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

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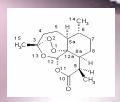
1 A brief overview of what we have done in this work

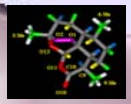
QSAR study on antimalarial artemisinins was performed by means of quantum chemical, chemometric and molecular graphics and modeling methods. Docking of some artemisinins to heme and hemoglobin was also carried out. The PLS model with four latent variables explaining 91.61% of $\log IC_{50}$ variance (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.

2 Artemisinin: A new compound whose derivatives represent a novel class of potent antimalarials. The malarial microorganism *Plasmodium Falciparum* has already exhibited resistance to known antimalarials, but not to artemisinins.

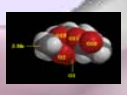
How does artemisinin look like???



2 D scheme

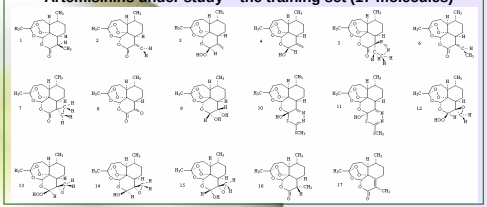


3D stick model



Space filling (CPK) models

3 Artemisinins under study – the training set (17 molecules)



4 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		

5 What are 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 artemisini-heme complex properties and heme-artemisinin interaction -> QSAR study, molecular graphics and modeling, other supporting methodologies (chemometric, data mining, structural comparisons etc.)

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

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

7 What were other methods used in this work?

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

8 QSAR results

<- QSAR data for the training set

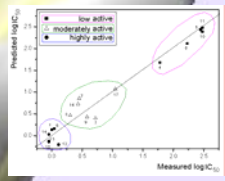
Molecule	E_{LUMO+1} / hartree	Q_9	Q_{10}	G1e	N_H	$\log IC_{50}$
1	0.2102	-0.0463	0.8191	0.1560	8	0
2	0.2072	-0.3045	0.9087	0.158	6	0.447
3	0.2137	-0.2299	0.8122	0.1560	6	0.301
4	0.2152	-0.331	0.9339	0.1690	6	1.78
5	0.1839	1.0207	0.4233	0.1540	6	2.45
6	0.2090	-0.4382	0.9799	0.1560	7	0.0414
7	0.2094	-0.1482	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	0.1530	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

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

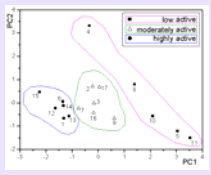
<- biological activities for the prediction set

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

9 More QSAR/chemometric results

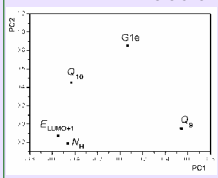


PLS plot: predicted *vs.* measured activities

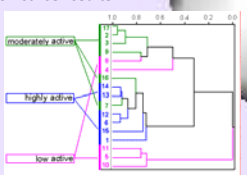


A PCA scores plot: PC1 *vs.* PC2.

10 More chemometrics results

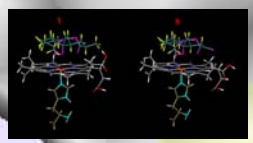


A PCA loadings plot: PC1 *vs.* PC2.

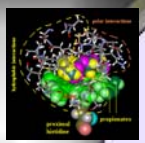


HCA dendogram of samples

11 Some molecular graphics & modeling results (docking)

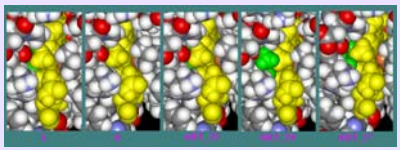


Substrat-heme-proximal histidine complexes optimized by MMFF94 after the Fe-O conformational study



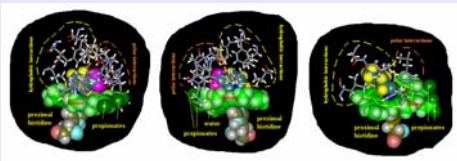
ART_24-heme-proximal histidine complex surrounded by hemoglobin amino-acids

12 More molecular graphics & modeling results (docking)



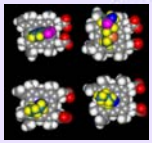
Artemisinins (green) and heme (yellow) as can be seen in a view towards the hemoglobin surface. The green area is proportional to the biological activity for these compounds.

13 Data mining & structural studies

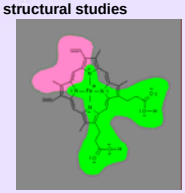


Substrate-heme-proximal histidine complex surrounded by residues of hemoglobin. Retrievals from PDB. Polar-polar and hydrophobic-hydrophobic interactions are visible.

14 More 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.



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

15 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(*meso*) in minimum energy artemisinin-heme-proximal histidine complexes ranges from -105° to -135°, 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&structural part)

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

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