Combined QSAR, Molecular Graphics and Modeling Study on Some C9,C10-substituted Artemisinins with Antimalarial Activity Against *Plasmodium Falciparum*

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A brief overview of what we have done in this work

This QSAR study on C9,C10-substituted antimalarial artemisinins was performed by using quantum chemical, chemometric and molecular graphics and modeling methods. Docking of some artemisinin derivatives to heme and hemoglobin was also carried out. The PLS model with four latent variables explaining 91.61% of $\log IC_{50}$ variance (Q^2 = 0.95 and R^2 = 0.96) was obtained. Molecular descriptors were LUMO+1 energy, atomic charges in 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 ten proposed artemisinin derivatives were predicted with antimalarial activity higher than the compounds reported in literature. Docking results confirmed the PLS results and gave more insight into the nature of heme-artemisinin and heme-hemoglobin interactions.

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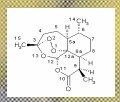
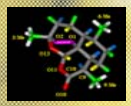
Artemisinin: A new compound whose derivatives represent a novel class of potent antimalarials. The malarial microorganism *Plasmodium Falciparum* exhibits high resistance to known antimalarials, what does not happen with artemisinins.

Artemisinin molecular structure



2 D scheme



3D stick model

Space filling (CPK) models

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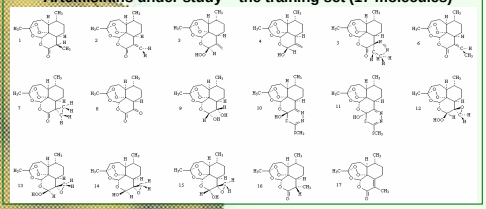
Artemisinins under study – the training set (17 molecules)



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Artemisinins under study – the prediction set (10 molecules)

Artemisinin substituted at C9 and C10:

ART_18	ART_19	ART_20
ART_21	ART_22	ART_23
ART_24	ART_25	ART_26
ART_27		

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The objectives of this study

-to propose new antimalarial artemisinins with predicted high activity – if possible, with activity higher than those clinically in use -> QSAR study

-to give more insight into artemisinin, heme and artemisinin-heme complex properties and heme-artemisinin interaction -> QSAR study, molecular graphics and modeling, other supporting methodologies (chemometric, data mining, structural comparisons etc.)

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The QSAR/chemometric methods

QSAR: -> biological activities from literature (Acton *et al*, *J Med Chem* **36** (1993)2552; Acton *et al*, *Planta Med* **53** (1987) 266.)

-> molecular descriptors: -> quantum chemical (HF-6-31G**): -> MO energy, E_{LUMO+1}
-> charge at C9, Q_9
-> charge at C10, Q_{10}
-> topological-structural: -> the number of H-atoms in contact with heme, N_H
-> electrotopological: -> an index from WHIM-3D, symmetry-related, G1e

-> regression method: -> PLS (Partial Least Squares), autoscaled data, leave-1-out crossvalidation

Chemometrics: -> HCA (Hierarquical Cluster Analysis), autoscaled data, incremental linkage
-> PCA (Principal Component Analysis), autoscaled data

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The other methods

Molecular graphics and modeling:
-> steric and electronic complementarity of artemisinin with heme
-> docking of artemisinin to heme -> MMFF94 conformational study around Fe-O1 bond
-> docking of artemisinin to hemoglobin A monomer -> MMFF94

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

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The QSAR results

Molecule	E_{LUMO+1}, hartree	Q_9	Q_{10}	G1e	N_H	$\log IC_{50}$
1	0.2102	-0.0463	0.8191	0.1560	8	0
2	0.2072	-0.3045	0.9087	0.158	6	0.447
3	0.2137	-0.2299	0.8122	0.1560	6	0.301
4	0.2152	-0.331	0.9339	0.1690	6	1.78
5	0.1839	1.0207	0.4233	0.1540	6	2.45
6	0.2090	-0.4382	0.9799	0.1560	7	0.0414
7	0.2094	-0.1482	0.8583	0.1560	7	0.716
8	0.1978	0.4336	0.7289	0.1600	6	2.23
9	0.2182	0.0517	0.5263	0.1569	6	0.580
10	0.1655	0.3708	0.7581	0.1530	6	2.48
11	0.1561	0.5379	0.2787	0.1520	6	2.48
12	0.2173	-0.4473	0.9853	0.1550	7	0.114
13	0.2165	-0.3053	0.8210	0.1550	7	-0.0458
14	0.2181	-0.2834	0.9305	0.1560	7	-0.0458
15	0.2164	-0.6318	1.1954	0.1560	7	-0.0458
16	0.2071	0.1139	0.7705	0.156	7	0.431
17	0.2053	-0.1689	0.8932	0.1580	6	1.045

<- QSAR data for the training set

Molecule	$\log IC_{50}$
ART_18	-0.129
ART_19	0.00351
ART_20	0.567
ART_21	1.61
ART_22	1.42
ART_23	1.22
ART_24	-0.538
ART_25	0.598
ART_26	-0.197
ART_27	-0.333

<- biological activities for the prediction set

The PLS model: Q^2 =.95, R^2 = 0.96, with 3 PCs (91.61% total variance explained)

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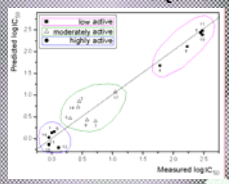
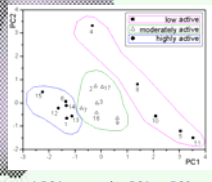
The QSAR/chemometric results



PLS plot: predicted vs. measured activities



A PCA scores plot: PC1 *vs.* PC2.

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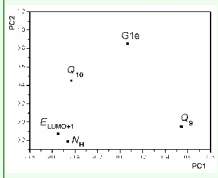
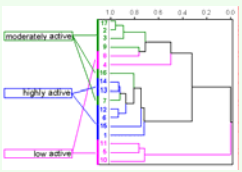
The chemometrics results



A PCA loadings plot: PC1 *vs.* PC2.



HCA dendogram of samples

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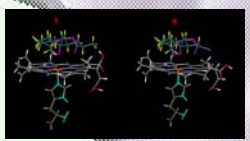
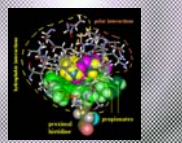
The molecular graphics & modeling results (docking)



Substrat-heme-proximal histidine complexes optimized by MMFF94 after the Fe-O conformational study



ART_24-heme-proximal histidine complex surrounded by hemoglobin amino-acids

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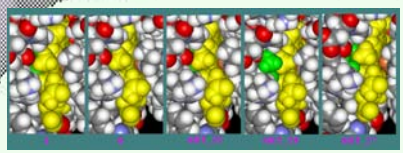
The molecular graphics & modeling results (docking)



Artemisinins (green) and heme (yellow), as can be seen in a view towards the hemoglobin surface. The green area is proportional to the biological activity for these compounds.

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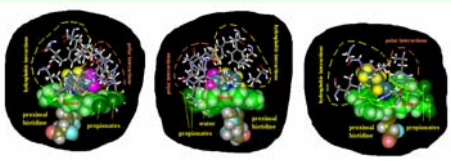
The Data mining and structural studies



The substrate-heme-proximal histidine complex surrounded by the residues of hemoglobin. Retrievals from the PDB. Polar-polar and hydrophobic-hydrophobic interactions are visible.

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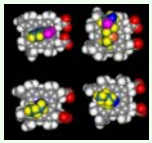
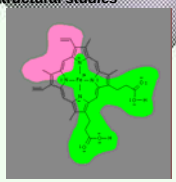
More data mining & structural studies



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



The preference for polar (green), hydrophobic (rose) or any (gray) substrate groups to interact with heme

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Conclusions

1) The artemisinins are mainly grouped as low, moderately and highly active compounds (see the HCA, PCA, PLS plots).

2) A fairly good PLS model predicts ART_**24** and ART_**27** to be more active than the compounds reported in literature (see the Tables).

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

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

5) The highly active artemisinins possess suitable substituents at C9 and C10 which are able to reach the hemoglobin exterior (see the color figures from the modeling, graphics and structural part)

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