CASE STUDY: **ATP SYNTHASE OF ACINETOBACTER BAUMANNII**

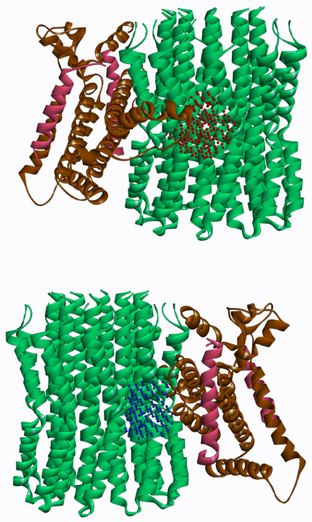
RECEPTOR.AI

BACKGROUND:

Challenging target: The ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) pathogen, *Acinetobacter baumannii*, is responsible for the development of a number of hospital-acquired infections as well as serious treatment problems. *A. baumannii* is the top priority pathogen on the list of the World Health Organization (WHO) due to a dramatic rise in multidrug resistance (MDR) during the past ten years, necessitating the urgent development of novel medicines. This study aims at discovering inhibitors of the *A. baumannii* ATP synthase.

METHODOLOGY:

- The crystal structure of A. baumannii F0 complex of ATP synthase was used for virtual screening.
- The binding pockets were deduced from literature data at the a/c subunit interfaces. There are “lagging” and “leading” pockets named by their relative position during the protein functioning cycle.
- The Drug-Target Interaction (DTI) model is used to select top 10% of compounds from the pre-processed 3,8M compounds library using the smart consensus function type
- The top 50K compounds are subject to molecular docking with AI rescoring into each of the binding pockets independently.
- Top 20% of compounds were selected by the smart consensus function of type 2 followed by the human triage.
- 122 final hit candidates were selected.
- Bacterial growth assay was used to test the potency of selected compounds.• The antimicrobial effect of inhibitors (IC_{50}) was determined.

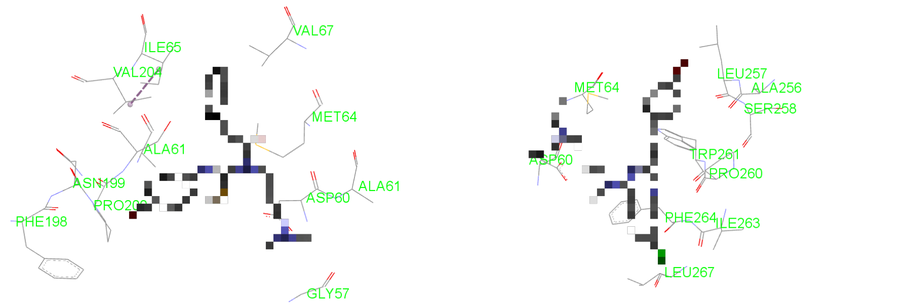


Structure of ATP synthase with the lagging (top) and leading (bottom) binding sites shown as colored spheres. c subunit is green , a subunit is brown, b subunit is crimson.

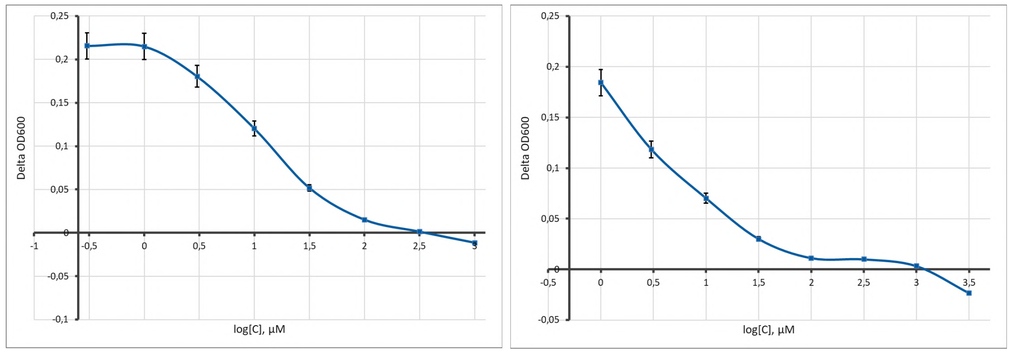
122	11	2	4 μM
hit candidates selected	compounds tested	potent compounds identified	IC_{50} value reached

RESULTS:

11 compounds out of 122 hit candidates were selected to start laboratory studies. 2 compounds were validated as hits. The compound R00439183 demonstrated the IC_{50} of 12.5 uM whereas compound R00676319 demonstrated the IC_{50} of 4 uM.



Binding mode of R00439183 (left) and R00676319 (right). Green dashed lines indicate hydrogen bonds, crimson - hydrophobic interactions, orange - charge.



Inhibition of A. baumannii culture growth by R00439183 (left) and by R00676319 (right).