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Computational Study of 2-Aminothiazole as Antiprion Lead Compound in the Treatment of Creutzfeldt-Jakob Disease Using an Approach Model of Hansch Quantitatif Structure Activity Relationship and Toxicity Prediction

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Research Article

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Abstract

Objective. Creutzfeldt-Jakob Disease (CJD) is a rare, degenerative, invariably fatal brain disorder. It affects about one person in every one million people per year worldwide. CJD usually appears in later life and runs a rapid course. Typically, onset of symptoms occurs about age 60, and about 90 percent of individuals die within 1 year. The first symptom of CJD is rapidly progressive dementia leading to memory loss, personality changes and hallucinations. Prions are infectious proteins that cause brain disorders like Mad Cow Disease and Creutzfeldt-Jakob Disease in humans. A computational study of quantitative structure activity relationship (QSAR) and toxicity prediction of 2-aminothiazole as an antiprion lead compounds in the treatment of Creutzfeldt-Jakob disease has done. **Method.** computational method using an approach model of Hansch-QSAR and ADMET Predictor. Increasing the concentration of 2-aminothiazole in the brain used model approach to Hansch-QSAR by varying physicochemical properties such as log P values, Homo-Lumo Energy and Molecular Refraction (MR). parameters were then used as descriptors for determining mathematical models that describe the quantitative structure activity relationship of 2-aminothiazole using linear regression, a statistical model of parabolic regression and multiple regression to obtained the conclusion. **Result.** The results proved that derivates compound of 2-aminothiazole as a potential antiprion. 2-aminothiazole compounds leads to potentially therapeutic antiprion Creutzfeldt–Jakob disease with separating the abnormal prions directly and inhibits the formation of abnormal prions. Steric (MR) and Lipophilic (π) were the parameter most closely related to improve the biological activity of the compound 2-aminothiazole derivatives. Log EC_{50} = 0.7311 + 0.00965 π (r=0.6097), and Log EC_{50}=-2.4385 + 0.0406 MR (r=0.57346). **Conclusion**. Small and liphopilic compounds which are very good for antiprion activity that could penetrate to the blood-brain barrier. 4-(2-(6-methylpyridin-2-yl amino)-thiazol-4-yl) benzene-1,2-diol compounds are the best antiprion activity and the lowest toxicity

Keywords: *2-Aminothiazole, antiprion lead compound, computed physicochemical parameters, Hansch QSAR, toxicity prediction*.

Introduction

Creutzfeldt–Jakob Disease (CJD) was a degenerative neurological disease. This disease often brings a nightmare on sufferers which ends with death. CJD usually appears in later life and runs a rapid course According to statistics made by the WHO, It affects about one person in every one million people per year worldwide. This means each year there were about 230 people who died with a population of 241 million in Indonesia due to this disease. Typically, onset of symptoms occurs about age 60, and about 90 percent of individuals die within 1 year.

The first symptom of CJD is rapidly progressive dementia leading to memory loss, personality changes and hallucinations. Prions are infectious proteins that cause brain disorders like Mad Cow Disease and Creutzfeldt-Jakob Disease in humans.

Ironically, it still little as the new active compounds known to potentially treat disease. One of them was 2-Aminothiazole as proven compounds leads to treating this disease. Based on this, the authors might driven to explore this issue, in hopes of taking part in helping develop a useful medicine for community.

The study was limited to the determination of the parameters of the physicochemical properties (lipophilicity, electronic and steric) 2-aminothiazole compounds of Log P, Homo-Lumo energy and MR. Hansch-QSAR approach model, observed the correlation parameter with biological activity using a linear regression, parabolic regression and multiple

regression, as well as the study of the toxicity of the compound 2-aminothiazole derivative used ADMET Predictor.

Material and Method

General Procedure of QSAR including selection a set of molecules interacting with the same target with known activities. Calculate features (e.g. physicochemical properties, with 2D, 3D), Divide the set to two subgroups: one for training and one for testing. Build a model: find the relations between the activities and properties (regression problem, statistic methods, machine learning approaches, etc.) Test the model on the testing dataset. In this study, 2-aminothiazole compounds modeling and all its derivatives made in two dimensions and three dimensions using Chem Draw Ultra software. Determination of parameters of lipophilic Hansch-Fujita (π) through calculation of the coefficient of octanol-water partition which was expressed in the following equation:

$$\pi_X = \log P_{SX} - \log P_{SH}$$

πX: a support group X against the nature of the parent compound solubility in the solvent system 1-octanol/water.
PSX: System partition coefficient 1-octanol/water substituted parent cluster compound x.
PSH: System partition coefficient 1-octanol/water as main compounds.

From the above equation, note that to calculate π to do experiments to determine the coefficient of n-Octanol-water as parent compounds and substituted compound x using Chem Draw Ultra could calculate Log P compounds. Then do the calculation π using Ms Excel 2007. So that the value of π could also be computed quickly. Determination of parameters of electronic energies of Homo-Lumo. Reactivity of molecules and hydroxyl functionality could be investigated by the leading orbital theory (frontier orbital theory) with the parameters energy molecular orbitals (Homo-Lumo Energy). Calculation of the energy of the Homo-Lumo was done using Chem 3D Ultra 8.0 program.

Determination of the molar refraction as steric parameters (MR). The molar refraction (MR) was calculated through equation Lorenz-Lorenz as follows:

$$MR = (n2-1) \times MW/(n2-2) \times d.$$

n= refraction index; d =density; MW=molecular weight.

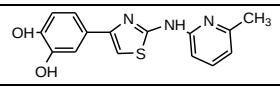
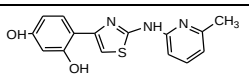
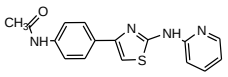
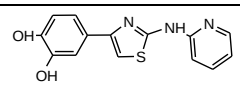
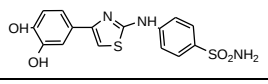
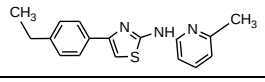
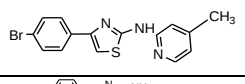
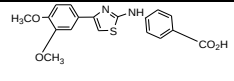
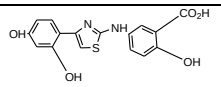
MR be calculated with ChemDraw Ultra 8.0 program. Then all parameters correlated by linear regression, parabolic regression and multiple regression to get the best correlation with the aim of obtaining the optimum concentration in the brain so that the therapy of diseases Creutzfelt-Jakob will take place effectively. The work was carried out using the program Statistica 7. After obtained the best correlation of all the above parameters was done using the toxicity test using ADMET Predictor software determined 2-aminothiazole compounds selectivity to the Creutzfelt-Jakob disease therapy.

Results and Discussion

In the study of Quantitative Structure Activity And Toxicity of 2-Aminothiazole For Leads Compounds (Guides) Antiprion In Creutzfeldt-Jakob Disease Therapy was used Hänsch QSAR models in computational approaches. Calculations performed various physicochemical parameters. Lipophilic properties (log P Hänsch-Fujita), the electronic parameters (Homo-Lumo Energy) and the steric parameter (MR) were then correlated with various correlation methods included linear regression, multiple regression and parabolic regression. There are important issues in applying the multiple linear regression from the fact that it provides sufficient parameters in each data could be adapted to the regression line. The consequence of this was the general regression analysis requires a number of compounds which were significantly larger than the parameter. Rule that was often used was three to six times the number of parameters to be considered. Due to the amount of 2-aminothiazole derivatives totaled only 9 compounds that in this study only used three parameters to meet the rules above.

Lipophilic Properties (π)

Tabel 1. Log P of 2-Aminothiazole Derivates

No.	Compounds	Structure	Log P
1	4-(2-(6-methylpyridin-2-ylamino)thiazol-4-yl)benzene-1,2-diol		4,62
2	4-(2-(6-methylpyridin-2-ylamino)thiazol-4-yl)benzene-1,3-diol		4,62
3	N-(4-(2-(pyridin-2-ylamino)thiazol-4-yl)phenyl)acetamide		3,6
4	4-(2-(pyridin-2-ylamino)thiazol-4-yl)benzene-1,2-diol		3,92
5	4-(4-(3,4-dihydroxyphenyl)thiazol-2-ylamino)benzenesulfonamide		3,28
6	N-(4-(4-ethylphenyl)thiazol-2-yl)-6-methylpyridin-2-amine		6,3
7	N-(4-(4-bromophenyl)thiazol-2-yl)-4-methylpyridin-2-amine		6,01
8	4-(4-(3,4-dimethoxyphenyl)thiazol-2-ylamino)benzoic acid		4,62
9	5-(4-(2,4-dihydroxyphenyl)thiazol-2-ylamino)-2-hydroxybenzoic acid		3,71

Tabel 2. Lipophilic (π) of 2-Aminothiazole Derivates

No.	Compounds	Log Ps-h	Log Ps-x	Πx
6	N-(4-(4-ethylphenyl)thiazol-2-yl)-6-methylpyridin-2-amine	0,95	6,3	5,35
7	N-(4-(4-bromophenyl)thiazol-2-yl)-4-methylpyridin-2-amine	0,95	6,01	5,06
1	4-(2-(6-methylpyridin-2-ylamino)thiazol-4-yl)benzene-1,2-diol	0,95	4,62	3,67
2	4-(2-(6-methylpyridin-2-ylamino)thiazol-4-yl)benzene-1,3-diol	0,95	4,62	3,67
8	4-(4-(3,4-dimethoxyphenyl)thiazol-2-ylamino)benzoic acid	0,95	4,62	3,67
4	4-(2-(pyridin-2-ylamino)thiazol-4-yl)benzene-1,2-diol	0,95	3,92	2,97
9	5-(4-(2,4-dihydroxyphenyl)thiazol-2-ylamino)-2-hydroxybenzoic acid	0,95	3,71	2,76
3	N-(4-(2-(pyridin-2-ylamino)thiazol-4-yl)phenyl)acetamide	0,95	3,6	2,65
5	4-(4-(3,4-dihydroxyphenyl)thiazol-2-ylamino)benzenesulfonamide	0,95	3,28	2,33

From the above data it can be seen that the compound No. 6 was a compound that π its value most. This was caused by the substitution of 4-ethylphenyl on 2-aminothiazole in forth position increases the solubility of 2-aminothiazole compounds in non-polar solvents. There were carbon chain extension will cause the compounds were more lipophilic than others compound of 2-aminothiazole derivatives.

Electronics Properties (Homo-Lumo Energy)

Tabel 3. Homo-Lumo Energy GAP Compound of 2-aminothiazole Derivatives

No.	Compounds	E_{HOMO} (eV)	E_{LuMO} (eV)	*gap*
1	4-(2-(6-methylpyridin-2-ylamino)thiazol-4-yl)benzene-1,2-diol	-8,546	-0,655	-7,891
2	4-(2-(6-methylpyridin-2-ylamino)thiazol-4-yl)benzene-1,3-diol	-8,751	-0,685	-8,066
3	N-(4-(2-(pyridin-2-ylamino)thiazol-4-yl)phenyl)acetamide	-8,252	-0,567	-7,685
4	4-(2-(pyridin-2-ylamino)thiazol-4-yl)benzene-1,2-diol	-8,588	-0,679	-7,909
5	4-(4-(3,4-dihydroxyphenyl)thiazol-2-ylamino)benzenesulfonamide	-8,635	-0,898	-7,737
6	N-(4-(4-ethylphenyl)thiazol-2-yl)-6-methylpyridin-2-amine	-8,728	-0,535	-8,193
7	N-(4-(4-bromophenyl)thiazol-2-yl)-4-methylpyridin-2-amine	-8,404	-0,466	-7,938
8	4-(4-(3,4-dimethoxyphenyl)thiazol-2-ylamino)benzoic acid	-8,466	-0,748	-7,718
9	5-(4-(2,4-dihydroxyphenyl)thiazol-2-ylamino)-2-hydroxybenzoic acid	-8,665	-0,819	-7,846

The greater gap of the compounds were likely to be easy giving up electrons and conversely the smaller gap of the value of these compounds tend to more readily accept electrons. While the results of Homo-Lumo Energy Ribosomal Binding Site (RBS) obtained were -8.565 and 0.660. From these results it could be concluded that the RBS acts as an electron acceptor because it has a greater Lumo Energy than Energy Homo. So it takes 2-aminothiazole compounds most reactive. From the above data it could be seen that the compound No. 8 has the greatest gap value was -7.718. It can be concluded compounds tend to be easier to provide electrons (reactive) than the other 2-aminothiazole derivatives.

Steric Properties (MR)

MR calculation 2-aminothiazole derivatives performed using ChemDraw Ultra 8.0 software and obtained the following results

Tabel 4. MR of 2 -Aminothiazole Derivates

No.	Compounds	MR [cm3/mol]
1	4-(2-(6-methylpyridin-2-ylamino)thiazol-4-yl)benzene-1,2-diol	81,74
2	4-(2-(6-methylpyridin-2-ylamino)thiazol-4-yl)benzene-1,3-diol	81,74
3	N-(4-(2-(pyridin-2-ylamino)thiazol-4-yl)phenyl)acetamide	86,34
4	4-(2-(pyridin-2-ylamino)thiazol-4-yl)benzene-1,2-diol	76,81
5	4-(4-(3,4-dihydroxyphenyl)thiazol-2-ylamino)benzenesulfonamide	92,03
6	N-(4-(4-ethylphenyl)thiazol-2-yl)-6-methylpyridin-2-amine	88,61
7	N-(4-(4-bromophenyl)thiazol-2-yl)-4-methylpyridin-2-amine	86,77
8	4-(4-(3,4-dimethoxyphenyl)thiazol-2-ylamino)benzoic acid	96,12
9	5-(4-(2,4-dihydroxyphenyl)thiazol-2-ylamino)-2-hydroxybenzoic acid	87,07

Substituents size difference was very important for the activity of a compound. Substituents that were too large will reduce the activity of the drug because it causes was not attached properly at the binding site. So the use of smaller Substituents preferable because it does not have to take the risk and reduce the activity of the compound. Judging from the above data compound No.4 Substituents was a compound with the smallest size that was the best compound to bind to receptors on the binding site.

Linear Regression

QSAR equation was a linear model that states the link between variations in biological activities with variations of properties (parameters) were calculated for a particular compound derivative. It aims to get the most influential parameters and work consistently towards the biological activity of the compound derivative.There were the result of linear regression of 2-aminothiazole derivatives were done using STATISTICA 7 software which can be seen in following graphs:.

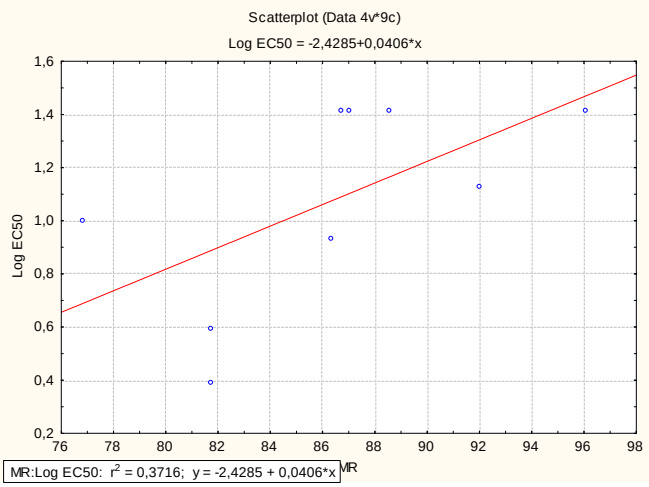


Fig. 2: Scatter plot of Log EC_{50} againts Steric Properties (MR)

Lipophilic Properties

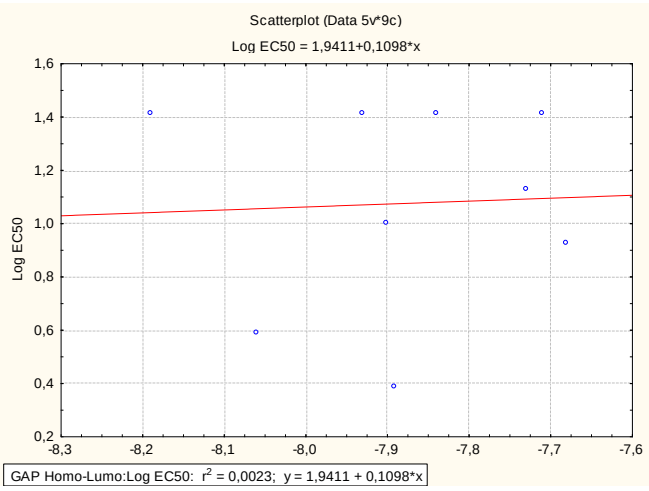
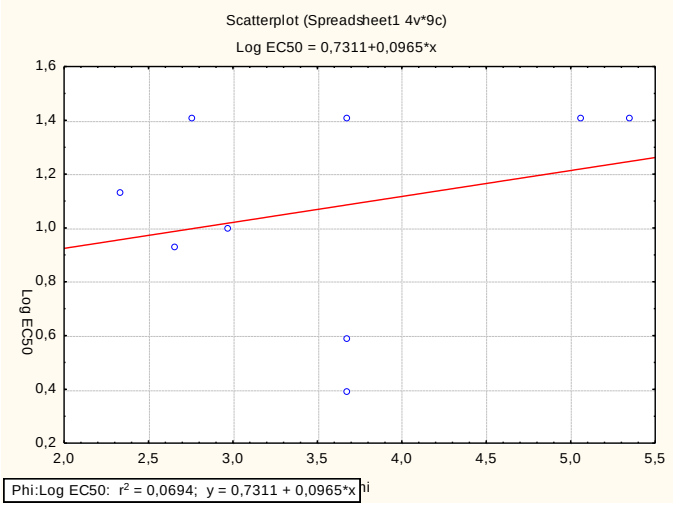


Fig 3: Scatter plot of Log EC_{50} againts Electronis Properties (HOMOs-L



The third graph above equation in estimating the average price for the EC_{50} values based on π, MR and Homo-Lumo gap. Quantized data variation with a correlation coefficient (r).Values may be reported to the probability of having a price r between 0 and 1. r = 0 means there were no relationship between the activity and the selected parameters. r = 1 indicates a perfect correlation between the parameters and activity.

Interpretation can be done using the following criteria:

1. r = 0: no correlation
2. r = 0 to 0.25: the correlation was very weak
3. r = 0.25 to 0.5: enough correlation
4. r = 0.5 to 0.75: strong correlation
5. r = 0.75 to 0.99: the correlation was very strong
6. r = 1: perfect correlation

It could be concluded that MR was a parameter that had a value that was closest to r 1 is 0.6095

So that the parameter most closely linked to the biological activity of 2-aminothiazole derivatives was MR.

Parabolic Regression

Table 5. Summary Data of Parabolic Regression of 2-aminothiazole Derivatives

No.	Compounds	Log 1/C	π	*gap* Homo-Lumo	MR
1	4-(2-(6-methylpyridin-2-ylamino)thiazol-4-yl)benzene-1,2-diol	0,39	3,67	-7,891	81,74
2	4-(2-(6-methylpyridin-2-ylamino)thiazol-4-yl)benzene-1,3-diol	0,59	3,67	-8,066	81,74
3	N-(4-(2-(pyridin-2-ylamino)thiazol-4-yl)phenyl)acetamide	0,93	2,65	-7,685	86,34
4	4-(2-(pyridin-2-ylamino)thiazol-4-yl)benzene-1,2-diol	1	2,97	-7,909	76,81
5	4-(4-(3,4-dihydroxyphenyl)thiazol-2-ylamino)benzenesulfonamide	1,13	2,33	-7,737	92,03
6	N-(4-(4-ethylphenyl)thiazol-2-yl)-6-methylpyridin-2-amine	1,41	5,35	-8,193	88,61
7	N-(4-(4-bromophenyl)thiazol-2-yl)-4-methylpyridin-2-amine	1,41	5,06	-7,938	86,77
8	4-(4-(3,4-dimethoxyphenyl)thiazol-2-ylamino)benzoic acid	1,41	3,67	-7,718	96,12
9	5-(4-(2,4-dihydroxyphenyl)thiazol-2-ylamino)-2-hydroxybenzoic acid	1,41	2,76	-7,846	87,07

Table 6. Parabolic Regression Data of 2-aminothiazole Derivatives Againts **π**

Regression Summary for Dependent Variable: Log 1/C (Data) R= ,57346188 R²= ,32885852 Adjusted R²= ,10514470 F(2,6)=1,4700 p

Summary Statistics; DV: Log 1/C (Data)	
	Value
Multiple R	0,573462
Multiple R²	0,328859
Adjusted R²	0,105145
F(2,6)	1,469996
P	0,302303
Std.Err. of Estimate	0,363771

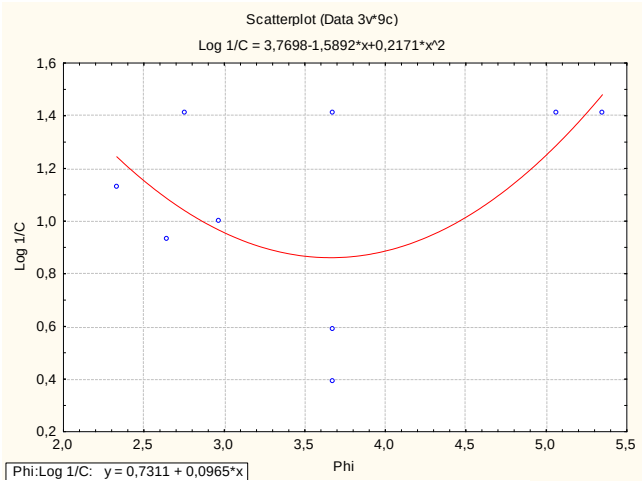


Fig.4: Scatterplot of Parabolic Regression of EC_{50} Against **π**

Table 7. Regression Result Dialog Of EC_{50} Against HOMO-LUMO Gap

Regression Summary for Dependent Variable: Log 1/C (Data) R= ,29881932 R²= ,08929299 Adjusted R²= ----- F(2,6)=,29414 p

Summary Statistics; DV: Log 1/C (Data)	
	Value
Multiple R	0,298819
Multiple R²	0,089293
Adjusted R²	-0,214276
F(2,6)	0,294144
p	0,755329
Std.Err. of Estimate	0,423750

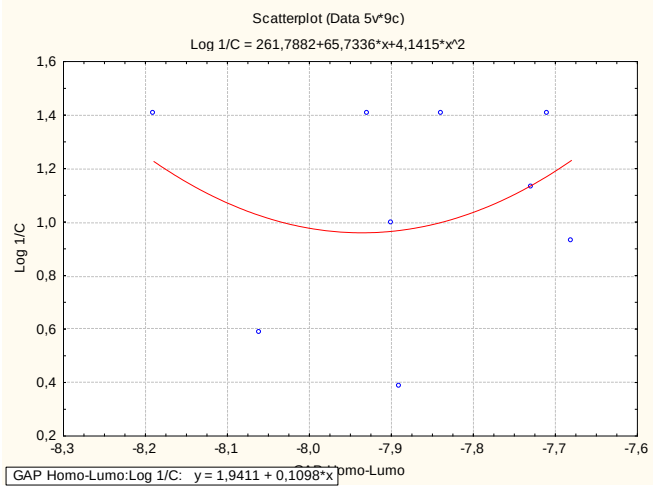


Fig 5: Parabolic Regression of EC_{50} Against Homo-Lumo Gap

Table 8. Regression Result Dialog of EC_{50} Against MR

Regression Summary for Dependent Variable: Log 1/C (Data) R= ,60971866 R²= ,37175685 Adjusted R²= ,16234246 F(2,6)=1,7752 p

Summary Statistics; DV: Log 1/C (Data)	
	Value
Multiple R	0,609719
Multiple R²	0,371757
Adjusted R²	0,162342
F(2,6)	1,775221
p	0,247961
Std.Err. of Estimate	0,351953

Statistics Summary

From the results shown above parabolic regression significance on all three parameters are used to gain the most value of r was close to 1 MR = 0.609719, followed by a final π = 0.573462 and GAP Homo-Lumo = 0.298819. Value F of statistic magnitude estimate / assess the statistical significance of the regression equation. From the statistical data on the most significant parameter was the value of MR with F = 1.775221.

The probability that there was no relationship between the activity of certain parameters determined by the value of P. From the above data proved GAP Homo-Lumo had the highest P-value was 0.755329 or 75.5%, so the nature of the reactivity of the compound 2-aminothiazole derivatives have no relationship to biological activity. While the calculation of the above statistical error rate estimation / prediction set at Standard erorr of Estimate. The smallest error rate among three parameters was the value Std.Err MR. of Estimate = 0.351953.

Multiple Regression

Here was the result of multiple regression for 2-aminothiazole derivatives on Table 9

Table 9. Regression Result Dialog using Log P parameters and Homo-Lumo Gap

Regression Summary for Dependent Variable: Log 1/C (Data) R= ,43473210 R²= ,18899199 Adjusted R²= ----- F(2,6)=,69910 p Summary Statistics; DV: Log 1/C (Data Seluruh Parameter)	
	Value
Multiple R	0,434732
Multiple R²	0,188992
Adjusted R²	-0,081344
F(2,6)	0,699100
P	0,533427
Std.Err. of Estimate	0,399883

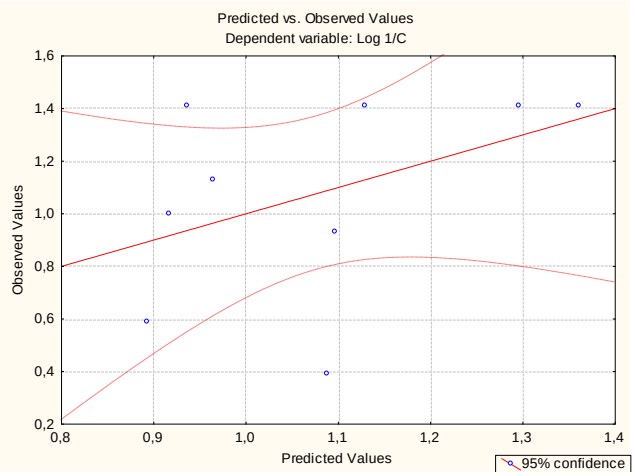


Fig 6: Predicted against observed values using the parameters of Log P and Homo-Lumo gap

Table 10. Regression and residual use LogP Parameters Homo-Lumo Gap.

Predicted & Residual Values (Data Seluruh Parameter) Dependent variable: Log 1/C

	Observed	Predicted	Residual	Standard	Standard	Std.Err.	Mahalanobis	Deleted	Cook's
1	0,390000	1,088268	-0,698268	0,07604	-1,74618	0,134013	0,009603	-0,786614	0,144864
2	0,590000	0,892602	-0,302602	-1,09438	-0,75673	0,244683	2,106353	-0,483703	0,182605
3	0,930000	1,095949	-0,165949	0,12199	-0,41499	0,215823	1,441447	-0,234157	0,033293
4	1,000000	0,916154	0,083846	-0,95350	0,20968	0,189582	0,909224	0,108156	0,005481
5	1,130000	0,964981	0,165019	-0,66143	0,41267	0,213872	1,399509	0,231135	0,031856
6	1,410000	1,128427	0,281573	0,31626	0,70414	0,301969	3,673029	0,655187	0,510269
7	1,410000	1,361145	0,048855	1,70832	0,12217	0,284182	3,151426	0,098706	0,010257
8	1,410000	1,295444	0,114556	1,31531	0,28647	0,260577	2,508106	0,199098	0,035087
9	1,410000	0,937031	0,472969	-0,82862	1,18277	0,183805	0,801303	0,599662	0,158370
Minimum	0,390000	0,892602	-0,698268	-1,09438	-1,74618	0,134013	0,009603	-0,786614	0,005481
Maximum	1,410000	1,361145	0,472969	1,70832	1,18277	0,301969	3,673029	0,655187	0,510269
Mean	1,075556	1,075556	-0,000000	-0,00000	-0,00000	0,225389	1,777778	0,043052	0,123564
Median	1,130000	1,088268	0,083846	0,07604	0,20968	0,215823	1,441447	0,108156	0,035087

Table 11. Regression Result Dialog using Parameter Log P and MR.

Regression Summary for Dependent Variable: Log 1/C (Data Seluruh Parameter) R= ,65101818 R^2= ,42382467 Adjusted R^2= ,23176622 F(2,6)=2,2067 p
Summary Statistics; DV: Log 1/C (Data Seluruh Parameter)

	Value
Multiple R	0,651018
Multiple R^2	0,423825
Adjusted R^2	0,231766
F(2,6)	2,206748
p	0,191278
Std.Err. of Estimate	0,337053

Residual Regression table using LogP and MR parameters can be viewed at Table 12.

Table 12. Regression Result Dialog using Homo-Lumo Gap Parameter and MR.

Regression Summary for Dependent Variable: Log 1/C (Data Seluruh Parameter) R= ,63949103 R^2= ,40894878 Adjusted R^2= ,21193170 F(2,6)=2,0757 p
Summary Statistics; DV: Log 1/C (Data Seluruh Parameter)

	Value
Multiple R	0,639491
Multiple R^2	0,408949
Adjusted R^2	0,211932
F(2,6)	2,075702
P	0,206479
Std.Err. of Estimate	0,341376

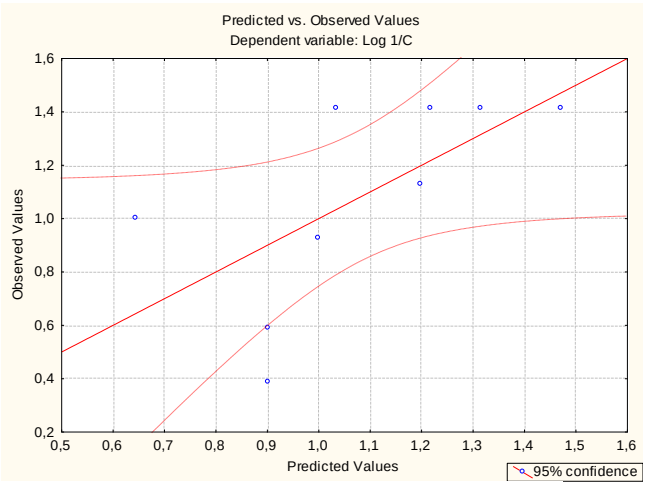


Fig.7. Predicted to observed values using parameter LogP and MR

Table 13 Regression Result Dialog using Parametersof LogP, Homo-Lumo Gap and MR.

Regression Summary for Dependent Variable: Log 1/C (Data) R= ,65120768 R^2= ,42407144 Adjusted R^2= ,07851430 F(3,5)=1,2272 p

Summary Statistics; DV: Log 1/C (Data)

	Value
Multiple R	0,651208
Multiple R^2	0,424071
Adjusted R^2	0,078514
F(3,5)	1,227211
p	0,391394
Std.Err. of Estimate	0,369144

Table 13. Residual Regression table using Log P Parameters, Homo-Lumo Gap and MR.

Predicted & Residual Values (Data) Dependent variable: Log 1/C

	Observed	Predicted	Residual	Standard	Standard	Std.Err.	Mahalanobis	Deleted	Cook' s
1	0,390000	0,896754	-0,506754	-0,71400	-1,37278	0,182417	1,064682	-0,670484	0,201402
2	0,590000	0,907884	-0,317884	-0,66956	-0,86114	0,226127	2,113071	-0,508814	0,178230
3	0,930000	0,991691	-0,061692	-0,33489	-0,16712	0,212178	1,754125	-0,092129	0,005145
4	1,000000	0,644620	0,355380	-1,72085	0,96271	0,258370	3,030174	0,696664	0,436202
5	1,130000	1,200987	-0,070987	0,50088	-0,19230	0,257431	3,001757	-0,138196	0,017040
6	1,410000	1,322214	0,087786	0,98497	0,23781	0,310009	4,753297	0,297856	0,114794
7	1,410000	1,208659	0,201341	0,53152	0,54543	0,283220	3,820291	0,489460	0,258725
8	1,410000	1,467110	-0,057110	1,56358	-0,15471	0,268890	3,355822	-0,121663	0,014409
9	1,410000	1,040081	0,369919	-0,14166	1,00210	0,184372	1,106781	0,492870	0,111176
Minimum	0,390000	0,644620	-0,506754	-1,72085	-1,37278	0,182417	1,064682	-0,670484	0,005145
Maximum	1,410000	1,467110	0,369919	1,56358	1,00210	0,310009	4,753297	0,696664	0,436202
Mean	1,075556	1,075556	-0,000000	-0,00000	-0,00000	0,242557	2,666667	0,049507	0,148569
Median	1,130000	1,040081	-0,057110	-0,14166	-0,15471	0,257431	3,001757	-0,092129	0,114794

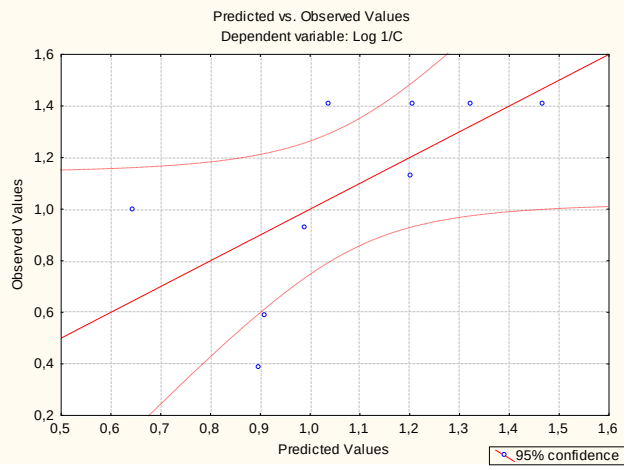


Fig. 8.: Predicted against observed values using LogP parameters, Homo-Lumo gap and MR.

In multiple regression was used on the entire parameter log P, Homo-Lumo gap and MR. Explanation for the data regression dialog result has been described as in the previous discussion of parabolic regression. Value of the correlation r was 0.651208 for all parameters of the biological activity of 2-aminothiazole derivatives. The declared value of r between all parameters and biological activity had a strong correlation. Significance value obtained is F = 1.227211. The probability that there were no relationship between the activity parameters obtained was p = 0.391394 or 39.1%. While the value of the standard error or erorr of estimates obtained was 0.369144. Regression result dialog was used to compare the predictions made by statistical observations. Observed in the column was the value obtained from the observation for the dependent variable. In the column predicted a regression equation yields a new study. Residual in the column represents the difference between the results of observations with the predictions. Residual values (+) states the observation of biological activity is greater than the predicted outcome. Meanwhile, when the residual value (-) states the biological activity of observations is smaller than the predicted outcome. In the next column, there are two columns Residual Standard is standardized predicted value on the dependent variable and standardized residual values. At Std.Err column is the value of the error on the predicted outcome. On the Mahalanobis distance is a measure column indicate whether the independent variables associated with observations. In the Deleted column residual is the residual value is not included in the regression analysis. At Cook&Apos; s column shows the difference between the value of B was computing with values to be obtained. After reviewing all of the data above, it can be assumed that the small hydrophobic substituents shown to increase the biological activity of 2-aminothiazole derivatives, while not overly influence the reactivity to increase activity.

Toxicity Test

Toxicity tests performed in this study to determine the potential toxicity of 2-aminothiazole derivatives on the body. Toxicity test was performed using the ADMET Predictor and the resulting data was as follows:

1. TOX_MRTD [mg/kg/day]

Showed that the maximum recommended therapeutic dose is administered as an oral dose for the compound No. 1, 6, 7, and 5 were <3.16. No. And to compound. 4, 3, 8 and 9 was more than 3.16. As for the compound No. 2 TOX_MRTD its value was doubtful. TOX_MRTD conducted a qualitative assessment.

2. TOX_ATTP [mmol/L]

Stated that pIGC50 for toxicity Tetrahymena pyriformis growth inhibitors which were compounds No. 9 was the smallest with a value of 0.327 TOX_ATTP and most of it was compound No. 6 and 7 with a value of 1.828 TOX_ATTP.

3. TOX_hERG_Filter

Showed that the possibility of hERG potassium channel inhibition in humans for compounds No. 1, 5, 4, 8, 9 and 2 was nontoxic. As for the compound No. 6, 7 and 3 were toxic.Assesment of TOX_hERG_Filter conducted qualitatively.

4. TOX_CABR

The results obtained indicate that the estimated trigger chromosomal aberrations for the mutagenic compound No. 1, 7, 5, 4, 9 and 2 were toxic. While the compound No. 6, 3 and 8 were nontoxic.

5. TOX_PHOS

The results obtained indicate that the cause phospholipidosis estimates for all 2-aminothiazole derivatives were nontoxic. TOX_PHOS conducted a qualitative assessment.

6. TOX_SGOT
Showed that the adverse effects of the human heart as a possible cause elevations in AST enzyme levels for compounds No. 1, 6, 5, 4, 3 and 8 were toxic. As for the compound No.7, 9 and 2 were nontoxic.
7. TOX_SGPT
Showed that the adverse effects of the human heart as a possible cause elevations in alanine aminotransferase enzyme levels for compounds No. 1, 6, 4, 3, 9 and 2 were toxic. And to compounds No. 5 and 8 were nontoxic. As for the compound No. 7 was questionable results. 2-aminothiazole derivatives were nontoxic.
8. TOX_MUT_Risk and TOX_MUT_Code
Showed that The risk of ADMET ADMET and codes for mutagenicity in S. typhimurium to compound. No 1, 6, 7, 4 and 3 were (1.0, m2). No. And to compounds No. 5, 8 and 9 were (0.0). As for the compound. No. 2 was (2.0, m2.m4)
9. TOX_Risk and TOX_Code
Showed that the risk of ADMET and ADMET codes for tendency toxic compounds No. 1 and 4 was (2, Hp.SG). As of compounds No. 6 and 3 was (4, Xr.Xm.Hp.SG). As of compounds No. 8, 9 and 2 were (1, Hp), As for compound No. 7 was (1, Xm). And to compound. No. 5 was (0, -).
From the above it could be concluded that the compound No. 1 was a compound of the safest in terms of toxicity.

Conclusion

The present study suggests that seeds of *Persea americana*, fruits and leaves of *Phalleria marcocarpa,* leaves of *Oxalis corniculata*, leaves of *Catharanthus roseus*, *Herbs of Scurulla artopurpurea*, seeds of *Swietenia mahogany*, leaves of *Gynura procumbens,* leaves of *Melia azedarach* L and leaves of *Hibiscus rosasinensis* possess angiotensin converting enzyme inhibitory that might be helpful in treating hypertension. Further investigations on the isolation of active compounds present in the extract and *in vivo* studies are necessary to identify a potential chemical entity for clinical use in the treatment of hypertension and other related cardiovascular disorders.

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

PEER REVIEW

Not commissioned; externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.