Eksakta : Berkala Ilmiah Bidang MIPA
VOLUME 23 NO 04 2022, pp 242-254
ISSN : Print 1411-3724 — Online 2549-7464
DOI : https://doi.org/10.24036/eksakta/vol23-iss04/334

Eksakta
Berkala Ilmiah Bidang MIPA
http://www.eksakta.ppj.unp.ac.id/index.php/eksakta

Article

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

Article Info

Article history :

Received August 17, 2022
Revised August 20, 2022
Accepted August 22, 2022
Published December 30, 2022

Keywords :

Free radicals, QSAR, antioxidant, AM1, statistic analysis

Nagmah Putri Dinda Toni[1], Fajriah Azra[1*], Mirella Fonda Maahury[2]

[1]Department of Chemistry, Faculty of Mathematics and Natural Science (FMIPA), Universitas Negeri Padang, Padang, Indonesia
[2]Department of Chemistry, Faculty of Mathematics and Natural Science (FMIPA), Universitas Pattimura, Ambon, 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.

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

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 [1-3]. The very reactive and unstable nature of free radicals in the body will cause cellular, tissue and genetic damage (mutations) [4-5]. Free radicals can oxidize nucleic acids, fats, proteins to cell DNA and can initiate degenerative diseases that affect overall organ function [6-9].

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 [10-11]. 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 [12-13]. 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 [14-15]. 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 [16-17]. 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 [18-19].

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 [20-22]. 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[23-25]. 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 [26-27]. 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 [28-29]. 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 [30-31]. 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 [32-33]. The AM1 semi-empirical method has a fairly high level of accuracy and relatively fast calculation time [34-35]. 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 [36-37].

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 [38-39]. 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 [40-41]. 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 [42].

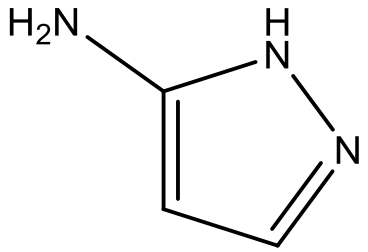

Figure 1. Structure of the compound 5-aminopyrazole

2.2 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.

2.3 Statistical Analisis

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.

2.4 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.

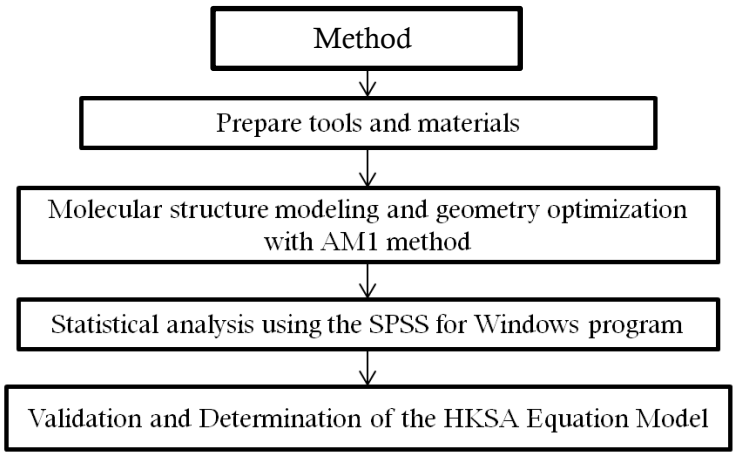

Figure 2. Research flow chart

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

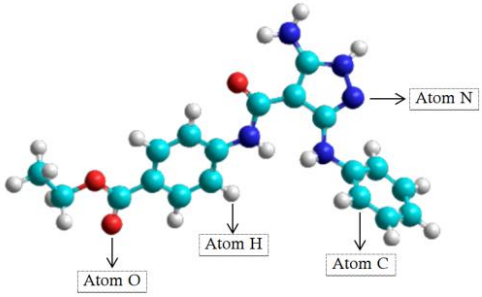

Figure 3. Compounds derived from 5-aminopyrazole (A1) using the HyperChem application

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 [43-44] . 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[45-46].

Table 1. Total energy data values before and after optimization

Compound code	Total energy before optimization (kkal/mol)	Total energy after optimization (kkal/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	-148395.1951583
A13	-129552.4778089	-144213.1377268
A14	-133041.2545380	-146882.5183293
A15	-127011.6576684	-142975.0270995
A16	-109436.8363894	-124121.2101224
A17	-113174.1154555	-127931.3669445
A18	-114676.5069925	-129435.1733602
A19	-109517.3681349	-123311.8378996
A20	-110268.4536258	-110403.8922110
A21	-111747.0291004	-111871.3440659

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 -108117.4006019 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 [45][47].

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 [23].

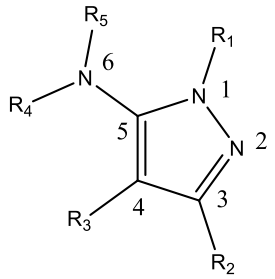

Figure 4. The structure of the compound 5-aminopyrazole

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	-0.25094	0.052319	-0.112761
A6	-0.137191	-0.096757	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	-0.305750
A10	-0.123146	-0.167194	0.132270	-0.313555	0.148603	-0.153547
A11	-0.123055	-0.165803	0.126990	-0.295927	0.146432	-0.153744
A12	-0.117212	-0.141312	0.081921	-0.230168	0.095777	-0.168999
A13	-0.052211	-0.140567	0.111475	-0.302031	0.084848	-0.103644
A14	-0.052629	-0.131429	0.097894	-0.298581	0.085895	-0.100184

A15	-0.043342	-0.146097	0.105682	-0.274448	0.079017	-0.096421
A16	-0.061398	-0.14631	0.108822	-0.286996	0.091751	-0.112293
A17	-0.157580	-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	-0.135597	0.086729	-0.278121	0.093794	-0.252696
A20	-0.128300	-0.127672	0.110623	-0.336653	0.071597	-0.175940
A21	-0.102315	-0.119622	0.112318	-0.313463	-0.003002	-0.069555

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 [48-49].

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 1/IC50 experimentally [45] 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 [45].

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 [50-51]. 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 [38][52].

Table 3. The best QSAR equation model and analysis results

Model	R	R *Square*	*Adjusted* R Square	*SE*	Sig	Fhit	Ftb	Fhit/ Ftab	PRESS
1	0.7240	0.5240	0.3210	0.1462	0.0680	2.5730	2.8500	1.0000	0.2994

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) [50].

The SE (Standard Error) value is a parameter measuring the value of the error variation in the experiment [45]. The SE value in model 1 is 0.1462. This fulfills the requirement that the SE value <0.3 [40]. 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 [38]. 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 [51] 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.

Commpound Code	Log IC50 Experiment	Log IC50 Prediction	y-y'	(y-y')^2
A1	1.422753941	1.588285410	-0.1655315	0.027400667
A2	1.523616419	1.533996888	-0.0103805	0.000107754
A3	1.765445018	1.701853484	0.0635915	0.004043883
A4	1.578180610	1.687906890	-0.1097263	0.012039857
A5	1.603360924	1.694934024	-0.0915731	0.008385633
A6	1.866818803	1.659218918	0.2075998	0.043097712
A7	1.530839779	1.560332586	-0.0294928	0.000869826
A8	1.543074235	1.504743900	0.0383303	0.001469215
A9	1.569139725	1.576436760	-0.0072970	5.32467E-05
A10	1.912700208	1.851319198	0.0613810	0.003767628
A11	2.016615548	1.854360828	0.1622547	0.026326594
A12	1.974741905	1.787973944	0.1867679	0.034882271
A13	1.760874638	1.854184678	-0.0933100	0.008706764
A14	1.804820679	1.852722664	-0.0479020	0.002294600
A15	1.878866337	1.896901392	-0.0180351	0.000325263
A16	1.699577591	1.868816518	-0.1692389	0.028641814
A17	1.545925329	1.526340156	0.0195851	0.000383579
A18	1.559547556	1.697969728	-0.1384222	0.019160698
A19	1.488550717	1.589160214	-0.1006095	0.010122271
A20	1.895367289	1.636399886	0.2589674	0.067064116
A21	1.662852233	1.679340648	-0.0164884	0.000271868
			PRESS	0.299415259

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 [52].

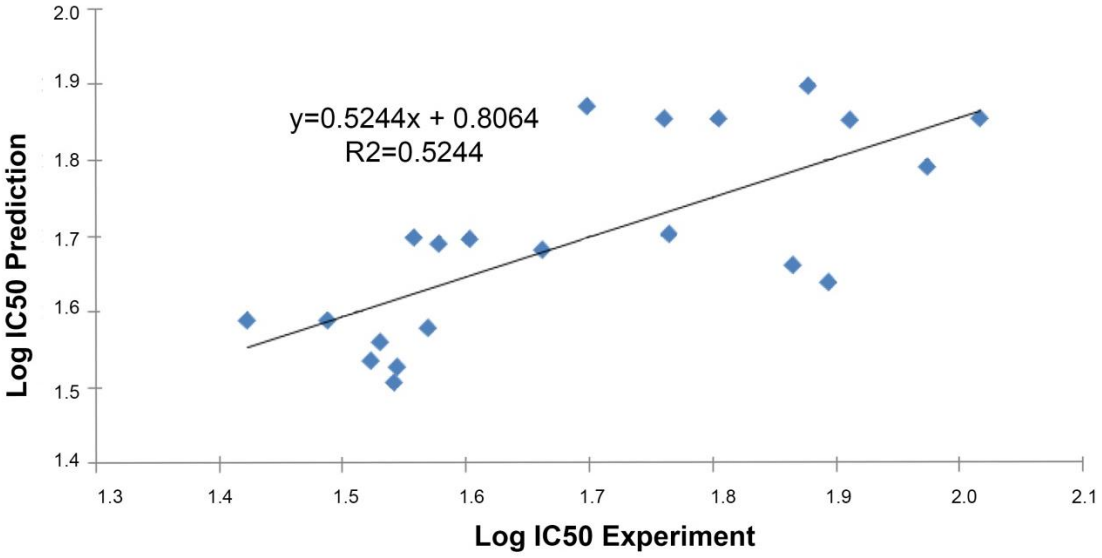

Figure 5. IC50 Log correlation curve experiment and prediction on model 1

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 :

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_6)

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 [53-54]. 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 [55-56].

4. Conclussion

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

References

[1] S. Di Meo and P. Venditti. (2020). Evolution of the Knowledge of Free Radicals and Other Oxidants. *Oxidative Medicine and Cellular Longevity*, vol. 2020. Hindawi Limited.

[2] Tsuneda, T., Sumitomo, H., Hasebe, M., Tsutsumi, T., & Taketsugu, T. (2022). Reactive orbital energy theory serving a theoretical foundation for the electronic theory of organic chemistry. *Journal of Computational Chemistry.*

[3] Singh, M., Nguyen, T. T., Balamurugan, J., Kim, N. H., & Lee, J. H. (2022). Rational manipulation of 3D hierarchical oxygenated nickel tungsten selenide nanosheet as the efficient bifunctional electrocatalyst for overall water splitting. *Chemical Engineering Journal*, 430, 132888.

[4] Z. Rui and J. Liu. (2020). Understanding of free radical scavengers used in highly durable proton exchange membranes. *Prog. Nat. Sci. Mater. Int.*, vol. 30, no. 6, pp. 732–742.

[5] Li, W., Li, B., Wu, B., Tian, B., Chen, X., Wang, C., ... & Peng, J. (2022). Free-Radical Cascade Generated by AIPH/Fe3O4-Coloaded Nanoparticles Enhances MRI-Guided Chemo/Thermodynamic Hypoxic Tumor Therapy. *ACS Applied Materials & Interfaces*, 14(26), 29563-29576.

[6] H. Y. Leong, C. W. Ooi, C. L. Law, A. L. Julkifle, T. C. Ling, and P. L. Show. (2018). Application of liquid biphasic flotation for betacyanins extraction from peel and flesh of Hylocereus polyrhizus and antioxidant activity evaluation. *Sep. Purif. Technol.*, vol. 201, pp. 156–166.

[7] Cao, G., Yang, S., Cao, J., Tan, Z., Wu, L., Dong, F., ... & Zhang, F. (2022). The role of oxidative stress in intervertebral disc degeneration. *Oxidative Medicine and Cellular Longevity*, 2022.

[8] Zhang, Y., Zhang, J., Wang, J., Chen, H., Ouyang, L., & Wang, Y. (2022). Targeting GRK2 and GRK5 for treating chronic degenerative diseases: Advances and future perspectives. *European Journal of Medicinal Chemistry*, 114668.

[9] Datta, S., Cano, M., Satyanarayana, G., Liu, T., Wang, L., Wang, J., ... & Handa, J. T. (2022). Mitophagy initiates retrograde mitochondrial-nuclear signaling to guide retinal pigment cell heterogeneity. *Autophagy*, 1-18.

[10] V. Fasiku (Oluwaseun), C. A. Omolo, and T. Govender. (2019). Free radical-releasing systems for targeting biofilms. *J. Control. Release*, vol. 322, pp. 248–273.

[11] Hu, Y., Zhao, G., Yin, F., Liu, Z., Wang, J., Qin, L., ... & Zhu, B. (2022). Effects of roasting temperature and time on aldehyde formation derived from lipid oxidation in scallop (Patinopecten yessoensis) and the deterrent effect by antioxidants of bamboo leaves. *Food Chemistry*, 369, 130936.

[12] A. Fekri, E. M. Keshk, A. G. M. Khalil, and I. Taha. (2021). Synthesis of novel antioxidant and antitumor 5-aminopyrazole derivatives, 2D/3D QSAR, and molecular docking. *Mol. Divers.*, no. 0123456789.

[13] Salem, I. M., Salem, I. M., El Sabbagh, O. I., Salama, I., & Ibrahim, T. S. (2022). A review on Synthesis and Biological Evaluations of Pyrazolo [3, 4-d] pyrimidine Schaffold. *Records of Pharmaceutical and Biomedical Sciences,* 6(1), 28-50.

[14] A. V. Bobrova *et al.* (2021). Facile synthesis and sulfonylation of 4-aminopyrazoles. *J. Mol. Struct.*, vol. 1230, pp. 1–7.

[15] Chang, K. C., Liu, P. F., Chang, C. H., Lin, Y. C., Chen, Y. J., & Shu, C. W. (2022). The interplay of autophagy and oxidative stress in the pathogenesis and therapy of retinal degenerative diseases. *Cell & Bioscience,* 12(1), 1-20.

[16] Y. Kaddouri, F. Abrigach, E. B. Yousfi, M. El Kodadi, and R. Touzani. (2020). New thiazole, pyridine and pyrazole derivatives as antioxidant candidates: synthesis, DFT calculations and molecular docking study. *Heliyon*, vol. 6, no. 1.

[17] Zhang, S., Wei, Y., Metz, J., He, S., Alvarez, P. J., & Long, M. (2022). Persistent free radicals in biochar enhance superoxide-mediated Fe (III)/Fe (II) cycling and the efficacy of CaO2 Fenton-like treatment. *Journal of Hazardous Materials,* 421, 126805.

[18] V. L. M. Silva, J. Elguero, and A. M. S. Silva. (2018). Current progress on antioxidants incorporating the pyrazole core. *Eur. J. Med. Chem.*, vol. 156, pp. 394–429.

[19] Eze, F. N., Jayeoye, T. J., & Singh, S. (2022). Fabrication of intelligent pH-sensing films with antioxidant potential for monitoring shrimp freshness via the fortification of chitosan matrix with broken Riceberry phenolic extract. *Food Chemistry,* 366, 130574.

[20] R. Abeynayake, S. Zhang, W. Yang, and L. Chen. (2021). Development of antioxidant peptides from brewers' spent grain proteins. *Lwt*, vol. 158.

[21] Meng, L., Wang, Z., Ji, H. F., & Shen, L. (2022). Causal association evaluation of diabetes with Alzheimer's disease and genetic analysis of antidiabetic drugs against Alzheimer's disease. *Cell & Bioscience,* 12(1), 1-16.

[22] Lam, H. Y. I., Guan, J. S., & Mu, Y. (2022). In silico repurposed drugs against monkeypox virus. *Molecules,* 27(16), 5277.

[23] S. Slavov and R. D. Beger. (2020). Quantitative structure–toxicity relationships in translational toxicology. *Curr. Opin. Toxicol.*, vol. 23–24, pp. 46–49.

[24] Staszak, M., Staszak, K., Wieszczycka, K., Bajek, A., Roszkowski, K., & Tylkowski, B. (2022). Machine learning in drug design: Use of artificial intelligence to explore the chemical structure–biological activity relationship. *Wiley Interdisciplinary Reviews: Computational Molecular Science*, 12(2), e1568.

[25] Eno, E. A., Louis, H., Ekoja, P., Benjamin, I., Adalikwu, S. A., Orosun, M. M., ... & Agwamba, E. C. (2022). Experimental and computational modeling of the biological activity of benzaldehyde sulphur trioxide as a potential drug for the treatment of Alzheimer disease. *Journal of the Indian Chemical Society,* 99(7), 100532.

[26] R. S. of N. D. as A. A. Hadanu, L. Adelin, and I. W. Sutapa. (2018). QSAR Studies of Nitrobenzothiazole Derivatives as Antimalarial Agents. *Makara J. Sci.*, vol. 22, no. 1, pp. 35–41.

[27] Mehmood, R., Mughal, E. U., Elkaeed, E. B., Obaid, R. J., Nazir, Y., Al-Ghulikah, H. A., ... & Sadiq, A. (2022). Synthesis of novel 2, 3-dihydro-1, 5-benzothiazepines as α -glucosidase inhibitors: In vitro, in vivo, kinetic, SAR, molecular docking, and QSAR studies. *ACS omega,* 7(34), 30215-30232.

[28] R. J. Boyd. (2019). Theoretical and Computational Chemistry. *Elsevier Inc*. Canada.

[29] Melnyk, N., Iribarren, I., Mates- Torres, E., & Trujillo, C. (2022). Theoretical perspectives in organocatalysis. *Chemistry–A European Journal,* 28(58), e202201570.

[30] V. Moreira de Olivera, M. Machado Marinho, and E. Silva Marinho. (2019) Semi-Empirical Quantum Characterization of the Drug Selexipag: HOMO and LUMO and Reactivity Descriptors. *Int. J. Recent Res. Rev.*, vol. 12, no. 2, pp. 15–20.

[31] Cong, Y., Zhai, Y., Chen, X., & Li, H. (2022). The Accuracy of Semi-Empirical Quantum Chemistry Methods on Soot Formation Simulation. *International Journal of Molecular Sciences,* 23(21), 13371.

[32] V. Bastikar, A. Bastikar, and P. Gupta. (2022) Quantitative structure-activity relationship-based computational approaches. *Elsevier Inc*. India.

[33] Cai, Z., Zafferani, M., Akande, O. M., & Hargrove, A. E. (2022). Quantitative structure–activity relationship (qsar) study predicts small-molecule binding to rna structure. *Journal of medicinal chemistry*, 65(10), 7262-7277.

[34] S. P. W. Zahra. (2021). Simulasi Dinamika Molekul Pada Efektivitas Proses Ekstraksi Minyak Atsiri Dari Kulit Jeruk Manis Laporan Tugas Akhir. *Universitas Pertamina*. Indonesia.
[35] Wang, L., Wang, J., Zhang, A., Huang, X. A., & Lei, H. (2022). Two binding epitopes modulating specificity of immunoassay for α-agonist detection: Quantitative structure–activity relationship. *Food Chemistry,* 371, 131071.
[36] F. Suhud, S. Siswandono, and T. Budiati. (2017). Sintesis dan Uji Aktivitas Senyawa 1-Benzil-3-benzoilurea Tersubstitusi Bromo, Kloro, Floro dan Triflorometil pada posisi para sebagai Agen Antiproliferatif, *MPI (Media Pharm. Indones)*, vol. 1, no. 3, pp. 154–163.
[37] Bunmahotama, W., Vijver, M. G., & Peijnenburg, W. (2022). Development of a Quasi–Quantitative Structure–Activity Relationship Model for Prediction of the Immobilization Response of Daphnia magna Exposed to Metal- Based Nanomaterials. *Environmental Toxicology and Chemistry,* 41(6), 1439-1450.
[38] A. La Kilo, L. O. Aman, I. Sabihi, and J. La Kilo. (2019). Studi Potensi Pirazolin Tersubstitusi 1-N dari Thiosemicarbazone sebagai Agen Antiamuba melalui Uji In Silico. *Indo. J. Chem. Res.*, vol. 7, no. 1, pp. 9–24.
[39] Parrilha, G. L., dos Santos, R. G., & Beraldo, H. (2022). Applications of radiocomplexes with thiosemicarbazones and bis (thiosemicarbazones) in diagnostic and therapeutic nuclear medicine. *Coordination Chemistry Reviews,* 458, 214418.
[40] Y. T. Male and I. W. Sutapa. (2018). Xanthon Menggunakan Hubungan Kuantitatif, vol. 11, no. 1.
[41] Kong, L., Deng, Z., & You, D. (2022). Chemistry and biosynthesis of bacterial polycyclic xanthone natural products. *Natural Product Reports,* 39(11), 2057-2095.
[42] Muh. Taufiq. (2021). Analisis Hubungan Kuantitatif Struktur Dan Aktivitas Senyawa Turunan Aminoalkanol Xanton Sebagai Antikanker Menggunakan Metode Semiempiris Austin Model 1. *UIN Alauddin Makassar*. Indonesia.
[43] Khattab, A. R., & Farag, M. A. (2022). Marine and terrestrial endophytic fungi: A mine of bioactive xanthone compounds, recent progress, limitations, and novel applications. *Critical Reviews in Biotechnology*, 42(3), 403-430.
[44] K. A. Rakhman, N. A. Limatahu, H. B. Karim, and M. I. Abdjan. (2019). Kajian Senyawa Turunan Benzopirazin sebagai Antimalaria Menggunakan Metode HKSA dan MLR, *EduChemia (Jurnal Kim. dan Pendidikan)*, vol. 4, no. 2, p. 112.
[45] Abate, M., Pagano, C., Masullo, M., Citro, M., Pisanti, S., Piacente, S., & Bifulco, M. (2022). Mangostanin, a xanthone derived from Garcinia mangostana fruit, exerts protective and reparative effects on oxidative damage in human keratinocytes. *Pharmaceuticals,* 15(1), 84.
[46] K. B. Wiberg and P. R. Rablen. (2018). Atomic Charges. *J. Org. Chem*, vol. 83, no. 24, pp. 15463–15469.
[47] Liu, S., & Luan, B. (2022). Benchmarking Various Types of Partial Atomic Charges for Classical All-Atom Simulations of Metal-Organic Frameworks. *Nanoscale.*
[48] E. Yuanita, Sudirman, N. K. T. Dharmayani, M. Ulfa, and J. Syahri. (2020). Quantitative structure–activity relationship (QSAR) and molecular docking of xanthone derivatives as anti-tuberculosis agents," *J. Clin. Tuberc. Other Mycobact. Dis.*, vol. 21, p. 100203.
[49] Hadrup, N., Frederiksen, M., Wedebye, E. B., Nikolov, N. G., Carøe, T. K., Sørli, J. B., ... & Hougaard, K. S. (2022). Asthma- inducing potential of 28 substances in spray cleaning products—Assessed by quantitative structure activity relationship (QSAR) testing and literature review. *Journal of Applied Toxicology,* 42(1), 130-153.
[50] N. R. Trindade *et al.* (2018). The newly synthesized pyrazole derivative 5-(1-(3 fluorophenyl)-1H-pyrazol-4-yl)-2H-tetrazole reduces blood pressure of spontaneously hypertensive rats via NO/cGMO pathway. *Front. Physiol.*, vol. 9, 3–12.

[51] Liu, Y., Tan, Y., Cheng, Z., Liu, S., Ren, Y., Chen, X., ... & Shen, Z. (2022). Quantitative structure-activity relationship (QSAR) guides the development of dye removal by coagulation. *Journal of Hazardous Materials,* 438, 129448.

[52] M. N. Kasmui and S. B. W. Kusuma. (2016). Analisis Hubungan Kuantitatif Struktur Dan Aktivitas Antimalaria Senyawa Turunan Quinoxalin, vol. 39, no. 2, pp. 98–106.

[53] Wang, L., Wang, J., Zhang, A., Huang, X. A., & Lei, H. (2022). Two binding epitopes modulating specificity of immunoassay for α-agonist detection: Quantitative structure–activity relationship. *Food Chemistry,* 371, 131071.

[54] S. Boudergua, M. Alloui, S. Belaidi, M. M. Al Mogren, U. A. A. Ellatif Ibrahim, and M. Hochlaf. (2019). QSAR Modeling and Drug-Likeness Screening for Antioxidant Activity of Benzofuran Derivatives. *J. Mol. Struct.*, vol. 1189, pp. 307–314.

[55] Hirpara, K. S., & Patel, U. D. (2022). Quantitative structure–activity relationship (QSAR) models for color and COD removal for some dyes subjected to electrochemical oxidation. *Environmental Technology,* 1-12.

[56] G. C. Soares Rodrigues, M. Dos Santos Maia, E. N. Muratov, L. Scotti, and M. T. Scotti,. (2020). Quantitative Structure-Activity Relationship Modeling and Docking of Monoterpenes with Insecticidal Activity against Reticulitermes chinensis Snyder and Drosophila melanogaster. *J. Agric. Food Chem.*, vol. 68, no. 16, pp. 4687–4698.