Research Article

Design of New Potential Antimalaria Compound Based on QSAR Analysis of Chalcone Derivatives

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ABSTRACT

Quantitative structure and activity relationship (QSAR) analysis was the sophisticated method in rational drug design, based on combination of statistical and computational chemistry calculations. Electronic and molecular descriptors for 31 chalcone derivatives were calculated using DFT/B3LYP. The best obtained QSAR equation was determined by multiple linear regression was log pIC_{50} = 30.719 (qC6) – 44.913 (qC7) – 101.702 (qC8) – 89.497 (qO16) -37.408 (E_{LUMO}) – 67.188. The equation has 95% conviction level with the statistical parameters n = 31, r = 0.968, r^2 = 0.937, adjusted r^2 = 0.920, SEE = 0.096, F_{calc}/F_{table} = 21.712 and PRESS = 0.174. This model was used to design 7 new potential antimalaria compounds of chalcone derivatives with the best log pIC_{50} value is -5.106; -6.421 and -8.305.

Keywords: Antimalaria, Chalcone, QSAR Analysis.

INTRODUCTION

Malaria, an infectious disease, is caused by protozoan parasites that infect human red-blood cells. There were 207 million cases annually and 627 thousand of them died mainly in Africa.[1] The mortality is due to the resistance of the *Plasmodium falciparum* parasite to antimalaria drugs such as chloroquine. Searching and developing the new chemicals (active compound) for antimalaria are important to solve the resistance problem.[2]

Chalcones (1,3-diphenyl-2-propane-1-ones), is one of the natural products compounds that shows various pharmacological activities such as antibacterial, antifungal,[3] antitumor,[4] anti-inflammatory,[5-6] antivirus,[7] antihypertensives,[8] and antimalaria.[9-13] The first reported chalcone as antimalaria was lichochalcone a which was isolated from Chinese liquorice roots and has IC_{50} value in 4.1 µM.[14] Lately, several studies were conducted to find the new antimalaria compounds based on chalcone derivatives.[15-20]

Understanding of the relationship between structure and activity is crucial in the design of the new chalcones derivatives which has the best antimalarial activity. Quantitative Structure and Activity Relationship Analysis (QSAR) is a well-established approach to design and predict the activity of new compound based on a combination of statistical and computational chemistry methods. Quantum mechanics calculation is used to calculate net atomic charges of each atom in a molecule, which is being the key factor to determine the activity of the compound.[21] Structure modification involved substitutions using electron donating and withdrawing groups are employed to investigate the influence of substituent to the net atomic charge values. Thus, the better anti-malarial activity can be obtained. The aims of this research are to investigate the key factor which influences antimalarial activity of chalcone compounds and to suggests the better antimalaria compound.

The QSAR studies of chalcone compounds (alkoxylated and hydroxylated chalcones) as antimalaria has been reported.[22-25] Each correlation was investigated by different approaches. Liu conducted QSAR analysis based on the similarity of the structure and antimalaria activity.[22] In other research, we found the QSAR analysis using 3-Dimensional methods such as COMFA (comparative molecular field analysis) which emphasize on the molecular parameter.[23-24] Furthermore, Neto (2014) carried out the QSAR analysis using electronic parameters of alkoxylated and hydroxylated chalcone compounds.[25] However, there is no comprehensive study for the whole set of chalcone derivatives from vanillin were studied by using a combination of electronic and molecular descriptors. In this research, we were investigated the key factor which influences antimalarial activity of chalcone compounds from vanillin using a combination of electronic and molecular descriptors and suggested the better antimalarial compound.

MATERIALS AND METHODS

Data Set

A total of 31 chalcone derivatives was taken from literature[8] and, was showed in Table 1. The selected data set compounds were determined based on following criteria, for having the basic structure of chalcone (1,3-diphenyl-2-propane-1-ones) and IC_{50} values less than 50 µM are chosen. The Inhibition concentration (IC_{50}) values were converted to logarithmic Inhibition concentration (log IC_{50}) as the dependent variable and listed in Table 1.

Procedure

Computational Methods

To choose the best computational method, ^{1}H-NMR chemical shifts were calculated using the Austin Model 1 (AM1), Hartree-Fock (HF) and Density Functional Theory (DFT) B3LYP and the results were then compared with experimental values (Table 2).

All quantum mechanical calculation was executed using Gaussian 09.[26] Correlation models were evaluated by multiple linear regression analysis using SPSS statistics 18.0.

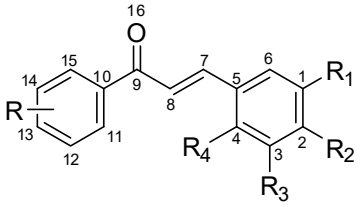
Validation of Model

The best model was chosen based on some statistical parameters such as r^2 value, F_{cal}/F_{tab}, standard estimation of error (SEE), and PRESS. Furthermore, the best selected model was used to calculate log IC_{50} (log pIC_{50}) values of the test set. The model was validated using criteria $r^2_{prediction} > 0.5$.[27]

RESULTS AND DISCUSSION

The results of ^{1}H - NMR chemical shift calculation were listed in Table 2. The compound (**9**) was used as a parameter because it has the best antimalarial activity.

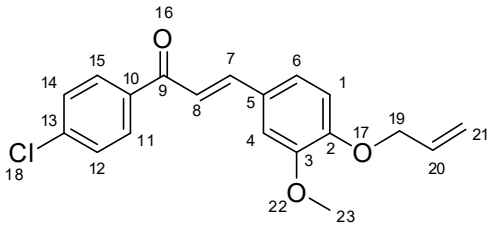
Table 1: Structure and antimalarial activity (Log IC_{50}) of chalcone derivatives[8]



Compound	R	R_1	R_2	R_3	R_4	Log IC_{50} (µM)
1	4-OH	Allyl	OH	OCH_3	H	1.585
2	4-Cl	Br	OH	OCH_3	H	1.447
3	4-Cl	Allyl	OCH_3	OCH_3	H	0.591
4	4-OCH_3	Allyl	OCH_3	OCH_3	H	0.633
5	3,4-OCH_2O-	Allyl	OCH_3	OCH_3	H	0.672
6	4-Br	Allyl	OCH_3	OCH_3	H	0.724
7	4-NO_2	Allyl	OCH_3	OCH_3	H	1.097
8	4-Cl	Allyl	O-Allyl	OCH_3	H	0.892
9[a]	4-Cl	H	O-Allyl	OCH_3	H	0.398
10[a]	3,4-diCl	H	O-Allyl	OCH_3	H	1.000
11	4-Br	H	O-Allyl	OCH_3	H	0.908
12	4-I	H	O-Allyl	OCH_3	H	0.929
13	4-F	H	O-Allyl	OCH_3	H	1.362
14	3-Cl	H	O-Allyl	OCH_3	H	0.724
15	4-OCH_3	H	O-Allyl	OCH_3	H	1.352
16[a]	3,4-O-CH_2-O-	H	O-Allyl	OCH_3	H	1.585
18	4-NH_2	H	O-Allyl	OCH_3	H	1.556
19	H	H	O-Allyl	OCH_3	H	1.580
20	4-O-Allyl	H	O-Allyl	OCH_3	H	0.869
21	4-Cl	H	H	OCH_3	O-Allyl	1.097
22	4-Cl	H	OCH_3	O-Allyl	H	1.255
23	4-Cl	H	OH	OCH_3	H	1.447
24	4-Cl	H	O-Prenyl	OCH_3	H	0.699
25	4-Cl	H	O-Butyl	OCH_3	H	1.170
26	4-Cl	H	O-CH_2-Ph-4-Br	OCH_3	H	0.903
27	4-Cl	OCH_3	O-Allyl	OCH_3	H	0.580
28[a]	4-Cl	H	O-Allyl	H	H	1.633
29[a]	4-Cl	H	H	H	O-Allyl	0.954
30	4-Cl	H	O-Allyl	O-Allyl	H	1.447
31[a]	4-Cl	H	O-Allyl	O-Allyl	H	0.531
32	3-O-Propyl 4-OCH_3	H	Cl	H	H	0.934

[a]) Compound test set

Table 2: The differences of the ^{1}H-NMR chemical shift by the experiment and computational method (δ, ppm)



Hydrogen atoms	δ Experiment	δ AM1	δ HF	δ DFT
1	6.92	6.96	6.23	6.70
4	7.17	6.02	5.09	6.44
6	7.22	7.44	6.63	6.88
7	7.97	6.46	5.94	6.63
8	7.37	6.83	5.97	7.03
11	7.79	8.08	7.52	7.58
12	7.48	7.06	6.42	6.67
14	7.48	6.87	6.23	6.49
15	7.79	7.47	6.73	6.98
19	4.68	5.72	4.10	5.37
20	6.03	6.16	5.55	5.93
21	5.47	5.14	4.55	5.07
23	3.95	4.54	3.33	3.98
Correlation		**0.846**	**0.897**	**0.932**

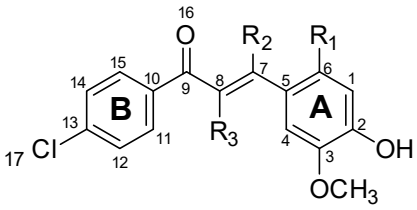
Table 3: Statistical parameters of 5 QSAR models of chalcone derivatives

Model	Variables	r	r^2	Adjusted r^2	SEE	F_{calc}/F_{table}	PRESS
1	qC1, qC5, qC6, qC7, qC8, qC10, qO16, E_{LUMO}, E_{HOMO}	0.969	0.939	0.902	0.106	9.902	0.168
2	qC1, qC5, qC6, qC7, qC8, qC10, qO16, E_{LUMO}	0.969	0.939	0.908	0.103	11.882	0.168
3	qC1, qC5, qC6, qC7, qC8, qO16, E_{LUMO}	0.969	0.939	0.913	0.099	14.334	0.169
4	qC5, qC6, qC7, qC8, qO16, E_{LUMO}	0.968	0.938	0.917	0.099	17.479	0.171
5	qC6, qC7, qC8, qO16, E_{LUMO}	0.968	0.937	0.920	0.096	21.712	0.174

Table 4: The difference of the experimental Log IC_{50} values and the prediction of Log pIC_{50} values of some models of 6 test set compounds.

Compound Test	Experimental Log IC_{50}	Calculated (Log pIC_{50}) (µM)				
		Model 1	Model 2	Model 3	Model 4	Model 5
9	0.398	0.788	0.788	0.785	0.778	0.750
31	0.531	0.639	0.639	0.611	0.602	0.598
29	0.954	1.079	1.078	1.060	1.070	0.881
10	1.000	1.063	1.064	1.068	1.061	1.087
16	1.585	1.616	1.617	1.616	1.611	1.660
28	1.633	1.664	1.663	1.655	1.656	1.664
PRESS		**0.1352**	**0.1350**	**0.1247**	**0.1190**	**0.1007**

Table 5: The new design of chalcone derivatives and its predicted antimalarial activity calculated using the best QSAR model



Compound	R_1	R_2	R_3	Log pIC_{50}	pIC_{50} (nM)
32	SO_2-OCH_3	H	H	-2.784	1.645
33	SO_2-OH	H	H	-3.459	0.348
34	Tosyl	H	H	-3.495	0.320
35	SO_2-$NHCH_3$	H	H	-4.394	0.040
36	SO_2-$N(CH_3)_2$	H	H	-5.106	0.008
37	SO_2-$N(CH_3)_2$	Cl	H	-6.421	0.00038
38	CO-N_2H_3	OH	H	-8.305	$0.0495x10^{-4}$

The calculation of compared ^{1}H-NMR chemical shift between experiment and computational methods (using DAM1, HF, and DFT), which was listed in Table 2, showed that the best correlation value (r) was obtained from using DFT methods (r=0.932), while using AM1 and HF was (r = 0.846) and (r = 0.897) respectively. This result clearly indicated that ^{1}H-NMR chemical shift data obtained from calculation using DFT/ B3LYP has a better agreement with those resulted from experimental measurement as compared to those calculated by AM1 and HF method, suggesting that DFT method described the chemical conformation of chalcone derivatives more accurately than does AM1 and HF methods. Therefore, DFT method has been selected as a calculation method for all antimalarial compounds in Table 1.

Selection of the Best Model

Five QSAR models with their statistical properties were obtained from multiple linear regression and were listed in Table 3. It could be confirmed that all the models showed good correlation between the biological activity and descriptors (r ≈ 0.9). Because of the closeness of r value from each model, the determination of the best model could not be deduced by only comparing the r value. Therefore, other statistical parameters such as F_{calc} / F_{tab} (significance models), SEE (standard error of the Estimate) and PRESS (predictive residual sum of square) must be calculated. Practically, these calculations could be more tedious and time consuming. Even so, because of its simplicities, model 5 could be chosen as the best QSAR models because it has the lowest number of variables and gave better statistical parameter values. The complete equation of the best model (model 5) was:

Log pIC_{50} = 30.719 (qC6) – 44.913 (qC7) – 101.702 (qC8) – 89.497 (qO16) –37.408 (E_{LUMO}) - 67.188

n = 31, r = 0.968, r^2 = 0.937, Adjusted r^2 = 0.920, SEE = 0.096, F_{calc}/F_{table} = 21.712, PRESS = 0.174

The values of r = 0.968 and r^2 = 0.937 indicated that the correlation between the independent variables and antimalarial activity was very significant. It confirmed that 96.8% of alteration of the antimalarial activity of the chalcone derivatives was caused by the change of independent variables (net charge of atoms C6, C7, C8, O16 and E_{LUMO}).

This result was in good agreement with previous reports that conjugation of the two aromatic rings was an essential feature of antimalarial activity because it would bind better with active site.[25,28-29]

The F_{calc}/F_{table} of model 5 was determined to be 21.712. The higher F_{calc} value than F_{table} showed that the correlation between descriptors (independent variable) and antimalarial activity (Log IC_{50}) has the 95% significance of conviction level. Meanwhile, the model 5 also has smallest SEE value than the others. It could be concluded that model 5 has the smallest deviation from the experimental data and could be used to design a new antimalarial compound.

Model validation

Determination of selected models for further prediction calculation of antimalarial activity was carried out by calculated the PRESS value from the prediction of Log pIC_{50} for each model toward 6 test set compounds and compared them with Log IC_{50} of experimental (as listed on Table 4). The calculation showed that PRESS value of model 5 gave the lowest (0.1007) value than others and indicated good similarity toward Log IC_{50} of experimental. This result also referred model 5 as the best model to predict antimalarial activity of chalcone compound from vanillin.

Figure 1 depicts the correlation between predicted log pIC_{50} by model 5 against the experimental value of log pIC_{50}. The result of the correlation showed that the model

5 could predict activities of 6 test set compounds very well with slope value and correlation coefficient (r^2) 0.919 and 0.935 respectively.

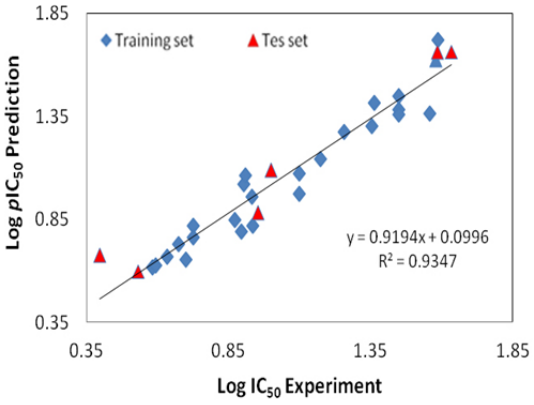


Figure 1: Plot of experimental versus predicted antimalarial activity values of model 5

Design of New Antimalarial Chalcone Derivatives

The best-obtained QSAR model was used as the reference to predict the activity in a design of new antimalarial compounds of chalcone derivatives from vanillin. In the QSAR equation of model 5, it could be shown that the more negative of the log pIC_{50} value gave better antimalarial activity. The negative net atomic charge of qC6 and the positive net atomic charge of qC7, qC8, qO16, and E_{LUMO} were recommended to get the negative value of log pIC_{50}. The negative value of atomic charge of qC6 could be obtained by substitution of electron withdrawing group. Whereas, the substitution of electron donating groups would gave a positive value of muliken atomic charge of qC7, qC8, qO16 (Table 5).

Table 5 showed that molecular design of chalcone derivatives with SO_3 has extremely high anti-malarial activity (nM). Substitution of electron withdrawing groups (SO_3) on position C6 could produce higher resonance on the ring A. The higher electron resonance would give lower E_{Lumo} energy and it could increase the anti-malarial activity. Electron donating groups on position C7 and C8 would encourage the electron resonance toward position C7 and C8 and cause the net charge of O was more negative.

CONCLUSION

In this study, the quantitative relationship between the structure of the chalcone derivatives and antimalarial activity was studied. The model 5 was the best model with the 95% conviction level using statistical parameters. The correlation was shown by the molecular properties of C6, C7, C8, O16, and E_{LUMO} atoms as the active center of antimalarial. The best QSAR model was used to design new antimalarial of chalcone derivatives in silico and it has better activity than the existing chalcone derivatives.

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REFERENCES

1. Sonin DL, Wakatsuki T, Routhu KV, Harmann LM, Petersen M, Meyer J, Strande JL, Protease-activated receptor 1 inhibition by SCH79797 attenuates left ventricular remodeling and profibrotic activities of cardiac fibroblasts, J. Cardiovasc. Pharmacol. Ther., 18, 2013, 460–475.
2. Kyaw MP, Nyunt MH, Chit K, Aye MM, Aye KH, Lindegardh N, Tarning J, Imwong M, Jacob CG, Rasmussen C, Reduced Susceptibility of Plasmodium falciparum to Artesunate in Southern Myanmar, PLoS ONE, 8, 2013, e57689.
3. Siddiqui ZN, Praveen S, Musthafa TNM, Ahmad A, Khan AU, Thermal solvent-free synthesis of chromonyl chalcones, pyrazolines and their *in vitro* antibacterial, antifungal activities, J. Enz. Inhib. Med. Chem., 27, 2012, 84-91.
4. Seo W., Ryu Y., Curtis-Long M., Lee C., Ryu H., Jang K., 2010, Evaluation of anti-pigmentary effect of synthetic sulfonylamino chalcone, *Eur. J. Med.Chem.,* 45, 2010, 2010-2017.
5. Rahman MA, Chalcone: a valuable insight into the recent advances and potential pharmacological activities, Chem. Sci. J., 2011, 2011, CSJ–29.
6. Seo W, Ryu Y, Long MC, Lee C, Ryu H, Jang K, Evaluation of anti-pigmentary effect of synthetic sulfonylamino chalcone, Eur. J. Med. Chem., 45, 2010, 2010-2017.
7. Trivedi JC, Bariwal JB, Upadhyay KD, Naliapara ED, Joshi SK, Pannecouque CC, Clercq ED, Shah AK, Improved and rapid synthesis of new coumarinyl chalcone derivatives and their antiviral activity, Tetrahedron Lett., 48, 2007, 8472-8474.
8. Bonesi M, Loizzo MR, Statti GA, Michel S, Tillequin F, Menichini F, The synthesis and Angiotensin Converting Enzyme (ACE) inhibitory activity of chalcones and their pyrazole derivatives, Bioorg. Med. Chem. Lett., 20, 1990-1993.
9. Li R, Chen X, Gong B, Dominguez JN, Davidson E, Kurzban G, Miller RE, Nuzum EO, Rosenthal PJ, McKerrow JH, *In vitro* antimalarial activity of chalcones and their derivatives. J. Med. Chem., 38, 1995, 5031–5037.
10. Kumar R, Mohanakrishnan D, Sharma A, Kaushik NK, Kalia K, Sinha AK, Sahal D, Reinvestigation of structure activity relationship of methoxylated chalcones as antimalarials: synthesis and evaluation of 2,4,5-trimethoxy substituted patterns as lead candidates derived from abundantly available natural β-asarone, Eur. J. Med. Chem., 45, 2010, 5292–5301.
11. Hans RH, Guantai EM, Lategan C, Smith PJ, Wan B, Franzblau SG, Gut J, Rosenthal PJ, Chibale K, Synthesis, antimalarial and antitubercular activity of acetylenic chalcones, Bioorg. Med. Chem. Lett., 20, 2010, 942–944.
12. Tadigoppula N, Korthikunta V, Gupta S, Kancharla P, Khaliq T, Soni A, Srivastava RK, Srivastava K, Puri SK, Raju KSR, Wahajuddin Sijwali PS, Kumar V, Mohammad IS, Synthesis and insight into the structure–activity relationships of

chalcones as antimalarial agents, J. Med. Chem., 56, 2013, 31−45.

13. Sharma N, Mohanakrishnan D, Shard A, Sharma UK, Kumar R, Richa, Sinha AK, Sahal D, Design, economical synthesis and antiplasmodial evaluation of vanillin derived allylated chalcones and their marked synergism with artemisinin against chloroquine resistant strains of *Plasmodium falciparum*, Eur. J. Med. Chem., 79, 2014, 350-368.

14. Chen M, Theander TG, Christensen SB, Hviid L, Zhai L, Kharazmi A, Licochalcone A, a new antimalarial agent, inhibits *in vitro* growth of the human malaria parasite *Plasmodium falciparum* and protects mice from *P. yoeli* infection, Antimicrob. Agents Chemother, 38, 1994, 1470-1475.

15. Guantai EM, Ncokazi K, Egan TJ, Gut J, Rosenthal PJ, Smith PJ, Chibale K, Design, synthesis and *in vitro* antimalarial evaluation of triazole-linked chalcone and dienone hybrid compounds, Bioorg. Med. Chem., 18, 2010, 8243–8256.

16. Sharma N, Mohanakrishnan D, Shard A, Sharma A, Saima Sinha AK, Sahal D, Stilbene - chalcone hybrids: design, synthesis, and evaluation as a new class of antimalarial scaffolds that trigger cell death through stage specific apoptosis, J. Med. Chem., 55, 2011, 297−311.

17. Sashidhara KV, Kumar M, Modukuri RK, Srivastava RK, Soni A, Srivastava K, Singh SV, Saxena JK, Gauniyal HM, Puri SK, Antiplasmodial activity of novel keto-enamine chalcone-chloroquine based hybrid pharmacophores, Bioorg. Med. Chem., 20, 2012, 2971–2981.

18. Sashidhara KV, Avula SR, Palnati GR, Singh SV, Srivastava RK, Puri SK, Saxena JK, Synthesis and *in vitro* evaluation of new chloroquine-chalcone hybrids against chloroquine-resistant strain of Plasmodium falciparum, Bioorg. Med. Chem. Lett., 22, 2012, 5455–5459.

19. Smit FJ, N'Da DD, Synthesis, *in vitro* antimalarial activity and cytotoxicity of novel 4-aminoquinolinyl-chalcone amides, Bioorg. Med. Chem., 22, 2014, 1128–1138.

20. Pingaew R, Saekee A, Mandi P, Nantasenamat C, Prachayasittikul S, Ruchirawat S, Prachayasittikul V, Synthesis, biological evaluation and molecular docking of novel Chalcone-coumarin hybrids as anticancer and antimalarial agents, Eur. J. Med.Chem., 85, 2014, 65-76.

21. Karelson M, Lobanov VS, Katritzky AR, Quantum-Chemical Descriptors in QSAR/QSPR Studies, Chem. Rev., 96, 1996, 1027–1044.

22. Liu M, Wilairat P, Go ML, Antimalarial Alkoxylated and Hydroxylated Chalones: Structure-Activity Relationship Analysis, J. Med. Chem., 44, 2001**,** 4443-4452.

23. Liu M, Wilairat P, Croft SL, Tand ALC, Go ML, Structure–Activity Relationships of Antileishmanial and Antimalarial Chalcones, Bioorg. Med. Chem., 11, 2003, 2729–2738.

24. Xue CX, Cui SY, Liu MC, Hu ZD, Fan BT, 3D QSAR studies on antimalarial alkoxylated and hydroxylated chalcones by CoMFA and CoMSIA, Eur. J. Med. Chem., 39, 2004, 745-753.

25. Neto AB, Lavarda FC, The correlation between electronic structure and antimalarial activity of alkoxylated and hydroxylated chalcones, Med. Chem. Res., 23, 2014, 580–586.

26. Frisch M.J., Trucks G.W., Schlegel H.B., Scuseria G.E., Robb M.A., Cheeseman J.R., Scalmani G., Barone V., Mennucci B., Petersson G.A., Nakatsuji H., Caricato M., Li X., Hratchian H.P., Izmaylov A.F., Bloino J., Zheng G., Sonnenberg J.L., Hada M., Ehara M., Toyota K., Fukuda R., Hasegawa J., Ishida M., Nakajima T., Honda Y., Kitao O., Nakai H., Vreven T., Montgomery Jr. J.A., Peralta J.E., Ogliaro F., Bearpark M., Heyd J.J., Brothers E., Kudin K.N., Staroverov V.N., Kobayashi R., Normand J., Raghavachari K., Rendell A., Burant J.C., Iyengar S.S., Tomasi J., Cossi M., Rega N., Millam J.M., Klene M., Knox J.E., Cross J.B., Bakken V., Adamo C., Jaramillo J., Gomperts R., Stratmann R.E., Yazyev O., Austin A.J., Cammi R., Pomelli C., Ochterski J.W., Martin R.L., Morokuma K., Zakrzewski V.G., Voth G.A., Salvador P., Dannenberg J.J., Dapprich S., Daniels A.D., Farkas Ö., Foresman J.B., Ortiz J. V, Cioslowski J., Fox D.J., 2009. Gaussian 09 Revision D.01.

27. Frimayanti N, Yam ML, Lee HB, Othman R., Validation of quantitative structure activity relationship (QSAR) model for photosensitizer activity prediction, Int. J. Mol. Sci., 12, 2011, 8626–8644.

28. Li R, Chen X, Gong B, Dominguez JN, Davidson E, Kurzban G, Miller RE, Nuzum EO, Rosentha PJ, *In vitro* antimalarial activity of chalcones and their derivatives, J. Med. Chem., 38, 1995, 5031–5037.

29. Motta LF, Gaudio AC, Takahata Y, Quantitative structure–activity relationships of a series of chalcone derivatives (1,3-diphenyl-2-propen-1-one) as anti Plasmodium falciparum agents (anti malaria agents), Internet Electron. J. Mol. Des., 5, 2006, 555–569.

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