

Computationally Guided Repositioning of Clinically Relevant Compounds Against *Plasmodium falciparum* Prolyl-tRNA Synthetase

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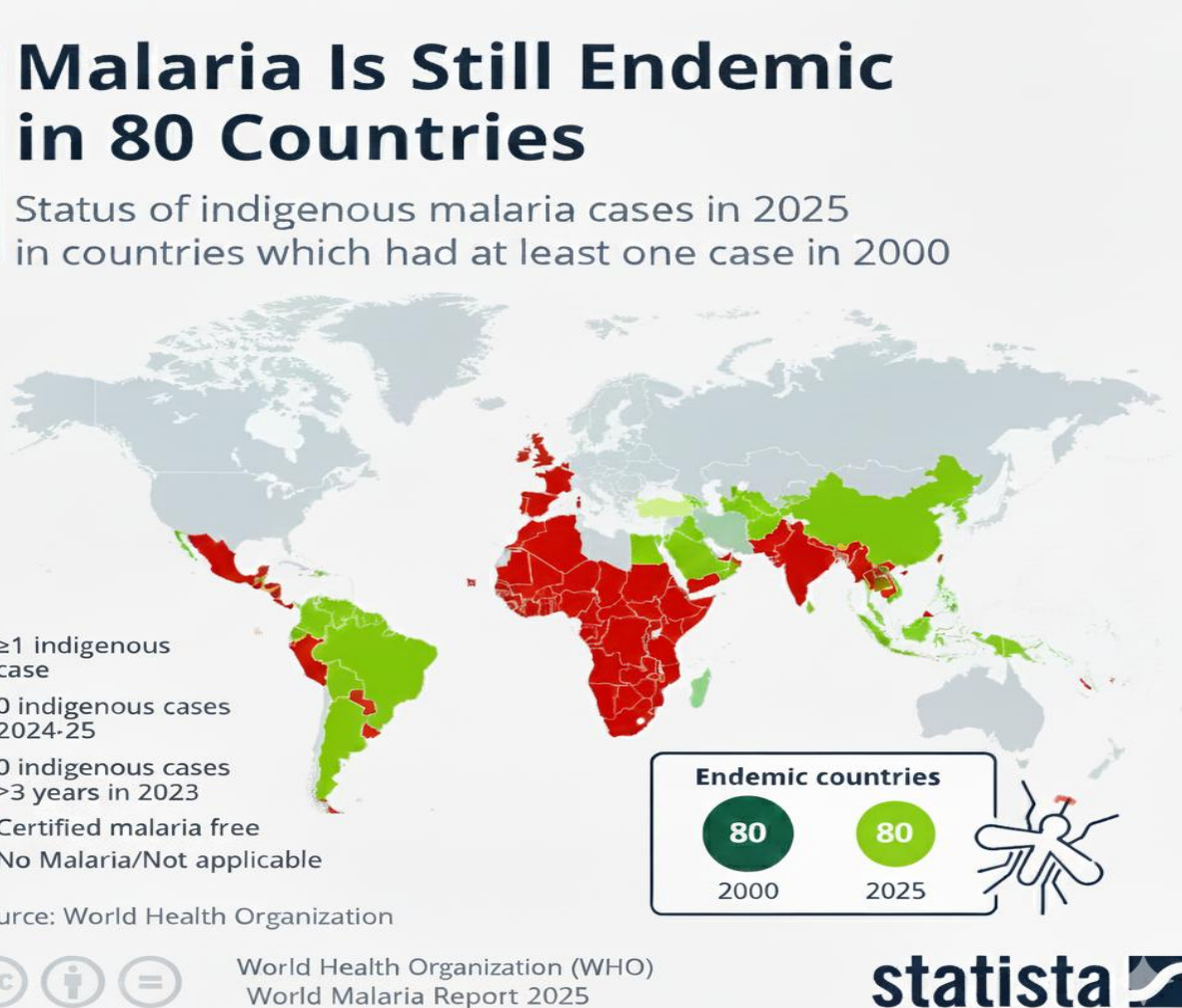
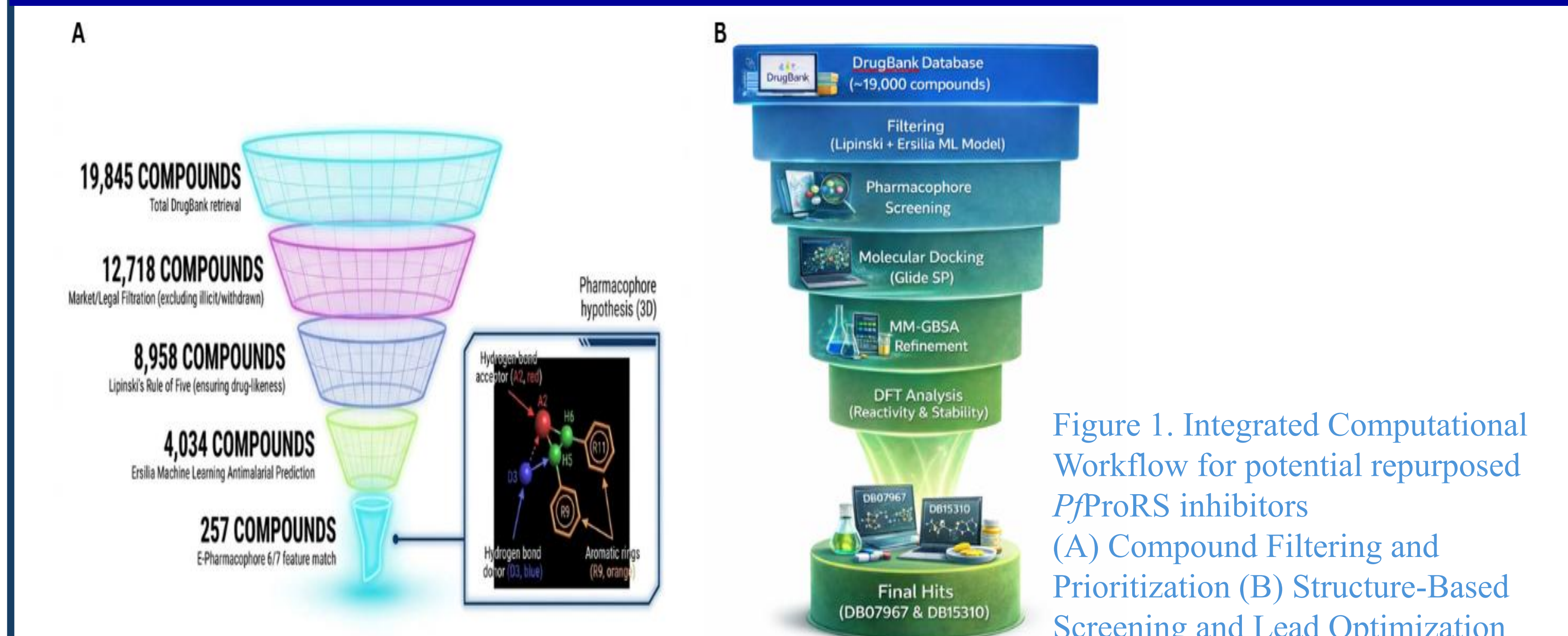
1. Introduction

Malaria remains a major global health challenge, with emerging artemisinin-resistant *Plasmodium falciparum* (Pf) strains threatening current treatment strategies.

Pf prolyl-tRNA synthetase (PfProRS), an essential enzyme that catalyzes proline attachment to tRNA during protein synthesis, is a promising drug target due to its structural-divergence from the human orthologue.

In this study, a SBVS of DrugBank compounds against PfProRS was performed, followed by MM-GBSA binding free energy and DFT analyses to identify promising repurposed antimalarials.

2. Methods



3. Results

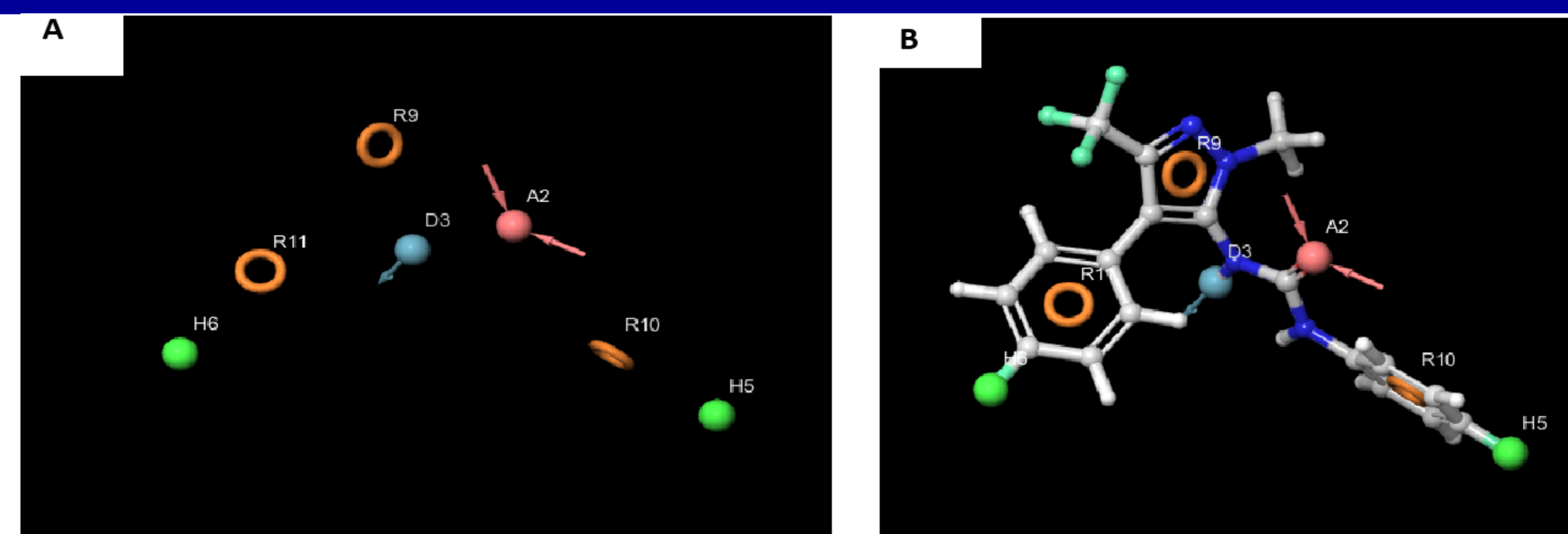


Figure 2. Pharmacophore Generation and Validation Using the Co-crystallized Ligand. (A) Derived pharmacophore showing key interaction features (A, D, and R). (B) Superimposition with the co-crystallized ligand confirming model validity.

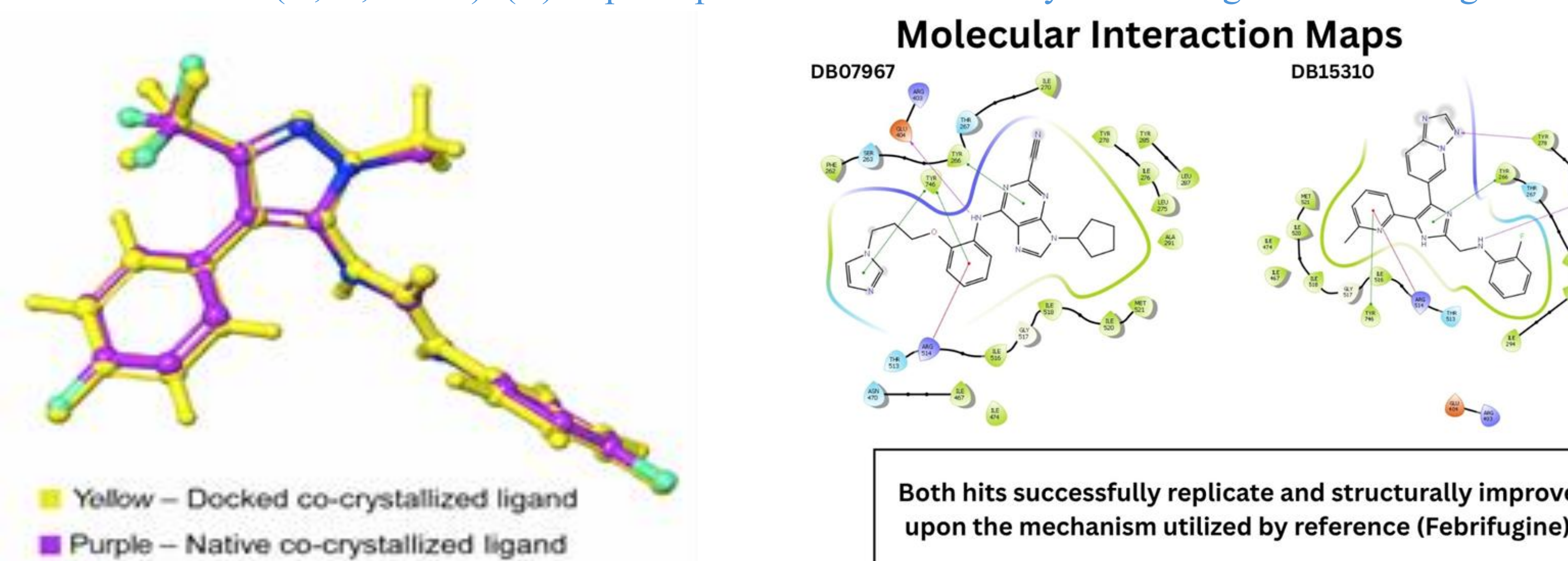
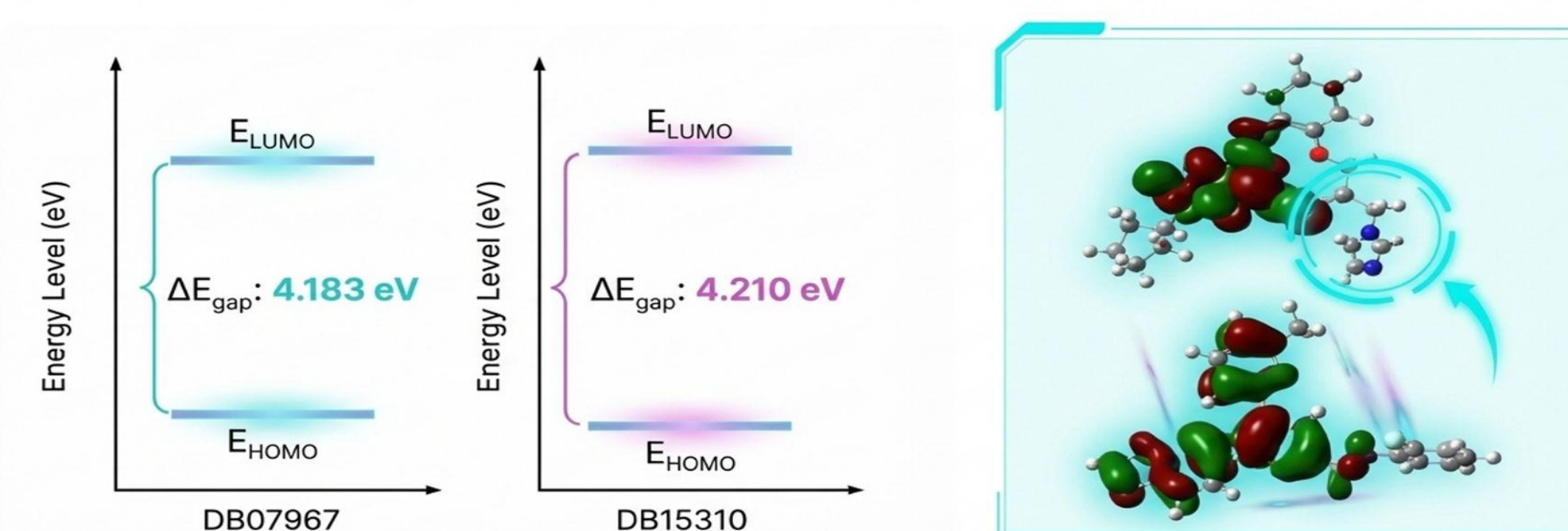


Figure 3. Validation of the molecular docking protocol by re-docking of the co-crystallized ligand.

Figure 4. Molecular Interaction Mapping of DB07967 and DB15310 within the PfProRS Active Site.

Electronic Properties & HOMO/LUMO Analysis



The Quantum Conclusion: A narrower band gap (4.183 eV) combined with higher electrophilicity (3.6820 eV) proves DB07967 has heightened chemical reactivity, functioning as a more effective electron donor to interact forcefully with the PfProRS target.

Figure 5. Electronic Structure Analysis Identifies DB07967 as a More Reactive and Promising PfProRS Inhibitor (Density functional theory analysis)

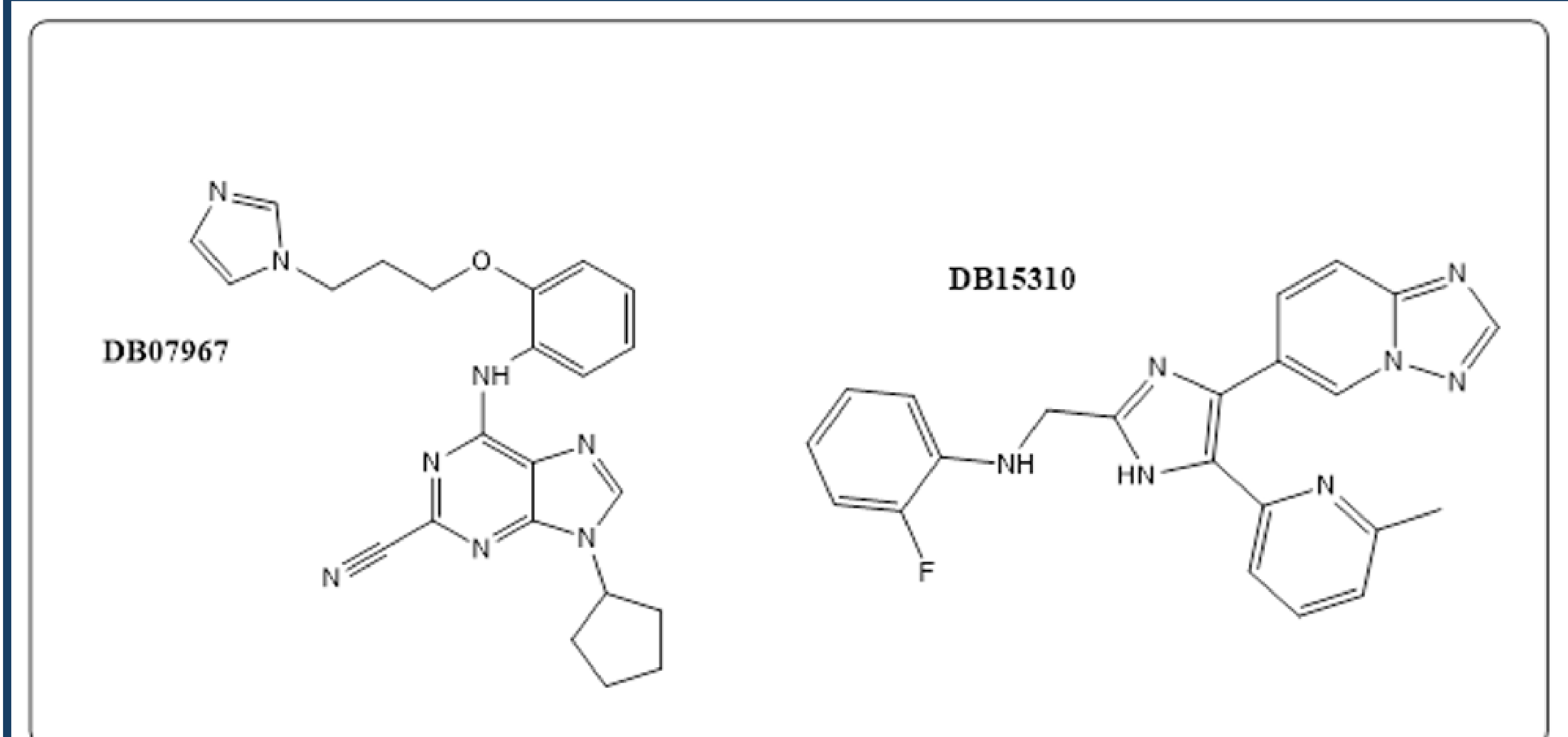


Figure 6. Chemical Structure of Top Hits (DB0796 and DB15310) with docking score of -9.17 kcal/mol and -9.12 kcal/mol

4. Conclusion

- DB07967 (9-cyclopentyl-6-[2-(3-imidazol-1-yl-propoxy)-phenylamino]-9H-purine-2-carbonitrile) and DB15310 (Vactosetib) emerged as promising hits.
- DB07967 showed the strongest binding affinity and most favorable electronic properties.

5. Recommendation

- in vitro* and *in vivo* studies
- Elucidate the mechanism of action and confirm PfProRS as the molecular target.

6. References

- WHO, World Malaria Report. 2025.
- T. A. Yuniarta, I. G. A. Sumartha, T. M. Fakh, R. Handayani, and D. S. F. Ramadhan, 'Discovery of Potential Prolyl-tRNA Synthetase Allosteric Inhibitor Through Virtual Screening and In Vitro Assay against Plasmodium falciparum', Jordan Journal of Pharmaceutical Sciences, 16, no. 4, pp. 880–900, 2023, doi: 10.35516/jjps.v16i4.1027.