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Quantitative Structure Activity Relationship (QSAR) Analysis of Antimicrobial *Escherichia Coli* by Transition Metal Complexes With 8-Hydroxyquinoline

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Complex Compound, 8-Hydroxyquinoline, DFT method, Antimicrobial, QSAR.

ABSTRACT. Structural modeling and computational optimization of molecular geometry havebeen carried out using ChemDraw Ultra 12.0 and Gaussian-09. The measured parameters are electronic, hydrophobic, and steric descriptors. The results of geometry optimization using the DFT method (B3LYP) with a basis set of 6-31G are the total energy and heat of formation of each complex compound. Determination of the relationship between descriptors and antimicrobial activity, which includes Log P, Polarizability, PSA, EHOMO, ELUMO, ΔEG, MD, Harary Index, Randic Index, and Wiener Index. The results of the correlation indicate a relationship with antimicrobial activity. Furthermore, the best HKSA equation model was determined using multilinear regression analysis in SPSS 25.

INTRODUCTION

Escherichia coli is a bacterium commonly found in the intestines of humans and animals. Public perception often associates bacteria with microscopic, harmful organisms responsible for various diseases. When E. coli spreads beyond the intestinal tract, it can cause infections. In addition to the large intestine, E. coli is prevalent in natural environments. The bacterium can proliferate rapidly after consuming contaminated food, such as milk or improperly processed products. Pathogenic strains of E. coli, when present in high concentrations, can cause diseases such as diarrhea [1]. E. coli is capable of growth across a temperature range of 7°C to 44°C, with optimal growth occurring at 35–37°C and a pH of 7–7.5 in humid environments. The bacterium is inactivated by adequate heating during food preparation. Thus, thorough cooking and proper hygiene are essential preventive measures against E. coli contamination [2]. Bacterial infections caused by E. coli are commonly treated with antibiotics. According to [3], antibiotics are secondary metabolites produced by microorganisms that, even at low concentrations, can inhibit or kill other organisms. Therefore, antibiotics function as antimicrobial agents derived from living organisms. The design of antimicrobial drugs can be approached computationally by analyzing the relationship between biological activity and molecular structure [4,5,6]. Experimental studies have demonstrated that 8-hydroxyquinoline complexes exhibit significant antimicrobial activity, particularly in inhibiting the growth of the tested microorganisms [7]. 8-Hydroxyquinoline (C9H7NO) is a polycyclic aromatic compound with a molecular weight of 145.16 g/mol, a relatively stable freezing point of 74-76°C, and a boiling point of 276°C. This compound can also dissolve in organic solvents and acids such as acetic acid. This ligand will be less stable if it can react with oxidants and metal ions, such as metal ions[8].

Iron metal (Fe) with atomic number 26, Copper metal (Cu) with atomic number 29, Cobalt metal (Co) with atomic number 27, Nickel metal (Ni) with atomic number 28, and Zinc metal (Zn) with atomic number 30. These metals are included in the transition group, which has empty d orbitals; this allows electron transitions to occur if the metal is conjugated with 8HQ. Cu2+, Co2+, In2+, Fe2+, and Zn2+ can form complexes with 8-hydroxyquinoline to determine antimicrobial activity before conducting laboratory experiments, namely using the Quantitative *Relationship of Activity Structure (HKSA) approach*. The HKSA method, often called QSAR (Quantitative Structure-Activity Relationship), is used to design new drugs because it enables the development of new compound structures with predicted activities derived from computational calculations [6,9,10].

Statistical analysis is employed to process research data and generate quantitative estimates. These analyses provide numerical evidence to support research findings. Initially, correlation analysis is conducted to examine the relationship between molecular descriptors and antimicrobial activity. A correlation is considered significant if the value approaches -1 (perfect negative) or +1 (perfect positive), while a value of 0 indicates no relationship[9]. Subsequently, multilinear regression analysis yields values for sample size (n), the correlation coefficient (R), the coefficient of determination (R2), the standard error (SE), and the resulting model equation.

RESEARCH METHOD

Modeling of Complex Compounds

Complex compounds were modeled using three-dimensional visualization in ChemDraw Ultra 12.0, and their geometries were optimized with the Density Functional Theory (DFT) method, specifically B3LYP with the 6-31G basis set. Molecular geometry optimization was performed to obtain stable molecular structures. This approach has demonstrated high effectiveness and efficiency, producing results that closely align with experimental data while minimizing computational time [11].

Descriptor Determination

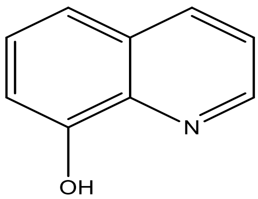
Electronic descriptors were determined using the DFT method via computational calculations with Gaussian-09, including HOMO and LUMO energies, the energy gap (ΔEG), and the dipole moment (MD). Hydrophobic and steric descriptors were calculated using the HKSA method in MarvinSketch 64-bit, yielding values for the partition coefficient (Log P), polarizability, polar surface area (PSA), Harary index, Randic index, and Wiener index, all of which were analyzed computationally.

Correlation Analysis and Multilinear Regression

Correlation and multilinear regression analyses were conducted using IBM SPSS Statistics 25. Correlation analysis examined the relationships between molecular descriptors and antimicrobial activity, while multilinear regression, using the Enter and Backward methods, was employed to develop the equation model. Validation of the HKSA equation model was performed by analyzing R, R2, and SE values, based on the differences between experimental and predicted Log P values for antimicrobial activity.

RESULTS AND DISCUSSION

Molecular Geometry Optimization of Fe Complex Compounds2+, With2+, Co2+, In2+ with 8-Hydroxyquinoline. Molecular structure modeling of the 8-hydroxyquinoline complex compound using the DFT method (Figure 1). This modeling was carried out as an initial step in obtaining descriptor data that would later produce an HKSA equation model. The complex compounds used in this study consisted of six compounds: 8HQ, [Fe(8HQ)2]2+, [Cu(8HQ)2]2+, [Co(8HQ)2]2+, [Ni(8HQ)2]2+, [Zn(8HQ)2]2+. Research on the 8HQ complex compound has been extensively conducted experimentally and has shown biological activity as an antimicrobial [7].



quinolin-8-ol

Figure 1. Basic Structure of 8-Hydroxyquinoline

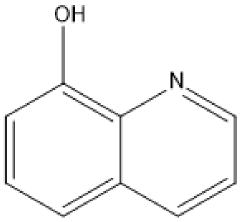
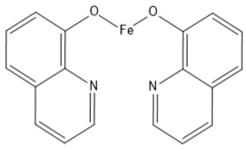
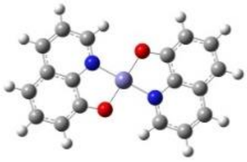
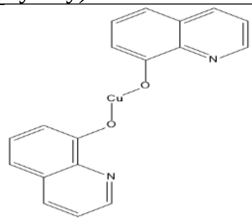
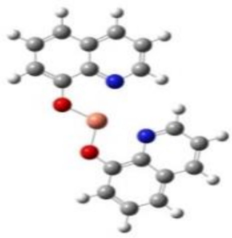
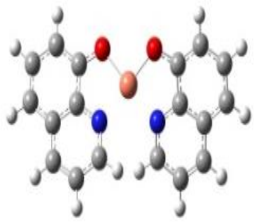
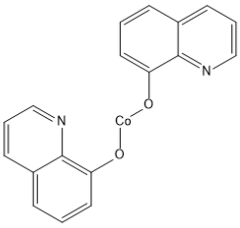
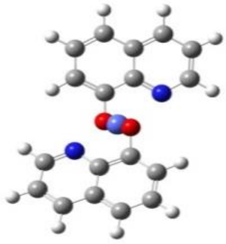
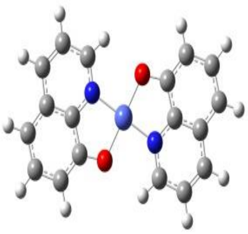
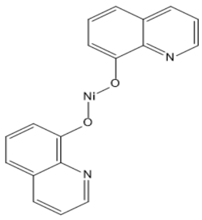
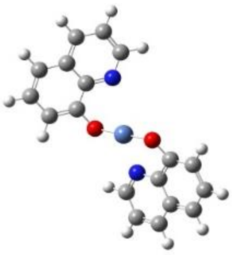
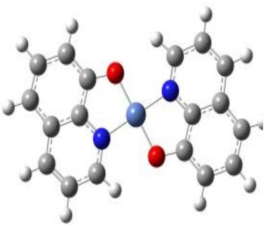
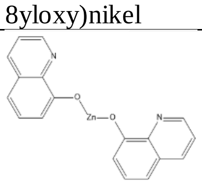
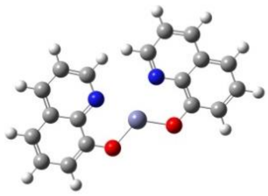
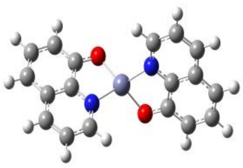
Molecular geometry optimization of the five complex compounds was performed to obtain optimal, stable structures. Simulations of the five complex compounds are shown in Figure 2. The bonds formed are caused by interactions between the outermost electrons of each atom. One factor influencing electron interactions in a molecule is electronegativity [12].

Table 1. Total Energy and Heat of Formation of Compound 8HQ with Fe^{2+}, Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}

Compounds	Total energy (kcal/mol)	Heat of formation (cal/mol-kelvin)
8HQ	93.475	30.563
$Fe(8HQ)_2$	176.356	68.407
$Cu(8HQ)_2$	175.887	69.564

$Co(8HQ)_2$	176.416	68.558
$Ni(8HQ)_2$	176.5	68.571
$Zn(8HQ)_2$	175.918	69.662

Table 2. Results of Modeling and Optimization of the Geometry of the Molecular Structure complexes Fe^{2+}, Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+} with 8HQ

Compounds Code	Phase 1 (ChemDraw Ultra)	Phase 2 (Chem3D Pro)	Optimation result (Gaussian)
8HQ			
$Fe(8HQ)_2$	 Bis(quinolin-8yloxy)iron		
$Cu(8HQ)_2$	 Bis(quinolin-8yloxy)copper		
$Co(8HQ)_2$	 Bis(quinolin-8yloxy)cobalt		
$Ni(8HQ)_2$	 Bis(quinolin-8yloxy)nikel		
$Zn(8HQ)_2$	 Bis(quinolin-8yloxy)zinc		

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Geometry optimization of the six compounds using the DFT method identified 8HQ as the optimal complex, with a total energy of 93,475 kcal/mol (Table 1). Molecular stability is indicated by lower total energy values. In Table 2, the Fe(8HQ)2, Co(8HQ)2, Ni(8HQ)2, and Zn(8HQ)2 complexes feature Fe, Co, Ni, or Zn as the central metal atom, with 8HQ acting as the ligand through its nitrogen (N) and oxygen (O) atoms. The resulting bonds are primarily covalent, with some coordinate covalent bonds [13]. This bonding arises from the empty orbitals on the metal atoms, which are occupied by electron pairs from the bidentate 8HQ ligand. According to valence bond theory (VBT), the bonding orbitals in Fe(8HQ)2, Co(8HQ)2, Ni(8HQ)2, and Zn(8HQ)2 are sp3 hybridized, resulting in a tetrahedral geometry. In contrast, Cu(8HQ)2 exhibits sp hybridization, leading to a linear geometry, as only the oxygen atom from the 8HQ ligand occupies the empty orbital on the copper atom.

Calculation of Complex Compound Descriptor Values

a. Descriptor Electronics

The electronic descriptor value is calculated using Gaussian 09 with the measured parameters, namely HOMO energy, LUMO energy, Gap energy (ΔEG), and dipole moment (D), using the DFT method. The dipole moment is the moment caused by the difference in electronegativity between the atoms in a molecule and is also a measure of the molecule's overall polarity. A molecule is polar if its dipole moment is> 0 and is nonpolar if the dipole moment = 0[14]. Based on Table 3, the value of each complex compound is> 0, so all of these complex compounds are polar compounds.

Determining the HOMO and LUMO energies is crucial in chemical reactions, as the transitions of the outermost electrons are a key factor in reactivity. The excitation of electrons from the HOMO to the LUMO requires a specific distance and energy. This energy is known as the energy gap (ΔEG), measured in eV. The Energy Gap (ΔEG) is related to a molecule's stability and reactivity, as reflected in the energy difference (Karim, 2019). Based on Table 3 of each compound, the value ΔEG 8HQ (0.15731 eV) is larger than that of other complex compounds, meaning that the 8HQ compound is more stable and less reactive. This is because it requires more energy to excite an electron from the HOMO to the LUMO. Meanwhile, the compound with the smallest value is [Fe(8HQ)2]2+ (0.11022 eV), so it is reactive and less stable because it requires less energy to experience electron excitation from HOMO to LUMO.

Table 3. Electronic Descriptor of 8HQ Compound With Fe^{2+}, Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}

Compounds Code	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔEG (eV)	Momen Dipol (D)
8HQ	-0.21013	-0.05282	0.15731	2.7997145
$Fe(8HQ)_2$	-0.17759	-0.06737	0.11022	0.0012369317
$Cu(8HQ)_2$	-0.19068	-0.07299	0.11769	7.5580001
$Co(8HQ)_2$	-0.18737	-0.06889	0.11848	0.021505581
$Ni(8HQ)_2$	-0.18097	-0.07003	0.11094	0.00045825757
$Zn(8HQ)_2$	-0.19242	-0.06739	0.12503	5.6598

b. Hydrophobic Descriptor

Hydrophobic descriptor values were calculated using the HKSA method with MarvinSketch 64-bit, measuring Log P, polarizability, and polar surface area (PSA) (Table 4). The Log P value reflects the compound's distribution between polar and non-polar phases; higher Log P values indicate a greater tendency to reside in the non-polar phase, facilitating membrane penetration and receptor binding. Lower Log P values suggest the compound remains in the polar phase, is only soluble in body fluids, and has limited membrane permeability. According to Table 4, Fe(8HQ)2 exhibits the highest Log P value (3.15), while 8HQ has the lowest (0.87).

Polar Surface Area (PSA) is the total surface area of a compound molecule. The higher the PSA value, the higher the polarity, thus increasing its solubility in body fluids [13]. This is inversely proportional to the Log P value (Table 4). The highest PSA value is observed for compound 8HQ (32.26 Å²), indicating a high level of polarity and greater solubility in body fluids during transport towards the cell membrane.

Table 4. Hydrophobic escriptor of compound 8HQ with Fe^{2+}, Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}

Compounds Code	Log P	Polar Surface Area (Å^2)	Polarizability (Å^3)
8HQ	0.87	32.26	17.99
$Fe(8HQ)_2$	3.15	24.94	37.69
$Cu(8HQ)_2$	2.91	24.94	37.90
$Co(8HQ)_2$	2.35	24.94	37.76
$Ni(8HQ)_2$	2.91	24.94	37.83
$Zn(8HQ)_2$	2.91	24.94	37.97

Polarizability describes the ease with which a molecule can form a temporary dipole and its chemical reactivity. Polarity is closely related to the number of electrons; the more electrons, the easier it is to polarize. Table 4 shows that the compound with the highest polarizability is Zn(8HQ)2 with a value of 37.97 Å3.

c. Steric Descriptor

The steric descriptor parameters consist of the Harary, Randic, and Weiner indices. These three indices were chosen for their simple calculations, which makes them more acceptable. In addition, these three indices have been widely used in HKSA research, and the simulation results are presented in Table 5. The calculation of the topology index is based on the calculation that atoms are viewed as peaks (atoms) and as edges (bonds) [15]. Therefore, it can be concluded that the more atoms that make up a molecule, the greater the value of the topology index will be. Based on (Table 5), the compound with a larger structure is shown in the compound Fe(8HQ)2, With(8HQ)2, Co(8HQ)2, Ni(8HQ)2, Ni(8HQ)2.

Table 5. Steric Descriptor Senyawa 8HQ with Fe(II), Cu(II), Co(II), dan Ni(II)

Compounds Code	Harary Index	Randic Index	Wiener Index
8HQ	27.85	8.40	140
$Fe(8HQ)_2$	92.25	16.36	970
$Cu(8HQ)_2$	92.25	16.36	970
$Co(8HQ)_2$	92.25	16.36	970
$Ni(8HQ)_2$	92.25	16.36	970
$Zn(8HQ)_2$	92.25	16.36	970

Statistical Determination of the HKSA Equation Model

The HKSA equation model in this study is determined using SPSS *version 25. In* general, *SPSS is* often used because it is more effective at processing both quantitative and qualitative data, as well as qualitative data translated into quantitative form [12]. The data generated from electronic, hydrophobic, and steric descriptors are then statistically analyzed using IBM SPSS Statistics *25.*

The statistical methods used were correlation and multilinear regression. Correlation analysis was conducted to identify which descriptors were associated with biological activity in the experiment. The independent variables were electronic, hydrophobic, and steric predictors, consisting of nine predictors: EHOMO, ELUMO,ΔEG, MD, PSA, polarizability, Harary index, Randic index, and Weiner index. While the dependent variable is the Log P value, the correlation is sought (Table 6).

The correlation results show that all descriptors are related to biological activity, as indicated by values approaching +1 and -1. The correlation results in Table 6 show that no values are 0, indicating that none of the descriptors are related to antimicrobial activity. A value of +1 indicates that the descriptor is closely related to Log P, approaching a perfect positive correlation. Meanwhile, -1 indicates an inverse relationship between the descriptor and Log P approaching a perfect negative value. Based on the correlation value criteria, the highest correlation value is Log P, namely 1, because the correlation value is positive, its effect on activity is directly proportional.

Then, using the multilinear regression method, the correlation analysis data were used to generate the HKSA equation model, because the independent variable data comprised more than one descriptor. The descriptors used were those with correlation values that met the criteria (Table 7).

Table 6. Descriptor Correlation Analysis

Descriptor	Correlation	Descriptor	Correlation
Log P	1	Polarizability	0.950
HOMO	0.906	PSA	-0.950
LUMO	-0.867	IH	0.950
EGap	-0.938	IR	0.950
MD	0.042	IW	0.950

Korelasi dengan nilai signifikan 0.05

Table 7. Statistical Parameter Data of the Equation Model

Best HKSA Models	Descriptor	n	R	R^2	SE	R Square Change
	IW, MD, EH, EL,	6	0.997	0.995	0.13696	0.995

The multilinear regression analysis produced an HKSA equation model with R, R2, and SE (Standard Error). Table 7 shows that the equation above is the best. The criteria for selecting the best equation for the HKSA method are to pay attention to the highest R (correlation coefficient) value, R2, and the highest coefficient of determination (coefficient of determination) with a value greater than 0.5 for the accepted multilinear regression equation. The results of the statistical analysis of the HKSA equation model can be written in the following mathematical equation:

Model HKSA : Log P = 19.233 + (0,001) IW + (0.133) MD + (73.314) EH + (54.504) EL

where n = 6, R = 0.997, R^2 = 0.5248, SE = 0,000

From the equation above, the predicted Log P values for each complex compound are obtained (Table 8).

Table 8. Result of Determining the Equation Model

Compounds Code	Log P	Log $P_{Prediksi}$
8HQ	0.87	0.87
$Fe(8HQ)_2$	3.15	3.203647313
$Cu(8HQ)_2$	2.91	2.941844013
$Co(8HQ)_2$	2.35	2.406487753
$Ni(8HQ)_2$	2.91	2.819763198
$Zn(8HQ)_2$	2.91	2.867257723

The Log P value indicates the distribution of 8HQ complex compounds with Fe2+, Cu2+, Co2+, and Ni2+ in biological systems. Higher Log P values indicate a greater tendency for the compound to reside in the non-polar phase, thereby enhancing membrane permeability and receptor binding. Lower Log P values suggest solubility in body fluids and limited membrane penetration. Table 8 shows that Fe(8HQ)2 exhibits the highest activity, while 8HQ has the lowest. Multilinear regression analysis identified a four-descriptor model as optimal, with R and R2 values approaching 1, indicating strong predictive capability. The most influential descriptors for antimicrobial activity are the Weiner index, dipole moment, HOMO energy, and LUMO energy. Selection of the best equation model requires validation, focusing on R, R2, and standard error (SE) values. An SE value close to zero indicates higher accuracy [16]. Validation can be further assessed by comparing experimental and predicted Log P values, as illustrated in Figure 2.

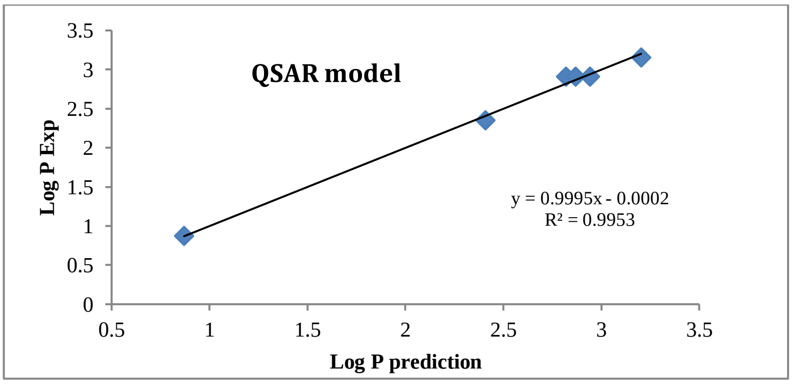

Figure 2. Correlation Curve Between Log P and Log P prediction

CONCLUSION

Based on the research that has been conducted, it can be concluded that the use of Google Sites in the chemistry learning media course received positive responses from both lecturers and students. Although most students were previously unfamiliar with Google Sites, they showed strong interest in learning it. After implementation, all students reported positive impacts, particularly in terms of accessibility, visual appeal, and its ability to integrate materials, videos, and assessments within a single link. Google Sites is considered feasible for implementation at the senior high school level due to its practicality, flexibility, and ease of use without requiring programming skills. Therefore, it can serve as an alternative digital learning media that supports prospective teachers in integrating technology into classroom practice.

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