Servolab Science News Vol.1(1): 71-77 (2022) 2 Figs. 3 Tabs.

ON THE MOLECULAR INTERACTION BETWEEN ITACONIC ACID AND ANTIMALARIAL COMPOUNDS BY EMPLOYING DFT CALCULATION

(SOBRE LA INTERACCIÓN MOLECULAR ENTRE EL ÁCIDO ITACÓNICO Y LOS COMPUESTOS ANTIMALARIALES EMPLEANDO EL CÁLCULO DE DFT)

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ABSTRACT

The molecular interactions between four widely used antimalarial, chloroquine, primaquine, quinine, and amodiaquine, with itaconic acid dimer, have been studied by the mean of the Density Functional Theory calculation in both vacuum and water environment, using B3LYP/ ++6-31G(d,p) basis set and PCM model of solvent. Chloroquine, primaquine, and quinine show a suitable interaction with the itaconic acid dimer, with binding energy into the range of -17 to -6.7 kcal/mol. These values of binding energies suggest the formation of stable and exothermic complexes in the field of physisorption energy. By contrast, the positive value of binding energy for amodiaquine indicates a slight chance to be absorbed into the hydrogel polymer. Furthermore, the NBO calculation and the second-order perturbation theory indicate a strong charge-transference from chloroquine and primaquine to the itaconic acid dimer. Besides, these results suppose the interactions are mainly polar where the hydrogen bond plays a pivotal role in the complex stabilization. On the other hand, the CPCM calculations suggest the chloroquine and primaquine complex are stables, with suitable values of both, LogP and dipole momentum, implying the swelling of these complex in water and the eventual drugs controlled delivery from the polymeric matrix.

Keywords: DFT, hydrogel, antimalarial, controlled drugs delivery, binding energy

RESUMEN

Las interacciones moleculares entre cuatro antipalúdicos ampliamente utilizados, cloroquina, primaquina, quinina y amodiaquina, con dímero de ácido itacónico, se han estudiado mediante

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el cálculo de la Teoría Funcional de la Densidad tanto en ambiente de vacío como de agua, utilizando B3LYP / ++ 6- Conjunto de bases 31G (d, p) y modelo PCM de disolvente. La cloroquina, primaquina y quinina muestran una interacción adecuada con el dímero del ácido itacónico, con una energía de enlace en el rango de -17 a -6,7 kcal / mol. Estos valores de energías de enlace sugieren la formación de complejos estables y exotérmicos en el rango de energía de fisisorción. Por el contrario, el valor positivo de la energía de unión para la amodiaquina indica una pequeña posibilidad de que se absorba en el polímero de hidrogel. El cálculo de NBO y la teoría de perturbación de segundo orden indican una fuerte transferencia de carga de cloroquina y primaquina al dímero del ácido itacónico. Además, estos resultados suponen que las interacciones son principalmente polares donde el enlace de hidrógeno juega un papel fundamental en la estabilización del complejo. Por otro lado, los cálculos de CPCM sugieren que el complejo de cloroquina y primaquina son estables, con valores adecuados tanto de LogP como del momento dipolar que implican el hinchamiento de estos complejos en agua y el eventual suministro controlado de fármacos desde la matriz polimérica.

Palabras clave: DFT, hidrogel, antipalúdico, administración controlada de fármacos, energía de unión.

INTRODUCTION

Malaria is a significant public health issue because it can potentially infect around 3.2 billion people worldwide. From 2016 until the present, 206 million people have been infected globally, mainly affecting children under five years old in regions with the highest incidence rates. Currently, several conventional antimalarial treatments seem to show several disadvantages (Murray et al. 2012; World Health Organization 2016).

The main disadvantages of conventional antimalarial treatment are the toxicity of the drugs applied and the lengthy treatment time. As a result, other organisms might be affected because the excess of toxic drugs can transfer to them during the treatment periods (Murray et al. 2012). On the other hand, antimalarial drugs have become ineffective due to the emergence of multidrug-resistant strains. Thus, the development of new antimalarial drugs and treatments is urgently needed (Murambiwa et al. 2011).

The development of new antimalarial drugs requires significant economic investments and long periods of in-depth research. Therefore, it has been proposing non-conventional treatments to treat this disease efficiently (Al Qaraghuli et al. 2017). These new methods of dosage allow supplying specific amounts of toxic antimalarial drugs to the organism, ultimately decreasing the risk of affecting other orgasms during the treatment (Santos-Magalhães et al. 2010; Fernàndez-Busquets et al. 2016).

Previous studies indicated that a transdermal with a hydrogel matrix patch could efficiently treat malaria. This method has the advantage that it can avoid the first step of the hepatic metabolism by delivering toxic drugs with desired rates. Therefore, diminishing the side effects of the medications in human organs. However, the main limitation of this method is the selection of the suitable hydrogel that will be applied to release specific antimalarial drugs with desired rates (Banga & Chien 1993; Iordanskii et al. 2000; Lee et al. 2008).

Itaconic acid is a monomer often used to synthesize hydrogels because this is innocuous, of low cost, and can easily adhere to the skin (Bera Dey & Chakrabarty 2015). Besides, this acid absorbs a high content of water and has a

high degree of biocompatibility. Furthermore, itaconic acid is a suitable compound for designing hydrogel-systems of drugs dosage (Katime & Rodríguez 2001; Tomiæ et al. 2006; Bera et al. 2015).

The antimalarial drugs often used are chloroquine, primaquine, quinine, and amodiaquine. These compounds are suitable to assess their affinity polymeric matrix because they have functional groups of polar nature that allow them to interact with the hydrogels (Karadaç et al. 1996; World Health Organization 2015).

Ultimately, this assessment will contribute to designing efficient hydrogels systems of dosage; however, each compound's intrinsic nature makes it challenging to perform a pure hydrogel that could have a similar affinity with all of them. Therefore, as a first critical step, assessing the compatibility between different hydrogels and the compounds above is necessary.

In this study, we assessed the molecular compatibility between a model hydrogel system built from itaconic acid and the most common antimalarial compounds: chloroquine (CQ), primaquine (PQ), quinine (QN), and amodiaquine (AQ). To this aim, we applied computational calculations at the level of DFT by using a B3LYP/++6-31G(d,p) basis set. In addition, several molecular descriptors were also calculated (e.g., interaction energy, Gibbs functional, molecular hardness and electronic population analysis).

MATERIALS AND METHODS

To optimize the structure of minimal energy of the antimalarial compounds (chloroquine, primaquine, quinine, and amodiaquine) and their dimers with Itanic acids (DAI), it applied the Density Functional Theory (DFT) at vacuum and water conditions by using Gaussian 16 for Linux. To this aim, the correlation-interchange method of Becke, Lee, and Yang-Parr with three parameters and the 6-31++G(d,p) basis set were used (Frisch et al. 2016).

A dimer of itaconic acid was used as a model for the hydrogel. The energy of interaction (DE_b) was applied as a reference to assess the compatibility between the modelled hydrogel and antimalarial compounds. Thus, negative values of DE_b indicates compatibility, while positive values suggest the opposite.

The values of DE_b were computed on the base set superposition error method energy (BSSE) described in equation 1:

$$\Delta E_b = E_{Complex} - \left| \frac{E_{Model}}{DAI} + E_{drugs} \right| + BSSE \quad (1)$$

$E_{complex}$, E_{Model}, and E_{drugs} were the energies of the DAI-drugs complexes, DAI, and antimalarial compounds, respectively. Finally, BSSE was the base-set superposition error method (Gutowski et al. 2016).

The electron flow direction was assessed by computing DN as indicated in equation 2:

$$\Delta N = \frac{(\mu_B - \mu_A)}{(n_B + n_A)} \quad (2)$$

Where μ and η refer to the electronic potential and global hardness, while A and B are the donor and acceptor molecules of electrons, correspondingly, negative values of ΔN indicated spontaneous electronic flow from A towards B, while positive values suggested an opposite flow direction.

Solvation energy (ΔGs) was computed by the continuous polarization method (C-PCM) as indicated in equation 3.

$$\Delta G_{Solv} = E_{water\_complex} - E_{gas\_complex} \quad (3)$$

Where $E_{water\_complex}$ and $E_{gas\_complex}$ correspondingly are the energy of the water and gas complex. The partition coefficient (logP) was also estimated by the Ghose-Crippen method (independent of the wavelength function). This coefficient can provide information about the swelling velocity of the hydrogel because it is a proxy of the hydrogel solubility in the water and lipid phase.

RESULTS AND DISCUSSION

The Newton-Rapson algorithm was applied over all geometrical conformations to assess antimalarial and complex DAI-antimalarial compounds' minimum energy structure (DAI = Dimer itaconic acid). Minimum energy structures are shown in **figure 1**. Dashed lines are used to highlight the dipolar interaction between DAI and antimalarial compounds.

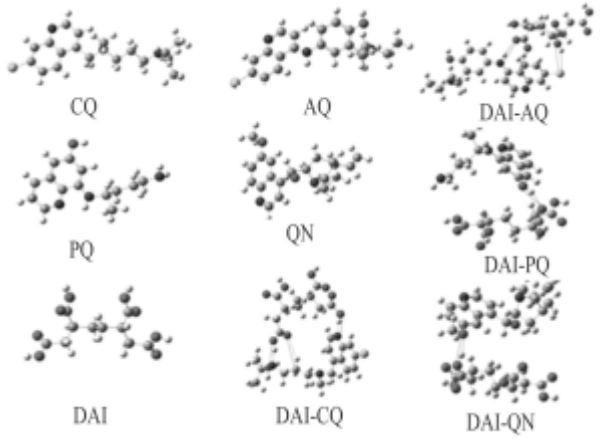

Figure 1. Minimum energy structure for all compounds studied herein, calculated at B3LYP/6-31++G (d, p) theory level.

Table 1 shows the optimization energy for the itaconic acid dimer (EH), antimalarial compounds (EF) and the respective complexes energy (EC), corrected by the mean of BSSE method, using the B3LYP/ 6-31++G(d,p) level of theory. It can note that QN, PQ, and CQ form exothermic complexes with the itaconic acid dimer. These results suggest the complete sorption of this antimalarial into the hydrogel matrix. Moreover, the binding energy means a physisorption process. However, the small and positive ΔE_b value for AQ indicates little interaction with the hydrogel matrix. According to **table 1**, the interaction order of antimalarial compounds with the hydrogel matrix is: ΔE_b(DAI-QN) <ΔE_b(DAI-CQ) <DE_b (DAI-PQ) < <ΔE_b (DAI-AQ).

Table 1. Molecular structure energies (kcal/mol) for the antimalarial (EF), hydrogel model (EH), complexes (EC) and the binding energy ΔE_b using B3LYP/6-31++G (d,p) theory level.

Complex	-EF (kcal/mol)	-EH (kcal/mol)	-EC (kcal/mol)	ΔE_b (kcal/mol)
DAI-CQ	832125.12	622131.36	1454271.55	-15.08
DAI-AQ	925653.64	622131.36	1547779.26	5.73
DAI-PQ	492270.73	622131.36	1114408.81	-6.72
DAI-QN	650453.11	622131.36	1272601.66	-17.20

Frontier molecular orbitals

Figure 2 shows the frontier orbital, HOMO, and LUMO, related to minimum energy structures for all compounds studied herein.

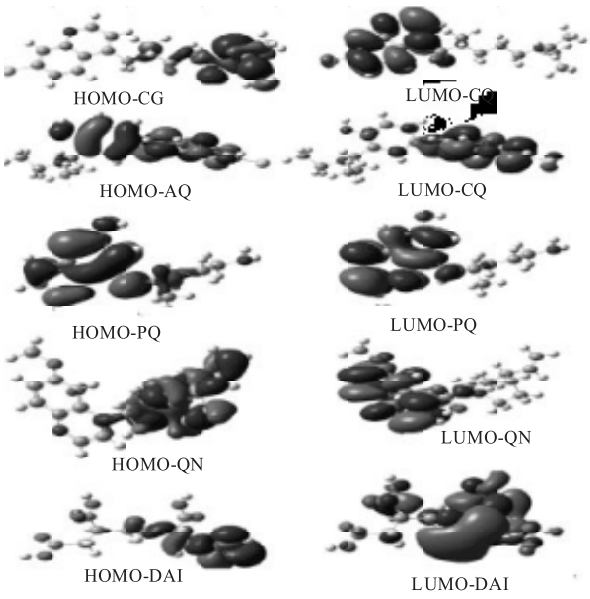

Figure 2. Frontier orbitals for the compounds studied herein, obtained at B3LYP/6-31++G(d, p).

A close inspection reveals that the CQ and QN have frontier orbitals features similar to itaconic acid ones. In addition, the HOMO and LUMO wave functions locate in specific regions, albeit different, of the structure. By contrast, frontier orbitals for AQ and PQ are scattered in the entire system. Thus, these results seem to point to a likely molecular recognition between CQ and QN with the itaconic acid; therefore, they have higher binding energy with hydrogel than AQ and PQ.

The molecular recognition between the itaconic acid and some of the antimalarial compounds guarantees spontaneous sorption into the hydrogel. These results are relevant evidence that encourages the use of itaconic acid hydrogel as a possible vehicle for the controlled delivery of CQ and QN.

Table 2 shows some molecular descriptors derivate from density functional theory. It can note that the band gap (LUMO-HOMO) of CQ and QN complexes is higher than the rest of the compounds, suggesting excellent stability for these complexes. Furthermore, the N values indicate a moderate electron transfer from antimalarial to the hydrogel. These results are associated with dipole-dipole interactions via intermolecular hydrogen bonds.

Table 2. Molecular descriptors for all DAI-antimalarial complexes, computed at B3LYP/6-31++G(d, p).

Molecular Descriptor	DAI-CQ	DAI-AQ	DAI-PQ	DAI-QN
-HOMO (kcal/mol)	153.88	134.17	119.40	136.01
-LUMO (kcal/mol)	55.19	45.73	30.97	43.96
LUMO-HOMO (kcal/mol)	98.67	88.44	88.44	92.06
Hardness global η (kcal/mol)	49.35	44.22	44.22	46.03
-Electronic potential, μ	104.56	89.95	75.19	89.96
-ΔN (hidrogel-antimalarial) kcal/mol	0.09	0.11	0.20	0.10

DAI: Itaconic Acid Dimer, AQ =amodiaquine; PQ=primaquine, QN =Quinine.

QSAR Properties

Table 3 shows values for three fundamental properties with significant influence on drug-delivery systems, i.e, lipophilicity (logP), dipole momentum (μ) and solvation free energy (ΔGsolvat, in Kcal/mol).

Table 3. QSAR properties for all complexes studied herein.

Molecular descriptor	DAI-CQ	DAI-AQ	DAI-PQ	DAI-QN
LogP	-10.17	-3.81	-6.83	-7.53
Dipole momentum (Debye)	12.23	7.65	1.67	4.97
ΔGsolvat (E_{H2O} -E_{gas})	-21.50	155.80	-22.42	-0.31

According to **table 3**, all of the complexes have LogP < 0; these results suggest that complexes could be soluble in physiologic fluids; additionally, except DAI-AQ complex, all of the complexes have momentum dipolar > 5 and negative solvation energy. These results on these descriptors guarantee the suitable molecular interaction between hydrogel chains and the water; thus, the hydrogel could swell and deliver the antimalarial compound.

In the case of DAI-AQ, the positive value of solvation energy suggests a little interaction with water. Thus, the swelling and the diffusion of the drug from hydrogel could be a no spontaneous process.

CONCLUSION

The entire results obtained in this work suggest the experimental study of itaconic acid-based hydrogel as CQ, PQ and QN delivery vehicle. In contrast, the controlled AQ delivery from itaconic acid could be ruled out because of the little affinity of AQ with itaconic acid hydrogel and the non-stability of the complex in the water environment.

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