4D-LQTAqsar ANALYSIS OF A SET OF ANTIMALARIAL COMPOUNDS

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Introduction

According to the World Health Organization (WHO)[1] the malaria occurs in over 100 countries, and more than 40% of the world's population is living at risk. The conventional chemotherapeutic agents have reduced its effectiveness, because the increasing of malaria parasites resistance to the existing drugs, causing a real threat to the control of malaria. Artemisinin and its derivatives emerged as a new class of antimalarials, which are effective against drug-resistant strains of *Plasmodium falciparum.*

This study aims the construction of QSAR models of a set of thirty-three artemisinin derivatives, including artemisinin as the lead drug, using partial least squares (PLS) regression. All biological data used in this work were expressed as logarithm of relative activity, logRA,[2] calculated considering equation 1.

log RA = log [(IC_{50} of artemisinin/ IC_{50} of the analogue) x (MW of the analogue/MW of the artemisinin)]   (**eq.1**)
where: MW = molecular weight

Artemisinin crystal structure retrieved from Cambridge structural Database, reference code *QNGHSU03*[3] (crystallography R factor 3.60%), was used as starting geometry to build all the ligands. The complete geometry optimizations of artemisinin and its derivatives were carried out employing MM+ force field, AM1 semiempirical method, *ab initio* HF/3-21G and HF/6-31G methods, and DFT using B3LYP/6-311++G** as basis set. The Gaussian, HyperChem, and 98W programs were used for molecular modeling calculations and PIROUETTE[4] package was employed to carry out the chemometric analysis.

All thermodynamic descriptors (van der Waals and electrostatic energy contributions) were calculated employing the LQTAgrid program, developed in our group (Barbosa, EG; Martins, JPA; Pasqualoto, KFM; Ferreira, MMC), using NH3+ as a probe, and considering the conformational profile (PC) of each ligand. The formalism employed in this work combines the advantages of the methods, CoMFA and independent-receptor 4D-QSAR.

Results and Discussion

The best QSAR model (N = 33) presented the following statistical parameters values: $q^2 = 0.59$; $r^2 = 0.77$; SEV = 0.37; SEC = 0.3; and, SEP = 0.28, using 4 latent variables. The resulting QSAR model was validated applying Y-randomization and *leave-N-out* (N = 1 to 10) methodologies.

The descriptors selected in the best QSAR models can be graphically visualized (*hot spots*) and are presented in fig. 1. Favorable and unfavorable energy contributions to the biological activity are shown as green (dark and light) and red (dark and light) spheres, respectively. Figure 1 shows the graphical visualization of the 4D descriptors selected in the best QSAR model. Lennard-Jones descriptors are presented as light color spheres and Coulombic descriptors as dark spheres, respectively.
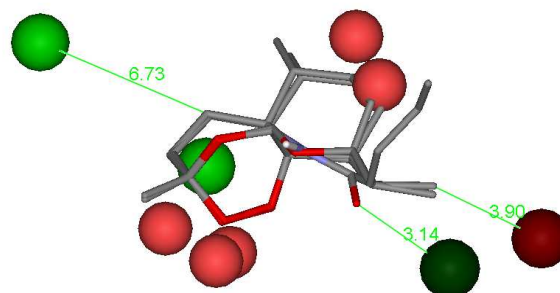

Figure 1. Superposition of two artemisinin derivatives and the 4D-descriptors selected in the best QSAR model.

Conclusions

The methodology applied in this study generated a QSAR model having a reasonable internal and external predictability. These findings can be helpful in the design of new antimalarial agents.

Acknowledgements

[1] http://www.who.int/malaria/ Accessed in 10/04/2008.
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