Pharmacological and molecular docking study of Imidazole derivatives: A Review

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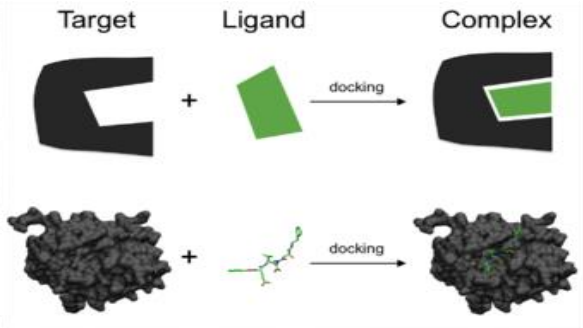
Abstract – Molecular docking is frequently employed in contemporary drug design to comprehend drug receptor interaction. In order to anticipate the structure of the intermolecular complex formed between two or more molecules, a process known as molecular docking. This optimization problem describes the "best-fit" orientation of a ligand that binds to a particular protein of interest. In these studies, we learned about the docking analysis of numerous activities, including anticancer, antibacterial, anti-diabetic, anti-inflammatory, anticonvulsant, and antioxidant. The acquired results demonstrate that, for powerful chemicals, tests and docking results are consistent. For executing the molecular design or modification of these imidazole derivatives, as well as for comprehending the action mechanism, these computational studies can provide some relevant references. Considering the well obtained in vitro results, it was thought worthy to perform molecular docking studies, hence screening the compounds, inculcating both in silico and in vitro results.

MOLECULAR DOCKING

In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when a ligand and a target are bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using, for example, scoring functions.



Schematic illustration of docking

A small molecule ligand to a protein target producing a stable complex. Docking of a small molecule into the crystal structure of the beta-2 adrenergic G-protein coupled receptor .The associations between biologically relevant molecules such as proteins, peptides, nucleic acids, carbohydrates, and lipids play a central role in signal transduction. Furthermore, the relative orientation of the two interacting partners may affect the type of signal produced (e.g., agonism vs antagonism). Therefore, docking is useful for predicting both the strength and type of signal produced. Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Characterization of the binding behavior plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes.[1]

Molecular docking may be defined as an optimization problem, which would describe the ‘‘best-fit’’ orientation of a ligand that binds to a particular protein of interest and is used to predict the structure of the intermolecular complex formed between two or more molecules. The most interesting case is the protein ligand interaction, because of its applications in medicines. Ligand is a small molecule, which interacts with protein’s binding sites. There are several possible mutual conformations in which binding may occur. These are commonly called binding modes. In modern drug designing, molecular docking is routinely used for understanding drug-receptor interaction. Molecular docking provides useful information about drug receptor interactions and is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to predict the affinity and activity of the small molecule.

molecular docking helps in studying drug /ligand or receptor protein interactions by identifying the suitable active sites in protein, obtaining the best geometry of ligand receptor complex and calculating the energy of interactions for different ligands to design more effective ligands.

The interaction energy is calculated in terms. Energy indicates a stable system and thus a likely binding interaction. The options available for docking are rigid docking where a suitable position for the ligand in receptor environment is obtained, flexible docking where the ligand is flexed via its torsion angles as well as the side chain of active site residues.[2-3]molecular docking is routinely used for understanding drug-receptor interaction. Molecular docking provides useful information about drug receptor interactions and is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to predict the affinity and activity of the small molecule. Imidazole and its derivatives have gained remarkable importance due to their widespread biological activities and their use in synthetic chemistry. Imidazole derivatives possess a broad spectrum of pharmacological activities such as, anti-inflammatory, analgesic, anti-convulsant, antitubercular antimicrobial, anticancer and anti-Parkinson activities. Imidazole and its derivatives are of great significance due to their important roles in biological systems, particularly in, enzymes as proton donors and/or acceptors, coordination system ligands and the base of charge–transfer processes. The imidazole nucleus appears in a number of naturally occurring products like, amino acids histidine and purines, which comprise many of the most important bases in nucleic acids.[4]

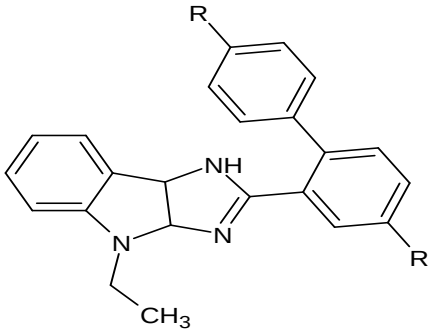
Imidazole

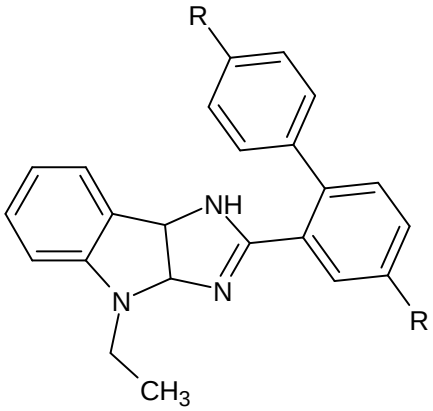
Imidazole nucleus forms the main structure of some wellknown components of human organisms, that is, the amino acid histidine, Vit-B12, a component of DNA base structure and purines, histamine, and biotin. It is also present in the structure of many natural or synthetic drug molecules, that is, cimetidine, azomycin, and metronidazole. Imidazole containing drugs have a broader scope in remedying various dispositions in clinical medicine Imidazole was first synthesized by Heinrich Debus in 1858, but various imidazole derivatives had been discovered as early as the 1840s. Its synthesis used glyoxal and formaldehyde in ammonia to form imidazole. This synthesis, while producing relatively low yields, is still used for creating C-substituted imidazole. Imidazole is a 5-membered planar ring, which is soluble in water and other polar solvents. It exists in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. Imidazole is a highly polar compound, as evidenced by a calculated dipole of 3.61D, and is entirely soluble in water. Imidazole is amphoteric; that is, it can function as both an acid and a base. The compound is classified as aromatic due to the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring. Medicinal chemistry concerns with the discovery, development, interpretation, and identification of the mechanism of action of biologically active compounds at the molecular level.[5]

Docking study of imidazole derivatives:

a. Anticancer activity-

Behbood Taheri et al: (2020): Cancer typically starts as a local illness, but over time, it spreads to other parts of the body, making treatment challenging. In developed nations, it is the main cause of death. In this day of science and technology, cancer is a stain on the face of humanity. There are currently many different kinds of anticancer medications on the market, but problems with toxicity, poor efficacy, and solubility have reduced the overall therapeutic indices. Thus, the fight against cancer is far from ended and the search for new, promising anticancer drugs continues. Imidazole is an alkaloid and aromatic diazole with strong anticancer properties. Using breast cancer cell lines MCF -7, the cytotoxic activity of five imidazole derivatives was assessed using a 3-(4, 5-dimethylthiazol-2-y-2,5-diphenyl tetrazolium bromide (MTT) assay.





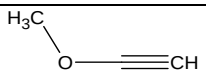
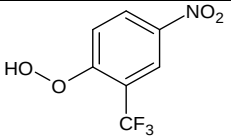
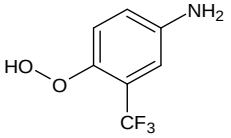
Compound	R	Dock score
C1		-12.77
C2		-11.33
C3		-13.48
C4	-NO2	-11.32
C5	-NH2	-12.08

Table 1

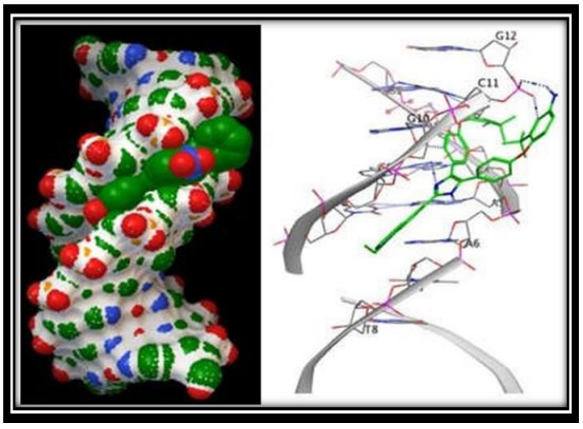
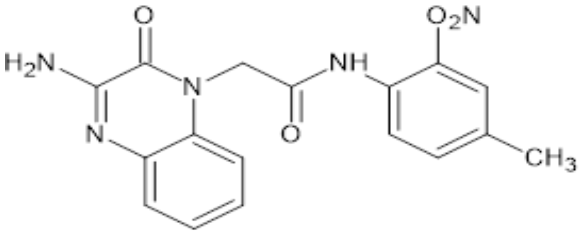


Figure No.01

The docking studies were performed using an in house batch script of AutoDock 4.2. Then mol2 format was converted PDBQT by MGL tools The 3D crystal structure of DNA as potential targets for our compounds were retrieved from protein data.(PSB Code- 1BNA) After removing water molecules, missing hydrogens were added and non-polar hydrogens were merged into their corresponding carbons using AutoDock Tools. The grid maps of the receptors were calculated using AutoGrid tools of AutoDock 4.2. the dock score of these derivatives shown in the Table 1.[6]

Antibacterial Activity:

A.M. Vijesh et al (2013): The recent expansion of antimicrobial drug research has occurred because there is a critical need for new antimicrobial agents to treat these life-threatening invasive infections. Imidazole and its derivatives have gained remarkable importance due to their widespread biological activities and their use in synthetic chemistry Aromatic heterocycles, particularly the imidazole ring, have been used in the last decades as structural skeletons to obtain different types of bioactive compounds with antibacterial, antifungal, anticancer, antiviral, antidiabetic, and other properties. The search for new potent drug molecules derived from imidazole continues to be an intense area of investigation in medicinal chemistry. The antibacterial activity of newly synthesized compounds was determined by well plate method in Mueller–Hinton Agar. The in vitro antibacterial activity was carried out against 24 h old cultures of bacterial strains. In this work, Escherichia coli, Bacillus subtilis, Salmonella typhimorium, Clostridium profingens and Pseudomonas aeruginosa were used to investigate the activity.



2-(3-amino-2-oxoquinoxalin-1(2*H*)-yl)-*N*-(2-hydroxy-4-methylphenyl)acetamide

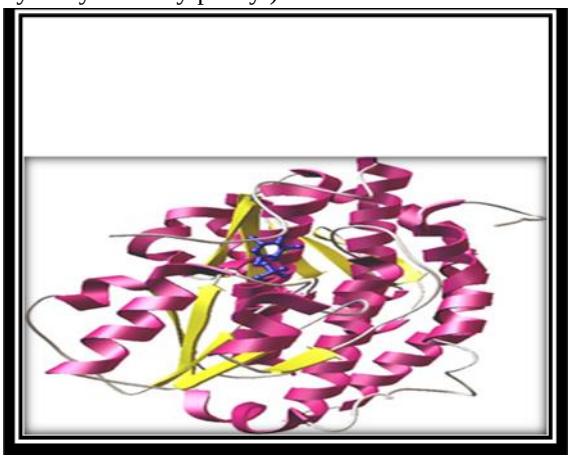


Figure No .02

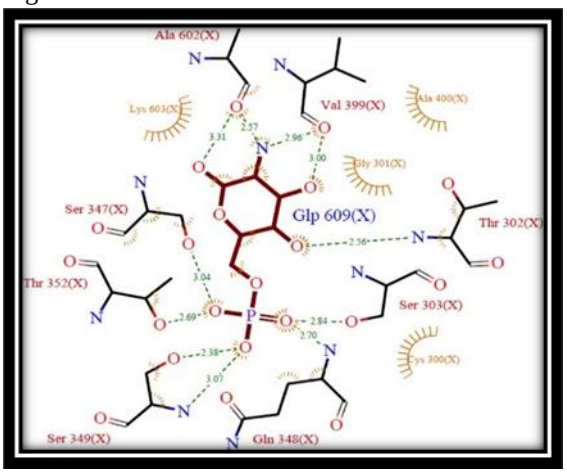
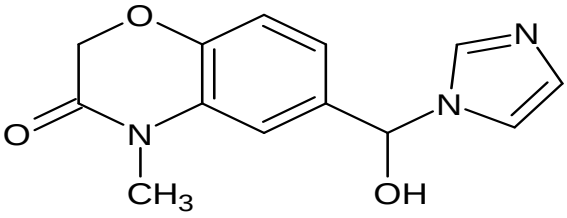


Figure No .03

Considering GlcN-6-P synthase as the target receptor it was downloaded from Protein data bank. comparative and automated docking studies with newly synthesized candidate lead compounds was performed to determine the best in silico conformation. The Lamarckian genetic algorithm, inculcated in the docking program AutoDock 4.2 was used for this docking study. PDB ID 2VF5 which was resolved at 2.90 A˚ using X-ray The docking of receptor GlcN-6-P with newly synthesized candidate ligands exhibited well established bonds with one or more amino acids in the receptor active pocket. The active pocket was considered to be the site where glucosamine-6-phosphatecomplexes in GlcN-6-Pof 2VF5. The active pocket consisted of 12 amino acid residues as Ala602, Val399, Ala400, Gly301, Thr302, Ser303, Cys300, Gln348, Ser349, Thr352, Ser347 and Lys603 as shown in Fig. 3. In silico studies revealed all the synthesized molecules showed good binding energy toward the target protein ranging from 8.01 to 6.91 kJ mol1.[7]

Antifungal Activity:

Antonio Macchiarulo et al (2002): Current available therapy in treating fungal infections can suffer from drug related toxicity, hazardous drug– drug interactions, non-optimal pharmacokinetics and development of drug resistance. Azoles are currently the most widely studied class of antifungal agents, and fluconazole is the agent of choice for Candida infections. 1,4-benzoxazine imidazole derivatives into the catalytic site of CA-CYP51. Although the binding site of azole inhibitors in the crystal of MT-CYP51 is filled by water molecules which mediate the interactions between ligands and enzymes, they were not considered during docking experiments because of the impossibility of predicting possible rearrangements of their positions upon binding of structurally diverse inhibitors.



6-[hydroxy(1*H*-imidazol-1-yl)methyl]-4-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one

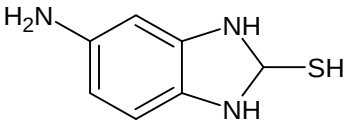
Figure No .04

For these docking study vlifeMDS 4.0 pune software was used and the receptor was downloaded from protein data bank having PDB ID (2XFH) Structure of cytochrome P450 EryK cocrystallized with inhibitor clotrimazole showing potent activity. The compounds were screened for their antifungal activity.[8]

Antidiabetic Activity:

Sardar Ali et al (2022): A series of 13 novel benzimidazoles was synthesized, characterized via MS and NMR techniques, and assessed for their in vitro *α*-glucosidase inhibitory potential. All the compounds showed prominent inhibition of the enzyme. The in vitro α-glucosidase inhibition potential of the target compounds was evaluated using acarbose as a standard antidiabetic drug. Molecular docking further supported the effective enzyme inhibition of these compounds in terms of the docking score, binding energy, and affinity. These promising results could be

utilized in drug development against type 2 diabetes mellitus.



5-amino-2,3-dihydro-1*H*-benzimidazole-2-thiol

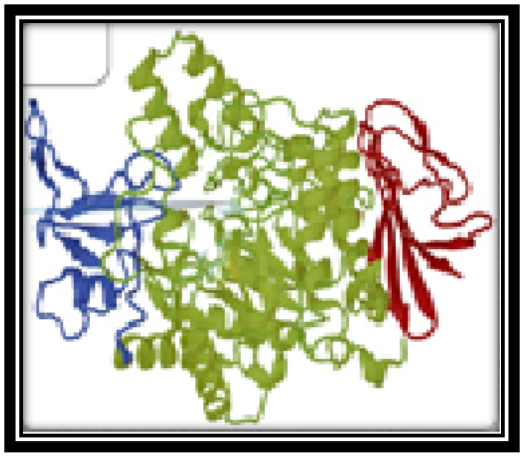


Figure No .05

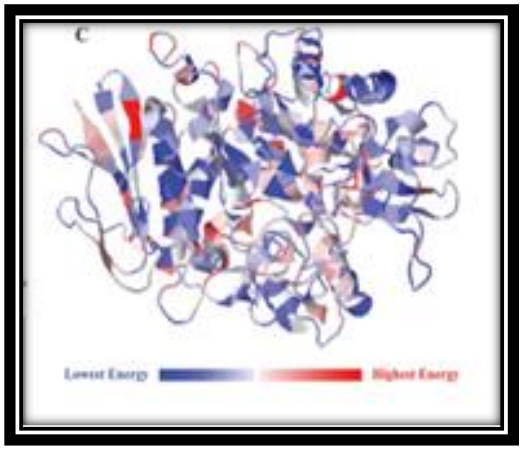
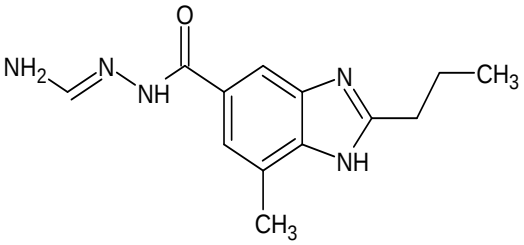


Figure No .06

To explore the interaction of the target compounds with the enzyme, a homology model of S. cerevisiae α-glucosidase (ID AF-P38158-F1) was downloaded from the AlphaFold Protein Structure Database where 7i showed the highest activity (IC50: 0.64 ± 0.05 μM). Molecular docking further supported the effective enzyme inhibition of these compounds in terms of the docking score, binding energy, and affinity. These promising results could be utilized in drug development against type 2 diabetes mellitus.[9]

Anti -Inflammatory activity:

Ramamurthy Katikireddy (2019): The compound were evaluated for in vitro anti-Inflammatory activity and based on their potential selected compounds were screened for in vivo anti-inflammatory and analgesic activity. The results indicate that the compound is effective against anti-inflammatory. The compounds were screened for their anti-inflammatory and analgesic activity based on their potential for antioxidant property. The tested compounds showed good to excellent anti-inflammatory activity.



N'-(7-methyl-2-propyl-1*H*-benzimidazole-5-carbonyl)methanehydrazonamide

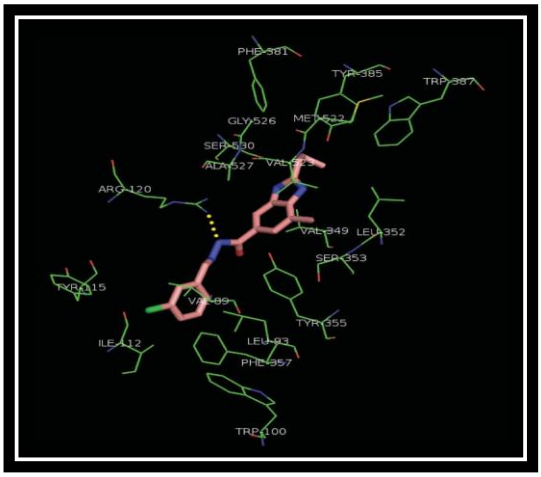


Figure No .07

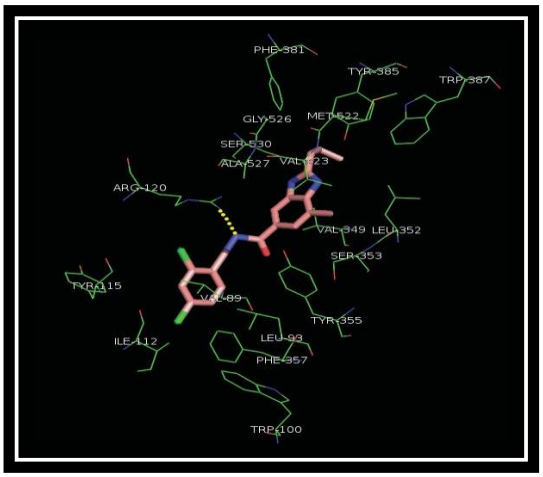


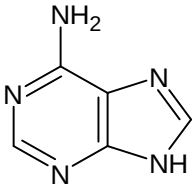
Figure No .08

Molecular modelling studies of selected compounds were carried out using Autodock vina software and

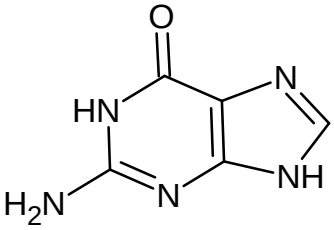
docking of all compounds was carried out on cyclooxygenase-2 complexed with indomethacin (PDB_ID 4COX, chain A). This protein PDB was retrieved from protein data bank.[10]

Antioxidant Activity:

Praveen Singh (2015): The hydrazone derivatives bearing a (benz)imidazole nucleus were designed, synthesized and evaluated for their antioxidant activity. All the synthesized compounds showed good to excellent antioxidant activity. Prior to the simulations, all bound ligands, cofactors, and water molecules were removed from the proteins. The macromolecule was checked for polar hydrogen, and torsion bonds of the inhibitors were selected and defined. Gasteiger charges were computed, and the Auto Dock atom types were defined using Auto Dock version 4.2,



9*H*-purin-6-amine



2-amino-1,9-dihydro-6*H*-purin-6-one

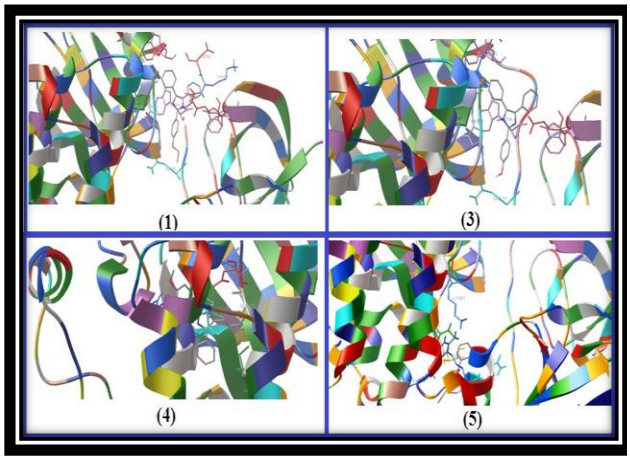
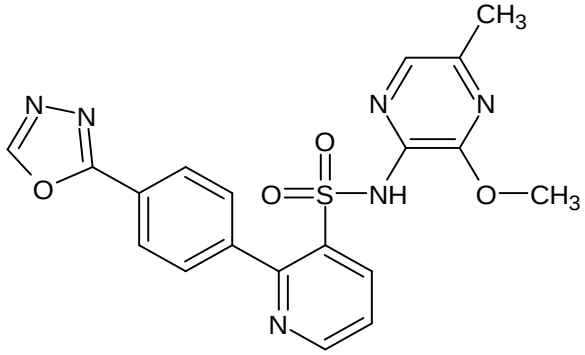


Figure No .09

The DPPH radical scavenging activity was undertaken to evaluate the effect of substituent on the antioxidant activities of the all synthesized compounds and shows promising activity. Reason for higher antioxidant activity of compound 10 and 16 are due to presence of indole, pyrazole group adjacent to imidazole ring that can stabilize an unpaired electron in general boost up the antioxidant capacity of the molecule. There for, these molecules could be developed for antioxidant agent.[11]

Anticonvulsant Activity:

S. Shashidhar Bharadwaj et al (2018): Benzimidazole-containing quinolinyloxadiazoles were synthesized. The novel synthesized compounds were characterized by spectral and analytical data and were screened for anticonvulsant activity. The results are correlated with docking studies. The molecular docking data provided positive correlation with in vitro anticonvulsant activity in comparison with the standards revealed that these compounds can act as potential inhibitors.



N-(3-methoxy-5-methylpyrazin-2-yl)-2-[4-(1,3,4-oxadiazol-2-yl)phenyl]pyridine-3-sulfonamide

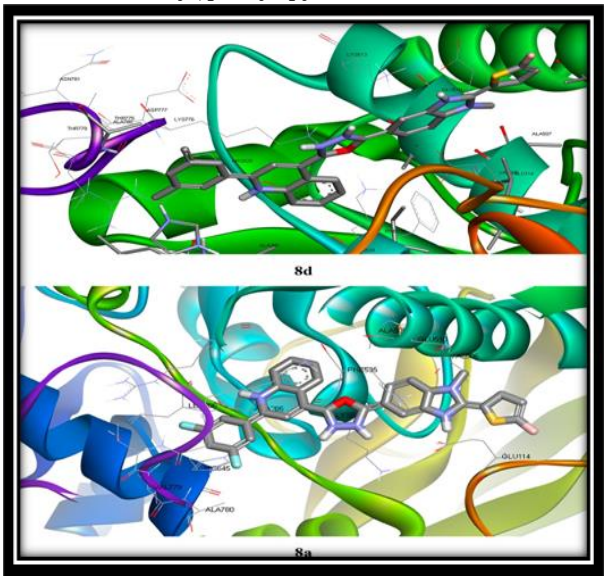


Figure No .10

For these docking study vlifeMDS 4.0 pune software was used and the receptor was downloaded from protein data bank having PDB ID (1EOU) crystal structure of human carbonic anhydrase ii complexed with an anticonvulsant sugar sulfamates showing potent activity. The compounds were screened for their anticonvulsant activity against subcutaneous PTZ induced seizures in mice.[12]

CONCLUSION

The current evaluation of imidazole derivative docking demonstrates that the computations were run using a variety of suitable software programs in order to determine the optimal position for each ligand inside the active region of the relevant receptor and cytoskeleton as suggested targets. These imidazole derivatives exhibited the highest docking energies based on the docking binding energies and had a better affinity for binding to the corresponding receptors.

According to the results of the current study, imidazole derivatives are an intriguing class of compounds with a wide variety of biological effects. Imidazole compounds exhibit anticancer, antibacterial, anti-inflammatory, anti-diabetic, antifungal, anticonvulsant, and other effects, according to a number of literature reviews. A number of compounds can be examined for intended pharmacological effect with high potency and low toxicity using the same methodology. Additionally, even little adjustments to the imidazole nucleus's substituents can boost activity. Recent improvements in the medicinal use of imidazole derivatives have shown greater efficacy and decreased toxicity. The Imidazole moiety has been found to have significant biological impacts thus far. It will be interesting to see if these alterations can eventually be employed as potent medications.

ACKNOWLEDGEMENT

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