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DESIGN AND MOLECULAR DOCKING STUDIES OF SOME 1,3,4-THIADIAZOLE DERIVATIVES

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ABSTRACT: In present investigation of some ethyl1-((5-amino-1, 3, 4-thiadiazol-2-yl) methyl) - 5 - ethyl-2, 6-dimethyl – 4 - phenyl-1, 4-dihydro pyridine-3-carboxylate are designed and docked active site of cavity 1# of open channel voltage gated calcium channel protein (3DVE). The compounds evaluated in silico (docking) to distinguish their hypothetical binding mode using the X-ray crystal structure of Ca^{2+}/CAM-CaV2.2 IQ domain complex 3DVE obtained from protein data bank as target protein Respectively. In this docking studies carried out the comparative docking experiments of designed compounds with known calcium blockers Ethosuximide, gabapentine with dock score calculated -4.9318,-4.6489 respectively. Obtained results were evaluated in terms of dock score into the active site of receptor. One of the conformers of compound Cl 123(C1)and AN 123 (C15),CH=CH 123 (C6),Fur 123 (C9) found to have lowest dock scores-3.2496 and -3.1749 , -2.8439, - 2.6359 respectively and said to have more affinity for active site of Ca^{2+}/CAM-CaV2.2 IQ domain complex receptor than other molecules. More the negative value of the energy of binding the better is affinity of the molecule to the receptor.

INTRODUCTION: 1,3,4-Thiadiazole have wide spectrum of biological activities including anticonvulsant activity. In addition to presently available anticonvulsant drugs viz. There is need to develop such new heterocycles with the expectation to have more anticonvulsant potential. There is an ever increasing need of research into newer molecules with lesser toxicities and side effects for treating epileptic seizures [1, 2].

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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 interms 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 of the low (negative) energy indicates a stable system and thus alikely 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 afavored geometry for receptor-ligand interactions is obtained, full flexible docking where the ligand is flexed via its torsion angles as well as the side chain of active site residues [3, 4].

MATERIALS AND METHODS:

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)

Structure Conformation Generation: Structures of compounds were sketched using the 2D structure draw application Vlife2Ddraw and converted to 3D structures. All the structures were minimized and optimized with the AMBER method taking the root mean square gradient (RMS) of 0.01 kcal/molA° and the iteration limit to 10,000. Conformers for each structure were generated using Monte Carlo be applying AMBER force field method and least energy conformer was selected for further study.

Preparation of protein: The PDB structures (www.rcsb.org) [3DVE] were downloaded and energy minimization of the protein complex. All the bound water molecules, ligands, and cofactors were removed (preprocess) from the proteins which were 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 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 the1, 3, 4-thiadizolesligands were sketched using built Vlife2Ddraw taken in.mol2 format. Converts it into 3D structure and perform 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.
- ✓ Lowest energy conformer was selected and used for docking.
- ✓ Docking was done by GA based docking.
- ✓ Cavity 7 was selected for docking.
- ✓ Dock score was calculated.
- ✓ Docked Complex was optimized.

Docking methodology: Docking study was performed on VlifeMDS version 4.3 on Lenovo computer, i3 processor with XP operating system. The GA-based ligand docking with genetic algorithm approximated a systematic search of positions, orientations, and conformations of the ligand in the enzyme binding pocket via a series of hierarchical filters. The minimum dock score of example may not be exactly reproducible because this is a Genetic Algorithm (GA) based run. However changing the different input parameters in 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 co crystallized ligand as possible.

Genetic Algorithm implemented in Molecular design suite (MDS) has been successfully employed to dock inhibitors into catalytic site of the receptor and to well correlate the obtained binding score with inhibitory activities of compounds. In this docking studies carried out the comparative docking experiments of designed compounds with known calcium blockers Ethosuximide, gabapentine respectively. Obtained results were evaluated in terms of docking score in to the active site of receptor **Fig. 1.** During the docking process the system search of conformational, orientational and positional space of the docked ligand and eliminating the unwanted conformation using the scoring, the structure available on PDB, using AMBER force field then is optimized. Batch docking in MDS of designed ligands is performed with Ca^{2+}/CAM-CaV2.2 IQ domain complex.

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 as well as 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 genetic algorithm, Piecewise Linear Pair wise Potential (PLP) and Grid algorithms to minimize the interaction energy between ligand and the receptor protein.

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 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 novel set of information.

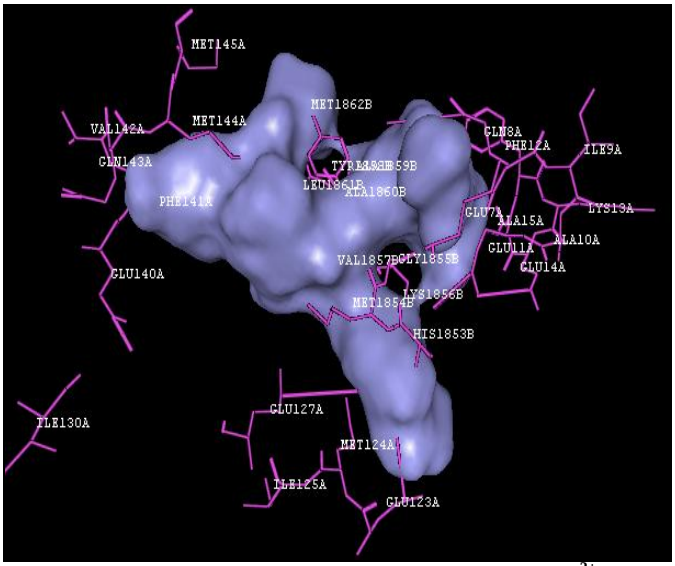


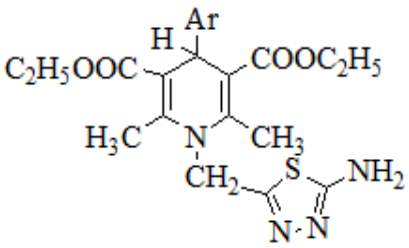
FIG. 1: THE OF ACTIVE SITE OF RESIDUES Ca^{2+}/CAM-CaV2.2 IQ DOMAIN COMPLEX RECEPTOR [3DVE] Cavity#1

The residues of active site of Ca^{2+}/CAM-CaV2.2 IQ domain complex receptor Cavity#1 are GLU7A, GLN8A, ILE9A, ALA10A, GLU11A, PHE12A, LYS13A, GLU14A, ALA15A, GLU123A, MET124A, ILE125A, GLU127A, ILE130A, GLU140A, PHE141A, VAL142A, GLN143A, MET144A, MET145A, HIS1853B, MET1854B, GLY1855B, LYS1856B, VAL1857B, TYR1858B, ALA1859B, ALA1860B, LEU1861B, and MET1862B.

The molecular docking studies of all possible three dimensional confirmations of 1,3,4-Thiadiazole containing1,4-dihydropyridines were done using Vlife MDS Biopredict amodule using cavity#1 of open channel voltage gated calcium channel protein (3DVE) and Crystal structure of Ca2+/CaM-CaV2.2 IQ domain complex obtained from Protein Data Bank as target proteins respectively. The intermolecular interactions in between the ligand and the protein (receptor) were investigated. It is 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 ethyl1-((5-amino-1, 3, 4-thiadiazol-2-yl) methyl)-5-ethyl-2,6-dimethyl - 4 - phenyl - 1,4 - dihydro pyridine-carboxylate Some of the molecules for which the confirmations shows lowest dock scores were selected to study their binding interaction with the cavity#1 of the receptor.

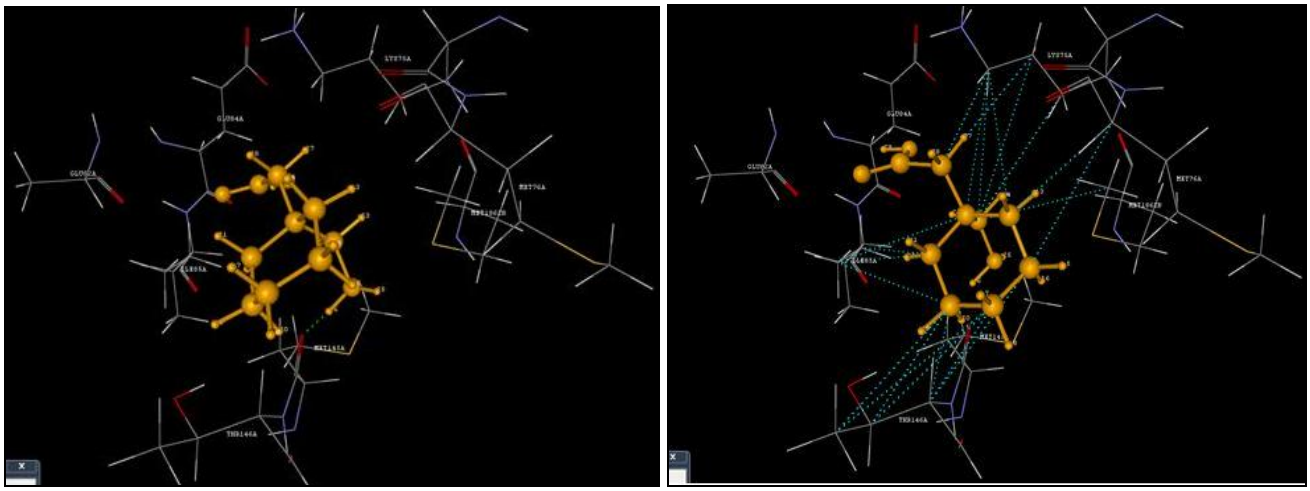
The Hydrophobic and Vander Waals interactions, hydrogen interaction with residues at cavity#1 of 3DVE were studied for Compound Cl 123 (Confirmor_C1)**;** the residues ASP118A, SER101A, ALA102A HIS107A, VAL121A, THR117A interact with the molecules during the binding as shown in **Fig. 6** and **7** and for the compound AN 123 (Confirmor_C15); ARG106A, ASP118A, HIS107A, ALA103A are the residues taking part in the interaction as shown in **Fig. 8**. For the Compound CH=CH123 (Conformer_C6); residues ARG106A, ALA102A, ASP118A, SER101A interact with the molecule during binding as shown in **Fig. 9** and for the compound Fur 123 (Conformer_C9) residues ARG106A, HIS107A, ASP118A, ALA 103A interact with the molecule during binding as shown in **Fig. 10.** The binding pattren of the docked molecules has been compared with few standard ligands like Ethosuximide and Gabapentin, their intercations are also shown in **Fig. 2** & **3** (for Ethosuximide**)** and in **Fig. 4** and **5 (**for Gabapentin)

TABLE 1: DOCKINGSCORESANDBINDINGENERGIESOFCONFORMATIONSOFETHYL1-((5-AMINO-1, 3, 4-THIADIAZOL - 2-YL) METHYL)-5-ETHYL-2, 6-DIMETHYL-4-PHENYL-1, 4-DIHYDROPYRIDINE-3-CARBOXYLATE



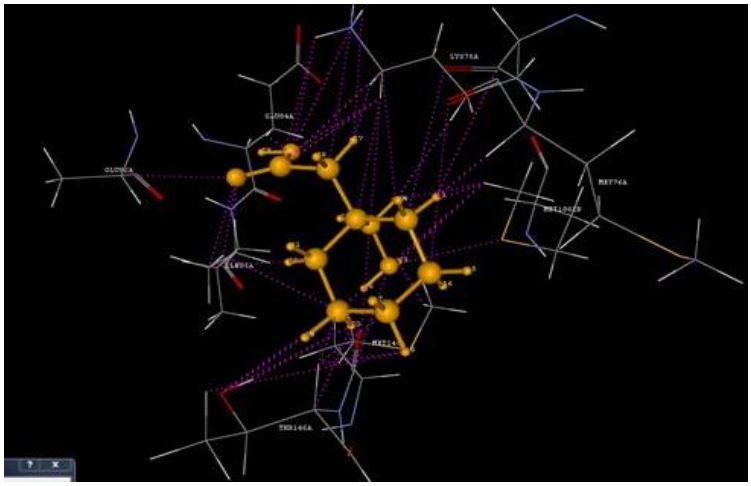
Conformation of compounds	Ar	Dock score	ΔG (Kcal/mol)
BZ123		- 2.146	-2075.05
N123		-2.374	-2075.06
Cl123		-3.249	-2073.43
OH123		-1.794	-2075.049
AN123		-3.174	-2075.05
Pcl123		-0.317	-2075.04
Furfural123		-2.635	-2075.047
CH=CH123		-2.843	-2075.3
F123		-2.117	-2075.05
Chr123		-2.359	-2097.58

Standard 1: Ethosuximide



(A) (B)

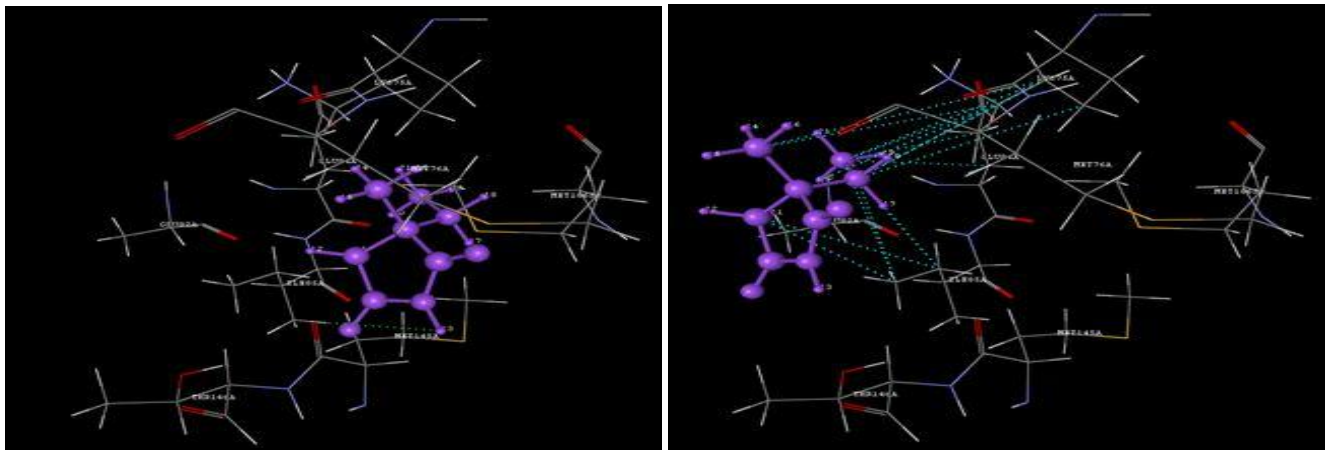
FIG. 2: BINDING INTERACTIONS OF ET 2_ C1WITH CAVITY # 1 OF 3DVE (Blue colour dotted lines indicate hydrophobic interactions and Green colour dotted lines indicates hydrogen interactions) It shows the Hydrogen (A) and Hydrophobic (B) interactions with cavity # 1 of Crystal structure of Ca2+/CaM-CaV2.2IQ domain complex [3DVE]. The ligand showed hydrophobic interaction with the residues LYS75A, GLU84A, ILE85A and Hydrogen interactions with the residues MET145A.



(C)

FIG. 3: VANDER WAALS INTERACTION OF ETHOSUXIMIDE WITH ACTIVE SITE OF THE RECEPTOR 3DVE. The ligand showed Vander Waals interaction with the residues LYS75A, GLU84A, ILE85A, MET145A, THR146A, and MET1862B

Standard 2: Gabapntine



(A) **(B)**

FIG. 4: BINDING INTERACTIONS OF ga3_ C4WITH CAVITY # 1 OF 3DVE Blue colour dotted lines indicate hydrophobic interactions and Green colour dotted lines indicates hydrogen interactions)

Figure 4 shows the Hydrogen (A) and Hydrophobic (B) interactions with cavity # 1 of Crystal structure of Ca2+/CaM-CaV2.2IQ domain complex [3DVE]. The ligand showed hydrophobic interaction with the residues LYS75A, THR146A, MET1862B, ILE85A and Hydrogen interactions with the residues MET145A

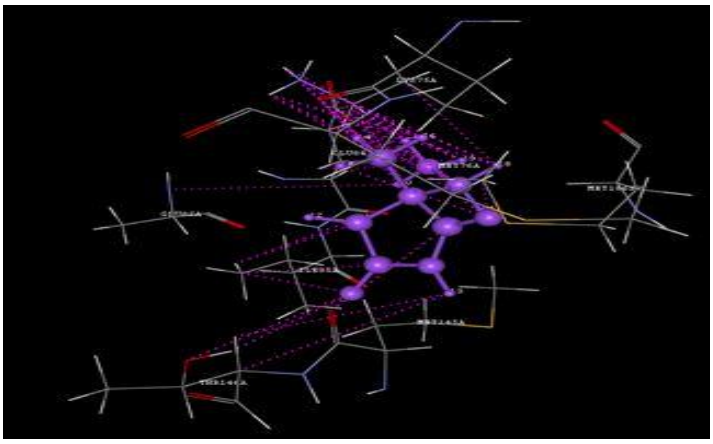
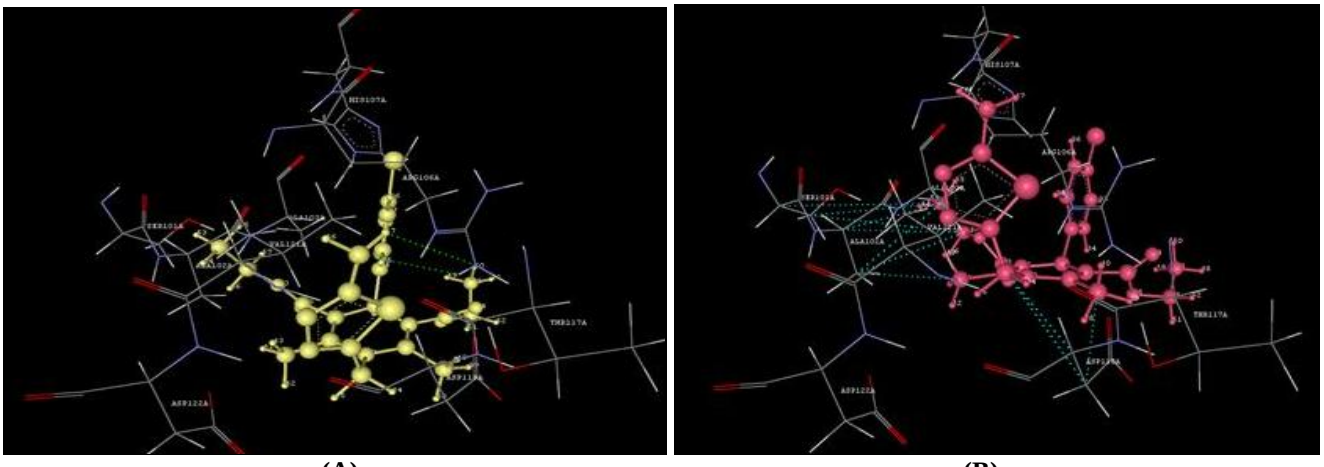


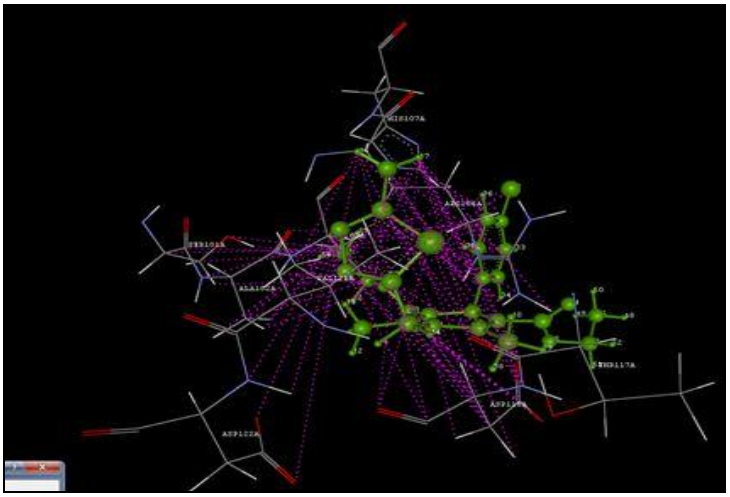
FIG. 5: VANDER WAALS INTERACTION OF GABAPENTIN WITH ACTIVE SITE OF THE RECEPTOR 3 DVE.

The ligand showed Vander Waals interaction with the residues LYS75A, GLU84A, ILE85A, MET145A, THR146A, and MET1862B, MET76A.



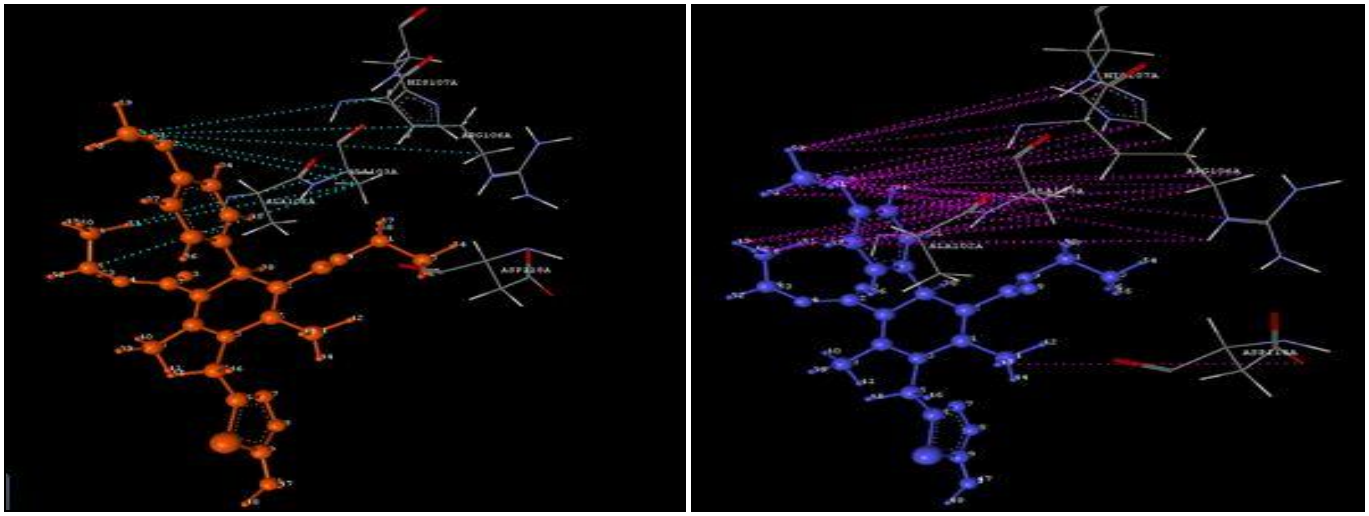
(A) **(B)**

FIG. 6: BINDING INTERACTIONS OF CL_ C1WITH CAVITY # 1 OF 3DVE (Blue colour dotted lines indicate hydrophobic interactions and Green colour dotted lines indicates hydrogen interactions)



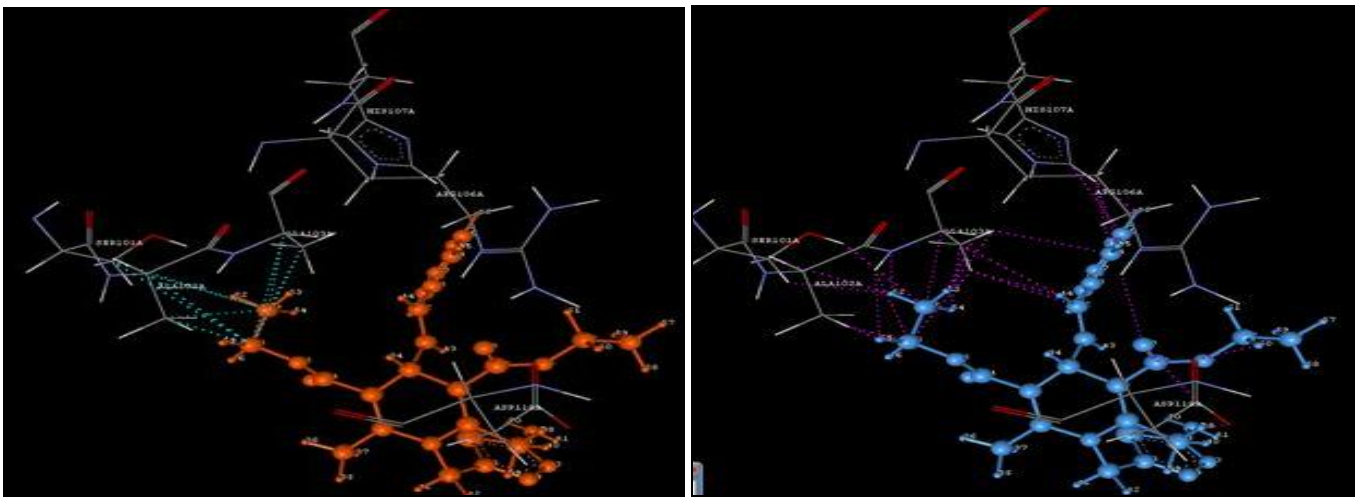
(C)

FIG. 7: VANDERWAALS INTERACTION OF LIGAND WITH RECEPTOR 3DVE



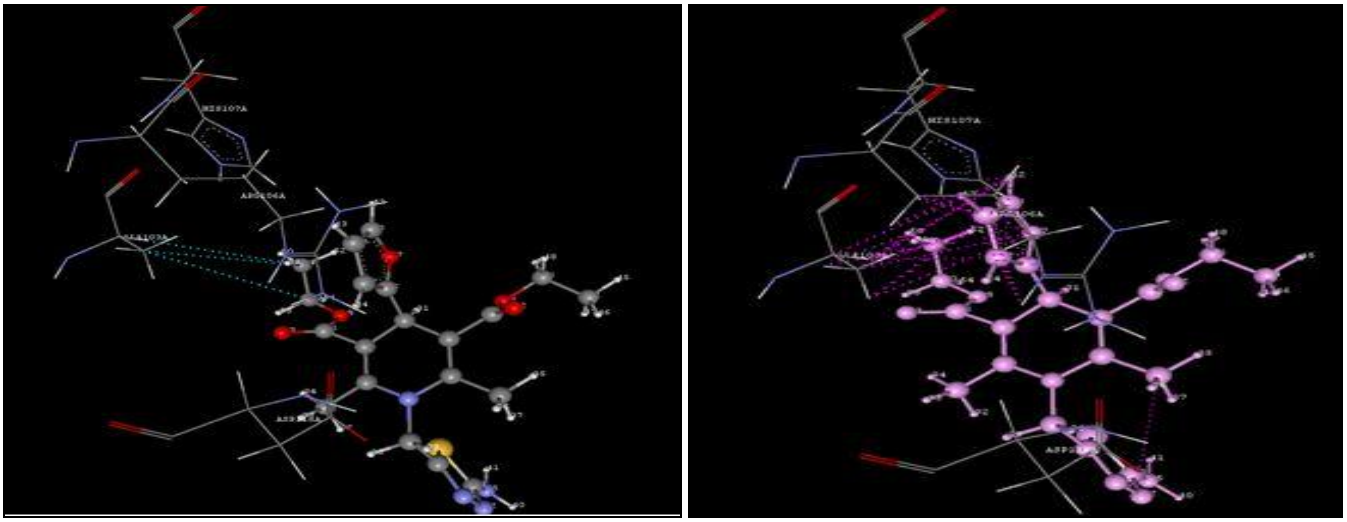
(A) **(B)**

FIG. 8: BINDING INTERACTIONS OF AN 123_C15WITH CAVITY # 1 OF 3DVE (Blue colour dotted lines indicate hydrophobic interactions and Magenta colour dotted lines indicates Vander Waals interactions)



(A) **(B)**

FIG. 9: BINDING INTERACTIONS OF CH=CH 123_C6 WITH CAVITY # 1 OF 3DVE (Blue colour dotted lines indicate hydrophobic interactions and Magenta colour dotted lines indicates Vander Waals interactions)



(A) **(B)**

FIG. 10: BINDING INTERACTIONS OF FUR 123_C9 WITH CAVITY # 1 OF 3DVE (Blue colour dotted lines indicate hydrophobic interactions and Magenta colour dotted lines indicates Vander Waals interactions)

CONCLUSION: The docking simulation suggested that the modifications in the series that results in better binding potential. The Vander walls, hydrophobic, hydrogen interactions are responsible for forming the stable compound of the ligands with ligands with receptor. The molecular docking studies resulted in highlighting the ligands and their conformations which efficiently fit into the cavity of target protein. For the compounds Cl123, AN123, CH=CH123, Fur123 the conformation fitted best into the cavity with lowest dock score is indicated in **Table 1** .

COMPETING INTERESTS: The author(s) declare(s) no conflict of interest.

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