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QSAR Analysis on Apigenin Derivative Compounds as Antioxidant Using Semiempirical Austin Model 1

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Quantitative structure-activity relationship (QSAR) analysis has been done on derivative compounds of apigenin. Apigenin is one of flavonoid group compound that potential as antioxidant. QSAR analysis was initiated by modelling the structures of compounds and calculating the descriptors of QSAR using Hyperchem software with semiempirical Austin Model 1 (AM 1) method. Determination of QSAR equation has been done using multilinear regression analysis method on one of the statistical data processing software. Of the 18 QSAR equation models, based on the value of R, R^2, SE and F obtained 4 QSAR equation models that qualified. The best QSAR equation model determined through the process of validation of the test set compounds. The validation result showed that the best QSAR equation model of the following equation:

$$-\log IC_{50} = 10.035 + (0.997\ \text{HOMO energy}) + (2.134\ \text{LUMO energy}) + (-0.045\ \text{hydration energy}) + (-0.056\ \log P) + (-0.341\ \text{Dipole}) + (-3.552\ \text{atomic charge of C5}) + (4.138\ \text{atomic charge of C5'})$$

The results of predicted IC_{50} on 91 apigenin derivative suggest that the hydration 50 compounds have better biological activity as antioxidant than apigenin and the compound 3,3',6-triamine apigenin is a compound with the smallest predicted IC_{50} value (1.76 μM).

Keywords: QSAR, Apigenin, Semiempirical Austin Model 1.

INTRODUCTION

Quantitative structure-activity relationship (QSAR) is one of computational chemistry scopes. QSAR can be used to study the relationship between molecular structure with it's biological activity that expressed quantitatively. QSAR based on the knowledge that the substances with a similar chemical structure (analog compounds) may have similar biological activity. QSAR method is suitable for predicting drug compounds that can act as antioxidants. Antioxidants are necessary to prevent or reduce illness due to free radicals. Bioactive compounds that can be used as an antioxidant are compounds having phenols group such as flavonoids, oligoresveratrol and phenolic acids. The antioxidant activity of the flavonoid derivatives has been carried out experimentally and computationally. Seyoum *et al.* [1] have managed to synthesize several compounds of derived flavonoid experimentally and antioxidant activity test has been done using DPPH radical scavenging activity. The results of these studies showed that the compound has many -OH groups on the aromatic ring have a good antioxidant activity, one such compound is apigenin with IC_{50} value of 436.4 μM [1].

Antioxidants can donate H atom on free radicals that free radicals turned into a more stable form [2]. Antioxidants serve as a barrier to oxidation only, it cannot stop the auto-oxidation process altogether. The inhibition of free radical formation by an antioxidant through a chain reaction of initiation to propagation [3]. Apigenin is an organic compound of the main group of flavonoids from celery belonging to the flavone group, apigenin could be developed into a compound that has potential as an antioxidant [4]. The potential antioxidant activity appeared cause electron donating groups such as -OH group on the aromatic ring at a specific position. The antioxidant activity test of flavonoids by using QSAR was reported by Perwira and Hadisaputro [5]. The antioxidant activity test of apigenin derivatives by replacing a hydrogen atom with an ethoxy and methoxy group against derivates of Chrysin was reported by Nisa [6].

This research aims to develop apigenin derivative, which is expected to have biological activity as antioxidant higher than parent compounds. This study using QSAR semiempirical AM 1 method. The level of accuracy of this method is quite high, whereas relatively fast calculation time [7]. Data processing is performed by the statistical method of regression

analysis multilinear because descriptors generated from a relatively large semiempirical methods.

EXPERIMENTAL

Twelve flavonoid derivative compounds as the experimental set compounds with the experimental IC_{50} value based on research of Seyoum *et al.* [1], 91 apigenin modification compounds were investigated.

Hardware: A set of computer with an Intel Dual Core processor, 1 GB RAM, 32-bit operating system.

Software: Hyperchem professional 8.0, one of the statistical data processing software, software microsoft excel.

General procedure

Calculation of molecular and electronic parameters: Flavonoid and apigenin derivative compounds used as research material created in two-dimensional (2D) structures using Hyperchem program, then the structure is equipped with a hydrogen atom and molecule models created in 3D to obtain the structure of the most stable state approach. Geometry optimization process to determine the molecular structure of the most stable performed using the semiempirical AM 1 method with the convergence limit is 0.001 kcal/A *i.e.* gradient limit energy change per change of position. Limit iterations are used amounted 32767. Optimization method used is the adjacency gradient method (Conjugate gradient) *i.e.* Polak Ribiere algorithm. Calculation of electronic and molecular parameters are stored in a file record (file.log). The data that contained in the recording file are such as net charge of atomic energy, total energy (kcal/mol), binding energy (kcal/mol), isolates energy (kcal/mol), electronics energy (kcal/mol), formation energy (kcal/mol), inter atomic energy (kcal/mol), HOMO energy (eV), ELUMO energy (eV), surface area (A^2), volume (A^3), hydration energy (kcal/mol), log P, refractivity (A^3), polarity (A^3), mass (amu), dipole (Debyes) and the charge of atoms can be seen in QSAR properties of Hyperchem program.

QSAR analysis of electronic and molecular parameters: QSAR analysis conducted by multilinear regression analysis using enter backward method to make QSAR equation models. The dependent variable was -log IC_{50} and independent variable used were electronic and molecular parameters that has been done the correlation analysis of them.

Steps to determine the best QSAR model of the equation is as follows:

• Determine training and test set compounds.

• QSAR equation models were determined using multilinear regression analysis. QSAR equation model obtained with various combinations of independent variables.

• Selection of the best QSAR equation model by taking into account statistics parameters such as R, R^2, SE and F.

• Validate QSAR equation models that qualified by making linear curve of predicted -log IC_{50} *versus* experimental -log IC_{50} of training and test set compounds.

• The equation model that predicted biological activity value (-log IC_{50}) was closest to the experimental biological activity value (-log IC_{50}) is the best QSAR equation model. This is indicated by the value of the slope of curve that most closely 1.

Design of new compounds: The electronic and molecular parameters of apigenin modification compounds, incorporated in the best QSAR equation model that previously obtained, to predict the value of antioxidant activity (-log IC_{50}). If the –log IC_{50} value of new compounds larger than previous compounds, the new compounds were predicted have antioxidant activity which is better than previous compounds.

RESULTS AND DISCUSSION

A total of 91 apigenin derivative compounds are calculated and optimized by AM 1 semiempirical method to determine the value of the electronic and molecular paramaters. The structure of apigenin is shown in Fig. 1.

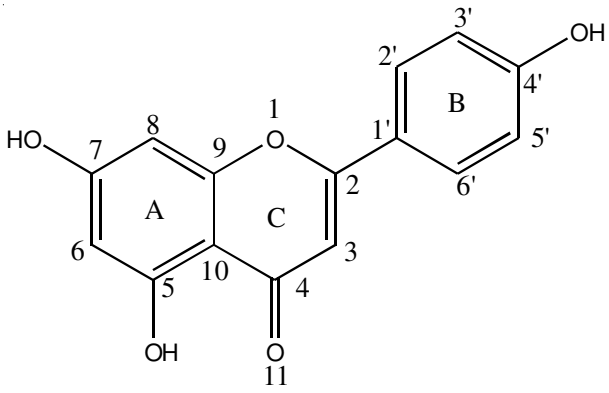

Fig. 1. Based structure of apigenin [1]

QSAR analysis with semiempirical AM 1 method: Determination of the QSAR equation using multilinear regression analysis by 12 flavonoid derived compounds that synthesized by Seyoum *et al.* [1] shown in Table-1. Correlation analysis showed in Table-2. There are 11 of electronic and moleculer parameters of 12 flavonoids derivative compounds that have a strong correlation to the -log IC_{50} value *i.e.* HOMO Energy, LUMO energy, hidration energy, log P, dipole, atomic charge of C3, C5, C8, C3', C5' and O11, these parameters called by descriptors. Descriptors were used to manufacture multi-linear regression model were performed using SPSS, the results obtained 18 models of multilinear equations as shown in Table-3.

TABLE-1
ANTIOXIDANT ACTIVITY OF SYNTHESIZED FLAVONOID COMPOUNDS [Ref. 1]

Flavonoid derivative compound	IC_{50} (μM)	-log IC_{50}
Apigenin	463.4	-2.666
8-Hydroxyflavone	166.3	-2.221
Chrysin	492.0	-2.692
Diosmetin	465.6	-2.668
7,8-Dihydroxyflavone	15.5	-1.19
5,7-Dihydroxy-3',4'-dimethoxyflavone	313.3	-2.496
Galangin	71.6	-1.855
Luteolin	11.0	-1.043
Quercetagetin	9.0	-0.955
Acacetin	529.7	-2.724
Fisetin	14.1	-1.148
Hesperetin	236.6	-2.374

TABLE-2
CORRELATION VALUES OF ELECTRONIC AND MOLECULAR PARAMETERS

Descriptors (QSAR properties)	Correlation value	Descriptors (atomic charge)	Correlation value
Total energy	-0.214	O1	-0.389
Binding energy	0.182	C2	-0.022
Isolated atoms energy	-0.223	C3	0.692
Electronic energy	-0.140	C4	0.005
Heat of formation	-0.378	C5	-0.559
Inter atom energy	0.127	C6	0.254
HOMO energy	0.408	C7	-0.132
LUMO energy	-0.630	C8	0.468
Surface area	-0.398	C1'	0.215
Volume	-0.206	C2'	0.034
Hydration energy	-0.536	C3'	0.448
log P	-0.420	C4'	-0.005
Refractivity	-0.154	C5'	0.471
Polarisability	-0.204	C6'	0.323
Mass	0.108	C9	-0.356
Dipole	-0.532	C10	0.084
		O11	0.508

Selection of the best QSAR equation model depend on the statistic parameters, such as R, R_2, F_{hit}/F_{tab} and SE. Based on them, there are 4 equation models that qualified *i.e.* models 12, 13, 14, and 16. Validation test using training and test set compounds showed in Figs. 2 and 3. Figs. 2 and 3 present the slope that closest one is the equation model 13 both in training set or test set compounds. Based on this, it can be concluded that the best QSAR equation model is model 13. Complete model of the best equation can be written as follows:

$-\log IC_{50}$ = 10.035 + (0.997 HOMO energy) + (2.134 LUMO energy) + (-0.045 hydration energy) + (-0.056 log P) + (-0.341 Dipole) + (-3.552 atomic charge of C5) + (4.138 atomic charge of C5')

R = 0.975 SE = 0.265752

R^2 = 0.951 Fhit/Ftab = 1,811 Sig.F = 0.018

Design of new compounds: Determination of substituents on phenyl group of apigenin compounds based on the diverse of subtituent properties. The properties of the substituents can affect steric factors, the activity of phenyl group and the polarity of compound. Design of new compounds and the predicted biological activity value ($-\log IC_{50}$) of derivative

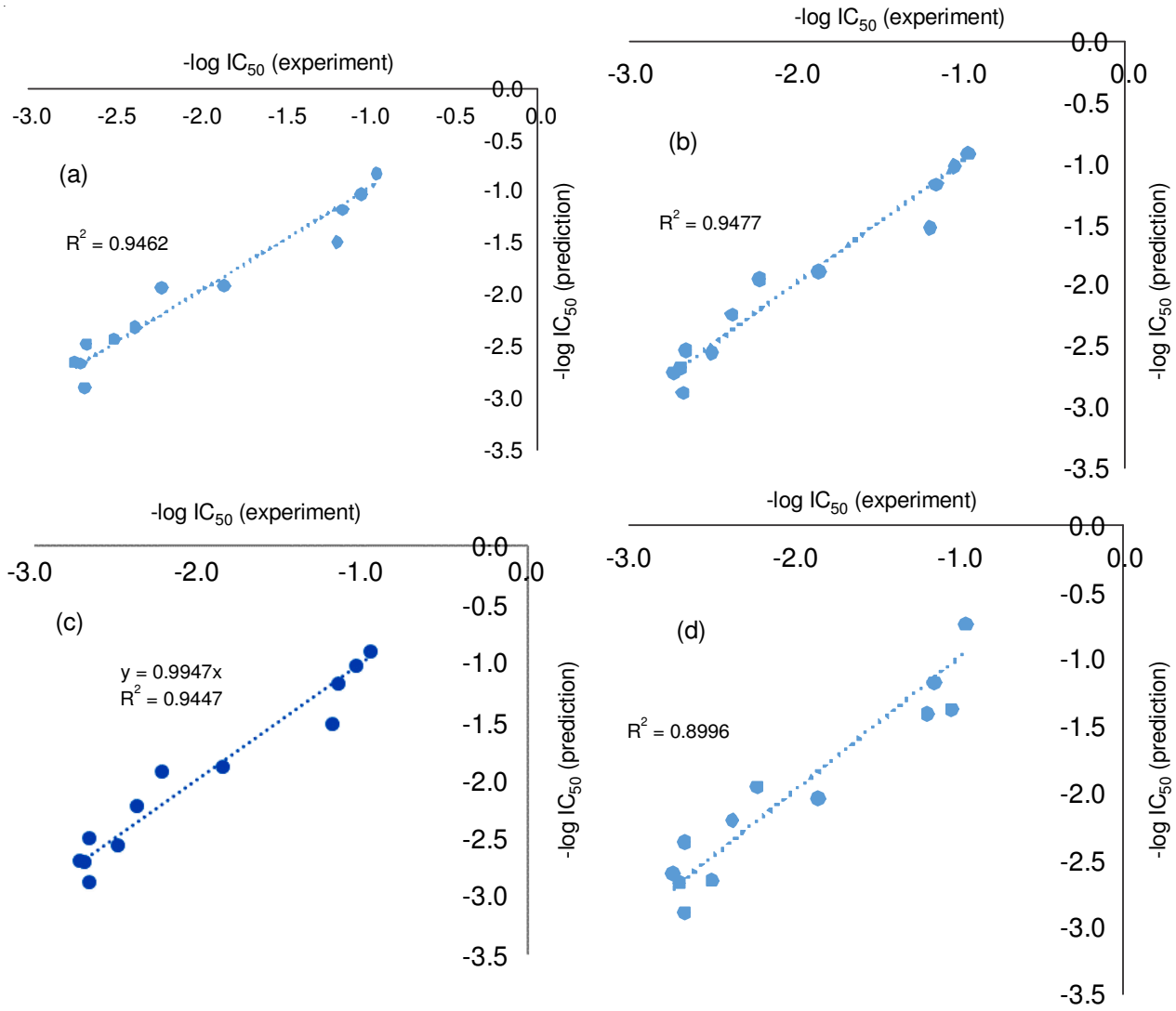

Fig. 2. Graph of $-\log IC_{50}$ (experiment) *vs.* $-\log IC_{50}$ (prediction) of Training Set Compounds by QSAR Equation Models a. 12, b. 13, c. 14, d. 16

TABLE-3
QSAR EQUATION MODELS

Models	Σ descriptors	Coefficient											R	R^2	SE	F	Sig.F
		Conc.	E_{HOMO}	E_{LOMO}	$E_{Hidration}$	log P	Dipole	C3	C5	C8	C3'	C5'	O11					
1	11	29.799	5.713	75.688	-0.746	0.247	-0.355	-1.990	-33.453	31.465	-4.875	225.238	-345.198	1.000	1.000	–	–	–
2	10	-0.109	0.016	5.752	-0.079	-0.053	-0.346	0.934	-6.424	–	0.956	12.627	-17.379	0.98	0.96	0.478187	2.41	0.466
3		2.675	0.152	3.648	-0.065	-0.025	-0.372	1.104	-3.906	0.283	1.654	–	-2.347	0.979	0.958	0.489966	2.29	0.476
4		15.273	2.606	37.743	0.393	0.15	-0.426	-0.194	-16.948	14.936	–	99.035	-157.867	0.991	0.982	0.316901	5.614	0.318
5		14.905	3.684	61.38	-0.608	0.156	-0.297	–	-28.464	25.242	3.527	180.349	-281.179	0.997	0.995	0.175417	18.549	0.179
6	9	9.63	0.847	3.511	-0.064	-0.006	-0.410	–	-3.525	0.05	1.399	1.54	–	0.978	0.956	0.354268	4.858	0.182
7		-0.734	0.077	6.389	-0.080	-0.085	-0.306	0.797	-7.641	–	–	20.286	-25.359	0.979	0.958	0.345723	5.112	0.174
8		13.86	2.454	37.248	-0.388	0.141	-0.416	–	-16.893	14.722	–	97.737	-156.280	0.991	0.982	0.224517	12.426	0.077
9	8	-1.169	-0.114	1.134	-0.035	-0.106	-0.261	1.703	-3.871	0.017	–	–	–	0.974	0.948	0.314669	6.869	0.07
10		4.087	0.392	1.073	-0.035	-0.084	-0.294	1.008	-3.345	–	–	–	2.518	0.974	0.949	0.311197	7.032	0.068
11		9.499	0.834	3.482	-0.063	-0.008	-0.410		-3.562	–	1.39	1.612	–	0.978	0.956	0.289266	8.197	0.055
12	7	-1.265	-0.124	1.123	-0.035	-0.107	-0.261	1.711	-3.885	–	–	–	–	0.974	0.948	0.272512	10.467	0.019
13		10.035	0.997	2.134	-0.045	-0.056	-0.341	–	-3.552	–	–	4.138	–	0.975	0.951	0.265752	11.036	0.018
14		11.007	1.062	1.082	-0.037	-0.056	-0.340	–	-2.702	–	–	–	5.604	0.973	0.947	0.274767	10.287	0.02
15	6	22.25	2.256	2.423	-0.037	0.08	-0.405	–	–	–	–	7.773	–	0.842	0.709	0.578178	2.028	0.228
16		2.959	0.315	1.941	-0.054	-0.097	-0.336	–	-4.098	–	–	–	–	0.953	0.908	0.324169	8.268	0.017
17		4.237	0.493	0.904	-0.025	0.012	-0.300	2.479	–	–	–	–	–	0.788	0.622	0.658914	1.369	0.374
18	5	10.959	1.195	2.102	-0.053	0.036	-0.415	–	–	–	–	–	–	0.732	0.536	0.666145	1.386	0.348

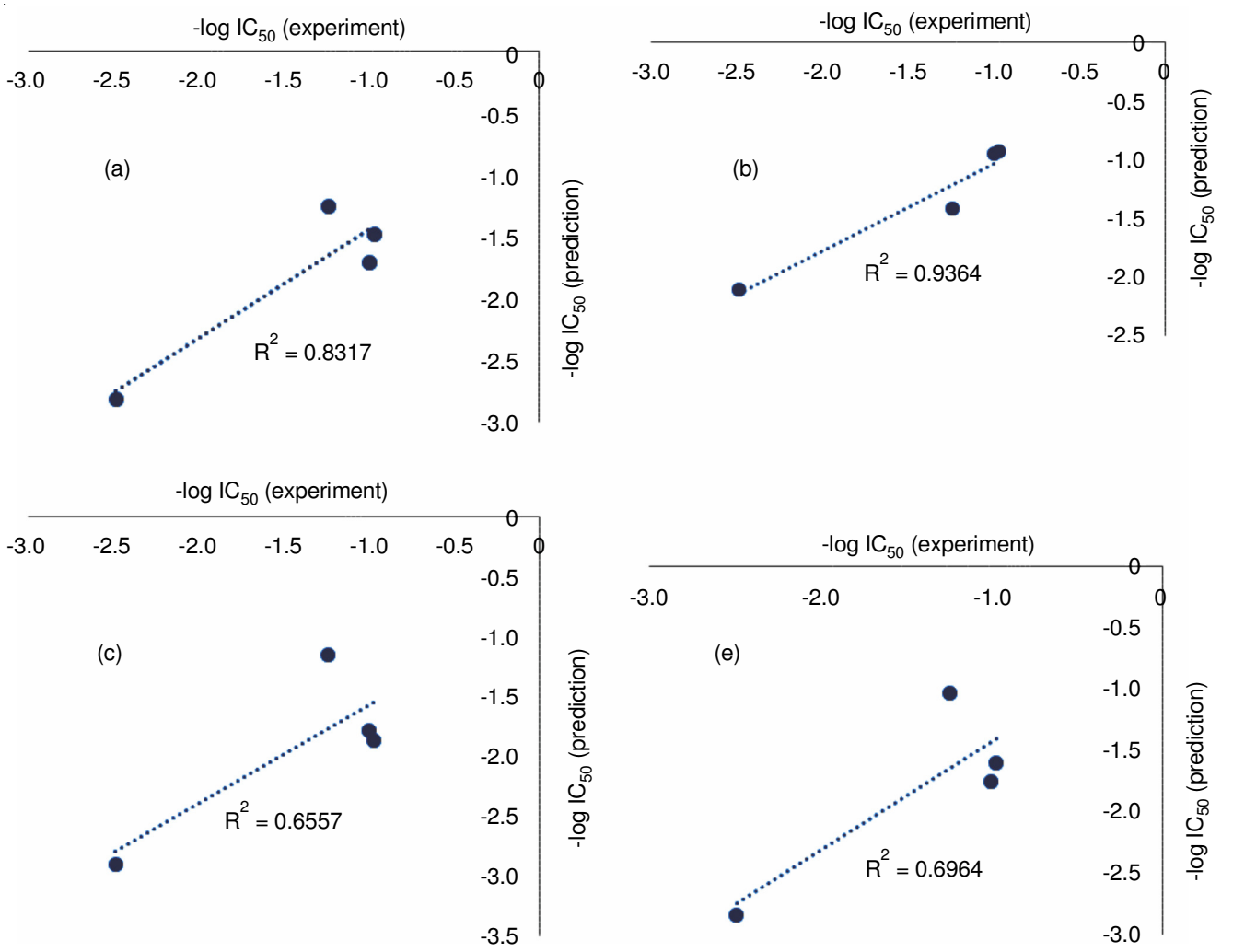

Fig. 3. Graph of –log IC_{50} (experiment) *vs.* –log IC_{50} (prediction) of Test Set Compounds by QSAR Equation Models a. 12, b. 13, c. 14, d. 16

apigenin compounds were calculated using QSAR equation model no 13 with 7 descriptors *i.e*. HOMO energy, LUMO energy, hydration energy, log P, dipole, charge of atom C5 and C5'. The value of QSAR properties and predict biological activity of apigenin modification compounds are shown in Table-4. There are 50 compounds of 91 new compounds were designed have biological activity as an antioxidant better than apigenin (-log IC_{50} > -2.46) and the rest have –log IC_{50} value < -2.46. These compounds need to be studied further to determine where the compound that allows or not to be synthesized and predict the level of physico-chemical compound stability.

TABLE-4
QSAR PROPERTIES AND PREDICTED BIOLOGICAL ACTIVITY VALUES OF APIGENIN MODIFICATION COMPOUNDS

S. No.	Structure modification compounds	E_{HOMO}	E_{LUMO}	log P	Dipole moment	Hydration energy	Atomic charge of C5	Atomic charge of C5'	-log IC_{50} predicted	IC_{50} predicted (μM)
1	3,3',6-Triamino apigenin	-8.560457	-0.7988247	-7.12	2.408	-34.51	0.191	-0.119	-0.24	1.76
2	3,6-Diamino apigenin	-8.564551	-0.7777809	-5.4	2.338	-30.18	0.191	-0.166	-0.67	4.63
3	3,3'-Diamino apigenin	-8.551504	-0.7806069	-5.4	2.728	-31.36	0.226	-0.119	-0.67	4.66
4	3-Amino apigenin	-8.555168	-0.7597413	-3.68	2.728	-27.03	0.226	-0.166	-1.11	12.98
5	3',6-Diamino apigenin	-8.9819	-0.940009	-5.52	2.612	-31.47	0.187	-0.121	-1.26	18.04
6	3,3'-Diisopropoxy apigenin	-8.769578	-0.9166063	-2.44	1.721	-21.7	0.224	-0.166	-1.62	41.74
7	3-Ethoxy apigenin	-8.78821	-0.8990007	-2.61	2.206	-23.7	0.225	-0.169	-1.68	48.24
8	3-Propoxy apigenin	-8.784455	-0.8965718	-2.14	2.148	-23.16	0.225	-0.169	-1.71	50.74
9	3,6-Diisopropoxy apigenin	-8.787726	-0.9122269	-2.44	1.812	-19.14	0.203	-0.171	-1.72	52.68
10	3,3',6-Trimethoxy apigenin	-8.821964	-0.9870727	-4.94	2.615	-23.93	0.202	-0.151	-1.75	55.91
11	3-Isopropoxy apigenin	-8.790239	-0.8949146	-2.2	2.314	-23.2	0.224	-0.17	-1.76	57.49
12	3,6-Diethyl apigenin	-9.031679	-0.639812	-0.86	2.536	-18.82	0.222	-0.164	-1.77	59.13
13	3,6-Diethoxy apigenin	-8.793	-0.9243251	-3.26	2.35	-21.03	0.202	-0.169	-1.79	62.14
14	3,3'-Diethoxy apigenin	-8.677953	-0.9212195	-3.26	3.03	-23.23	0.225	-0.153	-1.82	66.14
15	3-Ethyl apigenin	-9.130822	-0.6710842	-1.41	2.825	-22.74	0.223	-0.164	-1.83	67.97
16	3,3'-Dimethoxy apigenin	-8.80278	-0.9508577	-3.95	2.911	-25.07	0.225	-0.151	-1.84	68.84
17	3'-Amino apigenin	-8.974336	-0.9180944	-3.81	3.417	-28.3	0.222	-0.121	-1.84	69.06
18	3,6-Diprophyl apigenin	-9.023998	-0.6397715	-0.07	2.466	-17.37	0.222	-0.164	-1.85	70.75
19	3-Prophyl apigenin	-9.126325	-0.6718664	-1.02	2.8	-22.3	0.223	-0.164	-1.86	72.88
20	3,6-Dipropoxy apigenin	-8.788755	-0.9208829	-2.33	2.292	-19.65	0.202	-0.169	-1.88	75.20
21	6-Amino apigenin	-9.152322	-0.9140549	-3.81	2.734	-27.16	0.187	-0.165	-1.88	76.59
22	3-Isoprophyl apigenin	-9.113226	-0.6936785	-1.08	2.786	-22.25	0.223	-0.164	-1.89	77.66
23	3,3'-Dipropoxy apigenin	-8.675829	-0.9162049	-2.33	3.031	-22.12	0.225	-0.153	-1.91	81.28
24	3,6-Dimethyl apigenin	-8.986773	-0.7485262	-1.66	2.793	-20.62	0.222	-0.166	-1.93	84.95
25	3,3',6-Triethyl apigenin	-9.006891	-0.6134639	-0.31	2.916	-16.47	0.222	-0.163	-1.95	89.72
26	3-Methoxy apigenin	-8.923505	-0.9182227	-2.96	2.713	-24.47	0.224	-0.168	-1.97	93.38
27	3,6-Diisopropyl apigenin	-9.006232	-0.6684293	-0.2	2.588	-16.6	0.225	-0.164	-1.97	93.93
28	3,3',6-Triethoxy apigenin	-8.766841	-0.9475735	-3.92	3.15	-20.66	0.201	-0.152	-2.00	98.97
29	3,3'-Diethyl apigenin	-9.093587	-0.6453158	-0.86	3.199	-20.39	0.222	-0.163	-2.00	99.22
30	3-Methyl apigenin	-9.066276	-0.7708873	-1.81	2.985	-23.14	0.223	-0.165	-2.00	99.83
31	3,3',6-Trimethyl apigenin	-8.95921	-0.7234678	-1.5	3.102	-19.08	0.222	-0.164	-2.02	105.58
32	3,6-Dimethoxy apigenin	-8.93314	-0.9555849	-3.95	2.844	-23.32	0.202	-0.169	-2.03	106.31
33	3,3',6-Triisopropoxy apigenin	-8.85988	-0.889526	-2.68	2.61	-17.67	0.203	-0.167	-2.05	113.09
34	3,3'-Dimethyl apigenin	-9.026312	-0.7459894	-1.66	3.293	-21.6	0.223	-0.164	-2.08	121.58
35	3,3',6-Tripropyl apigenin	-8.997769	-0.6124284	0.88	2.899	-14.32	0.222	-0.164	-2.10	126.86
36	3,3'-Dipropyl apigenin	-9.086597	-0.644721	0.07	3.224	-19.26	0.222	-0.164	-2.10	127.04
37	3,3'-Diisopropyl apigenin	-9.064307	-0.6578956	-0.2	3.25	-19.26	0.223	-0.165	-2.11	129.20
38	3,3',6-Tripropoxy apigenin	-8.765627	-0.941258	-2.51	3.134	-18.72	0.202	-0.152	-2.15	139.70
39	3,3',6-Triisopropyl apigenin	-8.974573	-0.6325146	0.68	3.062	-13.61	0.225	-0.165	-2.21	163.75
40	3',6-Diethoxy apigenin	-8.999928	-0.927115	-3.39	3.455	-20.81	0.2	-0.148	-2.29	195.47
41	6-Ethoxy apigenin	-9.099217	-0.9142965	-2.74	3.069	-21.3	0.199	-0.165	-2.31	205.23
42	3',6-Dimethoxy apigenin	-9.245098	-0.9555846	-4.07	3.108	-23.41	0.201	-0.147	-2.32	210.03
43	3'-Fluoro apigenin	-9.27876	-1.071656	-2.69	1.844	-23.43	0.223	-0.146	-2.32	210.33
44	6-Methoxy apigenin	-9.123236	-0.9264793	-3.08	3.209	-22.84	0.2	-0.165	-2.33	211.41
45	6-Propoxy apigenin	-9.099226	-0.9134772	-2.27	3.04	-20.46	0.2	-0.165	-2.37	233.50
46	6-Methyl apigenin	-9.077527	-0.8708062	-1.93	3.316	-21.47	0.221	-0.165	-2.40	249.97
47	3',6-Dipropoxy apigenin	-8.998693	-0.9240405	-2.45	3.495	-19.39	0.2	-0.148	-2.41	259.10
48	3'-Ethoxy apigenin	-8.997789	-0.9066331	-2.74	3.986	-23.5	0.223	-0.148	-2.42	265.07
49	3'-Chloro apigenin	-9.250703	-1.029285	-2.31	2.319	-23.26	0.223	-0.159	-2.45	281.32
50	6-Ethyl apigenin	-9.08218	-0.8656428	-1.54	3.258	-20.05	0.221	-0.165	-2.46	286.72
51	Apigenin	-9.153569	-0.8916482	-2.09	3.496	-23.99	0.222	-0.165	-2.46	288.90
52	3',6-Dimethyl apigenin	-9.044193	-0.8423948	-1.78	3.635	-19.9	0.221	-0.163	-2.48	304.49
53	3'-Propoxy apigenin	-8.998101	-0.9048726	-2.27	4.049	-22.93	0.223	-0.148	-2.49	311.43
54	3'-Bromo apigenin	-9.261177	-1.032968	-2.04	2.276	-23.2	0.222	-0.166	-2.50	313.38
55	6-Prophyl apigenin	-9.078452	-0.8647889	-1.14	3.22	-19.03	0.221	-0.165	-2.51	321.56
56	3'-Methyl apigenin	-9.102895	-0.8626798	-1.93	3.813	-22.42	0.222	-0.163	-2.53	337.16
57	3'-Iodo apigenin	-9.260648	-1.025354	-1.57	2.336	-23.16	0.222	-0.168	-2.54	343.68
58	6-Isopropyl apigenin	-9.070211	-0.8669209	-1.21	3.211	-18.27	0.224	-0.165	-2.54	347.91
59	6-Isopropoxy apigenin	-9.088803	-0.9082264	-2.32	3.591	-19.89	0.201	-0.165	-2.56	363.89
60	3'-Isopropoxy apigenin	-9.045132	-0.9028666	-2.32	4.049	-22.57	0.223	-0.153	-2.57	371.59

S. No.	Structure modification compounds	E_{HOMO}	E_{LUMO}	log P	Dipole moment	Hydration energy	Atomic charge of C5	Atomic charge of C5'	-log IC_{50} predicted	IC_{50} predicted (μM)
61	3-Iodo apigenin	-9.336213	-0.8135195	-1.45	3.605	-23.27	0.224	-0.162	-2.58	376.89
62	3'-Ethyl apigenin	-9.096706	-0.8551436	-1.54	3.847	-21.58	0.222	-0.165	-2.59	384.67
63	3',6-Diethyl apigenin	-9.041427	-0.8291512	-0.99	3.614	-17.63	0.221	-0.165	-2.60	398.16
64	3',6-Diisopropoxy apigenin	-9.085415	-0.9244327	-2.56	3.537	-18.35	0.202	-0.16	-2.61	409.72
65	3-Chloro apigenin	-9.190999	-0.9136577	-2.19	3.655	-23.72	0.225	-0.165	-2.62	413.48
66	3,3'-Dichloro apigenin	-9.285499	-1.032654	-2.41	2.654	-23.01	0.225	-0.159	-2.62	415.02
67	3'-Isopropyl apigenin	-9.083437	-0.8444722	-1.21	3.98	-20.89	0.222	-0.165	-2.64	440.53
68	3'-Prophyl apigenin	-9.093341	-0.8535599	-1.14	3.895	-20.88	0.222	-0.165	-2.65	445.27
69	3-Bromo apigenin	-9.275011	-0.8777085	-1.91	3.701	-23.71	0.225	-0.164	-2.65	447.90
70	3,3'-Diiodo apigenin	-9.402372	-0.9280832	-0.93	2.813	-22.92	0.225	-0.166	-2.68	480.35
71	3',6-Diisopropyl apigenin	-9.022769	-0.821485	-0.33	3.552	-15.16	0.224	-0.166	-2.71	509.16
72	3',6-Diprophyl apigenin	-9.036078	-0.8269371	-0.2	3.626	-15.92	0.221	-0.165	-2.72	519.14
73	3,3'-Dibromo apigenin	-9.361982	-1.00055	-1.86	2.751	-22.95	0.225	-0.166	-2.72	526.45
74	3,3'-Difluoro apigenin	-9.229194	-1.208012	-3.16	2.703	-23.21	0.226	-0.146	-2.85	710.59
75	3'-Methoxy apigenin	-9.051057	-0.9049241	-3.08	4.537	-22.84	0.222	-0.193	-2.85	714.54
76	3-Fluoro apigenin	-9.081725	-1.047657	-2.56	4.115	-23.77	0.226	-0.165	-2.93	852.92
77	3',6-Difluoro apigenin	-9.348189	-1.210155	-3.29	3.077	-22.24	0.196	-0.146	-3.03	1076.89
78	3',6-Dichloro apigenin	-9.312223	-1.133573	-2.53	3.106	-21.67	0.234	-0.159	-3.10	1258.22
79	6-Chloro apigenin	-9.225289	-1.003353	-2.31	4.207	-22.4	0.233	-0.165	-3.11	1292.35
80	3,3',6-Trichloro apigenin	-9.344132	-1.143373	-2.63	3.082	-21.41	0.236	-0.159	-3.16	1437.15
81	6-Fluoro apigenin	-9.240176	-1.04191	-2.69	4.58	-22.8	0.195	-0.165	-3.16	1450.25
82	3,6-Dichloro apigenin	-9.257691	-1.031928	-2.41	4.12	-22.12	0.236	-0.165	-3.19	1558.31
83	6-Bromo apigenin	-9.251482	-1.011848	-2.04	4.265	-22.25	0.252	-0.165	-3.26	1839.76
84	3,3',6-Trifloro apigenin	-9.325351	-1.358246	-3.77	2.962	-22.01	0.198	-0.146	-3.28	1891.42
85	6-Iodo apigenin	-9.259751	-1.007794	-1.57	4.236	-22.11	0.255	-0.165	-3.30	1984.91
86	3',6-Dibromo apigenin	-9.355361	-1.145735	-1.98	3.151	-21.46	0.252	-0.166	-3.32	2075.95
87	3,6-Diiodo apigenin	-9.444082	-0.9430807	-0.93	4.171	-21.82	0.257	-0.162	-3.36	2316.51
88	3,6-Dibromo apigenin	-9.363900	-1.005829	-1.86	4.24	-21.96	0.254	-0.164	-3.38	2407.51
89	3',6-Diiodo apigenin	-9.371579	-1.133703	-1.05	3.18	-21.27	0.255	-0.168	-3.40	2495.52
90	3,3',6-Tribromo apigenin	-9.446257	-1.121234	-1.81	3.253	-21.2	0.254	-0.165	-3.41	2597.30
91	3,6-Difluoro apigenin	-9.183840	-1.209205	-3.16	4.575	-22.57	0.198	-0.164	-3.45	2825.69
92	3,3',6-Triiodo apigenin	-9.510005	-1.049168	-0.41	3.33	-21.03	0.257	-0.166	-3.45	2827.43

The calculation of biological activity value of apigenin derivative compounds showed that replacement of H atoms with alkoxy (methoxy, ethoxy, propoxy, isopropoxy) and amine group can improve antioxidant activity, whereas the replacement of H by halogen group can decrease the activity as antioxidants. This can occur because alkoxy and amines are compounds that have an ability to push the electrons on phenyl group and activate the aromatic ring so it cause the electron density in the aromatic ring was increases, while halogens were an electron-withdrawing group because the electronegativity was so high that tend to deactivated aromatic ring [8].

Table-4 presents the increasing antioxidant activity were not depend on position of substituents replacement, almost every position affects the activity. This is because that in the structure of flavonoids as antioxidants, all positions have an important role, the group on the aromatic rings A and C have an ability to influence the solubility and binding ability, while the group on the aromatic ring B affects the activity/reactivity of the compound to the free radicals [9]. These properties consistent with existing variables in the QSAR equation used in the calculation of predicted biological activity value. There are variables such as energy of HOMO and LUMO that affecting the holding capacity of a compound to other molecules, its relates to ability as an electron donor or acceptor [10], log P shows the solubility (hydrophilicity and hydrophobicity), the dipole shows how reactive the compound, the greater of dipole, the compounds are more reactive [11], hydration energy affect the ability of compounds to interact with water molecules and the atomic charge in the side chains (atom C5 and C5') affects how hard or easy to let go of the atom that attached to the aromatic ring.

QSAR analysis with multiple variables in the QSAR equation showed that the apigenin modification compounds that have the greatest predicted –log IC_{50} value is 3,3',6-triamine apigenin. It means that the compound has the smallest predicted IC_{50} value that indicate is the best as antioxidant than others. The predicted IC_{50} value of 3,3',6-triamine apigenin is 1.76 μM. 3,3',6-Triamine apigenin contained hydroxy and amine groups as the electrons driving force and activated of phenyl groups in the structure of flavonoids. It facilitates the transfer process of H atoms in the radical reaction. Although radical reactions take place quickly and easily, phenyl that binds hydroxy and amine group has a better resonance capability than the structures with other substituents, so the product formed is more stable compound. According to the theory of molecular orbital (MO), the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) have the greatest influence on the activity of compounds. The reaction between active molecule and receptor macromolecular operated on the frontier molecules orbitals. EHOMO is the energy of HOMO, which relate to the ability of electron donor. ELUMO is the energy of LUMO, which relate to the ability of acceptance of electronic [10]. High values

of HOMO energy indicates a tendency of the molecule to donate the electron, 3,3',6-triamine apigenin has the high HOMO energy so it is easy to donate electrons to free radicals. Structure of 3,3',6-triamine apigenin showed in Fig. 4.

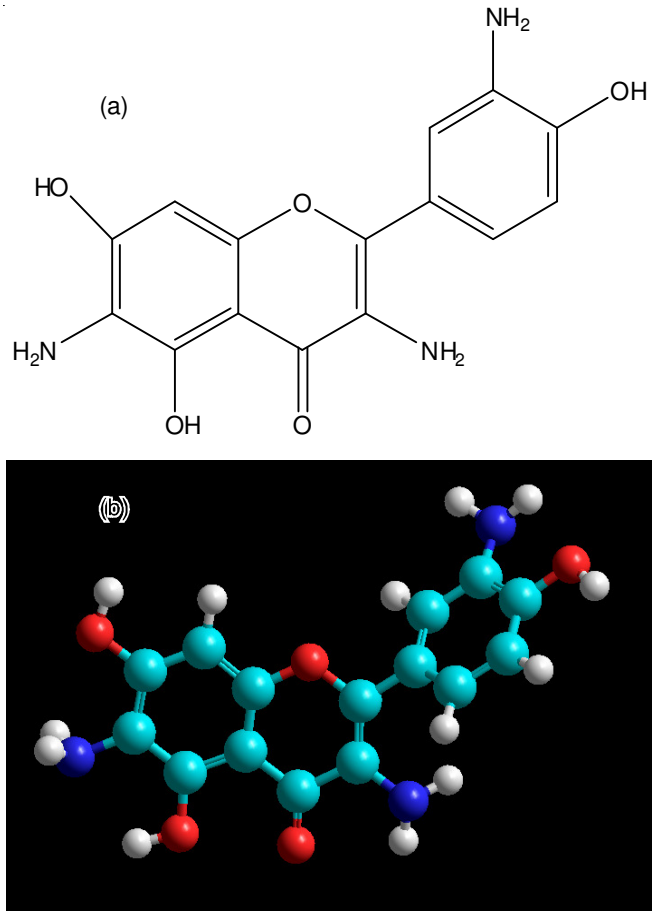

Fig. 4. Structure of 3,3',6-triamine apigenin (a) 2D, (b) 3D

Conclusion

Electronic and molecular parameters that affect the antioxidant activity of the apigenin modification compounds *i.e.* HOMO energy, LUMO energy, log P, hydration energy, dipole moment, atomic charge of C5 and C5'. The best QSAR equation as follows:

$$-\log IC_{50} = 10.035 + (0.997 \text{ HOMO energy}) + (2.134 \text{ LUMO energy}) + (-0.045 \text{ hydration energy}) + (-0.056 \log P) + (-0.341 \text{ Dipole}) + (-3.552 \text{ atomic charge of C5}) + (4.138 \text{ atomic charge of C5'})$$

Replacement of H atoms with alkoxy and amines substituent group tend to increase the activity of the compound as an antioxidant while replacement with halogen substituents groups tend to decrease the antioxidant activity of compounds. Of the 91 apigenin modification compounds obtained 50 compounds that have predicted antioxidant activity better than apigenin and 3,3',6-triamine apigenin is the best compound with predicted IC_{50} value is 1.76 μM.

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