BIOINFORMATION
Discovery at the interface of physical and biological sciences

open access www.bioinformation.net Hypothesis

Volume 8(8)

Molecular modeling and evaluation of binding mode and affinity of artemisinin-quinine hybrid and its congeners with Fe-protoporphyrin-IX as a putative receptor

Rajani Kanta Mahapatra[1, 2]*, Niranjan Behera[1] & Pradeep Kumar Naik[3]

[1]School of Life Sciences, Sambalpur University, Burla, Odisha-768019, India; [2]School of Biotechnology, KIIT University, Bhubaneswar, Odisha-751024, India; [3]Department of Biotechnology & Bioinformatics, JUIT, Solan, Himachal Pradesh-173 215, India; Rajani Kanta Mahapatra – Email: rmohapatra@kiitbiotech.ac.in; *Corresponding author

Received April 10, 2012; Accepted April 16, 2012; Published April 30, 2012

Abstract:
A recent rational approach to anti-malarial drug design is characterized as ''covalent biotherapy'' involves linking of two molecules with individual intrinsic activity into a single agent, thus packaging dual activity into a single hybrid molecule. In view of this background and reported anti malaria synergism between artemisinin and quinine; we describe the computer-assisted docking to predict molecular interaction and binding affinity of Artemisinin-Quinine hybrid and its derivatives with the intra-parasitic haeme group of human haemoglobin. Starting from a crystallographic structure of Fe-protoporphyrin-IX, binding modes, orientation of peroxide bridge (Fe-O distance), docking score and interaction energy are predicted using the docking molecular mechanics based on generalized Born/surface area (MM-GBSA) solvation model. Seven new ligands were identified with a favourable glide score (XP score) and binding free energy (ΔG) with reference to the experimental structure from a data set of thirty four hybrid derivatives. The result shows the conformational property of the drug-receptor interaction and may lead to rational design and synthesis of improved potent artemisinin based hybrid antimalarial that target haemozoin formation.

Keywords: Artemisinin-Quinine Hybrid, Molecular Docking, Fe-O Distance, Binding Affinity

Background:
Malaria is a non-contagious disease of chronic evolution that manifests in acute episodes **[1]**. Currently, millions of people in the tropical and subtropical zones of the world are affected by malaria **[1]**. The malaria parasite manifests disease condition only during its blood stage in its lifecycle. This part occurs largely within the red blood cell of the human host **[1],** where it digests a major proportion of the red cell haemoglobin **[2].** It has been demonstrated that *Plasmodium falciparum*, the causative agent of almost all fatal cases of malaria, detoxifies host haemoglobin-derived ferriprotoporphyrin IX (Fe (III) PPIX) in an acidic digestive vacuole (DV) mainly by converting it to haemozoin **[2].** Fe (III) PPIX produced by autoxidation of haeme (Fe (II) PPIX) released from haemoglobin is known to be capable of causing lipid peroxidation **[2]** and to destabilize membranes through a colloid osmotic mechanism **[2]**. Packaging Fe (III) PPIX into compact and highly insoluble haemozoin crystals decreases its pro-oxidant capacity **[3]** and likely also avoids colloid osmotic effects. Haemozoin is now known to be a crystalline cyclic dimer of Fe(III)PPIX in which the propionate group of one porphyrin moiety coordinates to the Fe(III) center of its partner and vice versa, while the second

propionic acid group of each Fe(III)PPIX hydrogen bonds to a neighbouring dimer in the crystal **[3]**.

The widely used quinoline drugs chloroquine, quinine, and mefloquine, as well as amodiaquine and the nonquinoline drugs such as halofantrine and lumefantrine are known to act against the blood stages of the infection by inhibiting detoxification of Fe (III) PPIX into haemozoin, resulting in a build-up of toxic Fe (III) PPIX **[2, 4]** and artemisinin cause a similar effect by reacting with haeme (FeII-protoporphyrin IX) to give free radicals and adducts **[5, 6]**. The artemisinins are the most effective antimalarial drugs with a remarkable therapeutic index **[6]**. As a fact World Health Organisation (WHO) has advocated the policy of Artemisinin-based combination therapy (ACTs) for treating *P.falciparum* malaria **[6]**. The rationale for this combination is that the artemisinin derivative rapidly clears 95% of the parasites and the remaining 5% are cleared by the longer half-life partner drug and thus the risk of recrudescence is minimized. Because of the paucity of promising novel antimalarial drugs under development and fear of loss of the artemisinin to resistance, in malaria drug combination therapy, the current trend is to co-formulate two or more agents into a single tablet, as a multicomponent drug **[7].** However, based on the wide interest in the hybrid molecules as well as numerous encouraging efficacy and toxicity reports, the next generation antimalarial may well be hybrid drugs as opposed to multicomponent ones. There are numerous advantages of employing hybrid molecules over multicomponent drugs in malaria therapy. Compared to the latter, hybrid drugs may be less expensive since, in principle, the risks and costs involved may not be different from any other single entity. Another advantage is that of the lower risk of drug–drug adverse interactions compared to multicomponent drugs **[7]**.

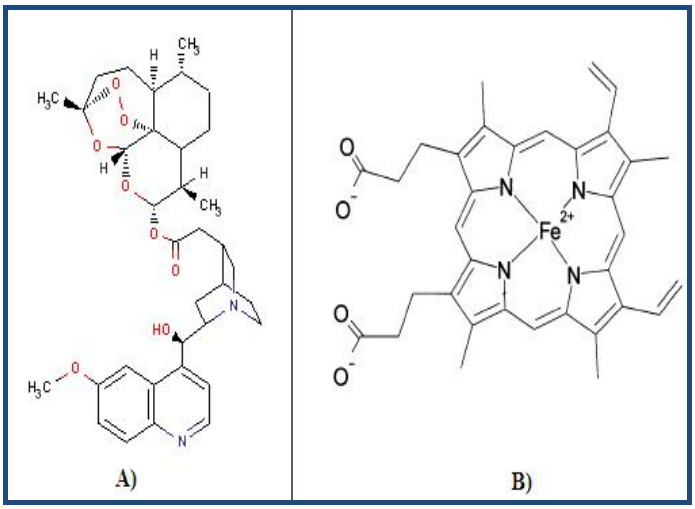


Figure 1: A) 2D molecular structure of Dihydroartemisinin-Quinine hybrid; **B)** 2D structure of Haeme

The mechanism of action of any drug is very important in drug development. Generally, the drug compound binds with a specific target, a receptor, to mediate its effects. Therefore, suitable drug–receptor interactions are required for high activity. Understanding the nature of these interactions is very significant and theoretical calculations, in particular the molecular docking method, seem to be a proper tool for gaining such understanding. The docking results obtained will give information on how the chemical structure of the drug should be modified to achieve of new and more effective drugs. As a proof-of-concept and the reported antimalarial synergism between artemisinin/other endoperoxides and quinine, we conceptualize to evaluate *in silico* the molecular interaction and binding affinity of a covalently linked artemisinin–quinine hybrid in which the vinyl functionality of quinine was modified to allow for the attachment of dihydroartemisinin **(Figure 1A)** with intra-parasite prosthetic haeme group of human haemoglobin **[8]**.The rationale behind the design was to address the fact that artemisinin is lipophilic, fast-acting but quickly eliminated drugs that is associated with high rates of recrudescence when used in monotherapy **[9]**. It was suggested that coupling of the slow-acting, relatively polar quinine derivative might increase the half-life of the artemisinin moiety. Current research in this field seems to endorse hybrid molecules as the next-generation antimalarial drugs **[10].**

Methodology:

Preparation of protein

Studies on the mode of action of artemisinin and its derivatives have shown that free haeme could be the molecule targeted by artemisinin in biological systems **[11-15].**Similarity spectrophotometric study revealed that quinine and related antimalaria drugs interact with Ferriprotoporphyrin-IX **[16]**.

So the X-ray structure of halofantrine-Ferriprotoporphyrin-IX (CCDC_659633) from the Cambridge Crystallographic Data Centre is used as initial structure in the preparation receptor binding site **[17].** Ferriprotoporphyrin-IX is a planar molecule with a strong positive charge on its central iron atom **(Figure 1B)**. After removal of halofantrine structure, the charge on the iron was assigned as +2 but the structure was kept the same. Hydrogen's were added to the model automatically via the Maestro interface **[18]** leaving no lone pair and using an explicit all-atom model. The multi-step Schrödinger's protein preparation tool (PPrep) was used for final preparation of receptor model. The complex structure was energy minimised using the OPLS-2005 force field and the conjugate gradient algorithm, keeping all atoms except hydrogen fixed. The minimisation was stopped either after 1000 steps or after the energy gradient converged below 0.01 KJ/mol.

Virtual library design

The virtual library of Artemisinin-Quinine hybrid analogues contain 34 compounds divided into nine sub libraries. All these compounds are taken from various sources belonging to different derivatives of Artemisinin and Quinine **[19-26]**.The following physiochemical parameters are considered for design of Artemisinin -Quinine hybrid derivatives. **(Table 1a-1h, see supplementary material)**.

Log P (partition coefficient)

The logP value of Artemisinin-Quinine-OH hybrid is estimated to be 5.57. In view of background; the logP value is set to be in the range of 4.5-6.10 **[27]**.

Molecular weight

The molecular weight of the hybrid molecule is estimated to be 622.74 g/mol. So the molecular weight kept below 650 g/mol to enhance the membrane permeability **[28].**

H-bond donor and acceptor
In designing inhibitor with reference to hydrogen bond donor and acceptor we have refereed to 'Lipinski rule of 5' which state that hydrogen bond donor and acceptor should not be more than 5 and 10 respectively **[29, 30].**

Sub lib-I:
Dihydroartemisinin-Quinine Hybrid-This library consist of only of one ligand. The structure is designed experimentally in which the vinyl functionality of quinine was modified to allow for the attachment of dihydroartemisinin.

Sub lib-II:
Artemisinin-Quinine Hybrid - This library consists of five ligands which are designed by attachment of Quinine moiety to the Artemisinin molecule at O-14.

Sub lib-III:
C9 Artemisinin-Quinine Hybrid- This library consists of two ligands in which the C9 substituted Artemisinin entity is attached to Quinine at O-14 position.

Sub lib-IV:
C3 Artemisinin-Quinine Hybrid- C3 substituted Artemisinin derivatives are attached to Quinine moiety and two hybrids are present in this sub library.

Sub lib-V:
C10 Artemisinin-Quinine Hybrid- This library consist of five ligands in which the C10 carbon atom of Artemisinin is modified and Quinine molecule is attached to it at C9 carbon atom.

Sub lib-VI:
Seco Artemisinin-Quinine Hybrid-This library is having three ligands (16-18) with logP in the range from 5.22 to 5.79.The Quinine molecule is attached to the seco artemisinin entity at C9 carbon atom.

***Sub lib-VII*:**
Miscellaneous Artemisinin-Quinine Hybrid- This library consists of four ligand in which various substitution in different carbon atom of Artemisinin molecule are attached to the Quinine entity.

Sub lib-IX:
Quinoline-Artemisinin Hybrid-Quinoline-Artemisinin sub library is having twelve ligands in which the various substitutions at quinoline ring of the Quinine molecule is attached to artemisinin phramacophore.

We used ISIS Draw 2.3 software for sketching structure and converting it its 3D representation by using ChemSketch 3D viewer of ACDLABS 12.0. LigPrep was used for final preparation of ligands from libraries for docking. LigPrep is a utility of Schrodinger software suit that combines tools for generating 3D structures from 1D (Smiles) and 2D (SDF) representation, searching for tatutomers and steric isomers and perform a geometry minimization of ligands. The ligands were minimized by means of Molecular Mechanics Force Fields (OPLS-2005) with default setting.

Docking procedure
It is quite important to have an accurate model for the haeme-Art-Qui-OH complex, because this knowledge can be used to design better and more potent antimalarial. The Schrodinger Glide program version 4.0 has been used for docking. After ensuring that receptor and ligand are in the correct form for docking, the receptor-grid file was generated using a grid-receptor generation program. The default size was used for the bounding and enclosing boxes. The grid box was generated at the centroid of the haeme. The ligands were docked initially using the 'standard precision' method. The best 10 poses and corresponding scores have been evaluated using Glide in single precision mode (Glide SP) .The pose with the lowest Glide SP score has been taken as the input for the Glide calculation in extra precision mode (Glide XP). To soften the potential for non-polar parts of the receptor, we scaled van der Waals radii of receptor atoms by 1.00 with partial atomic charge 0.25.

The docked poses were minimized using the local optimization feature in Prime and the energies of complex were calculated using the OPLS-AA force field and generalized-Born/surface area (GB/SA) continuum solvent model. The binding free energy (ΔG_{bind}) is then estimated using equation **[31]**.

$$\Delta G_{bind} = E_{R:L} - (E_R + E_L) + \Delta G_{solv} + \Delta G_{SA} \quad (1)$$

Where $E_{R:L}$ is energy of the complex, $E_R + E_L$ is sum of the energies of the ligand and unliganded receptor, using the OPLS-AA force field, ΔG_{solv} (ΔG_{SA}) is the difference between GBSA solvation energy (surface area energy) of complex and sum of the corresponding energies for the ligand and unliganded protein. Corrections for entropic changes were not applied in this type of free energy calculation.

Discussion:
Early reports have revealed that *P. falciparum* 3D7 strain growth was inhibited by much lower concentrations of the hybrid than that of quinine or artemisinin alone. This suggested that the actions of both quinine and artemisinin moieties were preserved. Moreover, when the activity of the hybrid was compared with that of a 1:1 mixture of quinine and artemisinin (on a mol quinine/mol artemisinin basis), the hybrid was about 3 fold superior. Similar results were obtained with the chloroquine-resistant strain FcB1 **Table 2 (see supplementary material**).

Prompted by the experimental study; a set of Artemisinin-Quinine hybrid with its 34 analogous structures have been computationally analyzed by molecular docking simulation to identify new analogues that have a similar mechanism of action yet superior activity. Glide 4.0 **[32]** in XP mode has been used to dock the library (I–IX) of Art-Qui-OH with the putative receptor Fe-PPIX. Interaction of Art-Qui-OH and its derivatives with Fe (II) PPIX (Iron (II)) involves binding between the endoperoxide bridges (O1 and O2) bridge of the hybrid to the front of the iron bridge of protoporphyrin-IX shown in **(Figure 2).**

The XP score of the experimental structure; dihydroartemisinin-quinine compound is computed to -7.485 kcal/mol. Out of 34 derivatives; seven novel ligands among the library; two from C3-Artemisinin-Quinine hybrid, three from C10-Artemisinin-Quinine hybrid and two from Miscellaneous Artemisinin-

Quinine hybrid have better Glide score. Previous studies showed that interactions between peroxide linkage in artemisinin compounds and haeme iron play major role in the binding mode, therefore, distances between haeme iron and two peroxide oxygen's; O1, O2 as well as O11 and O13 and ΔG_{bind} of these seven derivatives were monitored.

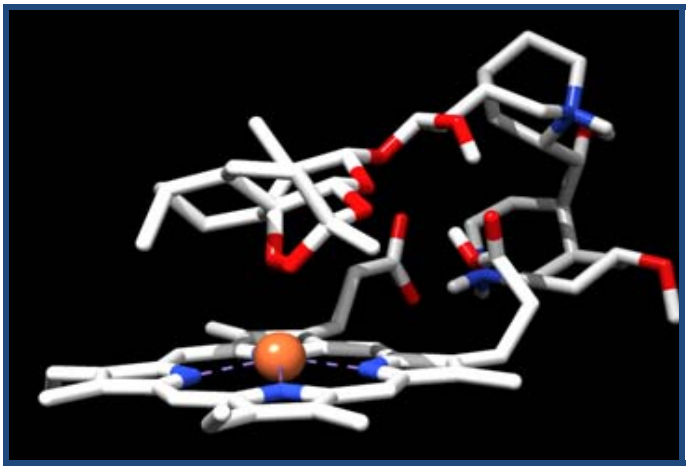


Figure 2: Representative docking Fe-(O1-O2) interaction of Dihydroartemisinin-Quinine hybrid with Fe-(II) PPIX as a putative receptor

For each of the seven ligands, the pose with the lowest Glide score was rescored using Prime/MM-GBSA approach. This approach is used to predict the free energy of binding for set of ligands to receptor. The ΔG_{bind} energies among the ligands vary in between -49.00 to-32.35 kcal/mol. The calculated relative binding energy ($\Delta\Delta G_{bind\text{-}cald}$) of the ligands was also obtained by using Art-Qui-OH as reference. The drop in calculated relative binding energy of the ligand provides a favourable energetic evaluation of the binding affinity **Table 3 (see supplementary material**).

In any binding energy calculation, the correct binding structure of each ligand has to be determined first prior to binding energy estimation. Excluding only one structure from C10 Artemisnin-Quinine hybrid; in other docking configuration it was observed that artemisinin moiety of the hybrid prefers to dock at endoperoxide oxygen's (O1 and O2), with O2–Fe as the shortest haeme–artemisinin distance and O1–Fe as the second shortest distance. Configuration of dihydroartemisinin-quinine hybrid had the peroxide oxygen O1 and O2 close to the haeme iron (3.273 Å & 2.817 Å) with O11 and O13 atom further removed (5.071 Å & 5.149 Å). The ΔG_{bind} value of the structure is -32.35 kcal/mol. Configuration of ligand 9 and 10 of C3-Artemisnin-Quinine hybrid series were almost identical. In both the cases O1 (3.281 and 3.282 Å) and O2 (2.817 and 2.825 Å) were closest, with other oxygen atom being further away: O11 (4.867 and 4.951 Å) and O13 (5.125 and 5.172 Å). The docked configuration of ligand 11 of C10 Artemisinin-Quinine hybrid the binding with the endoperoxide moiety of artemisinin is in a different configuration, and a stronger O11–Fe attraction is resulted (3.812 Å) than O1, O2 and O13 (6.487 Å, 6.176 Å and 5.325 Å). The relative binding energy ($\Delta\Delta G_{bind\text{-}cald}$) of the ligand is calculated to be -10.13 kcal/mol. Such deviation may be explained on the basis of stereochemistry of artemisinin analogues that is controlled by steric hindrance. The analogues which approach the haeme-iron as close as possible will have better interaction and thus a good glide score. However, owing to the planar structure of the Ferriprotoporphyrin-IX, the repulsion between artemisinin and the protoporphyrin ring prevents artemisinin from approaching haeme-iron. Ligand 12 and 14 of this group produce final orientation with a relative binding energy $\Delta\Delta G_{bind\text{-}cald}$ of -11.76 Kcal/mol and -5.08 kcal/mol. Both the configuration involved interaction of the peroxide-derived oxygen with the Fe atom of protoporphyrin-IX. In the most favourable configuration between haeme and miscellaneous Artemisinin-Quinine hybrid with a Gscore of -8.913 kcal/mol (the lowest), the iron is between 3.317 and 2.817 Å from each of the oxygen in the endoperoxide bridge (O1 & O2). This structure has the lowest (ΔG_{bind}) score of -49.00 kcal/mol. From the docking simulation study it revealed that the structure as well as orientation of Artemisnin-Quinine hybrid with respect to haeme has a significant effect on drug action. It could then be concluded that iron in haeme interacts with O2 more preferably than O1, a preference which might arise from the more negative charge at O2 and the steric hindrance at O1. This observation is in agreement with docking results reported by Shukla *et al.* **[33]**.

Artemisinin-Quinine hybrid molecule is novel due to its modified structure and has potent anti malaria activities with presence of artemisinin consisting of endo-peroxide Bridge. Studies suggest that the antimalarial activity of artemisinin is due to the interaction of its peroxide group with the prosthetic haeme group of human haemoglobin. Reduction of the peroxide group may lead to cytotoxic free radicals and electrophilic intermediates, which may be able to react which may be able to react with specific *P.falciparum* membrane associated proteins, leading to the parasite's death. As shown by Walsh *et al.*, 2007 their hybrid was highly active in vitro against the strains of *P. falciparum* 3D7 (with IC_{50} value 8.95 nM) and Chloroquine resistant strain *P.falciparum* FcB1 (IC_{50} value 9.59 nM).The reported results demonstrate a proof to the concept that linkage of artemisinin and quinine is being retained in a single molecule and possibly enhances the antimalarial activity of the parent compounds. It is likely that the hybrid can interact with haeme or its oxidation product haematin as a common target since these are both present in the eryhrocytic parasite.

There is no doubt that the hybrid molecules show potent and novel anti malarial activity. The next major steps, therefore, is to experimentally analyze the antimalaria activity by determining the IC_{50} value of Art-Qui-OH and its structural derivatives by BHIA (β-haematin inhibitory assay). Though the analogues ranged from poor to good binding affinity; the structures are yet to be synthesized. The information that we have obtained in this study may lead to the design and hopefully (synthesis) of more potent hybrid derivatives with receptor as haematin.

Conclusion:

We propose a model for the binding mode and binding affinity of Art-Qui-OH and its derivatives with a putative receptor. This model will help the rational design of new artemisinin based hybrid anti-malarial that target haemozoin formation.

Competing interests:

The authors have declared that no competing interests exist.

Acknowledgment:
The authors acknowledge R. Raghu, Schrödinger Inc. for providing trial license software for preparation of the manuscript.

References:

[1] ArauJo JQ *et al. Bioorg Med Chem*. 2008 **16** : 5021 [PMID: 18375130]
[2] Egan TJ, *J Inorg Biochem.* 2006 **100** : 916 [PMID: 16384600]
[3] Egan TJ, *J Inorg Biochemy*. 2008 **102**: 1288 [PMID: 18226838]
[4] Warhust DC *et al. Malar J*. 2003 **2**: 26 [PMID:14505493]
[5] Meshnick SR *et al. Antimicrobial Agents Chemother*. 1993 **37**: 1108 [PMID: 8517699]
[6] Cui L & Su XZ, *Expert Rev Anti Infect Ther*. 2009 **7**: 999 [PMID: 19803708]
[7] Morphy R & Rankovic Z, *J Med Chem*. 2005 **48**: 6523 [PMID: 16220969]
[8] Walsh JJ *et al. Bioorg Med Chem Lett*. 2007 **17**: 3599 [PMID: 17482816]
[9] Walsh JJ & Bell A, *Curr Pharm Des*. 2009 **15**: 2970 [PMID: 19754373]
[10] Muregi FW & Ishih A, *Drug Dev Res*. 2010 **71**: 20 [PMID: 21399701]
[11] Cheng F *et al. Bioorg Med Chem*. 2002 **10:** 2883 [PMID: 12110308]
[12] Jefford CW, *Curr Med Chem*. 2001 **8**: 1803 [PMID: 11772352]
[13] Wu WM *et al. J Am Chem Soc*. 1998 **120**: 3316
[14] Meshnick SR, *Int J Parasitol*. 2002 **32**: 1655 [PMID: 12435450]
[15] Haynes RK & Krishna S, *Microbes Infect*. 2004 **6**: 1339 [PMID: 15555542]
[16] Warhurst DC, *Biochem Pharmacol*. 1981 **24**: 3323 [PMID:7326041]
[17] De Villiers KA, *J Inorg Biochem*. 2008 **102**: 1660 [PMID:18508124]
[18] http://www.schrodinger.com.
[19] Woolfrey R *et al. J Comput Aided Mol Des*. 1998 **12**: 165 [PMID: 9690175]
[20] Acton N *et al. J Med Chem*. 1993 **36**: 2552 [PMID: 8355254]
[21] Lin AJ *et al. J Med Chem*. 1989 **32**: 1249 [PMID: 2657065]
[22] Posner GH *et al. J Med Chem*. 1992 **35:** 2459 [PMID:1619620]
[23] Avery MA *et al. J of Med Chem*. 1995 **38**: 5038 [PMID: 8544180]
[24] Avery MA *et al. J Med Chem*. 1993 **36**: 4264 [PMID: 8277509]
[25] Avery MA *et al. J of Med Chem*. 1996 **39**: 2900 [PMID: 8709124]
[26] Peter B, *Bioorganic & Medicinal Chemistry Letter*. 2005 **15**: 1015 [PMID: 15686903]
[27] Warhurst C *et al. Biochem Pharmacol*. 2007 **73**: 1910 [PMID: 17466277]
[28] Kristina M *et al. Bioorganic & Medicinal Chemistry*. 2009 doi: 10.1016/j.bmc.2009.06.065
[29] Veber DF, *J Med Chem*. 2002 **45**: 2615 [PMID:12036371]
[30] Lipinski CA, *Adv Drug Deliv Rev*. 2001 **46**: 3 [PMID: 11259830]
[31] Lyne PD *et al. J Med Chem*. 2006 **49**: 4805 [PMID: 16884290]
[32] Friesner RA *et al. J Med Chem*. 2004 **47**: 1739 [PMID: 17034125]
[33] Shukla KL *et al. J Mol Graph*. 1995 **13**: 215 [PMID: 8527414]

Edited by P Kangueane
Citation: **Mahapatra *et al.*** Bioinformation 8(8): 369-380 (2012)

BIOINFORMATION

open access

Supplementary material:

Table 1a: Dihydroartemisinin-Quinine hybrid

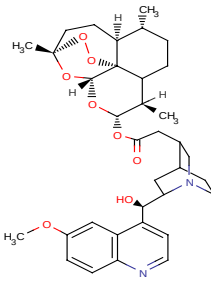
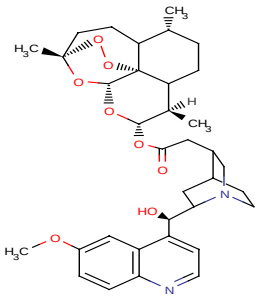
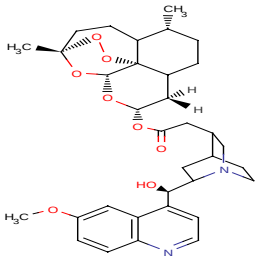
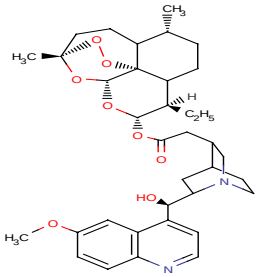
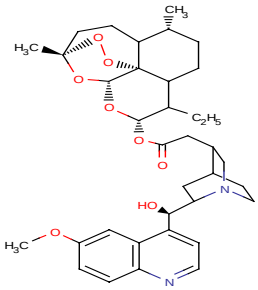
Sl. No	Structure	LogP	Molecular	Weight(g/mol)	XP Score (Kcal/mol)
1.		5.57	622.68		-7.485

Table 1b: Artemisinin-Quinine Analogous

Sl.No.	Structure	LogP	Molecular	Weight(g/mol)	XP Score (Kcal/mol)
2.		5.57	622.78		-6.802
3.		5.08	608.72		-6.914
4.		6.10	636.77		-6.950
5.		6.10	636.77		-6.932

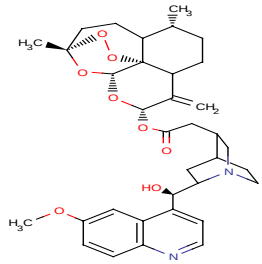
6.		5.75	620.73		-7.241

Table 1c: C9 Artemisinin-Quinine Hybrid

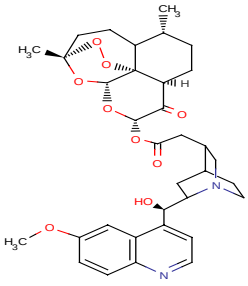
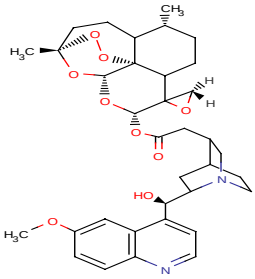
Sl. No	Structure	LogP	Molecular	Weight(g/mol)	XP Score (Kcal/mol)
7.		5.18	622.70		-5.310
8.		4.92	636.73		-5.450

Table 1d: C3 Artemisinin-Quinine Hybrid

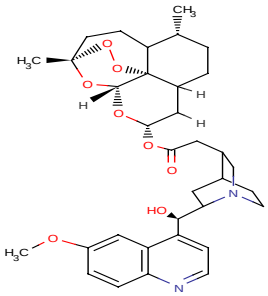
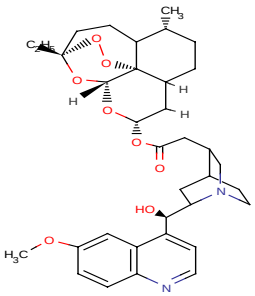
Sl. No.	Structure	LogP	Molecular	Weight(g/mol)	XP Score (Kcal/mol)
9.		5.08	608.72		-7.673
10.		5.61	622.74		-7.620

Table 1e: C10 Artemisinin-Quinine hybrid

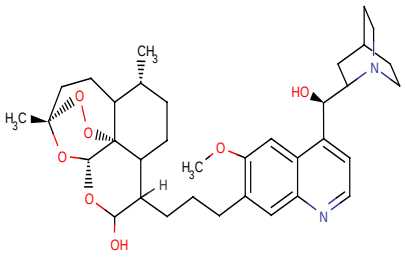
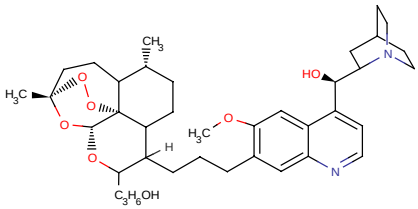
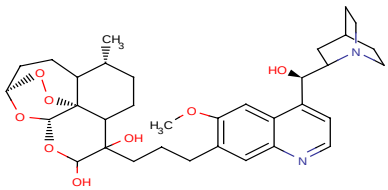
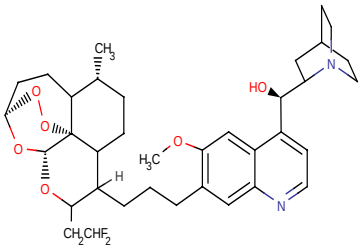
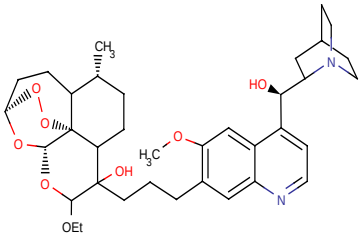
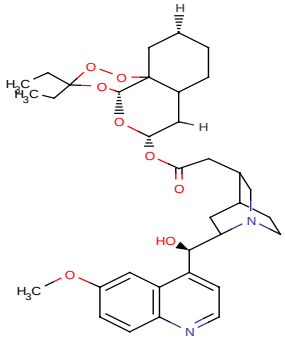
Sl. No.	Structure	LogP	Molecular Weight(g/mol)	XP Score(Kcal/mol)
11.		5.58	608.76	-7.722
12.		5.86	650.00	-7.815
13.		5.36	610.73	- 6.277
14.		5.93	642.77	-7.622
15.		6.08	638.79	-6.283

Table 1f: Seco-Artemisinin-Quinine Hybrid

Sl. No.	Structure	LogP	Molecular Weight(g/mol)	XP Score (Kcal/mol)
16.		5.79	610.73	-7.070

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 8(8): 369-380 (2012)

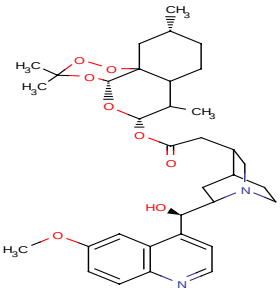
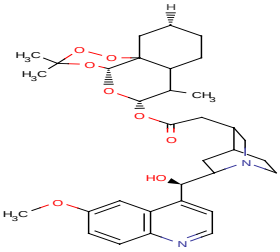
17.		5.71	610.73	-5.586
18.		5.22	596.71	-6.914

Table 1g: Miscellaneous Artemisinin-Quinine Hybrid

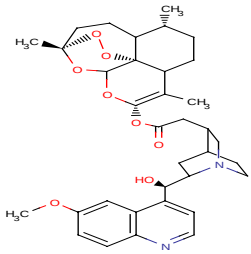
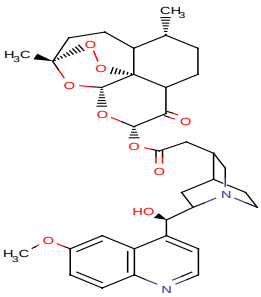
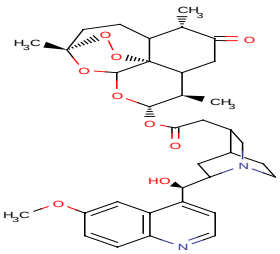
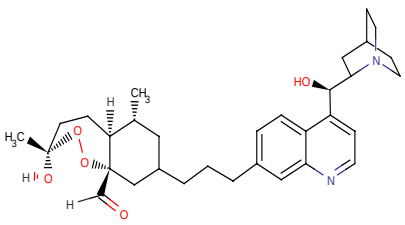
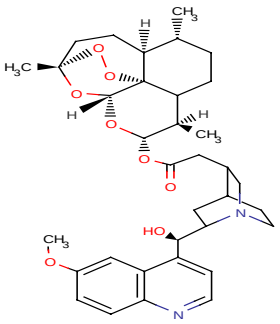
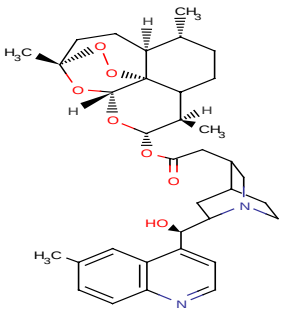
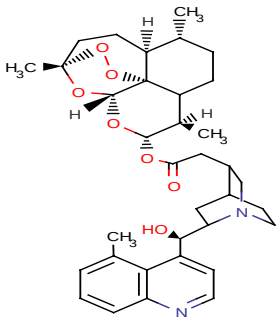
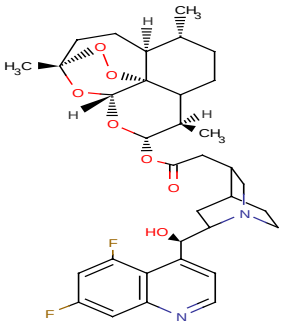
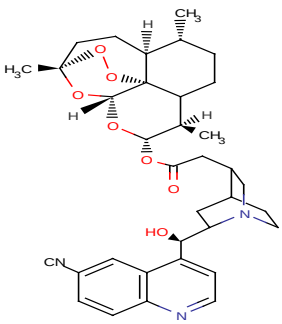
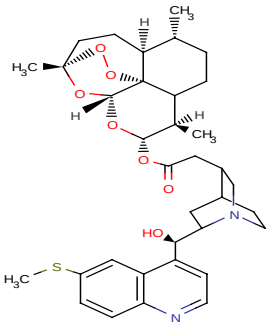
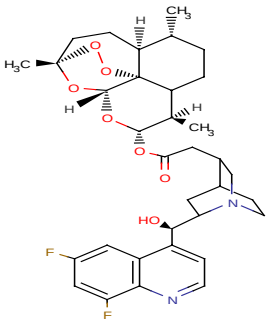
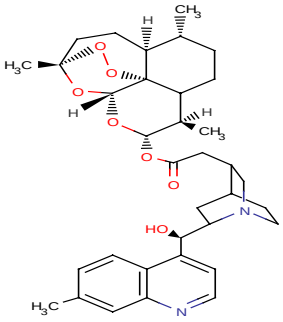
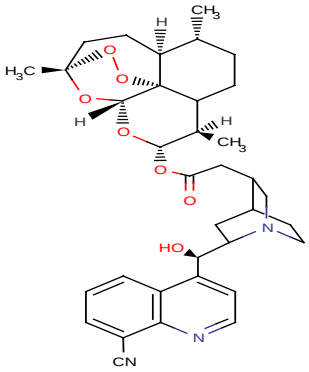
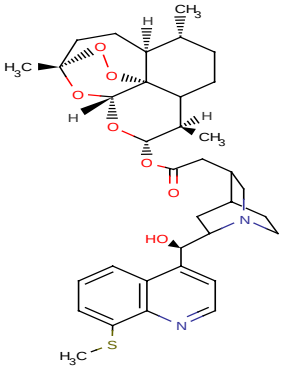
Sl. No.	Structure	LogP	Molecular Weight(g/mol)	XP Score (Kcal/mol)
19.		5.98	620.73	-7.600
20.		5.18	622.70	-6.768
21.		4.56	636.73	-8.913
22.		5.02	537.70	-6.671

Table 1h:Artemisinin-Quinoline Derivatives

Sl.No.	Structure	LogP	Molecular Weight(g/mol)	XP Score (Kcal/mol)
23.		5.57	622.74	-5.83
24.		5.94	606.74	-7.02
25.		5.94	606.74	-7.30
26.		5.89	628.70	-5.79
27.		5.06	617.73	-6.64

28.		5.97	638.83	-6.77
29.		5.70	628.70	-6.56
30.		5.94	606.74	-6.69
31.		4.79	617.73	-6.53
32.		5.97	638.81	-6.58

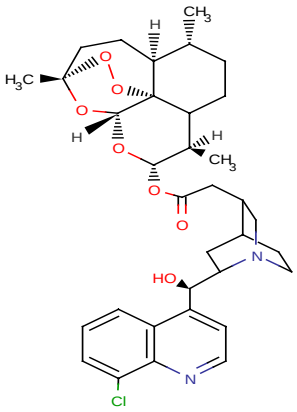
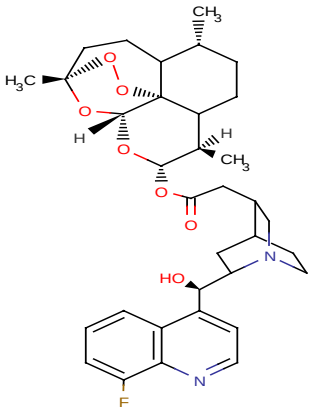
33. 	5.73	627.16	-6.54
34. 	5.90	610.71	-6.54

Table 2: Fifty percent inhibitory concentration (IC_{50}) of the Artemisinin-Quinine hybrid compared with the individual drugs **[8].**

Compound	3D7 (48 hrs)	3D7 (72 hrs)	FcB1 (48 hrs)	FcB2 (72 hrs)
	IC_{50}/nM/Final/Initial	*IC_{50}/nM/Final/Initial*	*IC_{50}/nM/Final/Initial*	*IC_{50}/nM/Final/Initial*
	Geometric mean IC_{50}/nM (95% confidence limit)			
Quinine	149 (95.1, 232)	73.5 (57.0, 94.6)	96.8 (74.5, 126)	75.3(59.0, 96.1)
Artemisinin	89.4 (40.7, 60.0)	45.5 (35.3, 58.6)	50.0 (43.7, 57.3)	55.0(39.0, 77.4)
Art-Qui-OH	8.95 (6.59, 12.2)	10.4 (6.06, 17.9)	9.59 (7.06, 13.0)	10.2(4.73, 21.9)
Quinine+ Artemisinin [a]	31.8 (27.4, 37.0)	28.6 (21.5, 38.2)	27.9 (26.5, 29.5)	26.3(24.7, 28.0)

Activities against cultured, asynchronous, blood-stage P. falciparum strains 3D7 and FcB1 were determined after 48 and 72 h using the parasite lactate dehydrogenase assay. Dose–response curves were used to determine the IC_{50} and the results are expressed as geometric means of IC_{50} from three duplicate determinations.

[a] *Values represent concentrations of each of quinine and artemisinin in a 1:1 ratio, for example, a combination of 31.8 nM quinine + 31.8 nM artemisinin inhibited the growth of 3D7 by 50% after 48 h.*

Table 3: XP Score and Prime-MM-GBSA energy of Art-Qui-OH and its derivatives with Fe (II) PPIX

Ligand	G Score	ΔG_{bind}	$\Delta\Delta G_{bind\text{-}cald}$	Fe-O_1 (Å)	Fe-O_2 (Å)	Fe-O_{13} (Å)	Fe-O11 (Å)
1	-7.485	-32.35	0.00	3.273	2.817	5.149	5.149
19	-7.600	-34.38	-2.03	3.298	2.853	5.214	4.934
10	-7.620	-36.57	-4.22	3.282	2.825	5.172	4.951
14	-7.622	-37.43	-5.08	3.330	2.731	4.998	4.772
9	-7.673	-41.30	-8.95	3.281	2.817	5.125	4.867
11	-7.722	-42.48	-10.13	6.487	6.176	5.235	3.812
12	-7.815	-44.11	-11.76	3.276	2.833	5.083	4.639
21	- 8.913	-49.00	-16.65	3.317	2.817	5.120	4.786

All the energy parameters are expressed in kcal/mol

$\Delta\Delta G_{bind\text{-}cald} = \Delta G_{bind\text{-}ligand} - \Delta G_{Art\text{-}Qui\text{-}OH}$