In Silico Screening and Generating for TrmD Inhibitors

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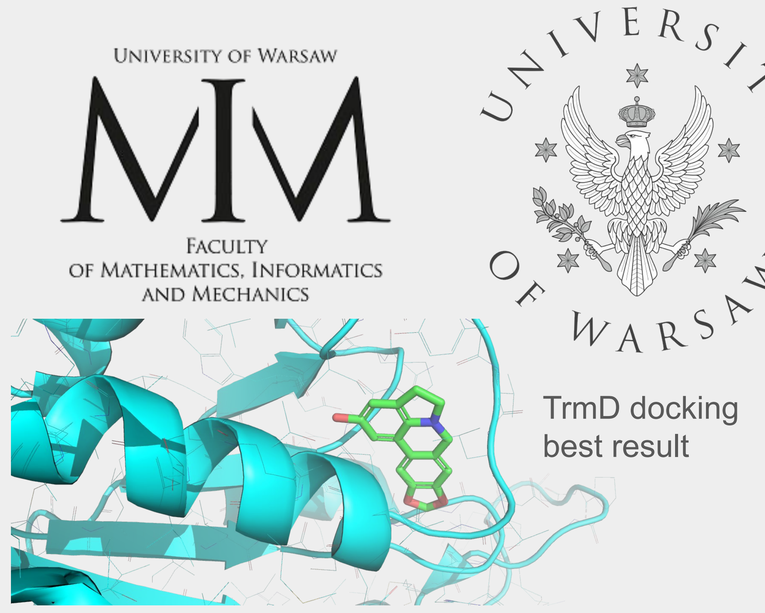
Introduction

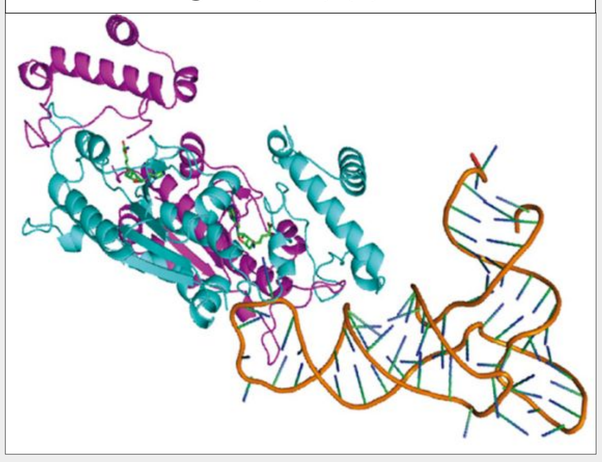
- The global rise of **bacterial antimicrobial resistance** (AMR) poses a critical threat to public health.
- To address that researchers are exploring novel targets like **TrmD**, tRNA methyltransferase enzyme that is responsible for methylating guanine at position 37 to form 1-methylguanosine (m1G37) in tRNAs containing a G36G37 motif, using **S-adenosyl-L-methionine (SAM)** as a methyl donor (1).

Why Target TrmD?

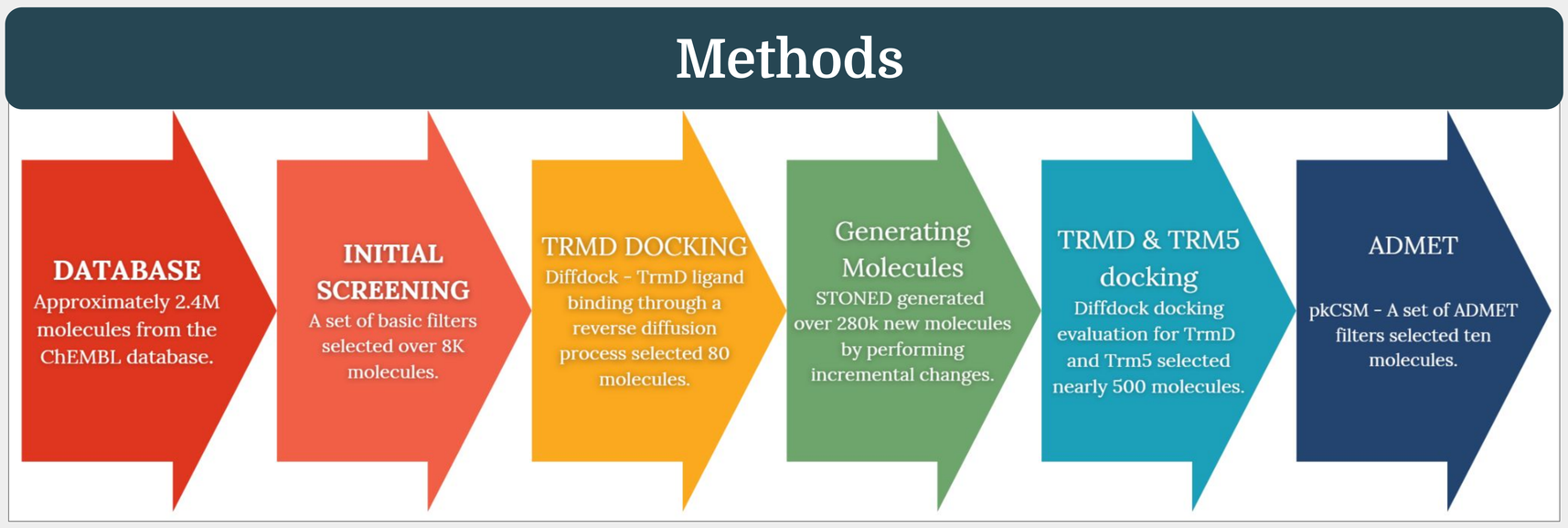
I. **Highly conserved** across bacterial pathogens.
II. **Essential** for bacterial survival, but absent in humans.
III. **Distinct from Trm5,** its eukaryotic counterpart, despite catalyzing the same reaction.



The TrmD dimer binds one tRNA and two sinefungins(SFN) (2).

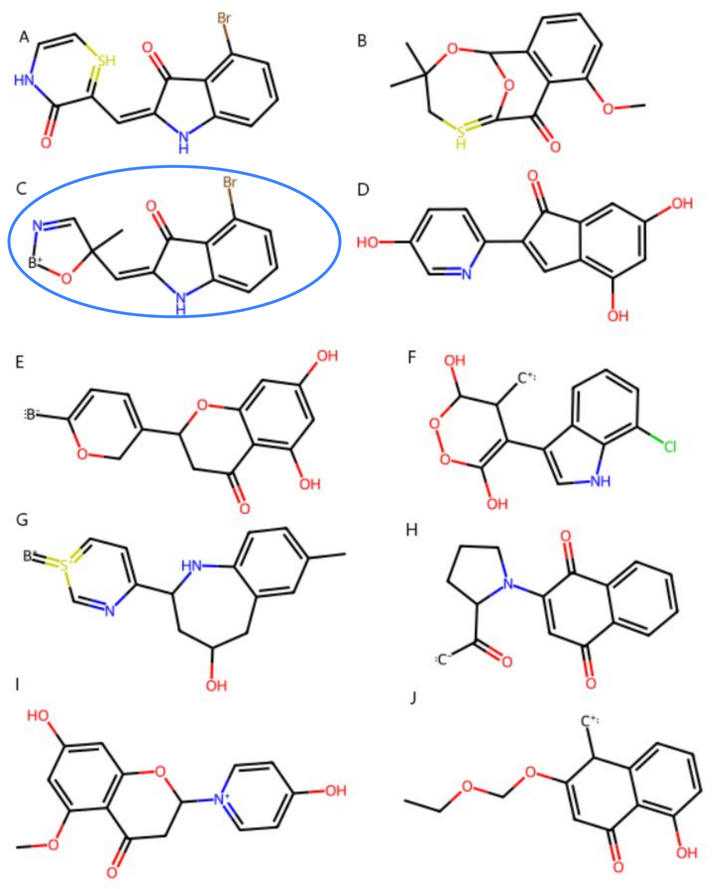


Methods

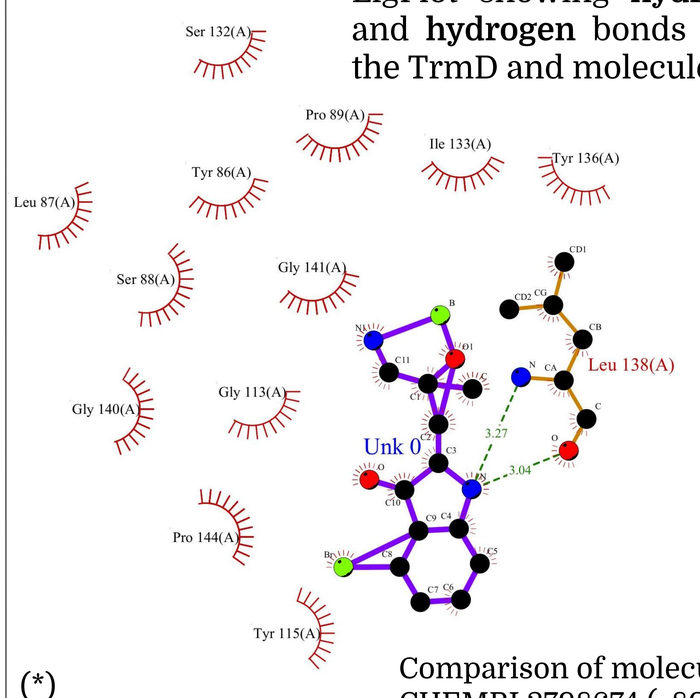


Results

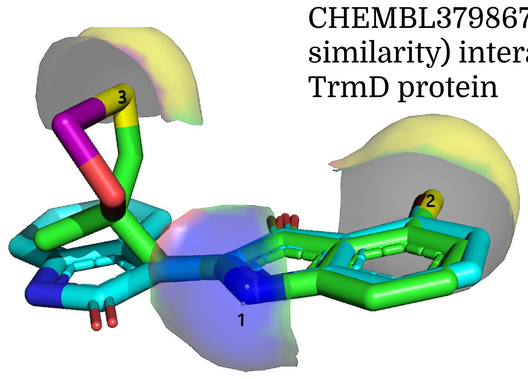
Structural formulas of the **top 10** molecules from ADMET analysis. The indicated molecules exhibit the **best distribution, absorption and toxicity properties**.
Among them, **molecule C** was selected for further analysis.



LigPlot showing **hydrophobic** and **hydrogen** bonds between the TrmD and molecule C



(*)



Comparison of molecule C and CHEMBL3798674 (~80% similarity) interactions with the TrmD protein

Conclusion

- The search for new inhibitors and a potential drug for drug-resistant bacterial strains is ongoing.
- The newly generated molecule C demonstrates enhanced **stability in binding** to the active site of TrmD(*).
- Our approach utilized DiffDock and STONED as representatives of innovative **ML applications in drug design**.
- Controlled generation of new molecules using STONED enables the analysis of many previously untested compounds to identify the best bindings to TrmD.
- The molecules proposed by our team demonstrate **favorable ADMET properties** and **progress in creating new bonds** with the molecular target.

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