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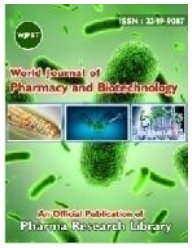

Research Article Open Access

Pharmacophore Design on Renin Inhibitors

S. P. Likitha Rao[*1], Anil Middah[1], Neeraj Tandan[2]

[1]*OPJS University, Rajasthan, India*
[2]*SARC (Scientific and Applied Research Centre), Hyderabad, India*

A B S T R A C T

The aim of present study was to develop renin inhibitor as anti-hypertensive drug. Selective inhibition of the renin has gained attraction as interesting approach to control hypertension and associated cardiovascular risk factors given its unique position in the renin-angiotensin system. Thus it regulates the body's mean arterial blood pressure. It is required in homeostasis of our body and the enzyme belongs to aspartic proteases family of enzyme converting angiotensinogen to angiotensin 1. Angiotensin has been originally reported as an inactive enzyme. Another enzyme known as angiotensin converting enzyme (ACE) protelytically converts in to angiotensin 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 the study is to screen various inhibitors and to design the pharmcophore. 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.

Keywords: Renin- angiotensin system (RAS), pharmacophore model, Docking.

A R T I C L E I N F O

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***Corresponding Author**
S. P. Likitha Rao
OPJS University, Rajasthan, India
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1. Introduction

Rennin-angiotensin system

Rennin activates the rennin-angiotensin system by cleaving angiotensinogen, produced by the liver, to yield angiotensin I, which is further converted into angiotensin II by ACE, the angiotensin- converting enzyme primarily within the capillaries of the lungs. Angiotensin II then constricts blood vessels, increases the secretion of the lungs. Angiotensin II then constrics blood vessels, increases the hypothalamus to activate thirst reflex, each leading to an increase in blood pressure[1]. The rennin-angiotensin system (RAS) is a key

regulator of blood pressure and body fluid volume, and acts primarily via the effects of the octapeptide hormone, angiotensin II (Ang II). Ang II is formed in a two-step process: the aspartic peptidase renin cleaves the Leu 10-val peptide bond of angiotensinogen to form angiotensin converting enzyme (ACE) into Ang II. Excessive RAS activity is believed to be an underlying cause of many pathological states, because Ang II increases blood pressure and exerts direct growth-promoting effects on cardiac[2] and renal [3] tissue that lead to end organ damage. Indeed, RAS inhibitors such as ACE inhibitors and Ang II receptor blockers (ARBs), have proven to be successful treatments for hypertension and heart failure [4,5].

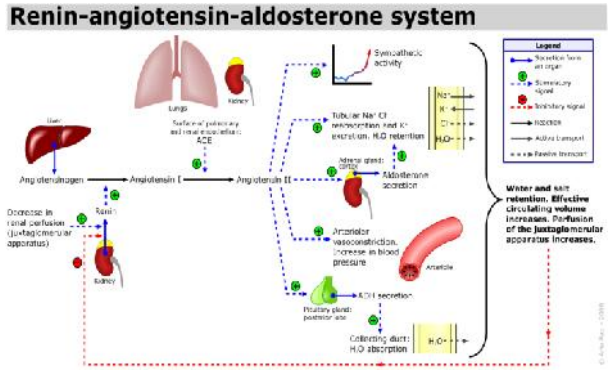


Figure 1: Renin-angiotensin-aldosterone system

Pharmacophore

A Pharmacophore is a molecular framework that carries (phoros) the essential part responsible for a drug's biological activity. It is a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity. It is alternatively described as an ensemble of interactive functional groups with defined geometry. CATALYST, software is used for Pharmacophore generation. The chemical functions used in the CATALYST include hydrogen-bonding acceptors and donors, and hydrophobic interactions. Catalyst generates pharmacophore hypotheses in terms of the 3D arrangement of chemical functions explaining the activity variations of compounds [6].

2. Materials and methods

Pharmacophore model Generation

Catalyst attempts to compute a model from training set data that correlates estimated activities with experimental activities as well as possible without over fitting the data. The model is a collection of chemical features distributed in 3D space that is intended to represent groups in a molecule that participate in important binding interact ions between drugs and their receptors. Estimated activities are computed by comparing how well the chemical features of a subject molecule overlap with the chemical features in the model (hypothesis). The ability of molecules to adjust their conformations in order to fit a receptor better is accommodated by considering molecules as collections of energetically reasonable conformations (conf models) during the analysis. The steps involved in Pharmacophore model generation is given in Figure.2

Molecules

- Conformational models
- Activity data is known
- Spans -4 orders of magnitude
- Features
- Generalized (eg. Hydrogen bond acceptor) Molecules/ select features Begin.

Pharmacophore: Present in actives/ not in inactives

Optimize

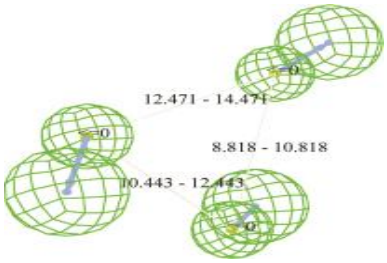
- Simulated annealing
- Score....Occam's Razor
- Steps (rotation, translation)
- Optimize reasonable pharmacophores

3. Result and Discussion

Results and Discussion:

Rennin Inhibitors:

The number of molecules in the database is 169. Of these, 71 are highly active, are 51 moderately active and 47 are low active Compounds. While the False positives and negatives, 16 and 12 respectively, are minimal, enrichment factor of 2.26 against a maximum value of 3.0 is a very good indication on the high efficiency of the screening. Of the 213 highly active molecules, 15 were predicted as moderately active and 4 were predicted as least active. In the 54 moderately active, 6 were predicted as low active and 3 as highly active. The model also predicted 3 of the low active molecules as moderately active and 2 more molecules from the same set as highly active. The steric and other interaction effects might have a subtle, yet crucial role on the predicted activity. While these additional groups may not prevent in identifying many low energy conformers or add any penalty for the total cost, but could be detrimental to fit these conformers in the active site. Thus, the features of Hyporefine 1 are relatively well optimized. However, in the case of highly active molecules, there are bulky groups present, which may decrease the ability of the hyporefine to select the most highly active molecules.



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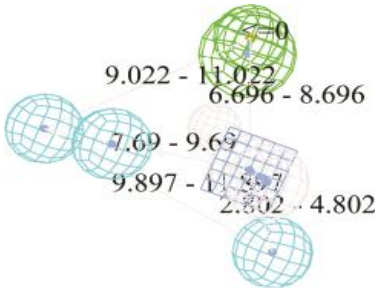

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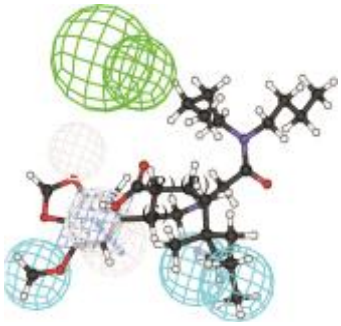

D

Figure 2: Pharmacophore model for RENIN

- Hip Hop model displayed with the distance between the features.
- Hypogen features with distance.
- Pharmacophore mapped to the most active molecule.
- Pharmacophore mapped to the least active molecule.

Model Validation and Knowledge based Screening

The purpose of the pharmacophore hypothesis generation is not just to predict the activity of the training set Compounds accurately but also to verify whether the pharmacophore models are capable of predicting the activities of Compounds of the test set series and classifying them correctly as active or inactive. The best pharmacophore hypothesis was used initially to screen the Renin Inhibitors. All queries were performed using the Best Flexible search databases/Spreadsheet method.

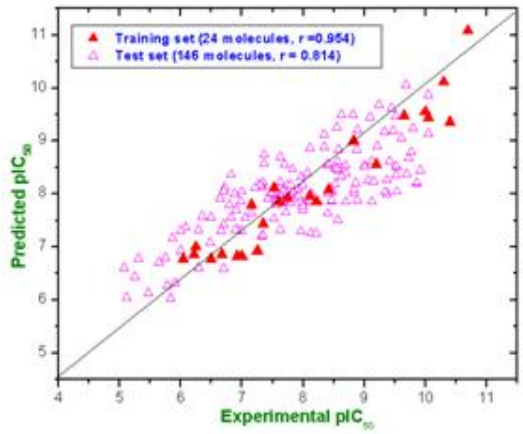

Figure 3: Graph showing the Correlation (r) between experimental and predicted activities. For the 146 test set molecules against Hypo-1 model along with 24 training set molecules for Renin Inhibitors.

Hyporefine 1 was used to screen the known high, medium and low active receptors of the test set. Database mining was performed in Catalyst software using the BEST flexible searching technique. A number of parameters such as hit list (Ht), number of active percent of yields (%Y), percent ratio of actives in the hit list (%A), enrichment factor of (E), False negatives, False positives and Goodness of hit score (GH) are calculated (Table 1) while carrying out the pharmacophore model and Virtual screening of test set molecules.

Table 1: Statistical parameters from screening test set molecules.

S. No	Parameter	Renin
1	Total molecules in database (D)	169
2	Total Number of actives in database (A)	71
3	Total Hits (Ht)	70
4	Active Hits (Ha)	66
5	% Yield of actives [(Ha/Ht)*100]	94.29
6	% Ratio of actives [(Ha/A)*100]	92.96
7	Enrichment factor (E) [(Ha*D)/(Ht*A)]	2.26
8	False Negatives [A - Ha]	5
9	False Positives [Ht - Ha]	4
10	Goodness of Hit Score$	0.87

4. Conclusion

Thus the pharmacophores generated from the Rennin Inhibitors can be used as a three-dimensional query in database searches to identify compounds with diverse structures that can function as potent inhibitors and evaluate how well any newly designed analogues maps on the pharmacophore before undertaking any further study including synthesis. Both these applications may help in identifying or designing analogues for further biological evaluation and optimization. The best quantitative pharmacophore model for all the three sets taken (in terms of predictive value) had in common one hydrogen bond acceptor, three hydrophobic and one ring aromatic features, indicating the importance of these groups in making the molecule a potent Rennin Inhibitors. The results are validated using the test set molecules. The most active molecule in the training set (in all the three cases) fits very well with this top scoring pharmacophore hypothesis. Virtual screening produced some false positives and a few false negatives. It is believed concurrent use or a consensus study, which readily minimizes these errors, could be an added tool for Pharmacophore model based virtual screening in order to produce reliable true positives and negatives. This work describes the synthesis of three analogues of Rennin Inhibitors. Pharmacophore studies found that all the newly synthesized Rennin Inhibitors and

their derivatives have molecular properties and also obeying the "Lipinski's" rule of five.

The pharmacological evaluation for the activity like antihypertensive will be done by Renal Artery Occlusion method.

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