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NBO Analysis by ONIOM and DFT (B3LYP) Calculations of Intramolecular and Intermolecular Interactions of Artemisinin, Quinine and Thirteen Manzamenones with H_2O or Alanine

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Abstract

This work was undertaken to analyze intramolecular and intermolecular interactions of Manzamenones from natural bond orbitals (NBO method). For their use in the treatment of malaria, the results of these molecules are compared to those of Artemisinin and Quinine. Manzamenones are a class of atypical fatty acids. They are isolated from a marine sponge of the genus Plakortis kenyensis. The analysis of intramolecular interactions compares the results of each molecule (Manzamenones, Artemisinin and Quinine) in the non-complexed state with those of its complex with a water molecule. Thus, for the same electron donors (i) and associated acceptors (j), the electron density (ED), stabilization energy E^2 related to the delocalization of i to j, the energies of the NBO orbitals ε_i and ε_j of the donor and acceptor, respectively, and element of the Fock matrix $F_{i,j}$ are determined and compared. The change in E^2 is used to deduce whether or not the molecule is stabilized after complex formation. These analyses allowed to match each Manzamenone to one of the two antimalarials. The intermolecular interactions were analyzed, for each molecule (Manzamenones, Artemisinin and Quinine), in two complexes. These complexes are obtained with a water molecule on the one hand and with an alanine molecule on the other hand. For these interactions, the electron donor and its electron density, the electron acceptor and its electron density as well as the donor—acceptor stabilization energy have been calculated. The ONIOM 2 method is used to study Manzamenones. Theoretical calculations

were done using density functional theory (B3LYP) by combining one of the two function bases 6-31++G(d,p) and 6-31+G(d,p).

Keywords

Malaria, Manzamenone, Artemisinin, Quinine, DFT, NBO, ONIOM, Stability

1. Introduction

Malaria is a febrile, hemolytic erythrocytopathy caused by the presence and multiplication in the blood of a hematzoan of the genus Plasmodium. It is transmitted to humans through the bite of a mosquito of the genus Anopheles [1]. Five (5) plasmodial species have been found in humans to date [2]: Plasmodium falciparum, Plasmodium vivax, Plasmodium malaria, Plasmodium ovale, and Plasmodium knowlesi recently described in humans.

Sub-Saharan Africa pays a heavy price to this disease with 90% of cases and 91% of deaths related to malaria [3]. In Côte d'Ivoire, malaria remains a major public health problem due to its morbidity, mortality and socio-economic impact [4]. For about 25 years, the parasite has been developing resistance to the main classes of drugs. This is the case with quinine, which is usually used in severe cases [5] [6] [7]. Manzamenones, from marine sources derived from sponges, can be increasingly extracted and used in the diversification of drug sources for the treatment of malaria [8]. These Manzamenones are atypical fatty acid derivatives, of bicyclic or spiro form, attached or not to a ring bearing long hydrocarbon chains substituted on the bicyclic. They are extracted from the marine sponge of the genus Plakortis kenyensis.

In a previous study, some molecular parameters including the interaction sites of Manzamenones, Quinine and Artemisinin were calculated and compared [9]. The present work examines the stability of the structural skeletons of these different molecules. It implements the NBO analysis method. For this purpose, in a first step, the intramolecular interactions in each non-complexed molecule and when complexed with a water molecule are compared. The aim is to identify the electron donors and electron acceptors involved in the interactions and the effects of these interactions on the stability of the molecular structure. A second analysis focuses on intermolecular interactions in complexes. Two complexes are formed with each molecule (Manzamenones, Artemisinin and Quinine) for this analysis; the one obtained with a water molecule and the one obtained with a 3-aminopropanoic acid molecule (alanine). In these complexes, electron donors, electron acceptors and stabilization energies are determined. Analyses of intramolecular and intermolecular interactions allow searching for structural stability similarities between each Manzamenone and antimalarial drugs.

All calculations are performed in the gas phase. The mixed ONIOM quantum chemical method was used for the Manzamenone calculations. Morokuma and

al [10] [11] [12] developed this method. It has often been used successfully on large molecules [13] [14] [15] [16]. ONIOM 2 calculations led to the use of the DFT method (B3LYP) associated with either the 6-31++G(d, p) or 6-31+G(d, p) function basis to describe the "model system". The "real system" is described with the semi-empirical AM1 method. Artemisinin and Quinine are described at the same level of theory used to study the "model system" of Manzamenones.

2. Studied Molecules and Theoretical Calculations

2.1. Studied Molecules: Manzamenone, Artemisinin, Quinine

The Manzamenones are heterocyclic atypical fatty acids. Thirteen (13) of these molecules, noted A, B, C, D, E, F, G, H, J, K, L, M and N, have been listed in the literature. They constitute, with Artemisinin and Quinine, the molecules studied in this work. Figure 1 shows their 2D structures.

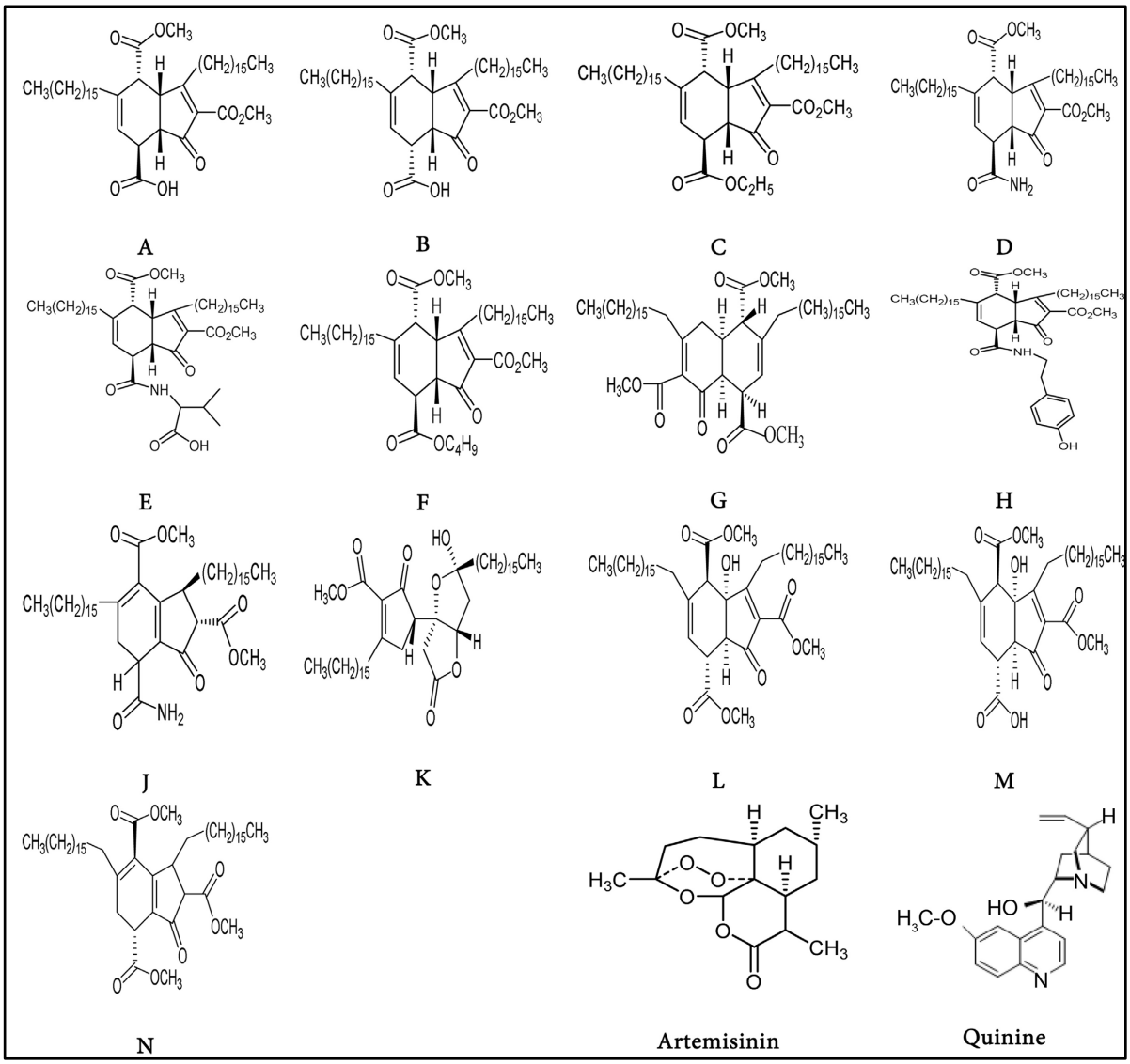


Figure 1. 2D structure of Manzamenones, Artemisinin and Quinine.

2.2. Theoretical Calculations Performed

2.2.1. Studied Molecules: Manzamenone, Artemisinin, Quinine

We used the ONIOM mixed method for the calculations. Its principle divides the studied system in several layers. Each of them is treated at a different level of calculation. In the case of a two-layer system (ONIOM 2), the one of interest in the study is the "model system". This is treated at the most elaborate level of theory. The layer of little interest or "real system" is calculated at a less sophisticated level. The "model system" is also treated at the same level of computation as the "real system". The final goal is to extrapolate the energy of the real system to the more sophisticated level. The total energy of the real system, determined by extrapolation from three independent calculations, is estimated using Equation (1). **Figure 2** shows the two-layer partitioning adopted for Manzamenones to perform the ONIOM calculations.

$$E_{\text{real}}^{\text{high}} = E_{\text{real}}^{\text{low}} + E_{\text{model}}^{\text{high}} - E_{\text{model}}^{\text{low}} \quad (1)$$

2.2.2. Levels of Theoretical Calculations

The calculations are performed with the Gaussian 09 software [17]. The method used is the density functional theory (DFT) [18]. The hybrid functional B3LYP like others associated with a large base of functions produce results in good agreement with the experiment [19]. Therefore, we have chosen this functional. Molecular geometries are optimized followed by vibrational frequency calculations. Two levels of theory have been used to perform the different calculations. These are B3LYP/6-31++G(d,p) and B3LYP/6-31+G(d,p).

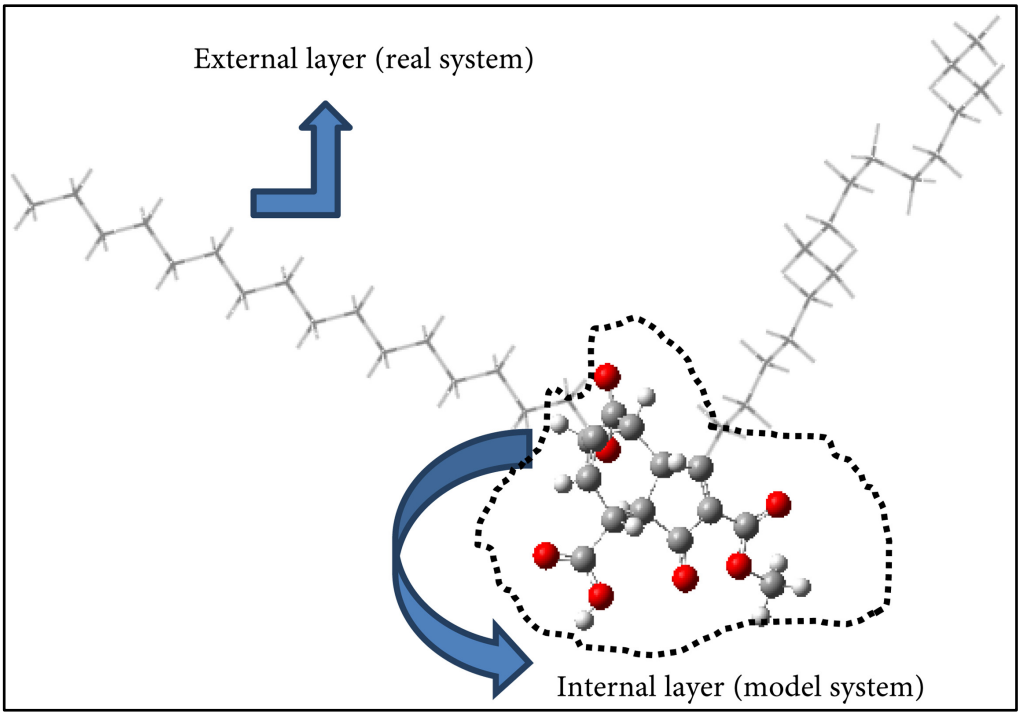


Figure 2. Model of a two-layer partitioning of the structure of a Manzamenone for ONIOM 2 calculation.

2.3. The Analysis of Natural Bond Orbital (NBO)

The goal of the NBO method is to propose a partition scheme of the functional space associated with the wave function in order to describe the electronic structure of the molecule using the simple formalism proposed by Lewis:

- ❖ core electron doublets;
- ❖ non-bonding doublets in the valence shell;
- ❖ bonding doublets resulting from the sharing of two electrons located in hybrid orbitals by two atoms.

The information on which the partition is made is contained in the molecular wave function. It allows obtaining the ideality gaps of the expected Lewis structure. These deviations should be described by the NBO method. In the NBO analysis, the donor-acceptor (bonding-antibonding) interactions are linked to the analysis of the possible interactions between the Lewis-type occupied NBOs (donors) and the non-Lewis-type vacant NBOs (acceptors). The estimation of their energies is done by the second order perturbation theory.

For each donor NBO (i) and acceptor NBO (j), the stabilization energy E^2 related to the delocalization from i to j, is explicitly estimated by the following Relation (2) [20].

$$E^2 = q_i \frac{\left(F_{i,j}\right)^2}{\varepsilon_i - \varepsilon_j} \tag{2}$$

$F_{i,j}$ is an element of the Fock matrix, q_i represents the occupancy of the donor orbital, ε_i and ε_j are the energies of the donor and acceptor NBO orbitals, respectively. Another interest of this analysis is to propose a localized description of the populations that translates the Lewis model.

3. Results and Discussion

All the results obtained are discussed in order to identify the different interactions between occupied and vacant orbitals in different molecular structures. The NBO method provides a possible picture of the "natural Lewis structure" of the system. It gives information about the interactions in the filled and virtual orbital spaces. The second-order Fock matrix was performed to evaluate the donor-acceptor interactions in the NBO analysis [21]. The result of the interactions is a loss of occupancy of a localized NBO of the idealized Lewis structure in an empty non-Lewis orbital. The NBO provides access to the electron donor orbitals, the acceptor orbitals and the stabilization energy resulting from the second order micro-perturbation theory [22]. The higher the value of this second order energy, E^2, the more intense the interaction between electron donors and electron acceptors.

The calculations were performed at the B3LYP/6-31++G(d,p) level for the non-complexed molecular structures and the complexes with the water molecule. They were made at the B3LYP/6-31+G(d,p) level for the complexes with alanine. Intramolecular interactions and intermolecular interactions were ex-

amined. The non-complexed molecular structures of Artemisinin, Quinine and Manzamenones were the subject of the intramolecular interaction analysis. These implicate the C-C and C-O bond orbitals in these molecules. For Manzamenones, the model system is studied. Intramolecular interactions were analyzed in the complexes with the water molecule. The aim is to detect possible variations of their stabilization energies after the complexation. As for the intermolecular interactions, the study was carried out on all the complexed molecules. These interactions involve the bonds of the donor and acceptor sites involved in the formation of the established hydrogen bond [23]. The donor or acceptor may come from the molecule under study or from the molecule used to complex (water or alanine).

3.1. Intramolecular Interactions

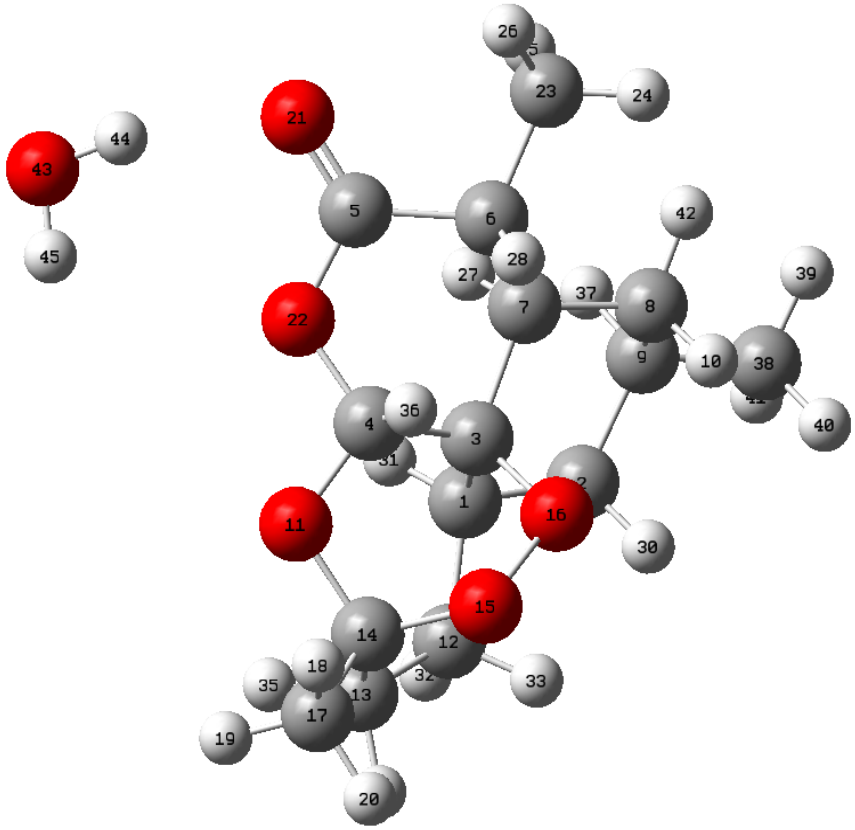
3.1.1. Case of Artemisinin and Quinine

Figure 3 shows the structures of the Artemisinin—H_2O and Quinine—H_2O complexes calculated at the B3LYP/6-31++G(d,p) level of calculation. The numbering of the atoms is indicated. It is the same in these non-complexed molecules and in the complexes.

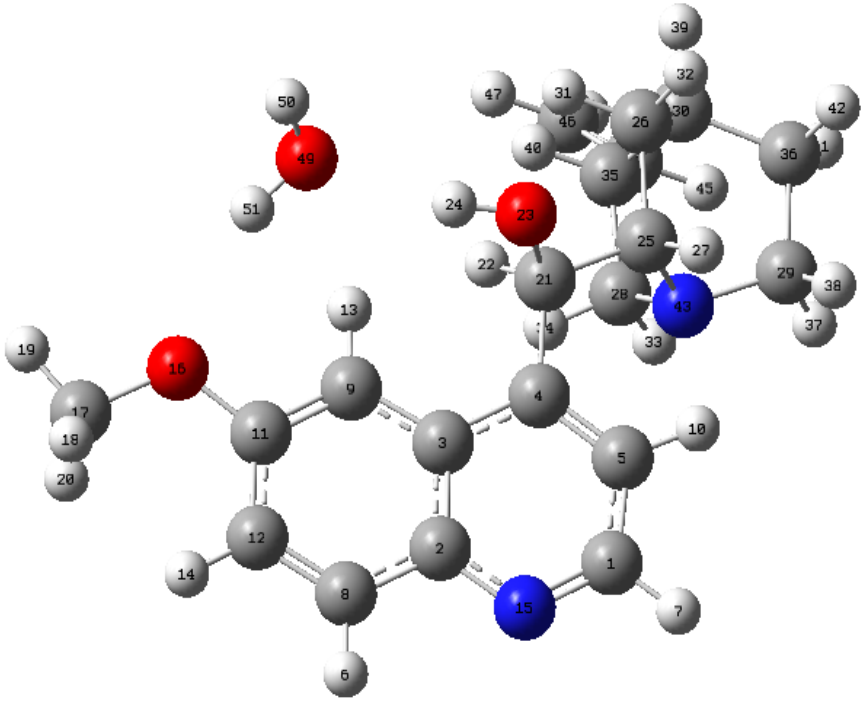
The results of the intramolecular interactions from the NBO analysis performed on non-complexed Artemisinin and Quinine complexed with a water molecule are reported in Table 1 and Table 2. These tables summarize the donors (i), acceptors (j), associated molecular orbital types, electron density (ED), stabilization energy E^2 related to the delocalization from i to j (E^2), NBO orbital energies ε_i and ε_j of the donor and acceptor, respectively, and Fock matrix element $F_{i,j}$.

Table 1 reveals that the complexation of Artemisinin with the water molecule induces only small changes in the parameters of its intramolecular interactions. For a given parameter, a monotonic variation is not observed. An increase in the stabilization energy E^2 is synonymous with a stronger intramolecular interaction. This results in a reinforcement of the stability of the structural skeleton of Artemisinin. The stabilization energies of the interactions involving the donors and acceptors σ (C5-C6) and σ^* (C5-O21), σ (C4-O22) and σ^* (C5-O21), σ (C5-O21) and σ^* (C4-O22) and then σ (C5-O21) and σ^* (C5-C6) increased after the formation of the Artemisinin—H_2O complex. Thus, these four interactions enhance the stability of the Artemisinin structure. On the contrary, the energies of the donor-acceptor interactions σ (C5-C6) and σ^* (C7-C8), σ (C4-O22) and σ^* (C3-O16), σ (C5-O22) and σ^* (C4-O11) have decreased. Overall, complexation contributes more to the increase in stabilization energies of intramolecular interactions in Artemisinin.

Table 2 shows that complex formation between Quinine and water molecules induces changes in the intramolecular interactions of Quinine. Only the σ-donor (C2-C3) and the associated σ^*-acceptor (C2-C8) have their stabilization energies slightly increased. All other stabilization energies between the different donors and associated acceptors decreased.



(A)



(B)

Figure 3. Structures of complexes with H_2O and numbering of Artemisinin (A) and Quinine (B).

Table 1. Analyses of intramolecular interactions in non-complexed Artemisinin and the Artemisinin—H_2O complex by the second-order perturbation theory of the Fock and NBO matrix.

Donors (i)	Type	ED (e)		Acceptors (j)	Type	ED (e)		E^2 (kcal mol^{-1})		$\varepsilon_i - \varepsilon_j$ (a.u)		$F_{i,j}$ (a.u)	
		Non-compl	compl			Non-compl	compl	Non-compl	compl	Non-compl	compl	Non-compl	compl
C5-C6	σ	1.9787	1.9788	C5-O21	σ^*	0.0198	0.0200	0.62	0.70	1.26	1.25	0.025	0.026
				C7-C8		0.0202	0.0200	3.07	3.01	1.02	1.03	0.050	0.050
C4-O22	σ	1.9847	1.9846	C3-O16	σ^*	0.0486	0.0485	0.91	0.89	1.10	1.10	0.028	0.028
				C5-O21		0.0198	0.0200	3.30	3.44	1.48	1.47	0.062	0.063
				O11-C14		0.0775	0.0790	1.27	1.27	1.11	1.11	0.034	0.034
C5-O22	σ	1.9866	1.9870	C4-O11	σ^*	0.0344	0.0333	1.86	1.74	1.21	1.22	0.043	0.041
C5-O21	σ	1.9958	1.9953	C6-C23	σ^*	0.0112	0.0111	0.86	0.85	1.27	1.29	0.03	0.030
				C4-O22		0.0482	0.0502	1.03	1.10	1.37	1.36	0.034	0.035
				C5-C6		0.0764	0.0725	0.88	0.92	1.44	1.45	0.032	0.033

Table 2. Analyses of intramolecular interactions in non-complexed Quinine and the Quinine—H_2O complex by the second-order perturbation theory of the Fock and NBO matrix.

Donors (i)	Type	ED (e)		Acceptors (j)	Type	ED (e)		E^2 (kcal mol^{-1})		$\varepsilon_i - \varepsilon_j$ (a.u)		$F_{i,j}$ (a.u)	
		Non-compl	compl			Non-compl	compl	Non-compl	compl	Non-compl	compl	Non-compl	compl
C2-C3	σ	1.9706	1.9715	C2-C8	σ^*	0.0238	0.0237	2.79	2.97	1.23	1.23	0.052	0.054
				C3-C9		0.0207	0.0209	2.94	2.85	1.24	1.24	0.054	0.053
C4-C5	σ	1.9766	1.9758	C1-C5	σ^*	0.0276	0.0279	2.12	2.05	1.26	1.25	0.046	0.045
C4-C21	σ	1.978	1.9775	C1-C5	σ^*	0.0276	0.0279	2.25	2.14	1.17	1.16	0.046	0.045
C8-C12	σ	1.9763	1.7515	C2-C8	σ^*	0.0238	0.0237	2.17	2.14	1.27	1.27	0.047	0.047
				C2-N15		0.0219	0.0217	4.09	3.14	0.87	1.23	0.053	0.055
C21-O23	σ	1.9864	1.9866	C4-C5	σ^*	0.0204	0.0207	1.55	0.79	1.35	1.41	0.041	0.03

3.1.2. Case of Manzamenones

Based on whether the "model systems" have structural similarities or not, the Manzamenones were grouped into three sets. Set 1 contains the molecules A, B, C, D, E, F, and H for their similarities. The Manzamenones L, M and N form set 2. The third set contains Manzamenones G, J and K; these do not show structural similarities.

The structures of the non-complexed Manzamenones and the complexes with a water molecule were optimized to the B3LYP/6-31++G(d,p) level of theory. The atoms of the "model system" are presented by balls with numbers to identify them. For each of sets 1 and 2, the results are illustrated from those of one of the Manzamenones in it.

Figure 4 shows the type of molecular structure obtained for the Manzamenone—H_2O complexes in set 1. The numbering of the atoms is the same in the non-complexed Manzamenone.

The formation of a complex between Manzamenone A and the water molecule

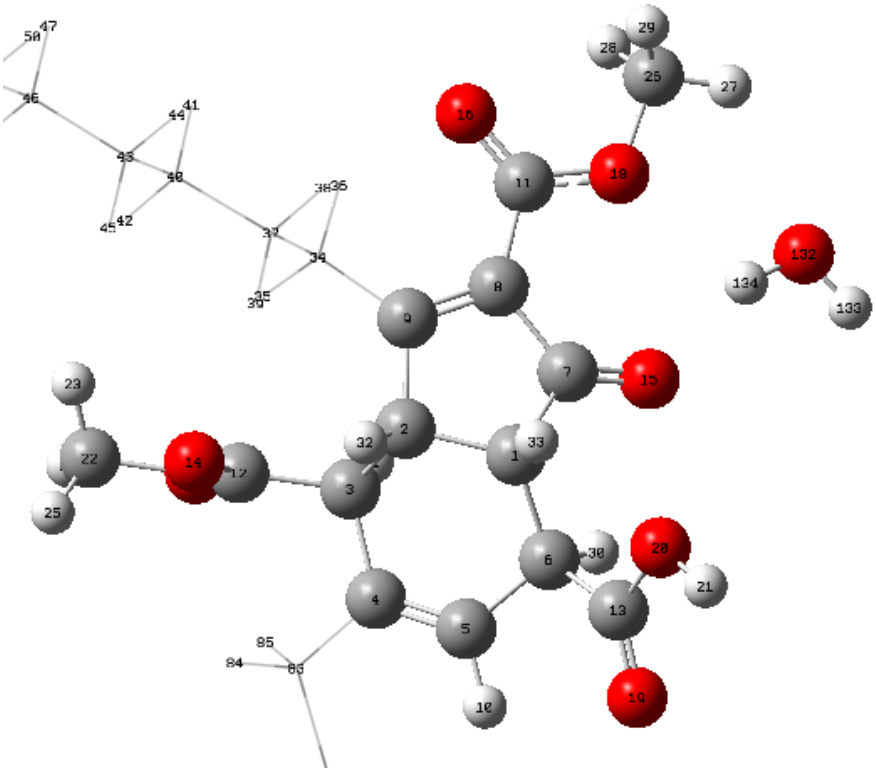


Figure 4. Optimized structure of a Manzamenone—H_2O complex and atom numbering: case of the A—H_2O complex.

causes a change in the intramolecular interactions in this molecule. The stabilization energies increased between certain donors and their associated acceptors. These are the σ (C2-C9) donor and each of the σ^* (C1-C2) and σ^* (C1-C6) acceptors, the σ (C8-C9) donor and the σ^* (C7-O15) acceptor, the σ (C7-O15) donor and each of the two σ^* (C1-C7) and σ^* (C7-C8) acceptors and then the π(C7-O15) donor and its π*(C8-C9) acceptor (**Table 3**). On the other hand, this energy decreased for other interactions between donors and acceptors after to the formation of the complex. This is the case between σ (C2-C9) and σ^* (C2-C3) strongly, σ (C4-C5) and each of the two acceptors σ^* (C3-C4) and σ^* (C5-C6) and finally σ (C8-C9) and σ^* (C2-C3) strongly. The overall balance of stabilization energy changes of intramolecular interactions indicates an increase of 3.63 kcal mol^{-1} versus a decrease of 21.84 kcal mol^{-1}. It appears that the interaction between a water molecule and Manzamenone A destabilizes this molecule like Quinine. The effect being more accentuated for this Manzamenone.

These analyses were performed for all Manzamenones in set 1. These have the same associated donors and acceptors as Manzamenone A. The molecules A and B present the same results because they are identical. For the other Manzamenones in set 1, the variations in interaction energy differ from one structure to another. Thus, the overall increase and decrease are estimated to be respectively: +1.91 kcal mol^{-1} and −0.27 kcal mol^{-1} for C; +6.85 kcal mol^{-1} and −3.07 kcal mol^{-1} for D; +0.86 kcal mol^{-1} and −2.23 kcal mol^{-1} for E; +1.87 kcalmol^{-1} and −0.89

Table 3. Analyses of intramolecular interactions in non-complexed Manzamenone A and the A—H_2O complex by the second-order perturbation theory of the Fock and NBO matrix.

Donors (i)	Type	ED (e)		Acceptors (j)	Type	ED (e)		E^2 (kcal mol^{-1})		$\varepsilon_i - \varepsilon_j$ (a.u)		$F_{i,j}$ (a.u)	
		Non-compl	compl			Non-compl	compl	Non-compl	compl	Non-compl	compl	Non-compl	compl
C2-C9	σ	1.9659	1.9665	C1-C2		0.0204	0.0205	0.73	0.76	0.98	0.99	0.024	0.025
				C1-C6	σ^*	0.0253	0.0255	2.21	2.28	1.00	1.00	0.042	0.043
				C2-C3		0.028	0.0279	19.74	0.82	0.04	0.96	0.025	0.025
C4-C5	σ	1.9764	1.9763	C3-C4	σ^*	0.0331	0.0330	2.36	2.35	1.13	1.13	0.046	0.046
				C5-C6		0.0191	0.0190	2.75	2.70	1.17	1.17	0.051	0.05
C8-C9	σ	1.9725	1.9730	C2-C3		0.028	0.0279	3.26	0.5	0.16	1.08	0.021	0.021
				C7-C8	σ^*	0.0728	0.0691	1.72	1.62	1.18	1.18	0.041	0.039
				C7-O15		0.0119	0.0127	3.73	3.91	1.28	1.31	0.062	0.064
C7-O15	σ	1.9961	1.9957	C1-C7	σ^*	0.0762	0.0710	0.71	1.05	1.46	1.48	0.029	0.036
				C7-C8		0.0728	0.0691	0.87	0.99	1.52	1.54	0.033	0.035
C7-O15	π	1.9795	1.9810	C8-C9	π^*	0.0221	0.1123	0.56	3.47	1.71	0.42	0.028	0.035

kcal mol^{-1} for F then +1.85 kcal mol^{-1} and −2.18 kcal mol^{-1} for H. These results show that the intramolecular interactions of Manzamenones C, D and F are more stabilized after the formation of a complex with the water molecule. The opposite is observed with manazmenones E and H.

Compared to the two antimalarials studied, the "model systems" of Manzamenones A, B, E, and H show similar "behavior" to Quinine in complexes with water. As for Manzamenones C, D, and F, they are similar to Artemisinin.

Figure 5 shows the type of molecular structure obtained for the Manzamenone—H_2O complexes of set 2. The numbering of the atoms is the same in the complexed Manzamenone.

The results of the intramolecular interaction parameters from the NBO analysis performed on non-complexed and complexed Manzamenone L (L—H_2O) are reported in Table 4.

The contents of Table 4 show some changes in the intramolecular interactions in the non-complexed Manzamenone L and in the L—H_2O complex. Analysis of the changes in stabilization energy indicates both increases and decreases. The donors and their associated acceptors that underwent an increase are σ (C8-C9) and σ^* (C7-C8) estimated at 0.10 kcal mol^{-1}, σ (C7-O23) and σ^* (C7-C8) estimated at 0.06 kcal mol^{-1}. The decrease in stabilization energies involves several associated donors and acceptors. These are:

- The σ (C2-C9) donor and its three acceptors σ^* (C1-C2), σ^* (C1-C6) and then σ^* (C1-C7) have their overall stabilization energy decreased by 0.29 kcal mol^{-1}.
- The σ-donor (C4-C5) and the σ^*-acceptor (C3-C4) destabilized by 0.26 kcal mol^{-1}.

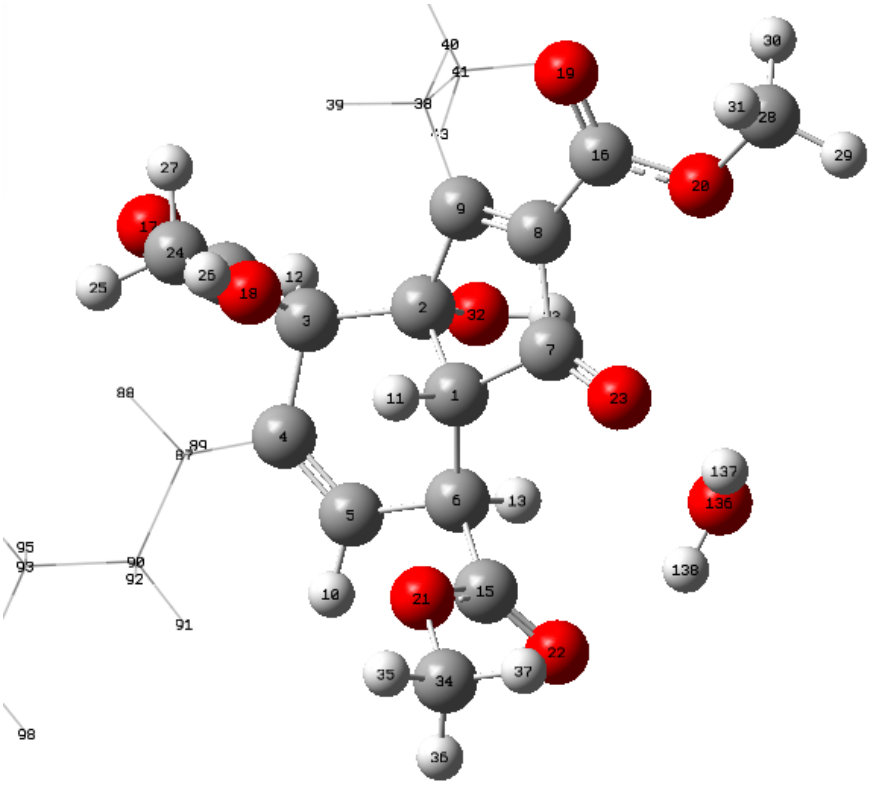


Figure 5. Optimized structure of a Manzamenone—H_2O complex and atom numbering: case of L—H_2O complex.

Table 4. Analyses of intramolecular interactions in non-complexed Manzamenone L and the L—H_2O complex by the second-order perturbation theory of the Fock and NBO matrix.

Donors (i)	Type	ED (e)		Acceptors (j)	Type	ED (e)		E^2 (kcal mol^{-1})		$\varepsilon_i - \varepsilon_j$ (a.u)		$F_{i,j}$ (a.u)	
		Non-compl	compl			Non-compl	compl	Non-compl	compl	Non-compl	compl	Non-compl	compl
C2-C9	σ	1.9656	1.9662	C1-C2		0.0421	0.0419	0.95	0.74	0.99	0.99	0.027	0.024
				C1-C6	σ^*	0.0252	0.0248	2.23	2.17	1.01	1.02	0.042	0.042
				C1-C7		0.0727	0.0712	0.62	0.60	0.95	1.03	0.022	0.022
C4-C5	σ	1.9790	1.9789	C3-C4	σ^*	0.0323	0.0322	2.38	2.12	1	1.11	0.044	0.044
				C5-C6		0.0197	0.0190	2.03	2.03	1.14	1.14	0.043	0.043
C8-C9	σ	1.9719	1.9718	C2-C3		0.0359	0.0355	1.69	1.67	1.11	1.11	0.039	0.038
				C2-C9	σ^*	0.0484	0.0484	1.12	1.12	1.13	1.12	0.032	0.032
				C7-C8		0.0774	0.0760	1.95	2.05	1.17	1.18	0.043	0.044
C7-O23	σ	1.9960	1.9952	C1-C7	σ^*	0.0727	0.0712	0.86	0.80	1.4	1.49	0.031	0.031
				C7-C8		0.0774	0.0760	0.83	0.89	1.51	1.53	0.032	0.034
C7-O23	π	1.9776	1.9773	C8-C9	π^*	0.1062	0.1070	4.06	3.75	0.41	0.42	0.037	0.036

- The σ donor (C8-C9) and σ^* acceptor (C2-C3) destabilized by 0.02 kcal mol^{-1}.
- The σ (C7-O23) donor and σ^* (C1-C7) acceptor decreased in energy by 0.06

kcal mol^{-1}.

- The π (C7-O23) and π* (C8-C9) acceptor are destabilized by 0.31 kcal mol^{-1}.

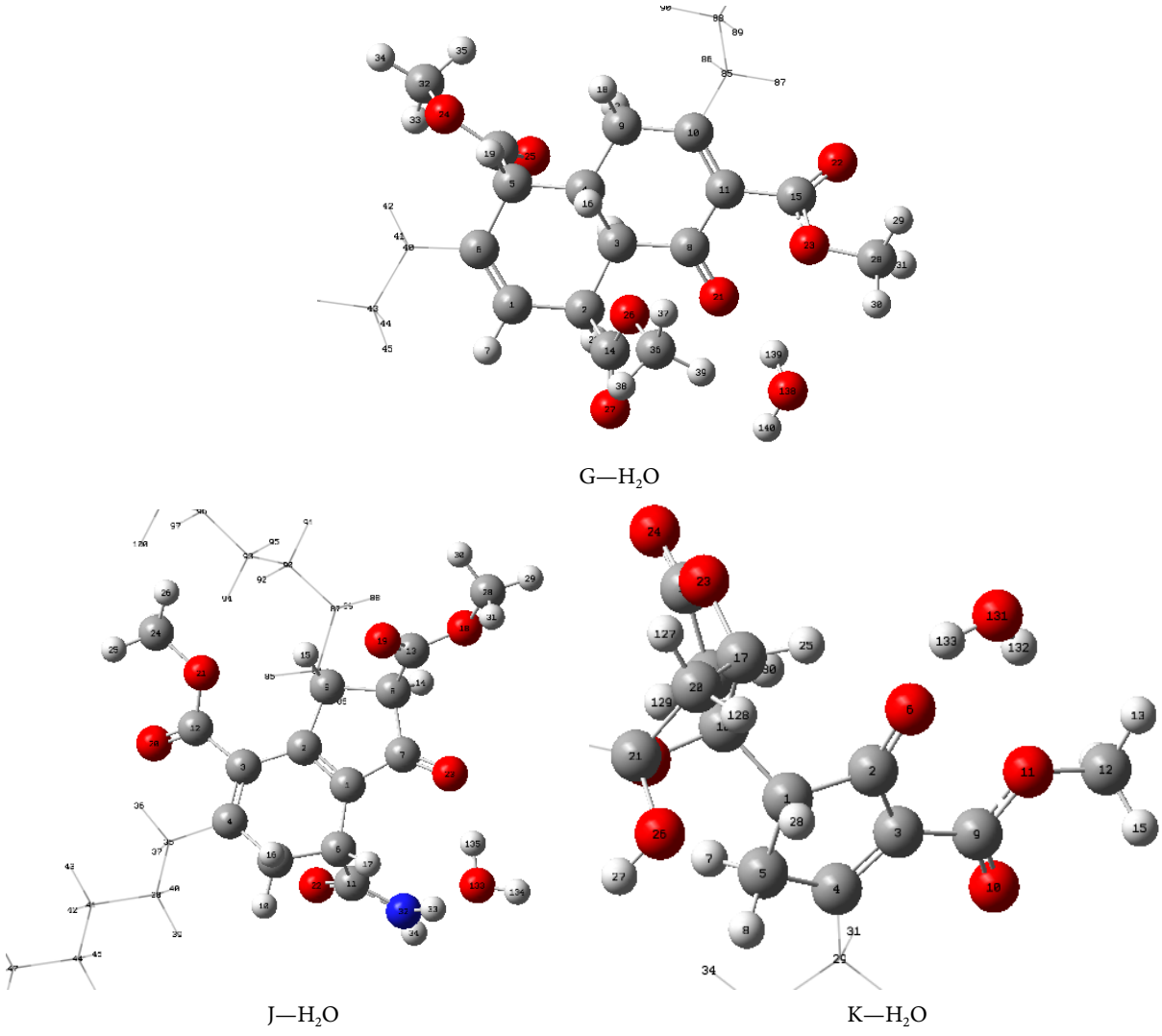
In summary, the structure of Manzamenone L, like that of Quinine, is more destabilized when it binds with a water molecule than in the non-complexed state.

With a few variations, the intramolecular interactions of Manzamenones M and N involve the same associated donors and acceptors as L. Variations in stabilization energies were estimated for these Manzamenones. After complex formation with H_2O, the overall increase in interaction energy between associated donors and acceptors is worth +0.45 kcal mol^{-1} and +4.36 kcal mol^{-1} respectively for these. As for the decrease in energy between associated donors and acceptors, it is worth −3.15 kcal mol^{-1} and −0.34 kcal mol^{-1} respectively. It follows that complex formation with H_2O destabilizes Manzamenone M and stabilizes N. From intramolecular interactions, Manzamenone M is close to Quinine while Manzamenone N is close to Artemisinin.

For Manzamenones G, J, and K in set 3, **Figure 6** shows the Manzamenone—H_2O complexes and the atom numbering. This numbering is the same in each non-complexed molecule. The results of the intramolecular interaction parameters are reconciled in **Tables 5-7** respectively.

Table 5 shows that the formation of the complex between Manzamenone G and a water molecule changes the intramolecular interactions in the structure of G. For the donors and their associated acceptors σ (C9-C10) and σ* (C4-C5), σ (C10-C11) and σ* (C8-O21) and then σ (C8-O21) and σ* (C3-C4) the interaction is strengthened by 0.05 kcal mol^{-1}, 0.44 kcal mol^{-1}, and 0.08 kcal mol^{-1} respectively. However with the donors and acceptors σ (C1-C6) and (σ* (C1-C2) then σ* (C5-C6)), σ (C10-C11) and σ* (C8-C11), σ (C8-O21) and σ* (C3-C8) then π (C8-O21) and π* (C10-C11) there is a decrease in stabilization energy. These changes are estimated to be −0.96 kcal mol^{-1}, −0.40 kcal mol^{-1}, −2.38 kcal mol^{-1}, −0.46 kcal mol^{-1} respectively. This results in an overall increase of 0.57 kcal mol^{-1} versus a decrease of 4.20 kcal mol^{-1}. Like Quinine, the interaction between a water molecule and Manzamenone G destabilizes it.

The results in **Table 6** show that the intramolecular interactions of Manzamenone J are modified when it forms a complex with a water molecule. Most of the donor and associated acceptor(s) pairs are stabilized after the formation of the J—H_2O complex. This is the case for the eight pairs consisting of donor σ (C1-C2) and three acceptors σ* (C1-C6), σ* (C1-C7) and then σ* (C2-C3), donor σ (C1-C7) with two acceptors σ* (C1-C2) and then σ* (C1-C6), donor σ (C3-C4) and its acceptor σ* (C2-C3), donor σ (C7-C23) with two acceptors σ* (C1-C2) and then σ* (C7-C8). These interactions are stabilized by 1.64 kcal mol^{-1}, 1.09 kcal mol^{-1}, 2.79 kcal mol^{-1} and 0.11 kcal mol^{-1} respectively; *i.e.*, overall by 5.63 kcal mol^{-1}. The associated donor and acceptor pairs σ (C1-C7) and σ* (C2-C3), σ (C7-O23) and σ* (C1-C7) and then π (C7-O23) and π* (C1-C2) are destabilized by 0.31 kcal mol^{-1}, 0.23 kcal mol^{-1} and 0.22 kcal mol^{-1} respectively.



G—H_2O

J—H_2O K—H_2O

Figure 6. Optimized structures of the Manzamenone—H_2O complexes in set 3.

Table 5. Analyses of intramolecular interactions in non-complexed Manzamenone G and the G—H_2O complex by the second-order perturbation theory of the Fock and NBO matrix.

Donors (i)	Type	ED (e)		Acceptors (j)	Type	ED (e)		E^2 (kcal mol^{-1})		$\varepsilon_i - \varepsilon_j$ (a.u)		$F_{i,j}$ (a.u)	
		Non-compl	compl			Non-compl	compl	Non-compl	compl	Non-compl	compl	Non-compl	compl
C1-C6	σ	1.9777	1.9780	C1-C2	σ^*	0.0195	0.0193	2.26	2.19	1.17	1.16	0.046	0.045
				C5-C6		0.0313	0.0309	3.27	2.41	0.81	1.13	0.046	0.047
C9-C10	σ	1.9733	1.9733	C4-C5	σ^*	0.0228	0.0228	1.99	2.04	1.00	1.00	0.040	0.040
				C4-C9		0.0175	0.0175	0.97	0.97	1.00	1.01	0.028	0.028
C10-C11	σ	1.9717	1.9726	C8-C11	σ^*	0.0666	0.0634	3.25	2.88	1.23	1.22	0.057	0.053
				C8-O21		0.0102	0.0110	1.95	2.39	1.36	1.33	0.046	0.051
C8-O21	σ	1.9934	1.9931	C3-C4	σ^*	0.0282	0.0278	0.52	0.60	1.45	1.44	0.025	0.026
				C3-C8		0.0653	0.0608	3.32	0.94	0.42	1.46	0.034	0.034
C8-O21	π	1.9720	1.9716	C10-C11	π^*	0.0262	0.0251	5.16	4.70	0.42	0.42	0.042	0.041

Table 6. Analyses of intramolecular interactions in non-complexed Manzamenone J and the J—H_2O complex by the second-order perturbation theory of the Fock and NBO matrix.

Donors (i)	Type	ED (e)		Acceptors (j)	Type	ED (e)		E^2 (kcal mol^{-1})		$\varepsilon_i - \varepsilon_j$ (a.u)		$F_{i,j}$ (a.u)	
		Non-compl	compl			Non-compl	compl	Non-compl	compl	Non-compl	compl	Non-compl	compl
C1-C2	σ	1.9700	1.9668	C1-C6		0.0288	0.0298	3.30	3.79	1.16	1.14	0.055	0.059
				C1-C7	σ*	0.0626	0.0598	1.98	2.58	1.22	1.22	0.044	0.050
				C2-C3		0.0309	0.0313	2.87	3.42	1.22	1.23	0.053	0.058
C1-C7	σ	1.9746	1.9749	C1-C2		0.0217	0.0227	3.06	3.78	1.31	1.32	0.057	0.063
				C1-C6	σ*	0.0288	0.0298	1.36	1.73	1.10	1.10	0.035	0.039
				C2-C3		0.0309	0.0313	4.73	4.42	1.17	1.18	0.066	0.065
C3-C4	σ	1.9696	1.9706	C2-C9	σ*	0.0302	0.0278	0.51	3.30	0.66	1.13	0.017	0.054
C7-O23	σ	1.9949	1.9956	C1-C2		0.0217	0.0227	0.82	0.86	1.72	1.69	0.034	0.034
				C1-C7	σ*	0.0626	0.0598	1.28	1.05	1.57	1.55	0.041	0.037
				C7-C8		0.0746	0.0709	0.67	0.74	1.44	1.41	0.028	0.029
C7-O23	π	1.9740	1.9779	C1-C2	π*	0.1681	0.1749	4.32	4.10	0.43	0.42	0.040	0.039

Table 7. Analyses of intramolecular interactions in non-complexed Manzamenone K and the K—H_2O complex by the second-order perturbation theory of the Fock and NBO matrix.

Donors (i)	Type	ED(e)		Acceptors (j)	Type	ED (e)		E^2 (kcal mol^{-1})		$\varepsilon_i - \varepsilon_j$ (a.u)		$F_{i,j}$ (a.u)	
		Non-compl	compl			Non-compl	compl	Non-compl	compl	Non-compl	compl	Non-compl	compl
C2-C3	σ	1.9753	1.9737	C2-O6	σ*	0.0120	0.0123	0.89	0.83	1.20	1.25	0.029	0.029
				C3-C4		0.0199	0.1286	2.91	3.34	1.25	1.29	0.054	0.059
C3-C4	σ	1.9727	1.9719	C2-C3	σ*	0.0723	0.0677	2.12	1.80	1.30	1.19	0.047	0.042
				C4-C5		0.0250	0.0253	1.05	1.46	1.24	1.16	0.032	0.037
C4-C5	σ	1.9738	1.9725	C1-C2	σ*	0.0747	0.0703	0.77	0.91	1.01	1.01	0.025	0.027
				C1-C5		0.0148	0.0156	0.70	1.02	1.01	1.01	0.024	0.029
C2-O6	σ	1.9951	1.9955	C2-C3	σ*	0.0723	0.0677	0.92	0.69	1.55	1.54	0.034	0.030
C2-O6	π	1.9797	1.9799	C3-C4	π*	0.0199	0.1286	3.42	3.52	0.40	0.42	0.034	0.035

That is a total decrease of 0.76 kcal mol^{-1}. Like Artemisinin, the interaction between a water molecule and Manzamenone J stabilizes its structure.

The data in Table 7 show that the stabilization energy of intramolecular interactions increased for the σ (C2-C3) donor and its σ* (C3-C4) acceptor, the σ (C3-C4) donor and its σ* (C4-C5) acceptor, the σ (C4-C5) donor and its two σ* (C1-C2) and then σ* (C1-C5) acceptors, and the σ (C2-O6) donor with its σ* (C1-C16) acceptor. All these interactions are stabilized by 1.40 kcal mol^{-1}. The donors and acceptors for which the intramolecular interaction is destabilized after complex formation are σ (C2-C3) and σ* (C2-O6), σ (C3-C4) and σ* (C2-C3), σ (C2-O6) donor and σ* (C2-C3) acceptor. The balance of these decreases is 0.61 kcal mol^{-1}. Manzamenone K complexed with a water molecule stabilizes its structure.

3.2. Intermolecular Interactions

This analysis is based on the optimized structures of the complexes formed between each molecule (Artemisinin, Quinine and the Manzamenones) with a water molecule and then with a 3-aminopropanoic acid molecule (Alanine). The study describes only the intermolecular interaction of the two sites involved in the formation of a hydrogen bond [23].

3.2.1. Case of Complexes with a Water Molecule

The structures of the complexes are the same as those used for the analysis of intramolecular interactions. The electron donors, associated acceptors, electron densities, and stabilization energies of the interactions were identified in the different complexes. The results are reported in **Table 8**.

Table 8. Electron donor site(s) and associated electron acceptor(s); stabilization energies of intermolecular interactions in complexes with a water molecule.

Complexes	Donors (i)	ED (e)	Acceptors (j)	ED (e)	E^2 (kcal mol^{-1})
Arte—H_2O	LP(1)O21	1.9711	σ^* (O43-H44)	0.0157	1.76
	LP(2)O21	1.8434	σ^* (O43-H44)	0.0157	4.58
Quin—H_2O	LP(1)O16	1.9615	σ^* (O49-H50)	0.0011	0.15
	LP(2)O16	1.8593	σ^* (O49-H50)	0.0011	0.20
A(B)—H_2O	LP(1)O15	1.9705	σ^* (O132-H133)	0.0004	113.26
	LP(2)O15	1.8722	σ^* (O132-H133)	0.0004	232.11
C—H_2O	LP(1)O84	1.9675	σ^* (O138-H140)	0.0003.	1.24
	LP(2)O84	1.8747	σ^* (O138-H140)	0.0003	0.51
D—H_2O	LP(1)O26	1.9688	σ^* (O133-H135)	0.0004	0.07
	LP(2)O26	1.8803	σ^* (O133-H135)	0.0004	166.54
E—H_2O	LP(1)O31	1.9692	σ^* (O148-H149)	0.0129	0.96
	LP(2)O31	1.8803	σ^* (O148-H149)	0.0129	0.30
F—H_2O	LP(1)O24	1.9679	σ^* (O144-H146)	0.0009	2.30
	LP(2)O24	1.8686	σ^* (O144-H146)	0.0009	26.67
G—H_2O	LP(1)O21	1.9711	σ^* (O138-H139)	0.0150	0.44
	LP(2)O21	1.8930	σ^* (O138-H140)	0.0005	1.25
H—H_2O	LP(1)O128	1.9657	σ^* (O150-H152)	0.0015	0.16
	LP(2)O128	1.8717	σ^* (O150-H152)	0.0015	0.09
J—H_2O	LP(1)O23	1.8700	σ^* (O133-H135)	0.0369	820.20
	LP(2)O23	1.9625	σ^* (O133-H134)	0.0013	0.34
K—H_2O	LP(1)O6	1.9668	σ^* (O131-H132)	0.0004	49.13
	LP(2)O6	1.8764	σ^* (O132-H132)	0.0004	0.75
L—H_2O	LP(1)O23	1.9755	σ^* (O136-H137)	0.0048	0.19
	LP(2)O23	1.8755	σ^* (O136-H137)	0.0048	0.06
M—H_2O	LP(1)O24	1.9694	σ^* (O133-H135)	0.0004	0.09
	LP(2)O24	1.8702	σ^* (O133-H135)	0.0004	3.24
N—H_2O	LP(1)O14	1.9681	σ^* (O135-H136)	0.0007	1.35
	LP(2)O14	1.8697	σ^* (O135-H137)	0.0283	1.88

The results contained in Table 8 show very clearly that in all the complexes formed with a water molecule, the electron donor is an oxygen atom. This one shares its lone pairs (Lone Pair: LP). The electron density of each LP is very close to 2. The acceptors have much lower electron densities than the donors. The stabilization energies of intermolecular interactions from NBO analyses vary for these complexes from 0.06 kcal mol^{-1} to 820.20 kcal mol^{-1}. For the most part, these interactions are weak with less than 5.00 kcal mol^{-1}. Three complexes stand out with much more stabilized interactions. These are those formed by Manzamenones A, D and J. The interactions are moderately stabilized for the complexes of Manzamenones F and K with H_2O. The other Manzamenones C, E, G, H, L, M and N with Artemisinin and Quinine show the least stable intermolecular interactions.

3.2.2. Case of Complexes with a 3-Aminopropanoic Acid Molecule (Alanine)

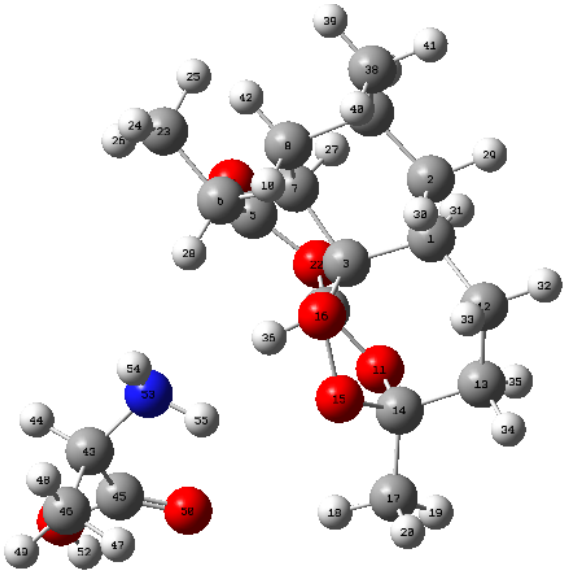
Figure 7 contains some examples of optimized structures of the thirteen complexes formed with an alanine molecule. The results of electron donors, associated acceptors, electron densities and calculated stabilization energies are reported in Table 9.

Table 9 shows that apart from Quinine, the electron donors of the other molecules are oxygen atoms. The committed electrons are the two lone pairs (Lone Pair: LP).

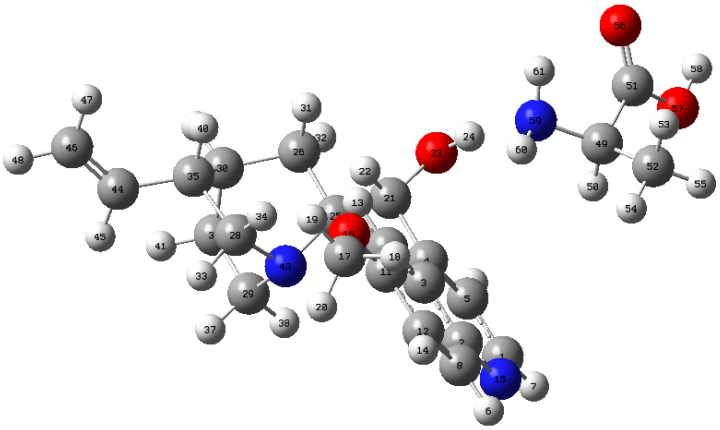
The electron densities of the donors are always very close to 2. In the complex with Quinine, the electron donor is the nitrogen of alanine. All acceptors have very low electron densities. The stabilization energies of the intermolecular interactions are low. They are globally between 0.06 kcal mol^{-1} and 5.00 kcal mol^{-1} except for Quinine. This one has the most important stabilization energy. It is worth 21.62 kcal mol^{-1}. The acceptors are N-H groups for all the molecules except Quinine and Manzamenone K. These two molecules have an O-H group as acceptor. Compared to Quinine, Artemisinin and the studied Manzamenones show very similar intermolecular interaction properties when complexed with alanine. This finding is in overall agreement with the results of the interaction energies of these complexes in a previous work [23].

4. Conclusion

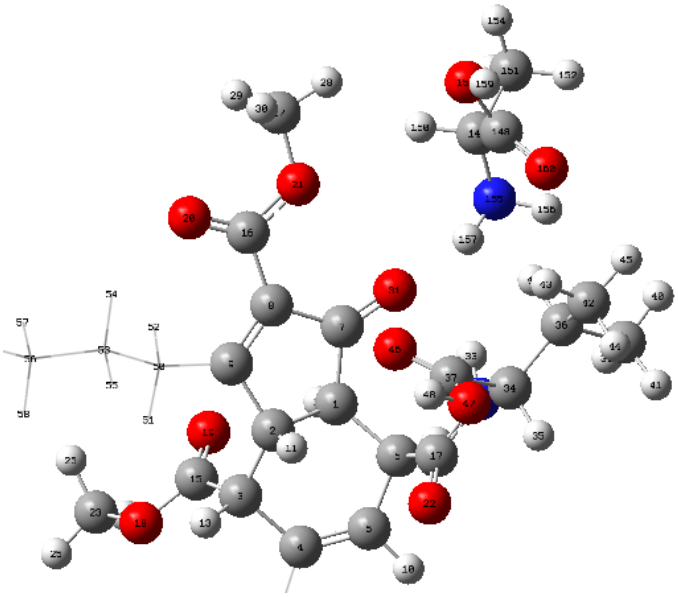
The NBO method was used to analyze the intramolecular and intermolecular interactions of the studied molecules. The intramolecular interactions were analyzed for each molecule in the non-complexed state and in its complex with a water molecule. Variations in the stabilization energy of the intramolecular interactions showed that the structures of Artemisinin and the Manzamenones C, D, F, N, J and K are stabilized after complexation. On the other hand, the structures of Quinine and Manzamenones A, B, E, H, L, M and G are destabilized when complexed with a water molecule. As for the analysis of intermolecular interactions, three structures stand out with much higher stabilization energies,



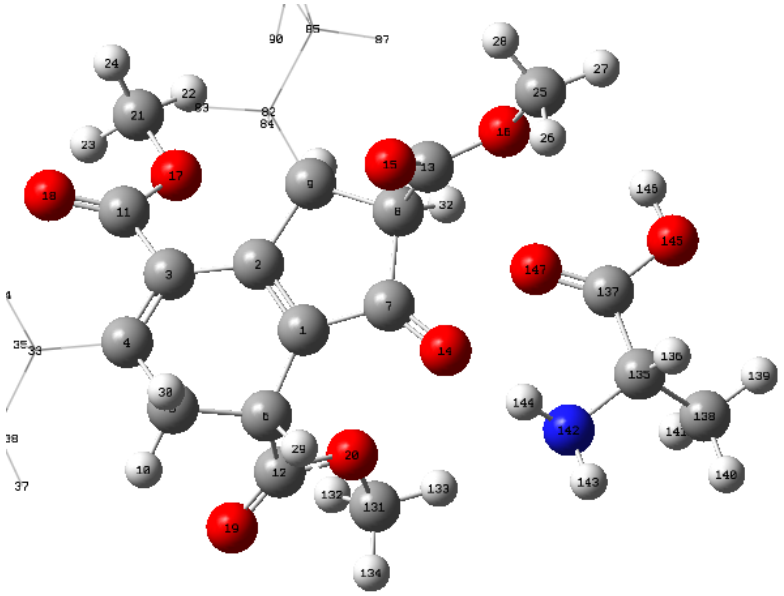
Artemisinin—Alanine



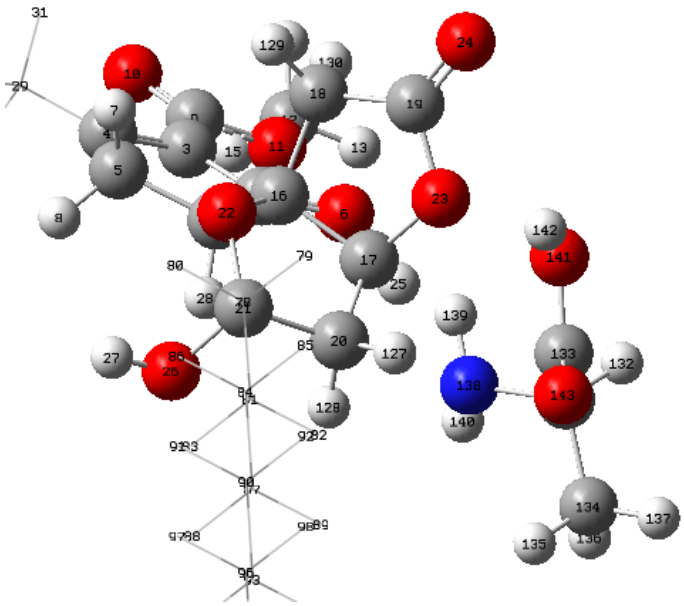
Quinine—Alanine



E—Alanine



N—Alanine



K—Alanine

Figure 7. Some optimized structures of complexes (molecules—alanine) from NBO analysis.

thus strongly stabilized. These are the complexes formed by Manzamenones A, D and J with water. Intermolecular interactions are moderately stabilized in the complexes of Manzamenones F and K. Manzamenones C, E, G, H, L, M and N as well as Artemisinin and Quinine show the least stable intermolecular interactions. The stabilization energies of intermolecular interactions are low for complexes with alanine. They are globally between 0.06 kcal mol^{-1} and 5.00 kcal mol^{-1} except for Quinine. This one has the most important stabilization energy. It is worth 21.62 kcal mol^{-1}. The electron acceptors are N-H groups for all the

Table 9. Electron donor site(s) and associated electron acceptor(s); stabilization energies of intermolecular interactions in complexes with an alanine.

Complexes	Donors (i)	ED (e)	Acceptors (j)	ED (e)	E^2 (kcal mol^{-1})
Arte—Ala	LP(1)O15	1.9724	σ^* (N53-H55)	0.0158	1.40
	LP(2)O15	1.9368	σ^* (N53-H55)	0.0158	0.69
Quin—Ala	LP(1)N59	1.9115	σ^* (O23-H24)	0.0534	21.62
	N59-H61	1.9889	σ^* (O23-H24)	0.0534	0.18
A(B)—Ala	LP(1)O15	1.9713	σ^* (N132-H134)	0.0524	2.38
	LP(2)O15	1.8708	σ^* (N132-H133)	0.0654	0.08
C—Ala	LP(1)O84	1.9706	σ^* (N138-H140)	0.0166	2.74
	LP(2)O184	1.8687	σ^* (N138-H139)	0.0101	0.06
D—Ala	LP(1)O26	1.9858	σ^* (N140-H142)	0.0250	3.84
	LP(2)O26	1.8744	σ^* (N140-H141)	0.0112	4.61
E—Ala	LP(1)O31	1.9658	σ^* (N155-H157)	0.0143	3.08
	LP(2)O31	1.8784	σ^* (N155-H157)	0.0143	0.46
F—Ala	LP(1)O24	1.9700	σ^* (N151-H153)	0.0257	2.83
	LP(2)O24	1.8700	σ^* (N151-H153)	0.0257	4.69
G—Ala	LP(1)O21	1.9675	σ^* (N145-H147)	0.0198	4.43
	LP(2)O21	1.8895	σ^* (N145-H147)	0.0198	1.82
H—Ala	LP(1)O128	1.9686	σ^* (N157-H158)	0.0202	2.24
	LP(2)O128	1.8772	σ^* (N157-H158)	0.0202	1.84
J—Ala	LP(1)O23	1.9695	σ^* (N140-H141)	0.0197	1.49
	LP(2)O23	1.8763	σ^* (N140-H141)	0.0197	0.85
K—Ala	LP(1)O23	1.9583	σ^* (O141-H142)	0.0242	2.32
	LP(2)O23	1.7964	σ^* (O141-H142)	0.0242	1.20
L—Ala	LP(1)O23	1.9698	σ^* (N136-H137)	0.0185	3.56
	LP(2)O23	1.8750	σ^* (N136-H137)	0.0185	1.99
M—Ala	LP(1)O33	1.971	σ^* (N133-H135)	0.0119	0.06
	LP(2)O33	1.8610	σ^* (N133-H135)	0.0119	0.07
N—Ala	LP(1)O14	1.9729	σ^* (N142-H143)	0.0164	1.33
	C7-O14	1.8759	σ^* (N142-H143)	0.0164	0.13

molecules except Quinine and Manzamenone K.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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