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Research Article

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Docking of Novel Reversible Monoamine Oxidase-B Inhibitors and their Antiparkinsonian Effect

Youssef Moutaouakkil[1*], Ilham Kandousi[2], Youness Boukharsa[1], Ahmed Bennana[3], Yahia Cherrah[3], Yassir Bousliman[3], Jamal Lamsaouri[1], Jamal Taoufik[1], Azeddine Ibrahimi[2] and M'hammed Ansar[1]

[1]Faculty of Medicine and Pharmacy, Laboratory of Medicinal Chemistry, Rabat Institute, University Mohamed V, Rabat, Morocco
[2]Faculty of Medicine and Pharmacy, Laboratory of Biotechnology, Rabat Institute, University Mohamed V, Rabat, Morocco
[3]Faculty of Medicine and Pharmacy, Laboratory of Pharmacology-Toxicology, Rabat Institute, University Mohamed V, Rabat, Morocco

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ABSTRACT

Background: *Monoamine oxidase is a flavoenzyme responsible for the oxidative deamination of neurotransmitter and dietary amines. Two isozymes of Monoamine oxidase , namely A and B, have been identified on the basis of their substrate preference and inhibitor selectivity. They are the well-known target for antidepressant, Parkinson's disease and neuroprotective drugs. In this research 3 reversible and Monoamine oxidase B selective inhibitors have been docked computationally to the active site of the MAO-B enzyme in order to demonstrate for the first time the potential of 5-(benzo(b)furan-2- ylmethyl)-6-methylpyridazin-3(2H)-one derives, ability to inhibit MAO-B in comparison with farnesol, one of reversible inhibitors.*
Methods: *3 reversible and Monoamine oxidase B selective inhibitors were docked with the active site of the Monoamine oxidase B enzyme in order to identify for the first time the potential of 5-(benzo(b)furan-2- ylmethyl)-6-methylpyridazin-3(2H)-one derives, ability to inhibit Monoamine oxidase B.*
Results and conclusion: *The results indicate that 5-(benzo(b)furan-2- ylmethyl)-6-methylpyridazin-3(2H)-one derives could be a good inhibitor for testing in vitro and in vivo against Monoamine oxidase B for treaty Parkinson's disease.*

Keywords: Docking ; Reversible MAO-B inhibitors; Pyridazinone

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INTRODUCTION

The oxidative desamination of the neurotransmitter and dietary amines is carried out mainly by a flavoenzyme linked to the outer mitochondrial membrane of the cell called monoamine oxidase (MAO) [1-3]. Two isozymes of MAO, namely A and B, have been identified on the basis of their substrate preference and inhibitor selectivity.
Antidepressants are drugs that inhibit MAO-A, and are thought to act by increasing the rate of central serotonin. Drugs used in the treatment of Parkinson's disease inhibit the MAO-B isoform, in turn, and are often associated with L-Dopa.9, so the dopamine metabolism in the brain, inhibitors are thought to enhance dopamine levels, particularly following therapy with LDopa. The intersection of the enzyme with the surface of the membrane is assumed to be near the entrance of the substrate or the inhibitor in the active sites of human MAO-B or MAO-A rat.

In the case of MAO-B, the substrate must negotiate a loop (residues 99-112), whose volume of 290 Å3 covers the inlet cavity. However, the four residues (Tyr326, Ile199, Leu171 and Phe168) form the boundary between the inlet cavity and the substrate cavity, which is a hydrophobic planar cavity with a volume of 490 Å3 occupied mainly by the redox active isoalloxazine cycle of Covalent, which binds the coenzyme FAD to the distal end. On the other hand, the active site of MAO-A is a unique hydrophobic cavity of ~ 550 Å in the human enzyme [4]. The fusion of the two cavities to a volume of ~ 700 Å3 is the result of the fact that the side chain of Ile199 is oriented towards an "open" conformation. These observations led to the hypothesis that Ile199 serves as a "gate" for separating the substrate and the MAOB inlet cavities.

The mutation of Ile199 to phenylalanine, as found in bovine MAO-B and in all known MAO-A sequences, yields an active enzyme that binds rasagiline and other irreversible inhibitors but is unable to bind reversible inhibitors of MAO-B 1,4-diphenyl-2-butene, chlorostyrylcaffeine and farnesol [1,5].

The studies indicate that 5-(benzo(b)furan-2- ylmethyl)-6-methylpyridazin-3(2H)-one derivees may have potential therapeutic value for the management of mental depression [6]. Our study is to perform docking in order to demonstrate for the first time the potential of 5-(benzo(b)furan-2- ylmethyl)-6-methylpyridazin-3(2H)-one derives, ability to inhibit MAO-B in comparison with farnesol, one of reversible inhibitors.

EXPERIMENTAL SECTION

The 5- (benzo (b) furan-2-ylmethyl) -6-methylpyridazin-3 (2H) -one gave three derivatives, in addition to specific reversible inhibitors. The 2D structure of these derivatives was obtained from the literature (Figure 1) [6]. The MarvinSketch software was used to realize the 3D structures of these molecules. The 3D structure of the farnesol was taken from PubChem. (Farnesol was used to conduct anchor studies).

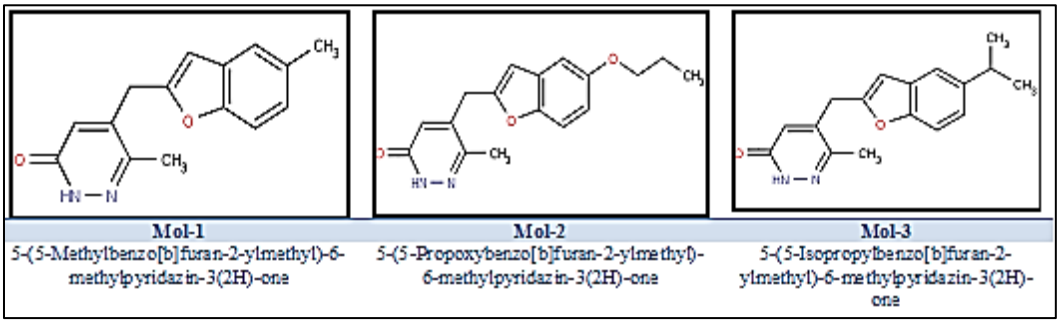

Figure 1: Names and structures of the selected, reversible MAO-B inhibitors used in our docking

The 3D structure of the MAO-B crystallized with the FAD in its substrate site was extracted from the Protein Data Bank (PDB), ID PDB:1S3E. The program AutoDock vina v.31 (2010) 455-461 was used to perform the docking and AutoDock Tools GUI (ADT) v.1.5.6 June _7_13 [7] to prepare, files for docking and to determine the gridbox. PyMOL was used to visualize the results [8]. Docking was carried out in the substrate cavity at the FAD site, considering the FAD N5 as the center of the docking grid box.

RESULTS AND DISCUSSION

The panel of Figure 2 (A B C and D) shows the results of the docking performed between the MAO-B and the ligands Mol-1, Mol-2; Mol-3 and farnesol. For all the figures the MAO-B is in cyan, the FAD is in red and the loop (residues 99-112) in yellow. The hydrogen bonds are represented by the yellow traits.

As shown in Figure 2, the 3 ligands may each have 3 hydrogen bonds with the receptor whilst farnesol can have only one bond. Table 1 below summarizes the results obtained.

A binding energy of -7.5 kcal/mol was observed with the anchor of Farnesol, a reversible inhibitor of MAO-B [1,4], but with a single hydrogen bond, a less stable complex is obtained. The binding energy of each ligand with the substrate site of MAO which is of the order of -9 and -10 kcal/mol supports the antiparkinsonian effect [8]. As shown in Figure 2, the three ligands may have interactions of more than two hydrogen bonds with MAO-B in the substrate cavity [1] showing great stability. The ligand (Mol-3) is considered to be the most stable relative to the others, given its low binding energy, followed by mol2 and mol1, which is probably due to the 5-isopropyl radical which gives it greater stability. The ligands interact with MAO-B via hydrogen bonds at the boundary between the inlet cavity and the substrate cavity formed by four residues (Tyr326, Ile199, Leu171 and Phe168) [1].

The Mol-1, Mol-2 and Mol-3 respectively involve the residues (Tyr398, Leu171, Ile199), (Ile199, Tyr398), and (Tyr398, Leu171) and bind all three to the Leu 171, one of the border residues, Which suggests an MAO-B inhibitory effect, but only mol1 and mol2 are specific reversible inhibitors due to their I199 mutation because the mutation of Ile199 to phenylalanine renders MOA-B unable to bind to specific reversible inhibitors such as 1.4 Diphenyl-2-butene, chlorostyrylcaffeine and farnesol [1,4].

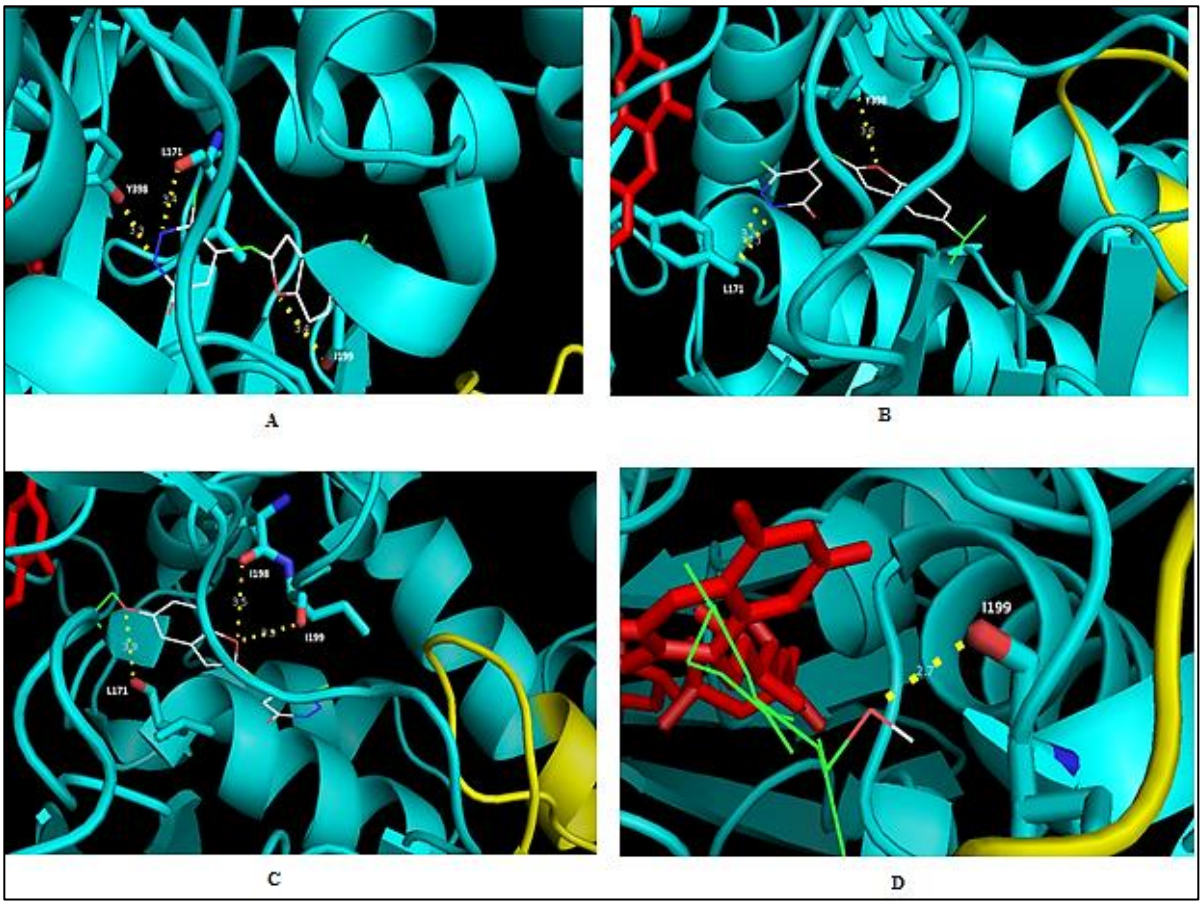

Figure 2 : PyMOL configuration representing the interactions ligands / MAO-B. A: Mol-1/ MAO-B, B: Mol-2/ MAO-B, C: Mol-3/ MAO-B, D: farnesol / MAO-B

Table 1: Hydrogen bonds identified in the progress dockings

Ligand	Affinity (kcal/mol)	Nomber of hydrogene bands ligand-receptor	Amino acids bound to the ligand	Nomber of bands ligand-aa	Bond length in Å
Mol-1	-9.7	3	Y398	1	3,3
			L171	1	3,4
			I199	1	3,4
Mol-2	-9.4	3	L171	1	3,9
			I198	1	3,5
			I199	1	3,9
Mol-3	-10.3	3	L171	2	3,3 - 3,2
			Y398	1	3,6
farnesol	-7.5	1	I199	1	2,7

CONCLUSION

In conclusion among the derivatives of 5- (benzo (b) furan-2-ylmethyl) -6-méthylpyridazin-3 (2H) -one there mol1 and mol2 whose antidepressant effect is shown may have an antiparkinsonian effect by Binding specifically to MAO-B With more affinity for MAO-B and will be more effective than farnesol.

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