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Discovering New Lead Moieties as ACE Inhibitors: A Computational Approach

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ABSTRACT

The development of a medication for the treatment of hypertension with more phrenological effect with fewer side effects is a major challenge for researchers in the field of drug discovery. An enzyme in the body that produces angiotensin II, a chemical that constricts blood arteries, is prevented from by ACE inhibitors. High blood pressure can result from this constriction, which makes the heart work harder. A multi-step virtual screening methodology was used in this study to discover the novel potential ACE inhibitors. Ligand-based pharmacophore modelling using Pharmagist was developed. Generated pharmacophore hypothesis was used to screen the ZINC database by ZINC pharmer. By the application of Data warrior tool further filtered and used for molecular docking using Auto dock Vina. Based on the binding affinity and the amino acid interaction the top 5 compounds were identified and further subsequently evaluated for ADMET properties by PKCSM web server. ZINC48286865 compound has the good binding affinity and good interaction with the ACE receptor, which can be further evaluated for the treatment of hypertension [1].

Keywords*: Hypertension, ACE receptor, Pharmacophore modelling, Molecular Docking*

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INTRODUCTION

Blood pressure is the force exerted by the body's main blood vessels, the arteries, as blood flows against their walls. Hypertension is the medical term for elevated blood pressure.The blood pressure is expressed as two digits. Systolic pressure, which is the first number, is the blood vessel pressure produced when the heart contracts or beats. The second number displays the pressure in the arteries between heartbeats [diastolic]. If the systolic and/or diastolic readings on two consecutive days of blood pressure testing are both below 140 millimetres of mercury, hypertension is considered to be present [1].

Based on their symptoms, the four basic forms of high blood pressure can be distinguished. The many forms of hypertension are listed here.Primary, Secondary, Malignant, and Resistant hypertension, is hypertension that is challenging to control despite taking a variety of drugs, including a diuretic [2]. About 10% of all cases of hypertension are caused by this type. Obesity, advancing age, or underlying medical illnesses like diabetes and kidney issues are among its common risk factors. There can be undiscovered secondary underlying reasons in people with resistant hypertension as well. This type of hypertension can typically be treated with thorough treatment regimens, medications, or by locating and treating the secondary underlying cause.Among other things, hypertension can gravely injure the heart. Atherosclerosis brought on by high pressure can lessen the flow of blood and oxygen to the heart. This higher pressure and reduced blood flow could lead to:

- Angina, a term for heartache.
- Heart attack, which occurs when the oxygen flow to the heart's muscle cells is interrupted.
- The heart suffers more damage the longer the blood flow is blocked.
- Irregular heartbeat, which can result in rapid death; heart failure, a condition where the heart is unable to efficiently pump blood and oxygen to the body's other vital organs.

Hypertension, which can rupture or obstruct the arteries feeding the brain with blood and oxygen, can potentially cause a stroke.
Moreover, kidney damage from hypertension might eventually progress to renal failure.
Target might be an enzyme, Nucleic Acid and protein that is used for in – silico method of drug designing is the identification of the drug target molecule employing Bid – informatics tools.
Angiotensin-converting enzyme [ACE] inhibitor medications work by relaxing the veins and arteries by reducing blood pressure. ACE inhibitors prohibit an enzyme in the body form synthesizing angiotensin II, a substance that narrows blood vessels. This constriction, which also makes the heart work harder, can lead to high blood pressure. Angiotensin II also secretes hormones that elevate blood pressure [3].
Symptoms in situations like: are prevented, treated, or improved with the use of ACE inhibitors.
elevated BP[hypertension]

- Cardiovascular disease
- Heart attack
- Certain long-term kidney conditions
- Cardiac arrests
- A condition that causes the skin and connective tissues to harden [scleroderma] [4].

Occasionally, an ACE inhibitor may be used with another blood pressure medication, such as a diuretic or calcium channel blocker. Direct renin inhibitors and angiotensin receptor blockers shouldn't be used together with ACE inhibitors. Rarely, ACE inhibitors might make some tissue areas enlarge [angioedema]. It may endanger life if throat swelling develops. The efficiency of ACE inhibitors is decreased by nonsteroidal anti-inflammatory medicines [NSAIDs], including naproxen sodium [Aleve] and ibuprofen [Advil, Motrin IB, among others] [5]. Pregnancy-related use of ACE inhibitors raises the baby's chance of birth abnormalities. Consult your doctor about other methods of treating high blood pressure if you are pregnant or intend to become pregnant [6].
Hence the present work focus to identify novel molecules to inhibit the COMT enzyme for the treatment of Parkinson's disease through the application of computational tools.

MATERIAL AND METHODS

Identification and preparation of the Target: The target protien was identified and retrieved from the PDB[Protien drug bank] with PDB ID 4BTL with the resolution of 1.80Å in the protien preparation water molecules, hetero groups and unwanted ligands were removed by using the software known as SPBDV and saved in the PDB format [7].
Identification of the ligands: The Drugs which are available in the market are selected through literature survey which are used as standard and the structures are Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolaprilare downloaded by the NCBI PubChem website In SDF format [8].
Pharmacophore modelling: A pharmacophore is a 3D framework created by mapping the physiologically powerful chemicals necessary for the ligand to attach to the appropriate target protein and interact with it. Molecule are subjected for pharmacophore modelling by uploading to free online tool called pharmagist in Sybyl Mol 2 format with mail ID. Serverconsiders a variety of ways to combine a submitted compounds to produce the pharmacophore in Jmol format [9].
Collecting data from zinc database: Pharmgist produces the number of aligned molecules like 7 aligned molecule one up on another gives a cluster in the JMol format, where the molecule with maximum aligned 7 or 6 molecules with high scoring are selected and downloaded, further these molecules were uploaded in free online tool for pharmacophore modelling I.e., ZINC pharma. Which will screen the zinc database and gives the molecules having same pharmacophoric features by submitting to query. After queries over zinc database give around more than a lakh hits of molecule, further obtained hits are filtered and get total of 950 small molecules [10].
Those above molecules are uploaded to the data warrior, where data warrior is free ware tool for doing pharmacophore modelling, these molecules are screened based on the standard drug physicochemical properties like molecular wight, log P, H donor, H acceptor, polar surface area, rotatable bond and steric centre. The SDF files for each of these compounds were retrieved and used for the molecular docking research [11].
Molecular docking studies: The protein is downloaded and prepared and ligands are downloaded and made cluster using Discovery studio in the form Mol SDF File and made ready for the docking studies.The docking studies was done using PyRx in which protein is loaded and made macromolecule and then Drug cluster is loaded and energy minimisation is done the protein and drug cluster is converted in to pdbqt format the grid box is identified and allowed for the docking and result is downloaded in the pdbqt form [12].

Building the protein -ligand complex: By using the PYMOL software which is used for the visualisation and to make complex here particular drug and protein is made complex and saved as PDB format [13].
Studying the protein -ligand interactions: The Discovery studio software is used for for both clustering the ligands and visualisation of the protein ligand interactions the complex obtained is loaded in the discovery studio and analysed for the interactions in the form of 2D and 3D structures [14].
ADME-T studies: The ADMET [absorption, distribution, metabolism, excretion, and toxicity] characteristics play a crucial role in deciding a molecule's fate inside the body. When a molecule is administered orally, a good absorption is a desired property. The distribution and absorption of a molecule throughout the system will be governed by the balance of lipophilic and hydrophilic groups in the structure. From a therapeutic standpoint, effectiveness and toxicity are important. The ADME-T studies is carried out using PKSCM online software [15].

RESULT AND DISCUSSION

Ligand-based pharmacophore modelling: The pharmacophore postulate was developed from ACE inhibitors byusing PharmaGist webserver.Molecule obtained from PharmaGist has one aromatic ring, 2 hydrogen bond acceptor at a specified distance. The result obtained from the PharmaGist is uploaded in the ZINCPharmer, it will screen and recover the compounds having same pharmacophoric features from the ZINC database.The developed pharmacophore model aids in locating the structural requirement to inhibit ACE. screened molecules were uploaded to the DataWarrior, further the molecules are filtered based on the physicochemical properties, I.e., the log p value, molecular weight, hydrogen donor, hydrogen acceptor and polar surface area, of the standard ACE inhibitors. Molecules were obtained as SDF files for molecular docking studies.
Molecular docking studies: The molecular docking studies of ACE inhibitors was done the main intention was to determine the major binding sites in the protein's active pocket with PDB ID 4BTL using Auto Dock Vina molecular docking was carried out. The Drugs which are used as standard and the structures arePerindopril, Candesartan, Losartan, Captopril, Lisinopril, Ramipril, Enalapril, Enalapril, Trandolapril, Quinapril, Fosinopril, Valsartan and Telmisartan are currently used in the market and among this Inhibitors Telmisarta Docking score was found to be high. -10.6Kcal/mol, which has conventional hydrogen bonding with THR435, VAL244, ARG45, Carbon hydrogen bonding withTYR407, SER24, GLY434, GLU43,Pi-alkyl interaction with ARG51, LUE273 Pi-Pi T shaped interaction with TYR402, Pi-Alkyl interaction with ARG51, LEU277. Therefore, this interaction helps to understand inhibitory properties of the COMT inhibitors. The compound was submitted to docking after being retrieved from the ZINC database using ZINCPharmar based on the pharmacophore. For molecular docking with the target protein PDB ID: 4BTL, 4 chemicals were chosen. The compounds with the best docking scores [most adverse] were obtained and used to compare the binding interactions of standard drugs. This comparison helps to categories the hit substance as an ACE inhibitor. The chemicals are identified based on the binding interaction. A docking score of between -10.9 and -9.5 kcal/mol is possible. A molecule named ZINC73152058 has been found by molecular docking with the best docking score of -10.9 kcal/mol and exhibits Pi-Pi T-shaped interaction with TRP262, Pi-Pi stacked bonding interaction with TYR315, ASP67, THR68, and conventional hydrogen bonding with employing AutoDock tools and the Bio via Discovery Studio Visualizer, the binding interactions between docked molecules and the proteins were found. Amino acid residue involved in binding interaction were TYR315, ASP67, THR68, TYR311, TYR65, TRP262,ILE270 and PHE312. These found molecules bind similarly to conventional compounds, according to the molecular docking studies. Hence, ACE can be inhibited by these 4 compounds. Figure 2 displays the chemical structures of the four docked molecules.

Table 1:DOCKING SCORE AND TYPE OF INTERACTION OF STANDARD DRUGS

Compound	Binding affinity	**Interacting residues**	**Type of Interaction**
Perindopril	-7	TRP193, LYS194, GLU249 MET90	Conventional hydrogen bond, Pi- cation, Pi-Alkyl, unfavourable Acceptor-Acceptor
Candesartan	-9.9	ASP191, GLU140, GLY167, TRP193, HIS192, ILE141, SER169, GLN170	Conventional hydrogen bond, Pi-sigma, Pi-Pi Shaped, Carbon Hydrogen bond
Losartan	-10	ASP191, ILE139, HIS192, TRP193, ILE141, GLU140, TYR118	Conventional hydrogen bond, Pi-Sigma, Pi-Pi T shaped, unfavoured Acceptor- Acceptor
Captopril	-6.5	PRO224, LYS194, MET90,	Conventional hydrogen bond, Unfavourable Donor-Donor, unfavourable Acceptor- Acceptor,

		ASN220, GLU249, ASP219	Pi-Cation, Pi-Alkyl
lisinopril	-7.9	LYS194, GLU249, MET90, ASP191	Conventional Hydrogen bond, Unfavourable Acceptor- Acceptor, Pi-Cation, Pi-Alkyl
Ramipril	-10.1	GLU249, MET90, ASP191 LYS194	Conventional Hydrogen bond, Carbon Hydrogen bond, Pi-Cation, Pi-Alkyl
Enalapril	-9.6	MET90, PRO224, TRP193, ASN220, GLU249	Conventional Hydrogen bond, Pi-Cation, Pi-Sigma, Pi-Pi stacked, Pi-Alkyl
Trandolapril	-10.3	GLU77, THR81, ASP94, LYS95, GLU84	Carbon Hydrogen Bond, Pi-Anion Pi-Alkyl
Quinapril	-10.2	TRP193, LYS194, GLU249 MET90	Conventional Hydrogen bond, Pi-Cation, Pi-Pi Stacked, Pi-Alkyl
Fosinopril	-8.5	TRP193, LYS194, GLU249, MET90	Conventional Hydrogen Bond, Unfavourable Acceptor-Acceptor, Pi-Alkyl, Pi-Cation
Valsartan	-7.8	ILE207 TYR69 TYR444 TYR407	Carbon hydrogen interaction Pi-Sigma interaction Pi-Pi Stacked interaction Pi-Pi T Shaped interaction
Telmisartan	-10.6	THR435, VAL244, ARG45 TYR407, SER24, GLY434, GLU43 ARG51, LUE273 TYR402 ARG51, LEU277	Conventional hydrogen bond interaction Carbon hydrogen bond interaction Pi-Alkyl interaction Pi-Pi T shaped interaction Pi-Alkyl interaction

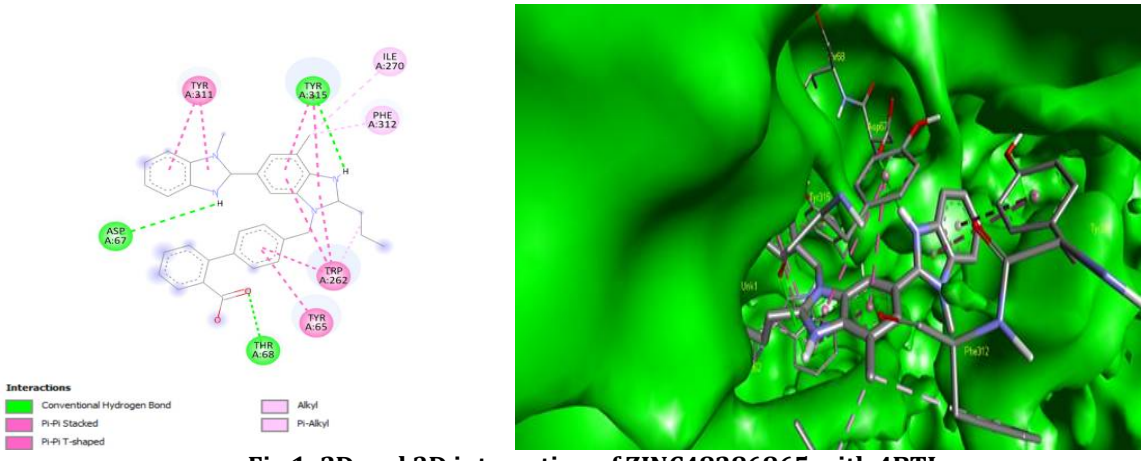

Fig 1: 2D and 3D interaction of ZINC48286865 with 4BTL

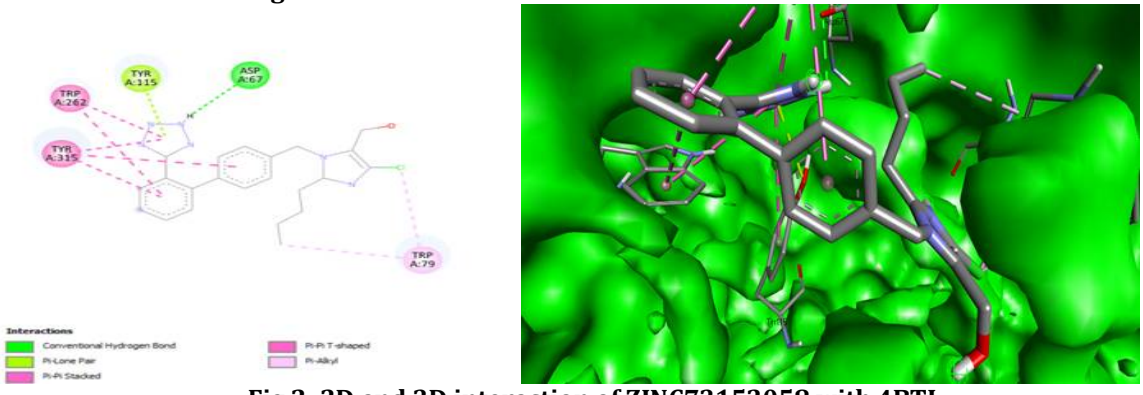

Fig 2: 2D and 3D interaction of ZINC73152058 with 4BTL

Table 2: Docking score of molecules obtained from ZINC database

ligand	Binding affinity	Interacting residues	Type of Interaction
ZINC48286865	-10.4	TYR315 LEU265 TRP262	Pi-Pi T-shaped Alkyl interaction Pi-alkyl interaction
ZINC73152058	-10.9	TYR315, ASP67, THR68 TYR311, TYR65, TRP262, ILE270, PHE312	Conventional hydrogen bond Pi-Pi stacked, Pi-Pi T-shaped Alkyl, Pi-alkyl interaction
ZINC40203678	-9.5	ARG773, PHE772 TYR615, TYR816 TRP763 LUE766	Conventional hydrogen bond Pi-Pi T -shaped, Pi-Pi stacked Pi-sigma Pi-alkyl interaction
ZINC58050703	-10.3	ASP67 TYR115 TRP262, TYR315 TRP79	Conventional hydrogen bond Pi-lone pair Pi-Pi T -shaped, Pi-Pi stacked Pi-alkyl interaction

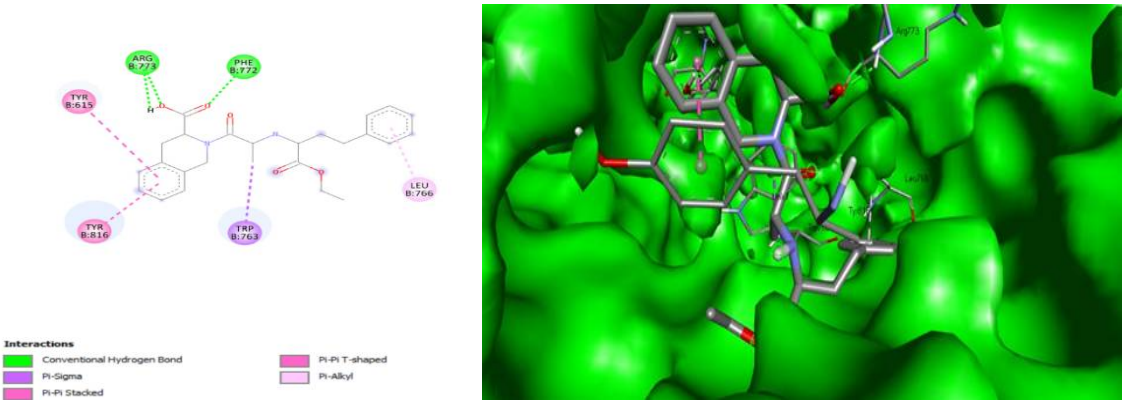

Fig 3: 2D and 3D interaction of ZINC40203678 with 4BTL

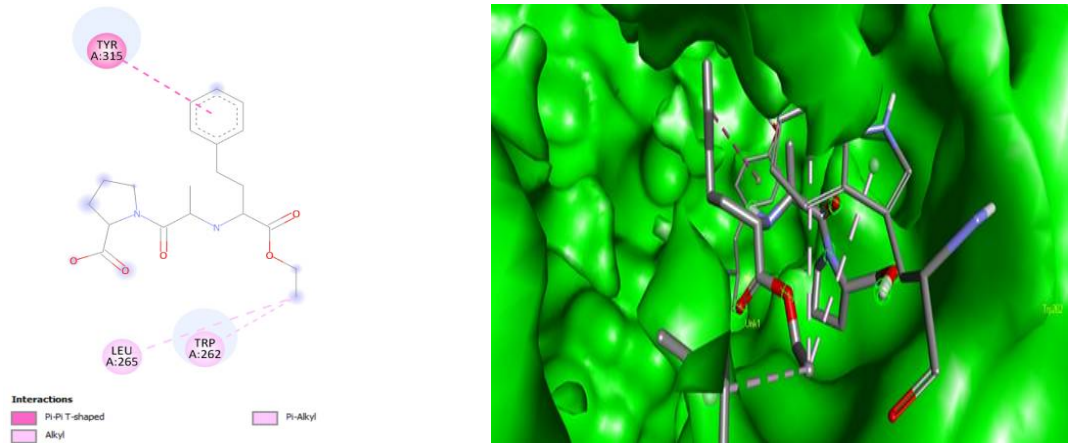

Fig 4: 2D and 3D interaction of ZINC58050703 with 4BTL

ADMET studies: The ADMET properties with the zinc database drug i.e., ZINC73152058 has good properties like water solubility, $CaCo_2$ permeability, CNS permeability and it is non hepatotoxic molecule, while other molecules are showing hepatotoxicity. The ADME-T studies is carried out using PKSCM online software.The zinc database molecule, ZINC73152058 will obey the Lipinski rule of five, by this the molecule can observed well by orally and it pass BBB and CNS to show its activity. The drug development process is sped up by the drug-likeness filters based on physicochemical characteristics. Drug-likeness rules/filters based on physicochemical features, however, have drawbacks, as demonstrated by several research.

Table 3: Drug ability studies of the ligands viz., parameters of Lipinski's rule of 5

Compound	Physical properties						Lipinski's rule
	Molecular weight	LOGP	Rotatable bonds	H-bond acceptors	H-bond donors	Surface area	
ZINC48286865	351.406	3.79	6	5	0	151.955	0
ZINC73152058	353.451	3.06	6	6	1	150.251	1
ZINC40203678	365.433	2.96	9	5	1	157.977	0
ZINC58050703	367.453	3.51	6	5	2	158.291	0

CONCLUSION

The standard drugs Perindopril, Candesartan, Losartan, Captopril, Lisinopril, Ramipril, Enalapril, Enalapril, Trandolapril, Quinapril, Fosinopril, Valsartan and Telmisartan, used to get ligand-based pharmcophore model. The model gives molecules with similar pharmacophoric feature which is obtained from ZincData base and Datawarrior, these molecules were docked via AutoDock Vina and evaluated based on docking score and binding interaction, 4 molecules are obtained. Further ADMET studies were done by using PKCSM and Swiss ADME online software. Which predicts the drug-likeness feature and oral rat chronic toxicity and hepatotoxicity. Based on the results molecule ZINC73152058 were predicted as the MAO-A inhibitor. Further *in vitro* and *in vivo* evaluation on the selected compound will lead to identify a potent lead as MAO-A inhibitor.

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CONFLICT OF INTEREST

The authors declare that no conflict of interest.

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