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ANTICANCER ACTIVITY OF BRYOSTATIN 1 FROM MARINE INVERTEBRATES NATURAL COMPOUND BUGULA NERITINA BY MOLECULAR DOCKING METHOD

Danni Ramdhani* and Resmi Mustarichie

Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Padjadjaran University, Sumedang, Indonesia.

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***Corresponding Author**
Danni Ramdhani
Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Padjadjaran University, Sumedang, Indonesia.

ABSTRACT

Objective: Bryostatin 1 is derived from an ommensal microorganism that is naturally found in marine invertebrates. This compound is known to have various activities, including anticancer agents in the activator mechanism of protein kinase C. This study aims to determine the mechanism of the anticancer activity of Bryostatin 1 through the molecular docking method. This computational study used several target receptors that have a dominant role in anticancer activity: Protein Kinase B, Vascular Endothelial Growth Factor Receptor-2 (VEGFR2), and Procaspase 7. **Materials and Methods:** The computational chemistry method was carried out through molecular docking using Pyrx, Avogadro, and Discovery Studio software. The molecular docking process was carried out using AutoDock Vina software and the results were visualized in 2D interactions with the Discovery Studio Visualizer. Docking evaluation was carried out by observing the parameters of the binding affinity score and the type of bond formed between the target receptor and the ligand compound. **Results:** Docking scores obtained by Bryostatin 1 against PKB -6.5 kcal/mol, VEGFR2 -7.2 kcal/mol, and Procaspase –5.4 kcal/mol. **Conclusion:** Evaluation of the docking binding affinity value can be concluded that the Bryostatin 1 compound has anticancer activity through an inhibitory mechanism of Procaspase 7.

KEYWORDS: Computational chemistry, molecular docking, Bryostatin 1, *Bugula neritina*, anticancer, binding affinity, protein kinase B, VEGFR2, procaspase 7.

INTRODUCTION

Bryostatin is composed of 20 members having a marolactone ring as a class of highly oxygenated macrolides. Bryostatin were first isolated from the bryozoan *Bugula neritina* by Pettit et al. in 1968 and characterized chemically in 1982.[1,2] This group has a pharmacological mechanism as a modulator for activating protein kinase C (PKC), and its prototype member Bryostatin-1 has a profile as a cancer chemotherapy.[3] This mechanism is related to its interaction at the diacylglycerol (DAG) site binding site of the C-1, C-19 and C-26 regulatory domains of PKC.[4,5]

Bryostatin 1 is derived from an ommensal microorganism that is naturally found in marine invertebrates. This compound is known to have various activities, including anticancer agents in the activator mechanism of protein kinase C. Bryostatin 1 has been found to be successful in treating human chronic lymphocytic leukemia, treating Alzheimer's disease in patients, as an anticancer agent in the activator mechanism of protein kinase C. Phase 2 testing in metastatic malignant melanoma.[6-10]

Molecular docking has been widely known and used by researchers for sreening the new active compound candidates through the interaction between the target compound and the receptor. Evaluation of the binding energy of the target compound and the receptor and also the type of bond formed can provide information about the activity of the compound against the desired receptor target.[12,13]

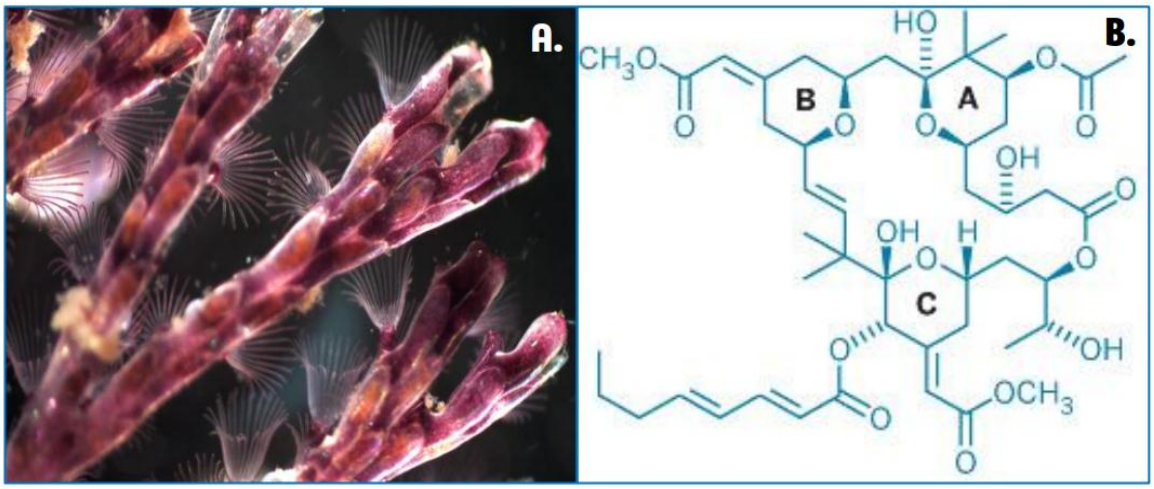

Figure 1: (a) *Bugula neritina;* (b) Bryostatin 1 Structure.

Bryostatin 1 compounds as targets of active compounds will interact with receptor targets responsible for cancer growth and physiology, namely: protein kinase B (PKB; PDB ID:

1GZN), Vascular Endothelial Growth Factor R2's receptor kinase (VEGFR2; PDB ID: 1VR2), and procaspase 7 (GDP ID: 1K88).

PKB is involved in the mechanism of cellular protein metabolism and phosphorylation processes, related to cell growth/apoptosis, cell differentiation and proliferation. PKB overexpression is related to information on the condition of tumor development (T-cell lymphoma) or prostate intraepithelial neoplasia.[14] Vascular endothelial growth factors (VEGFs) and receptors (VEGFRs) are responsible for the vasculogenesis cycle, the process of angiogenesis.[15] VEGFR2 causes pathological processes of angiogenesis, growth of tumor angiogenesis, regulates vascular permeability, expression of cell, and also antiapoptotic effects. Procaspase 7 is formed from 303 amino acid residues in a polypeptide chain. The formation of 175 large chain residues and 105 short chain residues through the mechanism of activation and removal of the amino acid Ile-Gln-Ala-Asp-2-Ser-Gly formed active caspase-7. Procaspase 7 is responsible for the process of cell apoptosis.[16]

MATERIALS AND METHODS

Software and Tools

AutoDock Vina 1.1.2, PyRx, discovery studio visualizer, avogadro.

Ligand preparation

Scientific data on xanthonin compounds and other ligands are listed in table 1.

Table 1: Ligands used in the study.

No	Ligand	Molecular Formula	References
1	Bryostatin 1	$C_{42}H_{68}N_6O_6S$	[4]
2	RPRTSSF	$C_{39}H_{66}N_{14}O_9$	[9]
3	Cilengitide	$C_{15}H_{27}N_7O_8$	[14]
4	RGDS	$C_{36}H_{59}N_{13}O_{11}$	[13]

Target Receptor and Ligan Preparations

The target receptor proteins related to cancer growth conditions were obtained from a protein data bank (http://www.rcsb.org); protein kinase B (PDB ID: 1GZN), receptor kinases R2 growth factor Endothelial Factor R2 (PDB ID: 1VR2), and procaspase 7 (PDB ID: 1K88).

The 3D ligand structure can be downloaded via https://pubchem.ncbi.nlm.nih.gov/. The obtained ligand file was then energy minimised, and converted into PDBQT file format.

Process and Evaluation of docking parameters

The docking process for Bryostatin 1 compounds and native ligands was carried out using AutoDock Vina 1.1.2 software. The use of grid boxes was set with a distance of 1 Å which makes the ligand movement space remain flexible to find the best position in the formation of bonds with the target receptor.

The evaluation of the docking results was carried out by analyzing the binding affinity score and also the type of bond formed.

RESULTS AND DISCUSSION

Ligand and Protein preparation

Bryostatin 1 and native ligands from each receptor were carried out in the first step of energy minimization, then the file format was changed to PDBQT. Physicochemical properties, 3D structure of ligands are summarized in table 2, and figure 2.

Table 2: Physiochemical properties of ligand.

No	Ligand	Molecular Weight (g/mol)	Hydrogen Bond Donor	Hydrogen Bond Acceptor	XLogP3-AA	Minimize Energy
1	Bryostatin 1	905.0	4	17	4.0	1730.52
2	RPRTSSF	875.0	14	14	-7.7	1277.93
3	Cilengitide	588.65	7	8	-1.0	1216.28
4	RGDS	433.42	9	10	-7.3	390.38

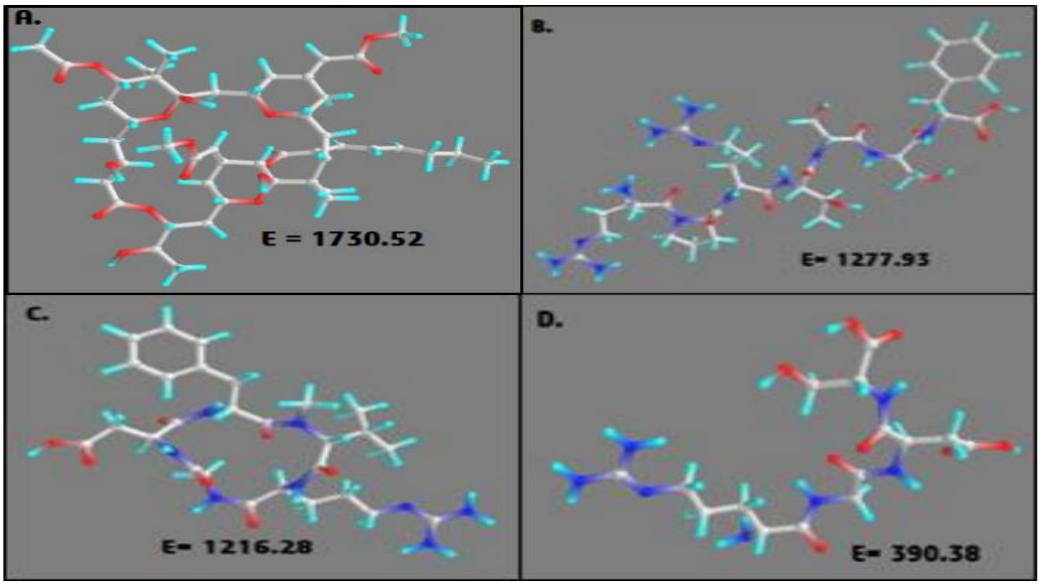

Figure 2: 3D ligand structure and energy minimized results: (A) Bryostatin 1, (B). RPRTSSF, (C) Cilengitide, (D) RPRTSSF.

The receptor protein was converted to PDBQT format, and docking simulations were performed for each native ligand and the binding affinity score was compared with the active compound Bryostatin 1 against the target of each receptor. 3D structure of the target receptor protein in figure 3.

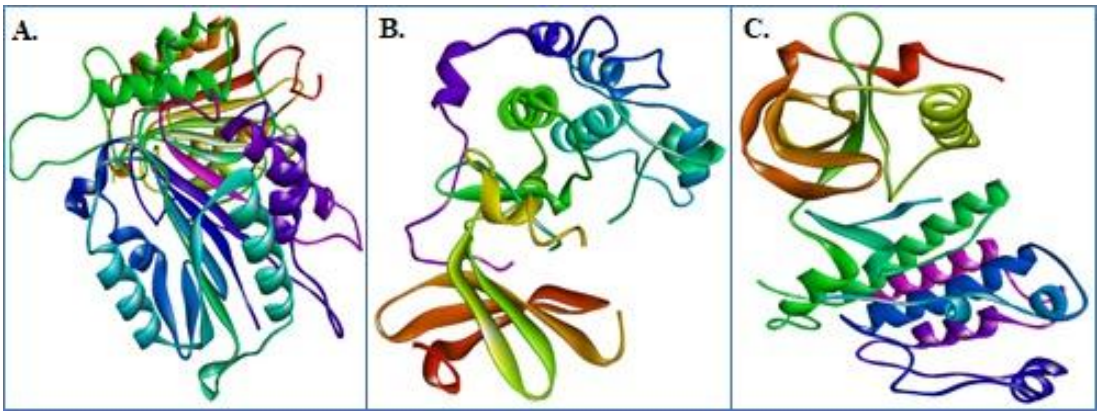

Figure 3: 3D structure of receptor, (A) Procaspase 7, (B) Protein Kinase B, (C) VEGFR2.

Docking analysis simulation

Molecular docking of bryostatin 1 compound with PKB receptor

The results of 2-D molecular docking visualization provide information that an interaction was formed between the RPRTSSF ligand and Bryostatin 1 against PKB receptor targets on the same amino acid Thr162, Phe163, Lys181, Val198, Glu200, Thr274, Asp275, Leu317, Glu315, and Thr327.

The RPRTSSF ligand and the PKB receptor form 3 hydrogen bonds in the amino acids Thr 199, Val 198, and Lys 181, while the Bryostatin 1 ligand has 3 hydrogen bonds on the amino acids Glu 200, Ser201, and Gly295.

The docking value of the RPRSSF ligand to the PKB receptor was -6.6 kcal/mol, while the Bryostatin 1 ligand to the PKB receptor was -6.5 kcal/mol.

Molecular docking of bryostatin 1 compound with VEGFR2 receptor

The results of the docking study on the VEGFR2 receptor showed that Bryostatin 1 and cilengitide ligands had the same interaction at the amino acid receptor Leu840, Val848, Cys919, Arg1032, and Cys1045. The cilengitide ligand formed 3 hydrogen bonds at the receptor, while Bryostatin 1 had 3 hydrogen bonds at Lys868, Asp1045, and Asp1046. The

docking score showed the binding affinity value of cilengitide was -8.2 kcal/mol, and Bryostatin 1 was -7.2 kcal/mol.

Molecular docking of bryostatin 1 compound with procaspase 7 receptor

The simulation results of the docking of the RGDS and Bryostatin 1 ligands to the procaspase 7 receptor showed that the two ligands had the same amino acid interactions at the receptors on Arg87, Asn88, His144, Lys285. The RGDS ligand formed 6 hydrogen bonds with the receptor on the amino acids Ser 231, Arg 187, Asp 93, Ser 239, Arg 233, and Arg 87. The Bryostatin 1 ligand forms 3 hydrogen bonds with receptors on the amino acids Arg87, Gly85, and His144.

The docking score showed that the Bryostatin-1 ligand had a lower binding affinity value of -5.4 kcal/mol and the RGDS ligand -6.9 kcal/mol.

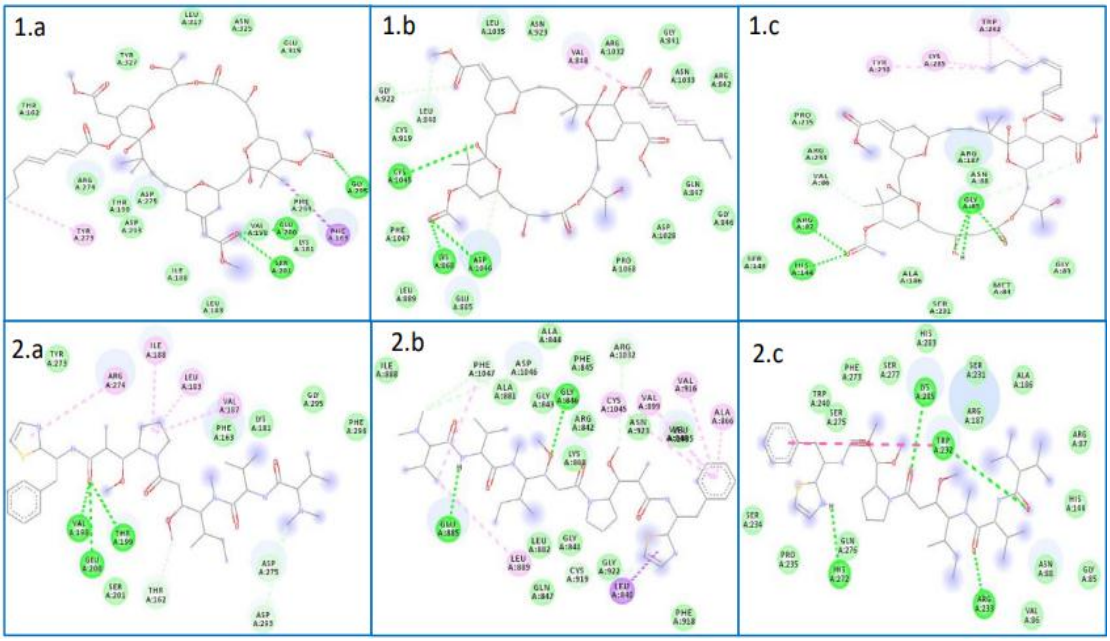

Figure 4: Interaction of Ligands and Target receptors. (1.a) RPRTSSF interaction with PKB, (1.b) Cilengitide interaction with VEGFR2, (1.c) RGDS interaction with Procaspase 7, (2.a) Bryostatin 1 with PKB, (2.b) Bryostatin 1 with PKB, (2.c) Bryostatin 1 with Procaspase 7.

Table 4: Comparative binding affinity of different ligands with receptors.

No.	Receptor	Ligand	Binding Affinity (kcal/mol)
1	Vascular Endothelial Growth Factor R2	Cilengitide Bryostatin 1	-8.2 -7.2
2	Procaspase 7	RGDS	-6.9

		Bryostatin 1	-5.4
3	Protein Kinase B	RPRTSSF Bryostatin 1	-6.6 -6.5

CONCLUSIONS

The data from the docking simulation showed that Bryostatin 1 compounds had a lower binding affinity value than all the native receptors ligand. It can be concluded that the Bryostatin 1 compound has activity that is not too dominant with the inhibition mechanism of the three receptors. Molecular docking can be performed on other cancer receptors to explore the specific mechanism of Bryostatin 1.

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