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Interaction of Monoamine Oxidase-B with a Series of Coumarin by Molecular Modeling Methods

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Molecular docking studies were performed with UCSF Chimera, to derive the affinity and mode of binding of the inhibitors to the active site of the monoamine oxidase-B. The optimization of the geometry of monoamine oxidase-B was performed using the force field AMBERff03.r1 and calculations the energy by AutoDock Vina implanted in the UCSF Chimera software. This work is to study the inhibition of monoamine oxidase-B which is an enzyme involved in the Parkinson's disease by methods of molecular modeling. These results will probably help in the development of an effective therapeutic tool in the fight against the development of Parkinson's disease.

Keywords: Monoamine oxidase-B, Parkinson's disease, Coumarin, Knime, Molecular docking, UCSF Chimera.

INTRODUCTION

Monoamine oxidase-B (MAO-B) is a mitochondrial protein located in the outer mitochondrial layer [1,2] and catalyzes the metabolism of neurotransmitters such as dopamine. Monoamine oxidase-B has therefore been of interest in the development of therapeutic agents for the treatment of Parkinson's disease [3,4]. In Parkinson's disease, there is a loss of dopaminergic neurons of the striatum leading to the characteristic movement associated symptoms. Inhibition of MAO-B leads to increased levels of dopamine and therefore provides symptomatic relief for these patients. Because MAO-B degrades dopamine and at the same time produces toxic by-products such as hydrogen peroxide and ammonia [5], inhibition of MAO-B is effective in alleviating the symptoms of Parkinson's disease [6]. Monoamine oxidase has been divided into two subtypes [7], MAO-A and MAO-B, on the basis of their amino acid sequence, substrate and inhibitor selectivity and tissue distribution. Monoamine oxidase-A inhibitors are prescribed for the treatment of mental depression and anxiety [8], while monoamine oxidase-B inhibitors are used with L-DOPA and/or dopamine agonists in the symptomatic treatment of Parkinson's disease.

Parkinson's disease is a common neurodegenerative disorder that affects about 1 % of the population over the age of 60 years [9]. The disease is characterized by the loss of dopamine neurons in the substantia nigra and the formation of inclusions, called Lewy bodies, in the midbrain [10]. Iron accumulation in the substantia nigra of Parkinson's disease patients was initially described 80 years ago [11]. Iron as a cofactor has multiple functions. It is involved in the transfer of oxygen and electrons, the synthesis of neurotransmitters and myelin, as well as several other functions that are essential to maintain normal central nervous system metabolism [9,12]. Pigmented neurons of the substantia nigra pars compacta are most vulnerable to neurodegeneration and iron accumulation in the substantia nigra may be directly related to the pathophysiology of the disease [13]. Understanding the mechanisms of Parkinson's disease-related nigral dopamine neuron degeneration and developing new therapeutic strategies to prevent and restore dopamine neuron damage, are the main goals of Parkinson's disease research [14].

Coumarins are a large family of compounds from both natural and synthetic origin and display a variety of pharmacological properties such as antidepressant [15,16], antioxidant [17], anti-inflammatory [18], antinociceptive [19], antitumor [20], antiasthmatic [21], antiviral [22]. Some natural coumarins show a low monoamine oxidase inhibitory potency [23]. While properly modified natural coumarins have been characterized as potent and selective monoamine oxidase inhibitors [24]. The identification of salient features within a coumarin template has helped in designing and synthesizing new analogs with enhanced monoamine oxidase inhibition activity.

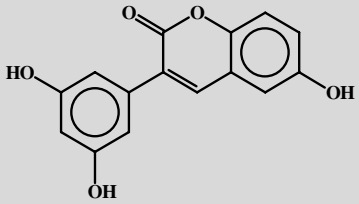
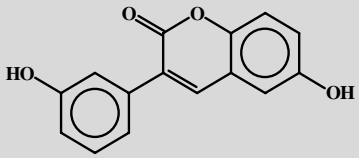
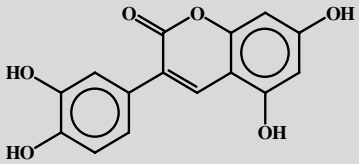
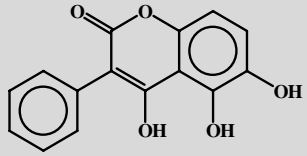
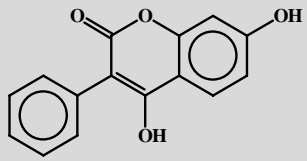
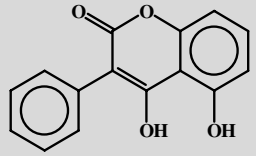
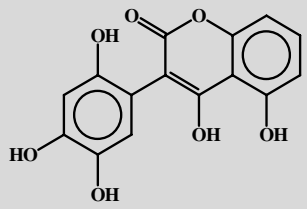
Recent studies pay special attention to their antioxidative and enzymatic inhibition properties, regarding their potential against ND [25]. Numerous functionalized coumarins have been displaying potent MAO and/or AChE inhibitory activities and some of them have been proposed for treating Alzhemier disease [26].

EXPERIMENTAL

Preparation of protein structure: The downloading of monoamine oxidase-B was made from the data base Brookhaven Protein Data Bank (access code 4CRT) [27] it is co-crystallized with inhibitor ASS234 multi-target to resolution (1.80 Å). The protein monoamine oxidase-B was prepared for molecular docking by adding all hydrogen atoms using standard procedures. The water molecules and other heteroatom's were deleted. The binding energy was observed for each ligand protein complex.

Preparation of ligands: The compounds were downloaded from pubchem small molecule library were search for molecules with the same skeleton that coumarin and are all download the structures of starting of formats 3D in the Table-1

TABLE-1
SIMILAR COMPOUNDS OF THE COUMARIN AND APPLICATION OF LIPINSKI'S "RULES OF 5" TO OUR LIGAND TEST

Ligands	log P	Cluster	Lipinski's	AM1 (u.a.)
 CID 11536337	2.414	Cluster-0	0	-0.2144933
 CID 44562470	2.820	Cluster-1	0	-0.1450174
 CID 52937587	2.169	Cluster-0	0	-0.2820153
 CID 54736541	2.900	Cluster-1	0	-0.2109010
 CID 12464343	2.820	Cluster-1	0	-0.1440558
 CID 54702662	3.145	Cluster-2	0	-0.1413305
 CID 71335585	2.088	Cluster-0	0	-0.3459077

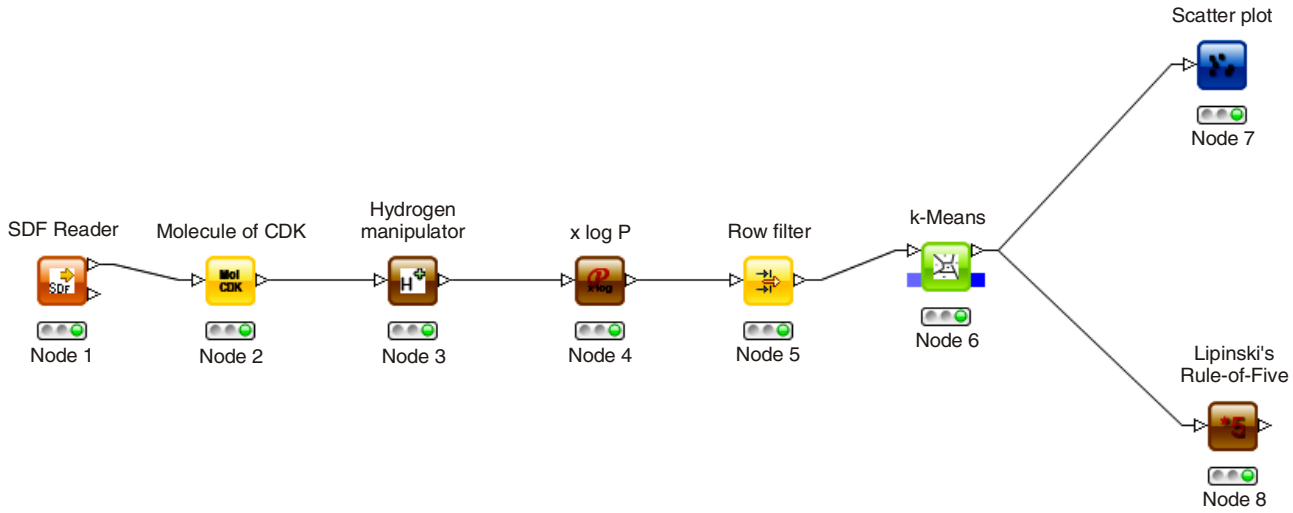


Fig. 1. Pipeline of nodes used in KNIME for database preparation for the virtual screening

(SDF file) for these structures were done using the pipeline program KNIME 2.7.0 (http://www.knime.org/) nodes (Fig. 1) to check rule of Lipinski's.

The optimization of all inhibitors was performed with Gaussview 2.1 (http://www.gaussview2.1.com/) implementing a semi-empérique method AM1 in the Table-1.

Lipinski's rule is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule was formulated by Christopher A. Lipinski in 1997, based on the observation that most medication drugs are relatively small and lipophilic molecules [28,29].

Lipinski's rule states that, in general, an orally active drug has no more than one violation of the following criteria:- molecular weight less than 500, Number of angles of rotations < 5, calculated log P (-2 < log P < 5), number of hydrogen-bond donors < 5, number of hydrogen-bond acceptors < 10. Results from the Lipinski's rule predictions are presented in (Table-1) were observed for all coumarin derivatives and suggested that the Lipinski rule is applicable.

RESULTS AND DISCUSSION

Molecular docking study: Molecular docking studies were performed with UCSF Chimera is an extensible program for interactive visualization and analysis of molecular structures and related data, including density maps, sequence alignments, docking results and molecular dynamics trajectories [30], to derive the affinity and mode of binding of the inhibitors to the active site of the MAO-B. The optimization of the geometry of MAO-B was performed using the force field AMBERff03.r1 [31] and by calculations of energy AutoDock Vina implanted in the UCSF Chimera software. AutoDock Vina, a new program for molecular docking and virtual screening, allows the execution host ligand-receptor calculations with AutoDock Vina. Vina uses a sophisticated optimization gradient method in its local optimization procedure. The gradient actually gives the optimization algorithm of a "sense of direction" from a single assessment [32].

Monoamine oxidase-B is an important target for developing new drugs against Parkinson's disease. Corresponding inhibitors are currently being explored as potential drugs for the clinical treatment of Parkinson's disease [33]. Inhibitors of MAO-B are used to relieve symptoms or slow the progression of Parkinson's disease [34].

The quality of docking results can be affected by the simplification of treating protein structures as rigid entities. Selective residue flexibility is an option available on several molecular docking tools [35], including Autodock Vina used in this work, was run several times to get various docked conformations and used to analyze the predicted docking energy. The binding sites for these molecules were selected based on the ligand binding pocket of the templates.

The different energies interactions between of the monoamine oxidase-B and different inhibitors are calculated during molecular docking, they are presented in the following Table-2.

From the results obtained in our work, it appears that the values obtained on interaction energies of AutoDock Vina implanted in the UCSF Chimera [30] are of the same order of magnitude for all inhibitors except two inhibitors: CID 52937587 and CID 71335585.

Molecular docking simulations were also performed to study the binding mode of the compounds CID 71335585 and CID 52937587 inside the MAO-B, The virtual screening obtained the best two drug-like molecules that are CID 71335585 and CID 52937587, which are require smaller energy than other molecules to bind with monoamine oxidase-B (Fig. 2).

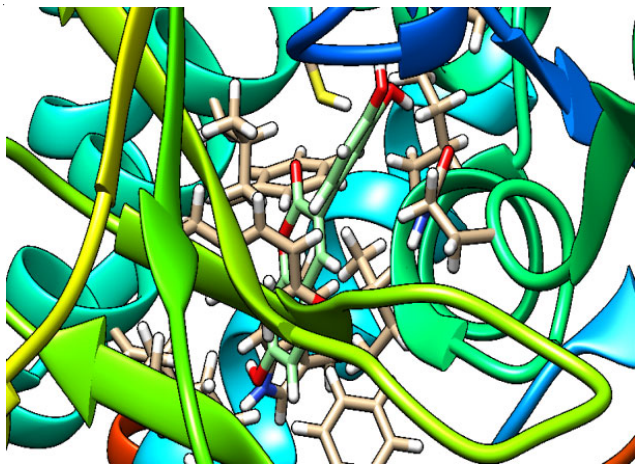
We measured the distances between the R groups of coumarin inhibitor and those side chains of amino acids making up the active site and possibly other groups the main chain of the enzyme responsible for interaction (which may cause a conformation favourable to a high complementarity resulting

TABLE-2
RESULTS OF MOLECULAR DOCKING OF DIFFERENT COUMARINS WITH MONOAMINE OXIDASE B

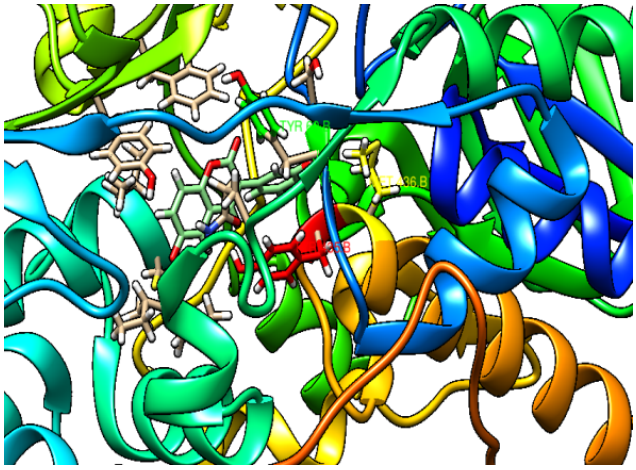
Compounds	CID 11536337	CID 44562470	CID 52937587	CID 54736541	CID 12464343	CID 54702662	CID 71335585
Score (Kcal/mol)	-7.9	-7.1	-9.4	-7.6	-7.3	-6.1	-9.8

TABLE-3
DISTANCES BETWEEN THE ACTIVE SITE AMINO ACIDS AND GROUPS OF INHIBITORS CID 71335585 AND CID 52937587

Compounds	Ile 199	Ile 198	Gln206	Cys172	Tyr 435	Leu171	Tyr 326
CID 71335585	2.689	2.921	3.176	2,599	1.612	3.101	3,370
CID 52937587	2.799	3.078	3.224	3.541	1.935	2.762	2.168



CID 52937587



CID 71335585

Fig. 2. Best three small molecules bind with binding site of MAO-B (CID 71335585 and CID 52937587)

in consistent activity). The measured distances vary between 1.612 and 3.541 Å for both complexes studied (Table-3). Knowing that the interactions between 2.5 and 3.5 Å are considered high and those between 3.1 and 3.55 Å are assumed averages. Interactions greater than 3.55 Å are weak or absent [36,37].

According to the hydrogen bond interactions of the amino acids of the active site of monoamine oxidase-B with various coumarins, one can predict the amino acids which form the active site. The cavity enzyme monoamine oxidase-B is formed in the following sequence of residues (Fig. 3): Ile 199, Ile 198, Gln206, Cys172, Tyr 435, Leu171, Tyr 326.

Following the appearance of active site residues in the majority of hydrogen bonding interactions with the various coumarins, it can be inferred that they are part of the inhibition of monoamine oxidase-B. The large number of interaction with the active site residues that confer inhibiteures CID 71335585 and CID 52937587 presents a better complementarity. The both inhibitors CID 71335585 and CID 52937587 would

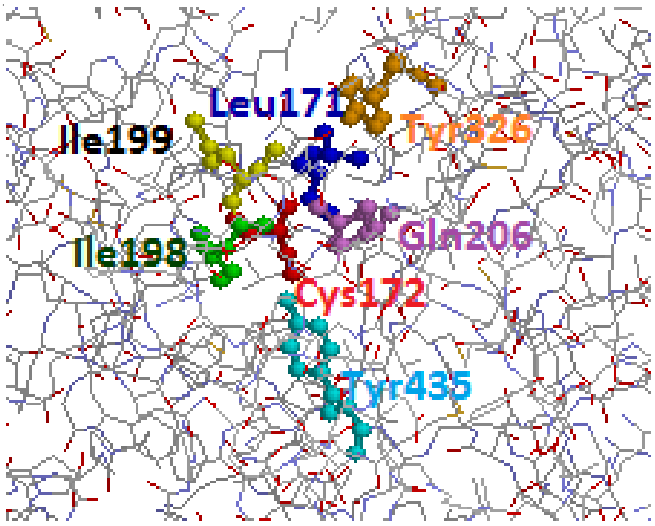


Fig. 3. Residues of the active site

probably be best to slow the progression of the enzym studied. Results of the enzymatic cavity dimensions:

The size of the interval of active site pocket containing a width of 11.35 Å and depth of 12 Å [37] (Fig. 4).

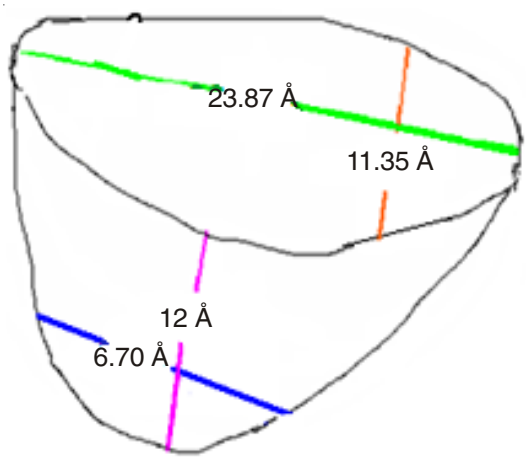


Fig. 5. Enzymatic cavity

Examination of the enzymatic cavity, calculating distances between the R inhibitors and those side chains of the constituent amino acids of the active site and calculated energies, confirm that the CID 71335585 and CID 52937587 inhibitors with the OH groups present a strong hydrogen bonding interaction and better complementarity with monoamine oxidase-B. The both inhibitors CID 71335585 and CID 52937587 would probably be best to slow the progression of the enzyme studied.

Conclusion

Virtual screening methods are routinely and extensively used to reduced cost and time of drug discovery. Monoamine oxidase-B inhibitors are the most important drugs for the

clinical management of Parkinson's disease. It has been clearly demonstrated that the approach utilized in this study is successful in finding two novel inhibitors CID 71335585 and CID 52937587 showed high binding affinity with a score of -9.8 and -9.4 kcal/mol respectively. According to the Lipinski criteria of drug likeness, all compounds were within the range set by Lipinski's rule of five and could be good candidate for drug development.

To conclude, given the results obtained in this work, which consists in the elucidation of the inhibition of Monoamine oxidase-B by the methods of molecular modeling, it appears that the CID 71335585 and CID 52937587 present probably a better contribution to inhibition by other to slow the progression of Parkinson's disease.

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