which do not fit well. The point marked as A has a smaller fold difference valued than expected whilst point B is Rhodamine B (fold difference of 12) which falls on top of Rhodamine 123 (fold difference of 5.7) which was part of the original training set. Hence, the PCs do not contain the information which separates Rhodamine B from Rhodamine 123. The point marked by the elipse was also part of the training set but now seems out of place with respect to the new test points and so this area needs to be probed further to identify the problem compounds. As the PCs are a summation of contributions from all the 2D descriptors (>1300) it is not that informative to examine the PCs for the few most influential, but one has noticed that larger molecules are towards the base of the cone, PC1 has descriptors which describe hydrophobicitiy, with shorter path lengths (<7) being positive contributors and longer ones (>=7) being negative. PC2 has charge descriptors prominent and interestingly a number of fluorine containing descriptors being negative contributors. PC3 has long path length pair-type descriptors being negative contributors and short path length pair-type descriptors being positive contributors.

CONCLUSIONS

Linear models which are derived from 'standard' molecular properties are not good general predictors of mouse P-gp liability. A non-linear PCA model has shown an unusual but generally effective clustering of compounds which are affected by P-gp in vivo in the mosuse. This model does not contain all the features needed to distinguish highly related compounds such as Rhodamines B and 123 and further work needs to be done to elucidate those features.

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Combined QSAR, molecular graphics and modelling study on some C9, C10-substituted artemisinins with antimalarial activity against *Plasmodium falciparum*

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INTRODUCTION

Today, it is estimated that 40% of the world's population is exposed to the risk of contracting malaria, with about 2.7 million deaths per year. The appearance of resistant strains of *Plasmodium falciparum* to some of the drugs in common clinical usage has made necessary further investigations of new classes of

compounds as artemisinins and its derivatives. The mechanism of artemisinin antimalarial activity includes heme-catalysed artemisinin activation into a very reactive radical, which then could covalently bind to parasite proteins, heme, hemozoin or other parasite molecule. This present status on artemisinin research throughout the world encourages to perform a QSAR study on novel artemisinin derivatives, and to give more insight into possible interactions between artemisinins and heme, and haemoglobin.

METHOD

QSAR study [1] on 17 antimalarial C9, C10-substituted artemisinins (Fig. 1) against *Plasmodium falciparum* (biological activities from literature [2,3]) was performed by means of quantum chemical (*ab initio* HF/6-31G* level), chemometric (Principal Component Analysis PCA, Hierarchical Cluster Analysis HCA, Partial Least Squares Regression PLS) and molecular graphics and modelling methods. Prediction of antimalarial activities for 10 proposed C9, C10-substituted artemisinins was performed. Docking of some artemisinins to heme and haemoglobin as well as structural studies on heme-substrate complexes was carried out also.

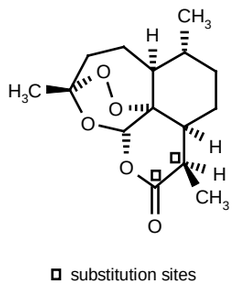

Fig. 1.

RESULTS

The samples are discriminated as less active, active and highly active in PCA and HCA (Figs. 2, 3). Molecular descriptors were *LUMO+1* energy, atomic charges in C9 (Q_9) and C10 (Q_{10}), the maximum number of hydrogen atoms that might make contacts with heme (*NH*), and a WHIM-3D index related to molecular symmetry (*G1e*) (Fig. 2). High *LUMO+1* and *HN*, low *G1e*, and high negative Q_9 and Q_{10} are important for binding strength of artemisinin to heme. The PLS model with four latent variables (Fig. 4) explaining 91.61% of $\log IC_{50}$ variance (Q^2 = 0.95 and R^2 = 0.96) was obtained. Two from 10 proposed artemisinin derivatives were predicted with antimalarial activities higher than the compounds reported in literature. The docking confirmed the PLS results and gave more insight into the nature of heme-artemisinin and haemoglobin-artemisinin interactions, and made it possible to conclude that the highest active artemisinins are able to penetrate from the active site hole to the protein exterior. The artemisinin ring system, besides being covalently bound to heme, is involved in polar-polar, H-bond, hydrophobic-hydrophobic, C-H...π and O...π

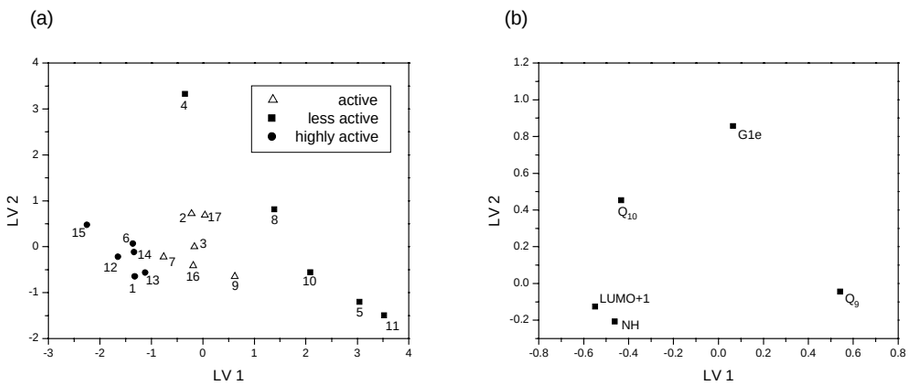

Fig. 2. (a) The PCA scores; and (b) loadings plot.

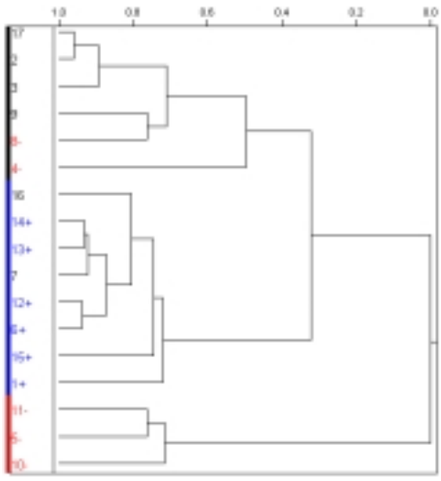

Fig. 3. The HCA dendogram for samples.

interactions with heme and globin residues. C9,C10-substituents can significantly influence these interactions. These findings are confirmed by crystal structures of heme (in hemoglobin) – substrate complexes.

CONCLUSIONS

The design of novel, highly potent C9, C10-substituted artemisinins should follow the hints found on the basis of QSAR methods, supported by molecular graphics and modeling and structural studies. The study of heme-artemisinin complexes, isolated or in haemoglobin, takes one of crucial roles in artemisinin design due to artemisinin activation by heme.

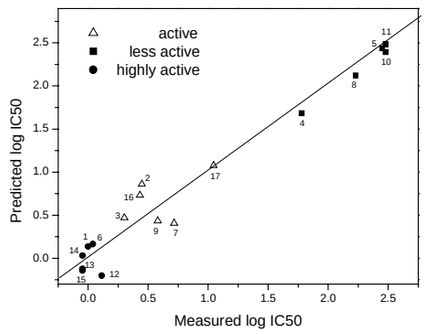

Figure 4. The PLS plot.

ACKNOWLEDGEMENT

The authors acknowledge FAPESP for financial support.

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Combination of molecular modelling and QSAR analysis in study of antimycobacterial activity of benzimidazole derivatives

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INTRODUCTION

The effort in our laboratories has been focused on development of new compounds with antimycobacterial activity for some years. Recently, we have described the synthesis and the antimycobacterial activity of benzylsulfanyl derivatives