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RESEARCH PAPER

QSAR and Ab Initio Studies of Quinolon-4(1H)–Imine Derivatives as an Antimalarial Agents

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Abbreviations:
QSAR : Quantitative Structure-Activity Relationship
HOMO : Highest Occupied Molecular Orbital
LUMO : Lowest Occupied Molecular Orbital

Abstract: Malaria is still the most dangerous disease threat in the world, including in Indonesia. In Indonesia, it is estimated that there are 20 million cases of malaria per year. Malaria resistance to conventional drugs requires the search for new antimalarial drugs. Molecular modeling can be a solution to these problems. An activity study of 22 quinolone-4 (1H) -imine derivatives as antimalarials was carried out using the QSAR Quantitative Structure-Activity Relationship method. The electronic and molecular descriptors were obtained from the Hartree-Fock HF / 6-31G ab initio calculation. The multiple linear regression (MLR) method was used to construct the QSAR model. The best QSAR models produced are: pEC_{50} = -4,177 + (37,902 x qC3) + (171,282 x qC8) + (9,061 x qC10) + (125,818 x qC11) + (-149,125 x qC17) + (191,623 x qC18), with statistical parameters, n = 22; r^2 = 0,910; SEE = 0,171; F_{hit}/F_{tab} = 4,510 dan PRESS = 0,697. The best QSAR equation model can be used as a reference for designing and predicting the antimalarial activity of Quinolon-4 (1H) -imine derivatives which have higher activity than the previous one.

Keywords: Quinolon-4 (1H) -imine, antimalarial, QSAR, *ab initio*

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INTRODUCTION

Malaria is one of the most dangerous types of disease in the world. Malaria is caused by five types of parasites from the genus Plasmodium that infect humans: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale Plasmodium malariae and Plasmodium knowlesi. An estimated 3.4 billion people are at risk of developing malaria each year. Throughout 2018 there were 228 million cases of malaria worldwide [1-5]. It is estimated that there are 18.6 million malaria cases per year in Indonesia [6-8]. Prevention steps are needed to minimize the high incidence of malaria in Indonesia. Among the preventive measures that can be taken is developing new antimalarial drugs.

The process of discovering and developing a new antibiotic drug takes ten years, including three years for discovery and seven years for development, and requires experimental steps, including design, synthesis, purification, identification, and activity testing. Each step in discovering a new antibiotic drug is complex, costly, and time-consuming, and the probability of errors is significant [9-11]. This experimental method needs to be supported by a theoretical or modeling approach to reduce costs and time. The relationship between electronic structure and geometry and molecules having a specific activity can be sought through a quantum chemical approach. This approach is known as the Quantitative Structure-Activity Relationship (QSAR) [12-15].

The QSAR approach is an extra termodynamic and computational-based descriptor approach to correlate biological activities in isolated receptors, cell systems and in vivo [16]. The quantitative structure-activity relationship analysis quality is largely determined by the quantum mechanics method used to optimize molecular geometry and calculations to obtain descriptors (parameters) that affect the molecular drug activity. The computational methods that are widely used in QSAR modeling [17].

Many studies of QSAR compounds with antimalarial activity of quinoline derivatives have been carried out, including by Li et al. [18] and Sahu et al. [19]. We also conducted a study of QSAR derivatives of Quinolon-4 (1H) -imine using statistical methods of multiple linear regression and artificial neural networks [20]. Batagin-Neto & Lavarda has conducted a QSAR study by correlating the electronic structure with the antimalarial activity of chalcone alkoxylate and hydroxylate compounds [21]. The molecular structure was optimized by the Ab Initio Hartree-Fock (HF) method. This article reports the results of a study of 22 compounds derived from Quinolon-4 (1H) -imines with an optimized antimalarial activity using the Hartree-Fock ab initio method.

MATERIALS AND METHODS

Basis Set

22 Quinolon-4 (1H) -imine molecules with an effective concentration (EC50) against Plasmodium falciparum W2, which causes malaria (Table 1) obtained from the publication of Ressurreição et al., [22]. The parent structure of the Quinolon-4 (1H) -imine compound is presented in Figure 1. The software used includes Gaussian® 09W, HyperChemTM 8.0.10, and SPSS® Release 16.0.0.

Procedure

Descriptor calculations

Descriptors that affect the activity of antimalarial molecules derived from Quinolon-4 (1H) -imine, which includes surface area, volume, partition coefficient (log P), refractivity, polarizability, and molecular mass, were calculated using HyperChem 8.0.10. HOMO energy, LUMO energy, and the difference between HOMO-LUMO energy, dipole moment, and net atomic charge are obtained from the Gaussian log file of the structure optimization results. An example of the compound from the optimization is shown in Figure 1.

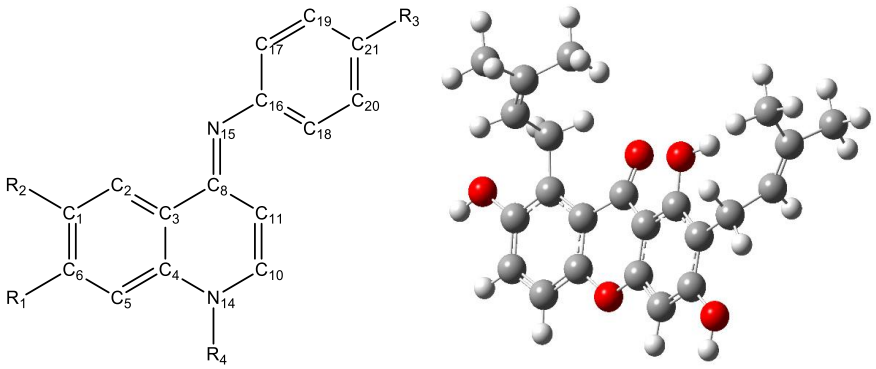

Figure 1. a) Structure of Quinolon-4 (1H) -imine b) 5g Compound Optimization Results.

Modeling began with random data grouping into training sets and test sets (Table 1). The QSAR model is generated from multiple linear regression analysis (MLR) between descriptors (independent variable) and pEC50 (dependent variable) using the backward method in the SPSS® Release 16.0.0 program. The resulting models are tested for validity based on the value of r^2, SEE, and the value of F_{count} / F_{table}. These parameters must meet the criteria, where the value of r^2> 0.6 [23]; SEE <0.3 [23]; F_{count} / F_{table} ≥ 1 [25]. The QSAR model, which fulfilled these statistical parameters, was further validated using a test set by considering the PRESS value. The model with the smallest PRESS value is chosen as the best QSAR model.

RESULTS AND DISCUSSION

Based on the MLR analysis using the backward method, eight models of the QSAR equation were produced (Table 2). The resulting QSAR model has an r^2 value greater than 0.89. It shows that the influence of the independent variables on antimalarial activity is considerable, which is more than 89%. The SEE value for all models is less than 0.171. This value shows that the accuracy of the resulting model for predicting new anti-malarial compounds is outstanding. Based on the values of r^2, SEE, and F_{hit} / F_{tab} (95% significance level), all the resulting models met the criteria for further validation. Model validation is done by calculating the value of the Predicted Residual Sum of Squares (PRESS) from the test set (Table 3) using equation (1).

$$\text{PRESS} = \sum(y_{exp} - y_{pred})^2 \qquad (1)$$

Where yexp is the experimental pEC50 and ypred is the predicted result pEC50. The best model is characterized by the smallest PRESS value [26]. The smallest PRESS value is shown by model 3, which is 0.697.

Thus, model 3 is the best QSAR model. The descriptor involved in the best QSAR model is reanalyzed using the enter method by entering all the data to obtain the final QSAR model used as a reference in designing new antimalarial compounds.

Table 1. Activity data of Quinolon-4 (1H) -imine [22] * Test set

No	R_1	R_2	R_3	R_4	IC_{50} (nM)	pEC_{50}
5a	Cl	H	Ph	N,N-diethylpropan-1-amine	491	2.7
5b	Cl	H	Ph	1-propylpyrrolidine	111	2.05
5c*	Cl	H	Ph	1-butylpiperidine	144	2.16
5d	Cl	H	Cl	1-butylpiperidine	259	2.41
5e	Cl	H	Br	1-butylpiperidine	74.0	1.87
5f*	Cl	H	H	1-butylpiperidine	273	2.44
5g	Cl	H	CH_3	1-butylpiperidine	331	2.52
5h*	Cl	H	F	1-butylpiperidine	369	2.57
5i	Cl	H	anisole	1-butylpiperidine	160	2.2
5j	CF_3	H	Ph	N,N-diethylpropan-1-amine	525	2.72
5k*	CF_3	H	Ph	1-propylpyrrolidine	226	2.35
5l	CF_3	H	Ph	1-butylpiperidine	360	2.56
5m	1-fluoro-4-methylbenzene	H	H	1-butylpiperidine	216	2.33
5n	1-fluoro-4-methylbenzene	H	Ph	1-butylpiperidine	55.4	1.74
5o	N-methylpyridin-2-amine	H	Ph	1-butylpiperidine	357	2.55
5p	Quinoline	H	Ph	1-butylpiperidine	53.7	1.73
5q	Cl	H	Ph	N,N-diethylbutan-1-amine	151	2.18
5r	Cl	H	Ph	N,N-diethylpentan-1-amine	67.6	1.83
5s	CF_3	H	Ph	N,N-diethylbutan-1-amine	144	2.16
5t*	CF_3	H	Ph	N,N-diethylpentan-1-amine	50.3	1.70
5u*	H	Cl	Ph	1-butylpiperidine	99.7	2.00
5v	H	CF_3	Ph	1-butylpiperidine	631	2.80

Table 2. QSAR Model MLR Analysis Results

Model	Descriptor	r^2	SEE	F_{hit}/F_{tab}
1	qC3, qC8, qC10, qC11, qN14 qC17, qC18, qC19	0,912	0,192	2,425
2	qC3, qC8, qC10, qC11, qC17, qC18, qC19	0,912	0,180	3,375
3	qC3, qC8, qC10, qC11, qC17, qC18	0,910	0,171	4,510
4	qC3, qC8, qC11, qC17, qC18	0,898	0,173	5,276

Table 3. Nilai PRESS Senyawa *Test Set*

Compound	pEC_{50} experiment	pEC_{50} predicted			
		Model 1	Model 2	Model 3	Model 4
5c	1,621	1,986	1,984	1,976	1,975
5f	2,002	1,375	1,373	1,388	1,320
5h	2,002	2,231	2,228	2,118	2,162
5k	2,002	1,607	1,606	1,618	1,657
5t	2,002	1,943	1,941	1,914	1,954
5u	1,338	1,478	1,476	1,496	1,394
PRESS		**0,758**	**0,758**	**0,697**	**0,740**

Based on this analysis, the QSAR equation model is generated:

$$pEC_{50} = -4,177 + 37,902 \times qC3 + 171,282 \times qC8 + 9,061 \times qC10 + 125,818 \times qC11 - 149,125 \times qC17 + 191,623 \times qC18 \quad (2)$$

With statistical parameters, n = 22; r^2 = 0,910; SEE = 0,171; F_{hit}/F_{tab} = 4,510 dan PRESS = 0,697.

The statistical parameters above show that the QSAR equation model obtained can be used to predict the activity (EC50) of new antimalarial compounds. This is also supported by the r^2 pred value for the entire data (Figure 2), which is 0.8511 fulfilling the specified criteria, namely> 0.5.

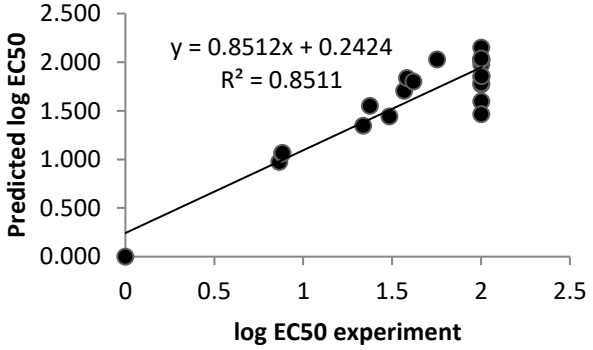

Figure 2. A plot of pEC50 Value of Experiment Results and Prediction Results for All Data

The negative descriptor coefficient in equation (2) indicates that increasing the descriptor value can cause the pEC50 value to be lower (the compound is more effective) against Plasmodium falciparum. Thus, to design a new antimalarial compound quinolon-4 (1H) - imine derivative with more effective activity against Plasmodium falciparum. In this case, it is necessary to pay attention to descriptors that affect antimalarial activity, in this case, the descriptors included in the QSAR equation.

CONCLUSION

Based on the study results, it was found that the best QSAR equation model with statistical parameters meet the specified criteria. This equation can be used as a reference for designing new antimalarial compounds and predicting their activity before synthesis in the laboratory. QSAR studies can be carried out with different geometric and statistical optimization methods to get better predictive results.

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