IDENTIFICATION OF MPTP BLOCKERS BY VIRTUAL SCREENING

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Emerging evidence indicates that mitochondrial permeability transition pore (mPTP) is important for maintenance of mitochondrial and neuronal function in aging and neurodegenerative disease.

Mitochondrial permeability transition (MPT) is described as an abrupt increase of inner membrane permeability to solutes with molecular mass of < 1500 Da, which leads to dissipation of the mitochondrial membrane potential and influx of cytosolic solutes, causing expansion of matrix and finally the release of cytochrome-c leading to caspase activation and cell death. Structurally the MPTP is thought to involve VDAC (voltage dependent anion channel) in the outer membrane, the ANT (adenine nucleotide translocase) in the inner membrane and CypD (Cyclophilin D) in the mitochondrial matrix. MPTP spans through both the inner and outer mitochondrial membranes. VDAC is a porin known by its role in metabolite transport across mitochondria and acts as entry for molecules from cytosol to mitochondria.

The peripheral benzodiazepine receptor (PBR) is a critical component of the mPTP. PBR is a small evolutionary conserved protein, located at the surface of the mitochondria where it is physically associated with the VDAC and ANT that form the backbone of mPTP. These findings and enigma about the mechanism of MPTP led us to identify novel inhibitors by ligand-based virtual screening using PBR agonists. The role of agonists in the inhibition of MPT is experimentally proved. In the present work, we developed ligand-based pharmacophore to identify novel inhibitors from commercial databases (namely, ChemDiv and Asinex). We identified 2 new leads by this screening flow.