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Structure Based Molecular Docking Studies of 2, 6-Diphenylpiperidin-4-Ol Derivatives Inhibition on Renin

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Abstract
Renin (4PYV) [1] has been considered to be a highly attractive paradigm to treat hypertension and to protect from end-organ damage [3]. In our work, the way of combined ligand- and structure-based approach was applied to analyze the interaction with 2,6-diphenylpiperidin-4-ol derivatives [2] on renin. 2,6-diphenylpiperidin-4-ol derivatives (D1-D7) was found to show similar structure of some Anti-hypertensive drugs via Qikprop. To further expound the binding modes of these inhibitors with 4PYV active sites, three docking programs, standard precision (SP) Glide, and extra precision (XP) Glide, Prime MM-GBSA were used. The characteristics of the active sites were then described by the conformations of the docking results. In conclusion 2,6-diphenylpiperidin-4-ol derivative with best binding energy was noted to have high potency against Hypertension and related diseases.

Keywords
2,6-diphenylpiperidin-4-ol derivatives, Renin, anti-Hypertensive, Blood Pressure, Maestero 11.9, Glide.

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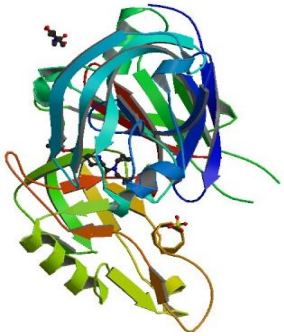
INTRODUCTION:
Hypertension is a major risk factor for cardiovascular diseases (CVDs), such as congestive heart failure, stroke, and myocardial infarction, which are the leading causes of death in industrialized countries. However, despite several classes of therapeutic drugs available, less than 30% of hypertensive patients achieve currently recommended blood pressure goals [4,5]. The renin-angiotensin-aldosterone system (RAAS) has long been established as being the key cascade in the regulation of blood pressure and homeostasis of body fluid volume. Renin cleaves angiotensinogen to release inactive peptide angiotensin I by converting enzyme (ACE) then generates angiotensin II, which induces an increase of blood pressure by vasoconstriction, sodium retention and altering vascular resistance [6]. Renin controls the first and rate-limiting step of the RAAS and has high specificity for its substrate angiotensinogen. Blockade of renin has been considered to be a highly attractive paradigm to treat hypertension and to protect from end-organ damage [7]. Thus targeting 4PYV with 2,6-diphenylpiperidin-4-ol derivatives (D1-D7) inhibitors leads directly to the down regulation of client proteins and attains Antihypertensive activity. 2,6-disubstituted-

piperidine derivatives are regarded as an important building block of many alkaloid natural products, therapeutic drugs and they serve a role as key intermediates for synthesis of various organic compounds [8-9]. The substituted piperidine derivatives are found to possess of various antimicrobial activities including anti-inflammatory, anti-tuberculosis, antipyretic, antibacterial, antifungal, etc [10-11]. The antimicrobial activities are improved or declined when the conformation of piperidine is swapped due to substitution on different position. Hence, analyzing the conformation of compound has become important in recent years. Accordingly, our investigation has demonstrated that substituted Piperidinols has a noteworthy role in drug designing. Thus the compounds were subjected to computational approach on Schrodinger Maestro 11.1 software which is the scientific leader in developing state of art of chemical simulation software for use in pharmaceutical and biotechnology research. This is a systematical combinations of ligand based and structure-based approaches provide an insight into 4PYV's active site and the interaction with 2,6-diphenylpiperidin-4-ol derivatives (D1-D7) by computational simulation. This method provided a significant strategy for 4PYV inhibitors' study.

Structure of Renin Protein (4PYV)



MATERIALS AND METHODS:

Chemical structures were sketched by Chemdraw software in Structure Data Format (SDF). The docking studies were performed with standard precision (SP) Glide, and extra precision (XP) Glide and MGBSA Prime in Schrodinger software.

Preparation of Protein:

X-ray crystalline Structure of protein 4PYV was imported from Protein Data Bank (PDB) to workspace, which further set to pre-process followed by review and modify to remove unwanted chains and residues, further refined under force field of OPLS3e. The result was monitored in job monitor.

Preparation of Ligands:

Structures of ligands sketched and saved in SDF format were imported via selecting file. The imported ligands (D1-D7) were set to minimize under force field OPLS3e. Minimization calculations can be performed on all structures of 2,6-diphenylpiperidin-4-ol derivatives.

Molecular Docking:

As for Glide docking, crystal structures of 4PYV should be prepared by the protein preparation wizard in Schrodinger ¨ suite. Afterwards, receptor grids were generated before docking with the active site determined by the position of co crystal ligand. Crystal structures of 4PYV were imported into Glide, defined as the receptor structure and the location of active site with a box. The OPLS3e force field was used for grid generation [12-13]. The standard precision (SP) and the extra precision (XP) protocols were set for docking studies with crucial residues, in constrained binding to get accurate results. Binding affinity was retrieved running Prime MM-GBSA. All other parameters were maintained as default.

RESULT AND DISCUSSION:

Validating active group of ligands (D1-D7):

The 2D structures of 2,6-diphenylpiperidin-4-ol derivatives, showed similar structures of known drugs for Hypertension, Blood pressure, depression etc., like Mirtazapine, Nomifensine, Mianserin, Racemorphan, Epinastine. Which assisted to confirm the target protein. All the compounds were run in Qikprop tool of Schrodinger Glide software to proceed for further elucidation.

Structure of 2,6-diphenylpiperidin-4-ol derivatives (D1-D7)

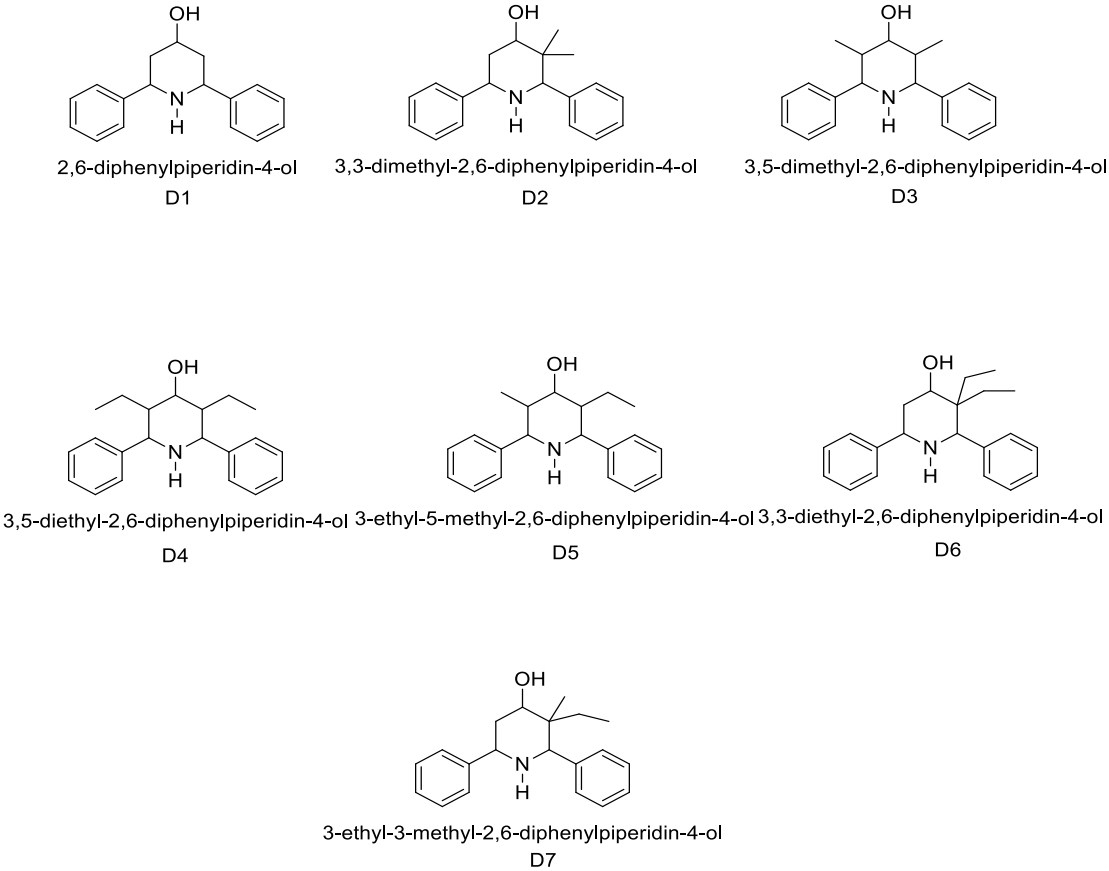


Figure 1

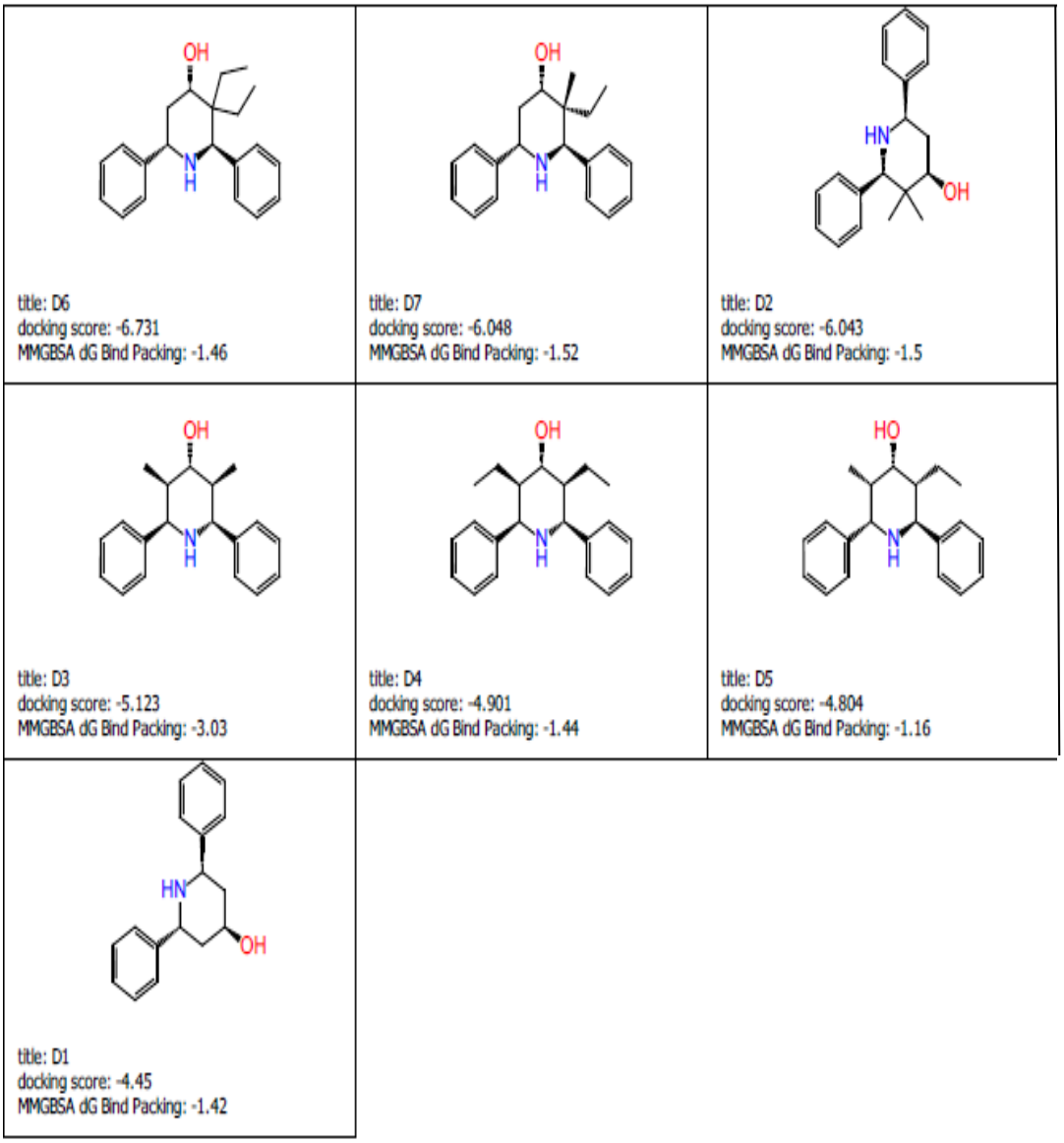
Molecular Docking.

To date, seven structures of ligands have been determined. Meanwhile, these ligands were used to conduct native docking to measure the docking conformations. Three different docking programs—SP Glide, and XP Glide, Prime MM-GBSA—were used for improving the accuracy of prediction. Then, Xscore followed by molecular docking was reliable and accurate for forecasting protein-ligand binding free energies (Table 1). The docking results were evaluated by comparing values of score energy, SP Glide, XP Glide, and Binding energy. Through analysis of these results of docking simulations, most binding energy scores could accurately forecast the ligand activities. The lowest binding energy and the highest docking score demonstrated that these compounds (ligands) presented well favorable interactions. The docked ligands D7, D6, D2 of 2,6-diphenylpiperidin-4-ol derivatives showed the best range of Docking score, XP Gscore and Binding energy. (Table 1).

Table 1

Title	Docking score	Glide gscore	XP GScore	MMGBSA
D1	-4.45	-4.45	-4.45	-17.45
D2	-6.043	-6.043	-6.043	-35.71
D3	-5.123	-5.123	-5.123	-10.92
D4	-4.901	-4.901	-4.901	-23.62
D5	-4.804	-4.804	-4.804	-22.66
D6	-6.731	-6.731	-6.731	-29.47
D7	-6.048	-6.048	-6.048	-30.64

Figure 2



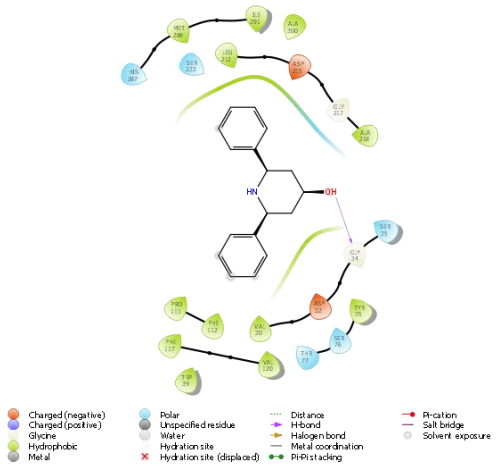
Inhibitor Binding Analysis:

The least binding energy and the most rational binding pattern between the inhibitors and 4PYV were selected by the three docking protocols. As expected, 2,6-diphenylpiperidin-4-ol derivatives (compounds D1–D7) bound in the active site validating the prediction by molecular docking with 4PYV.

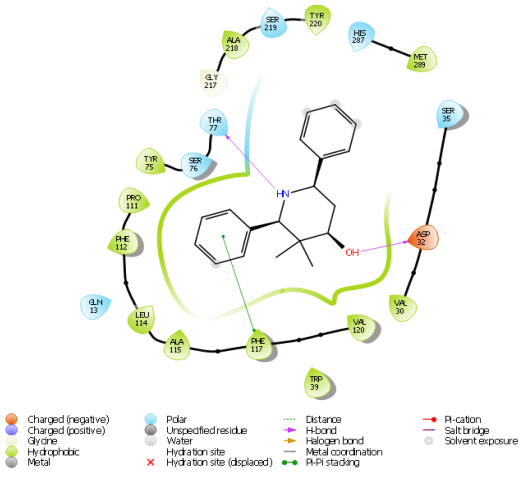
Among the set, three compounds were selected, which represented good interactions with the target protein, including compounds D2, D6, D7 (Figure 2).

From the docking results, the heterocycle of 3,3-dimethyl-2,6-diphenylpiperidin-4-ol (D2) shown interaction with THR-77, ASP-32, PHE-117 which had two Hydrogen bond interactions. *Viz* 3,3-diethyl-2,6-diphenylpiperidin-4-ol (D6) shown interaction with ASP-32, PHE-117 and 3-ethyl,3-methyl-2,6-diphenyl piperidin-4-ol (D7) shown interaction with ASP-32, PHE-117. However, it was noted that there is a hydrogen bond between the 3 derivatives of 2,6-diphenylpiperidin-4-ol (D2, D6, D7) and D2 was potent inhibitor.

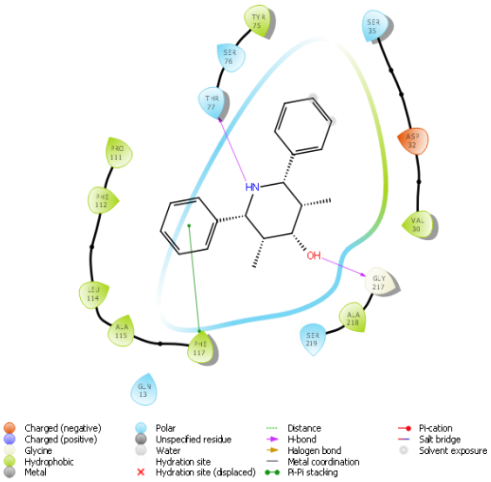
Figure 3



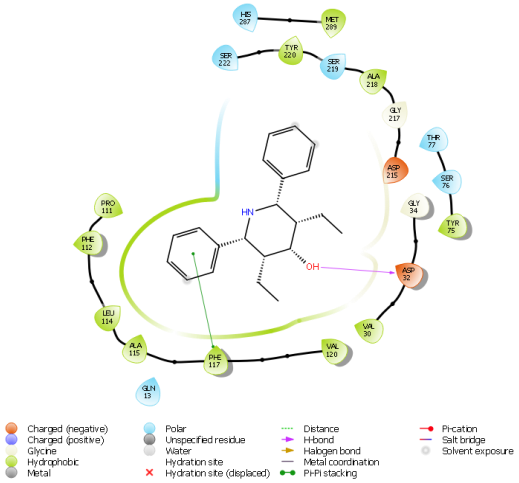
D1



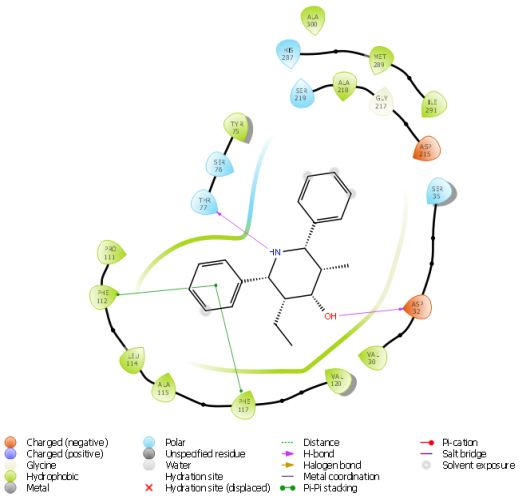
D2



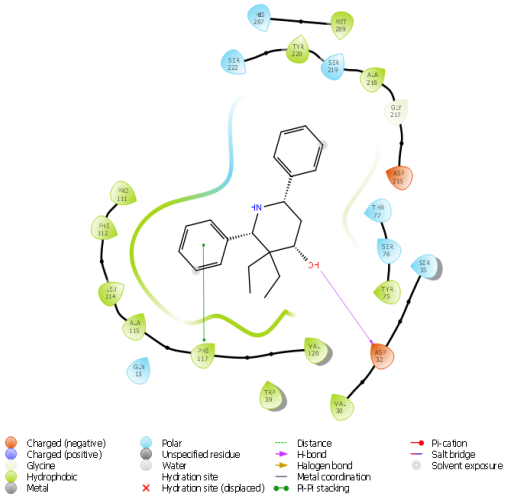
D3



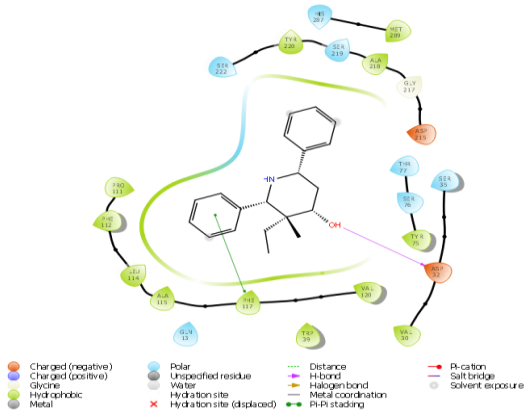
D4



D5



D6



D7

CONCLUSION:

In order to understand binding modes between 4PYV and 7 competitive ligands, the molecular docking was developed to reproduce experimental binding affinities for 7 inhibitors. To identify the docking accuracy about this target, docking simulation were evaluated by different docking programs. Interestingly, these docking results showed that a sole reference could not represent binding modes of all inhibitors. Interactions between compounds and the 4PYV active site. Docking results were merged which allowed us to weigh different binding patterns in the active sites. In a word, we identified that two hydrogen bond acceptors and an aromatic ring were essential anchoring points in 3,3-dimethyl-2,6-diphenylpiperidin-4-ol (D2) played a pivotal role in binding affinity. This provides lowest energy ligands, docked into the target pocket with best possible pose. The compound 3,3-dimethyl-2,6-diphenyl piperidin-4-ol (D2) are quantified using the docking score to act against anti-hypertensive activity. Which shall be further derivatised for designing an accurate drug for treating Hypertension, BP, Depression.

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