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Stability and Absorption of Fourteen Manzamenones, Artemisinin and Quinine Isolated and Complexed with H_2O, Alanine by ONIOM, DFT and TD-DFT Methods

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Abstract: This work is carried out on fourteen Manzamenones and two antimalarials (Quinine and Artemisinin). It was undertaken to compare their reactivity parameters on one hand and on the other hand, the absorption properties in the UV range for the isolated molecules and two types of complexes studied. Manzamenones are an atypical class of fatty acids. They are isolated from a marine sponge of the genus Plakortis kenyensis and used in the treatment of malaria. The study is based on quantum chemical calculations. First, we calculated and compared the reactivity parameters of the complexes to those of the isolated molecules. The levels of theory used to calculate the complexes of Manzamenones are ONIOM (B3LYP/6-31++G(d,p); AM1) and ONIOM (B3LYP/6-31+G(d,p); AM1). Those used to calculate the complexes of Quinine and Artemisinin are B3LYP/6-31++G(d,p) and B3LYP/6-31+G(d,p). Secondly, for each molecule and its two studied complexes, we have realized the UV absorption spectra. The time dependent density functional theory (TD-DFT) method was used for these calculations. These different comparisons allowed detecting similarities and differences between Manzamenones and antimalarials (Quinine and Artemisinin). These calculations showed that all these structures absorb in the UV-visible range with absorption maxima wavelengths between 200 nm and 350 nm. The possible red shift, bue shift, hyperchromic and hypochromic effects of the probes (water and alanine) were examined on the spectra.

Keywords: Malaria, Manzamenone, Absorption Spectra, TD-DFT, Reactivity, Level of Theory

1. Introduction

Malaria remains the most widespread and most dangerous parasitic disease in the world. It is caused by a haematozoan of the genus Plasmodium. It is transmitted to humans by the bite of a female mosquito of the genus Anopheles [1]. With 90% of cases and 91% of deaths related to malaria, sub-Saharan Africa pays a heavy price [2]. Malaria is an increasing factor of poverty because of its negative impact on economic and human development in endemic areas [3]. In Côte d'Ivoire, malaria is a major public health problem due to its morbidity, mortality and socio-economic repercussions [4]. Five parasites of the genus Plasmodium are responsible for this disease. However, the majority of deaths are caused by Plasmodium falciparum and Plasmodium vivax [5-8].

The parasite is increasingly developing resistance to the main classes of effective drugs (Quinine, Quinoline, Mefloquine and Artemisinin). Quinine is usually used in severe cases [9-11]. Like Quinine from vegetable sources, Manzamenones, derived from marine sponges, could be used in drug diversification for the treatment of malaria [12]. These molecules are atypical fatty acid derivatives, of bicyclic or spiro form, attached or not to a ring with the presence of long hydrocarbon chains substituted on the

bicyclic. In the genus Plakortis, they are present in different derivatives [13, 14]. The derivative, Manzamenone O, has antibacterial activity on the strain Micrococcus luteus, and antifungal activity on the strains Aspergillus niger and trichophyton mentagrophytes.

This work, dealing with fourteen Manzamenones and the two antimalarials (Quinine and Artemisinin), continues the comparison of some structural properties. The objective is to detect similarities and differences between Manzamenones and antimalarials. This project is part of the research dedicated to the fight against malaria.

Previous works, expose the comparison of reactivity properties as well as the interaction sites of Manzamenones to those of Quinine and Artemisinin [15]. Others have been applied to compare their lipophilicity and their complexation parameters with a water molecule and then with 3-aminopropanoic acid (Alanine), a protein residue of the polymerase [16].

The first part of this work compares, for each molecule, its reactivity parameters with those of its complexes with water and then with 3-aminopropanoic acid. The second part is focused on the analysis of the spectroscopic properties in the Ultra-Violet range. For each molecule and its two complexes, the spectra are calculated. They are compared to each other. All calculations are performed in gas phase. A mixed method of quantum chemistry "ONIOM 2" is used for the calculations of Manzamenones. The ONIOM method, developed by Morokuma et al [17-19], has often been used successfully on large molecules [20-23]. Quinine and Artemisinin are described with the DFT method (B3LYP).

2. Studied Molecules and Calculation Methods

2.1. Studied Molecules: Artemisinin, Quinine and Manzamenones

Fourteen (14) Manzamenones have been listed in the literature. Each one is identified by its structure and designated by a refcode. These molecules are heterocyclic atypical fatty acids. Except for three Manzamenones G, K and O, the structures of eleven (A, B, C, D, E, F, H, J, L, M and N) contain a bicyclo [4, 3, 0] nonane. The structure of G contains a [4, 4, 0] decane. Manzamenone K has a bicyclo [3, 3, 0] octane. Manzamenone O has a bicyclo [4, 3, 0] nonane and a second bicyclo [3, 3, 0] octane. Manzamenones A and B differ only in the configuration of carbon C_5.

Artemisinin and Quinine are chosen as references. Artemisinin contains a tetracycle and Quinine has a bicycle and a tricycle.

In sum, the structure of each molecule studied contains at least one policycle. The structures of Artemisinin and Quinine are in Figure 1; those of the Manzamenones in Figure 2.

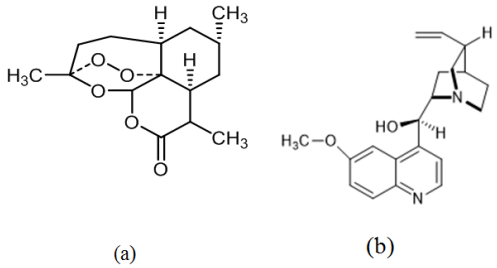


Figure 1. *Structures of Artemisinin (a) and Quinine (b).*

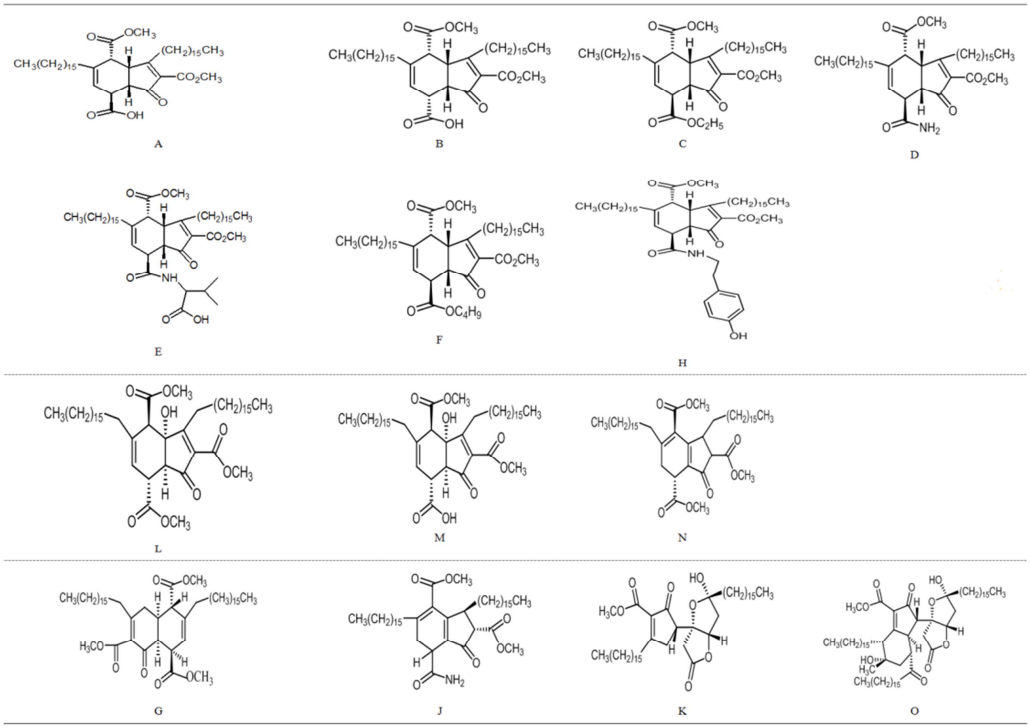


Figure 2. *Structures and refcodes of the studied Manzamenones.*

2.2. Methods of Calculation and Calculated Parameters

2.2.1. Methods of Calculation

(i). The ONIOM Method

The ONIOM method consists in splitting the studied system into several layers, each of them being treated at a different level of calculation. In the case of a two-layer system (ONIOM2), the complete system will be the real system while the part that is of particular interest will be the model. In previous work, we have applied this computational method to the Manzamenones in Figure 2 [15, 16]. In those works, like these, the partitioning of Manzamenones into "real" and "model" systems is shown in Figure 3.

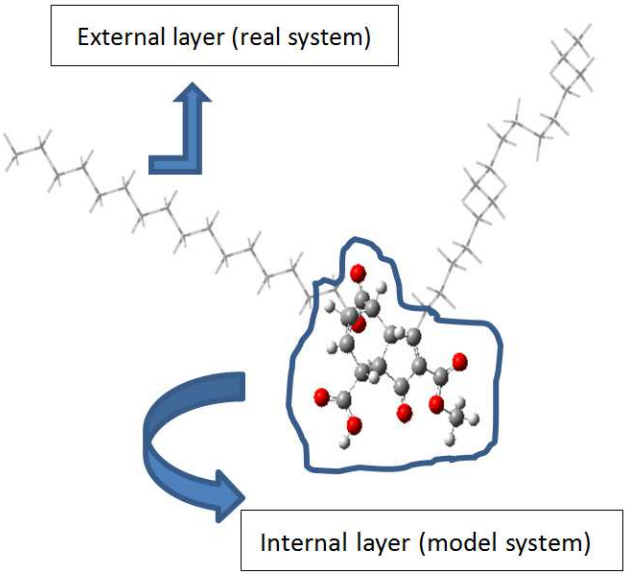


Figure 3. *Splitting of a Manzamenone---X complex (X = H_2O or Alanine) for calculations with the ONIOM 2 method.*

(ii). The Time-Dependent Density Functional Theory (TD-DFT)

Computing data on the excited electronic states of molecules is necessary for the understanding of any microscopic state in spectroscopy and photochemistry. Density functional theory is effective in determining many ground state properties with good accuracy. Gunnarsson and Lundqvist [24] proved that the Hohenberg-Kohn theorem can be extended to the lowest energy non-degenerate states of each irreducible representation of the symmetry group of the molecule. For the search of all excited states, one can extend the achievements of DFT to the treatment of molecular excitations. The TD-DFT [25-27] is thus a generalization of the density functional formalism. This generalization gives rise to a computational principle related to electronic excitation spectra.

The TD-DFT calculations allow determining and interpreting electronic absorption spectra. Certainly, in TD-DFT calculations, there are imprecisions on the fundamental state [25]. The method still suffers from a number of weaknesses [28]. It does not allow for the correct description of multi-configurational systems of excited states. Due to its limitation by the approximation of the exchange-correlation functional. However, the global shape of the calculated spectra is generally correct [29].

(iii). Calculation Software and Levels of Theory Used

All optimization calculations of the molecular structures were performed with the Gaussian 09 software [30]. These are followed by calculations of the vibration frequencies of the optimal structure. The method used is the density functional theory (DFT) [31]. Hybrid functionals such as B3LYP and others, associated with a large base of functions give values of molecular properties in good agreement with experimental results [32]. The complexes of Manzamenones with the water molecule are calculated at the ONIOM level (B3LYP/6-31++G(d,p); AM1). Those with alanine are calculated at the ONIOM level (B3LYP/6-31+G(d,p); AM1). The structures of Artemisinin and Quinine complexes with the same molecules are optimized at B3LYP/6-31++G(d,p) and B3LYP/6-31+G(d,p) respectively.

Chemissian and microcal origin pro 8 software were used to calculate the Ultraviolet-Visible absorption spectra. These spectra are calculated on the optimized structures of all the isolated molecules and all the complexes. The TD-DFT method is used to perform these calculations. They provide the absorption characteristics of the said structures.

2.2.2. Calculated Parameters

(i). Global Indices of Reactivity of Complexes

These are the energies E_{HOMO} and E_{LUMO} of the HOMO and LUMO boundary orbitals, the energy gap between these orbitals, the chemical potential (μ), hardness (η), electrophilicity (ω), and dipole moment (μ_D).

The chemical potential expresses the tendency of the electronic cloud to escape from the molecule. It is the slope of the total electronic energy E as a function of the number of electrons N; the external potential V(r) being constant. This descriptor is also equal to the opposite of the electronegativity χ as defined in relation (1) by Paulin and Mulliken [33-39].

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{V(r)} = -\chi \quad (1)$$

The chemical potential is also calculated from the ionization potential PI and the electron affinity AE. The relation (2) is used for this calculation.

$$\mu = -\frac{PI+AE}{2} = -\chi \quad (2)$$

The chemical potential is also calculated from the ionization potential PI and the electron affinity AE. The relation (2) is used for this calculation.

$$\eta = \left(\frac{\partial \mu}{\partial N}\right)_{V(r)} = \left(\frac{\partial^2 E}{\partial N^2}\right)_{V(r)} = \frac{1}{\sigma} \quad (3)$$

With the theory of acids and bases, developed by Pearson

[40], these quantities can be expressed in terms of ionization potential (IP) and electronic affinity (EA) according to formula (4).

$$\eta = \frac{1}{\sigma} = \frac{PI-AE}{2} \quad (4)$$

As for the ionization potential (IP) and the electronic affinity (EA), they correspond, in the approximation of Koopmans [41] to:

$$\mathrm{PI} = \mathrm{E_{HOMO}} \text{ et } \mathrm{AE} = \mathrm{E_{LUMO}}$$

In the theory of frontier molecular orbitals [42].

The electrophilicity index ω [43] is a descriptor developed to evaluate the ability of a molecule to promote electron transfer. It is calculated from the following relationship (5).

$$\omega = \frac{\mu^2}{2\eta} \quad (5)$$

The values of these molecular indices and dipole moments are obtained for structures optimized with the Gaussian 09 software at the indicated levels of theory.

(ii). The Spectral Constants

These are the wavelength at the absorption maximum, the electronic transitions, the oscillation strength, the lifetime of the excited states of the molecules.

The excited state corresponds to a temporary displacement of electrons from the fundamental layer to a higher level after absorption of a photon by the atom or molecule. The lifetime of the excited state is calculated according to the following formula (6) [44]:

$$\tau = \frac{1{,}499}{fE^2} \quad (6)$$

Where f and E are respectively the oscillation strength of the transition and the wave number in cm^{-1}.

All these constants are calculated with the Chemissian and microcal origin pro 8 software using the TD-DFT method.

3. Calculation Results and Discussion

3.1. Global Indices of Reactivity of Complexes

The indices of the complexes are compared to those of the non-complexed molecules (antimalarials and Manzamenones). For isolated molecules, these indices are available in a previous work [15]. The values of the global reactivity indices are reported in Tables 1 and 2. They are calculated at the level B3LYP/6-31++G(d,p) for the complexes with the water molecule and B3LYP/6-31+G(d,p) for those with alanine.

Table 1. *Values of the global indices of reactivity of the complexes with the water molecule.*

Complexes	E_{HOMO}(eV)	E_{LUMO}(eV)	ΔE(eV)	μ(eV)	η(eV)	ω(eV)	μ_D(D)
Arte---H_2O	-7.30	-1.37	5.93	-4.33	2.96	3.17	6.96
Quin---H_2O	-5.70	-1.58	4.12	-3.64	2.06	3.21	4.37
A(B)---H_2O	-10.58	-0.97	9.61	-5.77	4.80	3.47	3.98
C---H_2O	-10.59	-0.94	9.65	-5.76	4.82	3.44	4.35
D---H_2O	-9.97	-0.93	9.04	-5.45	4.52	3.28	1.74
E---H_2O	-10.37	-0.86	9.51	-5.61	4.75	3.31	4.94
F---H_2O	-10.37	-0.67	9.70	-5.52	4.84	3.14	2.92
G---H_2O	-10.43	-0.65	9.78	-5.54	4.89	3.14	7.55
H---H_2O	-8.91	-0.71	8.20	-4.81	4.09	2.82	3.49
J---H_2O	-9.44	-1.06	8.38	-5.24	4.18	3.29	3.13
K---H_2O	-10.88	-0.90	9.98	-5.89	4.98	3.48	7.27
L---H_2O	-10.52	-1.02	9.50	-5.77	4.74	3.50	4.03
M---H_2O	-10.63	-1.05	9.58	-5.83	4.78	3.55	4.49
N---H_2O	-9.69	-1.08	8.61	-5.38	4.30	3.37	4.57
O---H_2O	-10.34	-0.64	9.70	-5.49	4.84	3.11	6.45

The HOMO energy of Quinine and the four Manzamenones H, J, N and O increases after complex formation. This reflects an enhancement of their nucleophilic characters compared to the isolated states. In Artemisinin and the other Manzamenones, this property decreases after complex formation. The LUMO energy of Artemisinin and the five Manzamenones E, J, K, M and O decreases in the complexes. There is an amplification of their electrophilic properties. The energy gap is not modified for Quinine and Artemisinin. The energy gap is little modified for the Manzamenones E, K and O. The properties of the frontier orbitals bring the three Manzamenones E, K and O closer to Artemisinin.

As for the isolated molecules, the values of the chemical potentials of the complexes are all negative. These structures are all stable [45]. In both the isolated and complexed states, the chemical potentials of Manzamenones are lower than those of Artemisinin and Quinine. This parameter increases slightly for Quinine and Manzamenones D, H, J and N in the complexed state. It decreases for Artemisinin, Manzamenones A(B), C, E, F, G, K, L and M. It does not change with Manzamenone O.

The formation of a complex with the water molecule changes the dipole moment of each of the molecules studied. The higher the dipole moment, the greater the intermolecular interaction [46, 47]. It increased for Quinine, Artemisinin and

the following seven Manzamenones: C, E, G, H, K, N and O. The dipole moment decreased for Manzamenones A(B), D, F, J, L and M. In the complexed state, the interaction properties of the studied molecules are modified.

Table 2. *Global reactivity index values of the complexes with the 3-aminopropanoic acid molecule (Alanine).*

Complexes	E_{HOMO}(eV)	E_{LUMO}(eV)	ΔE(eV)	μ(eV)	η(eV)	ω(eV)	μ_D (D)
Arte---Ala	-6.82	-1.03	5.80	-3.92	2.89	2.65	5.10
Quin---Ala	-5.69	-1.63	4.06	-3.66	2.02	3.30	2.77
A(B)---Ala	-10.00	-0.90	9.10	-5.44	4.54	3.26	3.38
C---Ala	-9.70	-0.95	8.75	-5.32	4.37	3.24	7.17
D---Ala	-10.17	-0.74	9.44	-5.45	4.71	3.15	3.52
E---Ala	-10.09	-0.73	9.35	-5.40	4.67	3.12	2.27
F---Ala	-10.04	-0.67	9.37	-5.35	4.68	3.05	3.26
G---Ala	-9.74	-0.54	9.20	-5.14	4.59	2.87	5.44
H---Ala	-8.98	-0.84	8.14	-4.91	4.06	2.96	4.65
J---Ala	-9.34	-0.92	8.42	-5.13	4.21	3.12	3.24
K---Ala	-10.05	-0.91	9.14	-5.48	4.56	3.29	6.08
L---Ala	-9.86	-1.12	8.74	-5.48	4.37	3.44	3.54
M---Ala	-10.34	-0.77	9.56	-5.55	4.78	3.22	1.79
N---Ala	-9.57	-0.92	8.65	-5.24	4.32	3.18	3.65
O---Ala	-9,62	-0,74	8,88	-5,18	4,43	3,02	7,24

The HOMO energy of the four Manzamenones D, F, L and M decreases for complexes. The nucleophilic properties of these Manzamenones decrease when they form complexes with alanine. In the complexes of Artemisinin, Quinine and the other nine Manzamenones (A/B, C, E, G, H, J, K, N and O), this property is amplified. The LUMO energy increased in the complexes of Artemisinin, Quinine and the ten Manzamenones A(B), C, D, E, F, G, H, J, M and N. These molecules complexed with alanine have a decrease in their electrophilic properties.

For all molecules, the gap value is modified when they are complexed with alanine. This reflects an evolution of their reactivities (or their stabilities).

Chemical potentials are always negative and remain lower for complexes with Manzamenones.

The formation of a complex with the alanine molecule also modifies the dipole moment of the molecules. It increases for the complexes with Artemisinin, Quinine and Manzamenones C, D, H, K, N and O; decreases for those with Manzamenones A(B), E, F, G, J, L and M. In the complexed state, the interaction properties of the molecules studied are modified.

3.2. Absorption Properties of Isolated Molecules and Studied Complexes

This study focused on the isolated structures of Manzamenones, Artemisinin and Quinine; the structures complexed with a water molecule and the complexes with an alanine molecule.

In the isolated state, the structures of Manzamenones have been optimized with the mixed method (ONIOM 2; B3LYP/6-31++G(d,p):AM1). Those of Artemisinin and Quinine are obtained at B3LYP/6-31++G(d,p). All complexes with water are obtained at the level B3LYP/6-31++G(d,p). Those with alanine are obtained at the level B3LYP/6-31+G(d,p).

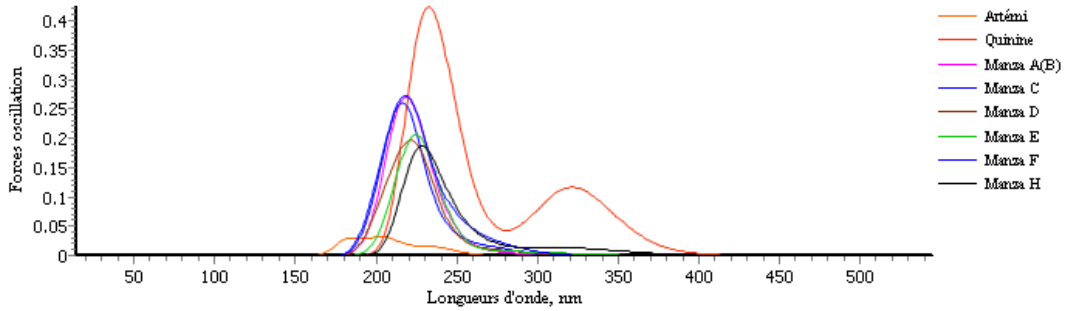
The absorption spectra of the different structures have been realized using TD-DFT calculations. First, the UV-Visible absorption spectra of the isolated molecules are compared between them. Then, those of the complexes are compared between them. Finally, the spectra of the isolated molecules are compared to those of the complexed forms. All these spectra are also compared to those of Artemisinin and Quinine isolated or complexed. For Manzamenones with structural similarities, their absorption bands, those of Artemisinin and Quinine are grouped in the same figure.

3.2.1. Absorption Spectra of Isolated Molecules

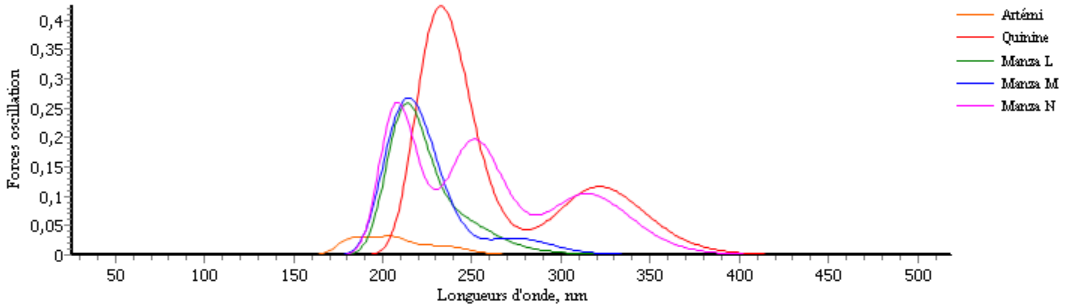
In their isolated states, all these molecules absorb between 170 and 400 nm, thus in the Ultra-Violet range. Artemisinin shows a very weak absorption with a band between 170 nm and 260 nm. The Quinine band has two absorption peaks; one with a very high intensity and the second with a lower intensity. All Manzamenones have higher absorption intensities than Artemisinin and lower than Quinine.

The absorption band of each of the Manzamenones A(B), C, D, E, F, G, H, L, and M has a single maximum. The absorption intensities of these Manzamenones are moderate. Manzamenone N shows three (03) absorption maxima. Two are of moderate intensities and one of low intensity. Compounds J and K each show two absorption peaks. They have moderate intensities for the K molecule. One is moderate and the second very weak for J. Manzamenone O has an absorption band of moderate intensity with a spur.

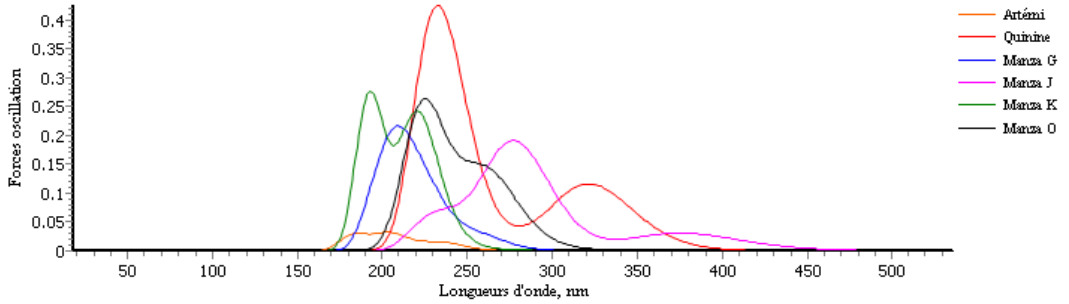
The main electronic transitions, the values of the wavelengths of the absorption maxima, the energy gaps between the levels implicated in the transitions, the transition oscillation strengths, and the lifetime, (τ) [48], have been determined for each structure. These data are reported in Table 3.



a: (A/B, C, D, E, F and H)



b: (L, M and N)



c: (G, J, K and O)

Figure 4. *UV-Visible absorption spectra of the isolated structures of Artemisinin, Quinine and Manzamenones: a (A/B, C, D, E, F and H), b (L, M, and N) and c (G, J, K and O).*

Table 3. *Energy gap (kcal.mol^{-1}), maximum wavelength (nm), oscillation strength (L.M^{-1}.cm^{-1}), lifetime (ns) of the main molecular transitions.*

Molecules	ΔE	λ_{max}	f	τ	Main transition
Arte	136.11	206.7	0.014	46.07	HOMO →$LUMO_{+3}$ (96%)
Quin	98.76	224.7	0.162	46.64	HOMO →$LUMO_{+8}$ (58%)
A(B)	222.86	220.5	0.126	57.65	$HOMO_{-6}$→LUMO (61%)
C	225.35	219.3	0.093	77.79	$HOMO_{-7}$→LUMO (79%)
D	217.79	223.3	0.081	92.16	$HOMO_{-7}$→LUMO (39%)
E	217.16	225.0	0.088	86.03	$HOMO_{-9}$→LUMO (88%)
F	227.58	219.5	0.165	43.76	$HOMO_{-5}$→LUMO (86%)
G	228.36	210.7	0.110	60.73	$HOMO_{-6}$→LUMO (81%)
H	187.22	225.6	0.079	96.81	$HOMO_{-8}$→LUMO (85%)
J	194.87	273.3	0.081	13.80	$HOMO_{-5}$→LUMO (89%)
K	230.37	220.5	0.192	37.96	$HOMO_{-7}$→LUMO (84%)
L	224.84	213.6	0.129	52.88	$HOMO_{-8}$→LUMO (77%)
M	229.29	209.6	0.058	11.40	$HOMO_{-3}$→$LUMO_{+3}$ (70%)
N	200.20	315.3	0.103	14.42	HOMO→LUMO (95%)
O	223.73	223.8	0.130	57.77	$HOMO_{-8}$→LUMO (69%)

The wavelengths of the absorption maxima associated with the main transitions are between 206 nm and 316 nm. They are all located in the Ultra -Violet range. They are associated with π→π* type transitions [49].

The Manzamenones G, L, and M have their absorption maxima (λ_max) closer to that of Artemisinin. In these

Manzamenones, the electronic transitions involve more basic orbitals than HOMO. For compound G, we have the HOMO-6→LUMO transition, for Manzamenones L, the transition is HOMO-8→LUMO. In Manzamenone M, it is a HOMO-3→LUMO+3 transition. In Artemisinin, the electronic transition implicates HOMO and $LUMO_{+3}$.

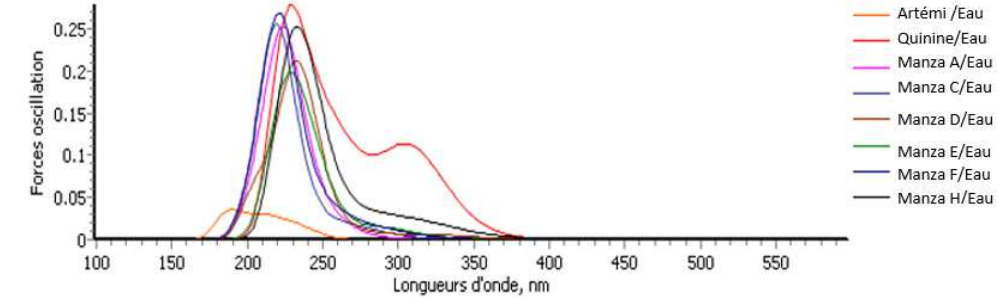
Except for J and N, the other Manzamenones (A/B, C, D, E, F, H, K, and O) and Quinine have major transition wavelengths between 220 and 225 nm. It is also observed that the transitions in all these Manzamenones are associated with electrons from lower orbitals than HOMO to LUMO. In Quinine, the transition implicates electrons from HOMO to one higher than LUMO.

It is noted that in Quinine and Artemisinin, the main transition would be from the HOMO → $LOMU_{+n}$ orbital. As for the Manzamenones, this transition would be from a $HOMO_{-n} \rightarrow LUMO$. Two Manzamenones stand out; the M with a main transition $HOMO_{-3} \rightarrow LUMO_{+3}$ and then the N whose main transition is HOMO→LUMO. In addition to Manzamenone J, these two molecules (M and N) have transitions that have the lowest lifetimes. These molecules are favorable to the fluorescence phenomenon. This reflects a higher fluorescence activity and relatively minimizes other forms of energy conversion [50]. A long duration could result in competition between fluorescence and other photophysical processes.

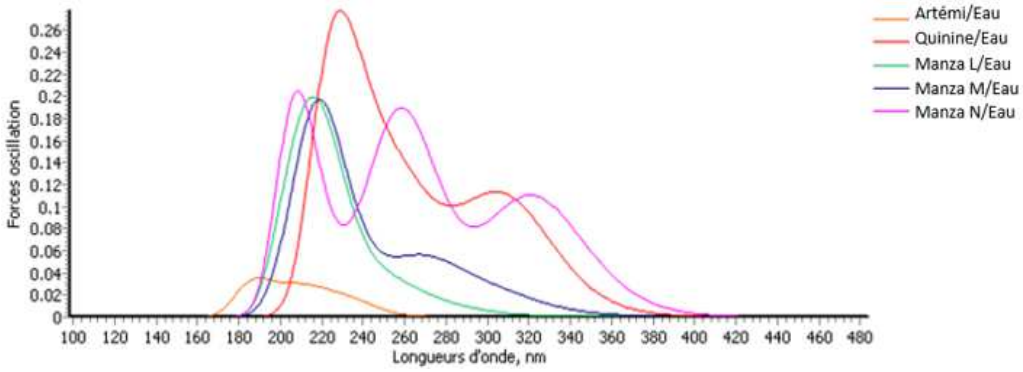
Quinine has the lowest energy gap, it is 98.76 kcal.mol^{-1}. Artemisinin has a higher energy gap, estimated at 138.11 kcal.mol^{-1}. The Manzamenones have much larger gaps than the reference molecules. The gap varies between 187 and 231 kcal.mol^{-1} in Manzamenones.

3.2.2. Absorption Spectra of the Complexes with the Water Molecule

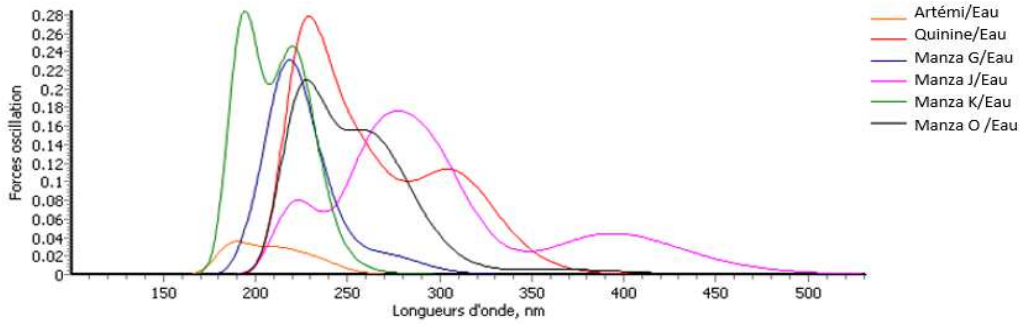
Figure 5 presents the absorption spectra of the complexes formed by Artemisinin, Quinine and Manzamenones with a water molecule.



a: (A/B, C, D, E, F and H)



b: (L, M and N)



c: (G, J, K and O)

Figure 5. *UV-Visible absorption spectra of complexes formed by Artemisinin, Quinine and Manzamenones: a (A/B, C, D, E, F and H), b (L, M, and N) and c (G, J, K and O) and a water molecule.*

Comparison with the spectra of the isolated molecules (Figure 4), reveals a change in the intensities of the absorption bands of the Quinine and Artemisinin complexes. Quinine exhibited a significant hypochromic effect and Artemisinin a weak hyperchromic effect.

The intensities of the absorption bands of Manzamenones are unchanged or minimally changed when complexed with a water molecule.

Finally, only the intensity of the absorption band of Quinine is really modified by this binding interaction with a water molecule.

For these complexes, Table 4 reports the major electronic transitions, the values of the wavelengths of the absorption maxima, the energy gaps between the levels involved in the transitions, the transition oscillation strengths and the lifetime, (τ) determined.

Table 4. *Energy gap (kcal.mol-1), maximum wavelength (nm), oscillation strength ($L.M^{-1}.cm^{-1}$), lifetime (ns) of the main transitions of complexes with the water molecule.*

Complexes	ΔE	λ_{max}	f	τ	Main Transition
Arte---H_2O	136.72	213.2	0.016	41.02	HOMO →LUMO (82%)
Quin---H_2O	95.08	225.1	0.213	35.57	$HOMO_{-1}$→$LUMO_{+4}$ (72%)
A(B)---H_2O	221.61	224.3	0.211	35.70	$HOMO_{-7}$→LUMO (85%)
C---H_2O	222.53	221.9	0.157	47.02	$HOMO_{-6}$→LUMO (74%)
D---H_2O	208.56	233.0	0.094	86.11	$HOMO_{-5}$→LUMO (44%)
E---H_2O	219.40	226.4	0.109	69.93	$HOMO_{-8}$→LUMO (66%)
F---H_2O	223.60	221.6	0.112	65.31	$HOMO_{-7}$→LUMO (47%)
G---H_2O	225.60	217.4	0.146	48.52	$HOMO_{-7}$→LUMO (68%)
H---H_2O	189.03	224.9	0.084	89.53	HOMO→$LUMO_{+4}$ (87%)
J---H_2O	193.07	295.7	0.112	11.67	$HOMO_{-5}$→LUMO (98%)
K---H_2O	230.12	220.5	0.216	33.67	HOMO→LUMO (94%)
L---H_2O	219.03	213.4	0.059	11.53	$HOMO_{-2}$→$LUMO_{+1}$ (54%)
M---H_2O	220.92	227.1	0.066	11.57	$HOMO_{-6}$→LUMO (97%)
N---H_2O	198.53	321.5	0.105	14.67	$HOMO_{-1}$→$LUMO_{+6}$ (95%)
O---H_2O	223.68	222.4	0.104	71.26	$HOMO_{-1}$→$LUMO_{+1}$ (41%)

The wavelengths of the absorption maxima associated with the major transitions are between 213 nm and 321 nm. These are π→π* transitions all located in the UV. Compared to those of isolated molecules, these wavelengths are generally higher. The binding interaction with the water molecule thus generates a red shift. The H, K and L molecules have their wavelengths unchanged. The Manzamenone O undergoes a weak blue shift.

The interaction with the water molecule changed the levels of the major electronic transitions in Artemisinin and Quinine. This transition was HOMO→LUMO+3 and became HOMO→LUMO for Artemisinin. In Quinine, it was HOMO →$LUMO_{+8}$ and became $HOMO_{-1} \rightarrow LUMO_{+4}$. Could these changes explain the changes in the absorption band intensities of these two molecules?

The main transitions of some Manzamenones also underwent changes with complexation. Manzamenones M and N whose transitions were $HOMO_{-3} \rightarrow LUMO_{+3}$ and HOMO→LUMO in the isolated state, respectively, become $HOMO_{-6} \rightarrow LUMO$ and $HOMO_{-1} \rightarrow LUMO_{+6}$. As for the Manzamenones K and O, they change from an electronic $HOMO_{-n} \rightarrow LUMO$ transition to a HOMO→LUMO and $HOMO_{-1} \rightarrow LUMO_{+1}$ transition respectively. The transition $HOMO_{-n} \rightarrow LUMO$ becomes $HOMO \rightarrow LUMO_{+4}$ in the compound H complex and $HOMO_{-2} \rightarrow LUMO_{+1}$ in the L molecule complex. For the Manzamenones A(B), C, D, E, F, G, and J, the $HOMO_{-n} \rightarrow LUMO$ form of the main electronic transition of the isolated state is not changed in the complex.

Overall, the lifetimes of the major transitions are lower in complexes than in isolated molecules. The exceptions are the Manzamenones F, M, N and O. The transitions in the complexes of Manzamenones J, L, M and N have the lowest lifetimes.

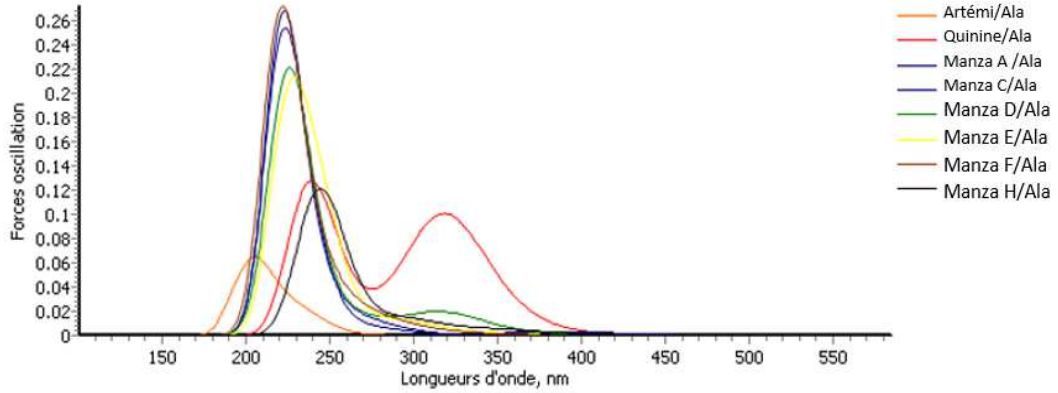
We note that the energy gaps are slightly modified in these structures compared to the isolated molecules. The Quinine complex still has the smallest energy gap; 95.08 $kcal.mol^{-1}$, followed by that with Artemisinin, 138.11 $kcal.mol^{-1}$. Those of the Manzamenones are more important; they vary between 189 and 231 $kcal.mol^{-1}$.

3.2.3. Absorption Spectra of Complexes with the 3-aminopropanoic Acid Molecule (Alanine)

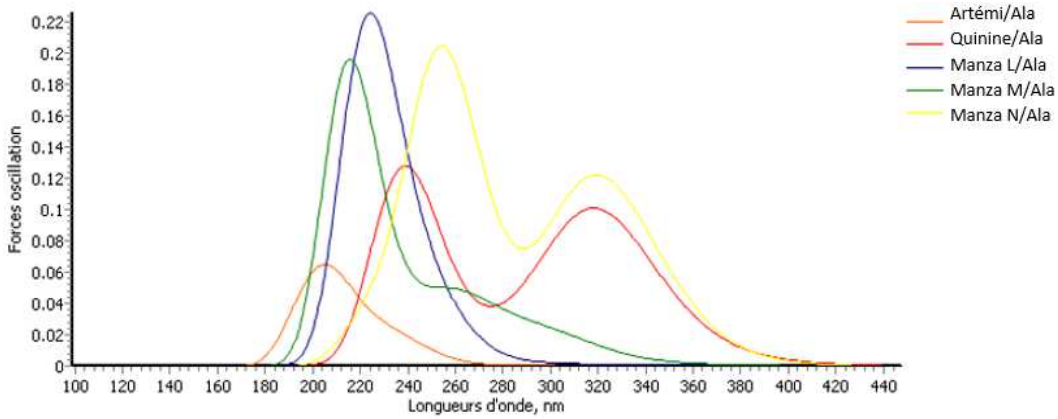
Figure 6 shows the absorption spectra of the complexes formed by Artemisinin, Quinine and Manzamenones with a 3-aminopropanoic acid molecule (Alanine).

Comparison of these spectra with those of Figure 4 of the isolated molecules reveals a high decrease in the intensities of both peaks of the absorption band of the Quinine complex. However, the Artemisinin complex has a larger increase in the intensity of the absorption maximum. Quinine and Artemisinin, upon complexing with alanine, undergo significant hypochromic and hyperchromic effects respectively.

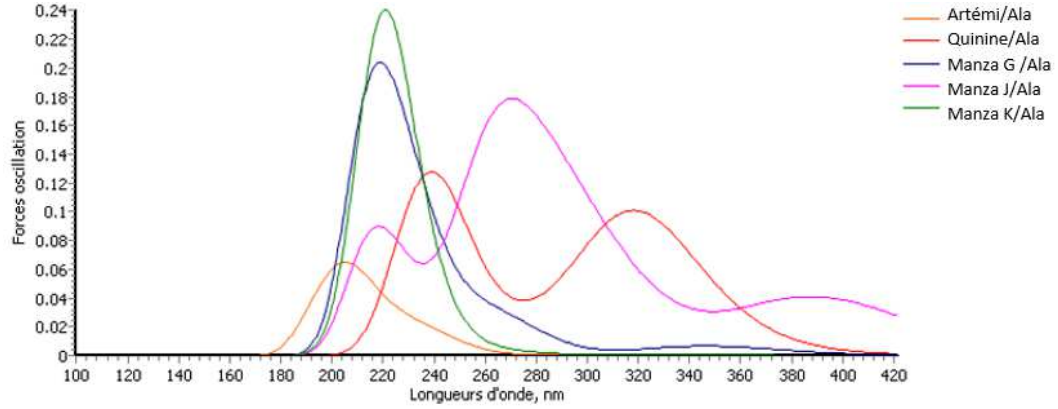
In the case of the Manzamenone complexes, the intensities of the absorption bands are either weakly decreased (weak hypochromic effect) or are not changed. The absorption bands of the Manzamenone complexes K and N show one peak (Figure 6c) and two peaks (Figure 6b) instead of two and three, respectively. The spectra of the Quinine and Manzamenone N complexes show similarities. They have two absorption maxima with identical and two slightly different wavelengths (Figure 6b).



a (A/B, C, D, E, F and H)



b (L, M, and N)



c (G, J, K and O)

Figure 6. *UV-Visible absorption spectra of complexes formed by Artemisinin, Quinine and Manzamenones: a (A/B, C, D, E, F and H), b (L, M, and N) and c (G, J, K and O) and a 3-aminopropanoic acid molecule (Alanine).*

In summary, our calculations show that a binding interaction with a water molecule or with an alanine molecule does not modify the UV absorption intensity of Manzamenones compared to Artemisinin and Quinine. There is a very remarkable hypochromic effect on the absorption of Quinine and a hyperchromic effect on Artemisinin. A very weak and often hypochromic effect with certain Manzamenones is hardly noticeable. Overall, the intensities of the absorption maxima with Manzamenones are slightly modified.

For complexes with alanine, Table 5 contains the main electronic transitions, the values of the wavelengths of the absorption maxima, the energy gaps between the levels implicated in the transitions, the transition oscillation strengths and the lifetime, (τ) determined.

Table 5. *Energy gap (kcal.mol-1), maximum wavelength (nm), oscillation strength ($L.M^{-1}.cm^{-1}$), lifetime (ns) of the main transitions of the complexes formed with 3-aminopropanoic acid (Alanine).*

Complexes	ΔE	λ_{max}	f	τ	Main Transition
Arte---Ala	133.64	212.1	0.020	32.41	$HOMO_{-1}$→$LUMO_{+4}$ (83%)
Quin---Ala	93.51	319.7	0.095	16.13	$HOMO_{-1}$→LUMO (92%)
A(B)---Ala	209.78	223.5	0.171	43.78	$HOMO_{-4}$→LUMO (76%)
C---Ala	201.74	222.5	0.201	36.79	$HOMO_{-5}$→LUMO (85%)
D---Ala	217.68	229.6	0.080	97.66	HOMO→$LUMO_{+1}$ (59%)
E---Ala	215.71	225.2	0.123	61.37	$HOMO_{-7}$→LUMO (81%)
F---Ala	216.15	221.5	0.111	65.95	$HOMO_{-1}$→$LUMO_{+1}$ (62%)
G---Ala	212.17	214.5	0.134	51.37	$HOMO_{-7}$→LUMO (80%)
H---Ala	187.66	245.0	0.043	20.93	$HOMO_{-1}$→$LUMO_{+2}$ (51%)
J---Ala	194.21	289.5	0.077	16.21	$HOMO_{-5}$→LUMO (96%)
K---Ala	210.71	220.3	0.201	31.14	$HOMO_{-6}$→LUMO (90%)
L---Ala	201.64	218.5	0.103	69.49	HOMO→LUMO (83%)
M---Ala	220.51	210.8	0.083	79.35	$HOMO_{-5}$→LUMO (46%)
N---Ala	199.46	258.1	0.089	11.20	$HOMO_{-6}$→LUMO (61%)

The wavelengths of the absorption maxima associated with the major transitions are between 210 nm and 320 nm. These are π→π* transitions all located in the UV. For each complex, λ_max is higher than for the isolated molecule. The binding interaction with the molecule produces a red shift. This effect is very remarkable with Quinine. In this complex, the transition associated with the second peak of the absorption band becomes the main one at 319.7 nm. For isolated Quinine and its complex with the molecule, the main transition corresponds to the first peak of the absorption band at 224.7 nm and 225.1 nm respectively. The binding interaction between Manzamenone N and alanine induces a blue shift on the absorption peak of its UV spectrum. The absorption peak wavelength decreases from 315.3 to 258.1 nm. Manzamenone K forms a complex with alanine whose absorption maximum wavelength is very little influenced by the binding interaction. According to our calculations, it is estimated at 220.5 nm for the isolated K molecule. This wavelength is 220.3 nm for the complex with alanine.

In the complexes obtained by binding interaction with the alanine molecule, the main electronic transitions of Quinine and most of the Manzamenones (nine) is of type $HOMO_{-n} \rightarrow LUMO$. Two Manzamenones, F and H as well as Artemisinin face a main transition $HOMO_{-1} \rightarrow LUMO_{+n}$. The transition in the Manzamenone D complex is from the $HOMO \rightarrow LUMO_{+1}$; that in the L molecule complex starts from the HOMO→LUMO orbital.

Except for Manzamenones D, F, J, L and M, the lifetimes of the main transitions are lower in the complexes than in the isolated molecules. The transitions of the complexes with Quinine and the Manzamenones J and N have the lowest lifetimes. We notice that the energy gaps are modified in the complexes compared to the isolated molecules. The general trend, according to our calculations, indicates smaller energy gaps in the complexes with alanine and larger ones for the isolated molecules. The gap values for the complexes with the water molecule are intermediate.

Table 6 below summarizes the energy levels implicated in the main transitions of the absorption spectra of the isolated molecules and complexes studied.

Table 6. *Main transitions in the different isolated and complex structures.*

molecules	Isolated	Complexes---H_2O	Complexes--- alanine
Arte	HOMO →$LUMO_{+3}$ (96%)	HOMO →LUMO (82%)	$HOMO_{-1}$→$LUMO_{+4}$ (83%)
Quin	HOMO →$LUMO_{+8}$ (58%)	$HOMO_{-1}$→$LUMO_{+4}$ (72%)	$HOMO_{-1}$→LUMO (92%)
A(B)	$HOMO_{-6}$→LUMO (61%)	$HOMO_{-7}$→LUMO (85%)	$HOMO_{-4}$→LUMO (76%)
C	$HOMO_{-7}$→LUMO (79%)	$HOMO_{-6}$→LUMO (74%)	$HOMO_{-5}$→LUMO (85%)
D	$HOMO_{-7}$→LUMO (39%)	$HOMO_{-5}$→LUMO (44%)	HOMO→$LUMO_{+1}$ (59%)
E	$HOMO_{-9}$→LUMO (88%)	$HOMO_{-8}$→LUMO (66%)	$HOMO_{-7}$→LUMO (81%)
F	$HOMO_{-5}$→LUMO (86%)	$HOMO_{-7}$→LUMO (47%)	$HOMO_{-1}$→$LUMO_{+1}$ (62%)
G	$HOMO_{-6}$→LUMO (81%)	$HOMO_{-7}$→LUMO (68%)	$HOMO_{-7}$→LUMO (80%)
H	$HOMO_{-8}$→LUMO (85%)	HOMO→$LUMO_{+4}$ (87%)	$HOMO_{-1}$→$LUMO_{+2}$ (51%)
J	$HOMO_{-5}$→LUMO (89%)	$HOMO_{-5}$→LUMO (98%)	$HOMO_{-5}$→LUMO (96%)
K	$HOMO_{-7}$→LUMO (84%)	HOMO→LUMO (94%)	$HOMO_{-6}$→LUMO (90%)
L	$HOMO_{-8}$→LUMO (77%)	$HOMO_{-2}$→$LUMO_{+1}$ (54%)	HOMO→LUMO (83%)
M	$HOMO_{-3}$→$LUMO_{+3}$ (70%)	$HOMO_{-6}$→LUMO (97%)	$HOMO_{-5}$→LUMO (46%)
N	HOMO→LUMO (95%)	$HOMO_{-1}$→$LUMO_{+6}$ (95%)	$HOMO_{-6}$→LUMO (61%)
O	$HOMO_{-8}$→LUMO (69%)	$HOMO_{-1}$→$LUMO_{+1}$ (41%)	

Six Manzamenones in the series have UV absorption spectra with the same type of main $HOMO_{-n} \rightarrow LUMO$ transitions in the isolated state and in both types of complexes. These are Manzamenones A(B), C, E, G, and J. In Artemisinin, Quinine, and the other Manzamenones, the main transition changes from one structure to the other. In both types of complexes, only the UV spectra of Manzamenone M is associated with a $HOMO_{-n} \rightarrow LUMO$ transition.

We determined the contributions of molecules to the formation of frontier orbitals in complexes with water. The

degrees of participation of interacting molecules in these orbitals would be indicators of their implications in electron exchange. We have therefore determined, in these complexes, the highest occupied molecular orbital for which the two interacting molecules have non-zero contributions. The percentages of their contributions are shown. This information is also determined for the lowest vacant molecular orbital. All these data are reported in the following Table 7.

Table 7. *Non-zero contributions of molecules (Artemisinin, Quinine or Manzamenones) and H_2O to the highest occupied ($HOMO_{-n}$) and lowest vacant ($LUMO_{+n}$) molecular orbitals of complexes with water.*

Complexes	Highest occupied MO with non-zero contributions			Low MO empty and Contributions to its formation		
	MO	% Art/Quin/manza	% H_2O	MO	% Art/Quin/manza	% H_2O
Arte---H_2O	$HOMO_{-1}$	86	14	LUMO	100	0
Quin---H_2O	$HOMO_{-10}$	99	1	$LUMO_{+3}$	98	2
A---H_2O	$HOMO_{-2}$	72	28	$LUMO_{+6}$	97	3
C---H_2O	$HOMO_{-3}$	89	11	LUMO	100	0
D---H_2O	$HOMO_{-3}$	99	1	$LUMO_{+9}$	97	3
E---H_2O	HOMO	84	16	LUMO	98	2
F---H_2O	$HOMO_{-2}$	99	1	$LUMO_{+5}$	95	5
H---H_2O	HOMO	85	15	$LUMO_{+1}$	98	2
L---H_2O	$HOMO_{-3}$	80	20	$LUMO_{+3}$	99	1
M---H_2O	$HOMO_{-10}$	99	1	LUMO	100	0
N---H_2O	$HOMO_{-3}$	78	22	$LUMO_{+2}$	99	1
J---H_2O	$HOMO_{-5}$	96	4	$LUMO_{+4}$	99	1
G---H_2O	$HOMO_{-3}$	79	21	LUMO	100	0
K---H_2O	$HOMO_{-2}$	86	14	LUMO	100	0
O---H_2O	$HOMO_{-12}$	81	19	LUMO	100	0

The data in Table 7 show that the molecule interacting with water predominantly or entirely forms the frontier orbitals of the complexes. The contribution of the water molecule is estimated to be more important in the formation of occupied high molecular orbitals. It ranges from 1 to 28% for these orbitals in these complexes. For the formation of the vacant low molecular orbitals, the water molecule contributes from 0 to 5%. These low contributions to the formation of the boundary molecular orbitals suggest that the non-bonding doublets of the water molecule are not involved in the electronic transitions. The effect of the water molecule on the absorption spectra was an increase in λ_max compared to the isolated molecules. It played more the role of an auxochromic group than a chromophore.

4. Conclusion

For the fourteen Manzamenones, Artemisinin and Quinine, comparison of the global reactivity indices of these molecules to those of their complexes with water and with alanine revealed that:

1) The interaction with the water molecule lowered the HOMO energy in the complexes of Artemisinin and ten Manzamenones. This decreases the nucleophilic character of these complexes compared to the isolated molecules. The exceptions to this finding are Quinine and the Manzamenones H, J, N and O.
2) In the complexes with alanine, the energy of the HOMO increases. Therefore, there is an amplification of the nucleophilic character of the complexes compared to the isolated molecules. The exceptions to this are the Manzamenones D, F, L and M.
3) The two probes (water and alanine) amplify the nucleophilic properties of Quinine and Manzamenones H, J, N and O. They decrease them for Manzamenones D, F, L and M.
4) We have an increase in general LUMO energy in the complex. Our LUMO energy calculations agree for Quinine and Manzamenones A, C, D, F, G, H, K, N and O. The exceptions are Artemisinin and the Manzamenones E, J, K, M and O complexed with the water molecule. Complexes with the alanine molecule of Manzamenones K, L and O are also exceptions.
5) We have a modification of the dipole moment by complexation. In the complexed state, the interaction properties of the studied molecules are thus modified.

The TD-DFT method was used to obtain the UV-Visible absorption spectra of the isolated molecules and the different complexes. These calculations showed that all these structures absorb in the UV-visible range with absorption maxima wavelengths between 200 nm and 350 nm. The electronic transitions associated with these absorptions are of the $\pi \rightarrow \pi^*$ type. For each spectra, the main transition was identified. A large comparison of the different spectra to each other was performed. Similarities and differences were established between Manzamenones and the two antimalarials (Artemisinin and Quinine). The possible red shift, bue shift, hyperchromic and hypochromic effects of the probes (water and alanine) were examined on the spectra.

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