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Structure-Antimalarial Activity Study of Artemisinin-Quinine Hybrids

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Abstract.

A new antimalarial treatment is required because of the resistance against most used drugs. Among the products that have contributed in this area is the artemisinin and quinine. This paper presents a study of artemisinin, quinine and their hybrids of this two molecules by the DFT computational method and the 6-31G* basis. The calculated molecular descriptors include frontier molecular orbital, Mulliken charges, electrostatic potential maps and others.

Key words: antimalarial, artemisinin and quinine hybrids, molecular descriptors.

INTRODUCTION

Malaria, also known as paludism, is a disease caused by a parasite of the genus Plasmodium, which is transmitted by the bite of female Anopheles mosquito. There are four species of Plasmodium that affect man: falciparum, vivax, malariae and ovale. The most common infection is caused by P. falciparum, in addition to producing the greatest number of death.[1]

Malaria, an infectious disease and AIDS are the most affecting diseases to man in Africa and the greater health problem in Central America[2,3] producing increased morbidity and mortality in the world.[4] In Colombia the resistance in certain areas is evident, in the case of P. Falciparum to chloroquine the resistance is up to 97% with an accelerated increase[5] in the last years.

Artemisinin, an active principle isolated from Artemisia Annua L, possesses a good antimalarial activity, especially against chloroquine-resistant stumps. This molecule is a sesquiterpene Lactone with function endoperoxidasa[6],.[7] Studies suggest that the antimalarial activity depends on the peroxide moiety, as an important feature of the pharmacophore .

The search for new molecules with antimalarial activity remains an area of great interest to the scientific community[8]. This work assesses antimalarial activity in silico of 46 new hybrid molecules of artemisinin and quinine.

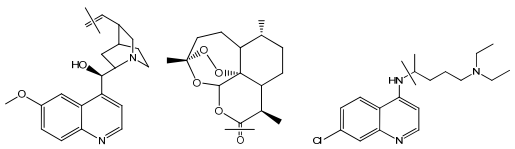
METHODOLOGY

Mechanic-quantum descriptors: HOMO, LUMO, molecular weight, LogP, Mulliken charges and electrostatic potential were calculated. The calculations were performed using DFT B3LYP and polarized base 6-31G*. All molecules were optimized to the non-appearance of imaginary frequencies, using the Gaussian 09W software

Lipinski and bioactivity factors were calculated with Molinspiration[9]. Other data such as the toxicological risk were determined by Osiris Property Explorer[10]. The equilibrium constant of the complex ligand-DNA (Log Keq) was also calculated [11].

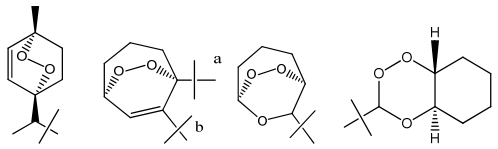
Artemisinin and Quinine Derivatives

The quinine-1, artemisinin-2 and chloroquine-3 were chosen as temples from which the modifications with substituents R1-R4 were proposed .Table 1 and 2



1 **2** **3**

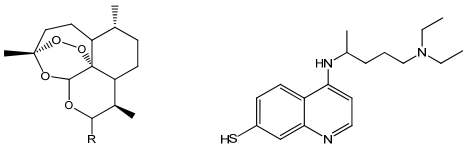
Figure 1.Structure of quinine-1, Artemisinin-2, chloroquine



R_1 **R_2** **R_3** **R_4**

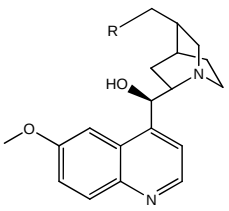
Figure 2. Substituents

In order to study the influence of specific functional groups, substitutions were made on the artemisinin-2 and chloroquine- 3, as shown below:



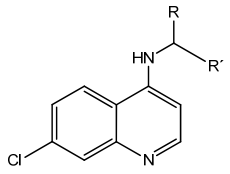
4 **5**

R=$OCOCH_3$	**4.1**
R= SO_2NH_2	**4.2**
R=SH	**4.3**



R=COOR´	R´
6	**1**
7	R_1
8	R_2
9	R_2 b
10	R_3
11	R_4
R=COR´	
12	R_1
13	R_2a
14	R_2 b
15	R_3
R=$COCH_2R$´	
16	R_1
17	R_2a
18	R_2 b
19	R_3
20	R_4

Table1.Proposed molecules derived from quinine-1



R = CH_3, R´=COOR´´	R´´
21	**1**
22	R_1
23	R_2
24	R_2 b
25	R_3
26	R_4
R = CH_3, R´=OR´´	
27	**1**
28	R_1
29	R_2
30	R_2 b
31	R_3
32	R_4
R = H, R´=CH_2R´´	
33	**1**
34	R_1
35	R_2a
36	R_2 b
37	R_3
38	R_4

Table 2. Proposed molecules derived from chloroquine-3.

Results

As shown in tables 3, 4 and 5, the bioactivity, toxicological risk and physical-chemical properties are reported respectively.

Physicochemical properties of R1 to R4 indicate that these molecules possess greater permeability. These substituents may offer advantages over the original compounds quinine-1, artemisinin-2 and chloroquine-3 due to a reduced risk of irritating effect. The bioactivity, showed similar behavior in R1 and R4, as well as the R2 and R3 structures

Molecule	Ligand GPCR	Mod. Ionic C.	Quinas as Inh.	Ligand R. Nuclear	Proteasa Inh.	Enz. Inh.
1	0.38	0.37	-0.05	0.10	0.18	0.11
2	-0.17	-0.31	-0.65	0	-0.19	0.39
3	0.32	0.32	0.38	-0.19	0.05	0.11
R_1	-0.26	0.03	-0.96	-0.33	-0.53	0.11
R_2	-1.62	-1.39	-2.20	-2.43	-2.15	-1.06
R_3	-1.72	-1.27	-2.32	-2.11	-2.18	-1.10
R_4	-0.56	0.02	-0.80	-0.47	-0.72	0.19

Table 3. Bioactivity data

Molecule	Mutagenic	Tumorigen	Irritant	Reprod. E.
1				
2				
3				
R_1				
R_2				
R_3				
R_4				

Table 4. Predicted toxicological risk

The fields highlighted in green correspond to the minor toxicological risks; fields in red indicate high risk

Molecule	Log P	PSA	P.M.	AEH	DEH
1	3.061	45.592	324.424	4	1
2	3.316	54.007	282.336	5	0
3	5.005	28.157	319.880	3	1
R_1	2.652	18.468	168.236	2	0
R_2	0.971	27.702	130.143	3	0
R_3	1.519	18.468	126.155	2	0
R_4	2.286	27.702	172.224	3	0

Table 5. Calculated physical-chemical properties. PSA indicates the area of polar surface, Hae and DEH corresponds to hydrogen bond acceptors and donors.

The quinine-1 has low toxicological risk as opposed to the chloroquine-3 showing to be more likely to be mutagenic and irritating. Due to tumorigenic risk reported for artemisinin-2, it was decided to take the 1-quinine and chloroquine-3 to study the effect of the above substitutions.

Tables 6, 7 and 8 show the results obtained for these molecules.

Molecule	Log P	PSA	P.M.	AEH	DEH
4.1	3.485	63.241	326.389	6	0
4.2	2.198	97.101	347.433	7	2
4.3	3.734	36.936	300.420	4	0
5	4.557	28.157	317.502	3	1

Table 6. Physical-chemical changes by substituent

Molecule	Mutagenic	Tumorigen	Irritant	Reprod. E.
4.1				
4.2				
4.3				
5				

Table 7. Predicted toxicological risk by substituent

Molecule	Ligand GPCR	Mod C. Ionic	Quinasas Inh.	Ligand R. Nuclear	Proteasa Inh.	Enz. Inh.
4.1	-0.03	-0.20	-0.45	0.14	0.05	0.47
4.2	0.06	-0.22	-0.38	0.11	0.18	0.51
4.3	-0.05	-0.19	-0.47	0.05	-0.03	0.47
5	0.25	0.06	0.24	-0.31	0.18	0.16

Table 8. Bioactivity data by substituent

Acetylated Artemisinin 4.1, slightly increases the physico-chemical properties, so the transfer across membranes is not affected. 4.1 to 4.3 substituents have higher bioactivity as enzyme inhibitors.

For the artemisinin-sulfonamide 4.2,it is observed an increase in the polar surface area and a decrease of the LogP which makes it possible to act as an inhibitor of proteases, nuclear receptor ligand and even as ligand of G protein-coupled receptors.

Structures with substitutions of thiol group, shown different behaviors for each molecule. The 4.3 artemisinin-thiol, increased its LogP, molecular weight and volume. With regards to the bioactivity, the behavior was favourable compared to the artemisinin-2 and similar to acetylated artemisinin 4.1. The 5 chloroquine-thiol, demonstrated a decrease in Log P and molecular weight. The chloroquine 3 has ability to act with all evaluated targets. In none of the cases the toxicological risk was modified.

The hybrids that possess the artemisinin-2 and all derivatives of quinine-1, reported minor physicochemical properties, bioactivity and toxicological risk compared to the rest of the group.

The molecules possessing the R2 and R3 substituents were shown to be very favorable. This suggests endoperoxide bridge is essential for the activity of the molecule.

It was determined that hybrids of quinine bonded by an ester shown good results with respect to the chloroquine. Ethers had higher favorability, especially with regard to bioactivity and physicochemical properties. The toxicological risk remained intact.

Bonding of quinine-1 hybrids through a ketone bond have good calculated properties. The group with the best results corresponds to the hybrids 13,17,19,35,37,38.

Frontier Orbital

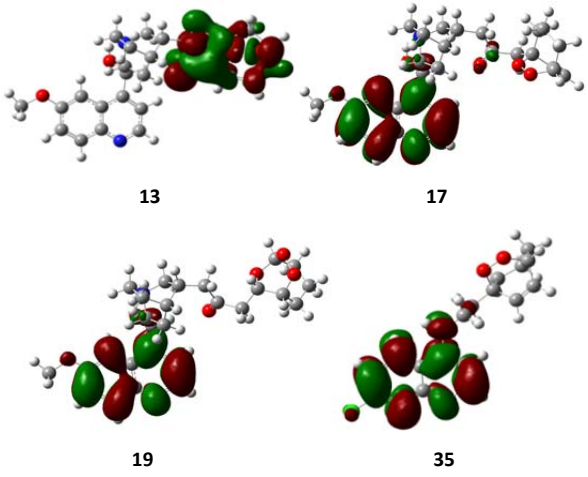
Irreversibility to the biological targets interaction is associated with toxic effects. In other words, the greater interaction between nucleophile-electrophile (where the nucleophile is a protein or DNA, and the electrophile is the substance in question), the greater the toxicity .The results show that as LUMO values are higher, electrophylicity of molecule will increase and thus will be a greater enzyme inhibitor

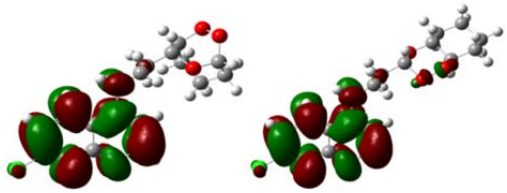
The data in table 9 show that compound 13 could irreversibly interact with biological targets, which could result in greater toxicity in the parasite.

Molecule	HOMO (eV)	LUMO (eV)
13	-5.761	-1.888
17	-5.395	-3.271
19	-5.358	-2.741
35	-6.104	-3.677
37	-6.025	-2.214
38	-6.005	-2.143

Table 9. HOMO and LUMO energy of the pre-selected hybrids

The LUMO molecular orbital of the pre-selected hybrids are shown in Figure 3.





37 ***38***

Figure 3. LUMO Molecular orbital of pre-selected hybrids

Electrostatic potential maps

The following images are the electrostatic potential of the pre-selected hybrids.

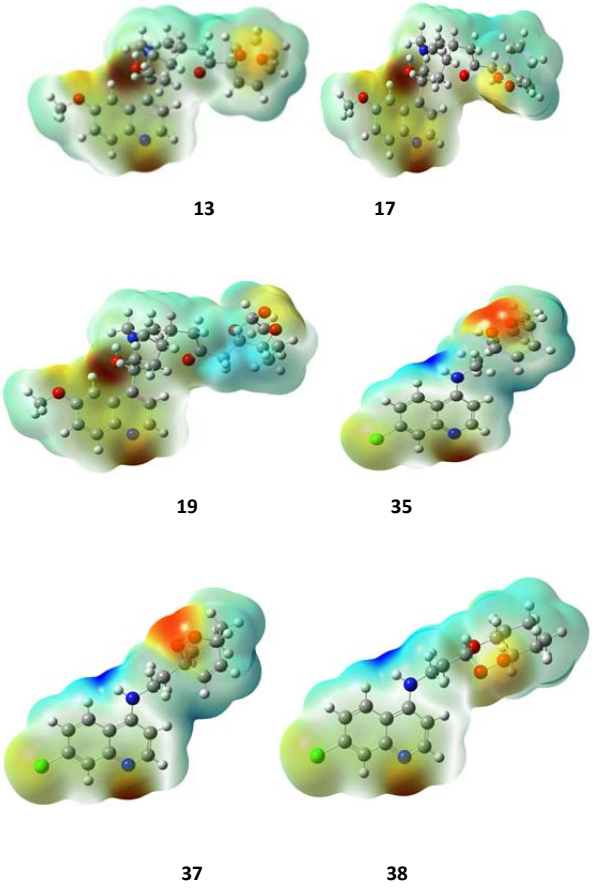


Image 1. Electrostatic potential maps of pre-selected hybrids

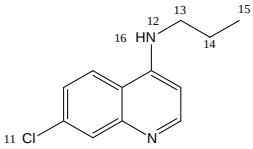
In general, the negative charges are concentrated on the oxygens of the endoperoxide bridge and the amino group of quinine ring.

In hybrids composed of chloroquine-3, the electron density around the halogen is affected by resonance effects.

Mulliken charges trends

Atom	37	35	38
N1	-0.167	-0.170	-0.191
C7	0.034	0.008	0.009
Cl11	0.425	0.428	0.422
N12	-0.689	-0.674	-0.681
C13	-0.224	-0.386	-0.319
C14	-0.395	0.153	-0.353
H16	0.411	0.416	0.409

Table 10. Mulliken charges of hybrids composed of chloroquine



In chloroquine-3 the 4-aminoquinoleinic group is considered to be a catallyst of the FPIX hemo.

The N1 is a weak base that helps the accumulation of compound, since in its protonated form is not able to cross the red blood cells and accumulate in the vacuola[12]. Negative charges of similar magnitude for selected compounds can be seen.

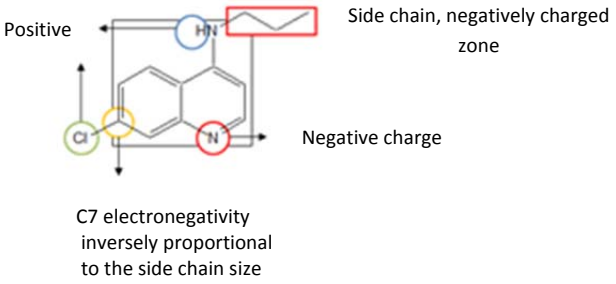
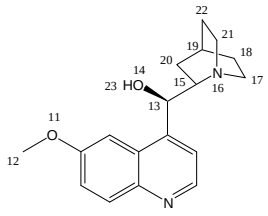
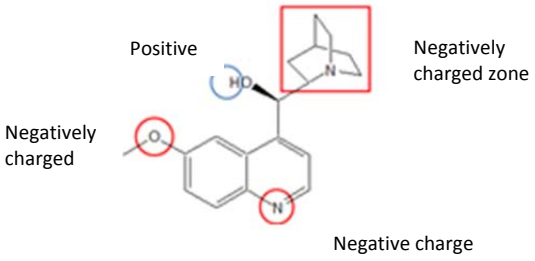


Figure 4.Charge distribution for 4-aminoquinine systems





Atom	13	17	18
N1	-0.152	-0.155	-0.162
O11	-0.394	-0.510	-0.510
C12	-0.277	-0.213	-0.213
C13	-0.226	-0.046	-0.043
O14	-0.460	-0.652	-0.650
C15	-0.494	0.001	0.003
N16	-0.130	-0.439	-0.437
C17	-0.131	-0.143	-0.143
C18	-0.580	-0.292	-0.261
C19	-0.110	-0.107	-0.106
C20	-0.429	-0.294	-0.291
C21	-0.686	-0.162	-0.143
C22	0.401	-0.082	-0.087
H23	0.453	0.404	0.405

Table 11. Mulliken charges of hybrids composed of quinine.

With regards to chlorine, is credited with the action of hemozoin formation inhibition. Position 7 of the ring is crucial in the structure, experimental studies with other halogens as bromine and iodine showed high resistance activity and sensibility[13]. C7 has a positive charge more intense in compound 37 probably increasing the strength of association with the hemo[9] by a greater electronegativity in the molecule, which can be compared with the action exerted by the bicycle of the quinine-1 which is an area of highly negative charges.

O11, O14 and bicycle in quinine-1 ring were shown to be negative. The H23 had the greatest positive charge in their group.

The molecules derived from quinine-1, present greater intensity of negatively charged atoms compared with chloroquine-3 compounds. This suggests a greater affinity with iron in the Ferry-protoporfine

Calculated Log Keq

Quinine and derivatives, exert their action through interaction with the parasite DNA base pairs.. It is presumed that its action is reinforced by the establishment of hydrogen bonding with the amino group of the side chain. The ability of selective accumulation in the Plasmodium is the main therapeutic action of these molecule[14]

Researches have showed statistically the possibility to determine the affinity of a molecule with the ADN.[12] In this way binding capacity was calculated by the following equations:

$$Log\ Keq = -0.255(\pm 0.100)XlogP - 0.003(\pm 0.002)PSA + 6.603(\pm 0.465)Eq.1$$

$$logKeq = -0.225(\pm 0.090)XlogP + 6.054(\pm 0.229)Eq.2$$

Molecule	*Keq* Equation 1	Keq Equation 2
1	2.992	1.324
2	2.986	1.320
3	2.943	1.285
13	2.990	1.323
17	2.983	1.317
19	2.999	1.330
35	2.962	1.301
37	2.988	1.321
38	2.965	1.303
R_1	3.003	1.333
R_2	3.045	1.367
R_3	3.031	1.356
R_4	3.012	1.340

Table 12. DNA binding affinity

The proposed structures showed affinity with comparable values with Keq of artemisinin-1, 2-quinine and chloroquine-3.

Based on the results of this study, hybrid 35 and 37 are finally proposed as antimalarial drugs, hybrid 35 and 37 comply with the Lipinski rule, maintain structural characteristics related to the biological activity in study and for having the highest scores as enzyme inhibitors. See table 13.

Molecule	logP	Enz. Inh.
13	3.133	0.43
17	3.403	0.38
19	2.772	0.37
35	4.232	0.62
37	3.235	0.58
38	4.106	0.51

Table 13. Bioactivity and logP for selected structures

CONCLUSIONS

The structural modifications suggest that certain groups such as acetyl and sulfonamide potentially improve the properties of artemisinin, increasing their bioactivity.

The type of binding is related to activity of hybrids, where side chains and the ketone bonds showed the best results.

The endoperoxide bridge proved to be a key moiety to the action of the through electrostatic maps potential and affinity for DNA.

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