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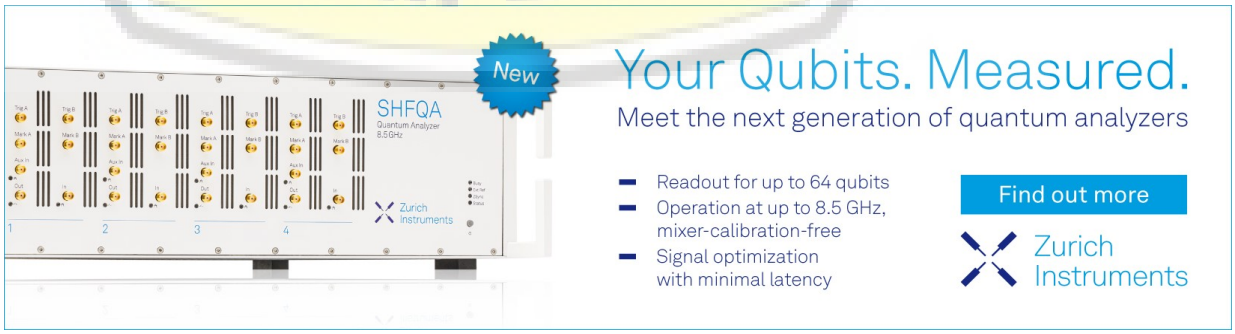

Molecular Modeling of Anti-Microbacterial Agent by QSAR Study of Diiodocoumarin Derivatives

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Abstract. Coumarins and their derivatives have biological activities such as anti-microbial, anticancer, antioxidant and anti-HIV properties.Molecular modeling using Quantitative Structure and Activity Relationship (QSAR) has been performed on a series of diiodocoumarin derivatives as effective antimicrobial agent. This research focus on a set of experimetally inhibition-zone diameter (mm/mg sample) value data of 5diiodocoumarin derivatives, that is 6,8-diiodocoumarin-3-carboxylate, 6,8-diiodocoumarin-3-carboxylic acid, 6,8-diiodocoumarin-3-carbonylchloride, N-(4-(2-Hydroxyethyl)phenyl)-6,8-diiodocoumarin-3-carboxamide, and N-(4-Hydroxyphenyl)-6,8-diiodocoumarin-3-carboxamide. The mathematical method multi linear regression calculation was used to build the QSAR model. QSAR analysis was employed on fitting subset using log (1/inhibition-zone diameter) as dependent variable and atomic net charges, dipole moment and partition coefficient in n-octanol/water as independent variables. The parameterized Model number 3 (PM3) method was carried out to calculate the quantum chemical descriptors, chosen to represent the electronic descriptors of molecular structures. The relationship between log (1/inhibition-zone diameter) and the descriptors was described by resulted QSAR model. The resulted QSAR model for caffeic acid derivatives as anti-microbial is presented below:

$$8.051+32.24C5+27.24O7+0.021\ logP$$

$$R = 1;\ R^2 = 0.999;\ SE = 0.008;\ Sig = 0.038$$

QSAR model for diiodocoumarin derivatives showed partition coefficient of n-octanol/water and atom charge in C5 and O7 gave significant effect as descriptors to the anti-microbial activity.N-(4-(2-Hydroxyethyl)phenyl)-6,8-diiodocoumarin-3carboxamide and N-(4-Hydroxyphenyl)-6,8-diiodocoumarin-3-carboxamide have higher anti-microbial activity because the presence of hydroxyphenylgroup increases the electron density value of O7 and C5.The calculated PRESS (Predicted Residual Error Sum of Square) value was 7.13E-05 which indicates the calculated log (1/inhibition-zone diameter) using QSAR Hansch Model of diiodocoumarinderivativesis similar with experimental data.

INTRODUCTION

Anti-microbacterial is a compound that can inhibit the growth and kill microorganisms [1-2]. The higher concentration of antimicrobial substances can make the faster of the microorganism cells are killed or slowed its growth. Antibacterial activity can be divided into five groups, namely antibacterial which inhibits bacterial cell metabolism, inhibits bacterial wall synthesis, interferes with bacterial cell membranes, inhibits bacterial cell protein synthesis, and inhibits synthesis or destroys nucleic acids from bacteria [3]. Therefore, we need a compound that can inhibit bacteria such as coumarin compounds [4].

Coumarin is a lactone compound from an orthocoumaric phenolic compound (an ortho hydroxyl cinnamic compound). Simple coumarin is a phenylpropanoid containing C6 benzene ring with C3 aliphatic chain as side chains [5-7]. Coumarin compounds can be found in phytochemical (benzopyran) poisons found in plants, especially in high concentrations such as vanilla, apricots, woodruff, lavender, mullein, strawberries, cherries, tonks, cinnamon, sweet clover, licorice, and bison grass which have taste like vanilla [8-12].

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The derivative of Iodo-organic based compounds have been used extensively in the medical world, as amebicides and diagnostic-imaging drugs (such as iodixanol, diatrizoic acid, iopamidol, and iohexol) [13-15]. the importance of iodo-organic compounds in medical aplication is an opportunity for the development of advanced materials as pharmacological agents [16-19].

The new anti-microbacterial compounds can be found by a modeling approach using computational chemistry concepts [20]. One application of computational chemistry that can be applied is the study of Quantitative Structure-Activity Relationship (QSAR) or quantitative relations of activity structure. QSAR studies quantitative correlations between molecular structure and the value of experimentally measured biological activities [21-25]. The research will analyze the relationship between the chemical structure and the bioactivity of 5 diiodocoumarin derivatives. In this study, QSAR analysis of diiodocoumarin derivatives was carried out by using antimicrobacterial activity studies (inhibition zone diameter of Staphyloccoccus aureus) as a function of electronic, hydrophobic, and steric variables.

MATERIALS AND METHODS

Equipments

This research, Intel (R) Celeron (C) CPU 1007U processor with 2048MB RAM was used as computer hardware. The Hyperchem 7.02 computational chemistry software waschosen for computational chemical calculations and SPSS 16.020 for statistical analysis. The chemdraw Ultra 8.0 was used to create 2D molecular structures.

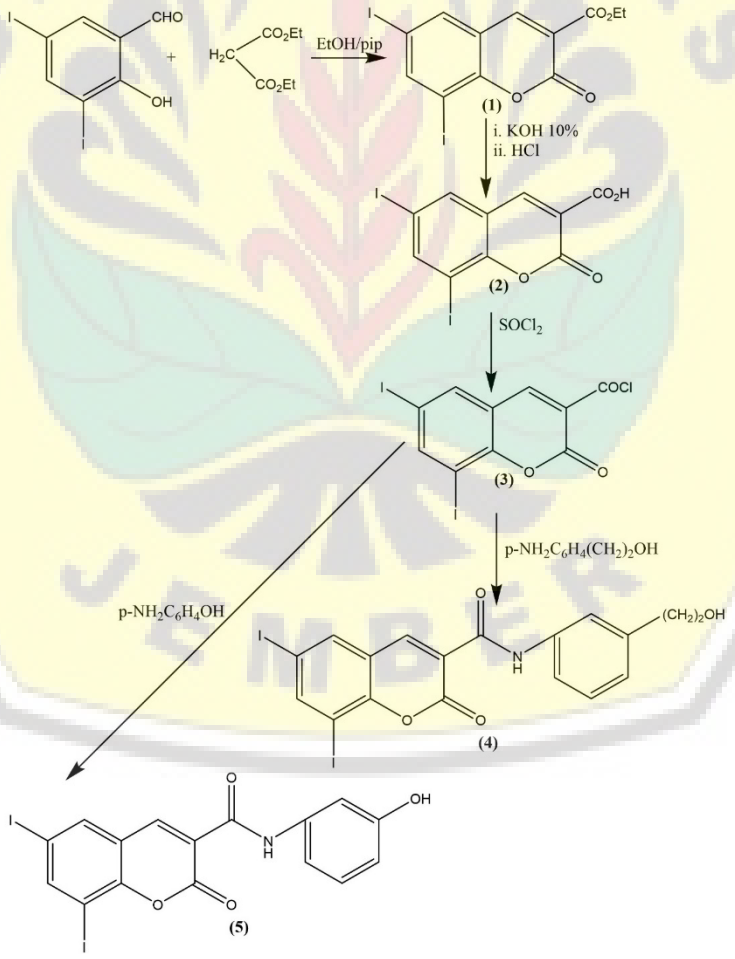

FIGURE 1. Diiodocoumarin derivatives [10]

Materials

The material in this study was antimicrobacterial activity (expressed in inhibition zone diameter) of diiodocoumarin derivative compounds obtained from the literature. The compound antimicrobacterial activity data were presented in table 1. The structure of the diiodocoumarin derivative compounds was shown in the following figure 1.

TABLE 1. The experimental antimicrobacterial activity of diiodocoumaric derivatives[10]

Compound	Symbol	antimicrobacterial activity	
		Inhibiton zone diameter (mm/mg sample)	Log Inhibiton zone diameter (mm/mg sample)
6,8-diiodocoumarin-3-carboxylate	DI1	15.3	-1.18
6,8-diiodocoumarin-3-carboxylic acid	DI2	16.5	-1.22
6,8-diiodocoumarin-3-carbonyl chloride	DI3	11.9	-1.08
N-(4-(2-Hydroxyethyl)phenyl)-6,8-diiodocoumarin-3carboxamide	DI4	24.6	-1.39
N-(4-Hydroxyphenyl)-6,8-diiodocoumarin-3-carboxamide	DI5	23.0	-1.36

Research Procedure

Determination of Descriptors. Determination of descriptors is an important step in determining the QSAR equation. The best QSAR equation will produce a pattern that can be used as a reference in predicting the structure with the best bioactivity. In this study there are several descriptorssuch as dipole moment (μ), atomic charge, and logarithmic partition coefficient (log P). Data descriptors and calculation methods for optimization are shown in table 2. The effect of each descriptor is determined through calculations by computational chemistry modelling with geometry optimization for each diiodocoumarin derivative structure. The 2D structure (two-dimensional structure) of the diiodocoumarin derivative is made using the Chemdraw Ultra 8.0 application. 2d structure is processed using Hyperchem with the addition of H atoms to produce 3D structures through the build menu. Atomic charge descriptors are analyzed on atoms with no. C4, C5, O7, C8, C9, C10.

TABLE 2. Descriptors and Calculation method

No	Descriptor	Unit	Symbol	Calculation Method
1	The atomic charge of C4, C5, O7, C8, C9, C10	Coulomb	qC4, qC5, qO7, qC8, qC9, qC10	Semiempirical method of PM3, Hyperchem, molecule optimization
2	dipole moment	Debye	μ	Semiempirical method of PM3, Hyperchem, molecule optimization
3	Partition coefficient of n-octanol/water	-	Log P	QSAR Properties, Semiempirical method of PM3, Hyperchem, molecule optimization

The position of the atoms was shownin Figure 2. The atomic charge was determined by the ratio between the positive charge (proton) and the negative charge (electron) held by the atom. Atoms with a high number of electrons had a negative charge and vice versa. The atomic charge indicated the electron density possessed by the atoms in a compound. The P log showed the hydrophobicity of the compound, while the dipole moment indicates the polarity of the molecule. Geometry structure optimization was done by minimizing molecular energy using the Polak-Ribiere algorithm method. Geometry structure optimization process was carried out to produce the most stable molecular conformation with the lowest energy. Optimization using PM3 semiempirical method was donewith a gradient value of 0.001 kcal/ Å.

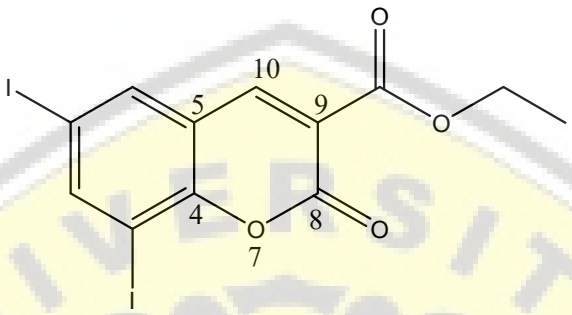

FIGURE 2. The labelof selected the atomic charge

QSAR analysis. The QSAR equation was used to determine the value of Inhibiton zone diameter (mm / mg sample) using multi-linear regression statistical analysis. Statistical analysis of multilinier regression was carried out using the SPSS application using data derived from molecular geometry optimization in the previous stage. Inhibiton zone diameter (mm / mg sample) was set as andependent variable and value combination of atomic charge, moment dipole, and partition coefficient in five derivatives of diiodocumarin compounds as independent variables. The final result was a regression equation using the QSAR approach as follows

$$\text{Log Inhibiton zone diameter (mm / mg sample)} = k1\log P + k2qC1 + k3qC2 + k4qC3 + k5qC4 + k6qC5 + k7qC12 + k8\mu + k9$$

Multilinier regression equation was the result of these calculations supported by other statistical units such as standard deviations (SE), correlation coefficients r, r^2, and significance values. The results of the multilinier regression equation will show descriptors that affect the biological activity of bioactive molecules.

RESULTS AND DISCUSSION

The Result of Descriptors calculation

In this study, five diiodocoumarin compounds were analyzed, 6,8-diiodocoumarin-3-carboxylate (DI1), 6,8-diiodocoumarin-3-carboxylic acid (DI2), 6,8-diiodocoumarin-3-carbonyl chloride (DI3) , N- (4- (2-Hydroxyethyl) phenyl) -6,8-diiodocoumarin-3 carboxamide (DI4), N- (4-Hydroxyphenyl) -6,8-diiodocoumarin-3-carboxamide (DI5) using the QSAR approach between Antimicrobacterial activity as a dependent variable (Table 1) with eight independent descriptors (Table 2). Table 3 shown the descriptor data obtained from the results of optimization of the geometry structure with hyperchem. The results shown that the longer side chains of the diiodocoumarin compound derivatives cause an increase in the octanol / water partition coefficient value and decrease the value of the dipole moment held by the compound. This indicate that the compound is becoming more non-polar.

Changes in the value of the atomic charge have significant values on the C5, O7, and C10 atoms. A significant change in the value of atomic charges has the potential to influence the value of biological activity possessed by bioactive compounds.

TABLE 3. Descriptor data as independent variables

No	Compound Symbol	Atomic Charge (Coulomb)						Dipole (deybe)	Log P
		C4	C5	O7	C8	C9	C10		
1	DI1	0.1450	-0.1648	-0.1384	0.4088	-0.2213	0.0726	3.825	1.23
2	DI2	0.1468	-0.1682	-0.1378	0.4087	-0.2200	0.0791	4.114	0.86
3	DI3	0.1503	-0.1746	-0.1342	0.4064	-0.2823	0.0986	4.996	1.33
4	DI4	0.1566	-0.1974	-0.1099	0.4197	-0.3605	0.0177	4.899	0.13
5	DI5	0.1596	-0.1566	-0.1598	0.2691	-0.2286	0.0706	2.324	0.32

The results of antimicrobial activity are shown as inhibitory zone diameter (mm / mg sample) of the diiodocoumarin compound listed in Table 1. Generally all compounds have good inhibitory activity against Staphylococcus aureus (NCTC-7447). The results showed DI4 produced the highest inhibitory activity compared to other diiodocoumarin derivative compounds. The DI1-DI3 compound exhibit a low biological activity value due to the absence of the benzene ring as a branch which reduces the stability of the molecule. In addition, the high electron density in the benzene branch chain causes electrons to be more attracted to the benzene branch so that the center of the inhibitory group, the carbonyl group, becomes more positive and is active as a bacterial inhibitor. The existence of a pull of electron density in both directions causes the compound to be more non-polar. This is consistent with geometry optimization results.

Analysis of QSAR on Diiodocoumarin Derivatives

Table 4 shown the best QSAR equation for diiodocoumarin derivatives. The descriptors dipol, logP, and net charge in C5, O7 have strong correlation to the antimicrobacterial activity. QSAR model for diiodocoumarin derivatives showed partition coefficient of n-octanol/water and atom charge in C5 and O7 gave significant effect as descriptors to the anti-microbial activity.N-(4-(2-Hydroxyethyl)phenyl)-6,8-diiodocoumarin-3carboxamide and N-(4-Hydroxyphenyl)-6,8-diiodocoumarin-3-carboxamide have higher anti-microbial activity because the presence of hydroxyphenylgroup increases the electron density value of O7 and C5. The existence of a pull of electron density in both directions causes, the carbonyl group, becomes more positive and is active as a bacterial inhibitor.

TABLE 4. The result of the best correlation between descriptors and antimicrobacterial activity

Equation	**8.051+32.24C5+27.24O7+0.021 logP**
R	1
R^2	0.999
SE	0.008
Sig	0.038

Table 5 showed the residual errors between experimental log P and calculated Log (1/inhibition-zone diameter) is ignorable with the value of 7.1297E-05. It indicates the calculation of calculated log (1/inhibition-zone diameter) using QSAR Hansch Model for diiodocoumarin derivatives has excellent agreement with experimental data of Log ($1/IC^{50}$).

TABLE 5. Experimental log (1/inhibition-zone diameter), calculated log (1/inhibition-zone diameter), and PRESS value

Compound	Experimental Log (1/inhibition-zone diameter)	Calculated Log (1/inhibition-zone diameter)	Residual error	[Residual error]^2
DI1	-1	-1.0054	5.4158E-3	2.9331E-05
DI2	-1.1139	-1.1082	-5.7211E3	3.2731E-05
DI3	-1.2041	-1.2045	3.8017E4	1.4453E-07
DI4	-1.3010	-1.3031	2.1258E3	4.5192E-06
DI5	-1.3424	-1.3446	2.1379E3	4.5708E-06
		PRESS		7.1297E-05

CONCLUSION

Best QSAR model for diiodocoumarin derivatives shown partition coefficient of n-octanol/water, dipole moment, and atomic charge of C5 and O7 gave significant effect to the antimicrobacterial activity. The resulted QSAR model for diiodocoumarin derivatives as antimicrobacterial is presented below:

$$8.051+32.24C5+27.24O7+0.021\ logP$$
$$R = 1;\ R^2 = 0.999;\ SE = 0.008;\ Sig = 0.038$$

In the future study, this research suggest to design good partition coefficient of n-octanol/water and dipole moment caffeic acid derivatives giving excellent bio-activity.

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