Journal of Applied Pharmaceutical Science Vol. 8 (01), pp. 021-028, January, 2018
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2018.8104
ISSN 2231-3354

Site Partition Enhanced Shape Based Docking and Molecular Dynamics Studies of G-Protein Coupled Receptor Acting Natural Ligands

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ARTICLE INFO

Article history:
Received on: 11/09/2017
Accepted on: 14/11/2017
Available online: 28/01/2018

Key words:
Docking, GPCR, LigandFit, Marine, mGluR5, Molecular Dynamics

ABSTRACT

The G-protein coupled receptors (GPCR) form a major group of the target for centrally acting drugs. One of the Class C GPCRs, mGluR5 plays a major role in the learning and memory of the brain. Under perturbed conditions, the activity may result in excito-toxicity, neuro-toxicity and also may lead to epilepsy. The competitive ligands for this receptor are in a greater demand in the pharmaceutical industry as the drugs to cure many Central Nervous System (CNS) disorders. A site partition enhanced shape based docking protocol was followed to identify the drug leads from the marine compounds that could competitively bind to the active site of mGluR5. The studies concluded a dienal derivative from *Plocamium corallorhiza* as the best lead. The molecular dynamics studies were performed for a period of 25 ns. The results were satisfactory on account of receptor-ligand interactions at the molecular level and pharmacokinetic properties. The results suggest that this lead may compete with the control ligand glutamate for the active site and could be a competitive ligand of mGluR5. The binding of this natural ligand to the extra-cellular site of mGluR5 would certainly change its post functions producing a therapeutic effect.

INTRODUCTION

Most of the important classes of centrally acting drugs bind to the G-Protein coupled Receptors (GPCR) to exhibit their pharmacological actions. These receptors are categorized into six main classes. The metabotropic glutamate receptors belong to class C or III of GPCR. These are glutamergic receptors activated by the excitatory neurotransmitter glutamate (Conn and Pin, 1997). Unlike Ionotropic glutamate receptors, mGluRs are not ion channels and they show a slow and steady action. These receptors help in the modulation of synaptic transmission and neuronal excitability throughout the central nervous system by activating the secondary messengers (Ferraguti and Shigemoto, 2006). They are of eight subtypes, classified into three main groups based on their homology, function, and pharmacology. Of which, the fifth subtype has been strategically proved as a potential target to treat neuro-inflammation, neuropathy, and epilepsy (Alexander and Godwin, 2006). It is widely expressed in the brain and hence an attractable drug target. It is activated by the excitatory neuro-transmitter glutamate. Glutamate binds to the extracellular active site and triggers the binding of G_q protein to the tail end of this receptor in the cytoplasmic region. This activation of mGluR5 leads to the hydrolysis of phosphor inositide phospholipids to inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 aids in the opening of calcium channels. These molecules act as secondary messengers and further activate the phosphokinases.

The mGluR5 agonists have been proved to increase the appetite in animal studies. This shows the importance of this receptor in the normal feeding behaviour of animals (Ploj *et al.*, 2010). The intracellular mGluR5 also plays an important role in hippocampal synaptic plasticity. Any perturbation in the normal functioning of mGluR5 leads to various abnormalities in the brain causing neural disorders (Black *et al.*, 2010). The literature also suggested the important role of this

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GPCR in epilepsy and this receptor could be a target for newer anti-epileptic drug (Notenboom *et al.*, 2005). Both the agonists and antagonists of mGluR5 have prospective pharmacological potentials. The first ligand CHPG ((RS)-2-chloro-5-hydroxyphenylglycin) acted as a selective agonist of mGluR5 and showed the potentiating response in NMDA-induced depolarizations in rat hippocampal slices (Doherty *et al.*, 1997). Many selective and highly potent mGlu5 receptor agonists were developed in later stages. There are several drug candidates still under the experimental stage. Most of them suffer from poor pharmacokinetic properties. There is a continued research in identifying the candidate for CNS disorders. The pharmaceutical industry is trying to find the potential leads for mGluR5.

The traditional drug designing approach suffers from huge time and money utilization. Hence the computational methods are applied to find the possible drug leads with favourable pharmacological properties. Docking is a routine technique that is applied to identify the leads from the available ligands (Das *et al.*, 2013). The drug leads suggested by the computational techniques have also performed well under experimental conditions (Mabkhot *et al.*, 2014). Since olden days, the traditional methods of disease management have been done with the products from plant and animal sources. The terrestrial plants offer a wide variety of phytochemicals with good healing capabilities. Similarly, the phytochemicals of marine origin have also been proved for their therapeutic potentials (Jimeno *et al.*, 2004). Dysiherbaine is marine sponge-derived amino acid that functions as mGluR5 agonist causing seizures in mice. This was experimentally proved (Sakai *et al.*, 2001). This shows that an antagonist of mGluR5 can be used to treat epilepsy. The natural compounds could be successful drug candidates because of their inherent ability to bind with the receptors present in the human. The aim of this work is to identify the possible drug leads from the marine phytochemicals as the competitive ligands to mGluR5 using site partition aided shape based docking. The site partition docking was applied to enhance the accuracy of finding more leads from the given dataset of ligands for the given active site. Since the best lead is to be CNS active, it's important physico-chemical property like Blood Brain Barrier crossing ability has also been studied. The behaviour of the best ligand within the receptor at the molecular level has been studied using molecular dynamics simulation for a time period of 25 ns. The significant parameters associated with molecular dynamics were also studied and compared with the glutamate. Our work has demonstrated the CNS acting potentials of the natural compounds with mGluR5 as the target.

MATERIALS AND METHODS

The hit to lead discovery was done with a well-known docking procedure. The crystal structure of the extracellular domain of mGluR5 bound with the excitatory neuro-transmitter glutamate (3LMK) was considered as the target (Drobovetsky *et al.*, 2010). The 3D structure of the target was retrieved from RCSB PDB (Berman *et al.*, 2000). The ligands of the natural source used for the screening study were retrieved from seaweed metabolite database (Davis and Vasanthi, 2011). The shape based docking protocol was applied to study the binding mode of the ligands in the active site of the target (Venkatachalam *et al.*, 2003). The protocol contained the preparation of both target and ligands. The preparation of ligands included the addition of hydrogen, removal of the duplicate molecule, fixing bad vacancies and generating 3D coordinates in biological ionization and tautomerization states. In case of the target, the hydrogen was added and the receptor sites were created. The 3D structure was enhanced using CHARMm forcefield and the putative binding sites were identified using the Eraser algorithm. The criteria like the location, volume, and shape of the binding sites were all used by the algorithm to filter the incompatible ligands, and to create shape-based alignments of candidate poses. The initial conformational search of the ligands was done using a Monte Carlo method. This method allowed multiple torsions to be changed in a single search step depending on the number of rotating atoms.

The binding efficiency of the ligands in the active sites was authenticated with the well-known scoring functions that consider the various charges and binding energy. Each scoring function has distinct features and considering more than one scoring function to quantify the interactions would produce the satisfactory result in obtaining the best lead from the dataset used in the docking (Kim *et al.*, 2011). DockScore is a simple force field based scoring function which provides the interaction energy as the sum of the ligand/protein interaction energy and the internal energy of the ligand. The other scoring functions used wereLigScore1, LigScore2, PLP1, PLP2, Jain, and PMF. The LigScores are empirical scoring functions that attempt to accurately predict the binding affinity between ligand molecules and their protein receptors (Krammer *et al.*, 2005). The Piece-wise Linear Potential (PLP) is a fast, simple docking energy function that correlates well with the receptor-ligand affinities. PLP1 and PLP2 are two available PLP scoring functions (Parrill and Reddy, 1999). The Jain scoring function depends explicitly on the formal charge values in the polar attractive and repulsive interaction terms. The Potential of Mean Force (PMF) scoring function is a statistical based approach using 3D structure databases to provide a fast and accurate prediction of receptor-ligand binding free energies (Muegge and Martin, 1999).

The spatio-temporal behaviour of the ligand in the active site was studied using molecular dynamics with GROMACS version 4.5.6 (Lindahl *et al.*, 2010). The crystal structure of the target had few missing residues (116-140, 370-377). Since the missing residues do not participate in the glutamate binding and other functions (UNIPROT-P41594-GRM5), we considered the protein structure as retrieved from the PDB for the dynamics studies (Uniprot Consortium, 2017). Moreover, the model built for structuring the missing residues was not satisfactory. Since the missing residues were distant from the active site, they may not change the conformation of the active site. The topology files for the ligands to use in molecular dynamics studies were generated using PRODRG server (Schüttelkopf and Van Aalten, 2004). The molecular dynamics was carried out for the target protein with glutamate and the best scoring ligand to compare their affinities. The proteins were minimized using GROMOS96 43a1 force field and any

duplicate atoms present were removed, followed by the correction in the missing hydrogen atoms and bonds in the protein structures. The proteins were saturated in SPC explicit water solvent system. The topology files of the ligands were added to the system. The total charges of the system were neutralised with the standard ions. The total charge was -2 for both the glutamate and the best scoring ligand bound receptor and they were neutralised with two sodium ions. This was followed by the removal of any steric clashes introduced during the process. The maximum number of steps for minimization was set to 50000 using the steepest descent algorithm. All the long ranged non-bonded interactions were treated well during the minimization step. After system relaxation, NVT and NPT simulations were performed sequentially for 100 ps using default conditions. During the simulations, position restraints were applied to the ligands and the target. A leap frog based molecular dynamics was followed for a period of 25 ns. The dynamics results were analysed by extracting the information from the trajectory files obtained during the simulations. The Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF), Radius of Gyration (R_g), Solvent Accessible Surface Area (SASA), and Hydrogen bonds (H-bonds) were analyzed and compared for both the ligands. The structural features of the ligand decide the pharmacological properties. The important properties like molecular weight, hydrogen bond donor & acceptor, Partition Coefficient, Polar Surface Area, Rotatable bonds, binding to serum albumin (LogKhsa), gut-blood barrier transport (Caco-2), Blood Brain Barrier transport (LogBB, MDCK) and percentage of human oral absorption were studied using Qikprop (Schrödinger, 2015).

RESULTS AND DISCUSSION

The ligand glutamate was removed from the target structure before docking. The CharmM forcefield was used for the energy minimization of the structure. The binding site prediction algorithm used by LigandFit, Eraser detected12 binding sites with varying volumes. These binding sites were compared with the original crystal structure to guarantee the probable position of attachment of glutamate to the receptor. The site 1 was considered as the active site for further docking study. The ligands binding to the first site would most likely compete with glutamate. The binding site 1 before partition could detect only glutamate as the probable ligand. The site partitioning was done to maximise the chance of screening many potential ligands from the dataset. The maximum number of partitions used to create the sub-sites was 10 (Figure 1). This site partitioning protocol enabled the LigandFit tool to detect many potential ligands. The ligands were allowed to have a maximum of 10 poses each. Out of 1026 ligands, 989 poses were failed to dock because of not matching with the shape of the active site. Only 59 ligands with a total of 562 poses were able to dock with the active site. The control ligand glutamate was also bound to this active site 1. This showed that the screening was not random and the docking procedure had the ability to screen the best possible ligands for the given active site. All 10 poses 50 ligands were docked to the active site indicating the strength of their structural affinity to the target.

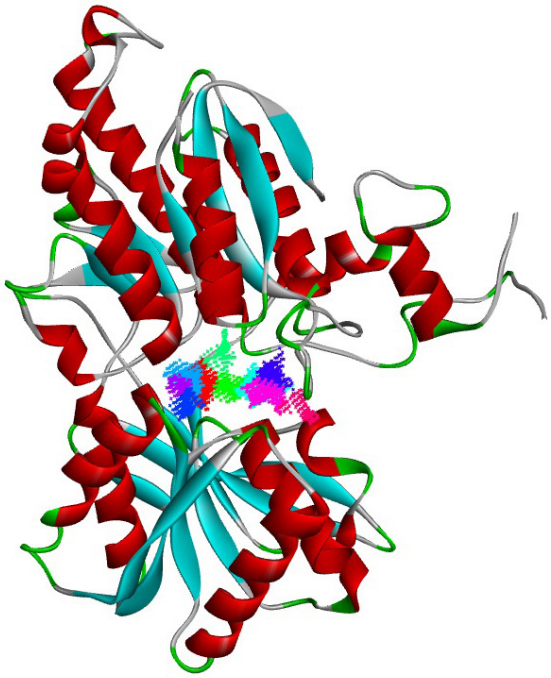

Fig. 1: Ten partitions in site 1.

The binding of the control ligand glutamate in the sub-site 4_8 showed the favourable amino acid interactions. Only the screened ligands that docked to this site were considered further. The docking results showed that only three ligands viz., RP056, BE001 and RP004 were docked at this site. The binding affinities of these ligands were studied in terms of different scoring systems (Figure 2). The ligand BE001 is phloroglucinol and its natural algal source is *Ecklonia stolonifera*. The research studies proved this compound to be hepato protective in tacrine-induced cytotoxicity (Kim *et al.*, 2005). This ligand was not considered for further studies due to its lower scores. The ligand RP004 belongs to protocatechualdehyde and its algal source is *Polysiphonia lanosa*. This has been experimentally proved as cytotoxic (Shoeib *et al.*, 2004). Due to this property, this compound was not considered further. The Dockscore of RP056 was higher than glutamate indicating that its interaction with the target as an energetically favourable one. The top scorer RP056 is 4-Bromo-8-chloro-3,7-dimethylocta-2,6-dienal, which is a halogenated monoterpene aldehyde isolated from the South African red algae *Plocamium corallorhiza* using dichloromethane and methanol solvents in the ratio 2:1.

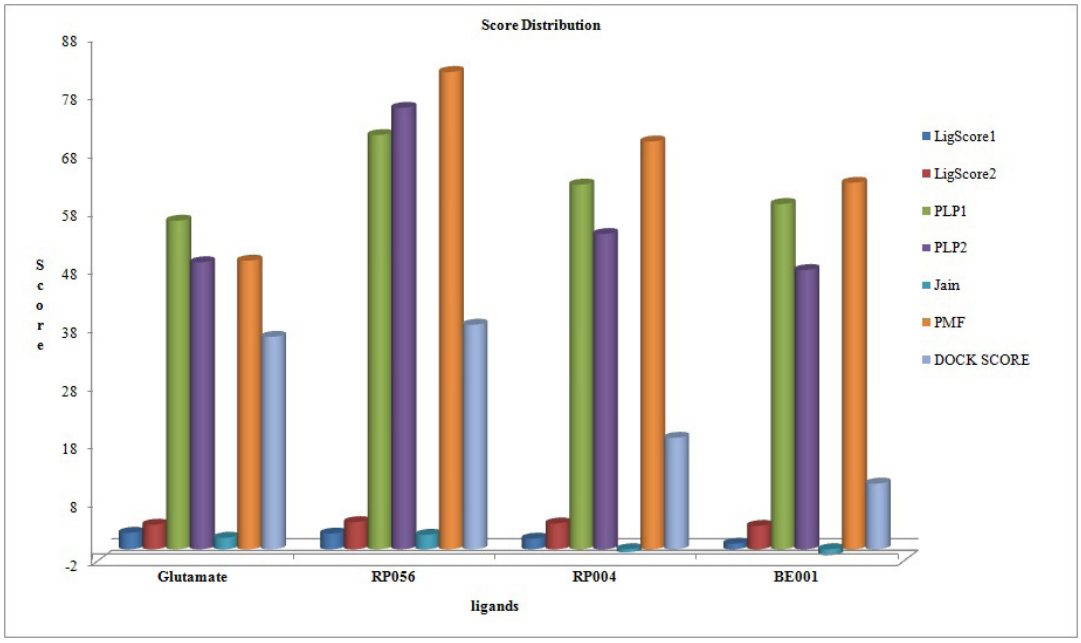

Fig. 2: Performance in terms of various scoring functions by the screened ligands in sub-site 4_8.

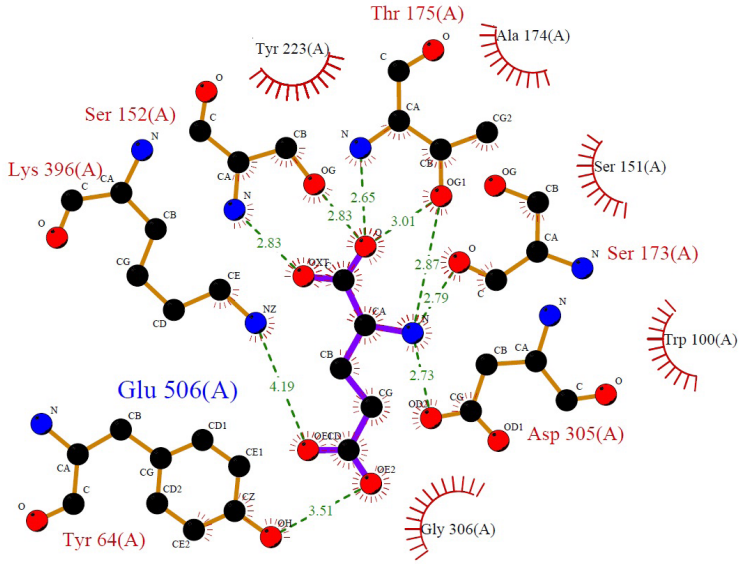

Fig. 3: Interaction of Glutamate with amino acids in the active site of mGluR5 as per the crystal data (3LMK).

The DockScore reflect the complementary features of the ligands and their potential as lead candidates for the given target. Though the other ligands bound to the same sub-site, they were not energetically fit. This was concluded from their poor DockScores. RP056 outperform glutamate in all scoring systems. The more negative PLP scores indicate the stronger affinity between RP056 and mGluR5. The ligand showed favourable bonded and non-bonded interactions with the active site residues. As per the crystal data, glutamate binds to the active site residues through hydrogen bonded or non – bonded interactions withY64, W100, S151, S152, S173, A174, T175, Y223 D305, G306 and K396 (Figure 3). This was extracted from the PDBsum database (Laskowski, 2001). RP056 was bound to neutral amino acid, S152 using a conventional hydrogen bond with a distance of 1.89Å. It also showed van der Waals interaction with G150, D305, G306, E279, R61, R68 and R310. The non-bonded interactions were observed between the electronegative halogen bromine attached to the alkyl group in the ligand and the side chains of K396, Y64 and W100. The electronegative atom chlorine in the ligand did not involve in any interactions in this active conformation. An

alkene group present in the ligand was attached to Y223 through the methyl side chain (Figure 4). All these amino acids are very crucial for the binding of the excitatory neurotransmitter glutamate to the extracellular domain of mGluR5 (Drobovetsky *et al.*, 2010). Any disturbances to this binding will lead to the loss of post synaptic functions of this receptor. This may lead to the halt of neuro toxicity induced by this receptor. The active site also prefers this particular conformation of the top scoring ligand RP056 as that of glutamate (Figure 5). This proves the competitive nature of the geometrical structure of RP056 for the active site.

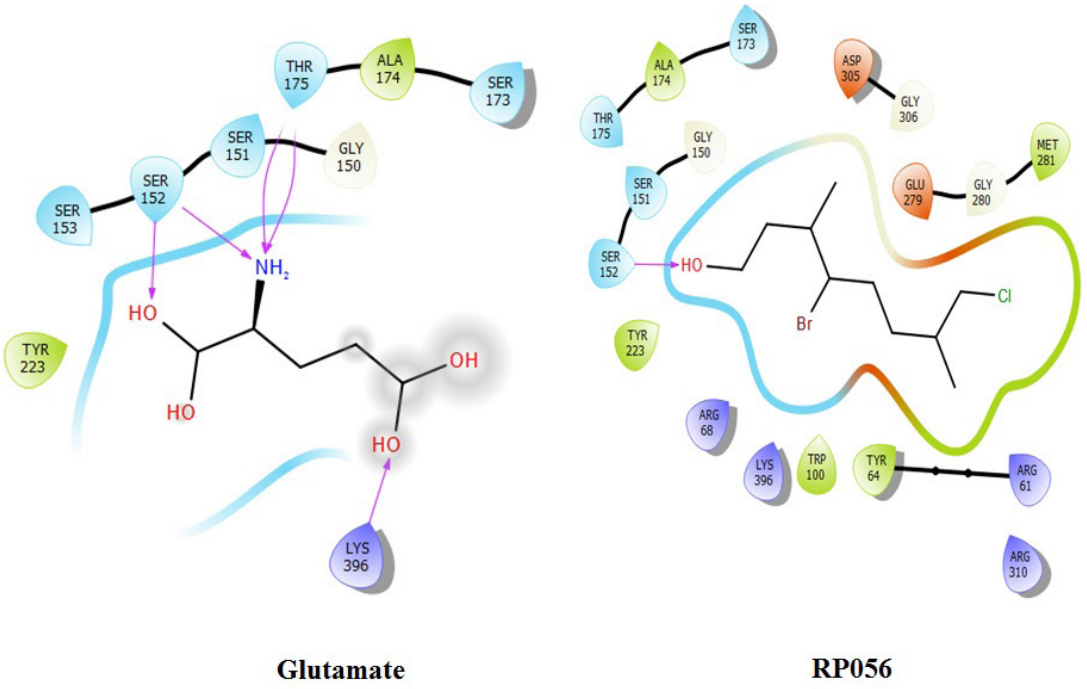

Fig. 4: Interactions of glutamate and RP056 with the active site residues. (Image produced using Maestro 11.1 Visualizer)

The dynamic behaviour of the ligands in the active site was studied using 25 ns molecular dynamics (Figure 6). The stability of ligand bound target was measured in terms of deviations and fluctuations. The RMSDs were calculated as a function of time in ns. The glutamate bound target exhibited a peak RMSD of 0.4 nm, whereas the RP056 bound target had a lower peak value of 0.3nm. From the graph, it can also be noted that the deviations were not random for RP056. The deviations were higher for RP056 till 10th ns; there onwards it maintained a near equilibrium state till 25th ns. This could explain the stability of the target structure upon binding to RP056. The periodicity of ups and downs in the deviations was looking alike for both glutamate and RP056 bound structures. The deviations were in the range of 0.2 to 0.3 for RP056. It took the value between 0.3 and 0.4 for glutamate. Hence, the energetically favourable binding would be with RP056. The flexible nature of the local structures also decides the stability of the whole protein structure. This was analysed by plotting the RMSF of every amino acid. The fluctuations of most of the amino acids in RP056 bound form were below 0.18 nm. The aminoacids present in the active site showed lower fluctuation in case of RP056 bound structure than that of the control ligand glutamate; hence we can conclude that the ligand did not change the overall topology of mGluR5. The Radius of gyration (R_g) measures the structural changes happen during simulations. This value was more or less equivalent for both the ligand bound forms between 7.5 and 15 ns. In the rest of the phases, the values were slightly larger for RP056. The more number of hydrogen bonds in the glutamate bound form would have made the structure rigid during simulation. The single hydrogen bond between RP056 and an active site residue allowed the structure to extend slightly during simulation. This was consistent with the hydrogen bond data obtained during simulation.

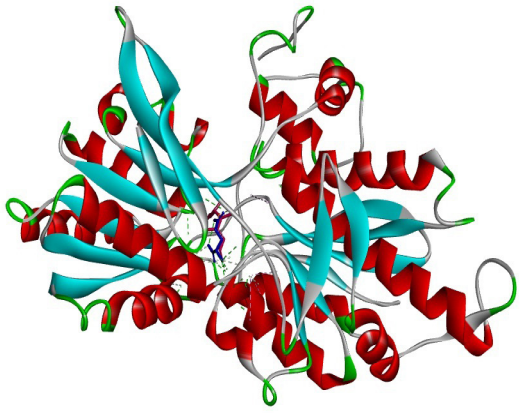

Fig. 5: Glutamate (blue) and RP056 (pink) docked in the active site.

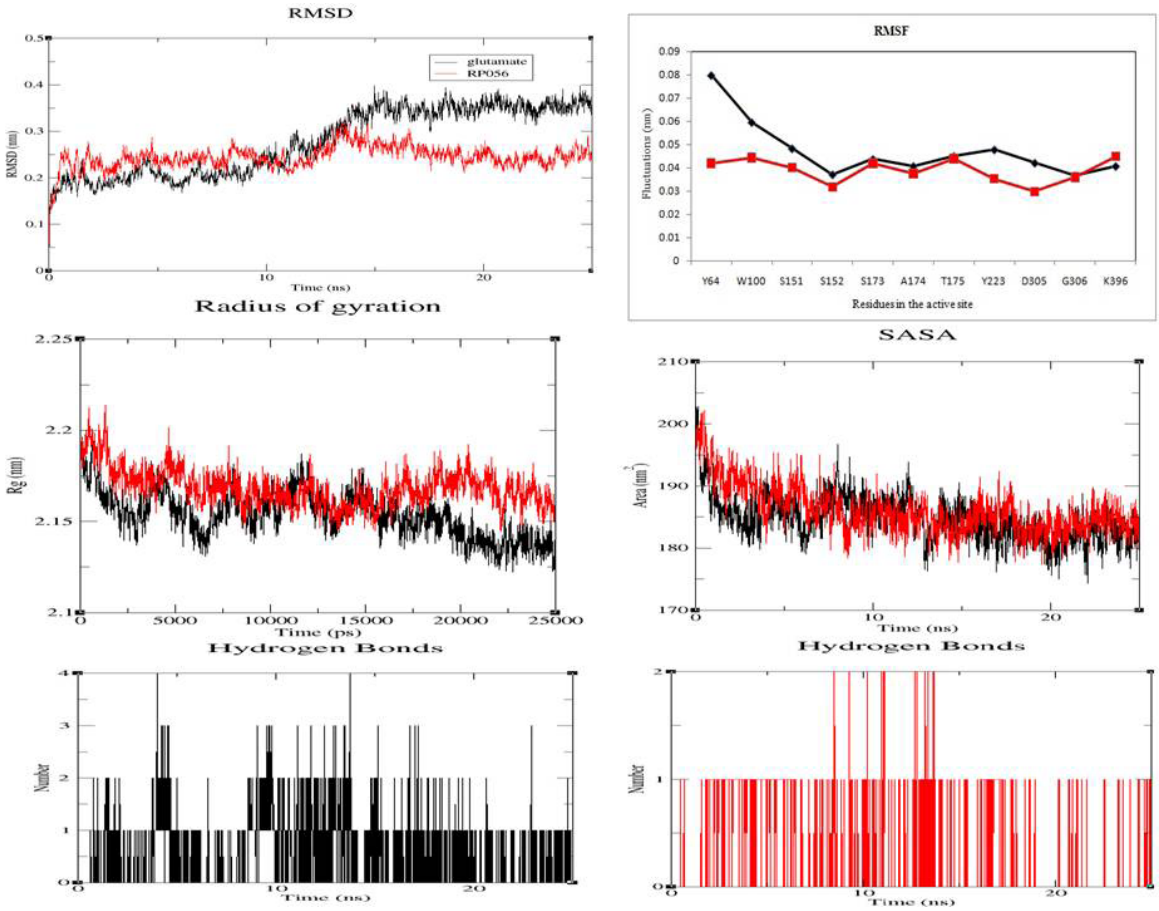

Fig. 6: Important parameters checked using dynamics simulations like RMSD, RMSF, Radius of Gyration (1 ns = 1000ps), SASA and Hydrogen bond count for target bound to glutamate (black) and RP056 (red).

Table 1: Important pharmacological relevant properties of RP056.

Properties	Predicted values	Preferred range
Compound Name	RP056, (2E,6E)-4-bromo-8-chloro-3,7-dimethylocta-2,6-dienal	
Molecular weight	265.57	≤400
LogPo/w	3.334	≤3.6
Hydrogen bond Donor	0	≤5
Hydrogen bond Acceptor	2	≤8
Polar Surface Area	37.956	≤120
Rotatable bond	4	≤5
LogKhsa	0.173	-1.5 TO 1.2
Caco-2	1629.37 nm/sec	≥25
LogBB	-0.09	-3.0 TO 1.0
MDCK	4197.33 nm/sec	≥25
% Human oral absorption	100	≥80% is high

The glutamate-mgluR5 complex initially had four hydrogen bonds. It maintained one to four hydrogen bonds during the course of simulation. The variation in the hydrogen bond could be due to the free movement of small sized glutamate inside the binding pocket. The marine metabolite, RP056 retained its only one hydrogen bond throughout the simulation period suggesting its restricted motility within the active site. The surface area measurements SASA explain the overall change in the shape of the structure. During most of the simulation time, the values of both the forms were in a close range. The SASA of the RP056 bound target was lower than the glutamate bound form during 7.5 and 15 ns. This reduction in SASA could be due to the inaccessibility of the target to the solvent upon binding to the ligand. The molecular dynamics analyses stood as evidence that the binding of RP056 to the target would have an impact on its structure. RP056 could invariably affect the binding of the original ligand glutamate to this target. Hence the perturbed activities which are due to the binding of glutamate to mGluR5 can be controlled by considering RP056 as an alternate ligand. The drug-like properties of RP056 are tabulated (Table 1). Crossing the Blood Brain Barrier (BBB) is very important for any CNS acting drug. The predictors like LogBB and MDCK were in perfect range, suggesting the CNS penetrating potential of this natural ligand. The Caco-2 and MDCK values of the ligand, higher than 500 was a significant indication of its transport across the gut and brain. The data obtained were in a very satisfactory range. The compounds from *Plocamium corallorhiza* have already demonstrated antimycobacterial activity (Saravanakumar, 2006). This proves the pharmacological potential of *Plocamium corallorhiza*. The natural compound from an algal source, RP056 can hence be considered as a lead molecule to function as

competitive ligand to glutamate in case of mGluR5. The competitive binding can control the wild behaviour of this receptor under impaired conditions.

CONCLUSION

The drug discovery processes can be improved and accelerated using computer based protocols. The discovery related to CNS disorders particularly consumes more money and time. The mGluR5 receptor has developed much potential as a drug target for various ailments. The docking results had strongly proved the profound affinity of this natural ligand towards the receptor. The molecular dynamic analyses also supported the fact that the binding of this ligand had brought changes to the receptor. The ligand with its satisfactory pharmaceutical relevant properties can well be considered as a drug candidate. Various scoring functions, amino acid interactions, molecular dynamics analyses and drug-like properties conclude the novelty of a monoterpene aldehyde compound from red algae to have CNS potentials. This compound has the ability to bind to the target in place of glutamate. This kind of interaction may inhibit the perturbed functions of mGluR5. Hence, this natural ligand RP056 can be suggested as a cure for the CNS disorders with respect to the target considered. The algal source of this marine chemical can also be considered as a treatment for excito and neuro toxicities induced by mGluR5. Based on the structural information of this ligand, a plethora of novel chemical scaffolds can also be designed using chemoinformatics methods.

CONFLICT OF INTEREST

The authors have done to declare.

ACKNOWLEDGEMENTS

The authors thank SRM University for providing infrastructure to perform this work. The authors sincerely acknowledge SRM Supercomputer Center (HPCC) for providing GROMACS application.

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How to cite this article:
Vijayasri S, Hopper W. Site Partition Enhanced Shape Based Docking and Molecular Dynamics Studies of G-Protein Coupled Receptor Acting Natural Ligands. J App Pharm Sci, 2018; 8 (01): 021-028.