

Combined Partial Least Squares and Quantum Chemical Study of Antimalarial Activity of Artemisinins

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Introdução

Malaria has been known since ancient times, as first described by Hippocratic in his writings. Today some 40% of the world population is exposed to malaria, resulting in about 3 million deaths per year. The most dangerous member of the *Plasmodium* gender that infects humans and is transmitted through Anopheles mosquito is *falciparum*. One of the ways in which this parasite destroys host cells is hemoglobin degradation to amino-acids and heme which are then used for parasite development and propagation, and detoxification of the most part of heme by polymerization. A number of drugs have been investigated for their efficacy against target molecules involved in these biochemical processes. The appearance of resistant strains of *falciparum* to some of those drugs has made necessary further investigation of new compounds with antimalarial activity. Artemisinin or *qinghaosu* and its derivatives, known as universal folk medicaments in China since ancient times [1], showed to be potential candidates against *falciparum*. Various studies suggested existence of several processes involving artemisinin: the first step of artemisinin action includes heme-catalyzed artemisinin activation into a very reactive radical, and the next is covalent binding of this radical to some parasite molecules. In this work [2], properties of a set of artemisinins are studied at *ab initio* level and related to antimalarial activity through Partial Least Squares regression (PLS) modeling.

Resultados e Discussão

PLS modeling. Five molecular descriptors, obtained from geometry-optimized molecular structures of 19 isolated artemisinins at B3LYP 6-31G** level, showed to be significantly correlated with biological activity against *Plasmodium falciparum* Sierra Leone clone D-6 resistant to mefloquine (in logIC₅₀ units): LUMO+1 energy, partial atomic charges at C9 and O11 atoms, a radial distribution function centered at 3.0 Å interatomic distance and weighted by atomic masses, and the maximum number of hydrogen atoms that might contact with heme. Use of these descriptors for 14/5 molecules in the training/external validation set

resulted in the best PLS model (three principal components explaining 89.55% of the total variance, $Q^2 = 0.83$ and $R^2 = 0.92$, SEP = 0.375) used to predict activity for 10 proposed artemisinins. There is a compound with activity predicted higher than any in literature, and consequently, a potential drug candidate. Principal Component and Hierarchical Cluster Analyses applied to the same descriptors for the training + external validation set clearly showed three classes of artemisinins with pronounced low, moderate and high antimalarial activity. Use of other molecular descriptors of various nature did not yield good PLS models. Traditional descriptors as molecular mass, HOMO and LUMO energies, lipophilicity logP, molecular volume and molar refractivity were also low correlated with the biological activity.

Quantum Chemical study. Molecular modeling of several artemisinin-heme-proximal histidine and artemisinin-hemoglobin complexes at MM level helped to rationalize stereoelectronic relationships between artemisinins and heme in terms of the four from five selected molecular descriptors. The role of LUMO+1 and not LUMO or HOMO energies was observed from MO plots which revealed that only LUMO+1 lobes discriminate artemisinins in accordance with their biological activity. These lobes are concentrated in basic structure of active artemisinins, and only in substituents in low active molecules.

Conclusões

Steric and electronic features of artemisinins that are directly responsible for artemisinin-heme interaction produced the best PLS models for their antimalarial activity and revealed new drug candidates.

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¹ Klayman, D. L., *Science* **1985**, 228, 1049.

² Pinheiro J. C., Kiralj R., Ferreira M. M. C., Romero O. A. S., *QSAR Comb. Sci.*, **2003**, 22, 830.

