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Research Article

MOLECULAR DOCKING STUDIES OF MAGE INHIBITORS IN THE TREATMENT OF LUNG CANCER

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ABSTRACT

The insilico methods for drug discovery are becoming increasingly powerful and useful. That in combination with increasing computer processor power. Lung cancer is the leading cause of cancer associated deaths Worldwide and has one of the poorest prognoses among all cancer types. A variety of melanoma antigen A (MAGE-A) genes are commonly detected in non-small cell lung cancers. Their biological function is not well characterized but may involve the regulation of apoptosis and cell cycle progression. In this study ligand-based drug design were employed to design novel MAGE inhibitors from Naringi crenulata found in Asia. The MAGE structure model was built in homology modeling based on known receptors of the same family. A phytochemicals of Naringi crenulata are analysed and optimized with the Argus lab to investigate the interactions between the target compounds and the amino acid residues of the Mage protein .All the compound have shown binding pose between from – 6.54 to -15.34.out of five compound 1,2-benzenedicarboxylic acid show best ligand energy -8.15Kcal/mol with 3 hydrogen bond of distance is 2.1,3.0 and 2.3

Keywords: Lung Cancer, Mage Protein, Docking, Modelling, Naringi Crenulata, Argus lab

INTRODUCTION

Cancer is a pathological state involving uncontrolled proliferation of tumor cells. Though, it is one of the most dangerous diseases in humans and presently there is a considerable scientific discovery of new anticancer agents from natural products [1]. However, the drugs used for this therapy have a narrow therapeutic index, and often the responses produced are only just palliative as well as unpredictable. In contrast, targeted therapy that has been introduced in recent years is directed against cancer-specific molecules and signaling pathways and thus has more limited nonspecific toxicities[2] Lung cancer was a rare disease at the start of 20th century, but exposures to new etiologic agents. While tobacco had been widely used throughout the world for centuries, the present pandemic of lung cancer followed the introduction of manufactured cigarettes with addictive properties, which resulted in a new pattern of sustained exposure of the lung to inhaled carcinogen[3].Lung cancer occurs in multiple histologic types as classified by conventional light microscopy. The four major types include squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell undifferentiated carcinoma. Together, these four types of lung cancer account for > 90% of lung cancer cases in the United States [4] Melanoma-associated gene expression (MAGE) antigens were first described in a melanoma cell line. This is a 12-member family of proteins encoded on chromosome Xq28. The precise cellular expression and biological functions of the MAGE antigens have not been completely elucidated. Also referred to as 'cancer–testis antigens', they are not expressed in normal tissues except the testis and placenta. In neoplastic lesions, they have been found to be expressed in 12–60% of solid malignant tumors including lung [5]. Type 1 MAGE expression has been documented in a broad variety of malignancies [6, 7]. Non–small cell lung cancers frequently express a variety of type 1 MAGE genes [8]. Proteasomal degradation of type 1 MAGE proteins generates several small peptides, which are subsequently expressed on the cell surface in association with MHC class I molecules. These peptides represent the target antigens for CTLs directed against MAGE-A-expressing cancer cells [9, 10– 11]. Based on these observations, type 1 MAGE protein–derived peptides are currently studied as targets for the development of cancer vaccines for non–small cell lung cancer and other malignancies [11].

MATERIALS AND METHODS

Swiss Prot Database

Swiss-Prot is a manually curated biological database of protein sequences. Swiss-Prot strives to provide reliable protein sequences associated with a high level of annotation, a minimal level of redundancy and high level of integration with other databases.

Homology modeling

Among all current theoretical approaches, comparative modeling is the only method that can reliably generate a 3D model of a protein from its amino acid sequence. Modeling of protein structures usually requires extensive expertise in structural biology and the use of highly specialized computer programs for each of the individual steps of the modeling process.[12]The method of homology modeling is based on the observation that protein tertiary structure is better conserved than amino acid sequence[13] The three dimensional structure of MAGE has been predicted using MODELLER9v8

(http://www.salilab.org/modeller/)

Model refinements and evaluation

The model generated by MODELLER9v8 was subjected to energy minimization using the steepest descent technique to eliminate bad contacts between protein atoms using swiss pdb viewer. Validation of modelled structure was carried out using Structure Analysis and Validation Server. It performs structure validation calculations using PROCHECK, PROVE, Verify3D, ERRAT and WHAT_IF programs. The validated result of the modeled protein from the server is an important part of comparative modeling process.

Active site prediction

After obtaining the final model, the possible binding sites of short neurotoxin were searched using Computed Atlas of Surface Topography of Proteins (CASTp). These include pockets located on protein surfaces and voids buried in the interior of proteins. CASTp includes a graphical user interface, flexible interactive visualization,

as well as on-the-fly calculation for user uploaded structures [14]

Docking

Docking the inhibitors against the active site of the MAGE Docking is a computational technique that samples conformations of small molecules in protein binding sites; scoring functions are used to assess which of these conformations best complements the protein binding site[15].The inhibitor and target protein was geometrically optimized and docked using docking engine Argus Dock.

RESULTS AND DISCUSSION

Molecular modeling (docking) study was carried out for compound like from Dioctyl phthalate, n-hexadecanoiac acid, Lupenone, 7-tetradecenal,(z)-and 1,2-benzenedicarboxylic acid from Naringi crenulata (1A-1I) fig 1(A,B,C,D and F) for Lung cancer.

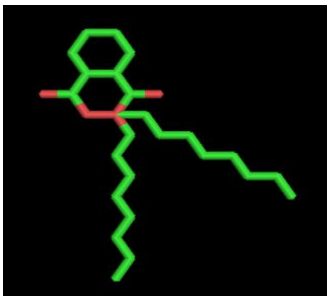


Fig -1a

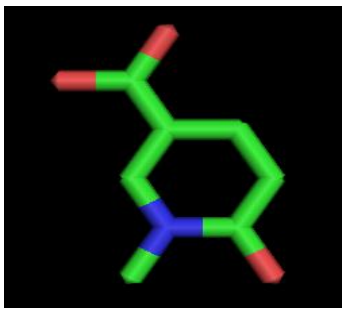
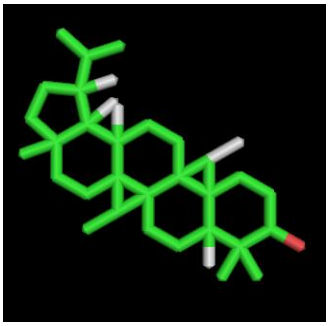


Fig -1b



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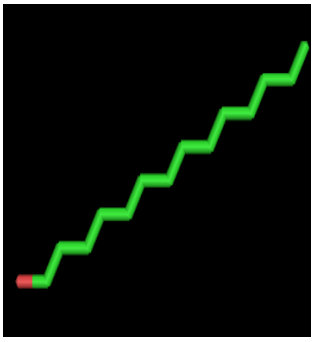

Fig -1d

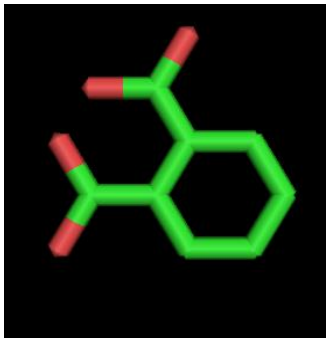

Fig -1e

Fig -1a, 1b, 1c, 1d, 1e: It Shows compound from Naringi crenulata plant Dioctyl phthalate, n-hexadecanoiac acid , Lupenone, 7-tetradecenal,(z)- And 1,2 benzenedicarboxylic acid

The potential active site amino acids were predicted using Castp. Among the 32 active sites predicted, pocket 1 found to be the best active site which contains 58 amino acids. Thus, the protein was targeted against pocket 1.Given the three-dimensional structure of a target receptor molecule usually a protein; chemical compounds having potential affinity towards it are designed rationally, with the aid of computational methods (Ooms, 2000). Figure 2 shows the structure of inhibitors target against the mage.

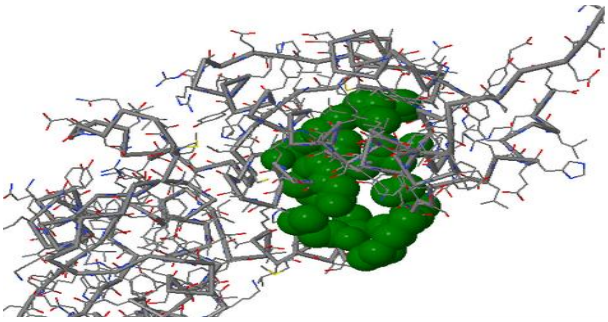

Fig. 2: Shows the Structure Targeted Mage Protein Predicted Using Castp

The target protein and inhibitors were geometrically optimized .Given the three-dimensional structure of a target receptor molecule usually a protein; chemical compounds having potential affinity toward sit are designed rationally, with the aid of computational methods. Detailed bioinformatics analysis offers a convenient methodology for efficient in silico preliminary analysis of possible function of new drug. Figure 3 shows the structure MAGE protein.

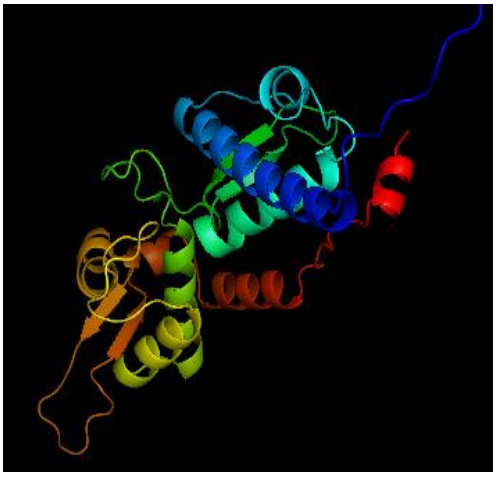

Fig. 3: Shows the structure MAGE protein visualised using pyMol

MAGE protein was subjected to homology search against PDB database using BlastP to identify significant structural homologs to be used as template for homology modelling. The results indicated the presence of MAGE super family domain and the best homolog was Model with 40 % identity with the query protein and thus served as a template for modelling and the modelled protein obtained is shown in Fig5 and Validation was done using Ramachandran map (Fig.3) after loop refinement.

All the five inhibitors were docked against active site of the target protein using Argus lab which gives an insight into the binding modes for the various inhibitors. Out of 5 inhibitors analyzed i.e. Dioctyl phthalate, n-hexadecanoiac acid, Lupenone, 1, 2-benzenedicarboxylic acid, 7-tetradecenal,(z)-. 1,2-benzenedicarboxylic acid has showed higher binding energy of 9.15 Kcal/mol against the target protein. The binding energy of all the inhibitors was shown in Table 1. Figure 4 represents the docked complex of the inhibitors to that of the target protein.

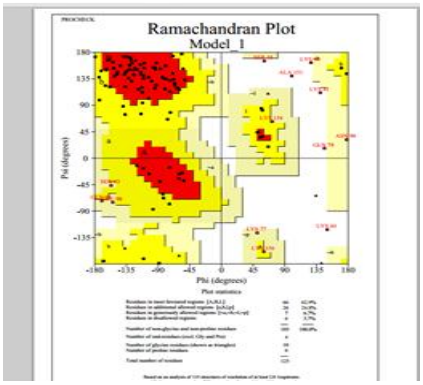

Fig.5: Ramachandran plot of Mage

Table 1: It shows the Docking results of Naringi crenulata derived compounds against MAGE protein

SI.NO	Drug name	Binding energy	Distance Of Hydrogen bonding	No. of Hydrogen Bonding
1	1,2-benzenedicarboxylic acid	-8.15Kcal/mol	2.1,3.0,2.3	03
2	Lupenone	-15.34Kcal/mol	3.4	01
3	n-hexadecanoiac acid	-6.14 Kcal/mol	2.9	01
4	7-tetradecenal,(z)-	-7.12	-	-
5	Dioctyl phthalate	-6.54	-	-

Docking complex of Mage protein and 1,2-benzenedicarboxylic acid

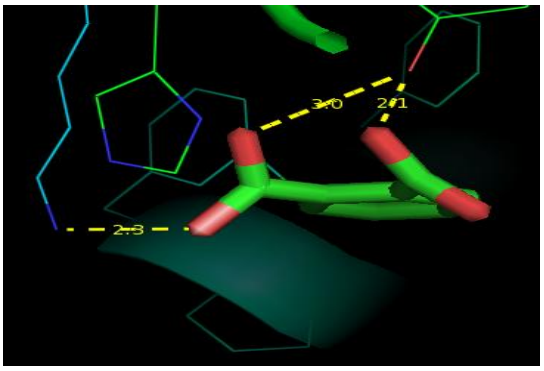

Fig. 4: Represents the Docked Complex of the Inhibitors to that of the Target Protein.

The Table 2 describes the molecular property of 1,2-benzenedicarboxylic acid (Table 2). 1,2-benzenedicarboxylic acid is a small sized molecule with a molecular weight of 166.13084 Da. It has two hydrogen bond donors and four hydrogen bond acceptors with two rotatable bond. The compound 1,2-benzenedicarboxylic acid has the LogP value of 0.7.Thereby it satisfies all the criteria of Lipinski's rule of five (Christopher et al., 1997).

Table 2: Molecular property of 1,2-benzenedicarboxylic acid

Molecular formula	$C_8H_6O_4$
Formula weight	166.13084 [g/mol]
A logp	0.7
No. of hydrogen acceptors	04
No. of hydrogen donors	02
Density	1.593 g/cm^3
Polarizability	0.148185A$^{\circ 3}$
Monoisotopic mass	166.026609 Da
Average mass	166.130798 Da

CONCLUSIONS

The present study indicates that the herbal plant Naringi crenulata can be used in the treatment of Lung cancer, which shows a strong binding affinity towards MEGA protein . This brings a strong focus towards these plant that, when administered during the treatment of lung cancer may block MEGA. Naringi crenulata showed the highest affinity towards MEGA compared to other compounds. This creates a strong hypothesis that the effects of complex formation by MEGA and Naringi crenulata contribute towards combating against Lung Cancer. Hence, MEGA PROTEIN may become a prospective target for inhibition of Lung cancer and may unlock a strong initiative in developing novel ligand which is specified towards it. Hence the compound specified in this work can undergo certain specification to improve its drug properties and could act as a best drug for lung cancer. The mechanism of action is lupenone to inhibit the activity of Mega that is involved in tumor proliferation

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