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In Silico Molecular Docking of Peptides in Respect to ACE2 with References to Their Anti-hypertensive Activities through CADD Tools

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ABSTRACT: *Hypertension is one of biggest global burden all over the world. Most of the people at different ages suffered in this disease. Various types of organs can affect with this hypertension problem. Medicines can control the hypertension or elevated blood pressure. But these existing medicines are not capable to solve the problems. The patients can take medicines for long times. Sometimes resistance can occurred due to prolonged administration of same medicines to patients. Now a days discovery of new molecules are very important. The present study represents in silico drug discovery of new molecules in respect to hypertension. ACE2 is one of the hopeful target for treating the hypertension. In this article, we have docked peptides in respect to ACE2. After that we screened one test peptide based on the molecular docking of test compounds through different in silico drug design tools with reference to ACE2.*

KEYWORDS: *Hypertension, ACE2, In silico drug design, Peptide analogues, RAAS, Bioinformatics, Cheminformatics, Molecular Docking.*

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I. INTRODUCTION

Hypertension is defined as uncontrolled elevation of blood pressure. When the blood pressure is above than 120 mm Hg (systolic) and 80 mm Hg (diastolic) then it can be called as Hypertension. Blood pressure generally ups and downs all over the whole day, but it can injure our heart and cause health problems if it longs high for a long period of time. We can also express hypertension, as high blood pressure. It is one of non communicable diseases. Now a days hypertension shows global trouble in worldwide. In every year from whole world many people died due to hypertension and its associated problems. Hypertension may affect total cardiovascular system like angina, arrhythmia, etc and entire kidney function. Globally every year 9.4 million people expired after affecting Hypertension [1].

Generally there are two types of hypertension. One is primary hypertension and another one is secondary hypertension. Primary hypertension is called as essential hypertension. It is very difficult to identify or recognize the patients who have this type of hypertension as most of the people having primary hypertension cannot feel any differences from people having normal blood pressure. Maximum causes for this hypertension is not well known to us. If we come to secondary hypertension we can state that this type of hypertension happen due to any disorders in organ like liver problem and kidney problem. It can occur due to medication [2-5].

If we look into the data provided by WHO, it will be shocking for us. According to WHO, there are top 10 diseases that causes most deaths globally. In the top list, there is various cardiovascular diseases (CVS) such as ischemic heart disease, stroke, etc. Currently its becoming silent killer. In order of overall number of lives lost, are associated with three broad diseases: cardiovascular diseases (ischemic heart disease, stroke), respiratory (chronic obstructive pulmonary disease, lower respiratory infections) and another one is neonatal conditions including birth asphyxia and birth trauma, neonatal sepsis and infections, and preterm birth complications [6-8].

For the last two decades (20 years) heart disease is leading reason for the deaths in worldwide. However, hypertension now kills more people than ever. The number of demises from cardiovascular disease enlarged by more than 2 million since 2000, to nearly 9 million in 2019. 16% of total deaths caused from all appearing for heart disease. More than half of the 2 million deaths were in the WHO Western Pacific region. Oppositely, the European region has seen a relative decrease in heart disease, with deaths falling by 15% [9-11].

An estimated 1.28 billion adults among 30-79 years worldwide having hypertension, most (two-thirds) living in lower income and middle income countries. An approximate 46% of adult people with high blood pressure or hypertension are completely unaware that they have the problems associated with high blood pressure disease. About 42% adult people with hypertension are identified, recognized, diagnosed and treated. Approximate 1 in 5 adults with hypertension have under regulated situation. Hypertension is a serious reason of premature or early death cases in worldwide. One of the targets of WHO in worldwide for non communicable diseases is to reduce the prevalence of hypertension by 33% between 2010 and 2030 [9-12].

Actually pathophysiology of hypertension related with the impairment of renal pressure natriuresis. The feedback system in which high blood pressure induces an increase in sodium and water excretion by the kidney that leads to a deduction of the blood pressure [9-13].

Existing treatment: Different classes of existing drugs are administered during hypertension [1-5,14]. The classes of drugs are:

1) Diuretics:
   a) Osmotic Diuretics: Mannitol
   b) Mercurial Diuretics: Chlormerodrin
   c) Loop diuretics: Frusemide
   d) Carbonic anhydrase inhibitors: Acetazolamide, Methazolamide.
   e) Thiazide like diuretics: Hydrochlorothiazide, Chlorthiazide.
   f) Potassium sparing diuretics: Spironolactone, Amiloride.
2) Drugs acting on rennin angiotensin aldosterone system (RAAS):
   a) Angiotensin converting enzyme (ACE) inhibitors: Captopril, Enalapril, Lisinopril, Fosinopril, Quinapril.
   b) Angiotensin receptor II blockers: Losartan, Valsartan.
   c) Renin inhibiror: Aliksiren
3) Drugs acting on symptholytics system:
   a) α adrenergic (adrenergic receptor) blockers: Prazosin, Doxazocin, Terazocin.
   b) β adrenergic (adrenergic receptor) blockers: Propranolol, Atenolol, Esmolol.
   c) Mixed α and β adrenergic (adrenergic receptors) blocker: Labetolol
   d) Centrally acting drugs: Clonidine, Methyldopa.
   e) Ganglion blocker: Trimethapan
   f) Adrenergic neuron blockers: Reserpine, Guabethidine.
4) Calcium channel blockers: Verapamil, Nifedipine.
5) Vasodilators:
   a) Arteriolar dialators: Hydralazine, Diazoxide
   b) Arteriolar and venular dialator: Sodium Nitroprusside

The mechanism of action of ACE inhibitors represent on obstructing the rennin angiotensin aldosterone system of human body. Literally it's quite complex process. This type of medication assists in relaxing of veins and arteries to decrease our blood pressure. Actually ACE inhibitors block an enzyme in body refraining from creating angiotensin II which helps in narrowing our blood vessels. It can cause high blood pressure [13-15].

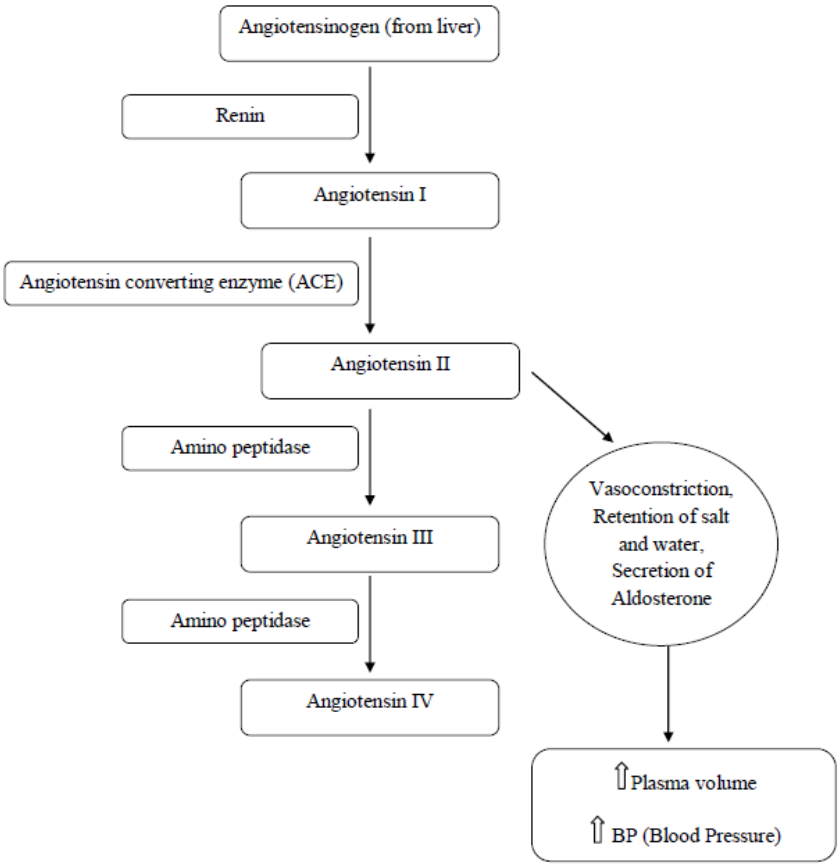


Figure 1: RAAS (Renin Angiotensin Aldosterone System)

Drug Resistance in Hypertension: Resistant hypertension is known as hypertension that is responsive to treatment and needed multiple does of medications to reach allowable blood pressure ranges.
If the following conditions are true and accurate then hypertension is called or known as resistant:

1) Blood pressure remains high (usually 120/80 mmHg and above).
2) Taking three different blood pressure medications at maximally tolerated doses.
3) Among the three blood pressure-lowering medications one is diuretic.
4) If hypertension requires four or more medications to be controlled it is also considered resistant hypertension.

Most common causes of resistance are Chronic renal disease, obstructive sleep apnoea, Poor patient adherence, inadequate doses or inappropriate combinations of antihypertensive drugs, excess alcohol intake, renal artery stenosis, etc [9-10, 16].

II. MATERIALS & METHODOLOGY

A) Software and web server: Pubchem, Protein data bank (PDB), PDBSUM, Autodock tools, UCSF Chimera, Rasmol, Padel descriptors, Chemdes, Pharmagist, Zinc pharmer and etc [17-21].

B) Methods:

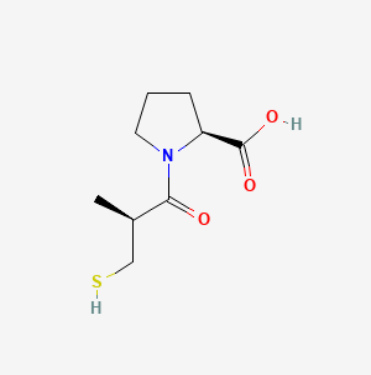
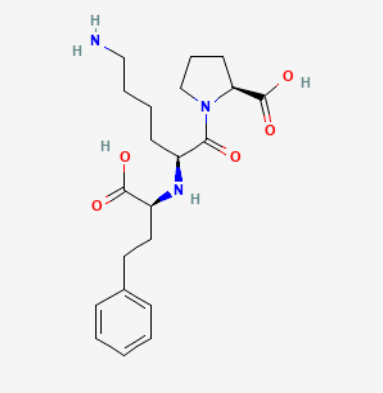
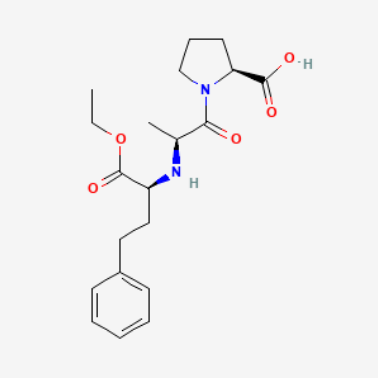
1) Target Selection: Selection of target (receptor), standard compounds and test samples can be selected.
2) Bioinformatics: From the protein data bank, receptor crystal complex structure (PDB code: 1R4L can be downloaded.
3) Active site prediction: From the ligplot analysis, the receptor active site coordinates can be generated.
4) Cheminformatics: From pubchem database, the standard and test ligand structure can be identifed.
5) Confirmation generation: The conformation of ligand and receptor structure can be generated through autodock tools.
6) Molecular docking: The docking study for standard and test molecules to the active site of receptor can be performed. The binding energy (Kcal/mol) can be observed.
7) Docking analysis: The docking analysis is also performed to know the accurateness of docking.
8) Identification of Pharmacophoric features: Pharmacophoric features of test sample can be identified through Pharmagist and Zinc pharmer.

9) Prediction of ADMET and filtering lipinski's rule: ADMET of test sample can be generated. Lipinski's filtration can be checked. Best on all data the test molecules are screened.

C) Criteria for Lipinski's rule of filtration [17-18, 22]:

1) Hydrogen bond donors should be within 5.
2) Hydrogen bond acceptors should be within 10.
3) The molecular mass should be within 500 daltons.
4) The partition coefficient that does not exceed 5.

III. RESULTS

Sl. No.	Name of Standard Compounds	Structure
1.	**Captopril**	
2.	**Lisinopril**	
3.	**Enalapril**	

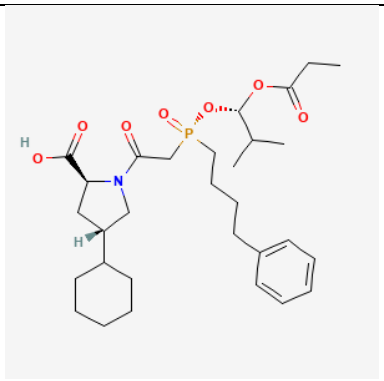
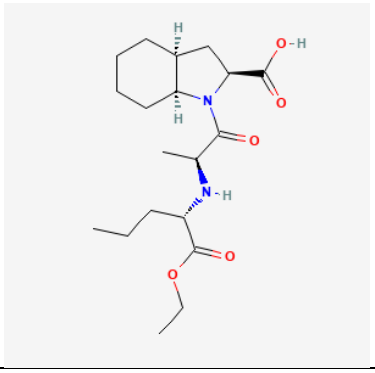
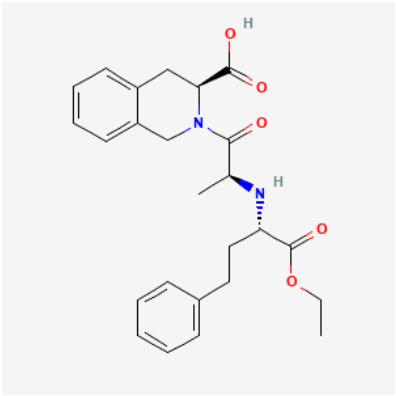
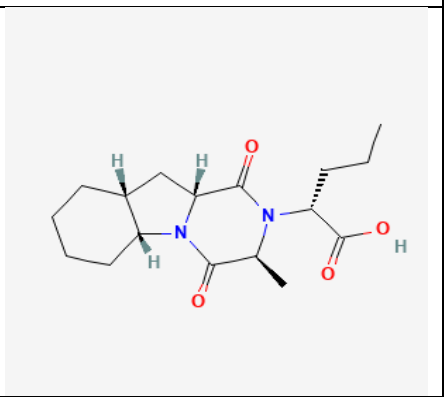
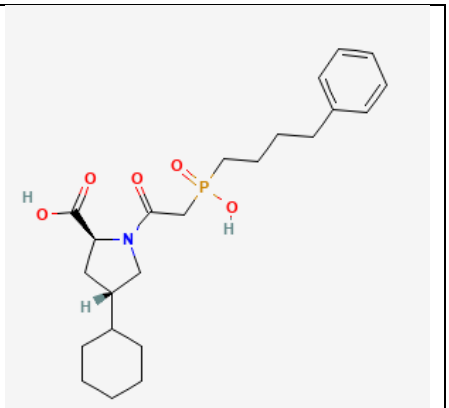
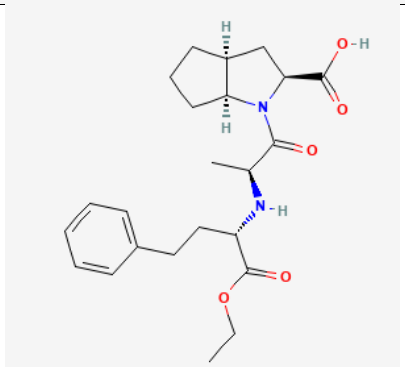
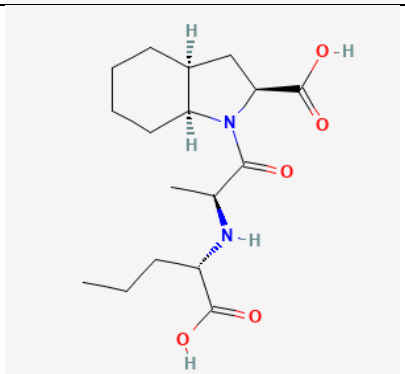
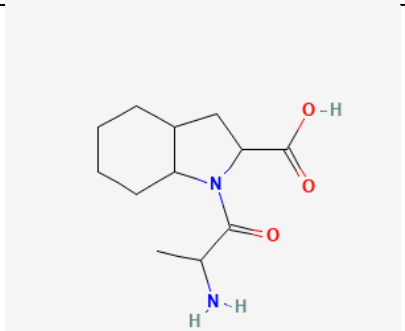
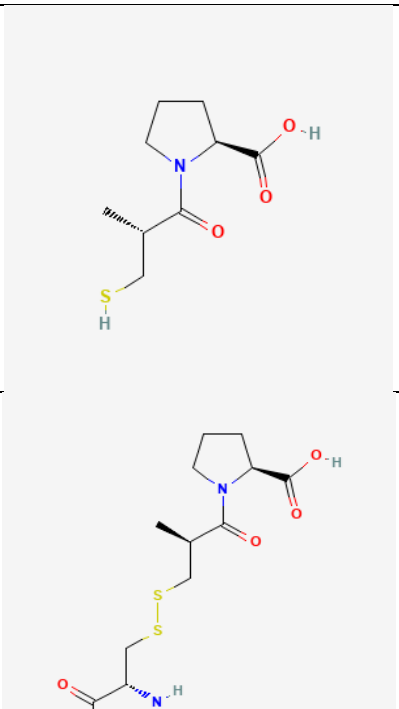
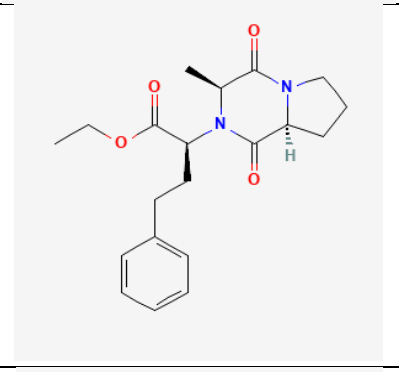
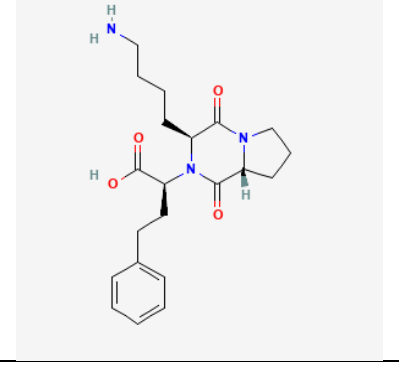
4.	**Fosinopril**	
5.	**Perindopril**	
6.	**Quinapril**	

Table 1: List of Standard compounds

Sl. No.	Test Compounds	Structure
1	**Test sample 1**	

2	**Test sample 2**	
3	**Test sample 3**	
4	**Test sample 4**	
5	**Test sample 5**	

6	**Test sample 6**	
7	**Test sample 7**	
8	**Test sample 8**	
9	**Test sample 9**	

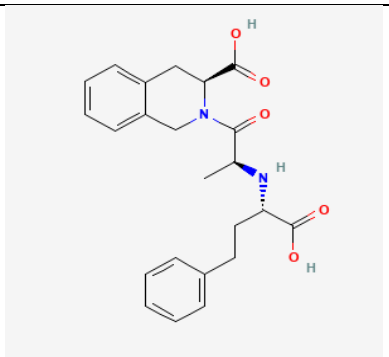
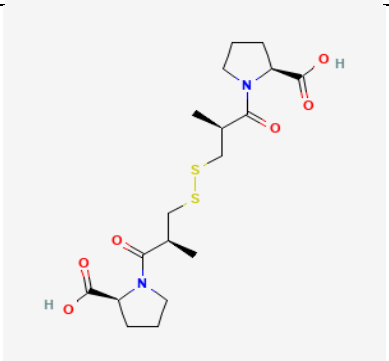
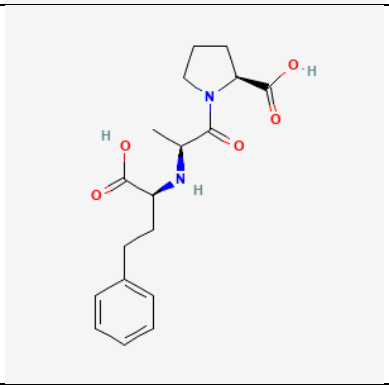
10	**Test sample 10**	
11	**Test sample 11**	
12	**Test sample 12**	

Table 2: List of test compounds

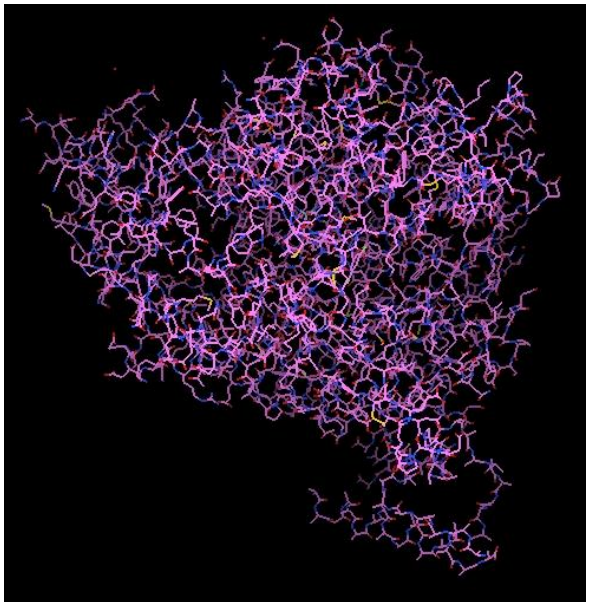
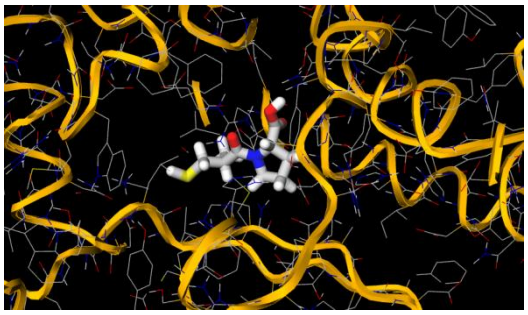
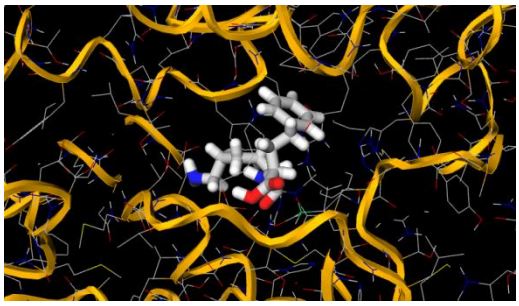
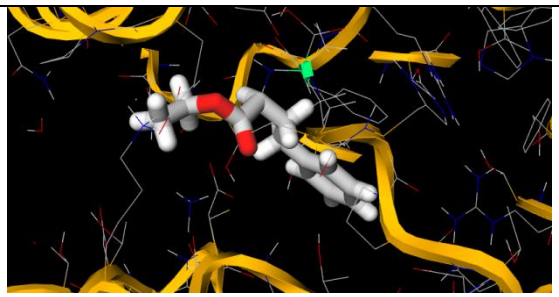
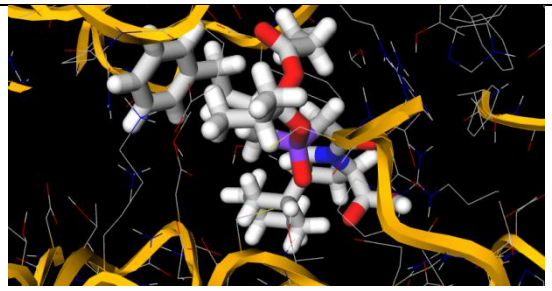


Figure 2: 3D structure of ACE2 (PDB code: 1R4L) visualized through auto dock tools

Receptor	X	Y	Z
ACE2 (PDB Code: 1R4L)	40.605	5.7864	27.835

Table 3: Receptor active site (co-ordinates)

Sl. No.	Name of the standard compounds	Docking result [Binding energy (Kcal/mol)]	Docking Image
1	Captopril	-5.7	
2	Lisinopril	-7.9	
3	Enalapril	-7.8	
4	Fosinopril	-8.6	

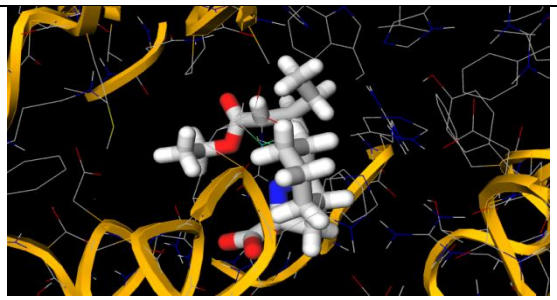
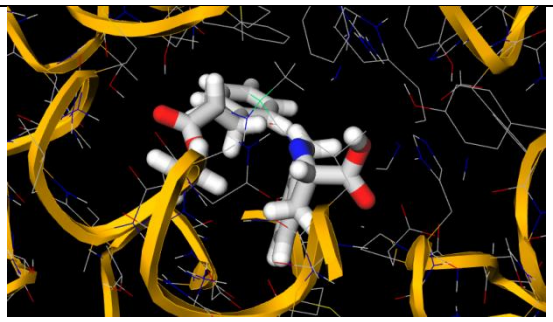
5	**Perindopril**	**-7.3**	
6	**Quinapril**	**-8.9**	

Table 4: Molecular docking of standard drugs to the active site of 1R4L

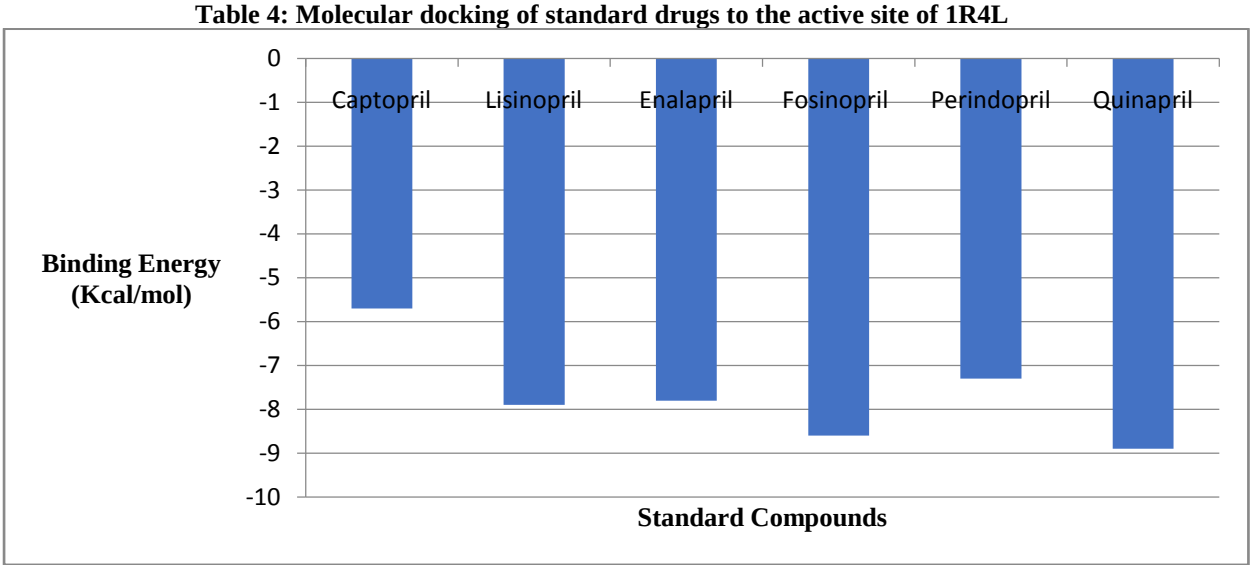
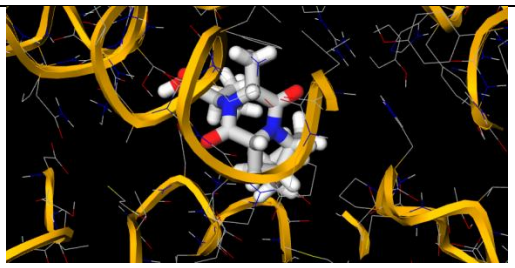
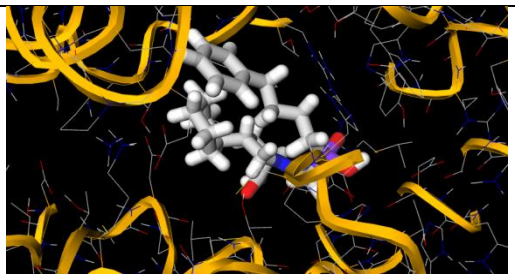
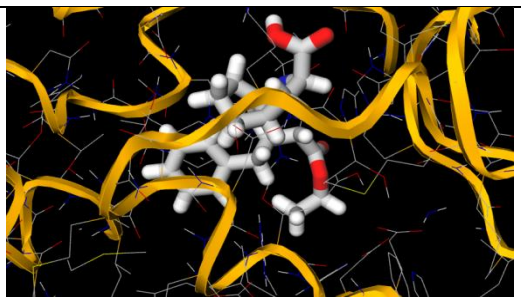
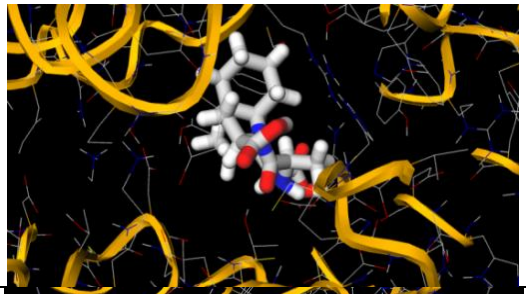
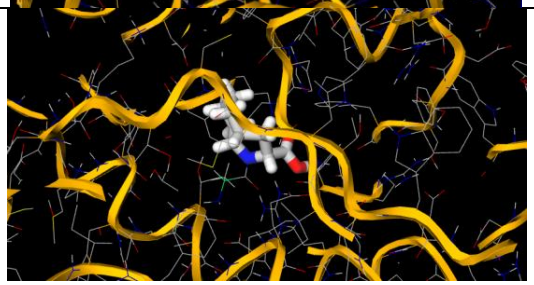
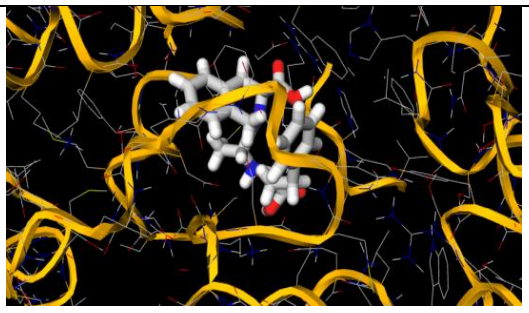
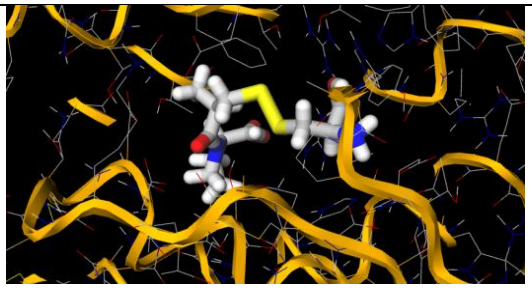


Figure 3: Graphical plot for molecular docking of standard drugs to the active site of 1R4L

Sl. No.	Test sample	Docking result [Binding energy (Kcal/mol)]	Docking Image
1	**Test sample 1**	**-7.6**	

2	**Test sample 2**	**-8.8**	
3	**Test sample 3**	**-8.4**	
4	**Test sample 4**	**-7.3**	
5	**Test sample 5**	**-6.8**	
6	**Test sample 6**	**-5.6**	
7	**Test sample 7**	**-6.8**	

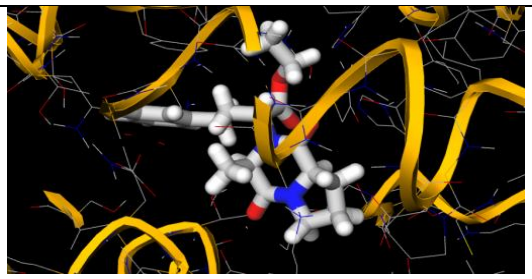
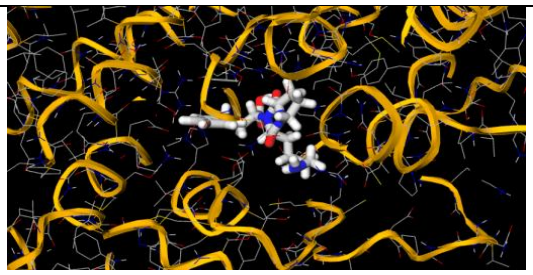
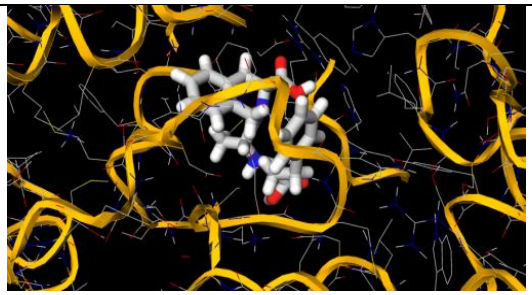
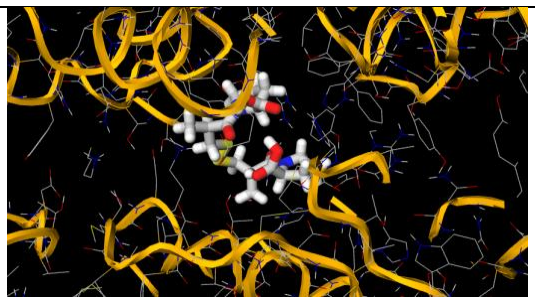
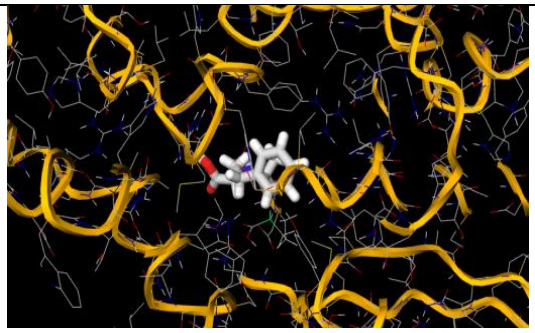
8	**Test sample 8**	**-8.8**	
9	**Test sample 9**	**-8.2**	
10	**Test sample 10**	**-9.5**	
11	**Test sample 11**	**-7.5**	
12	**Test sample 12**	**-7.7**	

Table 8: Molecular docking of test samples to the active site of 1R4L

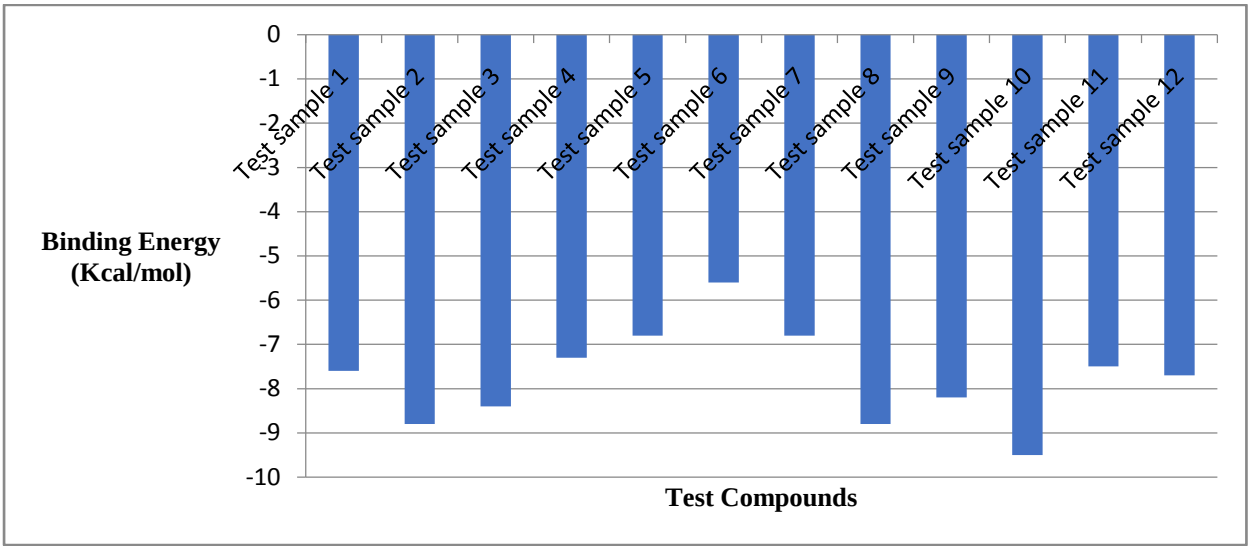


Figure 4: Graphical plot for molecular docking of test samples to the active site of 1R4L

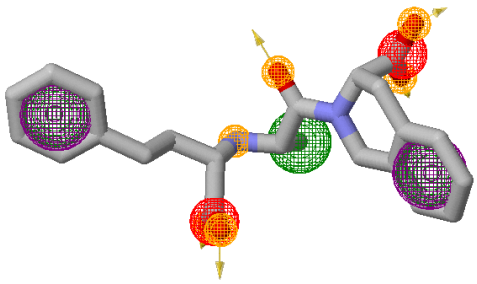
Test sample	Pharmacophoric structure	Features
Test sample 10		**Aromatic, Hydrogen bond acceptor, Hydrogen Donar, Negative ion and Hydrophobic**

Table 9: Pharmacophoric features of screened test compound (Screening based on molecular docking)

Test sample	Absorption level	BBB barrier level	Solubility level	Hepatotoxicity	Mutagenicity	Carcinogenicity
Test sample 10	Good	No	Good	No	No	No

Table 10: ADMET of screened test compound

IV. CONCLUSION

Hypertension shows risk day by day in worldwide. Especially different serious cardiac problems arise during Hypertension. Different types of new molecules can be prepared through *in silico* drug design tools within a very short period of time. ACE2 is important factor for representing the pathophsiology of hypertension. ACE2 (PDB code: 1R4L) was chosen through protein data bank (PDB). Various types of standard molecules can be identified. Based on the standard molecules, the test compounds can be generated. Total 12 (Twelve) test set compounds can be represented. All of the compounds including standard and test are properly docked to the active site of ACE2. Based on the docking efficiency (total binding energy in Kcal/mol) the test compounds were screened. The binding energy of test compound 10 was higher docking result (binding energy -9.5 Kcal/mol) among all of the test sets. So, test set 10 can be screened according to docking applications. The pharmacophoric features can be identified through *in silico* pharmacophores detecting tools. The essential feature of screened compound is aromatic, hydrogen bond acceptor, hydrogen bond donor, negative ion and hydrophobic. At lastly, filtration by lipinski's rule can be detected. The screened compound was passed through fulfilling of lipinski's rule of filtration.

Conflict of Interest: Nil

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