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DERIVATIVES OF CYCLOPROPYL AMINES AS AN INHIBITOR FOR HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)

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ABSTRACT

In silico methods help in identifying drug targets via bioinformatics tools. They can also be used to analyze the target structures for possible binding/ active sites, generate candidate molecules, check for their drug likeness, dock these molecules with the target , rank them according to their binding affinites , further optimize the molecules to improve binding characteristics. The present paper describes the molecular docking studies of cyclopropyl amines, derived from *Ephedra* plant, as inhibitors of HER2 for cancer. Docking studies cyclopropyl amines have been carried out in the active site of HER2 by using Auto Dock. The protein file of HER2 [PDB ID: 1MFG] was taken from the protein data bank. The lead moiety from cyclopropyl amines has shown best ligand pose -5.1981kcal/mol.All the derivatives of cyclopropyl amines have shown best ligand pose energy between -3.57 kcal/mol to -5.86 kcal/mol. Among them N-cyclopropyl-4-methoxybenzamide (1C), 3,4-dichloro-N-cyclopropylbenzamide(1E), 2-chloro-N-cyclopropylbenzamide and (1F) has shown best ligand pose like -5.86 kcal/mol, -5.50 kcal/mol, -5.29 kcal/mol and -5.05 kcal/mol with HER2 respectively. The theoretical results have shown a higher estimated binding energy of cyclopropyl amines suggesting a better anti-cancer activity and efficient inhibitor to treat breast cancer.

KEY WORDS: Ephedra, Cyclopropyl amines, Breast cancer, HER2, Auto dock.

INTRODUCTION

Cancer is a dreadful disorder developed due to some molecular changes within the cell. Cancer continues to represent the largest cause of mortality in the world and claims over 6 million lives every year. Cancer is a group of diseases characterized by unregulated division and spread of cells. The cancerous cells may occur in liquids, as in leukemia. Chemotherapy remains the principal mode of treatment for various cancers and is defined as the use of synthetic or natural agents (alone or combination) to block the development of cancer in humans[1-3]. By their original locations they are classified into various types of cancer, such as lung, colon, breast, or prostate cancer. Breast cancer is one of the most common types of cancers and cause of cancer death in women worldwide. Women with breast cancer have many treatment options. These include surgery, radiation therapy, chemotherapy, hormone therapy, and biological therapy. Many women receive more than one type of treatment. Surgery is the most common treatment for breast cancer[4]. Many of the established risk factors are linked to oestrogens. Risk is increased by early menarche, late menopause, and obesity in postmenopausal women, and prospective studies have shown that high concentrations of endogenous oestradiol are associated with an increase in risk. Childbearing reduces risk, with greater protection for early first birth and a larger number of births; breastfeeding probably has a protective effect. Both oral contraceptives and hormonal therapy for menopause cause a small increase in breast-cancer risk, which appears to diminish once use stops. Alcohol increases risk, whereas physical activity is probably protective. Mutations in certain genes greatly increase breast cancer risk, but these account for a minority of cases[5].

The human epidermal growth factor (HER) family of transmembrane receptors are potent mediators of normal cell growth and development. This family of receptors consists of four closely related type 1 transmembrane tyrosine kinase (TK) receptors: HER1 (epidermal growth factor receptor; EGFR), HER2, HER3 and HER4. Each receptor comprises an extracellular domain where ligand binding occurs, an α-helical transmembrane segment and an intracellular protein TK domain. Receptor dimerization (pairing) is an essential requirement for HER function and for the signalling activity of all HER receptors. However, HER receptors normally exist as inactive monomers with the molecules folded in such a way as to prevent dimerization. HER1, HER2 and HER3 are all implicated in the development and progression of cancer; the role of HER4 in oncogenesis remains less well defined. The HER2:HER3 heterodimer is considered the most potent HER receptor pair with respect to strength of interaction, ligand-induced tyrosine phosphorylation and downstream signalling,

and functions as an oncogenic unit. Indeed, HER3 may be a necessary partner for HER2 to act as an oncogene in tumours overexpressing HER2. Taking together their oncogenic capacity and their frequently aberrant expression or dysregulation in human tumours, members of the HER family are established targets for approved therapeutics and continue to be targets for the development of novel anticancer agents, including monoclonal antibodies (mAbs) that target the extracellular regions of the receptor and small-molecule TK inhibitors (TKIs) that prevent signal transduction via the receptor TK domain. HER2 over expression occurs in ~15%–20% of patients with breast cancer and is associated with aggressive disease and decreased survival[9]. A number of therapeutic approaches have been developed against HER2 including monoclonal antibodies and small molecule TKIs[6, 7, 8].

Natural and synthetic cyclopropanes bearing simple functionalities are endowed with a large spectrum of biological properties ranging from enzyme inhibitions to insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumor and antiviral activities.

MATERIALS AND METHODS

Swiss Prot Database

Swiss-Prot is a manually curate 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[9].

Protein Data Bank

The structure of the protein Her-2 with the PDB ID [1MFG] was retrieved from the Protein Data Bank. It is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids.

Active site prediction

After obtaining the final model, the possible binding sites of short HER2 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. These include pockets located on protein surfaces and voids buried in the interior of proteins. CastP server uses the weighted Delaunay triangulation and the alpha complex for shape measurements. It provides identification and measurements of surface accessible pockets as well as interior inaccessible cavities, for proteins and other molecules.

It measures analytically the area and volume of each pocket and cavity, both in solvent accessible surface (SA, Richards' surface) and molecular surface (MS, Connolly's surface). It also measures the number of mouth openings, area of the openings, and circumference of mouth lips, in both SA and MS surfaces for each pocket[10].

Preparing the derivatives of cyclopropylamines

Medicinal chemistry or Pharmaceutical Chemistry is a discipline at the intersection of chemistry and pharmacology involved with designing, synthesizing and developing pharmaceutical drugs[11]. The cyclopropylamines was synthesized from Kulinkovich-Szymoniak Reaction and further their derivatives were obtained by treating various acid[12].

Docking the inhibitors against the active site of the HER2

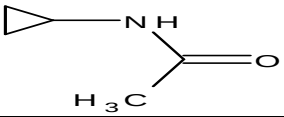
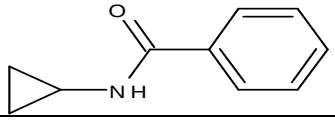
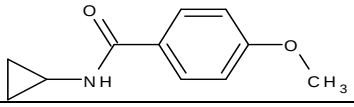
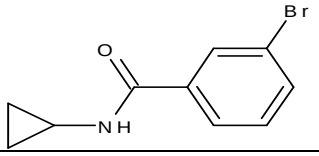
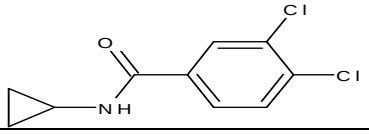
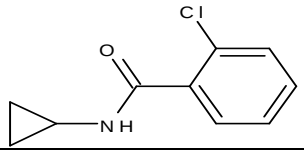
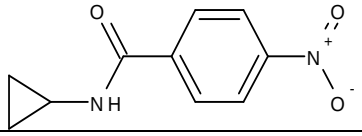
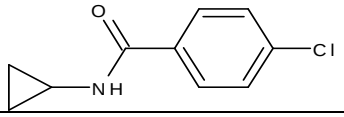
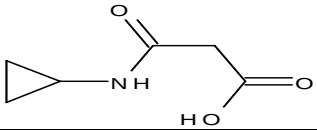
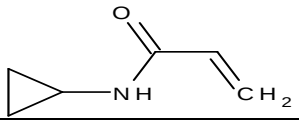
Molecular docking is a key tool in structural molecular biology and computer assisted drug designing[13]. Docking is a computational technique that samples conformations of small molecules in protein binding sites; scoring functions are used to assess which of these conformations best complements the protein binding site 13. The inhibitor and target protein was geometrically optimized and docked using the docking engine Auto Dock. (http://autodock.scripps.edu/). AutoDock is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure[14].

RESULTS AND DISCUSSION

Here the structure based drug design for the target HER2 (Figure.1) protein involved in cancer treatment is predicted by docking various components of cyclopropyl amines (Table no: 1) with HER2. The potential active site amino acids were predicted using CastP. The Figure. 2 show the active site of the target protein which has the surface area of 133.2 cubic angstroms and volume of 196.6 cubic angstroms. 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. The target protein and the inhibitors were geometrically optimized. All the ten inhibitors were docked against active site of the target protein HER2 using Auto Dock which gives as insight into the building modes for the various inhibitors. The schematic representations of all the compounds are shown in Figure 3. Out of 10 inhibitors analyzed (i.e. 1A, 1B, 1C, 1D, 1E, 1F, 1G, 1H, 1I, 1J) 1C has showed best binding energy of -5.86 Kcal/mol against the target

protein. The binding energy of all the inhibitors was shown in Table no 2. Figure 3 represents the best docked complex of the inhibitor 1C to that of the target protein.

Table No 1: Various derivatives of Cyclopropyl amines

Compound Code	Compound Name	Structure
1A	*N*-cyclopropylacetamide	
1B	*N*-cyclopropylbenzamide	
1C	N-cyclopropyl-4-methoxybenzamide	
1D	3-bromo-*N*-cyclopropylbenzamide	
1E	3,4-dichloro-*N*-cyclopropylbenzamide	
1F	2-chloro-*N*-cyclopropylbenzamide	
1G	*N*-cyclopropyl-4-nitrobenzamide	
1H	4-chloro-*N*-cyclopropylbenzamide	
1I	3-(cyclopropylamino)-3-oxopropanoic acid	
1J	*N*-cyclopropylprop-2-enamide	

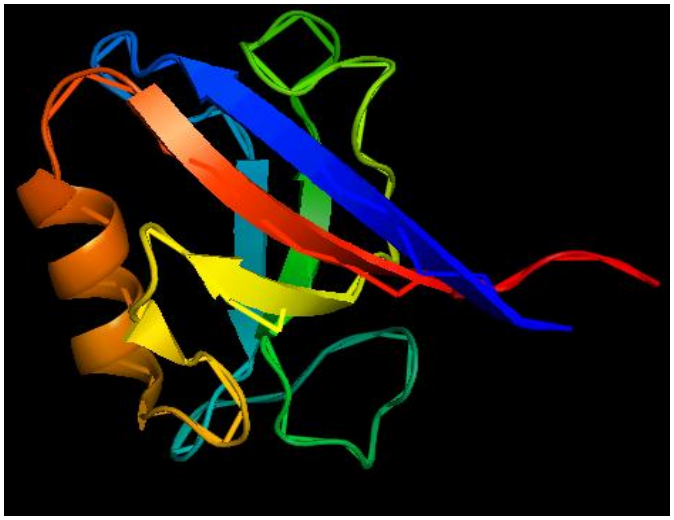


Fig: 1 Structure of HER2 protein (PDB ID: 1MFG)

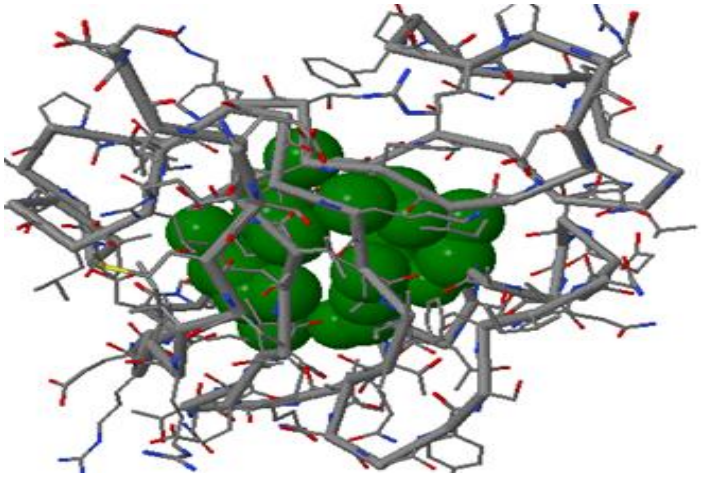


Fig: 2 Predicted active site of HER2 (PDB ID: 1MFG) from CASTp

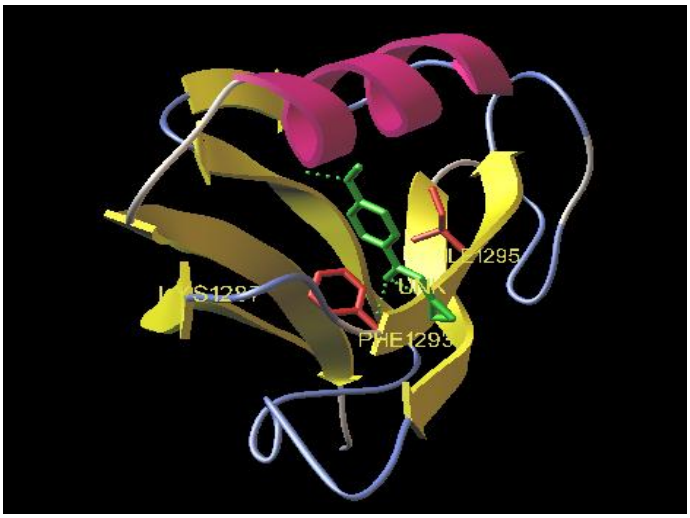


Fig: 3 Docked complex of HER2 (PDB ID: 1MFG) with inhibitor 1C

Table No 2: Summary of binding energy of all inhibitors against the target HER2 protein (PDB ID: 1MFG)

Sl.No	Compound Code	Binding Energy	Hydrogen bonds
a	Cyclopropyl amine	-5.19 kcal/mol	1
1	1A	-3.57 kcal/mol	1
2	1B	-4.85 kcal/mol	1
3	1C	-5.86 kcal/mol	3
4	1D	-4.88 kcal/mol	1
5	1E	-5.50 kcal/mol	0
6	1F	-5.29 kcal/mol	1
7	1G	-4.50 kcal/mol	1
8	1H	-5.05 kcal/mol	1
9	1I	-4.07 kcal/mol	2
10	1J	-3.83 kcal/mol	1

CONCLUSION

Derivatives studies of cyclopropylamines obtained from Ephedra plant are used in various diseases. In this study is mainly done to find out the inhibitory activity of cyclopropyl amines and their derivatives against HER2 for Breast cancer. By molecular docking studies it has been concluded that the theoretically designed cyclopropyl amine derivatives exhibits anticancer activity mainly for breast cancer than the parent compound cyclopropyl amine by inhibiting the enzyme human epidermal growth factor receptor (EGFR- HER 2).

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