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Molecular Modelling of 1H-Benzo [b] [1,5] Diazepine-2(3H)-one Derivatives and Docking Studies Against Receptor Associated Protein

Dinesh Rishipathak [a*], Dipak Patil [a] and Komal Ushir [a]

[a] Department of Pharmaceutical Chemistry, MET's Institute of Pharmacy, (Savitribai Phule Pune University), Bhujbal Knowledge City, Nashik-422003, Maharashtra, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

In the present investigation, some N1-benzoyl/ N1-(1,3,4-thiadiazol-2-yl amino acetyl) -7-substituted- 4-methyl-1,5-benzodiazepine-2-one were designed and docked at active site of cavity 1# of GABA-A receptor associated protein (1KJT) to distinguish from their hypothetical binding mode. The X-ray crystal structure of mammalian GABA-A receptor associated protein (1KJT) obtained from protein data bank was used as target protein. In this investigation the comparative analysis of the docking experiments of modelled compounds with known GABA agonist, Lofendazam was carried out. The dock scores calculated for Lofendazam was -4.7373. Among the modelled compounds, following conformation were found to have lower dock scores as indicated in bracket in comparison to other confermers; N1-benzoyl-7- bromo- 4-methyl-1,5-benzodiazepine-2-one, conformer_C3 (-5.0915), N1-(1,3,4-thiadiazol-2-yl amino acetyl) -7-chloro-4-methyl-1,5-benzodiazepine-2-one, Conformer_C2 (-4.6532). These conformers have more affinity for active site of GABA-A receptor associated protein than other molecules.

Keywords: Docking; GABA-A receptor associated protein; 1,5- benzodiazepines; conformers.

**Corresponding author: E-mail: drishipathak@gmail.com;*

1. INTRODUCTION

1, 5 benziodiazepines have wide spectrum of biological activities including anticonvulsant activity [1-2]. In addition to currently known anticonvulsant agents, there is a need to develop such new heterocycles with the hope of having greater anticonvulsant potential. For the treatment of epileptic seizures, there is an ever-increasing demand for research into novel compounds with fewer toxicities and side effects.There are various reports on docking studies of benzodiazepine containing heterocycles viz. traizole, pyrimidine, quinazoline [3-4]. The objective of the present investigation is to identify new active compounds for the target protein, GABARAP using the structure-based virtual screening.

The docking process involves two main steps: predicting the ligand conformation as well as its positioning within the active site and assessment of the binding affinity. Both of these procedures are concerned with sample methods and scoring schemes, respectively. Molecular docking helps by identifying potential active sites in proteins, determining the optimum shape of the ligand receptor complex, and estimating the binding energy for different ligands to create more effective ligands. The interaction energy is calculated in terms of dock score. The strength of the noncovalent interaction between two molecules after they docked is thus predited from the score. Most scoring functions are physics-based molecular mechanics, with force fields that estimate the energy of the low_(negative) energy indicates a stable system thus, alikely binding interaction.The options of docking are; rigid docking which obatins suitable position for the ligand in receptor environment, flexible docking obtains a favored geometry for receptor-ligand interactions is obtained, full flexible docking obtains the ligand's torsion angles as well as the side chains of active site residues. Thus 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 [5-7].

2. MATERIALS AND METHODS

2.1 Hardware and Software

All Docking studies and conformational analysis were performed using the Molecular Design Suite (VLife MDS software package, version 4.3; from VLife Sciences, Pune, India) on Lenovo computer, i3 processor with XP operating system.

2.2 Structure Conformation Generation

The 2D structure draw application of Vlife2Ddraw was used to sketch compound structures, which were then converted to 3D structures. The AMBER approach was used to reduce and optimise all of the structures, with a root mean square gradient (RMS) of 0.01 kcal/mol and a 10,000 iteration limit. Monte Carlo was used to construct conformers for each structure using the AMBER force field approach. The drug –protein complex with lowest dock score was chosen for further investigation of the types of interactions. (Fig. 1 shows the conformers for which the lowest dock score was obtained).

2.3 Preparation of protein

The protein, Crystal Structure of the GABA(A) Receptor Associated Protein, GABARAP [1KJT] (PDB DOI**:** 10.2210/pdb1KJT/pdb) was downloaded from www.rcsb.org and energy minimization of the protein was done. During preprocessing all the bound water molecules, ligands, and cofactors were removed from the protein which was saved in .pdb format. The side chains that were not close to the binding cavity and did not participate in salt bridges were neutralized. 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 AMBER force field. The minimization was terminated after completion of 5,000 steps or when the energy gradient dropped below 0.05 kcal/mol.

2.4 Preparation of ligands

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

VlifeMDS software was used to prepare the ligand for docking. This procedure is outlined as follows.

- ✓ 2D structures of ligands were drawn in Chemdraw.
- ✓ 2D Structures were converted to 3D.

- ✓ Conformers were generated and optimized.
- ✓ Docking was done by GA based docking.
- ✓ Cavity # 1 was selected for docking and dock score was calculated.
- ✓ Docked Complex was optimized.
- ✓ Lowest dock score complex was further studied. (Fig. 1 shows the conformers for which the lowest dock score was obtained)

2.5 Docking Methodology [8-10]

VLifeMDS allows users to dock various ligands in protein binding sites of their choice. VLifeMDS allows for both stiff (no torsional flexibility for the protein and ligand) and flexible (torsional flexibility for the ligand with rigid protein) docking. Molecular docking is the computer technique of looking for a ligand that fits both physically and energetically into a protein's binding site. The target protein in this study was created using knowledge-based protein or homology modelling. To minimise the interaction energy between ligand and receptor protein, VLifeMDS employs genetic algorithms, Piecewise Linear Pairwise Potential (PLP), and Grid algorithms. The molecular docking scores identify the ligands that bind with similar orientation as observed with reference ligands. Most of the ligands make good docking poses in comparison to the reference ligand. Selective ligands bound deep within the binding pocket region, implying that their form is complementary to that of the reference ligands.

VlifeMDS version 4.3 was used to conduct the docking investigation. Through a series of hierarchical filters, the GA-based ligand docking with genetic algorithm approximated a systematic search of locations, orientations, and conformations of the ligand in the enzyme binding pocket. Because this is a Genetic Algorithm (GA)-based run, the minimum dock score of example may not be exactly replicable. Changing the various input parameters in the GA Parameters dialogue box (such as Number of Generations, Translation, and Rotation Limits, for example) can result in dock scoring energies within the desired range and improved docked ligand orientation as close to that of the co crystallised ligand as possible.

The Genetic Algorithm, which is part of the Molecular Design Suite (MDS), has been successfully used to dock inhibitors into the receptor's catalytic region and to connect the acquired binding score with inhibitory activity. Comparative docking experiments of developed compounds with known GABA agonist Lofendazam were carried out in this docking study. The obtained results were compared to the active site of 1KJT in terms of docking score. During the docking procedure, the system searches the docked ligand's conformational, orientational, and positional space, eliminating undesirable conformations using scoring, and then optimising the structure using the AMBER force field. GABA-A receptor associated protein is used to do batch docking of proposed ligands in MDS.

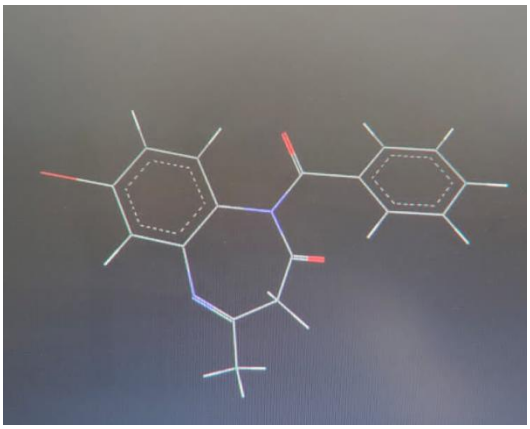
3. RESULTS AND DISCUSSION

3.1 Docking Results

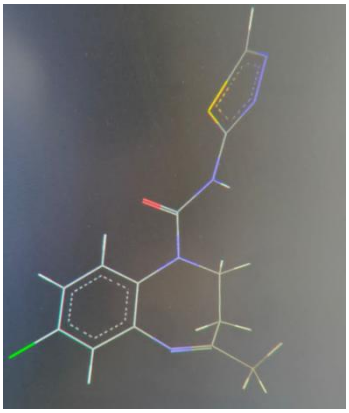
The molecular docking studies of all possible three dimensional confirmations of N^1-benzoyl/ N^1-(1,3,4-thiadiazol-2-yl amino acetyl) -7-substituted- 4-methyl-1,5-benzodiazepine-2-one were done using Vlife MDS Biopredicta module using cavity#1 against GABA-A receptor associated protein (1KJT) obtained from Protein Data Bank as target protein. The intermolecular interactions between the ligand and the protein (receptor) were investigated. It was processed by deleting the solvent molecule as well as correcting the structure with respect to bonds and the H-atoms.

Table 1 shows dock scores and binding energies of conformations of N^1-benzoyl-7-substituted- 4-methyl-1,5 -benzodiazepine-2-ones. Table 2 shows dock scores and binding energies of conformations of N^1-(1,3,4-thiadiazol-2-yl amino acetyl)-7-substituted-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 patterns of the docked molecules were compared with standard ligand, Lofendazam. Fig. 2 also depicts its intercations.

The Hydrophobic and Vander Waals interactions with residues at cavity#1 of 1KJT were studied for N^1-benzoyl-7-bromo-4-methyl-1,5-benzodiazepine-2-one (Compound 2; Conformer_C3); the residues PHE77A, LEU76A, VAL114A, GLU112A, ASP111A, SER110A, TYR109A, VAL44A interact with the molecules during the binding as shown in Fig. 3 and for the N^1-(1,3,4-thiadiazol-2-yl amino acetyl)-7-chloro-1,5-benzodiazepin-2-one (Compound 6; Conformer_C2); SER110A, ASP111A, GLU112A, VAL114A, ALA108A, TYR109A, PHE77A, LEU76A are the residues taking part in the interaction as shown in Fig. 4.



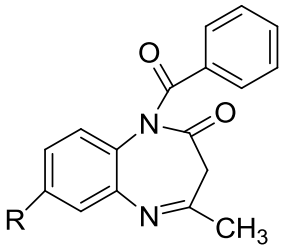
Compound 2; Conformer_C3



Compound 6; Conformer_C2

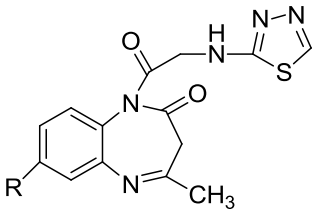
Fig. 1. Lowest dock score conformers

Table 1. Dock scores and binding energies of conformations of N^1-benzoyl-7-substituted- 4-methyl-1,5 -benzodiazepine-2-one



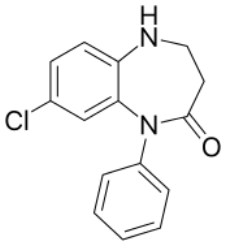
Conformation of compounds	R	dock score	ΔG (kcal/mol)
1_C4	-Cl	-5.0852	-15.2341
2_C3	-Br	-5.0915	-16.1032
3_C8	-F	-5.0640	-16.3924
4_C20	$-CH_3$	-5.0745	-12.5565
5_C1	$-OCH_3$	-4.5991	-16.6361
Lofendazam (Standard)	--	-4.7373	-17.3548

Table 2. Dock scores and binding energies of conformations of N^1-(1,3,4-thiadiazol-2-yl amino acetyl)-7-substituted-1,5-benzodiazepin-2-one



Conformation of compounds	R	dock score	ΔG (kcal/mol)
6_C2	-Cl	-4.653290	-23.4524
7_C2	-Br	-4.535921	-19.5515
8_C5	-F	-4.358920	-24.5772
9_C2	$-CH_3$	-4.614051	-18.9478
10_C4	$-OCH_3$	-4.162892	-30.1304

Standard : **Lofendazam**



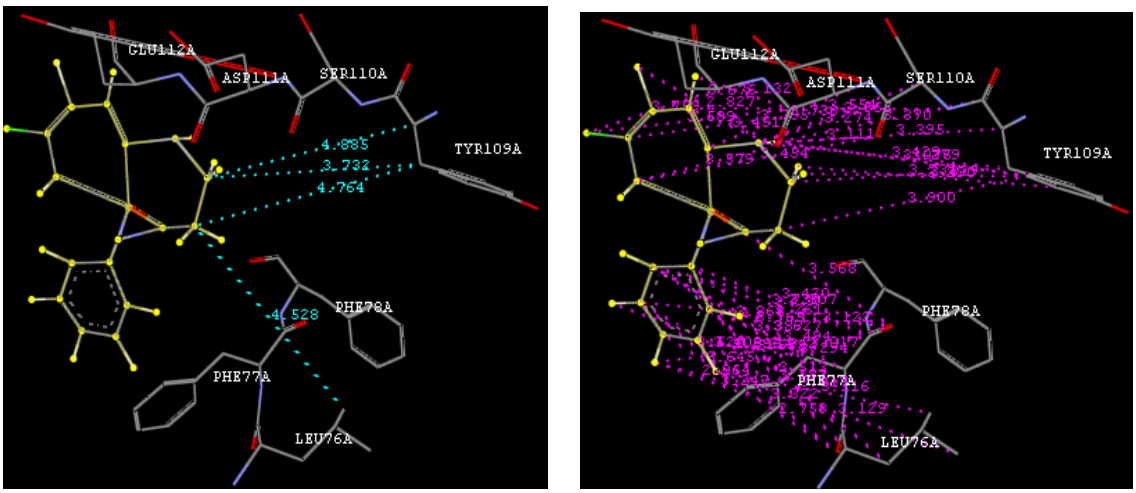


Fig. 2. Binding interactions of lofendazam with Cavity # 1 of 1KJT

(A) Blue colour dotted lines indicate hydrophobic interactions with the residues TYR109A and LEU76A
(B) Magenta colour dotted lines indicates Van der 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 2

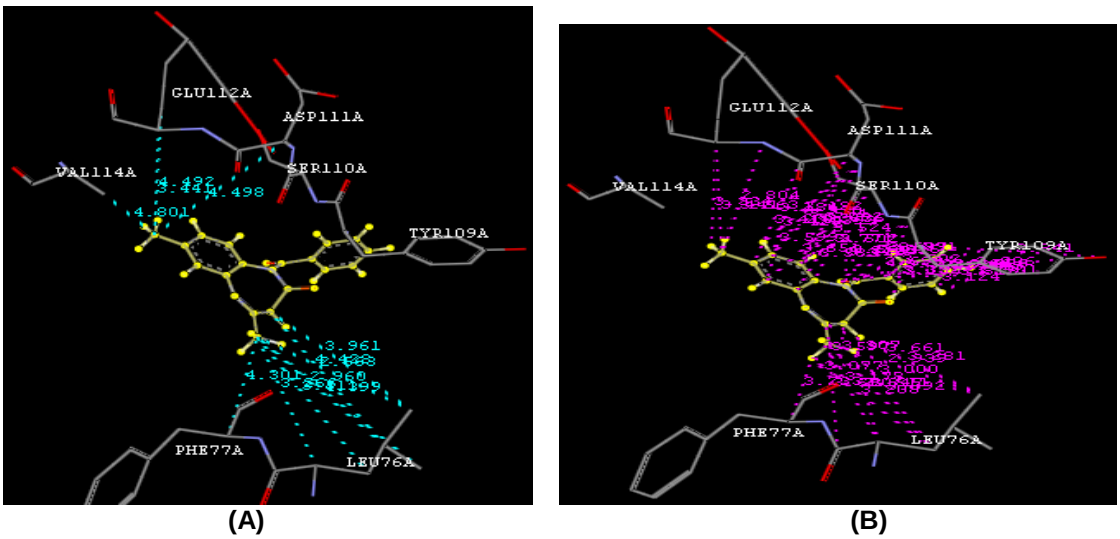
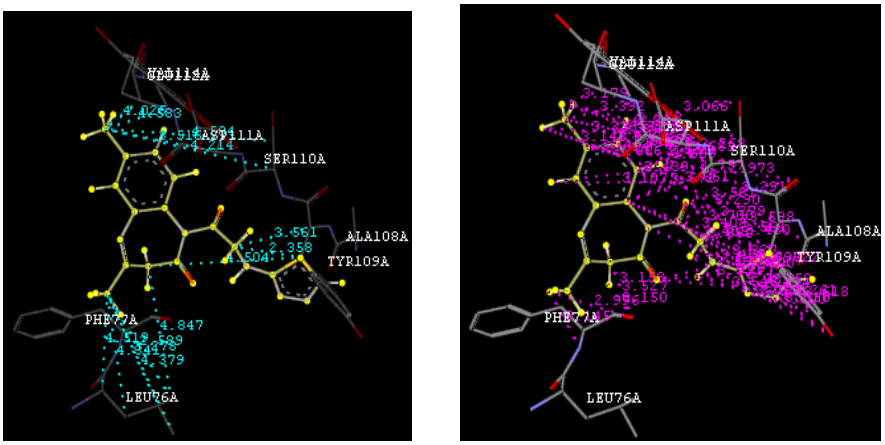


Fig. 3. Binding interactions of Compound 2_C3 with Cavity # 1 of 1KJT

(A) Blue colour dotted lines indicate hydrophobic interactions with residues PHE77A, LEU76A, Val114A, GLU112A, and ASP111A
(B) Magenta colour dotted lines indicates Van der Waals interactions with the residues VAL44A, ASP111A, SER110A, TYR109A, LEU76A, PHE77A and GLU112A.

Compound 6



(A) **(B)**

Fig. 4. Binding interactions of Compound 6_C2 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 molecular docking scores identified the ligands that bind with similar orientation as observed with standard ligand. Most of the ligands make good docking poses in comparison to the standard ligand. Selective ligands docked deeply within the binding pocket region suggesting their shape complementarily with the standard ligand. The Vander Walls, H-bonding and hydrophobic interactions of the ligands with receptor proteins were investigated, revealing a new set of data on the similarity of amino acid residues invloved in the intercation of the standarad, Lofendazam and the modelled compounds at the Cavity # 1 of 1KJT. It was found that PHE77A, LEU76A, GLU112A, ASP111A, SER110A, TYR109A are comparable amino acid resiudes among those invloved in the interaction with 1KJT. Thus the docking simulation suggested that the modifications in the series of N^1-benzoyl/ N^1-(1,3,4-thiadiazol-2-yl amino acetyl) -7-substituted- 4-methyl-1,5-benzodiazepine-2-one resulted in identification of ligands with better binding potential. The newly designed molecules viz. N^1-benzoyl-7- bromo- 4-methyl-1,5-benzodiazepine-2-one, N^1-(1,3,4-thiadiazol-2-yl amino acetyl) -7-chloro- 4-methyl-1,5-benzodiazepine-2-one can be prioritized for synthesis and can be studied for Pharmacological screeing.

4. CONCLUSION

The docking simulation suggested that the Vander Walls, hydrophobic interactions are responsible for forming the stable complex of the ligands with the GABA(A) Receptor Associated Protein (1KJT). The molecular docking studies resulted in highlighting the ligands and their conformations that fit efficiently into the cavity of target protein. N^1-benzoyl-7-bromo-4-methyl-1,5-benzodiazepine-2-ones (Compound 2; Conformer_C3) and N^1-(1,3,4-thiadiazol-2-yl amino acetyl)-7-chloro-1,5-benzodiazepin-2-one (Compound 6; Conformer_C2) are the conformations that fit best into the cavity of GABA(A) Receptor Associated Protein.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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