International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 06 Issue 06 June 2023
DOI: 10.47191/ijcsrr/V6-i6-66, Impact Factor: 6.789
IJCSRR @ 2023
www.ijcsrr.org

Potencial of Ursolic Acid Derivatives as Anti Breast Cancer

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ABSTRACT: Breast cancer is one of the biggest contributors to death in the world. Several treatment methods such as chemotherapy, hormonal therapy, radiation therapy, and surgery have shown side effects and resistance to breast cancer. Bioactive compounds are now an alternative in the development of drugs for breast cancer. Pearl grass is one of the plants reported to contain bioactive compounds that have inhibitory activity against breast cancer cells, namely ursolic acid. Most reports describe modifications of groups on its structure increasing the potential of ursolic acid as a breast cancer drug. This study aims to develop breast cancer drugs with raw materials of ursolic acid derivative compounds that are modified on the active side with groups that play an important role as anticancer using the Quantitative Structure and Activity Relationship (QSAR) method and molecular docking. The QSAR descriptors used are hydrophobic, steric, and electronic. The characters of each descriptor were computed using the SwissADME, Molinspiration, and NWChem programs with the DFT method, B3LYP function, and 6-31G* basis set. Molecular docking was performed using the AutoDock Tools 1.5.6 program and visualized using the Biovia Studio Visualizer program. The results showed that the regression coefficient (R^2) of the QSAR model had a high correlation of 0.985 with the compound (1S,2R,4aS,6aR,6bR,10S,12aR,12bR,14bS)-10-amino-1,2,6a,6b,9,9, 12a-heptamethyl-14-oxoicosahydropicene-4a(2H)-carboxylic acid became the best compound validated by the results of molecular docking which has a binding energy of -7.92 kcal/mol and an inhibition constant of 1.42 nM so that it can inhibit MCF-7 cells in breast cancer.

KEYWORDS: breast cancer, molecular docking, pearl grass, QSAR, ursolic acid.

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in 2020, with an estimated total of 2.3 million (11.7%) cases of all cancer in the world. The World Health Organization (WHO) noted that the total cases of cancer in Indonesia in 2020 reached 396,914 cases with a total death of 234,511 people [1]. In 70% of breast cancer cases, estrogen receptor (ER) or progesterone receptor (PR) proteins are found in cancer cells [2]. Several treatment methods currently used for breast cancer patients include chemotherapy, hormonal therapy, radiation therapy, and surgery [3]. However, breast cancer has shown resistance to this therapy and is often associated with side effects. Bioactive compounds from a plant are now an alternative in the development of drugs for breast cancer [4].

Pearl grass is a medicinal plant that has anti-inflammatory, antimalarial, antioxidant, anticancer, and hepatoprotective activities [5]. It has been reported that the ethanol extract of pearl grass exhibits inhibitory activity against human breast cancer cells (YMB-1) with an IC50 of 6.51 mg/ml [6]. In addition, other studies have also revealed that the ethanol extract of pearl grass has a cytotoxic effect on cancer cells and can be developed as a co-chemotherapy agent to increase the effectiveness of breast cancer treatment [7]. Based on its anticancer activity, research revealed that ursolic acid is the main metabolite responsible for anticancer activity in pearl grass [5].

Several reports have extensively explored the pharmacological properties of ursolic acid. In terms of anticancer properties, studies have shown that ursolic acid can modulate cellular transcription factors; growth factor receptors; inflammatory cytokines; and many other molecular targets that regulate cell proliferation, metastasis, apoptosis, angiogenesis, and autophagy of cancer cell lines through different mechanisms and signaling pathways [8]. In previous studies, it has been reported that the active site of ursolic acid is at C-2, C-3 (hydroxyl), and C12-C13 (double bond). Most reports describe the increase in ursolic acid potency by modifying groups at different positions [9]. Various functional groups that play an important role in anticancer activity are methoxy, amine, hydroxy, carbonyl, fluoro, chloro, bromo, and iodo groups [10]. In addition, the process of discovering new breast cancer drugs requires cancer cells as a target. MCF-7 cells are a suitable breast cancer cell line because they have estrogen receptors (ER) or progesterone receptors (PR) which are found in 70% of breast cancer cases in the world [11].

The in silico approach has attracted considerable interest because of its potential to accelerate drug discovery in terms of time, effort, and cost. Many new drug compounds have been successfully developed using computational methods [12]. The in silico tests

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that are often used are QSAR and molecular docking as carried out by Yadav et al, 2019 in determining the potential of ursolic acid derivatives for anticancer activity based on the T24 bladder cell line [13], and by Fadilah and Sanjaya, 2021 in determining the potency of Asiatic acid and its derivatives as anticataract [14].

Related to this, the researchers are interested in conducting breast anticancer activity tests of compounds modified from the ursolic acid structure which are known to have anticancer activity in the breast by combining the QSAR modeling approach and molecular docking. It is hoped that by modifying the structure of ursolic acid, a compound that has greater potential in deactivating MCF-7 cells is expected to be obtained. Until now, no research has been reported related to QSAR studies and molecular docking of ursolic acid derivatives to MCF-7 cells.

MATERIALS AND METHODS

Materials

The materials used in this study are ursolic acid derivative from the modified ursolic acid structure with groups that play an important role as anticancer on the active side based on previous research shown in Table I namely at position C-2 with groups OH, F, Cl, Br, I [15][16], C-3 with OH groups [9], O [16][17][18] and NH_2 [19], C-12 with O groups [18][20] and C-28 with COOH groups [9][17]. The cancer cell protein used in this study was MCF-7 cells with PDB code: 23WL obtained from https://www.rcsb.org.

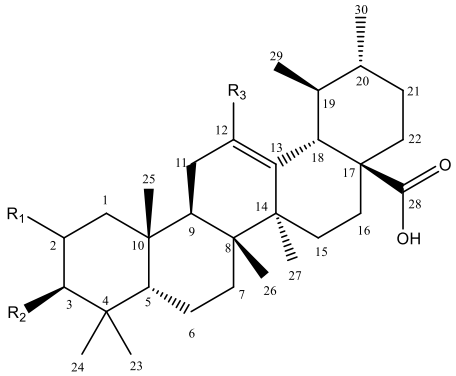

Figure 1. Structure of Ursolic Acid Derivatives

Table I. Ursolic Acid Derivative Compounds

Compound Code	R_1	R_2	R_3
A-1	OH	OH	O
A-2	OH	OH	-
A-3	-	OH	O
A-4	F	OH	O
A-5	F	OH	-
A-6	Cl	OH	O
A-7	Cl	OH	-
A-8	Br	OH	O
A-9	Br	OH	-
A-10	I	OH	O
A-11	I	OH	-
A-12	OH	O	O
A-13	OH	O	-
A-14	-	O	O
A-15	-	O	-
A-16	F	O	O

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A-17	F	O	-
A-18	Cl	O	O
A-19	Cl	O	-
A-20	Br	O	O
A-21	Br	O	-
A-22	I	O	O
A-23	I	O	-
A-24	OH	NH_2	O
A-25	OH	NH_2	-
A-26	-	NH_2	O
A-27	-	NH_2	-
A-28	F	NH_2	O
A-29	F	NH_2	-
A-30	Cl	NH_2	O
A-31	Cl	NH_2	-
A-32	Br	NH_2	O
A-33	Br	NH_2	-
A-34	I	NH_2	O
A-35	I	NH_2	-

Methods

Determination of Ursolic Acid Compounds in Pearl Grass Extract

Pearl grass obtained from Sidoarjo Regency as much as ± 2 kg was cleaned from impurities and dried. The dried pearl grass was then powdered and obtained ± 250 grams of pearl grass powder and macerated using 96% ethanol in a 1: 1 ratio for three days with frequent stirring. After three days, filtered and re-macerated for two days. The juice obtained was evaporated using a rotary evaporator and identification of ursolic acid compounds was carried out using a Liquid Chromatography Mass Spectrometry (LCMS) instrument [21].

QSAR

The structures of ursolic acid compounds identified in the LCMS test were drawn using the Chemdraw program and group modifications were made at the positions shown in Table I. Then compounds were selected that meet Lipinski's law and LD50 category III with the help of the pKCSM program. Compounds that passed the selection were geometry optimized using the Avogadro program and their descriptor values were calculated. The calculation of hydrophobic and steric descriptors used SwissAdme and MolInspiration programs while the calculation of electronic descriptors used Avogadro and NWChem programs with the DFT method, B3LYP function and 6-31G* basis set. The calculation results of all descriptors were analyzed by multiple linear regression with the backward method using the SPSS 25.0 program which will produce an QSAR model equation for ursolic acid derivative compounds. The best QSAR equation model was selected based on the R^2 value which is close to 1, as well as SEE (Standard Error of Estimate) and PRESS (Predictive Residual Sum of Squareter) which is close to 0 which is then used to determine which ursolic acid-derived compounds have more potential as breast anticancer drugs. Table II shows the parameters used to determine the QSAR equation of ursolic acid derivative compounds.

Table II. QSAR Parameters

Descriptor	Symbols	Description
Hydrophobic	Log P	Partition Coefficient
Steric	MW	Molecular Weight
	SA	Surface Area
	TPSA	Topology Polar Surface Area
	V	Volume

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	Homo	Homo Energy
	Lumo	Lumo Energy
Electronic	ΔLumo-Homo	Lumo - Homo Energy Gap
	H	Hydration Energy
	DM	Dipole Moment

Molecular Docking

Molecular docking was performed using Autodock Tools 1.5.6 program. by optimizing the breast cancer target structure with PDB code : 2W3L and saved in (.pdbqt) format, then optimizing ursolic acid derivative compounds saved in (.pdbqt) format. After that, adjusting the grid box settings and saved in (.gpf) format to determine the location of the ligand and target binding, then determining the docking parameters stored in (.dlg) format and calculated the lowest binding energy value and inhibition constant using Ubuntu 20.04.2. Determination of amino acids in the active side using Biovia Discovery Studio program.

RESULTS AND DISCUSSION

Result of LCMS Test

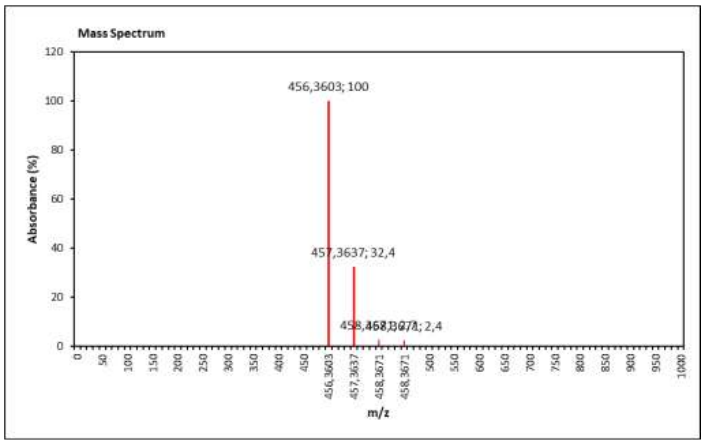

Figure 2. LCMS Test Result of Pearl Grass

The LCMS test shows that ursolic acid is a compound that has a relative molecular mass of 456.303 with an area of 846.36525 which is identified at the 46th peak, RT 23.519 with a composition of 0.80188%. Thus proving that ursolic acid compounds are contained in pearl grass plants. The structure of ursolic acid compounds identified in the LCMS test was drawn using the Chemdraw 15.0 program and group modifications were made so as to produce a series of ursolic acid derivative compound structures.

Selection Results of Ursolic Acid Derivative Compounds Based on Lipinski's Rule of Five and LD50 Category III

The ursolic acid-derived compounds obtained need to be selected to fulfill Lipinski's law and LD50 category III before entering the QSAR stage. It is pertinent that according to Lipinski's "Rule of Five", an orally active drug should not have more than one violation of the rule because poor drug absorption is more likely to occur when the chemical structure has a molecular weight greater than 500 Da, a calculated log P value greater than 5, has more than 5 hydrogen bond donors and has hydrogen bond acceptors greater than 10 [22]. In addition, compounds that are considered in silico and feasible to synthesize and continue with their activity tests in vitro and in vivo are compounds that have the best activity and do not have hepatotoxic effects and high toxicity effects, where these compounds are generally compounds with LD50 category III (slightly toxic) with an LD50 range of 500 < LD50 ≤ 5000 mg/kg [23][24][25][26]. Compounds that have gone through the selection stage are 20 compounds with codes A-1, A-2, A-3, A-4, A-5, A-7, A-12, A-1, A-14, A-15, A-16, A-17, A-19, A-24, A-25, A-26. A-27, A-28, A-29 and A-31.

Results of QSAR

Compounds that have gone through the selection stage are geometry optimized and the hydrophobic, steric and electronic descriptor values of the compounds are calculated which are used to model the QSAR equations shown in Table III.

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Table III. Descriptor Value of Ursolic Acid Derived Compounds

Compound Code	Log P	MW	SA	TPSA	V	Homo	Lumo	Δ Lumo-Homo	H	MD
A-1	4,96	488,70	210,99	94,83	487,93	-0,2615	-0,0139	0,2476	24,23	0,67
A-2	5,87	472,71	206,14	77,75	479,53	-0,2355	0,0363	0,2718	19,59	1,26
A-3	5,87	472,71	206,20	74,60	479,88	-0,2584	-0,0012	0,2572	21,77	4,15
A-4	5,89	490,70	210,37	74,60	484,84	-0,2594	-0,0012	0,2582	24,74	2,88
A-5	6,80	474,70	205,51	57,53	476,45	-0,2442	0,03024	0,2745	18,78	1,58
A-7	7,11	491,15	210,36	57,53	485,05	-0,2356	0,03689	0,2724	20,04	1,32
A-12	4,77	486,69	205,51	91,67	482,06	-0,2620	-0,0105	0,2514	27,16	4,14
A-13	5,69	470,69	205,57	74,60	473,67	-0,2443	-0,0288	0,2155	23,15	2,62
A-14	5,69	470,69	209,73	71,44	474,02	-0,2610	-0,0097	0,2513	24,80	2,44
A-15	6,60	454,69	204,88	54,37	465,63	-0,2356	-0,0101	0,2726	20,58	3,77
A-16	5,70	488,68	211,54	71,44	478,98	-0,2621	-0,0094	0,2526	28,87	4,32
A-17	6,62	472,68	204,88	54,37	470,58	-0,2440	-0,0378	0,2062	20,88	4,87
A-19	6,92	489,14	211,02	54,37	479,19	-0,2356	-0,0098	0,2258	22,23	4,90
A-24	4,46	487,72	206,69	100,62	491,2	-0,2594	-0,0012	0,2581	26,11	4,78
A-25	5,38	471,72	206,75	83,55	482,8	-0,2454	0,0315	0,2769	19,10	2,68
A-26	5,38	471,72	210,91	80,39	483,15	-0,2591	-0,0014	0,2577	22,46	2,91
A-27	6,30	455,72	201,89	63,32	474,76	-0,2356	0,0369	0,2725	15,26	1,92
A-28	5,39	489,71	210,91	80,39	488,11	-0,2603	-0,0012	0,2591	24,14	1,95
A-29	6,31	473,71	206,06	63,32	479,72	-0,2444	0,0298	0,2743	19,76	2,87
A-31	6,62	490,17	212,20	63,32	488,32	-0,2355	0,0370	0,2726	16,38	2,93

The descriptor values of the selected ursolic acid-derived compounds were statistically analyzed using backward method multiple linear regression using SPSS 25.0 program with hydrophobic descriptor or Log P as dependent variable and steric and electronic descriptors as independent variables. Log P served as the dependent variable as it is a parameter that plays an important role in drug discovery and compound design. Models that predict log P have been used and noticed to facilitate the drug design process which has helped in the development of other predictions [27]. In addition, Log P has been reported to have a significant influence on various pharmacokinetic properties such as absorption, distribution, excretion and permeability of drugs [28]. Statistical processing in this study resulted in six model equations shown in Table IV.

Table IV. Results of Multiple Linear Regression Analysis Backward Method of Ursolic Acid Derivative Compounds

Model	Variable	R	R^2	SEE	PRESS
1	DM, SA, Homo, ΔLumo-Homo, TPSA, H, V, MW	0,992	0,985	0,101194	0,15
2	DM, SA, Homo, TPSA, H, V, MW	0,992	0,985	0,114333	0,53
3	DM, SA, Homo, TPSA, H, MW	0,992	0,985	0,110530	1,32
4	DM, Homo, TPSA, H, MW	0,992	0,985	0,106709	0,17
5	DM, TPSA, H, MW	0,991	0,982	0,111676	0,88
6	TPSA, H, MW	0,989	0,979	0,117694	0,23

An acceptable model is a model with a small PRESS value, meeting the prediction R^2 criteria > 0.6 and SEE < 0.3 with a good R^2 value of more than 0.8 or close to 1 [29]. In Table IV, equation models 1-6 are known to have met the requirements because with a 95% correctness level they have a small PRESS value which is close to 0, has a good R^2 value of more than 0.8 and SEE value < 0.3. Model equation 1 is the best model because it has an R^2 value close to 1, as well as SEE and PRESS close to 0 from the six models that can be written with the following equation:

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Log P = 6.624 + (0.016*MW) + (-0.023*SA) + (-0.048*TPSA) + 0.005*V) + (8.315*Homo) + (0.443*ΔLumo-Homo) + (-0.020*EH) + (-0.038*MD)

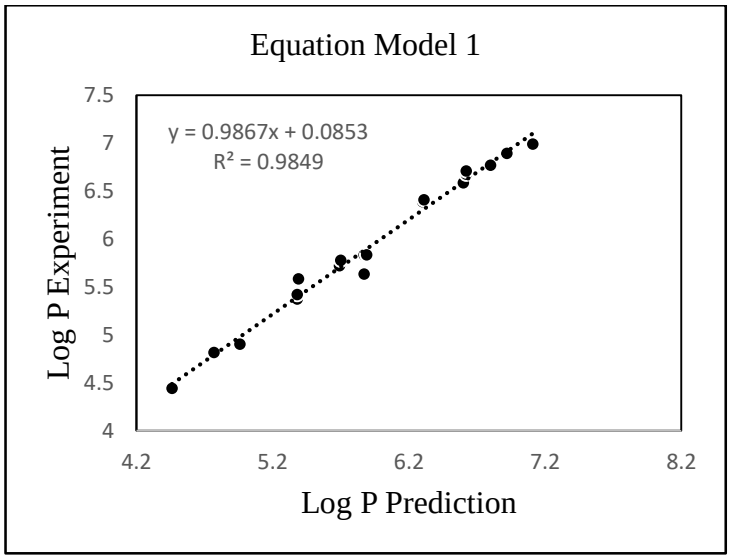

Figure 3. Graph of Equation Model 1

Drug development is required to have a high Log P value to meet the required selectivity and potency of the drug. Such demands arise as a result of the lipid properties of biological targets. For example, neurotransmitter pathway targets, anatomical targets, and/or intracellular targets require hydrophobic properties to achieve the desired action [30]. The larger or more positive the log P value, the more hydrophobic the molecule is and vice versa [31]. In general, more hydrophobic compounds are less soluble in aqueous media. However, hydrophobic compounds have good solubility in oils and lipids, therefore, they can be good candidates for lipid-based formulations [27]. Molecules that are too hydrophobic can be unfavorable because they will be retained longer on the lipid bilayer membrane and thus tend to have higher toxic properties. However, log P values that are too negative or too hydrophilic are also unfavorable, as the molecule becomes difficult or even unable to pass through the lipid bilayer membrane [31].

Based on the log P parameter, ursolic acid-derived compounds are hydrophobic because they have positive log P values, so they have good binding selectivity to target proteins and include compounds in the slightly toxic category based on LD50 values. Based on correlation analysis, it can be seen that the descriptors of dipole moment, surface area, homo, Δlumo-homo, tpsa, hydration energy, volume, and molecular weight to the Log P value show a very high correlation as shown by the regression value of 0.985.

The Log P PRESS value of each compound based on model equation 1 is then calculated to determine how good the prediction level is for the log P biological activity value of the experimental results [32]. The compound that has the highest level of prediction with a value close to 0, then the compound is the best compound based on the QSAR model [33]. The PRESS value of each compound is obtained from the subtraction of the experimental log P value from the squared log P value of model 1 prediction [34].

Table V. PRESS Value of Ursolic Acid Derived Compounds

Compound Code	Log P Experiment	Log P Prediction Model 1	PRESS
A-1	4,96	4,90	0,0036
A-2	5,87	5,83	0,0016
A-3	5,87	5,63	0,0576
A-4	5,89	5,83	0,0036
A-5	6,80	6,76	0,0016
A-7	7,11	6,98	0,0169
A-12	4,77	4,81	0,0016

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www.ijcsrr.org

A-13	5,69	5,71	0,0004
A-14	5,69	5,71	0,0004
A-15	6,60	6,58	0,0004
A-16	5,70	5,77	0,0049
A-17	6,62	6,67	0,0025
A-19	6,92	6,89	0,0009
A-24	4,46	4,44	0,0004
A-25	5,38	5,41	0,0009
A-26	5,38	5,37	0,0001
A-27	6,30	6,38	0,0064
A-28	5,39	5,58	0,0361
A-29	6,31	6,40	0,0081
A-31	6,62	6,71	0,0081

Based on the PRESS value, it is known that the best compound based on QSAR analysis is the compound with code A-26 with a value of 0.0001 which is the smallest value of the PRESS value of 20 compounds that have gone through the selection stage. So that compound A-26 is a compound that has the highest level of prediction of the biological activity value of log P experimental results.

Result of Molecular Docking

Molecular docking of ursolic acid-derived compounds with MCF-7 cells with PDB code: 2W3L aims to determine which ursolic acid-derived compounds have more potential as breast anticancer drugs to further validate the best compounds based on QSAR. Molecular docking is associated with the terms ligand and protein. Proteins are target sites where ligands can bind to exert specific activities. Molecular docking provides information about the ability of the ligand to bind to the protein known as binding energy [35]. The results of molecular docking can be analyzed by the binding energy value, inhibition constant, and amino acid residues of the test ligand [36].

Table VI. Molecular Docking Results of Ursolic Acid Derived

Compound Code	Binding Energy	Inhibition Constant	Amino Acid Residue
Ursolic Acid	-6,75	11,37	Phe63, Val92, Met74, Phe71, Leu96, Ala108
A-1	-6,72	11,84	Val92, Phe71,Phe112, Phe63, Leu96, Ala108, Arg68, Arg105, Tyr67
A-2	-6,86	9,43	Arg105, Leu96, Ala108, Tyr67, Phe71, Phe63, Asp70, Met74
A-3	-7,29	4,51	Arg26, Arg66, Arg68, Phe63, Tyr161, Gly104
A-4	-7,11	6,09	Phe63, Gly104, Tyr161, Arg66, Arg68, Arg26, Lys22
A-5	-7,13	5,98	Arg68, Arg105, Ala108, Phe63, Leu96, Met74, Phe71, Tyr67
A-7	-7,28	4,58	Val107, Phe63, Tyr67, Arg66, Tyr161, Pro163, Leu160, Ala72
A-12	-7,24	4,93	Ala72, Tyr161, Ser64, Lys22, Arg26, Val115, Phe71, Arg68
A-13	-7,18	5,49	Met74, Phe71, Tyr67, Ala108, Phe63, Arg68, Arg105, Leu96
A-14	-7,62	2,59	Val115, Phe71, Arg68, Ala72, Tyr161, Arg66, Lys22, Arg26, Ser64
A-15	-7,61	2,63	Arg105, Tyr67, Ala108, Phe63, Met74, Leu96
A-16	-6,97	7,75	Arg68, Arg105, Tyr161, Tyr67, Phe63
A-17	-7,61	2,63	Arg105, Phe63, Ala108, Leu96, Met74, Phe71, Tyr67
A-19	-7,79	1,94	Arg105, Tyr67, Phe63, Ala108, Leu96
A-24	-7,27	4,68	Pro163, Leu160, Gly162, Ala72, Tyr67, Phe63, Arg66, Tyr161
A-25	-7,41	3,72	Arg105, Ala108, Phe63, Val92, Glu95, Leu96
A-26	-7,98	1,42	Arg68, Arg26, Ser64, Arg66, Asp62
A-27	-8,29	839,08	Arg68, Asn102, Arg105, Phe63, Arg66, Ala59, Tyr161

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A-28	7,68	2,33	Arg68, Arg26, Ser64, Arg66, Asp62
A-29	-8,21	956,67	Val92, Glu95, Lau96, Phe63, Arg68, Arg105, Ala108
A-31	-7,89	1,66	Val107, Phe63, Tyr67, Arg66, Tyr161, Pro163, Leu160, Ala72

The strength of ligand binding is determined by the Gibbs free energy change, which is the sum of the enthalpy change (ΔH) and entropy change (T.ΔS) [37]. Binding energy is useful to show the strength of the association between the ligand and the protein. Where the association will be stronger and more stable when the binding energy value is lower and vice versa. [38].

The inhibition constant (Ki) is the concentration of inhibitor required to reduce the maximum rate of reaction to half [39]. Inhibitors with Ki values less than 100 μM are considered potent inhibitors. Inhibitors with Ki values higher than 100 μM are considered nonpotent inhibitors [40]. The smaller the inhibition constant value, the better and more effective the inhibitory activity [41]. The interaction between the ligand and the protein can be visualized from the amino acid residues of the molecular docking result which shows the active side of the protein bound by the ligand [42].

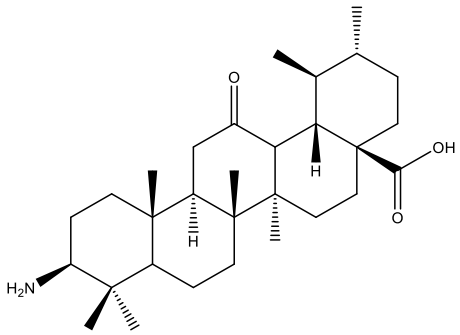

Figure 4. Structure of Compound A-26 (1S,2R,4aS,6aR,6bR,10S,12aR,12bR,14bS)-10-amino-1,2,6a,6b,9,9,12a-heptamethyl-14-oxoicosahydropicene-4a(2H)-carboxylic acid

Based on the results of molecular docking, it can be seen that the ursolic acid derivative compound that has the best inhibitory activity is compound A-26 shown in Figure 4. with a binding energy of -7.92 and an inhibition constant of 1.42. This value has a lower value than the main compound, ursolic acid with a binding energy of -6.75 and an inhibition constant of 11.37. So that compound A-26 is a better candidate for breast anticancer drugs than the ursolic acid compound.

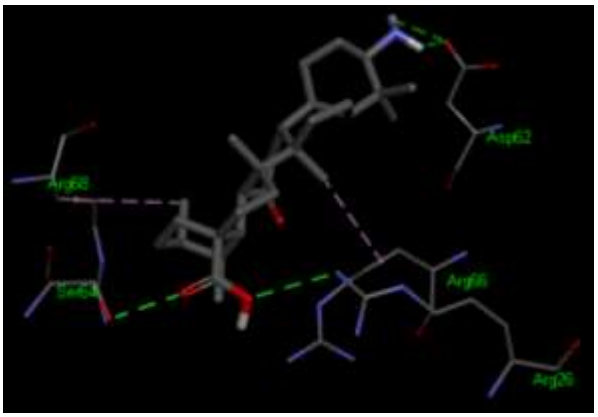

Figure 5. Visualization of Molecular Docking Results of Compound A-26 (1S,2R,4aS,6aR,6bR,10S,12aR,12bR,14bS)-10-amino-1,2,6a,6b,9,9,12a-heptamethyl-14-oxoicosahydropicene-4a(2H)-carboxylic acid with MCF-7 cells

Figure 5 shows the active side of MCF-7 cells that binds to compound A-26, namely amino acid residues Arg68, Arg26, Ser64, Arg66 and Asp62. The results obtained from molecular docking validate the results of QSAR which states that the best ursolic acid derivative compound as a breast anticancer drug candidate is compound A-26 (1S,2R,4aS,6aR,6bR,10S,12aR,12bR,14bS)-10-amino-1,2,6a,6b,9,9,12a-heptamethyl-14-oxoicosahydropicene-4a(2H)-carboxylic acid.

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 06 Issue 06 June 2023
DOI: 10.47191/ijcsrr/V6-i6-66, Impact Factor: 6.789
IJCSRR @ 2023
www.ijcsrr.org

CONCLUSION

Based on the results of the research conducted, it can be concluded that the regression coefficient (R^2) of the QSAR model shows a high correlation of 0.985 with the compound (1S,2R,4aS,6aR,6bR,10S,12aR,12bR,14bS)-10-amino-1,2,6a,6b,9,9, 12a-heptamethyl-14-oxoicosahydropicene-4a(2H)-carboxylic acid became the best compound validated by the results of molecular tethering which has a binding energy of -7.92 kcal/mol and an inhibition constant of 1.42 nM so that it can inhibit MCF-7 cells in breast cancer.

ACKNOWLEDGEMENTS

Thanks to the Department of Chemistry, Surabaya State University, which has provided computational chemistry laboratory facilities so that this research can be completed properly.

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International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 06 Issue 06 June 2023
DOI: 10.47191/ijcsrr/V6-i6-66, Impact Factor: 6.789
IJCSRR @ 2023
www.ijcsrr.org

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Cite this Article: Mas Idatul Umah, I Gusti Made Sanjaya (2023). Potencial of Ursolic Acid Derivatives as Anti Breast Cancer. International Journal of Current Science Research and Review, 6(6), 3772-3782