INSILICO DESIGN OF DIBENZAZEPINE DERIVATIVES AS GABA-A AGONIST

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***Abstract*- Convulsion is considered as the most common serious brain conditions. Surgery is the only way in the eradication of convulsion. This project aims at designing dibenzazepine derivatives as anticonvulsant agents by agonistic activity in GABA-A receptor. Different dibenzazepine derivatives were designed using ACD Lab Chemsketch12.0 software and their properties were predicted using Molinspiration software. The designed derivatives showing optimal physicochemical properties were selected for docking studies. The various methodology used in the study include random selection of drugs, ChemSketch for drawing 2D structure, docking using AutoDock program and visualising the output using PyMOL. The ligands which shows good binding score with GABA-A receptor were selected as anticonvulsant drugs and carbamazepine was selected as standard drug.**

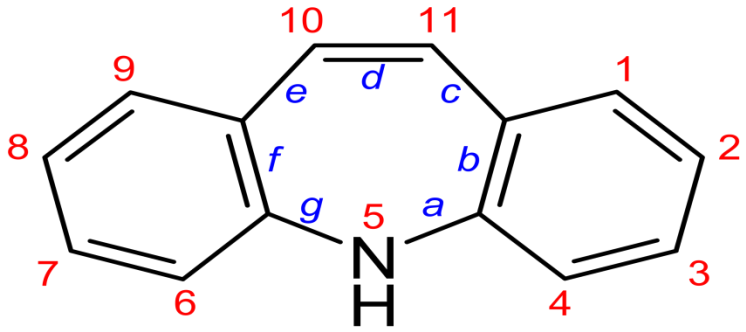
***Keywords*- Convulsion, *Insilico*, Chemsketch, Docking, PyMOL, Carbamazepine, GABA-A**

INTRODUCTION

Drug discovery aims at recognising a therapeutically active compound for treating diseases. This process is complicated involving candidate identification, synthesis, characterisation, validation, optimization, screening and assays as a proof of therapeutic efficacy. Once a compound prove its significance the process of drug development is initiated.[1]

Convulsion is the abnormal electrical activity in the brain, it is considered as the serious brain condition affecting more than 70% of the population. At times it may display symptoms and sometimes it shows no symptoms. It is characterised by epileptic seizures and has numerous neurobiological, cognitive, and psychosocial consequences. Convulsion is at the risk of immediate control as it' s lack may lead to shortened lifespan.[2]

Dibenzazepine (Iminostilbene) is a chemical compound with two benzene rings fused to an azepine group (7 or 8 membered ring containing a nitrogen atom). The chemical name of iminostilbene is 11H-benzo[b][1]benzazepine . Its molecular formula is $C_{14}H_{11}N$, and it has a molecular weight of 193.244 g. Iminostilbene can be directly obtained from iminodibenzyl on Pd,Ni,and Fe_2O_3 by vapour phase procedure. Iminostilbene can also be prepared by catalytic dehydration of iminodibenzyl at 550^0C on binary oxide system of Mn_2O_3-SnO_2. Iminostilbene is a well known polymerization inhibitor applied in industrial processes to control radical polymerization reaction.[3]



$GABA_A$ (G-AminoButyric Acid) agonist is the major inhibitory neurotransmitter receptors belonging to ligand gated ion channel. GABA is synthesised in presynaptic neurons catalysed by L-glutamic acid decarboxylase and acts on the postsynaptic receptors upon release from the synaptic vesicles. The 5 subunits of $GABA_A$ are arranged around the channel in counter-clockwise pattern. Each subunit has transmembrane spanning domains of 20 amino acids. The binding pocket for GABA is located at the interface between the alpha and the beta subunit.[4]

In this study, we have designed and docked a series of new dibenzazepine derivatives in search of potent anticonvulsant agents through *insilico* studies using AutoDock4.

MATERIALS AND METHODS

Insilico screening

Insilico screening of all the proposed structures of novel benzodiazaepine derivatives were carried out using various computational chemistry softwares such as ACD Lab/ChemSketch12.0, Molinspiration, PASS and AutoDock4.

Protein Data Bank

The protein data bank is a database for the three-dimensional structural data of large biological molecules, such as proteins and nucleic acids. The data, typically obtained by X-ray crystallography, NMR spectroscopy, or increasingly, cryo-electron microscopy, and submitted by biologists and biochemists from around the world, are freely accessible on the internet via the websites of its member organizations (PDBe, PDBj, RCSB, and BMRB). The PBD is overseen by an organization called the Worldwide Protein Data Bank, wwPDB.The PDB is a key in areas of structural biology, such as structural genomics. Most 3 major scientific journals and some funding agencies now require scientists to submit their structure data to the PDB. [5,6]

ACD/ Chemsketch

ACD/ChemSketch Freeware is a drawing package that allows one to draw chemical structures including organics, organometallics, polymers, and Markush structures. It also includes features such as calculation of molecular properties (e.g., molecular weight, density, molar refractivity etc.), 2D and 3D structure cleaning and viewing, functionality for naming structures (fewer than 50 atoms and 3 rings), and prediction of log P.

ACD/ChemSketch has the following major capabilities in that it provides for:

• Structure Mode for drawing chemical structures and calculating their properties.

• Draw Mode for text and graphics processing.

• Molecular Properties calculations for automatic estimation of formula weight, percentage composition, molar refractivity, molar volume, parachor, surface tension, density, dielectric constant, polarizability. [7,8]

Molinspiration

"Molinspiration" is an independent research organization focused on development and application of modern cheminformatic techniques, especially in connection with the internet. It offers broad range of cheminformatics software tools supporting molecule manipulation and processing, including SMILES and SD file conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure search or similarity and pharmacophore similarity search.

All the designed compounds were then subjected to Lipinski rule analysis using Molinspiration software to identify the biologically active compounds. Lipinski rule is also known as Pfizers rule of five / Lipinski's rule of 5. The rule was formulated by the scientist Christopher A Lipinski. [9]

The Lipinski rule of five states that an orally active drug should obey the following criteria in that it will have:

1. Not more than 5 hydrogen bond donors
2. Not more than 10 hydrogen bond acceptors
3. Molecular weight less than 500 Daltons
4. An octanol-water partition coefficient of log P not greater than 5
5. Not more than 5 rotatable bonds.

AutoDock

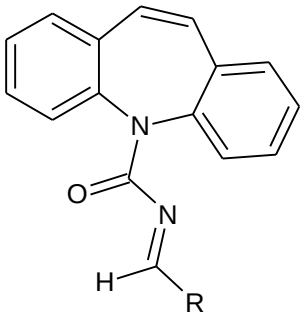
AutoDock is a combination of 3 C programs, AutoTors, which smoothens the input of ligand, AutoGrid, which calculates interaction energy based on macromolecular coordinates, and AutoDock, which performs the docking. The ligand traverse six spatial degrees of freedom-rotation and translation. AutoDock successfully reproduces crystallographically determined positions of ligands with up to about eight degrees of torsional freedom. For molecules with more degrees of freedom, the simulated annealing search does not adequately sample the possible conformational space. [10,11]

Docking

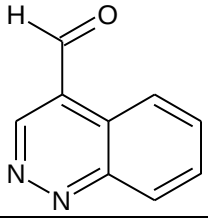
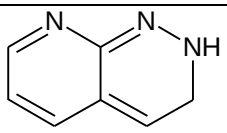
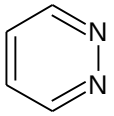
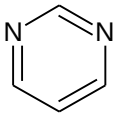
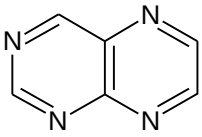
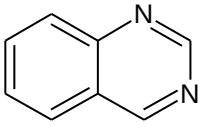
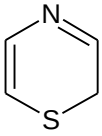
Molecular docking is used to predict the structure of the intermolecular complex formed between two molecules. The small molecule called ligand usually interacts with protein's binding sites. Binding sites are areas of protein known to be active in forming of complex with the ligands. There are several possible mutual conformations in which binding may occur. These are commonly called binding modes. It also predicts the strength of the binding, the energy of the complex, the types of signal produced and calculate the binding affinity between two molecules using scoring functions. [12,13]

RESULT AND DISCUSSION

Fifty analogues of dibenzazepines were designed using ACD Lab ChemSketch 12.0. Initially the designed fifty analogues were subjected to Lipinski rule analysis using Molinspiration software. From the Lipinski rule analysis, twenty five compounds were selected for further studies, since these compounds did not show any violations from the Lipinski rule of five.



N-[(E)-substitutedmethylidene]-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide Basic Structure

SLNO	R	NAME
A		cinnoline-4-carbaldehyde
B	 InChI=1S/C7H7N3/c1-2-6-3-5-9-10-7(6)8-4-1/h1-4,9H,5H2	pyrido[2,3-*c*]pyridazine-2(3*H*)-carbaldehyde
C	 InChI=1S/C4H4N2/c1-2-4-6-5-3-1/h1-4H	pyridazine-3-carbaldehyde
D	 InChI=1S/C4H4N2/c1-2-5-4-6-3-1/h1-4H	pyrimidine-4-carbaldehyde
E	 InChI=1S/C6H4N4/c1-2-9-6-5(8-1)3-7-4-10-6/h1-4H	pteridine-2-carbaldehyde
F	 InChI=1S/C8H6N2/c1-2-4-8-7(3-1)5-9-6-10-8/h1-6H	quinazoline-2-carbaldehyde
G	 InChI=1S/C4H5NS/c1-3-6-4-2-5-1/h1-3H,4H2	2*H*-1,4-thiazine-2-carbaldehyde

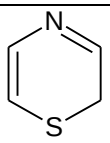
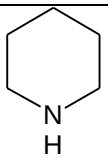
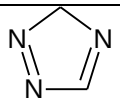
H	 InChI=1S/C4H5NS/c1-3-6-4-2-5-1/h1-3H,4H2	2*H*-1,4-thiazine-2-carbaldehyde
I	 InChI=1S/C5H11N/c1-2-4-6-5-3-1/h6H,1-5H2	piperidine-4-carbaldehyde
J	 InChI=1S/C2H3N3/c1-3-2-5-4-1/h1H,2H2	3*H*-1,2,4-triazole-3-carbaldehyde

Table No: 1 Structure and name of heterocyclic rings

Based on the docking score, among the twenty-five designed derivatives ten were selected as anticonvulsant agents as GABA- A agonist. The docking score of selected ten derivative showed in table.

SLNO	COMPOUND	DOCKING SCORE
A	*N*-[(*Z*)-(cinnolin-4-yl)methylidene]-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide	-9.3
B	*N*-[(*Z*)-(pyrido[2,3-*c*]pyridazin-2(3*H*)-yl)methylidene]-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide	-8.9
C	*N*-[(*Z*)-(pyridazin-3-yl)methylidene]-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide	-8.6
D	*N*-[(*Z*)-pyrimidin-4-ylmethylidene]-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide	-8.3
E	*N*-[(*E*)-pteridin-2-ylmethylidene]-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide	-8.2
F	*N*-[(*Z*)-(quinazolin-2-yl)methylidene]-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide	-7.9
G.	*N*-[(*Z*)-(2*H*-1,4-thiazin-2-yl)methylidene]-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide	-7.8
H	*N*-[(*Z*)-(1,3,4-oxadiazol-2-yl)methylidene]-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide	-7.6

I	*N*-[(*Z*)-(piperidin-4-yl)methylidene]-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide	-7.6
J	*N*-[(*Z*)-(3*H*-1,2,4-triazol-3-yl)methylidene]-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide	-7.5

Table no: 2 Docking score of selected ten compounds

DOCKING: The images of standard drug and selected ten derivatives were shown in figure

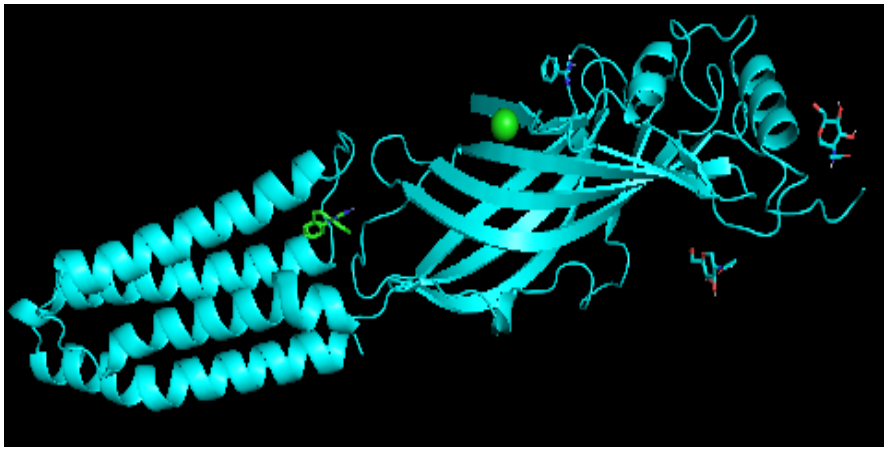


Figure 1: CARBAMAZEPINE with 4COF

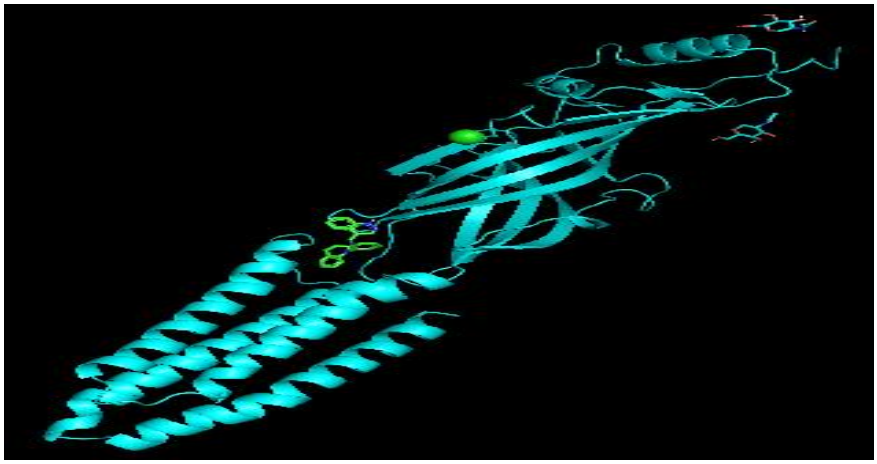


Figure 2: A with 4COF

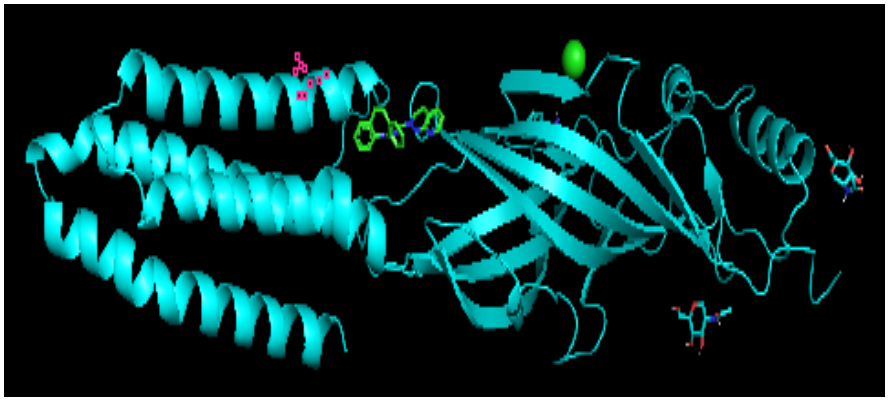


Figure 3: B with 4COF

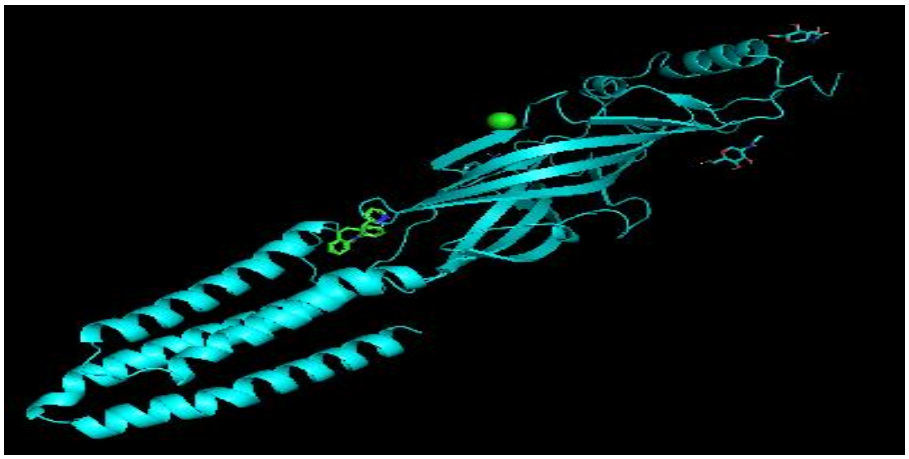


Figure 4: C with 4COF

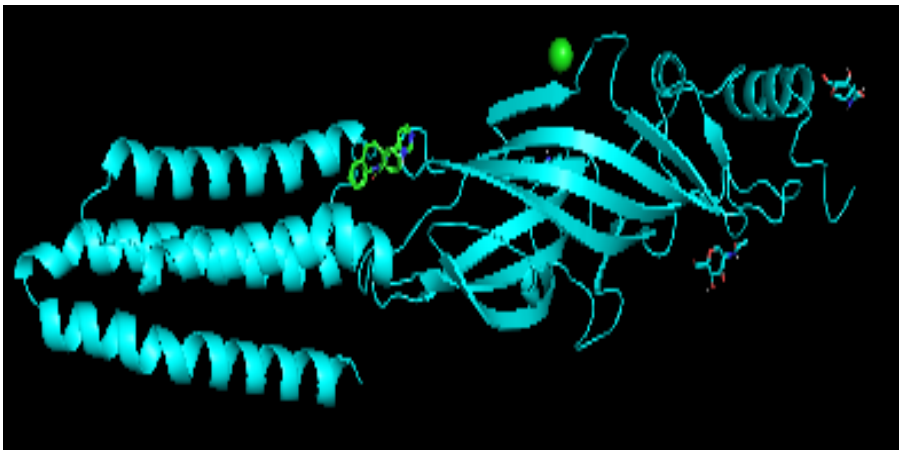


Figure 5: D with 4COF

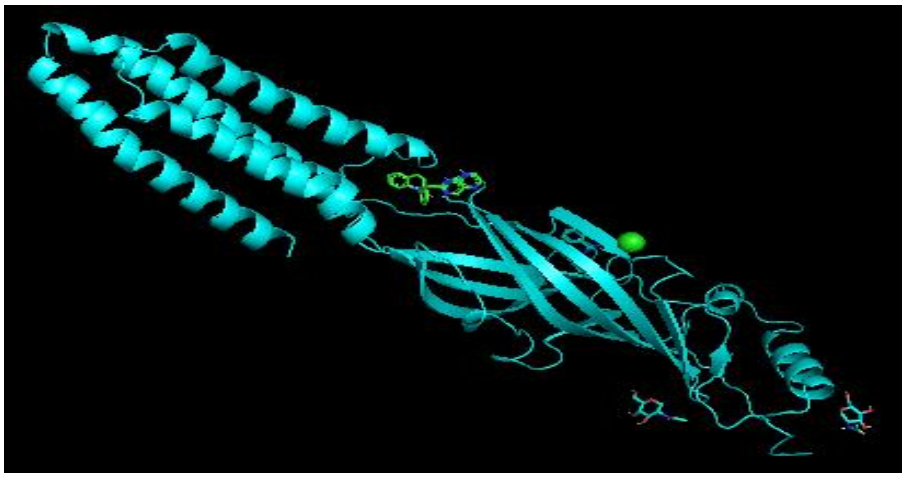


Figure 6:E with 4COF

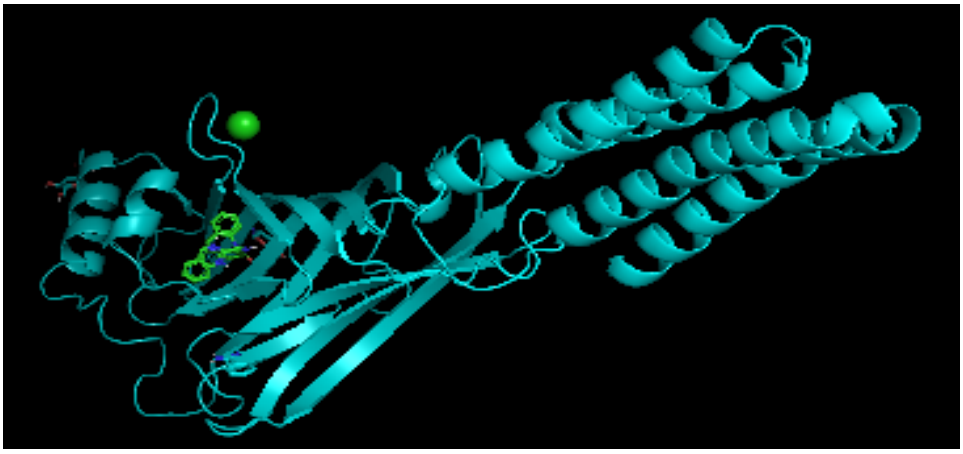


Figure 7: F with 4COF

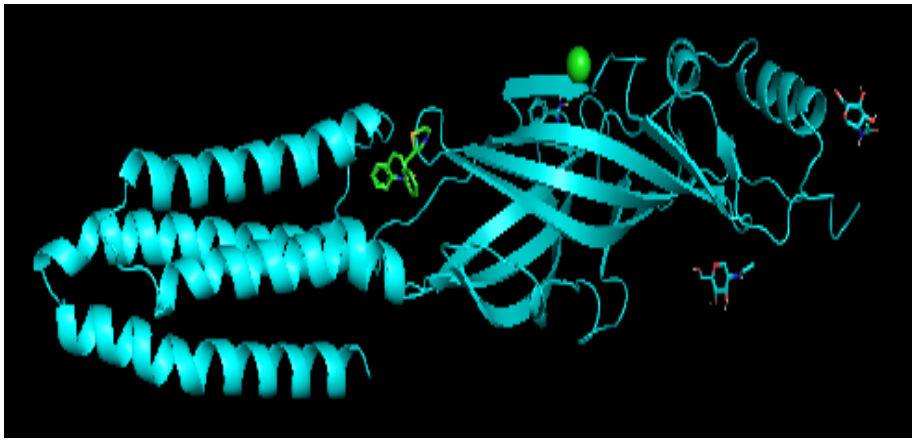


Figure 8: G with 4COF

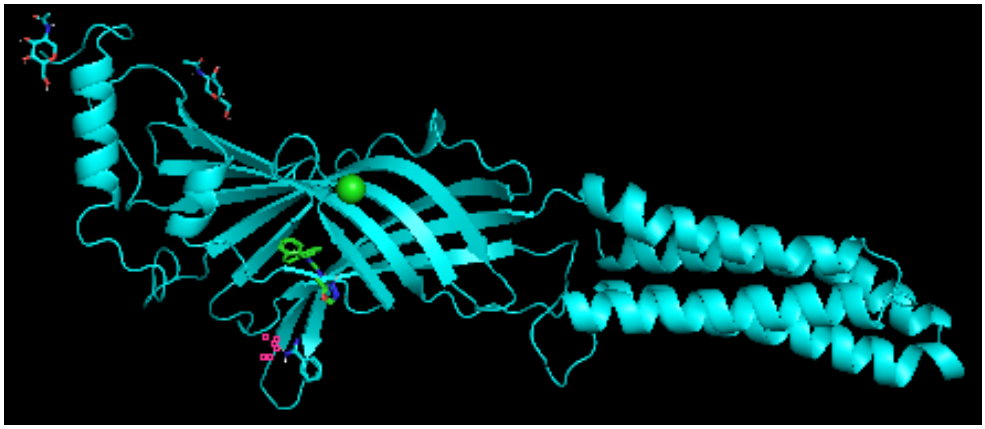


Figure 9: H with 4COF

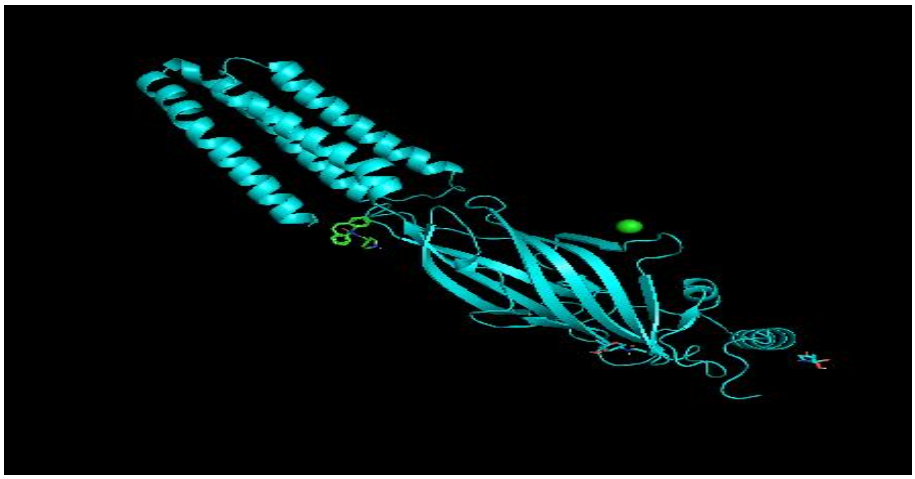


Figure 10: I with 4COF

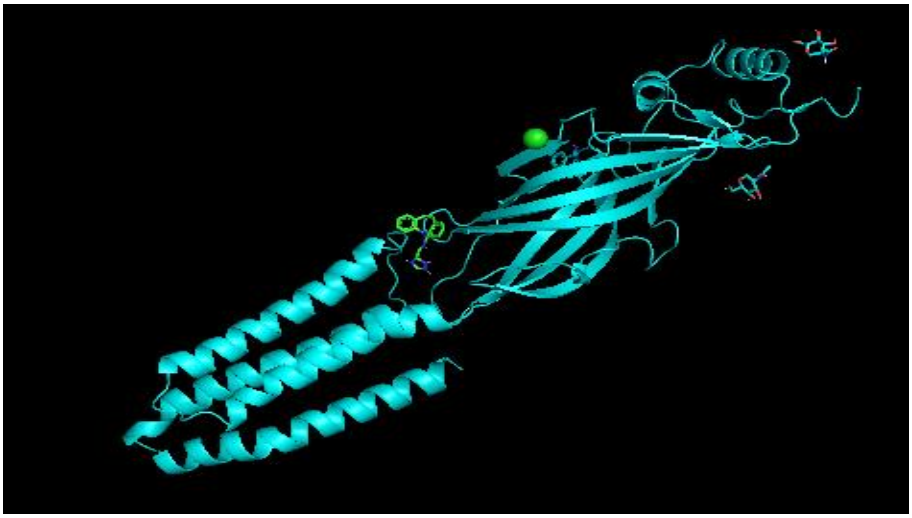


Figure 11: J with 4COF

CONCLUSION

The investigation that has been carried out in the present project, the results obtained for the same and the corresponding observations made were in accordance with the objectives laid down during commencement of the work.

Based on the literature survey, it was revealed that dibenzazepine derivatives can exert anticonvulsant activity. So fifty novel hybrid molecules dibenzazepine nucleus were designed using the ACD Lab ChemSketch 12.0 software. All the designed leads were then subjected to Lipinski rule analysis using Molinspiration software to identify the theoretically active compounds. In the present study, twenty five theoretically active lead compounds were identified.

The identified compounds were subjected to docking studies against the selected target proteins, GABA-A receptor(4COF) for anticonvulsant activity. From the docking results, compounds A-J which had the highest docking scores ranging from -9.3 to -7.5.

The newly designed dibenzazepine derivatives are expected to possess potent anticonvulsant activity than the available drugs.

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