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Study And Design Of 1-(5-Chloro-2-Hydroxyphenyl)-3-(3-Methylphenyl)Propane-1,3-Dione Derivatives As Aromatase Inhibitors

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Abstract:

The Series of 1-(5-chloro-2-hydroyphenyl)-3-(3-methylphenyl)propane-1,3-dione derivatives have several activities like, Anti-Microbial, Anti-Oxidant, Anti-Inflammatory and Anti-Cancer. Like aromatase inhibitor above maintained heterocyclic compounds derivatives inhibit estrogen with inhibition of estrogen production using aromatase. All estrogens are bio synthesized from androgens in presence of Aromatase cytochrome P450 known as catalytic biosynthesis. Aromatase inhibitors therefore constitute a frontline therapy for oestrogen-dependent breast cancer. Current research show molecular docking study **(1-(5-chloro-2-hydroyphenyl)-3-(3-methylphenyl)propane-1,3-dione)** with **PDB ID: 3 EQM**. We have design newly five compounds VPK-1,VPK-2,VPK-3,VPK-4,VPK-5, but Compound **VPK-2** show good docking score **(-8.8)** and compound VPK-1 show (-7.5) moderate docking score compare to Standard **Fadrazole (-7.2)** Respectively.

Keywords: Molecular docking, Aromatic Inhibitor,Chalcone, Auto Dock tool, Auto Dock vina.

INTRODUCTION

Molecular docking is a computational procedure in which the non-covalent bonding of molecules, e.g. a protein receptor and a ligand, is predicted. This prediction outputs the conformation and, usually, the binding affinity of the small molecule in its predicted minimal energy state and is used to virtually screen large libraries of compounds . Docking is composed of two main steps: sampling and scoring. Sampling refers to an extensive search of the adjust space of the molecules being docked. This adjust space is vast, due in part to both the receptor and ligand being flexible allowing for each molecule to adjust its shape due to the influence of the other. In order to constrain this large adjust space, the receptor is typically kept rigid. The other vital piece of molecular docking is the scoring function.

Molecular docking is of various types as follows: Protein-Protein docking, Protein-Ligand docking, Rigid ligand, and unbending receptor docking, Flexible ligand and inflexible receptor docking, Flexible ligand and adaptable receptor docking, Local move Monte Carlo inspecting.

(a) The ligand should possess suitably positioned hetero atom, which strongly interact with heme iron.

(b) The ligand should have a hydrophobic spacer moiety between heme coordinating group and hydrogen bond acceptor moiety.

(c) Aromates inhibitors need a chemical group that is able to accept H-bond from Arg375A present in active site.

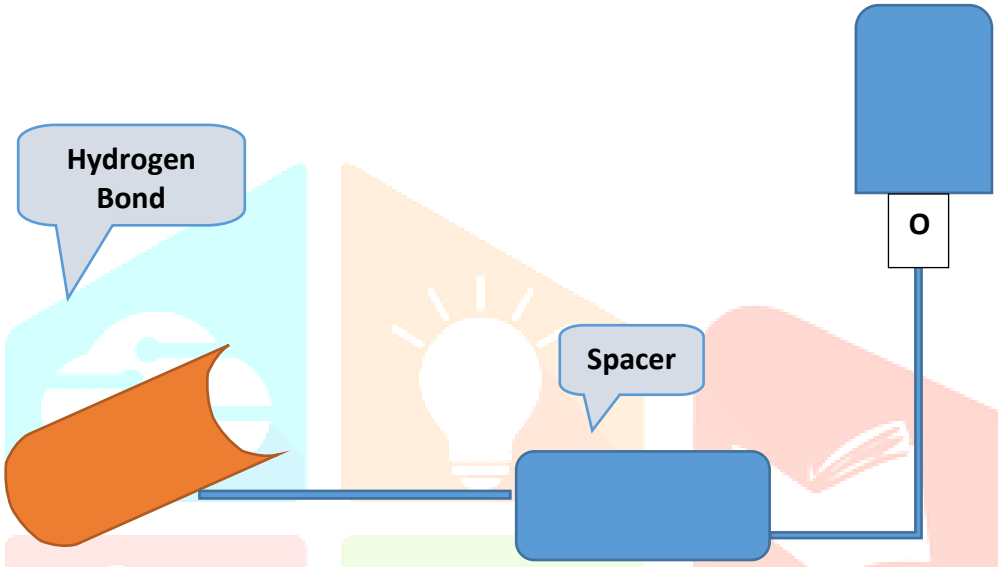
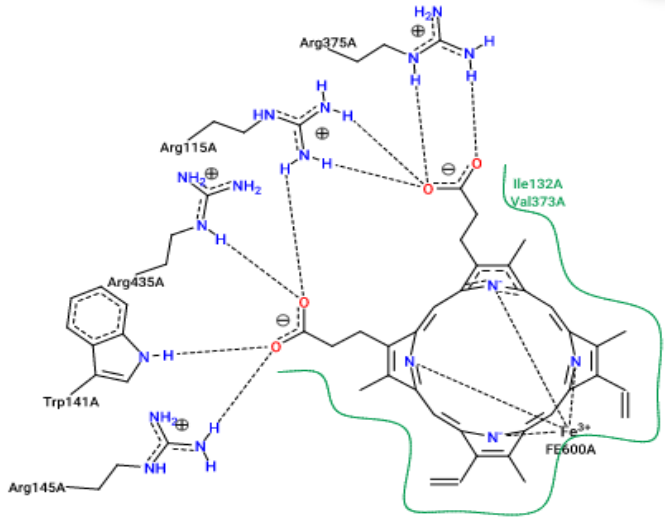


Fig. 1 : Pharmacophore Pattern of Aromates Inhibitors.

On the basis of literature and Pharmacophore structure of estrogen inhibitors,The aim of present work is to Studies on Design and Evaluation of Chalcone derivatives (i.e. VPK-1,VPK-2,VPK-3,VPK-4,VPK-5) for the anticancer .

In this research molecular docking we provide an atomic level explanation for the binding of newly designed Chalcone derivatives to the Aromatase active site.

Targete



Dig.1 Targeted Receptor Chain

Specific goal of objective is to design of medicinally important heterocyclic compounds towards Aromatic.

The present research project has been discussed under the following heads:

1. Design of the above target compounds.
2. To targate the perticular side (Arg375A).

2. Chalcone derivatives were screened for anti-Cancer activity.

The work carried out in the direction of achieving the targets molecules has been discussed under the "Result and Discussion" section.

Experimental work

Molecular Docking Study of Chalcones derivatives (VPK-1,VPK-2,VPK-3,VPK-4,VPK-5) with targeted proteins(3EQM).

A. For selective aromatase inhibitors PDB id: 3EQM used

Molecular docking of proposed 5 Chalcone derivatives were done with the help of Pymol 4.6.0 software in order to choose the derivatives which shows good interactions with target protein. Chalcone derivatives taken into consideration are shown in following (**Table: 1)**

Compound Code	T Chalcone Derivatives
VPK-1	1,3 propanedione,1-[4-(1-methylethyl)phenyl]-3-phenyl
VPK-2	1-(5-chloro-2-hydroyphenyl)-3-(3-methylphenyl)propane-1,3-dion)
VPK-3	1-(5-chloro-2-hydroxyphenyl)-3-phenyl-1,3-propanedione
VPK-4	1-(3-methoxyphenyl)-3-phenyl-1,3-propanedione
VPK-5	1,3-bis(4-methoxyphenyl)-1,3-propanedione

Table: 2

Following steps are taken in to consideration for molecular docking study:

1. Ligand preparation
2 .Protein preparation
3. Receptor grid generation
4. Protein ligand docking

4.1.1 Ligand preparation

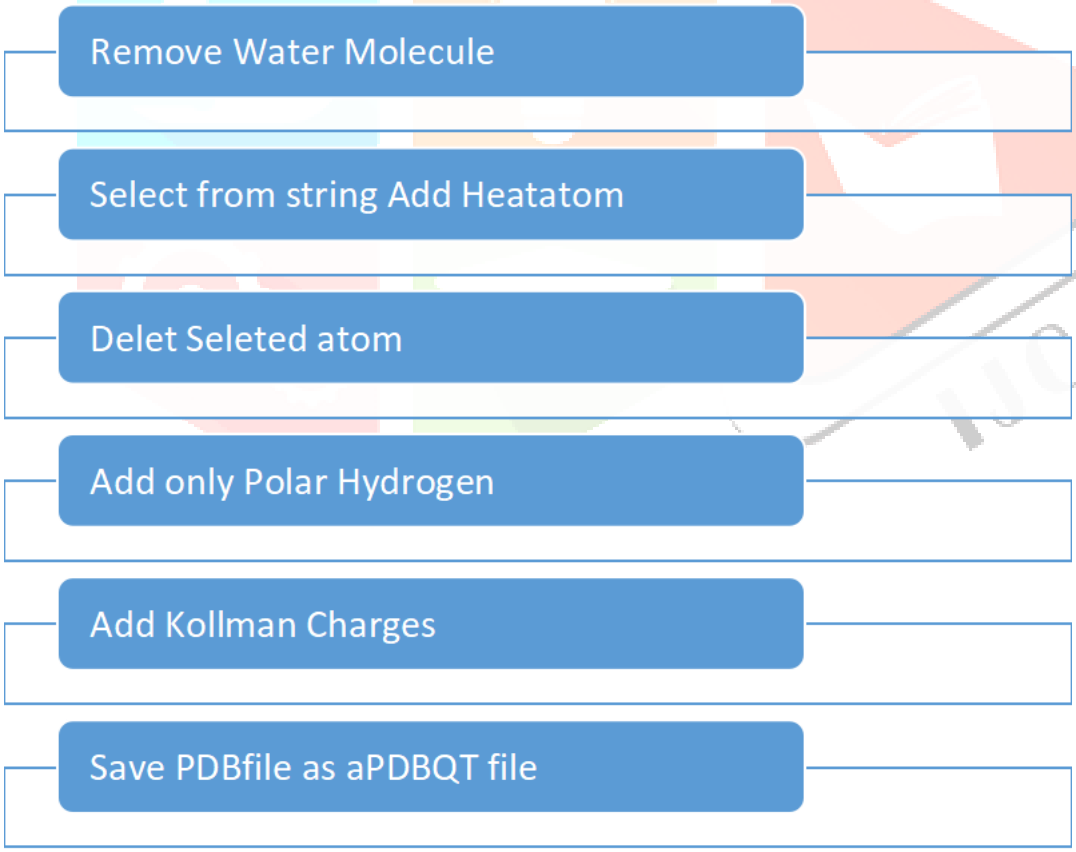
The ligand preparation was done by using Pymol application which consists of series of steps that perform conversion of SDF file into the PDB, apply correction to the structure by minimizing the proper bond angles and distances and optimize the structure by minimizing its energy through force-field OPLS3.

Depending on the objective, different ligands will be used for docking. It can be accessed from a variety of databases, such as ZINC or/and PubChem, or it can be sketched using the Chemsketch tool. Applying filters is frequently required to lower the amount of molecules that need to be docked. The net charge, molecular weight, polar surface area, solubility, commercial viability, similarity thresholds, and absorption, distribution, metabolism, excretion, and toxicity characteristics are a few examples. In the ligand

preparation process, ligand are obtained from pubchem in SDF form. In order to use that file for docking, we must convert it to pdbqt because the auto dock vina tool will not take it in that format. Therefore, we use Pymol programme to convert the ligand into pdb form and save. Drag the ligand into the auto dock tool to create a pdbqt file and save it. We used 5 different ligands

1. Protein Preparation

The crystal structure of human placental aromatase cytochrome P450 in complex with androstenedione (EC:1.14.14.1, 3EQM.pdb) has been obtained from the RCSBprotein data bank (http://www.pdb.org).Protein is a crucial component for molecular docking studies, and it is important to reduce the energy of protein molecules before conducting docking experiments with ligands. Using the protein preparation wizard programme, which was used to import proteins for the protein data library, both the protein and the ligand docking research were generated (PDB). Hydrogen, partial charges, side chains, and complete loop regions are frequently missing from proteins that are retrieved from the PDB, vendors, and other sources. Therefore, in order to overcome all of these obstacles, pre-processing of the proteins was done by choosing the following parameter



In 3EQM only A chain is present and we select that chain. protein is already docked with androstande and shows single A chain.

Receptor grid generation

Before launching a virtual screen with glide, grid generation must be completed. A grid by field that allows increasingly more precise scoring of the ligand poses represents the form and characteristics of the receptor. Glide creates grids for each conformation for receptors that take on more than one conformation upon binding to make sure that any potential actives are not overlooked. Glide's Receptor Grid Generation sub-menu was chosen from the Application menu in order to display the Receptor Grid Generation panel. There are three tabs on the Receptor Grid Generation panel that are used to provide settings for the receptor grid generation process. which are

- Receptor
- Site
- Constraints

Receptor

The docked structure that was acquired from the PDB contains both a receptor and a ligand. Either a molecule or an entry in the workspace can be used to identify the ligand. The ligand can be separated from the receptor when it was chosen in the workspace (Fig. 4.3). Dark green markers were used to highlight the ligand molecule, which was enclosed in a purple box. The area that the docked molecule can occupy to fulfil the first requirements of docking is defined by the purple bound box.

Site

A ligand molecule must be eliminated from the docked structure of a ligand with protein in order to identify the receptor site. For this, choose the centroid of the workspace ligand and click on advance settings. A green inner bounding box defining the space that the centroid of the docked molecule must occupy for the docking process to proceed will then display (Fig. 4.4).

Constraints

Based on structural or pharmacological information, glide restrictions are receptor-ligand interactions that are crucial for the binding modality. Setting restrictions enables Glide to filter out the ligands, their conformations, or poses in their evaluation of docking suitability that do not fulfil these requirements. Positional constraints, H-bond constraints, metal constraints, and hydrophobic constraints are the four different categories of Glide constraints. For creating the grid box, no limits were specified.

4. Protein Ligand Docking

five new Chalcone derivatives were created and docked on the Aromates enzyme for the docking process (PDB: 3EQM).for the protein ligand docking we use the AutoDock tool Software and for command autodock vina (Command prompt). the PDBQT files of Protein and Ligands are used.

The method of ligand docking aids in predicting ligand conformation and orientation (posing) inside a specified binding site, aiding in the interpretation of interactions between ligand atoms and protein amino acids as well as the binding affinity.

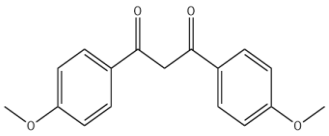
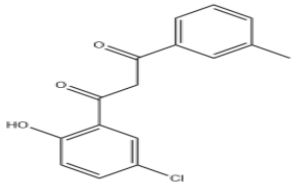
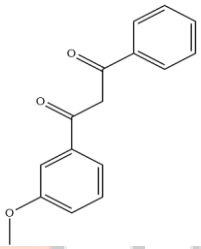
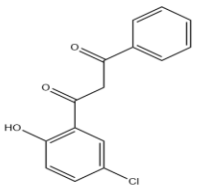
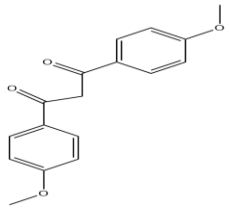
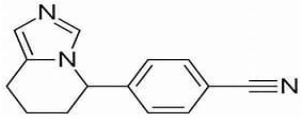
Sr.no.	Code	IUPAC Name	Molecular formula	Molecular weight(g/mol)	Structure
1	VPK-1	1,3 propandion ,1 –(4-(1-methyl)phenyl)-3-phenyl	$C_{18}H_{18}O_2$	266.3	
2	VPK-2	1-(5-chloro-2-hydroyphenyl)-3-(3-methylphenyl)propane-1,3-dion)	$C_{16}H_{13}ClO_3$	288.72	
3	VPK-3	(5-chloro 1--2-hydroxyphenyl)-3-phenyl-1,3-propanedione	$C_{15}H_{11}ClO_3$	274.7	
4	VPK-4	1-(3-methoxyphenyl)-3-phenyl-1,3-propanedione	$C_{16}H_{14}O_3$	254.28	
5	VPK-5	1,3-bis(4-methoxyphenyl)-1,3-propanedione	$C_{16}H_{26}N_2O_2$	278.39	
6	Standard (Fedrazole)	4-(5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-5-yl)benzonitrile	$C_{14}H_{13}N_3$	223.27	

Table. 3 Compound consider for Molecular docking

5. RESULTS AND DISCUSSION

The section includes the finding of research project and data collected during research work.

1. Molecular Docking Studies

1.1 Molecular docking study of chalcone derivatives on Aromates enzyme

1.1.1 Docking score and Protein-Ligand intraction

Molecular docking studies of all proposed Chalcone derivatives were carried using AutoDocktool software. Docking score is the function, designed to calculate the free energy of binding for a protein-ligand complex.

Total 5 molecules of chalcone derivatives were designed and docked on Aromates enzyme. Out of these, three molecules shows good interactions and Docking score as compared to standard Fedrazole are selected.

Sr.no.	Code	Docking score		NO. of position
		Highest	Lowest	
1	VPK-1	-7.5	-7.1	9
2	VPK-2	-8.8	-7.0	9
3	VPK-3	-7.5	-5.7	9
4	VPK-4	-7.7	-6.8	9
5	VPK-5	-7.0	-6.1	9
6	Standard (Fadrazole)	-7.2	-6.0	9

In all the docked compounds almost all ligands have Nine Docking postion with 3EQM, so preferences is given according to Docking score while shortlisting the molecules. Compounds **(VPK-1,VPK-2,VPK-3,VPK-4,VPK-5)** possesses Nine Docking Postion with 3EQM and having Docking score of **-7.5,-8.8,-7.5,-7.7-7.0** respectively. Standard **fadrazole has Nine Docking Postion and Docking score-7.2 .** Therefore from the docking result compound **(VPK-1,VPK-2,VPK-3,VPK-4)** are considered for the synthesis which may shows good aromatase inhibitors activity as compare to Fadrazole. The ligand interaction diagram of some of the selected compounds and fadrazole is given in **fig. (2,3,4,5,6,7).**

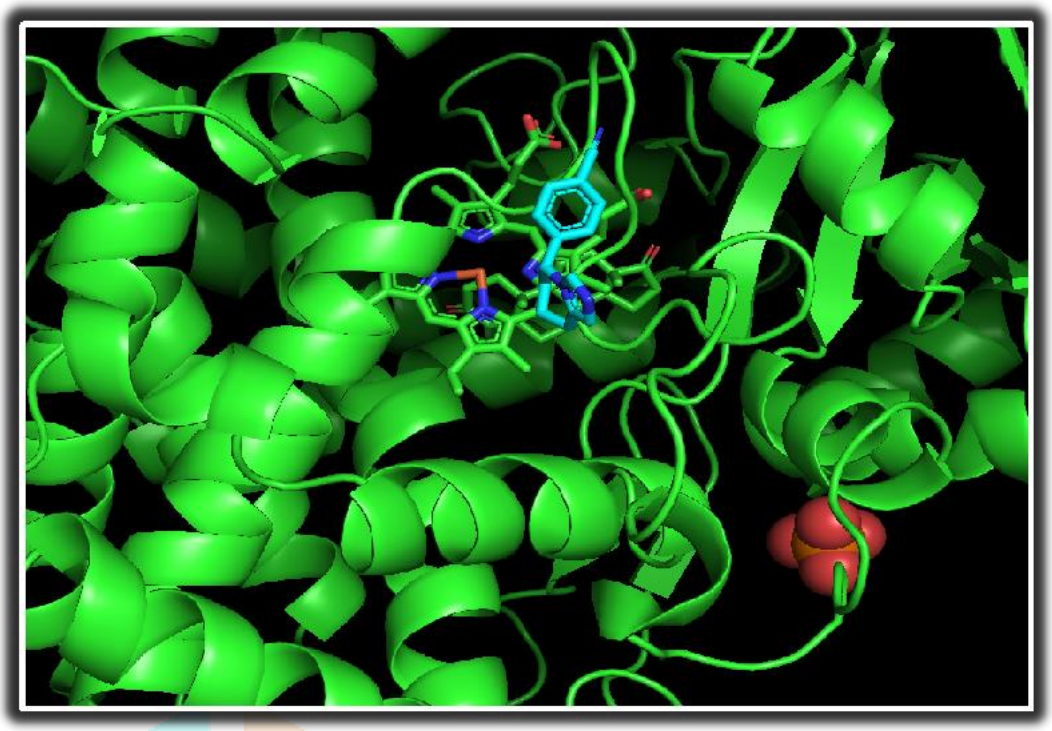


Fig. 2 Ribbon structure 3EQM enzyme with Fadrazole

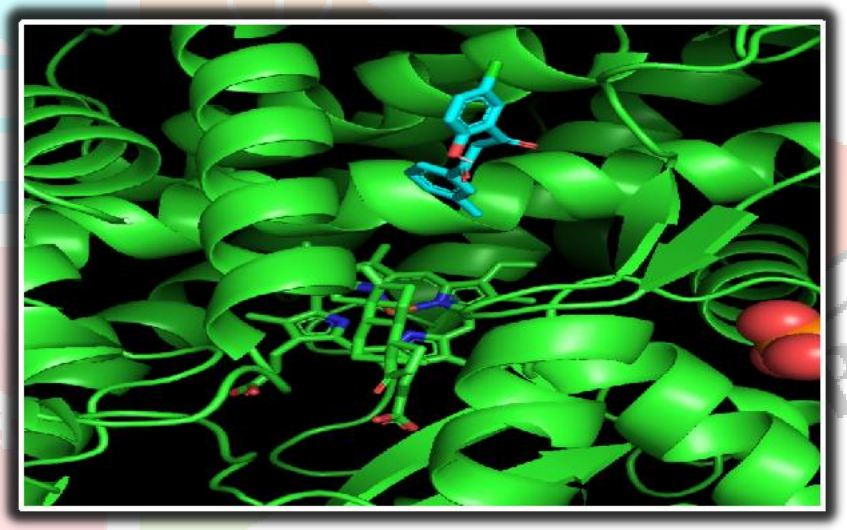


Fig. 7 Ribbon structure 3EQM enzyme with VPK-2

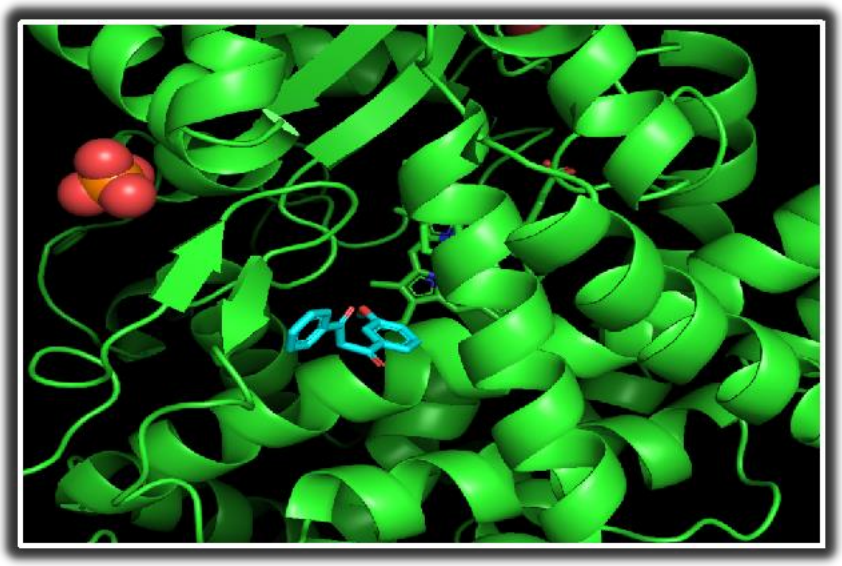


Fig. 5 Ribbon structure 3EQM enzyme with VPK-4

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