



Design and Molecular Docking Studies of Some 1,3,4-Oxadiazole Derivatives

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ABSTRACT

In the present investigation some N³-(5-aryl/substituted aryl)-1,3,4-oxadiazole-2-yl-methyl-5,5 disubstituted-2,4-imidazolidinedione derivatives and 2-(3,5-dicarboethoxy-2,6-dimethyl-4-substituted-1,4-dihydropyridin-1-yl-methyl)-5-substituted-1,3,4-oxadiazoles are designed and docked in to active site of Cavity # 1 of open channel voltage gated Sodium channel protein (4F4L) and Crystal structure of Ca²⁺/CaM-CaV2.1IQ domain complex (3DVM) obtained from Protein Data Bank as target proteins respectively. Further In-Silico docking analysis of designed ligands is performed to predict binding mode, orientations and affinity and is compared with the standards as Phenytoin for sodium channel protein and Ethosuximide for calcium channel protein. One of the conformation of the compounds R1211 (C-3) and DHP E06 (C-5) found to have lowest dock scores -5.34, -2.13 respectively and said to possess more affinity for receptor than other molecules.

Keywords: 1,3,4-oxadiazole, Dock score, Docking analysis.

INTRODUCTION

1,3,4-oxadiazoles have wide spectrum of biological activities including anticonvulsant activity. In addition to presently available anticonvulsant drugs viz. Hydantoins, Succinimides, Valproates, 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.¹⁻³

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 of dock score, scoring functions are fast approximate mathematical methods used to predict the strength of the non-covalent 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 pose; a low (negative) 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 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 chain of active site residues.⁴⁻⁵

MATERIALS AND METHODS

Hardware and Software

All Docking studies and conformational analysis were performed using the Molecular Design Suite (VLife MDS software package, version 4.2; 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/mol Å⁰ and the iteration limit to 10,000. Conformers for each structure were generated using Monte Carlo by applying AMBER force field method and least energy conformer was selected for further study.

Preparation of protein

The PDB structures [4F4L] and [3DVM] 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.⁶

Preparation of ligands

Structures of the 1,3,4-oxadiazole ligands 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.

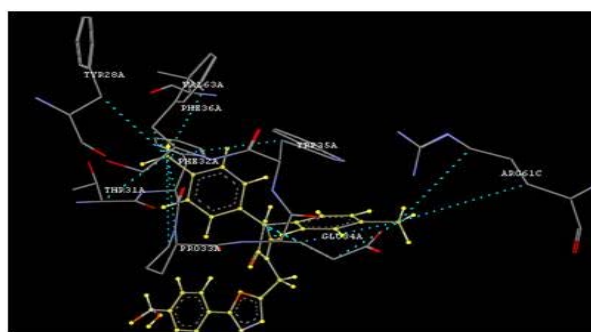
Docking methodology

Docking study was performed on VlifeMDS version 4.2 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. To pre-asses the anticonvulsant behavior of designed ligands on structural basis, docking studies were carried out and scoring functions, their binding affinities and orientation of designed compounds having blocking property of active site of the receptors. Genetic Algorithm implemented in Molecular design suite (MDS) has been successfully employed to dock the ligands into catalytic site of the receptor and to well correlate the obtained binding score with inhibitory activities of compounds. In

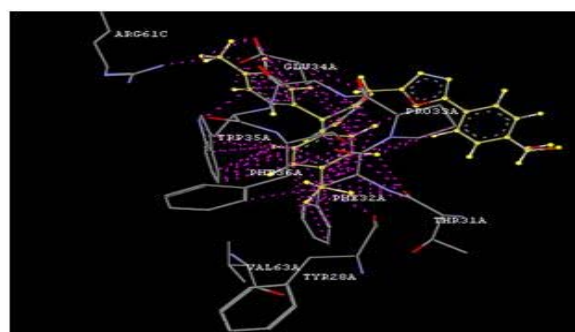
these docking studies, the comparative docking experiments of designed compounds with known Sodium channel blocker, Phenytoin and Calcium channel blocker, Ethosuximide was also carried out.^{7,9}

RESULTS AND DISCUSSION

The molecular docking studies of all possible three dimensional confirmations of 1,3, 4-oxadiazoles containing hydantoin and 1,4-dihydropyridines were done using V life MDS Biopredicta module using cavity # 1 of open channel voltage gated Sodium channel protein (4F4L) and Crystal structure of Ca²⁺/CaM-CaV2.1IQ domain complex (3DVM) 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 Docking scores and binding energies of conformations of N³-(5-aryl/ substituted aryl-1,3,4-oxadiazole-2-yl-methyl-5,5-disubstituted-2,4- imidazolidine dione derivatives. 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 with residues at cavity #1 of 4F4L were studied for Compound R1211 (Confirmor_C3) as shown in Figure 1, the residues ARG, TRP, TYR, THR, PRO, GLU, PHE interact with the molecules during the binding and for the compound N1211 (Confirmor_C2) as shown in Figure 2; GLU, TRP, PRO, PHE are the residues taking part in the interaction.

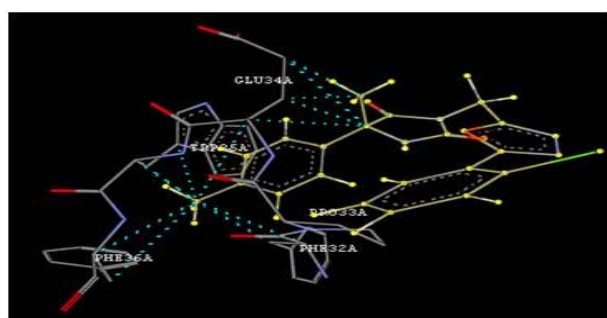


Hydrophobic interactions



Vander Waals interactions

Figure 1: Binding interaction of Compound R1211 (Confirmor_C3) with cavity # 1 of open channel voltage gated Sodium channel protein (4F4L)

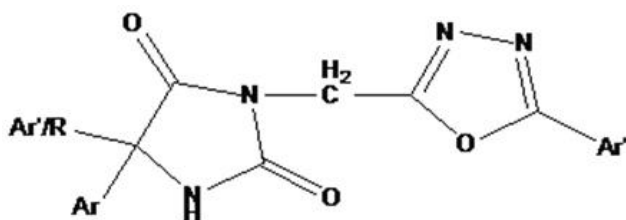


Hydrophobic interactions

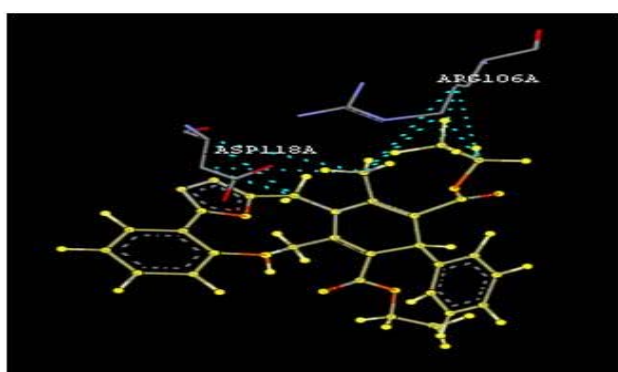


Vander Waals interactions

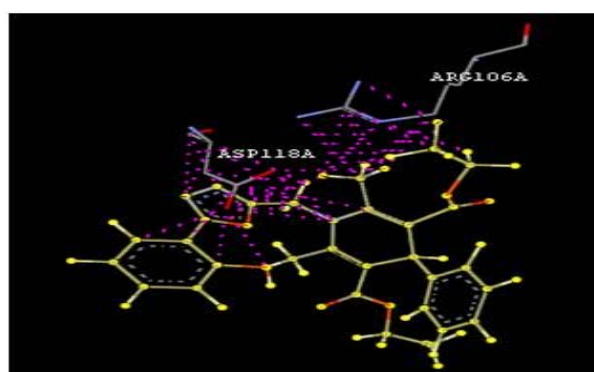
Figure 2: Binding interaction of Compound N1211 (Confirmor_C2) with cavity # 1 of open channel voltage gated Sodium channel protein (4F4L)

Table 1: Docking scores and binding energies of conformations of N³-(5-aryl/substituted aryl-1,3,4-oxadiazole-2-yl-methyl-5,5-disubstituted-2,4-imidazolidinedione derivatives

Conformer *	Ar	Ar'/R	Ar''	Dock Score	Binding energy ΔG (Kcal/mol)
Phenytoin_C6	-C ₆ H ₅	-C ₆ H ₅	-	-4.6637	-254.46
R1211_C3	<i>p</i> -CH ₃ -C ₆ H ₄	<i>p</i> -CH ₃ -C ₆ H ₄	<i>p</i> -NO ₂ -C ₆ H ₄	-5.3485	-29.49
L1211_C5	-C ₆ H ₅	-C ₆ H ₅	<i>o</i> -OH-C ₆ H ₄	-5.2811	216.09
V1214_C2	<i>p</i> -Cl-C ₆ H ₄	-CH ₃	<i>p</i> -NO ₂ -C ₆ H ₄	-5.2508	108.99
V1215_C1	<i>p</i> -Cl-C ₆ H ₄	-CH ₃	<i>o</i> -Cl-C ₆ H ₄	-5.1921	38.77
V1217_C2	-C ₆ H ₅	-CH ₃	-C ₄ H ₃ O	-5.0403	-50.30
N1211_C2	<i>p</i> -CH ₃ -C ₆ H ₄	-CH ₃	<i>o</i> -Cl-C ₆ H ₄	-5.0047	-237.58
C1211_C2	-C ₆ H ₅	-C ₆ H ₅	<i>o</i> -Cl-C ₆ H ₄	-5.0026	-210.75
V1220_C4	-C ₆ H ₅	-CH ₃	<i>o</i> -OH-C ₆ H ₄	-4.9645	49.09
O1211_C1	<i>p</i> -OCH ₃ -C ₆ H ₄	-CH ₃	<i>o</i> -OH-C ₆ H ₄	-4.8413	-25.78
V1219_C2	-C ₆ H ₅	-CH ₃	<i>o</i> -Cl-C ₆ H ₄	-4.8337	-19.40
V1221_C5	-C ₆ H ₅	-CH ₃	<i>p</i> -NO ₂ -C ₆ H ₄	-4.8303	-16.60
Y1211_C5	-C ₆ H ₅	-C ₆ H ₅	-C ₆ H ₅	-4.8191	26.18
V1213_C3	<i>p</i> -Cl-C ₆ H ₄	-CH ₃	-C ₄ H ₃ O	-4.7619	-231.97
V1212_C7	<i>p</i> -Cl-C ₆ H ₄	-CH ₃	-C ₆ H ₅	-4.7599	-46.29
U1211_C6	-C ₆ H ₅	-C ₆ H ₅	<i>p</i> -NO ₂ -C ₆ H ₄	-4.7297	39.95
S1211_C3	<i>p</i> -CH ₃ -C ₆ H ₄	-CH ₃	<i>p</i> -NO ₂ -C ₆ H ₄	-4.7271	104.46
Z1211_C3	<i>p</i> -CH ₃ -C ₆ H ₄	<i>p</i> -CH ₃ -C ₆ H ₄	-C ₆ H ₅	-4.7104	-189.34
W1211_C6	<i>p</i> -CH ₃ -C ₆ H ₄	-CH ₃	-C ₆ H ₅	-4.6642	55.99
P1211_C2	<i>p</i> -CH ₃ -C ₆ H ₄	-CH ₃	-C ₄ H ₃ O	-4.5987	38.08
M1211_C4	<i>p</i> -CH ₃ -C ₆ H ₄	<i>p</i> -CH ₃ -C ₆ H ₄	-C ₄ H ₃ O	-4.5464	157.33
V1222_C2	-C ₆ H ₅	-CH ₃	-C ₆ H ₅	-4.4584	133.37
V1211_C7	<i>p</i> -Cl-C ₆ H ₄	-CH ₃	<i>p</i> -OCH ₃ -C ₆ H ₄	-4.4279	60.40
X1211_C4	<i>p</i> -OCH ₃ -C ₆ H ₄	-CH ₃	-C ₆ H ₅	-4.4223	-28.59
V1218_C2	-C ₆ H ₅	-CH ₃	<i>p</i> -OCH ₃ -C ₆ H ₄	-4.4046	97.22

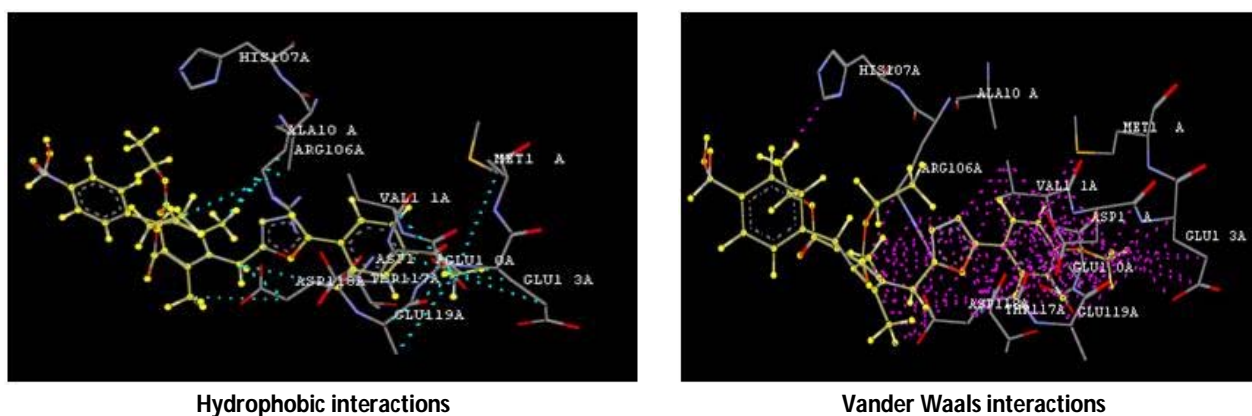


Hydrophobic interactions



Vander Waals interactions

Figure 3: Binding interaction of Compound DHP A05 (Conformer_C2) with cavity # 1 of Crystal structure of Ca²⁺/CaM-CaV2.1IQ domain complex (3DVM)

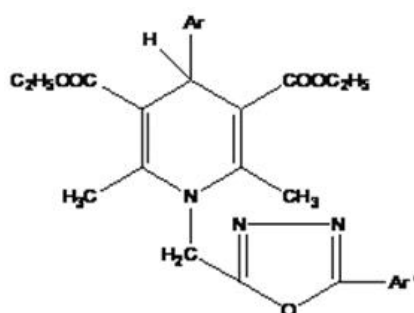


Hydrophobic interactions

Vander Waals interactions

Figure 4: Binding interaction of Compound DHP C02 (Confirmor_C1) with cavity # 1 of Crystal structure of Ca²⁺/CaM-CaV2.1IQ domain complex (3DVM)

Table 2: Docking scores and binding energies of conformations of 2-(3,5-dicarboethoxy-2,6-dimethyl-4-substituted-1,4-dihydropyridin-1-yl-methyl)-5-substituted-1,3,4-oxadiazoles



Conformer *	Ar	Ar'	Dock score	Binding energy ΔG(Kcal/mol)
Ethosuximide (3-ethyl-3-methylpyrrolidine-2,5-dione)			-4.5969	-333.82
DHPE06_C5	-C ₄ H ₃ O	-C ₄ H ₃ O	-2.1375	192.28
DHPD06_C3	<i>o</i> -Cl-C ₆ H ₄	-C ₄ H ₃ O	-1.9981	93.22
DHPD04_C3	<i>o</i> -Cl-C ₆ H ₄	<i>o</i> -Cl-C ₆ H ₄	-1.7782	100.28
DHPB04_C1	<i>p</i> -OCH ₃ -C ₆ H ₄	<i>o</i> -Cl-C ₆ H ₄	-1.6152	-8.64
DHPA06_C4	-C ₆ H ₅	-C ₄ H ₃ O	-1.3292	-52.24
DHPA04_C4	-C ₆ H ₅	<i>o</i> -Cl-C ₆ H ₄	-1.3281	-64.25
DHPE03_C2	-C ₄ H ₃ O	<i>p</i> -NO ₂ -C ₆ H ₄	-1.3009	-69.77
DHPA05_C2	-C ₆ H ₅	<i>o</i> -OH-C ₆ H ₄	-1.2958	-165.97
DHPB02_C5	<i>p</i> -OCH ₃ -C ₆ H ₄	<i>p</i> -OCH ₃ -C ₆ H ₄	-1.0585	79.05
DHPD01_C2	<i>o</i> -Cl-C ₆ H ₄	C ₆ H ₅	-1.0560	-391.37
DHPA01_C6	C ₆ H ₅	C ₆ H ₅	-0.9296	-43.07
DHPB01_C5	<i>p</i> -OCH ₃ -C ₆ H ₄	C ₆ H ₅	-0.7712	30.96
DHPE04_C6	C ₄ H ₃ O	<i>o</i> -Cl-C ₆ H ₄	-0.6638	-592.74
DHPA03_C1	-C ₆ H ₅	<i>p</i> -NO ₂ -C ₆ H ₄	-0.2058	-84.73
DHPE01_C5	-C ₄ H ₃ O	-C ₆ H ₅	-0.1278	-807.32
DHPE02_C4	-C ₄ H ₃ O	<i>p</i> -OCH ₃ -C ₆ H ₄	-0.1129	24.66
DHPC05_C3	<i>p</i> -NO ₂ -C ₆ H ₄	<i>o</i> -OH-C ₆ H ₄	-0.0573	118.67
DHPC01_C2	<i>p</i> -NO ₂ -C ₆ H ₄	-C ₆ H ₅	0.4370	-131.06
DHPC02_C1	<i>p</i> -NO ₂ -C ₆ H ₄	<i>p</i> -OCH ₃ -C ₆ H ₄	1.2815	-497.68
DHPD03_C4	<i>o</i> -Cl-C ₆ H ₄	<i>p</i> -NO ₂ -C ₆ H ₄	1.3210	19.30
DHPC03_C3	<i>p</i> -NO ₂ -C ₆ H ₄	<i>p</i> -NO ₂ -C ₆ H ₄	2.3585	-55.14

Table 2 shows Docking scores and binding energies of 2-(3,5-dicarboethoxy-2,6-dimethyl-4-substituted-1,4-dihydropyridin-1-yl-methyl)-5-substituted-1,3,4-oxadiazoles. Some of the 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 with residues at cavity #1 of 3DVM were studied for Compound DHP A05 (Confirmor_C2) as shown in Figure 3, the residues ARG, ASP interact with the molecules during the binding and for the compound DHP C02 (Confirmor_C1) as shown in Figure 4; GLU, HIS, ARG, ASP, VAL, ALA are the residues taking part in the interaction.

Validation of the docking protocol

The prediction of the potency or affinity of the ligand to the receptor done by considering some parameters such as dock score, the energy of binding of molecules with the Sodium channel protein or Calcium channel protein, Vander-walls interactions, hydrophobic interactions and rare charge interactions. The more the negative value of the energy of binding the better is affinity of the molecule to the receptor. The more the Vander-walls interactions shows that the ligand structure is having more number of bulky groups due to which Vander-walls interactions can be formed. If the hydrophobic interactions are more it shows that the ligand is having groups that can participate in the hydrophobic interactions. If the charge interactions are presents it helps finding more appropriate binding and so shows greater affinity to the receptor, contributing more potency.

CONCLUSION

The docking simulation suggested that the modifications in the series that results in better binding potential. The Vander-walls, hydrophobic 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 R1211, N1211, DHPE06, DHPA05, DHPC02 the conformation fitted best into the cavity with lowest dock score is indicated in Table 1 and Table 2.

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