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Design of new dihydrothiophenone derivatives with improved anti-malaria activity

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Abstract: This study uses quantum chemical methods to design new dihydrothiophenone derivatives with improved antimalarial activity. The molecules were optimized using the B3LYP/6-31G (d, p) level of theory. The application of the MLR method of the XLSTAT program allowed the development of a regression model. The developed model's statistical indicators (R^2=93.50 %, S=0.211, F=43.678) attest to the robustness and reliability. After the study on the substituents influencing the antimalarial activity, thirty (30) new CDH-coded molecules were generated, considering these effects. Twenty-four (24) of these new molecules showed higher values of inhibitory concentration potential than the parent compound **(pIC_{50}= 7.036).** In addition, the thermodynamic formation quantities formed at 298K were calculated. Lipinski's rule and antimalarial activities proved that these twenty-four new molecules could be used as antimalarial drugs.

Keywords: Design; Antimalarial activity; Dihydrothiophenone; QSAR; MLR

1. Introduction

The widespread parasitic infections of malaria worldwide and the difficulties in eradicating dormant forms of the plasmodium genus [1] are significant challenges for the scientific community searching for new drugs. Thus, predictive tools can be used to refine the profile of adverse effects and efficacy of a new molecule at an early stage; this strengthens the clinical evidence, which is sometimes considered insufficiently convincing, and facilitates the decision whether or not to move on to the next phase. A good part of the solutions can come from innovation in drug discovery tools and processes; this can be achieved by improving knowledge management and optimizing modeling tools, databases, and prediction methods [2,3].

The discovery of new molecules with specific therapeutic activities and minimal adverse side effects in the fight against malaria is a major challenge. To tackle the problem of drug resistance, various strategies have been developed to treat malaria [2,3].

However, Plasmodium is highly adaptable to its environment and develops numerous resistances, making some of the currently available molecules obsolete in many endemic territories. Furthermore, although most of these compounds have been known for a long time, their modes of action are not entirely understood. There is, therefore, an urgent need to find new molecules with new mechanisms of action to meet these needs. To do this, the scientific community is moving towards new research methods that consist of predicting the activities of molecules even before they are synthesized. In the context of our work, the mathematical model of multiple linear regression (MLR) and the domain of applicability (DA) established in a previous study [4] by the Quantitative Structure-Activity Relationship (QSAR) were used. The general objective of this work is to use the mathematical model shown by Konaté et al. [4] to design new antimalarial Dihydrothiophenone derivatives within the scope of applicability.

2. Materials and method

2.1. Design

The design of new antimalarial molecular entities remains a fundamental goal due to the emergence of resistant *PfDHODH* strains leading to high mortality rates associated with this disease. Among the existing approaches for designing new drugs, we have chosen to implement the fragmented strategy, which is the most recent one and is based on the basic concept that molecular complementarity is more quickly and efficiently explored with small molecular fragments [5].

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This approach involves the screening of organic molecules of very low molecular weight.

These differ from the molecules traditionally present in the chemical libraries of pharmaceutical companies and academic laboratories by their low molecular complexity and moderate size.

2.2. Basic structure

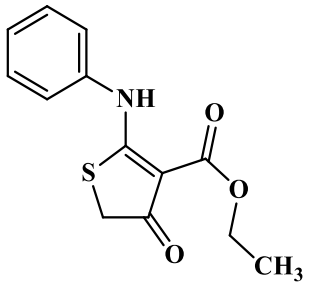


Figure 1. Common structure of Dihydrothiophenone (DH) molecules

2.3. Mathematical Model

The equation and statistical parameters of the model established by Konaté et al. [4] are presented below:

$$\mathbf{pIC_{50PfDHODH}=-0.06827*V_{(C=O)}-0.00255*\Delta_f H°+0.93880*\alpha_{(C\text{-}N\text{-}C)}+0.56459*I}$$

$$N = 16\,;\, R = 0.968\,;\, R^2 = 0.935;\, s = 0{,}211\,;\, F = 43.678;$$

$$p - value < 0.0001;\ TSS = 8.329;\ ESS = 7.795$$

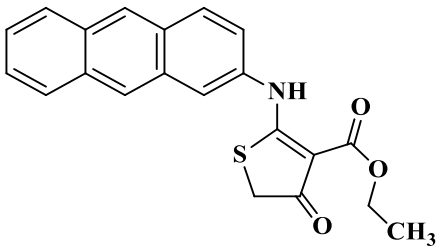
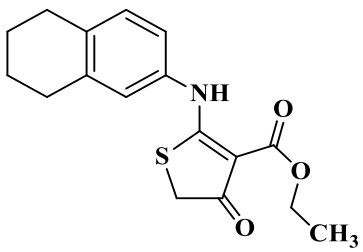
2.4. Selected structures

For the selection of structures, we evaluated the effects of substituents on antimalarial activity to determine which substituents influence the pIC_{50}. The methodology adopted is as follows :

- Classification of Dihydrothiophenone derivatives in descending order of pIC_{50};
- Identification of the substituents of the first two molecules with the highest pIC_{50} values.

After classifying the different DH derivatives, DH2 and DH17 [4] have the highest pIC_{50} values. Therefore, these compounds will serve as the basic structure for the design.

Table 1. Structures and pIC_{50} values of the different selected molecules.

Code	Molecular structure	pIC50
DH2		**6.705**
DH17		**7.036**

2.5. Thermodynamic formation parameters

The calculation of the thermodynamic quantities of the molecules was carried out using optimization and frequency calculations at the DFT/B3LYP/6-31G (d, p) level of theory. Such amounts as entropy change, enthalpy change, and free enthalpy change of formation of the new derivatives of antimalarial activity were determined through the following formulae proposed by Otchersky et al. [6].

$$\Delta H_f^0(M, 0K) = \sum_{atoms} x\Delta H_f^0(X, 0K) - \sum D_0 \qquad (1)$$

$$\Delta H_f^0(M, 298K) = \Delta H_f^0(M, 0K) + \left(H_M^0(298K) - H_M^0(0K)\right) - \sum_{atoms} x\left(H_X^0(298K) - H_X^0(0K)\right) \quad (2)$$

With:

$$\sum D_0 = \sum x\varepsilon_0 - \varepsilon_0(M) - \varepsilon_{ZPE} \quad (3)$$

$\sum D_0$: Atomisation energy;

$\varepsilon_0(M)$: Total energy of the molecule;

ε_{ZPE} : Zero-point energy of the molecule;

$H_X^0(298K) - H_X^0(0K)$: Enthalpy corrections for atomic elements. These values are included in Janaf table [7].

$H_M^0(298K) - H_M^0(0K) = H_{corr} - \varepsilon_{ZPE}(M)$: Enthalpy correction of the molecule

H_{corr} : Thermal correction enthalpy.

$$\Delta S_f^0(M, 298K) = S_M - \sum_{atoms} x\Delta S(298K) \quad (4)$$

x : Number of atoms of X in the molecule

$$\Delta G_f^0(M, 298K) = \Delta H_f^0(M, 298K) - T\Delta S_f^0(M, 298K) \quad (5)$$

2.6. Lipinski's rule of five

Lipinski defined a set of rules for estimating the oral bioavailability based on its two-dimensional (2D) structure. These rules for physico-chemical activities were defined after analyzing 2245 marketed drugs or drugs in the final stages of development [8].

- The molecular weight, which must be less than 500 g/mol;
- The number of hydrogen bond acceptor atoms which must be less than or equal to 10;
- The number of hydrogen bond donor atoms, which must be less than or equal to 5;
- The M LogP coefficient must be less than or equal to 5.

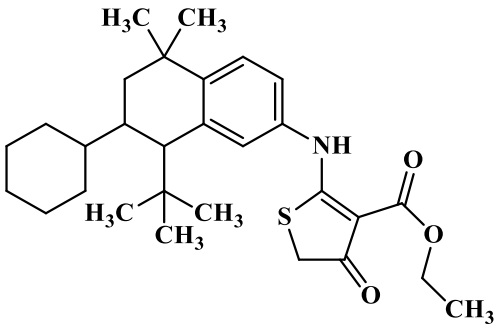
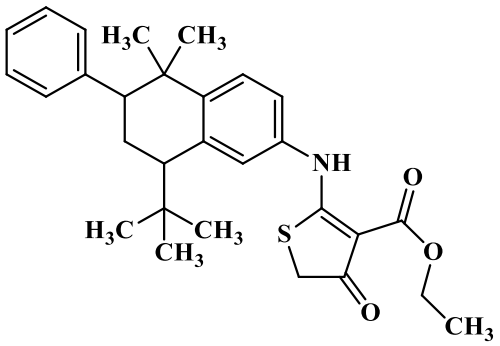
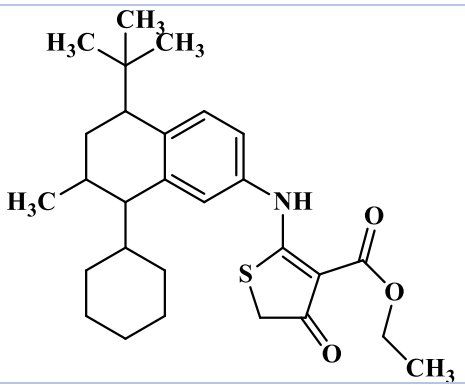
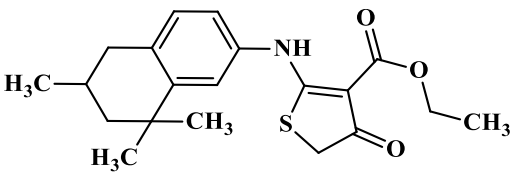
Compounds whose physico-chemical activities do not meet at least two (2) rules are highly likely to have absorption problems. These criteria correlate physicochemical activities with oral administration, and a molecule with two of the requirements outside these limits is less likely to be absorbed orally [8]. New compounds with better pIC_{50} values than the existing ones can be developed to improve antimalarial drug research.

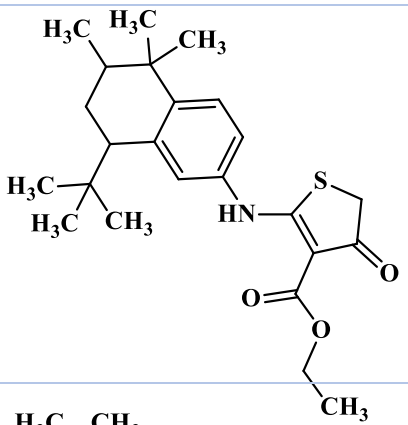
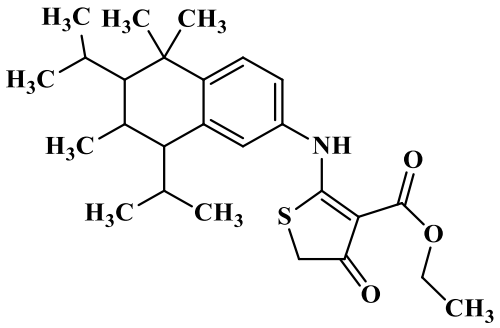
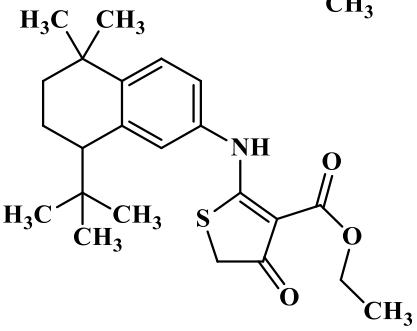
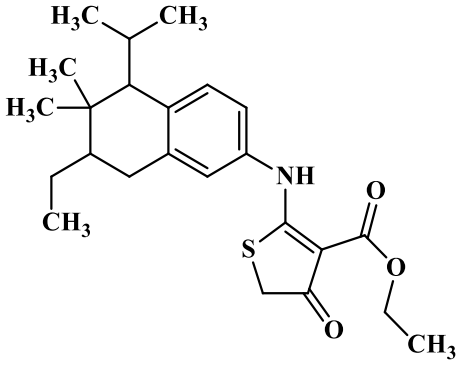
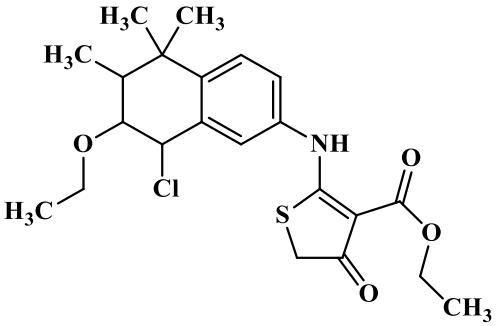
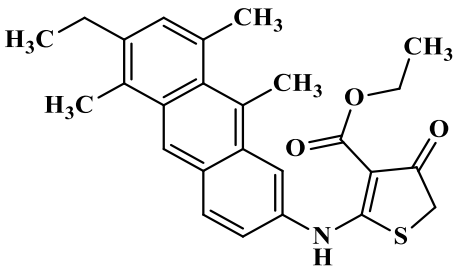
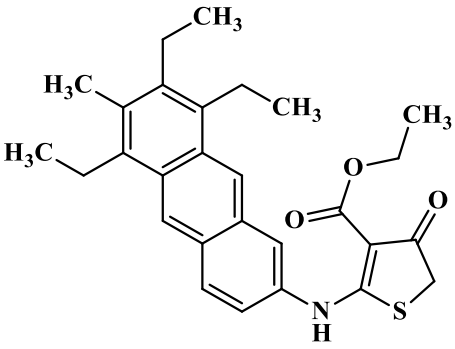
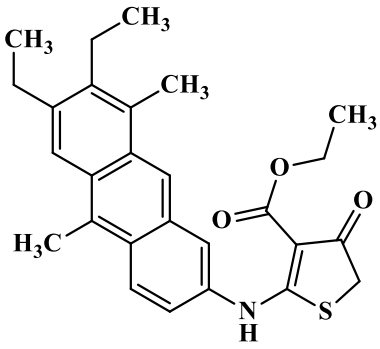
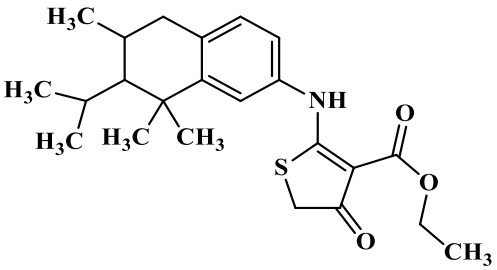
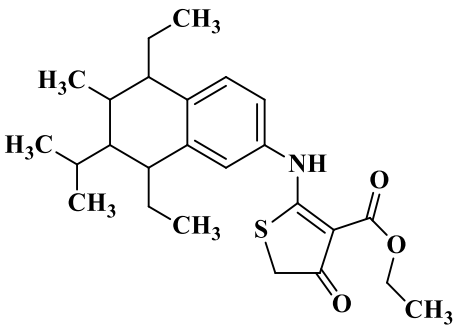
3. Results and discussion

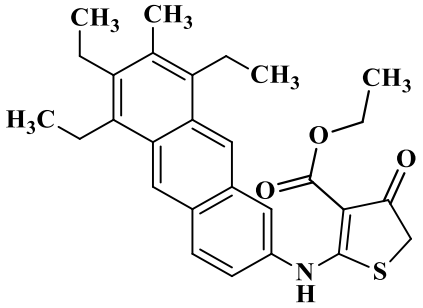
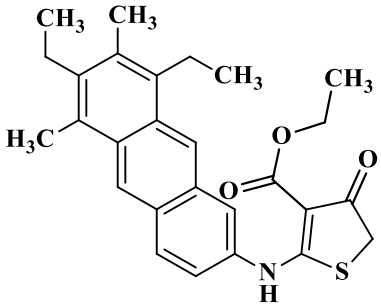
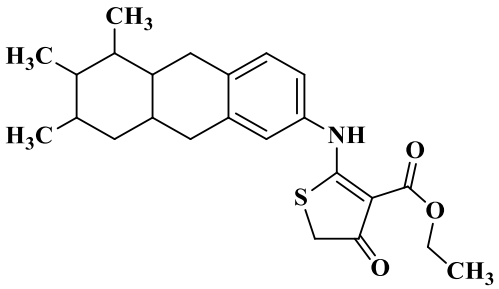
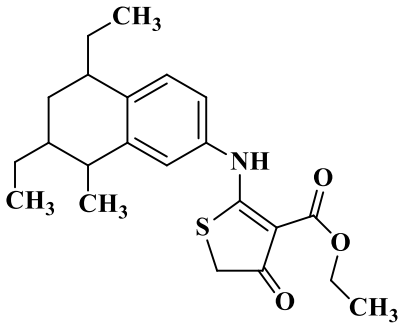
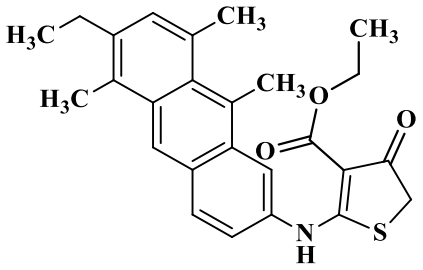
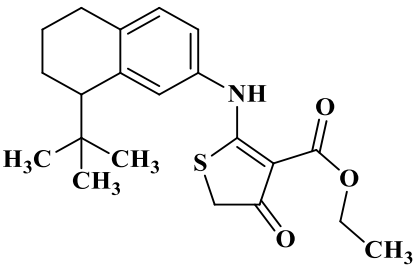
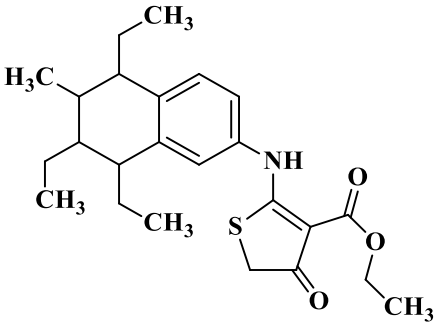
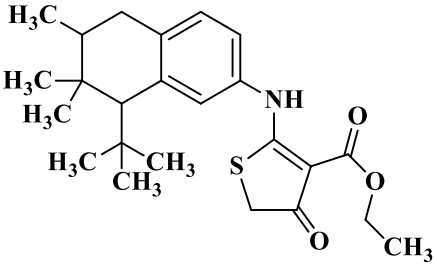
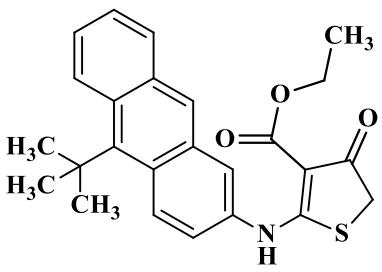
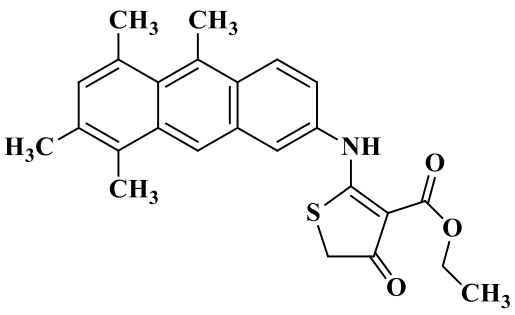
3.1. Molecular structures of new Dihydrothiophenone derivative

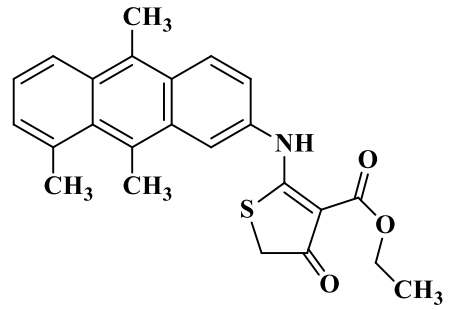
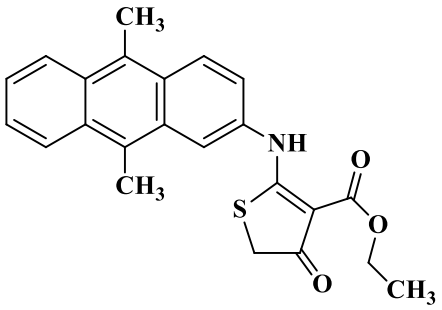
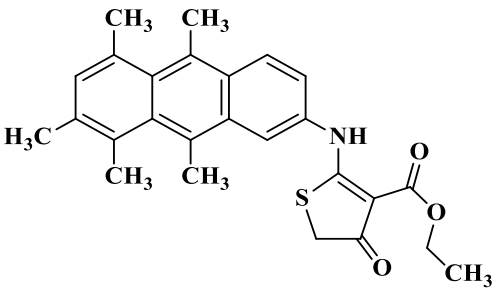
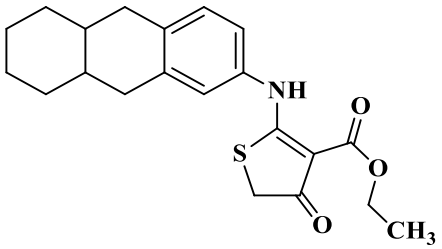
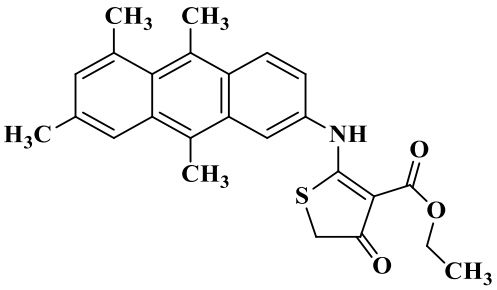
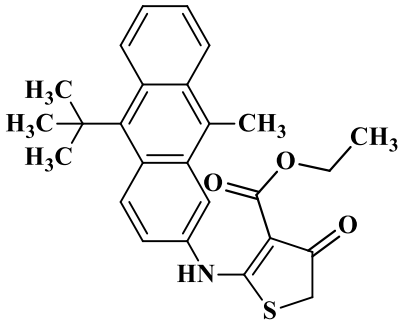
Considering the different substituents, some modifications on the structure of the molecules of Table 1. Therefore, the various structures obtained coded (CDH) are presented in Table 2.

Table 2. Molecular structures of new Dihydrothiophenone derivatives.

Code	Structure	Code	Structure
CDH 1		CDH 3	
CDH 2		CDH 4	

CDH 5		**CDH 7**	
CDH 6		**CDH 8**	
CDH 9		**CDH 12**	
CDH 10		**CDH 13**	
CDH 11		**CDH 14**	

CDH 15		**CDH 17**	
CDH 16		**CDH 18**	
CDH 19		**CDH 21**	
CDH 20		**CDH 22**	
CDH 23		**CDH 27**	

CDH 24		**CDH 29**	
CDH 25		**CDH 26**	
CDH 28		**CDH 30**	

The optimization of the geometry followed by the calculation of the frequencies of these different molecules at the level of the B3LYP/6-31G (d, p) theory, provides information on the value of the vibrational frequency of the carbonyl group (V(C=O)), the enthalpy of formation ($\Delta_f H°$), the carbon-nitrogen-carbon bond angle (α(C-N-C)) and the ionization potential I. Obtaining these values allowed us to predict the antimalarial activity (pIC_{50}) of these different molecules from the accepted QSAR model. Table 3 presents the different descriptor values and the expected pIC_{50} of these compounds.

3.2. Model descriptors predicted values of the potential inhibitor concentration pIC_{50}

The values of the model descriptors and the predicted values of the potential inhibitor concentration pIC50 were determined. The results of these values are shown in the table below.

The analysis of Table 3 shows that out of thirty (30) new molecules designed, twenty-four (24) have a pIC_{50} higher than the pIC_{50} of the parent compound (pIC_{50}=7.036). This means that all the new derivatives can be more active than the compounds in the experimental database.

Table 3. Model descriptors, predicted values of the potential inhibitor concentration pIC_{50}.

CODE	Vc=o	$\Delta_fH°_{298}$	α(c-n-c)	I(eV)	pIC_{50}
CDH 1	1771.170	-1466.518	130.228	5.813	8.362
CDH 2	1770.910	-1404.531	130.373	5.766	8.331
CDH 3	1770.980	-1460.343	130.041	5.813	8.184
CDH 4	1771.370	-1328.980	130.002	5.847	7.805
CDH 5	1771.060	-1246.803	130.210	5.830	7.801
CDH 6	1771.250	-1199.789	130.284	5.838	7.743
CDH 7	1771.250	-1336.011	129.802	5.821	7.628
CDH 8	1771.500	-1288.703	129.854	5.834	7.546
CDH 9	1773.970	-1253.459	129.999	6.045	7.543
CDH 10	1770.920	-1380.427	129.955	5.136	7.521
CDH 11	1771.320	-1196.629	130.018	5.834	7.478
CDH 12	1770.890	-1372.887	129.969	5.038	7.462
CDH 13	1770.530	-1333.918	129.958	5.105	7.414
CDH 14	1771.390	-1293.257	129.696	5.825	7.413
CDH 15	1770.970	-1381.077	129.802	5.138	7.377
CDH 16	1771.670	-1245.079	129.799	5.841	7.376
CDH 17	1771.210	-1380.275	129.756	5.159	7.327
CDH 18	1771.460	-1155.356	129.977	5.836	7.326
CDH 19	1770.650	-1279.978	130.008	5.100	7.312
CDH 20	1771.460	-1245.873	129.709	5.830	7.302
CDH 21	1771.570	-1104.936	130.082	5.851	7.298
CDH 22	1771.900	-1238.613	129.685	5.845	7.239
CDH 23	1771.340	-1214.144	129.922	5.252	7.103
CDH24	1771.180	-1181.682	130.059	5.164	7.110
CDH 25	1766.180	-1272.195	129.271	4.945	6.819
CDH 26	1771.730	-1099.715	129.584	5.846	6.802
CDH 27	1766.020	-1232.760	129.244	5.068	6.770
CDH 28	1766.310	-1221.672	129.309	5.019	6.759
CDH 29	1766.680	-1135.320	129.390	5.171	6.675
CDH 30	1768.210	-1261.186	128.116	5.212	6.606

3.3. Determination of the thermodynamic formation quantities

In order to verify the possible formation of the new, more active dihydrothiophenone derivatives, the standard thermodynamic quantities of formation, enthalpy of formation $\Delta_fH°$, the entropy of formation $\Delta_fS°$ and free enthalpy of formation $\Delta_fG°$ were determined. It should be noted that a change in enthalpy reflects the thermicity of a chemical reaction, while a change in entropy indicates the level of disorder in the system. Furthermore, a variation in free enthalpy reflects the spontaneity with which the reaction occurs. The different quantities were calculated at the B3LYP/ 6-31G (d, p) level of theory, and the values are given in Table 4.

The results in Table 4 show that all values of the standard thermodynamic quantities of molecule formation are negative. These negative values of enthalpy and free enthalpy reflect an exothermic reaction and a spontaneous reaction, respectively, under the conditions of the study. As far as entropy is concerned, a negative value indicates a decrease in disorder. Thus, the formation of all the compounds occurs spontaneously with a release of heat and a reduction in disorder. At this level, we note that the quantities determined at the theory B3LYP/6-31G (d, p) confirm that the formation of all these compounds is possible.

Table 4. Thermodynamic quantities of DH formation optimised at the B3LYP/ 6-31G (d, p) level.

CODE	$\Delta_fH°_{298}$	$\Delta_fG°_{298}$	$\Delta_fS°_{298}$
CDH 1	-1466.518	-811.234	-2197.829
CDH 2	-1404.531	-792.153	-2053.923
CDH 3	-1460.343	-805.413	-2196.646
CDH 4	-1328.980	-753.097	-1931.521
CDH 5	-1246.803	-706.92	-1810.774
CDH 6	-1199.789	-686.25	-1722.415
CDH 7	-1336.011	-744.765	-1983.044
CDH 8	-1288.703	-723.893	-1894.38
CDH 9	-1253.459	-755.588	-1669.863
CDH 10	-1380.427	-816.652	-1890.907
CDH 11	-1196.629	-682.505	-1724.38
CDH 12	-1372.887	-808.996	-1891.298
CDH 13	-1333.918	-796.323	-1803.101
CDH 14	-1293.257	-729.557	-1890.657
CDH 15	-1381.077	-816.881	-1892.321
CDH 16	-1245.079	-720.874	-1758.192
CDH 17	-1380.275	-816.355	-1891.395
CDH 18	-1155.356	-668.595	-1632.603
CDH 19	-1279.978	-767.959	-1717.319
CDH 20	-1245.873	-707.878	-1804.443
CDH 21	-1104.936	-642.869	-1549.780
CDH 22	-1238.613	-698.368	-1811.99
CDH 23	-1214.144	-726.782	-1635.625
CDH 24	-1181.682	-720.214	-1547.772
CDH 25	-1272.195	-709.916	-1885.893
CDH 26	-1099.715	-652.023	-1501.565
CDH 27	-1232.760	-745.698	-1633.613
CDH 28	-1221.672	-734.082	-1635.387
CDH 29	-1135.319	-700.161	-1459.528
CDH 30	-1261.186	-747.765	-1722.023

3.4. Determination of the Lipinski parameters

To verify the oral bioavailability of the molecules, we checked the different Lipinski criteria, namely, the molar mass (M), the number of hydrogen bond acceptor atoms (HBA), the number of hydrogen bond donor atoms (HBD), and the Moriguchi coefficient (M Logp). The values of these different parameters are given in Table 5.

Table 5. Lipinski parameters of the new Dihydrothiophenone derivatives.

Code	M(g/mol)	HBD	HBA	MLOG P
CDH 1	483.71	1	3	4.69
CDH 2	467.66	1	3	4.42
CDH 3	483.71	1	3	4.69
CDH 4	441.63	1	3	4.10
CDH 5	415.59	1	3	3.68
CDH 6	401.56	1	3	3.47
CDH 7	443.64	1	3	4.10
CDH 8	415.59	1	3	3.69
CDH 9	437.98	1	4	2.64
CDH 10	461.62	1	3	4.12

CDH 11	401.56	1	3	3.47
CDH 12	461.62	1	3	4.12
CDH 13	447.59	1	3	3.92
CDH 14	429.62	1	3s	3.89
CDH 15	461.62	1	3	4.12
CDH 16	413.57	1	3	3.68
CDH 17	461.62	1	3	4.12
CDH 18	387.54	1	3	3.26
CDH 19	433.56	1	3	3.72
CDH 20	415.59	1	3	3.68
CDH 21	373.51	1	3	3.54
CDH 22	415.59	1	3	3.68
CDH 23	419.54	1	3	3.51
CDH 24	405.51	1	3	3.30
CDH 25	433.56	1	3	3.72
CDH 26	371.49	1	3	3.04
CDH 27	419.54	1	3	3.51
CDH 28	419.55	1	3	3.50
CDH 29	391.48	1	3	3.09
CDH 30	433.57	1	3	3.73

Analysis of the data in Table 5 shows that the molar mass values of all compounds are below 500 g/mol. Also, the number of hydrogen bond donor atoms (HBD) values are all lower than 5. The number of hydrogen bond acceptor atoms (HBA) is lower than 10. At the (M Logp) level, all compounds have values below 5. Therefore, these compounds can be orally administered drugs.

3. Conclusion

The model established at the level of theory DFT/B3LYP/6-31G (d, p) allowed us to design 30 new compounds with more active values against Plasmodium falciparum strain from the series of molecules in the experimental database. The mathematical formula of the MLR model established in a previous study was used. Also, all compounds are within the range of applicability, so their predicted activity values are reliable. However, out of the 36 new molecules, fourteen (24) had inhibitory concentration potential (pIC_{50}) values higher than the parent compound. Then, the analysis of the thermodynamic formation quantities showed that all the compounds can be formed. Moreover, all the molecules respect the Lipinski rule, these molecules are therefore orally administrable and the proposed model will henceforth make it possible to reduce the time and cost of the synthesis as well as the determination of the antimalarial activity.

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