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IN-SILICO EVALUATION OF MOEXIPRIL AGAINST ACE ENZYME

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Keywords:

In-silico, Molecular docking, Target site, Cell simulation, Adverse reaction, Autodock, Covid-19, ADME

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ABSTRACT: On computers, *in-silico* studies are typically carried out where we forecast how any new compound would interact with the proteins found in our bodies or with any outside particles. Molecular docking, target site & adverse reaction of any newly created molecule, together with cell simulation, are all performed in an *in-silico* study. The advantage of *in-silico* research over other techniques is that it does not require the use of people, animals, or cell cultures; all that is required is a computer with the required software. *In-silico* analysis developed into one of the most crucial tools for all scholars throughout the world during the Covid -19. Results of any research project in an *in-silico* study are available immediately because of the utilisation of computers. Through the *in-silico* technique, research work is made incredibly simple. Understanding how any new drug will affect us, including its absorption, distribution, metabolism, excretion, and toxicity, is incredibly convenient for us. It is easier for us to predict the target location for each new molecule by utilising several servers & software. Different servers/software are utilised for *in-silico* studies, including Swiss ADME, Drulito, Autodock, Discovery Studio, Autodock Vena, and Ligplot.

INTRODUCTION: *In-silico* studies are conducted on or through computers, and the outcomes are used in the drug discovery process. The responses and target sites in human bodies to new chemical agents are the focus of *in-silico* research. In such instances, *in-silico* study becomes the greatest alternative owing to its low cost & speedy result interpretations. Experimentally, it becomes very expensive, complex & time-consuming process to discover the target site & response with human body for any certain chemical.

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Virtual screening, de novo design, *in-silico* ADMET prediction, sophisticated methods for figuring out protein-ligand interaction, and structured-based drug design are all common uses for *in-silico* research. These days, computers are utilised to identify the target protein for any drug molecule. Once the target site is found, various well-known compounds are virtually screened against it. This is followed by additional testing to see how the drug molecule interacts with the target protein.

By using computers, it is much simpler to identify the optimal group of molecules that can interact with the target protein in a flawless way than it would be to test every molecule individually.

Drug Design: If we define drug design, we can say that drug design is the identification of any new

molecule based on its target site. There are two types of drug design:

1. Rational drug design
2. Structure based drug design

Rational Drug Design: This method is used to create new drug molecules. New molecules are identified using computers by testing their efficacy, safety, and selectivity. Rational drug design can be accomplished through the use of any of the following methods: ligand-based drug design, structure-based drug design, homology modelling, and de novo design.

Structure Based Drug Design: This technique is being used for the first time to design drugs. This technique relies heavily on drug targets, which are typically enzymes or proteins. X-ray crystallography or nuclear magnetic resonance (NMR) methods were once used to predict the 3D structure of proteins. The interaction of new drug molecules with the 3D structure of protein is then tested. This technique is now widely used in the development of new drugs [1].

Methods of *In-silico* Study:

Docking: The orientation, conformation, and position of a small molecule (ligand) with respect to its binding or targeted sites are predicted in molecular docking. It is easier to understand the type of interaction that occurs between the ligand and its targeted site when the orientation, conformation, and position of the ligand are predicted. The actual binding site of any molecule is discovered using molecular docking, which can identify multiple binding positions for ligands with their target proteins. The best binding position is chosen from among all binding positions for further processing. Many docking programmes are available today, but the following are the most commonly used:

1. AutoDock
2. Ligand Docking Genetic Optimisation (GOLD)
3. FlexX and FlexE
4. DOCK
5. Internal Coordinate Mechanics (ICM)/flexible receptor docking algorithm based on ICM (IFREDA).

The only ways docking software differs from one another are protein and ligand flexibility, sampling algorithm, and scoring function.

Virtual High Throughput Screening: This method, abbreviated as vHTS, is used to assess the potential activity of a large number of compounds against their target site. Virtual high throughput screening is both costly and time consuming. It comes in two varieties:

1. Ligand based vHTS
2. Structure based vHTS

***In-silico* Fragment-Based Drug Design:** It is an alternative to virtual high throughput screening; in vHTS, each molecule (ligand) is tested for its activity with its target site, whereas in fragment-based drug design, several small molecules are combined to test their activity with their target site [2].

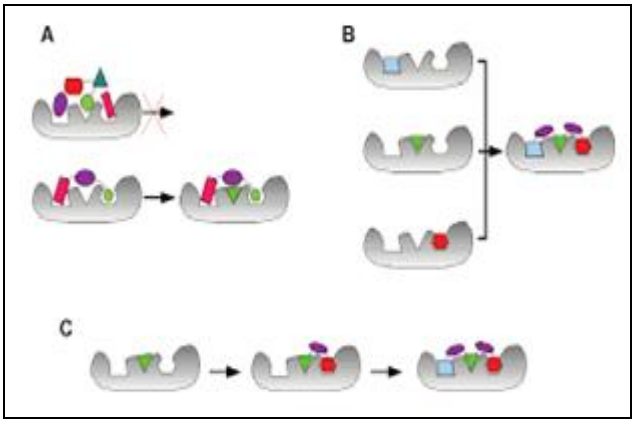


FIG. 1: HTS VS. FBD COMPARISON

Admet Predictions: We can use the *in-silico* method to not only check the interaction of any new drug molecule with its target site, but also to make predictions about the pharmacokinetics of any new drug molecule, such as its absorption, distribution, metabolism, elimination, and toxicity. There are several methods available for predicting ADMET of any new drug molecules, including:

1. Structure-based approaches to ADME property prediction.
2. Approaches based on data for predicting ADME properties.
3. Integrated pharmacokinetic models.

Structure-based Approaches to ADME Property Prediction: For their interaction, three-dimensional models of ligands and proteins are used, which are virtually analysed using the quantum mechanical method. If no suitable results are obtained, homology and pharmacophore models can be used. A few possible outcomes:

Molecular Modelling of Drug Metabolizing Enzymes: The 3D structure of a drug and its metabolising enzymes are analysed using the homology method to better understand their interaction.

Pharmacophore Model for Substrate Specificity Analysis: If we define pharmacophores, we can say that they are the important functions of any molecule that are required for its pharmacological activity. Structure activity data is used to determine the pharmacophores of any active compound by comparing their structures. 3D structures are required to determine how ligands bind to their receptors.

Pharmacophore modelling necessitates the following steps:

1. Identification of chemically equivalent atoms or groups based on physical or chemical properties.
2. Estimation of the relative 3-dimensional position of the possible pharmacophoric groups in the molecules' allowed low energy conformations.
3. When there are multiple options, weigh similar pharmacophoric groups.

Approaches Based on Data for Predicting ADME Properties: Several ADME processes of any compound can be predicted using data-driven approaches. Generally, ADME of any compound is predicted using QSAR methods based on its chemical structure.

Methods are divided into two steps:

1. To derive molecular descriptors from the chemical structure of the compounds.
2. Using multivariate statistical analyses, relate the target property to the descriptors.

Aside from these descriptors, various linear and nonlinear methods are used for multivariate analysis, including topological descriptors, fragment descriptors, and global physiochemical descriptors. There are also a few data-driven methods available that do not rely on mathematical models and instead rely on molecular similarity/dissimilarity, such as the k-nearest neighbour method and stochastic artificial neural network. A few possible outcomes:

QSAR Prediction of Solubility: It is critical to predict the solubility of any new compound because solubility can influence biological activity. Several algorithms are available to predict the solubility of a new drug.

Abraham et al developed a thermodynamic-based equation, which is as follows:

$$\log Sw=0.5-0.01(mp-25) -\log Kow$$

Where,

Sw= the solubility of a solid solute in water, mp the melting point, and Kow the octonol/water partition coefficient.

Abraham *et al.* provided an amended salvation energy relationship in order to predict the solubility of any new compound in water; the equation is as follows:

$$\log Sw = 0.510-1.020R2+0.813\pi_2^H+2.124\sum\alpha_2^H+4.187\sum\beta_2^H-3.337\sum\alpha_2^H\sum\beta_2^H 3.986Vx$$

R2 denotes excess molar refraction, π_2^H denotes dipolarity, $\sum\alpha_2^H$ denotes overall hydrogen bond acidity, $\sum\beta_2^H$ denotes overall hydrogen bond basicity, and Vx denotes Mc gowan characteristic volume [3]. Huuskonen *et al.* also developed an empirical method for predicting the solubility of any new drug using topological indices and artificial neural network modeling [3, 4].

QSAR Prediction of Intestinal Permeability: In addition to oral bioavailability, intestinal permeability is an important factor that must be predicted during drug development. To predict intestinal permeability, several quantitative descriptors with 2D or 3D molecular structure are used, such as fragment descriptors, hydrophobicity (logP), hydrogen bonding descriptors, topological

indices, polar surface area, and quantum chemical parameters. Aside from this, multiple linear regressions, such as partial least squares and artificial neural networks are used (ANN). QSAR studies have recently been conducted using Coco-2 cell monolayer as an intestinal model to predict permeability of any new compound across the intestine.

QSAR Prediction of Blood-Brain Barrier Permeability: Predicting the permeability of the blood-brain barrier is critical for understanding the therapeutic and side effects of drugs that act on the central nervous system. Abraham *et al.* established a relationship between log BB (distribution of solute between blood and brain) and excess molar refraction, dipolarity, hydrogen bond acidity and basicity, and molecular volume, and it was discovered that log BB increases with increasing solute size and decreases with decreasing solute dipolarity, hydrogen bond acidity, and hydrogen bond basicity. Lombardo *et al.* established a relationship between log BB and calculated solvation free energy in water. In addition, empirical approaches using molsurf quantum chemical descriptors and topological descriptors are used to predict the permeability of BBB [5].

Active Transport Process Prediction Using Comparative Molecular Field Analysis: Cramer *et al.* developed a 3D QSAR approach called comparative molecular field analysis (CoMFA). In order to observe changes in bilological properties, CoMFA evaluates the electrostatic and stearic field at regular grid points that surround a set of mutually aligned ligands. CoMFA provided contour maps; using these maps makes it easier to differentiate structures based on their affinity [6]. Swaan *et al.* investigated a structure affinity relationship for small intestinal oligopeptide carriers using comparative molecular field analysis (CoMFA) (PepT1) [7].

Oral Bioavailability Prediction Using a Stochastic Neural Network: The average weight of training pattern target values is calculated using a probability density function and a non-parametric estimator, namely a generalized regression neural network (GRNN). One advantage of GRNN is that output elucidation is very simple. Niwa *et al.* conducted research to predict human intestinal absorption of any new compound using 2D topological descriptors, which are easier to use and faster than any other neural network [8].

The K-Nearest Neighbour Method for Predicting Metabolic Stability: The k-nearest neighbour method is used to predict the metabolic stability of any new compound by calculating the weighted average property of the k-nearest compound in a database.

Integrated Pharmacokinetic Models: The primary goal of pharmacokinetic modelling is to predict the pharmacokinetics (ADME) of any new compound in the entire body by combining all pharmacokinetic models into a single model. This model aids in understanding the systemic behaviour of any new compound by incorporating physiological and biochemical parameters. A few possible outcomes:

Oral Absorption Prediction: Because oral absorption of any new drug compound is a complex process influenced by several factors such as physiochemical factors, physiological factors, and formulation factors, mass balance approaches have been developed to predict oral absorption of any new drug compound. Yu and Amidon created a compartmental absorption and transit (CAT) model to increase the rate of drug absorption. CAT's advanced software includes GastroPlusTM and IDEATM [9].

Hepatic Metabolism Prediction: Kinetic parameters derived from in vitro studies of any new drug compound related to drug metabolism are used to forecast in vivo situations. For this purpose, many empirical and allometric approaches have been developed [10].

Study *In-vitro, In-vivo* and *In-silico* Comparison: The *In-vitro* Method: In comparison to the *in-vivo* method, the *in-vitro* method is more cost effective and time efficient because no animals are used in the study. This method is more specific because it can be performed using any specific cells. Because we do not use any animals in this method, several risk factors remain unknown, and the results obtained by this method differ greatly from the *in-vivo* method.

The *In-vivo* Method: In the case of the *in-vivo* method, the animal is very important because all research is done on animals to check the absorption, distribution, metabolism, elimination, and toxicity of any new compound. Animal research is prohibited in order to protect endangered species. Using animals for research is difficult because all necessary conditions must be maintained; therefore, animal models are used for *in-vivo* studies.

The *In-silico* Method: *In-silico* methods differ from *in-vitro* and *in-vivo* methods in that they are less expensive, take less time, and do not require the use of animals. This method is based on data collected from software experiments. Because this method is based on predictions, the prediction values must be validated. *In-silico* research also necessitates improved explanation, description, and training [11].

MATERIALS & METHODOLOGY:

Materials:

Software used for *In-silico* Study: BIOVIA Discovery studio, DruLito, SWISS ADME, AutoDock Vina, PyMol & Ligplot.

Methods:

Construction of Ligand Library: To know the activity of Moexipril and its derivatives against Angiotensin converting enzyme (ACE), compounds information will be collected from natural source through searching scientific literature and databases.

Ligand Preparation: The 3D structure of each phytochemical will be downloaded from PubChem in SDF format and then converted into PDB files using Open Babel. The Reference molecules co-crystallize with protein will be used as a reference molecule. The structure of protein molecule will be downloaded from Protein Data Bank.

Protein Receptors Preparation: The 3D structure of Angiotensin-converting enzyme (ACE) will be downloaded from the Protein Data Bank. All water molecules, ions, and ligands will be removed from the protein molecule using PyMOL software. After that the addition of hydrogen atoms to the receptor molecule will be carried out by using MG Tools of AutoDock Vina software (Trott & Olson, 2010). The structure of protein will be saved in PDB format for further analysis.

Active Site Prediction: Before starting docking procedure, the center of mass of co-crystallized ligand will be analyzed by using the "centerofmass" command line in PyMOL software or co-ordinates will be determined from BIOVIA Discovery Studio Visualizer. The identified co-ordinates will be used to set the dimension and position of the grid box for site specific molecular docking process.

Drug Likeness and ADMET Analysis: Drug-likeness calculation will be performed to know the cytotoxicity activity of compounds for human by DruLiTo open-source software and SWISS ADME, ProTOX server. The pharmacological significance of a ligand is based on its drug bioavailability or drug-likeness which is calculated on the basis of certain physiochemical and structural properties. Therefore, all ligands will be evaluated for its drug like nature under Lipinski's rules of five by DruLiTo software.

Molecular Docking: Molecular docking will be performed into the active site of Angiotensin-converting enzyme (ACE) domain using Autodock vina (Trott & Olson, 2010) and PyRx which is open source software (GUI version 0.8 of autodock). A grid box from identified co-ordinates (x, y and z directions) of active site will be built with a grid spacing of 25 A°. Throughout the docking study the ligand molecules will be flexible and macromolecule kept as rigid. Docking will be performed to obtain a population of possible orientations and conformations for the ligand at the binding site. The best interactions better than that one of the positive control will be chosen with the lowest binding affinity pose or docking score. Molecule interactions between protein-ligand conformations, including hydrogen bonds and the bond lengths will be predicted by using Ligplot+ v.1.4.5 software

Visualization: The 2D Hydrogen and hydrophobic interactions of the protein-ligand complex structure will be performed by LigPlot+ v.1.4.5 program to identify the interactions of amino acid between protein and ligand complex. LigPlot depicts

hydrophobic bonds, hydrogen bonds, and their bond lengths in each docking pose.

RESULTS & DISCUSSION:

Retrieval of Protein Structure:

1. Protein pdb structure was obtained by using RCSB PDB online database.
2. It was done by searching the protein Name in the search bar of RCSB PDB and the protein with the lowest resolution was selected.
3. The Download File option was selected and the pdb format was selected to download the protein structure.

FIG. 2: SHOWING HOMEPAGE OF RCSB PDB

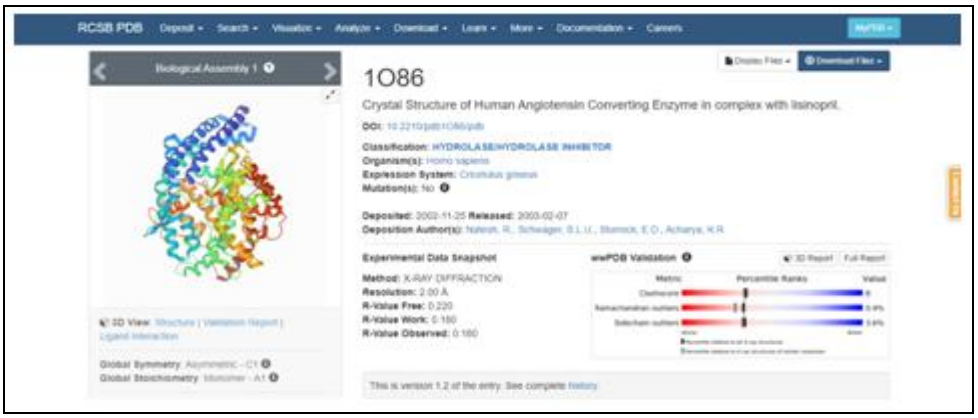


FIG. 3: SHOWING 1O86- PDB ENTRY OF ACE PROTEIN SELECTED FOR STUDY

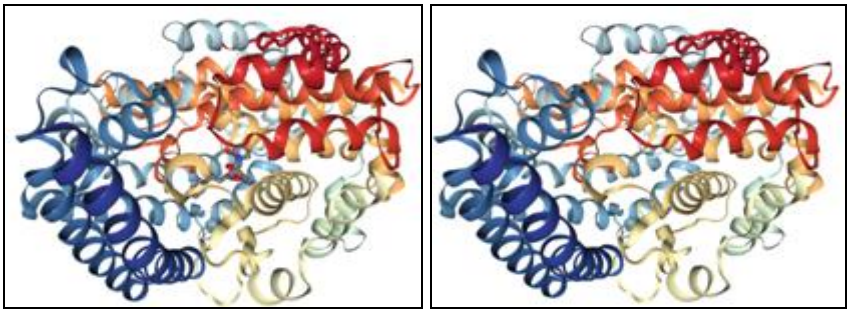


FIG. 4: (A) SHOWING 3D STRUCTURE OF PROTEIN WITH REFERENCE MOLECULE AND (B) SHOWING PROTEIN STRUCTURE WITHOUT REFERENCE MOLECULE

Retrieval of Ligand Structure:

1. To download the ligand structures an online database PubChem was used.
2. In the search bar ligand/drug name was searched and the compound that was best matched was selected.

3. To download the structure 3D sdf format was selected and it was then converted into pdb format by using software OpenBable because for docking pdb structure is required.
4. After downloading all were moved in a working folder to be further used for the analysis.

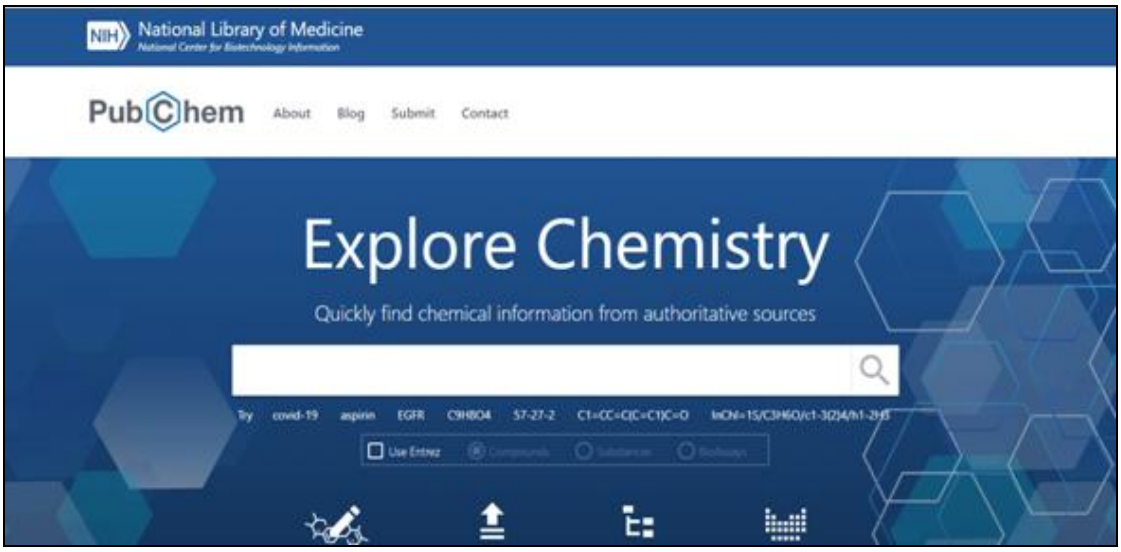


FIG. 5: SHOWING HOMEPAGE OF PUBCHEM DATABASE

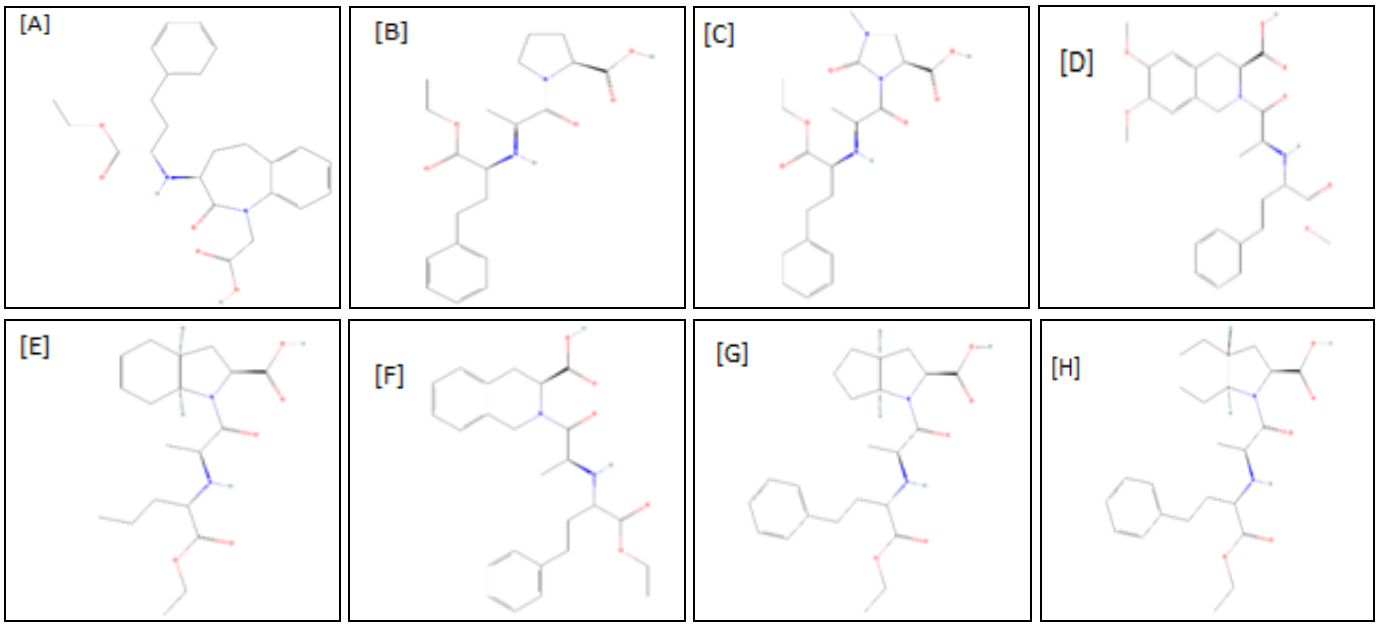


FIG. 6: SHOWING STRUCTURE OF THE SELECTED NON-SULFHYDRYL COMPOUNDS THAT WERE SELECTED FOR THE STUDY ALONG WITH THE MOEXIPRIL. A) BENAZEPRIL; B) ENALAPRIL; C) IMIDAPRIL; D) MOEXIPRIL; E) PERINDOPRIL; F) QUINAPRIL; G) RAMIPRIL; H) TRANDOLAPRIL

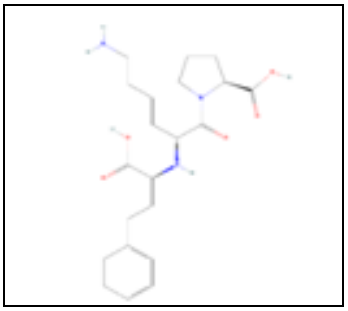


FIG. 7: SHOWING STRUCTURE OF THE REFERENCE MOLECULE LISINOPRIL

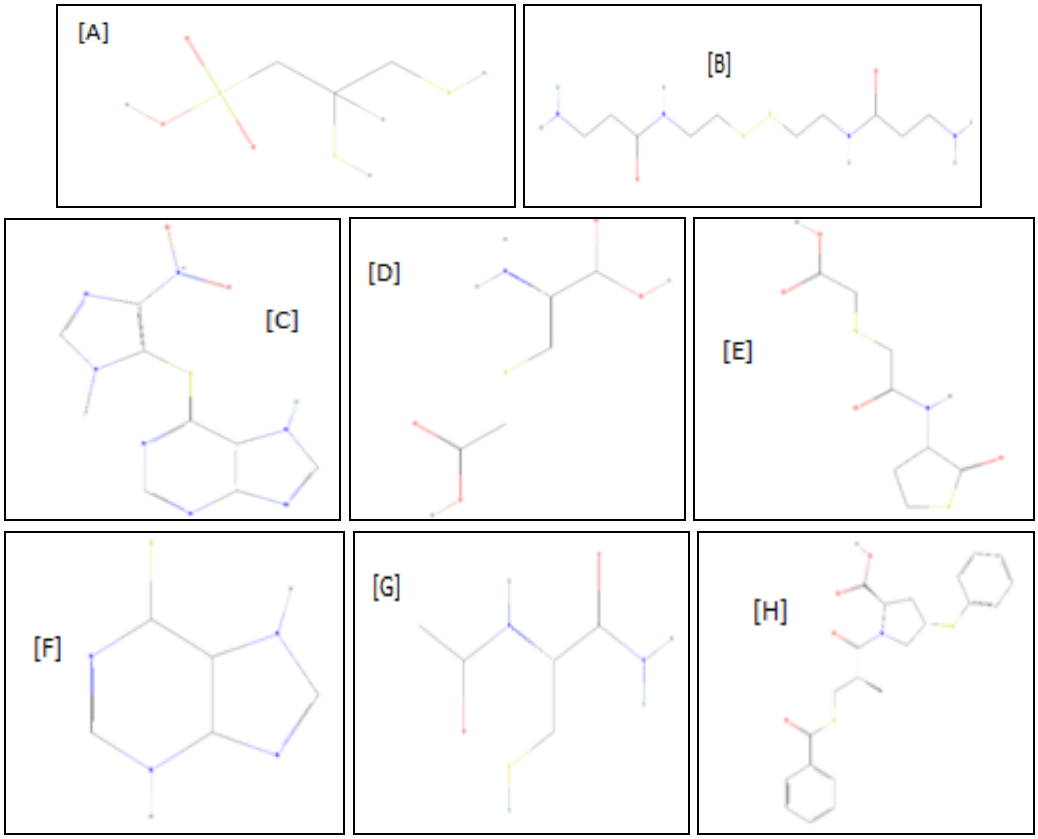


FIG. 8: SHOWING STRUCTURE OF THE SELECTED SULFHYDRYL COMPOUNDS THAT WERE SELECTED FOR THE STUDY. A) 2,3-DIMERCAPTO-1-PROPANESULFONIC ACID (DPSA); B) ALATHINE; C) AZATHIOPRINE; D) CARBOCYSTEINE; E) ERDOSTEINE; F) MERCAPTOPURINE; G) N-ACETYLCYSTEINE AMIDE (NAA); H) ZOFENOPRIL

Conversion from sdf to pdb format using OpenBable: The OpenBable GUI tool was downloaded for the conversion. And before uploading the ligand/drugs sdf file the file format **sdf-- MDL MOL** was chosen in the INPUT FORMAT section and then in the input file the 3dots were selected to upload the ligand file. After that in the OUTPUT FORMAT section pdb – Protein Data Bank format was selected and this time 3 dots were selected in the output file option to save the pdb file in the working folder and then the convert option was selected to finally save and convert that sdf file into the pdb file.

FIG. 9: SHOWING HOMEPAGE OF THE OPENBABLE GUI TOOL

Active Site Prediction using Discovery Studio (DS):

1. For docking purpose, the native ligand site was selected by using BIOVIA Discovery Studio 2020.
2. In the DS the File option was selected and then open to browse the working folder for the protein pdb file.
3. Then the arrow beside the protein structure was selected and extra Hetatm was deleted which were other than the reference molecule.
4. After that the tools option was selected and then the receptor-ligand interaction.
5. Then Define and edit Binding Site was chosen and hydrogens were added.
6. And from the Receptor Cavities, option with the name select site was selected.
7. By right click on the predicted site structure the attributed of site was slected.
8. The in the XYZ dimensions were copied and then saved in the working folder to be used further for site-specific Docking.

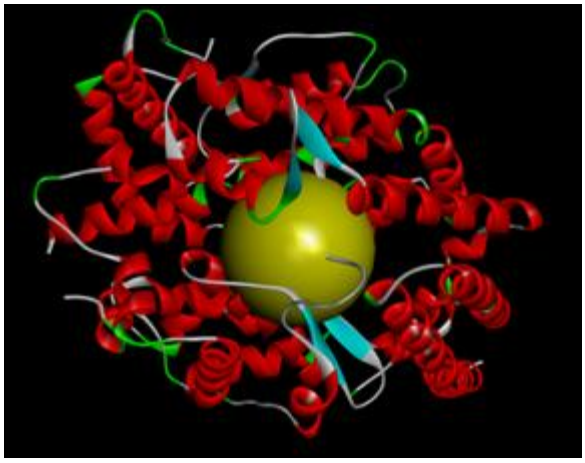


FIG. 10: SHOWING ACTIVE SITE OF THE PROTEIN WHERE THE NATIVE LIGAND IS ALREADY BIN

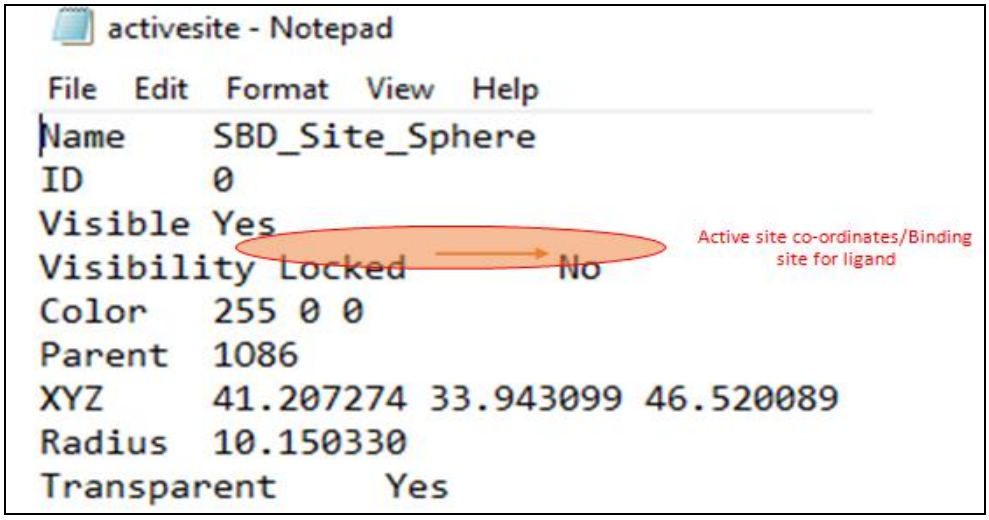


FIG. 11: SHOWING ACTIVE SITE DIMENSION OF THE ACE PROTEIN

Drug Likeness and ADMET/Pharmacokinetic Properties Prediction: This was done by using a software name as DruLito and another is an online tool SWISS ADME.

By using DruLito Software:

1. First a combined sdf file was prepared and saved using OpenBable and was saved as combined_ligands.
2. Then in DruLito software the combined file was uploaded by selecting the browse option to reach the working folder.
3. And after uploading the file the Calculate Properties was selected and then apply filter was chosen.
4. Lipinski's Rule was selected and in the file option Lipinskis Filtered Molecules was chosen to save the combined filtered molecules file.

Protocol for Splitting Combined SDF File of Filtered Ligands Generated from DruLito:

- First, python (latest version) was downloaded and installed in the laptop.

- Then, opened IDLE (python), after that clicked on file icon (top left), and selected new option.
- Then an untitled page was opened which was minimized.
- Next, right clicked on split_sdf and opened it with icon 'Edit with IDLE'.
- Simply copied the whole content of split_sdf file and pasted on the untitled page, which was previously minimized. (Note: Keep your combined sdf file with split_sdf file)
- Now, some changes were made in the file

1) 'f' always write your combined sdf file name without any modifications
2) 'Split_number' = 1
3) For 'print' (total number of ligands in the combined file always) for e.g., if total number of ligands are 10, then write print (10), without any space.

- At last, went on the Run icon on the top and clicked on 'run module', a pop-up appeared and clicked ok, then 'save as' the file with name and clicked on the save button.

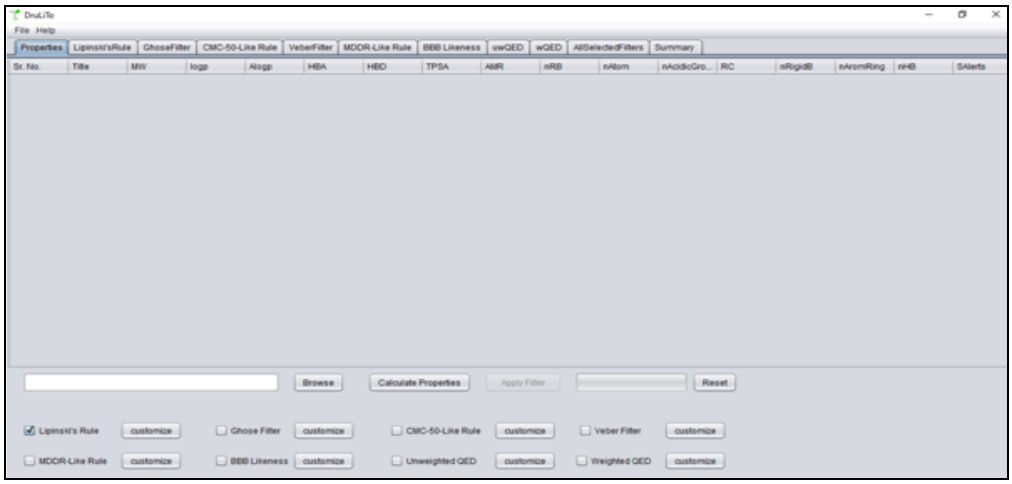


FIG. 12: SHOWING HOMEPAGE OF THE DRULITO

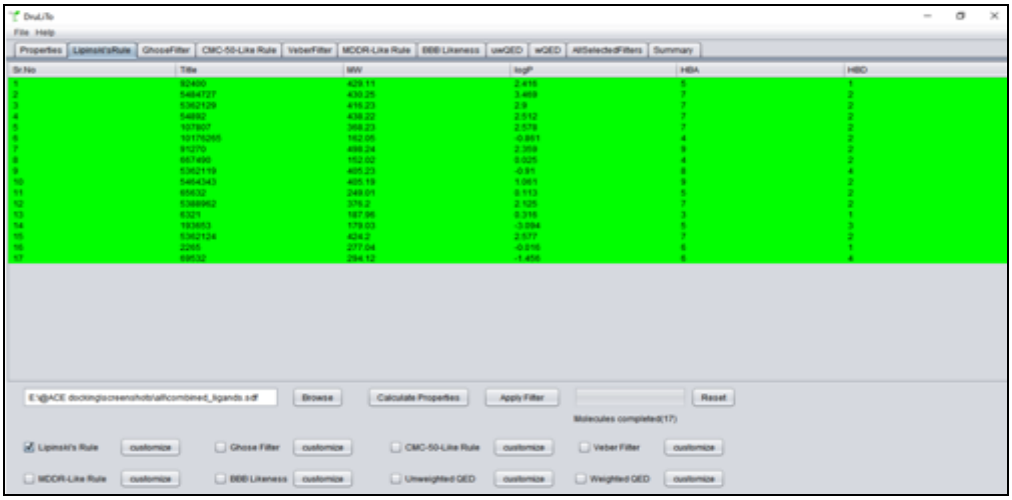


FIG. 13: SHOWING FILTERED MOLECULES THAT ARE ANALYSED BY USING DRULITO (GREEN COLOR INDICATED THAT ALL THE LIGANDS/DRUGS PASSED THE LIPINSKI RULE)

By using SWISS ADME:

1. SwissADME was browsed and the in the enter smiles option, canonical smiles obtained from PubChem database was pasted of all the compounds.
2. And then the Run option was chosen.
3. To view the boiled egg option, show boiled egg option was chosen

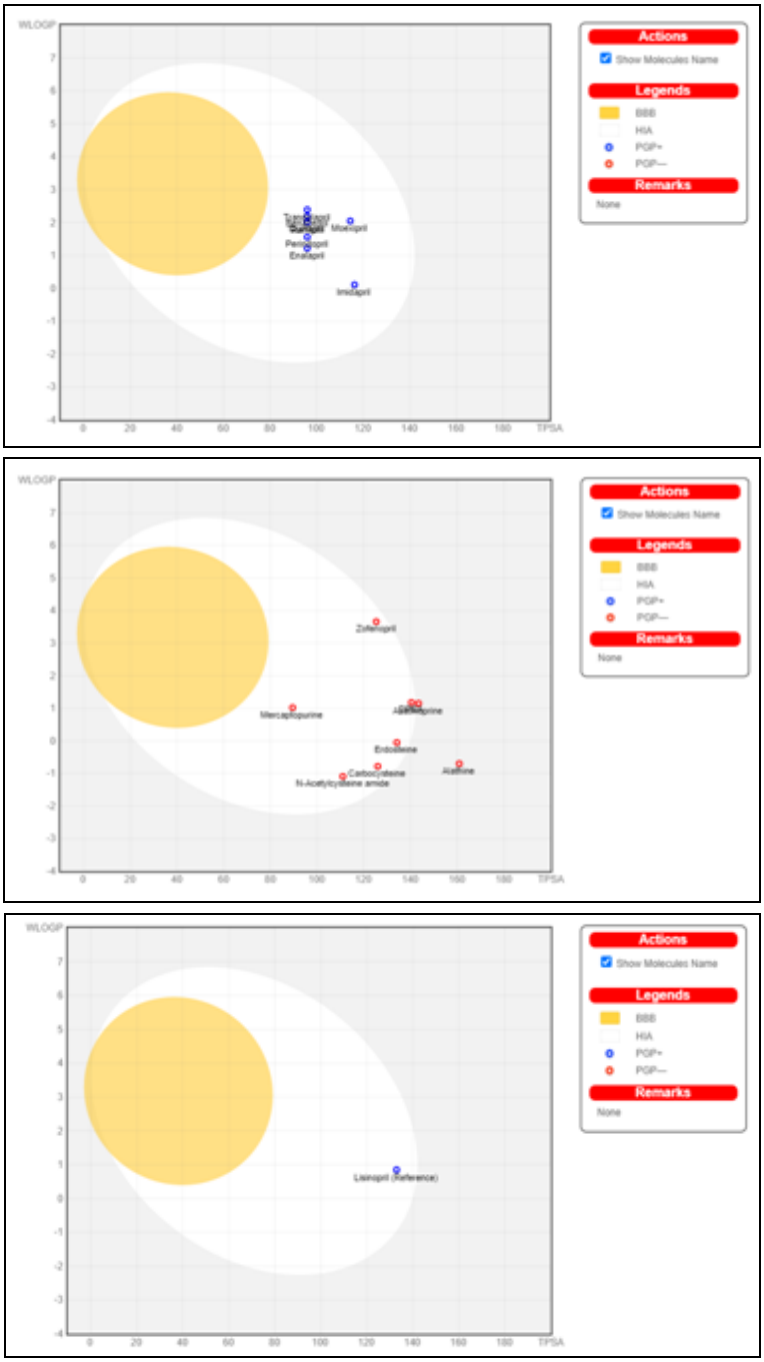


FIG. 14: THE BOILED-EGG MODEL REPRESENTING EVALUATION OF PASSIVE GASTROINTESTINAL ABSORPTION (HIA) WHITE PART AND BRAIN PENETRATION (BBB) YELLOW PART AND RED POINTS AS P-GP NEGATIVE

TABLE 1: PHARMACOKINETIC PROPERTIES OF THE PHYTOLIGANDS

Sl. No.	Ligands	Gastro-intestinal absorption	Blood-brain permeant	P-glycoprotein substrate	CYP450 1A2 inhibitor	CYP450 2C19 inhibitor	CYP450 2C9 inhibitor	CYP450 2D6 inhibitor	CYP450 3A4 inhibitor	Skin permeation as log Kp (cm/s)
				Non-Sulfhydryl Compounds						
1	Lisinopril (Reference)	High	No	Yes	No	No	No	No	No	-10.80 cm/s
2	Benazepril	High	No	Yes	No	No	No	Yes	Yes	-7.99 cm/s
3	Enalapril	High	No	Yes	No	No	No	No	No	-8.65 cm/s
4	Imidapril	High	No	Yes	No	No	No	No	No	-9.28 cm/s

5	Moexipril	High	No	Yes	No	No	No	No	Yes	-8.50 cm/s
6	Perindopril	High	No	Yes	No	No	No	No	No	-7.90 cm/s
7	Quinapril	High	No	Yes	No	No	No	Yes	Yes	-8.09 cm/s
8	Ramipril	High	No	Yes	No	No	No	Yes	Yes	-7.83 cm/s
9	Trandolapril	High	No	Yes	No	No	No	Yes	Yes	-7.53 cm/s
				Sulfhydryl Compounds						
10	2,3-Dimercapto-1-propanesulfonic acid	High	No	No	No	No	No	No	No	-7.62 cm/s
11	Alathine	Low	No	No	No	No	No	No	No	-9.85 cm/s
12	Azathioprine	Low	No	No	No	No	No	No	No	-7.92 cm/s
13	Carbocysteine	High	No	No	No	No	No	No	No	-9.61 cm/s
14	Erdosteine	High	No	No	No	No	No	No	No	-7.88 cm/s
15	Mercaptopurine	High	No	No	No	No	No	No	No	-7.22 cm/s
16	N-Acetylcysteine amide	High	No	No	No	No	No	No	No	-7.50 cm/s
17	Zofenopril	High	No	No	Yes	Yes	Yes	Yes	Yes	-5.80 cm/s

TABLE 2: ROLE OF PHARMACOKINETIC FACTORS

S. no.	Name	Function
1	Blood-brain Barrier	The blood-brain barrier (BBB) is a component of the neurovascular unit (NVU) and acts as the blood-brain interface, mediating communication between the central nervous system (CNS) and the periphery.
2	P-glycoprotein substrate	Efflux transporters such as P-glycoprotein play an important role in drug transport in many organs. In the gut, P-glycoprotein pumps drugs back into the lumen, decreasing their absorption. P-glycoprotein is one of the drug transporters that determine the uptake and efflux of a range of drugs.
3	CYP450 1A2 inhibitor	Cytochrome P450 1A2 (abbreviated CYP1A2), a member of the cytochrome P450 mixed-function oxidase system, is involved in the metabolism of xenobiotics in the body. In humans, the CYP1A2 enzyme is encoded by the CYP1A2 gene.
4	CYP450 2C19 inhibitor	CYP2C19 is an essential member of the CYP450 superfamily and it contributes about 16% of total hepatic content. The CYP2C19 gene provides instructions for making an enzyme that is found primarily in liver cells in a cell structure called the endoplasmic reticulum, which is involved in protein processing and transport.
5	CYP450 2C9 inhibitor	Cytochrome P450 family 2 subfamily C member 9 (abbreviated CYP2C9) is an enzyme protein. The enzyme is involved in metabolism, by oxidation, of both xenobiotics, including drugs, and endogenous compounds, including fatty acids.
6	CYP450 2D6 inhibitor	Cytochrome P450 2D6 (CYP2D6) is an enzyme that is responsible for breaking down (metabolizing) many of the drugs that are commonly used today and many important drug interactions.
7	CYP450 3A4 inhibitor	Cytochrome P450 3A4 (abbreviated CYP3A4) is an important enzyme in the body, mainly found in the liver and in the intestine. It oxidizes small foreign organic molecules (xenobiotics), such as toxins or drugs, so that they can be removed from the body.
8	Skin permeation as log Kp (cm/s)	The skin permeability (Kp) defines the rate of a chemical penetrating across the stratum corneum. This value is widely used to quantitatively describe the transport of molecules in the outermost layer of epidermal skin and indicate the significance of skin absorption.

Docking using AutoDock and Command Prompt:

1. AutoDockTools-1.5.7 was downloaded and in the file option Preference was selected.
2. In the Startup directory the name of the working folder was copied and made it default and set.
3. Now 2 things were done here, that is preparation of protein and the ligand.
4. So, by using Read Molecule option, Protein pdb file was uploaded in the AutoDock.
5. And all the water molecules were deleted by using delete water option in the edit menu.

6. Protein chain was opened to select all inhibitors and extra structure which were other than amino acid and then they were deleted by again using the edit menu.

7. On the same edit option hydrogens were selected and polar hydrogens were added along with the Kollman charges.

8. To save this prepared protein file in the pdbqt format, grid option was choosen then the macromolecule and then it was saved as protein.pdbqt.

9. Now to prepare ligand structure for docking, ligand pdb file was opened by the read molecule option.

10. In the AutoDock homepage, ligand option was chosen and then the input to add charges to the ligand structure.

11. And then using the output option, the pdbqt file of the ligand was saved.

12. Both these prepared ligands file were then further used in the config file and after that finally in the Command prompt to generate the log and output file. NOTE: config file was made in .txt format in the notepad by using the active site that was predicted using Discovery Studio.

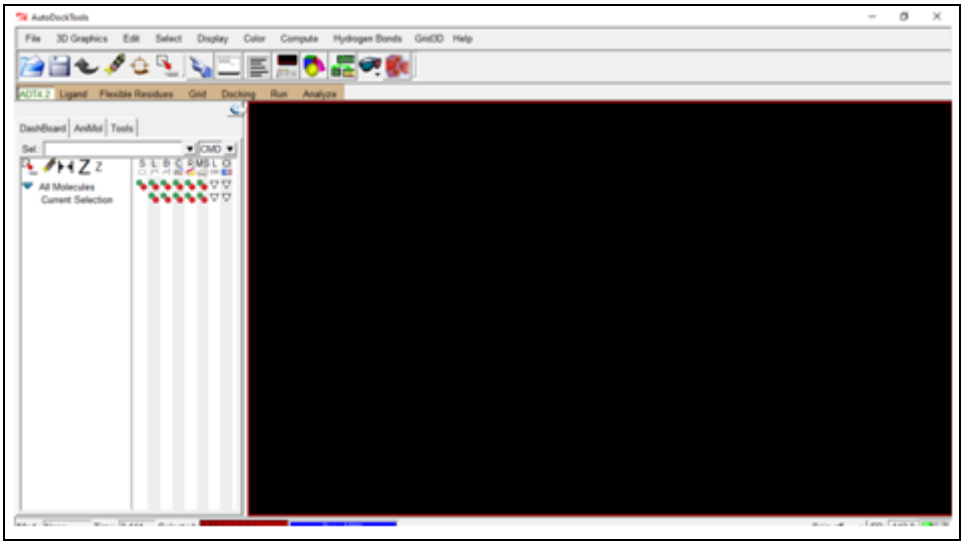


FIG. 15: SHOWING HOMEPAGE OF AUTODOCK

Generate Output File and log file by using Command Prompt:

1. In the Program File option of the C drive, the folder of "The Scripps Research Institute" was opened.

2. Then all 3 vina files were copied and pasted on the working folder.

3. Then the path of working folder was selected and typed cmd and clicked enter.

4. Then in command prompt window the command was given as vina.exe --config config.txt --log ligand.txt to generate the ligand output file and the log file that contain the data of the binding energy and then enter.

TABLE 3: SHOWING THE BINDING AFFINITY OF ALL THE DRUGS

S. no.	Pubchem ID	Phytochemicals Name	Binding Affinity
		Non-Sulfhydryl Compounds	
1	5362119	Lisinopril (Reference)	-7.8
2	5362124	Benazepril	-8.7
3	5388962	Enalapril	-7.6
4	5464343	Imidapril	-8.4
5	91270	Moexipril	-8.9
6	107807	Perindopril	-7.3
7	54892	Quinapril	-9.1

8	5362129	Ramipril	-8.2
9	5484727	Trandolapril	-8.1
		Sulfhydryl Compounds	
10	6321	2,3-Dimercapto-1-propanesulfonic acid	-4.5
11	69532	Alathine	-5.3
12	2265	Azathioprine	-7.2
13	193653	Carbocysteine	-5.2
14	65632	Erdosteine	-5.9
15	667490	Mercaptopurine	-5.4
16	10176265	N-Acetylcysteine amide	-4.9
17	92400	Zofenopril	-8.2

Docked Complex by PyMol: PyMOL (PyMOL2) was downloaded to make the complex file. In the File menu, Open option was selected and then output.pdbqt file was uploaded. Again using same options, protein.pdbqt file was uploaded.

And on the 1st position the docked complex was saved (because 1st position always have highest binding affinity) by going on the file and then export and after that pdb option and save by choosing PDB (*.pdb*.pdb.gz) format.

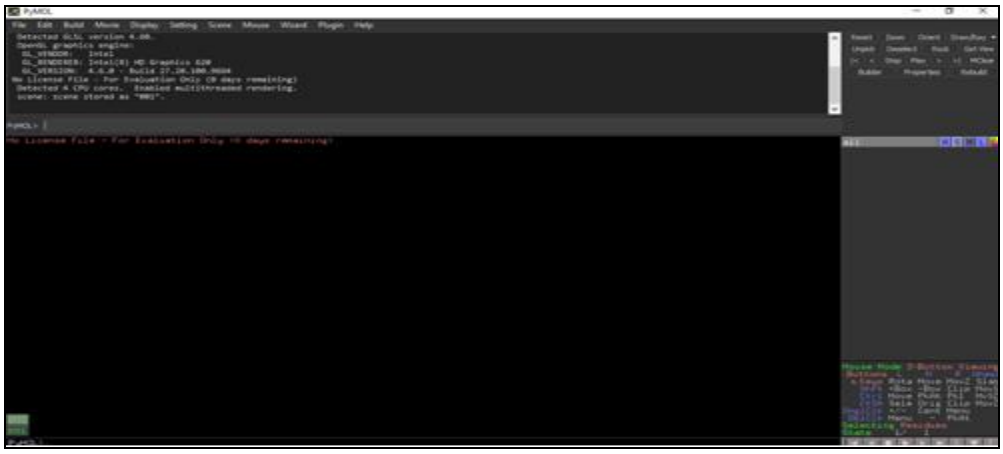
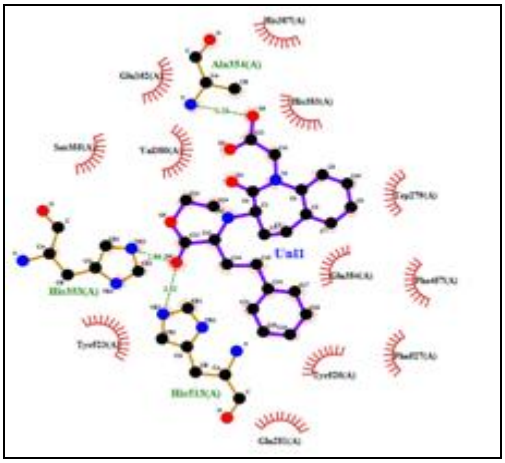


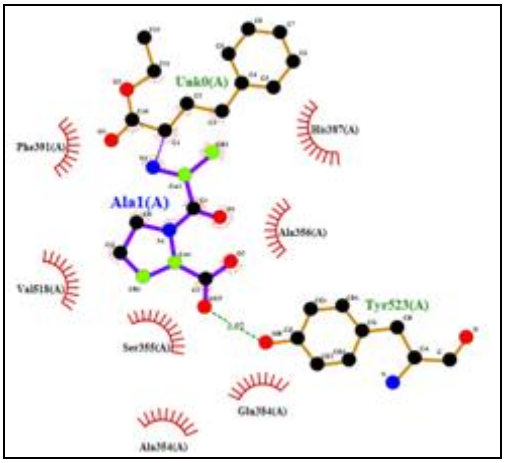
FIG. 16: SHOWING HOMEPAGE OF PYMOL

Result Interpretation of Protein-Ligand Interaction: The interpretation of the interaction was done by using 2 softwares, that are Ligplot+ and BIOVIA Discovery Studio.

By Ligplot+:

1. In the Ligplot+, went on the file option and then clicked open then PDB file and then browse.
2. The protein complex pdb file was uploaded and Run
3. In file option, Print Screen was chosen then Microsoft XPS Document Writer and clicked OK
4. Changed format to XPS doc. (*.xps) and click save, to save the ligand interaction file





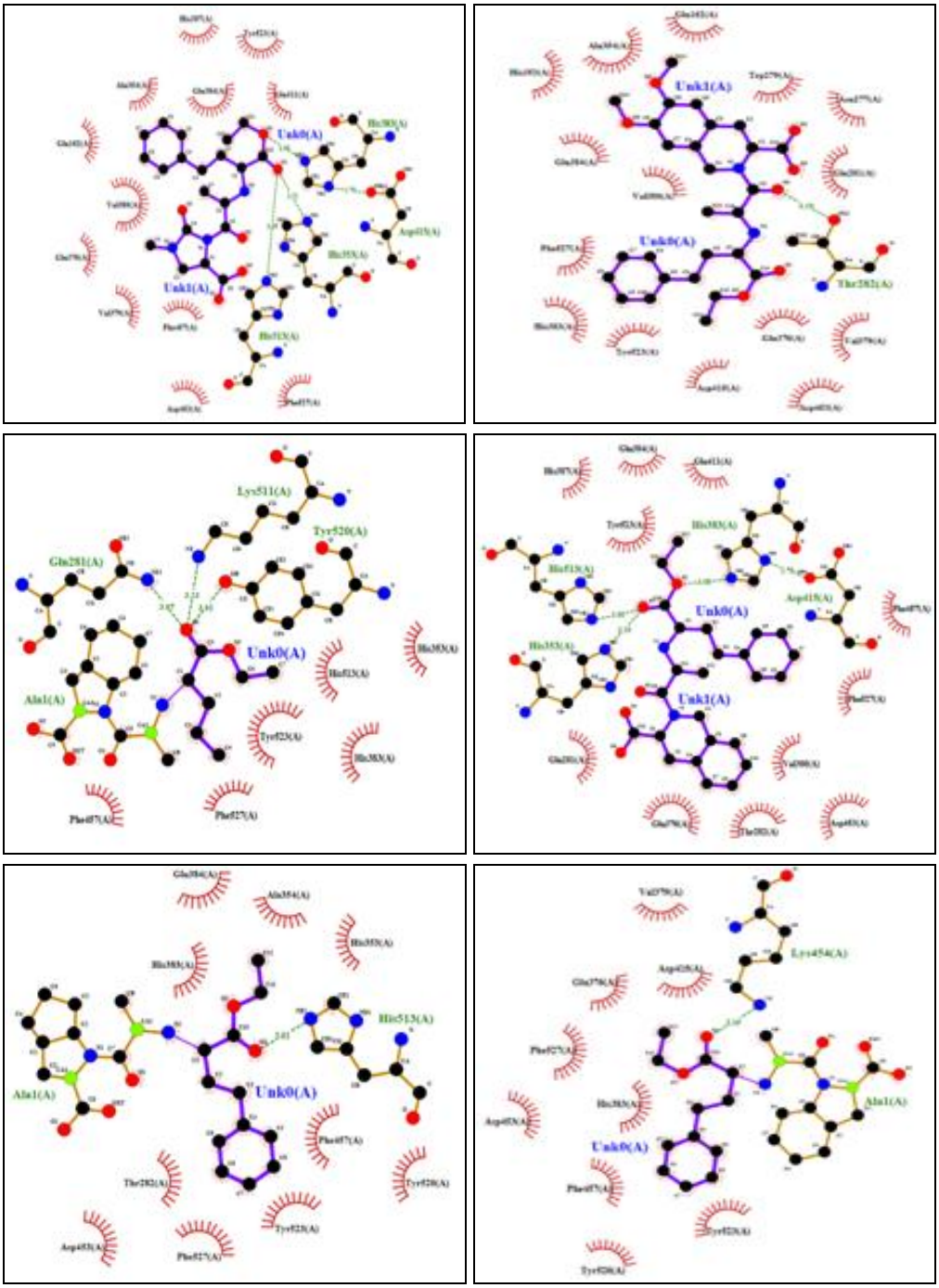


FIG. 17: SHOWING LIGPLOT INTERACTION OF THE NON-SULFHYDRYL COMPOUNDS ALONG WITH THE MOEXIPRIL. A) BENAZEPRIL; B) ENALAPRIL; C) IMIDAPRIL; D) MOEXIPRIL; E) PERINDOPRIL; F) QUINAPRIL; G) RAMIPRIL; H) TRANDOLAPRIL

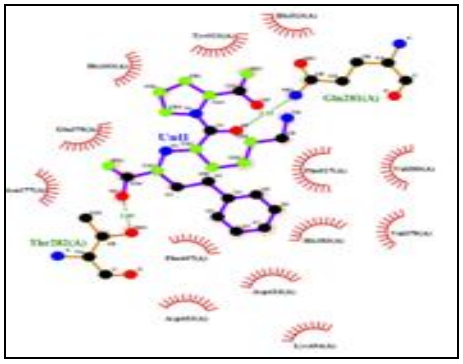


FIG. 18: SHOWING LIGPLOT INTERACTION OF THE REFERENCE MOLECULE LISINOPRIL

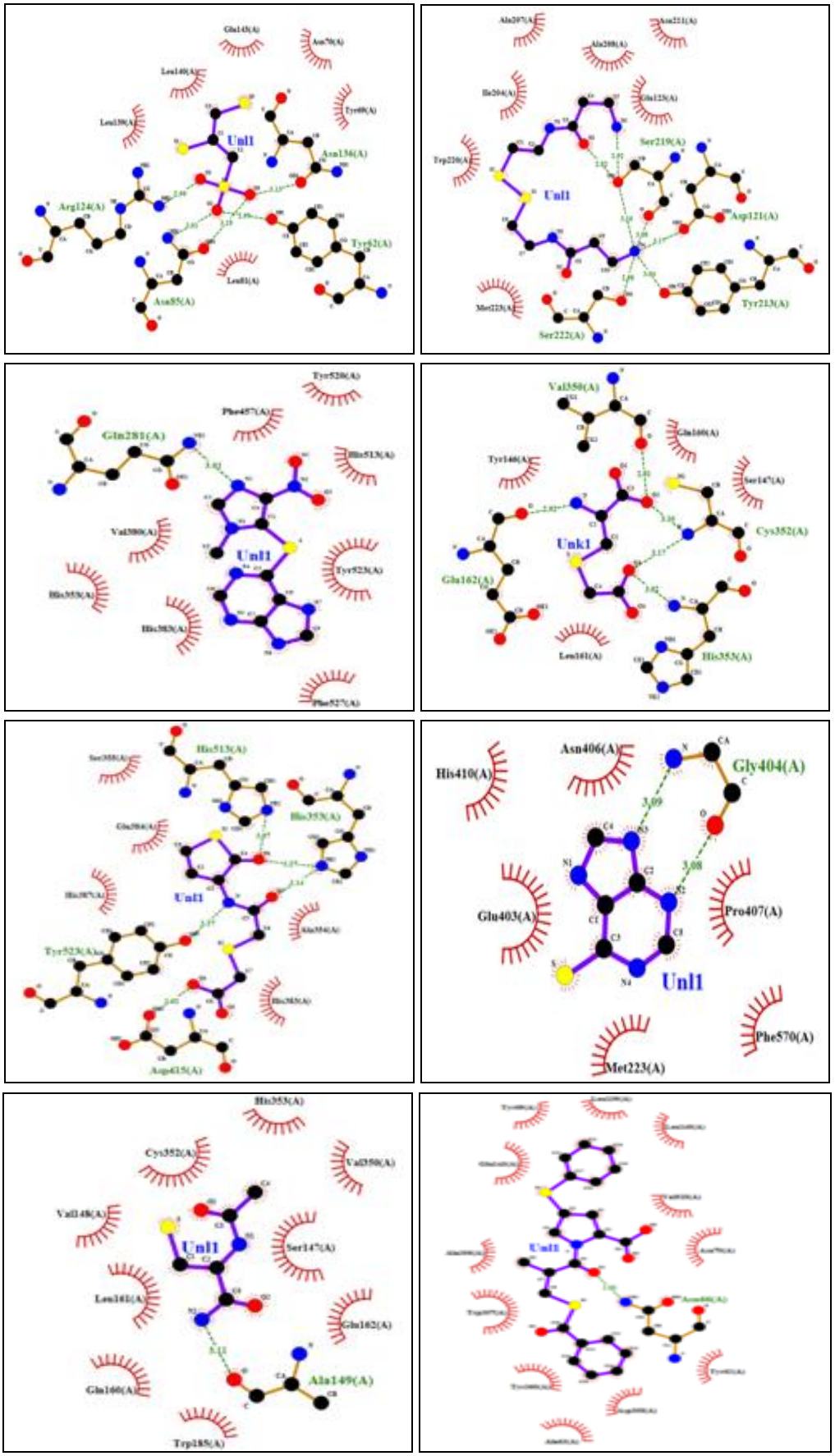


FIG. 19: SHOWING LIGPLOT INTERACTION OF THE SULFHYDRYL COMPOUNDS. A) 2,3-DIMERCAPTO-1-PROPANESULFONIC ACID; B) ALATHINE; C) AZATHIOPRINE; D) CARBOCYSTEINE; E) ERDOSTEINE; F) MERCAPTOPURINE; G) N-ACETYLCYSTEINE AMIDE; H) ZOFENOPRIL

By Discovery Studio:

1. In the Discovery studio protein complex pdb file was uploaded.
2. By clicking the name of protein complex, receptor was defined then the ligand groups were selected and the ligand was defined.
3. Then chosen Ligand interaction to view the 3D format of the interaction and then it was labelled (Labelling was done by choosing amino acid in object option)
4. For 2D diagram of the interaction, option with the name 2D interaction was selected.
5. Both the interaction file image was then saved by selecting File then Save as Image file and then clicked Save; Same for 2D interaction image.

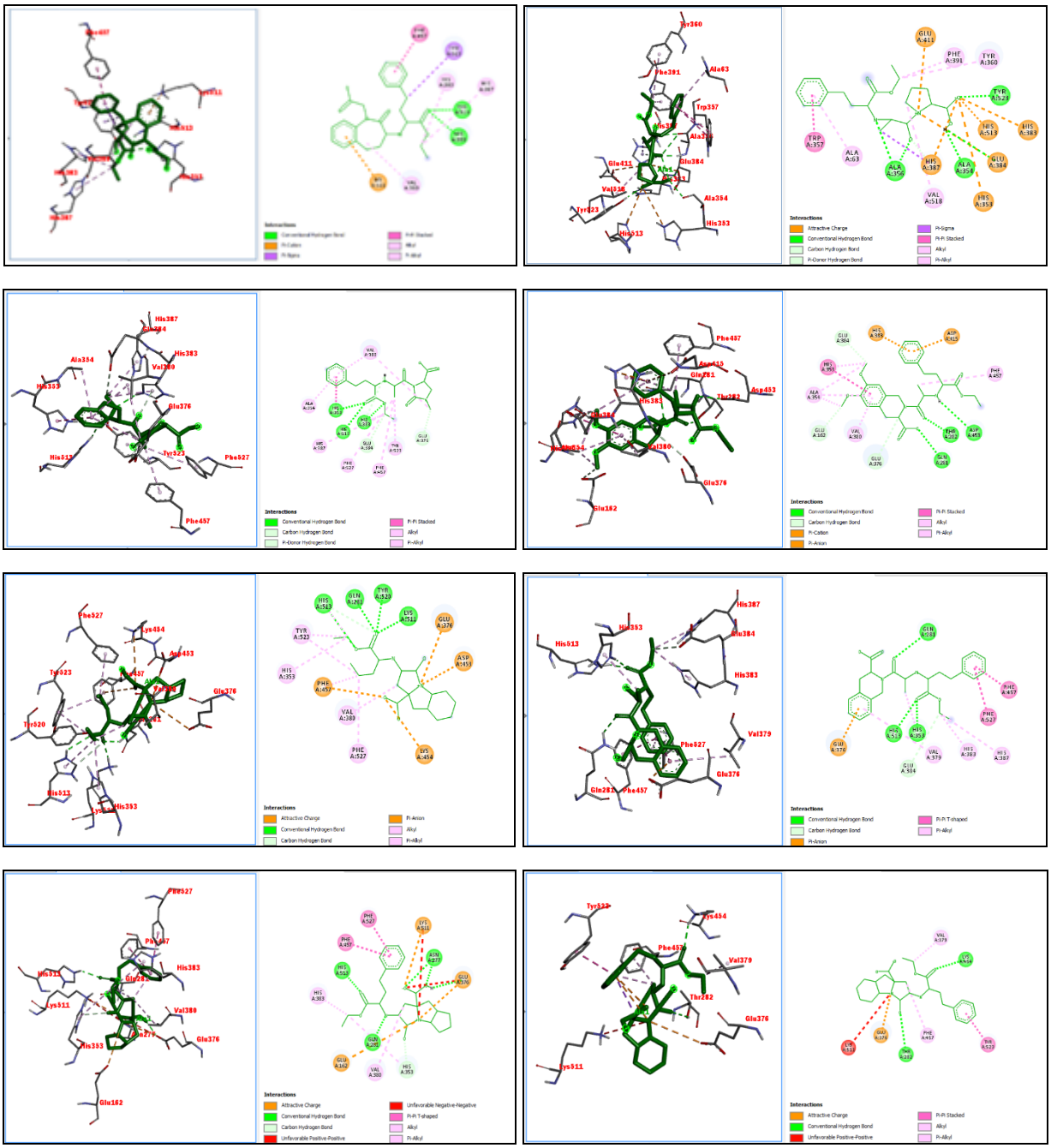


FIG. 20: SHOWING 3D AND 2D INTERACTION OF THE NON-SULFHYDRYL COMPOUNDS AS VISUALIZED BY DISCOVERY STUDIO. A) BENAZEPRIL; B) ENALAPRIL; C) IMIDAPRIL; D) MOEXIPRIL; E) PERINDOPRIL; F) QUINAPRIL; G) RAMIPRIL; H) TRANDOLAPRIL

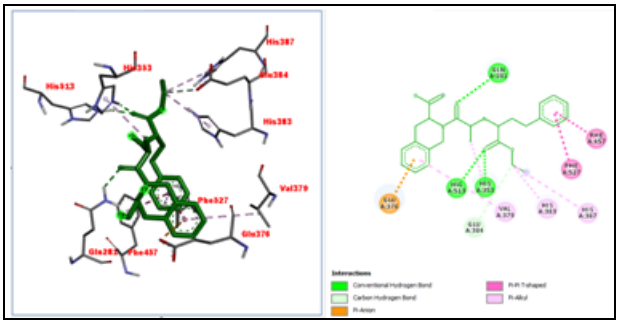


FIG. 21: SHOWING 3D AND 2D INTERACTION OF THE REFERENCE MOLECULE LISINOPRIL AS VISUALIZED BY DISCOVERY STUDIO

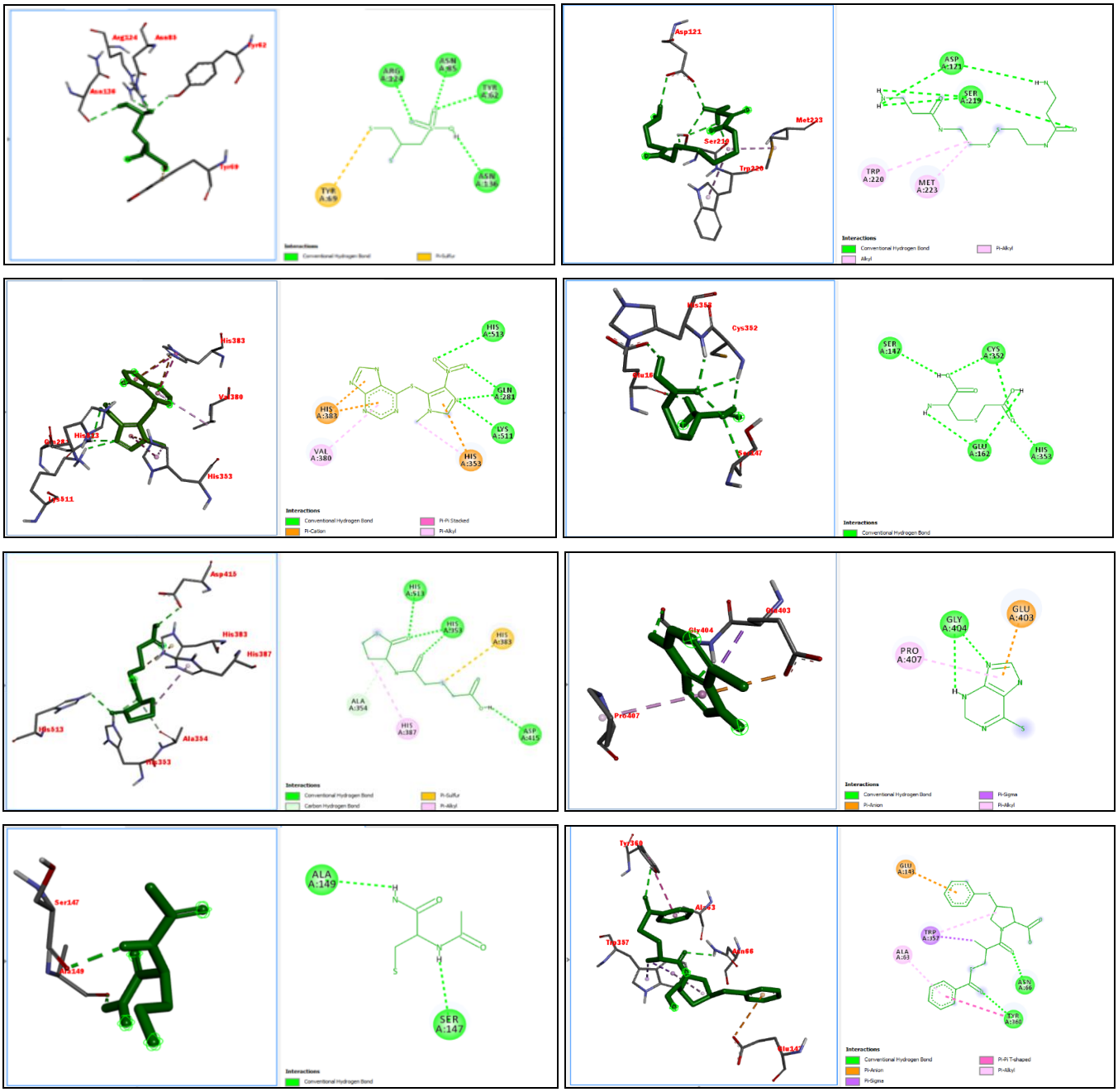


FIG. 22: SHOWING 3D AND 2D INTERACTION OF THE SULFHYDRYL COMPOUNDS AS VISUALIZED BY DISCOVERY STUDIO. A) 2,3-DIMERCAPTO-1-PROPANESULFONIC ACID; B) ALATHINE; C) AZATHIOPRINE; D) CARBOCYSTEINE; E) ERDOSTEINE; F) MERCAPTOPURINE; G) N-ACETYLCYSTEINE AMIDE; H) ZOFENOPRIL

DISCUSSION: It is clear that the *in-silico* method has a broad application in drug discovery because it is cost-effective and can provide accurate predictions about target sites in a short period of time. *In-silico* study methods include docking, virtual high throughput screening (vHTS), and *in-silico* fragment-based drug design. Similarly, various methods for ADMET prediction are available, including structure-based approaches, drug-based approaches, and integrated pharmacokinetic models. The carboxy-terminal His-Leu dipeptide from angiotensin I is cleaved by the angiotensin-converting enzyme (ACE), resulting in the production of the strong vasopressor octapeptide angiotensin II. For hypertension, heart failure, myocardial infarction, and diabetic nephropathy, ACE inhibitors are the first line of treatment. Thus, we retrieved the three-dimensional structure of human angiotensin-converting enzyme for this study from RCSB-PDB with ID 1O86. Ligands' three-dimensional structures were downloaded using the PubChem server. A total of 17 structures were downloaded, of which 9 were non-sulfhydryl compounds, and the remaining were sulfhydryl compounds. With the help of ADMET, Molecular docking, and Protein-ligand interaction study, it is significant that sulfhydryl compounds possess low affinity as an inhibitor against ACE compared to non-sulfhydryl compounds. Further, six non-sulfhydryl compounds, namely, Benazepril Imidapril, Moexipril, Quinapril, Ramipril, and Trandolapril, are more significantly effective agaisnt ACE comparatively to reference compound Lisinopril. Moreover, Quinapril and Moexipril are the most significant compounds found after docking and interaction studies. However, a molecular dynamics simulation and *in-vitro* study are still required to prove these results strongly.

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CONFLICT OF INTEREST: The authors declare that there is no conflict of interest regarding the publication of this article titled *"In-silico* Evaluation of Maxoprill against ACE Enzyme". The research was conducted independently, and no financial, commercial, or personal relationships were present that could be construed to influence the findings reported in this study. The authors have received no funding or sponsorship from any organization or company related to Maxoprill or ACE inhibitors.

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