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Ligand based Pharmacophore Modeling of some Angiotensin II Receptor Antagonist

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Abstract

Angiotensin receptor blockers (ARB's) are group of Antihypertensive drugs that act by blocking the effect of harmone Angiotensin II in the body there by lowering blood pressure. The discovery and development of ARB's is a demonstrative example of modern rational drug design. Major goal of modern drug design is identification and development of new ligands with high affinity of binding towards a given protein receptor .A very useful model for achieving this goal is pharmacophore . In the presented work, a 3 D pharmacophore has been developed in order to assist the discovery of some novel and potent angiotensin II receptor antagonist.Ligand based pharmacophore modelling has been done here, which is playing a key role for the identification of ligand features for the particular targets. Ligand Scout 3.00 has been used to predict the pharmacophoric features for Angiotensin II receptor antagonist. Result indicates that the in silico methods are useful in predicting the biological activity of the compound or compound library by screening it against a predicted pharmacophore.

Keywords: Angiotensin II, AT1, pharmacophore, ligand.

Introduction

The rennin–angiotensin aldosterone system is a proteolytic cascade that plays an important role in electrolyte homeostasis and in regulation of blood pressure. It is also involved in pathogenesis of hypertension and renal desease. The juxtaglomerular cells of kidney releases aspartic protease rennin, an enzyme responsible for conversion of angiotensinogen to inactive decapeptide angiotensin I. Angiotensin converting enzyme (ACE) cleaves angiotensin I to produce an octapeptide angiotensin II, which is main effector harmone of the RAAS. Drug design for developing novel synthetic antihypertensive drugs were mainly targared either to inhibition of Angiotensin II biosynthesis (ACE inhibitors) or to antagonism of Angiotensin II binding to its receptor (AT1 receptor)[1]. Angiotensin II blokers (ARBs) have been developed to produce more complete blockage of action of ANG II as well as an improved side effect profile[2]. Losartan was the first successful peptidomimic analog to be marketed against hypertension. Following it Valsartan was introduced by Peter Buhlmayer and co-workers which is an orally active non peptide Ang II antagonist, administered for regulation of high blood pressure[3-9]. Many replacements of the imidazole part of Losartan by other heterocycles have been published in literature and patents. Peter Buhlmayer and co-workers designed a novel series of orally active derivatives, in which the heterocycle of losartan has been replaced by an acylated aminoacid[10,11]. As per their finding the nature of the amino acid side chain was crucial for activity. High potency was achieved with several compounds derived from aliphatic amino acids. The findings demonstrate that good activity can also be achieved with amides derivatives of this unique structure and to a lesser extent with alcohol derivatives too[12]. The compound Valsartan of this series was found to have best activity in vivo and in vitro. Valsartan has a unique structure compared to all other AngII receptor antagonists. It was found to have the best potency efficacy and longest duration of action (up to 24 hrs). This is an example of scaffold morphing in which Du pont's Angiotensin II receptor Antagonist Losartan was used as starting material and was transformed to Valsartan.

In order to know about the type of inhibitor binding the target, knowledge of common properties of binding groups is must binding one. This can be achieved by modern drug design approach. Major goal of modern drug design is identification and development of new ligands with high affinity of binding towards a given protein receptor. A very useful model for achieving this goal is pharmacophore. Pharmacophore is a set of chemical and stearic interactions between a ligand and a macromolecule that are relevant to trigger a biological response. It is assemble of universal chemical features that characterize a specific mode of action of a ligand in the active site of a macromolecule in 3D space. Chemical features are Hydrogen bond, charge interactions and hydrophobic areas. This pharmacophoric pattern is the condition for ligand molecule interaction .Searching this chemical pattern in a large molecule data base allows us to find new scaffolds for developing lead structure.An early claim of scaffold morphing was made in 1994 by Buehlmayer et al. in which Du pont's Angiotensin II receptor Antagonist Losartan was used as starting material and was transformed to Valsartan. This is an example of computer aided scaffold morphing. Scaffold morphing involves a series of direct chemical transformation of structure with the aim to generate new chemo type with enhanced properties[14]. The facts discussed

above were utilized in the presented work, in order to develop a 3 D pharmacophore, to assist the discovery of some novel and potent angiotensin II receptor antagonist. They may provide guidance for the rational design of the proposed derivatives. While designing the derivatives importat facts which were taken in to consideration were about the common properties of binding groups essential for determination of type of inhibitor binding the target. Since amino acid recidues can often interact with the active site of receptors and play a pivotal role via H bond and charge effect, designing N terminal coupled amino acid derivatives were considered to be of specific interest[13]. Nitrogen containing building blocks often play important roles in drug design and provide enhanced interaction between pharmacophore and receptor sites. All these fact were considered so that the newly proposed ligands should have high affinity for binding towards a given protein receptor. Our present work is an attempt to assure that designing of the new derivatives was done in proper way which ensures that these derivatives will haves perfect binding to the receptor site.

Material and Methods

The present study was carried out using software ligand scout (version 3.0) [15]. Ligand scout is a soft ware tool that allows a rapid and transparently deriving 3D chemical feature-based pharmacophore from structural data of macromolecule and ligand complexes in a fully automated and convinient way[16]. It runs on all common operating systems. Ligand scout generates structure based as well as ligand based pharmacophore model. Here Ligand based pharmacophore model generation was performed using Ligand scout with default setting .Software gives the details of feature pattern, no of conformers formed, pharmacophore fit of the ligand matched with the selected pharmacophore.

The goal of ligand based pharmacophore modeling is to seek a common feature in the set of ligands. Soft ware creates ligand based pharmacophore from single or multiple ligand conformation. Ligand that binds to a particular target protein possess a similar binding mode. These known active ligands will act as training set for main pharmacophore generation.

Ligand based pharmacophore modeling requires a set of two or more input ligands to generate characteristic pharmacophore. They are then divided into training set, test set and ignored ligands. The training set molecules are used for the actual pharmacophore creation and the test set ligands are used to verify the resulting pharmacophore. The ligands not used in the process are the ignored ligands. The training set here consist of the series of orally active angiotensin II receptor antagonist given by Peter Buhlmayer and co-workers, in which the heterocycle of losartan has been replaced by an acylated aminoacid[12]. First of all these training set ligands were imported to the ligand set table. After this the newly designed N terminal coupled amino acid derivatives were also imported. They will act as test set.

After importing the ligands, the ligand set table shows the list of molecules which serve as input for pharmacophore. The molecules were overlapped according to their phamacophoric features and then several pharmacophoric models were created. The steps involved in model generation were: i. Defining and preparing ligand sets. ii. Ligand based pharmacophore creation iii. Visualization. Accordingly the input ligands were imported and were added to ligand set table. Now ligand conformations were created and available ligands were clustered according to multi conformational alignment score (clustering) and ligand based pharmacophore generation was started using suitable menu[17]. The 3D clustering algorithem performs fast alignment and clusters based on the similarity value between 0 and 1. The generated conformations were now ranked according to their no of conformations and pharmacophoric features like lippophilic points, H bond donors, H bond acceptors, positive and negative ionizable groups were projected on the molecules and their conformers. All conformations of the top ranked molecules were aligned using Inte –Ligand molecular alignment solutions. Common pharmacophoric features were interpolated and intermediate pharmacophore models were created. The intermediate pharmacophore models were then aligned to all conformation of the next molecule to generate a new set of intermediate combined pharmacophore. This continues until all molecules were processed. These were now ranked using several adjustable scoring functions. Range of score values depends upon the scoring function. The scoring function here produces normalized value ranging from 0-1, where one is optimum. It takes in to account chemical feature overlap, stearic overlap or both. After the ligand based pharmacophore generation process has finished the results are listed in the result table including name and score. Each entry of the result table represents a valid pharmacophore model i.e. it consist of at least three common chemical features. The ligand set table was automatically updated and provides additional information such as feature pattern, number of conformations and the pharmacophore fit of the ligand matched with the selected result pharmacophore. It can now be visualized how well the resulting pharmacophore fits to the ligand. The table also gives the score values which range from zero to one, where one is optimum. If at least three common chemical features can be identified throughout the whole alignment and interpolation process, the feature pharmacophore combination is considered to be successful.

Results and Discussion

In our study presented here, total four common chemical features were identified throughout the whole alignment and interpolation process, to successfully complete the pharmacophore combination feature. These are Hydrogen bond bond donors, Hydrogen bond acceptors, hydrophobic areas and aeromatic rings. As far as the score value is concerned, it ranges from zero to one, where one is optimum. In case of our newly designed N terminal coupled amino acid derivatives, score value lies between 0.8884 to 0.8354. These facts indicate that our

attempts of generating a pharmacophore are successful. The pharmacophore generated by Ligand Scout for training set showed four main features as hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), Hydrophobic features and aeromatic rings.

Figure-1 show 2D views of the pharmacophores of training set. Among these, compound no 4 (Valsartan) was reported to have best activity *in vivo* and *in vitro*. It showed best potency efficacy and longest duration of action. For ease of comparison 3D view of str 4 of training set is also shown here in figure-2. The features identified in green colors are hydrogen bond donors (HBD), red colored are hydrogen bond acceptors (HBA), yellow colour represents hydrophobic features and blue represent aeromatic rings.

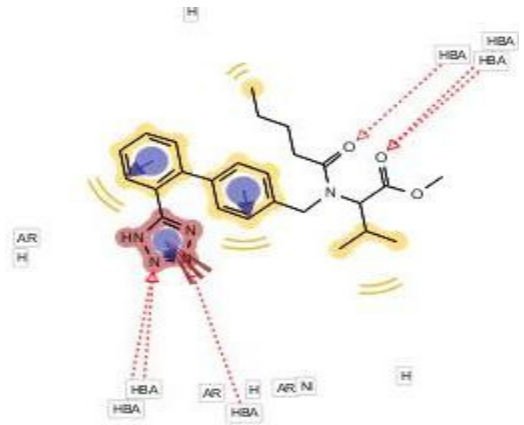
The pharmacophoric features shown by VH-1 to VH-4 (representative examples of newly designed derivatives involved as test set are shown in figure-3. The pharmacophore generated show consistency with the above mentioned features. It consistently shows hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), Hydrophobic features and aeromatic rings. On the whole these pharmacophoric features are shown in table-1.

The pharmacophores of all proposed ligands were then matched and after detailed analysis, a unique pharmacophore was identified. A common pharmacophore of Angiotensin II receptor antagonist obtained after superimposing is shown in figure-4.

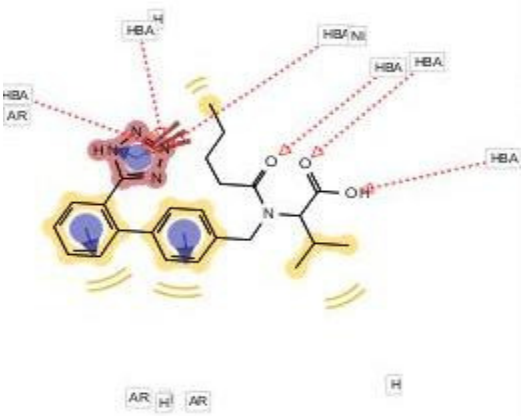
A comparative account of the pharmacophoric features of each group is shown in table-2. In case of ligands no 3,4and 5 of training set the number of hydrogen bond acceptors was found to be six and while it was five in case of ligands 6 of training set. All ligands of training set show three hydrophobic aeromatic rings. It was found that all the training set ligands uniformly show 4 hydrophobic areas.

On similar grounds the Phrmacophoric features of the newly proposed ligands can also be compared. The proposed ligand VH-1 and VH-2 show five and six hydrogen bond acceptors respectively while VH-3 and VH-4 show seven hydrogen bond acceptors and one H bond donor each. Ligands VH-1 to VH-4 uniformly show three hydrophobic aeromatic rings. The ligand VH-4 shows two hydrophobic areas while rest of them shows four hydrophobic areas.

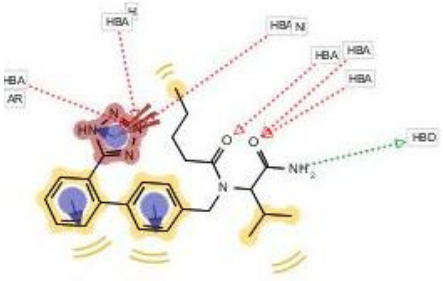
Minos-Timotheos et al. suggested a 3D Pharmacophore model with two hypothesis[15]. Both contain five chemical features, a negatively ionizable group, a hydrogen bond acceptor group and 3 hydrophobic sites. So our pharmacophoric features have improved as compared to the earlier reported ones. The comparision of pharmacophoric features at each step with standard compounds valsartan having similar pharmacophoric features shows the validation of predicted model.



3



4 (Valsartan)



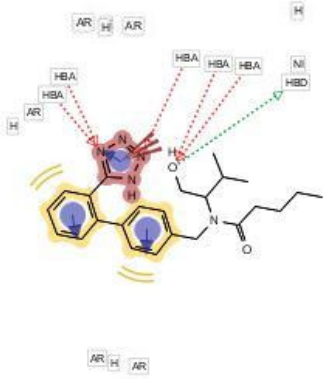


Figure-1
Pharmacophoric features shown by ligands included in training set

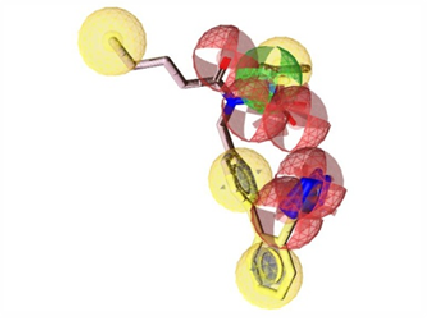
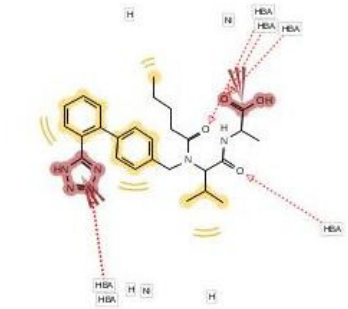
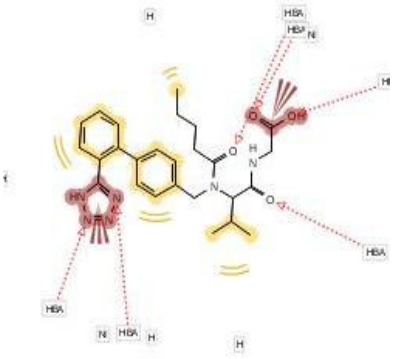


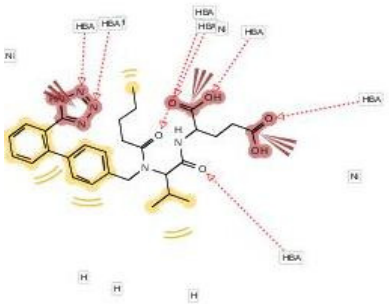
Figure-2
3D Pharmacophoric features of VALSARTAN



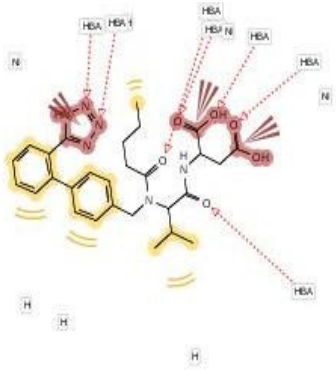
VH-1



VH-2



VH-3



VH-4
Figure-3
Various pharmacophoric features of test set ligands

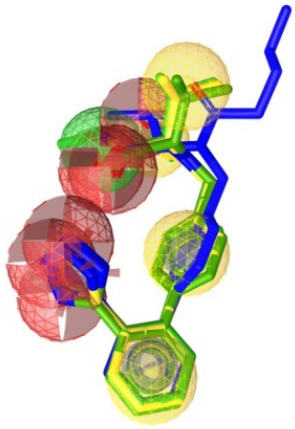


Figure-4
Proposed 3 D Pharmacophore for Angiotensin II receptor Antagonists

Conclusion

The present study done on Angiotensin II receptor antagonist for identifying common chemical features to generate a pharmacophore has broadened our vision for discovery of more specific drugs to be used as antihypertensives. The insights provided about the Hydrogen bond donors, Hydrogen bond acceptors, hydrophobic areas and aeromatic rings suggest the ways by which the sartans bind with the AT_1 receptor. Our predicted pharmacophore for angiotensin II receptor antagonist will help in the identification of type specific drugs for humans. More investigation in this direction will open ways for the discovery of more effective drugs.

Acknowledgement

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Table-1
Pharmacophoric features shown by the ligands

S. No	Ligands	Hydrogen bond acceptors	Hydrogen bond donors	Hydrophobic aeromatic rings	Hydrobhobic areas
1	3	+	-	+	+
2	4	+	-	+	+
3	5	+	-	+	+
4	6	+	-	+	+
5	VH-1	+	-	+	+
6	VH-2	+	-	+	+
7	VH-3	+	+	+	+
8	VH-4	+	+	+	+

Table-2
A Comparative account of the pharmacophoric features of the ligands

S. No	Ligands	Hydrogen bond acceptors	Hydrogen bond donors	Hydrophobic aeromatic rings	Hydrobhobic areas
1	3	6	-	3	4
2	4	6	-	3	4
3	5	6	-	3	4
4	6	5	-	3	4
5	VH-1	5	-	3	4
6	VH-2	6	-	3	4
7	VH-3	7	1	3	4
8	VH-4	7	1	3	2

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