Molecular docking approach of monoamine oxidase B inhibitors for identifying new potential drugs: Insights into drug-protein interaction discovery

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Abstract

Monoamine oxidase (EC, 1.4.3.4) or amine oxidoreductase catalyzes the oxidative deamination of biogenic amines. Abnormal action of the monoamine oxidase B has been associated with neurological dysfunctions including parkinson´s disorder. Monoamine oxidase B inhibitors divulged that these agents were effective in the therapeutic management of Parkinson's disease. Understanding the interaction of monoamine oxidase binding site with inhibitors is crucial for the development of pharmaceutical agents. At the molecular docking, the exact prediction of the binding modes between the inhibitors and protein is of central importance in structure-based drug design. In the current study, we examined two classes of monoamine oxidase B inhibitors. We applied Autodock tools 4.2, in order to set up the docking runs and predict the inhibitors binding free energy. The final product of molecular docking was clustered to specify the binding free energy and optimal docking energy conformation that is investigated as the best docked structure. Docking results indicate that the contribution of van der Waals interactions is greater than electrostatic interactions so that, it can be concluded that all of the inhibitors attached to a hydrophobic binding site in monoamine oxidase B. Among the total of molecules tested, it was proved that 2-(2-cycloheptylidenehydrazinyl)-4-(2,4-dichlorophenyl)-1,3-thiazole has the lowest binding free energy and the lowest Van der Waals energy and also the lowest inhibition constant and subsequently the most experimental affinity. As well as, we find out a possible relationship between the estimated results and experimental data. The selective information from this work is crucial for the rational drug design of more potent and selective monoamine oxidase B inhibitors based on the 8-benzyloxycaffeine scaffold.

***Keywords*:** monoamine oxidase B inhibitor, Parkinson´s disorder, molecular docking, binding free energy

Introduction

Monoamine oxidase (EC, 1.4.3.4) or amine oxidoreductase is a mitochondrial bound enzyme that contains flavinadenosine dinucleotide; monoamine oxidase catalyzes the oxidative deamination of biogenic amines, including exogenous amines, dietary amines, hormones, dopamine, serotonin and neurotransmitters (Coelho Cerqueira et al., 2010; Herraiz and Chaparro, 2005). Therefore, monoamine oxidases are virtually associated with higher brain functions. Two isoforms of monoamine oxidases have been described, i.e. monoamine oxidase A and monoamine oxidase B. Before their molecular characterization, the differences between these two isoforms were determined on the basis of substrate and inhibitor sensitiveness. Monoamine oxidase A selectively catalyzes the oxidation of norephinephrine and serotonin and is inhibited by clorgyline, whereas monoamine oxidase B selectively catalyzes the oxidation of benzylamine and phenylethylamine and is inhibited by deprenyl (Lewis et al., 2007; Nagatsu, 2004; Oreland, 2004). Abnormal action of the monoamine oxidase B isoform has been associated with neurological dysfunctions including parkinson´s disorder and alzheimer´s disorder whereas the monoamine oxidase A isoform seems to be associated with psychiatric considerations including depression and cardiac cellular degeneration (Bortolato et al., 2008). Furthermore, reports have described that the level of monoamine oxidase B in human beings raises four to five fold throughout aging and results in an increase in catalytic reaction products such as hydrogenperoxide and a decrease in certain neurotransmitter levels (Bortolato et al., 2008; Herraiz and Chaparro, 2005). Monoamine oxidase B inhibitors, such as D-deprenyl (selegiline) divulged that these agents were effective in the therapeutic management of Parkinson's disease. The rationale utilization of monoamine oxidase B inhibitors in parkinson's disorder is based on the concept that dopamine is deaminated by monoamine oxidase B. Inhibition of monoamine oxidase B about an increases the dopamine, and low levels of dopamine is associated with

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parkinson´s disease. Age related additions in monoamine oxidase B function, also the neuroprotective impressions of its inhibitors, have been studied as rational bases to apply monoamine oxidase B inhibitors in alzheimer's disorder (Bortolato et al., 2008; Jensen et al., 2006; Luhr et al., 2010). Regrettably, the usage of monoamine oxidase inhibitors might be confined, although they are often last line treatment, in some cases, by adverse effects such as those related to the co-administration of certain diets or drugs, which can lead to serious hypertensive and hyperpyretic crises (Bortolato et al., 2008). Hence, tremendous attempts have been undertaken to discover new pharmaceutical agent that are linked to monoamine oxidase inhibition. Hence, recognition of monoamine oxidase B inhibitors is a great interest in drug discovery (Geldenhuys et al., 2012).

Materials and Methods

Understanding the interactions of monoamine oxidase binding site with inhibitors are crucial for the development of pharmaceutical agents. Computer aided drug design is an applicable method that can study these interactions and describe significant characteristics for monoamine oxidase binding site recognition (Delogu et al., 2011; Harkcom and Bevan, 2007). Automated docking is widely applied for approximation of bio molecular complex and in order to analyze the structure-function processes and the bio molecular design. Drug design is the other application of docking. The precise interaction of agents or candidate molecules with their targets is crucial in the developmental procedure. Docking is applied to predict the binding orientation of small molecular drug candidates to protein targets, subsequently predicting the affinity and activity of the drug candidates (Goodsell, 2009; Morris et al., 2009; Morris et al., 2008). In addition, docking is often applied to predict binding affinities of drug candidates in virtual screening experiments and in considering structure-activity relationships to prioritize synthesis of new drugs (Wu et al., 2003). Docking of the small molecules into the structures of macromolecular targets and scoring their potential complementarity to binding site is widely applied in hit recognition new drugs. Indeed, there are a number of drugs whose development was heavily based on or influenced by structure-based drug design and screening strategies.

In the present work, our purpose was to distinguish correct poses of inhibitor in the binding pocket of monoamine oxidase B and to predict the affinity between the inhibitor and monoamine oxidase B. In other words, in this study docking procedure describes a process by which two molecules fit together in three-dimensional space (Kitchen et al., 2004). At the molecular docking, the exact prediction of the binding modes between the inhibitors and protein is of central importance in structure-based drug design (Taylor et al., 2002).

Ligand structure

Due to the special characteristics of monoamine oxidase, the researchers have focused on various aspects of it (Carroll et al., 2011; Chimenti et al., 2005; Chimenti et al., 2009; Chimenti et al., 2006; Delogu et al., 2011; Mu et al., 2012; Reniers et al., 2011; Strydom et al., 2010; Van der Walt et al., 2009). Since, some of these were the effective inhibitors against the monoamine oxidase B it may be a potential therapeutic agent for parkinson´s disease. Therefore, we select some of the potent inhibitors for the docking studies against monoamine oxidase B (Scheer et al., 2011; Strydom et al., 2010). In the current study, we examine two classes of monoamine oxidase B inhibitors; these two classes of inhibitors are 2-(2-cycloheptylidene hydrazinyl) and methyl cyclohexylidene hydrazinyl derivatives (8-benzyloxycaffeine analogues). Figure 1 shows the structure of inhibitors A1-A6 and figure 2 shows the structure of inhibitors B1-B5.

In the present study, molecular modeling of the inhibitors was carried out using Hyperchem 7 software. Hyperchem 7 was employed to draw and optimize the structure of inhibitors (Ivanciuc, 1996) For all initial structures geometric optimization calculations by use of molecular mechanics were performed and afterward the lowest energy conformers were optimized using the semiempirical PM3 method, the conjugate gradient and steepest descent algorithm. At the end these structures converted to .pdb format by Hyperchem 7 software. Optimized inhibitor structure was used as input file for docking (Froimowitz, 1993).

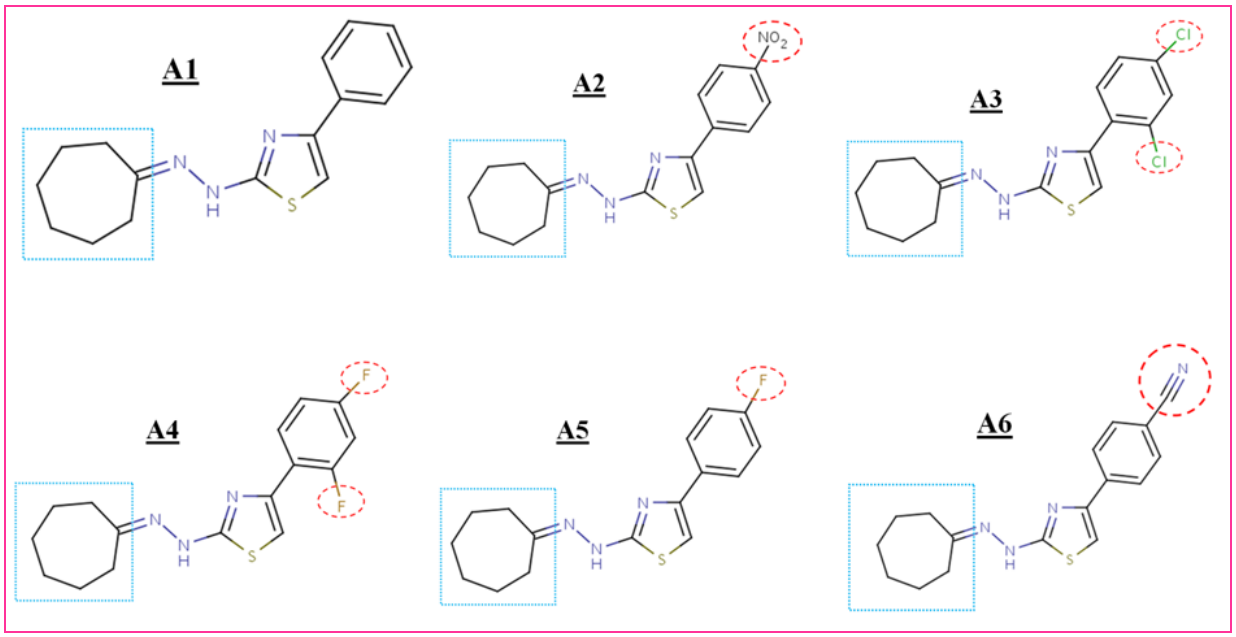

Figure 1. Structure of inhibitors A1-A6. [A1] 2-(2-cycloheptylidenehydrazinyl)-4-phenyl-1,3-thiazole, [A2] 2-(2-cycloheptylidenehydrazinyl)-4-(4-nitrophenyl)-1,3-thiazole, [A3] 2-(2-cycloheptylidenehydrazinyl)-4-(2,4-dichlorophenyl)-1,3-thiazole, [A4] 2-(2-cycloheptylidenehydrazinyl)-4-(2,4-difluorophenyl)-1,3-thiazole, [A5] 2-(2-cycloheptylidenehydrazinyl)-4-(4-fluorophenyl)-1,3-thiazole, [A6] 4-[2-(2-cycloheptylidenehydrazinyl)-1,3-thiazol-4-yl]benzonitrile.

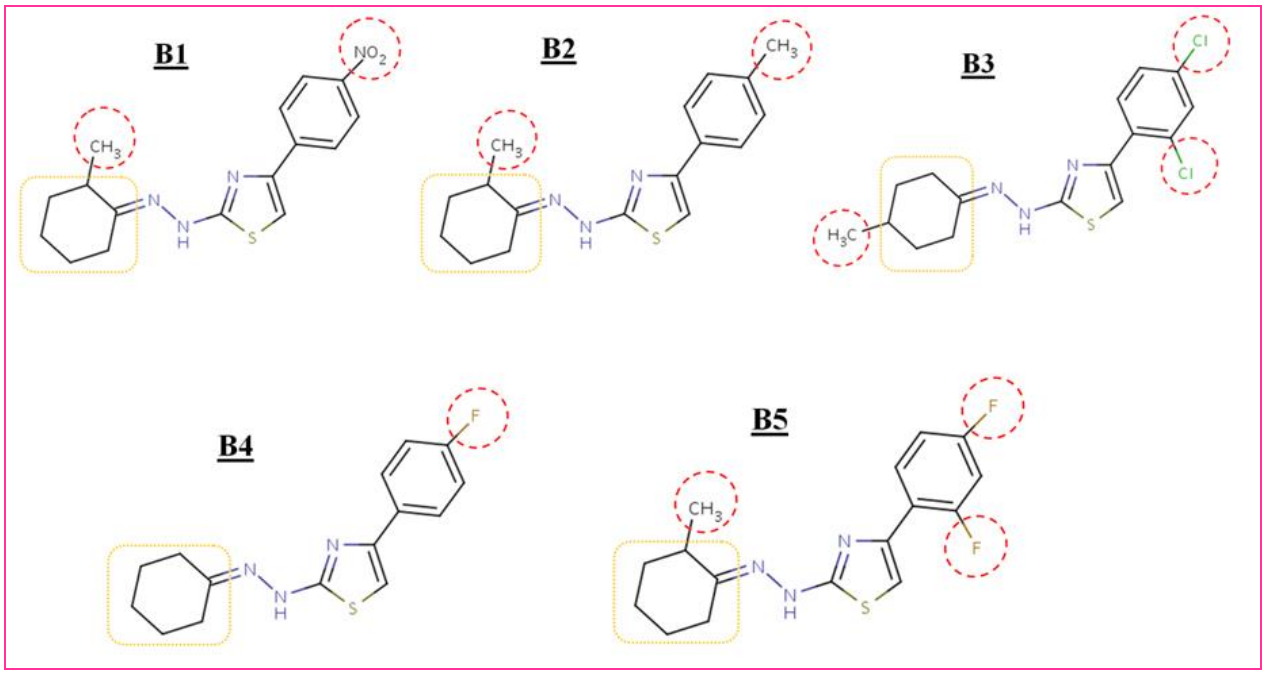

Figure 2. Structure of inhibitors B1-B5. [B1] 2-[(2E)-2-(2-methylcyclohexylidene)hydrazinyl]-4-(4-nitrophenyl)-1,3-thiazole, [B2] 2-[(2E)-2-(2-methylcyclohexylidene)hydrazinyl]-4-(4-methylphenyl)-1,3-thiazole, [B3] 4-(2,4-dichlorophenyl)-2-[2-(4-methylcyclohexylidene)hydrazinyl]-1,3-thiazole, [B4] 2-(2-cyclohexylidenehydrazinyl)-4-(4-fluorophenyl)-1,3-thiazole, [B5] 4-(2,4-difluorophenyl)-2-[(2E)-2-(2-methylcyclohexylidene)hydrazinyl]-1,3-thiazole.

Protein structure

In the current study, the protein X-ray crystal structure of human monoamine oxidase B with 1OJA code and X-ray diffraction at 1.70 Å resolution was received from the Protein Data Bank and was used as the receptor starting structure. This structure comprised a dimeric form of the human monoamine oxidase B, with each chain interacting

with FAD and a co-crystallized inhibitor codenamed ISN (isatin or indol-2,3-dione) and several water molecules. Figure 3 shows the x-ray crystal structure of monoamine oxidase B in complex with inhibitor ISN and FAD. For docking process, only the coordinates of chain A and FAD were considered as the receptor structure, and the co-crystallized inhibitor was removed for the docking studies. The presence of cofactors revealed to be essential for the definition of the docking site. We applied Autodock tools 4.2, in order to set up the docking runs and predict the inhibitors binding free energy.

Docking protocol

In the current study, AutoDockTools 4.2 was applied for docking process. AutoDockTools 4.2 uses a grid-based approach in order to allow exploring of the large conformational space available to drug candidate around an embedded protein in a grid, as well as to provide rapid evaluation of the binding energy of drug candidate conformations. A probe atom is consecutively located at each grid point, the interaction energy between the probe and the target protein is estimated, and the value is stored in the grid. This grid of energies may then be applied as a lookup table during the docking simulation (Morris et al., 2009; Morris et al., 2008)**.**

AutoDockTools 4.2 was employed to docking process of inhibitors to monoamine oxidase B (Morris et al., 2009). Initially, all of the polar hydrogens were added to the inhibitors and Gasteiger-Marsili atomic partial charges were set for them, and all the inhibitors rotatable bonds were adjusted in fewest atoms. The final inhibitor structures were saved in .pdbqt format. Then polar hydrogen was added to the protein crystal structure and the kollman atomic partial charge was set for monoamine oxidase B. The final protein structure was saved in .pdbqt format. An extended pdb format, called pdbqt, is applied for coordinate files, which include atomic partial charges and atom types; pdbqt files as well include data on the torsional degrees of freedom (Morris et al., 2008). Grid box was created by Autogrid 4 with 30 × 30 × 30 Å in x, y and z directions with 0.375 Å spacing and center of box was located on the active site according to co-crystallized inhibitor coordination. The monoamine oxidase B active site was easily distinguished as the hydrophobic cavity comprising the co-crystallized ligand ISN. The genetic algorithm was used to determine the probable accommodate for each inhibitor to monoamine oxidase B. Docking was performed with Lamarckian genetic algorithm (Genetic Algorithm combined with a local search) with population size of 150. Monoamine oxidase B kept rigid in docking process. The inhibitor structures were attributed flexible. In other words all the inhibitors rotatable bonds were adjusted in fewest atoms; note also that cyclic rotatable bonds are excluded. The other parameters were used as default docking parameters, except for the step size parameters that were chosen to be 0.2 (translation) and 5.0 degrees (quaternion and torsion). Finally, by setting all the parameters, inhibitors were docked to the monoamine oxidase B (Chimenti et al., 2004; Coelho Cerqueira et al., 2010; Harkcom and Bevan, 2007).

AutoDockTools contain a number of methods for considering the results of docking simulations, including tools for clustering results by conformational resemblance, visualizing conformations, visualizing interactions between ligands and proteins. At the end of a docking process, AutoDock writes the data on clustering and binding energies to the log file. The docking results were clustered with 2 Å root mean square deviation and were ranked according to the estimated binding free energy. The structure with proportional lower binding free energy and the most conformation in cluster was selected for the optimum docking conformation (Goodsell, 2009).

The intensity of the interaction between the inhibitor and the receptor can be evaluated experimentally and is often described as the dissociation constant, Kd, or by the concentration of inhibitor that inhibits activity by 50%, the IC50. The binding free energy is the thermodynamic quantity that is determined by equation 1 and is of interest in computational structure-based design (Brooijmans, 2009).

Equation 1

$$\Delta G_{bind} = \Delta G_{complex} - \left(\Delta G_{ligand} - \Delta G_{receptor}\right)$$

The relationship between the binding free energy ΔG and the experimentally determined Kd or IC50 is demonstrated in equation 2.

Equation 2

$$\Delta G_{bind} = -RT \ln K_{eq} = -RT \ln K_d = -RT \ln 1/IC_{50}$$

The interactions between the inhibitor and the receptor also can be measured by means of AutoDock 4.2. In the present work, our purpose was to attain an agreement between the docking results and experimental data.

The AutoDock 4.2 force field is designed to estimate the binding free energy of inhibitors to protein. It includes an updated charge-based

desolvation term, advances in the directionality of hydrogen bonds, and various improved models of the unbound state. AutoDock 4.2 applies a semi-empirical free energy force field and grid-based docking to assess conformations during docking process. Equation 3 represent the docking binding free energy, this formula automatically was computed by AutoDock 4.2 (Morris et al., 2008).

Equation 3

$$\Delta G_{binding} = [\Delta G_{intermolecular} + \Delta G_{internal} + \Delta G_{tors}] - [\Delta G_{unbound}]$$

In the above formula, the final intermolecular energy is calculated with equation 4, so that the final intermolecular energy involves in van der Waals, hydrogen bonding, desolvation and electrostatic contribution between the inhibitor and the protein binding site.

Equation 4

$$\Delta G_{intermolecular} = [\Delta G_{vdw} + \Delta G_{hbond} + \Delta G_{desolv}] + \Delta G_{elec}$$

Results

Molecular docking was applied to describe and find out the binding sites in monoamine oxidase B. The final product of molecular docking, as the best docked structure was clustered to specify the binding free energy and optimal docking energy conformation. As well as we consider the molecular docking results to elucidate their binding mode in the monoamine oxidase B.

Table 1 summarizes the docking results. In this study the inhibition constant (Ki) and the RMSD value for drug-like molecules were also determined. Negative values of predicted free energies of binding show that all inhibitors correctly docked to the crystal structure of the monoamine oxidase B. Docking results also indicate that the contribution of van der Waals interactions is greater than electrostatic interactions so that, it can be concluded that all of the inhibitors attached to a hydrophobic binding site in monoamine oxidase B. In other words, the non-polar interactions between monoamine oxidase B and inhibitors are the main factor in the connectivity features and they are the dominant component contributing to the binding affinity. Among the molecules tested of A class, A3 or 2-(2-cycloheptylidenehydrazinyl)-4-(2,4-dichlorophenyl)-1,3-thiazole demonstrated the lowest binding free energy (-11.96 kcal/mol). As well as, among the molecules tested of B class, B3 or 4-(2,4-dichlorophenyl)-2-[2-(4-methylcyclohexylidene)hydrazinyl]-1,3-thiazole demonstrated the lowest binding free energy (-11.54 kcal/mol). The more negative is the free binding energy, the more potent is the interaction.

According to the table 1, among the total of molecules tested, it was proved that A3 has the lowest binding free energy (-11.96 kcal/mol), Van der Waals energy (-13.14 kcal/mol) and also the lowest inhibition constant (1.70 n M) and subsequently the most experimental affinity. It was proved that after A3, B3 also has the lowest binding free energy (-11.54 kcal/mol), the lowest Van der Waals energy (-12.69 kcal/mol), the lowest inhibition constant (3.50 n M) and the most experimental affinity. In other words, A3 and B3 have the highest interactions and the more potential binding affinity for the enzyme binding site.

Special attention has been devoted to the substituent at thiazole ring. 2,4-dichlorophenyl substitution leads to the highest potential binding affinity at 2-(2-cycloheptylidenehydrazinyl) and methyl cyclohexylidene hydrazinyl derivatives. It has been found clearly that, in the presence of a dichlorophenyl substituent in the 2,4 position, the potency of inhibitor was increased.

The active site is frequently known from crystal structures of ligand-bound receptors. The distinguishing of active sites can play a central role in realizing protein function (Brooijmans, 2009).

The docking results indicate that all inhibitors bind to monoamine oxidase B active site; active site is a hydrophobic pocket that was surrounded by the aromatic and aliphatic residues. The active site of monoamine oxidase B constitutes of an entrance cavity and substrate cavity; depending on the nature of the ligand, two cavities can be separated or joined (Chimenti et al., 2004; Harkcom and Bevan, 2007).

In structure-based design, the known or predicted shape of the binding site is used to optimize the inhibitor as a best fit to the receptor. As well as, the orientations of these inhibitors in the active site are very important, with their Ki values, for rational drug design. In most of the cases, careful observations of the figures divulge that inhibitor positioning in the active site sits reasonably well. The binding manners and geometrical orientation of all compounds in the binding site were nearly identical, hence proposing that all the inhibitors have the same interactions with enzyme and occupied a common space in the receptor. Hydrophobic cavity of binding site constitutes the inner cavity of the active site, and comprises the residues such as Tyr 60, Leu171, Ile198, Gln206, Tyr326, Leu328, Phe343, Tyr398, Tyr435. Fig 4 shows the lowest energy configuration of A3-monoamine oxidase B complex. Observations of the docked conformation of A3 demonstrated

interactions with many residues; in this complex, A3 was located inside the cavity that comprising the residues such as Gly57, Gly58, Leu171, Ile198, Gln206, Tyr326, Phe343, Tyr398, Thr426, Gly434, Tyr435, Met436. And Fig 5 shows the lowest energy configuration of B3-monoamine oxidase B complex, B3 was located inside the cavity that containing the residues such as Gly57, Gly58, Tyr60, Leu171, Gln206, Tyr326, Phe343, Tyr398, Thr426, Gly434, Tyr435, Met436.

Other interactions proposed by the docking consequences were the hydrophobic interactions of the inhibitors hydrophobic groups, as they were observed oriented towards the co-crystallized ligand ISN, so that they have similar hydrophobic interactions. Fig 6-A shows the best virtual docking pose of A3 and the superimposition of A3 and ISN, and Fig 6-B shows the best virtual docking pose of B3 and the superimposition of B3 and ISN. In this docked conformation, the A3 and B3 interact with flavin moiety of the FAD via a hydrogen bond and show tight interactions with Gln206, Tyr326, Phe343, Tyr398 and Tyr435 (Fig 6 A-B). For superimposition of A3 and B3 with ISN, the indol ring is located between Tyr435 and Tyr398 in the hydrophobic cavity with an upright conformation to flavin ring of FAD. Therefore, AutoDock 4.0 viewed as reliable for docking A3 and B3, and related compounds into monoamine oxidase B.

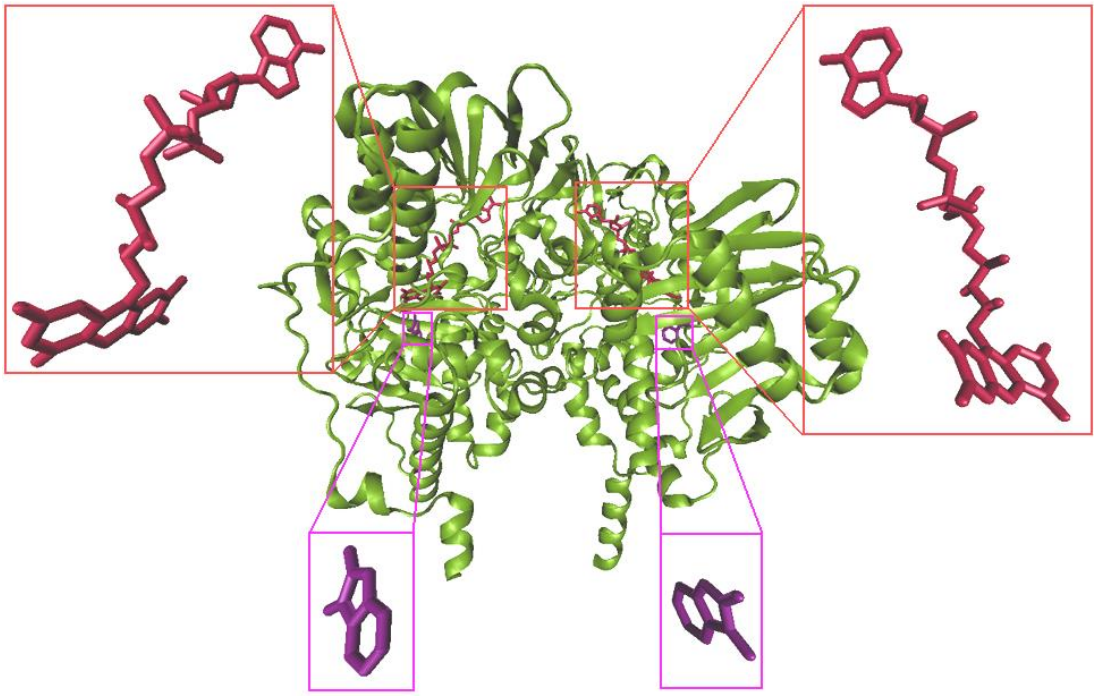

Figure 3. X-ray crystal structure of monoamine oxidase B in complex with inhibitor ISN (purple) and FAD (red).

Table 1. Autodock's binding free energy derived from the docking studies on monoamine oxidase B.

Inhibitor Index	$\Delta G_{binding}$	Ki	ΔG_{vdW}	ΔG_{ele}	ΔG_{inter}	ΔG_{tors}	$\Delta G_{unbound}$	RMSD	IC50
A1	-11.63	3.01	-12.82	-0.00	+0.05	+1.19	+0.05	160.981	2.7e-05
A2	-11.05	7.90	-12.13	-0.41	-0.16	+1.49	-0.16	159.024	1.1e-05
A3	-11.96	1.70	-13.14	-0.01	+0.12	+1.19	+0.12	159.562	0.00094
A4	-10.72	32.51	-11.43	+0.02	+0.04	+1.19	+0.04	156.675	1.6e-05
A5	-9.73	74.19	-10.67	+0.05	+0.57	+0.89	+0.57	155.853	4e-06
A6	-11.32	5.07	-12.50	-0.01	+0.01	+1.19	+0.01	159.498	4.6e-05
B1	-11.23	5.84	-12.34	-0.39	+0.00	+1.49	+0.00	157.532	3.2e-05
B2	-10.21	32.87	-11.39	-0.01	+0.17	+1.19	+0.17	157.254	0.000143
B3	-11.54	3.50	-12.69	-0.04	+0.14	+1.19	+0.14	160.077	0.009446
B4	-9.91	54.84	-11.13	+0.03	-0.16	+1.19	-0.16	156.619	4e-06
B5	-9.98	48.38	-11.17	-0.00	+0.12	+1.19	+0.12	156.271	1.4e-05

Abbreviations: ΔGbinding, Estimated Free Energy of Binding (kcal/mol); ΔGvdw, vander Waals or Lennard–Jones potential factor of binding free energy (kcal/mol); ΔGelec, electrostatic factor of binding free energy (kcal/mol); ΔGinter, Gibbs free energy of binding (kcal/mol); ΔGtors, torsional energy of binding (kcal/mol); ΔGunbound, unbound System's energy (kcal/mol); Ki, inhibition constant (nM); RMSD, reference root mean square deviation ; IC50 refers to the experimental predicted activity (mM). Refrence of inhibitor (Scheer et al., 2011; Strydom et al., 2010).

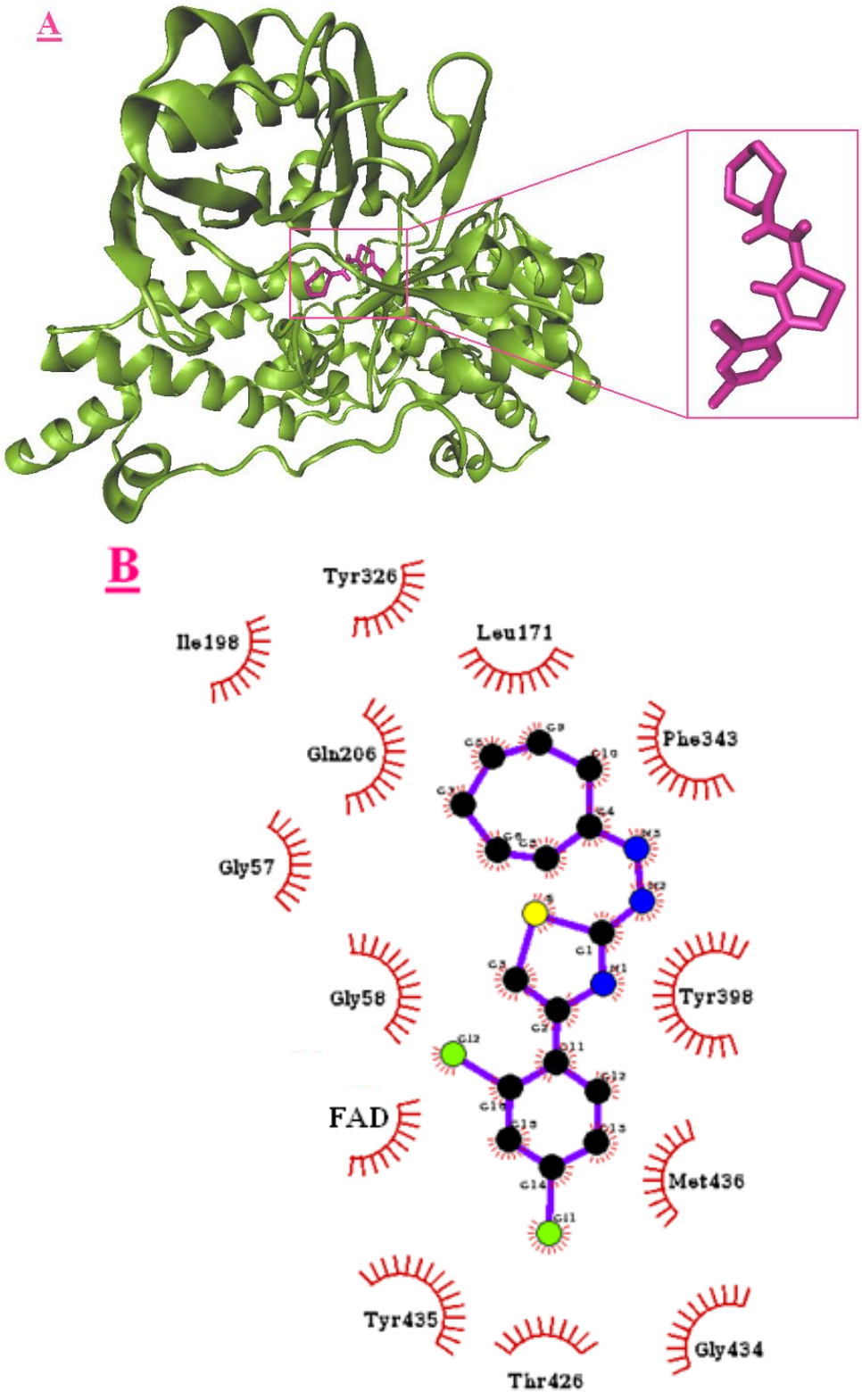

Figure 4. Docking result of A3 (magenta) with monoamine oxidase B. The lowest energy configuration of A3-monoamine oxidase B complex is demonstrated in VMD(A) and Ligplot (B) presentations. In Ligplot presentations (B), carbons are in black, nitrogens in blue and oxygens in red.

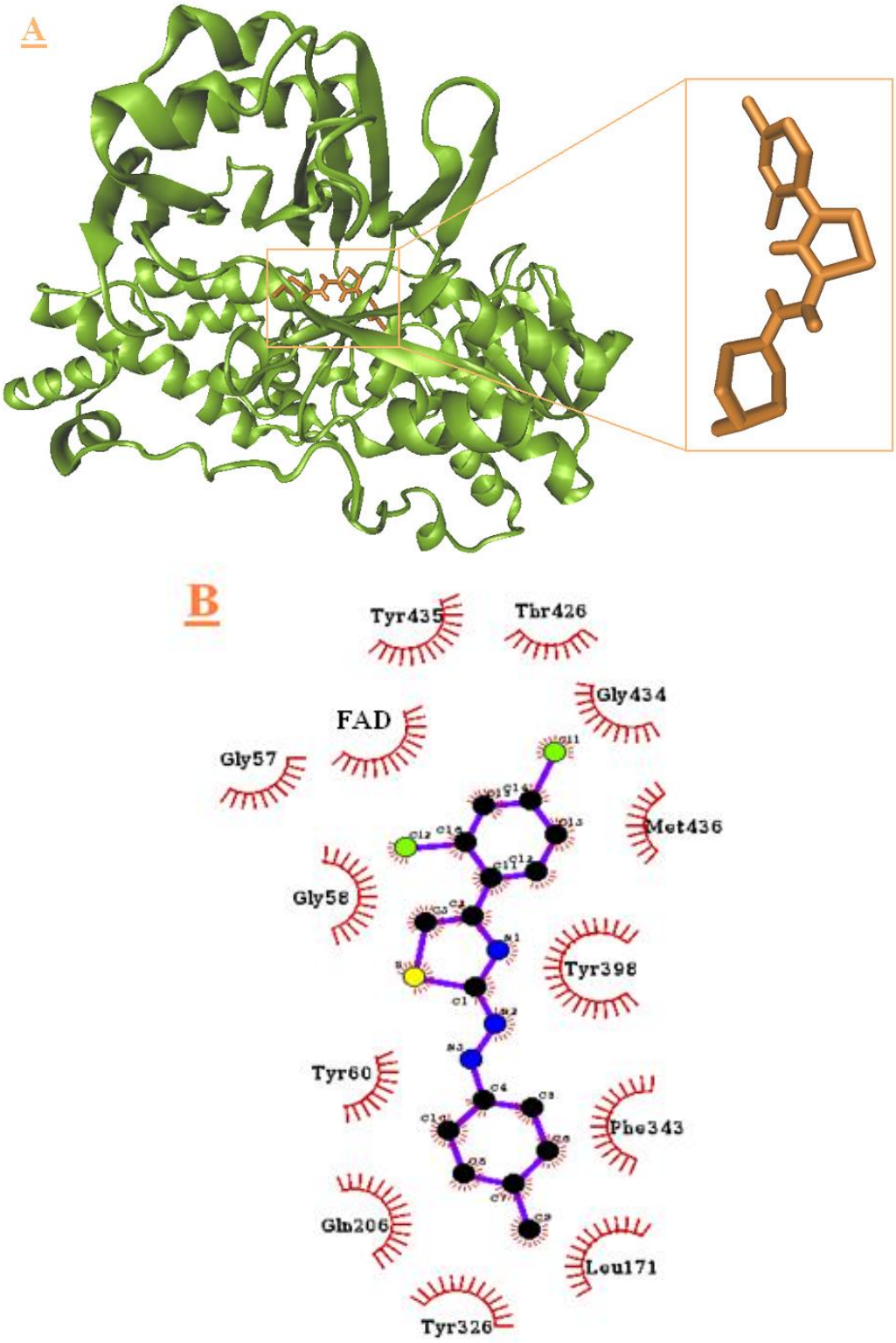

Figure 5. Docking result of B3 (orange) with monoamine oxidase B. The lowest energy configuration of B3-monoamine oxidase B complex is demonstrated in VMD(A) and Ligplot (B) presentations. In Ligplot presentations (B), carbons are in black, nitrogens in blue and oxygens in red.

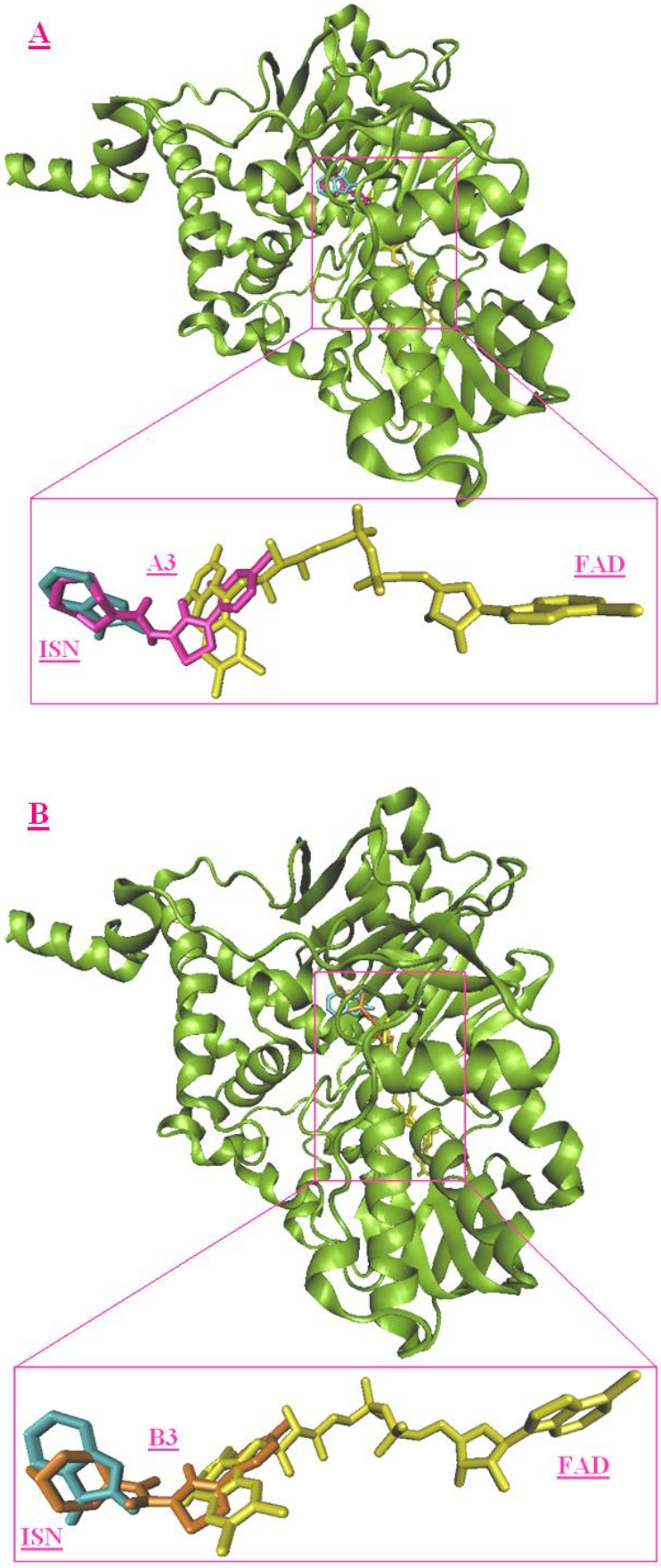

Figure 6. Best virtual docking pose of A3 and B3. (A), superimposition of A3 (magenta) and FAD (red) and ISN (purple); (B) superimposition of B3 (orange) and FAD (red) and ISN (purple).

Discussion

The target of this study was to carry out molecular docking to estimate the binding free energies and inhibition constants of tested monoamine oxidase B inhibitors and to compare these computational results with those of the experimentally obtained results.

In the resent study, we employed computational approaches, such as molecular docking to estimate the binding free energy of two classes of monoamine oxidase B inhibitors. Compare with the van der Waals and electrostatic energies for these components showed a significant share of the van der Waals energies. Our results clearly showed that non polar interactions play a significant role in determining the binding free energy. Our findings propose that (2,4-dichlorophenyl)-1,3-thiazole might demonstrate a crucial scaffold for the development of monoamine oxidase inhibitors. All inhibitors bind to monoamine oxidase B active site and subsequently inhibit it. So that they have potent affinity to the monoamine oxidase B and thus they can behave like as the pharmaceutical agents. Among the tested derivatives we preferred A3 and B3 as potent anti monoamine oxidase B agents. Understanding, an atomic-level of the catalytic and inhibition mechanisms of monoamine oxidase B could assist to search for rationally-designed inhibitors of monoamine oxidase B, and would be of significant importance monoamine oxidase B activity. In the present work, our purpose was to attain an agreement between the docking results and experimental data. We discovered good relationship between the estimated results and experimental data. The selective information from this work is crucial for the rational drug design of more potent and selective monoamine oxidase B inhibitors based on the 8-benzyloxycaffeine scaffold. Such observations can also help to study 8-benzyloxycaffeine, by increased metabolism of biogenic amines within some key areas of the central nervous system, as an effective scaffold for rational design of novel and potential drugs against diseases precipitated.

Note: All the figures are color in online version.

Acknowledgment

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