VIRTUAL SCREENING OF POTENT LIGAND AGAINST DIABETES TYPE 2

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Introduction:

Diabetes mellitus is one of the very common chronic diseases across the world and the number of diabetic patients is on the rise. The World Health Organization (WHO) estimates that about 200 million people all over the globe are suffering from diabetes and this figure is likely to be doubled by 2030. WHO says that about 80% of the deaths occur every year due to diabetes in middle-income countries [1]. The recently published Indian council for medical research-India diabetes (ICMR-INDIAB) national study reported that there are 62.4 million people with type 2 diabetes (T2DM) and 77 million people with prediabetes in India [2]. This will be increased to 100 million by 2030 [3]. T2DM predominantly affects older individuals in developed countries, while in developing nations like India, it is affecting the younger population in the prime of their working lives and thus poses an even greater threat to the health of these individuals [2,4].Metformin is widely used medicine in recent days for diabetes type 2. Structure similar to metformin is used as ligand to docked again DPP4

receptor & aldose reductase. Dipeptidyl peptidase-IV (DPP-IV), also known as adenosine deaminase complexing protein, is a protein that, in humans, is encoded by the DPP4 gene [5]. Inhibition of DPP-IV has been shown to be an appropriate treatment for T2DM [6]. DPP-IV specifically removes N-terminal dipeptides from substrates containing proline or alanine as the second residue, transforming them into inactive or even antagonistic species. The most imperative DPP-IV substrates are incretins, such as glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP), which stimulates insulin secretion [7]. Aldose reductase (AR) is the first enzyme of the polyol pathway and is widely distributed in mammalian tissues. Due to increased aldose reductase activity, the accumulation of intracellular sorbitol is also raised. It implicates the development of various secondary complications of diabetes mellitus [8].

Material & Methodology:

Receptors: DPP IV (PDB ID:- 4j3j), Aldose Reductase (PDB ID:- 1EF3)

Ligand:Coptisine (PubChem id:72322)
papaverine(4680)

Molecular docking: It is one of the most frequently used technique in structure-based drug design. Molecular docking can predict the binding-conformation and interactions of small molecule to the appropriate binding site within the target protein.

PyRx: Prepare the protein and ligand structures: The first step is to obtain the protein and ligand structures in the appropriate file format (e.g. PDB).

Install PyRx: PyRx is a graphical user interface for AutoDock Vina and is available as a free download from the PyRx website.

Load the protein and ligand structures into PyRx: Once PyRx is installed, the protein and ligand structures into PyRx: Once PyRx is installed, the protein and ligand structures can be loaded into the program by selecting the appropriate file from your computer or by copying and pasting the PDB code into the program.

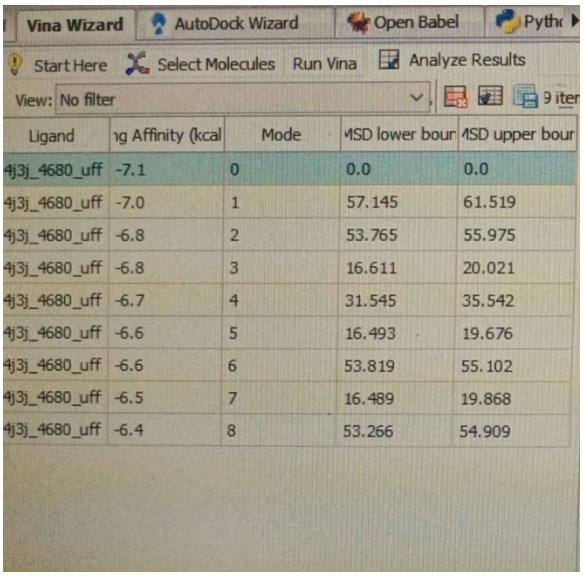
Define the docking box: The next step is to define the docking box, which is the region of space where the ligand will be docked to the protein. This can be done by selecting the protein chain and setting the boundaries of the docking box in PyRx.

Run the docking simulation: Once the docking box is defined, the docking simulation can be run by selecting the appropriate parameters and clicking the "Run" button in PyRx. This will run the AutoDock Vina algorithm, which will dock the ligand to the protein and generate a set of docking poses.

Analyze the docking results: The final step is to analyze the docking results, which can be done by using PyRx to view the generated docking poses and

compare them to the protein structure. The results can be filtered by binding energy, RMSD, and other criteria to identify the most promising poses for further analysis.

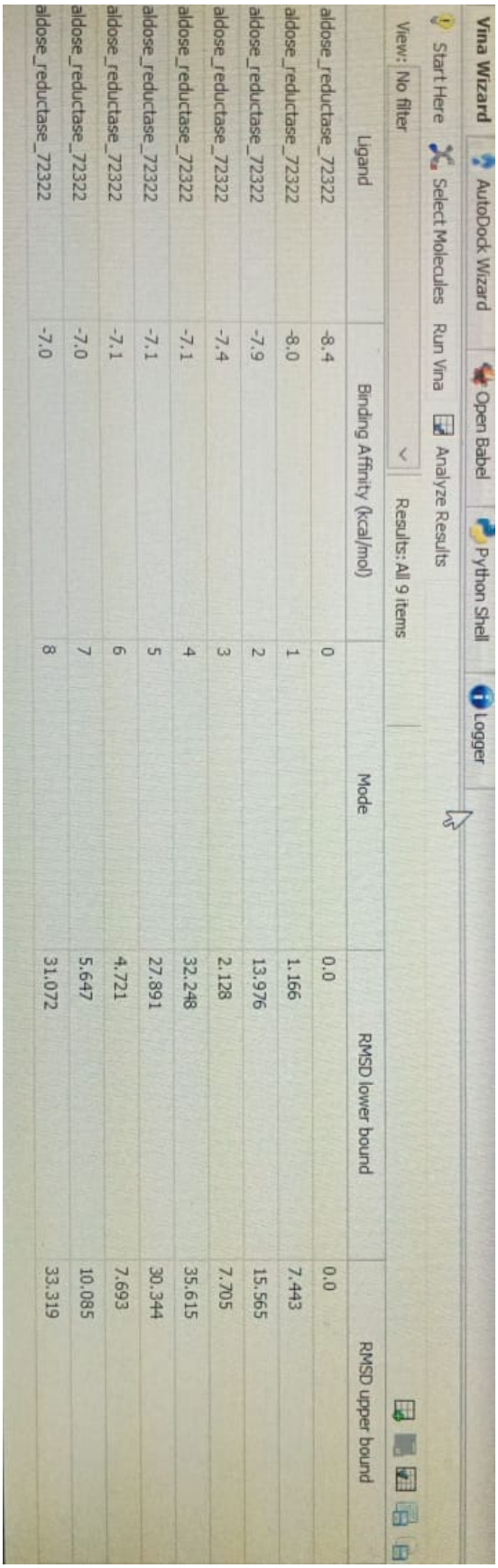
Result: Docking result we obtained are as follow:



Ligand	ng Affinity (kcal	Mode	MSD lower bour	MSD upper bour
4j3j_4680_uff	-7.1	0	0.0	0.0
4j3j_4680_uff	-7.0	1	57.145	61.519
4j3j_4680_uff	-6.8	2	53.765	55.975
4j3j_4680_uff	-6.8	3	16.611	20.021
4j3j_4680_uff	-6.7	4	31.545	35.542
4j3j_4680_uff	-6.6	5	16.493	19.676
4j3j_4680_uff	-6.6	6	53.819	55.102
4j3j_4680_uff	-6.5	7	16.489	19.868
4j3j_4680_uff	-6.4	8	53.266	54.909

1. Binding affinity of DPPIV with papaverine is found to be (-7.1)

2. Binding affinity of aldose reductase with coptisine is found to be (-8.4)



Ligand	Binding Affinity (kcal/mol)	Mode	RMSD lower bound	RMSD upper bound
aldose_reductase_72322	-8.4	0	0.0	0.0
aldose_reductase_72322	-8.0	1	1.166	7.443
aldose_reductase_72322	-7.9	2	13.976	15.565
aldose_reductase_72322	-7.4	3	2.128	7.705
aldose_reductase_72322	-7.1	4	32.248	35.615
aldose_reductase_72322	-7.1	5	27.891	30.344
aldose_reductase_72322	-7.1	6	4.721	7.693
aldose_reductase_72322	-7.0	7	5.647	10.085
aldose_reductase_72322	-7.0	8	31.072	33.319

Conclusion: More negative binding affinity of receptor with ligand shows that ligand bind more effectively with receptor.

Binding affinity of metformin with alpha glucosidase found is (-8.4) ,where as binding affinity of DPPIV with papaverine found is -7.1 & binding affinity of aldose reductase with coptisine is (-8.4). So we can conclude that coptisine is more efficiently bind to the aldose reductase than papaverine binds to DPPIV & coptisine is more potent ligand.

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