International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 06 Issue 07 July 2023
DOI: 10.47191/ijcsrr/V6-i7-06, Impact Factor: 6.789
IJCSRR @ 2023
www.ijcsrr.org

Potential of Aloin B Compound and its Derivatives as Type-2 Antidiabetic

Shevy Karunia Cahyaningtias[1], I Gusti Made Sanjaya[2]
[1,2] Department of Chemistry, Faculty of Mathematics and Natural Sciences, State University of Surabaya, Indonesia

ABSTRACT: Type-2 diabetes mellitus occurs due to suboptimal insulin function (insulin resistance) or decreased insulin function. Type-2 diabetes mellitus treatment is chronic and lifelong. One of the treatments is the use of insulin and oral anti-diabetic drugs. This treatment requires a long period of time and can cause unwanted side effects. Therefore, alternative treatments are needed with minimal side effects by utilizing herbal plants containing Aloin B compounds because they have been proven to be used as antidiabetic agents. These compounds can be found from the Aloe Vera plant (Aloe Vera l.). The aim of this study was to find compounds derived from Aloin B compounds that have the most potential as anti-diabetic type-2 by inhibiting the pancreatic α-amylase enzyme (code: 1B2Y) in breaking down starch in the body. The certainty of the presence of the compound Aloin B in the flesh of the aloe plant was confirmed by the LC-MS test. This research was conducted using the Quantitative Structure-Activity Relationship (QSAR) and Molecular Bonding method. The results showed that the ID S22 compound with the IUPAC name (S)-10-amino-1,2,8-trihydroxy-6-(hydroxymethyl) -10- ((2R,3R,4S,5S,6R) -2,3, 4,5-tetrahydroxy–6(hydroxymethyl) tetrahydro-2H-piran-2-yl) anthracene-9(10H)-one is the most potent compound from Aloin B derivatives as a type-2 antidiabetic agent in the mechanism of inhibiting α-enzyme action pancreatic amylase, based on the value of R2 = 0.980, the PRESS value of the compound was 0.0004, the binding energy value was -7.07 kcal/mol, the inhibition constant was 6.58 uM and the formation of hydrogen bonds between the compound and the amino acid residues aspirin, glycine, threonine and arginine.

KEYWORDS: Antidiabetic, Aloin B Derivatives, Molecular docking, pancreatic α-amylase enzyme, QSAR.

INTRODUCTION

Diabetes mellitus is a deadly disease. This is due to high levels of glucose in the blood as a result of the inability of the beta cells (β cells) of the pancreas to produce sufficient insulin or the use of insulin carried out by cells in the body is not effective (Berbudi et al., 2020). Around 425 million adults suffer from diabetes mellitus globally in 2017 (Tekulu et al., 2019). In Indonesia, according to the databox website, Indonesia ranks 5th with the most cases of diabetes mellitus in the world (Wiratama & Pradnya, 2022). From year to year the number of people with diabetes mellitus is increasing. Referring to data sources from the International Diabetes Federation, there were 10 million people with diabetes in 2015 in Indonesia, by 2040 it is predicted that the number of Indonesian citizens who are infected with diabetes mellitus will increase by 16.2 million Indonesians (Hana, 2020).

In general, diabetes mellitus is divided into two, namely diabetes mellitus type-1 and diabetes mellitus type-2. Type 1 diabetes mellitus occurs when an autoimmune reaction occurs with pancreatic beta cell proteins. In this type of pancreatic beta cells have been destroyed by an autoimmune process, so that insulin cannot be produced. Type-2 diabetes mellitus occurs because insulin function is not optimal (insulin resistance) or loss of insulin function. Glucose that enters the body cannot be converted into glycogen and triglycerides. Not optimal use of insulin results in high blood glucose. If not treated immediately, the pancreatic beta cells will be damaged (Organization, 2019). 9 The function of insulin itself is to regulate or control glucose that enters the body by giving signals to muscle, fat and liver cells to process glucose into glycogen and triglycerides. someone controls it (Organization, 2019).

Treatment of diabetes mellitus is chronic and lifelong. One of the treatments is the use of insulin and oral anti-diabetic drugs. This treatment requires a long period of time and can cause unwanted side effects. Therefore it is necessary to provide drugs that are effective and have minimal side effects and do not require large costs in their use or consumption. In the studies that have been carried out, several medicinal plants have been reported as having potential as anti-diabetic agents (Etxeberria et al., 2012) (Naveen & Baskaran, 2018). These plants work as antidiabetics through various mechanisms, such as increasing the quality and quantity of pancreatic β cells, accelerating the regeneration of pancreatic β cells, improving insulin action, becoming inhibitors of α-amylase and α-glucosidase enzymes and others (Anugrahini & Wahyuni, 2021) (Alam et al., 2019). One of the natural ingredients or plants that

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 06 Issue 07 July 2023
DOI: 10.47191/ijcsrr/V6-i7-06, Impact Factor: 6.789
IJCSRR @ 2023
www.ijcsrr.org

are widely used as traditional medicine and is believed to be able to treat various kinds of diseases is the aloe vera plant (Aloe vera.L) (Atanu et al., 2018) (Ananda & Zuhrotun, 2017).

In previous studies, it has been proven that aloe vera plants, especially the flesh of aloe vera plants, contain secondary metabolites such as flavonoids, alkaloids, quinones, saponins, tannins, glycosides, anthraquinones, and terpenoids. These compounds have pharmacological activities as anti-inflammatory, immunomodulatory, anti-bacterial, anti-fungal, antiviral, and anti-diabetic (Etxeberria et al., 2012) (Sarker & Grift, 2021) (Alejo et al., 2019). The flesh of the aloe vera plant has high properties because the ethanol extract of this plant contains glycoside and polyketide group compounds which can provide anti-diabetic effects through inhibition of the α-amylase and 10 α-glucosidase enzymes (Anugrahini & Wahyuni, 2021). Aloin B contained in the flesh extract of the aloe vera plant showed the highest inhibitory activity in the performance of the α-amylase enzyme with an IC50 of 0.34 mg/mL which was higher than acarbose (0.54 mg/mL) the positive control, indicating that the activity of the Aloe extract was related to with aloin and other anthrone compounds (Zhong et al., 2022).

Based on this research, researchers are interested in testing the antidiabetic activity of compounds modified from the aloin B structure which is a compound from the glycoside group and more precisely the anthraquinone glycoside group which has been known to have antidiabetic activity (Anugrahini & Wahyuni, 2021; Saleh Al-Sowayan & Mohammad AL-Sallali, 2023; Zhong et al., 2022). It is hoped that by modifying the structure of the aloin B compound, a compound that has greater potential in inhibiting the pancreatic α-amylase enzyme is obtained. To date, no research has been reported on the structure and activity quantitative relationship (QSAR) and molecular anchorage studies related to inhib

MATERIALS DAN METHODS

Materials

The material used is the compound Aloin B which is an anthraquinone glycoside compound obtained from 100 gram extract of the flesh of the aloe vera plant (Aloe vera.L) with 200 mL of 96% ethanol solution modeled by Avogadro and the 3D molecular structure of 1B2Y protein as a protein visualization was obtained from the Protein Data Base (PDB).

The tools used were digital scales, maceration bottles, vials, Rotary Evaporator, LC-MS, in silico assessment using a laptop set with Intel Core i3-233oM specifications, 500 GB, 2 GB RAM. The program used for molecular docking is Avogadro, and Autodock Tools 1.5.6. Calculation of steric, hydrophobic, and electronic computational descriptors using NWchem, Swiss ADME, Molinsipration, and Pkcsm programs. Compound visualization using the Discovery Studio 2019 Client program. The results of the computational descriptor multilinear regression analysis using SPSS 16.0 with the backward method.

Methods

A. Determination of Aloin B Compounds in Aloe Vera Plants

Determination of the Aloin B compound in the flesh of the aloe vera plant was carried out by analyzing the results of the ethanol extract of the aloe vera plant with LC-MS. Aloe vera flesh was cleaned of skin and mucus with distilled water, then weighed with a scale of 100 grams. The aloe vera meat that has been weighed is then put into the maceration bottle. Enter the 96% ethanol solution 200 mL which has been measured first using a measuring cup and then put it into the maceration bottle which already contains the flesh of the aloe vera plant. The maceration bottle was closed and then left to stand for 3 days and 2 nights and stirring was carried out as often as possible in the maceration process.

B. Selection of Derivative Aloin B Compound

The compound selection process was carried out by following the Lipinski rules and LD 50 category 3. The compounds obtained must comply with all Lipinski rules and may only violate one of the four existing rules. The rule is that the partition coefficient of okatanol-water (log P) is in the range of -0.4 to 5.6. (if more than 5 then the compound will be more hydrophobic) Not more than 5 hydrogen bond donors. (if more then it will be difficult to bond with the target compound) Not more than 10 hydrogen bond acceptors. (if more then it will be difficult to bind to the target compound). The molecular weight is not more than 500 mg/mol. (if more then the compound will be difficult to penetrate the wall of the target compound). LD 50 category 3 is used because it is a slightly toxic category.

C. Quantitative Structure-Activity Relationship

Modeling of Aloin B derivatives makes a 3-dimensional structure of Aloin B derivatives with good shapes and configurations using Avogadro. Optimizing the geometry of all Aloin B derived compound structures that have been made

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 06 Issue 07 July 2023
DOI: 10.47191/ijcsrr/V6-i7-06, Impact Factor: 6.789
IJCSRR @ 2023
www.ijcsrr.org

previously by running geometry optimization using Avogadro. Electronic descriptor data was collected using NWchem with the B3LYP Theory DFT method and Cosmo Solvation with a base set of 6-31G* to obtain HOMO descriptor values, LUMO, ΔLUMO-HOMO, Dipole Moments, and Hydration Energy, steric descriptor data in the form of MR, Volume, Surface Area, and Topology Polar Surface Area, and hydrophobic descriptor data in the form of partition coefficient (Log P) were obtained using Swiss ADME, Molinsipration, and Pkcsm programs. The descriptor data that has been collected is then performed a multilinear regression statistical analysis using the backword method in the SPSS program to determine the physicochemical properties of each Aloin B derivative compound. This analysis is performed to obtain the theoretical activity of the aloin B compound and its derivatives using the best QSAR equation

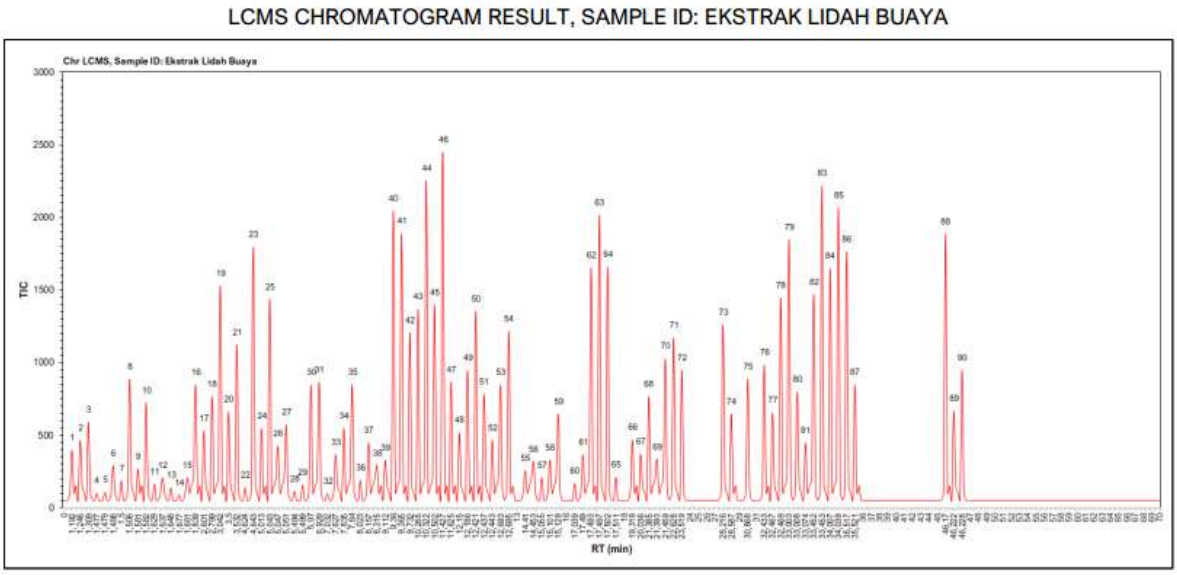
D. Molecular Docking

Preparation and Optimization of Pancreatic Alpha Amylase Enzyme Protein. Download the pancreatic α-amylase enzyme protein at https://www.ncbi.nlm.nih.gov/protein and then process the separation of water molecules and non-standard ligands or residues using the Discovery Studio 2019 Client. Then the macromolecule optimization process was carried out using the Autodock Tools 1.5.6 software. Optimization includes adding hydrogen atoms and setting grid box parameters to determine the location of the ligand molecule attachment. Macromolecular optimization results are saved in .pdbqt file format. Preparation and Optimization of Ligand compounds (Test Compounds) A 3-dimensional structure of aloin B derivative compounds was created using Avogadro and saved in the .pdb file format and then optimized using Autodock Tools and saved in the .pdbqt format. Molecular anchoring using Autodock Tools software The 3D structure of aloin B derivatives with target proteins was calculated for their inhibition and binding energy values using Autogrid and Autodock via Ubuntu 20.04. Analysis and Visualization of Molecular Docking Calculation results of molecular docking can be seen from the output in .dlg file format. Selection of results by choosing a ligand that has a low binding energy. Visualization of the position of each ligand with the target protein using the Discovery Studio 2019 Client program

RESULT AND DISCUSSION

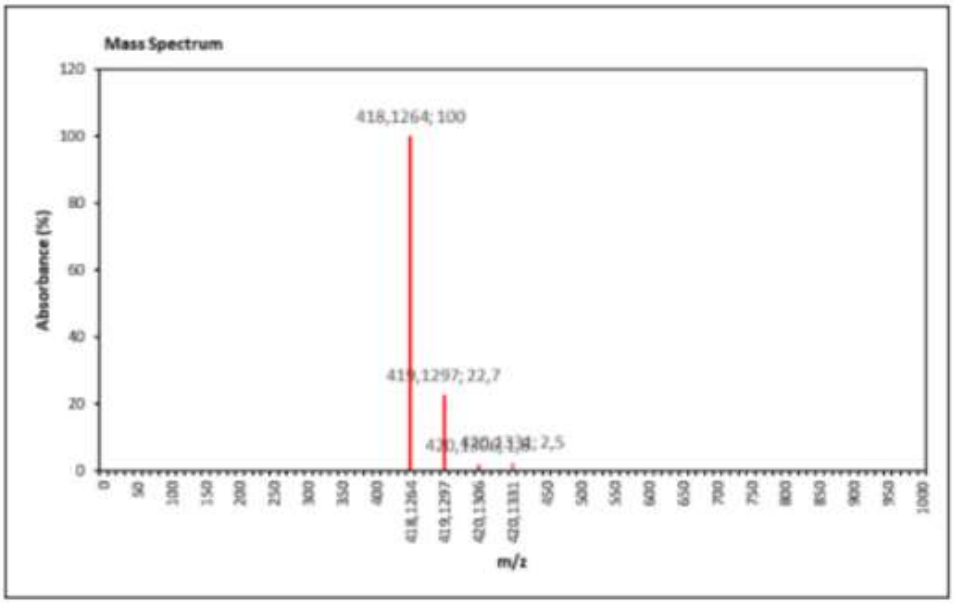
A. Determination of Aloin B Compounds in Aloe Vera Plants

The LC-MS test on the aloe vera plant extract that has been carried out has the following graphical results.

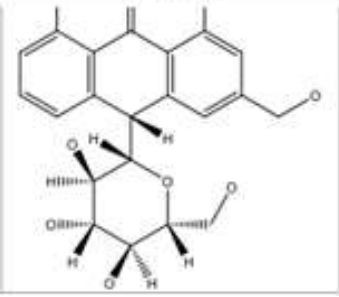


Gambar 1. Graph of LC-MS test results of aloe vera flesh extract

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 06 Issue 07 July 2023
DOI: 10.47191/ijcsrr/V6-i7-06, Impact Factor: 6.789
IJCSRR @ 2023
www.ijcsrr.org



Gambar 2. Aloin B compound peek graph

Peak number	RT (min)	Similarity index (%)	Curve area	Composition (%)	Compound Result	
					Analysis	Structure
62	17,497	92	2015,48654	2,72453	Chemical Formula: $C_{21}H_{22}O_9$ Exact Mass: 418.1264 Molecular Weight: 418,3980 m/z: 418.1264 (100.0%), 419.1297 (22.7%), 420.1331 (2.5%), 420.1306 (1.8%)	

Gambar 3. Image of LC-MS test results for Aloin B compound

From the graphic image above 99 compounds have been identified. Of the 99 compounds that have been obtained, the Aloin B compound is proven to exist with the peak graph number 62 as shown in the picture above. The Aloin B compound identified from the ethanol extract of aloe vera meat has a composition of 2.724%. The composition shows that 2.74% of all identified compounds are Aloin B compounds. From the graph above it can also be seen if Aloin B compounds have a fairly high peek where the content of these compounds is abundant. This is in accordance with research conducted by (Boudreau et al., 2017) (Kaparakou et al., 2021) (Hayes et al., 2022) (Khajeeyan et al., 2022) which says that aloin is one of the main components in aloe vera flesh extract.

B. Selection of Derivative Aloin B Compound

The presence of Aloin B compound was identified by testing the results of ethanol extract of 100 g of aloe vera flesh with 200 ml of 96% ethanol solution using LC-MS. The results of the analysis of the ethanol extract of aloe vera meat found 89 compounds, and the Aloin B compound was included. The results of the analysis test also found several derivatives of the Aloin B compound. The derived compounds that were successfully identified in the LC-MS test and the results of modified compounds for replacing the active group as derivatives of the Aloin B compound will be used in the selection of drug compounds as Type-2 Antidiabetics based on The Lipinski rule was carried out using the Swiss ADME and Lethal Dose 50 (LD50) program using the Pkcsm program (Khadse et al., 2019; Zhong et al., 2022). The following is a table of compound data that was successfully obtained.

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 06 Issue 07 July 2023
DOI: 10.47191/ijcsrr/V6-i7-06, Impact Factor: 6.789
IJCSRR @ 2023
www.ijcsrr.org

Table 1. Table of Aloin B Derivative Compounds

No	Compound ID	Lipinski Rules	LD50 (Kcal/mol)
1	S1	No	2.534
2	S2	No	2.478
3	S3	Yes	2.573
4	S4	No	2.768
5	S5	No	2.567
6	S6	No	2.478
7	S7	No	2.501
8	S8	Yes	2.724
9	S9	No	2.502
10	S10	No	2.065
11	S11	Yes	2.780
12	S12	No	2.498
13	S13	No	2.505
14	S14	Yes	2.586
15	S15	No	2.489
16	S16	Yes	2.057
17	S17	Yes	2.500
18	S18	No	2.499
19	S19	Yes	2.052
20	S20	No	2.508
21	S21	No	2.509
22	S22	Yes	2.509
23	S23	No	2.488
24	S24	Yes	2.495
25	S25	No	2.491
26	S26	No	2.487
27	S27	No	2.960
28	S28	Yes	2.506
29	S29	Yes	2.496
30	S30	Yes	2.549
31	S31	Yes	2.525
32	S32	No	2.675
33	S33	Yes	2.495
34	S34	Yes	2.483
35	S35	No	2.500
36	S36	No	2.553
37	S37	No	2.640
38	S38	No	2.506
39	S39	No	2.493
40	S40	No	2.509

From the selection results based on the Lipinski rule where the partition coefficient of okatanol-water (log P) is in the range of -0.4 to 5.6. (more than 5 then the compound will be more hydrophobic) Not more than 5 hydrogen bond donors. (if more then it will be difficult to bind to the target compound) Not more than 10 hydrogen bond acceptors. (if more then it will be difficult to bind to the target compound). The molecular weight is not more than 500 mg/mol. (if more then the compound will be difficult to

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 06 Issue 07 July 2023
DOI: 10.47191/ijcsrr/V6-i7-06, Impact Factor: 6.789
IJCSRR @ 2023
www.ijcsrr.org

penetrate the wall of the target compound). Of the four rules above, it has been agreed if a compound can be used as a medicinal ingredient by not violating more than one of these rules, and the LD 50 category 3 (Ukwenya et al., 2021). Of the 40 compounds obtained, the compounds with IDs S1 to S6 were derivatives of the Aloin B compound obtained from the test results of the aloe vera flesh extract using LC-MS, while the compounds with IDs S7 to S40 were derived compounds obtained from the modification of functional groups by placing efficient. Substitution of active groups uses hydroxy functional groups (OH) which are capable of forming hydrogen bonds with specific amino acids at the active sites of enzymes (Hilma et al., 2015; Girsang, 2020), nitrogen groups (N) as competitive inhibitors by blocking enzymatic reactions (Sofawati , 2012), and the carbonyl group (C=O) is also an inhibitor of enzymatic reactions for α-amylase enzymes (Gaspersz and Sohilait, 2019). Compounds that meet the requirements for further tests are compounds with ID S3, S8, S11, S14, S16, S17, S19, S22, S24, S28, S29, S30, S31, S33, S34. The next test was to find the descriptor values of the 15 compounds that met the requirements using the NWchem, Swiss ADME, Molinsipration, and Pkcsm programs.

C. Model analysis based on the Quantitative Structure-Activity Relationship method

Compounds that have been selected in the previous procedure were then analyzed for electronic descriptor values using NWchem with the B3LYP Theory DFT method and Cosmo Solvation with a 6-31G* basis set to obtain the descriptor values of HOMO, LUMO, ΔLUMO-HOMO, Dipole Moment, and Hydration Energy. Steric descriptor data in the form of MR, Volume, Surface Area, and Topology Polar Surface Area, and hydrophobic descriptor data in the form of partition coefficient (Log P) were obtained using the Swiss ADME, Molinsipration, and Pkcsm programs. And obtained the following data.

Table 2. Descriptor Data Table

ID	Mr (g/mol)	TPSA (Å)	SA (Å)	Log P	V(ML)	HOMO	LUMO	ΔLUMO-HOMO	Hydration Energy (kcal/mol)	Diole Moment (D)
S3	434.39	188.14	175.390	1.780	360.12	0.238805	0.063034	0.175771	42.75	3.876
S8	452.84	167.91	180.899	0.238	365.97	0.235881	0.054372	0.181509	39.22	4.52
S11	487.28	167.91	167.000	0.416	379.5	0.222252	0.052322	0.16993	39.07	5.443
S14	547.73	188.14	199.561	0.026	391.55	0.223035	0.061164	0.161871	45.93	4.365
S16	435.38	214.16	174.365	1.992	354.61	0.213484	0.054289	0.159195	44.36	3.845
S17	435.38	214.16	174.365	1.992	354.61	0.220615	0.055102	0.165513	43.86	4.324
S19	449.41	214.16	180.730	2.205	371.41	0.220688	0.062270	0.158418	42.11	4.161
S22	449.41	214.16	180.730	2.115	371.41	0.211957	0.059789	0.152168	43.33	5.845
S24	448.42	219.95	181.276	2.238	374.68	0.218735	0.060099	0.158636	42.73	4.624
S28	435.38	214.16	174.365	1.901	354.61	0.211935	0.052888	0.159047	43.77	4.185
S29	443.41	225.74	175.457	2.148	361.15	0.218673	0.053164	0.165509	43.27	3.909
S30	436.37	208.37	173.820	1.868	351.34	0.213653	0.054545	0.159108	44.26	4.018
S31	450.39	208.37	190.184	2.081	368.14	0.213572	0.062476	0.151096	44.66	4.61
S33	448.42	219.95	181.276	2.238	374.68	0.218463	0.060994	0.157469	44.08	4.724
S34	447.44	225.74	225.740	2.272	377.95	0.218502	0.061539	0.156963	43.45	3.757

In the analysis of the quantitative relationship between structure and activity, 10 descriptors are used. The descriptor data above will be analyzed using multilinear regression statistics using the backword method with the dependent hydrophobic descriptor, namely the partition coefficient (Log P) and the independent steric and electronic descriptors using SPSS 16.0 (Amini et al., 2020; La Kilo et al., 2021). The value of the partition coefficient (Log P) shows the effectiveness of the distribution of compounds in the human body, the higher the value, the easier it is to consume and dissolve in the human body (Zhu et al., 2022). The results of the multilinear regression statistical analysis using the backword method with the above descriptor data obtained five models of

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 06 Issue 07 July 2023
DOI: 10.47191/ijcsrr/V6-i7-06, Impact Factor: 6.789
IJCSRR @ 2023
www.ijcsrr.org

equations. Of the five equation models, the best equation is obtained from the prediction table below based on the value of the correlation coefficient (R) and the coefficient of determination (R2) close to 1 and the small value of Std. Error of the Estimate (SEE). R and R2 values that are close to 1 mean that the correlation between physicochemical and biological properties is very close, while SEE values that are close to zero indicate very small deviations (Amini et al., 2020).

Table 3. Table Data Model from SPSS Analysis

ID	Variable	R	R^2	SEE
1	MR, TPSA, SA, Volume, HOMO, LUMO, Hydration Energy, Dipole moment	0.992	0.983	0.15
2	MR, TPSA, SA, Volume, HOMO, LUMO, Dipole moment	0.992	0.983	0.14
3	MR, TPSA, SA, Volume, HOMO, LUMO	0.991	0.982	0.13
4	MR, TPSA, SA, HOMO, LUMO	0.990	0.980	0.13
5	MR, TPSA, SA, LUMO	0.987	0.974	0.14

In the table above, all models have R and R2 values that are close to 1, but SEE values that are closer to zero are models 3 and 4. After conducting validation tests by looking at the R, R2 SEE, and PRESS values of each model, model 4's equation is the the best because it meets all the validation tests performed. The R and R2 values are close to 1, the SEE values are close to 0, and the PRESS values are small. Then the following equation is obtained: Log P = 3.201+(-0.013*MR)+(0.023*TPSA)+(-0.007*SA)+(-11.468*HOMO)+(59.335*LUMO).

The experimental Log P regression value with Predicted Log P is 0.980, the meaning of this value is 98% of the compound explains the facts and the rest is explained by the residual variable. A good regression value is a value close to 1, and its validity can be recognized. The descriptors that influence this regression are MR, TPSA, SA, HOMO, and LUMO.

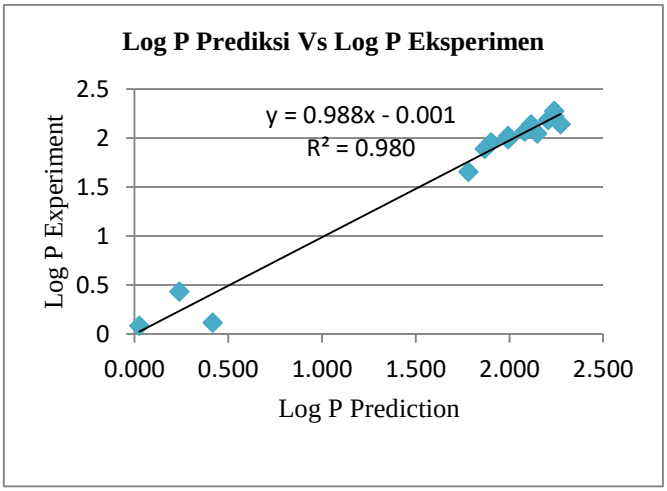


Figure 3. Graph of Log P Prediction VS Log P Experiment

From the graph above, it can be seen that the log P value indicates the strong influence of the descriptors involved, so that the best compound can be selected for validation using molecular anchoring. In addition, the PRESS (Predictive Residual Sum of Square) value can also be used to find out how well the QSAR equation has been obtained. The smaller the value (closer to 0), the better the compound is in becoming a drug candidate. The PRESS value is obtained from the squared result of the reduction between

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 06 Issue 07 July 2023
DOI: 10.47191/ijcsrr/V6-i7-06, Impact Factor: 6.789
IJCSRR @ 2023
www.ijcsrr.org

the experimental log P and the predicted P log. Based on the table below, compound number 8 has a log P value that is quite large and the PRESS value is 0, so that the compound's ability is then validated using the molecular docking method (Izadpanah et al., 2021; Pisani et al., 2022).

Table 4. Experimental P Log, Predicted P Log, and PRESS Data Tables

ID	Log P Experiment	Log P Prediction	PRESS
S3	1.78	1.65492665	0.015643
S8	0.238	0.430796312	0.03717
S11	0.416	0.115029934	0.090583
S14	0.026	0.08220356	0.003159
S16	1.9917	2.019188303	0.000756
S17	1.9917	1.98564935	3.66E-05
S19	2.205	2.183180466	0.000476
S22	2.115	2.136097439	0.000445
S24	2.238	2.218979185	0.000362
S28	1.901	1.9538239	0.00279
S29	2.148	2.047234976	0.010154
S30	1.868	1.890214971	0.000494
S31	2.081	2.064921764	0.000259
S33	2.238	2.275203306	0.001384
S34	2.272	2.141755629	0.016964

D. Molecular Docking analysis

After obtaining the results of the QSAR analysis, the next analysis is molecular docking. In molecular docking, the interaction between each compound and the target protein will be known. In this study, the protein coded 1B2Y was used. Molecular docking was performed to compare the ability of each compound to become a drug candidate. The interactions that will be studied are the bond energies that occur (Binding Energy) and the inhibition constant (Inhibition Constant). The best compound is chosen based on the low binding energy and inhibition constant values, the lower the binding energy value, the easier it is to bind to the target protein, the lower the inhibition constant value, the greater it can become an inhibitor in the target protein.

Table 5. Table of Binding Energy and Inhibition Constants

ID	Binding Energy	Inhibition Constants
S3	-6.61	14.36
S8	-7.02	7.11
S11	-6.51	16.79
S14	-6.15	31.18
S16	-6.37	21.41
S17	-5.41	107.54
S19	-5.94	44.25
S22	-7.07	6.58
S24	-6.64	13.54
S28	-6.88	9.08
S29	-5.94	44.37

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 06 Issue 07 July 2023
DOI: 10.47191/ijcsrr/V6-i7-06, Impact Factor: 6.789
IJCSRR @ 2023
www.ijcsrr.org

S30	-6.37	21.27
S31	-5.84	52.7
S33	-6.44	18.95
S34	-6.09	34.35

Based on the table above compound number 8, with the IUPAC name (S)-10-amino-1,2,8-trihydroxy-6-(hydroxylmethyl)-10-((2R,3R,4S,5S,6R)-2,3 ,4,5-tetrahydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl) anthracen-9(10H)-one, is confirmed to have the ability as a Type-2 anti-diabetic by inhibiting the action of the amylase enzyme in breaking down starch. This happened because the compound had the smallest binding energy and inhibitor constants, namely -7.07 kcal/mol and 6.58 uM. Next, visualization was carried out between the selected compounds and the target protein using Discofery Studio Fisualizer 2019 and obtained hydrogen bonds with residues of the amino acids aspirin, glycine, threonine, and arginine.

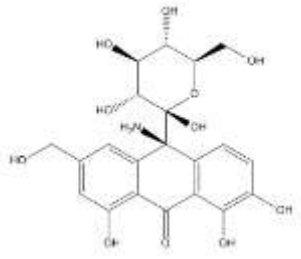
a)  b)  c) 

Figure 4. a) ID 22 compound, b) 1B2Y protein, c) Molecular docking between ID 22 compound and 1B2Y protei

This compound has the ability as a type-2 antidiabetic by inhibiting the action of the amylase enzyme based on the experimental Log P values, Predicted Log P, PRESS, binding energy and inhibition constants which have met the requirements

CONCLUSION

The compound with the most potential as a type-2 antidiabetic is a compound with an ID of 22. The compound has the IUPAC name (S)-10-amino-1,2,8-trihydroxy-6-(hydroxylmethyl)-10-((2R,3R,4S,5S,6R)-2,3,4,5-tetrahydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yl) anthracen-9(10H)-one. This has been proven by fulfilling all validation requirements for oral drugs and type-2 antidiabetics. The results of the validation were an R2 value of 0.980, a PRESS value of a compound of 0.0004, a binding energy value of -7.07 kcal/mol, an inhibition constant of 6.58 uM and the formation of hydrogen bonds between the compound and the amino acid residues of aspirin, glycine, threonine and arginine.

ACKNOWLEDGEMENTS

Thank you to the Department of Chemistry, State University of Surabaya, which has provided facilities in the form of a Computational Chemistry Laboratory so that this research can be completed properly.

REFERENCES

1. Abchir, O., Daoui, O., Belaidi, S., Ouassaf, M., Qais, F. A., ElKhattabi, S., Belaaouad, S., & Chtita, S. (2022). Design of novel benzimidazole derivatives as potential α-amylase inhibitors using QSAR, pharmacokinetics, molecular docking, and molecular dynamics simulation studies. *Journal of Molecular Modeling*, *28*(4), 106. https://doi.org/10.1007/s00894-022-05097-9
2. Alam, F., Shafique, Z., Amjad, S. T., & Bin Asad, M. H. H. (2019). Enzymes inhibitors from natural sources with antidiabetic activity: A review. *Phytotherapy Research*, *33*(1), 41–54. https://doi.org/10.1002/ptr.6211
3. Alejo, A. O., Ajayi, A. M., & Akinyele, B. O. (2019). Comparative Efficacy of Aloe vera (Linn) and Aloe schweinfurthii (Baker) Powdered Leaf Extracts in the Control of Some Plant Fungal Pathogens. *International Journal of Biochemistry Research & Review*, *25*(2), 1–9.

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 06 Issue 07 July 2023
DOI: 10.47191/ijcsrr/V6-i7-06, Impact Factor: 6.789
IJCSRR @ 2023
www.ijcsrr.org

4. Amini, H. W., Rahmawati, I., Darmayanti, R. F., & Susanti, A. (2020). A QSAR study on alkyl nitroderivatives of hydroxytyrosol as antioxidant. *AIP Conference Proceedings*, *2278*(1), 020019.
5. Ananda, H., & Zuhrotun, A. (2017). Aktivitas Tanaman Lidah Buaya (Aloe Vera Linn) Sebagai Penyembuh Luka. *Farmaka*, *15*(2), 82–89.
6. Anugrahini, C. P. H., & Wahyuni, A. S. (2021). Narrative Review: Aktivitas Antidiabetes Tanaman Tradisional Di Pulau Jawa. *Pharmacon: Jurnal Farmasi Indonesia*, 120–131.
7. Atanu, F. O., Avwioroko, O. J., & Momoh, S. (2018). Anti-diabetic effect of combined treatment with Aloe vera gel and Metformin on alloxan-induced diabetic rats. *Journal of Ayurvedic and Herbal Medicine*, *4*(1), 1–5.
8. Bendjedid, S., & Benouchenne, D. (2023). In silico studies for assessing physicochemical, pharmacokinetic and cytotoxicity properties of bioactive molecules identified by LC-MS in Aloe vera leaves extracts. *South African Journal of Botany*, *157*, 75–81. https://doi.org/10.1016/j.sajb.2023.03.052
9. Berbudi, A., Rahmadika, N., Tjahjadi, A. I., & Ruslami, R. (2020). Type 2 Diabetes and its Impact on the Immune System. *Current Diabetes Reviews*, *16*(5), 442–449. https://doi.org/10.2174/1573399815666191024085838
10. Boudreau, M. D., Olson, G. R., Tryndyak, V. P., Bryant, M. S., Felton, R. P., & Beland, F. A. (2017). From the Cover: Aloin, a Component of the Aloe Vera Plant Leaf, Induces Pathological Changes and Modulates the Composition of Microbiota in the Large Intestines of F344/N Male Rats. *Toxicological Sciences*, *158*(2), 302–318. https://doi.org/10.1093/toxsci/kfx105
11. Etxeberria, U., de la Garza, A. L., Campión, J., Martínez, J. A., & Milagro, F. I. (2012). Antidiabetic effects of natural plant extracts via inhibition of carbohydrate hydrolysis enzymes with emphasis on pancreatic alpha amylase. *Expert Opinion on Therapeutic Targets*, *16*(3), 269–297. https://doi.org/10.1517/14728222.2012.664134
12. Hana, F. M. (2020). Klasifikasi Penderita Penyakit Diabetes Menggunakan Algoritma Decision Tree C4.5. *Jurnal SISKOM-KB (Sistem Komputer Dan Kecerdasan Buatan)*, *4*(1), 32–39. https://doi.org/10.47970/siskom-kb.v4i1.173
13. Hawash, M., Jaradat, N., Shekfeh, S., Abualhasan, M., Eid, A. M., & Issa, L. (2021). Molecular docking, chemo-informatic properties, alpha-amylase, and lipase inhibition studies of benzodioxol derivatives. *BMC Chemistry*, *15*(1), 40. https://doi.org/10.1186/s13065-021-00766-x
14. Hayes, A. W., Clemens, R. A., & Pressman, P. (2022). The absence of genotoxicity of a mixture of aloin A and B and a commercial aloe gel beverage. *Toxicology Mechanisms and Methods*, *32*(5), 385–394.
15. Ibrahim, S. R. M., Mohamed, G. A., Khayat, M. T., Ahmed, S., Abo-Haded, H., & Alshali, K. Z. (2019). Mangostanaxanthone VIIII, a new xanthone from Garcinia mangostana pericarps, α-amylase inhibitory activity, and molecular docking studies. *Revista Brasileira de Farmacognosia*, *29*(2), 206–212. https://doi.org/10.1016/j.bjp.2019.02.005
16. Izadpanah, E., Riahi, S., Abbasi-Radmoghaddam, Z., Gharaghani, S., & Mohammadi-Khanaposhtanai, M. (2021). A simple and robust model to predict the inhibitory activity of α-glucosidase inhibitors through combined QSAR modeling and molecular docking techniques. *Molecular Diversity*, *25*(3), 1811–1825. https://doi.org/10.1007/s11030-020-10164-5
17. Kaparakou, E. H., Kanakis, C. D., Gerogianni, M., Maniati, M., Vekrellis, K., Skotti, E., & Tarantilis, P. A. (2021). Quantitative determination of aloin, antioxidant activity, and toxicity of Aloe vera leaf gel products from Greece. *Journal of the Science of Food and Agriculture*, *101*(2), 414–423.
18. Khadse, S. C., Amnerkar, N. D., Dave, M. U., Lokwani, D. K., Patil, R. R., Ugale, V. G., Charbe, N. B., & Chatpalliwar, V. A. (2019). Quinazolin-4-one derivatives lacking toxicity-producing attributes as glucokinase activators: Design, synthesis, molecular docking, and in-silico ADMET prediction. *Future Journal of Pharmaceutical Sciences*, *5*(1), 11. https://doi.org/10.1186/s43094-019-0012-y
19. Khajeeyan, R., Salehi, A., Dehnavi, M. M., Farajee, H., & Kohanmoo, M. A. (2022). Growth parameters, water productivity and aloin content of Aloe vera affected by mycorrhiza and PGPR application under different irrigation regimes. *South African Journal of Botany*, *147*, 1188–1198.
20. La Kilo, J., La Kilo, A., & Hamdiani, S. (2021). QSAR and Ab Initio studies of quinolon-4 (1H)-imine derivatives as antimalarial agents. *Acta Chimica Asiana*, *4*(1), 192–196.
21. Naveen, J., & Baskaran, V. (2018). Antidiabetic plant-derived nutraceuticals: A critical review. *European Journal of Nutrition*, *57*(4), 1275–1299. https://doi.org/10.1007/s00394-017-1552-6
22. Organization, W. H. (2019). *Classification of diabetes mellitus*.

23. Pisani, L., de Candia, M., Rullo, M., & Altomare, C. D. (2022). Hansch-Type QSAR Models for the Rational Design of MAO Inhibitors: Basic Principles and Methodology. In *Monoamine Oxidase: Methods and Protocols* (pp. 207–220). Springer.
24. Saleh Al-Sowayan, N., & Mohammad AL-Sallali, R. (2023). The effect of aloin in blood glucose and antioxidants in male albino rats with Streptozoticin-induced diabetic. *Journal of King Saud University - Science*, *35*(4), 102589. https://doi.org/10.1016/j.jksus.2023.102589
25. Sarker, A., & Grift, T. E. (2021). Bioactive properties and potential applications of Aloe vera gel edible coating on fresh and minimally processed fruits and vegetables: A review. *Journal of Food Measurement and Characterization*, *15*(2), 2119–2134. https://doi.org/10.1007/s11694-020-00802-9
26. Tekulu, G. H., Araya, E. M., & Mengesha, H. G. (2019). In vitro α-amylase inhibitory effect of TLC isolates of Aloe megalacantha baker and Aloe monticola Reynolds. *BMC Complementary and Alternative Medicine*, *19*(1), 206. https://doi.org/10.1186/s12906-019-2622-5
27. Ukwenya, V. O., Adelakun, S. A., & Elekofehinti, O. O. (2021). Exploring the antidiabetic potential of compounds isolated from Anacardium occidentale using computational aproach: Ligand-based virtual screening. *In Silico Pharmacology*, *9*(1), 25. https://doi.org/10.1007/s40203-021-00084-z
28. Wiratama, M. A., & Pradnya, W. M. (2022). Optimasi Algoritma Data Mining Menggunakan Backward Elimination untuk Klasifikasi Penyakit Diabetes. *Jurnal Nasional Pendidikan Teknik Informatika (JANAPATI)*, *11*(1), 1. https://doi.org/10.23887/janapati.v11i1.45282
29. Zhong, R., Chen, L., Liu, Y., Xie, S., Li, S., Liu, B., & Zhao, C. (2022). Anti-diabetic effect of aloin via JNK-IRS1/PI3K pathways and regulation of gut microbiota. *Food Science and Human Wellness*, *11*(1), 189–198. https://doi.org/10.1016/j.fshw.2021.07.019
30. Zhu, M., Su, H., Bao, Y., Li, J., & Su, G. (2022). Experimental determination of octanol-water partition coefficient (KOW) of 39 liquid crystal monomers (LCMs) by use of the shake-flask method. *Chemosphere*, *287*, 132407.