Chempublish Journal
Journal Homepage: online-journal.unja.ac.id/chp
Department of Chemistry
Faculty of Science and Technology
Universitas Jambi
ISSN (Online): ISSN 2503-4588
No. 23/E/KPT/2019

Article

Molecular Docking Study of Chalcone Analogue Compounds with Hydroxy and Methoxy Subtituents as Bcl-2 Inhibitors

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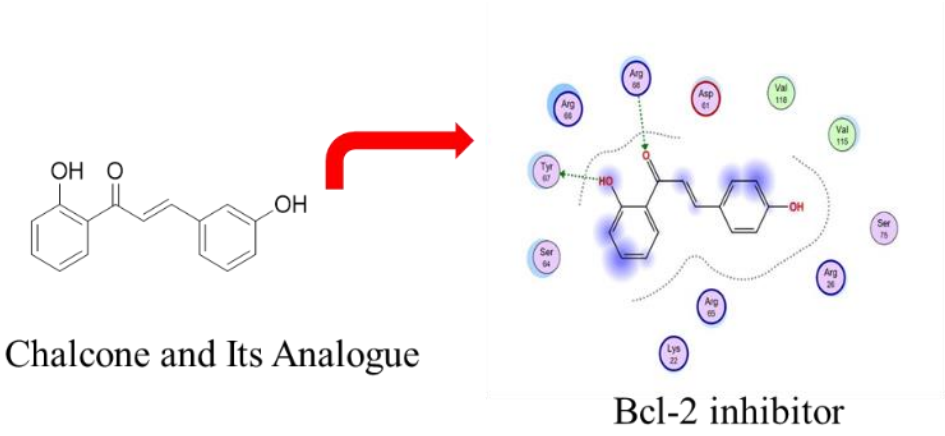
Abstract

Molecular docking study of 6 chalcone analogues with protein target from the crystallographic structure modeling of Bcl-2 protein with PDB code 2W3L was carried out using computational media using the Molecular Operating Environment (MOE) program. The aim of this study is to determine the potentiality of the 6 chalcone analogue compounds as Bcl-2 inhibitors using molecular docking studies. In this study, venetoclax was used as positive control. Based on docking results, binding free energy was used as information to know which wheather chalcone analogue compounds are active or not as Bcl-2 inhibitors. According to the docking results that have been carried out, it showed that the 6 chalcone analogue compounds have no potential as Bcl-2 inhibitors. Due to the superimposition of the 6 compounds that did not stick to the positive control and most importantly the binding free energy values (S) of the 6 chalcone analogue compounds were higher than the binding free energy values of the positive control (Venetoclax).

Keywords: *chalcone analogue compound, molecular docking, venetoclax , Bcl-2 inhibitors*

Graphical Abstract



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DOI: 10.22437/chp.v7i1.17487
Received 16 March 2022; **Accepted** 12 May 2023; **Available online** 30 July 2023

Introduction

Cancer is a group of diseases characterized by uncontrolled cell division and the ability of these cells to invade other biological tissues, either by direct growth in adjacent tissues (invasion) or by migration to a more distant place distant (metastatic) [1]. Cancer or well known as a malignant tumor is abnormality genetic cause change function or expression of genes that regulate cellular processes like growth, survival life and aging. Damage genetics can caused by materials chemical, radiation , agent microbe or Possible inherited (mutation *germline*) [2].

Breast cancer is one of the most common types of cancer suffered by the world's population. Based on dat a Global Cancer Observatory [3] from World Health Organization (WHO) points out case new cancer highest in the world i.e. cancer breast as many as 2.261.419 case new (11.7%) and 684.996 case death (6.95%). Case numbers of new cancer boobs in Asia i.e. 1.026.171 (10.8%), with case death 346.009 (6.0%). In Indonesia, there were 65.858 new cases of breast cancer (16.6%) and 22.430 (9.6%) cases of death [3].

Breast cancer is a group of diseases in which cells in the breast tissue change and divide in an uncontrolled manner, usually resulting in a lump or mass. Various kinds of cancer treatment have been carried out including surgery, radiation, use of anticancer drugs or chemotherapy. However, all these efforts have not yielded satisfactory results, and even the effects of failure of therapy and surgery have caused cancer cells to spread to other parts of the body [4].

In the treatment of breast cancer drug therapy is very expensive, so people prefer to use traditional medicine. This is because traditional medicine has low side effects. In addition to these conventional treatments , the community has also tried many alternative treatments using natural ingredients (natural medicines) obtained from nature [5]. One of the compounds derived from plants and has anticancer properties is the chalcone compound , this is reinforced by previous studies (Pratoko et al.[6], Mahapatra, et al.[7], and Oktaviani et al.[8]) who has conducted research for anticancer tests using the in-silico method.

Kalkon is compound precursor from class of flavonoids and is intermediates important in synthesis organic, like compound heterocyclic (flavones, flavanols, flavanons). Chalcone has been widely developed and synthesized to obtain its derivatives and to test its pharmacological activity. Besides being caused by the presence of unsaturated α β groups, the bioactivity of chalcone compounds is also influenced by the substituents attached to the two aromatic rings [9]. The substituents present in the two aromatic rings of the chalcone greatly affect the activity of the chalcone compound, such as the presence of a methoxy group in ring A affecting the anticancer activity [10]. Suwito et al.[11] compared the effect of the methoxy position on the B ring at positions C2, C3, and C4 on the activity of chalcone as an anticancer. This study showed that the methoxy group was most active as an anticancer at the C4 position. In the studies by Mai et al. , and Anwar et al.[12] the presence of a hydroxy group in ring A also shows potential activity as an anticancer agent.

In a study of Oktaviani et al. in 2019 it was stated that the chalcone compound is a strong candidate as a compound with great potential to be used as an anticancer drug [8]. One approach to the activity of chalcone compounds can be done with computational chemistry such as molecular docking. molecular docking is one of the computational methods used as a structure-based new drug discovery that measures the bond free energy between small molecules (ligands) and macromolecular targets (proteins) [13].

Molecular Docking can be used to predict whether a compound is active or not, such as chalcone derivatives. There are several advantages of the molecular method this docking, in between it is able to reduce the use of excessive tools and materials as well as save in financing, molecular docking can also be used to predict the activity of a compound that will interact with the active site of a protein [14].

Observation of molecular data results docking among them are the bond free energy involved in the process of ligand interaction with the receptor, the RMSD value, as well as the chemical bonds that are formed such as hydrogen bonds, van der Waals bonds, and bond hydrophobic [15,16].

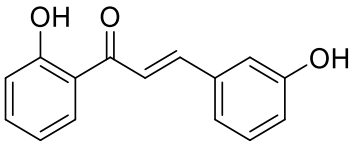
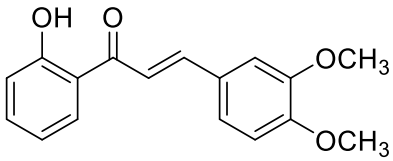
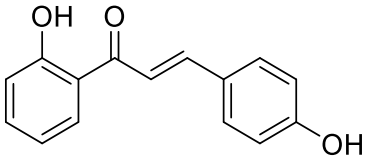
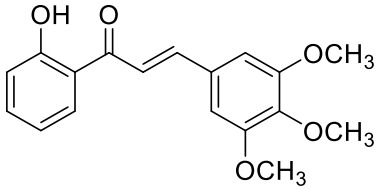
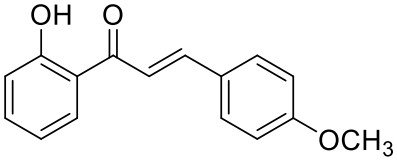
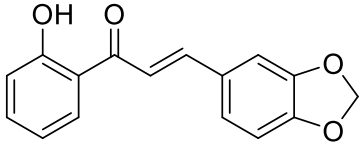
In breast cancer patients, Bcl2 levels have increased, Bcl-2 is a family of anti-apoptotic agents, this causes cells to not undergo the process of apoptosis. One of the drugs used in breast cancer chemotherapy is venetoclax. In breast cancer therapy venetoclax is used as a combination of cancer drugs in breast cancer therapy, venetoclax is a drug that works selectively by inhibiting Bcl-2 target protein by inhibiting Bcl-2 so that the apoptosis process can take place and the number of cancer cells can be reduced [17,18], this is a reference for authors using venetoclax as a positive control in docking simulations. In this study, a follow-up study was conducted on 6 chalcone analogues to determine the compound with the best bioactivity as a Bcl-2 inhibitor using in silico studies, namely molecular docking. The purpose of this study was to determine whether 6 chalcone analogues have potential as Bcl-2 inhibitors in T47D breast cancer cells.

Experimental Section

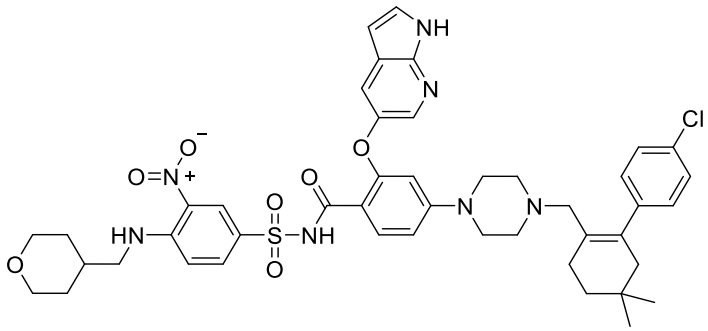
Materials

The materials used in molecular docking consists of a 2W3L target protein structure with PDB format. The ligand structures used are 6 chalcone analogue compounds that have been synthesized by Prieto-Martinez et al.[19] and venetoclax as a positive control (Table 1).

Tabel 1. Structure of 6 chalcone analogues and positive control (Venetoclax).

Code	Structure	Code	Structure
MC 7	 *(E)-1-(2-hydroxyphenyl)-3-(3-hydroxyphenyl) prop-2-en-1-one*	**MC 10**	 *(E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one*
MC 8	 *(E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one*	**MC 11**	 *(E)-1-(2-hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one*
MC 9	 *(E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one*	**MC 12**	 *(E)-3-(benzo[d][1,3]dioxol-5-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one*

MA 7



4-[4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohexen-1-yl]methyl]piperazine-1-yl]-N-[3-nitro-4-(oxan-4-ylmethylamino)phenyl]sulfonyl-2-(1H-pyrrolo[2,3-b]pyridine-5-yloxy)benzamide

Instrumentation

The tools used in this study consisted of computer hardware LG Intel (R) Core (TM) i7-8700 CPU, 3.20 GHz, with 16.0 GB of RAM. The software used on the computer is the *Chemdraw Professional* 15.0 program and the *Molecular program Operating Environment* (MOE) 2020. (*Chemical Computing Group*). All programs run with *Operating System Windows* 10 *Pro* 64 *bit*.

Procedure

Draw all the ligands on the chemdraw software after that it was *copied* to MOE and stored as a ligand database, the protein was downloaded and prepared on DSV and MOE software. After that, docking was done using MOE. Data analysis from molecular docking is based on energy free bond (S, kcal/mol) and RMSD values obtained from docking results are displayed in tabular form, image results are displayed in 2D and 3D. Then, the interaction between the ligand and the amino acids in the target protein was analyzed to determine the suitability of the amino acid to the venetoclax (positive control) and to observe the types of interactions that occur between the ligand and the receptor, such as hydrogen bonds, van der Waals bonds, and hydrophobic bonds.

Results and Discussions

The resulting porous ceramics

Docking results can be seen in Table. 2, for the bond-free energy value, the smaller the value, the better the pose of the ligand [20] and for the RMSD value, the smallest value of RMSD will be taken with a value limit of ≤ 2 Å, according to Prieto-Martínez et al.[19]. The docking method is said to be valid if it has an RMSD value of ≤ 2 Å. The RMSD value indicates that the deviation or error value occurs when docking. The smaller the RMSD value, the smaller the deviation or error that occurs when docking.

In addition, another parameter that must be considered is the bond free energy which is the energy required by a ligand to bind to its protein (receptor). The smaller the bond free energy value, the more difficult the interaction between the ligand and the protein can be released. This indicates that the ligand-protein complex is increasingly stable [21].

Hydrogen bonds are also considered because in general the molecular interactions that occur in the body are in the form of non-covalent interactions because non-covalent interactions help stabilize the macromolecular structure in cells. Hydrogen bonds are non-covalent bonds. Non-covalent interactions are interactions that are formed from the sharing of two electrons by two atoms. Hydrogen bonds involve the interaction of positively charged hydrogen atoms with electronegative atoms such as Flour (F), Nitrogen (N), and Oxygen (O) [22]. In addition, hydrogen bonds can also be formed between the H atom and the phenyl ring present in a drug compound [23].

Tabel 2. Docking results of chalcone analogues to the Bcl-2 target protein.

No	Code Compound Test	Parameter						
		Bond Free Energy (kcal/mol)	RMSD	Bond H	Interaction van der Waals	Interaction Other	Interaction Hydrophobic	Similarity Amino acid
1	**Venetoclax** (Control Positive)	**-8.9474**	**1.4288**	**ARG26, TYR67**	**GLU119, ASP62, GLU58**	**SER75, PRO163, LEU160, SER76, TYR161, ALA59, ALA72, GLY104, PHE63, PHE71, SER64**	**LYS22, ARG66, ARG65 ARG68, ARG69**	**-**
2	**MC7**	-4.7534	1.4349	**ARG66**	ASP61, **GLU119**	VAL115, VAL118, **SER75, TYR67, SER64**	**ARG26, ARG65, LYS22, ARG68**	9
3	**MC8**	-4.7707	1.5923	**ARG68, TYR67**	ASP61	VAL118, VAL115, **SER75,** SER64	**ARG66, LYS22, ARG65, ARG26**	7
4	**MC9**	-4.6253	1.5738	**ARG68**	**GLU119,** ASP61	VAL118, **SER64, TYR67,** VAL115, **SER75,** ASN122	ARG65, **ARG66, ARG26**	7
5	**MC10**	-4.7726	1.5402	**ARG66, ARG26**	ASP61, **ASP62**	**SER64,** ASN122	**LYS22, ARG65**	6
6	**MC11**	-5.1537	1.3197	**-**	**ASP62, GLU119**	**PHE63** , VAL107, **ALA59,** VAL115, VAL118, **PHE71, ALA72, SER75, GLY104, TYR161**	**ARG68, ARG26, ARG66**	12

Van der Waals bonds and hydrophobic bonds are also considered as supporting parameters to determine the stability of the ligand to the receptor so that a compound can be identified as having potential as an inhibitor for a type of disease.

In this study venetoclax was used as a positive control in the docking process. Venetoclax has another name Venclexta and has a tablet dosage form. In the treatment of breast cancer, venetoclax is combined with tamoxifen (20 mg) and venetoclax (200-800 mg) per day [24] The mechanism of action of venetoclax is that it works by inhibiting Bcl-2. Venetoclax works by inhibiting anti-apoptotic Bcl-2 protein by binding to anti-apoptotic Bcl-2 protein thereby preventing anti-apoptotic Bcl-2 protein from binding to BAX/BAK which is a family of pro-apoptotic Bcl-2 proteins. With the binding of anti-apoptotic Bcl-2 by venetoclax, BAX/BAK can activate the cell death process by releasing cytochrome c from mitochondria and activating caspase [25]. The structure of venetoclax has no similarity to the 2W3L protein-inherent ligand, so the docking process was carried out using the blind docking method. Blind docking is a docking method that does not determine the active site on the 2W3L protein [26].

Docking results from venetoclax showed that venetoclax has a bond free energy of -8.9474 kcal/mol and RMSD value of 1.4288. The hydrogen bonds that are formed are found in the amino acid residues Arg-26, Tyr-67. Van der Waals bonds are formed with the amino acid residues Glu-119, Asp-62, Glu-58. Hydrophobic bonds are formed at the amino acid residues Lys-22, Arg-66, Arg-65, Arg-68, Arg-69. The interactions that occur through bonds between ligands and other bonds are formed on the amino acid residues Ser-75, Pro-163, Leu-160, Ser-76, Tyr-161, Ala-59, Ala-72, Gly-104, Phe-63, Phe-71, Ser-64. This data shows the similarity of amino acids in other studies which have tested active in 2W3L proteins where the residues of the same amino acids are Tyr-67, Phe-63, Phe-71 [25].

Based on the results of the docking of the **MC7** compound (Figure 1), the bond free energy value was -4.7534 kcal/mol and the RMSD value was 1.4349. In these data compound 1 (**MC7**) has the same interaction of 9 amino acid residues with the positive control (Venetoclax), where the hydrogen bonds in **MC7** are formed at the Arg-66 amino acid residue, while in the positive control the hydrogen bonds are formed at the Arg-26 and Tyr-67 amino acid residues so that this compound does not have the same hydrogen bonds with the positive control. In the van der Waals bond, the **MC7** compound has one thing in common with positive control, namely the Glu-119 amino acid residue. The bond free energy produced by **MC7** is higher than the positive control, this too large difference in bond free energy causes the **MC7** compound to be difficult to bind to the active site of the receptor. Based on this, the **MC7** compound cannot be categorized as a compound that has the potential to act as a Bcl-2 inhibitor. Visualization of compound bonds with proteins as shown in Figure 2.

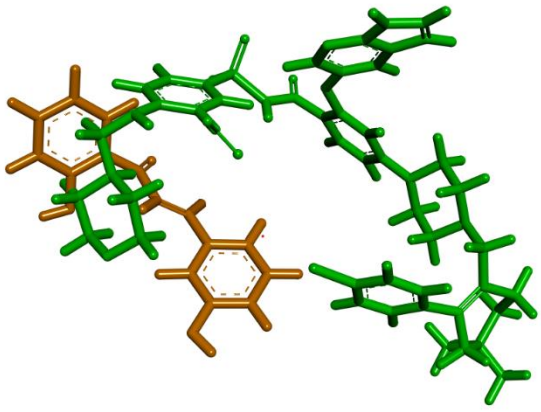
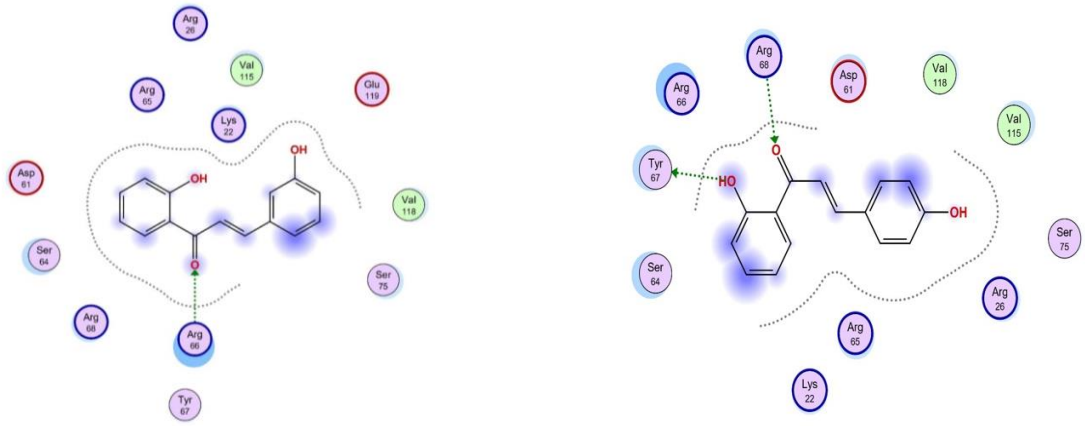


Figure 1. Visualization Results of **MC7** Compound Superimposition (Yellow) and Positive Control (Green).



(a) **(b)**

Figure 2. Visualization molecular docking of (a) compound 1 (MC7) and (b) compound 2 (MC8).

The docking results of compound 2 (**MC8**) on the target protein (2W3L) showed that the compound had a binding free energy value (kcal/mol) of -4.7707 and an RMSD value of 1.5923 (Figure 3). Compound 2 (**MC8**) has the same interaction of 7 amino acid residues with the positive control (Venetoclax). In the van der Waals bond, compound 2 (**MC8**) does not have the same amino acid as the positive control. The hydrogen bonds formed in **MC8** have 1 amino acid in common with the positive control, namely the Tyr-67 amino acid residue, in this case Tyr-67 acts as an acceptor for hydrogen bonds with hydroxy groups but the bond free energy that is formed at **MC8** is higher than the positive control so that the bond energy that is formed is unstable at the Bcl-2 receptor [26]. From these results it is estimated that the **MC8 compound** is not active against Bcl-2 receptors.

The docking results of compound 3 (MC9) on the target protein (2W3L) showed that the compound had a bond free energy value (kcal/mol) of -4.6253 and an RMSD value of 1.5738 (Figure 4). Compound 3 (MC9) has the same interaction of 7 amino acid residues with the positive control (Venetoclax). The hydrogen bonds formed in MC9 have nothing in common with the positive control. The van der Waals bond formed in MC9 has 1 amino acid in common, namely the Glu-119 amino acid residue.

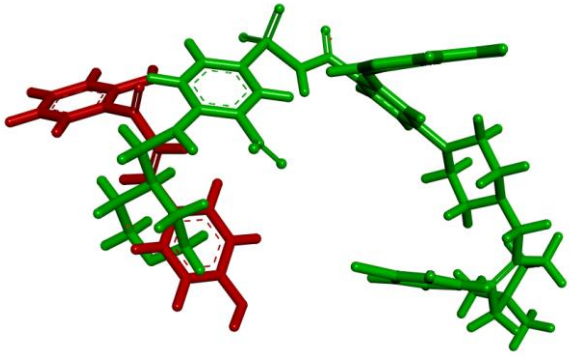


Figure 3. Visualization Results of **MC8** Compound Superimposition (Red) and Positive Control (Green).

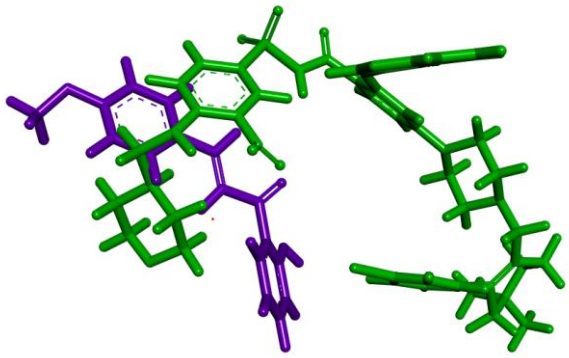


Figure 4. Visualization Results of **MC9** Compound Superimposition (Purple) and Positive Control (Green).

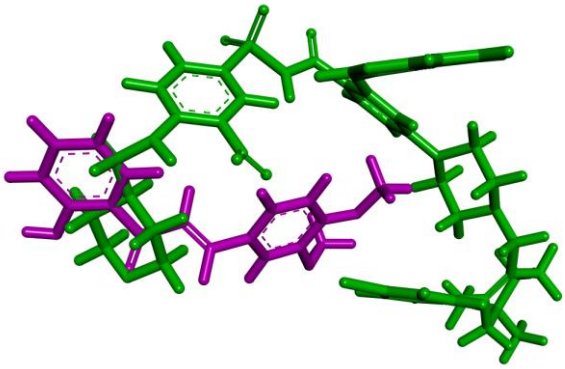


Figure 5. Visualization Results of **MC10** Compound Superimposition (Dark purple) and Positive Control (Green).

The bond free energy formed at MC9 is higher than the positive control so that the bond energy formed is unstable at the Bcl-2 receptor. From these results it is estimated that the MC9 compound is not active against the Bcl-2 receptor.

The docking results of compound 4 (MC10) in the face of the target protein (2W3L) showed that the compound had a bond free energy value (kcal/mol) of -4.7726 and an RMSD value of 1.5402. Compound 4 (MC10) has the same interaction of 6 amino acid residues to the positive control (Venetoclax). The van der Waals bond formed in MC10 has 1 amino acid similarity, namely the Asp-62 amino acid residue. In terms of the hydrogen bonds, the MC10 compound has 1 amino acid in common with the positive control, namely the Arg-26 amino acid residue, where the ketone group acts as an acceptor as can be seen in the 2D view in Figure 5.

The bond free energy formed in MC10 does not approach the bond free energy value of the positive control so that the stability of the MC10 bond is different from that of the positive control on the Bcl-2 receptor. From these results it is estimated that the MC10 compound is not active against Bcl-2 receptors.

The docking results of compound 5 (MC11) on the target protein (2W3L) showed that the compound had a bond free energy value (kcal/mol) of -5.1537 and an RMSD value of 1.3197 (Figure 6). Compound 5 (MC11) has the same interaction of 12 amino acid residues with the positive control (Venetoclax). Hydrogen bonds are not formed in MC11 so they don't have the same amino acids.

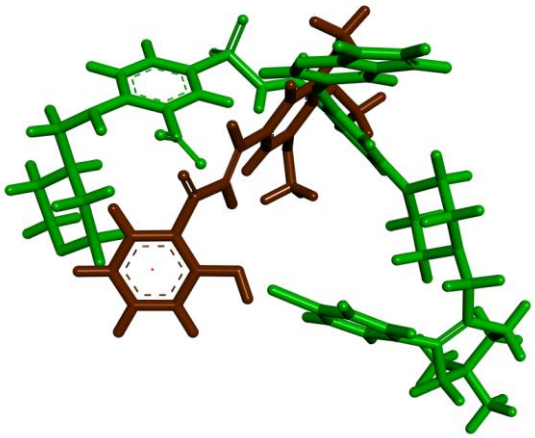


Figure 6. Visualization Results of Superimposition of **MC11** Compounds (Brown) and Positive Control (Green).

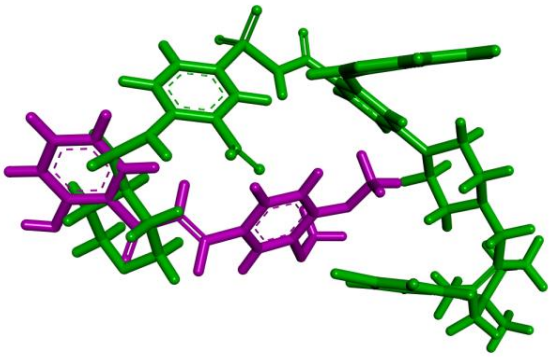


Figure 7. Visualization Results of Superimposition of **MC12** Compounds (Sky Blue) and Positive Control (Green).

The van der Waals bond formed in MC11 has 2 amino acids in common, namely the Glu-119 and Asp-62 amino acid residues. The bond free energy formed at MC11 is higher than the positive control so that the bond energy formed is unstable at the Bcl-2 receptor. From these results it is estimated that the MC11 compound is not active against the Bcl-2 receptor.

The docking results of compound 6 (MC12) on the target protein (2W3L) showed that the compound had a bond free energy value (kcal/mol) of -4.6939 and an RMSD value of 1.5137 (Figure 7). Compound 6 (MC12) has the same interaction of 8 amino acid residues with the positive control (Venetoclax). The hydrogen bonds formed in MC12 do not have the same amino acid residues as the positive control. The van der Waals bond formed on MC12 has 1 amino acid in common, namely the Asp-62 amino acid residue. The bond free energy formed at MC12 is higher than the positive control so that the bond energy formed is unstable at the Bcl-2 receptor. From these results it is estimated that the MC12 compound is not active against the Bcl-2 receptor.

Based on the docking results, compound 5 (MC11) has the smallest bond free energy value of -5.1537 kcal/mol and an RMSD value of 1.3197. However, this compound does not form hydrogen bonds and only has 2 similar amino acid residues in the van der Waals bond, compound 5 (MC11) has the highest similarity of amino acid residues, namely 12 amino acids with positive control. Compound 4 (MC10) has a bond free energy value (kcal/mol) of -4.7726 and an RMSD value of 1.5402. The MC10 compound has 1 similar amino acid residue in the hydrogen

bond and the ven der Waals bond also has 1 similar amino acid residue, the same amino acid residue that compound 4 (MC10) has, namely 6 amino acid residues with positive control. However, this compound has a high bond free energy compared to the positive control, making it difficult for the test compound to bind to the active site of the Bcl-2 protein.

Next, superimposition of 6 chalcone analogues was carried out. Superimposition was performed using the BIOVIA Discovery Studio Visualizer (DSV). Superimposition is used to determine the common features of all compounds, which may play a role in stabilizing the interaction between the ligand and the target protein. Based on the superimposition analysis of the 6 chalcone analogues, none of them attached to the positive control, so it can be concluded that none of the 6 chalcone analogues were active on the Bcl-2 target protein.

Conclusions

Based on the research results, it is known that the docking results of 6 chalcone analogues with the codes MC7, MC8, MC9, MC10, MC11, and MC12 are not expected to have potential as Bcl-2 inhibitors. This is due to the superimposition of the 6 compounds that do not stick to the positive control, but it is also due to the bond free energy (S) values of the 6 chalcone analogous compounds which are higher when compared to the bond free energy values of the positive control (Venetoclax).

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