Structure-activity relationship study of steroidal 1,2,4,5-tetraoxane animalarials using computational procedures

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Abstract: A three-dimensional QSAR pharmacophore model for antimalarial activity of steroidal 1,2,4,5-tetraoxanes was developed from a set of 17 substituted antimalarial derivatives out of 27 analogues that exhibited remarkable *in vitro* activity (below 100 ng/mL) against sensitive and multidrug-resistant *Plasmodium falciparum* malaria. The pharmacophore, which contains two hydrogen bond acceptors (lipid) and one hydrophobic (aliphatic) feature, was found to map well onto the potent analogues and many other well-known antimalarial trioxane drugs including artemisinin, arteether, artesunic acid, and tetraoxanes. The presence of at least one hydrogen bond acceptor in the trioxane or the tetraoxane moiety appears to be necessary for potent activity of this class of compounds. Docking calculations of some of these compounds with heme are consistent with the above observation as the proximity of the heme iron to the oxygen atom of the trioxane or the tetraoxane moiety favors potent activity of the compounds. Electron transfer from the oxygen of trioxane or the tetraoxane appears to be crucial for mechanism of action of the compounds. This information together with the pharmacophore should enable search for new peroxide containing antimalarial candidates from databases and custom designed synthesis of more efficacious and safer analogues.
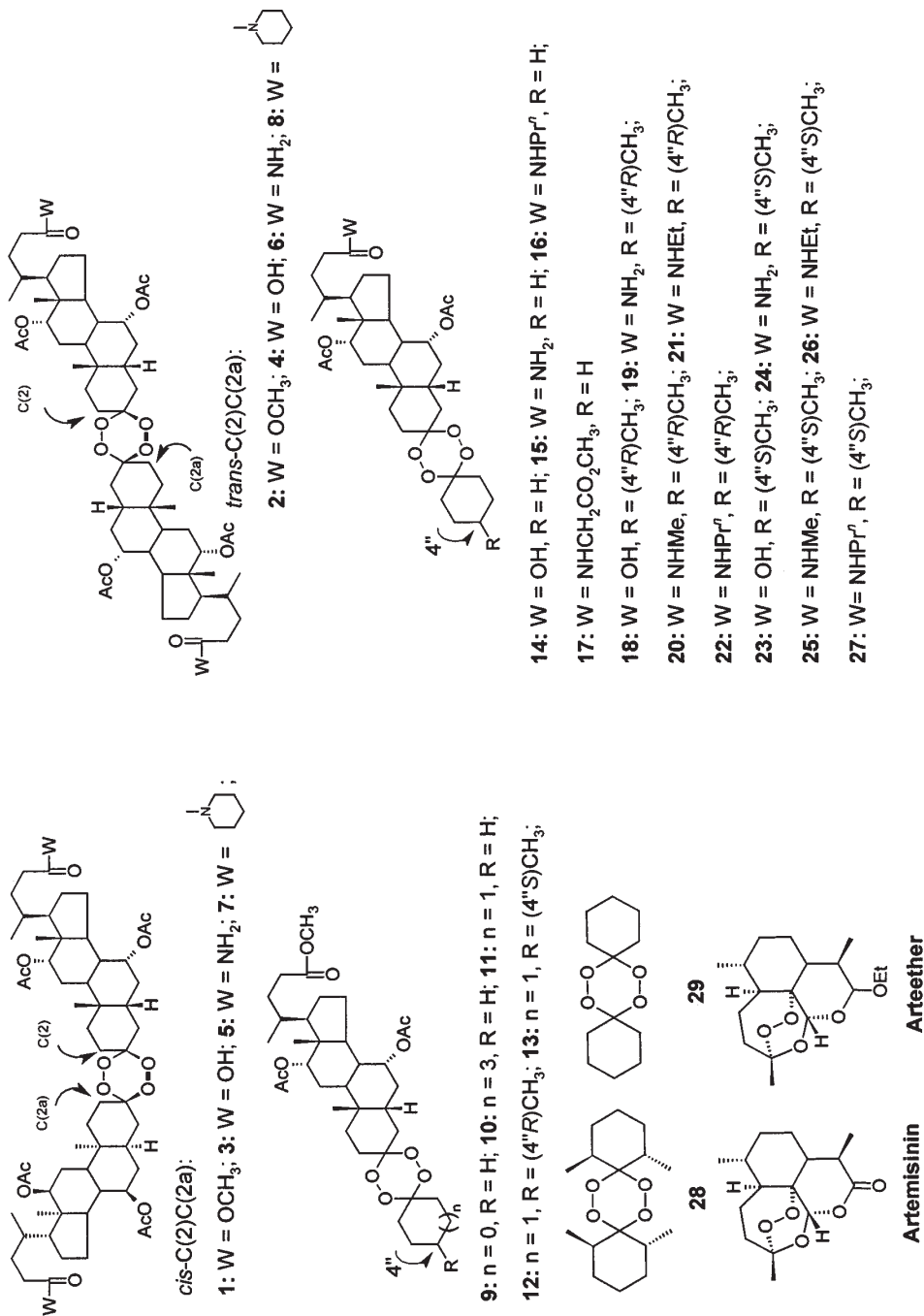
Keywords: QSAR; 3D pharmacophore; tetraoxane; malaria, steroids.

INTRODUCTION

Malaria is one of the most dangerous diseases affecting primarily poor people of tropical and subtropical regions. The death toll of over 1.5 million per year, and increasing resistance of standard antimalarial drugs, *e.g.,* chloroquine, justifies WHO's appeal for delivery of new drug entities.[1] The introduction of new antimalarial pharmacophore of artemisinin origin[2] paved the way for the discovery of

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cis-C(2)C(2a):

1: W = OCH₃; 3: W = OH; 5: W = NH₂; 7: W =

trans-C(2)C(2a):

2: W = OCH₃; 4: W = OH; 6: W = NH₂; 8: W =

9: n = 0, R = H; 10: n = 3, R = H; 11: n = 1, R = H;

12: n = 1, R = (4"*R*)CH₃; 13: n = 1, R = (4"*S*)CH₃;

14: W = OH, R = H; 15: W = NH₂, R = H; 16: W = NHPr^n, R = H;

17: W = NHCH₂CO₂CH₃, R = H

18: W = OH, R = (4"*R*)CH₃; 19: W = NH₂, R = (4"*R*)CH₃;

20: W = NHMe, R = (4"*R*)CH₃; 21: W = NHEt, R = (4"*R*)CH₃;

22: W = NHPr^n, R = (4"*R*)CH₃;

23: W = OH, R = (4"*S*)CH₃; 24: W = NH₂, R = (4"*S*)CH₃;

25: W = NHMe, R = (4"*S*)CH₃; 26: W = NHEt, R = (4"*S*)CH₃;

27: W= NHPr^n, R = (4"*S*)CH₃;

28

29

Artemisinin

Arteether

Scheme 1. Structures of examined tetraoxanes, artemisinin and arteether.

new lead compounds possessing a peroxide moiety.[3] Our own research,[4] and of others,[5] revealed a 1,2,4,5-tetraoxacyclohexane (tetraoxane) moiety as one of very promising antimalarial leads.

We earlier reported that steroidal tetraoxanes possessing two steroidal carriers show pronouced *in vitro* antimalarial activity against *Plasmodium falciparum*, with the more potent compounds exhibiting IC_{50} values as low as 9.29 nM.[4b] In addition, we recently reported the synthesis and *in vitro* antimalarial activity of 41 mixed steroidal tetraoxanes from which 12 were found to be more active than artemisinin on chloroquine-resistant *P. falciparum* W2 clone, compound **19** (Table I, Scheme 1) being one of the most potent antimalarials in vitro.[4c] Introduction of cholic acid derived tetraoxane carrier resulted in enhanced antimalarial activity, as compared to simple tetraoxanes, and very low toxicity: the lowest selectivity index (*SI*) value being 1400.[4b,4c] The activity of steroidal tetraoxanes is primarily shape-dependant. A clear difference between the *cis* and *trans* isomers was observed with the bis-steroidal series.[4b] The mixed steroidal tetraoxanes series with the (4"*R*) substituted compounds (Table I) were found to be significantly more active than corresponding (4"*S*) epimers.[4c]

In the light of the above findings, we set out to identify the quantitative structure–activity relationships between the compounds, and to build a pharmacophore model for activity to guide the design and synthesis of well tolerated target specific peroxide containing antimalarials.

EXPERIMENTAL

Chemicals

Bis-steroidal tetraoxanes (**1-8**) were prepared in a peroxyacetalization reaction directly from the corresponding ketone, followed by further functionalization of the C(24) ester group.[4b,4f] Mixed steroidal tetraoxanes were obtained by coupling of gem-dihydroperoxides with the corresponding ketones.[4c] Structure of the tetraoxanes **1** and **23** was derived by X-ray analyses.[4b,4c]

Biological testing

The *in vitro* antimalarial drug susceptibility screen was a modification of the procedures first published by Desjardins *et al.,* [6] with modifications developed by Milhous *et al.*[7] In brief, the assay relied on the incorporation of radiolabeled hypoxanthine by the parasites and inhibition of isotope incorporation was attributed to activity of known or candidate antimalarial drugs. For each assay, proven antimalarials were used as controls. The incubation period was 66 h and the starting parasitemia was 0.2 % with a 1 % hematocrit. The media used was an RPMI-1640 culture media with no folate or *p*-aminobenzoic acid (PABA) and 10 % normal heat inactivated human plasma. For quantitative *in vitro* drug susceptibility testing, two well-characterized *P. falciparum* malaria clones were used, W2 and D6.[8] W2 is a clone of the Indochina I isolate and is resistant to chloroquine and pyrimethamine, but susceptible to mefloquine. D6 is a clone from the Sierra I/UNC isolates and is susceptible to chloroquine and pyrimethamine, but has reduced susceptibilities to mefloquine and halofantrine.

Drugs were dissolved directly in dimethyl sulfoxide (DMSO) and diluted 400 fold with complete culture media. The compounds were then diluted 2-fold, 11 times, to give a concentration range of 1,048-fold. These dilutions were performed automatically by a Biomek 1000 or 2000 Liquid Handling System into 96-well microtiter plates. The diluted drugs were then transferred (25 µl) to test plates, 200 µl of parasitized eryhtrocytes (0.2 % parasitemia and 1 % hematocrit) were added,

and incubated at 37 °C in a controlled environment of 5 % CO_2, 5 % O_2 and 90 % N_2. After 42 h, 25 µl of ^{3}H-hypoxanthine was added and the plates incubated for an additional 24 h. At the end of the 66-hour incubation period, the plates were frozen at −70 °C to lyse the red cells and later thawed and harvested onto glass fiber filter mats by using a 96-well cell harvester. The filter mats were then counted in a scintillation counter and the data downloaded with the custom-made, automated analysis software developed at WRAIR. For each drug, the concentration response profile is determined and 50 % inhibitory concentrations (IC_{50}) are determined by using a nonlinear, logistic dose response analysis program.

METHODS

Method for generation of the 3D QSAR model

The three-dimensionl QSAR model for antimalarial activity of the tetraoxanes was carried out using the CATALYST 4.8 methodology.[9] The version 4.8 in CATALYST allows the excluded volume as an additional function that can be added for the automatic generation of the pharmacophore. The structures of 27 steroidal tetraoxanes (Table I) plus artemisinin, arteether, and two other tetraoxanes (**28** and **29**) were edited within CATALYST to create a separate stockroom of antimalarials of this class of compounds along into the CATALYST and energy minimized to the closest local minima using the generalized CHARMM-like force field as implemented in the program. Conformations ranging from 0–84 kJ/mol were generated for each of the tetraoxanes. Molecular flexibility was taken into account by considering each compound as a collection of conformers representing a different area of conformational space accessible to the molecule within a given energy range. The "best quality searching procedure" was adopted to select representative conformers over a 0–84 kJ/mol range above the computed global minimum. Since this search procedure in CATALYST can generate up to 250 conformers for each molecule within the 84 kJ/mol range, the conformational energy space generated above the lowest conformation can identify the best 3-dimensional arrangement of chemical functions explaining the activity variations among the training set. A prerequisite for development of a reliable 3D QSAR model of the compounds is the correlation of a characteristic and reproducible biological activity to structural information of the respective compound. The conformational model of 17 compounds (Table II) including artemisinin and arteether with diverse activities were taken from the stockroom of the tetraoxanes to create a truly diverse training set for generation of the pharmacophore that aims to identify the best three-dimensional arrangement of chemical functions explaining the activity variations among the training set (Table II). The training set with the *in vitro* activity data were used for automatic generation of hypotheses within CATALYST (HypoGen) using several chemical functions such as hydrogen bond acceptor, hydrogen bond donor, hydrophobic sites, positive ionizable and aromatic ring sites as the functional features to describe the antimalarial activity of the compounds. Quantum chemical calculations on the stereoelectronic properties of a few of these com-

TABLE I. Determined *in vitro* activities of tetraoxanes **1 – 27** against *P. falciparum* D−6 and W−2 strains

Compound	D-6 (ng/mL)	W-2 (ng/mL)
1	>99.97	>96
2	>99.97	>96
3	>100.31	> 99
4	>100.31	>99
5	23.74	18.79
6	128.58	59.35
7	885.26	417.94
8	254.05	124.62
9	24.3	17.18
10	32.11	13.26
11	13.63	10.77
12	6.48	3.27
13	15.99	8.54
14	18.98	11.93
15	7.33	2.94
16	9.77	4.5
17	15.23	7.45
18	0.97	0.62
19	0.74	0.37
20	3.86	2.34
21	3.84	2.6
22	2.18	2.58
23	19.74	11.26
24	12.7	8.94
25	10.79	7.69
26	10.32	6.57
27	57.41	56.11

pounds provided a preliminary guidance for the selection of the functional feature for development of the pharmacophoric model. Pharmacophore generation was

TABLE II. Estimated and experimentally determined (*P. falciparum* D6 strain) IC_{50} (ng/ml) values of the training set compounds

Training set	IC_{50} (expt.)	IC_{50} (predicted)	Error[*]
18	0.97	2.3	2.4
27	57.4	52.0	-1.1
6	128.6	69.0	-1.9
16	9.77	4.1	-2.4
7	885.3	210.0	-4.2
8	254.0	210.0	-1.2
5	23.7	72.0	3.0
10	32.1	30.0	-1.1
9	24.3	15.0	-1.6
1	100	70.0	-1.4
11	13.6	52.0	3.8
Artemisinin	4.7	8.2	1.7
Arteether	2.7	4.5	1.7
19	0.74	2.3	3.1
23	19.7	5.4	-3.6
28	1000	450	-2.2
29	38.0	79.0	2.1

[*]Values in the error column represent the ratio of the estimated activity to measured activity, or its negative inverse if the ratio is less than one.

carried out by setting the default parameters in the automatic generation procedure in CATALYST such as function weight 0.302, mapping coefficient 0, resolution 280 pm, and activity uncertainty 3. An uncertainty "Δ" in the CATALYST paradigm indicates an activity value lying somewhere in the interval from "activity divided by Δ" to "activity multiplied by Δ". The statistical relevance of the obtained pharmacophore is assessed on the basis of the cost relative to the null hypothesis and the correlation coefficient. The pharmacophores are than used to estimate the activities of the training set. These activities are derived from the best conformation generation mode of the conformers displaying the smallest root-mean square (RMS) deviations when projected onto the pharmacophore. HypoGen considers a pharmacophore that contains features with equal weights and tolerances. Each feature (*e.g.*, hydrogen-bond acceptor, hydrogen-bond donor, hydrophobic regions, positive ionizable group, *etc*.) contributes equally to estimate the activity. Similarly, each chemical feature in the HypoGen pharmacophore requires a match to a

corresponding ligand atom to be within the same distance of tolerance.[10] The method has been documented to perform better than a structure-based pharmacophore generation.[11]

Docking calculations

Docking calculations were performed on the tetraoxanes with heme using the Affinity module of the Insight II package,[12] adopting the ESFF (electrostatic force field) force field for assigning the potentials of both the ligands and heme. Affinity is a suite of programs in Insight II for automatic docking of a ligand (guest–**19** or **24**) to a receptor (host–heme). For a given assembly consisting of a ligand molecule and a receptor molecule, docking procedures in Affinity find out the best binding structures of the ligand to the receptor based on the energy of the ligand/receptor complex. This is an energy-driven method[13] that is particularly useful in structure-based drug design where the experimentally determined structure of a protein–ligand complex is unavailable.

The methodology in Affinity uses a combination of Monte Carlo type and simulated Annealing procedures to dock the guest molecule to the host. A key feature is that the "bulk" of the receptor, defined as atoms not in the binding (active) site specified, is held rigid during the docking process, while the binding site atoms and ligand atoms are movable. Non-bonded interactions can be calculated in many different ways: a grid based approach developed by Luty *et al.,*[14] a cell multipole approach, a group based cutoff approach, or a hard sphere steric method without electrostatics. Furthermore, Affinity allows incorporation of solvation effects by the method of Stouten *et al.*[15] In addition to the non-bonded interactions, various empirical penalty terms, a distance based H-bond term, a ligand confining term and a simple tethering term are included to aid in the process of docking.

The method offers a very flexible and powerful docking protocol that comprises elements from Monte Carlo, Simulated Annealing and Minimization. We present here an overview of how we have carried out the procedure. Firstly, a roughly docked complex of **19** and its derivative were prepared with heme. Affinity then performs an energy minimization to obtain the starting structure. This step was designed to remove bad contacts and poor internal geometry in the initial structure and to obtain a reasonable starting point for subsequent searches.

The ligand is then moved by a random combination of translation, rotation, and torsional changes. The random movement of the ligand represents both the conformational space of the ligand and its orientation with respect to the receptor. This has the advantage of overcoming any energy barrier on the potential energy surface. Subsequently the method checks the energy of the resulting randomly moved structure. If it is within the our specified energy tolerance parameter of the previous minimized structure, it is considered to have passed the first step and the structure is then subjected to energy minimization, the second step for fine-tuning

the docking. The final minimized structure is accepted or rejected based on the Metropolis energy criterion as implemented in the software and its similarity to structures found before. The Metropolis criterion is found to be best suited for finding a very small number of docked structures with very low energies, while the other energy range criterion is designed for finding more and diverse structures. In checking structure similarity, the RMS distances between the current structure and structures found so far are computed for ligand atoms. Since the Affinity module has the ability to employ different docking methodologies, such as simulated annealing and dynamics in conjunction with Monte Carlo minimization, after generating initial structures by the above method, we have further refined these structures with these procedures.

RESULTS AND DISCUSSION

3D-QSAR pharmacophore development and statistical analysis

The 3D-QSAR pharmacophore model for antimalaral activity of the steroidal tetraoxanes was found to have two hydrogen bond acceptor (lipid) functions and one hydrophobic function at a specific geometric location in 3D space (Fig. 1). It was developed from a set of 17 substituted steroidal tetraoxanes out of 27 derivatives including the parent compound, artemisinin, arteether, and two other tetraoxanes as shown in Scheme 1. The biological activity of the 17 compounds covers a wide range of activity, ranging from an IC_{50} of 0.74 ng/mL to 1000 ng/mL. Although two *P. falciparum* malaria parasite clones, designated as Sierra Leone (D6) and Indochina (W2) were used in the susceptibility testing, we used the IC_{50} values obtained from the D6 clones as the activity parameter to develop the pharmacophore model since the W2 clone results closely paralleled the D6 clones.

The pharmacophore was developed using the CATALYST[9] methodology by placing suitable constraints on the number of available features such as aromatic hydrophobic or aliphatic hydrophobic interactions, hydrogen bond donors, hydrogen bond acceptors, hydrogen bond acceptors (lipid), ionizable sites, aromatic ring sites, and excluded volume to describe the antimalarial activity of the tetraoxane
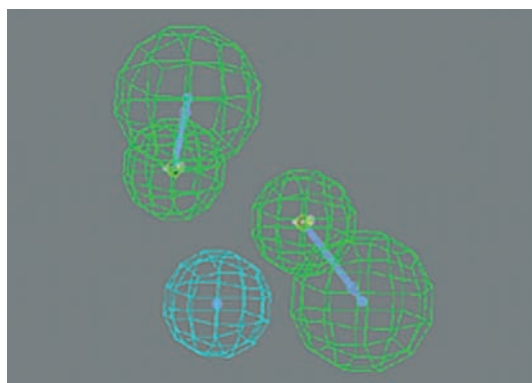

Fig. 1. Pharmacophore for antimalarial activity of the steroidal tetraoxanes; two hydrogen bond acceptor functions (green) and one aliphatic hydrophobic function (light blue).
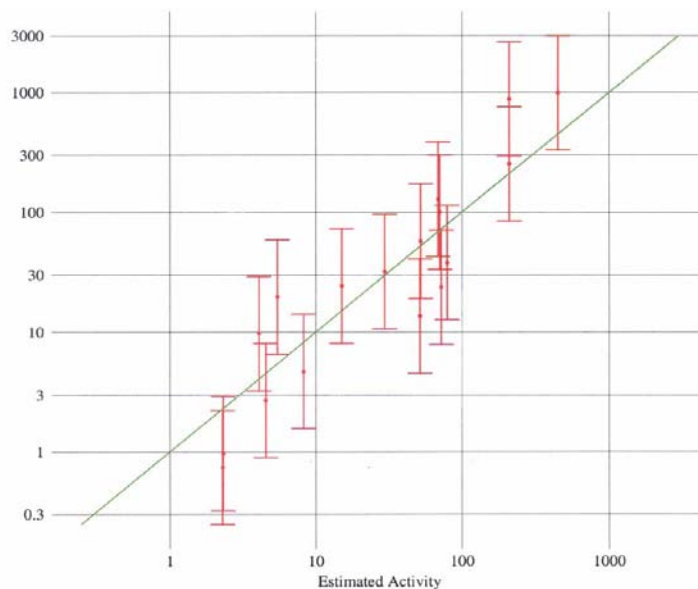
Fig. 2. Correlation ($R = 0.91$) line displaying the observed *versus* estimated IC_{50} values (ng/mL) of the training set by using the statistically most significant hypothesis derived from the W2 activities.

compounds. Quantum chemical calculations on the stereoelectronic properties of a few of these compounds provided guidance for selection of these physico-chemical features. During pharmacophore development, the molecules were mapped to the features with their predetermined conformations generated using the "fast fit" techniques in the CATALYST. The procedure resulted in the generation of 10 alternative pharmacophores for antimalarial activity of the compounds and appeared to perform quite well for the training set. The correlation coefficients were found to be between 0.91 and 0.86 for the ten models, and the RMS values ranged between 0.76 and 0.93. The total costs of the pharmacophores varied over a narrow range between 79.9 and 81.4 bits. The fixed cost and the null cost for the generation of the hypothesis are found to be 73.9 and 85.8, respectively, satisfying the acceptable range recommended in the cost analysis of the CATALYST procedure. However, due to the low cost range between the first and the tenth model it can be expected that there is high probability of representing a true correlation of the data. Significantly, the best pharmacophore characterized by two hydrogen bond acceptor (lipid) functions and one hydrophobic function (Fig. 1) is also statistically the most relevant pharmacophore. The estimated activity values along with the experimentally determined IC_{50} values for antimalarial activity of the compounds are presented in Table II. A plot of the experimentally determined IC_{50} values versus the calculated activities demonstrates a good correlation ($R = 0.91$) within the range of uncertainty 3, indicating the predictive power of the pharmacophore (Fig. 2). The
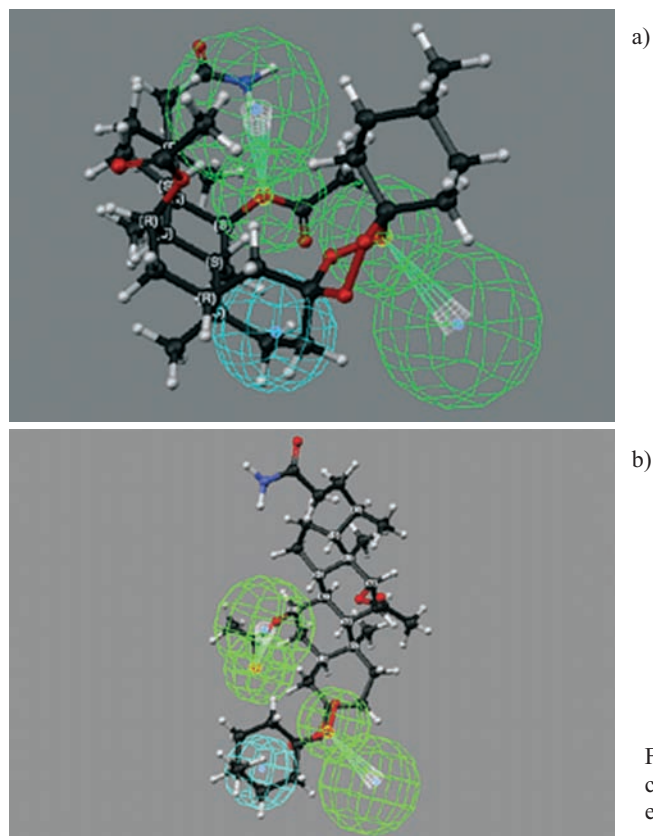
Fig. 3. Mapping of the pharma-
cophore on more potent analogu-
es: (a) **19** and (b) **24**.

highly potent analogues of the series map all the functional features of the best hy-
pothesis with high scores, whereas the less potent compounds either do not map at
all or map fewer of the features. For example, the more potent analogs of the train-
ing set such as **19** and **24** map well with the statistically most significant pharma-
cophore (Fig. 3a and 3b), whereas the less potent analogues such as **7** and **8** do not
map in the same way as the more potent compounds (Fig. 4a and 4b). It appears
that one of the hydrogen bond acceptors has to be mapped on an oxygen atom of
the tetraoxane moiety in order to be potent. In **7** and **8**, although the features of the
pharmacophore map on the molecule, none of the two hydrogen bond acceptors
map on any of the oxygen atoms of the tetraoxane oxygen moiety and perhaps due
to this inadequacy these two tetraoxanes are not as potent as the others.

To cross-validate the observed correlation we prepared a "test" set of 14 addi-
tional substituted tetraoxanes from the stockroom (Table III, Scheme 1) that were
tested for *in vitro* antimalarial activity against D6 and W2 clones of *P. falciparum*
identical to the original training set. However, this set of compounds was not used
for automatic generation of the pharmacophore and thus, was not used in determin-
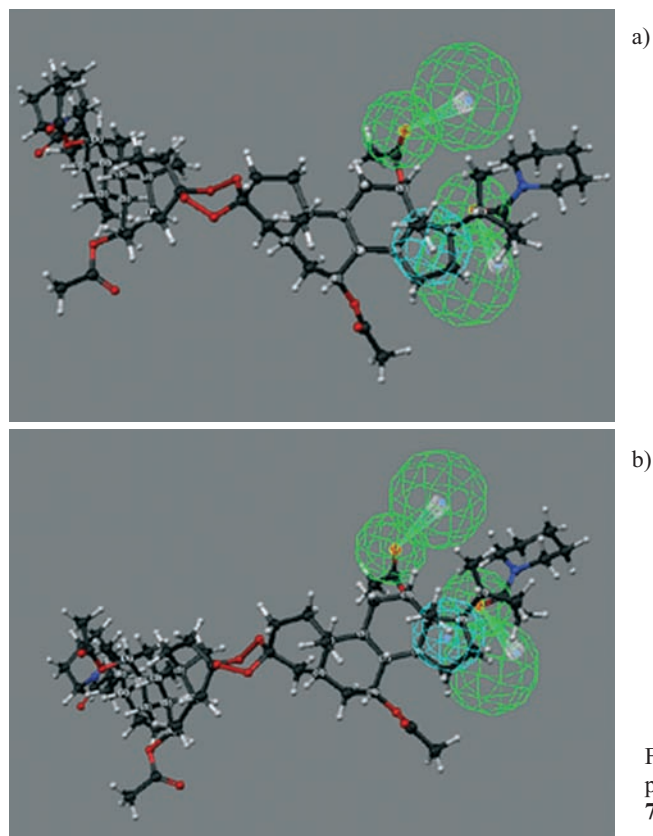ing the features of the pharmacophore generated in the original training set.

Fig. 4. Mapping of the pharmacophore on less potent analogues: (a) **7** and (b) **8**.

A fairly modest correlation ($R = 0.78$) was observed when a regression analysis was performed by mapping this test set onto the features of the pharmacophore (Fig. 5). The estimated and the measured IC_{50} values for the test set tetraoxanes along with the respective error ratios are also shown in Fig. 5 and Table III. The actual activity values are within the limits of uncertainty 3 (Table II), thus demonstrating the predictive power of the original pharmacophore. As observed in the training set, the more potent analogues of the test set such as **21** and **22** map well with the pharmacophore, whereas the less potent analogues of the test set do not map adequately.

TABLE III. Estimated and experimentally determined (*P. falciparum D6 strain*) IC_{50} (ng/ml) values of the test set compounds

Test set	IC_{50} (expt.)	IC_{50} (predicted)	Error*
2	99.9	70.0	-1.4
4	100.3	49.0	-1.1
13	16.0	6.3	-2.5
15	7.3	22.0	3.1

TABLE III. Continued

Test set	IC$_{50}$ (expt.)	IC$_{50}$ (predicted)	Error*
20	3.8	2.3	-1.7
22	2.2	2.3	1.0
25	10.8	4.4	-2.5
3	100.2	49.0	-2.0
12	6.5	2.3	-2.8
14	19.0	48.0	2.5
17	15.2	24.0	1.6
21	3.8	2.3	-1.7
24	12.7	4.8	-2.7
26	10.3	51.0	4.9

*Values in the error column represent the ratio of the estimated activity to measured activity, or its negative inverse if the ratio is less than one.
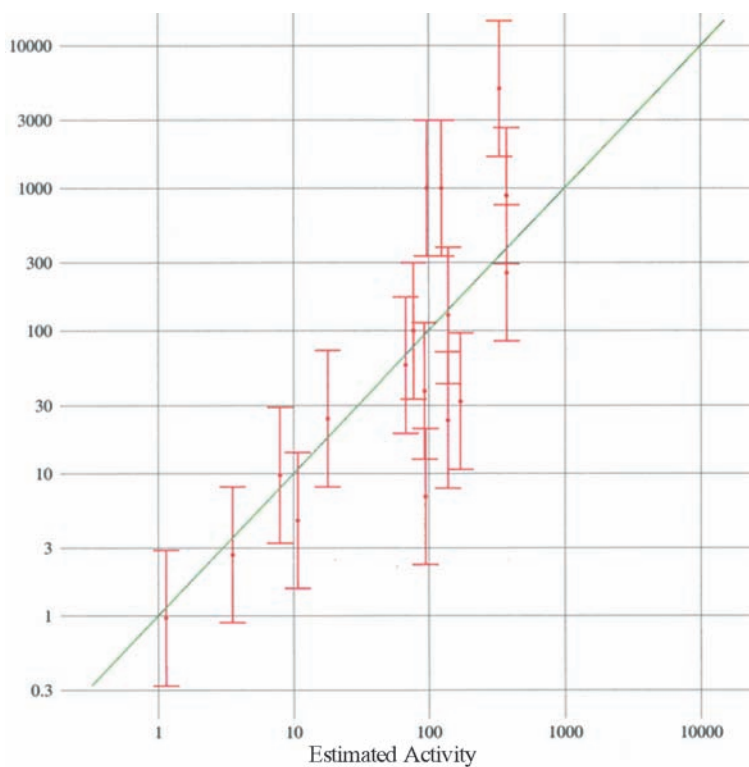
Fig. 5. Correlation ($R = 0.78$) line displaying the observed *versus* estimated IC$_{50}$ values (ng/mL) of the test set compounds by regressing the pharmacophore.
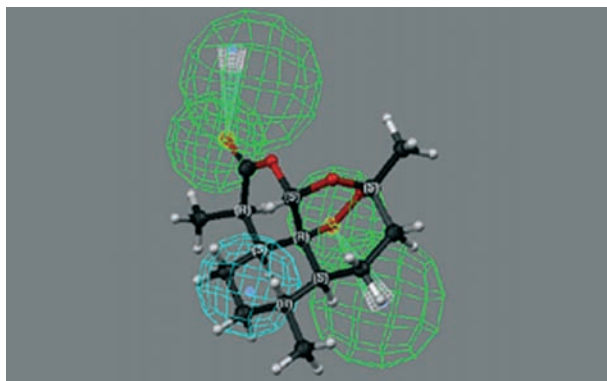
Fig. 6. Mapping of the pharmaco-
phore on artemisinin.
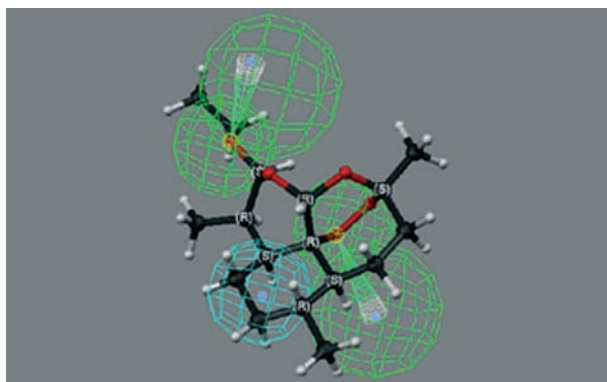
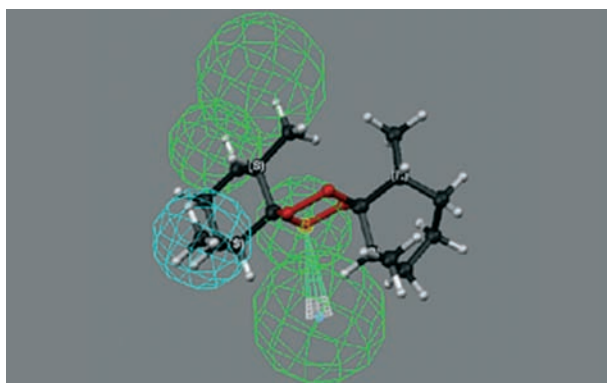Fig. 7. Mapping of the pharmaco-
phore on arteether.

Fig. 8. Mapping of the pharmaco-
phore on tetraoxane **28**.

To examine the validity of the pharmacophore against other trioxanes and tetraoxane containing antimalarials and to derive some insights about the possible target of action of the compounds, its features were mapped onto artemisinin (Fig. 6), arteether (Fig. 7), and on a tetraoxane, **28** (Fig. 8). Surprisingly, artemisinin and arteether map completely with the pharmacophore (Figs. 6 and 7) including one hydrogen bond acceptor feature on an oxygen atom of the trioxane moiety, whereas the tetraoxane does not map all the features. Interestingly, **28** is the least potent antimalarial of this series.

Docking calculations and analysis of the results

In order to better understand the mechanism of action of these tetraoxanes, we performed docking calculations with heme to assess the role of electron transfer in the compounds. By adopting the docking procedure as implemented in the affinity module of InsightII,[12] we calculated the minimum energy of the heme–compound docked structures of the two more potent analogues such as **19** and **24** and two less potent analogues such as **7** and **8**. The minimum energy values of the heme docked structures are as follows: **19** = –601.3, **24** = –461.0, **7** = –83.7, and **8** = –192.2
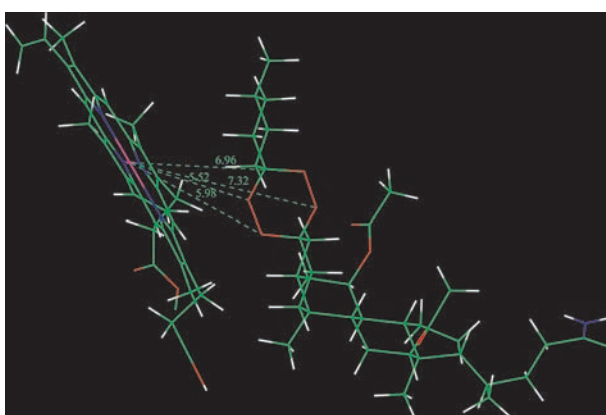
Fig. 9. Docked heme–19 structure.
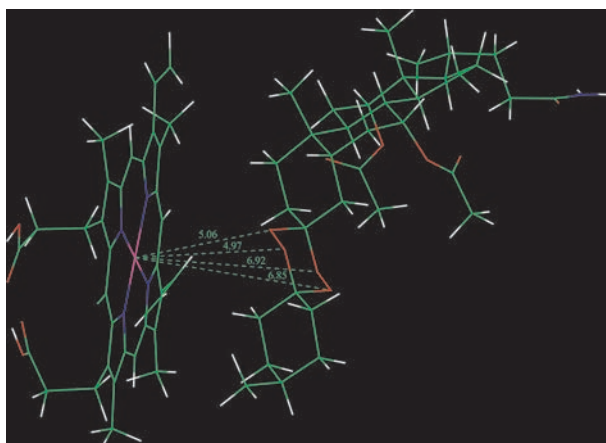
Fig. 10. Docked heme–**24** structure.
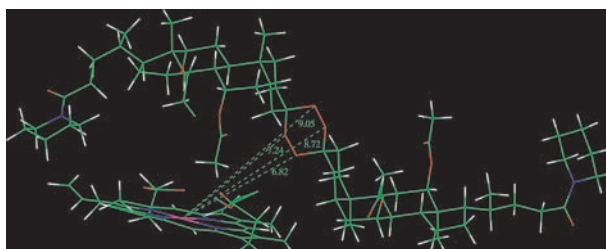
Fig. 11. Docked heme–**7** structure.

kJ/mol, respectively. Clearly, the more potent analogues have much lower energy minimized docked structures. Although the van der Waals contribution toward the interaction between **19** and **24** with heme was found to be approximately the same (152.4 kJ/mol), the electrostatic contribution of **19** toward the interaction is found to be significantly greater (-754.5 kJ/mol) than **24** (-625.5 kJ/mol). The average distance between Fe^{2+} and the oxygen atoms of the tetraoxane moiety in these docked structures were found to be 5.7 Å for **19**, 6.2 Å for **24**, 8.0 Å for **7**, and 10.1 Å for **8** (Figs. 9–12). These results suggest that proximity of the tetraoxane oxygen atoms to the heme iron (Figs. 9 and 10) may favor potent antimalarial activity of these compounds.
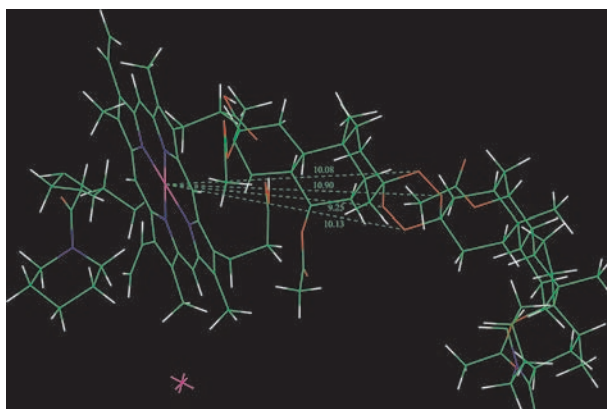

Fig. 12. Docked heme–8 structure.

We have also investigated the role of the peroxide bonds toward activity by calculating the hemolytic scission energy of the peroxide bonds on the optimized geometry of **19** and **24**. Triplet spin multiplicity state was used to calculate the total energy of this radical species at UHF/3-21G* (unrestricted split valence basis) level of quantum theory as described in an earlier study.[16] Calculations at higher levels of quantum theory, such as the UHF/6-31G** level could not be accomplished due to the large size of the molecules. However, our calculations using the UHF/3-21G* basis function indicate that compound **19** requires 30.6 kJ/mol less energy for scission of one of its peroxide bonds than **24** conforming to the observation that **19** is more reactive than **24** probably due to facile electron transfer from the peroxide oxygen atom of one of its peroxide bonds.

CONCLUDING REMARKS

The study organizes the molecular characteristics of a set of diverse steroidal tetraoxane derivatives that is both statistically and mechanistically significant for potent antimalarial activity and provides insight into a possible mechanism of action of the compounds to guide the search and synthesis for new compounds. In addition, the QSAR model unravels a possible rationale for the target-specific antimalarial activity of these compounds. The chemically significant molecular

characteristics disposed in a three dimensional space generated a pharmacophore that is found to be quite satisfactory in correlating true activity with the predicted activity of the compounds. Two hydrogen bond acceptors and one aliphatic hydrophobic site appear to be the required functional features for potent antimalarial activity of the compounds. A hydrogen bond acceptor function on at least one oxygen atom of the trioxane or the tetraoxane moiety appears to be crucial for potent activity. The observation is also consistent with the docking experiments which demonstrate that the proximity of these oxygen atoms to the iron of the heme is an important criterion for potent activity and electron transfer from tetraoxane oxygen is perhaps a key step in the mechanism of action of this class of compounds. The validity of the pharmacophore extends to structurally different classes of trioxanes and tetraoxanes, and thus provides a powerful template from which novel drug candidates may be identified for extended study. Since the identity of the target for antimalarial activity of the tetraoxanes remains unknown, this three-dimensional QSAR pharmacophore should aid the design of well-tolerated target-specific peroxide containing antimalarial agents.

И З В О Д

QSAR ИЗУЧАВАЊЕ СТЕРОИДНИХ 1,2,4,5-ТЕТРАОКСАНСКИХ АНТИМАЛАРИКА РАЧУНАРСКИМ МОДЕЛОВАЊЕМ

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Извршено је тродимензионално моделовање фармакофоре за антималаријску активност стероидних 1,2,4,5-тетраоксана на основу структура 17 супституисаних деривата, издвојених из групе од 27 аналога који показују изузетну *in vitro* антималаријску активност (испод 100 ng/mL) према осетљивим и резистентним сојевима *Plasmodium falciparum*-а. Утврђено је да се фармакофора, коју чине два акцептора водоничне везе (липидни) и једно хидрофобно место (алифатично), добро преклапа са структурама активних аналога као и са структурама неких познатих триоксанских антималарика, укључујући артемизинин, артеетар, артесунатну киселину као и са структурама неких других тетраоксана. За добру активност ове класе једињења важно је присуство бар једног акцептора водоничне везе на триоксанском или тетраоксанском делу структуре. Израчунавања интеракција неких од ових једињења са хемом сагласна су са претходно изнетим закључком да је близина гвожђа из хема и триоксанског или тетраоксанског атома кисеоника важна за добру активност ових једињења. Изгледа да је пренос електрона са триоксанског или тетраоксанског атома кисеоника основа механизма

дејства ових једињења. Извршена моделовања фармакофоре и интеракција ових једи-
њења се хемом могу бити од помоћи у синтези нових и ефикаснијих пероксидних
антималарика.

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