoline substitution leads to moderate activity against both strains.

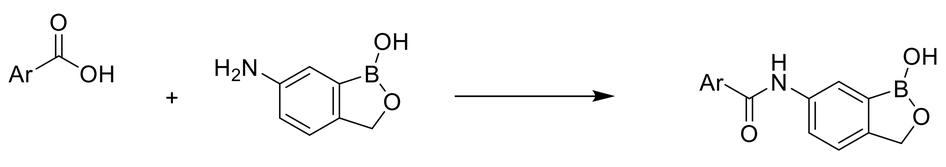
Presented series showed promising activity against different mycobacterial strains.

Presented series kept its activity against clinical isolates of MDR strains of *Mycobacterium tuberculosis*.

All tested compounds did not exert any activity against tested strains of bacteria and fungi.

The most active compound was PS-BZX-12 with MIC value 9.72 µM against *M. tuberculosis* H37Rv. This compound did not show toxicity against HepG2 cancer cell line.

Synthetic scheme



activated by proper agent

Yields 40-84%

References

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2. Rock, F.L. et al. An antifungal agent inhibits an aminoacyl-tRNA synthetase by trapping tRNA in the editing site. *Science* **316**, 1759-1761 (2007).
3. Palencia, A. et al. Discovery of Novel Oral Protein Synthesis Inhibitors of Mycobacterium tuberculosis That Target Leucyl-tRNA Synthetase. *Antimicrobial Agents and Chemotherapy* **60**, 6271-6280 (2016).
4.