PEER REVIEW

LEMBAR
HASIL PENILAIAN SEJAWAT SEBIDANG ATAU PEER REVIEW
KARYA ILMIAH : JURNAL ILMIAH

Judul Jurnal Ilmiah (Artikel)	: Qualitative Structure Activity Relationship Analysis of 1,3,4-Thiadiazole Derivaties as Anti-Inflamatory using Parameterized Model 3 Method
Penulis Jurnal Ilmiah*	: **Ponco Iswanto**, Maylani Permata S, Eva Vaulina YD, Sari Paramita
Jumlah Penulis	: 4 Orang
Status Penulis	: Penulis ke-1
Identitas Jurnal Ilmiah	:
a. Nama Jurnal	: Journal of Physics : Conference Series
b. Nomor ISSN	: 1742-65961
c. Edisi	: 1494(2020)011001
d. Penerbit	: IOP Publishing Ltd
e. DOI artikel	: 10.1088/1742-6596/1494/1/011001
f. Alamat web	:https://iopscience.iop.org/issue/1742-6596/1494/1
g. Terindeks di	: Scopus

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- [V] Jurnal Ilmiah Internasional/Intenasional bereputasi
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NIP : 197307052000031001
Jabatan : Lektor Kepala
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NIP : 197502212000031001
Jabatan : Lektor Kepala
Bidang Ilmu : Kimia
Unit Kerja : Fakultas MIPA

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4. Kelengkapan unsur kualitas penerbit : lengkap
5. Indikasi plagiasi : tidak ada indikasi plagiasi
6. Kesesuaian bidang ilmu : sesuai bidang ilmu, kimia pisik : komputasi kimia

Purwokerto,
Reviewer 1

.....

Nama : Uyi Sulaeman, S.Si.,M.Si.,Ph.D
NIP : 197307052000031001
Jabatan : Lektor Kepala
Bidang Ilmu : Kimia
Unit Kerja : Fakultas MIPA

Mengetahui,
Dekan FMIPA

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Drs. Sunardi, M.Si
NIP 19590715 199002 1 001

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6. Kesesuaian bidang ilmu : Sesuai

Purwokerto,
Reviewer 2

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Nama : Dadan Hermawan, S.Si.,M.Si.,Ph.D
NIP : 197502212000031001
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Mengetahui,
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ARTIKEL

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Java Heritage Hotel Purwokerto
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Soedirman's International Conference on Mathematics and Applied Sciences
SICoMAS 2019
23-24 October 2019, Purwokerto, Indonesia

Report from The Organizing Committee

It is indeed my great pleasure and honor to welcome you all to Soedirman's International Conference on Mathematics and Applied Sciences (SICoMAS) 2019. The conference running this year is the first SICoMAS series hosted by Faculty of Mathematics and Natural Sciences Jenderal Soedirman University. As the development of technology and management of world resources for our future based on the innovation in Mathematics and Sciences, this conference takes issue "Innovation in Mathematics and Applied Sciences for better future".

SICoMAS 2019 aims to provide a platform for researchers, lecturers, teachers, students, practitioners, and industrial professionals to share knowledge, exchange ideas, collaborate, and present research results in the fields of Mathematics, Chemistry, Physics, and their applications. Hence, my sincere gratitude goes to our four keynote speakers (Prof. Dr. Hadi Nur from University Teknologi Malaysia, Prof. Dr. Hirokazu Saito from Tokyo University of Science, Dr. Devi Putra , ST, M.Sc. from Pertamina Research and Tecnology, and Uyi Sulaeman, Ph.D. from Jenderal Soedirman University), and our six invited speakers (Prof. Dr. Youtoh Imai from Nishogakusha University, Prof. Riyanto, Ph.D. from Universitas Islam Indonesia, Dr. Moh. Adhib Ulil Absor from Gadjah Mada University, Bambang Hendriya Guswanto, Ph.D, Dadan Hermawan, Ph.D. and Dr. Eng. Mukhtar Effendi, M. Eng. from Jenderal Soedirman University) for sharing their expertise in this conference. My deepest appreciation also goes to our 80 presenters and 7 non presenters for their commitment to participate in this conference.

As the output of this conference, some selected papers in the field of chemistry will be published in Jurnal Molekul which is accredited Sinta 1; and other selected papers in the fields of Mathematics, Physics, Physical Chemistry, and Innovative Chemistry Education will be published in IOP Conference Series Journal. So, I greatly thank Jenderal Soedirman University, all our contributors, and all the members of the committee for the invaluable support that makes this conference a reality.
Finally, I would like to apologize for any short comings found in this conference; and hopefully this two-day conference will be engraved in your memory.

The chair of SICoMAS 2019

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Accepted papers received: 03 April 2020
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Qualitative Structure Activity Relationship Analysis of 1,3,4-Thiadiazole Derivatives as Anti-Inflamatory using Parameterized Model 3 Method

Qualitative Structure Activity Relationship Analysis of 1,3,4-Thiadiazole Derivatives as Anti-Inflamatory using Parameterized Model 3 Method

Ponco Iswanto *, Maylani Permata Saputri , Eva Vaulina Y.D and Sari Paramita

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Abstract. Quantitative Relationship Structure and Activity Relationship (QSAR) studies conducted on the anti-inflammatory activity of a series of 1,3,4-thiadiazole derivatives which aim to obtain an equation to predict the value of the anti-inflammatory activity of. As research material was experimental biological activity data of 28 1,3,4-thiadiazole derivatives which were divided into 25 fitting compounds and 3 test compounds. QSAR analysis was carried out based on multiple linear regression calculations of fitting compounds by plotting log BA as the dependent variable and the independent variable was the net charge of carbon and nitrogen atoms bound to the dressing group, dipole moment (μ), HOMO-LUMO, Log P, molecular weight, polarizability , hydration energy, and van der waals volume. The value of descriptors was obtained from calculations using the PM3 semi-empirical quantum mechanical method. The result of QSAR equation was:

Log BA = 68.112 – 8.482 (qC1) + 14.764 (qC15) + 1.071 (Log P) – 0.018 (MW) – 0.484 (μ) – 4.427E-5 (Polarizability) – 0.561 (E. Hydration) + 7.843 (HOMO) – 1.489 (LUMO)

n = 28, r = 0.861, SE = 0.170098, Fcalculate / Ftable = 2.02116, PRESS = 1.9665

1. INTRODUCTION

Computational chemistry presents molecular structure as a numerical model with quantum equations and classical physics. The available programs encourage scientists to produce easily and present molecular data including geometric, energy and electronic properties. A study in medical chemistry that often uses chemical computational chemistry methods was the study of Quantitative Structure-Activity Relationship (QSAR) [1].

The quantitative relationship between structure and activity is a step to increase efficiency and effectiveness in the search for new drug compounds (new drug discovery). This was because it can reduce costs, time and environmental pollutants. The concept of this research strongly supports the concept of green chemistry, which reduces environmental pollutants [2]. This research also really needs to be done because there are still many steps in designing new drug compounds that are carried out through trial and error steps and based on the experience or intuition of researchers. This intuitive

research was not included with quantitative data analysis of opportunities (statistics) or the probability of finding new drug compounds with better activity than they already existed.

The scope of applied computational chemistry can be used to make new drug compounds. The compound used in this study was 1,3,4-thiadiazole. The 1,3,4-thiadiazole compound was first introduced by Fischer in 1882. The 1,3,4-thiadiazole compound was reported to have many biological activities namely anti-biotics, anti-inflammatory and analgesic, anti-cancer, anti-parasitic, anti-viral, anti-convulsant, anti-depressant and antioxidant properties others [3] so it was interesting to study. Inflammation was the body's defense mechanism as a tissue response to anything that damages both local and into the body can be in the form of physics, chemistry, bacteria and parasites [4]. The many studies on anti-inflammatory activity of 1,3,4-thiadiazole derivatives as reported by Mahaputra [5], Sanmati [6], Skhair [7], and Kumar [8] make 1,3,4-thiadiazole derivatives very potentially used as an anti-inflammatory drug. so further research was needed to find the 1,3,4-thiadiazole compound that was the most effective for anti-inflammatory drugs. This research was conducted to find the best HKSA equation which can then be used to determine the best 1,3,4-thiadiazole derivative compound as an anti-inflammatory drug.

This study used the Parameterized Model 3 (PM3) semi-empirical calculation method. The method was initially parametrized for the basic organic elements C, H, N, and O and later extended to the halogens F, Cl, Br, and I [9]. The use of these methods is expected to obtain the best and linear calculations with existing experimental data because the PM3 method was a combination of measurements from the three previous methods namely NDDO, MNDO and AM1. In addition, the PM3 method was very good and quite useful as a calculation method for widely varying organic compounds [10].

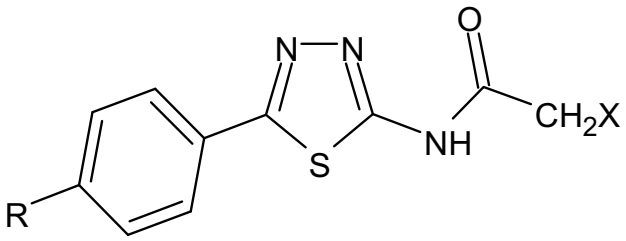
2. EXPERIMENTAL SECTION

2.1. Tools and Materials

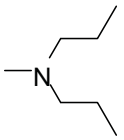
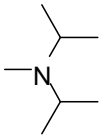
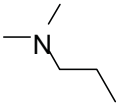
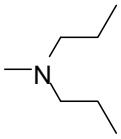
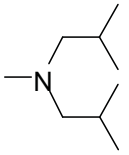
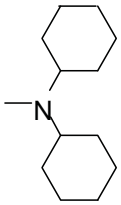
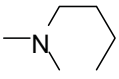
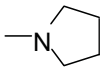
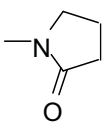
The tools used in this study consisted of hardware and software. The hardware used was a computer unit with Intel (R) Core (TM) i5-6500 Processor specifications, 8 GB Random Access Memory (RAM), and Windows 10 Home OS, while the software used was Hyperchem version 8.0 [11] for geometry optimization compound structure as well as QSAR and SPSS version 25 for data analysis on optimization results.

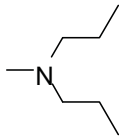
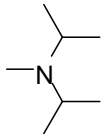
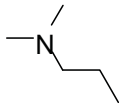
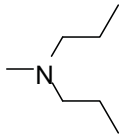
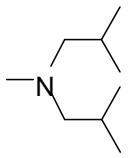
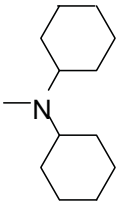
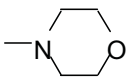
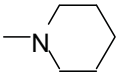
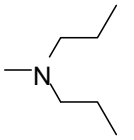
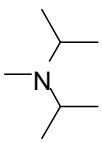
The materials used in this study were 28 structures and activities of 1,3,4-thiadiazole derived from Jain & Mishra [12] which were divided into 25 compounds for fitting compounds and 3 test compounds.

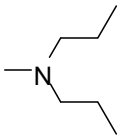
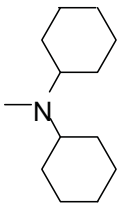
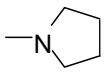
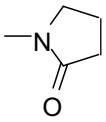
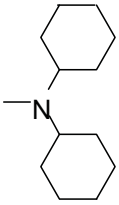
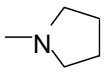
Figure 1. The main compound scructure of 1,3,4-thiadiazole derivatives



Tabel 1 The substituent structure of the fitting compounds of 1,3,4-thiadiazole and their anti-inflammatory activity in percent paw oedema inhibition per micromole of drug per kilogram of body weight

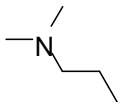
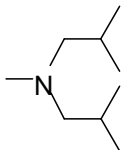
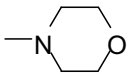
No.	R	X	Mol.Wt.	BA**	log BA
1	H		318.44	0.1546	-0.81
2	H		318.44	0.0818	-1.09
3	H		304.41	0.1391	-0.86
4	H		346.49	0.1286	-0.89
5	H		346.49	0.1088	-0.96
6	H		398.57	0.1139	-0.94
7	H		302.42	0.0777	-1.11
8	H		288.37	0.1235	-0.91
9	H		302.35	0.04317	-1.36

10	CH_3O-		348.46	0.09935	-1.00
11	CH_3O-		348.46	0.02986	-1.52
12	CH_3O-		334.44	0.1242	-0.91
13	CH_3O-		376.52	0.1075	-0.97
14	CH_3O-		376.52	0.03226	-1.49
15	CH_3O-		428.59	0.07346	-1.13
16	CH_3O-		334.39	0.0191	-1.72
17	CH_3O-		332.42	0.04746	-1.32
18	CH_3		332.46	0.0997	-1.00
19	CH_3		332.46	0.0475	-1.32

20	CH_3		360.52	0.1132	-0.95
21	CH_3		412.59	0.0943	-1.02
22	CH_3		302.39	0.0864	-1.06
23	CH_3		316.38	0.0181	-1.74
24	Cl		433.01	0.0371	-1.43
25	Cl		322.81	0.1014	-0.99

** = Percent percent paw oedema inhibition per micromole of drug per kilogram of body weight.

Tabel 2. The substituent structure of the test compounds of 1,3,4-thiadiazole and their anti-inflammatory activity in percent paw oedema inhibition per micromole of drug per kilogram of body weight

No	R	X	Mol. Wt.	BA**	Log BA
1	H		318.44	0.1637	-0.79
2	H		360.52	0.0721	-1.14
3	CH_3O-		318.39	0.0455	-1.34

** = Percent percent paw oedema inhibition per micromole of drug per kilogram of body weight.

2.2. Procedure

2.2.1. Geometry Optimization and Calculation of Descriptors

Each of the 1,3,4-thiadiazole derivatives (Tables 1 and 2) was made into two-dimensional (2D) structures using the Hyperchem program. Then added to the hydrogen atom using the Add H and Build model on the build menu, so we get a three-dimensional structure (3D). Click the setup menu, select semi-empirical PM3 in the method, then click start log on the file menu. The next step was to optimize the geometry of the structure by selecting geometry optimization from the compute menu. The calculation was done until the convergence limit was set at 0.001 kcal/(Å^6.mol). The optimization method used was the Polak-Ribiere algorithm. The geometry optimization process was complete when the bar appears (convergent = yes), the data starts to be saved by doing a stop log, to end the recording process of the calculation results. The structure with the most stable conformation was stored in the recorded data (.hin file) by selecting the save as menu on the file menu. After a stable structure was obtained, the calculation of geometry results in the form of log files (data records) with a single point calculation of the structure was recorded [13]. The data used in this QSAR study were data on the net charge of atoms, dipole moments, molecular weight, van der waals volume, Log P, polarisability, hydration energy, HOMO and LUMO energy.

Table 3. The Descriptors and procedure to get

Descriptors	Procedure
Net charge of atoms, dipole moments	Semi-empirical PM3, *Hyperchem*, geometry optimation
Molecular weight, van der waals volume, Log P, Polarisability, hidration energy	*QSAR Properties*, *Hyperchem*,
HOMO dan LUMO	*Single point, compute orbitals*, HOMO, LUMO

2.2.2. Statistical analysis of Multiple Linear Regression (MLR)

MLR statistical analysis begins by finding the best equation model with twenty five compounds fitting data to get the prediction equation model and the test data of three compounds for testing the equation model. MLR analysis on fitting data was done by the backward method. The dependent variable was Log BA and the independent variable was all the descriptors that were calculated. The procedure in backward elimination starts with a complete regression model, which includes all the appropriate independent variables, then tries to eliminate them one at a time [14]. After doing statistical analysis with MLR on the fitting data, there were several equation models. The models were tested for validity by considering the values of r, r^2, F, and SE to get the best equation model. According to Sembiring [15], the accepted equation must have a value of r (correlation coefficient)> 0.8. r^2 (determinant coefficient) approaches 1, $F_{calculate}/F_{table}$> 1 (F as a measure of the difference in the level of significance of the regression model), and SE (standard error) was small (a small SE value indicates that the error rate between the data and the model was relatively small).The best equation model was determined by considering the value of the four criteria above. The prediction equation model was then tested on the remaining three compounds as test data and the Predicted Sum of Squares (PRESS) value was calculated. The PRESS value can be found using the formula:

PRESS = $\sum$ (Experimental Log - Predicted Log)^2

The best equation model was the model that has the smallest PRESS value that will be used to determine the best QSAR model, then the final equation determination was determined from the independent variables involved in the best model of a total of 28 1,3,4-thiadiazole derivatives using the SPSS program with the enter method [16].

Table 4. Data calculation descriptors

NO	Log BA	qC_1	qC_{15}	qN	Log P	Molecular Weight	μ	Polaryzability	E hydration	HOMO	LUMO	Vvdw
Fitting compounds												
1	-0.81	-0.087	-0.087	-0.059	3.32	318.44	2.472	35.67	-8.20	-9.03	-1.04	983.98
2	-1.09	-0.087	-0.103	-0.059	3.21	318.44	2.623	35.67	-8.23	-9.04	-1.04	957.70
3	-0.86	-0.087	-0.086	-0.055	2.90	304.41	2.572	33.83	-8.51	-9.05	-1.06	938.03
4	-0.89	-0.087	-0.087	-0.059	4.11	346.49	2.468	39.34	-7.43	-9.03	-1.04	1091.95
5	-0.96	-0.087	-0.089	-0.060	4.12	346.49	2.584	39.34	-7.53	-9.05	-1.04	1062.27
6	-0.94	-0.087	-0.104	-0.052	4.87	398.57	2.585	45.13	-7.87	-9.04	-1.04	1167.20
7	-1.11	-0.087	-0.099	-0.071	2.42	302.39	2.025	33.06	-8.48	-9.00	-1.00	881.18
8	-0.91	-0.087	-0.095	-0.075	2.02	288.37	1.987	31.22	-8.68	-8.99	-0.99	845.79
9	-1.36	-0.086	-0.061	-0.065	1.14	302.35	1.935	31.31	-10.37	-9.10	-1.08	854.18
10	-1.00	0.099	-0.088	-0.059	2.33	348.46	3.071	38.14	-9.83	-8.75	-1.00	1062.54
11	-1.52	0.090	-0.104	-0.059	2.21	348.46	3.137	38.14	-9.85	-8.75	-1.00	1033.41
12	-0.91	0.090	-0.087	-0.055	1.91	334.44	3.128	36.30	-10.13	-8.76	-1.01	1015.87
13	-0.97	0.089	-0.088	-0.059	3.12	376.52	3.054	41.81	-9.05	-8.75	-1.00	1169.25
14	-1.49	0.090	-0.089	-0.059	3.13	376.52	3.090	41.81	-9.15	-8.75	-1.00	1138.84
15	-1.13	0.090	-0.107	-0.058	3.87	428.59	3.066	47.60	-9.63	-8.75	-1.00	1217.75
16	-1.72	0.090	-0.101	-0.064	0.36	334.39	2.761	34.33	-12.68	-8.77	-1.02	934.64
17	-1.32	0.089	-0.099	-0.070	1.43	332.42	2.506	35.53	-10.10	-8.71	-0.92	957.91
18	-1.00	-0.062	-0.087	-0.059	3.47	332.46	2.907	37.50	-7.01	-8.91	-1.03	1037.36
19	-1.32	-0.061	-0.103	-0.059	3.36	332.46	3.017	37.50	-7.03	-8.91	-1.03	1009.10
20	-0.95	-0.061	-0.088	-0.059	4.27	360.52	2.908	41.17	-6.23	-8.91	-1.03	1143.95
21	-1.02	-0.061	-0.105	-0.053	5.02	412.59	2.970	46.96	-6.67	-8.91	-1.26	1219.54
22	-1.06	-0.062	-0.095	-0.075	2.18	302.39	2.314	33.06	-7.48	-8.86	-0.98	896.82
23	-1.74	-0.062	-0.115	-0.058	1.30	316.38	1.597	33.14	-8.25	-8.84	-0.94	902.18
24	-1.43	0.121	-0.106	-0.058	4.64	433.01	1.846	47.06	-7.66	-9.06	-1.22	1184.4
25	-0.99	0.121	-0.095	-0.076	1.80	322.81	1.332	33.15	-8.32	-9.00	-1.16	888.27
Test compounds												
26	-0.79	-0.087	-0.086	-0.055	2.90	304.41	2.572	33.83	-8.51	-9.05	-1.06	938.03
27	-1.14	-0.087	-0.089	-0.060	4.12	346.49	2.584	39.34	-7.53	-9.05	-1.04	1062.27
28	-1.34	0.090	-0.101	-0.064	0.36	334.39	2.761	34.33	-12.68	-8.77	-1.02	934.64

The net charge of the atom in this study was chosen as a descriptor with the consideration that the charge and density of local electrons were very important in determining various chemical reactions and physicochemical properties of compounds. Descriptors based on the net charge of atoms in this case were useful for measuring intermolecular interactions. The net charge of an atom can be either positive or negative, depending on the group attached to the atom. The net charge of a positive-value atom was caused by the presence of electron-withdrawing groups such as methoxy, so that the electron density becomes smaller. The negatively charged atomic charge was caused by the presence of methyl, alkyl, or halide groups. These groups were electron-contributing groups, so that the electron density becomes greater [15].

The bipolar moment in relation to drug activity was very dependent on the target of the drug. If there was close contact between the target receptor molecules over a large enough, a large amount of inter-polar interaction energy will be formed. Polar moment values can be seen in log files obtained from geometry optimization. The bipolar moment value of each compound shows a different value as in table 4. The structure which was composed by the large variety of types of atoms that make it up will cause the bipolar moment value to increase. Compound 11 has the biggest dipole moment. This occurs because the diversity of atoms in compound 11 and also steric was quite large.

HOMO-LUMO energy describes the ease of a molecular system to experience excitation to a higher electronic state. HOMO-LUMO energy can also describe the stability of a molecule. A molecule with a large HOMO-LUMO orbital energy difference means that the molecule has high stability, so it has low reactivity in chemical reactions. Compound 9 has high stability so that its reactivity was low, while compound 21 has low stability so that its reactivity was high in chemical reactions.

The log P value was related to the distribution of drugs in the body. The more positive the log P value of compounds will tend to be in the non-polar phase rather than the polar phase, while the more negative the log P value of the compound will tend to be in the polar phase rather than the non-polar phase, which means the compound was only soluble in body fluids and was difficult to penetrate the membrane biology, so it can't bind to the receptors. Compound 16 has an octanol-water partition coefficient (log P) which was close to 0, 0.36, so that the compound has soluble properties in the body and was also easy to interact with receptors.

Polarisability was the ease of a molecule to form a momentary dipole or impact a molecule. The dipole attraction occurs because the molecule whose charge distribution was not symmetric was polar and has two different ends of the charge. Other descriptors such as hydration energy, van der waals volume and molecular weight were also considered to influence the biological activity of the 1,3,4-thiadiazole derivative compounds because they have different values of 1,3,4-thiadiazole derivatives although not very significant.

2.3. Results of Multiple Linear Regression (MLR)

Statistical Analysis SPSS calculation results backward MLR statistical analysis, from the statistical calculations obtained five QSAR equation models with parameters that were ready to be tested as listed in Table 5. The best recommended equation criteria in the QSAR method was the price correlation coefficient (r) must be greater of 0.8 and the calculated $F_{calculate}$ value must exceed the F_{table} price ($F_{calculate} / F_{table} > 1$) for a 95% confidence level [10].

Table 5. QSAR equation model results of Multiple Linear Regression (MLR) analysis method backward

Model	Variable	r	r^2	SE	$F_{calculate}/F_{table}$	PRESS
1	Vvdw, qC15, qC1, Polarisability, LUMO, qN, Dipole, E hidrasi, LogP, MW, HOMO	0.873	0.762	0.178	1.47	10.73
2	Vvdw, qC15, qC1, Polarisability, LUMO, Dipole, HydrationE, LogP, MW, HOMO	0.873	0.762	0.171	1.74	4.38
3	qC15, qC1, Polarisability, LUMO, Dipole, HydrationE, LogP, MW, HOMO	0.872	0.760	0.166	2.05	4.48
4	qC15, qC1, LUMO, Dipole, HydrationE, LogP, MW, HOMO	0.866	0.750	0.164	2.33	4.26
5	qC15, LUMO, Dipole, HydrationE, LogP, MW, HOMO	0.854	0.730	0.166	2.54	5.47

The QSAR equation models in Table 5 were then tested statistically based on r, r^2, SE and F values [17]. Based on the value of r and r^2, models 1 and 2 were better than models 3,4 and 5. Furthermore, reviewing the SE and $F_{calculate}$ / F_{table} model 2 has a smaller SE and $F_{calculate}/F_{table}$ greater than model 1. So the model was selected in this statistical test that was model 2.

Furthermore, model 2 was tested with PRESS to provide a real picture of the predictive ability of model 2. Draper and Smith [18] stated that the smaller the PRESS value of a QSAR equation model, the ability to predict biological activity. The PRESS value was obtained by entering the influential variables in Model 2 on the three existing test data as the PRESS value obtained was 4.389. Based on the test of statistical parameters conducted, model 2 was chosen as the best QSAR equation model. Model 2 as the best QSAR equation model was as follows:

Log BA = 56.225 – 5.269 (qC1) + 14.213 (qC15) + 1.035 (Log P) – 0.016 (MW) – 0.528 (μ) – 4.915E-5(Polarisability) – 0.450 (hydration E) + 6.400 (HOMO) – 1.38 (LUMO) – 0.001 (Vvdw)

n = 25, r = 0.873, SE = 0.171880, $F_{calculate}$ / F_{table} = 1.746, PRESS = 4.389

The final QSPR equation is obtained by multiple linear regression enter method to the fitting and testing data of 1,3,4-thiadiazole derivatives [19]. The results of the analysis were presented in table 6.

Table 6. QSAR equation model results of the Multiple Linear Regression (MLR) analysis of the enter method

Model	Variable	r	r^2	SE	$F_{calculate}/F_{table}$	PRESS
1	Vvdw, qC15, qC1, Polarisability, LUMO, Dipole, hydrationE, LogP, MW, HOMO	0.861	0.741	0.170	2.021	1.96

The results of linear regression give good enough results with a correlation coefficient value greater than 0.8, which was 0.861. This result was also supported by a small SE value, which was 0.741, the value of the $F_{calculate}$ / F_{table} ratio which was quite large, 2.02116 and the relatively small PRESS value calculation, which was 1.9665. The correlation graph between the predicted log BA activity and the experiments shown in Figure 2 also shows a slope that approaches 1. This means that the resulting equation can provide a fairly good prediction level. Calculation of the enter method was obtained by the final QSAR equation as follows:

Log BA = 68.112 – 8.482 (qC1) + 14.764 (qC15) + 1.071 (Log P) – 0.018 (MW) – 0.484 (μ) – 4.427E-5(Polarisability) – 0.561 (Hydration E) + 7.843 (HOMO) – 1.489 (LUMO)
n = 28, r = 0.861, SE = 0.170098, $F_{calculate}/F_{table}$ = 2.02116, PRESS = 1.9665

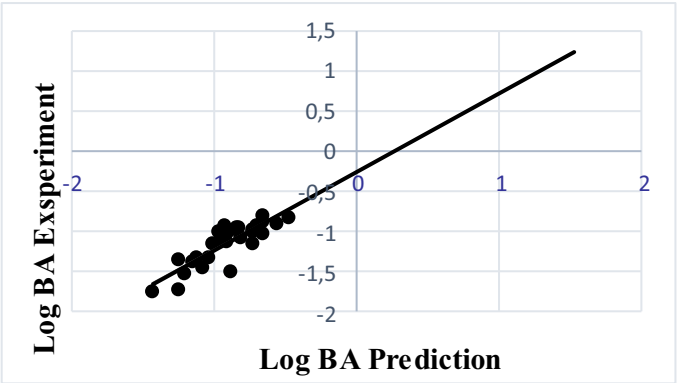


Figure 2. The figure of correlation between predictive and experimental Log BA in the 1,3,4-thiadiazole derivative series

3. CONCLUSION

Net charge of carbon atoms bound to groups R and X of 1,3,4-thiadiazole, log P, molecular weight, polar moment, polarisability, hydration energy, HOMO and LUMO results calculated by the PM3 semi-empirical method can be used to predict QSAR anti-inflammatory compounds 1,3,4-thiadiazole. The best QSAR equation of the 1,3,4-thiadiazole derivative compound is:

Log BA = 68.112 – 8.482 (qC1) + 14.764 (qC15) + 1.071 (Log P) – 0.018 (MW) – 0.484 (μ) – 4.427E-5(Polarisability) – 0.561 (Hydration E) + 7.843 (HOMO) – 1.489 (LUMO)
n = 28, r = 0.861, SE = 0.170098, $F_{calculate}/F_{table}$ = 2.02116, PRESS = 1.9665

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Qualitative Structure Activity Relationship Analysis of 1,3,4-Thiadiazole Derivatives as Anti-Inflamatory using Parameterized Model 3 Method

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Abstract. Quantitative Relationship Structure and Activity Relationship (QSAR) studies conducted on the anti-inflammatory activity of a series of 1,3,4-thiadiazole derivatives which aim to obtain an equation to predict the value of the anti-inflammatory activity of. As research material was experimental biological activity data of 28 1,3,4-thiadiazole derivatives which were divided into 25 fitting compounds and 3 test compounds. QSAR analysis was carried out based on multiple linear regression calculations of fitting compounds by plotting log BA as the dependent variable and the independent variable was the net charge of carbon and nitrogen atoms bound to the dressing group, dipole moment (μ), HOMO-LUMO, Log P, molecular weight, polarizability , hydration energy, and van der waals volume. The value of descriptors was obtained from calculations using the PM3 semi-empirical quantum mechanical method. The result of QSAR equation was:

Log BA = 68.112 – 8.482 (qC1) + 14.764 (qC15) + 1.071 (Log P) – 0.018 (MW) – 0.484 (μ) – 4.427E-5 (Polarizability) – 0.561 (E. Hydration) + 7.843 (HOMO) – 1.489 (LUMO)

n = 28, r = 0.861, SE = 0.170098, Fcalculate / Ftable = 2.02116, PRESS = 1.9665

1. INTRODUCTION

Computational chemistry presents molecular structure as a numerical model with quantum equations and classical physics. The available programs encourage scientists to produce easily and present molecular data including geometric, energy and electronic properties. A study in medical chemistry that often uses chemical computational chemistry methods was the study of Quantitative Structure-Activity Relationship (QSAR) [1].

The quantitative relationship between structure and activity is a step to increase efficiency and effectiveness in the search for new drug compounds (new drug discovery). This was because it can reduce costs, time and environmental pollutants. The concept of this research strongly supports the concept of green chemistry, which reduces environmental pollutants [2]. This research also really needs to be done because there are still many steps in designing new drug compounds that are carried out through trial and error steps and based on the experience or intuition of researchers. This intuitive

research was not included with quantitative data analysis of opportunities (statistics) or the probability of finding new drug compounds with better activity than they already existed.

The scope of applied computational chemistry can be used to make new drug compounds. The compound used in this study was 1,3,4-thiadiazole. The 1,3,4-thiadiazole compound was first introduced by Fischer in 1882. The 1,3,4-thiadiazole compound was reported to have many biological activities namely anti-biotics, anti-inflammatory and analgesic, anti-cancer, anti-parasitic, anti-viral, anti-convulsant, anti-depressant and antioxidant properties others [3] so it was interesting to study. Inflammation was the body's defense mechanism as a tissue response to anything that damages both local and in the body can be in the form of physics, chemistry, bacteria and parasites [4]. The many studies on anti-inflammatory activity of 1,3,4-thiadiazole derivatives as reported by Mahaputra [5], Sanmati [6], Skhair [7], and Kumar [8] make 1,3,4-thiadiazole derivatives very potentially used as an anti-inflammatory drug. so further research was needed to find the 1,3,4-thiadiazole compound that was the most effective for anti-inflammatory drugs. This research was conducted to find the best HKSA equation which can then be used to determine the best 1,3,4-thiadiazole derivative compound as an anti-inflammatory drug.

This study used the Parameterized Model 3 (PM3) semi-empirical calculation method. The method was initially parametrized for the basic organic elements C, H, N, and O and later extended to the halogens F, Cl, Br, and I [9]. The use of these methods is expected to obtain the best and linear calculations with existing experimental data because the PM3 method was a combination of measurements from the three previous methods namely NDDO, MNDO and AM1. In addition, the PM3 method was very good and quite useful as a calculation method for widely varying organic compounds [10].

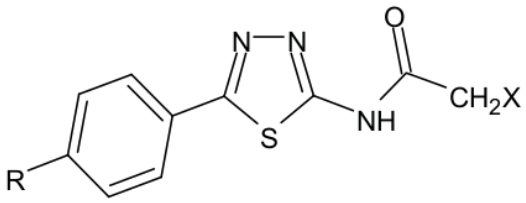
2. EXPERIMENTAL SECTION

2.1. Tools and Materials

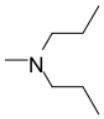
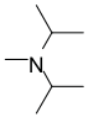
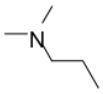
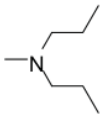
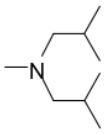
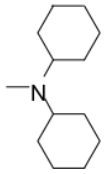
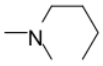
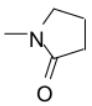
The tools used in this study consisted of hardware and software. The hardware used was a computer unit with Intel (R) Core (TM) i5-6500 Processor specifications, 8 GB Random Access Memory (RAM), and Windows 10 Home OS, while the software used was Hyperchem version 8.0 [11] for geometry optimization compound structure as well as QSAR and SPSS version 25 for data analysis on optimization results.

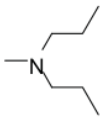
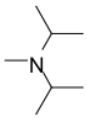
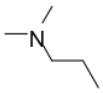
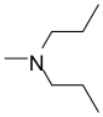
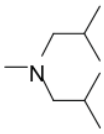
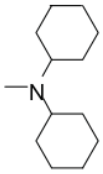
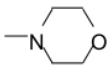
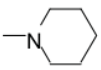
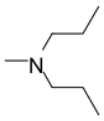
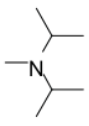
The materials used in this study were 28 structures and activities of 1,3,4-thiadiazole derived from Jain & Mishra [12] which were divided into 25 compounds for fitting compounds and 3 test compounds.

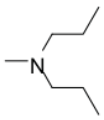
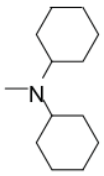
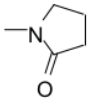
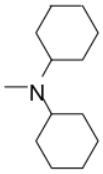
Figure 1. The main compound scructure of 1,3,4-thiadiazole derivatives



Tabel 1 The substituent structure of the fitting compounds of 1,3,4-thiadiazole and their anti-inflammatory activity in percent paw oedema inhibition per micromole of drug per kilogram of body weight

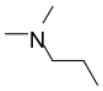
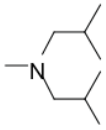
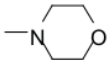
No.	R	X	Mol.Wt.	BA**	log BA
1	H		318.44	0.1546	-0.81
2	H		318.44	0.0818	-1.09
3	H		304.41	0.1391	-0.86
4	H		346.49	0.1286	-0.89
5	H		346.49	0.1088	-0.96
6	H		398.57	0.1139	-0.94
7	H		302.42	0.0777	-1.11
8	H		288.37	0.1235	-0.91
9	H		302.35	0.04317	-1.36

10	CH_3O-		348.46	0.09935	-1.00
11	CH_3O-		348.46	0.02986	-1.52
12	CH_3O-		334.44	0.1242	-0.91
13	CH_3O-		376.52	0.1075	-0.97
14	CH_3O-		376.52	0.03226	-1.49
15	CH_3O-		428.59	0.07346	-1.13
16	CH_3O-		334.39	0.0191	-1.72
17	CH_3O-		332.42	0.04746	-1.32
18	CH_3		332.46	0.0997	-1.00
19	CH_3		332.46	0.0475	-1.32

20	CH_3		360.52	0.1132	-0.95
21	CH_3		412.59	0.0943	-1.02
22	CH_3		302.39	0.0864	-1.06
23	CH_3		316.38	0.0181	-1.74
24	Cl		433.01	0.0371	-1.43
25	Cl		322.81	0.1014	-0.99

** = Percent percent paw oedema inhibition per micromole of drug per kilogram of body weight.

Tabel 2. The substituent structure of the test compounds of 1,3,4-thiadiazole and their anti-inflammatory activity in percent paw oedema inhibition per micromole of drug per kilogram of body weight

No	R	X	Mol. Wt.	BA**	Log BA
1	H		318.44	0.1637	-0.79
2	H		360.52	0.0721	-1.14
3	CH_3O-		318.39	0.0455	-1.34

** = Percent percent paw oedema inhibition per micromole of drug per kilogram of body weight.

2.2. Procedure

2.2.1. Geometry Optimization and Calculation of Descriptors

Each of the 1,3,4-thiadiazole derivatives (Tables 1 and 2) was made into two-dimensional (2D) structures using the Hyperchem program. Then added to the hydrogen atom using the Add H and Build model on the build menu, so we get a three-dimensional structure (3D). Click the setup menu, select semi-empirical PM3 in the method, then click start log on the file menu. The next step was to optimize the geometry of the structure by selecting geometry optimization from the compute menu. The calculation was done until the convergence limit was set at 0.001 kcal/(Å.mol). The optimization method used was the Polak-Ribiere algorithm. The geometry optimization process was complete when the bar appears (convergent = yes), the data starts to be saved by doing a stop log, to end the recording process of the calculation results. The structure with the most stable conformation was stored in the recorded data (.hin file) by selecting the save as menu on the file menu. After a stable structure was obtained, the calculation of geometry results in the form of log files (data records) with a single point calculation of the structure was recorded [13]. The data used in this QSAR study were data on the net charge of atoms, dipole moments, molecular weight, van der waals volume, Log P, polarisability, hydration energy, HOMO and LUMO energy.

Table 3. The Descriptors and procedure to get

Descriptors	Procedure
Net charge of atoms, dipole moments	Semi-empirical PM3, *Hyperchem*, geometry optimation
Molecular weight, van der waals volume, Log P, Polarisability, hidration energy	*QSAR Properties*, *Hyperchem*,
HOMO dan LUMO	*Single point, compute orbitals*, HOMO, LUMO

2.2.2. Statistical analysis of Multiple Linear Regression (MLR)

MLR statistical analysis begins by finding the best equation model with twenty five compounds fitting data to get the prediction equation model and the test data of three compounds for testing the equation model. MLR analysis on fitting data was done by the backward method. The dependent variable was Log BA and the independent variable was all the descriptors that were calculated. The procedure in backward elimination starts with a complete regression model, which includes all the appropriate independent variables, then tries to eliminate them one at a time [14]. After doing statistical analysis with MLR on the fitting data, there were several equation models. The models were tested for validity by considering the values of r, r^2, F, and SE to get the best equation model. According to Sembiring [15], the accepted equation must have a value of r (correlation coefficient)> 0.8. r^2 (determinant coefficient) approaches 1, $F_{calculate}/F_{table}$> 1 (F as a measure of the difference in the level of significance of the regression model), and SE (standard error) was small (a small SE value indicates that the error rate between the data and the model was relatively small).The best equation model was determined by considering the value of the four criteria above. The prediction equation model was then tested on the remaining three compounds as test data and the Predicted Sum of Squares (PRESS) value was calculated. The PRESS value can be found using the formula:

$PRESS = \sum (\text{Experimental Log} - \text{Predicted Log})^2$

The best equation model was the model that has the smallest PRESS value that will be used to determine the best QSAR model, then the final equation determination was determined from the independent variables involved in the best model of a total of 28 1,3,4-thiadiazole derivatives using the SPSS program with the enter method [16].

Table 4. Data calculation descriptors

NO	Log BA	qC_1	qC_{15}	qN	Log P	Molecular Weight	μ	Polaryzability	E hydration	HOMO	LUMO	Vvdw
Fitting compounds												
1	-0.81	-0.087	-0.087	-0.059	3.32	318.44	2.472	35.67	-8.20	-9.03	-1.04	983.98
2	-1.09	-0.087	-0.103	-0.059	3.21	318.44	2.623	35.67	-8.23	-9.04	-1.04	957.70
3	-0.86	-0.087	-0.086	-0.055	2.90	304.41	2.572	33.83	-8.51	-9.05	-1.06	938.03
4	-0.89	-0.087	-0.087	-0.059	4.11	346.49	2.468	39.34	-7.43	-9.03	-1.04	1091.95
5	-0.96	-0.087	-0.089	-0.060	4.12	346.49	2.584	39.34	-7.53	-9.05	-1.04	1062.27
6	-0.94	-0.087	-0.104	-0.052	4.87	398.57	2.585	45.13	-7.87	-9.04	-1.04	1167.20
7	-1.11	-0.087	-0.099	-0.071	2.42	302.39	2.025	33.06	-8.48	-9.00	-1.00	881.18
8	-0.91	-0.087	-0.095	-0.075	2.02	288.37	1.987	31.22	-8.68	-8.99	-0.99	845.79
9	-1.36	-0.086	-0.061	-0.065	1.14	302.35	1.935	31.31	-10.37	-9.10	-1.08	854.18
10	-1.00	0.099	-0.088	-0.059	2.33	348.46	3.071	38.14	-9.83	-8.75	-1.00	1062.54
11	-1.52	0.090	-0.104	-0.059	2.21	348.46	3.137	38.14	-9.85	-8.75	-1.00	1033.41
12	-0.91	0.090	-0.087	-0.055	1.91	334.44	3.128	36.30	-10.13	-8.76	-1.01	1015.87
13	-0.97	0.089	-0.088	-0.059	3.12	376.52	3.054	41.81	-9.05	-8.75	-1.00	1169.25
14	-1.49	0.090	-0.089	-0.059	3.13	376.52	3.090	41.81	-9.15	-8.75	-1.00	1138.84
15	-1.13	0.090	-0.107	-0.058	3.87	428.59	3.066	47.60	-9.63	-8.75	-1.00	1217.75
16	-1.72	0.090	-0.101	-0.064	0.36	334.39	2.761	34.33	-12.68	-8.77	-1.02	934.64
17	-1.32	0.089	-0.099	-0.070	1.43	332.42	2.506	35.53	-10.10	-8.71	-0.92	957.91
18	-1.00	-0.062	-0.087	-0.059	3.47	332.46	2.907	37.50	-7.01	-8.91	-1.03	1037.36
19	-1.32	-0.061	-0.103	-0.059	3.36	332.46	3.017	37.50	-7.03	-8.91	-1.03	1009.10
20	-0.95	-0.061	-0.088	-0.059	4.27	360.52	2.908	41.17	-6.23	-8.91	-1.03	1143.95
21	-1.02	-0.061	-0.105	-0.053	5.02	412.59	2.970	46.96	-6.67	-8.91	-1.26	1219.54
22	-1.06	-0.062	-0.095	-0.075	2.18	302.39	2.314	33.06	-7.48	-8.86	-0.98	896.82
23	-1.74	-0.062	-0.115	-0.058	1.30	316.38	1.597	33.14	-8.25	-8.84	-0.94	902.18
24	-1.43	0.121	-0.106	-0.058	4.64	433.01	1.846	47.06	-7.66	-9.06	-1.22	1184.4
25	-0.99	0.121	-0.095	-0.076	1.80	322.81	1.332	33.15	-8.32	-9.00	-1.16	888.27
Test compounds												
26	-0.79	-0.087	-0.086	-0.055	2.90	304.41	2.572	33.83	-8.51	-9.05	-1.06	938.03
27	-1.14	-0.087	-0.089	-0.060	4.12	346.49	2.584	39.34	-7.53	-9.05	-1.04	1062.27
28	-1.34	0.090	-0.101	-0.064	0.36	334.39	2.761	34.33	-12.68	-8.77	-1.02	934.64

The net charge of the atom in this study was chosen as a descriptor with the consideration that the charge and density of local electrons were very important in determining various chemical reactions and physicochemical properties of compounds. Descriptors based on the net charge of atoms in this case were useful for measuring intermolecular interactions. The net charge of an atom can be either positive or negative, depending on the group attached to the atom. The net charge of a positive-value atom was caused by the presence of electron-withdrawing groups such as methoxy, so that the electron density becomes smaller. The negatively charged atomic charge was caused by the presence of methyl, alkyl, or halide groups. These groups were electron-contributing groups, so that the electron density becomes greater [15].

The bipolar moment in relation to drug activity was very dependent on the target of the drug. If there was close contact between the target receptor molecules over a large enough, a large amount of inter-polar interaction energy will be formed. Polar moment values can be seen in log files obtained from geometry optimization. The bipolar moment value of each compound shows a different value as in table 4. The structure which was composed by the large variety of types of atoms that make it up will cause the bipolar moment value to increase. Compound 11 has the biggest dipole moment. This occurs because the diversity of atoms in compound 11 and also steric was quite large.

HOMO-LUMO energy describes the ease of a molecular system to experience excitation to a higher electronic state. HOMO-LUMO energy can also describe the stability of a molecule. A molecule with a large HOMO-LUMO orbital energy difference means that the molecule has high stability, so it has low reactivity in chemical reactions. Compound 9 has high stability so that its reactivity was low, while compound 21 has low stability so that its reactivity was high in chemical reactions.

The log P value was related to the distribution of drugs in the body. The more positive the log P value of compounds will tend to be in the non-polar phase rather than the polar phase, while the more negative the log P value of the compound will tend to be in the polar phase rather than the non-polar phase, which means the compound was only soluble in body fluids and was difficult to penetrate the membrane biology, so it can't bind to the receptors. Compound 16 has an octanol-water partition coefficient (log P) which was close to 0, 0.36, so that the compound has soluble properties in the body and was also easy to interact with receptors.

Polarisability was the ease of a molecule to form a momentary dipole or impact a molecule. The dipole attraction occurs because the molecule whose charge distribution was not symmetric was polar and has two different ends of the charge. Other descriptors such as hydration energy, van der waals volume and molecular weight were also considered to influence the biological activity of the 1,3,4-thiadiazole derivative compounds because they have different values of 1,3,4-thiadiazole derivatives although not very significant.

2.3. Results of Multiple Linear Regression (MLR)

Statistical Analysis SPSS calculation results backward MLR statistical analysis, from the statistical calculations obtained five QSAR equation models with parameters that were ready to be tested as listed in Table 5. The best recommended equation criteria in the QSAR method was the price correlation coefficient (r) must be greater of 0.8 and the calculated $F_{calculate}$ value must exceed the F_{table} price ($F_{calculate}$ / F_{table}> 1) for a 95% confidence level [10].

Table 5. QSAR equation model results of Multiple Linear Regression (MLR) analysis method backward

Model	Variable	r	r^2	SE	$F_{calculate}/F_{table}$	PRESS
1	Vvdw, qC15, qC1, Polarisability, LUMO, qN, Dipole, E hidrasi, LogP, MW, HOMO	0.873	0.762	0.178	1.47	10.73
2	Vvdw, qC15, qC1, Polarisability, LUMO, Dipole, HydrationE, LogP, MW, HOMO	0.873	0.762	0.171	1.74	4.38
3	qC15, qC1, Polarisability, LUMO, Dipole, HydrationE, LogP, MW, HOMO	0.872	0.760	0.166	2.05	4.48
4	qC15, qC1, LUMO, Dipole, HydrationE, LogP, MW, HOMO	0.866	0.750	0.164	2.33	4.26
5	qC15, LUMO, Dipole, HydrationE, LogP, MW, HOMO	0.854	0.730	0.166	2.54	5.47

The QSAR equation models in Table 5 were then tested statistically based on r, r^2, SE and F values [17]. Based on the value of r and r^2, models 1 and 2 were better than models 3,4 and 5. Furthermore, reviewing the SE and $F_{calculate}$ / F_{table} model 2 has a smaller SE and $F_{calculate}/F_{table}$ greater than model 1. So the model was selected in this statistical test that was model 2.

Furthermore, model 2 was tested with PRESS to provide a real picture of the predictive ability of model 2. Draper and Smith [18] stated that the smaller the PRESS value of a QSAR equation model, the ability to predict biological activity. The PRESS value was obtained by entering the influential variables in Model 2 on the three existing test data as the PRESS value obtained was 4.389. Based on the test of statistical parameters conducted, model 2 was chosen as the best QSAR equation model. Model 2 as the best QSAR equation model was as follows:

Log BA = 56.225 – 5.269 (qC1) + 14.213 (qC15) + 1.035 (Log P) – 0.016 (MW) – 0.528 (μ) – 4.915E-5(Polarisability) – 0.450 (hydration E) + 6.400 (HOMO) – 1.38 (LUMO) – 0.001 (Vvdw)

n = 25, r = 0.873, SE = 0.171880, $F_{calculate}$ / F_{table} = 1.746, PRESS = 4.389

The final QSPR equation is obtained by multiple linear regression enter method to the fitting and testing data of 1,3,4-thiadiazole derivatives [19]. The results of the analysis were presented in table 6.

Table 6. QSAR equation model results of the Multiple Linear Regression (MLR) analysis of the enter method

Model	Variable	r	r^2	SE	$F_{calculate}/F_{table}$	PRESS
1	Vvdw, qC15, qC1, Polarisability, LUMO, Dipole, hydrationE, LogP, MW, HOMO	0.861	0.741	0.170	2.021	1.96

The results of linear regression give good enough results with a correlation coefficient value greater than 0.8, which was 0.861. This result was also supported by a small SE value, which was 0.741, the value of the $F_{calculate}$ / F_{table} ratio which was quite large, 2.02116 and the relatively small PRESS value calculation, which was 1.9665. The correlation graph between the predicted log BA activity and the experiments shown in Figure 2 also shows a slope that approaches 1. This means that the resulting equation can provide a fairly good prediction level. Calculation of the enter method was obtained by the final QSAR equation as follows:

Log BA = 68.112 – 8.482 (qC1) + 14.764 (qC15) + 1.071 (Log P) – 0.018 (MW) – 0.484 (μ) – 4.427E-5(Polarisability) – 0.561 (Hydration E) + 7.843 (HOMO) – 1.489 (LUMO)
n = 28, r = 0.861, SE = 0.170098, $F_{calculate}/F_{table}$ = 2.02116, PRESS = 1.9665

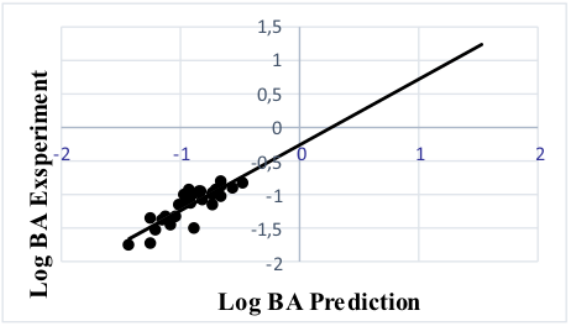


Figure 2. The figure of correlation between predictive and experimental Log BA in the 1,3,4-thiadiazole derivative series

3. CONCLUSION

Net charge of carbon atoms bound to groups R and X of 1,3,4-thiadiazole, log P, molecular weight, polar moment, polarisability, hydration energy, HOMO and LUMO results calculated by the PM3 semi-empirical method can be used to predict QSAR anti-inflammatory compounds 1,3,4-thiadiazole. The best QSAR equation of the 1,3,4-thiadiazole derivative compound is:

Log BA = 68.112 – 8.482 (qC1) + 14.764 (qC15) + 1.071 (Log P) – 0.018 (MW) – 0.484 (μ) – 4.427E-5(Polarisability) – 0.561 (Hydration E) + 7.843 (HOMO) – 1.489 (LUMO)
n = 28, r = 0.861, SE = 0.170098, $F_{calculate}/F_{table}$ = 2.02116, PRESS = 1.9665

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