Using docking studies to determine binding interactions of acridinyl, quinolinyl, and pyridinyl benzenesulfonamides with dihydrofolate reductase and in the *Plasmodium falciparum* folate pathway

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Abstract

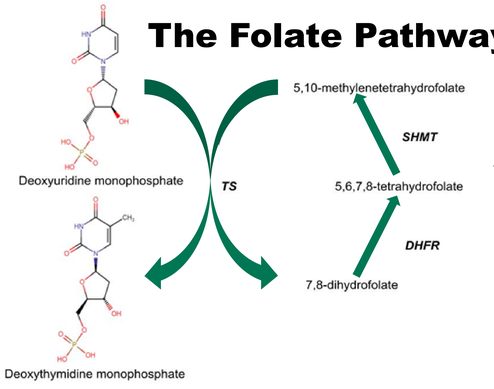
Malaria caused by the parasite *Plasmodium falciparum* is a scourge that continues to pose a great threat to humans worldwide due to increasing parasitic resistance that diminishes the efficacy of current antimalarial drugs. The folate pathway of *Plasmodium falciparum* serves as a promising drug target. Specifically, dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) are enzymes that are crucial precursors to cellular functions. In this study, the interactions and binding affinities of DHFR with three sulfonamide-based ligands, acridinyl (ACRS), quinolinyl (AQBS), and pyridinyl (APBS) benzenesulfonamides, were determined using AutoDock Vina. For example, ACRS binds to mutated DHFR enzyme isoforms with higher binding affinities (-9.5 kcal/mol) compared to artemisinin (-8.4 kcal/mol). This suggests that ACRS possesses features that enhance its interactions. Moreover, AQBS displayed affinities (-8.3 kcal/mol) with the same mutated DHFR enzyme that are on par with Artemisinin. The binding affinities for simulations with ligands in the vicinity of mutated residues indicate repulsion. Pharmacokinetic data also suggests that increased lipophilicity of ACRS plays a significant role in the binding process.

Antifolate/Antimalarial Drugs

Artemisinin | Sulfadoxine | Trimethoprim

- Sulfadoxine faces drug resistance [2]
- Low efficacy on artemisinin-resistant parasites [2]

The Folate Pathway [3]

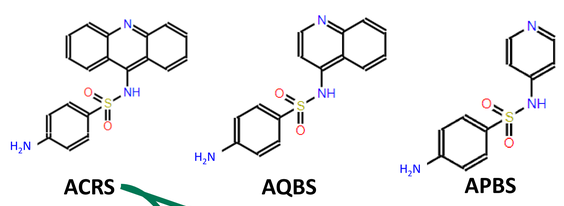


Aims and Motivations

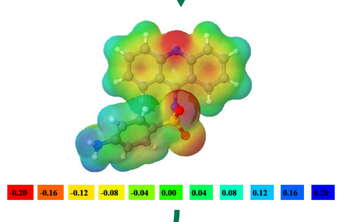
Impact of Sulfonamide and Pyridinyl Groups

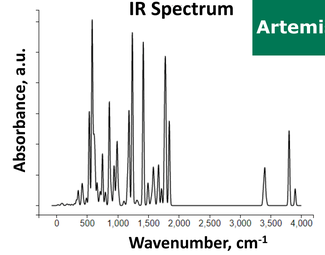
- Affinity with folate pathway enzymes
- Affinity to mutants of DHFR
- Critical binding features

Computational Methods



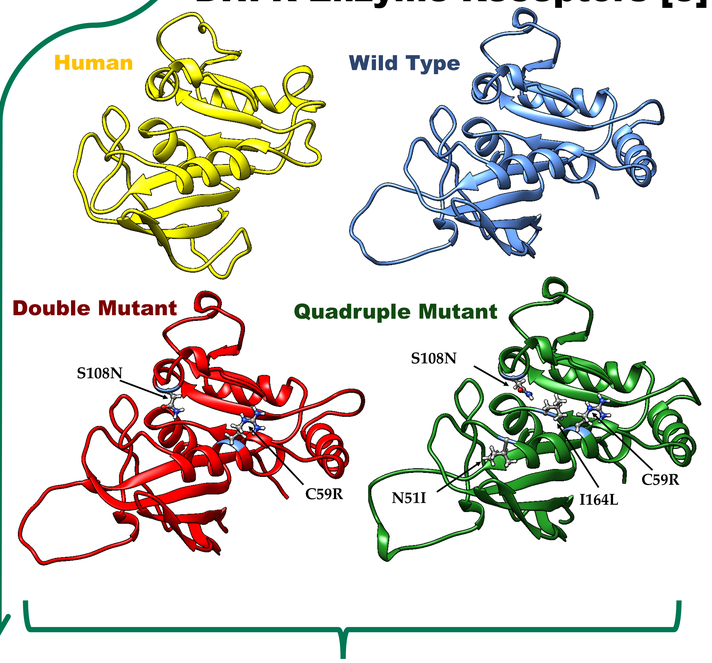
- Basis Set: 6-31G*
- DFT:BLYP3 method
- GAMESS [4]
- Bridges2 128 Cores

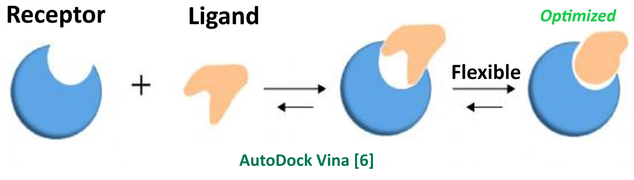




- Chimera
  - Load PDB
  - Refine receptor
  - Prep for docking

DHFR Enzyme Receptors [5]

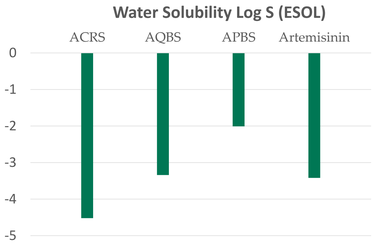


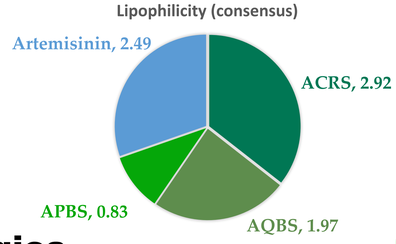


AutoDock Vina [6]

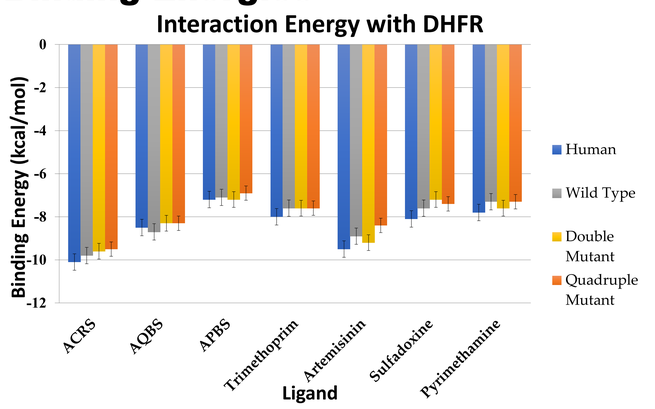
ADME Properties of Sulfonamides [7]

Ligand	H-bond Acceptors/ Donors	Polar Surface Area Å²
ACRS	Acceptors: 3 Donors: 2	93.46
AQBS	Acceptors: 3 Donors: 2	93.46
APBS	Acceptors: 3 Donors: 2	93.46
Artemisinin	Acceptors: 5 Donors: 0	53.99

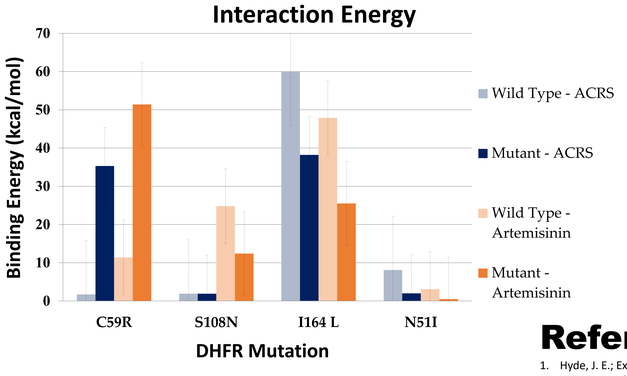




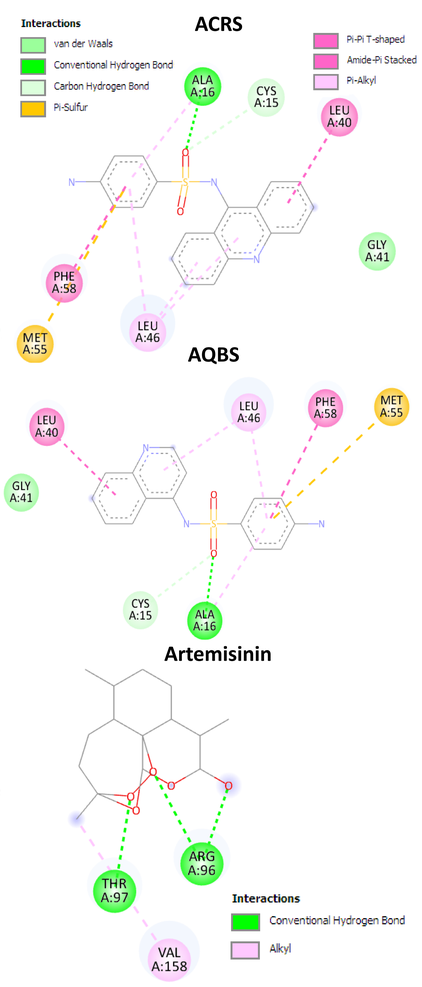
Binding Energies



Effect of Mutations



Binding Modes [8]



Conclusions

- ACRS and AQBS show binding affinities that are similar and greater than mainstay drugs.
- The addition of pi bonding in the sulfonamide drugs strengthened binding interactions.
- Lipophilicity has a positive correlation with binding affinities.
- ACRS can provide a foundation for further testing of sulfonamide antimalarial drugs.

References:

1. Hyde, J. E.; Exploring the folate pathway in Plasmodium falciparum, *Acta Trop.* **2005**, *94(3)*, 191-206
2. Mita, T; Tanabe, K; Evolution of Plasmodium falciparum drug resistance: implications for the development and containment of artemisinin resistance, *Jpn. J. Infect. Dis.* **2012**, *65*, 465-475
3. Berry, R. J.; Folate and DNA Methylation: A Review of Molecular Mechanisms and the Evidence for Folate's Role, *Adv. Nutr.* **2012**, *3*, 21-38
4. Barca, G. M. J.; et. al.; Recent developments in the general atomic and molecular electronic structure system, *J. Chem. Phys.* **2020**, *152*, 154102
5. Pettersen, E. F.; et. al.; UCSF Chimera – a visualization system for exploratory research and analysis, *J. Comput. Chem.* **2004**, *25(13)*, 1605-1612
6. Trott, O; Olson, A. J.; AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading, *J. Comput. Chem.* **2009**, *31*, 455-461
7. Daina, A.; Michielin, O.; Zoete, V.; SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules, *Sci. Rep.* **2017**, *7*, 42717
8. BIOVIA Discovery Studio, v21.1.0.20298; Dassault Systèmes: San Diego, **2021**.

Acknowledgements:

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