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Design and Preliminary Evaluation of Benzoxazolone-Based Agents for Targeting Mitochondrial-Located Translocator Protein

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Abstract : Translocator protein (18 kDa) TSPO is highly expressed during microglia activation in neuroinflammation. Although a number of PET ligands have been developed for the visualization of activated microglia, one of the advantageous approaches is to develop potential optical imaging (OI) probe. Our study involves computational screening, synthesis and evaluation of TSPO ligand through various imaging modalities namely PET/SPECT/Optical. The initial computational screening involves pharmacophore modeling from the library designing having oxo-benzooxazol-3-yl-N-phenyl-acetamide groups and synthesis for visualization of efficacy of these compounds as multimodal imaging probes. Structure modeling of monomer, Ala147Thr mutated, parallel and anti-parallel TSPO dimers was performed and docking analysis was performed for distinct binding sites. Computational analysis showed pattern of variable binding profile of known diagnostic ligands and NBMP via interactions with conserved residues along with TSPO's natural polymorphism of Ala147→Thr, which showed alteration in the binding affinity due to considerable changes in tertiary structure. Preliminary in vitro binding studies shows binding affinity in the range of 1-5 nm and selectivity was also certified by blocking studies. In summary, this skeleton was found to be potential probe for TSPO imaging due to ease in synthesis, appropriate lipophilicity and reach to specific region of brain.

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