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Pharmacophore Identification of Alternative HMG-CoA Reductase Inhibitor: A Computational Approach

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ABSTRACT

Statins are a class of drugs frequently prescribed to lower the cholesterol level. The major reason for statin discontinuation is due the development of statin-associated muscle symptoms and other side effects. The mechanisms behind these side effects have not been fully elucidated, it is essential to identify those at increased risk of developing side effects along with alternative treatment strategies. In this study, ligand-based docking approach has been used for drug identification. The pharmacophore hypothesis was generated from HMG-COA inhibitors using ZINC Pharmer to get 253 compounds. Further the molecules are filtered based on the physicochemical properties as per the Lipinski rule using data warrior. All these molecules obtained were subjected to molecular docking with active pockets for target HMG-CoA reductase utilizing Auto dock vina. Further, ADME/T studies were carried out for all the molecules. The standard atorvastatin was found to have good binding affinity with binding energy of -8.1 and the test compounds ZINC91435950, ZINC91435978 and ZINC91435977 showed best binding affinity score -7.1, -6.5 and -6.3 amongst all the compounds of study.

Keywords: *Molecular Docking, Pharmacophore Modeling, HMG-CoA reductase, Statins*

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INTRODUCTION

Coronary heart disease (CAD) most common cause of death worldwide, the coronary arteries are network of blood vessels on the surface of the heart, coronary heart disease is caused by narrowing the coronary artery walls by cholesterol deposition which develops into plaques. The function of coronary arteries is to supplying oxygen to the heart through blood vessels. When the arteries are narrowed by the cholesterols the movement of blood flows reduces and that can cause inflammation and hardening of walls of the blood vessels [1-2]. This disease leads to heart attack. The medicines that are used aim to reduce blood pressure or widen arteries. Drugs which are used in the treatment are blood thinning medicines like low dose aspirin, clopidogrel, etc. statins which is used in lowering the high cholesterol like atorvastatin, simvastatin, rosuvastatin etc. beta blockers include atenolol, bisoprolol, etc. Nitrates, ACE inhibitors, angiotensin-2 receptor blockers, calcium channel blockers and diuretics. The drawbacks are some medicines have side effects and the medicines should not be stopped they may worsen the symptoms [3].
The rate-limiting enzyme in cholesterol manufacture, 3-hydroxy-3-methylglutarylcoenzyme A (HMGCoA) reductase, which changes HMG-CoA into mevalonate, is inhibited by statins. Statins reduce plasma low-density lipoprotein (LDL) cholesterol by elevating the expression of LDL receptors and generating intracellular cholesterol depletion [4].Treatments for coronary heart disease includes lifestyle changes, risk factor management, and medications. Some people may also benefit from a procedure or surgery such as angioplasty, stent replacement, coronary artery bypass graft surgery (CABG), or off pump coronary artery bypass surgery, may also be necessary for the treatment of coronary artery disease [5-6]. Medications prescribed by doctors are statins with people with high cholesterol risk for lowering their total cholesterol level and which in turn will reduce the risk of heart attack and stroke. Statins are

considered as safer and more effective drug for most people, they have been linked to digestion problem, muscle pain and metal fuzziness in some people who take them rarely. Although statins are typically well tolerated, some people may experience side effects. Inadequate protein prenylation, a lack of coenzyme Q, which is necessary for mitochondrial electron transport and antioxidant protection, aberrant protein glycosylation brought on by a lack of dolichol, or a lack of selenoproteins are the causes of these consequences. The most common side effect of statins is myopathy, which can occasionally take the form of severe rhabdomyolysis. Hepatotoxicity, peripheral neuropathy, decreased myocardial contractility, and autoimmune disorders are less frequent negative effects [7].Modern drug discovery practices include a wide range of theoretical and computational methodologies, collectively known as computer-aided drug design (CADD). CADD techniques have played a significant role in the development of some medications that are currently being tested in clinical settings. These techniques have developed in tandem with experimental strategies employed in drug development. In order to enhance the lead compounds' biological features (such affinity and ADMET) and generate chemotypes from a nucleating site by merging fragments with improved function, CADD typically screens out huge compound libraries into smaller clusters of projected active compounds. CADD methods are becoming more well-liked and appreciated in both academic and pharmaceutical businesses. The CADD technique is efficient in terms of time and money. The CADD approach can be used in four stages. The first stage involves screening a small molecule library against the target using a virtual screening (VS) protocol to identify hits/leads. The second stage involves examining the specificity of the selected hits from VS using molecular docking in the active site of other known targets. The third stage involves predicting ADMET properties of the selected hit using *In silico* techniques, and the promising hits are referred to as leads. The fourth stage involves optimizing the leads' dimensional structure is accessible [8-9].

Hence the present study aims to identify novel lead moieties to inhibit HMGCoA reductase for the treatment of coronary heart disease through the application of computational tools.

MATERIAL AND METHODS

Drugs are identified from literatures and downloaded from PubChem data base: Drugs like atorvastatin, Fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin are downloaded in SDF format from PubChem [10].

Pharmacophore modelling: The biologically potent molecules required for the ligand to connect to the correct target protein and interact with it are mapped to produce a three-dimensional framework known as a pharmacophore. By uploading the molecule in Sybyl Mol 2 format along with a valid mail ID to the free online tool pharmagist, the molecule is then exposed to pharmacophore modeling. The service generates the pharmacophore in Jmol format by considering various methods to mix the input chemicals [11-14].

Collecting data from zinc database: The number of aligned molecules produced—for example, 7 aligned molecules stacked one on top of the other—give a cluster in the JMol format, from which the most aligned molecule or the six molecules with the highest scoring are chosen and downloaded. These molecules are then uploaded to the free online tool ZINC pharma for pharmacophore modeling. It will search the zinc database and return compounds with the same pharmacophoric characteristics after receiving a query. After more than lakh hits are returned from queries on the zinc database, the remaining hits are filtered to yield a total of 950 tiny molecules. The molecules are uploaded to the data warrior, a freeware tool for pharmacophore modelling, where they are screened according to the typical drug physicochemical characteristics including molecular weight, log P, H donor, H acceptor, polar surface area, rotatable bond, and steric center. For molecular docking experiments, all these compounds were obtained as an SDF download file [14-18].

Molecular Docking studies: After obtaining the compounds from Data Warrior, molecular docking experiments are performed on those molecules with the goal of determining the drug's greatest match and binding affinity to the desired protein. The first step in protein preparation for docking research is to choose and download the protein in pdb format from the Protein Data Bank with PDB ID 2bxr. the 3-angstrom resolution Xray crystallography of the target protein Human Monoamine Oxidase A in association with Clorgyline, Crystal Form A. Using the "Swiss pdb viewer," hetero groups, water molecules, and undesirable ligands were removed from the protein during protein production. Auto Dock Vina was used for docking, and all the ligands were created, reduced, and optimized. Using Auto Dock Vina, all of the ligands were produced, minimized, and optimized. PyMol version 2.4, a molecular visualization programmed by Discovery Studio, was used to further validate the docking methodology. Because it determines where the ligands will attach to the protein, the grid generation procedure is essential to the docking process. The grid is defined by the protein structure from the Protein Data Base

using the co-crystallized ligand that is present with the protein. The top 10 structures with the best docking scores were found after screening the docked output of all the ligands [19-20].

ADME-T studies: A molecule's fate within the body is largely determined by its ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties. A good absorption is sought when a molecule is delivered orally. The ratio of lipophilic and hydrophilic groups in a structure will determine how a molecule is distributed and absorbed throughout the system. Effectiveness and toxicity are crucial in terms of therapy. PKSCM online software is used to conduct the ADME-T experiments [21-22].

RESULT AND DISCUSSION

The drugs which are approved for HMG CoA reductase inhibitors include atorvastatin, Fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin used to get ligand-based pharmacophore model. The model gives molecules with similar pharmacophoric feature which is obtained from Zinc Data base and Data warrior, these molecules were subjected to docking by using Auto Dock Vina and based on docking score and binding interaction, 4 molecules are obtained. Next further ADMET studies were done by using PKCSM and Swiss ADME online software. Which predicts the drug-likeness feature and oral rat chronic toxicity and hepatotoxicity? Based on the result molecule ZINC91435950were predicted as the HMG CoA reductase inhibitor shown in table 1 and figure 1-4.

Table 1: Test and standard compounds binding affinity

Compounds	Binding affinity	ZINC ID	Binding affinity
Atorvastatin	-8.1	ZINC78841450	-6
Fluvastatin	-7.1	ZINC85695268	-5.5
Lovastatin	-7	ZINC85695663	-6.1
Pravastatin	-7.3	ZINC91435850	-5.6
Simvastatin	-6.3	ZINC91435921	-6.8
		ZINC91435950	-7.1
		ZINC91435977	-6.3
		ZINC91435978	-6.5

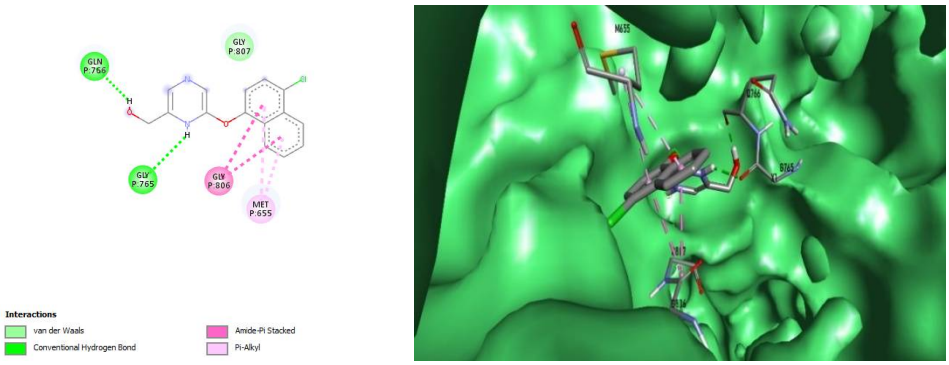

Fig 1: 2D and 3D view of molecular interaction of amino acid residues of HMG CoA Reductase with ZINC91435950

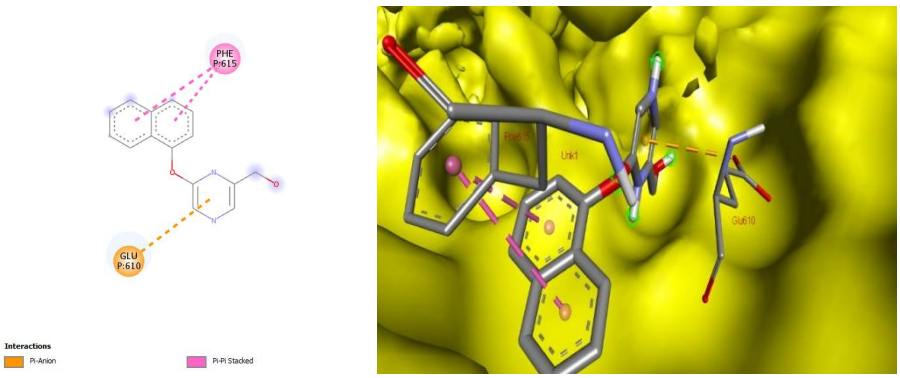

Fig 2: 2D and 3D view of molecular interaction of amino acid residues of HMG CoA Reductase with ZINC91435921

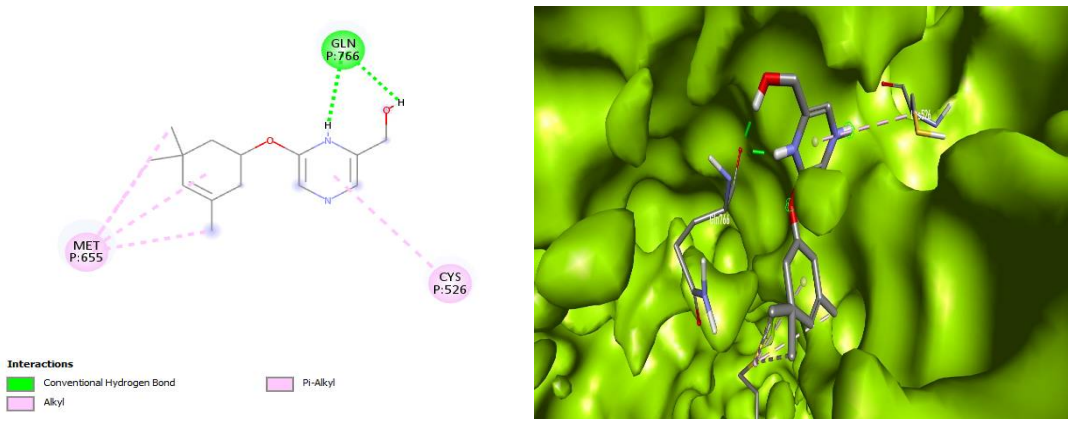

Fig 3: 2D and 3D view of molecular interaction of amino acid residues of HMG CoA Reductase with ZINC91435978

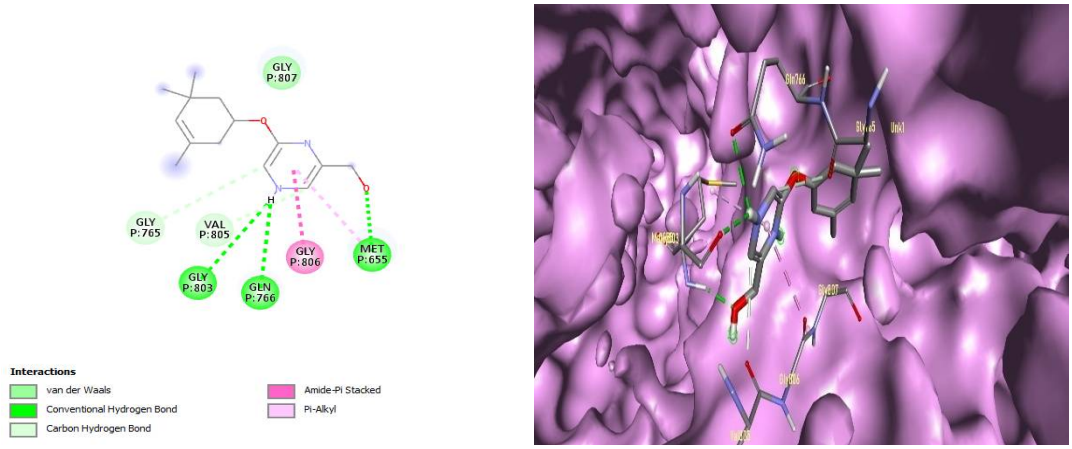

Fig 4: 2D and 3D view of molecular interaction of amino acid residues of HMG CoA Reductase with ZINC91435977

CONCLUSION

With a combination of pharmacophore modelling and molecular docking, some potential structures were screened as HMG CoA inhibitors. ZINC91435950 was found to be a best lead with good binding affinity with HMG CoA, which can be further validated by *in vitro* and *in vivo* methods.

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CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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