International Journal of Advance Research in Science and Engineering
Volume No 07, Issue No. 01, January 2018
www.ijarse.com
IJARSE
ISSN: 2319 - 8354

Computational studies of Acetamido-benzoxazolone derivatives as TSPO marker

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Abstract

Translocator Protein (18 kDa) TSPO, is widely distributed in the outer mitochondrial membrane and highly expressed during microglia activation in neuroinflammatory diseases. The binding data of first and second generation PET radioligands has revealed that TSPO binding sites varies with different affinities and they were differentiated as HABs, LABs and MABs. Also recently reported TSPO polymorphism (rs6971; Ala147Thr) predicts binding affinity variation. We have also studied a series of TSPO molecules through docking and MD simulation analysis (PDB: 2MGY). Computational data analysis showed pattern of variable binding profile of known diagnostic ligands and our screened ligands via interactions with conserved residues in the binding pocket (Val26, Leu49, Ile52, Trp107, Ala110, Ala147, and Leu150).

***Key Words**: CADD, Docking, Acetamido-benzoxazolone, TSPO*

INTRODUCTION

Varieties of ring system having hetro atom has been designed and synthesized for the application of different disease conditions in which computational drug design has helped a lot [1-16]. The 18-kDa translocator protein (TSPO), is proven biomarker for variety of neuroinflammation and few of the oncologic conditions [17-20]. TSPO is tryptophane rich five transmembranal (5TM) protein found on outer mitochondrial membrane of steroid synthesising and immunomodulatory cells. In case of neuronal damage or inflammation the expression level of TSPO get upregulated as an immunomodulatory response.

Our present study involves computational screening, synthesis and evaluation of potential optical imaging probe for TSPO neuroinflammation imaging. The initial computational screening involves pharmacophore modeling from the library designing as per the desired TSPO binding profile. Molecular rigid and flexible docking analysis was performed with structure of the TSPO, (PDB: 2MGY). Structure modeling of parallel and anti-parallel TSPO protein and Ala147Thr mutated model was performed and docking analysis was performed for variable TSPO binding sites.

METHDOLOGY

Computational Methodology

Molecular modeling investigations were carried out using an advanced molecular docking program GLIDE, version 9.7. During the docking process, initially GLIDE performs a complete systematic search of the conformational, orientational and positional space of the docked ligand and eliminating unwanted conformations using scoring and followed by energy optimization. PDB entry 2MGY taken for our studies. The following criteria were keeping in mind before choosing the protein- ligand complexes: non-covalent binding between protein and ligand, crystallographic resolution less than 2.5 Å and known experimental binding data. Preparation

of the protein for docking included removal of unnecessary heteroatom and solvent coupled with addition of hydrogen atoms, bond order for crystal ligand and protein were adjusted and minimized up to 0.30 Å RMSD. Using extra precision (XP) mode of GLIDE application, docking studies was performed on known compounds and designed compounds. Using 'Glide grid generation' the binding region was defined by a 17.04_9.31_0.58 Å box centerd on the centroid of the crystallographic ligand to confine the centroid of the docked ligand. No scaling factors were applied to the Van der Waals radii. Default settings were used for all the remaining parameters.

RESULTS & DISCUSSION

The molecular docking results in general elaborates all the necessary interaction between ligands and 18 kDa crystal structure including the ligand acceptor-protein donor interactions, aromatic-aromatic interactions, lipophilic- lipophilic interactions, hydrogen bond interactions, hydrophobic region in terms of glide XP score. .Best pose was selected on the basis of Glide score and the interactions formed between the ligands and active site amino acids.

Acetamidobenzoxazolone based six molecules were studied which are shown below. Their docking score has been presented in table 1.

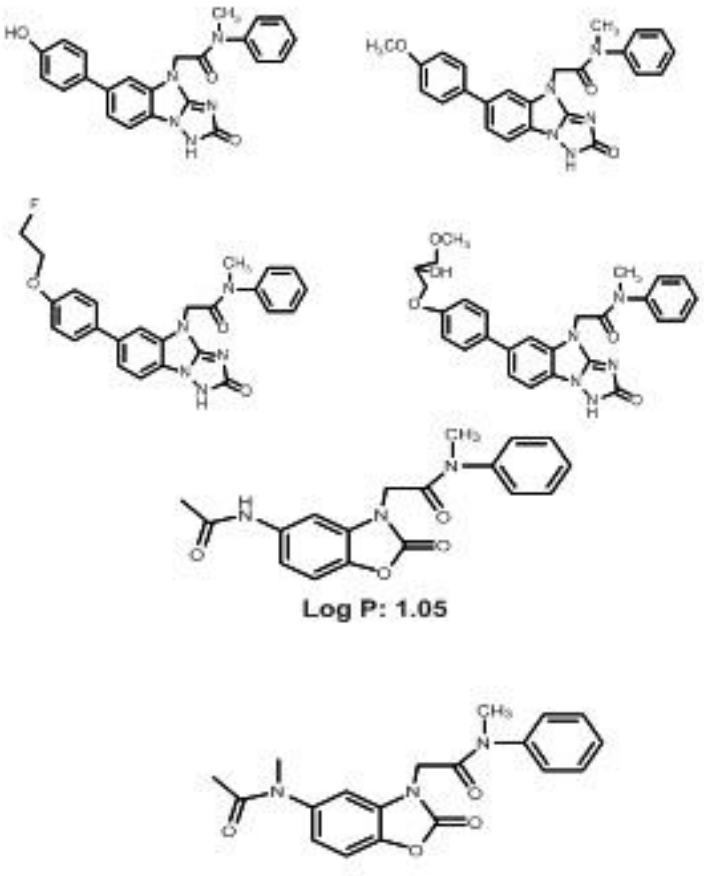

Figure 1:- Acetamidobenzoxazolone ligands used for computational studies

The docking score are shown in table 1.

ligand	Gscore
1	-3.509
2	-2.667
3	-2.776
4	-4.184
5	-2.747
6	-2.954

Table1:- Docking score of Acetamidobenzoxazolone ligands

Compound four having isopropyl alcohol group showed best result. Computational data analysis showed pattern of variable binding profile of known diagnostic ligands and our screened ligands via interactions with conserved residues in the binding pocket (Val26, Leu49, Ile52, Trp107, Ala110, Ala147, and Leu150).
The detail interaction with amino acid residues are shown in figure 2.

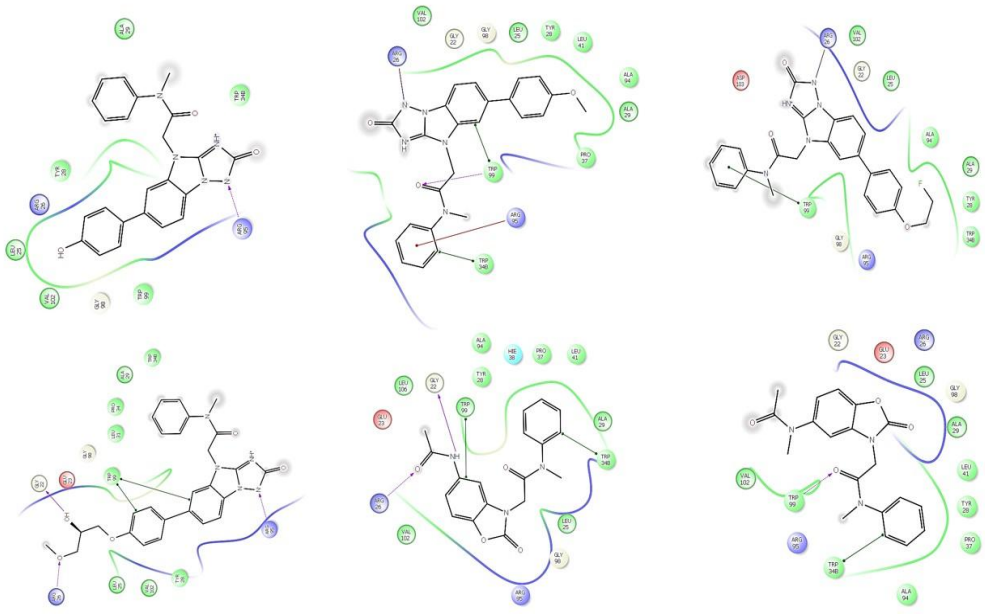

Figure 2:- 2D Protein-ligand interaction score of Acetamidobenzoxazolone ligands

CONCLUSION

A series of molecule based on acetamido-benzoxazone have been analysed computationally for binding with 18 kDa translocator protein which it showed very promising results.

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