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DESIGN AND MOLECULAR DOCKING STUDIES OF N^1-CHLOROACETYL-7-SUBSTITUTED- 4-METHYL-1, 5-BENZODIAZEPINE-2-ONE DERIVATIVES

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ABSTRACT: Molecular Docking is an effective and competent tool for *in-silico* screening. It is playing an important and ever-increasing role in rational drug design. The main application lies in this structure-based virtual screening is the identification of new active compounds towards a particular target protein. In present investigation, few N^1-chloroacetyl-7-substituted- 4-methyl-1, 5-benzodiazepine-2-one and 7-Substituted-4-methyl-1,5-benzodiazepin-2-one are designed and docked at active site of cavity 1# of GABA-A receptor-associated protein (1KJT) to identify their hypothetical binding mode. As a target protein, we used the X-ray crystal structure of mammalian GABA-A receptor-associated protein from the Protein Data Bank. The Molecular Design Suite was used in this study to conduct docking investigations and conformational analyses. The comparative docking experiments of designed compounds with known GABA agonist, Clobazam was carried out. The dock scores calculated for Clobazam was -5.2598. Among the designed compounds, following conformation were found to have lower dock scores as indicated in bracket; N1-chloroacetyl-7-bromo-4-methyl-1,5-benzodiazepine-2-one, Conformer_C4 (-4.7869) and 7-chloro-4-methyl-1,5-benzodiazepin-2-one, Conformer_C13 (-5.0485) and said to have better affinity for active site of GABA-A receptor-associated protein than other molecules.

INTRODUCTION: 1, 5 benziodiazepines have wide spectrum of biological activities, including anticonvulsant activity [1-2]. In addition to presently available anticonvulsant drugs, there is a need to develop novel derivatives with more anticonvulsant potential. There is an ever-increasing need for research into novel molecules with lesser toxicity and side effects for treating epileptic seizures. Various docking studies have been reported for benzodiazepine derivatives containing heterocycles *viz*. traizole, pyrimidine, quinazoline [3-6]. Molecular docking helps in studying drug/ligand or receptor/protein interactions by identifying the suitable active sites in the protein, obtaining the best geometry of the ligand-receptor complex, and calculating the energy of interactions for different ligands to design more effective ligands.

The interaction energy is calculated in terms of dock score; scoring functions are fast approximate mathematical methods used to predict the strength of the noncovalent interaction between two molecules after they have been docked. Most scoring functions are physics-based molecular mechanics force fields that estimate the energy. The low (negative) energy indicates a stable system

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and thus alikely binding interaction. The options available for docking are rigid docking, where a suitable position for the ligand in the receptor environment is obtained, flexible docking, where a favored geometry for receptor-ligand interactions is obtained, full flexible docking, where the ligand is flexed *via* its torsion angles as well as the side chains of active site residues [5-7].

MATERIALS AND METHODS:

Hardware and Software: All Docking studies and conformational analyses were performed using the Molecular Design Suite (VLifeMDS software package, version 4.3; from Life Sciences, Pune, India).

Structure Conformation Generation: Structures of compounds were sketched using the Vlife2D Draw application and converted to 3D structures. All the structures were minimized and optimized with the AMBER method taking root mean square gradient (RMS) of 0.01 kcal/mol A° and the iteration limit to 10,000. Each structure's conversion was generated using Monte Carlo by applying the AMBER force field method. The least energy conformer was selected for further study [8-9].

Preparation of Protein: The protein Crystal Structure of the GABA (A) Receptor Associated Protein, GABARAP, (1KJT) was downloaded from www.rcsb.org and energy minimization of the protein complex. All the bound water molecules, ligands, and cofactors were removed (preprocess) from the protein which was taken in.pdb format. The tool neutralized the side chains that were not close to the binding cavity and did not participate in salt bridges.

This step was then followed by restrained minimization of co-crystallized complex, which reoriented side-chain hydroxyl groups and alleviated potential steric clashes. The complex obtained was minimized using the AMBER force field. The minimization was terminated after either completion of 5,000 steps or after the energy gradient converged below 0.05 kcal/mol.

Preparation of Ligands: Structures of the 1,5 benzodiazepaines derivatives ligands were sketched using built Vlife 2D draw taken in mol2 format. Converted it into 3D structure and performed a geometry minimization of the ligands. AMBER Force Fields with default settings were used for the ligand minimization.

Docking Methodology: A docking study was performed on VlifeMDS version 4.3 on Lenovo computer, i3 processor with XP operating system. The GA-based ligand docking with a genetic algorithm approximated a systematic search of the ligand positions, orientations and conformations in the enzyme binding pocket *via* a series of hierarchical filters. The minimum dock score, for example, may not be exactly reproducible because this is a Genetic Algorithm (GA) based run. However, changing the different input parameters in the GA Parameters dialog box (like No of Generations, Translation, Rotation limits, *etc.*) can result in dock scoring energies within desired range and improvement in the orientation of docked ligand as close to that of the co-crystallized ligand as possible.

A genetic Algorithm implemented in the molecular design suite (MDS) has been successfully employed to dock inhibitors into the catalytic site of the receptor and correlate the obtained binding score with the inhibitory activities of compounds. These docking studies carried out the comparative docking experiments of designed compounds with known calcium blockers Ethosuximide and gabapentin, respectively. Obtained results were evaluated in terms of docking score into the active site of 1KJT. During the docking process, the system searches the docked ligand's conformational, orientational, and positional space and eliminates the unwanted confirmation using the scoring. The structure available on PDB, using the AMBER force field, is optimized. Batch docking in MDS of designed ligands is performed with GABA-A receptor-associated protein [10-11].

RESULTS AND DISCUSSION:

Docking Results: VLifeMDS provides a facility to dock different ligands in protein binding sites chosen by the user. VLifeMDS provides both rigid (no torsional flexibility for protein and a ligand) and flexible (torsional flexibility to ligand with rigid protein) docking of the molecules. The computational process of searching for a ligand that is able to fit both geometrically and energetically into the binding site of a protein is called molecular docking. Here in this study, the target protein was

generated through knowledge-based protein or homology modeling. VLifeMDS uses a genetic algorithm, Piecewise Linear Pairwise Potential (PLP) and Grid algorithms to minimize the interaction energy between ligand and the receptor protein. The molecular docking scores identified the ligands that bind with similar orientation as observed with reference ligands. Most of the ligands make good docking poses compared to the reference ligand. Selective ligands docked deeply within the binding pocket region, suggesting their shape complementarily with the reference ligands. The Vander Walls, H-bonding, and hydrophobic interactions of the ligands with receptor proteins were analyzed, which reveals a novel set of information. The molecular docking studies of all possible three-dimensional confirmations of N^1-chloroacetyl -7-substituted-4-methyl-1, 5 - benzodiazepine – 2 - one and 7-Substituted-4-methyl-1,5-benzodi- azepine-2-one were done using VlifeMDS Biopredict a module using cavity#1 of GABA-A receptor-associated protein (1KJT). The intermolecular interactions in between the ligand and the protein (receptor) were investigated. It is processed by deleting the solvent molecule and correcting the structure with respect to bonds and the H-atoms. **Table 1** shows Dock scores and binding energies of conformations of N^1-chloroacetyl – 7 – substituted – 4 - methyl-1,5-benzodiazepin-2-ones. **Table 2** shows Dock scores and binding energies of conformations of 7-substituted-4-methyl-1, 5-benzodiazepin-2-ones. Some of the molecules for which the confirmations shows lower dock scores were selected to study their binding interaction with the cavity#1 of the receptor. The binding pattern of the docked molecules has been compared with the standard ligand, Clobazam. It's interactions are also shown in **Fig. 1**. The Hydrophobic and Vander Waals interactions for N^1-chloroacetyl - 7 - bromo- 4 – methyl - 1, 5-benzodiazepine-2-ones (Compound 3; Conformor_C4) were studied at cavity#1 of 1KJT**;** the residues PHE77A, LEU76A, VAL114A, GLU112A, ASP111A, SER110A, TYR109A, VAL44A interact with the molecules during the binding as shown in **Fig. 2.** The Hydrophobic and Vander Waals interactions for 7-chloro-4-methyl-1,5-benzodiazepin-2-one (Compound 6; Conformor_C13) were studied at cavity#1 of 1KJT; the residues SER110A, ASP111A, GLU112A, VAL114A, ALA108A, TYR109A, PHE77A, LEU76A are the residues taking part in the interaction as shown in **Fig. 3**.

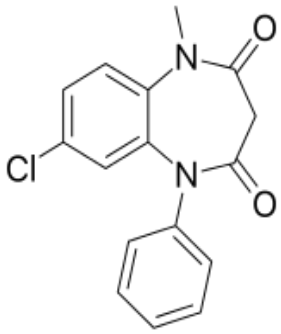
TABLE 1: DOCK SCORES AND BINDING ENERGIES OF CONFORMATIONS OF N^1-CHLOROACETYL-7-SUBSTITUTED-4-METHYL-1,5-BENZODIAZEPIN-2-ONE

Conformation of compounds	R	Dock score	ΔG (kcal/mol)
1_C12	-Cl	-4.769054	-16.1226
2_C5	-F	-4.451437	-17.6753
3_C4	-Br	-4.786992	-17.0146
4_C4	$-OCH_3$	-4.180516	-20.5896
5_C4	$-CH_3$	-4.598894	-16.4017

TABLE 2: DOCK SCORES AND BINDING ENERGIES OF CONFORMATIONS OF 7-SUBSTITUTED-4-METHYL-1, 5-BENZODIAZEPIN-2-ONE

Conformation of compounds	R	Dock score	ΔG (kcal/mol)
6_C13	-Cl	-5.048574	-17.3405
7_C10	-Br	-3.663538	-16.3842
8_C1	-F	-4.046493	-17.5037
9_C5	$-CH_3$	-3.144092	-13.7129
10_C5	$-OCH_3$	-3.958974	-19.0389

Standard: Clobazam



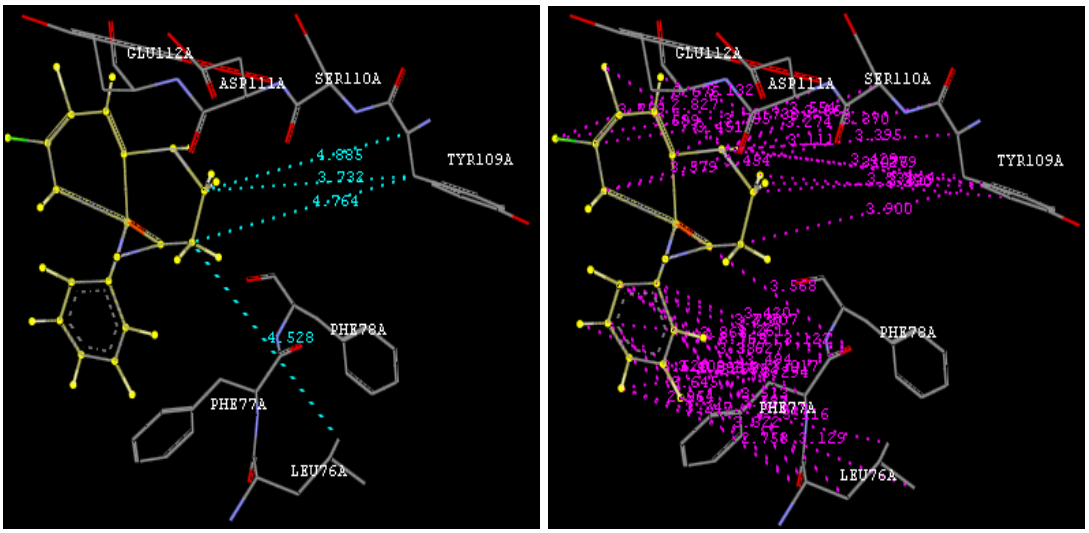


FIG. 1: BINDING INTERACTIONS OF CLOBAZAM WITH CAVITY # 1 OF 1KJT. (A) Blue colour dotted lines indicate hydrophobic interactions with the residues TYR109A and LEU76A. (B) Magenta colour dotted lines indicate Vander Waals interactions with the residues PHE77A, PHE78A, LEU76A, GLU112A, ASP111A, SER110A and TYR109A with cavity # 1 of Crystal structure of GABA-A receptor-associated protein (1KJT).

Compound 3:

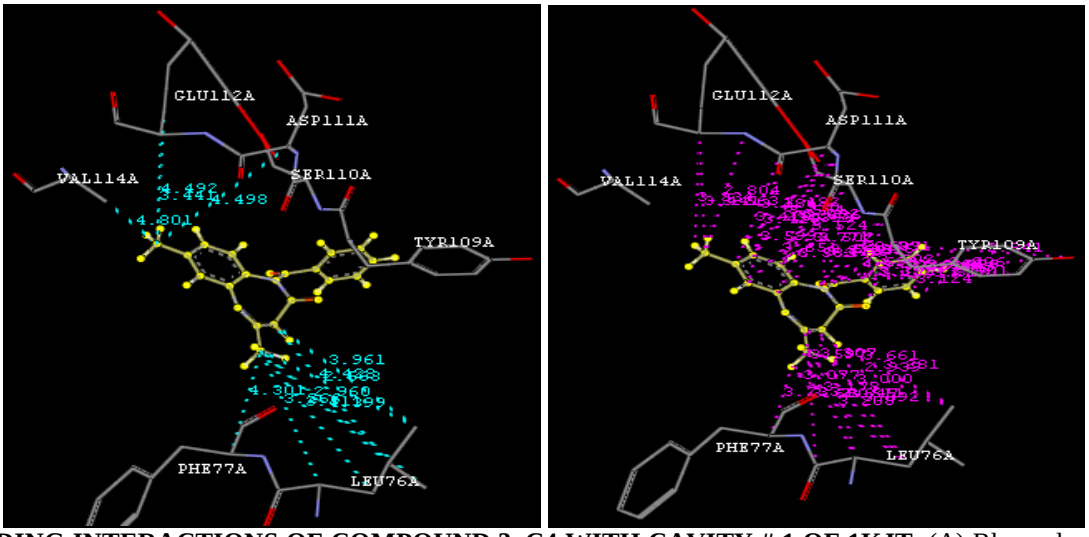


FIG. 2: BINDING INTERACTIONS OF COMPOUND 3_C4 WITH CAVITY # 1 OF 1KJT. (A) Blue colour dotted lines indicate hydrophobic interactions with residues PHE77A, LEU76A, Val114A, GLU112A, and ASP111A, (B) Magenta colour dotted lines indicates Vander Waals interactions with the residues VAL44A, ASP111A, SER110A, TYR109A, LEU76A, PHE77A and GLU112A.

Compound 6:

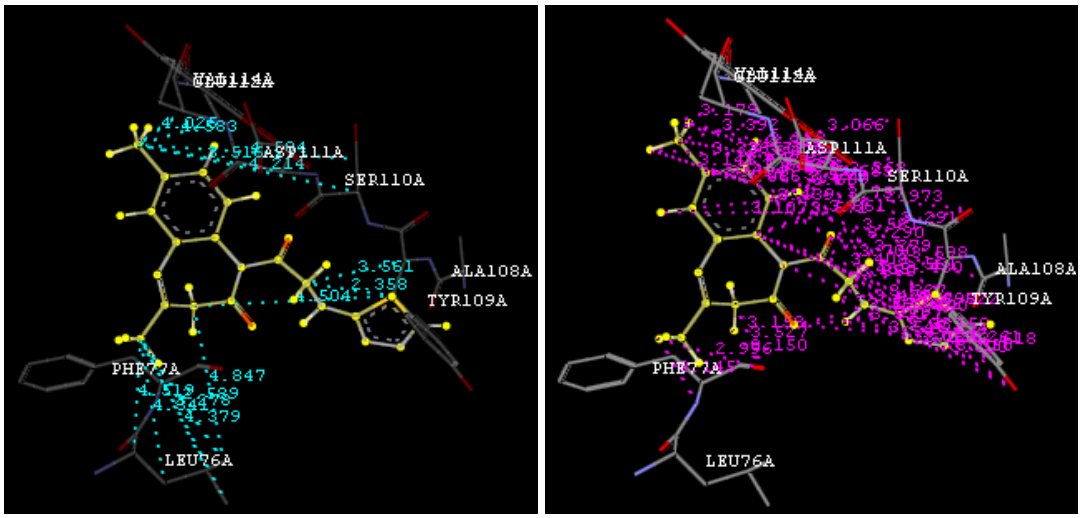


FIG. 3: BINDING INTERACTIONS OF COMPOUND 6_C13 WITH CAVITY # 1 OF 1KJT. (A) Blue colour dotted lines indicate hydrophobic interactions with the residues SER110A, ASP111A, GLU112A, VAL114, ALA108A, TYR109A, PHE77A and LEU76A**,** (B) Magenta colour dotted lines indicates Van der Waals interactions with residues SER110A, ASP11A, GLU112A, VAL114, ALA108A, TYR109A, PHE77A and LEU76A.

The Vander Walls, H-bonding, and hydrophobic interactions of the ligands with receptor proteins were analyzed, revealing a novel set of information regrading the similarity of amino acid residues participating in the interaction of the standard Clobazam and the designed compounds at the Cavity # 1 of 1KJT. It was found that amino acid residues *viz*. PHE77A, LEU76A, GLU112A, ASP111A, SER110A and TYR109A are similar residues among those interacting with 1KJT.

Thus the docking simulation suggested that the modifications in the series of N^1-chloroacetyl and 7-Substituted -4 - methyl-1, 5-benzodiazepin-2-one resulted in the identification of ligands with better binding potential. The Vander walls, hydrophobic interactions are responsible for forming the stable complexes of the ligands with the receptor.

CONCLUSION: The studies resulted in identyfing the ligands and their conformations which efficiently fit into the cavity of target protein. The newly designed molecules *viz*. N^1-chloroacetyl-7-bromo-4-methyl-1,5-benzodiazepine-2-one and 7-chloro-4-methyl-1,5-benzodiazepin-2-one can be priritized for synthesis and can be studied further for Pharmacological screeing.

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Authors' Statement:

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