INTERNATIONAL JOURNAL OF PHARMACEUTICS & DRUG ANALYSIS

VOL.6 ISSUE 2, 2018; 332 – 338 http://ijpda.com; ISSN: 2348-8948

MEDFOOD'18 [1st February 2018]

National Conference on Phytochemicals in Medicinal Plants and Food

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Research Article

Pompanopeptin B–An Ideal Drug For Treating Thyroid Cancer

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Date Received: 23rd January 2018; Date accepted: 29th January 2018; Date Published: 23rd February 2018

Abstract

Thyroid cancer is a common endocrine related cancer with a higher incidence in women than in men. Thyroid tumors are classified on the basis of their histopathology as papillary, follicular, medullary, and undifferentiated or anaplastic. Thyroid hormone receptor alpha 1, (THRA1) is responsible for the development of tumour and resistance to chemotherapy. The side effects of the available drugs make the need for the necessity of new improved drugs. Cyanobacterial resource offers a great scope for discovery of new drugs for cancer. Cyanobacterial novel bioactive compounds with unique biological activities may be useful in finding the potential drugs with greater efficacy, specificity for the treatment of human diseases. The aim of the present study was to predict the anticancer drug from the members of the cyanobacteria. *In silico* molecular docking was carried out between the cyanobacterial bioactive compounds, and thyroid cancer causing receptor. The highest energy value was produced by the Pompanopeptin B with thyroid hormone receptor alpha 1. From the above results, it is concluded that Pompanopeptin B, an ideal cyanobacterial drug can be employed as axbest drug for treating thyroid cancer without any side effects.

Keywords: Thyroid cancer, cyanobacterial bioactive compounds, glide, *in silico, Lyngbya confervoides,* pompanopeptin B.

Introduction

Thyroid cancer is a cancer originating from follicular thyroid cells. Thyroid cancer is three times more common in women than in men [1]. The most effective management of aggressive thyroid cancers is surgical removal of thyroid gland (thyroidectomy) followed by radioactive iodine ablation and TSH-suppression therapy. Chemotherapy or radiotherapy may also be used in cases of distant metastases or advanced cancer stage. Cancer treatments do not have potent medicine as the currently available drugs are causing side effects in some instances[2]. The side effects of the commercially available drugs make the need for the necessity of new improved drugs and hence, in this investigation a new drug from cyanobacterial origin has been tried showing high binding affinity with the receptor molecule of thyroid cancer.

Marine cyanobacteria are the most promising or-

ganism with potential benefits against cancer.Among marine cyanobacteria, the genus *Lyngbya* is considered to be the most prolific producer of natural products with over 200 compounds reported. *Lyngbya* is a genus of cyanobacteria, unicellular autotrophs that form the basis of the oceanic food chain. Lyngbya form long, unbranching filaments inside a rigid mucilage sheath. *Lyngbya* reproduce asexually. Their filaments break apart and each cell forms a new filament [3]. The genus Lyngbya appears to be an emerging source of bioactive peptides. Bioactive compounds from *Lyngbya confervoides* are considered to be a valuable pool of lead compounds in structure-based drug design and discovery [4]. Several compounds were found to inhibit the growth of cancer cell lines. Many of these compounds are bioactive and show potential for therapeutic use. It is possible that the ability to produce a wide range of defensive secondary metabolites has contributed to the high degree biological adaptation observed for cyanobacteria. These secondary metabolites often enable cyanobacteria to compete effectively in a variety of environments, and many have been presented as lead compounds for further cancer drug development [5].

Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to, in turn, predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs [6]. Therefore docking is useful for predicting the strength and binding nature of the receptor and ligand molecules [7]. The focus of molecular docking is to computationally simulate the molecular recognition process. The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized. Pompanopeptin B, a cyclic peptide isolated from the *Lyngbya confervoides*. In the present study pompanopeptin B is identified an ideal drug for thyroid cancer through molecular docking

Materials And Methods

Thyroid cancer causing hormone receptor alpha 1 (THRA1) protein structure was retrieved from protein databank [8] and the marine cyanobacterial bioactive compounds molecular structures were retrieved from Chemspider database [9]. The antigenicity was tested through TMHMM [10]. The possible ligand binding site was predicted using CASTp server [11]. The docking tool Glide was used for molecular docking (www.schrodinger.com/). In the present study with the help of Glide, Maestro, LigPrep and SiteMap were used to locate binding sites over the protein molecule and to conduct molecular docking of ligands with the protein molecules.

Results And Disscussion

Molecular Docking of Thyroid Receptor Hormone with Bioactive Compounds of Cyanobacteria

In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs [12]. Drug target discovery involves the identification of potential lead molecules against the various cancer causing receptor molecules. When considering the treatments for cancer, chemotherapy, targeted therapies, surgery, radiation and hormonal therapy are the various types that currently exist [13]. But these types of treatments, except for the target-based, are unable to distinguish cancerous cells from the normal and hence, the healthy cells are also commonly damaged in the process of treating the cancer. In this context, considering the above facts, the target based drug discovery is having higher potential over other methods[14]. Towards finding suitable inhibitors for receptor molecules of various cancer diseases, it is essential to find out the binding energy between the ligands and the receptors. This is normally done using molecular docking.

Fig.1. Prediction of exomembrane topology of thyroid hormone receptor alpha 1, (THRA1) through TMHMM

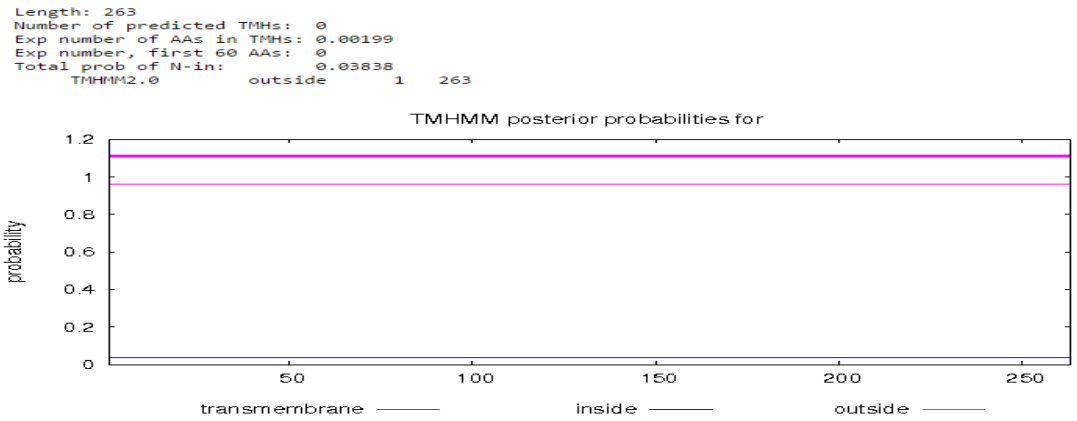
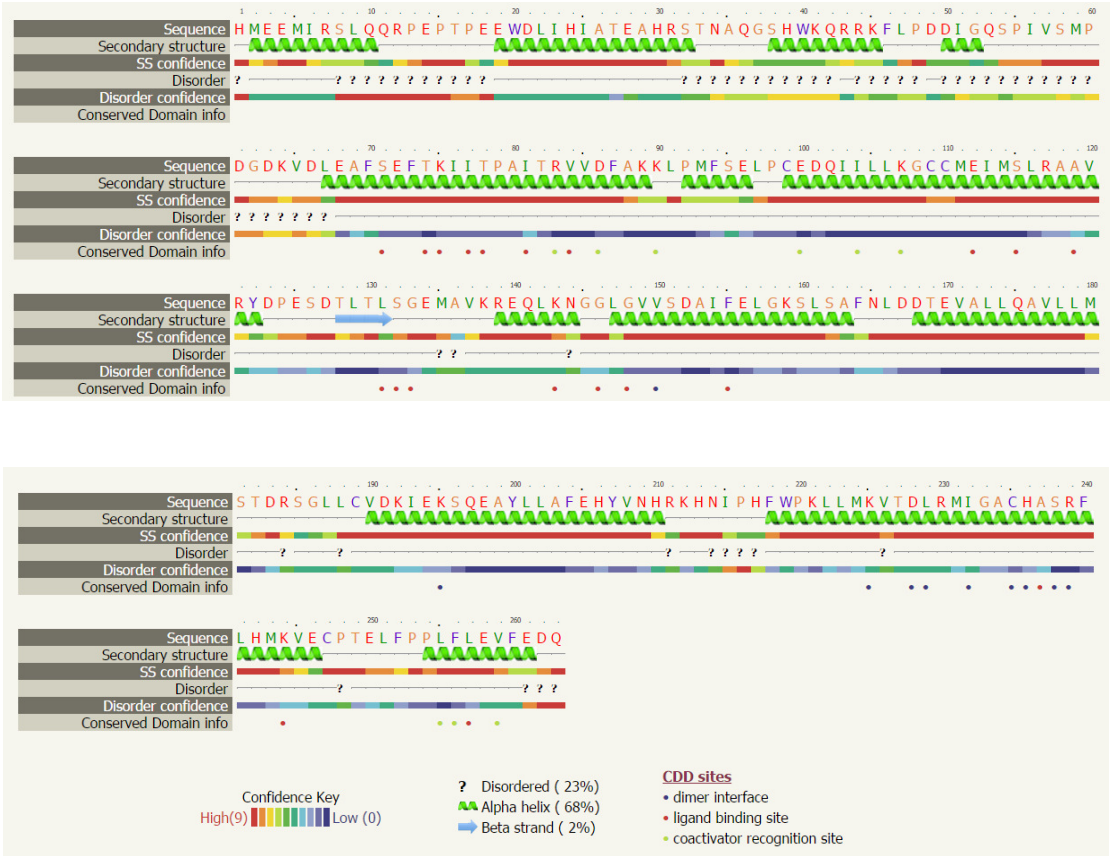


Fig.2. Secondary structure prediction of Thyroid hormone receptor alpha 1, (THRA1) through PHYRE-2



In the present study, molecular docking method is used for the prediction of cancer drug from cyanobacteria. Among the various members of marine cyanobacteria, *Lyngbya confervoides*, organism having high potential anticancer drug molecules. The thyroid cancer causing receptor molecule was taken for the study and checked the antigenicity through topology prediction (Fig.1). The secondary

structure was predicted through Phyre-2 (Fig.2). The receptor molecule is potential antigenic molecule. The enzyme contains 10 possible ligand binding sites and major active site was identified through high score of area and volume. In the thyroid cancer causing protein (Fig.3), out of 10 ligand binding sites (Table.1, Fig.4), 4 sites were identified as active

sites and site-1 was identified as the major active site (1.09633) for docking (Table.2, Fig.5). 198 cyanobacterial bioactive compounds were docked against thyroid cancer causing receptor. Among them pompanopeptin-B (Fig.6) have close interaction and maximum energy value with the thyroid cancer causing receptor (Table.3& Fig.7)

The recognition and affinity of ligands towards proteins was interpreted from the inter atomic distances and hydrogen bonding formed between the amino acid residues of docked protein-ligand complex structure. The prominent binding pockets and cavities in cancer causing receptors were identified using Glide module. Glide is commercial software used for docking and to predict the binding and active sites of proteins.

The interaction of thyroid cancer causing protein amino acid sequence with pompanopeptin B at inter atomic distance less than 5 Å showed that the interactions between the protein and ligand had occurred only in the active site pockets. The pocket of the active site was surrounded by 20 amino acids from which 14 of them were hydrophobic, 4 were polar, 1 Glycine and another one was charged positive (Fig.8). The docking study reveals that van der Waals forces play an important role in stabilizing the protein-ligand complex. The van der Waals interaction formed by the reactive amino acid residues of thyroid cancer causing protein with the ligand molecule lead to binding of receptor molecule and pompanopeptin B.

Fig.3. 3D structure of thyroid hormone receptor alpha 1, (THRA1)

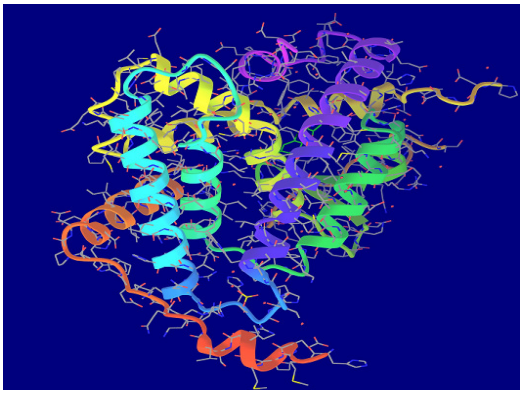


Fig.4.Possible ligand binding sites of thyroid hormone receptor alpha1, (THRA1)

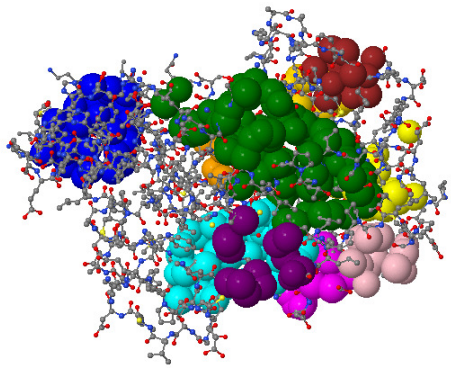


Fig.5. Active site of thyroid hormone receptor alpha 1, (THRA1)

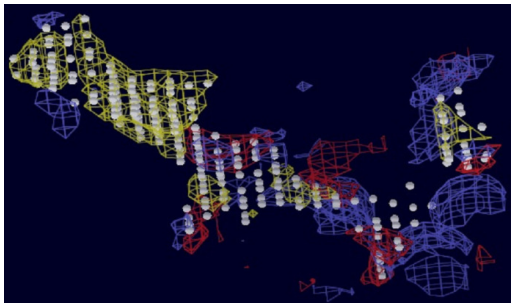


Fig.6. 3D structure of Pompanopeptin B

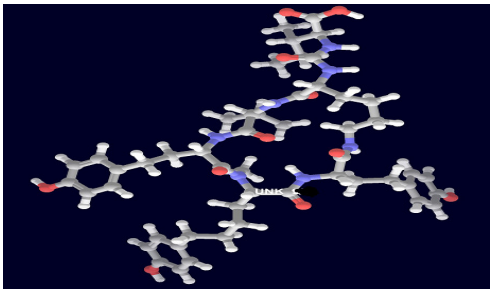


Fig.7.Molecular docking of thyroid hormone receptor alpha 1, (THRA1)with Pompanopeptin B

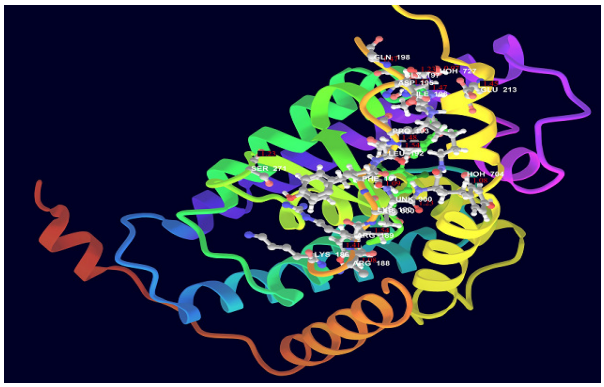


Fig.8. Molecular interaction of Pompanopeptin B drug with active binding site of receptor molecule Thyroid hormone receptor alpha 1, (THRA1)

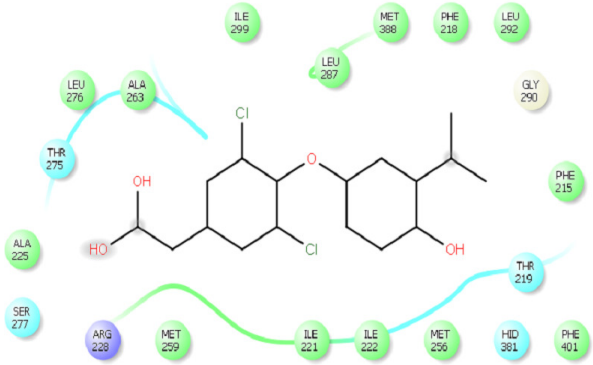


Table.1 Possible ligand binding sites of thyroid hormone receptor alpha-1

Sites	Area	Volume
Site-1	**671.8**	**829**
Site-2	397.9	520.6
Site-3	372.7	453.8
Site-4	109.3	151.6
Site-5	90.7	73
Site-6	72.8	55.7
Site-7	52.5	55
Site-8	109.6	120.8
Site-9	82.7	73.1
Site-10	62.4	47.1

Table.2. Active site scores of thyroid hormone receptor alpha 1,

Sites	1NAV
Site-1	**1.09633**
Site-2	0.981345
Site-3	0.873219
Site-4	0.553282

Table.3. Docking scores of thyroid hormone receptor alpha 1, with pompanopeptin B and some other bioactive compounds from Cyanobacteria

Cyanobacterial Bioactive Compounds with Thyroid Cancer (1NAV)	Glide Docking Score
27023336(**pompanopeptin B**)	**-6.482245**
17214383(lynbyastatin 4)	-6.440504
24662743(molasamide)	-6.302338
17262763(lyngbyastatin)	-6.168169
28284833 (symplocamide A2)	-6.089223
23310525(lynbyastatin)	-5.813547
9939878 (cryptopycin E)	-5.786625
23076612(lyngbyastatin 7)	-5.691801
27023225(symplocamide A1)	-5.551744
10214175(nostocyclopeptide A1)	-5.257326
10214176(nostocylopeptide A2)	-5.244545
23314421 (symplocamide A)	-5.203986
10343167(nostocylopeptide A3)	-5.134649
23310527 (lyngbyastatin 3)	-5.132118
27024666(tiglicamide B)	-5.113216
27024731(lyngbyastatin 10)	-5.111614
10481025(lybaybellin I)	-5.009848
27023335(pompanopeptin A)	-5.000765
8755848 (cryptopycin 5)	-4.957519
10478837(somocystinamide A2)	-4.951157
27024730(lyngbyastatin 9)	-4.879727
27025519(veraguamide L)	-4.878351
23076610(lynbyastatin 5)	-4.852679
9290490(somocystinamide A)	-4.732581
10242627(malyngamide Q)	-4.715018
10279681(dolastin13)	-4.634569
8161464 (cryptopycin F)	-4.607329
10193999(symplostatin 2)	-4.573523
9344966 (cryptopycin 326)	-4.569162
28289559(hoiamide D1)	-4.547022
10481022(lybaybellin F)	-4.489765
25032428(hoamide C)	-4.486371
10275264(malyngamide C)	-4.477207
25053061(caylobolide A1)	-4.461624
24687950(kemopeptine A)	-4.459464
10479339(lynbaysolide B1)	-4.442197
27025721(pitipeptolide D)	-4.425598
28283161(lynbaybellin E)	-4.408229
8158691 (cryptopycin G)	-4.362068

Thus, from the above results, it is revealed that cyanobacterial drug, pompanopeptin B produce high docking energy with receptor molecules of thyroid cancer. Pompanopeptin B could be success-

fully employed as an ideal and common drug for above said cancer.

Conclusion

The results of the present study clearly showed that pompanopeptin-B is capable of making a strong interaction and binding with thyroid receptor hormone as evidenced by its high binding energy. Based on the results of the above study, it can be concluded that the drug pompanopeptin- B is good drug and hence, it can be employed as an alternative drug for treating above said cancer without producing any side effects. However, further studies are needed to establish its anticancer potential against thyroid cancer based on the predictions of *in silico* studies.

Acknowledgement: The authors are thankful to the management of AVVM Sri Pushpam College (autonomous), Poondi, for providing them necessary facilities and support to carry out this work.

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