QSAR and Molecular Graphics and Modeling Study on Some Novel Artemisinins as Potent Antimalarials

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A brief overview of what we have done in this work

QSAR study on antimalarial artemisinins was performed by means of quantitative chemical, chemometric, and molecular graphics and modeling methods. Docking of some artemisinins to heme and hemoglobin was also carried out. The PLS model with four latent variables explaining 94.61% of logIC₅₀ variance (Q² = 0.95 and R² = 0.96) was obtained. Molecular descriptors were UMDH₂, atomic charge C9 and C10, the maximum number of hydrogen atoms that might make contact with heme, and a WHIM-3D index related to molecular symmetry. Two from the proposed artemisinin derivatives were predicted with antimalarial activity higher than the compounds used in literature. Docking results confirmed the PLS results and gave more insight into the nature of heme-artemisinin and heme-hemoglobin interactions.

What are the objectives of this study?

To propose new antimalarial artemisinins with predicted high activity – if possible, with activity higher than those currently in use – through QSAR study.

To give more insight into the artemisinin, heme, and artemisinin-heme complex properties and heme-artemisinin interaction through QSAR study, molecular graphics and modeling, other supporting methodologies (comparative, docking, structural comparisons, etc.)

What were the QSAR/chemometric methods used in this work?


-> molecular descriptors:
- quantum chemical (HF 6-31G**): MO energy, LUMO+1 energy, charge at C10
- topological-structural: the number of H-atoms in contact with heme, symmetry-related, G1e

-> regression method:
- PLS (Partial Least Squares), autoscaled data, leave-1-out validation
- PCA (Principal Component Analysis), autoscaled data

Data mining and structural studies

-> retrieval of relevant structures from CSD (Cambridge Structural Database) and PDB (Protein Data Bank)
- comparison of the retrieved structures with those from docking

Data mining & structural studies

Substrate-heme complexes retrieved from PDB. Orientation of the substrate with respect to heme is determined by distribution of polar and hydrophobic groups in the molecules.

At the end, we can conclude that... the artemisinins are mainly grouped as low, moderately and highly active compounds (see the HCA, PCA, PLS plots)

The fairly good PLS model predicts ART_24 and ART_27 to be more active than the compounds reported in literature (see the tables)

The torsion angle O2-O1-Fe-C(C) in minimum energy artemisinin-heme-proximal histidine complexes ranges from -105º to -135º, what could be expected as a general behavior of artemisinins (see color figures from the modeling & graphics part)

The artemisinin orientation with respect to heme is determined by polar-polar and hydrophobic-hydrophobic interactions between artemisinin, heme and amino-acid residues (see color figures from the modeling & graphics part)

The highly active artemisinins possess suitable substituents at C9 and C10 which are able to reach the heme proximal histidine (see color figures from the modeling & graphics part)

Thanks to FAPESP for the financial support.