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IN SILICO STUDY OF ANTICANCER MECHANISM OF THE MARINE BIOACTIVE COMPOUND TALTOBULIN

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ABSTRACT

Objective: Taltobulin, a synthetic counterpart of hemiasterlin, was first obtained from the marine sponge *Hemiasterella minor*, with potential antimitotic and antineoplastic activities. The principal objective of this study is to employ the molecular docking approach to ascertain the mechanism responsible for Taltobulin's anticancer action. Vascular Endothelial Growth Factor Receptor-2 (VEGFR2), Procaspase7 (Pro7), and Protein Kinase B (PKB) are three different receptors with significant anticancer activities that were exploited in this computational investigation. **Materials and Methods:** Molecular docking was completed using Pyrx and autodock Vina in the computational chemistry method. The outcomes were displayed in the discovery studio program's two-dimensional interfaces. Affinity for binding score values and the kind of chemical bond that forms between the ligand and target receptor were assessed during the docking evaluation process. **Results:** The results of the PKB, VEGFR2, and Procaspase 7 docking analyses were -6.2 kcal/mol, -6.8 kcal/mol, and –7.3 kcal/mol, respectively. **Conclusion:** Taltobulin's binding affinity score indicates dominant anticancer activity via procaspase7 in comparison to the native ligand-receptor.

KEYWORDS: molecular docking, taltobulin, *Hemiasterella minor*, anticancer, binding affinity, protein kinase B, VEGFR2, procaspase7.

INTRODUCTION

Apoptosis can be induced and cell division can be prevented by upsetting the dynamic equilibrium of the tubulin/microtubule system, which is essential to mitosis. Moreover, numerous anticancer medications have this system identified as a known target.[1-3] However, severe toxicity, drug resistance, and bioavailability issues are typically linked to the clinical usage of anti-tubulin medications.[4] New medications with improved qualities are required as a result of these limitations in the way that currently utilized compounds interact with tubulin.[5]

In the pursuit of additional promising active agents in this area, specifically seeking to identify agents that do not function as substrates for drug efflux pumps like P-glycoprotein.[6,7], and developed a keen interest in hemiasterlins.[8] A class of naturally occurring tripeptides known as hemosterlins was found and isolated from the marine sponge *Hemiastrella minor* in South Africa a few years ago.[9, 10] The most active members of the family bind in the tubulin vinca domain, exhibit cytotoxicity in the nanomolar range, and are extremely strong inhibitors of microtubule polymerization.[11,12]

Hemosterlins are excellent candidates for synthetic modification since they have a strong antimitotic action and a simple structural makeup compared to other known antimitotic drugs. Taltobulin (HTI-286, 2), a synthetic analogue of hemiasterlin 1 that replaces the 3-substituted indole ring with a phenyl group, has progressed to clinical trials.[18–22] The three significantly changed amino acids found in taltobulin and hemosterlins are in charge of the compound's stability and in vivo activity. They are known as pieces A (N-terminus), B (middle amino acid), and C (C-terminus) for simplicity's sake.[23]

In order to simulate the atomic-level interactions between a tiny molecule (ligand) and a recognizable macromolecule, reverse docking is employed extensively. To expedite the drug development process, candidate compounds can be evaluated by molecular docking and other bioinformatic techniques prior to conducting chemical modifications or in vitro cell culture-based experiments. Details about the molecule's activity against the targeted receptor target can be discovered by examining the binding energies of the target drug and the receptor, together with the type of bond that is created.[24, 25]

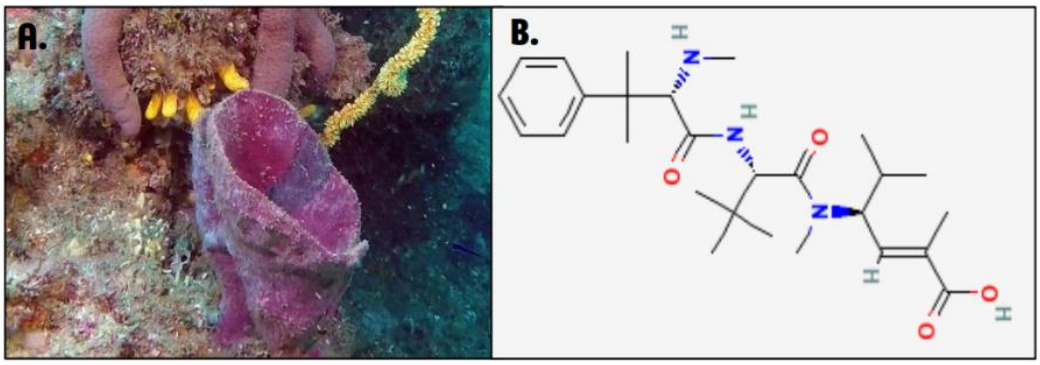

Figure 1: (a) *Hemiasterella minor; (*b) Taltobulin Structure.

In this article, the "control" proteins that are utilized to predict how the Taltobulin will bound to the molecular target are procaspase 7 (PDB ID: 1K88), protein kinase B (PKB; PDB ID: 1GZN), and the receptor kinase for vascular endothelial growth factor R2 (VEGFR2; PDB ID: 1VR2).

PKB is involved in cellular protein metabolism and phosphorylation, two processes linked to cell growth, differentiation, and death. PKB accumulation is associated with the ability to determine whether malignancies (such as T-cell lymphoma) or prostatic intraepithelial neoplasia are forming.[26] The angiogenesis cycle is regulated by vascular endothelial growth factors (VEGFs) and receptors (VEGFRs). In addition to regulating pathological angiogenesis, which leads to tumor formation, VEGFR2 also regulates cell expression, vascular permeability, and antiapoptotic effects.[27] Procaspase 7 is a polypeptide chain consisting of 303 residues of amino acids. To create active caspase-7, the amino sequence Ile-Gln-Ala-Asp-2-Ser-Gly was first activated and subsequently eliminated. Consequently, 175 big chain residues and 105 short chain residues were generated. The enzyme procaspase 7 is in charge of causing cell death.[28]

MATERIALS AND METHODS

Software and Tools

AutoDock Vina 1.1.2, PyRx, discovery studio visualizer.

Ligand Preparation

Table 1 provides scientific data on compounds containing taltobulin and additional ligands.

Table 1: Ligands used in the study.

No	Ligand	Molecular Formula	References
1	Taltobulin	$C_{27}H_{43}N_3O_4$	[2]
2	RPRTSSF	$C_{39}H_{66}N_{14}O_9$	[12]
3	Cilengitide	$C_{15}H_{27}N_7O_8$	[13]
4	RGDS	$C_{36}H_{59}N_{13}O_{11}$	[14]

Preparations for Target Receptor and Ligand

A protein data bank (http://www.rcsb.org) provided access to the target receptor proteins procaspase 7 (PDB ID: 1K88), receptor kinase R2 growth factor endothelial factor R2 (PDB ID: 1VR2), and protein kinase B (PDB ID: 1GZN).

The 3D ligand structure is available to participants at http://pubchem.ncbi.nlm.nih.gov. Following energy minimization, the ligand file was transformed into a PDBQT file format.

Analysis of Docking Parameters

Using AutoDock Vina 1.1.2, native ligands and taltobulin molecules were docked. The ligand movement space can remain flexible and reach the right position for forming interactions with the target receptor when the grid box spacing is one unit. The scores for binding affinity and the type of connection formed were used to evaluate the docking data.

RESULTS AND DISCUSSION

Ligand and Protein Target Preparation

Taltobulin and the natural ligands found in each receptor were used in the initial step of energy minimization, following which the file format was changed to PDBQT. The three-dimensional (3D) structure and physicochemical properties of ligands are shown in table 2 and picture 2.

Table 2: Physiochemical properties of ligand.

No	Ligand	Molecular Weight (g/mol)	Hydrogen Bond Donor	Hydrogen Bond Acceptor	XLogP3-AA	Minimize Energy
1	Taltobulin	548.6	3	5	2.6	659.75
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

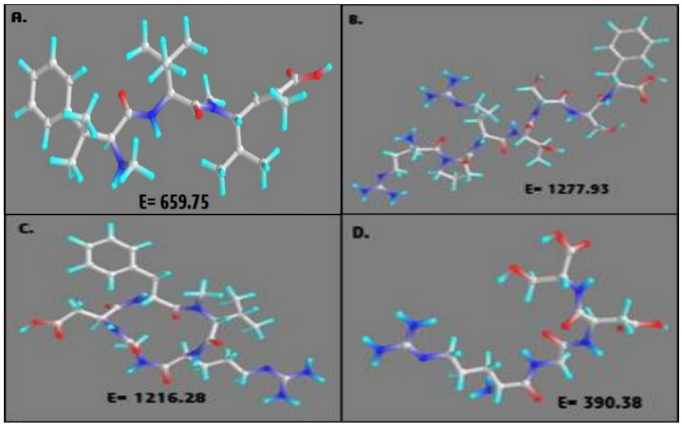

Figure 2: 3D ligand structure and energy minimized results: (A) Taltobulin, (B). RPRTSSF, (C) Cilengitide, (D) RPRTSSF.

Docking simulations were performed for each natural ligand subsequent to the receptor protein's conversion to PDBQT format. The binding affinity score for each receptor was then compared to the targets of each receptor and the active component, taltobulin. Figure 3 displays the target receptor protein's three-dimensional structure.

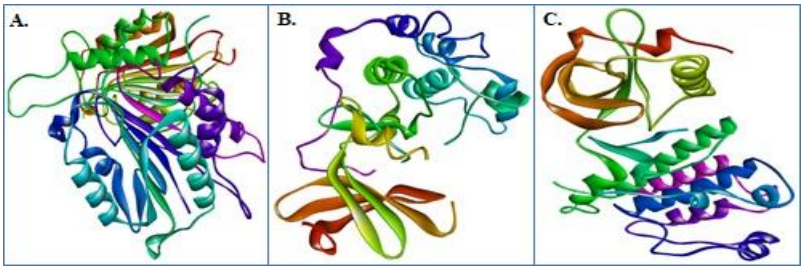

Figure 3: 3D structure of receptor, (A) Procaspase 7, (B) Protein Kinase B, (C) VEGFR2.

Docking Simulation Analysis of the Ligand-Receptor

Taltobulin docking with the PKB receptor

The 2-D molecular docking simulation results demonstrated that the same amino acids, Phe163, Lys181, Glu200, Arg274, and Asp275, were the sites of interaction between taltobulin and the RPRTSSF ligand and PKB receptor targets.

The RPRTSSF ligand and the PKB receptor establish three hydrogen bonds at amino acids Thr199, Val198, and Lys181. Furthermore, the taltobulin ligand forms three hydrogen bonds with the amino acids Lys181, rg 184, and Asp 293.

Compared to the RPRSSF ligand, the taltobulin ligand showed a docking value of -6.2 kcal/mol at the PKB receptor.

Taltobulin docking with the VEGFR2 receptor

Docking research discovered that taltobulin and cilengitide ligands interacted similarly with the VEGFR2 receptor at its amino acid receptors, Leu480, Gly841, Val848, Ala866, Phe918, Cys919, Asn923, and Asp1046, among others. At Cys1045, taltobulin produced a single hydrogen bond, while the cilengitide ligand at the receptor formed three.

Cilengitide had a binding affinity of -8.2 kcal/mol, but taltobulin had a less dominant affinity of -6.8 kcal/mol based on the docking score.

Taltobulin docking with the Procaspase 7 receptor

The RGDS and Taltobulin ligands demonstrate the same amino acid interactions at the procaspase 7 receptors on Arg87, Asn88, Thr90, His144, Arg187, Ser239, and Lys285 of the receptor, according to the projected results of the docking of the two ligands to the receptor. Six hydrogen bonds were established by the amino acids Ser 231, Arg 187, Asp 93, Ser 239, Arg 233, and Arg 87 between the RGDS ligand and the receptor. Three hydrogen bonds are simultaneously formed by the Taltobulin ligand and receptors on the amino acids Trp232, Arg187, and Asn88.

The taltobulin ligand was shown to have a higher binding affinity than the RGDS ligand, with values of -7.3 kcal/mol and -6.9 kcal/mol, respectively, according to the docking score.

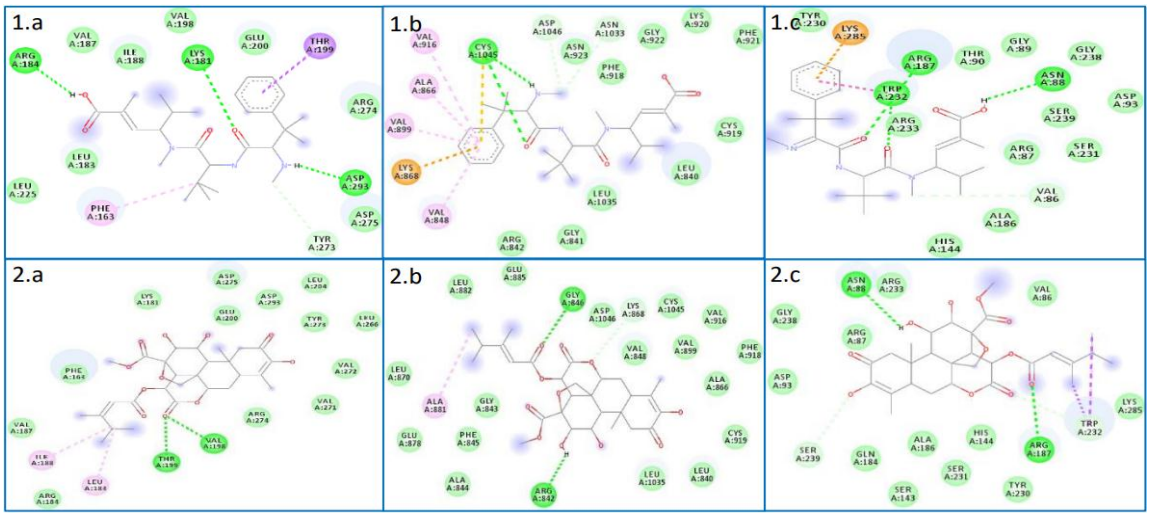

Figure 4: Interaction of ligands and target receptors: (1.a) RPRTSSF interaction with PKB; (1.b) Cilengitide interaction with VEGFR2; (1.c) RGDS interaction with

Procaspase7; (2.a) Taltobulin with PKB; (2.b) Taltobulin with VEGFR2; (2.c) Taltobulin with Procaspase 7.

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

No.	Receptor	Ligand	Binding Affinity (kcal/mol)
1	Vascular Endothelial Growth Factor R2	Cilengitide Taltobulin	-8.2 -6.8
2	Procaspase 7	RGDS Taltobulin	-6.9 -7.3
3	Protein Kinase B	RPRTSSF Taltobulin	-6.6 -6.2

CONCLUSIONS

According to data from docking simulations, the taltobulin molecule has a higher binding affinity value than the native receptor ligands of procaspase7. The natural chemical taltobulin, which inhibits the procaspase 7 receptor, is found to have more dominant activity than the native ligand-receptor.

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