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Pharmacophore Design on Renin Inhibitors

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Abstract: Renin is an angiotensinogenase enzyme that participates in the body's Renin-Angiotensin System (RAS) that mediates extra cellular volume i.e. that of the blood plasma, lymphandinterstitial and arterial vasoconstriction. Thus it regulates the body's mean arterial blood pressure. It is required in homeostatis of our body and the enzyme belongs to aspartic proteases family of enzymes converting angiotensinogen to angiotensin I. Angiotensin has been originally reported as an inactive enzyme. Another enzyme known as angiotensin converting enzyme (ACE) proteolytically converts it to angiotension II, which is responsible for maintaining blood pressure. The major limitation factor in maintaining blood pressure is enzyme conversion of active molecule which is a rate limiting step. Therefore, Renin is very critical in playing a catalytic role in mediating blood pressure by the Renin-Angiotensin System. The objective of this study is to screen various inhibitors and to design the pharmacophore. In the study MOE was used, a tool for Lead discovery. In the paper we report the feasibility of new compounds as a lead in the drug development for Renin inhibitor.

Key words: Renin-Angiotensin System (RAS) that mediates · Homeostatis of our body and the enzyme

INTRODUCTION

In blood circulation system, rennin breaks down (hydrolyzes) the enzyme known as angiotensinogen into peptide angiotensin I, which is secredted by liver cells and finally it is converted into angiotensin II by Angiotensin converting Enzyme (ACE). Ace primarily present primarily within the lung capillaries [1]. In physiology, the contriction of blood vesse occur in the presence of angiotension II resulting in the increasing secretion of ADH and aldosterone, which in turn stimulates the pituitary-hypothalamus and regulates an increase in blood pressure. Therefore, RAS system plays a vital physiological role in the homeostatis mechanism and development of new drug for regulating blood pressure is highly desirable.

Ligan receptor complex plays a crucial role in signal transduction mechanism in regulating intracellular and extracellular fluid balance. Similarly RAS system follows the similar mechanism in physiological homeostasis [2]. Early literature reports suggested four fold increase in rate limiting step of angiotensinogen to angiotensin when rennin binds with ATP6AP6 protein thereby resulting in production of rennin. The mechanism involved in this reaction involves phosphorylation of amino acid residues serine and threonin of ATP6AP6 protein after binding with rennin.

Several investigators reported in finding the strategies to inhibit the rennin activity which is a critical and rate limiting step in cascade of reactions resulting from rennin – angioptensin system. It is reported that RAS system is highly substrate specific which is the reason that it is identified as an very usefull and most promising target for drug discovery. There were also reports that 3D QSAR/CoMFA and CoMSIA studies done with a variety of substrate available as rennin inhibitors [3]. The usefulness with the high safety levels of rennin inhibitors in cardiovascular diseases is yet to be determined. Several investigators reported a variety of new compounds as rennin inhibitors, one such inhibitor is aliskiren which was evaluated for their safety level in RAS system regulation of homeostatis. Aliskiren was tested in QSAR/CoMFA and CoMSIA studies by applying docking studies and more than 25 new

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derivatives compounds possessing bioactivity were reported by several authors. Therefore such studies and the results gives a new approach in designing new bioactive rennin inhibitors.

Pharmacological studies of rennin inhibitors in *in vivo* models in antibody neutralization studies showed promising results in evaluating the potential of this drug. Similarly human clinical trials were tested in cardiovascular patients and reports were not satisfying with a few compounds, but methods were useful in purification and quantifying rennin. A few orally active substances of rennin inhibitors have been reported by few investigators in preliminary drug discovery programs, which usually comprise of low molecular weight polypeptides of various sizes which are resistant to enzymatic cleavage and proved as a useful and specific rennin inhibitors.

The pharmacological effects and therapeutic potential of rennin inhibitors proved that rennin inhibitors have the same effects as angiotensin converting enzyme inhibitors. [4]. The problems lies in bioavailability of these compounds at the site of action, because these compounds were reported to show poor oral bioavailability and clearance of these available rennin inhibitors in excretion limited their further utility as useful drugs. Therefore, newer compounds with better oral bioavailability with clear-cut mechanism of action and a slow and long reacting drug action are required for evaluating it as a full potential and promising drug and provides advantage over the ACE enzyme inhibitors or the more recently developed angiotensin II-receptor antagonists.

MATERIAL AND METHODS

PyMOL is an open-source, user-sponsored, molecular visualization system created by Warren Lyford DeLano and commercialized by DeLano Scientific LLC, which is a private software company dedicated to create useful tools that become universally accessible to scientific and educational communities [5]. The Protein Data Bank (PDB) is a repository for 3-D structural data of proteins and nucleic acids. The data, obtained by X-ray crystallography or NMR spectroscopy and submitted by biologists and biochemists from around the world, is submitted to this public domain and can be accessed free. The mission of the wwPDB is to maintain a single Protein Data Bank Archive of macromolecular structural data that is freely and publicly available to the global community. The PDB is a key resource in structural biology and is critical to more recent work in structural genomics. This database stores information about the exact location of all the atoms in a large biomolecules (although, usually without the hydrogen atoms, as their positions are more of a statistical estimate). If one is only interested in *sequence data*, such as amino acid sequence of a particular protein or the nucleotide sequence as a particular nucleic acid, the much larger databases from Swiss-Prot and the International Nucleotide S sequence Database Collaboration should be used. Each structure published in PDB receives a four-character alphanumeric identifier, its PDB ID. This should not be used as an identifier for biomolecules, since often several structures for the same molecule (in different environments or conformations) are contained in PDB with different PDB IDs.

UCSF Chimera is an extensible program for interactive visualization and analysis of molecular structures and related data, including density maps, supramolecular assemblies, sequence alignments, docking results, trajectories and conformational ensembles. High-quality images and movies can be created. Chemsketch is used to visualize a chemically intelligent drawing interface that provides a portal to an entire range of analytical tools and facilitates the transformation of structural or analytical data into professional, easy-to-decipher reports or presentations.

MOE's pharmacophore applications use a general notion of a pharmacophore. In MOE, pharmacophoric structural features are represented by labeled points in space. Each ligand is assigned an *annotation*, which is an encoding of the structural features in the ligand that may contribute to the ligand's pharmacophore [6]. Which structural features are encoded is determined by the currently selected *pharmacophore scheme*. A database of annotated ligands can be searched with a *query* that represents a pharmacophore hypothesis. A query is a collection of feature, feature constraint and volume restrictions that is applied to the annotation and atoms of a ligand conformation [7]. The result of such a database search is a set of ligand conformations for which all restrictions of the query are satisfied. Partial matches, where only a subset of the restrictions is met, are also possible. AutoDock3.0 is an example of unbiased type and its version 3.0 has a ligand mobilized by a generic algorithm method and evaluates a rapid grid-based energy. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure.

Initially the hydrogens were added to all the atoms in the ligand and ensured that their valences were completed [8]. This was done using this molecular modeling package (ADT). It was made sure that the atom types were correct before adding hydrogens. Depending on whether charged or neutral carboxylates and amides are desired the $_{p}$H was specified automatically.

Once the grid maps have been prepared by AutoGrid and the docking parameter file, or 'dpf', is ready, the user is ready to run an AutoDock job [9]. The docking results were viewed using "get-docked", a PDB formatted file was created [10]. It was called "lig.macro.dlg.pdb" and will contain all the docked conformations output by AutoDock in the "lig.macro.dlg" file. The target renin (id 2V0Z)[ref] protein was taken; water molecules and ions were removed from the protein. The protein was then modified and changed to a desired format (pdbqs) using ADT.

RESULT AND DISCUSSION

The renin inhibitors were selected from previous articles. Out of 53 compound the 29 compounds were shown best Pharmacophore groups by using MOE. The binding interactions and the active conformations are derived from the AutoDock program, using the genetic algorithm. The energy functions of the interactions are partly based on the conformational and non-bonded interactions. For the docking studies, the crystal structure of renin with aliskiren (2v0z, pdb code) was downloaded from protein data bank. From the crystal structure, the inhibitor and water molecules were removed. The maximum number of generic algorithm runs was set to 30 for each compound.

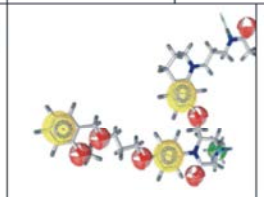
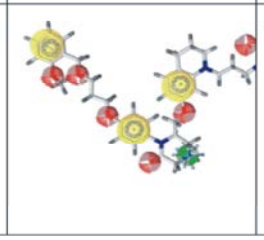
C. No	Pharmacophore	IC50 (nm)	Docking	LDE
Keto01		0.29		-18.53
Keto02		4.0		-18.43

Figure 1:

Comp: Keto 01

1.	N-H-OG (SER'76/3.11 Å)
2.	N-H-O (THR'12/2.55 Å)
3.	O-H-O (THR'12/3.32 Å)
4.	O-H-O (ALA'218/3.35 Å)

Raised blood pressure, especially systolic pressure (hypertension), confers a significant cardiovascular risk and public health concern and should be actively treated. One of the major systems involved in the elevation of the pressure is the renin-angiotensin system (RAS) and subsequently its inhibition will have beneficial effects to lower blood pressure and improve cardiovascular health.The renin inhibitors were selected from previous articles. Out of 53 compound the 29 compounds were shown best pharmacophoric groups by using MOE. Later to identify graphical the compounds were submitted to Ligandscout.

The binding interactions and the active conformations are derived from the AutoDock program, using the genetic algorithm. The energy functions of the interactions are partly based on the conformational and non-bonded interactions. For the docking studies, the crystal structure of renin with aliskiren (2v0z, pdb code) was downloaded from protein data bank. From the crystal structure, the inhibitor and water molecules were removed. The maximum number of generic algorithm runs was set to 30 for each compound [10-12].

In our study, we have built a pharmacophore model applying ligand-based pharmacophore generation approach, using MOE. The resulting best hypothesis consisted of five features: two hydrogen bond acceptor and three-ring aromatic function. The pharmacophore-based study indicates a possible steric, hydrophobic and hydrogen bond acceptor interactions of ligands to VEGFR-2. The pharmacophore-based CoMFA and CoMSIA results were indicated a combine interaction of steric, electrostatic and hydrophobic field effects. In receptor-guided study, we employed molecular docking and the docking-based alignment used for CoMFA/CoMSIA. The receptor-guided CoMFA and CoMSIA showed a combine interaction of steric, electrostatic and hydrogen bond acceptor effects. A positive bulkiness with hydrophobic effect could be desirable around positions 4 and 5. The hydrogen bond acceptor groups around carbonyl oxygen and nitrogen of pyrazolones moiety may facilitate the binding with hinge region and might be helpful to improve the activity.

Therefore, this study states the importance of small molecule libraries and their use to enhance drug discovery process prior synthesis. This approach to screen novel compounds as COX-2 inhibitors from ZINC database depends on various parameters such as Lipinski's rule of 5, pharmacophoric groups attached on the ligand, size of the dataset and compound libraries among others. Further, work can be extended to study the receptor-ligand interactions experimentally and evaluation of their biological activity would help in designing compounds based on virtual screening techniques.

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