Article

Modeling the Relationship of Net Atomic Charge with the Activity of 5-Aminopyrazole Derivative Compounds as Antioxidants with AM1 Method

Nagmah Putri Dinda Toni¹, Fajriah Azra"*

¹Department of Chemistry, Faculty of Mathematics and Natural Science (FMIPA), Universitas Negeri Padang, Padang, Indonesia

Abstract. This study was conducted to analyze the quantitative relationship between structure and net atomic charge modeling activity of 21 5-aminopyrazole derivatives as antioxidants. This study aims to determine the value of the net atomic charge and obtain the best HKSA equation. The method used in this study is the semi-empirical method of Austin Model 1 with geometry optimization. The selection of the best equation model is done by statistical analysis using the method of correlation analysis and multiple regression with Backward to the calculated descriptor data. From the results of the study, it was found that model 1 as the HKSA equation model was chosen with the equation Log IC₅₀ = Log IC₅₀ = 1.648+(0.914*qN₁)-(3.662*qN₂)-(1.99*qC₃)+( 0.004*qC₄)+(1.052* qC₅ )+(1.226*qN₆) where n = 6 ; R = 0.724 ; R² = 0.524 ; SE = 0.1462 ; Sig = 0.068 ; PRESS = 0.2994. This study shows that atomic charge plays an important role in enhancing antioxidant activity.

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Keywords: Free radicals, QSAR, antioxidant, AM1, statistic analysis

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Corresponding Author:
Fajriah Azra
Department of Chemistry, Faculty of Mathematics and Natural Science (FMIPA), Universitas Negeri Padang, Padang, Indonesia
Email: bunda_syasfa@yahoo.com

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1. Introduction
In the midst of the development of modern times, there are many changes in people's daily life patterns, especially in terms of diet, unhealthy eating patterns cause various kinds of diseases that can attack health. In addition, air pollution factors also play an important role in disturbing the health of the body, the increasing use of motorized vehicles in the community and industrial activities that are currently developing are a significant contributor to air pollution to the environment. Polluted air if we breathe will enter the body through the respiratory system and trigger the emergence of free radicals in the body. Free radicals are chemical species (atoms, molecules, or ions) that have one or more unpaired electrons in their outermost orbital and generally exhibit extraordinary reactivity [1]. The very reactive and unstable nature of free radicals in the body will cause cellular, tissue and genetic damage (mutations) [2]. Free radicals can oxidize nucleic acids, fats, proteins to cell DNA and can initiate degenerative diseases that affect overall organ function [3].

To overcome the excess of free radical compounds in the body, we need a compound that can act as an antidote to free radical activity. Compounds that can counteract the occurrence of free radicals are antioxidants that can prevent and inhibit the occurrence of free radical antioxidant reactions in lipid oxidation [4]. 5-aminopyrazole is a derivative of pyrazole which is a heterocyclic organic compound that has a nitrogen atom in close proximity, has important biological activities as antioxidant, antihypertensive, anti-depressant, anti-proliferative, neuroactive, anti-inflammatory, anti-viral, anti-pyretic, anti-inflammatory, glaucoma, sodium channel blockers and antimicrobials [5]. 5-aminopyrazole is able to play a role in absorbing or neutralizing free radicals so as to prevent degenerative diseases such as heart attacks, strokes, kidney failure, autoimmune and so on [6]. The reason for the need for the development of new antioxidants with higher activity is due to the increasing number of current oxidant triggering factors that can attack the body's health and the oxidative stress that occurs due to an imbalance between endogenous radicals and antioxidants as well as a decrease in the amount of oxygen and nutrients that cause tissue damage due to the production of radicals excess free [7]. The discovery of new antioxidants as drug candidates, is an active field of medicine chemical. Synthesis of compounds with antioxidant potential is increasing in recent years and a large number of diverse structural compounds have been published [8].

The process for the development of antioxidants (drugs in general) is a long and complex process starting from the design, synthesis, identification, purification and activity testing. This approach is not economically efficient because the demand for drugs against diseases tends to increase, even sometimes the results obtained have low activity. Better with existing compounds, of course it will waste time, energy and costs and cause a lot of waste [9]. An innovative method was successfully developed by Hansch and Fujita, namely computational chemistry that combines a quantitative relationship approach to the structure and activity of drug compounds. Not only can it overcome the problems of time, cost, effort and waste, but this method also avoids potential errors when designing new drug molecules that are run at low cost, less time and effort and produce no waste. The concept of the Hansch method explains that the relationship between chemical and biological activity of derived compounds can be described by analysis of a structure that depends on the descriptor [10]. Descriptor is a component that is used to explain the quantitative relationship between structures and activities that are processed into variables using multilinear regression equations.

In general, descriptors are used to describe the different characteristics that exist of chemical compounds in producing information about biological activity [11]. To be able to determine new antioxidant compounds, it is necessary to develop a molecular design by experimentation using a modeling approach with the concept - computational chemistry concepts [12]. The method that is often used in HKSA is the semi-empirical method. Modern computational-assisted molecular modeling is an important tool in the drug development process and structural characterization observed in semiempirical drug modeling based on quantum mechanics and molecular structure [13]. The first step in using QSAR is done by structural modeling or geometry optimization so that it can
find descriptors by calculating the AM1 method [14]. The AM1 semi-empirical method has a fairly high level of accuracy and relatively fast calculation time[15]. The parameters involved are electronic, steric and lipophilic parameters. Electronic properties affect drug interactions with receptors and the penetration of biological membranes, steric properties determine the compatibility of compound molecular interactions with receptors in cells, and lipophilic properties affect the ability of compounds to penetrate biological membranes [16].

The net atomic charge affects the electronic interactions that occur between interconnected atoms in a molecule. This interaction involves the electrons in the atoms that are bonded to each other so that it affects the value of the net atomic charge [17]. After obtaining the descriptor value, statistical analysis was carried out using multilinear regression analysis because it used more than one variable. Multilinear regression analysis was performed using SPSS for Windows program. Until the QSAR equation model was obtained from 21 5-aminopyrazole derivative compounds and the best 4 QSAR equations were selected to test the validation of the QSAR equation model by involving correlation analysis [18]. Thus the aim of this recent investigation was to focus on the net atomic charge of the 5-aminopyrazole compound using the AM1 method. The process of obtaining the net atomic charge value is carried out using the Hyperchem program and statistical analysis using multilinear regression methods and correlation analysis so that the QSAR equation is obtained.

2. Experimental Section
2.1 Materials
The tools used in this research include hardware and software. The hardware is a laptop with a specification of the Intel (R) Core(TM) i3-7020U CPU @ 2.30GHz and 4.00 GB RAM (3.89 GB usable) and the software is a program HyperChem Pro ver 8.0.10 which is used to perform geometry optimization and calculate physico-chemical parameters of derivatives 5-aminopyrazole compounds, SPSS for Windows version 22.0, Microsoft Office Excel Professional 2013 which is used for statistical calculations. While the study material in this study used data on the structure and activity of 21 derivatives of 5-aminopyrazole derivatives from the journal [5].

Figure 1. Structure of the Compound 5-aminopyrazole

2.2 Experiment Flow Chart
The research flow chart is shown in Figure 2
2.3 Molecular Structure Modeling and Geometry Optimization
Draw chemical structures in 2-dimensional and 3-dimensional for 21 derivative compounds of 5-aminopyrazole using the HyperChem Pro 8.0.10 program. After 3 dimensions were generated, geometry optimization was carried out for the 21 compounds, to achieve the goal of obtaining a stable structure and low energy potential, and optimizing using the AM1 method (Austin Model 1) to optimize the geometry of 21 5-aminopyrazole derivative compounds using Polak Ribiere with RMS 0.0001 \((10^{-4})\) as the limit of convergence. Then the energy data resulting from the optimized structure is stored in a notepad file.

2.4 Statistical Analysis
QSAR statistical analysis using multilinear regression. The first thing to do is to use the Microsoft Office Excel Professional 2013 program to prepare net atomic charge data and IC\(_{50}\) or biological activity. Then multilinear regression analysis with the SPSS program used the dependent variable and the independent variable from aryloxy metronidazole derivative compounds to find the equation QSAR.

2.5 Validation and Determination of the QSAR Equation Model
The QSAR equation model that has been selected is then validated by calculating the value of R, R\(^2\), F and SE (standard error). Furthermore, the model selection is carried out based on the PRESS (Predicted Residual Sum of Square) parameter.

3. Results and Discussion
To determine the quantitative relationship between the structure and activity of 5-aminopyrazole derivatives as antioxidants, modeling was carried out using the AM1 semi-empirical method. There are several things that have been done, namely structural modeling, geometry optimization, calculating the net atomic charge value and statistical analysis to obtain the QSAR equation from a series of 5-aminopyrazole derivatives.
3.1 Structural Modeling and Geometry Optimization

The molecular structure of the 5-aminopyrazole derivative was modeled using the HyperChem 8.0.10 application. The structure is modeled in 2 dimensions and 3 dimensions.

![Figure 3. Compounds derived from 5-aminopyrazole (A1) using the HyperChem application](image)

After obtaining the molecular structure of a series of 5-aminopyrazole derivatives, geometric optimization was carried out. Geometry optimization is the process of changing the conformational structure of the compound so that the conformation with the lowest energy is obtained. The purpose of geometry optimization is to obtain the structure of the compound in a stable condition where the compound has the lowest potential energy [19]. In geometry optimization, a stable conformation of the compound with the lowest potential energy is obtained by doing iterations where energy calculations occur when the conformational change of the compound occurs and occurs repeatedly until it reaches the convergence limit, in this study the convergence limit is 0.00001 kcal. If fulfilled, a stable compound with the lowest potential energy will be obtained[20].

| Compound Code | Total Energy before optimization (kcal/mol) | Total Energy after optimization (kcal/mol) |
|---------------|---------------------------------------------|-------------------------------------------|
| A1            | -95496.7200653                               | -108117.4006019                           |
| A2            | -108253.8537234                               | -135965.4335455                           |
| A3            | -174521.2669487                               | -173931.2984506                           |
| A4            | -121876.3180022                               | -137850.0258294                           |
| A5            | -140626.2668544                               | -156996.9650417                           |
| A6            | -95855.0679132                                | -139603.1703525                           |
| A7            | -112063.3259037                               | -130346.4753216                           |
| A8            | -119253.7952642                               | -134654.4927108                           |
| A9            | -143891.5803157                               | -159347.0608171                           |
| A10           | -133669.9717376                               | -156700.4905053                           |
| A11           | -144636.8856783                               | -159368.4053391                           |
| A12           | -134418.6991818                               | -148395.195183                            |
| A13           | -129552.4778089                               | -144213.1377268                           |
| A14           | -133041.2545380                               | -146882.5183293                           |
| A15           | -127011.6576684                               | -142975.0270995                           |
| A16           | -109436.8363894                               | -124121.2101224                           |
From the results of the calculation of the potential energy of the first 5-aminopyrazole derivative (A1) before optimization -95496.7200653 kcal/mol and after optimization, it is smaller, namely -108117.406019 kcal/mol as shown in Table 1. The potential energy proves that geometric optimization affects bond angles and distances between atoms so that energy changes occur until the lowest potential energy is obtained which indicates the molecular structure of the compound in a stable state has been reached [20].

3.2 Calculation of net atomic charge descriptor value
The descriptor calculation was carried out on 21 structures of 5-aminopyrazole derivatives that had been geometrically optimized. Quantitative Relationship Structure Antioxidant activity through computational chemical simulations to generate descriptors. Descriptor calculation to determine the value of physico-chemical properties of 5-aminopyrazole derivatives. The descriptor used in the study is the electronic parameter in the form of net atomic charge which is calculated using the AM1 semi-empirical method [15]. The net atomic charge of the 5-aminopyrazole derivative compound is qN1, qN2, qC3, qC4, qC5, qN6. This net atomic charge influences the determination of interactions that will involve electrons between atoms bonded together in a molecule, thus affecting the charge value of each atom[11].

Table 2. Data Value of Net Atomic Charge of 5-aminopyrazole Compound Derivatives

| Compound Code | qN1   | qN2   | qC3   | qC4   | qC5   | qN6   |
|---------------|-------|-------|-------|-------|-------|-------|
| A1            | -0.189069 | -0.123237 | 0.054686 | -0.340059 | 0.159437 | -0.322791 |
| A2            | -0.194111 | -0.148696 | 0.132113 | -0.270605 | 0.173548 | -0.326016 |
| A3            | -0.151744 | -0.125788 | 0.083685 | -0.330156 | 0.099963 | -0.167533 |
| A4            | -0.159701 | -0.114962 | 0.076967 | -0.247757 | 0.047359 | -0.106675 |
| A5            | -0.160823 | -0.117682 | 0.076792 | -0.250945 | 0.052319 | -0.112761 |
| A6            | -0.168719 | -0.097657 | 0.023141 | -0.302229 | 0.137396 | -0.256928 |
| A7            | -0.170663 | -0.102599 | 0.037986 | -0.299395 | 0.140792 | -0.308909 |
| A8            | -0.144436 | -0.111441 | 0.074905 | -0.252219 | 0.111671 | -0.315454 |
| A9            | -0.144802 | -0.127418 | 0.092494 | -0.282918 | 0.146602 | -0.30575  |
Based on the net atomic charge table, it can be seen that the N atoms (N1, N2, N6) are negatively charged, this is because the N atom is more electronegative than the other atoms in the compound, so the electrons in nearby atoms will be attracted to the N atom. The C atom in the C3 heterocyclic amino group is positively charged because it is double bonded to the N2 atom, while the C5 atom is also positively charged because it is single bonded to the N1 and N6 atoms so that the C atom is affected by the effects of the N atom's attraction [21].

3.3 Statistical Analysis
Statistical analysis was conducted to determine the quantitative relationship between chemical structure and biological activity through physical and chemical parameters that can be performed by statistical calculations with the help of a computer using the SPSS program. The statistical method used in the QSAR analysis is the correlation method and the multilinear regression method to produce the QSAR equation model. Correlation analysis was carried out to see the descriptors that had a biological activity relationship with Log IC50 experimentally[20] and their independent variables which included qN1, qN2, qC3, qC4, qC5, qN6. Correlation test aims to determine the level of closeness of the relationship between variables. The results of the correlation show that all the descriptors of 5-aminopyrazole derivatives have a relationship with biological activity as indicated by the criteria values that are close to +1 and -1 values and a significance value of <0.05[20].

After knowing the correlation between the net atomic charge descriptor and biological activity, statistical analysis was carried out using multilinear regression method. Multilinear regression was performed using the SPSS program which selected the independent variable data with Log IC50. The data from the multilinear regression analysis resulted in the QSAR model equation consisting of the 6 best descriptors where the results from the QSAR equation model obtained the values of R, R2, SE (Standard Error), Sig and Fhit, and PRESS [22]. The selection of the best QSAR equation model is carried out by taking into account the steric parameters, namely the price of R, R2, adjusted R2, SE, Sig, Fhit/Ftab, and PRESS. Determination of the best QSAR equation is with the criteria is the value of R2 > 0.6; SE value < 0.3; Fhit/Ftab value 1 [17].

|   | qN1 | qN2 | qC3 | qC4 | qC5 | qN6 |
|---|-----|-----|-----|-----|-----|-----|
| A10 | -0.123146 | -0.167194 | 0.13227 | -0.313555 | 0.148603 | -0.153547 |
| A11 | -0.123055 | -0.165803 | 0.12699 | -0.295927 | 0.146432 | -0.153744 |
| A12 | -0.117212 | -0.141312 | 0.081921 | -0.302031 | 0.084848 | -0.103644 |
| A13 | -0.052211 | -0.140567 | 0.111475 | -0.295927 | 0.146432 | -0.153744 |
| A14 | -0.043342 | -0.146097 | 0.097890 | -0.298581 | 0.085895 | -0.100184 |
| A16 | -0.128308 | -0.127672 | 0.110623 | -0.336653 | 0.091751 | -0.112293 |
| A17 | -0.15758 | -0.065337 | 0.048313 | -0.312411 | 0.150947 | -0.226998 |
| A18 | -0.134837 | -0.133504 | 0.093038 | -0.343185 | 0.213837 | -0.288841 |
| A19 | -0.186607 | -0.135797 | 0.086729 | -0.278121 | 0.093794 | -0.252696 |
| A20 | -0.128308 | -0.127672 | 0.110623 | -0.336653 | 0.071597 | -0.17594 |
| A21 | -0.102315 | -0.119622 | 0.112318 | -0.313463 | -0.003002 | -0.069955 |
The results of the QSAR equation model obtained an R value of 0.724. If the R value is closer to 1, the relationship between the independent variable and the dependent variable is getting stronger, meaning that the 6 descriptors involved in the regression model together have a strong relationship to the activity of the 5-aminopyrazole derivative. The R Square value of 0.524 describes the effect of the independent variable (descriptor) on the dependent variable (biological activity) [22]. The SE (Standard Error) value is a parameter measuring the value of the error variation in the experiment [20]. The SE value in model 1 is 0.1462. This fulfills the requirement that the SE value <0.3 [17]. The significance value (Sig) obtained is 0.068. The value of Fcount is directly proportional to the significance of the relationship when compared to Ftable, the higher the value of Fcount, the less likely it is that the relationship is due to chance [16]. The results of the Fhit/Ftab value > 1, which means that it can meet the significance requirements at the 95% confidence level, from model one the Fhit/Ftab value is obtained, namely 1. The PRESS value is the sum of the squares of the difference in the value of the biological activity of the experimental results with the predicted biological activity based on the best QSAR model. The smaller the PRESS value will produce a more accurate equation model, this is because the smaller the difference between the experimental inhibition activity and the predicted inhibitory activity generated from the equation model [23] from model 1, the PRESS value is 0.2994 which can be seen in table 4.

### Tabel 4. Log IC50 Data Value Experiment with Log IC50 Prediction Along with the PRESS Value from the Model 1.

| Compound Code | Log IC50 Eksperimen | Log IC50 Prediksi | y-y' | (y-y')^2 |
|---------------|---------------------|-------------------|------|---------|
| A1            | 1,422753941         | 1,58828541        | -0,1655315 | 0,027400667 |
| A2            | 1,523616419         | 1,533996888       | -0,0103805 | 0,000107754 |
| A3            | 1,765445018         | 1,701853484       | 0,0635913  | 0,004043883 |
| A4            | 1,57818061          | 1,68790689        | -0,0197263 | 0,012039857 |
| A5            | 1,603360924         | 1,694934024       | -0,0915731 | 0,008385633 |
| A6            | 1,866818803         | 1,659218918       | 0,20759988 | 0,043097712 |
| A7            | 1,530839779         | 1,560332586       | -0,0294928 | 0,000869826 |
| A8            | 1,543074235         | 1,5047439         | 0,0383034  | 0,001469215 |
| A9            | 1,569139725         | 1,57643676        | -0,007297  | 5,32467E-05 |
| A10           | 1,912700208         | 1,851319198       | 0,06138101 | 0,003767628 |
| A11           | 2,016615548         | 1,854360828       | 0,16225472 | 0,026326594 |
| A12           | 1,974741905         | 1,787973944       | 0,18676796 | 0,034882271 |
| A13           | 1,760874638         | 1,854184678       | -0,09331   | 0,008706764 |
| A14           | 1,804820679         | 1,852722664       | -0,047902  | 0,0022946 |
| A15           | 1,878866337         | 1,896901392       | -0,0180351 | 0,00325263 |
Validation tests can also be carried out by looking at the relationship or correlation between the Log IC50 value of the Experiment and the Log IC50 Prediction value which is displayed in the form of a correlation curve [24].

![Model 1](image)

**Figure 5.** IC50 Log Correlation Curve Experiment and Prediction on Model 1

The value on the correlation curve identifies that the Log IC50 value of the predicted equation molecule must have a close relationship with the Experimental IC50 Log which is marked by R Square value. From the data obtained, the best QSAR equation is found in model 1 which has met the criteria, to produce a mathematical equation:

\[
\text{Log IC}_{50} = 1.648+(0.914*qN_1)-(3.662*qN_2)-(1.99*qC_3)+(0.004*qC_4)+(1.052*qC_5)+(1.226*qN_3)
\]

with : n = 6 ; R = 0.724 ; R^2 = 0.524 ; SE = 0.1462 ; Sig = 0.068 ; PRESS = 0.2994

Looking at the value of the net atomic charge descriptor in the model equation 1, the net atomic charge plays an important role that greatly influences biological activity. It can be concluded that the lower the net atomic charge coefficient value, the lower the IC50 Log so that the biological activity will be better, in sum, to improve the QSAR models, research needs to be conducted with more activity data of similar compounds and molecular parameters [25]. There are many things that need to be considered in carrying out molecular modifications, biological activity is closely related to the 3D structure of the molecule and its electronic structure. The addition of substituents will change the unity of a compound, especially its physical/chemical properties. Through the prediction results with the QSAR equation model, it is hoped that compounds that have biological activity as needed will be produced [26].
4. Conclusion

Based on the results of the QSAR study, the atomic charge descriptor net which affects the antioxidant activity of the compounds 5-aminopyrazole derivatives are qN1, qN2, qC3, qC4, qC5, and qN6. HKSA equation in compounds 5-aminopyrazole derivatives that can be used as The model for predicting the antioxidant activity of 5-aminopyrazole derivatives is Log IC50 = 1.648+(0.914*qN1)-(3.662*qN2)-(1.99*qC3)+(0.004*qC4)+(1.052*qC5)+(1.226*qN6)

with: n = 6 ; R = 0.724 ; R2 = 0.524 ; SE = 0.1462 ; Sig = 0.068 ; PRESS = 0.2994

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