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Modeling Artemisinin Derivatives with Potent Activity against *P. falciparum* Malaria with *Ab Initio* and PLS Methods

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Modeling Artemisinin Derivatives with Potent Activity against *P. falciparum* Malaria with *Ab Initio* and PLS Methods

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Abstract

Motivation. Artemisinin (Qinghaosu) is a sesquiterpene containing the 1,2,4–trioxane–ring system and it has been used in China for treatment of *P. falciparum* malaria, a disease responsible for approximately 2.7 million deaths per year. A number of drugs have been investigated for their efficiency in treating malaria. However, the new strains of *P. falciparum* resistant to some of those drugs resulted in further investigation of new classes of compounds effective in treating malaria.

Method. HF *ab initio* and PLS methods were used to design the new artemisinin derivatives.

Results. Potent artemisinin derivatives, with activity against chloroquine sensitive *P. falciparum* malaria are proposed in this paper. The PLS model with three principal components explaining 98.5% of total variance, Q^2 = 0.592 and R^2 = 0.774, was obtained for 14 molecules. The most important descriptors in the QSAR model were LUMO+1 energy, Q_{10}, TSA, A_5, and MAXDP. Also, the MEP maps for artemisinin and artemisinin derivatives show that the compounds have similar MEP around the trioxane ring.

Conclusions. From a set of eleven proposed artemisinin derivatives, one new compound is predicted with antimalarial activity higher than the reported compounds in literature. Based on the HF *ab initio* calculations, MEP maps, and PLS QSAR models we propose for chemical synthesis and biological testing new artemisinin derivatives.

Keywords. Artemisinin derivatives; antimalarial activity; *P. falciparum* malaria; *Ab Initio* method; PLS method; QSAR, MEP maps.

Abbreviations and notations

Q_{10} atomic charge in atom C10	MEP, molecular electrostatic potential
Q_N, atomic charges on Nth atom.	MH, molecular hardness
A_N, Bond angles formed by atoms.	MR, molecular refractivity
A_5, Bond angles formed by O1, C12a, and C12.	MS, molecular softness
HYF, hydrophilicity index	χ, Mullikan electronegativity
MAXDP, maximal electrotopological positive difference	TSA, total surface area.

Dedicated to Professor Lemont B. Kier on the occasion of the 75th birthday.

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1 INTRODUCTION

Malaria is a disease that affects a large number of people every year, and is responsible for a large number of deaths each year. A number of drugs were investigated for their efficiency in treating malaria [1]. However, the new strains of *P. falciparum* resistant to some of those drugs resulted in further investigation of new classes of compounds, which might have effective action [2–6]. Also, computational [1,7–9] and QSAR studies [2,4,10–15] have been developed to unravel the mechanism of action of the antimalarial drugs and to give guidelines for the synthesis of new derivatives with improved efficiency.

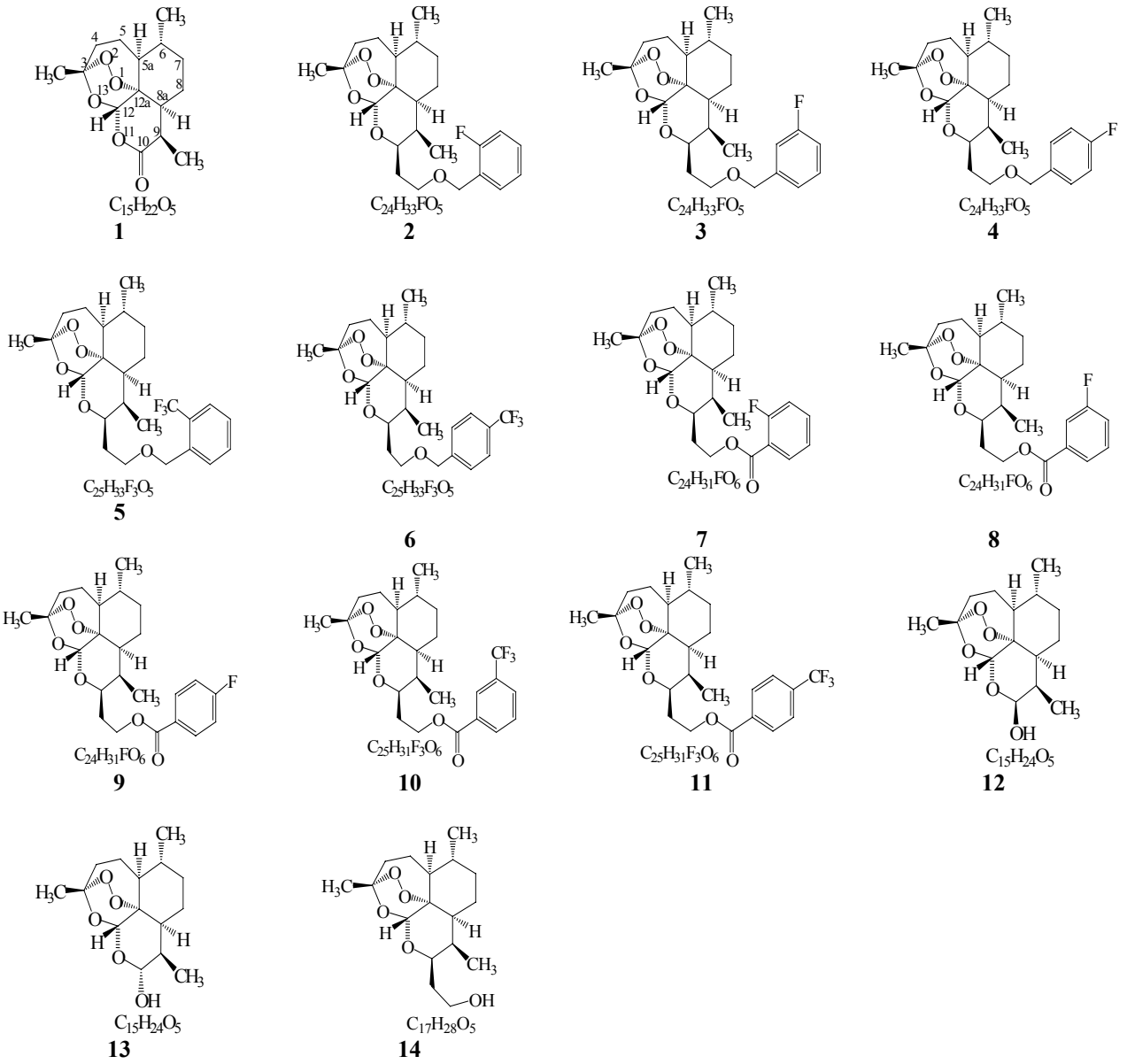

Figure 1. Artemisinin derivatives with antimalarial activity against *Plasmodium falciparum*.

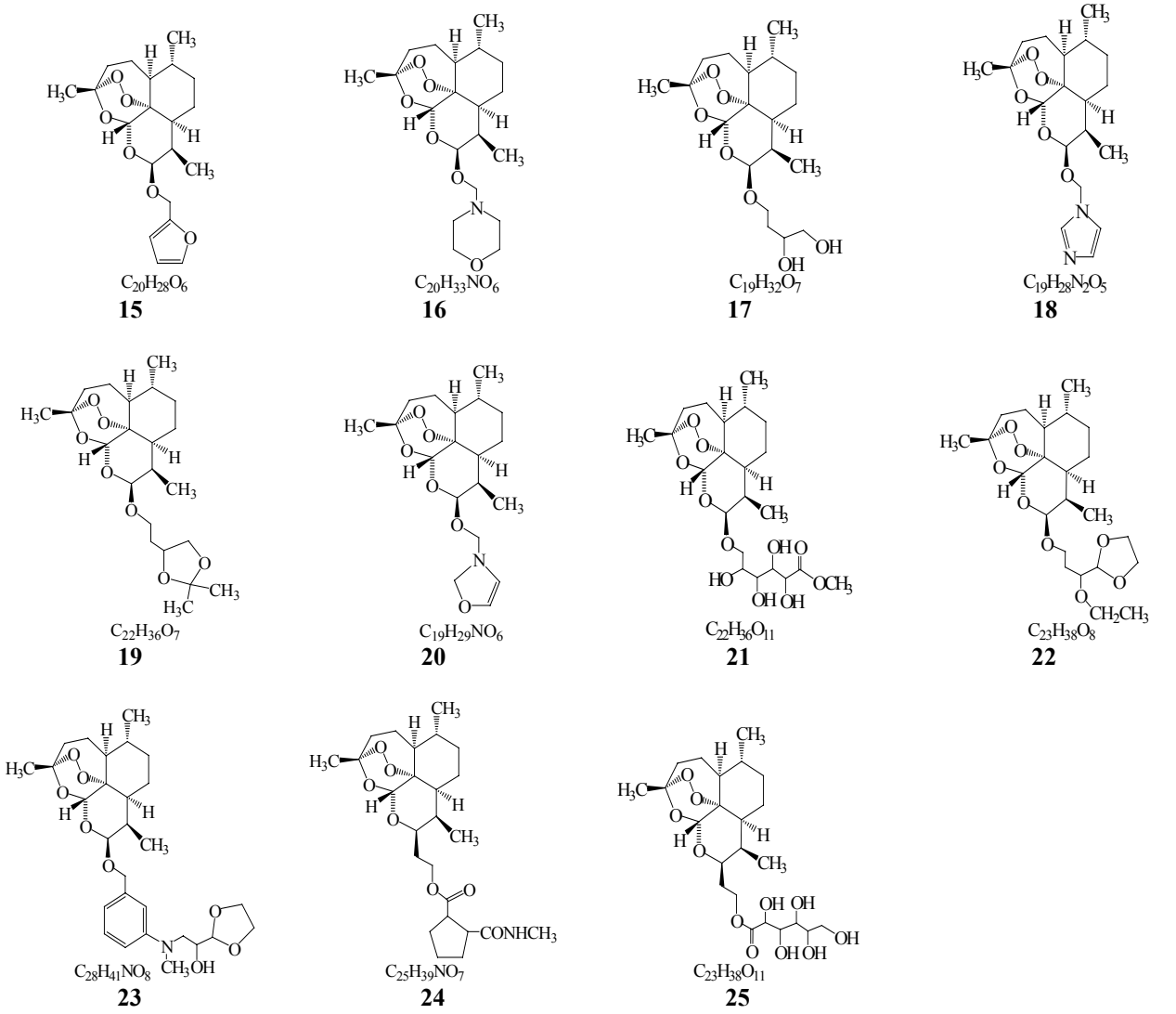

Figure 2. New proposed artemisinin derivatives with unknown antimalarial activity against *Plasmodium falciparum*.

Among the classes of drugs that are effective in clinical treatment of the *P. falciparum* malaria, there is a sesquiterpene containing the 1,2,4–trioxane–ring system, which is called by Occident as artemisinin and by Chinese as qinghaosu, including its derivatives. Artemisinin or qinghaosu was originally extracted from the herb *Artemisia annua* L., an ancient Chinese remedy used for the treatment of 52 kinds of diseases [16,17]. Its structure was determined by X–ray crystallography in 1979 [18]. Also, studies have been developed to elucidate the biosynthesis of artemisinin [18]. It has not known yet which is the real mechanism of artemisinin antimalarial activity. Various experimental and theoretical reports suggest the existence of several processes involving artemisinin, such as inhibition of heme polymerization breaking hemozoin into heme units or damaging the parasite [18–20]. The first step of the artemisinin action includes heme–catalyzed artemisinin activation into a very reactive radical, and the next covalent binding of the radical to parasite proteins or heme [19], hemozoin [21], reduced glutathione [22] or other parasite molecules.

On the other hand, experimental studies performed by Hynes *et al*. [23] and Hynes [24] have been demonstrated that the biological properties of artemisinin derivatives are not always related with chemical activity.

In this report, HF *ab initio* and PLS methods are employed in designing new artemisinin derivatives with activity against *P. falciparum* malaria. Initially, the compounds in Figure 1 [6] are studied with HF/3–21G** method [25,26]. PLS method [27,28] is then used to build a multivariate regression model, which leaded to unknown antimalarial activity of the new artemisinin derivatives as seen in Figure 2. Also, MEP maps for the studied compounds and proposed compounds are built and evaluated to identify common features in active molecules.

2 MATERIALS AND METHODS

The compounds in Figure 1 were tested *in vitro* against the chloroquine sensitive HB3 strain of *P. falciparum* malaria [6]. All of the artemisinin derivatives [6] are more potent than the artemisinin, except the derivatives **6** and **14**. The derivatives **2** and **3** demonstrated outstanding antimalarial potency. The derivative **2** is 15 times more potent than artemisinin and 5 times more potent than DHA in the studied screen [6]. All compounds were taken from literature and all used activities in this report are logarithms of $1/IC_{50} = -\log IC_{50} = pIC_{50}$. All studied compounds (Figure 1 and 2) were modeled using GaussView program [29] and a complete geometry optimization with the HF *ab initio*/3–21G** was carried out. The molecular structures obtained by HF *ab initio* method using the 3–21G** basis set [26] were compared to calculated ones with 3–21G, 6–31G basis sets [13] and with experimental values from literature [30]. The experimental values were determined by X–ray crystallography [30] and were retrieved from the Cambridge Structural Databases (CSD) [31] with REFCODE QNGHSU10 and crystallographic R factor 5.72% [30]. In Table 1, the experimental and theoretical values of artemisinin 1,2,4–trioxane ring parameters are shown. It shows that performed bond lengths are well described theoretically. Besides, all theoretical bond angles are nearly close to the obtained experimental values. Also, the torsion angles of the twist boat conformation adopted in the artemisinin show a very good agreement with the obtained 3–21G, 6–31G, 3–21G** basis sets in this work and the experimental values.

The quantum chemical properties calculations were performed using Gaussian 98 program and the DIRECT–SCF method [32] in conformation with the most stable molecule. The atom numbering adopted in Figure 1 (**1**) is the same used by O'Neill *et al*. [6]. The following quantum chemical descriptors were obtained: molecular HOMO, HOMO–1, LUMO and LUMO+1 energies, HOMO–LUMO gap, χ, MH, MS, μ, Q_N, bond lengths, bond angles and torsion angles. The atomic charges used in this work were generated by the CHELPG keyword through electrostatic potential [33]. The calculations of physicochemical properties were performed using the ChemPlus module [34]. The following physicochemical descriptors were obtained: TSA, Vol, MR, and logP. Also,

with the purpose of representing different sources of chemical information in terms of size and shape of a molecule, three–dimensional molecular descriptors were included. Those descriptors were obtained with the aid of WHIM–3D program [35].

Table 1. Experimental and calculated geometrical parameters of the artemisinin 1,2,4–trioxane ring

	HF/3–21G** (this work)	HF/6–31G [13]	HF/3–21G [13]	Experimental[a] [23]
Bond lengths (Å)				
O(2)–O(1)	1.462	1.447	1.462	1.474(4)
O(2)–C(3)	1.44	1.435	1.441	1.418(4)
C(3)–O(13)	1.436	1.435	1.436	1.448(4)
O(13)–C(12)	1.408	1.403	1.407	1.388(4)
C(12)–C(12a)	1.53	1.533	1.529	1.528(5)
C(12a)–O(1)	1.477	1.469	1.477	1.450(4)
Bond angles (degree)				
O(1)–O(2)–C(3)	107.07	108.8	107.1	107.7(2)
O(2)–C(3)–O(13)	107.31	106.76	107.28	107.1(2)
C(3)–O(13)–C(12)	115.7	117.3	115.67	113.6(3)
O(13)–C(12)–C(12a)	112.03	112.28	112.08	114.7(2)
C(12)–C(12a)–O(1)	111.589	110.91	111.57	111.1(2)
C(12a)–O(1)–O(2)	111.286	113.24	112.29	111.5(2)
Torsion angles (degree)				
O(1)–O(2)–C(3)–O(13)	–74.68	–71.84	–74.67	–75.5(3)
O(2)–C(3)–O(13)–C(12)	32.15	33.39	32.30	36.3(4)
C(3)–O(13)–C(12)–C(12a)	28.4	25.32	28.29	24.7(4)
O(13)–C(12)–C(12a)–O(1)	–50.769	–49.41	–50.86	–50.8(4)
C(12)–C(12a)–O(1)–O(2)	9.792	12.51	9.989	12.2(3)
C(12a)–O(1)–O(2)–C(3)	50.522	46.7	50.33	47.7(3)

Table 2. Descriptors selected for PLS analysis, experimental pIC_{50} and IC_{50} values and the correlation matrix

Compound	LUMO+1	Q_{10}	TSA	A_5	MAXDP	pIC_{50} (mol/l)	IC_{50} (nM)
1	0.2108	0.9534	443.08	111.589	5.122	8.52	3.04
2	0.1385	0.1858	628.22	109.95	5.804	9.66	0.22
3	0.1512	0.1904	657.73	109.84	5.349	9.49	0.32
4	0.1553	0.1907	659.46	109.84	5.055	9.14	0.73
5	0.126	0.1886	649.46	109.98	5.23	8.785	1.64
6	0.1342	0.1914	697.3	109.85	4.73	8.37	4.24
7	0.1382	0.1901	658.47	109.86	5.833	9.28	0.53
8	0.1382	0.1932	660.54	109.88	5.37	9.46	0.35
9	0.1268	0.1936	660.65	109.888	5.26	9.16	0.69
10	0.1089	0.1934	695.71	109.882	5.383	9.19	0.64
11	0.121	0.1943	696.88	109.895	5.351	9.27	0.54
12	0.2469	0.54	447.6	109.78	4.196	8.98	1.04
13	0.2391	0.5869	450.38	110.12	4.196	8.98	1.04
14	0.2406	0.1875	497.75	109.82	3.359	8.45	3.51
LUMO+1		0.649	–0.951	0.283	–0.802	–0.438	
Q_{10}			–0.808	0.837	–0.257	–0.383	
TSA				–0.496	0.655	0.415	
A_5					0.055	–0.364	
MAXDP						0.653	

All descriptors mentioned above have given us valuable information about the influence of electronic, steric, hydrophilic and hydrophobic features on the biological activity of drug molecules.

In this work, the molecular descriptors were selected so that they represent the features necessary to quantify the activity of the studied compounds against *P. falciparum* malaria. The analysis was started with 166 molecular descriptors and those that showed small correlation to the activity (<0.3) were discarded. Then, the PLS model was built with descriptors that in general supply larger regression vectors (>0.3).

PLS method [27, 28] was employed to construct a model in autoscaled data for 14 derivatives and it was validated by a leave–one–out cross–validation procedure. HCA and PCA [36,37] on the same autoscaled data were carried out for 14 molecules using PIROUETTE [38]. This software was also used to build the calibration model. For HCA, we used the ward linkage method. The visualization of the MEP results was done using MOLEKEL [39].

3 RESULTS AND DISCUSSION

3.1 PC and HC Analysis

Table 2 shows the descriptors (LUMO+1 energy, Q_{10}, TSA, A_5, and MAXDP) selected for data analysis, the experimental values of activity IC_{50} (nM) and pIC_{50} (mol/l) for the artemisinin derivatives and the correlation matrix including all data for 14 studied compounds. The correlation between descriptors is less than 0.96 as this table shows. The results present the first three PCs explains 98.6% of the original information for the 14 molecules: 67.5, 27.4, and 3.7% for PC1, PC2 and PC3, respectively. The plot of scores and loadings are shown in Figures 3 and 4. In Figure 3, the compounds are discriminated into two classes according to PC1. The most potent compounds are on the left size (**2**, **3**, **4**, **7**, **8**, **9**, **10**, **11**) and the least potent are on the right size (**1**, **12**, **13**, **14**). Derivatives **5** and **6**, although less potent compounds, are located with high active molecules in PCA.

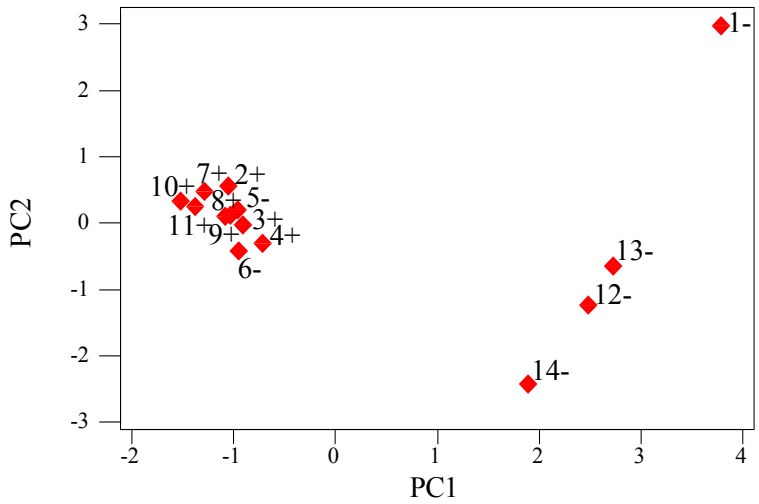

Figure 3. Plot of the PC1–PC2 scores for the 14 artemisinin derivatives with activity (plus sign = most potent) and (minus sign = less potent) against *P. falciparum* malaria.

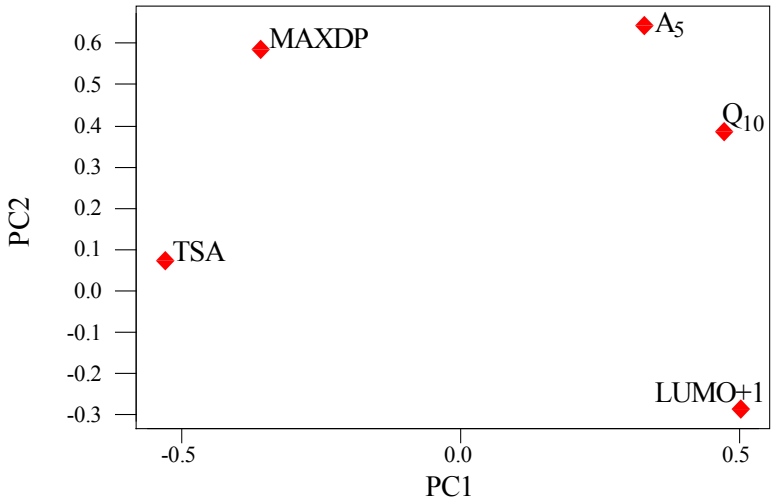

Figure 4. Plot of the PC1–PC2 loadings using the five descriptors selected to build the PLS model for the 14 artemisinin derivatives with activity against *P. falciparum* malaria.

Figure 4 shows the most potent compounds have generally major contribution of TSA and MAXDP, while the least potent ones have major contribution of LUMO+1 energy, Q_{10} and A_5 descriptors.

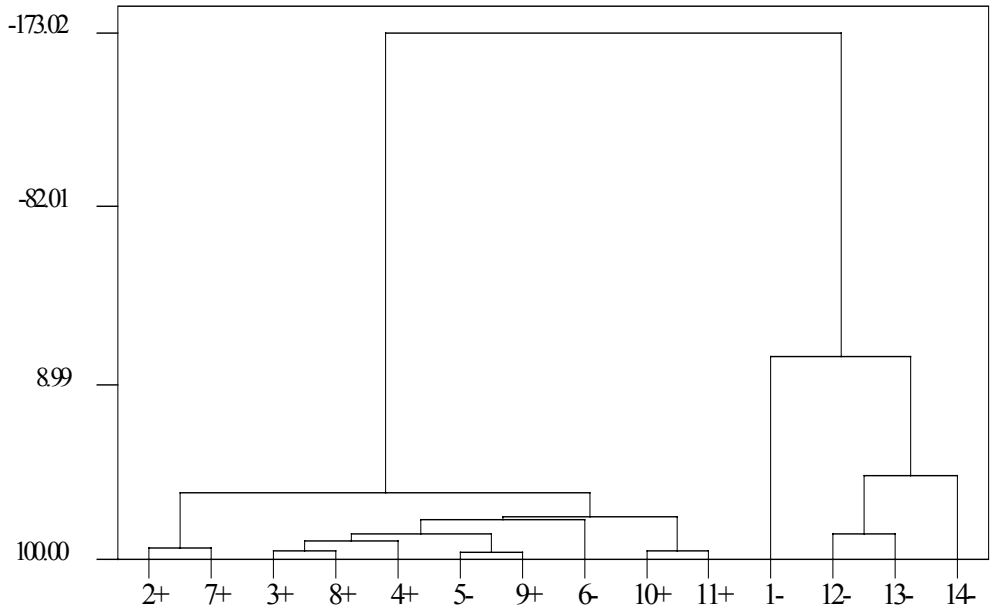

Figure 5. HCA dendogram for 14 artemisinins derivatives: more potent (plus sign) and less potent (minus sign) compounds.

Figure 5 shows the dendogram obtained in the HCA. According to this Figure, the compounds are fairly grouped into two classes, related to their activities: most potent and least potent molecules. The plus cluster contains the most active compounds (**2**, **3**, **4**, **7**, **8**, **9**, **10**, **11**) and minus cluster contains the least active compounds (**1**, **12**, **13**, **14**). In this Figure, the molecules **5** and **6** are situated with the most potent compounds in spite of their activity. In general lines, the results of the

HCA are similar to the PCA.

3.2 PLS Analysis

For the construction of the PLS model we used 14 artemisinin derivatives (calibration set). Three PCs showed to be significant and explained 98.5% of total variance. Figure 6 shows the plot of the correlation between the measured and the predicted pIC_{50} after the leave–one–out cross–validation procedure with 3 PCs model. In this Figure, the most active compounds are located in the upper side, while the least active compounds are situated in the bottom side. Molecules **5** and **6** were classified as the most active compounds by PCA and HCA, but they are less active according to experimental and predicted activities (Table 3). Table 3 shows experimental and predicted activities by PLS model. According to this table, molecules **5** and **6** were classified correctly as less active compound. The quality of the PLS model can be better noticed by the *SEP*, Q^2, and R^2 parameters and by numerical comparison between the measured and the predicted activities values which are shown in Table 3. According to this table, the agreement between the measured and predicted values is, in general, quite satisfactory, taking into account that artemisinin is a complicated molecular system. The parameters considered as criterion for explaining the performance of the PLS model are quite meaningful ($Q^2 = 0.592$ and $R^2 = 0.774$).

$$pIC_{50} = 0.371\ LUMO{+}1 - 0.006\ Q_{10} - 0.464\ TSA - 0.802\ A_5 + 1.283\ MAXDP$$
$$n = 14 \quad R = 0.88 \quad \%EV = 98.5 \quad R^2 = 0.775 \quad R^2_A = 0.674 \quad F_{(5,8)} = 5.48 \qquad (1)$$
$$PRESS = 0.86 \quad Q^2 = 0.600 \quad SEP = 0.248$$

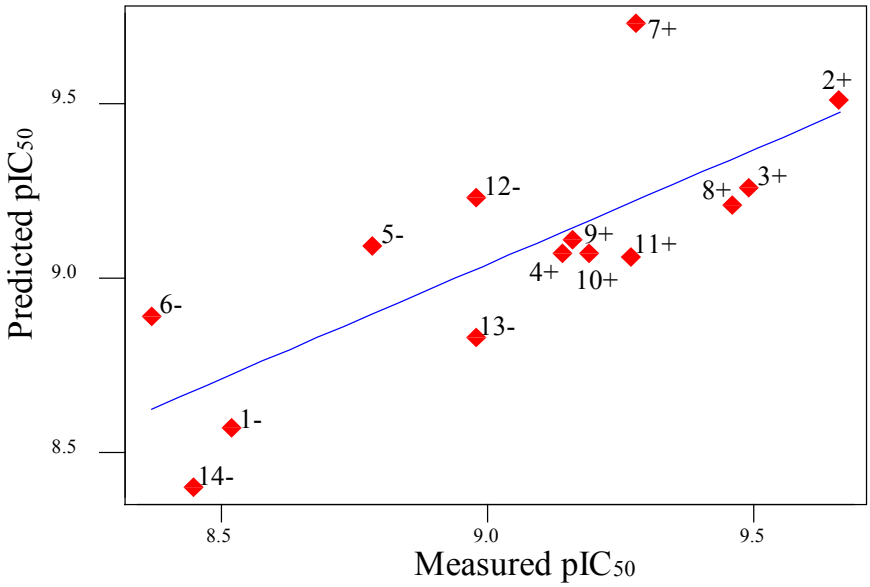

Figure 6. Measured versus predict pIC_{50} by PLS model using three PCs.

The regression model was applied to predict unknown antimalarial activities for eleven new artemisinin derivatives proposed by us and they were included in Figure 2 (prediction set). Table 4 shows the results of the prediction activities against *P. falciparum* malaria obtained with the application of the QSAR model. In this table, all compounds are predicted to be active and **24** is predicted to be more active than any derivatives 1–14 reported in literature [6]. Thus, compound **24** may be considered a new potent antimalarial artemisinin derivative.

Table 3. Measured and predict antimalarial activity (pIC_{50}) by a PLS model with three principal components and leave–one–out–validation

Compound	Measured	Predicted	Residuals
1	8.52	8.57	–0.05
2	9.66	9.51	0.15
3	9.49	9.26	0.23
4	9.14	9.07	0.07
5	8.785	9.09	–0.305
6	8.37	8.89	–0.52
7	9.28	9.73	–0.45
8	9.46	9.21	0.25
9	9.16	9.11	0.05
10	9.19	9.07	0.12
11	9.27	9.06	0.21
12	8.98	9.23	–0.25
13	8.98	8.83	0.15
14	8.45	8.40	0.05

Table 4. Predicted activity against *P. falciparum* malaria (pIC_{50}) for the compounds suggested by us (Figure 2)

Compound	pIC_{50}
15	7.82
16	7.90
17	8.34
18	7.75
19	7.72
20	7.80
21	8.77
22	7.73
23	8.46
24	9.70
25	9.20

3.3 Molecular Electrostatic Potential Maps

Bernardinelli *et al*. showed that artemisinin and artemisinin active derivatives have a region of negative potential of similar shape near the trioxane ring, but this region is displaced in inactive compounds. This negative region is due to the peroxide linkage and it is the most noticeable feature of the MEP [8]. Figure 7 shows the negative region of the artemisinin and the artemisinin derivatives (**1**, **2**, **3**) and proposed derivatives (**21**, **24**, **25**) in this work. This Figure shows the compounds **2**, **3**, **21**, **24** and **25** (all actives) have similar MEP round the essential trioxane ring to artemisinin (**1**).

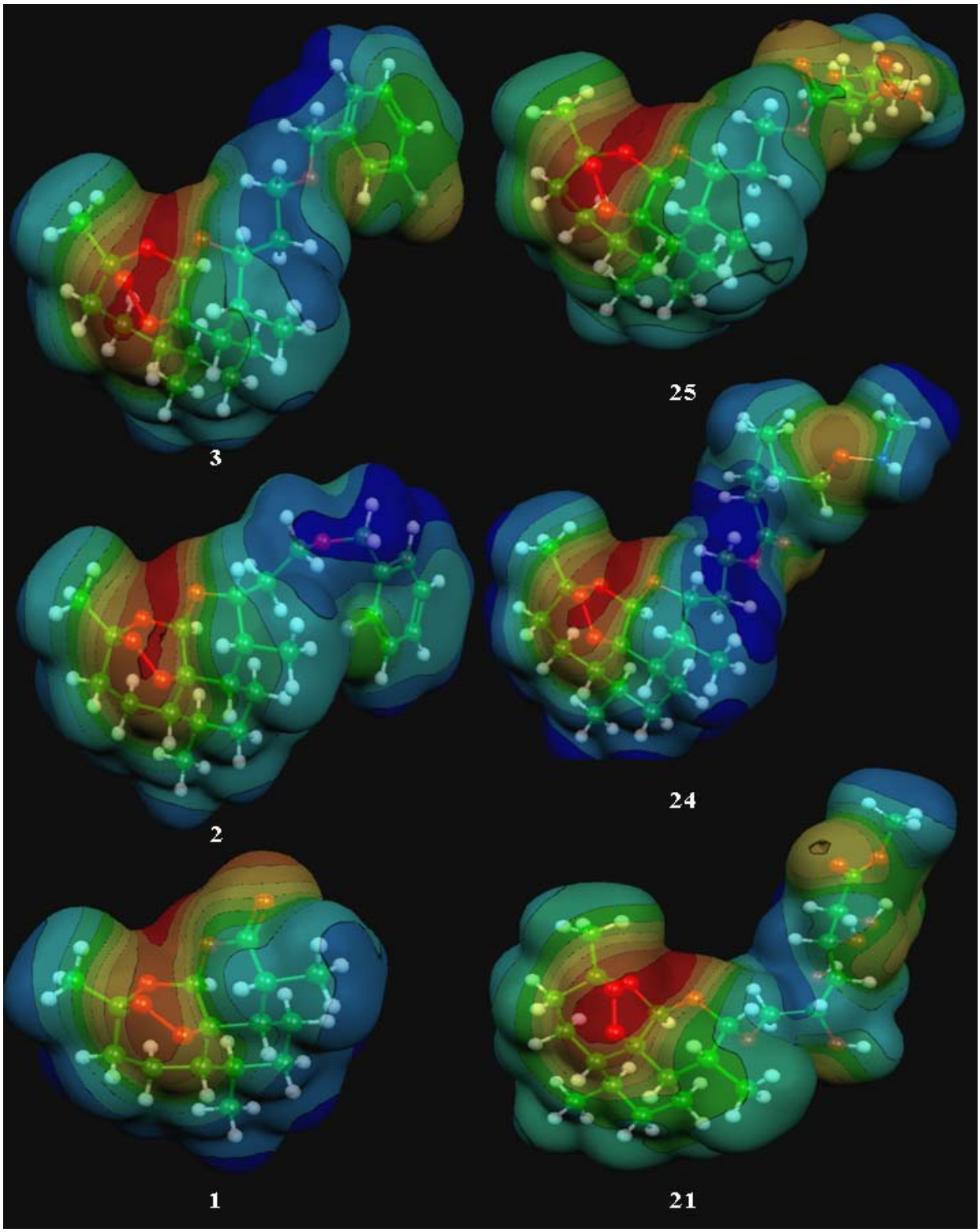

Figure 7. MEP maps for studied compounds (**1**, **2**, **3**) and proposed compounds (**21**, **24**, **25**).

4 CONCLUSIONS

A significant regression model by PLS method for artemisinin derivatives with antimarial activity against *P. falciparum* malaria was obtained based on the descriptors LUMO+1 energy, C_{10} (Q_{10}), TSA, A_5, and MAXDP. The regression model showed predictive ability and revealed, in general, that lower values for HOMO energy and A_5 combined with lower positive charge on the atom C_{10} (Q_{10}), higher TSA and MAXDP values increase the antimalarial activity against *P. falciparum* malaria. One new artemisinin derivatives was predicted to be active against *P. falciparum* malaria chloroquine sensitive higher than the compounds in literature. The results show that, depending on the polarity of ring–system moiety on C_{10} and if more oxygenated or soft base increasing both LUMO+1 and pIC_{50} are observed, the new studied compounds are active against *P. falciparum*. Synthesis of the new artemisinin derivatives drugs may follow the HF *ab initio* and Partial Least Squares methods results of this work, supported by the MEP maps showed here.

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