Research Article

Molecular Modelling and Docking Studies of Some Marine Natural Products as Lead for Anti-Cancer

***Vidhyeswari D[1]., A. Surendhar[1], A. Sivalingam[1], D. Velmurugan[2], T. Kannadasan[1]**

1. Department of Chemical Engineering, Coimbatore Institute of Technology, Coimbatore-641014, India.
2. Centre of Advanced Study in Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai-600025, India.

ABSTRACT

Inhibitors of Glycogen synthase kinase 3 beta are greatly useful for the treatment of cancer. Drug receptor interactions are being observed by Molecular docking studies. Some of the marine natural compounds like Dolastatin 15, Kahalalide F, Ara-A, Bromosphaerone, Cribrostatin 3, Spongiadiol and Pestalone have been selected and the existing anti cancer drug, HEPES [*4-[2-hydroxyethyl]-1-piperazineethanesulfonic acid*] has also been selected. These compounds have been screened through High throughput virtual screening (HTVS) method by extra precision mode for its anti-cancer activity. From the HTVS results, four marine natural compounds - Dolastatin 15, Ara-A, Spongiadiol and Pestalone, and the existing anti cancer drug, HEPES have also been selected on the basis of minimal glide energy and minimum docking score. Induced fit docking (IFD) studies has been carried out for those compounds and interactions have been noted. From the results of Induced fit docking studies, Dolastatin 15 has minimum docking score and minimum glide energy compared to other marine compounds and also the existing drug, HEPES. Pymol and ligplot picture have been drawn for the target protein, Glycogen synthase kinase 3 beta with Dolastatin 15 and HEPES for the determination of interaction. Dolastatin 15 has good affinity towards the active pockets. Thus it is the finest target for the treatment of cancer. Interaction studies were carried out by using Schrodinger suite.

Keywords: Dolastatin 15, GSKβ, HEPES, ligplot, molecular docking, pymol

Received 29 April 2013 Received in revised form 14 Feb 2014 Accepted 27 Feb 2014

***Address for correspondence:**
Vidhyeswari D,
Department of Chemical Engineering, Coimbatore Institute of Technology, Coimbatore-641014, India.
E-mail: ammudilip@gmail.com

INTRODUCTION

Cancer is an extensive group of various diseases, all concerning unregulated cell growth. It is medically termed as a malignant neoplasm. Cancer is the second largest deadly disease in the world. There are more than 100 types of cancer [1].

GSKβ negatively regulates many proto-oncogenic proteins and cell cycle regulators; one would predict that GSKβ may suppress tumorigenesis. Several studies indeed support that GSKβ functions as a ‘‘tumor suppressor’’ and represses cellular neoplastic transformation and tumor development. GSKβ also regulates cellular sensitivity/resistance to cancer chemotherapy [2].

HEPES is referred to as [*4-[2-hydroxyethyl]-1-piperazineethanesulfonic acid*]. It is currently used in the treatment of cancer. The objective of this study is to provide a better drug than the existing drug, HEPES.

Insilico studies are a computer simulation work which speed up the discovery of drug and are cost effective. Some of the examples are QSAR [Quantitative Structure-Activity Relationship], read across and virtual screening.

MATERIALS AND METHODS

Docking

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 [3]. Knowledge of the preferred orientation may be used to predict the strength of association or

binding affinity between two molecules using a scoring function. Docking has been widely used to suggest the binding modes of protein inhibitors. Most docking algorithms are able to generate a large number of possible structures, thus they also require a means to score each structure to identify those that are of the greatest interest. In general, the docking problem" is concerned with the generation and evaluation of plausible structures of intermolecular complexes. Docking was performed using Glide [4]. Glide docking uses a series of hierarchical filters to find the best possible ligand binding locations in a previously built receptor grid space. The filters include a systematic search approach, which samples the positional, con-formational, and orientation space of the ligand before evaluating the energy interactions between the ligand and the protein [4]. The Glide program is contained in Maestro 9.0 software [5]. Extra-precision [XP] module of Glide has been used. Default docking parameters were used. The docking hierarchy begins with the systematic con-formational expansion of the ligand followed by placement in the receptor site. Then minimization of the ligand in the field of the receptor is carried out using the OPLS-AA [6] force field with a distance-dependent dielectric of 2.0. The protein coordinates were extracted from the X-ray crystal structure [accession code in Protein Data Bank [PDB]: 1H8F]. The docking poses for each ligand were analyzed by examining their relative total energy score.

Marine compounds

Dolastatin 15, a seven-subunit depsipeptide derived from Dolabellaa-uricularia, is a potent antimitotic agent Indeed; numerous dolastatin 15 related peptides have been isolated from diverse marine cyanobacteria [7]. **Kahalalide F** [KF] is one of a family of dehydro-aminobutyric acid-containing peptides derived from the marine mollusk Elysiarufescens, a marine mollusc found in Hawaii. This mollusk is able to sequester chloroplasts from an alga to participate in the synthesis of secondary metabolites [8]. **Ara-A** [arabinosyladenineor] were isolated from the gorgonian Eunicellacavolini and is used as antiviral drug [9]. **Bromosphaerone** were isolated from the marine red alga Sphaerococcu-scoronopifolius from the Atlantic Ocean, sea coast of morocco [10]. **Cribrostatin 3,** blue marine sponge Cribrochalina sp. [11] collected in the Republic of Maldives. **Spongiadiol** is a tetracyclic furanoditerpeneisolated from deep-water [12]. **Pestalone** is a chlorinated benzophenone antibiotic. It is produced from a Pestalotia species of fungus, isolated from the surface of the brown alga Rosenvigea sp. From Bahamas, only when a unicellular marine bacterium was cocultured in the fungal fermentation [13].

RESULTS AND DISCUSSION (**Screening Results**)

Table 1: HTVS Results

Compound Name	Docking Score	Glide Energy Kcal/mol
Dolastatin 15	-3.888883	-47.759413
Pestalone	-6.623366	-39.956989
Ara-A	-5.632760	-33.946971
Bromosphaerone	-4.663613	-31.331942
1H8F	-3.982527	-27.607760
Spongiadiol	-4.794071	-23.336875
Cribrostatin 3	-1.482854	-17.399198

Through HTVS results, it is clearly shows that the docking score and glide energy of Dolastatin15, Pestalone, Ara-A, Bromosphaerone are lesser than HEPES. Khalalide F didn't give docking score and glide energy. It shows that there won't be any interaction between protein and ligand. Compounds with minimum glide energy and minimum docking score has been selected and Induced Fit Docking has been carried out.

Table 2: IFD Results

Compound Name	Docking Score	Glide Energy	Interactions		Distance
				O-H....O [ASP200]	2.786
	-5.072171	-34.826084		O-H....O [ASN95]	2.848
			[ASN95] N-H....O		3.023
				O-H....O [ASN186]	3.184
	-4.103179	-32.774528	[SER66] N-H....O		2.860
				O-H....O [GLU97]	2.837
CO-LIGAND				O-H....O [ASP200]	2.846
	-4.515961	-30.679562		O-H....O [GLU97]	3.070
			[ASN95] N-H....O		3.098
				O-H....O [ASP200]	2.963
	-4.050743	-31.278894	[SER66] O-H....O		3.077
			[PHE67] N-H....O		3.195
			[ARG96] N-H....O		2.855
				O-H....O [ASP200]	2.606
			[SER66] N-H....O		3.060
	-6.363153	-51.357673		O-H....O [GLY68]	2.990
				O-H....O [GLU97]	3.121
			[PHE67] N-H....O		3.376
			[ARG180]	N-H....O	3.138
PESTALONE	-5.694868	-48.860249		O-H....O [ALA204]	2.774
			[ARG96] N-H....O		2.954
	-6.353562	-46.706760	[SER66] O-H....O		2.711
				O-H....O [GLY68]	2.924
			[ARG96] N-H....O		2.969
	-5.341851	-44.308108		O-H....O [ASP200]	2.513
				O-H....O [SER66]	2.897
	-5.825825	-30.837464	[ARG96] N-H....O		2.971
			[SER66] N-H....O		2.888
			[ARG96] N-H....O		3.362
	-4.186648	-29.551146		O-H....O [LEU88]	3.043
SPONGIADIOL			[ASN95] N-H....O		3.239
			[ASN95] N-H....O		3.035
			[LYS85] N-H....O		3.214
	-4.708203	-29.362242		O-H....O [GLU97]	3.244
			[ASN95] N-H....O		2.946
	-5.165554	-29.057449		O-H....O [GLU97]	3.156
			[LYS205]	N-H....O	3.193
	-5.257825	-53.358391	[ARG96] N-H....O		2.953
			[ARG96] N-H....O		2.827
DOLASTATINS 15			[ARG96] N-H....O		3.370
	-3.505505	-41.500996	[LYS205]	N-H....O	3.313
	-2.331973	-32.378457	[ARG180]	N-H....O	3.039
				O-H....O [ASP200]	2.763
				O-H....O [ASP200]	2.001
	-7.282155	-44.539915	[SER66] O-H....O		3.073
			[SER66] N-H....O		2.847
			[PHE67] N-H....O		3.343
			[ASN95]N-H....O		3.264
				O-H....O [ASP200]	2.722
ARA-A	-6.153473	-38.695058	[LYS85] N-H....O		2.892
				O-H....O [ASP200]	2.722
				O-H....O [GLY68]	2.860
	-6.140888	-38.464927		O-H....O [ASP200]	2.528
			[PHE67] N-H....O		2.940
				O-H....O [GLY202]	3.057
	-5.628498	-37.071906		O-H....O [GLU97]	2.861
				O-H....O [LEU88]	2.854

From the table it is clearly shown that the docking score and glide energy of dolastatin 15, spongiadiol and ara-A are lesser than the docking score and glide energy of HEPES. Dolastatin 15 shows very low docking score and low glide energy.

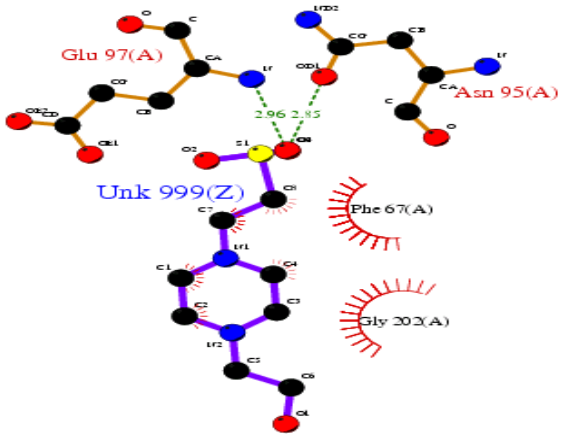

Figure 1: Ligplot for HEPES

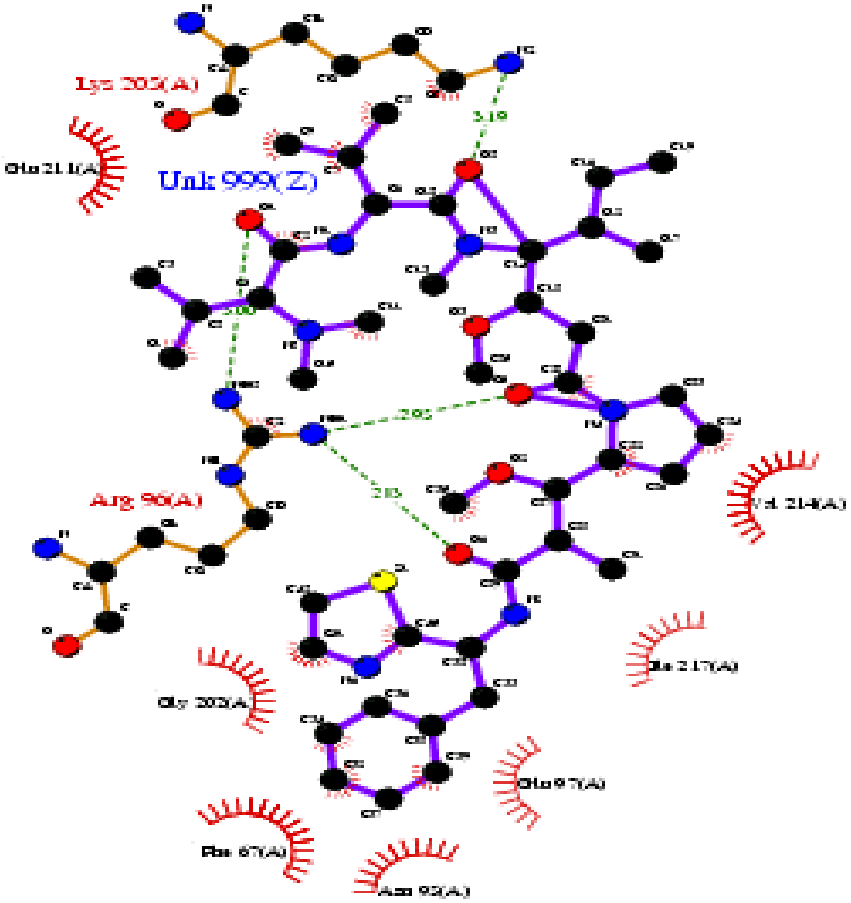

Figure 2: Ligplot for Dolastatin 15

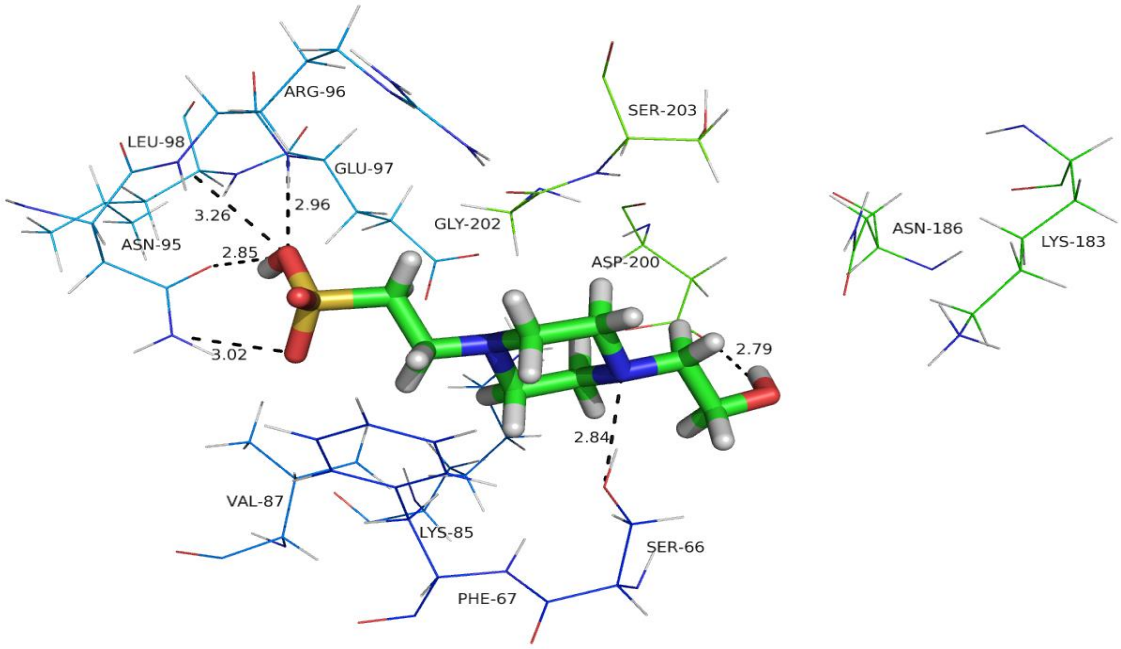

Figure 3: Pymol picture of HEPES

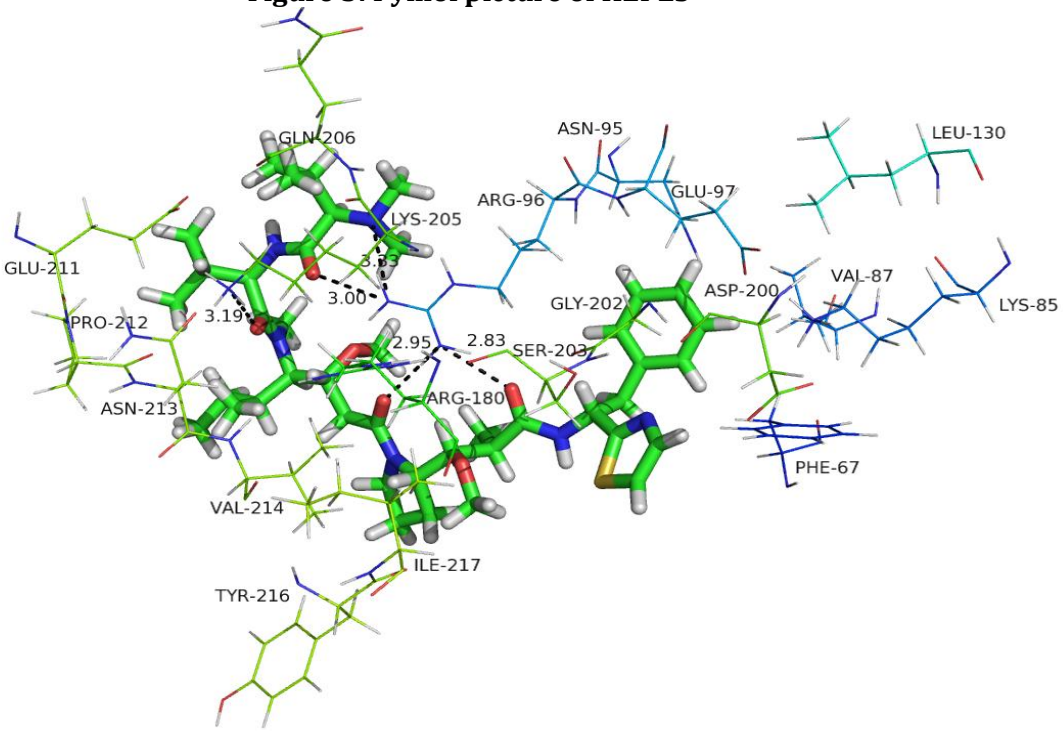

Figure 4: Pymol picture of dolastatin 15

The pymol and ligplot pictures of HEPES and Dolastatin 15 clearly explain the active site residues of dolastatin 15, matches to the active sites of hepes.

CONCLUSION

From this study, it has been concluded that Dolasatins 15 is the best compound among the various other marine natural compounds - Kahalalide F, Ara-A, Bromosphaerone, Cribrostatin 3, Spongiadiol and Pestalone, and the existing compound HEPES, analyzed by molecular docking method for the treatment of cancer. Dolastatins 15 shows very low glide energy og -53.358391 and low docking score of -5.257825 when compared to other compounds as well as existing drug. Also, the active site residues of Dolasatins 15, match to the active site residues of HEPES. The work can be extended for further analysis.

REFERENCES

1. "How many different types of cancer are there?: Cancer Research UK: Cancer Help UK". Retrieved, 11 May 2012.
2. G. Cai, J. Wang, X. Xin, Z. Ke, J. Luo, Phosphorylation of glycogen synthase kinase-3 beta at serine 9 confers cisplatin resistance in ovarian cancer cells, Int. J. Oncol. 31 [2007] 657–662
3. Lengauer T, Rarey M [1996]. "Computational methods for bio-molecular docking". *Curr. Opin. Struct. Biol.* **6** [3]: 402–6. doi:10.1016/S0959-440X[96]80061-3. PMID 8804827.
4. R.A. Friesner, J.L. Banks, R.B. Murphy, T.A. Halgren, J.J. Klicic, D.T. Mainz, et al., Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy, J. Med. Chem. 47 [2004] 1739–1749
5. Maestro, Version 9.0, Schrödinger, LLC, New York, NY, 2007.
6. W.L. Jorgensen, D.S. Maxwell, J. Tirado-Rives, Development and testing of the OPLS all-atom force field on conformational energetics and properties of organic liquids, J. Am. Chem. Soc. 118 [1996] 11225–11236.
7. Wender P A, Hinkle K W, Koehler M F, Lippa B. The rational design of potential chemotherapeutic agents: synthesis of bryostatin analogues. Med Res Rev., 19 [1999] 388-407.
8. Kan Y, Fujita T, Sakamoto B, A new cyclic depsipeptide from the hawaiian green alga bryopsis species. J Nat Prod., 62 [1999] 1169-72.
9. Natural Product Chemistry for Drug Discovery: edited by Anthony D. Buss, Mark S. Butler page 175.
10. Advances in Food and Nutrition Research Volume 64 Marine Medicinal Foods: Implications and Applications, Macro and Micro algae volumeedito: Se-Kwon Kim page 74
11. Antineoplastic agents 430. Isolation and structure of cribrostatins 3, 4, and 5 from the republic of Maldives cribrochalina species. Pettit GR, Knight JC, Collins JC, Herald DL, Pettit RK, Boyd MR, Young VG.
12. Natural Products: Drug Discovery and Therapeutic Medicine edited by Lixin Zhang [Ph. D.], Lixin Zhang, Arnold L. Demain, page 209.
13. Studies in Natural Products Chemistry, Volume 35 By Atta-urRahman, page 243.