Monoamine Oxidase Enzymes For Targeted In Silico Study Of New Inhibitors

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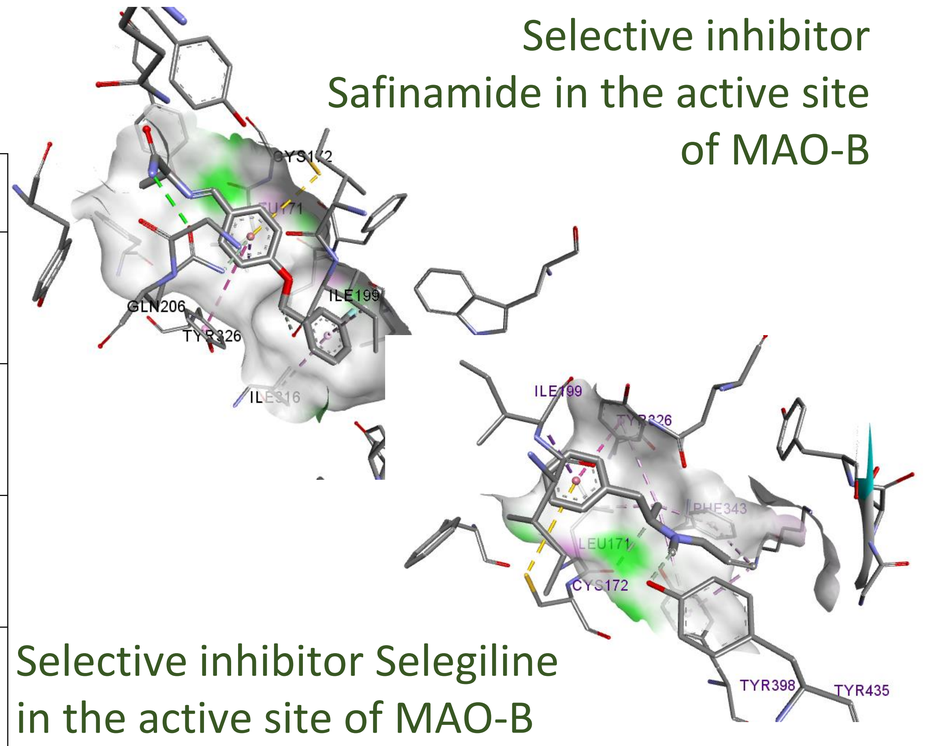
Introduction. The spectrum of cognitive impairment is very wide and ranges from normal cognitive decline with age to diseases of the central nervous system, including Alzheimer's disease, Parkinson's disease and others [1]. Inhibition of monoamine oxidase enzymes, which catalyzes the oxidative degradation of a number of neurologically important amine substrates, including dopamine, norepinephrine, epinephrine, serotonin and phenethylamine [2]. MAO inhibition has an overall neuroprotective effect by reducing oxidative stress caused by these enzymes. The development of new highly selective MAO-B and MAO-A inhibitors is an important task, as they can modify neurodegeneration processes and/or prevent its progression [3]. Modern technologies for the isolation of protein macromolecules of receptors and enzymes in conformation with the corresponding ligands, their crystallographic analysis, detailing of ligand-receptor interactions and mechanisms of modulation, agonism, antagonism or inhibition open up opportunities for preliminary in silico search for potential drugs, which allows optimising the drug design of new molecules**. The aim** of the present study was to analyse and separate the available macromolecules of monoamine oxidase enzymes in conformation with antiparkinsonian ligands and to validate the methodology of molecular docking with native ligands.

Materials and methods. The following programs were used Discovery studio Visualizer 2021, AutoDock Tool1.5.6rc3, Autodock Vina. Crystallographic data for all glutamate receptors were obtained from the Protein Data Bank.

Results and discussion. After analysing the existing ligand drugs among MAO inhibitors, we separated those with the highest efficacy in the treatment of PD and evaluated the presence of MAO macromolecules in conformation with the corresponding ligands in the Protein Data Bank. The list of all macromolecules available for *in silico* studies, validation characteristics, Grid box coordinates and sizes, as well as the binding energy of the reference ligand are given in the table 1. The docking methodology was validated by re-docking the native reference ligands – Safinamide, Seleginine, Pasagoline, Garmine - into the active site of MAO-B.

Table. 1 *Validation of methodology for docking into active sites of MAO A and B using native ligands*

Enzymes	PDBID/body excretion	Ligand	Active site	Grid box Coordinates/size	Binding energy, kcal/mol
MAO-B	2V5Z/ Komagataella pastoris	Safinamide is a selective inhibitor (competitive)	Chain A Gln206(2), Ile199(2), Leu171, Cys172, Tyr326, Ile316	x = 51,90, y = 156,46, z = -28,56; розмір x =22, y = 24, z = 22	-9,5
	2BYB/ Komagataella pastoris	Selegiline selective inhibitor (irreversible)	Chain A Tyr435, Leu171(2), Ile199, Cys172, Tyr326, Leu171, Tyr326, Phe343(2), Tyr398(4)	x = 52,47, y = 156,38, z = 26,30; розмір x =10, y = 14, z = 10	-7,0
	1S2Q/ Komagataella pastoris	Pasagiline selective inhibitor (irreversible)	Arg42, Tyr60, Met436, Tyr60, Ser59, Gln206, Tyr435, Gly57, Leu171, Tyr326, Phe343, Trp388(5)	x = 72,47, y = 256,38, z = 76,30; розмір x =20, y = 24, z = 14	-7.2
MAO-A	2Z5X/Homo sapiens	Garmin (selective inhibitor)	Tyr 69, Tyr 407, Tyr 444, Phe 208, Phe 352, Asn 101, Gln 215, Cys 32, Ile 325, Leu 337. Val 93, Glu 95, Tyr 109, Pro 112, Phe 208, Asp212	x = 40,58, y = 26,93, z = -14,54; розмір x =22, y = 20, z = 20	-8.7



Selective inhibitor Safinamide in the active site of MAO-B

Selective inhibitor Selegiline in the active site of MAO-B

Conclusions. The MAO structures available in the Protein Data Bank in conformation with the most effective inhibitors as antiparkinsonian agents were identified, the amino acid composition of the active sites was described, and the docking methodology for natin ligands was validated, which allows the use of docking parameters for their further application in in silico analysis.

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