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Comparison of Molecular Properties (Stabilities, Reactivity and Interaction) of Manzamenones and Two Antimalarial Drugs (Quinine and Artemisinin) Using Mixed Method Calculations (ONIOM) and DFT (B3LYP)

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Abstract

Malaria is a real public health problem. It's one of the pathologies that mobilize the scientific community. Resistance to existing treatments is the basis for the search for new treatments. Some molecules such as Manzamenones have shown important antimalarial properties. These molecules belong to the family of atypical fatty acid derivatives. This work presents the relative stabilities, some reactivity properties and the privileged sites of interaction by hydrogen bond of fourteen Manzamenones and two antimalarial drugs: quinine and Artemisinin. These analyses were performed using quantum chemical calculations. We employed the two-layer ONIOM calculation method; namely ONIOM (B3LYP/6-311++G (d, p): AM1) for the fourteen Manzamenones. The geometries of the two antimalarials are calculated at B3LYP/6-311++G (d, p). The electrostatic potential (ESP) calculation of all molecules is done at the B3LYP/6-31++G (d, p) level. The formation processes of the molecules are discussed from the thermodynamic quantities we have calculated. The relative stabilities, the energies of the frontier orbitals, the energy gaps, the dipole moment, etc., are evaluated and discussed. The electrostatic potential at the molecular surface has been used to identify the sites favorable to the formation of hydrogen bonds.

Keywords

Manzamenone, Antimalarial Drug, Quantum Chemistry, Reactivity, Electrostatic Potential

1. Introduction

Malaria is a parasitic disease caused by the infection of erythrocytes by a protozoan haematophagous Plasmodium species. It is transmitted to humans through the bite of an infected female Anopheles mosquito [1]. The vulnerable population is pregnant women and young children. In 2015, 214 million infections were reported, including approximately 438,000 deaths with 90% of deaths coming from the African region [2] [3] [4]. Malaria is caused by five parasites of the species Plasmodium, but the majority of deaths are caused by Plasmodium falciparum and Plasmodium vivax [2] [5] [6] [7]. Drugs such as Quinine, Quinoline, Mefloquine and Artemisinin have been effective in the treatment of this disease. Since about 25 years, the parasite has been developing resistance to the main classes of drugs. Quinine is the drug usually used in severe cases. Cases of resistance to this molecule have been recorded [8] [9] [10]. Manzamenones from marine sources derived from sponges may increasingly be extracted and used in the diversification of drug sources for the treatment of malaria [11].

Manzamenones 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 such as Manzamenones J, K and a trimer, Manzamenone O [12] [13]. These molecules have different biological activities. It is the case of Manzamenone O that presents an antibacterial activity on the strain *Micrococcus luteus*, and antifungal on the strains *Aspergillus niger* and *trichophyton mentagrophytes*. The research work already carried out on these molecules has focused on the biological analysis, synthesis and structural characterization of these molecules [11] [14]. For the diversity of their biological activities, especially the antimalarial activity, our work focuses on the analysis of the molecular properties and reactivity of the fourteen (14) Manzamenones listed in the literature. These data will be compared to those of two antimalarials: quinine and artemisinin. To achieve this, optimization calculations of the geometries of the molecules are performed in the gas phase. We have calculated the total energies, the thermodynamic quantities of formation and deduced the relative stabilities. The reactivity parameters are calculated. These include E_{HOMO} and E_{LUMO} energies to apply molecular frontier orbital theory, chemical softness and hardness, chemical potential and electrophilia index. For all Manzamenones, Quinine and Artemisinin, we performed an analysis of the electrostatic potential of the molecular surface. This analysis will allow us to detect the sites of intermolecular interactions for each molecule studied.

The optimization calculations of the Manzamenone geometries are done at the ONIOM level (B3LYP/6-311++G(d, p): AM1). The optimization of the structures of Quinine and Artemisinin is done at the level B3LYP/6-311++G(d, p). As for the calculations of the electrostatic potential, they are done at the level B3LYP/6-31++G(d, p).

2. Molecules Studied and Calculation Methods

2.1. Studied Molecules: Manzamenones, Quinine and Artemisinin

Fourteen (14) Manzamenones have been listed in the literature. These molecules are heterocyclic atypical fatty acids. According to the similarities or differences presented by these different structures, groupings were made. Three sets or groups have been constituted. The first set consists of seven Manzamenones whose reference codes (Refcodes) are A, B, C, D, E, F and H. These seven Manzamenones are six- and five-membered bicyclic compounds. Their basic skeleton, bicyclo [4, 3, 0] nonane, is given in **Figure 1**.

Manzamenones A and B differ only in the configuration of carbon C_5. They are thus said to be epimers. Manzamenones C, F and D are obtained from Manzamenone A by replacing in position 5 the carboxylic acid function respectively by ethyl ester, n-butyl ester and amide functions. As for Manzamenones E and H, their structures are obtained from that of Manzamenone A by replacing the hydroxyl group of the carboxylic acid function in position 5 with N-valinyl (E) and 4-ethylamine phenol (H).

Three Manzamenones of refcodes L, M and N compose a second group. They have the same basic skeleton as the Manzamenones of the first group. The hydroxyl group in position 1 distinguishes these molecules. The structure of Manzamenone L contains a methyl ester function at positions 2, 5 and 8. Manzamenone M is obtained by replacing the methyl ester function in position 5 by a carboxylic acid function. Concerning manzamenone N, its structure does not contain a hydroxyl group in position 1 on the bicyclo. It contains on the one hand the three esters functions like Manzamenone L and on the other hand two double bonds between C2-C3 and C1-C6. These two double bonds are conjugated with the carbonyl group.

Four Manzamenones of refcodes G, J, K and O form the third set. These molecules do not have a common skeleton structure.

The structures of the fourteen Manzamenones are shown in **Figure 2**, and those of Quinine and Artemisinin are in **Figure 3**.

2.2. Calculation Methods

2.2.1. ONIOM Method

The ONIOM method, developed by Morokuma *et al.* [15] [16] [17], has often been used successfully on large molecules [18] [19] [20] [21]. This method consists

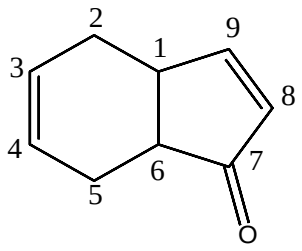

Figure 1. Basic structure and numbering of Manzamenones A, B, C, D, E, F and H.

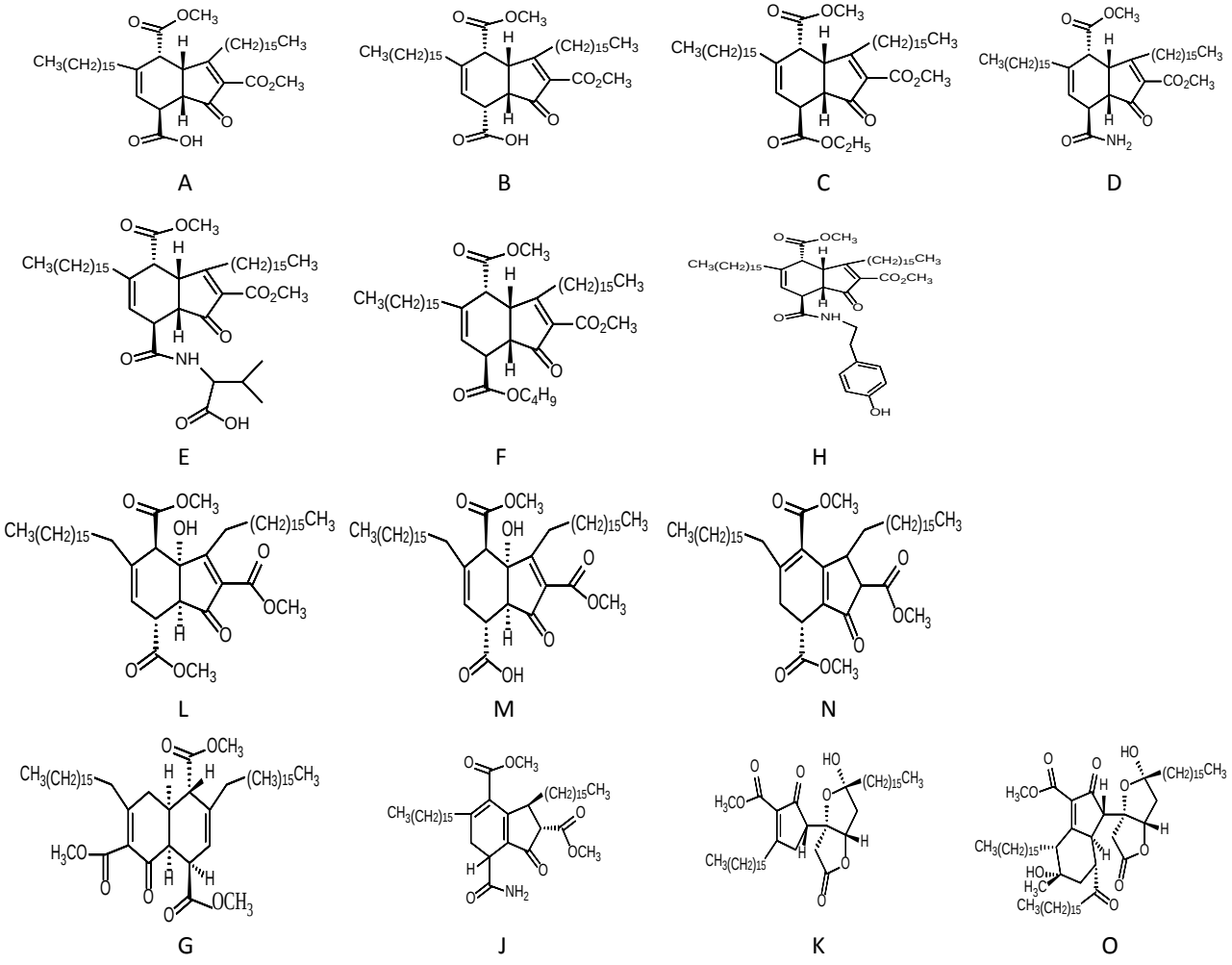

Figure 2. Structures of the 14 Manzamenones designated by their refcodes according to the sets (groups) formed.

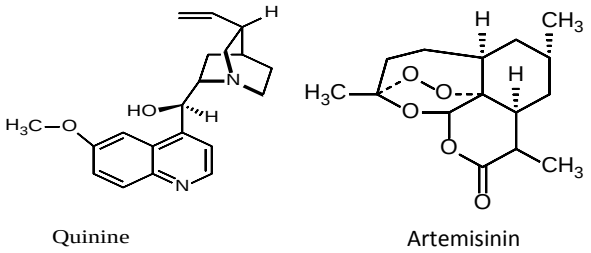

Figure 3. Structures of Quinine and Artemisinin.

in splitting the studied system into several layers. Each of these layers is treated at a different level of calculation. The model system will also be processed at the low level. The final goal is to extrapolate the energy of the real system to the high level. The total energy of the real system, determined by extrapolation from three independent calculations, will be calculated according to Equation (1).

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

The ONIOM2 partitioning adopted for Manzamenones for the application of this calculation method is shown in **Figure 4**.

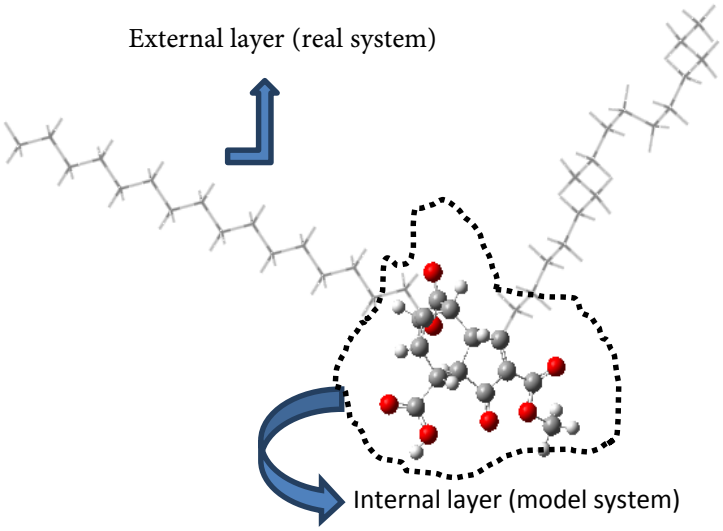

Figure 4. Model of a two-layer partitioning of the structure of a Manzamenone.

2.2.2. Validation of the Calculations of the Mixed Method ONIOM

The compatibility of the levels of theory chosen to formulate the mixed method necessarily involves the calculation of the error. The ONIOM method gives very good approximations when the error is zero or very small. Such a result means that the level of theory chosen for the real system combines perfectly with that chosen for the model system. However, for a non-zero error value, these levels are not compatible. The ONIOM method cannot therefore produce good approximations. In our ONIOM calculations (B3LYP/6-311++G(d, p): AM1), the low level is AM1 and B3LYP/6-311++G(d, p) is the high level. The structures of the real and model systems (**Figure 4**) in Manzamenones are optimized with these levels of theory respectively. The error estimate (E_{rr}) in the ONIOM method is defined as the energy difference between the real and model systems. It is calculated from the relation (2).

$$E_{rr} = E^{\text{ONIOM 2}} - E_{\text{real}}^{\text{high}} \tag{2}$$

Taking into account the expression of $E^{\text{ONIOM 2}}$ (1) the error can be given as:

$$E_{rr} = \left(E_{\text{model}}^{\text{high}} + E_{\text{real}}^{\text{low}} - E_{\text{model}}^{\text{low}}\right) - E_{\text{real}}^{\text{high}} \tag{3}$$

$$\text{Finally:}\quad E_{rr} = \left(E_{\text{real}}^{\text{low}} - E_{\text{model}}^{\text{low}}\right) - \left(E_{\text{real}}^{\text{high}} - E_{\text{model}}^{\text{high}}\right) \tag{4}$$

The evaluation of the error in the ONIOM 2 method (E_{rr}), requires either the calculation of the energies of the model system at the low and high levels ($E_{\text{model}}^{\text{low}}, E_{\text{model}}^{\text{High}}$) and the energies of the real system at the low and high levels ($E_{\text{real}}^{\text{low}}, E_{\text{real}}^{\text{high}}$), or the calculation of the energies $E^{\text{ONIOM 2}}$ and $E_{\text{real}}^{\text{high}}$.

2.2.3. Levels of Theory of Calculation

The calculations are performed with the Gaussian 09 software [22]. For the calculations with the mixed method (ONIOM), we used for the low level of theory the semi-empirical method AM1 [23]. For the high level of theory, the density functional theory (DFT) [24] is used. Previous theoretical works on the calcula-

tion of molecular properties have shown that hybrid functionals such as B3LYP and others, associated with an extended basis of functions lead to values in good agreement with experimental results [25]. The level of theory retained for the optimization and frequency calculations of the Manzamenone structures is B3LYP/6-311++G(d, p): AM1. The structures of Quinine and Artemisinin are calculated at the level is B3LYP/6-311++G(d, p). The electrostatic potential of the molecular surface of each of the molecules is calculated at the B3LYP/6-31++ G(d, p) level. The energetic, thermodynamic, stability parameters and the electrostatic interaction potential (ESP) were determined from these different calculations.

2.3. Reactivity Parameters

The chemical potential μ_{pot} is the tendency of the electronic cloud to escape from the molecule. It is an overall property of the molecular system. The chemical potential is also equal to the opposite of the electronegativity χ as defined by Paulin and Mulliken [26]-[32].

$$\mu_{\text{pot}} = \left(\frac{\partial E}{\partial N}\right)_{V(r)} = -\chi \tag{5}$$

It can be expressed by the ionization potential PI and the electronic affinity AE.

$$\mu_{\text{pot}} = -\frac{PI + AE}{2} = -\chi \tag{6}$$

The first derivative of the chemical potential regarding the electron number N leads to the chemical hardness η and are inverse the softness S [33] [34] [35].

$$\eta = \left(\frac{\partial \mu}{\partial N}\right)_{V(r)} = \left(\frac{\partial^2 E}{\partial N^2}\right)_{V(r)} = \frac{1}{\sigma} \tag{7}$$

According to the theory of acids and bases, developed by Pearson [28], these quantities can be expressed in terms of ionization potential (PI) and electronic affinity (AE).

$$\eta = \frac{1}{S} = \frac{PI - AE}{2} \tag{8}$$

The ionization potential (PI) and electronic affinity (AE) are easily obtained in the Koopmans approximation [36] by:

$$PI = -\varepsilon_{\text{HOMO}} \quad \text{et} \quad AE = -\varepsilon_{\text{LUMO}} \tag{9}$$

$\varepsilon_{\text{HOMO}}$ and $\varepsilon_{\text{LUMO}}$ are the energies of the highest occupied orbital (HOMO) and the lowest vacant orbital (LUMO), respectively. This is the theory of frontier molecular orbitals [37].

The electrophilia index ω [38] is a descriptor developed to evaluate the ability of a molecule to enhance electron transfer. It is calculated from the following relationship.

$$\omega = \frac{\mu^2}{2\eta} \tag{10}$$

2.4. Molecular Electrostatic Potential

The intermolecular interactions have a mainly an electrostatic nature [39]. This quantity is very often used to reveal molecular interaction sites [40] [41] [42]. The electrostatic potential (ESP) is defined by Equation (11) below.

$$V(r) = \sum_{A}^{\text{Noyaux}} \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')\mathrm{d}r'}{|r' - r|} \tag{11}$$

where Z_A is the charge of nuclei A, $R_A - r$ and $r' - r$ are respectively the proton-nuclei and proton-electron distances, and $\rho(r')$ is the electronic density.

In this work, we selected the electrostatic potential extrema calculated at the molecular surface, $Vs_{\max}$ and $Vs_{\min}$, to identify and analyze the respective HB donor and acceptor sites in Manzamenones. Indeed, several previous studies carried out on molecules of biological interest (nicotine and derivatives, progesterone) [43] [44] [45] have shown the interest of $Vs_{\min}$ for the study of HB acceptor sites.

3. Results and Discussion

3.1. Compatibility of Theory Levels in ONIOM 2

The ONIOM 2 method, formulated as indicated, was applied to the fourteen Manzamenones in **Figure 2**. The different energies of the real and model systems as well as the extrapolated energy $E^{\text{ONIOM 2}}$ were estimated. The error resulting from the compatibility of the calculation levels was also evaluated. The results are shown in **Table 1**.

Table 1. Values of model and real system energies calculated at high (B3LYP/6-311++G(d, p)) and low (AM1) levels, extrapolated energy and error from the ONIOM calculation on Manzamenones. Energies are in atomic units (a.u).

Manzamenones	$E^{\text{high}}_{\text{Model}}$	$E^{\text{low}}_{\text{Model}}$	$E^{\text{low}}_{\text{real}}$	$E^{\text{high}}_{\text{real}}$	$E^{\text{ONIOM 2}}$	E_{rr}
A	−1068.6054	−0.2091	−0.3671	−1068.7634	−1068.7633	0.0001
B	−1068.6054	−0.2091	−0.3671	−1068.7634	−1068.7633	0.0001
C	−1147.1472	−0.1035	−0.1943	−1147.2380	−1147.2380	0.0000
D	−1048.7187	−0.1155	−0.6369	−1048.4857	−1048.4858	0.0001
E	−1394.8377	−0.4473	−0.7949	−1395.1853	−1395.1853	0.0000
F	−1265.4073	−0.3979	−0.7308	−1265.7402	−1265.7402	0.0000
G	−1147.0794	−0.0349	−0.2284	−1147.2729	−1147.2729	0.0000
H	−1433.9104	−0.3238	−0.6699	−1434.2565	−1434.2565	0.0000
J	−1048.9075	−0.2894	−0.6225	−1049.2406	−1049.2407	−0.0001
K	−1030.6777	−0.4033	−0.7469	−1031.0213	−1031.0214	−0.0001
L	−1183.3285	−0.4091	−0.7565	−1183.6759	−1183.6759	0.0000
M	−1144.0296	−0.4285	−0.7671	−1144.3682	−1144.3683	−0.0001
N	−1108.1192	−0.3810	−0.7232	−1108.4614	−1108.4614	0.0000
O	−1414.6280	−0.4367	−0.9411	−1415.1324	−1415.1325	−0.0001

The analysis of the values for the fourteen Manzamenones shows that the error is zero or very close to zero. This means that the two levels are compatible and should lead to results with good approximations. The ONIOM calculations (B3LYP/6-311++G(d, p): AM1) can be used to study the structures of Manzamenones.

3.2. Thermodynamic Formation Quantities

The variations of enthalpies of formation, entropies of formation and free enthalpies of formation are calculated for the fourteen Manzamenones, Quinine and Artemisinin. These values are obtained at the B3LYP/6-311++G(d, p) level of theory in the gas phase at 273.15 K. They are reported in Table 2. Examples of optimized structures of Manzamenones (A, E, L and J), Quinine and Artemisinin are shown in Figure 5.

The values of the enthalpies of formation $\Delta_f H$ and free enthalpies of formation $\Delta_f G$ for each of the molecules studied are all negative. The formation processes of these different molecules are therefore spontaneous and exothermic. The results show that the entropy (disorder) increases during the formation processes of the molecules.

Analysis of the enthalpies of formation $\Delta_f H$ show that the Artemisnin formation process is the least energetic, −602,898.25 kcal·mol^{-1}. The heats of formation

Table 2. Thermodynamic quantities of formation of Manzamenones; calculated (in kcal/mol) at the ONIOM level (B3LYP/6-311++G(d, p): AM1). These quantities are calculated at the level B3LYP/6-311++G(d, p) for Quinine and Artemisinin.

Molecules	$\Delta_f H$	$\Delta_f G$	$\Delta_f S$
Artemisinin	−602,898.25	−602,937.04	38.79
Quinine	−650,320.69	−650,365.44	44.76
A	−670,130.44	−670,250.89	120.45
B	−670,130.44	−670,250.89	120.45
C	−719,441.03	−719,566.70	125.67
D	−657,649.81	−657,771.40	121.58
E	−874,643.31	−874,777.63	134.31
F	−793,431.31	−793,560.93	129.61
G	−719,439.99	−719,564.30	124.31
H	−899,152.30	−899,285.41	133.10
J	−657,637.67	−657,755.38	117.70
K	−646,217.05	−646,334.88	117.83
L	−741,986.20	−742,110.40	124.20
M	−717,337.32	−717,458.49	121.16
N	−694,789.68	−694,913.57	123.89
O	−886,866.71	−887,028.62	161.91

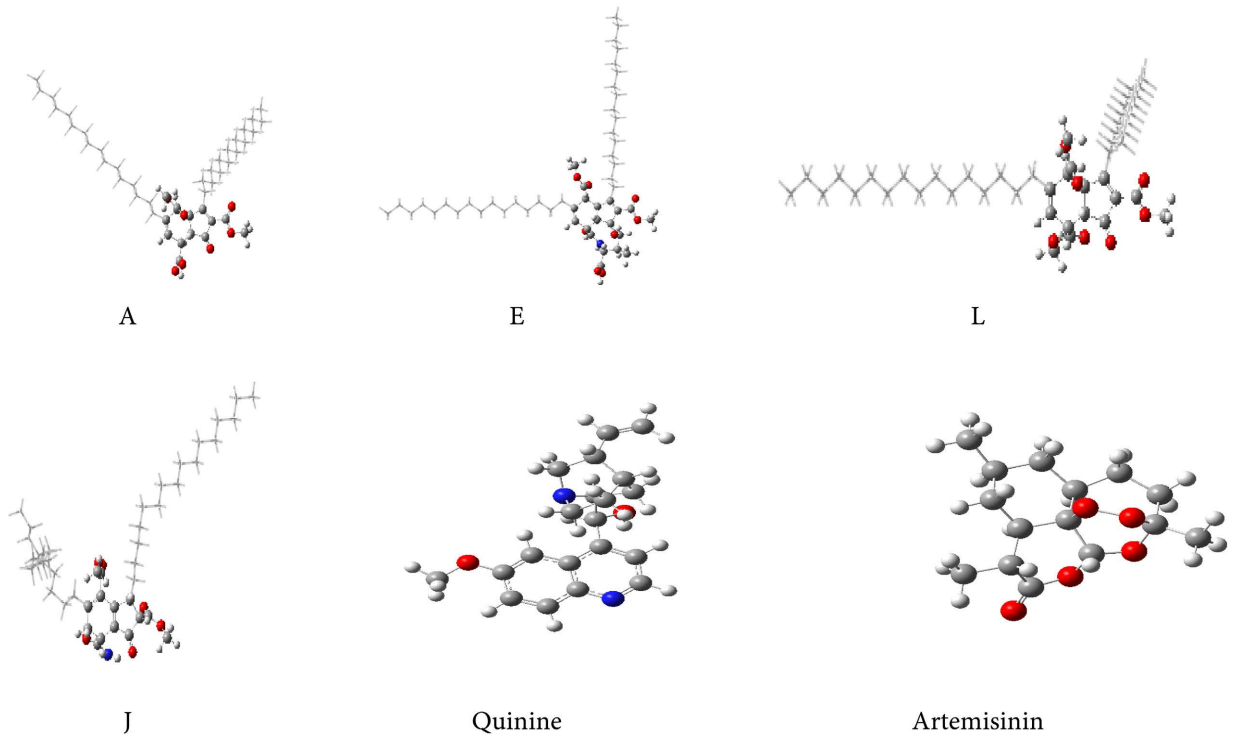

Figure 5. Optimized structures of some Manzamenones (A, E, L, J), Quinine and Artemisinin.

of Quinine, Manzamenones K, J and D are quite close in values. They are respectively −650,320.69 kcal·mol^{-1}, −646,217.05 kcal·mol^{-1}, −657,637.67 kcal·mol^{-1} and −657,649.81 kcal·mol^{-1}. According to the study conditions of this work, each of the presented molecules is obtained according to a spontaneous and exothermic process. The heats of formation of Manzamenones are between −646,217.05 kcal·mol^{-1} and −899,152.30 kcal·mol^{-1}. Their formation reactions are globally more energetic than those leading to the formation of Artemisinin and Quinine whose heats of formation are respectively −602,898.25 kcal·mol^{-1} and −650,320.69 kcal·mol^{-1}.

3.3. Global Reactivity Indexes

The reactivity parameters considered in this list of compounds are all global descriptors of molecular structures. They are HOMO (E_{HOMO}), LUMO (E_{LUMO}), chemical potential (μ_{pot}), electrophilia index (ω), chemical hardness (η), chemical softness (S), frontier orbital energy gap (ΔE), and dipole moment (μ_D). The energy values of the frontier orbitals and those of some global descriptors are shown in Table 3.

The total energies of Quinine, Artemisinin and the 14 Manzamenones are between −603,134.92 kcal·mol^{-1} and −900,039.00 kcal·mol^{-1}. They are therefore very stable molecules. Except for Artemisinin, the least stable of the described molecules is the Manzamenone K with a total energy of −646,996.83 kcal·mol^{-1}. Therefore, it was used as a reference to establish relative stability (ΔE_{tot}). According to our calculations, Quinine is more stable than this Manzamenone by

Table 3. Total energy (E_{tot}) and relative stability (ΔE_{tot}) in kcal mol^{-1}, frontier orbital energies (E_{HOMO} and E_{LUMO}), energy gap (ΔE), chemical potential (μ_{Pot}), chemical hardness (η) and electrophilia (ω) in eV, dipole moment (μ_D) in D, chemical softness (S) in eV^{-1}.

Molecules	E_{tot}	ΔE_{tot}	E_{HOMO}	E_{LUMO}	ΔE	μ_{Pot}	η	S	ω	μ_D
Artemisinin	−603,134.92	43,861.91	−7.11	−1.17	5.94	−4.14	2.97	0.34	2.89	4.16
Quinine	−650,590.45	−3593.62	−5.88	−1.77	4.12	−3.83	2.06	0.49	3.55	2.19
A	−670,914.89	−23,918.06	−10.31	−0.98	9.33	−5.65	4.66	0.21	3.42	5.84
B	−670,914.89	−23,918.06	−10.31	−0.98	9.33	−5.65	4.66	0.21	3.42	5.84
C	−720,262.50	−73,265.67	−10.24	−1.03	9.21	−5.64	4.61	0.22	3.45	3.82
D	−658,442.22	−11,445.39	−9.83	−1.32	8.52	−5.57	4.26	0.24	3.65	2.96
E	−875,520.64	−228,523.81	−10.22	−0.80	9.42	−5.51	4.71	0.21	3.23	2.38
F	−794,289.96	−147,293.13	−8.83	−0.90	7.93	−4.87	3.96	0.25	2.99	5.48
G	−720,261.98	−73,265.15	−9.94	−0.90	9.04	−5.42	4.52	0.22	3.25	6.38
H	−900,039.00	−253,042.17	−9.27	−1.28	7.99	−5.27	3.99	0.25	3.48	2.40
J	−658,430.01	−11,433.18	−9.92	−0.99	8.93	−5.46	4.47	0.22	3.33	8.49
K	−646,996.83	0.00	−10.87	−0.81	10.06	−5.84	5.03	0.20	3.39	5.57
L	−742,792.15	−95,795.32	−8.88	−1.04	7.84	−4.96	3.92	0.26	3.14	5.77
M	−718,125.41	−71,128.58	−10.06	−1.02	9.05	−5.54	4.52	0.22	3.39	4.74
N	−695,592.75	−48,595.92	−9.79	−1.43	8.36	−5.61	4.18	0.24	3.76	2.77
O	−888,038.08	−241,041.25	−10.36	−0.62	9.74	−5.49	4.87	0.21	3.09	4.79

about 3594 kcal·mol^{-1}. As for Artemisinin, it is less stable by about 43862 kcal·mol^{-1}. Compared to the reference, four Manzamenones are distinguished by a very high stability. These are Manzamenones H, O, E and F; they are more stable by 253,042.17 kcal·mol^{-1}, 241,041.25 kcal·mol^{-1}, 228,523.81 kcal·mol^{-1} and 147,293.13 kcal·mol^{-1} respectively.

The optimal structures of Manzamenones have HOMO energies between −8 eV and −11 eV. These energies do not vary according to the order of stability of these molecules. Artemisinin and Quinine have their highest HOMO; −7.11 eV and −5.88 eV respectively. However, Quinine has the lowest LUMO (−1.77 eV) of all the molecules in **Table 3**. Artemisinin has its LUMO (−1.17 eV) located in the energy range of the Manzamenone LUMO (−0.80 eV to −1.43 eV). With the lowest energy gap (4.12 eV), Quinine is more reactive than all other molecules, it is followed by Artemisinin (5.94 eV). The Manzamenones described have larger energy gaps that vary little between 7.84 eV and 10.06 eV. Manzamenones B and E have potent enzymatic activities [46]; M and N have antimicrobial activities [47]; A, F, and L have considerable anti-oxidant activities [48]; and A and O have anticancer activities [49]. These results indicate that the biological activities of these Manzamenones do not depend on the energy gap value.

The dipole moment is the descriptor resulting from the distance between the barycenters of the positive and negative charges. It depends, for a molecule, on

its geometry. This explains the remarkable differences between the values of the dipole moment of Manzamenones. All the Manzamenones studied in this work have their dipole moments between 2.38 D and 8.49 D.

They are all more polar than Quinine (2.19 D). The dipole moment of Artemisinin is 4.16 D. Being a parameter that reflects intermolecular interactions [50], these results show that all these molecules would have stronger intermolecular interactions than Quinine. Some Manzamenones (J, G, A, B, L, K, F, O and M) with higher dipole moments than Artemisinin would lead to stronger interamolecular interactions than this molecule. For the other Manzamenones (C, D, E, H and N), their molecular interactions would be weaker.

3.4. Determination of Molecular Interaction Sites

For the analysis of the electrostatic potential at the molecular surface, a numbering of the heteroatoms of all carbon atoms carrying hydrogen(s) is always adopted. When a carbon carries two or three hydrogens, an average value of the potential is calculated. The numbering adopted for the Vs_{min} and Vs_{max} assignments of Artemisinin and Quinine are shown in following **Figure 6**.

The different numbering of the atoms in the Manzamenone structures are made according to their similarities or differences. **Figure 7** shows these numberings.

Some examples of maps of the electrostatic potential calculated at the B3LYP/6-31++G(d, p) level are shown in **Figure 8**.

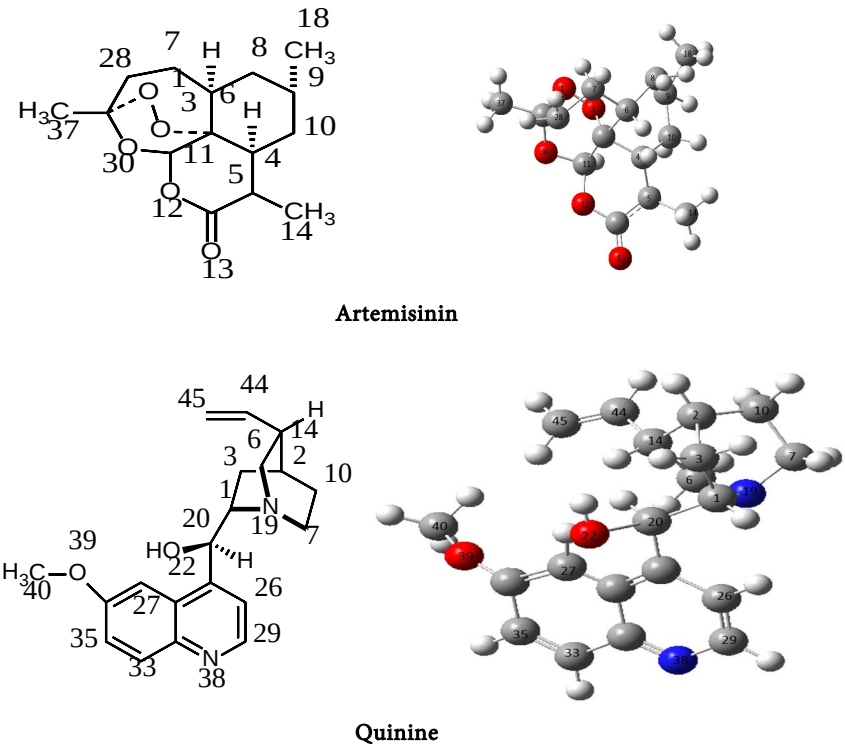

Figure 6. 2D and 3D structures showing the atomic numbering of Artemisinin and Quinine for the analysis of their ESP.

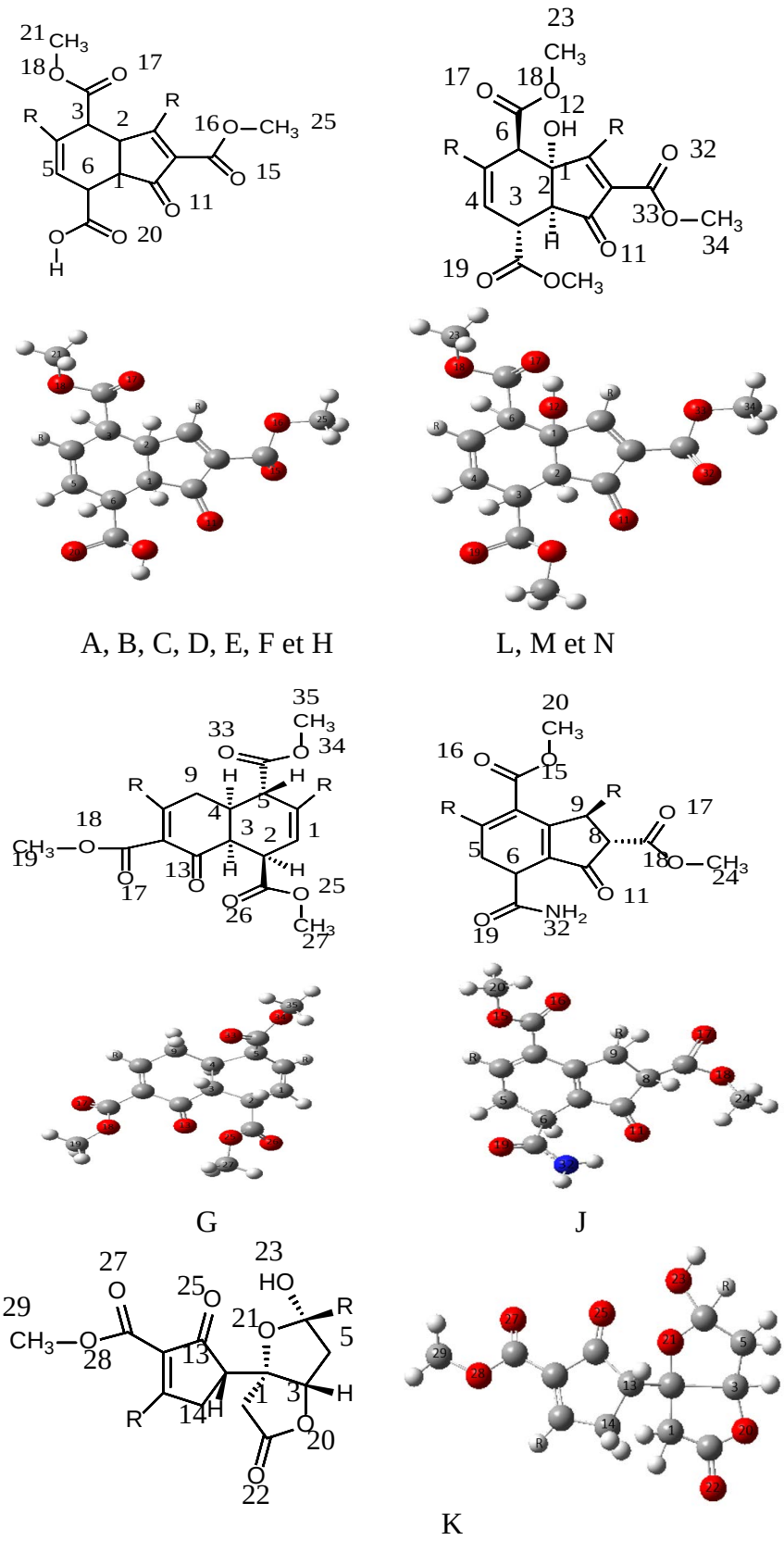

Figure 7. 2D and 3D structures of Manzamenones showing atomic numbering for ESP analysis.

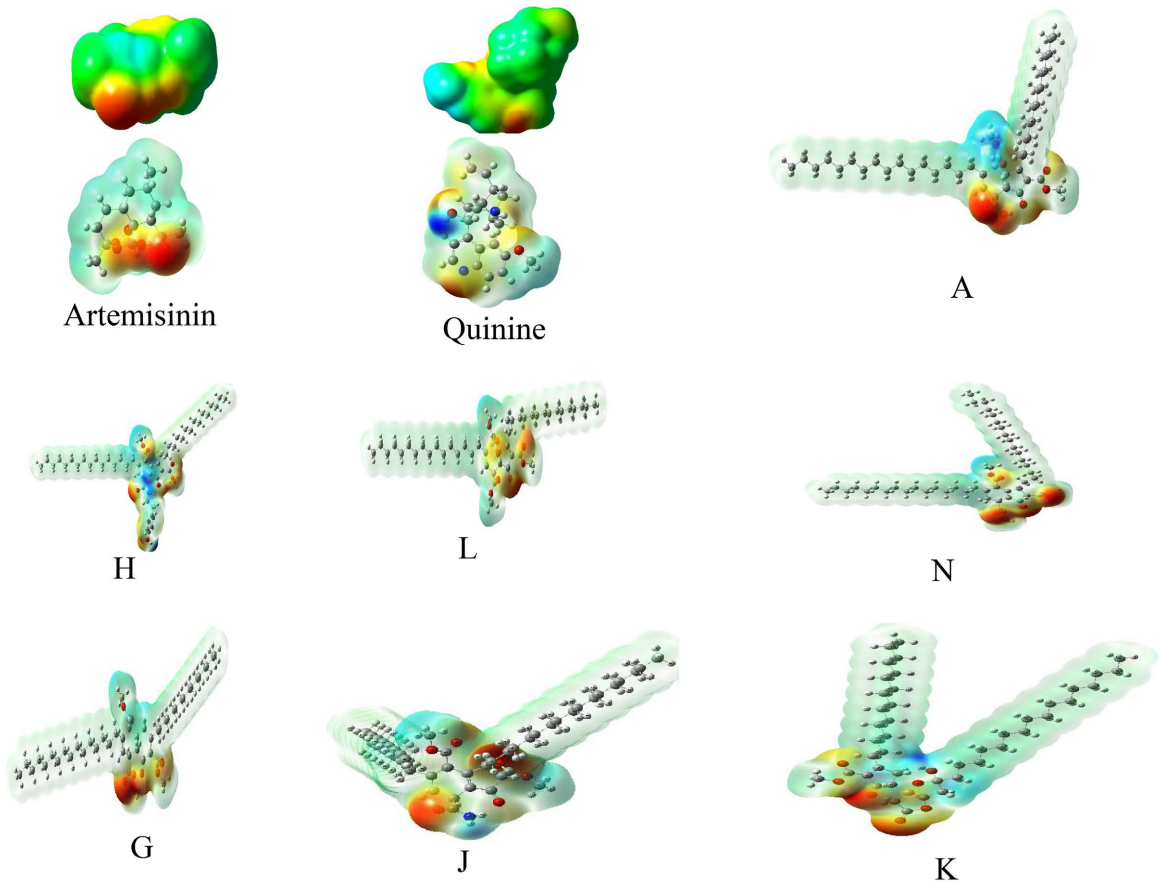

Figure 8. Electrostic potential maps of Quinine, Artemisinin and Manzamenones A, H, L, N, G, J and K.

The electrostatic potential maps of Artemisinin, Quinine, and thirteen Manzamenones were explored. Sites with Vs_{min} or Vs_{max} values were identified. These sites are reported in **Table 4**. They constitute, for Vs_{max}, the electron-rich regions thus hydrogen bond acceptors. The sites of Vs_{max} are poor in electrons; thus donors of hydrogen bonds.

The results in **Table 4** show that the Manzamenones classified in the first two sets (A, B, C, D, E, H, L, M and N) have three (3) preferred acceptor sites. The other molecules each have two (2) sites. The molecules with the lowest Vsmin values are the Manzamenones F, D, C, and L. For these Manzamenones, the acceptor power of said sites decreases in the following order: L > F > D and C.

However, among these molecules, Artemisinin has the strongest O_{13} LH acceptor site. All other (oxygen) acceptor sites of the studied molecules (Artemisinin, Quinine and Manzamenones) have little different acceptor powers.

The donor sites attached to the hydrogens of the OH and NH groups are the strongest. This is the case in Quinine and in the Manzamenones A(B), D, E, H, L, M, J and K. The OH donor site always has the strongest donor capacity. Manzamenone M contains two OH donors. This molecule could establish strong intermolecular interactions from these OH groups. The Manzamenones E and H each have an OH donor and an NH donor.

Table 4. Privileged acceptor and donor site(s) from the electrostatic interaction potential calculation.

Molecules	Artemisinin		Quinine		A(B)		C		D		E		F	
	sites	*Vs*	sites	*Vs*	sites	*Vs*	sites	*Vs*	sites	*Vs*	sites	*Vs*	sites	*Vs*
Acceptor(s) of HB	O_{13}	−58.76	O_{39}	−58.66	O_{11}	−58.54	O_{11}	−58.63	O_{11}	−58.60	O_{11}	−58.58	O_{11}	−58.62
	O_{30}	−58.67	O_{22}	−58.54	O_{15}	−58.57	O_{15}	−58.61	O_{15}	−58.60	O_{15}	−58.59	O_{15}	−58.60
					O_{20}	−58.61	O_{20}	−58.59	O_{20}	−58.65	O_{20}	−58.65	O_{20}	−58.61
Donor(s) of HB	$C_{11}H$	−2.76	$O_{22}H$	−2.61	$O_{22}H$	−2.57	C_3H	−2.87	$N_{31}H_2$	−2.68	$N_{24}H$	−2.68	$C_{25}H_3$	−2.86
											$O_{46}H$	−2.50		

Molecules	H		L		M		N		G		J		K	
	sites	*Vs*	sites	*Vs*	sites	*Vs*	sites	*Vs*	sites	*Vs*	sites	*Vs*	sites	*Vs*
Accetor(s) of HB	O_{11}	−58.60	O_{11}	−58.65	O_{11}	−58.57	O_{11}	−58.61	O_{17}	−58.6	O_{17}	−58.61	O_{23}	−58.58
	O_{15}	−58.54	O_{12}	−58.62	O_{19}	−58.60	O_{19}	−58.60	O_{26}	−58.63	O_{19}	−58.64	O_{25}	−58.57
	O_{20}	−58.60	O_{32}	−58.65	O_{32}	−58.60	O_{32}	−58.60						
Donor(s) of HB	$N_{32}H$	−2.72	$O_{12}H$	−2.67	$O_{12}H$	−2.54	$C_{23}H_3$	−2.86	C_5H	−2.87	$N_{32}H_2$	−2.67	$O_{23}H$	−2.48
	$O_{50}H$	−2.58			$O_{26}H$	−2.51			C_9H_2	−2.87				
									$C_{35}H_3$	−2.87				

4. Conclusions

This work presents the results of the comparative study of the stability, some reactivity properties and the electrostatic potential of the molecular surface of fourteen (14) Manzamenones with two antimalarials: Quinine and Artemisinin. The two-layer ONIOM method was used for the analysis of the stability and reactivity properties of Manzamenones. Thus, the model system and the two antimalarials are studied at the B3LYP/6-311++G(d, p) level. The real system in Manzamenones is described using the semi-empirical AM1 method. We have shown that the two levels of theory used are compatible with ONIOM calculations.

Our calculations revealed that the reactions of formation of Manzamenones are spontaneous and exothermic processes. The heats are between −646,217.05 kcal·mol^{-1} and −899,152.30 kcal·mol^{-1}. These reactions are more energetic than those leading to the formation of Artemisinin and Quinine whose heats of formation are respectively −602,898.25 kcal·mol^{-1} and −650,320.69 kcal·mol^{-1}.

Quinine, Artemisinin and the fourteen Manzamenones have their total energies between −603,134.92 kcal·mol^{-1} and −900,039.00 kcal·mol^{-1}. These molecules are globally stable. Artemisinin is the least stable molecule of all. Quinine is more stable than Manzamenone K. Four Manzamenones E, F, H and O showed very high stability. The two antimalarials have lower energy gaps than the fourteen Manzamenones ranging from 7.84 eV to 10.06 eV. All Manzamenones studied in this work are more polar than Quinine (2.19 D). The dipole moment of Artemisinin is estimated to be 4.16 D. For Manzamenones, it varies between 2.38

D and 8.49 D.

The analysis of the electrostatic potential at the molecular surface (ESP) of all the molecules allowed us to identify the sites Vs_{min}, rich in electrons thus acceptors of hydrogen bonds and the sites of Vs_{max} are poor in electrons; thus donors of hydrogen bonds.

Conflicts of Interest

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

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